Clinical Study Protocol

Study Title:	An Open-label Phase 1 Study to Assess the Safety, Tolerability, and Efficacy of IBI110 as Monotherapy and in Combination with Sintilimab in Subjects with Advanced Malignancies
Protocol No.:	CIBI110A101
Version date and version number:	04 Jul 2022/Version 8.1
Product Name:	IBI110
Study Phase:	Phase Ia/Ib
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu Province, China
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Sponsor Signature Page

Protocol Title: An Open-Label Phase I Study to Evaluate the Safety, Tolerability, and Efficacy of IBI110 as Monotherapy and in Combination with Sintilimab in Subjects with Advanced Malignancies

Project Number: CIBI110A101

Title	Name (Print)	Signature	Date
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Protocol synopsis

Protocol Number	CIBI110A101
Sponsor	Innovent Biologics (Suzhou) Co., Ltd.
Investigational drug	Recombinant fully human anti-lymphocyte activation gene 3 (LAG-3) monoclonal antibody (R&D code: IBI110)
Protocol Name	An Open-label Phase 1 Study to Assess the Safety, Tolerability, and Efficacy of IBI110 as Monotherapy and in Combination with Sintilimab in Subjects with Advanced Malignancies
Staging	Phase Ia/Ib
Version No./Date	V8.1/04 Jul 2022
Study Objectives	**Primary objective:** • To assess the safety and tolerability of IBI110 alone or in combination with sintilimab in subjects with advanced tumors. • To evaluate the anti-tumor activity of IBI110 alone or in combination with sintilimab in subjects with advanced tumors as assessed by RECIST V1.1. **Secondary objectives:** • To evaluate the pharmacokinetic (PK) profile of IBI110 alone or in combination with sintilimab in subjects with advanced tumors. • To evaluate the pharmacodynamic profile of IBI110 alone or in combination with sintilimab in subjects with advanced tumors. • To assess the immunogenicity of IBI110 alone or in combination with sintilimab in subjects with advanced tumors. **Exploratory Objectives:** • To explore the efficacy of IBI110 alone or in combination with sintilimab in subjects with advanced tumors using iRECIST. • Phase Ia: to explore the expression of LAG-3 in tumor tissues. • Phase Ib: to explore the amount of LAG-3 and PD-L1 expression in tumor tissue as potential biomarkers for predicting response.
Dose Limiting Toxicity (DLT)	Dose limiting toxicity (DLT) is defined as any of the following adverse events (AE) related to IBI110 alone or in combination with sintilimab occurring within 28 days (4 weeks) after the first dose according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 toxicity evaluation criteria: 1. Hematologic toxicity:

	• Grade 4 hematologic toxicity. • Grade 3 thrombocytopenia with bleeding tendency or requiring platelet transfusion. • Grade 3 febrile neutropenia (absolute neutrophil count < 1000/mm3 with fever, temperature > 38.3 ℃ or temperature ≥ 38.0 ℃ for more than 1 hour). 2. Non-hematologic toxicity: • ≥ Grade 3 immune-related adverse events (irAE, immune-related AE) (excluding: asymptomatic Grade 3 thyroid or adrenal or pituitary insufficiency and Grade 3 inflammatory reaction at tumor site). • Any Grade ≥ 3 non-haematological laboratory abnormality if: ➢ Need for treatment ➢ Lasts > 1 week 3. Any Grade 5 adverse event. 4. Other toxicities of any grade that need to be terminated prematurely after discussion between the investigator and the sponsor. **Note: The following are not considered dose limiting toxicities:** • Grade 3 or 4 infusion reactions (IRRs) were not considered dose limiting toxicities. However, in the event of a Grade 3 or 4 IRR, the subject was to be discontinued from study treatment and replaced with a new subject. If ≥ 2 subjects in a treatment group experience a Grade 3 or 4 IRR, enrollment must be held, and the sponsor needs to review the safety data from the study to determine whether to continue enrollment; • Grade 3 immune-related adverse events that can be recovered to ≤ Grade 1 or baseline within the expected time (21 days) with appropriate treatment. However, if such Grade 3 immune-related adverse events occur, they should be reviewed by the safety assessment committee to determine that they are not dose-limiting toxicities; • Adverse events due to other causes with clear evidence (e.g., adverse events due to disease progression) based on a joint discussion between the sponsor and the investigator.
Study Design	This is an open-label phase 1 study to evaluate the safety, tolerability, and efficacy of a fully human recombinant anti-lymphocyte activation gene-3 (LAG-3) monoclonal antibody (IBI110) alone or in combination with sintilimab in subjects with advanced malignancies. The study was divided into Phase 1a and Phase 1b. **Phase Ia** Phase 1a is a study to evaluate the safety, tolerability, and efficacy of single-agent IBI110.

	Phase 1a is divided into Part 1 single-agent dose escalation and Part 2 single-agent dose expansion. **Phase 1a Part 1 Single-agent Dose Escalation** Approximately 4 to 38 subjects with locally advanced, recurrent or metastatic solid tumors who have failed standard treatment will be enrolled, and dose escalation decisions will follow accelerated titration combined with the classical "3 +3" design. For dose escalation, 1 subject was enrolled at 0.01 mg/kg according to the accelerated titration method. After completing the 28-day DLT observation window, if no DLT occurred, 1 subject was enrolled at 0.1 mg/kg according to the accelerated titration method. After completing the 28-day DLT observation window, if no DLT occurred, 0.3 mg/kg was enrolled. Dose escalation was performed according to "3 +3", and traditional "3 +3" dose escalation was performed at 1 mg/kg, 3 mg/kg, 10 mg/kg and 20 mg/kg. If the first subject in the 0.01 mg/kg or 0.1 mg/kg dose group experiences a DLT during the DLT observation period, 3 additional subjects should be enrolled in the dose group [If more than 1 (including) of the additional 3 subjects experiences a DLT during the DLT observation period, the dose escalation should not be continued]. If no DLT was observed in the 3 re-enrolled subjects in the 0.01 mg/kg or 0.1 mg/kg dose groups, subsequent dose escalation (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, 20 mg/kg) was completed according to the "3 +3" design principle. For the group using the classical "3 +3" design, 3 subjects will be enrolled first. If none of the 3 subjects experience DLT during the DLT observation period, the next dose will be enrolled; If 1 (1/3) of the 3 subjects experienced a DLT during the DLT observation period, an additional 3 subjects were required for this dose group (a total of 6 subjects in this group at this time). If no DLT occurred in the additional 3 subjects, the subjects could enter the next dose group. If more than 1 (including) of the additional 3 subjects or 2 (including) of the total 6 subjects experience a DLT during the DLT observation period, dose escalation should not be continued. At the same time, 6 additional subjects are required in the previous dose group until the MTD is determined, so at least 6 subjects are required in the MTD dose group to be confirmed. For the 3 mg/kg dose group, if no 6 subjects were enrolled, additional 6 subjects were required to continue the PK/PD study; If 2 cases of DLT were observed in the 3 mg/kg dose group, 6 cases in the 0.3 mg/kg dose group were required to continue the PK/PD study. After completing the 28-day DLT observation window, subjects in the 0.01 mg/kg and 0.1 mg/kg dose groups were directly treated with equivalent doses of sintilimab 200 mg IV Q3W at the investigator's discretion based on the subject's ECOG PS assessment (see Section 5.1. 2 for details). Subjects in other dose groups

	will undergo radiological evaluation after completion of DLT observation. If radiological disease progression (based on RECIST V1.1) is documented, the subjects will receive sintilimab combination (or single agent) treatment (0.3 mg/kg, 1 mg/kg and 3 mg/kg dose groups will receive sintilimab 200 mg IV Q3W directly in combination with sintilimab 200 mg IV Q3W, 10 mg/kg and 20 mg/kg dose groups will receive 1.5 mg/kg IBI110 in combination with sintilimab 200 mg IV Q3W) according to the investigator's judgment (see Section 5.1. 2 for details) according to their ECOG PS assessment. If the safety of the above corresponding combination dose group is confirmed, the above corresponding dose of IBI110 Q3W in combination with sintilimab 200 mg IV Q3W will be administered; If the safety of the corresponding combination dose group is not confirmed at that time, the highest combination dose group with confirmed safety at that time will be treated with IBI110 Q3W in combination with sintilimab 200 mg IV Q3W; If the combination dose group with confirmed safety is not available at that time, subjects will receive sintilimab 200 mg IV Q3W monotherapy until disease progression (based on iRECIST, or RECIST v1.1 but not 5.1. 2), lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a total treatment duration of up to 24 months (including the time of previous treatment with IBI110 monotherapy). If there is no disease progression (based on RECIST V1.1) after the end of DLT observation to receive subsequent IBI110 treatment every 3 weeks, subjects with disease progression (based on RECIST V1.1) will receive sintilimab combination (or single agent) treatment (0.3 mg/kg, 1 mg/kg, 3 mg/kg dose groups will be directly combined with sintilimab 200 mg IV Q3W, 10 mg/kg and 20 mg/kg dose groups will receive 1.5 mg/kg IBI110 combined with sintilimab 200 mg IV Q3W) at the investigator's discretion (see Section 5.1. 2) according to ECOG PS assessment. If the safety of the above corresponding combination dose group is confirmed, the above corresponding dose of IBI110 Q3W in combination with sintilimab 200 mg IV Q3W will be administered; If the safety of the corresponding combination dose group is not confirmed at that time, the highest combination dose group with confirmed safety at that time will be treated with IBI110 Q3W in combination with sintilimab 200 mg IV Q3W; If the combination dose group with confirmed safety is not available at that time, subjects will receive sintilimab 200 mg IV Q3W monotherapy until disease progression (based on iRECIST, or RECIST v1.1 but not 5.1. 2), lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a total treatment duration of up to 24 months (including the time of previous treatment with IBI110 monotherapy).

	In order to fully explore the safety and efficacy of potentially effective dose, if the subjects who experience partial response (PR) or complete response (CR) with monotherapy during single-agent dose escalation, after completion of dose escalation, 6 subjects will be added to each dose group from the lowest dose group with PR or CR to the highest dose group with confirmed safety after completion of escalation (if there are less than 6 subjects in this dose group during escalation). The additional subjects will be preferentially included in the subjects with tumor types that experience PR/CR during single-agent dose escalation, and secondly, the subjects with tumor types that experience PR/CR during combination dose escalation may be considered. Every effort should be made to collect prior tumor tissue specimens from these supplemental subjects (especially if supplemental subjects experience CR/PR or shrinking SD) for further marker exploration. These additional subjects will undergo radiographic assessment after 28 days of observation, and if radiographic disease progression (based on RECIST V1.1) is documented, they will receive sintilimab plus IBI110 at the investigator's discretion (see Section 5.1. 2) based on the subject's PS assessment (0.3 mg/kg, 1 mg/kg, 3 mg/kg dose groups will directly combine with sintilimab 200 mg IV Q3W, 10 mg/kg dose group will receive 8 mg/kg IBI110 combined with sintilimab 200 mg IV Q3W, 20 mg/kg dose group will receive 10 mg/kg IBI110 combined with sintilimab 200 mg IV Q3W); If the safety of the above corresponding combination dose group is confirmed, the above corresponding dose of IBI110 Q3W in combination with sintilimab 200 mg IV Q3W will be administered; If the corresponding combination dose group has no confirmed safety at that time, the highest combination dose group with confirmed safety at that time will be treated with IBI110 Q3W plus sintilimab 200 mg IV Q3W until disease progression (based on iRECIST, or RECIST v1.1 but not 5.1. 2), lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a total treatment duration of up to 24 months (including previous treatment with IBI110 monotherapy). If there is no disease progression (based on RECIST V1.1) after the end of DLT observation to receive subsequent IBI110 treatment every 3 weeks, subjects with disease progression (based on RECIST V1.1) will receive sintilimab in combination with IBI110 at the investigator's discretion (see Section 5.1. 2) based on PS assessment (0.3 mg/kg, 1 mg/kg, 3 mg/kg dose groups will directly combine with sintilimab 200 mg IV Q3W, 10 mg/kg dose group will receive 8 mg/kg IBI110 in combination with sintilimab 200 mg IV Q3W, 20 mg/kg dose group will receive 10 mg/kg IBI110 in combination with sintilimab 200 mg IV Q3W); If the safety of the above corresponding combination dose group is confirmed, the above corresponding dose

	of IBI110 Q3W in combination with sintilimab 200 mg IV Q3W will be administered; If the corresponding combination dose group has no confirmed safety at that time, the highest combination dose group with confirmed safety at that time will be treated with IBI110 Q3W plus sintilimab 200 mg IV Q3W until disease progression (based on iRECIST, or RECIST v1.1 but not 5.1. 2), lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a total treatment duration of up to 24 months (including previous treatment with IBI110 monotherapy). The subjects included in the original dose escalation process will continue to follow the principle of transferring IBI110 monotherapy to Sindil combination (or single-agent) regimen as described in the previous paragraph. Safety after DLT observation period will also be included in the observation of safety and tolerability. After discontinuation of study treatment, subjects will enter Safety Follow-up and Survival Follow-up for 90 ± 7 days (every 3 months for ⩽ 90 days). Subjects with first disease progression may continue to receive treatment at the discretion of the investigator if they are clinically stable and meet the requirements (see Section 5.1. 2 for details) until the total duration of treatment reaches 24 months or until disease progression, loss to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment occurs, whichever occurs first. The total duration of treatment is generally no longer than 24 months, and if disease response or patient benefit exceeds 24 months, the investigator and sponsor should discuss whether the subject should continue to receive treatment. During or after the enrollment of subjects, the sponsor may make a systematic evaluation based on preliminary data and determine the subsequent escalation scheme after discussion with the investigator on the basis of weighing the risks and benefits of the subjects, such as whether to start single-agent dose expansion or combined dose escalation, advance or delay the enrollment of the study or further expand the enrollment, etc. **Phase 1a Part 2 Single Agent Dose Expansion** During the phase 1a escalation phase of single-agent IBI110 (e.g., after the completion of DLT observation in the 1 mg/kg dose group of single-agent IBI110) or after the end of escalation, the sponsor and the investigator will make a systematic evaluation based on the available preliminary data, and decide whether to carry out single-agent dose expansion and the timing of single-agent dose expansion on the basis of weighing the risks and benefits of subjects.

	Currently, based on the available clinical efficacy, safety, and PK results, a single-agent cohort expansion with a fixed dose of IBI110 200 mg Q3W IV infusion is proposed: **Cohort A1: Advanced solid tumors associated with viral infection that have failed standard therapy: Approximately 30 subjects will be enrolled, including hepatocellular carcinoma (HBV-or HCV-associated), Epstein-Barr virus (EBV) infection-associated nasopharyngeal carcinoma and gastric cancer, and human papillomavirus (HPV) infection-associated advanced solid tumors such as cervical cancer and head and neck squamous cell carcinoma, etc.** **Cohort A2: Other Advanced Solid Tumors: Approximately 30 subjects will be enrolled, including epithelial ovarian cancer, endometrial cancer, malignant melanoma (acral or cutaneous), and triple negative breast cancer.** Subjects will be treated with IBI110 200 mg IV Q3W, and subjects who experience disease progression (based on RECIST V1.1) during monotherapy will receive sintilimab combination therapy (IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W) based on PS assessments at the investigator's discretion (see Section 5.1. 2) until disease progression (based on iRECIST, or based on RECIST V1.1 but not 5.1. 2), lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first. The total duration of treatment will not exceed 24 months (including the total duration of monotherapy and combination therapy, and if disease response or patient benefit exceeds 24 months, the investigator and sponsor will discuss whether the subject will continue to receive treatment). Subjects who experience first disease progression (based on RECIST V1.1) during monotherapy or combination therapy may continue treatment if clinically stable and eligible subjects (see Section 5.1. 2 for details) at the discretion of the investigator until the total treatment time reaches 24 months (including the total duration of monotherapy and combination therapy, if disease response or patient benefit exceeds 24 months, the investigator and sponsor should discuss whether the subject will continue treatment) or disease progression, lost to follow-up or death, intolerable toxicity, withdrawal of informed consent, or other reasons for discontinuation of study treatment, whichever occurs first. After discontinuation of study treatment, subjects will enter Safety Follow-up and Survival Follow-up for 90 ± 7 days (every 3 months for ≤ 90 days). After the enrollment of 30 subjects in each group is completed, the sponsor can decide whether to further expand the enrollment or re-enroll after dose adjustment based on PK, preliminary efficacy and safety data.

	Phase Ib Phase 1b is a study to evaluate the safety, tolerability, and efficacy of IBI110 in combination with sintilimab. Phase Ib is divided into Part 1 combination dose escalation and Part 2 combination dose expansion. **Phase Ib Part 1 Combination Dose Escalation** In the combination dose escalation phase, 6 to 123 subjects with locally advanced, recurrent, or metastatic solid tumors who failed standard therapy were enrolled. Patients who have received prior treatment with checkpoint inhibitors such as anti-PD-1 or PD-L1 monoclonal antibodies cannot be enrolled in the combination dose escalation phase. During the Phase 1a escalation phase of single-agent IBI110 (e.g., after DLT observation is completed in the 0.3 mg/kg dose group) or after escalation, the sponsor and the investigator will determine the time to start dose escalation of the combination based on systematic evaluation of preliminary data and weighing the risks and benefits of the subjects. The starting dose for combination dose escalation was IBI110 0.3 mg/kg in combination with sintilimab 200 mg, and the combination dose escalation was performed according to the classical "3 +3" design. The DLT observation period is within 28 days (4 weeks) after the first dose. Dose Cohort 1: IBI110 0.3 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W. Dose Cohort 2: IBI110 0.7 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W. Dose Cohort 3: IBI110 1.5 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W. Dose Cohort 4: IBI110 3.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W. Dose Cohort 5: IBI110 5.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W. Dose Cohort 6: IBI110 8.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W. Dose Cohort 7: IBI110 10.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W. Dose Group 8: IBI110 20.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W. If no DLT occurs in the first 3 subjects in a dose group during the DLT observation period, the enrollment of the next dose group can be started;

	If 1 of the first 3 subjects in a dose group experiences a DLT during the DLT observation period, another 3 subjects will be added to the dose group; If ≤ 1 of 6 subjects in a dose group experience a DLT during the DLT observation period, the dose group will be considered tolerable; If 2 out of the first 3 subjects or ≥ 2 out of 6 subjects in a dose group experience a DLT during the DLT observation period, the dose group will be considered intolerable. The safety of each cohort after 4 weeks will also be included in the observation of safety and tolerability. All treatments until disease progression, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, for a maximum of 24 months, whichever occurs first. In order to fully explore the safety and efficacy of potentially effective combination doses, if subjects who experience partial response (PR) or complete response (CR) to monotherapy during single-agent dose escalation in Phase Ia, the combination dose group corresponding to the lowest dose group with PR or CR and subsequent combination escalation dose groups will be supplemented with 6 subjects in each dose group (if there are less than 6 subjects in this dose group during the escalation) after the safety of this dose group is confirmed. The additional subjects will be preferentially included in the subjects with tumor types who experience PR/CR during single-agent dose escalation or/and combination dose escalation. Every effort should be made to collect prior tumor tissue specimens from these supplemental subjects (especially if supplemental subjects experience CR/PR or shrinking SD) for further marker exploration. For the doses near the RP2D or target dose, multiple dose groups can be selected from the escalation dose groups to further expand by 10 ~ 15 subjects (per dose group) in order to provide detailed PK/PD/safety data. For the expanded dose group, subjects with consistent baseline conditions should be selected as far as possible (e.g., patients with tumor disease or similar number of treatment lines). At present, multiple dose groups will be further selected from dose group 4 (IBI110 3.0 mg/kg IV Q3W plus sintilimab) to the MTD dose group of combination dose escalation to continue to enroll 10-15 non-small cell lung cancer subjects without driver gene mutation who have not received any immune-related treatment and failed in first-line systemic chemotherapy. Subjects with the first occurrence of disease progression may continue to receive treatment if clinically stable and eligible subjects (see Section 5.1. 2 for details) at the discretion of the investigator until the total duration of treatment reaches 24 months or until disease progression, loss to follow-up or death,

	intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment occurs, whichever occurs first. During or after the enrollment of subjects, the sponsor will systematically evaluate the PK/PD, preliminary efficacy and safety data, and determine the subsequent trial protocol after discussion with the investigator on the basis of weighing the risks and benefits of subjects, such as whether to advance or delay the enrollment, further expand the enrollment and adjust the RP2D of IBI110 in combination with sintilimab for the Phase Ib extension study. **Phase Ib Part 2 Combination Dose Expansion** "3 +3" dose escalation will be performed in the first part of the study. The appropriate dose of IBI110 combined with sintilimab will be selected after data analysis, and the dosing frequency of IBI110 may be adjusted to QW according to the PK data and preliminary efficacy data observed in the combined escalation phase. Dose expansion study will be conducted. Phase Ib to investigate the antitumor activity of IBI110 in combination with sintilimab ± other treatments in different cancer types. IBI110 RP2D IV Q3W in combination with sintilimab 200 mg IV Q3W ± other treatments will be administered in 14 cohorts. The proposed RP2D is currently IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W ± other treatments. Once the established enrollment plan for each cohort is completed, the sponsor may decide whether to further expand enrollment or adjust the RP2D of IBI110 based on PK, preliminary efficacy, and safety data. Every effort should be made to collect prior tumor tissue specimens from subjects in these cohorts for further marker exploration. **Cohort B: Advanced hepatocellular carcinoma (HCC) without prior systemic therapy. A total of 20 to 30 subjects were planned to be treated with IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W and lenvatinib (8 mg daily for subjects weighing < 60 kg or 12 mg daily for subjects weighing ⩾ 60 kg).** **Cohort C: Recurrent or metastatic cervical cancer that has failed systemic therapy. It is planned to enroll 20 to 30 subjects to be treated with IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W.** **Cohort D: Advanced non-small cell lung cancer without driver mutations that have not received prior systemic therapy. Cohort D1 and Cohort D2 were divided according to the exploratory dose of IBI110 and study design.** Cohort D1: in Part I, it is planned to enroll 30 subjects to receive IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W and platinum-based doublet chemotherapy (adenocarcinoma: pemetrexed plus carboplatin Q3W; squamous cell carcinoma: paclitaxel plus carboplatin Q3W). In the second stage,

	subjects with squamous cell carcinoma will continue to be supplemented to 40 ~ 50 cases according to the previous efficacy. Cohort D2: Further dose optimization of IBI110 600mg in lung squamous cell carcinoma based on efficacy in squamous cell carcinoma patients in Cohort D1. "This cohort is a randomized, controlled, open-label study that will enroll approximately 100 subjects with squamous cell carcinoma and will be randomized in a 1: 1 ratio to the treatment arm (IBI110 600mg Q3W plus sintilimab 200mg IV Q3W plus paclitaxel and carboplatin Q3W) and the control arm (sintilimab 200mg IV Q3W plus paclitaxel and carboplatin Q3W)." During the course of the study, the sponsor and investigators will dynamically evaluate the efficacy and safety in the D2 treatment arm of Cohort. **Cohort E: Advanced small cell lung cancer (SCLC) who have received and failed at least one line of standard therapy. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.** **Cohort F: Advanced urothelial cancer (UC) who have received and failed at least one prior systemic therapy. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.** **Cohort G: Advanced renal clear cell carcinoma (RCC) who have received and failed at least one prior systemic therapy. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.** **Cohort H: Advanced hepatocellular carcinoma (HCC) after failure of immunotherapy. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.** **Cohort I: Advanced nasopharyngeal carcinoma (NPC) with immunotherapy failure. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.** **Cohort J: HER2-negative advanced gastric (GC) or gastroesophageal junction (GEJ) cancer not previously treated systemically. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W + oxaliplatin and capecitabine (XELOX). A total of 20-30 patients are planned to be enrolled.** **Cohort K: EBV infection-associated advanced gastric (GC) or gastroesophageal junction (GEJ) cancer that has failed standard therapy. IBI110 200 mg IV Q3W was administered in combination with sintilimab 200 mg IV Q3W, and a total of 20 subjects were planned to be enrolled.**

	Cohort L: Advanced Triple Negative Breast Cancer (TNBC) after failure of standard therapy. It is planned to enroll 20 to 30 subjects to be treated with IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W. **Cohort M: Advanced ovarian cancer after failure of platinum-containing chemotherapy regimen. It is planned to enroll 20 to 30 subjects to be treated with IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W.** **Cohort N: Locally advanced/metastatic melanoma not amenable to local therapy. In the first stage, 30 subjects are planned to be enrolled and divided into 2 dose groups. Dose group 1: IBI110 200 mg IV Q3W combined with sintilimab 200 mg IV Q3W, approximately 15 subjects will be enrolled; Dose Cohort 2: IBI110 10mg/kg IV Q3W in combination with sintilimab 200mg IV Q3W, approximately 15 subjects will be enrolled. If the efficacy in any dose group meets the expectation (ORR ⩾ 30% for skin type or ORR ⩾ 15% for acral/mucosal type), the corresponding population will continue to be expanded by 10 ~ 20 cases in this dose group.** **Cohort O: Advanced nasopharyngeal carcinoma (NPC) after failure of systemic therapy. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.** The above cohorts of IBI110 and sintilimab may be treated for up to 2 years or until disease progression, intolerable toxicity, withdrawal of consent, or other reasons for discontinuation of study treatment, whichever occurs first, and other drugs may be used at the discretion of the investigator until disease progression, intolerable toxicity, withdrawal of consent, or other reasons for discontinuation of study treatment, whichever occurs first. During or after enrollment of each cohort, the sponsor will adjust the characteristics of the subsequent enrollment population (e.g., LAG3 expression) based on the available efficacy data.
Inclusion Criteria	1. Phase 1a single-agent dose escalation: subjects with locally advanced, recurrent, or metastatic solid tumors who have failed standard therapy; Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not; 2. Phase Ib combination dose escalation: subjects with locally advanced, recurrent, or metastatic solid tumors who have failed standard therapy; No prior treatment with T-cell immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody; 3. Phase Ib expansion of IBI110 in combination with sintilimab in multiple dose cohorts:

	1） Non-small cell lung cancer who failed at least one line of systemic chemotherapy; 2） For subjects with non-squamous NSCLC, confirmation of EGFR, ALK, and ROS1 wild-type by tissue-based testing must be available; 3） No prior treatment with T-cell immune checkpoint inhibitors such as anti-PD-1/PD-L1 mAb. 4. Inclusion criteria for Phase 1a single-agent and Phase 1b combination dose expansion (Cohorts A to O): **Cohort A1 (IBI110 alone):** 1） Histologically confirmed (blood virological support) advanced solid tumors related to viral infection that have failed standard treatment: including: HBV or HCV infection-related hepatocellular carcinoma, Epstein-Barr virus (EBV) infection-related nasopharyngeal carcinoma and gastric cancer, human papillomavirus (HPV) infection-related advanced solid tumors such as cervical cancer and head and neck squamous cell carcinoma, etc.; 2） The above tumors that cannot be treated with radical surgical resection or radical radiotherapy and fail to receive standard treatment; 3） Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not. **Cohort A2 (IBI110 alone):** 1） Histologically/cytologically confirmed diagnosis of other advanced solid tumors: epithelial ovarian cancer (including fallopian tube and peritoneal cancer), endometrial cancer, malignant melanoma, and triple negative breast cancer; 2） The above tumors that cannot be treated with radical surgical resection or radical radiotherapy and fail to receive standard treatment; 3） Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not. **Cohort B: Advanced hepatocellular carcinoma without prior systemic therapy** 1） Histologically/cytologically confirmed hepatocellular carcinoma, or meeting the clinical diagnostic criteria of hepatocellular carcinoma specified by American Association for the Study of Liver Diseases (AASLD) or Guidelines for the Diagnosis and Treatment of Primary Liver Cancer; (Excluding histological types including fibrolamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, cholangiocarcinoma and other components); 2） Stage IIb and III patients who are not suitable for radical surgery or local treatment, or stage Ib and IIa patients who are inoperable due to poor liver

	reserve function (2019 edition) promulgated by National Health and Family Planning Commission for the diagnosis and treatment of primary liver cancer; 3） Non-diffuse liver cancer; 4） Child-Pugh score ≤ 7 points; 5） Has not received prior systemic anti-tumor therapy for recurrent or metastatic hepatocellular carcinoma; 6） No prior local treatment for liver cancer within 4 weeks prior to the first dose. **Cohort C: Recurrent or metastatic cervical cancer that has failed systemic therapy** 1） Histologically/cytologically confirmed incurable, recurrent or metastatic cervical cancer; 2） Patients in the recurrent or metastatic stage must have received platinum-based doublet chemotherapy, and have disease progression confirmed by imaging during or after treatment; 3） Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not. **Cohort D: Advanced NSCLC without driver mutations who have not received prior systemic therapy** 1) Histologically/cytologically confirmed inoperable recurrent and metastatic non-small cell lung cancer; 2) Stage IV according to the American Joint Committee on Cancer (AJCC) 8th edition staging manual; 3) For subjects with non-squamous NSCLC, confirmation of EGFR, ALK, and ROS1 wild-type by tissue-based testing must be available; 4) No prior systemic therapy for recurrent/metastatic disease; Time from end of prior (neo) adjuvant chemotherapy/adjuvant radiotherapy to disease recurrence > 6 months. **Cohort E: Advanced small cell lung cancer that has received and failed at least one line of standard therapy** 1) Histologically/cytologically confirmed small cell lung cancer; 2) Extensive stage according to American Veterans Lung Cancer Association VALG staging. 3) Patients who have received at least one platinum-containing regimen for recurrent or metastatic disease and have disease progression during or after the end of treatment, or are intolerant to the treatment; 4) No prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 mAb.

	Cohort F: Advanced urothelial cancer (UC) who have received and failed at least one prior systemic therapy 1） Histologically/cytologically confirmed urothelial carcinoma (including urothelial carcinoma or transitional cell carcinoma originating from renal pelvis, ureter or urethra) with lesions of different histological types (e.g. Minimal variation) is acceptable; 2） Patients with disease progression or chemotherapy intolerance after receiving at least one line of systemic chemotherapy for recurrent or metastatic disease; Progression during prior platinum-containing neoadjuvant or adjuvant therapy or relapse within 12 months after the end of treatment is considered as failure of first-line therapy and can be included in the study; 3） Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not. **Cohort G: Recurrent or metastatic clear cell renal cell carcinoma that has failed systemic therapy** 1) Histologically/cytologically confirmed recurrent and metastatic clear cell renal carcinoma; 2) Received at least one line of systemic therapy, including at least one anti-VEGFR/VGEF targeted drug, and experienced disease progression or intolerance; 3) Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not. **Cohort H: Advanced Hepatocellular Carcinoma after Immunotherapy Failure** 1） Advanced hepatocellular carcinoma confirmed by histology/cytology, or in accordance with the American Association for the Study of Liver Diseases (AASLD) or the diagnosis and treatment criteria for primary liver cancer (excluding the histological types including fibrolamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, cholangiocarcinoma and other components); 2） Stage IIb and stage III (BCLC stage C or stage B not suitable for local treatment) of primary liver cancer (2019 edition) promulgated by National Health and Family Planning Commission; 3） Non-diffuse liver cancer; 4） Child-Pugh score ≤ 7 points; 5） Patients who have received prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody and have radiologically confirmed disease progression; 6） No prior local treatment for liver cancer within 4 weeks prior to the first dose.

	Cohort I: Recurrent or Metastatic Nasopharyngeal Carcinoma after Failure of Immunotherapy 1) Histologically/cytologically confirmed non-keratinizing differentiated or undifferentiated nasopharyngeal carcinoma; 2) Have received at least one platinum-containing regimen and anti-PD-1/PD-L1 mAb for recurrent or metastatic disease and have radiographically confirmed disease progression or are intolerant to chemotherapy. **Cohort J: HER2-negative advanced gastric (GC) or gastroesophageal junction (GEJ) cancer not previously treated systemically** 1) Pathologically/cytologically confirmed inoperable locally advanced, recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma (including signet ring cell carcinoma, mucinous adenocarcinoma, hepatoid adenocarcinoma); 2) No prior systemic drug therapy for recurrent or metastatic disease; 3) Time from the end of prior (neo) adjuvant chemotherapy/adjuvant radiotherapy to disease recurrence > 6 months; 4) Known tumor tissue testing HER2 negative. **Cohort K: EBV infection-associated gastric and gastroesophageal junction cancer that has failed standard therapy** 1) Histologically/cytologically confirmed EBV infection-related unresectable locally advanced, recurrent or metastatic gastric and gastroesophageal junction cancer; 2) Previously received ≥ 1 line of systemic drug treatment failure or chemotherapy intolerance; 3) Prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody is acceptable. **Cohort L: Advanced Triple Negative Breast Cancer after Failure of Standard Therapy** 1） Histologically/cytologically confirmed unresectable locally advanced or metastatic triple negative breast cancer; 2） Previously treated with ≥ 1 line of systemic drug treatment failure or intolerance; 3） No prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 mAb. **Cohort M: Advanced Ovarian Cancer after Failure of Platinum-containing Chemotherapy Regimen** 1） Histologically/cytologically confirmed epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer;

	2） The BRCA1/2 gene test results of hematological test should be provided; If the hematological test is negative, the BRCA1/2 gene test results of tumor tissue shall be additionally provided; 3） Received a platinum-based regimen with disease progression during platinum-based therapy (platinum-refractory) or < 6 months (184 calendar days) from platinum-based therapy (at least 4 cycles) to disease relapse (platinum-resistant). Definition of relapse or progression (meeting any of the following criteria): a) unequivocally documented radiographic progression; b) Persistent elevation of CA-125 (CA-125 ⩾ 2 times the upper limit of normal, which should be confirmed 1 week later) with clinical symptoms or physical examination suggestive of disease progression; 4） No prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 mAb. **Cohort N: Locally advanced/metastatic melanoma not amenable to local therapy** 1） Patients with histologically and/or cytologically confirmed locally advanced (unresectable Stage III) or metastatic (Stage IV) melanoma (acral, mucosal, or cutaneous) that is not suitable for local therapy according to the 8th edition of the American Joint Committee on Cancer (AJCC); 2） Has received chemotherapy or targeted therapy (such as BRAF inhibitor, MEK inhibitor, KIT inhibitor), but must not have received systemic T cell immune checkpoint inhibitor treatment; > 6 months from end of treatment to disease recurrence for recurrent/metastatic disease if previously treated with (neo) adjuvant T-cell checkpoint inhibitors. **Cohort O: Advanced nasopharyngeal carcinoma (NPC) after failure of systemic therapy** 1) Histologically/cytologically confirmed non-keratinizing differentiated or undifferentiated nasopharyngeal carcinoma; 2) Patients who have received at least one platinum-containing regimen for recurrent or metastatic disease and have radiographically confirmed disease progression or chemotherapy intolerance after treatment; 3) No prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 mAb. **Enrollment criteria to be met for both Phase Ia and Phase Ib:** 5. Signed written informed consent and able to comply with protocol-specified visits and procedures. 6. Age ⩾ 18 years and ⩽ 75 years. 7. Expected survival time ⩾ 12 weeks.

	8. At least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST V1.1) (no prior radiotherapy). At baseline, accurately measured by computed tomography (CT) or magnetic resonance imaging (MRI) (intravenous contrast is preferred) as ≥ 10 mm in the long axis (except lymph nodes, which must have a short axis of ≥ 15 mm), and target lesions ≥ 2 x image slice thickness and suitable for accurate repeated measurements. Lesions located in a previously irradiated area can be considered measurable if they clearly demonstrate progression according to RECIST V1.1. 9. 0 or 1 according to Eastern Cooperative Oncology Group Performance Status (ECOG PS). 10. Female subjects of childbearing potential or male subjects whose partners are women of childbearing potential are required to use effective contraceptive measures throughout the treatment period and for 6 months after the treatment period. 11. Adequate organ and marrow function as defined by: 1) Hematology: Absolute neutrophil count (ANC) ≥ 1.5 × 109/L, platelet (PLT) ≥ 75 × 109/L, hemoglobin (HGB) ≥ 90 g/L (9.0 g/dL). (No cells and growth factors are allowed within 2 weeks before the first dose of study treatment, and no allogeneic blood transfusion is allowed within 1 week before the first dose of study treatment). 2) Liver function: blood total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN); If TBIL > 1.5 × ULN, conjugated bilirubin ≤ ULN; TBIL ≤ 3 × ULN for subjects with liver metastases or a history/suspicion of Gilbert's syndrome (persistent or recurrent hyperbilirubinemia, primarily high unconjugated bilirubin without evidence of hemolysis or liver lesions); Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 × ULN for subjects without liver metastases; ALT and/or AST ≤ 5 × ULN for subjects with liver metastases. Subjects with primary hepatocellular carcinoma were required to have TBIL ≤ 2 × ULN and ALT and/or AST ≤ 3 × ULN. 3) Renal function: serum creatinine (Cr) ≤ 1.5 × ULN, or creatinine clearance (CCr) ≥ 50 mL/min; Urine dipstick test results show urine protein < 2 +; For subjects with urine protein ≥ 2 + on urine dipstick at baseline, a 24-hour urine collection with < 1g of protein in the 24-hour urine should be performed. 4) Coagulation: APTT ≤ 1.5 × ULN, INR ≤ 1.5.

Exclusion Criteria	**Subjects with any of the following criteria were not to be included in the study:** 1. Previous exposure to any anti-LAG-3 antibody class. 2. Concurrent participation in another interventional clinical study, except in an observational (non-interventional) clinical study or in the survival follow-up phase of an interventional study. 3. Received any investigational drug within 4 weeks prior to the first dose of study treatment. 4. Received the last anti-tumor therapy within 4 weeks prior to the first dose of study drug: systemic chemotherapy (washout period of 2 weeks for oral fluoropyrimidines), endocrine therapy, targeted therapy (washout period of 2 weeks or 5 half-lives for small molecule targeted therapy, whichever is longer), immunotherapy, tumor embolization. Received the last dose of Chinese herbal medicine for an antineoplastic indication within 1 week prior to the first dose of study drug. 5. Use of immunosuppressive medications within 4 weeks prior to the first dose of study drug, excluding 1) Intranasal inhaled topical steroid therapy or local steroid injections (e.g., intra-articular injections); 2) Systemic corticosteroid therapy not exceeding physiologic doses of 10 mg/day prednisone or its equivalent; 3) Corticosteroids as prophylaxis for allergic reactions (e.g. CT premedication). 6. Need for long-term systemic hormonal or any other immunosuppressive drug therapy excluding inhaled corticosteroid therapy. 7. Receipt of a live attenuated vaccine within 4 weeks prior to the first dose of study treatment or planned during the study. 8. Major surgical procedure (craniotomy, thoracotomy, or laparotomy) or non-healing wound, ulcer, or fracture within 4 weeks prior to the first dose of study treatment. 9. Presence of toxicity (excluding alopecia or asthenia) caused by previous anti-tumor therapy that has not recovered to NCI CTCAE v5.0 grade 0 or 1 within 4 weeks prior to the first dose of study treatment; Includes immune-related adverse events (irAE) that have not recovered from immunotherapy, including irAE that are still under hormonal control and endocrine-related irAE that have not recovered to Grade 0-1 even with replacement therapy. 10. Prior immunotherapy such as anti-PD-1/anti-PD-L1 antibody or anti-CTLA-4 antibody was permanently discontinued due to ≥ Grade 3 irAE. 11. Known central nervous system (CNS) metastases and/or spinal cord

	compression and/or carcinomatous meningitis, history of leptomeningeal carcinoma. Patients with asymptomatic brain metastases (i.e., no neurological symptoms, no need for glucocorticoid treatment, and no lesion > 1.5 cm) or treated brain metastases that are symptomatic and stable are eligible to participate in the study as long as they meet all of the following criteria: measurable lesions outside the central nervous system; No metastasis in midbrain, pons, cerebellum, meninges, medulla oblongata or spinal cord; Patients may participate if they are clinically stable for at least 4 weeks, have no evidence of new or enlarging brain metastases, and have discontinued corticosteroid and anticonvulsant medication for at least 14 days prior to study treatment. 12. Active autoimmune or inflammatory disease (including inflammatory bowel disease [eg, ulcerative colitis or Crohn's disease], diverticulitis [except diverticulosis], celiac disease, systemic lupus erythematosus, Sarcoidosis syndrome or Wegener syndrome [granulomatosis with polyangiitis], Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.) or history within the previous 2 years (vitiligo, psoriasis, alopecia, or Grave's disease not requiring systemic treatment within the last 2 years, hypothyroidism requiring thyroid hormone replacement only, and type 1 diabetes mellitus requiring insulin replacement only may be enrolled). Known history of primary immunodeficiency. The presence of autoimmune disease was confirmed at the investigator's discretion only in patients with positive autoimmune antibodies. 13. Acute or chronic active hepatitis B [defined as hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody (HBcAb) positive and hepatitis B virus (HBV) DNA copies $\geqslant$ 1 $\times$ 104 copies/ml or $\geqslant$ 2000 IU/ml]; Or acute or chronic active hepatitis C (HCV) antibody-positive subjects with positive HCV antibody but negative RNA test are allowed (subjects with HCC with HCV RNA $\leqslant$ 103 copies/ml are allowed). 14. Past and current pulmonary diseases such as interstitial pneumonia, pneumoconiosis, drug-related pneumonia, pulmonary fibrosis, severely impaired pulmonary function, and current active pulmonary infection. 15. Patients with active pulmonary tuberculosis who are receiving anti-tuberculosis treatment or who have received anti-tuberculosis treatment within 1 year before the first dose of study drug. 16. Known history of allogeneic organ transplantation and allogeneic hematopoietic stem cell transplantation. 17. History of gastrointestinal perforation and/or fistula within 6 months prior to study enrollment and not cured by surgical treatment.

	18. Patients with uncontrolled third space effusion requiring repeated drainage, such as pleural effusion, ascites, pericardial effusion, etc. (patients who do not require drainage of effusion or have no significant increase in effusion after stopping drainage for 3 days can be enrolled). 19. The subject has a known history of severe allergic reactions to other monoclonal antibodies or hypersensitivity to components of the study drug formulation. 20. Uncontrolled intercurrent illness including, but not limited to: 1) HIV-infected persons (HIV antibody positive); 2) Active or clinically poorly controlled severe infection; 3) Symptomatic congestive heart failure (New York Heart Association Class II-IV) or symptomatic or poorly controlled arrhythmias such as ventricular tachycardia, atrial fibrillation, ventricular fibrillation, torsades de pointes, etc.; 4) History of congenital long QT syndrome or corrected QTc > 500ms at screening (calculated using Fridericia method); 5) History of myocarditis; 6) Uncontrolled arterial hypertension (systolic blood pressure ⩾ 160 mmHg or diastolic blood pressure ⩾ 100 mmHg) despite standard treatment; Baseline systolic blood pressure ⩾ 150 mmHg or diastolic blood pressure ⩾ 90 mmHg in combination with lenvatinib cohort; 7) Any arterial thromboembolic event, including myocardial infarction, unstable angina pectoris, cerebrovascular accident or transient ischemic attack, occurred within 6 months prior to enrollment; 8) Esophageal or gastric varices requiring immediate intervention (e.g., banding or sclerotherapy) or evidence of portal hypertension considered at high risk of bleeding according to the investigator's opinion or consulting gastroenterologist or hepatologist; Subjects with hepatocellular carcinoma who have experienced esophageal or gastric variceal bleeding due to portal hypertension within the past 6 months, or who have evidence of portal hypertension (including splenomegaly detected by imaging examination) must undergo endoscopy within 3 months to evaluate severe varices; 9) Any life-threatening bleeding event occurred within 3 months before enrollment and required medical intervention, such as blood transfusion therapy, surgery or local therapy, continuous drug therapy, etc.; 10) History of deep vein thrombosis, pulmonary embolism, or any other serious thromboembolism within 3 months prior to enrollment

	(implantable venous access port or catheter-derived thrombosis, or superficial vein thrombosis is not considered "serious" thromboembolism); Portal vein tumor thrombus involving the main trunk and bilateral primary branches, or the main trunk and superior mesenteric vein, or inferior vena cava tumor thrombus at the same time; 11) Uncontrolled metabolic disorder or other non-malignant organ or systemic disease or secondary reaction of cancer, which may lead to high medical risk and/or uncertainty of survival evaluation, and is not suitable for enrollment as judged by the investigator, or there are other conditions that are not suitable for enrollment as judged by the investigator; 12) Hepatic encephalopathy, hepatorenal syndrome or Child-Pugh B (> 7 points) or more severe cirrhosis; 13) History of intestinal obstruction (excluding intestinal obstruction that has been surgically cured) or the following diseases: extensive intestinal resection (partial colon resection or extensive small intestinal resection complicated by chronic diarrhea), Crohn's disease, ulcerative colitis, radiation colitis and other causes of chronic colitis, long-term chronic diarrhea and other intestinal diseases; 14) Significant malnutrition, such as the need for intravenous supplements; Except for correction of malnutrition more than 4 weeks prior to the first dose of study treatment; 15) Tumor invades surrounding important organs (such as mediastinal vessels, superior vena cava, trachea, esophagus, etc.) or there is a risk of esophagotracheal fistula or esophagopleural fistula; 16) After intraluminal stenting of the esophagus or trachea. 21. Other acute or chronic illness, psychiatric illness, or abnormal laboratory values that may increase the risk associated with study participation or study drug administration, or interfere with the interpretation of study results, and in the judgment of the investigator, the subject is listed as ineligible for participation in the study. 22. History of other primary malignancies, except: 1) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of recurrence; 2) Adequately treated carcinoma in situ with no evidence of disease recurrence; 3) Patients with other (multiple) tumors should meet at least the following requirements before enrollment at screening: a. No treatment is required for

	the combined tumors at present; b. For combined tumors, no known active disease for ⩾ 2 years prior to study enrollment. 23. Female subjects who are pregnant or lactating.
Study Drug Strength and Mode of Administration	• IBI110: 80 mg (4 ml) per vial for intravenous infusion • Sintilimab: 100 mg (10 ml)/vial, intravenous infusion • Other Investigational Drugs
Dose Group Design	**Phase Ia:** **Part 1 Single Dose Escalation** • Dose group 1: 0.01 mg/kg IBI110; • Dose Group 2: 0.1 mg/kg IBI110; • Dose Group 3: 0.3 mg/kg IBI110; • Dose group 4: 1 mg/kg IBI110; • Dose Group 5: 3 mg/kg IBI110; • Dose group 6:10 mg/kg IBI110; • Dose group 7:20 mg/kg IBI110. **Part 2 Single Agent Dose Expansion** • Cohort A1: IBI110 200mg IV Q3W; • Cohort A2: IBI110 200mg IV Q3W. **Phase Ib:** **Part 1 Combination Dose Escalation** • Dose Group 1: IBI110 0.3 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W; • Dose Cohort 2: IBI110 0.7 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W; • Dose Cohort 3: IBI110 1.5 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W; • Dose Cohort 4: IBI110 3.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W; • Dose Cohort 5: IBI110 5.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W; • Dose Cohort 6: IBI110 8.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W; • Dose Cohort 7: IBI110 10.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W;

	• Dose Group 8: IBI110 20.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W. **Part 2 Combination Dose Expansion** • Cohorts B, C, E ~ M, O: IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W ± other treatments. • Cohort D: IBI110 200 mg IV Q3W in combination with sintilimab 200mg IV Q3W + other treatments in Cohort D1; Cohort D2 treatment arm will receive IBI110 600 mg IV Q3W in combination with sintilimab 200mg IV Q3W plus other treatment, and the control arm will receive sintilimab 200mg IV Q3W plus other treatment only. • Cohort N: IBI110 200mg IV Q3W plus sintilimab 200mg IV Q3W or IBI110 10mg/kg IV Q3W plus sintilimab 200mg IV Q3W.
Evaluation Criteria	**Safety evaluation:** • Incidence, relatedness to trial drug and severity of all adverse events (including irAE), Treatment Emergent Adverse Events (TEAE) and Serious Adverse Events (SAE). • Changes in vital signs, physical examination findings and laboratory results before, during and after study treatment. • Immunogenicity evaluation: All subjects will be tested for anti-drug antibodies (ADA), and ADA-positive serum specimens will continue to be tested for neutralizing antibodies (NAb). **Efficacy evaluation:** • Response was evaluated according to RECIST V1.1. To evaluate ORR, Time to response (TTR), Duration of Response (DOR), Progression Free Survival (PFS), 6-month and 1-year PFS rate, disease control rate (DCR), Overall Survival (OS) and 6-month and 1-year survival rate after treatment. • To explore iORR, iDCR, iPFS, iDOR, and iTTR as assessed by iRECIST. **Pharmacokinetic (PK)/Pharmacodynamic Evaluations:** • To describe the single-and multiple-dose PK characteristics of the drug in humans, and determine the main PK parameters, including but not limited to: drug exposure (AUC), Cmax, clearance (CL), volume of distribution (V) and half-life (t1/2). • Blood samples were collected for analysis of pharmacodynamic parameters.
Statistical Methods	**Sample Size:** • Phase 1a is planned to enroll 4-38 subjects with advanced tumors in the single-agent dose escalation phase and 60 subjects in the single-agent dose expansion phase.

	• In Phase Ib, 6 to 123 subjects were planned to be enrolled in the combination dose escalation phase and 420 to 560 subjects in the combination dose expansion phase. **Statistical Analysis Methods:** • Descriptive statistics are mainly used, and inter-group comparisons are not performed in principle. Continuous variables will be described using number, mean, standard deviation, median, minimum and maximum. In addition, geometric mean and coefficient of variation will be provided for PK parameters. Categorical variables will be described using frequency and percentage. • The safety indicators (AE, laboratory tests, vital signs, etc.), immunogenicity and anti-tumor activity of IBI110 in subjects with advanced tumors will be summarized by stage and cancer type. • ORR, DCR and its 95% confidence interval (CI) will be calculated by dose, median progression-free survival, median overall survival, 6-month and 1-year PFS rate and survival rate will be estimated using Kaplan-Meier method, DOR, TTR and maintenance response rate at the time of data analysis cutoff will be calculated for subjects with objective response. **Exploratory Analysis:** • The iORR, iDCR and their 95% confidence intervals (CIs) were calculated by dose, Kaplan-Meier estimates of median iPFS and iPFS rates at 6 months and 1 year were used, and iDOR, iTTR, and maintenance response rate at the time of data analysis were calculated for subjects who achieved an objective response based on iRECIST assessment. • Descriptive statistics will be provided for the proportion of subjects with different expression levels of LAG-3 and PD-L1 in tumor tissues, and ORR and DOR in corresponding subgroups with different expression levels.

Study Visit schedule

Table 1-1. Schedule of Study Visits (Phase 1a Single-agent Dose Escalation-Applicable to the DLT Observation Period of IBI110 Monotherapy and Subsequent IBI110 Monotherapy)

Phase	Screening period	Treatment Period							End of Treatment Visit 19	Safety Follow-up 19	Survival Follow-up 20
		Cycle 1 (DLT observation period 28 days)						Cycle 2 and beyond (21 days/cycle)			
Days	**-28 ~-1**	**1**	**2**	**3**	**8**	**15**	**22**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
General Study Procedures											
Written informed consent1	X										
Inclusion/Exclusion Criteria	X										
Demographics/Past Medical History/Prior Therapy2	X										
Vital signs3	X	X			X		X	X	X	X	
Weight/Height4	X	X						X			
Physical examination	X				X		X	X	X	X	
ECOG PS score 5	X							X	X	X	
12-lead ECG6	X	X			X		X	X	X	X	
Hematology/blood biochemistry/urinalysis 7	X				X		X	X	X	X	
Blood myocardial enzymes and troponin 8	X							X	X	X	

Phase	**Screening period**	**Treatment Period**							**End of Treatment Visit 19**	**Safety Follow-up 19**	**Survival Follow-up 20**
		Cycle 1 (DLT observation period 28 days)						**Cycle 2 and beyond (21 days/cycle)**			
Days	**-28 ~-1**	**1**	**2**	**3**	**8**	**15**	**22**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
Coagulation function 9	X				X			X	X	X	
Pregnancy Test10	X								X	X	
Thyroid function11	X							X	X	X	
Autoantibodies12	X										
Immunogenicity (ADA, NAb) 13		X						X		X	
HIV, HBV and HCV14	X										
PK15		X	X	X	X	X	X	X		X	
Pharmacodynamics 15		X	X	X	X	X	X	X		X	
Assessment of Adverse Events16	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Survival Status		X X ⟷									
Subsequent Antineoplastic Therapy									X	X	X
Efficacy Assessments											
Tumor Imaging Assessment17	X							X	X	X	X
Study Drug Infusion											
IBI11018		X						X			

Phase	Screening period	Treatment Period							End of Treatment Visit 19	Safety Follow-up 19	Survival Follow-up 20
		Cycle 1 (DLT observation period 28 days)						Cycle 2 and beyond (21 days/cycle)			
Days	**-28 ~-1**	**1**	**2**	**3**	**8**	**15**	**22**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
Biomarkers											
Archival or fresh tissue samples21	X										

Remarks:

1. Signature of the Informed Consent Form (ICF) should be performed prior to any protocol-specified procedures. In order to reduce the psychological and physical trauma to the patients caused by repeated blood sampling or examination, the results of laboratory tests, ECG and imaging tests that meet the time window and technical requirements before signing of ICF can be accepted in the screening period of this study.
2. Tumor history includes: disease staging, date of diagnosis and previous treatment, including treatment for initial diagnosis, including chemotherapy, radiotherapy, surgical treatment, molecular targeted drugs (± chemotherapy), immune checkpoint inhibitors (such as anti-CTLA-4 antibody, anti-PD-1 antibody, anti-PD-L1 antibody), etc. The time of the last anti-tumor treatment before the first dose of study drug must be recorded.
3. Vital signs include: temperature, pulse, respiratory rate, and blood pressure. To be performed at screening, treatment, end of treatment, and safety follow-up, and as clinically indicated. During the DLT observation period, more frequent examinations will be performed on Days 8 and 22 (± 1 day), and additional examinations may be performed at the discretion of the investigator. See 6.4. 4.1 for the monitoring requirements for pulse and blood pressure.
4. Height measurements were performed at screening only. Body weight will be measured prior to each scheduled dose during the study. If the subject's body weight fluctuates less than 10% from baseline (day of first dose of study treatment), the baseline body weight can be used to calculate the dose. Otherwise, the actual dose was calculated according to the body weight on the scheduled day of administration.
5. ECOG PS assessment in the second cycle and thereafter should be performed before administration in this cycle to provide the basis for the investigator to determine whether the subject (when DLT observation is completed in 0.01 mg/kg and 0.1 mg/kg dose groups, or disease progression in other dose groups) is suitable for sintilimab treatment (single agent or in combination with IBI110). ECOG PS score was also performed at screening, end-of-treatment visit, and safety follow-up visit.

6. Timing of 12-lead ECG: to be performed at screening, within 30 minutes after the end of IBI110 infusion in each cycle, at the end of treatment and safety follow-up, and as clinically indicated. During the DLT observation period, examinations will be performed (more frequently) on Days 8 and 22 (± 1 day), or additional examinations may be performed at the discretion of the investigator.
7. Hematology includes: red blood cell (RBC), HGB, hematocrit (HCT), white blood cell (WBC), PLT, white blood cell differential [lymphocyte (LYM), ANC, monocyte (MONO), eosinophilic granulocyte (EOS), basophil (BASO)]. Blood biochemistry includes: liver function [TBIL, ALT, AST, Gama-glutamyl transferase (γ-GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), lactate dehydrogenase (LDH)], renal function [blood urea (UREA), Cr], blood electrolytes [sodium, Na, potassium, chloride, Mg, calcium, Ca, phosphate, P], amylase and Fasting Blood Glucose (FBG). Urinalysis includes: pH (-pH), urine white blood cells (UWBC), urine protein (UPRO), urine red blood cells (URBC)/urine occult blood (BLD) and urine glucose (UGLU). 24-hour proteinuria test should be performed for subjects with urine protein ≥ 2 + on urine dipstick test during screening period. Within 7 days prior to the first dose of study drug, within 3 days prior to each cycle of study drug administration from Cycle 2, and at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Inspections will be performed at the study site. During the DLT observation period, examinations will be performed on Days 8 and 22 (± 1 day), and additional examinations may be performed at the discretion of the investigator.
8. Blood myocardial enzyme spectrum and troponin examination shall include at least: Creatine Kinase (CK), creatine phosphokinase isoenzyme (CK-MB) and troponin. To be performed within 7 days prior to the first dose in the screening period, within 3 days prior to each subsequent dose in the second cycle, at the End of Treatment Visit, at the Safety Follow-up Visit, and as clinically indicated. For clinically significant ECG abnormalities or relevant medical history, symptoms and physical signs, other myocardial-related indicators, such as B-type brain natriuretic peptide (BNP), can be examined at the discretion of the investigator.
9. Coagulation test includes: Thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR). To be performed within 7 days prior to the first dose of study treatment and within 3 days prior to each dose of the second cycle thereafter, at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Inspections will be performed at each study site. During the DLT observation period, examinations will be performed at 8 days (± 1 day), and additional examinations may be performed at the discretion of the investigator.
10. Women of childbearing potential will have a urine or serum pregnancy test within 7 days prior to the first dose, or additional tests may be performed at the discretion of the investigator. If the urine pregnancy test cannot be confirmed as negative, a serum pregnancy test will be performed, whichever is the serum pregnancy result. Pregnancy testing will also be performed at the End of Treatment Visit and Safety Follow-up Visit. Inspections will be performed at each study site.
11. Thyroid function tests include: Free Triiodothyronine (FT3), FT4, and TSH. To be performed at screening, within 7 days prior to each cycle of study drug administration from Cycle 2, and at the Safety Follow-up Visit, at the End of Treatment Visit, and as clinically indicated. Other thyroid function tests should be considered if there are abnormalities. Inspections will be performed at the study site.

12. Autoantibody examination includes: antinuclear antibody, anti-double-stranded deoxyribonucleic acid (dsDNA) antibody and anti-thyroglobulin antibody. At screening, the investigator may determine the need to test for autoimmune antibodies based on past medical history and as clinically indicated. After the screening period, the investigator will determine whether to re-examine as clinically indicated. Inspections will be performed at the study site.
13. Immunogenicity testing will be performed within 1 hour prior to the start of IBI110 infusion at Cycles 1, 2, 4, 6, 8, 12, 16, then every 8 cycles thereafter (Cycles 24, 32, 40, etc., and so on), and at the Safety Follow-up Visit. "If a subject experiences an infusion reaction to IBI110, blood samples will be collected as close as possible to the onset of the event, when the event resolves, and approximately 30 days after the end of the event for pre-and post-immunogenicity analysis." Testing will be performed at a central laboratory and, if necessary, may detect drug concentrations in immunogenicity samples. Blood samples will not be collected for subjects who receive only sintilimab monotherapy after completion of DLT observation or due to disease progression. Blood samples will be collected for subjects who receive IBI110 plus sintilimab due to disease progression (cumulative cycle) according to Table 1-1.
14. Including HIV and HCV antibody tests (HCV RNA test should be performed if HCV antibody is positive), as well as hepatitis B five tests [hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb)] and HBV DNA tests. If HBsAg and/or only HBcAb were positive, further HBV DNA testing was performed. Testing will be performed at the study site during the screening period.
15. The timing of PK/PD tests is described in the PK/PD sampling schedule (Table 2). Tests will be performed at a central laboratory. Blood samples will not be collected for subjects who receive only sintilimab monotherapy after completion of DLT observation or due to disease progression. Blood samples will be collected for subjects who receive IBI110 combined with sintilimab due to disease progression (cumulative cycle) according to Table 2.
16. AE and laboratory safety assessments will be assessed according to NCI CTCAE v5.0. Refer to the description in Section 7 of the protocol for the definition, recording, relatedness judgment, severity judgment, reporting time limit and handling of AE and SAE.
17. Tumor assessment includes RECIST v1.1 assessment and iRECIST assessment, and no central imaging assessment will be performed in this study. Tumor imaging includes CT or MRI. The same imaging technique should be performed on the same subject during the study. The baseline assessment will be performed within 28 days prior to enrollment, and the investigator may collect the imaging results of 28 days prior to enrollment in the study for assessment. After completion of DLT observation (± 7 days), imaging assessment will be performed to determine whether to continue IBI110 monotherapy (except 0.01 mg/kg and 0.1 mg/kg dose groups). If disease progression (based on RECIST v1.1), sintilimab monotherapy or combination with IBI110 will be administered per protocol (see the abstract for details). Subsequent radiographic assessments will be performed on IBI110 monotherapy, and if progressive disease (based on RECIST v1.1) will be treated with sintilimab monotherapy or in combination with IBI110 per protocol (see abstract for details). Tumor imaging assessment will be performed every 6 weeks (± 7 days) after the first dose of study drug (if imaging assessment is performed after DLT observation, then imaging assessment will be performed every 6 weeks (± 7 days); if imaging assessment is not performed after DLT observation (0.1 mg/kg, 0.01 mg/kg), then imaging assessment will be performed every 6 weeks (± 7 days) after the first dose of IBI110 monotherapy, and subsequent dose of sintilimab monotherapy or combination therapy will be continued). Subjects with an initial documented response [complete response (CR) or partial response (PR)] will undergo radiographic assessment to confirm response 4 to 6 weeks later and every 6 weeks (± 7 days) thereafter until radiographic disease progression is documented. For subjects with

initial documentation of radiographic progressive disease (PD) (based on RECIST v1.1 criteria) while receiving sintilimab alone or in combination with IBI110, radiographic assessment must be performed at 4-6 weeks to confirm PD. If a subject is confirmed to continue receiving study drug (sintilimab alone or in combination with IBI110), imaging assessments will continue as originally planned until immune-confirmed progressive disease (iCPD) (based on iRECIST criteria). The iCPD adjudication is defined as at least an additional 5mm increase in target lesions or unequivocal progression of non-target lesions or an increase of at least 5mm in previously identified new lesions or other new lesions (based on iRECIST criteria). For subjects who discontinue treatment for reasons other than radiographic disease progression, radiographic assessments should be performed at the end of treatment and every 6 weeks (± 7 days) after discontinuation until any of the following events occur: initiation of new antineoplastic therapy, disease progression, withdrawal of consent, lost to follow-up or death, study termination, etc.

18. The first cycle of each dose group consists of DLT observation period (28 days), only on Day 1. Cycle 2 and every 3 weeks thereafter until disease progression, loss to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a maximum of 24 months. Subjects with first disease progression may continue to receive treatment if clinically stable and eligible subjects (see Section 5.1. 2 for details) at the discretion of the investigator until the total duration of treatment reaches 24 months or until recurrence of disease progression, loss to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment occurs, whichever occurs first.
19. The End of Treatment Visit was performed within 7 days after confirmation of end of treatment. Relevant tests that have been performed within 7 days prior to the end of the study may not be repeated at the discretion of the investigator. The Safety Follow-up Visit will occur 90 ± 7 days after the last dose or prior to the initiation of new antineoplastic therapy, whichever occurs first. Subjects who discontinue treatment due to drug-related adverse events will be followed until the adverse event resolves to Grade 0-1, symptoms stabilize, and the subject withdraws consent, whichever occurs first. See 6.2. 3 for details.
20. Survival follow-up: every 3 months (≤ 90 days) after the last dose, telephone visits are acceptable.
21. Subjects are required to provide archival or fresh tumor tissue samples (5 slides) that meet the testing requirements during the screening period as far as possible, and this sample will be used for biomarker research.

Table 1-2. Schedule of Study Visits (Phase 1a monotherapy dose escalation-follow Table 1-1 for IBI110 monotherapy followed by sintilimab)

Phase	Treatment Period (every 21-day cycle)						End of Treatment Visit 16	Safety Follow-up 16	Survival follow-up 17
	(IBI110 treatment) Cycle 1					Cycle 2 and beyond (21 days/cycle)			
Days	**1**	**2**	**3**	**8**	**15**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
General Study Procedures									
Vital signs1	X			X		X	X	X	
Weight/Height2	X					X			
Physical examination				X		X	X	X	
ECOG PS score3	X					X	X	X	
12-lead ECG4	X			X		X	X	X	
Hematology/blood biochemistry/urinalysis 5				X		X	X	X	
Blood myocardial enzymes and troponin 6						X	X	X	
Coagulation function 7				X		X	X	X	
Pregnancy Test8							X	X	
Thyroid function9						X	X	X	
Autoantibody10									
Immunogenicity (ADA, NAb) 11	X11					X		X	

Phase	**Treatment Period (every 21-day cycle)**						**End of Treatment Visit 16**	**Safety Follow-up 16**	**Survival follow-up 17**
	(IBI110 treatment) Cycle 1					**Cycle 2 and beyond (21 days/cycle)**			
Days	**1**	**2**	**3**	**8**	**15**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
PK12	X12	X	X	X	X	X		X	
Pharmacodynamics 12	X12	X	X	X	X	X		X	
Assessment of Adverse Events13	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	
Survival Status	X X	←							→
Subsequent Antineoplastic Therapy							X	X	X
Efficacy Assessments									
Tumor Imaging Assessment14						X	X	X	X
Study Drug Infusion									
IBI11015	X					X			
Sintilimab 15	X					X			

Remarks:

1. Vital signs include: temperature, pulse, respiratory rate, and blood pressure. To be performed during the treatment period, at the end of treatment, and at the safety follow-up visit, and as clinically indicated. Higher frequency examinations will be performed on Days 1 and 8 (± 1 day) of the first cycle (Sindil alone or in combination with IBI110), and additional examinations may be performed at the discretion of the investigator. See 6.4. 4.1 for the monitoring requirements for pulse and blood pressure.

2. Body weight will be measured prior to each scheduled dose during the study. "If the subject & '92; s body weight fluctuates less than 10% from baseline (the day of the first dose of study treatment with IBI110), the baseline body weight can be used to calculate the dose administered." Otherwise, the actual dose was calculated according to the body weight on the scheduled day of administration.
3. ECOG PS assessment should be performed before administration of each cycle to provide the basis for the investigator to determine whether the subject is suitable to receive sintilimab alone or in combination with IBI110. ECOG PS score was also performed at the End of Treatment Visit and Safety Follow-up Visit.
4. 12-lead ECG will be performed within 30 minutes after the end of infusion of IBI110 in each cycle (or within 30 minutes after the end of infusion of sintilimab in the case of sintilimab alone in each cycle), at the end of treatment and safety follow-up, and as clinically indicated. Tests will be performed (more frequently) on Day 8 of Cycle 1 (for Sindil alone or in combination with IBI110), or additional tests may be performed at the discretion of the investigator.
5. Hematology includes: red blood cell count (RBC), HGB, hematocrit (HCT), white blood cell count (WBC), PLT, white blood cell differential [lymphocyte count (LYM), ANC, monocyte count (MONO), eosinophil count (EOS), basophil count (BASO)]. Blood biochemistry includes: liver function [TBIL, ALT, AST, γ-glutamyl transferase (γ-GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), lactate dehydrogenase (LDH)], renal function [blood urea (UREA), Cr], blood electrolytes [sodium (Na), potassium (K), chloride (Cl), magnesium (Mg), calcium (Ca), phosphorus (P)], amylase and fasting blood glucose (FBG). Urinalysis includes: pH, urine white blood cells (UWBC), urine protein (UPRO), urine red blood cells (URBC)/urine occult blood (BLD), urine glucose (UGLU). To be performed within 7 days before the first dose of study drug (SINDILI alone or in combination with IBI110) (if performed according to Table 1-1, the test will not be repeated), within 3 days before the study drug administration of each cycle starting from Cycle 2 (for SINDILI alone or in combination with IBI110), at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. During the first cycle (of Sintili alone or in combination with IBI110), examinations will be performed on Day 8 (± 1 day), and additional examinations may be performed at the discretion of the investigator. Inspections will be performed at the study site.
6. Blood myocardial enzyme spectrum and troponin examination shall include at least: creatine phosphokinase (CK), creatine phosphokinase isoenzyme (CK-MB) and troponin. It will be performed within 7 days before the first dose (SINDILI alone or in combination with IBI110) (if the test has been performed according to Table 1-1, the test will not be repeated), within 3 days before each dose of the second cycle (for SINDILI alone or in combination with IBI110), at the end of treatment visit, safety follow-up visit, and as clinically indicated. Other myocardial-related indicators, such as B-type natriuretic peptide (BNP), can be examined at the investigator's discretion for clinically significant abnormalities in ECG or relevant medical history, symptoms and signs.
7. Coagulation test includes: thrombin time (TT), prothrombin (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR). Within 7 days before the first dose of the study drug (Sindili alone or in combination with IBI110) (if the test has been performed according to Table 1-1, the test will not be repeated), within 3 days before each dose of the second cycle (for Sindili alone or in combination with IBI110), at the end of treatment visit, safety follow-up visit, and as clinically indicated. During the first cycle (of Sintili alone or in combination with IBI110), examinations will be performed on Day 8 (± 1 day), and additional examinations may be performed at the discretion of the investigator. Inspections will be performed at each study site.

8. Additional tests may be performed at the discretion of the investigator. If the urine pregnancy test cannot be confirmed as negative, a serum pregnancy test will be performed, whichever is the serum pregnancy result. Pregnancy testing will also be performed at the End of Treatment Visit and Safety Follow-up Visit. Inspections will be performed at each study site.
9. Thyroid function tests include: free triiodothyronine (FT3), FT4, and TSH. To be performed within 7 days prior to study drug administration in each cycle (not to be repeated if performed according to Table 1-1 prior to the first dose), at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Other thyroid function tests should be considered if there are abnormalities. Inspections will be performed at the study site.
10. Autoantibody testing includes: antinuclear antibodies, anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, and anti-thyroglobulin antibodies. At screening, the investigator may determine the need to test for autoimmune antibodies based on past medical history and as clinically indicated. After the screening period, the investigator will determine whether to re-examine as clinically indicated. Inspections will be performed at the study site.
11. **Blood samples will not be collected for subjects who receive only sintilimab monotherapy after completion of DLT observation or due to disease progression. Blood samples will be collected for subjects who receive IBI110 combined with sintilimab due to disease progression as planned in Table 1-1 (cumulative cycle). Note: If a subject experiences an infusion reaction to IBI110 and/or sintilimab, blood samples will be collected as close as possible to the start of the event, when the event resolves, and approximately 30 days after the end of the event for pre-and post-immunogenicity comparative analysis.**
12. **Blood samples will not be collected for subjects who receive only sintilimab monotherapy after completion of DLT observation or due to disease progression. Blood samples will be collected for subjects who receive IBI110 combined with sintilimab due to disease progression as planned in Table 2 (cumulative cycle).**
13. AE and laboratory safety assessments will be assessed according to NCI CTCAE v5.0. Refer to the description in Section 7 of the protocol for the definition, recording, relatedness judgment, severity judgment, reporting time limit and handling of AE and SAE.
14. Tumor assessment includes RECIST V1.1 assessment and iRECIST assessment, and no central imaging assessment will be performed in this study. Tumor imaging includes CT or MRI. The same imaging technique should be performed on the same subject during the study. Tumor imaging assessment will be performed every 6 weeks (± 7 days) after the first dose of study drug (if imaging assessment is performed after completion of DLT observation, imaging assessment will be performed every 6 weeks (± 7 days); if imaging assessment is not performed after completion of DLT observation, imaging assessment will be performed every 6 weeks (± 7 days) after the first dose of IBI110 monotherapy (0.1 mg/kg, 0.01 mg/kg), and imaging assessment will be continued after subsequent administration of sintilimab monotherapy or combination therapy). For subjects with an initial documented response [complete response (CR) or partial response (PR)], radiographic assessment will be performed to confirm response after 4 to 6 weeks and every 6 weeks (± 7 days) thereafter until radiographic disease progression is documented. For subjects with initial documentation of radiographic progressive disease (PD) (based on RECIST v1.1 criteria) while receiving sintilimab alone or in combination with IBI110, radiographic assessment must be performed at 4-6 weeks to confirm PD. If a subject is confirmed to continue receiving study drug (sintilimab alone or in combination with IBI110), imaging assessments will continue to be performed as planned until immune-confirmed progressive disease (iCPD) (based on iRECIST criteria). The iCPD adjudication is defined as at least an additional 5mm increase in target lesions or unequivocal progression of non-target lesions or an increase of at least 5mm in previously identified new lesions or other new lesions (based on

iRECIST criteria). For subjects who discontinue treatment for reasons other than radiographic disease progression, radiographic assessments should be performed at the end of treatment and every 6 weeks (± 7 days) after discontinuation until any of the following events occur: initiation of new antineoplastic therapy, disease progression, withdrawal of consent, lost to follow-up or death, study termination, etc.

15. Sintilimab alone or IBI110 in combination with sintilimab (infusions of IBI110 followed by sintilimab) will be administered every 3 weeks until disease progression, lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a total treatment duration of up to 24 months (including the time of previous administration of IBI110 alone). Subjects with first disease progression may continue treatment if clinically stable and eligible (see Section 5.1. 2 for details) at the discretion of the investigator until the total duration of treatment reaches 24 months (including the time of previous administration of IBI110 alone) or until recurrence of disease progression, loss to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first.
16. The End of Treatment Visit was performed within 7 days after confirmation of end of treatment. Relevant tests that have been performed within 7 days prior to the end of the study may not be repeated at the discretion of the investigator. The Safety Follow-up Visit will occur 90 (± 7) days after the last dose or prior to the initiation of new antineoplastic therapy. Subjects who discontinue treatment due to drug-related adverse events will be followed up until the adverse event is resolved to Grade 0-1, the symptoms are stable, and the subject withdraws the informed consent, whichever occurs first. See 6.2. 3 for details.
17. Survival follow-up: every 3 months (≤ 90 days) after the last dose, telephone visits are acceptable.

Table 2. PK/PD Sampling Schedule (Phase 1a Single Dose Escalation)

Phase	**Treatment Period**													**Safety Follow-up**
	Cycle 1 (28 days, DLT observation period) 3										**Cycle 2 and beyond (21 days/cycle)**			
Days	**1**					**2**	**3**	**8**	**15**	**22**	**Day 1 of each cycle (± 3 days)**			**90 days (± 7 days)**
Blood Sampling Time 1	**-1h**	**During Infusion**	**Immediately after the end of infusion**	**1h after end of infusion**	**6h after start of infusion**	**24h**	**48h**	**168h**	**336**	**504h**	**-1h**	**During Infusion**	**Immediately after the end of infusion**	
Blood sampling time window			**+ 5min**	**± 5 min**	**± 15 min**	**± 1 h**	**± 2 h**	**± 8 h**	**± 12 h**	**± 24 hours**			**+ 5min**	
IBI110		X										X		
PK, Pharmacodynamics 2, 3, 4	X		X	X	X	X	X	X	X	X	X4		X4	X4

Remarks:

1. Blood was collected at the site contralateral to the infusion of the treatment. Blood samples will not be collected for subjects who receive only sintilimab monotherapy after completion of DLT observation or due to disease progression. Blood samples will be collected for subjects who receive IBI110 combined with sintilimab due to disease progression according to the original plan (cumulative cycle). Note: For combination therapy, infuse IBI110 followed by sintilimab, with "start of infusion" referring to the start of IBI110 infusion and "end of infusion" referring to the end of sintilimab infusion.
2. Pharmacodynamics refers to Soluble LAG-3 test, and its blood collection points are consistent with PK blood collection points.

3. The PK blood sampling points for Cycle 1 are: within 1h before the start of IBI110 infusion, immediately after the end of infusion (+ 5min), 1 h ± 5 min after the end of infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), 504 h ± 24 h (Day 22) after the start of infusion. If the dose on Cycle 2 Day 1 is delayed due to AE or other reasons, an additional 672 h ± 24 h (Day 29) will be required for Cycle 1.
4. Sampling time in Cycle 2 and Cycle 3 is within 1h before the start of infusion and immediately after the end of infusion (+ 5min); Time of blood collection in Cycle 4: within 1h before the start of infusion, immediately after the end of infusion (+ 5min), 1 h ± 5 min after the end of infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), 504 h ± 24 h (Day 22) after the start of infusion (i.e., within 1h before infusion in Cycle 5); Sampling time in Cycle 6, 8, 12 and 16: within 1h before the start of infusion and immediately after the end of infusion (+ 5min); One blood sample will be collected at the Safety Follow-up Visit.

Table 3. Schedule of Study Visits (Phase Ib Combined Dose Escalation)

Phase	Screening period	Combination Treatment Period							End of Treatment Visit 18	Safety Follow-up 18	Survival follow-up 19
		Cycle 1 (28-day DLT observation period)						Cycle 2 and beyond (21 days/cycle)			
Days	**-28 ~-1**	**1**	**2**	**3**	**8**	**15**	**22**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
General Study Procedures											
Written informed consent1	X										
Inclusion/Exclusion Criteria	X										
Demographics/Past Medical History/Prior Medications2	X										
Vital signs3	X	X			X		X	X	X	X	
Weight/Height4	X	X						X			
Physical examination	X				X		X	X	X	X	
ECOG PS score	X							X	X	X	
12-lead ECG5	X	X			X		X	X	X	X	
Hematology/blood biochemistry/urinalysis 6	X				X		X	X	X	X	
Blood myocardial enzymes and troponin 7	X							X	X	X	
Coagulation function 8	X				X			X	X	X	
Pregnancy Test9	X								X	X	
Thyroid function10	X							X	X	X	

Phase	**Screening period**	**Combination Treatment Period**							**End of Treatment Visit 18**	**Safety Follow-up 18**	**Survival follow-up 19**
		Cycle 1 (28-day DLT observation period)						**Cycle 2 and beyond (21 days/cycle)**			
Days	**-28 ~-1**	**1**	**2**	**3**	**8**	**15**	**22**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
Autoantibodies11	X										
Immunogenicity (ADA, NAb) 12		X						X		X	
HIV, HBV and HCV13	X										
PK14		X	X	X	X	X	X	X		X	
Pharmacodynamics 14		X	X	X	X	X	X	X		X	
Assessment of Adverse Events15	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Survival Status		X X ⟷									
Subsequent Antineoplastic Therapy									X	X	X
Efficacy Assessments											
Tumor Imaging Assessment16	X							X	X	X	X
Study Drug Infusion											
IBI11017		X						X			
Sintilimab 17		X						X			
Biomarkers											

Phase	Screening period	Combination Treatment Period							End of Treatment Visit 18	Safety Follow-up 18	Survival follow-up 19
		Cycle 1 (28-day DLT observation period)						Cycle 2 and beyond (21 days/cycle)			
Days	**-28 ~-1**	**1**	**2**	**3**	**8**	**15**	**22**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
Archived or fresh Tissue samples20	X										

Remarks:

1. Signature of the Informed Consent Form (ICF) should be performed prior to any protocol-specified procedures. In order to reduce the psychological and physical trauma to the patients caused by repeated blood sampling or examination, the results of laboratory tests, ECG and imaging tests that meet the time window and technical requirements before signing of ICF can be accepted in the screening period of this study.
2. Tumor history includes: disease staging, date of diagnosis and previous treatment, including treatment for initial diagnosis, including chemotherapy, radiotherapy, surgical treatment, molecular targeted drugs (± chemotherapy), immune checkpoint inhibitors (such as anti-CTLA-4 antibody, anti-PD-1 antibody, anti-PD-L1 antibody), etc. The time of the last anti-tumor treatment before the first dose of study drug must be recorded.
3. Vital signs include: temperature, pulse, respiratory rate, and blood pressure. To be performed at screening, treatment, end of treatment, and safety follow-up, and as clinically indicated. During the DLT observation period, more frequent examinations will be performed on Days 8 and 22 (± 1 day), and additional examinations may be performed at the discretion of the investigator. See 6.4. 4.1 for the monitoring requirements for pulse and blood pressure.
4. Height measurements were performed at screening only. Body weight will be measured prior to each scheduled dose during the study. If the subject's body weight fluctuates less than 10% from baseline (day of first dose of study treatment), the baseline body weight can be used to calculate the dose. Otherwise, the actual dose was calculated according to the body weight on the scheduled day of administration.
5. Timing of 12-lead ECG: to be performed at screening, within 30 minutes after the end of IBI110 infusion in each cycle, at the end of treatment and safety follow-up, and as clinically indicated. During the DLT observation period, examinations will be performed on Days 8 and 22 (± 1 day) (higher frequency), and additional examinations may be performed at the discretion of the investigator.
6. Hematology includes: red blood cell count (RBC), HGB, hematocrit (HCT), white blood cell count (WBC), PLT, white blood cell differential [lymphocyte count (LYM), ANC, monocyte count (MONO), eosinophil count (EOS), basophil count (BASO)]. Blood biochemistry includes: liver function [TBIL, ALT, AST, γ-glutamyl transferase (γ-GT), alkaline phosphatase

(ALP), albumin (ALB), total protein (TP), lactate dehydrogenase (LDH)], renal function [blood urea (UREA), Cr], blood electrolytes [sodium (Na), potassium (K), chloride (Cl), magnesium (Mg), calcium (Ca), phosphorus (P)], amylase and fasting blood glucose (FBG). Urinalysis includes: pH, urine white blood cells (UWBC), urine protein (UPRO), urine red blood cells (URBC)/urine occult blood (BLD), urine glucose (UGLU). 24-hour proteinuria test should be performed for subjects with urine protein ≥ 2 + on urine dipstick test during screening period. Within 7 days prior to the first dose of study drug, within 3 days prior to each cycle of study drug administration from Cycle 2, and at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Inspections will be performed at the study site. During the DLT observation period, examinations will be performed on Days 8 and 22 (± 1 day), and additional examinations may be performed at the discretion of the investigator.

7. Blood myocardial enzyme spectrum and troponin examination shall include at least: creatine phosphokinase (CK), creatine phosphokinase isoenzyme (CK-MB) and troponin. To be performed within 7 days prior to the first dose in the screening period, within 3 days prior to each subsequent dose in the second cycle, at the End of Treatment Visit, at the Safety Follow-up Visit, and as clinically indicated. Other myocardial-related indicators, such as B-type natriuretic peptide (BNP), can be examined at the investigator's discretion for clinically significant abnormalities in ECG or relevant medical history, symptoms and signs.
8. Coagulation test includes: thrombin time (TT), prothrombin (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR). To be performed within 7 days prior to the first dose of study treatment, within 3 days prior to each dose of subsequent cycle 2, at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Inspections will be performed at each study site. During the DLT observation period, examinations will be performed at 8 days (± 1 day), and additional examinations may be performed at the discretion of the investigator.
9. Women of childbearing potential will have a urine or serum pregnancy test within 7 days prior to the first dose, or additional tests may be performed at the discretion of the investigator. If the urine pregnancy test cannot be confirmed as negative, a serum pregnancy test will be performed, whichever is the serum pregnancy result. Pregnancy testing will also be performed at the End of Treatment Visit and Safety Follow-up Visit. Inspections will be performed at each study site.
10. Thyroid function tests include: free triiodothyronine (FT3), FT4, and TSH. To be performed at screening, within 7 days prior to study drug administration in each cycle starting Cycle 2, at the End of Treatment Visit, at the Safety Follow-up Visit, and as clinically indicated. Other thyroid function tests should be considered if there are abnormalities. Inspections will be performed at the study site.
11. Autoantibody testing includes: antinuclear antibodies, anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, and anti-thyroglobulin antibodies. At screening, the investigator may determine the need to test for autoimmune antibodies based on past medical history and as clinically indicated. After the screening period, the investigator will determine whether to re-examine as clinically indicated. Inspections will be performed at the study site.
12. Immunogenicity testing will be performed within 1 hour prior to the start of IBI110 infusion at Cycles 1, 2, 4, 6, 8, 12, 16, then every 8 cycles thereafter (Cycles 24, 32, 40, etc., and so on), and at the Safety Follow-up Visit. If a subject experiences an infusion reaction to IBI110 and/or sintilimab, blood samples will be collected as close as possible to the start of the event, when

the event resolves, and approximately 30 days after the end of the event for pre-and post-immunogenicity comparative analysis. Testing will be performed at a central laboratory and, if necessary, may detect drug concentrations in immunogenicity samples.

13. Including HIV and HCV antibody tests (HCV RNA test should be performed if HCV antibody is positive), hepatitis B five tests [hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb)] and HBV DNA tests. If HBsAg and/or only HBcAb were positive, further HBV DNA testing was performed. Testing will be performed at the study site during the screening period.
14. The timing of PK/PD tests is shown in the PK/PD sampling schedule (Table 4). Tests will be performed at a central laboratory.
15. AE and laboratory safety assessments will be assessed according to NCI CTCAE v5.0. Refer to the description in Section 7 of the protocol for the definition, recording, relatedness judgment, severity judgment, reporting time limit and handling of AE and SAE.
16. Tumor assessment includes RECIST v1.1 assessment and iRECIST assessment, and no central imaging assessment will be performed in this study. Tumor imaging includes CT or MRI. The same imaging technique should be performed on the same subject during the study. The baseline assessment will be performed within 28 days prior to enrollment, and the investigator may collect the imaging results of 28 days prior to enrollment in the study for assessment. Tumor imaging evaluations will be performed every 6 weeks (± 7 days) after the first dose of study drug. For subjects with an initial documented response [complete response (CR) or partial response (PR)], radiographic assessment will be performed to confirm response after 4 to 6 weeks and every 6 weeks (± 7 days) thereafter until radiographic disease progression is documented. For subjects with initial documentation of radiographic progressive disease (PD) (based on RECIST v1.1 criteria), if the subject continues to receive study drug after confirmation, imaging assessments for confirmation of PD (based on iRECIST criteria) must be performed at 4 to 6 weeks, then every 6 weeks (± 7 days) until immunologically confirmed progressive disease (iCPD) (based on iRECIST criteria). The iCPD adjudication is defined as at least an additional 5mm increase in target lesions or unequivocal progression of non-target lesions or an increase of at least 5mm in a previously identified new lesion or an additional new lesion (based on iRECIST criteria). For subjects who discontinue treatment for reasons other than radiographic disease progression, radiographic assessments should be performed at the end of treatment and every 6 weeks (± 7 days) after discontinuation until any of the following events occur: initiation of new antineoplastic therapy, disease progression, withdrawal of consent, lost to follow-up or death, study termination, etc.
17. Infusion of IBI110 followed by sintilimab. The first cycle of each dose group is DLT observation period (28 days), only on Day 1. Every 3 weeks until disease progression, lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a maximum of 24 months. Subjects with first disease progression may continue to receive treatment if clinically stable and eligible subjects (see Section 5.1. 2 for details) at the discretion of the investigator until the total duration of treatment reaches 24 months or until recurrence of disease progression, loss to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment occurs, whichever occurs first.
18. The End of Treatment Visit was performed within 7 days after confirmation of end of treatment. Relevant tests that have been performed within 7 days prior to the end of the study may not be repeated at the discretion of the investigator. The Safety Follow-up Visit will occur 90 ± 7 days after the last dose or prior to the initiation of new antineoplastic therapy. Subjects who

discontinue treatment due to drug-related adverse events will be followed until the adverse event resolves to Grade 0-1, symptoms stabilize, and the subject withdraws consent, whichever occurs first. See 6.2. 3 for details.

19. Survival follow-up: every 3 months (≤ 90 days) after the last dose, telephone visits are acceptable.
20. Subjects are required to provide archival or fresh tumor tissue samples (5 ~ 10 slides) that meet the testing requirements as far as possible during the screening period, which will be used for biomarker study.

Table 4. PK/PD Sampling Schedule (Phase Ib Combined Dose Escalation)

Phase	**Combination Treatment Period**												**Safety Follow-up**
	Cycle 1 (28 days, DLT observation period) 3									**Cycle 2 and beyond (21 days/cycle)**			
Days	**1**					**2**	**3**	**8**	**15**	**22**	**Day 1 of each cycle (± 3 days)**			**90 days (± 7 days)**
Blood Sampling Time 1	**-1h**	**During Infusion**	**Immediately after the end of infusion**	**1h after end of infusion**	**6h after start of infusion**	**24h**	**48h**	**168h**	**336**	**504h**	**-1h**	**During Infusion**	**Immediately after the end of infusion**	
Blood sampling time window			**+ 5min**	**± 5 min**	**± 15 min**	**± 1 h**	**± 2 h**	**± 8 h**	**± 12 h**	**± 24 hours**			**+ 5min**	
IBI110		X										X		
sintilimab		X										X		
PK/Pharmacodynamics 2, 3, 4	X		X	X	X	X	X	X	X	X	X4		X4	X4

Remarks:

1. Blood was collected at the site contralateral to the infusion of the treatment.
2. Pharmacodynamics refers to Soluble LAG-3 test, and its blood collection points are consistent with PK blood collection points.
3. The PK blood collection points set in Cycle 1 are: within 1h before the start of IBI110 infusion, immediately after the end of sintilimab infusion (+ 5min), 1 h ± 5 min after the end of sintilimab infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), and 504 h ± 24 h (Day 22) after the start of IBI110 infusion. If the dose on Day 1 of Cycle 2 is delayed due to AE or other reasons, an additional 672 h ± 24 h (Day 29) will be required in Cycle 1.
4. Sampling time in Cycle 2 and Cycle 3: within 1h before the start of IBI110 infusion and immediately after the end of sintilimab infusion (+ 5min); Blood sampling time in Cycle 4: within 1h before the start of IBI110 infusion, immediately after the end of sintilimab infusion (+ 5min), 1 h ± 5 min after the end of sintilimab infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2

h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), 504 h ± 24 h (Day 22) after the start of IBI110 infusion (i.e., sampling within 1h before infusion in Cycle 5); Sampling times in Cycles 6, 8, 12 and 16 were within 1h before the start of IBI110 infusion and immediately after the end of sintilimab infusion (+ 5min). One blood sample will be collected at the Safety Follow-up Visit.

Table 5. Schedule of Study Visits (Multiple Dose Expansion of IBI110 in Combination with Sintilimab, Phase Ia/Ib Dose Expansion-Cohorts A ~ O)

Phase	Screening period	Combination Treatment Period (every 21-day cycle)						End of Treatment Visit 18	Safety Follow-up 18	Survival follow-up 19
		Cycle 1					Cycle 2 and beyond (21 days/cycle)			
Days	**-28 ~-1**	**1**	**2**	**3**	**8**	**15**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
General Study Procedures										
Written informed consent1	X									
Inclusion/Exclusion Criteria	X									
Demographics/Past Medical History/Prior Medications2	X									
Vital signs3	X	X			X		X	X	X	
Weight/Height4	X	X					X			
Physical examination	X				X		X	X	X	
ECOG PS score	X						X	X	X	
12-lead ECG and cardiac ultrasonography5	X				X		X	X	X	
Hematology/blood chemistry/urinalysis/fecal occult blood6	X				X		X	X	X	

Phase	**Screening period**	**Combination Treatment Period (every 21-day cycle)**						**End of Treatment Visit 18**	**Safety Follow-up 18**	**Survival follow-up 19**
		Cycle 1					**Cycle 2 and beyond (21 days/cycle)**			
Days	**-28 ~-1**	**1**	**2**	**3**	**8**	**15**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
Blood myocardial enzymes and troponin 7	X				X		X	X	X	
Coagulation function 8	X				X		X	X	X	
Pregnancy Test9	X							X	X	
Thyroid function10	X						X	X	X	
Autoantibodies11	X									
Immunogenicity (ADA, NAb) 12		X					X		X	
HIV, HBV and HCV13	X									
EBV13	X						X	X		
PK14		X					X			
Pharmacodynamics 14		X					X			
Assessment of Adverse Events15	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	
Survival Status		X X ←					→			
Subsequent Antineoplastic Therapy								X	X	X
Efficacy Assessments										
Tumor Imaging Assessment16	X						X	X	X	X
Study Drug Infusion										
IBI11017		X					X			

Phase	Screening period	Combination Treatment Period (every 21-day cycle)						End of Treatment Visit 18	Safety Follow-up 18	Survival follow-up 19
		Cycle 1					Cycle 2 and beyond (21 days/cycle)			
Days	**-28 ~-1**	**1**	**2**	**3**	**8**	**15**	**Day 1 of each cycle (± 3 days)**	**End of Treatment**	**90 days (± 7 days) after end of treatment**	**Every 3 months**
Sintilimab 17		X					X			
Lenvatinib 17 (Cohort B: 1st line HCC)		X X⟷								
Paclitaxel/Carboplatin17 (Cohort D: First-line squamous NSCLC)		X					X			
Pemetrexed/Carboplatin17 (Cohort D: First-line non-squamous NSCLC)		X					X			
Oxaliplatin in combination with capecitabine17 (Cohort J: First-line HER2-negative GC)		X					X			
Biomarkers										
Archival or fresh tissue samples20	X									

Remarks:

1. Signature of the Informed Consent Form (ICF) should be performed prior to any protocol-specified procedures. In order to reduce the psychological and physical trauma to the patients caused by repeated blood sampling or examination, the results of laboratory tests, ECG and imaging tests that meet the time window and technical requirements before signing of ICF can be accepted in the screening period of this study.

2. Tumor history includes: disease staging, date of diagnosis and previous treatment, including treatment for initial diagnosis, including chemotherapy, radiotherapy, surgical treatment, molecular targeted drugs (± chemotherapy), immune checkpoint inhibitors (such as anti-CTLA-4 antibody, anti-PD-1 antibody, anti-PD-L1 antibody), etc. The time of the last anti-tumor treatment before the first dose of study drug must be recorded.
3. Vital signs include: temperature, pulse, respiratory rate, and blood pressure. To be performed at screening, treatment, end of treatment, and safety follow-up, and as clinically indicated. Higher frequency examinations will be performed on Days 1 and 8 (± 1 day) of Cycle 1, and additional examinations may be performed at the discretion of the investigator. See 6.4. 4.1 for the monitoring requirements for pulse and blood pressure.
4. Height measurements were performed at screening only. Body weight will be measured prior to each scheduled dose during the study. If the subject's body weight fluctuates less than 10% from baseline (day of first dose of study treatment), the baseline body weight can be used to calculate the dose. Otherwise, the actual dose was calculated according to the body weight on the scheduled day of administration.
5. Timing of 12-lead ECG: to be performed at screening (within 7 days before the first dose), within 3 days before the infusion of study drug in each cycle starting from Cycle 2, at the end of treatment and safety follow-up visit, and as clinically indicated. Higher frequency on Cycle 1 Day 8 (± 1 day), or additional tests may be performed at the discretion of the investigator. Cardiac ultrasound (only applicable to dose expansion cohorts using gatinib), performed at each tumor assessment, at the end of treatment and safety follow-up, and as clinically indicated.
6. Hematology includes: red blood cell count (RBC), HGB, hematocrit (HCT), white blood cell count (WBC), PLT, white blood cell differential [lymphocyte count (LYM), ANC, monocyte count (MONO), eosinophil count (EOS), basophil count (BASO)]. Blood biochemistry includes: liver function [TBIL, ALT, AST, γ-glutamyl transferase (γ-GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), lactate dehydrogenase (LDH)], renal function [blood urea (UREA), Cr], blood electrolytes [sodium (Na), potassium (K), chloride (Cl), magnesium (Mg), calcium (Ca), phosphorus (P)], amylase and fasting blood glucose (FBG). Urinalysis includes: pH, urine white blood cells (UWBC), urine protein (UPRO), urine red blood cells (URBC)/urine occult blood (BLD), urine glucose (UGLU). 24-hour proteinuria test should be performed for subjects with urine protein ≥ 2 + on urine dipstick test during screening period. Fecal occult blood testing is only applicable to dose expansion cohorts with lenvatinib. Within 7 days prior to the first dose of study drug, within 3 days prior to each cycle of study drug administration from Cycle 2, and at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Inspections will be performed at the study site. In the first cycle, examinations will be performed on Day 8 (± 1 day), and additional examinations may be performed at the discretion of the investigator.
7. Blood myocardial enzyme spectrum and troponin examination shall include at least: creatine phosphokinase (CK), creatine phosphokinase isoenzyme (CK-MB) and troponin. To be performed within 7 days prior to the first dose in the screening period, within 3 days prior to each subsequent dose in the second cycle, at the End of Treatment Visit, at the Safety Follow-up Visit, and as clinically indicated. In the first cycle, examinations will be performed on Day 8 (± 1 day), and additional examinations may be performed at the discretion of the investigator. Other myocardial-related indicators, such as B-type natriuretic peptide (BNP), can be examined at the investigator's discretion for clinically significant abnormalities in ECG or relevant medical history, symptoms and signs.
8. Coagulation test includes: thrombin time (TT), prothrombin (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR). To be performed within 7 days prior

to the first dose of study treatment, within 3 days prior to each dose of subsequent cycle 2, at the End of Treatment Visit, Safety Follow-up Visit, and as clinically indicated. Inspections will be performed at each study site. In the first cycle, examinations will be performed on Day 8 (± 1 day), and additional examinations may be performed at the discretion of the investigator.

9. Women of childbearing potential will have a urine or serum pregnancy test within 7 days prior to the first dose, or additional tests may be performed at the discretion of the investigator. If the urine pregnancy test cannot be confirmed as negative, a serum pregnancy test will be performed, whichever is the serum pregnancy result. Pregnancy testing will also be performed at the End of Treatment Visit and Safety Follow-up Visit. Inspections will be performed at each study site.
10. Thyroid function tests include: free triiodothyronine (FT3), FT4, and TSH. To be performed at screening, within 7 days prior to study drug administration in each cycle starting Cycle 2, at the End of Treatment Visit, at the Safety Follow-up Visit, and as clinically indicated. Other thyroid function tests should be considered if there are abnormalities. Inspections will be performed at the study site.
11. Autoantibody testing includes: antinuclear antibodies, anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, and anti-thyroglobulin antibodies. At screening, the investigator may determine the need to test for autoimmune antibodies based on past medical history and as clinically indicated. After the screening period, the investigator will determine whether to re-examine as clinically indicated. Inspections will be performed at the study site.
12. Immunogenicity testing is shown in Table 6. Testing will be performed at a central laboratory and, if necessary, may detect drug concentrations in immunogenicity samples.
13. HBV, HCV and HIV tests are required for all cohorts, including HIV and HCV antibody tests (HCV RNA test is required for HCV antibody positive), hepatitis B five tests [hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb)] and HBV DNA tests. If HBsAg and/or only HBcAb were positive, further HBV DNA testing was performed. Testing will be performed at the study site during the screening period. Plasma EBV-DNA testing will be performed in Cohort A1 (nasopharyngeal carcinoma, EBV gastric carcinoma), Cohort I (nasopharyngeal carcinoma), Cohort K (EBV gastric carcinoma), Cohort O (nasopharyngeal carcinoma) and will be collected within 7 days prior to the first dose, within 3 days prior to study drug administration at Week 2, at the next visit after the first disease response (CR or PR), and at the End-of-Treatment visit at the central laboratory.
14. The timing of PK/PD testing is described in the PK/PD/Immunogenicity Sampling Schedule (Table 6). Tests will be performed at a central laboratory.
15. AE and laboratory safety assessments will be assessed according to NCI CTCAE v5.0. Refer to the description in Section 7 of the protocol for the definition, recording, relatedness judgment, severity judgment, reporting time limit and handling of AE and SAE.
16. Tumor assessment includes RECIST V1.1 assessment and iRECIST assessment, and no central imaging assessment will be performed in this study. Tumor imaging includes CT or MRI. The same imaging technique should be performed on the same subject during the study. The baseline assessment will be performed within 28 days prior to enrollment, and the investigator may collect the imaging results of 28 days prior to enrollment in the study for assessment. Tumor imaging evaluations will be performed every 6 weeks (± 7 days) after the first dose of study drug. For subjects with an initial documented response [complete response (CR) or partial response (PR)], radiographic assessment will be performed to confirm response after 4 to 6 weeks and every 6 weeks (± 7 days) thereafter until radiographic disease progression is documented. For subjects with initial documentation of radiographic progressive disease (PD) (based on

RECIST v1.1 criteria), if the subject continues to receive study drug after confirmation, imaging assessments for confirmation of PD (based on iRECIST criteria) must be performed at 4 to 6 weeks, then every 6 weeks (± 7 days) until immunologically confirmed progressive disease (iCPD) (based on iRECIST criteria). The iCPD adjudication is defined as at least an additional 5mm increase in target lesions or unequivocal progression of non-target lesions or an increase of at least 5mm in a previously identified new lesion or an additional new lesion (based on iRECIST criteria). For subjects who discontinue treatment for reasons other than radiographic disease progression, radiographic assessments should be performed at the end of treatment and every 6 weeks (± 7 days) after discontinuation until any of the following events occur: initiation of new antineoplastic therapy, disease progression, withdrawal of consent, lost to follow-up or death, study termination, etc.

17. Multiple dose group expansion of IBI110 in combination with sintilimab: for multiple dose group expansion of sintilimab in combination with 3 mg/kg IBI110 to the MTD dose group of combination dose escalation, the dose will be administered once every 3 weeks. For subjects with first disease progression, if clinically stable and eligible subjects (see Section 5.1. 2 for details), the combination treatment with sintilimab may be continued once every 3 weeks until disease progression, lost to follow-up or death, intolerable toxicity, withdrawal of informed consent, or other reasons for discontinuation of study treatment (whichever occurs first), for a maximum of 24 months;

    Cohorts A1 and A2: IBI110 monotherapy will be administered every 3 weeks. For subjects with first disease progression, if clinically stable and eligible subjects (see Section 5.1. 2 for details), treatment with sintilimab may be continued every 3 weeks until disease progression, loss to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a maximum of 24 months (including the time of previous administration of IBI110 monotherapy);

    Cohort B: IBI110 in combination with sintilimab + lenvatinib, administered every 3 weeks followed by sintilimab, followed by lenvatinib orally daily until disease progression, lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a maximum of 24 months;

    Cohorts C ~ O: except for the control group of Cohort D2, it is IBI110 plus sintilimab ± other treatments. Infusion of IBI110 followed by sintilimab and then other drugs (if applicable) will be administered once every 3 weeks. The treatment course and cycle of each study drug are shown in Section 5.1. 1. Maintenance treatment with IBI110 in combination with sintilimab until disease progression, lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a maximum of 24 months. Cohort D2 control group will only receive sintilimab in combination with chemotherapy, and sintilimab will be maintained until disease progression, lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a maximum of 24 months.

    Subjects with first disease progression may continue to receive treatment if clinically stable and eligible subjects (see Section 5.1. 2 for details) at the discretion of the investigator until the total duration of treatment reaches 24 months or until recurrence of disease progression, loss to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment occurs, whichever occurs first. For specific dosing regimen, please refer to 5.2. 4 and 5.2. 5.

18. The End of Treatment Visit was performed within 7 days after confirmation of end of treatment. Relevant examinations that have been performed within 7 days prior to the end of the study may not be repeated at the discretion of the investigator. The Safety Follow-up Visit will occur 90 ± 7 days after the last dose or prior to the initiation of new antineoplastic therapy. Subjects

who discontinue treatment due to drug-related adverse events will be followed until the adverse event resolves to Grade 0-1, symptoms stabilize, and the subject withdraws consent, whichever occurs first. See 6.2. 3 for details.

19. Survival follow-up: every 3 months (≤ 90 days) after the last dose, telephone visits are acceptable.
20. Subjects are required to provide archival or fresh tumor tissue samples (Phase Ia: 5 slides, Phase Ib: 5-10 slides) that meet the testing requirements during the screening period as far as possible, and these samples will be used for biomarker study.

Table 6. PK/PD/Immunogenicity Sampling Schedule (Multiple Dose Cohort Expansion of Sintilimab in Combination with IBI110, Phase Ia/Ib Dose Expansion Cohorts A ~ O)

Phase	**Combination Treatment Period (every 21-day cycle)**						**Safety Follow-up**
	Cycle 1 (21 days) 2			**Cycle 2 and beyond (21 days/cycle)**			**90 days (± 7 days)**
Days	**1**			**Day 1 of each cycle (± 3 days)**			
Blood Sampling Time 1	**-1h**	**During Infusion**	**Immediately after the end of infusion**	**-1h**	**During Infusion**	**Immediately after the end of infusion**	
Blood sampling time window			**+ 5min**			**+ 5min**	
IBI110*		X			X		
Sintilimab *		X			X		
PK2			X	X2		X2	
Pharmacodynamics 3	X			X3			
Immunogenicity 4	X			X4			X

Remarks:

1. Blood was collected at the site contralateral to the infusion of the treatment. * Note: Cohorts A1 and A2 are IBI110 alone, and if the cohort is IBI110 in combination with sintilimab, infuse IBI110 followed by sintilimab.
2. **Cohorts A1 and A2: sparse PK sampling will be performed for any 12 subjects as follows: in Cycle 1, PK blood sampling will be performed immediately after the end of IBI110 infusion (+ 5min); Sampling times for both Cycles 2 and 4 were within 1 hour prior to the start of infusion and immediately after the end of infusion (+ 5min).**
   Cohorts B ~ O: Sparse PK sampling will be performed for any 12 subjects. If there are multiple dose groups in the same cohort, sparse PK sampling will be performed for any 12 subjects in each dose group. The details are as follows: PK blood sampling points set in Cycle 1 are: immediately after the end of infusion of sintilimab (+ 5min); Sampling times

for both Cycles 2 and 4 were within 1 hour prior to the start of IBI110 infusion and immediately after the end of sintilimab infusion (+ 5 minutes). PK samples will not be collected for the cohort receiving sintilimab 200mg IV Q3W + other treatment only.

Expansion of IBI110 in combination with sintilimab in multiple dose groups (3mg/kg ~ MTD): sparse PK samples will be collected from any 12 subjects in each dose group, specifically:

Sampling time in Cycle 1: immediately after the end of infusion of sintilimab (+ 5min);

Sampling time in Cycle 2 and Cycle 4: within 1 hour before the start of IBI110 infusion and immediately after the end of sintilimab infusion (+ 5 minutes).

3. **Double LAG-3 samples will be collected only from any 6 subjects in each dose group in the expansion cohorts of IBI110 plus sintilimab in multiple dose groups (3mg/kg-MTD), specifically: Blood collection time in Cycles 1, 2 and 4 is within 1 hour before the start of IBI110 infusion. PD (Double LAG-3) samples will not be collected from subjects in the other Phase Ia/Ib dose expansion cohorts. No PD samples will be collected in Cohort D2.**
4. All subjects in the Phase Ib expansion cohorts of IBI110 in combination with sintilimab in multiple dose cohorts (3mg/kg to MTD) and 12 subjects in the Phase Ia/Ib dose expansion-Cohorts A to O with sparse PK sampling will be tested for immunogenicity within 1 hour prior to the start of IBI110 infusion in Cycles 1, 2, 4, 8, and at the Safety Follow-up Visit.

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List of Abbreviations

缩略语	英文全称	中文全称
ADA	Anti-drug antibody	抗药抗体
ADR	Adverse Drug Reaction	药物不良事件
AE	Adverse Event	不良事件
ALB	Albumin	白蛋白
ALP	Alkaline phosphatase	碱性磷酸酶
ALT	Alanine transaminase	谷丙转氨酶
ANC	Absolute Neutrophil Count	绝对中性粒细胞计数
APTT	Activated partial thromboplastin time	活化部分凝血活酶时间
AR	Accumulation Ratio	积累率
AST	Aspartate amino transferase	谷草转氨酶
AUC	Area Under Curve	药时曲线下面积
BASO	Basophil	嗜碱性粒细胞
BNP	Brain natriuretic peptide	B 型脑利钠肽
Ca	Calcium	钙
CCr	Creatinine Clearance rate	肌酐清除率
ccRCC	Clear Cell Renal Cell Carcinoma	肾透明细胞癌
CDE	Center for Drug Evaluation	药品评审中心
cHL	classical Hodgkin disease	经典型霍奇金淋巴瘤
CI	Confidence Interval	置信区间
CK	Creatine Kinase	磷酸肌酸激酶
CL	Clearance	清除率
Cl	Chlorine	氯
C_{max}	maximum serum concentration of drug	药物最大浓度
C_{min}	minimum serum concentration of drug	药物最低浓度
CR	Complete Response	完全缓解
Cr	Creatinine	肌酐
CRA	Clinical Research Associate	临床监查员
CRF	Case Report Form	病例报告表
CRO	Contract research organization	合同研究组织
CSR	Clinical Study Report	临床研究总结报告
CT	Computed Tomography	计算机断层扫描
CTCAE	Common Terminology Criteria for Adverse Events	常见不良事件术语评定标准
CTLA-4	Cytotoxic T Lymphocyte Antigen -4	细胞毒 T 淋巴细胞相关抗原-4
DCR	Disease Control Rate	疾病控制率
DLT	Dose-limiting toxicity	剂量限制性毒性

缩略语	英文全称	中文全称
DOR	Duration of Response	持续缓解时间
dsDNA	double-stranded deoxyribonucleic acid	双链脱氧核糖核酸
EBV	Epstein-Barr virus	EB 病毒
EC	Ethics Committee	伦理委员会
ECG	Electrocardiogram	心电图
ECOG	Eastern Cooperative Oncology Group	美国东部肿瘤协作组
ECOGPS	Eastern Cooperative Oncology Group Performance Status	美国东部肿瘤协作组体力状态评分
eCRF	electronic case report form	电子病历报告表
EDC	Electronic Data Capture	电子数据采集
EDCS	Electronic Data Capture System	电子数据采集系统
EGFR	Epidermal Growth Gactor Receptor	表皮生长因子受体
EOS	eosinophilic granulocyte	嗜酸性粒细胞
FAS	Full analysis set	全分析人群
FBG	Fasting Blood Glucos	空腹血糖
FDA	Food and Drug Administration	食品药品监督管理局
FT3	Free Triiodothyronine	游离三碘甲状腺原氨酸
FT4	free Thyroxine	游离甲状腺素
GC	Gastric Cancer	胃癌
GCP	Good Clinical Practice	药物临床试验质量管理规范
GEJ	Gastroesophageal junctional cancer	胃食管交界癌
HBcAb	Hepatitis B core antibody	乙型肝炎病毒核心抗体
HBeAb	Hepatitis B e antibody	乙型肝炎 e 抗体
HBeAg	Hepatitis B e antigen	乙型肝炎 e 抗原
HBsAb	Hepatitis B surface antibody	乙型肝炎表面抗体
HBsAg	Hepatitis B surface antigen	乙型肝炎表面抗原
HBV	Hepatitis B virus	乙型肝炎病毒
HCC	hepatocellular carcinoma	肝细胞癌
hCG	human chorionic gonadotropin	血清人绒毛膜促性腺激素
HCT	Hematocrit	红细胞压积
HCV	Hepatitis C virus	丙型肝炎病毒
HGB	Hemoglobin	血红蛋白
HIV	Human Immunodeficiency Virus	人免疫缺陷病毒
HNSTD	highest non- severely toxic dose	最高非严重毒性剂量
HPV	Human papillomavirus	人乳突瘤病毒
iBOR	Immunity Best Overall Response	免疫最佳整体疗效
ICF	Informed Consent Form	知情同意书
iCPD	Immunity Confirmed Progression Disease	免疫确认进展
iCR	Immunity Complete Response	免疫完全缓解

缩略语	英文全称	中文全称
INR	international normalized ratio	国际标准化比值
iPR	Immunity Partial Response	免疫部分缓解
irAE	Immune-related Adverse Event	免疫介导不良事件
iRECIST	immune Response Evaluation Criteria in Solid Tumors	免疫实体瘤疗效评价标准
IRR	Infusion-related reaction	输注相关反应
iSD	Immunity Stable Disease	免疫疾病稳定
K	Potassium	钾
LAG-3	Lymphocyte Activation Gene 3	淋巴细胞活化基因-3
LDH	Lactate Dehydrogenase	乳酸脱氢酶
LYM	lymphocyte	淋巴细胞
Mg	Magnesium	镁
MHC	Major Histocompatibility Complex II	主要组织相容复合体 II
MONO	Monocyte	单核细胞
MRI	Magnetic Resonance Imaging	核磁共振成像
MTD	Maximal Tolerated Dose	最大耐受剂量
Na	Natrium	钠
Nab	Neutralizing Antibody	中和抗体
NAb	Neutralizing Antibody	中和抗体
nccRCC	Non Clear Cell Renal Cell Carcinoma	非透明细胞肾癌
NCI	National Cancer Institute	美国国立癌症研究所
NOAEL	No Observed Adverse Effect Level	未观察到损害作用的剂量
NSCLC	Non Small Cell Lung Cancer	非小细胞肺癌
ORR	Overall Response Rate	客观缓解率
OS	Overall Survival	总生存期
P	Phosphate	磷
PBMC	Peripheral Blood Mononuclear Cell	外周血单核细胞
PD	Progression Disease	疾病进展
PD-1	Programmed Cell Death -1	程序性死亡受体-1
PD-L1/2	Programmed Cell Death Ligand -1/2	程序性死亡配体-1/2
PFS	Progression Free Survival	无进展生存期
pH	-	酸碱度
PK	Pharmacokinetic	药物代谢动力学
PLT	Platelet	血小板
PR	Partial Response	部分缓解
PT	prothrombin Time	凝血酶原
RBC	Red Blood Cell	红细胞
RCC	Renal cell Carcinoma	肾细胞癌
RECIST	Response Evaluation Criteria in Solid Tumors	实体瘤疗效评价标准

缩略语	英文全称	中文全称
RF	Rheumatoid Factor	类风湿因子
RFS	Recurrent-free Survival	无复发率
RP2D	Recommended Phase 2 Dose	二期临床参考用药量
SAE	Severe Adverse Event	严重不良事件
SAP	Statistic Analysis Plan	统计分析计划
SD	Stable Disease	疾病稳定
SJS	Stevens-Johnson Syndrome	史蒂文斯-约翰逊综合征
SS	Safety Set	安全性分析人群
$T_{1/2}$	Half- life	半衰期
TBIL	Total Bilirubin	总胆红素
TEAE	Treatment Emergent Adverse Event	治疗期不良事件
TEN	Toxic Epidermal Necrolysis	中毒性表皮坏死松解症
TG-Ab	Anti-thyroglobulin Antibodies	抗甲状腺球蛋白抗体
TGI	Tumor Growth Inhibition Value	肿瘤抑制率
TIL	Tumor Infiltrating Lymphocyte	肿瘤浸润性 T 细胞
TKI	Tyrosine Kinase Inhibitor	酪氨酸激酶抑制剂
TP	Total Protein	总蛋白
TPS	Tumor proportion Scores	肿瘤比例评分
TRAE	Treatment Related Adverse Event	治疗相关不良事件
TSH	Thyroid Stimulating Hormone	促甲状腺激素
TT	Thrombin Time	凝血酶时间
TTR	Time to Response	至客观缓解时间
UC	Urothelial Carcinoma	尿路上皮癌
UGLU	Urinary Glucose	尿葡萄糖
ULN	Upper Limit of Normal Value	正常上限
UPRO	Urine Protein	尿蛋白
URBC	Urinary Red Blood Cells	尿红细胞
UREA	Urea	尿素
UWBC	Urinary White Blood Cells	尿白细胞
V	Volume of Distribution	分布体积
WBC	White Blood Cell	白细胞
WHO	World Health Organization	世界卫生组织
γ-GT	Gama-glutamyl Transpeptidase	γ-谷氨酰转肽酶

1 Study Background

1.1 Introduction

With the prolongation of human life expectancy and the change of life behavior, malignant tumor has become a serious threat to human health and the greatest threat to human life. According to data released by the National Cancer Registry (NCCRC) in January 2018, it is estimated that there were approximately 3.840,000 new cancer cases and 2.296,000 cancer deaths in China in 2014. The incidence of lung cancer is the first, about 782,000 new cases. Followed by gastric cancer (410,000 people), colorectal cancer (37,000 people), liver cancer (365,000 people), breast cancer (279,000 people), esophageal cancer (258,000 people). Among all cancer causes of death, lung cancer (27.3%) ranked first, followed by liver cancer (13.9%), gastric cancer (12.8%), esophageal cancer (8.4%), and colorectal cancer (7.8%) [1]. With the further development of aging population in China, the incidence and mortality of cancer will continue to rise. There is a huge unmet medical need for the treatment of advanced cancer in China.[错误!未找到引用源。]

In recent years, tumor immune checkpoint therapy has gradually become a hot research and development, and has made great breakthroughs. Different from traditional anti-tumor therapy, tumor immune checkpoint therapy does not act on tumor cells directly, but improves the function of T cells by blocking the inhibitory signal of T cell proliferation and activation, relieves the tolerance of immune system to tumor cells, and enhances the effective recognition and killing of T cells to tumor cells. Currently, tumor immune checkpoint targets that have shown significant clinical efficacy include Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) and programmed death receptor-1/ligand-1 (PD-1/PD-L1) [2]. However, with the deepening of the research and long-term follow-up of patients, immunotherapy with PD-1/PD-L1 as the main target still has the problem of drug resistance. Although the mechanism of drug resistance is not fully understood, it can be summarized into three categories: (1) insufficient generation of anti-tumor T cells; (2) Deficiency of tumor-specific T cells; (3) Impaired formation of memory T cells [3].[错误!未找到引用源。错误!未找到引用源。]

Lymphocyte Activation Gene 3 (LAG-3) is an important inhibitory receptor of immunoglobulin family, which is expressed on activated T cell lines and NK cells. The main ligand of LAG-3 is MHCII (major histocompatibility complex II) molecules. After

binding to MHC complex, LAG-3 can negatively regulate the proliferation, activation and dynamic balance of T cells, maintain homeostasis and participate in immune regulation, which is closely related to the occurrence and development of tumors. In addition, LAG-3 is expressed on Treg cells accumulating in tumor lesions and suppresses cytotoxic T cells. Preclinical studies have shown that blocking LAG-3 can promote T cell proliferation and enhance the function of cytotoxic T cells. [4]错误!未找到引用源。

The immunosuppressive function of LAG-3 coincides with the mechanism of PD-1 tolerance: LAG-3 not only inhibits the proliferation of CD8 + T cells with anti-tumor activity, but also directly affects their immune function. LAG-3 was found to be strongly associated with the severity of infection, as tumors share several common features with chronic infections: such as chronic antigen exposure and its subsequent development of immune dysregulation, i.e., T cell depletion. Patients with hepatitis B virus (HBV)-specific CD8 + TILs isolated from hepatocellular carcinoma (HCC) show significant upregulation of LAG-3 with consequent functional defects such as decreased production of IFN γ [4]. It is suggested that blocking LAG-3 may play a role in virus infection-related tumors. In addition, LAG-3 enhances the suppressive activity of regulatory T cells, further suppressing immune responses [5]. Blocking the interaction between LAG-3 and MHC II relieved the inhibitory effect of LAG-3 on T cell activation, restored the proliferation and activity of CD8 + T cells, and reduced the number of regulatory T cells. It also increases the sensitivity of T cell immune response. LAG-3 and PD-1 are both immunosuppressive checkpoint receptors, synergistic inhibition of LAG-3 and PD-1 can enhance immune response and inhibit tumor growth.错误!未找到引用源。错误!未找到引用源。

IBI110 is an IgG 4 κ recombinant fully human anti-LAG-3 monoclonal antibody independently developed by Innovent Biologics (Suzhou) Co., Ltd. It is composed of 1322 amino acids, including two heavy chains and two light chains, and is composed of 4 pairs of interchain disulfide bonds and 12 pairs of intrachain disulfide bonds. Molecular formula: C6436H9918N1682O2034S42 (disulfide bond is oxidized).

Available preclinical study results showed that IBI110 showed basically linear kinetics in the most pharmacologically and toxicologically relevant species, cynomolgus monkeys, and non-relevant species, rats, with little accumulation after multiple doses, and high safety. In vitro, IBI110 does not present a risk of cytokine release and hemolysis. In weakly related species mice, the increase in exposure after the last dose was less than dose-proportional, and some animals died, which may be related to drug-induced

immunogenicity, suggesting that immunogenicity should be concerned in clinical trials.

Based on the mechanism of action of IBI110 and preclinical data, it is hypothesized that IBI110 will more effectively inhibit the immune checkpoint signaling axis to achieve anti-tumor effects, which may further improve the efficacy of single-agent immunotherapy, overcome primary resistance, and possibly overcome the problem of resistance after treatment with anti-PD-1/PD-L1 monoclonal antibodies. To meet the urgent clinical needs, clinical studies are conducted to investigate the PK/PD characteristics of IBI110 alone and in combination with sintilimab in humans as well as its efficacy and safety against various solid tumors, especially Non Small Cell Lung Cancer (NSCLC), urothelial cancer and non-clear cell renal cancer. This is the first-in-human clinical Phase 1 study of IBI110. The study was divided into Phase 1a and Phase 1b. Phase 1a is a single-agent dose escalation and single-agent dose expansion of IBI110. Phase Ib is divided into two parts, the first part is the combination dose escalation in combination with sintilimab to determine the combination dose. The second part is a dose expansion study to evaluate efficacy in different cancer types. In addition, other data planned to be evaluated include immunogenicity, PK, pharmacodynamics of IBI110, etc., and to explore the correlation between relevant biomarkers and efficacy, so as to help screen more suitable patients.

1.2 Background of advanced neoplastic disease

Lung cancer

Lung cancer is the first leading cause of death in the world. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases. Although NSCLC patients with specific genetic mutations may benefit from targeted therapies. However, it is still impossible to avoid the emergence of resistance at specific time points. In this case, immunotherapy has entered the clinic and brought durable responses. Immune checkpoint inhibitors, particularly PD-1/PD-L1 inhibitors, exhibit unprecedented efficacy in anti-tumor therapy through a "brake-off" mechanism. Several clinical studies, such as Checkmate017, Checkmate057, Keynote-010, Poplar and OAK, have verified the efficacy of Nivolumab, Pembrolizumab and Atezolizumab in the second-line and above treatment of advanced NSCLC. In addition, encouraging results from the Keynote-024 study further promote the use of checkpoint inhibitors for the first-line treatment of advanced NSCLC with PD-L1 (Tumor Proportion Score, TPS)

expression ≥ 50%. Challenges, however, follow. Only a small proportion of patients (approximately 20%) respond to monotherapy in the absence of a well-defined biomarker to select an appropriate population. Moreover, resistance to PD-1/PD-L1 inhibitors was also observed. In this setting, a durable response is difficult to achieve with a single agent and only covers a small number of patients. [6]错误!未找到引用源。

Small cell lung cancer accounts for about 15%-20% of bronchogenic lung cancer. When small cell lung cancer is diagnosed, about 70% has been in extensive stage. Small cell lung cancer (SCLC) is characterized by high degree of malignancy, rapid cell doubling rate, easy to develop aggressively and distant metastasis. The five-year survival rate of patients with extensive stage is about 6%. At present, the treatment of small cell lung cancer progresses slowly, and the main chemotherapy regimen is etoposide/irinotecan/platinum. Although small cell lung cancer is relatively sensitive to chemotherapy initially, the response rate is about 60-70%, but the vast majority of patients will develop resistance within a few months. Immune checkpoint inhibitors are emerging in small-cell lung cancer. Currently approved immune checkpoint inhibitors in SCLC have been slow to progress, with the only drugs being Atezolizumab (FDA-approved for first-line treatment of extensive-stage SCLC in combination with standard chemotherapy etoposide/carboplatin), Nivolumab (FDA-approved for metastatic SCLC that has been treated with platinum-based chemotherapy and at least one other therapy), and Pembrolizumab (FDA-approved for metastatic SCLC that has been treated with platinum-based chemotherapy and at least one other therapy). Therefore, immunotherapy in small cell lung cancer still has a large space to explore.

Stomach cancer

Gastric cancer is the second most common cancer in our country. Gastric cancer has a high degree of malignancy and poor prognosis. The risk of recurrence of stage Ⅱ and Ⅲ gastric cancer is still about 1/3 within 5 years after adjuvant chemotherapy. In addition, most Chinese gastric cancer subjects have advanced disease at initial diagnosis and lose the chance of cure. The 5-year survival rate of advanced gastric cancer subjects is less than 10%. Chemotherapy drugs for advanced gastric cancer include fluorouracil or its derivatives (capecitabine and S-1), platinum drugs (cisplatin and oxaliplatin), taxanes (paclitaxel and docetaxel) and epirubicin. Some subjects can use targeted drugs, such as trastuzumab in combination with first-line chemotherapy for HER2-positive gastroesophageal junction adenocarcinoma and gastric adenocarcinoma, and anti-

vascular tyrosine kinase inhibitors such as apatinib for gastric cancer subjects who fail second-line chemotherapy. In recent years, immunotherapy has shown some efficacy in advanced gastric cancer. In the KEYNOTE-059 study [7], ORR and median TTR were 15.5% and 16.3 months, respectively, in subjects with positive PD-L1 expression (CPS $\geqslant$ 1), while in subjects with negative PD-L1 expression, ORR and median TTR were 6.4% and 6.9 months, respectively. Based on these results, the FDA expedited approval of Pembrolizumab in September 2017 for use in subjects with PD-L1 positive recurrent or advanced gastric cancer beyond the third line. The ongoing phase III KEYNOTE-062 trial [8] is evaluating the efficacy of Pembrolizumab alone or in combination with cisplatin and capecitabine (or 5-fluorouracil) as first-line treatment in subjects with PD-L1 positive gastric cancer. The ATTRACTION-2 (ONO-4538-12) study [9] was a Phase 3 randomized, double-blind, placebo-controlled clinical trial conducted in Japan, Korea, and Taiwan to evaluate the efficacy and safety of nivolumab in patients with advanced gastric and gastroesophageal junction cancer after multiple lines of therapy. The primary endpoint was overall survival, with a median overall survival of 5.26 months in the nivolumab group and 4.14 months in the placebo group ($p < 0.0001$), and nivolumab significantly reduced the risk of death by 37%. In addition, overall survival at 12 months was also significantly higher in the nivolumab group than in the placebo group (26.2% vs 10.9%). Nivolumab is therefore approved in Japan for advanced gastric and gastroesophageal junction cancer after failure of at least 2 systemic therapies. For the treatment of first-line gastric cancer and gastroesophageal junction cancer, the phase III clinical study Checkmate649 [10] published clinical study results in ASCO in 2020. In the population of subjects with PD-L1 expression CPS $\geqslant$ 5, the median OS of Nivolumab plus chemotherapy group (N=473) and chemotherapy alone group (N=482) was 14.4 months and 11.1 months, respectively; In the population of subjects with PD-L1 expression CPS $\geqslant$ 1, median OS was 13.8 months in the nivolumab plus chemotherapy group (N=789) and 11.6 months in the chemotherapy alone group (N=792), and median PFS was 7.7 months and 6.9 months, respectively, with the primary endpoint of comparing PFS between the two groups in the population of subjects with PD-L1 expression CPS $\geqslant$ 5, 7.7 and 6.0, respectively. The above results determined the efficacy of anti-PD-1 monoclonal antibody combined with chemotherapy in the first-line treatment of gastric cancer, and it was approved by FDA in April 2021 for marketing, but has not been approved in China. On the other hand, gastric cancer in Chinese has its own characteristics, including high incidence of distal gastric cancer, younger age at onset,

and more diffuse gastric cancer. Therefore, it is urgent to explore gastric cancer treatment strategies in line with the actual situation in China, and explore combination therapy with different mechanisms to improve the efficacy of anti-PD-1/PD-L1 monoclonal antibody in gastric cancer.[错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。]

Liver cancer

In 2012, there were 782,000 new liver cancer cases and 745,000 liver cancer deaths worldwide, of which about 50% occurred in China. Primary (70% ~ 90%) hepatocellular carcinoma (HCC) [11] is mainly caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol, diet-related factors and so on. In China, most cases of HCC are caused by chronic HBV infection, which leads to liver cirrhosis and eventually to HCC. Most subjects with HCC have locally advanced or metastatic disease at the time of onset and are not eligible for curative therapy. Such subjects have a poor prognosis, with a median survival time of only 7.9 months in the context of supportive treatment [12], and only 4.2 months for HCC subjects in the Asia-Pacific region mainly caused by viral hepatitis [13]. Therefore, there is an urgent need for effective treatments to meet the needs of subjects with advanced HCC in China and worldwide.[错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。]

Due to the heterogeneity of HCC and the diversity of etiologies, HCC is highly resistant to conventional systemic chemotherapy. Based on the SHARP study [12] and the REFLECT study [14], the multi-targeted kinase inhibitors sorafenib and lenvatinib were approved for marketing in subjects with inoperable advanced HCC. The median OS was 12.3 months and 13.6 months, respectively, and the median Time to Progression (TTP) was 3.7 months and 8.9 months, respectively. On May 29, 2020, FDA approved Roche's two-drug combination of atezolizumab + bevacizumab as the first-line treatment of advanced HCC. Based on the results of IMbrave150 trial, the treatment of HCC has entered a new era of anti-angiogenesis + immunotherapy. The IMbrave 150 study [15] was a global, open-label, multicenter Phase 3 study that enrolled subjects with unresectable, systemically untreated HCC. Subjects were randomized in a 2: 1 ratio to the following 2 arms: subjects in the Atezolizumab + Bevacizumab arm received Atezolizumab 1200 mg + Bevacizumab 15 mg/kg every 3 weeks; Subjects in the sorafenib arm received oral sorafenib 400 mg twice daily. At the time of the primary analysis (29 August 2019), the hazard ratio for death in the atezolizumab plus bevacizumab group versus the sorafenib group was 0.58 (95% CI, 0.42 to 0.79; $P < 0.001$).

At 12 months, overall survival was 67.2% (95% CI, 61.3 to 73.1) in the atezolizumab plus bevacizumab group and 54.6% (95% CI, 45.2 to 64.0) in the sorafenib group. Median progression-free survival was 6.8 months (95% CI, 5.7 to 8.3) and 4.3 months (95% CI, 4.0 to 5.6) in the groups, respectively (hazard ratio for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P < 0.001), and safety was favorable. In September 2020, Atezolizumab + Bevacizumab was approved for the first-line new indication of HCC in China. Therefore, multi-targeted kinase inhibitors targeting VEGF/VEGFR2 pathway, sorafenib or lenvatinib, are still the first-line treatment for advanced HCC in China. The overall objective response rate of single-agent treatment of both is not high, and the improvement of survival is not ideal. Anti-PD-1/PD-L1 mAb combination therapy for advanced HCC showed good safety and encouraging efficacy, which is worthy of further exploration.[错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。]

Breast cancer

Triple negative breast cancer (TNBC) is a kind of breast cancer whose expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) are all negative. The incidence of TNBC accounts for about 1/4 of breast cancer in China [16]. The median progression-free survival of TNBC patients is about 38.5 months, and the median survival is about 43.0 months. Both DFS and OS are lower than those of non-TNBC patients (75.7% vs 79.6%, 86.6% vs 93.5%) [17]. Triple negative breast cancer has a poor prognosis, and there is no targeted or effective targeted therapy at present. Triple negative breast cancer is characterized by relatively rich infiltrating lymphocytes around the tumor, which provides a very good immune microenvironment for the application of immune checkpoint inhibitors. Moreover, the mutation load of triple negative breast cancer is relatively large, which provides the antigen basis for the recognition of immune cells. In addition, the high expression of the immune checkpoint ligand PD-L1 in triple-negative breast cancer tissues provides a good target basis for the application of immune checkpoint inhibitors. Therefore, the effect of immunotherapy on TNBC is currently being actively explored. FDA approved the PD-L1 monoclonal antibody Atezolizumab in combination with nab-paclitaxel for the first-line treatment of PD-L1 positive unresectable locally advanced or metastatic triple negative breast cancer on March 8, 2019. At the same time, the progress of new immune checkpoint inhibitors in triple-negative breast cancer needs to be actively explored to provide more treatment options for patients.[错误!未找到引用源。错误!未找到引用源。]

Cervical cancer

Cervical cancer is the fourth most common malignant tumor in women worldwide and one of the most common gynecologic malignancies [18]. In 2018, there were about 570,000 new cases of cervical cancer and more than 310,000 deaths worldwide, of which China accounted for about 20% (about 106,000 cases) and 15% (about 48,000 cases), respectively [18], [19]. The incidence and mortality of cervical cancer in China are also higher than those in Western developed countries: the incidence of cervical cancer in the United States is the 13th (8.5/100,000) and the 12th (3.2/100,000) in female malignant tumors, while the incidence of cervical cancer in China is the 6th (15.4/100,000) and the 8th (6.9/100,000) in female malignant tumors, with the mortality being two times higher than that in the United States [19]. Although chemotherapy has improved the treatment of patients with metastatic or recurrent cervical cancer, only approximately one-third of patients respond to treatment and the median survival does not exceed 12 months [20]. Therefore, the clinical need for locally advanced, metastatic, recurrent cervical cancer after failure of first-line standard treatment is urgent to be addressed. Pembrolizumab as the first approved PD-1 inhibitor for the treatment of advanced cervical cancer offers an important second-line treatment option for selected patients with limited therapeutic benefit. Immunosuppressant combination therapy has become a new mode of treatment for recurrent and metastatic advanced cervical cancer, which is worthy of further clinical study.[错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。]

Urothelial carcinoma

Urothelial carcinoma is one of the most common malignant tumors of the genitourinary system, and 90% of the urothelial carcinoma occurs in the bladder. In 2014, there were 78,000 new cases and 32,000 deaths of bladder cancer in China, showing an upward trend [1]. About 549,000 new cases and nearly 200,000 deaths occur worldwide each year [21]. Stage IV metastatic disease is associated with a poor prognosis, with a 5-year survival rate of only 5%. Gemcitabine + cisplatin regimen is one of the first-line chemotherapy regimens for advanced bladder urothelial carcinoma, with high response rate, tolerable adverse reactions and an expected survival of 9 to 15 months. Most patients eventually develop disease progression after platinum-based chemotherapy and require further treatment. Single-agent chemotherapy, such as paclitaxel, docetaxel, gemcitabine and pemetrexed, is used in traditional second-line treatment, but has low efficacy and high toxicity. In the past 30 years, there has been no major breakthrough in the treatment

of advanced urothelial carcinoma, especially the second-line treatment is still in the exploratory stage. In recent years, immune checkpoint inhibitors have been found to be highly active in tumors with high PD-L1 expression and in tumors with high somatic mutation load. According to the Cancer Genome Atlas, bladder cancer has the third highest mutation rate, next only to lung cancer and melanoma. This fact has prompted the development of immune checkpoint inhibitors, particularly those targeting PD-1 or PD-L1, after platinum failure. The results of these studies led the FDA to approve five antibodies for urothelial cancer over a 1-year period, including Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab, and Avelumab. Predictive biomarkers for effective PD-1/PD-L1 inhibitors in advanced urothelial cancer are still lacking [22]. At the same time, the rationale for non-response or resistance to immunotherapy needs to be further addressed.[错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。]

Renal cell carcinoma

Renal Cell Carcinoma (RCC) is the most common malignant renal tumor, accounting for about 85% of all patients with renal cell carcinoma (RCC). In recent years, the incidence rate has increased year by year. RCC is not sensitive to chemotherapy, the overall response rate is about 6% on average, and the overall survival of patients has not improved. In recent years, the targeted therapy of advanced renal cell carcinoma has made great progress. Targeting different targets such as VEGFR, PDGFR, FGFR, c-MET, mTOR, etc. Sorafenib, sunitinib, axitinib, everolimus and pazopanib have been approved for targeted therapy of advanced renal cancer. At present, 11 targeted drugs have been approved by FDA for the treatment of advanced renal cancer, and advanced renal cancer has become the largest number of targeted drugs in the market [23]. Great breakthroughs have also been made in immunotherapy. The advent of immune checkpoint inhibitors such as PD-1, PD-L1, and CTLA-4 inhibitors has revolutionized the systemic treatment of many malignancies, including RCC, and clinical trials have also demonstrated efficacy and improved survival. But only a few patients responded. Combination immunotherapy is an active area of exploration and several clinical studies are ongoing. Some new immunotherapy targets such as LAG-3 are also being explored [24]. In 2004, the World Health Organization (WHO) classified the types of renal cell carcinoma: clear cell renal cell carcinoma (ccRCC) (> 75%), non-clear cell renal cell carcinoma (nccRCC) accounts for about 25%. Compared with common ccRCC, nccRCC has different pathogenesis, histological manifestation, clinical progression and outcome. Although the incidence is

low, there are few effective treatment strategies. Although multiple targeted agents are approved for the treatment of renal cell carcinoma, for nccRCC, the response rates of these agents are all significantly lower than for clear cell renal cancer. The survival of nccRCC is still poor with targeted drugs, although there is some improvement in the survival of nccRCC. A total of 43 patients with pathologically determined metastatic nccRCC or ccRCC with > 20% sarcomatoid and/or rhabdoid differentiation in tumor specimens were treated with PD-1/PD-L1 inhibitors in one study. The overall ORR was 19% in all groups, and the proportion of stable disease was 33%. The ORR varied by histology, being 43% for ccRCC with > 20% sarcomatoid and/or rhabdoid differentiation in tumor specimens, 29% for papillary RCC, and only 1 patient with translocation RCC achieved an objective response, with no patients with chromophobe RCC and unclassified RCC achieving an objective response. The ORR in patients treated with PD-1/PD-L1 inhibitor monotherapy was 13%, with an ORR of 18%, 50%, and 33% in patients with papillary RCC, ccRCC with sarcomatoid and/or rhabdoid differentiation in > 20% of tumor specimens, and translocated RCC, respectively [25]. Thus, differences in the efficacy of PD-1/PD-L1 inhibitors in patients with different histologies of RCC can be seen. How to improve the efficacy of immune checkpoint inhibitors in nccRCC remains to be further explored.[错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。]

Ovarian cancer

Ovarian cancer is the leading cause of death for women in developed countries, leading to about 184,000 deaths every year in the world [26], and it is increasing year by year in China. Because of the special anatomical location of the ovary, the early symptoms or signs of ovarian cancer are not obvious, leading to the majority of patients at the time of diagnosis of advanced disease [27]. The current first-line standard treatment for advanced ovarian cancer is platinum-based chemotherapy with poly (ADP-ribose) polymerase (PARP) inhibitors and/or anti-vascular endothelial growth factor (VEGF) inhibitors as subsequent maintenance therapy. However, subjects who are refractory to platinum (defined as disease progression during platinum-based therapy and maintenance therapy; or failure to achieve significant tumor shrinkage during platinum-based chemotherapy; or tumor recurrence within 6 months of the end of platinum-based therapy) lack effective subsequent therapy [28]. Tumor-infiltrating lymphocytes (TILs) can be observed around the tumor in patients with ovarian cancer by pathological examination, which provides the basis of immune microenvironment for the application of

immunotherapy in ovarian tumor. However, currently, only Pembrolizumab is recommended by guidelines for ovarian tumor patients with Microsatellite Instability-High (MSI-H), Mismatch Repair-Deficient (dMMR) or Tumor Mutational Burden (TMB) ≥ 10 mutations/million bases and no other suitable treatment regimen [29]. Several clinical studies are ongoing to explore the feasibility of immune checkpoint inhibitors in ovarian tumor patients.错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is one of the most common malignant tumors in head and neck, which originates from the mucosa of nasopharynx. About 5% ~ 8% of patients with nasopharyngeal carcinoma (NPC) have distant metastasis at diagnosis, and 30% ~ 60% of patients with locally advanced NPC will have distant metastasis. The prognosis for patients with recurrent or metastatic NPC is very poor, and the first-line treatment for recurrent or metastatic NPC is platinum-based two-agent chemotherapy (gemcitabine and cisplatin). OS of 29.1 months, ORR of 64% and PFS of 7 months were achieved in patients treated with first-line therapy. However, the 5-year overall survival rate for patients with overall advanced disease remains less than 10%. In addition, for patients who have failed first-line platinum-based chemotherapy, there is no standard post-line treatment regimen in China. The median survival time of patients who received second-line therapy or more was only 11.5 ~ 12.5 months. There is an unmet clinical need.

The most common pathological type in China is non-keratinizing carcinoma, which is highly associated with Epstein-Barr virus (EBV) infection. EBV DNA detection in blood can be used as an effective means of screening for nasopharyngeal carcinoma [30]. Since Epstein-Barr virus (EBV), which is closely related to NPC, can induce cancer cells to express high levels of PD-L1 [31], and EBV antigens contribute to immune evasion, anti-PD-1 mAbs have potential therapeutic utility in recurrent or metastatic NPC. There are several anti-PD-1/PD-L1 immunotherapy in the second-line and beyond population of recurrent and metastatic NPC, but single agent immunotherapy with known results has poor efficacy in the second-line treatment of NPC, similar to single agent chemotherapy, with ORR between 20% and 30%. The interim analysis results of a phase III study JUPITER-02 showed that toripalimab (anti-PD-1 monoclonal antibody) combined with gemcitabine/cisplatin in the first-line treatment of patients with recurrent or metastatic nasopharyngeal carcinoma significantly prolonged the progression-free survival compared with the standard first-line treatment of gemcitabine/cisplatin, and achieved the

expected primary study endpoint. The results of a multicenter, open-label, phase II pivotal registration clinical study POLARIS-02 showed: after 190 patients with recurrent/metastatic nasopharyngeal carcinoma who had previously failed systemic treatment received Toripalimab monotherapy, the median follow-up was 387.5 days, and the primary study endpoint ORR reached 20.5%; The secondary endpoints were median duration of response (mDOR) of 12.8 months, median progression-free survival (mPFS) of 1.9 months, and median overall survival (mOS) of 17.4 months. Tumors regressed in nearly half of the patients (45.6%), with 30% shrinkage ≥ 30%. In addition, in 92 patients who had failed at least 2 lines of systemic chemotherapy, toripalimab monotherapy had an ORR of 23.9%, a median DOR of 21.5 months, a DCR of 41.3%, and a median OS of 15.1 months [32]. Based on the results of this study, Toripalimab was approved by CFDA in February 2021 and formally approved for the treatment of patients with recurrent/metastatic NPC who failed to receive two or more lines of systemic therapy. Toripalimab is also the only immunotherapy drug approved for the treatment of NPC worldwide. It is foreseeable that anti-PD-1 monoclonal antibody will be increasingly used in recurrent or metastatic NPC. However, there is still a lack of effective treatment options for patients with recurrent or metastatic NPC who have progressed on prior anti-PD-1/PD-L1 therapy.[错误!未找到引用源。错误!未找到引用源。错误!未找到引用源。]

Melanoma

Melanoma has a high incidence in Europe and America, but a relatively low incidence in China, with an annual incidence of about 20,000 people. However, in recent years, the number of melanoma cases in China has increased significantly. In recent years, a breakthrough has been made in the treatment of advanced melanoma. In metastatic or unresectable melanoma with BRAF mutation, tyrosine kinase inhibitors targeting BRAF mutation (Vemurafenib and Dabrafenib) as single agent or combined with MEK inhibitors (Trametinib and Cobimetinib) have been approved as first-line standard treatment by US FDA; Two classes of immune checkpoint inhibitors (the anti-CTLA-4 monoclonal antibody Ipilimumab and the anti-PD-1 monoclonal antibody Nivolumab/Pembrolizumab) have been approved by the US FDA as first-line standard therapy for BRAF wild-type metastatic or unresectable melanoma as single agents or in combination [33]. At present, the standard treatment for patients with advanced melanoma in China is dacarbazine chemotherapy or high-dose interleukin-2, but the response rate is low, the survival benefit is limited, and the 5-year survival rate for patients with advanced melanoma is less than

5% [34].错误!未找到引用源。错误!未找到引用源。

1.3 Immune Checkpoint Inhibitors

Immune checkpoints are a class of immunosuppressive molecules. Their physiological function is to regulate the intensity and breadth of the immune response, thereby avoiding damage and destruction of normal tissues. Tumor cells often use the characteristics of immune checkpoints to escape the attack of immune cells. Currently, immune checkpoints that have been clinically validated include CTLA-4 and PD-1/PD-L1. Immune checkpoint inhibitors targeting CTLA-4 and PD-1/PD-L1 have good safety and broad indications, and have good clinical application prospects.

Currently, 6 PD-1/PD-L1 products have been approved by US FDA for marketing, including Nivolumab (trade name: OPDIVO), Pembrolizumab (trade name: KEYTRUDA), Atezolizumab (trade name: TECENTRIQ), Durvalumab (trade name: IMFINZI), AstraZeneca, Avelumab (trade name: BAVENCIO), and Cemiplimab (trade name: Libtayo). Indications include advanced melanoma, advanced NSCLC, advanced classical Hodgkin lymphoma, advanced renal cell renal carcinoma and advanced urothelial carcinoma, advanced head and neck cancer, advanced colorectal cancer, metastatic/locally advanced cutaneous squamous cell carcinoma, etc. In addition, there are a number of other indications that are currently in phase 3 clinical studies or marketing submissions. Among them, Nivolumab (nivolumab) and Pembrolizumab (pembrolizumab) are also approved for marketing in China for the second-line treatment of EGFR-and ALK-negative advanced NSCLC and unresectable or metastatic melanoma after failure of first-line treatment, respectively.

The marketing of these drugs confirms the increasing importance of CTLA-4 and PD-1/PD-L1 immune checkpoint inhibitors in tumor immunotherapy.

Checkpoint inhibitors that target PD-1/PD-L1 are then challenging. For patients without definitive biomarker screening, only approximately 20% respond to monotherapy [6]. Both primary and secondary resistance to anti-PD-1/PD-L1 antibodies have also been observed [35].错误!未找到引用源。错误!未找到引用源。

Unlike these targets, LAG-3 is mainly expressed on activated T cells, NK cells, B cells, and dendritic cells, but not on resting T cells, and has homology to CD4. LAG-3 has a higher affinity for MHC II than CD4, but a different binding site. The binding of LAG-3 to MHC II inhibits the proliferation and differentiation of T cells and down-

regulates immune responses. LAG-3 expressed on the surface of DC can enhance the ability of antigen presentation by binding to MHCII. Lsectin can also bind to LAG-3 and inhibit anti-tumor immune response by inhibiting IFN-γ secretion from antigen-specific effector T cells [4].错误!未找到引用源。

Blockade of LAG-3/MHC II is a new concept in the clinic, and there are no approved drugs, and a series of LAG-3/MHC II-targeted therapies are undergoing preclinical and early clinical studies. LAG-3 is a new target for cancer immunotherapy, and there are three anti-LAG-3 monoclonal antibodies with early clinical data. They are BMS-986016 (BMS, fully human IgG4), LAG525 (Novartis, human IgG4) and MK-4280 (Merck), which are mainly used for anti-tumor therapy.

The results of an open-label Phase 1/2 a study [36] evaluating the safety, tolerability, and efficacy of BMS-986016 as monotherapy or in combination with Nivolumab (anti-PD-1 monoclonal antibody) in subjects with advanced solid tumors showed that as of 07 April 2017, a total of 212 subjects were enrolled, including 55 melanoma patients who progressed after prior anti-PD-1/PD-L1 therapy. Among evaluable subjects (n=48), the objective response rate (ORR) was 13%. "For subjects with ≥ 1% LAG-3 expression in tumor-associated immune cells at tumor margins (n=25), the ORR was approximately 3-fold higher than for subjects with < 1% LAG-3 expression (n=14) (20% vs. 7.1%)." The most common (≥ 5%) TRAE were fatigue, diarrhea, and pruritus. The most common (> 1 patient) Grade 3/4 TRAE were colitis, amylase increased, conjunctivitis, AST increased, and lipase increased. "Among all subjects (n=212), 6 subjects discontinued treatment due to TRAE: pericarditis (Grade 2), colitis (Grade 3), hepatitis (Grade 3), aseptic meningitis (Grade 3), pancreatitis (Grade 3), and lipase increased (Grade 4) in 1 subject each." There were no treatment-related deaths. The safety profile of BMS-986016 in combination with nivolumab was consistent with the safety profile of nivolumab monotherapy.错误!未找到引用源。

Study LAG525X2101C [37] was an open-label Phase I/II study of LAG525 as monotherapy and in combination with Spartalizumab (anti-PD-1 mAb) (n=255). As of January 15, 1 case of complete response (CR) and 11 cases of partial response (PR) occurred among 121 evaluable subjects. CR subjects with thymoma were treated with LAG525 240 mg + Spartalizumab 300 mg Q3W. PRs occurred in mesothelioma (2), triple negative breast cancer (2), nasopharyngeal carcinoma (1), adrenocortical carcinoma (1), cervical carcinoma (1), urothelial carcinoma (1), gastric cancer (1), prostate cancer (1),

and solid tumor of unknown primary site (1). One additional mesothelioma subject experienced a PR after the data cutoff date. Several subjects receiving combination therapy had a response greater than 500 days. In terms of adverse events: The most common Treatment Related Adverse Event (TRAE) following LAG-525 monotherapy were fatigue (9%) and nausea (8%), and the most common TRAE following LAG-525 in combination with Spartalizumab were fatigue (19%), diarrhea (16%), and nausea (12%). Serious adverse events occurred in 7 subjects each in the LAG525 monotherapy and combination treatment groups. Dose escalation did not reach the maximum toxic dose and was generally well tolerated. The results suggest that the combination is more effective and well tolerated than the single drug. Phase II clinical studies are ongoing.[错误!未找到引用源。]

MK-4280 is a humanized, IgG4, anti-LAG-3 monoclonal antibody that prevents the binding of LAG-3 to its primary ligand, MHC class II molecules. Preliminary Phase 1/2 safety and efficacy data of MK-4280 were published by Merck at the Society for Cancer Immunotherapy (SITC) in November 2018 [38]. In this open-label, multi-arm, multi-center, dose-finding Phase 1/2 clinical registration study (NCT02720068), Merck is exploring anti-LAG-3 therapy. MK-4280 was evaluated as monotherapy (n=18) and in combination with Keytruda (n=15) in 33 subjects with metastatic solid tumors who had failed standard treatment regimens. Preliminary data showed that 1 partial response was observed in the single-agent group (6%, n=1/18) and 4 in the combination group (27%, n=4/15). The disease control rates were 17% and 40% in the single-agent and combination groups, respectively. Safety: MK-4280 was well tolerated as monotherapy and in combination with Keytruda and had a manageable safety profile at all dose levels with no occurrence of dose-limiting toxicities. Treatment-related adverse events (TRAE) occurred in 61% of patients in the single-agent group and 53% of patients in the combination group, with grade 3 or 4 toxicities occurring in 6% of patients in the single-agent group and 20% of patients in the combination group. Treatment interruptions occurred in 6% of the monotherapy group and 13% of the combination group. The most common TRAE (incidence $\geqslant$ 10%) were fatigue and arthralgia in the monotherapy group and fatigue, pyrexia, pruritus, and maculopapular rash in the combination group. MK-4280 is currently being evaluated as monotherapy and in combination with Keytruda for the treatment of solid tumors and hematological malignancies.[错误!未找到引用源。]

In summary, as immunotherapy is becoming the standard of care, there are

challenges with immunoassays targeting PD-1/PD-L1 as the primary target. For patients without definitive biomarker screening, only approximately 20% will respond to monotherapy. At the same time, the phenomenon of primary resistance and secondary resistance to anti-PD-1/PD-L1 antibodies has also been observed. As a result, an increasing number of patients will be refractory or relapsed after treatment with anti-PD-1/PD-L1 antibodies, and based on the results of the phase I/II studies described above, in patients refractory to anti-PD-1/PD-L1 antibodies, the combination of anti-LAG-3 antibodies may help resolve the problem of drug resistance and restore the function of depleted T cells, which may help patients to benefit more. The high expression of LAG-3 on TILs was significantly correlated with the high expression of PD-1 on TILs and PD-L1 on tumor cells. LAG-3 is associated with poor prognosis. LAG-3 positivity or both LAG-3 and PD-L1 positivity were associated with early postoperative recurrence. Study CA224-020 also suggested that subjects with ≥ 1% LAG-3 expression on tumor-associated immune cells within the tumor (n=25) had an approximately 3-fold higher ORR (20% versus 7.1%, respectively) compared to subjects with < 1% LAG-3 expression (n=14). It is suggested that the expression of LAG-3 can be used as a biomarker to select more suitable patients, which has important clinical value.

1.4 Study drug

IBI110 is an original recombinant fully human anti-lymphocyte activation gene 3 (LAG-3) monoclonal antibody developed by Innovent Biologics (Suzhou) Co., Ltd., which belongs to Class 1 innovator drug. This product can directly combine with LAG-3 on T cells, block the interaction between LAG-3 and MHC II, relieve the inhibitory effect of LAG-3 on T cell activation, and enhance the anti-tumor immune response of T cells. In addition, LAG-3 and PD-1 are both immunosuppressive checkpoint receptors, and synergistic inhibition of LAG-3 and PD-1 can enhance immune response and inhibit tumor growth.

Molecular structure: IBI110 is a recombinant fully human IgG 4 κ -type monoclonal antibody composed of 1322 amino acids, including two heavy chains and two light chains, and is composed of 4 pairs of interchain disulfide bonds and 12 pairs of intrachain disulfide bonds. Among them, the heavy chain is γ 4 type, composed of 446 amino acids; The light chain is of the kappa type and consists of 215 amino acids. The IBI110 heavy chain contains an N-glycosylation site at asparagine at position 297 of the heavy chain. The intact theoretical molecular weight of IBI110 is 147605.0 Da (G0F/G0F glycoform) and the measured molecular weight is 147605.8 Da, and its cleaved theoretical molecular

weight is 144716.3 Da and the measured molecular weight is 144717.0 Da; The theoretical molecular weight of heavy chain is 50303.4 Da (G0F glycoform), the observed molecular weight is 50302.9 Da, and the theoretical molecular weight of cleaved sugar is 48859.0 Da, the observed molecular weight is 48858.7 Da; The theoretical mass of the light chain is 23503.1 Da and the observed mass is 23502.3 Da. The observed intact, heavy and light chain masses of IBI110 are in agreement with the theoretical masses. The molecular formula of IBI110 is C6436H9918N1682O2034S42 (the disulfide bond is oxidized).

1.4.1 IBI110 Preclinical Study Results

During the IND (Investigational New Drug) study, adequate pharmacological and toxicological studies, including in vitro and in vivo pharmacodynamic studies, pharmacokinetic studies and toxicological studies, were conducted to elucidate the mechanism of action, pharmacodynamic, pharmacokinetic and toxicological characteristics of the product, and to fully assess the preclinical safety and efficacy of the product. Details are as follows:

- Affinity study: The binding capacity of IBI110 to human and cynomolgus monkey LAG-3 was equivalent, with KD of 1.30 E-10 ± 4. 63E-11 and 1.67 E-10 ± 6. 60E-11 M, respectively, which was about 20 times higher than that of mouse LAG-3 (2.65 E-09 ± 6. 07E-10 M). IBI110 did not bind to rat LAG-3. Therefore, cynomolgus monkey was the most relevant species for pharmacokinetic and toxicological studies of IBI110, while mouse was the weakly relevant species. IBI110 does not bind to human CD4, CD28, CD160, 2B4, PD-1, PD-L1, CTLA-4, TIM-3, BTLA, B7-1.

- In vitro activity study: The EC50 of IBI110 binding to human LAG-3 on HEK293-hLAG-3 cells was 0.305 nM, the EC50 of IBI110 binding to activated human CD4 + T cells was 0.019 nM, and the EC50 of IBI110 binding to cynomolgus monkey PBMC was 0.022 nM; The IC50 of IBI110 in blocking hLAG-3/MHCII binding at molecular level was 0.259 nM. The IC50 of IBI110 for blocking human LAG-3/MHCII binding at the cellular level was approximately 4.622 nM; IBI110 blocked MHCII/LAG-3 binding and activated downstream signaling with an EC50 of 0.903 nM. The RO for 50% occupancy of LAG-3 receptors on activated human CD4 + T cells by IBI110 was 0.041 nM; IBI110 alone did not promote IL-2 secretion from human CD4 + T cells, but in combination with sintilimab, it dose-dependently promoted IL-2 secretion from

CD4 + T cells, slightly superior to sintilimab; The Fc terminus of IBI110 only binds with strong affinity to FcRn and has no ADCC or CDC activity.

- In vivo activity study: in MC38-hPD-L1 (mouse colon cancer cells expressing hPD-L1) tumor-bearing mice model, neither IBI110 nor relatlimab alone had significant anti-tumor effect, while in combination with 1 mg/kg 11430 (anti-PD-1 antibody, which binds to mouse PD-1), the anti-tumor effect of IBI110 was superior to that of relatlimab at the same dose level, with TGI% of 98% and 50% at 1 mg/kg and 82% and 51% at 10 mg/kg, respectively.

- Pharmacokinetics: In the pharmacokinetic/toxicokinetic study, IBI110 showed basically linear kinetics in SD rats and cynomolgus monkeys within the dose range of 3-30 mg/kg, and basically no accumulation in animals after multiple doses; Within the dose range of 10 ~ 200 mg/kg, the exposure and dose increase ratio of IBI110 in SD rats and cynomolgus monkeys were basically the same, and there was basically no gender difference and accumulation. Within the dose range of 20 ~ 150 mg/kg, the exposure of IBI110 in BALB/c mice increased less than dose ratio after the third dose, and the exposure in females was slightly higher than that in males, without significant accumulation. The decreased exposure after multiple doses may be caused by anti-drug antibodies.

- Toxicology Studies: in toxicology studies, SD rats and cynomolgus rats were administered a single intravenous dose of 200 and 400 mg/kg IBI110, with a maximum tolerated dose (MTD) of 400 mg/kg. After repeated intravenous injection of 10, 50 and 200 mg/kg IBI110, the No Observed Adverse Effect Level (NOAEL) was 200 mg/kg in female SD rats, 50 mg/kg in male SD rats and 200 mg/kg in cynomolgus monkeys, indicating a high safety of IBI110 in the most relevant species, cynomolgus monkeys and non-relevant species, rats. In the 2-week repeated-dose toxicity study at 20, 50 and 150 mg/kg, some mice in each group showed hypoactivity after the third dose, and 3 and 1 male mice in 20 and 150 mg/kg groups died respectively, which may be related to the immunogenic response caused by IBI110. In vitro, IBI110 does not present a risk of cytokine release and hemolysis.

1.5 Risk Benefit Assessment

The risk/benefit assessment is based on the results of preclinical PK, PD, and

toxicology studies. IBI110 demonstrated anti-tumor efficacy in anti-tumor efficacy studies in tumor-bearing mice. The NOAEL of IBI110 was 200 mg/kg when administered intravenously to cynomolgus monkeys at doses of 10, 50 and 200 mg/kg once weekly for 3 consecutive times, indicating a good safety profile.

Study CA224-020 suggested that the most common Grade 3/4 treatment-related adverse events (TRAE) with anti-LAG-3 antibodies in combination with anti-PD-1 antibodies were colitis, amylase increased, mucosal inflammation, AST increased, and lipase increased. No treatment-related deaths were reported. The safety profile of the combination was consistent with that of single-agent nivolumab.

"Phase I/II clinical study of LAG525 in combination with Spartalizumab, adverse events: dose-limiting toxicities (Grade 3 ascites, lipase increased, vomiting; Grade 4 acute kidney injury in the LAG525 monotherapy group; Grade 3 hyperglycemia, pneumonia, brain tumor edema, asthenia; Grade 4 autoimmune hepatitis in the combination group) occurred in 4 subjects each in the single-agent group and the combination group, and were not dose-related." The common adverse events in the single-agent group were: fatigue (9%) and nausea (8%); In the combination group: fatigue (19%), diarrhea (16%), and nausea (12%); grade 3 or 4 adverse events occurred in 8% of patients in the monotherapy group and 8% of patients in the combination group. Increasing approximately with increasing dose of LAG525. No maximum tolerated dose (MTD) occurred in either the monotherapy or combination groups, and the overall tolerability was good. The results suggest that the combination is more effective and well tolerated than the single drug.

Based on the mechanism of action of this product and the clinical study safety information of products with the same mechanism, it is expected that the adverse events that may occur during the clinical trials of this product are mainly various immune inflammations caused by immune system activation, such as colitis, pneumonia, hepatitis, renal insufficiency and endocrine system inflammation. "Based on the available clinical data of anti-LAG-3 monoclonal antibody drugs, the drug is well tolerated and only a small proportion of subjects will discontinue the drug due to adverse events." Because the early symptoms of immune-related adverse events are variable, the investigator should pay special attention to the early symptoms and signs of various immune-related reactions in the clinical study, refer to the Management Manual for Immune-related Adverse Events provided separately by the sponsor, adjust the dose and give corresponding effective treatment according to Section 5.3 of the protocol, so as to reduce the risk of the subjects

using the drug. In addition, attention should be paid to exclude the subjects with autoimmune diseases in the clinical trial, so as to avoid aggravation of the original diseases caused by the activation of the immune system.

2 Study Objectives

2.1 Primary Objective

- To assess the safety and tolerability of IBI110 alone or in combination with sintilimab in subjects with advanced tumors.
- To assess the anti-tumor activity (per RECIST V1.1) of IBI110 alone or in combination with sintilimab in subjects with advanced tumors.

2.2 Secondary Objectives

- To evaluate the pharmacokinetic (PK) profile of IBI110 alone or in combination with sintilimab in subjects with advanced tumors.
- To evaluate the pharmacodynamic profile of IBI110 alone or in combination with sintilimab in subjects with advanced tumors.
- To assess the immunogenicity of IBI110 alone or in combination with sintilimab in subjects with advanced tumors.

2.3 Exploratory Objectives

- To explore the efficacy of IBI110 alone or in combination with sintilimab in subjects with advanced tumors using iRECIST.
- Phase Ia: to explore the expression of LAG-3 in tumor tissues.
- Phase Ib: to explore the amount of LAG-3 and PD-L1 expression in tumor tissue as potential biomarkers for predicting response.

3 Overall Study Design

This is an open-label phase 1 study to evaluate the safety, tolerability, and efficacy of a fully human recombinant anti-lymphocyte activation gene-3 (LAG-3) monoclonal antibody (IBI110) alone or in combination with sintilimab in subjects with advanced malignancies. The study was divided into Phase 1a and Phase 1b.

Phase 1a is divided into two parts: Part 1. IBI110 monotherapy dose escalation; Part 2. IBI110 monotherapy dose expansion. Study to assess the safety, tolerability, and efficacy of IBI110 as a single agent.

Part1 is an increasing dose of IBI110 monotherapy at 0.01 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg.

Part 2 is intended to use a fixed dose of IBI110 200 mg IV infusion. Enrollment in Cohort A1: advanced solid tumors related to viral infection that failed standard treatment: hepatocellular carcinoma related to hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, nasopharyngeal carcinoma and gastric cancer related to Epstein-Barr virus (EBV) infection, advanced solid tumors related to human papillomavirus (HPV) infection, such as cervical cancer, head and neck squamous cell carcinoma, etc.; Enrollment in Cohort A2: Other advanced solid tumors: including epithelial ovarian cancer, endometrial cancer, malignant melanoma (acral or cutaneous), and triple negative breast cancer. Subjects will be treated with IBI110 200 mg IV Q3W, and subjects who experience disease progression (based on RECIST V1.1) during monotherapy will receive sintilimab combination therapy (IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W) based on PS assessments at the investigator's discretion (see Section 5.1. 2) until disease progression (based on iRECIST, or based on RECIST V1.1 but not 5.1. 2), lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first. The total duration of treatment will not exceed 24 months (including the total duration of monotherapy and combination therapy, and if disease response or patient benefit exceeds 24 months, the investigator and sponsor will discuss whether the subject will continue to receive treatment).

Phase Ib is divided into two parts: 1. "3 +3" combination dose escalation of IBI110 in combination with sintilimab; 2. Combination dose expansion of IBI110 in combination with sintilimab ± other treatments.

Part 1: Combination Dose Escalation

Starting dose: IBI110 0.3 mg/kg in combination with sintilimab 200 mg for study enrollment. "3 +3" combination dose escalation was performed. The DLT observation period is within 28 days (4 weeks) after the first dose.

Dose Cohort 1: IBI110 0.3 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 2: IBI110 0.7 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 3: IBI110 1.5 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 4: IBI110 3.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 5: IBI110 5.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 6: IBI110 8.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 7: IBI110 10.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Group 8: IBI110 20.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Part2: Combination Dose Expansion

The study will be conducted in the first stage of "3 +3" dose escalation, and the appropriate dose of IBI110 combined with sintilimab ± other treatments will be selected after data analysis to conduct dose expansion study. To investigate the antitumor activity of IBI110 in combination with sintilimab ± other treatments in different cancer types. IBI110 RP2D IV Q3W in combination with sintilimab 200 mg IV Q3W ± other treatments in 14 cohorts:

Cohort B: Advanced hepatocellular carcinoma (HCC) without prior systemic therapy.

Cohort C: Recurrent or metastatic cervical cancer that has failed systemic therapy.

Cohort D: Advanced NSCLC without driver mutations that have not received prior systemic therapy.

Cohort E: Advanced small cell lung cancer who have received and failed at least one line of standard therapy.

Cohort F: Advanced urothelial cancer (UC) who have received and failed at least one prior systemic therapy.

Cohort G: Advanced renal clear cell renal cancer that has received and failed at least one prior systemic therapy.

Cohort H: Advanced hepatocellular carcinoma after failure of immunotherapy.

Cohort I: Advanced nasopharyngeal carcinoma after failure of immunotherapy.

Cohort J: HER2-negative advanced gastric (GC) or gastroesophageal junction (GEJ) cancer not previously treated systemically.

Cohort K: EBV infection-associated advanced gastric (GC) or gastroesophageal junction (GEJ) cancer that has failed standard therapy.

Cohort L: Advanced Triple Negative Breast Cancer (TNBC) after failure of standard therapy.

Cohort M: Advanced ovarian cancer after failure of platinum-containing chemotherapy regimen.

Cohort N: Locally advanced/metastatic melanoma not amenable to local therapy.

Cohort O: Advanced nasopharyngeal carcinoma (NPC) after failure of systemic therapy.

The above cohorts of IBI110 and sintilimab may be treated for up to 2 years or until disease progression, intolerable toxicity, withdrawal of consent, or other reasons for discontinuation of study treatment, whichever occurs first, and other drugs may be used at the discretion of the investigator until disease progression, intolerable toxicity, withdrawal of consent, or other reasons for discontinuation of study treatment, whichever occurs first.

During or after enrollment of each cohort, the sponsor will adjust the characteristics of the subsequent enrollment population (e.g., LAG-3 expression) based on the available efficacy data.

3.1 Design Rationale

This study is an open-label phase I study of IBI110 alone and in combination with sintilimab in subjects with advanced tumors to observe the safety, tolerability and anti-tumor activity of IBI110 alone and in combination with sintilimab as well as exploratory study of biomarkers.

3.1.1 Dose Selection Rationale

3.1. 1.1 Dose Selection Considerations for Escalation Studies

The recommended clinical starting dose of IBI110 is 0.01 mg/kg.

- The starting dose of IBI110 is based on a comprehensive consideration of in vivo active MABLEs, NOAELs in sensitive species, and clinical safety and efficacy information for the same target species.

Pharmacokinetics/Toxicokinetics:

- After a single dose of IBI110 in cynomolgus monkeys within the dose range of 3-200 mg/kg, the pharmacokinetics of IBI110 was linear; Clearance in cynomolgus monkeys was about 0.0324 L/day/kg and V1 was about 0.049 L/kg; Using the Allometric Scaling method, using indices of 0.85 and 1.0 for clearance and volume of distribution, respectively, the predicted human clearance is approximately 0.0204 L/day/kg and V1 is approximately 0.049 L/kg.

In vivo activity studies:

- 1 mg/kg, Q3D alone (total dose 4 mg/kg), Tumor Growth Inhibition Value (TGI) in MC38 tumor model was 29%; 10 mg/kg, Q3D alone (total dose 40 mg/kg), tumor inhibition (TGI) in MJ-1 tumor model was 3%; The equivalent HED for a dose of 4 mg/kg in mice is approximately 0.3 mg/kg (body surface area method) or 4 mg/kg (body weight method). The starting dose equivalent to the 40 mg/kg mouse dose was approximately 0.8 mg/kg (body surface area method) or 10 mg/kg (body weight method), respectively. The proposed starting dose of 0.1 mg/kg provides a safety margin of > 3-fold (body surface area method) and > 40-fold (body weight method), respectively.

In vitro and toxicological studies:

- The affinity parameter KD of IBI110 for human and cynomolgus monkey LAG-

3 antigen was 0.0304 nM and 0.0157 nM, respectively. The cynomolgus monkey is a sensitive species for IBI110.

- The NOAEL of IBI110 in cynomolgus monkeys following multiple doses (once weekly for a total of 5 doses) was 200 mg/kg and the HED was approximately 16.2 mg/kg (body surface area) and 200 mg/kg (body weight), respectively. The recommended starting dose of 0.1 mg/kg provides a 162-fold (body surface area method) and 2000-fold (body weight method) safety factor, respectively.
- The NOAEL of 200 mg/kg in cynomolgus monkeys produced an AUC0-28 of > 15947.2 Day * μg/mL, corresponding to an HED of approximately 316.8 mg/kg. The recommended starting dose provides a safety factor of approximately 3168-fold.

Evaluation of clinical safety, efficacy and cytokine release of like product:

- The co-target variety Relatlimab (BMS-986016) 80 mg + Nivolumab 240 mg was well tolerated, with positive antitumor activity and a safety profile comparable to nivolumab alone. A comparative study of cytokine release by peripheral blood and peripheral blood mononuclear cells (PBMC) from healthy volunteers showed that the effect of IBI110 on cytokine release by human whole blood and human PBMC was similar to that of the Relatlimab antibody.

Based on these analyses, a sub-efficacious dose of IBI110 is proposed as the clinical starting dose from a safety perspective. In order to avoid too many subjects exposed to the ineffective dose, it is proposed to include 1 subject in the 0.01 mg/kg dose group firstly. If there is no DLT, the subjects will not be increased at this dose level, and to continue to include 1 subject in the 0.1 mg/kg dose group. If there is no DLT, the subjects will not be increased at this dose level, and the subsequent "3 +3" dose escalation (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg and 20 mg/kg) will be conducted. For doses ≤ 10 mg/kg, semi-logarithmic dose escalation (approximately 3-fold) was used; For doses > 10 mg/kg, the escalation was based on a 2-fold increase of 20 mg/kg.

After comprehensive analysis, a series of doses of 0.01 mg/kg (n=1), 0.1 mg/kg (n=1), 0.3 mg/kg (n=3+3), 1 mg/kg (n=3+3), 3 mg/kg (n=3+3), 10 mg/kg (n=3+3) and 20 mg/kg (n=3+3) are recommended for dose escalation study.

3.1. 1.2 Dose Selection Considerations for Expansion Studies

Dose selection for IBI110 expansion studies was based on a comprehensive assessment of clinical safety, pharmacokinetics, pharmacodynamics, and clinical efficacy:

- Clinical Safety:

  IBI110 has a good safety profile over the dose range of 0.01 to 20mg/kg, and the safety profile is consistent across dose groups, with no subject experiencing a DLT event (cutoff date: 30 April 2022).

  As of 30 April 2022, a total of 54 subjects were enrolled in the Phase 1b dose escalation phase of IBI110 in combination with sintilimab. In the IBI110 dose range of 0.3 mg/kg to 10 mg/kg, no DLT events occurred and the safety was not dose-dependent. Thirteen subjects were treated with the combination of IBI110 10 mg/kg and sintilimab, with no treatment-related serious adverse events, and this dose group was well tolerated with a manageable safety profile.

		Treatment-emergent Adverse Events N (%)	Treatment-Related Adverse Events N (%)	Treatment-Related Serious Adverse Events N (%)
IBI110 0.3 mg/kg + sintilimab (N=3)	All Grades	3(100)	2(66.7)	0
	Grade ≥ 3	1(33.3)	1(33.3)	
IBI110 0.7 mg/kg + sintilimab (N=3)	All Grades	3(100)	3(100)	0
	Grade ≥ 3	2(66.7)	2(66.7)	
IBI110 1.5 mg/kg + sintilimab (N=3)	All Grades	3(100)	2(66.7)	1(33.3)
	Grade ≥ 3	1(33.3)	1(33.3)	
IBI110 3.0 mg/kg + Sintilimab (N=11)	All Grades	11(100)	10(90.9)	2(18.2)
	Grade ≥ 3	3(27.3)	3(27.3)	
IBI110 5.0 mg/kg + Sintilimab (N=15)	All Grades	13(86.7)	10(66.7)	1(6.7)
	Grade ≥ 3	2(13.3)	1(6.7)	

IBI110 8.0 mg/kg + sintilimab (N=6)	All Grades	5(83.3)	5(83.3)	2(33.3)
	Grade ≥ 3	3(50.0)	3(50.0)	
IBI110 10.0 mg/kg + sintilimab (N=13)	All Grades	9(69.2)	8(61.5)	0
	Grade ≥ 3	1(7.7)	1(7.7)	
Total (N=54)	All Grades	47(87.0)	40(74.1)	6(11.1)
	Grade ≥ 3	13(24.1)	12(22.2)	

- Clinical pharmacokinetics:

  At doses ≥ 3 mg/kg (200mg), IBI110 began to exhibit linear kinetics, with drug exposure sufficient to suppress the target. 3mg/kg (200mg) is the lowest potential effective dose.

- Clinical Pharmacodynamics:

  1） Soluble LAG-3: The concentration of soluble LAG-3 in peripheral blood increased with increasing dose after IBI110 administration over the dose range of 0.01-20mg/kg and reached a plateau at ≥ 10 mg/kg. LAG3 is induced in activated immune cells such as T cells and DCs, and is shed from the cell membrane by metalloproteinase 10 and metalloproteinase 17 to produce soluble LAG3. Soluble LAG3 in peripheral blood indicates activation of immune cells by IBI110 treatment and suggests that 10mg/kg (~ 600mg) is the potentially highest effective dose.

  2） CD4+/CD8 + T cells: IBI110 can regulate T cell activation, and at ≥ 3 mg/kg, the optimal CD4+/CD8 + T cell activation appears, suggesting that 3 (200mg) ~ 10mg/kg (~ 600mg) is the potential optimal effective dose range.

- Clinical efficacy:

  1) During the dose escalation phase of IBI110 monotherapy, only 1 subject in the 3mg/kg dose group had an objective response (PR), and 3mg/kg (200mg) is the potential lowest efficacious dose of IBI110.

  2) IBI110 (3mg/kg (200mg) to 10mg/kg) plus sintilimab showed positive clinical benefit (ORR ≈ 80%) in patients with sqNSCLC (cut-off date: 20

January 2022), supporting further exploration of the combination of IBI110 (3mg/kg (200mg) to 10mg/kg) plus sintilimab.

Based on the above comprehensive analysis, IBI110 (3mg/kg (200mg) ~ 10mg/kg (600mg)) + sintilimab was considered as the effective dose range. Further expansion of the 200mg and 600mg study doses of IBI110 is recommended in combination. It is expected that patient clinical benefit and dose optimization in the clinical development of the innovator can be achieved on the premise of subject safety.

3.1.2 Rationale for exploring PD-L1, LAG-3 as biomarkers

PD-L1 is mainly expressed on the surface of solid malignant tumor cells and antigen-presenting cells. Such as head and neck squamous cell carcinoma, melanoma, brain cancer, thyroid cancer, esophageal cancer, lung cancer, breast cancer, gastric cancer, colorectal cancer, liver cancer, pancreatic cancer, kidney cancer, bladder cancer, urothelial cancer, ovarian cancer and skin cancer and other tumors. PD-L1 expression is associated with shorter survival and poorer prognosis. In several clinical studies of Nivolumab and Pembrolizumab, PD-L1 expression in tumor tissues was positively correlated with efficacy [39]. Based on the above evidence, the amount of PD-L1 expression in tumor tissue may correlate with the response to immunotherapy, and biomarker exploration is warranted. The use of PD-L1 as a biomarker will provide a reference for later and combination use of sintilimab.[错误!未找到引用源。]

Yayi He analyzed the correlation between LAG-3 and PD-1, PD-L1 and Tumor Infiltrating Lymphocyte (TIL) and found that LAG-3 expression was correlated with PD-1 expression on TILs and PD-L1 expression on tumor cells. The high expression of LAG-3 on TILs was significantly correlated with the high expression of PD-1 on TILs and PD-L1 on tumor cells. The study also performed survival analysis on Recurrent-free Survival (RFS) and OS. LAG-3 is associated with poor prognosis. LAG-3 positivity or both LAG-3 and PD-L1 positivity were associated with early postoperative recurrence. [40][错误!未找到引用源。]

Study CA224-020 suggested that subjects with ⩾ 1% LAG-3 expression on tumor-associated immune cells within the tumor (n=25) had an approximately 3-fold higher ORR (20% versus 7.1%, respectively) compared to subjects with < 1% LAG-3 expression (n=14). It is suggested that LAG-3 can be used as a biomarker for screening patients. Based on the above evidence, the expression of LAG-3 in tumor tissues may be related

to the efficacy of immunotherapy, and it is necessary to explore biomarkers.

3.1.3 Rationale for Treatment after Disease Progression

Clinical data from marketed products suggest that a small number of subjects receiving immunotherapy may derive clinical benefit despite initial evidence of disease progression (per conventional response criteria) prior to clinical objective response and/or stable disease. As in studies of melanoma-based immunotherapy, a unique pattern of response, termed pseudoprogression, has emerged. This is unique to the immunotherapy itself. Its essence is an attack reaction of the activated immune cells to the tumor, which is a sign of effective treatment of tumor [41].[错误!未找到引用源。]

It is currently believed that this phenomenon may stem from two reasons. First, worsening inflammation within the tumor may result in an increase in tumor volume, as evidenced by an increase in measurable lesions and the appearance of new, visible, non-measurable lesions. The malignant and inflammatory portions of the mass may shrink over time, resulting in a clear radiographic response and improvement in clinical signs. Second, in some subjects, the anti-tumor immune response is slower to initiate, and its effectiveness in suppressing the tumor early is less than the tumor growth kinetics. Over time, antitumor activity will predominate and manifest as radiographic response and improvement in clinical signs. Therefore, for treated subjects, after initial RECIST V1.1-defined disease progression as assessed by the investigator, subjects will be allowed to continue study treatment if they are assessed to be clinically benefiting and tolerating study drug (see Section 5.1. 2 for details). The subject must be discontinued from study treatment upon recurrence of evidence of further progression.

3.2 Phase 1 Study Design

3.2.1 Dose-limiting toxicity (DLT)

Definition of DLT

According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 toxicity evaluation criteria, dose limiting toxicity (DLT) is defined as any of the following adverse events (AE) related to IBI110 alone or in combination with sintilimab occurring within 28 days (4 weeks) after the first dose:

1. Hematologic toxicity:

- Grade 4 hematologic toxicity.
- Grade 3 thrombocytopenia with bleeding tendency or requiring platelet transfusion.
- Grade 3 febrile neutropenia (absolute neutrophil count < 1000/mm3 with fever, temperature > 38.3 ℃ or temperature ≥ 38.0 ℃ for more than 1 hour).

2. Non-hematologic toxicity:
   - ≥ Grade 3 immune-related adverse events (irAE, immune-related AE) (excluding: asymptomatic Grade 3 thyroid or adrenal or pituitary insufficiency and Grade 3 inflammatory reaction at tumor site).
   - Any Grade ≥ 3 non-hematologic laboratory abnormality if:
     - Need for treatment
     - Lasts > 1 week
3. Any Grade 5 adverse event.
4. Other toxicities of any grade that need to be terminated prematurely after discussion between the investigator and the sponsor.

Note: The following are not considered dose limiting toxicities:

- Grade 3 or 4 infusion-related reactions (IRRs) are not considered dose-limiting toxicities. However, in the event of a Grade 3 or 4 IRR, the subject was to be discontinued from study treatment and replaced with a new subject. If ≥ 2 subjects in a treatment group experience a Grade 3 or 4 IRR, enrollment must be held, and the sponsor needs to review the safety data from the study to determine whether to continue enrollment;
- Grade 3 immune-related adverse events that can be recovered to ≤ Grade 1 or baseline within the expected time (21 days) with appropriate treatment. However, if such Grade 3 immune-related adverse events occur, they should be reviewed by the safety assessment committee to determine that they are not dose-limiting toxicities;
- Adverse events due to other causes with clear evidence (e.g., adverse events due to disease progression) based on a joint discussion between the sponsor and the

investigator.

3.2.2 Maximum tolerated dose (MTD)

The MTD is generally defined as the maximum dose at which ⩽ 1/6 subjects experience DLT in the first treatment cycle. If > 1/6 subjects experience DLT in a dose group, the dose group with a dose lower than this dose group is considered to be the MTD.

3.2.3 Dose Escalation Method

This is an open-label Phase 1 study to evaluate the safety, tolerability, and efficacy of IBI110 alone or in combination with sintilimab in subjects with advanced malignancies:

The study was divided into Phase 1a and Phase 1b:

Phase 1a is divided into two parts, Part 1 is IBI110 single-agent dose escalation and Part 2 is IBI110 single-agent dose expansion.

Phase Ib is divided into two parts, Part 1 is the combination dose escalation in combination with sintilimab to determine the combination dose. Part 2 is a dose expansion, efficacy study and marker exploratory study for different cancer types.

Phase Ia:

Phase 1a is a study to evaluate the safety, tolerability, and efficacy of single-agent IBI110.

Phase 1a Part 1 Single-agent Dose Escalation

Approximately 4 to 38 subjects with locally advanced, recurrent or metastatic solid tumors who have failed standard treatment will be enrolled, and dose escalation decisions will follow accelerated titration combined with the classical "3 +3" design. For dose escalation, 1 subject was enrolled at 0.01 mg/kg according to the accelerated titration method. After completing the 28-day DLT observation window, if no DLT occurred, 1 subject was enrolled at 0.1 mg/kg according to the accelerated titration method. After completing the 28-day DLT observation window, if no DLT occurred, 0.3 mg/kg was enrolled. Dose escalation was performed according to "3 +3", and traditional "3 +3" dose escalation was performed at 1 mg/kg, 3 mg/kg, 10 mg/kg and 20 mg/kg. If the first subject in the 0.01 mg/kg or 0.1 mg/kg dose group experiences a DLT during the DLT observation period, 3 additional subjects should be enrolled in the dose

group [If more than 1 (including) of the additional 3 subjects experiences a DLT during the DLT observation period, the dose escalation should not be continued]. If no DLT was observed in the 3 re-enrolled subjects in the 0.01 mg/kg or 0.1 mg/kg dose groups, subsequent dose escalation (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, 20 mg/kg) was completed according to the "3 +3" design principle.

For the group using the classical "3 +3" design, 3 subjects will be enrolled first. If none of the 3 subjects experience DLT during the DLT observation period, the next dose will be enrolled; If 1 (1/3) of the 3 subjects experienced a DLT during the DLT observation period, an additional 3 subjects were required for this dose group (a total of 6 subjects in this group at this time). If no DLT occurred in the additional 3 subjects, the subjects could enter the next dose group. If more than 1 (including) of the additional 3 subjects or 2 (including) of the total 6 subjects experience a DLT during the DLT observation period, dose escalation should not be continued. At the same time, 6 additional subjects are required in the previous dose group until the MTD is determined, so at least 6 subjects are required in the MTD dose group to be confirmed. For the 3 mg/kg dose group, if no 6 subjects were enrolled, additional 6 subjects were required to continue the PK/PD study; If 2 cases of DLT were observed in the 3 mg/kg dose group, 6 cases in the 0.3 mg/kg dose group were required to continue the PK/PD study.

After completing the 28-day DLT observation window, subjects in the 0.01 mg/kg and 0.1 mg/kg dose groups will be treated directly in combination with sintilimab 200 mg IV Q3W based on the ECOG PS assessment as judged by the investigator (see Section 5.1. 2 for details). Subjects in other dose groups will undergo radiological assessment after completing the DLT observation. If radiological disease progression (based on RECIST V1.1) is documented, they will receive sintilimab combination (or single agent) treatment (0.3 mg/kg, 1 mg/kg, 3 mg/kg dose groups will be directly combined with sintilimab 200 mg IV Q3W, 10 mg/kg and 20 mg/kg dose groups will be treated with 1.5 mg/kg IBI110 in combination with sintilimab 200 mg IV Q3W based on the ECOG PS assessment as judged by the investigator (see Section If the safety of the above corresponding combination dose group is confirmed, the above corresponding dose of IBI110 Q3W in combination with sintilimab 200 mg IV Q3W will be administered; If the safety of the corresponding combination dose group is not confirmed at that time, the highest combination dose group with confirmed safety at that time will be treated with IBI110 Q3W in combination with sintilimab 200 mg IV

Q3W; If there is no confirmed safety combination dose group at that time, subjects will receive sintilimab 200mg IV Q3W monotherapy until disease progression (based on iRECIST, or based on RECIST V1.1 but not 5.1. 2), lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a total treatment duration of up to 24 months (including the time of previous treatment with IBI110 monotherapy). If there is no disease progression (based on RECIST V1.1) after completion of the DLT observation period to receive subsequent IBI110 treatment every 3 weeks, subjects with disease progression (based on RECIST V1.1) will receive sintilimab combination (or single agent) treatment (0.3 mg/kg, 1 mg/kg, 3 mg/kg dose groups will receive sintilimab 200 mg IV Q3W directly in combination with sintilimab 200 mg IV Q3W, 10 mg/kg and 20 mg/kg dose groups will receive 1.5 mg/kg IBI110 in combination with sintilimab 200 mg IV Q3W) at the investigator's discretion (see Section 5.1. 2) based on ECOG PS assessment. If the safety of the above corresponding combination dose group is confirmed, the above corresponding dose of IBI110 Q3W in combination with sintilimab 200 mg IV Q3W will be administered; If the safety of the corresponding combination dose group is not confirmed at that time, the highest combination dose group with confirmed safety at that time will be treated with IBI110 Q3W in combination with sintilimab 200 mg IV Q3W; If there is no confirmed safety combination dose group at that time, subjects will receive sintilimab 200mg IV Q3W monotherapy until disease progression (based on iRECIST, or based on RECIST V1.1 but not 5.1. 2), lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a total treatment duration of up to 24 months (including the time of previous treatment with IBI110 monotherapy). Safety after DLT observation period will also be included in the observation of safety and tolerability. After discontinuation of study treatment, subjects will enter Safety Follow-up and Survival Follow-up for 90 $\pm$ 7 days (every 3 months for $\leqslant$ 90 days).

In order to fully explore the safety and efficacy of potentially effective dose, if the subjects who experience partial response (PR) or complete response (CR) with monotherapy during single-agent dose escalation, after completion of dose escalation, 6 subjects will be added to each dose group from the lowest dose group with PR or CR to the highest dose group with confirmed safety after completion of escalation (if there are less than 6 subjects in this dose group during escalation). The additional subjects

will be preferentially included in the subjects with tumor types that experience PR/CR during single-agent dose escalation, and secondly, the subjects with tumor types that experience PR/CR during combination dose escalation may be considered. Every effort should be made to collect prior tumor tissue specimens from these supplemental subjects (especially if supplemental subjects experience CR/PR or shrinking SD) for further marker exploration. These additional subjects will undergo radiographic assessment after 28 days of observation, and if radiographic disease progression (based on RECIST V1.1) is documented, they will receive sintilimab in combination with IBI110 at the investigator's discretion (see Section 5.1. 2 for details) based on the subject's PS assessment (0.3 mg/kg, 1 mg/kg, 3 mg/kg dose groups will be directly combined with sintilimab 200 mg IV Q3W, 10 mg/kg dose group will receive 8mg/kg IBI110 in combination with sintilimab 200 mg IV Q3W, 20 mg/kg dose group will receive 10mg/kg IBI110 in combination with sintilimab 200 mg IV Q3W); If the safety of the above corresponding combination dose group is confirmed, the above corresponding dose of IBI110 Q3W in combination with sintilimab 200 mg IV Q3W will be administered; If the corresponding combination dose group has no confirmed safety at that time, the highest combination dose group with confirmed safety at that time will be treated with IBI110 Q3W plus sintilimab 200 mg IV Q3W until disease progression (based on iRECIST, or RECIST v1.1 but not 5.1. 2), lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a total treatment duration of up to 24 months (including previous treatment with IBI110 monotherapy). If there is no disease progression (based on RECIST V1.1) after the end of DLT observation to receive subsequent IBI110 treatment every 3 weeks, subjects with disease progression (based on RECIST V1.1) will receive sintilimab in combination with IBI110 at the investigator's discretion (see Section 5.1. 2) based on PS assessment (0.3 mg/kg, 1 mg/kg, 3 mg/kg dose groups will directly combine with sintilimab 200 mg IV Q3W, 10 mg/kg dose group will receive 8mg/kg IBI110 in combination with sintilimab 200 mg IV Q3W, 20 mg/kg dose group will receive 10mg/kg IBI110 in combination with sintilimab 200 mg IV Q3W); If the safety of the above corresponding combination dose group is confirmed, the above corresponding dose of IBI110 Q3W in combination with sintilimab 200 mg IV Q3W will be administered; If the corresponding combination dose group has no confirmed safety at that time, the highest combination dose group with confirmed safety at that time will be treated with IBI110 Q3W plus sintilimab 200 mg

IV Q3W until disease progression (based on iRECIST, or RECIST v1.1 but not 5.1. 2), lost to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a total treatment duration of up to 24 months (including previous treatment with IBI110 monotherapy). Subjects enrolled in the original dose escalation process will continue to follow the principle of IBI110 monotherapy to Xindili combination (or single agent) regimen as described in the previous paragraph.

Subjects with first disease progression may continue to receive treatment if clinically stable and eligible subjects (see Section 5.1. 2 for details) at the discretion of the investigator until 24 months of treatment or recurrence of disease progression, loss to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first. The total duration of treatment is generally no longer than 24 months, and if disease response or patient benefit exceeds 24 months, the investigator and sponsor should discuss whether the subject should continue to receive treatment.

During or after the enrollment of subjects, the sponsor may make a systematic evaluation based on preliminary data and determine the subsequent escalation scheme after discussion with the investigator on the basis of weighing the risks and benefits of the subjects, such as whether to start single-agent dose expansion or combined dose escalation, advance or delay the enrollment of the study or further expand the enrollment, etc.

Dose escalation is described in the table below:

Table 7. Phase 1a Dose Escalation Method and Number of Subjects

Dose Group	Dose	Method of application	Number of Subjects
1	0.01 mg/kg	IV, Cycle 1 Day 1	1-4a
2	0.1 mg/kg	IV, Cycle 1 Day 1	1-4a
3	0.3 mg/kg	IV, Cycle 1 Day 1	3 + 3b, c
4	1 mg/kg	IV, Cycle 1 Day 1	3 +3 b,
5	3 mg/kg	IV, Cycle 1 Day 1	3 +3 b, c
6	10 mg/kg	IV, Cycle 1 Day 1	3 +3 b,
7	20 mg/kg	IV, Cycle 1 Day 1	3 +3 b,

Note: a. If 1 subject in the 0.01 mg/kg or 0.1 mg/kg dose group experiences a DLT during the DLT observation period, 3 additional subjects should be enrolled in this dose group, and the subsequent dose escalation (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, 20 mg/kg) will be completed using classical "3 +3" dose escalation. If more than 1 (including) of the additional 3 subjects experienced a DLT during the DLT observation period, the dose escalation should not be continued.

b. Subsequent dose escalations (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, 20 mg/kg) were completed using classical "3 +3" dose escalation.

c. For the 3 mg/kg dose group, if no 6 subjects were enrolled, additional 6 subjects were required to continue the PK/PD study; If 2 cases of DLT were observed in the 3 mg/kg dose group, 6 cases in the 0.3 mg/kg dose group were required to continue the PK/PD study.

* In case of PR/CR during escalation, 6 subjects will be added from the lowest dose group with response to the highest dose group with confirmed safety.

Phase 1a Part 2 Single Agent Dose Expansion

During the phase 1a escalation phase of single-agent IBI110 (e.g., after the completion of DLT observation in the 1 mg/kg dose group of single-agent IBI110) or after the end of escalation, the sponsor and the investigator will make a systematic evaluation based on the available preliminary data, and decide whether to carry out single-agent dose expansion and the timing of single-agent dose expansion on the basis of weighing the risks and benefits of subjects. A fixed dose of IBI110 200 mg IV infusion is proposed.

Cohort A1: Advanced solid tumors associated with viral infection that have failed standard therapy: Approximately 30 subjects will be enrolled, including hepatocellular carcinoma (HBV-or HCV-associated), Epstein-Barr virus (EBV) infection-associated nasopharyngeal carcinoma and gastric cancer, and human papillomavirus (HPV) infection-associated advanced solid tumors such as cervical cancer and head and neck squamous cell carcinoma, etc.

Cohort A2: Other Advanced Solid Tumors: Approximately 30 subjects will be enrolled, including epithelial ovarian cancer, endometrial cancer, malignant melanoma (acral or cutaneous), and triple negative breast cancer.

Phase Ib

Phase 1b is a study to evaluate the safety, tolerability, and efficacy of IBI110 in combination with sintilimab.

Phase Ib Part 1 Combination Dose Escalation

Patients who have received prior treatment with checkpoint inhibitors such as anti-PD-1 or PD-L1 monoclonal antibodies cannot be enrolled in the combination dose escalation phase. During the Phase 1a escalation phase of IBI110 monotherapy (e.g., after DLT observation for 0.3 mg/kg IBI110 monotherapy dose group is completed) or after the end of escalation, the sponsor and the investigator will make a systematic evaluation based on the available preliminary data, and determine the time to start dose escalation of the combination based on weighing the risks and benefits of the subjects. The starting dose for combination dose escalation was IBI110 0.3 mg/kg in combination with sintilimab 200 mg, and the combination dose escalation was performed according to the classical "3 +3" design. The DLT observation period is within 28 days (4 weeks) after the first dose.

Dose Cohort 1: IBI110 0.3 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 2: IBI110 0.7 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 3: IBI110 1.5 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 4: IBI110 3.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 5: IBI110 5.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 6: IBI110 8.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Cohort 7: IBI110 10.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Dose Group 8: IBI110 20.0 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W.

If no DLT occurs in the first 3 subjects in a dose group during the DLT observation period, the enrollment of the next dose group can be started;

If 1 of the first 3 subjects in a dose group experiences a DLT during the DLT

observation period, another 3 subjects will be added to the dose group;

If ≤ 1 of 6 subjects in a dose group experience a DLT during the DLT observation period, the dose group will be considered tolerable;

If 2 out of the first 3 subjects or ≥ 2 out of 6 subjects in a dose group experience a DLT during the DLT observation period, the dose group will be considered intolerable.

The safety of each cohort after 4 weeks will also be included in the observation of safety and tolerability. All treatments until disease progression, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, for a maximum of 24 months, whichever occurs first.

In order to fully explore the safety and efficacy of potentially effective combination doses, if subjects who experience partial response (PR) or complete response (CR) to monotherapy during single-agent dose escalation in Phase Ia, the combination dose group corresponding to the lowest dose group with PR or CR and subsequent combination escalation dose groups will be supplemented with 6 subjects in each dose group (if there are less than 6 subjects in this dose group during the escalation) after the safety of this dose group is confirmed. The additional subjects will be preferentially included in the subjects with tumor types who experience PR/CR during single-agent dose escalation or/and combination dose escalation. Every effort should be made to collect prior tumor tissue specimens from these supplemental subjects (especially if supplemental subjects experience CR/PR or shrinking SD) for further marker exploration.

For the doses near the RP2D or target dose, multiple dose groups can be selected from the escalation dose groups to further expand by 10 ~ 15 subjects (per dose group) in order to provide detailed PK/PD/safety data. For the expanded dose group, subjects with consistent baseline conditions should be selected as far as possible (e.g., patients with tumor disease or similar number of treatment lines). At present, multiple dose groups will be further selected from dose group 4 (IBI110 3.0 mg/kg IV Q3W plus sintilimab) to the MTD dose group of combination dose escalation to continue to enroll 10-15 non-small cell lung cancer subjects without driver gene mutation who have not received any immune-related treatment and failed in first-line systemic chemotherapy.

Subjects with first disease progression may continue to receive treatment if clinically stable and eligible subjects (see Section 5.1. 2 for details) at the discretion of the investigator until the total duration of treatment reaches 24 months or until recurrence of

disease progression, loss to follow-up or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment occurs, whichever occurs first.

During or after the enrollment of subjects, the sponsor will conduct a systematic evaluation based on PK/PD, preliminary efficacy and safety data, and determine the subsequent trial protocol after discussion with the investigator on the basis of weighing the risks and benefits of subjects, such as deciding whether to advance or delay the enrollment, further expand the enrollment and adjust the RP2D of IBI110 in combination with sintilimab for the Phase Ib extension study.

Phase Ib Part 2 Combination Dose Expansion

"3 +3" dose escalation will be performed in the first part of the study. The appropriate dose of IBI110 combined with sintilimab will be selected after data analysis, and the dosing frequency of IBI110 may be adjusted to QW according to the PK data and preliminary efficacy data observed in the combined escalation phase. Dose expansion study will be conducted. To investigate the antitumor activity of IBI110 in combination with sintilimab ± other treatments in different cancer types. IBI110 RP2D IV Q3W in combination with sintilimab 200 mg IV Q3W ± other treatments in 14 cohorts. The proposed RP2D is currently IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W ± other treatments. Once the established enrollment plan for each cohort is completed, the sponsor may decide whether to further expand enrollment or adjust the RP2D of IBI110 based on PK, preliminary efficacy, and safety data. Every effort should be made to collect prior tumor tissue specimens from subjects in these cohorts for further marker exploration.

Cohort B: Advanced hepatocellular carcinoma (HCC) without prior systemic therapy. A total of 20 to 30 subjects were planned to be treated with IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W and lenvatinib (8 mg daily for subjects weighing < 60 kg or 12 mg daily for subjects weighing ≥ 60 kg).

Cohort C: Recurrent or metastatic cervical cancer that has failed systemic therapy. It is planned to enroll 20 to 30 subjects to be treated with IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Cohort D: Advanced non-small cell lung cancer without driver mutations that have not received prior systemic therapy. Cohort D1 and Cohort D2 were divided according to the exploratory dose of IBI110 and study design.

Cohort D1: in Part I, it is planned to enroll 30 subjects to receive IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W and platinum-based doublet chemotherapy (adenocarcinoma: pemetrexed plus carboplatin Q3W; squamous cell carcinoma: paclitaxel plus carboplatin Q3W). In the second stage, subjects with squamous cell carcinoma will continue to be supplemented to 40 ~ 50 cases according to the previous efficacy.

Cohort D2: Based on the efficacy of patients with squamous cell carcinoma in Cohort D1, dose optimization in lung squamous cell carcinoma will be further explored. This cohort is intended to be a randomized, controlled, open-label study in which approximately 100 subjects with squamous cell carcinoma will be enrolled and randomized in a 1: 1 ratio to the treatment arm (IBI110 600mg Q3W plus sintilimab 200mg IV Q3W plus paclitaxel and carboplatin Q3W) and the control arm (sintilimab 200mg IV Q3W plus paclitaxel and carboplatin Q3W), respectively. During the course of the study, the sponsor and investigators will dynamically evaluate the efficacy and safety in the D2 treatment arm of Cohort.

Cohort E: Advanced small cell lung cancer (SCLC) who have received and failed at least one line of standard therapy. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.

Cohort F: Advanced urothelial cancer (UC) who have received and failed at least one prior systemic therapy. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.

Cohort G: Advanced renal clear cell carcinoma (RCC) who have received and failed at least one prior systemic therapy. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.

Cohort H: Advanced hepatocellular carcinoma (HCC) after failure of immunotherapy. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.

Cohort I: Advanced nasopharyngeal carcinoma (NPC) with immunotherapy failure. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.

Cohort J: HER2-negative advanced gastric (GC) or gastroesophageal junction (GEJ)

cancer not previously treated systemically. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W + oxaliplatin and capecitabine (XELOX). A total of 20-30 patients are planned to be enrolled.

Cohort K: EBV infection-associated advanced gastric (GC) or gastroesophageal junction (GEJ) cancer that has failed standard therapy. IBI110 200 mg IV Q3W was administered in combination with sintilimab 200 mg IV Q3W, and a total of 20 subjects were planned to be enrolled.

Cohort L: Advanced Triple Negative Breast Cancer (TNBC) after failure of standard therapy. It is planned to enroll 20 to 30 subjects to be treated with IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Cohort M: Advanced ovarian cancer after failure of platinum-containing chemotherapy regimen. It is planned to enroll 20 to 30 subjects to be treated with IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W.

Cohort N: Locally advanced/metastatic melanoma not amenable to local therapy. In the first stage, 30 subjects are planned to be enrolled and divided into 2 dose groups. Dose group 1: IBI110 200 mg IV Q3W combined with sintilimab 200 mg IV Q3W, approximately 15 subjects will be enrolled; Dose Cohort 2: IBI110 10 mg/kg IV Q3W in combination with sintilimab 200 mg IV Q3W, approximately 15 subjects will be enrolled. If the efficacy in any dose group meets the expectation (ORR $\geqslant$ 30% for skin type or ORR $\geqslant$ 15% for acral/mucosal type), the corresponding population will continue to be expanded by 10 ~ 20 cases in this dose group.

Cohort O: Advanced nasopharyngeal carcinoma (NPC) after failure of systemic therapy. IBI110 200 mg IV Q3W in combination with sintilimab 200 mg IV Q3W is planned to enroll a total of 20 to 30 subjects.

3.2.4 Subjects evaluable for DLT

DLT evaluable subjects were required to meet any of the following criteria:

1. The DLT occurred in the DLT observation window.
2. The observation of DLT observation window was completed.

Subjects who do not meet one of the above conditions need to be enrolled in a new subject supplement.

3.2.5 DLT handling measures and risk assessment

According to the mechanism of action of PD-1 and LAG-3 monoclonal antibodies and the clinical safety information of products with the same mechanism, it is expected that DLTs that may occur during this clinical trial are mainly due to various immune inflammations caused by immune system activation, such as colitis, pneumonia, hepatitis, renal insufficiency and endocrine system inflammation. In case of DLT or suspected DLT related to the study drug, timely handling should be performed according to the Section 5.3 Dose Modification of the protocol and the Management Manual for Immune-related Adverse Events. For subjects with abnormal liver function, monitoring and follow-up should be performed according to Section 7.7 of the protocol.

All DLTs or suspected DLTs should be reviewed by the Safety Assessment Committee for safety risk assessment to guide the further conduct of the study.

3.3 Safety Assessment Committee

The safety assessment committee was composed of relevant personnel from the sponsor and investigators. Safety assessment committee discussion was triggered due to unexpected safety events during the trial.

4 Study Population

4.1 Inclusion Criteria

Subjects were required to meet the following inclusion criteria:

1. Phase 1a single-agent dose escalation: subjects with locally advanced, recurrent, or metastatic solid tumors who have failed standard therapy; Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not;
2. Phase Ib combination dose escalation: subjects with locally advanced, recurrent, or metastatic solid tumors who have failed standard therapy; No prior treatment with T-cell immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody;
3. Phase Ib expansion of IBI110 in combination with sintilimab in multiple dose cohorts:
    1) Non-small cell lung cancer who failed at least one line of systemic chemotherapy;
    2) For subjects with non-squamous NSCLC, confirmation of EGFR, ALK, and

ROS1 wild-type by tissue-based testing must be available;

3) No prior treatment with T-cell immune checkpoint inhibitors such as anti-PD-1/PD-L1 mAb.

4. Inclusion criteria for Phase 1a single-agent and Phase 1b combination dose expansion (Cohorts A to O):

Cohort A1 (IBI110 alone):

1） Histologically confirmed (blood virological support) advanced solid tumors related to viral infection that have failed standard treatment: including: HBV or HCV infection-related hepatocellular carcinoma, Epstein-Barr virus (EBV) infection-related nasopharyngeal carcinoma and gastric cancer, human papillomavirus (HPV) infection-related advanced solid tumors such as cervical cancer and head and neck squamous cell carcinoma, etc.;

2） The above tumors that cannot be treated with radical surgical resection or radical radiotherapy and fail to receive standard treatment;

3） Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not.

Cohort A2 (IBI110 alone):

1） Histologically/cytologically confirmed diagnosis of other advanced solid tumors unrelated to viral infection: epithelial ovarian cancer (including fallopian tube and peritoneal cancer), endometrial cancer, malignant melanoma, and triple negative breast cancer;

2） The above tumors that cannot be treated with radical surgical resection or radical radiotherapy and fail to receive standard treatment;

3） Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not.

Cohort B: Advanced hepatocellular carcinoma without prior systemic therapy

1） Histologically/cytologically confirmed hepatocellular carcinoma, or meeting the clinical diagnostic criteria of hepatocellular carcinoma specified by American Association for the Study of Liver Diseases (AASLD) or Guidelines for the

Diagnosis and Treatment of Primary Liver Cancer; (Excluding histological types including fibrolamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, cholangiocarcinoma, etc.);

2） Stage IIb and III patients who are not suitable for radical surgery or local treatment, or stage Ib and IIa patients who are inoperable due to poor liver reserve function (2019 edition) promulgated by National Health and Family Planning Commission for the diagnosis and treatment of primary liver cancer;

3） Non-diffuse liver cancer;

4） Child-Pugh score ⩽ 7 points;

5） No prior systemic antineoplastic therapy for recurrent or metastatic hepatocellular carcinoma.

6） No prior local treatment for liver cancer within 4 weeks prior to the first dose.

Cohort C: Recurrent or metastatic cervical cancer that has failed systemic therapy

1） Histologically/cytologically confirmed incurable, recurrent or metastatic cervical cancer;

2） Patients in the recurrent or metastatic stage must have received platinum-based doublet chemotherapy, and have disease progression confirmed by imaging during or after treatment;

3） Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not.

Cohort D: Advanced NSCLC without driver mutations who have not received prior systemic therapy

1) Histologically/cytologically confirmed inoperable recurrent and metastatic non-small cell lung cancer;

2) Stage IV according to the American Joint Committee on Cancer (AJCC) 8th edition staging manual;

3) For subjects with non-squamous NSCLC, confirmation of EGFR, ALK, and ROS1 wild-type by tissue-based testing must be available;

4) No prior systemic therapy for recurrent/metastatic disease; Time from end of prior (neo) adjuvant chemotherapy/adjuvant radiotherapy to disease recurrence > 6 months.

Cohort E: Recurrent or metastatic small cell lung cancer that has received and failed first-line standard therapy

1) Histologically/cytologically confirmed small cell lung cancer;

2) Extensive stage according to American Veterans Lung Cancer Association VALG staging.

3) Patients who have received at least one platinum-containing regimen for recurrent or metastatic disease and have disease progression during or after the end of treatment, or are intolerant to the treatment;

4) No prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 mAb.

Cohort F: Advanced Urothelial Carcinoma (UC) with at least one prior systemic therapy that has failed

1) Histologically/cytologically confirmed urothelial carcinoma (including urothelial carcinoma or transitional cell carcinoma originating from renal pelvis, ureter or urethra) with lesions of different histological types (e.g. Minimal variation) is acceptable;

2) Patients with disease progression or chemotherapy intolerance after receiving at least one line of systemic chemotherapy for recurrent or metastatic disease; Progression during prior platinum-containing neoadjuvant or adjuvant therapy or relapse within 12 months after the end of treatment is considered as failure of first-line therapy and can be included in the study;

3) Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not.

Cohort G: Recurrent or metastatic clear cell renal cell carcinoma that has failed systemic therapy

1) Histologically/cytologically confirmed recurrent and metastatic clear cell renal carcinoma;

2) Received at least one line of systemic therapy, including at least one anti-

VEGFR/VGEF targeted drug, and experienced disease progression or intolerance;

3) Whether the patient has been treated with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody or not.

Cohort H: Advanced Hepatocellular Carcinoma after Immunotherapy Failure

1） Advanced hepatocellular carcinoma confirmed by histology/cytology, or in accordance with the American Association for the Study of Liver Diseases (AASLD) or the diagnosis and treatment criteria for primary liver cancer (excluding the histological types including fibrolamellar hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, cholangiocarcinoma and other components);

2） Stage IIb and stage III (BCLC stage C or stage B not suitable for local treatment) of primary liver cancer (2019 edition) promulgated by National Health and Family Planning Commission;

3） Non-diffuse liver cancer;

4） Child-Pugh score ≤ 7 points;

5） Patients who have received prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody and have radiologically confirmed disease progression;

6） No prior local treatment for liver cancer within 4 weeks prior to the first dose.

Cohort I: Recurrent or Metastatic Nasopharyngeal Carcinoma after Failure of Immunotherapy

1) Histologically/cytologically confirmed non-keratinizing differentiated or undifferentiated nasopharyngeal carcinoma;

2) Have received at least one platinum-containing regimen and anti-PD-1/PD-L1 mAb for recurrent or metastatic disease and have radiographically confirmed disease progression or are intolerant to chemotherapy.

Cohort J: HER2-negative advanced gastric (GC) or gastroesophageal junction (GEJ) cancer not previously treated systemically

1) Pathologically/cytologically confirmed inoperable locally advanced, recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma (including signet ring cell carcinoma, mucinous adenocarcinoma, hepatoid adenocarcinoma);

2) No prior systemic drug therapy for recurrent or metastatic disease;

3) Time from the end of prior (neo) adjuvant chemotherapy/adjuvant radiotherapy to disease recurrence > 6 months;

4) Known tumor tissue testing HER2 negative.

Cohort K: EBV infection-associated gastric and gastroesophageal junction cancer that has failed standard therapy

1) Histologically/cytologically confirmed EBV infection-related unresectable locally advanced, recurrent or metastatic gastric and gastroesophageal junction cancer;

2) Previously received ≥ 1 line of systemic drug treatment failure or chemotherapy intolerance;

3) Prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 monoclonal antibody is acceptable.

Cohort L: Advanced Triple Negative Breast Cancer after Failure of Standard Therapy

1） Histologically/cytologically confirmed unresectable locally advanced or metastatic triple negative breast cancer;

2） Previously treated with ≥ 1 line of systemic drug treatment failure or intolerance;

3） No prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 mAb.

Cohort M: Advanced Ovarian Cancer after Failure of Platinum-containing Chemotherapy Regimen

1） Histologically/cytologically confirmed epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer;

2） The BRCA1/2 gene test results of hematological test should be provided; If the hematological test is negative, the BRCA1/2 gene test results of tumor tissue shall be

additionally provided;

3） Received a platinum-based regimen with disease progression during platinum-based therapy (platinum-refractory) or < 6 months (184 calendar days) from platinum-based therapy (at least 4 cycles) to disease relapse (platinum-resistant). Definition of relapse or progression (meeting any of the following criteria): a) unequivocally documented radiographic progression; b) Persistent elevation of CA-125 (CA-125 ≥ 2 times the upper limit of normal, which should be confirmed 1 week later) with clinical symptoms or physical examination suggestive of disease progression;

4） No prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 mAb.

Cohort N: Locally advanced/metastatic melanoma not amenable to local therapy

1） Patients with histologically and/or cytologically confirmed locally advanced (unresectable Stage III) or metastatic (Stage IV) melanoma (acral, mucosal, or cutaneous) that is not suitable for local therapy according to the 8th edition of the American Joint Committee on Cancer (AJCC);

2） Has received chemotherapy or targeted therapy (such as BRAF inhibitor, MEK inhibitor, KIT inhibitor), but must not have received systemic T cell immune checkpoint inhibitor treatment; > 6 months from end of treatment to disease recurrence for recurrent/metastatic disease if previously treated with (neo) adjuvant T-cell checkpoint inhibitors.

Cohort O: Advanced nasopharyngeal carcinoma (NPC) after failure of systemic therapy

1） Histologically/cytologically confirmed non-keratinizing differentiated or undifferentiated nasopharyngeal carcinoma;

2） Patients who have received at least one platinum-containing regimen for recurrent or metastatic disease and have radiographically confirmed disease progression or chemotherapy intolerance after treatment;

3） No prior treatment with immune checkpoint inhibitors such as anti-PD-1/PD-L1 mAb.

Enrollment criteria to be met for both Phase Ia and Phase Ib:

5. Signed written informed consent and able to comply with protocol-specified visits and procedures.

6. Age ≥ 18 years and ≤ 75 years.

7. Expected survival time ≥ 12 weeks.

8. At least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST V1.1) (no prior radiotherapy). At baseline, accurately measured by computed tomography (CT) or Magnetic Resonance Imaging (MRI) (intravenous contrast is preferred) as ≥ 10 mm in the long axis (except lymph nodes, which must have a short axis of ≥ 15 mm), and a target lesion ≥ 2 times the image slice thickness and suitable for accurate repeated measurements. Lesions located in a previously irradiated area can be considered measurable if they clearly demonstrate progression according to RECIST V1.1.

9. 0 or 1 according to Eastern Cooperative Oncology Group Performance Status (ECOG PS).

10. Female subjects of childbearing potential or male subjects whose partners are women of childbearing potential are required to use effective contraceptive measures throughout the treatment period and for 6 months after the treatment period.

11. Adequate organ and bone marrow function (except for subjects treated with any cells and growth factors or blood transfusions within 2 weeks prior to the first dose of study treatment), defined as follows:

    1) Hematology: Absolute neutrophil count (ANC) ≥ 1.5 × 109/L, platelet (PLT) ≥ 75 × 109/L, hemoglobin (HGB) ≥ 90 g/L (9.0 g/dL). (No cells and growth factors are allowed within 2 weeks before the first dose of study treatment, and no allogeneic blood transfusion is allowed within 1 week before the first dose of study treatment).

    2) Liver function: blood total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN); If TBIL > 1.5 × ULN, conjugated bilirubin ≤ ULN; TBIL ≤ 3 × ULN for subjects with liver metastases or a history/suspicion of Gilbert's syndrome (persistent or recurrent hyperbilirubinemia, primarily high unconjugated bilirubin without evidence of hemolysis or liver lesions); Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 ×

ULN for subjects without liver metastases; ALT and/or AST $\leqslant$ 5 $\times$ ULN for subjects with liver metastases. Subjects with primary hepatocellular carcinoma were required to have TBIL $\leqslant$ 2 $\times$ ULN and ALT and/or AST $\leqslant$ 3 $\times$ ULN.

3) Renal function: serum creatinine (Cr) $\leqslant$ 1.5 $\times$ ULN, or creatinine clearance (CCr) $\geqslant$ 50 mL/min; Urine dipstick test results show urine protein < 2 +; For subjects with urine protein $\geqslant$ 2 + on urine dipstick at baseline, a 24-hour urine collection with < 1g of protein in the 24-hour urine should be performed.

4) Coagulation: APTT $\leqslant$ 1.5 $\times$ ULN, INR $\leqslant$ 1.5.

4.2 Exclusion Criteria

Subjects with any of the following criteria were not to be included in the study:

1. Previous exposure to any anti-LAG-3 antibody class.
2. Concurrent participation in another interventional clinical study, except in an observational (non-interventional) clinical study or in the survival follow-up phase of an interventional study.
3. Received any investigational drug within 4 weeks prior to the first dose of study treatment.
4. Received the last anti-tumor therapy within 4 weeks prior to the first dose of study drug: systemic chemotherapy (washout period for oral fluoropyrimidines is 2 weeks), endocrine therapy, targeted therapy (washout period for small molecule targeted therapy is 2 weeks or 5 half-lives, whichever is longer), immunotherapy, tumor embolization, etc. Received the last dose of Chinese herbal medicine for an antineoplastic indication within 1 week prior to the first dose of study drug.
5. Use of immunosuppressive medications within 4 weeks prior to the first dose of study drug, excluding

    1) Intranasal inhaled topical steroid therapy or local steroid injections (e.g., intra-articular injections);

    2) Systemic corticosteroid therapy not exceeding physiologic doses of 10 mg/day prednisone or its equivalent;

3) Corticosteroids as prophylaxis for allergic reactions (e.g. CT premedication).

6. Need for long-term systemic hormonal or any other immunosuppressive drug therapy excluding inhaled corticosteroid therapy.

7. Receipt of a live attenuated vaccine within 4 weeks prior to the first dose of study treatment or planned during the study.

8. Major surgical procedure (craniotomy, thoracotomy, or laparotomy) or non-healing wound, ulcer, or fracture within 4 weeks prior to the first dose of study treatment.

9. Presence of toxicity (excluding alopecia or asthenia) caused by previous anti-tumor therapy that has not recovered to NCI CTCAE v5.0 grade 0 or 1 within 4 weeks prior to the first dose of study treatment; Includes immune-related adverse events (irAE) that have not recovered from immunotherapy, including irAE that are still under hormonal control and endocrine-related irAE that have not recovered to Grade 0-1 even with replacement therapy.

10. Prior immunotherapy such as anti-PD-1/anti-PD-L1 antibody or anti-CTLA-4 antibody was permanently discontinued due to ≥ Grade 3 irAE.

11. Known central nervous system (CNS) metastases and/or spinal cord compression and/or carcinomatous meningitis, history of leptomeningeal carcinoma. Patients with asymptomatic brain metastases (i.e., no neurological symptoms, no need for glucocorticoid treatment, and no lesion > 1.5 cm) or treated brain metastases that are symptomatic and stable are eligible to participate in the study as long as they meet all of the following criteria: measurable lesions outside the central nervous system; No metastasis in midbrain, pons, cerebellum, meninges, medulla oblongata or spinal cord; Patients may participate if they are clinically stable for at least 4 weeks, have no evidence of new or enlarging brain metastases, and have discontinued corticosteroid and anticonvulsant medication for at least 14 days prior to study treatment.

12. Active autoimmune or inflammatory disease (including inflammatory bowel disease [eg, ulcerative colitis or Crohn's disease], diverticulitis [except diverticulosis], celiac disease, systemic lupus erythematosus, Sarcoidosis syndrome or Wegener syndrome [granulomatosis with polyangiitis], Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.) or history within the previous 2 years (vitiligo, psoriasis,

alopecia, or Grave's disease not requiring systemic treatment within the last 2 years, hypothyroidism requiring thyroid hormone replacement only, and type 1 diabetes mellitus requiring insulin replacement only may be enrolled). Known history of primary immunodeficiency. The presence of autoimmune disease was confirmed at the investigator's discretion only in patients with positive autoimmune antibodies.

13. Acute or chronic active hepatitis B [defined as hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibody (HBcAb) positive and hepatitis B virus (HBV) DNA copy number $\geqslant 1 \times 104$ copies/ml or $\geqslant$ 2000 IU/ml]; Or acute or chronic active hepatitis C virus (HCV) antibody-positive, HCV antibody-positive but RNA-negative subjects are allowed to enroll (subjects with HCC with HCV RNA $\leqslant$ 103 copies/ml are allowed to enroll).

14. Past and current pulmonary diseases such as interstitial pneumonia, pneumoconiosis, drug-related pneumonia, pulmonary fibrosis, severely impaired pulmonary function, and current active pulmonary infection.

15. Patients with active pulmonary tuberculosis who are receiving anti-tuberculosis treatment or who have received anti-tuberculosis treatment within 1 year before the first dose of study drug.

16. Known history of allogeneic organ transplantation and allogeneic hematopoietic stem cell transplantation.

17. History of gastrointestinal perforation and/or fistula within 6 months prior to study enrollment and not cured by surgical treatment.

18. Patients with uncontrolled third space effusion requiring repeated drainage, such as pleural effusion, ascites, pericardial effusion, etc. (patients who do not require drainage of effusion or have no significant increase in effusion after stopping drainage for 3 days can be enrolled).

19. The subject has a known history of severe allergic reactions to other monoclonal antibodies or hypersensitivity to components of the study drug formulation.

20. Uncontrolled intercurrent illness including, but not limited to:

    1) HIV-infected persons (HIV antibody positive);

    2) Active or clinically poorly controlled severe infection;

3) Symptomatic congestive heart failure (New York Heart Association Class II-IV) or symptomatic or poorly controlled arrhythmia such as ventricular tachycardia, atrial fibrillation, ventricular fibrillation, torsades de pointes, etc.);

4) History of congenital long QT syndrome or corrected QTc > 500ms at screening (calculated using Fridericia method);

5) History of myocarditis;

6) Uncontrolled arterial hypertension (systolic blood pressure ⩾ 160 mmHg or diastolic blood pressure ⩾ 100 mmHg) despite standard treatment; Baseline systolic blood pressure ⩾ 150 mmHg or diastolic blood pressure ⩾ 90 mmHg in combination with lenvatinib cohort;

7) Any arterial thromboembolic event, including myocardial infarction, unstable angina pectoris, cerebrovascular accident or transient ischemic attack, occurred within 6 months prior to enrollment;

8) Esophageal or gastric varices requiring immediate intervention (e.g., banding or sclerotherapy) or evidence of portal hypertension considered at high risk of bleeding according to the investigator's opinion or consulting gastroenterologist or hepatologist; Subjects with hepatocellular carcinoma who have experienced esophageal or gastric variceal bleeding due to portal hypertension within the past 6 months, or who have evidence of portal hypertension (including splenomegaly detected by imaging examination) must undergo endoscopy within 3 months to evaluate severe varices;

9) Any life-threatening bleeding event occurred within 3 months before enrollment and required medical intervention, such as blood transfusion therapy, surgery or local therapy, continuous drug therapy, etc.;

10) History of deep vein thrombosis, pulmonary embolism, or any other serious thromboembolism within 3 months prior to enrollment (implantable venous access port or catheter-derived thrombosis, or superficial vein thrombosis is not considered "serious" thromboembolism); Portal vein tumor thrombus involving the main trunk and bilateral primary branches, or the main trunk and superior mesenteric vein, or inferior vena cava tumor thrombus at the same time;

11) Uncontrolled metabolic disorder or other non-malignant organ or systemic disease or secondary reaction of cancer, which may lead to high medical risk and/or uncertainty of survival evaluation, and is not suitable for enrollment as judged by the investigator, or there are other conditions that are not suitable for enrollment as judged by the investigator;

12) Hepatic encephalopathy, hepatorenal syndrome or Child-Pugh B (> 7 points) or more severe cirrhosis;

13) History of intestinal obstruction (excluding intestinal obstruction that has been surgically cured) or the following diseases: extensive intestinal resection (partial colon resection or extensive small intestinal resection complicated by chronic diarrhea), Crohn's disease, ulcerative colitis, radiation colitis and other causes of chronic colitis, long-term chronic diarrhea and other intestinal diseases.

14) Significant malnutrition, such as the need for intravenous supplements; Except for correction of malnutrition more than 4 weeks prior to the first dose of study treatment.

15) Tumor invades surrounding vital organs (such as great mediastinal vessels, superior vena cava, trachea, esophagus, etc.) or there is a risk of esophagotracheal fistula or esophagopleural fistula.

16) After intraluminal stenting of the esophagus or trachea.

21. Other acute or chronic illness, psychiatric illness, or abnormal laboratory values that may increase the risk associated with study participation or study drug administration, or interfere with the interpretation of study results, and in the judgment of the investigator, the subject is listed as ineligible for participation in the study.

22. History of other primary malignancies, except:

1) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease recurrence;

2) Adequately treated carcinoma in situ with no evidence of disease recurrence;

3) Patients with other (multiple) tumors should meet at least the following requirements before enrollment at screening: a. No treatment is required for the

combined tumors at present; b. For combined tumors, no known active disease for ⩾ 2 years prior to study enrollment.

23. Female subjects who are pregnant or lactating.

4.3 Restrictions during the Study

- Subjects should not donate blood during their participation in this study and within 12 weeks after the last dose;
- Refer to Section 5.6 for dosing references for pregnant, childbearing potential, and lactating women.

4.4 Subject discontinued treatment

Discontinuation of treatment does not represent withdrawal from the study.

"Since some data on clinical events after discontinuation of treatment may be important for the study, this information must be collected until the subject & '92; s last scheduled visit, even if the subject has discontinued treatment."

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

Subjects must discontinue treatment but may continue to be monitored in the study for any of the following:

1. The subject or his or her legally acceptable representative requests to discontinue the treatment;
2. The occurrence of adverse events requiring discontinuation of treatment as specified in the protocol;
3. Occurrence of another malignancy requiring active treatment;
4. Subjects received new anti-tumor therapy;
5. Intercurrent illness that precludes further treatment;
6. The investigator decides to terminate the subject from the study;
7. Subject has a positive serum pregnancy test result;
8. Poor subject compliance;

9. In the opinion of the investigator, depending on the subject's clinical status or personal circumstances, continued administration of the study drug would place the subject at undue risk;
10. The maximum duration of study drug treatment was reached.

The reason for discontinuation from the study and the date of discontinuation will be collected for all subjects. For subjects who discontinue treatment but continue to be monitored in the study, all visits and procedures listed in the visit table (if applicable) should be completed, including Safety Follow-up and Survival Follow-up.

4.5 Subject Withdrawal from the Study

A subject has the right to withdraw from the study at any time for any reason and must be withdrawn if the subject or the subject's legally acceptable representative withdraws consent.

The Investigator may withdraw a subject from the study for the following reasons:

- Poor subject compliance;
- The occurrence of a clinical adverse event (AE), laboratory abnormality, or other medical condition for which continued participation would not be in the best interest of the subject;
- The subject met the exclusion criteria (new or previously unidentified) and could not continue in the study.

If a subject withdraws from the study, he/she will be discontinued from treatment and will be followed as specified in the protocol, but every effort will be made to persuade him/her to complete the safety follow-up visit and necessary follow-up imaging assessments.

The reason for withdrawal of a subject from the study should be recorded in the electronic case report form (eCRF). Subjects who signed the informed consent form but did not receive the study intervention may be replaced. Subjects who signed the informed consent form to receive study interventions, withdrew or were withdrawn/discontinued from the study, and could not be replaced.

4.6 Lost to follow-up

A subject will be considered lost to follow-up if he/she does not return to the study

site for 2 consecutive scheduled visits and cannot be contacted by the study site staff.

If a subject does not return to the study site for a specified study visit, the following actions must be taken:

- The site attempted to contact the subject, reschedule missed visits, explain to the subject the importance of adhering to the visit schedule, and confirm if the subject is willing and/or should continue in the study.

- Before the subject is deemed lost to follow-up, the investigator or designee will make every effort to recontact the subject (attempts should be made to make at least two phone calls and, if this is not possible, a letter should be sent to the subject at the most recent updated contact address). These attempts to contact the subject should be documented in the subject's medical record or study file.

If the subject still cannot be contacted, it will be considered lost to follow-up and withdrawn from the study.

5 Study Drug and Other Treatments

5.1 Treatment Regimen

5.1.1 Study Treatment Regimen

Subjects were given different doses of IBI110. See the following table for details:

Table 8. Dosage and Treatment Regimen

Medicinal Product	Dose/Amount	Dosing frequency	Usage method	Course/Treatment Cycle
Phase Ia Single Dose Escalation Phase				
IBI110*	0.01 ~ 20mg/kg	Q3W	Intravenous infusion	After the end of DLT observation period in Cycle 1 (28 days), the administration will be performed on Day 1 of each 21-day cycle starting from Cycle 2
Sintilimab *	200mg	Q3W	Intravenous infusion	After the DLT observation period of Cycle 1 (28 days), Cycle 2 starts every 21 days, with administration on Day 1 of each cycle*
* After the end of DLT observation period in Cycle 1 (28 days), 0.01 and 0.1 mg/kg are directly combined with sintilimab at equal doses; Imaging				

Medicinal Product	Dose/Amount	Dosing frequency	Usage method	Course/Treatment Cycle
evaluation will be performed in other dose groups. In case of progression, 0.3, 1 and 3mg/kg will be directly combined with sintilimab for treatment; 10, 20 mg/kg received 1.5 mg/kg IBI110 in combination with sintilimab (see Section 3.2. 3 for details).错误!未找到引用源。				
Phase 1a Single-agent Dose Expansion Phase (Cohorts A1, A2)				
IBI110*	200mg	Q3W	Intravenous infusion	Dosing on Day 1 of each 21-day cycle
Sintilimab *	200mg	Q3W	Intravenous infusion	Dosing on Day 1 of each 21-day cycle
& Subjects will be treated with IBI110 in combination with sintilimab if disease progression occurs during monotherapy (see Section 3 for details). 错误!未找到引用源。				
Phase Ib Combination Dose Escalation Phase				
IBI110*	0.3 ~ 20mg/kg	Q3W	Intravenous infusion	Dosing on Day 1 of each 21-day cycle
Sintilimab *	200mg	Q3W	Intravenous infusion	Dosing on Day 1 of each 21-day cycle
The DLT observation period is within 28 days (4 weeks) after the first dose (see Section 3.2. 3 for details).错误!未找到引用源。				
Phase Ib Combination Dose Expansion Phase				
All Cohorts				
IBI110*	Cohort D1: 200 mg; Cohort D2 treatment group: 600 mg; Cohort N: 200mg or 10mg/kg; Other Cohorts: 200 mg	Q3W	Intravenous infusion	Dosing on Day 1 of each 21-day cycle
Sintilimab *	200mg	Q3W	Intravenous infusion	Dosing on Day 1 of each 21-day cycle
Note: Only sintilimab will be administered in the control group of Cohort D2.				
Cohort B				
Lenvatinib *	< 60kg, 8mg daily; ≥ 60 kg, 12mg daily	Daily	Oral	/
Cohort D				
Pemetrexed ^ *	500mg/m2	Q3W	Intravenous infusion	Each 21-day cycle will be administered on Day 1 of each cycle.

Medicinal Product	Dose/Amount	Dosing frequency	Usage method	Course/Treatment Cycle
Carboplatin	AUC 5	Q3W	Intravenous infusion	Each 21-day cycle will be administered on Day 1 of each cycle for a total of 4 to 6 cycles.
Paclitaxel ^	175mg/m2	Q3W	Intravenous infusion	The study drug will be administered over 3 hours on Day 1 of each 21-day cycle for a total of 4 to 6 cycles.
Cohort J				
Oxaliplatin ^	130mg/m2	Q3W	Intravenous infusion	Each 21-day cycle will be administered on Day 1 of each cycle for up to 6 cycles.
Capecitabine ^ *	1000mg/m2/dose	BID	Oral	Dosing on Days 1-14 of each 21-day cycle.

^ Body Surface Area (BSA) (m2) = 0.0061 × Height (cm) +0.0128 × Weight (kg)-0.1529

* Lenvatinib, pemetrexed, capecitabine, IBI110, and sintilimab will be administered until disease progression, lost to follow-up, or death, intolerable toxicity, withdrawal of consent, or other reason for discontinuation of study treatment, whichever occurs first, for a maximum of 24 months.

5.1.2 Re-dosing after Disease Progression

Subjects with first progressive disease (PD) (primary PD) according to RECIST V1.1 criteria during treatment are required to meet all of the following criteria if they continue to receive combination therapy:

1. In the opinion of the investigator, there may be clinical benefit from continuing to receive the study treatment, and the disease has not progressed rapidly;
2. Able to tolerate the study drug;
3. Stable ECOG PS score;
4. Does not delay the management of serious complications requiring urgent intervention (e.g., CNS metastases);
5. Before continuing treatment with the study drug, the subject needs to be fully informed, and the investigator needs to elaborate on all foreseeable risks or discomforts and his treatment options.

The decision to continue treatment beyond progression, provided that the above criteria are met, will be based on a theoretical decision between the investigator and

sponsor medicine and documented in the study records.

Data will be collected for subjects who continue treatment after initial disease progression, and data variables will be collected according to the visit table.

For subjects with initial documentation of radiographic PD (based on RECIST V1.1 criteria), if the subject continues to receive study drug after confirmation, radiographic assessment to confirm PD (based on iRECIST criteria) must be performed at 4 to 6 weeks, then every 6 weeks (± 7 days) until immunologically confirmed progressive disease (iCPD) (based on iRECIST criteria). The iCPD adjudication is defined as at least an additional 5mm increase in target lesions or unequivocal progression of non-target lesions or an increase of at least 5mm in a previously identified new lesion or an additional new lesion (based on iRECIST criteria). Subjects with iCPD who do not complete combination therapy or monotherapy maintenance will be terminated prematurely.

For subjects who continue treatment after initial PD, if clinical symptoms worsen in the absence of radiographic evidence of re-PD, treatment discontinuation was deemed necessary by the investigator and recorded as "worsening of clinical symptoms". In such cases, the investigator should continue to perform radiographic assessments per protocol 6.3.

5.2 Study drug

The investigational drug in this study is recombinant fully human anti-lymphocyte activation gene-3 (LAG-3) monoclonal antibody (R&D code: IBI110);

Recombinant fully human anti-programmed cell death-1 (PD-1) monoclonal antibody (Sintilimab, R&D code: IBI308).

5.2.1 Description of Study Drug

The active ingredient of IBI110 is a recombinant fully human anti-lymphocyte activation gene 3 (LAG-3) monoclonal antibody.

IBI110 drug product is formulated as 20.0 mg/mL recombinant fully human anti-lymphocyte activation gene 3 (LAG-3) monoclonal antibody, 5.88 mg/mL sodium citrate (dihydrate), 21.07 mg/mL arginine hydrochloride, 0.70 mg/mL polysorbate 80, citric acid (anhydrous) to adjust pH to 6.0.

Manufacturer: Innovent Biologics (Suzhou) Co., Ltd.

The active ingredient of sintilimab is recombinant fully human anti-programmed

death-1 monoclonal antibody, with a concentration of 10.0 mg/ml. "A clear to slightly opalescent, colourless to pale yellow liquid, free from foreign matter." Excipients include 30.06 mg/ml mannitol, 3.73 mg/ml histidine, 5.88 mg/ml sodium citrate (dihydrate), 2.92 mg/ml sodium chloride, 0.0075 mg/ml disodium edetate, 0.2 mg/ml polysorbate 80, adjusted to pH 6.0 with citric acid (monohydrate).

Manufacturer: Innovent Biologics (Suzhou) Co., Ltd.

5.2.2 Labeling of Study Drug

- The minimum packaging unit of IBI110 is a box, each containing a vial of IBI110 for injection.
- The minimum packaging unit of sintilimab is a box, each box contains two sintilimab injections packaged in vials.
- Drug name/code, dosage form, strength, batch number, expiry date, storage conditions and sponsor are printed on the packaging box. The same information is printed on the vial and box labels, but there is no information on dosage form, precautions, and dosage and administration on the vial label.
- All boxes and vials are labeled "for clinical trial use only".

5.2.3 Storage of Study Drug

The shelf life of IBI110 finished product at 2 ℃ to 8 ℃ protected from light is tentatively set to 36 months, and the shelf life will be subsequently extended by changing the process based on the results of long-term stability.

The shelf life of Sintilimab Injection is 36 months when stored at 2 ℃ ~ 8 ℃, protected from light.

In case of turbidity, precipitation and other quality problems in the injection, the injection should be sealed immediately, and the sponsor should be notified immediately.

5.2.4 Preparation and Infusion of Study Drug

Subjects who meet the inclusion criteria during the screening period will be admitted to the study site ward 24 hours prior to dosing. All baseline safety assessments must be obtained prior to dosing.

The subject's vital signs will be observed on the day of administration, and the administration can be started after the corresponding blood sample collection is completed according to the visit requirements.

For the specific configuration and infusion requirements and precautions of IBI110 and sintilimab, please refer to the "CIBI110A101 Study Drug User Manual" provided by the sponsor.

5.2.5 Use of other investigational drugs

Concomitant lenvatinib and standard chemotherapeutic agents were formulated as described in the approved product labeling.

Lenvatinib

Lenvatinib was provided uniformly by the sponsor, and the dosage form of lenvatinib was capsule, and the strength used in this study was 4 mg/capsule. The study site was required to store and administer the drug in accordance with the approved package insert and the following principles were followed:

- Oral, once daily; 8mg daily if the subject's body weight is < 60kg; 12mg daily if the subject weighs ⩾ 60 kg.
- If a subject misses a dose and cannot take it within 12 hours, no missed dose is required and the next dose should be taken at the usual time.
- For oral medications, use the subject diary card to record medication intake.

Pemetrexed

Pemetrexed was supplied uniformly by the Sponsor as a sterile lyophilized powder for solution for injection for intravenous injection and was used in this study at a strength of 200 mg/syringe. The study site was required to store, prepare, and administer the drug in accordance with the approved package insert and to follow the following principles:

Dose Administered:

- 500mg/m2 as an intravenous infusion over 10 minutes. Each 21-day cycle will be administered on Day 1 of each cycle.

Preparation method:

- Dissolve in 8mL of preservative-free sodium chloride 9mg/mL (0.9%) solution for injection to a concentration of 25mg/mL. Slowly swirl until the powder is completely dissolved and the resulting solution is clear and colorless to yellow or yellowish-green in color is normal. The pH of the reconstituted solution is 6.6-7.8 and the solution requires further dilution.
- Before intravenous infusion, it is necessary to observe whether the drug solution has particles and color change; Do not infuse if particulate matter is found.
- The reconstituted pemetrexed solution must be further diluted to 100 mL with preservative-free sodium chloride 9mg/mL (0.9%) solution for injection for intravenous infusion over 10 minutes.
- The chemical and physical properties of reconstituted pemetrexed and infusion solutions are stable for 24 hours after reconstitution when stored refrigerated or at room temperature and light conditions. Pemetrexed reconstituted and infusion solutions prepared as described above contain no antimicrobial preservatives and are intended for single use only, and unused solutions should be discarded.
- Pemetrexed prepared as described above is intended for use in polyvinyl chloride (PVC) administration sets and intravenous infusion bags.
- Prior to intravenous infusion, only 0.9% Sodium Chloride Injection (preservative free) is recommended for reconstitution and further dilution prior to intravenous infusion. Pemetrexed is physically incompatible with calcium-containing diluents, including Lactated Ringer's Injection, USP and Ringer's Injection, USP, therefore, these solutions should not be used. The use of pemetrexed with other medicinal products and diluents has not been studied and is therefore not recommended.

Premedication:

- Corticosteroids: The incidence of rash was higher with pemetrexed in patients not premedicated with corticosteroids. Pre-administration of dexamethasone (or drugs of the same class) may reduce the incidence and severity of skin reactions. Method of administration: Dexamethasone 4 mg was administered orally twice daily for 3 consecutive days 1 day before, on the day of, and 1 day after pemetrexed administration.
- Vitamins: To mitigate toxicity, patients receiving pemetrexed therapy must take daily

low-dose folic acid or a multivitamin preparation containing folic acid. Duration of administration: at least 5 daily doses of folic acid within 7 days prior to the first dose of pemetrexed, throughout the treatment cycle, and 21 days after the last dose of pemetrexed. Vitamin B12 was also administered intramuscularly within 7 days prior to the first dose of pemetrexed and every 3 cycles thereafter, and subsequent doses of vitamin B12 could be administered on the same day as pemetrexed. Administration dose of folic acid: 350 ~ 1000 μg, with the usual dose of 400 μg; Vitamin B12 dose 1000 μg.

Carboplatin

Carboplatin was uniformly provided by the sponsor. The dosage form of carboplatin was injection, and the strength used in this study was 10mL: 100mg/syringe. The study site was required to store and administer the drug in accordance with the approved package insert and the following principles were followed:

- AUC=5

  Carboplatin dose (mg) = set AUC (mg/ml/min) × [GFR+25] (GFR was estimated using creatinine clearance calculation formula, see Appendix 3 for details)

- Each 21-day cycle will be administered on Day 1 of each cycle for a total of 4-6 cycles.

- Add into 250 ~ 500ml of 5% glucose injection for intravenous drip immediately before use. Once carboplatin has been diluted, it should be used up within 8 hours, and direct sunlight should be avoided when dripping and storing.

Paclitaxel

Paclitaxel was uniformly provided by the sponsor. The dosage form of paclitaxel was injection. The strength used in this study was 5ml: 30mg/vial. The study site was required to store and administer the drug in accordance with the approved package insert and the following principles were followed:

- The recommended dose is 175mg/m2 administered intravenously over 3 hours. Doses will be administered over 3 hours on Day 1 of each 21-day cycle for a total of 4 to 6 cycles.

- In order to prevent severe allergic reactions, dexamethasone 20mg is usually given

orally 12 and 6 hours before paclitaxel treatment or intravenously 30 to 60 minutes before paclitaxel treatment; Diphenhydramine (or its like drug) 50mg, intravenous injection or deep intramuscular injection 30 ~ 60 minutes before paclitaxel, and intravenous drip of cimetidine (300mg) or ranitidine (50mg) 30 ~ 60 minutes before the injection of this product.

- Must be diluted prior to instillation. Paclitaxel should be diluted in 0.9% sodium chloride injection, or in 5% glucose injection, or in 5% glucose plus 0.9% sodium chloride injection or in 5% glucose Ringer's solution to the final concentration of 0.3 ~ 1.2 mg/mL. The physicochemical properties of the paclitaxel solution are stable for up to 27 hours at ambient temperature (approximately 25 ℃) and room lighting. Before injecting such medicinal products, the solution and container should be inspected visually for particulate matter or a change in colour whenever possible. The infusion bottle and infusion set made of non-polyvinyl chloride material shall be used for dripping paclitaxel, and the infusion bottle and infusion set shall pass through the connected filter, and the microporous membrane of filter shall be less than 0.22 μm.

Oxaliplatin

Oxaliplatin was provided uniformly by the sponsor, and the dosage form of oxaliplatin was a sterile lyophilized powder for injection for intravenous injection. The strength used in this study was 50 mg/syringe. The study site was required to store and administer the drug in accordance with the approved package insert and the following principles were followed:

- The recommended dose is 130mg/m2 administered on Day 1 of each 21-day cycle for up to 6 cycles.
- Prepare with 5% glucose solution (do not prepare and dilute the product with saline solution). For the 50 mg package, add 10 ml of 5% glucose solution to reach the concentration of 5.0 mg/ml oxaliplatin; The prepared solution is removed from the bottle and immediately diluted with 250-500 ml of 5% glucose solution to a concentration above 0.2 mg/ml (the physicochemical stability of the solution is normally maintained between 2 ℃ and 8 ℃ for 24 hours). It is infused through a peripheral or central vein over 2-6 hours (if the patient experiences acute laryngospasm when oxaliplatin is infused at a rate that is completed within 2 hours,

the infusion should be extended to 6 hours for the next infusion).

- Precautions in use:

1. Injection materials containing aluminium must not be used.
2. Do not use undiluted.
3. Do not prepare or dilute the product with saline solutions.
4. Do not mix with any other medicine or use it through the same infusion channel. Flush the infusion line after the Oxaliplatin infusion is complete.
5. Flush the infusion line before infusing Oxaliplatin.
6. Only the recommended vehicle (5% dextrose solution) should be used.
7. If any precipitate is present in the prepared solution, it should not be used any more and should be destroyed in accordance with the regulatory requirements for the handling of hazardous materials.

Capecitabine

Capecitabine was provided uniformly by the Sponsor and was formulated as tablets and used in this study at a strength of 500 mg/tablet. Sites were required to store and administer the study drug in accordance with the approved package insert at an initial dose of 1000 mg/m2 and to conform to the following principles:

	标准剂量（1000mg/m²）bid			**-1 水平（75%）**			**-2 水平（50%）**		
体表面积（m^2）	每天总剂量（mg）	每次片数（片）500mg/片		每天总剂量（mg）	每次片数（片）500mg/片		每天总剂量（mg）	每次片数（片）500mg/片	
		早晨	晚上		早晨	晚上		早晨	晚上
[1.0,1.24]	2000	2	2	1500	2	1	1000	1	1
[1.25,1.49]	2500	3	2	1500	2	1	1000	1	1
[1.50,1.74]	3000	3	3	2000	2	2	1500	2	1
[1.75,1.99]	3500	4	3	2500	3	2	1500	2	1
2.0~	4000	4	4	3000	3	3	2000	2	2

- Swallow with water within 30 minutes after a meal (breakfast or supper) twice daily (approximately 12 hours apart) for 14 days followed by one week off, repeated every 3 weeks.

- The dose of capecitabine will be calculated in milligrams per square meter of body surface area (mg/m2) based on the height and weight of the subject, and the maximum total dose should not exceed 4000 mg/day.
- If a subject undertakes or misses a dose during the course of treatment, no additional dose will be added.
- If the drug is suspended due to adverse reactions, the drug should be administered orally as prescribed after the adverse reactions are recovered to ≤ Grade 1, and the dose not taken in the middle will not be supplemented.
- For oral medications, use the subject diary card to record medication intake.

5.3 Dose Modification

Prior to each dose of study drug on Day 1, subjects must have met dosing requirements for hematologic, hepatic, and renal function (ie, ANC ≥ 1.5 × 109/L, PLT ≥ 75 × 109/L, HGB ≥ 9 g/dL, TBIL ≤ 1.5 × ULN, ALT and AST ≤ 3 × ULN, ALT and AST ≤ 5 × ULN for subjects with liver metastases, albumin ≥ 28 g/L, Cr ≤ 1.5 × ULN or CCr ≥ 50 mL/min, INR ≤ 2, APTT ≤ 1.5 × ULN), and all toxicities must have resolved to Common Terminology Criteria for Adverse Events (CTCAE) V5.0 Grade 0-1 or baseline (except see Section 5.4. 2.2). In clinical practice, it is possible that the administration may deviate from the above administration requirements but can be determined by the investigator. If the investigator considers that the patient can tolerate the study drug, he/she may administer the study drug after communicating with the sponsor via email, and follow-up closely, and timely deal with the possible changes in the subsequent conditions.

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

5.3.1 Dose Modification

No dose adjustments of IBI110 were allowed throughout the study, unless the change in body weight was ≥ 10% from the Baseline Visit, and the actual dose was calculated based on the weight on the scheduled day of dosing. The general principles for the management of immune-related adverse events are shown in Table 9, and detailed toxicity management guidelines can be made by referring to the Sponsor's Immune-Related Adverse Event Management Manual or the latest official relevant handling guidelines for

appropriate drug modifications.

No dose adjustment of sintilimab was allowed throughout the study. See Table 10 and Package Insert of Sintilimab for drug adjustment.

Table 9. General Principles for the Management of Immune-Related Adverse Events

Drug-related toxicity	Severity	Management method
1. Dermal Toxicity		
Rash/inflammatory dermatitis	Grade 1	Continue medication
	Grade 2	Consider drug interruption
	Grade 3	Suspend the drug and consult a dermatologist to determine whether to resume the drug
	Grade 4	Withhold the drug and consult a dermatologist, and decide whether to continue the drug after symptoms recover and prednisone ≤ 10 mg/day
Bullous dermatosis	Grade 1	Continue medication
	Grade 2-3	Suspend the drug and consult a dermatologist to determine whether to resume the drug
	Grade 4	Permanent Discontinuation
Serious Cutaneous Adverse Events: SJS, TEN, AGEP, and DRESS	Grade 1 (none)	/
	Grade 2	The drug was discontinued and observed
	Grade 3	Suspend medication and consult dermatologist
	Grade 4	Permanent Discontinuation
2. Gastrointestinal Toxicity		
Colitis	Grade 1	Continue or hold until toxicity does not exceed Grade 1
	Grade 2	Withhold until symptoms recover to Grade 1
	Grade 3	Permanent discontinuation of CTLA-4 may be considered, and resumption of PD-1, PD-L1 agents upon recovery to Grade 1 or lower
	Grade 4	Permanent Discontinuation
Hepatitis	Grade 1	Continue medication and observe
	Grade 2 AST or ALT elevation Or Grade 2 TBIL elevation	Withhold dosing until the adverse reaction recovers to Grade 0-1 or resume dosing after the adverse reaction recovers to baseline

Drug-related toxicity	Severity	Management method
	Grade 3 AST or ALT elevation Or Grade 3 TBIL elevation	Withhold the dose until the adverse reaction recovers to Grade 0-1 or to baseline condition, and consider resuming the dose
	Grade 4 AST or ALT elevation Or Grade 4 TBIL elevation	Permanent Discontinuation
3. Pulmonary Toxicity		
Pneumonia	Grade 1	Withhold for radiographically confirmed exacerbation of pneumonia
	Grade 2	Hold until recovery to Grade 1 or lower
	Grade 3-4	Permanent Discontinuation
4. Endocrine Toxicity		
Primary hypothyroidism	Grade 1	The drug was continued and the patient was closely observed
	Grade 2	The drug was continued and the patient was closely observed
	Grade 3-4	Withhold until recovery to baseline after treatment
Hyperthyroidism	Grade 1	The drug was continued and the patient was closely observed
	Grade 2	Consider drug interruption until symptoms return to baseline
	Grade 3-4	Withhold until recovery to baseline after treatment
Primary adrenocortical insufficiency	Grade 1-2	Consider withholding until patient stabilizes on hormone replacement therapy
	Grade 3-4	Hold until patient stabilizes on hormone replacement therapy
Hypophysitis	Grade 1-2	Consider withholding until patient stabilizes on hormone replacement therapy
	Grade 3-4	Hold until patient stabilizes on hormone replacement therapy
Diabetes	Grade 1	The drug was continued and the patient was closely observed
	Grade 2	May withhold until blood glucose is controlled

Drug-related toxicity	Severity	Management method
	Grade 3-4	Hold until blood glucose is controlled and recovered to Grade 1 or lower
5. Musculoskeletal Toxicity		
Inflammatory arthritis	Grade 1	Continue medication
	Grade 2	Hold until symptoms are controlled and prednisone ≤ 10 mg/day
	Grade 3-4	Withhold the drug, and consult a rheumatologist to determine whether to continue the drug when the symptoms recover to Grade 1 or lower
Myositis	Grade 1	Continue medication
	Grade 2	Withhold until symptoms are controlled and CK is normal
	Grade 3-4	Withhold until recovery to Grade 1 or less without immunosuppression, and permanently discontinue if evidence of myocardial involvement
Polymyalgia-like syndrome	Grade 1	Continue medication
	Grade 2	Consider drug interruption until symptoms are controlled
	Grade 3-4	Withhold the drug, and consult a rheumatologist to determine whether to continue the drug when the symptoms recover to Grade 1 or lower
6. Nephrotoxicity		
Nephritis	Grade 1	Consider drug interruption based on other possible etiologies and baseline renal function
	Grade 2	Drug interruption
	Grade 3	Permanent Discontinuation
	Grade 4	Nephrology consultation
Symptomatic nephritis: follow-up	Grade 1	If return to baseline, resume routine creatinine monitoring
	Grade 2	Corticosteroid taper for at least 3 weeks if recovered to Grade 1
	Grade 3-4	Corticosteroid taper over at least 4 hours if recovered to Grade 1
7. Nervous System Toxicity		
Myasthenia gravis	Grade 1 (none)	/
	Grade 2	Withhold until symptoms recover
	Grade 3-4	Permanent Discontinuation
Guillain-Lee syndrome	Grade 1 (none)	/

Drug-related toxicity	Severity	Management method
	Grade 2-4	Permanent Discontinuation
Peripheral neurotoxicity	Grade 1	The standard of drug suspension was lowered and the symptoms were observed for one week; Closely observe the symptoms if the drug is continued
	Grade 2	Hold until recovery to Grade 1
	Grade 3-4	Permanent Discontinuation
Autonomic neuropathy	Grade 1	The standard of drug suspension was lowered and the symptoms were observed for one week; Closely observe the symptoms if the drug is continued
	Grade 2	Hold until recovery to Grade 1
	Grade 3-4	Permanent Discontinuation
Meningitis aseptic	Grade 1-4	Drug interruption
Encephalitis	Grade 1-4	Drug interruption
Transverse myelitis	Grade 1-4	Permanent Discontinuation
8. Hematotoxicity		
Autoimmune haemolytic anaemia	Grade 1	The drug was continued and the patient was closely observed
	Grade 2	Withhold the drug and consider whether to permanently discontinue the drug
	Grade 3-4	Permanent Discontinuation
Acquired thrombotic thrombocytopenic purpura	Grade 1-4	Drug suspension, hematology consultation
Hemolytic uremic syndrome	Grade 1-2	The drug was continued and the patient was closely observed
	Grade 3-4	Permanent Discontinuation
Aplastic anemia	Grade 1-2	The drug was discontinued, growth factor therapy was provided and close observation was performed
	Grade 3-4	Hold drug, provide growth factor therapy and monitor daily
Lymphopenia	Grade 1-2	Continue medication
	Grade 3	Continue medication and monitor blood routine and CMV weekly
	Grade 4	Drug interruption
Immune thrombocytopenia	Grade 1	The drug was continued and the patient was closely observed
	Grade 2-4	Hold the drug, and resume the drug after recovery to Grade 1
Acquired haemophilia	Grade 1-2	Drug interruption

Drug-related toxicity	Severity	Management method
	Grade 3-4	Permanent Discontinuation
9. Cardiovascular Toxicity		
Myocarditis, pericarditis, arrhythmia, ventricular dysfunction with cardiac failure and vasculitis	Grade 1	Drug interruption
	Grade 2-4	Permanent Discontinuation
Venous thromboembolism	Grade 1-3	Continue medication
	Grade 4	Permanent Discontinuation
10. Ocular Toxicity		
Uveitis/iritis	Grade 1	Continue medication
	Grade 2	Suspend the drug and consult an ophthalmologist
	Grade 3-4	Permanent Discontinuation
Episcleritis	Grade 1	Continue medication
	Grade 2	Suspend the drug and consult an ophthalmologist
	Grade 3-4	Permanent Discontinuation
Blepharitis	No classification definition	Continue medication unless symptoms persist and are severe

Table 10. Drug modification of sintilimab

Immune-related adverse reactions	Severity	Treatment Modification
Pneumonia	Grade 2	Withhold the dose until the adverse reaction recovers to grade 0-1
	Grade 3 or 4 or recurrent Grade 2	Permanent Discontinuation
Diarrhea and colitis	Grade 2 or 3	Withhold the dose until the adverse reaction recovers to grade 0-1
	Grade 4	Permanent Discontinuation
Hepatitis	Grade 2 AST or ALT elevation Or Grade 2 TBIL elevation	Withhold dosing until the adverse reaction recovers to Grade 0-1 or resume dosing after the adverse reaction recovers to baseline
	Grade 3 AST or ALT elevation Or Grade 3 TBIL elevation	Withhold the dose until the adverse reaction recovers to Grade 0-1 or to baseline condition, and consider resuming the dose
	Grade 4 AST or ALT elevation	Permanent Discontinuation

Immune-related adverse reactions	**Severity**	**Treatment Modification**
	Or Grade 4 TBIL elevation	
Nephritis	Grade 2 or 3 blood creatinine increased	Withhold the dose until the adverse reaction recovers to grade 0-1
	Grade 4 blood creatinine increased	Permanent Discontinuation
Endocrine disorders	Symptomatic Grade 2 or 3 hypothyroidism, Grade 2 or 3 hyperthyroidism, Grade 2 or 3 hypophysitis, Grade 2 adrenal insufficiency Grade 3 hyperglycemia or type 1 diabetes mellitus	Withhold the dose until the adverse reaction recovers to grade 0-1
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 hyperglycemia or type 1 diabetes mellitus	Permanent Discontinuation
Cutaneous adverse reactions	Grade 3	Withhold the dose until the adverse reaction recovers to grade 0-1
	Grade 4, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanent Discontinuation
Thrombocytopenia	Grade 3	Withhold the dose until the adverse reaction recovers to grade 0-1
	Grade 4	Permanent Discontinuation
Other immune-related adverse reactions	Grade 3 or 4 blood amylase increased or lipase increased Grade 2 or 3 pancreatitis Grade 2 myocarditis * Other Immune-Related Adverse Reactions with First Occurrence of Grade 2 or 3	Withhold until improved to Grade 0-1
	Grade 4 pancreatitis or recurrent pancreatitis of any grade Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 4 Other Immune-Related Adverse Reactions for the First Occurrence	Permanent Discontinuation
Recurrent or persistent	Recurrent Grade 3 or 4 (excl endocrinopathies)	Permanent Discontinuation

Immune-related adverse reactions	Severity	Treatment Modification
adverse reactions	Grade 2 or 3 adverse reactions that do not improve to Grade 0 ~ 1 within 12 weeks after the last dose (excluding endocrine diseases) Failure to reduce corticosteroids to ≤ 10 mg/day prednisone equivalent within 12 weeks of last dose	
Infusion reaction	Grade 2	Reduce the infusion rate or withhold the drug. When the symptoms are relieved, the drug can be resumed and closely observed
	Grade 3 or 4	Permanent Discontinuation

Note: The severity of adverse events was based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0).

* The safety of restarting IMBRUVICA when myocarditis improves to Grade 0-1 with treatment is unknown.

Drug interruption

- The maximum time interval allowed for drug interruption is 12 weeks (calculated from the last dose as the starting time point, i.e., the time interval between the two doses is no more than 12 weeks). If the subject does not recover to a status that would allow reintroduction of IBI110 and/or sintilimab within 12 weeks, the subject will permanently discontinue IBI110 and/or sintilimab and enter the Safety Follow-up Period, with the following exceptions:

  a) Corticosteroids were used for the treatment of AE, and the corticosteroid tapering process resulted in study drug interruptions for more than 12 weeks. "In such cases, the decision to continue study drug should be discussed with the sponsor & '92; s medical manager." Tumor imaging assessments were performed as planned and were not affected by dose interruption.

  b) Study drug interruption for more than 12 weeks due to treatment of an AE unrelated to study drug, etc. "In such cases, the decision to continue study drug should be discussed with the sponsor & '92; s medical manager." Tumor

imaging assessments were performed as planned and were not affected by dose interruption.

5.3.2 Treatment of infusion reactions

IBI110 and sintilimab contain only human immunoglobulin amino acid sequences and are not likely to cause infusion reactions or hypersensitivity reactions. However, such reactions may cause fever, chills, headache, rash, pruritus, arthralgia, hypertension or hypotension, bronchospasm and other symptoms. All Grade 3 and 4 infusion reactions that meet the definition of an SAE should be reported as SAE within 24 hours. Infusion reactions should be graded according to the NCI CTCAE v5.0 criteria. Please refer to the following or according to clinical routine for symptomatic treatment:

Grade 1 symptoms (mild reaction. No infusion interruption required; no additional intervention required).

Observe at bedside until the subject's symptoms recover.

Grade 2 symptoms (moderate reaction. Requires infusion interruption but promptly recovers after symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, fluids]).

Discontinue the study drug infusion, initiate an infusion of normal saline, and administer diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg with bedside observation until the subject's symptoms resolve. Administer corticosteroids or bronchodilators as needed. If the infusion is suspended, the infusion may be restarted at 50% of the previous infusion rate after symptoms have resolved. If no other symptoms are confirmed after 30 minutes of infusion, return to 100% of the previous infusion rate and observe closely. If symptoms reappear, study drug will be discontinued on the same day and diphenhydramine 50 mg IV will be administered and observed at bedside until the subject's symptoms resolve. The dose of study drug infused must be recorded on the eCRF. Subsequently, the following prophylactic medications were recommended before study drug administration: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before study drug administration. Corticosteroids (up to 25 mg hydrocortisone or equivalent, IV) may be administered as needed.

Grade 3-4 symptoms (severe reaction. Grade 3: prolonged symptoms [failure to recover promptly after symptomatic treatment and/or brief discontinuation of infusion]; reappearance after improvement; hospitalization for other sequelae.

Grade 4: life-threatening; pressor or ventilatory support).

The study drug infusion was immediately discontinued. Infusion of normal saline was started and treated as follows. A bronchodilator is recommended, epinephrine 0.2-1 mg 1: 1000 subcutaneously or 0.1-0.25 mg 1: 10000 intravenously, and/or diphenhydramine 50 mg IV plus methylprednisolone 100 mg (or equivalent). Subjects were observed until the investigator considered that the symptoms did not recur. Study drug was permanently discontinued. Investigators need to treat allergies according to guidelines. Observe at bedside until the subject's symptoms recover. In the event of delayed hypersensitivity reactions (e.g., local or generalized itching after 1 week of treatment), symptomatic treatment (e.g., oral antihistamines or corticosteroids) should be administered.

5.3.3 Modification of other medications

The investigator should adjust the dose of lenvatinib and related chemotherapy drugs according to the site's package inserts as well as the site's diagnosis and treatment routine. Detailed drug information can be referred to the corresponding package insert.

For the IBI110 + sintilimab in combination with other drugs cohort. If treatment is delayed due to other drug-related toxicities, the administration of sintilimab and IBI110 should be postponed until the toxicities have recovered to acceptable levels; If dosing is delayed due to sintilimab or IBI110-related immune adverse reactions, the other drugs can be administered on schedule at the discretion of the investigator.

5.4 Principles of Toxicity Management of Immune Checkpoint Inhibitors

The mechanism of action of IBI110/sintilimab is to promote the proliferation and activation of T cells by blocking the inhibitory effects of the immune system of LAG-3 and PD-1, respectively, which can cause autoimmune hyperfunction, leading to autoimmune diseases of multiple systems. Other immune checkpoint inhibitors such as Ipilimumab, Nivolumab, Pembrolizumab, and Atezolizumab have been associated with autoimmune AE such as immune-related pneumonia, diarrhea/enterocolitis, renal dysfunction, rash, hepatitis, endocrinopathy, and peripheral or central neuritis.

Preliminary Efficacy of Relatlimab in Combination with Nivolumab in Patients with Advanced Melanoma Previously Treated with Anti-PD-1/Anti-PD-L1 (Study CA224-020). The most common Grade 3/4 treatment-related adverse events (TRAE) were colitis, amylase increased, mucosal inflammation, AST increased, and lipase increased. No

treatment-related deaths were reported. The safety profile of the combination was consistent with that of single-agent nivolumab.

A Phase I/II Study of LAG525 in Combination with Spartalizumab in Malignant Tumors (NCT02460224). "In terms of adverse events, dose-limiting toxicities (Grade 3 ascites, lipase increased, vomiting; Grade 4 acute kidney injury in the LAG525 alone group; Grade 3 hyperglycemia, pneumonia, brain tumor edema, asthenia; Grade 4 autoimmune hepatitis in the combination group) occurred in 4 subjects each in the monotherapy group and in 4 subjects each in the combination group and were not dose-related." The common adverse events in the single-agent group were: fatigue (9%) and nausea (8%); In the combination group: fatigue (19%), diarrhea (16%), and nausea (12%); grade 3-4 adverse events occurred in 8% of patients in the monotherapy group and 8% of patients in the combination group. Increasing approximately with increasing dose of LAG525. No maximum tolerated dose (MTD) occurred in either the monotherapy or combination groups, and the overall tolerability was good. The results suggest that the combination is more effective and well tolerated than the single drug.

Once the above AE occur in the subjects in this study, the symptoms and signs of the subjects should be monitored, and relevant examinations should be performed to identify the etiology. If no alternative etiology (eg, disease progression, concomitant medications, and infections) is identified and requires treatment with corticosteroids and/or other immunosuppressants (except for endocrine events such as hyperthyroidism/hypothyroidism, hypophysitis, type 1 diabetes mellitus, and adrenal insufficiency, which may not be treated with immunosuppression but are still considered related to autoimmune hyperfunction caused by the study drug (IBI110 or sintilimab), these AE should be considered related to immune system hyperfunction caused by IBI110 or sintilimab and diagnosed as irAE.

Guidelines for dose modifications and toxicity management of potential irAE are provided in the Immune-Related Adverse Event Management Manual provided by the sponsor.

Due to inhibition of co-stimulatory T-cell activity via LAG3 and PD-1 pathways, and the limited number of subjects treated with IBI110 in combination with sintilimab to date, it is not possible to distinguish the specific drug relatedness of immune-related adverse events in combination. Therefore, it is recommended that both IBI110 and

sintilimab be discontinued in the event of an adverse event that requires dose interruption; When the adverse event has recovered to the premedication range, the investigator may, at the discretion of experience, resume both IBI110 and sintilimab, or gradually resume sintilimab and IBI110. Given the efficacy of IBI110 monotherapy, resumption of IBI110 alone is not recommended.

5.5 Concomitant Therapy

5.5.1 Prohibited Treatments

1) Other treatments for tumors, such as chemotherapy, immunotherapy, immunomodulatory therapy (such as thymosin), targeted therapy, hormone therapy, local treatment of target lesions, etc., which have significant impact on the efficacy evaluation of the investigational drug.
2) The traditional Chinese medicine with immunomodulatory effect and/or anti-tumor effect, Chinese patent medicine and other alternative treatments have significant impact on the efficacy evaluation of the investigational drug.
3) Immunosuppressants and high-dose corticosteroids (except for treatment of AE).
4) Immunoglobulins.
5) Receiving live attenuated vaccines.

5.5.2 Permitted Treatments

1) Medications that meet the protocol requirements as judged by the investigator (eg, concomitant medications used to treat disease-related symptoms and related AE).
2) Subjects who require long-term medication due to underlying diseases such as hypertension and diabetes can continue medication.
3) Local surgery or radiotherapy (excluding the lung) to a solitary lesion (excluding target lesions) while on study treatment.
4) Supportive treatment for relieving tumor-related symptoms is allowed, such as bisphosphonate therapy for bone metastasis and will not significantly affect the efficacy evaluation of the study drug.

5) Topical glucocorticoids, such as external skin use, eye drops, nasal spray, inhalation, etc., are allowed. Short-term use of hormones with the main purpose of pretreatment and anti-allergy is allowed.

5.5.3 Drug interactions

IBI110

There are no data on drug interactions with IBI110.

sintilimab

Sintilimab is a humanised monoclonal antibody and pharmacokinetic interaction studies with other medicinal products have not been performed. "Since monoclonal antibodies are not metabolized by cytochrome P450 (CYP) enzymes or other drug-metabolizing enzymes, inhibition or induction of these enzymes by concomitantly administered drugs is not expected to affect the pharmacokinetics of IMBRUVICA."

The use of systemic corticosteroids and other immunosuppressants prior to initiation of sintilimab treatment should be avoided due to potential interference with sintilimab pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressive agents may be used after initiation of sintilimab treatment if used to treat immune-related adverse reactions.

Lenvatinib

Chemotherapeutic drugs

Co-administration of lenvatinib, carboplatin, and paclitaxel had no significant effect on the pharmacokinetics of any of the 3 drugs.

Effects of lenvatinib on other medicinal products

In a drug-drug interaction (DDI) clinical study in cancer patients, plasma concentrations of midazolam, a sensitive CYP3A and Pgp substrate, were not altered in the presence of lenvatinib. Therefore, there is no apparent drug-drug interaction between lenvatinib and other CYP3A4/Pgp substrates.

Oral contraceptives

It is not known whether lenvatinib decreases the effectiveness of hormonal contraceptives, therefore women using oral hormonal contraceptives should add barrier

contraception.

Pemetrexed

Non-steroidal anti-inflammatory drugs (NSAIDs)

In patients with normal renal function (creatinine clearance ≥ 80 mL/min), high doses of nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen > 1600 mg/day) and higher doses of aspirin (≥ 1.3 g/day) may decrease the clearance of pemetrexed and increase the incidence of pemetrexed adverse events. Therefore, caution should be exercised when higher doses of NSAIDs or aspirin are coadministered with pemetrexed in patients with normal renal function (creatinine clearance ≥ 80 mL/min).

In patients with mild to moderate renal impairment (creatinine clearance ≥ 45-79 mL/min), concomitant administration of pemetrexed with higher doses of NSAIDs (e.g., ibuprofen) or aspirin should be avoided for 2 days before, on the day of, and for 2 days after administration of pemetrexed.

Because there are no data on the potential interaction of pemetrexed with NSAIDs with longer half-lives such as piroxicam or rofecoxib, patients with mild to moderate renal impairment who are taking such NSAIDs should discontinue the NSAIDs for at least 5 days before, on the day of, and 2 days after pemetrexed administration. If concomitant administration of NSAIDs is necessary, patients should be closely monitored for toxicity, particularly myelosuppression and gastrointestinal toxicity.

nephrotoxic drug

Pemetrexed is primarily eliminated by the kidneys as unchanged drug, primarily by tubular secretion and to a lesser extent by glomerular filtration. Concomitant use of nephrotoxic drugs (e.g., aminoglycosides, medullary diuretics, platinum compounds, cyclosporine) may result in delayed clearance of pemetrexed. Concomitant administration of other drugs that are excreted by the renal tubules (e.g., probenecid, penicillin) may also result in delayed elimination of pemetrexed. Caution should be exercised when these medicinal products are co-administered with pemetrexed. If necessary, creatinine clearance should be closely monitored.

Drugs Metabolized by Cytochrome P450 Enzymes

Pemetrexed has limited hepatic metabolism. Results from in vitro human liver

microsomal assays indicate that pemetrexed does not cause clinically meaningful inhibition of the metabolic clearance of drugs metabolized by CYP3A, CYP2D6, CYP2C9, and CYP1A2.

Common interactions for all cytotoxic drugs

Anticoagulant therapy is often used because of the increased risk of thrombosis in cancer patients. Patients who decide to use oral anticoagulants require increased frequency of INR (International Normalised Ratio) monitoring due to the high variability of individual anticoagulation status during the course of the disease and the potential interaction between oral anticoagulants and anticancer chemotherapy.

Live attenuated vaccine

Immunosuppressed states are common in cancer patients, therefore, concomitant administration of live attenuated vaccines is not recommended, except for the contraindicated yellow fever vaccine, which may be at risk of fatal systemic disease. The risk is increased in patients whose underlying disease already causes immunosuppression. Inactivated vaccines should be used if available (e.g. Poliomyelitis).

Carboplatin

1. Nephrotoxic drugs: Combination with other nephrotoxic drugs should be avoided.

2. Aminoglycosides: Caution must be exercised when carboplatin is used in combination with aminoglycosides for cumulative ototoxicity and nephrotoxicity, especially in patients with renal failure.

3. Loop diuretics: Caution must be exercised when carboplatin is used in combination with loop diuretics for cumulative nephrotoxicity and ototoxicity, especially in patients with renal failure.

4. Other myelosuppressive drugs: When used concomitantly, the dose and cycle must be carefully designed.

5. Other drugs with emetogenic effects: Vomiting is increased when administered concomitantly.

6. Other drugs: When using drugs concomitantly, the additive toxicity must be vigilant, especially when using drugs with myelosuppression or nephrotoxicity.

7. Live vaccines: Concomitant use with live vaccines increases the risk of fatal systemic vaccine disease. Therefore, concomitant use of live vaccines in immunosuppressed patients is not recommended.

Paclitaxel

1. Since quinupristin/dalfopristin is a cytochrome P450-3A4 enzyme inhibitor, concomitant administration may increase plasma concentrations of this drug. 2. The serum trough concentration levels of terazomib were increased approximately 1.5-fold with co-administration of terazomib. Clinical trials have proved that the combination of the two drugs has a better effect. 3. Cisplatin can reduce the clearance rate of this drug by about 1/3. If this drug is administered after cisplatin, it can produce more severe myelosuppression. 4. In combination with adriamycin, the study showed that the clearance of adriamycin was significantly decreased by continuous infusion of the drug for 24 hours followed by continuous infusion of adriamycin for 48 hours, and neutropenia and stomatitis were aggravated. 5. Administration of epirubicin immediately after administration of this drug may aggravate the toxicity of this drug. 6. Ketoconazole may inhibit the metabolism of this drug. 7. Fosphenytoin and phenytoin may decrease the effects of this drug by inducing cytochrome P450. 8. Vaccination with live vaccines (e. G. Rotavirus vaccine) while using this medicine may increase the risk of infection with live vaccines. Foreign data suggest that vaccination with live vaccines is prohibited when using this drug. In remission of leukemia patients, the interval after the end of chemotherapy at least three months before vaccination with live vaccines.

Oxaliplatin

No pharmacokinetic interaction was observed between 85 mg/m2 oxaliplatin and infusional 5-fluorouracil in patients dosed every two weeks, but an approximately 20% increase in plasma levels of 5-fluorouracil was observed in patients dosed with 130 mg/m2 oxaliplatin every 3 weeks. In vitro, the following drugs did not displace platinum from plasma proteins: erythromycin, salicylate, valproate, granisetron, and paclitaxel. In in vitro studies, oxaliplatin was neither metabolized by nor inhibited cytochrome P450 isoenzymes. Therefore, no P450-mediated drug-drug interactions are expected in patients. Since platinum-containing varieties are primarily eliminated by the kidney, although specific studies have not been conducted, concomitant use of potentially nephrotoxic compounds may reduce the clearance of these products.

Caution should be exercised when oxaliplatin is co-administered with other drugs known to cause QT interval prolongation. If concomitant use with such drugs occurs, the QT interval should be closely monitored.

Caution should be exercised when Oxaliplatin is coadministered with other drugs known to cause rhabdomyolysis.

Capecitabine

Capecitabine was used in combination with a large number of drugs, such as antihistamines, NSAIDs, morphine, paracetamol, aspirin, antiemetics, H2 receptor antagonists, and no clinically significant side effects were observed. Protein binding: capecitabine is low bound to serum proteins (64%) The potential for interaction with tightly protein-bound drugs by displacement is not predictable. Interactions with cytochrome P450 enzymes: No effect of capecitabine on human liver microsomal P450 enzymes was found in in vitro experiments.

5.6 Dosing during pregnancy, childbearing potential, or lactation

5.6.1 Pregnancy

Human IgG1 and IgG4 are known to cross the placental barrier and are not recommended during pregnancy. Pregnant women cannot be enrolled in this study.

5.6.2 Childbearing age

Female subjects of childbearing potential who are sexually active with a non-sterilized male partner, and non-sterile male subjects who are sexually active with a female partner of childbearing potential must use at least 1 of the acceptable effective methods of contraception listed in Table 11 from Screening until 6 months after the last dose and should discuss their discontinuation with a responsible physician after that time point. Periodic abstinence, rhythm methods, and extracorporeal sperm withdrawal methods are not acceptable methods of contraception. Females of childbearing potential are defined as those who have had menarche, have not undergone sterilization (i.e., bilateral tubal ligation, bilateral salpingectomy, or total hysterectomy), and have not yet reached menopause.

Table 11. Effective contraception (at least 1 method must be used)

Barrier method	IUD method	Hormonal method
Male condom with spermicide	With copper T-ring	Implants
Diaphragm plus spermicide	Progesterone-containing T-ring a	Hormonal contraceptive injection or injection
Diaphragm plus spermicide	Levonorgestrel-releasing IUD system (e.g., Mirena ®) a	Combined contraceptive pill
		Low-dose oral contraceptive pill
		Contraceptive patch

a. This is also considered a hormonal approach

Women were considered postmenopausal after 12 months of menopause without an alternative medical cause. The requirements according to age are as follows:

- Women > 50 years of age are considered postmenopausal if they have been amenorrheic for 12 months or more after cessation of exogenous hormone therapy and their luteinizing hormone and follicle-stimulating hormone levels are within the accepted postmenopausal range.
- Women ≤ 50 years of age were considered postmenopausal if they had been amenorrheic for 12 months or more after cessation of all exogenous hormonal therapy, had had radiation-induced oophorectomy with the last menses occurring > 1 year earlier, had had chemotherapy-induced amenorrheic with the last menses > 1 year apart, or had undergone surgical sterilization (bilateral oophorectomy or hysterectomy).

5.6.3 Lactation

It is not known whether IBI110/sintilimab is excreted in breast milk. "Considering that many drugs are present in breast milk, IBI110/sintilimab may be potentially toxic to infants." Lactating women who are breastfeeding cannot be enrolled in this study.

5.7 Treatment compliance

Study treatment was administered at the study site, and treatment compliance was monitored using drug receipt and dispatch records, subject medical records, and electronic case report forms (eCRFs).

5.8 Drug Recovery and Destruction

Used and partially used study drug containers for this study may be destroyed locally in accordance with applicable guidelines and procedures established by the study site and local institutions.

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

5.9 Records of Study Drug

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

5.10 Complaint Handling

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

Complaints related to concomitant drugs will be reported directly to the manufacturer according to the product description.

The Investigator or his/her designee is responsible for completing the following product complaint process as specified in this study:

A study-specific complaint form was used to document the reported product complaints and the associated complete description.

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

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

6 Study Assessments and Procedures

6.1 Subject Enrollment and Randomization Procedures

6.1.1 Subject Enrollment

The investigator will enroll subjects as follows:

1. Obtain informed consent with the subject's signature prior to any study-related procedures;

2. Subject eligibility was formally determined by the Principal Investigator or appropriately trained designee after reviewing the inclusion/exclusion criteria.

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

Subjects who do not meet the relevant criteria for this study (screen failures) may be rescreened. "If a subject is to be considered for re-screening, the investigator must contact the sponsor & '92; s medical manager." Each subject may be rescreened once. At the time of rescreening, the subject must re-sign the ICF and will be re-assigned an identification number.

6.1.2 Handling Procedures for Incorrectly Enrolled Subjects

The inclusion criteria must be strictly followed. "If a subject is found to be enrolled that does not meet the eligibility criteria, the sponsor & '92; s medical manager and the investigator will discuss whether to continue the subject in the study, with or without study drug." A subject may continue in the study and receive study drug if the investigator considers that continued participation in the study is medically appropriate for the subject and the sponsor's medical manager agrees with the investigator's decision. If the investigator considers continued participation in the study medically appropriate, but the sponsor's medical manager disagrees with the investigator's decision, the subject may not continue in the study (with or without study drug treatment). The Investigator will only allow subjects who are accidentally enrolled in the study to continue participation in the study after receiving written approval from the Sponsor.

6.1.3 Randomization and blinding

Subjects will not be randomized except for Cohort D2. The randomization method is detailed in Section 8.6. 1. This trial is an open-label trial, and blinding is not applicable.

6.2 Study Plan and Timing

There are three periods in this study: screening period (Day-28 to Day-1), treatment period visit, end-of-treatment visit (as early as possible)/safety follow-up (90 ± 7 days after the last dose) and survival follow-up (up to every 3 months, i.e., ≤ 90 days after the last dose).

6.2.1 Screening period

The following study procedures must be completed during the study screening period (Day-28 to Day-1) to ensure that subjects are eligible for the study (refer to the study visit table for visit intervals and frequencies):

- Signed informed consent form;
- Check the inclusion/exclusion criteria;
- Demographic data, past medical history and past medication history were recorded;
- Record vital signs, height and weight;
- Physical examination;
- ECOG PS score;
- 12-lead ECG (within 7 days prior to the first dose);
- Hematology, blood chemistry, urinalysis, fecal occult blood (within 7 days prior to the first dose, only the lenvatinib dose expansion cohort will be used for fecal occult blood test);
- Blood myocardial enzymes and troponin (within 7 days before the first dose);
- Coagulation function (within 7 days prior to the first dose);
- Pregnancy test (within 7 days before the first dose);
- Thyroid function (within 7 days before the first dose);
- Autoantibodies (the investigator will determine whether it is necessary to examine autoantibodies according to the past medical history of subjects and clinical indications);

- HIV, HBV, EBV and HCV (EBV only for Cohorts A1, I, K and O);
- Assessment of adverse events;
- Concomitant medications (within 28 days prior to the first dose);
- Tumor imaging assessment;
- Biomarker exploration (if applicable).

Detailed descriptions of tumor imaging assessments and safety assessments are provided in Sections 6.3 and 6.4, and biomarkers are provided in Section 6.8. The baseline assessment will be performed within 28 days prior to enrollment, and the investigator may collect the imaging results of 28 days prior to enrollment in the study for assessment.

6.2.2 Treatment Period Visits

The following items should be completed according to the time outlined in the trial flow chart (refer to the study visit table for visit intervals and frequencies):

- Vital signs and body weight were recorded, and if the subject's body weight fluctuated less than 10% from baseline (day of first dose of study treatment), the baseline body weight could be used to calculate the dose. Otherwise, the actual dose will be calculated according to the body weight on the scheduled day of administration;
- Physical examination;
- ECOG PS score;
- 12-lead ECG, cardiac ultrasound (cardiac ultrasound will be performed only in the dose expansion cohort of lenvatinib);
- Hematology, blood chemistry, urinalysis, fecal occult blood (only for dose expansion cohorts using lenvatinib);
- Blood myocardial enzymes and troponin;
- Coagulation function;
- Thyroid function;
- Immunogenicity;

- PK;
- Pharmacodynamics;
- Assessment of adverse events;
- Concomitant medication;
- Survival status;
- Tumor imaging assessment;
- Study drug administration;
- Biomarker exploration.

Detailed instructions for tumor imaging assessments, safety assessments, PK, pharmacodynamics, and immunogenicity blood sampling are provided in Sections 6.3, 6.4, 6.5, 6.6, and 6.7. See Section 6.8 for biomarker exploration.

6.2.3 End of Treatment/Safety Follow-up

At the end of study treatment or withdrawal from the study, the following tests should be performed if the subject does not have tests performed within 7 days prior to the end of the study (refer to the study visit table for visit intervals and frequencies):

- Vital signs;
- Physical examination;
- ECOG PS score;
- 12-lead ECG, cardiac ultrasound (cardiac ultrasound will be performed only in the dose expansion cohort of lenvatinib);
- Hematology, blood chemistry, urinalysis, fecal occult blood (only for dose expansion cohorts using lenvatinib);
- Blood myocardial enzymes and troponin;
- Coagulation function;
- Pregnancy test;
- Thyroid function;

- EBV (if applicable);
- Assessment of adverse events;
- Concomitant medication;
- Survival status;
- Subsequent anti-tumor therapy;
- Tumor imaging assessment (refer to Section 6.3).

The Safety Follow-up Visit should occur 90 ± 7 days after the last dose or prior to the initiation of new antineoplastic therapy, whichever occurs first. Subjects who discontinue treatment due to study drug-related adverse events will be followed until the adverse event resolves to Grade 0-1, the symptoms are stable, and the subject withdraws consent, whichever occurs first. Visits were as follows (refer to the study visit table for visit intervals and frequencies):

- Vital signs;
- Physical examination;
- ECOG PS score;
- 12-lead ECG, cardiac ultrasound (cardiac ultrasound will be performed only in the dose expansion cohort of lenvatinib);
- Hematology, blood chemistry, urinalysis, fecal occult blood (only for dose expansion cohorts using lenvatinib);
- Blood myocardial enzymes and troponin;
- Coagulation function;
- Pregnancy test;
- Thyroid function;
- Immunogenicity;
- PK (if applicable);
- Pharmacodynamics;

- Assessment of adverse events;
- Concomitant medication;
- Survival status;
- Subsequent anti-tumor therapy;
- Tumor imaging assessment (refer to Section 6.3).

Detailed instructions for tumor imaging assessments, safety assessments, PK, pharmacodynamics, and immunogenicity blood sampling are provided in Sections 6.3, 6.4, 6.5, 6.6, and 6.7.

6.2.4 Survival Follow-up

Subjects were contacted (telephone visits were acceptable) every 3 months (≤ 90 days) after the last dose of study drug to obtain information regarding survival as well as any subsequent systemic antineoplastic therapy and disease progression, whenever possible. For subjects without radiographic progression, long-term follow-up will continue until death or the end of the study. (Refer to Study Visit Form).

6.3 Efficacy Assessments

There will be no central imaging assessment in this study. The time windows for RECISITV1.1 and iRECIST assessments were consistent.

The method used to assess tumor burden at baseline must be the same as that used at each subsequent follow-up assessment (CT/MRI). Additional sites of involvement were examined as indicated by each subject's signs and symptoms. Baseline assessments should be performed within 28 days prior to the first dose of study medication. The investigator may collect imaging results for evaluation up to 28 days prior to study enrollment.

Tumor imaging assessments will be performed every 6 weeks (± 7 days) after the first dose of study drug. For subjects with an initial documented response [complete response (CR) or partial response (PR)], radiographic assessment will be performed to confirm response at 4 to 6 weeks and every 6 weeks (± 7 days) thereafter until radiographic PD (based on RECIST V1.1 criteria) is documented. For subjects with initial documentation of radiographic PD, radiographic assessments must be performed at 4 to 6 weeks to confirm PD. If the subject continues to receive study drug after confirmation,

imaging assessments will be performed every 6 weeks (± 7 days) until iCPD (based on iRECIST criteria), defined as at least an additional 5mm increase in target lesions or unequivocal progression of non-target lesions or at least a 5mm increase in a previously identified new lesion or identification of another new lesion (based on iRECIST criteria). See Study Visit Form for details.

For subjects who discontinue treatment for reasons other than radiographic disease progression, radiographic assessments should be performed at the end of treatment and every 6 weeks (± 7 days) after discontinuation until any of the following events occur: initiation of new antineoplastic therapy, disease progression, withdrawal of consent, and loss to follow-up or death.

Subjects with known or suspected brain metastases at screening should have a CT/MRI of the brain performed prior to the start of study treatment. This subset of subjects should be followed up during the study and CT/MRI assessments should be repeated at the same frequency as RECIST assessments. Brain metastases were assessed as non-target lesions.

If the investigator is unable to determine progression, particularly for non-target lesions and new lesions, the subject may continue treatment and have disease status re-assessed as clinically indicated or at the next scheduled assessment time point. If progression is confirmed by repeat scan, the date of progression should be the date of initial finding.

The primary analysis of this study will be based on tumor assessments performed by the study site using RECIST v1.1. The assessment method is provided in Attachment 4.

6.3.1 RECIST V1.1 Response Assessment

Efficacy will be evaluated according to RECIST V1.1, see Appendix 4. To evaluate ORR, TTR, DOR, PFS, 6-month and 1-year PFS rate, DCR, OS and 6-month and 1-year survival rate after treatment.

6.3.2 Immune Response Evaluation Criteria in Solid Tumors (iRECIST) Efficacy Evaluation

To explore iRECIST as a methodology to assess clinical benefit and to assess iORR, iDCR, iPFS, iDOR, and iTTR according to immune-related response criteria. The assessment method is provided in Attachment 5.

6.3.3 Other Efficacy Assessment Tests

If the investigator suspects or the subject has an indication of bone metastasis during the screening period, additional bone scan is required during the screening period to accurately determine the baseline lesions. If bone metastases are confirmed at baseline, bone scans may be performed every 6 months after subject enrollment or as clinically indicated and as frequently as recommended by the investigator during the treatment period.

For metastatic lesions that cannot be covered by CT (neck), chest, abdomen and pelvis, it is recommended to perform local CT or MRI scan for evaluation according to the frequency of tumor assessment.

6.4 Safety Assessments

6.4.1 Routine Laboratory Safety Assessments

Routine laboratory safety assessments include: hematology, coagulation, blood chemistry, and urinalysis. Routine laboratory safety assessments are presented in the table below:

Table 12. Routine Laboratory Safety Assessments

Blood routine	RBC, HGB, HCT, WBC, PLT, LYM, ANC, MONO, EOS, BASO
Coagulation function	TT, PT, APTT and INR
Blood biochemistry	TBILa, ALT, AST, γ-GT, ALP, ALB, TP, LDH, UREA, Cr, Na, K, Cl, Mg, Ca, P, Amylase and FBG
Urinalysis	PH, UPROb, UWBCc, URBCc/BLD, and UGLU
Fecal occult blood	Fecal occult blood testing for dose expansion cohorts using lenvatinib only
Myocardial related investigations	Troponin, CK-MB, CK, BNP (if necessary), etc.

a. If TBIL was ≥ 2 × ULN (and there was no evidence of Gilbert's syndrome), direct and indirect bilirubin were measured separately.

b. Subjects with urine protein ≥ 2 + on urine dipstick at baseline should have a 24-hour urine protein test.

c. White blood cells should be examined microscopically (if appropriate) and red blood cells should be examined with high power fields.

Refer to visit schedule for examination time.

6.4.2 Physical examination

Complete physical examination includes: general condition, head and neck (including ears, eyes, nose and throat), thyroid, lymph nodes, respiratory tract, breast (female), cardiovascular, abdomen, skin, musculoskeletal (including spine and extremities), genital/anal (if applicable), and neurological evaluation.

Refer to visit schedule for examination time.

Refer to Attachment 2 for ECOG PS scoring criteria.

6.4.3 12-lead electrocardiogram (ECG)

Resting 12-lead ECGs will be analyzed locally according to the Schedule of Visits.

The investigator completed a 12-lead ECG assessment on the day of the examination and recorded the assessment on the ECG. The same method of assessment should be used throughout the study.

The investigator should assess all ECGs according to the clinically significant abnormal/not clinically significant abnormal category. If it is a clinically significant abnormal finding, the investigator should record the finding as an AE in the eCRF.

6.4.4 Cardiac ultrasound

Cardiac ultrasound will be performed at the local laboratory according to the schedule of visits for the lenvatinib-only dose expansion cohorts.

On the day of examination, the investigator completed the cardiac ultrasound assessment and recorded the assessment results. The same method of assessment should be used throughout the study.

The investigator should assess all cardiac ultrasound according to the clinically significant abnormal/not clinically significant abnormal category. If it is a clinically significant abnormal finding, the investigator should record the finding as an AE in the eCRF.

6.4.5 Vital Signs

Vital signs will be performed as described in the Schedule of Study Visits. Vital

signs include temperature, pulse, respiratory rate, and blood pressure.

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

In the event of an AE/SAE, additional vital sign records may be collected on the eCRF (if applicable). Date and time of collection and measurement were recorded in the appropriate section of the eCRF.

6.4.5.1 **Pulse and blood pressure**

Blood pressure and pulse were measured after the subject had rested for at least 5 minutes. Date and time of collection and measurement were recorded in the appropriate section of the eCRF.

Dose Escalation Phase

During the first IBI110 infusion, blood pressure and pulse will be monitored at the start of the drug infusion (0 minutes ± 3 minutes) and then every 15 minutes (± 3 minutes) until the end of the infusion. The second time vital signs were assessed by monitoring as clinically indicated. If the infusion is longer than 60 minutes, BP and pulse should be measured at a higher rate following the above principles or as clinically indicated.

Dose Expansion Phase

During the first infusion of IBI110, blood pressure and pulse will be monitored at the start of the infusion (0 minutes ± 3 minutes) and then every 30 minutes (± 3 minutes) until 5 minutes after the end of the infusion. Vital signs were assessed by monitoring as clinically indicated at the start of the second infusion. If the infusion is longer than 60 minutes, BP and pulse should be measured at a higher rate following the above principles or as clinically indicated.

Blood pressure and pulse were collected at the start of the first sintilimab infusion (0 minutes ± 3 minutes), during the infusion (30 minutes ± 5 minutes), and at the end of the infusion (± 5 minutes). The second time vital signs were assessed by monitoring as clinically indicated. If the infusion is longer than 60 minutes, BP and pulse should be measured at a higher rate following the above principles or as clinically indicated.

6.4.5.2 **Body temperature and respiration**

On the day of scheduled dosing, body temperature and respiration should be collected prior to infusion.

6.4.6 Weight and Height

Height will be measured at screening only.

Body weight will be measured prior to each scheduled dose during the study. If the subject's body weight fluctuates less than 10% from baseline (day of first dose of study treatment), the baseline body weight can be used to calculate the dose. Otherwise, the actual dose was calculated according to the body weight on the scheduled day of administration.

6.4.7 Pregnancy test

A urine or serum human chorionic gonadotropin (β-hCG) pregnancy test will be performed within 7 days prior to the first dose of study drug for women of childbearing potential (as defined in 5.6. 2). If urine hCG is positive or negative, a serum β-hCG sample pregnancy test will be performed, whichever is the serum result. If the result is positive, the subject is not eligible/must be discontinued from the study. If pregnancy is suspected during the study, it should be repeated.

6.4.8 Autoantibody

Screening testing included antinuclear antibodies, anti-dsDNA antibodies, and anti-thyroglobulin antibodies. If irAE is suspected during the study, the recommended serum antibody test items refer to the following table:

Table 13. Recommended serum autoantibody testing

Immune-related organs	Antibodies
Gastrointestinal tract	None
Liver	Antinuclear antibody Anti-smooth muscle antibody, anti-liver-kidney microsomal antibody type I, anti-liver cytoplasmic matrix antibody type I
Lung	Antinuclear antibody Rheumatoid factor (RF) Anticentromere antibody Anti-ENA: Anti-Sm, Anti-RNP, Anti-SSA (Ro), Anti-SSB (La), Anti-

		Scl70, Anti-Jo
Endocrine	Thyroid	Anti-thyroglobulin antibodies (TG-Ab), anti-TPO antibody
	Diabetes	Anti-GAD antibodies, anti-insulin antibodies, and anti-carbonic anhydrase antibodies
	Addison's disease	Anti-21 hydroxylase antibody
	Hypophysitis	Anti-pituitary antibody
Skin		None
Polyarthritis		Antinuclear antibody Anti-ENA: anti-SSA, anti-SSB, anti-Sm Anti-CCP, Complement (CH50) C3/C4
Kidney		Antinuclear antibody Complement (CH50) C3/C4 Anti-ANCA antibody
Haematological disorder syndrome		Antinuclear antibody Coombs red blood cell test

6.4.9 Other Safety Tests Performed

Other safety tests performed include:

- Five items of hepatitis B: HBsAg, HBsAb, HBcAb, HBeAg, HBeAb.
- HBV-DNA, HCV-RNA: If HBsAg and/or HBcAb are positive, HBV DNA should be further tested, and HCV RNA should be tested if HCV antibody is positive.
- Plasma EBV-DNA testing (Phase Ia\ Ib dose expansion cohorts A, I, K, O).
- HIV antibody, HCV antibody.
- Thyroid function: TSH, FT3 and FT4.

6.4.10 Safety Assessment Committee

The safety assessment committee consisted of the sponsor and investigators. Safety assessment committee discussion may also be triggered due to sudden safety events and major changes in study drug dose during the course of the trial.

6.5 Pharmacokinetics

6.5.1 Specimen Collection

IBI110 monotherapy dose escalation

Refer to Visit Table 2 for examination time.

- The PK blood collection points for Cycle 1 are: within 1h before the start of IBI110 infusion, immediately after the end of infusion (+ 5min), 1 h ± 5 min after the end of infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), 504 h ± 24 h (Day 22) after the start of infusion. If the dose on Cycle 2 Day 1 is delayed due to AE or other reasons, an additional 672 h ± 24 h (Day 29) will be required for Cycle 1.
- Sampling time in Cycle 2 and Cycle 3 is within 1 hour before the start of infusion and immediately after the end of infusion (+ 5min).
- Blood collection time in Cycle 4: within 1h before the start of infusion, immediately after the end of infusion (+ 5min), 1 h ± 5 min after the end of infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), 504 h ± 24 h (Day 22) after the start of infusion (i.e., within 1h before infusion in Cycle 5).
- Sampling times in Cycles 6, 8, 12 and 16 were within 1 hour before the start of infusion and immediately after the end of infusion (+ 5min).
- One blood sample will be collected at the Safety Follow-up Visit.

IBI110 in combination with sintilimab dose escalation

Refer to Visit Table 4 for examination time.

- The PK blood collection points set in Cycle 1 are: within 1h before the start of IBI110 infusion, immediately after the end of sintilimab infusion (+ 5min), 1 h ± 5 min after the end of sintilimab infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), and 504 h ± 24 h (Day 22) after the start of IBI110 infusion. If the dose on Day 1 of Cycle 2 is delayed due to AE or other reasons, an additional 672 h ± 24 h (Day 29) will be required in Cycle 1.

- Sampling time in Cycle 2 and Cycle 3 will be within 1 hour before the start of IBI110 infusion and immediately after the end of sintilimab infusion (+ 5 minutes).
- Blood sampling time in Cycle 4: within 1h before the start of IBI110 infusion, immediately after the end of sintilimab infusion (+ 5min), 1 h ± 5 min after the end of sintilimab infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), and 504 h ± 24 h (Day 22) after the start of IBI110 infusion (i.e., within 1h before infusion in Cycle 5).
- Sampling times in Cycles 6, 8, 12 and 16 were within 1h before the start of IBI110 infusion and immediately after the end of sintilimab infusion (+ 5min).
- Blood samples will be collected once at the safety follow-up visit.

IBI110 alone or in combination with sintilimab dose expansion:

Refer to Visit Table 6 for examination time.

Phase Ib expansion of IBI110 combined with sintilimab in multiple dose groups (3mg/kg ~ MTD): PK sparse sample collection will be performed for any 12 subjects, specifically: sampling time in Cycle 1: immediately after the end of infusion of sintilimab (+ 5min); Sampling times for both Cycles 2 and 4 were within 1 hour prior to the start of IBI110 infusion and immediately after the end of sintilimab infusion (+ 5 minutes).

Cohorts A1 and A2: Sparse PK sampling for any 12 subjects as follows:

- The PK blood sampling point for Cycle 1 will be immediately (+ 5min) after the end of IBI110 infusion.
- Sampling times for both Cycles 2 and 4 were within 1 hour prior to the start of infusion and immediately after the end of infusion (+ 5min).

Cohorts B to O: Sparse PK sampling will be performed for any 12 subjects; if there are multiple dose groups in the same cohort, sparse PK sampling will be performed for any 12 subjects in each dose group, as follows:

- The PK blood collection points set in Cycle 1 are: immediately after the end of infusion of sintilimab (+ 5min);

- Sampling times for both Cycles 2 and 4 were within 1 hour prior to the start of IBI110 infusion and immediately after the end of sintilimab infusion (+ 5 minutes). PK samples will not be collected for the cohort receiving sintilimab 200mg IV Q3W + other treatment only.

Note: Cohorts A1 and A2 are IBI110 alone, and if the cohort is IBI110 in combination with sintilimab, infusions of IBI110 followed by sintilimab will be administered.

Approximately 3.5 mL of whole blood (Ia single dose escalation and Ia/Ib dose expansion cohorts) or 5 mL of whole blood (Phase Ib dose escalation) will be collected in coagulation-promoting vacutainers, serum separated, aliquoted and cryopreserved for Free PK analysis.

Refer to the Laboratory Manual provided by the central laboratory designated by the sponsor for details on sampling methods, sample storage and transportation.

The sponsor will comprehensively evaluate the PK characteristics, safety and efficacy data of IBI110 in subjects, and comprehensively analyze the available data, and may suspend or stop the PK sample collection of this study or a cohort, including but not limited to: 1) project stop or suspend; 2) Non-potential target indication population; 3) Subsequent PK samples are not expected to provide additional information to characterize the PK profile.

6.5.2 Determination of plasma drug concentration

IBI110 and sintilimab in serum will be determined by ELISA method and will be tested by the central laboratory designated by the sponsor. All subjects should have their plasma concentrations measured at the blood collection points specified in the protocol.

6.6 Pharmacodynamics

Soluble LAG-3 test

IBI110 monotherapy dose escalation

Refer to Visit Table 2 for examination time.

- Blood sampling for PD in Cycle 1 will be performed within 1h before the start of IBI110 infusion, immediately after the end of infusion (+ 5min), 1 h $\pm$ 5 min

after the end of infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), and 504 h ± 24 h (Day 22) after the start of infusion. If dosing on Cycle 2 Day 1 is delayed due to AE or other reasons, an additional 672 h ± 24 h (Day 29) will be required in Cycle 1.

- Sampling time in Cycle 2 and Cycle 3 is within 1 hour before the start of infusion and immediately after the end of infusion (+ 5min).
- Blood collection time in Cycle 4: within 1h before the start of infusion, immediately after the end of infusion (+ 5min), 1 h ± 5 min after the end of infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), 504 h ± 24 h (Day 22) after the start of infusion (i.e., within 1h before infusion in Cycle 5).
- Sampling times in Cycles 6, 8, 12 and 16 were within 1 hour before the start of infusion and immediately after the end of infusion (+ 5min).
- One blood sample will be collected at the Safety Follow-up Visit.

IBI110 in combination with sintilimab dose escalation

Refer to Visit Table 4 for examination time.

- The PD blood collection points for Cycle 1 are: within 1h before the start of IBI110 infusion, immediately after the end of sintilimab infusion (+ 5min), 1 h ± 5 min after the end of sintilimab infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), and 504 h ± 24 h (Day 22) after the start of IBI110 infusion. If the dose of Cycle 2 Day 1 is delayed due to AE or other reasons, an additional 672 h ± 24 h (Day 29) will be required for Cycle 1.
- Sampling time in Cycle 2 and Cycle 3 will be within 1 hour before the start of IBI110 infusion and immediately after the end of sintilimab infusion (+ 5 minutes).
- Blood sampling time in Cycle 4: within 1h before the start of IBI110 infusion, immediately after the end of sintilimab infusion (+ 5min), 1 h ± 5 min after the end of sintilimab infusion, 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (Day 8), 336 h ± 12 h (Day 15), and 504 h ± 24 h (Day 22) after

the start of IBI110 infusion (i.e., within 1h before infusion in Cycle 5).

- Sampling times in Cycles 6, 8, 12 and 16 were within 1h before the start of IBI110 infusion and immediately after the end of sintilimab infusion (+ 5min).
- Blood samples will be collected once at the safety follow-up visit.

IBI110 as a single agent or in combination with sintilimab dose expansion

Refer to Visit Table 6 for examination time.

Double LAG-3 samples will only be collected from any 6 subjects in each dose group in the expansion cohorts of IBI110 in combination with sintilimab in multiple dose groups (3mg/kg-MTD), and no PD samples will be collected in Cohort D2. Details are as follows:

- Blood sampling in Cycles 1, 2 and 4 was performed within 1 hour prior to the start of IBI110 infusion.
- PD (Double LAG-3) samples were stopped for the other expansion cohorts.

Approximately 3.5 mL of whole blood will be collected in a coagulant vacutainer, serum separated, aliquoted and cryopreserved for Soluble LAG-3 analysis.

Refer to the Laboratory Manual provided by the central laboratory designated by the sponsor for details on sampling methods, sample storage and transportation.

6.7 Immunogenicity evaluation indicators

Dose escalation of IBI110 alone and in combination with sintilimab

Immunogenicity testing will be performed within 1 hour prior to the start of IBI110 infusion at Cycles 1, 2, 4, 6, 8, 12, 16, then every 8 cycles thereafter (Cycles 24, 32, 40, etc., and so on), and at the Safety Follow-up Visit. "If a subject experiences an IBI110 infusion reaction, blood samples will be collected as close to the onset of the event as possible, at the time of resolution of the event, and approximately 30 days after the end of the event to allow for pre-and post-immunogenicity comparative analysis and, if necessary, for determination of drug concentrations in immunogenicity samples." (Refer to Visit Tables 1 and 3 for examination time).

IBI110 as a single agent and in combination with sintilimab dose expansion

Immunogenicity testing will be performed within 1 hour prior to the start of IBI110 infusion in Cycles 1, 2, 4, and 8, and at the Safety Follow-up Visit for all subjects in the Phase Ib expansion cohorts of IBI110 plus sintilimab in multiple dose cohorts (3mg/kg to MTD) and 12 subjects in the Phase Ia/Ib dose expansion-Cohorts A to O with sparse PK sampling. If necessary, drug concentrations in immunogenicity samples may be tested. (Refer to Visit Tables 5 and 6 for examination time).

Anti-drug antibody (ADA) will be tested for all subjects whose immunogenicity samples are collected. Serum specimens positive for ADA will continue to be tested for Neutralizing Antibody (NAb).

Five mL of whole blood will be collected in a coagulant vacutainer, serum separated, aliquoted and cryopreserved for ADA and NAb analysis.

Refer to the Laboratory Manual provided by the central laboratory designated by the sponsor for details on sampling methods, sample storage and transportation.

6.8 Biomarker evaluation indicators

6.8.1 Tissue biomarkers

If permitted by the Ethics Committee, tumor tissues should be collected from enrolled subjects at baseline in the dose escalation phase of Phase 1a and Phase 1b as far as possible. The time of tumor tissue sectioning is within 3 months (from signing of ICF).

For Phase Ia single-agent dose expansion and Phase Ib combination dose expansion, tumor tissues should be collected from enrolled subjects at baseline as far as possible. The time for obtaining tumor tissue is not required, and the time for slide preparation is within 3 months (before signing of ICF).

Phase 1a and single-agent dose expansion (Cohorts A1 and A2): Eligible tumor tissues include archived tumor tissues or 5 unstained 4-5 μm thick sections freshly collected and prepared at screening for detection of LAG-3 expression;

Phase Ib and combination dose expansion (Cohorts B ~ O): eligible tumor tissues include archived tumor tissues or 5-10 unstained sections with a thickness of 4-5 μm freshly collected and prepared at screening for detection of LAG-3 and PD-L1 expression.

Refer to the Laboratory Manual provided by the central laboratory designated by the

sponsor for details on the requirements for slide sampling, sample storage, transportation and analysis.

6.9 Storage and Destruction of Biological Samples

If necessary, additional analyses such as selectivity, parallelism, within-study thresholds, etc. may be performed using pooled or individual samples, which are necessary for further evaluation and validation of analytical methods. The results of these analyses may be included in the CSR or reported separately from the CSR.

Incurred sample reproducibility analysis will be assessed in parallel with biological sample testing. The results of these assessments will not be recorded in the CSR, but will be presented separately in the sample analysis report. After all necessary analyses, subject information will be desensitized (including anonymization and consolidation) and then disposed of or destroyed.

7 Safety Reporting and Adverse Event Management

7.1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial subject after signing the informed consent form, whether or not causally related to the study drug, which is considered an AE, including but not limited to the following:

- Exacerbation of pre-existing (before entering the clinical trial) medical condition/disease (including aggravation of symptoms, signs, laboratory test abnormalities);
- Any newly occurring untoward medical condition (including symptoms, signs, newly diagnosed diseases);
- Abnormal clinically significant laboratory values or results.

7.2 Definition of Serious Adverse Events

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

- Resulted in death, except death due to disease progression of study indication.
- Life-threatening ("life-threatening" in the definition is an AE in which the subject was at risk of death at the time of its occurrence, and does not include an

AE that might have caused death if the event were to worsen).

- Requires inpatient hospitalization or prolongation of existing hospitalization, excluding the following:

  a) Rehabilitation institutions;

  b) Sanatorium;

  c) Conventional emergency room admissions;

  d) Same-day surgery (e.g. Outpatient/same-day/ambulatory surgery);

  e) Hospitalization or prolongation of hospitalization not associated with worsening of an AE is not per se an SAE. For example, hospital admission due to pre-existing disease, without occurrence of new adverse events or aggravation of pre-existing disease (e.g., to check for persistent laboratory abnormalities before the trial); Hospitalization for administrative reasons (e.g., routine annual physical examination); Hospitalization specified in the trial protocol during the clinical trial (e.g., operating according to the requirements of the trial protocol); Elective hospitalization (e.g., elective surgery) that is not associated with worsening of the adverse event; Scheduled treatments or surgeries should be recorded throughout the trial protocol and/or in the baseline data of the individual subject; Admitted for blood product use only.

- Results in permanent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Other Important Medical Events: Important medical events may not be immediately life-threatening, death, or hospitalization, but are generally considered serious if medical action is required to prevent one of the above situations. Examples include critical treatment in an emergency room or allergic bronchospasm occurring at home, cachexia or convulsions that are not hospitalized, and the development of drug dependence or addiction.

7.3 CTCAE Grading of Adverse Events

The investigator will assess the severity of AE according to the five-grade criteria specified in NCI CTCAE v5.0.

Adverse event terms not included in the NCI CTCAE v5.0 will be graded according to the following CTCAE grading principles:

- Grade 1 mild; No symptoms or slight signs; Clinical or diagnostic observations only; No medical intervention required.
- Grade 2 moderate; Requires minimal, local or non-invasive treatment; Limitation of age-appropriate activities of daily living (e.g., cooking, shopping, using the phone, managing money, etc.).
- Grade 3 serious or clinically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization; Disability; Restricted in self-care activities of daily living (e.g., bathing, wearing and undressing, eating, using the toilet, and taking medications), but not bedridden.
- Grade 4 resulting in life-threatening consequences; Emergency treatment is required.
- Deaths related to Grade 5 AE.

7.4 Causal relationship judgment between adverse event and investigational drug

The investigator was required to assess the causal relationship between the study drug and each AE and answer "Yes" or "No" to the question "You believe that there is a reasonable possibility that the AE occurred due to the study drug."

When determining that there is a "reasonable possibility" that an AE is due to a drug, the following factors should be considered:

- Time course. Suspect drug exposure. Did the patient actually receive treatment with the suspect drug? Is there a reasonable temporal relationship between the onset of the AE and the suspect drug?
- Consistency of known drug properties. Is the AE consistent with previously reported events for the suspect drug (pharmacology and toxicology) or drugs of the same pharmacology class? Is the occurrence of the AE expected from the pharmacological properties?
- Dechallenge. Did the AE resolve or improve after discontinuation or reduction of the suspect drug?

- There are no alternative factors. The AE cannot be reasonably explained by another pathology, such as underlying disease, other drugs, other intrinsic or environmental factors.

- Re-challenge. Did the AE reappear after the suspect drug was stopped?

- Maybe something else. Could the adverse event not be explained by an alternative etiology, such as underlying disease, other drugs/vaccines, or other host or environmental factors?

When one or more factors are present, a "reasonable possibility" of an AE needs to be considered.

In contrast, if the above criteria are not applicable, if there is no clear evidence of exposure and a reasonable time course, or if any rechallenge (if performed) is negative or another possible cause of the AE, there may be no "reasonable possibility" of a causal relationship.

Based on the above factors, the investigator's medical assessment of the relationship of the study drug to the AE or its role in the AE was divided into the following two categories:

- Related, i.e., there is a reasonable possibility that the study drug was associated with the onset of the AE: there is evidence of exposure to the study drug. An AE with a reasonable temporal sequence from administration of the sponsor product. The AE is more likely to be explained by the study drug than by other causes.

- Unrelated, i.e., there is no reasonable possibility of a relationship between the study drug and the onset of the AE: e.g., the subject did not start treatment with the study drug; Or the AE did not occur in a plausible temporal relationship to exposure to the study drug; Or other factors more likely to explain the occurrence of the AE than the study drug.

7.5 Recording of Adverse Events

The investigator should use medical terminology/concepts to record AE or SAE. The use of spoken language and abbreviations should be avoided. All AE (including SAE) should be recorded on the Adverse Event Form of the eCRF.

7.5.1 Adverse event collection and time interval

Investigators were informed of adverse events by asking subjects non-inducing

questions.

All AE (including SAE), whether observed by the investigator or spontaneously reported by the subject, will be collected from the time of signing the informed consent form up to and including 30 days after the last dose if no new tumor treatment is initiated. All SAE and irAE were collected up to and including 30 to 90 days after the last dose of study drug if no new antineoplastic therapy was initiated. If a subject starts other antineoplastic therapy within 90 days after the last dose of study drug, only subsequent SAE and irAE related to study drug or study procedures will be collected.

For 90 days after the last dose of study drug, only SAE related to study drug or study procedures will be collected.

7.5.2 Follow-up of adverse events

Adverse events should be followed up until they are recovered to baseline or Grade 0-1 or the investigator considers that no further follow-up is required for reasonable reasons (e.g., no recovery or improvement). If the adverse event cannot be recovered, a reasonable explanation should be recorded in the eCRF. The recovery of the subject's AE or SAE and its date should be recorded in the eCRF and medical records, whether or not related to the study drug.

7.5.3 Contents of Adverse Event Records

The investigator should fully record any adverse event, including diagnosis (if no diagnosis, record symptoms and signs including laboratory abnormalities), start and stop dates and times (if applicable), CTCAE severity grade and change, whether it is a serious adverse event, action taken with the study drug, treatment given due to the AE and the outcome of the event, and relationship of the adverse event to the study drug.

For serious adverse events, the investigator should also provide the date the AE meets the criteria for an SAE, the date the investigator learns of the SAE, the rationale why the AE is an SAE, the hospitalization date, the discharge date, the probable cause of death, the date of death, whether an autopsy was performed, causality assessment with study procedures, causality assessment with other drugs, and other possible causes of the SAE. The investigator should also provide the judgment basis of relatedness and the description of SAE. In the SAE description, the subject's number, age, gender, height and weight should also be included; Indications and disease stages of the subjects treated with

the investigational drug and relevant systemic conditions; Occurrence, development, outcome and outcome of clinical course of SAE; Laboratory test results related to SAE (test time, unit and normal range must be provided); Previous history and concomitant diseases related to SAE as well as their occurrence and duration; Medication history related to SAE, concomitant drugs and their treatment initiation, duration, usage and dosage, etc.; Details of initiation, duration, and administration of study drug.

The items regarding AE recording are described below:

Diagnosis, symptoms and signs

If a diagnosis is already available, the diagnosis should be recorded on the eCRF rather than the individual signs and symptoms (e.g., liver failure should be recorded rather than jaundice, elevated transaminases, and asterixis). If signs and symptoms cannot be ascertained to be caused by the diagnosis at the time of reporting, they will be recorded as a separate AE/SAE. If it is determined that the signs and symptoms are caused by the diagnosis, only the diagnosis is reported separately and the symptoms and signs are included in the diagnosis. AE needs to delete the record of symptoms and signs, and SAE needs to send follow-up update report.

Adverse Events Secondary to Other Events

In general, adverse events secondary to other events (e.g., caused by other events or clinical sequelae) should be recorded as the primary event, unless the secondary event is serious or serious. However, secondary events with significant clinical significance should be recorded as separate adverse events in the eCRF if they occur at a different time from the primary event. If the relationship between the events is unclear, they should be recorded separately in the eCRF.

Persistent or Recurrent Adverse Events

A persistent adverse event is an adverse event that persists without resolution between the subject's two evaluation time points.

A recurrent adverse event is an adverse event that has resolved between the two evaluation time points but occurs later. The occurrence of the event should be recorded separately in the eCRF.

Laboratory test abnormality

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

Death

All deaths occurring during the whole trial, including the 90-day follow-up period after the last dose, regardless of whether they are related to the study drug, should be recorded in the death report form of the eCRF, and the SAE report form should be completed and reported to the sponsor in a timely manner. If a new tumor treatment is initiated within 90 days of the last dose or death occurs within 90 days of the last dose, it will not be reported to the sponsor as an SAE unless it is considered to be related to the study drug or study procedures.

If the death is definitely caused by tumor progression, it will not be recorded and reported as an SAE, but the investigator should record the death in the death report form eCRF and inform the sponsor in a timely manner. At the same time, every effort should be made to obtain reliable evidence of disease progression, including imaging, laboratory tests or clinical symptoms/signs, which should be analyzed and recorded in the medical records.

When recording death events, if the cause of death is clear, the cause of death will be recorded as an adverse event, the outcome of which is death, and the event will be reported as an SAE; If the cause of death is unknown at the time of reporting, it should be recorded as "unexplained death" on the adverse event form of the eCRF, and the "unexplained death" should be reported as an SAE first, and the exact cause of death should be further investigated.

Pre-existing medical condition

The existing symptoms/signs of subjects during the screening period should be recorded and reported as adverse events only when the severity, frequency and nature of the symptoms/signs are aggravated (except for the deterioration of the disease condition under study) after entering the trial. Changes from the previous state such as "increased headache frequency" should be reflected in the recording.

Disease progression

Progressive disease is defined as worsening of the subject's condition due to the

primary tumor targeted by the investigational drug, appearance of new lesions relative to the primary tumor, or progression of existing lesions. Disease progression is not reported as an AE; New signs and symptoms due to disease progression are not required to report AE; Worsening of pre-existing symptoms and signs due to disease progression, even if it meets the diagnostic criteria for SAE (causes death, is life-threatening, requires hospitalization or prolongation of hospitalization, results in permanent or significant disability/incapacity, results in congenital anomaly/birth defect, or other important medical events), will not be reported as an SAE in an expedited manner.

7.6 Expedited Reporting of SAE and Pregnancy

SAE Reporting:

Reporting period of SAE for serious adverse events occurring from the signing of the informed consent to 90 days (inclusive) after the last dose, the investigator must immediately fill in the Serious Adverse Event Report Form once he/she becomes aware of the SAE, sign and date it, and immediately report it to the PV Department of the sponsor within 24 hours of awareness: drugsafety@innoventbio.com. For death and life-threatening serious adverse events, the investigator should urgently follow up the missing information and provide a complete SAE report. If a subject starts a new anti-tumor therapy during this period, only adverse events related to the study drug, including serious adverse events, will be collected.

Serious adverse events occurring outside the above period should also be reported if they are considered to be related to the study drug.

Pregnancy

Drugs of the same class have safety risks of embryotoxicity, and all subjects of childbearing potential participating in clinical trials must take effective contraceptive measures.

If a female subject who is exposed to the drug becomes pregnant during the clinical trial, the subject should be excluded from the study, and the investigator should report the pregnancy to the sponsor within 24 hours of becoming aware of the pregnancy, and the "Faithful Clinical Trial Pregnancy Report/Follow-up Form" should be completed.

If the partner of a male subject exposed to the drug becomes pregnant during the clinical trial, the subject will continue the clinical trial, report the pregnancy to the sponsor

within 24 hours after the investigator learns of the pregnancy, and complete the "Faithful Clinical Trial Pregnancy Report/Follow-up Form".

The investigator will continuously monitor the pregnancy and follow up the pregnancy outcome until 8 weeks after delivery of the mother, and report the outcome to the sponsor.

If the pregnancy results in stillbirth, spontaneous abortion, fetal anomaly (any congenital anomaly/birth defect) and induced abortion for medical reasons, it will be considered as SAE and should be reported according to the SAE procedure and time limit.

If a subject also experienced an SAE during the pregnancy, it was to be reported according to the SAE reporting procedure.

7.7 Events of abnormal liver function

Abnormalities in AST and/or ALT levels accompanied by abnormally elevated total bilirubin levels that meet the following criteria and do not have other causes of liver injury will be considered as drug-induced liver injury. Such situations should always be considered important medical events.

Table 14. Hepatic impairment requiring reporting as an SAE

Baseline Period	Normal (AST/ALT and total bilirubin)	Abnormal (AST/ALT and total bilirubin)
Treatment Period	ALT or AST ⩾ 3 × ULN With total bilirubin ⩾ 2 × ULN And alkaline phosphatase ⩽ 2 × ULN And no hemolysis	AST or ALT ⩾ 8 × ULN With an increase in total bilirubin ⩾ 1 × ULN or a total bilirubin value ⩾ 3 × ULN

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

In addition to repeated AST and ALT tests, laboratory tests to be performed should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/international normalized ratio, and alkaline

phosphatase. Detailed medical history collection should include: history of alcohol consumption, acetaminophen, soft drugs, various supplements, traditional Chinese medicine, history of exposure to chemical drugs, family history, occupational exposure, sexual behavior history, travel history, history of contact with subjects with jaundice, surgery, blood transfusion, history of liver disease or allergic disease, history of heart disease, history of immune disease, etc. Further investigations may include tests for acute hepatitis A, B, C, and E, imaging of the liver (e.g., biliary tract), autoantibodies, and cardiac ultrasound. If repeat testing confirms that the laboratory criteria in the table above are met, the possibility of potential drug-induced liver injury should be considered in the absence of other causes of liver function test abnormalities, without waiting for all liver function etiological tests to be made. Such cases of potential drug-induced liver injury should be reported as SAE.

7.8 Management of Drug-Related Toxicities

The sponsor conducted periodic trial-level safety reviews during the conduct of the trial. Details including the frequency of the review and the type of data to be reviewed will be documented in a separate trial level safety review plan.

Immune-related adverse events

Given that the mechanism of action of IBI110 is to promote T-cell proliferation and activation, it is possible that immune-related adverse events (irAE) were observed during this study. Subjects should be monitored for signs and symptoms of irAE. If there is no clear alternative etiology (e.g., infection), it should be considered that the subject's signs or symptoms of the disease occurring in the trial are related to the immune system.

See Section 5.3 of the protocol for details on IBI110 dose modification and management principles for adverse events. Guidelines for the disposition of irAE are provided in the Immune-Related Adverse Event Management Manual provided by the sponsor.

8 Statistical Considerations

8.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will be written after the first subject is enrolled and finalized before database lock. The SAP will provide details of the analyses to be performed in this study and the presentation of the results.

8.2 Hypothesis testing

No formal hypothesis testing was performed.

8.3 Statistical Analysis Populations

The analysis populations included the Enrolled Analysis Set (ENR), Safety Set (SS), Full Analysis Set (FAS), PK Analysis Set and DLT Analysis Set:

1. Enrolled Analysis Set Population: Informed Consent Form Signed Population.
2. Safety analysis population: the population of subjects who received at least one dose of study drug.
3. Full Analysis Population: Subjects with measurable disease at baseline who received at least one dose of study drug.
4. PK analysis population: including all subjects who received at least one dose of study drug and had at least one valid measured concentration data after administration.
5. DLT analysis set: for the subjects in dose escalation, who experienced DLT during DLT observation period, or did not experience DLT but completed DLT observation, and met the drug exposure of at least 70% (i.e., 100% × actual dose in Cycle 1/planned dose ⩾ 70%).

The anti-tumor activity (clinical efficacy or PD parameters) will be evaluated using the FAS population, the safety data set will be used for safety analysis, the PK analysis population will be used for PK parameters analysis, and the DLT analysis set will be used for DLT evaluation.

8.4 Statistical Analysis Methods

8.4.1 General Methods of Statistical Analysis

Descriptive statistics are mainly used, and inter-group comparisons are not performed in principle. Continuous variables were described by number of cases, mean, standard deviation, median, maximum and minimum. For PK parameters, geometric means and coefficients of variation will also be provided. Categorical variables were described by frequency and percentage.

The safety indicators (AE, laboratory tests, vital signs, etc.), immunogenicity and anti-tumor activity of IBI110 in subjects with advanced tumors will be summarized by stage and cancer type.

ORR, DCR and its 95% CI were calculated by dose, median progression-free survival, median overall survival, 6-month and 1-year PFS rates and survival rates were estimated using Kaplan-Meier method, and DOR, TTR and maintenance response rate at the time of data analysis cutoff were calculated for subjects with objective response.

Each endpoint was analyzed according to Sections 8.4. 2 and 8.4. 3.

All statistical analyses were performed using SAS 9.2 (or higher).

8.4.2 Analysis of Primary Endpoint

8.4.2.1 **Safety indicators**

The analysis is presented in "8.4. 4 Safety Analysis".

8.4.2.2 **Evaluation of efficacy indicators**

All based on RECIST V1.1 criteria (except OS):

- Objective Response Rate (ORR)

$$ORR = \frac{CR + PR\text{的受试者例数}}{\text{总受试者数}} * 100\%$$ The binomial distribution was used to calculate its 95% CI

- Disease Control Rate (DCR)

$$DCR = \frac{CR + PR + SD\text{的受试者例数}}{\text{总受试者数}} * 100\%$$ The binomial distribution was used to calculate its 95% CI

Objective response rate and disease control rate were calculated based on the best response assessment of the tumor confirmed during the study.

- PFS

PFS: The time from the first dose of study drug to the first date of disease progression (radiographic) or death. Subjects who did not have disease progression or death were censored at the date of the last radiographic assessment. For subjects with no post-baseline radiographic evaluation or no documented death, the date of first dose of study

drug was used as the censoring date.

For the analysis of PFS, Kaplan-Meier estimates of median PFS and its 95% CI will be used, survival curve will be plotted, and PFS rates at 6 months and 1 year will be calculated.

- OS

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

OS will be analyzed using Kaplan-Meier estimates of median OS, and survival curves will be plotted, and 6-month and 1-year survival rates will be calculated.

- DOR

For subjects with response (CR or PR), duration of response: the time from the date of first response to disease progression or death; for subjects without disease progression or death, the date of the last radiographic assessment will be used as the censoring date.

DOR was summarized and tabulated for subjects who responded.

- TTR

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

Time to response was summarized and tabulated for subjects who responded.

- Maintenance of remission rate

For subjects with an objective response (CR or PR), the proportion of subjects who maintained a response as of the end of the study.

8.4.3 Analysis of secondary endpoints

- PK Analysis

PK parameters include but are not limited to: area under curve (AUC), Cmax, clearance (CL), volume of distribution (V) and half-life (t1/2). Descriptive statistics of mean, standard deviation, CV, maximum and minimum of each parameter.

For the expansion cohort with sparse PK sampling only, descriptive statistics will be

provided for the distribution of IBI110 plasma concentrations after single and multiple doses.

All PK plasma concentration-time data from this study and useful PK data from other studies of IBI110 will be pooled as necessary, if data permit, and a separate population PK analysis will be performed using a population pharmacokinetic model-based approach, and the results of the analysis will be summarized in a separate report.

- Immunogenicity indicators

The positive rates of anti-drug antibodies and neutralizing antibodies were calculated, and the antibody levels of positive subjects were tabulated.

- Pharmacodynamic variables

Including but not limited to descriptive statistics of changes in pharmacodynamic indicators.

8.4.4 Safety Analysis

DLT analysis set will be used for DLT evaluation, and SS population will be used for other safety analysis. Safety indicators include DLT, drug exposure, adverse events, laboratory tests, vital signs, ECG, etc. Data will be summarized by phase and cohort. Adverse events will be summarized in total.

8.4.4.1 **Drug Exposure**

The study drug exposure and administration time (number of cycles) of subjects during the study can be summarized by dose level, tumor type and total.

8.4.4.2 **Adverse Events**

All adverse events will be coded using MedDRA.

The incidence (frequency) and distribution of severity of AE, TEAE, Adverse Drug Reaction (ADR), SAE, etc. will be summarized by SOC and PT in MedDRA coding according to NCI CTCAE v5.0.

Subjects who discontinued the study drug due to adverse events, subjects who experienced SAE and subjects who died will be listed (at least including AE start date, end date, severity, relationship to the drug, action taken and outcome).

8.4.4.3 **Laboratory Tests**

Observed values and changes from baseline for laboratory tests were analyzed using descriptive statistics. Shift tabulations will be presented between baseline grade and worst grade on trial according to NCI CTCAE v5.0 grading criteria.

8.4.4.4 **ECG examination**

Descriptive statistics will be used to describe the changes of ECG parameters from baseline. Cross classification tables will be used to describe the normal and abnormal changes before and after treatment, and data listings will be provided.

8.4.4.5 **Vital Signs, Physical Examinations, and Other Safety-Related Examinations**

Descriptive statistics of vital signs test results and changes from baseline will be provided.

Subjects with abnormal changes from baseline in physical examination will be presented in a listing.

8.4.5 Compliance Analysis

The SS population was used for the analysis of compliance.

The proportion and frequency of subjects who violated the intended dosing regimen were summarized.

Compliance with study medication dosing will be summarized.

Proportion of subjects completing the study, proportion of subjects completing different treatment periods.

8.4.6 Baseline characteristics of subjects

Descriptive statistics of demographic characteristics (gender, age) of subjects; Diagnosis and treatment information of the indication disease (tumor type, pathological diagnosis, clinical staging, previous treatment); Other baseline information: such as height and weight (body mass index, body surface area), ECOG PS score, non-tumor history, surgical history, previous/concomitant/new concomitant drugs, etc.

8.4.7 Interim Analysis

No interim analysis is planned for this study.

8.4.8 Adjustment for Multiple Comparisons and Multiplicity

No multiplicity adjustment was taken into account.

8.4.9 Data listings for valid subjects

In addition to subject data listings, tumor evaluation (evaluation date, lesion status, evaluation results) and efficacy indicators for subjects with CR and PR will be listed separately.

8.4.10 Exploratory Analysis

- The iORR, iDCR and their 95% CIs were calculated by dose level, Kaplan-Meier estimates of median iPFS and iPFS rates at 6 months and 1 year were used, and iDOR, iTTR, and maintenance response rate at the time of data analysis were calculated for subjects who achieved an objective response based on iRECIST assessment.
- Descriptive statistics will be provided for the proportion of subjects with different expression levels of LAG-3 and PD-L1 in tumor tissues, and ORR and DOR in corresponding subgroups with different expression levels.

8.5 Determination of Sample Size

No formal sample size estimation will be performed for this clinical study:

Phase 1a: 4 to 38 subjects with advanced tumors in the single-agent dose escalation phase and 60 subjects in the single-agent dose expansion phase.

Phase Ib: Planned enrollment: 6 to 123 subjects in the combined dose escalation phase. 420 to 560 subjects in combination dose expansion phase.

8.6 Measures for bias control

8.6.1 Randomization and blinding

Subjects will not be randomized except for Cohort D2. The IWRS system will be used for static randomization of subjects in Cohort D2, and the randomization numbers will be generated using the block randomization method. Successfully screened subjects will be randomized in a 1: 1 ratio to the treatment arm (IBI110 600mg Q3W plus sintilimab 200mg IV Q3W plus paclitaxel and carboplatin Q3W) or the control arm

(sintilimab 200mg IV Q3W plus paclitaxel and carboplatin Q3W).

This trial is an open-label trial, and blinding is not applicable.

8.6.2 Assessment of Blinding Maintenance

Not applicable.

8.6.3 Unblinding and Emergency Unblinding

Not applicable.

9 Quality Assurance and Quality Control

In accordance with GCP guidelines, the sponsor is responsible for implementing and maintaining quality assurance and quality control systems according to corresponding standard operating procedures to ensure that the conduct of clinical trials and the collection, recording and reporting of data comply with the protocol, GCP and corresponding regulatory requirements.

9.1 Clinical Monitoring

The sponsor or a contract research organization (CRO) authorized by the sponsor will perform clinical monitoring for this study. CRAs should perform monitoring in accordance with the standard operating procedures of the Sponsor or CRO and have the same rights and responsibilities as the Sponsor's CRAs. The monitor should maintain regular communication with the investigator and the sponsor.

Prior to the start of the study, the monitor will assess the competence of the study site and report problems with facilities, technical equipment, or medical personnel to the sponsor. During the study, the monitor will be responsible for monitoring whether the investigator has obtained written informed consent from all subjects and whether the data records are correct and complete. At the same time, the monitor will also compare the data entered into the eCRF with the original data and inform the investigator of any errors or omissions. The monitor will also control protocol compliance at the study site, arrange for the supply of study drug, and ensure that the drug is stored under appropriate conditions.

Monitoring visits will be conducted as required by applicable laws and regulations. Beginning with subject enrollment, each site will undergo regular monitoring visits. After each visit to the investigator, the monitor should submit a written report to the sponsor.

9.2 Data Management/Coding

Electronic Data Capture (EDC) system will be used in this study, and study data will be entered into the eCRF by the investigator or authorized study personnel. Prior to site initiation or data entry, the investigator and authorized study personnel will be appropriately trained and appropriate security measures will be taken for the computers and other equipment used.

Data entry into the eCRF should be completed as soon as possible during or after the visit and updated at any time to ensure that it reflects the latest developments of the subjects participating in the study. To avoid differences in the assessment of results by different evaluators, it is recommended that baseline and all subsequent efficacy and safety assessments for the same subject be performed by the same person. The investigator was required to review the data to ensure the accuracy and correctness of all data entered into the eCRF. If certain assessments are not performed during the course of the study, or certain information is not available, not applicable, or unknown, the investigator should record it in the eCRF. The investigator should electronically sign the data after verification.

The monitor (Clinical Research Associate, CRA) will review the eCRFs and assess their completeness and consistency, and the CRA will compare the eCRFs with the source documents to ensure the consistency of key data. All data entries, corrections, and modifications will be the responsibility of the Investigator or his/her designee. The data in the eCRF were submitted to the data server and any changes to the data were recorded in the audit trail, i.e. The reason for the change, operator name, time and date of the modification were recorded. The roles and permissions of the site personnel responsible for data entry will be pre-determined. In case of data query, CRA or data management personnel will issue the query in EDC, and the site staff will be responsible for answering the query. The EDC system will record the audit trail of queries, including the investigator's name, time, and date.

Unless otherwise specified, the eCRF will only be used as a form for data collection and not as source data. Source documents are all records used by the investigator or hospital, related to the subject, and capable of proving the existence of the subject, the inclusion/exclusion criteria and his/her participation in this study, including laboratory records, ECG results, pharmacy dispensing records, subject folders, etc.

The investigator is responsible for maintaining all source documents and for monitoring them by the CRA at each visit. In addition, the investigator was required to submit a completed eCRF for each enrolled subject, regardless of the duration of the enrolled subject's participation in the study. All supporting documents (e.g., laboratory or hospital records) submitted with the eCRF should be carefully verified for the protocol number and subject number, and all personal privacy information (including subject name) should be deleted or illegible to protect subject privacy. The investigator certifies by electronically signing the record that he/she has reviewed the record and vouch for the accuracy of the data in the record. The electronic signature will be completed using the user ID and password of the investigator. The date and time of the signature will be automatically attached by the system. The investigator may not share the user ID and password with other personnel. Changes to data in the eCRF should be made according to the workflow defined in the EDC system. All changes and reasons for changes will be documented in the audit trail.

Adverse events, concomitant diseases/medical history, etc. will be coded. The coding dictionary will be described in the Clinical Study Report (CSR).

9.3 Quality Assurance Audit

Quality assurance audits of the study site, study database, and associated study documents may be conducted by the sponsor or authorized representatives of the sponsor during the course of the study, and inspections of the study site, study database, and associated study documents may also be conducted at the discretion of the appropriate regulatory authorities. When notified of an inspection by a regulatory authority, the investigator was to notify the sponsor immediately.

Site audits were conducted by the sponsor's Quality Assurance Unit. Audits included: drug supplies, required trial documents, records of the informed consent process, and consistency of the case report forms with source documents. Audit content and scope may also be added as appropriate. After reasonable notification, the investigator should allow auditors entrusted by the sponsor to conduct trial-related audits and inspections by regulatory authorities. The main purpose of the audit or inspection is to verify that the rights or health of the subjects participating in the trial are protected, that the informed consent is signed and the trial process is properly conducted, and that all data related to the evaluation of the study drug are handled and reported in accordance with the pre-

planned arrangement, protocol, facilities, ethical standard operating procedures, GCP and applicable regulatory requirements. The investigator should have direct access to all trial documents, original records and raw data.

10 Ethics

10.1 Ethics Committee

The sponsor or its authorized representative of the sponsor will prepare relevant documents to be submitted to the Ethics Committee (EC) of the study site, including the trial protocol, informed consent form, investigator's brochure, subject recruitment materials or advertisements and other documents required by regulations, and submit them to the corresponding EC for review and approval. Written approval from the EC must be obtained and provided to the Sponsor prior to initiation of the study. The EC approval letter must clearly describe the name, number and version number of the study protocol as well as the version number of other documents (such as informed consent form) and approval date. The investigator should notify the sponsor of the EC's written comments on the delay, suspension or re-approval.

The site must comply with the requirements of the site's EC. It may include protocol amendments, ICF amendments, subject recruitment materials amendments to be submitted to EC for review and approval, local safety reporting requirements, periodic reports and updates according to EC regulations, and final report submission. All of the above documents and EC approvals must be provided to the Sponsor or its designee.

10.2 Ethics of this study

The study process and informed consent shall comply with the Declaration of Helsinki, relevant GCP requirements and relevant laws and regulations of China concerning drug and data protection.

GCP provides ethical, scientific and global quality standards for the design, conduct, recording, and reporting of clinical studies involving human subjects. This study will be conducted in accordance with GCP and relevant national regulations and in accordance with the relevant ethical principles in the Declaration of Helsinki to protect the rights, safety and well-being of the subjects.

The investigator is required to comply with the procedures specified in this trial protocol and shall not make changes without the permission of the sponsor. Any protocol

deviations will be reported to the EC, the Sponsor, or regulatory authorities.

10.3 Subject Information and Informed Consent

The possible risks and benefits of the study will be explained to potential subjects using an Informed Consent Form (ICF) that will be understandable before any study procedures are initiated. The ICF statement should specify that the informed consent is voluntary and the possible risks and benefits of participating in the study should be specified, and the subject may withdraw from the study at any time. The investigator can only enroll a subject after fully explaining the details of the study, satisfactorily answering the subject's questions and giving sufficient time for consideration, and obtaining the written consent of the subject or his/her legal representative. All signed informed consent forms must be in the investigator's file or in the subject's folder.

The investigator is responsible for explaining the content of the informed consent to the subject and obtaining the informed consent form signed and dated by the subject or his/her legally acceptable representative prior to the start of the study. After signing, the investigator should send the subject a copy of the signed informed consent form. The investigator should record the informed consent process in the trial source documents.

10.4 Subject Data Protection

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

Precautions were taken to ensure the confidentiality of documents and to prevent identification of subjects. However, under special circumstances, some individuals may see genetic data and personal identification codes for a subject. For example, in the event of a medical emergency, the sponsor, its representative physician, or investigator will be aware of the subject identification code and have access to the subject's genetic data. In addition, access to relevant documents is required by the relevant regulatory authorities.

11 Study Management

11.1 Data Handling and Record Retention

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

Study documents should be properly retained for future access or data traceability. Safety and environmental risks should be considered when preserving documents.

No study documents will be destroyed without the written permission of the Sponsor and the Investigator. Only after notifying and obtaining written consent from the Sponsor, the Investigator/study site may transfer the study documents to other parties who comply with the document retention requirements or to other locations where they meet the requirements.

11.2 Access to Raw Data/Documents

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

11.3 Protocol Amendment

Any amendments to the protocol that may be appropriate during the course of the study will be communicated and agreed upon by the Sponsor and the Investigator. The sponsor should ensure that protocol amendments are submitted to regulatory authorities in a timely manner.

All amendments to the protocol will be retained as protocol supplements. Any amendment to the protocol should be submitted to the Ethics Committee for approval or filing according to the provisions of the Ethics Committee. If required, it should also be submitted to regulatory authorities for approval and, if required, approved by the EC and regulatory authorities before implementation (except for changes to the protocol to eliminate an immediate hazard to trial subjects).

11.4 Investigator Responsibilities

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

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

11.5 Publication Policy

All data generated in this study are confidential information of the Sponsor. The

Sponsor has the right to publish the results of the study. Information on the publishing policies of the sponsor and investigators will be described in the clinical trial agreement.

All information related to this trial (not limited to the following documents: protocol, Investigator's Brochure) must be strictly confidential. The investigator must be aware that the scientific or medical information derived from this trial may have commercial value to the sponsor. The investigator shall keep the information and data related to this trial confidential. If the information related to this trial or the conclusions drawn from the trial are to be published publicly, the investigator shall negotiate with the sponsor in advance and obtain the written consent of the sponsor. In order to protect their own rights and interests, the sponsor may require the investigator not to publish information related to the trial before the investigational product is approved for marketing.

The sponsor has the right to publish or publish information or data related to this trial or to report it to the drug regulatory authorities. If the sponsor needs to include the name of the investigator in the publication, publication, or advertisement, the investigator's consent should be obtained.

11.6 Finance and Insurance

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

12 References

[1]. Chen W, Sun K, Zheng R, et al. Cancer incidence and mortality in China, 2014. Chin J Cancer Res. 2018; 30 (1): 1-12.

[2]. Herzberg B1, Campo MJ1, Gainor JF2, et al. Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer. Oncologist. 2017 Jan; 22 (1): 81-88.

[3]. Jenkins RW1, Barbie DA, Flaherty KT. Mechanisms of resistance to immune checkpoint inhibitors. Br J Cancer. 2018 Jan; 118 (1): 9-16.

[4]. Andrews LP, Marciscano AE, Drake CG, et al. LAG-3 (CD223) as a cancer immunotherapy target. Immunol Rev. 2017 Mar; 276 (1): 80-96.

[5]. Huang CT, Workman CJ, Flies D, et al. Role of LAG-3 in regulatory T cells. Immunity. 2004 Oct; 21 (4): 503-13.

[6]. Meng Qiao, Tao Jiang, Shengxiang Ren, et al. Combination Strategies on the Basis of Immune Checkpoint Inhibitors in Non-Small-Cell Lung Cancer: Where Do We Stand? Clin Lung Cancer. 2018 Jan; 19 (1): 1-11.

[7]. Fuchs CS, Doi T, Jang RW, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients with Previous Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncol. May 10, 2018; 4 (5).

[8]. https://www.clinicaltrials.gov/ct2/show/NCT02494583?term=KEYNOTE-062&rank=1

[9]. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Dec 2; 390 (10111): 2461-2471.

[10]. Markus Moehler, Kohei Shitara, Marcelo Garrido, et al. Nivolumab Plus Chemotherapy Versus Chemotherapy as First-Line Treatment for Advanced Gastric Cancer/Gastroesophageal Junction Cancer/Esophageal Adenocarcinoma: First Results of the CheckMate 649 Study.

[11]. Torre, L A, et al. Global Cancer Statistics, 2012. CA a cancer J Clin. 2015; 65 (2), 87-108.

[12]. Llovet, J M, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359, 378-390.

[13]. Cheng, A L, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomized, double-blind, placebo-controlled trial. Lancet Oncol. 2009; 10 (1), 25-34.

[14]. Kudo, M, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomized phase 3 non-inferiority trial. Lancet. 2018; 391 (10126), 1163-1173.

[15]. Finn R S, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020; 382 (20): 1894-1905.

[16]. Yuan Zhongyu, Wang Shusen, Zhu Meiqin, et al. Clinical characteristics and prognosis of different molecular subtypes of breast cancer [J]. Chin J Cancer, 2008, 30 (6): 456-461.

[17]. Hong Lei, Wei Suju, Ma Jing, et al. Analysis of Prognostic and Survival Factors in 501 Patients with Triple Negative Breast Cancer [J]. China Health Statistics, 2015, 32 (1): 66-67.

[18]. Abu-Rustum NR, Yashar CM, Bean S, et al. NCCN Guidelines Insights: Cervical Cancer, Version 1.2020. J Natl Compr Canc Netw. 2020; 18 (6): 660-666.

[19]. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: cancer today. Lyon, France: International Agency for Research on Cancer, 2018. https://gco.iarc.fr/today (accessed July 3, 2020).

[20]. Stergios Boussios, et al. Management of Patients with Recurrent/Advanced Cervical Cancer Beyond First Line Platinum Regimens: Where Do We Stand? A Literature Review. Crit Rev Oncol Hematol. 2016 Dec; 108: 164-174.

[21]. Bray F, Ferlay J, Soerjomataram I, et al. Global Cancer Statistics 2018: GLOBOCAN estimates of incidences and mortalities worldwide for 36 cancers in 185 counties. CA Cancer J Clin. 2018 Nov; 68 (6): 394-424.

[22]. Mar í a T. B,, MSHugo E. Vel á zquez, et al. Is This Patient With Metastatic Bladder Cancer a Candidate for Second-Line Immunotherapy Treatment? Volume: 32Issue: 2. Feb 15, 2018. Cancernetwork.com

[23]. Choueiri TK, Motzer RJ. Systemic Therapy for Metastatic Renal-Cell Carcinoma. N Engl J Med. 2017 Jan 26; 376 (4): 354-366.

[24]. Ghatalia P, Zibelman M, Geynisman DM, et al. Checkpoint Inhibitors for the Treatment of Renal Cell Carcinoma. Curr Treat Options Oncol. 2017 Jan; 18 (1): 7.

[25]. McKay RR, Boss é D, Xie W, et al. The Clinical Activity of PD-1/PD-L1 Inhibitors in Metastatic Non-Clear Cell Renal Cell Carcinoma. Cancer Immunol Res. 2018 Jul; 6 (7): 758-765.

[26]. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidences and Mortality Worldwide for 36 Cancers in 185 Countries.

[27]. Matulonis UA, Sood AK, Fallowfield L et al. Ovarian cancer. Nat Rev Dis Primers 2016; 2: 16061.

[28]. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. Ovarian Cancer, Version

2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19 (2): 191-226. Published 2021 Feb 2.

[29]. Efficacy and Safety of Pembrolizumab in Previous Treated Advanced Neuroendocrine Tumors: Results from the Phase II KEYNOTE-158 Study.

[30]. Yu-Pei Chen, et al. Nasopharyngeal carcinoma. Lancet. 2019 Jul 6; 394 (10192): 64-80.

[31]. Zhang J, Fang W, Qin T, et al: Co-expression of PD-1 and PD-L1 predictions poor output in nasopharyngeal carcinoma. Med Oncol 32: 86, 2015.

[32]. Feng-Hua Wang, Xiao-Li Wei, et al. Efficiency, Safety, and Correlative Biomarkers of Toripalimab in Previous Treated Recurrent or Metastatic Nasopharyngeal Carcinoma: A Phase II Clinical Trial (POLARIS-02). Journal of Clinical Oncology 2021 39: 7, 704-712.

[33]. Coit DG, Thompson JA, Algazi A, et al. Melanoma, version 2.2016 clinical practice guidelines in oncology. JNCCN J Natl Compr Cancer Netw. 2016; 14 (4): 450-73.

[34]. Guo Jun. Advances in the treatment of melanoma. Science and Technology Bulletin. 2014; 32 (26): 15-21.

[35]. O 'Donnell JS, Long GV, Scolyer RA, et al. Resistance to PD1/PDL1 checkpoint inhibition. Cancer Treat Rev 2017; 52: 71-81.

[36]. Ascierto PA, et al. Initial Efficacy of Anti-Lymphocyte Activation Gene-3 (anti-LAG-3; BMS-986016) in Combination with Nivolumab in Patients with Melanoma Previous Treated with Anti-PD-1/PD-L1 Therapy. J Clin Oncol 2017; 35: 9520-9520.

[37]. Hong, David, et al. Phase I/II Study of LAG525 ± Spartalizumab (PDR001) in Patients with Advanced alignances. Novartis, ASCO 2018. 4 June 2018.

[38]. Nehal Lakhani, Todd M. Bauer, Anson K. Abraham, et al. The anti-LAG-3 antibody MK-4280 as mono and in combination with pembrolizumab for advanced solid tumors: first-in-human phase 1 dose-finding study.Abstract # O26 MERCK, SITC 2018. 7 Nov, 2018.

[39]. Passiglia F1, Bronte G1, Bazan V1, et al. PD-L1 expression as predictive biomarker in patients with NSCLC: a pooled analysis. Oncotarget. 2016 Apr 12; 7 (15): 19738-47.

[40]. Yayi He, Hui Yu, Leslie Rozeboom, et al. LAG-3 Protein Expression in Non-Small Cell Lung Cancer and Its Relationship with PD-1/PD-L1 and Tumor-Filtering Lymphocytes. Journal of Thoracic Oncology. Vol. 12 No. 5: 814-823.

[41]. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: Guidelines for Response Criteria for Use in Trials Testing Immunotherapy. Lancet Oncol. 2017 Mar; 18 (3): e143-e152.

13 Appendix

Appendix 1: Investigator Signature Page

Protocol Title: An Open-label Phase I Study to Evaluate the Safety, Tolerability, and Efficacy of IBI110 as Monotherapy and in Combination with Sintilimab in Subjects with Advanced Malignancies.

Protocol No.: CIBI110A101

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

Instructions for Investigators: Please sign and date this signature page, and print the name, title of the investigator and the name of the study site, and return to Xinda Biopharmaceutical (Suzhou) Co., Ltd. After signing.

I have read the entire contents of this protocol and warrant that this study will be conducted as required:

Investigator Signature: _____ Date: _____

Printed Name: _____

Title of Investigator: _____

Site Name/Address: _____

Appendix 2: Performance Status Scoring Criteria (ECOG PS)

Activity Score	Description
0	Asymptomatic, fully active, and able to carry out unrestricted activities.
1	Symptomatic, fully ambulatory, but limited in physically strenuous activities, able to carry out light or sedentary tasks, such as light housework, office work.
2	Symptomatic, ambulatory, capable of all selfcare but unable to carry out any physical activity, and awake approximately 50% of the time (confined to bed < 50% of daytime).
3	Symptomatic, limited self-care ability, confined to bed or chair > 50% of waking hours, but not yet bedridden.
4	Completely incapacitated, completely incapable of self-care, bedridden.
5	Death.

Appendix 3: Creatinine Clearance Calculation

Creatinine clearance calculated by the Cockcroft-Gault formula

Serum creatinine concentration in mg/dl is calculated by the formula:

$$\text{Creatinine clearance in males (mL/min)} = \frac{(140\text{-Age}) \times (\text{Weight})\ a}{72 \times \text{serum creatinine}}$$

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

Serum creatinine concentration (mol/L) is calculated by the formula:μ

$$\text{Creatinine clearance in males (mL/min)} = \frac{(140\text{-Age}) \times (\text{Weight})\ a}{0.818 \times \text{serum creatinine}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140\text{-age}) \times (\text{weight})\ a}{0.818 \times \text{serum creatinine}}$$

a: Age in years and weight in kg.

Appendix 4: Response Evaluation Criteria in Solid Tumors Version 1.1 (excerpted)

(Response Evaluation Criteria in Solid Tumors RECIST Version 1.1)

1. Measurability of tumor at baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be classified as measurable or non-measurable according to the following definitions:

1.1. 1 Measurable disease

Tumor lesions: at least one diameter that can be accurately measured (to be recorded as the largest diameter) with the following minimum lengths:

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

10 mm by clinical routine examination (tumor lesions that cannot be accurately measured by calipers should be recorded as non-measurable);

Chest X-ray 20 mm;

Malignant lymph nodes: Pathologically enlarged and measurable, an individual lymph node must be ⩾ 15 mm in the short axis by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

1.1. 2 Non-measurable disease

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes ⩾ 10 mm to < 15 mm short axis) and non-measurable lesions. Non-measurable lesions include meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, lymphangitic carcinomatosis of the skin/lung, abdominal masses that cannot be confirmed by imaging and followed up, and cystic lesions.

1.1. 3 Special Considerations for Lesion Measurements

Bone lesions, cystic lesions, and lesions previously treated with local therapy need to be specifically noted:

Bone lesions:

1) 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;

2) Lytic bone lesions or mixed lytic/blastic lesions with defined soft tissue components that meet the definition of measurability described above can be considered as measurable lesions if they can be evaluated with cross-sectional imaging techniques such as CT or MRI;

3) Blastic lesions are non-measurable.

Cystic lesions:

1) Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions because they are simple cysts by definition, neither measurable nor non-measurable;

2) Cystic metastases that meet the definition of measurability described above can be considered as measurable lesions. However, if non-cystic lesions are present in the same subject, they should be preferred as target lesions.

Locally treated lesions:

Lesions located in sites that have been irradiated or other loco-regional therapy are generally considered non-measurable unless there is unequivocal progression in the lesion. The protocol should describe in detail the conditions under which these lesions are measurable.

1.2 Description of measurement method

1.2. 1 Lesion Measurements

All tumor measurements will be recorded in the metric system at the time of clinical evaluation. All baseline assessments of tumor lesion size should be performed as close as possible to the start of treatment and must be completed within 28 days (4 weeks) prior to the start of treatment.

1.2. 2 Evaluation method

The same techniques and methods should be used for baseline and subsequent measurements of lesions. All lesions must be evaluated by imaging, except those that cannot be evaluated by imaging but can only be evaluated by clinical examination.

Clinical lesions: Clinical lesions will be considered measurable only if they are superficial and ⩾ 10 mm in diameter when measured (e.g., skin nodules, etc.). For subjects with skin lesions, it is recommended that a color photograph containing a ruler to measure the size of the lesion be used for archiving. When lesions are evaluated by both imaging and clinical examination, imaging evaluation should be selected whenever possible because imaging is more objective and can be repeated at the end of the study.

Chest X-ray: Chest CT should be preferred when tumor progression is an important endpoint because CT is more sensitive than X-ray, especially for new lesions. Chest X-ray is indicated only if the lesion being measured is well-defined and the lungs are well ventilated.

CT, MRI: CT is currently the best reproducible method available for response assessment. The definition of measurability in this guideline is based on CT scan slice thickness ⩽ 5 mm. If CT slice thickness is greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI may also be acceptable in some cases (e.g., full body scans).

Ultrasound: Ultrasound should not be used as a method of measurement to measure lesion size. Ultrasonography is not repeatable after the end of the measurement due to its operational dependency and does not guarantee the identity of the technique and measurement between different measurements. If a new lesion is identified by ultrasound during the trial, it should be confirmed by CT or MRI. If radiation exposure from CT is considered, MRI may be used instead.

Endoscopy, laparoscopy: The use of these techniques for objective tumor assessment is not recommended, but they can be used to confirm CR when biopsies are obtained and to confirm recurrence in trials where recurrence after CR or surgical resection is an endpoint.

2. Assessment of tumor response

2.1 Target Lesion Assessment

Complete Response (CR): Disappearance of all target lesions and reduction in short axis of all pathological lymph nodes (both target and non-target) to < 10 mm.

Partial Response (PR): at least a 30% decrease from baseline in the sum of diameters of target lesions.

Progressive disease (PD): at least a 20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters of all target lesions measured throughout the study (the baseline value will be taken as reference if the baseline value is the smallest); In addition, an absolute increase of at least 5 mm in the sum of diameters must be met (the appearance of one or more new lesions is also considered progressive disease).

Stable disease (SD): Neither a decrease to the level of PR nor an increase to the level of PD in target lesions, taking as reference the smallest sum diameters on study.

2.2 Considerations for Target Lesion Assessment

Lymph nodes: Even if lymph nodes identified as target lesions decrease to within 10 mm, the actual short axis value corresponding to baseline should be recorded at each measurement (in the same anatomical plane as the baseline measurement). This means that if a lymph node is a target lesion, it cannot be said that the lesion has completely disappeared even if the criteria for complete response are met, since the short axis of a normal lymph node is defined as < 10 mm. Target nodal lesions should be recorded in a specific location in the CRF or other recording methods: for CR, all nodal short axis must be < 10 mm; For PR, SD and PD, the actual short axis measurement of target nodes will be included in the sum of the diameters of target lesions.

Target lesions that are too small to measure: in clinical studies, all lesions (nodal or non-nodal) recorded at baseline should have their actual measurements recorded again at subsequent assessments, even if they are very small (e.g., 2 mm). But sometimes it may be too small to make the CT scan so blurry that the radiologist has difficulty defining the exact value and may report it as "too small to measure." When this occurs, it is important to record the previous value on the eCRF form. If in the opinion of the radiologist, the lesion may have disappeared, it should also be recorded as 0 mm. If a lesion is present but blurry and cannot be accurately measured, the default value is 5 mm. (Note: Lymph nodes are unlikely to be present because they typically have a measurable size under normal conditions or are often surrounded by adipose tissue as they are in the retroperitoneum; however, if such a situation does not allow measurement, the default value is 5 mm). The default value of 5 mm is derived from the cut thickness of the CT scan (this value does not change according to the different cut thickness values of CT). Providing this default value will reduce the risk of erroneous evaluation since the same

measurement is not likely to be repeated. However, it should be reiterated that if the radiologist is able to provide an exact value for the size of the lesion, the actual value must be recorded even if the lesion is less than 5 mm in diameter.

Separated or Combined Lesions: When a non-nodal lesion splits into fragments, the longest diameters of the separate portions are added together to calculate the sum of the diameters of the lesions. Similarly, for coalescent lesions, the planes between the coalescent segments can be used to distinguish them, and the respective maximum diameter can be calculated. However, if the combination is inseparable, the longest diameter should take the longest diameter of the whole coalescing lesion.

2.3 Assessment of Non-Target Lesions

This section defines tumor response criteria for non-target lesions. Although some non-target lesions are actually measurable, they do not need to be measured and only need to be assessed qualitatively immediately at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes are non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesions and/or persistence of tumor marker level above normal.

Progressive Disease: Unequivocal progression of existing non-target lesions. Note: The appearance of one or more new lesions is also considered progressive disease.

2.4 Special Considerations for Assessment of Progression of Non-Target Lesions

The additional explanation for the definition of progression of non-target disease is as follows: When a subject has measurable non-target disease, to define unequivocal progression on the basis of non-target disease, even if the target disease is assessed as stable or partial response, the overall worsening in non-target disease must be sufficient to warrant discontinuation of treatment. A general increase in the size of one or more non-target lesions is often not sufficient to meet the criteria for progression; therefore, it is almost rare for a change in non-target disease alone to define overall tumor progression in the presence of stable or partial response of target disease.

When a subject has non-measurable non-target disease: This occurs in some Phase 3 trials when the inclusion criteria do not specify that measurable disease must be present.

The overall assessment will also refer to the above criteria, but in this case there is no measurable disease. Worsening in non-target disease cannot be easily assessed (by definition: all non-target lesions must be truly non-measurable), so when the increase in overall disease burden due to the change in non-target disease is comparable in magnitude to PD in target disease, a valid test is needed to assess unequivocal progression in non-target disease based on the definition of unequivocal progression. This is described as an increase in tumor burden corresponding to an additional 73% increase in volume (corresponding to a 20% increase in diameter of a measurable lesion). Another example is peritoneal exudation from "trace" to "large"; Lymphangiopathy from "local" to "widespread"; Or described in the protocol as "sufficient to change treatment". Examples include pleural effusion ranging from trace to large, lymphatic involvement spreading from the primary site to distant sites, or may be described in protocols as "warranting a change in therapy". If unequivocal progression is observed, the subject should be considered as having progressed overall at that time point. It is preferable to have objective criteria applicable to the assessment of non-measurable disease, note that the added criteria must be reliable.

2.5 New lesions

The appearance of new malignant lesions predicts disease progression; Therefore, some evaluation of new lesions is very important. There are no specific criteria for radiographic detection of lesions, however the finding of a new lesion should be unequivocal. For example, progression cannot be attributed to differences in imaging techniques, changes in imaging modality, or lesions other than tumor (e.g., some so-called new bone lesions are simply healing of the original lesion, or recurrence of the original lesion). This is important when a subject has a partial or complete response of baseline lesions, e.g. Necrosis of a liver lesion may be identified as a new cystic lesion on the CT report when it is not.

Lesions detected at follow-up but not at baseline will be considered new lesions and indicate disease progression. For example, a subject with visceral disease at baseline who has metastases on CT or MRI will be considered as evidence of progressive disease, even if he does not have a cranial examination at baseline.

If a new lesion is equivocal, for example due to its small size, further treatment and follow-up evaluation are required to confirm whether it is a new lesion. If repeat testing

confirms that it is a new lesion, the time to progression should be counted from the time it was first identified.

FDG-PET assessment of disease generally requires additional testing to complement this, and it is reasonable to combine FDG-PET with CT to assess progression (especially for new suspected disease). New lesions can be identified by FDG-PET using the following procedures:

A negative FDG-PET at baseline followed by a positive FDG-PET at follow-up indicates disease progression.

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

If the positive FDG-PET at follow-up identifies a new lesion consistent with the CT scan, this is disease progression.

If a positive FDG-PET at follow-up is not confirmed by CT as a new lesion, additional CT should be performed to confirm the lesion (if confirmed, the time of progression begins with the initial abnormal FDG-PET).

If a positive FDG-PET at follow-up is consistent with a pre-existing lesion on CT that does not progress radiographically, there is no progression.

2.6 Description of Missing Assessments and Not Evaluable

If a lesion cannot be imaged or measured at a particular time point, the subject is not evaluable at that time point. If only a subset of lesions can be evaluated at an assessment, this is generally considered not evaluable at that timepoint unless there is evidence that the missing lesions do not affect the response assessment at the given timepoint.

2.7 Special Notes for Efficacy Assessment

When nodal lesions are included in the overall target lesion assessment and the nodes decrease in size to "normal" size (< 10mm), they will still have a lesion size scan report. In order to avoid overestimating what is reflected by an increase in nodal size, measurements will be recorded even if the node is normal. As already mentioned, this means that subjects with complete response will not be recorded as 0 on the eCRF.

If confirmation of response is required during the course of the trial, repeated "non-measurable" time points will complicate the best response assessment. The analysis plan for the trial must specify that these missing data/assessments can be accounted for when

determining efficacy. For example, in most trials, a subject's response of PR-NE-PR can be considered a confirmed response.

Symptomatic progression should be reported when a subject experiences a global deterioration in his/her health condition requiring discontinuation of treatment without objective evidence. Every effort should be made to assess objective progression even after treatment discontinuation. Symptomatic deterioration is not an assessment description of an objective response, it is a reason for discontinuation of treatment. The objective response of such subjects will be evaluated by target and non-target lesions as shown in Tables 3-1 ~ 3-3.

Conditions defined as early progression, early death, and non-evaluability are study specific and should be clearly described in each protocol (depending on treatment interval and treatment cycle).

In some cases, it is difficult to distinguish a local lesion from normal tissue. When the assessment of complete response is based on this definition, it is recommended that a biopsy be performed before a response assessment of complete response of local lesions is made. FDG-PET is used as a similar assessment to biopsy for response confirmation of complete response when some subjects have abnormal radiographic findings in local lesions that are considered to represent fibrosis or scarring of the lesion. In such cases, the use of FDG-PET should be prospectively described in the protocol, supported by reports in the specialized medical literature for this condition. However, it is important to recognize that the limitations of FDG-PET and biopsy, including their resolution and sensitivity, may lead to false-positive results in the assessment of complete response.

Attached Table 3-1 Time Point Response-Subjects with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall response
CR	CR	None	CR
CR	Non-CR/Non-PD	None	PR
CR	Not evaluable	None	PR
PR	Non-progressive or not fully evaluable	None	PR
SD	Non-progressive or not fully evaluable	None	SD
Not fully assessed	Non-Progressive	None	NE

Target Lesions	Non-Target Lesions	New Lesions	Overall response
PD	Any condition	Yes or No	PD
Any condition	PD	Yes or No	PD
Any condition	Any condition	Yes	PD

Note: CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NE=not evaluable.

Attached Table 3-2 Time Point Response-Subjects with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall response
CR	None	CR
Non-CR or Non-PD	None	Non-CR or Non-PD
Not fully assessed	None	Not evaluable
Indeterminate PD	Yes or No	PD
Any condition	Yes	PD

Note: For non-target lesions, "non-CR/non-PD" is defined as a response superior to SD. As SD is increasingly used as an endpoint to evaluate response, a non-CR/non-PD response was developed to address the non-specified absence of measurable disease.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic or necrotic lesions in pre-existing lesions), treatment may continue until the next assessment. If disease progression is confirmed at the next assessment, the date of progression should be the previous date of suspected progression.

Attached Table 3-3 Best overall response requiring confirmation of CR and PR

First Time Point Overall Response	Overall Response at Subsequent Timepoints	Best overall response
CR	CR	CR
CR	PR	SD, PD or PRa
CR	SD	SD if SD lasts for sufficient time, otherwise PD
CR	PD	SD if SD lasts for sufficient time, otherwise PD
CR	NE	SD if SD lasts sufficient time, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD

First Time Point Overall Response	Overall Response at Subsequent Timepoints	Best overall response
PR	PD	SD if SD lasts for sufficient time, otherwise PD
PR	NE	SD if SD lasts sufficient time, otherwise NE
NE	NE	NE

Note: CR is complete response, PR is partial response, SD is stable disease, PD is progressive disease, and NE is not evaluable. Superscript "a": If CR truly occurred at the first timepoint, any disease that occurred at a subsequent timepoint would remain PD at a subsequent timepoint even if the subject met PR criteria relative to baseline (since disease would reappear after CR). Best response is determined by the occurrence of SD within the shortest treatment interval. However, sometimes the first assessment is CR, but subsequent time point scans suggest that small lesions still appear to be present, so that the subject's response should actually be PR rather than CR at the first time point. In this case, the initial CR determination should be revised to PR and the best response is PR.

2.8 Response Assessment/Confirmation of Response Duration

2.8. 1 Confirmation of response

For non-randomized clinical studies where tumor response is the primary endpoint, confirmation of PR and CR is mandatory to ensure that response is not the result of misevaluation. In studies where stable disease or progressive disease is the primary endpoint, confirmation of response is no longer required because it is not valuable for the interpretation of trial results. In the case of SD, at least one measurement met the SD criteria specified in the protocol at the shortest interval after the start of the trial (generally not less than 6 to 8 weeks).

2.8. 2 Overall Response

The duration of overall response is measured from the time the measurement first meets the criteria for CR or PR (whichever is first measured) to the first true documentation of recurrent or progressive disease (taking the smallest measurement recorded in the trial as a reference for progressive disease). The time to overall complete response is the time from the time the measurement first meets the criteria for CR to the first true documentation of disease recurrence or progression.

2.8. 3 Stable Disease

The time from the start of treatment to disease progression (in randomised trials, from the time of randomisation), taking as reference the smallest sum in the trial (if the baseline sum is the smallest, this is the reference for the calculation of PD). The clinical relevance of stable disease varies from study to study and from disease to disease. If the proportion of subjects who maintain a minimum duration of stabilization is used as an endpoint in a particular trial, the protocol should specifically specify the minimum time interval between two measurements in the definition of SD.

Note: The duration of response, stable disease, and PFS are influenced by the frequency of follow-up after baseline evaluation. Defining a standard follow-up frequency is outside the scope of this guideline. The frequency of follow-up should take into account many factors, such as type and stage of disease, duration of treatment, and standard practices. However, limitations in the accuracy of these measured endpoints should be taken into account if comparisons between trials are necessary.

Appendix 5: Immune Response Evaluation Criteria in Solid Tumors (iRECIST)

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

1. Efficacy Assessment of iRECTIST

Immunotherapy may promote the infiltration of immune cells, resulting in a transient increase in tumor size or the detection of otherwise undetectable lesions. This criterion is identical to RECIST V1.1 in many respects, but the assessment of cases such as increased tumor burden or appearance of new lesions, which may not reflect true tumor progression, is modified.

Key differences are described below. All efficacy measures assessed using iRECIST will be preceded by a prefix of "i". iRECIST timepoint response and best overall response will be recorded separately.

1.1 Confirmed progression

Unlike RECIST v1.1, iRECIST requires confirmation of disease progression and introduces both iUPD (unconfirmed progression) and iCPD (confirmed progression) criteria. Scan to confirm progression may be performed as early as week 4 post iUPD and no later than week 8 post iUPD.

If there is still an increase in tumor burden from the last measurement, iCPD will be determined as evidenced by one or more of the following:

- Continued increase in tumor burden based on disease progression (compared to nadir) of target, non-target or new lesions as defined by RECIST v1.1
    a) Worsening of target lesions as indicated by an absolute increase of at least 5mm in the sum of measurements
    b) Unequivocal progression of non-target lesions as indicated by increased tumor burden
    c) Increase in previously identified new lesions (at least 5 mm absolute increase in the sum of the measurements of new target lesions) or other new lesions
- Other lesions (target lesions, non-target lesions or new lesions) that have not previously demonstrated tumor progression meet RECIST v1.1 criteria for

progression, including other new lesions

If iUPD is not confirmed at the next assessment, the corresponding response assessment will be recorded (iUPD if iUPD is still met and does not worsen, and iSD, iPR, or iCR compared to baseline will be recorded). As shown in Table 4-2, prior iUPD does not affect documentation of iCR, iPR, or iSD at subsequent assessment time points or at best overall response when iCPD is not achieved at the next response assessment.

1.2 New Lesions

New lesions should be measured and assessed according to RECIST v1.1 (up to 5 lesions, no more than 2 per organ, at least 10 mm in the longest diameter (at least 15 mm in the short axis for nodal lesions)) and should be clearly identified as new target lesions and new non-target lesions to distinguish them from baseline target and non-target lesions.

New lesions should meet the definition of new target lesions and new non-target lesions to be recorded as iUPD (or iCPD). Measurements of such target lesions should not be calculated in the sum of the target lesion measurements defined at baseline. Measurements of these new target lesions should be recorded in a separate CRF.

Confirmation of disease progression in new lesions may occur when an absolute increase of at least 5 mm in the sum of the measurements of new target lesions or an increase in the volume of new non-target lesions (unequivocal increase is not required) or the appearance of additional new lesions on radiographic assessments performed at least 4 weeks (but not more than 8 weeks) after iUPD.

For all subjects, the immune best overall response (iBOR) from the start of treatment to the end of treatment will be defined as specified in Schedule 4-3.

2. Duration of Response and Stable Disease (RECIST v1.1 and iRECIST)

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

Duration of stable disease will be calculated from the start of treatment until disease progression, and the smallest measurements on study (including baseline) will also be taken as reference.

Attached Table 4-1. RECIST v1.1 and iRECIST

	RECIST v1.1	iRECIST
Definition of measurable and non-measurable lesions; Number and Location of Target Lesions	Measurable lesions with a long diameter of 10 mm or greater (15 mm for lymph node lesions); Up to 5 lesions (2 per organ); Other lesions are non-target lesions (lymph node lesions must be ≥ 10 mm in short axis)	No change; However, new lesions will be recorded separately on the case report form according to RECIST v1.1 criteria (will not be counted as the sum of target lesion measurements at baseline)
CR, PR or SD	Unable to document PD before CR, PR, or SD	May have iUPD (one or more) but not iCPD prior to iCR, iPR, or iSD
Confirmed CR, PR	Required for non-randomized trials only	Same as RECIST v1.1
Confirm SD	Unnecessary	Same as RECIST v1.1
New Lesions	Will be assessed as PD, but will not be measured	The assessment will be iUPD and will be recorded as iCPD when the next assessment meets the following criteria ● Appearance of other new lesions or ● Increase in volume of new lesions (increase of ≥ 5 mm in the sum of measurements of new target lesions or increase of any new non-target lesion) New lesions that have not been previously documented can also confirm iCPD
Independent blinded review and central image acquisition	Recommended in some cases	Collection of images is recommended for all studies (but not for independent review)
Confirmation of PD	Not required (unless not specified)	Need
Consider subject's clinical status	Not considered in the evaluation	Continuation of medication after iUPD will take into account whether the subject is clinically stable (see definition)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; iCR: complete immune response; iPR: immune partial response; iSD: stable immune disease; iUPD:

Immune unconfirmed progression; iCPD: immune confirmation progression;

Attached Table 4-2: iRECIST Response Records at Different Assessment Points

This efficacy assessment				
Target Lesions*	Non-target lesions*	New lesions*	Results of efficacy evaluation	
			No prior iUPD**	Prior iUPD**, ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
No change or decrease from last assessment in iUPD	No change or decrease from last assessment in iUPD	Yes	NA	If new lesions have been previously identified and have increased in size (≥ 5 mm increase in SOM for new target lesions or increase in new non-target lesions), iCPD may be confirmed. If new lesions are unchanged (volume or number) from last assessment, remain iUPD
iSD, iPR, iCR	iUPD	No	iUPD	Increase in the volume of non-target lesions (no unequivocal PD per RECIST v1.1 is required) to confirm iCPD, otherwise iUPD remains
iUPD	Non-iCR/Non-iUPD; iCR	No	iUPD	An iCPD is confirmed if the following criteria are met, otherwise it remains an iUPD: ● ≥ 5 mm increase in SOM of target lesions, otherwise remaining iUPD
iUPD	iUPD	No	iUPD	An iCPD is confirmed if the following criteria are met, otherwise it remains an iUPD: ● Increase in SOM of target lesions by ≥ 5 mm and/or by previously identified iUPD

				● Increase in non-target lesions on iUPD (previous assessment-no definitive PD required)
iUPD	iUPD	Yes	iUPD	An iCPD is confirmed if the following criteria are met, otherwise it remains an iUPD: ● Increase in SOM of target lesions by ⩾ 5 mm and/or by previously identified iUPD ● Increase in non-target lesions on iUPD (no unequivocal PD required) and/or ● Increase in volume or number of previously identified new lesions
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	An iCPD is confirmed if the following criteria are met, otherwise it remains an iUPD: ● Increase in volume or number of previously identified new lesions
* Refer to RECIST v1.1 principles. In the absence of pseudoprogression, the criteria for CR, PR, and SD are consistent between RECIST v1.1 and iRECIST. ** For any type of lesion. *** Found at last assessment prior to this assessment.				

iCR: complete immune response; iPR: immune partial response; iSD: stable immune disease; iUPD: Immune unconfirmed progression; iCPD: immune confirmation progression; SOM: Sum of measured values; NA: Not applicable: NE: Not evaluable

Attached Tables 4-3. Best overall response by iRECIST criteria

Best overall response					
1st assessment	2nd assessment	3rd assessment	4th assessment	5th assessment	Best overall immune response
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR

iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, iCPD, NE	iSD
iUPD	iCPD	Any	Any	Any	iCPD
iUPD	iUPD (without iCPD)	iCPD	Any	Any	iCPD
iUPD	NE	NE	NE	NE	iUPD

- For example only-more situations may exist but the same principles are followed
- This table assumes a randomized study design and does not require confirmation of CR or PR
- For subjects with only non-target lesions at baseline, assessments at each timepoint will be recorded as iCR or non-CR/non-PD only, but not shown in the table for ease of presentation

iCR: complete immune response; iPR: immune partial response; iSD: stable immune disease; iUPD: Immune unconfirmed progression; iCPD: immune confirmation progression; SOM: Sum of measured values; NA: Not applicable: NE: Not evaluable

Appendix 6: Grading, conversion and calculation formulas involved in the clinical study

<table>
<tr><th>Formula Name</th><th>Calculation method</th></tr>
<tr><td>QTc Fridericia formula</td><td>QTcF = QT/(RR ^ 0.33), RR is the normalized heart rate value, calculated by dividing 60 by heart rate. Note: The units of RR are seconds and the units of QT are milliseconds.</td></tr>
<tr><td>New York Heart Association Classification</td><td>Class I patients had cardiac disease but no limitation of physical activity. General physical activity does not cause excessive fatigue, palpitations, wheezing, or angina.
Class II patients have cardiac disease such that physical activity is mildly limited. It is asymptomatic at rest, but general physical activity causes excessive fatigue, palpitations, wheezing, or angina.
Class III patients have cardiac disease such that physical activity is significantly limited. It is asymptomatic at rest, but less than usual physical activity can cause excessive fatigue, palpitations, wheezing, or angina.
Class IV patients have cardiac disease, cardiac insufficiency or angina at rest, and discomfort is increased by any physical activity.</td></tr>
<tr><td>Endoscopic grading of esophageal varices</td><td>Mild (G1): Straight or slightly tortuous esophageal varices without RC.
Moderate (G2): Straight or slightly tortuous esophageal varices with RC or serpentine tortuous esophageal varices without RC.
Severe (G3): Oesophageal varices with serpentine tortuosity and RC or food Tubular varices are beaded, nodular, or neoplastic (with or without RC).
Note: RC: Red color, red syndrome: including whiplash sign, blood blister sign, etc., indicating that varicose veins are easy to bleed.</td></tr>
<tr><td>Hormone dose conversion (mg)</td><td>Cortisone 25 = Hydrocortisone 20 = Prednisone (Prednisone) 5 = Prednisolone 5 = Methylprednisolone 4 = Triamcinolone 4 = Betamethasone 0.6 = Dexamethasone 0.75</td></tr>
<tr><td>Child-Pugh classification evaluation system</td><td>
<table>
<tr><th>Measurements</th><th>1 point</th><th>2 points</th><th>3 points</th></tr>
<tr><td>Total Bilirubin 1 (mg/dl)
Total bilirubin (μ mol/L)</td><td>< 2.0
< 34</td><td>2.0 ~ 3.0
34 ~ 51</td><td>> 3.0
> 51</td></tr>
<tr><td>Serum albumin (g/dL)
Serum albumin (g/L)</td><td>> 3.5
> 35</td><td>2.8 ~ 3.5
28 ~ 35</td><td>< 2.8
< 28</td></tr>
<tr><td>INR2
OR
Prothrombin time, prolonged (sec)</td><td>< 1.7

< 4.0</td><td>1.7 ~ 2.3

4.0-6.0</td><td>> 2.3

> 6.0</td></tr>
</table>
</td></tr>
</table>

	Ascites	None	Mild (easy to control with medication)	Moderate to severe (Poor control)
	Hepatic Encephalopathy3	None	Class I-II (mild to moderate)	Grade III-IV (severe or comatose)

Score	**Grading**	**One-year survival rate**	**Two-year survival rate**
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Appendix 7: Common First-line Chemotherapy Regimens for Non-small Cell Lung Cancer

Time and cycle: 21 days as a cycle, 4 ~ 6 cycles.

	Chemotherapy regimen	**Dose**	**Duration of administration**
NP regimen	Vinorelbine	25 mg/m2	Day 1, 8
	Cisplatin	75 mg/m2	Day 1
TP Protocol	Paclitaxel	135-175 mg/m2	Day 1
	Cisplatin	75 mg/m2	Day 1
	Or carboplatin	AUC = 5 ~ 6	Day 1
GP Protocol	Gemcitabine	1000 ~ 1250 mg/m2	Day 1, 8
	Cisplatin	75 mg/m2	Day 1
	Or carboplatin	AUC = 5 ~ 6	Day 1
DP Protocol	Docetaxel	75 mg/m2 or 60 mg/m2	Day 1
	Cisplatin	75 mg/m2	Day 1
	Or carboplatin	AUC = 5 ~ 6	Day 1
AP protocol	Pemetrexed	500 mg/m2	Day 1
	Cisplatin	75 mg/m2	Day 1
	Or carboplatin	AUC = 5 ~ 6	Day 1

Excerpted from: CSCO Guidelines for the Diagnosis and Treatment of Primary Lung Cancer 2020 V1

Appendix 8: Common First-line Chemotherapy Regimens for Gastric Cancer

HER2 status	Level I recommendation	Level II recommendation	Level III recommendation
Positive	Trastuzumab in combination with fluoropyrimidine/capecitabine + cisplatin (Class 1A evidence)	Trastuzumab in combination with other first-line chemotherapy regimens (e.g., oxaliplatin + capecitabine or S-1 + cisplatin) (Class 2B evidence)	Trastuzumab in combination with other first-line chemotherapy regimens (except anthracyclines) (3 types of evidence)
Negative	• Cisplatin + fluoropyrimidine (5-fluorouracil/capecitabine/S-1) (Class 1A evidence); • Oxaliplatin + fluoropyrimidine (5-fluorouracil/capecitabine/S-1) (Class 2B evidence); • Docetaxel + 5-fluorouracil/capecitabine/S-1 (Class 2B evidence); • Paclitaxel + 5-fluorouracil/capecitabine/S-1 (Class 2B evidence).	Three-drug combination regimen (e.g., DCF/mDCF for patients with good physical strength and high tumor burden) (Class 2A evidence); Single agent regimen (e.g. Fluoropyrimidine-or paclitaxel-based therapy) for patients with poor physical strength (Class 2B evidence).	Three-drug combination regimens such as ECF and mECF are suitable for those with better physical strength and high tumor burden (Class 2A evidence); Irinotecan-based chemotherapy (type 3 evidence)

From: Wang et al. The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer. Cancer Commun (2019) 39: 10.