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A Phase II, Single-center, Single-arm Clinical Trial on the Efficacy and Safety of Anti-PD-1 antibody (IBI308) Combined with Anlotinib for the Treatment of Recurrent or Advanced Endometrial Cancer

Principal investigator: Chief Derector Jundong Li

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Protocol Synopsis

Study Title	A Phase II Single-center, Single-arm Clinical Trial on the Efficacy and Safety of Anti-PD-1 antibody (IBI308) Combined with Anlotinib for Recurrent or Advanced Endometrial Cancer
Study objective	To examine the efficacy and safety of anti-PD-1 monoclonal antibody (IBI308) combined with anlotinib for recurrent or advanced endometrial cancer.
Study design	A non-randomized, single-arm, open-label, phase II clinical trial
Principal investigator	Jundong Li
Inclusion criteria	1. Women aged > 18 years; 2. Histologically confirmed endometrial cancer; 3. Recurrent or advanced endometrial cancer with at least one treatment with systemic platinum-based chemotherapy; • Low probability of cure for recurrent endometrial cancer with surgery and/or radiotherapy and failure of at least one systemic platinum-based chemotherapy after recurrence. • Newly diagnosed advanced endometrial cancer persisting after standard treatment with surgery ± radiochemotherapy and at least one systemic platinum-based chemotherapy. 4. Objectively measurable lesions based on Response Evaluation Criteria In Solid Tumors (RECIST 1.1) and at least one target lesion; • In principle, lesions in the field of previous radiotherapy are considered non-target unless there is radiological evidence of progression or a biopsy with progression within 90 days after radiotherapy. 5. Eastern Cooperative Oncology Group (ECOG) score of 0–2; 6. Expected survival >3 months; 7. Major organ function fulfilling the following criteria (correction of the following parameters and supportive treatment are permitted one week before enrollment);

	• Absolute neutrophil count ≥1.5 × 10^9/L, platelet count ≥70 × 10^9/L, hemoglobin ≥80 g/L • Alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5 times upper limit of normal (ULN) (<5 times for patients with liver metastases) and total bilirubin ≤ 1.5 times ULN • Serum creatinine ≤ 1.5 times ULN • International normalized ratio (INR) <1.5 times ULN • Proteinuria ≤ (+) • Thyroid-stimulating hormone (TSH) ≤1 time ULN (measure FT3 and FT4 if TSH abnormal; subjects with normal FT3 and FT4 can be enrolled) 8. Voluntarily signed informed consent form.
Exclusion criteria	1. Presence of carcinosarcoma in pathology specimen (including malignant mixed Müllerian tumor, uterine leiomyosarcoma, and endometrial stromal sarcoma); 2. Received other antineoplastic drugs 4 weeks before the first dose; 3. Underwent major surgery in the past 28 days or expected to undergo major surgery during the study period; 4. Received radiotherapy 21 days before drug administration (palliative radiotherapy within 2 weeks for subjects with bone metastases); 5. Prior therapy with anti-PD-1 antibody; 6. Grade >1 unresolvable and persistent adverse reaction caused by previous treatment (except for alopecia and grade >2 neurotoxicity); 7. Patients currently on immunosuppressants or systemic steroid treatment (dose >10 mg/day prednisone or another equivalent steroid) and still on immunosuppressive treatment 2 weeks before enrollment. 8. Other malignant tumors in the last 5 years (except for adequately treated *in situ* malignant tumors such as breast cancer, bladder carcinoma, cervical carcinoma *in situ*, basal cell carcinoma, or squamous cell carcinoma of the skin); 9. Psychotropic substance abuse that the subject is unable to discontinue or subjects with mental disorders; 10. Central nervous system disorders including uncontrolled epilepsy and symptomatic brain metastases;

	11. A digestive disorder that affects drug absorption (such as atrophic gastritis). 12. Patients with an active ulcer, intestinal perforation, or unresolved intestinal obstruction and patients with digestive tract perforation 28 days before enrollment; 13. Uncontrolled hypertension (blood pressure >140/90 mmHg) after adequate conventional treatment; 14. Severe cardiovascular disease: unstable angina, myocardial infarction, class III–IV heart failure (NYHA criteria), and grade 2 and above peripheral vascular disorder 6 months before enrollment; 15. Severe arrhythmia requiring drug control and a clinically significant prolonged QT interval (>470 ms); 16. Active bleeding or a bleeding tendency; 17. Arterial/venous thrombosis 6 months before enrollment, such as cerebrovascular events (including stroke, transient ischemic attacks, subarachnoid hemorrhage), deep vein thrombosis, and pulmonary embolism; 18. Active infections, such as HIV/AIDS or other severe infections; 19. Any active autoimmune disease or history of autoimmune disease (including but not limited to autoimmune hepatitis, interstitial pneumonia, hepatitis, enteritis, nephritis, hyperthyroidism, hypophysitis, vasculitis, uveitis) or patients who require systemic steroid and/or immunosuppressant treatment (such as asthma requiring steroid-bronchodilator treatment); 20. Received a live vaccine within 30 days before the first dose; 21. Known allergy to any of the study drugs; 22. Women of child-bearing age must have a negative pregnancy test and follow strict contraceptive measures during the trial; 23. Patients deemed unsuitable for enrollment by the investigator.
Treatment withdrawal criteria	1. Subject withdraws informed consent; 2. Radiologic examination shows disease progression; • Since pseudoprogression occurs with PD-1, confirmation should be performed 4–6 weeks after the first disease progression result except for

	significant clinically rapid progression or patients with an unstable general condition. 3. The cumulative treatment period with anti-PD-1 antibody reaches 2 years; 4. Radiological examination shows that drug discontinuation can be considered for CR subjects who have completed 6 cycles of drug administration. 5. Intolerable toxicity; 6. Poor compliance; 7. Loss to follow-up. 8. The investigator considers that the subject must withdraw from the study.
Treatment regimen	IBI308: Product name (sintilimab), 200 mg intravenous infusion, qd，d1，q3w, Anlotinib: 12 mg/tablet, one tablet daily, orally half an hour before breakfast, d1–d14, and 1 treatment cycle lasting 3 weeks. The patient will take the study drug until protocol-stipulated treatment withdrawal criteria are fulfilled.
Sample size calculation Statistical methods	Simon's 2-stage design was used for sample size estimation. An alpha of 0.05 (one-tailed), a beta of 0.2, and a power of 0.8 were used. Based on existing literature, the objective response rate (ORR) of anti-PD-1 monoclonal antibody monotherapy in advanced or PD-L1-positive recurrent endometrial carcinoma after failure of first-line chemotherapy is 13%. Assuming that IBI308 combined with anlotinib can increase efficacy by 26%, the ORR is 39%. At least 23 patients are needed. Seven patients will be enrolled in stage 1. When the number of valid patients < 2, combination therapy is considered not superior to monotherapy, and this trial will be terminated. Otherwise, 16 subjects will be enrolled in stage 2. The trial is rejected if there are ≤5 patients with ORR in the two stages. Percentages, χ^2 test, and analysis of variance are used to analyze efficacy. Descriptive methods and percentages will be used for safety analysis.
Efficacy evaluation	RECIST (v1.1) and irRECIST criteria are used for radiologic tumor evaluation after the 2nd treatment cycle (± 7 days) and after week 4 (±7 days) after the start of dosing. Subsequently, radiologic tumor evaluation will be performed once every 3 treatment cycles (± 7 days) until the 10th cycle. After the 10th cycle, radiologic tumor evaluation will be performed every 4

	treatment cycles (± 7 days). Additional examinations can be performed if clinical progression occurs.
Study markers	Primary study markers • Objective response rate (ORR) Secondary study markers • Duration of response (DOR): • Disease control rate (DCR) • Time to objective response (TTR) • Clinical benefite rate (CBR） • Progression-free survival (PFS) • Probability of PFS > 6 months and 12 months • Overall survival (OS) • Evaluation of the safety and tolerability of IBI308 combined with anlotinib
Version number	v1

List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CR	Complete Response
Cr	Creatinine
CRF	Case Report Form
DCR	Disease control rate
DO	Duration of response
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
irAE	Immune-related Adverse Event
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall Survival
PD-1	Programmed cell death 1
PFS	Progression Free Survival
PR	Partial Response
RECIST	Response evaluation criteria in solid tumors
SAE	Severe Adverse Event
SD	Stable Disease
TBIL	Total bilirubin
TMB	Tumor mutation burden
TTR	Time to response
ULN	Upper limit of normal

Table 1. Study Visit Schedule

Period	Screening period	Treatment period						Maintenance therapy	Safety visit	Survival visit
Time window	Day-28 before dosing	Cycle 1			Subsequent cycles			One treatment cycle of 21 days (± 3 days)	30 days after the last dose (± 3 days)	Once every 3 months (± 3 days)
		C1/d1	C1/d8/d15	C1/d21	C2-x/d1	C2-x/d8	C2-x/d15			
		−3	± 3	± 3	−3	± 3	± 3			
Clinical study information										
Informed consent form[1]	X									
Inclusion/exclusion criteria	X									
Demographics/past medical history	X									
Concomitant medications	X				X					

Vital signs[2]	X				X					
Weight/height and physical examination[3]	X				X					
Laboratory tests										
Routine blood tests[4]		X	X		X	X	X	X	X	
Blood chemistry[5]		X			X			X	X	
Routine urine tests[6]		X			X			X	X	
Routine Stool test[7]		X			X			X	X	
Coagulation function[8]		X			X					
Thyroid function test[9]	x				d1 of Cycle 2 and d1 of every 3 subsequent cycles				X	
Tumor markers	X				X			X		
Hepatitis B, hepatitis C test[10]	X				If positive, hepatitis B DNA and hepatitis C RNA will be measured on d1 ± 7d in every 2 cycles					
HIV test[10]	X									
Pregnancy test[11]	X									

12-lead electrocardiogram		X			X			X	X	
Clinical evaluation examination										
ECOG scoring	X				X					
Evaluation of adverse events[12]	From the signing of the informed consent form to 30 days after the last dose									
Quality of life questionnaire[13]		X			X[8]				X	
Administration of investigational product										
IBI308 administration		X			X					
Anlotinib administration	Administration is recorded daily on d1–d14 of every treatment cycle									
Efficacy evaluation										
Radiologic tumor evaluation[14]	X	Evaluation is performed once after the 2nd treatment cycle (C3) and once after the 4th treatment cycle (C5). Subsequently, an evaluation will be performed once after the 7th cycle (C8) and once after the 10th cycle (C11). After the 10th cycle, an evaluation will be performed once every 4 treatment cycles, and the time window for radiological evaluation is ± 7 days.								
Follow-up after treatment has ended										

Progressive disease	Radiologic evaluation is performed every 3 months after the last dose until disease progression							
Biomarker exploration								
Biomarker blood sampling/sample collection	X							

1. The informed consent form should be signed by subjects before any procedures outlined in the protocol.

2. Vital signs include body temperature, pulse, respiratory rate, and blood pressure.

3. Height is only measured during the screening period. Weight is measured before every dose, except for physical examination during the screening period; physical examination abnormalities during the trial only need to be recorded in the CRF.

4. Routine blood tests include RBC, HGB, HCT, WBC, PLT, and white blood cell categories [LYM, ANC, MONO, EOS, BASO].

5. Blood chemistry includes liver function tests [TBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH], renal function tests [UREA, Cr]，blood electrolytes [Na, K, Cl, Mg]，amylase, lipase, blood lipids [total cholesterol (CHO), triglycerides (TG), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol], and fasting blood glucose.

6. Routine urine tests include UWBC, UPRO, URBC, UGLU. Any subjects with ≥2+ proteinuria in routine urine tests must undergo 24-hour urine protein quantification during the screening period.

7. Routine stool test should include stool routine.

8, Coagulation function tests should include PT, APTT, INR, D-dimer, and fibrin degradation products.

9. Thyroid function test should include TSH, FT3, and FT4. Only TSH is tested from Cycle 2 onwards and once every 3 cycles if there are no abnormalities.

10. HIV and HCV antibody tests and 5-item hepatitis B (HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb) tests must be completed within 28 days before the first dose. HCV antibodies are tested during the screening visit. HCV-RNA load will be measured for HCV antibody-positive subjects once every 3 weeks (21±3

days) starting from the first dose or earlier when clinically indicated. 5-Item hepatitis B tests are performed during the screening visit. For HBsAg and/or HBcAb-positive subjects, HBV-DNA load will be measured once every 3 weeks (21±3 days) starting from the first dose or earlier when clinically indicated.

11. Women of child-bearing age should undergo a urine or blood pregnancy test within 3 days before the first dose during the screening period. A serum pregnancy test will be performed if the urine pregnancy test cannot determine pregnancy; the serum pregnancy test result will prevail.

12. AE and laboratory test safety assessment will be based on CTCEA v4.03. The definitions, documentation, correlation judgment, severity judgment, reporting deadline, and management of AEs and SAEs will be based on the descriptions in the protocol.

13. EORTC QLQ-EN24 will be used as the quality of life questionnaire, and the evaluation will be performed on the day of the first dose (before dosing) and at every radiologic evaluation. The quality of life questionnaire must be performed at the same time if unscheduled radiologic evaluations are performed.

14. Tumor evaluation includes irRECIST and RECIST 1.1. Radiologic tumor examinations usually include contrast-enhanced CT or MRI. The examination sites must include the chest, abdomen, and pelvic cavity. Enhanced cranial MRI scan must be performed at baseline for patients with suspected signs or symptoms of central nervous system metastases. The type of radiologic examinations received by a subject during the study period should be the same. Baseline evaluation will be performed within 28 days before the first dose. Radiologic tumor evaluation will be performed once in Week 2 (± 7 days) and Week 4 (±7 days) after the start of dosing. Subsequently, radiologic tumor evaluation will be performed once every 3 treatment cycles (± 7 days) until the 10th cycle. After the 10th cycle, radiologic tumor evaluation will be performed once every 4 treatment cycles (± 7 days). After the investigator has evaluated the first radiologic progression based on irRECIST, current treatment can be continued if the patient has stable clinical disease without significant progression, and radiologic evaluation will be performed after 4–6 weeks for confirmation (based on irRECIST). If progression is not confirmed, study treatment can be continued.

1. Study Background and Theoretical Basis

1.1. Epidemiology of endometrial cancer

Endometrial cancer is a malignant tumor of the endometrium (distinguished from leiomyosarcoma that forms in the myometrium). Endometrial cancer is **the most common reproductive tumor in women** in developed countries, and its incidence is increasing [1]. The incidence of endometrial cancer has increased in China due to lifestyle changes. In economically developed regions of China, endometrial cancer has surpassed cervical cancer to become the reproductive tract malignant tumor with the highest incidence. According to the latest statistics from the National Cancer Center of China, it is estimated that there are 63400 cases of uterine cancer and 21800 deaths in 2015 in China [2]. The mortality rate of endometrial cancer has also increased. This increase may be due to the proportion of patients with advanced endometrial cancer and high-risk endometrial cancer. The diagnosis and treatment of endometrial cancer have become increasingly important in the field of gynecological oncology.

1.2. Pathological and molecular biology characteristics of endometrial cancer

The pathological subtypes of endometrial cancer include endometrioid carcinoma, clear cell carcinoma, serous carcinoma, and carcinosarcoma. Endometrioid carcinoma is classified as type I endometrial cancer, clear cell carcinoma, serous carcinoma, and carcinosarcoma as type II endometrial cancer based on pathogenesis and molecular characteristics[3]. Type I endometrial cancer has a better outcome and a recurrence rate of 20%, while the recurrence rate of type II endometrial cancer is approximately 50%[4]. A study published in Nature in 2013 analyzed 307 endometrioid carcinomas, 53 endometrial serous carcinomas, and 13 mixed endometrial cancers. The data from that study was obtained from the TCGA database. The study results classified endometrial cancer into 4 subtypes: ultramutated/polymerase ε [POLE]–mutated (7%), hypermutated/MSI [MSI-H] (30%), copy number low/microsatellite stable [MSS] (65%), and copy number high/serous like (26%)[5]. Patients with POLE mutations had the best outcome, and most had highly differentiated endometrial cancer. The molecular changes of copy number high/serous-like carcinoma are similar to ovarian serous carcinoma. They had the poorest outcome and were mostly endometrial serous carcinoma and poorly differentiated endometrioid carcinoma. **POLE-mutated and microsatellite unstable types account for approximately 37% of endometrial cancers and have a moderate-high tumor mutation burden. This fact is one of the biological and theoretical bases for immunotherapy of endometrial cancer.**

1.3 Current status of treatment for advanced and recurrent endometrial cancer

Endometrial cancer is limited to the uterus (FIGO stage I-II) in 60%–70% of patients on diagnosis. Local (FIGO stage III) and distal (FIGO stage IV) metastasis comprise 21% and 8% of patients, respectively [6]. The 5-year survival of FIGO stage I–II, FIGO stage III, and

FIGO stage IV are 74%–91%, 57%–66%, and 20%–26%, respectively [6, 7]. Although endometrial cancer has a good prognosis, there is a lack of effective treatments for advanced and recurrent endometrial cancer, and median survival is only 12–15 months [8-10]. The NCCN guidelines recommend using chemotherapy combined with radiotherapy ± surgery as personalized multimodal therapy for advanced endometrial cancer with distal metastases or advanced cancer unsuitable for surgery and chemotherapy-based multimodal therapy for non-pelvic local recurrence. Retrospective studies showed that distal metastasis is an important factor that affects survival in patients with advanced and recurrent endometrial cancer. S**ystemic treatment is the cornerstone for treating advanced or recurrent endometrial cancer.** A phase III clinical trial published in the New England Journal of Medicine in 2019 enrolled 736 patients and compared chemoradiotherapy with chemo-monotherapy for stage III to IVA endometrial cancer. Patients receiving chemoradiotherapy experienced lower local recurrence, but greater distant metastasis and ultimately progression-free survival (PFS) did not increase [11].

Although systemic chemotherapy is the basis of advanced and recurrent endometrial cancer treatment, **the response of endometrial cancer to chemotherapy is moderate, and there are limited options. Therefore, research on systemic therapeutic regimens for endometrial cancer is key to increasing survival.** NCCN guidelines recommend paclitaxel combined with carboplatin as first-line chemotherapy for advanced/recurrent endometrial cancer. The overall response rate is 40%–62%, and the median survival time is 13–19 months. A phase III clinical trial, GOG209, enrolled 1381 patients with advanced or recurrent endometrial cancer and compared paclitaxel combined with carboplatin (TC regimen) against paclitaxel, doxorubicin, and cisplatin (TAP regimen). The interim analysis showed that there was no statistical difference in PFS (14 vs. 14 months) and OS (32 vs. 38 months) between the TC and the TAP group, but the TC group experienced fewer side effects [8].

Other recommended combination chemotherapy regimens include carboplatin/cisplatin combined with liposomal doxorubicin or doxorubicin. The GOG177 trial compared the combination of cisplatin plus doxorubicin (AP) against cisplatin plus doxorubicin with paclitaxel (TAP) in the treatment of advanced or recurrent endometrial cancer. In the AP group, the objective response rate (ORR) was 34%, and median PFS 12.3 months. In the TAP group, the ORR was 57%, and median PFS 15.3 months. The differences were statistically significant. However, the guideline currently still recommends the AP regimen as the first choice due to toxicity in the TAP group. Other combination therapy regimens include carboplatin/cisplatin combined with docetaxel/ifosfamide, paclitaxel combined with ifosfamide, etc. The efficacy of these combination regimens for advanced/recurrent endometrial cancer ranges from 31% to 81%, but the duration of response is relatively short, and the median survival reported in clinical studies is around one year [12, 13].

Paclitaxel is recommended as the single-agent monochemotherapy of choice in the

treatment of recurrent endometrial cancer. Other options include docetaxel, albumin-bound paclitaxel, doxorubicin, liposomal doxorubicin, topotecan, ifosfamide, carboplatin, and cisplatin. The objective overall response of single-agent monochemotherapy as first-line and second-line chemotherapy for recurrence ranges from 21 to 36% and 4% to 27%, respectively [14, 15].

1.4. The Use of Antiangiogenic Drugs in Advanced/Recurrent Endometrial Cancer

Antiangiogenic drugs exhibit a certain efficacy in the treatment of advanced and recurrent endometrial cancer. Examples include bevacizumab, sunitinib, and lenvatinib single-agent monotherapies, with an efficacy of 12%–15% [16, 17]. A phase II clinical study of bevacizumab for persistent or recurrent endometrial cancer showed a response rate of 13.5% and overall survival (OS) of 10.5 months [18]. A phase II clinical study of oral sunitinib for advanced endometrial cancer in patients who experienced treatment failure with prior chemotherapy reported an ORR of 14% and median PFS of 5.4 months. This result is comparable to the response rate of second-line monochemotherapy in recurrent endometrial cancer (4%–27%) [19]. The NCCN guidelines also recommend bevacizumab plus paclitaxel and carboplatin for advanced and recurrent endometrial cancer.

1.5. Immunotherapy for Endometrial cancer

As mentioned above, **approximately 37% of endometrial cancer cases involve POLE mutation or MSI with a high antigen load resulting from the growing tumor. Up to 80% of endometrial cancer cases show high PD1 or PD-L1 expression**; thus, PD1 or PD-L1 serves as a potential molecular marker for immunotherapy [20]. In a phase II clinical trial (NCT01876511) of pembrolizumab for MMR-deficient solid tumors in patients with at least one chemotherapy failure, 53% (8/15) of endometrial cancer patients achieved an objective response with a disease control rate of 73%; a complete response was seen in 3 patients [21]. In the KEYNOTE-28 trial, 48% of endometrial cancer patients had positive PD-L1 expression during the screening period, and 24 patients were finally enrolled. The ORR of pembrolizumab monotherapy in these patients who failed multiple rounds of chemotherapy was 13% [22]. Compared with the efficacy of second-line single-agent chemotherapy in recurrent endometrial cancer, data from these small-sample size trials were quite satisfactory. **At present, pembrolizumab (anti-PD-1 monoclonal antibody) has obtained FDA approval for MSI or MMR-deficient solid tumors, including endometrial cancer. M**ore clinical studies have attempted to increase therapeutic efficacy for recurrent endometrial cancer by combining immunotherapy and chemotherapy or other targeted therapies, particularly for patients who lack useful biomarkers. In summary, immunotherapy has become a hot spot in endometrial cancer treatment and offers new hope.

1.6 Background of the investigational drugs

IBI308 is an IgG4 monoclonal antibody that can specifically bind to PD-1 molecules on the surface of lymphocytes, blocking the PD-1/programmed cell death-1 ligand-1 (PD-L1) pathway that results in tumor immune tolerance and reactivating antitumor activity of lymphocytes to achieve tumor treatment. IBI308, nivolumab, and pembrolizumab all have the same target but different amino acid sequences. A phase Ia pharmacokinetics study in patients with advanced solid tumors found that increased *in vivo* exposure to sintilimab is almost proportional to a dose increase in the 1–10 mg/kg range, suggesting linear pharmacokinetics. After a single dose of sintilimab was administered to subjects with solid tumors, the clearance half-life (Geo.Mean [CV%]) was 14.4 [28.9%] days, the clearance rate 11.5[42.5%]mL/h, the steady-state volume distribution 5.43[34.4%]L and the apparent volume distribution 5.77[33.2%]L, with PK characteristics similar to other anti-PD-1 antibodies already on the market (nivolumab and pembrolizumab). The efficacy data of IBI308 come mostly from a phase II key single-arm study (ORIENT-1) of IBI308 monotherapy in the treatment of recurrent or refractory classical Hodgkin lymphoma. Ninety-six patients were enrolled in ORIENT-1, the ORR of the per-protocol set was 65.5%, and the 97% CI was 50.5%–78.6%, which was consistent with the results of the efficacy analysis. Phase III studies on sintilimab have been conducted in several solid tumors, including non-small-cell lung cancer (ORIENT-12).

Anlotinib (AL3818) was approved by the National Medical Products Administration (NMPA, formerly China Food and Drug Administration or CFDA) on May 10th, 2018. Anlotinib is an orally administered tyrosine kinase inhibitor targeting VEGFR, FCFR, EGFR, c-Kit, PDGFR, and c-Met. Preclinical studies show that anlotinib can selectively recognize and bind to VEGFR2 to promote its autophosphorylation and inactivation, inhibiting the proliferation of human umbilical vein endothelial cells and angiogenesis. These results were validated again in the subcutaneous mouse tumor model. A phase I clinical trial on the tolerability and pharmacokinetics (NCT01833923) of anlotinib for advanced solid tumors and a phase II clinical study of anlotinib as a third-line drug for refractory advanced lung cancer (ALTER0302) have been completed. The results show that the side effects of anlotinib are controllable, and anlotinib has broad-spectrum antineoplastic effects on solid tumors. Also, since it is an orally administered drug, anlotinib increases patient compliance. Therefore, investigating the efficacy and safety of anlotinib in the treatment of advanced or recurrent endometrial cancer is of immense significance.

In summary, we will conduct a clinical study to evaluate the efficacy, safety, and tolerability of IBI308 combined with anlotinib for advanced or recurrent endometrial cancer and perform an exploratory analysis on the prognostic factors affecting efficacy.

2. Study Objective

2.1 Primary objective

To assess the objective response rate (ORR) of IBI308 combined with anlotinib for the treatment of recurrent/advanced endometrial cancer based on the irRECIST and RECIST (1.1) criteria.

ORR = complete remission (CR) + partial remission (PR).

2.2 Secondary objectives

- To assess the duration of response (DoR) of IBI308 combined with anlotinib for recurrent/advanced endometrial cancer based on irRECIST and RECIST (1.1) criteria.
- To assess the disease control rate (DCR) of IBI308 combined with anlotinib for recurrent/advanced endometrial cancer based on irRECIST and RECIST (1.1) criteria.
- To assess the time to objective response (TTR) of IBI308 combined with anlotinib for recurrent/advanced endometrial cancer based on irRECIST and RECIST (1.1) criteria.
- To assess the progression-free survival (PFS) of IBI308 combined with anlotinib for recurrent/advanced endometrial cancer based on irRECIST and RECIST (1.1) criteria.
- To assess overall survival (OS) of IBI308 combined with anlotinib for recurrent/advanced endometrial cancer based on irRECIST and RECIST (1.1) criteria.
- To assess the 12-month OS rate of IBI308 combined with anlotinib for recurrent/advanced endometrial cancer based on irRECIST and RECIST (1.1) criteria.
- The incidence of adverse events and serious adverse reactions.

2.3 Exploratory purpose

- To explore the possible effects of PD-L1 expression on efficacy.
- To explore molecular biology markers that can predict efficacy.

3. Study Design

3.1. Overall design

This is a prospective, single-arm, open-label phase II clinical trial in which IBI308 intravenous chemotherapy is combined with oral administration of anlotinib for recurrent or advanced endometrial cancer. The primary objective is to assess the ORR of IBI308 intravenous chemotherapy combined with anlotinib for recurrent or advanced endometrial cancer in patients who failed first-line chemotherapy based on the irRECIST and RECIST 1.1 criteria. Subjects will receive IBI308 200 mg intravenously q3w and anlotinib 12 mg qd d1–

d14 q3w po until a protocol-stipulated treatment termination event occurs. Subject visits will continue after treatment has ended.

Evaluation is performed once after the 2nd treatment cycle (C3) and once after the 4th treatment cycle (C5) since the first dose. Subsequently, an evaluation will be performed once after the 7th treatment cycle (C8) and once after the 10th treatment cycle (C11). After the 10th cycle, an evaluation will be performed once every 4 treatment cycles, and the time window for radiologic evaluation is ± 7 days.

Simon's 2-stage design was used for sample size estimation, with an alpha of 0.05 (one-tailed) and a beta of 0.2 (power of 0.8). Based on existing literature, the ORR of anti-PD-1 monoclonal antibody monotherapy for advanced or recurrent PD-L1-positive endometrial carcinoma in patients who failed first-line chemotherapy is 13%. Assuming that a combination of IBI308 and anlotinib can increase efficacy by 26%, the overall ORR is 39%. The data from at least 23 patients are required to obtain results. Seven patients will be enrolled in stage 1. When the number of valid patients ≤1, combination therapy will be considered not superior to monotherapy, and this trial will be terminated. Otherwise, 16 subjects will be enrolled in stage 2. The trial is rejected if the total number of patients with ORR in the two stages is ≤5.

The intention-to-treat principle will be adopted in the efficacy analysis, and all enrolled subjects will be included. Frequency and percentage will be used for categorical data, and the χ^2 test or exact probability will be used for intergroup comparison. Mean and standard deviation (or median and interquartile range) will be used for quantitative data. The t-test or a non-parametric test will be used for intergroup comparison, the K-M method for survival estimation, and the log-rank test for intergroup comparison.

4. Trial Population

4.1 Inclusion criteria

(1) Women aged > 18 years;

(2) Histologically confirmed endometrial cancer;

(3) Recurrent or advanced endometrial cancer with at least one treatment with systemic platinum-based chemotherapy;

- Low chance of a cure for recurrent endometrial cancer with surgery and/or radiotherapy and failure of at least one treatment with systemic platinum-based chemotherapy after recurrence.
- Newly diagnosed advanced endometrial cancer persisting after standard treatment with surgery ± radiochemotherapy and at least one treatment with systemic platinum-based chemotherapy.

(4) Objectively measurable lesions based on RECIST 1.1 criteria and at least one target lesion;

- In principle, lesions in the field of previous radiotherapy are considered as non-target lesions unless there is radiological evidence of progression or a biopsy with progression within 90 days after radiotherapy.

(5) Eastern Cooperative Oncology Group (ECOG) score of 0–2;

(6) Expected survival >3 months;

(7) Major organ function fulfills the following criteria (correction of the following parameters and supportive treatment are allowed 1 week before enrollment);

- Absolute neutrophil count ≥1.5 × 10^9/L, platelet count ≥70 × 10^9/L, hemoglobin ≥80g/L
- Alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5 × upper limit of normal (ULN) (<5× for patients with liver metastases) and total bilirubin ≤ 1.5 × ULN
- Serum creatinine ≤ 1.5 × ULN
- International normalized ratio (INR) <1.5 × ULN
- Proteinuria ≤ (+)
- Thyroid-stimulating hormone (TSH) ≤1 × ULN (measure FT3 and FT4 if TSH abnormal; subjects with normal FT3 and FT4 can be enrolled)

(8) Voluntarily signed informed consent form.

4.2 Exclusion criteria

(1) Presence of carcinosarcoma in pathology specimen (including malignant mixed Müllerian tumor, uterine leiomyosarcoma, and endometrial stromal sarcoma);

(2) Received other antineoplastic drugs within 4 weeks before the first dose;

(3) Underwent major surgery within the past 28 days or expected to undergo major surgery during the study period;

(4) Received radiotherapy 21 days before drug administration (palliative radiotherapy within 2 weeks for subjects with bone metastases);

(5) Prior therapy with anti-PD-1 antibody;

(6) Grade >1 unresolvable and persistent adverse reaction caused by previous treatment (except for alopecia, grade >2 neurotoxicity):

(7) Patients currently on immunosuppressants or systemic steroid treatment for immunosuppression (dose >10 mg/day prednisone or another equivalent steroid) and still on immunosuppressive treatment within 2 weeks before enrollment.

(8) Other malignant tumors in the last 5 years (except for adequately treated *in situ* malignant tumors, such as breast cancer, bladder carcinoma, cervical carcinoma *in situ*, basal cell carcinoma, or squamous cell carcinoma of the skin);

(9) A history of psychotropic substance abuse that the subject is unable to discontinue or subjects with mental disorders;

(10) Central nervous system disorder: including epilepsy not controlled by drugs and symptomatic brain metastases;

(11) A digestive disorder that affects drug absorption (such as atrophic gastritis).

(12) Patients with an active ulcer, intestinal perforation, or unresolved intestinal obstruction, and patients with digestive tract perforation within 28 days before enrollment;

(13) Hypertension not controlled by drugs (blood pressure >140/90 mmHg after adequate conventional treatment);

(14) Severe cardiovascular disease: unstable angina, myocardial infarction, class III–IV heart failure (NYHA criteria), and grade 2 and above peripheral vascular disorder within 6 months before enrollment;

(15) Severe arrhythmia requiring drug control and a clinically significant prolonged QT interval (>470 ms);

(16) Subjects with active bleeding or a bleeding tendency;

(17) Subjects with arterial/venous thrombosis within 6 weeks before enrollment, such as cerebrovascular events (including stroke, transient ischemic attacks, subarachnoid hemorrhage), deep vein thrombosis, and pulmonary embolism;

(18) Active infection, such as HIV/AIDS or other severe infections;

(19) Any active autoimmune disease or history of autoimmune disease (including but not limited to autoimmune hepatitis, interstitial pneumonia, hepatitis, enteritis, nephritis, hyperthyroidism, hypophysitis, vasculitis, uveitis) or patients who require systemic steroid treatment and/or immunosuppressant treatment (such as asthma requiring steroid-bronchodilator treatment);

(20) Received a live vaccine within 30 days before the first dose;

(21) Known allergy to any of the study drugs;

(22) Women of child-bearing age must have a negative pregnancy test and follow strict contraceptive measures during the trial;

(23) Patients deemed unsuitable for enrollment by the investigator.

4.3. Removal criteria

Subjects enrolled in this trial who meet one of the following criteria will be removed:

(1) Enrolled subjects who do not satisfy the inclusion criteria/satisfy the exclusion criteria and are wrongly enrolled.

(2) Subjects with serious protocol violations.

4.4. Withdrawal criteria

If any of the following situations occur during this trial, the investigator must discontinue the trial and withdraw the subject. Before withdrawal, the investigator must complete the last evaluation of various markers. The reason and date of the subject's withdrawal will be recorded in detail, and a safety visit shall be performed within 30 days after withdrawal.

（1） The subject withdraws informed consent and requests to withdraw from the trial;

（2） Radiological examinations show tumor progression;

*If the subject's clinical disease is stable without significant progression, existing treatment can be continued after a discussion is held with the patient, and informed consent is obtained. Following this, a radiologic evaluation will be performed after 4–6 weeks for confirmation, and treatment can be discontinued if progression is reconfirmed.

（3） Occurrence of serious adverse events;

（4） Occurrence of intolerable toxicity;

（5） Other complications that in the investigator's judgment, make it inappropriate for the subject to continue;

（6） The subject has poor compliance and does not take the drug on time or at the prescribed dose or does not comply with the study procedures;

（7） Simultaneous use of other antineoplastic drugs;

（8） Death of the Subject;

（9） Loss to follow-up.

5. Investigational Drug and Treatment Design

5.1. Investigational drug

- IBI308

IBI308 (sintilimab) is a sterile injection, and its main active ingredient is recombinant fully human anti-programmed death receptor-1 monoclonal antibody. Its strength is 10 ml:100 mg.

The preparation and infusion of IBI308 (sintilimab) are as follows:

(1) 2 vials of sintilimab injection are removed and added to 100 mL 0.9% (weight/volume) sterile physiological saline solution.

(2) The infusion bag is gently inverted to mix and ensure drug homogeneity in the bag. Avoid vigorous shaking, which will produce bubbles. If a lot of bubbles are produced, leave the bag to stand until the bubbles have disappeared.

(3) The drug is administered through a 0.2–1.2 μm in-line filter (a controlled infusion duration of 30–60 minutes is recommended).

- Anlotinib

Anlotinib hydrochloride tablets (FOCUS V) is a commercially available oral antineoplastic agent. Strengths: 8 mg, 10 mg, and 12 mg. Administration: orally administered with warm water half an hour before breakfast.

5.2 Treatment protocol

- IBI308 (sintilimab) 200 mg/d, d1, intravenous chemotherapy, q3w.

In this study, the administration method for sintilimab is mainly based on safety and exposure (concentration)-response (PD-1 receptor occupancy) relationship data in earlier studies. Under the premise that no significant abnormality in drug clearance is observed in the subject, it is expected that a steady state can be achieved by continuous infusion of BI308 sintilimab 200 mg q3w for 84 consecutive days (4 times). The expected mean trough concentration at steady state is approximately 26 μg/mL, and peripheral and target organ PD-1 receptor occupancy can be maintained. The maximum treatment duration of sintilimab is 24 months. During the study, subjects will receive continuous treatment until a protocol-stipulated treatment termination event occurs.

- Anlotinib hydrochloride: 12 mg/tablet, qd, po, d1-d14, q3w.

Until disease progression or an intolerable adverse reaction occurs. If a missed dose occurs, an additional dose should not be taken if the next dose is less than 12 hours. If the investigator determines that continuing oral anlotinib can benefit the patient at the end of the study, oral anlotinib can continue after the patient has signed the informed consent.

6. Dose Modification

6.1. Overall principles

Dose modification must be based on the most severe drug toxicity that occurred in the previous dosing cycle. Three days before each dosing of the investigational drug on Day 1, the blood, liver, and renal function test results of the subject must meet the dosing requirements. All other toxicities must be resolved to CTCAE v4.03 Grade 0–1 or baseline

level (except for alopecia, fatigue, special regulations in the protocol, or other conditions that are deemed not clinically significant by the investigator). If the subject is not dosed as scheduled due to drug toxicity, the next dose can be delayed. If an investigational drug needs to be suspended/permanently discontinued due to investigational drug-related toxicity or other reasons, other investigational drug(s) can be used independently if the corresponding criteria are met. All dose modifications must be recorded in the file, including the reason and management.

AEs related to sintilimab exposure may stem from immunological etiologies. These immune-related AEs (irAEs) may occur within a short period after the first dose or several months after the last dose of sintilimab. They may affect more than one system simultaneously. Based on existing clinical trial data, most irAEs are reversible and can be managed by drug dosing interruption, administration of glucocorticoids, and/or other supportive treatments. For suspected irAEs, an appropriate evaluation must be performed to confirm the etiology or rule out other causes. Other procedures or tests, such as bronchoscopy, endoscopy, or skin biopsy, can be included in this evaluation. Sintilimab will be suspended or permanently discontinued, and glucocorticoids will be administered based on irAE severity. For dose modification and toxicity management guidelines for potential irAE, please refer to the “Management manual for immune-related adverse event” provided by the pharmaceutical company.

6.2. IBI308 (sintilimab) dose modification

Sintilimab dose modification is not permitted during the entire study. Table 3 shows the principles of suspension and permanent discontinuation for sintilimab. If the dose delay occurs during sintilimab treatment (3 weeks per cycle), all future dosing dates will be delayed to ensure that the dosing interval between sintilimab treatment cycles is 21 ± 3 days.

Table 2. Dose modification protocol for IBI308 (sintilimab)-related toxicity

Sintilimab-related adverse events	Severity	Dose modification
Hematological toxicity	Grade 1–3	Drug discontinuation not required
	Grade 4	Drug interruption
Pneumonitis	Grade 2 pneumonitis	Drug interruption
	Recurrent Grade 2 to Grade 4 pneumonitis	Permanent drug discontinuation
Diarrhea/enterocolitis	Grade 2 or 3 diarrhea or enterocolitis	Drug interruption

	Grade 4 diarrhea or enterocolitis	Permanent drug discontinuation
Dermatitis	Grade 3 dermatitis	Drug interruption
	Grade 3–4 dermatitis	Permanent drug discontinuation
Impaired hepatic function	Grade 2 AST, ALT, or TBIL increased in subjects with normal baseline AST, ALT, or TBIL; ≥50% increase in AST, ALT, or TBIL (reaching grade 2 requirement) lasting <7 days in subjects with baseline AST, ALT, or TBIL> ULN.	Drug interruption
	Grade 3 or 4 AST, ALT, or TBIL increased in subjects with normal baseline AST, ALT, or TBIL; ≥50% increase in AST, ALT, or TBIL (reaching grade Grade 3 or 4 requirements) lasting ≥7 days in subjects with baseline AST, ALT, or TBIL> ULN.	Permanent drug discontinuation
Hypophysitis	Grade 2 hypophysitis	Drug interruption
	Grade 3–4 hypophysitis	Permanent drug discontinuation
Adrenal insufficiency	Grade 2 adrenal insufficiency	Drug interruption
	Grade 3 or 4 adrenal insufficiency	Permanent drug discontinuation
Hyperthyroidism	Grade 3–4 hyperthyroidism	Permanent drug discontinuation
Hyperglycemia	Grade 3 hyperglycemia	Drug interruption
	Grade 4 hyperglycemia	Permanent drug discontinuation
Renal impairment	Grade 2–3 increase of creatinine	Drug interruption
	Grade 4 increase of creatinine	Permanent drug discontinuation
Neurotoxicity	Grade 2 neurotoxicity	Drug interruption
	Grade 3–4 neurotoxicity	Permanent drug discontinuation
Other AEs	First occurrence of other Grade 3 AE	Drug interruption
	Second occurrence of the same Grade 3 AE	Permanent drug discontinuation

	Grade 3 AE that cannot be resolved to Grade 0–2/baseline level within 7 days or Grade 0–1/baseline level within 14 days	Permanent drug discontinuation
	Grade 4 AE	Permanent drug discontinuation

The maximum suspension period permitted for sintilimab is 12 weeks. If the subject cannot recover to a state in which sintilimab can be used again within 12 weeks, sintilimab will be permanently discontinued, and the follow-up of the subject will begin, except for the following 2 situations:

- Sintilimab suspension for more than 12 weeks due to glucocorticoid use and dose reduction of glucocorticoids for irAE treatment. In this situation, the investigator must discuss and decide whether to continue with sintilimab. Radiologic examination for efficacy evaluation will be performed as scheduled and not affected by drug suspension.

- AE unrelated to sintilimab but related to treatment resulting in sintilimab suspension for more than 12 weeks. In this situation, a discussion with the investigator on whether to continue sintilimab treatment is required. Radiologic examination for efficacy evaluation will be performed as scheduled and not affected by the suspension.

6.3 **Management of sintilimab-related infusion reactions**

Sintilimab may lead to severe or life-threatening infusion reactions, including severe hypersensitivity reactions or anaphylaxis. Signs and symptoms often occur during drug infusion or salvage therapy after infusion and usually resolve completely within 24 hours after infusion. Table 4 shows the management guidelines for sintilimab-related infusion reactions.

Table 3. Management guidelines for sintilimab-related infusion reactions

NCI CTCAE v4.03 grades	**Treatment**	**pretreatment for subsequent doses**
Grade 1: mild reaction; infusion interruption not indicated; intervention not indicated	Strengthen monitoring of vital signs based on the medical indications of the patient until the investigator deems that the subject's condition is stable.	None
Grade 2: Treatment or infusion interruption indicated, but	Stop infusion and monitor symptoms. Other appropriate drug treatments may include but are not limited to intravenous infusion, antihistamines, NSAIDs, paracetamol, anesthesia. Strengthen monitoring of vital signs based on the medical	The subject can receive the following pretreatment drugs 1.5 hours (±30 minutes) before sintilimab infusion: 50 mg diphenhydramine (or

symptomatic treatment (such as antihistamines, non-steroidal anti-inflammatory drugs [NSAIDS], anesthesia, intravenous fluid supplementation) should be performed as soon as possible to enable rapid response; ≤24 hours of prophylactic drug use is indicated	indications of the patient until the investigator deems that the subject's condition is stable. If symptoms alleviate within 1 hour after drug infusion is stopped, the infusion can be restarted at 50% of the initial infusion rate (e.g., decrease from 100 mL/hr to 50 mL/hr). Otherwise, the drug will be interrupted until symptoms abate, and the subject should receive pretreatment before the next scheduled dose. For subjects who still develop Grade 2 toxicity after receiving sufficient pretreatment, further study treatment must be permanently discontinued.	equivalent dose of antihistamine), Oral administration of 500–1000 mg paracetamol (or equivalent dose of antipyretic)
Grade 3: Long duration (rapid response does not occur even after symptomatic treatment and/or temporary interruption of infusion); symptoms recur after initial improvement; inpatient treatment is required due to other clinical sequelae (such as kidney injury, lung infiltration) Grade 4: Life-threatening, vasopressor or ventilator support indicated	Stop infusion Other appropriate drug treatments may include but are not limited to: Adrenaline**, intravenous infusion, antihistamines, NSAIDs, paracetamol, anesthesia, Oxygen, vasopressor, corticosteroids. Strengthen monitoring of vital signs based on the medical indications of the patient until the investigator deems that the subject's condition is stable. Inpatient treatment may be indicated. **Adrenaline must be immediately administered if anaphylaxis occurs. Further investigational drug treatment will be permanently discontinued.	No subsequent treatment
The ward should be equipped with appropriate resuscitation equipment, and the physician should be contactable at any time during the dosing period. For further information, please refer to the Common Terminology Criteria for Adverse Events (CTCAE v4.03)(http://ctep.cancer.gov)		

6.4 **Dose modification for anlotinib**

If the investigator confirms that toxicity is mainly caused by anlotinib, dose reduction for

anlotinib alone is acceptable. If toxicity caused by 2 or more drugs cannot be confirmed, dose reduction should be performed for all related drugs. If anlotinib dosing is delayed during treatment (3 weeks per cycle), all future dosing dates will be delayed to ensure that the dosing interval between anlotinib treatment cycles is 21±3 days. The anlotinib cycles and sintilimab cycles will be synchronized as much as possible by adjustments of permissible time windows.

The adverse reactions caused by **anlotinib** can be managed with symptomatic treatment, drug discontinuation, and/or dose modification. It is recommended that the dose be adjusted under the physician's guidance according to the severity of the adverse reaction: ① First dose modification: 10 mg, qd; ② Second dose modification: 8 mg, qd. If a third dose modification is required, the drug should be permanently discontinued.

When on 8 mg doses, the dose can be increased to 10 mg if necessary, depending on the adverse reaction.

When a drug-related adverse reaction occurs, the general rules in Table 3 should be consulted for dose modifications. When adverse reactions such as abnormal liver function [including ALT elevation, AST elevation, or total bilirubin elevation], proteinuria, decreased platelet count, or a bleeding event occur, dose modification and management are performed according to the principles in Tables 4–7.

Table 3. General rules of anlotinib dose modification for various grades of adverse reactions

Adverse reaction grade	Dosing time	Dose modification principle
Grade 3	Drug interruption until adverse reaction resolves to grade <2	Subsequent doses are reduced by one level; If the patient does not recover after 2 weeks, consider permanent discontinuation of the drug.
Grade 4	Drug interruption until adverse reaction resolves to grade <2	Subsequent doses are reduced by one level. Consider permanent drug discontinuation if the patient does not recover after 2 weeks, or consider permanent drug discontinuation based on the physician’s judgment.

Table 4. Dose modification principles and management recommendations in case of abnormal hepatic function

Adverse reaction grade	Dose modification principle	Management recommendations
Grade 2 (normal baseline)	Drug interruption. If AE resolves to grade <2 within 2 weeks, continue the drug treatment at a dose reduced by one level	Aggressive hepatoprotective treatment should be performed, and hepatic function is monitored once every week
Grade 2 (Abnormal baseline)	Continue drug treatment at the original dose	
Grade 3	Drug interruption. If AE resolves to grade <2 within 2 weeks, continue drug treatment at a dose reduced by one level	Aggressive hepatoprotective treatment should be performed, and hepatic function is monitored once every 2 weeks until toxicity restores to Grade <2 or can be explained by other reasons
Grade 4	Permanent drug discontinuation	Aggressive hepatoprotective treatment should be performed, and hepatic function is monitored 1–2 times every week until toxicity resolves to Grade <2 or can be explained by other reasons

Table 4. Dose modification principles and management recommendations in case of proteinuria

Adverse reaction grade	Dose modification principle	Management recommendations
Grade 2, routine urine protein test ++, but 24 h urine protein quantitation test result of 1.0 g–2.0 g (not including).	Maintain original dose	Aggressive symptomatic treatment should be provided, and a routine urine test is performed once every week
Grade 2, routine urine protein test ++ or above, but 24 h urine protein quantitation test result of 2.0g–3.5 g (not including).	Drug interruption If AE resolves to grade <2 within 2 weeks, continue drug treatment at a dose reduced by one level.	Aggressive symptomatic treatment should be performed, and the drug permanently discontinued if the AE occurs for a 3rd time.
Grade 3: 24 h urine protein quantitation test result of ≥3.5 g	Drug interruption If AE resolves to grade <2 within 2 weeks, continue drug treatment at a dose reduced by one level.	Aggressive symptomatic treatment should be performed, and the drug permanently discontinued if the AE occurs for the 3rd time.

Table 6. Dose modification principles and management recommendations for decreased platelet count

Adverse reaction grade	Dose modification principle	Management recommendations
Grade 2, platelet count of 50–75 × 10^9/L	Drug interruption. If AE resolves to grade <2 within 1 week, continue drug treatment at the original dose	A routine blood test is performed once every 2–3 days; in the subsequent dosing period, a routine blood test is performed once a week
	Drug interruption. If AE resolves to grade <2 within 2 weeks, continue the drug treatment at a dose reduced by one level	A routine blood test is performed once every 2–3 days; in the subsequent dosing period, a routine blood test is performed once a week
Grade 3, platelet count of 25–50 × 10^9/L	Drug interruption If AE resolves to grade <2 within 2 weeks, continue the drug treatment at a dose reduced by one level.	A routine blood test is performed once every 2–3 days, and in the subsequent dosing period, a routine blood test is performed once a week
Grade 4: Platelet count of <25 × 10^9/L	Permanent drug discontinuation	A routine blood test is performed daily until AE resolves to Grade ≤2 and aggressive symptomatic treatment is performed

Table 7. Dose modification principles and management recommendations in bleeding events

Bleeding event	Dose modification principle	Management recommendations
Grade 2	Drug interruption. If AE resolves to grade <2 within 2 weeks, continue drug treatment at a dose reduced by one level	Aggressive symptomatic treatment should be performed
Grade ≥3	Permanent drug discontinuation	Emergency medical intervention should be performed

Drug administration in patients with hepatic or renal insufficiency:

There is no relevant data on the effects of anlotinib in patients with hepatic or renal insufficiency. Clinical studies have shown that long-term use could result in liver injury and proteinuria. It is recommended that this product be used with caution under the guidance of a physician based on clinical conditions and laboratory test results for patients with hepatic and renal insufficiency. This product is prohibited in patients with severe hepatic and renal insufficiency.

Strong CYP1A2 and CYP3A4/5 inhibitors (such as ciprofloxacin or ketoconazole) may increase the plasma concentration of this product. It is recommended that drugs with no or the lowest inhibitory effects on these enzymes should be selected as concomitant medications.

CYP1A2 and CYP3A4/5 inducers (such as omeprazole or rifampin) may decrease the plasma concentration of this product. It is recommended that drugs with no or the lowest inducing effects on these enzymes should be selected as concomitant medications.

6.5 Precautions for anlotinib

Bleeding: VEGFR inhibitor antineoplastic agents may increase the risk of bleeding. In clinical studies of anlotinib, this product increased the risk of hemoptysis. However, the clinician should be reminded to pay close attention to this risk.

This product should be used with caution in patients with coagulation abnormalities. Prothrombin time and international normalized ratio should be closely monitored when using this product. The drug should be interrupted if a Grade 2 bleeding event occurs, and drug treatment should be continued at a dose reduced by one level after AE resolves to Grade <2 within 2 weeks. The drug should be permanently discontinued if a Grade 3 or above bleeding event occurs.

Blood pressure increase: A blood pressure increase is the most common adverse reaction of this product. In clinical studies, it was observed that anlotinib could mildly to moderately increase blood pressure. This AE occurs 1 week after dosing and can normally be controlled with conventional antihypertensive medications. **Blood pressure should be monitored every day in the first 6 weeks of dosing.** Blood pressure should be periodically monitored in subsequent doses, and active communication with the physician is required when blood pressure increases. Conventional antihypertensive treatment can mostly control the blood pressure increase. An uncontrollable blood pressure increase can usually be relieved by dose reduction or discontinuation of this product.

If a blood pressure increase occurs, antihypertensive treatment or dose modification of this product should be performed under the guidance of the specialist. Drug interruption is recommended if a Grade 3/4 blood pressure increase occurs. If a Grade 3/4 blood pressure increase recurs after dosing is resumed, subsequent doses can be reduced by one level. Drug discontinuation is recommended if the adverse reaction persists. This product should be discontinued in patients who develop a hypertensive crisis.

Cardiotoxicity: It was observed in clinical studies that anlotinib could cause electrocardiogram abnormalities, including a prolonged QT interval. The drug should be used with caution in patients with a known medical history of a prolonged QT interval (QTc≥480

ms). In patients on anlotinib who take antiarrhythmic drugs or have related underlying heart disease, bradycardia, and electrolyte disturbance, electrocardiography should be performed every 2–3 weeks to evaluate the QT interval.

Electrocardiography and cardiac function should be closely monitored during the dosing period. Drug interruption is recommended if a Grade 3/4 adverse reaction occurs. If a Grade 3/4 adverse reaction recurs after dosing is resumed, subsequent doses can be reduced by one level. Drug discontinuation is recommended if the adverse reaction persists. Drug discontinuation is recommended for patients who develop Grade III–IV heart failure or patients with a left ventricular ejection fraction <50% on Doppler echocardiography.

Stroke risk: Although a stroke event has yet to be observed in existing clinical trials of anlotinib, hypertension and hyperlipidemia are common adverse reactions of anlotinib and constitute a high-risk factor for stroke. Long-term use of this product may increase stroke risk. Therefore, it is recommended that blood pressure, blood lipids, and other stroke risk factors should be closely monitored in high-risk stroke patients to prevent stroke.

Epilepsy: Epilepsy was observed in patients in the anlotinib arm in clinical trials. It has not been confirmed whether this product can cause epilepsy or increase the risk of epilepsy. This product should be used with caution under the guidance of a physician for patients with a medical history of epilepsy.

Dermotoxicity: Hand-foot-skin reaction (swelling and pain in the palms and soles or erythema of the fingers and toes) is a common adverse skin reaction with this type of drug. A Grade 1 hand-foot-skin reaction is characterized by painless mild skin changes or dermatitis (e.g., erythema, edema, hyperkeratosis); a Grade 2 hand-foot-skin reaction is characterized by painful skin changes (e.g., desquamation, blisters, bleeding, swelling, and hyperkeratosis) and affects instrumental activities of daily living; a Grade 3 hand-foot-skin reaction is characterized by severe skin changes (e.g., desquamation, blisters, bleeding, swelling and hyperkeratosis) and accompanied by pain, which affects activities of daily living.

For patients with a Grade 1 hand-foot-skin reaction, observation is continued, and supportive treatment is not required. For a Grade 2 or above hand-foot-skin reaction, symptomatic treatment should be considered, including enhancing skin care, maintaining skin cleanliness, and avoiding secondary infection; pressure or abrasion should be avoided; use of a moisturizer or lubricant and topical application of urea- and corticosteroid-containing lotions or lubricants are recommended; topical antifungal or antibiotic treatment could be adopted when necessary.

If a Grade ≥3 hand-foot-skin reaction occurs, subsequent doses can be reduced by one level (see [Administration Method and Dosage]). Drug discontinuation is recommended if the adverse reaction persists.

Hypothyroidism: Baseline thyroid function tests are recommended, and patients with hypothyroidism should receive the corresponding standard treatment before treatment with this product. All subjects should be closely monitored for signs and symptoms of hypothyroidism while on treatment. Thyroid function tests should be performed for patients with signs and symptoms of hypothyroidism, and corresponding standard treatment should be provided.

Proteinuria: Proteinuria is a common adverse reaction of anlotinib. In clinical studies, it was observed that oral administration of anlotinib could induce proteinuria. Anlotinib should be used with caution, and close monitoring is required for patients with renal insufficiency. It is recommended that periodic routine urine tests be performed. A 24 h urine protein measurement should be performed for patients with 2 continuous ≥++ urine protein results. Dose interruption, dose modification, and permanent drug discontinuation should be performed based on the severity of the adverse reaction.

Hyperlipidemia: During clinical trials, the anlotinib group had more severe hyperlipidemia. Patients with hyperlipidemia should switch to a low-fat diet. For patients with Grade 2 or above hypercholesterolemia (≥7.75 mmol/L) or Grade 2 or above hypertriglyceridemia [≥2.5 × ULN], HMG-CoA reductase inhibitor (atorvastatin, etc.) or a suitable lipid-lowering drug should be used.

Hepatotoxicity: In clinical studies, it was observed that oral administration of anlotinib could induce transient transaminase elevation or total bilirubin elevation. This product should be used with caution in patients with underlying serum transaminase and total bilirubin elevations. Studies have not been performed in patients with hepatic insufficiency; therefore, anlotinib should be used with caution. Close monitoring is required for patients with a medical history of hepatic insufficiency (hepatic function be tested once within the first 3 weeks of drug administration). This drug is prohibited in patients with severe hepatic insufficiency. Drug interruption is recommended if a Grade 3/4 transaminase and total bilirubin elevation occurs. At the same time, serum transaminase and total bilirubin should be monitored until their levels significantly decrease before resuming dosing. If a Grade 3/4 adverse reaction recurs after dosing is resumed, subsequent doses can be reduced by one level. Drug discontinuation is recommended if the adverse reaction persists.

Diarrhea: Product absorption may be affected if taken by patients with diarrhea. Therefore, diseases causing diarrhea should be actively treated. This product can be taken under the guidance of the physician after improvement. Drug interruption is recommended if Grade 3/4 diarrhea occurs when taking this product. If Grade 3/4 diarrhea recurs after dosing is resumed, subsequent doses can be reduced by one level. Drug discontinuation is recommended if the adverse reaction persists.

Wound healing complications: Studies of the effects of anlotinib on wound healing have yet to be conducted. In clinical studies, patients with unhealed wounds from major

surgeries within the past 4 weeks were excluded. Since there is limited evidence on when the patients can take anlotinib after surgery, it is recommended that this product be temporarily discontinued before surgery and for 30 days after surgery.

Effects on driving and machinery operation: Fatigue may occur during dosing. Patients should pay attention when driving or operating machinery.

7. Concomitant Treatment

7.1 Permitted concomitant therapies

Drugs that conform to the protocol requirements in the investigator's judgment (e.g., concomitant drugs used to treat disease-related symptoms and treatment-related AEs)

- Subjects who require long-term drug use for underlying diseases such as hypertension and diabetes can continue their previous drug treatment.
- Local surgery, minimally invasive treatment, or radiotherapy for isolated lesions (excluding the target lesion) during the study treatment period.
- Supportive treatment that alleviates tumor-related symptoms is permitted, such as bisphosphonate treatment for bone metastases.
- Topical glucocorticoid treatment is permitted, such as topical skin applications, eyedrops, nasal spray, inhalations, etc.
- Prophylactic use of colony-stimulating factors (G-CSF or GM-CSF) or erythropoietin is prohibited. Therapeutic use of colony-stimulating factors is permitted if febrile neutropenia and Grade 3–4 neutropenia occurs after the first course of treatment or if the investigator deems that conditions that threaten the patient's life may occur. Corresponding G-CSF or GM-CSF support can be administered in subsequent treatment courses depending on the patient's condition.
- Antihypertensive, antiemetic, antibiotic, analgesia, vitamins, oral dexamethasone, and blood products can be used as supportive treatment. Mouthwashes can be used for stomatitis treatment or prophylaxis.
- If hypothyroidism occurs during treatment, the investigator should provide treatment and monitoring based on the most feasible medical practices. An endocrinologist should be consulted, and management should be performed based on his/her recommendation. If hypothyroidism (Grade ≥1) occurs, thyroid hormone replacement therapy should be provided, and thyroid function tests should be performed more frequently. Subjects who receive thyroid hormone replacement therapy due to Grade 2 or 3 hypothyroidism should

continue treatment with the investigational drug at the initial dose. The investigational drug should be discontinued in subjects who develop Grade 4 hypothyroidism.

7.2. Prohibited concomitant therapies

The following treatments are prohibited during the study treatment period, and the subject must be asked whether he/she has received any new drug at each visit.

- Systemic chemotherapy or biologic therapy other than the study drug that has antineoplastic effects (except for cytokines used to treat adverse events caused by chemotherapy) and Chinese patent medicine with antineoplastic effects.
- Drugs with immunoregulatory effects, including but not limited to non-specific immunoregulators (e.g., thymosin, interferon, interleukin, immunoglobulin, gamma globulin), and Chinese patent medicines with immunoregulatory effects.
- Chemotherapeutic agents that are not stipulated in this protocol.
- Investigational drugs other than sintilimab.
- Radiotherapy used to control tumors (palliative radiotherapy is permitted as long as it is not used for the target lesion, such as radiotherapy for alleviating pain from bone metastases and symptoms of brain metastases).
- Live vaccines during the study. Injections of inactivated influenza vaccine for seasonal influenza are permitted, but live attenuated influenza vaccines for intranasal use are prohibited.
- Corticosteroids. Inhalational steroids are permitted for patients with asthma or chronic obstructive pulmonary disease. Corticosteroids are permitted for temporary use to alleviate dyspnea. Corticosteroids are permitted for the treatment of immune-related AEs. Note: Prophylactic use of corticosteroids to prevent anaphylaxis (e.g., pretreatment before intravenous administration of contrast agent or chemotherapy drug) is permitted.
- Prohibited drugs mentioned in the exclusion criteria.

8. Schedule of Events

This trial comprises three stages (screening period, treatment period, and end of treatment) after each patient signs the informed consent form.

8.1. In the screening period (Day-28 to Day-1), the following study procedures must be completed to ensure that the subject is eligible for this study:

- The informed consent form has been signed;

- Review of inclusion and exclusion criteria;
- Medical history including but not limited to demographic data, past medical history, past treatment history for endometrial cancer, and past and concomitant medications.
- Physical examination: height, weight, body surface area, vital signs (heart rate, blood pressure), comorbidities, and other discomforts;
- ECOG scoring;
- Electrocardiography (within 3 days before the 1st dose)
- Blood routine/blood biochemistry/urine routine/stool routine (within 3 days before the 1st dose);
- Coagulation function tests (within 3 days before the 1st dose);
- Pregnancy test;
- Thyroid function test;
- HIV antibodies, Hepatitis B-five test (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) and HBV-DNA (if the subject is positive for HBsAg and HBeAg), HCV antibody and HCV-RNA (if the subject is positive for HCV antibody);
- Evaluation of adverse events;
- Radiologic tumor evaluation;
- Pathology consultation
- Archived or fresh tumor tissue samples (non-essential).

8.2 Test items during the treatment period

- Physical examination: weight, vital signs, ECOG scoring once before each dose;
- 12-lead electrocardiography;
- Blood routine (3 days before dosing in every treatment course and once a week during treatment, the number of tests can be increased if WBC < 3.0×10^9/L, N < 1.5×10^9/L, Hb < 80g/L, PLT < 75×10^9).
- Blood biochemistry (3 days before dosing in every treatment course);
- Stool and urine test (3 days before dosing in every treatment course);
- Coagulation function test (3 days before dosing in every treatment course);

- Tumor markers (should at least include CA125, CA199, and HE4): tested once before dosing in every treatment course until tumor progression or when the investigator deems it necessary to increase the number of tests;

- Thyroid function test once before dosing in the 1st and 2nd treatment courses and once every 3 treatment courses thereafter;

- HBV-DNA and/or HCV-RNA (if applicable, once every 2 cycles);

- Adverse event evaluation (closely monitored items during drug administration include blood pressure abnormalities, hand-foot-skin reaction, nausea, vomiting, diarrhea, fever, and fatigue). Grading is performed according to CTCAE v4.03.

- Recording of concomitant medications;

- Radiologic tumor evaluation (see Table 1 for details)

    - Administration of investigational drug;

    - Quality of life evaluation.

8.3 Safety visit

8.4 The safety follow-up is performed 30 ± 3 days after the last dose or before new antineoplastic therapies. The safety visit includes the following activities: Recording of vital signs, weight, physical examination, ECOG-PS score, 12-lead electrocardiography, routine blood/blood chemistry/urine results, coagulation function results, thyroid function, adverse event evaluation, concomitant medications, and subsequent antineoplastic treatment (if applicable).

8.5 Survival visit

An outpatient or telephone follow-up will be performed 1 month after the last dose for every subject; adverse events and concomitant medications within 1 month of the end of treatment will be recorded. Subsequent follow-up on overall evaluation data will be performed until disease progression or new antineoplastic treatment starts. Subsequent antineoplastic treatment and its start date will be recorded, and survival follow-up will be performed.

If the subject withdraws from the study due to toxicity symptoms, withdrawal of informed consent, and disease progression, it will be considered the end of treatment. The reason for treatment discontinuation, the treatment end date, and the withdrawal date will be recorded. At the end of treatment, adverse reactions and concomitant treatments within 30 days after the last dose of the investigational drug will be collected.

9. Efficacy Evaluation

9.1. Tumor imaging and disease evaluation principles

Tumor radiologic examinations usually include contrast-enhanced CT or MRI. The examination sites must include the chest, abdomen, and pelvic cavity. Cranial MRI scans must be performed at baseline for patients with suspected signs or symptoms of central nervous system metastases. Radiologic examinations received by a subject during the study period should be of the same type. Radiologic examinations will be performed on other suspected affected sites (such as the cranium) based on the subject´s clinical signs and symptoms. Contrast-enhanced CT is the tumor evaluation method of choice. MRI will be used if contrast-enhanced CT is contraindicated. Slices of 10 mm or thinner are used for chest, abdominal, and pelvic CT and MRI scans, and 5 mm slices for continuous spiral CT scans. For clinically measurable superficial lesions (such as skin nodules, palpable lymph nodes), a color photograph containing a scale to show the lesion dimensions used to estimate lesion size is recommended.

During the screening, the study site investigator will confirm the presence of measurable lesions based on RECIST1.1 and irRECIST criteria to confirm the subject´s eligibility. There should be a maximum of 5 target lesions in total and 2 target lesions per organ.

During the screening, the first tumor radiologic examination must be performed within 28 days before treatment. Evaluation is performed once after the 2nd treatment cycle (C3) and once after the 4th treatment cycle (C5). Subsequently, an evaluation will be performed once after the 7th cycle (C8) and once after the 10th cycle (C11). After the 10th cycle, an evaluation will be performed once every 4 treatment cycles, and the time window for radiologic evaluation is ± 7 days. Additional examinations can be performed if clinical progression occurs. The investigator will simultaneously evaluate RECIST1.1 and record the results, but this will not be used as a reference for treatment. After the investigator has completed the first radiologic evaluation of disease progression based on irRECIST, current treatment can be continued if the patient has stable clinical disease; radiologic evaluation will be performed after 4–6 weeks for confirmation (based on irRECIST). Treatment will be discontinued if progression is confirmed. If progression is not confirmed, study treatment can be continued until PD is confirmed by radiologic evaluation. An unscheduled radiologic evaluation can be performed at any time if the patient suffers unstable clinical disease during the study.

The definition of unstable clinical disease is as follows:

- Development of clinically significant signs and symptoms suggesting disease progression (including worsening laboratory test values)
- Decrease in ECOG PS score

- Rapid disease progression
- Tumor progression at important anatomical sites that requires other emergency medical interventions (such as spinal cord compression)

Patients who require treatment discontinuation for reasons other than disease progression shown in the radiologic evaluation should undergo radiologic evaluation at the end of treatment and after that at scheduled time points stipulated in the protocol until any one of the following events occurs: start of new antineoplastic therapy, objective disease progression, withdrawal of informed consent by the subject, loss to follow-up, or death.

Baseline cranial CT/MRI examination should be performed before starting study treatment in subjects with known or suspected brain metastases at screening. During the study period, cranial CT/MRI evaluation should be performed on these subjects, and brain metastases are considered non-target lesions for evaluation.

If the investigator cannot determine whether disease progression has occurred, particularly for non-target lesions and new lesions, the subject can continue treatment until clinical symptoms occur or the next scheduled evaluation where radiologic evaluation is repeated. If disease progression is confirmed, then the date of progression should be the initial date of discovery. For subjects who discontinue treatment due to treatment completion or reasons other than objective disease progression, radiologic tumor evaluation should be performed once at treatment completion/discontinuation. A subsequent radiologic evaluation should be performed according to a protocol-stipulated radiologic examination schedule until one of the following situations occurs: start of new antineoplastic therapy, objective disease progression, death, or end of the study, whichever comes first.

9.2 Tumor measurement

At baseline, the investigator will classify the lesions as measurable lesions (lesion with at least one precise longest diameter measurement ≥20 mm by CT or MRI or at least one precise longest diameter measurement ≥10 mm by spiral CT) and non-measurable lesion (solid lesion, bone lesion, meningeal lesion, pleural effusion and ascites, pericardial effusion lower than the aforementioned threshold for measurable lesions; abdominal masses and cystic lesions that cannot be confirmed and evaluated by routine radiologic techniques) based on RECIST 1.1 and irRECIST criteria.

The target lesions should involve affected organs. At most 5 target lesions should be recorded for every organ, and the total number of all target lesions should not exceed 10. Measurement and recording will be performed at baseline and all stipulated time points. Target lesions should be selected based on size (lesions with the largest diameter) and suitability for repeated accurate measurements (radiologic or clinical method). A primary lesion can only be classified as a target lesion if it can be accurately measured.

The longest diameter of every target lesion should be recorded. The longest diameters of all target lesions and their sum will be calculated and recorded. During treatment, the sum of the longest diameters at baseline will be used as a reference to determine the objective response of measurable tumors.

All non-measurable lesions and other measurable lesions that are not selected as target lesions should be identified as non-target lesions and recorded at baseline. The measurement data of these lesions are not required, but the presence and disappearance of these lesions during the entire study should be tracked.

The same technique and method should be used for pretreatment baseline measurement and efficacy assessment. CT, MRI, and other measurement methods with high repeatability and ease of data storage should be used.

During overall response evaluation, ultrasound should not be used to measure tumor lesions that are clinically difficult to measure (such as visceral lesions). Ultrasound evaluation can be considered an alternative for clinical evaluation of superficial palpable lymph nodes, subcutaneous nodules, and thyroid nodules. Ultrasound examinations also help confirm the complete disappearance of superficial lesions usually evaluated via clinical examination.

An increase in tumor markers does not constitute objective evidence of tumor exacerbation. However, a radiologic examination should be immediately repeated if there is an increase in these tumor markers to confirm whether an objective worsening has occurred.

9.3. Tumor response evaluation (measurable lesions)

- Target lesion:

Complete response (CR): Disappearance of all visible lesions after baseline evaluation, the absence of new lesions, tumor markers decrease to normal levels and maintained for 4 weeks;

Partial response (PR): The sum of maximum diameters of all target lesions decreased ≥30% compared to baseline, the absence of new lesions maintained for 4 weeks;

Stable disease (SD): Changes in the sum of maximum diameters of all target lesions is between PR and PD;

Progressive disease (PD): The sum of maximum diameters of all target lesions increased ≥20% compared with the sum in original target lesions (including baseline) or occurrence of a new lesion.

- Non-target lesion:

CR: Complete disappearance of non-target lesions after the baseline period and tumor markers decrease to normal levels;

Non-CR/non-PD: Presence of one or more non-target lesion; “stable or decreased”;

PD: Overall worsening of existing measurable lesions or confirmed progression or appearance of one or more new lesions.

When measurable tumors satisfy the response or stable (SD) criteria during the treatment period, cytological confirmation is mandatory for all cancer sources causing an occurrence or worsening of an effusion to distinguish between a response and SD or PD.

9.5. Overall response determination

Overall evaluation of disease response involves all parameters listed in the following table. The best overall response refers to the best response recorded from the start of treatment to disease progression/recurrence (the lowest measurement recorded since the start of treatment is used as a reference for determining tumor worsening). The best response of the patient is determined by the measurement method and confirmation criteria.

Table 8. Timepoint efficacy determination based on irRECIST criteria.

Overall efficacy evaluation:

Target lesion	Non-target lesion	New lesion	Overall response
CR	CR	None	CR
CR	Non-CR/SD	None	PR
PR	PD absent	None	PR
SD	PD absent	None	SD
PD*	Any response	Present or absent	PD
Any response	PD	Present or absent	PD
Any response	Any response	Present	PD

*Reconfirmation according to irRECIST criteria is required

9.4 Endpoint criteria

Primary endpoint:

Objective response rate (ORR): Defined as the proportion of patients whose tumor volume shrunk to the pre-stipulated value and maintained for more than 4 weeks; i.e., ORR = CR +

PR. The internationally accepted RECIST 1.1 and irRECIST criteria are used for solid tumor evaluation. ORR is used as the primary endpoint for the clinical trial.

Secondary endpoints:

Duration of response (DoR): Time from first evaluation of CR or PR until evaluation of PD or death from any cause. For patients who did not experience PD or death, the last radiologic tumor evaluation date will be the censor date.

Disease control rate (DCR): The proportion of subjects with CR, PR, or SD based on RECIST 1.1 criteria in the analysis set.

Time to response (TTR): Time from start of treatment to first objective response (CR or PR). For patients that did not experience CR or PR, the last radiologic tumor evaluation date will be the censor date.

Progression-free survival (PFS): Defined as time from subject enrollment to tumor progression or death.

Overall survival (OS): Time from start of treatment to death. If the subject is still alive at the end of the study, the “last known date of subject survival” will be the censor date.

12-month OS rate: The proportion of patients that are alive at month 12 after starting treatment.

9.5 Safety assessment

The investigator or qualified designated staff will assess adverse events in every subject during the study, and the follow-up period according to the trial schedule and adverse events will be graded and recorded according to CTCAE v4.03. The characteristics of the adverse event will be determined based on the following aspects: severity, causality, toxicity grade, and measures adopted for the investigational treatment.

All AEs with an unknown etiology that occur during the study must be assessed to determine whether it is an irAE.

9.5.1 Definition of adverse events

Adverse event (AE): An adverse event refers to any untoward medical event that occurs in a clinical trial subject after receiving a drug and does not necessarily have a causal relationship with the treatment. Any untoward medical event from the moment the subject signed the informed consent form and received the investigational drug to 1 month after the treatment has ended is considered an AE, regardless of whether it has a causal relationship with the investigational drug.

Serious adverse event (SAE): refers to an AE that occurs at any dose of the investigational drug or at any time during the observation period that requires hospitalization, prolongation of hospitalization, permanent or serious disability or causing life-threatening events, death, a congenital anomaly or deformity.

9.5.2. Adverse event determination criteria

Adverse reactions should be assessed based on the Common Terminology Criteria for AEs (NCI CTCAE v4.03 grading criteria). The following criteria can be used to assess AEs that are not listed in the NCI toxicity grading criteria:

• Grade 1 (mild): the presence of discomfort that does not affect normal daily activities;

•Grade 2 (moderate): severity of discomfort insufficient to decrease or affect normal daily activities;

•Grade 3 (severe): Unable to work or carry out normal daily activities;

•Grade 4 (fatal): results in disability or death.

9.5.3 Criteria for determining the causality between AEs and investigational drugs

•Definitely related: The reaction occurs in a plausible time relationship to drug administration. The reaction is a recognized pharmacological phenomenon of the investigational drug. The reaction improves on drug discontinuation and reappears when the drug is given again.

• Possibly related: The reaction occurs in a plausible time relationship to drug administration. The reaction is a recognized pharmacological phenomenon of the investigational drug. The clinical state of the subject or other treatments may also produce this reaction.

• Possibly unrelated: The reaction does not occur in a plausible time relationship to drug administration and does not match the type of reaction known to the investigational drug. The clinical state of the subject or other treatments may also produce this reaction.

• Definitely unrelated: The reaction does not occur in a plausible time relationship to drug administration. The reaction is a recognized pharmacological phenomenon of the non-investigational drug and can also be explained by the subject's clinical status or other treatments. The reaction disappears on disease improvement or discontinuation of other treatments, and repeated use of other treatments causes this reaction to occur.

• Not assessable: There is no clear relationship between the time of onset of reaction and time of drug administration. The reaction is similar to the recognized pharmacological phenomenon of the investigational drug. The clinical state of the subject or other treatments may also produce this reaction.

9.5.4. Documentation and reporting of adverse reactions

The specific description of the AE, its time of onset, end time, severity, frequency, and whether treatment is required (if required, please record all administered treatments), and correlation between the AE and the investigational drug as judged by the investigator should be recorded in detail.

When an AE occurs, the observing physician can decide whether to terminate observation based on the patient's condition, and an adverse event should be followed up until it resolves. Medical documents related to adverse events should be recorded in the source document, including notification forms for laboratory tests (such as X-ray, electrocardiography), and test results slip. If the subject is unable to continue receiving treatment with the investigational drug due to trial completion or subject discharge from the hospital, the investigator should submit the case summary of the subject (including descriptions of treatment arrangements and whether adverse event follow-up is required) to the physician that is responsible for treating the subject. This information will also be recorded in the source document.

When an SAE occurs, the principal investigator and the institution must be immediately notified by phone within 24 hours regardless of whether there is a close relationship with the investigational drug. The "Serious adverse event (SAE) report" should be filled in, signed, and dated. The SAE report will immediately be faxed to the Ethics committee, NMPA, and the regulatory authority of the region where the investigator is located. The symptoms, severity, time of onset, time of management, measures used, follow-up duration and follow-up methods, and outcome should be recorded in detail for SAEs.

10. Storage of Biological Samples and Measurement

10.1 Biological samples that may be collected during the study

- Primary and/or recurrent/metastatic tumor tissues
- Blood before and during treatment

10.2.Proposed test items

- Professor Xiaofeng Zhu's laboratory will contact relevant sequencing companies for whole-exome sequencing of tumor tissues
- Professor Xiaofeng Zhu's laboratory will perform immunohistochemistry and immunofluorescence (including but not limited to PD-1, PD-L1, and lymphocyte molecular markers such as CD4, CD8) on tumor tissues
- Professor Xiaofeng Zhu's laboratory will carry out methylation tests of tumor tissues

- Professor Xiaofeng Zhu's laboratory will perform ELISA, plasma free nucleotide test, and flow cytometry of patients' blood samples.

10.3 Sample storage and post-processing

Patients' samples will be stored in Professor Xiaofeng Zhu's laboratory. After the clinical trial has ended, these samples may be used for related fundamental studies.

11 Data management and statistical analysis

11.1 Definition of statistical analysis sets

Full analysis set (FAS): Analysis of all enrolled patients who took at least one dose of the drug will be performed according to the intent-to-treat principle. The last observation carried forward is used for patients whose data were not captured for the entire duration of the study.

Per-protocol set (PPS): All patients who completed 2 cycles or more of treatment, conformed to the study protocol, had good compliance, did not use prohibited drugs during the study, and whose case report forms are completed as required. No imputation will be performed for missing data. Statistical analysis of FAS and PPS are simultaneously performed for drug efficacy analysis.

Safety analysis set (SAS): All enrolled patients who had at least taken one dose of the study drug and whose safety after drug administration had been recorded. This dataset will be used for safety analysis.

11.2. Statistical analysis plan

Baseline data will be analyzed based on the FAS. Full analysis set (defined as all included patients) and safety analysis set (defined as patients had at least one cycle of treatment) were used for efficacy analysis and safety analysis, respectively. In general, categorical data will be summarized using number of patients (n), frequency and percentages. Two-sided exact 95% confidence intervals (CIs) based on the Clopper-Pearson method will be provided to summarize the binomial proportion of the ORR and DCR for both RECISTv1.1 and irRECIST assessments where applicable. Continuous data will be summarized using the number of patients, mean, standard deviation, median, first and third quartiles (Q1, Q3), minimum, and maximum. Time-to-event analyses will be performed using Kaplan-Meier (KM) methods. Medians of PFS and DOR were analyzed using the Kaplan-Meier curve, and 95% CIs were calculated with a generalized Brookmeyer and Crowley method. We calculated the probabilities of patients achieving a PFS > 6 months or > 12 months using the Kaplan-Meier product-limit method, and reverse Kaplan-Meier calculated the Greenwood Formula Follow-up time. Cox regression models were used to test the association between clinicopathologic and genetic characteristics and PFS, and a P-value < 0.05 was considered significant. For genomic analysis, P-value < 0.1 was considered statistically significant. All statistical analyses

about cilinical listings will be performed using SAS v9.4 or higher. Gene analysis will be performed suing R V4.1.0 or higher

12. Ethical Standards

12.1. Informed consent

The study physician is responsible for a complete and comprehensive introduction of the study objectives, drug performance, possible toxic side effects, and potential risks, patients' rights, items to be complied with, and risk and benefits to the patient or his/her proxy before the subject is enrolled. Patients must sign the informed consent form before enrollment, and the signed form will be retained in the CRF.

12.2. Subjects' benefits

The investigational drugs used in this study are free of charge. Relevant insurance will be purchased for the patients in this study at around 250 RMB/person. The maximum compensation is around 30,000/person. The insurance will guarantee the subjects' safety.

12.3. Subject compensation

Compensation claims arising from the investigational drug should be settled in accordance with the related clinical trial regulations of the hospital and the Chinese government.

12.4. Ethical standards, laws, and regulations

The clinical trial must comply with the "2004 Declaration of Helsinki," "Good Clinical Practice (GCP)" released by the NMPA, and pertinent laws and regulations. The ethics committee of the leading site must approve this protocol before the study can be initiated. Any revisions to the study protocol during the study must be reported to the ethics committee and filed.

13. Study Management

13.1 Case report form

The primary objective is to obtain the data required by the study protocol in a complete, accurate, clear, and prompt manner. Data in the case report form should be identical to the source documents.

The case report form must be filled completely and clearly (use a black or blue ballpoint pen to comply with legal document requirements). All revisions and corrections must be performed and confirmed by the investigator, and the date of revision/correction must be stated. Errors must be clearly retained and not covered by corrected data (such as the use of correction fluid). The investigator must state his/her reason for revising important data.

For information/notes missing in the medical record, lines should be drawn in the empty spaces in the case report form to avoid subsequent unnecessary investigations.

The case report form is a regulatory document that must be submitted to the hospital authorities.

13.2. Study documents and storage

The investigator should have a document on the study objectives. This document should be included in all essential study-related documents. These documents will be archived based on hospital and national regulations at the end of the study.

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Appendix 1. ECOG Scale of Performance Status (ECOG PS).

Activity score	Description
0	Asymptomatic, fully active, able to carry on all pre-disease activities without restriction.
1	Symptomatic, restricted in physically strenuous activity but ambulatory, and able to carry out work of a light or sedentary nature, such as light housework and office work.
2	Symptomatic, ambulatory, and capable of self-care but unable to carry out any work activities, up and about >50% of waking hours.
3	Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but is not bedridden.
4	Completely disabled, cannot carry on any self-care, bedridden.
5	Dead.