Efficacy and safety of sintilimab and anlotinib in combination with gemcitabine plus cisplatin as first-line therapy in patients with advanced biliary tract cancer: a randomized, open-label, multicentre, phase 2 SAGC study

Version number: Version 1.0

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Research Institution : Zhejiang Cancer Hospital

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Clinical Study Protocol Signature page

Name of clinical study Protocol: Efficacy and safety of sintilimab and anlotinib in combination with gemcitabine plus cisplatin as first-line therapy in patients with advanced biliary tract cancer: a randomized, open-label, multicentre, phase 2 SAGC study

I agree to carry out clinical research according to the protocol described in this document, and affirm that I shall comply with the requirements of the Criterions for the Quality Control of Clinical Trial of drugs and relevant laws and regulations during the clinical research process.

Center name: Zhejiang Cancer Hospital

Principal person in charge : _____

Date: _____

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Summary of Protocol

Protocol number	Version 1.0 / 10 August 2019
Protocol name	Efficacy and safety of sintilimab and anlotinib in combination with gemcitabine plus cisplatin as first-line therapy in patients with advanced biliary tract cancer: a randomized, open-label, multicentre, phase 2 SAGC study
Classification	Investigator initiated clinical trials
Character	A prospective, randomized, controlled, multicenter phase II clinical trial
Applicant	Zhejiang Cancer Hospital
Principal person in charge	Jieer Ying
Participants	Newly diagnosed patients with unresectable or metastatic biliary tract cancer who have not previously received systemic therapy
Objective	To evaluate the efficacy and safety of sintilimab and anlotinib in combination with gemcitabine plus cisplatin versus gemcitabine plus cisplatin as first-line therapy in newly diagnosed patients with unresectable or metastatic biliary tract cancer
Participant Selection	**Inclusion Criteria:** 1. Patients who are voluntary and sign an informed consent document. 2. Age between 18-75 years (including 18 and 75), no gender preference. 3. Expected survival ≥ 12 weeks 4. ECOG performance status 0 or 1 within 7 days prior to the first dose. 5. In women of child-bearing age, pregnancy test should be negative within 28 days prior to registration, and effective contraception during the treatment period should be adopted within 60 days after the last dose. In this trial, women of child-bearing age are defined as sexually mature women with: 1) no history of hysterectomy or bilateral ovariectomy; 2) natural menopause < continuous 24 months (amenorrhea after cancer treatment does not preclude fertility) (i.e., having menstruation at any time within preceding continuous 24 months); female spouses of male subjects who are of child-bearing age should also follow the above contraceptive requirements. 6. Adequate organ function. （1）Blood test (no blood transfusion, no usage of G-CSF and no medication for correction within 14 days prior to screening): neutrophil count ≥ 1.5×10^9/L

platelets ≥ 75×10^9/L
hemoglobin ≥ 90g/L
（2）Biochemical test (no albumin transfusion within 14 days prior to screening):
serum creatinine ≤ 1.5× upper limit normal (ULN), or creatinine clearance > 50 mL/min;
total bilirubin ≤ 1.5×ULN (total bilirubin ≤ 3× ULN in patients with Gilbert syndrome);
AST and ALT ≤ 2.5× ULN; for patients with hepatic metastases, AST and ALT ≤ 5× ULN;
INR ≤ 2.3 or prothrombin time (PT) exceeding normal control range ≤ 6 seconds;
urine protein < 2+ (if urine protein ≥ 2+, 24-hour urine protein quantitation could be considered, and if 24-hour urine protein quantitation < 1.0g, the patient can be included).
（3）Cardiac function: NYHA < grade 3; LCEF ≥ 50%;

7. In patients with active HBV infection: HBV-DNA should < 500 IU/mL (if measured by copy/ml, HBV-DNA should <2500 copy/mL); patients should be willing to receive antiviral therapy during the treatment period. Patients with positive HCV-DNA should receive antiviral therapy according to local guidelines with liver function ≤ CTCAE grade 1.
8. Patients should have adequate nutritional condition, i.e., BMI≥ 18 kg/m2, weight ≥ 40 kg, and albumin ≥ 3.0 g/dL.
9. Histologically and/or cytologically-confirmed diagnosis of local advanced or metastatic cholangiocarcinoma (including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder carcinoma), which is incurable and unresectable.Having at least one site of measurable lesion (RECIST Version 1.1). Target lesion of tumor progression within previous radiation filed or locally-treated area could be considered as measurable.

Exclusion Criteria:
Patients who meet any of the following conditions will be excluded from the trial:

1. Patients who previously received systemic treatment for advanced unresectable or metastatic cholangiocarcinoma will be excluded. Neoadjuvant or adjuvant therapy is acceptable if treatment is completed at least 6 months prior to randomization and shows no progression.
2. Patients suffering from other active malignancies within 5 years or coexisting with cholangiocarcinoma, except adequately treated localized neoplasms including, but not limited to: basal cell or

	squamous cell skin cancer, superficial bladder cancer, in situ prostate cancer, in situ cervical cancer, and in situ breast cancer. 3. Patients who are preparing for or have previously undergone organ or allogenic bone marrow transplantation. 4. Patients with symptomatic moderate or severe ascites requiring paracentesis and drainage (except patients with imaging showing mild ascites but no clinical symptoms); or patients with uncontrolled or moderate and severe pleural or pericardial effusion. 5. Patients who have a history of gastrointestinal hemorrhage within preceding 6 months or gastrointestinal hemorrhagic tendency, e.g., esophagogastric varices with a risk of hemorrhage, active peptic ulcer, fecal occult blood being continuously positive (if fecal occult blood is positive at baseline, reexamination can be considered; if reexamination is still positive, esophagogastroduodenoscopy (EGD) should be considered; if EGD indicates esophagogastric varices with a risk of hemorrhage, then the patient will be excluded). 6. Patients with hereditary or acquired bleeding tendency (e.g., coagulation dysfunction) or thrombophilia, e.g., hemophilia patients; or patients who are currently receiving or recently received (within preceding 10 days) full-dose anticoagulant or thrombolytic agents orally or by injection for therapeutic purposes (prophylactic usage of low-dose aspirin or low molecular heparin is acceptable). 7. Patients who are receiving or recently received (within preceding 10days) aspirin (>325 mg/d (maximum antiplatelet dose)) or dipyridamole, ticlopidine, clopidogrel and cilostazol. 8. Patients who have a history of thrombosis or embolism within preceding 6 months, including cerebrovascular events (transient ischemic attack, cerebral hemorrhage and cerebral infraction) and pulmonary embolism. 9. Patients with uncontrolled heart disease or relevant symptoms, e.g., (1) heart failure with NYHA > 2 (Appendix 5) or UCG showing LVEF <50%; (2) unstable angina; (3) a history of myocardial infraction within preceding 1 year; (4) supraventricular or ventricular arrhythmia with clinical significance indicating treatment or intervention; (5) QTc > 450ms (male); QTc > 470ms(female) (QTc is calculated by Fridericia law; if QTc is abnormal, it can be continuously measured 3 times with an interval of 2 minutes, taking the average). 10. Patients with hypertension uncontrolled by drug or treatment (SBP≥140 mmHg or DBP≥90 mmHg) (based on≥2 measurements

	and taking average); or patients with a history of hypertensive emergency or hypertensive encephalopathy. 11. Patients who have severe vascular diseases (e.g., aortic aneurysm requiring surgical repair or with recent peripheral arterial thrombosis) within preceding 6 months. 12. Patients with severe, unhealed or open wounds, and active ulcers or untreated fractures. 13. Patients who received major operation (except diagnosis) within preceding 4 weeks, or who are expected to receive major operation during the trial period. 14. Patients who are unable to swallow tablets, or with malabsorption syndrome or any condition that may affect gastrointestinal absorption. 15. Patients with aeroperitoneum that cannot be explained by puncture or recent surgery. 16. Patients with brain metastases before or at present 17. Patients suffering from uncontrolled systemic diseases including, but not limited to: diabetes, hypertension, pulmonary fibrosis, acute pulmonary disease, interstitial lung disease, cirrhosis, angina and severe arrhythmia. 18. Patients suffering from interstitial pneumonia or ILD, or with a history of interstitial pneumonia or ILD requiring hormone therapy, or with other pulmonary fibrosis， organic pneumonia(e.g., obliterative bronchiolitis), pneumoconiosis, drug-induced pneumonia and idiopathic pneumonia that may interfere with the diagnosis and management of immune-related pulmonary toxicity; or patients with CT image indicating active pneumonia or severely impaired pulmonary function during screening. Radiation pneumonia is acceptable in the radiation field. Patients with active tuberculosis will be excluded. 19. Patients suffering from active autoimmune disease or with a history of autoimmune disease that may recur (including, but not limited to: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hypophysitis, vasculitis, nephritis, hyperthyroidism and hypothyroidism [patients controlled only by hormone replacement therapy are acceptable]) will be excluded; patients with dermatosis requiring no systemic treatment, including vitiligo, psoriasis and alopecia, are acceptable; patients win T1DM controlled by insulin therapy, or patients with completely-relieved childhood asthma requiring no intervention in adulthood are acceptable; patients with asthma requiring bronchodilator intervention will be excluded. 20. Patients who received immunosuppressive drug or systemic hormone therapy to achieve immunosuppression

	(prednisone>10mg/d or hormones of equivalent effects) within preceding 14 days. 21. Patients who received strong CYP3A4/CYP2C19 inducer including rifampin (and its analogs) and hypericum perforatum or strong CYP3A4/CYP2C19 inhibitor within preceding 14 days. 22. Patients who have a history of severe allergies to any monoclonal antibody or anti-angiogenic targeted drugs. 23. Patients who had severe infection within preceding 4 weeks including, but not limited to: infection, bacteremia and complications of severe pneumonia resulting in hospitalization; or patients who received therapeutic antibiotics orally or intravenously within preceding 2 weeks (prophylactic usage of antibiotics [e.g., prevention of urinary tract infection or exacerbation of COPD] is acceptable). 24. Patients with innate or acquired immunodeficiency (e.g., patients infected with HIV) 25. Patients who previously received anti-PD-1 therapy or other immunotherapies targeting PD-1/PD-L1, or tyrosine kinase inhibitor therapy. 26. Palliative radiotherapy for non-target lesions to control symptoms is acceptable, but should be completed at least 2 weeks prior with adverse events not recovering to ≤CTCAE grade 1 27. Patients who received attenuated live vaccine within preceding 28 day, or who are expected to receive the vaccine during sintilimab treatment or within 60 days after the last dose of sintilimab. 28. Patients who received anti-tumor cytotoxic chemotherapy, biotherapy (e.g., monoclonal antibody), immunotherapy (e.g., IL-2 or interferon) or other investigational drugs within 4 weeks prior to registration. 29. Patients with other factors that may affect the outcomes or lead to withdrawal (judged by the researcher), including alcohol abuse, drug abuse, other serious disease (including mental illness) requiring combined treatment, significantly abnormal laboratory test index, and family or society factors that may affect patient safety. 30. Patients who previously received antitumor therapy and prior toxicity has not recovered to CTCAE grade 0-1, aside from the following conditions: （1）alopecia; （2）hyperpigmentation; （3）peripheral neurotoxicity recovered to < CTCAE grade 2; （4）long-term toxicity caused by radiotherapy cannot recover (judged by the researcher).

	31. Patients who have active tuberculosis (TB) and are receiving anti-TB therapy, or who received anti-TB therapy within 1 year prior to screening. 32. Patients who are pregnant or lactating.
Exit Criteria	Patients could voluntarily withdraw from the study at any time. If any of the following events occur, the patient must withdraw from the study: Progressive disease (PD) When an adverse event (AE) or a serious adverse event (SAE) occurred, the investigator determined that the patient was not appropriate for further treatment or that the patient and family members refused further treatment Pregnant Patients with grade 3/4 adverse events were unable to complete treatment according to the trial protocol after dose adjustment Unexpected and intolerable adverse reactions occurred Medical or ethical reasons influenced the continuation of the study
Background	Because of its insidious onset, most patients with biliary tract cancer (BTC) are already in the advanced stage when seeking medical treatment, which is not suitable for surgical treatment. It is characterized by high malignancy, intractable treatment and poor prognosis. Presently, first-line therapy for newly diagnosed patients with unresectable or metastatic biliary tract cancer is mainly chemotherapy, including gemcitabine combined with cisplatin (GC) and gemcitabine combined with S-1 (GS). The OS rate is about 30% in 1 year, and PFS is 5-8 months. The survival benefit of chemotherapy is limited in patients with unresectable or metastatic BTC. In recent years, studies have preliminarily shown promising immune check-point inhibitor (ICI) in BTCs. Several studies have shown that ICI can increase the 1-year OS rate to 27.6%-52.3% in patients with BTC who have failed standard therapy, and can significantly prolong PFS. At present, studies on immunotherapy combined with vascular targeting agents have shown strong efficacy in multiple tumor species, and FDA has granted several anti-PD-1/PD-L1 combined with anti-vascular targeting agents as breakthrough therapy. In China, Professor Zhao Haitao applied lenvatinib combined with anti-PD-1 inhibitor to 30 patients with BTC who were retreated. The result showed that ORR was 25%, the median PFS was 5.4 months, and the OS was 12.5 months, but the efficacy was still limited. The result of analysis in IMpower150 study suggested that anti-PD-L1 plus chemotherapy plus vascular targeting agents could significantly improve the OS of initially treated lung cancer patients. The new adverse reactions were not observed, and the overall adverse reactions were within a controllable range. To further improve the outcomes of first-line therapy in newly diagnosed patients with

	unresectable or metastatic BTC. This randomized controlled study was designed. The purpose of this study was to explore the efficacy and safety of sintilimab and anlotinib in combination with gemcitabine plus cisplatin compared with gemcitabine plus cisplatin as first-line therapy for newly diagnosed patients with unresectable or metastatic BTC.
Design	**Experimental group:** Gemcitabine: 1000mg/m^2, days 1; Cisplatin: 25mg/m^2, days 1 and 8; Anlotinib: initially 10 mg, po qd, days 1-14; Sintilimab: 200mg ivgtt, day 1; Q3W; **Control group：** Gemcitabine:1g/m^2, days 1 and 8; Cisplatin: 25mg/m^2, days 1 and 8; Q3W；
Outcomes	**Primary Endpoint:** 12-month OS rate **Secondary Endpoints:** Overall Survival (OS) Progress free survival (PFS) Objective response rate (ORR) 3/4 Adverse Events (AE) was determined by NCI-CTCAE, Version 5.0
Safety	Property, incidence, severity and causality of adverse events/reactions AEs will be assessed as defined by NCI-CTCAE, Version 5.0 Changes in vital signs, physical examination and laboratory values
Sample size	The ABC-02 study reported a total of 204 cases of patients diagnosed with advanced BTC who received a combination treatment of gemcitabine and cisplatin (GC). The observed 12-months OS was approximately 30%. In this study, it is hypothesized that by incorporating sitilimab and anlotinib along with gemcitabine plus cisplatin, the 12-months OS rate can be increased from the previous GC regimen's 25% to 55%, representing a significant improvement. In order to achieve statistical significance with a two-tailed inspection level of 5% and accounting for a potential loss rate of up to 10%, the duration for patient recruitment has been established at 24 months. It is anticipated that patient recruitment will span approximately 12 months. Power analysis calculations indicate that a sample size exceeding 80 is necessary to attain a power of over 80%.
Research time	Expected enrollment time of the first participant: January 2020 The enrollment time of the last participant is expected: January 2021 Estimated time of study completion: January 2022
Summary and Analysis	**Efficacy Analysis:**

	12-month OS rate and hazard ratios with two-sided 95% confidence interval (CIs) were calculated. OS were estimated based on Kaplan-Meier (KM) method, and the 95% confidence intervals on both sides were calculated. PFS and ORR is calculated with a 95% confidence interval. **Safety Analysis:** Safety analysis will be based on descriptive statistical summary. Statistical summary will be made for AE, SAE, drug-related AE, AE leading to dose adjustment, AE leading to trial withdrawal, laboratory data, vital signs, and etc. This standard includes, but is not limited to, the following analysis and summary: The incidence and severity of AE; Analysis of association between AE and drugs; Outcome analysis of AE; Analysis of serious AE; Descriptive statistical summary of laboratory data and vital sign; Incidence of abnormal laboratory indicators; Analysis of positive abnormal changes in laboratory indicators from baseline; Summary and classification of post-baseline vital sign;

Schedule of Activities

Study Period	**Screening Phase -14d**	**Study Intervention Phase 21-Day Cycles**					**Survival Follow-up (Telephone Follow-up)**
		Cycle 1 ±3d	**Cycle2 ±3d**	**Cycle3 ±3d**	**Cycle4 ±3d**	**Cycle 5 to last Cycle±3d**	**Every 6 Weeks**
Baseline Information							
Informed Consent	√						
Demographics	√						
Medical Histories	√						
Prior Anti-tumour Treatment	√						
Vital Signs	√	√	√	√	√	*	
Blood Pressure [a]	√	√	√	√	√	*	
Laboratory Test							
Complete Blood Count	√	√	√	√	√	*	
Urinalysis	√	√	√	√	√	*	

Chemistry Panel and Liver Panel	√	√	√	√	√	*	
Thyroid Function	√	√	√	√	√	*	
Coagulation Function	√	√	√	√	√	*	
Myocardial Enzyme	√	√	√	√	√	*	
Infectious Disease Screening [b]	√	√	√	√	√	*	
ECG	√	√	√	√	√	*	
Tumor biomarker	√	√	√	√	√	*	
Tumor Imaging (CT or MRI) [c]	√	**Tumor imaging should be performed every 6 weeks**					
Other Clinical Assessments, Examinations							
Adverse Event Monitoring		√	√	√	√	*	
ECOG Performance Status	√	√	√	√	√	*	
Administration of Study Intervention							
Gemcitabine [d]		√	√	√	√	*	
Cisplatin [e]		√	√	√	√	*	

Anlotinib Hydrochloride [f]		√	√	√	√	*	√
Sintilimab [g]		√	√	√	√	*	
Concomitant Medication [h]	√	√	√	√	√	*	√
Drug Compliance		√	√	√	√	*	
Survival Follow-up [j]							
Time to Disease Progression[k]							√
Date of Death							√
Subsequent Anti-neoplastic Treatment[l]							√

Notes：**1、All observation indicators and examination (including imaging assessments) should follow calendar days and not be adjusted for cycle delays.**

（1） *：Same as cycle 2；

（2） a：Blood Pressure：Blood pressure will be tested daily for 3 days after each cycle of medication. If blood pressure is abnormal on all 3 tests, follow up daily until normal. If blood pressure is normal, blood pressure will be checked once a week thereafter and followed up daily until normal if abnormalities are found；

（3） b：Includes Anti-HIV, HBs Ag, Anti-HBs, HBe Ag, Anti-HBe, Anti-HBc, HBV DNA viral load、Anti-HCV and HCV RNA viral load。

（4） c：The preferred choice is enhanced CT (including the chest, abdomen, and pelvic cavity). If the patient is allergic to CT contrast agents, abdominal and pelvic enhanced MRI and chest plain CT can be used instead.

（5） d：Gemcitabine 1000 mg/m2 IV on Day 1 and Day 8 Q3W. The dosage is adjusted according to the specific situation.

（6） e：Cisplatin 25 mg/m2 IV on Day 1 and Day 8 Q3W. The dosage is adjusted according to the specific situation.

（7） f：Anlotinib Hydrochloride 10 mg po QD Day1-14, The dosage is adjusted according to the specific situation.

（8） g：Sintilimab 200 mg IV Day1, Q3W for experimental groups. Dose adjustment was not allowed.

（9） h：Documentation of other anti-neoplastic drugs and adverse effects (e.g. hypertension) management drugs;

（10） i：Drug Compliance：At the start of the first day of each treatment cycle, drug doses, counts and compliance for the previous cycle are calculated and recorded in the CRF;

（11） j：Survival Follow-up：All anticancer therapy will be recorded until time of death or termination of survival follow up.If a clinic visit is not feasible, follow up information may be obtained via other means of contact (eg, telephone, video call,mail, or email) every 6 weeks.

（12） k：Time to Disease Progression：Tumor imaging should be performed every 6 weeks until progressive disease, initiation of other anti-neoplastic treatment, death, or end of study.

（13） l：Subsequent anti-cancer treatment needs to be recorded during survival follow-up.

Version 1.0
10 August 2019

1. Research Background

1.1 Current status of biliary tract cancer treatment

Biliary tract cancer (BTC) starts insidiously and has no obvious symptoms in the early stage, most patients are already in advanced stage when they are diagnosed and are not suitable for surgery. Its malignancy is high, treatment is difficult, and prognosis is extremely poor. The average survival of untreated advanced biliary tract cancer patients is only 3~4 months. A multicenter, randomized controlled, phase III clinical study (UK-ABC-02) conducted by Valle J showed that the first-line treatment of advanced biliary tract cancer with gemcitabine in combination with cisplatin (GC) had a DCR of 81.4%, median OS is 11.7 months and PFS is 8 months. And compared to gemcitabine (GEM) alone, the combination group had a 32% lower risk of death, while toxic effects were tolerated [1]. The GC regimen is the first-line standard treatment for locally advanced and metastatic biliary tract cancer. The result of JCOG1113 study shows non-inferiority of gemcitabine in combination with S-1 (GS) to GC in terms of overall survival (Median OS：Group GC is 13.4m and Group GS is 15.1m；HR, 0.95; 90% CI, 0.78~1.15; P=0.046)[2]. The median PFS was 5.8 and 6.8 months in the GC and GS groups (HR, 0.86; 95% CI, 0.70 to 1.07), with RRs of 32.4% and 29.8% respectively. Therefore, the GS regimen is also the first-line standard treatment for patients with advanced BTC. China have the highest incidence of BTC in the world and highest malignancy degree. However, BTC is not sensitive to conventional chemotherapy and is less sensitive to chemotherapy than other gastrointestinal tract tumors such as colon cancer. There is a lack of treatment options for advanced BTC and treatment faces a great dilemma.

1.2 Immunotherapy in BTC

In 2010, immune checkpoint inhibitor Ipilimumab achieves favorable efficacy in metastatic melanoma, increasing median OS by 4 months [3]. After that immunotherapy started to become a hot area of cancer research. Immune checkpoint inhibitors include inhibitors of CTLA-4 and PD-1/PD-L1. PD-1 (programmed cell death protein 1) belongs to the CD28 co-receptor family and has 2 ligands, PD-L1 and

PD-L2. PD-1 is expressed on the surface of immune cells such as thymic T cells, activated T cells, B cells, and natural killer cells, while PD-L1 is expressed on tumor cells, virus-infected cells, parenchymal cells, antigen-presenting cells and so on. PD-1 binds to PD-L1 and acts primarily in the immune effector phase. inhibiting T cell activation, reducing cytokine production and attenuating cytokine activity by attenuating antigen-specific signaling from effector CD8+ T cells. Inhibits T-cell activation by attenuating antigen-specific signaling from effector CD8+ T cells, reduces cytokine production, attenuates cytokine activity, regulates antibody quality and quantity through the action of CD4+ T cells and antigen-presenting B cells, and ultimately suppresses antitumor immunity [4]. PD-1 inhibitors are monoclonal antibodies to PD-1 that help restore T-cell activity by blocking the linkage of PD-1 to PD-L1. PD-1 inhibitors have been approved by the FDA for 12 indications, covering melanoma, non-small cell lung cancer, Hodgkin's lymphoma, head and neck cancer, bladder cancer, MSI-H solid tumors, large B-cell lymphoma, gastric cancer, and cervical cancer. In recent years, immunotherapy has been explored in BTC and has shown great promise. KEYNOTE-028 (KN028) and KEYNOTE-158 (KN158) basket studies used Pembrolizumab (pembro) for advanced biliary tract cancer which have failed after receiving standard therapy. KN158 enrolled 104 patients with a PR rate of 8% (6/104), OS of 7.4 months (95% CI, 5.5-9.6), PFS of 2.0 months (95% CI, 1.9-2.1), and a 12-month OS rate of 32.7%; KN028 enrolled 24 patients with a PR rate of 13% (3/23), OS of 6.2 months (95% CI, 3.8-10.3), PFS of 1.8 months (95% CI, 1.4-3.7), and a 12-month OS rate of 27.6% [5]. Nivolumab treatment 54 patients with progressing after at least first-line treatment advanced refractory BTC , 10 cases of PR (22%), 17 cases of SD (37.8%), DCR of 60% (27/45), median PFS of 3.98 months (95% CI, 2.33-5.98), median OS of 14.22 months (95% CI, 6.64-NA), 12-month PFS rate of 24.1%, and 12-month OS rate of 52.3%[6]. Prof. Qin in China treated 43 cases of advanced biliary tract cancer with camrelizumab in combination with FOLFOX4 or GEMOX in first line with ORR 7.0%, DCR 67.4%, median TTR 1.9 months (1.8-2.1), median DOR 5.3 months (3.7-7.0), median PFS not reached[7]. A single-arm exploratory study of 26 patients with biliary tract cancer treated with SHR-1210 in combination with GEMOX

first-line by Prof. Chen in China showed 12 cases of PR (46.15%), 12 cases of SD (46.15%) and 2 cases of PD (7.69%), with long-term data pending further follow up [8]. The above study showed that immunotherapy, either alone or in combination with chemotherapy, showed good long-term efficacy in both first and second line. The efficiency of immunotherapy alone is not high in hepatobiliary malignancies (15-20%).

1.3 VEGFR tyrosine kinase inhibitors in BTC

Vascular endothelial growth factor mainly contains six members: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and PIGF (placenta growth factor). Their receptors include VEGFR1~3, which participate in MAPK pathway, PI3K-Akt pathway, Ca2+-phospholipid-dependent kinase pathway and so on. The signaling pathway mediated by the binding of VEGF and VEGFR-2 controls the proliferation, survival, and migration of vascular endothelial cells. By altering the permeability of blood vessels, the formation of new blood vessels is inhibited, thereby inhibiting tumor growth and preventing its metastasis [9]. The angiogenesis inhibitors targeting the VEGF pathway mainly include VEGF monoclonal antibodies, VEGFR monoclonal antibodies, VEGFR tyrosine kinase inhibitors, etc. VEGFR tyrosine kinase inhibitors include drugs such as sunitinib, sorafenib, anlotinib hydrochloride, and regorafenib. Prof. Sun treated 43 chemotherapy refractory advanced metastatic biliary adenocarcinoma patients with regorafenib monotherapy, with a median PFS of 15.6 weeks (90% CI, 12.9-24.7), a median OS of 31.8 weeks (90% CI, 23.3-74.3), an ORR of 11%, and a DCR of 16%. The proportion of patients who survived to 12 and 18 months was 40% and 32%, respectively [10].

1.4 Combination of immunotherapy and VEGFR tyrosine kinase inhibitors

More and more evidence suggested that sustained angiogenesis and immune suppression are interrelated processes. VEGF has been shown to reduce the interaction between immune cells and endothelial cells by downregulating the expression of cell adhesion molecule such as ICAM-1 and VCAM-1 in angiogenesis. VEGF has also been shown to directly inhibit the maturation of dendritic cells (DCs) and activate antigen-specific regulatory T cells (Treg) [11]. The combination of anti-vascular therapy and immunotherapy has shown good synergistic effects in both basic

and clinical studies. Prof. Zhao Haitao used lenvatinib combined with PD-1 inhibitor to treat 30 patients with recurrent cholangiocarcinoma. The ORR was 25%, but the disease control rate could reach 90%, with a median PFS of 5.4 months and OS of 12.5 months [12]. However, the efficacy was still limited. The mid-term OS analysis results of the IMPower150 study suggest that the strong combination model of PD-L1+carboplatin+paclitaxel+bevacizumab can significantly improve the OS of naive treated lung cancer patients, and they did not observe any new adverse reactions. The overall adverse reactions are within the controllable range [13].

1.5 The plan of this study

Anlotinib hydrochloride is an inhibitor of receptor tyrosine kinases, targeting vascular endothelial growth factor receptors (VEGFR1–3), fibroblast growth factor receptors (FGFR1–3), KIT, and PDGFRα/β. Anlotinib hydrochloride has a more wider angiogenic kinase inhibition spectrum(for example, for Met, FGFR1/2/3); it also has significant inhibitory activity against some of the kinase targets under investigation, such as Aurora-B, c-FMS, DDR1, etc; it has significant inhibitory activity against a variety of kinase mutants, such as PDGFRα, cKit, Met, EGFR, etc., and its inhibitory activity against the mutants is even stronger than that against the wild type [13]. Sintilimab is a recombinant fully human IgG4 type PD-1 monoclonal antibody that has been shown to block the PD-1 pathway in multiple preclinical in vitro trials. The completed preclinical pharmacodynamics, animal pharmacokinetics, and toxicology studies have shown that Sintilimab has characteristics such as clear targets, reliable cell line sources, and good drug stability. And it has also shown good activity in various preclinical studies that have been completed [14]. Chemotherapy based on gemcitabine is currently the standard treatment for unresectable or advanced BTC. Based on the above background, we design this randomized, controlled, multicenter phase II clinical trial to compare the efficacy and safety of gemcitabine + cisplatin + sintilimab + anlotinib hydrochloride to gemcitabine + cisplatin in the first-line treatment of initial treating non-surgically resectable or metastatic biliary tumors patients.

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2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

Aiming to compare efficacy and safety between sintilimab plus anlotinib in combination with gemcitabine/cisplatin and gemcitabine/cisplatin as first-line therapy in participants with advanced and/or unresectable biliary tract cancer

2.2 Endpoints

1）Primary Endpoints：

12-month OS rate

2）Secondary Endpoints：

Overall Survival (OS)

Progress free survival (PFS)

Objective response rate (ORR)

3/4 Adverse Events (AE) was determined by NCI-CTCAE, Version 5.0

3）Exploratory Endpoints：

Prediction of the efficacy and analysis of prognostic biomarkers of immunotherapy for BTC

3. Study design

This is a multicenter, randomized, controlled phase 2 study, which plans to enroll 80 unresectable or metastatic biliary duct cancer patients from multiple hospitals who have not received systemic therapy for metastatic disease, with randomized 1:1 into the experimental group and control group. This study plan from the start in January 2020, recruit the end time about as of January 2021, is expected to the end of the test time for January 2022. Participants should not allow to accept other systemic anti-tumor treatment before the disease progression. And subsequent treatment after disease progression was administered at the discretion of the investigator. Tumor imaging by CT/MRI chest, abdomen and pelvis is required at all scheduled imaging time points (CT is strongly preferred) in each participant. Imaging should continue to be performed until disease progression is identified by the investigator, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

3.1 Study Intervention(s) Administered

Each treatment cycle was defined as 3 weeks (21 days) and treatment continued until disease progression or toxicity was not tolerated or up to 2 years; up to 8 cycles of chemotherapy.

Experimental group:

gemcitabine: 1 g/m^2, on Day 1 and 8;

cisplatin: 25 mg/m^2, Day 1 and 8;

Anlotinib hydrochloride: 10 mg is taken orally once a day, d1-14;

sintilimab 200 mg iv d1;

repeat it every three weeks;

Control group:

gemcitabine: 1 g/m^2, on Day 1 and 8;

cisplatin: 25 mg/m^2, Day 1 and 8;

repeat it every three weeks;

3.2 Efficacy Assessments

Imaging assessment must be performed 6 weeks (42 days±7 days) from the date of randomization.

3.3 Survival follow-up

Participants survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Follow-up can be conducted by telephone to the participant or his family.

3.4 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 90 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first.

3.5 Sample size calculation

The ABC-02 study reported a total of 204 cases of patients diagnosed with advanced BTC who received a combination treatment of gemcitabine and cisplatin (GC). The observed 12-months OS was approximately 30%. In this study, it is hypothesized that by incorporating sitilimab and anlotinib along with gemcitabine plus cisplatin, the 12-months OS rate can be increased from the previous GC regimen's 25% to 55%, representing a significant improvement. In order to achieve statistical significance with a two-tailed inspection level of 5% and accounting for a potential loss rate of up to 10%, the duration for patient recruitment has been established at 24 months. It is anticipated that patient recruitment will span approximately 12 months. Power analysis calculations indicate that a sample size exceeding 80 is necessary to attain a power of

over 80%.

4. Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place. Participation in the clinical trial is voluntary and has the right to withdraw from the trial at any time at any stage of the trial without discrimination and retaliation, that their medical treatment and rights are not affected, and have rights to receive other anti-cancer treatments. The personal information of participations must be kept confidential.

5. STUDY POPULATION

5.1 Inclusion Criteria:

(1) Patients who are voluntary and sign an informed consent document.
(2) Age between 18-75 years (including 18 and 75), no gender preference.
(3) Expected survival ≥ 12 weeks
(4) ECOG performance status 0 or 1 within 7 days prior to the first dose.
(5) In women of child-bearing age, pregnancy test should be negative within 28 days prior to registration, and effective contraception during the treatment period should be adopted within 60 days after the last dose. In this trial, women of child-bearing age are defined as sexually mature women with: 1) no history of hysterectomy or bilateral ovariectomy; 2) natural menopause < continuous 24 months (amenorrhea after cancer treatment does not preclude fertility) (i.e., having menstruation at any time within preceding continuous 24 months); female spouses of male subjects who are of child-bearing age should also follow the above contraceptive requirements.
(6) Adequate organ function.
Blood test (no blood transfusion, no usage of G-CSF and no medication for correction within 14 days prior to screening):
   i. neutrophil count ≥ 1.5×109/L
   ii. platelets ≥ 75×109/L
   iii. hemoglobin ≥ 90g/L
Biochemical test (no albumin transfusion within 14 days prior to screening):
   iv. serum creatinine ≤ 1.5× upper limit normal (ULN), or creatinine

clearance > 50 mL/min;

v. total bilirubin ≤ 1.5×ULN (total bilirubin ≤ 3× ULN in patients with Gilbert syndrome);

vi. AST and ALT ≤ 2.5× ULN; for patients with hepatic metastases, AST and ALT ≤ 5× ULN;

vii. INR ≤ 2.3 or prothrombin time (PT) exceeding normal control range ≤ 6 seconds;

viii. urine protein < 2+ (if urine protein ≥ 2+, 24-hour urine protein quantitation could be considered, and if 24-hour urine protein quantitation < 1.0g, the patient can be included).

(7) Cardiac function:NYHA < grade 3; LCEF ≥ 50%;

(8) In patients with active HBV infection: HBV-DNA should < 500 IU/mL (if measured by copy/ml, HBV-DNA should <2500 copy/mL); patients should be willing to receive antiviral therapy during the treatment period. Patients with positive HCV-DNA should receive antiviral therapy according to local guidelines with liver function ≤ CTCAE grade 1.

(9) Patients should have adequate nutritional condition, i.e., BMI≥ 18 kg/m2, weight ≥ 40 kg, and albumin ≥ 3.0 g/dL.

(10) Histologically and/or cytologically-confirmed diagnosis of local advanced or metastatic cholangiocarcinoma (including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma and gallbladder carcinoma), which is incurable and unresectable.

(11) Having at least one site of measurable lesion (RECIST Version 1.1). Target lesion of tumor progression within previous radiation filed or locally-treated area could be considered as measurable.

5.2 Exclusion Criteria:

Patients who meet any of the following conditions will be excluded from the trial:

(1) Patients who previously received systemic treatment for advanced unresectable or metastatic cholangiocarcinoma will be excluded. Neoadjuvant or adjuvant therapy is acceptable if treatment is completed at least 6 months prior to randomization and shows no progression.

(2) Patients suffering from other active malignancies within 5 years or coexisting with cholangiocarcinoma, except adequately treated localized neoplasms including, but not limited to: basal cell or squamous cell skin cancer, superficial bladder cancer, in situ prostate cancer, in situ cervical cancer, and in situ breast cancer.

(3) Patients who are preparing for or have previously undergone organ or allogenic bone marrow transplantation.

(4) Patients with symptomatic moderate or severe ascites requiring paracentesis and drainage (except patients with imaging showing mild ascites but no clinical symptoms); or patients with uncontrolled or moderate and severe pleural or pericardial effusion.

(5) Patients who have a history of gastrointestinal hemorrhage within preceding 6 months or gastrointestinal hemorrhagic tendency, e.g., esophagogastric varices with a risk of hemorrhage, active peptic ulcer, fecal occult blood being

continuously positive (if fecal occult blood is positive at baseline, reexamination can be considered; if reexamination is still positive, esophagogastroduodenoscopy (EGD) should be considered; if EGD indicates esophagogastric varices with a risk of hemorrhage, then the patient will be excluded).

(6) Patients with hereditary or acquired bleeding tendency (e.g., coagulation dysfunction) or thrombophilia, e.g., hemophilia patients; or patients who are currently receiving or recently received (within preceding 10 days) full-dose anticoagulant or thrombolytic agents orally or by injection for therapeutic purposes (prophylactic usage of low-dose aspirin or low molecular heparin is acceptable).

(7) Patients who are receiving or recently received (within preceding 10days) aspirin (>325 mg/d (maximum antiplatelet dose)) or dipyridamole, ticlopidine, clopidogrel and cilostazol.

(8) Patients who have a history of thrombosis or embolism within preceding 6 months, including cerebrovascular events (transient ischemic attack, cerebral hemorrhage and cerebral infraction) and pulmonary embolism.

(9) Patients with uncontrolled heart disease or relevant symptoms, e.g., (1) heart failure with NYHA > 2 (Appendix 5) or UCG showing LVEF <50%; (2) unstable angina; (3) a history of myocardial infraction within preceding 1 year; (4) supraventricular or ventricular arrhythmia with clinical significance indicating treatment or intervention; (5) QTc > 450ms (male); QTc > 470ms(female) (QTc is calculated by Fridericia law; if QTc is abnormal, it can be continuously measured 3 times with an interval of 2 minutes, taking the average).

(10) Patients with hypertension uncontrolled by drug or treatment (SBP≥140 mmHg or DBP≥90 mmHg) (based on≥2 measurements and taking average); or patients with a history of hypertensive emergency or hypertensive encephalopathy.

(11) Patients who have severe vascular diseases (e.g., aortic aneurysm requiring surgical repair or with recent peripheral arterial thrombosis) within preceding 6 months.

(12) Patients with severe, unhealed or open wounds, and active ulcers or untreated fractures.

(13) Patients who received major operation (except diagnosis) within preceding 4 weeks, or who are expected to receive major operation during the trial period.

(14) Patients who are unable to swallow tablets, or with malabsorption syndrome or any condition that may affect gastrointestinal absorption.

(15) Patients with aeroperitoneum that cannot be explained by puncture or recent surgery.

(16) Patients with brain metastases before or at present

(17) Patients suffering from uncontrolled systemic diseases including, but not limited to: diabetes, hypertension, pulmonary fibrosis, acute pulmonary disease, interstitial lung disease, cirrhosis, angina and severe arrhythmia.

(18) Patients suffering from interstitial pneumonia or ILD, or with a history of interstitial pneumonia or ILD requiring hormone therapy, or with other pulmonary fibrosis， organic pneumonia(e.g., obliterative bronchiolitis), pneumoconiosis,

drug-induced pneumonia and idiopathic pneumonia that may interfere with the diagnosis and management of immune-related pulmonary toxicity; or patients with CT image indicating active pneumonia or severely impaired pulmonary function during screening. Radiation pneumonia is acceptable in the radiation field. Patients with active tuberculosis will be excluded.

(19) Patients suffering from active autoimmune disease or with a history of autoimmune disease that may recur (including, but not limited to: autoimmune hepatitis, interstitial pneumonia, uveitis, enteritis, hypophysitis, vasculitis, nephritis, hyperthyroidism and hypothyroidism [patients controlled only by hormone replacement therapy are acceptable]) will be excluded; patients with dermatosis requiring no systemic treatment, including vitiligo, psoriasis and alopecia, are acceptable; patients win T1DM controlled by insulin therapy, or patients with completely-relieved childhood asthma requiring no intervention in adulthood are acceptable; patients with asthma requiring bronchodilator intervention will be excluded.

(20) Patients who received immunosuppressive drug or systemic hormone therapy to achieve immunosuppression (prednisone>10mg/d or hormones of equivalent effects) within preceding 14 days.

(21) Patients who received strong CYP3A4/CYP2C19 inducer including rifampin (and its analogs) and hypericum perforatum or strong CYP3A4/CYP2C19 inhibitor within preceding 14 days.

(22) Patients who have a history of severe allergies to any monoclonal antibody or anti-angiogenic targeted drugs.

(23) Patients who had severe infection within preceding 4 weeks including, but not limited to: infection, bacteremia and complications of severe pneumonia resulting in hospitalization; or patients who received therapeutic antibiotics orally or intravenously within preceding 2 weeks (prophylactic usage of antibiotics [e.g., prevention of urinary tract infection or exacerbation of COPD] is acceptable).

(24) Patients with innate or acquired immunodeficiency (e.g., patients infected with HIV)

(25) Patients who previously received anti-PD-1 therapy or other immunotherapies targeting PD-1/PD-L1, or tyrosine kinase inhibitor therapy.

(26) Palliative radiotherapy for non-target lesions to control symptoms is acceptable, but should be completed at least 2 weeks prior with adverse events not recovering to ≤CTCAE grade 1

(27) Patients who received attenuated live vaccine within preceding 28 day, or who are expected to receive the vaccine during sintilimab treatment or within 60 days after the last dose of sintilimab.

(28) Patients who received anti-tumor cytotoxic chemotherapy, biotherapy (e.g., monoclonal antibody), immunotherapy (e.g., IL-2 or interferon) or other investigational drugs within 4 weeks prior to registration.

(29) Patients with other factors that may affect the outcomes or lead to withdrawal (judged by the researcher), including alcohol abuse, drug abuse, other serious disease (including mental illness) requiring combined treatment, significantly

abnormal laboratory test index, and family or society factors that may affect patient safety.

(30) Patients who previously received antitumor therapy and prior toxicity has not recovered to CTCAE grade 0-1, aside from the following conditions:

(31) alopecia;

(32) hyperpigmentation;

(33) peripheral neurotoxicity recovered to < CTCAE grade 2;

(34) long-term toxicity caused by radiotherapy cannot recover (judged by the researcher).

(35) Patients who have active tuberculosis (TB) and are receiving anti-TB therapy, or who received anti-TB therapy within 1 year prior to screening.

(36) Patients who are pregnant or lactating.

5.3 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

Participants may discontinue study intervention at any time for any reason or be dropped from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator, placed the participant at unnecessary risk from continued administration of study intervention
- The participant has a confirmed positive serum pregnancy test.
- Unacceptable toxicity.
- Radiographic disease progression.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy, that requires active treatment.
- Medical or ethical reasons for influencing the continuation of the study;

6. Study endpoints

Primary endpoint	12-months OS rate
Secondary endpoints	Overall survival (OS) Progression-free survival (PFS)

	Objective Response Rate (ORR) Grade 3 / 4 AE

7. Study Procedures

7.1 General Procedures

1) Medical history: detail the history of tumor-related diseases, autoimmune diseases, infectious diseases, endocrine diseases, cardiovascular diseases, thrombosis and hemorrhagic diseases, and organ-specific diseases. Intestinal function assessment includes the baseline number of stools, traits and other bowel habits.
2) Physical examination: a general physical examination, including blood pressure, breathing, pulse, body temperature, and body weight. Physical examination of each system. Whole-body skin and mucous membrane examination, pay attention to the scope and type of existing lesions.
3) Routine hematology examination: blood routine, urine routine, stool routine, liver and kidney function, coagulation function, tumor markers (CEA, CA-199, CA125) examination, viral testing (HBV, HCV, HIV).
4) Imaging examination: chest and abdominal pelvic CT/MRI.
5) Cardiac function tests: electrocardiogram, myocardial enzyme (CK).
6) Pulmonary function tests were performed as judged by the investigator.
7) Endocrine function test: Thyroid function (TSH, free T4 is recommended for all patients, and repeat testing before each treatment).

7.2 Reserve the samples

Baseline tumor tissue specimen (patient voluntary principle), disease progression rebiopsy tissue specimen (patient voluntary principle),

7.3. Medical products

Research medication

Overview of the drugs

1)Way of obtaining the drugs

The Investigator must ensure that all investigational drugs are used only for

participations in this clinical trial and their dose and usage should comply with the trial and will not be used for treatment that is not in the study.

The test drug should be stored under the storage conditions specified in this study protocol.

The monitor is responsible for monitoring the supply, use, storage of clinical trial drugs and the processing process of surplus drugs.

Gemcitabine and cisplatin were paid by patients under standard of insurance care. Anlotinib hydrochloride and sintilimab are gifts and their management, distribution and recovery are the responsibility of special personnel. The investigator must ensure that all investigational drugs are only used for participatiions in this study, the dose and usage shall follow the test protocol, and that investigational drugs in this study are not allowed to be used for treatment not included in this study.

2) Dosage form, appearance, packaging, and preservation of the study medicinal product

Anlotinib hydrochloride capsules

Manufacturer: Cia Tai Tianqing Pharmaceutical Group Co., Ltd

dosage form: capsule agent

Specification: 10 mg; 8 mg

Packaging: 7 pieces / plate / box

Usage: oral

Expiry date: 18 months

Storage: shaded, closed, stored below 25℃. (National requirements of reference test for specific storage conditions)

Sintilimab infusion

Formulation form: sterile water injection dosage form

Specification: 100mg / 10ml / bottle

Composition: Active ingredient: Sintilimab (recombinant full human programmed death receptor 1 monoclonal antibody).

The excipients in this product are as follows: mannitol, histidine, sodium citrate (dihydrate), sodium chloride, disodium edesate, polysorbate 80, citric acid

(monohydrate), water for injection.

Storage conditions: keep the medicine bottle in the original packaging in a refrigerated environment of 2~8 C to avoid light, freezing and shock.

Expiry date: 24 months

The preparation of drugs used in the test conforms to the Good Practice for Good Manufacturing, and the quality meets the quality standards of clinical trials.

3)The configuration method of sintilimab

Do not shake the bottle during the configuration, restore the bottle to room temperature (25℃ or below) before use, and remove the bottle at room temperature (25℃ or below) for up to 24 hours before dilution. The jection should be visually inspected for the presence of suspended particles and discoloration. This product is a clear to micro emulsion light, colorless to pale yellow liquid, no foreign body. If visible particles are observed, the vial should be discarded. Two bottles of this injection (200mg) were drawn and transferred to an intravenous infusion bag containing 9 mg/ml (0.9%) sodium chloride solution with a final concentration range of 1.5~5.0mg/ml. Turn the dilution gently and mix. From a microbiological perspective, the product must be used immediately upon diluted and must not be frozen. The stability study shows that 2~8 ℃ can be stored for 24 hours, and the 24 hours include up to 6 hours under 20~25 ℃ indoor light (6 hours including administration time). After refrigeration, the vial and / or IV bag must be restored to room temperature before use. The tube used for infusion must be equipped with a sterile, heat-free, low-protein binding tube filter (pore size 0.2 μ m). The infusion time was between 30 to 60 min. Do not use the same infusion tube and other drugs simultaneously. This product is intended for single use only. Any unused drug remaining in the vial must be discarded.

8. The adjustment of medication in the study

8.1 General principle

Hematology, liver, and kidney function must meet administration requirements before day 1 of each study drug administration, and all toxicities associated with study drug administration must have been resolved to the common standard term for adverse Events (CTCAE) V5.0 0-1 level or baseline (except for hair loss and fatigue).

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

8.2 Dose Modification of sintilimab

The dose of sintilimab was not allowed to be adjusted during the whole study. AEs associated with sintilimab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of sintilimab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of sintilimab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue sintilimab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 1.

Table 1 Recommended therapeutic adjustments for sindillimab

Immune-related adverse reactions	**order of severity**	**Therapeutic adjustment**
Pneumonia	Grade 2	Administration was suspended until the adverse reactions recovered to grade 0~1 *
	Grade 3 or 4, or recurrent grade 2	Permanent withdrawal
Colitis	Grade 2 or 3	Administration was suspended until the adverse reactions recovered to grade 0~1 *
	Grade 4, or recurrent grade 3	Permanent withdrawal
Hepatitis	Grade 2, aspartate transferase (AST) or alanine transferase (ALT) > 3-5 times the upper normal limit (ULN), or total bilirubin > 1.5-3 times the ULN	Administration was suspended until the adverse reactions recovered to grade 0~1 *
	Grade ≥3, AST or ALT> 5 times ULN, or total bilirubin > 3 times ULN	Permanent withdrawal
	For patients with liver metastases with grade 2 elevated AST or ALT at the baseline of treatment, the increase in AST or ALT from baseline was ≥50% and lasted ≥1 week	Permanent withdrawal

Immune-related adverse reactions	**order of severity**	**Therapeutic adjustment**
Nephritis	Grade 2, creatinine > 1.5 to ≤3 times ULN	Administration was suspended until the adverse reactions recovered to grade 0~1 *
	≥ grade 3, creatinine > 3 times ULN	Permanent withdrawal
Endocrine disease	Symptomatic pituitaritis Type 1 diabetes mellitus with hyperglycemia ≥ grade 3 (blood sugar >250mg/dl or 13.9mmol/L) or associated ketoacidosis Hyperthyroidism ≥ grade 3	Administration was suspended until the adverse reactions recovered to grade 0~1 *. For patients with grade 3 or 4 endocrine disease who have improved to grade 2 or lower and have clinical symptoms that can be controlled by hormone replacement, sindillizumab therapy may be considered after a gradual reduction in corticosteroid dose (if needed), otherwise therapy should be discontinued. Hypothyroidism can be managed with alternative therapy without discontinuance of sindillizumab therapy.
Cutaneous adverse reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Administration was suspended until the adverse reactions recovered to grade 0~1 *。
	Grade 4 or confirmation of SJS or TEN	Permanent withdrawal
Infusion reaction	Grade 3 or 4	Permanent withdrawal
Other immune-related adverse reactions	Depending on the severity and type of reaction (grade 2 or 3)	Administration was suspended until the adverse reactions recovered to grade 0~1 *
	Grade 3 or 4 myocarditis	Permanent withdrawal
	Grade 3 or 4 encephalitis	
	Grade 3 or 4 Guillain-Barre syndrome	
	Grade 4 or relapsed grade 3	Permanent withdrawal

Note: Toxicity rating was based on the National Cancer Institute Standard for the Assessment of Adverse Events in General Terms, 5th Edition (NCI-CTCAE v5.0).

* Sintilimab should be permanently discontinued if treatment-related adverse reactions do not return to grade 0 to 1 within 12 weeks of the last sindillimab dose, or if the corticosteroid dose cannot be reduced to ≤10 mg/ day of prednisone or equivalent within 12 weeks.

The safety of restarting sintilizumab therapy in patients with a history of immune-associated myocarditis is unclear.

sintilimab should be permanently discontinued under the following circumstances:

1) Grade 4 or recurrent grade 3 adverse events.

2) Grade 2 or 3 adverse reactions persist despite treatment adjustment.

If treatment with sintilimab is temporarily or permanently discontinued during the combination therapy due to an intolerable toxic reaction, then, according to the investigator's judgment, Patients may continue treatment with anlotinib hydrochloride until disease progression, occurrence of an intolerable toxic reaction, initiation of a new antitumor therapy, withdrawal of informed consent, loss of follow-up or death, decision of the investigator or sponsor to terminate, or the patient completes 24 months of treatment, whichever occurs first.

The maximum interval allowed for drug suspension is 12 weeks. If the patient does not recover enough to resume sintilimab within 12 weeks, sintilimab is permanently discontinued. Except in the following two cases:

a) Glucocorticoid administration for curing immune-associated adverse events (irAE), and glucocorticoid tapering resulted in sintilimab being suspended for more than 12 weeks.

b) Discontinuation of sintilimab for more than 12 weeks for treatment of AE unrelated to sintilimab. Reinstatement of sintilimab requires a return to 0-1 or baseline AE with an ECOG PS score of 0-1.

Sintilimab may cause severe or life-threatening infusion reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually occur during or shortly after infusion and are usually fully resolved within 24 hours of completion of infusion. Guidelines for the management of sindillizumab associated infusion reactions are shown in Table 2.

Table 2 Guidelines for the management of sintilimab infusion reactions

CTCAE classification	Therapy	Pretreatment during subsequent administration
Grade 1 Mild reaction; No need to interrupt infusion; No intervention	Based on the patient's medical indications, the patient's vital signs are monitored intensively until the investigator deems the patient stable.	No
Grade 2 Treatment or interruption of infusion is required, but symptomatic treatment (such as antihistamines, non-steroidal anti-inflammatory drugs [NSAIDS], anesthetics, intravenous fluids) should be performed as soon as possible after rapid response; Prophylactic medication ≤24 hours should be taken	Discontinue fluids and monitor symptoms. Other appropriate medications may include, but are not limited to: Intravenous infusion Antihistamine NSAIDS Anesthetic Based on the patient's medical indications, the patient's vital signs are monitored intensively until the investigators consider the patient stable. If symptoms resolve within one hour of stopping the infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/h to 50 mL/h). Otherwise, medication should be suspended until symptoms resolve, and the patient should receive pretreatment before the next scheduled dosing For patients with grade 2 toxicity despite adequate pretreatment, further investigational drug therapy should be permanently discontinued.	Patients received the following pretreatments 1.5 hours (±30 minutes) before sindillizumab infusion: Oral Diphenhydramine 50 mg (or equivalent dose antihistamine). Oral acetaminophen 500-1000 mg (or equivalent dose of antipyretic).
Grade 3 or 4: Prolonged duration (i.e. failure to produce a rapid response after symptomatic administration and/or brief interruption of infusion); Symptoms recurred after initial	Stop the infusion. Other appropriate medications may included, but are not limited to: Adrenaline ** Intravenous infusion Antihistamine NSAIDS	There was no follow-up administration

CTCAE classification	Therapy	Pretreatment during subsequent administration
improvement; Hospitalization is required for other clinical sequelae (e.g., kidney damage, lung infiltration) Grade 4: Life-threatening; Hypertensive medication or ventilation support is required	Anesthetic Oxygen Pressor Corticosteroid Based on the patient's medical indications, the patient's vital signs are monitored intensively until the investigators consider the patient stable. Hospital treatment may be required. ** Use epinephrine immediately if allergic reaction occurs. Patients should permanently discontinue further investigational drug therapy.	
Appropriate first aid equipment should be provided in the ward and a physician should be accessible at all times during medication administration. For further information, see CTCAE V5.0（http://ctep.cancer.gov）		

8.3 Dose adjustment of anlotinib hydrochloride

Dosing adjustments due to anlotinib hydrochloride related toxicity include: dosing suspension, dosing mode adjustment (Dose adjustment: 8 mg, once daily,d1-d14,Q3W; permanent discontinuation if 8mg is not tolerated) and termination of medication. No callbacks will be allowed after anlotinib hydrochloride administration is adjusted during the study.

If the subject missed anlotinib hydrochloride on the day, the next dose should be taken as planned the next day, and the next day does not need to be doubled. Subjects should contact the investigator immediately if they have taken an excessive dose of anlotinib hydrochloride.

If AE clearly associated with anlotinib hydrochloride occurred during the trial，such as hypertension, albuminuria, hand and foot syndrome, Anlotinib hydrochloride could be suspended，after the toxicity has recovered，then the original dose could be given, the dosing mode could be adjusted or the dosing appropriately could be stopped，and after termination of anlotinib hydrochloride administration, subjects may continue sintilimab monotherapy.

Based on the experience of previous clinical studies, confirmed immune related toxicities occurred during the trial, especially immune pneumonia, hepatitis, elevated

AST or ALT or blood bilirubin, diarrhea or colitis, elevated blood creatinine, etc, sintilimab should be suspended at the same time (refer to sintilimab administration delay standard) and anlotinib hydrochloride as well， When toxicity is restored to ≤ grade 1 or baseline level (for those with abnormalities in ALT, AST and TBIL and other laboratory indicators at baseline), medication can be resumed. It is recommended to resume sintilimab first, and after medication and observation for 7 to 14 days without significant abnormalities, anlotinib hydrochloride administration can be started (if 8mg is still intolerable, Stop taking them permanently.).

Changes in blood pressure should be routinely monitored during the medication，

If grade 3 hypertension (systolic blood pressure is greater than or equal to 160mmHg or diastolic blood pressure is greater than or equal to 100mmHg or requires more than one antihypertensive medication) occured, it is recommended to suspend anlotinib hydrochloride and start antihypertensive therapy under the guidance of a specialist. anlotinib hydrochloride was resumed when blood pressure dropped to the normal range (systolic < 140mmHg and diastolic < 90mmHg). If hypertension persists, the administration method of anlotinib hydrochloride should be adjusted. For patients with hypertensive crisis (systolic blood pressure greater than or equal to 180mmHg or diastolic blood pressure greater than or equal to 120mmHg, and/or accompanied by progressive target organ dysfunction), treatment should be terminated immediately and aggressive symptomatic treatment (hypotension, dehydration, stopping convulsions, etc.) should be given.

For hematologic toxicity ≥ grade 3 or non-hematologic toxicity ≥ grade 2, anlotinib hydrochloride dose suspension and administration mode adjustment are required.

For non-hematologic toxicity, manageable nausea, vomiting, and fever (below 38℃) with a definite cause may be treated with aggressive symptomatic management first, without the need for immediate dose suspension or adjustment of administration.

In case of abnormal symptoms/signs or laboratory indicators during the test, timely treatment should be taken, and corresponding dose adjustment is recommended by referring to the following table:

Table 3 Dose adjustment table of anlotinib hydrochloride

Drug-related toxicity		Classification	Dose-pause or not	Restore the administration standard	Anlotinib hydrochloride dose adjustment methods	Criteria for termination of medication
Anlotinib	Hematologic toxicities	Grade 1 and 2	No	—	—	—

hydrochloride related toxicity		Grade 3	Yes (except reduced lymphocyte count)	Until toxicity returns to ≤ grade 2	First time: original dose; Second time: 8 mg, once daily, d1-14, Q3W	Anlotinib hydrochloride administration should be discontinued if grade 3 or above hematologic toxicity occured again after adjustment
		Grade 4	Yes	Until toxicity returns to ≤ grade 2	First time: 8 mg, once daily, d1-14, Q3W	
	Other non-hematologic toxicities *	Grade 1	No	—	—	—
		Grade 2 (sustained ≥7d)	Yes	Until toxicity returns to ≤ grade 1	Original dose	—;
		Grade 3	Yes	Until toxicity returns to ≤ grade 1	First time: 8 mg, once daily, d1-14, Q3W	Anlotinib hydrochloride administration should be discontinued if grade 3 nonhematologic toxicity occurred again after adjustment
	Hypertension	Grade 3 (After corrective treatment)	Yes	Until toxicity returns to ≤ grade 1	First time: original dose; Second time: 8 mg, once daily, d1-14, Q3W	Anlotinib hydrochloride administration was discontinued when grade 3 hypertension recurred after adjustment
		Hypertensive crisis	Yes	—	Permanent discontinuation of anlotinib hydrochloride	Discontinue Anlotinib hydrochloride
Drug-related toxicity		Classification	Dose-pause or not	Restore the administration standard	Anlotinib hydrochloride dose adjustment methods	Criteria for termination of medication

	Proteinuria (without a significant increase in creatinine)	Grade 3 (24h urinary protein quantification)	Yes	Until toxicity returns to ≤ grade 2	First time: 8 mg, once daily, d1-14, Q3W	Anlotinib hydrochloride administration should be discontinued if grade 3 proteinuria occurred again after adjustment
	Hand-foot syndrome	Grade 3	Yes	Until toxicity returns to ≤ grade 1	First time: 8 mg, once daily, d1-14, Q3W	Anlotinib hydrochloride administration should be discontinued if grade 3 hand-foot syndrome occurred again after adjustment
	Headache	Grade 2 headache after symptomatic treatment persist ≥7 days, or grade 3 headache	Yes	Until toxicity returns to ≤ grade 1	First time: 8 mg, once daily, d1-14, Q3W	Anlotinib hydrochloride administration should be discontinued after adjustment if symptoms occurred again

*: In case of cerebral hemorrhage, ≥ grade 2 pulmonary hemorrhage, ≥ grade 3 other hemorrhage, arterial thrombosis, leucoencephalopathy syndrome, gastrointestinal perforation, and nephrotic syndrome during the trial, anlotinib hydrochloride administration should be discontinued and symptomatic treatment should be actively performed. Subsequent treatment with sintillimab monotherapy should be determined depending on the recovery of toxicity of the subjects.

Subjects with significant toxicity that persists after symptomatic treatment during the study period, including grade 2 nonhematological toxicity (excluding asymptomatic grade 2 hypertension) and abnormal laboratory indicators (excluding albuminuria <2g/24h) lasting for 2 weeks or more, may be considered to suspend medication based on subjects' tolerance. In the follow-up study, the modulated administration of anlotinib hydrochloride was selected.

During the study, the investigator may incorporate the above dose-adjustment regulations to give appropriate dosing adjustments in the event of drug-related toxicity occurring in the combined subjects(if the subjects have multiple Grade 2 study drug related toxicities and have poor tolerance to the study drug), the administration pattern

of anlotinib hydrochloride can be adjusted after suspension of medication and recovery of toxicity.

8.4 Drug supply

Anlotinib hydrochloride and sintilimab were provided free of charge in this study, and other costs were reimbursed by the patients according to their medical insurance.

9. Clinical Evaluation

9.1 Effectiveness Indicators

1) Primary endpoint and observation methods：12-months OS rate

2) Secondary endpoints and observation methods:：

   a) Overall Survival（OS）：From the time of randomization to the time of death from any cause, the last follow-up is usually calculated as the time of death for subjects who have been lost to follow-up prior to death.

   b) Progression-Free-Survival（PFS）： The date from random to the first occurrence of disease progression or death from any cause, which comes first.

   c) Objective Response Rate (ORR）： Refers to the proportion of patients whose tumors have shrunk to a certain amount and remain there for a certain period of time, including CR and PR cases. Objective tumor response was assessed using mRECIST criteria.

10. Safety Assessments

10.1 Definition

Adverse Event（AE）：

AE is any adverse medical event that occurs in a subject or clinical subject and is not necessarily causally related to the treatment. Therefore, AE can be any adverse or unintended sign (e.g. including abnormal laboratory results), symptom or transient drug-related illness that should be considered to be related to drug use.

Adverse events occurring before and after treatment are considered adverse events based on management needs. Therefore, safety monitoring (reporting of adverse events or serious adverse events) should be performed from the time subjects were enrolled to

the end of the study. Adverse events that occur during the signing of the informed consent and the initiation of the study treatment are also considered AEs.

Adverse Drug Reaction（ADR）：

All toxic and unintended reactions to a drug associated with any dose should be considered adverse drug reactions (ADRs).The response to the drug means that there is at least a reasonable possibility of a causal relationship between the drug and AE, which means that this relationship cannot be excluded.

Serious Adverse Event（SAE）：

SAE refers to all adverse medical events that occur at any drug dose: death and life-threatening. Note: "serious" and "life-threatening" are defined as the risk of death when the adverse event occurs, rather than assuming that a more serious adverse event may lead to the death of the patient. If SAE occurs in the course of the experiment, the researcher should immediately take appropriate protective measures for the subjects and report to the main researcher within 24 hours. The researcher should fill in the "serious adverse event report form" and sign and date the report.

SAE includes:

a) Death or Life-threatening
b) Hospitalization or Prolonged hospitalization
c) Cause a permanent disability
d) Carcinogenic Teratogenic

Other events that should be handled as SAEs:

Drug exposure during pregnancy / lactation. In principle, pregnancy and lactation are the exclusion criteria. If a pregnancy occurs during the study, the patient should immediately withdraw from the study and inform the investigator immediately and follow up the patient throughout the pregnancy and postpartum. Even if the mother and child are completely normal without any adverse events, the consequences should be recorded. Even if the pregnancy is not a SAE, use the SAE report form.

Events that should not be handled as SAEs:

Disease progression is generally not judged as an SAE (but if the symptoms and signs of disease progression meet the criteria for an SAE, it can be reported as an SAE).

Death itself is a consequence and is not considered a SAE (the primary cause of death, the main AE causing death should be recorded and reported as SAE, "death" is reported as the consequence of the corresponding AE; if death has no exact cause, death itself may be reported as SAE).

Death within 1 month of initiation of medication should be reported as SAE; death 1 month after initiation of medication will not be reported as SAE if death is due to disease progression.

Due to the severity of the disease, certain conditions identified as SAEs in this study may need to be excluded from the immediate report:

A. Alternative hospitalization and surgical treatment

B. Alternative hospitalization is intended to simplify treatment or research measures

1) Record of adverse events and assessment methods

AEs are described in medical terms, all AEs should be recorded in the appropriate section of the Case Report Form (CRF), and the SAE report form (including initiation or follow-up reports) should be completed. All participations in the trial shall be included in the summary, and the causes of the cases dropped out or excluded during the summary shall be explained. If there are cases of death or severe toxic reaction in the trial, a detailed case report should be made.

The cause of death should be found out, with emphasis on the relationship with experimental drugs. Unalleviated adverse events are followed up, and all adverse events should be followed until they are properly resolved or the condition is stable.

The following aspects of each event should be recorded in the CRF

Time of occurrence（Start time）、Time of recovery（End time）

AEs were assessed and graded by the Investigator as defined in NCI-CTC version 4.0:

Grade I (mild): feeling uncomfortable, but do not affect normal daily activities;

Grade II (moderate): uncomfortable enough to reduce or affect normal daily activities;

Grade III (severe): unable to work or normal daily activities;

Grade IV: life-threatening or disabling;

Grade V: death.

The possible association between AE and experimental drugs was evaluated according to the five-level classification of "definitely relevant, likely relevant, possible relevant, possible irrelevant, irrelevant". The first three levels were judged to be related to experimental drugs. When calculating the incidence of adverse reactions, the three were taken as numerators, and all subjects used to evaluate safety were taken as denominators.

Table 5 Criteria for determining the relationship between adverse events and drugs

Standards	Definitely	Likely	Possible	Possible	Irrelevant
Reasonable chronological	Y	Y	Y	Y	N
Types of response to the	Y	Y	Y	N	N
Removing the cause can	Y	Y	Y/N	Y/N	N
Readministration can be	Y	?	?	?	N
The reaction may have an	N	N	N	Y	Y

Measures taken for research drugs (none, discontinuation of treatment, dose reduction, delayed treatment, slowing down of intravenous infusion) and other measures (none, combination of drugs, need or extension of hospitalization, surgery, delay of chemotherapy, discontinuation of chemotherapy, reduction of chemotherapy)

Consequences are defined as follows: recovery with sequelae, recovery without sequelae, uncured but without treatment, uncured requiring treatment, and death. Whether the change in toxicity grade / severity is serious: yes or no. If the patient has the same AE several times, it must be recorded and re-evaluated each time.

The criteria for determining whether an abnormal objective test result should be

reported as an adverse event are as follows:

The test results are related to concomitant symptoms (and / or)；

The examination results require other diagnostic examinations or therapeutic measures / surgical intervention (and / or)；

The test results lead to a change in the subject's drug dose or termination of the trial, requiring additional concomitant medication, or other treatment (and / or)；

Only for the purpose of repeating an abnormal examination, but does not meet any of the above conditions, does not constitute an adverse event. Any abnormal test results determined to be incorrect are not required to be reported as adverse events.

Reporting system for serious adverse events

The reporting period of serious adverse events should start from the subject's signing of the informed consent form to 90 calendar days (including 30 days) after the last use of the study drug.In case of serious adverse events, whether it is the first report or follow-up report, you must immediately fill in the "Clinical Research serious adverse events (SAE) report form", sign and date it, and fax it to CHIATAI TIANQING Drug Safety Group, Clinical Inspector, Principal researcher, Ethics committee of group leader unit and research unit within 24 hours of the researcher's knowledge.

Serious adverse events that occur 90 days after the last administration are generally not reported unless they are suspected to be related to research drugs.

Serious adverse events should be recorded in detail, including symptoms, severity, correlation with experimental drugs, occurrence time, treatment time, measures taken, follow-up time and mode, and outcome.If the researcher believes that a serious adverse event has nothing to do with the trial drug, but is potentially related to the study conditions (such as termination of the original treatment, or complications during the trial), this relationship should be described in detail in the description section of the serious adverse events page of the medical record report.If the intensity of an ongoing serious adverse event or its relationship with the tested drug changes, the follow-up report of the serious adverse event should be sent to the co-sponsor immediately.All serious adverse events should be followed up to recovery or stability.

11. Concomitant Medications

11.1 Prohibited medications for participants with sintilimab

Immunosuppressants are not allowed during the ongoing study (except for the treatment of drug-related AE). Systemic corticosteroids > 10mg/ days (prednisone or equivalent), except for treatment or control of drug-related AE during treatment or short-term prophylactic treatment. Live vaccines are not allowed within 30 days prior to the first dose of study intervention and while participating in the study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines.

11.2 Prohibited medications for participants with anlotinib

In vitro studies have shown that anlotinib hydrochloride is mainly metabolized by CYP1A2 and CYP3A4/5 through liver P450 enzyme, followed by CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6. Strong inhibitors and inducers of CYP3A can significantly accelerate or slow down the clearance rate of anlotinib by increasing or decreasing the exposure of anlotinib. Therefore, strong inhibitors and inducers of CYP3A need to be disabled (see the list of common strong inhibitors and inducers of CYP3A below).When combined with other drugs, it is recommended to choose alternative drugs that have no inhibition or induction of CYP3A4. If they must be used at the same time with strong inhibitors or inducers of CYP3A4, it is necessary to consider whether to adjust the dose in combination with clinical observation.

11.3 Concomitant medications allowed

1) Antiviral therapy

Participants with HBV infection and with HCV infection are required to receive antiviral treatment according to local standards. Antiviral therapy is recommended as follows:

Participants with HBV infection, such as HBsAg positive, have already started antiviral therapy before entering the study and the virus control is satisfactory (HBV-DNA < 500IU/mL), then continue antiviral therapy. Those with unideal virus control should switch to entecavir and join in the study when HBV-DNA < 500IU/mL. Participants with HBV infection during the screening period were treated with entecavir immediately and could be enrolled into the study when HBV-DNA < 500IU/mL.

Participants with HCV infection, such as HCV-RNA positive, must receive antiviral treatment in accordance with local standard guidelines for hepatitis C diagnosis and treatment.

2) Steroid

Allow local use of steroids, such as topical, eye, nasal, intra-articular, inhaled, etc. Corticosteroids allowed for adrenal replacement therapy. Corticosteroids that are allowed to be used to treat adverse reactions. Allow short-term use of steroids that are used to prevent and treat allergic reactions (to prevent allergy to contrast media or to treat other allergic reactions).

3) Other systemic treatments

During the study, the participants were allowed to receive the best supportive treatment. Bisphosphate therapy is allowed for bone metastasis.

4) Palliative local treatment

Palliative treatment is allowed for local non-target lesions that cause obvious symptoms, such as bone pain, local radiotherapy or surgery, as well as the treatment of pleural and ascites, etc., provided that the following conditions are met: these lesions were known to exist when they were enrolled in the group, for participants who need local treatment due to worsening symptoms during the study, the researchers have to determine whether the disease is progressing. Participants with progressive disease must meet the criteria for continuing treatment after progression . During the period of palliative local treatment, patients should suspend the experimental drugs until the end of the recovery period of palliative treatment.

The contents of palliative treatment should be recorded in detail in eCRF and medical records, including treatment date, location, treatment method, dose, adverse reactions and so on.

12. data management and statistical analysis

12.1 Information collection and data management

1) Completion and transfer of case report forms

The case report form is completed by the investigator and must be completed for each enrolled case. The completed Case Report Form is reviewed by the Clinical Supervisor and the first link is transferred to the Data Manager for data entry and administration.

2) Data entry and modification

Data entry and management is the responsibility of an independent data management unit. Data entry and management is carried out by data managers using the EpiData 3.0 software to prepare data entry programs. To ensure the accuracy of the data, two data managers should double-enter and double-check the data independently. For queries on the case report form, the data manager will write a data rating questionnaire (DRQ) and send a query to the investigator via the clinical monitor. The researcher should answer and return the question as soon as possible, and the data manager should correct, confirm and enter the data based on the researcher's answer, and if necessary, reissue the DRQ

3) Data locking

After confirming that the correct database has been created, the data is locked by the principal investigator, the sponsor, and the statistical analyst. No further changes are made to the locked data file.

12.2 Statistical analysis

Full Analysis Set (FAS Set): The efficacy analysis was performed on all cases with 1 dose of the drug according to the principle of intention-to-treat (ITT). For cases where the full course of treatment was not observed, the last observation was carried forward to the final outcome of the trial (LOCF).

Per-protocol Set (PPS Set): All cases that were compliant with the trial protocol, had good adherence, had taken at least 2 cycles of medication (subjects who took more than one cycle of medication and had clear imaging evidence of disease progression were also included in the PPS Set), did not take prohibited medication during the trial, and completed the required sections of the case report form. No imputation of missing data was performed. Statistical analysis of drug efficacy was performed on both the FAS and the PPS.

The Safety Analysis Set (SAS Set)：The Safety Analysis Set (SAS) is a set of all patients who have been enrolled, have used the trial drug at least once, and have a record of post-dose safety. This data set is used for safety analysis.

12.3 Statistical Analysis Plan

All statistical analyses will be calculated using SAS 9.1.3 statistical analysis software programming. All statistical tests will be performed using a two-sided test and a p-value ≤ 0.05 will be considered statistically significant for the difference tested, with a 95% confidence interval.

This trial was analysed separately according to the initial dose grouping administered and the dose grouping administered at the end of treatment.

Baseline data were analysed by full analysis set and all validity indicators were analysed by full analysis set and per-protocol Set; safety analysis was conducted using the safety analysis set.

The measures for each visit in the different treatment groups will be statistically described using mean ± standard deviation or median (min, max). Comparisons will be made with the baseline values at the screening period, using paired t-tests to compare within-group differences before and after. Changes before and after treatment in each group will be compared using analysis of variance (ANOVA) or rank sum tests. Statistical descriptions of the count data for each visit in the different treatment groups were made using frequency (composition ratio). Changes before and after treatment in each group were tested using the $\chi 2$ test for exact probability or non-parametric tests.

1) Shedding analysis: mainly descriptive analysis will be used, if necessary, the $\chi 2$ test or the calculation of Fisher's exact probability will be used for comparison of the total shedding rate and shedding due to AE in each group.

2) Analysis of balance of underlying values: ANOVA or $\chi 2$ tests were used to compare demographic information with other indicators of underlying values to measure how well balanced the groups were.

3) Validity analysis: For the comparison of clinical efficiency and clinical benefit rates between the two groups, the CMH-$\chi 2$ test with and without central stratification was used to compare the efficacy of the two groups respectively, and 95% confidence intervals were calculated for the differences between the groups. For the indicators PFS and OS, the product-limit method was used and the OS at 25%, 50% (median) and 75% PFS and different times after treatment initiation were calculated according to the actual data, and the Log- Rank test was used to compare the indicators between the two groups.

4) Safety analysis: Descriptive statistical analysis was used to tabulate the AEs that occurred in this trial, comparing the incidence of AEs in each group using *Fisher's* exact probability method if necessary. Laboratory test results were described as normal before the trial but abnormal after treatment and in relation to the test drug if abnormal changes occurred.

13. quality control and quality assurance

The clinical research unit must be a clinical research base for pharmaceutical products identified by the State Drug Administration as having clinical research conditions;

Researchers must be physicians trained in clinical trials and work under the supervision of a senior professional;

Pre-test inspection of the clinical ward must conform to standardised requirements and ensure that resuscitation equipment is available;

Administration of medication by professional nursing staff with detailed information on the administration of medication to ensure compliance;

Each research centre must strictly follow the study protocol and complete the case observation form faithfully;

Supervisors should follow standard operating procedures and monitor the conduct of clinical trials to ensure that all data are recorded and reported correctly and completely, that all case report forms are completed correctly and are consistent with the original data, and that the trials are conducted in accordance with the clinical study protocol;

In the event of an SAE, the supervisor must promptly inform the research unit and, if necessary, temporarily suspend the study;

Each study unit participating in a trial should be subject to audit by the sponsor and the drug regulatory authority, and it is particularly important that investigators and their associates facilitate and provide time for monitoring and audit.

14. Case report form (CRF) recording, transmission and maintenance

14.1 Records of the CRF

All case report forms are printed in triplicate in carbonless format, with the first page being the original page printed on white paper and the last two pages printed on pink and yellow paper respectively. To ensure that the handwriting on the duplicate pages is clear, registrants are asked to fill in all items vigorously with a black ballpoint pen, taking care to use a liner to avoid contaminating the cleanliness of the paper surface of adjacent forms. the CRF is completed by the investigator and must be completed for each enrolled case. when completing the CRF, the investigator should take note of the following:

1) All cases were observed according to the above protocol and the CRF was carefully completed;
2) Careful documentation of patient medication;
3) The medical record and CRF are the original records and may not be altered, and any corrections made may not alter the original record, but may only be justified by an additional narrative, signed and dated by the physician participating in the clinical trial;
4) All laboratory data from clinical trials should be recorded, as should laboratory data within the normal range, and data that are significantly high or clinically acceptable should be verified with the necessary explanation from the physician participating in the clinical trial;

5) Take care that the CRF is completed in clear, uncluttered handwriting and that the generic name of the drug is used as much as possible, rather than the trade name.

14.2 Transfer of CRF

After the start of the study, hospital investigators are requested to submit the completed CRFs and the three CRFs of terminated studies and excluded cases to the lead unit via the supervisor in a timely manner. After detailed inspection by the lead unit, the first white original sheet will be left behind and the pink and yellow sheets will be returned for the hospital summary and statistical analysis of the data. After the study is fully completed, the pink pages are kept by the hospitals and the yellow pages are handed over to the sponsors for retention.