Clinical Research Protocol

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一、 Title

A Prospective,Exploratory Study of Irinotecan Liposome,5-Fluorouracil/Calcium Folinate,Oxaliplatin,and Adebelimab in Combination with Radiotherapy for Resectable or Borderline Resectable Pancreatic Cancer with High-Risk Factors

二、 Study Background

1.Pancreatic Cancer Background

Pancreatic cancer is a highly malignant digestive system tumour with extremely poor prognosis.In recent years,both incidence and mortality rates have shown a significant upward trend both domestically and internationall.According to global cancer statistics from 2020 [11,approximately 495,000 new cases of pancreatic cancer are diagnosed annually worldwide,with approximately 466,000 deaths attributed to the disease each year. Based on the anatomical relationship between the tumour and blood vessels,pancreatic cancer is classified into three types:resectable,borderline resectable,and unresectable.Borderline resectable pancreatic cancer(BRPC)refers to cases without distant metastasis;where the superior mesenteric vein-portal vein has narrowing,twisting,or obstruction,but can be safely reconstructed after resection;Invasion of the gastroduodenal artery up to the level of the hepatic artery but not involving the celiac trunk;tumor invasion of the superior mesenteric artery not exceeding 180 degrees of its circumference.With accurate preoperative screening and assessment,a reasonable surgical plan,and comprehensive postoperative

adjuvant therapy, some patients with borderline resectable cases can benefit from improved survival outcomes [2]. Resectable pancreatic cancer (RPC) refers to pancreatic cancer that has not invaded the celiac trunk, superior mesenteric artery, or common hepatic artery, has not invaded the superior mesenteric vein or portal vein, or has invaded the superior mesenteric vein and portal vein but has not exceeded 180 °, and has a regular venous contour, and can be resected curatively through surgery [2].

Pancreatic cancer has an insidious onset, with approximately 80% of patients diagnosed at an advanced stage, thereby losing the opportunity for curative surgical resection. Only 15–20% of patients have the opportunity to undergo curative surgery at the time of initial diagnosis [3]. However, even after surgical resection, many patients experience early recurrence, resulting in extremely poor prognosis, indicating that relying solely on surgery to control the disease remains highly limited [4].

2. Current Status of Diagnosis and Treatment for Borderline Resectable/Resectable Pancreatic Cancer

Adjuvant chemotherapy following surgical resection in pancreatic cancer patients helps delay recurrence and improve overall survival [5]. However, due to postoperative complications or delayed recovery, 20–30% of patients do not undergo adjuvant chemotherapy, limiting the efficacy of treatment [6,7]. Compared to adjuvant chemotherapy, the concept of neoadjuvant chemotherapy (NAC) may be a more attractive option. Since the tumour's blood supply remains intact, neoadjuvant chemotherapy achieves higher concentrations of chemotherapeutic agents in the tumour microenvironment, resulting in stronger tumour suppression [8]. The advantages of neoadjuvant chemotherapy include but are not limited to: (1) eliminating circulating tumour cells and distant micrometastases in the patient's body, thereby reducing the risk of rapid recurrence after surgery; (2) local tumour shrinkage and improved vascular infiltration, which helps to increase the rate of R0 resection; (3) identifying highly malignant tumours that may not benefit from surgery [9,10].

Currently, an increasing number of surgeons and oncologists are adopting the concept of preoperative chemotherapy. In recent years, neoadjuvant therapy has become increasingly important in the treatment of borderline resectable pancreatic cancer. The main neoadjuvant chemotherapy regimens recommended in guidelines are gemcitabine plus albumin-bound paclitaxel [11] and the FOLFIRINOX regimen [12]. Paniccia et al. reported the results of a study on BR-PDAC patients receiving FOLFIRINOX neoadjuvant therapy: 94% underwent R0 resection, with a median follow-up time of 14.5 months and median overall survival (OS) not yet reached [13]. Choi et al.'s study also demonstrated the efficacy of FOLFIRINOX in neoadjuvant therapy for BR-PDAC [14]. Some studies compared the incidence of postoperative complications between the neoadjuvant therapy group and the direct surgery group, finding that the two groups were largely similar. Hank et al. observed that the incidence of postoperative complications was 52% and 56% in the neoadjuvant therapy group and direct surgery group, respectively, with severe complication rates of 14% and 17%, respectively. However, patients who received neoadjuvant therapy had shorter hospital stays [15]. In terms of complications, neoadjuvant therapy often reduces the incidence of postoperative pancreatic fistula. Hank et al. found that the incidence of postoperative pancreatic fistula was significantly lower in the neoadjuvant therapy group compared to the direct surgery group (3.8% vs. 13.8%) [15]. Although the safety and efficacy of neoadjuvant therapy for locally advanced pancreatic cancer (LAPC) and borderline resectable pancreatic cancer (BRPC) have been established, the applicability of neoadjuvant chemotherapy for resectable pancreatic cancer (RPC) remains controversial. The advantages and disadvantages of applying neoadjuvant chemotherapy in RPC patients remain a current research focus in the field.

Currently, there is no standard neoadjuvant treatment regimen for pancreatic cancer. Recent neoadjuvant-related clinical trials primarily reference chemotherapy regimens for advanced pancreatic cancer, which may include chemotherapy and/or radiotherapy. Recommended chemotherapy regimens include the FOLFIRINOX regimen, gemcitabine combined with paclitaxel (albumin-bound), gemcitabine combined with cisplatin (for

BRCA1/2 mutations), and gemcitabine combined with tegafur [16,17]. At the 2023 ASCO conference, updated data from the NAPOLI-3 study showed that liposomal irinotecan combined with oxaliplatin, 5-fluorouracil, and calcium folinate (NALIRIFOX) achieved the OS endpoint compared to the AG regimen as first-line treatment for metastatic pancreatic cancer patients, demonstrating clinical significance [18]. Based on this study, the NCCN guidelines have included the NALIRIFOX regimen as a recommended first-line treatment for advanced pancreatic cancer [19].

Given the efficacy and safety advantages of irinotecan liposome over irinotecan in the field of pancreatic cancer, this study will further explore the efficacy and safety of irinotecan liposome, 5-fluorouracil/ calcium folinate, oxaliplatin, and adebelimab in combination with radiotherapy for resectable or borderline resectable pancreatic cancer with high-risk factors, aiming to identify a more effective treatment regimen for BRPC and RPC patients to improve survival outcomes.

3. HR070803 (Irinotecan Liposome)

3.1. Characteristics and Advantages of HR070803

Irinotecan is a semi-synthetic derivative of camptothecin, and its hydrochloride salt (irinotecan hydrochloride, CPT-11) is a cytotoxic anticancer drug commonly used in clinical practice for the treatment of colorectal cancer. Currently available formulations include irinotecan hydrochloride injection and its freeze-dried powder for injection. After intravenous administration, the free drug is directly exposed to the slightly alkaline physiological environment, where the lactone ring in its structure is prone to hydrolysis, converting it into the carboxylate form and thereby losing its activity, reducing drug efficacy; additionally, this formulation has significant toxic side effects, primarily manifested as severe neutropenia and severe delayed diarrhoea.

In recent years, liposomal anticancer drugs have become a hot topic in research and development. As a new type of drug delivery system, liposomes

have the following characteristics:

Protective effect: Some drugs have poor stability, such as camptothecin-based drugs, which are unstable under slightly alkaline physiological conditions. The saturated lactone ring in their structure can transform into a carboxylate form, and the lactone ring is an essential structural component for their anticancer activity. Therefore, when such drugs are encapsulated by liposomes, their lactone rings are effectively protected by the unique bilayer structure and properties of liposomes, which encapsulate them within the aqueous phase of the liposomes.

Passive targeting: ① When liposome particle size is large, they may be phagocytosed by the reticuloendothelial system (RES) upon entering the body, leading to accumulation of liposome drugs in organs rich in reticuloendothelial cells such as the liver, spleen, and lymph nodes, but also reducing their concentration in the kidneys, heart, and brain tissue; ② When liposome particle size is small, the EPR effect can be utilised to achieve accumulation of liposomes at solid tumour sites: In normal tissues, the gaps between microvascular endothelial cells are dense and structurally intact, making it difficult for large molecules and lipid particles to pass through. In contrast, solid tumour tissues have abundant blood vessels with wider gaps between vessel walls and poorer structural integrity, and lack lymphatic drainage, resulting in selective high permeability and retention of large molecules and lipid particles in solid tumours. This phenomenon is referred to as the high permeability and retention effect of solid tumour tissues, abbreviated as the EPR effect.

Sustained-release properties: Liposomes act as drug carriers, enabling slow release of the drug from the liposomes to achieve sustained-release effects. This allows the drug to continue exerting its effects throughout the cell growth cycle, thereby enhancing the therapeutic index.

Our company's HR070803 combines protective properties, passive targeting, and sustained release characteristics: Irinotecan is encapsulated within the aqueous phase of the liposome, protecting the active structure of the lactone ring; Additionally, our liposomes have an average particle size

of <100 nm ("invisible" liposomes), reducing uptake by the reticuloendothelial system (RES) and enabling targeted distribution to tumours via the EPR effect, thereby enhancing drug targeting; our liposomes as drug carriers release drugs slowly, achieving sustained-release effects. Clinical study results from abroad indicate that liposomal formulation significantly enhances the antitumour efficacy of irinotecan while reducing its toxicity.

3.2. Early Exploration and Research Progress in the Field of Pancreatic Cancer

Preclinical studies suggest that the efficacy of irinotecan liposome formulations is significantly higher than that of conventional injectable formulations, with efficacy over 10 times greater in certain tumour types; even for certain irinotecan-resistant tumour strains, it exhibits good antitumour activity. In acute toxicity tests, the toxicity of the liposome formulation is lower than that of conventional formulations; in long-term toxicity tests, it is comparable to conventional formulations; allergic reaction symptoms are relatively controllable. Therefore, irinotecan liposome is a highly effective antitumour drug with benefits far outweighing the risks. In preclinical studies, it was also found to have significant efficacy in pancreatic cancer PANC 0504 and human pancreatic cancer BxPC-3 models.

· YLTKL- Ⅰa-1 Study:

A completed single-centre, open-label, single-arm, 3+3 dose-escalation study of intravenous infusion of HR070803 in patients with advanced solid tumours, with the primary objective of evaluating dose-limiting toxicity (DLT) and maximum tolerated dose (MTD), while also assessing safety and pharmacokinetic characteristics.

The dosing regimen was as follows: each dose group (75 mg/m², 94 mg/m², 113 mg/m², and 151 mg/m²) was diluted with 250 mL of 0.9% sodium chloride injection solution and then administered via intravenous infusion, with the infusion completed within 90 − ± −5 minutes. Each dosing cycle was 3 weeks, with one administration per cycle, for a total of two consecutive cycles.

A total of 32 patients with advanced solid tumours who had failed standard treatment or were unable to undergo standard treatment were enrolled in this study, including 3 patients in the 75 mg/m² group, 12 patients in the 94 mg/m² group, 14 patients in the 113 mg/m² group, and 3 patients in the 151 mg/m² group.

For detailed study results, please refer to the HR070803 Investigator's Brochure.

·YLTKL-Ib Study:

A completed single-centre, open-label, single-arm, 3+3 dose-escalation study in patients with advanced solid tumours receiving intravenous infusion of HR070803 in combination with 5-FU/LV, aimed at determining the DLT and MTD of HR070803, evaluating its safety and pharmacokinetic characteristics, and preliminarily assessing efficacy.

The administration regimen was as follows: each dose group (57, 75, 94, 113 mg/m²) was diluted with 250 mL of 0.9% sodium chloride injection solution, followed by intravenous infusion over 90 minutes (± 5 minutes), with 100 mL of normal saline used for flushing after infusion completion. 200 mg/m² of LV was diluted with 100 mL of 0.9% sodium chloride injection and administered after the HR070803 infusion, with the infusion completed over 30 minutes (± 5 minutes). 2000 mg/m² of 5-FU is diluted with 0.9% sodium chloride injection to 230 mL and administered as a continuous intravenous infusion after completion of LV administration, with a total infusion time of 46 hours (± 2.5 hours). Each treatment cycle lasts 2 weeks, with one administration per cycle.

This study enrolled 15 patients with advanced solid tumours who had failed standard therapy or were unable to undergo standard therapy, conducting a dose-escalation study with two dose groups (57 and 75 mg/m²). The 57 mg/m² dose group included 12 patients, and the 75 mg/m² dose group included 3 patients.

For detailed study results, please refer to the HR070803 Investigator's Brochure.

·HR-IRI-APC Study:

A completed randomised, double-blind, single-blind, parallel-controlled, multicentre clinical trial comparing the efficacy and safety of HR070803 combined with 5-FU/LV versus placebo combined with 5-FU/LV as second-line treatment for locally advanced or metastatic pancreatic cancer after failure of gemcitabine therapy. The study enrolled 298 patients who met the inclusion and exclusion criteria, randomly assigned in a 1:1 ratio to the treatment group (HR070803 60 mg/m² combined with 5-FU/LV) or the control group (placebo combined with 5-FU/LV). Patients will receive treatment according to the randomised dosing regimen until disease progression (imaging or clinical deterioration) or the occurrence of intolerable toxicity.

As of 18 November 2021, a total of 228 OS events had been observed. Analysis of the 228 OS events revealed that the median OS in the experimental group and the control group was 7.39 months (95% CI: 6.05, 8.41) and 4.99 months (95% CI: 4.27, 6.01). The experimental group had a 37% lower risk of death compared to the control group (hazard ratio [96.4% CI] was 0.63 [0.48, 0.84]; P = 0.0019). The combination of HR070803 with 5-FU/LV significantly prolonged overall survival compared to the combination of HR070803 placebo with 5-FU/LV, with the difference being statistically and clinically significant. Additionally, the combination of HR070803 with 5-FU/LV also prolonged progression-free survival (PFS) and time to progression (TTF), and improved the objective response rate (ORR) and CA19-9 tumour marker response rate.

The results of this study were presented at the 2022 ESMO Congress. This treatment regimen was designed based on the Chinese context, with all enrolled patients being Chinese, and it has the potential to become the standard second-line treatment regimen for advanced pancreatic cancer in China.

3.3 UGT1A1*28/*6 gene homozygous mutation

In the HR-IRI-APC study, patients with homozygous UGT1A1*28/*6 mutations had their starting dose reduced by one level (47 mg/m²). If no adverse reactions occurred during the first cycle, the dose was increased to the starting dose level in subsequent cycles. However, multiple studies on the standard formulation of irinotecan and its analogue Onivyde (®) have shown that patients with the UGT1A1*28 homozygous mutation have higher rates and severity of haematological toxicity and diarrhoea compared to non-homozygous mutation carriers. Therefore, initial dose adjustments are often made for patients with the UGT1A1*28 homozygous mutation. Recent studies with the standard formulation of irinotecan have confirmed a dose-dependent relationship between the UGT1A1*28 gene homozygous mutation, SN-38 concentration, and safety. Only when administering moderate to high doses (> 150 mg/m², calculated as hydrochloride) of the standard formulation of irinotecan is there a significant association between UGT1A1*28 homozygous mutation and haematological toxicity, with an increased risk of grade 3 − 4 haematological toxicity. However, when administering low doses (100 − 125 mg/m², once weekly, based on hydrochloride equivalent) of the standard formulation of irinotecan, the incidence and severity of haematological toxicity were similar between individuals with homozygous and heterozygous mutations in the UGT1A1*28 gene [7]. The product label for the standard formulation of irinotecan (CAMPTO®) states that for individuals with a homozygous mutation in the UGT1A1*28 gene, the initial dose of irinotecan should be the standard dose, with monitoring for haematological toxicity. The relationship between the UGT1A1 genotype and irinotecan-related diarrhoea is not yet fully understood [18]. In summary, the current evidence supporting dose adjustment for patients with the UGT1A1*28 homozygous mutation is insufficient.

In terms of mechanism of action, the relationship between UGT1A1*28 gene polymorphism, SN-38 concentration, and haematological toxicity appears to depend on the SN-38 metabolic load of UGT enzymes. In the use of standard irinotecan formulations, this dose-dependent relationship can be observed in patients with the UGT1A1*28 homozygous mutation; however, irinotecan liposomes can disperse the SN-38 load through slow

release, keeping it within the metabolisable range of UGT enzymes. A study in patients with advanced gastric cancer (PEP0206) supports this, showing that plasma SN-38 Cmax was approximately 50% lower with 100 mg/m² irinotecan liposome formulation compared to 300 mg/m² irinotecan standard formulation [19]. Even in patients with homozygous UGT1A1*28 mutations and reduced UGT enzyme activity, the low SN-38 load of irinotecan liposomes may remain within the tolerable range for UGT enzyme metabolism.

Referring to data from the Phase III NAPOLI-1 study of Onivyde (®) in second-line pancreatic cancer, a total of 114 subjects received Onivyde (®) + 5-FU/LV treatment. Seven subjects had a homozygous mutation in the UGT1A1*28 gene, with an initial dose of 60 mg/m². Among these, three subjects had their dose increased to 80 mg/m² in subsequent cycles, two maintained 60 mg/m², one was increased to 80 mg/m² and then reduced back to 60 mg/m², and one was reduced to 40 mg/m². After dose adjustment, the SN-38 exposure levels in UGT1A1*28 homozygous mutation carriers increased by only 18%. After further adjusting for other variables in the population PK model, the SN-38 clearance rates were consistent between UGT1A1*28 homozygous mutation carriers and non-homozygous mutation carriers. Considering that SN-38 exposure may be influenced by both the UGT1A1*28 genotype and other factors, it was ultimately concluded that the sole influence of the UGT1A1*28 genotype may not be significant, and thus, adjusting the dose based on the UGT1A1*28 homozygous mutation has limited clinical significance [20].

Patients with the UGT1A1*6 homozygous mutation had higher SN-38 levels, lower glucuronidation, and higher bilirubin levels compared to wild-type individuals. The mutation rate of the UGT1A1*6 homozygous mutation in Asian populations is comparable to that of the UGT1A1*28 homozygous mutation, while it is rare in European and American populations [21]. A study of irinotecan liposome combined with SHR-1316 and 5-FU as first-line therapy for advanced oesophageal cancer showed that approximately 8.7% (2/23) of patients had the UGT1A1*28/*6 homozygous mutation. One of these patients received an initial dose of 56 mg/m², with subsequent cycles at 75 mg/m². The other participant received 56 mg/m² for the first two

doses, followed by 75 mg/m² for subsequent cycles. Both participants experienced TRAEs of grades 1 –2, with no SAEs occurring.

Based on the above data, it is recommended that for patients with the UGT1A1*28/*6 homozygous mutation, the starting dose of may be reduced by one level (47 mg/m²) in accordance with the HR-IRI-APC study. If no adverse reactions occur during the first cycle, the dose may be increased to the starting dose level in subsequent cycles; If the patient has not undergone genotyping, no initial dose adjustment is made, and haematological toxicity and diarrhoea incidence should be monitored during the study.

4. Adbelimab

4.1. Adbelimab Overview

Adebelimab is a humanised anti-PD-L1 monoclonal antibody independently developed by Hengrui Medicine. It specifically binds to the PD-L1 molecule to block the PD-1/PD-L1 pathway, reactivating the immune system's anti-tumour activity to achieve the therapeutic effect. Similar products such as Atezolizumab (trade name: Tecentriq), Avelumab (trade name: Bavencio), and Durvalumab (trade name: Imfinzi) have been approved for marketing in the United States. In January 2022, the drug marketing authorisation application for Adbelimab in combination with chemotherapy as first-line treatment for extensive-stage small cell lung cancer was accepted by the National Medical Products Administration (NMPA). Multiple clinical studies of Adbelimab injection are currently underway to evaluate its antitumour activity in various solid tumours. On 14 May 2022, the results of the Phase III clinical study of Adbelimab for the treatment of extensive-stage small cell lung cancer were formally published in full online in the internationally authoritative academic journal The Lancet Oncology, with the study results setting a new record for overall survival in first-line immunotherapy for extensive-stage small cell lung cancer.

4.2. Clinical Research Progress of Adbelimab

·SHR-1316-I-101 Study:

The efficacy data from the Chinese Phase I study (SHR-1316-I-101) showed that among the 41 enrolled subjects, 37 underwent at least one post-baseline imaging assessment, with 10 achieving partial response (PR), including 5 cases of nasopharyngeal carcinoma/nasopharyngeal malignant tumours, 1 each of neuroblastoma, melanoma, small cell lung cancer, non-small cell lung cancer, and primary unknown metastatic squamous cell carcinoma, 14 achieved stable disease (SD), and 13 experienced disease progression (PD). The objective response rate (ORR) was 24.4%, and the disease control rate (DCR) was 58.5%.

·CAPSTONE-1 Study:

The CAPSTONE-1 study is a national, multicentre Phase III clinical trial aimed at evaluating the safety and efficacy of advelumab in combination with chemotherapy as first-line treatment for extensive-stage small cell lung cancer. The primary endpoint is overall survival (OS), with secondary endpoints including progression-free survival (PFS), objective response rate (ORR), duration of response (DoR), disease control rate (DCR), and safety. The study lasted 21 months and enrolled 462 patients, with 230 receiving advelumab in combination with chemotherapy and 232 receiving placebo in combination with chemotherapy. The results showed that Adbelimab combined with chemotherapy as first-line treatment for extensive-stage small cell lung cancer achieved a median overall survival (OS) of 15.3 months (vs. 12.8 months for chemotherapy), a 2-year survival rate of 31.3% (vs. 17.2% for chemotherapy), and a median progression-free survival (PFS) of 5.8 months, significantly reducing the risk of disease progression by 33% compared to the chemotherapy group. In the trial, the safety profile of Adveliomab in combination with chemotherapy was consistent with previous similar clinical trials, and the incidence of Grade 3 treatment-related adverse events was comparable to that of the placebo plus chemotherapy control group. ≥

三、 Study Objective

To evaluate the efficacy and safety of irinotecan liposome, 5-fluorouracil/calcium folinate, oxaliplatin, and adebelimab in combination with radiotherapy for resectable or borderline resectable pancreatic cancer with high-risk factors.

1. Primary objective: The primary endpoint is the R0 resection rate in patients with resectable or borderline resectable pancreatic cancer with high-risk factors treated with irinotecan liposome, 5-fluorouracil/calcium folinate, oxaliplatin, and adebelimab combined with radiotherapy, defined as the proportion of participants assessed as having achieved R0 resection postoperatively.

2. Secondary objectives:

- PCR, defined as the absence of residual tumour cells in the primary tumour or sampled lymph nodes following surgery after neoadjuvant therapy.

- EFS, defined as the time from randomisation to the first occurrence of tumour progression rendering surgery impossible, postoperative recurrence/metastasis, or death, whichever occurs first;

- OS, defined as the time from the start of treatment to death from any cause;

- ORR, as assessed by the investigator according to RECIST v1.1 criteria, defined as the proportion of participants with the best overall response of CR or PR. If the response is CR or PR, participants must undergo a follow-up evaluation 4 weeks after the initial assessment;

- Safety endpoints: adverse events (AE)/serious adverse events (SAE) (assessed according to NCI-CTCAE 5.0 criteria), etc.

四 、 Study design type, principles, and trial procedures

1. Study Design

This study is a prospective, single-arm, exploratory study aimed at evaluating the efficacy and safety of irinotecan liposome, 5-fluorouracil/calcium folinate, oxaliplatin, and adebelimab in combination with radiotherapy for resectable or borderline resectable pancreatic cancer with high-risk factors, with a planned enrolment of 37 patients.

After screening and meeting the inclusion and exclusion criteria, patients who signed informed consent will receive neoadjuvant therapy with irinotecan liposome, 5-fluorouracil/calcium folinate, oxaliplatin, and adebelimab (every 2 weeks, with 2 weeks as one cycle) for a total of 4 cycles of preoperative chemotherapy combined with immunotherapy, concurrently with 5 sessions of short-course radiotherapy:

- Patients assessed as eligible for curative surgery via abdominal contrast-enhanced CT/MRI undergo surgery within 10－20 days after completion of neoadjuvant therapy. An abdominal contrast-enhanced CT/MRI is performed 4 － 6 weeks post-surgery, and the adjuvant therapy regimen is determined by the investigator;

- For patients assessed by abdominal contrast-enhanced CT/MRI as ineligible for curative surgical resection, the investigator may select a subsequent treatment regimen based on their judgment, and patients will continue to be followed up until disease progression, inability to tolerate toxic side effects, or withdrawal of informed consent.

Safety visits: After enrolment, safety visits will be conducted on Day 1 of each treatment cycle prior to surgery, prior to surgery, on Day 1 of each treatment cycle post-surgery, and at the end of treatment. Safety visits will be conducted every 12 weeks post-treatment (including blood counts and

liver/kidney function tests). Survival follow-up will be conducted every 3 months.

Imaging assessment: All lesions will be recorded and assessed according to RECIST v1.1. Unless otherwise specified, the permissible window period for imaging examinations is ± 7 days. During the study period, unscheduled imaging examinations may be conducted when tumour recurrence or metastasis is suspected.

Screening period: Imaging studies of the chest, abdomen, and pelvis are required. The abdomen and pelvis must undergo contrast-enhanced MRI/CT scans (slice thickness ≤ 5mm), and the chest must undergo CT scans (slice thickness ≤ 5mm). Patients suspected of having brain metastases must also undergo contrast-enhanced MRI/CT of the head to rule out brain metastases. When bone metastasis is confirmed or clinically suspected, bone scan examinations are required to rule out bone metastasis. Assessment of tumour baseline must be conducted within 2 weeks prior to randomisation. If the investigator determines that imaging examinations can represent the subject's baseline status, the baseline imaging examinations may be extended to within 4 weeks prior to enrolment;

Neoadjuvant therapy: After completing 4 cycles of preoperative neoadjuvant chemotherapy + short-course radiotherapy, an abdominal (enhanced MRI/enhanced CT) examination is performed. If metastasis to other sites is suspected, additional imaging examinations of those sites are required, preferably under the same conditions as the screening period, including scanning method, slice thickness, and contrast agent use;

Postoperative: Within 4 – 6 weeks post-surgery, perform abdominal imaging (enhanced MRI/enhanced CT). If metastasis to other sites is suspected, additional imaging studies of those sites should be conducted;

Tumour recurrence follow-up: Imaging examinations should be conducted every 12 weeks after the start of adjuvant therapy. Abdominal imaging (enhanced MRI/enhanced CT) should be performed, and if metastasis to other sites is suspected, additional imaging examinations of those

sites should be conducted. Imaging assessments should continue until imaging progression or recurrence, receipt of other anticancer treatments, withdrawal of informed consent, loss to follow-up, or death.

2. Study procedures

This study is a prospective, single-arm, exploratory trial designed to evaluate the efficacy and safety of irinotecan liposome, 5-fluorouracil/calcium folinate, oxaliplatin, and adebelimab in combination with radiotherapy for resectable or borderline resectable pancreatic cancer with high-risk factors, with a planned enrolment of 37 patients.

After screening, eligible patients who signed informed consent will receive neoadjuvant therapy with irinotecan liposome, 5-fluorouracil/calcium folinate, oxaliplatin, and adebelimab (2 weeks per cycle) for a total of 4 cycles of preoperative chemotherapy combined with immunotherapy, concurrently with 5 sessions of short-course radiotherapy:

Patients assessed by abdominal contrast-enhanced CT/MRI as eligible for curative surgery will undergo surgery within 10 –20 days after the completion of neoadjuvant therapy. An abdominal contrast-enhanced CT/MRI will be performed 4 –6 weeks post-surgery, and the adjuvant therapy regimen will be determined by the investigator.

Patients assessed by abdominal contrast-enhanced CT/MRI as ineligible for curative surgical resection may select subsequent treatment regimens based on the investigator's judgment and continue follow-up until disease progression, intolerance to toxic side effects, or withdrawal of informed consent.

Safety visits: After enrolment, safety visits will be conducted on Day 1 of each treatment cycle prior to surgery, prior to surgery, on Day 1 of each

treatment cycle post-surgery, and at the end of treatment. Safety visits will be conducted every 12 weeks post-treatment (including complete blood count and liver/kidney function tests). Survival follow-up will be conducted every 3 months.

Imaging assessment: All lesions will be recorded and assessed according to RECIST v1.1. Unless otherwise specified, the permissible window period for imaging examinations is ± 7 days. During the study period, unscheduled imaging examinations may be conducted when tumour recurrence or metastasis is suspected.

Screening period: Imaging studies of the chest, abdomen, and pelvis are required. The abdomen and pelvis must undergo contrast-enhanced MRI/CT scans (slice thickness ≤ 5mm), and the chest must undergo CT scans (slice thickness ≤ 5mm). Patients suspected of having brain metastases must also undergo contrast-enhanced MRI/CT of the head to rule out brain metastases. When bone metastasis is confirmed or clinically suspected, bone scan examinations are required to rule out bone metastasis. Assessment of tumour baseline must be conducted within 2 weeks prior to randomisation. If the investigator determines that imaging examinations can represent the subject's baseline status, the baseline imaging examinations may be extended to within 4 weeks prior to enrolment;

Neoadjuvant therapy: After completing 4 cycles of preoperative neoadjuvant chemotherapy + short-course radiotherapy, an abdominal (enhanced MRI/enhanced CT) examination is performed. If metastasis to other sites is suspected, additional imaging examinations of those sites are required, preferably under the same conditions as the screening period, including scanning method, slice thickness, and contrast agent use;

Postoperative: Within 4 – 6 weeks post-surgery, perform abdominal imaging (enhanced MRI/enhanced CT). If metastasis to other sites is suspected, additional imaging studies of those sites should be conducted;

Tumour recurrence follow-up: Imaging examinations should be conducted every 12 weeks after the start of adjuvant therapy. Abdominal

(enhanced MRI/enhanced CT) examinations should be performed, and if metastasis to other sites is suspected, additional imaging examinations of those sites should be conducted. Imaging assessments should continue until imaging progression or recurrence, receipt of other anticancer treatments, withdrawal of informed consent, loss to follow-up, or death.

五、 Case selection

The study population for this research consists of pancreatic cancer patients with high-risk factors or those with tumours that are marginally resectable. Eligible participants are a crucial guarantee for achieving the objectives of this clinical trial. Participants must meet the following criteria to be eligible for inclusion in this trial. All medical or non-medical conditions of each participant are considered when determining eligibility for the trial.

Before a subject is enrolled in the study, the investigator or their team members should review, confirm, and document whether the subject is suitable for participation in the study.

1. Inclusion criteria:

Patients must meet the following criteria to be eligible for inclusion in this study:

1) Age 18 – 75 years, no gender restriction;

2) Histologically or cytologically confirmed pancreatic cancer (originating from pancreatic ductal epithelium) as assessed by an MDT, with clinical records indicating resectable or borderline resectable pancreatic cancer accompanied by high-risk factors. (According to the 2022 edition of the CSCO guidelines, borderline resectable pancreatic cancer is defined as: ① Tumour contact with the portal vein-superior mesenteric vein >180°, or contact with≤ 180°, combined with irregular venous contours or venous thrombosis, but can be completely resected and safely reconstructed; tumour contact with the inferior vena cava; ② (Pancreatic head/uncinate process tumours) Tumour contacts the common hepatic

artery but does not involve the celiac trunk or the origin of the left or right hepatic arteries, allowing for complete resection and safe reconstruction; tumour contacts the superior mesenteric artery ≤ 180 ° ; tumour contacts variant arteries (e.g., accessory right hepatic artery, substitute right hepatic artery, substitute common hepatic artery, etc.). (Pancreatic body/tail tumours) Tumour contacts the superior mesenteric artery ≤ 180 ° ; tumour contacts the celiac trunk ≤ 180 ° .) (According to the CSCO Guidelines 2022 edition, high-risk factors include "very high CA19-9 levels, a large primary tumour, extensive regional lymph node metastasis, severe weight loss, and extreme pain." In this study, high-risk factors are defined as "CA19-9 > 200 U/mL, tumour diameter > 2 cm, and N1 or higher.")

3) At least one measurable lesion as the target lesion (according to RECIST v1.1 criteria);

4) No prior anticancer therapy (including radiotherapy, ablation, chemotherapy, targeted therapy, immunotherapy, etc.) or investigational drug therapy;

5) ECOG performance status: 0 – 1;

6) Expected survival period (≥) of less than 3 months;

7) Good major organ function, i.e., meeting the following criteria (without receiving any blood components or growth factors within 14 days prior to randomisation):

(1) Neutrophils≥ 1.5 × 10^9 /L; platelets≥ 80 × 10^9 /L; haemoglobin≥ 9 g/dl; serum albumin≥ 3 g/dl;

(2) Total bilirubin ≤ 1.5 times the upper limit of normal (biliary obstruction allows for biliary drainage); ALT and AST ≤ 3 times the upper limit of normal (for patients with liver metastases, this may be relaxed to≤ 5 times the upper limit of normal);

(3) Serum creatinine≤ : 1.5 times the upper limit of normal; creatinine clearance≥ : 60 ml/min;

(4) INR ≤ 1.5 times the upper limit of normal and APTT ≤ 1.5 times the upper limit of normal (for patients receiving stable doses of anticoagulant therapy such as low-molecular-weight heparin or warfarin, and with INR within the expected therapeutic range of the anticoagulant, screening may be performed);

(5) Electrocardiogram: QTcF≤ 450 ms (male), ≤ 470 ms (female);

(6) Echocardiogram: LVEF (left ventricular ejection fraction)≥ 50%;

(8) Reproductive-age women must undergo a blood pregnancy test within 3 days prior to randomisation, with a negative result, and agree to use appropriate contraceptive methods during the trial and for 6 months post-treatment. For men, this should involve surgical sterilisation or agreement to use appropriate contraceptive methods during the study and for 3 months post-treatment;

9) Participants voluntarily join this study and sign an informed consent form.

2. Exclusion criteria:

If the patient has any of the following conditions, they are ineligible for inclusion in this study:

1) Pancreatic cancer originating from non-pancreatic ductal epithelium, including pancreatic neuroendocrine cancer, pancreatic acinar cell carcinoma, pancreatic blastoma, and solid-pseudopapillary tumours;

2) Patients with known central nervous system metastases;

3) Severe gastrointestinal dysfunction (bleeding, obstruction; inflammation greater than grade 2; diarrhoea greater than grade 1);

4) Patients with third-space effusions (e.g., massive pleural effusion) that cannot be stabilised (i.e., no intervention required after removal of the

drainage tube) within the two weeks prior to randomisation, excluding ascites;

5) Patients with clinically symptomatic ascites requiring paracentesis or drainage, or those who have undergone ascites drainage within the past 3 months (excluding those with only imaging-detected minimal ascites that is controllable and asymptomatic);

6) Known interstitial lung disease, except for interstitial changes visible only on imaging studies;

7) Known peripheral neuropathy (CTCAE≥ Grade 3);

8) Known dihydrofolate reductase deficiency (low activity) or absence;

9) Severe infection (CTCAE > Grade 2) within 4 weeks prior to enrolment, such as severe pneumonia requiring hospitalisation, bacteraemia, or infection-related complications; symptoms or signs of infection requiring intravenous antibiotic treatment within 2 weeks prior to randomisation (excluding prophylactic antibiotic use);

10) Received any of the following treatments:

· Concomitant medications containing strong inhibitors/inducers of CYP3A4, CYP2C8, or strong inhibitors of UGT1A1 within 2 weeks prior to enrolment;

· Received radiation therapy within 2 weeks prior to enrolment;

· Undergone major surgery (e.g., thoracotomy, laparotomy, etc.) within 4 weeks prior to enrolment;

· Received treatment with any other investigational drugs within 4 weeks prior to enrolment, unless it was an observational (non-interventional) clinical study or follow-up for an interventional clinical study.

11) Abnormal coagulation function, bleeding tendency, or currently receiving thrombolytic or anticoagulant therapy. Prophylactic use of

low-dose aspirin (≤ e 100 mg/day) or low-molecular-weight heparin (enoxaparin 40 mg/day or equivalent doses of other low-molecular-weight heparins) is permitted;

12) Uncontrolled cardiac symptoms or diseases, such as: (1) NYHA class 2 or higher heart failure; (2) unstable angina; (3) myocardial infarction within the past 6 months; (4) clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention;

13) History of malignant tumours other than pancreatic cancer within the past 5 years prior to enrolment, excluding adequately treated cervical carcinoma in situ, basal cell carcinoma, or squamous cell carcinoma of the skin;

14) Known allergy to irinotecan liposome, other liposome products, oxaliplatin, 5-FU, calcium folinate, adebepilumab, or any component of the aforementioned products;

15) Known cases of acquired immunodeficiency syndrome (AIDS) or HIV-positive individuals, or active syphilis infection;

16) History of clear neurological or psychiatric disorders, including epilepsy or dementia;

17) Participants deemed by the investigator to have other factors that may necessitate premature termination of the study, such as non-compliance with the protocol, presence of other severe illnesses (including mental disorders) requiring concomitant treatment, clinically significant abnormalities in laboratory test results, or family or social factors that may affect participant safety or data collection.

3. Exclusion criteria

Reasons for a subject withdrawing from the study may include:

1) The subject withdraws informed consent and refuses further follow-up;

2) Loss to follow-up;

3) Death of the subject;

4) The sponsor terminated the study.

4. Study termination criteria

The termination criteria for this study include but are not limited to:

1) Identification of unexpected, significant, or unacceptable risks to patients;

2) Major deviations from the protocol are identified during the conduct of the trial;

3) The investigational drug/treatment is ineffective, or continuing the trial is deemed meaningless;

4) The sponsor decides to terminate the study due to reasons such as severe delays in patient enrolment or frequent protocol deviations.

六、 Study Methods and Technical Approach

Neoadjuvant Chemotherapy and Immunotherapy

1) Oxaliplatin for injection: dose of 85 mg/m², intravenous infusion over 2 hours or according to the clinical practice of the research centre;

2) Liposomal irinotecan: dose of 56.5 mg/m², administered as a 90-minute intravenous infusion (± 30 minutes);

3) Calcium folinate: dose of 200 mg/m², completed via intravenous infusion over 30 minutes or according to the clinical practice of the research centre;

4)5-Fluorouracil:Dose of 2000 mg/m²,administered as an intravenous infusion over 46=48 hours or according totheclinical practice of the research centre;

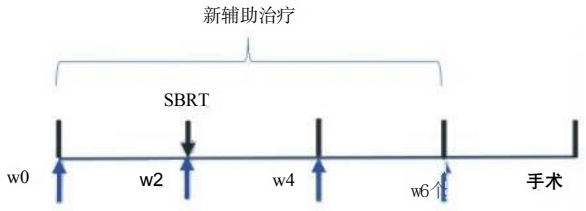
5)Adalimumab:1200 mg,administered as an intravenous infusion over 30-60 minutes on Day 1,every 4 weeks;

Each treatment cycle lasts 14 days,with a total of 4 cycles.All medications are administered on Day 1.If the patient is known to be a homozygous carrier of the UGT1A1*28/*6 mutation,the starting dose of irinotecan liposome is reduced by one level (47 mg/m²).If no adverse reactions occur during the fist cycle,the dose isincreased to the starting dose level for subsequent cycles f the patient has not undergone genotyping,no initial dose adjustment is made,and haematological toxicity and diarhoea incidence should be monitored during the study.The above chemotherapy doses are recommended doses;investigators may determine the initial dose based on the patient's tolerance.

Concurrent short-course radiotherapy:

Stereotactic body radiation therapy (SBRT)is used,targeting only the primary tumour and metastatic lymph nodes,without prophylactic iradiation of adjacent lymph nodes.The total dose is 25 Gy,administered as 5 Gy/fraction over 5 fractions.

The specific treatment process is as follows:



七、 Observation items

1. Primary efficacy endpoints

- R0 resection rate, defined as the proportion of participants assessed as having achieved R0 resection postoperatively.

2. Secondary efficacy endpoints

- OS, defined as the time from the start of treatment to death from any cause;

- EFS, defined as the time from randomisation to the first occurrence of tumour progression rendering surgery impossible, postoperative recurrence/metastasis, or death;

- Objective response rate (ORR) assessed by investigators according to RECIST v1.1 criteria, defined as the proportion of participants with the best overall response of complete response (CR) or partial response (PR). If a response of CR or PR is achieved, participants must undergo a follow-up evaluation 4 weeks after the initial assessment to confirm the response;

- PCR, defined as the absence of residual tumour cells in the resected primary tumour or sampled lymph nodes following neoadjuvant therapy;

- Safety endpoints: adverse events (AE)/serious adverse events (SAE) (assessed according to NCI-CTCAE 5.0 criteria), etc.

八、 Efficacy evaluation criteria

1. Efficacy Evaluation

Efficacy endpoints include R0 resection rate (primary endpoint), EFS, OS, ORR, and pCR rate.

2. Efficacy Evaluation Methods

This study uses RECIST 1.1 to evaluate tumour response/progression in participants; postoperative pathological specimens are used to assess R0 resection rate and pCR rate, with evaluation criteria detailed in Appendix 1.

3. Safety Evaluation

3.1. Surgical Safety

This includes assessing the incidence and severity of postoperative complications based on the Clavien-Dindo grading system, as well as summarising and analysing the surgical duration and hospitalisation duration of participants in the experimental and control groups.

3.2. Adverse Events

The severity of adverse events was assessed according to the CTCAE v5.0 criteria. During the trial, adverse event reports should be completed truthfully, including the type of adverse event, incidence rate, onset and resolution times, severity, relationship to the study drug, duration, measures taken, and outcome.

3.3. Other Safety Indicators

Blood, urine, and stool samples will be collected according to the trial flowchart and analysed in local laboratories. Physical examinations include height (only at baseline), head and face, skin system, lymph nodes, eyes, ears, nose, and throat, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, nervous system, and mental status. Vital signs include temperature, blood pressure, pulse, and respiratory rate (all measured after 5 minutes of rest).

ECOG performance status.

九、 Observation of adverse events.

1. Adverse events (AE)

Adverse events (AEs) refer to adverse medical events that occur in patients after receiving a medication, but they are not necessarily causally related to the treatment. AEs can include any unfavourable, unexpected symptoms, signs, laboratory test abnormalities, or diseases, and at least include the following situations:

- Pre-existing medical conditions/diseases that worsened after the start of the study drug (including worsening of symptoms, signs, or laboratory test abnormalities) are recorded as AEs;
- Any new adverse event: any new adverse medical condition (including symptoms, signs, or newly diagnosed diseases);
- Abnormal laboratory test results with clinical significance.

Diagnostic or therapeutic invasive procedures (e.g., surgery) or non-invasive procedures should not be reported as AEs; however, if the underlying disease condition leading to such procedures meets the definition of an AE, it should be reported. For example, acute appendicitis occurring during the AE reporting period should be reported as an AE, while the appendectomy performed as a result should be recorded as the treatment method for that AE.

Researchers should document any AEs experienced by patients in detail, including: AE name, onset and resolution times, severity (grading according to the 5.0 version of the NCI CTCAE), AE-drug relationship, duration, measures taken regarding the study drug due to the AE, outcome, and whether it was a serious adverse event. All AEs occurring from the start of study drug administration until the end of the safety follow-up period should be recorded.

1.1. Criteria for assessing the severity of adverse events ( )

Refer to the NCI-CTCAE Version 5.0 grading criteria for drug-related adverse events. If an AE not listed in the NCI-CTCAE Version 5.0 table occurs, the following criteria may be used:

Grade	Clinical Description of Severity
1	Mild; no clinical symptoms or only mild clinical symptoms; only clinical or laboratory abnormalities; no treatment required;
2	Moderate; requires minor, local, or non-invasive treatment; age-appropriate activities of daily living (ADL) with the use of assistive devices are limited; ADL refers to activities such as cooking, shopping, making phone calls, and counting money;
3	Severe condition or medically significant symptoms but not currently life-threatening; leading to hospitalisation or prolonged hospital stay; resulting in disability; limitations in self-care ADL. Self-care ADL includes bathing, dressing, undressing, eating, using the toilet, taking medication, etc., but not bedridden;
4	Life-threatening; Requiring emergency treatment;
5	Death related to the adverse event (AE);

Note the distinction between the severity and seriousness of adverse events. For example, "severe headache" may be classified as severe in terms of severity, but it cannot be listed as a serious adverse event (SAE) unless it meets the criteria for an SAE.

1.2. Assessment of the Relationship Between AEs and the Study Drug

Investigators should comprehensively assess the relationship between AEs and the study drug, such as whether the occurrence of AEs has a reasonable temporal sequence with drug administration, the characteristics of the study drug, the toxicological and pharmacological effects of the study drug, whether the patient is using other concomitant medications, the patient's underlying medical conditions, medical history, family history, and de-challenge and re-challenge reactions, among other factors. The relationship between adverse events and the study drug should be assessed using a five-tier classification system: "definitely related," "possibly related," "possibly unrelated," "definitely unrelated," and "unable to determine."

The criteria for assessment can be referenced in the table below:

Association Evaluation	Temporal Relationship	Known	De-sensitisation	Re-excitation	Other explanations
Definitely related	+	+	+	+	-
Possibly related	+	±	±?	?	±?
Possibly unrelated	±?	-	±?	?	±?
Definitely unrelated	—	—	—	—	+

Unable to evaluate	The necessary information for evaluation is unavailable

1. + indicates positive or affirmative; – indicates negative or unfavourable; ± indicates difficult to determine; ? indicates unknown.

2. Time-relatedness: Whether there is a reasonable time relationship between the administration of the drug and the occurrence of the adverse reaction.

3. Known: Whether the adverse reaction aligns with the known adverse reaction types associated with the medication.

4. De-sensitisation: Does the adverse reaction disappear or improve after discontinuing or reducing the medication?

5. Re-exposure: Does the same adverse reaction reoccur upon re-administration of the suspected medication?

6. Other explanations: Can the adverse reaction be explained by the effects of concomitant medications, progression of the patient's condition, or the influence of other treatments?

1.3. Adverse Drug Reactions (ADRs)

Adverse drug reactions (ADRs): These refer to harmful reactions unrelated to the intended use of a drug that occur when a qualified drug is used in accordance with normal dosage and administration guidelines. When a patient experiences an adverse reaction unrelated to the intended use of the medication, and the possibility of a causal relationship between the reaction and the medication cannot be ruled out, it should be reported in accordance with the "report any suspected reaction" principle. The scope of reporting includes adverse reactions occurring under normal dosage and administration, as well as harmful reactions occurring under off-label use, such as use beyond the indicated indications, excessive dosing, or use in contraindicated conditions, as well as suspected harmful reactions caused by medication quality issues.

If the investigator assesses the relationship between an adverse event (AE) and the investigational drug as "definitely related," "possibly related," or "unable to determine," the AE is considered an adverse reaction to the investigational drug.

2. Serious Adverse Events (SAE)

2.1. Definition of SAE

A serious adverse event (SAE) refers to an adverse event occurring during the study that meets one or more of the following criteria:

- Events resulting in death;
- Life-threatening events (the term "life-threatening" refers to events/reactions that pose a risk of death to the patient at the time of occurrence; it does not refer to events/reactions that may lead to death if they worsen further);
- Requiring hospitalisation or prolongation of existing hospitalisation;
- Events resulting in permanent or severe disability/functional loss;
- Congenital anomalies or birth defects;
- Other important medical events, which are events/reactions that, although not immediately life-threatening, fatal, or requiring hospitalisation, may, according to reasonable medical and scientific judgement, pose a risk to the patient or may require intervention [such as medication or surgery] to prevent the serious consequences listed in the above definitions.

2.2. Hospitalisation

Adverse events resulting in hospitalisation (even if less than 24 hours) or extension of existing hospitalisation in the study should be considered

SAEs.

However, hospitalisation or extension of hospital stay due to the following circumstances does not need to be reported as an SAE:

- Rehabilitation facilities
- Nursing homes
- Routine emergency room admission (less than 24 hours)
- Same-day surgery (e.g., outpatient/same-day/non-bedridden surgery)
- Social reasons (e.g., medical insurance reimbursement)

Hospitalisation or prolonged hospital stay unrelated to an adverse event (AE) is not considered a serious adverse event (SAE). This may include, but is not limited to, the following situations:

- Hospitalisation due to pre-existing conditions without the occurrence of new adverse events or worsening of pre-existing conditions (e.g., for laboratory test abnormalities that have persisted since before the trial);
- Hospitalisation for administrative reasons (e.g., annual routine physical examinations);
- Elective hospitalisation unrelated to adverse events (e.g., elective cosmetic surgery);
- Scheduled treatments or surgeries should be documented in the entire trial protocol and/or the patient's baseline records;
- Hospitalisation solely due to the use of blood products.

2. AE/SAE reporting

2.1. Collection and follow-up of AEs/SAEs

Collection of AE/SAE information begins at the start of the patient's first treatment* and continues until the end of the safety follow-up period. The safety follow-up period is 30 days (± 3 days) after the last use of the study drug or before the subject begins new anticancer treatment. If death occurs during the safety follow-up period, it must be reported as an SAE.

All AEs/SAEs should be followed up until the end of the safety follow-up period or until they resolve, remit to baseline levels or ≤ Grade 1, reach a stable state, or are adequately explained (e.g., loss to follow-up, death).

Investigators should inquire about any AE/SAE that occurred since the previous visit during each visit and promptly provide follow-up information in response to any queries received.

After the safety follow-up period, investigators are not required to actively monitor patients for AEs; however, if any SAEs related to the study drug are identified, they should be reported promptly.

*The date of first treatment is defined as the time when the patient first received treatment with the irinotecan liposome-based combination regimen.

2.2. SAE reporting procedure

If an SAE occurs, whether it is the first report or a follow-up report, the investigator must immediately complete the "Clinical Trial SAE Report Form," sign it, and date it. The investigator must report the SAE to the relevant departments and the drug safety department of the drug manufacturer (hengrui_drug_safety@hengrui.com) within 24 hours of becoming aware of it.

All SAEs should be documented in detail, including symptoms, severity (refer to NCI-CTC 5.0 grading), relationship to the investigational drug, time

of occurrence, time of intervention, measures taken regarding the investigational drug due to the SAE, follow-up time and method, and outcome. If the investigator believes that an SAE is unrelated to the investigational drug but potentially related to study conditions (e.g., discontinuation of prior therapy or concomitant conditions during the trial), this relationship should be detailed in the narrative section of the Clinical Trial SAE Report Form. If the severity of an ongoing SAE or its relationship to the study drug changes, a follow-up report should be submitted immediately. If the investigator believes that previously reported SAE information was misreported, corrections, withdrawals, or downgrades may be made in the follow-up report, and reported in accordance with the SAE reporting procedure.

2.3. Reporting of non-serious adverse reactions and other special circumstances

If the investigator determines that an AE is "definitely related," "possibly related," or "unable to determine" to the investigational drug, the AE is considered an adverse reaction of the investigational drug. Monthly reports of new/updated non-serious ADR information should be submitted to the drug manufacturer's Drug Safety Department (hengrui_drug_safety@hengrui.cnom) in tabular form.

Other special circumstances may not meet the definition of an adverse event but still require collection to comply with regulatory requirements. Special circumstances include but are not limited to: medication errors, drug misuse, occupational exposure, etc.

2.4. Pregnancy Reporting

If a female patient becomes pregnant during the study, the patient should immediately discontinue use of the study drug and withdraw from the study. If the partner of a male patient becomes pregnant during the study, the patient may continue in the study. If pregnancy occurs between the start of study drug use and the end of the safety follow-up period, the investigator must complete the "Clinical Study Pregnancy Report/Follow-up

Form" within 24 hours of learning of the pregnancy event and report it to the relevant department. Within 15 days of learning of the pregnancy event, the investigator must complete the "Clinical Study Pregnancy Report/Follow-up Form" and report it to the Drug Safety Department of the drug manufacturer (hengrui_drug_safety@hengrui.com).

The investigator should follow up on the pregnancy outcome until one month after the mother's delivery and report the results to the relevant departments and the drug manufacturer's drug safety department (hengrui_drug_safety@hengrui.com). If the pregnancy outcome is ectopic pregnancy, spontaneous abortion, foetal intrauterine death, neonatal death, or congenital abnormalities, it is considered a serious adverse event (SAE) and must be reported in accordance with the SAE reporting timelines.

If a patient is pregnant and an SAE occurs during the collection of AE/SAE information, the Clinical Trial SAE Report Form must also be completed, and reporting must be conducted in accordance with the SAE reporting procedures.

2.5. Disease Progression and Death Reporting

Disease progression is defined as a worsening of the patient's condition caused by the study indication. This includes progression based on imaging evidence and progression of clinical symptoms and signs. New metastases from the primary tumour or progression of existing metastases are considered disease progression. Events resulting in life-threatening conditions, requiring hospitalisation or prolonging hospital stay, or leading to permanent or severe disability/functional loss due to symptoms and signs of disease progression should not be reported as SAEs. If there is any uncertainty regarding whether an SAE is caused by disease progression, it should be reported as an SAE.

In the study population of this study, "disease progression" is an expected occurrence and should not be reported as an AE term. When disease progression occurs, events used to confirm disease progression should be reported as AEs. For example, if a patient experiences seizures

determined to be related to brain metastasis, the AE term should be recorded as "seizures," not "disease progression" or "brain metastasis."

During the safety follow-up period, deaths assessed by the investigator as potentially caused by symptoms or signs related to disease progression should be reported as SAEs. However, the term "death" should not be used as an AE or SAE term; instead, it should be recorded as the outcome of the event. Adverse events that cause or contribute to death should be recorded as SAE terms. If the cause of death is unknown and cannot be determined at the time of reporting, the SAE term should be recorded as "death of unknown cause."

2.6. Initiation of other new anticancer treatments

If a subject initiates other anticancer treatments before the end of the safety follow-up period, for non-fatal SAEs, unless suspected to be related to the investigational drug, the reporting deadline is the start of the new anticancer treatment. If death occurs during the safety follow-up period, it must be reported as an SAE regardless of whether the subject received other treatments.

2.7. Abnormal liver function tests

If abnormal AST and/or ALT levels are accompanied by an abnormal increase in total bilirubin levels, and the following conditions (1), (2), and (3) are met without any other identifiable cause, such cases should be reported as important medical events and reported according to the SAE procedure.

· Abnormal ALT or AST

Baseline normal: ALT or AST > 3 × ULN during treatment;

Baseline abnormal: During treatment, ALT or AST > 2- × s of baseline levels, and values > 3- × s of ULN; or values > 8- × s of ULN.

·TBIL abnormalities

Baseline normal: Treatment-period TBIL > 2 × ULN;

Baseline abnormal: Treatment-period TBIL increase >1 × ULN or value >3 × ULN.

- No haemolysis, and alkaline phosphatase <2, × ULN (or information not available)

If a patient experiences abnormal AST and/or ALT levels concurrent with an abnormal increase in total bilirubin levels during the safety follow-up period, it is recommended that the patient return to the research centre for evaluation and confirmation as soon as possible (preferably within 48 hours) after the abnormal results are known.

十、 Quality control and quality assurance of the study

Statistical Analysis Study Flowchart

Project/Assessment Time (Window Period)	Screening period		Preoperative neoadjuvant therapy period	Surgical Treatment Period		Postoperative adjuvant therapy period	Post-treatment follow-up visit [33]	Follow-up period	
	Within 4 weeks prior to randomisation	Within 10 days prior to randomisation	Cycles 1–4 [32]	Within 1–2 weeks after the last dose of neoadjuvant therapy		Cycles 1–n (Cycle 1 begins 4–6 weeks post-surgery)		Safety follow-up period [34]	Tumour progression/recurrence and survival follow-up [35]
			CnD1 (± 3d)	Preoperative	Surgery (±3 days)	CnD1 (± 3d)	(±7 days)		
Baseline data									
Sign informed consent [1]	√								
Inclusion and exclusion criteria	√	√							
Demographic characteristics	√								
Tumour history [2]	√								
Other medical history [3]	√								
Laboratory Tests, Clinical Examinations/Assessments									

Project/Assessment Time (Window Period)	Screening period		Preoperative neoadjuvant therapy period	Surgical Treatment Period		Postoperative adjuvant therapy period	Post-treatment follow-up visit [33]	Follow-up period	
	Within 4 weeks prior to randomisation	Within 10 days prior to randomisation	Cycles 1–4 [32]	Within 1–2 weeks after the last dose of neoadjuvant therapy		Cycles 1–n (Cycle 1 begins 4–6 weeks post-surgery)		Safety follow-up period [34]	Tumour progression/recurrence and survival follow-up [35]
			CnD1 (± 3d)	Preoperative	Surgery (±3 days)	CnD1 (± 3d)	(±7 days)		
Complete blood count [4]		√	√	√		√	√		
Blood biochemistry [5]		√	√	√		√	√		
Blood amylase [6]		√	Perform as needed						
Urinalysis [7]		√	√	√		√	√		
Fecal occult blood test [8]		√	Perform as needed						
Coagulation function test [9]		√	√	√		√	√		
Thyroid function test [10]	√	√	Perform as needed						
Physical examination [11]		√	√	√		√			
Vital signs [12]		√	√	√		√	√		

Project/Assessment Time (Window Period)	Screening period		Preoperative neoadjuvant therapy period	Surgical Treatment Period		Postoperative adjuvant therapy period		Post-treatment follow-up visit [33]	Follow-up period	
	Within 4 weeks prior to randomisation	Within 10 days prior to randomisation	Cycles 1–4 [32]	Within 1–2 weeks after the last dose of neoadjuvant therapy		Cycles 1–n (Cycle 1 begins 4–6 weeks post-surgery)			Safety follow-up period [34]	Tumour progression/recurrence and survival follow-up [35]
			CnD1 (± 3d)	Preoperative	Surgery (±3 days)	CnD1 (± 3d)		(±7 days)		
12-lead electrocardiogram [13]	√	√	√(Once every two cycles)		√	√(Once every 2 cycles)				
Echocardiogram [14]	√	√	Performed as needed							
Cardiac enzyme panel [15]		√	√			√	√	√		
Blood pressure monitoring [16]		√	√			√	√			
Virological testing [17]		√	Perform as needed							
Pregnancy screening [18]		√	Perform as needed							
ECOG-PS score [19]		√	√	√		√	√	√		
CA19-9 testing [20]	√	√	√	√		√	√	√		

Project/Assessment Time (Window Period)	Screening period		Preoperative neoadjuvant therapy period	Surgical Treatment Period		Postoperative adjuvant therapy period		Post-treatment follow-up visit [33]	Follow-up period	
	Within 4 weeks prior to randomisation	Within 10 days prior to randomisation	Cycles 1–4 [32]	Within 1–2 weeks after the last dose of neoadjuvant therapy		Cycles 1–n (Cycle 1 begins 4–6 weeks post-surgery)			Safety follow-up period [34]	Tumour progression/recurrence and survival follow-up [35]
			CnD1 (± 3d)	Preoperative	Surgery (±3 days)	CnD1 (± 3d)		(±7 days)		
Surgical safety [21]					√					
Adverse events [22]			√	√	√	√	√	√	√	
Concomitant medication/adjuvant therapy [23]			√	√	√	√	√	√	√	
Study drug										
Irinotecan liposome [24]			√			√	√			
Oxaliplatin [25]			√			√	√			
LV [26]			√			√	√			
5-FU [27]			√			√	√			
Adelbelimab [28]			√			√	√			
Efficacy assessment										
Imaging studies [29]	√			√		√	Imaging studies every 12 weeks			
Pathological					√					

Project/Assessment Time (Window Period)	Screening period		Preoperative neoadjuvant therapy period	Surgical Treatment Period		Postoperative adjuvant therapy period		Post-treatment follow-up visit [33]	Follow-up period	
	Within 4 weeks prior to randomisation	Within 10 days prior to randomisation	Cycles 1–4 [32]	Within 1–2 weeks after the last dose of neoadjuvant therapy		Cycles 1–n (Cycle 1 begins 4–6 weeks post-surgery)			Safety follow-up period [34]	Tumour progression/recurrence and survival follow-up [35]
			CnD1 (± 3d)	Preoperative	Surgery (±3 days)	CnD1 (± 3d)		(±7 days)		
assessment [30]										
Follow-up after treatment										
Time to disease progression/recurrence										√
Survival information [31]										√
Subsequent anticancer treatment										√

[1]. Signing the informed consent form: Baseline information collection for participants begins after signing the informed consent form, with no more than 28 days allowed between signing and randomisation; if examinations conducted during the window period prior to signing the informed consent form meet the screening criteria, they may also be used as baseline period

; this study allows participants who fail screening prior to randomisation one opportunity for re-screening, which requires re-signing the informed consent form and re-registration to obtain a new participant number;

[2]. Tumour history: This includes past history related to pancreatic cancer, current medical history, initial diagnosis, pathological diagnosis, imaging examination information, treatment history (e.g., surgery, local ablation, radiotherapy), etc.

[3]. Other medical history: including drug allergy history, history of diagnosis and treatment of other diseases, and history of tumours other than pancreatic cancer

[4]. Complete blood count: white blood cells (WBC), neutrophils (NEU), lymphocytes (LYM), red blood cells (RBC), haemoglobin (Hb), and platelets (PLT). Conducted within 10 days prior to randomisation, at neoadjuvant therapy day 1 (CnD1), prior to surgery, at postoperative adjuvant therapy day 1 (CnD1), at the end of treatment, and every 12 weeks during the tumour progression/recurrence follow-up period.

[5]. Blood biochemistry: Total Bilirubin (TBIL), Direct Bilirubin (DBIL), Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (AKP), Gamma-Glutamyl Transferase (γ-GT), Total Protein (TP), Albumin (ALB), Urea/ Blood Urea Nitrogen (BUN), Creatinine (Cr), Endogenous Creatinine Clearance (Ccr), Uric Acid (UA), Fasting Blood Glucose (GLU), Triglycerides (TG), Cholesterol (CHO), Potassium (K), Sodium (Na), Chloride (Cl), Calcium (Ca), Phosphorus (P). Within 10 days prior to randomisation, during neoadjuvant therapy CnD1, prior to surgery, during adjuvant therapy CnD1 post-surgery, at the end of treatment, and every 12 weeks during the tumour progression/recurrence follow-up period. Additionally, TBIL, DBIL, ALT, AST, AKP, γ-GT, TP, ALB, BUN, Cr, and UA should be measured every 12 weeks during the tumour progression/recurrence follow-up period ( ) and the adjuvant therapy follow-up period ( ).

[6]. Serum amylase: Only performed within 10 days prior to randomisation. During treatment, it may be performed at the investigator's discretion. If serum amylase is abnormal and clinically significant, serum lipase should be tested.

[7]. Urinalysis: Urine protein (U-PRO), urine glucose (U-GLU), urine occult blood (BLD), urine red blood cells (U-RBC), urine white blood cells (U-WBC). If two consecutive semi-quantitative tests show protein 2+, a 24-hour urine protein quantification test should be performed; this test should be conducted within 10 days prior to randomisation, at neoadjuvant therapy CnD1, prior to surgery, at postoperative adjuvant therapy CnD1, at the end of treatment, and every 12 weeks during follow-up for tumour progression/recurrence.

[8]. Fecal occult blood: During the screening period, if fecal occult blood is positive, a follow-up test is required. If fecal occult blood remains positive after the follow-up test, a gastroscopy is required. Within 10 days prior to randomisation and during treatment, it may be performed at the investigator's discretion. If fecal occult blood is positive, the investigator must make a judgment, and a gastroscopy may be performed if necessary.

[9]. Coagulation function: International Normalised Ratio (INR), Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT), Fibrinogen (FIB); within 10 days prior to randomisation, at neoadjuvant therapy CnD1, prior to surgery, at adjuvant therapy CnD1 post-surgery, at the end of treatment, and every 12 weeks during the tumour progression/recurrence follow-up period.

[10]. Thyroid function: Serum free triiodothyronine (FT3), free thyroxine (FT4), and serum thyroid-stimulating hormone (TSH); only within 10 days prior to randomisation. Additional tests may be conducted during the study period and at the end of the study if deemed necessary by the investigator.

[11]. Physical examination: Includes height (collected only during the screening period), weight, head and face, skin system, lymph nodes, eyes, ears, nose, and throat, mouth, respiratory system, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, nervous system, and mental status. A comprehensive physical examination is conducted within 10 days prior to randomisation during the screening period and at the end of treatment. During the study period, only weight or physical examinations of abnormal areas are conducted.

[12]. Vital signs: Temperature, pulse, respiratory rate, and blood pressure are measured within 10 days prior to randomisation, on CnD1 of neoadjuvant therapy, prior to surgery, on CnD1 of adjuvant therapy post-surgery, at the end of treatment, and every 12 weeks during the tumour progression/recurrence follow-up period.

[13]. 12-lead electrocardiogram: Within 10 days prior to randomisation, during neoadjuvant therapy (C1D1, C3D1), prior to surgery, during adjuvant therapy (C1D1, C3D1), at the end of treatment, and every 12 weeks during the tumour progression/recurrence follow-up period. If an abnormal electrocardiogram with clinical significance is detected, two additional confirmations must be performed. Additional tests may be added at the investigator's discretion to confirm the diagnosis, such as a 24-hour Holter monitor.

[14]. Echocardiogram: Must include LVEF (%). This test must be supplemented within 2 weeks prior to randomisation and during the study period if there are significant clinically significant ECG abnormalities.

[15]. Cardiac enzyme panel: creatine kinase MB isoenzyme (CK-MB), troponin T (cTnT)/troponin I (cTnI), and lactate dehydrogenase (LDH); Conducted within 10 days prior to randomisation, at neoadjuvant therapy day 1 (CnD1), prior to surgery, at postoperative adjuvant therapy day 1 (CnD1), at the end of treatment, and every 12 weeks during the tumour progression/recurrence follow-up period.

[16]. Blood pressure monitoring: The trial group must undergo blood pressure monitoring during the trial period: Blood pressure monitoring is performed by the patient themselves and recorded in the patient diary card. Specific operational guidelines: prior to each blood pressure measurement, smoking and coffee consumption are prohibited for 30 minutes, and the patient must rest quietly for at least 10 minutes. Measurements are taken in a seated position with the elbow at heart level, and the same side is used for each measurement. During the first two treatment cycles, blood pressure is measured at least three times weekly. If blood pressure is abnormal, daily monitoring is required; if normal, measurements are reduced to at least twice weekly after the second cycle.

It is recommended to follow the 2018 revised edition of the Chinese Hypertension Prevention and Treatment Guidelines (<)> : Measure at least twice, with an interval of 1 ~ 2 minutes. If the difference is ≤ 5 mmHg, take the average of the two measurements; if the difference is> 5 mmHg, measure again and take the average of the three measurements.

[17]. Virological testing: Includes HIV-Ab (screening phase only), HBV, and HCV infection testing. HBV testing requirements: HBV serology (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) must be tested. If HBsAg is positive, further quantitative testing for HBV-DNA is required. HCV testing requirements: HCV-Ab must be tested. If positive, further quantitative testing for HCV-RNA is required. HBsAg-positive patients must undergo HBV-DNA testing preoperatively, prior to TACE, during adjuvant therapy on C1D1 and C4D1 (experimental group), and at the end of treatment. HCV-Ab-positive patients must undergo HCV-RNA testing preoperatively and at the end of treatment. During the study period and at the end of the study, additional virological testing may be conducted if deemed necessary by the investigator.

[18]. Pregnancy testing: Women of childbearing potential must undergo a blood pregnancy test within 72 hours prior to randomisation. Additional tests may be conducted as necessary to rule out pregnancy. During the trial, the investigator may conduct tests as necessary based on the patient's condition, and at the end of the trial.

[19]. ECOG PS score: Within 10 days prior to randomisation, at CnD1 of neoadjuvant therapy, prior to surgery, at CnD1 of adjuvant therapy post-surgery, at the end of treatment, and every 12 weeks during the follow-up period for tumour progression/recurrence.

[20]. CA19-9 testing: Within 28 days prior to randomisation, on day 1 of neoadjuvant therapy, prior to surgery, on day 1 of adjuvant therapy post-surgery, at the end of treatment, and every 12 weeks during the tumour progression/recurrence follow-up period.

[21]. Surgical safety: Postoperative complications in pancreatic cancer surgery should be assessed and graded according to the Clavien-Dindo classification system, and surgical duration and hospital stay should be recorded.

[22]. Adverse events: Adverse events should be recorded from the time of informed consent signing until the end of the safety follow-up period. All AEs/SAEs should be followed up until symptoms resolve, or clinically relevant laboratory values return to baseline and/or ≤ Grade 1, or are reasonably explained (e.g., loss to follow-up, death), or until the event is ultimately confirmed to be unrelated to the study drug or study process at the end of the safety follow-up period. The best possible outcome and clear determination of drug-relatedness should be obtained whenever possible. End of safety follow-up period: 30 (±3) days after the

last use of the study drug.

[23]. Concomitant medications/adjuvant therapies: Collect information on concomitant medications/adjuvant therapies (excluding solvent-based medications and surgical anaesthetics) from 28 days prior to signing the informed consent form until the end of the safety follow-up period: record the drug name, dosage, route of administration, frequency of administration, purpose of administration, and start and end dates. After the safety follow-up period, concomitant medications and concomitant therapies should only be recorded if they are related to the study drug.

[24]. Liposomal irinotecan: dose of 56.5 mg/m^2, intravenous infusion over 90 minutes (+30 minutes), on Day 1, administered once every 2 weeks, with a 2-week cycle, and cumulative use before and after surgery not exceeding one year.

[25]. Oxaliplatin: Dose of 85 mg/m^2, intravenous infusion over 2 hours or as per the clinical practice of the research centre, on Day 1, administered every 2 weeks, with 2 weeks constituting one study cycle, and the cumulative duration of use before and after surgery not exceeding one year.

[26] LV: Dose of 200 mg/m^2, administered as a 30-minute intravenous infusion or according to the clinical practice of the research centre, on Day 1, administered every 2 weeks, with 2 weeks constituting one study cycle, and the cumulative duration of use before and after surgery not exceeding one year.

[27]. 5-FU: Dose of 2000 mg/m^2, administered as an intravenous infusion over 46–48 hours or according to the clinical practice of the research centre, on Day 1, administered once every 2 weeks, with 2 weeks constituting one study cycle, and the cumulative duration of use before and after surgery not exceeding one year.

[28]. Adalimumab: Dose of 1200 mg, administered as an intravenous infusion over 30–60 minutes, on Day 1, every 4 weeks, with a cumulative duration of use before and after surgery not exceeding one year.

[29]. Imaging studies: All lesions are recorded and assessed according to RECIST 1.1. Unless otherwise specified, the allowable window period for imaging studies is ±7 days. During the study period, unscheduled imaging studies may be performed when tumour recurrence or metastasis is suspected.

[30]. Pathological assessment: Postoperative assessment of R0 resection rate, pathological response, and extent of surgical resection.

[31]. After trial treatment termination, survival status and subsequent anticancer treatment information may be collected every 6 months via clinical follow-up or telephone follow-up until the subject dies, is lost to follow-up, the sponsor terminates the study, or other study termination criteria are met (whichever occurs first).

[32]. If the pre-treatment screening examinations planned prior to the first dose administration were completed during the screening period and conducted within 10 days prior to the first dose administration, these examinations may not need to be repeated prior to the first cycle of treatment.

[33]. Treatment completion visit: The treatment completion visit should only begin after permanent discontinuation of the study drug; if the relevant examinations were completed within one week prior to treatment completion, these examinations do not need to be repeated at this visit.

[34]. Safety follow-up: Safety follow-up is required for trial group participants who have completed the final administration of the study drug (permanently discontinued administration of liposomal irinotecan, oxaliplatin, 5-FU/LV, and adebelimab) and completed the treatment completion visit. The safety follow-up period is 30 (±3) days after the last use of the study drug.

[35]. Tumour progression/recurrence and survival follow-up: Tumour progression/recurrence and survival follow-up begins immediately after the treatment completion visit. Participants undergo regular imaging examinations, blood counts, liver and kidney function tests (including TBIL, DBIL, ALT, AST, AKP, γ-GT, TP, ALB, BUN, Cr, UA), and CA19-9 testing every 12 weeks. Survival follow-up is conducted every 3 months (±7 days) for participants.

十一、 Sample Size Calculation

This trial uses irinotecan liposome,5-fluorouracil/calcium folinate,and oxaliplatin with or without adebelimab for resectable or borderline resectable pancreatic cancer with high-risk factors,with the primary efficacy endpoint being the R0 resection rate.Based on the ESPAC-5F study,the direct surgery R0 resection rate was 14%,and the R0 resection rate after neoadjuvant chemotherapy was 23%.Therefore,it is anticipated that this study (neoadjuvant chemoradiotherapy)could increase the R0 resection rate to 34%,with a dropout rate of 10%,necessitating the enrolment of 37 cases.

1.Statistical analysis population

This study will establish the intention-to-treat analysis set(ITT)and safety analysis set (SS) (evaluable set)in accordance with the relevant guidelines of the NMPA and ICH.The entire data analysis process will undergo strict quality control to ensure the authenticity of the assessment data.

(1) Intention-to-treat analysis set(ITT):Includes all participants.(2)Safety analysis set (SS): The SS set will include patients who have received at least one treatment and have at least one post-treatment safety follow-up record.Safety data will be analysed in the SS set,and efficacy data will be analysed in the ITT set.Baseline data will be described for the ITT population.(3)Evaluable Set (ES):Patients who signed the informed consent form,were enrolled in the study,received combination therapy based on irinotecan liposome,and had at least one efficacy assessment.

2.Statistical Analysis Methods

2.1.General Principles of Statistical Analysis

The statistical analysis in this study primarily involves descriptive statistics and exploratory analysis, without pre-specified research hypotheses.

Unless otherwise specified,all hypothesis tests in this study were performed using two-sided tests, with a significance level of $\alpha=0.05$.If the p-value was less than 0.05,the difference being tested was considered statistically significant.All confidence intervals were calculated using a two-sided 95%confidence level.

All data will be analysed using appropriate statistical measures based on data type:for continuous data,means,standard deviations,medians,maximum values,and minimum values will be reported;

for categorical and ordinal data,frequencies,percentages,and/or incidence rates will be reported.

All statistical analyses will be conducted using SAS version 9.4 or higher,in accordance with a pre-specified statistical analysis plan (SAP).The SAP will detail all statisticalanalysis-related specifics, including but not limited to:the generation of statistical analysis-related derived variables,statistical methods for safety/efficacy evaluation,handling of missing data,and the format and content of tables. The SAP will be completed prior to the locking of the study database.

2.2.Primary Efficacy Endpoint Analysis

The analysis of the primary endpoint will be based on the ITT population.

The primary efficacy endpoint of this study is the R0 resection rate,which willbe summarised as the number and percentage of subjects achieving R0 resection.

For the time-to-event secondary efficacy endpoints EFS and OS,the number and percentage of participants who experienced an OS event or were lost to follow-up will be summarised,and the types of events and reasons for loss to follow-up willbe summarised statistically.The median values will be estimated using the Kaplan-Meier method,and the 95%confidence interval for the median OS will be estimated using the Brookmeyer-Crowley method,with survival curves plotted.

For ORR,the number and percentage of participants achieving objective response(best response being CR/PR)will be calculated,and the 95%CI for ORR will be calculated using the Clopper-Pearson method.

2.3.Baseline characteristic analysis

Statistical descriptions were performed for demographic characteristics,medical history, comorbidities,and other baseline characteristic data.Baseline characteristic analysis was conducted using the ITT()population.

3.4.Safety endpoint analysis

The SS set was primarily used,with a focus on descriptive statistical analysis.All adverse events (AEs)were coded using MedDRA and graded according to the NCI CTCAE v5.0 grading system. Adverse event analysis primarily focused on treatment-emergent adverse events (TEAEs),defined as

adverse events occurring on or after the first day of study drug administration.

Laboratory test results,vital signs,electrocardiograms,and other data will be analysed using a conversion table to compare baseline and post-baseline values.

十二、 Ethical Considerations in Clinical Research

The clinical study will adhere to relevant regulations such as the Declaration of Helsinki of the World Medical Association.The clinical study will only be conducted after the trial protocol has been approved by the Ethics Committee prior to the start of the study.Prior to enrollment in this study,the investigator is responsible for fully and comprehensively informing the subject or their representative about the purpose,procedures,and potential risks of the study,and obtaining written informed consent.The subject should be informed of their right to withdraw from the study at any time,and the informed consent form should be retained as part of the clinical study documentation.Personal privacy and data confidentiality of the subjects will be protected throughout the study.

十三、 Study Progress

1.Estimated date of enrollment of the first subject:2024.06.01

2.Expected date of enrollment of the last subject:2025.06.1

3.Expected study completion date:2025.12.01

十四、 References

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Project leader's signature: Date: