Drug clinical research approval No. of State Food and Drug Administration: 2011l01239

Prospective study of nimotuzumab combined with gemcitabine versus placebo plus gemcitabine in the treatment of K-RAS wild type locally advanced or metastatic pancreatic cancer Randomized controlled, double-blind, multicenter clinical trial

Identifiers: NCT02395016

Sponsor: Biotech Pharmaceutical Co., Ltd

Version number: Version 1.1

Version date: 16 June 2014

Protocol title page

Protocol No.	BPL-Nim-PC-1
Research topic	A prospective, randomized, double-blind, multicenter registered clinical trial of nimotuzumab combined with gemcitabine versus placebo plus gemcitabine in the treatment of locally advanced or metastatic pancreatic cancer of K-RAS wild type
Sponsor	Biotech Pharmaceutical Co., Ltd located in the 2 rongjingdong street, Beijing Economic and Technological Development Zone, 100176
Study Drug	Nimotuzumab injection
To increase the indication	Locally advanced or metastatic pancreatic cancer
Version date	16 June 2014
GCP statement	The study was carried out in accordance with the provisions of the declaration of Helsinki and the good practice for quality management of clinical trials of drugs, and the required documents were filed according to the requirements of the state and local food and drug administration.
Confidentiality statement	This document is confidential and contains the property right information of Baitai biopharmaceutical Co., Ltd(Biotechplc.com). and is only used for review or execution trial of this study. Without the approval of Biotech Pharmaceutical Co., Ltd., other personnel and units are prohibited from spreading, copying, publishing or applying.

CATALOG

Abbreviation list

AE	adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
β-HCG	Human chorionic gonadotropin
CBR	Clinical benefit response
CR	Complete remission or response
CTCAE	Common Terminology Criteria for Terminology of adverse events
DCR	Disease control rate
DRQ	Data Re Query
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
Hb	Hemoglobin
HIV	HIV
IgG	Immunoglobulin
mAb	Monoclonal Antibody
mg	Milligram
NCI	National Cancer Institute
Nimotuzumab	Nimotuzumab
NYHA	New York Heart Association
PD	Progression Disease
PFS	Progression Free Survival
PR	Partial remission or response
ORR	Objective remission/response rate
OS	Overall Survival
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse events
SD	Stable disease
SOP	Standard operating procedures
SD	Stable disease
TKI	Tyrosine kinase inhibitors
TTP	Time to disease progression

Summary

Name of study drug	Nimotuzumab injection
Clinical trial topic	A prospective study of nimotuzumab combined with gemcitabine versus placebo plus gemcitabine in the treatment of locally advanced or metastatic pancreatic cancer of wild type K-RAS, Randomized controlled, double-blind, multicenter clinical trial
Purpose of the trial	1. Primary purpose Objective to compare and evaluate the overall survival (OS) of nimotuzumab combined with gemcitabine versus placebo plus gemcitabine in the treatment of locally advanced or metastatic pancreatic cancer of wild type K-RAS 2. Secondary purpose （1） Time to disease progression (TTP), progression free survival (PFS) （2） Objective response rate (ORR),Disease control rate(DCR) （3） Clinical benefit response (CBR) （4） Safety (according to NCI-CTCAE v4.03)
Design	Prospective, randomized, parallel controlled, double-blind, multicenter clinical trial

Inclusion Criteria	1. Age: 18-75 years old; 2. Physical status KPS ≥ 60; 3. Locally advanced pancreatic adenocarcinoma diagnosed by histopathology or cytology who is not suitable for radical radiotherapy or surgery, or recurrent and metastatic pancreatic adenocarcinoma (who should be ≥ 6 months before the last adjuvant chemotherapy); 4. According to RECIST version 1.1 evaluation criteria, who should be at least one measurable and evaluable objective lesion (the longest diameter of target lesion detected by spiral CT is ≥ 10 mm; if there is only lymph node metastasis, the shortest diameter is ≥ 15 mm); 5. The expected survival time was more than 12 weeks; 6. K-RAS in tumor tissue was wild type; 7. Serum AST / ALT ≤ 2.5 times the upper limit of normal value (ULN), with liver metastasis, AST / ALT ≤ 5 times ULN; Total bilirubin ≤ 2 times ULN, if liver metastasis , less than 3 times ULN; Absolute granulocyte count ≥ 1.5×10^9/L ;platelet ≥100×10^9/L; Hemoglobin ≥ 90g / L; Creatinine clearance rate ≥ 60ml / min; 8. They voluntarily participated in the study, signed informed consent forms and had good compliance; 9. The patients of childbearing age and their spouses are willing to take contraceptive measures.

Exclusion criteria	1. Prior to this study, the following treatments were received: a. Anti-tumor chemotherapy and molecular targeted therapy as palliative measures b. The target lesion had received radiotherapy without progression c. Within 4 weeks or participating in other therapeutic / intervention clinical trials 2. Major surgery was performed within 4 weeks; 3. There were brain metastasis or pia mater metastasis; 4. Had a history of other malignancies other than pancreatic cancer (except for the cured cervical carcinoma in situ or skin basal cell carcinoma and other malignant tumors that had been cured for 5 years); 5. Ascites with symptoms and requiring clinical treatment were complicated; 6. Accompanied by other serious diseases, including but not limited to: a. Uncontrollable congestive heart failure (NYHA grade III or IV, see APPENDIX 5), unstable angina pectoris, poorly controlled arrhythmia, uncontrolled moderate or above hypertension (SBP > 160mmHg or DBP > 100mmHg) b. Active infection c. Uncontrolled diabetes d. Mental illness affecting informed consent forms and / or protocol compliance e. HIV infection f. There were serious diseases that other researchers considered unsuitable for this study 7. Allergy to anti EGFR antibody preparations is known.

Evaluating indicator	1. Effectiveness evaluation: OS, TTP, PFS, DR, ORR, DCR and CBR evaluation time point: imaging examination (8,16,24 weeks, etc., once every 8 weeks);For patients with CR or PR, the curative effect should be confirmed after 4 weeks. 2. Safety evaluation: adverse events were evaluated according to NCI-CTC AE v4.03.All patients who had received at least one study drug treatment were included in the safety analysis. All adverse events were recorded and evaluated. Physical examination and ECG, Blood routine, urine routine, blood biochemistry, vital signs were monitored and evaluated regularly.
Number of subjects	A total of 276 cases were planned to be selected and randomly allocated according to the ratio of 1:1. 138 cases in the trial group and 138 cases in the control group.
Case allocation	Competitive enrollment among centers

Administration regimen	Trial group: treated with nimotuzumab combined with gemcitabine; Control group: received placebo (nimotuzumab simulant) combined with gemcitabine. **1**）Nimotuzumab injection / placebo: 400mg / w, intravenous drip, infusion time more than 60 minutes, once a week, until the disease progression or intolerable toxic reaction or the subject asked to withdraw from the trial. **2**）Gemcitabine: 1000mg /m^2, intravenous drip for no less than 30 minutes, continuous use for 3 weeks, rest for 1 week (D1, D8, D15; Q28 days), every 4 weeks as a cycle, until the disease progression or intolerable toxic reaction or the subject asked to withdraw. At the first treatment, nimotuzumab / placebo should be given on the same day as gemcitabine, and then gemcitabine should be given 1 hour after the end of nimotuzumab / placebo infusion. Since then, nimotuzumab / placebo and gemcitabine were treated on the same day in the same order as before. When intolerable chemotherapy toxicity occurs, chemotherapy can be stopped, but nimotuzumab / placebo should be continued; However, when intolerable toxicity of nimotuzumab occurs, the use of nimotuzumab can be stopped, but chemotherapy should be continued. Subjects without other specific anti-tumor treatment was allowed during the overall trial.
Trial schedule	It is expected to complete the enrollment within 24 months.
Statistical methods	SAS 9.2 software was used for statistical analysis.PPS was used to evaluate the efficacy of PPS. The safety index was analyzed by SS data.

1. Research background

According to the World Health Organization statistical bulletin published in 2014, the incidence and mortality of pancreatic cancer in 2012 ranked 12th and 7th respectively in malignant tumors; The standardized incidence of pancreatic cancer in the world population is 4.9/100000 in men and 3.6/100000 in women. Among them[1] which is higher in developed countries and regions than in developing countries and regions. In 2014, the American Cancer Association reported that the incidence and mortality of pancreatic cancer in the United States were increasing, and the 5-year relative survival rate of pancreatic cancer increased from 2% to 6% from 1975 to 2009, which was the cancer with the lowest improvement in survival[1-2].In China, the incidence of pancreatic cancer is also on the rise. The standardized incidence rates of pancreatic cancer in men and women are 4.5/100000 and 2.8/100000 respectively. It is estimated that 65700 new cases and 63700 deaths[1]will occur in 2014. According to the data of China Cancer annual report, the incidence and mortality of pancreatic cancer in China ranked seventh in 2010, reaching 40400 and 57700[[3-4], respectively.

The early diagnosis of pancreatic cancer is very difficult, and the treatment effect is not ideal. The mortality rate is high, and the 5-year survival rate is only 4.1%.Complete tumor resection is the only possible cure for pancreatic cancer, but only 5-15% of patients can perform radical surgery, and the median survival time is less than 12-18 months. The 2-year survival rate is 20-35%, and the 5-year survival rate is 5-10%.At the first visit to doctor, about 25% of patients with pancreatic cancer had locally advanced pancreatic cancer, and the median survival time was 6-9 months. About 60-70% of patients with metastatic pancreatic cancer had a median survival of 3-5 months[5-12].At present, there is a lack of effective drugs and regimens for locally advanced or metastatic pancreatic cancer. Burris et al[13] found that survival time and clinical benefit rate of gemcitabine were better than that of 5-FU, which confirmed the therapeutic status of gemcitabine in advanced pancreatic cancer, but[13] survival time was less than 6 months. After that, a number of phase III trials compared gemcitabine with other cytotoxic drugs compared with gemcitabine monotherapy, and no evidence was found to be superior to gemcitabine monotherapy. Recently, a phase III clinical study showed that albumin paclitaxel combined with gemcitabine significantly prolonged the survival time and long-term survival rate[14-16], that is, the 1-year survival rate was increased by 59% (35% vs. 22%), the 2-year survival rate was

doubled (9% vs. 4%), and the risk of death was reduced by 28%;PFS, ORR and other end points were significantly improved; Based on this result, which was approved by US FDA in September 2013 for albumin paclitaxel combined with gemcitabine for the first-line treatment of adult metastatic pancreatic cancer[17-19];However, according to the National Institute for Health and Clinical Excellence (NICE), the toxicity and side effects of albumin paclitaxel in the treatment of metastatic pancreatic cancer are obvious and can not be fully proved to be better than other treatment drugs. Therefore, it is not included in the national medical insurance reimbursement.

Previous studies have shown that epidermal growth factor (EGF) and its receptor (EGFR) has been involved in the occurrence and development of malignant tumors. It plays an important role in the process. In recent years, substantial progress has been made in the research of EGFR targeted therapy. EGFR inhibitors combined with chemotherapy have the characteristics of high efficiency and low toxicity, which can be used to treat a variety of tumors, EGFR inhibitors can be divided into two categories: one is tyrosine kinase inhibitor (TKI) acting on the intracellular domain of EGFR receptor, including gefitinib (ireasa®), erlotinib (taceva®), etc. The other is monoclonal antibodies (mAbs) acting on the extracellular domain of EGFR receptor, including cetuximab (C225), panitumumab (vectibix®) and nimotuzumab (trade name: taixinsheng®) etc.

It is known that EGFR expression is about 30% - 89% in pancreatic cancer, and it is associated with high invasiveness and poor prognosis of patients. In a double-blind, placebo-controlled phase III trial of patients with advanced or metastatic pancreatic cancer, 569 patients were randomly assigned to receive erlotinib (an EGFR-TKI) combined with gemcitabine or gemcitabine monotherapy[21]. Results: compared with gemcitabine monotherapy group, 569 patients with advanced or metastatic pancreatic cancer were randomly assigned to receive erlotinib (an EGFR-TKI) combined with gemcitabine or gemcitabine monotherapy[21],There were statistically significant improvements in OS (HR = 0.82; P = 0.038) and PFS (HR = 0.77; P = 0.004) in erlotinib group; The median survival time was 6.24 months in the combination group, and 23% in the 1-year survival rate, while 5.91 months and 17% in the single drug group. Adverse reactions such as rash and diarrhea increased in the combined group, but most of them were grade 1 or grade 2.Therefore, erlotinib combined with gemcitabine has been approved by FDA for the first-line treatment of locally advanced

unresectable or metastatic pancreatic cancer. The NCCN guidelines also recommend gemcitabine combined with erlotinib as one of the treatment options for locally advanced or metastatic pancreatic cancer in good physical condition.

Nimotuzumab is a new generation of recombinant humanized monoclonal antibody against EGFR with moderate affinity(10^{-9})。 In 2008, it has been approved by the Ministry of foreign countries for the treatment of nasopharyngeal carcinoma, and has been approved by the Ministry of China and other countries for the treatment of esophageal cancer. In China, clinical trials of nimotuzumab combined with radiotherapy and chemotherapy are being carried out in China. The doses of nimotuzumab from 100mg to 800mg show good safety. In 2013, German scholars reported a randomized, double-blind, controlled phase II clinical trial[22]of gemcitabine combined with nimotuzumab in the treatment of advanced pancreatic cancer compared with gemcitabine combined with placebo[22]. A total of 192 patients were included in the study, with nimotuzumab 400mg /w, with good safety and no severe toxicity. Only 13% of patients had skin toxicity of 1/2 grade. The median survival time (mOS): 8.7 months in the experimental group vs. 6.0 months in the control group (P = 0.21), and the median progression free survival (MPFs): 5.4 months in the experimental group vs. 3.7 months in the control group (P = 0.06), but the 1-year survival rate was 34.4% in the experimental group and 19.5% in the control group (P = 0.034).Further stratified analysis showed that MPFs: 5.5 months in the experimental group vs. 3.2 months in the control group (P = 0.0096) in the patients ≥ 62 years old; mOS: 8.8 months in the experimental group vs. 5.2 months in the control group (P = 0.034).

A non-randomized, open, one arm clinical trial[23]of nimotuzumab combined with gemcitabine in the treatment of patients with unresectable locally advanced or metastatic pancreatic cancer[23]was reported by Chinese scholars. 18 subjects were enrolled in this study. They received nimotuzumab 200mg/w combined with gemcitabine 1000mg / m^2.The results show that, The disease control rate (DCR) was 55.6%, mOS was 9.29 months (3 months-20.43 months), mPFS was 3.71 months, and 1-year survival rate was 38.9%.During the study period, 16 patients (88.8%) had at least one AE, of which 6 patients (33.3%) had grade 3 AE and no grade 4 AE. The most common AE was gastrointestinal reaction (77.8%), followed by myelosuppression (neutropenia 44.4%, thrombocytopenia 11.1%), and grade 1 rash in 11.1% of patients. All toxic reactions were tolerable during the treatment, and no

patient terminated the clinical trial because of AE. It is suggested that nimotuzumab combined with gemcitabine in the treatment of advanced pancreatic cancer is safe and may improve the curative effect. It is worth carrying out randomized large sample clinical trials.

In order to verify whether nimotuzumab is effective in the treatment of advanced pancreatic cancer and expand its indications, with the approval of the national CFDA (approval No.: 2011l01239), Baitai biological Co., Ltd(Biotechplc.com). has entrusted the 81st Hospital of the Chinese people's Liberation Army and the Affiliated Cancer Hospital of Fudan University of Shanghai as the leading units of this clinical study. A double-blind, multicenter, registered clinical trial was conducted to determine the efficacy and safety of nimotuzumab combined with gemcitabine in the treatment of locally advanced or metastatic pancreatic cancer in Chinese with wild-type K-RAS.

2. Research purpose

2.1 Primary purpose

Objective to evaluate and compare the overall survival (OS) of nimotuzumab combined with gemcitabine versus placebo plus gemcitabine in the treatment of K-RAS wild-type locally advanced or metastatic pancreatic cancer.

2.2 Secondary purpose

1) Time to disease progression (TTP), progression free survival (PFS).
2) Objective response rate (ORR), disease control rate (DCR).
3) Clinical benefit response (CBR).
4) Objective to evaluate the safety of nimotuzumab combined with gemcitabine (according to NCI-CTCAE v4.03).

3. Research overall design

In order to observe and evaluate the efficacy of nimotuzumab combined with gemcitabine in the treatment of locally K-RAS wild type. In this study, prospective, randomized, parallel controlled, double-blind, multicenter clinical trial was used to evaluate the efficacy and safety of advanced or metastatic pancreatic cancer.

3.1 Multicenter research

At the same time, a number of national cancer centers were selected for competition.

3.2 Central random

Taking into account the following factors, DAS for IWRS was used to assign random numbers and dispense drugs. Four stratification factors and factor levels were set up.

Tumor locations:

○ Body and tail of pancreas

○ Head of pancreas

Have you had surgery

○ yes

○ no

Have you had biliary obstruction been treated

○ yes

○ no

Have you received adjuvant chemotherapy

○ yes

○ no

3.3 Control drug selection

In this trial, placebo combined with gemcitabine was used as a parallel control drug.

3.4 Blinding method

In this study, a double-blind and single simulation method was used. The package, shape and odor of nimotuzumab simulator were consistent with those of the trial drug (nimotuzumab) to ensure that the subjects and researchers were in a blind state during the trial.

3.5 Sample size

In this study, 276 subjects were enrolled, 138 in the experimental group and 138 in the control group (see the sample size estimation for statistical analysis).

4 Study population

4.1 Inclusion criteria

1. Age: 18-75 years old;
2. Physical status: KPS ≥ 60 score
3. Locally advanced pancreatic adenocarcinoma diagnosed by histopathology or cytology that is not suitable for radical radiotherapy or surgery, or recurrent and metastatic pancreatic adenocarcinoma (it should be more than 6 months before the last adjuvant chemotherapy);
4. According to recist1.1, there was at least one objective lesion that could be measured and evaluated (the longest diameter of the target lesion detected by spiral CT is more than or equal to 10 mm. If only lymph node metastasis occurs, the shortest diameter is required ≥15mm）;
5. The expected survival time was more than 12 weeks;
6. K-Ras in tumor tissue was wild type;
7. Serum AST /ALT ≤ 2.5 times the upper limit of normal value (ULN), and AST / ALT ≤ 5 times ULN in patients with liver metastasis; Total bilirubin ≤ 2 times ULN, total bilirubin ≤ 3 times ULN in patients with liver metastasis; Absolute granulocyte count ≥1.5×10^9/L; Platelet≥100×10^9/L; Hemoglobin ≥ 90g / L; Creatinine clearance rate ≥ 60ml / min;
8. Patients voluntarily participated in the trial, signed informed consent forms and had good compliance;
9. The patients of childbearing age and their spouses are willing to take contraceptive measures.

4.2 Exclusion criteria

1. Prior to this study, the following treatments were received:
    a) Anti-tumor chemotherapy and/or molecularly targeted therapy as a palliative means
    b) The target lesion had been previously treated with radiotherapy without progression
    c) Within 4 weeks or participating in other therapeutic / intervention clinical trials;
2. Major surgery was performed within 4 weeks;
3. There were brain metastasis or pia mater metastasis;
4. Having a history of malignancy other than pancreatic cancer (except for cervical cancer or basal cell carcinoma that has been cured and other malignant tumors that have been cured for more than 5 years);
5. Ascites with symptoms and requiring clinical treatment were complicated;
6. Accompanied by other serious diseases, including but not limited to:
    a) Intractable congestive heart failure (NYHA grade III or IV, see APPENDIX 5), unstable heart failure, angina pectoris, poorly controlled arrhythmia, uncontrolled moderate or above hypertension (SBP > 160mmHg or DBP > 100mmHg),
    b) Active infection.
    c) Uncontrolled diabetes
    d) Mental illness affecting informed consent and / or protocol compliance
    e) HIV infection
    f) Other researchers think who is not suitable to participate in the experiment.
7. Allergy to anti-EGFR antibody preparations is known.

4.3 Exit criteria

4.3.1 Withdraw from research

1) Subjects can withdraw from the study at any time without any reason;
2) If the subjects withdraw from the study ahead of time, the final visit should be conducted according to the study schedule.

4.3.2 Treatment of withdrawal from study medication

In any of the following situations, the subject must withdraw from the study, but should continue to receive follow-up:

1) In case of clinically related events that seriously affect the safety of the subjects, the researcher or the sponsor considers it necessary to terminate the treatment;
2) Imaging examination was used to judge the disease progression;
3) Pregnancy occurred during treatment;
4) If it is necessary to use the drug without permission, the researchers of each center shall discuss with the main researchers to decide whether the subjects need to withdraw from the study;
5) The subjects were lack of compliance and seriously violated the protocol.

4.4 Termination criteria

In case of any of the following circumstances, the study may be terminated in advance after negotiation between the sponsor and the research center:

1) New information leads to adverse risk- benefit judgment of the study drug, such as:

a) Evidence of ineffective study treatment
b) Obtain evidence of any significant but previously unknown adverse reactions or unexpected increase in the degree or incidence of known adverse reactions, or other adverse safety.

2) The sponsor and the research center believe that the study can not be continued regardless of medical or ethical factors;
3) The subjects were slow to complete the study in an acceptable time;
4) The trial drug was withdrawn from the marketing for safety reasons.

5 Study drug and administration plan

5.1 Research drug

Nimotuzumab injection, produced by Biotech Pharmaceutical Co., Ltd., is a colorless and clear solution with the specification of 50mg / 10ml / piece (packed in vials).Each vial (capacity 13.5ml) contains 10ml of nimotuzumab solution, the concentration of mAb is 5 mg / ml, and the purity is not less than 95%.The composition of each component in the vial is shown in the table below.

Table 1 The composition of nimotuzumab injection and its components

Components	Content / ml	Content / 10.0 ml
h-R3 monoclonal antibody	5 mg	50 mg
Sodium dihydrogen phosphate	0.45 mg	4.5 mg
Sodium dihydrogen phosphate	1.8 mg	18.0 mg
sodium chloride	8.60 mg	86.0 mg
Polysorbate 80	0.2 mg	2.0 mg

Note:h-R3 monoclonal antibody is not included in placebo, other ingredients, appearance and specifications are the same as those of nimotuzumab injection.

The product should be stored at 2-8 ℃, and freezing is strictly prohibited; After diluted in normal saline, it can keep stable for 12h at 2-8 ℃ and 8h at room temperature. If the diluted solution is stored for more than the above time, it should not be used. The trial drugs nimotuzumab injection / placebo and gemcitabine were provided by Biotech Pharmaceutical Co., Ltd. for free, including labels and packages for clinical trials.

5.2 Grouping and administration scheme

The trial was divided into two groups.

The experimental group was treated with nimotuzumab and gemcitabine;

The control group was treated with placebo (nimotuzumab simulant) and gemcitabine.

1) Nimotuzumab injection / placebo: 400mg /w , intravenous drip, infusion time more than 60 minutes, once a week, until the disease progression or intolerable toxic reaction, or the subject asked to withdraw from the trial.

   Usage method: 400 mg (8 pieces) of nimotuzumab injection / placebo was added into 250 ml sterile normal saline for dilution, and the intravenous drip time was not less than 60 min. the patient's condition should be closely monitored during the course of administration and within 1 hour after the end of administration. In addition to sterile normal saline, nimotuzumab solution should not be mixed with any intravenous infusion drugs.

2) Gemcitabine: 1000mg / m^2, intravenous drip no less than 30 minutes, continuous use for 3 weeks, rest for 1 week (D1, 8, 15; Q28 d) every 4 weeks until the disease progressed or intolerable toxic reaction occurred, or the subject asked to withdraw from the trial.

3) Usage method: each bottle (containing gemcitabine 200mg or 1000mg) should be injected with 5ml or 25ml sterile normal saline at least (containing gemcitabine concentration ≤ 40mg / ml), shaking to dissolve. The required dosage can be further diluted with sterile normal saline. The prepared gemcitabine solution should be stored at room temperature and used within 24 hours. Gemcitabine solution should not be refrigerated to prevent crystallization. According to the solubility of the drug, the concentration of the diluted drug should not exceed 40mg / ml. if the concentration is greater than 40mg / ml, it may lead to incomplete dissolution of the drug, which should be avoided.

At the first treatment, nimotuzumab / placebo should be given on the same day as gemcitabine, and then gemcitabine should be given 1 hour after the end of nimotuzumab / placebo infusion. Since then, nimotuzumab / placebo and gemcitabine were treated on the same day in the same order as before.

5.3 Dose adjustment

5.3.1 Adjustment of trial drug (nimotuzumab / placebo)

During the study, the weekly dose of nimotuzumab / placebo should be given strictly according to the trial design, and should not be adjusted at will.

The toxicity of either placebo or nimotuzumab can be adjusted according to the relevant study. In case of grade 3 or 4 adverse reactions (except allergy / hypersensitivity and blood pressure drop) during the trial, the researcher can adjust the dosage of nimotuzumab / placebo once according to the situation of the subjects to 200mg, if the toxicity can be recovered to grade 1 or below, the dose of nimotuzumab / placebo can be restored to 400mg, and the follow-up treatment can be continued at this dose. If grade 3 or 4 adverse reactions related to nimotuzumab / placebo occur again, they will not recover after the drug dose is reduced to 200mg, and follow-up treatment will be continued at this dose.

Subjects must withdraw from nimotuzumab / placebo treatment but remain in the study for chemotherapy if any of the following conditions occur:

1) Grade 3 or 4 allergy / hypersensitivity occurred;

2) Subjects and / or researchers request or consider it necessary to terminate nimotuzumab / placebo treatment in the event of AE;

If possible, subjects who terminated treatment before disease progression would still be evaluated every 8 weeks until disease progression.

In case of serious adverse events (SAE) related to the drug, such as anaphylactic shock, the drug should be stopped immediately and treated actively. The patient should be reported according to the prescribed procedures. At the same time, the patient should stop the treatment of nimotuzumab. If chemotherapy is delayed or terminated due to chemotherapy-related toxicity, the treatment with nimotuzumab can be continued.

Table 2 Treatment and dose adjustment of hypersensitivity

Hypersensitivity (taixinsheng® related: respiratory spasm, dyspnea): CTC classification	Treatment measures
Grade 1	Drop rate reduced to 50%, close monitoring to prevent deterioration. The duration of infusion was not more than 4 hours.
Grade 2	Stop the infusion. Give bronchodilator, oxygen and other medical measures. Once the allergy / hypersensitivity is recovered or reduced to grade 1, continue infusion at 50% of the original drip rate, and monitor closely to prevent deterioration.
Grade 3 or 4	Stop immediately and cut off the infusion pipeline of the subjects. Give adrenaline, bronchodilator, antihistamine drugs, intravenous infusion, vasopressor drugs, oxygen inhalation and other medical measures. The patient must withdraw from treatment immediately and no longer receive nimotuzumab.

The common adverse reactions of nimotuzumab were fever, hypotension, nausea, dizziness and rash; Generally, it can be relieved by itself without affecting the continuous treatment. The lower incidence of adverse reactions included muscle pain, dyskinesia, dry mouth, flushing, weakness of lower limbs, drowsiness, loss of sense of direction, elevated creatinine level, leukopenia, hematuria, chest pain and cyanosis of the lips, which can be treated with conventional doses of analgesics and / or antihistamines.

Table 3 treatment and dose adjustment of blood pressure drop

NCI-CTCAE classification: decreased blood pressure	Treatment measures
Grade 1-2	The drop rate of nimotuzumab was reduced by 50%.
Grade 3 or 4	Symptomatic treatment, rehydration; Monoguanidine was discontinued.

Table 4 treatment and dose adjustment of skin rash

NCI-CTCAE classification: rash	Treatment measures
Grade 1-2	The drop rate of taixinsheng® was reduced by 50%.
Grade 3 or 4	Hydrocortisone ointment or erythromycin ointment was used locally and evaluated 2 weeks later; If no remission, in addition to the above measures plus oral kairuitan®, if necessary, the impact dose of methylprednisolone can be given to reduce the dose of taixinsheng® by 25%;If co-infection occurs, Using appropriate antibiotics.

5.3.2 Gemcitabine dose adjustment

In principle, all patients should be given the planned chemotherapy dose. If necessary, the dose can be adjusted according to the most serious hematology or other toxicity. Any patient who needs to reduce the dose will continue to receive the reduced dose treatment in the subsequent treatment cycle. If patients have multiple

toxicities and the principle of dose adjustment is different, the minimum dose should be selected. If any patient has already reduced the dose twice, it is necessary to reduce the dose for the third time due to the toxic reaction, chemotherapy must be stopped. Chemotherapy can be delayed for up to 2 weeks, otherwise the chemotherapy needs to be terminated. The treatment of nimotuzumab was not delayed or terminated due to chemotherapy-related toxicity. If chemotherapy is terminated permanently, nimotuzumab monotherapy can be continued until the disease progresses.

The dose adjustment of gemcitabine is shown in the following table:

Table 5 Gemcitabine dose adjustment level

Dose level	0	-1（80%）	-2（50%）
Gemcitabine (mg / m^2)	1000	800	500

5.3.2.1 Hematological toxicity

Patients receive the drug treatment in this study for the first time, they must have neutrophil ≥ 1.5×10^9/L, platelet ≥ 100×10^9/L, before starting chemotherapy, and the delay time of chemotherapy should not exceed 2 weeks. If hematologic toxicity occurs in the follow-up chemotherapy, and the patient does not recover to neutrophil ≥ 1.5×10^9/ L within 2 weeks, platelet count will be increased no more than or equal to 80×10^9/L, the chemotherapy should be terminated. If the patient is unable to receive chemotherapy due to toxicity, the administration can be delayed for 1 week, If the patients still can not receive chemotherapy after 1 week delay, they can continue to delay for 1 week. Once the delay exceeds 2 weeks, the patients will terminate the treatment; However, tumor evaluation should be carried out according to the original plan even if the treatment delay occurs.

There is no need to reduce the dose of gemcitabine if grade 1 thrombocytopenia occurs; When grade 2 thrombocytopenia occurred, gemcitabine dose "reduced to 80% of the original plan"; When grade 3 thrombocytopenia occurs, gemcitabine dose is "reduced to 50% of the original plan". When grade 4 thrombocytopenia occurs, gemcitabine must be stopped. According to the minimum values of platelets and neutrophils in the previous cycle, the following dose adjustments were made to the following cycles of chemotherapy:

Table 6 Hematologic toxicity and gemcitabine dose adjustment

Platelet count ($\times 10^9$/L)	Absolute neutrophil count ($\times 10^9$/L)	Gemcitabine dose level
< lower limit of normal value ~ 75.0 and must	>1	0
50~<75 or	0.5~<1	-1
25 ~ < 50 or	< 0.5 (once)	-2
<25 or	< 0.5 (twice in a row)	Drug withdrawal

5.3.2.2 Non hematological toxicity

Patients who use gemcitabine should have regular clinical examination of liver and kidney function to detect whether non hematologic toxicity occurs. According to the patient's tolerance to gemcitabine, the dose can be reduced in each treatment cycle or one treatment cycle. According to the clinician's opinion, the treatment can be stopped until the toxicity disappears. For non hematotoxicity, gemcitabine can be adjusted according to the highest level of toxicity. Patients with serum bilirubin ≤Grade 2 and ALT/AST must be recovered The neurotoxicity recovered to ≤ NCI-CTCAE 2 or baseline level. The dosage adjustment is shown in the table below

Table 7 Nausea / vomiting and gemcitabine dose adjustment

NCI-CTCAE classification v4.03	Gemcitabine dose level
Grade 0-2 (grade 3 nausea / vomiting)	0
Grade 3 (except grade 3 nausea / vomiting)	-2 or stop taking medicine
Grade 4	Drug withdrawal

If any of the following conditions occur, the subject must withdraw from chemotherapy, but can continue to receive nimotuzumab treatment in the study:

1) Intolerable toxicity such as grade 3 nausea and / or grade 4 vomiting still occurred after prophylactic treatment;

2) Any definite grade 4 drug-related toxicity;

3) Delayed chemotherapy for more than 2 weeks.

If possible, subjects who terminated treatment before disease progression would still be evaluated every 8 weeks until disease progression.

5.4 Combination therapy

During the study period, the drugs that can be used together according to the needs are as follows:

Adjuvant therapy, including prophylactic drugs, such as blood component transfusion, granulocyte colony-stimulating factor (G-CSF), antidiarrheal, antiemetic and analgesic drugs, are allowed and can be operated according to the clinical routine of each center;

When the adverse events caused by the trial drug need to be treated, the drugs for symptomatic treatment can be given; Symptomatic treatment of skin toxicity, including softeners or other topical drugs, analgesics and vitamins B6, etc;

When patients have symptoms due to other reasons, symptomatic drugs can be used.

All drugs used at the same time should be recorded and explained on the CRF form.

During the period of clinical research administration, other anti-tumor chemotherapy drugs and molecular targeted drugs, Chinese patent medicines with anti-pancreatic cancer indications and anti-tumor immune agents (thymosin and interferon, etc.) are not allowed to be used.

6 Research steps and evaluation

6.1 Research process

All study reviews are summarized in the study flow chart in Appendix 1.

6.1.1 Screening period check (I)

The following will be carried out and recorded before screening period inspection (II)

Assignment of subject number

Signed written informed consent forms

The time of diagnosis, the location of TNM and the date of diagnosis were analyzed

10-20 tumor specimens were collected for K-RAS detection

6.1.2 Screening period examination (II)

Only the subjects whose tumor tissue test result is K-RAS wild type can carry out the following examination. The following items must be carried out and recorded:

Verification of inclusion and exclusion criteria

Collect demographic data (date of birth, gender and race)

Medical history

Physical examination (height, weight, within 7 days before screening)

Vital signs (heart rate, blood pressure, respiration, body temperature, detected within 7 days before screening)

Clinical benefit response (CBR) (detected 2-7 days before the first treatment of the study)

ECG (within 2 weeks before screening)

Blood biochemistry (ALT, AST, AKP, BIL, BUN, Cr, CRP) (detected within 7 days before screening)

Blood routine and electrolyte test (within 7 days before screening)

Serum CA19-9 (detected within 7 days before screening)

Routine urine test (within 7 days before screening)

Pregnancy test (only for women of childbearing age, within 7 days before screening)

Baseline assessment of tumor imaging (chest and abdominal spiral CT findings within 21 days before screening)

The eligible subjects were assigned random number

6.1.3 Baseline visit

Only qualified subjects can enter the baseline visit. the following items must be carried out and recorded:

Physical examination (within 7 days before the first treatment)

Vital signs were detected within 7 days before treatment

Body surface area (within 7 days before the first treatment)

Clinical benefit response (CBR) (detected within 2-7 days before the first treatment)

ECG (within 2 weeks before the first treatment)

Blood routine and electrolyte examination (within 7 days before the first treatment)

Blood biochemistry (ALT, AST, AKP, BIL, BUN, Cr, CRP) (detected within 7 days before the first treatment)

Serum CA19-9 (within 7 days before the first treatment)

Routine urine test (within 7 days before the first treatment)

Pregnancy test (only for women of childbearing age, within 7 days before the

first treatment)

Baseline assessment of tumor imaging (chest and abdominal spiral CT findings within 21 days before screening)

If the screening results are within the time window, there is no need to repeat the detection in the baseline period.

6.1.4 Treatment visit

Gemcitabine was given on day 1, day 8 and day 8,15. Four doses of nimotuzumab / placebo were given on day 22.The following inspections and records are required:

physical examination

Body surface area

Clinical benefit response (CBR)

Blood routine and electrolyte examination

Blood biochemistry (ALT, AST, AKP, BIL, BUN, Cr, CRP)

Serum CA19-9

Evaluation of drug combinations and current medical interventions

Adverse events were observed and outcomes were recorded at any time (NCI-CTCAE v4.03)

Other examinations (if necessary)

Hematological examination should be provided within 48 hours before each chemotherapy, and the times can be increased according to the situation.

6.1.5 The efficacy evaluation visit was conducted every 8 weeks

The following assessments will be conducted at the 8-week assessment visit:

Physical examination

Vital signs

Clinical benefit response (CBR)

CT or MRI scan for the evaluation of tumor efficacy

Blood routine and electrolyte examination

Blood biochemistry (ALT, AST, AKP, BIL, BUN, Cr, CRP)

Serum CA19-9

Combination and current medical interventions

Evaluation of adverse events (NCI-CTCAE v4.03)

Imaging examination in different periods should use the same detection technology as that in the baseline period. If the efficacy evaluation result is CR or PR, imaging examination should be carried out 4 weeks after the initial evaluation to confirm the curative effect. The time window of efficacy evaluation is ±7 days.

6.1.6 Final cancer assessment visit

The following assessments will be performed at the final cancer assessment visit:

Physical examination

Vital signs

Clinical benefit response (CBR)

Blood routine and electrolyte examination

Blood biochemistry (ALT, AST, AKP, BIL, BUN, Cr, CRP)

Urine routine

Serum CA19-9

Imaging examination (chest and abdomen spiral CT)

Evaluation of adverse events (follow up to 30 days after the last medication, NCI-CTCAE v4.03)

6.1.7 Evaluation of early termination and withdrawal

Patients must be terminated early during the trial. The reason and date of termination should be recorded in the patient's medical records and case report forms.

When patients terminate the study, the investigator should complete all exit procedures as far as possible.

Once the patients have disease progression, they should be followed up until death.

If the patient stops treatment for any reason other than disease progression or death, follow-up should be conducted every 8 weeks (including tumor evaluation, toxicity, survival) until PD or receiving anti-tumor therapy outside the protocol.

6.1.8 Follow-up

Follow up will be conducted every 3 months. The following items need to be evaluated:

Survival state of subjects

Any new anti-tumor treatment

Any study drug-related AE was followed up until the AE was stable or the outcome was known

6.2 Assessment

6.2.1 Demographic and other baseline characteristics

All baseline visit evaluations must be performed after confirmation of K-RAS status and within 14 days before randomization. Tumor evaluation earlier than 14 days before randomization could not be used in this study. Complete the following checks:

1) Demographic data: date of birth, gender and race need to be collected.
2) K-ras evaluation: after the subjects sign the informed consent, the K-RAS status of tumor samples will be evaluated. K-ras status will be centrally assessed by a designated central pathology laboratory. Researchers must be clear about the results of K-RAS test before the next step of screening subjects.
3) Diagnosis of primary tumor: the date of diagnosis, histology, location of the lesion and the diagnosis time must be recorded TNM staging.
4) Medical history collection: to be recorded:

   Other than pancreatic cancer

   Treatment for diseases other than pancreatic cancer within 14 days before

the start of the study (i.e. within 14 days before randomization)

Previous treatment for pancreatic cancer, including chemotherapy, adjuvant chemotherapy, radiotherapy and surgery

Concomitant treatment: the concomitant treatment and the medical measures received at baseline were recorded.

5) Pregnancy test: the urine pregnancy test must be negative for all female subjects with fertility (within 7 days before the start of study treatment).
6) Physical examination: height, weight and vital signs (heart rate, blood pressure, respiration, body temperature, etc.).
7) Laboratory examination: mainly including blood routine (Hb, WBC, ANC, PLT), electrolyte (K+,Na+, Cl-, Ca2+, Mg2+), urine routine (pH, protein, RBC, WBC) and blood biochemistry (ALT, AST, AKP, BIL, BUN, Cr, CRP).
8) Auxiliary imaging examination: CT or MRI scan will be performed within 21 days of the first treatment to record the tumor status at baseline; At the same time, the number of organs with metastasis was confirmed, and target and non-target lesions were designated.
9) Tumor evaluation: tumor specialist examination, including tumor related symptoms and physical examination of superficial lesions, combined with imaging examination to determine the detailed staging, measure the size of metastasis before treatment, and fill in the relevant forms.
10) Behavior status score (KPS score standard, see APPENDIX 2).
11) Pain assessment: including pain intensity and consumption of analgesics, see section 6.2.2.2 and APPENDIX 4.

6.2.2 Efficacy evaluation

The primary efficacy evaluation index was overall survival time (OS), and the secondary efficacy evaluation indexes were time to disease progression (TTP), progression free survival (PFS), objective remission rate (ORR), disease control rate (DCR), and clinical benefit response (CBR).

6.2.2.1 Efficacy evaluation criteria

According to RECIST 1.1 (see APPENDIX 3 for details), the patients were divided into complete remission (CR) and partial remission(PR), stable (SD), progressive (PD).Response evaluation was performed every 8 weeks. if the patient achieved CR, or PR should be confirmed 4 weeks after the first evaluation.

Partial or incomplete tumor evaluation will not be included in TTP, PFS, ORR, DCR unless the observable lesions have been evaluated as progression (according to recist1.1).

6.2.2.2 Efficacy evaluation index

Overall survival (OS) refers to the time from randomization to death due to any cause. Record the time of contact with the patient and the last visit before death. For patients who were still alive at the time point of the final analysis, the last contact time was taken as the survival time. In the analysis of survival and follow-up treatment, all patients were followed up until death, loss of follow-up or termination of the study. The log rank test will be used to analyze the overall survival.

Time to disease progression (TTP): defined as from the date of randomization to the first observation of the disease. The time (days) between progression (imaging or clinical progress, whichever is earlier).The actual date of tumor evaluation will be used for calculation. The time to progression for patients who did not progress at the time of analysis or death will be calculated as the date of the last tumor evaluation. The time of disease progression was analyzed by the same method as OS.

Progression free survival (PFS): the time a patient survives without significant tumor progression. If the appearance of new lesions is regarded as the standard of progression, the time point of progress is the date when the new lesions are observed for the first time. Progression free survival was defined as the time from randomization to death in patients who died of any other cause before disease progression was recorded. Patients without progression or death (i.e., progression free survival) at the time of the last tumor assessment will be used as the end point.

Objective response rate (ORR): refers to the proportion of patients whose tumor volume has reduced to a predetermined value and can maintain the minimum time limit, which is generally (CR + PR)%.Remission usually refers to the period from the beginning of curative effect to the confirmation of tumor progression. Both CR and PR subjects need to be confirmed and evaluated according to RECIST Standard Version 1.1.

Disease control rate (DCR): refers to the percentage of cases with remission and stable lesions after treatment in the total number of evaluable cases, that is, DCR = (CR + PR + SD)%.

Clinical benefit response (CBR): only symptomatic patients were evaluated in the study, including pain (intensity of pain and consumption of analgesics), PS (performance status, evaluated according to KPS), and weight change. See APPENDIX 4 for evaluation criteria.

Symptomatic pancreatic cancer was defined as having at least one of the following manifestations at baseline:

1) KPS 60 or 70 score;

2) They received morphine / opioid analgesia;

3) The score of MPAC was more than or equal to 20;

If the patients were asymptomatic at the time of admission, and the above symptoms appeared during the treatment, the evaluation was started when the symptoms appeared CBR.

Table 8 Clinical benefit response assessment requirements

Evaluation items	Evaluation method	Evaluation time point
Pain intensity (pain log card)	Vas100 (visual scale): on the horizontal line of 0-100 mm, the left "0" is painless, and the "100" at the right end is extremely painful. Patients are marked on the horizontal line to represent their own degree of pain.	Patients were recorded daily to the pain log card. The researchers evaluated each week before treatment. ● Observation phase: the pain intensity was recorded 2-7 days before the start of treatment, and the average vas100 score was used as the baseline pain intensity score. ● Treatment stage: record daily
Consumption of analgesics (pain log card)	Total daily dose of analgesics	Patients were recorded daily to the pain log card. The researchers evaluated each week before treatment. ● Observation stage: the dosage of analgesic drugs was recorded 2-7 days before the start of study treatment; The average daily dose of analgesics received by the patients two days before the start of the study was used as their baseline analgesic consumption and will be used as a reference for CBR assessment. ● Treatment stage: record daily
PS	KPS scoring standard	They were evaluated by the researchers once a week before treatment
weight		They were evaluated by the researchers once a week before treatment

The vas 100 score in the pain log card and the consumption of all analgesic treatment were transcribed on the CRF form by the researchers. The weekly analgesic treatment consumption will be calculated as the average daily analgesic treatment consumption.

6.2.3 Safety assessment

6.2.3.1 Definition

Definition of adverse event (AE): it refers to the adverse medical events that occur after the subjects in clinical trials receiving a drug. No matter whether there was any adverse event within 30 days after the treatment, the adverse event was judged to be adverse from the beginning to the end of the study.

Adverse drug reaction (ADR): refers to the normal usage and dosage of qualified drugs. Present adverse reactions not related to the purpose of medication or accidental. Adverse reactions in this study: adverse events determined to be related to the trial drug.

Serious adverse event (SAE), including hospitalization, prolonged hospital stay, disability, life-threatening or death, and congenital malformation occurred during the clinical study.

*Note: 1) adverse events should not be included in the disease progression (PD according to the protocol) due to the development and deterioration of the tumor itself; However, PD related deaths during or within 30 days after the end of protocol treatment should be reported as SAE. 2) Obstructive jaundice or cholangitis caused by pancreatic cancer itself is not considered as a serious adverse event.

6.2.3.2 Evaluation method

1）During the protocol treatment, or within 30 days after the end of the protocol treatment or before the start of other treatments other than the study protocol, the observed AE were evaluated according to the observation, examination items and the process specified in the process. All kinds of AE and their grades were recorded in CRF.

The observed AE were evaluated according to NCI-CTCAE v4.0.3.

2）Causal relationship with treatment plan

Any abnormal symptoms, signs, laboratory tests or other special examinations in the clinical study should be recorded in detail, and their correlation should be

evaluated. According to the criteria of adverse reaction / event analysis, the association evaluation was divided into: 1- positive correlation;2 - probably related;3 - may be relevant;4 - may not be relevant;5 - definitely not be relevant.

① There was a reasonable relationship between the time of starting medication and the occurrence of suspicious adverse reactions;

② Whether the suspected adverse reactions conform to the known adverse reaction types of the drug;

③ Whether the suspected adverse reactions can be explained by the effect of combined drugs, the patient's clinical condition or the influence of other treatments;

④ Whether the suspected adverse reactions disappeared or alleviated after drug withdrawal or reduction;

⑤ Whether the same reaction reappeared after repeated exposure to the suspected drug. Causal criteria: according to the above 1 ~ 5 indicators in order to determine.

Table 9 Judgment of causality of adverse reactions

Judge the result	Judgment index				
	①	②	③	④	⑤
Definitely	+	+	—	+	+
It's probably related	+	+	—	+	?
It may be relevant	+	+	+	±	?
Probably not	+	—	±	±	?
Definitely not	—	—	+	—	—

Note: + "means affirmative;"-" means negative;"±' means that it is difficult to affirm or negate "?" The expression is not clear.

The relationship between adverse events (including serious adverse events) and drugs should be determined as far as possible. If it is determined that it is definitely related, it is likely to be related and may be related, the three levels will be regarded as drug-induced adverse reactions, and whether they are serious adverse events will be considered according to the severity.

6.2.3.3 Emergency report and response of serious adverse events

When serious adverse events occur during the treatment period or within 30 days after the end of the treatment, they should be treated according to the following provisions. However, severe obstructive jaundice or cholangitis caused by pancreatic cancer itself is not an urgent report.

In case of serious adverse events in the process of clinical study, the researcher should immediately take appropriate treatment measures for the subjects, and report to the drug supervision and administration department, the health administration department and the sponsor within 24 hours, report to the ethics committee in time, and sign the report date.

The sponsor and the researcher shall promptly study the serious adverse events occurred, take necessary measures to ensure the safety and interests of the subjects, report to the drug administration and health administration department in time, and inform other researchers of clinical research involving the same drug.

SAE records should record the symptoms, severity, occurrence time, treatment time, measures taken, follow-up time and method, and outcome.

Table 10 serious adverse event reports and contact numbers

Reporting unit	Telephone / fax	contacts
Responsible unit ethics committee		
Baitai biopharmaceutical Co., Ltd(Biotechplc.com)	010-51571020-8834	Wang Yan
CFDA drug registry		
CFDA Department of drug safety		

6.2.3.4 Pregnancy Report

Pregnancy during the study period must be recorded and reported in the pregnancy report form. In order to ensure the safety of the subjects, the pregnancy must be reported within 2 weeks after learning of its occurrence. Follow up is necessary to determine the outcome (including early termination of pregnancy) and maternal and child status. Pregnancy complications and termination of pregnancy for medical reasons must be reported as AE or SAE. Spontaneous abortion must be reported as SAE.

In addition, researchers must collect as much information as possible about the pregnancy of their female sexual partners after male subjects were enrolled in the study. Pregnancy information must be reported as described above.

6.3 Biomarkers

In addition to K-RAS status assessment (one of the inclusion criteria), this study will also carry out biomarker detection and exploratory analysis. During the study, formalin fixed and paraffin embedded tumor sections (10-20 pieces / patient) will be collected for candidate gene expression research and immune histo-chemical study.

A central laboratory will be designated by the sponsor for K-RAS testing, and patients with wild-type K-RAS can enter the screening period (2).

Other biomarkers except K-RAS were tested in the central laboratory designated by the sponsor after the sample collection

7 Blinding and randomization

7.1 Blinding and blind base preservation

In this study, a dynamic random variance minimization method was used. Das for IWRS automatically assigned random numbers according to the level of influencing factors. After the last subject assigned random numbers, the randomization project manager derived the first level blind seal from the random system and handed it over to the sponsor, including the second level blind background made during on-site blinding, Two copies of the blind base were sealed to the sponsor and the clinical research unit respectively.

The drug distribution packaging was participated by blinders of the statistical unit and the personnel unrelated to the trial from the applicant. According to the treatment group corresponding to the drug package number generated by the software, the drug package number and drug verification code of the trial drug and control drug were filled in (or pasted) on the label. In this study, the central randomized system was used to distribute drugs according to the visit period, so the drugs were packaged according to the visit period, and the random number of each subject was unique. The package number is different, but the corresponding treatment plan is the same. The process of drug blinding is written into a document form by the blinder, that is, the blinding record. All the blinders sign on the blinding record and keep it as one of the documents of the clinical trial.
The drug package number and verification code information were imported into Das for IWRS system after the completion of blinding for drug distribution.

7.2 Emergency envelope

An emergency letter (e-mail) will be set up for each random number, which will record the treatment group corresponding to the drug package number received by the subject. The emergency letter is used for emergency blind breaking, and the operation is strictly authorized. Only the research director of each center can open the electronic emergency letter. The operation track will retain the electronic signature, date and reading reason of the reader.

7.3 Emergency unblinding

When the subjects were aware of the adverse events, they were able to handle the adverse events. It should be operated by the researcher, and record the reason, time and place of breaking the blind in detail, and input the electronic signature. Within 24 hours after breaking the blind, inform the clinical trial responsible (leading) unit, clinical inspectors and relevant statistical personnel, and explain the reasons for breaking the blind. The cases after breaking the blind should be regarded as falling off cases, and the case data should be kept intact.

7.4 Unblinding requirements

In this study, double blinding method is adopted. When all the data are entered into the database in duplicate, and the final statistical plan is confirmed through Q & A, verification, blinding review, the database will be locked. At this time, the first blinding is carried out by the main researchers of this study together with the statisticians, that is, the blind background of the corresponding groups (group A or group B) corresponding to the random number is revealed, so as to conduct statistical analysis of all the data after grouping. After the analysis was completed, the second blinding was performed by the main researchers at the clinical research summary meeting. All blinding procedures should be recorded.

8 Drug management

8.1 Drug specifications

1) Nimotuzumab injection, specification: 50mg / 10ml / Cilin bottle, production: Biotech Pharmaceutical Co., Ltd.
2) Gemcitabine, specifications: 200mg, 1000mg lyophilized powder injection, sold in the market, purchased by Biotech Pharmaceutical Co., Ltd. and provided free of charge.
3) Placebo (nimotuzumab injection simulator): preparation buffer solution, specification: 10ml / vial, production: Biotech Pharmaceutical Co., Ltd.

8.2 Drug packaging and labeling

There were 8 drugs in each package, which was the dosage of one visit period. The contents of drug package labels include drug package number, drug verification code, indication, usage, expiration date, storage conditions and drug supplying unit, and the words "for clinical research use only" are marked (see the figure below).

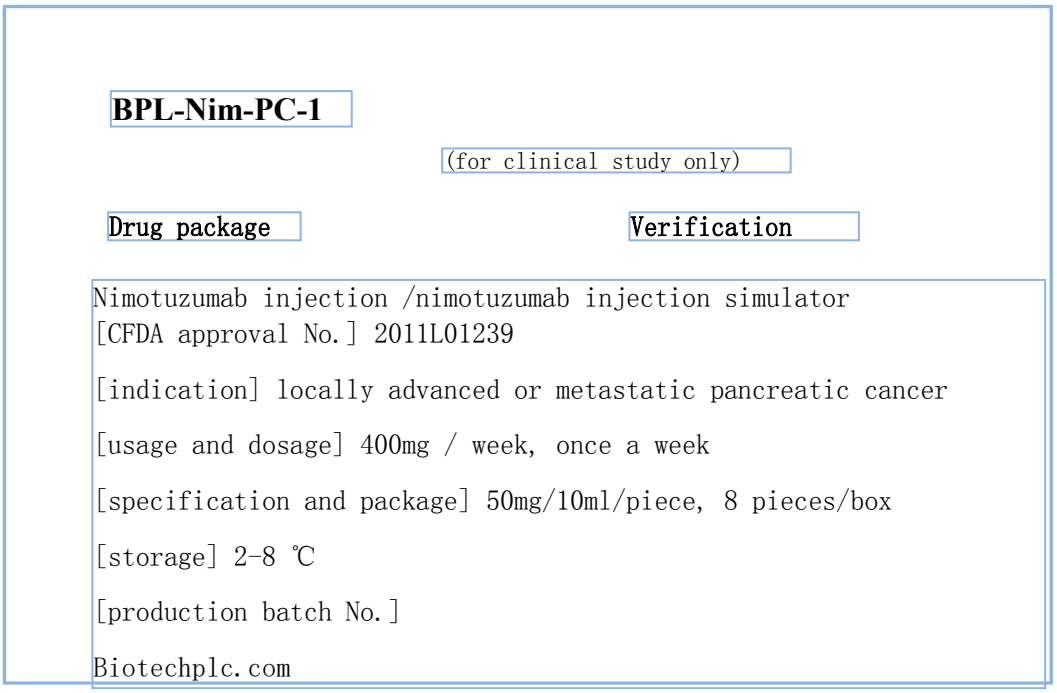

Figure 1 drug package label

8.3 Drug delivery methods

In this study, central randomization was used. First, appropriate drugs were delivered to each research center according to the expected progress of the trial, and then drugs were timely distributed according to the actual progress during the trial. They were distributed to the subjects by the trial medication management personnel of the research center. All drug distribution processes should be recorded accordingly. In order to ensure the timely supply of drugs, the central random system sets the drug storage alert quantity in advance. Once the stock is insufficient, the inspector can timely distribute the drugs according to the drug package number prompted by the system. After confirming that the drugs delivered to the research unit, the system will issue the drugs with corresponding package numbers to the applicants. The same procedure is used to adjust drugs between centers.

After the subjects were screened and qualified, the researchers logged into the central random system, input the general information such as the subject's abbreviation, gender, age and other general information and dynamic random influencing factors information, applied for the random number, and recorded the random number of the subject in the course of the large medical record. Then, the drug issuer will apply for the drug number for the subject according to the random number, and the system will display the drug package number that the subject should apply for. When the drug number on the outer packaging system is consistent with that of the drug delivery system, the drug delivery system will display the drug number.

8.4 Management

Each research unit should establish strict storage and distribution system of clinical research drugs. The application unit shall send the research drug directly to each research center by special personnel, and establish a complete drug acceptance procedure. Each research unit establishes a pharmacy or designates a special research medication administrator for management. The drug should be stored and transported at 2-8 ℃ without freezing. A special "clinical research drug use record form" was established to register the date of drug release, drug number, subject serial number, recipient, drug administrator, etc. The researchers should distribute the drugs according to the order of each patient's visit, and should not choose the serial number.

After the completion of the study, the unused drugs will be collected by the sponsor and destroyed after being checked and kept for a proper time.

9 Research progress and completion time

The enrollment of the patients is expected to be completed from December 2014 to December 2016.

10 Data management and statistical analysis

10.1 Data management

10.1.1 Electronic data management

① DAS for EDC is used in the test data management.

② Construction of electronic case report form (eCRF): the data manager builds eCRF according to the research protocol.

③ EDC system users use role and authority dual control. All users accessing EDC need to fill in the user account application forms. After confirmation and approval of the sponsor, the system administrator creates the project administrator account and grants the project administrator permission. The project administrator user applies to create the account of researcher, research assistant (CRC), supervisor, inspector, data manager and grant different permissions to access EDC. such as the researchers of each center can only see the contents of the center and have the right to revise the data, the sponsor can only browse the EDC; The inspectors can read the EDC data of each center without the authority to revise the data, but can ask some questions.

④ Data entry: research assistants (CRC) are designated by the main researchers of each institution, and CRC will input the original data into eCRF timely and accurately. eCRF is not the original record.

⑤ Data verification: at the same time of data entry, EDC conducts logic verification, and sends out system questions in real time. In addition to system queries, data administrators conduct manual verification on text data, and issue manual queries if there are problems.

⑥ On site verification of source data (SDV): the inspectors log in DAS for EDC at the research sites of each center, and 100% check the consistency of eCRF data with the original data. If problems are found, they can issue questions online at any time.

⑦ Question answer: the researcher can answer the question online in real time or

download the list of questions, and the researcher can answer the question offline, and then the CRC will input the question content into EDC. The data manager and the supervisor shall reply to the questions answered by the researcher, and issue the questions again if necessary until the data is "clean".

⑧ All the data were locked and analyzed by the participants and administrators, and then all the data were confirmed and analyzed by the participants and administrators. After all the data are locked, the data administrator will import it into the designated database and submit it to the statisticians for statistical analysis. The locked data can not be edited again. The problems found after data locking can be corrected in the statistical analysis program after confirmation. After the data is locked, the researcher and the sponsor should sign the relevant documents if there is definite evidence to prove that it is necessary to unlock the data.

⑨ Unblinding: in this study, the second blinding method was used. After all the research data were locked, the main researchers (PI) and The statisticians and the sponsor discuss the statistical plan together, and uncover the blind, that is, the group corresponding to the random number (After blinding, any modification to the database must be agreed in writing by the clinical research leader, biostatistician and data manager. After the statistical analysis, the second blinding was performed by the main researchers at the clinical research summary meeting. All blinding procedures should be recorded.

⑩ eCRF archiving: at the end of the trial, the eCRF and PDF electronic documents of each subject were generated, and the CD was recorded in the research unit, and the retention period was 7 years after the completion of the experiment.

EDC shutdown: after the trial, the data administrator will apply for EDC shutdown, cancel all account access rights after obtaining the permission of the sponsor, and close the EDC (i.e. offline) after the data is fully backed up. Within 7 years after the completion of the trial, the data management center can open the EDC system after making an appointment.

10.1.2 Develop data management plan

① The data management plan is written by the data administrator.

② The data management plan will serve as the guidance document for the whole data management process, and then all processes shall operate according to the time and

method defined therein.

③ The data management plan includes:

- Management of data management plan, such as ownership, cover rules, catalog, etc.
- The general situation of the study, such as the purpose of the study, the overall design of the study, etc.
- Schedule of data management work. In this schedule, the start and finish time of each link should be reflected. At the same time, the schedule should be coordinated with the overall schedule of the clinical trial.
- Allocation of users and permissions: including EDC system administrator (admin) and data administrator (DM), investigator, CRC, CRA, etc.
- Data management design, including database design and logical verification design.
- Data processing regulations
- Quality control data
- EDC off
- Data security measures
- EDC system emergency plan

10.2 Statistical analysis

10.2.1 Sample size estimation

In this study, overall survival (OS) was taken as the main efficacy index. According to the literature[13], OS of gemcitabine monotherapy group was 6 months. In this study, it was predicted that the OS of the experimental group could be improved by adding nimotuzumab up to 8.7 months, according to the bilateral testα=0.05,1-β=0.80. Enrollment is completed within 24 months, and trials are expected to be completed 12 months after observation until the last case enrolled. The study group and the control group had a ratio of 1:1. Considering the deletion factor of 20%, the total number of cases was determined to be 276 cases, 138 cases in the experimental group and the control group.

If the death event of the last case did not reach 80% after 12 months, the experiment continued to observe until the death event reached 80%.

10.2.2 Analysis data set

① Full analysis set (FAS): all the cases that were randomized into groups, used the study drug at least once, and had the evaluation data of post medication efficacy at least once. When the main efficacy indicators were missing, the previous results were carried forward according to the intention to treat (ITT) analysis. FAS is the main analysis set. Only FAS analysis without carrying forward was used for secondary efficacy indicators.

② Per protocol set (PPS): refers to the set of cases that meet the inclusion criteria, do not meet the exclusion criteria, and complete the treatment plan, i.e. analyze the cases that meet the trial protocol, have good compliance, and complete the contents specified in CRF (PP analysis).PP analysis was mainly used for the main efficacy indicators.

③ Safety data set (SS): the actual data that has been treated at least once and recorded by safety indicators. The missing value of safety shall not be carried forward; Some excluded cases that can be evaluated were included, such as the cases whose age exceeded the inclusion criteria, but did not include the cases that could not be judged for safety due to the use of prohibited drugs. The incidence of adverse reactions was determined by the number of cases in the safety set as the denominator.

10.2.3 Statistical method

The endpoint analysis will be performed after 80% of deaths.

(1) Case analysis

The total number of selected and completed cases in each center were listed, and three analysis data sets (FAS, PPS, SS) were determined.

The cases of shedding and rejection and their causes were listed.

(2) Demographic data and baseline analysis

Baseline and other demographic characteristics were as follows:

The number of cases, mean value, standard deviation, median, minimum value and maximum value were calculated by continuous variable.

Count and grade data were used to calculate frequency and composition ratio.

Inferential statistical results (P values) are listed as descriptive results.

(3) Compliance analysis

Analysis of medication compliance: compare whether the two groups of patients used the study drug on time and in accordance with the amount, and did not use the drugs prohibited in the scheme.

Analysis of combined drug use: the number of drug users in each combination should be counted and listed in detail.

(4) Efficacy analysis

Analysis of main therapeutic indexes

Overall survival (OS), the median survival time, quartile time and 95% confidence interval of the two groups were listed respectively. Log rank test was used to compare the two groups, and Kaplan Meier curve of OS was drawn. Taking dynamic random influencing factors as covariates, the Cox proportional hazard model was used to calculate HR and its 95% confidence interval (CI).

Analysis of secondary efficacy indicators

Progression free survival (PFS), the median survival time, quartile time and 95% confidence interval of the two groups were listed respectively. Log rank test was used to compare the two groups, and Kaplan Meier curve of OS was drawn. Taking dynamic random influencing factors as covariates, the Cox proportional hazard model

was used to calculate HR and its 95% confidence interval (CI).

The median time to disease progression (TTP), the median survival time, quartile time and 95% confidence interval of the two groups were listed respectively. Log rank test was used to compare the two groups, and Kaplan Meier curve of OS was drawn. Taking dynamic random influencing factors as covariates, the Cox proportional hazard model was used to calculate HR and its 95% confidence interval (CI).

Objective remission rate (ORR) was calculated and used $\chi 2$ test was used to compare the difference between groups. The logistic regression model was used to calculate the ratio and 95% of the ratio Confidence interval (CI).

The disease control rate (DCR) was calculated at the end of the experiment, and CMH was used-χ^2test.

Clinical benefit response (CBR), the clinical benefit response efficiency of the two groups at the end of the trial was calculated respectively CMH-χ^2test.

(5) Safety analysis

- The incidence of adverse events and adverse reactions and their 95% confidence interval (CI) were calculated.
- The frequency and frequency of adverse events and adverse reactions were listed by system, and the percentage was calculated
- Detailed list of various adverse event cases
- Detailed list of various adverse reactions
- The abnormal rate of abnormal ECG and abnormal turn rate after physical examination were increased
- The laboratory indexes, ECG, abnormal cases of physical examination and clinical explanation were listed.

10.2.4 Statistical software and general requirements

- SAS 9.2 software was used for analysis.
- All statistical tests were performed with bilateral test. If p value is less than or equal to 0.05, the difference will be considered to be statistically significant.
- Detailed statistical methods will be provided in the statistical analysis plan.

11 Quality control of clinical research

During the study, the clinical supervisors assigned by the sponsor regularly visited the research hospital according to the standard operating procedures, so as to ensure that all contents of the study protocol were strictly observed and the correctness and authenticity of the research data were filled in.

- The participants must be trained in a unified way, recording methods and judgment criteria.
- The whole clinical research process should be conducted in a strictly blind state.
- In order to ensure the authenticity and reliability of eCRF, researchers should record the contents of eCRF truthfully, carefully and carefully according to the requirements of eCRF.
- The criteria for abnormal laboratory examination were determined according to the normal reference range of clinical research units and that of this study. The judgment standard shall prevail.
- All observation results and findings in clinical research should be verified to ensure the reliability of the data and ensure that the conclusions in the clinical study come from the original data.
- In view of the possible shedding, active measures should be taken, and the case shedding rate of each research unit should be controlled within 10%.

12 Ethical requirements and informed consent

Before the start of this clinical study, the written consent forms of the ethics committee should be obtained. According to the guidelines of the GCP, any modification of the study protocol requires the approval of the ethics committee. If these modifications may cause harm to patients, the contents of informed consent should be updated and signed by the patients participating in the study. This clinical study must follow the Helsinki Declaration and the relevant Chinese clinical research norms and regulations.

Before a subject is enrolled in this study, the research physician must fully introduce the purpose, procedure and possible risks of the clinical study to the subject or the subject's legal representative. Subjects should be informed that they have the right to withdraw from the study at any time and under any circumstances. Before enrollment, each subject or the legal representative of the subject must sign the

informed consent form in duplicate (copy kept by the subject).It is the responsibility of the study physician to obtain informed consent forms before each subject enters the study and keeps it as a study file.

13 Data preservation

In order to ensure the evaluation and supervision of the State Food and Drug Administration and the sponsor on the clinical research, the clinical research unit should keep all the research data and original records of the whole process of the clinical research, including the confirmation of all subjects (which can effectively check different records, such as CRF and original hospital records), all signed informed consent forms, CRF, and Detailed records of drug distribution, etc. The research unit should keep these clinical data until 5 years after the clinical end.

All the data of this clinical study belongs to the sponsor. Except as required by State Drug Administration (SDA), the researcher shall not provide it to any third party in any form without the written consent of the sponsor.

14 Researchers

Omit

15 References

1. GLOBOCAN 2012. http://globocan.iarc.fr/Pages/fact_sheets_population.aspx.
2. Siegel R1, Ma J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29.
3. Ni QuanxingCurrent status of clinical epidemiology of pancreatic cancerPancreatology2006; 2: 65-68.
4. Chen W, Zheng R, Zhang S, et al. Annual report on status of cancer in China, 2010. Chin JCancer Res. 2014;26(1):48-58.
5. Xiong HQ, Carr K, Abbruzzese JL.Cytotoxic chemotherapy for pancreatic cancer: Advancesto date and future directions.Drugs. 2006;66(8):1059-72.
6. Li D, Xie K, Wolff R, Abruzzese JL.Pancreatic Cancer.Lancet. 2004; 363 (9414): 1049-57.
7. Van Cutsem E, Aerts R, Haustermans K, Systemic treatment of pancreatic cancer.Eur JGastroenterol Hepatol. 2004;16(3):265-74.
8. Carmichael J.Clinical response benefit in patients with advanced pancreatic cancer. Role ofgemcitabine.Digestion. 1997;58(6):503-7.
9. Eckel F, Schneider G, Schmid RM. Pancreatic cancer: a review of recent advances.ExpertOpin Investig Drugs. 2006; 15(11): 1395-410.
10. Oettle H, Arnold D, Hempel C, et al.The role of gemcitabine alone and in combination in thetreatment of pancreatic cancer.Anticancer Drugs. 2000; 11(10):771-86.
11. Rocha Lima CM, Flores AM. Gemcitabine doublets in advanced pancreatic cancer: should wemove on? J Clin Oncol. 2006;24(3):327-9.
12. Xiong HQ, Rosenberg A, LoBuglio A. Cetuximab, a monoclonal antibody targeting theepidermal growth factor receptor, incombination with gemcitabine for advanced pancreatic
    cancer: a multicenter phase II Trial.J Clin Oncol. 2004;22(13):2610-6.
13. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial.J Clin Oncol. 1997;15(6):2403-13.
14. Von Hoff DD,oRamanathan RK,aBorad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advancedpancreatic cancer: a phase I/II trial. J Clin Oncol. 2011;29(34):4548-54.

15. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-703.
16. Hoy SM. Albumin-bound Paclitaxel: a review of its use for the first-line combination treatment of metastatic pancreatic cancer.Drugs. 2014;74(15):1757-68.
17. Saif MW. U.S. Food and Drug Administration approves paclitaxel protein-bound particles (Abraxane®) in combination with gemcitabine as first-line treatment of patients with metastatic pancreatic cancer.JOP. 2013;14(6):686-8.
18. Cecco S, Aliberti M, Baldo P, et al. Safety and efficacy evaluation of albumin-bound paclitaxel.Expert Opin Drug Saf. 2014;13(4):511-20.
19. Thota R,Pauff JM,Berlin JD.Treatment of metastatic pancreatic adenocarcinoma: a review.Oncology (Williston Park). 2014;28(1):70-4.
20. Wang Liwei, Chen Donghui, Li Qi, etcConsensus of Chinese experts on comprehensive diagnosis and treatment of pancreatic cancer (2014 Edition)Journal of clinical oncologyApril 2014, Volume 19, issue 4
21. Vickers MM, Powell ED, Asmis TR, et al.Comorbidity, age and overall survival in patients with advanced pancreatic cancer - results from NCIC CTG PA.3: a phase III trial of gemcitabine plus erlotinib or placebo. Eur J Cancer. 2012 Jul;48(10):1434-42.
22. Dirk Strumberg, Beate Schultheis, Matthias Philip Ebert, et al. Phase II, randomized, double-blind placebo-controlled trial of nimotuzumab plus gemcitabine compared with gemcitabine alone in patients (pts) with advanced pancreatic cancer (PC).,2013 ASCO AnnualMeeting. J Clin Oncol 31,2013（suppl；abstr 4009）.
23. Dan Su, Shun-Chang Jiao, Li-JieWang, et al. Efficacy of nimotuzumab plus gemcitabineusage as first-line treatment in patients with advanced pancreatic cancer. Tumour Biol. 2014;35(3):2313-8.

APPENDIX 1: Schedule

project		Screening period (I)	Screening period (II)	Baseline period	Treatment period Cycle1(W1-4)…….				Every 8 weeks	Final cancer visit assessment	Every 3 months Follow up 5)
					D1	D8	D15	D22			
Informed consent forms		×									
Assignment of subject screening number		×									
Tumor diagnosis		×									
Tissue specimen collection		×									
K-RAS detection		×									
Random number assignment of subjects			×								
Check the inclusion and exclusion criteria			×								
Demographic data			×								
Medical history			×								
Physical examination			×	▲	×	×	×	×	×	×	
CBR 1）	Pain intensity		×	▲	According to MPAC visual analog scale, the patients were evaluated once a day						
	Analgesics consumption		×	▲	×	×	×	×	×	×	
	KPS score		×	▲	×	×	×	×	×	×	
	Weight		×	▲	×	×	×	×	×	×	

Vital signs		×	▲	×	×	×	×	×	×	
Body surface area			×	×	×	×	×	×		
Electrocardiogram		×	★					×	×	
Routine blood test		×	▲	×	×	×	×	×	×	
Electrolyte		×	▲	×	×	×	×	×	×	
Blood biochemistry		×	▲	×	×	×	×	×	×	
Serum CA19-9		×	▲	×	×	×	×	×	×	
Urine routine		×	▲							
Pregnancy check 2)		×	▲							
Imaging baseline assessment 3)		×	■					×	×	
Nimotuzumab / placebo Administration				×	×	×	×	×		
Gemcitabine administration				×	×	×		×		
Adverse event assessment 4)				Keep a record						
Combination therapy				Keep a record						
Follow up survival				Keep a record						

Note:

▲*: the examination results within 1 week before administration can be directly included in the baseline results, and repeated measurement is not necessary.*

★*:the examination results within 2 weeks before administration can be directly included in the baseline results without repeated measurement.*

■*: the examination results within 3 weeks before administration can be directly included in the baseline results without repeated measurement.*

1) Clinical benefit rate evaluation: including pain (intensity of pain and consumption of analgesics), PS (performance status, evaluated according to KPS), and weight change. The pain intensity and the

consumption of analgesics were recorded once a day and evaluated by CBR once a week. See APPENDIX 4 for details.

2) It is only applicable to those with fertility.

3) Imaging examination in different periods should use the same detection technology as that in the baseline period. If the evaluation result is CR or PR was performed at 4 weeks after the initial evaluation, and the time window for efficacy evaluation was ±7 days.

4) Adverse events were followed up to 30 days after the last medication.

5) For patients who withdraw from the trial, the observation items in the following table should be followed up:

	After withdrawal, the subjects could still come to the hospital for follow-up	The subjects could not come to the hospital for follow-up after withdrawal
Tumor evaluation of disease progression before withdrawal	1) Survival status was recorded (once every 3 months) 2) KPS score (once every 3 months) 3) New adverse events were recorded up to 1 month after the last administration of the trial drug 4) Record any anti-tumor treatment	The following items were followed up by telephone: 1) Survival status (once every 3 months) 2) New adverse events were recorded up to 1 month after the last administration of the trial drug 3) Any anti-tumor treatment given by the hospital
Evaluation of disease progression without withdrawal	1) Tumor imaging examination and evaluation were performed according to the experimental schedule 2) Survival status was recorded(once every 3 months) 3) KPS score (once every 3 months) 4) New adverse events were recorded up to 1 month after the last administration of the trial drug 5) Record any anti-tumor treatment	The following items were followed up by telephone: 1) Survival status (once every 3 months) 2) New adverse events were recorded up to 1 month after the last administration of the trial drug 3) Any anti-tumor treatment given by other hospital 4) The date and basis of judging disease progression in other hospital

APPENDIX 2: KPS score

Karnofsky functional status scoring criteria

Physical condition	score
Normal, no symptoms and signs	100
Able to perform normal activities with minor symptoms and signs	90
Normal activity with reluctance, with some symptoms or signs	80
Cares for self but does not maintain normal life and work	70
Capable of most self-care, but occasionally requires assistance	60
Often require care	50
Cannot carry on any self-care and requires special care and assistance	40
inability to take care of themselves severely	30
Very ill, requiring hospitalization and aggressive supportive care	20
Critically ill, near death	10
Death	0

APPENDIX 3:Criteria for evaluating the efficacy of solid tumors (version 1.1)

1 Tumor measurability at baseline

1.1 definition

At baseline, tumor lesions / lymph nodes were classified as measurable and unmeasurable according to the following definitions:

1.1.1 Measurable lesions

Tumor focus: at least one diameter can be accurately measured (recorded as the maximum diameter), and its minimum length is as follows:

- CT scan 10 mm (no more than 5mm thick)
- Clinical routine examination instrument 10 mm (tumor lesions that cannot be accurately measured by diameter measuring instrument should be recorded as non-measurable)
- Chest X-ray 20 mm
- Malignant lymph nodes: pathological enlargement and measurable, single lymph node CT scan short diameter must be ≥ 15 mm. The thickness of CT scan should not exceed 5 mm. During baseline and follow-up, only short diameter was measured and followed up.

1.1.2 Unmeasurable lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph node short diameter ≥ 10 mm to < 15 mm) and unmeasurable lesions. Unmeasurable lesions include meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, cutaneous / pulmonary carcinomatous lymphangitis, abdominal mass that cannot be diagnosed and followed up by imaging, and cystic lesions.

1.1.3 Special considerations on lesion measurement

Bone lesions, cystic lesions and lesions previously treated with local treatment need to be noted:

Bone lesions:

- Bone scan, PET scan or plain film are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;
- When osteolytic lesions or mixed osteolytic / osteogenic lesions have definite soft tissue components and the soft tissue components meet the above measurable definition, these lesions can be regarded as measurable lesions if they can be

evaluated by tomographic imaging techniques such as CT or MRI;

- Osteogenic lesions are unmeasurable.

Cystic lesions:

- The lesions that meet the definition criteria of simple cyst in radiology should not be considered as malignant lesions because they are defined as simple cysts. They are neither measurable nor unmeasurable lesions;
- If it is cystic metastasis and meets the above definition of measurability, it can be regarded as measurable lesions. However, if there are non-cystic lesions in the same patient, non-cystic lesions should be preferred as the target lesions.

Local treatment of lesions:

- A lesion located at a site that has been treated with radiotherapy or other local regional therapy is generally considered as a non-measurable lesion unless there is definite progression of the lesion. The protocol should describe in detail the conditions under which these lesions are measurable.

1.2 Description of measurement method

1.2.1 Lesion measurement

In clinical evaluation, all tumor measurements were recorded in metric system. All baseline assessments of tumor size should be completed as close as possible to the start of treatment and within 28 days (4 weeks) before treatment.

1.2.2 Evaluation method

The same techniques and methods should be used for baseline assessment and subsequent measurement of lesions. All lesions must be evaluated by imaging, except those that cannot be evaluated by imaging but only by clinical examination.

Clinical lesions: only when the clinical lesions are located on the superficial surface and the diameter is greater than or equal to 10 mm, can they be considered as measurable lesions (such as skin nodules).For patients with skin lesions, it is recommended to measure the size of lesions with a ruler color photos as archive. When the lesions are evaluated by imaging and clinical examination at the same time, because imaging is more objective and can be reviewed repeatedly at the end of the study, imaging evaluation should be selected as far as possible.

Chest X-ray: when tumor progression is an important end point, chest CT should be preferred because CT is more sensitive than X-ray, especially for new lesions.

Chest X-ray examination is only applicable when the boundary of the measured lesion is clear and the lung ventilation is good.

CT, MRI: CT is currently the best and repeatable method for the evaluation of curative effect. The definition of measurability in this guideline is based on CT scan slice thickness ≤ 5 mm. If the CT slice thickness is greater than 5 mm, the minimum measurable lesion should be 2 times of the slice thickness. MRI is also acceptable in some cases (e.g. whole body scan).

Ultrasound: ultrasound should not be used as a measurement method to measure the size of lesions. Because of its operation dependence, ultrasound examination does not have repeatability after measurement, and can not guarantee the consistency of different measurement techniques and measurements. If ultrasound is used to detect new lesions during the trial, CT or MRI should be used to confirm. If the radiation exposure of CT is considered, MRI can be used instead.

Endoscopy, laparoscopy: these techniques are not recommended for objective tumor evaluation, but they can be used to confirm CR when biopsy specimens are obtained, or in trials with recurrence after CR or surgical resection as the study endpoint.

Tumor markers: tumor markers cannot be used alone to evaluate the objective response of tumors. However, if the marker level exceeds the upper limit of normal at baseline, it must return to normal level when used to evaluate complete remission. When the tumor marker is included in the measurement, it is necessary to take into account the tumor markers. Specific criteria for remission of CA-125 (recurrent ovarian cancer) and PSA (recurrent prostate cancer) have been published. Moreover, the international gynecological cancer organization has formulated the CA-125 progress standard, which will be added to the objective evaluation standard of ovarian cancer first-line treatment program.

Cytology / histology techniques: these techniques can be used to identify PR and Cr (e.g., residual benign tumor tissue is often present in the lesions of germ cell tumors) under specific conditions specified in the protocol. When exudation may be a potential side effect of a treatment (such as treatment with paclitaxel compounds or angiogenesis inhibitors) and the measurable tumor meets the criteria of remission or disease stability, the occurrence or aggravation of tumor related exudation during treatment can be diagnosed by cytological techniques to distinguish remission (or

disease stability) from disease progression.

2 Evaluation of tumor remission

2.1 Evaluation of all tumors and measurable lesions

In order to evaluate objective remission or possible future progress, it is necessary to evaluate the total tumor load of all tumor lesions at baseline, which can be used as a reference for later measurement results. In clinical protocols with objective remission as the primary treatment endpoint, only patients with measurable lesions at baseline were included. Measurable lesions are defined as the presence of at least one measurable lesion. For those trials with disease progression (disease progression time or fixed date progression degree) as the primary treatment endpoint, the protocol inclusion criteria must specify whether it is limited to patients with measurable lesions or not.

2.2 Baseline records of target and non target lesions

When there is more than one measurable lesion at baseline, all lesions should be recorded and measured, with a total of no more than 5 lesions (no more than 2 lesions per organ). As the target lesions, all the involved organs should be represented (that is, patients with only one or two cumulative organs can select at most two or four target lesions as baseline measurement lesions).

Target lesions must be selected based on size (longest diameter), be representative of all organs involved, and measurements must be reproducible. Sometimes, when the largest lesion can not be measured repeatedly, it can be re selected.

Lymph nodes need special attention because they are normal tissues and can be detected by imaging even without tumor metastasis. Pathological lymph nodes defined as measurable nodules or even target lesions must meet the following criteria: CT measurement of short diameter ≥ 15 mm. The baseline only needs to detect the short diameter. Radiologists usually use the short diameter of the nodule to determine whether the nodule has metastasis. The sagittal plane or the sagittal plane of the MRI was used to detect the axial plane. The minimum value is the short diameter. For example, a 20 mm×A 30 mm abdominal nodule with a short diameter of 20 mm can be regarded as a malignant and measurable nodule. In this example, 20 mm is the measurement of the nodule. Nodules ≥ 10 mm but < 15 mm in diameter should not be

considered as target lesions. However, nodules less than 10 mm do not belong to the category of pathological nodules and need not be recorded and further observed.

The sum of the calculated diameters of all target lesions (including the longest diameter of non nodular lesions and the short diameter of nodular lesions) will be reported as the sum of baseline diameters. If lymph node diameter is included, as mentioned above, only the short diameter is included. The sum of baseline diameters will be used as a reference value for the baseline level of the disease.

All the other lesions, including pathological lymph nodes, can be regarded as non target lesions and need not be measured but be recorded during baseline evaluation. such as "existing", "missing" or in rare cases "clear progress". Extensive target lesions can be recorded with the target organs (e.g., massive enlargement of pelvic lymph nodes or large-scale liver metastasis).

2.3 Mitigation criteria

2.3.1 Target lesion assessment

Complete response (CR): all target lesions disappeared, and the short diameter of all pathological lymph nodes (including target and non-target nodules) must be reduced to < 10 mm.

Partial response (PR): the sum of the target lesion diameters was reduced by at least 30% from baseline.

Disease progression (PD): Taking the minimum value of the sum of all measured target lesion diameters in the whole experimental study as reference, the relative increase of diameter sum is at least 20% (if the baseline measurement value is the minimum, the baseline value is used as reference); In addition, an increase of at least 5 mm in the absolute value of diameter sum must be satisfied (the presence of one or more new lesions is also considered as disease progression).

Disease stability (SD): the reduction of the target lesion did not reach PR, and the increase did not reach the PD level, which was between the two. The minimum value of the sum of diameters can be used as a reference.

2.3.2 Considerations of target lesion evaluation

Even if the diameter of the lymph node was within 10 mm, the value of the actual short diameter corresponding to the baseline is still recorded for each measurement, it was consistent with the actual measurement of the lymph node. This

means that if the lymph node is a target lesion, even if it reaches the criteria of complete remission, it cannot be said that all the lesions have disappeared, because the short diameter of normal lymph nodes is defined as < 10 mm. Target lymph node lesions need to be specifically recorded at specific locations in CRF tables or other recording modalities. For CR, the short diameter of all lymph nodes must be less than 10 mm; For PR, SD and PD, the actual measurement of the short diameter of the target lymph node will be included in the sum of the target lesion diameters.

Target lesions too small to be measured: in clinical studies, all lesions recorded at baseline (nodular or non-nodule) should be re-recorded in subsequent assessments, even if the lesion is very small (e.g. 2 mm).However, sometimes it may be too small to make CT images very blurred, and it is difficult for radiologists to define the exact value, which may be reported as "too small to measure". When this happens, it is important to record a value on the CRF table. If the radiologist thinks that the lesion may have disappeared, it should also be recorded as 0 mm. If the lesion does exist, but it is vague, and the accurate measurement value cannot be given, the default value is 5 mm。(Note: this condition is unlikely to occur in lymph nodes, which normally have measurable size or are often surrounded by adipose tissue as in the retroperitoneal cavity; however, if the measurement value cannot be given, the default value is 5 mm).The default value of 5 mm is derived from the cutting thickness of CT scan (this value does not change with different cutting thickness values of CT).Since the probability of recurrence of the same measurement is small, providing this default value will reduce the risk of miscalculation. However, it should be reiterated that if the radiologist can give the exact value of the lesion size, even if the lesion diameter is less than 5 mm, the actual value must be recorded.

Separated or combined lesions: when the non nodular lesions split into fragments, the longest diameters of the separated parts were added up to calculate the sum of the diameters of the lesions. Similarly, combined lesions can be distinguished by the plane between the junctional parts, and their maximum diameters are calculated. However, if the combination is inseparable, the longest diameter should be the longest of the whole body.

2.3.3 Evaluation of non target lesions

In this part, we define the remission criteria of non-target tumor. Although some non target lesions can be measured in practice, there is no need for measurement, and only

qualitative evaluation is needed at the time point specified in the protocol.
Complete response (CR): all non-target lesions disappeared and tumor markers returned to normal level. All lymph nodes were of non-pathological size (short diameter < 10 mm).
Non persistent or non-persistent or multiple tumor markers.
Disease progression: clear progression of existing non-target lesions. Note: the presence of one or more new lesions is also considered as disease progression.

2.3.4 Special considerations for evaluation of progression of non target lesions

The definition of progression of non-target lesions is explained as follows: when patients have measurable non target lesions, even if the target lesions are assessed as stable or partial remission, to make a clear definition of progression on the basis of non-target lesions, the overall deterioration of non-target lesions must reach the extent that treatment must be terminated. However, the general increase in the size of one or more non target lesions is often insufficient to meet the progression criteria. Therefore, when the target lesions are stable or partially remitted, it is almost rare to define the overall tumor progression only by the changes of non-target lesions.

When non target lesions are not measurable: in some phase III trials, this occurs when the inclusion criteria do not specify that measurable lesions must exist. The overall assessment was based on the above criteria, but there was no measurable data for the lesion in this case. It is not easy to evaluate the deterioration of non-target lesions (according to the definition: all non-target lesions must be truly unmeasurable). Therefore, when the overall disease load caused by the changes of non-target lesions is equivalent to the disease progression of the target lesions, it is necessary to establish an effective detection method to evaluate according to the definition of non-target lesions. If described as an increase in tumor load, it is equivalent to an additional 73% increase in volume (equivalent to a 20% increase in measurable lesion diameter).Another example is peritoneal effusion from "trace" to "large amount"; Lymphangiopathy changed from "local" to "widespread"; Or described as "enough to change the treatment" in the protocol. Examples include pleural effusion ranging from trace to large, lymphatic involvement spreading from the primary site to the distant, or may be described in the protocol as "therapeutic changes are necessary.". If a definite progression is found, the patient should be considered as disease progression in general at that point in time. It is better to have objective criteria for the evaluation of

unmeasurable lesions. Note that the increased criteria must be reliable.

2.3.5 New lesions

The appearance of new malignant lesions indicates the progress of the disease; Therefore, it is very important to evaluate the new lesions. At present, there is no specific standard for imaging detection of lesions, however, the discovery of a new lesion should be clear. For example, progress cannot be attributed to differences in imaging techniques, changes in imaging morphology, or other lesions other than tumors (e.g., some so-called new bone lesions are merely the cure of the original lesions or the recurrence of the original lesions).This is very important when a patient's baseline lesion shows partial or complete response. For example, a case of necrosis of a liver lesion may be identified as a new cystic lesion on CT, but it is not.

New lesions detected in the follow-up and not detected in the baseline will be considered as new lesions. For example, if a patient with visceral lesions found at baseline has metastases when he has a CT or MRI cranial examination, the patient's intracranial metastases will be considered as the basis for disease progression, even if he does not have a cranial examination at baseline.

If a new lesion is unclear, such as due to its small shape, further treatment and follow-up evaluation are needed to confirm whether it is a new lesion. If repeated examinations confirm that it is a new lesion, the time of disease progression should be counted from the time of its initial discovery.

FDG-PET evaluation of lesions generally requires additional detection for supplementary confirmation. It is reasonable to combine FDG-PET and CT findings to evaluate the progress (especially for new suspicious diseases). FDG-PET can be used to confirm the new lesions, according to the following procedures:

The baseline FDG-PET was negative, and the follow-up FDG-PET was positive, indicating the progression of the disease.

No baseline FDG-PET was performed, and the subsequent FDG-PET results were positive

If the follow-up FDG-PET positive results show that new lesions are consistent with CT findings, it is proved that the disease is progressing.

If the follow-up FDG-PET positive results found new lesions can not be confirmed by CT examination results, it needs to be confirmed by CT (if confirmed, the time of disease progression starts from the abnormal findings of previous FDG-

PET).

If the positive results of FDG-PET follow-up are consistent with the existing lesions examined by CT, and the lesions have no progress in imaging detection, then the disease has no progress.

2.4 Evaluation of the best overall efficacy

The best overall efficacy evaluation is the best efficacy record from the beginning of the trial to the end of the trial, taking into account any necessary conditions for confirmation. Sometimes the curative effect reaction appears after the treatment, so the scheme should make clear whether the curative effect evaluation after the treatment is considered in the best overall curative effect evaluation. The protocol must define how the new treatment affects the best response before any progression. The best response depends on the results of target and non-target lesions and the performance of new lesions. In addition, it also depends on the nature of the trial, the requirements of the protocol and the criteria for measuring the results. Specifically, in non-randomized trials, efficacy response is the primary objective, and efficacy confirmation of PR or Cr is necessary to determine which is the best overall response.

2.4.1 Point in time response

It is assumed that there will be therapeutic response at specific time points of each protocol. Table 1 provides a summary of the overall response at each time point for a population of patients with measurable disease at baseline.

If the patient has no measurable lesions (no target lesions), the assessment can be seen in Table 2.

2.4.2 Missing lesions evaluations and non-evaluative explanations

If there is no imaging or measurement of the lesion at a specific point in time, the patient cannot be evaluated at that point in time. If only part of the lesions can be evaluated in a single evaluation, this situation is usually regarded as no evaluation can be made at any time point, unless there is evidence that the missing lesion will not affect the evaluation of response at a given time point. This is likely to happen in the case of disease progression. For example, a patient has 3 total number of lesions 50 mm, but only 2 lesions can be evaluated, the total is 80 mm, and the patient will be evaluated as disease progression, regardless of the impact of the missing lesions.

2.4.3 Optimal total response: all time points

Once all the data of the patient are available, the optimal total response can be determined.

Evaluation of the best overall response when the study does not need to confirm complete or partial response: the best response in the trial was the best response at all time points(for example, a patient is evaluated as SD in the first cycle, PR in the second cycle, and PD in the last cycle, but the best total response is PR. when the best overall response is SD, it must meet the minimum time from baseline specified in the protocol. If the criteria for the shortest time are not met, even the best overall response evaluation is SD, it is not recognized The best overall response of the patient will depend on subsequent evaluation. For example, a patient was evaluated as SD in the first cycle and PD in the second cycle, but it did not meet the minimum time requirement of SD, and the best overall response was PD. The loss of follow-up for the same patients who were evaluated as SD in the first cycle would be considered as non evaluable.

When the study needs to confirm the complete or partial response, the assessment of the best total response: complete or partial remission can be declared only when each subject meets the criteria of partial or complete remission specified in the trial and is confirmed again at a subsequent time point (usually four weeks later) specifically mentioned in the protocol. In this case, see Table 3 for the best total response.

2.4.4 Special tips for efficacy evaluation

When nodular lesions are included in the total target lesion assessment and the nodule size is reduced to "normal" size (< 10 mm), they still have a lesion size scan report. In order to avoid overestimation of the situation reflected by the increase in nodule size, the measurement results will be recorded even if the nodule is normal. As mentioned earlier, this means that subjects with complete remission will not have a zero on the CRF table.

Repeated "unmeasurable" time points will complicate the assessment of optimal efficacy if efficacy confirmation is required during the trial. The analysis plan of the trial must state that these missing data / assessments can be explained clearly in determining efficacy. For example, in most trials, the response of a subject's PR-NE-PR can be regarded as the confirmation of curative effect.

Symptomatic progression should be reported when the subject's overall health

deterioration requires discontinuation of treatment, but there is no objective evidence to prove it. Objective progress should be evaluated as far as possible even after the termination of treatment. Symptomatic deterioration is not an evaluative description of an objective response: it is the reason for discontinuation of treatment. The objective response of such subjects will be evaluated by the target and non-target lesions shown in Tables 1 to 3.

Defined as early progression, early death and non-evaluable conditions are special cases of the study and should be clearly described in each protocol (depending on treatment interval and treatment cycle).

In some cases, it is difficult to distinguish local lesions from normal tissues. When the assessment of complete response is based on such a definition, we recommend that biopsy be performed prior to the evaluation of the efficacy of complete remission of local lesions. FDG-PET was used to evaluate the efficacy of complete remission when abnormal imaging results of local lesions in some subjects were considered to represent focal fibrosis or scar formation. In this case, the application of FDG-PET should be prospectively described in the protocol, and supported by the reports of specialized medical literature on this situation. However, it must be realized that the limitations of FDG-PET and biopsy (including the resolving power and sensitivity of both) will lead to false positive results in complete remission assessment.

Evaluation at each time point - subjects with target lesions (including or without non target lesions)

Target lesion	Non target lesions	New lesions	Total remission
CR	CR	Non	CR
CR	Non PD / non CR	Non	PR
CR	Cannot be evaluated	Non	PR
PR	Not progressing or fully evaluated	Non	PR
SD	Not progressing or fully evaluated	Non	SD
Not fully evaluated	Non progress	Non	NE
PD	Any situation	Yes or non	PD
Any situation	PD	Yes or non	PD
Any situation	Any situation	Yes	PD

CR = complete remission	PR = partial remission	SD = stable disease	PD = disease progression NE = cannot be evaluated

Evaluation at each time point - subjects with non-target lesions only

Non target lesions	New lesions	Total remission
CR	Non	CR
Non CR or non PD	Non	Non CR or non PD
Not fully evaluated	Non	Cannot be evaluated
Indeterminate PD	Yes or Non	PD
Any situation	Yes	PD

Note: for non-target lesions, "non CR / non PD" refers to better efficacy than SD.As the SD is increasingly used as an end point for evaluating efficacy, non CR / non PD outcomes are developed to address the absence of measurable lesions.

For unclear progression findings (such as very small, uncertain new lesions; cystic or necrotic lesions of the original lesions), treatment can continue until the next evaluation. If disease progression is confirmed in the next assessment, the date of progression should be the date of previous suspected progression.

The best overall efficacy of CR and PR needs to be confirmed

The first time point with total remission	The after time point with total remission	The best total remission
CR	CR	CR
CR	PR	SD，PD or PR[a]
CR	SD	SD if it lasts long enough, PD otherwise
CR	PD	SD if it lasts long enough, PD otherwise
CR	NE	SD if it lasts long enough, NE otherwise
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if it lasts long enough, PD otherwise
PR	NE	SD if it lasts long enough, NE otherwise
NE	NE	NE

Note: CR is complete remission, PR is partial remission, SD is disease stability, PD is disease progression, NE is not evaluable. Superscript "a": if CR really occurs at the first time point and any disease occurs at a subsequent time point, even if the subject's efficacy meets the PR criteria relative to the baseline, the efficacy evaluation at the later time point is still PD (because the disease will recur after CR).The best response depends on the presence of SD within the shortest treatment interval. However, sometimes CR was evaluated for the first time, but subsequent time point scanning showed that small lesions still appeared. Therefore, in fact, the curative effect of subjects should be PR rather than CR at the first time point. In this case, the first CR judgment should be modified to PR, and the best response is PR.

2.5 Frequency of tumor reassessment

The frequency of tumor re-evaluation during treatment depends on the treatment plan and should be consistent with the type and schedule of treatment. However, in phase II trials where the benefit of treatment is not clear, it is reasonable to follow up every 6-8 weeks (the time design is at the end of a cycle), and the length of time interval can be adjusted under special programs or circumstances. The protocol should specify which tissue sites need to be evaluated at baseline (usually those that are most likely to be closely related to the metastatic lesions of the tumor type studied) and the frequency of evaluation repetition. Under normal circumstances, target lesions and non target lesions should be evaluated at each evaluation. In some optional cases, the evaluation frequency of some non target lesions can be smaller. For example, if the curative effect evaluation of the target disease is confirmed as CR or the progression of bone lesions is suspected, bone scan is required.

At the end of treatment, re-evaluation of the tumor depends on whether the response rate or the time to an event (progression / death) is taken as the end point of the clinical trial. If it is the time of occurrence (e.g. TTP / DFs / PFS), it is necessary to conduct the routine repeated evaluation specified in the protocol. Especially in randomized controlled trials, the scheduled evaluation should be listed in the schedule (e.g. 6-8 weeks in the treatment or 3-4 months after the treatment), and should not be affected by other factors, such as treatment delay, administration interval and any other events that may lead to unbalanced treatment arm in the selection of disease evaluation time.

2.6 Efficacy evaluation / confirmation of remission

2.6.1 confirm

For non-randomized clinical studies with efficacy as the main end point, the efficacy of PR and CR must be confirmed to ensure that the efficacy is not the result of evaluation error. This also allows for a reasonable interpretation of the results when historical data are available, but the efficacy in the historical data of these trials should

also be confirmed. But in other cases, such as randomized trials (phase II or phase III) or studies with disease stability or disease progression as the primary endpoint, efficacy confirmation is no longer required because it is not valuable for the interpretation of trial results. However, the elimination of the requirement of efficacy confirmation will make the central review of prevention of deviation more important, especially in non-blind experimental studies.

In the case of SD, at least one measurement meets the SD standard specified in the protocol within the shortest time interval (generally no less than 6-8 weeks) after the start of the trial.

2.6.2 The total remission period

The total remission period is the time from the first measurement of CR or PR (whichever is measured first) to the time when the disease relapse or progression is first recorded (the minimum measurement recorded in the trial is used as a reference for disease progression).The total complete remission time was the time from the first time the CR criteria were measured to the time when the disease relapsed or progressed.

2.6.3 Stable period of disease

It is the time from the beginning of treatment to the progression of disease (in randomized trials, from the time of randomization), with the smallest sum in the trial as the reference (if the baseline sum is the smallest, it is used as the reference for PD calculation).The clinical relevance of stable disease varies with different studies and diseases. If, in a particular trial, the proportion of patients who maintain the shortest stable period is taken as the end point, the protocol should specify the shortest time interval between the two measurements in SD definition.

Note: remission, stabilization and PFS are affected by the frequency of follow-up after baseline evaluation. The definition of standard follow-up frequency is not within the scope of this guideline. The frequency of follow-up should consider many factors, such as disease type and stage, treatment cycle and standard specification. However, if the comparison between tests is needed, the limit of accuracy of these measurement end points should be considered.

APPENDIX 4 Clinical benefit response (CBR)

CBR included pain (intensity of pain and consumption of analgesics), PS (performance status, evaluated according to KPS) and weight changes.

Clinical benefit assessment classification

Main evaluation criteria:
Pain
① Pain intensity (assessed daily with MPAC 0-100 visual analogue scale)
Positive: improvement ≥ 50% compared with baseline and lasting for ≥ 4 weeks (assuming minimum pain score ≥ 20)
Negative: any deterioration compared with baseline lasted for 4 weeks
Stable: any other results
② Consumption of analgesics (evaluated according to the consumption of equivalent dose of morphine, once a week)
Positive: compared with baseline, the consumption of analgesic drugs was more than or equal to 50%, and the minimum improvement was ≥ 10%
Negative: any deterioration compared with baseline lasted for 4 weeks
Stable: any other results
KPS physical status score: once a week
Positive: KPS 50, 60, 70 patients, compared with the baseline, the improvement was more than 20 KPS score, and lasted for more than 4 weeks
Negative: any deterioration ≥ 20 KPS score compared with baseline and lasting for more than 4 weeks
Stable: any other results
Secondary evaluation criteria: Weekly evaluation
Weight
Positive: weight gain > 7% (non-fluid retention) compared with baseline and lasting for more than 4 weeks
Non positive: any other results

According to the standard[13] developed by Burris et al., the classification of CBR was evaluated. Effective: there is at least one positive improvement in the CBR index (pain, physical status or weight change) and no negative indicator is found, which can be rated as a clinical benefit case. Stable: pain, physical condition or weight change were rated as stable; Invalid: one of the three indicators was aggravated.

APPENDIX 5: NYHA classification

NYHA classification: the classification of heart failure, NYHA classification is based on the degree of activity of inducing heart failure symptoms, the damage of cardiac function is divided into four grades. This protocol was proposed by the New York Heart Association (NYHA) in 1928.In fact, NYHA classification is actually a classification of severity of symptoms in patients with stage C and stage D.

Grade I: Patients with heart disease, but the amount of daily activities is not limited, general physical activities do not cause excessive fatigue, palpitations, asthma or angina pectoris.

Grade II: the physical activity of patients with heart disease is slightly limited. There are no conscious symptoms at rest. General physical activity causes excessive fatigue, palpitation, asthma or angina pectoris.

Grade III: Patients with heart disease, so that physical activity is significantly restricted. Rest without symptoms, but less than general physical activity can cause excessive fatigue, palpitations, asthma or angina pectoris.

Grade IV: Patients with heart disease can not engage in any physical activity, and have symptoms of heart failure in resting state, which aggravates after physical activity.

AHA supplement to the 1928 NYHA classification grade of cardiac function (1994)

According to ECG, exercise load test, X-ray, echocardiography, radiology and other objective examination results, the second classification was made.

Grade A: objective evidence of no cardiovascular disease

Grade B: objective evidence of mild cardiovascular disease;

Grade C: objective evidence of moderate cardiovascular disease;

Grade D: objective evidence of severe cardiovascular disease

Signature page

Scheme No.: BPL-Nim-PC-1

Protocol Title: a prospective, randomized, double-blind, multicenter clinical trial of nimotuzumab combined with gemcitabine versus placebo plus gemcitabine in the treatment of locally advanced or metastatic pancreatic cancer of wild type K-RAS

Trial drug: nimotuzumab injection

All parties stated that the clinical trial protocol was jointly formulated by the sponsor, the researcher and the statistician. I agree to perform my duties in accordance with the provisions of the declaration of Helsinki and the code for quality management of clinical trials of drugs, and conduct this clinical trial in strict accordance with the requirements of the clinical trial protocol.