Patient Derived Organoid-guided Personalized Treatment Versus Treatment of Physician's Choice in Patients With Relapsed and Refractory Breast Cancer：a Multicenter, Randomized, Controlled Phase III Trial

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1. Background of the study

Breast cancer is the leading cause of morbidity and mortality among women in the world. 2.26 million new cases of breast cancer were diagnosed globally in 2020, surpassing lung cancer (2.21 million cases) for the first time to become the world's top cancer [1]. China is a big country for breast cancer , there were about 306,000 new cases of breast cancer in 2016, accounting for about 16.72% of all new cancers [2]. In 2020, new cases of breast cancer increased to approximately 420,000, resulting in nearly 120,000 deaths. Although the overall cure rate of breast cancer has greatly improved over the past three decades with the improvement of comprehensive treatments, a considerable proportion of patients still experience recurrence and metastasis. Taking my country as an example, approximately 71,700 women died of breast cancer in 2016, accounting for approximately 25% of all breast cancers [2]. Therefore, the prevention and treatment of breast cancer still has a long way to go.

As research on tumour-like organs intensifies, we have new hope for breast cancer treatment [3, 4]. Tumour organoids are three-dimensional cell culture models that mimic the growth environment of a tumour in vivo, providing a model that is closer to the reality of tumour research. Compared with traditional cell culture models, tumour organoids can better simulate tumour heterogeneity, drug response and metastatic behaviour [5] . Currently, tumour organoid models of lung cancer [6], hepatocellular carcinoma [7], pancreatic cancer [8], bladder Cancer [9] gastric Cancer [10] and endometrial cancer[11] have been successfully established, and breast cancer organoids have also become a useful preclinical model. The main applications of tumour organoids in breast cancer treatment include predicting drug response, screening anticancer drugs, investigating tumour resistance, and optimising individualised treatment regimens [12]. Firstly, by using tumour-like organs, we can predict a patient's response to a specific drug [13, 14]. This predictive ability is essential for physicians to select the most appropriate drug for a patient [13, 14]. This predictive ability is crucial for doctors to choose the most appropriate treatment

regimen, which can help achieve better treatment outcomes at an early stage. Secondly, tumour organoids have also been used to screen new anti-cancer drugs. While traditional drug screening methods usually require a lot of time and resources, tumour organoids are able to screen drugs in a shorter period of time, improving the efficiency of drug development [15] . In addition, tumour organoids are also important for the study of tumour drug resistance. By simulating the process of tumour drug resistance, we can better understand the resistance mechanism and thus develop more effective anti-cancer drugs. Finally, tumour organoids can also be used to optimise individualised treatment plans. Each patient's tumour is unique, and tumour organoids can help us understand the characteristics of each patient's tumour and thus develop a more personalised treatment plan. Tumour organoids will play an increasingly important role in the future treatment of breast cancer.

This study will make use of tumour-derived organoids to tailor the most appropriate drug dosage and treatment regimen for each patient, thereby avoiding the use of unnecessary drugs on patients and reducing the waste of healthcare resources, which in turn will allow for a more effective treatment of breast cancer, thus improving the survival rate and quality of life of patients.

1.2 Basis for study design

Treatment of advanced breast cancer has long been challenging. Genomic profiling provides treatment options for some patients, but there are also many cases where genomic profiling fails to specify effective interventions or where patients develop tolerance to drugs associated with genomic alterations. This makes it critical to find more effective treatments and predictive tools. PDO is an easy-to-operate tool that serves as a three-dimensional cell culture that simulates the physiological and pathological characteristics of a specific organ or tissue, providing a new way to solve this problem. In breast cancer research, organoids can simulate the heterogeneity of tumor tissue and provide a more realistic model for research. Research into breast cancer organoids for personalized treatment is still in the developmental stages. By cultivating a patient's breast cancer cell lines and observing their response to

different drugs, the most effective treatments can be found. In addition, organoids can also be used to test new anti-tumor drugs, providing a useful tool for new drug development. Previous studies have shown that PDO has strong biological fidelity to its original tumor and that precision treatment based on PDO drug screening can bring survival benefits to breast cancer patients.

Clinical practice shows that for patients with advanced multi-line treatment, not every patient can participate in clinical research or find suitable treatment based on genetic testing results. These patients still need to explore more feasible and effective treatment options. Based on this, we The research team successfully established a breast cancer organoid platform in the early stage, customized a personalized drug library containing breast cancer anti-tumor drugs, and conducted drug screening on most organoids. According to the results of our drug screening, it can be seen that some drugs not only The anti-tumor effect is limited and can promote tumor growth. Patients can follow our experimental results to choose drugs that are more likely to be effective and avoid drugs that may promote tumor progression, thereby improving the treatment effect and prolonging survival. This provides personalized treatment for breast cancer. Provides new ideas and methods.

2 Purpose of the study

2.1 Purpose of the study

2.1.1 Main purpose

-Observation of the efficacy of an organoid-guided personalised treatment plan for oncology patients in comparison with a physician's choice of plan for the treatment of patients with recurrent refractory breast cancer.

2.1.2 Secondary objectives

-To observe the safety and tolerability of patient-derived organoid-guided personalized treatment regimens versus physician-selected regimens in patients with relapsed and refractory breast cancer.

3 Experimental design

3.1 Summary of the experimental design

3.1.1 Subject population/treatment group allocation

This multicenter, open-label, randomized phase III trial is investigating organoid-guided treatment (OGPT) versus treatment of physician's choice (TPC) in previously treated breast cancer. effectiveness and safety. Randomization will be stratified by molecular subtype, presence of visceral metastases, and number of prior chemotherapy treatments for advanced or metastatic disease. Subjects in the OGPT group will receive the treatment predicted to be most effective by PDO susceptibility screening, and subjects in the TPC group will receive the treatment selected by the attending physician. The main population included in the study is patients with refractory breast cancer who have received multiple lines of treatment in the past and have at least one measurable target lesion according to RECIST1.1 standards.

After meeting the enrollment conditions, randomization will be performed, and patients will be randomly assigned to the experimental group or the control group in a 1:1 ratio. Randomization will be conducted centrally by the GCP institution of this research center. After the subjects sign the informed consent form, the researcher will assign them an identification code based on the order of enrollment. The code consists of 3 digits, representing the subject serial number. The researcher Fill in the identification code into the "Subject Identification Code Table" and save it. This trial is an open study without blinding.

Treatment: Subjects randomly assigned to OGPT need to provide sufficient tissue for organoid culture. After successful organoid culture, drug screening will be performed, and they will be treated with drugs predicted to be sensitive by PDO drug susceptibility screening.

Subjects in the TPC arm will receive treatment with one of the following regimens selected by the physician following NCCN guidelines: capecitabine, gemcitabine, vinorelbine, and eribulin. If it is HER2-positive, anti-HER2 therapy can be combined with it, except for ADC drugs.

3.1.2 Efficacy variables

3.1.2.1 Main efficacy parameters

Progression-free survival (PFS)

3.1.2.2 Secondary efficacy parameters

- Objective Rate of Effectiveness (ORR)
- Duration of remission (DOR)
- Overall survival (OS)
- Duration of Continuous Remission (DCR)

3.1.3 Security variables

- Adverse events and serious adverse events

- Symptoms and signs

- Laboratory tests

- Sudden adverse events in treatment leading to dosage adjustments, interruptions in administration, delays, non-administration, and/or discontinuation of study medication

3.1.4 Assessment of quality of life

Quality of life was assessed using the EQ-5D (Euro QoL five-dimensions questionnaire) and the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30) scales were used to assess patients' quality of life.

3.2 Duration of the experiment

The trial is intended to have 24 months of enrolment and 24 months of follow-up, and is expected to last 48 months from the enrolment of the first subject to the analysis of the data. Except in the event of progression, or death, subjects are expected to complete the visit schedule specified in the protocol.

3.2 Study endpoints

3.2.1 Criteria for evaluating efficacy

Evaluation was performed according to the criteria for the evaluation of the efficacy of solid tumours (RECIST) version 1.1, as detailed in Appendix 1.

3.2.2 Primary endpoints

-Progression-free survival (PFS)

3.2.3 Secondary endpoints

- Objective Rate of Effectiveness (ORR)
- Duration of remission (DOR)
- Overall survival (OS)
- Duration of Continuous Remission (DCR)
- Safety and tolerability (type, frequency, severity, relationship of adverse events to study treatment, physical examination, vital signs, laboratory tests, co-administration/treatment, and dose adjustment)
- Quality of life assessment of patients

3.2.4 Exploratory molecular marker studies

Tumour samples (primary and/or metastatic), blood specimens are collected and preserved for future exploratory studies of factors that have the potential to influence or predict efficacy (including efficacy and safety) of the treatment, with the following key measurements (but not limited to):

Other biomarkers, whole exome sequencing (WES), ctDNA testing, etc.

3.3 Evaluation of therapeutic efficacy

3.3.1 Timing of efficacy evaluations

Efficacy evaluations will be performed prior to administration of the study drug, every 2 courses during chemotherapy, and at completion or withdrawal for all patients.

3.3.2 Means of efficacy evaluation

The evaluation of the efficacy of the treatment before the administration of drugs and after each chemotherapy, maintenance treatment, visceral lesion sites require evaluation by CT, MRI or PET-CT, and surface lesions require evaluation by physical examination by the physician and truthfully recorded in the original medical record as objective evidence. Suspected invasive sites can be screened with chest

radiographs or ultrasound, but when a lesion is clearly present, it must be evaluated with CT or MRI.

4 Trial population

4.1 Test centers

Sun Yat-sen University Cancer Center

Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University

Foshan First People's Hospital

4.2 Number of cases

This trial is expected to enrol 302 subjects with recurrent refractory breast cancer patients within 24 months.

4.3 Inclusion criteria

(1) Voluntarily participate and sign the informed consent form

(2) Aged over 18 years old, regardless of gender;

(3) Locally advanced or metastatic breast cancer confirmed by histopathology;

(4) Received ≥2 previous lines of anti-tumor treatment and developed resistance to standard treatment;

(5) Life expectancy ≥3 months;

(6) ECOG performance status 0 to 2;

(7) Have measurable or/and evaluable lesions (non-radiotherapy target areas) (lesion evaluation is based on Recist1.1 standards);

(8) No serious organ (main organ: heart, lung, liver, kidney) functional abnormalities (refer to respective standards);

(9) Routine blood test: white blood cells (WBC) ≥3 × 109/L; absolute neutrophil count (ANC) ≥1.5 × 109/L; platelets (PLT) ≥100 × 109/L; hemoglobin (Hgb) ≥8g /dL;

(10) Blood biochemical indicators: AST (SGOT), ALT (SGPT) ≤ 2.5 × upper limit of normal value (ULN) (in the case of no liver invasion) or ≤ 5 × upper

limit of normal value (ULN) (in the case of liver invasion) Bottom); total bilirubin (TBIL) ≤ ULN; serum creatinine clearance calculated according to the CG formula > 30 mL/min

(11) Coagulation function: prothrombin time (PT), international normalized ratio (INR) ≤ 1.5 × ULN (unless warfarin is being used for anticoagulation);

(12) Able to comply with the research visit plan and other program requirements;

(13) All patients of childbearing age must agree to take effective contraceptive measures during the study and within 6 months of stopping treatment. Female patients of childbearing age must have a negative urine pregnancy test before treatment.

Subjects must meet all of the following additional criteria to be included in the OGPT group:

1) No absolute contraindications to tissue-invasive procedures required to obtain organoid cultures。

2) Sufficient tissue can be provided for organoid culture: biopsy samples (length >1cm, 3 strips), surgical resection samples (total volume >1cm^3, weight >0.2g), thoracentesis, abdominal puncture, pericardiocentesis and other malignant effusion samples (pleural effusion >500mL, ascites >500m) and confirmed to contain malignant tumor cells.

4.4 Exclusion criteria:

(1) The medical history and comorbidities are as follows:

a. The patient is participating in other interventional clinical studies or the end of treatment in the previous clinical study is less than 4 weeks;（2） Those who have been treated less than 4 weeks since the last anti-tumor treatment (radiotherapy, chemotherapy, targeted therapy, immunotherapy or local-regional treatment); the adverse reactions related to anti-tumor treatment (except alopecia) after previous systemic anti-tumor treatment

have not returned to NCI- Patients with CTC AE ≤ grade 1;

b. Other active malignant tumors that require simultaneous treatment;

c. Known history of organ transplantation and allogeneic hematopoietic stem cell transplantation;

d. For subjects who have undergone major surgery or severe trauma, the effects of the surgery or trauma have been eliminated for less than 14 days before enrollment;

e. Patients with active pulmonary tuberculosis need to be excluded. Patients suspected of having active pulmonary tuberculosis should have chest X-rays, sputum, and clinical symptoms and signs to rule out the disease. Patients with a history of active pulmonary tuberculosis infection within the previous year must be excluded, even if they have been treated; patients with a history of active pulmonary tuberculosis infection more than 1 year ago must also be excluded, unless it is proven that the course and type of anti-tuberculosis treatment previously used are satisfactory. appropriate;

f. Severe acute or chronic infection requiring systemic treatment

g. Suffering from heart failure (New York Heart Association Class III or IV) and despite receiving appropriate medical treatment, poorly controlled coronary artery disease or arrhythmia, or a history of myocardial infarction within 6 months before screening patient.

(2) Pregnant or lactating women.

(3) No anti-tumor treatment is planned.

(4) Known to have a positive history of human immunodeficiency virus (HIV) test or known to have acquired immunodeficiency syndrome (AIDS);

(5) Untreated active hepatitis (hepatitis B: HBsAg positive and HBV DNA ≥ 500IU/mL; hepatitis C: HCV RNA positive and abnormal liver function); combined with hepatitis B and hepatitis C co-infection;

(6) Hypersensitivity to any study drug;

4.5 Culling Criteria:

1) Those who are found to be incompatible with the case selection criteria after selecting subjects;

2) Those who have taken the drug less than 2 times continuously after being selected, and the objective efficacy cannot be evaluated (but adverse reactions can be evaluated);

3) Patients who violate the requirements of the trial protocol.

4.6 Exit criteria

Patients can withdraw from a clinical trial at any time and for any reason. If the researcher believes that it is not appropriate to continue taking the medication, the researcher may also ask the patient to withdraw based on the interests of the patient.

If one of the following conditions occurs to a subject during the trial, the investigator should arrange for the subject to interrupt treatment and withdraw from the trial:

1) The subjects have poor compliance and cannot take the medicine on time and in the right amount;

2) The use of other anti-tumor treatments affects the judgment of results;

3) Adverse reactions occur and the researcher determines that it is not appropriate to continue this clinical study;

4) The subject withdraws voluntarily if he or she is unwilling to continue this clinical study.

Before withdrawing from the trial, the latest follow-up and assessment of various efficacy and adverse reaction indicators must be completed, and the reasons and dates of withdrawal of the withdrawing patients must be recorded in detail.

5 Research flow chart

Item	Pre-enrolment baseline assessment (within 2 weeks prior to	Organ-Guided Therapy (OGPT) or Therapy of Physician's Choice (TPC) per procedure	Examination at the end of 2, 4 and 6 courses of combined treatment

	enrolment)		
Imaging (CT/MRI/PET-CT chest, abdomen, pelvis)	X		X
Pathological examination/consultation	X		
Entry Audit	X		
Signed informed consent	X		
Population statistics	X		
Detailed history and complete physical examination	X	X	X
Clinical biochemistry, urine and faecal laboratory tests	X	X	X
routine blood test	X	X	X
blood tumour marker	X	X	X
Urine pregnancy test	X		
electrocardiography	X	X	X
tumour specimen	X		
blood specimen	X	X	
ECOG score	X	X	X
undesirable incident		X	X
Accompanying treatment records		X	X
Quality of life assessment, PRO assessment	X	X	
Confirmation of tumour progression and survival status		X	X

6 Research steps

6.1 Screening

The investigator gave informed consent to subjects who were eligible for enrolment and the next study step could only be performed if the subject signed the

latest version of the informed consent form. The investigator, in conjunction with the inclusion/exclusion criteria of the protocol, assessed the subjects' tumour characteristics based on the imaging data (tumour histopathology, CT/MRI chest, abdomen and pelvis plain + enhancement, endoscopy, ultrasound as a complementary means to CT, PET/CT scanning not routinely performed at the centre), which included tumour site, number, size, extent of invasion of the large blood vessels, The assessment includes tumour location, number, size, extent of macrovascular invasion, cancer embolism, extent of surrounding tissue invasion, etc., and should be recorded in the medical record, and the imaging data should be collected and stored as a source file. If the imaging examination cannot be obtained or is not accepted by the investigator within two weeks before enrolment, the subject will be recommended to undergo another CT in our hospital, and the investigator will re-evaluate the judgement based on this examination and record it.

6.2 Baseline

Before enrollment, the following aspects need to be reviewed to ensure compliance with inclusion/exclusion criteria and to obtain baseline data:

- Chest + Abdomen + Pelvic CT (plain + enhanced)
- Blood tumor markers
- Tumor histopathology or cytology
- If the subject develops relevant abnormal clinical symptoms or signs, and the researcher suspects that they are caused by distant metastasis of the tumor, relevant imaging examinations and/or laboratory examinations may be performed:
    - ○ Suspect brain and nervous system metastasis, perform MRI examination
    - ○ If bone invasion is suspected, perform ECT examination
- Blood routine, urine routine, stool routine + occult blood test, electrocardiogram
- Liver function (aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transpeptidase, total bilirubin, albumin, prealbumin), renal function

(creatinine), electrolytes, blood glucose, blood amylase

- Coagulation function (prothrombin time)
- Urine pregnancy test (female subjects of childbearing age)
- Vital signs, height, weight, physical examination
- ECOG score
- Collect the subject’ s past diabetes, treatment history, and allergy history and record them in the medical record

Based on the imaging report, combined with other laboratory tests and symptoms and signs, the researcher determines whether the subject has disease progression and records it in the medical record.

6.3 Enrolment

The researcher will determine whether the subject meets the enrollment conditions based on the inclusion/exclusion criteria and comprehensive baseline examination results, imaging and pathology results. If so, the researcher will obtain the results based on the patient's informed consent and number the subject (trial code). For successfully enrolled subjects, researchers need to obtain a copy of their ID card for archiving.

6.4 Treatment

6.4.1 Treatment implementation

Subjects randomly assigned to OGPT will undergo PDO drug susceptibility screening to predict effective treatment. Patients need to provide sufficient tissue for organoid culture. After successful organoid culture, drug screening will be performed. Subsequently, sensitive drugs will be screened based on the drug. Get treatment.

Subjects in the TPC arm will receive treatment with one of the following regimens selected by the attending physician following NCCN guidelines: capecitabine, gemcitabine, vinorelbine, and eribulin. If it is HER2-positive, anti-HER2 therapy can be combined with it, except for ADC drugs.

According to the current standard treatment, patients should receive antiemetic drugs when receiving chemotherapy. It is recommended to use a standard antiemetic regimen. Optional antiemetic drugs include 5-HT3 receptor antagonists, dexamethasone or combined NK-1 receptor antagonists. agent (fosaprepitant, aprepitant, etc.), determined by the investigator.

In exceptional circumstances (e.g., dosing is withheld due to the need to manage AEs or infusion-related reactions), subsequent administration of study drug may be delayed to the second day of each cycle.

Test drugs and preparations

1. Specific medications for patients in the test group are based on PDO drug sensitivity results. The current customised personalised drug screen library of the subject group is as follows, and the corresponding drugs may be subsequently adjusted according to the availability of marketed drugs:

Epirubicin hydrochloride	Sunitinib Malate	Erlotinib	Pemetrexed	Gemcitabine	Lenvatinib	5-Fluorouracil	Doxorubicin hydrochloride	Docetaxel	Ifosfamide
Temozolomide	Gefitinib	Olaparib	Cyclophosphamide hydrate	Capecitabine	Dasatinib	Axitinib	Nilotinib	Crizotinib	Imatinib Mesylate
Vinblastine sulfate	Abemaciclib	Ixazomib	Cabazitaxel	Pazopanib	Neratinib	Enzalutamide	Irinotecan	Bleomycin Sulfate	Paclitaxel
Etoposide	Lapatinib	Sorafenib tosylate	Methotrexate	Everolimus	Palbociclib	Decitabine	Cabozantinib	Tegafur	Alpelisib
Alectinib	Ribociclib	Vinorelbine ditartrate	Idasanutlin	Erdafitinib	Ipatasertib	Glumetinib	Topotecan	Larotrectinib	Regorafenib Hydrochloride
Pralsetinib	Afatinib	Bendamustine	Savolitinib	Sotorasib					

According to the results of drug sensitivity, all the drugs applied in the test group will be used according to the instructions or guidelines, the specific dosage and time intervals refer to the instructions of the corresponding drugs, some patients may be involved in the use of super-indications, this part of the application of the drug will be communicated to the patient, under the condition that the patient is fully informed, clear risks and benefits of the application of the drug, and the specific dosage will refer to the corresponding instructions.

2.Table 1 Dose selection and time of administration for each patient in the control group

Research drug	Dosages	Frequency of administration	Route of administration
Gemcitabine	1000mg/m2	Day 1, Day 8 of each 21-day cycle	intravenous
Capecitabine	1000mg/m2	Days 1-14 of each 21-day cycle	Oral
Vinorelbine	25 mg/m2 (IV); 60mg/m^2 (oral)	Day 1, Day 8 of each 21-day cycle	Oral/intravenous
Eribulin	1.4 mg/m2	Day 1, Day 8 of each 21-day cycle	intravenous

Labelling and packaging

Drugs in the OGPT and TPC groups were selected as marketed drugs, with labels and packaging identical to the commodity specifications, and labels bearing the following markings: [drug name], [drug number], [serial number], [product lot number], and [expiry date].

storage conditions

The investigator has the responsibility for the clinical trial drug count. Trial drugs are to be stored according to relevant standards and meet temperature control requirements.

Cycle Time Setting

Chemotherapy in this trial is administered at intervals recommended by the drug's specification or the drug's clinical trial until disease progression or intolerable toxicity is discontinued. Pre- and post-dose investigations are required to assess safety events before and after each course of treatment, and imaging studies are repeated every 2 courses of treatment during the course of treatment.

6.4.3 Pre-treatment manoeuvres

The following actions need to be completed within one week prior to dosing:

- CT chest, abdomen, pelvis (plain + enhanced)
- blood tumour marker
- Routine blood, urine, faecal + occult blood test, electrocardiograms
- Liver function (alanine aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, albumin, prealbumin), renal function (creatinine), electrolytes, blood glucose, blood amylase
- Coagulation (prothrombin time)
- Urine pregnancy test (female subjects of childbearing age)
- Vital signs, height, weight, physical examination
- ECOG score
- History of previous diabetes mellitus, treatment and allergy history of the subject is taken and recorded in the medical record

6.4.4 Therapeutic administration

Subjects were administered drugs according to established cycles. The investigator decides whether or not to administer the chemotherapeutic agent and the

dose adjustment to be administered based on the subject's prior treatment and pre-dose laboratory test results. When a subject develops intolerable chemotherapy toxicity, the investigator may reduce or discontinue the chemotherapy (refer to Dose Adjustment Regulations), provided that the investigator documents the reason for the reduction or discontinuation in the medical record.

Common toxicities of chemotherapeutic agents include nausea, vomiting, abdominal pain, diarrhoea, haematopenia (WBC, RBC, PLT, ANC, etc.), and abnormalities in liver and kidney function. If leakage occurs during the administration of chemotherapeutic agents, it may result in skin damage or even necrosis. Any adverse events occurring during the study, whether or not related to the study drug, should be treated with appropriate monitoring and recorded truthfully in the medical record.

6.4.5 Post-treatment examinations

Relevant laboratory tests need to be completed at the end of the study drug (may overlap with the next pre-treatment test):

- Routine blood, routine urine, routine faeces + occult blood test, ECG
- Liver function (alanine aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, albumin, prealbumin), renal function (creatinine), electrolytes, blood glucose, blood amylase
- Coagulation (prothrombin time)
- blood tumour marker

6.5 Follow-up visits

When subjects are treated with study drug (end of regimen or early discontinuation for any reason, except death), CT is repeated every 2 courses (6 weeks) during the dosing period; CT is repeated every 3 months after discontinuation of the drug until disease recurrence, progression, or metastasis occurs, after which time it is changed to a telephone visit for survival follow-up of the patient, which will

be performed every 3 months until the patient's death or until the trial is analysed for a second study (whichever occurs sooner). whichever occurs earlier). Tumour progression and death events were to be recorded, as well as concomitant relevant treatments. All anticancer treatments received by the subject prior to death are recorded in the follow-up record.

6.6 Completion of the test

The trial was considered completed when the subject experienced a progression/death event before the second study analysis condition was met. The trial was also considered completed if no recurrence/metastasis/death occurred by the time the second analysis condition was met. The time frame for completion of the trial was defined as follows:

- If progression has occurred but the investigational drug was not immediately stopped, the last administration of the investigational drug is the date of completion of the trial.

- If the test was terminated because the second analysis was reached, the date of completion of the test is entered as the date of the end of the test, i.e. when the second analysis was reached.

- In case of death, the date of completion of the trial is the time of death of the subject

6.7 Suspension test visits

The following assessments should be completed at the same time as withdrawal, if possible, once there has been an event that terminates the trial. If the subject is terminating the trial because of an adverse event, the subject needs to be followed to the greatest extent possible until the investigator determines that the adverse event has recovered, stabilized, or is unchangeable.

The following procedures need to be performed during the termination trial visit:

- Investigators must inform subjects of the need to withdraw from the trial and

the reasons for withdrawal

- Detailed record of the reason for the subject's early withdrawal from the trial, date of withdrawal from the trial, in the Scientific Medical Record and Case Report Form (CRF).

- A security assessment is required, including:

  ○ Physical examination

  ○ Weight and vital signs

  ○ Blood test, urine test, faecal test + occult blood test, ECG

  ○Blood tumour markers

  ○ Liver and kidney function, prothrombin time

  ○ ECOG score

  ○ Accompanying medication and adverse event reports

- Regular follow-up of subjects by the investigator or authorised person

How to record the time of termination of the test:

- If pregnancy occurs, the date of the urine pregnancy test with a positive result is used to terminate the test.

- If the trial is terminated due to a combination of treatments that is contrary to the protocol, the date of commencement of the combination of treatments will be used to terminate the trial.

- In the event of an adverse event that results in or prevents compliance, the date of the last imaging/lab evaluation in the study for that subject will be used as the time of termination of the trial

- If a subject is lost to follow-up, the trial is terminated on the date of the last follow-up visit with clear survival information.

- If the subject or his/her legal representative requests or is specifically requested by the investigator to withdraw from the study, the termination of the trial shall occur on the date of such request by the subject or his/her legal representative or the investigator.

6.8 Programme departures

The investigator should conduct the study in accordance with the protocol and the appropriate laws and regulations. Written approval from the Principal Investigator is required before performing protocol deviations.

The investigator or authorized personnel should document and explain this protocol deviation. If a subject is ineligible for enrolment or has received the wrong dose of trial treatment and has used the study drug at least once, it is necessary to collect the relevant data and notify the ethics committee of the deviation in accordance with the relevant procedures for safety reasons.

6.9 Laboratory tests

Specimens of blood, urine, and faeces are collected several times during the test, before each cycle of dosing. The following specific parameters need to be measured:

- WBC/ANC/RBC/PLT/Hb
- Glutamate aminotransferase/glutamate aminotransferase/gamma-glutamyl transpeptidase/total bilirubin/albumin/prealbumin/electrolytes/creatinine
- prothrombin time
- blood tumour marker
- blood tumour marker
- Urine routine/facal routine + occult blood test
- Blood glucose/blood amylase
- Urine pregnancy test

All laboratory tests were performed in our laboratory department and followed the relevant hospital protocols and the use of the hospital's reference values for screening tests as a reference for screening indicators. The investigator must review the results and sign for confirmation. For clinically significant laboratory results, they must be reported as medical history or adverse events.

6.10 Imaging

Review imaging is required before every 2 cycles of treatment and every 3 months after the end of medication. Included:

- CT Chest + Abdomen + Pelvis (Plain + Enhanced)

7 Treatment and restraint

7.1 Treatment

7.1.1 Rules and duration of treatment

Subjects must be dosed according to the protocol before progression occurs until completion of the dosing regimen, and at the end of the regimen receive follow-up as required until the end of the second study analysis.

After progression has occurred in a subject, it is up to the investigator to decide whether or not to continue the trial dosing treatment based on the subject's condition, and if the trial dosing is continued. It may be discontinued at any time prior to the end of the trial as determined by the investigator. At the end of the course of treatment, the subject is not required to continue the study drug as prescribed.

7.1.2 Dose adjustment

Dose withholding was defined as a therapeutic regimen interruption (i.e., drug administration delayed beyond the visit window). A dose hold is defined as an infusion interruption. Every effort should be made to administer the study drug according to the planned dose and schedule. In the event of serious toxicity, dose administration may be delayed and/or reduced according to the guidelines below. Reasons for dose adjustments or delays, supportive measures taken, and outcomes will be documented in the patient's medical record.

The dose adjustment guidelines in this section are not a substitute for clinical judgement. Dosage may be withheld or adjusted at the discretion of the investigator for other reasons (e.g., adverse events, weight loss, laboratory findings). Interruption of dosing is permitted if it is due to a medical/surgical event or for logistical reasons unrelated to study treatment (e.g., unrelated medical event, patient leave, and/or

holiday). However, it is recommended that patients should continue study treatment within 3 weeks of the planned interruption.

For AEs that have been present at baseline, dose adjustments will be based on the change in toxicity grade, as determined by the investigator. For example, if a patient has experienced Grade 1 frailty at baseline and elevates to Grade 2 during treatment, this would be considered a relative Grade 1 change and the dose adjustment would be aimed at a reduction to Grade 1 toxicity.

When several toxicities of varying severity occur simultaneously, dose adjustments should be based on the highest level observed.

If the investigator believes that the toxicity is due to only one portion of the study treatment and the dose for that portion has been withheld or adjusted according to the following guidelines, the other portion may continue to be administered if there are no contraindications.

In the event of a chemotherapy-related toxicity, chemotherapy will be withheld until the toxicity reaches baseline levels or ≤ grade 1 (whichever is more severe) prior to the next chemotherapy administration, with the exception of alopecia, grade 2 fatigue, or other adverse events that, in the opinion of the investigator, will not affect the assessment of the safety of the study drug. If AE does not subside within 10 days, no further chemotherapy will be administered for this cycle. If the AE subsides within 21 days, chemotherapy will be administered on the first day of the next treatment cycle as originally scheduled.

If severe neutropenia (ANC <0.5x 109/L for 1 week or more) occurs during treatment, the dose of the subsequent course of therapy should be reduced by 20%. If severe neutropenia occurs again as described above, the subsequent treatment dose should be adjusted downward by 20-25%. The chemotherapy regimen should be permanently discontinued if the chemotherapeutic agent has been withheld for more than 2 cycles (6 weeks) from the expected date of treatment, or if a 2-dose reduction is not tolerated (as shown in Table 3).

Table 1 Chemotherapy dose adjustments for cytotoxicity of chemotherapeutic agents in the

TPC group

Undesirable incident		Treatment
Neutropenia	Level 3 (0.5-0.99 x 10^9 /L)	Chemotherapy withheld until recovery to ≤ grade 1 (≥ 1.5 x 10^9 /L); restarted at full dose
	Level 4 (<0.5 x 10^9 /L) (lasting 1 week or more)	1. Chemotherapy withheld until recovery to ≤ grade 1; all subsequent doses reduced by 1 dose level 2. If a second dose reduction occurs after a dose reduction, all subsequent doses are reduced by an additional dose level. 3. If a third occurrence occurs, discontinue chemotherapy.
Thrombocytopenia	Level 2	1. Chemotherapy withheld until return to normal; restarted at full dose
	≥3	1. Chemotherapy withheld until recovery to ≤ grade 1; all subsequent doses reduced by 1 dose level 2. If a second dose reduction occurs after a dose reduction, all subsequent doses are reduced by an additional dose level. 3. If a third occurrence occurs, discontinue chemotherapy.
Renal insufficiency	≥3	1. Chemotherapy withheld until recovery to ≤ grade 2; all subsequent doses reduced by 1 dose level 2. If a second dose reduction occurs after a dose reduction, all subsequent doses are reduced by an additional dose

		level. 3. If a third occurrence occurs, discontinue chemotherapy.

NOTE: The investigator may decide to use supportive measures/treatment and/or secondary prevention rather than dose reduction in the next cycle if it is in the best interest of the patient and consistent with clinical practice. Dose adjustment recommendations are provided for informational purposes only.

8.1.3 Treatment allocation and blinding

8.1.3.1 Identification codes

After subjects sign the informed consent form, the investigator will assign them an identification code based on the order of enrolment, which consists of a 3-digit number representing the subject's serial number, and the investigator will fill in the identification code in the Subject Identification Code Form and save it. This trial is an open study and is not blinded.

8.1.3.2 Enrolment randomization

Patients will be randomized in a 1:1 ratio to either the trial or control group. Randomization will be centrally randomized by the GCP facility at the centre of this study, using a validated random number generation system to generate the randomization list, with the clinical trial support team supervising the retention of the randomization code. All personnel directly involved in the execution and analysis of the trial will not have access to the randomization table until the database is locked.

8.1.4 Compliance control

This trial requires that subjects are able to return to the hospital as scheduled to complete all dosing cycles and related examinations in accordance with the protocol.

The number of cycles of medication, the actual amount and duration of the test drug received per cycle, and the reason for deviation from the treatment plan should be recorded in the original medical record and CRF to determine the compliance of the subjects. The investigator needs to maintain close contact and communication with the subject, try to explain any questions the subject may have about any of the medical procedures and medical events during the study, and also inform that low compliance may result in being asked to withdraw from the trial in order to improve the subject's adherence.

8.2 Test constraints

8.2.1 Permitted concomitant medications and treatments

- May receive conventional standard supportive care
- Can be treated for any underlying disease (including diabetes)

8.2.2 Prohibited concomitant medicines and treatments

- Use of other clinical study drugs is not permitted during the study
- Chemotherapeutic agents other than those specified in this protocol are not permitted during the study period
- No other systemic anti-tumour therapy, including chemotherapy, radiotherapy, radiofrequency ablation, molecular targeted therapy, is permitted prior to progression

8.2.3 Necessary Concomitant Medications and Treatments

- In the event of infection, the appropriate sensitive antibiotics must be administered.
- For information on other drugs that may interact with the test drug and affect its metabolism, pharmacokinetics, or excretion, refer to the relevant drug handbook.
- Any co-administration of medication or treatment during the study should be accurately documented in the medical record and the CRF

8.2.4 Subject restraint

- Must return to the hospital on time to complete all programme-required examinations and laboratory tests

- Cannot leave the hospital during inpatient treatment

- The need to report any discomfort to the researcher in a timely manner

- Women of childbearing age are required to use appropriate contraception throughout the treatment phase of the trial and for 6 months after the trial has ended

9 Therapeutic assessment

9.1 Assessment of the screening period

The enrolment assessment must be completed no later than 14 days prior to study drug administration. After obtaining informed consent, the investigator will perform the appropriate clinical assessments on the subject (see 6.1 and 6.2).

9.2 Assessment of the treatment period

The appropriate clinical assessment of the subject (see 6.4.4 and 6.4.6) is required prior to the start of each treatment cycle and within 3 days of its completion in order to make a correct assessment of efficacy (see below).

9.3 Assessment of efficacy

9.3.1 Efficacy variables

- See 3.4.3

9.3.2 Description of procedures

- See 3.2.2

9.4 End of study treatment (EOT) assessment

An EOT evaluation should be performed on all patients ending study treatment, and the following procedures will be completed:

- Physical examination, weight, vital signs, ECOG score

- Combined medication and combined treatment assessment

- Serum EBV DNA copy number

- Blood count, liver and kidney function, blood glucose

- Imaging is determined by follow-up time

- Peripheral neuropathy assessment

- Adverse event assessment (see 10.3)

9.5 Follow-up of disease recurrence and metastasis

See 6.5, 6.6, 6.7

9.6 Follow-up of overall survival

See 6.5, 6.6, 6.7

10 Security variables

10.1 Description of variables and protocols

- Symptoms and signs
- Laboratory tests
- Adverse Events (AE) and Serious Adverse Events (SAE)

Any abnormal symptoms, signs (including clinically significant laboratory findings), or medical diagnoses recorded by medical personnel from the time of subject enrolment until treatment with the trial drug must be documented in the medical record and CRF.

After enrolment, the investigator is required to perform appropriate laboratory tests according to the protocol and record the results in the medical record and CRF, and clinically significant abnormal results should be recorded as adverse events.

10.2 Symptoms and signs

10.2.1 Medical history and concomitant medication

A complete medical history of the subject needs to be recorded. All concomitant medications between Day 1 of Cycle 1 and 30 days after the last use of the test drug need to be documented, including changes in dosage, changes in reasons for use, etc.

10.2.2 Physical examination and weight

A complete physical examination should include an assessment of the following

components, but is not limited to an assessment of the vital organs of the body:

- Head, ears, eyes, nose, throat
- Lungs and respiratory system
- Cardiovascular system
- Gastrointestinal system
- central nervous system, CNS
- skins
- lymphatic system
- Muscular and skeletal system
- Endocrine and metabolic system

All inconsistencies with the baseline examination need to be documented in the medical record and CRF.

10.2.3 Electrocardiogram

Electrocardiograms were required before and after each treatment cycle, including a baseline electrocardiogram assessment that was also required prior to the first treatment cycle. Any clinically significant change from baseline was to be reported as an adverse event and recorded in the subject's medical record and CRF.

10.2.4 Imaging

Imaging assessments, including CT scans, are to be performed as required by the protocol, including a baseline CT examination prior to the first treatment cycle. Any clinically significant change from baseline needs to be reported as an adverse event and documented in the subject's medical record and CRF. If additional imaging evaluations are performed as part of the subject's routine work-up, they will also need to be evaluated and determined to be adverse events.

10.3 Adverse events

10.3.1 Definitions

Any undesired medical event related or unrelated to treatment that occurs after the use of a drug by a subject in a clinical trial is an adverse event. It can be any unfavourable and undesired abnormal result of signs, symptoms, laboratory tests, etc., irrespective of whether it is related to the drug or not. All adverse events should be recorded on the CRF form. The intensity of the adverse event is graded according to the grading method recommended by the NCI Common Toxicity Criteria Grading System.

Clinical supervisors must systematically collect and verify information on adverse events during visits to the study centre when examining the patient's clinical history (raw data reconciliation). Adverse events that are not resolved at the time of assessment need to be followed up until they are resolved. For adverse events that cannot be resolved within the clinically possible observation period (e.g., blindness, neurotoxicity, loss of limbs, etc.), the investigator will classify them as permanently unresolved, and the time of resolution of the event will be left blank in the CRF table.

10.3.2 Adverse event correlation

The investigator should make an assessment of the possible association between the adverse event and the study drug and the combined drug, rated with reference to the following 5-level classification criteria:

（1） Definitely relevant: the reaction appears in a reasonable chronological order after administration of the drug, the reaction is consistent with the type of reaction known to occur with the suspected drug; it improves after discontinuation of the drug, and the reaction occurs again with repeated administration of the drug.

（2） Possibly relevant: the reaction appears in a reasonable chronological sequence after administration of the drug and the reaction is consistent with the type of reaction known to occur with the suspected drug; the patient's clinical status or other therapeutic modalities are also likely to produce the reaction.

（3） Possibly unrelated: the reaction appears less consistent with a reasonable chronology of events following administration of the drug, the reaction is less

consistent with the type of reaction known to occur with the suspected drug; the patient's clinical status or other therapeutic modalities are likely to produce the reaction.

（4） Unrelated: the reaction does not appear in a reasonable chronological order after administration of the drug, the reaction has a type of reaction consistent with that known for non-test drugs; the patient's clinical status or other treatment modalities may have produced the reaction, the reaction is eliminated by improvement of the disease state or cessation of the other treatment modalities, and the reaction occurs by repetition of the other treatment modalities.

（5） Unable to assess: the reaction appears in no clear relation to the chronological sequence after administration of the drug, is similar to the type of reaction known to occur with the drug, and other drugs used at the same time may cause the same reaction.

Items (1), (2) and (5) above were recorded as adverse reactions to the study drug.

Incidence of adverse reactions = number of cases of adverse reactions/total number of cases × 100%.

10.3.3 Serious adverse events

A serious adverse event was defined as an undesired adverse event occurring at any dose of the drug and meeting any of the following criteria: 1) resulting in death; 2) life-threatening as a result of the test drug; 3) resulting in hospitalisation or prolonged hospitalisation; 4) permanent or significant loss of function/disability; and 5) teratogenicity or carcinogenicity.

Some events that require hospitalisation or prolonged hospitalisation may not be reported as serious adverse events, including 1) hospitalisation for non-adverse events for social reasons; 2) hospitalisation for elective surgery, investigations or other treatments that were booked prior to entry into the study; and 3) tumour progression and related events.

10.3.4 Reporting forms

Reporting of serious adverse events requires the use of the SAE report form.

10.3.5 Serious Adverse Event Reporting-Investigator Procedures

Reporting of serious adverse events requires the use of the SAE report form. In the event of a serious adverse event (drug-related or not), the investigator should send the completed initial report to the Ethics Committee of Guangzhou Sun Yat-sen University Cancer Prevention and Control Centre, the head unit (Guangzhou Sun Yat-sen University Cancer Prevention and Control Centre, Tel: 020-87343363), the head unit (Guangzhou Sun Yat-sen University Cancer Prevention and Control Centre, Tel: 020-87343363), and as soon as possible, send the final report (including the serious Adverse event regression, etc., if the serious adverse event is death, it is not necessary to send out the final report retroactively) completed and reported again to the above departments.

10.4 Pregnancy events in clinical trials

Any subject participating in the trial should notify the organisers if a pregnancy event occurs. Although pregnancy is not strictly an AE, all pregnancies need to be followed up to completion for outcome determination. This information is highly relevant to drug safety and public health. It is the responsibility of the investigator to report all pregnancies in the trial using the Pregnancy Event Report Form.

If a pregnancy event occurs in the subject or spouse within 30 days of administration or discontinuation of the test drug, the investigator is required to contact a higher authority to discuss the management of the subject. Reporting of a pregnancy event will include the expected date of delivery and a Pregnancy Event Report Form will be submitted within 24 hours of the pregnancy event in accordance with the procedures for reporting to the SAE. If termination of pregnancy is required, an estimated time of termination is required.

If a pregnancy event occurs with the subject's spouse, rather than the subject

herself, the completion of the Pregnancy Event Report Form needs to include the subject's screening number, initials, and date of birth. Details about the spouse need to be recorded in the narrative section of the Pregnancy Event Report Form. The subject/spouse should be followed until the end of the trial. If the pregnancy is terminated before the expected date of delivery, the investigator needs to record this as such. At the end of the pregnancy, the investigator will need to record the adjudicated pregnancy outcome.

11 Rules for withdrawal and cessation of research

11.1 Patient Withdrawal

A patient may withdraw from a clinical trial at any time and for any reason and without prejudice to the investigator's right to treat his/her disease. The investigator has the right, in the interest of the subject, to ask the subject to withdraw for any reason, including concomitant disease, adverse events, or treatment failure. The Clinical Research Core Group reserves the right to ask a subject to withdraw for protocol violations, administrative reasons, or other valid and ethical reasons.

Although subject withdrawal should be avoided whenever possible, it is important to know that subject withdrawal does occur in clinical research. Regardless of when a subject withdraws from a study and for any reason, a final study evaluation of the subject must be completed and the reason for withdrawal must be noted. All documentation regarding the subject must be as complete as possible. As long as the patient has not withdrawn his/her consent, these withdrawn patients should be followed up and their disease status recorded as if they had not withdrawn.

The researcher must follow up with those who drop out due to poor adherence to obtain reasons for not attending follow-up appointments. When a patient withdraws, the study will do its best to complete and report the observations as fully as possible. As long as the patient has not withdrawn his consent, these patients will continue to be followed up, if possible, and the disease will be recorded as if they had not withdrawn.

Withdrawals due to concomitant illness or adverse events must be recorded in detail on the observation form with all other appropriate and valuable information.

11.2 Early termination of studies

Reasons for early termination may include external events, recurrence of serious adverse events, elevated treatment-related mortality, or insufficient enrolment in the clinical trial. All investigators will be notified in writing when a clinical study is terminated early. Any Investigator who wishes to discontinue participation in this clinical study must immediately inform the Principal Investigator of his/her decision.

11.2.1 Follow-up of the study

11.2.2 Follow-up time

Subjects were followed up at the end of treatment or withdrawn from the study for other reasons at three-monthly intervals, which was changed to six-monthly after two years, until the end of the entire study.

11.2.3 Content of the follow-up visit

Subject follow-up included collection of subject's chief complaint, physical examination, blood and urine routine, biochemical routine and tumour evaluation. Record the above follow-up in the original medical record. Tumour evaluation should be completed in the CRF form**.**

12 Statistical analyses

12.1 Statistical analyses of populations

- Full analysis population (FAS): includes all subjects who entered randomisation and received the study drug (test or control drug) at least once.The FAS is the primary dataset for the evaluation of the primary efficacy and secondary efficacy indicators.

- Protocol-eligible population (PPS): includes all subjects in the analysis set who did not experience a major protocol deviation, completed the study in accordance with

the protocol or remained under observation until the second analysis endpoint of the trial, did not receive any other comorbid treatments during the period that could potentially affect the efficacy of the study medication, and remained in good adherence. Delineation criteria were determined by the study and statistical parties prior to data analysis.

- Safety analysed population (SS): includes all subjects who have received the study drug once and have a post-dose safety record.

12.2 Statistical methods

Once the trial protocol was finalised, a statistical analysis plan was developed by a professional statistician in consultation with the principal investigator. SPSS 26.0 statistical software was used. All statistical tests were performed using one-sided or two-sided tests as needed, and a P value of less than 0.05 would be considered statistically significant for testing differences. Quantitative indicators will be described by calculating the mean, standard deviation, median, minimum, maximum, lower quartile, upper quartile, and categorical indicators will be described by the number of cases and percentage of each category. Comparison of the general conditions of the two groups will be analysed according to the types of indicators, with paired samples t-test or Wilcoxon rank-sum test for between-group comparisons of quantitative data, chi-square test or Fisher's exact probability method for categorical data, and Wilcoxon rank-sum test or CMH test for hierarchical data.Survival such as PFS will be analysed with log rank test and COX regression. Analyses were performed.

12.2.1 Enrolment and Completion

In principle, all patients who met the inclusion/exclusion criteria were enrolled, and the number of enrollments and completions were summarized with a list of shedding cases. Detailed list of different data set sizes, case distribution, comparison of total shedding rates, and reasons for termination for each group. Patients'

demographic characteristics (age, height, vital signs, etc.), medical history, and medication history were described, and age, height, and weight were compared between the two groups to measure the comparability of data.

12.2.2 Compliance analysis

- Medication adherence analysis: Follow-up of patients to see if they are using the trial medication on time and in the correct dosage, and are not using medications and foods prohibited in the programme

- Co-medication analysis: the number of co-medications needs to be counted and tabulated in detail to statistically analyse the potential impact of co-medication on the efficacy of the trial medication.

12.2.3 Analysis of baseline data

According to the baseline indicators listed in 6.2, n-values, means, standard deviations, medians, minimums, and maximums will be described for continuous data, and frequencies and percentages for each group will be described for categorical data.

12.2.4 Analysis of efficacy

Analysed for FAS and PPS

12.2.4.1 Main efficacy analyses

Progression-free survival (PFS), PFS being the time from the start of randomization to disease progression or death of the patient due to all causes, will be analyzed using Kaplan-Meier curves depicting changes in the trial groups.

12.2.4.2 Secondary efficacy analysis

Duration of remission (DOR),Overall survival (OS) will be analyzed using a Kaplan-Meier curve depicting the change in the trial group at the time of analysis, and subjects who withdrew early from the trial prior to the study analysis will have a cut-off time of the time of the last tumour imaging assessment or the time of the last follow up visit, whichever is later. Objective Rate (ORR), the sum of partial and complete remission rates. Disease Control Rate (DCR), defined as the sum of the CR rate, the PR rate and the Stable Disease (SD) rate.SD is defined as neither sufficient

contraction to qualify as PR (referenced to the sum of diameters at baseline) nor sufficient increase to qualify as PD (referenced to the sum of minimum diameters during the study period).

12.2.5 Security analysis

This included monitoring and recording all AEs and SAEs (including number of events versus subject incidence), routine blood and biochemical parameters, body weight, vital signs, physical examination, and all therapies and concomitant medications. Safety indicators include: body weight, vital signs, clinical laboratory parameters, and AE. For laboratory parameters, actual values at each evaluation, change from baseline, and classification of abnormality (below, normal, or above the reference range) will be tabulated according to treatment subgroups, and change over time; for body weight, vital signs will be tabulated according to treatment subgroups, and change from baseline according to treatment subgroups, and change from actual values at each evaluation, and change over time.

The ratio of the number of subjects who developed AE during treatment to the number of subjects available for safety evaluation was calculated using the term to indicate AE incidence.AE incidence will be summarised using the Research Data Coding System (MedDRA) organ classification and standard terminology. AEs occurring during treatment are defined as AEs occurring on or after the day of the first dose through to the day of the last dose or before +30 days or the day of termination of treatment.The severity of toxic reactions is graded according to the NCI-CTCAE version 3.0. When analysed by subject, subjects with more than one occurrence of the same event were counted only once and the worst CTCAE-graded event was selected.

All AEs were tabulated to describe in detail the type, grade, frequency of occurrence, severity, and duration, as well as the relationship to the test drug, management measures, and regression.

12.3 Sample size calculation

The study was a randomized controlled design and the primary study endpoints

included PFS, which is defined as the time from the start of randomisation to disease progression or death of the patient due to various causes. Based on the available clinical data, the following parameters were used to calculate the sample size:

1. Duration of enrolment = 24 months, duration of follow-up = 24 months (overall 48 months), with reference to the results of previous studies and our centre's clinical experience, PFS = 3.5 months in the control group, assuming that the PFS improves to 5.3 months in the experimental group.

2. $\alpha = 0.05$ (bilateral).

3. The effectiveness of the test is 80 per cent.

Based on the above parameter considerations, according to the logrank test for PFS, and taking into account the 10% dropout rate during the course of the study, 302 subjects were required to be enrolled, 151 in the control group and 151 in the experimental group.

13 Regulatory matters

13.1 Ethics and GCP compliance

All investigators must implement the study in compliance with the requirements of the Good Clinical Practice (GCP) for the management of drug clinical studies, ethics regulations, and study protocols as described in International Conference on Harmonisation (ICH) guideline E6.

- Approved by the Institutional Review Board/Ethics Committee (IRB/EC): The investigator shall be required to obtain approval from the Ethics Committee of the study protocol, revisions to the study protocol, informed consent, the investigator's manual, and any documents that may be required or requested prior to the initiation of this study.

- Ethical considerations for the conduct of the study: The study protocol and SOPs must follow the GCP requirements and the Declaration of Helsinki on Ethical Guidelines for Medical Research on Human Subjects.

- Subject information and informed consent: The principal investigator or his/her

authorised person will be responsible for obtaining informed consent. The background of the study and the benefits and risks of participation should be clearly explained. Subjects will be provided with a signed and dated copy of the informed consent form and the original will be retained by the investigator. Acknowledgement of informed consent should be documented in the subject's medical record prior to any testing or intervention (including screening and evaluation) under this study protocol.

- Subject data protection: Subjects should not be identified by name in any study report. Study reports will be used for research purposes only. Every effort will be made to ensure the confidentiality of subjects' personal medical data.

13.2 Responsibilities of the researcher

- Ensure that persons assisting in this study are fully aware of the protocol, revisions, study treatments, and study-related duties and functions. The investigator should have a list of assistant investigators and other qualified personnel who have been assigned important study-related duties.

- Responsible for keeping records of all patients who have signed the informed consent form and who are screened for entry into the study. For patients who fail screening, the reason must be documented in the source document for that patient.

- During the monitoring visit, the investigator or his/her authorized personnel must review the data, resolve queries, and allow direct access to patient records (medical records, study-related charts, etc.) for primary source verification. The investigator must complete the CRF in a timely and accurate manner.

13.3 Informed Consent

Before subjects are enrolled in the trial, the investigator must explain to them the purpose of the trial, the methodology, the possible benefits, the potential risks, and the possible discomforts. Subjects will be informed that participation in the trial is voluntary, that they may withdraw at any time, and that participation or non-participation in the trial will have no effect on the treatment of their disease.

Subjects' right to privacy will be protected.

Subjects or guardians should have sufficient time to read the informed consent form and ask questions. Prior to enrolment, the subject or his/her guardian must sign the informed consent form and the subject retains a copy of the informed consent form.

13.4 Good Clinical Practice (GCP)

This clinical study will be conducted in accordance with the Declaration of Helsinki and the Chinese Good Clinical Practice (GCP). The study protocol must be approved by the ethics committee of the unit responsible for the clinical study before implementation. The investigator will ensure that this clinical study is conducted in compliance with the laws, regulations, scientific and ethical standards of the People's Republic of China regarding medical research. If this study protocol is found to be in need of revision during the course of the study, the revised study protocol must be submitted again to the Ethics Committee of the unit responsible for the study for record/approval before implementation. If important new information concerning the study drug is found, the informed consent form shall be revised in writing and sent to the Ethics Committee of the responsible unit for approval, and the consent of the subjects shall be obtained again.

13.5 Confidentiality of subjects' personal data

The information collected in this trial is limited to what is necessary for the study of the effectiveness and safety of the drug. The collection and use of this data will be in accordance with the relevant laws and regulations for the protection of privacy.

13.6 Programme revisions

The study protocol may be revised during the course of the study if there is a genuine need to do so in order to guide the next steps of the study. Protocol revisions must be made in accordance with GCP regulations, and draft revisions to the protocol must be developed by the investigators and organisers in the light of the progress of

the study, and must be reviewed and approved by the Ethics Committee before they are implemented. The revised protocol approved by the Ethics Committee must become part of the revised protocol.

13.7 Institutional Review Board/Independent Ethics Committee Review and Approval

Prior to commencement of the study, the study protocol, informed consent form, and any other appropriate documents will be submitted to the IRB/EC with a cover sheet or form listing the documents submitted, the date of release, and the research centre(s) for which approval is required. If applicable, documents will also be submitted to the regulatory agency as required by local law.

14 Data management and record-keeping

14.1 Data management

14.1.1 Data processing

Investigators are required to fill in the CRF with data from enrolled subjects; patients who fail screening are not required to do so. The investigator should ensure that the CRF is filled out accurately and completely, and that the original records are also kept intact. CRF completion for each enrolled subject must be completed on time. Completed CRFs will be reviewed and transferred to the data manager of this trial for data entry and management.

14.1.2 Data entry

Data entry and management is the responsibility of the designated data management unit. The data manager uses computer software to prepare data entry procedures for data entry and management. In order to ensure the accuracy of the data, proofreading should be carried out by others at the end of the entry.

14.1.3 Coding of medical information

The following tools will be used for coding medical information:

- MedDRA 11.0 (medical history and adverse events)
- WHO Drug 2008.03 (concomitant medication)
- NCI-CTCAE 5.0 (toxic reactions)

14.1.4 Data review

The established database is reviewed by the principal investigator, data manager, and statistical analyser, and the database is locked after confirmation of the research dataset and statistical analysis plan.

14.2 Record-keeping

In accordance with GCP guidelines, the principal investigator must preserve all information related to the clinical trial, such as subject medical records, drug disposal records, signed informed consent forms, and ethics committee approvals, for a period of five years after the termination of the clinical trial.

14.3 Raw data/document permissions

Any observation and examination results in the clinical trial should be timely, accurately, completely, standardised and truthfully recorded in the medical record and correctly filled in the CRF by the investigator, and should not be changed arbitrarily. If it is indeed due to filling in the error, any corrections made by the investigator should keep the original record clearly legible, and be signed by the person who made the corrections with his/her name and time. Raw data/documentation must be properly stored in the research centre in accordance with ICH GCP and local regulations.

Higher authorities and drug regulatory authorities may monitor, audit, and inspect the clinical trial implementation process and raw data/source documents. Supervisors, auditors, and regulatory authorities have the right to verify all trial-related raw data/source documents, but do not have the right to make corrections. If a problem is found, the investigator must be informed to make corrections and sign.

15 Specimen collection and storage

15.1 Standard operating procedures for specimen collection

Subject specimens were collected according to the standard operating procedure (SOP) for the collection of blood samples and tumour tissue specimens from our tissue bank.

15.2 Storage of specimens

Subject specimens will be stored by the principal investigator. After patients have signed informed consent for enrolment, their postoperative tumour tissue will be routinely retained in paraffin and frozen specimens, and the tumour specimens (paraffin) will be made into tissue microarrays after completion of enrolment of all subjects. Blood samples will be centrifuged and serum and blood cells will be stored separately.

16 Quality control and quality assurance

16.1 Data quality assurance

In order to ensure the completeness, accuracy and reliability of the data, the following measures were taken in this study: selecting qualified and experienced research units and researchers; using lectures and written materials, etc., to introduce the contents of the study protocol in detail to the researchers before the start of the study, and to work together to formulate solutions to any problems that may occur; regular verification of the completeness and accuracy of the data by the supervisors; if any doubt is found in the data , the researchers should be communicated with and confirmed or corrected in a timely manner; blind verification of the data was carried out during the statistical phase. If there is a bias, it is confirmed or corrected by the researcher.

16.2 Monitoring

16.2.1 Purpose of monitoring

Ensure that clinical trials are conducted in strict accordance with protocols and relevant regulations, guaranteeing data integrity, reliability and consistency of multi-centre data, while coordinating the uniformity of trial progress.

16.2.2 Content of monitoring

Supervisors visit the clinical research unit regularly to monitor and report on the conduct of the trial, and the supervisors have the right to verify the original information of all patients related to the study. The monitoring mainly includes: whether the subjects meet the enrolment criteria; whether the case report form (CRF) is completed in a timely, accurate, complete and credible manner; whether the method and dose of medication used by the subjects are in accordance with the protocol; whether all the adverse events are recorded in the CRF form; and to ensure that all the errors or omissions have been corrected, and signed and dated by the investigator.

Supervisors are also responsible for passing on information in various forms, including information on the normal values of clinical tests, to ensure that there is a scientifically consistent system of clinical testing between the participating units and the team leader.

In the event of serious adverse events or deaths (including chemotherapy-related deaths) related or unrelated to this study during the course of the clinical trial, the managing physician or the host hospital will immediately take appropriate management measures.

17 Audit

A representative of the sponsor may visit the research unit to audit all study records for this trial, including original documents, and compare them to the CRF form. The study unit will be informed of the appropriate preparations prior to the audit. A similar inspection may be conducted by the Medicines Control Agency. In this case, the investigator should notify the sponsor immediately.

18 Publication policy

The results of this study may be published in medical journals and magazines or used for teaching purposes. In addition, this study and its results may be submitted for inclusion in all appropriate health research agency registries, as well as posted on health agency research registry websites (e.g., ClinicalTrials.gov), as required by local health agency regulations. First authors were selected based on several considerations including, but not limited to: study participation, contribution to protocol development, and analysis and input in the study manuscript, associated abstracts, and presentations.

19 Clinical Trial Management Information

19.1 Organisational units

Affiliation: Sun Yat-sen University Cancer Prevention and Treatment Centre

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Postcode: 510060

20.bibliography

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21 Researcher's statement

I wish to sign my name and agree to the following:

I have read the protocol and I agree with it and acknowledge all the necessary details of the implementation of the research process as described in the protocol. I will carry out and endeavour to complete the study as designed and specified in the protocol and within the time-frame specified. Under my management/supervision, I will give a copy of the protocol and related information to the researchers involved in the trial. I will discuss these documents with them to ensure that they fully understand the study protocol and study procedures. I will inform them that this information is confidential and belongs to the research centre and that it will not be disclosed to third parties. I understand that recruitment may be terminated or stopped at any time by the Ethics Committee, a higher authority, or the Drug Administration for any reason, or if I believe it is necessary to protect the best interests of the subjects. I agree to conduct the study in full compliance with the requirements of the SFDA, the Ethics

Committee, and the ICH GCP.

Signature of researcher Date

22 Appendix

Appendix 1 Criteria for evaluating the efficacy of solid tumours version 1.1

(Response Evaluation Criteria in Solid Tumors RECIST Version 1.1)

1 Tumour measurability at baseline level

1.1 Definitions

At the baseline level, tumour lesions/lymph nodes will be classified as measurable and non-measurable as defined below:

Measurable lesions

Tumour lesion: at least one accurately measurable diameter line (recorded as the maximum diameter) with the following minimum lengths:

- CT scan 10 mm (CT scan layer thickness not more than 5 mm)
- Routine clinical examination instruments 10 mm (tumour lesions that cannot be accurately measured with a calibrating instrument should be recorded as non-measurable)
- Chest X-ray 20 mm
- Malignant lymph nodes: pathologically enlarged and measurable, the short diameter of the CT scan of a single lymph node must be ≥15 mm (CT scan layer thickness of no more than 5 mm is recommended). At baseline and follow-up, only short diameters are measured and followed up.

Non-measurable lesions

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with short diameters ≥10 mm to <15 mm) and non-measurable lesions. Unmeasurable lesions included: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, carcinomatous lymphadenopathy of the skin/lungs, abdominal masses that could not be diagnosed and followed up on imaging, and cystic lesions.

Special considerations on lesion measurement

Bone lesions, cystic lesions and lesions previously treated locally require special mention:

Bone lesions:

- Bone scans, PET scans or plain films are not suitable for measuring bone lesions, but can be used to confirm the presence or absence of bone lesions;
- Osteolytic lesions or mixed osteolytic/osteogenic lesions with a defined soft tissue

component that meets the above definition of measurability may be treated as measurable lesions if they can be evaluated with tomographic imaging techniques such as CT or MRI;

- Osteogenic lesions are non-measurable lesions.

Cystic lesions:

- A lesion that meets the radiological imaging criteria for the definition of a simple cyst should not be considered malignant because it is a simple cyst by definition and is neither a measurable nor a non-measurable lesion;
- If a cystic metastatic lesion is present and meets the above definition of measurability, it can be treated as being a measurable lesion. However, if a non-cystic lesion is present in the same patient, the non-cystic lesion should be preferred as the target lesion.

Locally treated lesions:

- Lesions located at sites that have been treated with radiotherapy or with other local regional treatments are generally treated as non-measurable lesions, unless the lesion shows definite progression. The study protocol should describe in detail the conditions under which these lesions are measurable.

1.2 Description of measurement methods

Lesion measurement

All tumour measurements should be recorded in metric metres at the time of clinical evaluation. All baseline ratings of tumour lesion size should be completed as close to the start of treatment as possible and must be completed within 28 days (4 weeks) prior to the start of treatment.

Evaluation methodology

The same techniques and methods should be used for baseline evaluation of lesions and subsequent measurements. All lesions must be evaluated using imaging, except for lesions that cannot be evaluated with imaging but only with clinical examination.

Clinical lesions: Clinical lesions are only considered measurable if they are superficial and ≥ 10 mm in diameter when measured (e.g. skin nodules, etc.). For patients with skin lesions, it is recommended to archive colour photographs containing scale measurements of the size of the

lesion.

When lesions are evaluated using both imaging and clinical examination, imaging should be used whenever possible because it is more objective and can be reviewed repeatedly at the end of the study.

- Chest X-ray: When tumour progression is an important study endpoint, chest CT should be used in preference to X-ray because it is more sensitive than X-ray, especially for new lesions. Chest X-ray testing is indicated only when the measured lesion is well defined and the lungs are well ventilated.
- CT, MRI: CT is currently the best available reproducible method for efficacy evaluation. The definition of measurability in this guideline is based on a CT scan layer thickness of ≤5 mm. If the CT layer thickness is greater than 5 mm, the minimum measurable lesion should be twice the layer thickness.MRI is also acceptable in some cases (e.g., whole-body scan).
- Ultrasound: Ultrasound should not be used as a measurement for lesion size. Ultrasound is not reproducible at the end of the measurement due to its operational dependency and does not guarantee homogeneity of technique and measurement between measurements. If a new lesion is detected using ultrasound during the trial, it should be confirmed using CT or MRI. MRI can be used instead if the radiation exposure of CT is taken into account.
- Endoscopy, laparoscopy: the use of these techniques is not recommended for objective tumour evaluation, but this method can be used to confirm CR in the case of biopsy specimens obtained, and also in trials where the study endpoint is recurrence or surgical resection after CR.
- Tumour markers: Tumour markers cannot be used alone to evaluate objective tumour remission. However, if the marker level exceeds the upper limit of normal at baseline, it must return to normal when used to evaluate complete remission. Because tumour markers vary from disease to disease, this needs to be taken into account when writing measurement criteria into the protocol. Specific criteria for CA-125 remission (recurrent ovarian cancer) and PSA (recurrent prostate cancer) remission have been published. The International Organisation for Gynaecological Cancer has developed

criteria for CA-125 progression, which will soon be added to the objective tumour assessment criteria for first-line treatment regimens for ovarian cancer.

- Cytological/histological techniques: These techniques can be used to identify PR and CR in specific circumstances as defined by the protocol (e.g. residual benign tumour tissue is often present in the lesions of germ cell tumours). When exudation may be a potential side effect of a therapy (e.g. treatment with paclitaxel compounds or angiogenesis inhibitors) and the measurable tumour meets the criteria for remission or disease stabilisation, the appearance or exacerbation of tumour-associated exudation during the course of treatment may be confirmed by cytological techniques to differentiate remission (or disease stabilisation) from disease progression.

2 Assessment of tumour remission

2.1 Assessment of target lesions

- Complete remission (CR): disappearance of all target lesions and the short diameter of all pathological lymph nodes (both target and non-target) must be reduced to <10 mm.

- Partial remission (PR): The sum of the diameters of the target lesions is reduced by at least 30% from the baseline level.

- Progression of Disease (PD): A relative increase in the sum of the diameters of the target lesions of at least 20% (or the baseline value if the baseline measurement is the smallest), referenced to the minimum of the sum of the diameters of all the target lesions measured throughout the experimental study; in addition to this, an increase in the sum of the diameters of at least 5 mm in absolute terms must be met (the presence of one or more new lesions is also considered to be a progression of the disease).

- Stable Disease (SD): The target lesion has not decreased to the extent of PR, nor has it increased to the level of PD, and is somewhere in between, the smallest value of the sum of the diameters can be used as a reference for the study.

2.2 Considerations for target lesion assessment

- Lymph nodes: Even if a lymph node identified as a target lesion is reduced to less than 10 mm, the value of the actual short diameter corresponding to the baseline (in line with the anatomical plane at the time of the baseline measurement) should be recorded at each measurement. This means that if a lymph node is a target lesion, even if the criteria for complete remission are met, the lesion cannot be said to have disappeared completely, because the short diameter of a normal lymph node is defined as <10 mm. Target lymph node lesions need to be recorded exclusively at specific locations on the CRF form or in other recording modalities: for CR, the short diameters of all lymph nodes must be <10 mm; for PR, SD, and PD, the short diameters of target lymph nodes will be included in the target node short diameter (<10 mm), and the actual measurement will be included in the target node short diameter. The actual measurement will be included in the sum of the target lesion diameters.
- Target lesions too small to measure: In clinical studies, all lesions (nodular or non-nodular) recorded at baseline should have the actual measurements re-recorded in subsequent evaluations, even if they are very small (e.g. 2 mm). However, sometimes the lesion may be too small to be reported as "too small to measure" because the image on the CT scan is very blurred and it is difficult for the radiologist to define the exact value. When this happens, it is important to record a value on the CRF chart. If the radiologist thinks that the lesion may have disappeared, this should also be recorded as 0 mm, or 5 mm if the lesion is present but too faint to give a precise measurement. (Note: This is unlikely to be the case with lymph nodes, which normally have measurable dimensions or are often surrounded by adipose tissue, as is often the case in the retroperitoneal space; however, if this is also the case, it is important to record a value on the CRF chart. The default value of 5 mm is derived from the cut thickness of the CT scan (this value does not change depending on the cut thickness value of the CT). Providing this default value will reduce the risk of incorrect assessment, as the chance of the same measurement being repeated is small. However, it is important to reiterate that if the radiologist can give an exact value for the size of the lesion, the actual value must be recorded even if the lesion diameter is less than 5 mm.
- Separated or bound lesions: When a non-nodular lesion splits into fragments, the longest

diameters of the separated parts are added together to calculate the sum of the diameters of the lesions. Similarly, in the case of united lesions, they can be distinguished by the planes between the united parts, and their respective maximum diameters are then calculated. However, if the union is inextricably linked, the longest diameter should be taken as the longest diameter of the fused lesion as a whole.

2.3 Assessment of non-target lesions

This section defines the remission criteria for tumours with non-target lesions. Although some non-target foci are actually measurable, they need not be measured, but only qualitatively assessed at the time points specified in the programme.

- Complete remission (CR): disappearance of all non-target lesions and return of tumour markers to normal levels. All lymph nodes were non-pathological in size (short diameter <10 mm).
- Non-complete remission/non-disease progression: presence of one or more off-target lesions and/or persistence of tumour marker levels above normal.
- Disease progression: Definite progression of a pre-existing non-target lesion. Note: The appearance of one or more new lesions is also considered as disease progression.

2.4 Special considerations for the assessment of progression of non-target lesions

An additional explanation of the definition of progression of a non-target lesion is as follows: when a patient has a measurable non-target lesion, even if the target lesion is assessed as stable or in partial remission, a clear definition of progression on the basis of the non-target lesion must be satisfied that the overall deterioration of the non-target lesion has reached a level that necessitates the discontinuation of therapy. A general increase in the size of one or more non-target lesions is often insufficient to meet the criteria for progression, and therefore it is almost rare that overall tumour progression can be defined on the basis of changes in non-target lesions alone when the target lesion is stable or in partial remission.

When none of the patient's non-target lesions are measurable: in some phase III trials this occurs when the inclusion criteria do not specify that measurable lesions must be present. The overall assessment is still based on the criteria above, but because there are no measurable data on the lesions in this case. Worsening of non-target lesions is not easily assessed (by definition: it is necessary that all non-target lesions are truly unmeasurable), so when changes in non-target

lesions result in an increase in overall disease load equivalent to the presence of disease progression in the target lesion, a clear definition of progression based on non-target lesions requires the establishment of a validated assay for this assessment. This is described, for example, as an increase in tumour load equivalent to an additional 73% increase in volume (equivalent to a 20% increase in measurable lesion diameter). For example, peritoneal leakage from "trace" to "massive"; lymphadenopathy from "localised" to "widely disseminated"; or in the protocol, a clear definition of progression. "or described in the protocol as "sufficient to warrant a change in therapy". Examples include pleural exudate ranging from trace to massive, lymphatic involvement spreading from the primary site to distant sites, or may be described in the protocol as "necessitating a change in therapy". If definite progression is identified, the patient should be considered to have progressed overall at that point in time. It is desirable to have objective criteria that can be applied to the assessment of non-measurable lesions, noting that additional criteria must be reliable.

2.5 New lesions

The appearance of new malignant lesions signals disease progression; therefore some evaluation of new lesions is important. There are no specific criteria for detecting lesions on imaging, however the detection of a new lesion should be unequivocal. For example, progression cannot be attributed to a difference in imaging technique, a change in imaging morphology, or a lesion other than the tumour (e.g., some so-called new bone lesions are simply a cure of the original lesion, or a recurrence of the original lesion). This is important when a patient has a partial or complete response to a baseline lesion, e.g., a case of necrosis in a liver lesion may be designated as a new cystic lesion on the CT report when it is not.

Lesions that have been detected at follow-up but not at baseline examination will be considered new and suggestive of disease progression.

For example a patient with a visceral lesion on baseline examination who is found to have metastases when he undergoes a cranial examination with CT or MRI will have intracranial metastatic lesions that will be considered as the basis for disease progression, even if he did not undergo a cranial examination at the time of the baseline examination.

If a new lesion is ill-defined, e.g., due to its small morphology, further treatment and follow-up evaluation is required to confirm that it is a new lesion. If repeated investigations

confirm that it is a new lesion, then the time of disease progression should be counted from the time of its initial discovery.

Evaluation of lesions by FDG-PET generally requires additional testing for supplemental confirmation, and a combination of FDG-PET and supplemental CT findings is reasonable for evaluating progression (especially in new suspected disease). New lesions that can be clarified by FDG-PET are performed according to the following procedure:

A negative baseline FDG-PET test result followed by a positive FDG-PET test at follow-up indicates disease progression.

No baseline FDG-PET was performed and the follow-up FDG-PET was positive:

Disease progression was demonstrated if new lesion foci detected by positive FDG-PET findings on follow-up were consistent with trans-CT findings.

If new lesions detected by positive findings on follow-up FDG-PET are not confirmed by CT findings, additional CT is required to confirm them (if confirmed, the time to disease progression is counted from the time when the abnormality was detected on the prior FDG-PET examination).

Disease is not progressive if positive findings on follow-up FDG-PET are consistent with a pre-existing lesion by CT that has not progressed on imaging tests.

2.6 Assessment of missing and non-evaluable notes

If a lesion could not be imaged or measured at a specific time point, the patient was not evaluable at that time point. If only a portion of a lesion can be evaluated in an evaluation, this is generally considered to be an inability to evaluate at that time point unless there is evidence to confirm that the missing lesion does not affect the evaluation of the efficacy response at the specified time point.

2.7 Special tips for efficacy assessment

When a nodular lesion is included in the total target lesion assessment while that nodule is large there is a lesion size scan reported. To avoid over-assessment based on what is reflected by an increase in nodule size, measurements will be recorded even if the nodule is normal. As already mentioned, this means that subjects whose efficacy is a complete remission will not be recorded as 0 on the CRF form either.

If efficacy confirmation is required during the course of the trial, repeated "non-measurable" time points will complicate the assessment of optimal efficacy. The trial's analysis plan must indicate

that these missing data/assessments can be accounted for when determining efficacy. For example, in most trials, a subject's PR-NE-PR response can be taken as confirmation of efficacy.
When reduced to a "normal" size (<10 mm), they will still be

Symptomatic progression should be reported when a subject experiences an overall deterioration in health requiring discontinuation of the administered treatment, but there is no objective evidence of it. Objective progression should be assessed as far as possible even after termination of treatment. Symptomatic deterioration is not an assessed description of objective response: it is the reason for discontinuing treatment. Objective response in subjects like that will be assessed by the target and non-target lesion profiles shown in Tables 1 to 3.
Conditions defined as early progression, early death and non-assessable are study exceptions and should be clearly described in each protocol (depending on the treatment interval and treatment cycle).

In some cases, it is difficult to identify localised lesions from normal tissue. When the assessment of complete remission is based on such a definition, we recommend biopsy prior to performing an efficacy assessment of a localised lesion in complete remission. FDG-PET has been used as a similar assessment criterion to biopsy for efficacy confirmation of complete remission when abnormalities in localised lesion imaging findings in some subjects are thought to represent lesion fibrosis or scar formation. In such cases, the use of FDG-PET should be described prospectively in the protocol, supported by reports in the specialist medical literature for this condition. However, it must be realised that the limitations of FDG-PET and biopsy (including their high resolution and sensitivity) will lead to false-positive results in the assessment of complete remission.

Table **1** Time-point responses: subjects with target lesions (including or excluding non-target lesions)

target lesion	non- target lesions	new lesions	overall
CR	CR	No	CR
CR	No CR / non PD	No	PR
CR	Cannot	No	PR
PR	Not progressing or not fully	No	PR
SD	Not progressing or not fully	No	SD
cannot be fully	non-pro	No	NE
PD	Any case	Yes or no	PD

Any case	PD	Yes or no	PD
Any case	Any case	yes	PD
CR=complete remission	PR= partial remission	SD=stable disease	PD=disease progression

Table **2** Time Point Response-Subjects with Non-Target Lesions Only

non- target lesions	new	overall remission
CR	No	CR
Non-CR or non-PD	No	Non-CR or non-PD
Cannot be fully assessed	No	Cannot evaluate
Unspecified PD	Yes or	PD
Any case	yes	PD

Note: For non-target lesions, "non-CR/non-PD" refers to efficacy that is superior to SD. As SD is increasingly used as an endpoint indicator for evaluating efficacy, non-CR/non-PD efficacy was developed to target situations where no lesion is specified to be measurable. For unclear progression findings (e.g., very small indeterminate new lesions; cystic or necrotic lesions in pre-existing lesions) treatment may continue until the next assessment. If disease progression is confirmed at the next assessment, the date of progression should be the date of the previous suspected progression.

Table **3 CR** and **PR** efficacy required to confirm optimal total remission

First time point overall	Subsequent time points	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR [a]
CR	SD	If SD lasts for a sufficient period of time , then SD, otherwise it should be PD
CR	PD	If SD lasts for a sufficient period of time , then SD, otherwise it should be PD
CR	NE	If SD lasts for a sufficient period of time , then SD, otherwise it should be NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD lasts for a sufficient period of time , then SD, otherwise it should be PD
PR	NE	If SD lasts for a sufficient period of time , then SD, otherwise it should be NE
NE	NE	NE

Note: CR is complete remission, PR is partial remission, SD is stable disease, PD is progressive disease, and NE is not evaluable. Superscript "a": if CR actually occurs at the first time point and any disease occurs at a subsequent time point, then even if the subject's efficacy relative to baseline meets the criteria for PR, his/her efficacy will still be evaluated as PD at a subsequent time point (because disease will reappear after CR). Optimal remission

depends on whether SD occurs within the shortest treatment interval; however, sometimes the first evaluation is a CR, but subsequent time point scans suggest that small lesions appear to persist, so that the subject's outcome at the first time point should in fact be a PR rather than a CR. In this case, the first CR judgement should be modified to a PR, and the best response is a PR.

2.8. Efficacy evaluation / confirmation of remission period

Confirmation of efficacy

For non-randomized clinical studies with tumor response as the main endpoint, the efficacy of PR and CR must be confirmed to ensure that the efficacy is not the result of evaluation errors. In studies with disease stabilization or disease progression as the primary endpoint, confirmation of efficacy is no longer required because it is of no value to the interpretation of trial results. In the case of SD, within the shortest time interval after the start of the trial (generally not less than 6 to 8 weeks), at least one measurement meets the SD standard specified in the protocol.

Overall remission period

Overall response period is measured from the time when criteria for CR or PR (whichever is measured first) are first measured to the time when disease relapse or progression is first documented (using the smallest measurement recorded in the trial as the reference for disease progression). Overall complete response time is measured from the time when CR criteria are first met to the first true documented disease recurrence or progression.

Stable disease stage

is the time from the start of treatment to disease progression (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 calculations). The clinical relevance of stable disease varies between studies and among different diseases. If the proportion of patients remaining stable for a minimum period of time is used as the study endpoint in a particular trial, the protocol should specifically state the minimum time interval between two measurements in the definition of SD.

Note: The period of remission, stability, and PFS are affected by the frequency of follow-up after baseline assessment. Defining standard follow-up frequency is outside the scope of this guideline. The frequency of follow-up should take into account many factors, such as disease type and stage, treatment cycle and standard specifications. However, if comparisons between trials are

required, limitations in the accuracy of these measurement endpoints should be considered.

2.9 PFS/TTP

Many trials in advanced tumors use PFS or TTP as the primary endpoint. If the protocol requires that all patients have measurable disease, assessment of progress is relatively simple. An increasing number of trials are allowing patients with and without measurable disease to enter the trial. In this setting, the clinical findings of disease progression in patients with no measurable disease must be clearly described in detail. Because progression dates are often ascertained, the observation time points should be arranged the same for each trial group.

Appendix 2: Eastern Cooperative Oncology Group physical status score (ECOG score)

Level (points)	Description of physical condition
0	Asymptomatic, completely normal mobility, no difference from before onset of illness
1	With symptoms, able to move around freely and engage in light physical activities, including general housework or office work, but cannot engage in heavier physical activities
2	If you have symptoms, you can move around freely and take care of yourself, but you have lost the ability to work. You can get up and move around no less than half of the time during the day.
3	Symptomatic, can only partially take care of himself, spends more than half of the day in bed or in a wheelchair, but not bedridden
4	Total loss of function, unable to take care of oneself, bedridden
5	die