# Informed Consent Form

Project name: 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

Informed consent form version number: 1.0 December 12, 2023

Research institution:

Principal investigator: Shi Yanxia

Patient Name: Patient Name Abbreviation:

Dear participants

Now we invite you to participate in a study entitled "Multicenter, randomized, controlled phase III trial of the individualized treatment scheme guided by organ derived from tumor patients versus the scheme selected by doctors to treat patients with recurrent and refractory breast cancer". Before participating in this study, please carefully read this informed consent form and make a cautious decision on whether to participate. You can ask your research doctor/researcher for any questions you don't understand and ask them to explain until you fully understand. Before making a decision to participate in this study, you can have thorough discussions with your family and friends. If you are participating in other studies, please inform your research doctor or researchers. The main content of this study is as follows:

## [Research background]

The incidence rate and mortality of breast cancer among women rank first in the world. In 2020, the number of new breast cancer cases in the world will reach 2.26 million, surpassing lung cancer (2.21 million cases) for the first time and becoming the world's largest cancer. China is a big country of breast cancer. In 2016, there were about 306000 new cases of breast cancer in China, accounting for 16.72% of all new cancers. In 2020, the number of new cases of breast cancer increased to about 420000,

causing nearly 120000 deaths. With the improvement of comprehensive treatment, the overall cure rate of breast cancer has increased significantly in the past three decades, but there are still a considerable proportion of patients with recurrence and metastasis. Take China as an example. In 2016, about 71700 women died of breast cancer, accounting for about 25% of all breast cancer. Therefore, the prevention and treatment of breast cancer still has a long way to go.

With the deepening of research on tumor like organs, we have new hope for the treatment of breast cancer. Tumor like organs are a three-dimensional cell culture model that can simulate the growth environment of tumors in vivo, providing a more realistic tumor research model. Compared to traditional cell culture models, tumor like organs can better simulate the heterogeneity, drug response, and metastasis behavior of tumors. At present, lung cancer, liver cancer, pancreatic cancer, bladder cancer, gastric cancer, endometrial cancer and other tumor like organ models have been successfully established, and breast cancer like organs have also become a useful preclinical model. In the research of breast cancer treatment, the main applications of tumor like organs include predicting drug reactions, screening anticancer drugs, studying tumor resistance and optimizing individualized treatment schemes. Firstly, by using tumor like organs, we can predict the patient's response to specific drugs. This predictive ability is crucial for doctors to choose the most suitable treatment plan and can help achieve better treatment outcomes in the early stages. Secondly, tumor like organs are also used to screen for new anti-cancer drugs. Traditional drug screening methods typically require a significant amount of time and resources, while tumor like organs can screen drugs in a relatively short period of time, improving the efficiency of drug development. In addition, tumor like organs are also of great significance for studying tumor drug resistance. By simulating the process of tumor drug resistance, we can better understand the mechanism of drug resistance and develop more effective anti-cancer drugs. Finally, tumor like organs can also be used to optimize personalized treatment plans. Each patient's tumor has its own uniqueness, and tumor like organs can help us understand the tumor characteristics of each patient and develop more personalized treatment plans. Tumor like organs will play an

increasingly important role in the treatment of breast cancer in the future.

The purpose of the study is to study the effect of individualized treatment scheme guided by organ of tumor origin on patients with recurrent and refractory breast cancer compared with the scheme selected by doctors. For this reason, we need you to provide tumor puncture/surgical tissue for research.This study has been approved by the Ethics Committee of the Sun Yat-sen University Cancer Center, which is an organization that protects the rights and interests of patients/participants.

**[Overview of research design and research process]**

This multicentre, open-label, randomised phase III trial is designed to investigate the efficacy and safety of organoid-guided treatment (OGT) versus treatment of physician's choice (TPC) in previously treated refractory breast cancer. Patients with advanced, recurrent and refractory breast cancer will be randomised in a 1:1 ratio to the trial group or the control group.

**Screening period**

If you agree to participate in this clinical study, your doctor or members of their research team will first evaluate whether the study is suitable for you. To determine this situation, you will undergo a comprehensive medical examination before enrollment, including:

**Medical history:** Your doctor will ask you some questions about your breast cancer and general health, as well as your recent medication or other treatment. It is important to inform the doctor of all medications or other treatments you are using, including any medications you have purchased yourself.

**Physical examination:** Your doctor will examine your body, including measuring height, weight, heart rate, and blood pressure. Your doctor will also evaluate your daily living abilities.

**Laboratory examination:** Your doctor will provide you with a test report for hematological examination, which includes blood routine, biochemical, urine routine, coagulation function, tumor markers, and virological testing. We need you to cooperate with the nurse to complete the blood drawing and fecal sample collection work.

Your doctor may be able to understand your heart condition through electrocardiograms or echocardiography.

**Imaging examination:** Your doctor will analyze the results of your CT, MRI, bone scan and other imaging examinations to determine the location and size of your lesion and related information.

If you are a woman with fertility, a urine pregnancy or blood pregnancy test will be conducted 7 days before the start of the study treatment to confirm that you are not pregnant.

If the results of these tests indicate that participating in this clinical study may put your health at risk, your doctor will not recommend you to enter this study and will discuss other treatment options with you. But if these test results show that you are suitable for the study, you can choose to join the clinical study.

**Treatment stage**

If you agree to participate in this study, you will be randomly assigned to the experimental group for organoid culture and drug sensitivity. Subsequently, sensitive drugs will be selected for treatment based on drug screening. If you are assigned to the TPC group, you will be treated according the drugs selected by the doctor, such as capecitabine, gemcitabine, vinorelbine, and eribulin. The specific dosage and time interval of medication will refer to the NCCN guidelines and drug instructions.

The subjects in the OGT group will receive PDO drug sensitivity screening, which predicts effective treatment. You need to provide sufficient tissue for organoid culture, and drug screening will be conducted after successful organoid culture. The

specific medication will be determined based on the PDO drug sensitivity results. At present, the personalized drug screening library customized by the research group is as follows, and corresponding drugs may be adjusted according to the situation of marketed drugs in the future:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 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 drug sensitivity results, all drugs used in the experimental group will be used according to the recommended instructions or guidelines. The specific dosage and time interval will refer to the instructions of the corresponding drugs. Some drug sensitivity results may involve use of drugs beyond indications. The application of these drugs will be communicated with you, and with your full knowledge and clear understanding of the risks and benefits, you will agree to use them. The specific dosage and dosage will also refer to the corresponding instructions. The subjects in the TPC group will receive treatment selected by the attending physician. The subjects in the TPC group will receive treatment with one of the following regimens selected by the attending physician following the NCCN guidelines: capecitabine, gemcitabine, vinorelbine, and eribulin. If HER2 is positive, it can be combined with anti HER2 treatment, except for ADC drugs. The specific medication is as follows:

| Research drug | Dosages | Frequency of administration | Route of administration |
|---|---|---|---|
| Gemcitabine | 1000mg/$m^2$ | Day 1, Day 8 of each 21-day cycle | intravenous |
| Capecitabine | 1000mg/$m^2$ | Days 1-14 of each 21-day cycle | oral |
| Vinorelbine | 25 mg/$m^2$ (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 |

**Physical examination:** Your doctor will examine your body, including measuring height, weight, heart rate, and blood pressure.Your doctor will also evaluate your daily living abilities.

**Blood examination:** Before the start of each treatment course, your doctor will provide you with a laboratory report for hematological examination, which includes tests for blood routine, blood biochemistry, urine routine, coagulation function, tumor markers, etc.We need you to cooperate with the nurse to complete the blood drawing and fecal sample collection work.

**Imaging examination:** From the first administration, tumor imaging evaluation is conducted every 2 sessions (6 weeks ± 7 days), followed by tumor imaging evaluation (CT, MRI, bone scan, etc.) every 9 weeks± 7 days to clarify your disease condition and the effectiveness of drug treatment.The research doctor will make corresponding treatment decisions based on the tumor assessment results until you first receive objective imaging evidence of disease progression (PD).

Your doctor may arrange an electrocardiogram test for you to understand your heart condition.

**Accompanying treatment:** Your doctor will inquire about the recent use of medication or other treatments. It is important to inform the doctor of all medications or other treatments you are using, including any medications you have purchased yourself.

**Record adverse events:** Your doctor will ask you about any discomfort you have experienced since the last chemotherapy, including the specific date and extent of discomfort, and whether there has been any improvement.

**Follow up stage**

When you enter the follow-up period after completing the trial treatment. The safety follow-up should be completed 90 days (± 7 days) after the end of the trial treatment, including re-examination of your blood routine, biochemistry, urine routine, electrocardiogram, tumor markers, as well as vital sign measurement and physical examination to evaluate your safety after medication. After the trial treatment is completed, an imaging examination will be conducted on you approximately every 90 days (± 7 days) to evaluate the efficacy until your condition progresses, other anti-tumor treatments are used, or the study ends, whichever occurs first.

**[Benefits and Risks]**

**1. Possible benefits:** Your medical condition may or may not improve through treatment in the experimental or control group.Your tumor may or may not decrease.

Your participation in this clinical study will provide important information for medical science research, including the effectiveness and safety of organ like guidance for individualized treatment of refractory breast cancer patients, which may help to benefit patients with recurrent refractory breast cancer in the future.

**2. Possible risks:** As you are aware, medication treatment often produces adverse reactions, which require immediate reporting to your doctor. The occurrence of adverse reactions is caused by the mechanism of action of the drug itself, which does not mean that there is no therapeutic effect, nor does it absolutely mean that treatment should be terminated. You can also consult your responsible doctor for relevant information. The research doctor will closely monitor your condition, and if any adverse reactions occur, you must promptly notify the doctor. Your doctor will determine if you have any side effects and will use other medications to treat you to reduce side effects or discomfort.

The adverse reactions of the experimental group drugs refer to the specific medication instructions, while the common adverse reactions of the control group drugs are as follows:

**Common adverse reactions of gemcitabine:**

**Respiratory system:** There are few reports of pulmonary symptoms or severe pulmonary symptoms related to gemcitabine treatment, such as pulmonary edema, interstitial pneumonia, or adult respiratory distress syndrome (ARDS). The causes of these lung symptoms are currently unclear. Once it occurs, consideration should be

given to discontinuing gemcitabine. Early adoption of supportive treatment measures may help alleviate the condition.

**Reproductive urinary system:** Clinical manifestations similar to hemolytic uremic syndrome (HUS) are rare in patients receiving gemcitabine treatment. If there are symptoms of microvascular hemolytic anemia, such as a rapid decrease in hemoglobin with thrombocytopenia, and an increase in serum bilirubin levels, creatinine levels, urea nitrogen or lactate dehydrogenase levels, medication should be stopped immediately. Even if the medication is stopped, the patient's renal function damage may still be irreversible, so dialysis treatment should be given.

**Cardiovascular system:** Reports of heart failure are very rare. There have been reports of arrhythmia, especially supraventricular arrhythmia. Vascular: Clinical manifestations related to peripheral vasculitis and gangrene are rarely reported.

**Skin and accessory organs:** Reports of severe skin reactions, including exfoliative dermatitis and bullous rash, are very rare. There have been reports of severe skin and dermatomyositis type muscle symptoms in previously irradiated areas after continuous radiation therapy and gemcitabine treatment.

**Hepatobiliary system:** Increased liver function indicators, including aspartate aminotransferase (AST), alanine aminotransferase (ALT) γ- Reports of elevated levels of glutamyltranspeptidase (GGT), alkaline phosphatase, and bilirubin are rare.

Injury, poisoning, and complications that occur during the course of the disease: there have been reports of radiation memory reactions.

**Common adverse reactions of eribulin:**

In the Chinese population, the most common adverse reactions observed in patients (≥ 20%) treated with eribulin are arranged in descending order, including a decrease in white blood cell count (92.8%), a decrease in neutrophil count (89.8%), an increase in aspartate aminotransferase (39.0%), an increase in alanine aminotransferase (34.1%), anemia (27.7%), fatigue (21.6%), and a decrease in hemoglobin (20.1%). In the Chinese population, the most common grade 3 or above adverse reactions in patients (≥ 5%) treated with eribulin are decreased neutrophil count (79.9%), decreased white blood cell count (63.6%), and decreased granulocyte

count (9.1%)

**Common adverse reactions of vinorelbine**

Hematological and lymphatic system diseases are very common: they mainly cause bone marrow suppression with neutropenia (G3: 24.3%, G4: 27.8%), recover within 5-7 days after neutropenia reaches its lowest point, and do not accumulate over time. Anemia (G3-4: 7.4%). Common: Thrombocytopenia may occur (G3-4:2.5%), but severe thrombocytopenia is rare.

Gastrointestinal diseases are very common: stomatitis (G1-4:15% for single drug treatment), nausea and vomiting (G1-2:30.4%, G3-4:2.2%), and antiemetic treatment can reduce their incidence. The main symptom of monotherapy with this product (G3-4:2.7%) and combination with other chemotherapy drugs (G3-4:4.1%) is constipation, which is rare to develop into paralytic intestinal obstruction. Common: Mild to moderate diarrhea may occur frequently. Rare: Paralytic intestinal obstruction, treatment can resume after intestinal peristalsis returns to normal.

Systemic diseases and administration site conditions are very common: injection site reactions include erythema, burning pain, venous discoloration, and local phlebitis (G3-4:3.7% as a single chemotherapy drug). Common: Patients treated with this product experience fatigue, fever, and pain in different areas, including chest pain and tumor site pain. Rare: Local necrosis appears. The correct placement of intravenous needles or catheters and extensive rinsing of the veins after injection can alleviate these effects.

**Common adverse reactions of capecitabine**

Capecitabine tablets first manifest as varying degrees of gastrointestinal reactions, including anorexia, bloating, nausea, decreased appetite, aversion to greasiness, abdominal pain, diarrhea, and other symptoms. In addition, there may often be numbness, sensory abnormalities, taste disorders, dizziness, headaches, and other neurological symptoms in the peripheral sensory nerves of the hands and feet.

Some patients may experience liver dysfunction, manifested by increased transaminases and bilirubin levels.The systemic adverse reactions caused by capecitabine often manifest as fatigue, drowsiness, and fatigue. Some patients may

experience skin damage such as rash, erythema, hair loss, and dry skin. For patients with underlying heart disease, capecitabine tablets may cause cardiac toxicity, resulting in cardiogenic chest pain, myocardial ischemia, heart failure, arrhythmia, and tachycardia.

You must report any adverse reactions you experience to us when enrolled in clinical research.Any drug has inevitable adverse reactions, especially chemotherapy drugs. Some of these adverse reactions are common, preventable or treatable, while others are rare or even unreported.The supervising doctor will also take preventive measures for common adverse reactions in advance, or adjust medication dosage and change treatment plans based on your own adverse reactions. At present, advanced tumors are still incurable diseases, and any treatment plan may progress or have poor therapeutic effects.

**[Other treatments available]**

Whether you participate or not in this clinical study is entirely based on your own wishes. Participating in this study is not your only option for treatment. If you do not participate in this clinical study, your doctor will recommend suitable treatment methods based on your actual physical condition, such as radiotherapy and chemotherapy, targeted drugs, immunotherapy, supportive therapeutic therapy, etc., or participate in other clinical studies.

**[Collection, processing, and preservation measures for biological samples]**

To explore factors that may affect or predict efficacy (including efficacy and safety), your doctor or members of their research team will take samples of your tumor tissue and blood for exploratory analysis. After you sign the informed consent form, you need to take 15 paraffin blocks or white slides from the primary or metastatic lesion, tissue samples from the superficial tumor puncture you performed in the ultrasound department, and samples from the surgery room after surgery for organoid culture and drug screening. During the screening period, efficacy evaluation, and tumor progression, 10ml of peripheral blood will be collected separately, along with routine blood collection. No additional blood collection points will be added. Blood samples will be tested for serum markers and ctDNA, and the tested samples will be destroyed.

After the completion of the final report of this study, except for the organoid specimens stored in the refrigerator or liquid nitrogen tank where Shi Yanxia's research group is located, your remaining biological samples and any isolates will be

destroyed.

**[Participation/Termination Principle]**

Your participation in this study is entirely voluntary. If you are unwilling toparticipate or continue to participate in this study, your rights will not be affected in any way. You may withdraw from this study at any time without discrimination or retaliation, and your medical treatment and rights will not be affected as a result.

If you do not follow medical advice or consider your health and benefits, doctors and researchers may also require you to withdraw before the study is completed. If the doctor deems it necessary, please continue to cooperate in receiving laboratory tests and physical examinations related to the end of the study.

During the research period, if there is any important information about the disease or any medication that may affect your decision to continue participating in this study, your doctor will notify you promptly.

You can stay informed of information and research progress related to this study at any time. If you have any questions related to this study, or if you experience any discomfort or injury during the research process, or if you have any questions about the rights and interests of participants in this study, you can contact the supervising doctor.You can also consult our ethics committee.

**[Related expenses]**

After enrollment, organoid culture and corresponding drug screening were completely exempted.The cost of therapeutic and adjuvant therapy drugs, as well as examination related expenses, will be borne by you personally.Each blood point will be compensated with 200 yuan, and each biopsy will be compensated with 200 yuan.

**[Compensation Clause]**

If you experience any discomfort, new changes in your condition, or any unexpected situations during the study, regardless of whether they are related to clinical research, you should promptly notify your doctor, who will make a judgment and provide medical treatment. If adverse events related to this clinical study occur during the clinical trial, we will compensate for them in accordance with Chinese

laws, regulations, and insurance regulations.

**[Confidential Information]**

Your privacy rights will be protected, and all personal information you participate in this study will be kept confidential.Your and other identifiable information will be deleted and replaced with a number that is associated with your identification information. During this clinical study, your personal data, especially medical results, will be collected, stored, and evaluated. The ethics committee, applicant units and their authorized representatives, as well as the national drug regulatory department, may access your information when needed for work.The research results, including laboratory tests and other test data, may be published, but this behavior is only for scientific research purposes and your name will not appear in any research reports or public publications.

After the completion of this clinical study, the data obtained from this study may also be used for other studies or for further data analysis, with confidentiality as listed above.

# Informed consent bookmark page

**I agree to declare that** I have carefully read and understood all the information in the informed consent form for this clinical study. I confirm that I have sufficient time to consider whether to participate in the clinical trial, and all questions have been satisfactorily answered. I have the right to consult at any time and will receive answers.I am aware that participating in this clinical study is voluntary and I have the right to decide to withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected. I will receive a copy of this informed consent form with signed name and date.Finally, I am willing to participate in this study and follow the doctor's advice.

Subject signature:

Signature Date:Year Month Day

**Legal representative** ***(if applicable)***

Signature of legal representative:_____

Signature date:_____Year____Month____Relationship between day and subject:_____

**Researcher's statement:** I confirm that I have provided detailed explanations and information to the subjects regarding the nature, purpose, requirements, and potential risks of this study, and have answered all relevant questions from the subjects. The subjects voluntarily agreed to participate in this study. The subject has received a signed informed consent form. According to national laws and regulations and the plan of this study, I will accurately carry out clinical research and take necessary measures to ensure the rights and safety of the above-mentioned subjects.

Researcher's signature:

Signature Date: Year Month Day