INFORMED CONSENT FORM

(English Version)

Participant Information Page

Study title: A ctDNA-based, multicentre, open-label, randomized, controlled, phase II trial of afatinib in combination with GEMOX chemotherapy as the adjuvant treatment in patients with ErbB pathway mutated, resectable gallbladder cancer

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Dear participant:

You have been diagnosed with ErbB-pathway mutated gallbladder cancer, and will be invited to participate in a randomized, open-label, and multicentre study of afatinib in combination with GEMOX as adjuvant therapy after surgery. The study will be conducted at Renji Hospital, Xinhua Hospital, and Ruijin Hospital, all affiliated to Shanghai Jiao Tong University School of Medicine, and Zhongshan Hospital Affiliated to Fudan University, and at least 102 subjects are expected to participate. This study has been reviewed and approved by the Ethics Committee of Renji Hospital, Shanghai Jiaotong University School of Medicine.

The information provided below will help you decide whether to participate in this study or not. Your participation in this study is completely voluntary and your decision will not affect your normal treatment at our hospital. If you choose to participate in this study, our research team will make every effort to ensure your safety and rights during the study!

Please read this informed consent carefully and ask any questions you may have to your study doctor or the investigator. The background, purpose, process and other important information of this study are as follows:

1. BACKGROUND

Gallbladder cancer (GBC) is one of the most common and lethal tumors of the biliary tract system with 5% of 5-year survival rate. GBC lacks typical symptoms at early stages but rapidly undergoes cancer malignant transformation that is characterized with rigorous tumor infiltration and metastasis. To date, while no powerful means are available for curing GBC, surgical treatment is the mainstay of this intractable malignancy. Unfortunately, previous studies from our group reported that the resection rate of GBC in China is only 44.7% after diagnosis and the radical resection rate is even less than half (18.84%-21.59%). Thereof, a large population of cancers fall into non-surgical therapy including radiotherapy, chemotherapy and targeted therapy. Our group recently have completed a clinical trial that comparing efficacy of GEMOX (gemcitabine combined with oxaliplatin) vs. modified FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) in the prognosis of patients with unresectable locally advanced or metastatic GBC. The result is still unsatisfactory as the median survival time of
patients treated with GEMOX is 7 months vs. mFOLFIRINOX 9 months. Therefore, it is critically important to find alternative therapeutic strategies for GBC. Targeted therapy is emerging as more effective interventions than traditional radiotherapy and chemotherapy. A number of clinical trials have demonstrated the efficacy of targeted therapy in hematological tumors, lung cancer as well as biliary tract cancer (BTC). Our team previously found that high-frequency somatic mutations in the ErbB pathway (including EGFR, ERBB2, ERBB3, ERBB4 and their downstream genes) up to 36.8% accounted for the occurrence and development of GBC. At present, afatinib, a targeted drug for the ErbB pathway, has been approved for clinical treatment in EGFR-positive lung cancer and also engaged for clinical research on cholangiocarcinoma. Preclinical studies have discovered that afatinib can inhibit the invasiveness of GBC cell lines and reduce the tumor size of GBC xenografts. Given these evidences, here, we set up a clinical trial to test the hypothesis that afatinib may help improve the prognosis of patients with ErbB pathway mutated GBC.

cTNA, refers to cell free DNA released into the blood by apoptotic and necrotic cells from tumors in situ, metastatic foci or CTCs. Currently, based on the rapid development of advanced detection technology, such as digital PCR and the next-generation sequencing (NGS), ctDNA-based liquid biopsy has received remarkable attention to monitor tumour burden and response to therapy. Several studies in gastrointestinal cancers reported that ctDNA dynamic changes may be predictive markers to monitor therapy efficacy. Therefore, we add ctDNA detection of participants to monitor disease progression and evaluate the therapeutic effects of afatinib on the recurrence and metastasis of GBC.

2. STUDY PURPOSE

The aim of this study is to evaluate the clinical efficacy and safety of afatinib in combination with GEMOX as an adjuvant therapy in resectable GBC patients with ErbB pathway mutation by monitoring the dynamic changes of ctDNA.

3. STUDY PROCESS

(1) How many people will participate in the study?

A minimum of 102 patients will be enrolled from national four top-ranked hospitals in Shanghai, China (Renji Hospital, Ruijin Hospital, and Xinhua Hospital, all affiliated to Shanghai Jiao Tong University School of Medicine, and Zhongshan Hospital Affiliated to Fudan University).

(2) What are the study procedures?

A. Screening

Before you are enrolled in the study, your medical history will be asked, and you will be screened for ErbB pathway mutations by NGS using blood and tumor tissue samples. Inclusion and exclusion criteria are listed below in details:

Inclusion criteria

Participants must:
Be pathologically diagnosed with GBC that is resectable.

Have ErbB pathway mutations (EGFR, ERBB2, ERBB3, ERBB4) both on surgical tumor tissue samples and preoperative blood samples based on NGS.

Sign written informed consent. (If the participant is unable to read or sign, the legal representative shall sign the informed consent form. For participants who are incapable of expressing consent, their legal representative shall be told the introduction and explanation above, and sign the informed consent)

Age: 18-80 years old

Have stable vital signs and an Eastern Cooperative Oncology Group (ECOG) performance status ≤1;

Show pathologically at least stage T2 or positive lymph nodes or R1 resection, according to the 8th American Joint Committee on Cancer (AJCC) TNM staging system, which is fit for adjuvant therapy, and have an evaluation of survival greater than 18 weeks;

Have important organs to be functional including bone marrow, kidney and liver: leucocytes>3000/μL, with an absolute neutrophil count>1500/μL, platelets >75000/μL, hemoglobin≥9 g/dL, total bilirubin ≤3.0×institutional upper limit of the normal (ULN), aspartate aminotransferase (AST)/alanine transaminase levels (AST)≤5×institutional ULN, creatinine clearance≥30 mL/min;

Agree to use adequate contraception prior to and during the study specific for women bearing child and men.

Exclusion criteria

Participants with any of the following conditions or characteristics are excluded:

- ALL without presence of ErbB pathway mutations either in tumor tissue samples or in blood samples.
- Have targeted therapy or chemotherapy before enrollment. Have experienced radiotherapy but have not progressed prior to this study.
- Participate in other therapeutic/interventional clinical trials;
- Have not been disease-free for at least 5 years of other cancers prior to registration, EXCEPT for curatively treated cervical cancer in situ and non-melanoma skin cancer.
- Have uncontrolled concurrent illness including but not limited to: uncontrolled congestive heart failure (New York Heart Association (NYHA) class ≥3), unstable angina pectoris, uncontrolled cardiac arrhythmia, uncontrolled hypertension (defined by systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg despite optimal medical management).
- Are ongoing or active infection;
- Have uncontrolled diabetes;
- Have active autoimmune system diseases requiring long-term use of steroids;
- Have any history of organ allograft;
- Experience substance abuse, medical, psychological or social conditions that may interfere with the patient’s ability to understand informed consent and participation in the study or evaluation of the study results.
- Keep any serious illness or medical conditions that are not suitable for the study.

B. Intervention

After determining that you are eligible to participate in the study based on inclusion and exclusion criteria, you will be collected and randomly assigned to treatment:
**Test group:** afatinib 40mg once daily (afatinib 40mg from Day 1 to Day 21, Boehringer-Ingelheim) combined with GEMOX chemotherapy (gemcitabine 1000 mg/m² on days 1 and 8 of each cycle by IV infusion, Eli Lilly and Company and oxaliplatin 100 mg/m² on day 1 of each cycle by IV infusion, Jiangsu Hengrui Medicine Co., Ltd.)

**Control group:** GEMOX chemotherapy (gemcitabine 1000 mg/m² on days 1 and 8 of each cycle by IV infusion, and oxaliplatin 100 mg/m² on day 1 of each cycle by IV infusion)

**C. Follow-Up**

After the last time receiving therapy, follow-up data will be collected during your visits to the hospital every 3 months till death or reaching 3 years after enrollment.

(3) How long will the study last?

This study will last for **3 years** from the time you receive treatment, and the end of the study will be reached when GBC relapses indicated by contrast enhanced MRI/CT in the enrolled cases. If the patient participates in the trial **treatment for 6 cycles** without recurrence, the endpoint will also be reached. After tumor recurrence, and the patients will continue to be followed up **every 3 months** till death or reaching 3 years after enrollment.

You may drop out of the study at any time without losing any benefits to which you are entitled. However, if you decide to withdraw during the study, you are encouraged to talk to your doctor first. If you experience a serious adverse event, or if your study doctor feels it is not in your best interest to continue in the study, he or she may decide to withdraw you from the study. The sponsor or regulatory agency may also terminate during the study period. However, your withdrawal will not affect your normal medical treatment and rights. If you withdraw from the study for any reason, you may be asked about your participation in the study. You may also be asked for a medical examination and follow-up questionnaire if your doctor deems it necessary.

(4) Information and biological specimens collected during the study

Within 28 days prior to starting treatment, your doctor will take and record your medical history, combined medications and adverse events, also perform an ECHO and enhanced contrast CT or MRI. Within 7 day prior to treatment, your vital signs and weight will be measured, and an ECOG PS score will be performed in conjunction with the following tests:

- complete blood counts
- urinalysis
- hemostasis (PT、APTT、TT、FIB、INR)
- electrolytes (Na, K, P, Ca, Mg)
- liver/renal function (ALT, AST, ALP, GGT, TBIL, DBIL, Alb, BUN, Cr)
- tumor markers (CA19-9, CEA, CA125)
- myocardial enzyme spectrum (cTnI, CK, LDH)
- thyroid function (FT3, FT4, TSH, TT3, TT4)

These clinical assessments are also obtained at a series of scheduled timepoints (see the study schedule for details).

In addition, both blood and tissue samples are collected for this trial to detect ErbB pathway mutations (EGFR, ERBB2, ERBB3, ERBB4) through NGS.
1) Blood samples
10 milliliter of venous blood samples is collected from you at scheduled timepoints (see the study schedule for details) in Streck Cell-Free DNA Blood Collection Tubes. Samples are centrifuged to extract cell free DNA (cfDNA) to detect mutations.

2) Tissue Samples
Tumor and para-cancerous tissue samples are collected during surgery, cryopreserved in liquid nitrogen, and stored in the biobank of Renji hospital, Shanghai Jiao Tong University School of Medicine to detect mutated tissue DNA. Formalin-fixed and paraffin-embedded tumor sections are collected as well for further study.

All data obtained will be kept strict and stored electronically on a database with secured and restricted access. An encryption will be used for data transfer, with removal for any information able to identify individuals. Data will be only deidentified for analysis at the completion of this study.

4. RISKS AND BENEFITS

(1) What are the risks of participating in this study?

The risks you may incur by participating in this study are as follows. You should discuss these risks with your study doctor.

1) Drug Adverse Reaction
Toxic side effects caused by gemcitabine, oxaliplatin and afatinib may occur during any phase of the study.
Adverse reactions related to the chemotherapy drugs (gemcitabine and oxaliplatin) include: nausea, vomiting, bloating, diarrhea, constipation, loss of appetite, fever, malaise, joint and muscle pain, hair loss, peripheral neuritis, impairment of liver and kidney function, and bone marrow suppression (decreased white blood cells, platelets, and hemoglobin), etc.
Conducted clinical studies have reported that most common adverse events associated with afatinib are diarrhea and skin rash.
Investigational medicinal product (IMP) are subject to unanticipated or unpredictable risks in clinical trials, including unpredictable types and severity of risks, such as rapid disease progression, unanticipated serious adverse events related or unrelated to treatment, which may cause you harm. If you experience any discomfort, or new changes in your condition, or any unexpected events during the treatment, whether it is related to the drug or not, you should promptly notify your doctor, who will make a judgment and provide medical treatment.

2) ctDNA based liquid biopsy
The ctDNA detection does not cause any harm to the body, but the sample collection is still minimally invasive to the body. Therefore, we collect an additional 10 ml of peripheral blood along with the routine blood test to avoid unnecessary inconvenience and harm to you. There may be minor discomfort, including temporary pain, local bruising, a few cases of mild dizziness, or, rarely, needle infection. If you experience any discomfort after a blood sample collection, whether it is related to the test or not, you should promptly notify your doctor, who will make a judgment and provide medical treatment.

3) Others
You will need to come to the hospital for regular follow-up visits and assessments (imaging included) to evaluate efficacy and safety of afatinib, which may cause inconvenience and more frequent exposure to low doses of radiation.

(2) What are the benefits of participating in the study?

The IMP may decrease the disease progression in some participants, but we cannot guarantee this. You can get information about your health from the physical examination and laboratory tests done in the study. Although there may be no direct benefit to you from participation in this study, your participation may benefit future patients who are suffering from the same disease. This study will give you free NGS reports of both ctDNA and tumor tissue, which will provide genetic information related to tumor development and prognosis. This information, especially from continuous ctDNA detection, can be very helpful in guiding your subsequent treatment and monitor tumor recurrence and metastasis.

5. ALTERNATIVE TREATMENT OPTIONS

In addition to participating in this study, you may receive other treatments as adjuvant therapy for GBC, including radiation therapy, chemotherapy, and immunotherapy. Your study doctor will discuss the possible risks, the advantages and disadvantages of other treatment options with you. Please decide whether to participate in this study after fully discussion. You do not have to participate in this study to get treatment for your disease. Other alternative treatments may be available to you which are defined as follows:

- Other clinical studies that your doctor may know of to your disease.
- The best supportive treatment to minimize your pain or discomfort, etc.

6. USE OF RESEARCH RESULTS AND CONFIDENTIALITY OF PERSONAL INFORMATION

Results conducted through this program may be published in medical journals with the understanding and assistance of you and other participants, but we will keep your study records confidential as required by law. The personal information of study participants will be kept strictly confidential, and your personal information will not be disclosed unless required by relevant laws. If necessary, government administrative departments, hospital ethics committees and other relevant researchers can access your data according to regulations.

7. RESEARCH EXPENSES AND RELATED COMPENSATION

(1) Cost of drugs used in the study and related examinations

Afatinib is provided for free until the end of the treatment specified in the study protocol. GEMOX chemotherapy is at your own expense. In addition, you will be solely responsible for the expenses incurred by you for any examination, hospitalization, and treatment other than this study, as well as for the routine treatment and examination required for any concurrent disease.
(2) Compensation for participation in the study

There are no additional compensation for this study.

(3) Compensation/compensation after damage

For participants who suffer damage related to this study, the sponsor will bear the treatment cost and corresponding economic compensation in accordance with Chinese laws and regulations.

8. RIGHTS OF PARTICIPANTS AND RELEVANT MATTERS NEEDING ATTENTION

(1) Your rights

Your participation in the study is voluntary throughout the entire process. If you decide not to participate in this study, it will not affect other treatments you should receive. If you decide to participate, you will be asked to sign this written informed consent. You have the right to withdraw from the trial at any stage without discrimination or unfair treatment, and your medical treatment and rights will not be affected.

(2) Matters needing attention

Before enrollment, you will undergo screening to confirm if you are eligible for the study. You are required to provide true information about your medical history and current medical condition. During treatment and follow-up visits, you must come to the hospital at the scheduled timepoints. Your follow-up visits are very important because your doctor will determine if the treatment you are receiving is actually working. You should not use other chemotherapy, targeted or immunotherapy drugs for GBC during the study. If you need other treatments, please contact your doctor in advance.

9. RELEVANT CONTACT INFORMATION

If there is any significant new information during the study that may affect your willingness to continue to participate, your doctor will inform you promptly. If you are interested in your own study data, or you would like to know the findings after this study, you may ask any questions about this study at any time and receive answers accordingly. Please contact doctor Mao Yang at **********.
Participant Signature Page

Participant Consent Statement:
- □ I have been informed of the purpose, background, process, risks and benefits of this study. I have plenty of time and opportunity to ask questions, and I am satisfied with the answers.
- □ I am also told who to contact when I have questions, want to report difficulties, concerns, suggestions for research, or want further information, or to help with research.
- □ I have read this informed consent and agree to participate in this study.
- □ I understand that I may choose not to participate in the study or withdraw from the study at any time during the study without any reason.
- □ I already know that if I get worse, or if I have a serious adverse event, or if my study doctor decides it's not in my best interest to continue, he or she will decide to withdraw me from the study. The funder or regulatory agency may terminate during the study without my consent. If this happens, the doctor will inform me and the study doctor will discuss other options with me.
- □ I will be provided with a copy of the informed consent which contains my signature and that of the investigator.

Participant Signature:

Date:

Tel:

(NOTE: If participant has no capacity/limited capacity, legal representative signature and date will be required)

Legal Representative's Signature:

Date:

Tel:

Investigator Statement:

I have explained the entire process of this study in detail, particularly, the possible risks and benefits of participating.

Investigator Signature:

Date:

Tel: