Fuquinitinib combined with FOLFOXIRI-HAIP is used as a Later-line Treatment for Patients with advanced Colorectal Cancer Liver Metastasis.

Written informed consent for clinical research

Dear Subject,

We invite you to participate in the project "fuquinitinib combined with FOLFOXIRI-HAIP for the late-line treatment of patients with advanced colorectal cancer liver metastasis" approved by West China Hospital of Sichuan University. The study will be conducted at the West China Hospital Hospital, Sichuan University, and it is estimated that 24 subjects will volunteer to participate. This study has been reviewed and approved by the Biomedical Ethics Review Board of West China Hospital, Sichuan University.

1. Why was this study conducted?

Colorectal cancer is a common malignant tumor of the digestive tract and one of the most common malignant tumors in China. Treatment of patients with metastatic colorectal cancer (mCRC) is usually palliative with systemic therapy that includes chemotherapeutic agents such as fluorouracilides, irinotecan, and oxaliplatin; Angiogenesis inhibitors, such as bevacizumab; And the use of monoclonal antibodies such as cetuximab in patients with wild-type RAS. Regorafenib and fuquinitinib are small molecule multi-targeted tyrosine kinase inhibitors in third-line treatment. Fuquinitinib is an oral chemotherapy drug and has shown efficacy in patients with chemotherapy-refractory colorectal cancer.

The safety and efficacy of fuquilitinib monotherapy in patients with mCRC was demonstrated in a randomized, double-blind, placebo-controlled, multicenter phase III study (FRESCO). There was a significant difference in median overall survival between fuquilitinib and placebo. Currently fuquilitinib capsules (trade mark: Ayute ®) has obtained the drug marketing approval from the China Food and Drug Administration on September 5, 2018, and its indication is for the treatment of patients who have previously received fluoropyrimidines, oxaliplatin and irinotecan-based chemotherapy. And mCRC patients who had received or were ineligible for anti-vascular endothelial growth factor (VEGF) therapy or anti-epidermal growth factor receptor (EGFR) therapy (RAS wild-type).

Three-drug regimen FOLFOXIRI(oxaliplatin, fluorouracil, irinotecan and leucovorin) is superior to two-drug FOLFOX or FOLFIRI in the treatment of advanced colorectal cancer, and can be used as a first-line treatment for some patients. The concept of hepatic arterial infusion chemotherapy (HAIC) originated in Japan, which can selectively deliver drugs to

tumors, reduce the impact on normal liver cells, minimize systemic side effects, and reduce systemic toxicity. Haic has become one of the standard treatments for primary hepatocellular carcinoma in China. Hepatic artery infusion pump chemotherapy (HAIP) is based on HAIC. The arterial port can be placed subcutaneously for a long time, and drugs can be administered regularly or at any time as needed, which avoids the damage and pain caused by repeated arterial puncture and intubation and reduces the cost of treatment.

The aim of this study is to prospectively collect and analyze the efficacy and safety of fuquinitinib combined with FOLFOXIRI-HAIP regimen in the late-line treatment of patients with metastatic colorectal cancer.

2. What do you need to do to participate in the study?

This study was a prospective, single-center, phase II clinical study. The treatment was selected by the doctor according to the patient's condition and wishes. The expected number of participants in our center is 24. If you agree to participate in this study, you will need to sign this informed consent form. If you meet the inclusion criteria and do not meet the exclusion criteria, you will be enrolled in the study.If you are enrolled in this study, we will collect your relevant clinical information (routine examination and evaluation items) as follows:

① Basic information: gender, age, BMI.

② Laboratory tests: blood biochemistry, blood routine, urine routine, coagulation function, immunological test.

③ Imaging examination: magnetic resonance imaging, ultrasound, CT examination.

④ Tumor markers were detected: alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9.

This study will collect and analyze the medical information data generated in your routine clinical practice to evaluate the safety and efficacy of furoquintinib-containing FOLFOXIRI-HAIP. Therefore, we will collect all adverse events from the time you sign this informed consent until 28 days after the last dose of study medication. In addition, we hope that you will continue to cooperate with us in the post-treatment follow-up period, which began after you received your last dose of the study medication. The study was expected to last 3 years.

In this study, the remaining specimens of routine detection will be used for research.

3. What are the treatment options?

If you do not participate in the study or if you withdraw from the study, you may still receive other standard treatment options. Including but not limited to other chemotherapy

drugs, targeted therapy, immunotherapy, etc. Each treatment has its own potential risks and benefits, depending on your condition, the treatment option chosen, and your individual health status.

4. **Who should not participate in the study?**

If you (1) have not signed the informed consent form; (2) Patients with contraindications to fuquetinib, oxaliplatin, fluorouracil, irinotecan and leucovorin; (3) women with a positive pregnancy test or lactation; (4) Patients were ineligible to participate in the study if they had any other conditions considered by the investigator to be unsuitable for the study.

5. **What are the risks of participating in a study?**

Fuquilitinib therapy may cause myelosuppression, including anemia, neutropenia, leukopenia, and thrombocytopenia. Gastrointestinal toxicity may also occur, manifested as nausea, vomiting, and diarrhea. These risks are usual care risks and would have existed without participation in the study. To address these risks, the patients' condition will be closely monitored.

HAIP (hepatic artery infusion pump chemotherapy) requires admission and placement of infusion ports. Percutaneous femoral artery catheterization was performed using Seldinger's method, and the catheter was placed in the celiac trunk or common hepatic artery for angiography. If the intrahepatic target lesions were distributed in the left and right livers, bilateral femoral artery ports should be placed if necessary after full evaluation by the surgeon. It may lead to the risk of bleeding, infection, pain and other risks. To cope with these risks, the study will be performed as gently as possible, strictly aseptic, and closely monitor the patient's condition.

6. **What are the possible benefits of participating in the study?**

It is possible that your condition will improve by taking part in this study, and the study will help to determine which treatments are safer and more effective for other patients with a condition similar to yours. In addition, participation in research can contribute to medical research and promote the advancement of medical knowledge and treatment. However, patients may not benefit.

7. **Do I have to pay any fees to participate in the study?**

To participate in this study, patients should pay for the normal examination and treatment costs during the treatment. This study will not provide a transportation subsidy for patients to return to the hospital for examination, 200 yuan per person.

If any damage occurs, the research team will provide you with timely treatment. If the damage is judged by the investigators to be related to this study, the corresponding treatment

costs will be borne by the study (the study has purchased clinical research insurance for you).

8. **Is personal information confidential?**

Your research data will be stored in West China Hospital of Sichuan University, and your medical records will be accessible to investigators, research authorities, and ethics review boards. Your personal identity will not be disclosed in any public report of the results of this study. We will make every effort to protect the privacy and personal information of your personal medical data within the scope permitted by law.

9. **Do I have to participate in the study?**

Participation in this study is completely voluntary. You may refuse to participate in the study, or withdraw from the study at any stage without discrimination or retaliation, and your medical treatment and rights and interests will not be affected. If you decide to withdraw from this study, please contact your doctor for proper medical management.

Subject Statement: I have read the above introduction about this study, and my researcher has fully explained and explained to me the purpose of this study, the procedure, the possible risks and potential benefits of participating in this study, and answered all my relevant questions. Participation in this study was voluntary.

I agree □ or refuse□ to use my data and biological specimens for research other than this study.

Subject name in block letters:_____

Signature of subject:_____ Date:__ __ __ __ Year __ __ Month __ __Day

Subject's contact number:_____ Mobile phone number:_____

Signature of legal representative in block letters:_____

Relationship with subjects:_____

Signature of legal representative:____Date:__ __ __ __ Year __ __ Month __ __Day

Reasons for signing by legal representative:_____

Name of Witness in block letters：_____

Signature of witness:_____Date:__ __ __ __ Year __ __ Month __ __Day

Reasons for signing by Witness:_____

Physician Statement: I have explained the study details to the above volunteer and provided him/her with an original signed informed consent form. I confirm that the circumstances of the study were explained to the subjects in detail, in particular the ethical principles and requirements of possible risks and benefits, free of charge and compensation, damage and compensation, voluntary and confidentiality arising from participation in the study.

Signature of the doctor:_____Date:__ __ __ __ Year __ __ Month __ __Day

Doctor's contact number:_____

Biomedical Ethics Review Committee, West China Hospital, Sichuan University

Contact number:028-85422654，028-85423237