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

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## 1. Background

About 30-50% of patients with colorectal cancer have liver metastases at the time of diagnosis. Surgical resection is the standard radical treatment for patients with resectable colorectal cancer liver metastases, but only about 20% of patients with colorectal cancer liver metastases can achieve long-term survival after surgical treatment, and more than 70% of patients with colorectal cancer liver metastases are initially unresectable or relapse after liver resection. There is still a lack of effective treatment for unresectable colorectal liver metastases. Previous studies have shown that 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. However, most patients with metastatic CRC have disease progression despite receipt of first - or second-line systemic therapy. Fuquinitinib, an oral small molecule vascular endothelial growth factor receptor (VEGFR) inhibitor developed in China, has a limited effect on improving overall survival in patients with advanced metastatic colorectal cancer. Transarterial embolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) are two interventional methods for the treatment of liver metastases from colorectal cancer. Hepatic arterial infusion pump chemotherapy (HAIP) is based on HAIC. The arterial port can be placed in the femoral artery for a long time, and the drug can be given regularly or at any time according to the need. Therefore, the aim of this study is to explore the survival benefits and prognostic factors of fuquinitinib combined with FOLFOXIRI-HAIP in the third-line or beyond treatment of advanced colorectal cancer patients with liver metastasis.

## 2. Aim and Content of the Study

2.1 Aim of the study

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.

2.2 Content of the study

- Inclusion criteria:

a. Men and women over 18 years old;

b. Colorectal cancer confirmed by pathology or cytology, with liver metastasis only, or liver as the main metastatic tumor burden site, and unable to undergo surgical resection or unwilling to undergo surgical resection;

c. Patients who had received oxaliplatin, fluorouracil, or irinotecan chemotherapy with or without EGFR monoclonal antibody or VEGFR monoclonal antibody;

d. The main organ function (liver, kidney, heart, lung) was normal and Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 to 2.

E. All participants were willing to participate in this clinical study, and were required to sign the corresponding informed consent. They had good compliance during the treatment and follow-up process, and were willing to cooperate with the relevant research process.

- Exclusion Criteria:

a. Prior treatment with TACE, HAIC or fuquinitinib；

b. Combined with primary malignant tumors of other systems except colorectal cancer;

c. Allergy to study medication;

d. Major organ functions (liver, kidney, heart, lung) were severely abnormal.

2.3 Sample size: 24

This single-center, single-arm, a phase 2 clinical trial performed at the West China Hospital. Sample size calculation used a two-stage Simon's optimal design with nominal alpha and beta values of 5% and 20%, respectively. The null hypothesis stated that ORR would be ≤ 10%, versus an alternative hypothesis of ORR ≥ 35%. Accounting for a 10% dropout rate, at least 24 patients were required for this study. This study included 8 patients in Stage 1and 39 patients in Stage 2. Stage 2 enrollment was only initiated after ≥ 1 partial response had been observed in 8 treated patients. The study adhered to the guidelines outlined in the Declaration of Helsinki and has been approved by the Ethics Committee of West China Hospital, Sichuan University. All patients provided written informed consent for participation in the study.

2.4 Outcome Measures

Eligible patients were enrolled from January 2023 to receive furoquininib plus FOLFOXIRI-HAIP. The baseline data (including age, gender, some blood indicators before treatment, primary tumor location, tumor stage, pathological differentiation type, gene mutation status, number of previous treatment lines, size and number of liver metastases), adverse reactions, overall survival (OS) and progression-free survival (PFS) were collected and summarized.

The primary endpoint of the study was objective response rate (ORR). The secondary endpoints included overall progression-free survival (PFS), overall survival (OS), liver-specific PFS and safety evaluation. ORR was defined as the proportion of patients with the best overall response of complete response (CR) and partial response (PR). OS was defined as the duration from the initiation of treatment to loss to follow-up or death. PFS was defined as the duration from the start of treatment to disease progression or death.

**3. Statistical analysis**

Continuous variables were expressed as means ± standard deviations (SD), along with the minimum and maximum values. For non-normally distributed data, the IQR was used. Categorical variables were presented as frequencies and percentages. The Kaplan-Meier method was used to analyze OS and PFS in the overall population with estimated medians and 95% CIs presented. Survival curves were performed using R software version 4.2.2 (http://www.Rproject.org).

**4. Ethical principles and requirements of clinical research**

Clinical research will follow the Declaration of Helsinki of the World Medical Assembly and the Ethical Review Measures for Biomedical Research involving Human Subjects of the National Health and Family Planning Commission of the People's Republic of China and other relevant regulations, including the principles and requirements of informed consent, privacy protection, research free of charge and compensation, risk control, protection of special subjects and compensation for research-related damages. The clinical study was carried out after approval of the trial protocol by the ethical review board prior to the initiation of the study. Before each subject is enrolled in the study, the investigator is responsible for providing the subject or/and his/her legal representative with a complete and comprehensive introduction of the purpose, procedures and possible risks of the study, and signing a written informed consent form, so that

the subject knows that their participation in the clinical study is completely voluntary. They may refuse to participate or withdraw from the study at any stage without discrimination or retaliation, and their medical treatment and rights and interests will not be affected. Informed consent should be retained as a clinical research document for future reference to effectively protect the personal privacy and data confidentiality of subjects.

**5. References**

[1] DASARI A, LONARDI S, GARCIA-CARBONERO R, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study[J/OL]. The Lancet, 2023, 402(10395): 41-53. DOI:10.1016/S0140-6736(23)00772-9.

[2] MAYER R J, VAN CUTSEM E, FALCONE A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer[J/OL]. The New England Journal of Medicine, 2015, 372(20): 1909-1919. DOI:10.1056/NEJMoa1414325.

[3] GROTHEY A, VAN CUTSEM E, SOBRERO A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial[J/OL]. Lancet (London, England), 2013, 381(9863): 303-312. DOI:10.1016/S0140-6736(12)61900-X.

[4] LI J, QIN S, XU R H, et al. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial[J/OL]. JAMA, 2018, 319(24): 2486-2496. DOI:10.1001/jama.2018.7855.

[5] LÉVI F A, BOIGE V, HEBBAR M, et al. Conversion to resection of liver metastases from colorectal cancer with hepatic artery infusion of combined chemotherapy and systemic cetuximab in multicenter trial OPTILIV[J/OL]. Annals of Oncology, 2016, 27(2): 267-274. DOI:10.1093/annonc/mdv548.

[6] LI J, QIN S, XU R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial[J/OL]. The Lancet Oncology, 2015, 16(6): 619-629. DOI:10.1016/S1470-2045(15)70156-7.

[7] PRAGER G W, TAIEB J, FAKIH M, et al. Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer[J/OL]. The New England Journal of Medicine, 2023, 388(18): 1657-1667. DOI:10.1056/NEJMoa2214963.

[8] VERHEIJ F S, KUHLMANN K F D, SILLIMAN D R, et al. Combined Hepatic Arterial Infusion Pump and Systemic Chemotherapy in the Modern Era for Chemotherapy-Naive Patients with Unresectable Colorectal Liver Metastases[J/OL]. Annals of Surgical Oncology, 2023, 30(13): 7950-7959. DOI:10.1245/s10434-023-14073-3.

[9] KRUL M F, KOK N F M, OSMANI H, et al. Hepatic arterial infusion pump chemotherapy combined with systemic chemotherapy for borderline resectable and unresectable colorectal liver metastases: phase II feasibility study[J/OL]. The British Journal of Surgery, 2024, 111(4): znae089. DOI:10.1093/bjs/znae089.

[10] LOUPAKIS F, CREMOLINI C, MASI G, et al. Initial Therapy with FOLFOXIRI and Bevacizumab for Metastatic Colorectal Cancer[J/OL]. New England Journal of Medicine, 2014, 371(17): 1609-1618. DOI:10.1056/NEJMoa1403108.