

# BMJ Open Pathological response and safety of FOLFOXIRI for neoadjuvant treatment of high-risk relapsed locally advanced colon cancer: study protocol for a single-arm, open-label phase II trial

Xiaorong Chen,<sup>1</sup> Weibing Leng,<sup>1</sup> YuWen Zhou,<sup>2</sup> Yongyang Yu,<sup>3</sup> Wenjian Meng,<sup>4</sup> Peng Cao,<sup>1</sup> Ziqiang Wang,<sup>4</sup> Meng Qiu <sup>1</sup>

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XC, WL and YZ contributed equally.

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For numbered affiliations see end of article.

**Correspondence to**  
Dr Meng Qiu;  
qiumeng@wchscu.cn and  
Dr Ziqiang Wang;  
wangziqiang@scu.edu.cn

## ABSTRACT

**Introduction** Neoadjuvant chemotherapy (NAC) has been demonstrated effective in several tumours, but its benefit has not yet been elucidated in colorectal cancer, especially locally advanced colorectal cancer (LACRC).

**Methods and analysis** This is a single-arm, open-label, prospective phase II exploratory clinical trial. Patients with LACRC will receive four cycles of NAC with 5-fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI), followed by operation and then adjuvant chemotherapy with capecitabine and oxaliplatin for two to five cycles or single-agent capecitabine for five cycles, or observation. The primary endpoint is the rate of tumour regression grade (TRG) 0–2 in the resected tumour tissue, which is evaluated by experienced pathologists according to the Ryan R TRG grading system. Secondary endpoints include objective response rate, pathologic complete response, microscopically complete resection rate, progression-free survival, distant metastasis-free survival, overall survival, toxicity and compliance to study treatment, molecular markers, quality of life to study treatment and the number of patients with 30-day postoperative mortality. The objective of this study is to analyse the efficacy and safety of FOLFOXIRI as the NAC regimen in patients with LACRC and to identify a promising treatment strategy in this setting.

**Ethics and dissemination** Written informed consent will be required from and provided by all patients enrolled. The study protocol has been approved by the independent ethics committee of West China Hospital, Sichuan University (approval number: 2021403). This study will demonstrate the potential benefit of NAC with the FOLFOXIRI regimen. Results will be shared with policymakers and the academic community to promote the clinical management of colon cancer.

**Trial registration number** NCT05018182.

## INTRODUCTION

Colon cancer is the third most common malignant neoplasm and ranks second in terms of cancer-related mortality worldwide. In resectable colorectal cancer, locally advanced

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a single-arm, open-label, prospective phase II exploratory clinical trial.
- ⇒ Simon's two-stage optimal approach will allow for early termination due to the absence of treatment efficacy in the first stage.
- ⇒ No control group is used in this clinical trial.

colorectal cancer (LACRC) accounts for approximately 10–15%.<sup>1 2</sup> LACRC is usually defined as T3 tumours with ≥5 mm invasion beyond the muscularis propria, T4 (direct invasion into adjacent structures) or extensive regional lymph node involvement, without distant metastases.<sup>3</sup> Colon cancer and rectal cancer located >10 cm from the anal verge share similarities in the model of cancer recurrence and have a similar beneficial effect on disease-free survival of adjuvant chemotherapy.<sup>4</sup> To date, complete oncologic resection followed by adjuvant chemotherapy is still considered as the standard treatment modality for patients with LACRC. This multidisciplinary approach confers excellent disease-free survival and overall survival (OS), but the local recurrence or distant metastasis rate remains high (about 30%–50%).<sup>5 6</sup> Concerning therapy modality, Asian guidelines recommend an extensive lymphadenectomy for patients with LACRC, while Western guidelines suggest neoadjuvant chemotherapy (NAC) following the publication of the preliminary results of the FOxTROT trial.<sup>7</sup> Therefore, LACRC still represents a major therapeutic challenge in resectable colorectal cancer.

Neoadjuvant chemoradiation or NAC plus neoadjuvant chemoradiation followed by surgery shows superior outcomes to up-front

surgery and has been introduced into the standard care of locally advanced rectal cancer.<sup>8</sup> There are several factors favouring NAC, such as eradication of potential lymph node metastases and/or distant metastases, examination of the tumour chemosensitivity to guide adjuvant chemotherapy and reduction of tumour cell-shedding due to surgical trauma.<sup>5</sup> In addition, NAC could also increase the likelihood of a complete resection (R0) margin for patients with LACRC. R0 resection strongly correlates with recurrence and survival in colorectal cancer.<sup>9</sup> There is increasing evidence to support the usefulness of NAC in LACRC; however, its safety, efficacy and side effect profile have not yet been completely elucidated. In FOxTROT trial, NAC for locally advanced operable colorectal cancer has been demonstrated feasible with acceptable toxicity and perioperative morbidity.<sup>10</sup> However, in this study, most patients were staged as T3, and the efficacy of two-agent chemotherapy regimen (oxaliplatin plus fluorouracil) was not adequate. In addition, valid biomarkers to predict the early efficacy of NAC have not been explored in this trial. Most recent studies focus on finding effective biomarkers to predict outcome and provide precise treatment, like dMMR/MSI-H despite being a marker of improved prognosis in stage II, which is not associated with a favourable prognosis in stage III/IV colon cancer.<sup>11 12</sup> Intensification of chemotherapy using fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI) has been demonstrated to higher progression-free survival (PFS, 12.1 vs 9.7 months) and OS (31.0 vs 25.8 months) than two-agent regimen (fluorouracil and irinotecan) in patients with metastatic colorectal cancer.<sup>13</sup> Also, in PRODIGE 23 trial, the FOLFOXIRI regimen before preoperative chemoradiotherapy significantly improved outcomes compared with preoperative chemoradiotherapy in patients with locally advanced rectal cancer.<sup>14</sup>

NAC may eradicate microscopic metastatic cancer cells earlier than adjuvant chemotherapy, reduce cancer cell spillage during surgery and lessen the invasiveness of surgical resection. Theoretically, FOLFOXIRI regimen will be more suitable for the demand of NAC. While inaccurate radiological tumour staging might result in over-treatment or missing optimal surgical time for low-risk patients, the population with a high-risk of recurrence (including T4a/b or (and) N2/fused lymph nodes or (and) positive extramural vascular invasion (EMVI+) or (and) circumferential resection margin (CRM)  $\leq 2$  mm) is the most suitable cohort for NAC.<sup>15</sup> Based on the above, we carry out such a phase II clinical trial to observe the pathological remission rate and safety of FOLFOXIRI for high-risk relapsed LACRC.

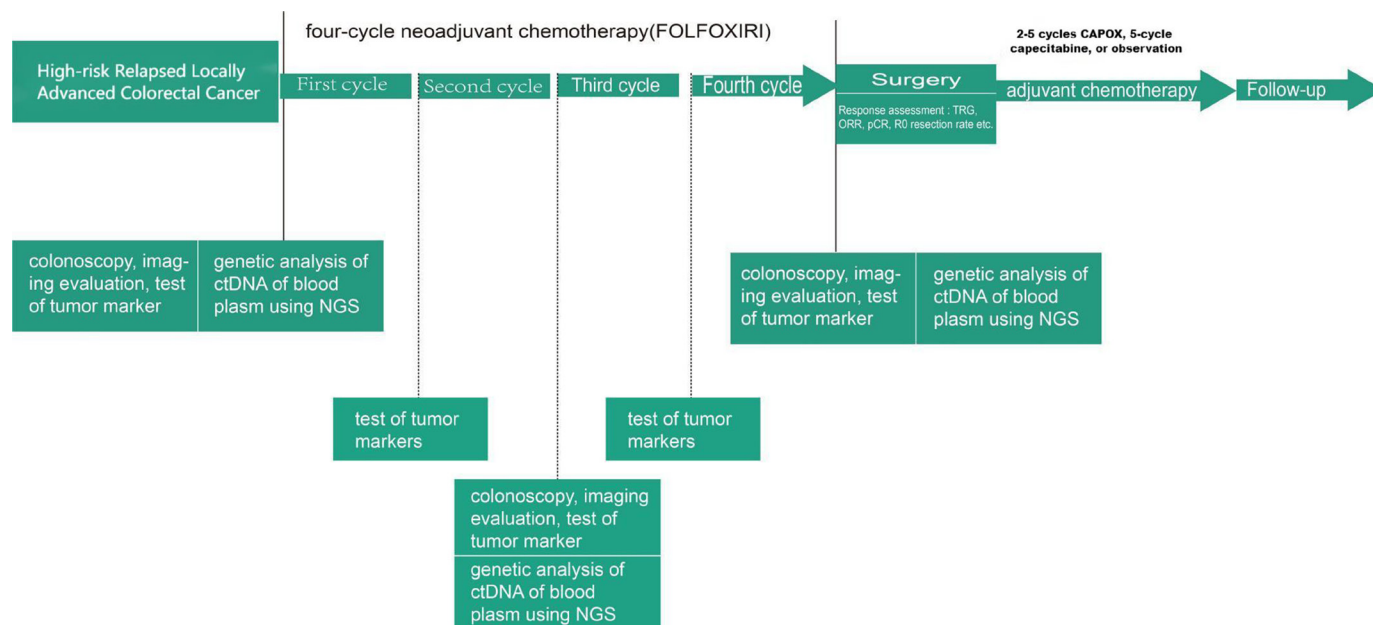
## METHODS AND ANALYSIS

### Study design

This study is designed as a prospective, open-label, single-arm phase II exploratory clinical trial, which aims at exploring the efficacy and safety of FOLFOXIRI for NAC of patients with high-risk relapsed LACRC. It is hoped that the NAC regimen of FOLFOXIRI could achieve a higher tumour regression grade (TRG) than the previous two-agent regimen. This trial is registered with ClinicalTrials.gov. The study flowchart is summarised in figure 1.

All eligible patients will receive four cycles of NAC with 5-FOLFOXIRI, followed by operation and adjuvant chemotherapy with capecitabine and oxaliplatin (CAPOX) for two to four cycles, single-agent capecitabine for five cycles or observation.

In the neoadjuvant setting, eligible patients will receive intravenous oxaliplatin 85 mg/m<sup>2</sup>, irinotecan 150 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup> and 5-FU 2800 mg/m<sup>2</sup> given as an



**Figure 1** Flowchart. ctDNA, circulating tumour DNA; CAPOX, capecitabine and oxaliplatin; FOLFOX-IRI, 5-fluorouracil, oxaliplatin, and irinotecan; NGS, next-generation sequencing.

intravenous bolus every 2 weeks. According to the operative TRG, patients will receive adjuvant chemotherapy or observation. The adjuvant chemotherapy regimen consists of CAPOX (intravenous oxaliplatin (130 mg/m<sup>2</sup>, once a day) on day 1 and oral capecitabine (1000 mg/m<sup>2</sup>, two times per day) on days 1 to 14) or single-agent capecitabine (1000 mg/m<sup>2</sup>, oral, two times per day, on days 1 to 14), which will be repeated every 3 weeks.

Post-treatment follow-up assessments include the physical examination, tumour markers including carcinoembryonic antigen (CEA), CA19-9, CA72-4, CT scans and digital rectal examination. Tumour markers will be evaluated every 3 months, while assessment of imaging materials will be done every 6 months.

## Patients

Patient selection is based on the following inclusion and exclusion criteria.

### Inclusion criteria

- ▶ Age: 18–75 years old; sex: male or female.
- ▶ Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.
- ▶ American Society of Anesthesiologists scores of I–II.
- ▶ Histologically proven colorectal carcinoma (defined as cancer that is located >10 cm from the anal verge by endoscopy).
- ▶ Unequivocal radiological evidence of locally advanced cancer based on thin slice spiral CT or MRI (defined as T4a/b or (and) N2/fused lymph nodes or (and) positive EMVI+ or (and) CRM ≤2 mm). Pelvic MRI will be used to provide useful information in the prediction of the CRM before radical surgery, since pelvic MRI is able to provide accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia.
- ▶ No distant metastases (distant organ or (and) distant lymph node metastases) assessed by CT scan or other radiographic examination.
- ▶ For patients with T4b, R0 resection was expected to be achieved, including the necessarily combined organ resection by multidisciplinary team (MDT) discussion.
- ▶ No history of 5-Fu and platinum drug allergy.
- ▶ Adequate bone marrow function: hemoglobin ≥9 g/dL; platelet >100×10<sup>9</sup>/L; white blood cell >3.5×10<sup>9</sup>/L and neutrophil granulocyte ≥1.5×10<sup>9</sup>/L.
- ▶ Adequate hepatobiliary function: ASAT and ALAT of 2.5x upper limits of normal (ULN) or less, alkaline phosphatase of 2.5x ULN or less, total bilirubin 1.5x upper normal level or less.
- ▶ Adequate renal biochemistry: glomerular filtration rate >50 mL/min calculated by the Wright or Cockcroft formula or EDTA clearance >70 mL/min.
- ▶ For women of childbearing potential, the patient must have a negative pregnancy test ≤72 hours before initiating study treatment and agree to avoid pregnancy during and for 6 months after study treatment. For males with a partner of childbearing potential,

the patient must agree to use adequate, medically approved, contraceptive precautions during and for 90 days after the last dose of study treatment.

- ▶ Patient is able and willing to provide written informed consent for the study.

### Exclusion criteria

- ▶ Patients with Lynch syndrome.
- ▶ Rectal cancer is located 10 cm or less from the anal verge.
- ▶ Any patient for whom radiotherapy is advised by the MDT.
- ▶ Patient with evidence of distant metastases or peritoneal nodules (M1).
- ▶ Severe intestinal complications on initial clinical or imaging assessment: perforation, obstruction, uncontrollable bleeding.
- ▶ Another serious medical condition is judged to compromise the ability to tolerate neoadjuvant therapy and/or surgery.
- ▶ Pre-existing or concurrent other malignancies (including concurrent colon cancer), except for cured basal cell carcinoma of the skin and carcinoma in situ of the cervix.
- ▶ Pregnant or breastfeeding women.
- ▶ Patients with severe cardiovascular disease and diabetes mellitus cannot be easily controlled.
- ▶ Persons with mental disorders.
- ▶ Patients with severe infections.
- ▶ Patients on thrombolytic/anticoagulant therapy, bleeding quality or coagulation disorders; or aneurysms, strokes, transient ischaemic attacks, arteriovenous malformations in the past year.
- ▶ Previous history of renal disease with urine protein on urinalysis or clinically significant renal function abnormalities.

### Recruitment

Patients are recruited and screened from West China Hospital, Sichuan University from August 2021. Patients screened out will be evaluated for eligibility according to inclusion and exclusion criteria by oncologists, provided with a participant information sheet, and asked to offer their written consent. Participants have the right to withdraw from the study at any time for any reason.

### Description of intervention

All eligible patients will be first given chemotherapy, then radical surgery and chemotherapy again after the surgery.

In the neoadjuvant setting, eligible patients will receive an NAC regimen with FOLFOXIRI repeated every 2 weeks. And then, according to postoperatively pathological findings and adverse events of NAC, patients will receive CAPOX for two-five cycles or capecitabine for five cycles. For those who resisted NAC, observation will be chosen.

During chemotherapy, adverse events were evaluated once in each cycle. Patients will discontinue the

treatment of capecitabine/oxaliplatin when they occur severe adverse events, including grade 4 or worse leucopenia, grade 3 or worse digestive tract adverse events, grade 2 or worse anaemia and thrombocytopenia, and grade 2 or worse liver and kidney dysfunction. If the adverse events decrease to grade 0–1 within 5 days after treatment, the original dose of capecitabine/oxaliplatin should be restored, otherwise, the dose should be reduced to 80%. If adverse events persist after dose reduction, discontinuation should be considered. Fluorouracil/oxaliplatin treatment should be discontinued if these adverse events persist for more than 3 days after treatment and dosage reduction or appear another newly grade 2 or worse adverse event. Chemotherapy should be discontinued in case of any grade 4 adverse events except for leucopenia.

### Study visits

To ensure adequate follow-up and assessment, study visits are planned based on the study design and specific to the disease treatment:

- ▶ At baseline: diagnosis of colon cancer confirmed by histopathology examination; tumour imaging assessment including chest CT scan, abdominal/pelvic CT/MRI (scan plus enhancement), tumour markers (CEA, CA199, CA72-4, etc), biomarkers (MSI/MMR, Ki67, RAS and BRAF), circulating tumour DNA (ctDNA), ECOG score, and so on.
- ▶ During chemotherapy: haematology (white blood cells, neutrophils, platelet count, haemoglobin, etc), biochemistry (total bilirubin, alkaline phosphatase, AST, ALT, electrolyte (Na<sup>+</sup>, K<sup>+</sup>, CL<sup>-</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>) and so on) once or two times every week; tumour imaging assessment and tumour markers every two cycles during NAC.
- ▶ Postoperative follow-up should be divided into two subgroups:
  - Early postoperative period (within 30 days after surgery): evaluation of perioperative complications like vital signs, wound infection, anastomatic leak and bronchopneumonia, and Clavien-Dindo classification.
  - Late postoperative period (after 30 days since surgery has been performed): tumour markers, haematology, biochemistry and tumour imaging assessment in week 4 before receiving adjuvant chemotherapy or observation. Then, patients undergoing adjuvant chemotherapy will be assessed tumour markers, haematology and biochemistry each cycle, tumour assessment every two cycles. In addition, no matter undergoing adjuvant chemotherapy or observation, patients will receive electronic gastroscopy and colonoscopy within half a year after radical surgery; tumour markers every 3 months, and tumour assessment every 6 months for 3 years and then once a year.

**Table 1** Ryan R TRG grading system

TRG grades	Description
TRG 0	No residual cancer cells
TRG 1	Single cancer cells or small groups of cancer cells
TRG 2	More residual cancer but outgrown by fibrosis
TRG 3	Extensive residual tumour with minimal or no regression

TRG, tumour regression grade.

### Outcome measures

This is an open-label, single-arm, prospective phase II exploratory clinical trial. The primary endpoint is the pathological response rate of patients receiving our proposed treatment for high-risk relapsed LACRC. The pathological response is defined as the rate of TRG 0–2 in the resected tumour tissue according to Ryan R TRG grading system, which grades tumour response on a four-point scale (table 1).<sup>1</sup> Objective response rate, defined as the rate of patients with partial or complete response, will also be evaluated to determine the therapeutic response of NAC based on modified Response Evaluation Criteria In Solid Tumours criteria before surgery.<sup>16</sup> In addition, this trial will also assess pathologic complete response, R0 resection rate, PFS, distant metastasis-free survival (DMFS) and OS. OS is defined as the time from the initial diagnosis to death from any cause. Adverse events related to preoperative chemotherapy will be assessed and graded in all patients who administered at least on a dose of the assigned treatment by investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, V.4.0). Serious adverse events refer to any event, whether or not a causal relationship has been established with the study, that is fatal; is life threatening; requires or prolongs ongoing hospital stay; results in persistent or substantial disability/incapacity or any clinically significant event affecting the safety of the participants. Also, the relation between the dynamic change of ctDNA and the efficiency of chemotherapy and TRG during preoperative chemotherapy will be explored.

### Sample calculation

The FOxTROT trial was initiated to investigate the feasibility, efficacy and safety of NAC in patients with locally advanced operable colon cancer. The results were promising and 20.1% of tumours in the NAC cohort showed marked to complete regression.<sup>10</sup> Thus, we assumed a TRG 0–2 rate of 35% in this clinical trial. The clinical trial was designed using Simon's two-stage optimal approach, which allowed for early termination due to the absence of treatment efficacy (figure 2). The first stage required 27 study subjects treated with the FOLFOXIRI regimen and if more than five cases developed TRG 0–2, the study would enrol 36 additional patients in the second stage for a total of 63 subjects. The sample size shall be 10% larger

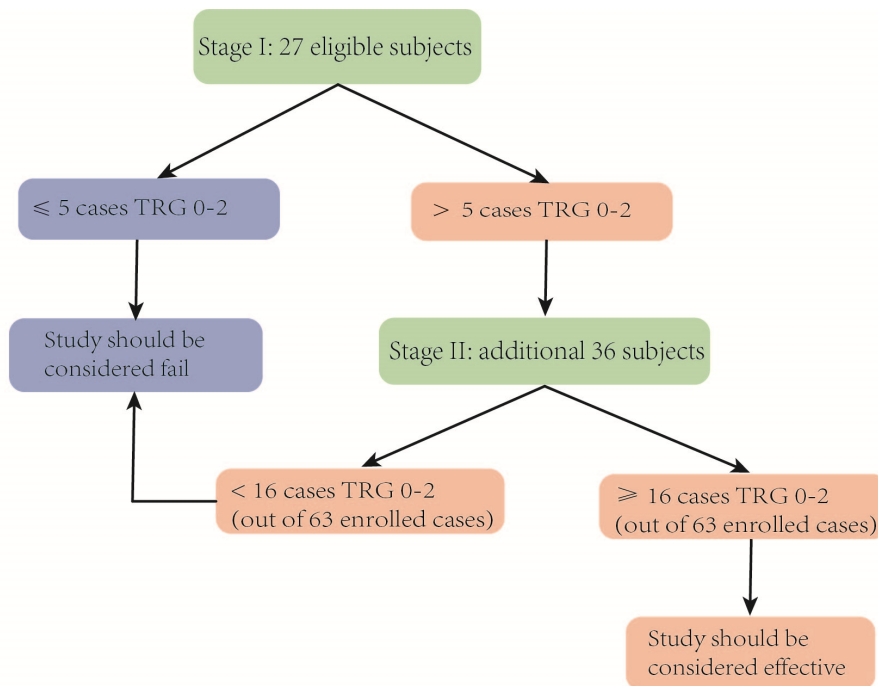


Figure 2. Simon's two-stage design  
Abbreviation: TRG, tumor regression grade

**Figure 2** Simon's two-stage design. TRG, tumour regression grade.

due to the possibility of drop-out. Therefore, a total of 69 subjects will be enrolled.

### Statistical analysis

The primary outcome measure is the proportion of TRG 0–2 in patients receiving our proposed treatment for high-risk relapsed LACRC, which will be analysed based on the intention to treat (ITT) population. Descriptive statistics will be used for clinicopathological characteristics and safety evaluation. Mean values and SD will be provided for continuous endpoints. Also, the frequency and percentage distributions will be provided for discrete data. The Kaplan-Meier methodology will be used to estimate PFS, DMFS and OS in an ITT population. Univariate and multivariate survival analyses were conducted using the Cox proportional hazard model, and the HRs with 95% CI were calculated. The statistical analysis will be carried out using the SPSS V.25.0 software (IBM, Armonk, New York) and R software V.3.6.2 (<http://www.R-project.org>). The significance level is set at  $p < 0.1$ , and all statistical tests will be two sided.

### ETHICS AND DISSEMINATION

Written informed consent will be required for patients enrolled. This study will be conducted under the Declaration of Helsinki, without causing any extra harm or risks to patients. The protocol has been approved by the independent ethics committee of West China Hospital, Sichuan University (approval number: 2021403) and has been prospectively registered in the US National Library of Medicine.

### Patient and public involvement

Patients were not involved in the protocol development and study design. Oncologists who work in the abdominal tumour group are involved in patient screening to assess eligibility for the study. The results will be disseminated to the public through seminars, public talks and peer-reviewed journals.

### DISCUSSION

Complete mesocolic excision followed by adjuvant treatment is the optimal treatment for patients with LACRC, while distant metastasis remains the main cause of recurrence after surgery. NAC has several advantages and has been demonstrated effective in other neoplasms. However, very little is known about the efficacy and safety of NAC in patients with LACRC since few studies are available in the literature. This may be the reason why there is a lack of more widespread use of NAC in LACRC, despite the theoretical advantages.<sup>17</sup> In addition, the FOLFOXIRI regimen has become one of the first-line chemotherapeutic modalities for its high efficacy, although its toxicity is also severe.<sup>18</sup> We designed this study to investigate the treatment efficacy and safety of FOLFOXIRI for NAC for patients with LACRC with high-risk relapsed features.

FOxTROT study has shown that preoperative chemotherapy combining two chemotherapeutic agents (oxaliplatin and 5-fluorouracil) presents a significant effect on tumour down staging and could be used safely in colon cancer patients without distant metastasis.<sup>10</sup>

Our study was registered at ClinicalTrials.gov on 18 August 2021. Patient accrual began in April 2022.

Patients' follow-up will be performed for at least 3 years or until disease progression or death.

#### Author affiliations

<sup>1</sup>Department of Colorectal Cancer Center, Sichuan University West China Hospital, Chengdu, Sichuan, China

<sup>2</sup>Department of Biotherapy, Sichuan University West China Hospital, Chengdu, Sichuan, China

<sup>3</sup>Department of Gastrointestinal Surgery, Sichuan University West China Hospital, Chengdu, Sichuan, China

<sup>4</sup>Department of Colorectal Cancer Center, West China Hospital of Sichuan University, Chengdu, Sichuan, China

**Contributors** XC collected data, reviewed the literature and wrote the manuscript. WL and Y-WZ collected data, wrote and revised the manuscript. YY, WM and PC revised the manuscript. MQ and WZ design and revised the manuscript. All authors read and approved the final manuscript.

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**Competing interests** None declared.

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**Patient consent for publication** Not applicable.

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#### ORCID iD

Meng Qiu <http://orcid.org/0000-0003-3722-6938>

#### REFERENCES

- 1 Arnold M, Sierra MS, Laversanne M, *et al*. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017;66:683–91.
- 2 Klaver CEL, Gietelink L, Bemelman WA, *et al*. Locally advanced colon cancer: evaluation of current clinical practice and treatment outcomes at the population level. *J Natl Compr Canc Netw* 2017;15:181–90.
- 3 Gosavi R, Chia C, Michael M, *et al*. Neoadjuvant chemotherapy in locally advanced colon cancer: a systematic review and meta-analysis. *Int J Colorectal Dis* 2021;36:2063–70.
- 4 Swets M, Breugom AJ, Gelderblom H, *et al*. Should rectal cancer located 10–15 cm from the anal verge be defined as colon cancer. *Ann Oncol* 2017;28:664–5.
- 5 Arredondo J, Pastor E, Simó V, *et al*. Neoadjuvant chemotherapy in locally advanced colon cancer: a systematic review. *Tech Coloproctol* 2020;24:1001–15.
- 6 Lieberman DA, Rex DK, Winawer SJ, *et al*. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US multi-society task force on colorectal cancer. *Gastroenterology* 2012;143:844–57.
- 7 Pellino G, Warren O, Mills S, *et al*. Comparison of Western and Asian guidelines concerning the management of colon cancer. *Dis Colon Rectum* 2018;61:250–9.
- 8 Sauer R, Becker H, Hohenberger W, *et al*. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731–40.
- 9 Bhangu A, Ali SM, Darzi A, *et al*. Meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer. *Colorectal Dis* 2012;14:1457–66.
- 10 Foxtrot Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. *Lancet Oncol* 2012;13:1152–60.
- 11 Hestetun KE, Rosenlund NB, Stanisavljević L, *et al*. Stage-dependent prognostic shift in mismatch repair-deficient tumors: assessing patient outcomes in stage II and III colon cancer. *Front Oncol* 2022;12:853545.
- 12 Amelio I, Bertolo R, Bove P, *et al*. Liquid biopsies and cancer omics. *Cell Death Discov* 2020;6:131.
- 13 Loupakis F, Cremolini C, Masi G, *et al*. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014;371:1609–18.
- 14 Conroy T, Bosset J-F, Etienne P-L, *et al*. Neoadjuvant chemotherapy with folfoxirinox and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22:702–15.
- 15 Goffredo P, Zhou P, Ginader T, *et al*. Positive circumferential resection margins following locally advanced colon cancer surgery: risk factors and survival impact. *J Surg Oncol* 2020;121:538–46.
- 16 Therasse P, Arbuck SG, Eisenhauer EA, *et al*. New guidelines to evaluate the response to treatment in solid tumors. *JNCI* 2000;92:205–16.
- 17 Jakobsen A, Andersen F, Fischer A, *et al*. Neoadjuvant chemotherapy in locally advanced colon cancer. A phase II trial. *Acta Oncol* 2015;54:1747–53.
- 18 Montagnani F, Chiriatti A, Turrisi G, *et al*. A systematic review of FOLFOXIRI chemotherapy for the first-line treatment of metastatic colorectal cancer: improved efficacy at the cost of increased toxicity. *Colorectal Dis* 2011;13:846–52.