

# Multicenter, Randomized, Phase III Trial of Neoadjuvant Chemoradiation With Capecitabine and Irinotecan Guided by *UGT1A1* Status in Patients With Locally Advanced Rectal Cancer

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## abstract

**PURPOSE** Differentiating the irinotecan dose on the basis of the uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) genotype improves the pathologic complete response (pCR) rate. In this study, we further investigated preoperative irinotecan combined with capecitabine-based chemoradiotherapy for locally advanced rectal cancer.

**PATIENTS AND METHODS** We conducted this randomized, open-label, multicenter, phase III trial in China. Eligible patients with clinical T3-4 and/or N+ rectal adenocarcinoma, *UGT1A1* genotype \*1\*1 or \*1\*28 were randomly allocated to the control group: pelvic radiation of 50 Gy/25 fractions with concurrent capecitabine, followed by oxaliplatin and capecitabine; or the experimental group: radiation with capecitabine combined with weekly irinotecan 80 mg/m<sup>2</sup> for patients with *UGT1A1*\*1\*1 or 65 mg/m<sup>2</sup> for patients with *UGT1A1*\*1\*28, followed by irinotecan and capecitabine. The primary end point was pCR. This trial was registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02605265).

**RESULTS** Of the 360 patients initially enrolled, 356 were evaluated as the modified intention-to-treat population (n = 178 in both groups). Surgery was performed in 87% and 88% of patients in the control and experimental groups, respectively. The pCR rates were 15% (n = 27 of 178) and 30% (n = 53 of 178) in the control and experimental groups (risk ratio, 1.96; 95% CI, 1.30 to 2.97; *P* = .001). Four and 6 patients achieved complete clinical response in the control and experimental groups, respectively. Grade 3-4 toxicities were recorded in 11 (6%) and 68 (38%) patients in the control and experimental groups, respectively (*P* < .001). The commonest grade 3-4 toxicities were leukopenia, neutropenia, and diarrhea. The overall surgical complication rate was not significantly different between the two groups (11% v 15%; *P* < .001).

**CONCLUSION** Adding irinotecan guided by *UGT1A1* genotype to capecitabine-based neoadjuvant chemoradiotherapy significantly increased complete tumor response in Chinese patients.

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## ASSOCIATED CONTENT

### Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

Preoperative chemoradiotherapy (CRT) followed by surgery is the standard treatment of locally advanced rectal cancer.<sup>1,2</sup> However, the pathologic complete response (pCR) rate is only 10% to 15%, and the distant metastasis rate is > 30%. Adding a second drug during neoadjuvant treatment may yield a better tumor response and reduce the risk of metastasis.<sup>3</sup> Oxaliplatin showed a good clinical outcome in early exploratory studies. However, phase III trials did not confirm that addition of oxaliplatin to neoadjuvant CRT improved the pCR rate or long-term survival; instead, it caused more treatment-related adverse events.<sup>4-8</sup>

Therefore, whether adding a second drug to neoadjuvant CRT can improve the clinical outcome remains controversial.

The efficacy of irinotecan as combination neoadjuvant CRT has been investigated in studies with small sample sizes.<sup>9-13</sup> However, there is concern about its poor tolerability in Western populations and especially its propensity to cause neutropenia and diarrhea. The maximum tolerated dose (MTD) of irinotecan has been determined to be only 40-60 mg/m<sup>2</sup> per week when used concurrently with 5-fluorouracil-based CRT.<sup>14,15</sup> In the RTOG 0247 study, which explored irinotecan and oxaliplatin in combination with capecitabine-based

## CONTEXT

### Key Objective

Irinotecan has been investigated for its efficacy when combined with neoadjuvant chemoradiotherapy (CRT), but there has been concern about its poor tolerability. The *UGT1A1* genotype has become the key determinant of irinotecan dosing. In this trial, we assessed the benefit of adding irinotecan to the treatment of patients undergoing neoadjuvant chemoradiotherapy. To our knowledge, this is the first phase III trial to use *UGT1A1* genotype to guide irinotecan dose when used in combination with capecitabine-based neoadjuvant CRT.

### Knowledge Generated

The results showed that additional irinotecan guided by *UGT1A1* genotype can increase the pCR rate from 15% to 30% compared with capecitabine-based neoadjuvant chemoradiotherapy. More toxicities were induced by irinotecan, particularly leukopenia, neutropenia, and diarrhea.

### Relevance

Under the guidance of *UGT1A1* genotype, an increased dose of irinotecan added to standard CRT might become an improved strategy to achieve a better tumor regression in patients with locally advanced rectal cancer.

neoadjuvant CRT, the doses of irinotecan and capecitabine needed to be reduced significantly, which might explain the worse pCR rate with irinotecan (10% in the irinotecan group v 21% in the oxaliplatin group) reported in that study.<sup>16</sup> However, the irinotecan group demonstrated higher overall and disease-free survival rates than did the oxaliplatin group.<sup>17</sup>

More recently, uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) activity has become the key determinant of whether the irinotecan dose can be increased.<sup>18-20</sup> Irinotecan is converted to SN-38, which is subsequently inactivated by *UGT1A1* and excreted via the bile.<sup>21</sup> There is an important association between the *UGT1A1* genotype and the SN-38 inactivation rate, which influences the likelihood of toxicity. Several dose-escalation studies have found that the MTD of irinotecan decreased with an increasing number of defective *UGT1A1* alleles,<sup>22-25</sup> confirming that the irinotecan dose can be guided by the *UGT1A1* genotype.

We hypothesized that the irinotecan dose administered to patients undergoing neoadjuvant CRT could be guided by the *UGT1A1* genotype. In our previous dose-escalation and expansion studies, 80 mg/m<sup>2</sup> and 65 mg/m<sup>2</sup> were identified as the weekly MTDs of irinotecan for patients with the *UGT1A1*\*1\*1 and \*1\*28 genotypes, respectively, when administered in combination with capecitabine-based CRT.<sup>26</sup> The aim of the current study was to assess the benefit of adding irinotecan to treatment of patients undergoing neoadjuvant CRT.

## PATIENTS AND METHODS

### Study Design and Participants

In this multicenter, randomized, prospective, open-label phase III clinical trial, we compared the therapeutic benefit of capecitabine-based neoadjuvant CRT with that of

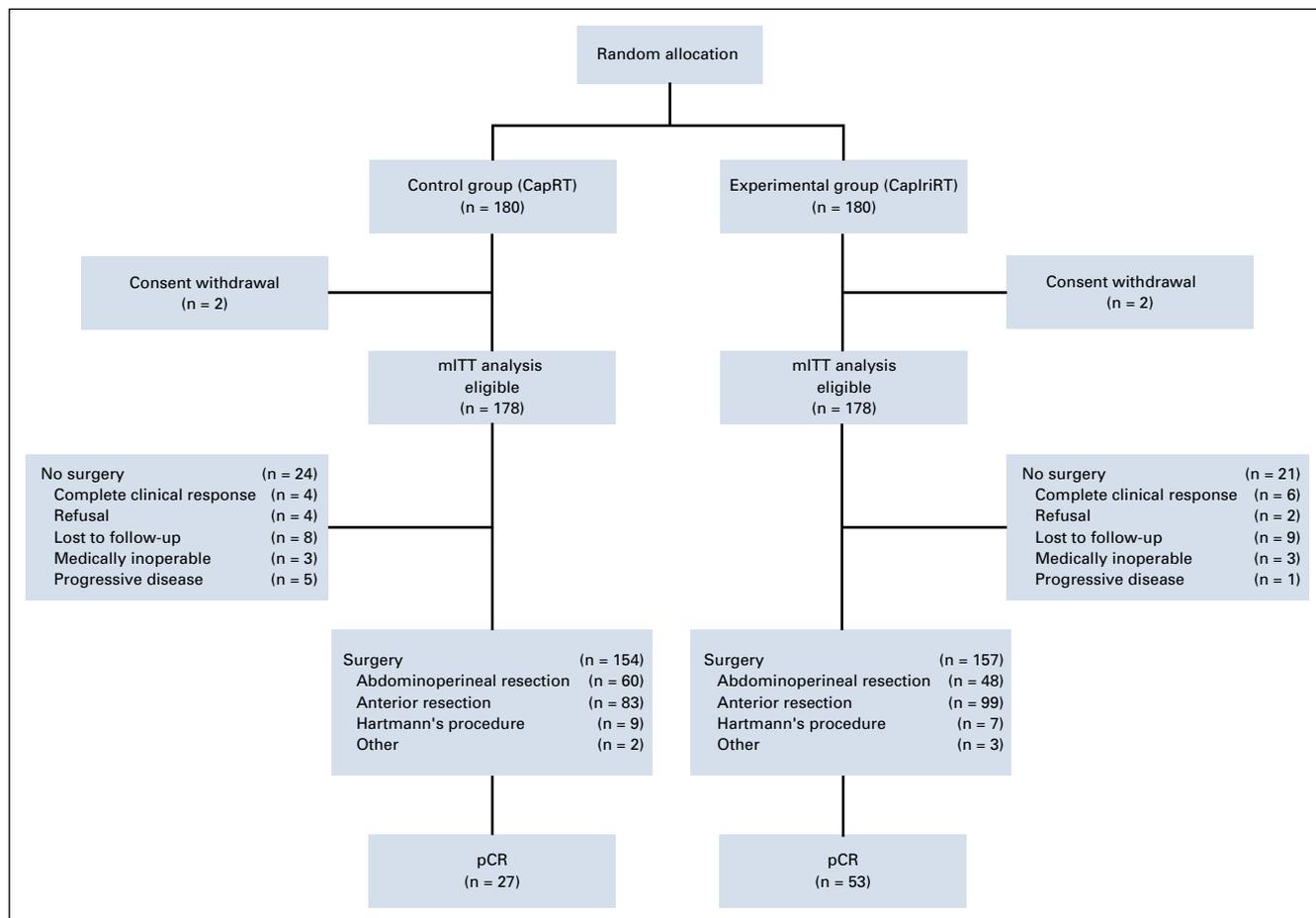
irinotecan plus capecitabine-based CRT in patients with locally advanced rectal cancer who were treated at 17 radiation oncology centers in China. The study protocol was approved by the central ethics committee of Fudan University Shanghai Cancer Center (Shanghai, China) and the institutional review boards of all participating institutions. All patients provided written informed consent before participation.

Patients were eligible if they were aged 18-75 years and had histopathologically confirmed rectal adenocarcinoma located  $\leq$  10 cm above the anal verge and clinical stage T3-4 and/or N+ disease on pelvic magnetic resonance images. Conventional chest and abdominal computed tomography (CT) scans were used to confirm the absence of distant metastases. Other inclusion criteria were a Karnofsky performance status score  $\geq$  70, a *UGT1A1* genotype of \*1\*1 or \*1\*28, and adequate bone marrow function (defined as a hemoglobin level  $\geq$  9 g/dL, neutrophil count  $\geq$  1,500/ $\mu$ L, and platelet count  $\geq$  100,000/ $\mu$ L), liver function (total bilirubin level  $<$  1.5 times the upper limit of normal; albumin level  $>$  30 g/L; and aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels  $<$  2.5 times the upper limit of normal), and kidney function (creatinine concentration below the upper limit of normal).

The exclusion criteria were a history of malignancy, with the exception of adequately treated basal cell carcinoma of the skin or cervical carcinoma in situ; previous chemotherapy or pelvic radiotherapy; pregnancy or lactation; known dihydropyrimidine dehydrogenase deficiency; or a serious illness, such as unstable angina or myocardial infarction, within the previous 12 months.

### *UGT1A1* Genotyping

All patients underwent *UGT1A1* genotyping. Before treatment, 2 mL of venous blood was collected, and blood



**FIG 1.** CONSORT diagram. CapRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine; CapIriRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine and irinotecan; mITT, modified intention-to-treat; pCR, pathologic complete response.

samples were collected using DNA extraction kits (QIAamp DNA Blood Midi Kit; QIAGEN, Venlo, the Netherlands). Polymerase chain reaction assay was performed in a 25- $\mu$ L reaction with 2.5  $\mu$ L of 15 mM Mg<sup>2+</sup>, 2  $\mu$ L of 2.5 mM deoxyribonucleotide triphosphates, 5 U Taq, and 30 ng of DNA. The following primers were used: forward, 5'-TCC CTGCTACCTTGTGGAC-3' and reverse, 5'-AGCAGGCC AGGACAAGT-3'. The reaction was run for 40 cycles at 94°C for 15 seconds, 60°C for 25 seconds, and 72°C for 30 seconds. Genotypes were assigned on the basis of the number of thymine-adenine repeats in each allele.

**Randomization and Masking**

Eligible patients were randomly allocated to receive radiotherapy with concurrent capecitabine (CapRT) or concurrent capecitabine and irinotecan (CapIriRT). The patients were assigned centrally through a web interface (varied permuted block design with a block size 2-6) hosted by the Fudan University Biostatistics Central Office (Shanghai, China). The patients were stratified by clinical T stage (cT3 v cT4), tumor distance from the anal verge ( $\leq$  5 cm v  $>$  5 cm), and UGT1A1 genotype (\*1\*1 v \*1\*28).

**Treatment Procedure**

The control group (CapRT) received pelvic radiation at a dose of 50 Gy/25 fractions, delivered with a 6-10-MV photon beam via intensity-modulated radiation therapy with concurrent capecitabine 825 mg/m<sup>2</sup> twice daily 5 d/wk, followed by a cycle of capecitabine plus oxaliplatin (XELOX) 2 weeks after the end of CRT (oxaliplatin 130 mg/m<sup>2</sup> on day 1 and capecitabine 1,000 mg/m<sup>2</sup> twice daily on days 1-14). The experimental group (CapIriRT) received pelvic radiation at a dose of 50 Gy/25 fractions with capecitabine 625 mg/m<sup>2</sup> twice daily 5 d/wk and weekly irinotecan, followed by a cycle of capecitabine plus irinotecan (XELIRI) 2 weeks after completion of CRT (irinotecan 200 mg/m<sup>2</sup> on day 1 and capecitabine 1,000 mg/m<sup>2</sup> twice daily on days 1-14). Irinotecan was administered at a weekly dose of 80 mg/m<sup>2</sup> among patients with the UGT1A1\*1\*1 genotype and 65 mg/m<sup>2</sup> among those with the UGT1A1\*1\*28 genotype. Details of the irradiation techniques and treatment volumes are provided in the Data Supplement.

Surgery was scheduled for 8 weeks after completion of CRT. Total mesorectal excision was mandatory, whereas

**TABLE 1.** Baseline Patient Characteristics

| Characteristic               | CapRT Group<br>(n = 178) | CaplriRT Group<br>(n = 178) |
|------------------------------|--------------------------|-----------------------------|
| Age, years                   |                          |                             |
| Mean (SD)                    | 56 (10)                  | 54 (10)                     |
| Median (range)               | 59 (28-75)               | 54 (24-74)                  |
| Sex                          |                          |                             |
| Male                         | 125 (70)                 | 131 (74)                    |
| Female                       | 53 (30)                  | 47 (26)                     |
| ECOG performance status      |                          |                             |
| 0                            | 157 (88)                 | 156 (88)                    |
| 1                            | 21 (12)                  | 22 (12)                     |
| BMI, kg/m <sup>2</sup>       |                          |                             |
| < 18.5                       | 12 (7)                   | 9 (5)                       |
| 18.5-25.0                    | 115 (65)                 | 123 (69)                    |
| ≥ 25                         | 47 (26)                  | 42 (24)                     |
| Unknown or missing           | 4 (2)                    | 4 (2)                       |
| Clinical T category          |                          |                             |
| cT1-2                        | 6 (3)                    | 5 (3)                       |
| cT3                          | 141 (79)                 | 144 (81)                    |
| cT4                          | 31 (17)                  | 29 (16)                     |
| Clinical N category          |                          |                             |
| cN0                          | 8 (4)                    | 13 (7)                      |
| cN+                          | 170 (96)                 | 165 (93)                    |
| Distance from anal verge, cm |                          |                             |
| ≤ 5                          | 104 (58)                 | 106 (60)                    |
| > 5                          | 74 (42)                  | 72 (40)                     |
| <i>UGT1A1</i> genotype       |                          |                             |
| *1*1                         | 133 (75)                 | 133 (75)                    |
| *1*28                        | 45 (25)                  | 45 (25)                     |
| Baseline CEA level           |                          |                             |
| Normal                       | 99 (56)                  | 105 (59)                    |
| Abnormal                     | 79 (44)                  | 72 (40)                     |
| Unknown or missing           | 0 (0)                    | 1 (1)                       |

NOTE. Data are reported as No. (%) unless otherwise stated.

Abbreviations: BMI, body mass index; CapRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine; CaplriRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine and irinotecan; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; *UGT1A1*, uridine diphosphate glucuronosyltransferase 1A1.

the surgical approach (anterior resection or abdominal-perineal resection [APR]) and whether a temporary colostomy was used were at the discretion of the surgeon. Other types of surgery (Hartmann's procedure, intersphincteric resection, and transanal local excision) were permissible at the surgeon's discretion. Five cycles of

adjuvant XELOX chemotherapy were administered regardless of the pathologic result.

### Pathology Procedures

Resected specimens were processed and examined as previously described.<sup>27</sup> Pathologists were blinded to each patient's treatment plan and evaluated surgical specimens independently. The extent of residual tumor was classified according to the eighth edition of the International Union Against Cancer's TNM staging system. All resected lymph nodes were examined according to standard procedures. If there were < 12 lymph nodes, two pathologists performed the examination to ensure reliable results. pCR was defined as an absence of tumor cells in the surgical specimens from the primary tumor and the regional lymph nodes (ypTON0). Tumor regression grade was evaluated according to the criteria devised by Edge et al.<sup>28</sup>

### Data Management and Statistical Analysis

This study was primarily designed to detect an increase in the pCR rate from 12% in the CapRT group to 25% in the CaplriRT group, and the pCR rate in the intention-to-treat (ITT) population was the primary end point. According to our calculation, 360 eligible patients would need to be recruited to detect this difference with an  $\alpha$  of 0.05 (two-tailed) and a  $\beta$  of 0.15. However, some patients refused to undergo surgery because they obtained a complete response to neoadjuvant therapy; therefore, two sensitivity analyses were planned to confirm stable results, including the pCR rate in the surgical population and the overall CR rate (pCR plus clinical complete response [cCR]) in the ITT population.

For patients who had a good tumor response and refused APR, a watch-and-wait policy was adopted. These patients received six cycles of consolidation chemotherapy and were monitored closely with digital examination and endoscopy every 1-2 months and chest and abdominal CT and pelvic magnetic resonance imaging (MRI) every 3 months. The cCR was defined as the absence of palpable tumor on digital examination, the absence of residual tumor on pelvic MRI or endoscopy, and a sustained absence of residual tumor for at least 12 months after CRT.

The secondary end points included toxicities, quality of life, tumor regression grade, sphincter preservation, surgical complications, local control, disease-free survival (DFS), and overall survival (OS). Preoperative acute toxicity and surgical complications were recorded according to the National Cancer Institute Common Toxicity Criteria, version 4.0. Survival time was calculated from the date of randomization to the date of event or the last follow-up. Events were defined as local failure for local control, tumor recurrence or death from any cause for DFS, and death from any cause for OS. Categorical variables are presented as frequencies and continuous variables as means and standard deviations if normally distributed or medians if not normally distributed. Categorical variables were compared

**TABLE 2.** Treatment Compliance Among Patients Who Received Preoperative Chemoradiotherapy

| Treatment Compliance  | CapRT Group<br>(n = 178) | CaplriRT Group<br>(n = 178) |
|---|--------------------------|-----------------------------|
| Radiotherapy  |                          |                             |
| Full dose (≥ 50 Gy)   | 176 (99)                 | 171 (96)                    |
| ≥ 90% of planned  | 178 (100)                | 175 (98)                    |
| ≥ 80% of planned  | 178 (100)                | 176 (99)                    |
| Capecitabine during radiotherapy                              |                          |                             |
| Full dose (≥ 25 days)   | 176 (99)                 | 171 (96)                    |
| ≥ 90% of planned  | 178 (100)                | 175 (98)                    |
| ≥ 80% of planned  | 178 (100)                | 176 (99)                    |
| No. of irinotecan cycles during radiotherapy (weekly courses) |                          |                             |
| 5   | NA                       | 60 (34)                     |
| ≥ 4   | NA                       | 125 (70)                    |
| ≥ 3   | NA                       | 158 (89)                    |
| Consolidation chemotherapy                                    |                          |                             |
| None  | 6 (3)                    | 7 (4)                       |
| Capecitabine alone  | 2 (1)                    | 7 (4)                       |
| XELOX   | 170 (96)                 | NA                          |
| XELIRI  | NA                       | 164 (92)                    |

NOTE. Data are reported as No. (%) unless otherwise stated.

Abbreviations: CapRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine; CaplriRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine and irinotecan; NA, not applicable; XELIRI, capecitabine plus irinotecan; XELOX, capecitabine plus oxaliplatin.

between the two groups using the  $\chi^2$  test or Fisher exact test with the log-rank test for survival data. Analysis items for which  $P < .05$  were considered statistically significant.

**RESULTS**

From November 2015 to December 2017, 360 patients were recruited at 17 centers in China; nine patients with a \*28\*28 genotype were excluded. After randomization, we excluded four patients who withdrew consent to participate before receiving any treatment. As a post hoc decision, the remaining 356 patients constituted the modified ITT (mITT) population, replacing the ITT population for additional analysis. We allocated 178 patients to each treatment group (Fig 1). The patients' baseline demographic and clinical characteristics were well balanced (Table 1).

All patients (100%) in the CapRT group received ≥ 90% of the full dose of radiotherapy and capecitabine. In the CaplriRT group, 175 patients (98%) received ≥ 90% of the full dose of radiotherapy and capecitabine, and 125 (70%) received at least four cycles of weekly irinotecan (Table 2).

After neoadjuvant CRT completion, six patients (3%) in the CapRT group and seven (4%) in the CaplriRT group did not receive any consolidation chemotherapy. In total, 170 patients (96%) in the CapRT group received XELOX and 164 (92%) in the CaplriRT group received XELIRI. Another two patients (1%) in the CapRT group and seven (4%) in the CaplriRT group received one cycle of capecitabine alone between the end of CRT and surgery (Table 2).

Grade 3-4 toxic effects were recorded among 11 patients (6%) in the CapRT group and 68 (38%) in the CaplriRT group ( $P < .001$ ; Table 3). The most common grade 3-4 toxicities during CRT in the CapRT group versus the CaplriRT group, respectively, were leukopenia (3% v 25%), neutropenia (2% v 20%), and diarrhea (2% v 13%).

A total of 154 patients (87%) in the CapRT group and 157 (88%) in the CaplriRT group underwent surgery. The median intervals between the end of CRT and surgery were 61 days (range, 45-104 days) in the CapRT group and 62 days (range, 44-156 days) in the CaplriRT group. Sixty patients (39%) in the CapRT group and 48 (31%) in the CaplriRT group underwent APR ( $P = .120$ ; Table 4). The two groups had similar proportions of patients with post-operative complications of grade 3 or worse (11% v 15%;  $P = .268$ ). No patient died within 60 days of surgery.

Complete resection was achieved in 148 patients (96%) in the CapRT group and 153 (97%) in the CaplriRT group, with circumferential resection margins of ≤ 1 mm in seven

**TABLE 3.** CRT-Related Toxic Reactions Among Patients Who Received Preoperative Chemoradiotherapy

| Grade 3-4 Adverse Event        | CapRT group<br>(n = 178) | CaplriRT group<br>(n = 178) |
|--------------------------------|--------------------------|-----------------------------|
| Toxicity (NCI-CTC version 4.0) | 11 (6)                   | 68 (38)                     |
| Hematologic                    |                          |                             |
| Leukopenia                     | 8 (4)                    | 55 (31)                     |
| Neutropenia                    | 6 (3)                    | 45 (25)                     |
| Anemia                         | 3 (2)                    | 35 (20)                     |
| Thrombocytopenia               | 1 (1)                    | 4 (2)                       |
| Febrile neutropenia            | 0 (0)                    | 3 (2)                       |
| GI                             |                          |                             |
| Diarrhea                       | 1 (1)                    | 5 (3)                       |
| Nausea                         | 4 (2)                    | 32 (18)                     |
| Vomiting                       | 3 (2)                    | 24 (13)                     |
| Proctitis                      | 0 (0)                    | 4 (2)                       |
| Radiation dermatitis           | 0 (0)                    | 1 (1)                       |
| Anorexia                       | 1 (1)                    | 9 (5)                       |
|                                | 2 (1)                    | 2 (1)                       |
|                                | 0 (0)                    | 6 (3)                       |

NOTE. Data are reported as No. (%) unless otherwise stated.

Abbreviations: CapRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine; CaplriRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine and irinotecan; CTC, Common Terminology Criteria; NCI, National Cancer Institute.

**TABLE 4.** Surgical Procedures and Surgical Complications Among Patients Who Underwent Surgery

| Characteristic                                | CapRT Group<br>(n = 154) | CapIriRT Group<br>(n = 157) |
|---|--------------------------|-----------------------------|
| Type of surgery                               |                          |                             |
| Abdominoperineal resection                    | 60 (39)                  | 48 (31)                     |
| Anterior resection                            | 83 (54)                  | 99 (63)                     |
| Hartmann procedure                            | 9 (6)                    | 7 (4)                       |
| Local excision                                | 2 (1)                    | 3 (2)                       |
| Overall surgical complications,<br>grades 3–4 | 17 (11)                  | 24 (15)                     |
| Wound infection                               | 5 (3)                    | 8 (5)                       |
| Anastomotic stenosis                          | 1 (1)                    | 2 (1)                       |
| Anastomotic leakage                           | 4 (3)                    | 8 (5)                       |
| Delayed wound healing                         | 4 (3)                    | 3 (2)                       |
| Ileus/obstruction                             | 3 (2)                    | 2 (1)                       |

NOTE. Data are reported as No. (%) unless otherwise stated.

Abbreviations: CapRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine; CapIriRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine and irinotecan.

(5%) and three (2%) patients, respectively (Table 5). pCR was achieved in 27 patients (18%) in the CapRT group and 53 (34%) in the CapIriRT group (risk ratio, 1.93; 95% confidence interval [CI], 1.28 to 2.89;  $P = .001$ ) in the surgical population. Negative nodes were reported in 112 patients (73%) in the CapRT group and 116 (74%) in the CapIriRT group (Table 5). The pCR rates in the mITT population were 15% ( $n = 27$  of 178) in the CapRT group and 30% ( $n = 53$  of 178) in the CapIriRT group (risk ratio, 1.96; 95% CI, 1.30 to 2.97;  $P = .001$ ).

In the CapRT group, four patients opted to undergo a watch-and-wait approach after achieving cCR, and 20 did not proceed to surgery for various reasons, including refusal, loss to follow-up, being medically inoperable, and progressive disease; the respective numbers in the CapIriRT group were 6 and 15. The two sensitivity analyses showed similar results for the primary end point (Data Supplement).

## DISCUSSION

To our knowledge, this is the first phase III trial to evaluate the use of the *UGT1A1* genotype to guide the irinotecan dose when used in combination with capecitabine-based neoadjuvant CRT in patients with rectal cancer. The primary end point was reached in that the pCR rate increased from 15% in the CapRT group to 30% in the CapIriRT group. However, the addition of irinotecan was also associated with a significant increase in the frequency of grade 3–4 toxicities (38%), particularly leukopenia (25%), neutropenia (20%), and diarrhea (13%), although rates of sphincter preservation and surgical complications

remained similar. The local control, DFS, and OS data reflecting the long-term prognosis are not yet mature; we plan to report survival outcomes separately in approximately 3 years.

Irinotecan inhibits topoisomerase I and is an effective chemotherapeutic agent for colorectal cancer. Preclinical studies have shown that radiation kills tumor cells in the G2 phase through M phase but spares cells in the S phase, which are targeted by irinotecan.<sup>29</sup> Therefore, irinotecan should have a favorable synergistic effect when used in combination with radiotherapy. However, the addition of irinotecan to neoadjuvant CRT did not achieve good tumor regression in previous phase I/II trials (Data Supplement), likely owing to inadequate doses. Klautke et al<sup>30</sup> reported that pCR was achieved in 16%–35% of patients who received a total irinotecan dose of 240 mg/m<sup>2</sup> but not in patients who received a total dose of 200 mg/m<sup>2</sup>. Therefore, we hypothesized that irinotecan could be an ideal radiosensitizer only at a sufficient dose. However, because of serious irinotecan-induced toxicities, it has been difficult to verify this hypothesis in clinical trials.

Understanding the relationship between the *UGT1A1* genotype and irinotecan toxicities has renewed interest in therapeutic approaches to rectal cancer. Several trials have reported significant differences in the MTD of irinotecan in patients with *UGT1A1* variants.<sup>20–25,31</sup> Unfortunately, few studies with large sample sizes have been conducted, possibly because of concerns of toxicity. However, the prevalence of *UGT1A1* variants differs between White and Asian populations. The \*1\*1 and \*1\*28 genotypes are observed in 46% and 39% of White patients, respectively,<sup>20</sup> and 80% and 16% of Asian patients, respectively.<sup>32</sup> Therefore, the irinotecan dose recommended for White patients may be unsuitable for Asian patients. We conducted a pilot study of *UGT1A1*-guided irinotecan dosing for neoadjuvant CRT. The MTD of irinotecan went up to 80 mg/m<sup>2</sup> per week in patients with the \*1\*1 genotype and 65 mg/m<sup>2</sup> per week in patients with the \*1\*28 genotype. These doses were significantly higher than those in previous studies and may have contributed to the increased pCR rates.<sup>26,33</sup> On the basis of those results, we conducted the present phase III trial to assess whether an increased dose of concurrent irinotecan would be beneficial.

Conventionally, radical surgery is scheduled 6–10 weeks after the end of long-course CRT, without any consolidation therapy during the interval between CRT and surgery. Some studies showed that adding consolidation chemotherapy between the end of CRT and surgery could improve clinical outcomes.<sup>34</sup> However, it is unclear how many cycles of consolidation chemotherapy are optimal. We decided to add one cycle of consolidation chemotherapy without delaying surgery. This strategy has demonstrated efficiency and safety in previous trials.<sup>35,36</sup> We administered one cycle of XELOX in the control group and one cycle of XELIRI in the experimental group to maintain consistency with the drug

**TABLE 5.** Pathologic Characteristics of Patients Who Underwent Surgery

| Characteristic                           | CapRT Group<br>(n = 154) | CapIriRT Group<br>(n = 157) |
|--|--------------------------|-----------------------------|
| Completeness of local tumor resection    |                          |                             |
| R0                                       | 148 (96)                 | 153 (97)                    |
| R1                                       | 1 (1)                    | 1 (1)                       |
| R2                                       | 3 (2)                    | 0 (0)                       |
| Not applicable because of local excision | 2 (1)                    | 3 (2)                       |
| Circumferential resection margin, mm     |                          |                             |
| > 1                                      | 120 (78)                 | 101 (64)                    |
| ≤ 1                                      | 7 (5)                    | 3 (2)                       |
| Not applicable per pCR finding           | 27 (18)                  | 53 (34)                     |
| Pathologic T category                    |                          |                             |
| ypT0                                     | 30 (19)                  | 58 (37)                     |
| ypT1                                     | 8 (5)                    | 4 (3)                       |
| ypT2                                     | 30 (19)                  | 30 (19)                     |
| ypT3                                     | 69 (45)                  | 56 (36)                     |
| ypT4                                     | 17 (11)                  | 9 (6)                       |
| Pathologic N category                    |                          |                             |
| ypN0                                     | 112 (73)                 | 116 (74)                    |
| ypN1                                     | 29 (19)                  | 33 (21)                     |
| ypN2                                     | 13 (8)                   | 8 (5)                       |
| Pathologic stage                         |                          |                             |
| 0  | 27 (18)                  | 53 (34)                     |
| I  | 34 (22)                  | 27 (17)                     |
| IIA                                      | 45 (29)                  | 31 (20)                     |
| IIB                                      | 5 (3)                    | 5 (3)                       |
| IIC                                      | 1 (1)                    | 0 (0)                       |
| IIIA                                     | 7 (5)                    | 11 (7)                      |
| IIIB                                     | 30 (19)                  | 28 (18)                     |
| IIIC                                     | 5 (3)                    | 2 (1)                       |
| Tumor regression grade                   |                          |                             |
| 0  | 30 (19)                  | 57 (36)                     |
| 1  | 27 (18)                  | 20 (13)                     |
| 2  | 58 (38)                  | 65 (41)                     |
| 3  | 39 (25)                  | 15 (10)                     |

NOTE. Data are reported as No. (%) unless otherwise stated.

Abbreviations: CapRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine; CapIriRT, radiotherapy at a dose of 50 Gy with concurrent capecitabine and irinotecan; pCR, pathologic complete response.

used in concurrent CRT. Although XELIRI might be challenged for its tolerance, its good efficacy and acceptable toxicity profiles in Eastern Asian populations have been proven.<sup>37</sup>

This phase III trial evaluating irinotecan in neoadjuvant CRT for patients with rectal cancer under the guidance of the *UGT1A1* genotype has some limitations. First, only the *UGT1A1*\*28 allele was used to guide the irinotecan dose. Other biomarkers, such as the *UGT1A1*\*6 allele, that have also shown a correlation with irinotecan-induced toxicities were not considered. Particularly, the *UGT1A1*\*6 allele shows a compensation for the reduced frequency of the *UGT1A1*\*28 allele in Asians.<sup>38</sup> Combining the *UGT1A1*\*28 and *UGT1A1*\*6 alleles in our studies and clinical practice warrants more attention. Second, our surgical resection rate of approximately 87% was lower than that in previous phase III trials for oxaliplatin, mainly because some patients with a lower tumor burden refused APR regardless of whether cCR was achieved. During at least 12 months of follow-up, 10 patients were deemed to have achieved cCR. Third, patients in the experimental group were exposed to oxaliplatin, irinotecan, and fluorouracil during the perioperative period. This might complicate treatment options in the event of disease recurrence. However, the RTOG0247 study found a long-term survival benefit from early exposure to three chemotherapy agents.<sup>17</sup> If our trial demonstrates a longer OS, it is worth re-evaluating the sequence of these three drugs for locally advanced rectal cancer.

The ongoing phase III ARISTOTLE trial being conducted in the United Kingdom was also designed to determine the benefit of irinotecan in neoadjuvant CRT. The main difference between ARISTOTLE and our trial is that patients in ARISTOTLE receive a fixed irinotecan dose of 60 mg/m<sup>2</sup> per week for four cycles without *UGT1A1* genotype-based guidance. At the 2020 ASCO annual meeting, it was reported that patients in the irinotecan group of ARISTOTLE did not reach a higher pCR rate. We believe the main reason for this was that the irinotecan dose was insufficient. However, as mentioned, there are differences in the genotype prevalence and irinotecan tolerance between White and Asian populations. We need to fully consider such differences when assessing the generalizability of our results.

In conclusion, under the guidance of the *UGT1A1* genotype, an increased irinotecan dose in combination with CRT significantly improved the clinical response rate with acceptable toxicities in Chinese patients with locally advanced rectal cancer.

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Ji Zhu, Anwen Liu, Xinchun Sun, and Luying Liu contributed equally to this work. Sanjun Cai and Zhen Zhang contributed equally to this work.

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## CLINICAL TRIAL INFORMATION

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## DATA SHARING STATEMENT

Individual participant data and a data dictionary defining each field will be available after publication of long-term results, in compliance with relevant national laws and regulations, via leoon.zhu@gmail.com.

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#### **AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

##### **Multicenter, Randomized Phase III Trial of Neoadjuvant Chemoradiation With Capecitabine and Irinotecan Guided by *UGT1A1* Status in Patients With Locally Advanced Rectal Cancer**

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