



CONSENSUS

# The “Chinese Expert Consensus on the Clinical Application of the Chinese Modified Triplet Combination with Irinotecan (CPT-11), Oxaliplatin (LOHP), Continuous Infusion 5-Fluorouracil, and Leucovorin for Colorectal Cancer”

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## Abstract

Colorectal cancer is the second most common malignant tumor in China. The FOLFOXIRI regimen, which combines 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan, is a high-intensity and highly effective chemotherapy regimen. However, the original regimen is poorly tolerated in Chinese patients. In order to promote the standardization and rational application of FOLFOXIRI regimen by clinicians in China, the “Chinese Expert Consensus on the Clinical Application of the Chinese Modified Triplet Combination with Irinotecan (CPT-11), Oxaliplatin (LOHP), Continuous Infusion 5-Fluorouracil, and Leucovorin for Colorectal Cancer” was formulated by the Committee of Colorectal Cancer in Chinese Southwest Oncology Group. Based on the mechanism underlying the combined three drugs and toxicity profile, the dosage of Chinese modified FOLFOXIRI (cmFOLFOXIRI) regimen and the management of adverse reactions are proposed. This consensus recommended that the FOLFOXIRI regimen be used in neoadjuvant, conversion, and palliative therapy for colorectal cancer under specific conditions. This consensus aimed to drive the application of cmFOLFOXIRI in the field of colorectal cancer in order to bring benefits to colorectal cancer patients.

**Key words:** colorectal cancer; FOLFOXIRI; China; expert consensus

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## Background

The incidence of colorectal cancer is increasing every year and has become the second most common malignant tumor in China, with >380,000 new cases/year [1]. Among them, ~60% of patients have distant metastasis at first diagnosis or during the course of the disease and require chemotherapy. Although target therapy has made some progress and immunotherapy is undoubtedly the first-line choice in colorectal cancer patients with microsatellite instability-high/mismatch repair deficiency (MSI-H/dMMR), cytotoxic chemotherapy is the primary line of treatment, especially in the colorectal cancer population with microsatellite stability/mismatch repair proficiency (MSS/pMMR) [2]. Currently, only three types of cytotoxic drugs are proven effective in colorectal cancer, including fluorouracil (5-fluorouracil and capecitabine), oxaliplatin, and irinotecan. The rational design of drug combinations is yet a promising strategy to prolong survival and improve patients' quality of life.

The FOLFOXIRI regimen—a combination of 5-fluorouracil (5-FU)/calcium leucovorin, oxaliplatin, and irinotecan—is a highly effective chemotherapy regimen. A number of phase III randomized-controlled trials of advanced colorectal cancer have proven that, compared to patients receiving the traditional FOLFOX or FOLFIRI regimen, patients receiving the FOLFOXIRI regimen have a better objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Presently, the FOLFOXIRI regimen has become one of the recommended chemotherapy regimens for the treatment of advanced colorectal cancer according to the National Comprehensive Cancer Network (NCCN) guidelines, the European Society for Medical Oncology guidelines, and the Chinese Society of Clinical Oncology (CSCO) guidelines.

However, due to the high incidence of adverse reactions and poor patient tolerance of the FOLFOXIRI regimen, especially in Chinese and other Asian populations, the clinical application of the FOLFOXIRI regimen is limited. In addition, relevant clinical research data are mostly based on European and American populations; however, there is no uniform standard for drug usage and dosage. Therefore, we need to urgently make a unified understanding of how to continue to advance to determine the method of use, adverse reactions, and adjust doses. In order to guide clinicians in China to use the FOLFOXIRI regimen for the treatment of colorectal cancer, the Chinese Southwest Oncology Group organized relevant experts in this field. Based on this systematic review of domestic and foreign literature, objective analysis of relevant research data, combined with clinical experience and adapting to the characteristics of patients in China, a consensus was achieved.

## Applicable population

### FOLFOXIRI in a palliative treatment setting

#### Experts' recommendation

The Chinese modified FOLFOXIRI (cmFOLFOXIRI) combined with bevacizumab is recommended as the first-line palliative treatment for patients who meet the following criteria: unresectable locally advanced or metastatic disease, MSS/pMMR, age 18–75 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1 if age is <70 years, or ECOG performance status 0 if age is 71–75 years.

#### Treatment administration

First-line treatment is cmFOLFOXIRI plus bevacizumab and the efficacy is evaluated every four cycles; patients without disease progression after eight cycles enter maintenance therapy (5-FU/LV or capecitabine + bevacizumab). Subsequently, patients who develop disease progression during maintenance treatment enter reinduction or second-line therapy. If the oxaliplatin-related peripheral neurotoxicity is lower than grade 2, cmFOLFOXIRI plus bevacizumab can be recommended as the second-line treatment.

#### Illustration

Among the patients with colorectal cancer in China, the proportion of metastatic disease is ~30%–40% and the 5-year survival rate of metastatic colorectal cancer patients is only 12%. Falcone *et al.*<sup>3</sup> carried out a series of prospective clinical trials exploring the efficacy of FOLFOXIRI in advanced colorectal cancer and published the phase I/II study in 2002, which confirmed the efficacy and safety of FOLFOXIRI in advanced colorectal cancer for the first time. In 2007, a phase III multicenter randomized-controlled trial showed that FOLFOXIRI is the first-line treatment of metastatic colorectal cancer; FOLFOXIRI has a significantly higher response rate (RR) than FOLFIRI plus bevacizumab (RR, 60% vs 34%,  $P < 0.0001$ ) [4].

After entering the era of targeted therapy, the TRIBE study confirmed that the triplet FOLFOXIRI plus bevacizumab significantly improves the outcomes of patients with metastatic colorectal cancer compared with FOLFIRI plus bevacizumab. The median PFS was 12.1 months in the experiment group vs 9.7 months in the control group ( $P = 0.003$ ) and the ORR was 65% vs 53% ( $P = 0.006$ ) [5]. This study laid the foundation for FOLFOXIRI plus bevacizumab as the first-line treatment in the palliative treatment of advanced colorectal cancer. Falcone *et al.* [6] further carried out the TRIBE-2 study, which was designed to verify whether the triplet FOLFOXIRI plus bevacizumab (experimental group) was superior to preplanned sequential chemotherapy in mFOLFOX6 and FOLFIRI (control group). The primary endpoint of the study, median PFS2 (defined as the time from randomization to disease progression, according to RECIST 1.1, on any treatment administered after first disease progression or death from any cause), was 19.2 and 16.4 months in the study and control groups, respectively ( $P < 0.001$ ). The study also showed that FOLFOXIRI induced a tumor response. During the first-line treatment, the ORR was 62% and 50% ( $P = 0.002$ ), the R0 resection rate was 17% and 12% ( $P = 0.047$ ), and the PFS was 12.0 and 9.8 months ( $P < 0.001$ ) in the study and control groups, respectively. The proportions of the two groups who continued second-line treatment were 88% and 82%, and the reintroduction rate of FOLFOXIRI in the second-line treatment of the experimental group was 69%. After the first progression, the PFS of second-line treatment in the two groups was 6.2 and 5.6 months ( $P = 0.11$ ), and no significant difference was detected in the incidence of grade 3–4 adverse events between the two groups [6]. The result of the present study further laid the foundation for bevacizumab combined with FOLFOXIRI in the first-line palliative treatment, whereas other studies compared the triplet therapy with doublet; all the relevant studies are summarized in Table 1 [4–8].

Presently, FOLFOXIRI combined with bevacizumab has been recommended by NCCN and CSCO guidelines as the standard first-line treatment for patients with advanced colorectal

**Table 1.** Summary of randomized-controlled clinical trials of FOLFOXIRI compared with FOLFIRI/FOLFOX in the first-line treatment of metastatic colorectal cancer

Author (study name, year)	Trial phase	Study population	Treatment arms	No. of patients	Median age (range), years	PS (%)	ORR (%)	PFS (months)	P-value	OS (months)	P-value
Souglakos et al. [7](HORG, 2006)	III	Age ≥18 years ECOG PS 0-2	FOLFOXIRI FOLFIRI	138 147	66 (25-82) 66 (39-84)	36% 38%	43% 34%	TTP: 8.4 TTP: 6.9	0.17	21.5 19.5	0.337
Falcone et al. [4](GONO, 2007)	III	Age 18-75 years (18-70 years) ECOG PS 0 (71-75 years)	FOLFOXIRI FOLFIRI	122 122	62 (27-75) 64 (21-75)	61% 61%	66% 41%	9.8 6.9	0.0006	22.6 16.7	0.032
Cremolini et al. [5](TRIBE, 2014)	III	Age of 18-75 years ECOG PS 0-2 (18-70 years) ECOG PS 0 (71-75 years)	FOLFOXIRI + bev FOLFIRI + bev	252 256	61 (29-75) 60 (29-75)	90% 90%	65% 53%	12.1 9.7	0.003	31.0 25.8	0.054
Hurwitz et al. [8] (STEAM, 2016)	I	Age of 18-75 years ECOG PS 0-2 (18-70 years) ECOG PS 0 (71-75 years)	FOLFOXIRI + bev	93	58 (23-75)	67%	72%	11.7	<0.01	concurrently 34.0 sequentially 28.3	Pc = 0.20 Ps = 0.49
Cremolini et al. [6] (TRIBE2, 2020)	III	Age 18-75 years ECOG PS 0-2 (18-70 years) ECOG PS 0 (71-75 years)	FOLFIRI + be FOLFOXIRI + bev	95 339	58 (34-73) 60 (53-67)	54% 86%	62% 62%	9.5 PFS1: 12.0 PFS2: 19.2	P1 = 0.0002 P2 = 0.0005	30.7 27.4	0.032
			FOLFOX + bev	340	61 (52-67)	85%	50%	PFS1: 9.8 PFS2: 16.4		22.5	

FOLFOXIRI, 5-Fluorouracil + Oxaliplatin + Irinotecan; FOLFIRI, 5-Fluorouracil + Irinotecan; FOLFOX, 5-Fluorouracil + Oxaliplatin; bev, bevacizumab; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; TTP, time to progress.

cancer. Therefore, FOLFOXIRI plus bevacizumab was recommended for patients with metastatic colorectal cancer as the first-line palliative treatment, followed by sequential maintenance and the reintroduction of FOLFOXIRI plus bevacizumab after disease progression. For metastatic left-sided colorectal cancer patients with wild-type RAS/BRAF, NCCN recommends anti-epidermal growth factor receptor (EGFR) monoclonal antibody combined with FOLFOX/FOLFIRI chemotherapy as the first-line treatment. However, clinical evidence on whether FOLFOXIRI combined with anti-EGFR can be used as a first-line palliative treatment strategy for this population of patients is insufficient.

#### Treatment recommendations for special populations

Treatment recommendations for special populations: v-raf murine sarcoma viral oncogene homolog B (BRAF) mutation was critical in patients with advanced colorectal cancer. Several studies reported that V600E is the most common mutation site in the BRAF gene [9]. About 5%–12% of patients with metastatic colorectal cancer have the BRAF V600E mutation, which indicates poor prognosis or rapid disease progression [10, 11]. In a subgroup analysis of the TRIBE study, patients with metastatic colorectal cancer with the BRAF mutation were treated with FOLFOXIRI + bevacizumab ( $n=16$ ) and FOLFIRI + bevacizumab ( $n=12$ ). The median PFS and OS of the two groups were 7.5 vs 5.5 months and 19.0 vs 10.7 months, respectively [12]. Therefore, for colorectal cancer patients with the BRAF V600E mutation, FOLFOXIRI combined with bevacizumab is more effective than other chemotherapy regimens. Concurrently, NCCN guidelines recommend FOLFOXIRI combined with bevacizumab as the first-line treatment regimen of colorectal cancer patients with the BRAF V600E mutation and ECOG PS score 0–1.

#### FOLFOXIRI in a conversion treatment setting

##### Experts' recommendation

cmFOLFOXIRI combined with bevacizumab is recommended as the conversion chemotherapy regimen for patients who meet the following criteria: metastatic colorectal cancer that is initially unresectable but has only liver and/or lung metastasis and/or locally treatable lymph node metastasis, MSS/pMMR, age 18–75 years, and ECOG performance status  $\leq 1$  if age  $<70$  years or ECOG performance status 0 if age is 71–75 years. Moreover, cmFOLFOXIRI in combination with anti-EGFR monoclonal antibody (cetuximab) is recommended as the first-choice conversion therapy for left-sided colorectal cancer patients with wild-type RAS/BRAF.

##### Treatment administration

Imaging evaluation is performed every four cycles of cmFOLFOXIRI plus targeted agents. The multidisciplinary team (MDT) discusses whether it is acceptable to receive radical/destructive local treatment, including primary tumors and metastases surgery, thermal ablation, and stereotactic radiotherapy. FOLFOX with or without targeted therapy can be recommended to patients who need to undergo radical surgery after treatment and the total duration of the perioperative chemotherapy is 6 months (for those using bevacizumab, the drug is stopped for 6 weeks before the operation and 6–8 weeks after the operation). For patients who have received  $>12$  cycles of conversion chemotherapy and still could not receive radical surgery or other local treatment, as assessed by MDT, maintenance therapy (5-FU/leucovorin or capecitabine with or without targeted therapy) is recommended.

##### Illustration

Liver metastasis occurs in ~50% of patients with colorectal cancer during the course of the disease, which is one of the leading causes of death [13]. Currently, the NCCN guidelines classify colorectal cancer liver metastases as initially resectable and unresectable, which need to be evaluated and classified based on MDT discussion. The potentially resectable liver metastasis refers to the metastatic liver lesion closely related to the critical structure of the liver. In this case, the satisfactory surgical margin could not be marked or sufficient liver volume could not be retained after the resection, which might be transformed to resectable after chemotherapy. The FOLFOXIRI regimen increased the tumor resection rate for initial unresectable metastatic colorectal cancer compared with the FOLFIRI/FOLFOX regimen (Table 2) [4–8, 14, 15]. In METHEP, 125 patients with initial unresectable or potentially resectable colorectal cancer liver metastases were included [14]. The results showed that compared with standard doublet chemotherapy, FOLFIRINOX showed a high effective rate, with a conversion rate of  $\leq 67\%$  [14]. The OLIVIA multinational, randomized phase II trial included previously untreated patients with initially unresectable liver metastases from colorectal cancer. The results showed that the overall resection rate (R0/R1/R2) of bevacizumab plus FOLFOXIRI was significantly higher than that of bevacizumab plus mFOLFOX6 (61% and 49%, respectively). The R0 resection rates were 49% and 23%, the ORR was 81% and 62%, and the median PFS was 18.6 and 11.5 months, respectively. Although the toxicity of the experimental group is higher than that of the control group, it can be controlled [15].

In POCHER, the study showed that cetuximab combined with FOLFOXIRI administered as conversion chemotherapy can achieve 60% of the R0 resection rate in patients with initially unresectable liver metastases from wild-type RAS/BRAF colorectal cancer [16]. The FOCULM is a two-group, multicenter, phase II trial, which evaluated the addition of cetuximab to cmFOLFOXIRI as conversion therapy. A total of 101 wild-type BRAF/RAS Chinese patients with initially unresectable colorectal liver-only metastasis and ECOG physical status scores of 0 to 1 were enrolled. The cetuximab plus cmFOLFOXIRI group achieved a significantly higher rate of no evidence of disease (NED) (70.1% vs 41.2%,  $P=0.005$ ) and an increased ORR (95.5% vs 76.5%,  $P=0.010$ ) compared with the FOLFOXIRI group. PFS and OS were both improved in the cetuximab plus cmFOLFOXIRI group, while the incidence of grade 3 and 4 adverse events was similar between the two groups. As for the reported adverse events of liver function, the incidence of grade 3 or above alanine aminotransferase or aspartate aminotransferase elevation was higher in the combination group than in the chemotherapy-alone group (7.5% vs 5.9%,  $P=0.005$ ). Among them, 8 patients underwent R0 resection surgery plus thermal ablation and 18 patients underwent thermal ablation therapy for liver metastases, with no significant adverse events reported [17]. A prospective, randomized, multicenter phase II study (VOLFI study) in Germany showed that for wild-type RAS metastatic colorectal cancer with an ECOG physical status score of 0 to 1, the experimental group (FOLFOXIRI combined with panitumumab) had a higher ORR (85.7% vs 54.5%,  $P=0.0013$ ) and secondary resection rate than the control group (FOLFOXIRI) [18]. Further analysis indicated that the tumor RR was related to the location of the tumor. The ORR of the left-sided and right-sided tumors in the experimental group was 90.6% and 60.0% ( $P=0.0288$ ), respectively, whereas no significant difference was observed in the control group. In patients with left-sided primary tumors, the ORR of the experimental and control groups

Table 2. Resection rate after FOLFOXIRI vs FOLFIRI/FOLFOX in the first-line treatment of metastatic colorectal cancer in randomized-controlled clinical trials

Author (study name, year)	Trial phase	Study population	Treatment arms	No. of patients	Median age (range), years	PS 0 (%)	CRC patients with LM only (%)	ORR (%)	Resection (%)	RO resection (%)
Souglakos et al. [7] (HORG, 2006)	III	Age ≥18 years ECOG PS 0-2	FOLFOXIRI FOLFIRI	138 147	66 (25-82) 66 (39-84)	36% 38%	NR NR	43% 34%	10% 4%	9% 3%
Falcone et al. [4] (GONO, 2007)	III	Age of 18-75 years ECOG PS 0-2 (18-70 years) ECOG PS 0 (71-75 years)	FOLFOXIRI FOLFIRI	122 122	62 (27-75) 64 (21-75)	61% 61%	34% 32%	66% 41%	NR NR	All: 15% LM only: 36% All: 6% LM only: 12%
Ychou et al. [14] (METHEP, 2013)	II	Initially unresectable or not optimally resectable liver metastases	FOLFIRINOX FOLFOX/FOLFIRI	30 30	64 (43-74) 63 (43-73)	77% 72%	100% 100%	73% 60%	67% 40%	30% 23%
Gruenberger et al. [15] (OLIVIA, 2015)	II	Age ≥18 years ECOG PS 0-1 Initially unresectable liver metastases	FOLFOXIRI + bev FOLFIRI + bev	41 39	63 (32-77) 57 (28-80)	56% 80%	100% 100%	81% 62%	61% 49%	49% 23%
Cremolini et al. [5] (TRIBE, 2014)	III	Age 18-75 years ECOG PS 0-2 (18-70 years) ECOG PS 0 (71-75 years)	FOLFOXIRI + bev FOLFIRI + bev	252 256	61 (29-75) 60 (29-75)	90% 90%	23% 18%	65% 53%	NR NR	15% 12%
Hurwitz et al. [8] (STEAM, 2019)	II	Age of 18-75 years ECOG PS 0-2 (18-70 years) ECOG PS 0 (71-75 years)	FOLFOXIRI + bev FOLFIRI + bev	93 95	58 (23-75) 58 (34-73)	67% 54%	30% 28%	72% 62%	17% 8%	16% 6%
Cremolini et al. [6] (TRIBE2, 2020)	III	Age of 18-75 years ECOG PS 0-2 (18-70 years) ECOG PS 0 (71-75 years)	FOLFOXIRI + bev FOLFOX + bev	339 340	60 (53-67) 61 (52-67)	86% 85%	31% 28%	62% 50%	NR NR	17% 12%

FOLFOXIRI, 5-Fluorouracil + Oxaliplatin + Irinotecan; FOLFIRI, 5-Fluorouracil + Oxaliplatin; FOLFOX, 5-Fluorouracil + Oxaliplatin; bev, bevacizumab; ORR, objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; CRC, colorectal cancer; LM, liver metastasis; NR, not reported.



was 90.6% and 60.0% ( $P=0.0039$ ), respectively, whereas in the right-sided primary tumors, the difference in ORR between the two groups was not statistically significant [18].

In summary, patients with wild-type RAS/BRAF left-sided metastatic colorectal cancer undergoing FOLFOXIRI combined with anti-EGFR therapy could achieve a high ORR and R0 resection rate; this regimen is suitable for patients with an optimal physical status score and an urgent need for tumor regression in conversion therapy. Table 3 summarizes the clinical trials of anti-EGFR monoclonal antibodies (cetuximab or panitumumab) combined with chemotherapy to treat liver metastases from colorectal cancer [16, 17, 19–22].

### FOLFOXIRI in neoadjuvant therapy for advanced colorectal cancer

#### Experts' recommendation

cmFOLFOXIRI is recommended as a neoadjuvant therapy regimen for patients who meet the following criteria: locally advanced (cT3–cT4 or N2) rectal cancer, age 18–75 years, ECOG performance status  $\leq 1$  if age was  $\leq 70$  years or ECOG performance status 0 if age was 71–75 years.

#### Treatment administration

Typically, four to six cycles of cmFOLFOXIRI are recommended as the preoperative neoadjuvant, followed by tumor regression evaluation with pelvic-enhanced magnetic resonance imaging (MRI). Chemoradiotherapy is considered according to the MDT discussion and the experience in different sites.

#### Illustration

Neoadjuvant therapy is critical in local tumor shrinkage to ensure tumor R0 resection, reducing micrometastases to reduce the risk of tumor recurrence and increasing the anal-preservation rate to improve patients' quality of life [23]. A high-intensity FOLFOXIRI regimen in neoadjuvant therapy achieves tumor downstaging and reduces the risk of post-operative recurrence; meanwhile, it reduces the complication rates of surgery and improves the quality of life after surgery. The FORTUNE study is a single-arm phase II clinical trial designed to evaluate the efficacy of preoperative cmFOLFOXIRI plus selective radiotherapy in locally advanced

rectal cancer [24]. A total of 106 patients with locally advanced rectal cancer were enrolled in this study and treated with four to six cycles of cmFOLFOXIRI chemotherapy before surgery; selective radiotherapy was considered according to tumor regression. The pathological complete response (pCR) rate reached 20.4% (21/103), the downstage rate (ypT0–2N0M0) reached 42.7% (44/103), and the overall chemotherapy was well tolerated. After cmFOLFOXIRI chemotherapy, 12 patients underwent long-term radiotherapy and chemotherapy, and the pCR rate was 41.7% (5/12). The pCR rate of 92 patients who did not receive long-term radiotherapy, including 2 patients receiving chemotherapy plus short-term radiotherapy, was 17.4% (16/92) [24].

In 2020, the American Society of Clinical Oncology meeting reported the results of the PRODIGE 23 study, which is a multicenter phase III study of mFOLFOXIRI with or without radiotherapy for the treatment of locally advanced rectal cancer. A total of 461 patients with rectal cancer (cT3–4NxM0) were enrolled in the study. Participants in the experimental group were administered with six cycles of mFOLFIRINOX chemotherapy, followed by concurrent long-course chemoradiotherapy and then six cycles of mFOLFOX6 chemotherapy after total mesorectal excision (TME). The participants in the control group received only concurrent long-course chemoradiotherapy and then mFOLFOX6 chemotherapy for 6 months after TME. The preliminary results showed that compared with the control group, the experimental group had a higher pCR rate (27.8% vs 12.1%,  $P < 0.001$ ), a higher 3-year disease-free survival rate (75.7% vs 68.5%,  $P = 0.034$ ), and a higher 3-year metastasis-free survival rate (78.8% vs 71.7%,  $P = 0.017$ ); both regimens were well tolerated [25]. Therefore, FOLFOXIRI neoadjuvant chemotherapy plus selective concurrent chemoradiotherapy is considered an effective and safe treatment strategy for patients with locally advanced rectal cancer. In addition, several clinical trials of FOLFOXIRI for neoadjuvant therapy have been being carried out for rectal cancer (Table 4) [24–27].

Currently, the 2020 version of the NCCN guidelines recommend that 12–16 weeks of FOLFOXIRI followed by concurrent chemoradiotherapy can be considered neoadjuvant chemotherapy for cT4N + locally advanced rectal cancer [28]. None of the studies has yet reported FOLFOXIRI as the neoadjuvant regimen for colon cancer treatment.

**Table 3.** Summary of clinical trials of anti-epidermal growth factor receptor monoclonal antibodies (cetuximab or panitumumab) combined with chemotherapy conversion for the treatment of colorectal cancer liver metastases

Author (study name, year)	Treatment arms	No. of patients	ORR (%)	Resection (%)	R0 resection (%)	Median survival time (months)
Study population: initially unresectable liver metastases						
Ji et al. [19] (2013)	FOLFOX6 + cet	73	73%	49%	27%	NR
Folprecht et al. [20] (CELIM, 2010)	FOLFOX6/FOLFIRI + cet	57	NR	NR	28%	NR
Ye et al. [21] (BELIFE, 2013)	mFOLFOX6/FOLFIRI	68	29%	NR	7%	21.0
	mFOLFOX6/FOLFIRI + cet	70	57%	NR	26%	30.9
Hu et al. [17] (FOCULM, 2020)	cmFOLFOXIRI	34	77%	29%	21%	33.2
	cmFOLFOXIRI + cet	67	96%	55%	36%	NM
Study population: initially unresectable or not optimally resectable liver metastases						
Folprecht et al. [20] (CELIM, 2010)	FOLFOX6 + cet	56	68%	42%	38%	35.8
	FOLFIRI + cet	55	57%	43%	30%	29.0
Carrato et al. [22] (PLANET-TTD, 2017)	FOLFOX4 + pan	38	74%	45%	34% <sup>a</sup>	37
	FOLFIRI + pan	39	67%	59%	46% <sup>a</sup>	41
Study population: initially not optimally resectable liver metastases						
Garufi et al. [16] (POCHER, 2010)	chrono-IFLO + cet	43	79%	79%	60 <sup>a</sup>	37

FOLFOXIRI, 5-Fluorouracil + Oxaliplatin + Irinotecan; FOLFIRI, 5-Fluorouracil + Irinotecan; FOLFOX, 5-Fluorouracil + Oxaliplatin; cet, cetuximab; pan, panitumumab; ORR, objective response rate; NR, not reported; NM, not met.

**Table 4.** Summary of clinical trials of FOLFOXIRI neoadjuvant therapy for rectal cancer

Author (study name, year)	Trial phase	Study population	Treatment arms	No. of patients	PCR (%)	R0 resection (%)	Local recurrence rate	DFS
Rouanet et al. [26] (GRECCAR-4, 2020)	II	Age $\geq$ 8 years	FOLFOXIRI 4 cycles	10	10%	100%	0	5-DFS: 80%
		ECOG PS 0–2	Immediate surgery, if $\geq$ 75% tumor volume reduction by MRI	19	58%	100%	0	5-DFS: 89.5%
		MRI staging T3c-4 or MRF+	Standard radiochemotherapy, if $\geq$ 75% tumor volume reduction by MRI	52	13.5%	83%	1.9%	5-DFS: 72.9%
		>1 cm from the anal verge	Standard radiochemotherapy, if <75% tumor volume reduction by MRI	49	20%	88%	7.8%	5-DFS: 72.8%
Zhang et al. [24] (FORTUNE, 2019)	II	Age of 18–70 years ECOG PS 0–1 MRI staging T3–4 or N+ <12 cm from the anal verge	cmFOLFOXIRI 4–6 cycles, selective radiation after assessment by MRI	103	20.4%	99.0%	7.8%	2-DFS: 85.6% 3-DFS: 78.9%
Conroy et al. [25] (PRODIGE-23, 2020)	III	Age of 18–75 years ECOG PS 0–1 MRI staging T3–4 <15 cm from the anal verge	FOLFOXIRI 6 cycles, then radiochemotherapy, followed by surgery at an interval of 7 weeks	231	27.8%	NR	4.8%	2-DFS: 75.7%
			Capecitabine-based concurrent radiochemotherapy, followed by surgery at an interval of 7 weeks	230	12.1%	NR	7%	3-DFS: 68.5%
Masi et al. [27] (TRUST, 2019)	II	Age of 18–75 years ECOG PS 0–2 (18–70 years) ECOG PS 0 (71–75 years) MRI staging: high-risk T3 (MRF+, $\leq$ 6 cm from the anal verge, T3c~3d), T4, or stage III <12 cm from the anal verge	Induction FOLFOXIRI plus bevacizumab for 6 cycles, followed by chemoradiotherapy with capecitabine plus bevacizumab	48	36.4%	97.8%	NR	2-DFS: 80.45%

ECOG PS, Eastern Cooperative Oncology Group performance status; DFS, disease-free survival.

### Usage and dosage of the cmFOLFOXIRI regimen

cmFOLFOXIRI consists of an oxaliplatin 85 mg/m<sup>2</sup> intravenous infusion over 120 min, irinotecan 150–165 mg/m<sup>2</sup> over 90 min, folinic acid 400 mg/m<sup>2</sup> over 120 min, and 5-FU 2,400–2,800 mg/m<sup>2</sup> over a 46–48 h continuous infusion on day 1 every 2 weeks.

For targeted therapy, bevacizumab 5 mg/kg was administered by intravenous infusion on day 1 every 2 weeks. It should be given over 90 min for the first infusion and then over 30–60 min every 2 weeks. Cetuximab 500 mg/m<sup>2</sup> was administered by intravenous infusion on day 1 every 2 weeks; this intravenous infusion should be given for >120 min for the first time followed by >60 min.

Since the Asian population is less tolerable than the European population, the clinical application of the standard FOLFOXIRI regimen for colorectal cancer in China, even in the entire Asian region, is limited. The results of a phase I dose-finding study showed that the maximum tolerated dose of FOLFOXIRI in Japanese patients with advanced colorectal cancer is 165 mg/m<sup>2</sup> for irinotecan, 85 mg/m<sup>2</sup> for oxaliplatin, and

2,400 mg/m<sup>2</sup> for 5-FU. Thus, the recommended dose of FOLFOXIRI is 150 mg/m<sup>2</sup> of irinotecan, 85 mg/m<sup>2</sup> of oxaliplatin, and 2,400 mg/m<sup>2</sup> of 5-FU [29]. In nine patients with evaluable lesions, the ORR reached 89% and the overall toxicity is manageable. In China, Deng's group modified the FOLFOXIRI regimen based on the characteristics of the Chinese population, the mechanism of the combined three drugs, and the data of previous studies. Platinum is a dose-dependent drug for efficacy and the dose should not be adjusted, while 5-FU has a wide range of applications and a low value is recommended. An overlap of toxicity of fluorouracil and irinotecan indicated that the dose of irinotecan was reduced by 20%. Thus, a cmFOLFOXIRI regimen indicated that the dose of irinotecan was reduced from 180 mg/m<sup>2</sup> in the original regimen to 150–165 mg/m<sup>2</sup>; 5-FU was reduced from 3,200 mg/m<sup>2</sup> to 2,400–2,800 mg/m<sup>2</sup>. Another retrospective study enrolled 113 patients with locally advanced colorectal cancer and 199 patients with metastatic colorectal cancer who received cmFOLFOXIRI with or without a targeted therapy (bevacizumab or cetuximab) regimen. For patients with metastatic

colorectal cancer, the disease-control rate was 93.8%, the ORR was 63.8%, and the partial RR reached 61.6%. Regarding the safety of patients, the incidence rates of grade 3/4 neutropenia,

fatigue, and anemia were 22.1%, 11.2%, and 8.9%, respectively, and the incidence of serious adverse events, including febrile neutropenia and intestinal perforation, was 6.4% [30]. The

**Table 5.** Dose adjustment of common adverse events of the cmFOLFOXIRI regimen

Adverse event	Grade	Irinotecan	Oxaliplatin	5-Fluorouracil
Neutropenia	Grade 4	80%	80%	100%
Febrile neutropenia	Grade 3/4	80%	80%	100%
Thrombocytopenia	Grade 3/4	80%	80%	100%
Alanine aminotransferase	Grade 3/4	80%	80%	100%
Aspartate aminotransferase	Grade 3/4	80%	80%	100%
Serum total bilirubin	Grade 3/4	80%	80%	100%
Diarrhea	Grade 3	80%	100%	80%
Diarrhea	Grade 4	60%	100%	80%
Oral mucositis	Grade 3	80%	100%	80%
Oral mucositis	Grade 4	80%	100%	60%
Myocardial infarction	Grade 3/4	100%	100%	STOP

In the case that the adverse event meets neither the standard of dose reduction nor the standard of administration for the prescribed time of the next cycle, which occurs twice or more repeatedly, following which the decline in the dose. If the dose was reduced twice, the drug should be discontinued. The original dose in this table refers to the dose of the previous chemotherapy, all of which was reduced based on the previous dose.

**Table 6.** Management strategies for adverse events requiring special attention

Adverse event	Grade 3–4 (%) [24, 30]	Recommendations
Neutropenia	22.2%–42.5%	<ul style="list-style-type: none"> <li>Hematopoietic functions in baseline were evaluated before treatment for every patient</li> <li>Prophylactic use of filgrastim (G-CSF) or sargramostim (GM-CSF) is recommended</li> <li>In addition to bone marrow suppression, splenomegaly and hypersplenism should be focused on, and local treatment of the spleen if necessary</li> <li>Dose adjustment of chemotherapeutic drugs is required for grade 4 neutropenia</li> <li>Occurrence of febrile neutropenia requires dose adjustment and therapeutic antibiotics for infections</li> </ul>
Diarrhea	2%–6%	<ul style="list-style-type: none"> <li>Early-onset diarrhea usually occurs on the day of medication, mainly accompanied by cramping abdominal pain, tearing, sweating, increased saliva, hypotension, dizziness, and blurred vision. In severe cases, atropine 0.25 mg can be injected subcutaneously, along with intravenous rehydration therapy</li> <li>Delayed diarrhea: dose-limiting toxicity, which usually appears after 24 h of medication, with an incidence of 80%–90%, of which 39% are severe. The median time of occurrence was 5 days after medication, lasting for an average of 4 days, and severe cases can be fatal. Loperamide (Imodium) can be administered orally: the first dose is 4 mg and then 2 mg every 2 h. Continue to use the medication for 12 h after the last watery defecation and generally do not exceed 48 h. If diarrhea persists for &gt;48 h, seek medical attention immediately</li> <li>Dose adjustment of chemotherapeutic drugs is required for grade 3–4 diarrhea</li> </ul>
Fatigue	3.8%–11.2%	<ul style="list-style-type: none"> <li>Evaluate the patient's nutritional status before treatment and intervene</li> <li>Add nutritional support during treatment</li> <li>Strengthen health survey</li> </ul>
Intestinal obstruction	2.9%–4.8%	<ul style="list-style-type: none"> <li>Evaluate the size of the primary tumor and the risk of obstruction before treatment, and use laxatives if necessary to keep the bowel open</li> <li>Pay attention to the use of antiemetic drugs during treatment. Long-acting 5-HT antagonists are not recommended for patients at a high risk of obstruction</li> <li>Deal with difficulties in defecation in time</li> <li>Strengthen dietary guidance</li> <li>If intestinal obstruction occurs during treatment and conservative medical treatment is ineffective, preventive stoma surgery could be considered</li> </ul>
Intestinal perforation	2.2%	<ul style="list-style-type: none"> <li>Evaluate the size of the primary tumor and the risk of perforation before treatment, and keep the bowel open</li> <li>Once perforation occurs during treatment, immediately evaluate the operation and provide the best supportive treatment</li> </ul>



FORTUNE and FOCULM studies further verified that reducing the dose is beneficial to clinical management [17, 24]. The adverse events of cmFOLFOXIRI are significantly lower than those reported in the TRIBE and OLIVIA trials. However, the efficacies of cmFOLFOXIRI and TRIBE or OLIVIA are equivalent. Therefore, cmFOLFOXIRI is suitable for the Chinese population. Currently, the TRIBE-C (ClinicalTrials.gov, NCT04230187) trial is ongoing to evaluate the efficacy and safety of cmFOLFOXIRI combined with bevacizumab for advanced colorectal cancer compared with those of mFOLFOX6 combined with bevacizumab, which aimed to prove the efficacy of dose-modified cmFOLFOXIRI in patients with metastatic colorectal cancer in China.

### Adverse events of cmFOLFOXIRI: prevention and management

cmFOLFOXIRI has a manageable safety profile in colorectal cancer after dose modification. The common grade  $\geq 3$  adverse events include neutropenia, diarrhea, and fatigue. The dose intensity of the FOLFOXIRI regimen used in the TRIBE-2 study might be extremely high. In terms of adverse events in the TRIBE-2 study, the most common grade  $\geq 3$  adverse events in the FOLFOXIRI group during first-line treatment were diarrhea (17%) and neutropenia (50%) [6]. However, the occurrence rate of grade  $\geq 3$  neutropenia in the Chinese colorectal cancer population with cmFOLFOXIRI was 42.5% and the occurrence rate of diarrhea, fatigue, and nausea and vomiting were only 2%, 3.8%, and 8.5%, which were lower than those of the standard dose of FOLFOXIRI. Thus, the completion rate of chemotherapy was improved [24, 30]. In addition, the occurrence rate of common adverse events of cmFOLFOXIRI combined with targeted therapy was not significantly increased compared with that in cmFOLFOXIRI alone. In FOCULM, except for the significantly higher occurrence rate of acne-like rash (55.2% vs 5.9%,  $P < 0.001$ ), the occurrence rate of other adverse events did not increase in cmFOLFOXIRI combined with cetuximab compared with that in cmFOLFOXIRI alone [17].

The risks of patients were assessed and the adverse events with respect to the clinical application of cmFOLFOXIRI were identified. In addition, the metabolic enzyme UGT1A1 in the liver and intestines could glucuronidate the active molecule SN-38 of irinotecan, thereby reducing the adverse events [31]. Some studies confirmed that UGT1A1\*28 and UGT1A1\*6 are related to chemotherapy-related diarrhea and neutropenia induced by irinotecan [32, 33]. In 2015, the US FDA considered UGT1A1\*28 polymorphism as a predictor of irinotecan-induced toxicity. In the Asian population, the mutation frequency of UGT1A1\*28 gene is lower, whereas the mutation frequency of UGT1A1\*6 is higher [34]. Therefore, UGT1A1 could be tested before irinotecan chemotherapy and guide dose adjustment and drug selection. Although the adverse events of the cmFOLFOXIRI regimen are manageable after dose modification, they are still higher than those of the FOLFOX/FOLFIRI regimen. During treatment, patients' adverse events should be closely monitored and the dose modification after grade 3 toxicities (NCI CTCAE 5.0) is summarized in Table 5. Specific attention should be paid to adverse events, such as fatigue, neutropenia, diarrhea, intestinal obstruction, and intestinal perforation (Table 6).

### Conclusions

The FOLFOXIRI regimen has gradually transferred from the palliative therapy of advanced colorectal cancer to the neoadjuvant therapy of locally advanced colorectal cancer. The application of this regimen in the field of colorectal cancer continues to

advance, benefiting colorectal cancer patients. Simultaneously, cmFOLFOXIRI improved the tolerance of the Chinese population by reducing the dose of irinotecan and 5-FU, ultimately improving the efficacy for the patients. Nonetheless, additional studies are required in the future to make the cmFOLFOXIRI regimen precise and customized to improve the efficacy and avoid over-treatment.

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## Authors' Contributions

Y.H. D. drafted the manuscript. All authors critically revised the manuscript and approved the final version to be submitted.

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## Conflict of Interest

None declared.

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