XELOX/XELIRI Alternative Regimen as First-line Treatment of Metastatic Colorectal Cancer (CCRCTO-2:TROT)： A Randomized, Open, Controlled, Multicentric Phase II Trial

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Background

- Since 2000, the combination of three drugs and targeted drugs has further improved the survival of metastatic colorectal carcinoma (mCRC), while the incidence of side effects of triple regimens over grade 3 are much higher than double regimens. Since adjusting the dosage of drugs can't avoid serious toxicity, here we present a new method of optimizing the scheme by adjusting the time and mode of administration.

Method

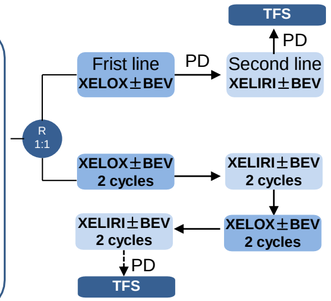
- TROT is a randomized, open, controlled, multicentric phase II trial.
- The enrolled patients were randomized to receive the following two treatment options:
- Arm A (Control group): XELOX±Bevacizumab (BEV)[a] was applied in the first line until imaging progression or intolerance appeared, and XELIRI±BEV[b] was applied in the second line until imaging progression or intolerance appeared.
- Arm B (Therapy group): XELOX±BEV and XELIRI±BEV were applied alternately (alternately every 2 cycles) until imaging progress or intolerance appeared in one of the regimens.

a. XELOX±BEV regimen: Oxaliplatin, 130mg/m^2 (＞2h, d1); Capecitabine, 1000mg/m^2,bid,d1-14; Bev,7.5mg/kg, d1, every 21 days as one cycle.
b. XELIRI±BEV regimen: Irinotecan, 180mg/m^2 (＞2h, d1); Capecitabine, 1000mg/m^2,bid,d1-14; Bev,7.5mg/kg, d1, every 21 days as one cycle

Figure 1 Study Design

Key Eligibility Criteria

- Age 18-75 years;
- Patients with unresectable colorectal adenocarcinoma;
- No prior chemotherapy and the target lesion has not received radiotherapy;
- ECOG PS 0-1;
- At least one measurable lesion per RECIST v1.1;



- Imaging evaluation will be performed every 2 cycles (6 weeks) after enrollment treatment by RECISIT v1.1.
- The primary endpoint is to compare the efficacy of these two proposed treatment strategies in terms of time to failure of strategy (TFS) and secondary objectives were objective response rate (ORR), disease control rate (DCR), overall survival (OS) and safety. The efficacy evaluation standard is RECISIT v1.1.
- The enrolled patients take the medication until the disease progression, lost to follow-up, death or a patient starts a new anti-tumor drug.

Result

- 66 patients (＜75y) were enrolled in the study. 4 patients in the arm A and 2 patients in the arm B were lost to follow or fall off. The analysis of curative effect has been evaluated in 29 patients in the arm A whose median age is 55y and in 31 patients in the arm B whose median age is 57y.

Table 1 Baseline characteristics

Characteristics	Arm B(Therapy group) (n=31)	Arm A(Control group) (n=29)
Median age, years	57	55
Male/Female	20/11	14/15
ECOG, no. (%)		
0	27（87.1%）	26（89.7%）
1	4（12.9%）	3（10.3%）
Primary tumor location, n (%)		
Left	24（77.4%）	22（75.9%）
Right	7（22.6%）	7（24.1%）
Previously received adjuvant therapy, n (%)	9（29%）	6（20.7%）
Metastasis, n (%)		
Liver metastasis	9（29%）	16（55.2%）
Lung metastasis	2（6.5%）	3（10.3%）
Multiple metastases	20（64.5%）	10（34.5%）
Resection of primary tumor, n (%)	17（54.8%）	22（75.9%）
KRAS, n (%)		
KRAS wild-type	11（35.5%）	12（41.4%）
KRAS wild-type mutation	15（48.4%）	11（37.9%）
BRAF, n (%)		
BRAF wild-type	19（61.3%）	21（72.4%）
BRAF wild-type mutation	7（22.6%）	2（6.9%）
Combined BEV, n (%)	15（48.4%）	15（51.7%）

Efficacy

- ORR was 27.6% in the first-line treatment and 11.5% in the second-line treatment in the arm A versus 67.7% in the arm B (P =0.002).
- The DCR was 89.7% in the first-line treatment and 57.7% in the second-line treatment in the arm A versus 100% in the arm B (P =0.213). The rate of early tumor shrinkage (ETS) was 64.5% and the deepness of response (DpR) was 46% in the arm B.

Table 2 Response in response-evaluable patients

Best Response	Therapy group (n=31)	First line in control group(n=29)	Second line in control group(n=26)	P (Therapy group vs. First line in control group)
CR	2	0	0	
PR	19	8	3	
SD	10	18	12	
PD	0	3	11	
ORR	67.7%	27.6%	11.5%	0.002
DCR	100%	89.7%	57.7%	0.213

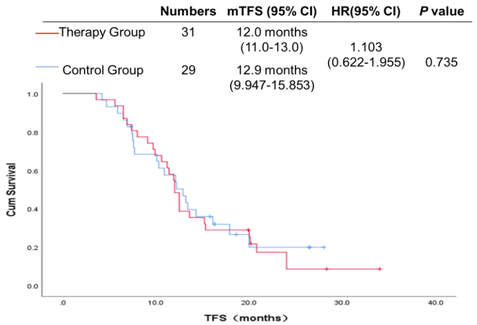


Figure 2. The primary endpoint: median TFS was 12.9 months in arm A versus 12.0 months in arm B (P=0.735,HR=1.103) by Kaplan-Meier analysis. There was no statistically significant difference in mTFS between the two groups.

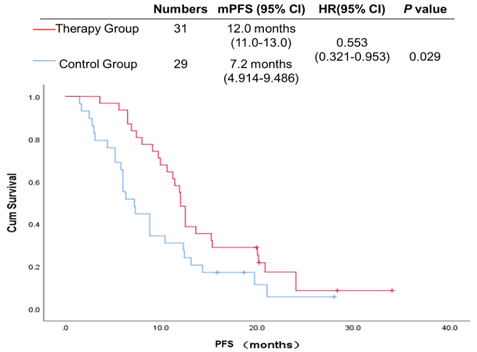


Figure 3. Patients in the therapy group had a significantly longer mPFS than these in control group (12.0 vs. 7.2 months, P=0.029, HR=0.553).

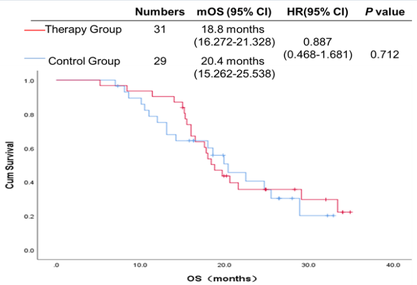


Figure 4. There was no statistically significant difference in mOS between the two groups (18.8 vs.20.4 months, p=0.712, HR=0.887)

Table 3 Adverse Events Data are n (%)

Adverse Events	Therapy group (n=31)			Control Group (n=29)			P (Therapy group vs. Control Group in Grade 3-4)
	Grade 1	Grade 2	Grade 3-4	Grade 1	Grade 2	Grade 3-4	
Neurotoxicity	4	1	1（3.2%）	4	16	8（27.6%）	0.023
Nausea	11	2	1（3.2%）	17	6	5（17.2%）	0.168
Hand-foot syndrome	7	0	0	20	5	4（13.8%）	0.105
Fatigue	2	0	0	5	2	0	
Alopecia	12	16	0	5	15	5 (17.2%)	0.051
Diarrhoea	3	1	2 (6.5%)	4	8	8 (27.6%)	0.065
Thrombocytopenia	3	0	2 (6.5%)	7	11	10 (34.5%)	0.007
Anemia	3	0	1 (3.2%)	6	6	4 (13.8%)	0.311
Leukopenia	5	3	1 (3.2%)	10	7	7 (24.1%)	0.045
Neutropenia	5	3	2 (6.5%)	10	7	10 (34.5%)	0.007
All adverse events			10 (32%)			21 (72.4%)	0.002

Conclusion

- XELOX/XELIRI alternate regimen±BEV, compared with first-line XELOX followed by XELIRI after disease progression±BEV, can improve the effect of tumor shrinkage and significantly reduce treatment-related side effects in mCRC patients with widespread metastasis, and this alternate regimen may become an alternative for patients who can't tolerate the three-drug combination regimen.