Comparison of *UGT1A1* Polymorphism as Guidance of Irinotecan Dose Escalation in *RAS* Wild-Type Metastatic Colorectal Cancer Patients Treated With Cetuximab or Bevacizumab Plus FOLFIRI as the First-Line Therapy

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Uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*) polymorphism plays a crucial role in the increased susceptibility and toxicity of patients to irinotecan. This retrospective, observational study compared the clinical outcomes and adverse events (AEs) in *RAS* wild-type metastatic colorectal cancer (mCRC) patients treated with cetuximab or bevacizumab plus FOLFIRI with *UGT1A1* genotyping and irinotecan dose escalation as the first-line therapy. In total, 173 patients with mCRC with *RAS* wild-type were enrolled. Among them, 98 patients were treated with cetuximab, whereas 75 patients were treated with bevacizumab. All patients received irinotecan dose escalation based on *UGT1A1* genotyping. We compared the progression-free survival (PFS), overall survival (OS), objective response rates (ORRs), disease control rates (DCRs), metastatectomy, and severe adverse events (SAEs) between the two groups. The clinical effects of primary tumor sidedness and target therapy crossover were further analyzed. Over a median follow-up of 23.0 months [interquartile range (IQR), 15.0–32.5 months], no significant differences were observed between the cetuximab and bevacizumab groups in PFS [18.0 months vs. 14.0 months; 95% confidence interval (CI), 0.517–1.027; hazard ratio (HR), 0.729; $p = 0.071$], OS (40.0 months vs. 30.0 months; 95% CI, 0.410–1.008; HR, 0.643; $p = 0.054$), ORR (65.3% vs. 62.7%; $p = 0.720$), DCR (92.8% vs. 86.7%; $p = 0.175$), metastatectomy (36.7% vs. 29.3%; $p = 0.307$), and SAEs ($p = 0.685$). Regardless of primary tumor sidedness and target therapy crossover, no significant differences were noted in efficacy and safety between the two groups (all $p > 0.05$). Our results revealed that patients with wild-type *RAS* mCRC, regardless of biologics, with *UGT1A1* genotyping can tolerate escalated doses of irinotecan and potentially achieve a more favorable clinical outcome without significantly increased toxicity.

Key words: *UGT1A1* polymorphism; Metastatic colorectal cancer (mCRC); Irinotecan dose escalation; Biologics; Efficacy; Safety

INTRODUCTION

Despite recent advances in medicine, the management of patients with metastatic colorectal cancer (mCRC) remains challenging because of considerable interindividual differences in therapeutic responses. In recent years, pharmacogenomics has been adopted for the personalization of mCRC treatment[1]. Typically, majority of patients with mCRC receiving first-line treatment might require later lines of therapy. Therefore, first-line

treatment is the most critical phase of therapy, and its effects on patient outcomes might be more prominent than those of any subsequent line. For example, absolute improvements in median overall survival (OS) even with intensive second-line regimens tend to be relatively minimal[2–4]. However, the incremental OS gain provided by the addition of biological agents to chemotherapy and the mainstay treatment for patients with mCRC is still represented by doublet or triplet chemotherapy of compounds with fluoropyridine backbones combined with oxaliplatin, irinotecan, or both[5–7].

Irinotecan-based chemotherapy is a standard first-line or second-line regimen for mCRC. However, irinotecan has dose-limiting toxicity, mainly neutropenia and delayed-onset diarrhea. *UGT1A1* gene polymorphism is differently distributed among different ethnicities, which may lead to various toxicity and efficacies of irinotecan[8]. Even with the same ethnicity, the gene frequency differs in varying geographical regions[9]. The recommended irinotecan dose in FOLFIRI (leucovorin + fluorouracil + irinotecan) is 180 mg/m^2 based on a dose-finding study[10]. The recommended dose is considerably lower than that tolerated in patients with *UGT1A1*1/*1* and **1/*28* genotypes[10,11]. Our retrospective studies have also demonstrated that patients with mCRC who underwent *UGT1A1* genotyping may receive escalated irinotecan doses to obtain a better clinical response with comparable toxicity[12–14]. The recommendations of the Pan-Asian European Society for Medical Oncology (ESMO) consensus guidelines showed that it depends on the prevalence of *UGT1A1* polymorphisms per country whether a lower irinotecan threshold dose for *UGT* genotyping may be used[15].

In this retrospective, observational study, we compared the efficacy and safety following different doses of irinotecan in 173 *RAS* wild-type patients with mCRC treated with first-line FOLFIRI plus cetuximab or bevacizumab.

MATERIALS AND METHODS

Patients and Study Design

In this retrospective, observational study, patients with mCRC with histologically proven synchronous or
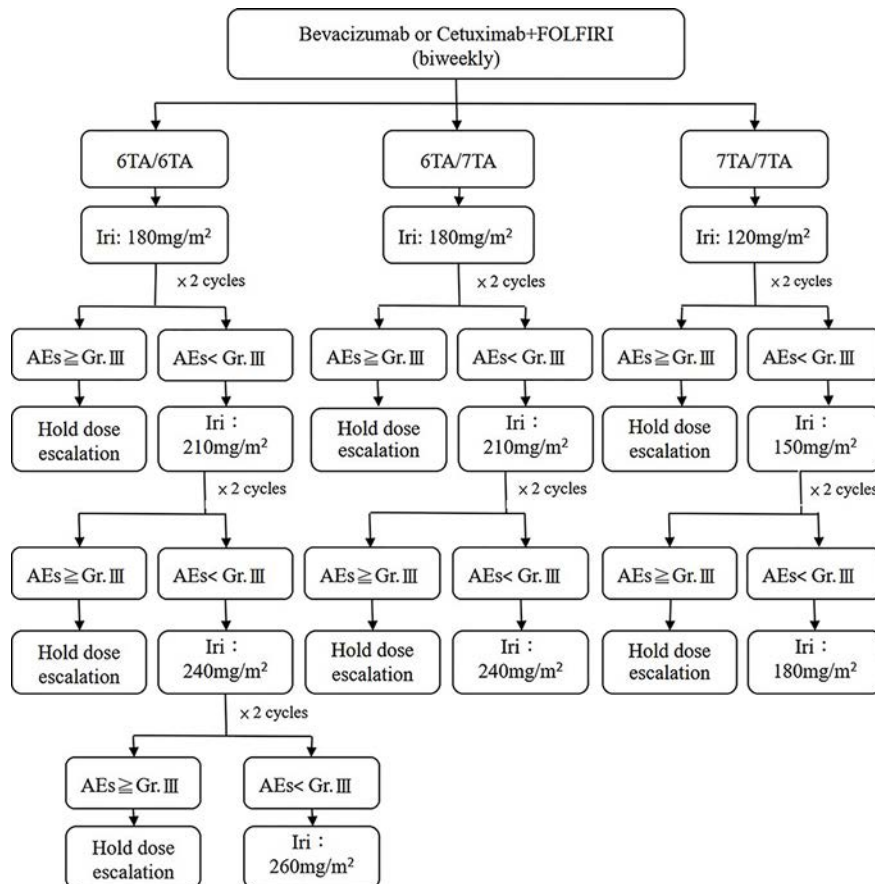
Figure 1. Flowchart of patient disposition. AEs, adverse events; Gr., grade; Iri, irinotecan.

metachronous adenocarcinoma were enrolled. All participants received routine *KRAS* (codons 12, 13, 59, 61, 117, and 146), *NRAS* (codons 12, 13, 59, 61, 117, and 146), *BRAF* (codon 600), and *UGT1A1* genotyping tests. The patients with *RAS* wild-type received irinotecan dose escalation according to their *UGT1A1* genotyping. Irinotecan dose escalation was based on *UGT1A1* polymorphisms and adverse events (AEs) observed after two cycles of dose adjustment, and escalation was terminated if grade III/IV AEs occurred (Fig. 1). We included data on patients' demographic (age and gender), clinical [Eastern Cooperative Oncology Group (ECOG) performance status], and tumor (primary tumor site, *UGT1A1* status, *RAS* status, *BRAF* status, and number and sites of metastases) characteristics.

In this study, we retrospectively analyzed 173 patients with mCRC receiving cetuximab or bevacizumab combined with FOLFIRI as the first-line treatment. Each group was divided into three subgroups on the basis of their *UGT1A1* genotype.

Subgroup 1: UGT1A1 6TA/6TA

The treatment regimen comprised cetuximab (500 mg/m^2) or bevacizumab (5 mg/kg) as a 120-min intravenous (IV) infusion on day 1, followed by irinotecan (180 mg/m^2) plus normal saline 500 ml as a 4-h IV infusion, and leucovorin (200 mg/m^2) plus 5-FU (2,800 mg/m^2) plus 500 ml of IV normal saline for 42 to 48 h; this regimen was repeated once every 2 weeks. The AEs, hematological or nonhematological, were observed during the treatment course. If the AEs were below grade II, the dose was gradually escalated in increments of 30 mg/m^2. The estimated maximal dose of irinotecan was 260 mg/m^2.

Subgroup 2: UGT1A1 6TA/7TA

The procedure was the same as that for subgroup 1, but irinotecan was initiated at 180 mg/m^2 once every 2 weeks, and the estimated maximal dose was 240 mg/m^2.

Subgroup 3: UGT1A1 7TA/7TA

The procedure is the same as that for subgroup 1, but irinotecan was initiated at 120 mg/m^2 once every 2 weeks, and the estimated maximal dose was 180 mg/m^2.

Written informed consent was obtained from each participant. The study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital [KMUHIRB-E(I)-20200036].

Genomic DNA Extraction and UGT1A1, RAS, and BRAF Genotyping

To analyze constitutional gene polymorphisms, DNA was first extracted from 4 ml of peripheral blood using a PUREGENE DNA isolation kit (Gentra Systems, Minneapolis, MN, USA). The patients' genomic DNA was then analyzed using direct sequencing to determine the *UGT1A1* promoter region genotype. Detailed genotyping procedures were previously reported[16].

For *RAS* genotyping, macrodissected paraffin-embedded samples were then placed in sterile tubes. After deparaffinization and rehydration, DNA was isolated using a PUREGENE DNA isolation kit. The primers used in this study were designed using primer 3 free software (https://primer3.org/). The sequences of the forward and reverse primers were 5′-TCATTATTTTTATTATAAGGCCTGCTGAA-3′ and 5′- CAAAGACTGGTCCTGCACCAGTA-3′, respectively. The polymerase chain reaction (PCR) volume was 40 μl, and the PCR conditions for *KRAS* were as follows: 94.0°C for 10 min; 35 cycles of denaturation for 30 s at 94.0 °C, annealing for 60 s at 56.0°C, and primer extension for 30 s at 72.0°C; and final hold for 7 min at 72.0°C. Fragment analysis of the PCR products was conducted to verify the genotypes using automated capillary electrophoresis on an ABI PRISM 310 Genetic Analyzer system and Genotyper software (Applied Biosystems, Foster City, CA, USA).

For *BRAF* mutation analysis, we extracted DNA from formalin-fixed, paraffin-embedded (FFPE) CRC tissue samples for clinical *BRAF* mutation analysis by direct sequencing. Detailed genotyping procedures were previously reported[14].

Efficacy and Safety Outcome Measures

Assessment of the tumor responses was typically performed after every six cycles of the interventional regimen. Response measurements are based on the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1[17]. The AEs were monitored and graded in each cycle according to the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCT-CTCAE) Version 4.3 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm).

Progression-free survival (PFS) was defined as the time from the date of enrollment until the first documentation of progression, regardless of the patient's treatment status. OS was defined as the time from the date of enrollment until the date of death or the last date of follow-up. The complete responses and partial responses were defined as objective response rate (ORR), and disease control rate (DCR) was defined as confirmed complete responses, partial responses, and stable disease cases.

Target Agent Crossover Therapy

In this retrospective, observational study, we observed the effects of target therapy crossover. If the first-line regimen failed, the patients received other biologics under stable ECOG status. According to the reimbursement of

the National Health Insurance Administration of Taiwan, the second-line regimen would be FOLFOX after first-line treatment failure of FOLFIRI plus target agents. The third-line regimen could be FOLFIRI plus cetuximab in wild-type *RAS* mCRC patients, but self-paid bevacizumab in mutant *RAS* mCRC patients. The OS was used as an endpoint of target agent crossover therapy.

Statistical Analysis

The analyses included patients who completed the sixth cycle of treatment and were not lost to follow-up. Continuous variables are presented as the mean ± standard deviation, and dichotomous variables as numbers and percentages. All statistical analyses were performed using SPSS v21.0 (SPSS, Chicago, IL, USA). The clinicopathological characteristics of the two groups were compared using Pearson's chi-square test. Cox regression analysis was used to estimate the hazard ratios (HRs) for all independent variables in the model. PFS and OS were evaluated using the Kaplan–Meier method, and the log-rank test was used to compare time-to-event distributions. Statistical significance was set to a value of $p < 0.05$.

RESULTS

Patients' Population and Disposition

Between August 2014 and February 2020, 245 patients were initially enrolled, and 173 patients were finally analyzed. The patient flowchart is presented in Figure 2. Except for age, primary lesion site, and *BRAF* status, the baseline demographics and characteristics were similar between the two groups (Table 1). Most patients (70.7%) were less than 65 years old. In the bevacizumab group, 12.0% had mutant *BRAF* status, and in the cetuximab group, most patients had left-sided mCRC (88.7%). The database for the final analysis was locked on March 31, 2021. At the cutoff time for analysis, the median follow-up time was 23.0 months [interquartile range (IQR), 15.0–32.5 months].
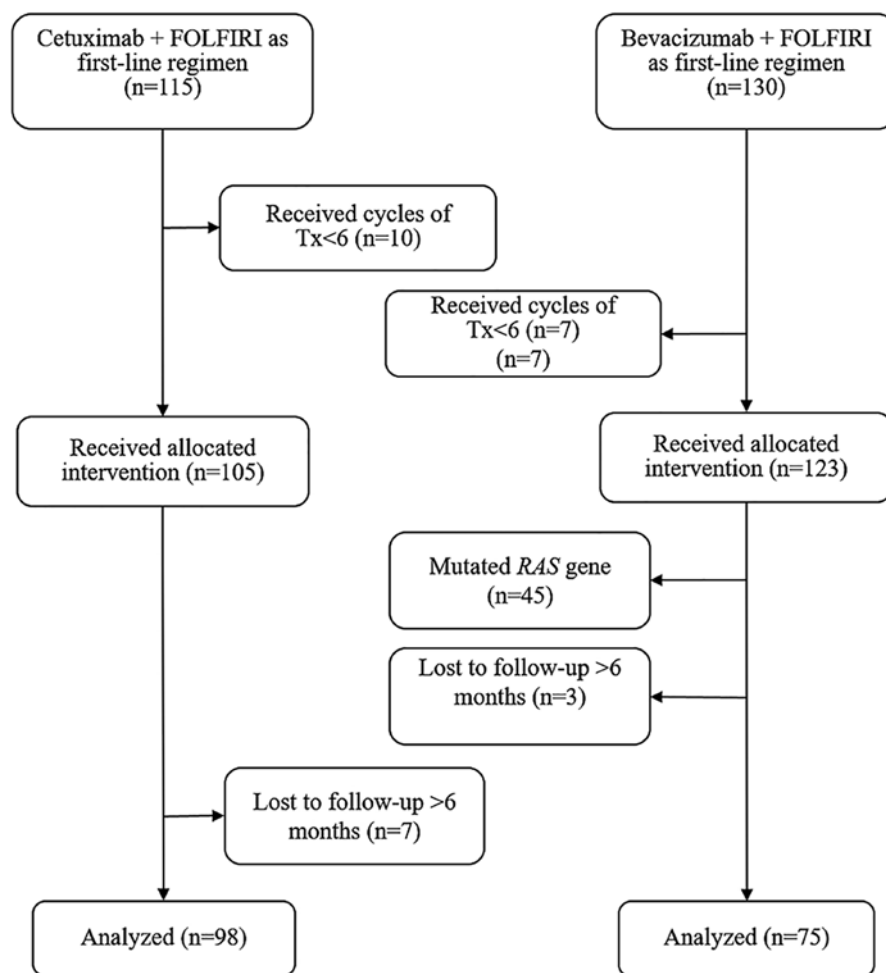
Figure 2. Patient selection flowchart. FOLFIRI, leucovorin + fluorouracil + irinotecan; Tx, treatment. Escalated dose of irinotecan according to *UGT1A1* polymorphisms.

Table 1. Baseline Characteristics of the 173 Enrolled Wild-Type *RAS* Patients With Metastatic Colorectal Cancer Under Chi-Square Analysis Between the Cetuximab Group and the Bevacizumab Group

Baseline Data	N	Cetu Group (N = 98)	Beva Group (N = 75)	p Value
Gender				0.176
Male	109	66 (67.3%)	43 (57.3%)	
Female	64	32 (32.7%)	32 (42.7%)	
Age (years)				0.304
Median (range)		63.0 (34.0–88.0%)	57.0 (25.0–81.0%)	
Age (years)				0.013
<65	104	51 (52.0%)	53 (70.7%)	
≥65	69	47 (48.0%)	22 (29.3%)	
ECOG PS				0.126
0 + 1	170	95 (96.9%)	75 (100.0%)	
2	3	3 (3.1%)	0 (0%)	
Primary lesion site				0.009
Left-sided	142	87 (88.7%)	55 (73.3%)	
Right-sided	31	11 (11.3%)	20 (26.7%)	
Synchronous/metachronous				0.124
Synchronous	104	54 (55.1%)	50 (66.7%)	
Metachronous	69	44 (44.9%)	25 (33.3%)	
***BRAF* genotyping**				0.008
Wild type	162	96 (97.9%)	66 (88.0%)	
Mutant type	11	2 (2.1%)	9 (12.0%)	
***UGT1A1* genotyping**				0.245
(6,6)	137	82 (83.7%)	55 (73.3%)	
(6,7)	32	14 (14.3%)	18 (24.0%)	
(7,7)	4	2 (2.0%)	2 (2.7%)	
Metastatic sites				0.642
Liver	69	41 (41.8%)	28 (37.3%)	
Lungs	23	15 (15.3%)	8 (10.7%)	
Liver + lungs	15	8 (8.2%)	7 (9.3%)	
Others	66	34 (34.7%)	32 (42.7%)	
No. of metastatic sites				0.546
1	133	77 (78.6%)	56 (74.7%)	
≥2	40	21 (21.4%)	19 (25.3%)	
Subsequent target therapy				0.590
Yes	63	34 (34.7%)	29 (38.7%)	
No	110	64 (65.3%)	46 (61.3%)	
MSI status				<0.001
MSI-H	6	1 (1.0%)	5 (6.7%)	
MSI-L	66	49 (50.0%)	17 (22.7%)	
No tested	62	34 (34.7%)	28 (37.3%)	
No surgery	39	14 (14.3%)	25 (33.3%)	

Values are number (*N*) with percentage in parentheses. Cetu group, cetuximab group; Beva group, bevacizumab group; ECOG PS, the Eastern Cooperative Oncology Group performance status; Left-sided, descending colon + sigmoid colon + rectosigmoid colon + rectum; Right-sided, cecum + ascending colon + transverse colon; Synchronous, metastatic lesions occurred initially; Metachronous, metastatic lesions occurred at least 6 months after resection of the primary lesion; Subsequent target therapy, cetuximab changes to anti-VEGF drug or bevacizumab changes to anti-EGFR drug after progression; MSI, microsatellite instability; MSI-H, microsatellite instability high; MSI-L, microsatellite instability low; No tested, means that the MSI status test has not been performed on the resected specimen; No surgery, means that patients have not received surgery.

Efficacy Outcomes

No significant differences were observed between the cetuximab and bevacizumab groups in ORR (65.3% vs. 62.7%, $p = 0.720$), DCR (92.8% vs. 86.7%, $p = 0.175$), and metastatectomy (36.7% vs. 29.3%, $p = 0.307$) (Table 2). In the cetuximab group, the median PFS was 18.0 months and 29 (29.6%) of 98 patients were progression free at the final follow-up, whereas in the bevacizumab group, the median PFS was 14.0 months and 11 (14.7%) of 75 patients were progression-free at the final follow-up [HR, 0.729; 95% confidence interval (CI), 0.157–1.027; $p = 0.071$] (Fig. 3A). The median OS was 40.0 and 30.0 months in the cetuximab and bevacizumab groups, respectively, and 64 (65.3%) and 31 (41.3%) patients, respectively, were still alive at the final follow-up of the OS data cutoff (HR, 0.643; 95% CI, 0.410–1.008; $p = 0.054$) (Fig. 3B). Although the cetuximab group was not superior to the bevacizumab group in terms of PFS and OS, it seemed to have nonsignificantly higher survival.

We further analyzed the efficacy of subgroups from the viewpoint of sidedness. In the subgroup of left-sided mCRC, no significant difference was noted between the two groups in the ORR (63.3% vs. 70.9%, $p = 0.345$), DCR (91.8% vs. 89.1%, $p = 0.564$), and metastatectomy (37.9% vs. 30.9%, $p = 0.393$) in Table 3. Among the left-sided patients with mCRC, the median PFS was 16.0 months in the cetuximab group and 14.0 months in the bevacizumab group (HR, 0.759; 95% CI, 0.522–1.104; $p = 0.149$) (Fig. 4A), and the median OS was 40.0 months versus 31.0 months (HR, 0.666; 95% CI, 0.403–1.102; $p = 0.114$) (Fig. 4B). Among the right-sided patients with

mCRC, no significant difference was noted between the two groups in DCR (100.0% vs. 80.0%; $p = 0.112$) and metastatectomy (27.3% vs. 25.0%; $p = 0.890$), but ORR was significantly different (81.8% vs. 40.0%; $p = 0.025$) (Table 4). The median PFS was 25.0 and 14.0 months in the cetuximab and bevacizumab groups, respectively (HR, 0.545; 95% CI, 0.221–1.348; $p = 0.189$) (Fig. 5A), and the median OS was 29.0 and 24.0 months, respectively (HR, 0.538; 95% CI, 0.185–1.563; $p = 0.254$) (Fig. 5B). We compared the PFS and OS between the 6TA/6TA group and the 7TA/7TA group after irinotecan dose escalation based on *UGT1A1* genotyping. There were no significant differences in PFS and OS ($p = 0.091$ and $p = 0.799$, respectively).

Efficacy of Target Agent Crossover Therapy

Among the 173 analyzed patients with mCRC, 63 patients (34 from the cetuximab group and 29 from the bevacizumab group) received target therapy crossover. The OS of the cetuximab group was not superior to that of the bevacizumab group (40.0 vs. 35.0 months; HR, 0.734; 95% CI, 0.345–1.560; $p = 0.421$) (Fig. 6). Notably, 25 (73.5%) of 34 patients from the cetuximab group received bevacizumab as the third-line therapy, but 25 (86.2%) of 29 patients from the bevacizumab group received cetuximab as the third-line therapy because of reimbursement.

Safety Measures

For the 173 patients with mCRC, irinotecan-related grade III/IV AEs occurred in 25.5% and 26.7% of patients

Table 2. The Comparison of Efficacy Between the Cetuximab Group and the Bevacizumab Group Under Chi-Square Analysis

Efficacy	N	Cetu Group ($N = 98$)	Beva Group ($N = 75$)	p Value
Response				0.570
Complete response (CR)	3	2 (2.2%)	1 (1.4%)	
Partial response (PR)	108	62 (63.2%)	46 (61.3%)	
Stable disease (SD)	45	27 (27.5%)	18 (24.0%)	
Progressive disease (PD)	17	7 (7.1%)	10 (13.3%)	
ORR				0.720
CR + PR	111	64 (65.3%)	47 (62.7%)	
SD + PD	62	34 (34.7%)	28 (37.3%)	
DCR				0.175
CR + PR + SD	156	91 (92.8%)	65 (86.7%)	
PD	17	7 (7.2%)	10 (13.3%)	
Metastatectomy				0.307
Yes	58	36 (36.7%)	22 (29.3%)	
No	115	62 (63.3%)	53 (70.75)	

Values are number (N) with percentage in parentheses. Cetu group, cetuximab group; Beva group, bevacizumab group; ORR, objective response rates; DCR, disease control rates. All mCRC patients with wild-type *RAS* gene.
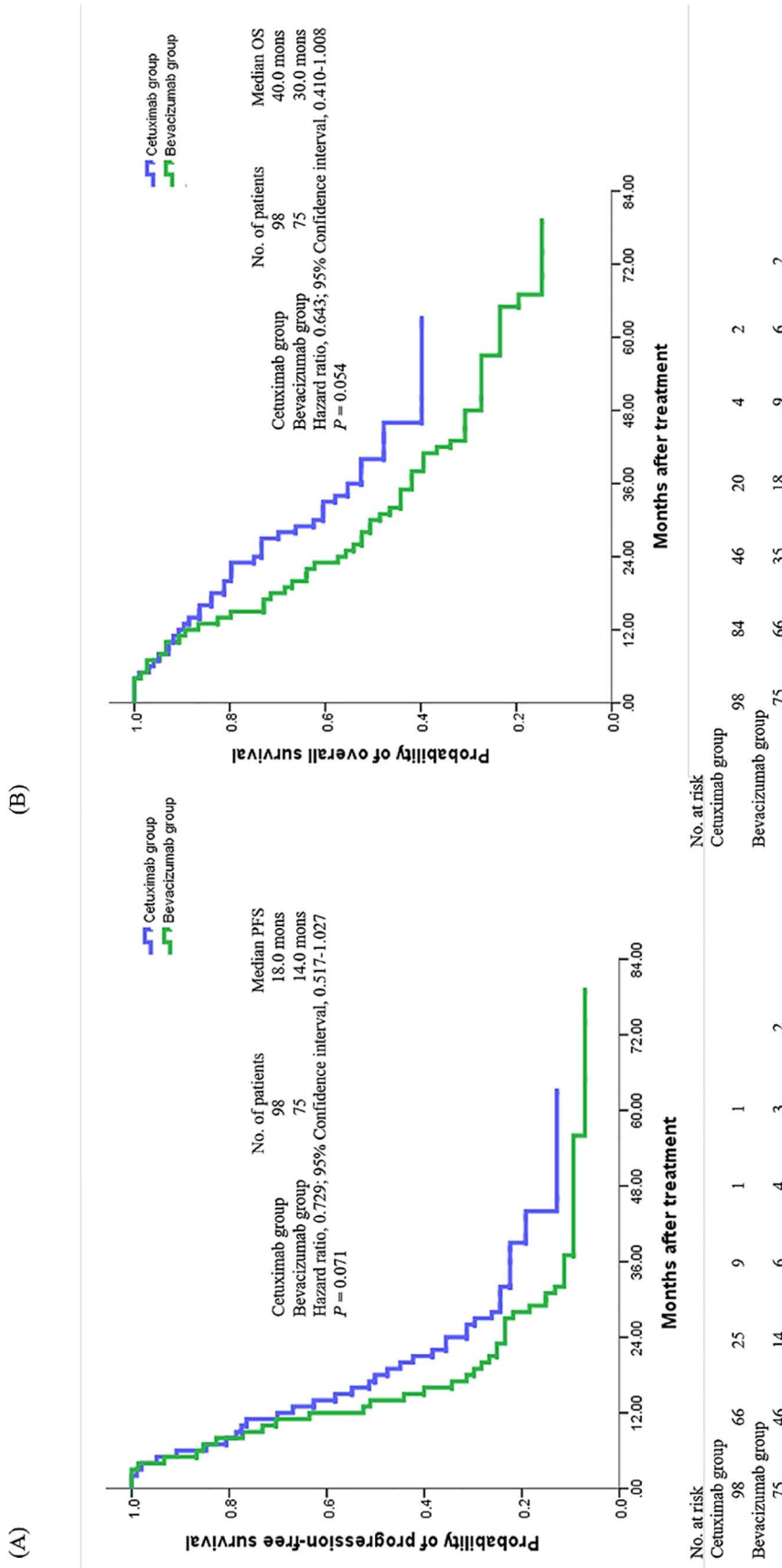
Figure 3. The 173 *RAS* wild-type patients with mCRC including 98 patients with cetuximab plus FOLFIRI (blue line) and 75 patients with bevacizumab plus FOLFIRI (green line). (A) Progression-free survival [18.0 months *vs.* 14.0 months; hazard ratio (HR), 0.729; 95% confidence interval (CI), 0.517–1.027; *p* = 0.071]. (B) Overall survival (40.0 months *vs.* 30.0 months; HR, 0.643; 95% CI, 0.410–1.008; *p* = 0.054).

Table 3. The Comparison of Efficacy for 142 Left-Sided mCRC Patients Between the Cetuximab Group and the Bevacizumab Group Under Chi-Square Analysis

Efficacy	N	Cetu Group (N = 87)	Beva Group (N = 55)	p Value
Response				0.307
Complete response (CR)	2	2 (2.4%)	0 (0.0%)	
Partial response (PR)	92	53 (60.9%)	39 (70.9%)	
Stable disease (SD)	35	25 (28.7%)	10 (18.2%)	
Progressive disease (PD)	13	7 (8.0%)	6 (10.9%)	
ORR				0.345
CR + PR	94	55 (63.3%)	39 (70.9%)	
SD + PD	48	32 (36.7%)	16 (29.1%)	
DCR				0.564
CR + PR + SD	129	80 (91.8%)	49 (89.1%)	
PD	13	7 (8.2%)	6 (10.9%)	
Metastatectomy				0.393
Yes	50	33 (37.9%)	17 (30.9%)	
No	92	54 (62.1%)	38 (69.1%)	

Values are number (N) with percentage in parentheses. Left-sided, descending colon + sigmoid colon + rectosigmoid colon + rectum; Right-sided, cecum + ascending colon + transverse colon; N, number; Cetu group, cetuximab group; Beva group, bevacizumab group; ORR, objective response rates; DCR, disease control rates. All mCRC patients with wild-type *RAS* gene.

in the cetuximab and bevacizumab groups, respectively ($p = 0.658$) (Table 5). The most common severe AEs were neutropenia in both groups (7.1% and 8.0%, respectively). No significant differences were noted in the left-sided patients with mCRC (25.3% vs. 25.5%; $p = 0.871$) and right-sided patients with mCRC (27.3% vs. 30.0%; $p = 0.434$) (Table 6). Neutropenia was still the most common severe AE regardless of sidedness (6.8% vs. 7.3% in left-sided mCRC, and 9.1% vs. 10.0% in right-sided mCRC). No gastrointestinal tract bleeding or perforation related to bevacizumab was found in the bevacizumab group. The AEs less than grade III between the 6TA/6TA and 7TA/7TA groups were compared. In the 6TA/6TA group, the incidences of grade I and grade II AEs were 32.4% and 24.9%, respectively. Simultaneously, the incidences of grade I and grade II AEs were 50.0% and 50.0% in the 7TA/7TA group, respectively. It showed that it was not significant ($p = 0.853$).

DISCUSSION

Despite the advances in medicine, classical chemotherapy remains the first-line treatment of cancer, especially metastatic tumors. Tumor drug resistance and potential side effects are the main limiting factors in cancer treatment. The novel findings of *UGT1A1* genotyping-guided irinotecan dose escalation in the present study were as follows: (1) anti-VEGF inhibitors or anti-EGFR inhibitors plus irinotecan dose escalation as the first-line treatment in mCRC patients seemed to have favorable PFS and OS.

(2) OS seemed not significantly different in the crossover therapy of biologics used in this study under irinotecan dose escalation. (3) Irinotecan dose escalation combined with biologics does not significantly increase the incidence of severe AEs, regardless of vascular endothelial growth factor (VEGF) inhibitor or epidermal growth factor receptor (EGFR) inhibitor.

CRC is a heterogeneous group of tumors at the intertumoral and intratumoral levels. With advances in mCRC treatment over the past 20 years, the median OS has surpassed 40 months in a select patient group with the incorporation of targeted agents into cytotoxic chemotherapy regimens[18,19]. Currently, two promising classes of molecularly targeted compounds have been introduced for the clinical management of mCRC: EGFR antagonists and angiogenesis inhibitors[20]. One large trial, CALGB/SWOG 80405, which compared the cetuximab or bevacizumab plus chemotherapy as first-line therapy in mCRC, revealed that the median OS was 30.0 and 29.0 months and the median PFS was 10.5 and 10.6 months in the cetuximab and bevacizumab groups, respectively[21]. The addition of cetuximab or bevacizumab to FOLFIRI was compared in a phase III study (the FIRE-3 trial) in patients with *KRAS* (exon 2) codon 12/13 wild-type mCRC as first-line therapy; the results demonstrated the median OS was 28.7 and 25.0 months and median PFS was 10.0 and 10.3 months in the two groups, respectively[18]. In our study, the median OS and PFS of the two groups significantly improved, and the severe adverse events (SAEs)
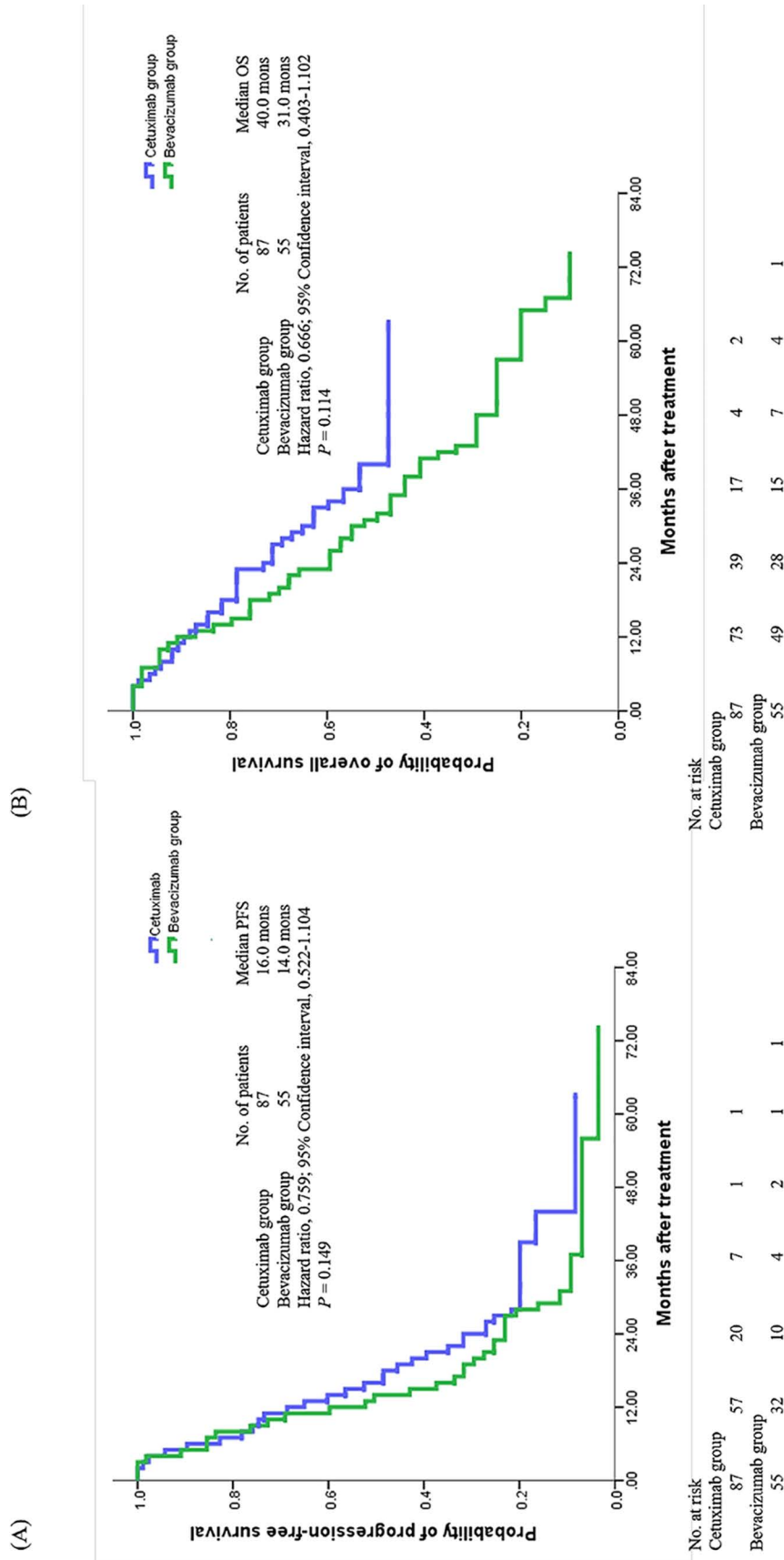
Figure 4. The 142 *RAS* wild-type and left-sided patients with mCRC including 87 patients with cetuximab plus FOLFIRI (blue line) and 55 patients with bevacizumab plus FOLFIRI (green line). (A) Progression-free survival (16.0 months vs. 14.0 months; HR, 0.759; 95% CI, 0.522–1.104; $p = 0.149$). (B) Overall survival (40.0 months vs. 31.0 months; HR, 0.666; 95% CI, 0.403–1.102; $p = 0.114$).

Table 4. The Comparison of Efficacy for 31 Right-Sided mCRC Patients Between the Cetuximab Group and the Bevacizumab Group Under Chi-Square Analysis

Efficacy	N	Cetu Group (N = 11)	Beva Group (N = 20)	p Value
Response				0.078
Complete response (CR)	1	0 (0.0%)	1 (5.0%)	
Partial response (PR)	16	9 (81.8%)	7 (35.0%)	
Stable disease (SD)	10	2 (18.2%)	8 (40.0%)	
Progressive disease (PD)	4	0 (0.0%)	4 (20.0%)	
ORR				0.025
CR + PR	17	9 (81.8%)	8 (40.0%)	
SD + PD	14	2 (18.2%)	12 (60.0%)	
DCR				0.112
CR + PR + SD	27	11 (100.0%)	16 (80.0%)	
PD	4	0 (0.0%)	4 (20.0%)	
Metastatectomy				0.890
Yes	8	3 (27.3%)	5 (25.0%)	
No	23	8 (72.7%)	15 (75.0%)	

Values are number (N) with percentage in parentheses. Cetu group, cetuximab group; Beva group, bevacizumab group; ORR, objective response rates; DCR, disease control rates. All mCRC patients with wild-type *RAS* gene.

were acceptable and did not increase with irinotecan dose escalation. In the FIRE-3 study, the association with longer OS suggests that FOLFIRI plus cetuximab might be the preferred first-line regimen for patients with mCRC with the *KRAS* exon 2 wild-type. Furthermore, a per-protocol analysis of FIRE-3 in 2021 showed that FOLFIRI plus cetuximab resulted in a significantly higher ORR and longer OS compared with FOLFIRI plus bevacizumab among patients with left-sided tumors[22]. In our study, we demonstrated that the cetuximab group has nonsignificantly better PFS and OS than the bevacizumab group. However, ORR was also not significantly different between the groups, so we escalated the dose of irinotecan in the patients with left-sided mCRC.

The sidedness of the colon is an independent prognostic factor for survival in metastatic disease[23]. Two recent meta-analyses have concluded that right-sided colon cancer carries poorer prognosis than left-sided tumors, irrespective of race, adjuvant chemotherapy, number, and quality of studies included[24,25]. A retrospective study suggested that the addition of anti-EGFR antibodies to chemotherapy has no benefit for right-sided metastatic colon cancer[26]. Our study revealed no significant difference in the prognosis regardless of mCRC sidedness that irinotecan dose escalated based on the *UGT1A1* genotype combining with anti-EGFR inhibitor (cetuximab) or anti-VEGF inhibitor (bevacizumab) as the first-line regimen.

Folprecht et al. found a correlation between response rates and metastasectomy in select populations[27]. For metastatic disease, the 2016 ESMO guidelines recommended that the most effective protocol should be based

on the clinical response[28]. Furthermore, two phase II trials demonstrated a higher ORR and resectability rate in the high-dose irinotecan group[29,30]. In our previous prospective study, we demonstrated that irinotecan dose escalation with bevacizumab can improve the ORR and metastasectomy[31]. Similarly, the current study indicated that the escalated-dose group had a better ORR (65.3% vs. 62.7%) and metastasectomy rates (36.7% vs. 29.3%) in the cetuximab and bevacizumab groups, respectively. The potential emergence of cancer cell resistance in EGFR-expressing cancers treated with EGFR inhibitors may explain the refractoriness to these drugs in some cancer patients. VEGF is secreted by cancer cells and regulates tumor-induced endothelial cell proliferation and permeability[32]. Its upregulation in association with resistance to cetuximab has been reported in experimental models[32,33]. In the clinical setting, such phenotypic changes could favor the use of anti-VEGFs as a second-line therapy after the first-line cetuximab therapy. Similarly, our study indicated that 73.5% of patients received bevacizumab as the second-line therapy after failure of first-line cetuximab. Nevertheless, OS was not significantly different in either crossover arm.

Studies have demonstrated dose-dependent associations between the *UGT1A1* 7TA genotype and irinotecan-induced toxicity[34,35], and *UGT1A1* 7TA genotyping is used to reduce dose-limiting neutropenia without affecting its efficacy[36]. Shulman et al. also indicated that the *UGT1A1* 7TA genotype is strongly associated with severe hematological toxicity and poorer survival in irinotecan-treated patients[37]. By contrast, our study emphasizes that
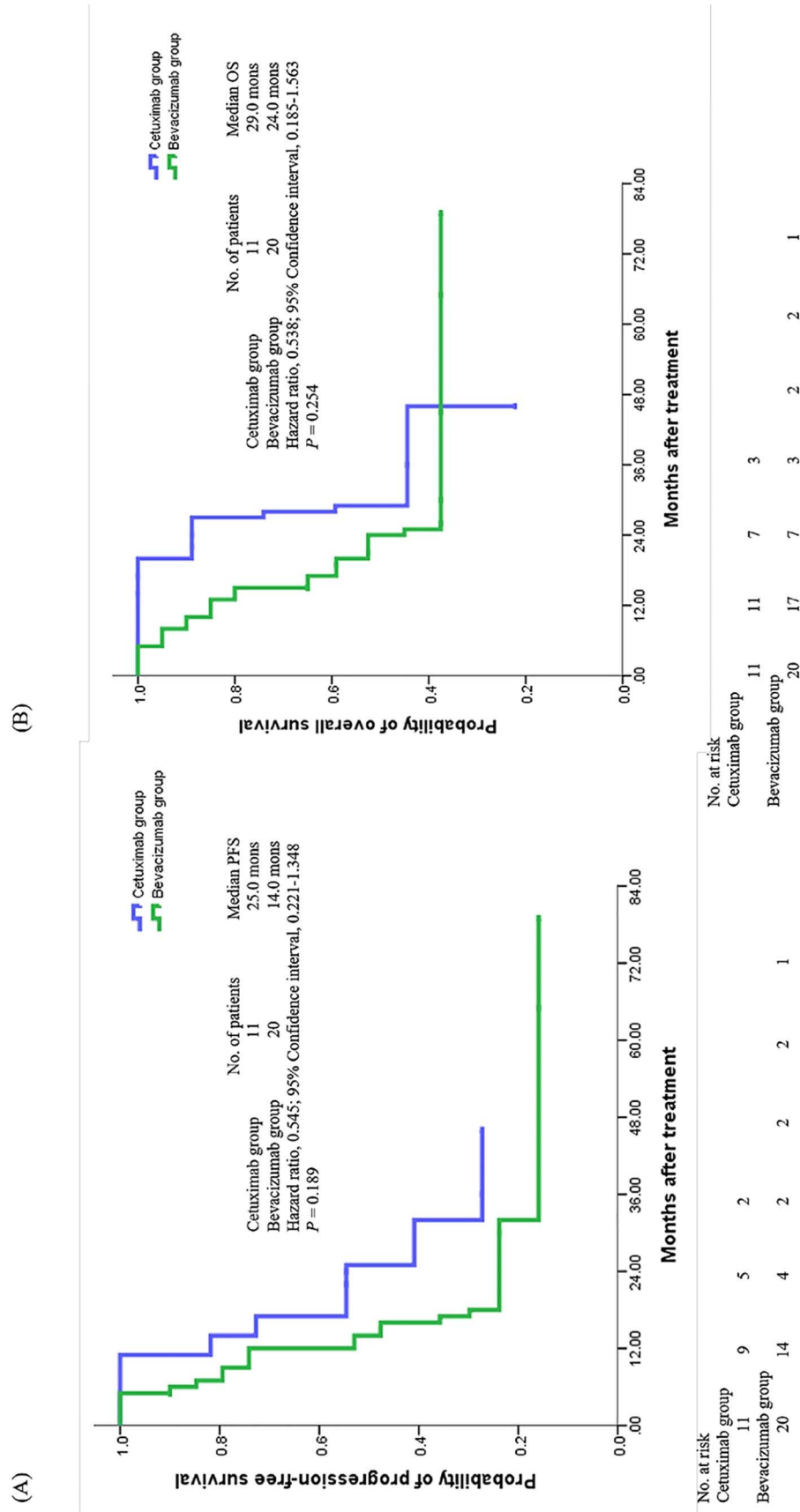
Figure 5. The 31 *RAS* wild-type and right-sided patients with mCRC including 11 patients with cetuximab plus FOLFIRI (blue line) and 20 patients with bevacizumab plus FOLFIRI (green line). (A) Progression-free survival (25.0 months vs. 14.0 months; HR, 0.545; 95% CI, 0.221–1.348; $p = 0.189$). (B) Overall survival (29.0 months vs. 24.0 months; HR, 0.538; 95% CI, 0.815–1.563; $p = 0.254$).
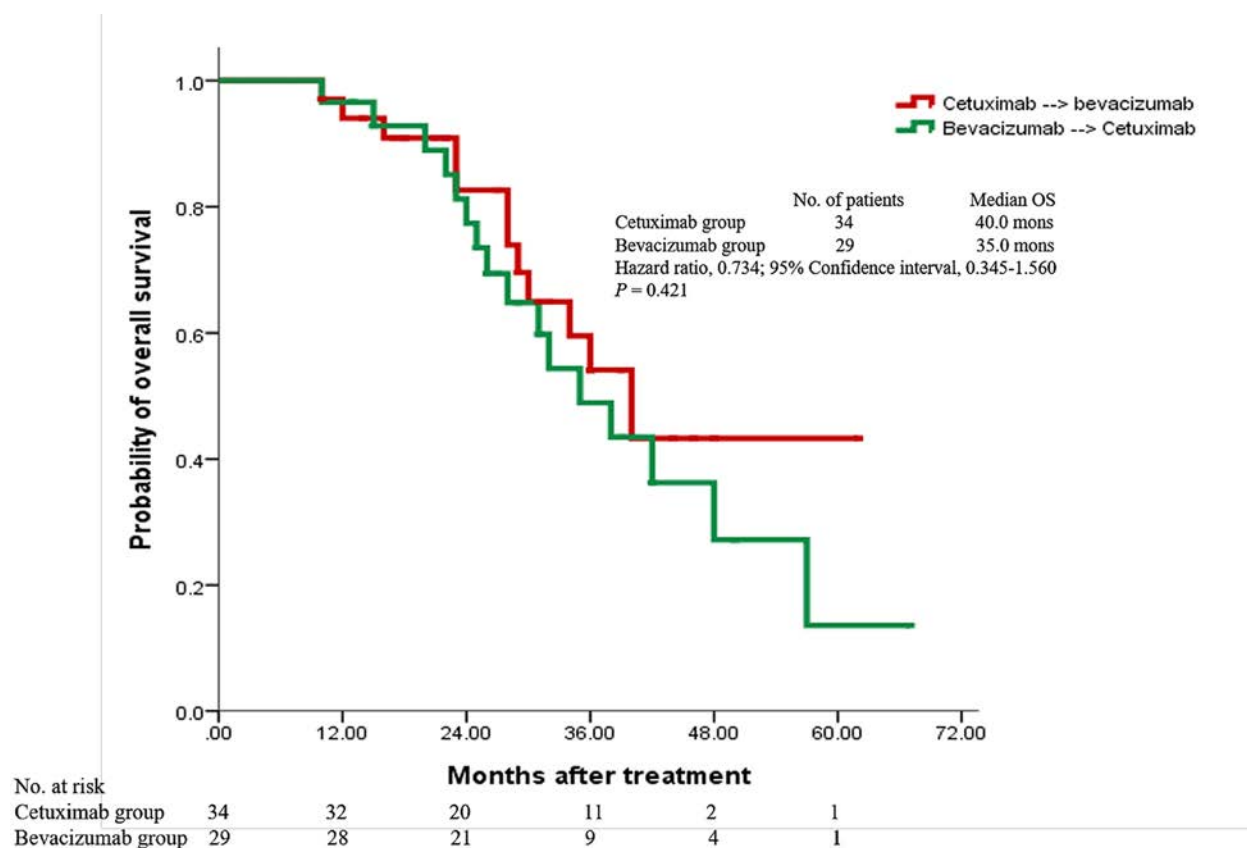
Figure 6. The 63 patients with crossover therapy of target agents including 34 patients from the cetuximab group (red line) and 29 patients from the bevacizumab group (green line). The overall survival was not significantly difference between the two groups (40.0 months vs. 35.0 months; HR, 0.734, 95% CI, 0.345–1.560; $p = 0.421$).

UGT1A1 6TA genotyping for irinotecan dose escalation is relevant to its maximal therapeutic effect. Furthermore, the implication of dose escalation is essential for Asian populations because they inherit the *UGT1A1* 6TA allele more frequently than Caucasian populations[38,39].

Genotyping-guided, patient-specific dose optimization represents an approach to individualize therapy[40]. In the Pan-Asian adapted ESMO consensus guidelines, recommendation 7b showed that *UGT1A1* genotyping remains an option and is recommended to be conducted in patients

Table 5. The Comparison of Severe Adverse Events (≥Grade III) of 173 mCRC Patients Between the Cetuximab Group and Bevacizumab Group

	Cetuximab ($N = 98$)	Bevacizumab ($N = 75$)	*p* Value
Events	25 (25.5%)	20 (26.7%)	0.658
Neutropenia	7 (7.1%)	6 (8.0%)	
Anemia	4 (4.1%)	6 (8.0%)	
Oral mucositis	2 (2.0%)	1 (1.3%)	
Diarrhea	0 (0.0%)	2 (2.6%)	
Paresthesia	3 (3.1%)	0 (0.0%)	
Nausea/vomiting	4 (4.1%)	3 (4.0%)	
Liver function impairment	1 (1.0%)	2 (2.6%)	
Renal function impairment	3 (3.1%)	0 (0.0%)	
Alopecia	1 (1.0%)	0 (0.0%)	

All mCRC patients with wild-type *RAS* gene.

Table 6. The Comparison of Severe Adverse Events (≥Grade III) of 142 Left-Sided mCRC Patients and 31 Right-Sided mCRC Patients Between the Cetuximab Group and Bevacizumab Group

	Cetuximab (N = 87)	Bevacizumab (N = 55)	p Value	Cetuximab (N = 11)	Bevacizumab (N = 20)	p Value
Events	22 (25.3%)	14 (25.5%)	0.871	3 (27.3%)	6 (30.0%)	0.434
Neutropenia	6 (6.8%)	4 (7.3%)		1 (9.1%)	2 (10.0%)	
Anemia	4 (4.6%)	4 (7.3%)		0 (0.0%)	2 (10.0%)	
Oral mucositis	2 (2.3%)	1 (1.8%)		0 (0.0%)	0 (0.0%)	
Diarrhea	0 (0.0%)	1 (1.8%)		0 (0.0%)	1 (5.0%)	
Paresthesia	2 (2.3%)	0 (0.0%)		1 (9.1%)	0 (0.0%)	
Nausea/vomiting	4 (4.6%)	3 (5.4%)		0 (0.0%)	0 (0.0%)	
Liver function impairment	1 (1.1%)	1 (1.8%)		0 (0.0%)	1 (5.0%)	
Renal function impairment	2 (2.3%)	0 (0.0%)		1 (9.1%)	0 (0.0%)	
Alopecia	1 (1.1%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	

Left-sided, descending colon + sigmoid colon + rectosigmoid colon + rectum; Right-sided, cecum + ascending colon + transverse colon. All mCRC patients with wild-type *RAS* gene.

with a suspicion of *UGT1A1* deficiency reflected by low conjugated bilirubin or in patients where an irinotecan dose >180 mg/m^2 per administration is planned. Patients with a favorable *UGT1A1* genotype (homozygous wild 6TA/6TA and heterozygous 6TA/7TA) can be treated with high-dose irinotecan without significant toxicity[15].

The limitations of this study were as follows: (1) it was a retrospective, observational study; (2) some patients were excluded because of noncompletion of six cycles (17 patients) and loss to follow-up over 6 months (10 patients); (3) the *UGT1A1*6 polymorphism may be a potential predictor of severe irinotecan-related neutropenia, but pretherapeutic *UGT1A1*6 genotyping was not performed in this study according to Pan-Asian adapted ESMO consensus guidelines; and (4) because of certain circumstances of the patient, not all of the patients can receive escalated irinotecan dose based on the *UGT1A1* genotyping.

In summary, our study provides evidence that higher-than-recommended doses of irinotecan might be safely implemented in the FOLFIRI regimen plus anti-EGFR inhibitor or anti-VEGF inhibitor for patients with mCRC with *UGT1A1* 6TA/6TA and *UGT1A1* 6TA/7TA genotypes and that pretherapeutic *UGT1A1* genotyping-guided dose adjustment can achieve a more favorable outcome. Therefore, individualized dosing for patients with mCRC receiving a regular dose of irinotecan may be feasible to improve efficacy without increasing toxicity, regardless of sidedness and crossover therapy. However, a further prospective, randomized study is warranted to validate our observational results.

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