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Impact of *UGT1A1* genotype on the efficacy and safety of irinotecan-based chemotherapy in metastatic colorectal cancer

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Abbreviations: AE, adverse event; AXEPT, Asian XELIRI Project; CI, confidence interval; DHH, double heterozygous or homozygous; FOLFIRI, fluorouracil plus leucovorin with irinotecan; HR, hazard ratio; mCRC, metastatic colorectal cancer; mXELIRI, modified capecitabine plus irinotecan; OS, overall survival; PFS, progression-free survival; SH, single heterozygous.

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Abstract

The phase III AXEPT study showed the noninferiority of modified capecitabine plus irinotecan (mXELIRI) with or without bevacizumab relative to fluorouracil, leucovorin, and irinotecan (FOLFIRI) with or without bevacizumab as a second-line treatment for metastatic colorectal cancer. We evaluated the associations between the *UGT1A1* genotype linked to adverse events—caused by irinotecan—and the efficacy and safety of mXELIRI and FOLFIRI. The *UGT1A1* genotype was prospectively determined and patients were categorized into three groups according to WT (*1/*1), single heterozygous (SH; *28/*1 or *6/*1), and double heterozygous or homozygous (DHH; *28/*28, *6/*6, or *28/*6). Overall survival (OS), progression-free survival, response rate, and safety were assessed. The *UGT1A1* genotype was available in all 650 randomized patients (WT, 309 [47.5%]; SH, 291 [44.8%]; DHH, 50 [7.7%]). The median OS was 15.9, 17.7, and 10.6 months in the WT, SH, and DHH groups, respectively, with an adjusted hazard ratio (HR) of 1.53 (95% confidence interval [CI], 1.12-2.09; $P = .008$) for DHH vs WT or SH. The median OS in the mXELIRI and FOLFIRI arms was 18.1 vs 14.3 months (HR 0.80; 95% CI, 0.62-1.03) in the WT group, 16.3 vs 18.3 months (HR 1.04; 95% CI, 0.79-1.36) in the SH group, and 13.0 vs 9.1 months (HR 0.71; 95% CI, 0.39-1.31) in the DHH group, respectively. Modified capecitabine plus irinotecan with or without bevacizumab could be a standard second-line chemotherapy in terms of efficacy and safety regardless of the *UGT1A1* genotype.

KEYWORDS
capecitabine, colorectal cancer, irinotecan, *UGT1A1*, XELIRI

1 | INTRODUCTION

The combination of fluorouracil with irinotecan (FOLFIRI) is widely accepted as a standard cytotoxic chemotherapy regimen for mCRC, either as a first- or second-line treatment.[1,2] Additionally, FOLFIRI combined with a molecular targeted agent (ie, bevacizumab, ramucirumab, aflibercept, cetuximab, panitumumab) is commonly selected as a second-line therapeutic option.[3-6]

Irinotecan is converted to its active metabolite (SN-38) by carboxylesterase and glucuronidated to SN-38G by UPD-glucuronosyltransferase encoded by the *UGT1A1* gene. As such, patients who are heterozygous or homozygous for *UGT1A1*28* and *UGT1A1*6* polymorphisms have reduced ability to form SN-38G and delayed SN-38 metabolism compared with those who do not carry these polymorphisms.[7] The use of irinotecan in patients with such polymorphisms has been associated with the occurrence of more serious AEs such as neutropenia or diarrhea.[8-10] However, the appropriate dose and efficacy of irinotecan for patients homozygous for *UGT1A1*28* or *6, or heterozygous for both *UGT1A1*28* and *6 is yet to be determined. The prescription information for irinotecan as approved by the US FDA states that "when administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of irinotecan should be considered for patients known to be homozygous for the *UGT1A1*28* allele." Importantly, Toffoli et al suggested an association between *UGT1A1*28* homozygosity and greater efficacy, despite more severe toxicity; however, other studies failed to find any significant impact of *UGT1A1* genotypes on survival.[8,11-13] As such, an individualized dose for irinotecan in this patient population has yet to be established by large-scale prospective clinical studies.

Recently, the phase III AXEPT study found the noninferiority of mXELIRI with or without bevacizumab relative to FOLFIRI with or without bevacizumab in terms of OS as a second-line treatment for patients with mCRC.[14] In the AXEPT study, *UGT1A1* genotyping was mandatory at the screening stage. Here, we report the results of a preplanned analysis of the AXEPT study that evaluated the associations between the *UGT1A1* genotype and the safety and efficacy of irinotecan-based regimens.

2 | MATERIALS AND METHODS

2.1 | Patients

The detailed eligibility criteria for this study have been previously reported.[14] In brief, patients aged 20 years or older with histologically confirmed mCRC, ECOG performance status of 0-2, adequate organ function, and disease progression or intolerance to

first-line chemotherapy were eligible for enrollment. The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was reviewed and approved by the institutional review board of each study site prior to the initiation of the study. All patients provided written informed consent.

2.2 | Study design and administration of drugs

Patients were centrally randomly assigned at a 1:1 ratio to receive either FOLFIRI with or without bevacizumab or mXELIRI with or without bevacizumab. The FOLFIRI regimen consisted of irinotecan 180 mg/m^2 plus leucovorin 400 mg/m^2 plus fluorouracil 400 mg/m^2 bolus, all on day 1, followed by fluorouracil 2400 mg/m^2 given as a 46-hour continuous infusion with or without bevacizumab 5 mg/kg on day 1, repeated every 2 weeks. The mXELIRI regimen consisted of irinotecan 200 mg/m^2 on day 1, plus capecitabine 800 mg/m^2 twice daily on days 1-14 with or without bevacizumab 7.5 mg/kg on day 1, repeated every 3 weeks. A reduced starting dose of irinotecan of 150 mg/m^2 was given in patients identified as homozygous for *UGT1A1*6* or *UGT1A1*28* or double heterozygous for both *UGT1A1*6* and *UGT1A1*28*, regardless of the treatment arm. Detailed treatment modifications were as previously described.[14]

2.3 | *UGT1A1* genotyping

The *UGT1A1* genotype was determined using the Invader assay (Sekisui Medical Co. Ltd.), the TaqMan assay and PCR direct sequencing (DNA Link, Inc), and the *UGT1A1* Genotype Detection Kit (Shanghai Yuanqi Bio-Pharmaceutical Co. Ltd.). The *UGT1A1*28* polymorphism has seven TA repeats in the promoter region (TATA) instead of the six repeats in WT *UGT1A1*; thus, the genotypes were designated as WT (*UGT1A1*28* 6/6), heterozygous (*UGT1A1*28* 6/7), and homozygous (*UGT1A1*28* 7/7). Similarly, the *UGT1A1*6* polymorphism involves an amino acid substitution in exon 1 (211G>A); as such, the genotypes were designated as WT (*UGT1A1*6* G/G), heterozygous (*UGT1A1*6* G/A), and homozygous (*UGT1A1*6* A/A). Accordingly, we stratified patients into three groups: WT (*UGT1A1*6* G/G or **28* 6/6), SH (*UGT1A1*6* G/G and **28* 6/7, or *UGT1A1*6* G/A and **28* 6/6), and DHH (*UGT1A1*6* G/A and **28* 6/7, *UGT1A1*6* A/A, or **28* 7/7).

2.4 | End-points and assessments

The end-points of this study were OS, PFS, objective response rate, and safety. Tumor responses were assessed according to the RECIST guideline version 1.1. Overall survival was defined as the time from the date of randomization to death from any cause. Progression-free survival was defined as the time from the date of randomization to disease progression or death from any cause. Adverse events were assessed according to the NCI's Common Terminology Criteria for Adverse Events version 4.0. Relative dose intensity was calculated as the total dose of each drug actually administered divided by the planned dose during the protocol treatment.

2.5 | Statistical analysis

Survival end-points were estimated using the Kaplan-Meier method and compared with log-rank test. The HRs and associated 95% CIs for the comparison of OS and PFS between different *UGT1A1* genotypes were calculated using the Cox proportional hazards models adjusted by country (Japan vs South Korea vs China), ECOG performance status (0-1 vs 2), number of metastatic sites (1 vs >1), previous use of oxaliplatin treatment (yes vs no), and concurrent bevacizumab treatment (with vs without). The objective response rate and incidences of AEs were assessed with the χ^2 test and Fisher's exact test, respectively. The significance level was set to .05. All statistical analyses were carried out using SAS versions 9.3 and 9.4.

3 | RESULTS

3.1 | Patients

In total, 650 patients were enrolled between December 2, 2013 and August 13, 2015, and the cut-off for data accrual was July 28, 2017. Nine patients were identified as ineligible after enrolment (five for recurrence more than 6 months after last dose of adjuvant chemotherapy, and one each for use of aspirin for more than 325 mg/d, baseline hemoglobin less than 9.0 g/dL, baseline total bilirubin more than 1.5 mg/dL, and active gastrointestinal bleeding) and 21 patients did not receive any study treatment. The dataset for full analysis used for the efficacy end-point included all 650 patients, of whom 620 received at least one dose on protocol and were included in the safety analysis. The *UGT1A1* genotypes of the patients were as follows: WT (n = 309; 47.5%), SH (n = 291; 44.8%), and DHH (n = 50; 7.7%) (Figure 1); the proportions of patients carrying the different genetic polymorphisms were similar among different countries (Table S1). The baseline demographics and disease characteristics were generally well-balanced among the three groups, with the exception of the higher percentages of patients with right-sided tumors and those without liver metastasis in the DHH group (Tables 1 and S2).

3.2 | Treatment efficacies according to *UGT1A1* genotypes

During a median follow-up of 15.8 months (interquartile range, 8.7-24.9 months), the median PFS was 7.1 (95% CI, 6.5-8.3), 8.6 (95% CI, 7.3-9.9), and 5.3 (95% CI, 3.9-9.9) months in the WT, SH, and DHH

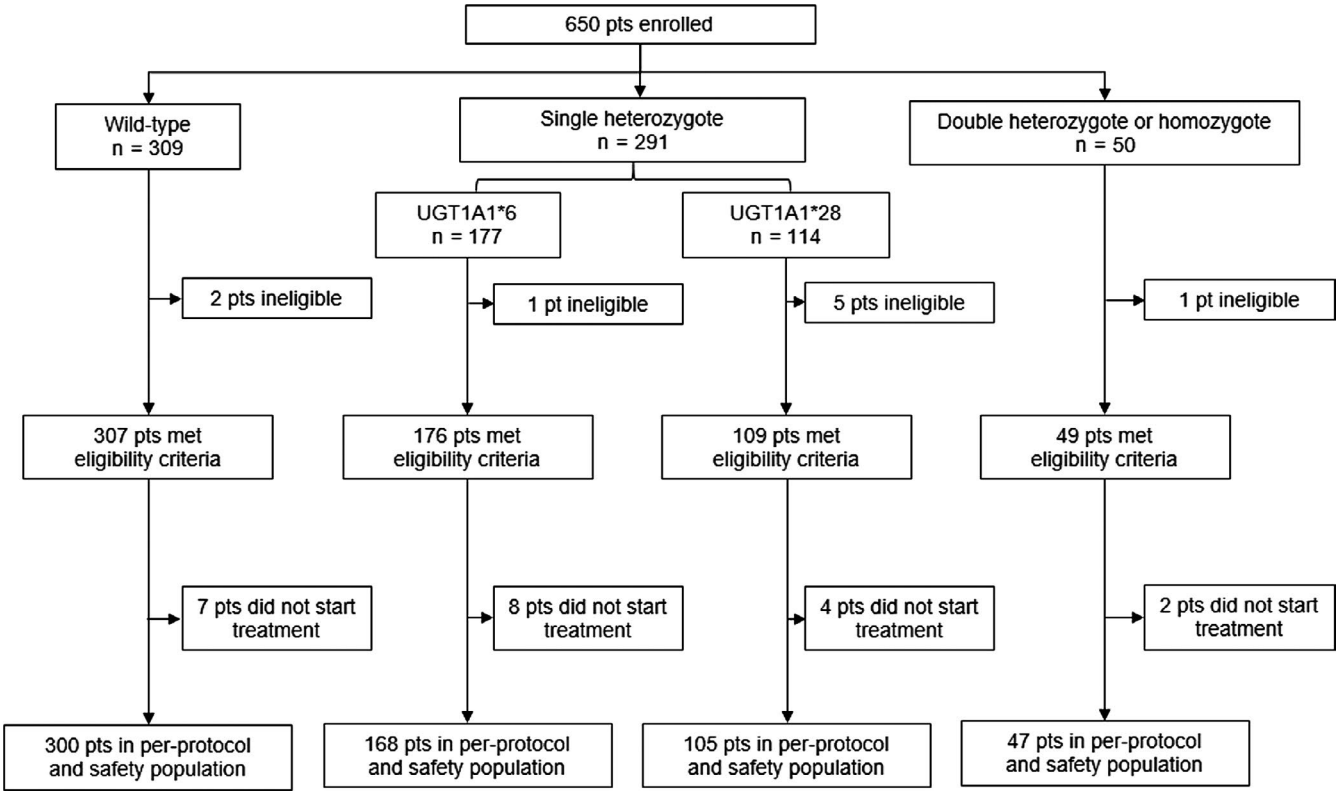


FIGURE 1 Patient flow diagram in the Asian XELIRI Project (AXEPT) study of modified capecitabine plus irinotecan with or without bevacizumab or fluorouracil, leucovorin, and irinotecan with or without bevacizumab as second-line treatment for metastatic colorectal cancer

groups, respectively (Figure 2A). During the same period, the median OS was 15.9 (95% CI, 14.5-18.1), 17.7 (95% CI, 15.5-19.7), and 10.6 (95% CI, 8.0-14.1) months in the WT, SH, and DHH groups, respectively (Figure 2B). The adjusted HR for OS in the DHH group vs WT or SH groups was 1.53 (95% CI, 1.12-2.09; $P = .008$).

3.3 | Treatment efficacies in FOLFIRI and mXELIRI arms according to *UGT1A1* genotypes

The median PFS of patients in the mXELIRI and FOLFIRI arms was 8.3 vs 6.8 months (HR 0.88; 95% CI, 0.70-1.12; $P = .299$) in the WT group, 8.7 vs 8.8 months (HR 1.06; 95% CI, 0.83-1.35; $P = .626$) in the SH group, and 6.5 vs 4.8 months (HR 0.73; 95% CI, 0.41-1.32; $P = .295$) in the DHH group (Figure 3A). The median OS in the mXELIRI and FOLFIRI arms was 18.1 vs 14.3 months (HR 0.80; 95% CI, 0.62-1.03; $P = .077$) in the WT group, 16.3 vs 18.3 months (HR 1.04; 95% CI, 0.79-1.36; $P = .805$) in the SH group, and 13.0 vs 9.1 months (HR 0.71; 95% CI, 0.39-1.31; $P = .271$) in the DHH group (Figure 3B). No differences were observed in PFS and OS for each treatment among *UGT1A1*6* and *UGT1A1*28* (Figure S1). Among the 620 evaluable patients, the proportion of patients achieving an objective response was lower in the FOLFIRI arm than in the mXELIRI arm of the DHH group (response rate 0% vs 17.4%, $P = .033$) (Tables 2 and S3).

3.4 | Safety and treatment intensity in FOLFIRI and mXELIRI arms

The safety profiles of FOLFIRI and mXELIRI have been previously reported.[14] The most common grade 3-4 AEs of special interest in the FOLFIRI and mXELIRI arms were neutropenia (42.9% and 16.8%, respectively) and diarrhea (3.2% and 7.1%, respectively). Adverse events tended to be similar regardless of the *UGT1A1* genotype. Overall, grade 3-4 neutropenia was more common in the FOLFIRI arm than in the mXELIRI arm (35.9%, 50.4%, and 45.8% vs 17.0%, 15.7%, and 21.7%, respectively, in the WT, SH, and DHH groups) (Table 3). Grade 3-4 neutropenia was more likely to occur during the earlier cycles (up to #4) than during later cycles in both treatment groups. Especially with the FOLFIRI regimen, grade 3-4 neutropenia developed more frequently during the earlier cycles in the DHH group than in the WT and SH groups (Table S4). Grade 3-4 diarrhea was more common in the mXELIRI arm than the FOLFIRI arm (Table 3). Grade 3-4 neutropenia and diarrhea tended to be more common in patients with the *UGT1A1*6* genotype than those with the *UGT1A1*28* genotype (Table S5).

In the FOLFIRI arm, the relative dose intensity of irinotecan was lower in the DHH group (62.1%) than in the WT (74.6%) and SH (73.1%) groups. In the mXELIRI arm, the relative dose intensities of irinotecan were 85.7%, 84.6%, and 86.1% in the WT, SH, and DHH groups, respectively (Table 4). Discontinuation of study treatment for unacceptable toxicity was more common among DHH patients treated with FOLFIRI (16.7%)

TABLE 1 Baseline characteristics of patients with metastatic colorectal cancer, grouped according to *UGT1A1* genotype (WT, single heterozygous [SH], or double heterozygous or homozygous [DHH])

	Patients, n (%)			
	WT (n = 309)	SH (n = 291)	DHH (n = 50)	*P*[a]
Age, median (range), y	60.0 (24-85)	61.0 (27-84)	62.0 (25-78)	.5303[b]
Treatment arm				
FOLFIRI with or without BV	158 (51.1)	140 (48.1)	26 (52.0)	.7232
XELIRI with or without BV	151 (48.9)	151 (51.9)	24 (48.0)	
Sex				
Male	183 (59.2)	174 (59.8)	28 (56.0)	.8806
Female	126 (40.8)	117 (40.2)	22 (44.0)	
Country				
Korea	107 (34.6)	103 (35.4)	18 (36.0)	.9784
China	77 (24.9)	66 (22.7)	12 (24.0)	
Japan	125 (40.5)	122 (41.9)	20 (40.0)	
ECOG PS				
0-1	307 (99.4)	288 (99.0)	49 (98.0)	.6287
2	2 (0.6)	3 (1.0)	1 (2.0)	
Primary tumor location[c]				
Right side	78 (25.2)[d]	69 (24.2)[e]	17 (34.0)	
Left side	237 (76.7)[d]	221 (77.5)[e]	33 (66.0)	
No. of metastatic sites				
1	107 (34.6)	112 (38.5)	16 (32.0)	.5035
>1	202 (65.4)	179 (61.5)	34 (68.0)	
Adjuvant chemotherapy				
Yes	75 (24.3)	73 (25.1)	11 (22.0)	.8908
No	234 (75.7)	218 (74.9)	39 (78.0)	
Prior oxaliplatin				
Yes	300 (97.1)	285 (97.9)	49 (98.0)	.7789
No	9 (2.9)	6 (2.1)	1 (2.0)	
Prior anti-EGFR Ab therapy				
Yes	48 (15.5)	49 (16.8)	8 (16.0)	.9097
No	261 (84.5)	242 (83.2)	42 (84.0)	
Prior BV				
Yes	89 (28.8)	85 (29.2)	16 (32.0)	.8767
No	220 (71.2)	206 (70.8)	34 (68.0)	
Concomitant BV in this study				
Yes	256 (82.8)	243 (83.5)	42 (84.0)	.9659
No	53 (17.2)	48 (16.5)	8 (16.0)	
KRAS status				
WT	121 (39.2)	125 (43.0)	17 (34.0)	.4395
Mutant	101 (32.7)	77 (26.5)	16 (32.0)	
Unknown	87 (28.2)	89 (30.6)	17 (34.0)	

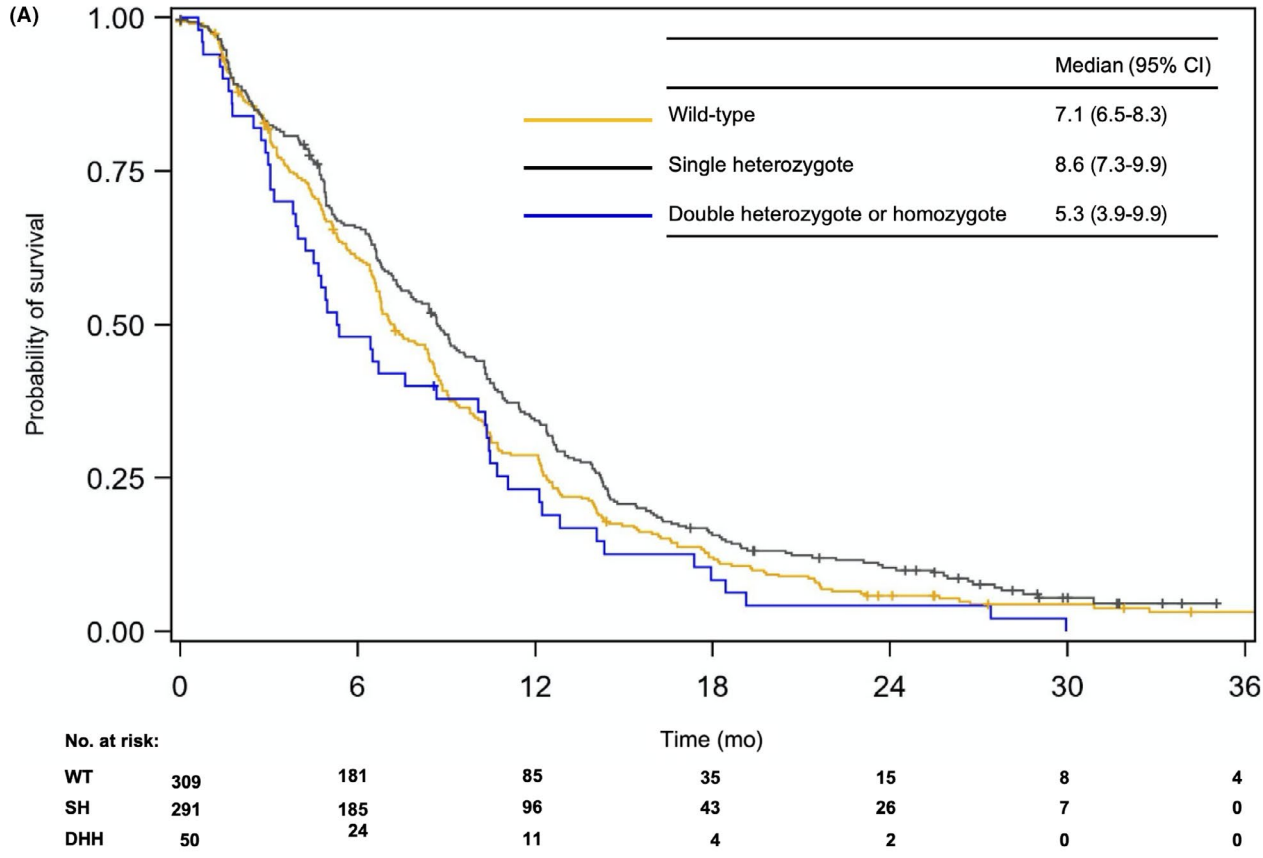
Abbreviations: BV, bevacizumab; EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin, plus irinotecan; PS, performance status; XELIRI, capecitabine plus irinotecan.

[a]χ^2 test (except for [b]one-way ANOVA); comparing proportion of each characteristic.

[c]No comparison made because of duplicate aggregation.

[d]Total numbers do not match as six patients had duplicates for WT.

[e]Total numbers do not match as five patients had with duplicates for SH.



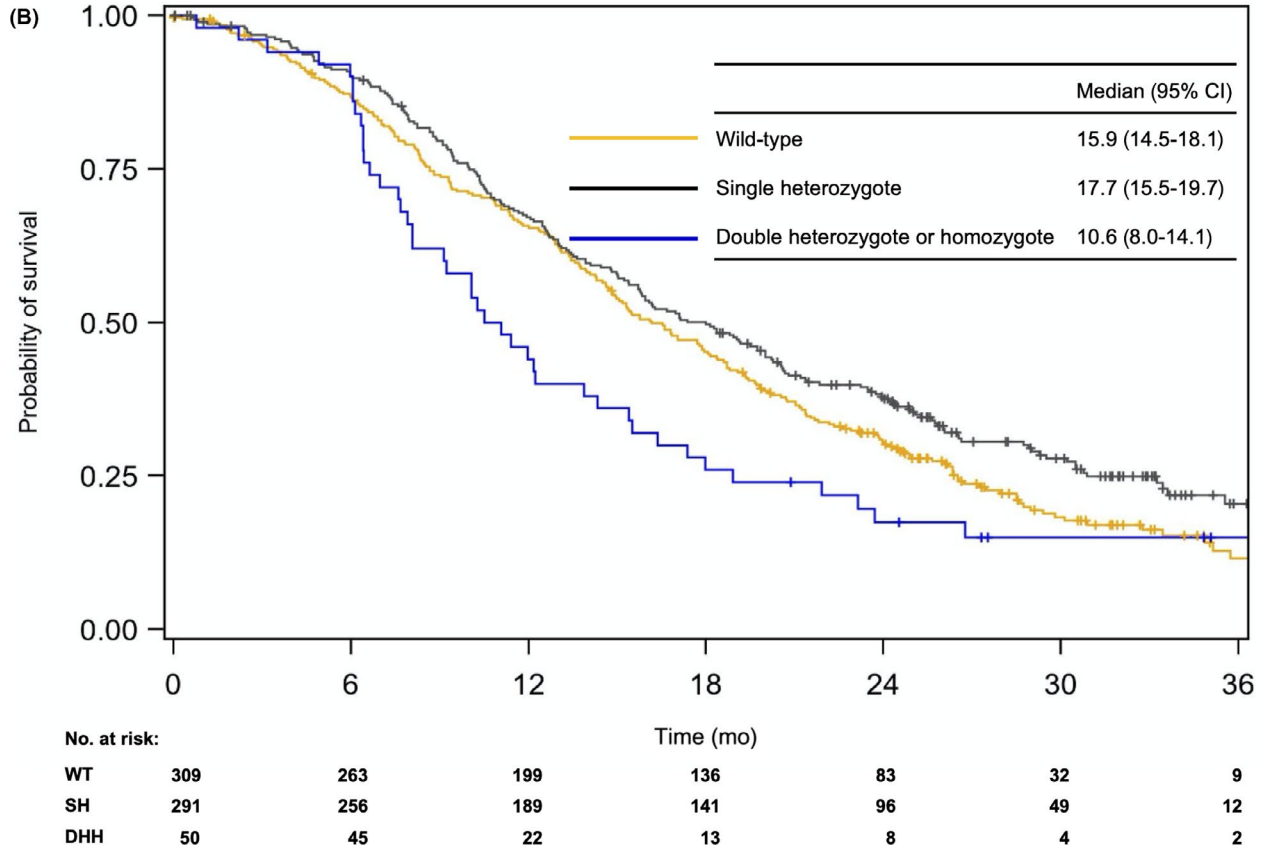
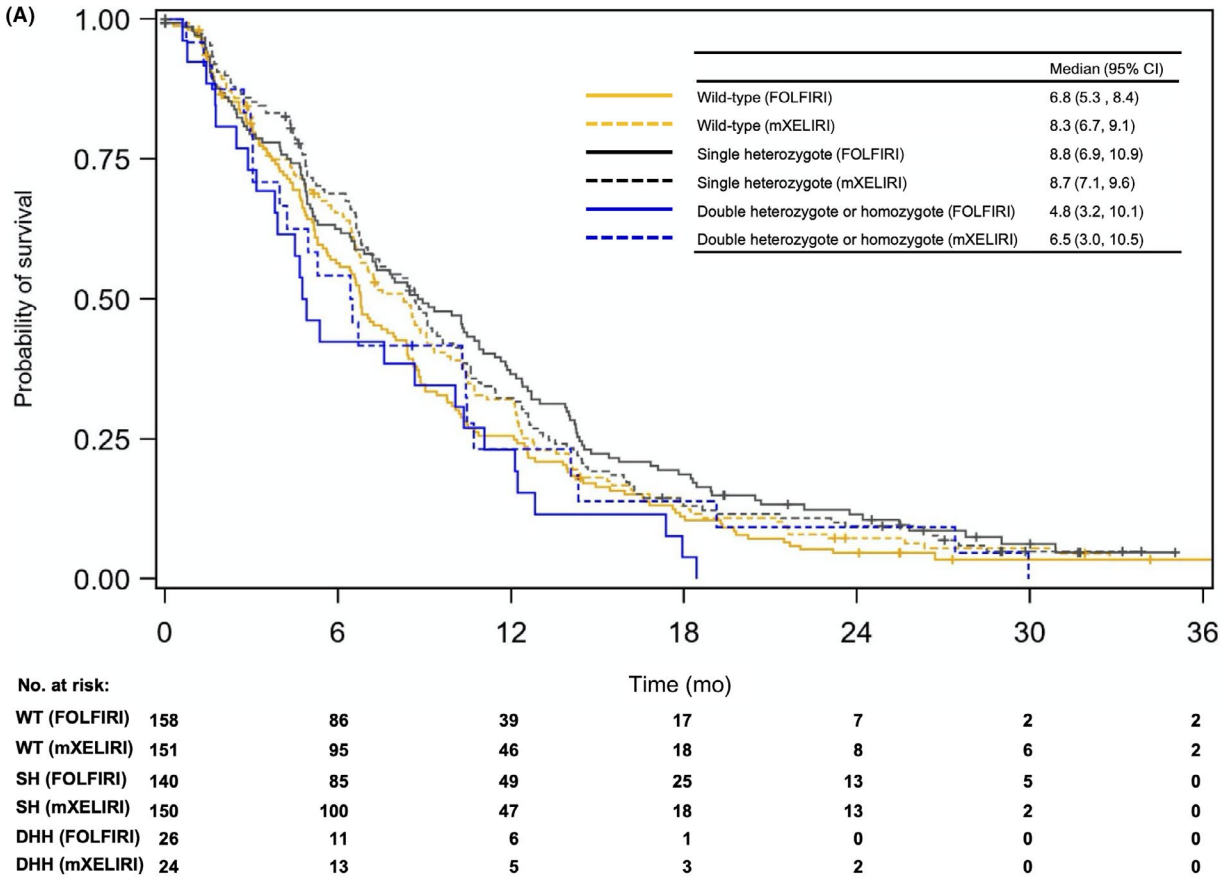


FIGURE 2 Kaplan-Meier analysis of (A) progression-free survival and (B) overall survival in patients with metastatic colorectal cancer according to *UGT1A1* genotypes. CI, confidence interval; DHH, double heterozygous or homozygous; SH, single heterozygous



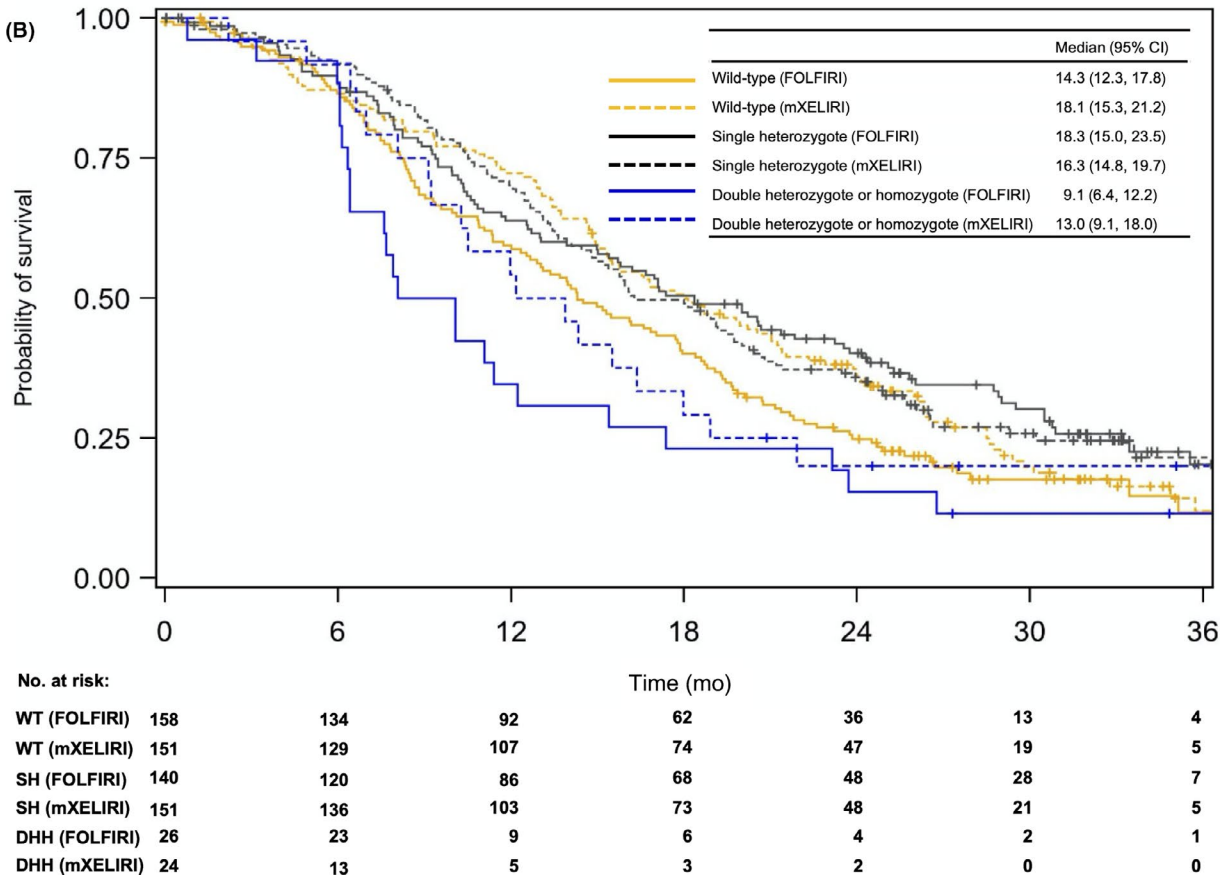


FIGURE 3 Kaplan-Meier analysis of (A) progression-free survival and (B) overall survival in patients with metastatic colorectal cancer according to *UGT1A1* genotypes and treatment groups. CI, confidence interval; DHH, double heterozygous or homozygous; FOLFIRI, fluorouracil, leucovorin, plus irinotecan; SH, single heterozygous; mXELIRI, modified capecitabine plus irinotecan

TABLE 2 Response rates in patients with metastatic colorectal cancer, grouped according to *UGT1A1* genotype (WT, single heterozygous [SH], or double heterozygous or homozygous [DHH]) and treatment (fluorouracil, leucovorin, plus irinotecan [FOLFIRI] or capecitabine plus irinotecan [XELIRI])

	Patients					
	WT		SH		DHH	
	FOLFIRI (n = 153)	mXELIRI (n = 147)	FOLFIRI (n = 133)	mXELIRI (n = 140)	FOLFIRI (n = 24)	mXELIRI (n = 23)
Complete response	2 (1.3)	8 (5.4)	0 (0.0)	5 (3.6)	0 (0.0)	0 (0.0)
Partial response	28 (18.3)	28 (19.0)	27 (20.3)	30 (21.4)	0 (0.0)	4 (17.4)
Stable disease	88 (57.5)	76 (51.7)	63 (47.4)	77 (55.0)	15 (62.5)	12 (52.2)
Progressive disease	29 (19.0)	26 (17.7)	32 (24.1)	18 (12.9)	6 (25.0)	6 (26.1)
Not evaluable	6 (3.9)	9 (6.1)	11 (8.3)	10 (7.1)	3 (12.5)	1 (4.3)
Objective response	30 (19.6)	36 (24.5)	27 (20.3)	35 (25.0)	0 (0.0)	4 (17.4)
	$P = .308$		$P = .354$		$P = .033$	

Note: Data are shown as n (%).

TABLE 3 Grade 3 or 4 toxicities in the safety population of study patients with metastatic colorectal cancer, grouped according to *UGT1A1* genotype (WT, single heterozygous [SH], or double heterozygous or homozygous [DHH]) and treatment (fluorouracil, leucovorin, plus irinotecan [FOLFIRI] or modified capecitabine plus irinotecan [mXELIRI])

	FOLFIRI			mXELIRI		
	WT (n = 153)	SH (n = 133)	DHH (n = 24)	WT (n = 147)	SH (n = 140)	DHH (n = 23)
Any	73 (47.7)	78 (58.6)	15 (62.5)	49 (33.3)	47 (33.6)	9 (39.1)
Leucopenia	13 (8.5)	16 (12.0)	6 (25.0)	7 (4.8)	7 (5.0)	2 (8.7)
Neutropenia	55 (35.9)	67 (50.4)	11 (45.8)	25 (17.0)	22 (15.7)	5 (21.7)
Anemia	7 (4.6)	5 (3.8)	1 (4.2)	3 (2.0)	4 (2.9)	3 (13.0)
Thrombocytopenia	1 (0.7)	0 (0.0)	0 (0.0)	2 (1.4)	1 (0.7)	1 (4.3)
Febrile neutropenia	9 (5.9)	3 (2.3)	1 (4.2)	2 (1.4)	6 (4.3)	2 (8.7)
Nausea	4 (2.6)	3 (2.3)	2 (8.3)	4 (2.7)	6 (4.3)	3 (13.0)
Diarrhea	2 (1.3)	8 (6.0)	0 (0.0)	7 (4.8)	15 (10.7)	0 (0.0)
Mucositis	5 (3.3)	4 (3.0)	0 (0.0)	2 (1.4)	2 (1.4)	1 (4.3)
Fatigue	4 (2.6)	2 (1.5)	2 (8.3)	5 (3.4)	5 (3.6)	0 (0.0)
Hand-foot syndrome	1 (0.7)	0 (0.0)	0 (0.0)	3 (2.0)	2 (1.4)	1 (4.3)

Note: Data are shown as n (%).

when compared with mXELIRI (8.7%). After discontinuation of protocol treatment, third-line chemotherapy was given to 60.1% of WT patients in the FOLFIRI arm and 58.3% of WT patients in the mXELIRI arm. These values were 55.0% and 62.3% in the SH group, and 65.4% and 54.2% in the DHH group, for the FOLFIRI and mXELIRI arms, respectively.

4 | DISCUSSION

Here, we showed that mXELIRI with or without bevacizumab is non-inferior to FOLFIRI with or without bevacizumab in terms of OS, regardless of the *UGT1A1* genotype. No significant differences were found in the PFS and objective response between the treatment groups regardless of *UGT1A1* genotypes. Adverse events such as neutropenia were less common in the mXELIRI arm than in the FOLFIRI arm across all *UGT1A1* genotypes. Our results suggest that mXELIRI with bevacizumab could become one of the standard treatments for colorectal cancer as a second-line treatment regardless of the *UGT1A1* genotype.

Another interesting finding from the current study is that patients with the DHH genotype had significantly worse OS than patients with WT or SH genotypes, especially in the FOLFIRI arm. The same trends were observed for objective response rate and PFS. This is in contrast to the results of the study by Toffoli et al,[8] which reported that FOLFIRI consisting of irinotecan 180 mg/m^2 as the first-line chemotherapy achieved a higher response rate (67%) in patients homozygous

TABLE 4 Relative dose intensity in patients with metastatic colorectal cancer, grouped according to *UGT1A1* genotype and treatment regimen

	WT		SH				DHH			
	FOLFIRI, %	mXELIRI, %	FOLFIRI, %	P^a	mXELIRI, %	P^a	FOLFIRI, %	P^a	mXELIRI, %	P^a
Irinotecan	74.6	85.7	73.1	*.749*	84.6	*.478*	62.1	*.143*	86.1	*.928*
Capecitabine	–	85.7	–		85.5	*.669*	–		85.2	*.632*
5-FU bolus	89.8	–	87.8	*.792*	–		96.3	*.752*	–	
5-FU infusion	74.3	–	73.8	*.922*	–		62.2	*.184*	–	

Abbreviations: 5-FU, 5-fluorouracil; DHH, double heterozygote or homozygote; FOLFIRI, fluorouracil, leucovorin, plus irinotecan; SH, single heterozygote; XELIRI, capecitabine plus irinotecan.

[a]Wilcoxon rank sum test for the same WT and same arm. The italic values were no significant differences.

for *UGT1A1*28* than WT (40%) or SH (42%) patients. Such a difference in the efficacy is likely due to different ethnicity, as homozygosity for *UGT1A1*6* was observed exclusively in Asian populations and the frequency of *UGT1A1*6* is higher than *UGT1A1*28* in Asian populations.[15,16] Regarding the *UGT1A1*6* and **28* alleles, our findings revealed that more patients with the *UGT1A1*6* genotype developed grade 3-4 neutropenia and diarrhea compared with patients carrying the *UGT1A1*28* genotype. A dose-finding study of irinotecan monotherapy with 150 mg/m^2 in Japanese patients with *UGT1A1* SH and/or DHH genotype showed dose reductions or delayed treatment in subsequent cycles because of grade 3 or 4 neutropenia.[17] In fact, compared with patients with other genotypes, DHH patients were more likely to develop grade 3-4 neutropenia during the early treatment cycles, more so especially in the FOLFIRI group than in the mXELIRI group. We considered the possibility that the inferior PFS for FOLFIRI compared with mXELIRI might reflect the higher rate of treatment discontinuation as a result of unacceptable toxicity associated with FOLFIRI. Therefore, FOLFIRI with irinotecan 150 mg/m^2 might have been overdosed in some cases in the DHH group.

Higher irinotecan dose intensity (86.1% vs 62.1%) and improved safety (grade 3 or higher toxicities, 39.1% vs 62.5%) were evident in the mXELIRI arm compared with the FOLFIRI arm in the DHH group. Efficacy as assessed by PFS and OS was better with the mXELIRI regimen than the FOLFIRI regimen in the DHH group (6.5 vs 4.8 months, and 13.0 vs 9.1 months, respectively); however, these differences were not statistically significant, which is probably due to the limited sample size. Although the superiority of mXELIRI could not be proven, the median PFS and OS were both longer in the mXELIRI group than in the FOLFIRI group by 1.7 months (HR 0.73; 95% CI, 0.41-1.32) and 3.9 months (HR 0.71; 95% CI, 0.39-1.31), respectively. These data suggest that mXELIRI can be given safely to patients with the DHH genotype while maintaining efficacy.

Our study has several limitations. First, because the concentration of drug in the blood was not quantified, we do not know whether the concentration of the active form of a poor metabolizer was increased in the blood, thereby leading to a higher efficacy due to greater SN-38 levels. Second, biases could have been present because the distribution of right-sided colon cancer, which is a prognostic factor in patients with colorectal cancer, was not adjusted in this study in order to investigate the usefulness of *UGT1A1* genotyping. Third, the sample size might have been too small to rigorously compare the efficacy of mXELIRI- and FOLFIRI-based treatments in the DHH group. Finally, it is difficult to conclusively suggest an appropriate dose of irinotecan for FOLFIRI in the DHH group, although it might have been necessary to further reduce the starting dose to 120 mg/m^2 irinotecan, or to eliminate the bolus infusion of fluorouracil.

Although *UGT1A1* genotyping was mandatory in this study, it is not recommended in routine practice. Real-world data showed that the proportion of patients with DHH genotypes for *UGT1A1* was 7%-10% and that they did not tolerate the standard FOLFIRI regimen containing 180 mg/m^2 irinotecan.[8] Therefore, *UGT1A1* genotyping would be considered prior to treatment with FOLFIRI containing irinotecan 180 mg/m^2 when extra caution is required due to comorbidities or older age. Despite the establishment of some recommendations, routine upfront *UGT1A1* genotyping is not currently carried out. This could be because there have been few prospective studies that evaluated the clinical effects of genotype-directed dosing.[18,19] Other challenges for routine *UGT1A1* testing to avoid severe neutropenia include added costs and long turnaround time.

Precision medicine based on next-generation sequencing of tumor tissues is becoming a standard-of-care in mCRC and other cancers, and the costs thereof are covered by insurance in several countries such as the United States, Germany, Korea, and Japan. Recently, the MI-ONCOSEQ study produced reliable germline pharmacogenetics information on several clinically relevant pharmacogenes (eg, *TPMT*, *DYPD*, and *CYP2C19*).[20] Further updates on *UGT1A1* through prospective studies are needed. Integration of germline pharmacogenetics into tumor sequencing programs and the bioinformatics workflow will provide a unique opportunity to streamline and maximize the clinical benefit of genome testing without additional genotyping costs.

In conclusion, mXELIRI with or without bevacizumab as second-line chemotherapy for mCRC was efficacious and had an acceptable AE profile regardless of the *UGT1A1* genotype.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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