Original Article

Clinical Implications of *UGT1A1**28 Genotype Testing in Colorectal Cancer Patients

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BACKGROUND: Metastatic colorectal cancer is frequently treated with irinotecan, a topoisomerase-I inhibitor. The *UGT1A1* gene encodes for an enzyme that metabolizes irinotecan, and its genetic variants were shown to be associated with increased drug toxicity. We evaluated clinical outcomes associated with the *UGT1A1**28 variant. **METHODS:** The study included 329 colorectal cancer patients from the Israeli population-based Molecular Epidemiology of Colorectal Cancer study who were treated with a chemotherapy regimen that included irinotecan. Patients with metastases or disease recurrence were followed up for a median period of 2 years after occurrence of the event. Study end points were appearance of grade 3-4 hematological and gastroenterological toxicity, hospitalization due to toxic events (mostly neutropenia, fever, diarrhea, or vomiting), length of hospitalization, and overall survival. *UGT1A1**28 was genotyped from peripheral blood DNA by fragment analysis and reported as number of TATA sequence repeats in the promoter of the gene. **RESULTS:** The 7/7 variant of *UGT1A1**28 was detected in 11.9% of the 329 participants. Grade 3-4 hematological toxicity was significantly higher in 7/7 carriers compared with 6/7 and 6/6 carriers (48.0%,10.2%, and 7.7% respectively; $P < .001$), as was the risk of toxicity-related hospitalization (45.8%, 25.3%, and 14.4% respectively; $P = .001$). Both short-term death within 2 months of treatment start (12.8%, 5.2%, and 2.9%, respectively) and median overall survival (1.6, 2.0, and 2.4 years, respectively; $P = .01$) were significantly worse in the 7/7 carriers. The age/stage-adjusted hazard ratio for patients with the 7/7 genotype compared with 6/6 was 1.7 (95% confidence interval, 1.1-2.3). **CONCLUSIONS:** The *UGT1A1**28 7/7 genotype is strongly associated with severe hematological toxicity and higher hospitalization rate and predicts lower survival of colorectal cancer in users of irinotecan. ***Cancer* 2011;117:3156–62.** *© 2011 American Cancer Society.*

KEYWORDS: irinotecan, colorectal cancer, *UGT1A1*, toxicity, survival.

Metastatic colorectal cancer is frequently treated with irinotecan (CPT-11), a topoisomerase-I inhibitor.[1] The gene *UGT1A1* encodes an enzyme that catalyzes the glucuronidation of the active irinotecan metabolite SN-38, which is eliminated in the liver by metabolic alteration to an inactive form SN-38G.[2] Irinotecan toxicity is observed relatively commonly, and myelosuppression (neutropenia) and diarrhea are the most commonly reported dose-limiting toxicities.[3,4] Homozygosity for the *UGT1A1**28 allele (7/7) has been shown to be associated with irinotecan-related hematological[5-13] or gastrointestinal[11,14-16] toxicity. These findings led the U.S. Food and Drug Administration in 2005 to require that gene-related information be added to the drug product label.[17] It is as yet unclear if carriers of the different genetic variants also have a different prognosis[7,8,18,19] or differ in number or length of hospitalizations.[11] We retrospectively evaluated the association between *UGT1A1* genetic variation, prevalence of severe toxicity, and survival of irinotecan-treated colorectal cancer patients in a large cohort of consecutive patients.

MATERIALS AND METHODS

Patients

Patients diagnosed with colorectal cancer within the framework of the Molecular Epidemiology of Colorectal Cancer (MECC) study and who were treated with irinotecan-based chemotherapy (FOLFIRI, IFL, TEGAFIRI, XELIRI) for metastatic disease were included in this subanalysis. The MECC study is a population-based case-control study of all

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newly diagnosed colorectal cancer patients in Northern Israel. A total of 2135 patients from phase 1 of the study, which took place in 1998-2004, served as the source for the patients participating in the current analysis. The study was approved by the institutional review board committees of Carmel Medical Center (Haifa, Israel) and the University of Michigan (Ann Arbor, MI).

The methods of the MECC study have been described previously.[20] In brief, patients with newly diagnosed colorectal cancer and their population-based, randomly selected, age/sex/residence/ethnicity-matched controls were identified. After signing a consent form, the patients were interviewed using an extensive questionnaire and gave a venous blood sample, which was further separated into DNA, serum, and lymphocytes.

Baseline clinical information included data extracted from pathology reports of all patients (stage at diagnosis, grade, tumor location in the colon, histological type).

Follow-Up

The medical records of 2135 patients with colorectal cancer recruited in phase 1 of the MECC study were sought. Of these, 2039 (95.5%) were retrieved with either full follow-up data (n = 1762) or partial follow-up data (n = 277). Ninety-six records could not be found, either because the patient was diagnosed at a very early stage and did not undergo oncological surveillance or because the patient died shortly after diagnosis. Medical records were extracted to provide information about events of tumor recurrence, appearance and location of metastases, appearance of second primary tumors in or outside the colon, as well as detailed treatment information. Date of death and cause of death were available from the Israeli population register.

Among the 2039 MECC patients, 387 patients were identified as having been treated with irinotecan-based chemotherapy and serve as the study group for this report. Blood samples were available for genetic analysis for 329 (85.0%) patients. The time of first evidence of an event (metastasis or local recurrence) was recorded or imputed as the time of start of treatment if the time of the event was missing in the record (in 23 [5.9%] patients). Records of 214 (65.0%) patients with genetic analyses could be retrieved and were studied for evaluation of events of hematological or nonhematological toxicity.

Laboratory Assays

Genomic DNA extracted from blood was used for genotyping either via simple determination of the TATA box sequence in patient DNA or via implementation of fragment analysis. Isolation of the UGT promoter region, which carries the *28 mutation, was performed using the following primers: 5′-TTC CAG CCA GTT CAA CTG TTG-3′ (forward), 5′-GCC TTT GCT CCT GCC AG-3′ (reverse). Polymerase chain reaction (PCR) products underwent a sequencing PCR reaction using BigDye Terminator reagents (Applied Biosystems). Forward primer was used for reaction initiation. Products were purified using a BigDye XTerminator purification kit (Applied Biosystems) and were sequenced with the 3130xl Genetic Analyzer (Applied Biosystems). Fragment analysis was performed by isolating the UGT promoter region via PCR reaction with the following FAM labeled primers: 5-FAM′-AAA TTC CAG CCA GTT CAA CTG TTG TT-3′ (forward), 5′-GCC TTT GCT CCT GCC AG-3′ (reverse). PCR products were diluted at 1:20, and 1 μL was added to a reaction solution containing 8.5 μL formamide and 0.5 μL GeneScan-500 ROX Size Standard (Applied Biosystems). Fragment analysis was performed with the 3130xl Genetic Analyzer. The polymorphism *UGT1A1*28* is characterized by the presence of an additional TA repeat in the TATA sequence of the *UGT1A1* promoter [(TA)7TAA, instead of (TA)6TAA]. Fragment analysis determines fragment size with a 211-nucleotide fragment for the 6 TA repeats and a 213-nucleotide fragment for the 7 TA repeats. Genotype data were available for 329 patients.

Statistical Analysis

The statistical analysis included an analysis of the risk of severe adverse effects in irinotecan-treated colorectal cancer patients and an analysis of the survival of irinotecan-treated patients. The adverse effects analysis included 214 patients with full treatment information and genotype who were also among the 329 patients included in the survival analysis genotype data. The association between *UGT1A1*28* genotypes and demographic variables were tested using chi-square tests (exact test when appropriate).

The association between *UGT1A1*28* genotype and the incidence of grade 3-4 toxicities were tested using Armitage test for trend. Similarly, the association with toxicity-related hospitalization mortality (death within 2 months of treatment initiation) was assessed. Overall survival was calculated from the date of first metastases (or recurrence) diagnosis to date of death or final date of study participation. Overall survival was presented using Kaplan-Meier curves and was compared using a log-rank test. The Cox proportional hazards model was used to

Table 1. Demographic and Clinical Comparison of Study Subgroups

	Overall Series (n=387)	Genotyped Patients (n=329)	Patients With Toxicity Data (n=214)
Sex			
Men	48.7%	48%	46.3%
Women	51.3%	52%	53.7%
Ethnicity			
Jewish	83.9%	82.4%	85%
Non-Jewish	16.1%	17.6%	15%
Age at diagnosis, y, mean±SD	63.1±11.4	62.9±11.6	63.1±10.9
Evidence for metastasis at diagnosis	53.3%	52.9%	50%
Median (IR) of time from diagnosis to treatment, wk	48 (13-108)	48 (13-109)	44 (11-99)
Overall survival			
No. of deaths (%)	338 (87.3%)	286 (86.9%)	185 (88.5%)
Median overall survival, y[a]	2.8	2.8	2.8

SD indicates standard deviation; IR, interquartile range.
[a] From time of initial diagnosis.

Table 2. Demographic and Clinical Characteristics of Patients

		UGT1A1*28 Genotype			
	Patients	**6/6**	**6/7**	**7/7**	***P***
Total population, No. (%)	329 (100)	137 (41.6)	153 (46.5)	39 (11.9)	
Sex, No. (%)					.135[a]
Men	158 (48)	61 (38.6)	82 (51.9)	15 (9.5)	
Women	171 (52)	76 (44.4)	71 (41.5)	24 (14)	
Ethnicity, No. (%)					.207[a]
Jewish	271 (82)	109 (40.2)	132 (48.7)	30 (11.1)	
Non-Jewish	58 (18)	28 (48.3)	21 (36.2)	9 (15.5)	
Age at diagnosis, y, mean± SD[b]		62±11.9	63.6±11.6	63.1±10.6	.487[b]
Stage at diagnosis					.077[a]
1		4.6%	2.1%	2.8%	
2		26.9%	12.6%	19.4%	
3		27.7%	31.5%	30.6%	
4		40.8%	53.8%	47.2%	
Unknown, No.		7	10	3	

[a] Chi-square test.
[b] Analysis of variance.

estimate the hazard ratio (HR), with adjustment for age, ethnicity, and existence of metastasis at initial diagnosis.

RESULTS

*UGT1A1**28 genotype-specific toxicity of irinotecan-based treatments was studied in 214 colorectal cancer patients, and genotype-specific overall survival was studied in 329 irinotecan-treated colorectal cancer patients.

No significant differences in patient demographics and clinical data (stage at diagnosis or overall survival) were noted among the overall series, in patients with genotype-specific survival data, and in all patients with irinotecan treatment and toxicity data (Table 1).

Genotype Frequency

*UGT1A1**28 genotypes 6/6, 6/7, and 7/7 were detected in 41.6%, 46.5%, and 11.9% of patients, respectively (Table 2). Genotype distribution was not significantly different between Jewish patients (11.1% with 7/7 variant) and non-Jewish patients (15.5% with 7/7 variant) and between men (9.5% with 7/7) and women (14.0% with 7/7). No difference was noted between the genetic subtypes, in age at diagnosis or stage at presentation (Table

Table 3. Differences in Time From Diagnosis, Metastatic Disease, and Treatment

	UGT1A1*28 Genotype				
	6/6 (n=137)	6/7 (n=153)	7/7 (n=39)	All (n=329)	*P*
Time from initial diagnosis to treatment start, wk, median (IR)	62 (22-122)	39 (11-86)	42 (11-97)	48 (13-109)	.014[a]
Time from first metastasis/recurrence to treatment start, wk, median (IR)	13 (6-38)	11 (5-23)	13 (8-38)	12 (6-30)	.13[a]
Irinotecan-based treatment protocol[b]					.69[c]
FOLFIRI	42%	37%	28%	38%	
IFL	37%	44%	44%	41%	
Other (TEGAFIRI, XELIRI)	21%	19%	28%	21%	

IR indicates interquartile range.
[a] Kruskal-Wallis test.
[b] In patients with genotype and full oncological follow-up.
[c] Chi square test.

Table 4. Grade 3-4 Toxicity in Irinotecan-Treated Colorectal Cancer Patients

	UGT1A1*28 Genotype				
	6/6 (n=91)	6/7 (n=98)	7/7 (n=25)	All (n=214)	*P* for Trend
Grade 3-4 toxicity					
Hematological, No. (%)	7 (7.7)	10 (10.2)	12 (48.0)	29 (13.6)	≤.001
Leucopenia	6.6%	6.1%	32%	9.3%	.005
Neutropenia	5.5%	8.2%	24.0%	8.9%	.019
Neutropenic fever	0	2.0%	24.0%	3.7%	≤.001
Nonhematological, No. (%)	31 (34.1)	29 (29.6)	7 (28)	67 (31.3)	.46
Diarrhea	27.5%	18..4%	20%	22.4%	.20
Vomiting	4.4%	12.2%	20%	9.8%	.015
Infection	4.4%	7.1%	0	5.1%	.82
Mucositis	2.2%	1%	0	1.4%	.73
Time to toxicity, wk, median (IR)	5.9 (2.1-8.6)	3.2 (2.1-5.9)	2.1 (1.2-3.1)	3.1 (2-6.9)	.016
Hospitalization due to toxicity					
Yes, No. (%)	13 (14.4)	24 (25.3)	11 (45.8)	48 (23)	.001
Unknown, No.	1	3	1		
Short-term death[a]	2.9%	5.2%	12.8%	5.2%	.027

IR indicates interquartile range.
[a] Within 2 months of treatment onset, based on all treated patients.

2). However, the 6/6 genotype tended to be diagnosed with a lower proportion of stage 4.

Treatment Characteristics

Treatment protocols in our series included FOLFIRI (38%), IFL (41%), and other regimens (XELIRI, TEGAFIRI [21%]). No difference in treatment protocols was noted between the groups with different genotypes (Table 3). In the overall irinotecan-treated series, treatment was initiated at a median time of 48 weeks after initial diagnosis, and 12 weeks from diagnosis of metastases or recurrence with a wide time range. Patients with the 6/6 genotype had a significantly longer time to treatment start than patients with the 6/7 or 7/7 genotype (62 weeks versus 39 weeks and 42 weeks, respectively) (Table 3). This longer time was a reflection of a significantly longer time to development of metastases/recurrence and was not due to differences in time of treatment initiation after metastases were detected.

Drug Toxicity

Among the 214 patients who had detailed treatment and toxicity information, a total of 164 grade 3-4 toxicity events were reported in 98 (46.9%) patients. The most common toxicity events were diarrhea (22.4%), vomiting (9.8%), leucopenia (9.3%), neutropenia (8.9%),

infection (5.1%), neutropenic fever (3.7%), and mucositis (1.4%) (Table 4).

The median (interquartile range) time from start of treatment to appearance of the first event of grade 3-4 toxicity was 5.9 (2.1-8.6) weeks for the *UGT1A1**28 6/6 genotype and 3.1 (2.1-5.9) weeks for the 6/7 genotype, and the shortest time was 2.1 (1.2-3.1) weeks for patients with the 7/7 genotype ($P = .016$).

Hematological toxicity was significantly more common in patients with the 7/7 genotype, (48% compared with 10.2% and 7.7% in the 6/7 and 6/6 genotypes; P for trend $<.001$). A similar elevated event rate was observed for leucopenia, neutropenia, and neutropenic fever (Table 4).

There were no significant differences between patients with the genetic subtypes in the rate of nonhematological grade 3-4 toxicities, although vomiting was found to be significantly increased with an additional copy of a 7 allele.

Hospitalization due to toxicity was recorded in 48 patients (23%). The frequency of hospitalization was significantly higher among the 7/7 genotype group (45.8%) compared with the 6/6 group (14.4%) and 6/7 group (25.3%) (P for trend = .01). The median number of hospitalization days, for patients who were hospitalized, was similar across genotype groups (6, 5, and 5 for the 6/6, 6/7, and 7/7, respectively).

The pattern of increased toxicity and increased hospitalization rate among patients with the 7/7 genotype was noted in all treatment protocol types (data not shown).

When toxicity analysis was stratified by ethnicity, the apparent association of the 7 allele with increased hematological grade 3-4 toxicity was observed in both Jewish and non-Jewish patients (data not shown).

Seventeen deaths were observed in the 2-month period after the start of irinotecan-based treatment. Death rates significantly increased with an additional copy of the 7 allele (2.9%, 5.2%, and 12.8% for the 6/6, 6/7, and 7/7 genotypes, respectively; P for trend = .027).

Overall Survival

Among the 329 patients available for this analysis, a total of 286 deaths of any cause (86.9%) occurred during the follow-up period, which started at the date of first metastasis or local recurrence event. The median follow-up period (from event) was 2 years (6 years for patients who were alive at the end of the follow-up period).

The median overall survival for the 3 genotype groups was significantly different (2.4, 2.0, and 1.6 years for the 6/6, 6/7, and 7/7 genotypes, respectively; $P = .008$, log-rank test) (Figure 1). The HR comparing patients with the 7/7 genotype and the 6/6 genotype, when adjusted for age and stage at diagnosis (stage 4 vs other), was 1.7 (95% confidence interval [CI], 1.1-2.5). When analysis was stratified according to ethnicity, the adjusted HR comparing the 7/7 genotype with the 6/6 genotype was 1.6 (95% CI, 1.0-2.5) for Jewish patients and 2.2 (95% CI, 0.99-5.0) for non-Jewish patients. The age/stage/ethnicity-adjusted HR for death in patients with the 7/7 genotype compared with the 6/6 genotype was 1.7 (95% CI, 1.1-2.3; $P = .010$).

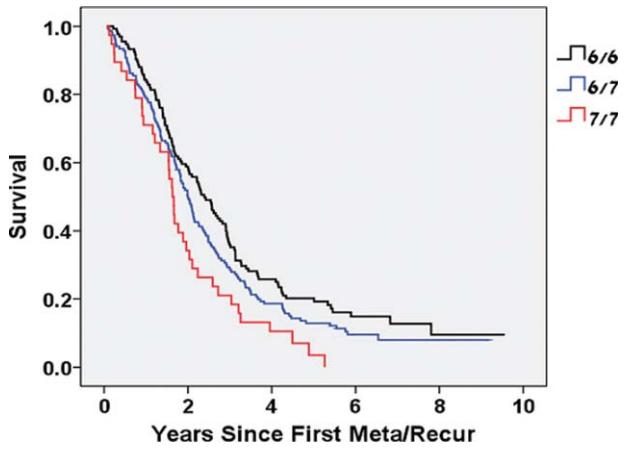

Figure 1. The Kaplan-Meier curve for overall survival (measured from first metastasis or recurrence event) by *UGT1A1**28 genotype is shown. $P = .008$ (log-rank test). The age/stage/ethnicity-adjusted hazard ratio (7/7 vs 6/6) was 1.7 (95% confidence interval, 1.1-2.3; $P = .01$).Meta/Recur indicates metastasis/recurrence.

Analysis of survival from time of initial diagnosis yielded similar results, with worse survival for the 7/7 genotype (median survival time of 3.5, 2.8, and 2.1 years for the 6/6, 6/7, and 7/7 genotypes, respectively; $P = .003$ [log-rank test]) (Figure 2) and an elevated age/stage/ethnicity-adjusted HR for death for the 7/7 genotype of 1.6 (95% CI, 1.1-2.4; $P = .015$).

DISCUSSION

Our data suggest a significantly higher rate of complications and worse survival among irinotecan-treated patients with advanced colorectal cancer who carry the 7/7 variant of *UGT1A1**28.

Our finding of a higher rate of grade 3-4 toxicity in irinotecan-treated patients who were carriers of the 7/7 variant is in line with findings in most other studies with different treatment protocols.[5-16] A previously reported

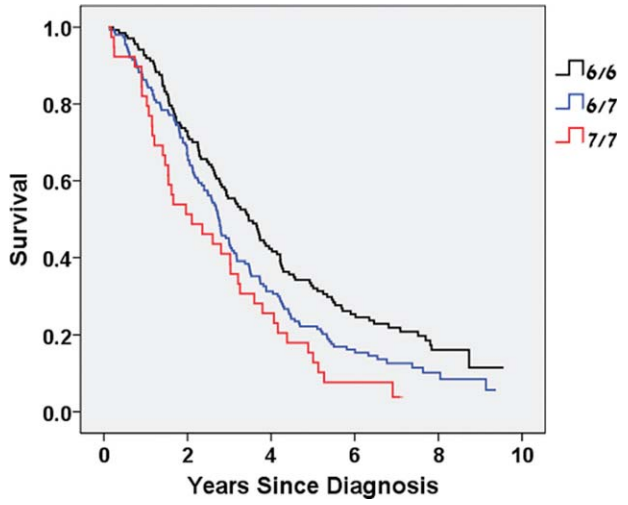

Figure 2. The Kaplan-Meier curve for overall survival (measured from the time of diagnosis) by *UGT1A1**28 genotype is shown ($P = .003$ [log-rank test]). The age/stage/ethnicity-adjusted hazard ratio (7/7 vs 6/6) was 1.6 (95% confidence interval, 1.1-2.4; $P = .015$).

meta-analysis[11] suggested that such higher toxicity of at least hematological adverse effects is only seen when treatments with doses >150 mg/m^2 were employed. Although we were unable to retrospectively calculate the exact doses given to our patients, the treatment protocols used in our study suggest that most patients were likely within the range of commonly used low-dose therapeutics. The many different irinotecan treatment regimens (eg, IFL, capecitabin/irinotecan, raltitrexed/irinotecan, FOLFIRI, FOLFOXIRI) used in the different trials included in the meta-analysis could make it difficult to compare their results with ours.

In our data, no events of neutropenic fever were noticed among individuals with the 6/6 variant. This is in line with a recent *UGT1A1* genotype-driven phase 1 study of irinotecan[18] that demonstrated the possibility of irinotecan dose escalation in patients with *UGT1A1* wild-type homozygous TA6/TA6 of up to 370 mg/m^2 every 2 weeks. We see great importance in further investigation of the *UGT 1A1* genotype dose-response relationship, evaluation of the clinical effectiveness, and use of *UGT1A1* genotyping as related to true clinical benefit of different irinotecan protocols.

Whereas most irinotecan pharmacogenetic trials have focused on the predictive role of *UGT1A1* variants on toxicity, only a few trials have evaluated the prognostic value of these genetic markers.[7,8] Our study demonstrated a clear survival advantage for wild-type variants among patients who were treated with irinotecan of any regimen. A prospective study[7] with a comparable study population reported limited higher hematological toxicity in 22 FOLFIRI-treated carriers of the 7/7 variant and found that these patients also had a higher response rate but no significant survival difference. However, their median follow-up time was only 15 months, within which only 52% of the participants died. A second retrospective smaller study[8] in a Chinese population did not detect any association between the genetic status and progression-free or overall survival, but had only 6 patients with the 7/7 variant. Our much longer follow-up time, with a median overall survival as high as 2.4 years, together with our larger number of participants (especially carriers of the 7/7 variant), could explain the difference between our findings and the findings of other studies. Possible explanations for a survival disadvantage in 7/7 carriers of the *UGT1A1* gene include suboptimal treatment due to the severity of adverse effects and discontinuation of treatment. In addition, the mutation that influences glucoronidation processes in the liver could be of wider importance, because the liver is not only the leading site of metastases development in colorectal cancer patients, it is also the metabolic site of many other chemotherapeutic agents. If these factors are of importance, a survival disadvantage of 7/7 carriers would also be expected in patients who have not been treated with irinotecan-based regimen. To our knowledge, such data have not yet been reported yet.

The source of data for these analyses was a comprehensive population-based series of colorectal cancer patients diagnosed in Israel over the past decade. In this sense, these data represent a real-life experience of patients not involved in clinical trials, but rather being treated according to commonly used protocols. Therefore, our retrospective data might have a certain level of selection bias, because decisions about treatment initiation and type of treatment could differ between doctors and patients. This is a possible explanation for different irinotecan administration protocols in our study population. Another possible weakness of studies performed outside a trial setup could be a difference in quality of collected data. We had to rely on data that appeared in the medical records, but we were also able to rely on electronic records that have a close to absolute validity for events such as death, hospitalization, length of hospitalization, and more. Regardless of the possibility of selection bias and information bias, there is no reason to expect them to differentially influence our results, because the genetic status of the involved patients was not known to the treating physicians or study researchers at time of treatment. In

addition, the prevalence of the 7/7 variant in our series was similar to the prevalence of the variant reported in other Caucasian populations. Genotyping for *UGT1A1* was not incorporated into clinical practice or treatment choices for the patients included in our population-based study, thus the total proportion of patients with the 7/7 variant treated with irinotecan-based regimens is similar to the overall prevalence of the variant. Chemotherapy regimens and dosages were not influenced by genotype at the time these patients were treated.

*UGT1A1**28 7/7 genotype is strongly associated with severe toxicity and hospitalizations and with lower overall survival in patients with advanced disease treated with irinotecan. These data support the US Food and Drug Administration's recommendation and product labeling to tailor treatment plans for patients with colorectal cancer.

CONFLICT OF INTEREST DISCLOSURES

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