

A phase II trial of UGT1A1 genotype-guided FOLFIRI plus bevacizumab as first-line therapy for advanced, unresectable colorectal cancer

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Abstract

Background: FOLFIRI is a standard regimen for metastatic colorectal cancer (mCRC). We hypothesized that a pharmacogenomic-directed strategy where more efficient irinotecan metabolizers (*UGT1A1* *1/*1 homozygotes and *1/*28 heterozygotes) receive higher-than-standard irinotecan doses would improve progression-free survival (PFS) compared to non-genotype selected historical controls with acceptable toxicity.

Methods: In this phase II multicenter study irinotecan dosing in first-line FOLFIRI and bevacizumab for mCRC was based on *UGT1A1* genotype with *1/*1, *1/*28, and *28/*28 patients receiving 310 mg/m², 260 mg/m², and 180 mg/m², respectively. Primary endpoint was PFS. Secondary endpoints were investigator and patient-reported adverse events, and estimation of overall survival (OS).

Results: One-hundred patients were enrolled with 91 evaluable for PFS and 83 evaluable for best response. Median PFS was 12.5 months (90% CI 10.9, 15.4), shorter than the anticipated alternative hypothesis of 14 months. PFS by genotype was 12.5 months (90% CI 10.9, 17.4) for *1/*1, 14.6 months (90% CI 11.8, 17.5) for *1/*28, and 6 months (90% CI 2.3, 7.7) for *28/*28, respectively. OS was 24.5 months (90% CI 19.1, 30.7) and by genotype was 26.5 (90% CI 19.1, 32.9), 25.9 (90% CI 17.6, 37.7), and 13.4 (90% CI 2.3, 20.5) months for *1/*1, *1/*28, and *28/*28, respectively. G3/4 toxicity was similar between all subgroups, including diarrhea and neutropenia.

Conclusions: A pharmacogenomic-directed irinotecan strategy improved PFS in the *1/*1 and *1/*28 genotypes with higher rates of neutropenia and similar rates of diarrhea compared to expected with standard FOLFIRI dosing. However, improvements in response rate and PFS were modest. This strategy should not change standard practice for mCRC patients in the first-line setting.

Key words: colorectal cancer; irinotecan; FOLFIRI; bevacizumab.

Implications for practice

This study showed that a pharmacogenomic-driven strategy for irinotecan dosing based on *UGT1A1* genotype in patients with metastatic colon cancer should not be considered standard of care, but rather be considered on a case-by-case basis.

Introduction

As the second most common cause of cancer-related death in the United States, metastatic colorectal cancer (mCRC) is a prevalent and lethal disease.¹ We saw a rapid expansion of the drug armamentarium for mCRC around the turn of the century with successive FDA approvals of irinotecan (1998), oxaliplatin (2004), bevacizumab (2004), and cetuximab (2004) that incrementally increased median survival from approximately 9 to 12 months to over 2 years. Since then, major drug advances have been restricted to molecular subtypes of BRAF p.V600E, mismatch repair deficient, and HER2 amplified cancers, which together comprise a minority of mCRC. As we await novel therapies to target mCRC in patients who do not harbor such characteristics, strategies to optimize the therapies we already have may offer benefits in survival over our current standards.

One potential strategy for improving outcomes with current treatments is chemotherapy dose escalation. Irinotecan with 5-fluorouracil (FOLFIRI) is one of 2 equally effective chemotherapy doublets for mCRC,² which when paired with bevacizumab or anti-EGFR therapy represents a standard of care in first-line mCRC. Though in practice irinotecan dosing is not typically genotypically driven,³ common polymorphisms in the *UGT1A1* gene are well described to affect irinotecan metabolism through variable rates of glucuronidation of irinotecan's active metabolite, SN-38. The *UGT1A1* *1/*1 (normal) genotype is associated with faster rates of glucuronidation and inactivation of SN-38, the active metabolite of irinotecan, while the *28 variant is associated with decreased metabolism leading to increased exposure to SN-38.⁴ As a result, carriers of the *28 polymorphism have higher rates of neutropenia^{5,6} and the FDA package insert for irinotecan states the *28/*28 genotype as a risk factor for severe neutropenia and recommends considering an initial dose reduction in these patients.⁷

Though *UGT1A1* genotype unequivocally affects irinotecan metabolism, there are ample data that standard and higher doses of irinotecan can be safely administered to *28 carriers. Among 250 patients treated with FOLFIRI, rates of grade 3 or greater neutropenia were higher for *28 homozygotes (13.6%), and *28 heterozygotes (5.3%) than for *1 homozygotes (1.7%); however, there was not a significant association between genotype and infectious complications or non-hematologic toxicities.⁶ Further, there is a large body of evidence that much higher doses of irinotecan (350-500 mg/m²) alone or in combination can be tolerated in unselected populations,⁸⁻¹² and that doses up to 400 mg/m² are tolerable when given as monotherapy in *28 homozygotes.¹³ The current study is built on the results of a prior phase I dose-escalation genotype-directed trial, which reported doses of 370 mg/m² and 310 mg/m² as the maximally tolerated dose of irinotecan for patients with *1/*1 and *1/*28 genotypes when given as part of FOLFIRI. Higher doses of irinotecan, when guided by genotype, have been associated with longer survival when survival was a secondary endpoint,¹⁴⁻¹⁶ and more recently multiple studies have been performed suggesting increased efficacy using a *UGT1A1* guided dosing strategy.^{17,18}

Given that FOLFIRI has a well-established safety profile at standard dose, and that higher doses of irinotecan have been tolerated in multiple-dose escalation studies in patients with *UGT1A1* *1/*1 and *1/*28 genotypes, we hypothesized that irinotecan doses higher than standard among patients

with mCRC and *1/*1 or *1/*28 genotypes would result in greater clinical benefit than standard FOLFIRI dosing. We designed this multicenter single-arm phase II trial using a genotype-driven dosing strategy to determine if administering higher doses of irinotecan in FOLFIRI to non-*28 homozygotes would prolong progression-free survival (PFS) compared with historical PFS in patients receiving first-line therapy for mCRC. Given the potential for severe toxicity, stopping rules for severe neutropenia and diarrhea were used and patient-reported toxicity monitoring was incorporated into each cycle.

Materials and methods

Patients

Eligible patients were recruited from one of 5 community and academic cancer programs in the US. Patients were eligible if they had treatment naïve mCRC for which curative surgery was not possible as determined by local investigators. Prior adjuvant chemotherapy was allowed. All patients were required to have an adequate hepatic, renal, and hematologic function, and those patients with significant vascular surgeries or cardiovascular events within 6 months, inadequately controlled hypertension (> 140 mmHg systolic, > 90 mmHg diastolic), or non-healing wounds were excluded due to the use of bevacizumab. See [Supplementary Material](#) for protocol with full inclusion/exclusion criteria.

At the time of enrollment, the available CLIA-certified *UGT1A1* genotype assays did not test for the uncommon *6 allele which is found almost exclusively in people of Asian descent. With the available assay, carriers of the *6 allele would be classified as *1. As the *6 allele confers *UGT1A1* deficiency similar to the *28 allele, patients of Asian descent were excluded from this trial for their safety.¹⁹ As is standard of care practice, *RAS* and *BRAF* status were obtained via commercial next generation sequencing. This study was approved by the institutional review boards at all participating sites and the coordinating center, the University of North Carolina at Chapel Hill and abided by the Declaration of Helsinki. All patients provided written informed consent prior to participation.

Treatments

All patients were treated with standard dose bevacizumab at 5 mg/kg, leucovorin 400 mg/m², and 5-FU 400mg/m² bolus followed by 2400 mg/m² by continuous infusion over 46 hours every 2 weeks. Irinotecan was dosed based on genotype with 180 mg/m², 260 mg/m², and 310 mg/m² for *UGT1A1* *28/*28, *1/*28, and *1/*1 genotypes, respectively. Filgrastim or peg-filgrastim was not permitted with cycle 1 day 1 but was permitted with subsequent cycles. Treatment was continued until progression, although irinotecan could be stopped after 4 months of therapy if a maintenance approach was deemed appropriate by the treating investigator.

Toxicity monitoring

All patients who received a single cycle of treatment on study were eligible for toxicity endpoints. Toxicity was assessed at the time of each treatment using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and by the Patient-reported Outcomes version of the CTCAE for toxicities of special concern for

irinotecan: diarrhea, constipation, mouth sores, fatigue, nausea, vomiting, abdominal pain, headache, shortness of breath, decreased appetite, and dysphagia.

Statistical design and safety stopping rules

The primary endpoint was PFS from time of study enrollment to progression or death from any cause. A sample size of 100 patients was selected to ensure 86 patients would be evaluable to detect a change in median PFS from a historical estimate of 10.5^{20,21} to 14 months, assuming a one-sided, alpha of 0.05, with 80% power and 24 months of follow-up. Patients were evaluable for PFS if they received at least 2 cycles of therapy and had their disease re-evaluated at 2 months. 91/100 patients met these criteria. Of the 9 not evaluable for PFS, 3 withdrew due to side effects/complications, 3 withdrew due to patient preference, 1 due to MD discretion, 1 due to compliance issues, and 1 due to patient insurance issues. PFS and OS were estimated using the Kaplan-Meier method, and medians and 90% CIs are reported.

Pre-specified secondary endpoints include overall survival, response rate according to RECIST 1.1, and treatment-emergent adverse events, all stratified by genotype.

Of the 100 enrolled patients, 83 patients were evaluable for best response. Of the 17 patients not evaluable for response, 5 withdrew due to side effects/complications, 5 withdrew due to patient preference, 3 died on study prior to first imaging, 1 had progression not radiographically documented, 1 removed per MD discretion, 1 due to compliance issues, and 1 due to patient insurance issues.

Sequential boundaries were established to suspend the trial for excess gastrointestinal toxicity or to guide use of prophylactic growth factors in the cases of excess febrile neutropenia or grade 3 or higher infection within the first 28-day cycle of therapy.²² Using the NCI CTCAE v. 4.0, diarrhea \geq grade 3 or grade 2 diarrhea that persisted $>$ 48 hours despite maximum supportive care would be counted in the toxicity rate for the purposes of early stopping; this Pocock-type stopping boundary, which assumes that a toxicity rate of 0.30 is acceptable, but anything $>$ 30% is unacceptable, was used with the probability of crossing the boundary of 0.05 if the true toxicity rate is equal to 0.30.

A similar rule was used to inform the need for prophylactic peg-filgrastim, with the assumption that a toxicity rate of 0.20 is acceptable, but anything $>$ 20% is unacceptable. If the true toxicity rate is equal to 0.20, the probability of crossing the boundary is .05. This level of acceptable febrile neutropenia

prior to prophylactic use of growth factors was based on the American Society of Clinical Oncology (ASCO) guidelines on use of growth factors.²³

The study was monitored by the UNC Lineberger Data Safety Monitoring Committee. Study enrollment was temporarily halted after the occurrence of 5 bowel perforations on study. The DSMC was convened to determine if the study should be stopped early for any concern for an increase of bevacizumab-related bowel perforations with dose-escalated irinotecan. The DSMC and multicenter investigative team reviewed the cases and determined that the 5 perforations were not more than would be expected by chance given the rate of up to 3% reported in the bevacizumab package insert; therefore, the study resumed and completed enrollment.

Descriptive summaries of attributable toxicities are reported for all $n = 100$, since they all received at least 1 dose of drug.

Results

A total of 100 patients were enrolled on the study with 47, 43, and 10 patients with $*1/*1$, $*1/*28$, and $*28/*28$ genotype, respectively (Table 1). Median age was 58 (range 19-79), 48% were female, and 59% had 2 or more sites of metastatic disease. The median follow-up time was 40.5 months (interquartile range: 9.2, 51.6). The median number of 28-day cycles administered was 7 for $*1/*1$ (range 1-37), 7 for $*1/*28$ (range 1-42), and only 5.5 for $*28/*28$ (range 1-20).

Based on 91 evaluable patients for PFS, the study had an overall PFS of 12.5 months (90% CI 10.9, 15.4) (Figure 1A). By genotype PFS was 12.5 months (90% CI 10.9, 17.4), 14.6 months (90% CI 11.8, 17.5), and 6.0 months (90% CI 2.3, 7.7) for $*1/*1$, $*1/*28$, and $*28/*28$, respectively. Combined overall survival was 24.5 months (90% CI 19.1, 30.7) (Figure 1B) and by genotype was 26.5 (90% CI 19.1, 32.9), 25.9 (90% CI 17.6, 37.7), and 13.4 (90% CI 2.3, 20.5) for $*1/*1$, $*1/*28$, and $*28/*28$, respectively.

In regard to response, patients with the $*1/*1$ genotype had a partial response (PR) rate of 61% (25/41) and a complete response (CR) rate of 7% (3/41), with the $*1/*28$ genotype a PR rate of 47% (17/36) and a CR rate of 8.3% (3/36), and with the $*28/*28$ genotype a PR rate of 50% (3/6) and no patients achieved a CR (Table 2).

The most common reasons for treatment discontinuation were progression (40% $*1/*1$, 28% $*1/*28$, 40% $*28/*28$), adverse events/side effects treatment related or not (13%

Table 1. Enrolled patient characteristics.

	All N = 100	$*1/*1$ N = 47	$*1/*28$ N = 43	$*28/*28$ N = 10
Age median (range)	58 (19-79)	59 (38-79)	59 (19-72)	62 (52- 76)
Female n (%)	48 (48%)	22 (47%)	18 (42%)	8 (80%)
Race				
Black	12 (12%)	3 (6%)	7 (16%)	2 (20%)
White	83 (83%)	40 (85%)	35 (81%)	8 (80%)
Sites of metastatic disease				
1	41 (41%)	20 (43%)	18 (42%)	3 (30%)
≥ 2	59 (59%)	27 (57%)	25 (58%)	7 (70%)
Somatic mutation				
KRAS or NRAS Mutated	28 (28%)	9 (19%)	13 (30%)	5 (50%)
BRAF V600E	8 (8%)	6 (13%)	2 (5%)	0 (0%)

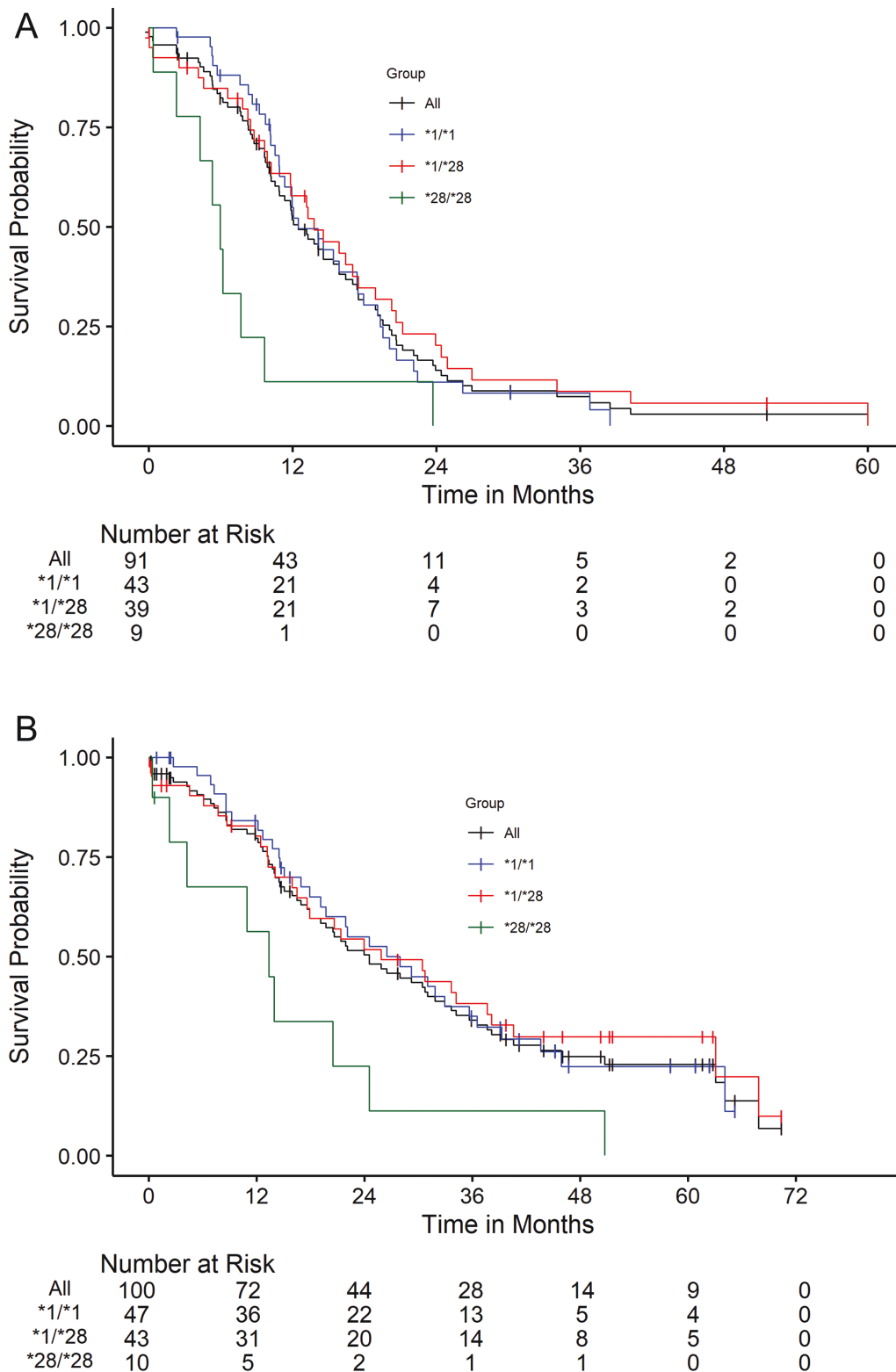


Figure 1. (A) PFS overall and by genotype. (B) OS overall and by genotype.

*1/*1, 9% *1/*28, 20% *28/*28), and provider discretion (9% *1/*1, 14% *1/*28, and 0% *28/*28). Six patients dropped from FOLFIRI to 5-FU maintenance after at least 4 months of therapy, none of which due to hematologic toxicity. Three of these patients had a *1/*1 genotype and three patients had a *1/*28 genotype. The most common grade 3

or higher investigator-reported treatment-related toxicities across all groups were neutropenia (49%), diarrhea (12%), and hypertension (10%) which did not differ across genotype (Table 3). Only 2 patients experienced febrile neutropenia.

Patient reports of severe irinotecan-related toxicities were also similar across all genotypes. Nine patients were excluded

Table 2. Best response per patient by genotype.

	All N = 83	*1/*1 N = 41	*1/*28 N = 36	*28/*28 N = 6
Complete response	6 (6%)	3 (7%)	3 (8%)	0
Partial response	45 (54%)	25 (61%)	17 (47%)	3 (50%)
Stable disease	27 (32%)	10 (24%)	14 (39%)	3 (50%)
Progression	5 (6%)	3 (7%)	2 (6%)	0

from patient-reported toxicities due to the sub-study not being offered at one site (4), refusal to participate (4), or patient did not complete any patient-reported outcome questionnaires (1). The most common patient-reported grade 3/4 toxicities were fatigue and pain (21% each), constipation (19%) for *1/*1; fatigue (24%), constipation (20%), and pain (29%) for *1/*28; and anorexia (37%), fatigue (25%), and pain (38%) for *28/*28 genotypes.

Five patients experienced bowel perforation on study treatment, including 4 colonic and one small bowel that were not necessarily at the site of the primary tumor. The last irinotecan dose administered prior to perforation ranged between 140 and 310 mg/m². All patients had received bevacizumab. Perforations occurred immediately following cycle 1 day 1 (2) in cycle 2 (1), cycle 3 (1), and cycle 4 (1). Grade 2 diarrhea had been reported in one patient, the remainder reported either no diarrhea (2) or grade 1 diarrhea (2). The maximal RECIST response was 36%, suggesting robust response was not the underlying cause. All patients were subsequently removed from study.

Five patients died on study (1 in *1/*1, 2 in *1/*28, and 3 in *28/*28 groups, respectively). Four deaths were deemed possibly related to study treatment; these included one patient with bowel perforation who declined intensive treatment and transitioned to comfort care, one with cardiac arrest deemed possibly related to bevacizumab, one with stroke possibly related to bevacizumab, and one with unspecified sudden death.

Discussion

In this phase II trial of genotype-directed irinotecan dosing as a part of FOLFIRI and bevacizumab in patients with untreated mCRC, we found that increased irinotecan doses were tolerable with expected irinotecan-related toxicities. However, this resulted in only modest improvements in response rate and PFS than reported with standardly dosed FOLFIRI and bevacizumab in CALGB 80405 and the FIRE-3 trial, which reported median PFS with standard 180 mg/m² irinotecan dosing of 10.5 months and 10.3 months, respectively.^{16,19} Furthermore, the objective response rate in patients with *1/*1 genotype who received 320 mg/m² of irinotecan as a starting dose was higher (68%) than in reported comparable trials, however, this benefit was not seen in *1/*28 or *28/*28 treated patients. Thus, while increased dosing of irinotecan could be considered a potential strategy for unique circumstances when a robust response is needed, considering triplet chemotherapy would likely be of more benefit.^{24,25}

The outcomes of patients homozygous for *28 were notably inferior with a median PFS of only 6 months in the 10 treated patients despite an ORR of 50%. Given the

similar response rates and no *BRAF* mutations identified in the *28/*28 cohort, it is not clear whether this short PFS reflects less tolerable treatment or may be related to chance in a small 10-patient cohort. Interestingly, patients in the *28/*28 cohort received a median 1.5 cycles less of therapy, which could explain the discrepant results being related to a less robust patient population, more aggressive disease, or higher chemotherapy-related toxicity. With a 10-patient sample size, conclusions regarding the *28/*28 genotype cannot be conclusively made.

A fatal gastrointestinal syndrome characterized by severe diarrhea, neutropenia, and sepsis was described in clinical trials with irinotecan and bolus 5-FU regimens early in irinotecan's development.²⁶ Although prior irinotecan dose escalation studies did not show any such signal, this gastrointestinal syndrome was our primary safety concern. We found that despite dose intensification in all cohorts, the rate of grade 3 or higher diarrhea was only 10%-12.8% across genotypes which compares favorably to rates seen with FOLFIRI and bevacizumab first-line treatment in FIRE-3 and TRIBE of 13% and 11%.^{21,27} Neutropenia rates were considerably higher in our study, with 49% experiencing grades 3-4 neutropenia (46%-51% across the arms); however, febrile neutropenia occurred in only 2 treated patients. In light of the history of fatal gastrointestinal toxicity we evaluated whether this could be the etiology of the bowel perforations seen in study; however, no patient had higher than grade 2 diarrhea leading up to bowel perforation, and therefore perforations were determined to be more likely related to bevacizumab.²⁸

The data of this study align with that of multiple prior studies reporting that patients carrying the *28 polymorphism are likely to experience more neutropenia with standard irinotecan doses, but that rates of severe diarrhea or other severe toxicities are not increased. This body of evidence, although not suggestive of need for dose reduction of irinotecan for *28/*28 homozygotes, is not sufficient to draw any conclusions due to small sample size.

There were several limitations to our study including small sample size particularly of *28/*28 homozygotes, and the lack of a control group randomized to standard-of-care dosing which limited us to toxicity comparisons with historical data and comparisons across genotypes treated with differing dose levels.

Conclusions

Irinotecan doses of 180 mg/m² and higher are safe across *UGT1A1* genotypes, however, genotype-guided irinotecan dose escalation did not result in meaningfully improved outcomes for patients with metastatic colorectal cancer.

Table 3. Investigator and patient-reported treatment related G3 or higher adverse events occurring in 5% or more of patients.

	*1/*1, irinotecan 310 mg/m ²		*1/*28, irinotecan 260 mg/m ²		*28/*28, irinotecan 180 mg/m ²			
	Investigator- reported G3 or higher (n = 100)	Patient-reported severe (n = 91)	Investigator- reported G3 or higher (n = 47)	Patient-reported severe (n = 42)	Investigator- reported G3 or higher (n = 39)	Patient-reported severe (n = 41)	Investigator- reported G3 or higher (n = 10)	Patient-reported severe (n = 8)
General								
Fatigue	8 (8.0%)	21 (23.1%)	2 (4.3%)	9 (21.4%)	5 (11.6%)	10 (24.4%)	1 (10.0%)	2 (25.0%)
Heme + Infection								
Febrile neutropenia	2 (2.0%)		1 (2.1%)		0		1 (10.0%)	
Neutropenia	49 (49.0%)		24 (51.1%)		20 (46.5%)		5 (50.0%)	
Sepsis	2 (2.0%)		1 (2.1%)		0		1 (10.0%)	
Leukopenia	8 (8.0%)		2 (4.3%)		3 (6.98%)		3 (30.0%)	
Lymphopenia	6 (6.0%)		0		5 (11.6%)		1 (10.0%)	
Anemia	7 (7.0%)		1 (2.1%)		3 (7.0%)		3 (30.0%)	
Thrombocytopenia	7 (7.0%)		2 (4.3%)		2 (4.7%)		3 (30.0%)	
GI								
Nausea	4 (4.0%)	5 (5.5%)	1 (2.1%)	2 (4.8%)	2 (4.7%)	2 (4.9%)	1 (10.0%)	1 (12.5%)
Vomiting	6 (6.0%)	2 (2.2%)	2 (4.3%)	1 (2.4%)	3 (7.0%)	1 (2.4%)	1 (10.0%)	0
Diarrhea	12 (12.0%)	44 (48.3%)	6 (12.8%)	19 (45.2%)	5 (11.6%)	22 (53.7%)	1 (10.0%)	3 (37.5%)
Mucositis	9 (9.0%)	10 (11.0%)	4 (8.5%)	4 (9.5%)	3 (7.0%)	5 (12.2%)	2 (20.0%)	1 (12.5%)
Renal/ Electrolyte								
Cardiovascular								
Hypertension	10 (10.0%)		5 (10.6%)		4 (9.3%)		1 (10.0%)	

Author contributions

Hanna K. Sanoff (Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing—original draft, Writing—review & editing), Allison M. Deal (Data curation, Formal Analysis, Validation, Writing—review & editing), Jai Patel (Investigation, Writing—review & editing), Jonathan D. Sorah (Formal Analysis, Writing—original draft, Writing—review & editing), Jacquelyne Gaddy (Investigation, Writing—review & editing), Bert O’Neil (Investigation, Writing—review & editing), Anita Turk (Investigation, Writing—review & editing), William Irvin (Investigation, Writing—review & editing), Jeremiah Boles (Investigation, Writing—review & editing), Michael S. Lee (Investigation, Writing—review & editing), Autumn McRee (Investigation, Writing—review & editing), Alexis C. Wardell (Data curation, Formal Analysis, Writing—review & editing), Karen E. Weck (Investigation, Methodology, Writing—review & editing), Ethan Basch (Conceptualization, Investigation, Methodology, Writing—review & editing), William A. Wood (Conceptualization, Investigation, Methodology, Writing—review & editing), Federico Innocenti (Conceptualization, Funding acquisition, Investigation, Writing—review & editing)

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Conflicts of interest

H.K.S. has received research funding from Amgen, AstraZeneca, Roche, Bristol-Myers Squibb, Pfizer, BioMed Valley Discoveries, Rgenix, and Exelixis. M.S.L. is employed by Johnson and Johnson (currently; not at time of research), reports consulting/advisory roles with Imvax, G1 Therapeutics, Delcath Systems, Bayer Health, Johnson and Johnson, research funding (to institution) with Arcus Biosciences, Erasca, Repare Therapeutics, Merck, TriSalus Life Sciences, Boehringer Ingelheim, Xilis, and EpimAb Biotherapeutics. F.I. is an AbbVie employee and owns stocks from the company, and is a patent holder on UGT1A1 testing for patients treated with irinotecan. The other authors indicated no financial relationships.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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