Original Article

North Central Cancer Treatment Group N0543 (Alliance): A Phase 2 Trial of Pharmacogenetic-Based Dosing of Irinotecan, Oxaliplatin, and Capecitabine as First-Line Therapy for Patients With Advanced Small Bowel Adenocarcinoma

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BACKGROUND: Oxaliplatin in combination with either 5-fluorouracil or capecitabine is commonly used as first-line therapy for patients with small bowel adenocarcinoma. The addition of irinotecan improves survival in other gastrointestinal tumors but at the cost of hematologic toxicity. The authors performed a phase 2 cooperative group study (North Central Cancer Treatment Group N0543, Alliance) using genotype-dosed capecitabine, irinotecan, and oxaliplatin (gCAPIRINOX), with dosing assigned based on UDP glucuronosyltransferase family 1 member A1 (*UGT1A1*) genotype to test: 1) whether the addition of irinotecan would improve outcomes; and 2) whether *UGT1A1* genotype-based dosing could optimize tolerability. **METHODS:** Previously untreated patients with advanced small bowel adenocarcinoma received irinotecan (day 1), oxaliplatin (day 1), and capecitabine (days 2-15) in a 21-day cycle and were dosed with gCAPIRINOX according to *UGT1A1*28* genotypes (6/6, 6/7, and 7/7). **RESULTS:** A total of 33 patients (17 with the 6/6 genotype, 10 with the 6/7 genotype, and 6 with the 7/7 genotype) were enrolled from October 2007 to November 2013; 73% were male, with a mean age of 64 years (range, 41-77 years). Location of the primary tumor included the duodenum (58%), jejunum (30%), and ileum (9%). The regimen yielded a confirmed response rate of 37.5% (95% confidence interval, 21%-56%), with a median progression-free survival of 8.9 months and a median overall survival of 13.4 months. Neither hematologic toxicity (grade $\geq$3 in 52.9%, 30.0%, and 33.3%, respectively, of the 6/6, 6/7, and 7/7 genotype groups) nor tumor response rate (41.2%, 33%, and 33%, respectively) were found to differ significantly by *UGT1A1* genotype. **CONCLUSIONS:** *UGT1A1* genotype-directed dosing (gCAPIRINOX) appears to be feasible with favorable rates of hematologic toxicity compared with prior 3-drug studies in unselected patients. Larger studies would be needed to determine the regimen's comparability to oxaliplatin and capecitabine (CapeOx) alone or if response/toxicity differs among patients with different *UGT1A1* genotypes. ***Cancer* 2017;123:3494-501**. © *2017 American Cancer Society.*

KEYWORDS: duodenal, ileal, jejunal, small bowel adenocarcinoma, UDP glucuronosyltransferase family 1 member A1 (*UGT1A1*).

INTRODUCTION

Small bowel adenocarcinoma (SBA) is a rare malignancy that often is diagnosed in its late stages, with metastatic disease. Due to its rarity, SBA is historically understudied, and as such to our knowledge there is no clear, consistent standard of care. To date, small prospective clinical studies have evaluated chemotherapy for patients with SBA, the first of which examined the use of mitomycin C, doxorubicin, and 5-fluorouracil (5-FU) with minimal therapeutic effect noted, which likely explains why the study was performed in the early 1980s but not reported until 2005.[1] More recently, oxaliplatin-based therapies have been demonstrated to have activity and have emerged as a potential standard of care in the frontline setting. Overman et al demonstrated a high response rate (50%) in 30 patients who received combination therapy with oxaliplatin and capecitabine (CapeOx), although the trial also included 12 patients (40%) with ampullary carcinoma,

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which may not necessarily behave in a similar clinical fashion.[2] The median progression-free survival (PFS) and overall survival (OS) were 9.4 months and 15.5 months, respectively. This study demonstrated that small bowel carcinoma is indeed a chemosensitive disease, with response rates and activity of chemotherapy, namely 5-FU and oxaliplatin-based therapy, similar to those of other gastrointestinal malignancies such as gastric[3] or colorectal cancer.[4] Xiang et al performed a study using leucovorin, 5-FU, and oxaliplatin (FOLFOX) in SBA and demonstrated response rates (48%), median PFS (7.8 months), and median OS (15.2 months) similar to those of the CapeOx study,[5] confirming the activity of an oxaliplatin-based doublet in SBA.

In a phase 1 study of irinotecan, oxaliplatin, 5-FU, and leucovorin, 2 of 5 patients with SBA achieved partial responses to the regimen.[6] However, the recommended phase 2 schedule proved too toxic in a cooperative group colorectal cancer study.[7] A triplet combination of oxaliplatin, irinotecan, and 5-FU has demonstrated a survival benefit in patients with pancreatic and colorectal cancers.[8-11] UDP glucuronosyltransferase family 1 member A1 (*UGT1A1*), the metabolic enzyme involved in the clearance of SN-38, the active metabolite of irinotecan, has common polymorphisms in the number of TA repeats (6 vs 7), and affects the toxicity profile of irinotecan (including risk of neutropenia and diarrhea) and its efficacy.[12-17] A 7/7 genotype is perhaps best known as the most common cause of Gilbert syndrome, a generally asymptomatic indirect hyperbilirubinemia.[18] Genotype-driven dosing for irinotecan has been successfully accomplished in early-phase trials.[17,19] A phase 1 trial with genotype-dosed capecitabine, irinotecan, and oxaliplatin (gCAPIRINOX) was performed at the Mayo Clinic using *UGT1A1* genotyping performed prospectively in parallel cohorts to determine the appropriate dose for the 3 common genotypes, with the identification of higher tolerable doses in patients with the 6/6 genotype compared with patients with the 6/7 and 7/7 genotypes with comparable total SN-38 exposure.[20] Using the doses identified in that study for each genotype (6/6, 6/7, and 7/7), the North Central Cancer Treatment Group (NCCTG) performed a pharmacogenetic-based phase 2 study (N0543) in patients with advanced SBA. The NCCTG is now a part of the Alliance for Clinical Trials in Oncology.

MATERIALS AND METHODS

Inclusion criteria were unresectable locally advanced or metastatic SBA; measurable disease; a life expectancy $\geq$12 weeks; Eastern Cooperative Oncology Group performance score of 0, 1, or 2; age $\geq$18 years; at least 4 weeks since major surgery and at least 2 weeks since radiotherapy; and adequate blood counts and organ function. Key exclusion criteria included prior therapy for advanced small bowel cancer (although adjuvant 5-FU and leucovorin were allowed if therapy had ended $\geq$3 months before registration), serious intercurrent illness, or current other malignancy.

Before registration, each participant signed an Institutional Review Board-approved, protocol-specific informed consent in accordance with federal and institutional guidelines. After registration, patients underwent germline blood DNA testing for *UGT1A1* genotype by polymerase chain reaction with fragment analysis by capillary gel electrophoresis in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory (Mayo Medical Laboratories). Patients were assigned to treatment cohorts based on the number of TA repeats at the *28 locus, at doses based on the phase 1 study as follows: patients with the 6/6 genotype received irinotecan at a dose of 150 mg/m^2 (day 1), oxaliplatin at a dose of 100 mg/m^2 (day 1), and capecitabine at a dose of 1600 mg/m^2 divided twice daily (days 2-15) in a 21-day cycle (arm A); patients with the 6/7 genotype received irinotecan at a dose of 150 mg/m^2 (day 1), oxaliplatin at a dose of 85 mg/m^2 (day 1), and capecitabine at a dose of 400 mg/m^2 divided twice daily (days 2-15) (arm B); and patients with the 7/7 genotype received irinotecan at a dose of 75 mg/m^2 (day 1), oxaliplatin at a dose of 85 mg/m^2 (day 1), and capecitabine at a dose of 400 mg/m^2 divided twice daily (days 2-15) (arm C). Patients then were treated until disease progression or intolerance, and reimaged at 8-week intervals or as clinically indicated.

For celiac disease screening, tissue transglutamase immunoglobulin A was assessed using an enzyme-linked immunoadsorbent assay on baseline serum levels in a CLIA-approved laboratory (Mayo Medical Laboratories). Results were reported to the principal investigator (R.R.M.), and positive results (>10 U/mL) were reported to the treating physician. Mismatch repair (MMR) status was determined by immunohistochemistry for detected absence of staining for MutL homolog 1 (MLH1); MutS homolog 2 (MSH2); MSH6; and PMS1 homolog 2, mismatch repair system component (PMS2) on tumor tissue from prior surgery or biopsies, and interpreted by an expert pathologist (T.C.S.).

Statistical Analysis

The primary objective of the current phase 2 study was to report the percentage of patients with a confirmed tumor

response across all treatment arms combined. The genotype-based treatment arms were pooled for toxicity and efficacy analyses, although secondary analyses explored potential differences among treatment arms. All patients who met the eligibility criteria, signed a consent form, and initiated treatment were included in the primary analysis.

A 2-stage, phase 2, 3-outcome design[21] was used to test whether there was sufficient evidence to determine whether the confirmed response rate was at least 30%, a rate the study team viewed as clinically promising compared with the data from treatment with mitomycin C, doxorubicin, and 5-FU (the only available benchmark at the time the current study was initiated) versus at most 10%, a rate the study team viewed as not clinically promising. When the FOLFOX data of Overman et al[2] became available, a decision was made to complete accrual rather than redesign the study based on new endpoint criteria given the rarity of the tumor type and the paucity of data in a cooperative group setting. With 33 patients, this trial carried 90% power to detect a tumor response rate of 30%, with a .04 level of significance. A stage 1 analysis was to be performed after the first 16 evaluable patients were enrolled. If $\leq$1 responses were observed in this initial cohort, further accrual to the trial was to be abandoned. If $\geq$2 responses were observed, the study would proceed to full accrual, in which $\geq$7 confirmed responses among the first 33 eligible patients would be considered promising and worthy of further study. A 95% confidence interval (95% CI) for the percentage of patients with a tumor response was calculated using the exact binomial method.

Secondary endpoints include descriptive summaries of adverse events, PFS, and OS. In addition, exploratory secondary analyses estimated the efficacy (response and survival) separately by genotype (treatment arm), MMR status, and tumor location. Adverse events (AEs) were summarized as the maximum grade for each AE and patient, in which those AEs at least possibly related to treatment were reported. PFS was defined as the time from randomization to the first occurrence of either disease progression or death from any cause. OS was defined as the time from study registration to death from any cause. Time-to-event distributions were estimated with the Kaplan-Meier method,[22] in which the log-rank test was used to compare these Kaplan-Meier estimates for different subgroups of interest (ie, treatment arm, MMR status). The Fisher exact test was used for the associations of categorical variables and the Kruskal-Wallis test was used to assess the associations between continuous variables and categorical variables with $\geq$3 categories. All statistical tests for secondary endpoints were 2-sided, in which a P value $<.05$ was considered to be statistically significant. Data collection was conducted by the Alliance Statistics and Data Center. All analyses were performed by Alliance statisticians using SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC).

The principal investigator and the study statistician reviewed the study periodically (at least twice per year, as per the Data and Safety Monitoring Board schedule) to identify accrual, toxicity, and any endpoint problems that might be developing.

RESULTS

A total of 33 patients were enrolled on to the current trial from October 2007 to November 2013 across 15 NCCTG/Alliance treating locations. One patient later was found to have experienced a major treatment violation during cycle 1 because he or she received double the expected dose, and therefore this patient was excluded from all efficacy analyses. All 33 patients were included in the demographic, treatment data, and adverse event data summaries.

Baseline patient characteristics are summarized in Table 1 overall and by genotype (treatment arm). The median time from preregistration (including genotyping if not already completed) to first treatment was 10 days (range, 0-52 days). No significant differences were found between the treatment arms. The median age of the patients was 64 years (range, 41-77 years), 24 patients (73%) were male, and 30 patients (91%) had an Eastern Cooperative Oncology Group performance score of 0 or 1. The most common tumor location was the duodenum (19 patients [58%]), followed by the jejunum (10 patients [30%]) and ileum (3 patients [9%]). Other baseline characteristics are summarized in Table 1. Despite prior reports of celiac disease being present in up to 8% of patients with SBA,[23] none of 33 patients tested was found to have positive serology for tissue transglutamase immunoglobulin A.

Treatment Data

Among all patients, a median of 6 cycles of therapy was administered (range, 1-32 cycles). All patients went off study treatment. The reasons for going off study treatment were similar between the 3 genotype groups (P =.10). The majority of patients withdrew from treatment due to progressive disease (58%). Additional reasons for ending treatment consisted of AEs (18%), patient refusal (6%), and other miscellaneous reasons.

TABLE 1. Characteristics of the Participants

Characteristic	Arm A (6/6 Genotype) N = 17	Arm B (6/7 Genotype) N = 10	Arm C (7/7 Genotype) N = 6	Total N = 33	*P*
Age					.66[a]
Median (range), y	64.0 (41.0-75.0)	66.5 (42.0-77.0)	62.5 (43.0-74.0)	64.0 (41.0-77.0)	
Sex					.23[b]
Male	12 (70.6%)	9 (90.0%)	3 (50.0%)	24 (72.7%)	
ECOG performance score					.95[b]
0	9 (52.9%)	5 (50.0%)	3 (50.0%)	17 (51.5%)	
1	7 (41.2%)	4 (40.0%)	2 (33.3%)	13 (39.4%)	
2	1 (5.9%)	1 (10.0%)	1 (16.7%)	3 (9.1%)	
Race					.42[b]
White	16 (94.1%)	10 (100.0%)	5 (83.3%)	31 (93.9%)	
Black or African American	1 (5.9%)	0 (0.0%)	1 (16.7%)	2 (6.1%)	
Ethnicity					1.00[b]
Not Hispanic or Latino	16 (94.1%)	10 (100.0%)	6 (100.0%)	32 (97.0%)	
Unknown: patient is unsure of their ethnicity	1 (5.9%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	
Primary tumor location					.39[b]
Duodenum	9 (52.9%)	7 (70.0%)	3 (50.0%)	19 (57.6%)	
Jejunum	7 (41.2%)	2 (20.0%)	1 (16.7%)	10 (30.3%)	
Ileum	1 (5.9%)	1 (10.0%)	1 (16.7%)	3 (9.1%)	
Cannot discern	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (3.0%)	
Prior RT					.68[b]
Yes	2 (11.8%)	0 (0.0%)	0 (0.0%)	2 (6.1%)	
No	15 (88.2%)	10 (100.0%)	6 (100.0%)	31 (93.9%)	
Prior chemotherapy					.42[b]
Yes	1 (5.9%)	0 (0.0%)	1 (16.7%)	2 (6.1%)	
No	16 (94.1%)	10 (100.0%)	5 (83.3%)	31 (93.9%)	
MMR status					1.00[b]
dMMR	2 (25.0%)	0 (0.0%)	1 (33.3%)	3 (21.4%)	
pMMR	6 (75.0%)	3 (100.0%)	2 (66.7%)	11 (78.6%)	

Abbreviations: dMMR, mismatch repair-deficient; ECOG, Eastern Cooperative Oncology Group; MMR, mismatch repair; pMMR, mismatch repair-proficient; RT, radiotherapy.
[a] *P* value was derived using the Kruskal-Wallis test.
[b] *P* value was derived using the Fisher exact test.

Efficacy Data

A total of 32 patients were evaluable for efficacy measures. Of the first 16 eligible patients, 7 patients had a confirmed tumor response, which allowed for continuation to full accrual. In all 32 evaluable patients, there were 12 confirmed tumor responses (10 partial responses and 2 complete responses), which met the protocol-defined criteria for success with an overall confirmed response rate of 38% (95% CI, 21%-56%). Response rates were found to be similar between treatment arms and tumor locations ($P = 1.00$) (Table 2). Sufficient tissue for MMR analysis was available for 14 patients. We noted a higher observed response rate in patients with MMR-deficient (dMMR) tumors compared with patients with MMR-proficient tumors (67% vs 27%), but this failed to reach statistical significance, possibly due to small numbers ($P = .51$). Among all patients, 14 achieved a best response of stable disease (44%). The overall clinical benefit rate (stable disease plus response) was 26 of 32 patients (81%). Waterfall plotting (Fig. 1) demonstrated that the majority of patients experienced some shrinkage of their tumor in each treatment arm, although not necessarily meeting the criteria for a confirmed partial or complete response, and activity was observed regardless of treatment arm, MMR status, or primary tumor site (see Supporting Information Figs. s1-3).

Of the 32 patients evaluable for survival, 31 had died at the time of last follow-up, with a follow-up of 59.4 months in the 1 patient who was still alive. The median OS among all patients was 13.4 months (95% CI, 10.5-18.1 months), which was similar across treatment arms (range, 12.1-15.7 months [$P = .52$]) and primary tumor sites (range, 12.4-16.8 months [$P = .63$]) (see Supporting Information Fig. s4). The median PFS was 8.9 months (95% CI, 4.7-10.8 months) and also was found to be similar across treatment arms ($P = .38$) and primary tumor sites ($P = .59$) (see Supporting Information Fig. s5). Finally, for those tumors for which tissue was available for the determination of MMR status, dMMR (3 tumors) versus MMR proficiency (11 tumors) was not found to be prognostic for OS (12.2 vs 10.0 months [$P = .44$]) or PFS (10.6 vs 7.1 months [$P = .61$]) (see Supporting

TABLE 2. Confirmed Responses Overall and by Other Subgroups of Interest

	Success/Total (%)	95% Binomial Exact CI	Fisher Exact Test *P*
Confirmed Response			
Pooled across all patients	12/32 (37.5)	21.1-56.3	
Treatment arm			1.00
A (6/6 genotype)	7/17 (41.2)	18.4-67.1	
B (6/7 genotype)	3/9 (33.3)	7.5-70.1	
C (7/7 genotype)	2/6 (33.3)	4.3-77.7	
Tumor location			1.00
Duodenum	7/18 (38.9)	17.3-64.3	
Ileum	1/3 (33.3)	0.8-90.6	
Jejunum	4/10 (40.0)	12.2-73.8	
MMR status			.51
dMMR	2/3 (66.7)	9.4-99.2	
pMMR	3/11 (27.3)	6.0-61.0	

Abbreviations: CI, confidence interval; dMMR, mismatch repair-deficient; MMR, mismatch repair; pMMR, mismatch repair-proficient.

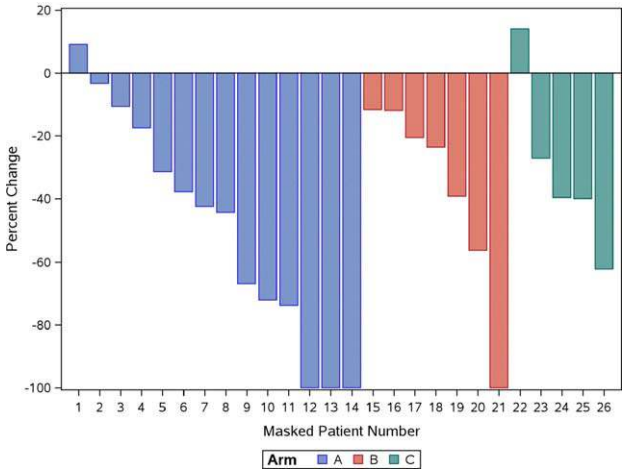

Figure 1. Waterfall plot of maximal response for each patient with small bowel adenocarcinoma who was treated with pharmacogenetic-based dosing of capecitabine, irinotecan, and oxaliplatin (gCAPIRINOX) by treatment arm. Patients with the UDP glucuronosyltransferase family 1 member A1 (*UGT1A1*)*28 6/6 genotype were assigned to receive irinotecan at a dose of 150 mg/m^2 (day 1), oxaliplatin at a dose of 100 mg/m^2 (day 1), and capecitabine at a dose of 1600 mg/m^2 divided twice daily (days 2-15) in a 21-day cycle (arm A). Patients with the 6/7 genotype were treated with irinotecan at a dose of 150 mg/m^2 (day 1), oxaliplatin at a dose of 85 mg/m^2 (day 1), and capecitabine at a dose of 400 mg/m^2 divided twice daily (days 2-15) (arm B). For patients with the 7/7 genotype, irinotecan was administered at a dose of 75 mg/m^2 (day 1), oxaliplatin at a dose of 85 mg/m^2 (day 1), and capecitabine at a dose of 400 mg/m^2 divided twice daily (days 2-15) (arm C).

Information Fig. s6), although the analyses were underpowered to detect a small or even moderate difference in outcome.

Adverse Events

All 33 patients were evaluable for AEs (Table 3). Of these 33 patients, 26 (79%) had an AE of grade ≥3 that was at least possibly related to treatment. Among all 33 patients, 6 (18%) had a grade 4 AE and 1 patient had a grade 5 AE (suicide, unrelated to treatment). No significant differences were found for the overall AE rates between treatment arms. Commonly occurring grade 3/4 AEs (≥5) consisted of neutropenia (9 patients; 27%), leukopenia (6 patients; 18%), dehydration (5 patients; 15%), diarrhea (7 patients; 21%), nausea (8 patients; 24%), and vomiting (6 patients; 18%). The numbers were too small for statistical comparisons between treatment arms to be meaningful for the individual AEs. Diarrhea of any grade was reported in 88% of patients in treatment arm A (6/6 genotype) (53% with grade 1, 6% with grade 2, and 29% with grade 3), 90% of patients in treatment arm B (6/7 genotype) (50% with grade 1, 20% with grade 2, and 20% with grade 3), and 50% of patients in treatment arm C (7/7 genotype) (17% with grade 1, 33% with grade 2, and 0% with grade 3). There were no reports of grade 4/5 diarrhea in any treatment arm. Grade 3/4 neutropenia was noted in 29% of patients in treatment arm A, 30% of patients in treatment arm B, and 17% of patients in treatment arm C. Grade 3 febrile neutropenia was reported in 1 patient in treatment arm A (6%) and 1 patient in treatment arm B (10%). Detailed data regarding AEs are noted in see Supporting Information Table s1.

DISCUSSION

Although to the best of our knowledge there are no randomized controlled clinical trials establishing a clear standard of care for patients with SBA published to date, several phase 2 trials have provided evidence of the clinical activity of chemotherapeutic regimens for this disease. Given the similar PFS and OS reported in the current study compared with that of CapeOx[2] and FOLFOX,[5] it may be that the addition of irinotecan does not

TABLE 3. Frequency of AEs[a] by Treatment Arm (N = 33)

	Arm	No.	%	*P*
Grade ≥3 AE	All	26	78.8	
	A	14	82.4	.84[b]
	B	7	70.0	
	C	5	83.3	
Grade ≥4 AE	All	6	18.2	
	A	4	23.5	.83[b]
	B	1	10.0	
	C	1	16.7	
Grade ≥3 hematologic AE	All	14	42.4	
	A	9	52.9	.57[b]
	B	3	30.0	
	C	2	33.3	
Grade ≥4 hematologic AE	All	4	12.1	
	A	2	11.8	1.00[b]
	B	1	10.0	
	C	1	16.7	
Grade ≥3 nonhematologic AE	All	22	66.7	
	A	12	70.6	.88[b]
	B	6	60.0	
	C	4	66.7	
Grade ≥4 nonhematologic AE	All	2	6.1	
	A	2	11.8	0.66[b]

Abbreviation: AE, adverse event.
Patients with the UDP glucuronosyltransferase family 1 member A1 (*UGT1A1*)*28 6/6 genotype were assigned to irinotecan at a dose of 150 mg/m^2 (day 1), oxaliplatin at a dose of 100 mg/m^2 (day 1), and capecitabine at a dose of 1600 mg/m^2 divided twice daily (days 2-15) in a 21-day cycle (arm A). Patients with the 6/7 genotype were treated with irinotecan at a dose of 150 mg/m^2 (day 1), oxaliplatin at a dose of 85 mg/m^2 (day 1), and capecitabine at a dose of 400 mg/m^2 divided twice daily (days 2-15) (arm B). For patients with the 7/7 genotype, irinotecan was administered at a dose of 75 mg/m^2 (day 1), oxaliplatin at a dose of 85 mg/m^2 (day 1), and capecitabine at a dose of 400 mg/m^2 divided twice daily (days 2-15) (arm C).
[a] All AEs possibly, probably, or definitely related to treatment.
[b] *P* value was derived using the Fisher exact test.

significantly add to the activity of CapeOx alone. However, such a view would not account for the differing clinical outcomes for single-center trials versus a cooperative group trial, such as the current study. One of the more salient aspects of the current study is the reliance on genotyping to determine dosing, because this represents what to our knowledge is the first pharmacogenetically dosed clinical trial for SBA. It is important to note that we were successful in implementing genotyping within the context of a multi-institutional trial. Moreover, this approach appears to account for our relatively favorable AE profile, and the relative consistency of the outcomes across treatment arms supports this approach.

In the study population, gCAPIRINOX was found to be well tolerated overall, and it appears the triplet regimen dosed based on *UGT1A1* genotype may have an improved safety profile compared with what has been reported with the combination of leucovorin, 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX) and infusional 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI), with the appropriate caveats for comparisons across studies.[8,10,24] As potentially expected given the impact of *UGT1A1* genotype primarily on neutropenia,[14] we identified a 27% rate of grade 3/4 neutropenia compared with a rate of 46% to 59% for FOLFIRINOX/FOLFOXIRI (see Supporting Information Table s2), although the rate of diarrhea was comparable to slightly higher at 21% versus 13% to 20%% for FOLFIRINOX/FOLFOXIRI. There did not appear to be notable differences in toxicity rates among the 3 treatment arms in the current study (Table 3) (see Supporting Information Table 1), although the small numbers of patients precluded the identification of moderate differences. For patients with the 7/7 genotype alone (treatment arm A), grade 3/4 neutropenia occurred in 29% of patients, with a 6% rate of febrile neutropenia, whereas the rate of diarrhea was higher at 29%, perhaps partially as a result of the higher dosing of capecitabine. To our knowledge, results with the combination of capecitabine, oxaliplatin, and irinotecan have not been published to date, aside from an unsuccessful phase 1 study of CAPIRINOX in combination with radiotherapy for patients with rectal cancer.[25] A neoadjuvant pancreatic cancer study using capecitabine, oxaliplatin, and irinotecan (CAPOXIRI) (ClinicalTrials.gov identifier NCT01760252) currently is ongoing. Ideally, in the current study, the doses of irinotecan alone would have been assigned based on *UGT1A1* genotype, but the prior phase 1 study determined the doses assigned.

There may exist a subset of patients with dMMR tumors who may be candidates for immune checkpoint inhibitor/anti-programmed cell death protein 1 (PD-1) therapy based on the recent report of pembrolizumab therapy demonstrating responses in patients with dMMR tumors with a noncolorectal diagnosis. Among the trials reported were 2 patients with SBA, although their outcomes are not reported specifically.[26] In the current study, approximately 21% of patients with tissue available for testing were found to have dMMR status by immunohistochemistry, which appears to be a notably higher percentage than the rate of 5% observed in metastatic colon cancer.[27,28] Thus, although SBA is a rare disease compared with colorectal cancer, there is likely a notable opportunity for immune checkpoint blockade in SBA.

There may be biological differences in SBA according to the site of the primary tumor. Much like colorectal cancer,[29,30] there appears to be genetic heterogeneity among sites of SBA primary tumor origination, with high microsatellite instability appearing more often in more proximal tumors and *KRAS* mutations more commonly

in duodenal cancers (57%) versus tumors in the jejunum (29%) and ileum (14%).[31] Expression levels of human epidermal growth factor receptor 2 (HER2) appear to be lowest in proximal tumors and highest in ileal tumors. These findings appear to argue against the commonly held opinion that proximal tumors have more gastric cancer-like characteristics whereas distal tumors behave more similarly to colorectal cancer. How this impacts the outcome and assessment of the effect of therapy is not yet clear. Although analysis of the current study did not reveal a statistically significant difference in survival among primary tumor sites, it is not ruled out. Given the relative rarity of SBA, it is unlikely that studies dedicated to tumor site alone (eg, duodenum) will ever be practical, even on a global scale.

The lack of celiac disease in these patients with advanced SBA is surprising given prior observations.[23] It could well be that celiac disease makes no significant contribution to attributable risk in SBA and that as such it is a rare complication of a relatively rare condition. The other possibilities could be that the presence of celiac disease may permit the earlier detection of adenocarcinoma of the proximal small intestine because of gastrointestinal symptoms associated with celiac disease, and thus these patients are biased toward an earlier stage at diagnosis than those included in the current study. In at least 1 prior observation, patients with celiac disease were found to have an improved survival.[32] Larger studies will be needed to identify the contribution of underlying celiac disease to SBA.

There is a strong need for collaborative studies to advance the care of patients with rare cancers such as SBA. To that effect, the International Rare Cancers Initiative, a cooperative venture between Cancer Research UK, the National Cancer Institute, the European Organisation for Research and Treatment of Cancer, the French National Cancer Institute, and the National Cancer Institute of Canada, has included SBA in its first round of targeted cancers.[33] Prospective trials are needed to establish standards of care for therapy for patients with resected and metastatic SBA, and experience has demonstrated this likely can be achieved only through a cooperative international collaboration.

Conclusions

In the current study, dosing of irinotecan, oxaliplatin, and capecitabine in patients with SBA appears tolerable, and substantial antitumor activity was noted. By dosing with a pharmacogenomic-based regimen, we were able to demonstrate the feasibility of genotype-based dosing for a rare tumor type. We observed reasonable rates of toxicity and notable antitumor activity.

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CONFLICT OF INTEREST DISCLOSURES

Robert R. McWilliams has acted as a paid member of the Advisory Board for Bristol-Myers Squibb and Merrimack. Elise Horvath has been employed as a medical director for Astellas since August 2016, which was after the current study was written.

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