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ORIGINAL REPORT

Racial Differences in Advanced Colorectal Cancer Outcomes and Pharmacogenetics: A Subgroup Analysis of a Large Randomized Clinical Trial

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Racial disparities in colorectal cancer (CRC) survival are documented, but there are few data on comparative response to chemotherapy. A subgroup analysis of a multisite National Cancer Institute–sponsored trial (N9741) was performed comparing outcomes of black and white patients with metastatic CRC receiving uniform treatment.

Patients and Methods
Adverse events (AEs), response rate (RR), time to progression (TTP), overall survival (OS), and dose-intensity were examined as a function of self-reported race in 1,412 patients treated with irinotecan/fluorouracil, fluorouracil/oxaliplatin, or irinotecan/oxaliplatin. Pharmacogenetic analysis was performed on 486 patients with blood available for germline DNA analysis.

Results
OS was 1.5 months shorter and TTP was 0.6 months shorter in black than white patients (OS: hazard ratio [HR] = 1.13; 95% CI, 0.90 to 1.42; TTP: HR = 0.91, 95% CI, 0.73 to 1.13); neither difference was statistically significant. RR was significantly higher in whites (41%) than blacks (28%; $P = .008$). Grade 3 or greater AEs were also higher in whites (48%) than blacks (34%; $P = .004$). These relationships were maintained in multivariate models adjusting for arm, age, sex, and performance status. There was no difference in dose-intensity of delivered therapy. Significant racial differences in prevalence of pharmacogenetic variants were observed, although small sample size precluded investigating the relationship between treatment, race, and genotype.

Conclusion
OS and TTP are similar in black and white patients treated per protocol with standardized therapy for metastatic CRC. However, RR and AEs vary considerably by race. The marked racial differences in relevant pharmacogenetics, a potential explanation for differing RR and AEs, are worthy of future study.

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INTRODUCTION

Racial disparities in outcome are well described in cancer. Compared with white patients, minority groups are more likely to be diagnosed with and die from cancer in the United States.[1] Blacks have a higher incidence of colorectal cancer (CRC), are more likely to present with advanced disease, and, stage for stage, are more likely to die from their disease.[2-5] Recent data indicate that this gap between black and white patients is growing because the incidence and mortality of CRC are decreasing faster in whites than blacks.[3,4]

The reasons underlying racial/ethnic disparities in CRC are likely multifactorial. Societal factors influence survival because people of lower socioeconomic status are less likely to have access to regular care, screening, and cancer treatment.[1,2,6-8] Racial differences in CRC biology—blacks are more likely to present at a younger age, with right-sided,[9,10] low- to moderate-grade tumors[9]—might also mediate outcome differences, just as the preponderance of basal-like breast cancer in young black women explains some of their poorer overall survival (OS) when diagnosed with breast cancer.[11] Finally, interpatient differences in drug efficacy and tolerability are mediated, at least in part, by inherited differences in drug metabolism (pharmacogenetics). Race may be a proxy for pharmacogenetic differences because toxicities or response-modifying genotypes may occur at different frequencies among races.[12] However, there is little comparative data regarding the response and toxicity of chemotherapy regimens among different racial groups.

Given that there are marked differences in outcomes between self-described blacks and whites in population-based studies, we thought it important to compare outcomes of these groups in a trial setting where factors potentially related to cancer outcome, such as access and treatment, are uniform. Although race and ethnicity are partially societal constructs rather than biologic groupings, particularly in the United States where white genetic admixture into groups of African descent may be as high as 20%, self-reported race may be as good a marker of genetic ancestry as genetic clustering.[13-15]

Thus, we explored the hypothesis that biologic differences exist between black and white patients with regard to chemotherapy efficacy by performing a subgroup analysis by self-reported race in patients treated on North Central Cancer Treatment Group trial N9741, a randomized controlled trial funded by the National Cancer Institute of bolus irinotecan/fluorouracil (FU)/leucovorin (LV) (IFL) versus oxaliplatin/infusional FU/LV (FOLFOX) and bolus irinotecan and oxaliplatin (IROX).[16] We also explored the association between race and common genetic variants of irinotecan, oxaliplatin, and FU metabolizing enzymes to see if racial differences in variant distribution might account for differences in clinical outcomes.

PATIENTS AND METHODS

Patients

Patients were treated with IFL, FOLFOX, or IROX as first-line treatment of metastatic CRC.[16] Patients with untreated metastatic CRC were enrolled through one of the following five National Cancer Institute–sponsored cooperative groups (detailed eligibility criteria are available elsewhere[16]): North Central Cancer Treatment Group, Cancer and Leukemia Group B, Eastern Cooperative Oncology Group, Southwest Oncology Group, and National Cancer Institute of Canada Clinical Trials Group. All patients signed informed consent. The protocol was approved by the institutional review board of each participating site.

Treatment and Study Measures

Patients were randomly assigned via a dynamic allocation to ensure assignment was balanced for performance status (PS), prior adjuvant chemotherapy, prior immunotherapy, age, and randomizing location. Race was not a stratification factor. Treatment, which is described in detail elsewhere,[16] consisted of IFL, FOLFOX4 (oxaliplatin, LV, and bolus then continuous-infusion FU), or IROX administered until time of disease progression, unmanageable toxic effects, or withdrawal of consent.

The primary objective of N9741 was to compare time to progression (TTP) in the control arm (IFL) to TTP in the experimental arms (FOLFOX and IROX). Secondary end points included OS, response rate (RR), and adverse events (AEs). TTP was calculated from study entry to disease progression. Deaths occurring within 30 days of treatment discontinuation were considered progression. OS was calculated from enrollment to death or last contact. Patients who died or were lost to follow-up were assumed to have experienced progression at the time they were last documented as being progression free unless contradictory data were available. Response was classified according to the following: complete response, disappearance of all disease and no new lesions; partial response, $\geq$ 50% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions; and progression, $\geq$ 25% increase in the size of measurable tumor or any new disease. Dose-intensity was calculated as protocol-specified dose compared with actual delivered dose at cycles 1, 3, 6, and 12. The self-reported race (white or black) of each participant was recorded at the time of random assignment.

Pharmacogenetic Testing

A total of 520 patients consented to have their blood drawn for pharmacogenetic testing, 486 of whom characterized themselves as black or white and were included in the analysis. Evaluation of 34 single nucleotide polymorphisms, insertion/deletion, or repeat variants in enzymes associated with FU, irinotecan, or oxaliplatin metabolism was performed using pyrosequencing technology, as previously reported.[17]

Statistical Analysis

The objectives of this secondary analysis of N9741 data were to investigate the association between race and clinically relevant outcomes and to investigate the association between genotype and race. Because the number of nonwhite, nonblack minority patients was small (n = 94, 6.2%), the analysis compared outcomes between black and white patients only.

Univariate associations between race and OS; TTP; RR; dose-intensity at cycles 1, 3, 6, and 12; and commonly occurring AEs were performed using χ^2 tests for RR and AEs and log-rank tests for the time-to-event variables of TTP and OS. White patients serve as the reference groups for all hazard ratios (HRs) and odds ratios (ORs). Comparisons were made across all patients and within each treatment arm. Multivariate logistic regression and Cox proportional hazards model were used to further investigate these associations, adjusting for treatment arm, age, sex, and baseline PS. Race-treatment interaction terms were included in the models, with significance testing by the likelihood ratio test. All HRs presented are based on the multivariate models.

Associations between race and genotype were tested using χ^2 tests. The small number of black patients with pharmacogenetic data (n = 36) precluded modeling the relationship between race, toxicity, and genotype. All statistical tests are two-sided, with $P < .05$ denoting statistical significance.

RESULTS

Of the 1,414 patients included in the analysis, 1,297 (92%) were white, and 117 (8%) were black. Baseline characteristics were similar across races, although black patients were slightly younger than whites (Table 1).

Treatment Efficacy

Across all treatment arms, OS time was slightly shorter in blacks than whites, with a median OS of 16.3 months (95% CI, 13.3 to 18.5

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Black Patients No.	Black Patients %	White Patients No.	White Patients %	*P*
Patient population	116	8	1,296	92	
Age, years					.004
Median	58		61		
Range	22-85		26-88		
Sex					.36
Male	66	57	793	61	
Female	50	43	503	39	
Treatment arm					.52
IFL	39	34	371	29	
FOLFOX	50	43	590	46	
IROX	27	23	335	26	
Baseline PS					.42
0-1	109	94	1,237	96	
2	7	6	57	4	
Prior adjuvant therapy					.06
Yes	24	21	185	14	
No	92	79	1,109	86	
Disease status					.25
Measurable	103	89	1,098	85	
Assessable	13	11	196	15	

Abbreviations: IFL, irinotecan/fluorouracil/leucovorin; FOLFOX, oxaliplatin/fluorouracil/leucovorin; IROX, irinotecan/oxaliplatin; PS, performance status.

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months) for black patients and 17.8 months (95% CI, 16.9 to 18.7 months) for white patients (HR = 1.13; 95% CI, 0.90 to 1.42; Fig 1; Table 2). In patients treated with IFL, OS for black patients was reduced compared with white patients (15.2 months for whites *v* 12.2 months for blacks; HR = 1.54; 95% CI, 1.08 to 2.21; *P* = .02). Differences in OS between white and black patients treated with IROX (5.3 months) and FOLFOX (2.5 months) were not statistically significant. Median TTP was similar when pooling across all treatment arms, with a median TTP of 7.4 months (95% CI, 6.5 to 9.7 months) in black patients and 8.0 months (95% CI, 7.4 to 8.3 months) in white patients (HR = 0.91; 95% CI, 0.73 to 1.13).

By interaction testing, there was suggestive evidence that the effect of treatment arm on OS varied by race (Tables 2 and 3). Compared with IFL, the survival benefit of IROX was greater in blacks (HR for death = 0.43 comparing IROX with IFL) than whites (HR for death = 0.90; interaction *P* = .007). Compared with FOLFOX, IROX was superior to FOLFOX in blacks (HR for death = 0.72 in favor of IROX), and FOLFOX was superior to IROX in whites (HR for death = 1.31 in favor of FOLFOX; interaction *P* = .027). However, TTP was longer for FOLFOX compared with IFL or IROX in all patients regardless of race, casting doubt on the clinical relevance of nominally statistically significant interactions for OS.

RR was lower for black patients (28%) than whites (41%), regardless of treatment arm (*P* = .008). This difference was most pronounced among FOLFOX-treated patients (28.6% black, 48% white; *P* = .008). In a multivariate logistic regression model for tumor response adjusting for age, sex, PS, and treatment arm, black patients were significantly less likely to respond to treatment than white patients (OR = 0.56; 95% CI, 0.37 to 0.86).

The rate of resection after initiation of chemotherapy did not differ by race (1.7% in blacks *v* 2.3% in whites; *P* = 1.0); receipt of second-line chemotherapy all did not differ by race (71% in blacks *v* 73% in whites; *P* = .55). Among those initially treated with FOLFOX, more white patients (60%) received second-line irinotecan than did black patients (42.5%; *P* = .017). Among those initially treated with IFL, there was no difference in receipt of second-line FOLFOX (33% of blacks *v* 38% of whites; *P* = .54).

AEs

The rate of severe AEs was lower in black patients, with 34% of blacks and 48% of whites experiencing a grade 3 or higher AE (*P* = .004; adjusted OR = 1.73; 95% CI, 1.2 to 2.6; Table 4). This difference was largely a result of a higher rate of grade 3 diarrhea in white patients (5% black *v* 17% white; *P* < .001). The increased rate of

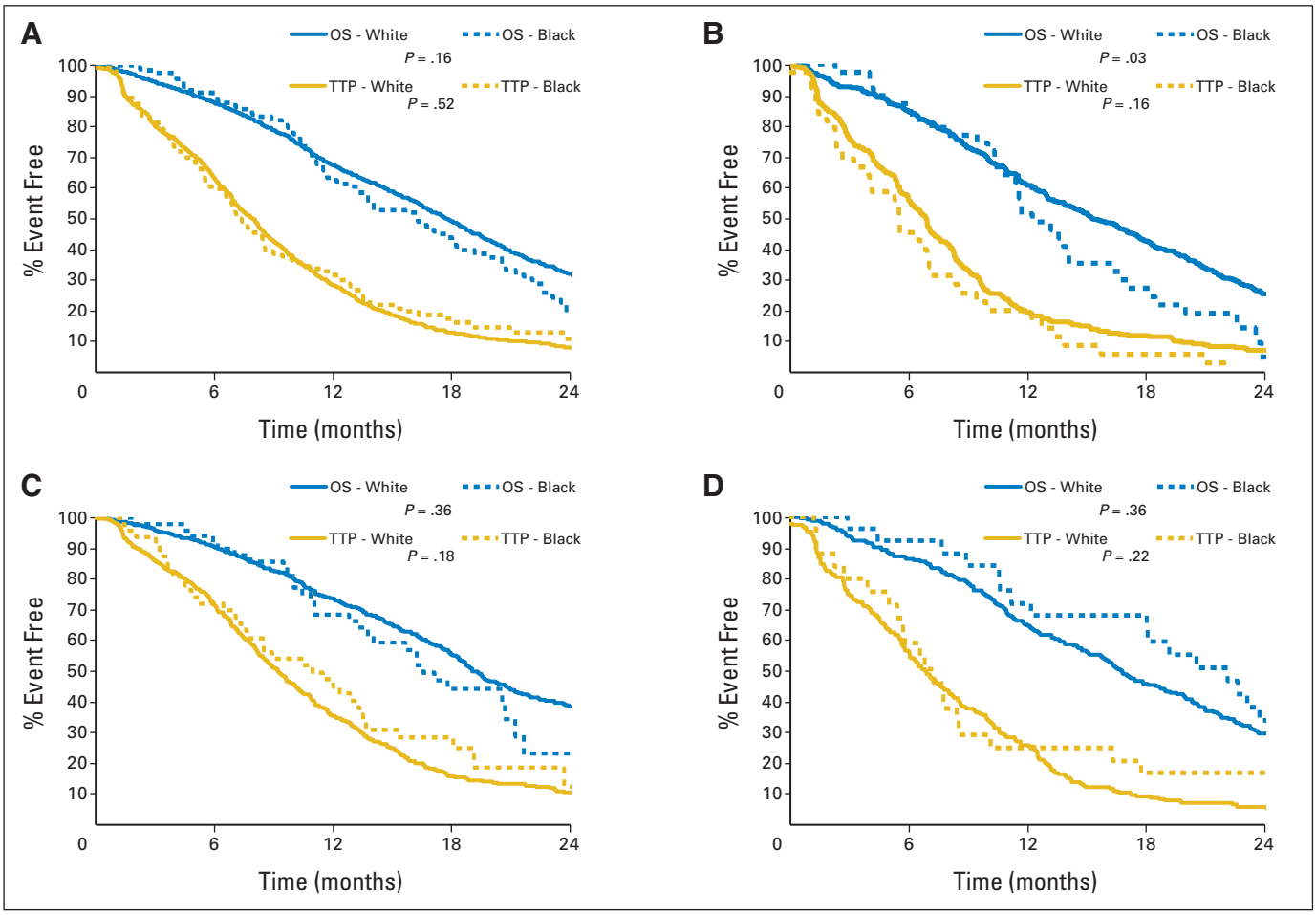

Fig 1. Kaplan-Meier plots of time to progression (TTP) and overall (OS) survival for (A) all patients and by arm: (B) irinotecan, fluorouracil, and leucovorin; (C) oxaliplatin, fluorouracil, and leucovorin; and (D) irinotecan and oxaliplatin.

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Table 2. RR, TTP, and OS Comparisons by Race Within Treatment Arm

Treatment Arm and Race	OS				TTP				RR			
	Median (months)	HR*	95% CI	*P*	Median (months)	HR*	95% CI	*P*	%	OR*	95% CI	*P*
Overall		1.13	0.90 to 1.42	.28		0.91	0.73 to 1.13	.38		0.56	0.37 to 0.86	.008
Black	16.3				7.4				28.3			
White	17.8				8.0				40.9			
IFL		1.54	1.08 to 2.21	.02		1.33	0.94 to 1.89	.11		0.80	0.38 to 1.68	.56
Black	12.2				5.5				28.2			
White	15.2				6.8				32.8			
FOLFOX		1.26	0.87 to 1.83	.23		0.80	0.57 to 1.14	.21		0.42	0.22 to 0.80	.008
Black	16.6				11.0				28.6			
White	19.1				9.2				48.0			
IROX		0.70	0.43 to 1.14	.15		0.73	0.46 to 1.18	.20		0.63	0.25 to 1.56	.31
Black	22.1				7.3				28.0			
White	16.8				6.9				37.5			

Abbreviations: RR, response rate; TTP, time to progression; OS, overall survival; HR, hazard ratio; OR, odds ratio; IFL, irinotecan, fluorouracil, and leucovorin; FOLFOX, oxaliplatin, fluorouracil, and leucovorin; IROX, irinotecan and oxaliplatin.
*HR and OR both compared blacks with whites (referent).

diarrhea in whites was present across all treatment arms; however, it was most profound in the two irinotecan-containing arms (IFL: OR = 3.6; 95% CI, 1.1 to 11.9; IROX: OR = 3.6; 95% CI, 0.8 to 15.6). There were no important differences in the rates of grade 4 neutropenia, grade 3 paresthesias, or vomiting between white and black patients. Despite differences in the rates of severe AEs, there was no meaningful difference in the dose delivered at cycles 1, 3, 6, and 12 by race for any treatment arm (Appendix Tables A1 to A4, online only).

Pharmacogenetics

A pharmacogenetic analysis was performed in 486 patients (black: n = 36, 7%). Baseline characteristics of these patients did not differ from the entire study population. Multiple highly significant associations between genotype and race were observed (Table 5). The frequencies of genetic variants in four genes related to irinotecan metabolism (*ABCB1*, *CYP3A4*, *CYP3A5*, and *UGT1A1*) were significantly associated with race. In particular, the homozygous *UGT1A1*28* genotype (also called 7/7), which has been associated with higher risk of grade 3 to 4 neutropenia,[18] was more common in blacks than whites (14% *v* 9%, respectively). Toxicity or efficacy variants for FU, including *DPYD*2A* and *TYMS TSER*, were not different in frequency between black and white patients.

DISCUSSION

In this analysis of similarly staged black and white patients treated with uniform chemotherapy and clinical follow-up, we found no meaningful differences in OS or TTP between races. A statistically significant 3-month shorter survival in black patients treated with IFL was observed; however, this difference was not present for the current standard of care regimen, FOLFOX. Compared with white patients, however, black patients treated on N9741 were considerably less likely to have an objective tumor response and less likely to have severe AEs from chemotherapy. We identified a number of highly significant associations between race and genotype of drug-metabolizing enzymes. Although these findings are provocative, our small sample size

Table 3. RR, TTP, and OS Comparisons by Treatment Arm Within Racial Groups

Outcome	IFL	FOLFOX	IFL:FOLFOX HR	IFL:FOLFOX 95% CI	IFL:FOLFOX *P**	IROX	IROX:IFL HR	IROX:IFL 95% CI	IROX:IFL *P*†	IROX:FOLFOX HR	IROX:FOLFOX 95% CI	IROX:FOLFOX *P*‡
Median OS, months												
Black	12.2	16.6	1.84	1.10 to 3.08	.027	22.1	0.43	0.23 to 0.80	.005	0.72	0.38 to 1.38	.36
White	15.2	19.1	1.46	1.25 to 1.70	< .0001	16.8	0.90	0.76 to 1.05	.29	1.31	1.12 to 1.53	.004
Median TTP, months												
Black	5.5	11.0	2.56	1.54 to 4.25	.0007	7.3	0.70	0.39 to 1.24	.09	1.66	0.90 to 3.08	.32
White	6.8	9.2	1.44	1.52 to 1.67	< .0001	6.9	0.97	0.83 to 1.14	.85	1.41	1.22 to 1.63	< .0001
RR, %												
Black	28.2	28.6	NA	NA	.97	28.0	0.93	0.28 to 3.10	.99	0.88	0.28 to 2.7	.96
White	32.8	48.0	0.52	0.40 to 0.69	.0001	37.5	1.24	0.91 to 1.70	.20	0.65	0.49 to 0.86	.002

Abbreviations: RR, response rate; TTP, time to progression; OS, overall survival; HR, hazard ratio; OR, odds ratio; IFL, irinotecan, fluorouracil, and leucovorin; FOLFOX, oxaliplatin, fluorouracil, and leucovorin; IROX, irinotecan and oxaliplatin; NA, not available.
*IFL *v* FOLFOX.
†IFL *v* IROX.
‡IROX *v* FOLFOX.

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Table 4. AEs by Treatment Arm and Race

Treatment Arm and Race	Total No. of Patients	Any Grade 3+ AE		Any Severe AE		Grade 4 Neutropenia		Grade 3 Diarrhea		Grade 3+ Paresthesias		Grade 3+ Vomiting	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Overall													
Black	116	76	66*	40	34†	10	9	6	5*	11	9	7	6
White	1,296	1,021	79	618	48	107	8	219	17	108	8	58	4
IFL													
Black	39	22	56‡	11	28‡	4	10	3	8‡	1	3	1	3
White	371	273	74	167	45	20	5	85	23	6	2	11	3
FOLFOX													
Black	50	36	72§	18	36	4	8	1	2§	8	16	2	4
White	590	486	82	269	46	72	12	59	10	81	14	14	2
IROX													
Black	27	18	67	11	41	2	7	2	7§	2	7	4	15
White	335	262	78	182	54	15	4	75	22	21	6	33	10

Abbreviations: AE, adverse event; IFL, irinotecan, fluorouracil, and leucovorin; FOLFOX, oxaliplatin, fluorouracil, and leucovorin; IROX, irinotecan and oxaliplatin.
*$P < .001$.
†$P < .01$.
‡$P < .05$.
§$P = .05$ to .1.

precludes conclusions about whether these differences explain the associations of drug toxicity and tumor response with race.

Despite the increasing gap between black and white Americans with regard to incidence and survival from CRC,[3,4] this and other investigations controlling for imbalances in stage at presentation and treatment received have found similar treatment efficacy in white and black CRC patients. In three subgroup analyses of patients treated with adjuvant CRC therapy, black patients had similar disease-free survival and OS as white patients; small absolute differences in OS were largely attributable to non-CRC causes.[19-21] In a study of care at Veterans' Administration hospitals where access is essentially equal between blacks and whites[22] and in studies using population-based databases able to adjust for stage at presentation, socioeconomics, and treatment received, the black-white survival disparity is markedly reduced.[2,5] Together with our findings of minimal racial differences in survival and no differences in TTP in metastatic CRC when treatment is uniform, these studies suggest that any inherent racial differences in CRC are, at most, a small contributing factor to CRC prognosis.

We did note a number of differences between black and white patients that warrant further consideration. First, we found that black patients are less likely to achieve an objective response than white patients, which is a potentially important difference because lower RRs might translate to a lower rate of resection with curative intent. RR is clearly a marker for an increased chance of metastectomy. In N9741, FOLFOX was associated with a higher RR (45%) compared with IFL (31%) and IROX (35%),[16] and oxaliplatin-treated patients were more likely to undergo metastectomy than those treated with IFL.[23] In our analysis, there was no difference in metasectomy rate by race; however, this trial was conducted at a time when the potential benefits of resection of metastatic disease was just beginning to be understood.

One supposition for the lower RR in blacks is the increased proportion of lower grade tumors, which may grow more slowly and be less likely to respond to treatment—analogous to the differences between low-grade and intermediate-grade lymphomas. Another possible explanation for the lower RR among black patients is the higher proportion of black patients who received prior adjuvant therapy (21% of black patients *v* 14% of white patients). In an analysis of prognostic factors of cancer outcomes from this same trial, we found that patients receiving prior adjuvant therapy had a lower objective RR (33%) than previously untreated patients (39%; OR = 0.64; 95% CI, 0.47 to 0.87).[24] Adjusting for prior adjuvant therapy, however, did not change the likelihood of response in multivariate models. Additionally, although RR was significantly lower for black patients treated with all regimens, TTP differed minimally between the groups, suggesting that RR may be a poor surrogate for treatment efficacy in this cohort.

However, the lower RR in blacks might occur because of pharmacogenetic differences resulting in blacks having lower drug exposure despite equal dose-intensity. We did find a clinically and statistically significant difference in the rate of severe AEs between blacks and whites; this difference was largely attributable to an absolute 12% higher rate of severe diarrhea in white patients. In a similar subgroup analysis of the adjuvant trial INT 0089, black patients were also less likely than white patients to have severe diarrhea (8% *v* 23%, respectively; $P < .001$),[19] supporting a true differential risk of severe diarrhea from both combination chemotherapy and FU/LV. Although we cannot be certain that AE reporting was performed equally in blacks and whites—there may be societal differences in willingness to report certain AEs—we have no reason to believe that this difference is solely the result of an ascertainment bias. Rather, it likely represents differences in the frequency of currently unrecognized genetic variants that regulate risk of diarrhea from chemotherapy.

By interaction testing, we found that, compared with both IFL and FOLFOX, the OS benefit of IROX depended on patient race. Specifically, IROX provided a significant improvement compared with IFL and a trend toward benefit over FOLFOX in black patients. This is primarily a result of the high 22.1-month median survival time of black patients on the IROX arm, which is based on only 26 patients. Coupled with no improvement on the TTP and RR end points for

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Table 5. Genotype-Race Associations

Genotype	Black (n = 36) No. of Patients	%	White (n = 450) No. of Patients	%	*P*
Fluorouracil genes					
*DPYD*2A*					.57
G/G	35	97	442	98	
A/G	0	0	4	1	
Missing	1	3	4	1	
*DPYD*5*					.45
A/A	25	69	285	63	
A/G and G/G	9	26	139	31	
Missing	2	6	26	6	
*DPYD*9A*					< .0001
A/A	8	22	267	59	
A/G and G/G	28	78	180	40	
Missing	0	0	3	1	
MTHFR (*A222V, E429A, and R549Q*)					.021
G/G and T/T	2	6	98	22	
T/G, T/T, C/T, C/C	34	94	352	78	
Missing	0	0	0	0	
TYMS 1494del					.011
Other	26	72	224	50	
A/A	10	28	223	49	
Missing	0	0	3	1	
TYMS TSER					.56
2/2 or 2/3	25	69	303	67	
3/3	9	25	138	31	
Missing	2	6	9	2	
Irinotecan genes					
ABCB1 3435C>T					< .0001
Other	17	47	364	81	
C/C	18	50	78	17	
Missing	1	3	8	2	
*CYP3A4 *1B and *3*					< .0001
A/G, G/G, T/C	32	89	33	7	
A/A or T/T	4	11	414	92	
Missing	0	0	3	1	
*CYP3A5*3*					< .0001
C/T and T/T	31	86	48	10	
C/C	5	14	401	89	
Missing	0	0	1	1	
*UGT1A1*28*					.0081
6/6	4	11	206	45	
6/7	15	42	196	44	
7/7	5	14	39	9	
Missing	12	33	9	2	
*ABCC2*3*					.051
Other	21	58	161	36	
A/A	1	3	46	10	
Missing	14	39	423	54	
Oxaliplatin genes					
ERCC1 N118N					< .0001
Other	10	28	372	83	
C/C	22	61	57	13	
Missing	4	11	21	4	
ERCC2 K751Q					.32
Other	32	89	383	85	
G/G	3	8	66	14	
Missing	1	3	1	1	

(continued in next column)

Table 5. Genotype-Race Associations (continued)

Genotype	Black (n = 36) No. of Patients	%	White (n = 450) No. of Patients	%	*P*
ERCC2 D711D haplotype					.0002
A/A	1	3	71	16	
A/B	7	20	162	36	
B/B	16	44	89	20	
Missing	12	33	128	28	
GSTP1 I105V					.069
T/T	9	25	192	43	
C/T	18	50	196	44	
C/C	7	19	47	10	
Missing	2	6	15	3	
GSTM1 deletion					< .0001
Absent	1	3	228	51	
Present	34	94	222	49	
Missing	1	3	0	0	
XRCC1 R399Q					.0006
Other	10	28	255	57	
C/C	25	69	182	40	
Missing	1	3	13	3	
ABCG2 Q141K					.017
G/T or T/T	1	3	90	20	
G/G	29	80	327	73	
Missing	6	17	33	7	

IROX in black patients, this observed association may be a consequence of the small sample size, rather than a biologic effect, and requires confirmation in other clinical trials.

We found that the frequencies of many allelic variants of importance to irinotecan, oxaliplatin, and FU differ between blacks and whites. This is not surprising because dramatic differences in genetic variants have been described from both the Human Genome Project and HapMap initiatives.[12,25,26] However, the clinical relevance of these racial differences is unclear. The *UGT1A1* 7/7 genotype is associated with a higher risk of severe neutropenia,[18] yet the greater frequency of the 7/7 genotype in black patients did not result in a heightened risk of this toxicity. Similarly, the distribution of *GSTM1*0*, which was associated with decreased likelihood of severe neutropenia in FOLFOX-treated patients in a pharmacogenetic analysis of N9741,[27] was inconsistent with the clinical findings of our subgroup analysis; black patients were much more likely to have the low-risk *GSTM1*0* (94% in blacks *v* 49% in whites), but there was no difference in the incidence of severe neutropenia events. On the basis of this preliminary data, a single genotypic difference is unlikely to account for the observed racial variation in AEs and RR; rather, if these differences are genetically determined, they are likely mediated by a complex interplay of genotypes.

If confirmed, the lower rates of AEs experienced by black patients in this study might allow for dose-escalation trials to overcome the lower RR noted among black patients. There are data to suggest a dose-response effect for single-agent irinotecan, data that are of particular interest given the poor survival of black patients treated with IFL in N9741. Escalation of single-agent irinotecan from a dose of 250 mg/m^2 to 500 mg/m^2 was possible in some patients treated in a

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randomized phase II trial of standard versus escalating or individualized dosing based on prognostic determinants.[28] This study showed a trend toward higher RR in patients who were able to undergo dose escalation, although in this small trial, dose escalation prolonged neither TTP nor OS.

A more promising strategy than race-based dose escalation, however, is the ascertainment of objective predictors of treatment response, such as genotype. We found marked racial differences in frequency of polymorphisms of important CRC chemotherapy-related genes. Although no one gene emerged as a clear causal candidate, future studies with adequate sample size to model the three-way association between toxicity, race, and genotype will hopefully identify a complex of genes that may underlie the racial discrepancy in response and severe diarrhea. This strategy may have broad applicability across races, ethnicities, and disease processes and, in time, deliver on the promise of genotype-guided treatment approaches.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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