original reports

Outcomes in Black and White Patients With Metastatic Renal Cell Carcinoma Treated With First-Line Tyrosine Kinase Inhibitors: Insights From Two Large Cohorts

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abstract

PURPOSE To investigate whether black race is an independent predictor of overall survival (OS) in metastatic renal cell carcinoma (mRCC).

METHODS We performed a retrospective 2-cohort (International Metastatic Renal Cell Carcinoma Database Consortium [IMDC] and trial-database) study of patients with mRCC treated with first-line tyrosine kinase inhibitors (TKIs). Unmatched (UM) and matched (M) analyses accounting for imbalances in region, year of treatment, age, and sex between races were performed. Cox models adjusting for histology, number of metastatic sites, nephrectomy, and IMDC risk compared time to treatment failure (TTF; IMDC cohort), progression-free survival (PFS; trial-database cohort), and OS.

RESULTS The IMDC cohort included 73 black versus 3,381 (UM) and 1,236 (M) white patients. The trial-database cohort included 21 black versus 1,040 (UM) and 431 (M) white patients. Median OS for black versus white patients was 18.5 versus 25.8 months in the IMDC group and 21.0 versus 25.6 months in the trial-database group. Differences in OS were not significant in multivariable analysis in the IMDC group (hazard ratio [HR]$_M$, 1.0; 95% CI, 0.7 to 1.5; HR$_{UM}$, 1.1; 95% CI, 0.8 to 1.4) and trial-database (HR$_M$, 1.5; 95% CI, 0.8 to 2.7; HR$_{UM}$, 1.4; 95% CI, 0.8 to 2.6) cohorts. TTF for black patients was shorter in the UM IMDC cohort (HR$_{UM}$, 1.4; 95% CI, 1.1 to 1.8; $P = .003$), but not in the M analysis. PFS was shorter for black patients in both analyses in the trial-database cohort (HR$_M$, 2.3; 95% CI, 1.4 to 3.9; $P = .002$; HR$_{UM}$, 2.3; 95% CI, 1.4 to 3.9; $P = .002$).

CONCLUSION Black patients had more IMDC risk factors and worse outcomes with TKIs versus white patients. Race was not an independent predictor of OS. Strategies to understand biologic determinants of outcomes for minority patients are needed to optimize care.

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INTRODUCTION

Every year, approximately 400,000 people worldwide are diagnosed with renal cell carcinoma (RCC).[1] Globally, the incidence of RCC varies by geographic region and race. In recent years, the black population in the United States has observed the most noticeable increase in RCC incidence rates.[2,3] Additionally, epidemiologic studies have identified that the proportion of patients with non–clear-cell RCC is higher among black populations relative to non-Hispanic white cohorts.[4]

Reports from the linked SEER cancer registry and Medicare databases between 1986 and 1999,[5] the National SEER database between 1992 and 2007,[6] and the California Cancer Registry between 1988 and 2004[2] concluded that black patients with RCC have shorter overall survival (OS) compared with white patients with RCC. A retrospective single-institution study using a clinical trial population from 1992 to 2002 to mitigate confounders also reported racial disparities in outcomes.[7] A more contemporary cohort of patients from the National Cancer Database showed improvement in patient outcomes independent of race after the introduction of vascular endothelial growth factor (VEGF)-targeted therapy in 2006 to 2011 compared with 1998 to 2004.[8] However, the survival gap between black and white populations persisted in this analysis. Collectively, these studies suggest that black patients with RCC have worse outcomes than their white counterparts.

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

This study examined outcomes in black versus white patients with metastatic renal cell carcinoma (mRCC) treated with inhibitors of the vascular endothelial growth factor pathway.

Knowledge Generated

Although race itself does not appear to be an independent predictor of overall survival in patients with mRCC, black patients tend to present with more adverse clinical features and have a shorter median survival than white patients. The study also highlights the under-representation of black patients in registries and clinical trials.

Relevance

Better understanding of biologic differences may help to optimize treatment and close the survival gap between races. Greater representation of black patients with mRCC in clinical trials is essential to ensure results are generalizable to all patients.

These disparities in survival are thought to reflect an interplay of socioeconomic factors, culture, environment, and differing underlying disease biology. The prevalence of RCC risk factors, such as hypertension, chronic kidney disease, obesity, cigarette smoking, lifestyle, and occupational/drug exposures, differs among black and white populations.[9] However, evidence to support that such factors influence the disparity in incidence and the natural history of RCC is lacking.[9]

Health care administrative databases do not account for important variations in baseline disease characteristics, such as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups[10] or the burden of disease; it is therefore unclear whether the racial disparity in survival previously reported would exist after accounting for these confounders. To better understand the effects of racial differences among patients with metastatic RCC (mRCC), this study examined outcomes in black patients compared with matched and unmatched white cohorts in the IMDC database and in a trial-database cohort from a pooled clinical trials database.

METHODS

Study Population

The study examined 2 independent groups of patients with mRCC. Patients were restricted to centers from North America and Northern Europe. The IMDC cohort included patients from a clinical retrospective and multi-institution database of consecutive patients with mRCC. The trial-database cohort was developed from a pooled RCC database of 12 prospective phase II (ClinicalTrials.gov identifiers: NCT00077974, NCT00137423, NCT00267748, NCT00338884, NCT00054886, NCT00835978) and phase III (ClinicalTrials.gov identifiers: NCT00083889, NCT00678392, NCT00920816, NCT00065468, NCT00474786, NCT00631371) clinical trials in patients with advanced RCC. For both cohorts, eligible patients had a confirmed diagnosis of mRCC of any histology (locally or centrally confirmed), were of black or white race, and were in receipt of a VEGF tyrosine kinase inhibitor (TKI) as first-line therapy or after cytokines. Baseline patient characteristics, IMDC risk groups (favorable [0 risk factors], intermediate [1 to 2 risk factors], or poor [$\geq$ 3 risk factors]), sites and number of metastases, history of nephrectomy, and clinical outcomes were extracted from both databases. IMDC risk factors included $<$ 1 year from diagnosis to systemic therapy, Karnofsky performance score $<$ 80%, hemoglobin less than the lower limit of normal, corrected calcium level greater than the upper limit of normal (ULN), neutrophil count greater than the ULN, and platelet count greater than the ULN. This study was approved by the ethics research board of each institution.

Study Design

Unmatched and matched cohort designs for race were conducted. For the unmatched analysis, all eligible patients were included. For the matched analysis, the coarsened exact matching procedure with variable ratio matching was performed.[11,12] The black and white study arms were matched by region (Canada, Northern Europe, United States), year of TKI initiation (2003 to 2007, 2008 to 2012, 2013 to 2016), age ($<$ 50, 50 to 59, 60 to 69, $\geq$ 70 years), and sex to eliminate any imbalances in these factors between the 2 racial categories. Weights were assigned to the matched white study arm, accounting for variable ratios (number of white *v* black patients) across strata from the matching procedure.[11,12]

Statistical Methods

Unless specified otherwise, identical statistical analyses and matching procedure were performed in the IMDC and trial-database cohorts. Baseline patient and disease characteristics were reported as absolute numbers and percentages. The χ^2 test was used to compare the distribution of and difference in objective response rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 between racial categories. The distribution of OS, time to treatment failure (TTF) for the IMDC cohort, and progression-free survival (PFS) for

the trial-database cohort were estimated using Kaplan-Meier methodology. OS was defined as treatment start or randomization (for the trial-database only) until death; if death was not observed, patients were censored at the time they were last known to be alive. TTF was defined as the time of starting TKI treatment until discontinuation or death, or, if they remained on therapy, patients were censored at their last assessment. PFS was the time of the randomization or protocol treatment initiation until progression of the disease or death; patients who had not experienced disease progression were censored at their last assessment.

Cox multivariable regression analysis assessed the adjusted hazard ratio (HR) and 95% CI for the black versus white study arms. For the matched analysis, the models were adjusted for patient and disease characteristics, including histology (clear-cell and non–clear-cell RCC), number of metastases, nephrectomy status, and IMDC risk groups; weights were applied to the models accounting for variable ratios across strata from the matching procedure.[11,12] For the unmatched full analysis, additional variables (sex, age, and duration of TKI treatment) were also included in the multivariable models. An "unknown" category was included in the model if missing values were present for a categorical covariable, to limit exclusion of black patients from the analysis.

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Statistical significance was assumed at a 2-sided α error level $< .05$.

RESULTS

Matching

The IMDC cohort consisted of 3,454 patients identified from the North American and Northern European subsets of the IMDC, where 73 (2%) were black and 3,381 (98%) were white. In the trial-database cohort, 1,061 patients were identified: 21 (2%) black and 1,040 (98%) white (Fig 1**)**. The matching procedure was successful for both datasets based on Sturges' rule.[11,12] The procedure resulted in an average of 17:1 match (1,236 white to 73 black patients) in the IMDC cohort and 21:1 (431 white to 21 black patients) in the trial-database cohort.

Baseline Characteristics

Baseline and disease characteristics for both cohorts are summarized in Table 1. Overall, the groups were well balanced. At treatment initiation, there was a greater proportion of black patients with non–clear-cell histology, < 1 year interval from diagnosis to treatment, and anemia in the IMDC cohort in both matched and unmatched analyses. Although there was no difference in the rate of prior nephrectomy in the unmatched analysis, matching resulted

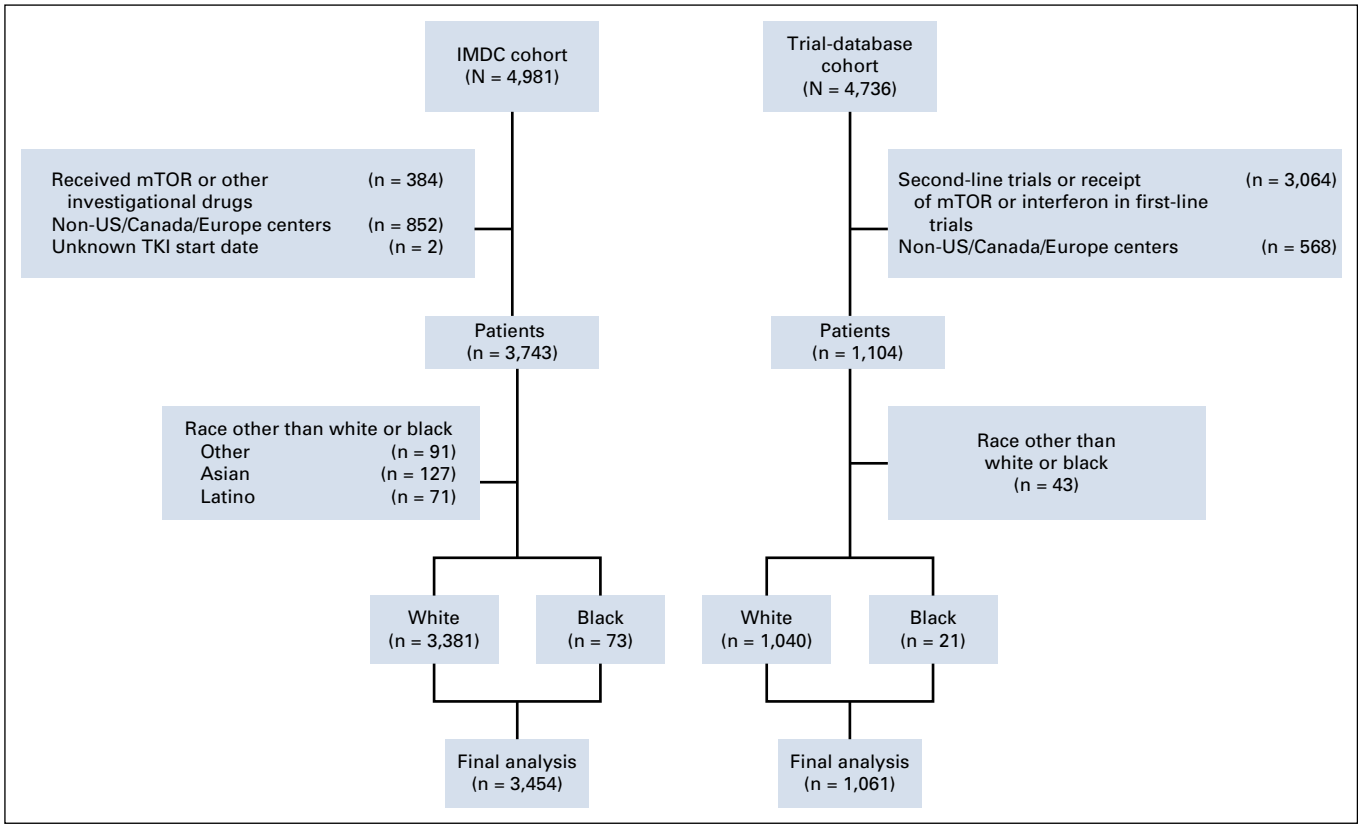

FIG 1. Flow diagram. IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor.

TABLE 1. Baseline Patient and Disease Characteristics

	IMDC Cohort						Trial-Database Cohort					
	Black		White				Black		White			
			Matched		Unmatched				Matched		Unmatched	
	n = 73		n = 1,236		n = 3,381		n = 21		n = 431		n = 1,040	
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Matched variables												
Age at TKI initiation												
Median (IQR), years	60	52-67	60	53-68	62	55-69	58	54-65	61	55-66	61	54-68
< 50	12	16	203	16	393	12	4	19	26	6	129	12
50-59	24	33	406	33	990	29	9	43	166	39	321	31
60-69	22	30	372	30	1,226	36	5	24	187	43	383	37
≥ 70	15	21	254	21	765	23	3	14	52	12	207	20
Missing	0		0		7		0		0		0	
Male sex	55	75	931	75	2,434	72	15	71	334	77	727	70
Region												
Canada	15	21	254	21	699	21	1	5	4	1	**31**	**3*****
Northern Europe	3	4	51	4	1,395	41	1	5	32	7	**461**	**44**
United States	55	75	931	75	1,287	38	19	90	395	92	**548**	**53**
Year of TKI initiation												
2003 to 2007	32	44	542	44	**1,193**	**35*****	11	52	259	60	489	47
2008 to 2012	38	52	643	52	**1,449**	**43**	10	48	172	40	551	53
2013 to 2016	3	4	51	4	**739**	**22**	0		0		0	
Unmatched variables												
Histology												
Clear cell	49	74	**1,034**	**89*****	**2,834**	**88*****	18	86	399	93	961	92
Non–clear cell	17	26	**127**	**11**	**385**	**12**	3	14	32	7	79	8
Missing	7		75		162		0		0		0	
Sarcomatoid differentiation												
Absent	57	86	957	88	2,430	87	20	95	418	97	1,014	98
Present	9	14	126	12	376	13	1	5	13	3	26	2
Missing	7		153		575		0		0		0	

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TABLE 1. Baseline Patient and Disease Characteristics (Continued)

	IMDC Cohort						Trial-Database Cohort					
	Black		White				Black		White			
			Matched		Unmatched				Matched		Unmatched	
	n = 73		n = 1,236		n = 3,381		n = 21		n = 431		n = 1,040	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
No. of metastatic sites												
1	17	24	246	20	659	21	4	20	97	23	179	17
> 1	55	76	990	80	2,553	79	16	80	330	77	852	83
Missing	1		0		169		1		4		9	
Prior nephrectomy												
No	18	25	**194**	**16***	603	18	2	10	70	16	**352**	**34***
Yes	55	75	**1,042**	**84**	2,776	82	19	90	361	84	**688**	**66**
Missing	0		**0**		2		0		0		**0**	
Karnofsky performance score												
≥ 80	56	86	1,035	84	2,571	81	21	100	416	97	1,006	97
< 80	9	14	201	16	614	19	0		15	3	34	3
Missing	8		0		196		0		0		0	
Diagnosis to first-line TKI < 1 year												
No	24	33	**556**	**45***	**1,494**	**46***	6	29	148	34	375	36
Yes	49	67	**680**	**55**	**1,765**	**54**	15	71	283	66	665	64
Missing	0		**0**		**122**		0		0		0	
Low hemoglobin												
No	17	25	**568**	**46****	**1,527**	**49*****	9	43	**309**	**72****	**732**	**71****
Yes	50	75	**668**	**54**	**1,602**	**51**	12	57	**121**	**28**	**297**	**29**
Missing	6		**0**		**252**		0		**1**		**11**	
High calcium												
No	57	88	1,144	93	2,514	86	16	84	300	82	779	85
Yes	8	12	92	7	400	14	3	16	66	18	134	15
Missing	8		0		467		2		65		127	
High neutrophil count (> ULN)												
No	58	92	1,057	86	2,537	84	16	80	347	82	808	84
Yes	5	8	179	14	483	16	4	20	75	18	150	16
Missing	10		0		361		1		9		82	

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TABLE 1. Baseline Patient and Disease Characteristics (Continued)

	IMDC Cohort						Trial-Database Cohort					
	Black		White				Black		White			
			Matched		Unmatched				Matched		Unmatched	
	n = 73		n = 1,236		n = 3,381		n = 21		n = 431		n = 1,040	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
High platelet count (> ULN)												
No	53	79	1,027	83	2,509	83	16	80	365	85	878	86
Yes	14	23	209	17	530	17	4	20	65	15	148	14
Missing	6		0		342		1		1		14	
IMDC risk group												
Favorable	7	11	253	20	564	19	2	12	87	25	215	26
Intermediate	36	58	705	57	1,587	54	11	65	193	54	468	56
Poor	19	31	278	23	765	26	4	23	75	21	150	18
Missing	11		0		465		4		76		207	

NOTE. Missing values were excluded for percentage and χ^2 test. For matched white patients, numbers and percentages were weighted values to account for variable ratios (number of white patients versus number of black patients) across strata from the matching procedure. Bold type indicates significance.

Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; TKI, tyrosine kinase inhibitor; ULN, upper limit of normal.

*$P \leq .05$.

**$P \leq .01$.

***$P \leq .001$.

in a higher rate of nephrectomy in white compared with black patients (84% *v* 75%; *P* = .04).

In the trial-database cohort, baseline anemia was more frequent in black compared with white patients in both matched and unmatched analyses. Unlike the IMDC cohort, rate of nephrectomy was higher in the black versus white study arm in the unmatched analysis (90% *v* 66%; *P* = .02). The difference in rate of nephrectomy between races was not significant in the matched analysis. The number of patients with non–clear-cell RCC in the trial-database cohort was limited (n = 82; 8%) because they were excluded from some of the pooled clinical trials composing this dataset.

Overall Survival

There were 2,382 (69%) deaths observed in the IMDC cohort. The median follow-up for patients who were alive was 34 months. The estimated median OS for white patients was 25.8 months (95% CI, 23.1 to 28.8 months) and 25.1 months (95% CI, 23.7 to 26.7 months) in the matched and unmatched analyses, respectively, compared with 18.5 months (95% CI, 13.8 to 26.1 months) for black patients (Fig 2; Table 2). The difference was not statistically significant in the multivariable analysis (matched cohort HR [HR_M], 1.0; 95% CI, 0.7 to 1.5; and unmatched cohort HR [HR_{UM}], 1.1; 95% CI, 0.8 to 1.4). The Cox model presented in Table A1 shows that all clinical predictors other than race were strongly associated with OS.

In the trial-database cohort, the median follow-up of patients who were alive was 24.9 months. The estimated OS in white patients was 25.5 months for the matched and 25.6 months for the unmatched analyses, whereas the median OS in black patients was 21.0 months (Fig 3; Table 2). The difference did not reach statistical significance in the multivariable analysis (HR_M, 1.5; 95% CI, 0.8 to 2.7; HR_{UM}, 1.4; 95% CI, 0.8 to 2.6; Table 2). Again, all other predictors, except for histology, were associated with survival (Table A1).

TTF, PFS, and Response Rates

In the IMDC cohort, the estimated median TTF was 4.6 months (95% CI, 4.0 to 7.3 months) in black patients versus 7.3 months (95% CI, 6.4 to 8.1 months) and 7.6 months (95% CI, 7.1 to 8.0 months), respectively, in the matched and unmatched white cohorts (Fig A1). TTF was significantly longer in white patients in the unmatched analysis (adjusted HR_{UM}, 1.4; 95% CI, 1.1 to 1.8; *P* = .003), but the difference did not reach statistical significance in the matched analysis, although there was a trend in the same direction (adjusted HR_M, 1.2; 95% CI, 1.0 to 1.6; *P* = .1; Table 2). Non–clear-cell histology was associated with increased risk of treatment failure after adjusting for other predictors (adjusted HR, 1.4; 95% CI, 1.2 to 1.5; *P* < .0001). ORR was lower in black versus matched and unmatched white patients: 13% versus 27% (*P* = .01) and 24% (*P* = .04), respectively.

In the trial-database cohort, the estimated PFS was 5.3 months in black patients compared with 10.5 and 10.7 months in the matched and unmatched white cohorts, respectively (Fig A2). The differences were statistically significant in both analyses (Table 2). ORR was 11% in black patients and 41% (*P* = .01) and 39% (*P* = .01) in the matched and unmatched white cohorts, respectively.

DISCUSSION

This study examined the disparity in oncologic outcomes between black and white patients with mRCC who received front-line VEGF TKIs in 2 independent cohorts. Contrary to

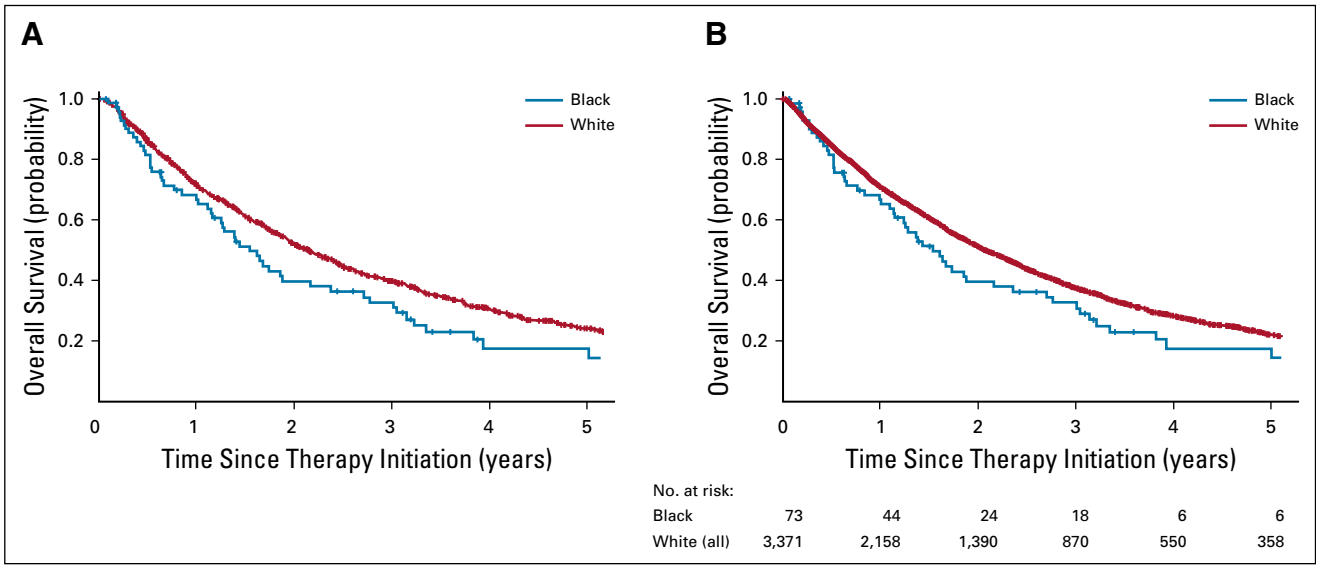

FIG 2. Kaplan-Meier estimate of overall survival by race in the (A) matched* and (B) unmatched dataset of the International Metastatic Renal Cell Carcinoma Database Consortium cohort. (*) Number of patients at risk for the matched analysis is not reported as Kaplan-Meier plot is based on weighted estimates.

TABLE 2. Oncologic Outcomes of Black Versus White Patients With Metastatic Renal Cell Carcinoma

	IMDC Cohort					Trial-Database Cohort				
	Matched Analysis			Unmatched Analysis		Matched Analysis			Unmatched Analysis	
Outcome	Black	White	*P*	White	*P*	Black	White	*P*	White	*P*
Overall survival										
No. of patients (No. events)	73 (52)	1,236 (904)		3,371 (2,330)		21 (12)	431 (210)		1,040 (509)	
Median (95% CI), months	18.5 (13.8 to 26.1)	25.8 (23.1 to 28.8)		25.1 (23.7 to 26.7)		21.0 (6.1 to NE)	25.5 (23.4 to 31.1)		25.6 (23.7 to 29.6)	
HR (95% CI), black *v* white	1.0 (0.7 to 1.5)[a]		.9	1.1 (0.8 to 1.4)[b]	.7	1.5 (0.8 to 2.7)[a]		.18	1.4 (0.8 to 2.6)[a]	.21
TTF/PFS[c]										
No. (No. of events)	73 (71)	1,236 (1,147)		3,355 (2,986)		21 (16)	431 (292)		1,040 (719)	
Median (95% CI), months	4.6 (4.0 to 7.3)	7.3 (6.4 to 8.1)		7.6 (7.1 to 8.0)		5.3 (1.8 to 9.8)	10.5 (9.2 to 11.3)		10.7 (9.7 to 11.0)	
HR (95% CI), black *v* white	1.2 (0.95 to 1.6)[a]		.1	1.4 (1.1 to 1.8)[b]	**.003**	2.3 (1.4 to 3.9)[a]		**.002**	2.3 (1.4 to 3.9)[a]	**.002**
ORR										
No. evaluable	63	969		2,776		18	410		989	
No. (%)	8 (13)	267 (27)	**.01**	672 (24)	**.04**	2 (11)	169 (41)	**.01**	390 (39)	**.01**

NOTE. Significance assumed for $P \leq .05$. Bold type indicates significance.

Abbreviations: HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure.

[a]Adjusted for histology, number of metastases, nephrectomy status, IMDC risk group.

[b]Adjusted for sex, age at targeted therapy initiation, year of tyrosine kinase inhibitor initiation (2003 to 2007, 2008 to 2012, 2013 to 2016), histology, number of metastases, nephrectomy status, IMDC risk group.

[c]TTF (IMDC cohort); PFS (trial-database cohort).

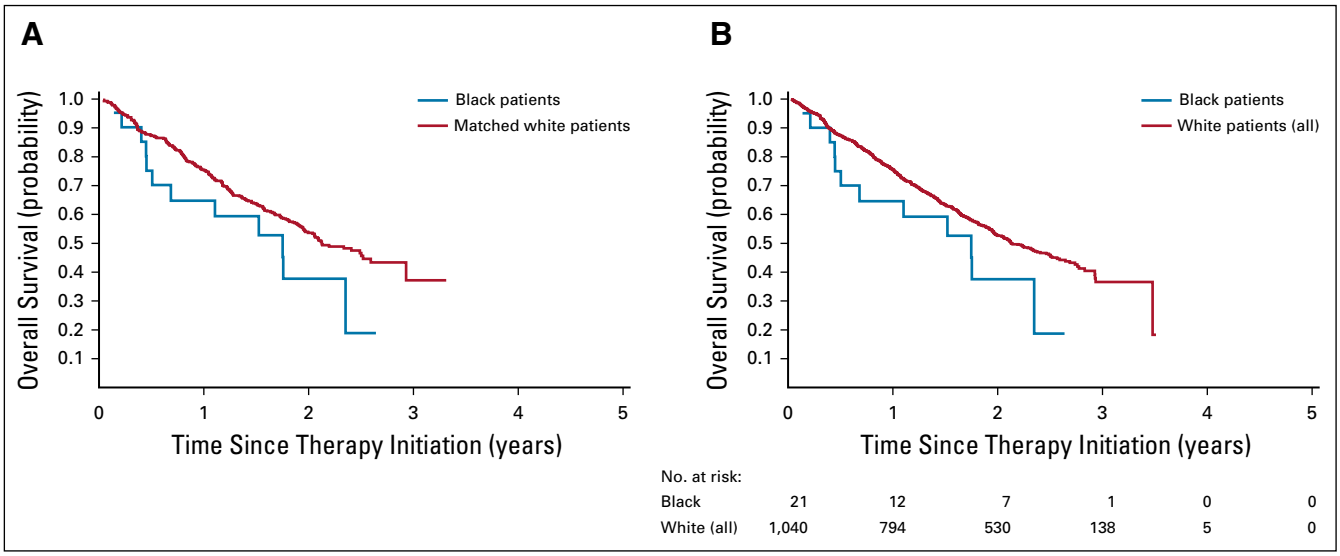

FIG 3. Kaplan-Meier estimate of overall survival by race in the (A) matched* and (B) unmatched dataset of the trial-database cohort. (*) Number of patients at risk for the matched analysis is not reported as Kaplan-Meier plot is based on weighted estimates.

previous reports from large health care administrative databases, this study accounted for important prognostic factors validated in mRCC and assessed the effectiveness of VEGF TKIs in a black population. Importantly, race was not found to be independently associated with OS. The study suggests, however, that TTF and PFS in patients treated with VEGF TKIs were shorter in the black versus white patients. The study also highlights the underrepresentation of black race in the IMDC database and clinical trials (2%) versus their prevalence in the community (US, 13.4%; Canada, 3.4%) and the need to increase enrollment of black and other minorities in clinical trials and registries.[11,12]

Reasons behind the disparity in RCC survival between black and white racial groups reported in the literature have not been fully elucidated. Similar to these previous studies,[2,5-7] the current study found that median OS in the black cohort was shorter compared with the white cohort, but the difference may be explained by higher rates of adverse clinical features among the black patients, as seen in the multivariable analysis. Black patients in the current study had more IMDC risk factors, including a higher rate of time from diagnosis to RCC treatment < 1 year, suggesting that black patients are more likely to present with synchronous metastases or to experience recurrence shortly after radical nephrectomy, which is a known independent adverse predictor of survival in RCC.[13] The increased risk factors for black patients at diagnosis may suggest later referral to oncologists. After adverse clinical features were accounted for in the multivariable models, race no longer appeared to be a determinant of survival.

Unlike most published studies from large administrative databases, only patients with mRCC who were treated with VEGF TKIs at an academic center (IMDC cohort) or as part of a clinical trial (trial-database cohort) were included in the current analysis. Therefore, cancer staging, access to health care, disparity in treatment, and, to some extent, socioeconomic factors were not as likely to be significant confounders in the current study.

The findings also suggest that black patients with mRCC do not benefit from VEGF TKI therapy to the same extent as their white counterparts. Although there was only a trend toward shorter TTF in the matched analysis of the IMDC cohort, the unmatched analysis, as well as the matched and unmatched analyses of the trial-database cohort, demonstrated statistically significantly shorter TTF/PFS among black patients. Accordingly, the response rate to treatment with VEGF TKIs was also markedly lower in the black arm of the current study.

It is plausible that genomic and/or epigenomic variations in tumors between races are responsible for the lower effectiveness of VEGF TKIs in black patients. A study using The Cancer Genome Atlas (TCGA) reported that clear-cell RCC in black patients was less likely to harbor a *VHL* mutation.[14] Accordingly, tumors from black patients have a relative downregulation of *HIF* and *VEGF* pathways that, in turn, may result in lower activity of VEGF-targeted therapies. Differences in disease biology between races were also identified in the papillary RCC subset of the TCGA.[15] In their report, tumors derived from black compared with white patients were more likely to be enriched in immune-related pathways such as the B-cell receptor and NOD-like receptor signaling pathways. This observation poses the hypothesis that black patients may experience differential responses to immunotherapy-based regimens; however, to our knowledge, there is no clinical study examining the relative effectiveness of immunotherapy in black patients with RCC.

The distribution of RCC subtypes is another biologic variation between black and white patients. In the IMDC cohort that comprised a consecutive series of patients with RCC treated at academic institutions, black patients were twice as likely as white patients to present with non–clear-cell RCC histology (26% *v* 12%). However, the distribution of histology cannot be interpreted in the trial-database cohort because non–clear-cell RCC subtypes were excluded from many of the clinical trials that comprised the cohort. Furthermore, similar findings were reported from data in the SEER Program.[4] In this study, the greater proportion of patients with non–clear-cell RCC was mainly driven by the enrichment of patients with papillary RCC of black ancestry compared with white race (23% *v* 9%).[4]

Differences in molecular landscapes of cancer according to race have been described in multiple solid tumors, including colorectal cancer, lung cancer, and gliomas.[16] Increasingly, biologic differences in "omics" is thought to contribute to some of the racial disparities observed in cancer outcomes. In patients with prostate cancer, for instance, multiple differences in epigenomics, genomics, androgen signaling, and microRNA alterations have been reported between black and white racial groups.[17,18] Although the causality between racial differences in tumor biology and outcome disparity cannot be established directly, better understanding of these biologic differences may help to optimize treatment and close the survival gap between races.

Because the current standard front-line therapies for mRCC are shifting toward immunotherapy-based regimens, prospective studies assessing the relative efficacy of checkpoint inhibitors among black patients are warranted. It is essential that clinical trials and prospective biorepositories enroll more black patients to extend the generalizability of clinical trial findings and biomarker studies to nonwhite patients and to assist clinicians in selecting treatments with the highest efficacy among all available options.

Other clinical factors and determinants of health not measured in the current study may contribute to the racial disparity observed in published epidemiologic studies. Among others, access to health care, demographic and economic barriers to treatment, comorbidities, and adherence to oral TKI therapies were not accounted for in the current study and may influence prognosis at the population level. Despite the large cohorts of patients included, the number of black patients was small relative to the number of white patients; results should therefore be interpreted with caution. To help mitigate any bias this may have introduced, a matched analysis was reported of a group of white patients who shared as many demographic characteristics as possible with the black patients. Also of note, however, is that most patients were treated either in an academic center or enrolled in a clinical trial; therefore, results from the study may not be fully generalizable to the general population. Finally, the effectiveness of TKIs was reported as TTF in the IMDC cohort and PFS in the trial-database cohort because of the structure of the datasets. These 2 endpoints should be interpreted differently.

In summary, although race itself does not appear to be an independent predictor of OS in patients with mRCC, black patients tend to present with more adverse clinical features and have a shorter median survival than white patients. This analysis also suggests lower activity of VEGF TKIs in black versus white patients. Greater representation of those of black race in clinical trials is essential to ensure results are generalizable to all patients.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394-424, 2018
2. Stafford HS, Saltzstein SL, Shimasaki S, et al: Racial/ethnic and gender disparities in renal cell carcinoma incidence and survival. J Urol 179:1704-1708, 2008
3. Vaishampayan UN, Do H, Hussain M, et al: Racial disparity in incidence patterns and outcome of kidney cancer. Urology 62:1012-1017, 2003
4. Olshan AF, Kuo TM, Meyer AM, et al: Racial difference in histologic subtype of renal cell carcinoma. Cancer Med 2:744-749, 2013
5. Berndt SI, Carter HB, Schoenberg MP, et al: Disparities in treatment and outcome for renal cell cancer among older black and white patients. J Clin Oncol 25:3589-3595, 2007
6. Chow WH, Shuch B, Linehan WM, et al: Racial disparity in renal cell carcinoma patient survival according to demographic and clinical characteristics. Cancer 119:388-394, 2013
7. Tripathi RT, Heilbrun LK, Jain V, et al: Racial disparity in outcomes of a clinical trial population with metastatic renal cell carcinoma. Urology 68:296-301, 2006
8. Rose TL, Deal AM, Krishnan B, et al: Racial disparities in survival among patients with advanced renal cell carcinoma in the targeted therapy era. Cancer 122:2988-2995, 2016
9. Lipworth L, Tarone RE, McLaughlin JK: Renal cell cancer among African Americans: An epidemiologic review. BMC Cancer 11:133-141, 2011
10. Heng DY, Xie W, Regan MM, et al: Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. J Clin Oncol 27:5794-5799, 2009
11. Nazha B, Mishra M, Pentz R, et al: Enrollment of racial minorities in clinical trials: Old problem assumes new urgency in the age of immunotherapy. Am Soc Clin Oncol Educ Book 39:3-10, 2019
12. Statistics Canada: Census profile, 2016 Census. https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/prof/index.cfm?Lang=E
13. Donskov F, Xie W, Wells JC, et al: Synchronous vs metachronous metastatic disease: Impact of time to metastasis on outcome in metastatic renal cell carcinoma patients treated with targeted therapy. Ann Oncol 28 (suppl_5):v295-v329, 2017
14. Krishnan B, Rose TL, Kardos J, et al: Intrinsic genomic differences between African American and white patients with clear cell renal cell carcinoma. JAMA Oncol 2:664-667, 2016
15. Paulucci DJ, Sfakianos JP, Skanderup AJ, et al: Genomic differences between black and white patients implicate a distinct immune response to papillary renal cell carcinoma. Oncotarget 8:5196-5205, 2017
16. Heath EI, Lynce F, Xiu J, et al: Racial disparities in the molecular landscape of cancer. Anticancer Res 38:2235-2240, 2018
17. Kumar S, Singh R, Malik S, et al: Prostate cancer health disparities: An immuno-biological perspective. Cancer Lett 414:153-165, 2018
18. Huang FW, Mosquera JM, Garofalo A, et al: Exome sequencing of African-American prostate cancer reveals loss-of-function *ERF* mutations. Cancer Discov 7:973-983, 2017

APPENDIX

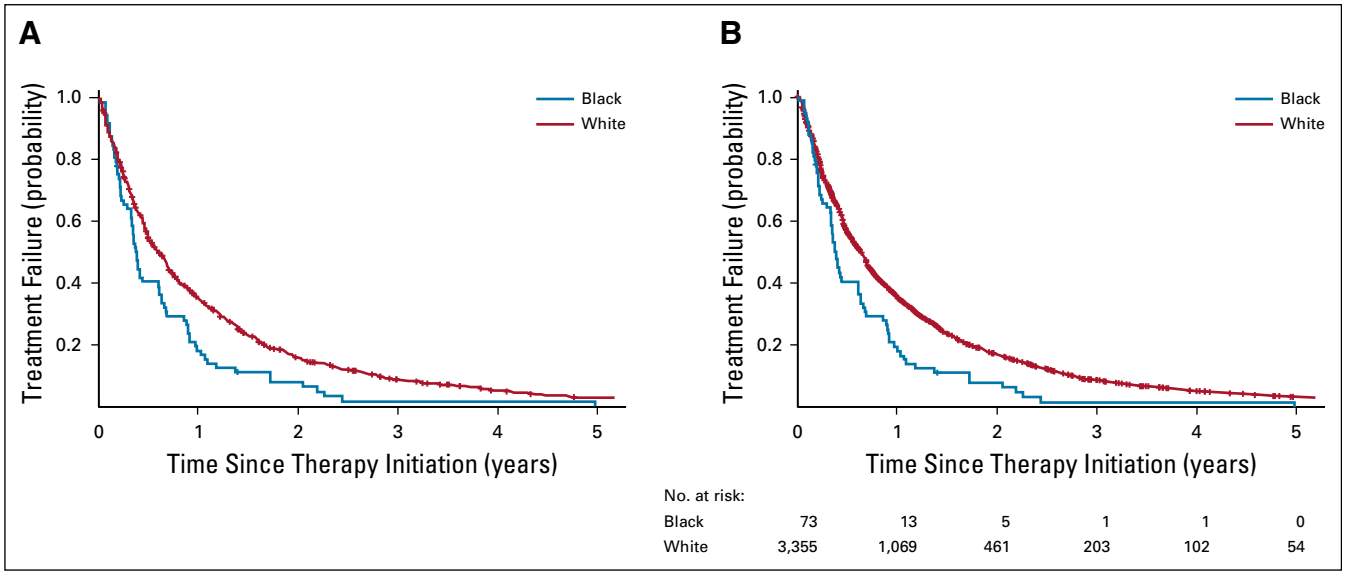

FIG A1. Kaplan-Meier estimate of time to treatment failure by race in the (A) matched* and (B) unmatched dataset of the International Metastatic Renal Cell Carcinoma Database Consortium cohort. (*) Number of patients at risk for the matched analysis is not reported as Kaplan-Meier plot is based on weighted estimates.

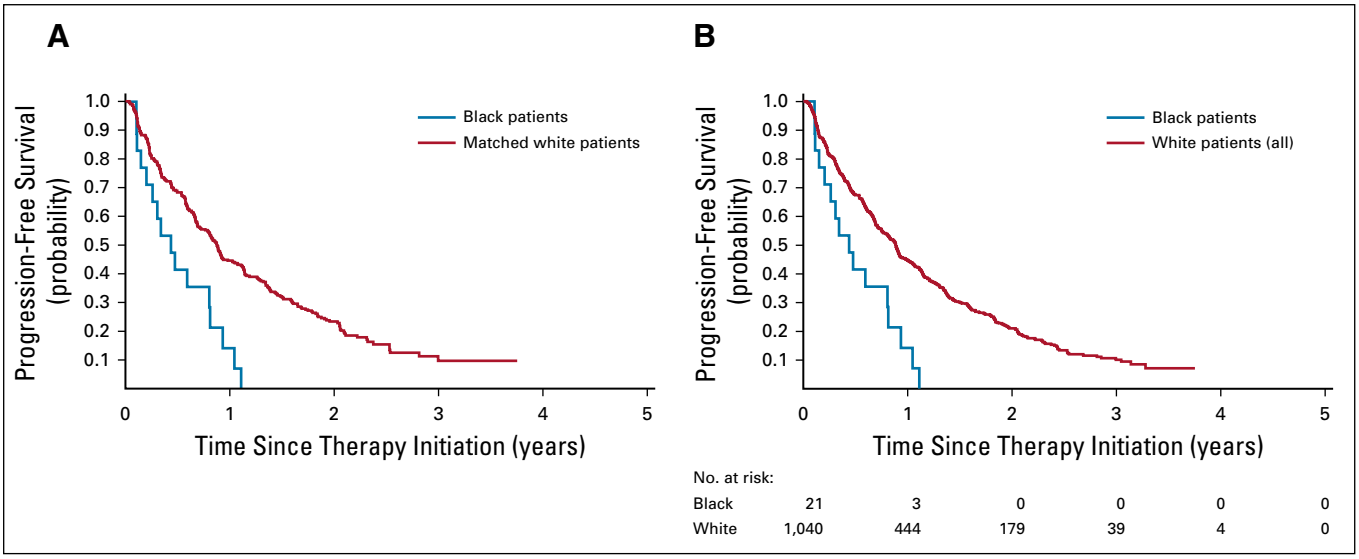

FIG A2. Kaplan-Meier estimate of progression-free survival by race in the (A) matched* and (B) unmatched dataset of the trial-database cohort. (*) Number of patients at risk for the matched analysis is not reported as Kaplan-Meier plot is based on weighted estimates.

TABLE A1. Cox Multivariable Model for Overall Survival in the Matched Cohorts

	IMDC Cohort			Trial-Database Cohort		
Cox Model	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Black *v* white	1.0	0.7 to 1.5	.9	1.5	0.8 to 2.7	.2
Histology: non–clear cell *v* clear cell	1.6	1.2 to 2.1	.001	1.3	0.8 to 2.2	.2
No. metastases: > 1 *v* 1	1.6	1.3 to 1.9	< .0001	0.5	0.4 to 0.8	.001
Prior nephrectomy: yes *v* no	0.5	0.4 to 0.6	< .0001	1.6	1.1 to 2.2	.009
IMDC risk factor: intermediate *v* favorable	1.5	1.2 to 1.8	< .0001	4.3	2.4 to 7.5	< .0001
IMDC risk factor: poor *v* favorable	3.7	2.9 to 4.8	< .0001	9.6	5.3 to 17.4	< .0001
IMDC risk factor: missing *v* favorable	—	—	—	3.8	2.0 to 7.0	< .0001

Abbreviations: HR, hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium.

