ORIGINAL ARTICLE

Racial Differences in Systemic Immune Parameters in Individuals With Lung Cancer

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Received 26 June 2024; revised 10 October 2024; accepted 13 October 2024
Available online 19 October 2024

ABSTRACT

Introduction: Racial and ethnic disparities in the presentation and outcomes of lung cancer are widely known. To evaluate potential factors contributing to these observations, we measured systemic immune parameters in Black and White patients with lung cancer.

Methods: Patients scheduled to receive cancer immunotherapy were enrolled in a multi-institutional prospective biospecimen collection registry. Clinical and demographic information were obtained from electronic medical records. Pretreatment peripheral blood samples were collected and analyzed for cytokines using a multiplex panel and for immune cell populations using mass cytometry. Differences between Black and White patients were determined and corrected for multiple comparisons.

Results: A total of 187 patients with NSCLC (Black, 19; White, 168) were included in the analysis. Compared with White patients, Black patients had greater comorbidity (median Charlson Comorbidity Index 5 versus 3; $p = 0.04$) and were more likely to have received previous chemotherapy (79% versus 47%; $p = 0.03$). Black patients had significantly lower levels of CCL23 and CCL27 and significantly higher levels of CCL8, CXCL1, CCL26, CCL25, CCL1, IL-1b, CXCL16, and IFN-γ (all $p < 0.05$, false discovery rate < 0.1). Black patients also exhibited greater populations of nonclassical CD16+ monocytes, NKT-like cells, CD4+ cells, CD38+ monocytes, and CD57+ gamma delta T cells (all $p < 0.05$).

Conclusions: Black and White patients with lung cancer exhibit several differences in immune parameters, with Black patients exhibiting greater levels of numerous

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Cite this article as: von Itzstein MS, Liu J, Mu-Mosley H, et al. Racial differences in systemic immune parameters in individuals with lung cancer. *JTO Clin Res Rep* 2024;5:100751

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2024.100751

proinflammatory cytokines and cell populations. The etiology and clinical significance of these differences warrant further evaluation.

Keywords: Cytokines; Immune cells; Disparities; Immunotherapy; Lung cancer; Race

Introduction

The incidence, presentation, and outcomes of many cancers differ according to patient race. For instance, Black patients have greater incidence and mortality from prostate cancer.[1] Compared with White patients, Black individuals develop lung cancer after less smoking, at younger age, at more advanced stage, and have decreased survival.[2]

To evaluate these observations further in the immuno-oncology era, studies have also evaluated immune parameters according to patient race and ethnicity. IL-6 and CRP levels are elevated in healthy Black populations compared with White populations.[3] Differences also exist within oncology populations. For instance, Black patients with prostate cancer have higher levels of CXCL2 and CXCL5 than do White patients.[4] In resected lung cancer specimens, cell proliferation pathways and macrophage subtypes differ between Black and White patients.[5]

Given the persistent racial health disparities in lung cancer presentation and outcomes and the growing awareness of differences in inflammatory markers across populations, we analyzed systemic cytokines and immune cell populations in White and Black patients with NSCLC.

Methods

Study Protocol and Clinical Data

This was a prospective multi-institutional registry study approved by the University of Texas Southwestern Institutional Review Board (IRB #STU 082015-053) and the IRBs of all participating centers. Patients provided written informed consent before undergoing any study-specific procedures.

For this study, eligible patients had a diagnosis of NSCLC and were planned for but had not yet initiated immune checkpoint inhibitor (ICI)-based therapy, including concurrent and sequential combination regimens. Enrolled individuals underwent collection of clinical data from the electronic medical record (including age, sex, race, cancer stage and histology, systemic treatment history, body mass index, tumor programmed death-ligand 1 expression, smoking status, autoimmune disease history, and use of systemic immunosuppressive medications within 30 days of starting ICI). We collected Charlson comorbidity index (maximum score 37) data based on previously published guidelines using International Classification of Diseases codes within the previous 1 year of the cancer diagnosis.[6,7] Peripheral blood samples were collected before ICI initiation.

For this analysis, we analyzed patients with NSCLC of any stage who self-identified as non-Hispanic Black or non-Hispanic White.

Biospecimen Processing and Cytokine Analysis

As previously described,[8] we used the Bio-Plex Pro Human Chemokine 40-plex Panel (Bio-Rad Laboratories, Hercules, CA) on a Luminex 200 System to measure plasma cytokines. Supplementary Table 1 lists the cytokines included in the panel. Cytokine concentrations were transformed on a $\log_2$ scale and batch-corrected using the ComBat parametric empirical Bayes framework.[9]

Cytometry by Time of Flight

Cryopreserved peripheral blood mononuclear cells were thawed and stained with a panel of 36 antibodies (metal isotope-labeled conjugates, Maxpar Direct Immune Profiling Assay Panel by Standard BioTools). We analyzed cells on a Helios mass cytometer (Standard BioTools). Data were normalized and analyzed with gating on CD45+ cells using the cloud-based computational platform OMIQ.ai (Dotmatics Software Company). We identified cluster immune phenotypes following standard immunophenotyping for the Human Immunology Project.

Statistical Analysis

We used chi-square tests, Fisher's exact tests, and Mann-Whitney *U* tests to assess for associations between case characteristics and race. Log_2-transformed and batch-corrected cytokine values were compared between the two groups using the Mann-Whitney *U* test. To account for multiple comparisons, the Benjamini–Hochberg procedure was applied to evaluate false discovery rates (FDRs). All analyses were conducted with R (version 4.1.3) or GraphPad Prism 10.2.3. We defined significance as p less than 0.05 and for cytokine analysis p less than 0.05 and FDR less than 0.1.

Pathway Analysis

We used the online tool string-db.org to analyze pathway interactions among cytokines exhibiting significant ($p < 0.05$; FDR < 0.1) differences between Black

Table 1. Clinical Characteristics in the Overall Cohort and According to Race

Characteristic, n (%)	Overall, (N = 187[a]), n (%)	White, (N = 168[a]), n (%)	Black, (N = 19[a]), n (%)	*p* Value
Age, y				0.54
≥65	121 (65)	107 (64)	14 (74)	
<65	66 (35)	61 (36)	5 (26)	
Sex				0.76
Male	107 (57)	95 (57)	12 (63)	
Female	80 (43)	73 (43)	7 (37)	
Cancer stage				
II	2 (1)	2 (1)	0 (0)	0.07
III	33 (18)	26 (15)	7 (37)	
IV	152 (81)	140 (83)	12 (63)	
Histology				1
Squamous	39 (21)	35 (21)	4 (21)	
Nonsquamous	148 (79)	133 (79)	15 (79)	
PD-L1				0.09
<1%	35 (35)	28 (31)	7 (64)	
1-49%	36 (35)	33 (37)	3 (27)	
≥50%	30 (30)	29 (32)	1 (9)	
Smoking status				0.62
Former	118 (73)	102 (71)	16 (84)	
Current	19 (12)	18 (13)	1 (5)	
Never	25 (15)	23 (16)	2 (11)	
Pack years				
Median (IQR)	30 (15, 50)	34 (14, 50)	25 (19, 44)	0.53
BMI				0.32
<18.4	5 (3)	5 (3)	0 (0)	
18.5-24.9	62 (39)	55 (38)	7 (39)	
25-29.9	57 (35)	53 (37)	4 (22)	
>30	37 (23)	30 (21)	7 (39)	
Line of systemic therapy				0.33
First	93 (55)	85 (56)	8 (42)	
Second	55 (32)	46 (30)	9 (47)	
Third and above	22 (13)	20 (13)	2 (11)	
Previous therapy[b]				0.03
None	71 (42)	68 (45)	3 (16)	
Immunotherapy	6 (3)	5 (3)	1 (5)	
Chemotherapy without immunotherapy	86 (51)	71 (47)	15 (79)	
Targeted or other without chemotherapy or immunotherapy	7 (4)	7 (5)	0 (0)	
Autoimmune disease				1
Yes	19 (10)	2 (13)	17 (14)	
No	115 (61)	14 (88)	101 (86)	
Charlson comorbidity score				0.04
Median (IQR)	3 (2-6)	3 (2-5)	5 (2-10)	
Pre-ICI immunosuppression[c]				0.26
Yes	20 (15)	16 (14)	4 (25)	
No	114 (85)	102 (86)	12 (75)	

[a]Categories that do not contain a sum of 187 cases in the overall column, 168 cases in the White column, or 19 cases in the Black column represent missing data.
[b]Including systemic therapy (adjuvant, concurrent, etc.) for nonmetastatic disease.
[c]Within 30 days of starting ICI.
BMI, body mass index; ICI, immune checkpoint inhibitor; IQR, interquartile range; PD-L1, programmed death-ligand 1.

and White patients. Both Gene Ontology (biological process) and Pathways (Kyoto Encyclopedia of Genes and Genomes [KEGG] Pathways and wikiPathways) were analyzed.

Results

A total of 187 patients (Black, 19; White, 168) were identified for this study. Among these individuals, 57% were male, 65% were above 65 years old, and 81% had stage IV disease. Additional case characteristics are found in Table 1. Age, sex, race, and cancer stage and histology were available for all patients. For other variables, the number of cases with available data was as follows: programmed death-ligand 1 status (N = 100, 53%), smoking status (N = 162, 87%), pack-year history (N = 170, 91%), systemic treatment history (N = 170,

91%), autoimmune disease (N = 134, 72%), immunosuppression use (N = 134, 72%), and Charlson comorbidity index (N = 161, 86%). Black patients were more likely to have previous chemotherapy (79% versus 47%; $p = 0.03$) and a higher Charlson comorbidity index (median 5 versus 3; $p = 0.04$). There was a near-significant trend toward earlier stage disease in Black patients ($p = 0.07$).

Cytokine levels were available for all 187 patients. Among the 40 cytokines analyzed, 35 (88%) had results that met technical criteria for inclusion in the study. Of these cytokines, 10 (29%) exhibited statistically significant differences between Black and White patients (Fig. 1). For eight of the cytokines with significant differences between races (80%), levels were higher in Black patients, with CCL23 and CCL27 representing the only exceptions. Supplementary Table 2 displays levels of all 35 included cytokines according to race.

Pathway analysis of the 10 cytokines with significant differences ($p < 0.05$; FDR < 0.1) indicated strong associations with five inflammatory signaling pathways, including IL-17, NF-kappa B, TNF, and NOD-like receptor signaling pathway (Supplementary Fig. 1).

We performed sensitivity subgroup analyses limited to patients with stage IV disease (Supplementary Table 3) and former smokers (Supplementary Table 4) to determine whether cytokine differences between races persisted when controlling for these variables. We observed a similar trend in cytokine differences for both subgroup analyses; however, some cytokine differences became nonsignificant in the subgroup analysis, likely due to smaller sample sizes and loss of statistical power.

We analyzed peripheral blood mononuclear cells by cytometry by time of flight for 48 patients (Black, 16; White, 32; 26%). Among 62 identified immune cell clusters (Fig. 2*A*), seven (11%) had statistically significant differences between races (Fig. 2*B* and Supplementary Fig. 2), all of which were elevated in Black patients ($p < 0.05$) (Fig. 2*C*). These included monocytes, natural killer (NK) T cell-like (NKT-like) cells, CD4+, and gamma-delta T cells ($\gamma\delta$T).

Discussion

Immune responses play central roles in cancer development and progression, including chronic stressors associated with racial and ethnic disparities. We observed significant differences between Black and White patients for approximately 30% of evaluated cytokines/chemokines and approximately 10% of evaluated immune cell populations.

For almost all parameters, proinflammatory cytokine levels were higher in Black persons. Notably, almost all observed racial differences also seemed to have favorable prognostic implications for White individuals. The cytokine with substantially higher levels among White patients was CCL23, which in cancer tissue correlates with the presence of macrophages, PD-1, CTLA-4, TIGIT, LAG-3, and TIM-3 immune checkpoints,[10] and is associated

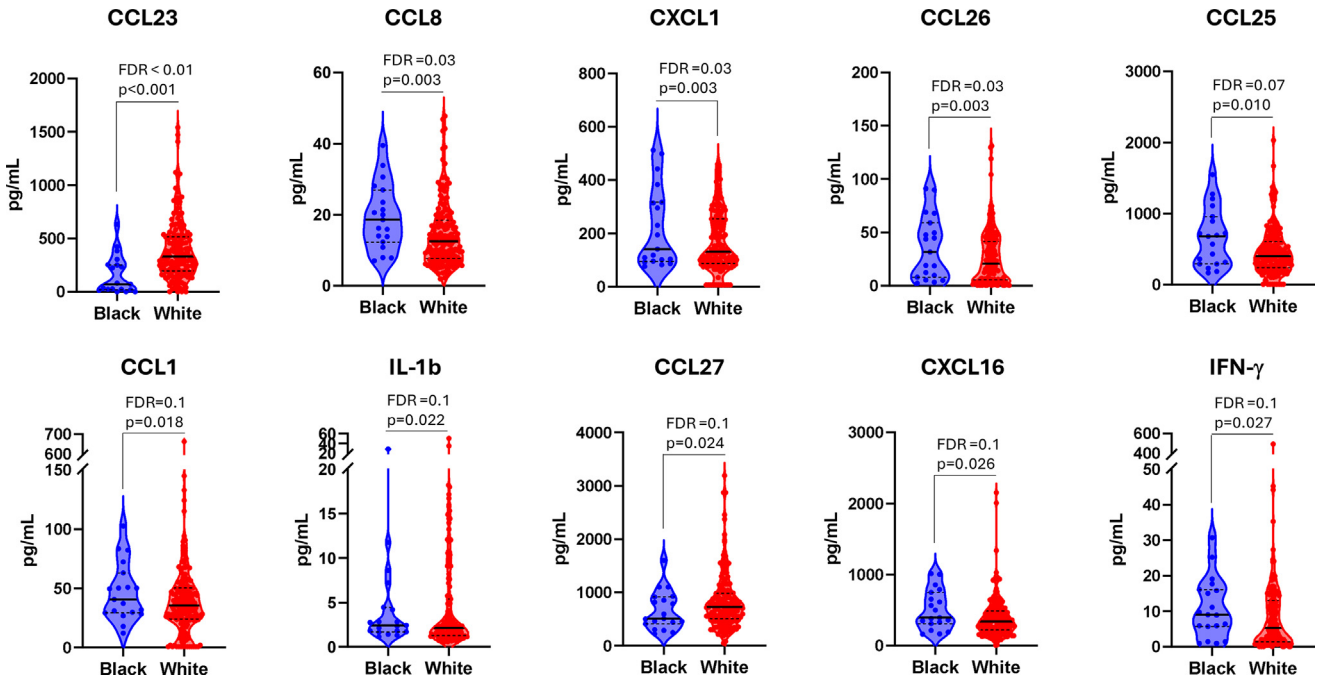

Figure 1. Cytokine analysis. Ten of 35 analyzed cytokines exhibited significant differences ($p < 0.05$ and FDR < 0.1) between Black and White populations. FDR, false discovery rate.

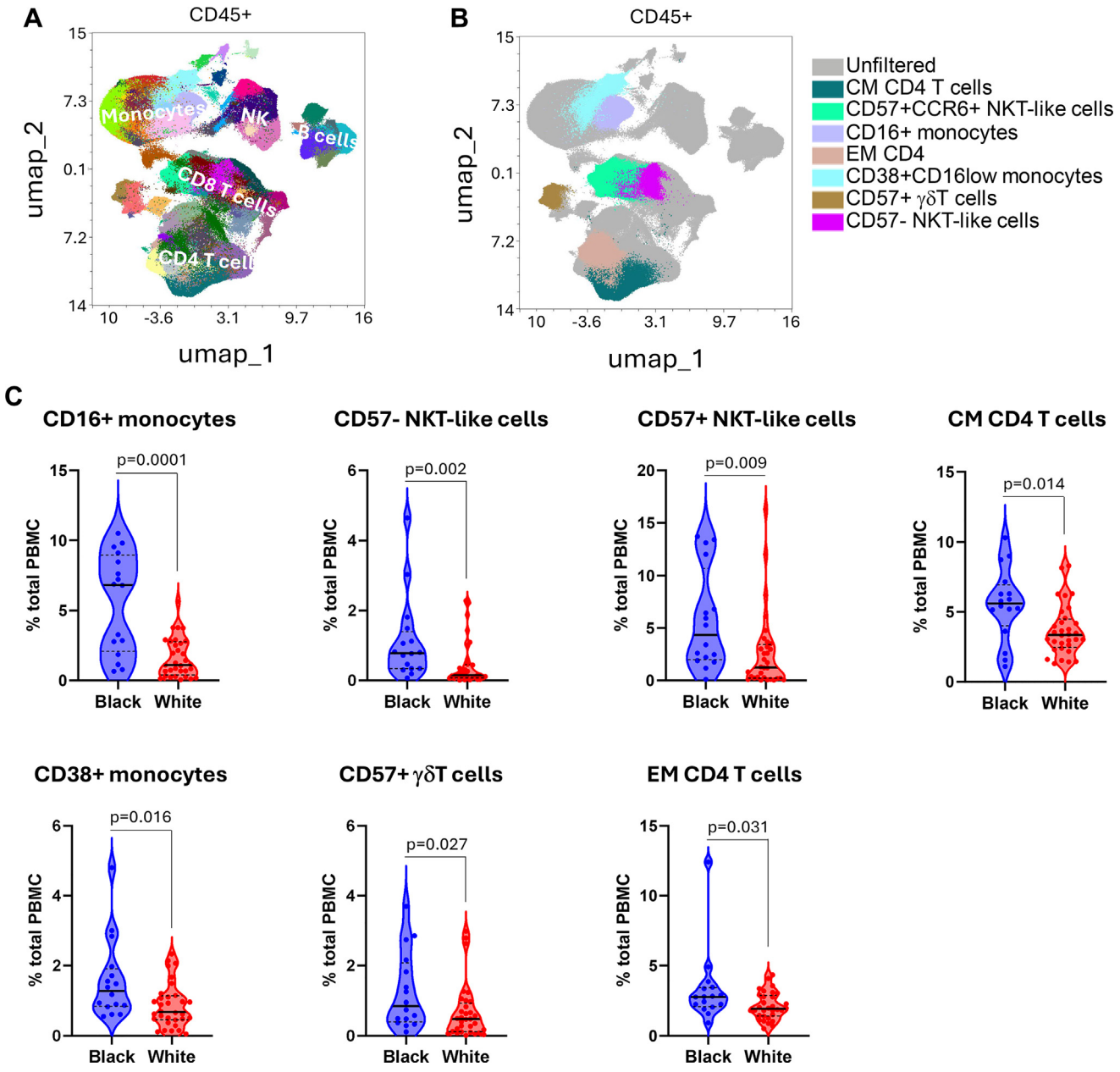

Figure 2. Immune cell profiling by CyTOF analysis. (*A*) UMAP revealing 62 clusters (with major cell populations revealed) identified by PhenoGraph-guided metaclustering of CD45+ cells in PBMCs. An equal number of cells per sample (38,614 cells/sample) in a total of 48 Black and White patients to create the UMAP map. (*B*) UMAP revealing seven of 62 clusters (11%) with significant differences between Black and White populations. (*C*) Seven immune cell subsets exhibited significant differences between Black and White populations. Plots reveal median with interquartile range. *P* values by Mann-Whitney *U* test. CM, central memory; CyTOF, cytometry by time of flight; EM, effector memory; NKT, natural killer T; PBMC, peripheral blood mononuclear cells; UMAP, uniform manifold approximation and projection.

favorable outcomes in immunotherapy-treated patients with lung cancer.[11] Conversely, CCL8, CXCL1, and CCL26—all significantly higher in Black patients in this study—promote tumorigenesis and cancer progression in various malignancies.[12–14]

Results from the analysis of immune cell populations seem to correlate with our cytokine findings. We observed higher levels of nonclassical monocytes and NKT-like cells in Black patients. Nonclassical (CD16+) monocytes have potent inflammatory properties, serving as the primary producers of IL-1β, which was elevated in Black compared with White patients. Among other cytokines, activated NKT cells produce IFN-γ,[15] which was elevated in Black patients.

The effect of these cells and their cytokines is to create a proinflammatory state. Further evaluation of

these cellular findings is warranted as higher macrophage or CD4+ T cells can lead to a tolerant tumor microenvironment that does not allow immune-mediated rejection. In contrast, NK cells and gamma-delta T cells are associated with cancer cell rejection and killing. Therefore, future efforts to evaluate subsets of these cell types to determine their transcriptional phenotype to infer activity are warranted.

Our observations correspond to findings in other populations. For instance, Black patients with prostate cancer have lower levels of CCL23 than do White patients with prostate cancer.[4] Nevertheless, in a population study evaluating inflammatory markers associated with risk of lung cancer in Black and White individuals, IFN-γ was associated with lung cancer risk in both races.[16] Among the five markers uniquely elevated in Black patients, the three included in our data set (IL-10, MCP-4/CCL13, and MIP-1/CCL3) were not associated with race in this study. Although our study focused on a different research question (comparing immune parameters in patients with existing lung cancer according to race), reasons for these differences are unclear. Our study expands on this previous study by incorporating a more extensive cytokine multiplex panel, additional analysis of circulating cell populations, and computational biological pathway analyses. Importantly, several markers identified in our and other studies in oncology populations have also been linked to other exposures. As an example, experiencing racial discrimination is associated with increased levels of proinflammatory cytokines (IL-1b, IL-6, IL-8, IL-10, TNF-α, and IFN-γ) in Black adolescents.[17]

Reasons for our observed differences are not known. Black patients were more likely to have received previous chemotherapy. Previous studies have mixed findings, with some finding reduced cytokine levels after chemotherapy and others finding increased levels.[18,19] Black patients also had higher comorbidity burden. Again, the existing literature provides mixed results. Serum cytokine levels may be elevated in specific conditions, such as autoimmune disease (which were not more common in Black patients in this study), but do not necessarily correlate with general comorbidity burden.[20,21] The potential for confounding factors when considering differences between Black and White patients is consistent with the increasing recognition that race and ethnicity represent social constructs rather than biologic variables.[22]

This study focused exclusively on baseline inflammatory and immune cell characteristics. Future studies could also evaluate how these change with treatment. Especially in the context of ICI therapy, immune parameters may predict favorable responses or potential for immune-related adverse events. Comparing absolute differences in inflammatory/immune cell levels and changes from baseline to follow up will provide deeper insight into the dynamic nature of the host immune system during ICI therapy for lung cancer.

A key limitation of this study is the limited number of Black patients, which in part reflects our inability to enroll patients at clinical sites providing care to large numbers of under-represented minorities during the coronavirus disease 2019 pandemic. We also lack information on socioeconomic status, which may influence inflammatory states and immune markers. Owing to the relatively small size of the study, subgroup analyses for former smokers and patients with stage 4 disease may be underpowered. Furthermore, the heterogeneity of cancer stage, histology, line of therapy, and treatment precludes meaningful assessment of clinical outcomes, such as progression-free survival and overall survival. Strengths of the study include multicenter participation and inclusion of immune cell populations and pathway analysis in addition to cytokines.

Despite a relatively small sample size, this study reveals a more proinflammatory cytokine and cellular phenotype for Black patients with lung cancer. Although Black patients tended to have earlier stage cancer in our cohort, almost all identified differences in Black patients are generally associated with worse outcomes. Further studies investigating the etiology and modulation of these observations are warranted.

CRediT Authorship Contribution Statement

Mitchell S. von Itzstein: Concept and design; Writing the manuscript; Editing and reviewing the manuscript; Data abstraction and curation; Critical analysis and interpretation of data.

Jialiang Liu: Writing – original draft; Writing - review & editing; Statistical analysis.

Hong Mu-Mosley: Writing - review & editing; Assay performance.

Farjana Fattah: Writing - review & editing; Assay performance.

Jason Y. Park: Writing - review & editing.

Jeffrey A. SoRelle: Writing - review & editing, Critical analysis and interpretation of data.

J. David Farrar: Writing - review & editing; Critical analysis and interpretation of data.

Mary E. Gwin: Writing - review & editing; Data abstraction and curation.

David Hsiehchen: Writing - review & editing; Enrollment of patients.

Yvonne Gloria-McCutchen: Writing - review & editing.

Edward K. Wakeland: Writing - review & editing.

Suzanne Cole: Writing - review & editing, Enrollment of patients.

Sheena Bhalla: Writing - review & editing, Enrollment of patients.

Radhika Kainthla: Writing - review & editing, Enrollment of patients.

Igor Puzanov: Writing - review & editing, Enrollment of patients.

Benjamin Switzer: Writing - review & editing, Enrollment of patients, Data abstraction and curation.

Gregory A. Daniels: Writing - review & editing, Enrollment of patients.

Yousef Zakharia: Writing - review & editing, Enrollment of patients.

Montaser Shaheen: Writing - review & editing, Enrollment of patients.

Jianjun Zhang: Writing - review & editing, Critical analysis and interpretation of data.

Yang Xie: Writing - review & editing, Statistical analysis.

David E. Gerber: Concept and design, Writing - original draft, Writing - review & editing, Enrollment of patients, Critical analysis and interpretation of data, Administrative support.

Disclosure

Dr. Park is a co-founder and Chief Laboratory Officer of OncoSeer Diagnostics, Inc. Dr. Cole reports receiving research funding from QED, Merck, and the Food and Drug Administration. Dr. Bhalla reports receiving consulting fees from AstraZeneca, Merus, Mirati, and Novocure. Dr. Puzanov reports receiving consulting fees from IO Biotech and having stock ownership from IDEAYA Biosciences, Compugen Ltd., and Perspective Therapeutics. Dr. Zhang reports receiving grants from Merck, Hengix, and Summitt; grants and personal fees from Johnson & Johnson and Novartis; and personal fees from Bristol Myers Squibb, AstraZeneca, GenePlus, Innovent, Varian, Catalyst, and Hengrui outside of the submitted work. Dr. Gerber reports receiving consulting fees from Catalyst Pharmaceuticals; having U.S. patent 11,747,345; having pending patents 17/045,482, 63/386,387, 63/382,972, and 63/382,257; receiving research funding from AstraZeneca, Karyopharm, and Novocure; participating in advisory boards for AstraZeneca, Daiichi Sankyo, Elevation Oncology, Janssen Scientific Affairs, Jazz Pharmaceuticals, Regeneron Pharmaceuticals, and Sanofi; having stock shares in Gilead; and serving as co-founder and Chief Medical Officer of OncoSeer Diagnostics, Inc. The remaining authors declare no conflict of interest.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

The authors thank Ms. Dru Gray for assistance with manuscript preparation.

This work is funded in part by the National Institute of Allergy and Infectious Disease (1U01AI156189-01; to Drs. Gerber, Wakeland, and Xie), an American Cancer Society-Melanoma Research Alliance Team Award (MRAT-18-114-01-LIB; to Dr. Gerber), a V Foundation Robin Roberts Cancer Survivorship Award (DT2019-007; to Dr. Gerber), a Physician-Scientist Institutional Award from the Burroughs Wellcome Fund (to Dr. von Itzstein), the University of Texas Lung Cancer Specialized Program of Research Excellence (SPORE) (P50CA070907-21), the University of Texas Stimulating Access to Research in Residency (UT-StARR, R38HL150214 to Dr. Gwin), and the Harold C. Simmons Comprehensive Cancer Center Data Sciences Shared Resource and Biomarker Research Core (1P30 CA 142543-03). The funders were not involved in the study design, conduct, or reporting.

Data Availability

The data sets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100751.

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