Real-world multiple myeloma risk factors and outcomes by non-Hispanic Black/African American and non-Hispanic White race/ethnicity in the United States

Tondre Buck,[1] Monique A. Hartley-Brown,[2] Yvonne A. Efebera,[3] Carter P. Milner,[4] Jeffrey A. Zonder,[5] Paul G. Richardson,[2] Taylor Salinardi[6°] and Megan S. Rice[6°]

[1]Spartanburg Medical Center, Center for Research and Cancer Institute, Spartanburg, SC; [2]Division of Hematologic Malignancy, Department of Medical Oncology, Jerome Lipper Multiple Myeloma Center, Harvard Medical School, Dana-Farber Cancer Institute, Boston, MA; [3]Division of Blood and Marrow Transplant and Cellular Therapy, OhioHealth, Columbus, OH; [4]Division of Hematology and Medical Oncology, Department of Medicine, University of Mississippi Medical Center, Jackson, MS; [5]Department of Oncology, Barbara Ann Karmanos Cancer Institute, Wayne State University, Detroit, MI and [6]Sanofi, Cambridge, MA, USA

°Current address TS: Azurity Pharmaceuticals, Woburn, MA, USA.

°Current address MSR: Vertex Pharmaceuticals Incorporated, USA.

Correspondence: T. Buck
tbuck@gibbscc.org

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Abstract

Examination of the impact of race and ethnicity on multiple myeloma (MM) outcomes has yielded inconsistent results. This retrospective, real-world (RW) study describes patient, disease, and treatment characteristics (and associations with survival outcomes) among newly diagnosed MM patients of non-Hispanic (NH) Black/African American (AA) and NH White race/ethnicity in the US. We included patients from the nationwide Flatiron Health electronic health record-derived de-identified database who initiated first line of therapy (LOT) for MM between January 1, 2016 and March 31, 2022. Of 4,614 patients in our study cohort, 23.3% were NH Black/AA. Non-Hispanic Black/AA patients were younger than NH White patients at diagnosis (median 68 *vs*. 71 years) and more likely to be female (53.4% *vs*. 43.5%). Rates of high-risk cytogenetics and 1q21+ were similar between races/ethnicities. The most common primary regimen used was lenalidomide-bortezomib-dexamethasone (50.1% of NH Black/AA and 48.1% of NH White patients). Receipt of stem cell transplantation during first LOT was less common among NH Black/AA (16.5%) than NH White (21.9%) patients. Unadjusted RW progression-free survival (rwPFS) and overall survival (rwOS) were similar between races/ethnicities. After multivariable adjustment, NH Black/AA race/ethnicity was associated with slightly inferior rwPFS (hazard ratio [HR]=1.13; 95% confidence interval [CI]: 1.01-1.27). The difference in rwOS (HR=1.12; 95% CI: 0.98-1.28) was not statistically significant. In general, associations between risk factors for rwPFS and rwOS were consistent between races/ethnicities. Findings from this analysis help to inform clinicians about the impact of race/ethnicity on MM treatment paradigms and outcomes in the US.

Introduction

Multiple myeloma (MM) is a malignancy characterized by the proliferation of terminally differentiated plasma cells in the bone marrow. It is the second most common hematologic cancer in the US and the most common hematologic malignancy among people of Black/African American (AA) race.[1] In fact, the rate of new MM cases and MM-related deaths is over two times higher among Black/AA adults than White adults in the US,[1] which may be partially due to biological or genetic differences between races. According to the Surveillance, Epidemiology and End Results (SEER) data on MM prevalence, in 2020, over 34,000 Black/AA patients who were diagnosed with MM between 1992 and 2019 were alive with the disease.[2] Despite currently making up only 14.2% of the US population,[3] people of Black/AA race are expected to comprise roughly 24% of the newly diagnosed MM (NDMM) population by 2034.[4]

With the advent of novel therapies including autologous stem cell transplant (SCT), immunomodulatory drugs (IMiD), proteasome inhibitors (PI), monoclonal antibodies (mAb), and chimeric antigen receptor T-cell (CAR T) therapies, survival has improved for MM patients in recent decades.[5] Notably, survival was slower to improve among Black/AA than White patients through 2012.[5,6] Several studies have shown that Black/AA patients may be less likely to receive SCT, PI, IMiD, front-line

triplet induction therapies for NDMM (and more recently approved immunotherapies for relapsed MM[7-9]) compared with their White counterparts.[6,10-13] Interestingly, Black/AA race has also been linked, albeit inconsistently, with more favorable cytogenetic profiles than White race, including a lower prevalence of high-risk features such as del(17p) and t(4;14).[11,14,15] To date, analyses of real-world (RW) datasets have yielded discrepant associations between race and survival outcomes. Analyses of US-based datasets from the SEER Program,[12] Veterans Affairs (VA),[16] and Flatiron Health[17] have shown similar, or even improved, overall survival (OS) among Black/AA patients, particularly when there is equal access to care. However, analysis of the international Multiple Myeloma Research Foundation CoMMpass dataset[11] found that Black/AA patients with MM have inferior OS to White patients, which is only partially abrogated by receipt of SCT and triplet therapies. Differences in RW findings highlight the importance of continually examining data that reflect current trends in the uptake of novel therapies and treatment strategies, as well as growing awareness of racial/ethnic disparities in cancer care. As such, the objective of this retrospective, observational cohort study was to provide an up-to-date examination of associations between patient, disease, and treatment characteristics and survival outcomes by non-Hispanic (NH) Black/AA and NH White race/ethnicity in the US.

Methods

Study design and data source

This retrospective, observational cohort study used the nationwide Flatiron Health electronic health record (EHR)-derived, de-identified database of MM patients treated in the US. The Flatiron Health database is a longitudinal database, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction.[18,19] During the study period, the de-identified data originated from approximately 280 US cancer clinics (~800 sites of care).

Patient selection

We included patients from the Flatiron Health MM Cohort whose race was recorded as "White" and ethnicity was not equal to "Hispanic or Latino" (NH White), whose race was recorded as "Black or African American" and ethnicity was not equal to "Hispanic or Latino" (NH Black/AA), and whose first line of therapy (LOT) was initiated between January 1, 2016 and March 31, 2022. Exclusion criteria are provided in the *Online Supplementary Appendix*.

Assessments and outcomes

Patient, disease, and treatment characteristics were examined by race/ethnicity. RW progression-free survival (rwPFS) and rwOS, indexed to first LOT, were examined by race/ethnicity, overall and for subgroups defined by various patient, disease, and treatment characteristics. rwPFS was defined as the time from start of front-line therapy to the date of first progression event (informed by International Myeloma Working Group criteria and incorporating abstracted M-spike values and structured free light chain values) or death. Progression events occurring within 30 days after therapy initiation were excluded, as such events are not expected to reflect progression on the therapy of interest. As the timing and frequency of laboratory tests can vary (with less frequent testing associated with longer rwPFS), a sensitivity analysis was conducted to exclude patients with a gap of more than 180 days between the date of progression event and the previous lab test. rwOS was defined as the time from start of front-line therapy to the date of death.

Statistical analysis

Patient, disease, and treatment characteristics by race/ethnicity were summarized descriptively, using mean (standard deviation) and/or median (interquartile range [IQR]) for continuous variables and frequencies and percentages for categorical variables. The Kaplan-Meier (K-M) method was used to analyze rwPFS and rwOS for the overall populations of NH Black/AA and NH White patients, with median (95% confidence interval [CI]) reported for both outcomes. Differences in rwPFS and rwOS between races/ethnicities, overall and within subgroups were assessed using unadjusted, age-adjusted, and multivariable (MV)-adjusted Cox proportional hazards models that adjusted for age at start of first LOT, sex, practice type, region of residence, M-protein subtype at diagnosis, International Staging System (ISS) stage at diagnosis, Eastern Cooperative Oncology Group performance status (ECOG PS) at start of first LOT, cytogenetic risk, 1q21+, estimated glomerular filtration rate (eGFR) at start of first LOT, and time from diagnosis of MM to start of first LOT. Likelihood ratio tests were used to evaluate whether associations between the selected factors and rwPFS and rwOS differed by race/ethnicity.

Further details of Methods are provided in the *Online Supplementary Appendix*.

Results

Patient demographics and clinical characteristics

A total of 4,614 patients with MM had initiated first LOT and were included in the study cohort (*Online Supplementary Figure S1*); 1,077 (23.3%) patients were NH Black/AA and 3,537 (76.7%) patients were NH White. Baseline patient, disease, clinical, and first LOT characteristics are shown in Tables 1 and 2. Patients of NH Black/AA race/ethnicity were slightly younger than NH White patients on average, with a median age of 68 years *versus* 71 years, respectively, at both MM diagnosis and start of first LOT. A higher proportion of NH Black/AA than NH White patients were female (53.4% *vs*. 43.5%) and from the Southern US (63.0% *vs*. 36.2%),

but fewer were treated in academic practices (12.9% *vs*. 16.1%). Rates of commercial insurance coverage were similar between NH Black/AA and NH White patients (44.0% *vs*. 46.4%, respectively), as were rates of coverage under a patient assistance program (8.6% *vs*. 6.5%); however, rates of Medicare/Medicare+ coverage were higher among NH White patients (20.7%) than NH Black/AA patients (15.2%). Rates of high-risk cytogenetics [defined as the presence of ≥1 of del(17p), t(4;14), or t(14;16)] and 1q21+ (defined as gain [3 copies] or amplification [≥4 copies] of 1q21) were similar between NH Black/AA and NH White patients (14.7% *vs*. 16.1% and 18.4% *vs*. 21.1%, respectively). Rates of individual high-risk cytogenetic abnormalities (HRCA) were also similar between groups: t(4;14) 5.1% *vs*. 5.5%, t(14;16) 3.9% *vs*. 2.7%, and del(17p) 8.4% *vs*. 10.0% for NH Black/AA and NH White patients, respectively. Median time from MM diagnosis to start of first LOT was similar for NH Black/AA patients (1.06 months; IQR, 0.68-1.52) and NH White patients (1.03 months; IQR, 0.68-1.48).

Line 1 treatment characteristics

Most NH Black/AA and NH White patients (52.7% in each group) received a PI + IMiD-based regimen as initial therapy during the first LOT (Table 3). Similar percentages of NH Black/AA (6.9%) and NH White (8.3%) patients received an mAb-based regimen as their initial therapy. The most common primary regimen used for both groups was lenalidomide-bortezomib-dexamethasone (50.1% of NH Black/AA patients and 48.1% of NH White patients) (*Online Supplementary Table S1*). Receipt of SCT during the first LOT was less common among NH Black/AA patients (16.5%) than NH White patients (21.9%). Among those receiving SCT, rates of post-SCT consolidation (6.2% *vs*. 8.6%) and post-SCT maintenance therapy (64.0% *vs*. 63.7%) were similar between NH Black/AA and NH White patients, respectively.

Real-world progression-free survival

The rwPFS population consisted of 3,922 patients (*Online Supplementary Figure S1*). In K-M analyses, median rwPFS

Table 1. Baseline patient characteristics, overall and by race/ethnicity.

Characteristic, N (%) unless otherwise noted	All patients N=4,614	NH Black/African American patients N=1,077	NH White patients N=3,537
Age in years at MM diagnosis Median (IQR)	70 (62-77)	68 (60-75)	71 (63-78)
Age in years at MM diagnosis (categorical years) <65 65 - <75 ≥75	 1,420 (30.8) 1,623 (35.2) 1,571 (34.1)	 411 (38.2) 372 (34.5) 294 (27.3)	 1,009 (28.5) 1,251 (35.4) 1,277 (36.1)
Age in years at start of first LOT Median (IQR)	70 (62-77)	68 (60-75)	71 (63-78)
Age in years at start of first LOT (categorical years) <65 65 - <75 ≥75	 1,408 (30.5) 1,621 (35.1) 1,585 (34.4)	 406 (37.7) 374 (34.7) 297 (27.6)	 1,002 (28.3) 1,247 (35.3) 1,288 (36.4)
Sex Female Male	 2,114 (45.8) 2,500 (54.2)	 575 (53.4) 502 (46.6)	 1,539 (43.5) 1,998 (56.5)
Region of residence South Not South*	 1,957 (42.4) 2,657 (57.6)	 678 (63.0) 399 (37.1)	 1,279 (36.2) 2,258 (63.8)
Practice type Academic Community Academic and community	 708 (15.3) 3,832 (83.1) 74 (1.6)	 139 (12.9) 929 (86.3) 9 (0.8)	 569 (16.1) 2,903 (82.1) 65 (1.8)
Insurance Commercial Health Plan Medicare Medicare+ Patient Assistance Program Other Missing	 2,114 (45.8) 594 (12.9) 302 (6.6) 323 (7.0) 566 (12.3) 715 (15.5)	 474 (44.0) 121 (11.2) 43 (4.0) 93 (8.6) 168 (15.6) 178 (16.5)	 1,640 (46.4) 473 (13.4) 259 (7.3) 230 (6.5) 398 (11.3) 537 (15.2)

*Defined as patients from the Northeast, Midwest, West, of other part of the United States (or those with missing data). IQR: interquartile range; LOT: line of therapy; MM: multiple myeloma; NH: non-Hispanic.

Table 2. Disease, clinical, and first line of therapy characteristics, overall and by race/ethnicity.

Characteristic, N (%) unless otherwise noted	All patients N=4,614	NH Black/African American patients N=1,077	NH White patients N=3,537
M-protein type			
IgG	2,541 (55.1)	649 (60.3)	1,892 (53.5)
IgA	946 (20.5)	175 (16.3)	771 (21.8)
Light chain	895 (19.4)	198 (18.4)	697 (19.7)
Other	48 (1.0)	9 (0.8)	39 (1.1)
Missing	184 (4.0)	46 (4.3)	138 (3.9)
ISS stage at diagnosis			
Stage I	1,022 (22.2)	268 (24.9)	754 (21.3)
Stage II	964 (20.9)	194 (18.0)	770 (21.8)
Stage III	961 (20.8)	191 (17.7)	770 (21.8)
Missing	1,667 (36.1)	424 (39.4)	1,243 (35.1)
Cytogenetic risk (assessed at any time)			
High risk*	727 (15.8)	158 (14.7)	569 (16.1)
Standard risk	1,339 (29.0)	317 (29.4)	1,022 (28.9)
Missing	2,548 (55.2)	602 (55.9)	1,946 (55.0)
t (4;14)			
Present	248 (5.4)	55 (5.1)	193 (5.5)
Absent	2,084 (45.2)	478 (44.4)	1,606 (45.4)
Missing	2,282 (49.5)	544 (50.5)	1,738 (49.1)
t (14;16)			
Present	138 (3.0)	42 (3.9)	96 (2.7)
Absent	2,073 (44.9)	468 (43.5)	1,605 (45.4)
Missing	2,403 (52.1)	567 (52.7)	1,836 (51.9)
del(17p)			
Present	445 (9.6)	90 (8.4)	355 (10.0)
Absent	2,715 (58.8)	656 (60.9)	2,059 (58.2)
Missing	1,454 (31.5)	331 (30.7)	1,123 (31.8)
1q21+† (assessed at any time)			
Present	945 (20.5)	198 (18.4)	747 (21.1)
Absent	1,660 (36.0)	403 (37.4)	1,257 (35.5)
Missing	2,009 (43.5)	476 (44.2)	1,533 (43.3)
eGFR‡ (mL/min/1.73 m^2) at start of first LOT			
<60	1,777 (38.5)	381 (35.4)	1,396 (39.5)
≥60	2,081 (45.1)	527 (48.9)	1,554 (43.9)
Missing	756 (16.4)	169 (15.7)	587 (16.6)
ECOG PS at start of first LOT			
0	1,097 (23.8)	282 (26.2)	815 (23.0)
1	1,205 (26.1)	278 (25.8)	927 (26.2)
≥2	633 (13.7)	157 (14.6)	476 (13.5)
Missing	1,679 (36.4)	360 (33.4)	1,319 (37.3)
Year of first LOT start			
2016	809 (17.5)	167 (15.5)	642 (18.2)
2017	776 (16.8)	166 (15.4)	610 (17.3)
2018	799 (17.3)	179 (16.6)	620 (17.5)
2019	796 (17.3)	183 (17.0)	613 (17.3)
2020	675 (14.6)	188 (17.5)	487 (13.8)
2021	631 (13.7)	159 (14.8)	472 (13.3)
2022	128 (2.8)	35 (3.3)	93 (2.6)
Time in months from MM diagnosis to first LOT start			
Median (IQR)	1.06 (0.68–1.52)	1.06 (0.68–1.52)	1.03 (0.68–1.48)

*High-risk cytogenetics were defined as the presence of ≥1 of del(17p), t(4;14), or t(14;16). †1q21+ was defined as gain (3 copies) or amplification (≥4 copies) of 1q21. ‡Assessed using the MDRD equation. ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; Ig: immunoglobulin; IQR: interquartile range; ISS: International Staging System; LOT: line of therapy; MDRD: modification of diet in renal disease; MM: multiple myeloma; NH: non-Hispanic; PS: performance status.

from start of first LOT was similar for the overall populations of NH Black/AA (26.0 months; 95% CI: 23.2-30.2) and NH White (27.2 months; 95% CI 25.6-29.4) patients (Figure 1). Unadjusted and age-adjusted Cox proportional hazard models showed similar rwPFS among NH Black/AA and NH White patients (*Online Supplementary Table S2*); however, after MV adjustment, NH Black/AA race/ethnicity was associated with statistically inferior rwPFS (MV-adjusted hazard ratio [HR]=1.13; 95% CI: 1.01-1.27) when using NH White race/ethnicity as the reference; Figure 2). MV-adjusted analyses examining associations between selected patient and disease characteristics and rwPFS by race/ethnicity are shown in Figure 2 (full subgroup analyses are shown in *Online Supplementary Table S3*). Age of ≥75 years at start of first LOT (compared with age of <65 years), ECOG PS of ≥2 (compared with ECOG PS of 0), ISS Stage II or III disease at diagnosis (compared with Stage I disease at diagnosis), and the presence of 1q21+ (compared with the absence

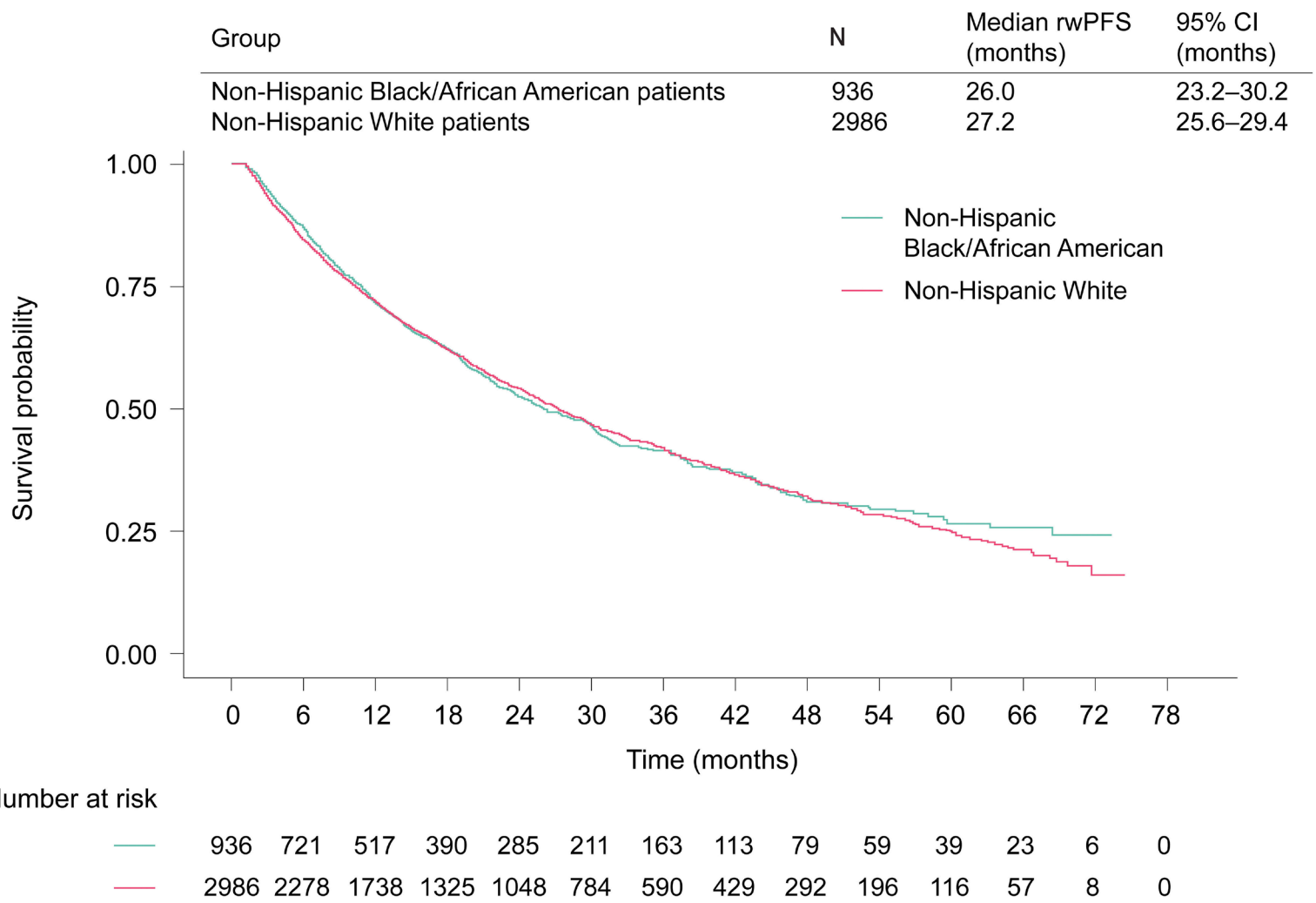

Figure 1. Kaplan-Meier analysis of real-world progression-free survival from start of first line of treatment by race/ethnicity. CI: confidence interval; LOT: line of therapy; rwPFS: real-world progression-free survival.

Table 3. Line 1 treatment, overall and by race/ethnicity.

Line 1 treatment, N (%)	All patients N=4,614	NH Black/African American patients N=1,077	NH White patients N=3,537
PI-based*	581 (12.6)	138 (12.8)	443 (12.5)
IMiD-based*	591 (12.8)	131 (12.2)	460 (13.0)
PI+IMiD-based*	2431 (52.7)	568 (52.7)	1,863 (52.7)
Chemotherapy-based†	641 (13.9)	165 (15.3)	476 (13.5)
mAb-based‡	368 (8.0)	74 (6.9)	294 (8.3)
Other§	<5 (< 0.1)	<5 (< 0.5)	<5 (< 0.1)

*Regimens containing only the drug class(es) listed (+/- steroids). †Regimens containing at least one chemotherapy agent (+/- steroids), that could also include PI and IMiD but not mAb or "other" drugs (see footnote §). ‡Regimens containing at least 1 mAb agent (+/- steroids), that could also include PI, IMiD, and chemotherapy agents but not "other" drugs (see footnote §). §Included BCMA-targeting drugs (eg, belantamab mafodotin, idecabtagene vicleucel) or those with novel mechanisms of action (e.g., panobinostat, selinexor, melflufen). BCMA: B-cell maturation antigen; IMiD: immunomodulatory drug; mAb: monoclonal antibody; NH: non-Hispanic; PI: proteasome inhibitor.

of 1q21+) were associated with statistically inferior rwPFS for both NH Black/AA and NH White patients. Age of 65-74 years (compared with age of <65 years) and the presence of high-risk cytogenetics (compared with standard-risk cytogenetics) were similarly associated with worse rwPFS among both NH Black/AA and NH White patients but were only statistically significant among NH White patients. Likelihood ratio tests confirmed that associations between selected factors and rwPFS were not statistically different between races/ethnicities. rwPFS K-M and MV-adjusted Cox model findings were confirmed by sensitivity analyses that excluded patients with more than a 180-day gap between progression event and previous laboratory test (*Online Supplementary Figure S2; Online Supplementary Table S3*).

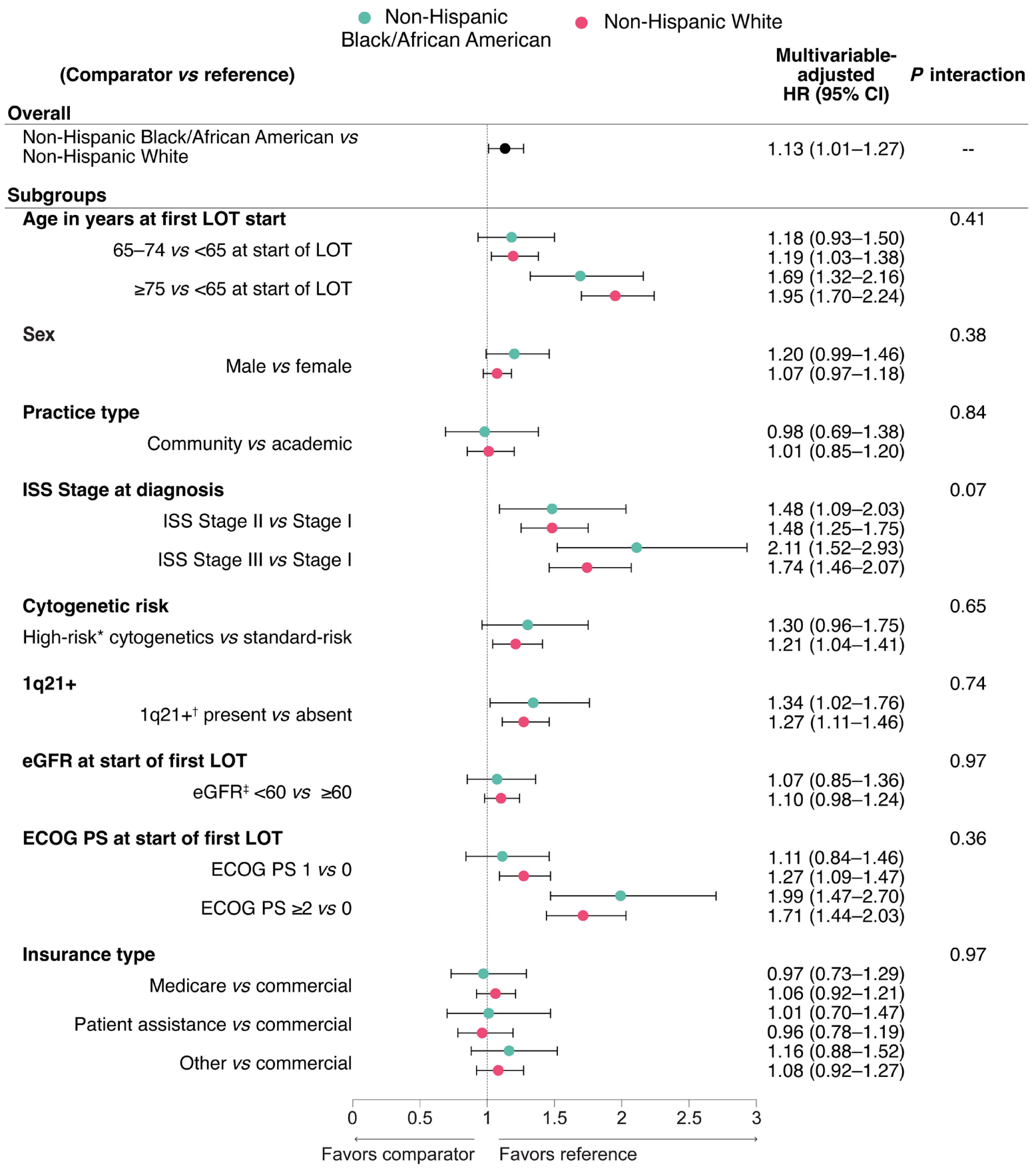

Figure 2. Multivariable-adjusted Cox proportional hazards model of real-world progression-free survival from start of first line of treatment, by race/ethnicity, overall and for select subgroups. *High-risk cytogenetics were defined as the presence of ≥1 of del(17p), t(4;14), or t(14;16). †1q21+ was defined as gain (3 copies) or amplification (≥4 copies) of 1q21. ‡Assessed using the MDRD equation; expressed as mL/min/1.73 m^2. CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; eGFR: estimated glomerular filtration rate; HR: hazard ratio; ISS: International Staging System; LOT: line of therapy; MDRD: modification of diet in renal disease; MV: multivariable; PS: performance status; rwPFS: real-world progression-free survival.

Real-world overall survival

In Kaplan-Meier analyses, median rwOS from the start of first LOT was similar for the overall populations of NH Black/AA (65.1 months; 95% CI: 58.2-not reached) and NH White (60.5 months; 95% CI: 58.4-66.1) patients (Figure 3). Unadjusted and age-adjusted Cox proportional hazards models showed similar rwOS among races/ethnicities (*Online Supplementary Table S4*). After MV-adjustment, NH Black/AA patients had inferior rwOS compared to NH White patients, however this difference was not statistically significant (HR=1.12; 95% CI: 0.98-1.28; Figure 4). MV-adjusted analyses examining associations between selected patient and disease characteristics and rwOS from start of first LOT, by race/ethnicity, are shown in Figure 4 (full subgroup analyses are shown in *Online Supplementary Table S5*). Age of 65 to <75 years and age of ≥75 years at start of first LOT (both compared with age of <65 years) were associated with statistically inferior rwOS for both NH Black/AA and NH White patients; this association was particularly strong for the ≥75 years age group. ECOG PS of ≥2 (compared with ECOG PS of 0), ISS Stage II or III disease at diagnosis (compared with Stage I disease at diagnosis), eGFR <60 mL/min/1.73 m^2 (compared with eGFR ≥60 mL/min/1.73 m^2), and the presence of high-risk cytogenetics (compared with standard-risk cytogenetics) were also associated with statistically inferior rwOS for both races/ethnicities. The presence of 1q21+ (compared with the absence of 1q21+) was similarly associated with worse rwOS among both groups but was only statistically significant among NH White patients. Likelihood ratio tests confirmed that associations between selected factors and rwOS were not statistically different between races/ethnicities.

Discussion

This study used recent, EHR-derived data to retrospectively analyze patient and treatment characteristics as well as survival outcomes for patients of NH Black/AA and NH White race/ethnicity in the US. Adding to findings from previous RW analyses, our study complements findings from prospective clinical trials, which may not be fully generalizable to the RW population. To our knowledge, this study is the first to evaluate both rwPFS and rwOS using robust MV-adjusted modeling among numerous subgroups of NH Black/AA and NH White patients.

Consistent with previous analyses of multiple RW data sets,[6,11,17,20,21] NH Black/AA patients in our study were younger than NH White patients at diagnosis and start of first LOT. The percentage of female patients was higher among the NH Black/AA than the NH White cohort, reflective of the slight weighting of the Flatiron Health database toward patients in the Southern region of the US,[19] where the most recent US Census data shows higher-than-average representation of both females and people of Black/AA race.[22,23] The percentage of patients with eGFR <60 mL/min/1.73 m^2 at start of first LOT was slightly higher among NH White than NH Black/AA patients (*Online Supplementary Appendix; Online*

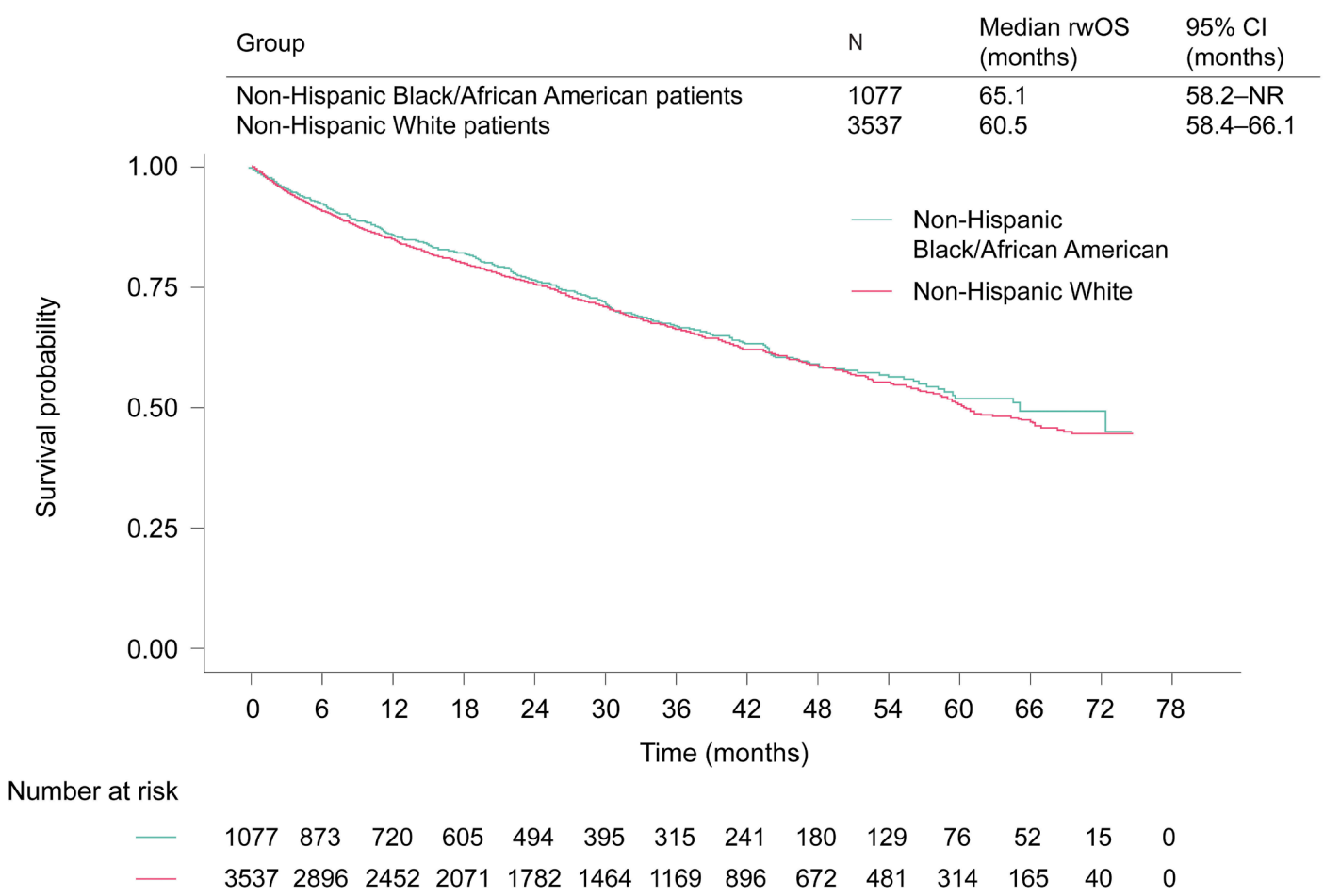

Figure 3. Kaplan-Meier analysis of real-world overall survival from start of first line of treatment by race/ethnicity. CI: confidence interval; LOT: line of therapy; NR: not reached; rwOS: real-world overall survival.

Supplementary Table S6), but NH White patients with eGFR <50 mL/min/1.73 m^2 at start of first LOT were slightly more likely than their NH Black/AA counterparts to have at least one eGFR ≥60 mL/min/1.73 m^2 during the first LOT.

African ancestry has been associated with a significantly lower prevalence of HRCA such as del(17p) and t(4;14).[14] The presence of individual HRCA including del(17p), t(4;14) and t(14;16) was similar between NH Black/AA and NH White patients, as was the presence of 1q21+, which is also consistent with earlier analyses of the Flatiron Health MM database[24] and the international CoMMpass database.[11]

In our study and other RW and administrative database studies, Black/AA race has been associated with lower rates of SCT use despite younger age at diagnosis.[11-13,17,21] Our

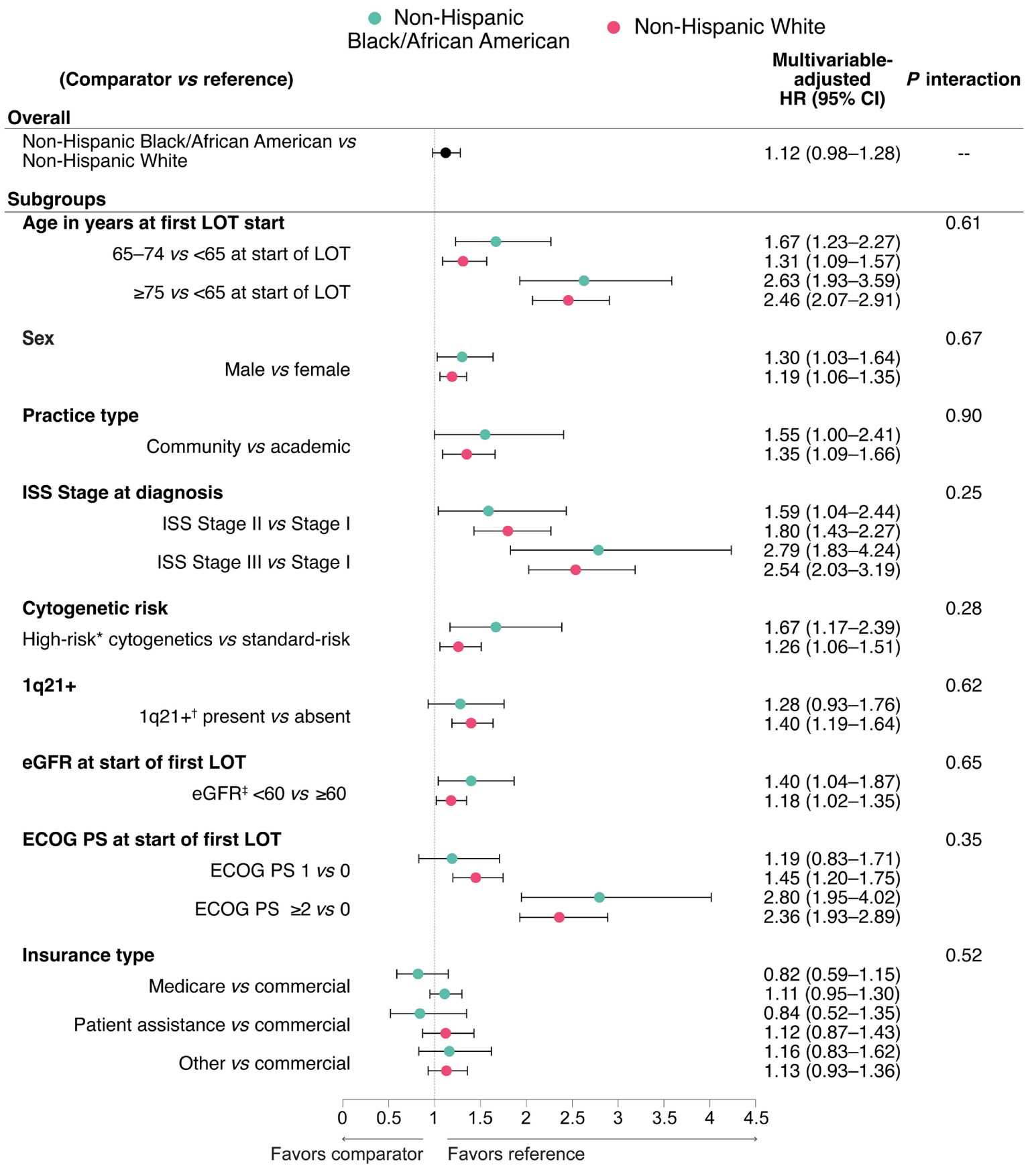

Figure 4. Multivariable-adjusted Cox proportional hazards model of real-world overall survival from start of first line of treatment, by race/ethnicity, overall and for select subgroups. *High-risk cytogenetics were defined as the presence of ≥1 of del(17p), t(4;14), or t(14;16). †1q21+ was defined as gain (3 copies) or amplification (≥4 copies) of 1q21. ‡Assessed using the MDRD equation; expressed as mL/min/1.73 m^2. CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; eGFR: estimated glomerular filtration rate; HR: hazard ratio; ISS: International Staging System; LOT: line of therapy; MDRD: modification of diet in renal disease; MV: multivariable; PS: performance status; rwOS: real-world overall survival.

study was not designed to examine any differential benefit of SCT between NH Black/AA and NH White patients, though this remains an important clinical question. Black/AA patients comprised nearly 20% of the study population in the phase III DETERMINATION trial,[25] which prospectively randomized patients with NDMM to lenalidomide-bortezomib-dexamethasone with and without early SCT and with all patients receiving lenalidomide maintenance until progression. In the overall population, SCT significantly improved PFS but not OS. In a preplanned subgroup analysis, PFS benefit of SCT appeared evident in the population of White patients but not among Black/AA patients. Notably, the trial was not powered to definitively evaluate PFS among subgroups, but rather to be hypothesis-generating; hence, findings among Black patients are being further evaluated to better understand how racial differences may mediate differential benefit from SCT and further analyses from this important study are anticipated with great interest.

Black/AA patients have also been reported as less likely than White patients to receive PI + IMiD-based therapies such as front-line triplet induction therapy that contains lenalidomide and bortezomib.[10-13] A US-based, retrospective chart review of daratumumab users between November 2015 and May 2020 also found notable disparity in first-line daratumumab use (4.5% of Black patients *vs*. 9.2% of White patients).[26] Rates of lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab use were similar between races/ethnicities in our study, suggesting that adoption of standard-of-care regimens has started to equalize across races/ethnicities within US-based community practices.

Notably, the time frame of our analysis (January 2016 through March 2022) does not fully reflect the emergence of anti-CD38 mAb into the NDMM setting. Results from MAIA[27] (daratumumab-lenalidomide-prednisone *vs*. lenalidomide-prednisone) and ALCYONE[28] (daratumumab-bortezomib-melphalan-prednisone *vs*. bortezomib-melphalan-prednisone), which led to Food and Drug Administration indications in the setting of newly diagnosed disease, were first published in 2019 and 2018, respectively. Completed and ongoing studies of triplet and quadruplet regimens containing anti-CD38 MAb (i.e., isatuximab, daratumumab) may lead to additional approvals in the first-line space.

Though RW endpoints inherently differ from those used in clinical trials, the use of rwPFS as a meaningful outcome is becoming more common.[11,24,29-31] Utilizing Flatiron Health's rules for PFS, the unadjusted and age-adjusted Cox proportional hazards models used in our study demonstrated similar rwPFS results for NH Black/AA and NH White patients with NDMM, whereas MV-adjusted Cox models showed slightly inferior rwPFS among NH Black/AA patients. This is an important finding, particularly given the size of our cohort and reflection of community-based practice in the US.

Our analysis also suggested slightly inferior MV-adjusted rwOS for NH Black/AA patients compared with NH White patients with NDMM, though this difference was not statistically significant. This lack of a significant association aligns with findings from an earlier analysis of Black/AA and White patients in the Flatirion Health MM database who initiated first-line therapy between 2011 and 2019.[17] Notably, other RW studies and analyses of administrative datasets have yielded discrepant results. Analysis of the Multiple Myeloma Research Foundation's CoMMpass data set,[11] pooled from 90 sites worldwide, found that Black patients had inferior OS compared with White patients (age-adjusted HR=1.7; 95% CI: 1.2-2.4), which was only partly attenuated by receipt of triplet therapy and SCT. A VA study,[32] SEER-based analysis,[12] and RW analysis of the Connect MM Registry[21] found that Black/AA patients have equal, if not better, survival outcomes than their White counterparts when access to care is equal. These discrepant findings likely reflect differences in sites of care (e.g., US-based community clinics or VA system *vs*. international practice sites) and varying time periods of analyses, both of which may lead to important differences in available therapies or cultural awareness. In addition, population-based studies or those using administrative data (e.g., SEER data) may use different methods of data extraction and may not fully account for other factors (e.g., socioeconomic status, cultural barriers) that may impact outcomes.

We found that associations between patient and disease characteristics and survival outcomes were generally consistent between NH Black/AA and NH White patients. Importantly, the impact of high-risk cytogenetics on survival outcomes in MM patients remains less than fully understood. Alignment of our findings with those of other analyses is complicated by differences in how high-risk cytogenetics are characterized. In an analysis of patients in the Flatiron Health MM database using a slightly earlier time frame (January 2011 to May 2021), Calip *et al.*[24] also examined the differential impact of high-risk cytogenetics on MM outcomes between races. However, they examined the association between number of HRCA (0, 1, or 2+) and rwPFS and rwOS, defining HRCA as 1q21+, del(17p), t(4;14), t(14;16) and t(14;20). Compared with patients with no HRCA, White and Black patients of any age with exactly 1 HRCA had statistically inferior rwPFS and rwOS, whereas having "double-hit MM" (2+ HRCA) was differentially predictive of poor survival across races.[24] Applying these same definitions of HRCA to an analysis of the international CoMMpass database, Derman *et al.*[11] found more widely discrepant associations between 1 and 2+ HRCA and PFS and OS among White and Black patients. Though differences in data abstraction between studies may contribute to discrepant findings, the lack of a uniform definition of high-risk cytogenetics complicates the ability to determine which cytogenetic abnormalities have the greatest impact on MM patient outcomes. Moving forward, the closer alignment in how cytogenetics are characterized within key staging/risk-defining systems (e.g., the Second Revision of the International Staging System[33] and the IMWG[34]) may increase uniformity of these definitions across studies.

Strengths of our study include adequate representation of NH Black/AA patients (23.3% of our overall study population),

which aligns with epidemiological trends and the estimated incidence of MM in Black/AA patients in the US.[4,35] Calculation of *P* interaction values strengthens our ability to state that certain variables did not differentially impact outcomes between races/ethnicities. The Flatiron Health MM Cohort predominantly comprises patients treated within community practices in the US. As such, the resulting study cohorts may not be fully representative of patients treated at US-based academic centers or international centers. As with most EHR-based studies, our analysis is subject to potential missing or erroneous data and may not have captured all treatment received by patients. Our study was not able to precisely characterize 1q21 copy number to distinguish between gain (3 copies) or amplification (≥4 copies), which may affect the degree of risk imparted by the cytogenetic abnormality. In addition, we did not examine t(11;14) in our cohort due to a high level of missing data and variable conclusions in the literature about its prognostic effects in both the general MM population and the AA population. Indeed, efforts to better characterize the impact of gain *versus* amplification of 1q21 and t(11;14) in RW populations should be sought.

In our study, unadjusted rwPFS and rwOS were similar between patients of NH Black/AA and NH White race/ethnicity. However, after multivariable adjustment, NH Black/AA race/ethnicity was associated with slightly inferior PFS, reflecting the need for a greater understanding of underlying factors that might contribute to survival differences between patients of different races/ethnicities, and how such factors may differ between patients seeking care at community versus academic sites. As additional therapies become available, periodic re-examination of RW data will be necessary to capture any differential use or survival impact of emerging treatment options. Strategies to improve the reliability and accuracy of abstracted data from EHR and their statistical interpretation will strengthen the ability of RW studies to meaningfully augment learnings from clinical trials. Continued efforts should be made to equalize access to care among patients of different races/ethnicities and to increase representation of patients of non-White race in clinical trials of MM. This, in turn, should impact favorably on the ability of current and future phase III study results to translate meaningfully into RW practice.[36]

Disclosures

TB discloses speakers bureau, advisory panels, and consultancy for Sanofi and Bristol Myers Squibb. MHB discloses consultancy honorarium from AbbVie, Bristol Myers Squibb/Celgene, GSK, Janssen, Karyopharm and Sanofi; speakers honorarium from Multiple Myeloma Research Foundation and Cancer Care. YAE discloses consultancy honorarium/speakers bureau from Takeda, Oncopeptides, Janssen, GSK, Alnylam, Sanofi, Pfizer and Adaptive; advisory board membership of Takeda, Oncopeptides, Janssen, GSK, Alnylam, Sanofi and Pfizer; research support from Bristol Myers Squibb/Celgene; independent adjudication committee membership of Takeda and ORCA. CM discloses speakers bureau at AstraZeneca, Bristol Myers Squibb, Blueprint Medicine and BeiGene. JAZ discloses research support from Bristol Myers Squibb and Janssen; discloses advisory role at Bristol Myers Squibb, Janssen, Prothena, Alexion, Takeda and Regeneron; independent data safety monitoring committee chair at Bristol Myers Squibb. PGR discloses consulting for Oncopeptides, Celgene/Bristol Myers Squibb, Karyopharm, Sanofi, and GSK; research grants from Oncopeptides, Celgene/Bristol Myers Squibb, Karyopharm and Takeda. TS and MSR are employed by Sanofi at the time of the study; may hold stock and/or stock options in the company.

Contributions

TB, TS, and MSR were involved in the conception and design of the study. MSR was responsible for data analysis. TB, MHB, YAE, CM, JAZ, PGR, TS, and MSR participated in data interpretation, manuscript writing, review, and final approval of the submitted version of the manuscript.

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Data-sharing statement

The data that support the findings of this study have been originated by Flatiron Health, Inc. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to dataaccess@flatiron.com.

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