



### TO THE EDITOR:

# With equal access, African American patients have superior survival compared to white patients with multiple myeloma: a VA study

Nathanael R. Fillmore,<sup>1-3,\*</sup> Sarvari V. Yellapragada,<sup>4,5,\*</sup> Chizoba Ifeorah,<sup>4,5</sup> Ansh Mehta,<sup>6</sup> Diana Cirstea,<sup>1,7</sup> Paul S. White,<sup>1,7</sup> Gustavo Rivero,<sup>4,5</sup> Andrew Zimolzak,<sup>1,5</sup> Saiju Pyarajan,<sup>1,2</sup> Nhan Do,<sup>1,7</sup> Mary Brophy,<sup>1,7</sup> and Nikhil C. Munshi<sup>1-3</sup>

<sup>1</sup>VA Boston Healthcare System, Boston, MA; <sup>2</sup>Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; <sup>3</sup>Dana-Farber Cancer Institute, Boston, MA; <sup>4</sup>Michael E. DeBakey VA Medical Center, Houston, TX; <sup>5</sup>Section of Hematology and Oncology, Baylor College of Medicine, Houston, TX; <sup>6</sup>University of South Alabama Hospitals, Mobile, AL; and <sup>7</sup>Department of Medicine, Boston University School of Medicine, Boston, MA

Multiple myeloma (MM) constitutes 1.8% of malignancies in the United States, and its incidence is significantly higher among African Americans (AAs) than whites.<sup>1,2</sup> Therefore, the impact of race on the disease biology and clinical outcomes of MM is an important area of research.<sup>3,4</sup> Recent studies have found significant and increasing racial disparities in overall survival (OS) since the introduction of high-dose and novel agent-based therapies.<sup>5-10</sup> Limited access to novel therapies has been considered partly responsible for the lower OS in AAs, and a number of studies have reported such racial disparities in the use of both novel therapies and transplantations.<sup>11-17</sup> For example, a SEER data study of 35 842 MM patients reported significantly lower use of novel agents and autologous transplantations specifically in AAs.<sup>15</sup> In contrast, data from several smaller studies, including a meta-analysis of clinical trials data, suggest that if access to care is equalized, disparities seen elsewhere may not be observed.<sup>18-23</sup> Because lack of access to therapies can predominantly affect OS, investigation as to whether other disease-related features may also contribute to differences in outcome has been limited.<sup>20</sup> However, the significantly higher incidence of MM in AAs may suggest differences in disease-initiating events that could also potentially affect outcome. Here, we have investigated the impact of racial disparities on outcome in a large MM patient population at Veterans Affairs (VA) hospitals with equal access to health care for all patients.

Patients diagnosed with MM in the VA's nationwide electronic health records were identified using the VA Corporate Data Warehouse under a protocol approved by the VA Boston Healthcare System Institutional Review Board. Patients were identified using International Classification of Diseases codes for MM. To minimize the possibility of misclassification, patients were required to have at least 3 MM International Classification of Diseases-coded visits on different days and were required to have received at least 1 agent associated with MM treatment other than corticosteroids after the date of diagnosis. Patients who had no outpatient visits in the year before diagnosis were excluded, because these patients might not have been regular users of the VA system, and thus, their data could have been incomplete. Because the focus of this study was racial disparities between AAs and whites, patients not identified as AA

or white were also excluded from our final analyses. Patient demographics, including drugs and therapies used, were identified through structured data in the VA Corporate Data Warehouse.

We identified 15 717 patients who satisfied the criteria for symptomatic MM in the VA health care system between 2000 and 2017. Of these, 3254 were AA and 8845 were white veterans. Patient characteristics listed in Table 1 are similar to SEER data.<sup>2</sup> Median OS of veterans in this study was 4.62 years (95% confidence interval [CI], 4.50-4.74 years). Age at diagnosis had a substantial impact on OS, with median OS decreasing from 7.5 years among veterans diagnosed in their 40s to 5.9, 5.2, 3.5, and 2.6 years for those in their 50s, 60s, 70s, and 80s, respectively ( $P < .001$ ). We next evaluated median OS between AA and white patients and observed that median OS was 5.07 years (95% CI, 4.70-5.44 years) for AA and 4.52 years (95% CI, 4.38-4.65 years) for white veterans (log-rank  $P < .001$ ; Figure 1A).

Because AAs are diagnosed with MM at a younger age, and we observed a substantial impact of age on outcome, we stratified patients by age (age  $< 65$  and  $\geq 65$  years at diagnosis). We still observed that among patients age  $< 65$  years at diagnosis, AA patients had a significantly superior median OS (7.07 years; 95% CI, 6.36-7.70 years) compared with whites (5.83 years; 95% CI, 5.44-6.09 years; log-rank  $P < .001$ ). OS was similar across race in patients age  $\geq 65$  years; median OS was 3.69 years (95% CI, 3.45-4.05 years) for AA and 4.04 years (95% CI, 3.90-4.19 years) for white patients (log-rank  $P = .63$ ; Figure 1B-C).

Because age at diagnosis could have accounted for some differences in OS even after stratifying around age 65 years, a Cox analysis, with age included as a continuous-time covariate, was performed in each stratum (age  $< 65$  and  $\geq 65$  years). We observed similar results; in those age  $< 65$  years, we observed a significant decrease in age-adjusted risk of death in AA compared with white patients (hazard ratio [HR], 0.86; 95% CI, 0.79-0.94;  $P = .001$ ), whereas we did not observe significant difference in age-adjusted risk of death between AA and white patients age  $\geq 65$  years at diagnosis (HR, 1.05; 95% CI, 0.98-1.13;  $P = .18$ ).

**Table 1. Cohort demographics, transplantation, and novel therapy use**

Characteristic	Full cohort, % (n)	AAs, % (n)	Whites, % (n)	P
<b>Age at diagnosis, y</b>				<.001
Median	69.5	65.6	70.1	
IQR	62.6-77.0	58.6-73.6	63.5-77.5	
<b>Sex</b>				<.001
Female	2.2 (262)	3.4 (110)	1.7 (152)	
Male	97.8 (11 837)	96.6 (3144)	98.3 (8693)	
Rural	33.6 (4026)	17.1 (554)	39.7 (3472)	<.001
<b>Income, \$</b>				<.001
Mean	45 800	29 700	51 900	
SD	74 300	31 300	84 200	
<b>ISS stage</b>				.942
I	24.2 (761)	24.2 (230)	24.2 (531)	
II	35.9 (1132)	36.3 (346)	35.8 (786)	
III	39.9 (1257)	39.5 (376)	40.1 (881)	
Transplantation	9.4 (1136)	10.1 (330)	9.1 (806)	.092
<b>Novel therapy at induction</b>				.213
Thalidomide	23.1 (2791)	19.8 (645)	24.3 (2146)	<.001
Lenalidomide	38.8 (4692)	37.4 (1216)	39.3 (3476)	.056
Bortezomib	31.3 (3786)	40.4 (1314)	27.9 (2472)	<.001
Thalidomide and bortezomib	1.7 (205)	2.4 (78)	1.4 (127)	<.001
Lenalidomide and bortezomib	9.9 (1195)	12.7 (414)	8.8 (781)	<.001
<b>Novel therapy over lifetime</b>				.293
Thalidomide	31.0 (3752)	28.0 (912)	32.1 (2840)	<.001
Lenalidomide	60.0 (7254)	60.0 (1953)	59.9 (5301)	.948
Bortezomib	46.6 (5634)	57.9 (1885)	42.4 (3749)	<.001
Thalidomide and bortezomib	11.7 (1418)	13.8 (449)	11.0 (969)	<.001
Lenalidomide and bortezomib	30.9 (3744)	38.5 (1253)	28.2 (2491)	<.001

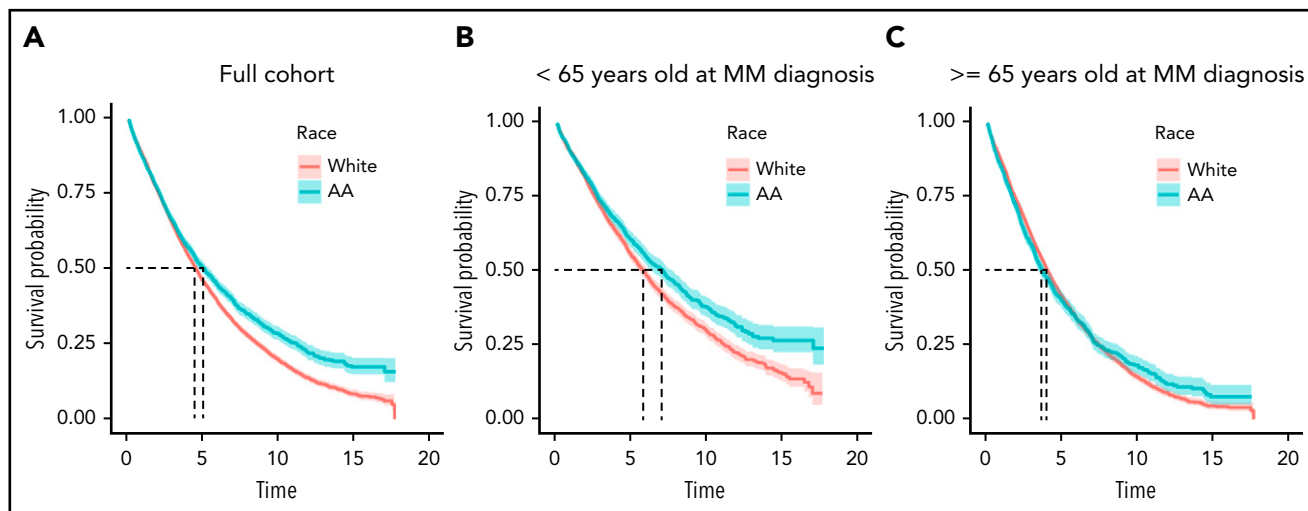
Reported are characteristics for AAs, whites, and the full cohort (AAs and whites together), as well as *P* values relative to the difference between races. Novel therapy includes thalidomide, lenalidomide, pomalidomide, bortezomib, carfilzomib, and ixazomib.

IQR, interquartile range; ISS, International Staging System; SD, standard deviation.

A number of prior studies have reported superior outcomes for white patients compared with AAs, and a common theory for this has been lack of access to health care, because of both social and financial reasons, in AA MM patients. To explain the possible role of health care access in our patient population, we investigated use of novel agents and stem cell transplantation (SCT). We observed no racial disparity at the VA in overall use of novel agents at induction, whether immunomodulatory drugs or proteasome inhibitors, with 82.5% of AA and 81.5% of white patients receiving novel therapy (*P* = .21) at induction (Table 1). In the most recent 5-year period (2012-2017), when both proteasome inhibitors and immunomodulatory drugs had become standard of care, patterns of use showed equal utilization, but use of novel therapy at induction had increased to 93.8% (AAs, 94.0%; whites, 93.7%; *P* = .72). Patterns of use were also similar when looking at lifetime exposure to novel therapy (AAs, 90.8%; whites, 90.2%; *P* = .29), as well as use of SCT (AAs, 10.1%; whites, 9.1%; *P* = .09).

Although there was no significant difference between races in the percentage of patients receiving novel agents at induction,

there was a significant difference in the type of agent used. Bortezomib was used more frequently among AAs, thalidomide was used more frequently among whites, and lenalidomide was used at similar rates, whereas lenalidomide-bortezomib combination was used more frequently among AAs (Table 1). Nevertheless, these differences do not account for the superior survival among younger AAs; AAs had superior or equal survival to whites in every treatment subgroup in the age <65 years stratum (thalidomide: 6.2 vs 5.4 years; log-rank *P* = .004; lenalidomide: 10.2 vs 7.7 years; *P* = .071; and bortezomib: 7.0 vs 5.1 years; *P* < .001 in AA vs white veterans, respectively) and equal survival in the age ≥65 years stratum (log-rank *P* = .140 for each treatment group). In a multivariate Cox analysis, race remained independently associated with a significantly lower risk of death in AAs than whites among patients age <65 years (HR, 0.79; 95% CI, 0.72-0.87; *P* < .001), even after adjusting for age, sex, rurality, income, stage, transplantation, and the categories of therapy at induction listed in Table 1. In the group age ≥65 years, race was still not a significant factor (HR, 0.99; 95% CI, 0.92-1.07; *P* = .859) after making these adjustments.



**Figure 1. OS is shown (in years) for the full cohort and stratified at age <65 and ≥65 years at MM diagnosis.** For the full cohort (A), median OS is 5.07 years for AAs and 4.52 years for whites (log-rank  $P < .001$ ). For <65 years (B), median OS is 7.07 years for AAs and 5.83 years for whites (log-rank  $P < .001$ ). For ≥65 years (C), median OS is 3.69 years for AAs and 4.04 years for whites (log-rank  $P = .63$ ).

These results suggest that in the VA system, with a lack of significant racial difference in use of novel therapies or SCT in MM, OS may be superior in AA patients, particularly in the younger population. Taken with previous research in other health care systems that does demonstrate disparities, our study suggests disparity may be primarily due to socioeconomic factors. Furthermore, the improved outcomes in AA MM patients also raise an important question about possible differences in disease biology. This is relevant, because incidence of MM is twofold higher in both men and women in AA compared with white patients.<sup>2</sup> This has been observed in AA patients and native African patients, as reported in a study involving incidence of plasma cell disorder in Ghana.<sup>24</sup> Along with differences in incidence, the age of onset and superior OS in AAs now highlight the need to further investigate race-related biological and genomic differences in the disease process to develop diagnostic, preventative, and therapeutic approaches.<sup>25</sup>

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## Authorship

Contribution: N.R.F., S.V.Y., and N.C.M. conceived and designed the study; N.R.F. prepared and analyzed the data; all authors provided scientific input; N.R.F., S.V.Y., and N.C.M. wrote the manuscript; and all authors edited and critically reviewed the final version of the manuscript.

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M.B. receives research funding from Novartis. N.C.M. is a consultant for Celgene and Takeda and on the board of directors for OncoPep. The remaining authors declare no competing financial interests.

ORCID profiles: N.R.F., 0000-0002-8058-3423; P.S.W., 0000-0001-8345-0573.

Correspondence: Nikhil C. Munshi, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215; e-mail: nikhil\_munshi@dfci.harvard.edu.

## Footnote

\*N.R.F. and S.V.Y. contributed equally to this work.

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**TO THE EDITOR:**

## Archeogenetics of *F11* p.Cys38Arg: a 5400-year-old mutation identified in different southwestern European countries

María Eugenia de la Morena-Barrio,<sup>1,\*</sup> Salam Salloum-Asfar,<sup>1,2,\*</sup> Julio Esteban,<sup>3</sup> Belén de la Morena-Barrio,<sup>1</sup> Carmen Altisent,<sup>4</sup> Laura Martín-Fernández,<sup>5-7</sup> Paul Gueguen,<sup>8</sup> Jose Padilla,<sup>1</sup> Antonia Miñano,<sup>1</sup> Rafael Parra,<sup>4</sup> Vicente Vicente,<sup>1</sup> Francisco Vidal,<sup>5,9,10</sup> Frederic Bauduer,<sup>11,†</sup> Pablo Carbonell,<sup>12,†</sup> and Javier Corral<sup>1,†</sup>

<sup>1</sup>Servicio de Hematología y Oncología Médica, Hospital Universitario Morales Meseguer, Centro Regional de Hemodonación, Universidad de Murcia, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Murcia, Spain; <sup>2</sup>Neurological Disorders Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Education City, Qatar Foundation, Doha, Qatar; <sup>3</sup>Servicio de Hematología Hospital, Virgen del Castillo de Yecla, Murcia, Spain; <sup>4</sup>Unidad de Hemofilia, Hospital Universitario Vall d'Hebron, Barcelona, Spain; <sup>5</sup>Coagulopatías Congénitas, Banc de Sang i Teixits, Barcelona, Spain; <sup>6</sup>Unitat de Genòmica de Malalties Complexes, Institut d'Investigació Biomèdica Sant Pau, Barcelona, Spain; <sup>7</sup>Fundación Española de Trombosis y Hemostasia, Madrid, Spain; <sup>8</sup>Laboratoire de Génétique Moléculaire, INSERM U1078, CHRU de Brest, Brest, France; <sup>9</sup>Unitat de Diagnòstic i Teràpia Molecular, Vall d'Hebron Institut de Recerca, Universitat Autònoma de Barcelona, Barcelona, Spain; <sup>10</sup>CIBER de Enfermedades Cardiovasculares, Barcelona, Spain; <sup>11</sup>UMR 5199 PACEA, Université de Bordeaux, Pessac, France; and <sup>12</sup>Centro de Bioquímica y Genética Clínica, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

Factor XI (FXI) is a key element for the amplification of thrombin generation, which participates in the contact pathway. This explains why FXI deficiency has minor physiological relevance but protects against thrombotic events, supporting FXI as an excellent target for antithrombotic treatments.<sup>1,2</sup>

FXI deficiency (MIM #612416) has been considered a rare disorder that might reach relatively high prevalence in certain populations. The best example is within the Ashkenazi Jews, demonstrating an incidence of 8% of heterozygous individuals for 2 mutations: p.Glu117Ter and p.Phe283Leu, which account

for 98% of alleles.<sup>3</sup> So far, 220 different causative mutations have been identified throughout the FXI gene (*F11*) (<http://www.factorix.org/>). Recently, the exome-based data obtained from >60 000 individuals (Exome Aggregation Consortium) have revealed new information regarding genetic variation in *F11*, showing (a) profound differences in heterozygous frequency among populations, and (b) evidence of recurrent and ethnic-specific mutations: (1) p.Phe223Leu in Africans (23.5% of all mutated alleles); (2) p.Gln263Ter and p.Leu424CysfsTer in East Asians (28.2% and 20.5%, respectively); and (3) p.Ala412Thr in Latinos (25%).<sup>4</sup>