Assuring that African Americans Share in the Progress in Multiple Myeloma

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Disclosures

Consultant: Astrazeneca, Janssen, Pfizer

Board/ Stock Options: Dynamic Cell Therapies, C4 Therapeutics, Next RNA, Oncopep, Starton, Window

Therapeutic Advances in Multiple Myeloma

Proteasome inhibitors: bortezomib, carfilzomib, ixazomib; immunomodulatory drugs: thalidomide, lenalidomide, pomalidomide; HDAC inhibitor: panobinostat; monoclonal antibodies: elotuzumab, daratumumab, and isatuximab; nuclear transport inhibitor: selinexor; CAR T cell: idecel, ciltacel; bispecific T cell engager: teclistamab, elranatamab, talquetamab

Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy; now under evaluation earlier in disease course, SMM

Minimal residual disease negativity (MRD-) associated with prolonged PFS and OS in NDMM (transplant-eligible and -ineligible) and RRMM

32 FDA approvals (16 agents), median patient survival prolonged 3-4 fold, from 3 to at least 8-10 years, and MM is a chronic illness in many patients

Health Disparities

Longer time: symptoms to diagnosis for Black Americans[1]

Black Americans are younger by about 5 y at diagnosis[2]

Myeloma and MGUS are more than twice as common in Black Americans[3,4]

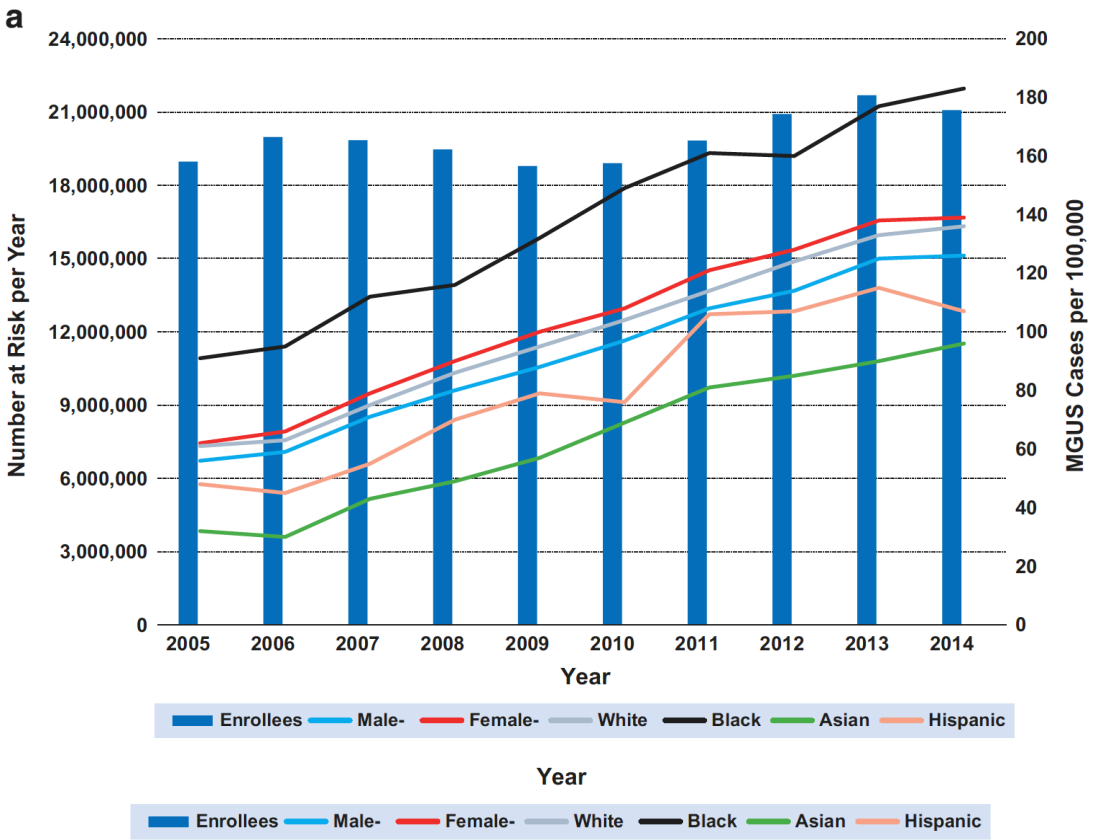
Black Americans are less likely to receive transplant, triplets, trials, and CAR T[5

Black Americans have biologic differences with less high-risk cytogenetics, including less del(17p)[9] and more t(11;14)[10]

Black Americans can achieve equal or better outcomes **when** they receive therapy[11]

1. Mikhael J et al. *Am J Med*. 2023;136:33-41; 2. Ailawadhi S et al. *Br J Haematol*. 2012;158:91-98; 3. Waxman AJ et al. *Blood*. 2010;116:5501-5506; 4. Landgren O et al. *Blood Cancer J*. 2017;7:e618-e618; 5. Derman BA et al. *Blood Cancer J*. 2020;10:80; 6. Ahmed N et al. *Transplant Cell Ther*. 2022;28:358-364; 7. Ailawadhi S et al. *Blood Cancer J*. 2018;8(7):67; 8. Al Hadidi S et al. *JAMA Netw Open*. 2022;5:e228161; 9. Kazandjian D et al. *Blood Cancer J*. 2019;9:15; 10. Baughn LB et al. *Blood Cancer J*. 2018;8:96; 11. Fillmore NR et al. *Blood*. 2019;133:2615-2618.

Monoclonal Gammopathy of Undetermined Significance (MGUS)



- 3% of population at age 50
- Increases with age
- 3 times more common in African Americans
- Younger age for African
- Americans
- 3 times more common in familial cases

Go et al Leukemia 2016; 30: 1443-6.

MM Family History

Familial clustering is greater in Black patients with MM

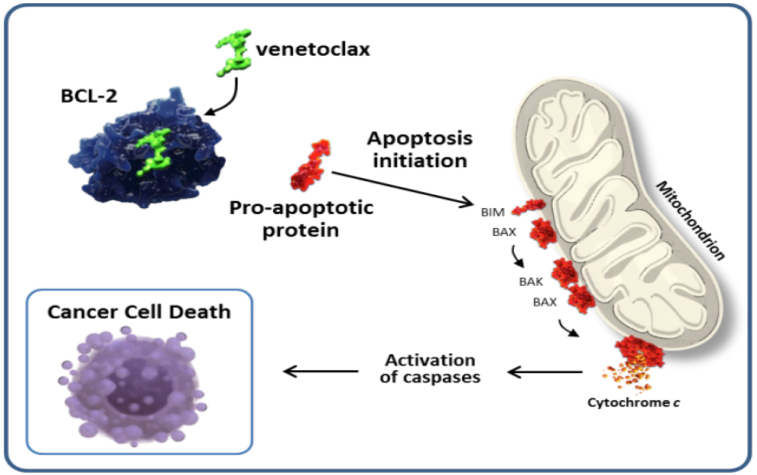
- Positive family history
- Case control study, 1986-1989
  - MM risk with family history of MM: OR 3.7 (95% CI 1.2-12)
- MAGE Study, UAB
  - MM risk with family history of MM: OR 3.75, effect greater for B (OR 20.9; 95% CI 2.59-168) than W (OR 2.04; 95% CI 0.83-5.04)

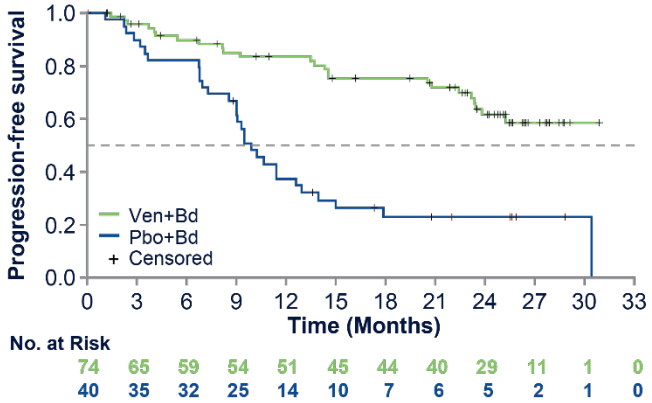
Jain M et al. *Am J Hematol.* 2009;84(1):34-38.
Brown LM et al. *Cancer.* 2000;85(11):2385-2390.
VanValkenburg ME et al. *Cancer Causes Control.* 2016;27(1):81-91.

Biological Differences in Myeloma

African Americans more commonly have IgH translocations than European ancestry: t(11:14), t(14:16), t(14:16) May have therapeutic implications: venetoclax

African Americans less likely than whites to have TP53/17p deletions





Venetoclax and bortezomib in t(11;14) or *BCL2*^{high} RRMM

Baughn et al Blood CA J 2018: 8: 96-106; Kazandijian et al Blood Cancer J 2019; 9:15

Biological Differences in Myeloma

Vitamin D deficiency is a predictor for poor overall survival in patients with MM, even after adjusting for age and stage.

This difference is only observed in white patients, not African Americans, even with a lower threshold for deficiency.

Fillmore et al JNCI 2021; 113: 691-8; Blood Advances 2020; 4: 1643-6.

Among 2243 VA patients with MM, del17p in 8.83% of patients, 5.56% in African American versus 10.52% in whites ($p<0.001$); in patients <65 years, 4.34% in African American versus 9.8% in white ($p=0.004$).

No significant difference in survival between African American and white patients with del17p regardless of age category, suggesting that del17p carries a poor prognosis across race and age.

Fillmore et al Blood Advances 2021; 5: 3511-14.

Differences in MM Presentation

Covariate	No. of Patients (%)				Adjusted P^a
	White, N = 25,823	Hispanic, N = 2624	Black, N = 5789	Asian, N = 1486	
At diagnosis					
Hypercalcemia	2494 (9.7)	244 (9.3)	629 (10.9)	126 (8.5)	.586
Renal dysfunction	2910 (11.3)	347 (13.2)	830 (14.3)	190 (12.8)	<.001
Anemia	4370 (16.9)	475 (18.1)	1269 (21.9)	274 (18.4)	<.001
Bone fracture	4349 (16.8)	371 (14.1)	661 (11.4)	222 (14.9)	<.001
Dialysis	155 (0.6)	25 (1.0)	60 (1.0)	14 (0.9)	.118
After diagnosis					
Hypercalcemia	2789 (11.8)	303 (12.6)	822 (15.3)	148 (10.7)	.063
Renal dysfunction	4883 (20.7)	554 (23.0)	1461 (27.2)	316 (22.9)	<.001
Anemia	5788 (24.6)	597 (24.8)	1684 (31.4)	333 (24.1)	<.001
Bone fracture	5528 (23.5)	529 (21.9)	898 (16.7)	275 (19.9)	<.001
Dialysis	557 (2.4)	87 (3.6)	225 (4.2)	50 (3.6)	<.001

DRIVE Rank Score 5

Ailawadhi S et al Cancer 2018; 124: 1710-21

Multiple Myeloma in African Americans

Incidence rates higher in African Americans than whites:
15.9 vs 7.5 cases per 100,000, respectively

Mortality higher in African Americans than in whites:
5.6 vs 2.4 deaths per 100,000, respectively

SEER: 1973-2005: African Americans higher OS, but 5 year relative survival rates increased for whites (26.3% to 35%, $p<0.005$), but not African Americans (31% to 34%)

De Sanctis et al CA Cancer J 2019; 69: 211-13.
Waxman et al Blood 2010; 116: 5501-6

Clinical Trial Differences

2003 - 2017 FDA New Drug Applications in myeloma:
Low rates of African American patient enrollment in pivotal (4.5%) and international (1.8%) trials

2002 - 2011 Cooperative Group clinical trials:
13% African American patient enrollment, compared to 16.5% for prior 10 years.
Most do not include novel agents or stem cell transplant.

NB: African American patients treated with novel agents in FDA approval trials or in Veterans Administration Hospital system have similar or even improved outcome.

Ailawadhi et al Blood CA J 2018; Pulte et al Blood Advances 2018; Fillmore et al Blood 2019; 2615-17

FDA Analysis of Multiple Myeloma Trials Supporting Approval

(**19 trials with N=10157 patients** matched to results reported in prescribing information (USPI)

Enrollment of **Black pts at 4%** in the pooled dataset and Asians at 7% as compared to **84% of White pts**
15.8 new cases per 100,000 persons among Black pts as compared to 6.9 cases in White (2019 SEER)

ORR: Data shows **no conclusive differences** in the different race categories. Trend of the point estimates indicate Black pts have lower odds to respond as compared to White pts, Asian pts have higher odds to respond than White pts, 95% CIs span one

Similar trends by drug classes, IMIDS, PI and anti-CD38, low number of patients in these subgroups

PFS: No difference in PFS between Black and White pts or Asian and White pts

OS: **No statistically significant differences** observed other than US vs Row
Patients in the **US do better than pts in RoW (Rest of World)**
Point estimates indicate **trends of Black and Asian pts to do better than White pts**
In the US: Black pts trending towards slightly lower hazard than White pts
In RoW: Lower numbers for Black pts, Asian pts showing trends to do better than White pts.
There are insufficient patients to draw conclusion in some of the subgroups by race and region.

Bindu Kanapuru, MD. Laura Fernandes, PhD
FDA/AACR Workshop 2020
Gormley et al BCD 2021; 2:119-24.

MGUS/SMM and MM at Veterans Administration Healthcare System

VA System: 15,717 patients, MVP 1189 patients

- .

Characteristic	Value
Race	
African-American	**22.0% (3254)**
White	**60.0% (8845)**
Other or Unknown	**18.0% (2867)**
Sex	
F % (count)	**2.2% (262)**
M % (count)	**97.8% (11837)**

Characteristic	Value
Age at Diagnosis (sd)	69.0 (10.1)
Rural % (count)	33.6% (4026)
Income (sd)	$45800 (74300)
Possible Agent Orange Exposure % (count)	13% (1900)

NB: Access to stem-cell transplant and novel therapy (IMiD and PI) is equal for African-American (AA) and Caucasian VA patients

Drive Rank Score 5

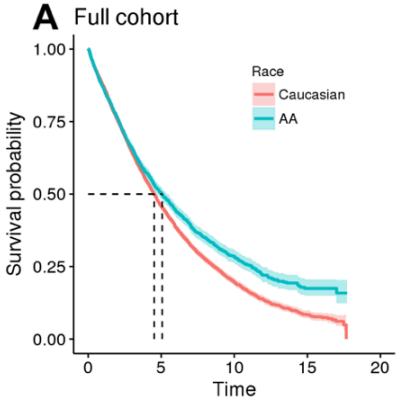
Fillmore NR et al Blood 2019; 133: 2615-18.

Lack of Disparity in MM Survival: Better unadjusted OS for African-Americans

Substantial difference in OS
between AA and white patients, with
AA having superior survival.

Median OS:
5.07 years (95% CI 4.70-5.44) for AA
4.52 years (95% CI 4.38-4.65) for Caucasian
(P<1e-15).

However, age has a substantial effect on OS, and
AA have earlier diagnosis: AA 66.0 years old, Caucasian 70.2 (P<0.001)

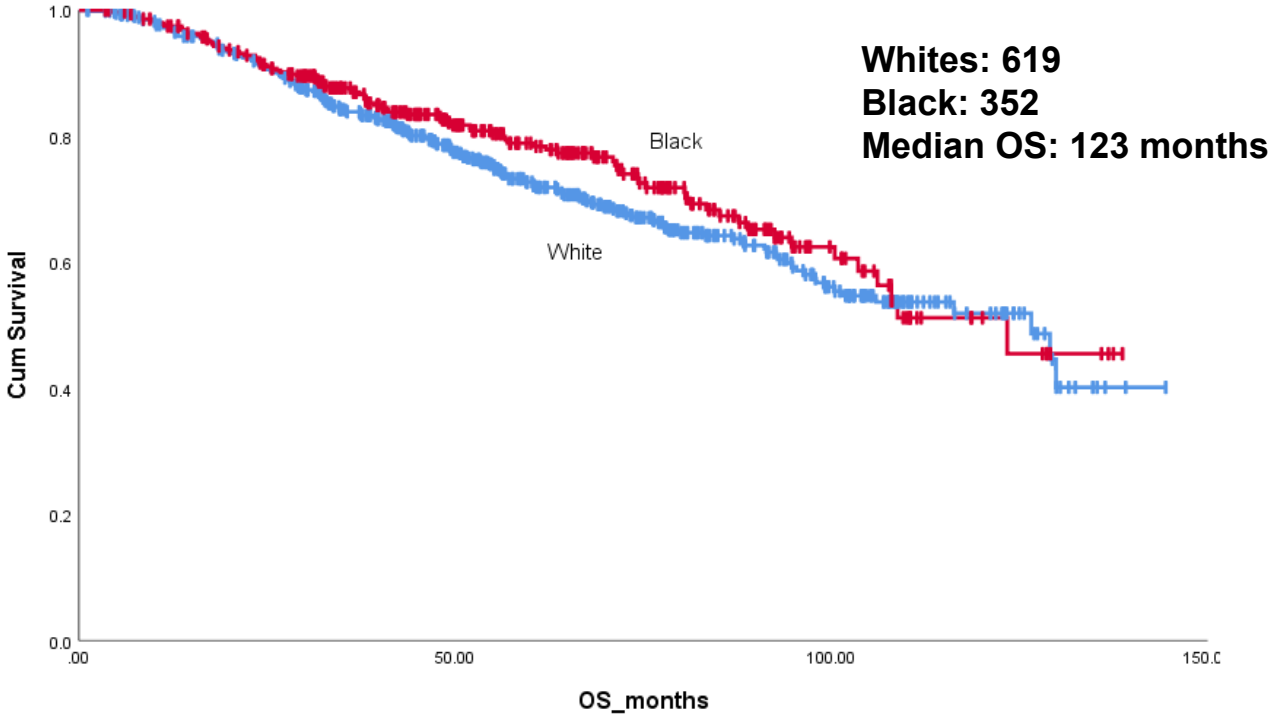


Conclusion: With equal access, African American patients have superior survival compared to white patients with multiple myeloma

Fillmore NR et al Blood 2019; 133: 2615-18.

DRIVE Rank Score 5

RVD induction, ASCT, with Risk Stratified Maintenance: Overall Survival By Race



DRIVE Rank Score 2

Joseph, Nooka et al. JCO 2020; 38: 1928-37

Impact of Race and Ethnicity on CAR T Outcome

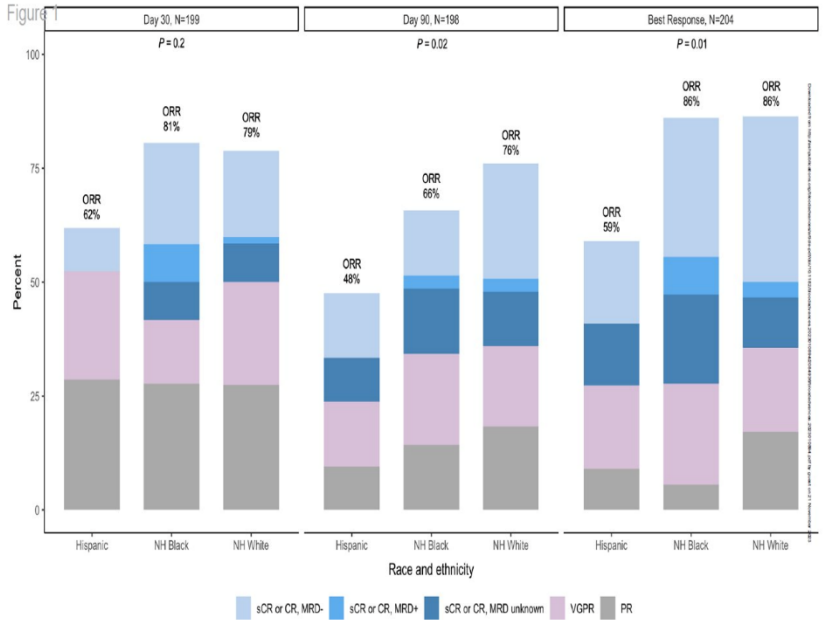
Pooled data from 207 RRMM patients (11% Hispanic, 17% Black, and 72% White) treated with standard of care ide-cel CAR-T across 11 centers

Black patients were **more likely to develop** compared to White and Hispanic patients:

- **Any grade CRS** (97% vs. 77% vs. 85%, respectively; *P* = .04)
- **Longer median hospital stay** (13.5 vs. 9.0 vs. 8.0 days, respectively; P = .006)
- No differences in incidence of CRS ≥ grade 3, any grade ICANS or ICU admission

ORR was lower among Hispanic patients (59%) compared to Black (86%) and White patients (86%; *P* = .01),

No racial and ethnic differences in progression-free or overall survival



DRIVE Rank Score 5

Peres LC et al Blood Adv 2023, in press.

Barriers to Clinical Trial Enrollment

System level barriers
- Lack of clinical trial infrastructure
- Insurance

Individual level
- Mistrust
- Fear related to research participation
- Inadequate information about research
- Access/Convenience of participation
- Strict eligibility criteria not reflecting real world patients

Hamel et al. Cancer Control. 2016; 23: 327–37

FDA Analysis of Screen Failures in Myeloma

Retrospective analysis of 16 trials submitted to the FDA from 2006-2019 to support approval of MM therapies

- Analyze the rates and reasons for trial ineligibility by race and ethnicity

Black patients (24%), and Other race (23%) had higher ineligibility rates compared to Whites (17%) and Asians (12%)

Failure to meet "Hematologic Lab Criteria"(19%) and failure to meet "Treatment Related Criteria"(17%) were the most common reasons for Black ineligibility

ASH Abstract #4762: In Determination Trial,153 pts were tested for Duffy-null phenotype (benign ethnic neutropenia)

- *8.5% Duffy-null: 64.7% blacks & 1.5% non-black*

Category	White N=1338	Black N=88
Failure to meet treatment related criteria	167 (12%)	15 (17%)
Failure to meet Hematology lab	171 (11%)	17 (19%)
Failure to meet Disease related	368 (28%)	16 (18%)
Failure to meet Renal function	44 (3%)	4 (5%)

Kanapuru B et al Blood 2023; 142: 235-43; Zonder et al ASH 2023 (abstr)

Strategies for Increasing African American Accrual to Clinical Trials

- creating community advisory boards
- delivering culturally targeted education programs
- partnering with community-based organizations serving the African American community
- improving access to clinical care and support services
- myeloma awareness events
- faculty diversity
- leadership buy-in
- addressing the problem: trials of real world patients

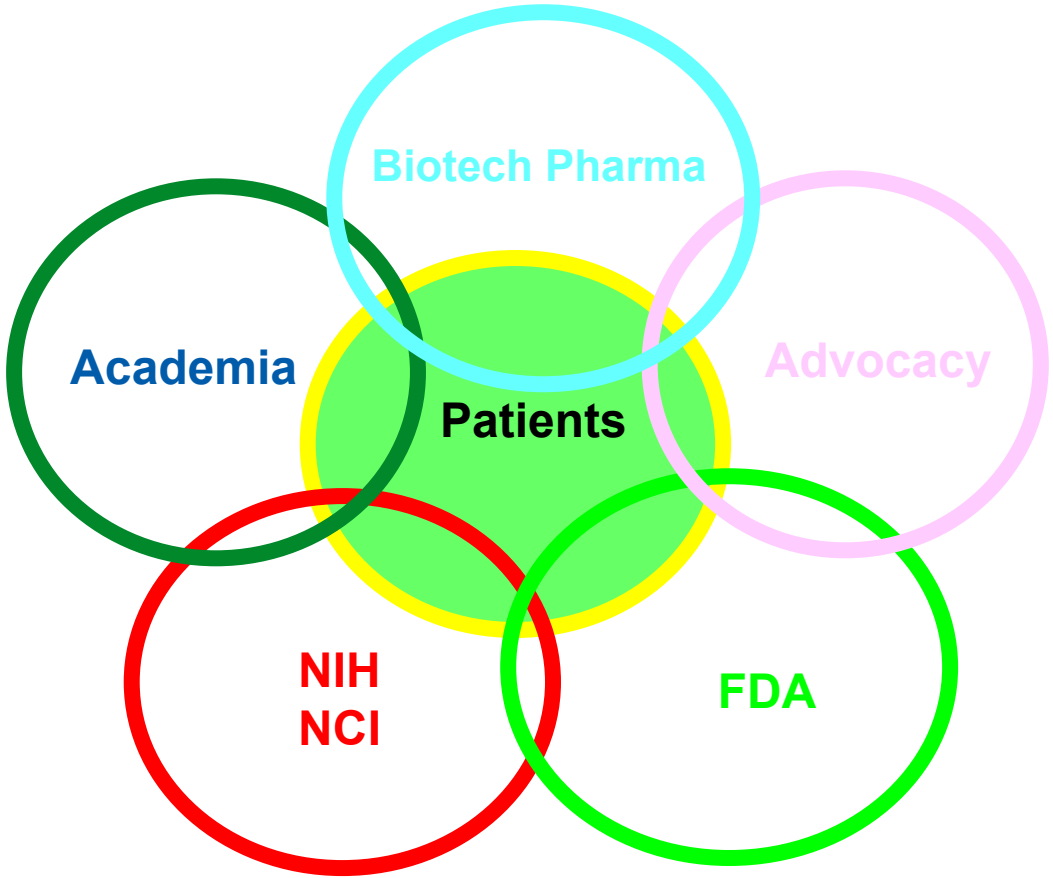
Collaborative Model Fosters Rapid Translation and Access to Novel Agents in Multiple Myeloma

Advocacy

- AACR
- ASH
- ASCO
- ACS
- LLS

MM Specific

- MMRF/C
- IMF
- IMS



Workshop: FDA-AACR Workshop to Examine Under-Representation of African Americans in Multiple Myeloma Clinical Trials

Chairpersons:

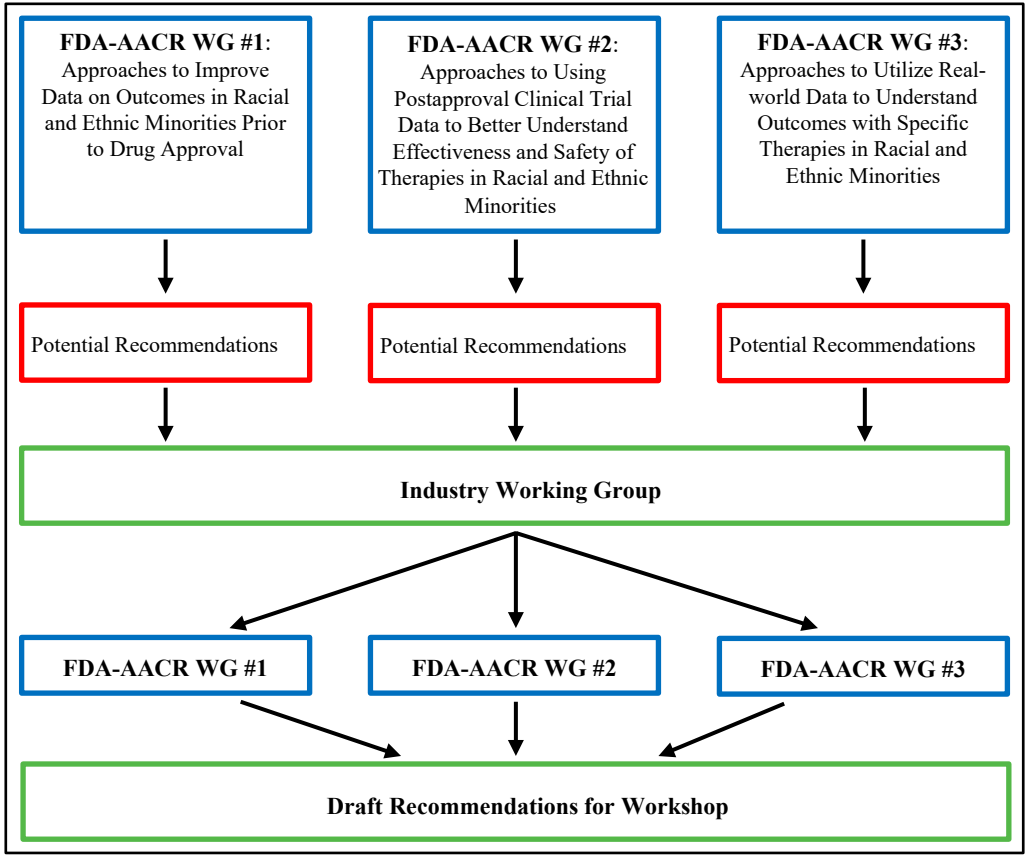
FDA **Lola A. Fashoyin-Aje, MD, MPH, Acting Deputy Director, Division of Oncology, Office of Oncologic Diseases, CDER, FDA**

Nicole J. Gormley, MD, Acting Director, Division of Hematologic Malignancies, Office of Oncologic Diseases, CDER, FDA

Paul G. Kluetz, MD, Deputy Director, Oncology Center of Excellence, FDA

AACR Kenneth C. Anderson, MD, FAACR, Chair, AACR Regulatory and Policy Subcommittee
Program Director, Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute
Kraft Family Professor of Medicine, Harvard Medical School

Working Group Process



FDA and AACR partnered on this workshop, forming working groups of experts to develop recommendations for improving and understanding data on outcomes and effectiveness of multiple myeloma therapies in African Americans in preapproval, post-approval, and real-world settings.

Gormley et al Blood Cancer Discovery; 2021; 2:119-24.

Working Group 1 Recommendations: Discussion Highlights

Broad support for using a diversity officer and/or score to assure prospective enrollment and achievement of accrual goals for African Americans.

A collaborative effort to reform clinical trial design, endpoints, and inclusion/exclusion criteria to reflect real-world experience should be undertaken.

Educating whole healthcare teams on cultural sensitivity and competence is imperative.

There is a need for consideration of biologically-based clinical trials in African Americans (i.e., venetoclax in t(11;14)/high Bcl-2 patients).

Gormley et al Blood Cancer Discovery; 2021; 2:119-24

Working Group 2 Recommendations: Discussion Highlights

Recognize the complexity of all issues involved in under-representation; there will not be a one-size-fits-all solution to improve enrollment.

Early-stage collection of genomic data will allow us to better understand the disease and safety and efficacy of drugs in different patient subpopulations.

If we don't get enough data on African Americans in pre-approval trials, there are numerous strategies for aggregating them in the post-approval setting.

Education of the community is important and must be done carefully and intentionally (i.e., for genomics).

Gormley et al Blood Cancer Discovery; 2021; 2:119-24

Working Group 3 Recommendations: Discussion Highlights

Real-world data, currently, are better suited to asking than to answering questions.

> **Different sources are better for different types of questions (i.e., claims data for safety questions).**

Identifying a common set of minimal data elements and harmonizing line-of-treatment definitions and real-world endpoints will improve the utility of real-world data sources and allow for easier pooling and comparing of data.

Gormley et al Blood Cancer Discovery; 2021; 2:119-24

Clinical Trial Diversity Action Plans

Call to Action:

Gormley N, Fashoyin-Aye LK, Locke T, Unger JM, Little RF, Nooka A, Mezzi K, Pop-McKiver M, Kobos R, Biru Y, Williams TH, Anderson KC: Recommendations on eliminating racial disparities in multiple myeloma therapies: a step toward achieving equity in healthcare.

Blood Cancer Discovery 2021; 2: 119-24.

A series of roundtable meetings convened by the AACR last year, during which representatives from 30 pharmaceutical and biotech companies and the U.S. Food & Drug Administration (FDA) Oncology Center of Excellence (OCE) discussed current practices, key challenges, and potential solutions to improve diversity in clinical trials

2023 Consolidated Appropriations Act requires clinical trial sponsors to submit Diversity Action Plans to the FDA as part of their study protocols.

FDA-AACR-ASA Workshop Overall Survival in Oncology Clinical Trials on July 18, 2023 , chaired by Nicole Gormley, MD (FDA) and Ken Anderson MD (AACR) included focus on achieving diversity.

1980 and Ongoing-Stem cell transplant
2000 and Ongoing- Novel agents
2020 and Ongoing-Immune therapies

In the future, targeted and immune therapies Including CART/BiTEs will be incorporated into initial treatment of MM to achieve durable MRD- responses and restore memory anti-MM immunity, allowing patients to be disease free and off all therapy.

"Cure is Growing Old and Dying from Something Else"

Francesca Thompson, MD
1986

NB Need to assure that all patients have access to clinical trials and these advances.