Hematologic Malignancies: with a focus on Multiple Myeloma

Racial differences in clinical trial participation and therapeutic outcomes

Building **Health Equity** and
Multi-Directional Trust in Cancer Care

A Skills and Knowledge Based Webinar Series

In Partnership With NPAF National Patient Advocate Foundation

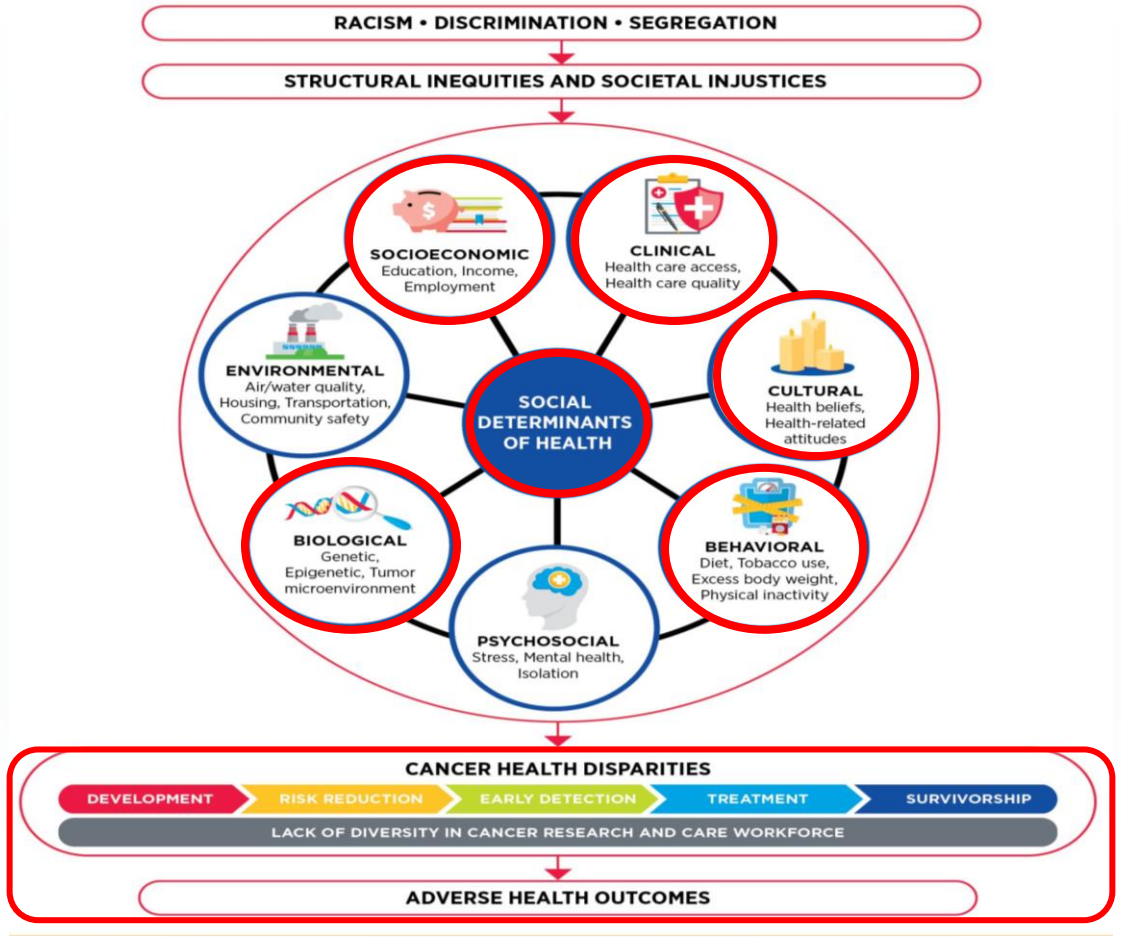
PIM Postgraduate Institute for Medicine

Bio Ascend™

Outline

- Why do Disparities Exist in Myeloma?
- Race and Incidence of Multiple Myeloma
- Differences in Risk, Biology and Presentation
- Differences in Myeloma Survival and Treatment Response
- Disparities in Clinical Trials
- Solutions: Clinical Trials

Why Do Cancer Health Disparities Exist In Myeloma?

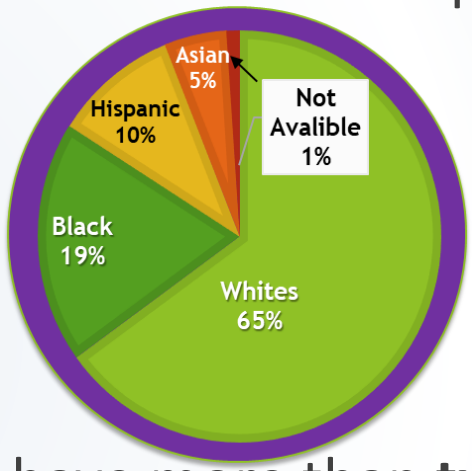


AACR. Accessed May 19, 2023. https://cancerprogressreport.aacr.org/disparities/.

Race and Incidence of Myeloma

- Overall incidence is slightly higher in men at 8.8 per 100,000 than women at 5.7 per 100,000.

US myeloma population by ethnicity:



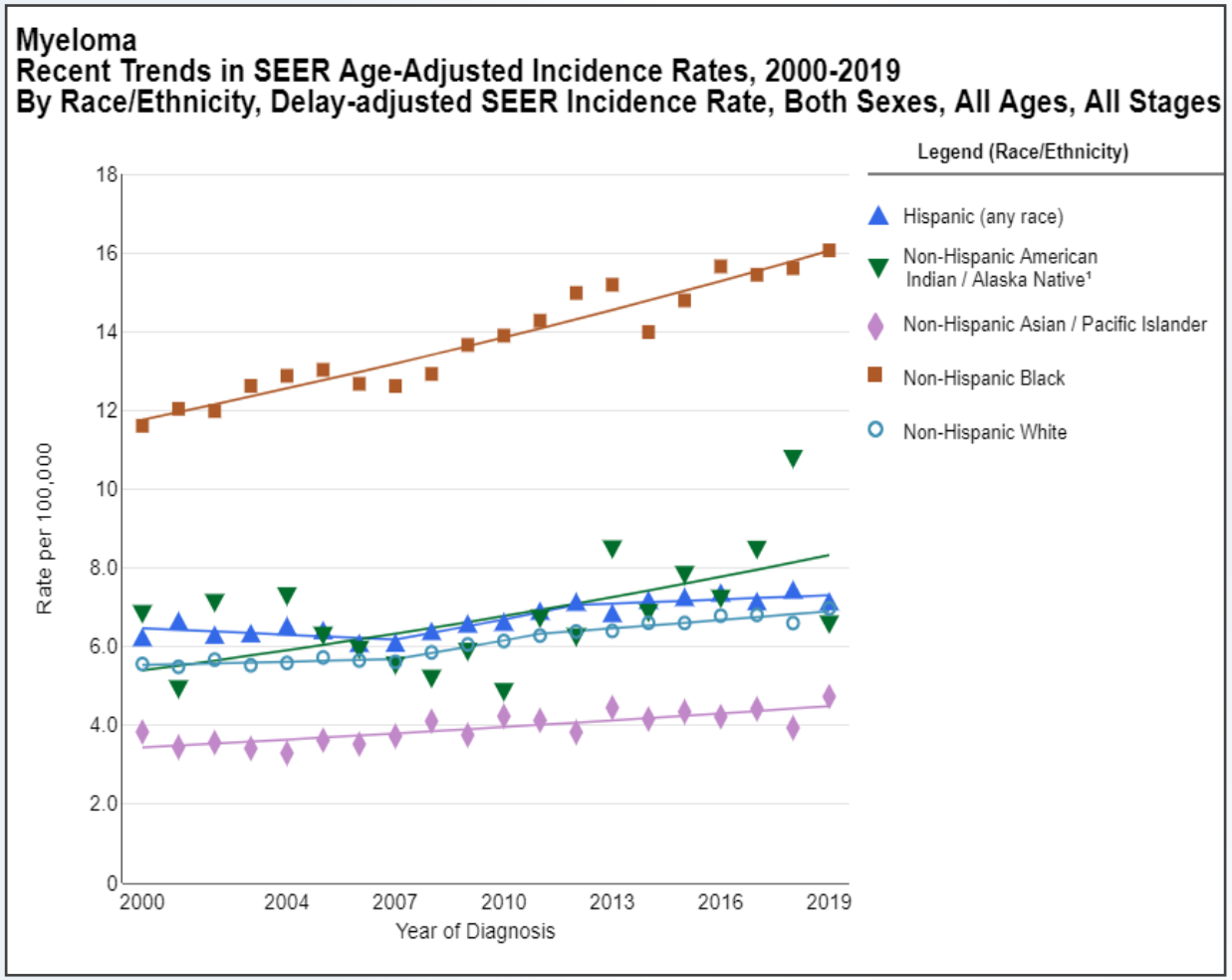
- Black patients have more than **twice** the myeloma incidence of White patients
  - This mirrors the higher incidence of MGUS.

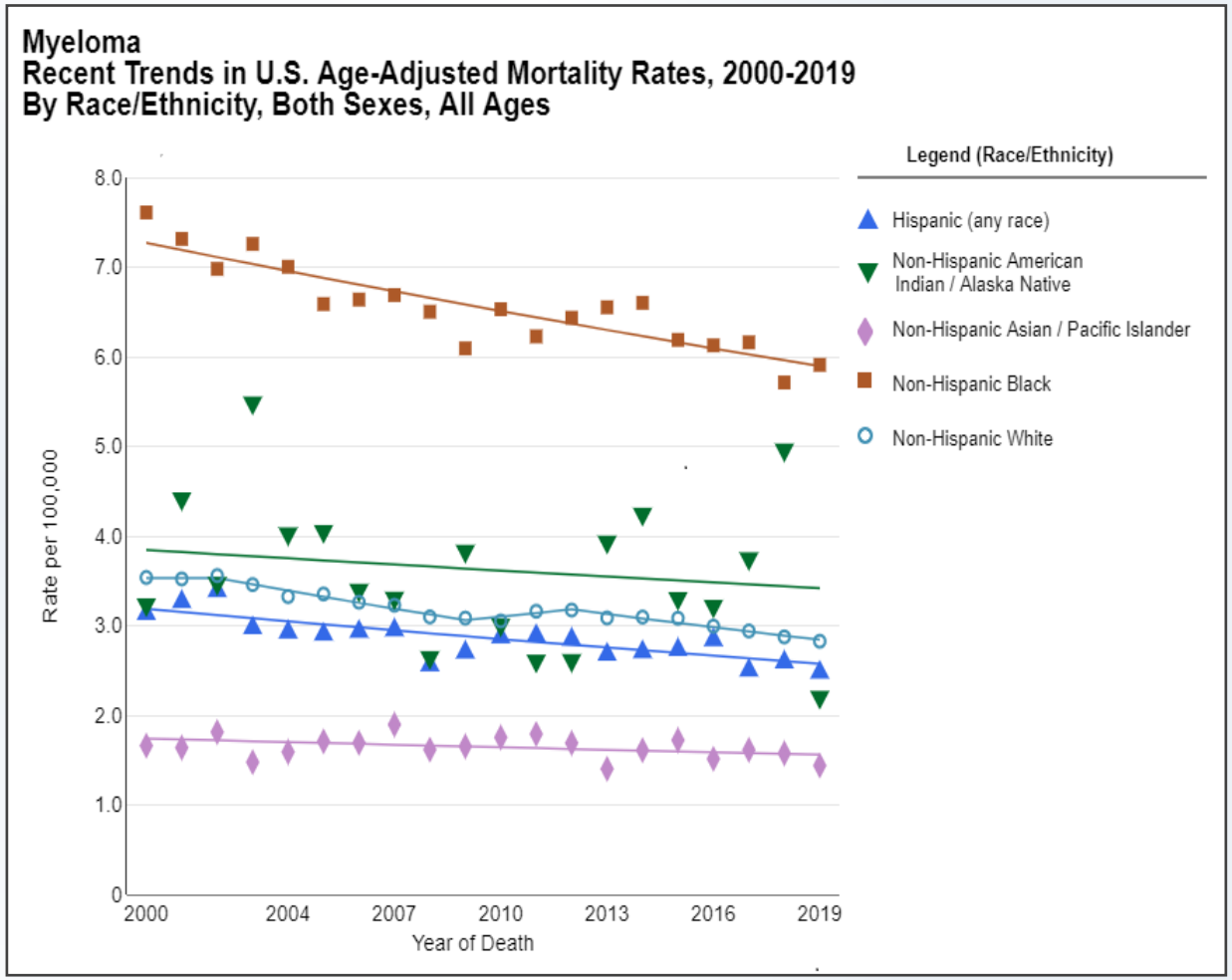
- **Black patients have the highest risk of myeloma of any race/ ethnic group in the world.**

MGUS = monoclonal gammopathy of undetermined significance.

NCI SEER. Accessed May 19, 20223. www.seer.cancer.gov. Greenberg AJ, et al. *Leukemia.* 2012;26(4):609-14. NCI SEER. http://seer.cancer.gov/statfacts/html/mulmy.html.

US Multiple Myeloma Incidence and Mortality by Race/ Ethnicity





NCI SEER. Accessed May 19, 2023. https://seer.cancer.gov/statistics-network/explorer/application.html.

Differences in Myeloma Risk, Biology, Presentation

- Compared to White patients, Black patients:
  - ✓ Tend to be diagnosed at a younger age
    - Mean age at diagnosis was 65.8 and 69.8 years for Black patients and White patients, respectively (P < .001)
  - ✓ More likely to present with anemia, renal failure and hypercalcemia
  - ✓ Higher incidence of IgA and Free Light chain subtypes
  - ✓ Less likely to have high risk cytogenetics (del 17p, t(4;14), additions 1q)
    - t(11;14), t(14;16), or t(14;20) was significantly higher in the 120 individuals with highest African ancestry (≥80%) compared with the 235 individuals with lowest African ancestry

Blood Ca J 8, 67 (2018). https://doi.org/10.1038/s41408-018-0102-7. Baughn et al Blood CA J 2018: 8: 96-106. Munjuluri et al Blood 2019; 134 Suppl:4388. Blood, 116(25), 5501–5506. Cancer 2018;124:1710-21. Leukemia. 2012 Apr;26(4):609-14. Blood. 2019;133(24):2615-8. Blood Cancer Journal (2022) 12:63 ; https://doi.org/10.1038/s41408-022-00653-1.

Differences in Myeloma Therapy and Survival

- Compared to White patients, Black patients:
  - ✓ Experience significant delays from diagnosis to treatment
    - Black patients and Hispanic patients had a longer time from MM diagnosis to novel therapy initiation vs White patients (median:5.2 & 4.6 vs 2.7mo)
  - ✓ Less likely to receive standard of care triplet (RVD) induction therapy and autologous stem cell transplant

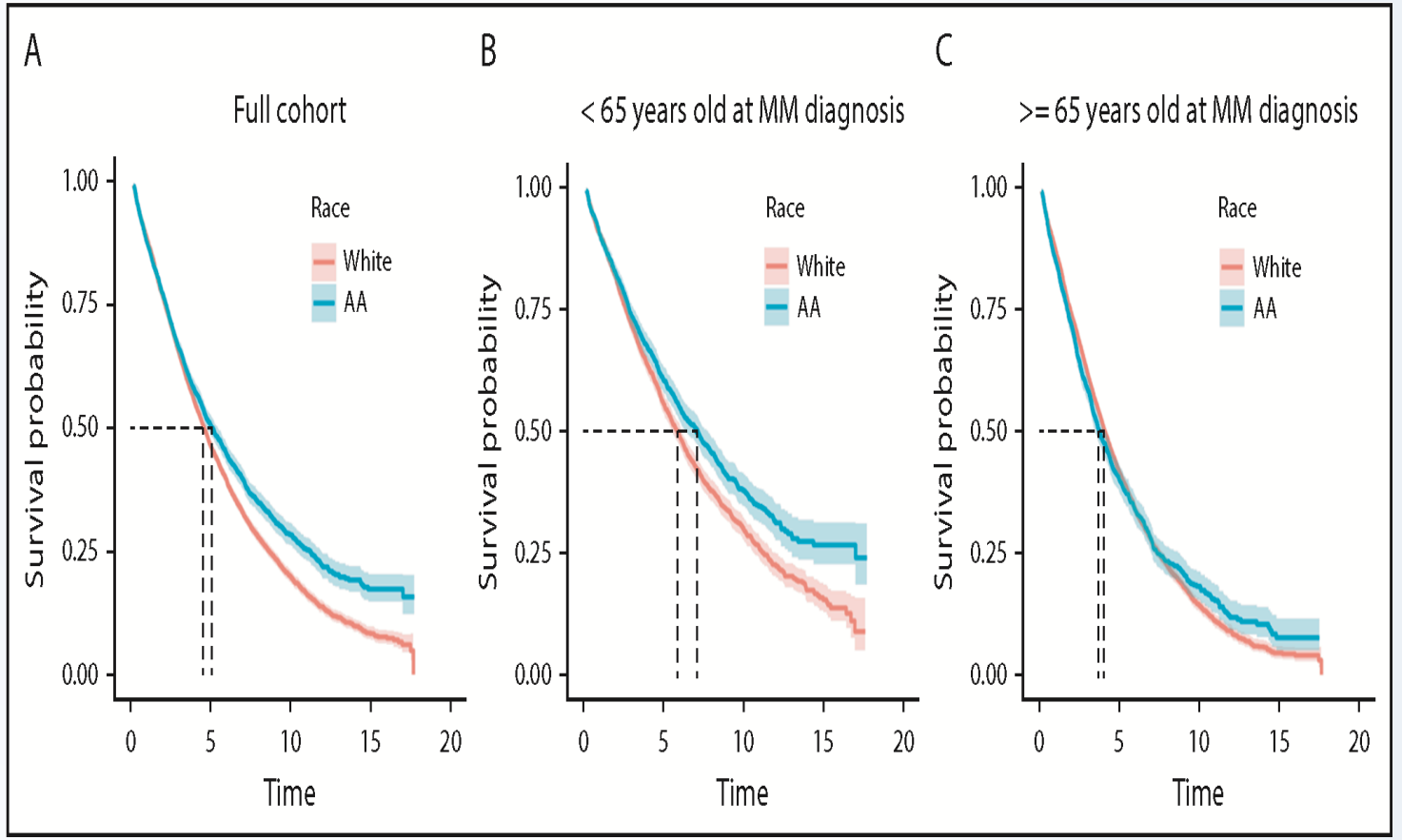
Treatment Type	Use in Black Patients	Use in White Patients	*P* Value
Triplet therapy	47%	61%	.004
Stem cell transplantation	30%	40%	.034

  - ✓ With equal access to care, have equivalent/better outcomes

Ailawadhi S, et al. Blood Adv. 2019;22;3(20):2986-2994; Necamp J, et al. Presented at: ASH;2016. Abstract 4502.. Ailawadhi S, et al. Cancer Med. 2017;6(12):2876-2885.

All Things Being Equal…The VA Myeloma Study

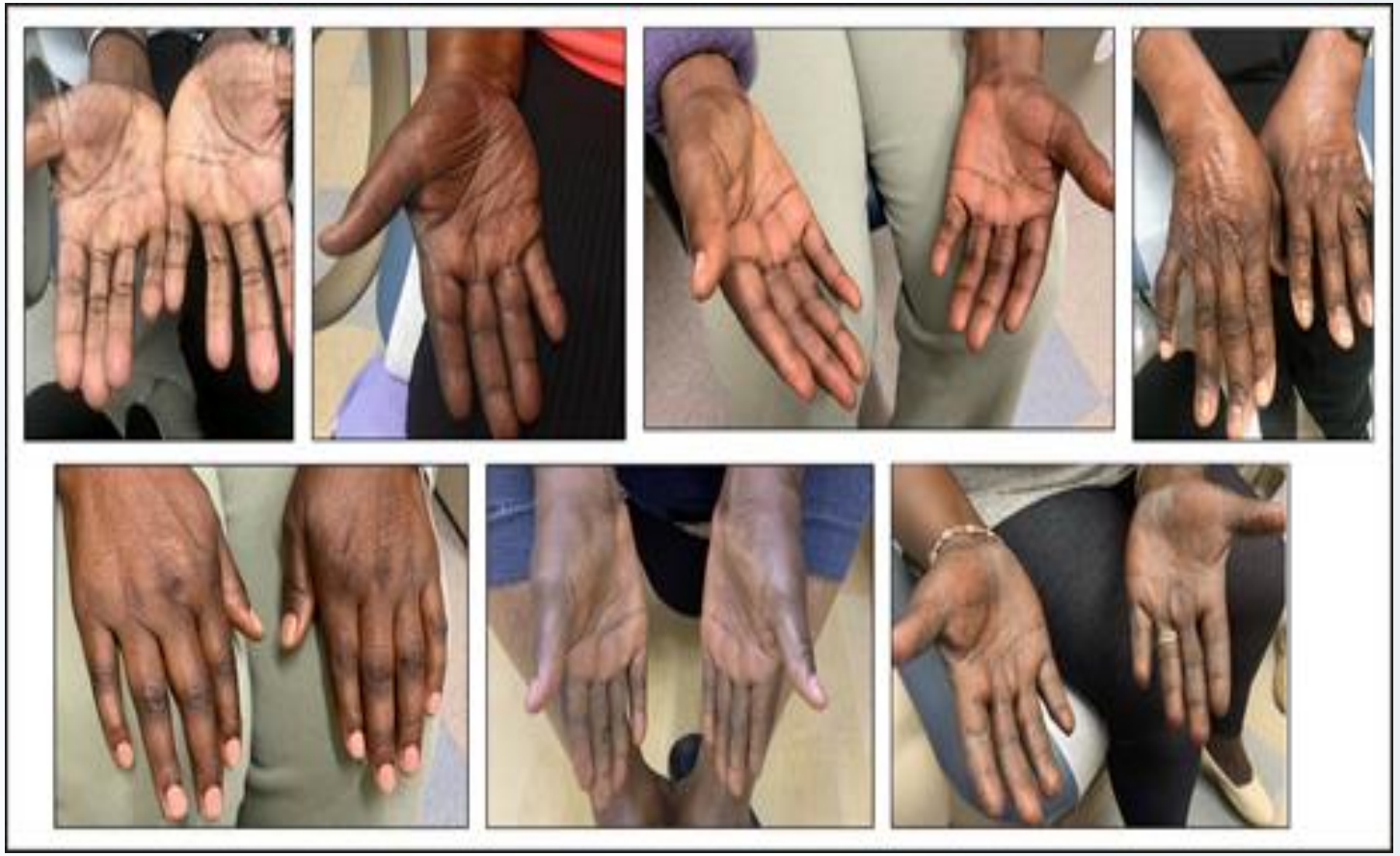
- Outcomes of 15,717 (3254:Black patients; 8845:White patients) MM patients the VA health care system between 2000 and 2017 were analyzed
- Black patients had superior median OS (7.07 years; 95% CI, 6.36-7.70 years) compared with White patients (5.83 years; 95% CI, 5.44-6.09 years; log-rank *P* < .001
  - The difference was not significant for patients age >65 years.
- No racial disparity at the VA in overall use of novel agents or ASCT



Fillmore NR, et al. *Blood*. 2019;133(24):2615–2618

But There Are Differences… Toxicity of IMiDs

- In the pivotal registration trials for the IMiDs, <2% of patients were Black
- In 2021 Boston Medical Center published their experience between 2013 and 2020 of 106 patients Rxed thalidomide, lenalidomide, or pomalidomide
- **Hyperpigmentation (skin darkening) was reported by 20 Black patients (40.8%) and 2 non-Black patients (3.5%).**



Milrod C, et al. *Blood*. 2021;137(21):2987-2989.

But There Are Differences...Toxicity Proteosomes Inhibitors

- 140 NDMM Black patients were matched with 140 non-Black patients on age, sex, BMI, and route of bortezomib administration
- By logistic regression model, **the incidence of peripheral neuropathy was *higher* in Black patients** in both univariate (odds ratio, 1.61; 95% CI: 1.00-2.61; p=0.052) and multivariable analyses (odds ratio, 1.64; 95% CI 1.01-2.67; p=0.047)

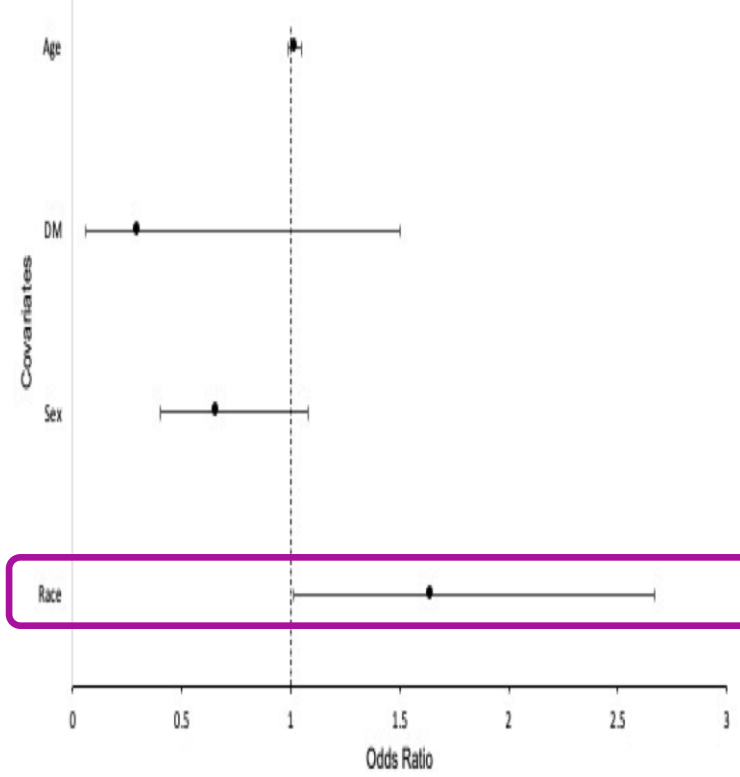


Figure 1. Impact of age, pre-existing DM diagnosis, sex and race on risk of BIPN using univariate logistic regression model.

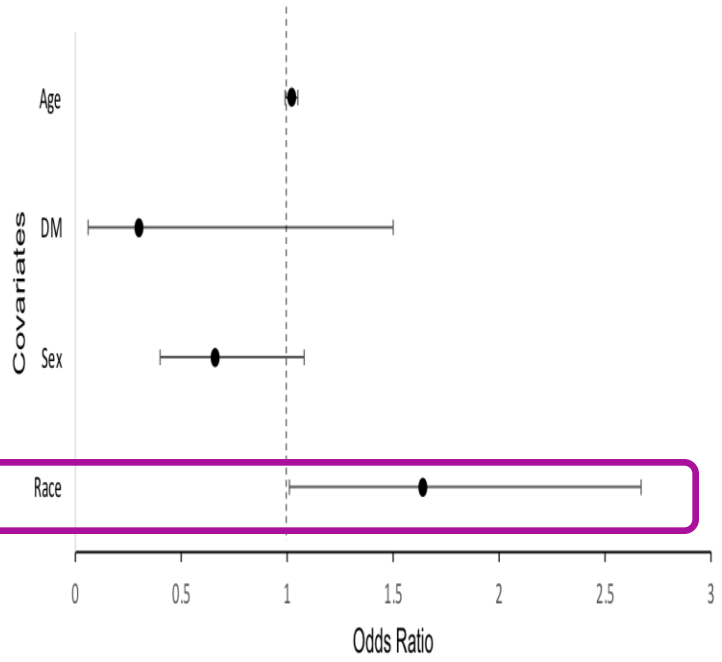


Figure 2. Impact of age, pre-existing DM diagnosis, sex and race on risk of BIPN using multivariate logistic regression model.

NDMM = newly diagnosed multiple myeloma.

Sun L, et al. *Blood.* 2022;140 (Suppl 1):7131–7132.

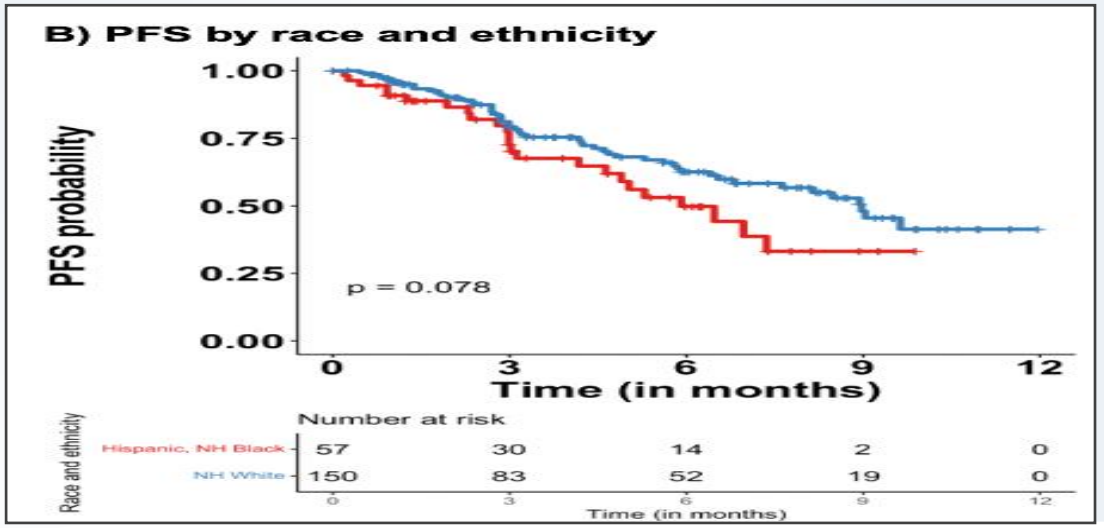
But There Are Differences… CAR-T Race Subanalysis

- 215 RRMM patients treated with standard of care idecabtagene vicleucel (ide-cel), CAR T-cell therapy for across 11 US sites
- Black patients were more likely to develop compared to White and Hispanic patients:
  - Any grade CRS (84% vs 76% vs 97%, respectively; P=0.05),
  - Longer hospital stay (median of 9 vs 8 vs 12.5 days, respectively; P=0.01),
  - Experience severe (i.e., grade ≥ 3) prolonged cytopenias (≥ 30 days post infusion; 72% vs 56% vs 87%, respectively; P=0.07)
- Hispanic and Black patients combined had worse PFS compared to White patients (median PFS of 5.9 vs 9.0 months; P=0.08)

A) Distribution of selected patient and clinical characteristics by race and ethnicity

Selected characteristics	Race and ethnicity: Hispanic (Any race), n=21 Median (Range) or n (%)	Non-Hispanic Black, n=36 Median (Range) or n (%)	Non-Hispanic White, n=150 Median (Range) or n (%)	P
Female sex	6 (29)	21 (58)	57 (38)	0.04
Baseline CRP	0.6 (0.0, 84.4)	3.5 (0.1, 286.0)	0.8 (0.0, 275.4)	0.03
Baseline ferritin	354 (20, 4862)	721.5 (22, 8537)	314.5 (9, 27260)	0.06
Any grade CRS	16 (76)	33 (97)	125 (84)	0.05
Length of hospital stay, days	8 (6, 21)	12.5 (7, 68)	9 (5, 69)	0.01
Grade ≥ 3 cytopenia ≥ 30 days	9 (56)	26 (87)	83 (72)	0.07

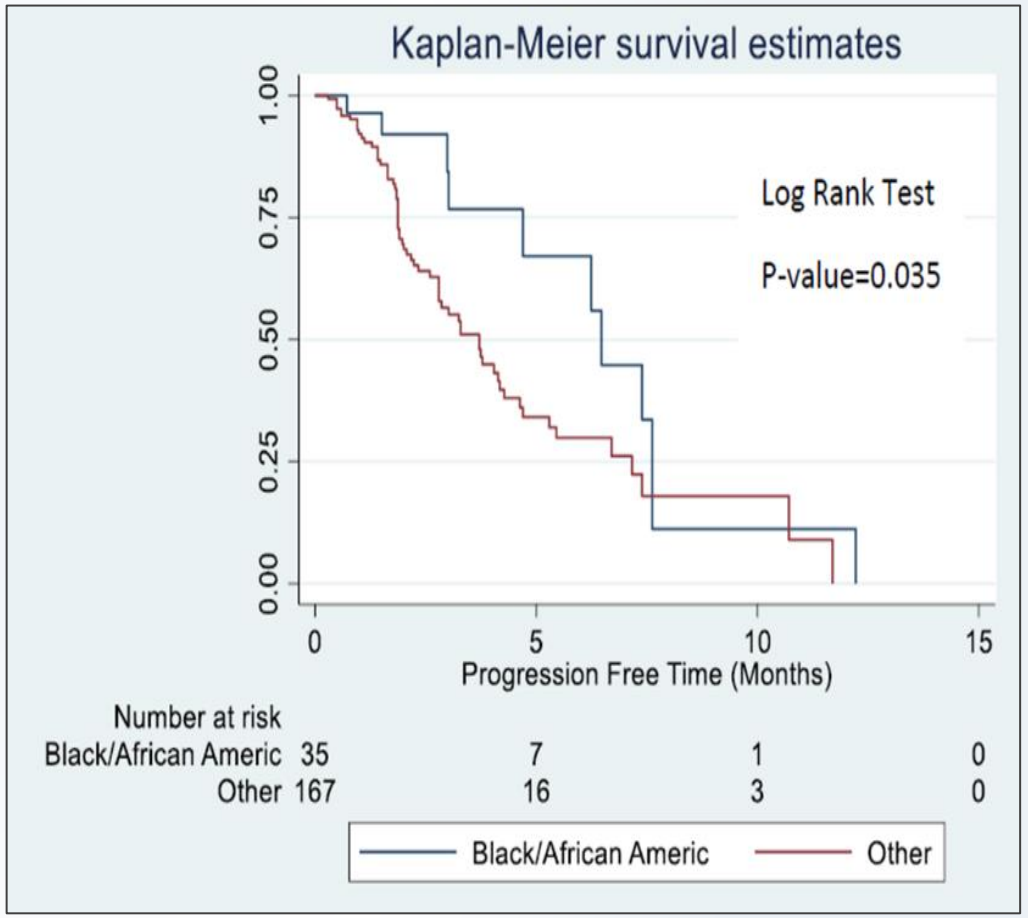
CRP: C-reactive protein, CRS: cytokine release syndrome.



Peres LC, et al. *Blood*. 2022;140 (Suppl 1):623–625

But There Are Differences… Selinexor Race Sub analysis

- A subgroup analysis of outcomes between Black patients and other races phase 2 STORM trial of Selinexor
- Although the overall response rates were the same, Black patients had a **longer PFS of 6.5 months compared with 3.7 months** for other races (P=0.035)
- This longer PFS cannot be explained by differences in stage, prior therapy, cytogenetic risk, stage, depth of response, degree of refractoriness, duration of Selinexor therapy, or toxicity



Cole CE, et al. Presented at: ASCO;2023. Abstract e20016

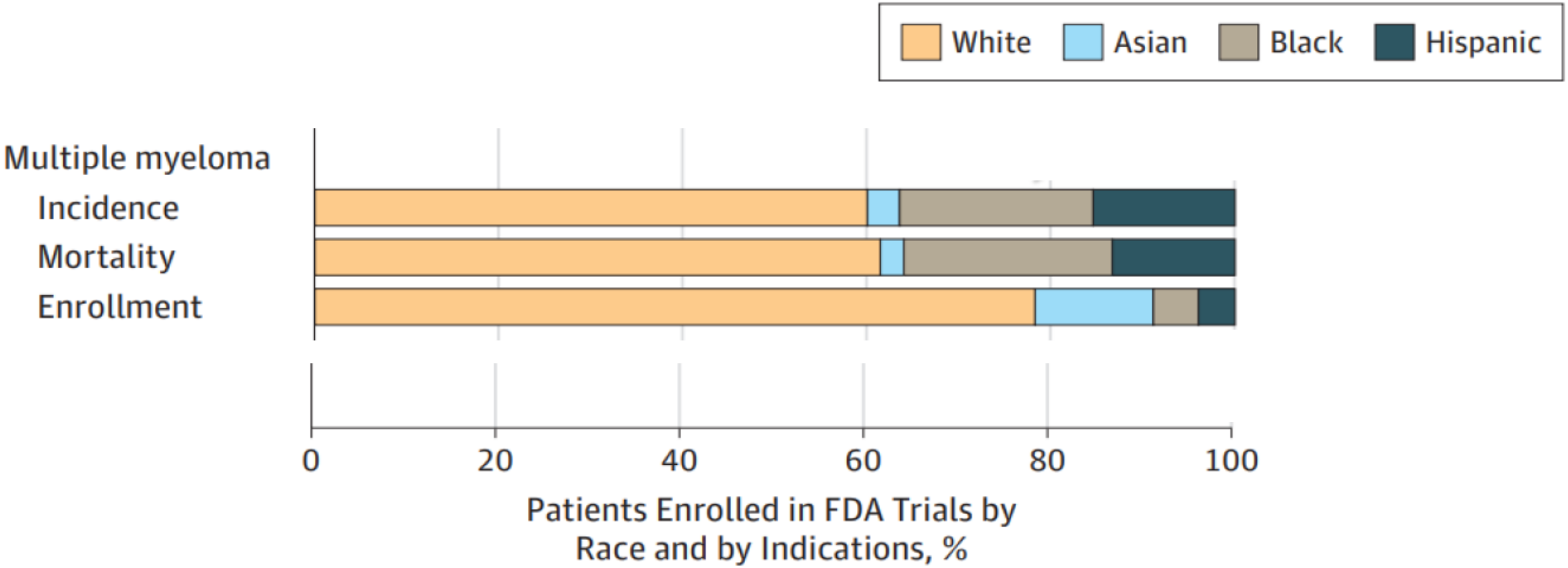
Importance of Minority Participation in Clinical Trials

"The ability to trust and apply the results of a clinical trial, as well as transfer them into clinical practice, is related to the type and number of patients enrolled in that trial."

"If trials do not include minorities, then there is a question of whether or not the results of the studies are relevant to everyone across the board."

NIH. Accessed May 19, 2023. http://www.cancer.gov/newscenter/benchmarks-vol6-issue4/page1

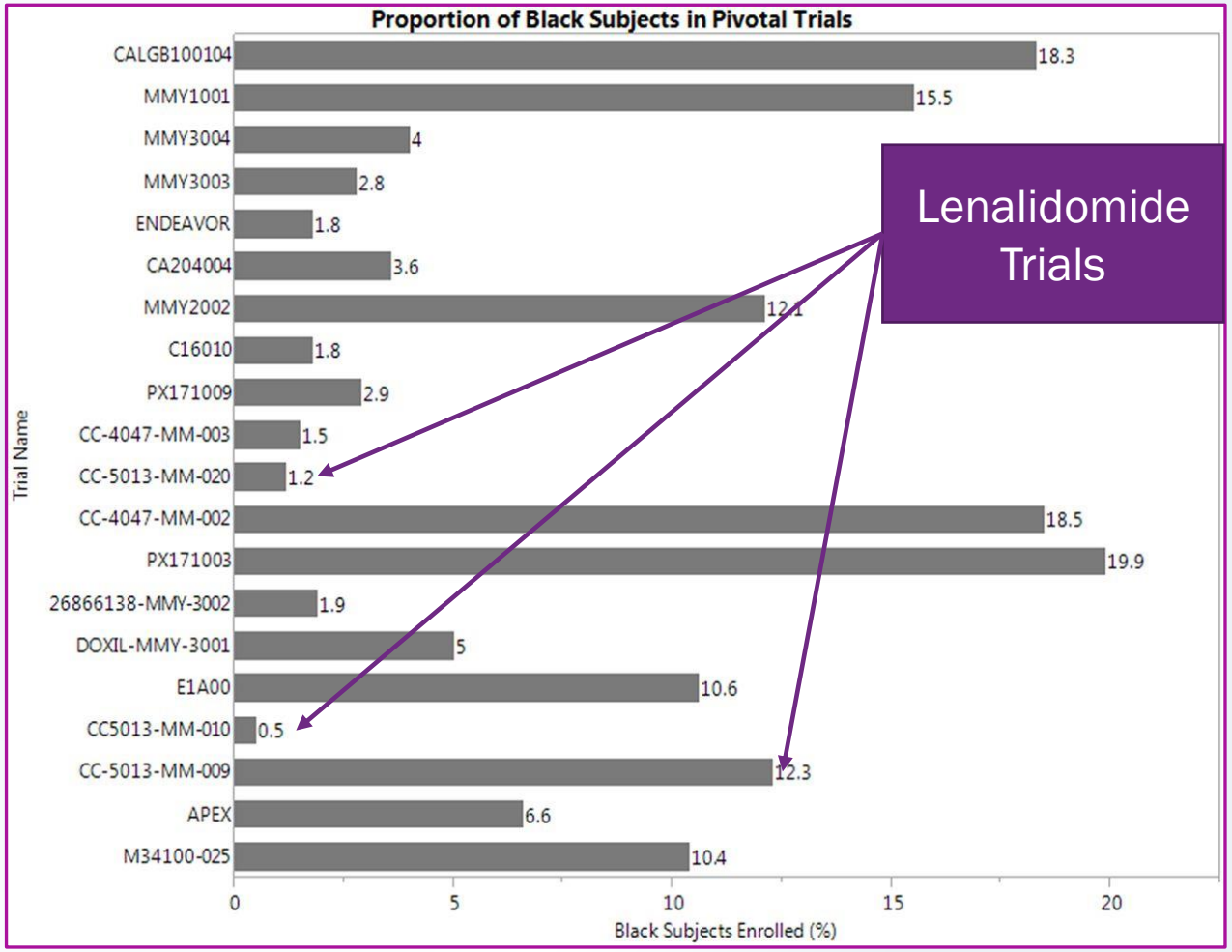
Relative Differences in Myeloma Incidence, Mortality, and Enrollment in Clinical Trials Leading to FDA Drug Approval



Loree JM, et al. *JAMA Oncol*. 2019;5(10):e191870

Racial Enrollment in Myeloma Clinical Trials

- Review of the FDA database for new drug applications submitted between 2003 and 2017
- Results:
  - 23 trials were submitted for approval during this time period
  - 20 of the trials included information on race
  - **Median enrolled percentage of Black patients was 4.5%**
    - Range 0.5% to 19.9% of the trial population
  - Trials with higher U.S enrollment had better enrollment of Black patients
    - Median percentage of U.S. Black patients was 10.5%



Bhatnagar V, et al. *Blood.* 2017;130:435248

Largest Analysis Characterizing Race Outcomes in Trials Supporting MM Drug Approvals In The US

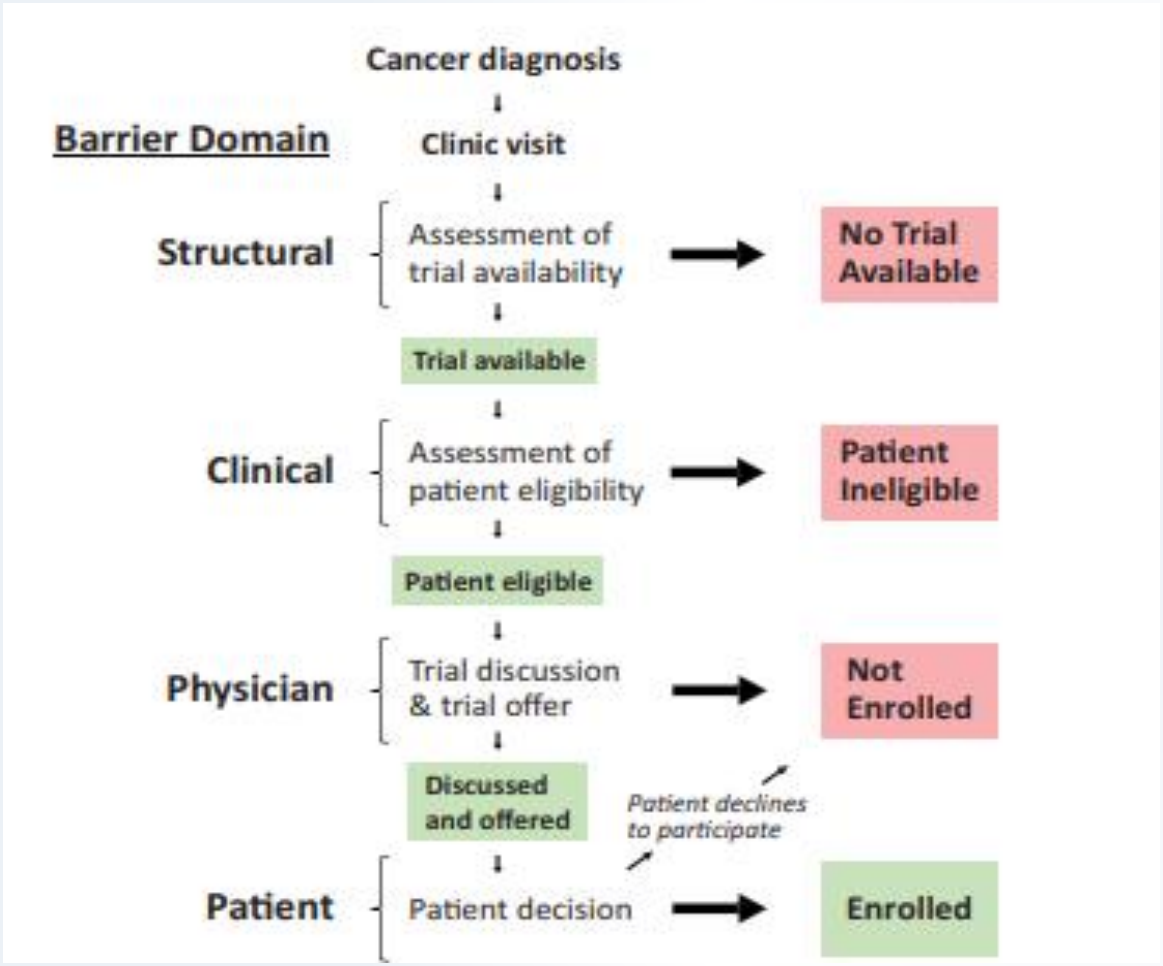
- Pooled analysis 10,157 patients from 19 global trials submitted to the FDA to support approval of MM therapeutics between 2006 and 2019
- Black and Hispanic patients were underrepresented in the trials supporting FDA approval of MM drugs.
  - Black patients were primarily enrolled in the United States

Table 1. Demographics by region

	Total (N = 10 157)	United States (n = 1719)	RoW (n = 8438)
Age, y			
Median (IQR)	68 (60-73)	64 (57-71)	68 (61-74)
<65	3771 (37)	896 (52)	2875 (34)
65-84	5646 (56)	711 (41)	4935 (58)
≥85	739 (7)	112 (7)	627 (7)
Race			
American Indian or Alaska Native	4 (<1)	1 (<1)	3 (<1)
Asian	693 (7)	19 (1)	674 (8)
Black	405 (4)	311 (18)	94 (1)
Native Hawaiian or other Pacific Islander	10 (<1)	3 (<1)	7 (<1)
Other	180 (2)	47 (3)	133 (2)
Unknown	330 (3)	38 (2)	292 (3)
White	8535 (84)	1300 (76)	7235 (86)
Ethnicity			
Hispanic or Latino	420 (4)	95 (6)	325 (4)
Not Hispanic or Latino	7705 (76)	1275 (74)	6430 (76)
Unknown	2032 (20)	349 (20)	1683 (20)
Sex			
Female	4619 (45)	748 (44)	3871 (46)
Male	5538 (55)	971 (56)	4567 (54)

Kanapuru B, et al. *Blood Adv*. 2022;6(6):1684-1691

Barriers to Cancer Clinical Trials



No Clinical Trial Available for which they are Eligible 77%

Not Asked to Participate 8%

Patient Says "No"

Patient Says "Yes"

85% of patients are unable to participate by structural and clinical barriers

Unger JM, et al.J Natl Cancer Inst. 2019;111(3):245-255. Unger JM, et al.J Natl Cancer Inst. 2021;113(3):244-257.

FDA–AACR Workshop on Eliminating Racial Disparities in Myeloma

- In March of 2020 the FDA collaborated with the American Association for Cancer Research (AACR) to conduct the workshop to examine under-representation of Black patients in Myeloma clinical trials
- Recommendations were made to improve the conduct of preapproval, postappoval, and real-world data clinical trials
- The results of this meeting were published in *Blood Cancer Discovery* in March of 2021

SCIENCE IN SOCIETY

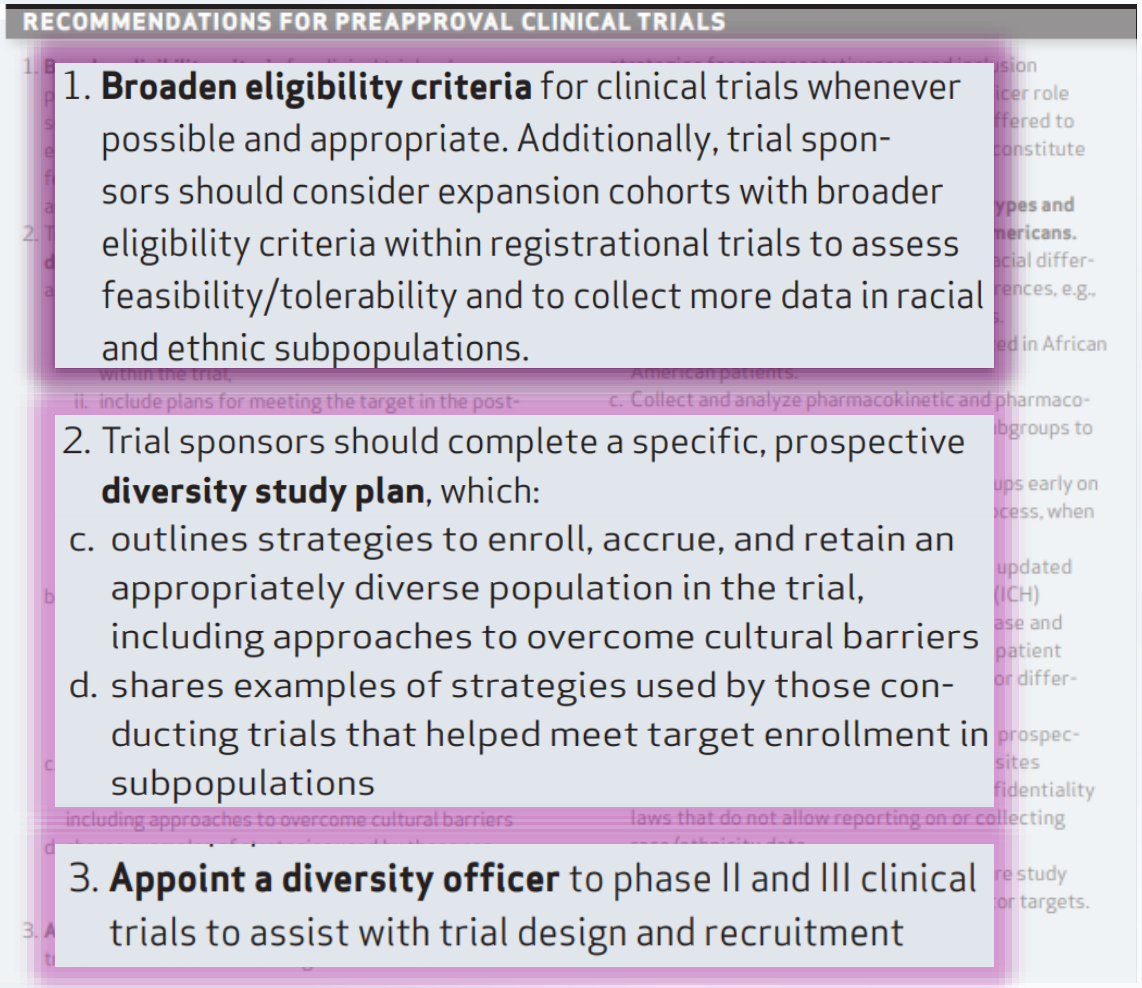
Recommendations on Eliminating Racial Disparities in Multiple Myeloma Therapies: A Step toward Achieving Equity in Healthcare

Nicole Gormley[1], Lola Fashoyin-Aje[1], Trevan Locke[2], Joseph M. Unger[3], Richard F. Little[4], Ajay Nooka[5], Khalid Mezzi[6], Mihaela Popa-McKiver[7], Rachel Kobos[8], Yelak Biru[9], Tiffany H. Williams[10], and Kenneth C. Anderson[11]

Summary: African Americans are at higher risk of multiple myeloma (MM) yet are underrepresented in clinical trials and reap fewer benefits from novel therapies of the disease. To improve representation of African Americans in MM clinical trials, researchers, healthcare providers, patients, industry partners, and regulators at an FDA-AACR workshop developed recommendations to all stakeholders. The outlined principles offer a road map to addressing disparities broadly in clinical trials.

Gormley N, et al. *Blood Cancer Discov*. 2021;2(2):119-124

FDA–AACR Workshop on Eliminating Racial Disparities in Myeloma

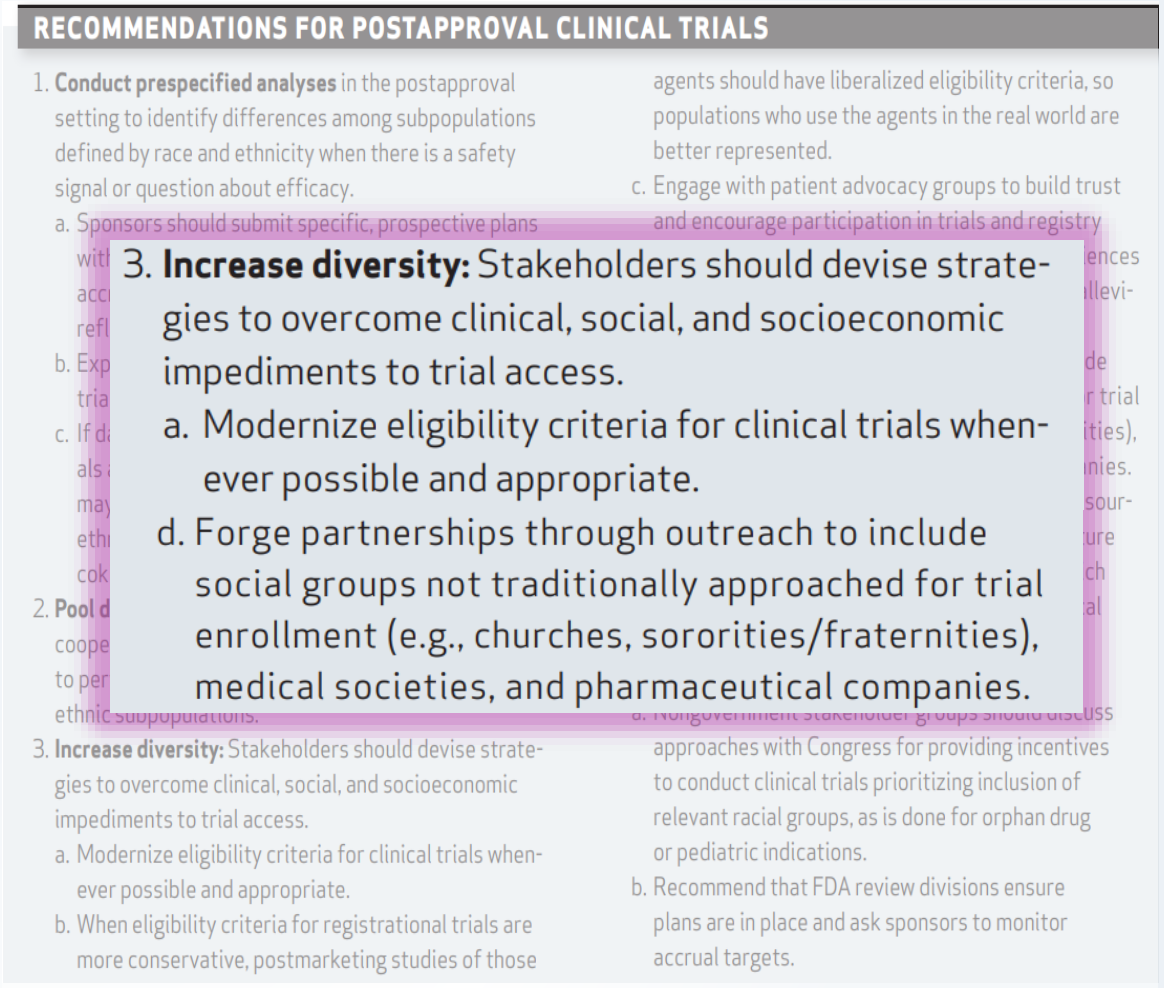


RECOMMENDATIONS FOR PREAPPROVAL CLINICAL TRIALS

1. **Broaden eligibility criteria** for clinical trials whenever possible and appropriate. Additionally, trial sponsors should consider expansion cohorts with broader eligibility criteria within registrational trials to assess feasibility/tolerability and to collect more data in racial and ethnic subpopulations.

2. Trial sponsors should complete a specific, prospective **diversity study plan**, which:
   c. outlines strategies to enroll, accrue, and retain an appropriately diverse population in the trial, including approaches to overcome cultural barriers
   d. shares examples of strategies used by those conducting trials that helped meet target enrollment in subpopulations

3. **Appoint a diversity officer** to phase II and III clinical trials to assist with trial design and recruitment



RECOMMENDATIONS FOR POSTAPPROVAL CLINICAL TRIALS

1. **Conduct prespecified analyses** in the postapproval setting to identify differences among subpopulations defined by race and ethnicity when there is a safety signal or question about efficacy.
   a. Sponsors should submit specific, prospective plans
   b. Exp
   c. If da
2. **Pool d**
   coope
   to per
   ethnic subpopulations.
3. **Increase diversity:** Stakeholders should devise strategies to overcome clinical, social, and socioeconomic impediments to trial access.
   a. Modernize eligibility criteria for clinical trials whenever possible and appropriate.
   b. When eligibility criteria for registrational trials are more conservative, postmarketing studies of those agents should have liberalized eligibility criteria, so populations who use the agents in the real world are better represented.
   c. Engage with patient advocacy groups to build trust and encourage participation in trials and registry

3. **Increase diversity:** Stakeholders should devise strategies to overcome clinical, social, and socioeconomic impediments to trial access.
   a. Modernize eligibility criteria for clinical trials whenever possible and appropriate.
   d. Forge partnerships through outreach to include social groups not traditionally approached for trial enrollment (e.g., churches, sororities/fraternities), medical societies, and pharmaceutical companies.

   approaches with Congress for providing incentives to conduct clinical trials prioritizing inclusion of relevant racial groups, as is done for orphan drug or pediatric indications.
   b. Recommend that FDA review divisions ensure plans are in place and ask sponsors to monitor accrual targets.

Gormley N, et al. *Blood Cancer Discov*. 2021;2(2):119-124

FDA Initiative to Increase Racial and Ethnic Diversity in Clinical Trials

"Going forward, achieving greater diversity will be a key focus throughout the FDA to facilitate the development of better treatments and better ways to fight diseases that often disproportionately impact diverse communities."

-FDA Commissioner Robert M. Califf, M.D.

April 13, 2022

https://www.fda.gov/news-events/press-announcements/fda-takes-important-steps-increase-racial-and-ethnic-diversity-clinical-trials

FDA Initiative to Increase Racial and Ethnic Diversity in Clinical Trials

- Recommendation that sponsors of medical products develop and submit a *Race and Ethnicity Diversity Plan* to the agency early in clinical development, based on a framework outlined in the guidance
- "FDA will evaluate the Race and Ethnicity Diversity Plan as an important part of the sponsor's development program."

FDA. Accessed July 8, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations

FDA Analysis of Trial Screen Failures in Myeloma

- Retrospective pooled analysis of 16 clinical trials submitted to the FDA 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%) subgroups had higher ineligibility rates compared to White patients (17%)
- Failure to meet Hematologic Lab Criteria (19%) and failure to meet Treatment Related Criteria (17%) were the most common reasons for ineligibility among Black patients
  - Failure to meet Disease Related Criteria was the most common ineligibility reason for White (28%) and Asian patients (29%)

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;blood.2022018657.

Acceptance in Clinical Trial Does Not Vary By Race/ Ethnicity

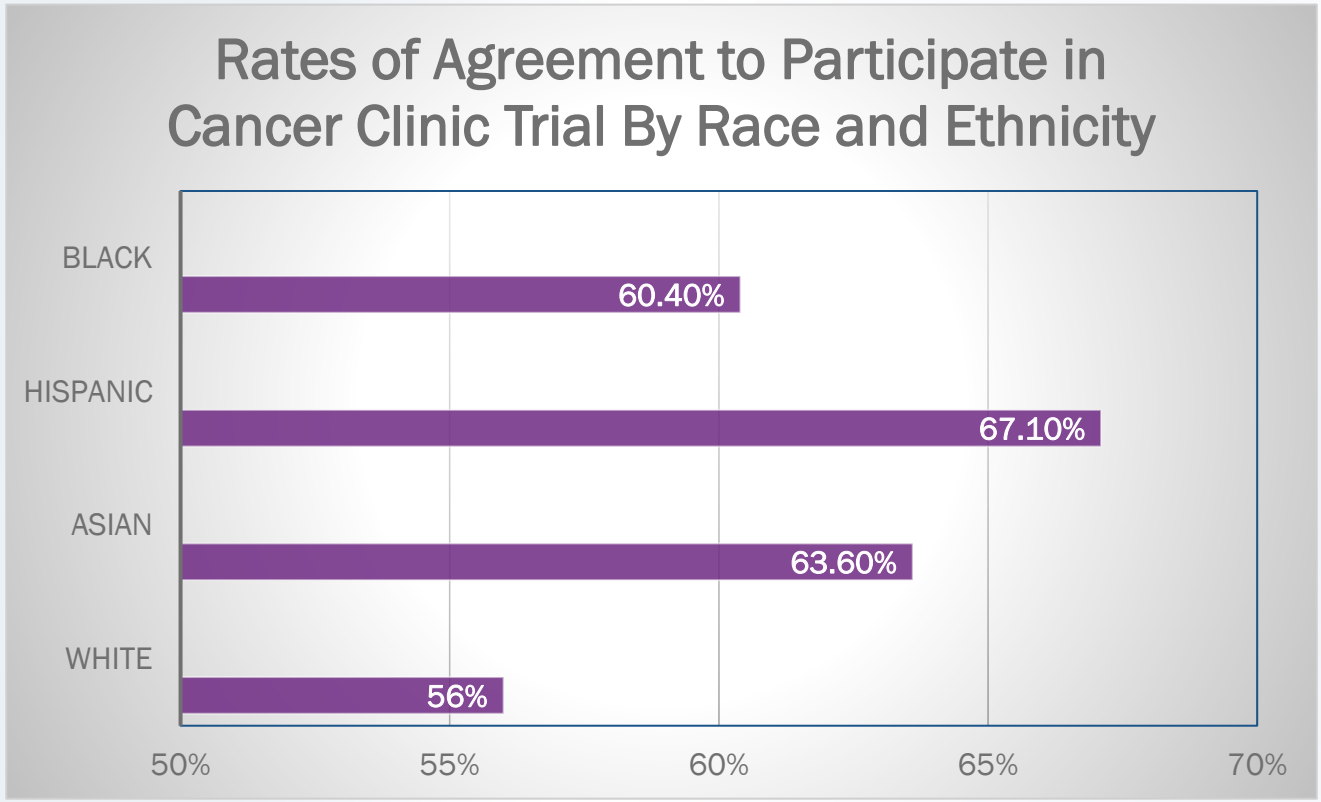


Table 4. Rates of agreement to participate if offered a trial by race and ethnicity

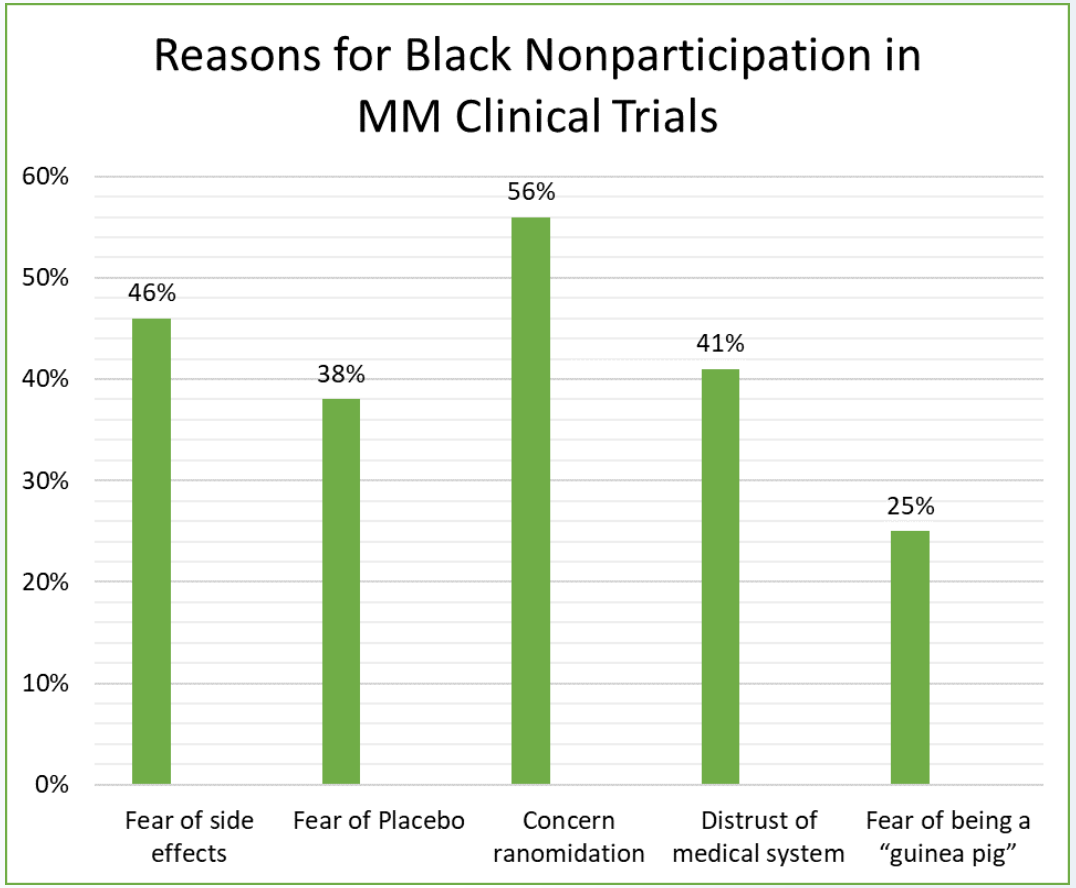
Comparison group	White	Black	Hispanic	Asian
All studies				
No. of studies	16	15	8	6
Rate, % (95% CI)	56.0 (47.3 to 64.5)	60.4 (49.5 to 70.8)	67.1 (57.4 to 76.2)	63.6% (39.2 to 85.3)

There is no evidence that participation in cancer clinical trials differs by race or ethnicity

The main reasons for nonparticipation were treatment choice or lack of interest.

Facilitators of Black Patients in Myeloma Clinical Trials

- 2021, the Cancer Support Community conducted an online survey to gain insights on perceptions of clinical trials among 97 Black multiple myeloma patients and 101 caregivers/care partners
- Facilitators for participation in a clinical trial
  - Understanding potential side effects (66%)
  - My health care team speaks to me about trials (65%)
  - **Compensation offered for transportation, childcare, or time off work (62%)**
  - **My family/community support my decision (61%)**



Saxton C, et al. *J Clin Oncol*. 2022;40;(Suppl 16):12137

Solutions for Diverse Clinical Trials in Myeloma

Clinical trial design

- Develop a diversity plan with specific enrollment goals
- Broaden eligibility criteria when feasible; start with the assumption that all patients should be eligible
- Standardize the capture race/ethnicity data and publish the results
- Utilize publicly available guidance documents as a starting point, such as those released by the FDA and the published joint statement by the FDA and AACR

Clinical trial operations

- Reduce burden on trial participants (via fewer on-site study visits, telemedicine, financial support, e-consent, etc.)
- Select racially/ethnically diverse study sites; begin developing relationships with potential sites early; utilize hub-and-spoke model
- Require implicit bias training
- Support diversity in healthcare providers, trial support staff, and researchers

Patient/community education and engagement

- Obtain patient input early in the drug development process
- Integrate basic information and education about clinical trials into routine health & community-based systems of care in more rural and minority communities
- Educate patients with easily understandable materials
  - Utilize question prompt lists
  - Offer plain language summaries
  - Utilize technology (eg educational videos)
  - Offer translated materials

Manuscript in submission

Patient Case

- ✓ 57 year old Black male with R-ISS Stage I multiple myeloma receives induction therapy with lenalidomide, bortezomib and dexamethasone (RVD). He achieves a complete response and undergoes autologous stem cell transplantation. His transplant goes well, and he is now on lenalidomide maintenance but now states that he has nonpainful/ nonpruritic darkening of the palms of his hands and soles of his feet.

What would you do next for this patient?

1. Immediately discontinue lenalidomide
2. Discuss with the patient that this is not due to the lenalidomide
3. Refer to dermatology
4. Validate the patient's concerns and discuss this might not be reversable even with cessation
5. Ignore his concerns

Milrod C, et al. *Blood*. 2021;137(21):2987-2989.

Conclusions

- Patients of African descent have twice the incidence and mortality rates of Myeloma than other races/ethnicities
- The biology and presentation of myeloma of patients of African descent appears to be different than those of European descent
- With equal delivery of care, survival of patients of color with myeloma can be equal with a suggestion that myeloma biology may favor patients of African descent
- Patients of minority race with myeloma have had less increase in population-level survival in the early 21st century than white patients
- We need appropriate representation in myeloma clinical trials to ensure that new drugs will work equally as well for African American myeloma patients
- There are on-going strategies which can mitigate some of the health disparities in multiple myeloma

Pulte ED, et al. Blood Adv. 2018;2(2):116-119.