

FDA-AACR Workshop to

EXAMINE UNDER-REPRESENTATION OF AFRICAN AMERICANS IN MULTIPLE MYELOMA CLINICAL TRIALS

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BACKGROUND

Multiple myeloma (MM) is a cancer of plasma cells, or mature B lymphocytes, which proliferate in the bone marrow, crowding out normal blood-forming cells. MM is characterized by low blood counts, leading to anemia, thrombocytopenia, and/or leukopenia; bone pain and fragility; high blood calcium levels; kidney dysfunction; and increased susceptibility to infections, among other signs and symptoms. In many patients, signs and symptoms will not manifest until the disease is advanced, making early detection difficult and uncommon. Traditional treatment regimens for MM include chemotherapy, radiation, and stem cell transplantation. Stem cell transplant (SCT) remains the standard of care for eligible patients, often leading to months or years of remission when employed early after diagnosis. In addition, novel therapies approved by the U.S. Food and Drug Administration (FDA) over the past 20 years, such as immunomodulators, proteasome inhibitors, and monoclonal antibodies, have increased treatment options and extended overall survival for patients with MM.

Over 30,000 new MM cases are diagnosed in the United States each year, and over 12,500 deaths will result. As of 2015, it was estimated that 124,733 Americans were living with MM (1). Incidence of this disease is not uniform throughout the population; MM is more common in men than women, and among African Americans compared to whites. Indeed, incidence rates in African Americans are more than double those seen in whites (15.9 vs. 7.5 cases per 100,000), a trend that extends to mortality (5.6 vs. 2.4 MM deaths per 100,000 for African Americans compared to whites) (2).

Differences in disease incidence and characteristics among African American and white patients with MM may be due to underlying genetic abnormalities. Patients with high African ancestry are more likely than those with high European ancestry to have translocations involving the immunoglobulin heavy chain (IgH) gene on chromosome 14, specifically t(11;14), t(14;16), or t(14;20) (3); the latter two chromosomal translocations convey high risk of developing MM. Conversely, African Americans are less likely than whites to have deletion of TP53/17p, which is associated with shortened survival (4). Together, these biological differences suggest that African Americans, although genetically predisposed to developing MM, may develop a less aggressive subtype than whites.

Despite higher mortality (a function of disease incidence), a retrospective analysis of data from the nine original National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) registries showed that African Americans diagnosed with MM from 1973-2005 had statistically



significant higher overall survival than whites diagnosed in the same years (5). However, overall survival doesn't tell the whole story. Five-year relative survival rates (RSRs; the ratio of observed to expected survival for a specific group) increased significantly for whites throughout the study period, from 26.3 percent to 35.0 percent ($p < 0.005$). Concomitant increases were not seen in the African American study population, with five-year RSRs only increasing from 31.0 percent to 34.1 percent (5). The hypothesis that this racial disparity was due, at least in part, to unequal access to novel therapies has borne out in subsequent studies.

An analysis of new drug application and biologic license application submissions to the Division of Hematology at the FDA for MM indications between 2003 and 2017 revealed median enrollment of African Americans to pivotal trials was only 4.5 percent (range 0.5 percent to 19.9 percent) (6). Furthermore, if the trials were conducted internationally, as increasing numbers of trials supporting drug approvals are, the median enrollment of African Americans decreased to 1.8 percent (6). Among nine large MM clinical trials conducted by NCI Cooperative Groups, enrollment of African Americans fared better, at 13 percent for the 10 years from 2002-2011 (7). However, this represents a decrease from the previous 10-year period, when African American enrollment was 16.5 percent, and most racial/ethnic minority patients participated in trials that did not involve novel agents or SCT (7).

Considering that African Americans account for 13 percent of the U.S. population and 20 percent of individuals who are diagnosed with MM (6), their under-representation in MM clinical trials presents serious problems. Due to underlying genetic and biological differences between African Americans and whites with MM, it is possible that clinical trials may not adequately or accurately characterize the safety and efficacy of approved drugs in a key constituency. This lack of representativeness could have both regulatory and health consequences.

APPROACH

To address these issues, the FDA has partnered with the American Association for Cancer Research (AACR) to present the Workshop to Examine Under-representation of African Americans in Multiple Myeloma Clinical Trials. Under the leadership of workshop cochairs Kenneth C. Anderson, MD, FAACR (Dana-Farber Cancer Institute); Lola A. Fashoyin-Aje, MD, MPH (FDA); Nicole J. Gormley, MD (FDA); and Paul G. Kluetz, MD (FDA), working groups composed of researchers, physicians, patients, statisticians, and regulators were formed to develop recommendations for improving and understanding data on outcomes and effectiveness of MM therapies in African Americans in preapproval, postapproval, and real-world settings (see Working Group Rosters). Those recommendations were then shared with representatives from industry to get input on the feasibility and likelihood of acceptance. Figure 1 describes the iterative discussion process employed to develop these recommendations.



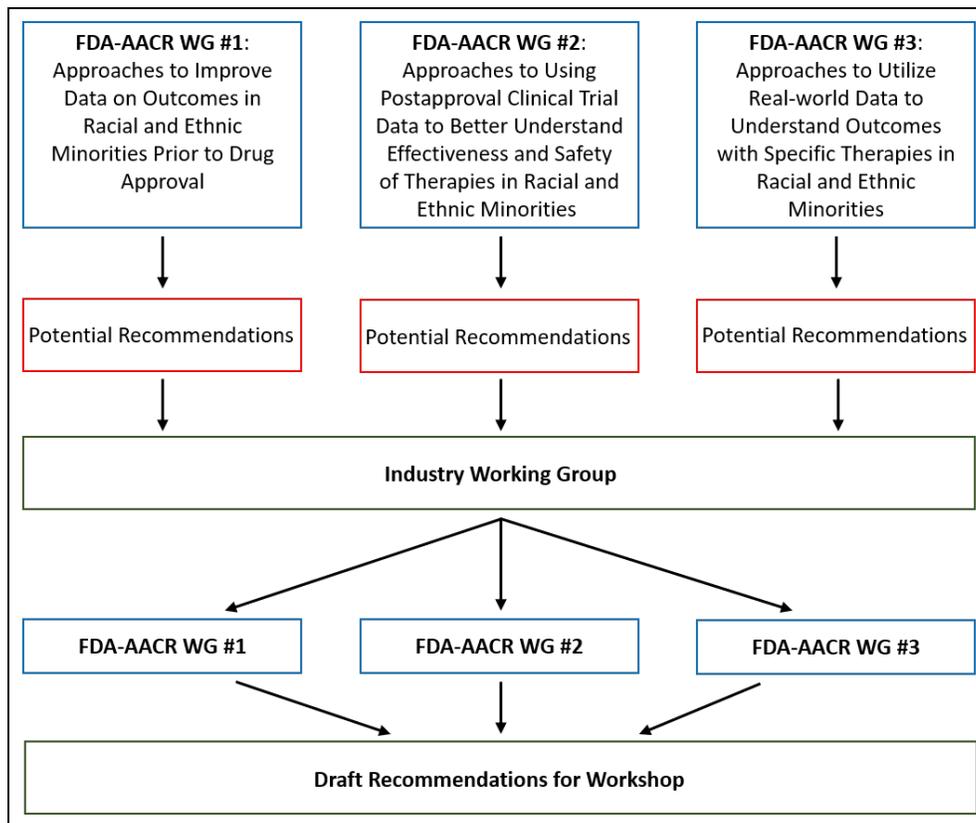


Figure 1. Sequence of discussions employed by working groups to develop draft recommendations.

PURPOSE OF WORKSHOP

The purpose of this workshop is to present the recommendations in a public forum to discuss and to gather additional feedback from stakeholders. Workshop participants are asked to consider the following:

- The genetics and biology underlying racial and ethnic differences in MM;
- Enrollment characteristics and outcomes of African American patients in MM trials and real-world data sources;
- The limitations of currently available data on racial and ethnic minorities with MM; and
- Approaches to increase our knowledge of the safety and effectiveness of anti-myeloma therapeutics in racial and ethnic minorities.

WORKING GROUP 1 RECOMMENDATIONS: APPROACHES TO IMPROVE DATA ON OUTCOMES IN RACIAL AND ETHNIC MINORITIES PRIOR TO DRUG APPROVAL

- Develop principles for promoting diversity and promote adherence to those principles through trial “registration.”
 - Set concrete targets for trial enrollment based on disease epidemiology/ incidence and current evidence that addresses biological and cultural barriers.
 - Consider review or publication incentives for adhering to principles.
 - Share examples of strategies that help to meet target enrollment.
- Study plans should include proposals for how appropriate populations will be included in trials and how targets will be met.
 - The goal should be for trial populations to be representative of disease incidence from an early stage.
- Prespecify what subgroup analyses should be performed and the endpoints which will be assessed.
 - Potentially ask for modeling on the effects of having more or fewer patients than expected for a given subgroup.
 - Explore potential alternative endpoints, including minimal residual disease.
- Design trials around type and stage of the disease, and the subtypes most commonly seen in African Americans.
 - Study the genetics of multiple myeloma patients, exploring potential variables that affect differences in outcome.
 - Pursue safety signals detected in African American patients, or other subpopulations, as thoroughly as possible.
 - Collect and analyze PK/PD data, pursue signals in subpopulations to the extent that is reasonable.
- Trials should reflect U.S. clinical practice (standard-of-care).
- Recommend that randomized phase II and phase III clinical trials involve a diversity officer to help design the trial and recruitment strategies, including predetermined goals for representativeness/inclusion.
 - Define this role and offer training for sponsors and investigators on the characteristics of a “good” diversity officer.
- Provide grant funding dedicated to studying subpopulation signals.
 - NCI could potentially play a role.
- Consider prioritizing the inclusion of African American patients over global patients with African ancestry.



- Educate investigators and referring physicians on cultural competence and stress the importance of community engagement.

WORKING GROUP 2 RECOMMENDATIONS: APPROACHES TO USING POSTAPPROVAL CLINICAL TRIAL DATA TO BETTER UNDERSTAND EFFECTIVENESS AND SAFETY OF THERAPIES IN RACIAL AND ETHNIC MINORITIES

- Liberalize eligibility criteria for clinical trials whenever possible and appropriate.
 - 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.
 - Additionally, sponsors should consider approaches that utilize expansion cohorts with liberalized eligibility criteria within registrational trials to assess feasibility/tolerability and to collect more data in racial and ethnic subpopulations.
- Data on racial outcomes should be gathered early and throughout development, when feasible, to inform investigations later.
 - Collect genomic data with updated ICH guidelines to establish bases for differences in outcomes.
 - Emphasize the importance of prospectively collecting this data to investigators. Ex-U.S. trial sites may have confidentiality laws that do not allow reporting on or collecting race/ethnicity data.
- Conduct prespecified, exploratory analyses to identify differences among subpopulations defined by race and ethnicity when there is a safety signal or question about efficacy.
 - These exploratory analyses should be described in the trial protocol.
 - If safety signals are detected or insufficient data are generated in registrational trials, it may be necessary to carry out a pilot study or expansion cohort of a phase I trial in African Americans to generate data necessary to test the hypothesis that there are PK/PD differences among races/ethnicities.
- Pool or merge data across studies of older drugs (e.g., lenalidomide) by the pharmaceutical industry and cooperative groups to aggregate sufficient numbers for racial and ethnic subpopulations to perform exploratory analyses that assess safety and efficacy.
- Stakeholders should devise strategies to address clinical, social, and socioeconomic impediments to trial access.
 - Forge partnerships through outreach to include pharmaceutical companies, social groups not traditionally approached for trial enrollment (e.g., barbershops, churches, sororities/fraternities), and medical societies.



- Develop precompetitive programs that make resources available to support clinical trial infrastructure in treatment locations that are race/ethnicity rich but have not traditionally been part of the clinical trial ecosystem.
- Recommend that industry sponsors submit specific, prospective plans with detailed strategies for enrolling African Americans into studies in numbers reflective of disease prevalence and for tracking accrual.
 - Recommend that FDA review divisions assure plans are in place and ask sponsors to monitor accrual targets.
- Design postapproval studies to retrospectively collect data from patients who received standard-of-care therapy vs. experimental therapy to better account for selection bias.
- Engage with patient advocacy groups to build trust and encourage participation in trials and registry studies.
 - Having patients share their trial experiences with others considering clinical trials can help alleviate fears or concerns about joining a trial.
- Stakeholder groups (nongovernment employee-based groups) should discuss approaches with Congress to provide incentives to sponsors that encourage the conduct of clinical trials that prioritize the inclusion of relevant subpopulations such as is done for orphan drug or pediatric indications.

WORKING GROUP 3 RECOMMENDATIONS: APPROACHES TO UTILIZE REAL-WORLD DATA TO UNDERSTAND OUTCOMES WITH SPECIFIC THERAPIES IN RACIAL AND ETHNIC MINORITIES

- Perform a brief inventory of efficacy and tolerability data in African Americans in existing multiple myeloma registries with the goal of describing an ideal registry and minimal data elements necessary to ask and answer pertinent questions.
- Require sponsors to set targets for representativeness and inclusion (e.g., for recruitment, accrual, and retention) during clinical study, including by planning for enhanced outreach to African Americans and other patient groups.
 - Encourage sponsors to hit set targets in premarket trials.
 - Require sponsors to set prospective plans for how to meet targets in the postmarket setting if goals are not met in premarket trials.
 - If plans include the use of supplemental real-world data, sponsors should prespecify what analyses will incorporate those data and recognize the lack of randomization to control for unknown confounders.



- Meta-analyses combining data from multiple trials could be performed to evaluate patient subpopulations studied in a clinical trial environment.
- Use real-world evidence from studies such as INSIGHT MM, CONNECT MM, and others to refine research questions and to generate hypotheses concerning efficacy and tolerability in African American multiple myeloma patients in the real world.
 - When using real-world evidence to interrogate safety and efficacy, be very specific about the questions being asked and the sufficiency of the underlying data.
 - Define real-world endpoints for multiple myeloma.
 - Capture safety lab data in a different way to better understand tolerability from real-world data.
- Discuss, determine, and disseminate a common reporting framework for multiple myeloma real-world data with minimal data elements that all stakeholders accept as the minimal amount of data that was collected and should be abstracted.
- If evidence from meta-analyses or real-world data indicates the need to investigate a critical hypothesis about how a cancer drug may work differently in a patient subpopulation, further evaluation should be undertaken, preferably by means of a randomized trial.
 - If the conduct of a randomized trial is not feasible, practical, or timely, prospective studies should be conducted, or the use of existing real-world data should be used for further assessment that can contribute to the understanding of the causal inference in convincing fashion.
- Use real-world data to study specific subpopulations, such as African Americans, which could, in turn, generate hypotheses for clinical trials enriched for African American participation.



REFERENCES

1. Ailawadhi S, Parikh K, et al. Racial disparities in treatment patterns and outcomes among patients with multiple myeloma: a SEER-Medicare analysis. *Blood Adv.* 2019; 20 (3): 2986-2994.
2. DeSantis C, Miller K, et al. Cancer Statistics for African Americans, 2019. *CA Cancer J Clin.* 2019; 69 (3): 211-233.
3. Baughn L, Pearce K, et al. Differences in genomic abnormalities among African individuals with monoclonal gammopathies using calculated ancestry. *Blood Cancer J.* 2018; 8 (10): 96-106.
4. Munjuluri A, Fillmore N, et al. With equal access, African Americans with Non-del17p multiple myeloma have superior overall survival, but del17p still carries poor prognosis across race: A VA study. *Blood.* 2019; 134 (Supplement 1): 4388.
5. Waxman A, Mink P et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. *Blood.* 2010; 116 (25): 5501-5506.
6. Bhatnagar V, Gormley N, et al. FDA analysis of racial demographics in multiple myeloma trials. *Blood.* 2017; 130 (Supplement 1): 4352.
7. Ailawhadi S, Jacobus S, et al. Disease and outcome disparities in multiple myeloma: exploring the role of race/ethnicity in the Cooperative Group clinical trials. *Blood Cancer J.* 2018; 8 (7): 67-74.

