

Disparities in Castration-Resistant Prostate Cancer Trials

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All progress is precarious, and the solution of one problem brings us face to face with another problem.

—Martin Luther King Jr^(pp82-83)

Disparities in health care delivery and outcomes are complex and longstanding. Many such disparities derive from limited access to health care, socioeconomic barriers, and cultural differences—each of which can result in minorities receiving suboptimal care, and ultimately in inferior outcomes. Recently published SEER data again underscore the undeniable disparities in cancer outcomes across ethnic groups.^{1a} Understanding the drivers of these disparities is relevant for all subpopulations, but for black men with prostate cancer, this is especially true, as there are specific action items of timely importance.

Black men with prostate cancer have a 2.5-fold greater risk of lethal prostate cancer compared with white men.^{1a} Hispanic men with prostate cancer have demonstrated increased incidence rates and also have inferior survival rates when compared with white males. The increased incidence of advanced prostate cancer among Hispanic men, however, appears to be principally related to barriers in health care access (ie, education level, socioeconomic status, insurance status, and so on); when these factors are corrected for, no significant difference in lethal prostate cancer rates are found (odds ratio: 1.23 [95% CI, 0.73 to 2.08]).² In contrast, black men appear to retain an independently increased risk for advanced disease despite corrections for access to health care (odds ratio 2.26 [95% CI, 1.43 to 3.58]). However, a major component of prostate cancer disparities is not simply whether patients have access to care, but also the dissemination of knowledge of the potential survival and quality of life benefit of optimal therapies.

In the past decade, we have seen unprecedented progress in treatment options for men with prostate cancer. Since 2009, five

therapies gained US Food and Drug Administration approval for improving survival in castration-resistant prostate cancer (CRPC): sipuleucel-T,³ abiraterone,^{4,5} enzalutamide,^{6,7} cabazitaxel,⁸ and radium-223 chloride.⁹ Even as we affirm and celebrate this unprecedented progress, such strides raise additional questions. With an ever-expanding array of treatment options, we now must ensure a pathway for all patients to receive optimal therapy. Wissing et al¹⁰ conducted a recent retrospective analysis of 17 clinical trials regarding prostate cancer prevention or treatment in six countries over the past 20 years. The analysis demonstrated a consistent under-representation of racial minorities in clinical trials, with approximately 5% of the studied patient population constituting black men. Unfortunately now more than ever, despite the new arsenal of cancer therapies for CRPC, representation of black men in these clinical trials to ascertain ethnic differences in clinical benefit is simply inadequate.

Seven landmark phase III randomized controlled trials³⁻⁹ were performed to solidify US Food and Drug Administration approval of the five new therapeutic options for CRPC since 2009. As shown in [Table 1](#), a total of 7,275 men were enrolled on these seven clinical trials. Each trial demonstrated improvements in overall survival and met their primary end point. This has generated a resurgence of hope for the nearly 30,000 men who suffer from lethal prostate cancer.^{1a} However, only 3.3% (n = 240) in total from all seven trials were black men. This rate should appear low to any reader, but the magnitude of under-representation is dramatically lower than would be expected.

Recently, in response to these disparities, an action plan was implemented and reported from five National Cancer Institute (NCI)-designated cancer centers demonstrating an improvement in

Table 1. Summary of Enrollment of Black Men Onto CRPC Trials

Enrollment	Sipuleucel-T	Radium-223 Chloride	Enzalutamide (pre-chemo)	Enzalutamide (post-chemo)	Abiraterone (pre-chemo)	Abiraterone (post-chemo)	Cabazitaxel	All Patients With CRPC in RCTs	Expected Black Enrollment*
Total patients	512	809	1,717	1,199	1,195	1,088	755	7,275	
Random assignment	2:1	2:1	1:1	2:1	2:1	1:1	1:1	—	
Percent black	5.8	2.0	2.0	3.9	3.6	2.8	5.3	3.3	15.8
No. of black patients	30	16	34	47	43	30	40	240	1,149
No. of black patients receiving trial drug	23	11	21	31	29	15	20	150	673

Abbreviations: chemo, chemotherapy; CRPC, castration-resistant prostate cancer; NCI, National Cancer Institute; RCT, randomized controlled trial.

*Based on (1) conservative NCI enrollment data that 66% of the available black population enrolls onto NCI clinical trials; (2) the US population is approximately 12% black; (3) there is a greater than two-fold increase in the incidence of lethal prostate cancer in black men.^{1a,9}

black patient trial participation. The five centers enrolled a median of 100% of black patients expected based on catchment data, with a wide range of participation from 66% to 112%.¹¹ The center with the lowest enrollment (66%) has a similar representative black population as the United States (approximately 12%). Although the enrollment at this NCI center is suboptimal, it is far superior to the enrollment of black patients on CRPC trials. Considering that 12% of the American population is black, and there is a more than two-fold increased risk for a black male to have CRPC compared with a white male, the ideal representation is expected to be approximately 24% in CRPC trials. However, the current enrollment is only 3.3%, or a mere one seventh of what it ideally would be. Even when factoring in that some NCI centers enroll only 66% of the expected black population, one would anticipate at least a 16% black trial enrollment for patients with prostate cancer. This translates into an 80% underrepresentation of black men in CRPC clinical trials from what a conservative estimate would yield.

These landmark clinical trials were designed as randomizations of standard-of-care versus the investigational therapy.¹² Four of the trials randomized patients in a 2:1 fashion,^{3,4,6,9} with approximately twice the number of patients receiving the investigational therapy over a placebo, while the other three used a 1:1 random assignment.^{5,7,8} As a result, only 150 black men received an investigational therapy out of the 7,275 men enrolled. Therefore, only 11 to 31 black men actually received an investigational agent per trial, thus making it near futile to perform subgroup analysis and assess efficacy among black men.

The objective of this piece is not to point out flaws in these landmark practice-changing trials. Disparities in clinical trial enrollment are multilevel and complex. We do not know the enrollment targets for black men in each of the accruing institutions, and there is a remote, yet unlikely, possibility that enrollment actually reflected the local population demographics. Furthermore, some of the trials were accrued primarily by European centers (up to 85% of enrollment), and our comparisons are solely extrapolated from black population and enrollment estimates in the United States. However, it should be emphasized that the United States appears to enroll the largest number of racial minorities onto prostate cancer trials in comparison to other countries, suggesting that this issue is relevant worldwide.¹⁰ Regardless, a legacy of these trials is that we cannot independently assess these therapies in black men. To further mitigate the expansion of prostate cancer disparities in black males, dedicated investigation is warranted. The benefit may surpass our expectations, or deviate from what we anticipate.

Now that these novel therapies have been granted US Food and Drug Administration approval, there are several options on multiple levels to assess the benefits these agents can provide for black men. From a government and community level, this includes supporting the creation of multicenter, prospective cancer registries among centers serving large black populations, such as the North Carolina-Louisiana Prostate Cancer Project.¹³ Such efforts might be improved with coordination from federal agencies such as the recently created (2010) US Food and Drug Administration Office of Minority Health to help prioritize which therapy to investigate in a systematic manner. Furthermore, considering the large number of black males currently living with CRPC and the thousands who will progress to CRPC per year in the United States, from an institutional level, there is ample

opportunity to address this gap through dedicated black male clinical trials. One such trial is currently accruing black men with prostate cancer to determine the correlation between germline polymorphisms and antitumor activity of abiraterone (clinical trial NCT01735396). From an industry level, another option comes from Project Data Sphere, which hopes to gain insights into unanswered questions from pooling clinical trial data from tens of thousands of patients sponsored by both industry and academic centers.¹⁴ From a patient and provider level, we not only need to have a greater appreciation for the factors that impede black trial enrollment, but must implement strategies to overcome these obstacles from the inception of the clinical trial.^{15,16} Lastly, the key drivers in tumor biology that confer the discrepant prognosis for black men with prostate cancer remain unknown. If and when these advances are discovered, enrollment based on specific genomic or epigenetic characteristics, rather than simply the phenotype of race, may ultimately be the best way to determine the efficacy of therapy for each individual. Regardless of the method, we are faced with ample opportunities to determine the optimal therapy for all men with CRPC.

As Dr. King noted, progress is precarious. Recent advances in treatments of advanced prostate cancer also illuminate unexpected ethnic disparities. As we celebrate the tremendous innovations in treatment, we must also turn our attention to maximizing the access and efficacy of such treatments to all. Moving forward, we should make dedicated and focused efforts to investigate these practice-changing therapies among black men to provide insight on the best ways to provide optimal care for all.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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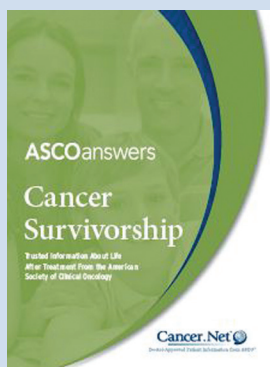
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