Overall Survival of Black and White Men With Metastatic Castration-Resistant Prostate Cancer Treated With Docetaxel

Susan Halabi, PhD¹; Sandipan Dutta, PhD¹; Catherine M. Tangen, PhD²; Mark Rosenthal, MD³; Daniel P. Petrylak, MD⁴; Ian M. Thompson Jr, MD⁵; Kim N. Chi, MD⁶; John C. Araujo, MD, PhD⁷; Christopher Logothetis, MD⁷; David I. Quinn, MBBS, PhD⁸; Karim Fizazi, MD, PhD⁹; Michael J. Morris, MD¹⁰; Mario A. Eisenberger, MD¹¹; Daniel J. George, MD¹; Johann S. De Bono, MD, PhD¹²; Celestia S. Higano, MD²; Ian F. Tannock, MD, PhD¹³; Eric J. Small, MD¹⁴; and William Kevin Kelly, DO¹⁵

PURPOSE Several studies have reported that among patients with localized prostate cancer, black men have a shorter overall survival (OS) time than white men, but few data exist for men with advanced prostate cancer. The primary goal of this analysis was to compare the OS in black and white men with metastatic castration-resistant prostate cancer (mCRPC) who were treated in phase III clinical trials with docetaxel plus prednisone (DP) or a DP-containing regimen.

METHODS Individual participant data from 8,820 men with mCRPC randomly assigned in nine phase III trials to DP or a DP-containing regimen were combined. Race was based on self-report. The primary end point was OS. The Cox proportional hazards regression model was used to assess the prognostic importance of race (black v white) adjusted for established risk factors common across the trials (age, prostate-specific antigen, performance status, alkaline phosphatase, hemoglobin, and sites of metastases).

RESULTS Of 8,820 men, 7,528 (85%) were white, 500 (6%) were black, 424 (5%) were Asian, and 368 (4%) were of unknown race. Black men were younger and had worse performance status, higher testosterone and prostate-specific antigen, and lower hemoglobin than white men. Despite these differences, the median OS was 21.0 months (95% CI, 19.4 to 22.5 months) versus 21.2 months (95% CI, 20.8 to 21.7 months) in black and white men, respectively. The pooled multivariable hazard ratio of 0.81 (95% CI, 0.72 to 0.91) demonstrates that overall, black men have a statistically significant decreased risk of death compared with white men ($P < .001$).

CONCLUSION When adjusted for known prognostic factors, we observed a statistically significant increased OS in black versus white men with mCRPC who were enrolled in these clinical trials. The mechanism for these differences is not known.

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INTRODUCTION

In the United States, black men have a higher incidence of prostate cancer than white men, with age-adjusted incidence rates of 162.7 and 100.8 per 100,000, respectively.¹ Black men with prostate cancer are more likely to be diagnosed at an earlier age with higher grade and metastatic disease than white men.² Furthermore, black patients have a higher mortality rate as a result of prostate cancer and less favorable outcomes than white patients.¹⁻¹¹ A vast body of research has focused on the disparities in the incidence of clinical and pathologic parameters between black and white men with localized prostate cancer that have an impact on outcomes, such as prostate-specific antigen (PSA) recurrence and prostate cancer-specific death.²⁻¹⁰ Several of the studies were based on cancer registries (state and SEER) or were from academic centers.¹²⁻¹⁸ Among men with early-stage disease who undergo radical prostatectomy, blacks have worse outcomes than whites.² This

disparity in outcomes has been attributed to racial differences in hormone levels, diet, genetic and molecular alterations, cancer treatment and screening, access to health care, and the suggestion that black men are genetically predisposed to more-aggressive disease.¹⁹

In contrast, data on racial disparities in men with advanced prostate cancer are limited.¹⁹⁻²² With the use of data from a randomized trial of men with metastatic hormone-sensitive prostate cancer treated with orchiectomy with or without flutamide—Southwest Oncology Group (SWOG) 8894—Thompson et al¹⁹ reported that black men are at an increased risk of death compared with white men. The median overall survival (OS) times for black and white men were 26 and 35 months, respectively. The adjusted hazard ratio (HR) for death was 1.39 (95% CI, 1.10 to 1.77; $P = .007$) for black men compared with white men, though an important confounder lies in the fact that patients enrolled in SWOG 8894 predated PSA

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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screening. Although Thompson et al and Tangen et al²⁰ evaluated cancer disparities in men with metastatic hormone-sensitive prostate cancer, we previously reported a pooled analysis of disparities in men with metastatic castration-resistant prostate cancer (mCRPC) enrolled in eight phase II and III trials from 1991 to 2002. The median survival time was 15 months (95% CI, 12 to 18 months) for black men versus 14 months (95% CI, 13 to 15 months) for white men.²¹ In a multivariable analysis, the HR for death was 0.77 for black compared with white men.²² A limitation of our prior analysis in patients with mCRPC, given the time frame of the studies included, was the relatively low proportion of patients treated with docetaxel (18%), the first and most widely used chemotherapeutic agent with a demonstrated survival advantage for men with mCRPC.

Two pivotal phase III trials—TAX 327 (Docetaxel Plus Prednisone or Mitoxantrone Plus Prednisone for Advanced Prostate Cancer) and SWOG 9916 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00004001) identifier: NCT00004001)—led to the approval of docetaxel for mCRPC. However, the relative efficacy of docetaxel in black compared with white men is largely unknown because of the limited number of black men enrolled in these two studies.^{23,24} We therefore undertook a meta-analysis of multiple phase III trials in men with mCRPC treated with docetaxel, including TAX 327 and SWOG 9916, to compare survival outcomes in black versus white men.

METHODS

We performed a systematic literature search from January 2004 to July 2015 using PubMed and [ClinicalTrials.gov](https://clinicaltrials.gov/) to identify phase III trials of docetaxel and prednisone (DP) versus DP plus an experimental agent that were reported between 1999 and 2015.²³⁻³² Details on how trials were selected are presented elsewhere.³³ Participants were men with prostate cancer who had progressive metastatic disease after androgen deprivation therapy and, when relevant, anti-androgen withdrawal. To be included, a trial had to satisfy the following criteria: institutional review board approval, phase III trial in which men with chemotherapy-naïve mCRPC were treated with DP, and OS as the primary end point.

Data

We requested individual patient data from each identified trial from the trial sponsor or the National Clinical Trials Network (NCTN) coordinating group. Data included race (which was self-reported), date of randomization, date of last observation or follow-up, date of death, survival status at the date of last observation, cause of death, treatment assignment, date of birth (or age in years), date of initial diagnosis, date of metastatic diagnosis, hemoglobin, PSA, performance status, alkaline phosphatase, creatinine, testosterone, Gleason score, prior radiation therapy, prior and current hormone therapy, site of metastases at baseline, and stratification factors. Data were submitted to the Department of Biostatistics and Bioinformatics at Duke

University (S.H.) where they were analyzed. The study was approved by the Duke University institutional review board.

Statistical Analysis

The primary end point was OS, which was defined as the interval between the date of randomization and date of death as a result of any cause. The main objectives of this analysis were to estimate the pooled HR and to test the hypothesis that black men had worse OS than white men. Data on 8,820 men from nine phase III clinical trials were pooled; trials that compared DP with DP plus an experimental agent failed to show significant differences in OS between their arms.²³⁻³² Analyses were performed to estimate the pooled HR for death of all men whose treatment included DP. In addition, sensitivity analyses were performed for patients enrolled in NCTN trials, patients who were randomly assigned to DP only (ie, excluding patients who received experimental therapy), and patients enrolled in NCTN trials who were randomly assigned to DP-only arms.

We used the χ^2 and Wilcoxon rank sum tests to compare the baseline clinical characteristics between black and white men. Similar to our previous meta-analysis, we used a two-stage approach.³³⁻³⁵ In the first stage, the HRs from each of the nine trials were estimated, and the trial-specific estimates were combined to obtain an overall estimate of the HR and the estimated variance. We first computed weighted average coefficients, 95% CIs, and the Q- and I^2 statistics for the coefficients. Next, we took the exponential of the coefficients and computed the 95% CIs.

We used the Q- and I^2 statistics to test for heterogeneity across the nine trials. The Q-statistic tested for the homogeneity of the HRs across the nine studies, whereas the I^2 statistic described the proportion of the total variation in the study estimates that is the result of heterogeneity.

We applied a modified intention-to-treat analysis within each clinical trial, where the analyses were based on all randomly assigned patients except for those in TAX 327 and SWOG 9916^{23,24}; these trials contained nondocetaxel arms, so we excluded patients in these arms from the analysis. In addition, within each trial, we used the Cox proportional hazards regression model to adjust for the following baseline prognostic variables: age, performance status, site of metastases, PSA, hemoglobin, and alkaline phosphatase. Furthermore, we applied the Kaplan-Meier method to estimate the OS distribution by racial group. Finally, we summarized the individual and pooled HR estimates and present the results with 95% CIs in forest plots.

RESULTS

Trials Identified

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of how the trials were identified and screened. The 10 trials that met the inclusion criteria were TAX 327,²³ SWOG 9916,²⁴

FIG 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of how the trials were identified and screened. DP, docetaxel and prednisone; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival.

Androgen-Independent Prostate Cancer Study of Calci-
triol Enhancing Taxotere ([ClinicalTrials.gov](#) identifier:
NCT00043576),²⁵ Cancer and Leukemia Group B (CALGB)
90401 ([ClinicalTrials.gov](#) identifier: NCT00110214),²⁶ EN-
THUSE 33 ([ClinicalTrials.gov](#) identifier: NCT00617669),²⁷

SWOG 0421 ([ClinicalTrials.gov](#) identifier: NCT001340546),²⁸
VENICE ([ClinicalTrials.gov](#) identifier: NCT00617669),²⁹
READY ([ClinicalTrials.gov](#) identifier: NCT00744497),³⁰
MAINSAIL ([ClinicalTrials.gov](#) identifier: NCT00988208),³¹ and
SYNERGY ([ClinicalTrials.gov](#) identifier: NCT01188187).³² The
nine trials enrolled 8,820 patients with mCRPC who were
treated with DP or a DP-containing regimen between 1999
and 2014 (Table 1). The data from one trial, ASCENT
([ClinicalTrials.gov](#) identifier: NCT00043576), was not
available.

Distribution of Race

Of the 8,820 patients, 7,528 (85%) were white, 500 (6%)
were black, 424 (5%) were Asian, and 368 (4%) were
classified as unknown or other. Seven hundred ninety-two
(424 Asian and 368 other) patients were excluded from the
analysis; thus, 8,028 men were included in the meta-
analysis. Separate analyses are under way for the Asian
men enrolled in these trials. Seventy-one percent of pa-
tients were enrolled in industry-sponsored trials, whereas
29% were enrolled in NCTN trials. The NCTN trials enrolled
a higher proportion of black men than did the industry trials
(12% v 4%; Appendix Fig A1, online only).

Table 2 presents the baseline characteristic of the included
patients. Overall, the median age was 69 years; 94%
of patients had a performance status of 0 or 1. The median
hemoglobin, PSA, and alkaline phosphatase levels were
12.9 g/dL, 97 ng/mL, and 138 U/L, respectively. Com-
parison of baseline characteristics of black and white men
revealed several statistically significant differences. Al-
though statistically significant, the difference in median age
was relatively small (black men, 68 years; white men, 69
years). Ninety percent of black men had a performance

TABLE 1. Summary of Trials Included in the Meta-Analysis

Trial (ClinicalTrials.gov Identifier)	Total Sample Size, No.	Calendar Year of Recruitment	Treatment Arms (No. of patients)
SWOG 9916 ²⁴ (NCT00004001)	674	Oct 1999-Jan 2003	Docetaxel + estramustine (n = 338) Mitoxantrone + prednisone (n = 336)
TAX 327 ²³	1,006	Mar 2000-Jun 2002	Docetaxel + prednisone (n = 669) Mitoxantrone + prednisone (n = 337)
CALGB 90401 ²⁶ (NCT00110214)	1,050	May 2005-Dec 2007	Docetaxel + prednisone + bevacizumab (n = 524) Docetaxel + prednisone (n = 526)
SWOG 0421 ²⁸ (NCT00134056)	994	Aug 2006-May 2010	Atrasentan + docetaxel (n = 498) Placebo + docetaxel (n = 496)
VENICE ²⁹ (NCT00519285)	1,224	Aug 2007-Feb 2010	Docetaxel + prednisone + aflibercept (n = 612) Docetaxel + placebo (n = 612)
ENTHUSE 33 ²⁷ (NCT00617669)	1,052	Jan 2008-May 2011	Docetaxel + zibotentan (n = 524) Docetaxel + placebo (n = 528)
READY ³⁰ (NCT00744497)	1,522	Oct 2008-Apr 2011	Docetaxel + dasatinib (n = 762) Docetaxel + placebo (n = 760)
MAINSAIL ³¹ (NCT00988208)	1,059	Nov 2009-Nov 2011	Docetaxel + prednisone + lenalidomide (n = 533) + placebo (n = 526)
SYNERGY ³² (NCT01188187)	1,022	Aug 2010-Apr 2014	Docetaxel + prednisone + custirsen (n = 510) Docetaxel + prednisone (n = 512)

Abbreviations: CALGB, Cancer and Leukemia Group B; SWOG, Southwest Oncology Group.

FIG 2. (A) Kaplan-Meier curves of overall survival (OS) by race and (B) forest plot with hazard ratios (HRs) comparing black men with white men (reference group, white men; $Q = 10.738$; $df = 8$; $P = .217$; $I^2 = 0.255$). CALGB, Cancer and Leukemia Group B; ENTHUSE 33 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00617669) identifier: NCT00617669); MAINSAIL ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00988208) identifier: NCT00988208); NR, not reported; READY ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00744497) identifier: NCT00744497); SYNERGY ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01188187) identifier: NCT01188187); SWOG, Southwest Oncology Group; SWOG 0421 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00134056) identifier: NCT00134056); SWOG 9916 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00004001) identifier: NCT00004001); SWOG 90401 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00110214) identifier: NCT00110214); TAX 327 (Docetaxel Plus Prednisone or Mitoxantrone Plus Prednisone for Advanced Prostate Cancer; VENICE ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00519285) identifier: NCT00519285).

status of 0 to 1 versus 95% of white men. For black and white men, respectively, median testosterone levels were 20 and 18 ng/mL ($P < .001$), median PSA levels were 127 and 85 ng/mL ($P < .001$), and median hemoglobin levels were 12 and 13 g/dL ($P < .001$).

Clinical Outcomes

We tested the hypothesis that black men with mCRPC have a shorter median OS time than white men. The median

follow-up time was 31 months among surviving patients; a total of 5,045 deaths were observed (event rates, 68% v 62% in black and white men, respectively). Figure 2A shows the Kaplan-Meier OS curves for the two groups. There was no difference in survival distribution between black and white men (median OS, 21 months).

HRs comparing the median OS of black versus white men by trial and pooled across all trials in 8,208 men are shown in Figure 2B. Overall, marginal variability was observed in

FIG 3. (A) Kaplan-Meier curves of overall survival (OS) by race and (B) forest plot with hazard ratios (HRs) comparing black men with white men enrolled in the National Cancer Institute National Clinical Trials Network (reference group, white men; $Q = 0.216$; $df = 2$; $P = .898$; $I^2 = 0.000$).

median OS for black men across trials. The HRs for death for black versus white men were less than 1, which indicates that black men had longer survival duration than white men when adjusted for prognostic factors. The pooled multivariable HR was 0.81 (95% CI, 0.72 to 0.91), which demonstrates that black men have a statistically significant decreased risk of death compared with white men ($P < .001$).

We also estimated the median OS time in black and white men enrolled in the NCTN trials because this may be representative of community practices. The median OS was also longer in black than in white men in the three trials sponsored by the NCTN (overall median OS, 21 v 20 months in black and white men, respectively; Fig 3A). In 2,309 men with mCRPC enrolled in NCTN trials, the pooled multivariable HR was 0.76 (95% CI, 0.66 to 0.88), which indicates that black men have a decreased risk of death

compared with white men when adjusted for baseline prognostic factors (Fig 3B).

For 4,172 men who were randomly assigned to DP alone, median OS was 22 months in black men versus 21 months in white men (Appendix Fig A2A, online only). The pooled multivariable HR was 0.79 (95% CI, 0.67 to 0.93), which again demonstrates that black men have a decreased risk of death compared with white men when adjusted for prognostic factors (Appendix Fig A2B).

For 1,316 men randomly assigned in NCTN trials and treated with DP alone, the median OS was 23 months for black men and 19 months for white men (Appendix Fig A3A, online only). The pooled multivariable HR was 0.71 (95% CI, 0.58 to 0.87), which again demonstrates that black men had a decreased risk of death compared with white men when adjusted for prognostic factors (Appendix Fig A3B).

TABLE 2. Baseline Characteristics by Racial Group

Baseline Variable	Racial Group			P
	White	Black	Total	
No. of patients	7,528	500	8,028	
Median age, years (25 th , 75 th percentile)	69.0 (63-74)	67.6 (60-73)	69 (63-74)	< .001
Performance status, %				
0	45	42	45	< .001
1	50	48	50	
Median PSA, ng/mL	85 (31-247)	127 (45-350)	86 (31-253)	< .001
Median hemoglobin, g/dL (25 th , 75 th percentile)	13 (12-14)	12 (12-13)	13 (12-14)	< .001
Median testosterone missing, No. (%)	18 (27)	20 (18)	18 (27)	< .001
Median alkaline phosphatase, U/L (25 th , 75 th percentile)	138 (85-284)	127 (82-263)	137 (85-283)	.144
Site of metastases, %				.035
Lymph nodes	7	6	7	
Bone/bone + lymph nodes	72	69	73	
Lung	9	12	9	
Liver	8	6	8	
Randomly assigned to docetaxel + prednisone, %	52	57	52	.030

Abbreviation: PSA, prostate-specific antigen.

DISCUSSION

This analysis is the largest to our knowledge that compares the OS of black and white men with mCRPC enrolled in phase III clinical trials. Although the median survival was similar, the pooled HR was 0.81 for black men compared with white men, which indicates that after adjustment for baseline prognostic factors, black men had a 19% lower risk of death than white men.

We observed a more striking difference when we estimated the median survival duration and pooled HR in patients enrolled in the NCTN trials. The median survival times were 21 months for black men and 20 months for white men. After adjusting for important prognostic factors, the pooled HR was 0.76 for black men compared with white men.

Our results are in agreement with a prior analysis that included 1,183 men with mCRPC, where we found statistically significant racial differences for OS (HR for death, 0.77; $P = .004$), which favored black men.²² By using the Registry of Sipuleucel-T Therapy in Men With Advanced Prostate Cancer, Freedland et al³⁶ also reported better survival for black men than for white men. This is in contrast to an analysis performed using the SEER registry where Aizer et al³⁷ reported a higher HR of prostate cancer mortality in black men compared with other racial groups. These discrepancies may be the result of differences in the patients reported (population based in the SEER data set v our report of selected patients receiving therapy in prospective clinical trials). On the basis of the prospective databases we queried, we were able to describe baseline patient characteristics known to be prognostic of OS. The HR for death favoring black men

was observed despite that black men had statistically significant worse performance status, higher testosterone levels, higher PSA levels, and lower hemoglobin levels.

The reasons for overall worse OS for black men with prostate cancer are likely multifactorial and not fully understood. By contrast, in this selected population of men with mCRPC treated in clinical trials with DP, black men had an improved survival outcome. The reasons for this discrepant survival cannot be ascertained from these data but could be attributed to selection bias or possible biologic differences between prostate cancers in black and white men. Furthermore, racial differences possibly existed in pharmacologic and pharmacokinetic criteria (absorption, distribution, metabolism, excretion, and toxicity) that would influence drug levels and exposure kinetics that, in turn, conceivably could influence the performance of a therapeutic agent such as docetaxel. Alternatively, a number of genes, including *p53*, have been shown to modulate taxane or docetaxel sensitivity in prostate cancer cells, and racial differences in expression modulation of these genes could be invoked as a potential explanation for these observations.³⁸⁻⁴¹

The US-based NCTN trials were successful in enrolling a higher proportion of black men than industry trials (12% v 4%). Despite inclusion of 500 black men in this meta-analysis, the proportion of black men is low compared with the estimated US black population of approximately 14%. Many black men with mCRPC may not qualify for trials because of comorbidities, financial challenges, or lack of access to trials. Lack of health care, delayed time to diagnosis, and racial preferences about diagnosis and

treatments are important factors that could affect the survival of black men. Focused efforts to enhance enrollment of black men and other under-represented groups in clinical trials should be pursued. Our results raise the question about whether future phase III clinical trials in mCRPC should be stratified upfront by race and include treatment by race comparisons in the analysis. In addition to stratification by race, it will be important to collect data prospectively that might discern racial differences in absorption, distribution, metabolism, excretion, and toxicity criteria.

The strength of our study derives from the fact that all included patients were enrolled in phase III clinical trials and the data were prospectively collected. Moreover, our study incorporated detailed information about treatment and known prognostic variables. However, several limitations of

this meta-analysis exist as a result of the study's retrospective nature. The study population was highly selected, and not all prognostic factors across the trials were available for the analysis, which underscores the challenges in performing such analyses because of limitations in the harmonization of data collected across phase III studies. Consequently, these results are not generalizable to patients who do not have mCRPC, who are treated with nondocetaxel therapies, and who are not treated in a prospective interventional trial.

In summary, this large meta-analysis provides evidence that black men with mCRPC treated with DP in clinical trials had improved survival outcomes compared with white men when adjusted for baseline prognostic factors. Our understanding of these differences is limited and underscores the need for additional research.

AFFILIATIONS

- ¹Duke University Medical Center, Durham, NC
- ²Fred Hutchinson Cancer Research Center, Seattle, WA
- ³The Royal Melbourne Hospital, Parkville, VIC, Australia
- ⁴Yale University School of Medicine, New Haven, CT
- ⁵UT Health Science Center, San Antonio, TX
- ⁶BC Cancer Agency Vancouver Centre, Vancouver, BC
- ⁷The University of Texas MD Anderson Cancer Center, Houston, TX
- ⁸University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA
- ⁹Gustave Roussy, Villejuif, France
- ¹⁰Memorial Sloan Kettering Cancer Center, New York, NY
- ¹¹The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD
- ¹²The Institute of Cancer Research and The Royal Marsden National Health Service Foundation Trust, Sutton, United Kingdom
- ¹³Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada
- ¹⁴University of California San Francisco, San Francisco, CA
- ¹⁵Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA

CORRESPONDING AUTHOR

Susan Halabi, PhD, Duke University Medical Center, 2424 Erwin Rd, Suite 11088, Durham, NC 27710; e-mail: susan.halabi@duke.edu.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHOR CONTRIBUTIONS

Conception and design: Susan Halabi, Christopher Logothetis, David I. Quinn, Karim Fizazi, Johann S. De Bono, Eric J. Small, William Kevin Kelly
Provision of study material or patients: Mark Rosenthal, Ian M. Thompson Jr, Kim N. Chi, John C. Araujo, David I. Quinn, Karim Fizazi, Michael J. Morris, Johann S. De Bono, Celestia S. Higano, Ian F. Tannock
Collection and assembly of data: Susan Halabi, Catherine M. Tangen, Daniel P. Petrylak, Ian M. Thompson Jr, Kim N. Chi, David I. Quinn, Karim Fizazi, Johann S. De Bono, Celestia S. Higano, Ian F. Tannock, William Kevin Kelly
Data analysis and interpretation: Susan Halabi, Sandipan Dutta, Catherine M. Tangen, Mark Rosenthal, Daniel P. Petrylak, John C. Araujo, Christopher Logothetis, David I. Quinn, Karim Fizazi, Michael J. Morris, Mario A. Eisenberger, Daniel J. George, Johann S. De Bono, Celestia S. Higano, Eric J. Small, William Kevin Kelly
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Overall Survival of Black and White Men With Metastatic Castration-Resistant Prostate Cancer Treated With Docetaxel**

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Susan Halabi

Consulting or Advisory Role: Eisai, Ferring Pharmaceuticals

Daniel P. Petrylak

Stock and Other Ownership Interests: Bellicum Pharmaceuticals, Tyme
Consulting or Advisory Role: Bayer AG, Bellicum Pharmaceuticals, Dendreon, Johnson & Johnson, Exelixis, Ferring Pharmaceuticals, Millennium Pharmaceuticals, Medivation, Pfizer, Roche, Sanofi, Tyme, Astellas Pharma, AstraZeneca, Eli Lilly

Research Funding: Progenics Pharmaceuticals, Johnson & Johnson, Dendreon, Sanofi, Endocyte, Genentech, Merck, Astellas Pharma, Medivation, Novartis, Agensys, AstraZeneca, Bayer AG, Eli Lilly, Innocrin Pharmaceuticals, MedImmune, Millennium Pharmaceuticals, Pfizer, Roche, Sotio, Seattle Genetics, Clovis Oncology

Expert Testimony: Celgene, Sanofi

Ian M. Thompson Jr

Consulting or Advisory Role: MagForce, Profound Medical, Rapamycin Holdings

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Kim N. Chi

Honoraria: Sanofi, Janssen Pharmaceuticals, Astellas Pharma, Bayer AG

Consulting or Advisory Role: ESSA Pharma, Astellas Pharma, Janssen Pharmaceuticals, Sanofi, Eli Lilly, ImClone, Amgen, Bayer AG

Research Funding: Janssen Pharmaceuticals (Inst), Astellas Pharma (Inst), Bayer AG (Inst), Sanofi (Inst), Tokai Pharmaceuticals (Inst), Eli Lilly (Inst), ImClone (Inst), Bristol-Myers Squibb (Inst), Merck (Inst), Roche (Inst)

Christopher Logothetis

Honoraria: Astellas Pharma, Bayer AG, Sanofi, Janssen Pharmaceuticals

Consulting or Advisory Role: Astellas Pharma, Bayer AG, Sanofi, Janssen Pharmaceuticals

Research Funding: Astellas Pharma, Bristol-Myers Squibb, Bayer AG, Sanofi, Novartis, Janssen Pharmaceuticals

David I. Quinn

Honoraria: Bayer AG, Astellas Pharma, Pfizer, Genentech, Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Dendreon, Exelixis, Sanofi, Janssen Pharmaceuticals, Novartis, Mundipharma, Pharmacyclis

Consulting or Advisory Role: Astellas Pharma, Pfizer, Bristol-Myers Squibb, Genentech, Roche, Merck Sharp & Dohme, Bayer AG, Exelixis, AstraZeneca, Sanofi, Dendreon, EMD Serono, Janssen Pharmaceuticals, Amgen, Eisai, Novartis, US Biotech

Research Funding: Millennium Pharmaceuticals (Inst), Genentech (Inst), Roche (Inst), Sanofi (Inst), GlaxoSmithKline (Inst)

Karim Fizazi

Honoraria: Janssen Pharmaceuticals, Sanofi, Astellas Pharma, Merck

Consulting or Advisory Role: Janssen Pharmaceuticals, Bayer AG, Astellas Pharma, Sanofi, Orion Pharma, CureVac, AstraZeneca, ESSA Pharma, Roche, Genentech, Clovis Oncology, Amgen

Travel, Accommodations, Expenses: Amgen, Janssen Pharmaceuticals

Michael J. Morris

Consulting or Advisory Role: Astellas Pharma, Bayer AG, Endocyte, Advanced Accelerator Applications, Blue Earth Diagnostics, Tokai Pharmaceuticals, Tolmar Pharmaceuticals

Research Funding: Bayer AG (Inst), Sanofi (Inst), Endocyte (Inst), Progenics Pharmaceuticals (Inst), Corcept Therapeutics (Inst), Roche (Inst), Genentech (Inst)

Travel, Accommodations, Expenses: Bayer AG, Endocyte

Mario A. Eisenberger

Leadership: Veru

Stock and Other Ownership Interests: Veru

Honoraria: Sanofi, Pfizer

Consulting or Advisory Role: Astellas Pharma, Ipsen, Bayer AG, Sanofi, Pfizer

Research Funding: Sanofi, Tokai Pharmaceuticals, Genentech

Travel, Accommodations, Expenses: Bayer AG, Astellas Pharma, Sanofi, Pfizer, Veru

Daniel J. George

Honoraria: Sanofi, Bayer AG, Exelixis

Consulting or Advisory Role: Bayer AG, Exelixis, Pfizer, Sanofi, Astellas Pharma, Innocrin Pharmaceuticals, Bristol-Myers Squibb, Genentech, Janssen Pharmaceuticals, Merck Sharp & Dohme, Myovant Sciences

Speakers' Bureau: Sanofi, Bayer AG, Exelixis

Research Funding: Exelixis (Inst), Genentech (Inst), Roche (Inst), Janssen Pharmaceuticals (Inst), Novartis (Inst), Pfizer (Inst), Astellas Pharma (Inst), Bristol-Myers Squibb (Inst), Millennium Pharmaceuticals (Inst), Acerta Pharma (Inst), Bayer AG (Inst), Dendreon (Inst), Innocrin Pharmaceuticals (Inst)

Expert Testimony: Novartis

Travel, Accommodations, Expenses: Bayer AG, Exelixis, Genentech, Roche, Medivation, Merck, Pfizer

Johann S. De Bono

Honoraria: AstraZeneca, Sanofi, Astellas Pharma, Pfizer, Genentech, Roche

Consulting or Advisory Role: AstraZeneca, Sanofi, Genentech, Roche, Astellas Pharma, Bayer AG, Pfizer, Merck Sharp & Dohme, Merck Serono, Boehringer Ingelheim

Research Funding: AstraZeneca (Inst), Genentech (Inst), Sanofi (Inst)

Patents, Royalties, Other Intellectual Property: Abiraterone rewards to inventors (Inst), poly (ADP-ribose) polymerase inhibitors, and DNA repair defects (Inst)

Travel, Accommodations, Expenses: AstraZeneca, Astellas Pharma, GlaxoSmithKline, Orion Pharma, Sanofi, Genmab, Taiho Pharmaceutical, QIAGEN, Vertex Pharmaceuticals

Celestia S. Higano

Employment: CTI BioPharma (I)

Leadership: CTI BioPharma (I)

Stock and Other Ownership Interests: CTI BioPharma (I)

Honoraria: Genentech

Consulting or Advisory Role: Bayer AG, Ferring Pharmaceuticals, Orion Pharma, Astellas Pharma, Clovis Oncology, Blue Earth Diagnostics, Myriad Genetics, Tolmar Pharmaceuticals, Janssen Pharmaceuticals, Hinova Pharmaceuticals

Research Funding: Aragon Pharmaceuticals (Inst), AstraZeneca (Inst), Dendreon (Inst), Genentech (Inst), Medivation (Inst), Emergent BioSolutions (Inst), Bayer AG (Inst), Pfizer (Inst), Roche (Inst), Astellas Pharma

Travel, Accommodations, Expenses: Bayer AG, Astellas Pharma, Clovis Oncology, Blue Earth Diagnostics, Ferring Pharmaceuticals, Genentech, Orion Pharma, Menarini, Myriad Genetics, Pfizer, Hinova Pharmaceuticals

Ian F. Tannock

Consulting or Advisory Role: Janssen Pharmaceuticals, Roche, Genentech, Bayer AG

Eric J. Small

Stock and Other Ownership Interests: Fortis Pharma Consulting, Harpoon Therapeutics

Honoraria: Janssen Pharmaceuticals

Consulting or Advisory Role: Fortis Pharma Consulting, Janssen Pharmaceuticals

Research Funding: Janssen Pharmaceuticals (Inst), Merck (Inst)

Travel, Accommodations, Expenses: Janssen Pharmaceuticals

William Kevin Kelly

Honoraria: Sanofi

Consulting or Advisory Role: Sanofi

Research Funding: Sanofi (Inst), Novartis (Inst), Janssen Pharmaceuticals (Inst)

Other Relationship: Sanofi

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APPENDIX

FIG A1. Frequency distribution of black and white men across trials. CALGB, Cancer and Leukemia Group B; CALGB 90401 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00110214) identifier: NCT00110214); ENTHUSE 33 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00617669) identifier: NCT00617669); MAINSAIL ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00988208) identifier: NCT00988208); READY ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00744497) identifier: NCT00744497); SWOG, Southwest Oncology Group; SWOG 9916 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00004001) identifier: NCT00004001); SYNERGY ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01188187) identifier: NCT01188187); TAX 327 (Docetaxel Plus Prednisone or Mitoxantrone Plus Prednisone for Advanced Prostate Cancer); VENICE ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00519285) identifier: NCT00519285).

FIG A2. (A) Kaplan-Meier overall survival (OS) curves by race and (B) forest plot with hazard ratios (HRs) comparing black with white men randomly assigned to the DP arm only (reference group, white men; $Q = 9.778$; $df = 8$; $P = .281$; $I^2 = 0.182$). MAINSAIL ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00988208) identifier: NCT00988208); NR, not reported; READY ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00744497) identifier: NCT00744497); SYNERGY ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01188187) identifier: NCT01188187); VENICE ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00519285) identifier: NCT00519285).

FIG A3. (A) Kaplan-Meier overall survival (OS) curves by race and (B) forest plot with hazard ratios (HRs) comparing black men with white men in patients enrolled in the National Cancer Institute National Clinical Trials Network and docetaxel and prednisone arm only (reference group, white men; $Q = 0.441$; $df = 2$; $P = .802$; $I^2 = 0.000$). CALGB, Cancer and Leukemia Group B; CALGB 90401 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00110214) identifier: NCT00110214); SWOG, Southwest Oncology Group; SWOG 0421 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00134056) identifier: NCT00134056). SWOG 9916 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00004001) identifier: NCT00004001).