

2020

Comparative Survival of Asian and White Metastatic Castration-Resistant Prostate Cancer Men Treated With Docetaxel

Susan Halabi

Sandipan Dutta
Old Dominion University, s1dutta@odu.edu

Catherine M. Tangen

Mark Rosenthal

Daniel P. Petrylak

See next page for additional authors

Follow this and additional works at: https://digitalcommons.odu.edu/mathstat_fac_pubs



Part of the [Diseases Commons](#), [Mathematics Commons](#), and the [Statistics and Probability Commons](#)

Original Publication Citation


Halabi, S., Dutta, S., Tangen, C. M., Rosenthal, M., Petrylak, D. P., Thompson, I. M., Jr., . . . Kelly, W. K. (2020). Comparative survival of Asian and white metastatic castration-resistant prostate cancer men treated with Docetaxel. *JNCI Cancer Spectrum*, 4(2), pkaa003 doi:10.1093/jncics/pkaa003

This Article is brought to you for free and open access by the Mathematics & Statistics at ODU Digital Commons. It has been accepted for inclusion in Mathematics & Statistics Faculty Publications by an authorized administrator of ODU Digital Commons. For more information, please contact digitalcommons@odu.edu.

Authors

Susan Halabi, Sandipan Dutta, Catherine M. Tangen, Mark Rosenthal, Daniel P. Petrylak, Ian M. Thompson Jr., Kim N. Chi, Johann S. De Bono, John C. Araujo, Christopher Logothetis, Mario A. Eisenberger, David I. Quinn, Karim Fizazi, Michael J. Morris, Celestia S. Higano, Ian F. Tannock, Eric J. Small, and William Kevin Kelly

Comparative Survival of Asian and White Metastatic Castration-Resistant Prostate Cancer Men Treated With Docetaxel

Susan Halabi , PhD,^{1,*} Sandipan Dutta, PhD,² Catherine M. Tangen, PhD,³ Mark Rosenthal, MD,⁴ Daniel P. Petrylak, MD,⁵ Ian M. Thompson Jr, MD,⁶ Kim N. Chi, MD,⁷ Johann S. De Bono, MD, PhD,⁸ John C. Araujo, MD,⁹ Christopher Logothetis, MD,⁹ Mario A. Eisenberger, MD,¹⁰ David I. Quinn, MD,¹¹ Karim Fizazi, MD, PhD,¹² Michael J. Morris, MD,¹³ Celestia S. Higano, MD,¹⁴ Ian F. Tannock, MD,¹⁵ Eric J Small, MD,¹⁶ William Kevin Kelly, DO¹⁷

¹Department of Biostatistics and Bioinformatics, School of Medicine, Duke University, Durham, NC, USA; ²Department of Mathematics and Statistics, Old Dominion University, Norfolk, VA, USA; ³Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; ⁴Department of Medical Oncology, Peter MacCallum Cancer Centre, Parkville, Australia; ⁵Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁶President, Christus San Rosa Hospital Medical Center, San Antonio, TX, USA; ⁷Medical Oncology, British Columbia Cancer Agency - Vancouver Centre, Vancouver, BC, USA; ⁸Division of Clinical Studies, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, UK; ⁹Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ¹⁰Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; ¹¹Genitourinary Oncology, Department of Medicine University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA; ¹²Medical Oncology, Gustave Roussy, Villejuif, France; ¹³Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; ¹⁴Department of Medicine, University of Washington School of Medicine and Fred Hutchinson Cancer Research Center, Seattle, WA, USA; ¹⁵Department of Medical Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; ¹⁶Department of Medicine, and University of California San Francisco Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; and ¹⁷Medical Oncology and Urology, Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA, USA

*Correspondence to: Susan Halabi, PhD, Department of Biostatistics and Bioinformatics, School of Medicine, Duke University, 2424 Erwin Road, Suite 11088, Durham, NC 27710, USA (e-mail: susan.halabi@duke.edu).

Abstract

There are few data regarding disparities in overall survival (OS) between Asian and white men with metastatic castration-resistant prostate cancer (mCRPC). We compared OS of Asian and white mCRPC men treated in phase III clinical trials with docetaxel and prednisone (DP) or a DP-containing regimen. Individual participant data from 8820 men with mCRPC randomly assigned on nine phase III trials to receive DP or a DP-containing regimen were combined. Men enrolled in these trials had a diagnosis of prostate adenocarcinoma. The median overall survival was 18.8 months (95% confidence interval [CI] = 17.4 to 22.1 months) and 21.2 months (95% CI = 20.8 to 21.7 months) for Asian and white men, respectively. The pooled hazard ratio for death for Asian men compared with white men, adjusted for baseline prognostic factors, was 0.95 (95% CI = 0.84 to 1.09), indicating that Asian men were not at increased risk of death. This large analysis showed that Asian men did not have shorter OS duration than white men treated with docetaxel.

In the United States, the age-adjusted incidence and mortality rates for prostate cancer are much lower for Asian American men compared with white men (1). Individuals of Asian descent are estimated to constitute around 7% of the US population. There are few data regarding disparities in overall outcomes between Asian and white men with metastatic castration-resistant prostate cancer (mCRPC). Moreover, the relative efficacy of docetaxel in Asian men with mCRPC compared with white men is largely unknown because of the small number of Asian men enrolled on the pivotal studies that led to the approval of docetaxel for this indication (2,3). To address these limited data, we performed a pooled analysis of multiple phase

III trials in men with mCRPC treated with docetaxel, with the goal of comparing overall survival (OS) in Asian vs white men.

We included 8820 men who participated in phase III trials of docetaxel and prednisone (DP) vs DP plus an experimental agent (2–11). Men enrolled in these trials between 1990 and 2014 had a diagnosis of prostate adenocarcinoma, developed progressive metastatic disease during androgen deprivation therapy, and, when relevant, progressed despite antiandrogen withdrawal (2–11).

Data on 7952 white and Asian men from nine phase III trials were pooled, regardless of treatment arm, because these trials comparing DP with DP plus an experimental agent had failed to

Received: August 21, 2019; Revised: December 16, 2019; Accepted: January 21, 2020

© The Author(s) 2020. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Table 1. Baseline characteristics of 7952 Asian and white men with mCRPC*

Baseline characteristic	Asian (n = 424)	White (n = 7528)	Total (n = 7952)
Median age (25th, 75th percentile), y	69.0 (62.0, 73.0)	69.0 (63.0, 74.0)	69.0 (63.0, 74.0)
Performance status, %	95.2	94.5	94.5
0	50.4	44.6	44.9
1	44.8	49.9	49.6
Median PSA (25th, 75th percentile), ng/ml	60.1 (19.1, 170.0)	84.9 (30.5, 246.6)	83.5 (29.8, 243.0)
Median alkaline phosphatase (25th, 75th percentile), U/L	150.0 (91.5, 343.5)	138.0 (85.0, 284.0)	138.0 (86.0, 288.0)
Median hemoglobin (25th, 75th percentile), g/dL	12.2 (11.0, 13.4)	13.0 (11.8, 14.2)	13.0 (11.8, 14.1)
Median testosterone (25th, 75th percentile), ng/dL	15.0 (7.3, 25.0)	18.0 (10.0, 26.0)	18.0 (10.0, 26.0)
Site of metastases, %			
LN only	4.5	6.7	6.6
Bone only	46.5	42.4	42.7
Bone + LN	27.4	29.7	29.5
Lung	5.0	9.0	8.8
Liver	12.5	8.4	8.6
Other visceral	3.8	2.8	2.8
Randomized to docetaxel and prednisone arm (%)	56.6	51.7	51.7
Median follow-up time (range)	28.1 (0.0–63.8)	30.8 (0.0–94.2)	30.7 (0.0–94.2)

*LN = Lymph Nodes; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen.

show statistically significant differences in OS between their arms (2–11). The main objective of this analysis was to estimate the adjusted pooled hazard ratio (HR) for death. Two-stage fixed effect approach was used in analyzing the data (12,13). In the first stage, hazard ratios from each of the trials were estimated. In the second stage, estimates from individual trials were combined to obtain an overall estimate of the HR along with the variance. We computed weighted average coefficients, 95% confidence intervals (CI) for the coefficients, and Cochran Q's and I^2 statistics for testing heterogeneity across the trials (12,13). Within each trial, we employed the proportional hazards model (this assumption was not verified) to adjust for age, ECOG performance status, prostate-specific antigen, alkaline phosphatase, hemoglobin, and sites of metastases.

The median age at diagnosis and the proportion of patients with performance status of 0–1 were similar in Asian and white men (Table 1). Baseline laboratory parameters predictive of OS were slightly less favorable in Asian compared with white men (median hemoglobin of 12.2 g/dL vs 13.0 g/dL; median alkaline phosphatase of 150 U/L vs 138 U/L). Proportionally, more Asian men had the liver as a site of metastases than white patients (12.5% vs 8.4%). However, prostate-specific antigen levels were slightly lower in Asian men: 60.1 ng/mL vs 84.9 ng/mL. The median follow-up time was 30.7 months (95% CI = 30.2 to 31.2 months) among surviving patients, with a total of 4969 deaths observed (event rates of 62.7% in Asian and 62.5% in white men).

The median OS were 18.8 months (95% CI = 17.4 to 22.1 months) and 21.2 months (95% CI = 20.8 to 21.7 months) for Asian and white men, respectively (Figure 1A). However, when adjusting for important prognostic factors, the pooled hazard ratio for death in Asian men was 0.95 (95% CI = 0.84 to 1.09; Figure 1B) vs white men, demonstrating that Asian men had no statistically significant differences in their risk of death.

Focusing on men who participated in the “National Cancer Institute” National Clinical Trials Network (NCI NCTN) trials is critical because these studies enrolled patients in the United States, and complete information on race and ethnicity was collected. When the three NCI NCTN trials were considered separately, the median OS was shorter in Asian men (15.8 months, 95% CI = 11.4 to 27.6 months) than white men (20.0 months, 95%

CI = 19.2 to 20.9 months). In the 2022 white and 28 Asian men who were enrolled in the NCI NCTN trials, the pooled multivariable hazard ratio for death for Asian vs white men was 1.24 (0.81– 1.89) (See new [supplementary Figure 1A](#), available online). This difference might reflect true differences in outcomes for the NCI NCTN Asian men, or simply the very small number of Asian men accrued to the NCI NCTN trials. Thus, caution should be exerted in interpreting the pooled hazard ratio from the NCI NCTN trials.

In 4108 patients treated with DP alone, the median OS were 18.4 months (95% CI = 15.9 to 22.2 months) and 20.8 months (95% CI = 20.1 to 21.5 months) in Asian and white patients, respectively. In multivariable analysis, the pooled hazard ratio for death was 1.04 (95% CI = 0.86 to 1.24) ([Supplementary Figure 1B](#), available online). Several authors indicated that Asian men have less tolerance for docetaxel, and thus their dose is often lower than the standard dose of 75 mg/m² (14–19). In this analysis, we had no access to dosing information or limited information about toxicity and are unable to confirm that docetaxel is poorly tolerated in the Asian population.

The main limitation of this analysis is that the patient population was highly selected. Also, this study does not account for heterogeneity among the population of Asian men with prostate cancer, and race was not further categorized in these clinical trials. It is possible that Asian men born or living in the United States might have different characteristics and outcomes to Asian men living in Asia.

A striking difference in terms of accrual patterns between industry and the NCI NCTN trials was observed in these trials. Whereas the industry trials, which were mostly conducted outside the United States, were successful in enrolling a higher proportion of Asian patients with mCRPC (6%), the US-based NCTN trials lagged behind and only enrolled 1% (28 patients) ([Supplementary Figure 2](#), available online). The proportion of Asian patients enrolled on the US-based NCTN trials is much lower than the estimated US Asian population of about 6% and much lower than the 3.4% of Asian patients who are diagnosed with prostate cancer. This observation has been confirmed in other analyses (20–23). Barriers to participation of underrepresented populations in cancer trials include clinical, structural, and attitudinal (physicians and patients) factors and vary by demographic and socioeconomic

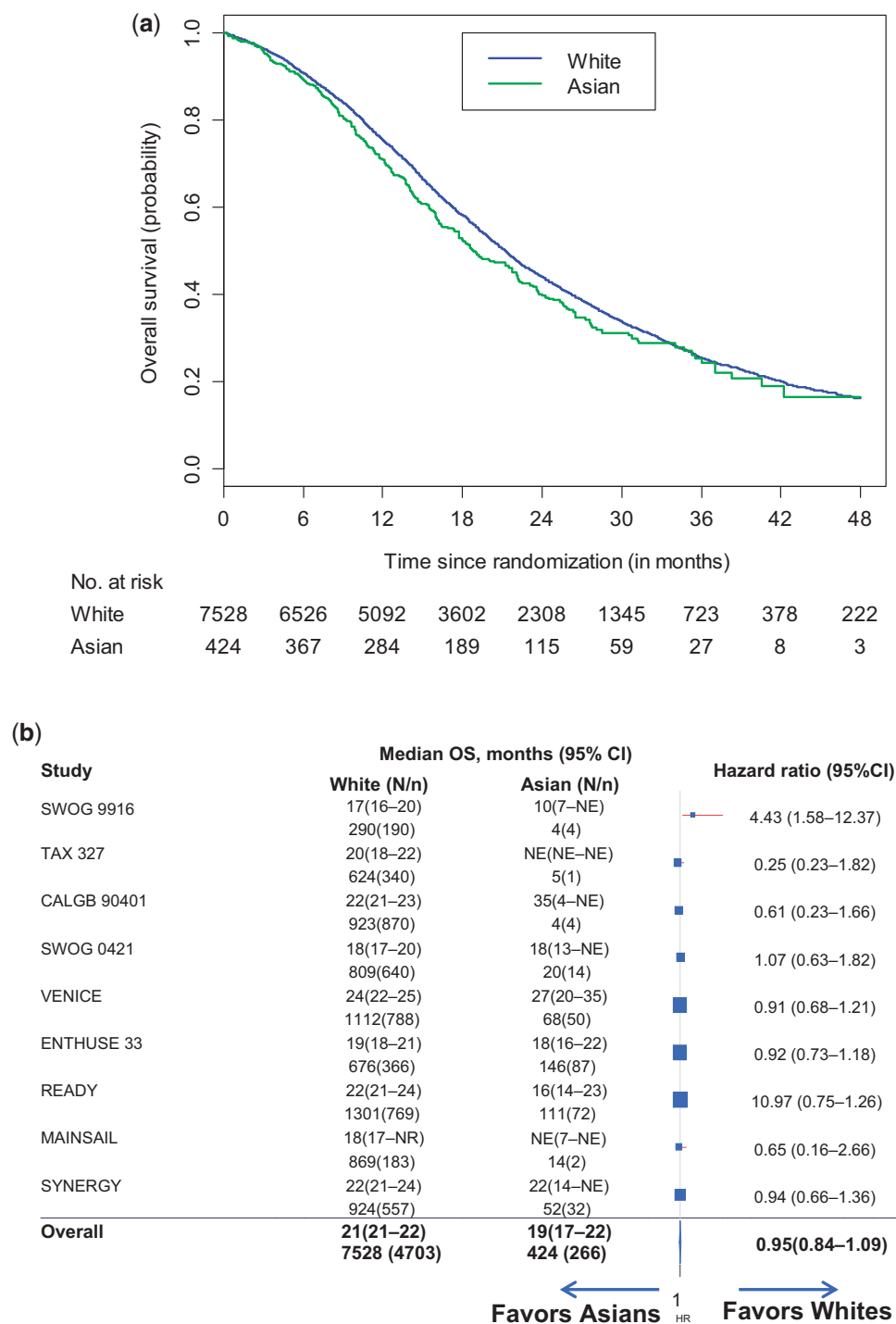


Figure 1. (A) Kaplan–Meier overall survival (OS) curves by white and Asian patients. (B) Forest plot with hazard ratios (HR) for OS comparing Asian men with white men (reference group = white men; $Q=11.721$, $df=8$, $P=0.164$; $I^2=0.317$). CI = confidence interval; N = number of patients; n = number of deaths; NE = not estimated.

factors (24–26). Specific reasons for lack of participation of Asian patients in clinical trials are largely unknown because this population is understudied. Efforts to increase participation of Asian patients with mCRPC in prostate cancer trials are urgently needed.

Funding

This research was supported in part by the US Army Medical Research W81XWH-15-1-0467 and in part by National Institutes

of Health/National Cancer Institute grant awards to SWOG, U10CA180888 and U10CA180819.

Notes

Conflicts of Interest: SH reports other from Bayer, Eisai and Ferring; outside the submitted work; DPP Consultant fees: Ada Cap (Advanced Accelerator Applications), Amgen, Astellas,

AstraZeneca, Bayer, Bicycle Therapeutics (added 1/2020), Boehringer Ingelheim, Bristol Myer Squibb, Clovis, Eli Lilly, Exelixis, Incyte, Janssen, Pfizer, Pharmacyclics, Roche Laboratories, Seattle Genetics, Urogen. Grant Support: Ada Cap (Advanced Accelerator Applications), Astellas, AstraZeneca, Bayer, Bristol Myer Squibb, Clovis, Eli Lilly, Endocyte, Genentech, Innocrin, MedImmune, Merck, Novartis, Pfizer, Progenics, Roche Laboratories, Sanofi Aventis, Seattle Genetics ; Ownership interest/investment: Bellicum, Tyme (sold 10/2019); KC reports grants and personal fees from Janssen, Astellas, Sanofi, Bayer, Roche, and AstraZeneca, outside the submitted work; JDB has served on advisory boards and received fees from many companies including Astra Zeneca, Astellas, Bayer, Boehringer Ingelheim, Cellcentric, Daiichi, Genentech/Roche, Genmab, GSK, Janssen, Merck Serono, Merck Sharp & Dohme, Menarini/Silicon Biosystems, Orion, Pfizer, Qiagen, Sanofi Aventis, Sierra Oncology, Taiho, Vertex Pharmaceuticals. He is an employee of The ICR, which have received funding or other support for his research work from AZ, Astellas, Bayer, Cellcentric, Daiichi, Genentech, Genmab, GSK, Janssen, Merck Serono, MSD, Menarini/Silicon Biosystems, Orion, Sanofi Aventis, Sierra Oncology, Taiho, Pfizer, Vertex, and which has a commercial interest in abiraterone, PARP inhibition in DNA repair defective cancers and PI3K/AKT pathway inhibitors (no personal income). He was named as an inventor, with no financial interest, for patent 8,822,438. He has been the CI/PI of many industry sponsored clinical trials. JDB is a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in this article are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health; CL reports honoraria and consultant fees from Sanofi, Bayer, Janssen, Astellas Pharma. In addition, he reports research grants from Sanofi, Bayer, Janssen, Astellas Pharma and Pfizer; DIQ reports Compensated consultant: Astellas, Bayer, BMS, Advanced Accelerator Applications, Roche/Genentech, Janssen, Merck, Novartis, Pfizer. Travel: Astellas, Bayer, BMS, Genentech, Merck, Pfizer. Research to institution: Bayer, BMS, Roche/Genentech, Merck, Pfizer; KF : Participation to advisory boards/honorarium for: Astellas, Bayer, Curevac, Janssen, MSD, Orion, Sanofi ; MJM reports consultant fees from Bayer, Endocyte, Advanced Accelerator Applications, Blue Earth Diagnostics, Tokai Pharmaceuticals, Tolmar Pharmaceuticals, ORIC Pharmaceutical. Travel: Bayer, Endocyte. In addition he reports research funding to the institution from Bayer, Sanofi, Endocyte, Progenics, Corcept Therapeutics, Roche/Genentech; CSH reports other from Aptevo, Aragon Pharma, Astellas, AstraZeneca, Bayer, Clovis, Dendreon, EFFECTOR Therapeutics, Emergent, Ferring, Genentech, Hoffman-Larocche, Medivation, and Pfizer. She reports personal fees from Aptevo, Asana, Astellas, Bayer, Blue Earth Diagnostics, Pharma, fees from Clovis, Dendreon, Endocyte, Ferring, Hinova, Janssen, Merck, Myriad, Orion, Pfizer, Tolmar, Carrick Therapeutics, Novartis, outside the submitted work; IFT reports other from Sanofi, during the conduct of the study; other from Janssen, Bayer, Roche-Genentech, outside the submitted work; EJS reports consultant fees and honoraria from Fortis, Janssen Oncology, Beigene, Tolero Pharmaceuticals. Travel from Janssen. In addition, he reports research grants to institution from Janssen, Merck; These authors have no COI (Drs. Halabi, Dutta, Tangen, Rosenthal, Thompson Jr, Araujo, Eisenberger, Kelly).

This analysis was approved by the Duke University Medical Center Instructional Review Board. The authors would like to thank the Alliance, SWOG, AstraZeneca, BMS, Celgene, Oncogenex, Regeneron, and Sanofi for sharing their data and making this analysis possible. The funders had no role in this research.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019; 69(1):7–34.
2. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004; 351(15):1502–1512.
3. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004;351(15):1513–1520.
4. Scher HI, Jia X, Chi K, et al. Randomized, open-label phase III trial of docetaxel plus high-dose calcitriol versus docetaxel plus prednisone for patients with castration-resistant prostate cancer. *J Clin Oncol.* 2011;29(16):2191–2198.
5. Kelly WK, Halabi S, Carducci M, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol.* 2012;30(13):1534–1540.
6. Araujo JC, Trudel GC, Saad F, et al. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. *Lancet Oncol.* 2013;14(13):1307–1316.
7. Fizazi K, Higano CS, Nelson JB, et al. Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol.* 2013;31(14):1740–1747.
8. Quinn DI, Tangen CM, Hussain M, et al. Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): a randomised phase 3 trial. *Lancet Oncol.* 2013;14(9):893–900.
9. Tannock IF, Fizazi K, Ivanov S, et al. Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomised trial. *Lancet Oncol.* 2013;14(8):760–768.
10. Petrylak DP, Vogelzang NJ, Budnik N, et al. Docetaxel and prednisone with or without lenalidomide in chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (MAINSAIL): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol.* 2015;16(4):417–425.
11. Chi KN, Higano CS, Blumenstein B, et al. Custirsen in combination with docetaxel and prednisone for patients with metastatic castration-resistant prostate cancer (SYNERGY trial): a phase 3, multicentre, open-label, randomised trial. *Lancet Oncol.* 2017;18(4):473–485.
12. Halabi S, Kelly WK, Ma H, et al. Meta-analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. *J Clin Oncol.* 2016;34(14):1652–1659.
13. Halabi S, Dutta S, Tangen CM, et al. Overall survival of black and white men with metastatic castration-resistant prostate cancer treated with docetaxel. *J Clin Oncol.* 2019;37(5):403–410.
14. Ang JW, Tan MH, Tay MH, Toh CK, Ng QS, Kanesvaran R. Outcomes of dose-attenuated docetaxel in Asian patients with castrate-resistant prostate cancer. *Ann Acad Med Singapore.* 2017;46(5):195–201.
15. Kita Y, Shimizu Y, Inoue T, Kamba T, Yoshimura K, Ogawa O. Reduced-dose docetaxel for castration-resistant prostate cancer has no inferior impact on overall survival in Japanese patients. *Int J Clin Oncol.* 2013;18(4):718–723.
16. Zhou T, Zeng SX, Ye DW, et al. A multicenter, randomized clinical trial comparing the three-weekly docetaxel regimen plus prednisone versus mitoxantrone plus prednisone for Chinese patients with metastatic castration refractory prostate cancer. *PLoS One.* 2015;10(1):e0117002.
17. Poon DMC, Chan T, Chan K, et al. Preliminary efficacy and tolerability of chemohormonal therapy in metastatic hormone-naïve prostate cancer: the first real-life experience in Asia. *Asia Pac J Clin Oncol.* 2018;14(4):347–352.
18. Poon DM, Ng J, Chan K. Importance of cycles of chemotherapy and postdocetaxel novel therapies in metastatic castration-resistant prostate cancer. *Prostate Int.* 2015;3(2):51–55.
19. Kim HS, Lee JY, Lee SJ, et al. A retrospective feasibility study of biweekly, reduced-dose docetaxel in Asian patients with castrate-resistant, metastatic prostate cancer. *BMC Urol.* 2017;17(1):63.
20. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA.* 2004;291(22):2720–2726.
21. Alexander GA, Chu KC, Ho R. Representation of Asian Americans in clinical cancer trials. *Ann Epidemiol.* 2000;10(8):S61–S67.
22. Paterniti DA, Chen MS, Chiechi C, et al. Asian Americans and cancer clinical trials: a mixed-methods approach to understanding awareness and experience. *Cancer.* 2005;104(S12):3015–3024.

23. Chen MS, Lara PN, Dang JHT, Paterniti DA, Kelly K. Twenty years post-NIH revitalization act: renewing the case for enhancing minority participation in cancer clinical trials. *Cancer*. 2014;120(Suppl 7):1091–1096.
24. Duma N, Aguilera JS, Paludo J, et al. Representation of minorities and women in oncology clinical trials: review of the past 14 years. *J Oncol Pract*. 2018;14(1):e1–e10.
25. Unger JM, Cook E, Tai E, Bleyer A. Role of clinical trial participation in cancer research: barriers, evidence, and strategies. *Am Soc Clin Oncol Educ Book*. 2016;35:185–198.
26. Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. *J Natl Cancer Inst*. 2019;111(3):245–55.