

Prostate-Specific Antigen Changes As Surrogate for Overall Survival in Men With Metastatic Castration-Resistant Prostate Cancer Treated With Second-Line Chemotherapy

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ABSTRACT

Purpose

Prostate-specific antigen (PSA) kinetics, and more specifically a $\geq 30\%$ decline in PSA within 3 months after initiation of first-line chemotherapy with docetaxel, are associated with improvement in overall survival (OS) in men with metastatic castration-resistant prostate cancer (mCRPC). The objective of this analysis was to evaluate post-treatment PSA kinetics as surrogates for OS in patients receiving second-line chemotherapy.

Patients and Methods

Data from a phase III trial of patients with mCRPC randomly assigned to cabazitaxel plus prednisone (C + P) or mitoxantrone plus prednisone were used. PSA decline ($\geq 30\%$ and $\geq 50\%$), velocity, and rise within the first 3 months of treatment were evaluated as surrogates for OS. The Prentice criteria, proportion of treatment explained (PTE), and meta-analytic approaches were used as measures of surrogacy.

Results

The observed hazard ratio (HR) for death for patients treated with C + P was 0.66 (95% CI, 0.55 to 0.79; $P < .001$). Furthermore, a $\geq 30\%$ decline in PSA was a statistically significant predictor of OS (HR for death, 0.52; 95% CI, 0.43 to 0.64; $P < .001$). Adjusting for treatment effect, the HR for a $\geq 30\%$ PSA decline was 0.50 (95% CI, 0.40 to 0.62; $P < .001$), but treatment remained statistically significant, thus failing the third Prentice criterion. The PTE for a $\geq 30\%$ decline in PSA was 0.34 (95% CI, 0.11 to 0.56), indicating a lack of surrogacy for OS. The values of R^2 were < 1 , suggesting that PSA decline was not surrogate for OS.

Conclusion

Surrogacy for any PSA-based end point could not be demonstrated in this analysis. Thus, the benefits of cabazitaxel in mediating a survival benefit are not fully captured by early PSA changes.

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INTRODUCTION

Investigators have long been challenged by the lack of surrogate end points for clinical trials in men with metastatic castration-resistant prostate cancer (mCRPC).¹⁻⁵ True surrogacy requires meeting several rigorous statistical criteria defined by Prentice (Prentice criteria).⁶ The degree of surrogacy can also be measured by the proportion of treatment effect explained (PTE).⁷ Reductions in serum prostate-specific antigen (PSA) with systemic therapy may reflect reductions in tumor burden, which may be linked to improved long-term outcomes; this has been a natural intermediate end point to assess surrogacy. Kelly et al¹ first proposed the use of post-therapy changes in PSA from baseline as an intermediate marker of response in patients with

mCRPC. Numerous subsequent reports confirmed that patients with mCRPC who had experienced $\geq 50\%$ decline in PSA from baseline had improved survival, compared with those patients who did not achieve $\geq 50\%$ reduction in PSA.²⁻⁴ In retrospective studies, several investigators have reported that PSA decline $\geq 50\%$ correlated with improved survival. Not all investigators have correlated PSA decline from baseline with improved survival.^{8,9} However, Petrylak et al^{10,11} demonstrated that both $\geq 30\%$ and $\geq 50\%$ decline in PSA satisfied the Prentice criteria in patients with mCRPC treated with first-line chemotherapy, whereas $\geq 50\%$ decline in PSA failed to meet the surrogacy criteria as measured by PTE. By contrast, Armstrong et al¹² found that although $\geq 30\%$ decline in PSA after docetaxel treatment in the phase III TAX327 trial fulfilled the

Prentice criteria, the degree of surrogacy as measured by PTE in this decline was modest.¹³ Evidence to support PSA decline as a surrogate for overall survival (OS) across multiple agent classes and mechanisms of action is lacking.

The primary objective of this analysis was to evaluate whether $\geq 30\%$ decline in PSA within 3 months of treatment initiation was a surrogate end point of OS in patients with mCRPC receiving second-line chemotherapy (cabazitaxel or mitoxantrone) after progression with docetaxel. A secondary objective was to assess whether $\geq 50\%$ decline in PSA was a surrogate end point for OS. In addition, we performed exploratory analysis of other PSA kinetics as surrogate end points for OS.

PATIENTS AND METHODS

Patients

This analysis used data from the TROPIC trial, a phase III trial of 755 men with mCRPC previously treated with a docetaxel-containing regimen.¹⁴ Participants were randomly assigned to receive either 12 mg/m² mitoxantrone intravenously over 15 to 30 minutes plus oral prednisone 10 mg daily (M + P) or cabazitaxel 25 mg/m² administered over 1 hour every 3 weeks in combination with prednisone (C + P). Eligible patients had progressive mCRPC after treatment with a docetaxel-based regimen, Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate hematologic, hepatic, renal, and cardiac function. Those who received mitoxantrone, radiotherapy, or other cancer therapies within 4 weeks before enrollment were excluded. Details of eligibility have been previously reported.¹⁴

End Points

The primary end point of the clinical trial was OS, which was defined as the time from random assignment to date of death resulting from any cause. Secondary end points were $\geq 50\%$ decline in PSA using the Prostate Cancer Working Group 2 criteria.¹⁵ Serum PSA was measured at baseline and then every 3 weeks until progression, with a PSA response per protocol defined as $\geq 50\%$ decline from baseline PSA, if baseline PSA was > 0.2 ng/mL and was maintained for at least 3 weeks.

For the purposes of this analysis, the surrogate end point to be examined was $\geq 30\%$ decline in PSA. The rationale for using this end point as a binary was to confirm the findings reported in patients with mCRPC after docetaxel treatment.^{11,12} Similar to previous studies, $\geq 30\%$ was defined as a decline $\geq 30\%$ from the baseline PSA measurement at any time within the first 90 days of treatment.^{11,12} In a case in which confirmation was required, there had to be a second consecutive decline at least 21 days after the first decline. Ranges of PSA decline/rise and velocity were explored as markers of OS. PSA velocity was calculated as the slope of log PSA (log₂ scale) by time based on the least squares method using at least two postbaseline PSA measurements. PSA rise was computed as percent increase from the baseline PSA measurement. An indicator variable was created if the percent value was \geq the percent specified in the analysis.

Data Analysis

As part of a research federal grant, this analysis was approved by the Duke University Institutional Review Board. We used the logistic regression model to test whether treatment arm predicted $\geq 30\%$ and $\geq 50\%$ decline in PSA and employed three different approaches to evaluate whether PSA decline or PSA rise was a surrogate end point for OS. These approaches were: one, Prentice criteria; two, PTE; and three, meta-analysis. The Prentice criteria define a surrogate as a “response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true end point.”^{6(p432)} To test the Prentice criteria, we fit a series of three proportional hazards models of OS with the following covariates: model one, included treatment arm; model two, included PSA decline (or rise) as a surrogate marker; and model three, included both treatment arm and PSA decline (or rise). To fulfill the Prentice

criteria, a marker is considered a surrogate end point if it is statistically significantly associated ($P < .05$) with OS in both univariate models. However, in the multivariable model, the marker but not treatment arm needs to be statistically significant. The Schoenfeld test was used to check for the proportional hazards assumption, and there was no evidence that this was violated in these three models.¹⁶

PTE is obtained from two proportional hazards models and is computed as 1 minus the ratio of the estimated regression coefficient for treatment effect in model three (adjusted) over estimated regression coefficient for treatment arm in model one (unadjusted).⁷ A value of 1 for the PTE indicates a perfect surrogate end point, whereas a value of 0 represents no surrogacy. The 95% CI for PTE was computed using a nonparametric bootstrapped procedure to estimate the variance-covariance matrix of the estimated regression coefficients for unadjusted and adjusted treatment effects (models one and three).⁷

Following Burzykowski et al¹⁷ and Busye et al,¹⁸ we considered a meta-analytic approach to assess the surrogacy of PSA decline for OS. The meta-analysis procedure allows one to evaluate the surrogacy from individual and trial levels. The trial level assessed the overall prediction power of the surrogate end point on the true end point, whereas the individual level evaluated the strength of the dependency between surrogate end point and true end point after adjusting for the treatment effect. A surrogate end point is considered valid if it presents a high degree (closer to one) of association at both the trial and individual levels.

The data in this report were from a single trial, and to implement the meta-analysis framework, we randomly partitioned the TROPIC data into five clusters and assumed that each cluster was obtained from an independent trial. The number five was chosen to ensure the number of patients in each treatment group was ≥ 50 within each fold. Because the partitioning was performed randomly, the procedure was repeated 500 times. The global odds ratio (OR) and R² were averaged over 500 replicates.

The Kaplan-Meier estimator was used to estimate the OS distributions by patients who experienced and did not experience $\geq 30\%$ and $\geq 50\%$ decline in PSA. R software (R Foundation for Statistical Computing, Vienna, Austria) was used for the data analyses, and all statistical tests were two sided.

RESULTS

Baseline Characteristics

Of the 755 patients enrolled onto the TROPIC trial, 17 patients did not have PSA data at baseline, and 85 patients had PSA < 0.20 ng/mL and were excluded from the analysis. The current analysis was based on 653 patients (86%) who had sufficient PSA data post-treatment. Participants in this analysis had similar baseline characteristics compared with patients who did not have PSA decline data. Moreover, the survival distributions were not different between patients who were and were not included in the analysis (log-rank $P = .852$).

Baseline clinical and laboratory characteristics of the 653 patients are summarized in Table 1. A majority were white, with a median age of 67 years; 91% had Eastern Cooperative Oncology Group performance status of 0 to 1; 54% had measurable disease. Median PSA was 170 ng/mL (interquartile range [IQR], 68 to 465). There were no differences between the two arms with respect to baseline variables (Table 1).

PSA Decline

Median PSA decline in each arm was 31.1% (IQR, 0 to 61.4) and 0% (IQR, 0 to 31.2) for C + P and M + P, respectively. Two hundred fifty men (38%) experienced $\geq 30\%$ decline in PSA from baseline (51% with C + P; 26% with M + P), whereas 25% of patients had $\geq 50\%$ decline in PSA (33% with C + P; 26% with M + P). Treatment

Table 1. Baseline Characteristics of Patients With PSA Decline Data by Treatment Arm

Characteristic	M + P (n = 325)	C + P (n = 328)	Total (N = 653)
Age, years			
Median	67	68	67
25th and 75th percentile	62-73	62.75-73	62-73
Race, %			
White	81	86	84
Asian	9	6	8
Black	6	5	6
Other	3	3	3
ECOG PS, %			
0	32	39	35
1	59	54	56
2	10	7	8
Disease extent, %			
Metastatic	95	97	96
Bone	89	83	86
Visceral	25	23	24
Locoregional	4	3	4
PSA, ng/mL			
Median	169.5	169.5	169.5
25th and 75th percentile	68.4-479.2	68.6-449.5	68.4-465.0
Alkaline phosphatase, U/L			
Median	153.5	149.5	150.5
25th and 75th percentile	94.2-312.0	82.2-288.5	89.0-300.0
Hemoglobin, g/L			
Median	120	119	120
25th and 75th percentile	109.0-130.0	109.4-129.2	109.0-130.0
Measurable disease, %	56	53	54
Baseline pain, %	46	49	48
Prior hormonal therapy, %			
Hormonal	99	99	99
Irradiation	62	65	64
Surgery	54	52	53
Biologic	10	8	9
No. of chemotherapy lines, %			
1	70	67	69
2	22	26	24
≥ 2	8	7	8
No. of docetaxel regimens, %			
1	86	84	85
2	12	14	13
≥ 2	2	2	2

Abbreviation: C + P, cabazitaxel plus prednisone; ECOG PS, Eastern Cooperative Oncology Group performance status; M + P, mitoxantrone plus prednisone; PSA, prostate-specific antigen.

arm significantly predicted $\geq 30\%$ decline in PSA for patients receiving C + P (OR, 3.02; 95% CI, 2.17 to 4.21; $P < .001$) compared with patients receiving M + P.

There were 449 deaths observed among 653 patients, and median follow-up time among 204 surviving patients was 16.4 months (95% CI, 14.8 to 18.5). Median OS by PSA decline by arm is listed in Table 2.

Test for Surrogacy

The Prentice criteria. Prentice operational criteria were applied.⁶ First, treatment arm was a statistically significant predictor of OS (Fig 1A). The observed hazard ratio (HR) for death for patients treated with C + P was 0.66 (95% CI, 0.55 to 0.79; $P < .001$) compared with

Table 2. OS by Treatment Arm and Percent Decline in PSA Within 3 Months of Treatment

Decline in PSA (%)	M + P		C + P		Total
	No. of Patients	Median OS (months)	No. of Patients	Median OS (months)	Median OS (months)
≥ 0	154	15.1	242	16.3	15.6
≥ 5	143	14.8	237	16.3	15.5
≥ 10	129	14.8	221	16.5	15.5
≥ 20	108	15.2	192	16.7	15.9
≥ 25	94	15.2	178	17.2	16.1
≥ 30	83	15.4	167	17.2	16.2
≥ 40	67	15.2	143	18.0	16.6
≥ 50	55	15.2	108	19.7	16.9
≥ 60	43	15.1	84	20.5	17.8
≥ 70	25	14.5	59	22.6	17.2
≥ 80	14	15.1	44	NA	22.6
≥ 90	7	10.6	21	22.6	22.6

Abbreviations: C + P, cabazitaxel plus prednisone; M + P, mitoxantrone plus prednisone; OS, overall survival; PSA, prostate-specific antigen.

patients treated with M + P. The observed median survival times were 15.0 (95% CI, 14.0 to 16.3) and 12.7 months (95% CI, 11.2 to 13.6) for C + P and M + P, respectively. Second, $\geq 30\%$ decline in PSA was a statistically significant predictor of OS, with an HR for death of 0.52 (95% CI, 0.43 to 0.64; $P < .001$) among patients who experienced $\geq 30\%$ PSA decline compared with those who did not (Fig 1B). Third, in a multivariable model with $\geq 30\%$ PSA decline and treatment arm, both PSA decline and treatment arm remained statistically significant. The adjusted HR for treatment arm was 0.76 (95% CI, 0.62 to 0.92; $P < .005$). Because of this, the third Prentice criterion was not met.

In addition, $\geq 50\%$ decline in PSA was also tested for surrogacy of OS. Following the same steps described in the previous paragraph, treatment arm significantly predicted $\geq 50\%$ decline in PSA with patients treated with C + P having an OR of 2.41 (95% CI, 1.66 to 3.49; $P < .001$) compared with patients treated with M + P. PSA decline $\geq 50\%$ from baseline was also a statistically significant predictor of OS (HR for death, 0.56; 95% CI, 0.44 to 0.71; $P < .001$) among patients who experienced $\geq 50\%$ PSA decline compared with those who did not (Fig 2). The observed median survival times were 15.0 (95% CI, 14.0 to 16.3) and 12.7 months (95% CI, 11.3 to 13.6) for C + P and M + P, respectively. Similar to the analysis for $\geq 30\%$ PSA decline in PSA, after adjusting for $\geq 50\%$ PSA decline, treatment arm remained a statistically significant predictor of survival. The adjusted HR for death for patients treated with C + P was 0.71 (95% CI, 0.59 to 0.86; $P = .005$) compared with patients treated with M + P. Thus, $\geq 50\%$ decline in PSA also failed to meet the third Prentice criterion.

PSA decline as a continuous surrogate end point was also explored as a potential surrogate of OS. In multivariable analysis, the adjusted HR for death decline for patients treated with C + P was 0.78 (95% CI, 0.64 to 0.95; $P = .01$) compared with patients treated with M + P. Thus, PSA decline as a continuous outcome did not meet the third criterion of Prentice.

PTE. As a measure of degree of surrogacy within this trial, the PTE analysis of the 0% to 90% decline in PSA within 3 months after treatment was undertaken. PTE for $\geq 30\%$ decline in PSA was 0.34 (95% CI, 0.11 to 0.56), whereas PTE for $\geq 50\%$ decline in PSA was

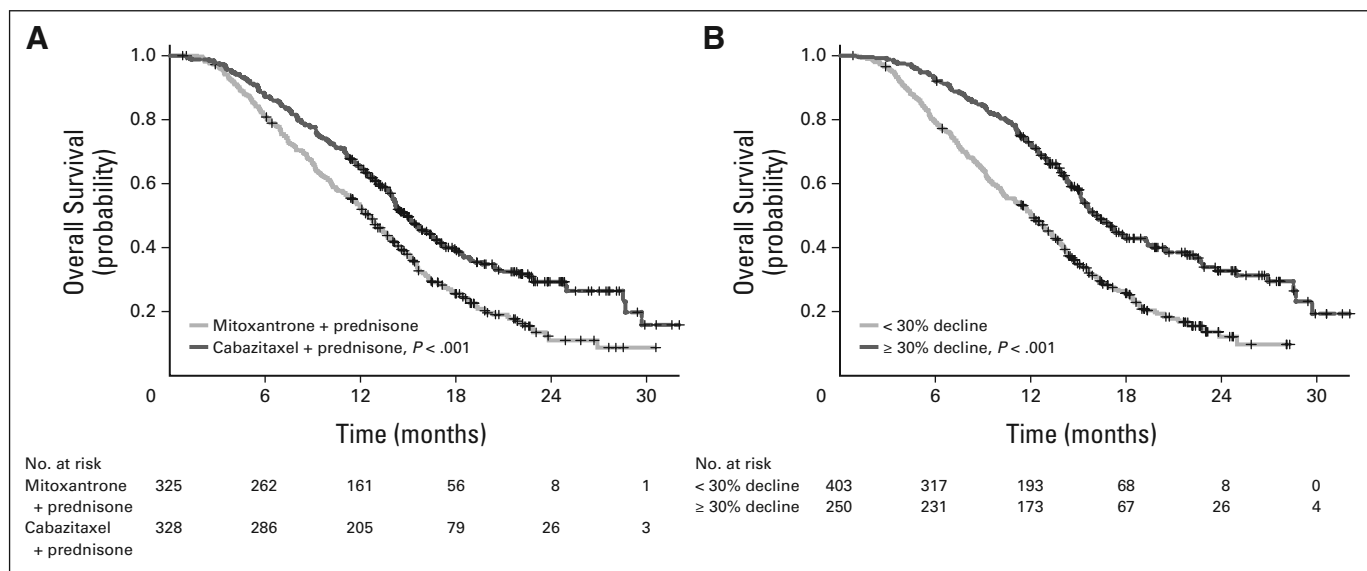


Fig 1. (A) Treatment arm predicting for overall survival. (B) Greater than or equal to 30% decline in prostate-specific antigen predicting overall survival.

0.20 (95% CI, 0.05 to 0.35). The lower bound of the 95% CI did not exceed 0.50, suggesting a lack of surrogacy (Appendix Fig A1A, online only). A similar analysis using a confirmatory PSA value after a decline of either $\geq 30\%$ or $\geq 50\%$ failed to provide evidence of surrogacy for survival.

PSA rise. Exploratory analyses of a 0% to 90% rise in PSA within 3 months after treatment were performed (Appendix Fig A1B, online only). The lower bounds of the 95% CI were < 0.50 , implying a lack of surrogacy for PSA rise. The results were similar when confirmation of PSA rise was required, with the lower bound not meeting the PTE requirement for surrogacy (data not shown).

Meta-analytic approach. Associations between $\geq 30\%$ and $\geq 50\%$ decline in PSA and OS are presented in Figure 3. At the individual level, global ORs for $\geq 30\%$ (Fig 3A) and $\geq 50\%$ decline in PSA were 2.46 (95% CI, 2.45 to 2.47) and 2.08 (95% CI, 2.07 to 2.09), respectively (Fig 3C). At the trial level, R^2 s for $\geq 30\%$ and

$\geq 50\%$ decline in PSA were 0.30 (95% CI, 0.27 to 0.32; Fig 3B) and 0.27 (95% CI, 0.25 to 0.3; Fig 3D), respectively. The association between PSA decline as a continuous surrogate and OS is shown in Appendix Figure A2 (online only). R^2 s were 0.62 (95% CI, 0.61 to 0.62) and 0.50 (95% CI, 0.47 to 0.52) at the individual and trial levels, respectively. The values of R^2 were < 1 , suggesting that PSA decline is not a surrogate for OS.

DISCUSSION

In this analysis, surrogacy for any PSA-based end point could not be demonstrated using either the Prentice criteria or PTE. In addition, an analysis based on split sample in random subgroups did not demonstrate trial-level surrogacy. Although surrogacy for some PSA-based end points has been met in patients with mCRPC receiving primary docetaxel-based chemotherapy, surrogacy does not seem to be maintained for second-line chemotherapy used in the postdocetaxel setting. To our knowledge, this is the first analysis of these surrogate end points in patients receiving second-line chemotherapy.

OS remains the gold-standard end point in phase III trials of mCRPC, and although retrospective analyses have demonstrated some modest degree of surrogacy for PSA decline, these intermediate end points have not been prospectively validated.^{11,12,19} The need for surrogate markers of OS will only increase as more agents are approved for the treatment of patients with mCRPC.²⁰⁻²³ Fortunately, these agents lead to prolonged survival for patients; however, their open-label use will push survival farther out. Moreover, their use subsequent to clinical-trial treatment may reduce the hypothesized effect size of the therapies being evaluated.²⁰⁻²³ The dilution will require larger trial sizes, longer follow-up periods, or larger effect sizes if OS is to be used as the primary end point, all of which make the OS end point less desirable.

It has become increasingly common to use $\geq 30\%$ decline in PSA as an end point for all patients with mCRPC based on the original first-line data. It is with these concerns in mind that we evaluated the

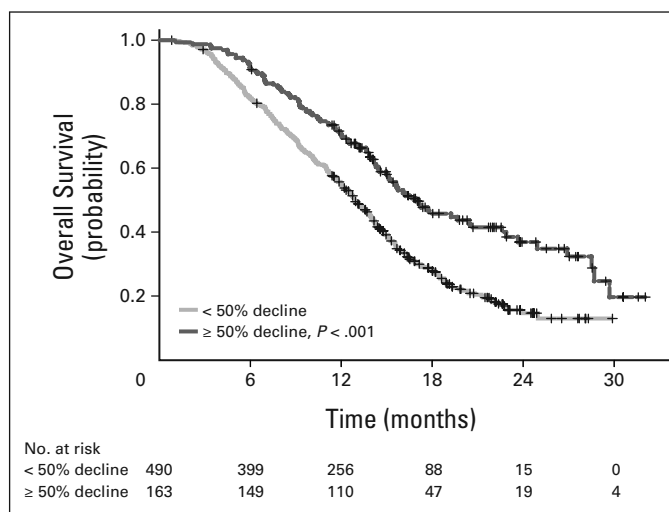


Fig 2. Greater than or equal to 50% decline in prostate-specific antigen predicting overall survival.

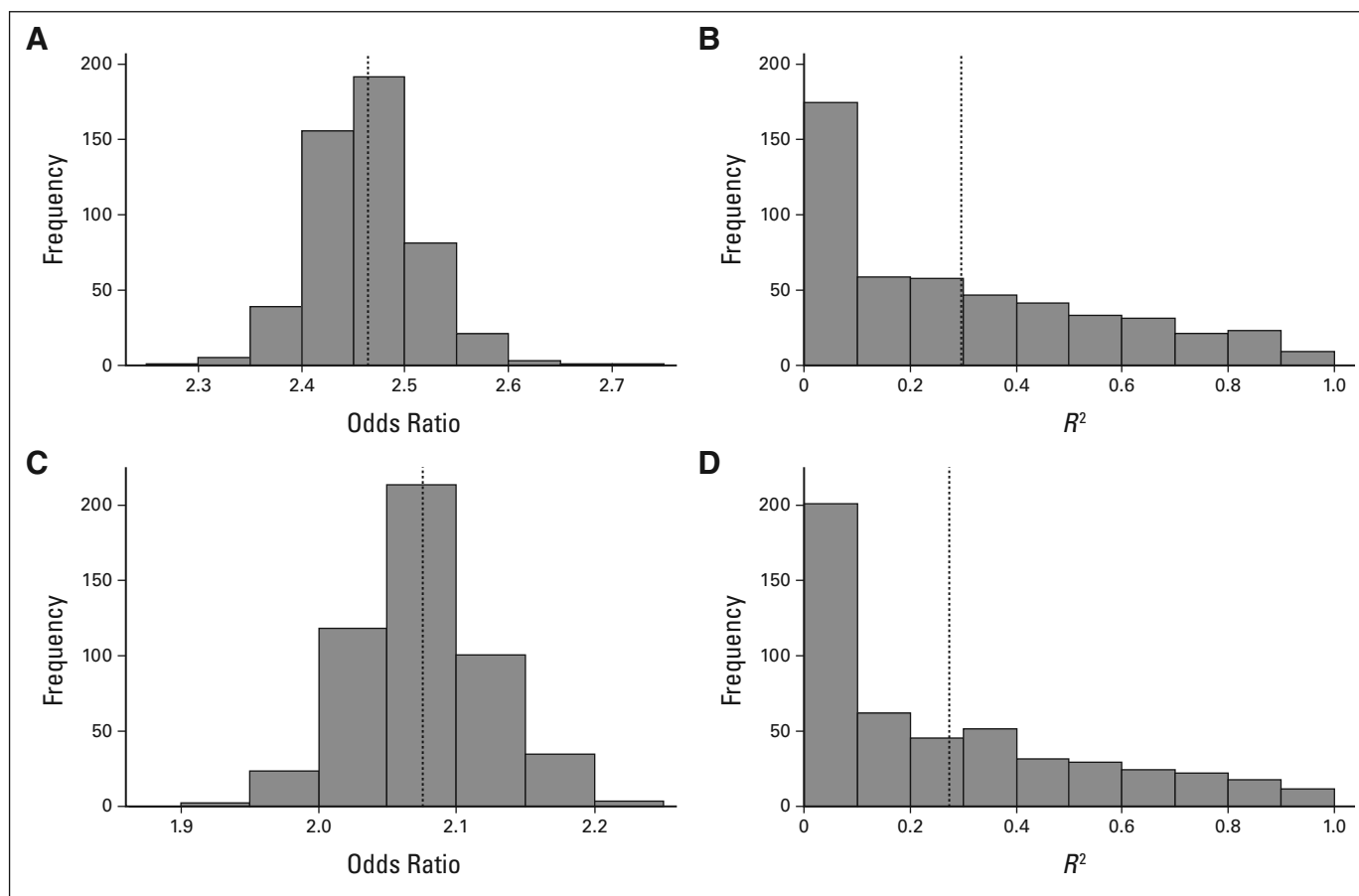


Fig 3. (A, C) Individual and (B, D) trial-level effects for (A, B) $\geq 30\%$ and (C, D) $\geq 50\%$ decline in prostate-specific antigen. Dashed line indicates empirical mean.

utility of PSA kinetics as surrogates for OS in patients with mCRPC in a trial involving second-line chemotherapy. Our analysis impugns the utility of PSA or PSA kinetics as surrogates for OS in patients with mCRPC receiving second-line chemotherapy. Furthermore, the data demonstrate that there are different disease states within the group of patients with mCRPC. There are a number of potential explanations for why PSA kinetics may have some utility as a surrogate in patients treated with first-line chemotherapy, but not those treated with second-line therapy. First, the benefit of cabazitaxel in improving OS may not be mediated through PSA-dependent mechanisms.²⁴ PSA may decline for reasons unassociated, or not linearly associated, with cell killing by second chemotherapy treatment.²⁵ Stated alternatively, patients with mCRPC previously treated with first-line docetaxel may have selected prostate cancer cells with a greater degree of dissociation between PSA decline and cancer-cell killing. Although there are no data to support this possibility, it is also possible that cabazitaxel, as opposed to docetaxel, has a narrower spectrum of activity while still resulting in PSA declines.

Although the results of these data suggest that measures of PSA are not appropriate as surrogate markers of clinical benefit in this setting, it should be recognized that the only reason it was even possible to evaluate PSA kinetics using the Prentice criteria for surrogacy in this setting was because cabazitaxel prolonged OS in men with mCRPC.⁶ However, the Prentice criteria do not determine trial-level surrogacy. Several authors have used different approaches to the vali-

ation of surrogate end points, such as individual-level surrogacy based on individual patient data.²⁶⁻³⁰ Thus, an intermediate end point of OS may be of great clinical trial utility, even if it does not meet the Prentice criteria. The successful identification of a surrogate, such as progression-free survival, for OS would have wide-ranging implications for the design, conduct, and analysis of trials in this population.

There are many strengths to the analysis reported in this article. First, post-therapy changes in PSA have been considered as both binary and continuous outcomes. Second, different analytic approaches were undertaken where both individual-level and trial-level surrogacy associations were assessed. Although the Prentice criteria establish only individual-level surrogacy after adjusting for treatment, the meta-analytic approaches consider association at both individual and trial levels. Finally, because the data are from a trial in which patients were treated with cabazitaxel, an innovative approach was implemented where the data were randomly divided into five clusters, and each cluster was assumed to come from an independent trial. Although data splitting is a useful tool, it cannot substitute for a true meta-analysis. As new drugs and new paradigms are introduced, additional validation will be warranted.

In summary, based on this extensive analysis, there is no evidence that PSA kinetics are appropriate markers of clinical benefit, and as such, they cannot be used as surrogates for OS in patients with mCRPC receiving second-line chemotherapy after progression with

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