Clinical Outcomes and Survival Surrogacy Studies of Prostate-Specific Antigen Declines Following Enzalutamide in Men with Metastatic Castration-Resistant Prostate Cancer Previously Treated with Docetaxel

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BACKGROUND: In the AFFIRM trial, enzalutamide significantly increased overall survival (OS) for men with metastatic castration-resistant prostate cancer (mCRPC) after chemotherapy versus placebo and significantly decreased prostate-specific antigen (PSA) levels. The goal of this post hoc analysis was to associate levels of PSA decline from baseline after enzalutamide with clinical outcomes in the postchemotherapy mCRPC setting. METHODS: Men in the AFFIRM trial (n = 1199) were grouped by maximal PSA decline in the first 90 days of treatment. Kaplan-Meier estimates evaluated the association of defined PSA changes from baseline with OS, progression-free survival (PFS), radiographic PFS (rPFS), and pain response. Each PSA decline category was assessed for OS surrogacy using Prentice criteria, proportion of treatment effect explained (PTE), and proportion of variation explained. RESULTS: Men treated with enzalutamide had improved OS (hazard ratio, 0.63; \(P < .001\)) and higher rates of PSA decline (odds ratio, >19.0; \(P < .001\)) versus placebo. PSA declines of any, >30%, >50%, and >90% with enzalutamide were strongly associated with greater OS, PSA PFS, rPFS (\(P < .001\)), and pain response (\(P < .026\)) versus PSA increase/no decline. Any, >30%, and >50% declines in PSA resulted in the PTE range of 1.07-1.29, where treatment was no longer significant after adjustment for decline measures (\(P > .20\)). CONCLUSIONS: PSA declines of any, >30%, and >50% following enzalutamide were associated with greater clinical and pain response and improvements in PFS and OS. Surrogacy of PSA decline for OS was not fully established, possibly due to lack of PSA declines with placebo, and discordant results between PSA and imaging responses over time, and because some declines were not durable due to rapid resistance development. However, a lack of PSA decline by 90 days following enzalutamide treatment was a poor prognosis indicator in this setting. Conclusions from sensitivity analyses of maximal PSA decline from baseline over the entire treatment period are consistent with PSA declines restricted to the first 90 days. Cancer 2017;123:2303-11. © 2017 The Authors. Cancer published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: enzalutamide, metastatic castration-resistant prostate cancer, prostate-specific antigen, surrogate endpoint, survival.

INTRODUCTION

Metastatic prostate cancer remains highly lethal worldwide despite recent therapeutic advances, including docetaxel, cabazitaxel, sipuleucel-T, abiraterone acetate, enzalutamide, and radium-223. Survival times for men with metastatic castration-resistant prostate cancer (mCRPC) vary depending on known prognostic risk factors. Clinical trials involving metastatic prostate cancer may be confounded by posttreatment options that impact mortality, limiting the ability to discern survival benefits.

Intermediate endpoints, including serum prostate-specific antigen (PSA) changes, may help determine therapeutic efficacy and prognostic effect due to therapeutic responses, facilitate therapeutic agent selection in phase 1 and 2 clinical trials, and aid decision-making for treatment continuation. PSA is directly regulated by androgen receptor (AR) transcriptional activity and is therefore a pharmacodynamic biomarker that reports on-target activity of AR-directed agents.
therapies. Posttherapy PSA declines have been explored as potential surrogates for overall survival (OS) in men with mCRPC. In 2 randomized phase 3 trials for docetaxel and prednisone treatment, associations of PSA decline of \( \geq 30\% \) and \( \geq 50\% \) were found with OS. Additionally, a randomized phase 3 trial of cabazitaxel and prednisone treatment found an association for PSA decline of \( \geq 30\% \) and OS. However, surrogacy of these PSA declines was not established. Although the current recommendations for clinical trials conducted in men with CRPC include descriptive reporting of PSA declines, such declines are not accepted as endpoints for registration. Importantly, the agents used in these trials were cytotoxic and did not affect AR transcription directly, unlike novel androgen signaling-directed therapies such as enzalutamide.

Enzalutamide targets AR, an oncogenic receptor known to contribute to castration-resistant prostate cancer progression. In the phase 3 randomized AFFIRM trial, enzalutamide treatment significantly prolonged life and resulted in higher frequency of PSA declines versus placebo in men with mCRPC previously treated with docetaxel. We explored PSA declines as prognostic indicators of OS, progression-free survival (PFS), and pain response and for surrogate associations with improved OS for enzalutamide.

PATIENTS AND METHODS

**Study Design and Conduct**

The AFFIRM trial (NCT00974311) was a randomized, double-blind, placebo-controlled, phase 3 trial assessing the efficacy and safety of enzalutamide in men with mCRPC. Full trial protocol details have been described previously. Briefly, eligible men had a histologically confirmed diagnosis of prostate cancer, castrate levels of testosterone (<50 ng/dL), previous treatment with docetaxel, and progressive disease according to Prostate Cancer Clinical Trials Working Group (PCWG) 2 criteria. Men were randomized 2:1 to receive 160 mg/d of oral enzalutamide (n = 800) or placebo (n = 399).

**Analysis of PSA Decline**

Serum PSA was measured before randomized treatment initiation at baseline and at or after the 12 week visit (~90 days) to preserve the study blind until disease progression, concurrent with restaging scans with computed tomography and bone scan reassessments. Earlier values were not obtained to maintain study blinding. Additional PSA measurements were conducted at 17 and 21 weeks after treatment initiation. In this post hoc analysis, participants were grouped by maximal unconfirmed PSA decline during the first 90 days of enzalutamide treatment (Supporting Fig. 1).

**Surrogacy Evaluation**

Statistical surrogacy was evaluated for each percentage category of unconfirmed posttreatment PSA decline from baseline, achievement of posttreatment PSA levels of \( \leq 0.2 \) ng/mL from baseline during the first 90 days of enzalutamide treatment, and confirmed PSA declines that may have incorporated values beyond 90 days. Surrogacy was described using Prentice criteria, proportion of treatment effect explained (PTE), and proportion of variation explained (PVE).

The Prentice criteria require 4 statistical analyses: 1) whether treatment has a significant effect on survival; 2) whether treatment has a significant effect on PSA decline; 3) whether PSA decline has a significant impact on survival; and 4) whether PSA decline captures the full effect of treatment on survival. Cox models assessed Prentice criteria 1, 3, and 4 according to statistical tests, and logistic regression assessed criterion 2. PTE, the percentage change of treatment effects estimated from 2 Cox models with or without adjusting for the surrogate, was assessed using the point estimate discussed by Lin et al; its confidence interval (CI) estimate can extend beyond the 0-1 range. PTE is an approximation of the proportion of net effect on outcome explained by the effect of the surrogate. Ranges near 0 indicate lack of surrogacy, and ranges of or near 1 indicate evidence consistent with surrogacy. According to the Prentice criteria, a valid surrogate marker must capture all treatment effects on the endpoint (ie, survival), and be biologically explained by either treatment-related toxicities independent of the surrogate effect or confounded by more aggressive disease in those patients who had not experienced PSA decline after treatment with enzalutamide, resulting in a negative treatment effect after adjusting for the surrogate in the Cox model. Because the 95% CI for PTE may contain ranges of values \( \geq 1 \), evidence of surrogacy was evaluated by examining the lower bound of the 95% CI, where PTE values less than the lower bound can be excluded with 2.5% confidence.

PVE (\( R^2 \)) estimates the degree of variation in survival explained by the predictor of survival in the Cox model. PVE ranges from 0 to 1; adding treatment to the surrogate Cox model should not significantly increase PVE under conditions of surrogacy.
RESULTS

Prognostic Association of PSA Decline With Clinical Outcomes

In the AFFIRM trial, the median baseline PSA was 108 ng/mL (range, 0.2-11,794.1 ng/mL) for men treated with enzalutamide (n = 800) and 128 ng/mL (range 0-19,000 ng/mL) for men receiving placebo (n = 399). Enzalutamide treatment significantly increased survival for men with mCRPC versus placebo (hazard ratio, 0.63; 95% CI, 0.53-0.75; \( P < .001 \)).\(^7\) Fulfilling Prentice criterion 1, and was strongly associated with each PSA decline (Prentice criterion 2) versus placebo (odds ratio, \( > 19.0; P < .001 \)). The odds ratio for PSA \( \leq 0.2 \) ng/mL was not calculable.

The proportion of men randomized to enzalutamide with confirmed PSA declines by 3 months of therapy depended on the magnitude of the PSA decline and ranged from 40% (any PSA decline within 90 days) to 1.3% (achievement of a posttreatment \( \leq 0.2 \)) as shown in Supporting Table 1. Documented PSA increase/no decline by 90 days on enzalutamide treatment was rarely followed by subsequent falls in PSA levels at later points (PSA flare phenomenon; n = 11, 1.4%). These data demonstrate that PSA declines are strongly associated with enzalutamide treatment.

Men were next grouped by maximal confirmed PSA decline within the first 90 days of enzalutamide treatment to examine the prognostic association of PSA decline with clinical outcomes (Prentice criterion 3). Compared with an increase/no decline in PSA levels, declines of any, \( \geq 30\% \), \( \geq 50\% \), and \( \geq 90\% \) within the first 90 days of enzalutamide treatment were associated with longer OS (Table 1; Fig. 1), PSA PFS (Table 1; Fig. 2), and rPFS

### Association of PSA Decline With Clinical Outcome and Pain Response

Statistical analyses used to assess associations between OS, PFS, and pain response and different posttreatment PSA declines from baseline during the first 90 days of enzalutamide treatment are described in the Supporting Information.

### TABLE 1. Median OS, PFS, Radiographic PFS, and Percentage of Patients With Pain Response by Level of PSA Decline From Baseline Within the First 90 Days of Treatment With Enzalutamide

| Greatest PSA Decline From Baseline (n) | Median OS, Months (95% CI) | 12-Month OS, KM Estimate (SE) | 16-Month OS, KM Estimate (SE) | Median PSA PFS, Months (95% CI) | Median rPFS, Months (95% CI) | Pain Response,\( ^{a} \) n/N (%) |
|-------------------------------------|-----------------------------|--------------------------------|--------------------------------|--------------------------------|-----------------------------|-------------------------------|
| Unconfirmed PSA decline             |                             |                                |                                |                                |                             |                               |
| Increase/no decline (141)           | 11.6 (10.0-15.1)            | 48.9 (4.38)                    | 34.0 (5.17)                    | 2.9 (2.8-3.7)                  | 3.3 (2.8-5.5)               | 6/36 (16.7)                   |
| \( \geq 30\% \) (449)               | NYR (NYR-NYR)               | 83.6 (1.81)                    | 72.9 (2.60)                    | 8.5 (8.3-10.8)                 | 11.5 (11.0-13.6)            | 54/111 (48.6)                |
| \( \geq 50\% \) (372)               | NYR (NYR-NYR)               | 86.6 (1.83)                    | 76.1 (2.78)                    | 8.5 (8.3-11.0)                 | 13.6 (11.2-13.9)            | 45/89 (50.6)                 |
| \( \geq 90\% \) (147)               | NYR (NYR-NYR)               | 92.4 (2.34)                    | 84.3 (3.84)                    | 11.4 (10.8-NYR)                | 16.1 (13.6-18.3)            | 18/32 (56.3)                 |
| \( \leq 0.2 \) ng/mL (15)           | NYR (NYR-NYR)               | 100.0 (NE)                     | 100.0 (NE)                     | NYR (13.8-NYR)                 | 13.5 (10.8-NYR)             | 1/3 (33.3)                   |
| Any PSA decline (527)               | NYR (18.8-NYR)              | 80.1 (1.39)                    | 69.1 (2.42)                    | 8.3 (8.3-8.5)                  | 11.0 (10.7-11.2)            | 63/138 (45.7)                |
| Confirmed PSA decline               |                             |                                |                                |                                |                             |                               |
| Increase/no decline (349)           | 12.7 (11.4-13.8)            | 53.26 (2.74)                   | 36.5 (3.30)                    | 4.6 (4.6-4.6)                  | 5.5 (5.3-5.6)               | 32/100 (32.0)                |
| \( \geq 30\% \) (285)              | NYR (NYR-NYR)               | 96.0 (1.27)                    | 90.9 (2.15)                    | 11.1 (11.0-13.8)               | 16.1 (13.8-16.6)            | 34/65 (52.3)                 |
| \( \geq 50\% \) (245)              | NYR (NYR-NYR)               | 96.7 (1.24)                    | 91.8 (2.26)                    | 11.1 (11.1-14.0)               | 16.5 (13.8-18.1)            | 28/55 (50.9)                 |
| \( \geq 90\% \) (100)              | NYR (NYR-NYR)               | 97.9 (1.45)                    | 97.9 (1.45)                    | NYR (13.8-NYR)                 | NYR (16.1-NYR)              | 12/19 (63.2)                 |
| \( \leq 0.2 \) ng/mL (10)           | NYR (NYR-NYR)               | 100.0 (NE)                     | 100.0 (NE)                     | NYR (13.8-NYR)                 | NYR (8.2-NYR)               | 0/1 (0)                      |
| Any PSA decline (319)               | NYR (18.8-NYR)              | 95.7 (1.22)                    | 88.9 (2.24)                    | 11.1 (8.9-11.1)                | 13.9 (13.6-16.5)            | 37/74 (50.0)                 |

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; NYR, not yet reached; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; SE, standard error.

\(^a\) \( \geq 2\)-point reduction in worst pain score in men with pain score \( \geq 4 \) at baseline.
Median OS for men with PSA increase/no decline was 12.7 months; OS for confirmed PSA declines of any, ≥30%, ≥50%, and ≥90% was not yet reached (Table 1). Because only 10 men had a PSA decline of 0%-30% with enzalutamide, this group was not included in further analyses. Across all assessed levels of confirmed PSA decline from baseline within the first 90 days of enzalutamide treatment, 16-month OS rates were not yet reached.

Figure 1. Kaplan-Meier plot of overall survival by level of greatest confirmed PSA decline from baseline within the first 90 days of treatment with enzalutamide. Abbreviations: CI, confidence interval; NYR, not yet reached; PSA, prostate-specific antigen.

Figure 2. Kaplan-Meier plot of time to PSA progression by level of greatest confirmed PSA decline from baseline within the first 90 days of treatment with enzalutamide. Abbreviations: CI, confidence interval; NYR, not yet reached; PSA, prostate-specific antigen.
ranged from 36.0% to 100% (Table 1). Analyses for unconfirmed PSA thresholds yielded similar results (Table 1). In men treated with enzalutamide, those with confirmed PSA declines of ≥30% had consistently greater OS versus men with PSA decline of <30% (Fig. 4).

The median duration of PSA PFS for men with PSA increase/no decline and confirmed PSA declines of ≥30% and ≥50% was 4.6 months (95% CI, 4.6-4.6), 11.1 months (95% CI, 11.0-13.8), and 11.1 months (95% CI, 11.1-14.0), respectively (Table 1). The median duration of PSA PFS and rPFS had not been reached for men with confirmed PSA declines of ≥90% and ≤0.2 ng/mL (Table 1). The median rPFS duration for men with PSA increase/no decline and confirmed PSA decline of ≥30% and ≥50% were 5.5 months (95% CI, 5.3-5.6), 16.1 months (95% CI, 13.8-16.6), and 16.5 months (95% CI, 13.8-18.1), respectively (Table 1; Fig. 3). Analyses of unconfirmed PSA thresholds yielded similar results (Table 1).

Confirmed PSA declines of ≥30%, ≥50%, and ≥90% within 90 days of enzalutamide treatment were associated with a greater proportion of men with pain response (52.3%, 50.9%, and 63.2%, respectively) compared with increase/no decline in PSA levels (32.0%; P < .026 for all; Table 1). Similar trends were observed in the proportion of men with pain response within 90 days of enzalutamide treatment for all unconfirmed PSA thresholds (Table 1).

### PSA Declines as Surrogates for OS

Because PSA decline was strongly associated with posttreatment outcomes, we quantified the surrogate associations for OS. Prentice criteria 1-3 were met for any PSA decline and declines of ≥30%, ≥50%, and ≥90% (Supporting Table 2). For Prentice criterion 4, we examined the impact of treatment on OS after adjustment for each surrogate PSA decline level. For any, ≥30%, and ≥50% PSA declines, the introduction of this surrogate into a model of treatment effect on OS demonstrated that treatment effect lost statistical significance (Supporting Table 2), fulfilling a necessary but insufficient element for Prentice criterion 4. The other evaluated levels of PSA declines did not fulfill surrogacy, despite strong associations with outcomes. Patterns of increase observed with the PVE criterion (R²) were consistent with surrogacy for PSA declines of ≥30%, ≥50%, and ≥90% (Supporting Table 2). PSA response levels exhibited considerably stronger correlations with survival than treatment; the addition of treatment to the model with PSA response did not effectively change R².

Confirmed and unconfirmed PSA declines of any, ≥30%, and ≥50% within the first 90 days of
enzalutamide treatment resulted in point estimates for PTE from 0.90 (95% CI, 0.55-1.26) to 1.29 (95% CI, 0.73-1.85; Supporting Table 1). These thresholds also resulted in treatment effect no longer remaining significant after adjustment for decline measures (P ≥ .20; hazard ratio range, 0.96-1.14). We next examined the lower bounds of the 95% CI for PTE to ascertain which surrogate seemed more strongly associated with OS. Based on analyses of PTE, confirmed PSA declines of any and ≥30% had 95% CI lower bounds of PTE modestly higher than those of PSA declines of ≥50% (0.76 and 0.66 versus 0.55, respectively; Supporting Table 1). Levels of unconfirmed PSA declines yielded similar results (Supporting Table 1), as did analyses using posttreatment PSA values beyond the 90-day period (data not shown).

DISCUSSION

In the AFFIRM trial, enzalutamide significantly increased OS for men with mCRPC treated with chemotherapy versus placebo and was strongly associated with PSA declines (Prentice criterion 1).7 In this post hoc analysis, PSA declines from baseline within the first 90 days of enzalutamide treatment were associated with improved clinical and pain response, indicating a strong clinical association of PSA decline with outcomes. Our results, extending analyses to all posttreatment PSA values, were similar to those observed using the best PSA decline within 90 days of treatment; these results suggest that although posttherapy PSA changes provide significant prognostic information for mCRPC patients, they are not always a surrogate for survival and must be interpreted with caution. These results should facilitate patient–physician decision-making that considers the net clinical benefit of continuing therapy over time, based on patient symptoms, imaging, and biomarkers such as PSA changes. In addition, absence of PSA decline at 90 days after enzalutamide treatment was a marker of poor prognosis and OS at approximately 1 year. These data suggest that PSA monitoring during treatment with enzalutamide provides useful prognostic information during enzalutamide therapy.
Rapid radiographic progression within 3 months was observed in some men with mCRPC who experienced a PSA decline, indicating intrinsic or rapidly acquired resistance and illustrating the importance of computed tomography and bone scan surveillance over time, and highlighting the need for additional therapies to improve PFS and OS in these men. Furthermore, 4%-5% of men with an early PSA increase on enzalutamide at day 90 will go on to develop radiographic responses, illustrating a disconnection between early PSA changes and clinical benefit in individual patients with mCRPC. Whereas early PSA changes are strongly associated with prognosis across all men with mCRPC, at an individual level such PSA changes can be either transient or not reflective of the overall benefit of enzalutamide treatment and suggest the ongoing need for additional assessments. We recommend that PSA changes alone should not be used clinically in the management of patients with mCRPC treated with enzalutamide, despite the prognostic information the changes provide.

The results from the AFFIRM trial are, in part, consistent with previous clinical trials in men with mCRPC that demonstrated that PSA declines within 3 months of treatment were associated with improved OS but did not fulfill all surrogacy criteria. These results are also consistent with recent post hoc analyses of clinical trial data in which PSA declines of ≥30% and ≥50% from baseline at day 28 after treatment with enzalutamide, abiraterone acetate, or orteronel were shown to be significantly associated with improved OS in patients with mCRPC. Full surrogacy was not demonstrated in the present study, possibly due to the rarity of PSA declines with placebo treatment and due to discordant results observed in some men between PSA declines and radiographic changes and the development of rapid clinical or radiographic progression in others, despite an early PSA decline.

Few PSA declines were observed with placebo, demonstrating that PSA declines are strongly associated with enzalutamide use and with long-term clinical outcomes. Despite this, the discordance between PSA changes and radiographic progression or response suggests that surrogacy would not be fulfilled even with an active comparator, given that radiographic progression is associated with shortened survival in this setting. However, PSA declines from baseline within 90 days of treatment explained a substantial amount of the effect of enzalutamide on survival; treatment effect of enzalutamide on survival was lost after adjustment for these PSA decline thresholds. Despite satisfying most criteria for surrogacy, the occasional disconnect between PSA and radiographic changes and the short-term nature of such PSA changes in some men illustrates the need for careful documentation and assessment of multiple disease phenotypic manifestations to determine whether a patient with mCRPC is still clinically benefitting from therapy, as detailed in the PCWG3.

These results affirm the PCWG2 and PCWG3 recommendation to monitor changes in each manifestation of disease separately and report changes in PSA, imaging, and other manifestations of disease progression, as PSA alone may not capture the full biology and resistance phenotype in patients with progressive disease. We emphasize the importance of not using PSA changes alone in clinical decision-making or the phase 3 clinical trial endpoint design for treatment of men with mCRPC, and the importance of using patient-reported symptoms, radiographic changes, and changes in other known prognostic biomarkers to determine whether patients benefit from systemic therapies. Although early PSA decline at these 3 posttreatment thresholds captured a proportion of the survival benefit associated with enzalutamide treatment in AFFIRM, isolated PSA changes should be considered in the context of patients’ quality of life, overall burden of disease, treatment tolerability, and alternative therapies/goals of care. Additionally, PSA changes alone may not reflect clinical benefit with all systemic therapies. These recommendations are included in the recently updated PCWG3 guidelines. However, for AR-directed therapies in phase 2 trials, PSA decline is an important pharmacodynamic biomarker indicating the on-target effect of drugs of this class, and elevations and indication of a lack of activity represent a need for a change in therapy. PSA decline should be a reportable outcome to help assess clinical and biological activity of these agents over time in men with castration-resistant prostate cancer.

Another noteworthy finding of the present analysis was the rarity of late PSA declines following initial PSA increases at 3 months (PSA flare) with enzalutamide treatment. This was observed in 1.4% of men, suggesting that PSA values at 3 months provide important prognosis information to communicate to patients. Earlier PSA changes (before 12 weeks) may be present, but they were not measured in this study per protocol. It remains unknown whether short-term transient rises in PSA with enzalutamide treatment may occur. Confirmatory PSA declines after 12 weeks were less common but were more strongly associated with favorable prognosis than unconﬁrmed declines. Although we did not observe discordant radiographic progression in men with unconfirmed PSA decline at this early 3-month time point when using
PCWG2 and PCWG3 radiographic progression criteria, rapid radiographic progression may still occur in men who achieve PSA decline before confirmation of this decline is achieved. In addition, we found that a lack of PSA decline at 3 months is helpful in determining who may benefit from research strategies examining additional or alternative approaches. Recent data suggest that whereas rPFS is also associated with OS in men with mCRPC, surrogacy has not been established for this endpoint and thus, an early PSA response determination may be useful in clinical trial eligibility of men with poor prognosis with mCRPC treated with enzalutamide.

Men who had PSA rises or insufficient decline (<30%) had a less favorable clinical outcome when treated with enzalutamide versus placebo, indicating a subset of men with either less AR-driven castration-resistant prostate cancer, tumors with disrupted genomic regions around the PSA locus, or with AR-variant driven castration-resistant prostate cancer, where PSA may not reflect AR activity in all cases. Men with mCRPC who do not respond well to enzalutamide treatment may also harbor more aggressive or heterogeneous cancers that would generally respond poorly to multiple types of systemic therapy. These men may be responsible for the point estimates of PTE >1, in which early enzalutamide treatment permits the identification of this poor prognosis group of patients. Although it is possible that enzalutamide treatment leads to a worse outcome in these patients compared with placebo, it is more likely that enzalutamide treatment leads to the identification of this poor prognosis group.

In conclusion, PSA declines of any, ≥30%, and ≥50% within 90 days of enzalutamide treatment were shown to be strongly associated with the clinical benefit of enzalutamide treatment in men with mCRPC who had previously received docetaxel. Given that PSA declines of >0%, ≥30%, ≥50%, and higher are strongly associated with clinical benefit after enzalutamide treatment, the absence of such PSA declines may assist in optimizing clinical outcomes by identifying men with mCRPC who develop early resistance to AR-directed therapy.

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CONFLICT OF INTEREST DISCLOSURES
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AUTHOR CONTRIBUTIONS
De Phung: performed the formal analyses and data validation, curation, and visualization. Carl Dmuchowski: performed the formal analyses and data validation, curation, and visualization.

All authors contributed to the conceptualization, methodology, investigation, data analysis and interpretation, writing, reviewing, and approval of every development stage.

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