Correlation between Prostate-Specific Antigen Kinetics and Overall Survival in Abiraterone Acetate–Treated Castration-Resistant Prostate Cancer Patients

Xu S. Xu, Charles J. Ryan, Kim Stuyckens, Matthew R. Smith, Fred Saad, Thomas W. Griffin, Youn C. Park, Margaret K. Yu, An Vermeulen, Italo Poggesi, and Partha Nandy

Abstract

Purpose: We constructed a biomarker-survival modeling framework to explore the relationship between prostate-specific antigen (PSA) kinetics and overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC) patients following oral administration of 1,000 mg/day of abiraterone acetate (AA).

Experimental Design: The PSA-survival modeling framework was based on data from two phase III studies, COU-AA-301 (chemotherapy pretreated, n = 1,184) and COU-AA-302 (chemotherapy naïve, n = 1,081), and included a mixed-effects tumor growth inhibition model and a Cox proportional hazards survival model.

Results: The effect of AA on PSA kinetics was significant (P < 0.0001) and comparable between the chemotherapy-naïve and -pretreated patients. PSA kinetics [e.g., PSA nadir, PSA response rate (≥30%, 50%, and 90%), time to PSA progression, PSA doubling time (PSADT)] were highly associated with OS in both populations. The model-based posttreatment PSADT had the strongest association with OS (HR ~0.9 in both populations). The models could accurately predict survival outcomes. After adjusting for PSA kinetic endpoints, the treatment effect of AA was significant on survival of both the Cox model and the Prentice criteria of surrogacy were met for the PSA kinetic endpoints. A strong correlation was also observed between PSA and radiographic progression-free survival.

Conclusions: The analysis revealed a consistent treatment effect of AA on PSA kinetics and strong associations between PSA kinetics and OS in chemotherapy-pretreated and -naïve patients, thereby providing a rationale to consider PSA kinetics as surrogate endpoints to indicate clinical benefit in AA-treated patients with mCRPC regardless of chemotherapy treatment.

Introduction

Prostate cancer, especially metastatic castration-resistant prostate cancer (mCRPC; ref. 1), accounts for a large proportion of the global cancer burden (2). As androgen signaling remains important to mCRPC progression, androgen suppression therapy remains a rational therapeutic approach. Questions, however, remain about how to more accurately predict therapeutic benefit and long-term survival outcomes for patients with mCRPC.

Abiraterone acetate (AA) is the prodrg of abiraterone, a first-in-class therapy that selectively and irreversibly inhibits 17α-hydroxylase/C17, 20-lyase [cytochrome P450C17 (CYP17)], a key enzyme in androgen biosynthesis (3, 4). Abiraterone suppresses adrenal and tumoral androgens, resulting in undetectable serum testosterone concentrations (3–6). AA plus prednisone has been shown to improve overall survival (OS) and radiographic progression-free survival (rPFS) in patients with chemotherapy-pretreated (study COU-AA-301) or chemotherapy-naïve (study COU-AA-302) mCRPC (7–9).

The surrogacy and predictive performance of prostate-specific antigen (PSA) kinetics in mCRPC patients has not been established and contradictory findings have been reported (10–15). However, the previous evaluations were based mainly on the data from studies for treatment of mCRPC with chemotherapies. The significant antitumor effect of AA confirms that mCRPC remains hormonally driven and dependent on androgen receptor signaling (16). Because PSA kinetics may be related to activity at the androgen receptor (17), the data (i.e., PSA, and clinical outcomes) collected in two phase III studies, COU-AA-301 and COU-AA-302, provided a unique opportunity to apply quantitative modeling to understand the interplay between kinetics of PSA following treatment and survival in mCRPC patients following treatment with AA, a noncytotoxic agent.
We constructed a biomarker-survival modeling framework to link OS with PSA kinetics following AA administration in patients with mCRPC.

Materials and Methods
Study design and data collection
COU-AA-301 and COU-AA-302 were phase III, multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of 1,000 mg daily AA plus 5 mg twice-daily prednisone (abiraterone arm) versus placebo plus prednisone (prednisone arm) in chemotherapy-pretreated and naïve patients with mCRPC, respectively. In COU-AA-301, 1,195 patients were randomized (2:1) into the abiraterone and prednisone arms, whereas in COU-AA-302, 1,088 patients were randomized (1:1). Patients were kept on study treatment until radiographic or clinical evidence of disease progression. Per protocol, PSA progression was not used as the sole indicator for disease progression or as a criterion for treatment discontinuation.

For COU-AA-301, the scheduled PSA measurements were conducted at screening, every three cycles (day 1 of cycles 1, 4, 7), and at the end-of-treatment visit. For COU-AA-302, PSA measurements were taken at screening, day 1 of cycles 1, 3, 5, 7, and 10, every three cycle after cycle 10, and at the end-of-treatment visit. The median number of cycles of AA treatment given was 8 and 15 for COU-AA-301 and COU-AA-302, respectively. Serum PSA concentrations were assessed, with a median of three and six measurements (range, 1–13 measurements) collected per patient. No PSA values were collected after progression on either of the clinical trials. The COU-AA-301 and COU-AA-302 datasets contained 552 (46.2%) and 333 (30.6%) mortality events, respectively.

Details on the study designs have been described previously (7, 9). Patients with neuroendocrine differentiation were explicitly excluded from these studies. Both studies were approved by the Institutional Review Boards of the participating institutions and were conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki. All patients provided written informed consent.

PSA kinetic model
A longitudinal PSA kinetic model was developed to describe PSA kinetics, the antitumor effect of abiraterone, and treatment resistance after AA administration. The models were developed using data from patients who received at least one dose of study drug and for whom a minimum of one post-treatment PSA measurement was available. Initial analysis showed that a tumor growth inhibition model (18–21) best described the longitudinal pharmacodynamic PSA response instead of a bieponential model (22), a mixed exponential and linear model (23), or a mixed Weibull and linear model (23, 24). Details on this model are in Supplementary Appendix SI (Supplementary Table S1).

Survival model
Cox proportional hazards (PH) analyses were performed using the survival package in R 2.14.0 (25). Univariate Cox models were developed for individual model-predicted PSA kinetic endpoints. Multivariate Cox PH models were constructed from selected PSA kinetic endpoints and baseline covariates. Prentice criteria (26) for surrogacy were evaluated using the methods previously described (27). As rPFS was the coprimary endpoint in COU-AA-302, the association between PSA endpoints and rPFS was also explored using univariate Cox PH models. For the COU-AA-301 and -302, PSA kinetics were estimated separately. Details of this analysis are in Supplementary Appendix SII.

Results
PSA kinetic model
The PSA kinetic model provided an overall excellent adherence to individual PSA concentrations, indicated by a diagnostic plot of the observed and predicted PSA concentrations for individual subjects (Supplementary Fig. S1) as the data are uniformly and closely distributed around the line of identity. The parameter estimates of the final PSA kinetic models for chemotherapy-pretreated and naïve patients are listed in Supplementary Table S1. On the basis of the model, the estimated drug effect (AA + prednisone vs. prednisone) was similar in both populations. Compared with prednisone alone, treatment effect of AA on the PSA kinetics increased by 1.21-fold (0.93–1.53) and by 1.44-fold (1.14–1.77) for chemotherapy-pretreated and naïve patients, respectively.

A wide range of model-predicted PSA summary endpoints based on the PSA kinetic model (Supplementary Appendix SII) were derived to explore the relationship between OS and PSA kinetics. In addition, PSA response rates (≥30, 50, and 90%) based on the observed data were investigated. The descriptive statistics of these PSA endpoints are summarized in Table 1. Predicted PSA response rates ≥30, 50, and 90% at week 12 were greater in the abiraterone versus prednisone arms for both chemotherapy-naïve and -pretreated patients as well as with other PSA response endpoints evaluated [e.g., maximal% PSA decline, time to PSA nadir, time to progression by both the PSA Working Group 1 (PSAWG1) and Prostate Cancer Working Group 2 (PCWG2) criteria, PSA nadir doubling time and PSA doubling time from baseline (PSADT), observed PSA response rate (≥30, 50, and 90%)]. PSA value at the end of treatment was higher (203.9 ± 641.0 vs. 757.1 ± 1,389.8 for chemotherapy naïve vs. -pretreated, respectively).
with prednisone compared with AA (101.7 ± 288.3 vs. 504.0 ± 1,035.6).

Survival model

In the univariate analysis described in Supplementary Appendices S1 and SII, all model-derived PSA measures were significantly associated with OS (P < 0.0001), suggesting that PSA data are highly correlated with OS (Table 2).

The model-predicted posttreatment PSADT had the strongest association with OS in chemotherapy-pretreated patients, evidenced by the greatest concordance (0.72). Similarly, PSADT was among the three PSA kinetic measures with the strongest association with OS in chemotherapy-naïve patients. The other two endpoints were time to PSA progression based on the criteria from both PSAWG1 and PCWG2. The PSADT explained most of the variability in the survival data ($R^2 = 20\%$) in both populations. As survival data are often less informative compared with continuous response variables, prognostic factors can often only explain a small fraction of individual variation (30). Therefore, the model-predicted PSADT was selected to construct the multivariate survival models.

Table 3 presents the HR for each covariate in the final multivariate Cox PH models for chemotherapy-pretreated and -naïve patients. For both populations, the PSADT had the strongest association with OS, explaining at least 13% variability in the survival data after adjusting for other significant covariates. The HRs for PSADT in the chemotherapy-pretreated and -naïve patients were almost identical (HR ~0.9), suggesting similar association between PSA kinetics and OS. That is, as the model-predicted PSADT increased by 1 month, the relative hazard reduced by 10%.

Table 2. Univariate survival analysis of the relationship between model-predicted and observed PSA endpoints and OS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Chemotherapy-naïve (n = 1,081)</th>
<th>Chemotherapy-pretreated (n = 1,184)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Maximum% PSA decline</td>
<td>0.99 (0.98-0.99)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to PSA nadir (mo)</td>
<td>0.76 (0.73-0.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nadir PSA value (ng/mL)</td>
<td>1.43 (1.35-1.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA response rate at wk 12 (&gt;30%), n (%)</td>
<td>0.4 (0.32-0.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA response rate at wk 12 (&gt;50%), n (%)</td>
<td>0.45 (0.36-0.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA response rate at wk 12 (&gt;90%), n (%)</td>
<td>0.39 (0.26-0.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to PSA progression (mo)</td>
<td>0.87 (0.85-0.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to PSA progression (mo)</td>
<td>0.83 (0.81-0.86)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA nadir doubling time (mo)</td>
<td>0.88 (0.87-0.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA doubling time from baseline (PSADT) (mo)</td>
<td>0.91 (0.89-0.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA value (EOT; ng/mL)</td>
<td>1.47 (1.38-1.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA response rate (&gt;30%), n (%)</td>
<td>0.32 (0.25-0.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA response rate (&gt;50%), n (%)</td>
<td>0.50 (0.24-0.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA response rate (&gt;90%), n (%)</td>
<td>0.22 (0.14-0.35)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviation: R², explained variability.

*PSA progression defined by PSAWG1; defined as a 50% increase in PSA above nadir for patients who experienced a PSA decline of 50% on treatment, a 25% increase in PSA above nadir for patients who experienced a PSA decline <50% on treatment, and a 25% increase in PSA above starting baseline for patients who did not experience any PSA decline on treatment—provided in each case that the PSA increase was at least 5 ng/mL (28).

*PSA progression defined by PCWG2; defined as a rising PSA that is greater than 2 ng/mL higher than the nadir; the rise has to be at least 25% over nadir and the rise has to be confirmed by a second PSA measurement obtained at least 3 weeks later (29).

*Based on observed data.
From our analysis of covariates (Supplementary Appendix SII), several covariates were important predictors of outcomes in the multivariate survival models. Baseline lactate dehydrogenase explained approximately 5.4% [HR, 2.75 (per log unit rise in IU/L); P < 0.0001] and 3.6% [HR, 4.41 (per log unit rise in IU/L); P < 0.0001] of the survival variability in the chemotherapy-pretreated and naïve patients, respectively. Although baseline albumin was a significant prognostic factor for chemotherapy-pretreated patients [HR, 0.36 (per unit increase in g/dL); P < 0.0001], it was not significant for chemotherapy-naïve patients. Conversely, baseline hemoglobin was found to be significantly associated with OS for chemotherapy-naïve patients [HR, 0.86 (per unit increase in g/dL); P = 0.0008], but not chemotherapy-pretreated patients. In addition, lower baseline body weight was associated with poorer survival prognosis for chemotherapy-pretreated patients [HR, 0.88 (per 10 kg increase in weight); P < 0.0001], whereas older age was a risk factor for chemotherapy-naïve patients [HR, 1.34 (per 10 years increase in age); P < 0.0001]. As expected, the chemotherapy-pretreated patients with a baseline Eastern Cooperative Oncology Group (ECOG) score of 2 had higher risk than those with an ECOG score of 0 or 1 (HR, 2.01; P < 0.0001). There was no statistically significant difference in the risk between an ECOG score of 0 or 1 in either population. Finally, time since prior chemotherapy (HR, 0.99; P = 0.03) was marginally significant for the chemotherapy-pretreated patients, explaining only 0.18% survival variability after adjusting for other prognostic factors.

The predicted survival curves based on the PSA-survival models matched the observed Kaplan–Meier curves (Fig. 1).

**Treatment effect after adjusting for PSA kinetics**

The HRs, 95% confidence intervals (CI), and P values for the treatment effect of AA after adjusting for the tested PSA kinetic endpoints are presented in Table 4 for chemotherapy-pretreated and naïve patients. On the basis of the data from chemotherapy-pretreated patients, the effect of AA on survival was no longer statistically significant (P > 0.05) after adjusting for the majority (10 of 14) of the PSA endpoints. For model-predicted PSA nadir, PSA value at end of treatment, ≥90% PSA response rate at week 12, and ≥90% observed PSA response rate, the OS were found to be marginally associated with AA...
treatment after adjusting for those PSA endpoints. For chemotherapy-naïve patients, the treatment effect was no longer significant for OS after adjusting for eight of the 14 PSA endpoints. After adjusting for the other six PSA endpoints (four PSA progression measures, time to PSA nadir, and PSA nadir), an opposing treatment effect (i.e., HR >1) was observed. All of the PSA response rate endpoints [model-predicted PSA response rates (≥30, 50, and 90%) at week 12 and observed PSA response rate (≥30, 50, and 90%)] explained all of the variability in OS due to treatment effect in chemotherapy-naïve patients, while model-predicted ≥30 and 50% PSA response rates at week 12 and observed ≥30 and 50% PSA response rate explained the treatment effect on OS in chemotherapy-pretreated patients. The good predictive performance of the PSA response rates is further illustrated in Supplementary Fig S2.

Table 4. Treatment effect after adjusting for PSA endpoints

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy-naïve (n = 1,081)</th>
<th>Chemotherapy-pretreated (n = 1,184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum% PSA decline</td>
<td>1.37 (1.08-1.75)</td>
<td>1.09 (0.92-1.31)</td>
</tr>
<tr>
<td>Time to PSA nadir (m)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Nadir PSA value (ng/mL)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>PSA response rate at wk 12 (≥30%), n (%)</td>
<td>0.97 (0.67-1.44)</td>
<td>1.0 (0.64-1.56)</td>
</tr>
<tr>
<td>PSA response rate at wk 12 (≥50%), n (%)</td>
<td>1.04 (0.82-1.31)</td>
<td>0.8 (0.77-1.09)</td>
</tr>
<tr>
<td>PSA response rate at wk 12 (≥90%), n (%)</td>
<td>0.85 (0.69-1.07)</td>
<td>0.75 (0.63-0.90)</td>
</tr>
<tr>
<td>Time to PSA progression (m)</td>
<td>1.37 (1.25-1.50)</td>
<td>1.15 (0.98-1.35)</td>
</tr>
<tr>
<td>Time to PSA progression (m)</td>
<td>0.97 (0.83-1.16)</td>
<td>0.97 (0.80-1.16)</td>
</tr>
<tr>
<td>PSA nadir doubling time (m)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>PSA doubling time from baseline (PSADT) (m)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>PSA value (EOT; ng/mL)</td>
<td>1.16 (0.93-1.44)</td>
<td>1.15 (0.98-1.36)</td>
</tr>
<tr>
<td>PSA response rate (≥30%), n (%)</td>
<td>1.22 (0.96-1.54)</td>
<td>0.99 (0.83-1.38)</td>
</tr>
<tr>
<td>PSA response rate (≥50%), n (%)</td>
<td>1.17 (0.93-1.47)</td>
<td>0.92 (0.77-1.09)</td>
</tr>
<tr>
<td>PSA response rate (≥90%), n (%)</td>
<td>0.98 (0.79-1.22)</td>
<td>0.78 (0.66-0.93)</td>
</tr>
</tbody>
</table>

NOTE: HR for treatment effect before adjusting for PSA endpoints (i.e., in a univariate model): chemotherapy-naïve (HR, 0.75; 95% CI, 0.61-0.93; P = 0.01; ref. 9); chemotherapy-pretreated (HR, 0.65; 95% CI, 0.54-0.77; P < 0.001; ref. 7).

*PSA progression defined by PSAWG1; defined as a 50% increase in PSA above nadir for patients who experienced a PSA decline of 50% on treatment, a 25% increase in PSA above nadir for patients who experienced a PSA decline ≤50% on treatment, and a 25% increase in PSA above starting baseline for patients who did not experience any PSA decline on treatment—provided in each case that the PSA increase was at least 5 ng/mL (28).

**PSA progression defined by PCWGG2; defined as a rising PSA that is greater than 2 ng/mL higher than the nadir; the rise has to be at least 25% over nadir, and the rise has to be confirmed by a second PSA measurement obtained at least 3 weeks later (29).

Based on observed data.

Association between PSA kinetics and rPFS in COU-AA-302

Table 5 presents the HR, P-values, R², and concordance index for each PSA endpoint in the univariate Cox PH models for chemotherapy-naïve patients. All of the PSA endpoints were also strongly associated with rPFS (P < 0.0001). The PSA endpoints generally explained more variability in rPFS than in OS, as evidenced by higher R² and concordance between the PSA endpoints and rPFS.

Discussion

OS is frequently considered the gold standard to assess the outcome of anticancer therapies, though it often requires a long follow-up and can be confounded by the availability of other active therapies. In conjunction with survival analysis, pharmacodynamic tumor growth models have been developed and used for non–small cell lung cancer (23), colon cancer (21, 23), and...
breast cancer (23, 31) to predict the impact of drug activity on survival and to examine study designs before the start of expensive trials. Therefore, methods of connecting treatment use and exposure to survival outcomes early on may benefit the therapeutic decision-making process. As the mechanism of action of abiraterone involves the disruption of androgen signaling, PSA kinetics is a rational readout for patient outcomes, further validated by similar associations observed between PSA and OS in chemotherapy-pretreated and -naïve patients in this analysis, and by good predictive performance of survival outcome with PSA as the intermediate biomarker.

Although surrogacy of PSA metrics as a clinical endpoint has not been established (10–13), PSA is routinely used as an intermediate biomarker, and posttreatment changes in PSA have been associated with OS in mCRPC clinical trials (26, 27, 29, 32–36). Current survival models confirm that PSA kinetics are an intermediate endpoint predictive of OS in both chemotherapy-pretreated and -naïve patients with mCRPC following AA administration. Multiple commonly used PSA summary measures can be derived from longitudinal measurements. It is not surprising that PSA endpoints that include later progression phase (e.g., PSADT) tend to have stronger correlation with OS as they may carry richer information. However, the time needed to capture the later progression phase is usually quite long and does not allow for an early readout. Although PSA response endpoints represent only part of the information available in the longitudinal data (e.g., the initial declining phase due to treatment; refs. 10, 12), they may provide early indication of magnitude of long-term survival benefit. The current analysis suggests that the PSA response endpoints were sufficient to explain the variability in OS due to the treatment effect (Table 4 and Supplementary Fig. S1) although their correlation with OS was not as strong as that of PSADT and time to PSA progression (Table 2). PSA response rates have been utilized as an early readout of clinical benefit at interim/futility analysis of phase III clinical trials for novel investigational agents for treatment of patients with metastatic prostate cancer (37). It should be mentioned that early PSA flare/rise may occur in some patients after AA treatment (38). PCWG2 recommends evaluating PSA response after 12 weeks (29). The model-based analysis generated a consistent effect of AA on PSA kinetics in the two populations, and revealed a strong association between PSA kinetics and survival in both populations. Also, the effect of AA on survival was no longer statistically significant after adjusting for most PSA kinetic endpoints in both studies. Therefore, the Prentice criteria were met for those PSA endpoints in both chemotherapy-pretreated and -naïve populations.

In a recent analysis of the TROPIC trial, a phase III trial of cabazitaxel in patients with mCRPC with prior docetaxel exposure, Halabi and colleagues noted that PSA kinetics (e.g., ≥50% PSA declines) failed to satisfy the Prentice criteria (14). Halabi and colleagues explained that the benefit of cabazitaxel in improving OS may not be mediated through PSA-dependent mechanisms. As a direct inhibitor of androgen biosynthesis rather than a cytotoxic chemotherapy, abiraterone may have a more PSA-dependent mechanism than cabazitaxel, as PSA kinetics may be related to activity at the androgen receptor (17). In other words, changes in PSA kinetics may be a direct consequence of the clinical activity of AA. Our analysis of the Prentice criteria further supports this hypothesis regarding the PSA-dependent mechanism of abiraterone.

In chemotherapy-naïve patients, a significant, but opposite treatment effect (i.e., HR >1) remained after adjusting for six PSA endpoints (four PSA progression measures, time to PSA nadir, and PSA nadir), indicating that these PSA endpoints may slightly overpredict the treatment effect in COU-AA-302. For example, Fig. 1 shows that the treatment effect was slightly overpredicted by PSADT between days 200 and 600 in COU-AA-302. The treatment effect on OS in COU-AA-302 might be confounded by switching therapies after radiographic progression, since more patients in the prednisone arm (74%) than in the abiraterone arm (59%) received subsequent therapies. The use of subsequent therapies may reduce the size of the expected effect of the therapies being evaluated (7, 9, 39, 40) and therefore may explain the model overprediction and the opposite treatment effect after adjusting for some PSA endpoints.

rPFS by PCWG2 criteria has been commonly used as a key endpoint in recent phase III trials (41). Along with OS, rPFS was the coprimary endpoint in study COU-AA-302 (9, 41, 42). Previous analysis of COU-AA-302 data has shown a strong, positive correlation (0.72) between rPFS and OS using Spearman correlation. Our model suggests that the model-based treatment effect on PSA kinetics for patients with different treatment experiences (chemotherapy-pretreated vs. -naïve). The treatment effect on OS were also similar for the chemotherapy-pretreated (HR, 0.65; 95% CI, 0.54–0.77; P < 0.0001; ref. 7) and -naïve (HR, 0.75; 95% CI, 0.61–0.93; P = 0.0097) patients (9), indicating that PSA kinetics may have value as a surrogate endpoint (18).

Prentice has proposed a set of statistical conditions (‘Prentice criteria’; ref. 26) for demonstrating surrogacy using data from a single study. This includes the caveats that the treatment must have a statistically significant effect on the biomarker endpoint and on survival; the biomarker endpoint must be statistically significantly prognostic for survival; and, in a multivariate model, there must not remain a statistically significant treatment effect on survival when the model is adjusted for the biomarker endpoint. Significant treatment effects were found on survival in both chemotherapy-pretreated and -naïve populations, consistent with previous analyses (7, 9). The current analysis demonstrated a significant, similar treatment effect of AA on 31 PSA kinetics in the two populations, and revealed a strong association between PSA kinetics and survival in both populations. Also, the effect of AA on survival was no longer statistically significant after adjusting for most PSA kinetic endpoints in both studies. Therefore, the Prentice criteria were satisfied for those PSA endpoints in both chemotherapy-pretreated and -naïve populations.
Disclosure of Potential Conflicts of Interest
C.J. Ryan reports receiving speakers bureau honoraria from Janssen. M.R. Smith is a consultant/advisory board member for Johnson & Johnson. No potential conflicts of interest were disclosed by the other authors.

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Conception and design: X.S. Xu, C.J. Ryan, M.R. Smith, F. Saad, T.W. Griffin, P. Nandy
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): X.S. Xu, C.J. Ryan, K. Stuyckens, F. Saad, T.W. Griffin
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): X.S. Xu, C.J. Ryan, K. Stuyckens, M.R. Smith, F. Saad, T.W. Griffin, Y.C. Park, A. Vermeulen, I. Poggesi, P. Nandy
Writing, review, and/or revision of the manuscript: X.S. Xu, C.J. Ryan, K. Stuyckens, M.R. Smith, F. Saad, T.W. Griffin, M.K. Yu, A. Vermeulen, I. Poggesi, P. Nandy

References

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Study supervision: T.W. Griffin, I. Poggesi, P. Nandy
Other (provided clinical data and analysis): Y.C. Park

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