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European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Benjamin L. Maughan and Mario A. Eisenberger on pp. 732–733 of this issue

Prostate-specific Antigen Decline After 4 Weeks of Treatment with Abiraterone Acetate and Overall Survival in Patients with Metastatic Castration-resistant Prostate Cancer

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Article info

Article history:
Accepted February 21, 2016

Associate Editor:
Giacomo Novara

Keywords:
Abiraterone acetate
Metastatic castration-resistant prostate cancer
Prostate-specific antigen

Abstract

Background: The availability of multiple new treatments for metastatic castration-resistant prostate cancer (mCRPC) mandates earlier treatment switches in the absence of a response. A decline in prostate-specific antigen (PSA) is widely used to monitor treatment response, but is not validated as an intermediate endpoint for overall survival (OS).
Objective: To evaluate the association between early PSA decline and OS following abiraterone acetate (AA) treatment.
Design, setting, and participants: We identified mCRPC patients treated with AA before or after docetaxel at the Royal Marsden NHS Foundation Trust between 2006 and 2014. Early PSA decline was defined as a 30% decrease in PSA at 4 wk relative to baseline, and early PSA rise as a 25% increase.
Outcome measurements and statistical analysis: Association with OS was analyzed using multivariate Cox regression and log-rank analyses. Spearman's rho correlation coefficient (r) was calculated to evaluate the association between PSA changes at 4 wk and 12 wk.
Results and limitations: There were 274 patients eligible for this analysis. A 30% PSA decline at 4 wk was associated with longer OS (25.8 vs 15.1 mo; hazard ratio [HR] 0.47, $p < 0.001$), and a 25% PSA rise at 4 wk with shorter OS (15.1 vs 23.8 mo; HR 1.7, $p = 0.001$) in both univariate and multivariable models. The percentage PSA decline at 4 wk was significantly correlated with the percentage PSA change at 12 wk ($r = 0.82$; $p < 0.001$). Patients achieving a 30% PSA decline at 4 wk were 11.7 times more likely to achieve a 50% PSA decrease at 12 wk (sensitivity 90.9%, specificity 79.4%). Limitations include the retrospective design of this analysis.
Conclusions: Patients not achieving 30% PSA decline after 4 wk of AA have a lower likelihood of achieving PSA response at 12 wk and significantly inferior OS. Prospective multicentre validation studies are needed to confirm these findings.
Patient summary: Prostate-specific antigen (PSA) is commonly used to evaluate response to treatment in metastatic castration-resistant prostate cancer. Expert recommendations discourage reliance on PSA changes earlier than 12 wk after treatment initiation. Our data suggest that early PSA changes are associated with survival in patients receiving abiraterone acetate.

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http://dx.doi.org/10.1016/j.eururo.2016.02.055

1. Introduction

Prostate cancer (PCa) is the most common malignancy in men and the second leading cause of death from cancer [1]. Almost 34% of men for whom radical treatment fails develop incurable metastatic disease [2]. Androgen deprivation is the mainstay of therapy for advanced PCa, but progression to a castration-resistant state invariably occurs after a median time of 18–24 mo [3], while the median time from diagnosis of metastatic disease to death is 40.7 mo [4]. Evaluation of treatment responses in metastatic PCa remains challenging [5]. Bone represents the likeliest site of metastases, and almost 90% of patients have radiologic evidence of bone metastases [6,7], but this is non-evaluable according to Response Evaluation Criteria in Solid Tumors (RECIST) [8]. The consensus criteria of the Prostate Cancer Working Group (PCWG2) are used to report PCa outcomes in clinical trials. These rely on a composite measure of clinical, radiologic, and serologic (prostate-specific antigen [PSA] changes) outcomes to define response to treatment and progression [9].

PSA continues to be widely used to monitor PCa [10,11]. PCWG2 criteria recommend reporting PSA response as a continuous variable in the form of waterfall plots, although both 30% and 50% PSA declines are also commonly reported, usually at nadir and at 12 wk, and both are associated with improved survival [9]. A 30% PSA decline consistently has a stronger association with survival than a 50% PSA decline [12–14]. Similarly, PSA progression according to PCWG2 criteria is associated with shorter survival [15,16]. Despite this, studies have not validated PSA decline as a surrogate of overall survival (OS), although a recently published pooled analysis of the COU-301 and COU-302 trials indicated that PSA kinetics, including PSA doubling time, satisfied the Prentice criteria for OS surrogacy [17].

Defining the best time to assess response is also challenging. According to PCWG2 criteria, progression should not be determined during the first 12 wk because of late responses and flare reactions [9,18,19]. Insufficient data have therefore been reported regarding the clinical relevance of early PSA changes in mCRPC patients treated with abiraterone acetate (AA) [20]. We hypothesized that an early decline in PSA by $\geq$30% after 4 wk of treatment with AA is associated with improved OS and a 50% PSA decline at 12 wk, and that a PSA increase of $\geq$25% after 4 wk of treatment is associate with much poorer outcome and a high likelihood of a 50% PSA increase at 12 wk. If confirmed, these data could guide future studies on earlier treatment termination for insensitive disease.

2. Patients and methods

2.1. Study design and data collection

Patients with biochemically or histologically confirmed progressive mCRPC and castrate levels of testosterone treated with AA outside of clinical trials at the Royal Marsden NHS Foundation Trust between January 2006 and December 2014 were considered eligible for analysis. Additional inclusion criteria were the availability of PSA data at 4 and 12 wk after AA treatment initiation. A physical examination, including Eastern Cooperative Oncology Group performance status (ECOG PS), and laboratory studies, including a full blood count, routine biochemistry comprising albumin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and PSA, were carried out at baseline and at visits every 4 wk. Patients were reviewed every 4 wk until disease progression occurred or treatment was discontinued for other reasons. Radiographic evaluation with computed tomography and bone scans was performed every 12–16 wk.

2.2. Endpoint definition

OS was defined as the time between treatment initiation and either the date of death or of last follow-up for surviving patients. PSA decline endpoints evaluated were consistent with published consensus guidelines [9]. PSA response at 12 wk was defined as either a 30% or a 50% decline in PSA relative to baseline, confirmed by a second reading at least 3 wk later. Early PSA response was defined as a 30% decline in PSA at 4 wk relative to baseline. Early and 12-wk PSA declines were also calculated as a continuous value, expressed as the percentage decline relative to baseline. PSA progression at 12 wk was defined as a 25% increase relative to baseline or, in cases with an initial PSA decline, relative to nadir, and a minimum PSA level of 2 ng/ml, confirmed by a second reading at least 3 wk later. Early PSA progression was defined as a 25% increase at 4 wk relative to baseline.

2.3. Statistical analysis

Results are presented as the median and interquartile range (IQR) for continuous variables and as number and percentage frequency for categorical variables. Kaplan-Meier analysis was used to estimate survival. Association between PSA changes (response and/or progression) and survival was evaluated in univariable and multivariable Cox regression models. Continuous variables with skewed distributions (PSA, LDH, ALP) were log-transformed. Only variables with a significant association with outcome ($p < 0.05$) in univariable analysis were selected for testing in multivariable models. Spearman's rho correlation coefficient (r) was calculated to assess the association between the percentage PSA decline at 4 and 12 wk. The association between early PSA changes (response or progression) and PSA response or progression at 12 wk was evaluated using logistic regression models. We calculated odds ratios (ORs) and risk ratios (RRs) and the corresponding 95% confidence interval (CI). Sensitivity and specificity analyses were performed. To calculate predictive values, PSA response rates for the COU-301 and COU-302 trials were used for the postchemotherapy and prechemotherapy cohorts, respectively, as recently reported [21,22]. Statistical analyses were performed using SPSS version 20 (IBM, Armonk, NY, USA).

3. Results

3.1. Patient characteristics

Between January 2006 and December 2014, 488 patients were treated with AA at the Royal Marsden NHS Foundation Trust. Of these, 274 patients were treated outside a clinical trial with valid baseline, week 4, and week 12 PSA values, and were therefore eligible for this analysis; 117 and 157 patients received AA before and after chemotherapy, respectively (Supplementary Fig. 1). The clinical characteristics are summarized in Table 1. Postchemotherapy patients had significantly higher PSA, ALP, and neutrophil to lymphocyte ratio, significantly lower hemoglobin and

Table 1 – Patient characteristics and outcome [a]

Characteristics	All patients	Prechemotherapy cohort	Postchemotherapy cohort	*p* value
Number (*n*)	274	117	157	
Prostate-specific antigen μg/l	132 (40–409)	61 (25–194)	259 (77–668)	0.000
Hemoglobin g/l	11.8 (10.4–12.9)	12.5 (11.2–13.6)	11.1 (10.1–12.6)	0.002
Albumin g/l	35 (32–38)	37 (34–39)	35 (31–37)	0.001
Alkaline phosphatase U/l	131 (70–303)	106 (65–202)	165 (82–348)	0.000
Lactate dehydrogenase U/l	182 (152–243)	174 (151–223)	196 (154–272)	0.055
Neutrophil to lymphocyte ratio	3.5 (2.4–5.5)	3.2 (2.1–4.4)	3.7 (2.5–6.4)	0.009
ECOG PS, *n* (%)				
0–1	244 (89.1)	113 (96.6)	131 (83.4)	0.006
2–3	24 (8.8)	2 (1.7)	22 (14)	
Metastases, *n* (%)				0.167
Bone	117 (42.7)	51 (43.6)	66 (42)	
Bone + lymph nodes	92 (33.6)	34 (29.1)	58 (36.9)	
Bone + lymph nodes + visceral	11 (4)	2 (1.7)	9 (5.7)	
Lymph nodes	26 (9.5)	16 (13.7)	10 (6.4)	
Lymph nodes + visceral	2 (0.7)	2 (1.7)	0	
Visceral	2 (0.7)	0	2 (1.3)	
None	11 (4)	7 (6)	4 (2.5)	
Pain, *n* (%)				0.000
Yes	72 (28.1)	15 (12.8)	62 (39.5)	
No	170 (62)	90 (76.9)	80 (56.3)	

Outcome	All patients	Prechemotherapy cohort	Postchemotherapy cohort	OR (95% CI) [*p* value]
30% PSA response at 12 wk, *n* (%)				0.39 (0.24–0.64) [<0.001]
Confirmed	121 (44.2)	67 (57.3)	54 (34.4)	
Unconfirmed	14 (5.1)	4 (3.4)	10 (6.4)	
No response	139 (50.7)	46 (39.3)	93 (59.2)	
50% PSA response at 12 wk, *n* (%)				0.41 (0.25–0.68) [0.001]
Confirmed	99 (36.1)	56 (47.9)	43 (27.4)	
Unconfirmed	9 (3.3)	3 (2.5)	6 (3.8)	
No response	166 (60.6)	58 (49.6)	108 (67.5)	
PSA progression at 12 wk, *n* (%)	64 (23.4)	21 (17.9)	43 (27.4)	1.7 (0.96–3.11) [0.068]
Survival, mo (95% CI)	19.8 (16.5–23.1)	36.4 (24.3–48.5)	13.3 (10.9–15.8)	2.8 (2.01–3.89) [<0.001]

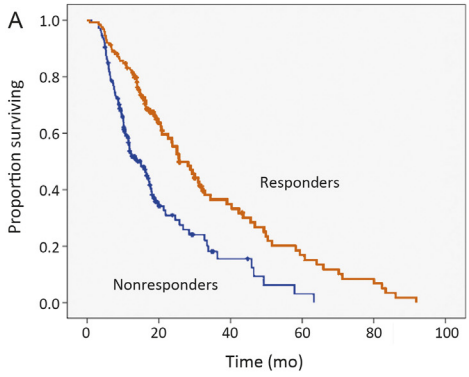
[a] Data for continuous variables are presented as median (interquartile range).
CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; OR = odds ratio.

albumin, worse ECOG PS, and higher rates of pain in comparison to the prechemotherapy cohort. There was no difference in metastatic disease distribution. The overall median follow-up was 14.6 mo (IQR 9–20.6); 181 patients (66.1%) had died by last follow-up, 58 (49.6%) in the prechemotherapy and 123 (76.9%) in the postchemotherapy cohort. Median OS was 19.8 mo (95% CI 16.5–23.1) and was longer in the prechemotherapy cohort (HR 2.8, 95% CI 2–3.9; Table 1). The median PSA change at 12 wk was –25% (IQR –73.8% to +40.7%); 135 patient (49.3%) achieved a 30% PSA decline and 108 (39.4%) a 50% PSA decline. Confirmed PSA declines were commoner in the prechemotherapy group (57.3% vs 34.4%; $p < 0.001$). Sixty-four patients (23.4%) had confirmed PSA progression at 12 wk; the rate of PSA progression was higher in the postchemotherapy cohort (27.4% vs17.9%; $p = 0.068$; Table 1).

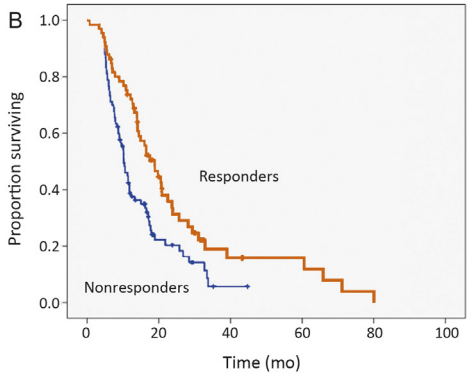
3.2. PSA decline at 4 wk after AA treatment initiation

The median PSA change at 4 wk after treatment initiation was –21.2% (IQR –58% to +21.9%), and 126 patients (46%) achieved a 30% PSA decline at 4 wk. Early PSA decline was more frequent in the prechemotherapy cohort (52.1% vs 41.4%; $p = 0.078$). Overall, a 30% PSA decline at 4 wk was associated with substantially longer OS (25.8 vs 15.1 mo; HR 0.47, $p < 0.001$; Fig. 1A) in univariable and multivariable Cox regression models (Table 2 and Supplementary Table 1). Similar results were observed when analyzing the postchemotherapy and prechemotherapy cohorts separately (Table 2, Fig. 1B,C).

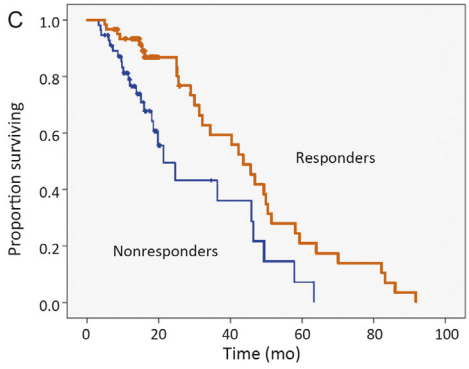
Moreover, out of 126 patients with a 30% PSA decline at 4 wk, 106 (84.1%) achieved a confirmed 30% PSA decline and 90 (71.4%) a confirmed 50% PSA decline at 12 wk. Critically, among patients without a PSA decline at 4 wk, only 15 (10.1%) and nine (6.1%) had confirmed 30% and 50% PSA declines, respectively, at 12 wk. Moreover, the percentage PSA decline at 4 wk was significantly correlated with the percentage PSA change at 12 wk ($r = 0.82$; $p < 0.001$). Similar findings were observed for both the prechemotherapy and postchemotherapy cohorts (Table 3). Furthermore, patients achieving a 30% PSA decline at 4 wk were 8.3 times more likely to have a 30% PSA decline at 12 wk, and



	N	Median OS (95% CI)	HR (95% CI)
Response	148	25.8 (20.0–31.5)	0.47 (0.35–0.65)
No response	126	15.1 (11.1–19.2)	$p < 0.001$



	N	Median OS (95% CI)	HR (95% CI)
Response	65	18.9 (14.5–23.2)	0.57 (0.39–0.83)
No response	92	10.4 (8.7–12.1)	$p = 0.003$



	n	Median OS (95% CI)	HR (95% CI)
Response	61	43.6 (35.4–51.8)	0.43 (0.25–0.76)
No response	56	21.4 (14.2–28.7)	$p = 0.004$

Fig. 1 – Kaplan-Meier curves for overall survival (OS) for a decrease in prostate-specific antigen of ≥30% at 4 wk as a dichotomous variable: (A) overall study population, (B) post-chemotherapy population, and (C) pre-chemotherapy population. CI = confidence interval; HR = hazard ratio calculated from Cox regression models.

11.7 times more likely to have a 50% PSA decline at 12 wk. Early PSA response had sensitivity of 87.6% (95% CI 80.6–92.3%) and specificity of 86.9% (95% CI 80.7–91.4%) for detection of a 30% PSA response at 12 wk (Table 4), and sensitivity of 90.9% (95% CI 83.6–95.1%) and specificity of 79.4% (95% CI 72.8–84.8%) for detection of a 50% PSA response at 12 wk.

We defined the positive predictive value (PPV) as the probability of achieving a biochemical response at 12 wk for patients with an early PSA decline, and the negative predictive value (NPV) as the probability that patients with no decline at 4 wk will lack a 12-wk PSA response. We used the PSA data reported in the COU-301 (45.9%) and COU-302 (74.2%) trials for the prevalence of a 12-wk PSA response in the postchemotherapy and prechemotherapy cohorts, respectively. Early PSA response had PPV of 85.5% and 95.2%, and NPV of 94.8% and 63.1% for the postchemotherapy and prechemotherapy cohorts, respectively (Table 4).

3.3. *Rising PSA at 4 wk after AA treatment initiation*

Overall, 102 patients (37.2%) experienced a 25% PSA rise after 4 wk of AA, of whom 36/117 were (30.8%) in the prechemotherapy group and 66/157 (42%) in the postchemotherapy group (nonsignificant trend, $p = 0.056$). Patients with an early 25% PSA rise had significantly shorter OS than those without a 25% PSA rise (15.1 vs 23.8 mo; HR 1.7, 95% CI 1.3–2.4; $p = 0.001$) in both univariable and multivariable models (Table 2, Supplementary Table 2). A 25% PSA rise after 4 wk was associated with poorer outcome in both the prechemotherapy and postchemotherapy cohorts (Table 2).

Table 2 – Early prostate-specific antigen (PSA) response or progression and survival

	n (%)	Survival (mo)	HR (95% CI)	*p* value
Early PSA response				
All patients				
≥30% PSA response	126 (46)	25.8 (20–31.5)	0.47 (0.35–0.65)	<0.001
<30% PSA response	148 (54)	15.1 (11.1–19.2)		
Postchemotherapy cohort				
≥30% PSA response	65 (41.4)	18.9 (14.5–23.2)	0.57 (0.39–0.83)	0.003
<30% PSA response	92 (58.6)	10.4 (8.7–12.1)		
Prechemotherapy cohort				
≥30% PSA response	61 (52.1)	43.6 (35.4–51.8)	0.43 (0.25–0.76)	0.004
<30% PSA response	56 (47.9)	21.5 (14.2–28.7)		
Early PSA progression				
All patients				
PSA progression	10 (37.2)	15.1 (9.7–20.6)	1.73 (1.26–2.37)	0.001
No PSA progression	172 (62.8)	23.8 (19.1–28.5)		
Postchemotherapy cohort				
PSA progression	66 (42)	10.3 (8.1–12.5)	1.85 (1.17–2.92) [a]	0.008
No PSA progression	91 (58)	16.3 (13.6–19)		
Prechemotherapy cohort				
PSA progression	36 (30.8)	21.4 (14.7–28.2)	2.43 (1.24–4.76) [b]	0.009
No PSA progression	81 (69.2)	43.6 (28.6–58.7)		

CI = confidence interval, HR = hazard ratio.
[a] Multivariable model for postchemotherapy cohort including baseline PSA (log-transformed), hemoglobin, albumin, alkaline phosphatase (log-transformed), lactate dehydrogenase (log-transformed), neutrophil to lymphocyte ratio (log-transformed), Eastern Cooperative Oncology Group performance status, and pain.
[b] Multivariable model for prechemotherapy cohort including baseline alkaline phosphatase (log-transformed), lactate dehydrogenase (log-transformed), and Eastern Cooperative Oncology Group performance status.

Table 3 – Prostate-specific antigen (PSA) response at 4 wk and 12 wk

	30% PSA response at 4 wk, *n* (%)		RR (95% CI)	*p* value
	No	Yes		
All patients				
30% PSA response at 12 wk				
No response	133 (89.9)	20 (15.9)	8.3 (5.1–13.5)	<0.001
Response	15 (10.1)	106 (84.1)		
50% PSA response at 12 wk				
No response	139 (93.9)	36 (28.6)	11.7 (6.1–22.3)	<0.001
Response	9 (6.1)	90 (71.4)		
Postchemotherapy cohort				
30% PSA response at 12 wk				
No response	89 (96.7)	14 (21.5)	24.1 (7.8–73.7)	<0.001
Response	3 (3.3)	51 (78.5)		
50% PSA response at 12 wk				
No response	91 (98.9)	23 (35.4)	59.4 (8.4–421)	<0.001
Response	1 (1.1)	42 (64.6)		
Prechemotherapy cohort				
30% PSA response at 12 wk				
No response	44 (78.6)	6 (9.8)	4.2 (2.5–7)	<0.001
Response	12 (21.4)	55 (90.2)		
50% PSA response at 12 wk				
No response	48 (85.7)	13 (21.3)	5.5 (2.9–10.6)	<0.001
Response	8 (14.3)	48 (78.7)		

CI = confidence interval; RR = relative risk.

Of 102 patients experiencing a 25% PSA rise at 4 wk, 49 (48%) experienced confirmed PCWG2 PSA progression (25% increase) at 12 wk; this early PSA rise was significantly associated with confirmed progression at 12 wk ($p < 0.001$). Patients experiencing a 25% PSA rise at 4 wk were 5.5 times more likely to have PCWG2 PSA progression at 12 wk (Table 5). Of the patients with a 25% PSA rise at 4 wk, nine (8.8%) and four (3.9%) achieved confirmed 30% and 50% PSA responses, respectively, after 12 wk on AA. An early 25% PSA rise at 4 wk remained significantly associated with 12-wk PCWG2 PSA progression for the postchemotherapy and prechemotherapy cohorts (Table 5). A 25% PSA rise at 4 wk had sensitivity of 76.6% (95% CI 64.9–85.3%) and specificity of 74.8% (95% CI 68.5–80.2%) for detection of confirmed progression at 12 wk (Table 4).

Table 4 – Sensitivity, specificity, and predictive value [a] of early (4 wk) PSA response and progression

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
All patients				
30% PSA response	87.6 (80.6–92.3)	86.9 (80.7–91.4)		
PSA progression	76.6 (64.9–85.3)	74.8 (68.5–80.2)	–	–
Postchemotherapy cohort				
30% PSA response	94.4 (84.9–98.1)	86.4 (78.5–91.7)	85.5 (78.3–90.6)	94.8 (85.9–98.2)
PSA progression	30.9 (20.3–44)	83.3 (74.9–89.3)	–	–
Prechemotherapy cohort				
30% PSA response	82.1 (71.3–89.5)	88 (76.2–94.3)	95.2 (90.2–97.7)	63.1 (50.3–74.2)
PSA progression			–	–

PSA = prostate-specific antigen; CI = confidence interval, NPV = negative predictive value, PPV = positive predictive value.
[a] To estimate the PPV and NPV of a 30% PSA response, the prevalence was estimated using the rates of 30% PSA response at 12 wk for the COU-301 (postchemotherapy cohort) and COU-302 (prechemotherapy cohort) trials, respectively.

Table 5 – Prostate-specific antigen (PSA) progression at 4 and 12 wk

	PSA progression at 12 wk, *n* (%)		RR (95% CI)	*p* value
	No	Yes		
All patients				
No PSA progression at 4 wk	157 (91.3)	15 (8.7)	5.5 (3.3–9.3)	<0.001
PSA progression at 4 wk	53 (52)	49 (48)		
Postchemotherapy cohort				
No PSA progression at 4 wk	81 (89)	10 (11)	4.5 (2.4–8.6)	<0.001
PSA progression at 4 wk	33 (50)	33 (50)		
Prechemotherapy cohort				
No PSA progression at 4 wk	76 (93.8)	5 (6.2)	7.2 (2.9–18.1)	<0.001
PSA progression at 4 wk	20 (55.6)	16 (44.4)		

CI = confidence interval; RR = relative risk.

4. Discussion

Better tools to assess treatment responses are needed to improve care for patients with advanced PCa, with patients currently receiving 12 wk of a new treatment before a switch decision is made owing to challenges in imaging bone disease [23]. Treatment switch decisions are frequently driven by alternative biomarkers (particularly PSA) and symptoms; this impacts progression-free survival measures, which may not always correlate with OS [24]. Post-treatment PSA changes correlate with prognosis but are not validated as a surrogate for survival [14–16]. Nonetheless, monthly PSA tests during treatment are commonly used to monitor responses, with a recent survey indicating that specialists frequently advise treatment switches before 12 wk on a novel treatment have elapsed [25]. Assessing PSA changes in the first 12 wk of treatment with novel androgen receptor (AR) signaling inhibitors is therefore of major practical relevance to routine patient care. We arguably describe the first correlation between PSA decline after 4 wk of AA + prednisolone treatment and outcome. We report that a PSA decline of 30% and PSA rise of 25% after only 4 wk of AA + prednisolone could identify patients who may or may not be benefitting from AA treatment, indicating a need for further validation studies to evaluate this critically important question.

Overall, we report that patients with a PSA decline of 30% at 4 wk have substantially longer OS, with an 8.3-fold higher likelihood of a response at 12 wk. Of these patients, 78.5% and 90% in the prechemotherapy and postchemotherapy populations, respectively, had a 50% PSA decline at 12 wk. Conversely, only 15.9% of patients with a 30% PSA decline at 4 wk did not meet the response criteria at 12 wk (Table 3). However, concerns regarding misinterpretation of such early PSA changes have been raised because of late decreases in PSA reported for ≥20% of mCRPC patients treated with docetaxel [26] and cabazitaxel [19]. This phenomenon, described by some as *PSA flare*, may not be associated with a worse outcome [19]. Indeed, in a post hoc analysis of TAX-327 it was estimated that PSA flare (defined as any PSA rise not reaching the progression criterion or a rise that satisfied the progression criterion but with a later measurement that was <50% of the baseline value) occurred in 16.7% of patients [18]. However, drugs targeting AR signaling, such as abiraterone and enzalutamide, may have a very different relationship to early PSA decreases, since PSA is a excellent pharmacodynamic biomarker of AR signaling in the absence of aberrations of the PSA promoter or key regulators of PSA production and secretion [27].

Conversely, we report that a 25% PSA rise at 4 wk was associated with a 5.5-fold higher likelihood of biochemical progression at 12 wk. Overall, only nine (3.2%) and four (1.5%) patients with a 25% PSA rise at 4 wk achieved 30% and 50% PSA decreases, respectively, at 12 wk; this early PSA increase was associated with worse prognosis in prechemotherapy (21.4 vs 43.6 mo; HR 1.85, 95% CI 1.17–2.92; $p < 0.009$) and postchemotherapy (10.3 vs 16.3 mo; HR 2.43, 95% CI 1.24–4.76; $p < 0.008$) cohorts. The frequency of a 25% PSA rise at 4 wk was similar in the prechemotherapy and postchemotherapy populations, possibly reflecting the ~30% of patients with AA-refractory disease regardless of

prior docetaxel therapy. The data also indicate that a PSA response is very uncommon after a 25% PSA rise at 4 wk. A previous retrospective study reported an 8.7% (9/103) flare rate on AA as second-line treatment [20]. Our data may differ because of our more stringent definition of flare, in accordance with PCWG criteria.

Finally, this study is limited by its retrospective nature and requires further validation in prospective studies. Moreover, it involved outcomes for patients at a single institution, so confirmation, preferably in multicentre international studies, is required.

5. Conclusion

PSA changes as early as 4 wk after AA initiation are highly associated with OS and PSA response at 12 wk in both prechemotherapy and postchemotherapy (docetaxel) settings. PSA flare is uncommon following AA. Prospective trials are now warranted to further validate these findings to give clinicians robust data that can assist them with earlier decisions to switch treatment.

Author contributions: Johann S. de Bono had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: de Bono, Rescigno, D Lorente.
Acquisition of data: Rescigno, Bianchini, Ferraldeschi, Sideris, Smith, Kolinsky, Mehra, Jayaram, Zafeiriou, Mateo, Reid.
Analysis and interpretation of data: Rescigno, Lorente.
Drafting of the manuscript: Rescigno.
Critical revision of the manuscript for important intellectual content: de Bono, Attard, Dearnaley, Parker.
Statistical analysis: Lorente.
Obtaining funding: de Bono.
Administrative, technical, or material support: Sumanasuriya, Perez-Lopez, Tunariu.
Supervision: de Bono.
Other: None.

Financial disclosures: Johann S. de Bono certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This work was supported by a Movember/Prostate Cancer UK Centre of Excellence Program grant and Prostate Cancer Foundation Project grants. Gerhardt Attard is supported by a Cancer Research UK Clinician Scientist Fellowship. David Lorente was the recipient of a grant from the Spanish Medical Oncology Society (BECA SEOM para la Investigación Traslacional en el Extranjero). The sponsors played a role in data analysis and in manuscript preparation and review.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.02.055.

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