

Early Post-treatment Prostate-specific Antigen at 4 Weeks and Abiraterone and Enzalutamide Treatment for Advanced Prostate Cancer: An International Collaborative Analysis

Pasquale Rescigno^{a,b,c}, David Dolling^d, Vincenza Conteduca^e, Mattia Rediti^{a,f}, Diletta Bianchini^b, Cristian Lolli^e, Michael Ong^g, Haoran Li^g, Aurelius G. Omlin^h, Sabine Schmid^h, Orazio Caffoⁱ, Andrea Zivi^j, Carmel J. Pezaro^k, Courtney Morley^k, David Olmos^l, Nuria Romero-Laorden^l, Elena Castro^l, Maria I. Saez^m, Niven Mehraⁿ, Stella Smeenkⁿ, Spyridon Sideris^f, Thyerry Gil^f, Patricia Banks^o, Shaneen K. Sandhu^o, Cora N. Sternberg^p, Ugo De Giorgi^e, Johann S. De Bono^{a,b,*}

^aThe Institute of Cancer Research, Sutton, UK; ^bThe Royal Marsden NHS Foundation Trust, Sutton, UK; ^cUniversity of Naples Federico II, Naples, Italy; ^dClinical Trials and Statistics Unit, The Institute of Cancer Research, London, UK; ^eIstituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), IRCCS, Meldola, Italy; ^fJules Bordet Institut, Brussels, Belgium; ^gThe Ottawa Hospital Cancer Centre, Ottawa, Canada; ^hDepartment of Medical Oncology and Haematology, Cantonal Hospital St. Gallen, University of Bern, Bern, Switzerland; ⁱSanta Chiara Hospital, Trento, Italy; ^jOspedale dell'Angelo Mestre, AULSS3 Serenissima, UOC Oncologia, Venice, Italy; ^kMonash University and Eastern Health, Box Hill, Australia; ^lSpanish National Cancer Research Center, Madrid, Spain; ^mHospital Virgen de la Victoria, Malaga, Spain; ⁿDepartment of Medical Oncology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; ^oDivision of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; ^pEnglander Institute for Precision Medicine, Weill Cornell Medicine, New York-Presbyterian, New York, NY, USA

Article info

Article history:

Accepted June 12, 2019

Associate Editor:

Paul Nguyen

Keywords:

Prostate cancer
Prostate-specific antigen
Abiraterone acetate
Enzalutamide
Overall survival

Abstract

Background: Declines in prostate-specific antigen (PSA) levels at 12 wk are used to evaluate treatment response in metastatic castration-resistant prostate cancer (mCRPC). PSA fall by $\geq 30\%$ at 4 wk (PSA4w30) has been reported to be associated with better outcome in a single-centre cohort study.

Objective: To evaluate clinical relevance of early PSA decline in mCRPC patients treated with next-generation hormonal treatments (NGHTs) such as abiraterone and enzalutamide.

Design, setting, and participants: This was a retrospective multicentre analysis. Eligible patients received NGHT for mCRPC between 6 January 2006 and 31 December 2017 in 13 cancer centres worldwide, and had PSA levels assessed at baseline and at 4 and/or 12 wk after treatment. PSA response was defined as a $\geq 30\%$ decline (progression as a $\geq 25\%$ increase) from baseline.

Outcome measurements and statistical analysis: Association with overall survival (OS) was analysed using landmark multivariable Cox regression adjusting for previous chemotherapy, including cancer centre as a shared frailty term.

Results and limitations: We identified 1358 mCRPC patients treated with first-line NGHT (1133 had PSA available at 4 wk, and 948 at both 4 and 12 wk). Overall, 583 (52%) had a PSA4w30; it was associated with longer OS (median: 23; 95% confidence

* Corresponding author. Division of Clinical Studies, The Institute of Cancer Research, 1 Cotswold Road, London SM2 5NG, UK. Tel.: +44 02087224028; Fax: +44 02086427979.
E-mail address: johann.de-bono@icr.ac.uk (J.S. De Bono).

interval [CI]: 21–25) compared with no change (median: 17; 95% CI: 15–18) and progression (median: 13; 95% CI: 10–15). A PSA12w30 was associated with lower mortality (median OS 22 vs 14; hazard ratio = 0.57; 95% CI = 0.48–0.67; $p < 0.001$). PSA4w30 strongly correlated with PSA12w30 ($\rho = 0.91$; 95% CI = 0.90–0.92; $p < 0.001$). In total, 432/494 (87%) with a PSA4w30 achieved a PSA12w30. Overall, 11/152 (7%) patients progressing at 4 wk had a PSA12w30 (1% of the overall population).

Conclusions: PSA changes in the first 4 wk of NGHT therapies are strongly associated with clinical outcome from mCRPC and can help guide early treatment switch decisions.

Patient summary: Prostate-specific antigen changes at 4 wk after abiraterone/enzalutamide treatment are important to determine patients' outcome and should be taken into consideration in clinical practice.

© 2019 The Author(s). Published by Elsevier B.V. on behalf of European Association of Urology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Prostate-specific antigen (PSA) is still widely used for diagnosis and treatment evaluation of prostate cancer [1,2], with the consensus criteria of the Prostate Cancer Working Group (PCWG3) defining response to treatment and progression based on composite measures of clinical, radiologic, and PSA changes [3]. PCWG3 criteria suggest reporting PSA response as waterfall plots; however, a 30% PSA decline at 12 wk after treatment initiation has strongly been associated with improved overall survival (OS) from metastatic castration-resistant prostate cancer (mCRPC) [4–6]. Conversely, PSA progression, defined as a 25% increase from baseline/nadir, has been correlated with a poor outcome [7,8]. More recently, PSA kinetics has been reported to meet OS surrogacy criteria [9]. Evaluation of PSA earlier than 12 wk from treatment initiation has traditionally been discouraged because of the possibility of late responses and flare reactions in patients [3,10,11] treated with taxanes.

We have previously reported a single-institution retrospective study showing that early falls in PSA by $\geq 30\%$ after 4 wk of treatment with abiraterone acetate (AA), this being a pharmacodynamic measure of androgen receptor blockade, are associated with improved OS as well as biochemical responses after 12 wk in both the pre- and the postchemotherapy setting, with PSA “flares” being rare after AA [12]. In the present analyses, we report on an international study involving 13 cancer centres evaluating the association between early PSA changes (after 4 wk of treatment) and outcomes from mCRPC after AA and enzalutamide. We envisioned that early PSA changes could help facilitate earlier treatment switch decisions.

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 and/or

enzalutamide outside of a clinical trial between 06 January 2006 and 31 December 2017 in 13 cancer centres worldwide were considered eligible for this analysis. Additional inclusion criteria were the availability of PSA levels assessed at baseline, and after 4 and/or 12 wk of treatment; a physical examination, including Eastern Cooperative Oncology Group performance status; and routine safety blood test laboratory studies, including a full blood count (haemoglobin, neutrophil, and lymphocyte count) and biochemistry comprising alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) at baseline and during treatment. Every institution has received ethic board approval for the treatment of patient data. All patients' data were anonymised and handled according to the Data Protection Act.

2.2. Endpoint definition

OS was defined as the time between treatment initiation and the date of either death or the last follow-up for surviving patients.

PSA decline endpoints evaluated were consistent with published consensus guidelines (PCWG3). The percentage change in PSA from baseline at 4 and 12 wk was categorised as a decline ($\geq 30\%$ decrease), progression ($\geq 25\%$ increase), or no change. A PSA reading not meeting the criteria of either response or progression was considered as “no change”.

2.3. Statistical analysis

Baseline characteristics are compared by chemotherapy status. Differences by chemotherapy status in categorical characteristics were tested using Fisher's exact test and continuous variables were compared using the Wilcoxon rank-sum test. The Kaplan-Meier method and landmark multivariable Cox models were used to assess for differences in OS, including cancer treatment centre as a shared frailty term. The multivariable Cox model included categorical PSA change; chemotherapy status; treatment; Gleason index; tumour, node, and metastasis status at diagnosis; opiate use at the start of treatment; haemoglobin; ALP; LDH; and neutrophil-lymphocyte ratio (NLR). Haemoglobin, LDH, ALP, and NLR were log transformed. Approximately 70% of patients were missing one or more of these characteristics. To avoid a loss in efficiency in the multivariable analysis, multiple imputation by chained equations was used to generate 40 imputations, and per-imputation estimates were combined using Rubin's rules. A multivariable fractional polynomial Cox model was used to determine the association of OS with continuous change in PSA and the previously specified multivariable

Table 1 – Baseline characteristics.

Characteristic	Prechemotherapy (N = 530)		Postchemotherapy (N = 603)		p value ^a	Total (N = 1133)	
	N	%	N	%		N	%
PSA change at week 4							
No change	156	29	188	31	0.75	344	30
Progression	95	18	111	18	–	206	18
Decline	279	53	304	50	–	583	52
Gleason score at diagnosis							
<8	250	47	269	45	0.70	519	46
≥8	212	40	252	42	–	464	41
Missing	68	13	82	14	–	150	13
M status at diagnosis							
M0	243	46	226	38	0.01	469	41
M1	261	49	351	58	–	612	54
Missing	26	5	26	4	–	52	5
N status at diagnosis							
N0	232	44	196	33	<0.001	428	38
N1	110	20.8	168	28	–	278	26
Missing	188	36	239	40	–	427	38
T status at diagnosis							
T < 3	131	25	122	21	<0.001	253	22
T ≥ 3	243	46	222	37	–	465	41
Missing	156	29	259	43	–	415	37
Opiates at start of NGHT							
No	417	79	328	54	<0.001	745	66
Yes	94	18	256	43	–	350	31
Missing	19	4	19	3	–	38	3
Metastatic disease at start of NGHT							
Bone	244	46	224	37	<0.001	468	41
LND	78	15	50	8	–	128	11
Visc	5	1	6	1	–	11	1
Bone + LND	140	26	226	38	–	366	32
Bone + Visc	16	3	26	4	–	42	4
LND + Visc	6	1	11	2	–	17	2
Bone + LND + Visc	35	7	58	10	–	93	8
Missing	7	1	1	0	–	8	1
Lab values at start of NGHT							
	Median	IQR	Median	IQR	p value ^b	Median	IQR
PSA	56	20–132	99	30–339	<0.001	73	25–234
Hb	12	11–13	12	10–13	<0.001	12	11–13
ALP	108	75–182	139	77–307	<0.001	117	76–233
LDH	206	164–302	213	172–332	0.03	210	168–317
NLR	3	2–4	3	2–4	0.2	3	2–4

ALP = alkaline phosphatase; Hb = haemoglobin; IQR = interquartile range; LDH = lactate dehydrogenase; LND = lymph node disease; NGHT = next-generation hormonal treatment; NLR = neutrophil-lymphocyte ratio; PSA = prostate-specific antigen; Visc = visceral disease.

^a Fisher's exact test.
^b Wilcoxon rank-sum test.

covariates. The cancer treatment centre could not be included in this model as a shared frailty term and so was included as a categorical covariate.

3. Results

We identified 1358 patients treated with either AA or enzalutamide as a first-line hormonal agent for mCRPC in the pre- or post-chemotherapy settings. A total of 1133 patients had a PSA result available after 4 wk with survival data, while 948 had PSA results available at both 4- and 12-wk time points; of these, 938 had survival data. The overall patient characteristics are summarised in Table 1; 583 of 1133 (52%) patients had a ≥30% PSA decline at 4 wk. Out of the 948 patients with PSA results available at both 4 and 12 wk, 432 of 494 (87%) patients achieved a PSA

decline at 4 and 12 wk. PSA at 4 and 12 wk were strongly correlated ($\rho = 0.91$; 95% confidence interval [CI]: 0.90–0.92; $p < 0.001$). Conversely, 11 of 152 (7%) patients progressing by PSA at 4 wk, which represented 1.1% of

Table 2 – Relationship between week-4 and week-12 PSA changes for patients on first regimen of abiraterone acetate or enzalutamide.

PSA change at week 4	PSA change at week 12		
	No change	Progression	Decline
No change	113 (37%)	100 (33%)	89 (29%)
Progression	19 (13%)	122 (80%)	11 (7%)
Decline	48 (10%)	14 (3%)	432 (87%)

PSA = prostate-specific antigen.

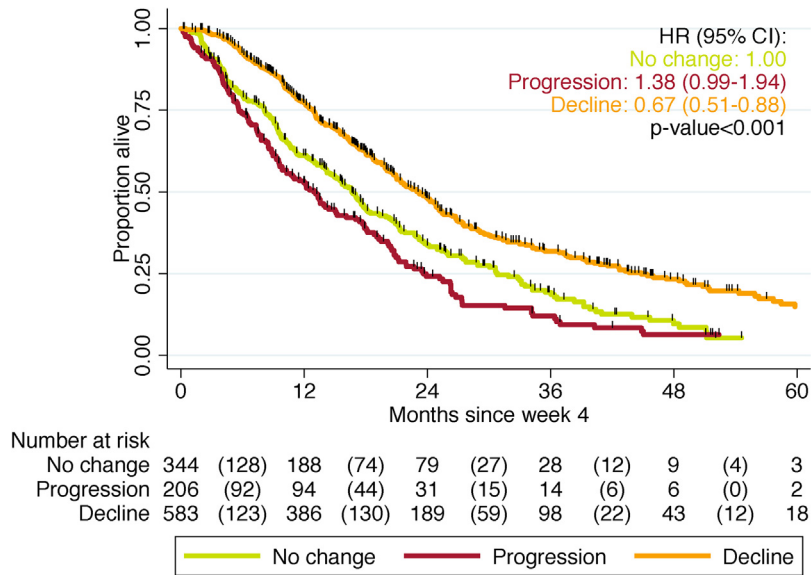


Fig. 1 – Kaplan-Meier curves of overall survival by change in PSA at 4 wk. CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.

the overall population, met the criteria for a 30% PSA decline at 12 wk (Table 2).

A ≥30% PSA decline at 4 wk was associated with longer OS (median: 23 mo; 95% CI: 21–25) compared with patients with no change (median: 17; 95% CI: 15–18) and progression (median: 13 mo; 95% CI: 10–15; Fig. 1). The results from multivariable Cox models, adjusting for known prognostic factors from mCRPC such as ALP, LDH, and NLR, are shown in Table 3. Patients with a ≥30% PSA decline at 4 wk had a reduced incidence of mortality compared with patients with no change (adjusted hazard ratio [aHR]: 0.67; 95% CI: 0.51–0.88, $p < 0.001$); there was no statistically significant evidence of a difference in terms of reduced mortality for patients with a ≥25% increase compared with patients with no change (aHR: 1.38; 95% CI: 0.99–1.94). The results at 12-wk time point were similar, with a ≥30% PSA decline associated with longer OS (median: 22 mo; 95% CI: 19–24; HR: 0.71, 95% CI: 0.50–1.02, $p < 0.001$) compared with patients with no change (median: 16 mo; 95% CI: 12–18) and progression (median: 11 mo; 95% CI: 8–13; Fig. 2). When abiraterone and enzalutamide groups were considered separately, there was no evidence that the association between OS and PSA falls differed by first-line treatment. The multivariable Cox model results are shown in Table 4; there was no formal evidence of a difference in survival for patients with no change at 12 wk compared with those with a ≥30% decline (HR: 0.71; 95% CI: 0.50–1.02) or a ≥25% increase (HR: 1.44; 95% CI: 0.97–2.14).

The results from the multivariable analyses studying PSA change as a continuous variable are displayed in Supplementary Tables 1 and 2, and Supplementary Figures 1 and 2.

3.1. Performance on second hormonal agent after AA/enzalutamide

The PSA response rate at 4 and 12 wk for the second regimen of AA or enzalutamide was available for

Table 3 – Landmark (week 4) multivariable Cox model for association with overall survival.

	n	%	HR	95% CI	p value
PSA change after 4 wk					
No change	344	30	1.00	-	<0.001
Progression	206	18	1.38	0.99–1.94	-
Decline	583	52	0.67	0.51–0.88	-
Chemotherapy status					
Prechemotherapy	531	47	1.00	-	<0.001
Postchemotherapy	602	53	1.67	1.26–2.22	-
PSA change × chemotherapy status					
No change and postchemotherapy	188	31	1.00	-	0.75
Progression and postchemotherapy	111	18	0.87	0.57–1.34	-
Decline and postchemotherapy	303	50	0.89	0.63–1.25	-
Treatment					
Abiraterone	911	80	1.00	-	0.13
Enzalutamide	222	20	0.84	0.67–1.05	-
Gleason Index at diagnosis					
<8	519	53	1.00	-	0.86
≥8	464	47	1.02	0.85–1.22	-
M status at diagnosis					
M0	469	43	1.00	-	0.79
M1	612	57	1.02	0.86–1.22	-
N status at diagnosis					
N0	428	61	1.00	-	0.44
N1	278	39	1.08	0.88–1.32	-
T status at diagnosis					
T <3	253	35	1.00	-	0.89
T ≥3	465	65	0.98	0.80–1.21	-
Opiates at start of treatment					
No	745	68	1.00	-	<0.001
Yes	350	32	1.46	1.22–1.73	-
Lab values at start of treatment					
Med	IQR	HR	95% CI	p value	
Hb (log ₁₀ g/dl)	1.08	1.02–1.11	0.95	0.62–1.46	0.8
ALP (log ₁₀ U/l)	2.07	1.88–2.37	2.28	1.86–2.81	<0.001
LDH (log ₁₀ U/l)	2.32	2.23–2.50	1.62	1.14–2.28	0.007
NLR (log ₁₀)	0.48	0.30–0.62	1.57	1.12–2.20	0.008
ALP = alkaline phosphatase; CI = confidence interval; Hb = haemoglobin; HR = hazard ratio; IQR = interquartile range; LDH = lactate dehydrogenase; NLR = neutrophil-lymphocyte ratio; PSA = prostate-specific antigen.					

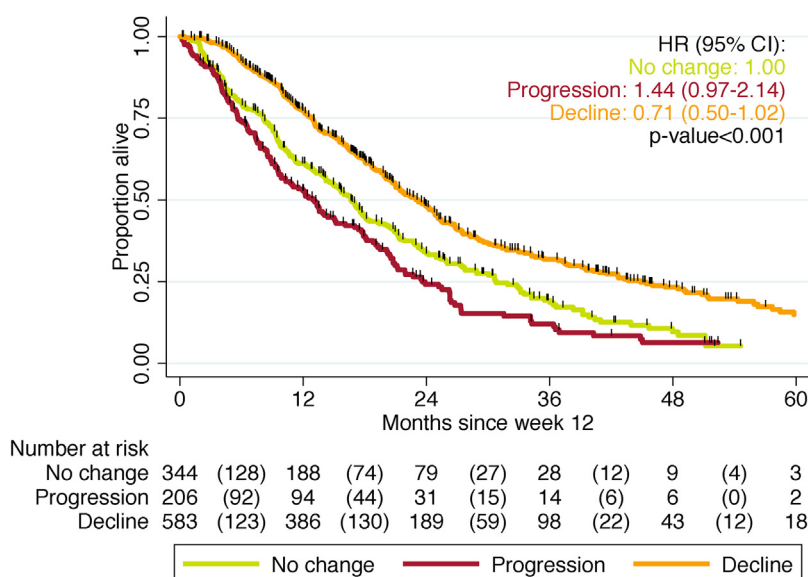


Fig. 2 – Kaplan-Meier curves of overall survival by change in PSA at 12 wk. CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.

Table 4 – Landmark (week 12) multivariable Cox model for association with overall survival.

	n	%	HR	95% CI	p value
PSA change at week 12					
No change	179	19	1.00	–	<0.001
Progression	231	25	1.44	0.99–2.14	–
Decline	528	56	0.71	0.50–1.02	–
Chemotherapy status					
Prechemotherapy	426	45	1.00	–	0.006
Postchemotherapy	512	55	1.73	1.17–2.57	–
PSA change at week 12 × chemotherapy status					
No change and postchemotherapy	103	20	1.00	–	0.4
Progression and postchemotherapy	134	26	0.97	0.59–1.59	–
Decline and postchemotherapy	275	54	0.79	0.50–1.24	–
Treatment					
Abiraterone	756	81	1.00	–	0.1
Enzalutamide	182	19	0.81	0.63–1.05	–
Gleason Index at diagnosis					
<8	435	53	1.00	–	0.9
≥8	383	47	1.01	0.82–1.23	–
M status at diagnosis					
M0	405	45	1.00	–	0.9
M1	495	55	0.99	0.82–1.19	–
N status at diagnosis					
N0	369	61	1.00	–	0.7
N1	236	39	1.05	0.84–1.31	–
T status at diagnosis					
T <3	216	36	1.00	–	0.9
T ≥3	390	64	1.01	0.80–1.28	–
Opiates at start of treatment					
No	616	68	1.00	–	<0.001
Yes	294	32	1.42	1.18–1.71	–
Lab values at start of treatment Med IQR HR 95% CI p value					
Hb (log ₁₀ g/dl)	1.08	1.02–1.11	0.90	0.54–1.51	0.7
ALP (log ₁₀ U/l)	2.07	1.89–2.36	2.15	1.72–2.70	<0.001
LDH (log ₁₀ U/l)	2.32	2.23–2.50	1.50	1.08–2.09	0.02
NLR (log ₁₀)	0.48	0.30–0.61	1.76	1.21–2.56	0.003

ALP = alkaline phosphatase; CI = confidence interval; Hb = haemoglobin; HR = hazard ratio; IQR = interquartile range; LDH = lactate dehydrogenase; NLR = neutrophil-lymphocyte ratio; PSA = prostate-specific antigen.

168 patients (Supplementary Table 3). A PSA decline of ≥30% at 4 wk was observed in 42/168 (25%) patients and that at 12 wk was observed in 42/168 (25%) patients. There was less concordance between observed PSA declines on second next-generation hormonal treatment (NGHT). Overall, 29/42 (69%) patients with a PSA decline at 4 wk had a PSA decline at 12 wk. There was no evidence in a univariable logistic regression model that the time on previous NGHT was associated with a PSA decline of ≥30% at 12 wk (odds ratio = 0.93 per year on treatment; 95% CI: 0.56–1.54; $p = 0.77$).

Finally, the results from the multivariable analyses studying PSA changes at both week 4 and week 12 are displayed in Supplementary Table 4, and indicate that the presence of a 30% PSA fall at 4 wk confirmed at 12 wk associates with superior OS when compared with all the other possible PSA outcomes.

4. Discussion

Evaluation of responses to treatment for mCRPC remains challenging. In the localised setting, a PSA increase of >0.5 ng/ml after prostatectomy or 2 ng/ml above the nadir after radical radiotherapy has been proved to be a sensitive biomarker to identify men who are at a high risk of relapse or death [13,14]. On the contrary, in the metastatic setting, consensus criteria based on PSA and radiologic biomarkers are inconsistently utilised. A recent study inquiring into clinical management decisions of physicians in mCRPC has shown that despite being considered an important biomarker, 41.4% of the interviewed population disregarded changes in PSA before 12 wk of treatment had elapsed, while the majority of physicians (90.5%) switched treatment based only on clinical progression [15].

A PSA decline by ≥30% after 12 wk of treatment start has been associated with OS in mCRPC [4–6]; more recently, PSA

performances at 12 wk have also been reported as a criterion for treatment switch in the TAXYNERGY study [16]. In this study, PSA declines were associated with taxane responses, and decreased androgen receptor nuclear localisation and increased microtubule bundling in circulating tumour cells [16]. Nevertheless, PCWG3 criteria have discouraged treatment decisions based on early PSA changes, since flare reactions within the first 12 wk of treatment have been described in approximately a third of patients treated with docetaxel and cabazitaxel [3,10,11]. In our previously reported single-centre retrospective analysis, on a cohort of 274 mCRPC patients treated at the Royal Marsden Hospital, we have reported that a 30% PSA decline at 4 wk was associated with longer OS, significantly correlating with PSA falls at 12 wk [12]. In the current analysis, we have collected survival data for 1133 mCRPC patients treated with AA or enzalutamide (NGHT) in 13 cancer centres worldwide. We have confirmed the clinical relevance and prognostic value of early PSA declines in patients treated with NGHT before or after chemotherapy. Unlike chemotherapy, in this study, we can confirm that an early PSA flare, defined as an increase of >25% in the first 4 wk followed by a decline of >30% from baseline at wk 12, is very uncommon following AA and enzalutamide, involving only 1% of the overall population treated with NGHT. These data corroborate our previous single-centre analyses and other experiences on patients treated with AA [12].

Our results may also be important to the hormone-sensitive prostate cancer (HSPC) setting. In the LATITUDE study, a prospective randomised phase 3 trial randomising newly diagnosed metastatic HSPC men to either AA and androgen deprivation therapy (ADT) or placebo and ADT, investigators showed that PSA response and time to PSA nadir correlated with radiographic progression-free survival and OS. Patients who reached their PSA nadir in <6 mo had a median time to death of 29.57 mo, while patients who achieved a PSA nadir after 12 mo or more did not reach the median time to death [17]. However, the clinical utility of this biomarker is unclear, as the time to nadir and the depth of nadir can be determined only retrospectively. The LATITUDE study included a PSA assessment at week 4; according to our results, it could be of interest to analyse PSA decline at 4 wk as a surrogate biomarker of clinical outcome even in this patient population. Therefore, early identification of patients benefiting from NGHT could be of paramount importance for optimal treatment delivery and cost effectiveness in HSPC. Prior versions of the PCWG criteria were based on mCRPC; new versions should consider specific surrogate of response and clinical outcome also in HSPC.

Our study also investigated the likelihood of achieving a PSA decline from second-line NGHT after prior exposure to AA or enzalutamide. A 30% PSA reduction was much less common in this second-line NGHT setting at both 4 and 12 wk compared with patients treated with NGHT as first line (respectively, 25% vs 51.3% and 25% vs 56.1%). These data confirm what was previously reported in a multicentre, single-arm, open-label study, where patients with progressing mCRPC after ≥ 24 wk of AA plus prednisone treatment were enrolled to receive second-line enzalutamide. In this

study, the unconfirmed PSA response rate was 27% (48 of 181) with a median time-to-PSA progression of 5.7 mo [18], demonstrating that second-line enzalutamide has modest antitumour activity in this selected population [18]. Although less striking, our analyses now show that early PSA declines are also associated with PSA response at 12 wk in the setting of second-line NGHT. Therefore, we hypothesise that the lack of a $\geq 30\%$ PSA fall at 4 wk could be used to discontinue patients from second-line NGHT, saving patients from time on ineffective therapy and avoiding the poor utilisation of health-care resources.

Finally, we acknowledge that despite the clinical relevance of these international multicentre analyses, this study remains limited by its retrospective nature with a risk of selection bias and requires validation in prospective studies.

5. Conclusions

PSA changes as early as 4 wk after initiation of NGHT are significantly associated with OS and PSA response at 12 wk in both pre- and postchemotherapy settings, while a PSA early flare after NGHT exposure is very uncommon, according to our definition. Early PSA changes are also able to predict a response to second-line NGHT, allowing early treatment change and avoiding unnecessary therapies, toxicities, and expenses for patients. Nevertheless, despite our data coming from a large multicentre population, prospective trials are now warranted to further validate these findings to obtain robust evidence for 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: Rescigno.

Acquisition of data: Conteduca, Rediti, Bianchini, Lolli, Li, Schmid, Zivi, Morley, Romero-Laorden, Saez, Smeenk, Sideris, Banks.

Analysis and interpretation of data: Rescigno, de Bono.

Drafting of the manuscript: Rescigno, Dolling.

Critical revision of the manuscript for important intellectual content: Conteduca, Ong, Omlin, Caffo, Zivi, Pezaro, Castro, Olmos, Mehra, Sideris, Gil, Sandhu, Sternberg, De Giorgi, de Bono.

Statistical analysis: Dolling.

Obtaining funding: de Bono.

Administrative, technical, or material support: Bianchini, Rediti.

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: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2019.06.008.

References

- [1] Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate Specific Antigen. *J Clin Oncol* 1999;17:3461–7.
- [2] Kelly WK, Scher HI, Mazumdar M, Vlamis V, Schwartz M, Fossa SD. Prostate-specific antigen as a measure of disease outcome in metastatic hormone-refractory prostate cancer. *J Clin Oncol* 1993;11:607–15.
- [3] Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials 3. *J Clin Oncol* 2016;34:1402–18.
- [4] Sridhara R, Eisenberger MA, Sinibaldi VJ, Reyno LM, Egorin MJ. Evaluation of prostate-specific antigen as a surrogate marker for response of hormone refractory prostate cancer to suramin therapy. *J Clin Oncol* 1995;13:2944–53.
- [5] Hussain M, Goldman B, Tangen C, et al. Prostate-specific antigen progression predicts overall survival in patients with metastatic prostate cancer: data from Southwest Oncology Group Trials 9346 (Intergroup Study 0162) and 9916. *J Clin Oncol* 2009;27:2450–6.
- [6] Petrylak DP, Ankerst DP, Jiang CS, et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG99-16. *J Natl Cancer Inst* 2006;98:516–21.
- [7] Armstrong AJ, Garrett-Mayer E, Ou Yang YC, et al. Analysis of prostate-specific antigen decline as a surrogate for overall survival in metastatic hormone-refractory prostate cancer (HRPC): a TAX327 analysis. *J Clin Oncol* 2007;25:3965–70.
- [8] Halabi S, Armstrong AJ, Sartor O, et al. Prostate-specific antigen changes as surrogate for overall survival in men with metastatic castration-resistant prostate cancer treated with second line chemotherapy. *J Clin Oncol* 2013;31:3944–50.
- [9] Xu XS, Ryan CJ, Stuyckens K, et al. Correlation between prostate-specific antigen kinetics and overall survival in abiraterone acetate treated castration-resistant prostate cancer patients. *Clin Cancer Res* 2015;21:3170–7.
- [10] Berthold DR, Pond GR, Roessner M, et al. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life. Response and survival in the TAX-327 study. *Clin Cancer Res* 2008;14:2763–7.
- [11] Angelelrgues A, Maillet D, Fléchon A, et al. Prostate-specific antigen flare induced by cabazitaxel-based chemotherapy in patients with metastatic castration-resistant prostate cancer. *Eur J Cancer* 2014;50:1602–9.
- [12] Rescigno P, Lorente D, Bianchini D, et al. Prostate-specific antigen decline after 4 weeks of treatment with abiraterone acetate and overall survival in patients with metastatic castration-resistant prostate cancer. *Eur Urol* 2016;70:724–31.
- [13] Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591–7.
- [14] Royce TJ, Chen MH, Wu J, et al. Surrogate end points for all-cause mortality in men with localized unfavorable-risk prostate cancer treated with radiation therapy vs radiation therapy plus androgen deprivation therapy: a secondary analysis of a randomized clinical trial. *JAMA Oncol* 2017;3:652–8.
- [15] Lorente D, Ravi P, Mehra N, et al. Interrogating metastatic prostate cancer treatment switch decisions: a multi-institutional survey. *Eur Urol Focus* 2018;2:235–44.
- [16] Antonarakis ES, Tagawa ST, Galletti G, et al. Randomized, noncomparative, phase II trial of early switch from docetaxel to cabazitaxel or vice versa, with integrated biomarker analysis, in men with chemotherapy-naïve, metastatic, castration-resistant prostate cancer. *J Clin Oncol* 2017;35:3181–8.
- [17] Matsubara N, Chi KN, Ozguroglu M, et al. LATITUDE study: PSA response characteristics and correlation with overall survival (OS) and radiological progression-free survival (rPFS) in patients with metastatic hormone-sensitive prostate cancer (mHSPC) receiving ADT + abiraterone acetate and prednisone (AAP) or placebo (PBO). *Ann Oncol* 2018;29:viii271–3.
- [18] de Bono JS, Chowdhury S, Feyereabend S, et al. Antitumour activity and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with abiraterone acetate plus prednisone for ≥ 24 weeks in Europe. *Eur Urol* 2018;74:37–45.