ANTICANCER RESEARCH *42*: 165-172 (2022)
doi:10.21873/anticanres.15470

The Role of Fast and Deep PSA Response in Castration-sensitive Prostate Cancer

ROBERTO IACOVELLI[1], CHIARA CICCARESE[1], ORAZIO CAFFO[2], UGO DE GIORGI[3], UMBERTO BASSO[4], MARCELLO TUCCI[5], CLAUDIA MOSILLO[6], MARCO MARUZZO[4], FRANCESCA MAINES[2], CHIARA CASADEI[3], MICHELE MILELLA[7] and GIAMPAOLO TORTORA[1]

[1]*Medical Oncology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy;*
[2]*Department of Medical Oncology, Santa Chiara Hospital, Trento, Italy;*
[3]*Department of Medical Oncology, Scientific Institute Romagnolo for the Study and Treatment of Cancer (IRST) IRCCS, Meldola, Italy;*
[4]*Medical Oncology Unit 1, Istituto Oncologico Veneto IOV IRCCS, Padua, Italy;*
[5]*Division of Medical Oncology, Department of Oncology, University of Turin, San Luigi Gonzaga Hospital, Turin, Italy;*
[6]*Medical Oncology Unit, Azienda Ospedaliera Santa Maria di Terni, Terni, Italy;*
[7]*Medical Oncology Unit, Azienda Ospedaliera Universitaria Integrata (AOUI), Verona, Italy*

Abstract. *Background: Outcomes of castration-sensitive prostate cancer (CSPC) have improved owing to new therapies and early treatment, previously reserved for castration-resistant disease (CRPC). Prostatic-specific antigen (PSA) remains the most used marker to follow-up patients under treatment, but only limited data are available about the prognostic role of its changes over time and the impact of response to subsequent therapies. This analysis aims to assess the prognostic role of the magnitude and velocity of PSA response in CSPC and describe how this may affect the outcome to subsequent treatment outcomes in CRPC. Patients and Methods: A retrospective analysis was performed on patients with de novo CSPC referring to six oncology centers in Italy. Clinical and pathological features were recorded. PSA response (PSA50), defined as a decrease > 50% compared to baseline, PSA velocity (PSAv), defined as any decrease in PSA levels over time and the deep and fast PSA response (4mPSA50), defined as the PSA response reached within the threshold of 4 months from the beginning of androgen deprivation therapy (ADT) have been evaluated for their impact on survival. Survivals were estimated using the Kaplan-Meier method and compared across groups using the log-rank test. Cox proportional-hazard models, stratified according to baseline characteristics, were used to estimate hazard ratios for overall survival (OS). Results: A totals of 94.4% of patients had PSA50, which was correlated to longer OS compared to patients without PSA50 (56.0 vs. 14.8 months; p<0.001). The median PSAv was 6.9 (ng/dl)/month, which was predictive for longer OS: Each decrease of 1 (ng/dl)/month was able to improve OS by 0.2% (HR=0.998, 95%CI=0.997-1.000; p=0.008). A total of 47.9% of patients reached 4mPSA50, with a median OS and progression-free survival (PFS) to ADT-based therapy of 101.0 and 23.4 months compared to 41.9 and 11.0 months for those who did not (p<0.001), respectively. The independent prognostic role of 4mPSA50 was retained even when evaluated in multivariable analysis adjusted for other baseline characteristics and early docetaxel for CSPC. In CRPC, 4mPSA50 evaluated during CSPC retains its prognostic role even if it does not predict a different outcome between patients treated with abiraterone/enzalutamide or taxanes. Conclusion: Achieving a deep and fast PSA response correlates with a better outcome in patients with de novo mCSPC, also positively influencing the prognosis of the subsequent first-line therapy for CRPC disease.*

Correspondence to: Roberto Iacovelli, MD, Ph.D., Fondazione Policlinico Universitario A. Gemelli IRCCS, Medical Oncology Unit, Largo Agostino Gemelli 8, 00168 Rome, Italy. Tel: +39 0630156318, e-mail: roberto.iacovelli@policlinicogemelli.it

Key Words: Prostate cancer, metastatic castration-sensitive prostate cancer, mCSPC, PSA response, first-line therapy.

Prostate cancer (PC) can present with synchronous metastases at the time of initial cancer diagnosis, a condition defined as *de novo* metastatic castration-sensitive prostate cancer (mCSPC). In developed countries, *de novo* mCSPC accounts for only 4% of all PC, and represents a biologically aggressive disease marked by poor prognosis with a 5-year OS rate of about 35% (1-3).

In recent years, survival outcomes of mCSPC men have been improving owing to the evolved strategy of moving life-prolonging treatment options from the castration-resistant phase of the disease (CRPC) forward to the hormone-sensitive setting. Nowadays, the mCSPC treatment algorithm includes new drugs, *e.g.*, docetaxel and new-generation hormonal agents like abiraterone, enzalutamide, or apalutamide, which are added to androgen deprivation therapy (ADT) at an early stage (4-10). The availability of several therapies, not directly compared to each other, complicates the decision-making process. Indeed, besides the profoundly different toxicity profile of chemotherapy and hormonal agents, a reliable molecular and clinical prognostic stratification of mCSPC patients is an urgent need to select for the most appropriate therapy, monitor its efficacy, and identify the ideal administration sequence, which defines optimal and personalized patient management. To date, the main two clinical prognostic models used in the castration-sensitive setting, borrowed from CHARTEED and LATITUDE trials, identify the disease volume (extension of bone metastatic involvement and presence of visceral metastases) as the principal feature influencing patient prognosis (4, 6). However, lack of full correspondence between the two classifications together with the uncertainty about a clear benefit (or the absence of a benefit) of new therapies for some categories of patients (*i.e.*, docetaxel for low-volume patients, abiraterone for low-risk) pushes research forward to identify validated and reproducible prognostic factors. The aim of our analysis was to evaluate the role of PSA response, in terms of magnitude and velocity from the beginning of ADT, and evaluate the possible impact of a deep and fast PSA response on subsequent therapy lines (first-line treatment for CRPC disease).

Patients and Methods

Patients. Medical records of patients affected by *de novo* metastatic prostate cancer, referred to six oncology centers, were screened to find those with metastatic disease at diagnosis. Patients were excluded if baseline characteristics such as histologic diagnosis, extension of disease, or type of treatment were not available. Other baseline characteristics required for study inclusion were: prostate cancer diagnosis with evidence of primary metastatic spread at bone scan, computed tomography (CT), magnetic resonance imaging (MRI), or Choline PET/CT, at time of diagnosis, availability of ECOG performance status, ADT (±docetaxel) initiation and at least one follow-up visit after the initial diagnosis.

PSA was evaluated at baseline and nadir. The latter was the lowest value reported during treatment with ADT or the combination of ADT and docetaxel. PSA response (PSA50) was defined as a decrease >50% compared to baseline; PSA velocity (PSAv) was defined as any decrease in PSA levels over time (ng/dl)/month. Patients with deep and fast PSA response (4mPSA50) were defined in case of a PSA response reached within the threshold of 4 months from the beginning of ADT. The primary endpoint of the present analysis was to assess if patients with PSA50, PSAv, and deep and fast PSA response (4mPSA50) had a better outcome compared to those who did not. The secondary endpoint was to investigate if deep and fast PSA response during treatment for CSPC can be used as a predictive factor for subsequent first line CRPC therapy.

Statistics. Descriptive statistics were used to characterize patients at baseline, which was defined as the date of ADT beginning. Overall survival (OS) was evaluated from the beginning of ADT to death or last follow-up, whichever occurred first; while the castration-resistant overall survival (crOS) was evaluated from the beginning of first line therapy for CRPC to death or last follow-up, whichever occurred first. Progression free survival (PFS) during ADT was evaluated from the beginning of ADT to CRPC diagnosis or last follow-up, whichever occurred first.

All survivals were estimated by the Kaplan-Meier method, and compared across groups using the log-rank test. Cox proportional-hazard models, stratified according to the baseline characteristics, were used to estimate hazard ratios for OS and PFS. All the variables were significant if $p<0.05$. The PASW software (Predictive Analytics SoftWare; v 25; IBM SPSS) was used for the analysis.

Results

Patients. Four hundred and fifteen *de novo* mCSPC patients were reviewed; 215 patients had complete data about PSA and were included in the final analysis. All patients received ADT, while additionally early docetaxel was administered in 28.8% of cases. Other baseline characteristics of the included patients are reported in the Table I. After a median follow-up of 36.1 months, 33% of patients died and 78.6% progressed to ADT with or without docetaxel. The median OS in the whole cohort was 55.0 months (95%CI=47.4-62.5) and the median PFS on ADT was 16.4 months (95%CI=14.6-18.3).

Effect of PSA response and velocity on OS for CSPC. In the overall cohort, 94.4% of patients had PSA50, which correlated significantly to longer OS compared with those without PSA50 (56.0 *vs*. 14.8 months; $p<0.001$). The median PSAv was 6.9 (ng/dl)/month, and it was predictive of longer OS. Indeed, each decrease of 1 (ng/dl)/month was able to improve the OS by 0.2% (HR=0.998, 95%CI=0.997-1.000; $p=0.008$). Given the correlation of both PSA50 and PSAv to OS, we investigated the outcome of patients with both these variables and therefore with deep and fast PSA response: these have been combined in the PSA50 reached within 4 months from the beginning of ADT (4mPSA50). One hundred and three (47.9%) patients reached 4mPSA50; these patients had a median OS of 101.0 months compared to 41.9 months of those who did not ($p<0.001$) (Figure 1A). This benefit was maintained even if a landmark analysis was performed excluding patients who died within six months ($p<0.001$).

The independent prognostic role of 4mPSA50 was retained even when this variable was included in the multivariable analysis adjusted for other baseline characteristics and early

Table I. *Baseline characteristics of included patients*.

Characteristics	Patients N=215
Median age (years)	69.6
Median PSA (ng/dl)	51.0
Gleason Score ≥8 (%)	51.4
Presence of pain (%)	33.8
Site of metastases (%)	
Bone	79.5
Pelvis	70.2
Spine	53.0
Legs/arms	34.9
Skull	22.3
Ribs	12.6
≥3 lesions	52.1
Lymph-nodes	36.7
Visceral (lung, liver)	25.1
CHAARTED Classifications (%)	
High volume	54.0
Low volume	46.0
LATITUDE Classifications (%)	
High risk	45.6
Low risk	54.4
Docetaxel for CSPC (%)	28.8

dl: Deciliter; N: number; ng: nanograms; PSA: prostate specific antigen.

docetaxel (Table II). In patients with high disease volumes according to CHAARTED definition, only 43.1% reached 4mPSA50 compared to 53.5% of patients with low volume, but the difference was not significant (p=0.13). On the contrary, the median PSAv was significantly higher in patients treated with early docetaxel compared to those who were not (–16.6 *vs*. –5.3; *t*-test p=0.026).

Patients with 4mPSA50 had a median PFS to ADT-based therapy of 23.4 compared to 11.0 months of those without a deep and fast PSA response (p<0.001) (Figure 1B). This benefit was maintained even a landmark analysis excluding patients who progressed within six months (p<0.001) or in those who received (20.7 *vs*. 11.0; p=0.058) or not (24.6 *vs*. 10.7; p<0.001) early docetaxel.

Effect of PSA response on first-line therapy for CRPC. In the overall population after progression to ADT-based therapy, 126 out of 215 (46.8%) evaluable patients received first-line CRPC therapy; among these, 75 patients were treated with androgen receptor-targeted agents [(ARTA) *i.e*., abiraterone or enzalutamide] and 51 with taxanes-based therapy. No differences in distribution of therapy type were found between patients with or without 4mPSA50 (p=0.75). The median OS was 29.8 months for patients treated with ARTA, 24.1 months for those treated with taxanes and 11.9 months for those who did not receive any therapy (ARTA or taxanes *vs*. none p<0.05; ARTA *vs*. taxanes p=0.93) (Figure 2).

In the overall cohort 4mPSA50 remained a prognostic factor after the beginning of first line therapy for CRPC (mOS 27.8 *vs*. 20.1 months; p=0.011). In patients previously treated with ADT alone, the median OS was 29.7 months, for those treated with ARTA and 27.8 months for those treated with docetaxel, but the difference was not significant (p=0.94). This difference remains not significant for patients with (39.1 *vs*. 27.8 months; p=0.83) or without 4mPSA50 (29.3 *vs*. 23.6 months; p=0.89). In patients previously treated with ADT plus early docetaxel, no significant difference in survival was observed between patients treated with ARTA compared with those who received cabazitaxel (median OS was 12.8 months *vs*. 12.6 months, p=0.34). This difference remains not significant for patients with (NR *vs*. 16.5 months; p=0.97) or without 4mPSA50 (12.8 *vs*. 12.6 months; p=0.12).

Discussion

PSA represents a useful biomarker in the management of prostate cancer (11). While the negative prognostic value of PSA is substantially ascertained, uncertainty in the clinical significance of PSA changes during treatments makes PSA a questionable predictor of response to therapy.

Several data support the association of PSA with poor prognosis of mCRPC men. Both high pre-treatment PSA levels and short PSA doubling time (PSADT <55 days) at baseline of mCRPC receiving chemotherapy were independently associated with shorter overall survival in an exploratory analysis of 686 men enrolled in the TAX-327 study (12). Similarly, baseline PSA independently impacted OS in the cohort of 1,088 mCRPC patients treated with either abiraterone acetate/prednisone or placebo/prednisone within the COU-AA-302 trial (13). In addition, also the kinetics of PSA values could impact prognosis, as observed in a retrospective analysis of the SWOG 99-16 study that reveled an association between PSA decline during docetaxel chemotherapy and prolonged survival (14). Analogously, an early PSA response in mCRPC patients treated with androgen receptor targeted agents (ARTA) is also linked with improved prognosis (15).

Concerning the predictive role of PSA in the castration-resist setting, it has well-recognized limitations. In particular, taxanes can be responsible of PSA flares at the beginning of treatment in mCRPC patients (16, 17). Nevertheless, the lack of a PSA decline seems not predictive of docetaxel and cabazitaxel efficacy, suggesting that the benefit of taxanes in improving OS may be independent from PSA-related mechanisms (18, 19). The lack of a full concordance between PSA and radiographic or clinical progression in mCRPC men under ARTA treatment makes PSA a doubtful biomarker to use as a unique parameter in clinical practice. Indeed, discordance between PSA changes and radiological progression was

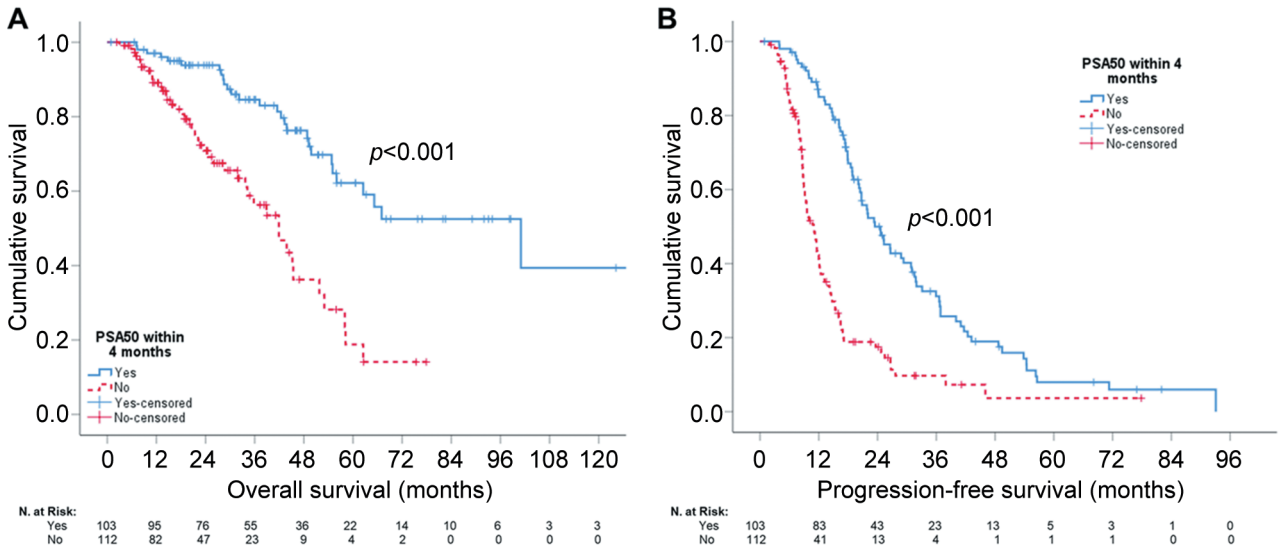

Figure 1. *Overall survival (A) and progression-free survival (B) in patients with or without PSA >50% reduction within 4 months.*

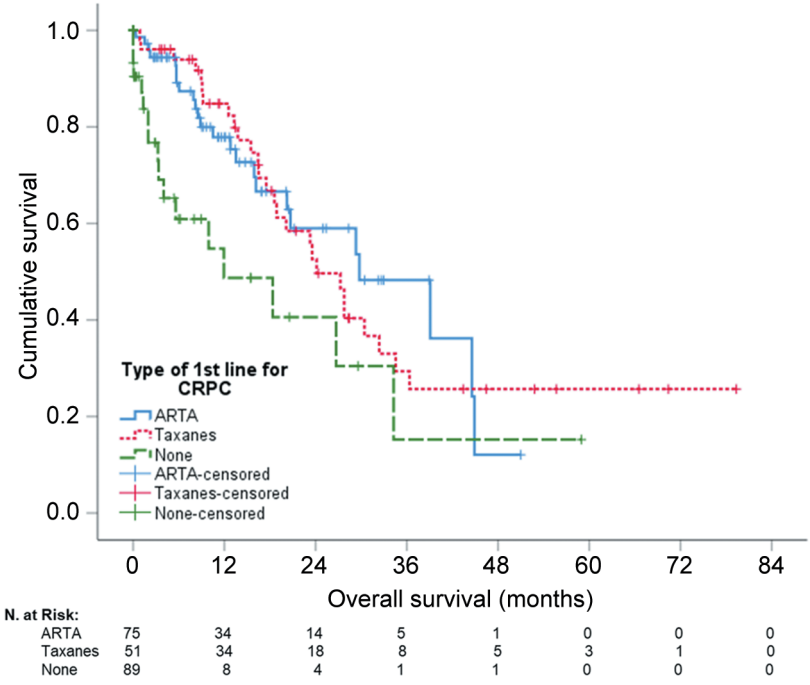

Figure 2. *Overall survival of castration-resistant prostate cancer (CRPC) patients who received androgen receptor targeted agents (ARTA), taxanes or no therapy.*

described in mCRPC patients treated with enzalutamide, both before and after docetaxel therapy (20-22). However, a rapid PSA decline (within the first 90 days after the start of enzalutamide) was associated with longer OS and higher pain response (20). The interesting role of PSA kinetics as an early bridging endpoint of long-term clinical efficacy of abiraterone was also evaluated analyzing several PSA kinetics endpoints (including PSA nadir, PSA response rate [≥30%, 50%, and 90%], time to PSA progression, PSADT). This biomarker-survival modeling framework revealed a strong association

Table II. *Multivariable analysis for overall survival.*

Variable	Univariat analysis			Multivariat analysis		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
4mPSA50 (Y/N)	0.30	0.18-0.50	<0.001	3.33	1.79-6.21	<0.001
Docetaxel (Y/N)	0.47	0.25-0.87	0.017	1.51	0.68-3.33	0.31
Gleason ≥8	1.88	0.92-3.86	0.084	1.35	0.59-3.07	0.48
Visceral metastases	0.90	0.50-1.61	0.72			
≥3 bone mets	2.13	1.30-3.49	0.003	0.93	0.50-1.72	0.82
Age (cont.)	1.03	1.00-1.06	0.047	1.05	1.01-1.09	0.015
Pain (Y/N)	2.32	1.44-3.75	0.001	2.10	1.15-3.74	0.015

CI: Confidence interval; cont: continuous variable; HR: hazard ratio; Hr: high risk; HV: high volume; LR: low risk; LV: low volume; N: no; PSA50: PSA response >50%; 4mPSA50: decrease of PSA>50% within four months; Y: yes.

between PSA kinetics, OS and radiographic PFS (especially for PSADT) (23). A relationship between PSA response at 3 months and treatment duration and patient survival was also observed in a French observational TAU study of abiraterone in chemo-pretreated mCRPC patients (24). Other similar analyses reported a positive correlation between early (within 4 weeks from the beginning of second-generation anti-hormonal agents) and deep (>50%) PSA response with patient clinical outcomes (25-28).

The accuracy of PSA seems higher in the castration-sensitive setting. Three different studies identified a correlation between higher PSA values at 7 months after initiating ADT with shorter survival, suggesting the absolute PSA value as an independent predictor of OS. Data from the Southwest Oncology Group (SWOG) 9346 trial, a phase III study comparing continuous *versus* intermittent androgen blockage in mCSPC men, revealed that patients who achieved 7-month PSA ≤0.2 ng/dl had significantly longer survival than those who did not achieve this threshold. Analogously, men with a PSA decline between 0.3 and 4 ng/ml had improved OS compared to those whose PSA remained >4 ng/ml after 7 months from ADT initiation, with mOS of 75, 44 and 13 months, respectively. Therefore, the 7-month PSA milestone of 4 ng/ml or less after ADT therapy was suggested as a strong survival predictor (28).

A recent confirmatory analysis came from 719 mCSPC patients enrolled in the CHAARTED study; 7-month PSA ≤0.2 ng/dl remains a prognostic factor for longer survival, regardless of the early addition of docetaxel to ADT. Stratifying patients for three different 7-months PSA cut-offs (PSA ≤0.2 ng/dl, >0.2-4.0, >4 ng/dl), median OS were 60.4, 51.9 and 22.2 months respectively. Moreover, this study demonstrated that the early addition of docetaxel to ADT increased the possibility of achieving a lower PSA value with consequent improved survival, confirming PSA ≤ 0.2 ng/ml as a prognostic marker (29). However, no data are available concerning the superiority of reserving the addition of docetaxel (as well as the novel generation hormonal agents) to ADT only for those patients who do not achieve a 7-month PSA ≤0.2 ng/ml. A retrospective study of 101 patients with synchronous metastases from PC and treated with ADT alone for the castration-sensitive disease (with upfront docetaxel in 8% of cases) confirmed the prognostic role of PSA at 7 months. Indeed, mOS was significantly shorter in patients with PSA >4.0 ng/dl compared with patients with PSA between 0.3 and 4.0 ng/dl (22.2 *vs*. 54.0 months; p=0.0001). The result of this small patient group (n=6) with PSA ≤0.2 ng/dl (mOS 40.5 months) did not reach statistical significance. A favorable prognostic value was also found for the different cutoff of PSA ≤ 1.0 ng/dl, with mOS of 55 *vs*. 32 months in favor of those patients with a lower PSA value (30). All these studies suggested that failure to achieve a PSA ≤0.2 ng/ml 7 months after ADT initiation might identify patients who benefit from earlier intensification of therapy. In line with these results, our study confirmed ADT as a milestone of CSPC therapy, given a biochemical response rate in almost all patients (PSA50 94.4%); it reinforced the prognostic role of this biomarker, showing a strong correlation between PSA50 and improved survival. Moreover, our analysis supported the good prognostic value of a rapid PSA decrease (correlation between PSAv <6.9 [ng/dl]/month and longer OS), showing a significant association between each PSA decrease of 1 (ng/dl)/month and 0.2% of reduced risk of death. Of note, about half of the patients meeting both variables, therefore, those with deep and fast PSA response, had better outcomes compared with those who did not (mOS 101.0 months *vs*. 41.9 months, p<0.001) regardless of other baseline characteristics and early use of docetaxel. The secondary objective of our study was to investigate if deep and fast PSA response assessed during treatment for CSPC could be used as a predictive factor for the subsequent fist-line CRPC therapy. We found that 4mPSA50 remained a prognostic factor after the beginning of first-line therapy for CRPC (mOS 27.8 *vs*. 20.1 months; p=0.011), regardless of the treatment type

received both for the CSPC (ADT *versus* ADT plus early docetaxel) and for the CRPC disease (taxanes *versus* ARTA).

This study has several limitations. Given the retrospective design, all analyses are subject to selection biases and imbalances in unquantified variables. Therefore, the use of the median value instead of a predetermined threshold defining the PSAv, as well as the arbitrary and a posteriori choice of the 4-month limit to define the PSA response as fast (4mPSA50) may affect the relevance of the results.

In conclusion, we found that achieving a deep and fast PSA response correlates with a better outcome in patients with *de novo* mCSPC, positively influencing the prognosis also of the subsequent firs-line therapy for CRPC disease. It is of utmost importance to define a-priori the best timing of PSA changes, and to state clearly the role of PSA decrease as predictive factor of treatment response. Although PSA is an easy, not expensive, and well-established biochemical test, it is important to highlight that PSA50, PSAv, and 4mPSA50 (as well as a decline of PSA value ≤ 0.2 ng/ml after 7 months of ADT) are on-treatment variables, useless to direct upfront patients who might benefit from early intensification of ADT with chemotherapy or hormonal agents; therefore, their applicability in daily clinical practice should be restricted. Predictive pretreatment biomarkers are needed to guide clinicians in the difficult process of treatment selection within a sequential strategy.

Conflicts of Interest

Iacovelli Roberto: was advisor for Astella, BMS, Janssen, MSD, Pfizer and Sanofi and a speaker for Astellas, Janssen, MSD, Pfizer and Sanofi. Orazio Caffo is an advisor to Janssen, MSD and Bayer, and a speaker for Astellas, AstraZeneca, Bayer,Janssen, MSD, Pfizer and Sanofi. Ugo De Giorgi was consultant of Astellas Pharma,Bayer, BMS, Ipsen, Janssen, MSD, Novartis, Pfizer,Roche and Sanofi. Umberto Basso was advisor to Janssen, Pfizer and Novartis and speaker for BMS, Pfizer, Novartis, Pierre-Fabre and Sanofi. Marco Maruzzo was advisor to Pfizer, BMS, Janssen, MSD, Merck Serono and Ipsen. All Authors declared no conflicts of interest.

Authors' Contributions

Collection of the data: CC, UB, MT, CM, MM, FM, CC, MM. Data interpretation: RI, CC, UDG, OC, UB, GT. Statistical analysis: RI. Manuscript writing: RI, CC. Manuscript approval: all Authors.

Acknowledgements

Thanks to Dr Franziska Michaela Lohmeyer for supporting us in the revision of English language and in the editing of the manuscript.

References

1 Buzzoni C, Auvinen A, Roobol MJ, Carlsson S, Moss SM, Puliti D, de Koning HJ, Bangma CH, Denis LJ, Kwiatkowski M, Lujan M, Nelen V, Paez A, Randazzo M, Rebillard X, Tammela TL, Villers A, Hugosson J, Schröder FH and Zappa M: Metastatic prostate cancer incidence and prostate-specific antigen testing: New insights from the European Randomized Study of Screening for Prostate Cancer. Eur Urol *68(5)*: 885-890, 2015. PMID: 25791513. DOI: 10.1016/j.eururo.2015.02.042

2 James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, Hetherington J, Hoskin PJ, Jones RJ, Laing R, Lester JF, McLaren D, Parker CC, Parmar MKB, Ritchie AWS, Russell JM, Strebel RT, Thalmann GN, Mason MD and Sydes MR: Survival with newly diagnosed metastatic prostate cancer in the "Docetaxel Era": Data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). Eur Urol *67(6)*: 1028-1038, 2015. PMID: 25301760. DOI: 10.1016/j.eururo.2014.09.032

3 Berg KD, Thomsen FB, Mikkelsen MK, Ingimarsdóttir IJ, Hansen RB, Kejs AM and Brasso K: Improved survival for patients with *de novo* metastatic prostate cancer in the last 20 years. Eur J Cancer *72*: 20-27, 2017. PMID: 28024263. DOI: 10.1016/j.ejca.2016.11.025

4 Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, Wong YN, Hahn N, Kohli M, Cooney MM, Dreicer R, Vogelzang NJ, Picus J, Shevrin D, Hussain M, Garcia JA and DiPaola RS: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med *373(8)*: 737-746, 2015. PMID: 26244877. DOI: 10.1056/NEJMoa1503747

5 James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, Ritchie AW, Parker CC, Russell JM, Attard G, de Bono J, Cross W, Jones RJ, Thalmann G, Amos C, Matheson D, Millman R, Alzouebi M, Beesley S, Birtle AJ, Brock S, Cathomas R, Chakraborti P, Chowdhury S, Cook A, Elliott T, Gale J, Gibbs S, Graham JD, Hetherington J, Hughes R, Laing R, McKinna F, McLaren DB, O'Sullivan JM, Parikh O, Peedell C, Protheroe A, Robinson AJ, Srihari N, Srinivasan R, Staffurth J, Sundar S, Tolan S, Tsang D, Wagstaff J, Parmar MK and STAMPEDE investigators: Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet *387(10024)*: 1163-1177, 2016. PMID: 26719232. DOI: 10.1016/S0140-6736(15)01037-5

6 Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, Ye D, Feyerabend S, Protheroe A, De Porre P, Kheoh T, Park YC, Todd MB, Chi KN and LATITUDE Investigators: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med *377(4)*: 352-360, 2017. PMID: 28578607. DOI: 10.1056/NEJMoa1704174

7 James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, Ritchie AWS, Amos CL, Gilson C, Jones RJ, Matheson D, Millman R, Attard G, Chowdhury S, Cross WR, Gillessen S, Parker CC, Russell JM, Berthold DR, Brawley C, Adab F, Aung S, Birtle AJ, Bowen J, Brock S, Chakraborti P, Ferguson C, Gale J, Gray E, Hingorani M, Hoskin PJ, Lester JF, Malik ZI, McKinna F, McPhail N, Money-Kyrle J, O'Sullivan J, Parikh O, Protheroe A, Robinson A, Srihari NN, Thomas C, Wagstaff J, Wylie J, Zarkar A, Parmar MKB, Sydes MR and STAMPEDE Investigators: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med *377(4)*: 338-351, 2017. PMID: 28578639. DOI: 10.1056/NEJMoa1702900

8 Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, Coskinas X, Frydenberg M, Hague WE, Horvath

LG, Joshua AM, Lawrence NJ, Marx G, McCaffrey J, McDermott R, McJannett M, North SA, Parnis F, Parulekar W, Pook DW, Reaume MN, Sandhu SK, Tan A, Tan TH, Thomson A, Tu E, Vera-Badillo F, Williams SG, Yip S, Zhang AY, Zielinski RR, Sweeney CJ and ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group: Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med *381(2)*: 121-131, 2019. PMID: 31157964. DOI: 10.1056/NEJMoa1903835

9 Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez Soto Á, Merseburger AS, Özgüroğlu M, Uemura H, Ye D, Deprince K, Naini V, Li J, Cheng S, Yu MK, Zhang K, Larsen JS, McCarthy S, Chowdhury S and TITAN Investigators: Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med *381(1)*: 13-24, 2019. PMID: 31150574. DOI: 10.1056/NEJMoa1903307

10 Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, Alcaraz A, Alekseev B, Iguchi T, Shore ND, Rosbrook B, Sugg J, Baron B, Chen L and Stenzl A: ARCHES: A randomized, Phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol *37(32)*: 2974-2986, 2019. PMID: 31329516. DOI: 10.1200/JCO.19.00799

11 Iacovelli R, Ciccarese C, Schinzari G, Rossi E, Maiorano BA, Astore S, D'Angelo T, Cannella A, Pirozzoli C, Teberino MA, Pierconti F, Martini M and Tortora G: Biomarkers of response to advanced prostate cancer therapy. Expert Rev Mol Diagn *20(2)*: 195-205, 2020. PMID: 31986925. DOI: 10.1080/14737159.2020.1707669

12 Armstrong AJ, Garrett-Mayer ES, Yang YC, de Wit R, Tannock IF and Eisenberger M: A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. Clin Cancer Res *13(21)*: 6396-6403, 2007. PMID: 17975152. DOI: 10.1158/1078-0432.CCR-07-1036

13 Miller K, Carles J, Gschwend JE, Van Poppel H, Diels J and Brookman-May SD: The Phase 3 COU-AA-302 study of abiraterone acetate plus prednisone in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: Stratified analysis based on pain, prostate-specific antigen, and Gleason score. Eur Urol *74(1)*: 17-23, 2018. PMID: 28939004. DOI: 10.1016/j.eururo.2017.08.035

14 Petrylak DP, Ankerst DP, Jiang CS, Tangen CM, Hussain MH, Lara PN Jr, Jones JA, Taplin ME, Burch PA, Kohli M, Benson MC, Small EJ, Raghavan D and Crawford ED: Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. J Natl Cancer Inst *98(8)*: 516-521, 2006. PMID: 16622120. DOI: 10.1093/jnci/djj129

15 Fuerea A, Baciarello G, Patrikidou A, Albigès L, Massard C, Di Palma M, Escudier B, Fizazi K and Loriot Y: Early PSA response is an independent prognostic factor in patients with metastatic castration-resistant prostate cancer treated with next-generation androgen pathway inhibitors. Eur J Cancer *61*: 44-51, 2016. PMID: 27151554. DOI: 10.1016/j.ejca.2016.03.070

16 Thuret R, Massard C, Gross-Goupil M, Escudier B, Di Palma M, Bossi A, de Crevoisier R, Chauchereau A and Fizazi K: The postchemotherapy PSA surge syndrome. Ann Oncol *19(7)*: 1308-1311, 2008. PMID: 18356135. DOI: 10.1093/annonc/mdn062

17 Angelergues A, Maillet D, Fléchon A, Ozgüroglu M, Mercier F, Guillot A, Le Moulec S, Gravis G, Beuzeboc P, Massard C, Fizazi K, de La Motte Rouge T, Delanoy N, Elaidi RT and Oudard S: Prostate-specific antigen flare induced by cabazitaxel-based chemotherapy in patients with metastatic castration-resistant prostate cancer. Eur J Cancer *50(9)*: 1602-1609, 2014. PMID: 24725337. DOI: 10.1016/j.ejca.2014.03.015

18 Berthold DR, Pond GR, Roessner M, de Wit R, Eisenberger M, Tannock AI and TAX-327 investigators: 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 *14(9)*: 2763-2767, 2008. PMID: 18451243. DOI: 10.1158/1078-0432.CCR-07-0944

19 Halabi S, Armstrong AJ, Sartor O, de Bono J, Kaplan E, Lin CY, Solomon NC and Small EJ: 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 *31(31)*: 3944-3950, 2013. PMID: 24101043. DOI: 10.1200/JCO.2013.50.3201

20 Armstrong AJ, Lin P, Higano CS, Iversen P, Sternberg CN, Tombal B, Phung, Parli T, Krivoshik A and Beer TM: Prognostic association of prostate-specific antigen decline with clinical outcomes in men with metastatic castration-resistant prostate cancer treated with enzalutamide in a randomized clinical trial. Eur Urol Oncol *2(6)*: 677-684, 2019. PMID: 31274110. DOI: 10.1016/j.euo.2018.11.005

21 Armstrong AJ, Saad F, Phung, Dmuchowski C, Shore ND, Fizazi K, Hirmand M, Forer D, Scher HI and Bono J: 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. Cancer *123(12)*: 2303-2311, 2017. PMID: 28171710. DOI: 10.1002/cncr.30587

22 Bryce AH, Alumkal JJ, Armstrong A, Higano CS, Iversen P, Sternberg CN, Rathkopf D, Loriot Y, de Bono J, Tombal B, Abhyankar S, Lin P, Krivoshik A, Phung D and Beer TM: Radiographic progression with nonrising PSA in metastatic castration-resistant prostate cancer: post hoc analysis of PREVAIL. Prostate Cancer Prostatic Dis *20(2)*: 221-227, 2017. PMID: 28117385. DOI: 10.1038/pcan.2016.71

23 Xu XS, Ryan CJ, Stuyckens K, Smith MR, Saad F, Griffin TW, Park YC, Yu MK, Vermeulen A, Poggesi I and Nandy P: Correlation between prostate-specific antigen kinetics and overall survival in abiraterone acetate-treated castration-resistant prostate cancer patients. Clin Cancer Res *21(14)*: 3170-3177, 2015. PMID: 25829400. DOI: 10.1158/1078-0432.CCR-14-1549

24 Houédé N, Beuzeboc P, Gourgou S, Tosi D, Moise L, Gravis G, Delva R, Fléchon A, Latorzeff I, Ferrero JM, Oudard S, Tartas S, Laguerre B, Topart D, Roubaud G, Agherbi H, Rebillard X and Azria D: Abiraterone acetate in patients with metastatic castration-resistant prostate cancer: long term outcome of the Temporary Authorization for Use programme in France. BMC Cancer *15*: 222, 2015. PMID: 25884302. DOI: 10.1186/s12885-015-1257-2

25 Rescigno P, Lorente D, Bianchini D, Ferraldeschi R, Kolinsky MP, Sideris S, Zafeiriou Z, Sumanasuriya S, Smith AD, Mehra N, Jayaram A, Perez-Lopez R, Mateo J, Parker C, Dearnaley DP, Tunariu N, Reid A, Attard G and de Bono JS: 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 *70(5)*: 724-731, 2016. PMID: 26965561. DOI: 10.1016/j.eururo.2016.02.055

26 Schiff JP, Cotogno P, Feibus A, Steinwald P, Ledet E, Lewis B and Sartor O: Early prostate-specific antigen response post-abiraterone as predictor of overall survival in metastatic castrate-resistant prostate cancer. BMC Cancer *19(1)*: 524, 2019. PMID: 31151428. DOI: 10.1186/s12885-019-5729-7

27 Caffo O, Veccia A, Maines F, Bonetta A, Spizzo G and Galligioni E: Potential value of rapid prostate-specific antigen decline in identifying primary resistance to abiraterone acetate and enzalutamide. Future Oncol *10(6)*: 985-993, 2014. PMID: 24941984. DOI: 10.2217/fon.14.24

28 Hussain M, Tangen CM, Higano C, Schelhammer PF, Faulkner J, Crawford ED, Wilding G, Akdas A, Small EJ, Donnelly B, MacVicar G, Raghavan D and Southwest Oncology Group Trial 9346 (INT-0162): Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol *24(24)*: 3984-3990, 2006. PMID: 16921051. DOI: 10.1200/JCO.2006.06.4246

29 Harshman LC, Chen YH, Liu G, Carducci MA, Jarrard D, Dreicer R, Hahn N, Garcia JA, Hussain M, Shevrin D, Eisenberger M, Kohli M, Plimack ER, Cooney M, Vogelzang NJ, Picus J, Dipaola R, Sweeney CJ and ECOG-ACRIN 3805 Investigators: Seven-month prostate-specific antigen is prognostic in metastatic hormone-sensitive prostate cancer treated with androgen deprivation with or without docetaxel. J Clin Oncol *36(4)*: 376-382, 2018. PMID: 29261442. DOI: 10.1200/JCO.2017.75.3921

30 Nieder C, Haukland E, Pawinski A and Norum J: Seven-month prostate-specific antigen (PSA) is prognostic in patients with prostate cancer initially diagnosed with distant metastases. Med Oncol *35(4)*: 46, 2018. PMID: 29508104. DOI: 10.1007/s12032-018-1110-y

Received July 28, 2021
Revised November 12, 2021
Accepted November 16, 2021