Potencial role of early Prostate-Specific Antigen changes at 4 Weeks for predicting overall survival in Metastatic Castration-Resistant Prostate Cancer patients treated with abiraterone or enzalutamide

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ABSTRACT

Objectives. Prostate-specific antigen (PSA) is the only biochemical marker useful in the follow-up of prostate cancer. Although determination of progression during the first 12 weeks is not recommended, because of the possibility of late responses and flare reactions, several studies have shown a strong association between early PSA reduction and oversall survival (OS). The main goal was to evaluate the change in PSA levels and its potential influence on OS in chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) patients in routine clinical practice. Methods: This observational retrospective study was performed in a Spanish tertiary hospital and included men with chemotherapy-naïve mCPRC who started treatment with abiraterone or enzalutamide between 2012 and 2018. Results: Ninety patients were included. A favourable trend in OS was observed in patients with early PSA response (≥30% from baseline at week 4) although no statistically significant [HR 0,70 (95%CI 0,30–1,14), p=0,153]. At week 12, most patients with an early PSA response achieved a confirmed 30% PSA reduction and, at that time, such a reduction was significantly correlated with improved OS [HR 0,56 (95%CI 0,33–0,94), p=0,025].

A negative trend in OS was observed in patients with early progression, defined as ≥25% increase at week 4, but without statistical significance [HR 1,65 (95%CI 0,96-2,85), p=0,066]. Early PSA progression was significantly correlated with PSA progression at week 12 and, at that point, a PSA increase ≥25% from baseline was significantly associated with shorter OS [HR 2,02 (95%CI 1,17–3,47), p=0,010].

Keywords: Androgen Receptor Antagonists, Prostate-Specific Antigen, Castration-Resistant Prostate Cancer.

Papel potencial de los cambios tempranos en el Antígeno Prostático Específico a las 4 semanas para predecir la supervivencia global en pacientes con cáncer de próstata metastásico resistente a la castración tratados con abiraterona o enzalutamida

RESUMEN

Objetivos: El Antígeno Prostático Específico (PSA) es el único marcador bioquímico útil en el seguimiento del cáncer de próstata. Aunque no se recomienda determinar la progresión antes de las 12 semanas por posibles respuestas tardías y reacciones flare, varios estudios han mostrado una asociación entre la reducción temprana del PSA y la supervivencia global (SG). El objetivo principal fue evaluar el cambio en los niveles de PSA y su influencia en la SG en pacientes con cáncer de próstata metastásico resistente a castración (CPRCm) quimioterapia-naïve en práctica clínica. Métodos: Estudio observacional retrospectivo en un hospital terciario que in-

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cluyó pacientes con CPRCm quimioterapia-naïve que comenzaron tratamiento con abiraterona o enzalutamida entre 2012 y 2018. Resultados: Se incluyeron noventa pacientes. Se observó una tendencia favorable en la SG en pacientes con respuesta temprana del PSA (reducción ≥30% en la semana 4), aunque no estadísticamente significativa [HR 0,70 (IC95% 0,30–1,14), p=0,153]. En la semana 12, la mayoría de pacientes con respuesta temprana lograron una reducción mantenida del 30% y, en ese momento, se correlacionó con una mejor SG [HR 0,56 (IC95% 0,33–0,94), p=0,025]. Se observó una tendencia negativa en la SG en pacientes con progresión temprana, definida como un aumento del ≥25% en la semana 4, pero sin significación estadística [HR 1,65 (IC95% 0,96-2,85), p=0,066]. La progresión temprana del PSA se correlacionó con dicha progresión en la semana 12 y, en ese punto, un aumento del PSA ≥25% se asoció con una menor SG [HR 2,02 (IC95% 1,17–3,47), p=0,010].

Palabras clave: Antagonistas de Receptores de Andrógenos, Antígeno Prostático Específico, Cáncer de próstata resistente a castración.

INTRODUCTION

Prostate cancer (PC) is an androgen-dependant disease. Although it initially responds to androgen suppression therapy[1], response eventually transits to castration resistance, during which progression occurs despite castrate levels of testosterone. This state is defined as metastatic castration-resistant prostate cancer (mCRPC).

The approval of new drugs in recent years has led to a breakthrough in the treatment of mCPRC. Docetaxel, abiraterone acetate, enzalutamide and radium-223[2] have been followed by apatulamide, darolutamide and, in selected cases, inhibitors of poly(adenosine diphosphate-ribose) polymerase. Current life expectancy for mCRPC is around 3 years[3].

The availability of multiple treatments increases doubts about the optimal treatment strategy. Today, it is still unknown how these treatments should be used to achieve the best results, so it remains an important research topic[2].

To date, prostate-specific antigen (PSA) is the only biochemical marker that has proven to be useful in the follow-up of patients with PC, 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]. Although PCWG3 criteria do not recommend determination of progression during the first 12 weeks because of the possibility of late responses and flare reactions[4-6], there are studies reporting that a rapid decline in PSA values is associated with a relevant clinical benefit[7-12].

We hypothesised that an early PSA decrease would identify patients most likely to benefit from androgen pathway inhibitors as well as those in whom early progression predicts poor outcomes.

MATERIALS AND METHODS

The main object of the present study was to demonstrate that an early PSA decline of ≥30% after 4 weeks of treatment with abiraterone and enzalutamide correlates with improved OS and that a PSA increase of ≥25% after 4 weeks of treatment correlates with lower OS. In addition, we aimed to find if PSA response and progression at week 4 are associated with PSA values at week 12. If confirmed, these data could provide guidance for further studies on earlier treatment change in patients that are likely to show rapid disease progression and could benefit from alternative treatments in an optimal timeframe.

This observational retrospective study was performed in a Spanish tertiary hospital (Hospital Universitario La Paz) and included chemotherapy-naive men with mCPRC who initiated treatment with abiraterone or enzalutamide during a period of 6 years, between September 2012 and November 2018. The study end date was October 2020.

Both drugs were dispensed at the outpatient hospital pharmacy. Patients included in the study were identified using the pharmacy database Farmatools®, the electronic registration system used for drugs dispensed in our Pharmaceutical Care clinics. Patients baseline (at inclusion time) demographics, clinical characteristics and treatment patterns were obtained from electronic patient record, including age, Gleason Score (GS), Eastern Cooperative Oncology Group (ECOG) Performance Status, use of opioid analgesia for pain control, site(s) of metastasis at diagnosis, number of bone lesions, haemoglobin (Hb), alkaline phosphatase (ALP) and PSA baseline levels, date and reasons for treatment discontinuation or death.

During treatment, patients are usually checked monthly for hematological parameters and PSA levels. They also undergo regular imaging test, at the start of treatment and after 6 to 12 months or whenever PSA levels increase. The study measured baseline, 4 and 12 weeks after treatment PSA levels, as well as nadir and progression PSA levels and dates.

The following definitions were used to characterize outcomes during treatment with abiraterone or enzalutamide: early PSA response, PSA response at week 12, early progression of PSA and progression of PSA at week 12. Early PSA response was defined as ≥30% decline in PSA at week 4 from baseline and PSA response as ≥30% decline in PSA from baseline at week 12. Early progression of PSA was defined as ≥25% increase in PSA at week 4 and progression of PSA at week 12 as a ≥25% increase in this week.

The study protocol was approved by the Hospital Ethics Committee (CEIm).

STATISTICAL ANALYSIS

The main outcome was overall survival (OS), defined as the time between treatment initiation and either the date of death or of last follow-up for surviving patients. Patients known to be alive or lost to follow-up on the day of the study end were censored.

Baseline characteristics (at diagnosis time) were summarized using descriptive statistics (median value and range for continuous variables, absolute frequencies and percentage for categorical variables).

PSA response (reduction and progression at weeks 4 and 12) was tested for univariate association with OS. Before univariate analysis, PSA responses were categorized according to previous definitions (early response vs no; early progression vs no; response at week 12 vs no; progression at week 12 vs no).

The OS analysis was estimated with Kaplan–Meier. Curve comparisons were analysed with the Log-Rank test. The median value and the confidence interval (CI) were estimated when possible. All analyses were considered bilateral with 95% confidence. The software used was SAS Enterprise Guide 8.2.

In addition, the association between early response and PSA response at week 12 and between early progression and PSA progression at week 12 was analyzed using Fisher´s test.

RESULTS

Between September 2012 and November 2018, 90 patients with mCRPC were enrolled, 57 were treated with abiraterone and 33 with enzalutamide in the chemotherapy-naïve setting. The clinical characteristics are summarized in Table 1.

Median overall follow-up was 24,9 months [interquartile range (IQR) 16,4–37,5]; 72 patients (80%) had died by the last follow-up, 46 (80,7%) in the abiraterone group and 26 (78,8%) in the enzalutamide group. Disease progression was the main reason for treatment discontinuation (87,8%); 8 patients were still on treatment at the time of data cut-off. Of the 82 patients who discontinued, 52,4% received docetaxel as second line therapy, 42,7% died or received palliative care and a minority (4.9%) received other subsequent treatments (cyclophosphamide and radium-223).

Table 1. Baseline characteristics

Parameter	Value
Median age, yr (IQR)	78 (55-93)
ECOG Performance status, n (%)	
0-1	76 (86,4)
2	12 (13,6)
Pain (need of opioids), n (%)	
Yes	31 (34,4)
No	59 (65,6)
Gleason score, n (%)	
≤8	40 (54,8)
>8	33 (45,2)
Exclusively lymph node metastases, n (%)	13 (14,6)
Visceral metastasis, n (%)	25 (28,1)
≥3 bone lesions, n (%)	50 (56,2)
Median PSA, ng/mL (range)	16 (0,4-968,3)
PSA class, *n* (%)	
<50 ng/ml	59 (65,6)
≥50 ng/ml	31 (34,4)
<20 ng/ml	45 (50)
≥20 ng/ml	45 (50)
Median Hb value, g/dL (range)	13,1 (8-17,2)
Hb class, *n* (%)	
<12 g/dL	22 (25)
≥12 g/dL	66 (75)
Median ALP value, UI/L (range)	97 (48-755)
ALP class, *n* (%)	
≤116 UI/L	51 (58,6)
>116 UI/L	36 (41,4)

ECOG= Eastern Cooperative Oncology Group; **PSA** = Prostate-Specific Antigen; **Hb=**Haemoglobin; **ALP=** Alkaline Phosphatase.

Median OS was 26,9 months (95% CI 19,7-34,1); no difference was found between the two treatment groups (30,8 months in abiraterone group and 23,5 in enzalutamide group; p=0,310).

Only 8 patients who had no serum PSA levels at weeks 4 and 12 were excluded from the analysis. Any PSA decline was observed in 70 patients (82,3%). An early PSA response (≥30% from baseline at week 4) was found in 45 patients (54,9%). Median OS was 32,6 months in early responders (95% CI 23,6-41,5) compared with 27,3 months (95% CI 13,6-31,0) in those without an early response. Although a favourable trend in OS was observed at week 4 in biochemically responsive patients, no significant statistical advantage was found [HR 0,70 (95%CI 0,30–1,14), p = 0,153]. Results are shown in Figure 1.

At week 12, out of 45 patients with an early PSA response, 43 (95.6%) achieved a confirmed 30% PSA reduction. Altogether 56 patients (68,3%) achieved a PSA reduction of ≥ 30% at week 12 (Table 2).

Figure 1. Kaplan-Meier curves of overall survival by early PSA response

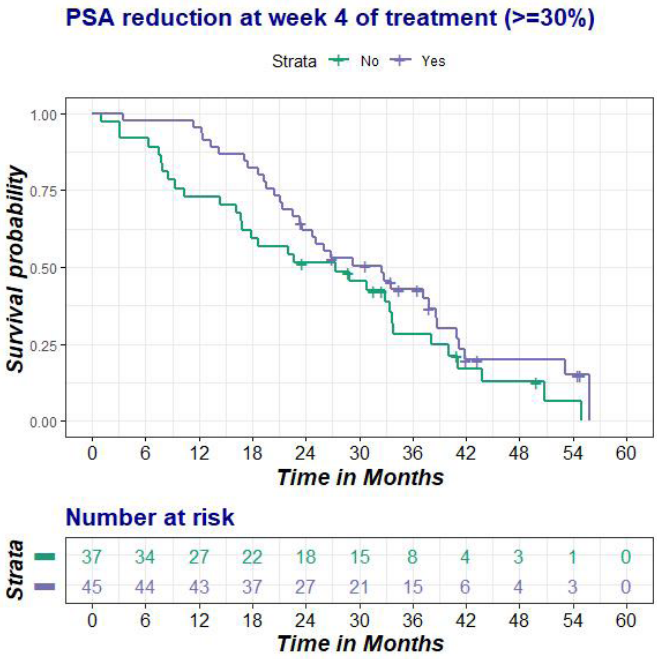
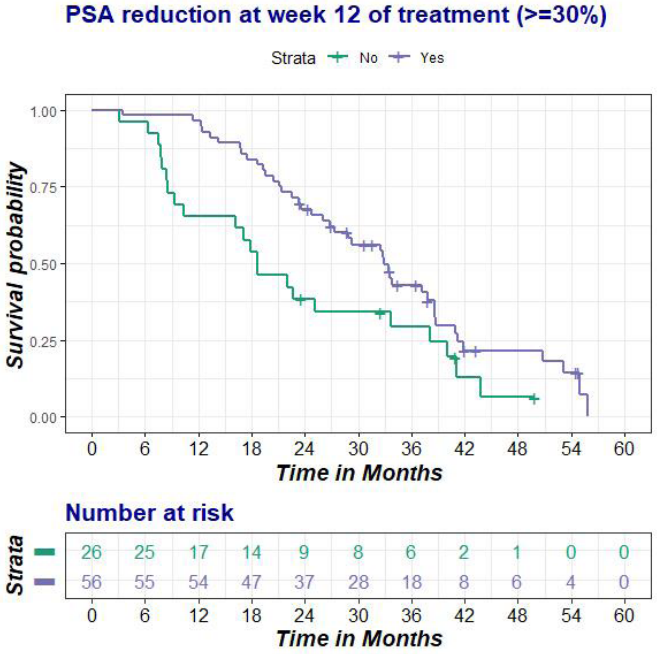


Table 2. PSA reduction ≥30% at week 4 vs PSA reduction ≥30% at week 12

		PSA reduction ≥30% at week 12 (n)		
		No	**Yes**	**Total**
PSA reduction ≥30% at week 4 (n)	**No**	24	13	37
	Yes	2	43	45
	Total	26	56	82

PSA = Prostate-Specific Antigen; **n**= Number of patients.

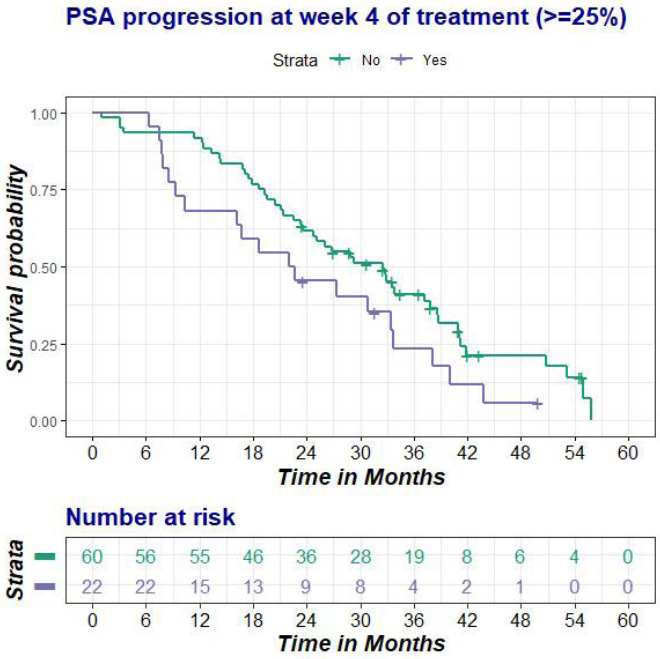
Figure 2. Kaplan-Meier curves of overall survival by PSA response at week 12.



In addition, a ≥30% PSA decrease at week 12 was significantly correlated with improved OS, resulting in a 44% reduction in the risk of death [HR 0,56 (95%CI 0,33–0,94), p = 0,025]. Median OS in responders at week 12 was 32,9 months (95% CI 27,5-38,2) compared with 18,7 months (95% CI 11,6-25,7) for patients who did not achieve an early response. Results are shown in Figure 2. The percentage PSA decline at 4 week was significantly correlated with the percentage PSA reduction at 12 week (p<0,001).

Early progression of PSA was found in 22 patients (26,8%). In patients with early progression, OS was reduced compared to those without progression at week 4 ; 22,1 months (95% CI 10,2-33,9) versus 32,6 months (95% CI 25,3-39,9) respectively. A negative trend in OS was observed in patients with early progression, but without statistical significance [HR 1,65 (95%CI 0,96-2,85), p = 0,066]. Results can be observed in Figure 3.

Figure 3. Kaplan-Meier curves of overall survival by early PSA progression



At week 12 from treatment initiation, 16 of these 22 patients (72,7%), maintained this PSA rise. Only 6 patients (27,3%) did not maintain this increase in PSA levels, and 4 of them even had a flare reaction with a decrease of more than 30%. A total of 19 patients (23,2%) experienced PSA progression at week 12 (Table 3).

Table 3. PSA increase ≥25% at week 4 vs PSA increase ≥25% at week 12

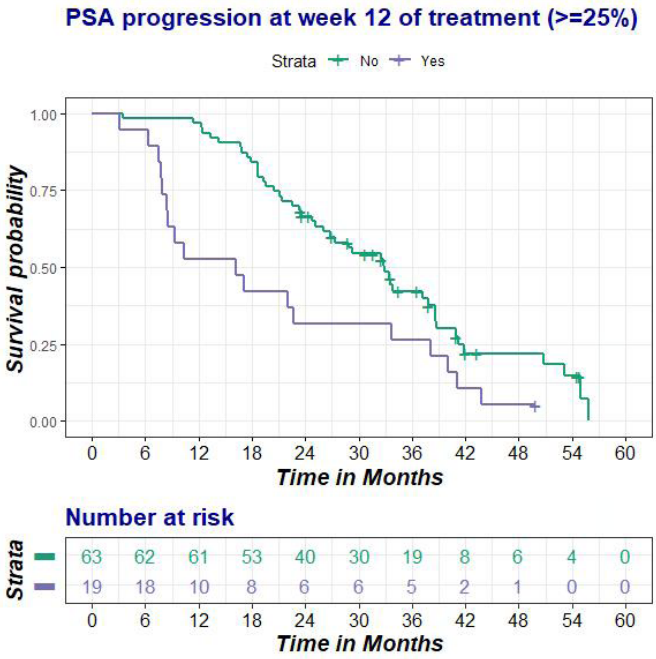
		PSA increase ≥25% at week 12 (n)		
		No	Yes	Total
PSA increase ≥25% at week 4 (n)	No	57	3	60
	Yes	6	16	22
	Total	63	19	82

PSA = Prostate-Specific Antigen; **n**= Number of patients

Biochemical progression at week 12 was significantly associated with shorter OS. Patients with a PSA increase ≥25% from baseline had a 2-fold increased risk of death [HR 2,02 (95% CI 1,17–3,47), p = 0,010].

The median OS in patients with biochemical progression at week 12 was 16,2 months (95% CI 1,2-31,1) compared with 32,7 months (95% CI 27,7-37,8) in patients who did not have such progression. Results are shown in Figure 4.

Figure 4. Kaplan-Meier curves of overall survival by PSA progression at week 12



Early PSA progression was significantly correlated with PSA progression at week 12 (p<0,001).

DISCUSSION

Hormonal drugs prolong survival in patients with mCRPC. Abiraterone and enzalutamide have been available for years for the treatment of patients with mCPRC who have not received prior chemotherapy.

There is a need to find biomarkers that can identify patients who have greater clinical benefit. Patients early classified as having low chance of response could receive alternative therapies, included participation in clinical trials.

The optimal time to assess PSA response is a matter of debate. A 30% decrease in PSA in the nadir and after 12 weeks is associated with improved survival[13-15]. On the other hand, PSA progression according to PCWG3 criteria is associated with a shorter survival time[3]. However, although PCWG3 criteria[3] advise against assessing changes in PSA before 12 weeks of treatment due to late responses and flare reactions[4-6], recent studies have shown a correlation between an early PSA response and better clinical outcomes[7-12].

Our findings are consistent with previous studies, showing a correlation between PSA response and OS. Patients who achieve a 30% PSA decline after 4 weeks of treatment are more likely to maintain this response at week 12, and achieved significantly better OS. This indicates that it is possible to identify most patients who benefit very early.

Nearly three quarters of patient who had biochemical progression at week 4 had a confirmed progression at week 12, which was associated with shorter OS. However, the remaining 27% of patients with early biochemical progression did not show progression at week 12. This indicates that early PSA progression may help identify patients who are refractory to these treatments, but there is a percentage in whom progression at week 4 is not confirmed thereafter. Even if decisions cannot be made at week 4, a closer clinical follow-up of patients with early PSA progression who may be susceptible to early treatment modification seems appropriate. Early detection of non-responders would allow an early switch of treatment, which would reduce costs and avoid the use of hormonal therapies in patients who do not benefit.

Prospective multicentre validation studies are needed to confirm the predictive capacity of PSA variations for survival. Despite the usefulness of the PSA value as a monitoring variable, we must keep in mind that the decision to change treatment in mCRPC is not based exclusively on biochemical progression data, but clinical and radiological features carry greater weight.

Several limitations of this study should be mentioned. This was a retrospective study performed at a single tertiary-care hospital. Despite the small sample size, the study has sufficiently powered to determine the impact of PSA response and PSA progression at week 12 on clinical outcomes. However, the results observed in the fourth week of treatment show a trend but do not reach statistical significance. Furthermore, this is a real-world analysis of abiraterone and enzalutamide with a long follow-up period, providing much needed insight into the real-world use of both drugs. It is necessary to continue the analysis of patients with mCRPC in different settings to increase the evidence and support the optimisation of therapy in clinical practice.

CONCLUSIONS

Our results confirm that a PSA response at week 12 is associated with a longer OS, while biochemical progression at the same week is associated with a shorter OS.

Early PSA reduction can provide clinically meaningful information as there is a clear trend towards better clinical outcomes and almost all patients who respond at week 4 also respond at week 12.

Early progression was associated with a higher probability of progression at week 12, but allows the identification of patients who are more likely to fail hormonal therapy and who are also suitable for a closer follow up.

However, flare reactions were observed in some patients, so early biochemical progression does not necessarily indicate progression at week 12.

Further studies are needed to confirm the validity of early changes in PSA kinetics and provide stronger evidence to assist clinical decisions such as a change in treatment.

BIBLIOGRAFÍA

1. So AI, Hurtado-Coll A, Gleave ME. Androgens and prostate cancer. World J Urol. noviembre de 2003;21(5):325-37.

2. García Trevijano Cabetas M, Escario-Gómez M, González-Del Valle L, Sobrino Jiménez C, Bilbao Gomez-Martino C, Romero-Garrido JA, et al. Real-world outcomes of abiraterone and enzalutamide in first-line treatment of metastatic castration-resistant prostate cancer: which patients benefit most? Eur J Hosp Pharm. 7 de octubre de 2021;ejhpharm-2021-002798.

3. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 20 de abril de 2016;34(12):1402-18.

4. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol Off J Am Soc Clin Oncol. 1 de marzo de 2008;26(7):1148-59.

5. Berthold DR, Pond GR, Roessner M, de Wit R, Eisenberger M, Tannock AIF, 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 Off J Am Assoc Cancer Res. 1 de mayo de 2008;14(9):2763-7.

6. Angelergues A, Maillet D, Fléchon A, Ozgüroglu M, Mercier F, Guillot A, et al. Prostate-specific antigen flare induced by cabazitaxel-based chemotherapy in patients with metastatic castration-resistant prostate cancer. Eur J Cancer. junio de 2014;50(9):1602-9.

7. Rescigno P, Dolling D, Conteduca V, Rediti M, Bianchini D, Lolli C, et al. Early Post-treatment Prostate-specific Antigen at 4 Weeks and Abiraterone and Enzalutamide Treatment for Advanced Prostate Cancer: An International Collaborative Analysis. Eur Urol Oncol. 12 de julio de 2019;

8. Rescigno P, Lorente D, Bianchini D, Ferraldeschi R, Kolinsky MP, Sideris S, 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(5):724-31.

9. Facchini G, Caffo O, Ortega C, D'Aniello C, Di Napoli M, Cecere SC, et al. Very Early PSA Response to Abiraterone in mCRPC Patients: A Novel Prognostic Factor Predicting Overall Survival. Front Pharmacol [Internet]. 2016 [citado 10 de marzo de 2020];7. Disponible en: https://www.frontiersin.org/articles/10.3389/fphar.2016.00123/full

10. Fuerea A, Baciarello G, Patrikidou A, Albigès L, Massard C, Di Palma M, et al. 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 Oxf Engl 1990. 2016;61:44-51.

11. Kato H, Furuya Y, Miyazawa Y, Miyao T, Syuto T, Nomura M, et al. Consequences of an Early PSA Response to Enzalutamide Treatment for Japanese Patients with Metastatic Castration-resistant Prostate Cancer. Anticancer Res. 2016;36(11):6141-9.
12. Caffo O, Veccia A, Maines F, Bonetta A, Spizzo G, Galligioni E. Potential value of rapid prostate-specific antigen decline in identifying primary resistance to abiraterone acetate and enzalutamide. Future Oncol Lond Engl. mayo de 2014;10(6):985-93.
13. 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 Off J Am Soc Clin Oncol. diciembre de 1995;13(12):2944-53.
14. Hussain M, Goldman B, Tangen C, Higano CS, Petrylak DP, Wilding G, 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 Off J Am Soc Clin Oncol. 20 de mayo de 2009;27(15):2450-6.
15. Petrylak DP, Ankerst DP, Jiang CS, Tangen CM, Hussain MHA, Lara PN, et al. Evaluation of prostate-specific antigen declines for surrogacy in patients treated on SWOG 99-16. J Natl Cancer Inst. 19 de abril de 2006;98(8):516-21.