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Original Research

Impact of progression at baseline and on-treatment progression events in three large prostate cancer trials

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KEYWORDS
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Abstract ***Background:*** There is a discussion about the optimal timing to initiate or switch treatment in metastatic castration-resistant prostate cancer (mCRPC). This post hoc analysis of 3 large trials for men with mCRPC examined the influence of the type of progression at initiation of first-line chemotherapy, as well as the type of progression during treatment, on treatment outcomes.

Methods: Data from the phase III studies VENICE (n = 1224), TAX327 (n = 1006) and FIRSTANA (n = 1168) were used as independent data sets. Type of progression was defined as follows: prostate-specific antigen (PSA) only (group 1), radiological (±PSA) (group 2) or pain (±PSA, ± radiological) progression (group 3). The impact of baseline type of progression on overall survival (OS) was evaluated in multivariate Cox regression analysis with backward elimination, stratified for the Eastern Cooperative Oncology Group performance score and treatment arm.

Results: The median OS (arms combined) from treatment initiation in VENICE was 28.6, 26.3 and 16.9 months for G1, G2 and G3, respectively (hazard ratio: 1.14 [95% confidence interval

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{CI}: 0.92−1.41%] in G2 and 2.13 [95% CI: 1.75−2.59%] in G3 compared with G1). Multivariate analysis (arms combined) showed that pain progression at baseline was an independent predictor of poor OS. Similar findings were observed in the TAX327 and FIRSTANA data sets. During treatment, pain or radiological progression preceded PSA progression in ~55% of the patients. The retrospective characteristic of this study is a limitation.

Conclusions: The type of progression at baseline strongly predicts OS in men with mCRPC treated with first-line chemotherapy. During treatment, pain and/or radiological progression preceded PSA progression as the first progression event in ~55% of the patients. This finding has the prospect to be incorporated in clinical guidelines and to be practice changing because it implies the need for regular imaging and not to rely on PSA progression alone.

1. Introduction

Management of metastatic castration-resistant prostate cancer (mCRPC) has evolved in the past decade, with 6 agents having demonstrated overall survival (OS) benefit in phase III trials [1−9], and median OS from time to initiation therapy for mCRPC has increased from approximately one year in the 1990s [10] to ~19 months in 2004 [1,2] and is currently approaching three years [9,11].

Current guidelines [12] and consensus conference reports [13] recommend abiraterone or enzalutamide for asymptomatic/mildly symptomatic chemotherapy-naive men, and chemotherapy is recommended for overtly symptomatic patients. An important challenge is to determine when therapies should be initiated, halted or changed, at the time when patients are still asymptomatic or at the time they have disease-related symptoms. Although the type of progression is collected at enrolment in most phase III trials, its impact on clinical outcomes has not been evaluated precisely. Moreover, criteria for disease progression weighted by importance vary in clinical practice, leading towards different timing to initiate or switch therapy. This prompted us to investigate the relationship between the type of progression at initiation of first-line chemotherapy and treatment outcomes and the type of progression events during treatment.

2. Patients and methods

We used the VENICE study [14], TAX327 [1] and FIRSTANA [15] as independent data sets of patients with mCRPC treated with first-line chemotherapy. VENICE was tested first because all patients received the standard treatment with docetaxel (DOC).

VENICE was a multinational phase III trial conducted on 1224 patients with mCRPC who were randomised between 2007 and 2010 to receive 75 mg/m^2 of DOC: 75 mg/m every 3 weeks plus 5 mg of prednisone twice daily combined with aflibercept (6 mg/kg every 3 weeks) or placebo [14]. TAX327 was a multinational study conducted on 1006 patients with mCRPC who were randomised between 2000 and 2002 to receive 3-weekly DOC (75 mg/m^2) (DOC75), weekly DOC (30 mg/m^2) or 3-weekly mitoxantrone (12 mg/m^2) therapy, each arm combined with 5 mg of prednisone twice daily [1]. FIRSTANA was a multinational phase III trial randomising 1168 patients with mCRPC between 2011 and 2013 to receive in first-line DOC75 or cabazitaxel (CAB) (either 25 mg/m^2 [CAB25] or 20 mg/m^2 [CAB20] every 3 weeks) plus prednisone (5 mg twice daily) [15]. The primary end-point of VENICE, TAX327 and FIRSTANA was OS; further details are provided in the original reports. All studies were approved by an independent institutional review board at each participating institution, and written informed consent was obtained from all participants.

Serum prostate-specific antigen (PSA) was measured at baseline and every 3 weeks during therapy. Standard imaging was performed at baseline and every 6−9 weeks during therapy and repeated at 4 weeks to confirm progression. Pain was recorded by the patients on a daily basis for 7 days before randomisation using the Present Pain Intensity (PPI) scale from the McGill-Melzack questionnaire [16]. The score ranged from 0 to 5, with higher scores indicating greater pain. A daily analgesic score (AS) was also calculated for 7 days before randomisation, assigning a score of 4 for a standard dose of narcotic analgesics and a score of 1 for a standard dose of non-narcotic analgesics [1]. The patients were required to have a stable level of pain for at least 7 days before randomisation. Pain progression at baseline was assumed to have occurred if pain at baseline was defined by a mean PPI of 2 or more and/or a mean AS of 10 or more over the 7 days before randomisation. PSA progression at baseline was based on increasing serum levels of PSA on at least two consecutive measurements obtained at least one week apart with a value of at least 2 ng/ml, and radiological progression (rPFS) was based on new findings on bone scans and/or increase in measurable or non-measurable lesions.

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Table 1
Baseline characteristics of patients, all arms combined, in VENICE, TAX327 and FIRSTANA.

Baseline type of progression	VENICE (n = 1026)				TAX327 (n = 999)				FIRSTANA (n = 1051)			
Type of progression, n (%)	G1, 231 (22.5)	G2, 348 (33.9)	G3, 447 (43.6)	p-value	G1, 82 (8.2)	G2, 459 (46)	G3, 458 (46)	p-value	G1, 362 (34.4)	G2, 244 (23.2)	G3, 445 (42.3)	p-value
Disease history												
Metastatic disease at initial diagnosis, n (%)	116 (57.4)	104 (35.0)	226 (59.5)	<0.001	6[b] (37.5)	34[b] (32.7)	50[b] (41.3)	0.412	165 (53.6)	76 (38.2)	222 (58.9)	<0.001
Gleason score 8−10 at diagnosis, *n (%)*	115 (52.8)	150 (44.8)	217 (51.8)	0.092	24 (44.4)	130 (40.9)	142 (42.1)	0.863	165 (51.1)	125 (53)	229 (56.8)	0.283
Prior local therapy[a], n (%)	108 (46.8)	227 (65.2)	216 (48.3)	<0.001	38 (46.3)	250 (54.5)	278 (60.7)	0.019	171 (47.2)	159 (65.2)	232 (52.1)	<0.001
Duration of first ADT, median (months)	15.2	17.8	12.0	<0.001	16.3	16.1	14.1	0.427	12.0	13.0	9.0	0.022
Clinical characteristics at randomisation												
PSA, median (ng/mL)	54.4	74.3	123.5	<0.001	109.8	98.8	146.5	0.001	60.3	63.3	96	0.004
ALK, median (UI/L)	122.5	104	104	<0.001	152	170	300	<0.001	109	96.5	170	<0.001
Hb, median (g/dL)	13.1	12.9	12.3	<0.001	13.4	13.0	12.4	<0.001	13.0	13.1	12.4	<0.001
Neutrophil count, median (giga/L)	4.1	4.4	4.6	0.003	4.2	4.5	4.6	0.062	3.9	4.1	4.5	<0.001
dNLR, median	1.7	2.0	2.1	<0.001	1.8	2.1	2.2	0.001	2.5	2.9	3.2	<0.001
Metastatic sites, n (%)												
Lymph nodes only	13 (5.7)	37 (10.6)	11 (2.5)	<0.001	5 (6.3)	31 (6.8)	13 (2.9)	<0.001	27 (7.5)	24 (9.8)	13 (2.9)	<0.001
Bone	161 (70.0)	200 (57.5)	302 (67.6)		61 (77.2)	311 (67.9)	343 (75.4)		211 (58)	99 (41)	231 (52)	
Visceral	56 (24.3)	111 (31.9)	134 (30.0)		13 (16.5)	116 (25.3)	99 (21.8)		55 (15)	65 (27)	104 (23)	

Hb, haemoglobin; dNLR, derived neutrophil-to-lymphocyte ratio; ALK, alkaline phosphatase; ADT = androgen deprivation therapy; G1 = PSA progression only; G2 = radiological progression (± PSA progression); G3 = pain progression (± PSA and/or radiological progression); PSA = prostate-specific antigen.
p-values: to indicate the significance of differences between G1, G2 and G3.
[a] Prior prostatectomy or radical prostate radiotherapy and/or palliative prostate radiotherapy.
[b] Many missing data on this parameter.

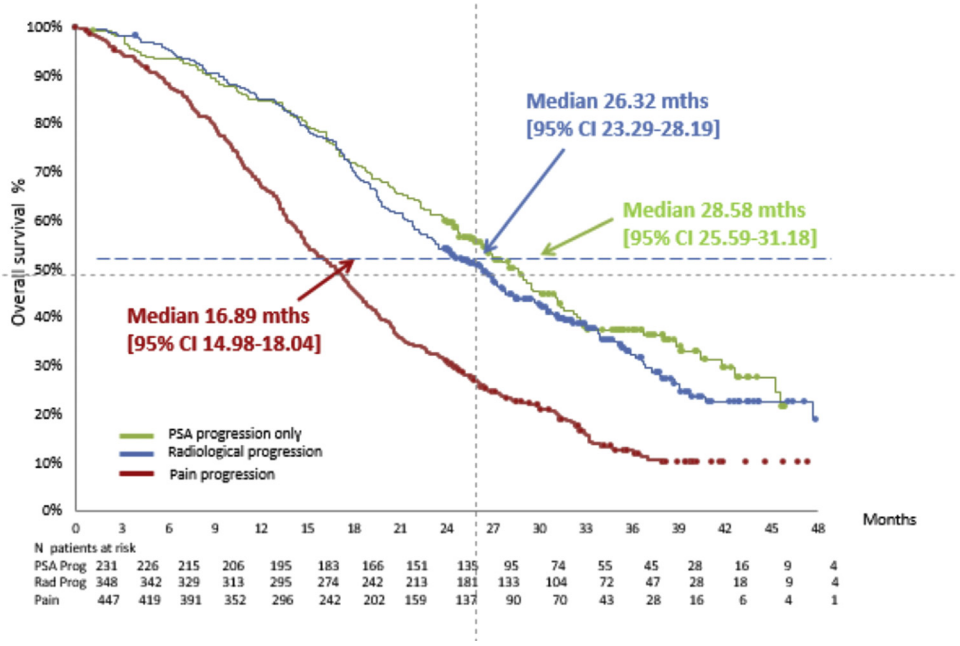

Fig. 1. Kaplan–Meier estimates of OS from randomisation according to the type of progression in VENICE, all arms combined. OS = overall survival; CI = confidence interval; PSA = prostate-specific antigen.

The primary objective of this analysis was to explore the prognostic impact of the type of progression at initiation of first-line chemotherapy (baseline) on OS. To control for a lead-time bias, OS was also calculated from the date of diagnosis of mCRPC (estimated by the date of start of subsequent anticancer therapy after the first androgen deprivation therapy [ADT] [1]). The type of progression was defined as follows: PSA only (group 1, G1); radiological (± PSA progression) (group 2, G2) and pain progression (± PSA, ± rPFS) (group 3, G3). Data from all patients randomised, regardless of the treatment arm, were analysed. Univariate and multivariate Cox regression analyses with backward elimination (5% level) were performed, all arms combined, stratified for the Eastern Cooperative Oncology Group performance score (0–1 vs. 2) and treatment arm. The

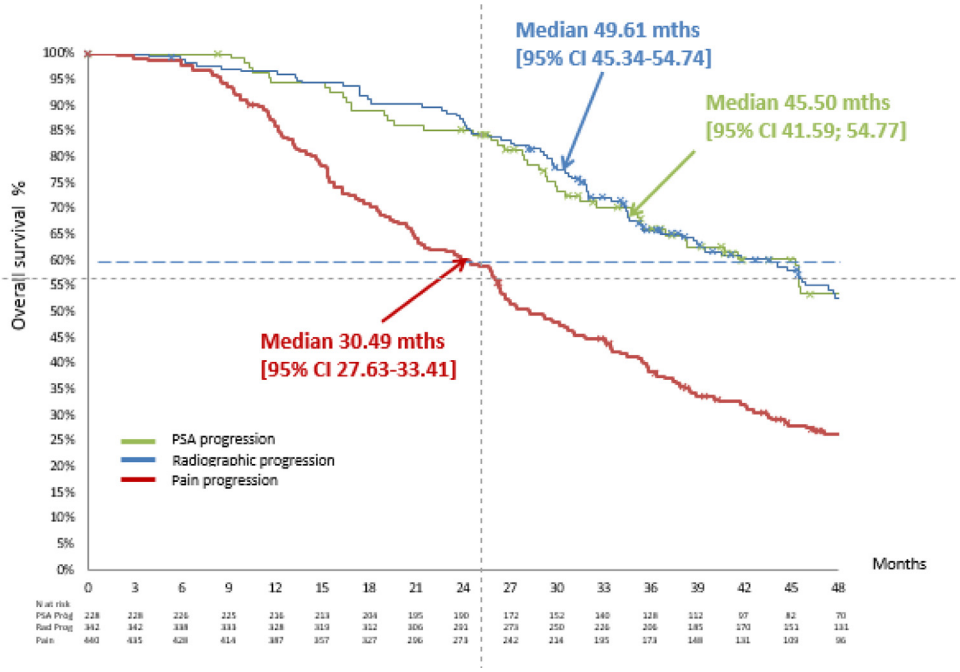

Fig. 2. Kaplan–Meier estimates of OS from mCRPC diagnosis according to the type of progression in VENICE, all arms combined. OS = overall survival; mCRPC = metastatic castration-resistant prostate cancer; CI = confidence interval; PSA = prostate-specific antigen.

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Table 2
Multivariate model for OS in VENICE, TAX327 and FIRSTANA, all arms combined.

Variable	VENICE		TAX327		FIRSTANA	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age						
< median	Ref		–		–	
≥ median	1.24 (1.06; 1.44)	0.006	–		–	
ALK at baseline						
< median	Ref		Ref		Ref	
≥ median	1.63 (1.39; 1.91)	<0.001	1.33 (1.09; 1.63)	0.005	2.17 (1.83; 2.57)	<0.001
Duration of initial ADT						
≥ median	Ref		–		–	
< median	1.40 (1.20; 1.63)	<0.001	–		–	
dNLR						
< median	Ref		–		Ref	
≥median	1.26 (1.08; 1.46)	0.004	–	0.002	1.29 (1.08; 1.54)	0.005
Neutrophil count						
< median	–		Ref		Ref	
≥median	–		1.32 (1.12; 1.60)	0.001	1.21 (1.02; 1.45)	0.031
Haemoglobin at baseline						
≥ median	Ref		Ref		Ref	
<median	1.41 (1.21; 1.65)	<0.001	1.26 (1.05; 1.50)	0.012	1.79 (1.52; 2.11)	<0.001
Type of progression at baseline						
PSA only	Ref		Ref		Ref	
Radiological	1.12 (0.9; 1.39)		1.33 (0.90; 1.97)		0.91 (0.72; 1.15)	
Pain	1.70 (1.38; 2.09)	<0.001	2.12 (1.44; 3.12)	<0.001	1.23 (1.03; 1.48)	0.012
Metastatic sites						
Lymph nodes (LNs) only	–		Ref		–	
Bone ± LN	–		1.79 (1.02; 3.16)		–	
Visceral (±LN, ± bone)	–		3.26 (1.83; 5.80)	<0.001	–	
PSA at baseline						
<median	–		Ref		–	
≥ median	–		1.55 (1.29; 1.86)	<0.001	–	
PSA doubling time						
≥ median (2 months)	–		–		Ref	
< median	–		–		1.42 (1.21; 1.66)	<0.001

PSA = prostate-specific antigen; CI = confidence interval; OS = overall survival; ADT = androgen deprivation therapy; dNLR = derived neutrophil-to-lymphocyte ratio; Ref = reference value; – = variable did not retain significance in multivariate analysis or was not part of the model.

following variables were tested: age; Gleason score at diagnosis; duration of initial ADT; prior therapy with curative intention (radical prostatectomy or prostate radiation therapy); metastatic sites (lymph nodes only, bone ± lymph nodes, visceral ± bone, ± lymph nodes); PSA and PSA doubling time (DT) [17], haemoglobin (Hb), alkaline phosphatase (ALK), derived neutrophil-to-lymphocyte ratio (dNLR) [1] and neutrophil count at randomisation. Lactate dehydrogenase was not included because it was not collected in TAX327 and VENICE trials. Age, duration of initial ADT, PSA, PSA DT, Hb, ALK, neutrophil count and dNLR were dichotomised according to their medians. Fisher's exact test was used for all categorical variables, and the Kruskal–Wallis test, for all continuous variables.

Secondary objectives were to determine median progression-free survival for PSA (PSA-PFS), rPFS and pain progression during treatment with the schedule of DOC75, CAB20 and CAB25. The weekly DOC arm of TAX327 and aflibercept arm of VENICE were not analysed separately because they are not licensed. PSA-PFS was defined as time to PSA progression (defined as an increase of ≥25% from the nadir for men with no PSA response or of ≥ 50% for all others in TAX327 and based on PCWG2 criteria [18] for VENICE and FIRSTANA), and rPFS was defined as time from randomisation to radiographic progression (based on World Health Organization criteria for patients with at least one bidimensionally measurable lesion in TAX327 [1] or PCWG2 criteria [18] in VENICE and FIRSTANA). Pain progression during treatment was defined as time to increased PPI of at least one point from the nadir, increased AS from baseline of at least 25% or requirement for palliative radiation therapy [1]. PSA response was defined based on PCWG2 criteria [18].

3. Results

Baseline characteristics were comparable between the 3 data sets (Table 1). Patients with pain at baseline had more often poor prognostic features.

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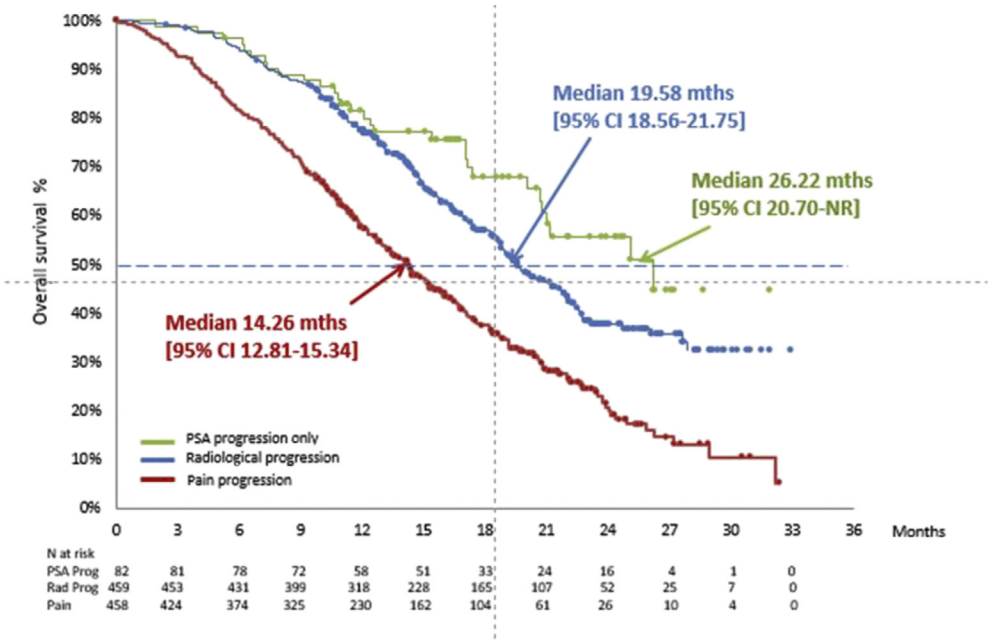

Fig. 3. Kaplan–Meier estimates of OS from randomisation according to the type of progression in TAX327, all arms combined. OS = overall survival; CI = confidence interval; PSA = prostate-specific antigen.

3.1. Prognostic value of the type of progression at baseline

3.1.1. VENICE

Progression type at baseline was available for 1026 of 1224 randomised patients: 22% PSA progression only (G1), 34% rPFS (G2) and 44% pain progression (G3). The median follow-up was 35 months.

The median OS (both arms combined) was 28.6 months in G1, 26.3 months in G2 and 16.9 months in G3 ($p < 0.001$) (Fig. 1). Hazard ratios (HRs) for the risk of death were 1.14 (95% confidence interval [CI]: 0.92–1.41%) in G2 and 2.13 (95% CI: 1.75–2.59%) in G3 compared with G1. The median OS from diagnosis of mCRPC was 45.5 months in G1, 49.6 months in G2 and 30.5 months in G3 ($p < 0.001$) (Fig. 2).

Univariate analysis of variables potentially influencing OS is provided in Supplementary Table 1 (S1). In multivariate analysis, pain (G3) was a strong predictor of poor OS, with an HR of 1.70 (95% CI: 1.38–2.10) versus PSA progression only (G1) (Table 2). Other significant variables included older age (HR: 1.24), high ALK (HR: 1.63), low Hb (HR: 1.41), high dNLR (HR: 1.26) and a short duration of initial ADT (HR: 1.40).

3.1.2. TAX327

The progression type at baseline was available in 999 of 1006 patients randomised: 8% PSA progression only (G1), 46% rPFS (G2) and 46% pain progression (G3). The median follow-up was 14.2 months.

The median OS (all arms combined) was 26.2 months in G1, 19.6 months in G2 and 14.3 months in G3 ($p < 0.001$) (Fig. 3). HRs for death were 1.41 (95% CI: 0.96–2.06) in G2 and 2.40 (95% CI: 1.64–3.51) in G3 compared with G1. The median OS from diagnosis of mCRPC was 63.4 months in G1, 47.0 months in G2 and 30.2 months in G3 ($p < 0.001$) (Fig. 4). Again, multivariate analysis showed that pain at baseline (G3) was a strong predictor of poor OS (HR: 2.12). Other variables with significant impact included a high level of ALK (HR: 1.34), a low level of Hb (HR: 1.26), a high neutrophil count (HR: 1.32), site of metastatic lesions (bone versus lymph nodes, HR: 1.79; visceral versus lymph nodes, HR: 3.26) and PSA at baseline $\geq$ median (HR: 1.55).

3.1.3. FIRSTANA

The progression type was available for 1051 of 1168 patients randomised: 362 (34%) PSA progression only (G1), 244 (23%) rPFS (G2) and 445 (42%) pain progression (G3). The median follow-up was 24 months.

The median OS (all arms combined) was 27.7 months in G1, 30.6 months in G2 and 18.5 months in G3 ($p < 0.001$) (Fig. 5). The HRs for death were 0.94 (95% CI: 0.75–1.17) in G2 and 1.63 (95% CI: 1.36–1.95) in G3 compared to G1. The median OS from diagnosis of mCRPC was 51.1 months in G1, 59.9 months in G2 and 37.4 months in G3 ($p < 0.001$) (Fig. 6). Multivariate analysis showed again the significance of pain progression at baseline (HR: 1.23). Other variables with significant impact on OS included a high level of ALK (HR: 2.17) and low level of Hb (HR: 1.79), high dNLR (HR: 1.29) and neutrophil count (HR: 1.21) and a short PSA DT (HR: 1.42).

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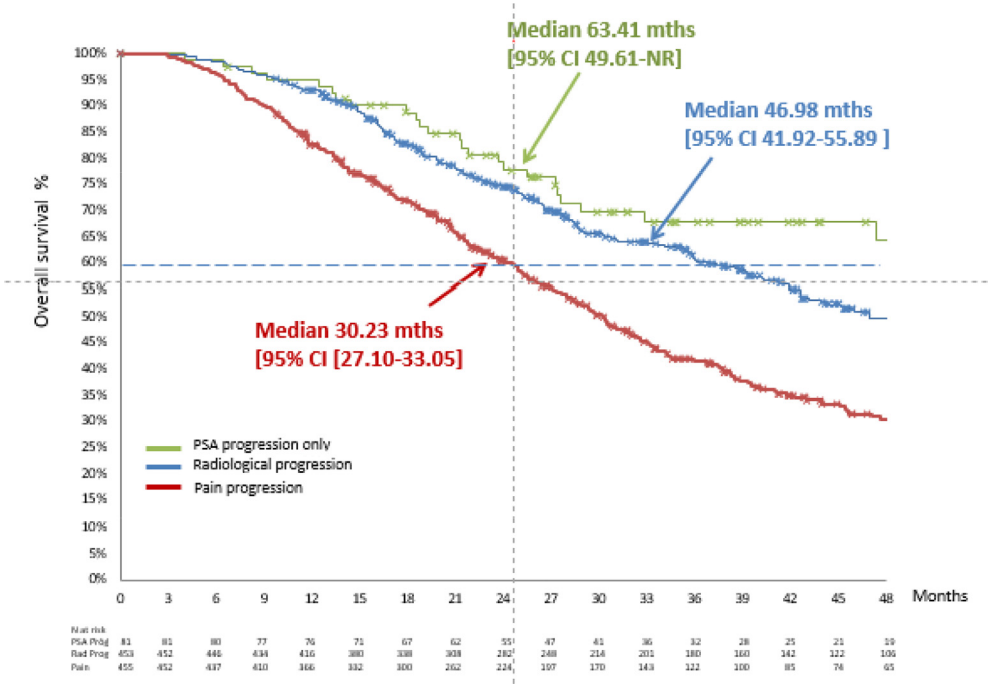

Fig. 4. Kaplan–Meier estimates of OS from mCRPC diagnosis according to the type of progression in TAX327, all arms combined. OS = overall survival; mCRPC = metastatic castration-resistant prostate cancer; CI = confidence interval; PSA = prostate-specific antigen.

3.2. Impact of the type of progression at baseline on activity of mCRPC therapies

In all data sets and irrespective of treatment arm, patients with pain at baseline (G3) had shorter OS, lower median values of PSA-PFS, rPFS and pain-PFS and reduced PSA response (Table S2).

3.3. Type of progression during treatment

A first progression event during treatment was available for 496 patients treated with DOC75 in VENICE, 578 patients treated in TAX327 (both arms) and 918 patients treated in FIRSTANA (all arms). Patients had an increase in pain as the first progression event in 38.5% (191/496) patients in VENICE, 35.8% (191/533) in TAX327 and 45.6% (419/918) in FIRSTANA, and this was more frequent in patients with pain at baseline.

PSA progression was a first progression event in 54.8% (272/496) patients in VENICE; 40.7% (217/533) in TAX327 and 43% (395/918) in FIRSTANA. rPFS occurred as a first event in 3.4–31.6% of patients (Table 3).

4. Discussion

This post hoc analysis, using three large independent databases of patients with mCRPC (VENICE, TAX327 and FIRSTANA) resulted in several key findings.

First, the type of progression at initiation of first-line chemotherapy predicts OS. In all data sets, patients with pain (G3) had almost 1-year shorter OS than those with PSA progression only (VENICE 28.6 vs. 16.9 months; TAX327 26.2 vs. 14.3 months; FIRSTANA 27.7 vs. 18.5 months, respectively). There was no significant difference between patients with PSA only or radiological progression at baseline. Second, a high percentage (~55%) of patients developed pain and/or rPFS during treatment as a first progression event, without PSA progression and irrespective of the type of progression at baseline.

Although the data do not inform on whether or not earlier initiation of chemotherapy during the course of mCRPC would influence OS, there is probably an optimal window of opportunity to initiate therapies because potential subsequent life-extending lines of treatment might be missed in patients who have become symptomatic. In addition, when patients become symptomatic, they may no longer be able to receive a taxane-based treatment owing to frailty, complications, bone events or other causes. We believe these findings may help to decide on initiation of first-line treatment.

In the past decade, several risk groups and nomograms have been developed to predict prognosis in men treated with first-line chemotherapy and to estimate survival, predominantly based on pretreatment variables [19–22]. The prognostic significance of the type of progression at baseline, defined as measurable progressive disease versus progression on a bone scan versus

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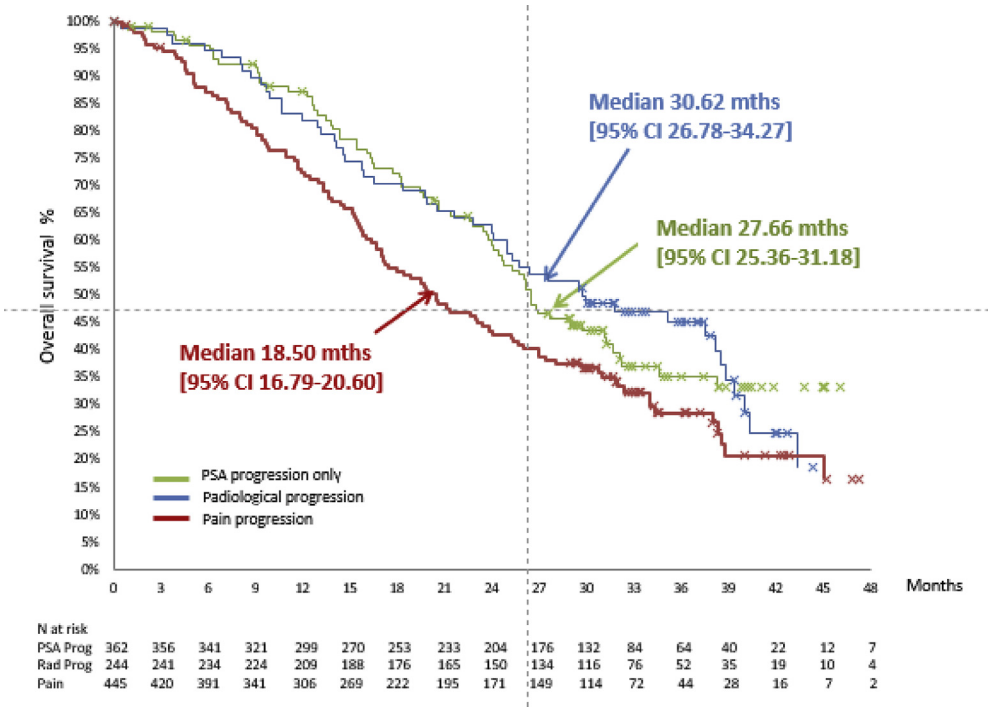

Fig. 5. Kaplan–Meier estimates of OS from randomisation according to the type of progression in FIRSTANA, all arms combined. OS = overall survival; CI = confidence interval; PSA = prostate-specific antigen.

PSA progression only, was previously suggested in a post hoc analysis of the TAX327 study [20]. Progression by measurable disease or the bone scan was associated with an increased risk of death compared with PSA progression alone. A negative impact of pain on survival has also been described in an independent cohort of 145 patients treated with DOC or mitoxantrone [23]. However, these analyses did not inform precisely on

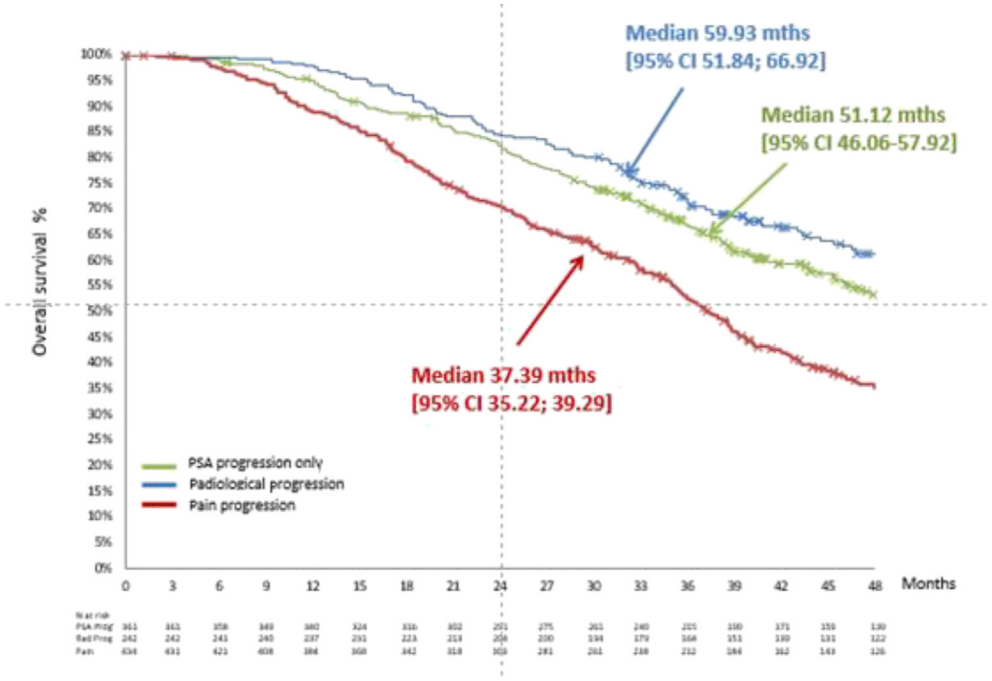

Fig. 6. Kaplan–Meier estimates of OS from mCRPC diagnosis according to the type of progression in FIRSTANA, all arms combined. OS = overall survival; mCRPC = metastatic castration-resistant prostate cancer; CI = confidence interval; PSA = prostate-specific antigen.

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Table 3
Progression events during treatment according to the type of progression at randomisation for treatment with docetaxel (75 mg/m^2 q3w), mitoxantrone (12 mg/m^2 q3w) and cabazitaxel (20 and 25 mg/m^2 q3w).

Progression at baseline	First progression event during treatment					
	Docetaxel (VENICE)	Docetaxel (TAX327)	Mitoxantrone (TAX327)	Docetaxel (FIRSTANA)	Cabazitaxel 20 (FIRSTANA)	Cabazitaxel 25 (FIRSTANA)
G1	PSA only, 56 (54.3%)	PSA only, 9 (42.9%)	PSA only, 12 (48%)	PSA only, 59 (50%)	PSA only, 47 (53.4%)	PSA only, 46 (45.5%)
	Pain, 32 (31.1%)	Pain, 7 (33.3%)	Pain, 7 (28%)	Pain, 43 (36.4%)	Pain, 38 (43.2%)	Pain, 48 (47.5%)
	Radiological, 15 (14.6%)	Radiological, 5 (23.9%)	Radiological, 6 (24%)	Radiological, 16 (13.6%)	Radiological, 3 (3.4%)	Radiological, 7 (6.9%)
	No progression, 8	No progression, 7	No progression, 3	No progression, 19	No progression, 16	No progression, 20
G2	PSA only, 89 (52.7%)	PSA only, 47 (39.5%)	PSA only, 44 (37.6%)	PSA only, 32 (46.4%)	PSA only, 29 (39.2%)	PSA only, 26 (36.6%)
	Pain, 59 (34.9%)	Pain, 40 (33.6%)	Pain, 36 (30.8%)	Pain, 22 (31.9%)	Pain, 33 (44.6%)	Pain, 31 (43.7%)
	Radiological, 21 (12.4%)	Radiological, 32 (26.9%)	Radiological, 37 (31.6%)	Radiological, 15 (21.7%)	Radiological, 12 (16.2%)	Radiological, 14 (19.7%)
	No progression, 7	No progression, 35	No progression, 34	No progression, 12	No progression, 11	No progression, 7
G3	PSA only, 127 (56.7%)	PSA only, 51 (42.1%)	PSA only, 54 (41.5%)	PSA only, 45 (37.8%)	PSA only, 71 (49.3%)	PSA only, 40 (29.9%)
	Pain, 31 (13.8%)	Pain, 51 (42.1%)	Pain, 50 (38.5%)	Pain, 61 (51.3%)	Pain, 60 (41.7%)	Pain, 83 (61.9%)
	Radiological, 66 (29.5%)	Radiological, 19 (15.7%)	Radiological, 26 (20%)	Radiological, 13 (10.9%)	Radiological, 13 (9.0%)	Radiological, 11 (8.2%)
	No progression, 3	No progression, 31	No progression, 25	No progression, 16	No progression, 15	No progression, 17

PSA = prostate-specific antigen.

differences in terms of clinical outcomes between patients progressing by PSA only, radiologically or clinically (represented by pain).

A known progression model in patients with mCRPC, with PSA progression as the most frequent primary event, followed by rPFS and finally pain progression [9,11], is based on median values of PSA, radiological and pain progression in patients with mCRPC treated mainly with androgen-targeting agents. Based on individual progression event analysis in our study, we observed that irrespective of the type of progression at baseline, pain and/or rPFS were the first on-treatment progression events in more than half of men. Our finding of pain progression as a first progression event in a substantial percentage of men is in agreement with a recent post hoc analysis of the CHAARTED study for patients with hormone-sensitive prostate cancer [24], indicating that one should be aware that clinical progression can precede PSA progression.

The PCWG3 guidelines [25] recommend continuing treatment in case of PSA progression only until radiological or clinical progression manifests. However, in daily practice, PSA is a leading parameter, and imaging during treatment may not always be scheduled every 3 months as in clinical trials. In addition, in the absence of PSA progression, imaging may not always be performed at the first signs of pain, and the use of symptoms to guide therapy is not included in guidelines.

Our data, derived from a situation with regular visits and imaging owing to the context of a clinical trial, show the importance to not rely on PSA only.

Based on the baseline characteristics, the patients presenting with pain represent a high-risk subset with unfavourable clinical and laboratory parameters. Differences in baseline characteristics of enrolled patients in trials may thus affect outcomes substantially. The COU-AA-302 [9] and PREVAIL trials [6] included asymptomatic patients and showed a median OS of approximately 35 months in the entire cohort. In the VENICE trial, the median OS was 21.2 months in the entire cohort (mainly symptomatic) but reached 29.4 months in those patients with rising levels of PSA only. The high prevalence of pain at enrolment might also explain the OS in the FIRSTANA trial [15]. Future trials in mCRPC should include a stratification for mode of disease progression before study entry.

A strength of this study is the use of three large prospectively conducted phase III trials and the large number of patients. However, the study has several limitations. First, this was a retrospective and unplanned analysis of VENICE, TAX327 and FIRSTANA. Second, this study only applies to patients with mCRPC treated with first-line chemotherapy, although the results could be applicable to daily practice [26,27] and to the design of therapeutic trials [26,27]. Third, the TAX-327 and VENICE trials were conducted before the clinical availability of abiraterone, enzalutamide, radium-223 and CAB, which may have confounded the survival analyses.

5. Conclusions

The type of progression at initiation of first-line chemotherapy is a robust prognostic marker reflected by almost 1-year shorter median OS in patients with

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pain progression at baseline than in patients with PSA progression only.

In view of multiple lines of systemic treatment nowadays available, postponing initiation of chemotherapy or changing therapy despite repeated increases in the level of PSA until either radiological or clinical progression may lead to missed windows of opportunity. This study provides data about survival outcomes and on-treatment progression events with taxane-based chemotherapy in this specific clinical space. Pain and/or rPFS preceding PSA progression as a first progression event during first-line chemotherapy occurred in half of the men. This finding has the prospect to be changing as per practice and to be incorporated in clinical guidelines because it emphasises regular visits and imaging and not to rely on PSA progression alone.

Conflict of interest statement

D.G.R. reports travel reimbursement from Sanofi and provided consultancy for Bayer, Faron Pharmaceuticals and Servier. N.D. reports no conflicts of interest. I.F.T. reports data monitoring reimbursement from Janssen and Roche. B.T serves as an advisor and investigator for Sanofi-Aventis; Janssen Pharmaceuticals, Inc., Takeda, Astellas Pharma, Inc. and Kyocyt. M.E. provided consultancy for Sanofi. F.M. reports funding from Sanofi, shares in the company Stat Process, and in its subsidiary: Health Data Process, Alicante, Spain, contractor for Astra Zeneca.. K.F. reports honoraria from and serves as a consultant for Amgen, Astellas, Bayer, Clovis, CureVac, Janssen, Orion and Sanofi. O.S. has a consultant or advisory role for Astellas, Bavarian Nordic, Bayer, Bellicum, Biscayne, Johnson & Johnson, Medivation, OncoGenex, Sanofi, Algeta, Aragon and Pfizer and reports research funding from Bayer, Johnson & Johnson, Progenics, Sanofi, Algeta, Takeda and Algeta ASA. S.O. reports fees from Sanofi, Janssen and Astellas. R.d.W. serves as a consultant for Sanofi, Merck, and Roche and reports fees from Merck.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.10.029.

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