

Article

Impact of Extraskkeletal Metastases on Skeletal-Related Events in Metastatic Castration-Resistant Prostate Cancer with Bone Metastases

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Abstract: The therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has substantially evolved over the last decade. Nonetheless, a better understanding of bone-targeted agents (BTAs) action in mCRPC remains an unmet need. The use of BTAs aims to reduce the incidence of skeletal-related events (SREs) in patients with mCRPC. Less frequent BTA schedules are currently being studied to minimize adverse events. In this study, the impact of metastatic compartment (bone and extraskkeletal metastases (BESM) vs. bone-only metastases (BOM)) on bone biomarker kinetics, time to first on-study SRE, and symptomatic skeletal events (SSEs) is evaluated. This is a retrospective analysis of the prospective, randomized, multicenter clinical trial of denosumab vs. zoledronic acid in patients with mCRPC and bone metastases. A total of 1901 patients were included, 1559 (82.0%) with BOM and 342 with BESM (18.0%). Bone metastases burden was balanced between groups. Baseline levels and normalization rates of corrected urinary N-terminal telopeptide and bone alkaline phosphatase did not differ between groups. However, BESM patients had a higher risk of SREs (adjusted HR 1.21; 95% CI 1.01–1.46; $p = 0.043$) and SSEs (adjusted HR 1.30; 95% CI 1.06–1.61; $p = 0.014$). This difference was more pronounced in the first 12 months of BTA treatment. In mCRPC, strategies of BTA schedule de-escalation may take into account presence of extraskkeletal metastases.

Keywords: prostate cancer; metastatic castration-resistant prostate cancer; bone-targeted agents; bone metastases; visceral metastases

1. Introduction

Prostate carcinoma is one of the most common cancers in men globally and the second cause of cancer death in this gender in Europe [1,2]. In these patients, bone is the most common site of metastatic disease (>90% of patients) [3] and bone metastases are frequently associated with detrimental bone outcomes—collectively referred to as skeletal-related events (SREs; pathological fracture, spinal cord compression, and radiotherapy or surgery to bone), which negatively impact quality of life and

survival [3–6]. Many metastatic castration-resistant prostate cancer (mCRPC) patients also present metastatic disease outside the bone, with the type of metastatic spread (i.e., the metastatic compartment) having strong prognostic survival implications. In a meta-analysis with over 8000 mCRPC patients from nine phase III trials, men with visceral metastases had worse overall survival (OS)—13.5 months (95% confidence interval (CI) 12.7–14.4 months) for patients with liver metastases and 19.4 months (95% CI 17.8–20.7 months) for those with lung metastases compared with 20.8 months for patients with bone-only metastases (BOM) (95% CI 20.8–21.9 months) [7].

Metastatic bone disease disrupts bone metabolism [8,9], weakening the structural integrity of bone and leading to skeletal-related events (SREs) [9]. Prostate cancer cells secrete factors, such as bone morphogenic proteins (BMPs), TGF β , and endothelin-1 (ET-1), which increase osteoblastic activity and lead to osteoblastic metastases [10,11]. In this setting, bone-targeted agents (BTAs; denosumab and zoledronic acid (ZA)) reduce bone resorption and bone metastases-associated morbidity [1,4,5]. Bone biomarkers have been used to capture BTA action in bone, and both their baseline and post-BTA values are strongly prognostic [8,12–15].

While being generally well-tolerated drugs, in a patient population with increasingly longer survival, BTAs cumulative exposure has become a cause for concern, especially due to jaw osteonecrosis risk [3,16,17]. De-escalation strategies have been studied, aiming to provide the same efficacy as the standard schedule while improving patient adherence and safety. In fact, results from several studies have shown that the 12-weekly de-escalation regimen is noninferior to the 4-weekly dosage regimen in patients with bone metastases [17,18]. However, the use of the 12-week schedule might be troublesome in some patients, namely those with previous SREs and metastatic disease outside the bone [19]. Exploratory studies have shown that the type of metastatic spread (i.e., metastatic compartment as assessed by bone-only metastases (BOM) vs. bone plus extraskelatal metastases (BESM)) may impact SRE risk. In a cohort of breast cancer patients with bone metastases, patients with BESM displayed shorter interval until first SRE (HR 1.62, 95% CI 1.01–2.60, $p = 0.0449$) compared with patients with BOM [20], consistently high urinary N-terminal telopeptide (uNTX) levels, and an unpredictable pattern of bone marker variation over time, which was not normalized with BTAs [20]. Based on these findings, we hypothesized that patients with BESM may have increased bone marker levels and higher risk of SREs and symptomatic skeletal events (SSEs) than those with BOM.

In this large study of mCRPC with bone metastases, we investigated the impact of the metastatic compartment (BOM vs. BESM) on bone biomarker levels at baseline and after BTA introduction, time to first and subsequent on-study SREs/SSEs and OS.

2. Results

2.1. Cohort Description

A total of 1901 patients receiving either denosumab or ZA were identified for this study from the NCT00321620 trial, 1559 (82.0%) with BOM and 342 (18.0%) with BESM. Patient, disease, and treatment characteristics are summarized in Table 1. Compared to patients with BOM, patients with BESM were younger (≤ 65 years—31.5% vs. 40.4%, $p = 0.013$), had higher body mass index (BMI; median 27.7 (interquartile range (IQR) 25.3–30.5) vs. 26.9 (IQR 24.3–29.8) Kg/m², $p = 0.003$), more frequently had node-positive disease at diagnosis (N1—74.0% vs. 0.0%, $p < 0.001$), and had higher total prostate-specific antigen (PSA) levels at diagnosis (≥ 10 ng/mL—88.6% vs. 83.9%, $p = 0.029$). More patients with BESM were under chemical castration (76.3% vs. 63.8%) compared with patients with BOM. While on trial, more BESM patients received (26.6% vs. 11.1%, $p < 0.001$) or had previously received (39.8% vs. 19.9%, $p < 0.001$) chemotherapy or radiotherapy (39.2% vs. 30.2%, $p = 0.001$) compared with BOM patients.

Table 1. Patient demographic/clinicopathological characteristics and type of concomitant treatment according to metastatic compartment.

Characteristic	Overall Cohort	BOM	BESM	<i>p</i> -Value (BOM vs. BESM)
Number of patients, <i>n</i> (%)	1901 (100)	1559 (82.0)	342 (18.0)	-
Demographic and clinicopathological characteristics				
Age, years				
Median	74	74	66	<0.001
P25–P75	65–76	65–76	64–75	
Range	35–96	35–96	45–86	
Age (years), <i>n</i> (%)				
≤50	14 (0.7)	10 (0.6)	4 (1.2)	0.013
>50 to ≤65	615 (32.4)	481 (30.9)	134 (39.2)	
>65 to ≤75	726 (38.2)	605 (38.8)	121 (35.4)	
>75	546 (28.7)	463 (29.7)	83 (24.3)	
ECOG performance status, <i>n</i> (%)				
≤1	1768 (93.0)	1448 (92.9)	320 (93.6)	0.652
2	133 (7.0)	111 (7.1)	22 (6.4)	
Body mass index				
Median	27.0	26.9	27.7	0.003
IQR	24.5–30.0	24.3–29.8	25.3–30.5	
Missing, <i>n</i> (%)	47 (2.5)	39 (2.5)	8 (2.3)	
T stage at disease diagnosis, <i>n</i> (%)				
T1–T2	725 (44.8)	604 (45.8)	121 (40.5)	0.172
T3	693 (42.8)	559 (42.4)	134 (44.8)	
T4	200 (12.4)	156 (11.8)	44 (14.7)	
Missing	283 (14.9)	240 (15.4)	43 (12.6)	
N stage at disease diagnosis, <i>n</i> (%)				
N0	1648 (86.7)	1559 (100)	89 (26.0)	<0.001
N1	253 (13.3)	0	253 (74.0)	
M stage at disease diagnosis, <i>n</i> (%)				
M0	832 (55.7)	685 (55.9)	147 (54.9)	0.760
M1	662 (44.3)	541 (44.1)	121 (45.1)	
Missing	407 (21.4)	333 (21.4)	74 (21.6)	
Gleason score, <i>n</i> (%)				
≤6	355 (18.7)	297 (19.0)	58 (17.0)	0.452
7	744 (39.1)	614 (39.4)	130 (38.0)	
≥8	802 (42.2)	648 (41.6)	154 (45.0)	
PSA at disease diagnosis, ng/mL				
Median	60	57	78	0.021
IQR	19–213	18–207	23–247	
PSA at disease diagnosis, <i>n</i> (%)				
<10 ng/mL	290 (15.3)	251 (16.1)	39 (11.4)	0.029
≥10 ng/mL	1611 (84.7)	1308 (83.9)	303 (88.6)	
Time from cancer diagnosis to bone metastases, months				
Median	24.5	23.9	27.2	0.784
IQR	1.8–68.6	2.0–69.3	1.2–66.4	

Table 1. Cont.

Characteristic	Overall Cohort	BOM	BESM	<i>p</i> -Value (BOM vs. BESM)
Type of bone metastases, <i>n</i> (%)				
Lytic	71 (4.8)	57 (4.6)	14 (5.6)	0.109
Blastic	1138 (76.5)	961 (77.6)	177 (71.4)	
Mixed	278 (18.7)	221 (17.8)	57 (23.0)	
Unknown/Not seen	414 (21.8)	320 (20.5)	94 (27.5)	
Number of bone metastases, <i>n</i> (%)				
≤2	1255 (66.0)	1021 (65.5)	234 (68.4)	0.484
>2 to ≤4	329 (17.3)	271 (17.4)	58 (17.0)	
>4	317 (16.7)	267 (17.1)	50 (14.6)	
Type of visceral metastases, <i>n</i> (%) ¹				
Liver			36 (10.5)	-
Lung			58 (17.0)	
Other sites	-	-	294 (86.0)	
TPrevious SRE, <i>n</i> (%)				
Yes	463 (24.4)	388 (24.9)	75 (21.9)	0.248
No	1438 (75.6)	1171 (75.1)	267 (78.1)	
Treatment characteristics				
BTA type, <i>n</i> (%)				
Zoledronic acid	943 (49.6)	764 (49.0)	181 (52.9)	0.291
Denosumab	945 (49.7)	783 (50.2)	160 (46.8)	
No BTA	13 (0.7)	12 (0.8)	1 (0.3)	
Previous bisphosphonate treatment, <i>n</i> (%)				
Yes	57 (3.0)	48 (3.1)	9 (2.6)	0.660
No	1844 (97.0)	1511 (96.9)	333 (97.4)	
Castration type, <i>n</i> (%)				
Castration type, <i>n</i> (%)	1256 (66.1)	995 (63.8)	261 (76.3)	<0.001
Chemical	92 (4.8)	85 (5.5)	7 (2.1)	
Surgical	553 (29.1)	479 (30.7)	74 (21.6)	
Currently receiving CT, <i>n</i> (%)				
Yes	264 (13.9)	173 (11.1)	91 (26.6)	<0.001
No	1637 (86.1)	1386 (88.9)	251 (73.4)	
Previous CT, <i>n</i> (%)				
Yes	446 (23.5)	310 (19.9)	136 (39.8)	<0.001
No	1455 (76.5)	1249 (80.1)	206 (60.2)	
Previous RT, <i>n</i> (%)				
Yes	604 (31.8)	470 (30.2)	134 (39.2)	0.001
No	1297 (68.2)	1089 (69.8)	208 (60.8)	
Previous prostatectomy, <i>n</i> (%)				
Yes	313 (16.5)	247 (15.8)	66 (19.3)	0.119
No	1588 (83.5)	1312 (84.2)	276 (80.7)	
Previous antineoplastic surgery (any), <i>n</i> (%)				
Yes	832 (43.8)	655 (42.0)	177 (51.8)	0.001
No	1069 (56.2)	904 (58.0)	165 (48.3)	

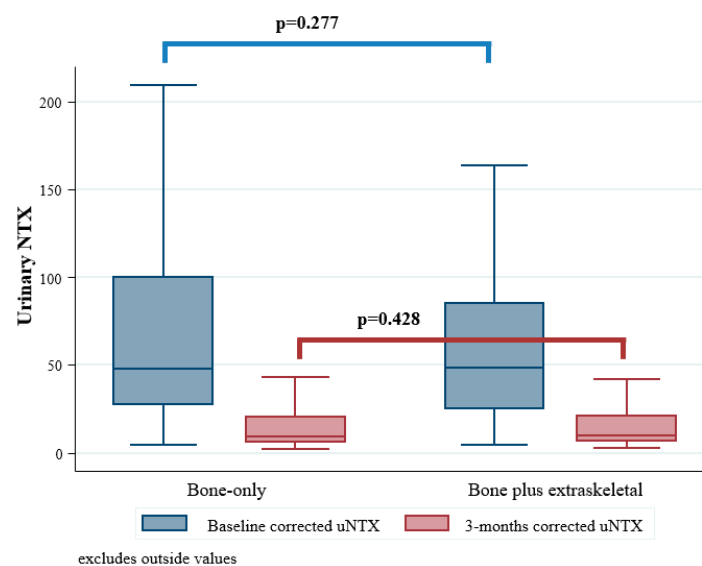
BOM, bone-only metastases; BTA, bone-targeted agent; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; BESM, bone and extraskelatal metastases; IQR, interquartile range; PSA, prostate-specific antigen; RT, radiotherapy; SRE, skeletal-related event. ¹ Patients could present with metastases in several visceral sites. As missing data aren't considered for the nonmissing proportion of patients, proportion sum may exceed 100% in cases of missing data.

2.2. Bone Disease-Specific Characteristics

Bone disease-specific characteristics were balanced between groups, namely time from cancer diagnosis to bone metastases (27.2 months in BESM vs. 23.9 months in BOM group, $p = 0.784$), bone metastases burden (>2 lesions—31.6% in BESM vs. 34.5% in BOM group, $p = 0.300$), and proportion of patients facing previous SREs (78.1% in BESM vs. 75.1% in BOM group, $p = 0.248$). Previous bisphosphonate use was similar between groups (no previous use—97.4% in BESM vs. 96.9% in BOM group, $p = 0.660$), as well as BTA type (ZA—52.9% in BESM vs. 49.0% in BOM group, denosumab—46.8% in BESM vs. 50.2% in BOM group, $p = 0.291$).

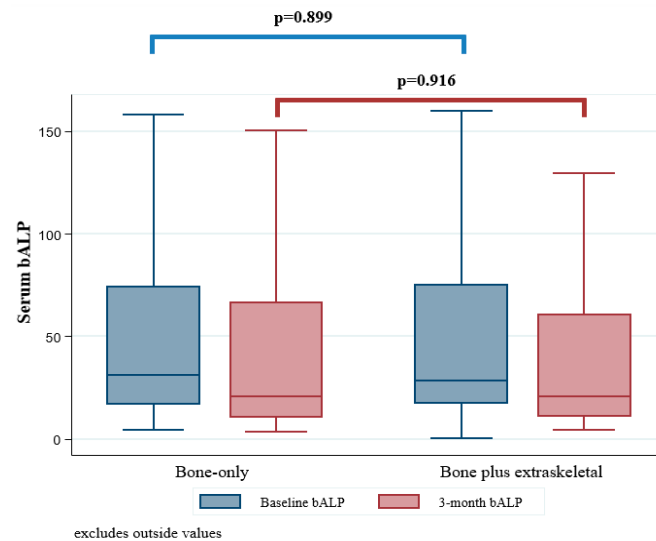
2.3. Bone Marker Variation

At baseline, mean corrected urinary N-telopeptide (uNTX) levels were 48 nmol BCE/mmol creatinine (IQR 27–100) in BOM and 48 nmol BCE/mmol creatinine (IQR 25–85) in BESM patients ($p = 0.277$) (Figure 1 and Table S1). The proportion of patients with corrected uNTX normalization at 3 months was 80.2% ($n = 364$) and 85.6% ($n = 77$; $p = 0.234$), respectively (Figure 1A). Mean bone alkaline phosphatase (bALP) levels at baseline were 31 ng/mL (IQR 17–74) in BOM and 29 ng/mL (IQR 17–75) in BESM patients ($p = 0.899$). The proportion of patients with bALP normalization at 3 months was 29.0% ($n = 236$) in BOM and 32.9% ($n = 56$) in bone plus BESM patients ($p = 0.310$; Figure 1B).



(A) Corrected urinary N-telopeptide (uNTX)

Figure 1. Cont.



(B) Bone alkaline phosphatase (bALP)

Figure 1. Bone markers at baseline and week 13. (A) Corrected uNTX at baseline and week 13; (B) bALP at baseline and week 13. bALP, bone alkaline phosphatase; uNTX, urinary N-terminal telopeptide.

2.4. Skeletal-Related Events

After a median follow-up of 20.1 months (IQR 15.9–23.8; balanced between arms), 27.9% ($n = 530$) of patients developed an on-study SSE and 38.2% ($n = 727$) an on-study SRE in the overall cohort (Table 2). The proportion of patients developing SREs was similar between groups (42.1% in BESM vs. 37.4% in BOM group). No substantial differences were found regarding SRE pattern, such as number of SRE and type of SRE (Table 2).

Table 2. Occurrence and type of SREs according to metastatic compartment.

Characteristic	BOM	BESM	<i>p</i> -Value
Development of any on-study SRE, <i>n</i> (%)			
Yes	583 (37.4)	144 (42.1)	0.105
No	976 (62.6)	198 (57.9)	
Development of symptomatic on-study SREs, <i>n</i> (%)			
Yes	417 (26.8)	113 (33.0)	0.019
No	1142 (73.3)	229 (67.0)	
Number of SREs			
Median (IQR)	0	0	0.099
Min.–max.	0–1	0–1	
Number of SREs, <i>n</i> (%)			
0	976 (62.6)	198 (57.9)	0.224
1	383 (24.6)	91 (26.6)	
2	127 (8.1)	38 (11.1)	
≥3	73 (4.7)	15 (4.4)	
Pts with radiotherapy to bone as first SRE, <i>n</i> (%) ¹			
Yes	309 (53.0)	78 (54.2)	0.802
No	274 (47.0)	66 (45.8)	
Pts with pathological fracture as first SRE, <i>n</i> (%) ¹			
Yes	233 (40.0)	55 (38.2)	0.697
No	350 (60.0)	89 (61.8)	

BOM, bone-only metastases; BESM, bone and extraskelatal metastases; IQR, interquartile range; pts, patients; SRE, skeletal-related events. ¹ Only patients with on-study SREs.

At 12 and 24 months, 64.1% (95% CI 61.3–66.8) vs. 55.9% (95% CI 49.4–61.8) and 44.2% (95% CI 40.3–48.0) vs. 35.8% (95% CI 27.4–44.3) of patients in BOM and BESM groups were free of SREs, respectively. The median time to an SRE was 14.9 months (IQR 5.6- not reached (NR)) for patients with BESM and 19.8 months (IQR 7.2–34.0) for patients with BOM. In univariate analysis, patients with BESM had a 25% higher risk of developing an SRE compared to patients with BOM (hazard ratio (HR) 1.25, 95% CI 1.04–1.51, $p = 0.015$) (Figure 2). Consistent results were found in multivariate analysis (HR 1.21, 95%CI 1.01–1.46, $p = 0.043$) and in multiple failure-time analysis (Table 3). In univariate analysis, features also associated with increased SRE risk included ECOG-PS 2 vs. ≤ 1 (HR 1.36, 95%CI 1.01–1.82, $p = 0.043$); higher total PSA levels at diagnosis (≥ 10 ng/mL—HR 1.23, 95%CI 1.02–1.50, $p = 0.035$); previous SREs (HR 1.45, 95%CI 1.23–1.70, $p < 0.001$); previous (HR 1.29, 95%CI 1.09–1.52, $p = 0.003$) or current (HR 1.40, 95%CI 1.15–1.70, $p = 0.001$) chemotherapy treatment; and previous radiotherapy treatment (HR 1.26, 95%CI 1.09–1.47, $p = 0.002$).

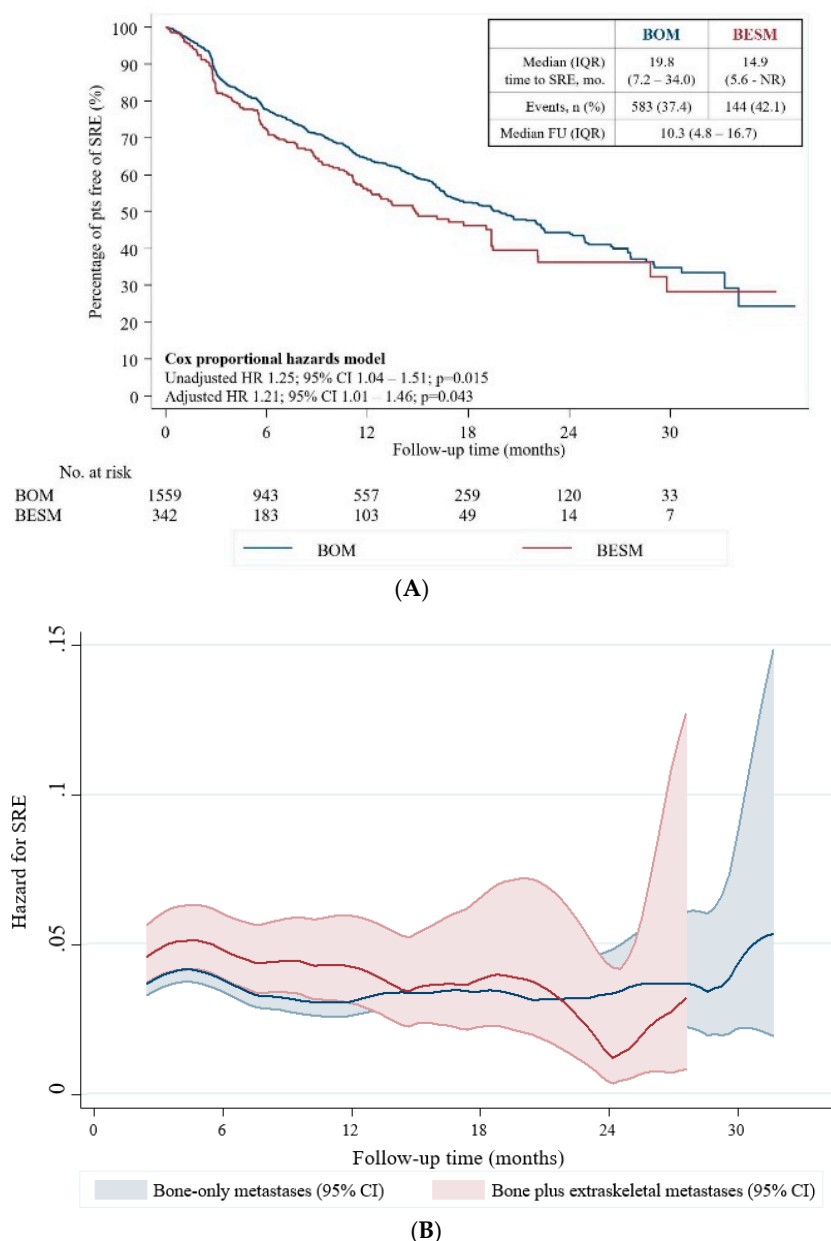


Figure 2. (A) Time-to-first on-study SRE; (B) Hazard for first on-study SRE. BESM, Bone and extraskeletal metastases; BOM, bone-only metastases; CI, confidence interval; ESD, extraskeletal disease; HR, hazard ratio; IQR, interquartile range; NR, not reached; pts, patients; SRE, skeletal-related event.

Table 3. Risk for development of first on-treatment SRE.

Characteristic	Risk for SRE Development		
	HR	95% CI	<i>p</i> -Value
Univariate analysis			
Metastatic compartment			
Bone-only	Reference	Reference	0.015
Bone + extraskeletal metastases	1.25	1.04–1.51	
Age (years)			
≤50	Reference	Reference	0.014
>50 to ≤65	0.47	0.26–0.85	0.002
>65 to ≤75	0.38	0.21–0.70	0.006
>75	0.43	0.23–0.79	
ECOG performance status			
≤1	Reference	Reference	0.043
2	1.36	1.01–1.82	
Gleason score			
≤6	Reference	Reference	0.795
7	0.97	0.79–1.20	0.977
≥8	1.19	0.98–1.46	
PSA at disease diagnosis, ng/mL			
<10	Reference	Reference	0.035
≥10	1.23	1.02–1.50	
Type of bone metastases			
Lytic	Reference	Reference	0.648
Blastic	0.92	0.63–1.33	0.738
Mixed	0.93	0.62–1.41	
Number of bone metastases			
≤2	Reference	Reference	0.162
>2	1.12	0.96–1.30	
Previous SREs			
No	Reference	Reference	<0.001
Yes	1.45	1.23–1.70	
Castration type			
Chemical	Reference	Reference	0.001
Surgical	0.49	0.33–0.75	
Both	0.78	0.66–0.93	0.004
Currently receiving chemotherapy			
No	Reference	Reference	0.001
Yes	1.40	1.15–1.70	
Previous chemotherapy			
No	Reference	Reference	0.003
Yes	1.29	1.09–1.52	
Previous radiotherapy			
No	Reference	Reference	0.002
Yes	1.26	1.09–1.47	

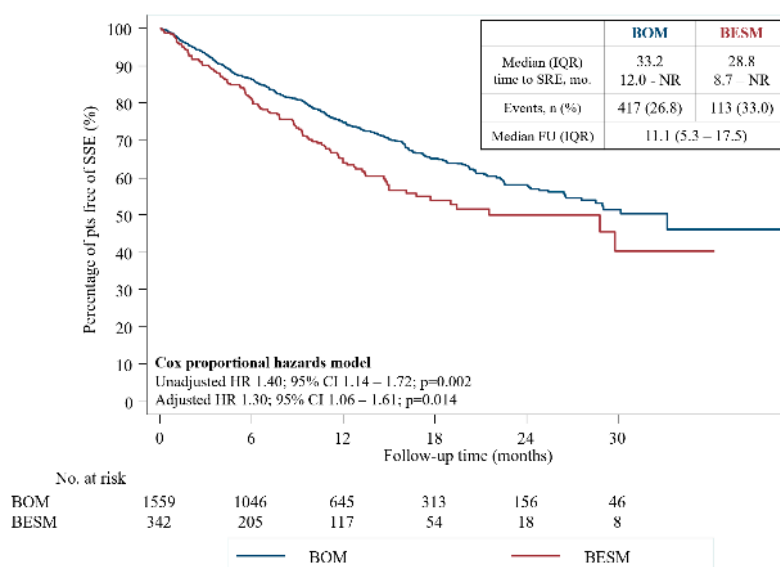
Table 3. Cont.

Characteristic	Risk for SRE Development		
	HR	95% CI	p-Value
Previous anti-neoplastic surgery (any)			
No	Reference	Reference	0.600
Yes	0.96	0.83–1.11	
Multivariate model 1; n = 1901			
Covariates: Age, ECOG PS, Gleason score, PSA at diagnosis, number of bone lesions, previous SREs, castration type, and previous surgery and radiotherapy.			
Metastatic compartment			
Bone-only	Reference	Reference	0.043
Bone + extraskeletal metastases	1.21	1.01–1.46	
Andersen-Gill model for multiple failure-time data			
Unadjusted HR 1.28; 95% CI 1.04–1.58; p = 0.018; Adjusted HR 1.23; 95% CI 1.00–1.52; p = 0.048			

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PSA, prostate-specific antigen; SRE, skeletal-related event.

2.5. Symptomatic Skeletal Events

At 12 and 24 months, 74.7% (95% CI 72.1–77.1) vs. 64.2% (95% CI 57.8–69.8) and 58.0% (95% CI 54.1–61.6) vs. 50.1% (95% CI 41.9–57.7) of patients in BOM and BESM groups were free of SSEs, respectively. Median time to an SSE was 33.2 months (IQR 12.0–NR) for patients with BESM and 28.8 months (IQR 8.7–NR) for patients with BOM (Figure 3). In univariate analysis, patients with BESM had a 40% higher risk of developing an SSE compared with patients with BOM (HR 1.40, 95% CI 1.14–1.72, p = 0.002). Consistent results were found in multivariate analysis (HR 1.30, 95% CI 1.06–1.61, p = 0.014) and multiple failure-time analysis (Table 4). In univariate analysis, features also associated with a higher SSE risk included higher total PSA levels at diagnosis (≥10 ng/mL—HR 1.29, 95% CI 1.02–1.96, p = 0.031); previous SREs (HR 1.63, 95% CI 1.35–1.96, p < 0.001); previous (HR 1.32, 95% CI 1.09–1.60, p = 0.004) or current (HR 1.47, 95% CI 1.17–1.84, p = 0.001) chemotherapy; and previous radiotherapy (HR 1.48, 95% CI 1.24–1.76, p < 0.001).



(A)

Figure 3. Cont.

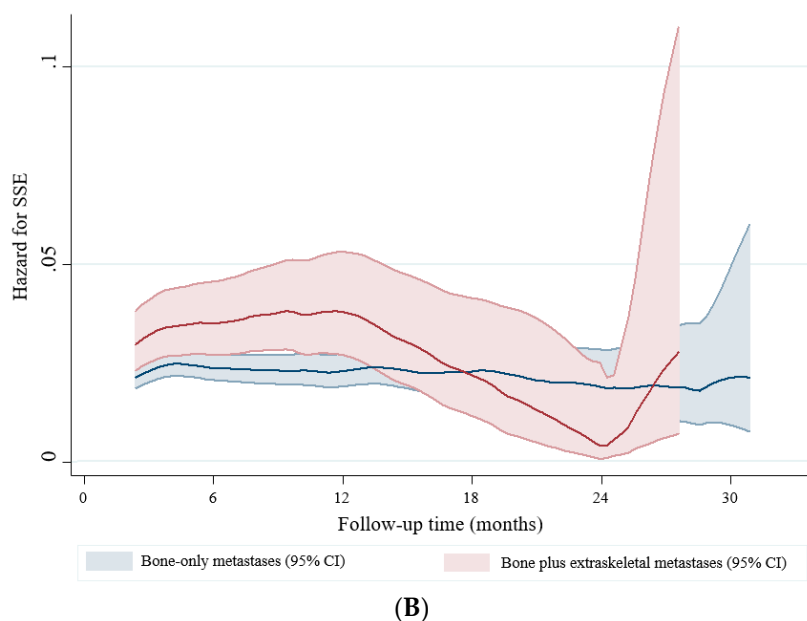


Figure 3. (A) Time-to-first on-study SSE; (B) Hazard for first on-study SSE. Hazards model.BESM, Bone and extraskeletal metastases; BOM, bone-only metastases; CI, confidence interval; ESD, extraskeletal disease; HR, hazard ratio; IQR, interquartile range; NR, not reached; pts, patients; SSE, symptomatic skeletal event.

Table 4. Risk for development of first on-treatment SSE.

Characteristic	Risk for SSE Development			
	HR	95% CI	p-Value	
Univariate analysis				
Metastatic compartment				
	Bone-only	Reference	Reference	0.002
	Bone + extra-bone metastases	1.40	1.14–1.72	
Age (years)				
	≤50	Reference	Reference	0.063
	>50 to ≤65	0.53	0.27–1.03	
	>65 to ≤75	0.38	0.19–0.73	
	>75	0.34	0.17–0.68	
ECOG performance status				
	≤1	Reference	Reference	0.055
	2	1.39	0.99–1.95	
Gleason score				
	≤6	Reference	Reference	1.188
	7	0.92	0.72–1.19	
	≥8	1.27	1.01–1.62	
PSA at disease diagnosis, ng/mL				
	<10	Reference	Reference	0.031
	≥10	1.29	1.02–1.63	
Type of bone metastases				
	Lytic	Reference	Reference	0.952
	Blastic	0.99	0.63–1.55	
	Mixed	0.90	0.55–1.48	

Table 4. Cont.

Characteristic	Risk for SSE Development		
	HR	95% CI	p-Value
Number of bone metastases			
≤2	Reference	Reference	0.454
>2	1.07	0.89–1.28	
Previous SREs			
No	Reference	Reference	<0.001
Yes	1.63	1.35–1.96	
Castration type			
Chemical	Reference	Reference	<0.001
Surgical	0.37	0.21–0.64	
Both	0.67	0.54–0.82	
Currently receiving chemotherapy			
No	Reference	Reference	0.001
Yes	1.47	1.17–1.84	
Previous chemotherapy			
No	Reference	Reference	0.004
Yes	1.32	1.09–1.60	
Previous radiotherapy			
No	Reference	Reference	<0.001
Yes	1.48	1.24–1.76	
Previous antineoplastic surgery (any)			
No	Reference	Reference	0.439
Yes	0.93	0.79–1.11	
Multivariate model; n = 1901			
Covariates: Age, ECOG PS, Gleason score, PSA at diagnosis, number of bone lesions, previous SREs, castration type, and previous surgery and radiotherapy			
Metastatic compartment			
Bone-only	Reference	Reference	0.014
Bone + extraskelatal metastases	1.30	1.06–1.61	

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PSA, prostate-specific antigen; SRE, skeletal-related event; SSE, symptomatic skeletal event.

2.6. Overall Survival

After a median follow-up of 16.6 months (IQR 10.7–23.9; balanced between arms), 49.2% ($n = 935$) of patients in the overall cohort died, 47.3% ($n = 738$) in the BOM and 57.6% ($n = 197$) in the BESM group (Table S1). Median time to death was 15.8 months (IQR 8.2–27.9) for BESM and 20.5 months (IQR 9.8–NR) for BOM group. In univariate analysis, BESM patients had a 38% higher risk of death compared to BOM patients (HR 1.38, 95% CI 1.17–1.61; $p < 0.001$).

3. Discussion

The treatment of mCRPC has substantially evolved over the last decade, namely with the introduction of new therapeutic options. However, bone remains a major metastatic site in mCRPC, with important morbidity, quality of life, and survival implications. Assessment of a high-quality cohort derived from one of the largest clinical trials of mCRPC patients treated with BTAs is a major opportunity to improve knowledge and optimize BTA use in mCRPC.

Visceral metastases have long been considered a negative prognostic factor for survival in mCRPC [7,12,21]. In this large and high-quality cohort of patients with mCRPC and bone metastases receiving BTAs, patients with bone plus extraskeletal metastases had a similar baseline and 3-month normalization patterns of bone remodeling markers as patients with bone-only metastases, but a higher risk of SREs, SSEs, and death irrespective of bone disease volume and disease aggressiveness features. This difference was more evident in the first year after diagnosis of mCRPC with bone metastases.

Bone metastatic niche is a rich source of growth factors and other soluble molecules that are released by bone metabolism activation from mCRPC bone metastases [12,20,22]. Several of these biomarkers, such as uNTX and bALP, are amenable to serum or urine quantification and constitute strong predictors of survival and SRE risk in patients with bone metastases from several tumor types [8,12,20,22]. Indeed, a 2016 study by Lipton et al., using an integrated analysis of three similar phase III trials, showed that patients with bone turnover markers above the median after 3 months of antiresorptive therapy had significantly worse clinical outcomes, including OS and bone disease progression, compared to patients with bone turnover markers below the median [8].

In the present study, bone biomarker assessment, at baseline and 3 months after initiation of BTA therapy, was used to dissect the prognostic implications of different metastatic spread patterns (i.e., metastatic compartments) by analyzing patients with BOM and BESM. While a previous study of patients with breast cancer and bone metastases showed that BESM patients had a numerical trend for persistently higher uNTX levels and an erratic uNTX variation during ZA treatment [20], in the present cohort bone markers did not differ according to metastatic compartment both at baseline and at 3 months. While the nature of the present cohort provides a more definitive assessment on how bone biomarkers differ at baseline and vary over time, the short-term assessment (3 months) restricts the longitudinal understanding of bone marker dynamics at longer time intervals. In addition, despite the fact that all bone metastases activate bone metabolism, bone-forming vs. bone-degrading components are differently impacted in patients with bone metastases from breast and prostate cancer [23,24], a fact that may also contribute to explain the observed difference.

Despite similar bone biomarker levels at baseline and comparable short-term variation, patients with BESM had higher SRE and SSE risk compared with patients with BOM, and this seems to be particularly relevant within the first 12 months after diagnosis. The added SRE risk in patients with BESM was also identified by Tanaka and colleagues in a cohort of 534 breast cancer women who developed bone metastases [19]. The present study confirms that result in a large cohort of mCRPC patients, and taken together these findings challenge the current trend towards a reduced BTA scheduling frequency from every 4 weeks to every 12 weeks (especially for ZA) across all mCRPC patients [16,25,26]. Specifically, this study supports the hypothesis that the metastatic compartment has impact in bone outcomes and may be taken into account when considering de-escalation strategies to better tailor such approaches. Therefore, patients with BESM are at higher SRE risk and should receive a more conservative treatment schedule (i.e., every 4 weeks), at least during the first year of treatment. It remains unknown whether humoral factors affecting bone resorption are produced by extraskeletal metastases and/or whether cancer cells can circulate from different metastatic sites (outside of bone to bone and vice versa) to restimulate microenvironment [10,20,21]. Despite similar metastatic bone disease burden and disease biology, this cohort shows an impact of BESM on SRE that is not captured by corrected uNTX and bALP levels. This may suggest that these biomarkers are not the best surrogates for such humoral factors. While the present study does not directly address these issues, it discloses new research avenues with potential therapeutic impact for optimizing bone outcomes in patients with mCRPC and raises relevant questions to understand cancer dynamics during advanced-stage of disease.

As anticipated, patients with BESM displayed worse survival outcomes. This is consistent with previous studies [21,27,28] and raises awareness of a patient population for whom novel approaches are urgently required.

Despite the high-quality data and having included a large cohort with long-term follow-up, the present study has intrinsic limitations. It was a retrospective analysis, therefore subject to residual confounding, notwithstanding methodological accuracy. While all models were controlled for disease biology (Gleason score) and burden (bone metastases number), full disease biology is not captured by these features, which may partially explain the study findings.

4. Materials and Methods

4.1. Design and Study Population

This was a retrospective analysis of the prospective, randomized, multicenter registration clinical trial of denosumab vs. ZA in patients with mCRPC and bone metastases (NCT00321620) [4]. All participating patients were selected. Figure 4 details patient enrollment in the several preplanned analyses. Bone metastases diagnosis and extraskelatal metastases screening were conducted as prespecified per NCT00321620 protocol.

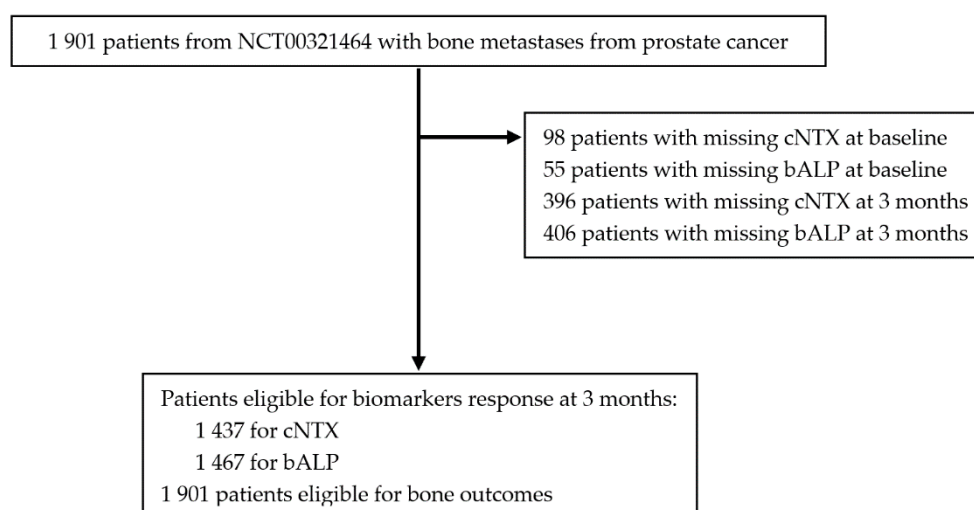


Figure 4. Consort study flowchart. bALP, bone alkaline phosphatase; BPI, Brief Pain Score; cNTX, corrected N-terminal telopeptide.

4.2. Study Aim and Outcomes

The main aim of this study was to investigate how metastatic compartment (BOM vs. BESM) impacts clinical outcomes and bone metabolism in patients with prostate cancer receiving BTAs. Specifically, the impact of metastatic compartment (BOM vs. BESM) on uNTX and bALP levels at baseline and normalization rates from baseline to 3 months was studied. We subsequently analyzed its impact on time to first on-study SRE/SSE and on OS. The 3-month-after-antiresorptive-treatment time point was selected to provide adequate therapy response time (no further time points were available). Outcomes were defined as per the study protocol [4].

4.3. Bone Marker Determination

In the NCT00321620 trial [4], urine specimens (from second morning void) and venous blood samples were collected to measure bone metabolism biochemical markers in all patients. Urinary bone marker to creatinine ratio was assessed for uNTX. Serum bone-specific alkaline phosphatase was also quantified. A central laboratory (Mayo Medical Laboratories, Rochester, MN, USA) performed urine and serum biochemical bone metabolism marker measurements for all patients. Normal uNTX cut-off was <64 nmol BCE/mmol creatinine and bALP cut-off was <22 ng/mL [13].

4.4. Statistical Analysis

Descriptive statistics of baseline clinical, pathological, and treatment characteristics were performed for the overall cohort and for BOM and BESM subgroups. Univariate comparisons were performed using a chi-square or *t*-test, as appropriate.

uNTX and bALP variation from baseline to 3 months according to metastatic compartment was tested using paired *t*-test. Time-to-event outcomes, survival, and cumulative incidence were plotted using the Kaplan–Meier method. Univariate and multivariate differences between survival rates according to metastatic compartment were tested using standard univariate and multivariate Cox proportional hazards model and the Andersen and Gill model for multiple failure time data. Multivariate analyses were corrected for age, ECOG-PS, Gleason score, total PSA at diagnosis, number of bone lesions, previous SREs, castration type, and previous surgery or radiotherapy. Given the strong association between visceral involvement and chemotherapy, no adjustment was performed for previous or current chemotherapy treatment.

All tests were two-sided with a 95% confidence interval (CI), and *p*-value < 0.05 was considered statistically significant. Statistical analyses were conducted using Stata 13.1 (<https://www.stata.com/>, StataCorp LP, College Station, TX, USA).

4.5. Ethical Statement

Approval from appropriate research Ethics Committees was obtained from each study center. All patients provided written informed consent before any study-specific procedure.

5. Conclusions

In this large mCRPC registration and high-quality study, despite similar bone marker levels at baseline and at 3 months, patients with bone metastases plus extraskelatal metastases had higher risk of SRE and SSE than patients with BOM. Given the higher risk for adverse outcomes, strategies of BTA schedule de-escalation should consider the impact of metastatic compartment, particularly during the first treatment year.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2072-6694/12/8/2034/s1>, Table S1. Bone biomarkers according to metastatic compartment.

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Conflicts of Interest: A. Mansinho performed consulting activities for Amgen and Novartis outside the scope of this study. A. Ferreira received a travel grant and performed consulting activities for Roche and Novartis outside the scope of this study. L. Costa performed consulting activities for Amgen and Novartis outside the scope of this study. The remaining authors declare no conflicts of interest.

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