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ARTICLE

Clinical Research

Bone targeted therapy and skeletal related events in the era of enzalutamide and abiraterone acetate for castration resistant prostate cancer with bone metastases

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Abstract

Background In an era of multiple life-prolonging therapies for metastatic castration resistant prostate cancer (mCRPC), the optimal timing of initiation and duration of antiresorptive bone targeted therapy (BTT) to prevent skeletal related events (SREs) is unknown.

Methods To assess practice patterns of BTT use and its associations with clinical outcomes in a high-volume center in the modern era of metastatic CRPC management, a retrospective cohort of patients treated for mCRPC with BM between 2007 and 2017 was identified from a single institutions clinical research database. Study endpoints included time from the diagnosis of CRPC to the onset of SRE or OS. Cox proportional hazards model assessed association of BTT use with time to first SRE and OS.

Results In total, 249 patients were identified; median follow-up was 7.7 (95%CI: 5.7–10.2) years. On multivariable analysis, patients with 4 or more BM at diagnosis of mCRPC who received BTT with abiraterone acetate or enzalutamide as first line therapy had a 42% reduced risk of developing an SRE (HR 0.58; 95%CI: 0.36–0.95) compared to those who never received BTT or received it in second line. No such effect was observed in patients with 1–3 BM. No OS difference was noted in patients who received BTT, whether with first line therapy or without. This study is limited by retrospective nature at a single institution.

Conclusions Our hospital registry data indicate a potential benefit in terms of SRE prevention for early use of antiresorptive BTT in combination with life prolonging CRPC therapies for patients with CRPC and at least 4 BM.

Introduction

Bone metastases (BM) are the most common site of distant disease in metastatic prostate cancer [1]. Among those with castration resistant disease (mCRPC), more than 90% of patients have BM. When associated with skeletal related events (SREs) such as pathologic fracture, spinal cord compression or need for surgery or radiation therapy to the bone, BM not only affect quality of life but have also been associated with a detriment in overall survival (OS) [2–4]. This in turn is associated with increased cost to health care system [5]. In CRPC, Zoledronic acid and denosumab are two antiresorptive bone targeted therapies (BTTs) proven to prevent SREs in men with BM. Twenty-four months of monthly zoledronic acid 4 mg intravenously decreased risk of SREs by 36%, and delayed time to first SRE by 167 days [6, 7]. The RANK ligand inhibitor denosumab when given 120 mg subcutaneously monthly delayed time to first SRE by 18% compared to zoledronic acid [8]. However, in hormone sensitive disease, monthly zoledronic acid did not delay time to first SRE in two randomized control trials though in exploratory analysis there was a benefit in patients with a pre-existing SRE [9, 10].

The pivotal antiresorptive BTT mCRPC studies were done prior to approval of abiraterone acetate (AA),

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enzalutamide (E), radium-223, and cabazitaxel [11–14]. Each of these agents are proven to improve OS and reduce risk of SREs. Therefore, the optimal time to layer on BTT with other mCRPC life prolonging therapies and duration of use are unknown. These questions are even more paramount with rising 5 year survival rates in mCRPC [15], and with the knowledge that long term denosumab and zoledronic acid use is rarely associated with osteonecrosis of the jaw (ONJ) and, in case of zoledronic acid, renal impairment [16]. We therefore performed a retrospective analysis of patients seen at a single academic center to define the practice patterns of SRE prevention, BTT use, and outcomes (time to first SRE and OS) in the era of multiple life-prolonging therapies for mCRPC.

Patients and methods

The study was performed in accordance with the Declaration of Helsinki; all patients were consented for their clinical data collection and the protocol was approved by DF/HCC IRB. All data were reviewed and extracted from a Dana-Farber Cancer Institute IRB-approved clinical database of 249 patients with CRPC and BM who started enzalutamide (E) or abiraterone acetate plus prednisone (AA) as first or later line of therapy for CRPC, (serum testosterone <50 ng/dL with either radiologic or biochemical progression) [17] at any time between 2007 and 2017. For those without a testosterone recorded, it was presumed that castration was achieved with gonadotropin release hormone analogs or antagonists and patients were confirmed to have had medical or surgical castration at time of CRPC.

Clinical data including age at prostate cancer diagnosis, race, time of metastatic disease presentation and diagnosis of CRPC, baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), and number of BM by radiology assessment on bone scan at diagnosis of CRPC were attained, in addition to pathologic data (Gleason score at time of diagnosis). The location of the BM was not annotated; prior radiated BM were counted when assessing number of BM. SRE was defined as pathologic fracture, radiation to bone, spinal cord compression, or bone surgery. Data on all systemic therapies utilized for CRPC, the timing and duration of BTT, as well as date of each SRE was collected from physician review of electronic medical records.

Statistical analysis

The analysis endpoints included time to SRE onset, defined as time from diagnosis of CRPC to first documented SRE, and OS defined as time from diagnosis of CRPC until time of death or last follow-up. BTT included use of zoledronic acid or denosumab at any dosing schedule given at least every 12 weeks. Because the analysis focused on the BTT use with first line CRPC therapy, (defined as starting within 3 months of starting first line therapy for CRPC up to 30 days before starting second line therapy) those that started BTT with subsequent lines of therapy for CRPC or <30 days from starting second line therapy for CRPC grouped in those who did not receive BTT with first line therapy.

Clinical and disease characteristics were summarized as median and range for continuous variables, and as number and percentage for categorical variables. The SRE characteristics were summarized, including the event rate per patient as well as the average number of SREs when a patient experienced such events. The SRE rate per 100 person-years was calculated to provide the estimates of incidence for such patient population during the respective follow-up time. The distributions of OS and time to SRE onset were summarized using the Kaplan Meier method according to BTT use status. The estimated medians with two-sided 95% confidence interval (CI) of time-to-event endpoints according to the BTT groups are provided.

To investigate the associations of BTT use with time to SRE as well as OS, Cox proportional hazard (CoxPH) models were conducted and the estimated hazard ratio (HR) and 95% CI were reported. To account for potential confounding factors, a multivariable analysis (MVA) adjusting for the patient and disease characteristics to include disease at diagnosis, prior SRE, and therapy received in first line setting for CRPC, were performed. Subgroup analysis looking at association of time to events with BTT based on disease volume (1–3 BM vs ≥4 BM based on CHAARTED analysis showing worse clinical outcomes with this cut-point, albeit in mHSPC) [18] was also performed when BTT by disease volume interaction was indicated. CoxPH model with a time varying BTT use variable (to account for a subset of patients received delayed BTT at 2nd CRPC) was performed as sensitivity analysis. All p values were two-sided with <0.05 considered to be statistically significant. R software version 3.3.1 (https://www.r-project.org/) was used for the statistical analyses.

Results

The analysis cohort included 249 men treated for CRPC from 2007 to 2017, with a median follow-up of 7.7 years (95% CI 5.7–10.2). The cohort was evenly divided between patients who received BTT with first CRPC treatment ($n =$ 124, 50%) and those who did not ($n = 125$). Of the latter patients, 85 never received BTT, while 40 received BTT with second or later lines of therapy for CRPC during the

follow-up time. Differences in clinical and demographic characteristics, as well as treatments received for CRPC are presented in Table 1. Median age was 67, and most patients had ECOG PS <1. Number of bones metastases (1–3 vs ≥4) was evenly distributed, and treatment received was comparable between these two groups. AA and E together accounted for 76% of all first line therapies for CRPC, although AA was given more frequently (59% vs. 17%). Zoledronic acid or denosumab was given monthly in 53 and 64% of the time; some patients received both, though never concurrently (Table 2).

SRE characteristics are summarized in Table 3. Overall, 152 (61%) patients experienced at least one SRE, with the average of 1.8 (range = 1.6) per patient. The incidence of overall SRE per 100 patient-years for the cohort was 30%; the most common SRE was palliative RT, with an incidence rate of 24% per 100 patient-years. There was no indication that BTT use reduced risk of SRE onset with first line therapy for CRPC (HR = 0.8, 95%CI: 0.56–1.14). However, subgroup analysis by number of BM (BTT by disease volume interaction, $p = <0.02$) revealed that BTT delayed onset of SREs only in patients receiving first line CRPC therapy with 4 or more BM: HR for SREs in the 4 or more BM cohort was 0.58 (95% CI 0.36–0.96, p = 0.03), compared to 1.24 (0.75–2.02, p = 0.4) for those with 1–3 BM (Fig. 1). Other clinical factors independently associated with time to SRE on MVA were first presentation with *de novo* metastatic hormone sensitive prostate cancer and prior SRE (Table 4). In a sensitivity analysis using a CoxPH model with time varying covariates to incorporate timing of BTT (124 initiated with first line treatment while 40 initiated second line, among them 23 had SRE onset after BTT start with second CRPC treatment and thus counted as receiving BTT at 2nd line therapy for CRPC) the model estimates were consistent (MVA HR = 0.84 (95%CI: 0.59–1.2), data not shown), indicating that counting only BTT use with first line CRPC therapy is reasonable for estimating this effect (Table 4). However, there was no strong evidence of improvement in OS when BTT was used in first line CRPC versus later or never (MVA HR = 0.8; 95%CI:0.58–1.12) (Fig. 1).

Table 1 Patient demographics and treatment history.

Factor	Total $N = 229$	Delayed or No BTT $N = 125$	BTT with 1st line CRPC tx $N = 124$
Median follow-up (95%CI), years	7.7 (5.7–10.2)	6.6 (5.3–10.8)	9.3 (5.7 to NA)
White *N* (%)	229(92)	119(95)	110(89)
Disease at diagnosis, *N* (%)			
Localized	158(63)	92(74)	66(53)
Metastatic	91(37)	33(26)	58(47)
Dx Gleason Score, *N* (%)			
4--6	12[5]	8(7)	4(4)
7	59(26)	36(31)	23(21)
8--10	157(69)	72(62)	85(76)
Unknown/Missing	21	9	12
Age at CRPC (Years)			
Median (IQR)	67 (61,72)	68 (61,72)	66 (60,73)
Range	[45,88]	[45,88]	[45,87]
ECOG PS at CRPC, *N* (%)			
0	224(90)	113(90)	111(90)
1 + 2	25(10)	12(10)	13(10)
PSA at CRPC (ng/ml)			
Median (IQR)	2.0 (1.2,5.7)	2.0 (1.2,6.1)	1.8 (1.3,5.1)
Disease volume at CRPC, No.(%)			
1–3 bone metastases	140(56)	88(70)	52(42)
>=4 bone metastases	109(44)	37(30)	72(58)
SREs prior to CRPC, *N* (%)			
Palliative radiation	15(6)	3(2)	12(10)
Spinal cord compression	4(2)	1(1)	3(2)
Surgery to bone	3(1)	2(2)	1(1)
1st Line Therapy for CRPC, *N* (%)			
Abiraterone	146(59)	79(63)	67(54)
Docetaxel	60(24)	17(14)	43(35)
Enzalutamide	42(17)	29(23)	13(10)
Radium 223	1(0)	0(0)	1(1)
2nd Line therapy for CRPC, *N* (%)			
None	20(8)	13(10)	7(6)
Abiraterone	66(27)	28(22)	38(31)
Cabazitaxel	16(6)	8(6)	8(6)
Docetaxel	67(27)	37(30)	30(24)
Enzalutamide	65(26)	32(26)	33(27)
Radium 223	15(6)	7(6)	8(6)

BTT bone targeted therapy, *CRPC* castrate resistant prostate cancer, *IQT* interquartile range, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *PSA* prostate specific antigen, *SRE* skeletal related events.

Discussion

To our knowledge, this is the largest dataset exploring the relationship between use of antiresorptive BTT with first line therapy for CRPC in the modern era of therapies. BTT is an integral part of the management of mCRPC, with both zoledronic acid and denosumab approved in this setting based on phase 3 data [6–8]. AA and E both reduce rates of symptomatic SREs in those patients who receive these agents after docetaxel, though the rates of SRE remain over 20% [19, 20]. However, less than 50% of patients received BTT in these studies, and the effect of skeletal disease burden on rates of future SREs has not been well defined by prospective randomized trials. Post hoc analysis of patients

Table 2 Summary of bone targeted therapy utilized.

	Frequency	N (%)
Zoledronic acid ($N = 121$)	q4–6wks	64(53)
	q8–12wks	39(32)
	>12wks or none	18(15)
Denousmab ($N = 80$)	q4–6wks	51(64)
	q8–12wks	21(26)
	>12wks or none	8(10)

Wks weeks.

treated with AA or placebo for CRPC in the pre-docetaxel setting showed that concomitant BTT use significantly improved OS, and increased both time to deterioration in PS and time to opiate use for cancer-related pain [21].

The importance of BTT in first line CRPC therapy is supported by our data, but also generates the hypothesis of a nuanced risk-based approach. First, our data support that prior SRE impacted the decision to start BTT; 13% of men treated with BTT had had prior SRE while only 5% who were not treated with BTT had prior SRE. Given the poor outcomes in patients with a prior SRE, treatment with BTT in addition to anticancer therapy should be used whenever possible regardless of number of bone metastases. While there is a clear need for SRE prevention for patients with mCRPC with 4 or more BM, it is possible that BTT can be safely delayed to the second line mCRPC setting in those with low volume BM at CRPC diagnosis who have a longer OS. This may allow the optimal timing and duration of BTT, limiting the dosing to the two years where the risk: benefit is best characterized as adverse events such as ONJ accumulate with longer duration of BTT dosing. Specifically, in this latter group of patients, the efficacy of anticancer therapy declines with later lines of therapy and risks of SREs increases, so they may benefit from layering on BTT only once progression (PSA or radiographic) is observed on first line therapy.

Following therapy with docetaxel, median OS and time to PSA progression with enzalutamide and AA were 18.4 and 8.3 months [22], versus 14.8 and 5.6 months, respectively [23]. However, when used prior to docetaxel, the OS and time to PSA progression for enzalutamide or AA were 35.3 and 20 months [12, 24], versus 34.7 and 16.5 months, respectively [11, 25]. While data are not available for timing of SREs with AA in both settings, treatment with enzalutamide delayed time to first SRE by 16.7 months and 31 months in the post and pre-docetaxel setting, respectively [22, 24]. Moreover, it is hypothesized that patients who progress to mCRPC after being on AA, enzalutamide, or apalutamide for metastatic hormone sensitive disease or M0 CRPC have outcomes like those for second line therapy in the mCRPC setting, and would benefit from layering BTT at this stage regardless of the number of BM. Although patients with 1–3 bone metastases did not have reduced rates of SRE with BTT, there was a trend toward an OS benefit with BTT use, though CIs are wide (HR 0.91, 95% CI 0.61–1.36). This may underscore the overall importance of BTT in the management of CRPC, as although 50% did not start BTT at time first mCRPC, it was 34% of patients who never started BTT as some practitioners delayed BTT if BM was low until second line when cancer control is less and bone protection need is greater. At the same time, it is possible there is a variable associated with early initiation of BTT that we did not account for (such as patients with poor renal function have no or delayed BTT use and it is the poor renal function which could be associated with shorter OS) or soft tissue only disease.

There was no improvement in SRE when monthly zoledronic acid was added to testosterone suppression in mHSPC, and when denosumab monotherapy was added to patients with M0 CRPC (i.e., rising PSA without BM on conventional imaging with suppressed testosterone), the appearance of BM was only delayed in men with rapid PSA doubling time [9, 26]. The degree of benefit from use of BTT in first line mCRPC is highest in those with a higher burden of BM, which we defined *a* priori as 4 or more; this cut-point was chosen based on evidence that it was a poor prognostic marker seen in front line metastatic hormone sensitive disease [18]. Early initiation of BTT was also beneficial in those with any history of SRE, independent of number of BM. Those with fewer than 4 BM are likely to have a longer duration of cancer control with first line CRPC therapy and appear to have no clear benefit from layering on BTT with first line therapy. While generally considered to have a low rate of adverse events, monthly dosing for BTT is not without toxicities including hypocalcemia, hypophosphatemia, infusion reactions (with zoledronic acid), and ONJ. Rates of ONJ approaching 2% at a median of only 11 months of use though incidence of ONJ can be decreased over 50% with preventative measures [27, 28].

It should also be made clear, our data do not address the use and need for osteoporosis management in mHSPC, M0CRPC and mCRPC where zoledronic acid is dosed at 5 mg every 12 months (as opposed to 4 mg monthly) and denosumab is dosed at 60 mg every 6 months (as opposed to 120 mg monthly) [29]. Data on osteoporosis was not collected in our analysis and it is critical that all patients should be evaluated for osteoporosis dosing and appropriate management implemented as indicated.

In our dataset, only one patient received the alpha-emitter radium-223 as first line therapy for CRPC. There is increasing data that when added to radium-223, concomitant BTT is associated with a lower risk for developing an SRE [30]. The importance of BTT had been further

Table 3 Skeletal related events (SRE) characteristics overall and according to BTT status.

N	Total *N* = 249	No or delayed BTT *N* = 125	BTT with 1stCRPC Rx *N* = 124
Patient with SRE (%)	152(61)	71(57)	81(65)
Mean (Range) SRE per patient > =1 SRE	1.8[1,6]	1.8[1,6]	1.8[1,6]
Total SREs, N	279	130	149
Type of SRE, N (% of total SREs) Palliative RT	223(80)	104(80)	119(80)
Pathological fracture	14(5)	8(6)	6(4)
Spinal cord compression	28(10)	7(5)	21(14)
Surgery to bone	14(5)	11(8)	3(2)
Total person years	940	464	476
Overall SRE per 100 patient years	29.7	28	31.3
SRE per 100 patient years by type Palliative RT	23.7	22.4	25
Pathological fracture	1.5	1.7	1.3
Spinal cord compression	3	1.5	4.4
Surgery to bone	1.5	2.4	0.6

BTT bone targeted therapy, *CRPC* castration resistant prostate cancer, *SRE* skeletal related event.

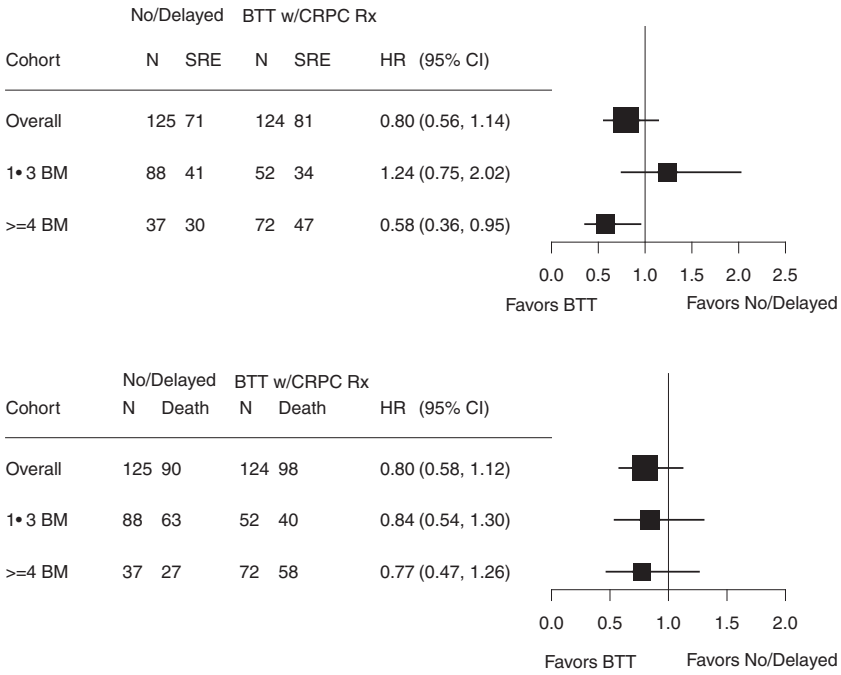

Fig. 1 Multivariable forrest plots for SRE and OS by disease volume. ***Adjusted for disease status at diagnosis, prior SREs, first targeted therapy. BM bone metastases, CRPC castration resistant prostate cancer, BTT bone targeted therapy.

reinforced by the completed ERA 223 trial and ongoing PEACE III trials looking at addition of abiraterone acetate and enzalutamide respectively to radium. In ERA 223, patients were randomized AA with or without concomitant radium 223; not only did this combination not improve symptomatic skeletal event free survival compared to AA alone, it was also associated with an increased risk of bone fractures, including osteoporosis related fractures [4]. Given this finding, the ongoing PEACE III trial looking at radium-223 plus enzalutamide versus enzalutamide alone was amended to mandate addition of BTT. In analysis of patients prior to the amendment when only 42.6% of patients were on BTT, increased risk of fractures (33%) was noted with the addition of radium-223 to enzalutamide versus 13% with enzalutamide alone, which is comparable to what has been reported previously; [31] this increased risk with radium-223 plus enzalutamide was nearly eliminated when the trial was modified [32]. Moreover, the observation that 42% of patients were not getting BTT highlights lack of universal use of BTT when used with first-line enzalutamide similar to what was seen in our analysis. These studies highlight that BTT is a critical aspect in management of CRPC; our data do not refute this.

Table 4 Univariable and multivariable analysis on factors related to skeletal related events.

Overall ($n = 249$)	Factors	SRE HR (95% CI)	OS HR (95% CI)
UVA	BTT Use (At diagnosis CRPC vs not)	0.96(0.69–1.35)	0.87(0.64–1.18)
MVA			
	BTT (At diagnosis CRPC vs not)	0.8(0.56–1.14)	0.8(0.58–1.12)
	Disease at diagnosis (Localized vs metastatic)	1.82(1.25–2.65)	1.58(1.13–2.2)
	Prior SRE (yes vs no)	1.73(1.04–2.87)	1.16(0.7–1.92)
	First CRPC therapy (Abiraterone/ Enzalutamide vs other)	0.74(0.51–1.07)	0.97(0.69–1.36)
1–3 bone metastases ($n = 140$),			
UVA	BTT Use (At diagnosis CRPC vs not)	1.33 (0.85–2.1)	0.91(0.61–1.36)
MVA			
	BTT (At diagnosis CRPC vs not)	1.24 (0.75–2.02)	0.84(0.54–1.3)
	Disease at diagnosis (Localized vs metastatic)	2.62 (1.5–4.58)	1.87(1.14–3.07)
	Prior SRE (yes vs no)	0.72 (0.2–2.58)	0.83(0.28–2.53)
	First CRPC therapy (Abiraterone/ Enzalutamide vs other)	0.9 (0.51–1.61)	0.84(0.52–1.36)
4 or more bone metastases ($n = 109$),			
UVA	BTT Use (At diagnosis CRPC vs not)	0.69 (0.43–1.09)	0.81(0.51–1.29)
MVA			
	BTT (At diagnosis CRPC vs not)	0.58 (0.36–0.95)	0.77(0.47–1.26)
	Disease at diagnosis (Localized vs metastatic)	1.54 (0.96–2.47)	1.42(0.91–2.23)
	Prior SRE (yes vs no)	2.03 (1.15–3.6)	1.19(0.67–2.12)
	First CRPC therapy (Abiraterone/ Enzalutamide vs other)	0.57 (0.34–0.94)	1.1(0.67–1.81)

Stratified by disease volume in overall cohort analysis.

Cox proportional hazard model adjust for the risk factors of Disease status, prior SRE and first targeted therapy, stratified by disease volume only for the overall cohort.

SRE skeletal related event, *OS* overall survival, *CRPC* castration resistant prostate cancer, *UVA* univariable analysis, *MVA* multivariable analysis.

Our data have several limitations. It is a retrospective analysis from a single institution and it is unclear if the patterns of use can be extrapolated to the other centers. Furthermore, Given the small number of patients who initiated BTT with subsequent lines of therapy for CRPC, a dedicated analysis comparing early BTT with later initiation could not be performed; however, CoxPH model estimates were consistent, indicating that counting only BTT use at first line is reasonable for estimating the effect. Furthermore, our data do not address dosing strategies for BTT other than monthly, even though over 40% of the patients were dosed with intervals longer than 6 weeks. For zoledronic acid, there is some evidence in solid tumors (including prostate cancer) that every 3 month dosing was equivalent to every 4 week dosing [33]. However, this was shown in a very heterogenous group of patients, including those with metastatic hormone sensitive disease where monthly zoledronic acid was shown not to be beneficial. Smaller studies showed similar results with de-escalation of denosumab [34]. Finally, our analysis was limited to SREs not SSEs, which may be a late event occurring after multiple lines of therapy and to truly judge the benefit of BTT, all patients should be followed until death. To that extent, the median follow-up was 7.7 years and there are only 20% survivors is very long for a CRPC cohort and captures the most informative data.

In conclusion, our data indicate that even in the era of life-prolonging therapies for mCRPC, men with 4 or more BM clearly benefit from initiation of BTT with first line CRPC therapy to reduce their risk for SREs. On the other hand, further work is required to define optimal timing for commencing BTT in patients with 1–3 BM, especially in those responding to the anticancer therapy regardless of line of therapy.

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Compliance with ethical standards

Conflict of interest BM: discloses payment for consulting with Bayer, Astellas, Astra Zeneca, Seattle Genetics, Exelixis, Nektar, Pfizer, Janssen, Genentech, and EMD Serono. He received research support to Dana Farber Cancer Institute (DFCI) from Bristol Myers Squibb, Calithera, Exelixis, Seattle Genetics. C.S.: discloses a consulting or advisory at Sanofi, Janssen, Astellas Pharma, Bayer, Genentech, AstraZeneca, Pfizer, Lilly Celgene Research Funding: Janssen Biotech (Inst), Astellas Pharma (Inst), Sanofi (Inst), Bayer (Inst), Sotio (Inst), Dendreon (Inst). He has patents, Royalties, Other Intellectual Property for Pathenolide (Indiana University): dimethylaminoparthenolide (Leuchemix); Exelixis: Abiraterone plus cabozantinib combination. He owns stock in Leuchemix; LZ, KG, EF, GS, and CE report no conflict of interest.

Ethics approval The study was performed in accordance with the Declaration of Helsinki; all patients were consented for their clinical data collection and the protocol was approved by DF/HCC IRB.

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