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Radium-223 (Xofigo) with concurrent abiraterone or enzalutamide: predictive biomarkers of improved overall survival in a clinically advanced cohort

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ABSTRACT

Purpose: Radium-223 (Xofigo) is the first therapy with bone tropism for metastatic castrate-resistant prostate cancer (mCRPC) that has been shown to improve overall survival (OS). Although radium-223 has a positive effect on OS in men with mCRPC, there has been a paucity of reports from community practitioners, especially with regard to concurrent abiraterone and enzalutamide therapy. Significant differences in patient characteristics encountered may exist.

Patients and methods: We conducted a retrospective study of men with mCRPC who received at least 1 cycle of radium-223 (n = 35). Baseline pain and ECOG PS as well as concurrent usage of abiraterone or enzalutamide were recorded. Side effect profiles for each patient throughout treatment were noted.

Results: Baseline cohort characteristics include a median age of 75 years. 37% had an ECOG PS $\geq$ 2 and 23% reported severe pain at baseline. 31% received concomitant enzalutamide 31% concomitant abiraterone. Patients treated concurrently with either abiraterone or enzalutamide did not display additional toxicity. Median cohort OS was 10 months. Patients with no or mild pain had longer median OS than those with moderate or severe pain, 14 versus 7 months

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($P = 0.028$). Patients with ECOG PS < 2 had longer median OS than those with ECOG PS ≥ 2, 13 versus 10 months ($P = 0.0233$).

Conclusion: This study highlights key differences in patient characteristics encountered by community practitioners. In this population, which presented with clinically advanced disease, there was an improved survival benefit for those treated earlier in their disease. Radium-223 was well tolerated and concurrent treatment with abiraterone or enzalutamide did not add additional toxicity. These 2 points seem to advocate for aggressive and early treatment of patients with radium-223 in the community.

Introduction

Prostate cancer remains the second leading cause of cancer death in men with 26,120 deaths annually, accounting for approximately 8% of all male cancer related deaths.[1] With modern therapies and improved early detection, the 5-year relative survival rate for localized disease has approached 100%, but declines to only 28% for patients diagnosed at distant stages.[2] Despite promising new therapeutic regimens,[3-6] most patients eventually progress to an androgen-insensitive state.[4,7] Patients with metastatic castrate-resistant prostate cancer (mCRPC) commonly have radiographic evidence of osteoblastic[8] bone metastases.[9-11]

Radium-223 is the first calcium mimetic alpha particle emitting radioisotope approved for mCRPC shown to improve overall survival (OS).[11] The ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) trial demonstrated a 3.6-month improvement in OS for radium-223 versus placebo.[11] Beta particle emitting therapies Strontium-89 and Samarium-153 Lexidronam selectively target areas of bone metastasis and reduce pain, but have failed to show a similar survival benefit.[12]

Subsequent trials have reported a median OS of 16 months for patients treated with at least 1 cycle of radium-223,[13] slightly greater than ALSYMPCA 14.9 months.[11] Later trials expanded treatment criteria to include asymptomatic bone metastasis and concomitant treatment with novel endocrine agents abiraterone and enzalutamide–2 therapies not yet available in ALSYMPCA.[11,13] Patients treated concurrently with both novel and standard endocrine agents had improved median OS.[13]

Biomarkers associated with radium-223 have been note. Transient reductions in serum prostatic-specific antigen (PSA) have been associated with radium-223 administration.[11] Comparatively the reduction in total serum alkaline phosphatase is greater than the reduction in serum PSA.[11] Retrospective reviews report increased median post-treatment PSA, but decreased median post-treatment alkaline phosphatase.[14] Postadministration decline in alkaline phosphatase is more common than that of PSA.[15]

Posthoc analysis has identified baseline predictive markers of improved survival, including lower pain scores, better performance status, normal alkaline phosphatase concentrations, and hemoglobin greater than 10 g/dL.[13] Alkaline phosphatase[16,17] and pain from bone metastasis[10] have been shown to predict OS independent of PSA levels in men with mCRPC.

Although radium-223 improves OS in men with mCRPC, there has been paucity of reports by community practitioners. Here we report a community experience with a radium-223 cohort outside of the context of clinical trials. We compare reported baseline characteristics with survival benefits to our own population and note the safety profile of radium-223 with concurrent abiraterone and enzalutamide usage.

Table 1
Baseline demographics.

Characteristic	Radium-223 (N = 35)
Age: median (range)	75 (47-90)
<65	4 (11%)
≥65	31 (89%)
Race-No (%)	
Caucasian	27 (77%)
Native American	2 (6%)
Hispanic	6 (17%)
ECOG PS-No (%)	
0	2 (6%)
1	20 (57%)
2	10 (29%)
3	3 (9%)
GS at diagnosis of prostate cancer-No (%)	
5-7	13 (37%)
≥8	17 (49%)
missing	5 (14%)
Pain at baseline- No (%)	
No pain	5 (14%)
Mild	12 (34%)
Moderate	10 (29%)
Severe	8 (23%)
PSA at baseline, ng/mL-Median (95%CI)	71 (43-119)
ALP at baseline, U/L-Median (95%CI)	163 (116-259)
Novel ADT therapy*–no (%)	
Enzalutamide	27 (77%)
Abiraterone	24 (69%)
Both	18 (51%)
None	2 (6%)
Reason for discontinuation–no (%)	
Clinical progression	13 (37%)
Side effects (diarrhea)	1 (3%)
Treatment delay†	1 (3%)

Abbreviations: ADT, Androgen deprivation therapy; ALP, alkaline phosphatase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GS, gleason score; PSA, prostatic-specific antigen.

* Concomitant or prior therapy.

† Patient encountered long delay in treatment due to socioeconomic issues.

Methods

Patient and study design

The study cohort was composed of mCRPC patients who received at least 1 cycle of radium-223, identified via ICD coding. Clinical data were retrospectively collected into a secure database. Previous or concurrent therapy was divided by date of first radium-223 dose. Number of bone metastasis or concurrent oncologic therapies were not limiting to cohort selection. Radium-223 was given intravenously at 4-week intervals, maximum of 6 cycles, with blood draws approximately 1-week before administration. Radium-223 dosage was 50 KBq/kg (1.35 μCi/kg).

Statistical analysis

Statistical analysis was performed on all patients who received at least 1 cycle of radium-223. Descriptive statistics were used to characterize patients. Analyses of OS utilizing Kaplan-Meier survival estimates with Log-rank test comparison was conducted for sub-

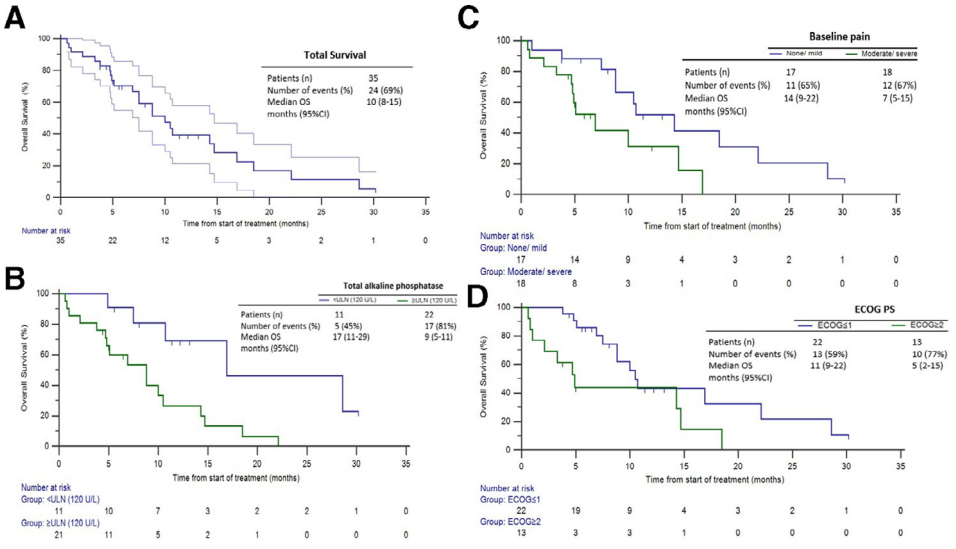

Fig. 1. Overall survival by (A) total cohort with 95% CI. (B) Baseline total alkaline phosphatase concentration, $P = 0.0070$. ULN, upper limit of normal. Data missing for 2 patients. (C) Baseline pain score, $P = 0.0281$. (D) ECOG PS, $P = 0.0223$. ECOG PS, eastern cooperative oncology group performance status. Censored patients as hash marks.

group analysis, with hazard ratio generation. All statistical analysis performed using MedCalc software.

Results

A total of 35 patients treated with at least 1 cycle or radium-223 were reviewed. Median cohort age was 75 years. 63% of patients had an ECOG PS < 2 while 37% had an ECOG PS ≥ 2. 14% of patients reported no pain a baseline, 23% reported severe pain. 94% patients received either prior or concomitant enzalutamide or abiraterone. Thirty-one percent of patients received concomitant enzalutamide and 31% received concomitant abiraterone (Table 1).

A median of 5 radium-223 injections were administered. Fifty-seven percent of patients received all 6 planned injections. Thirty-seven percent of patients discontinued therapy due to clinical progression and 1 patient discontinued therapy due to diarrhea. Hematologic and non-hematologic adverse drug events were recorded during the treatment period. The most common toxicities were fatigue (71%), anemia (49%), and nausea (23%). There were no toxicities reported greater than grade III in the cohort (Table 2).

Median cohort OS was 10 months. Twenty-four (69%) deaths were reported and 11 (31%) patients were censored (Fig 1A).

In baseline subgroup analysis, patients with alkaline phosphatase levels less than the upper limit of normal (120 U/L) had longer median OS than those with alkaline phosphatase levels equal to or greater than the upper limit of normal, 17 versus 9 months, hazard ratio (HR) 0.28 (95% confidence interval [CI] 0.12-0.62), $P = 0.007$ (Fig 1B). Patients with no or mild pain had longer median OS than those with moderate or severe pain, 14 versus 7 months, HR 0.40 (95% CI 0.17-0.95) $P = 0.028$ (Fig 1C) and patients with ECOG PS < 2 had a longer median OS than those with an ECOG PS ≥ 2, 13 versus 10 months, HR 0.43 (95% CI 0.17-1.11), $P = 0.0233$ (Fig 1D).

Patients with a baseline PSA less than cohort median of 71 ng/mL had longer median OS than those with PSA levels equal to or greater than median, 10.5 versus 10 months, HR 0.75

Table 2
Treatment-emergent adverse events, as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events. Concurrent ENZ or ABI denotes either agent with Radium-223.

	All patients (n = 35)				Concurrent ENZ or ABI (n = 19)				Radium-223 alone (n = 16)			
Adverse Event Grade	All	I	II	III	All	I	II	III	All	I	II	III
Hematologic												
Anemia	18 (51%)	14 (40%)	4 (11%)	0	7 (37%)	6 (32%)	1 (5%)	0	11 (69%)	8 (50%)	3 (19%)	0
Thrombocytopenia	6 (17%)	6 (17%)	0	0	4 (21%)	4 (21%)	0	0	2 (13%)	2 (13%)	0	0
Neutropenia	3 (9%)	2 (6%)	1 (3%)	0	2 (11%)	1 (5%)	1 (5%)	0	1 (6%)	1 (6%)	0	0
Leucopenia	2 (6%)	1 (3%)	1 (3%)	0	1 (5%)	1 (5%)	0	0	1 (6%)	0	1 (6%)	0
Nonhematologic												
Nausea	8 (23%)	8 (23%)	0	0	3 (16%)	3 (16%)	0	0	5 (31%)	5 (31%)	0	0
Vomiting	3 (9%)	3 (9%)	0	0	1 (5%)	1 (5%)	0	0	2 (13%)	2 (13%)	0	0
Diarrhea	3 (9%)	1 (3%)	0	2 (6%)	1 (5%)	0	0	1 (5%)	2 (13%)	1 (6%)	0	1 (6%)
Constipation	1 (3%)	1 (3%)	0	0	0	0	0	0	1 (6%)	1 (6%)	0	0
Fatigue	25 (71%)	18 (51%)	4 (11%)	3 (9%)	11 (58%)	9 (47%)	0	2 (11%)	14 (88%)	9 (56%)	4 (25%)	1 (6%)
Peripheral Edema	6 (17%)	4 (11%)	2 (6%)	0	3 (16%)	2 (11%)	1 (5%)	0	3 (19%)	2 (13%)	1 (6%)	0

Abbreviations: ABI, abiraterone; ENZ, enzalutamide.

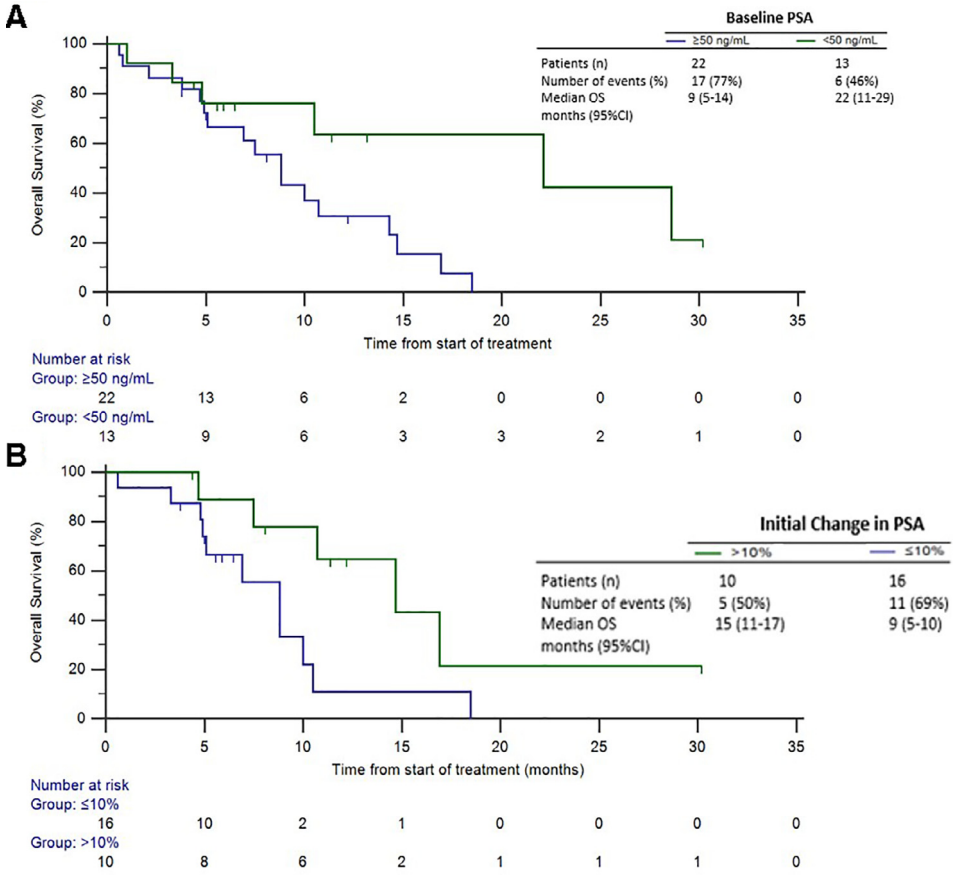

Fig. 2. Overall survival by PSA characteristics. (A) Baseline PSA, $P = 0.02247$. (B) Reduction in PSA after first radium-223 administration, $P = 0.0394$. Data missing for 9 patients.

(95% CI 0.33-1.68), $P = 0.23$. Patients with baseline PSA less than 50 ng/mL had longer median OS than those with PSA greater than or equal to 50 ng/mL, 22 versus 9 months, $P = 0.0247$ (Fig 2A). After the first radium-223 administration, patients with a greater than 10% reduction in serum PSA had a longer median OS than those with a change less than or equal to 10%, 15 versus 9 months, $P = 0.0394$ (Fig 2B). Select patient subgroup hazard ratios are displayed (Fig 3).

Discussion

Proposed differences accounting for improved survival in subsequent studies compared to the original ALSYMPCA trial include the inclusion of patients with asymptomatic bone metastasis, as well as the inclusion of concurrent abiraterone and enzalutamide treatment regimens.[11,13] While our cohort included patients with asymptomatic bone metastasis and most received either prior or concomitant enzalutamide or abiraterone, median OS was comparatively shorter.

Key differences in community population characteristics may account for survival differences. Compared to previously reported trials[11,13] our cohort was both older and more ethnically diverse, with close to 1 quarter of patients self-identifying as non-Caucasian. At baseline our

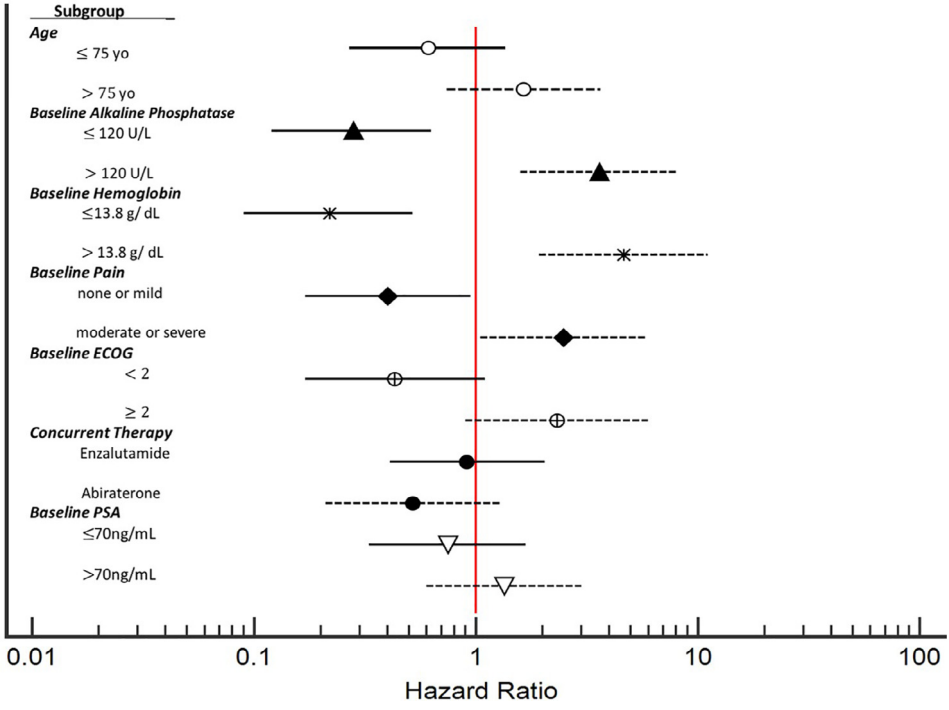

Fig. 3. Selected cohort subgroup analysis. Median cohort = 75 years. alkaline phosphatase upper limit of normal = 120 U/L. Laboratory reference, hemoglobin lower limit of normal = 13.8 g/dL. Median cohort PSA = 71 ng/mL.

cohort presented with poorer performance statuses, having 3 times the proportion of patients with a baseline ECOG PS ≥ 2 comparatively[11,13] and baseline pain reported as severe was almost 5 times more common.[13] These results highlight the discrepancies between clinical trial and community encountered patient characteristics.

Completion of all 6 radum-223 cycles was similar to previous cohorts,[11,13] therefore would not likely contribute to survival differences among studies. Studies of similar size have reported lower completion rates.[15]

Cohort median OS was longer in patients with better ECOG PS and lower reported pain scores at baseline, findings previously mirrored.[13] In men with mCRPC, pain from bone metastasis has been shown to predict OS independent of PSA levels[10]. Consequently in our cohort, the greater proportion of patients with poorer ECOG PS and higher pain scores, may explain a lower median OS. It is important to note that the ALSYMPA trial reported pain utilizing a World Health Organization score, which incorporates opioid usage.[11]

Normal baseline alkaline phosphatase concentration is associated with improved survival.[10,16,17] Both normal alkaline phosphatase concentrations and lower baseline PSA values were identified as predictive biomarkers of cohort survival. These findings may suggest a benefit to those treated presumably earlier in their disease. Although the reduction in PSA post radium-223 administration has been reported to be not well sustained,[11] the degree of PSA reduction post 1 cycle of radium-223 was predictive of survival in our cohort, potentially suggestive of biomolecular responsive to therapy.

Radium-223 was well tolerated, with no reported toxicities greater than grade III (Table 2). Rates of common adverse drug effects were similar to other published reports[11,13,18,19] and concurrent usage of abiraterone or enzalutamide with radium-223 did not add significant additional toxicities. With the exception of mild increases in grade I neutropenia and thrombocytopenia

adverse events were actually less common with concurrent usage. These findings may argue that the usage of abiraterone or enzalutamide with radium-223 may be blunting cancer progression. With less cancer burden or with blunted progression, there may be less adverse reactions. It should be noted however that there was a low number of absolute side effects reported across all cohort patients, mostly grade I or II.

Conclusions

This study highlights key differences in patient characteristics encountered by community practitioners. In our population, there was an improved survival benefit for those patients treated presumably earlier in their disease: lower alkaline phosphatase values, better performance statuses, and lower pain scores. Radium-223 was well tolerated in this cohort and concurrent treatment with abiraterone or enzalutamide did not add additional toxicity. These 2 points seem to advocate for aggressive and early treatment of mCRPC patients with radium-223 in the community. Study limitations include the low total number patients reviewed. It is noted that increased reports from community practitioners are needed.

References

1. Siegel R, Miller K, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66:7–30.
2. Miller KD, Siegel R, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *Cancer J Clin*. 2016;66:271–289.
3. Prostate Cancer Trialists Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. *Lancet*. 2000;355:1491–1498.
4. Horwich A, Parker C, de Reijke T, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 vi106–14.
5. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med*. 2015;373:737–746.
6. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomized controlled trial. *Lancet*. 2016;387:1163–1177.
7. Eisenberger MA, Simon R, O'Dwyer PJ, et al. A reevaluation of nonhormonal cytotoxic chemotherapy in the treatment of prostatic carcinoma. *J Clin Oncol*. 1985;3:827–841.
8. Roodman GD. Mechanisms of bone metastasis. *N Engl J Med*. 2004;350:1655–1664.
9. Dawson NA, McLeod DG. The assessment of treatment outcomes in metastatic prostate cancer: Changing endpoints. *Eur J Cancer*. 1997;33:560–565.
10. Halabi S, Vogelzang NJ, Kornblith AB, et al. Pain predicts overall survival in men with metastatic castration-refractory prostate cancer. *J Clin Oncol*. 2008;26:2544–2549.
11. Parker C, Nilsson S, Heinrich D, et al. for the ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369:213–223.
12. Roque IFM, Martinez-Zapata MJ, Scott-Brown M, et al. Radioisotopes for metastatic bone pain. *Cochrane Database Syst Rev*. 2011;7 CD003347.
13. Saad F, Carles J, Gillessen S, et al. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial. *Lancet Oncol*. 2016;17:1306–1316.
14. Hague C, Logue J. Clinical experience with radium-223 in the treatment of patients with advanced castrate-resistant prostate cancer and symptomatic bone metastases. *Ther Adv Urol*. 2016;8:175–180.
15. Jadvar H, Challa S, Quinn DI, et al. One-year postapproval clinical experience with Radium-223 dichloride in patients with metastatic castrate-resistant prostate cancer. *Cancer Biother Radiopharm*. 2015;30:195–199.
16. Sonpavde G, Pond GR, Berry WR, et al. Serum alkaline phosphatase changes predict survival independent of PSA changes in men with castration-resistant prostate cancer and bone metastasis receiving chemo- therapy. *Urol Oncol*. 2012;30:607–613.
17. Armstrong AJ, Febbo PG. Using surrogate biomarkers to predict clinical benefit in men with castration-resistant prostate cancer: an update and review oftheliterature. *Oncologist*. 2009;14:816–827 48.
18. Parker C, Finkelstein SE, Michalski JM, et al. Efficacy and safety of radium-223 dichloride in symptomatic castration-resistant prostate cancer patients with or without baseline opioid use from the phase 3 alsympca trial. *Euro Urol*. 2016;70:875–883.
19. Vogelzang N, Coleman RE, Michalski JM, et al. Hematologic safety of radium-223 dichloride: baseline prognostic factors associated with myelosuppression in the ALSYMPCA Trial. *Clin Genitourin Cancer*. 2016;15:42–52.