

ORIGINAL ARTICLE

Radium-223 in Asian patients with castration-resistant prostate cancer with symptomatic bone metastases: A single-arm phase 3 study

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Abstract

Aim: Radium-223, a targeted alpha therapy, is approved widely for the treatment of patients with metastatic castrate-resistant prostate cancer, based on a pivotal phase 3 study in predominantly white patients. We investigated the efficacy and safety of

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radium-223 in Asian patients with castrate-resistant prostate cancer and metastatic bone disease.

Methods: This multicenter, prospective, single-arm, open-label phase 3 trial evaluated the efficacy and safety of the standard radium-223 regimen (55 kBq/kg every 4 weeks for six cycles) in patients from Asian countries. The primary endpoints were the safety and overall survival.

Results: A total of 226 patients were enrolled and received at least one dose of radium-223. Median overall survival was 14.0 months (95% confidence interval [CI], 11.2–17.4). Median time to total alkaline phosphatase and prostate-specific antigen progression were 7.5 (95% CI, 6.8–7.7) and 3.6 (95% CI, 3.1–3.7) months, respectively. Median skeletal-related event-free survival was 26.0 months (95% CI, 12.6–not reached). Grade ≥ 3 treatment-emergent adverse events were reported in 103 (46%) of 226 patients, with anemia being the most common event (34 [15%] patients). Grade ≥ 3 drug-related treatment-emergent adverse events occurred in 39 (17%) of 226 patients. Serious treatment-emergent adverse events were reported in 65 (29%) of 226 patients. Seven (3%) patients had an adverse event leading to death; none were considered to be related to radium-223.

Conclusion: The results of this study support the use of the standard radium-223 regimen for the treatment of Asian patients with castrate-resistant prostate cancer and symptomatic bone metastases.

KEYWORDS

Asian patients, bone metastases, castrate-resistant prostate cancer, radium-223, targeted alpha therapy

1 | INTRODUCTION

Prostate cancer is the second most common cancer among men globally and the sixth most common cancer among Asian men.¹ Prostate cancer incidence rates vary more than 17-fold between different world regions, with the highest incidence rates reported in Australia and New Zealand, Northern and Western Europe and North America, and the lowest in South-Central Asia.^{1–3} However, over the past few decades a number of socioeconomic factors and improved diagnostic practices, together with changes in lifestyle patterns in Asia, has resulted in a marked increase in prostate cancer incidence and mortality rates,⁴ which are expected to almost double by 2030.^{1,5,6} The differences in incidence between Asia and countries like Australia and New Zealand, may reflect not only differences in lifestyle, but also the prevalence of the use of prostate-specific antigen (PSA) testing in those countries which, although not generally recommended for routine screening, may detect slow growing asymptomatic cancers.^{7,8}

Prostate cancer is diagnosed at a more advanced stage in certain Asian countries,⁵ including Malaysia and China.^{9,10} A Malaysian study reported that >50% of cancers are diagnosed as stage 4 disseminated disease,⁹ whereas in Japan and Korea, 10% and 13% of patients present with distant disease.^{11,12} A regional real-world study in China compared patient and disease characteristics in 2016–2017

and 2010–2011. Patients in the 2016–2017 group, compared with the 2010–2011 group, were younger at diagnosis, had lower PSA levels, and a higher proportion of patients were low and intermediate risk as defined by the European Association of Urology guidelines.¹³ The use of radical prostatectomy and radiation therapy increased from 48% to 77% and the rates of hormone therapy decreased from 32% to 4% in the 2016–2017 group compared with the 2011–2012 group.¹³ A retrospective study analyzed clinical data of Chinese patients who had developed metastatic castrate-resistant prostate cancer (mCRPC) from 2012 to 2016 and reported that 75% of Chinese patients presented with a delayed diagnosis of CRPC and 91% with bone metastasis.¹⁴ Limited treatment options for these patients was recognized as an important unmet clinical need.¹⁴

In Asian countries, access to agents other than cytotoxic chemotherapy may vary across the region.¹⁵ In China, radical prostatectomy or radical radiotherapy are the main treatment options for localized prostate cancer, and androgen deprivation therapy (ADT) is often used for the treatment of advanced disease,¹⁶ whereas patients with mCRPC also often receive docetaxel following first- or second-line hormonal therapy.¹⁷

Radium-223 dichloride (radium-223), a targeted alpha therapy, introduces clustered and difficult-to-repair DNA double-strand breaks, which induce cell cycle arrest and cell death in exposed

cells.^{18,19} Radium-223 significantly prolonged overall survival and time to first symptomatic skeletal-related event, improved quality of life (QoL) in patients with mCRPC and symptomatic bone metastases and had a favorable safety profile when compared with placebo, as demonstrated in the pivotal phase 3 ALSYMPCA study conducted in predominantly white patients (94%).^{20,21} Based on this registrational study, radium-223 was first approved for the treatment of patients with CRPC and symptomatic bone metastases in Europe and the United States.^{8,22} Consequently, the radium-223 benefit in Asian patients needed to be explored further. In Japanese patients with mCRPC, radium-223 was well tolerated and showed similar efficacy to radium-223-treated patients in the ALSYMPCA study.²³ Thus, the aim of this phase 3 study was to investigate the efficacy and safety of radium-223 in Asian, other than Japanese, patients with CRPC and symptomatic bone metastases.

2 | MATERIALS AND METHODS

2.1 | Patients

This was a single-arm, prospective, interventional, open-label, multicenter phase 3 study of radium-223 for the treatment of Asian patients with CRPC and symptomatic bone metastases carried out at 26 study centers in mainland China, Taiwan, South Korea, and Singapore. The quality of the data for all treated patients at one center in China was found to be unreliable. Therefore, these data were excluded. Eligible patients were aged ≥ 18 years, who were diagnosed with progressive bone predominant mCRPC/hormone refractory prostate cancer, with at least two skeletal metastases on imaging but without visceral metastases, and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2. Full inclusion criteria are listed in the Supplementary Materials and Methods.

Patients were excluded if they had serum testosterone ≥ 50 ng/dL or 1.7 nmol/L, had been treated with an investigational drug, any anticancer drug, including chemotherapy, abiraterone, enzalutamide and sipuleucel-T, within 4 weeks prior to screening. Other exclusion criteria are detailed in the Supplementary Materials and Methods.

All patients provided written, informed consent. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice and applicable local laws and regulations. The protocol was approved by the independent ethics committees at all participating sites. The study is registered with ClinicalTrials.gov Identifier: NCT01810770.

2.2 | Procedures

Patients received radium-223 55 kBq/kg (based on the National Institute of Standards and Technology update²⁴) by intravenous injection every 4 weeks up to a total of six injections. The protocol-specified conditions for radium-223 dose delays and discontinuations, and permit-

ted concomitant standard of care treatment, are described in Supplementary Materials and Methods.

2.3 | Outcomes

The primary endpoint was to evaluate the safety and efficacy (overall survival) of radium-223 in an Asian population of patients with CRPC and symptomatic bone metastases. Secondary endpoints included assessments of changes in total alkaline phosphatase (ALP), total ALP normalization, time to total ALP progression, changes in PSA, time to PSA progression, time to first skeletal-related event (SRE) and SRE-free survival (both defined in Supplementary Materials and Methods), time to occurrence of first start of any other anticancer treatment, time to occurrence of first deterioration of ECOG PS, time to pain progression and change in QoL. Exploratory objectives comprised quantitative evaluation of bone scans and resource utilization.

2.4 | Assessments

Adverse events were coded according to Medical Dictionary for Regulatory Activities version 20.1 and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. The assessment period for adverse events was from the time the patient signed the informed consent up to 30 days after the last dose of study medication.

Changes in total ALP and PSA levels were defined as a $\geq 30\%$ and a $\geq 50\%$ reduction of the blood ALP or PSA level compared with the baseline value. Confirmed total ALP response was considered to be a $\geq 30\%$ and a $\geq 50\%$ reduction of the blood total ALP level, compared with the baseline value, confirmed by a second total ALP value approximately 4 or more weeks later. Confirmed PSA response was considered to be a $\geq 50\%$ reduction of the PSA blood level, compared with the baseline value, confirmed by a second PSA value approximately 4 or more weeks later. Total ALP and PSA normalization was defined as the return of the total ALP or PSA value to within the normal range at 12 weeks after the start of treatment in two consecutive measurements (at least 2 weeks apart) in patients who had total ALP or PSA levels above the upper limit of normal at baseline. Time to total ALP progression in patients with no total ALP decline from baseline was defined as the time from the start of study treatment to a $\geq 25\%$ increase from the baseline value at a time point that is at least 12 weeks from baseline. In patients with an initial total ALP decline from baseline, time to total ALP progression was defined as the time from the start of study treatment to a $\geq 25\%$ increase above the nadir value (confirmed by a second value obtained 3 or more weeks later). Time to PSA progression in patients with no PSA decline from baseline was defined as the time from the start of therapy to a $\geq 25\%$ increase from the baseline value and an increase in absolute value of ≥ 2 ng/mL, at least 12 weeks from baseline. In patients with an initial PSA decline from baseline, time to PSA progression was defined as the time from the start of therapy to a

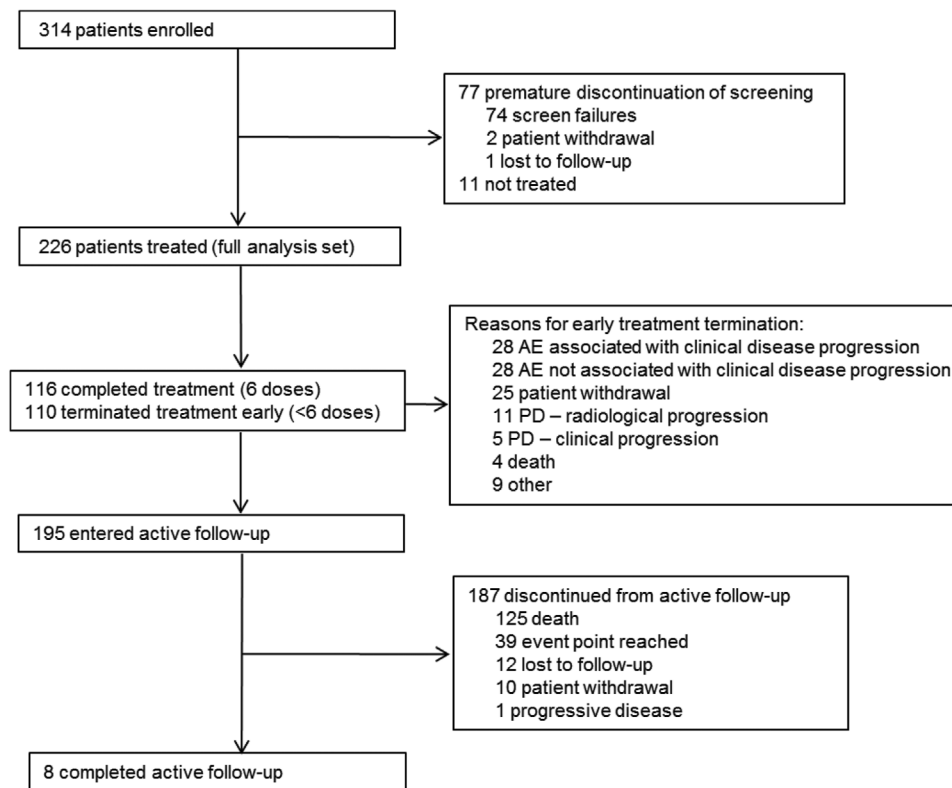


FIGURE 1 Study profile. AE, adverse events; PD, progressive disease

$\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir value (confirmed by a second value obtained 3 or more weeks later).

QoL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire that comprises a 27-item self-report questionnaire measuring general health-related QoL in patients with cancer (FACT-General) and a 12-item prostate cancer subscale, the European Quality of Life-5 Dimensions (EQ-5D) questionnaire that includes a visual analogue scale (VAS), and the Brief Pain Inventory-Short Form (BPI-SF) questionnaire.

2.5 | Statistical analyses

Safety and efficacy analyses were performed in the full analysis set, which comprised all patients who had received at least one dose of radium-223. The primary efficacy endpoint was overall survival, defined as the time from the day of the first study drug injection to death due to any cause. Patients alive at the time of analysis were censored at their last known alive date. Assessments for the secondary endpoints are detailed in Supplementary Materials and Methods.

Summary statistics for categorical data were calculated. Kaplan-Meier analysis was performed for time-to-event variables. All analyses are descriptive and no formal statistical testing was planned.

Assuming an exponential survival time distribution with a median of 14 months, uniform accrual of a total of 230 patients for 22 months, and a 36-month follow-up period from the time the first patient was treated, it was predicted that approximately 160 deaths would be

observed at the end of the follow-up period, with an approximate 95% confidence interval (CI) for the median survival time of 12.1–16.6. Statistical analyses were performed using SAS release 9.1 or higher (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

Two hundred and twenty-six patients enrolled between March 2013 and June 2016 at 25 centers (14 in China, 4 in Taiwan, 4 in South Korea, and 3 in Singapore) received at least one dose of radium-223 (full analysis set; Figure 1). Baseline characteristics are summarized in Table 1. All 226 patients were Asian; 192 (85%) were from China. The median age at baseline was 70 years (range 47–93) and 165 (73%) were aged ≥ 65 years. All 226 patients had received prior systemic anticancer therapy; 82 (36%) had received prior docetaxel and 73 (32%) any prior radiotherapy. The majority of patients (70%) had an ECOG PS of 0–1, and 111 (49%) had >20 bone metastases (Table 1).

Patients received a median of six radium-223 injections, with 116 (51%) of 226 patients completing all six scheduled injections. The primary reasons for patients failing to complete all six planned injections were adverse events associated or not associated with disease progression ($n = 28$ [12%] in each case; Figure 1). Delays or interruptions in treatment occurred in 55 (24%) of 226 patients; the most common reason being adverse events (Table S1).

Median follow-up was 11.3 months. Median overall survival was 14.0 months (95% CI, 11.2–17.4); 152 (67%) of 226 patients had an

TABLE 1 Baseline characteristics

| | Full analysis set N = 226 |
|--|------------------------------|
| Median age, years [range] | 70 [47–93] |
| <65 years | 61 (27) |
| ≥65 years | 165 (73) |
| Median weight, kg | 67.0 |
| ECOG PS | |
| 0 | 33 (15) |
| 1 | 146 (65) |
| ≥2 | 47 (21) |
| Gleason score at initial diagnosis | |
| 5–7 | 60 (27) |
| 8–10 | 155 (69) |
| Missing | 11 (5) |
| Median time since diagnosis of prostate cancer, months (n = 207) | 36.6 |
| Median time since diagnosis of bone metastases, months (n = 192) | 21.1 |
| Median alkaline phosphatase, U/L | 151.1 |
| <220 | 140 (62) |
| ≥220 | 86 (38) |
| Median prostate-specific antigen, μg/L | 131.3 |
| Median hemoglobin, g/dL | 12.3 |
| Extent of bone disease | |
| <6 metastases | 33 (15) |
| 6–20 metastases | 63 (28) |
| >20 metastases | 111 (49) |
| Superscan | 4 (2) |
| Missing | 15 (7) |
| Use of BHA at first radium-223 dose | |
| Denosumab | 3 (1) |
| Bisphosphonates | 58 (26) |
| Prior radiotherapy | |
| Yes | 73 (32) |
| No | 153 (68) |
| Prior systemic anticancer therapy | |
| Yes ^a | 226 (100) |
| Docetaxel | 82 (36) |
| Cabazitaxel | 7 (3) |
| Abiraterone | 35 (15) |
| Enzalutamide | 7 (3) |

Abbreviations: BHA, bone health agent.; ECOG PS, Eastern Cooperative Oncology Group performance status.

Note: Data are n (%) unless otherwise specified.

^a Selected prior systemic anticancer therapies are shown.

event and 74 (33%) patients were censored (Table 2, Figure S1A). The prior use of docetaxel had no apparent effect on median overall survival (14.0 months, 95% CI, 9.3–17.7 in patients who had received prior docetaxel versus 13.9 months, 95% CI, 11.1–18.4 in patients who had not). SREs were reported in 32 (14%) of 226 patients, including 17 (8%) who received external beam radiation therapy, 9 (4%) with spinal cord compression, 5 (2%) with symptomatic pathological bone fractures and 1 (<1%) with tumor-related orthopedic surgical intervention (Table 2). SRE-free survival from the date of treatment to the date of first SRE or death was 26 months (78 events in 148 patients; Table 2; Figure S1B). The percentage change in ALP and PSA levels at week 12 from baseline and time to ALP and PSA progression are summarized in Table 2 and Figure S1C–F.

Treatment-emergent adverse events (TEAEs) of any grade were reported in 212 (94%) of 226 patients (Table 3 and Table S2). The most common adverse events of any grade were anemia (82 [36%] patients) and nausea (59 [26%] patients). Grade ≥3 TEAEs were reported in 103 (46%) of 226 patients. The most common grade ≥3 TEAEs were anemia and bone pain, reported in 34 (15%) and 12 (5%) patients, respectively (Table 3). Drug-related TEAEs occurred in 139 (62%) of 226 patients, with the most common at grade ≥3 being anemia, reported in 25 (11%) patients (Table S3). Platelet count decreased in 8 (4%) patients. Treatment-emergent serious adverse events (SAEs) were reported in 65 (29%) of 226 patients; the most frequent were anemia and hematuria reported in 9 (4%) and 7 (3%) of patients, respectively. TEAEs causing radium-223 dose interruption were reported in 25 (11%) of 226 patients; the most common were anemia (9 [4%] patients) and platelet count decreased (4 [2%] patients). Forty-six (20%) of 226 patients had TEAEs resulting in discontinuation of radium-223; the most common were anemia (15 [7%] patients), platelet count decreased (4 [2%] patients) and bone pain (4 [2%] patients). Seven (3%) of 226 patients had adverse events leading to death (cardiopulmonary failure; multiple organ dysfunction syndrome; metastases to liver; prostate cancer stage IV; respiratory failure; death [n = 2]); none were deemed to be related to radium-223.

Radium-223 treatment showed clinical benefits in health-related QoL. The mean change in the EQ-5D VAS score from the baseline was positive for all the scheduled visits indicating the improvement of the EQ-5D VAS score throughout the study and the post-treatment period (Figure 2A). The mean change in the EQ-5D utility score from the baseline was positive for most of the scheduled visits, although negative values were reported for the active follow-up visits 2, 4, 8 and 9 (Figure 2B). The FACT-P total score improved from the baseline throughout the treatment period (Figure 2C), whereas the bone pain severity score improved from the baseline at every scheduled post-baseline assessment to the end of treatment and generally continued to improve throughout the active follow-up period (Figure 2D).

4 | DISCUSSION

In this single-arm phase 3 study, we have shown that the efficacy and safety profiles of radium-223 in Asian patients are consistent with

TABLE 2 Efficacy endpoints

| Parameter | Full analysis set N = 226 |
|---|------------------------------|
| Overall survival | |
| Deaths, n (%) | 152 (67) |
| Censored, n (%) | 74 (33) |
| Median, months | 14.0 |
| 95% CI | 11.2–17.4 |
| Total ALP | |
| Median change of total ALP at week 12 from baseline, % (n = 162) | –34.1 |
| 95% CI | –34.1–23.3 |
| Total ALP response rate | |
| Confirmed ≥30% reduction compared with baseline value, n (%) | 108 (48) |
| 95% CI | 41.1–54.5 |
| Confirmed ≥50% reduction compared with baseline value, n (%) | 56 (25) |
| 95% CI | 19.3–30.9 |
| Total ALP normalization at 12 weeks, ^a n (%) (n = 138) | 32 (23) |
| 95% CI | 16.4–31.1 |
| Time to total ALP progression | |
| Events, n (%) | 87 (38) |
| Censored, n (%) | 139 (62) |
| Median, months | 7.5 |
| 95% CI | 6.8–7.7 |
| PSA | |
| Median change of PSA level at week 12 from baseline, % (n = 162) | 46.4 |
| Range | –98.1–2145.0 |
| PSA response rate | |
| Confirmed ≥30% reduction compared with baseline value, n (%) | 46 (20) |
| 95% CI | 15.3–26.2 |
| Confirmed ≥50% reduction compared with baseline value, n (%) | 31 (14) |
| 95% CI | 9.5–18.9 |
| PSA normalization at 12 weeks, ^a n (%) | 4 (2) |
| 95% CI | 0.5–4.5 |
| Time to PSA progression | |
| Events, n (%) | 152 (67) |
| Censored, n (%) | 74 (33) |
| Median, months | 3.6 |
| 95% CI | 3.1–3.7 |
| Skeletal-related event-free survival, n (%) | |
| Any event | 78 (35) |
| Death | 46 (20) |
| Spinal cord compression | 9 (4) |

(Continues)

TABLE 2 (Continued)

| Parameter | Full analysis set N = 226 |
|--|------------------------------|
| Symptomatic pathological bone fractures | 5 (2) |
| Tumor-related orthopedic surgical intervention | 1 (< 1) |
| External beam radiotherapy | 17 (8) |
| Censored | 148 (65) |
| Median, months | 26.0 |
| 95% CI | 12.6–NR |

Abbreviations: ALP, alkaline phosphatase; NR, not reached; PSA, prostate-specific antigen.

Note: Data are n (%) unless otherwise specified.

^aTotal ALP and PSA responses were those confirmed by a second assessment carried out approximately 4 or more weeks after the first.

TABLE 3 Treatment-emergent adverse events that occurred in at least 5% of patients

| Adverse event ^a | Safety population, N = 226 | | | |
|----------------------------------|----------------------------|---------|---------|---------|
| | Any grade | Grade 3 | Grade 4 | Grade 5 |
| Any | 212 (94) | 88 (39) | 8 (4) | 7 (3) |
| Hematologic | | | | |
| Anemia | 82 (36) | 33 (15) | 1 (< 1) | 0 |
| White blood cell count decreased | 32 (14) | 1 (< 1) | 0 | 0 |
| Platelet count decreased | 28 (12) | 8 (4) | 2 (< 1) | 0 |
| Nonhematologic | | | | |
| Nausea | 59 (26) | 3 (1) | 0 | 0 |
| Decreased appetite | 42 (19) | 6 (3) | 0 | 0 |
| Weight decreased | 39 (17) | 1 (< 1) | 0 | 0 |
| Constipation | 33 (15) | 1 (< 1) | 0 | 0 |
| Bone pain | 35 (15) | 12 (5) | 0 | 0 |
| Diarrhea | 22 (10) | 1 (< 1) | 0 | 0 |
| Vomiting | 22 (10) | 1 (< 1) | 0 | 0 |
| ALT increased | 19 (8) | 3 (1) | 0 | 0 |
| AST increased | 17 (8) | 5 (2) | 0 | 0 |
| Hematuria | 17 (8) | 7 (3) | 0 | 0 |
| Edema peripheral | 12 (5) | 1 (< 1) | 0 | 0 |
| Urinary tract infection | 12 (5) | 1 (< 1) | 0 | 0 |
| GGT increased | 12 (5) | 3 (1) | 0 | 0 |
| Urinary retention | 12 (5) | 1 (< 1) | 0 | 0 |
| Hypertension | 12 (5) | 8 (4) | 0 | 0 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.

Note: Data are n (%).

^aReported according to preferred term ordered by any NCI-CTCAE grade in ≥5% of patients.

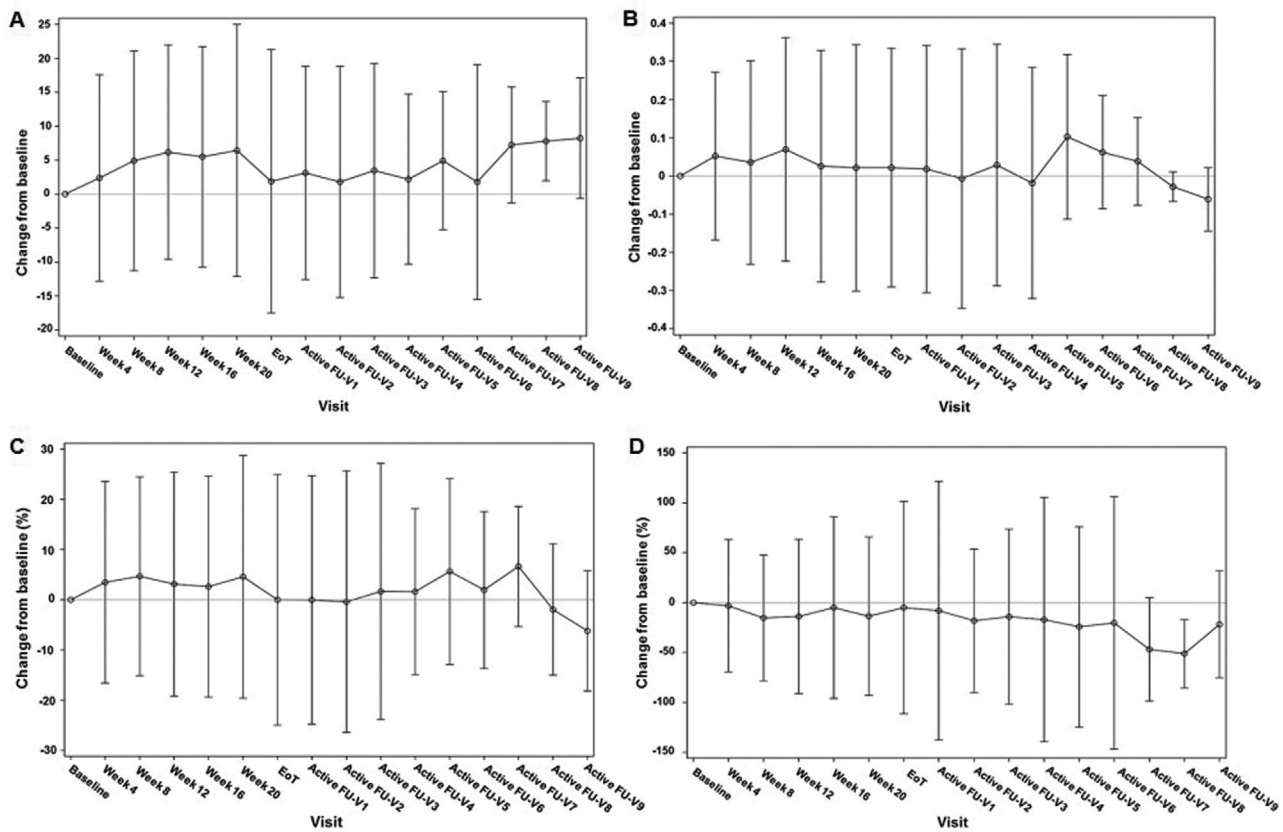


FIGURE 2 Changes in quality of life scores from baseline (full analysis set). The mean (\pm SD) change in scores from baseline by visit during the treatment and the follow-up period measured by the QoL assessments using the FACT-P, the EQ-5D and the BPI-SF questionnaires. (A) change from the baseline in the EQ-5D VAS score; (B) change from the baseline in the EQ-5D utility score; (C) percentage change from the baseline in the FACT-P version 4 total score; (D) percentage change from the baseline in the BPI-SF-pain severity index score. Abbreviations: BPI-SF, Brief Pain Inventory-Short Form; EoT, end of treatment; EQ-5D, European Quality of Life-5 Dimensions; EQ-5D VAS, EQ-5D Visual Analogue Scale; FACT-P, Functional Assessment of Cancer Therapy-Prostate; FU, follow-up; QoL, quality of life; SD, standard deviation; V, visit

those reported in radium-223 clinical development studies conducted in Western countries.^{20,25} In general, a single-arm trial design has inherent limitations due to the inability to discern between the efficacy of treatment, a placebo effect and the natural course of disease.²⁶ The lack of the placebo comparator arm in a clinical trial may complicate the interpretation of the study results.²⁶ However, at the time of the conception and design of the current Asian study, randomization and inclusion of a placebo control arm was considered to be unjustifiable as the results of a global, placebo-controlled ALSYMPCA study in patients with mCRPC became available.²⁰ Despite these limitations, in this single-arm study, the patient eligibility and selection criteria were designed to be similar to those in the global ALSYMPCA trial,²⁰ except for the geographical region of recruitment and race or ethnicity. Therefore, a comparison of radium-223 efficacy and safety between the current Asian and the predominantly white ALSYMPCA patient population, including the placebo arm, is likely to be meaningful.

Median overall survival results were similar between both ethnic groups. In the randomized controlled ALSYMPCA trial, radium-223 extended overall survival by 3.6 months compared with the placebo arm (14.9 months vs 11.3 months),²⁰ and it was slightly shorter

(14.0 months) in the Asian patient population in this single-arm study. Notably, the ALSYMPCA study performed the overall survival analysis from the time of randomization to death due to any cause, whereas in this study it was from the time of first study drug injection to death of any cause.

Some differences were seen in patient baseline characteristics, including the extent of metastatic disease, median PSA and ALP levels, and prior systemic anticancer therapies, in the current and the ALSYMPCA study, although the baseline characteristics were generally similar in both studies. A higher proportion of patients in this study had ECOG PS ≥ 2 scores (21% vs 13% in the ALSYMPCA trial) and >20 metastases (49% vs 32% in the ALSYMPCA study),²⁰ suggesting that the patients in this study had more advanced disease. Notably, Asian patients had lower baseline median PSA and ALP levels compared with those in the ALSYMPCA study.²⁰ The proportion of patients who had received prior docetaxel differed between the two studies; only 36% of Asian patients in this study had received prior docetaxel therapy compared with 57% of radium-223-treated patients in the ALSYMPCA trial.²⁰ Both studies included patients who were unfit to receive chemotherapy and had otherwise limited treatment options. For Asian patients, this represents an important unmet clinical need.

Radium-223 was generally well tolerated in Asian patients. The most frequently reported adverse events were related to bone marrow function (anemia, white blood cell and platelet count decreased) and gastrointestinal disorders, such as nausea and loss of appetite. In the ALSYMPCA study, the most common hematologic adverse events were anemia (31%) and thrombocytopenia (12%), whereas the most frequently reported nonhematologic adverse events were bone pain (50%), nausea (36%), fatigue (26%) and diarrhea (25%) in patients treated with radium-223.²⁰ Interestingly, any grade bone pain was reported in only 15% of patients in this study, which probably cannot be attributed to the similar rate of opioid use at baseline in the current (46% of patients) and the ALSYMPCA (56% of patients) studies,²⁰ but could potentially be explained by the fact that TEAEs were recorded within 12 weeks after the last radium-223 injection in the ALSYMPCA study, but only within 30 days in this study. Overall, the radium-223 safety profiles were similar in this trial in Asian patients and the ALSYMPCA trial in white patients. However, treatment-emergent SAEs occurred at a lower rate in Asian patients (29%) than in the radium-223 treatment arm in the ALSYMPCA study (47%).²⁰

The incidence of pathologic fractures in radium-223-treated patients was lower in this than in the ALSYMPCA study (0.9% vs 4%, respectively);²⁰ in both studies patients did not receive concomitant abiraterone, as it was either unavailable at the time or was not permitted in this study. A retrospective study of 17,359 Chinese patients with prostate cancer reported an increased fracture incidence associated with ADT or orchiectomy, but the magnitude of increase was lower in Chinese than in Western patients, suggesting causes related to population or clinical practice differences between Asian and Western countries.²⁷

Patients with bone-metastatic CRPC often experience pain, which is one of the main causes of impaired QoL. Furthermore, additional secondary complications, including anorexia, asthenia and cachexia, related to bone metastases may also develop.²⁸ In the ALSYMPCA study, radium-223 treatment improved QoL.²¹ The evaluation of the EQ-5D utility and the FACT-P scores in the ALSYMPCA study showed that radium-223 was associated with a greater improvement in QoL over the treatment and follow-up periods compared with placebo, and a higher percentage of patients treated with radium-223 showed a clinically meaningful improvement in the EQ-5D utility and the FACT-P scores compared with patients in the placebo arm.²¹ In this study, a trend toward an improvement in the EQ-5D utility and the FACT-P total scores was observed at all post-baseline evaluations in the treatment period, compared with the baseline score. For the EQ-5D VAS and the BPI-SF scores, a trend toward improvement was reported throughout the post-baseline period.

The current and the ALSYMPCA studies provide further evidence that radium-223, a first-in-class targeted alpha therapy, is effective and safe in ethnically diverse patients with CRPC and symptomatic bone metastases. Conversely, beta-particle emitting radionuclides, such as samarium-153 and strontium-89, have shown no advantage in prolonging survival in patients with mCRPC, perhaps due to poor efficacy and safety profiles.^{29,30}

5 | CONCLUSIONS

This study shows that the efficacy and safety profiles of radium-223 in Asian patients with CRPC and symptomatic bone metastases are similar to those previously reported in the registrational ALSYMPCA study. In particular, median overall survival was comparable between the two populations and no new safety concerns were highlighted in Asian patients. Therefore, Asian patients with CRPC and symptomatic bone disease may benefit from the standard radium-223 regimen.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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