Chemotherapy Following Radium-223 Dichloride Treatment in ALSYMPCA

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BACKGROUND. Radium-223 prolongs overall survival in patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases, regardless of prior docetaxel. Whether or not chemotherapy can be safely administered following radium-223 treatment is of clinical importance. An exploratory analysis of prospectively collected data, from the ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) patient subgroup who received chemotherapy after radium-223 or placebo treatment, was conducted to evaluate the safety and efficacy of chemotherapy following radium-223.

METHODS. In ALSYMPCA, CRPC patients with symptomatic bone metastases and no visceral metastases were randomized 2:1 to receive six injections of radium-223 (50 kBq/kg IV) or placebo plus best standard of care, stratified by prior docetaxel, baseline alkaline phosphatase, and current bisphosphonate use. In this exploratory analysis, chemotherapy agents administered following study treatment were identified; timing and duration were calculated. Hematologic safety was reviewed, and overall survival analyzed.

RESULTS. Overall, 142 radium-223 and 64 placebo patients received subsequent chemotherapy; most common were docetaxel (70% radium-223, 72% placebo) and mitoxantrone (16% radium-223, 20% placebo). The majority of patients (61% radium-223, 58% placebo) had received prior docetaxel. Radium-223 patients started subsequent chemotherapy later than...
placebo patients; chemotherapy duration was similar between groups. In radium-223 and placebo patients receiving subsequent chemotherapy, median hematologic values (hemoglobin, neutrophils, and platelets) remained nearly constant up to 18 months following start of chemotherapy, regardless of prior docetaxel treatment. A low percentage of patients in both groups had grades 3–4 hematologic values (<10%). Platelet count decline, from last measurement before chemotherapy, was numerically greater in radium-223 versus placebo patients. Median overall survivals from start of chemotherapy were 16.0 and 15.8 months following radium-223 and placebo, respectively.

CONCLUSIONS. Chemotherapy following radium-223, regardless of prior docetaxel, is feasible and appears to be well tolerated in patients with CRPC and symptomatic bone metastases. Prostate 76:905–916, 2016. © 2016 The Authors. The Prostate published by Wiley Periodicals, Inc.

KEY WORDS: radium-223; prostate; chemotherapy; safety; alpha emitter; bone

INTRODUCTION

Radium-223 dichloride (radium-223) is a calcium mimic that specifically targets bone. It decays by emitting high-energy alpha particles that penetrate tissue only to a depth of about 2–10 cell diameters (<100 μM), resulting in highly localized cell killing with minimal damage to surrounding normal tissue including bone marrow cells [1–3]. As a result, radium-223 presents less risk to cells in the bone marrow than external beam radiation therapy (EBRT) and the radiation emitted by other radionuclides used in cancer therapy.

The phase 3 ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) trial with radium-223 in patients with CRPC and symptomatic bone metastases enrolled both patients who had received prior docetaxel and patients who had not [4], unlike other pivotal trials that enrolled docetaxel-naive or post-docetaxel patients only [5–10]. In ALSYMPCA, radium-223, compared with placebo, prolonged median overall survival (14.9 vs. 11.3 months) and reduced risk of death by 30% (hazard ratio [HR] 0.70; 95%CI: 0.58–0.83; P < 0.001), regardless of whether patients had received prior docetaxel (HR 0.70) or not (HR 0.69), establishing the benefits of radium-223 irrespective of prior docetaxel exposure [4,11].

Radium-223 was well tolerated regardless of prior docetaxel exposure, with a low overall incidence of grades 3–4 myelosuppression [11]. Furthermore, preliminary results from an ongoing phase I/IIa study show that a radium-223 plus docetaxel combination therapy is feasible, provided that the docetaxel dose is attenuated and radium-223 is dosed less frequently [12].

The impact of radium-223 on the safety of subsequently administered chemotherapy has not been specifically studied. There has been a reluctance to administer chemotherapy after radioisotope therapy, because of concern that radiation effects in the bone marrow could compromise the safety of chemotherapy [13]. Also, as hematologic parameters often decline over the course of the disease regardless of therapy, hematologic adverse events (AEs) and bone marrow failure may complicate the clinical course of patients with advanced CRPC [14,15]. An exploratory analysis of prospectively collected data, from the ALSYMPCA patient subgroup who received chemotherapy after completing their assigned study drug treatment, was conducted to evaluate the safety of chemotherapy following radium-223.

METHODS

ALSYMPCA Study Design and Patients

ALSYMPCA was a randomized phase III, double-blind, placebo-controlled trial conducted at 136 centers in 19 countries comparing the efficacy and safety of radium-223 plus best standard of care (BSoC) with placebo plus BSoC in the treatment of patients with CRPC, at least two bone metastases, symptomatic bone disease (either regular analgesic use or treatment with EBRT within the previous 12 weeks, for cancer-related bone pain), and no known visceral metastases [4]. BSoC was defined as the routine care provided at each center (e.g., local EBRT, glucocorticoids, anti-androgens, ketoconazole, or estrogens such as diethylstilbestrol or estramustine). Chemotherapy, hemibody external radiotherapy, and other systemic radionuclides were not permitted during the period from first injection to four weeks after last injection of study drug.

ALSYMPCA eligibility requirements have been published in detail elsewhere [4]. Patients should have received prior docetaxel if available or, if not, were considered either unfit for docetaxel or declined the treatment. The primary end point was overall survival. Safety was assessed on the basis of AEs, hematologic values, clinical laboratory values, and findings on electrocardiography and physical examination. The follow-up period was three years. The study protocol was reviewed and approved by the
institutional review board at each participating center, and all patients provided written informed consent.

Randomization and Masking

In ALSYMPCA, patients were randomized 2:1 to receive six intravenous injections of radium-223 (50 kBq/kg IV) or matching placebo once every four weeks and were stratified by prior docetaxel use (yes vs. no), baseline alkaline phosphatase level (<220 U/L vs. ≥220 U/L), and current bisphosphonate use (yes vs. no). Randomization was done with an interactive voice response system, taking into account trial stratification factors. The randomization number was provided to the site investigators, but the assigned treatment was not. Because radium-223 is radioactive, an individual not masked to treatment at each center calculated study drug volume and filled the syringe for masked distribution. All others (patients, investigators, and study funders) were masked to the randomization of the original study.

Patients included in this exploratory analysis were the subgroup of all randomized patients who received subsequent chemotherapy after treatment with radium-223 or placebo. Therefore, the comparability of radium-223 and placebo patients who received subsequent chemotherapy is not assured by the initial randomization of the original study.

Procedures

Chemotherapy was not permitted within the four weeks prior to randomization, during the study treatment period, or within four weeks after the last injection of study drug but was permitted at the investigator’s discretion thereafter. During the follow-up period, complete blood counts (CBCs) were conducted at each of nine follow-up visits: one visit every two months for the first six months, and every four months thereafter. CBC schedules had no clear relationship to chemotherapy administered because of varying chemotherapy start times among patients. From 12 weeks after the last study treatment, AEs were recorded only if considered to be related to study drug.

Outcomes—Exploratory Analysis

In this analysis, hematologic safety and overall survival were assessed among patients in the chemotherapy and docetaxel post-study drug subgroups who had previously received radium-223 or placebo. AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE). Overall survival was defined as time from start of chemotherapy to date of death.

Statistical Analysis

This exploratory analysis includes prospectively collected data up to the ALSYMPCA study cutoff date of March 2014. Analyses were not powered to assess differences between radium-223 and placebo within the chemotherapy or docetaxel post-study drug subgroups. The chemotherapy post-study drug subgroup included patients who received any chemotherapy following treatment with radium-223 or placebo. The docetaxel post-study drug subgroup included patients who received docetaxel following treatment with radium-223 or placebo (and may have received one or more different types of chemotherapy). Time from randomization to start of chemotherapy, time from end of study treatment to start of chemotherapy, duration of first chemotherapy, and time from first chemotherapy to stop of last chemotherapy (from chemotherapy start to end of treatment or database lock if still on treatment) were calculated using descriptive statistics. CBCs were summarized by 2-month protocol-specified intervals using descriptive statistics. Hazard ratios were calculated using a Cox proportional hazards regression model. Subgroup analyses were performed to assess treatment effects based on prior docetaxel use. Fisher’s exact test was used to calculate P values for patients with hematologic laboratory values corresponding to grade three or four AEs. Maximum change from baseline in platelets by prior docetaxel use was assessed using the Wilcoxon rank sum test. This trial is registered at ClinicalTrials.gov (NCT00699751).

RESULTS

A total of 921 patients were enrolled in ALSYMPCA between June 2008 and February 2011, 614 in the radium-223 group and 307 in the placebo group (Fig. 1). A total of 407 (66%) radium-223 and 168 (55%) placebo patients entered long-term follow-up. The chemotherapy post-study drug subgroup comprises 206 (22%) patients and includes 142 (23%) patients from the radium-223 group and 64 (21%) patients from the placebo group who received chemotherapy following study treatment (Fig. 1). Demographics and baseline characteristics, including prior docetaxel use and baseline hemoglobin and platelet values, for patients in the chemotherapy post-study drug subgroup were similar between radium-223 and placebo groups. The majority of radium-223 (87 [61%]) and placebo (37 [58%]) patients in the chemotherapy post-study drug subgroup had also received docetaxel prior to study treatment (Table I).

Compared with the entire ALSYMPCA intent-to-treat (ITT) population, the chemotherapy post-study
drug subgroup were somewhat younger and had less extensive disease (Fig. 1), and a higher percentage of patients in the chemotherapy post-study drug subgroup had received all six injections of study drug (Table II). Within the chemotherapy post-study drug subgroup, more radium-223 patients (79%) received all six injections compared with placebo patients (58%) (Table II), and 79% and 88% of radium-223 and placebo patients, respectively, withdrew early from the study (Fig. 1). Primary reasons for patient withdrawal are listed in Supplementary Table SI.

**Chemotherapy Following Study Drug**

Docetaxel was the most commonly administered chemotherapy agent, received by 70% (100/142) and 72% (46/64) of radium-223 and placebo patients, respectively. Other commonly administered chemotherapy agents included mitoxantrone (16% [23/142] radium-223, 20% [13/64] placebo), cyclophosphamide (10% [14/142] radium-223, 11% [7/64] placebo), estramustine (4% [6/142] radium-223, 8% [5/64] placebo), and carboplatin (3% [4/142] radium-223, 5% [3/64] placebo). Patients in the chemotherapy post-study drug subgroup may have received one or more chemotherapy regimens. There was a longer time from randomization to start of chemotherapy for radium-223 (9.1 months) compared with placebo patients (7.5 months). The median time from the last dose of study drug (radium-223 or placebo) to the first dose of chemotherapy was 3.8 months for radium-223 and 2.6 months for placebo. Median duration of first chemotherapy was 4.6 months in the radium-223 group and 4.2 months in the placebo group (Table III).

**Hematologic Laboratory Values**

Median values for hematologic laboratory parameters (hemoglobin, neutrophils, and platelets) from last measurement before start of chemotherapy (baseline) to 18 months following start of first chemotherapy are shown for both treatment groups in the chemotherapy post-study drug subgroup (Table IV). Although patient dropout rate during this period was high, it was generally balanced between treatment groups (Fig. 1). Median baseline values for neutrophils and platelets were somewhat lower for patients in the radium-223 group than for the placebo group (Table III). The percentage of patients with hematologic values corresponding to AEs of CTCAE grade 3 or 4 from baseline
TABLE I. Demographics and Baseline Characteristics for Patients in the Chemotherapy Post-Study Drug Subgroup Versus the ALSYMPCA Intent-to-Treat (ITT) Population

| Characteristic                        | Chemotherapy post-study drug subgroup | ALSYMPCA ITT population |
|---------------------------------------|---------------------------------------|-------------------------|
|                                       | Radium-223                            | Placebo                 | Radium-223              | Placebo               |
|                                       | n = 142                               | n = 64                  | N = 614                 | N = 307               |
| Median age (range), y                 | 68 (49–85)                            | 68 (50–82)              | 71 (49–90)              | 71 (44–94)            |
| Age >75 y, n (%)                      | 20 (14)                               | 12 (19)                 | 171 (28)                | 90 (29)               |
| Caucasian race, n (%)                 | 133 (94)                              | 60 (94)                 | 575 (94)                | 290 (95)              |
| Baseline ECOG PS ≤1, n (%)            | 136 (96)                              | 57 (89)                 | 536 (87)                | 265 (86)              |
| Extent of disease, n (%)              |                                       |                         |                         |                       |
| <6 metastases                         | 33 (24)                               | 15 (23)                 | 101 (17)                | 38 (12)               |
| 6–20 metastases                       | 60 (43)                               | 34 (53)                 | 258 (42)                | 146 (48)              |
| >20 metastases                        | 37 (26)                               | 12 (19)                 | 198 (32)                | 92 (30)               |
| Superscan                             | 10 (7)                                | 3 (5)                   | 54 (9)                  | 30 (10)               |
| WHO ladder for cancer pain, n (%)     |                                       |                         |                         |                       |
| 0                                     | 0 (0)                                 | 0 (0)                   | 12 (2)                  | 2 (1)                 |
| 1                                     | 70 (49)                               | 31 (48)                 | 257 (42)                | 137 (45)              |
| 2                                     | 37 (26)                               | 20 (31)                 | 151 (25)                | 78 (25)               |
| 3                                     | 35 (25)                               | 13 (20)                 | 194 (32)                | 90 (29)               |
| Total ALP ≥220 U/L, n (%)             | 41 (29)                               | 17 (27)                 | 348 (57)                | 169 (55)              |
| Current bisphosphonate use, n (%)     | 69 (49)                               | 30 (47)                 | 250 (41)                | 124 (40)              |
| Prior docetaxel, n (%)                | 87 (61)                               | 37 (58)                 | 352 (57)                | 174 (57)              |
| EBRT ≤12 weeks of screening, n (%)    | 19 (13)                               | 5 (8)                   | 99 (16)                 | 49 (16)               |
| Platelets, median (range) × 10^9/L b   | 244 (99–560)                          | 251 (108–459)           | 244 (69–643)            | 240 (51–580)          |
| Neutrophils, median (range) × 10^9/L b | 4.1 (1.7–13.7)                       | 4.1 (2.1–9.7)           | 4.5 (1.2–17.1)          | 4.6 (1.4–14.3)        |
| Albumin, median (range), g/dL         | 12.6 (9.0–15.7)                       | 12.6 (8.7–15.4)         | 12.2 (8.5–15.7)         | 12.1 (8.5–16.4)       |
| Total ALP, median (range), U/L        | 119.0 (32.0–2681.0)                   | 139.5 (36.0–2165.6)     | 211.0 (32–6431)         | 223.0 (29–4005)       |
| LDH, median (range), U/L              | 284.0 (135.0–1297.0)                  | 322.5 (132.0–1022.0)    | 315.5 (108–2171)        | 335.5 (132–386)       |
| PSA, median (range), μg/L             | 85.6 (4.1–848.0)                      | 66.4 (3.6–3457.0)       | 146.3 (3.8–6026.0)      | 172.9 (1.5–14500.0)   |

ALP, alkaline phosphatase; EBRT, external beam radiation therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; WHO, World Health Organization.

*aBaseline is defined as the time the patients entered the study.

*bSelected data from the ALSYMPCA safety population.
up to 18 months following first post-study drug chemotherapy was generally low (< 10%), but tended to be more common among patients in the radium-223 group (Table V). Grades 3 or 4 hemoglobin, neutrophil, and platelet values were recorded in 8%, 10%, and 6% of radium-223 and 4%, 2%, and 2% of placebo patients, respectively (Table V). No statistically significant differences were found between treatment groups in frequency of hematologic laboratory values corresponding to grade 3 or 4 AEs (Table V). Maximum percentage decreases from baseline in platelets were numerically greater in the radium-223 group than in the placebo group, but did not appear to be associated with prior docetaxel treatment (prior docetaxel: yes, \( P = 0.400 \); no, \( P = 0.350 \)) (Fig. 2C and D). Hemoglobin and neutrophils were similar in the two treatment groups, indicating little effect of radium-223 treatment on hematologic toxicity of subsequent chemotherapy (Fig. 2A and B).

Hematologic laboratory values were also assessed according to docetaxel use prior to enrollment in ALSYMPCA. Among the patients in the chemotherapy post-study drug subgroup, 87/142 (61%) in the radium-223 group and 37/64 (58%) in the placebo group received docetaxel prior to receiving the study drug. Hematologic parameters for patients who received docetaxel prior to radium-223 were similar to those for patients who did not, with no apparent differences between treatment groups up to 18 months (Supplementary Table SII).

**Survival**

Incidence and cause of death were similar between treatment groups, during and within 30 days of

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**TABLE II. Extent of Study Drug Exposure for Patients in the Chemotherapy Post-Study Drug Subgroup Versus the ALSYMPCA Intent-to-Treat (ITT) Population**

|                      | Chemotherapy post-study drug subgroup | ALSYMPCA ITT population |
|----------------------|---------------------------------------|-------------------------|
|                      | Radium-223 n = 142                    | Placebo n = 64          | Radium-223 N = 614 | Placebo N = 307 |
| Number of study injections, median (range) | 6 (2–6) | 6 (1–6) | 6 (0–6) | 5 (0–6) |
| Duration of study treatment, median (range), days | 141 (28–177) | 141 (1–175) | 141 (1–196) | 129 (1–190) |
| Number of study drug injections received, n (%) | 1 0 (0) | 3 (5) | 18 (3) | 21 (7) |
|                      | 2 6 (4) | 8 (12) | 37 (6) | 36 (12) |
|                      | 3 9 (6) | 7 (11) | 48 (8) | 37 (12) |
|                      | 4 9 (6) | 3 (5) | 60 (10) | 34 (11) |
|                      | 5 6 (4) | 6 (9) | 47 (8) | 29 (9) |
|                      | 6 112 (79) | 37 (58) | 389 (63) | 145 (47) |

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**TABLE III. Timing and Duration of Post-Study Drug Chemotherapya**

|                      | Radium-223 n = 142 | Placebo n = 64 |
|----------------------|---------------------|----------------|
| All chemotherapies, n | 142                 | 64             |
| Time from randomization to start of chemotherapy, median (range), months | 9.1 (1.8–35.6) | 7.5 (1.6–26.4) |
| Time from end of study treatment to start of chemotherapy, median (range), months | 3.8 (0–30.4) | 2.6 (0.1–20.5) |
| Duration of first chemotherapy, median (range), months | 4.6 (0–59.0) | 4.2 (0–60.8) |
| Time from first chemotherapy to stop of last chemotherapy, median (range), months | 6.2 (0–60.9) | 8.5 (0–60.8) |
| Docetaxel, n          | 100                 | 46             |
| Time from randomization to start of docetaxel, median (range), months | 9.2 (1.9–35.6) | 7.3 (1.6–24.7) |
| Time from end of study treatment to start of docetaxel treatment, median (range), months | 3.9 (0–30.4) | 2.4 (0.1–19.3) |
| Duration of first docetaxel treatment, median (range), months | 5.0 (0–59.0) | 4.5 (0–60.8) |
| Time from first docetaxel treatment to stop of last docetaxel treatment, median (range), months | 5.8 (0–60.9) | 4.9 (0–60.8) |

*a*For some patients with missing treatment end date, duration was calculated from start of treatment (any chemotherapy or docetaxel) until data cutoff date, contributing to long range values.

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**The Prostate**
completing chemotherapy (Table VI). In the radium-223 group, 29% of patients died while receiv-
ing chemotherapy, as did a similar proportion of patients in the placebo group (33%). The most com-
mon cause of death was prostate cancer-related death in 90% and 95% of patients in the radium-223 and placebo groups, respectively. The proportion of patients who died of nonskeletal metastases was higher in the placebo group (24%) than in the radium-223 group (15%).

Prior treatment with radium-223 did not appear to have a detrimental effect on overall survival with subsequent chemotherapy, when compared with chemotherapy following placebo. Median overall survival from start of chemotherapy was 16.0 months in patients previously treated with radium-223 and 15.8 months in patients previously treated with placebo.

**Docetaxel Following Study Treatment**

The most common chemotherapy agent administered following study treatment in ALSYMPCA was docetaxel; therefore, the safety of docetaxel following radium-223 treatment was specifically assessed. Patients in this docetaxel post-study drug subgroup may have also received subsequent chemotherapy with other agents, so data presented here do not

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**TABLE IV. Median Hematologic Values for Patients in the Chemotherapy Post-Study Drug Subgroup**

| Parameter                  | Radium-223 (n = 142) | Placebo (n = 64) |
|----------------------------|----------------------|-----------------|
| Hemoglobin, g/dL           |                      |                 |
| Baselinea                  | 142                  | 64              |
| Month 2                    | 82                   | 42              |
| Month 4                    | 69                   | 25              |
| Month 6                    | 50                   | 22              |
| Month 8                    | 35                   | 10              |
| Month 10                   | 30                   | 17              |
| Month 12                   | 28                   | 8               |
| Month 14                   | 25                   | 6               |
| Month 16                   | 12                   | 3               |
| Month 18                   | 17                   | 8               |
| Neutrophils (absolute) × 10⁹/L |                      |                 |
| Baselinea                  | 142                  | 64              |
| Month 2                    | 78                   | 38              |
| Month 4                    | 66                   | 23              |
| Month 6                    | 46                   | 19              |
| Month 8                    | 33                   | 9               |
| Month 10                   | 27                   | 16              |
| Month 12                   | 24                   | 8               |
| Month 14                   | 19                   | 5               |
| Month 16                   | 11                   | 3               |
| Month 18                   | 14                   | 7               |
| Platelets × 10⁹/L          |                      |                 |
| Baselinea                  | 142                  | 64              |
| Month 2                    | 82                   | 42              |
| Month 4                    | 69                   | 25              |
| Month 6                    | 50                   | 22              |
| Month 8                    | 35                   | 10              |
| Month 10                   | 29                   | 17              |
| Month 12                   | 28                   | 8               |
| Month 14                   | 25                   | 6               |
| Month 16                   | 12                   | 3               |
| Month 18                   | 17                   | 8               |

*Last nonmissing measurement prior to start of first post-study drug chemotherapy. Months 2–18 represent 2-month time windows following first date of chemotherapy. Timing of hematology laboratory values is determined according to start of chemotherapy, not by protocol-defined visits.
reflect a pure population of patients treated with docetaxel alone.

Demographics and baseline characteristics, study drug exposure, and disposition were similar to those in the chemotherapy post-study drug subgroup (Supplementary Tables SIII–SV). Consistent with the chemotherapy post-study drug subgroup, there was a longer time from randomization to start of docetaxel for patients in the radium-223 group (9.2 months) compared with the placebo group (7.3 months). The median time from the last dose of study drug to the first dose of docetaxel was 3.9 months for the radium-

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**TABLE V. Percentage of Patients With Hematologic Laboratory Values Corresponding to Grades 3 and 4 Adverse Events in the Chemotherapy Post-Study Drug Subgroup**

| Parameter                          | Radium-223 (n = 142) | Placebo (n = 64) |
|------------------------------------|----------------------|-----------------|
|                                    | N  | n (%)     | N  | n (%)     |
| Hemoglobin, <8–6.5 g/dL or <6.5 g/dL|    |           |    |           |
| Baselinea                          | 142| 4 (3)     | 64 | 1 (2)     |
| Month 2                            | 82 | 5 (6)     | 42 | 1 (2)     |
| Month 4                            | 69 | 3 (4)     | 25 | 1 (4)     |
| Month 6                            | 69 | 0 (0)     | 22 | 0 (0)     |
| Month 8                            | 35 | 1 (3)     | 10 | 0 (0)     |
| Month 10                           | 30 | 2 (7)     | 17 | 0 (0)     |
| Month 12                           | 28 | 1 (4)     | 8  | 0 (0)     |
| Month 14                           | 25 | 2 (8)     | 6  | 0 (0)     |
| Month 16                           | 23 | 0 (0)     | 3  | 0 (0)     |
| Month 18                           | 17 | 0 (0)     | 8  | 0 (0)     |
| Total individual patientsb         | 116| 9 (8)     | 49 | 2 (4)     |
| *P* valuec                         |    |           |    | 0.509     |

Neutrophils (absolute) <1–0.5 × 10⁹/L or <0.5 × 10⁹/L/L

| Parameter                          | Radium-223 (n = 142) | Placebo (n = 64) |
|------------------------------------|----------------------|-----------------|
|                                    | N  | n (%)     | N  | n (%)     |
| Baselinea                          | 142| 1 (1)     | 64 | 0 (0)     |
| Month 2                            | 78 | 5 (6)     | 38 | 1 (3)     |
| Month 4                            | 66 | 2 (3)     | 23 | 0 (0)     |
| Month 6                            | 46 | 1 (2)     | 19 | 0 (0)     |
| Month 8                            | 33 | 0 (0)     | 9  | 0 (0)     |
| Month 10                           | 27 | 2 (7)     | 16 | 0 (0)     |
| Month 12                           | 24 | 0 (0)     | 8  | 0 (0)     |
| Month 14                           | 19 | 1 (5)     | 5  | 0 (0)     |
| Month 16                           | 11 | 0 (0)     | 3  | 0 (0)     |
| Month 18                           | 14 | 0 (0)     | 7  | 0 (0)     |
| Total individual patientsb         | 114| 11 (10)   | 48 | 1 (2)     |
| *P* valuec                         |    |           |    | 0.112     |

Platelets <50–25 × 10⁹/L or <25 × 10⁹/L/L

| Parameter                          | Radium-223 (n = 142) | Placebo (n = 64) |
|------------------------------------|----------------------|-----------------|
|                                    | N  | n (%)     | N  | n (%)     |
| Baselinea                          | 142| 1 (1)     | 64 | 1 (2)     |
| Month 2                            | 82 | 4 (5)     | 42 | 1 (2)     |
| Month 4                            | 69 | 1 (1)     | 25 | 0 (0)     |
| Month 6                            | 50 | 0 (0)     | 22 | 0 (0)     |
| Month 8                            | 35 | 2 (6)     | 10 | 0 (0)     |
| Month 10                           | 29 | 1 (3)     | 17 | 0 (0)     |
| Month 12                           | 28 | 0 (0)     | 8  | 0 (0)     |
| Month 14                           | 25 | 1 (4)     | 6  | 0 (0)     |
| Month 16                           | 23 | 0 (0)     | 3  | 0 (0)     |
| Month 18                           | 17 | 0 (0)     | 8  | 0 (0)     |
| Total individual patientsb         | 116| 7 (6)     | 49 | 1 (2)     |
| *P* valuec                         |    |           |    | 0.438     |

*aLast nonmissing measurement prior to start of first post-study drug chemotherapy. Months 2–18 represent 2-month time windows following first date of chemotherapy. Timing of hematology laboratory values is determined according to start of chemotherapy, not by protocol-defined visits.

*bTotal individual patients with any post-baseline laboratory measurement.

*cP values reflect data in the row above (total individual patients with post-baseline laboratory measurement).
Fig. 2. Maximum percentage decrease from baseline values for hemoglobin (A), neutrophils (B), platelets (C), and platelets by prior docetaxel treatment (D).
223 group and 2.4 months for the placebo group. The median duration of first docetaxel therapy was 5.0 months in the radium-223 group and 4.5 months in the placebo group (Table III).

Hematologic assessments for patients with docetaxel following study treatment were consistent with the overall chemotherapy post-study drug subgroup. Median hematologic values remained generally constant over time, regardless of prior docetaxel exposure (Supplementary Tables S VI and S VII). Maximum percentage decreases from baseline in hemoglobin and neutrophils were similar between radium-223 and placebo patients (Supplementary Fig. S1A and B). The maximum percentage decrease in platelet counts was somewhat greater in radium-223 patients, consistent with the entire chemotherapy post-study drug subgroup, and did not appear to be associated with prior docetaxel treatment (prior docetaxel: yes, $P = 0.279$; no $P = 0.197$) (Supplementary Fig. S1C and D). The decrease in platelets in this subgroup and in the overall chemotherapy post-study drug subgroup was likely a consequence of radium-223 treatment, rather than of docetaxel following radium-223, as a higher incidence of grades 3–4 thrombocytopenia (although in <10% of patients) was reported with radium-223 versus placebo in ALSYMPCA [4].

For the docetaxel post-study drug subgroup, median overall survival from start of docetaxel was 17.5 and 16.7 months in patients previously treated with radium-223 or placebo, respectively. Prostate cancer-related death remained the most common cause of death in both treatment groups (Supplementary Table S VIII).

**DISCUSSION**

In this exploratory analysis, no safety concerns were identified with chemotherapy following radium-223, and no detrimental effects on overall survival were observed. These findings represent an initial step in defining how radium-223 affects the safety of subsequent chemotherapy, an issue that will be further addressed as radium-223 is used earlier in the treatment of patients with CRPC [16].

Of note, among the 142 radium-223 patients who received subsequent chemotherapy, most (79%) had received all six planned radium-223 doses, which is the recommended regimen in the product label and as used in the ALSYMPCA trial. Interestingly, a substantial proportion (61%) of patients received docetaxel before radium-223 and received subsequent chemotherapy following radium-223 treatment; 39% of patients who received chemotherapy following radium-223 were chemotherapy naive. Data presented here indicate that the use of chemotherapy following radium-223 is feasible regardless of prior docetaxel use.

Several limitations of this exploratory analysis need to be considered in interpreting its findings regarding broader questions of treatment sequencing. The chemotherapy post-study drug subgroup of ALSYMPCA may have been affected by post-randomization factors; therefore, the comparability of radium-223 and placebo patients who received subsequent chemotherapy is not assured by the initial randomization of the original study. Hematologic data used in the exploratory analysis were recorded at intervals specified by the ALSYMPCA follow-up schedule, rather than as time points determined for the optimal assessment of the hematologic toxicity related to chemotherapy. Consequently, sample collections may not have coincided with the expected nadirs in hemoglobin, neutrophil, and platelet counts. In addition, the median values reported may obscure a small number of patients who may have had severe but transient myelosuppression following chemotherapy. Data for

| TABLE VI. Deaths During or Within 30 Days of Completing Chemotherapy in the Chemotherapy Post-Study Drug Subgroup |
|---------------------------------------------------------------|
|                                                      | Radium-223 | Placebo |
|                                                      | n = 142    | n = 64  |
| Number (%) of deaths while still on chemotherapy          | 41 (29)    | 21 (33) |
| Prostate cancer-related death, n (%)                      | 37 (90)    | 20 (95) |
| - Skeletal metastases                                     | 31 (76)    | 15 (71) |
| - Other metastases                                       | 6 (15)     | 5 (24)  |
| Non-prostate cancer-related death, n (%)                  | 4 (10)     | 1 (5)   |
| - Bronchopneumonia                                       | 1 (2)      | 0 (0)   |
| - Cardiopulmonary failure                                | 0 (0)      | 1 (5)   |
| - Cerebral hemorrhage                                    | 1 (2)      | 0 (0)   |
| - Respiratory failure                                    | 1 (2)      | 0 (0)   |
| - Sepsis                                                 | 1 (2)      | 0 (0)   |
precise dosing and intervals of the chemotherapy regimens were not collected. Because of a high patient dropout rate during the follow-up period, the analysis was not designed with the statistical power to fully assess hematologic safety between radium-223 and placebo in the chemotherapy post-study drug subgroup. The safe use of other agents following treatment with radium-223 remains to be studied. Agents with potential myelosuppressive effects include cabazitaxel, and poly(ADP-ribose) polymerase inhibitors such as olaparib.

Radium-223 significantly prolonged median overall survival compared with placebo, irrespective of prior treatment with docetaxel (prior docetaxel: HR 0.70; 95%CI: 0.56–0.88; P = 0.002; no prior docetaxel: HR 0.69; 95%CI: 0.52–0.92; P = 0.01) [11]. The ALSYMPCA trial also showed that patients who received prior docetaxel had more hematologic toxicity than those who were docetaxel naïve, although the incidence of grade three or four thrombocytopenia was less than 10% in both groups [4,11]. The data in the present safety analysis in the chemotherapy post-study drug subgroup suggest that chemotherapy may be safely given after radium-223, an important finding especially if radium-223 is to be considered earlier in the course of the disease. Additionally, survival with chemotherapy was similar between treatment groups, suggesting that prior treatment with radium-223 did not compromise the efficacy of subsequent chemotherapy. At this time, although we know from ALSYMPCA that radium-223 can be safely administered before or after docetaxel, and that docetaxel may be safely administered before radium-223 [11], we support the concept of prospective studies to fully understand the efficacy and safety of chemotherapy following radium-223 treatment.

CONCLUSION

This exploratory analysis of ALSYMPCA data represents the first and only evaluation of the safety of chemotherapy following radium-223 treatment, and identifies no significant safety concerns; thus, the use of chemotherapy after radium-223 is not contraindicated.

FINANCIAL DISCLOSURES

OS reports grants and personal fees from Bayer and Bayer AS (formerly Algeta ASA) during the conduct of the study. PH has nothing to disclose. REC reports a consultancy relationship with Novartis. SN reports an advisory relationship with Bayer. NJV reports a consultancy relationship with Bayer, outside the submitted work. OP reports employment with Bayer HealthCare. KS reports employment with Bayer AS (formerly Algeta ASA). MT reports a statistical consultancy relationship with Bayer HealthCare, during the conduct of the study and outside the submitted work. CP reports grants and personal fees from Bayer and personal fees from Janssen, BNIT, Sanofi-Aventis, and Takeda, outside the submitted work.

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