1.5-Year Posttreatment Follow-up of Radium-223 Dichloride Safety in Patients With Castration-Resistant Prostate Cancer and Symptomatic Bone Metastases From ALSYMPCA: Characterization of Hematologic Safety Profiles

BACKGROUND

- Myelosuppression, a frequent complication in patients with metastatic castration-resistant prostate cancer (CRPC), may result from the disease itself or from its treatment¹
- Several agents, including docetaxel and cabazitaxel, approved for use in patients with CRPC have been associated with increased risk of myelotoxicity^{2,3}
- Radium-223 dichloride (radium-223) is a first-in-class alpha-emitting radiopharmaceutical with a potent and highly targeted cytotoxic effect on bone metastases⁴
- High linear energy transfer radiation causes predominantly nonrepairable double-stranded DNA breaks^{5,6}
- Unlike beta-emitting radiopharmaceuticals, including strontium-89 and samarium-153, which are associated with significant myelotoxicity, the short range of alpha particles (< 100 μ M, 2-10 cell diameters) may spare hematopoietic bone marrow and produce a more tolerable safety profile^{5,6}
- Early experience with radium-223 suggested a low incidence of clinically significant myelosuppression⁷
- ALSYMPCA phase 3 study (Figure 1)



- In ALSYMPCA,
- Radium-223 improved median overall survival versus placebo by 3.6 months $(HR = 0.70; 95\% CI, 0.58-0.83)^{8}$
- Radium-223 was well tolerated and was associated with a low incidence of hematologic adverse events (AEs), similar to that of placebo⁸ (Table 1)

Table 1. ALSYMPCA Hematologic AEs of Interest (Safety Population,* N = 901)						
Dationts With AEs	All Gra	des	Grade 3 or 4			
n (%)	Radium-223, n = 600	Placebo, n = 301	Radium-223, n = 600	Placebo, n = 301		
Anemia	187 (31)	92 (31)	76 (13)	39 (13)		
Neutropenia	30 (5)	3 (1)	13 (2)	2 (1)		
Thrombocytopenia	69 (12)	17 (6)	38 (6)	6 (2)		

pmprised patients who received at least 1 dose; 1 patient in the placebo group received 1 and is included in the radium-223 safety analysis. AE = adverse event.

- metastases⁸
- previous 12 weeks⁸
- profile

- injection)

- (Figure 2)

Figure 2. A	LSYN
2008	2
First patient's first visit	

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> Based on ALSYMPCA, radium-223 is approved for the treatment of patients with CRPC with symptomatic bone metastases and no known visceral

– Symptomatic: requiring the use of opioid or nonopioid analgesic or external beam radiation therapy (EBRT) for cancer-related bone pain within the

• Long-term safety monitoring of radium-223 is essential for a complete safety

 Here, we present the 1.5-year long-term hematologic safety analysis of radium-223 from ALSYMPCA

METHODS

 All patients in ALSYMPCA were to enter a designated follow-up period of approximately 2.5 years (starting 4 wk after last injection until 3 y after first

 Patients were to be evaluated at 9 follow-up visits (every other month for the first 0.5 y, every 4 mo during years 1 and 2) (Figure 1)

• Only treatment-related AEs were reported

 AEs were graded according to the Common Terminology Criteria for Adverse Events Version 3.0

 Additional long-term safety data were assessed by specific diseases including acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), aplastic anemia, and new primary cancer in bone or other organs

• Data reported here are from ~1.5 years after last patients' final injection



RESULTS

- Of 921 patients in the intent-to-treat population (radium-223, n = 614; placebo, n = 307), 574 entered follow-up (radium-223, n = 406; placebo, n = 168)
- Demographics and baseline characteristics of patients entering follow-up were similar between treatment groups (Table 2)

Table 2. Patient Demographics and Baseline Clinical Characteristics (Intent-to-Treat Patients Who Entered Designated Long-term Follow-up*)					
Characteristic	Radium-223, n = 406	Placebo, n = 168			
Age Median (range), y	71 (49-90)	70 (44-86)			
Race, n (%) Caucasian	376 (93)	159 (95)			
Total ALP, n (%) < 220 U/L ≥ 220 U/L	252 (62) 154 (38)	115 (69) 53 (32)			
Current use of bisphosphonates, n (%) Yes	170 (42)	73 (44)			
Prior docetaxel use, n (%) Yes	234 (58)	94 (56)			
ECOG performance status score, n (%) < 1	367 (90)	155 (92)			
 WHO ladder for cancer pain, n (%) 0-1 (no pain or mild pain; no opioid use) 2 (moderate pain; occasional opioid use) 3 (severe pain; regular daily opioid use) 	192 (47) 106 (26) 108 (27)	84 (50) 47 (28) 37 (22)			
EBRT within 12 weeks of screening, n (%) Yes	54 (13)	21 (13)			
Extent of disease, n (%) < 6 metastases 6-20 metastases > 20 metastases/superscan	87 (22) 174 (43) 143 (35)	30 (18) 88 (52) 50 (30)			
Hemoglobin, median (range), g/L	13 (9-16)	12 (9-16)			
Albumin, median (range), g/L	40 (25-53)	41 (24-50)			
PSA, median (range), μg/L	104 (4-5837)	113 (2-3958)			
LDH, median (range), U/L	274 (76-1969)	299 (132-1714)			
Total ALP, median (range), U/L	162 (32-2681)	164 (29-2166)			

*Percentages may not sum to 100 due to rounding ALP = alkaline phosphatase; EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; WHO = World Health Organization.

- Most patients entering follow-up had completed all 6 injections of study treatment (radium-223, 335/406 [83%]; placebo, 119/168 [71%])
- Median follow-up time for patients entering follow-up was 10.4 months with radium-223 and 7.6 months with placebo
- 322/406 (79%) radium-223 patients and 145/168 (86%) placebo patients were withdrawn from the study during the follow-up period
- Primary reasons (for radium-223 and placebo, respectively) include death (65%, 59%), patient request (6%, 4%), disease progression (2%, 5%), and other (2%, 16%)
- In the disease-specific follow-up, there were no reports of AML, MDS, or new primary bone cancer
- New primary cancers in other organs were identified in 2 radium-223 patients and 3 placebo patients and considered not related to study drug (Table 3)

investigator request (2%, 2%), lost to follow-up (2%, 0%), AEs (1%, 1%),

Table 3. Posttreatment Primary Cance	er in Other Organs Am
in Safety Population Who Entered De	esignated Long-term F

Radium-223, N = 404	Placebo, N = 167
Bladder cancer (follow-up visit 1)	Squamous cell carcinoma of the left hand (follow-up visit 2)
Lymph node metastases not originating from prostate cancer (follow-up visit 6)	Adenocarcinoma rectum and adenocarcinoma sigmoideum (follow-up visit 4)
	Skin cancer (follow-up visit 7)

*571 patients entered the designated follow-up period (radium-223, n = 404; placebo, n = 167

HEMATOLOGIC SAFETY PROFILE

- The most common treatment-related AEs reported among radium-223 patients during follow-up were hematologic (Table 4)
- In-depth analyses of treatment-related hematologic AEs are shown in Tables 5 and 6

Table 4. Hematologic Treatment-Related AEs* Reported Among Patients in Safety Population Who Entered Designated Long-term Follow-up ⁺							
	Radium-223, N = 404 Placebo, N = 167						
Posttreatment Follow-up AE, n (%)	All Grades	Grades 3-4	All Grades	Grades 3-4			
Anemia	11 (3)	5 (1)	5 (3)	1 (1)			
Aplastic anemia	1 (< 1)	1 (< 1)	0	0			
Leukopenia	2 (< 1)	2 (< 1)	0	0			
Neutropenia	2 (< 1)	2 (< 1)	0	0			
Thrombocytopenia	4 (1)	0	0	0			
Transmont related AEs are AEs considered related to study drug by the investigator; some patients have more than 1 AE recorded							

*Treatment-related AEs are AEs considered related to study drug by the investigator; some patients have more than 1 AE recorded. [†]571 patients entered the designated follow-up period (radium-223, n = 404; placebo, n = 167).

- Treatment-related leukopenia, neutropenia, or thrombocytopenia occurred in 7 radium-223 patients and no placebo patients (Table 5)
- Of the 7 patients, 6 had received prior docetaxel chemotherapy, and 4 had extent of disease (EOD) grade 3

Table 5. Data and Characteristics for the 7 Radium-223 Patients With Either Leukopenia, Neutropenia, or Thrombocytopenia

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Hematologic AE (Grade)	Thrombo- cytopenia (Grade 1)	Leukopenia/ Neutropenia (Grade 3)	Leukopenia (Grade 4)	Thrombo- cytopenia (Grade 2)	Thrombo- cytopenia (Grade 2)	Neutropenia (Grade 3)	Thrombo- cytopenia (Grade 1)
Age, y	65	68	74	61	64	79	72
Baseline ECOG score*	1	1	1	0	1	0	1
WHO ladder score for cancer pain ⁺	3	1	1	1	3	3	2
EOD (grades) [‡]	3	3	3	2	1	1	3
Prior docetaxel	Yes	Yes	Yes	Yes	Yes	No	Yes
Concomitant cancer treatment	LHRHa, zoledronic acid	LHRHa, zoledronic acid	LHRHa, prednisolone	LHRHa	LHRHa, dexamethasone, diethylstilbestrol, zoledronic acid	LHRHa, zoledronic acid	LHRHa, prednisone
Radium-223 injections received, n	6	6	5	6	6	5	6
Status of follow-up	Completed	Withdrew (patient request)	Withdrew (death)	Completed	Withdrew (death)	Withdrew (death)	Withdrew (disease progression)

*0 = fully active; 1 = physically strenuous activity restricted.

⁺1 = mild, no opioid use; 2 = moderate, occasional opioid use; 3 = severe, regular daily opioids.

 $^{+}1 = < 6$ metastases; 2 = 6-20 metastases; 3 = > 20 metastases

AE = adverse event; ECOG = Eastern Cooperative Oncology Group; EOD = extent of disease; LHRHa = luteinizing hormone-releasing hormone analog; WHO = World Health Organization.

ong Patients

• Treatment-related grade 3-4 anemia occurred in 5 radium-223 patients and 1 placebo patient (Table 6)

Table 6. Data and Characteristics for Patients With Grade 3-4 Anemia						
Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Treatment Group	Placebo	Radium-223	Radium-223	Radium-223	Radium-223	Radium-223
Age, y	60	55	71	78	72	69
Baseline ECOG score*	1	0	1	1	1	2
WHO ladder score for cancer pain ⁺	1	1	3	2	1	2
EOD (grades) [‡]	3	3	4	2	3	3
Prior docetaxel	Yes	Yes	Yes	No	Yes	No
Concomitant cancer treatment	None	Dexamethasone, LHRHa	Dexamethasone, LHRHa	LHRHa	Zoledronic acid	Pamidronate disodium, LHRHa
Injections received, n	6	5	6	6	6	6
Status of follow-up	Withdrew (death)	Withdrew (disease progression)	Withdrew (death)	Withdrew (death)	Withdrew (death)	Withdrew (patient request)

*0 = fully active; 1 = physically strenuous activity restricted.

 $^{\dagger}1 = mild$, no opioid use; 2 = moderate, occasional opioid use; 3 = severe, regular daily opioids. $^{+}1 = < 6$ metastases; 2 = 6-20 metastases; 3 = > 20 metastases.

ECOG = Eastern Cooperative Oncology Group; EOD = extent of disease; LHRHa = luteinizing hormone-releasing hormone analog; WHO = World Health Organization.

- Aplastic anemia was reported in 1 radium-223 patient (patient 5 in Table 6)
- Aplastic anemia was diagnosed by bone marrow biopsy and was considered probably related to study drug by the investigator

CONCLUSIONS

- Long-term follow-up of ~1.5 years after last patient's last injection showed no new safety concerns
- Hematologic toxicity appeared to be associated with prior docetaxel and greater EOD, and was not affected by the number of radium-223 injections received

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