Abstract MP52-04

2-Year Follow-up of Radium-223 Re-treatment in an International, Open-Label, Phase 1/2 Study in Patients With Castration-Resistant Prostate Cancer and Bone Metastases

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BACKGROUND

Radium-223 Dichloride (Radium-223)

- First targeted alpha therapy approved for patients with metastatic castration-resistant prostate cancer (mCRPC) (**Figure 1**)[1]
  - Shown to improve survival versus placebo in the phase 3 ALSYMPCA trial[2]
  - Well tolerated with low rates of myelosuppression[2]

Figure 1. Radium-223 Mechanism of Action

- Efficacy and safety from ALSYMPCA are based on a dosing regimen of 1 injection (55 kBq/kg IV) every 4 weeks for a total of 6 injections[1]
- Early results of this international, open-label, phase 1/2 study (re-treatment study; NCT01934790) showed that re-treating patients with up to 6 additional radium-223 injections was well tolerated with favorable effects on disease progression[5]

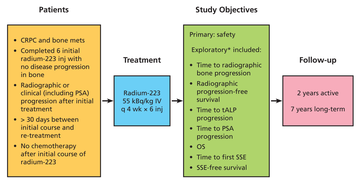
RATIONALE AND OBJECTIVES

- Re-treatment with radium-223 may be well tolerated and provide further benefit to patients who received an initial course of 6 radium-223 injections
- Reported here are safety and efficacy results from a 2-year follow-up of the radium-223 re-treatment study (NCT01934790) in patients with bone-metastatic CRPC

METHODS

- Study design is presented in **Figure 2**

Figure 2. Radium-223 Re-treatment Study Design



*Exploratory end points were calculated from start of radium-223 re-treatment. CRPC = castration-resistant prostate cancer; inj = injections; mets = metastases; OS = overall survival; PSA = prostate-specific antigen; SSE = symptomatic skeletal event; tALP = total alkaline phosphatase.

Eligibility

- Eligible patients had CRPC and bone metastases and previously completed 6 initial radium-223 injections with
  - No progression in bone (according to Prostate Cancer Working Group 2 [PCWG2] criteria) during first treatment course
  - Radiographic progression or clinical progression (defined as 2 subsequent values showing prostate-specific antigen increase [≥ 2 ng/mL] or substantial worsening of pain) after initial treatment
  - Adequate hematologic values
- Patients were ineligible if they had radium-223–related serious or grade 3 or 4 adverse events (AEs), during or after initial treatment, that did not resolve or led to treatment discontinuation
- No chemotherapy after initial course of radium-223 was permitted
- No concomitant chemotherapy or systemic radioisotopes (or investigational drugs) were permitted
- Other concomitant agents were permitted at investigator's discretion

Study Dates

- 2-year active follow-up period began at final data cutoff (June 11, 2015); last patient last visit (LPLV) was April 12, 2017
  - Efficacy data reported here are cumulative from first patient first visit (FPFV) (December 22, 2013) to LPLV (N = 44)
  - Safety data reported here are from active follow-up (final data cutoff to LPLV; n = 34)

RESULTS

Patients

- 44 patients were re-treated with radium-223 (**Table 1**)
  - Median time from end of initial radium-223 treatment to re-treatment was 6 months (range, 1.2-17.1 mo)
  - All patients had ≥ 2 prior hormonal regimens; 32 of 44 (73%) had failed hormonal agents (ie, abiraterone or enzalutamide)
  - 20 of 44 (45%) had ≥ 1 prior chemotherapy regimen
  - 29 of 44 (66%) completed re-treatment with all 6 injections
- 34 of 44 (77%) patients entered the 2-year active follow-up

Table 1. Demographics and Baseline Characteristics

	Re-treatment N = 44
Age, median (range), y	71 (52-91)
ECOG PS, n (%)	
0	14 (32)
1	27 (61)
2	3 (7)
Extent of disease, bone metastases, n (%)	
< 6	18 (41)
6-20	15 (34)
> 20, not superscan	6 (14)
Superscan	5 (11)
Prior systemic anticancer therapies, n (%)	
Docetaxel	20 (45)
Abiraterone	27 (61)
Enzalutamide	13 (30)
Prior bone-supportive therapies, n (%)	
Bisphosphonates	5 (11)
Denosumab	21 (48)
Laboratory values, median (range)	
Hemoglobin, g/dL	12 (9-16)
Albumin, g/L	39 (32-44)
PSA, µg/L	68 (< 1-2349)
LDH, U/L	203 (115-532)
tALP, U/L	85 (29-705)

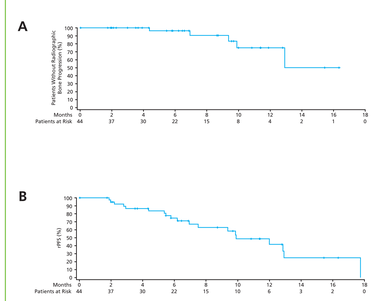
ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; PSA = prostate-specific antigen; tALP = total alkaline phosphatase.

Safety

- No new safety concerns were observed during active follow-up
  - One treatment-related AE was reported: anemia in 1 of 34 (3%) patients; this event was a worsening of an existing AE
  - No serious drug-related AEs were reported
- At the end of active follow-up, 2 of 34 (6%) patients had grade 1 anemia; no patients had any grade 1-4 neutropenia or thrombocytopenia
- One new primary malignancy was reported: basal cell carcinoma in 1 of 34 (3%) patients; it was diagnosed 12 days after the first radium-223 dose and was determined by the investigator to be unrelated to the study drug
- 28 of 44 (64%) enrolled patients died; 23 of 28 (82%) deaths occurred during active follow-up; the most common cause of death was progressive disease

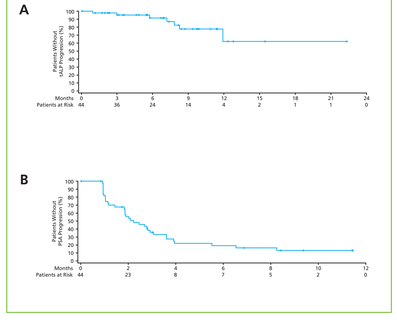
Exploratory Efficacy

Figure 3. Kaplan-Meier Analysis of Time to Radiographic Bone Progression (A) and Radiographic Progression-Free Survival (rPFS) (B)



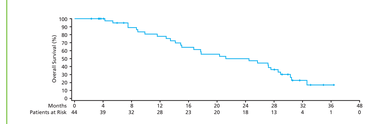
- Median time to radiographic bone progression was not reached (**Figure 3A**)
  - Maximum follow-up time for radiographic bone progression was 16.3 months
  - 5 of 44 (11%) patients had radiographic bone progression
- Median radiographic progression-free survival (rPFS) was 9.9 months (**Figure 3B**)
  - Maximum follow-up time for rPFS was 17.7 months
  - 19 of 44 (43%) patients had an rPFS event (radiographic progression or death)

Figure 4. Kaplan-Meier Analysis of Time to Total Alkaline Phosphatase (tALP) (A) and Prostate-Specific Antigen (PSA) (B) Progression



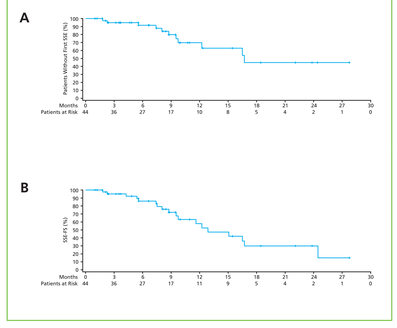
- Median time to tALP progression was not reached by the end of the 2-year follow-up (**Figure 4A**)
  - Maximum follow-up time for tALP progression was 22.3 months
  - 7 of 44 (16%) patients had tALP progression
- Median time to PSA progression was 2.2 months (**Figure 4B**)
  - Maximum follow-up time for PSA progression was 11.4 months
  - 35 of 44 (80%) patients had PSA progression

Figure 5. Kaplan-Meier Analysis of Overall Survival



- Median overall survival (OS) was 24.4 months (**Figure 5**)
  - Median follow-up for OS was 31.6 months
  - 28 of 44 (64%) patients died

Figure 6. Kaplan-Meier Analysis of Time to First Symptomatic Skeletal Event (SSE) (A) and SSE-Free Survival (SSE-FS) (B)



- Median time to first symptomatic skeletal event (SSE) was 16.7 months (**Figure 6A**)
  - 14 of 44 (32%) patients experienced at least 1 SSE
    - 3 patients were censored because of new cancer treatment, leaving 11 of 44 (25%) patients for inclusion in the Kaplan-Meier analysis
  - First SSEs were external beam radiation therapy for bone pain (10 of 44 [23%]), pathologic bone fracture (3 of 44 [7%]), and spinal cord compression (1 of 44 [2%])
- Median SSE-free survival (SSE-FS) was 12.8 months (**Figure 6B**)
  - 18 of 44 (41%) patients had an SSE-FS event (SSE or death)
- Maximum follow-up time for SSEs and SSE-FS was 27.8 months

CONCLUSIONS

- Re-treatment with radium-223 was well tolerated in this selected patient population and led to minimal hematologic toxicity
- OS and SSE-FS results indicate that re-treatment with radium-223 may be an option for CRPC patients with bone metastases who previously benefited from a first radium-223 treatment course; this requires further evaluation in larger prospective trials

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