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Three-year Safety of Radium-223 Dichloride in Patients with Castration-resistant Prostate Cancer and Symptomatic Bone Metastases from Phase 3 Randomized Alpharadin in Symptomatic Prostate Cancer Trial

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Abstract

Background: In Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, radium-223 versus placebo prolonged overall survival with favorable safety in castration-resistant prostate cancer patients with symptomatic bone metastases. Long-term radium-223 monitoring underlies a comprehensive safety and risk/benefit assessment.
Objective: To report updated ALSYMPCA safety, including long-term safety up to 3 yr after the first injection.
Design, setting, and participants: Safety analyses from phase 3 randomized ALSYMPCA trial included patients receiving ≥1 study-drug injection (600 radium-223 and 301 placebo). Patients (405 radium-223 and 167 placebo) entered long-term safety follow-up starting 12 wk after the last study-drug injection, to 3 yr from the first injection. Forty-eight of 405 (12%) radium-223 and 12/167 (7%) placebo patients completed follow-up, with evaluations every 2 mo for 6 mo, then every 4 mo until 3 yr.
Outcome measurements and statistical analysis: All adverse events (AEs) were collected until 12 wk after the last injection; subsequently, only treatment-related AEs were

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collected. Additional long-term safety was assessed by development of acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), aplastic anemia, and secondary malignancies. Data analysis used descriptive statistics.

Results and limitations: During treatment to 12 wk following the last injection, 564/600 (94%) radium-223 and 292/301 (97%) placebo patients had treatment-emergent AEs (TEAEs). Myelosuppression incidence was low. Grade 3/4 hematologic TEAEs in radium-223 and placebo groups were anemia (13% vs 13%), neutropenia (2% vs 1%), and thrombocytopenia (7% vs 2%). Ninety-eight of 600 (16%) radium-223 and 68/301 (23%) placebo patients experienced grade 5 TEAEs. Long-term follow-up showed no AML, MDS, or new primary bone cancer; secondary non–treatment-related malignancies occurred in four radium-223 and three placebo patients. One radium-223 patient had aplastic anemia 16 mo after the last injection. No other cases were observed. Limitations include short (3-yr) follow-up.

Conclusions: Final long-term safety ALSYMPCA analysis shows that radium-223 remained well tolerated, with low myelosuppression incidence and no new safety concerns.

Patient summary: Updated Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial findings show that radium-223 remained well tolerated during treatment and up to 3 yr after each patient's first injection.

1. Introduction

Radium-223 is a first-in-class targeted alpha therapy for castration-resistant prostate cancer (CRPC) and symptomatic bone metastases with minimal myelosuppressive effects [1,2]. The relatively large size of alpha particles, coupled with the high linear energy transfer of emitted particles, results in a short path length and localized area of cell destruction (<100 μm; 2–10 cell diameters), inducing predominantly nonrepairable double-stranded DNA breaks [3]. Unlike beta particles emitted from strontium-89 and samarium-153, the much shorter range of alpha particles spares hematopoietic bone marrow and produces a more tolerable safety profile.

Agents approved for use in patients with CRPC have been associated with significant toxicities. These include the taxanes docetaxel and cabazitaxel, which have a range of chemotherapy-related effects [4–6]. Beta-emitting radiopharmaceuticals such as strontium-89 and samarium-153, used for pain palliation in CRPC patients with bone metastases, are associated with significant myelosuppression [1,2,7,8].

In the phase 3 Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, radium-223 plus best standard of care (BSoC), versus placebo plus BSoC, prolonged median overall survival by 3.6 mo (14.9 vs 11.3 mo; $p < 0.001$) [9]. Additionally, radium-223 was well tolerated and associated with a low incidence of grade 3 or 4 myelosuppression (radium-223 vs placebo: anemia, 13% vs 13%; neutropenia, 2% vs 1%; and thrombocytopenia, 7% vs 2%). Based on ALSYMPCA efficacy and safety results, radium-223 was approved for treatment of patients with CRPC and symptomatic bone metastases and no known visceral metastases.

Although these radium-223 safety data are reassuring, long-term safety monitoring of radium-223 is essential to provide a comprehensive safety profile, including post-treatment adverse event (AE) data, and to afford clinicians a higher level of confidence in radium-223 overall safety. This article reports radium-223 final safety data from ALSYMPCA trial. Data presented are updated from previously reported safety results [9], with additional long-term safety from 12 wk after each patient's last injection up to 3 yr after their first injection.

2. Patients and methods

2.1. Patients and study design

Complete ALSYMPCA study methods were previously reported [9,10] and are summarized here (ClinicalTrials.gov number, NCT00699751). Eligible patients had symptomatic and progressing CRPC and ≥2 bone metastases with no visceral metastases, Eastern Cooperative Oncology Group performance status ≤2, life expectancy ≥6 mo, and adequate baseline hematologic, renal, and liver functions. Patients either had previous docetaxel treatment or were unsuitable for or declined docetaxel. Patients were randomized 2:1 to radium-223 50 kBq/kg (55 kBq/kg following the National Institute of Standards and Technology [NIST] update) [11] plus BSoC or placebo plus BSoC every 4 wk for 24 wk (six injections; Fig. 1). BSoC was defined as routine care provided at each center and included external beam radiation therapy for bone pain as indicated. Randomization was done with an interactive voice response system, taking into account trial stratification factors. After study unblinding, placebo patients who still met the eligibility criteria were offered radium-223 (placebo crossover patients).

The long-term safety follow-up period started 12 wk after the last study-drug injection (end of treatment) and continued until 3 yr from the first study-drug injection. During follow-up, patients were evaluated every 2 mo for 6 mo, then every 4 mo for up to 3 yr (Fig. 1).

The primary ALSYMPCA end point was overall survival; secondary end points included acute and long-term safety.

2.2. Study assessments

Safety assessments included AEs, graded according to Common Terminology Criteria for Adverse Events version 3.0. Treatment-emergent AEs (TEAEs) included all AEs that started after the first injection up to 12 wk after the last injection. Post-treatment follow-up AEs were those that started >12 wk after the last injection during long-term safety follow-up and were reported only if considered treatment related by the investigator. Additional long-term safety data were assessed by occurrence of specific diseases, including acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), aplastic

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