Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial

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BACKGROUND
In the previously reported ALSYMPCA trial in patients with castration-resistant prostate cancer and symptomatic bone metastases, overall survival was significantly longer in patients treated with radium-223 dichloride (radium-223) than in patients treated with placebo. In this study, we investigated safety and overall survival in radium-223 treated patients in an early access programme done after the ALSYMPCA study and before regulatory approval of radium-223.

METHODS
We did an international, prospective, interventional, open-label, single-arm, phase 3b study. Enrolled patients were aged 18 years or older with histologically or cytologically confirmed progressive bone-predominant metastatic castration-resistant prostate cancer with two or more skeletal metastases on imaging (with no restriction as to whether they were symptomatic or asymptomatic; without visceral disease but lymph node metastases were allowed). Patients received intravenous injections of radium-223, 50 kBq/kg (current recommendation 55 kBq/kg after implementation of National Institute of Standards and Technology update on April 18, 2016) every 4 weeks for up to six injections. Other concomitant anticancer therapies were allowed. Primary endpoints were safety and overall survival. The safety and efficacy analyses were done on all patients who received at least one dose of the study drug. The study has been completed, and we report the final analysis here. This study is registered with ClinicalTrials.gov, number NCT01618370, and the European Union Clinical Trials Register, EudraCT number 2012-000075-16.

FINDINGS
Between July 22, 2012, and Dec 19, 2013, 839 patients were enrolled from 113 sites in 14 countries. 696 patients received one or more doses of radium-223; 403 (58%) of these patients had all six planned injections. Any-grade treatment-emergent adverse events occurred in 523 (75%) of 696
patients; any-grade treatment-emergent adverse events deemed to be related to treatment were reported in 281 (40%) patients. The most common grade 3 or worse treatment-related treatment-emergent adverse events were anaemia in 32 (5%) patients, thrombocytopenia in 15 (2%) patients, neutropenia in ten (1%) patients, and leucopenia in nine (1%) patients. Any grade of serious adverse events were reported in 243 (35%) patients. Median follow-up was 7.5 months (IQR 5-11) and 210 deaths were reported; median overall survival was 16 months (95% CI 13-not available [NA]). In an exploratory analysis of overall survival with predefined factors, median overall survival was longer for:

- patients with baseline alkaline phosphatase concentration less than the upper limit of normal (ULN; median NA, 95% CI 16 months-NA) than for patients with an alkaline phosphatase concentration equal to or greater than the ULN (median 12 months, 11-15);
- patients with baseline haemoglobin levels 10 g/dL or greater (median 17 months, 14-NA) than for patients with haemoglobin levels less than 10 g/dL (median 10 months, 8-14);
- patients with a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (median NA, 17 months-NA) than for patients with an ECOG PS of 1 (median 13 months, 11-NA) or an ECOG PS of 2 or more (median 7 months, 5-11); and for patients with no reported baseline pain (median NA, 16 months-NA) than for those with mild pain (median 14 months, 13-NA) or moderate-severe pain (median 11 months, 9-13). Median overall survival was also longer in patients who received radium-223 plus abiraterone, enzalutamide, or both (median NA, 95% CI 16 months-NA) than in those who did not receive these agents (median 13 months, 12-16), and in patients who received radium-223 plus denosumab (median NA, 15 months-NA) than in patients who received radium-223 without denosumab (median 13 months, 12-NA).

**INTERPRETATION**

Our findings show that radium-223 can be safely combined with abiraterone or enzalutamide, which are now both part of the standard of care for patients with metastatic castration-resistant prostate cancer. Furthermore, our findings extend to patients who were asymptomatic at baseline, unlike those enrolled in the pivotal ALSYMPCA study. The findings of prolonged survival in patients treated with concomitant abiraterone, enzalutamide, or denosumab require confirmation in prospective randomised trials.

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