Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial

Oliver Sartor, Robert Coleman, Sten Nilsson, Daniel Heinrich, Svein I Helle, Joe M O'Sullivan, Sophie D Fosså, Aleš Chodacki, Paweł Wiechno, John Logue, Anders Widmark, Dag Clement Johannessen, Peter Hoskin, Nicholas D James, Arne Solberg, Isabel Syndikus, Nicholas J Vogelzang, C Gillies O'Bryan-Tear, Minghua Shan, Øyvind S Bruland, Christopher Parker

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Tulane Cancer Center, New Orleans, LA, USA (Prof O Sartor MD); **Weston Park Hospital, Sheffield Cancer Research Centre, Sheffield, UK** (Prof R Coleman MD); **Karolinska University Hospital, Radiumhemmet, Stockholm, Sweden** (Prof S Nilsson MD); **Akershus University Hospital, Department of Oncology, Lørenskog, Norway** (D Heinrich MD); **Haukeland University Hospital, Bergen, Norway** (S I Helle MD); **Centre for Cancer Research and Cell Biology, Queen's University, Belfast, UK** (Prof J M O'Sullivan MD); **Oslo University Hospital, Radiumhospital, Oslo, Norway** (Prof S D Fosså MD); **Hospital Chomutov, Nuclear Medicine Department, Chomutov, Czech Republic** (A Chodacki MD); **Centrum Onkologii–Instytut im Marii Skodowskiej-Curie, Warsaw, Poland** (P Wiechno MD); **Christie Hospital, Manchester, UK** (J Logue FRCR); **Umeå University, Department of Radiation Sciences, Oncology, Sweden** (Prof A Widmark MD); **Ullevål University Hospital, Oslo, Norway** (D C Johannessen MD); **Mount Vernon Hospital Cancer Centre, Northwood, Middlesex, UK** (Prof P Hoskin MD); **Cancer Research Unit, University of Warwick, Coventry, and University Hospital, Birmingham NHS Trust, Birmingham, UK** (Prof N D James MD); **St Olavs Hospital, Trondheim, Norway** (A Solberg MD); **Clatterbridge**

Summary

Background Bone metastases frequently cause skeletal events in patients with metastatic castration-resistant prostate cancer. Radium-223 dichloride (radium-223) selectively targets bone metastases with high-energy, short-range α-particles. We assessed the effect of radium-223 compared with placebo in patients with castration-resistant prostate cancer and bone metastases.

Methods In this phase 3, double-blind, randomised ALSYMPCA trial, we enrolled patients who had symptomatic castration-resistant prostate cancer with two or more bone metastases and no known visceral metastases, who were receiving best standard of care, and had previously either received or were unsuitable for docetaxel. Patients were stratified by previous docetaxel use, baseline total alkaline phosphatase level, and current bisphosphonate use, then randomly assigned (2:1) to receive either six intravenous injections of radium-223 (50 kBq/kg) or matching placebo; one injection was given every 4 weeks. Randomisation was done with an interactive voice response system, taking into account trial stratification factors. Participants and investigators were masked to treatment assignment. The primary endpoint was overall survival, which has been reported previously. Here we report on time to first symptomatic skeletal event, defined as the use of external beam radiation to relieve bone pain, or occurrence of a new symptomatic pathological fracture (vertebral or non-verterbal), or occurence of spinal cord compression, or tumour-related orthopeadic surgical intervention. All events were required to be clinically apparent and were not assessed by periodic radiological review. Statistical analyses of symptomatic skeletal events were based on the intention-to-treat population. The study has been completed and is registered with ClinicalTrials.gov, number NCT00699751.

Findings Between June 12, 2008, and Feb 1, 2011, 921 patients were enrolled, of whom 614 (67%) were randomly assigned to receive radium-223 and 307 (33%) placebo. Symptomatic skeletal events occurred in 202 (33%) of 614 patients in the radium-223 group and 116 (38%) of 307 patients in the placebo group. Time to first symptomatic skeletal event was longer with radium-223 than with placebo (median 15·6 months [95% CI 13·5–18·0] *vs* 9·8 months [7·3–23·7]; hazard ratio [HR]=0·66, 95% CI 0·52–0·83; p=0·00037). The risks of external beam radiation therapy for bone pain (HR 0·67, 95% CI 0·53–0·85) and spinal cord compression (HR=0·52, 95% CI 0·29–0·93) were reduced with radium-233 compared with placebo. Radium-223 treatment did not seem to significantly reduce the risk of symptomatic pathological bone fracture (HR 0·62, 95% CI 0·35–1·09), or the need for tumour-related orthopaedic surgical intervention (HR 0·72, 95% CI 0·28–1·82).

Interpretation Radium-223 should be considered as a treatment option for patients with castration-resistant prostate cancer and symptomatic bone metastases.

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Introduction

Skeletal events arise from disease-related complications of bone metastases.[1,2] In patients with metastatic castration-resistant prostate cancer, skeletal events occur frequently, and are a major cause of prostate cancer-specific morbidity and increased economic burden of the disease.[3–6] Skeletal events are regularly defined as pathological bone fracture, spinal cord compression, orthopaedic surgical intervention, or radiation to bone.[7–11] Bone metastases and skeletal events are associated with reduced survival in metastatic castration-resistant prostate cancer;[12] skeletal events are known to impair quality of life and, in the case of spinal cord compression, lead to neurological damage.[1] Thus, prevention and delay of skeletal events are important objectives in managing patients with metastatic castration-resistant prostate cancer.

Historically, skeletal events were monitored in clinical trials through periodic radiological review and referred to in the medical literature as skeletal-related events.[7–11] Skeletal events that are symptomatic and identified

clinically are different from asymptomatic radiologically detected events, and are a more clinically relevant endpoint. Events assessed in this manner are called symptomatic skeletal events.[13]

Radium-223 dichloride (radium-223) is a targeted α-emitter that emits high-energy, localised α-particles, with a tissue range of less than 100 μm.[14] As a calcium mimetic, radium-223 has a natural bone-seeking capability and preferentially binds to newly formed bone matrix, targeting osteoblastic metastatic lesions.[15,16] The high-energy, short-range α-particle radiation predominantly induces irreparable double-stranded DNA breaks resulting in potent cytotoxic activity localised to target areas, while minimising damage to bone marrow and adjacent healthy tissue.[15–17]

Efficacy and safety of radium-223 were assessed in a phase 3 multinational study (ALSYMPCA) comparing radium-223 plus best standard of care versus placebo plus best standard of care in patients with castration-resistant prostate cancer and bone metastases.[18] Overall survival was significantly longer with radium-223 than with placebo (median survival: 14·9 months *vs* 11·3 months; hazard ratio [HR] 0·70; 95% CI 0·58–0·83; p<0·0001) and was well tolerated, with low myelosuppression rates and few adverse events.[18] These results led to the approval from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA)[13] of radium-223 for treating patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastases.

Here we present secondary endpoint data from ALSYMPCA, along with post-hoc analyses to further establish the effect of radium-223 on symptomatic skeletal events in men with castration-resistant prostate cancer and bone metastases.

Methods

Study design and patients

ALSYMPCA was a phase 3, randomised, double-blind, placebo-controlled study done at 136 centres (appendix) in 19 countries in patients with metastatic castration-resistant prostate cancer. Eligible patients were aged 18 years or older; had progressive, symptomatic castration-resistant prostate cancer with two or more bone metastases on bone scintigraphy and no known visceral metastases; were receiving best standard of care; and had received docetaxel, or were not eligible for, or had declined docetaxel treatment.[18] Patients were required to have a serum testosterone concentration of 50 ng/dL or less; serum prostate-specific antigen (PSA) concentration of 5 ng/mL or less; symptomatic disease, defined as either regular use of analgesic medication for cancer-related bone pain or treatment with external beam radiation therapy for bone pain within the previous 12 weeks; an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less; and a life expectancy of at least 6 months. Patients also had to have adequate haematological, liver, and renal function, as determined by laboratory tests, which included having: absolute neutrophil counts of $1·5\times10^9$ cells per L; platelet counts of 100×10^9 cells per L; total bilirubin concentrations 1·5 times the upper limit of normal (ULN) or lower; and creatinine concentrations 1·5 times the ULN or lower.

We excluded patients if they had received chemotherapy within the previous 4 weeks or had not recovered from adverse events due to chemotherapy. Additional exclusion criteria were previous hemibody external radiotherapy; systemic radiotherapy with radioisotopes within 24 weeks; a blood transfusion or use of erythropoietin-stimulating agents within 4 weeks; malignant lymphadenopathy more than 3 cm in the short-axis diameter; a history of (or presence of) visceral metastases; imminent or established spinal cord compression; unmanageable faecal incontinence; or presence of serious illness or medical condition (eg, uncontrolled infection, Crohn's disease, ulcerative colitis, bone marrow dysplasia). All patients gave written informed consent. The review boards at all participating centres approved ALSYMPCA.

Randomisation and masking

Eligible patients were stratified by previous docetaxel use (yes or no), baseline total alkaline phosphatase (ALP) concentration (<220 U/L or ≥220 U/L), and current bisphosphonate use (yes or no), then randomly assigned in a 2:1 ratio to receive six intravenous injections of either radium-223 (50 kBq/kg) or placebo (saline); one injection was given every 4 weeks.

Patient randomisation was done with a list of randomisation codes organised in predetermined block size (six) within each stratum. Randomised treatment allocation was done with an interactive voice response system (IVRS), taking into account trial stratification factors. In view of the radioactive nature of radium-223, an unmasked individual at every centre was responsible for calculating the study drug volume and filling the blinded syringe; all other individuals were masked to the treatment group, including patients, investigators, and study funders. Patients' randomisation number and treatment allocation were sent to the unmasked person at the study centre who was responsible for preparing the study drug. The study was unblinded following the planned interim analysis, after the independent data monitoring committee recommended early trial discontinuation as a consequence of a radium-223 survival benefit, and crossover of patients in the placebo group to radium-223 treatment.

Procedures

Radium-223 was manufactured by the Institute for Energy Technology, Isotope Laboratories, Kjeller, Norway. All patients continued to receive the best standard of care available at each centre (eg, local external beam radiation therapy, corticosteroids, antiandrogens, ketoconazole, or oestrogens such as diethylstilbestrol or estramustine), apart from chemotherapy, hemibody external radiation

Cancer Centre, Clatterbridge Health Park, Bebington, Wirral, UK (I Syndikus FRCR); **Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA** (Prof N J Vogelzang MD); **Algeta ASA, Kjelsaas, Oslo, Norway** (C Gillies O'Bryan-Tear MRCP); **Bayer Healthcare, Whippany, NJ, USA** (M Shan PhD); **Norwegian Radium Hospital and Faculty of Medicine, University of Oslo, Oslo, Norway** (Prof Ø S Bruland MD); **and The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Sutton, Surrey, UK** (C Parker MD)

Correspondence to:
Prof Oliver Sartor, Medical Director Tulane Cancer Center, Departments of Medicine and Urology, Box SL-42, 1430 Tulane Avenue, Tulane Medical School, New Orleans, LA 70112, USA
osartor@tulane.edu

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