Radionuclides

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Introduction

In the phase 3 ALSYMPCA trial, radium-223 plus best standard of care was associated with improvements in overall survival (OS) and symptomatic skeletal events (SSEs) compared with placebo plus best standard of care in men with castrate-resistant prostate cancer (CRPC) and symptomatic bone metastases.[1,2] Radium-223 was also associated with a favourable safety profile with low rates of myelosuppression, suggesting that retreatment may be well-tolerated and provide additional benefits in this patient population. Several studies presented at ASCO 2016 have explored the use of radium-223 in other populations of men with prostate cancer.

Retreatment with radium-223 is well-tolerated and shows promising early effects on OS, time to first SSE, and pain

At ASCO 2016, Sartor and colleagues reported initial findings from an international, prospective, open-label phase 1/2 trial in 44 patients with bone-metastatic CRPC who were retreated with radium-223 following an initial treatment with six courses and no disease progression in bone.[3] All patients had radiologic or clinical progression after initial radium-223 treatment, with adequate hematologic values. Concomitant agents were allowed at the discretion of the investigator, excluding cytotoxic treatment, and initiation of new abiraterone or enzalutamide treatment was not permitted during radium-223 treatment. The first patient visit was January 19, 2014, and the data cutoff date was June 11, 2015. Active followup will continue for two years after the last radium-223 injection.

A total of 29 (66%) of the retreated patients received all six injections, with a median time from the end of initial radium-223 treatment of six months. There were three (7%) cases of Grade 3 or 4 treatment-related adverse events (AEs) (thrombocytopenia, anemia, and dehydration), and no Grade 5 hematologic AEs occurred. At the time of reporting, five (11%) patients had died and eight (18%) had experienced a first SSE. Median OS, time to first SSE, and SSE-free survival had not yet been reached. Five (14%) of 36 evaluable patients with a baseline worst pain score of 7 or lower experienced pain progression, with a 24-week pain progression rate of 20%. The median time to pain progression had not yet been reached. These preliminary data suggest that retreatment with radium-223 should be studied in larger prospective trials, as it may provide benefit in those patients who have progressed on six cycles of radium-223.

Combination of radium-223 and docetaxel is well-tolerated, and improves time to prostate-specific antigen progression and progression-free survival in men with metastatic CRPC

The unique mechanism of action (MOA) and favourable safety profile of radium-223 make it a suitable candidate for use in combination with other anti-cancer agents. An ongoing phase 1/2a trial is exploring the safety and efficacy of radium-223 in combination with docetaxel in men with progressing CRPC and two or more bone metastases. Morris and colleagues presented updated results of the trial at ASCO 2016.[4] Patients were randomly assigned in a 2:1 ratio to five cycles of radium-223 (50 kBq/kg every six weeks) plus 10 cycles of docetaxel 60 mg/m^2 every three weeks (n=36), or 10 cycles of docetaxel 75 mg/m^2 every three weeks with an option to step down to 60 mg/m^2 (n=17). Patients treated with both radium-223 and docetaxel had a lower percentage of Grade 3/4 treatment-emergent adverse events (TEAEs) (48% vs. 62%) and serious TEAEs (21% vs. 31%) compared with those who received docetaxel alone. Two patients treated with docetaxel alone experienced febrile neutropenia compared with none of the patients in the combination therapy. There was no clinically significant thrombocytopenia in either arm. Patients in the combination treatment arm had longer time to prostate-specific antigen (PSA) progression, progression-free survival (PFS), and total and bone-specific alkaline phosphatase progression compared with those treated only with docetaxel. These promising results suggest a need for further studies exploring the efficacy and safety of the com-

bination of radium-223 and docetaxel in men with metastatic CRPC (mCRPC).

Other combination treatments with radium-223 are currently being explored. At ASCO 2016, Smith et al presented a poster outlining the design for a phase 3 trial combining radium-223 with abiraterone acetate and prednisone in asymptomatic or mildly symptomatic chemotherapy-naïve patients with bone-predominant mCRPC.[5]

Giving radium-223 earlier in the course of prostate cancer treatment may increase the likelihood of receiving a full course of treatment

The ability to identify patients who are most likely to receive the total six injections of radium-223 — and are therefore most likely to receive the full benefits of this therapy — would be valuable. A phase 3b open-label expanded access program (EAP) provided patients with access to radium-223 prior to regulatory approval and evaluated its safety and efficacy in patients with progressive bone-predominant mCRPC.[6] Prognostic factors associated with 1–4 vs. 5–6 injections were also identified. In contrast to ALSYMPCA, the EAP allowed for the inclusion of asymptomatic patients and those with prior or concomitant treatment with abiraterone or enzalutamide.

In ALSYMPCA, patients who received 1–4 injections had a median OS of 6.2 months and those who received 5–6 injections had a median OS of 17.9 months.[1] In the EAP study, median OS was 6.3 months in patients who received 1–4 injections and had not been reached in those who received 5–6 injections (Fig. 1). Patients who received 5–6 injections in the EAP study had less pain, lower Eastern Cooperative Oncology Group (ECOG) score, lower PSA level, and higher hemoglobin levels at baseline (Table 1). These exploratory analyses suggest that patients with less advanced disease are more likely to receive the full course of radium-223 treatment. As such, use of this treatment earlier in the course of a patient's disease may allow patients to receive the full course. Whether there is truly a causal relation between number of radium-223 injections and OS requires confirmation in a prospective, randomized trial.

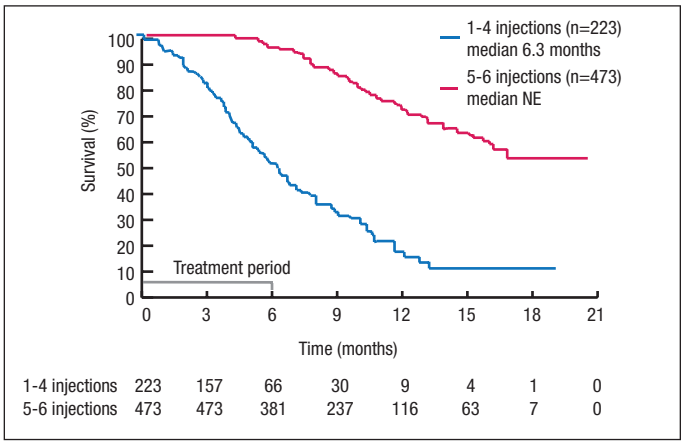

Fig. 1. Overall survival of patients who received 1–4 vs. 5–6 injections of radium-223 in the Expanded Access Program.[6]

Table 1. Baseline characteristics of patients who received 1-4 vs. 5-6 injections of radium-223 in the Expanded Access Program[6]

Baseline characteristics	Radium-223 1-4 injections (n=223)	Radium-223 5-6 injections (n=473)
Age, median years	72	72
Weight, median kg	81	81
ECOG PS 2, %	20	9
Baseline pain moderate-severe, %	35	18
Total ALP > ULN, %	72	56
Albumin, median g/L	39	40
Hemoglobin, median g/dL	11	12
PSA, median µg/L	298	97
Total ALP, median U/L	217	134
Time since prostate cancer diagnosis, months	59	70
Prior docetaxel treatment, %	62	59

ALP: alkaline phosphatase; ECOG PS: Eastern Cooperative Oncology Group performance status; PSA: prostate-specific antigen; ULN: upper limit of normal.

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