BACKGROUND

- Bone metastases are the main cause of disability and death in men with castration-resistant prostate cancer (CRPC).
- Radium-223 chloride (Alpharadin™) is a first-in-class alpha-pharmaceutical where the alpha-particle has a high and highly targeted antitumor effect on bone metastases and a highly tolerable side effect profile.
- Bone-targeted radium-223 emits alpha-particles with an ultra-short range of 2-10 nanometers, generating highly localized and intense radiation in the immediate vicinity of the alpha-particle radiation induces lethal double-stranded DNA breaks, resulting in a high cytotoxic effect in the target area containing metastatic cancer cells. The short path length of the alpha-particles also ensures that toxicadjacent healthy tissue and potentially the bone marrow is kept to a minimum.

METHODS AND STUDY DESIGN

- Patients with CRPC and bone metastases were treated in 2 randomized phase II studies. BC1-02 was a phase II placebo-controlled study of radium-223 (50 kBq/kg) every 4 weeks for 12 weeks (Figure 1). BC1-03 was a phase II placebo-controlled study of radium-223 (80 kBq/kg) every 4 weeks for 12 weeks (Figure 2).
- The studies were designed to assess the safety, tolerability, pharmacology, and antitumor effect on bone metastases (eg, survival, pain relief), and changes in PSA and ALP of radium-223 in patients with CRPC and bone metastases.

RESULTS

BC1-02 Study

- 24-Month Overall Survival
  - Radium-223 improved OS for 4.5 months versus placebo (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.60-0.98; P = .035) for patients with CRPC and bone metastases (OS 46 vs 39 wk, respectively; HR 0.76 [0.60-0.98]; Table 2).
  - In the placebo-controlled phase II study (BC1-02), radium-223 showed a statistically significant improvement in overall survival (OS), compared with placebo, and a consistent improvement in pain relief and disease-related biomarkers such as prostate-specific antigen (PSA) and bone alkaline phosphatase (ALP).
  - Baseline ALP values have been shown to be prognostic for survival in men with metastatic prostate cancer; however, the relationship between a change in baseline ALP in patients receiving treatment and the subsequent effect on OS has not been completely determined.

ALP Normalization and Overall Survival

- In total, 548/684 (84%) patients enrolled in the BC1-02 study had an above-normal baseline total ALP value. In the radium-223 group, 28/33 (85%) patients had an above-normal baseline total ALP value versus 28/31 (90%) patients in the placebo group.
- Of the 58 patients with an elevated baseline total ALP value, 2 had no postbaseline value; thus, the analysis of normalization was based on 56 patients.
- After treatment, 13/25 (52%) patients (95% CI 31-73%) in the radium-223 group and 4/31 (13%) patients (95% CI 3-31%) in the placebo group had an ALP value of ≤ 128 U/L after treatment (Figure 3).

Conclusions

- Bone-targeted radium-223 demonstrated a significant antitumor effect on bone metastases and a highly tolerable side effect profile.
- Baseline ALP values have been shown to be prognostic for survival in men with metastatic prostate cancer; however, the relationship between a change in baseline ALP in patients receiving treatment and the subsequent effect on OS has not been completely determined.

REFERENCES