Prostate cancer

TARGETING BONE METASTASES IN CRPC

Alan So, MD, FRCSC, Associate Professor, Department of Urologic Sciences, University of British Columbia; Research Scientist, Prostate Centre, Vancouver General Hospital.

TRIAL SUMMARY: Ra-223 improves overall survival of advanced prostate cancer patients with bone metastases


Radium-223 chloride (Ra-223) targets bone metastases (mets) with high energy alpha particles of extremely short range (<100 μm). ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer), a Phase III, double-blind, randomized, multinational study, compared overall survival (OS) and safety of Ra-223 plus best standard of care (BSC) vs placebo plus BSC in patients with bone mets in castration-resistant prostate cancer (CRPC).

Eligible patients had progressive, symptomatic CRPC with ≥2 bone mets on scintigraphy and no known visceral mets. Patients were receiving BSC and had either previously received docetaxel, refused docetaxel or were docetaxel-ineligible. The study randomized 922 pts (Ra-223, n=615; placebo, n=307) to receive 6 injections of Ra-223 (50 kBq/kg IV [intravenous]) every 4 weeks or matching placebo; they were stratified by prior docetaxel use, baseline alkaline phosphatase level and current bisphosphonate use. A planned interim analysis (IA) was conducted to assess the effect of Ra-223 on the primary endpoint (OS) using a predefined threshold.

Survival data were compared using a stratified log-rank test. Of 809 patients in the IA data set, 445 (55%) received prior treatment with docetaxel. Ra-223 significantly improved OS in patients with CRPC with bone mets vs placebo (2-sided p=0.00185; hazard ratio [HR]=0.695; 95% confidence interval [CI]=0.552–0.875; median OS 14.0 months vs 11.2 months, respectively). Safety and tolerability of Ra-223 were highly favourable and showed low incidence of myelosuppression (Grades 3/4 neutropenia in 1.8% and 0.8% and thrombocytopenia in 4% and 2% of the Ra-223 and placebo groups, respectively).

According to the study conclusions, Ra-223 is an effective therapy that improved OS with a highly favourable safety profile, and may provide a new standard of care for the treatment of CRPC patients with bone mets.

COMMENTARY: Ra-223, an alpha-particle-emitting radiopharmaceutical, specifically targets bone metastases by acting as a calcium mimic. Initially presented at the 2011 European Multidisciplinary Cancer Congress in Stockholm, the ALSYMPCA trial was presented again at the American Society of Clinical Oncology 2012 Genitourinary Cancers Symposium (ASCO GU), with additional data addressing secondary endpoints, including skeletal-related events (SREs). This trial randomized in a 2:1 fashion 922 patients with CRPC who had either previously received docetaxel or who were “unfit” for docetaxel to Ra-223 or placebo. Patients were required to have ≥2 bone metastases and no visceral metastases.

Median OS was 14 months in the Ra-223 arm vs 11.2 months in the placebo group (HR=0.695, 95% CI=0.552–0.875; p=0.00185). Subgroup analysis revealed that the benefit of Ra-223 was not influenced by prior chemotherapy or bisphosphonate use. Compared to placebo, Ra-223 significantly prolonged time to first SRE (HR=0.610; p=0.00046) and reduced the need for radiation to bone (23% vs 27%, HR=0.65; p=0.0038), spinal cord compression (3% vs 6%, HR=0.44; p=0.16) and pathologic bone fracture (4% vs 7%, HR=0.45; p=0.013). As well, time to prostate-specific antigen (PSA) progression was improved in the Ra-223 treated patients (HR=0.671; p=0.00015).

Overall, Ra-223 was well tolerated, with no differences in Grade 3/4 adverse events. Compared to placebo, patients on Ra-223 had higher rates of neutropenia (4% vs 1%) and thrombocytopenia (8% vs 6%). As well, there was a higher rate of diarrhea in patients on Ra-223 (34 % vs 13% in the placebo arm), thought to be due to the excretion of Ra-223 in the small intestine.

This bone metastases-targeting agent provides another therapy in the armamentarium for the treatment of CRPC. Based on the OS benefit in this patient population, it is currently being assessed by the US Food and Drug Administration (FDA). However, its long-term effects on bone marrow response are still unknown. Although this trial included both chemotherapy-treated patients and those who

<table>
<thead>
<tr>
<th>Patients reporting AEs, n (%)</th>
<th>Ra-223 (n=509*)</th>
<th>Placebo (n=253*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>450 (88)</td>
<td>237 (94)</td>
</tr>
<tr>
<td>Grade 3 or 4 AEs</td>
<td>257 (51)</td>
<td>150 (59)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>220 (43)</td>
<td>139 (55)</td>
</tr>
<tr>
<td>Discontinued due to AEs</td>
<td>68 (13)</td>
<td>51 (20)</td>
</tr>
</tbody>
</table>

*Patients who received ≥1 injection; AE=adverse events

© 2012 Parkhurst, publisher of Oncology exchange. All rights reserved.
Already known
• The 2011 European Multidisciplinary Cancer Congress reported that radium-223 chloride significantly improved overall survival in patients with castration-resistant prostate cancer and symptomatic bone metastases.

What this study showed
• The ALSYMPCA trial confirmed the overall survival benefit with radium-223 in this patient population. Compared to placebo, radium-223 also reduced the need for radiation to bone, spinal cord compression and pathologic bone fracture, as well as longer time to PSA progression.

Next steps
• Radium-223 may be available soon as a new treatment for CRPC patients with bone metastases, but its long-term effects on bone marrow response need further study.

were unfit for chemotherapy, incorporating this treatment sooner in the treatment paradigm of CRPC (i.e. chemotherapy-naive) may be difficult due to its unknown effects on the bone marrow response to chemotherapy.

One must be careful in direct comparison of this study to other CRPC trials, such as AFFIRM assessing MDV3100 and COU-AA-301 assessing abiraterone, as a high proportion of patients in those studies had visceral metastases, an exclusion criterion for the ALSYMPCA trial. As well, the AFFIRM and COU-AA-301 trials were conducted strictly with chemotherapy-resistant patients. Regardless, this trial now proves the survival benefit of Ra-223 in CRPC with bony metastases in patients who were either treated with docetaxel or ineligible for chemotherapy, and adds to the treatment options that will be available soon in the treatment of advanced prostate cancer.

Disclosure: Dr. So reports no conflict of interest relevant to his articles.