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Oncology & Hematology

Radium-223 Could Alter Metastatic Prostate Cancer Management

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FROM THE EUROPEAN MULTIDISCIPLINARY CANCER CONGRESS

VITALS

Major Finding: Median overall survival was 14.0 months with radium-223 chloride vs. 11.1 months with placebo (HR, 0.69; *P* = .00185).

Data Source: Phase III, randomized ALSYMPCA trial in 922 patients with castration-resistant prostate cancer and symptomatic bone metastases.

Disclosures: Dr. Parker reported serving as an uncompensated consultant to Algeta ASA and Bayer Healthcare Pharmaceuticals, which sponsored the trial. A coauthor reported an ownership interest in and previous employment with Algeta. A second coauthor is a Bayer employee.

STOCKHOLM – The investigational agent radium-223 chloride cut the risk of dying during follow-up by 30% among men with symptomatic, castration-resistant prostate cancer and bone metastases, and resulted in less toxicity than did placebo in a phase III, randomized trial.

Results of the preplanned interim analysis were strong enough to prematurely stop the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial, and caused a stir at the European Multidisciplinary Cancer Congress.

After a maximum follow-up of 3 years, median overall survival was significantly increased from 11.1 months with placebo to 14.0 months with radium-223 chloride (Alpharadin) (hazard ratio, 0.695; *P* = .00185).

Dr. Chris Parker

The survival benefit was maintained across all subgroups studied, regardless of baseline alkaline phosphatase (ALP) level, current bisphosphonate use, prior docetaxel (Taxotere) use, and Eastern Cooperative Oncology Group performance status, lead author Dr. Chris Parker reported.

"In my opinion, radium-223, which has a completely novel mechanism of action, is likely to become a new standard treatment for this disease," he said.

"This is a very important finding, certainly practice changing, and very likely could become the standard of care ... all over the world," European Cancer Organization (ECCO) president Dr. Michael Baumann of the Technical University of Dresden (Germany) said during a press briefing.

Likewise, Dr. Jean Charles Soria of the Institut de Cancérologie Gustave Roussy in Villejuif, France, and cochair of the congress scientific program said that "this is really practice changing, and pending regulatory approval, I think this is going to be a major player in prostate cancer management."

Current bone-targeting therapies such as denosumab (Xgeva) have been shown to improve symptom control but not survival in patients with castration-resistant prostate cancer (CRPC) and bone metastases. More than 90% of men with metastatic CRPC have evidence of bone metastases, conferring almost a fivefold greater risk of death.

Radium-223 chloride is not approved in the United States or Europe, but was granted fast track designation by the Food and Drug Administration in August 2011. Approval could come by the end of 2012, said Dr. Parker, a consultant clinical oncologist at the Royal Marsden Hospital in Sutton, England.

Radium-223 acts as a calcium mimic, and targets new bone growth in and around bone metastases via heavy alpha particles that have an ultrashort range of less than 100 mcm. It takes only a single alpha particle to kill a cancer cell, and the short penetration results in highly localized tumor-cell killing and minimal collateral damage, Dr. Parker explained.

He suggested that it would be relatively straightforward for hospitals to offer radium-223 because it takes 5 minutes to administer as an injection in the outpatient setting. Storage would be limited because of the drug's short half-life of 11 days, but the agent would not require special radiation protection because alpha radiation is stopped by a piece of paper.

ALSYMPCA randomized 922 patients to best standard treatment plus

six injections every 4 weeks of radium-223 (50 kBq/kg) or to placebo. The patients had symptomatic CRPC, at least two bone metastases, and no known visceral metastases; they had previously received or were unfit for docetaxel. Notably, 40% of patients had more than 20 metastases on bone scintigraphy, and 60% had previously received docetaxel.

Radium-223 significantly prolonged the time to first skeletal-related event from 8.4 months with placebo to 13.6 months (*P* = .00046; HR, 0.61), Dr. Parker said at the joint congress of the ECCO, the European Society for Medical Oncology (ESMO), and the European Society of Radiotherapy and Oncology (ESTRO).

All other secondary end points were met by radium-223 over placebo, including time to total ALP progression (HR, 0.163; *P* less than .00001); time to prostate-specific antigen progression (HR, 0.671; *P* = .00015); total ALP response, defined as a 30% reduction (43% vs. 3%; *P* less than .001); and total ALP normalization (33% vs. 1%; *P* less than .001).

Dr. Parker pointed out that "ALSYMPCA is one of a very few phase III trials in which the placebo arm had more toxicity than the active intervention arm."

Hematologic events were slightly increased in patients treated with radium-223, compared with placebo, but were rare, he said. There was also an excess of mild diarrhea and vomiting, but severe GI toxicity was not seen.

The placebo arm had more grade 3 or 4 adverse events than did the radium-223 arm (59% vs. 51%), more serious adverse events (55% and 43%), and more treatment discontinuations (20% vs. 13%). Of note, best standard treatment could include bisphosphonates, palliative radiotherapy, and hormonal therapies.

Pain was not studied as part of this trial, but was shown in a previous phase II study to be improved. Quality of life data will be reported at a later date, he said.

Discussant Dr. Wim J.G. Oyen of the St. Radboud University Medical Center Nijmegen, the Netherlands, said that based on phase I/II data suggesting that combining beta radiation–emitting agents with chemotherapy prolongs overall survival, the next logical step would be to add radium-223 in regimens of combination therapy.

"It's so extremely well tolerated, I do not think we will experience synergistic toxicity, but we may very well experience synergistic effect," he said.

Dr. Oyen said that clinicians could further improve patient outcome by using radium-223 in the adjuvant setting (for example, in patients at high risk of developing clinically overt bone metastases). He said it is widely known that the smaller the tumor, the more advantage an alpha particle has over a beta particle; thus, microscopic disease would theoretically be the better indication over macroscopic disease.

Dr. Parker said in an interview that his preference would be to combine radium-223 with abiraterone acetate (Zytiga) because both improve survival and are extremely well tolerated, but they work in completely different ways.

Two small phase I/II trials are currently underway. One combines radium-223 with docetaxel in patients with CRPC and bone metastases. The second is studying radium-223 in breast cancer patients who have bone-dominant disease and are no longer eligible for endocrine therapy.

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