Editorial Commentary

Radium-223 plus abiraterone in metastatic castration-resistant prostate cancer: a cautionary tale

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Metastatic castration-resistant prostate cancer (mCRPC) spreads to bone in up to 90% of patients and can be associated with pain, skeletal-related events (SREs), reduced mobility with quality of life impairment, and shortened overall survival (OS) (1-4). Over the past several years, treatment options for mCRPC have expanded, and now include cytotoxic agents (docetaxel, cabazitaxel), oral hormonal therapies targeting the androgen receptor (abiraterone, enzalutamide, apalutamide), targeted alpha-particle therapy (radium-223), immunotherapy (sipuleucel-T), and bone-supportive agents (zoledronate, denosumab) that reduce SREs (5-7). It is not yet clear, however, how to sequence or combine available agents in routine clinical practice. Bone disease remains a leading contributor of morbidity and mortality for patients with metastatic prostate cancer. Researchers thus continue to search for novel combinations of proven therapies to improve survival and quality of life for these patients. This was the intention of the ERA-223 study (NCT02043678), a trial that investigated a novel combination of radium-223 dichloride with abiraterone acetate.

Combining abiraterone and radium-223 seemed logical and was thought to be promising for several reasons. Radium-223 is a targeted alpha-particle radiopharmaceutical that was FDA-approved based on the results of the prospective, randomized, double-blind, placebo-controlled phase III ALSYMPCA trial (8). In that pivotal study, radium-223 led to a 30% reduction in death compared to placebo. Secondary analyses further supported its benefit, demonstrating a reduction in relative risk and delayed time to first symptomatic skeletal event (SSE) (HR, 0.66), while also improving patient health-related quality of life when compared to placebo. The benefits of radium-223 were accentuated if patients received concomitant bisphosphonates or denosumab. In addition, analysis of an early-access, phase 3b open-label study suggested (in a hypothesis-generating fashion) a potential survival benefit when radium-223 was combined with abiraterone or enzalutamide (9). Thus, the concept of combining radium-223 and abiraterone was primed for a prospective clinical trial. Each treatment appeared to have a unique toxicity profile, without known overlapping side effects. Yet, the published outcome of the ERA-223 study was a negative trial, with a very concerning toxicity signal (10). Why then, did the trial not meet its primary end point, and why were bone fractures increased with the combination of radium-223 and abiraterone?

To answer these questions, let us first review the details of the trial. The ERA-223 study enrolled patients with early-stage mCRPC disease and combined abiraterone, an agent not available at the time of ALSYMPCA, with radium-223. This randomized, double-blind, placebo-controlled, phase III trial included 806 patients with mCRPC, with at least two bone metastases that were asymptomatic or mildly symptomatic, had an ECOG performance status of 0 or 1, were chemotherapy-naïve, and without brain or visceral metastases. Importantly, the use of approved bone-supportive agents (bisphosphonates or denosumab) was only allowed if patients were already receiving them at the time of study entry. Patients were randomized (1:1) to receive abiraterone acetate, at a dose of 1,000 mg daily together with 10 mg of prednisone/prednisolone daily, plus radium-223, at a dose of 55 kBq/kg every four weeks for up to six cycles, versus abiraterone and prednisone/prednisolone alone. The primary endpoint of ERA-223 was SSE-free survival. SSEs were defined as the use of external-beam radiation therapy to relieve bone pain, new symptomatic pathological bone fractures, spinal cord compression or tumor-related orthopedic surgical intervention. Secondary endpoints included OS, radiographic progression-free survival (rPFS), time to chemotherapy initiation, time to opiate use for cancer-related pain, and safety.

Surprisingly, the trial was unblinded prematurely after more fractures and deaths were observed in the abiraterone/radium-223 group than in the abiraterone/placebo group. In the initial analysis, patients in the combination arm were at risk of dying earlier by a median of 2.6 months and had significantly more fractures than patients who received abiraterone alone. As the data matured, there was no statistically significant difference between groups with respect to OS, although there were numerically more deaths in the abiraterone/radium-223 group (P=0.13). However, the overall increased risk of fracture in the combination arm was 29% *vs.* 11% by investigator assessment, and the results were confirmed by independent central review. As a result of this increase in fracture rates, the combination strategy is no longer recommended, and all living patients are undergoing close monitoring. In addition, the European Society of Medical Oncology (ESMO) guidelines have restricted the use of radium-223 to patients who have had two previous treatments for mCRPC or are not candidates for other systemic treatments (11). To what can we attribute these differences? And should the broader role of radium-223 be reconsidered in light of the ERA-223 trial results?

The placebo arm of the ERA-223 study produced results that were comparable to the prior COU-AA-301 and COU-AA-302 studies investigating the role of abiraterone acetate in post-chemotherapy and pre-chemotherapy mCRPC patients (12,13). For example, the abiraterone-alone arm of the ERA-223 trial demonstrated an OS of 33.3 months (survival in the historical COU-AA-302 study was 34.7 months). The baseline characteristics were also generally similar across studies. In ERA-223, median age was 71 years. Approximately 60% of patients had a Gleason score of ≥8; median PSA was 30 ng/mL; two-thirds of patients had ≥5 bone metastases; and bone-health agents were used at baseline in approximately 40% of patients. The statistical model of ERA-223 planned for a median SSE-free survival of 21 months for patients in the control arm (abiraterone alone). The combination arm (radium-223 plus abiraterone) was expected to yield a 39% improvement, which corresponded to a median SSE-free survival of 29 months. This rationale was based on the ALSYMPCA trial, with a hazard ratio of 0.70 for radium-223 compared with placebo. Both COU-AA-301 and COU-AA-302 had a median time to first skeletal event of about 25 months. Thus, the control arm in ERA-223 performed as expected. So why the finding of increased fractures?

Fracture events, as specified in the trial design, were reviewed by an independent central committee. Among patients in the combination arm with at least one fracture confirmed by independent assessment (76 *vs.* 23 in control arm), nearly half of the fractures were related to osteoporosis [37 (49%) *vs.* 4 (4%) for abiraterone alone; a dramatic difference] (10). Pathological fractures related to bone metastases were similar across groups (25% in combination group *vs.* 26% in control), and traumatic fractures were numerically higher in the control arm (57% *vs.* 36% in combination arm). This breakdown by fracture type highlights the complexity of these trial results. These data seem to imply a positive effect of combining abiraterone and radium-223 with respect to reducing pathologic and traumatic fractures, although this was potentially negated by the marked increased risk of osteoporotic (i.e., fragility) fractures in the combination arm. Therefore, we would advocate the need for further study before abandoning the idea of combining radium-223 with standard-of-care therapies (other than abiraterone) in mCRPC.

Adding more agents naturally increases expected toxicities. This may be related to drug-therapy interactions, as well as cumulative long-term exposures to drugs with negative metabolic effects. It is well known that by targeting the androgen receptor, abiraterone leads to a further decline in peripheral and tissue androgen levels. Perhaps a drug-drug interaction potentiates the bone-targeting effects, increasing the risk of fragility fractures. Notably, in COU-AA-301, further depletion of testosterone with the addition of abiraterone to prednisone approximately doubled the risk of both non-pathological fractures (5.9% *vs.* 2.3 %) as well as pathological fractures (15.3% *vs.* 6.2%) compared with prednisone alone (13). Furthermore, several interesting observations are also worth pointing out. The first relates to the timing of the events observed in the ERA-223 trial. In ERA-223, both radium-223 and abiraterone were added in the first 6 months of the mCRPC diagnosis. Interestingly, most of the fractures in the ERA-223 study seemed to correlate with this early time course, with most fracture events occurring in the first 6 to 12 months on study. Was radium-223 started too early in these patients? Would the results be different if radium-223 was added later or perhaps sequentially after a few months of initial abiraterone therapy? In the COU-AA-302 study, the Kaplan-Meier curves for median OS in the two arms were superimposable for nearly one year and then separated much later (12). This highlights a necessary question to investigate the optimal timing with regards to layering radium-223 to other androgen-directed therapies.

Also well described is the flair phenomenon on bone scans that is related to abiraterone. To this end, patients may present with apparent new bone lesions, which improve on follow-up scans and are not related to disease progression (14). This is thought to be due to increased sclerosis in areas of prior bone metastases induced by effective anti-cancer therapy, rather than true worsening of metastatic disease at these osseous sites. Paradoxically, this newly sclerotic bone may be more fragile than other areas of physiological bone deposition. Along these lines, were some of the events noted in ERA-223 possibly related or potentiated by these flair phenomena? Would the rates of osteoporotic fractures be different if patients had been on abiraterone for at least 3 months and then started on radium-223 afterwards, to escape this flair phenomenon? Though it will be difficult to explicitly define the biologic reasons for the observed results of ERA-223, we can question whether differences in fracture risk would have been seen with an alternative study design. Finally, all of the patients enrolled in ERA-223 had castration-resistant disease. It is known that androgen deprivation therapy accelerates osteopenia and osteoporosis, and that abiraterone use further suppresses androgen levels. Would a DEXA scan at baseline have revealed imbalances in baseline bone-health status between the two groups?

As a bone-seeking, rather than a tumor-targeting agent, radium-223 accumulates in hydroxyapatite areas surrounding osseous tumor lesions and selectively binds to newly formed bone stroma in osteoblastic metastases. It is naturally absorbed at sites of active mineralization in bone, concentrating at the bone surface without the need for a bone-directed carrier molecule (15). In the ERA-223 trial, patients had bone-metastatic CRPC and thus had increased osteoclastic activity, which has been shown to be important in the establishment and progression of skeletal metastases as well as fractures (16). Combine this with increased bone loss (having been on androgen deprivation for extended periods of time) and inhibition of osteoblasts (which is regulated by the androgen receptor) with radium-223, and patients may have been primed for SREs. Therefore, we hypothesize that imbalances likely occurred that may have explained the high rate of fractures in the intervention arm of ERA-223.

In terms of the study outcomes, an important observation is that in a *post-hoc* analysis of ERA-223, use of bone-health agents at baseline was substantially less common in patients who had a fracture than in those who did not (in both study arms). In men receiving bone-health agents, 15% experienced a fracture in the radium-223 arm *vs.* 7% in the control arm. Though not statistically assessed, this was lower than the 37% and 15% prevalence of fractures noted in the two arms without bone-supportive agents. Other secondary/exploratory endpoints in the ERA-223 study were not significantly different. These included: time to cytotoxic chemotherapy, time to opiate use for pain, time to PSA progression, and time to deterioration in health-related quality of life. Outcomes were broadly equivalent in the two arms.

Thus, we tend to agree with the ESMO recommendations that radium-223 should not be used in combination with abiraterone and prednisone/prednisolone. At this time, we would also caution against the combination of radium-223 with other active androgen-directed agents (e.g., enzalutamide, apalutamide), unless it is within the context of a clinical trial. Furthermore, radium-223 should only be used in patients with bone-related symptoms, and without visceral disease or bulky nodal disease, in line with its current FDA and EMA indications, and may not be optimal in patients with a low number of bone metastases. However, we do not generally agree with the ESMO guidelines that radium-223 should be restricted to patients who have already received two prior systemic treatments for mCRPC, since this agent has been associated with a proven survival benefit in the phase III ALYSYMPCA study, which led to its 2013 FDA approval.

Patients with mCRPC demonstrate limited benefit to sequential treatment with abiraterone followed by enzalutamide (or *vice versa*), and thus novel therapy combinations are still needed (17). Several gene mutations and splice variants are known to occur in the androgen receptor that are linked to resistance or response to hormonal therapies (18). These genomic alterations are not expected to interfere with the efficacy of radiopharmaceutical drugs. Radium-223 therefore represents a logical and perhaps necessary alternative treatment following disease progression on either abiraterone or enzalutamide (or both). How to optimally time and sequence radium-223 relative to taxane therapies, androgen-directed therapies, or other systemic agents, remains to be determined. However, this is an important question that needs to be resolved because all of these agents are used commonly (and are often being combined already) in the community setting.

The ERA-223 study is a humbling reminder of the importance of conducting confirmatory phase III clinical trials, as a previously reported phase II study had suggested clinical benefits with this combination in terms of quality-of-life and pain relief, without an observed increase in toxicity (19). This is in line with several previously reported positive phase II studies which have led to negative phase III results when subsequently explored in larger cohorts (20,21). Concomitant treatment of radium-223 with abiraterone, and more generally with either cytotoxic chemotherapy or other radionuclides, should not be used in routine practice unless prospective results exist supporting their combined use. The hope remains for layering radium-223 on top of other therapeutic agents, though optimal timing and sequencing need to be determined. Additional phase II and III studies incorporating radium-223 are ongoing, and are designed to evaluate combinations with enzalutamide, sipuleucel-T, and other approved and experimental agents (ClinicalTrials.gov: NCT02346526, NCT02463799, NCT02225704, NCT01929655, NCT02194842).

In conclusion, the ERA-223 study highlights the importance of bone health, a topic in need of quality improvement, as it represents an area of high-value care for men with castration-resistant prostate cancer. It is clear that osteoporotic fractures occur in addition to, and perhaps separate from, other SREs. Although use of bisphosphonates or denosumab lowered the fracture risk in the combination arm of ERA-223, the increase in fracture risk was still there, with 15% *vs.* 7% of patients still experiencing fracture. Importantly, 80% of the fractures in the combination arm occurred in patients not receiving bone-health agents, and only 20% occurred in those who were. For the 32 patients in the placebo arm with fractures, 75% occurred in patients without bone-health agents; only 25% occurred in those who receiving bone-health agents. Given the demonstrated benefit of both bisphosphonates and denosumab on SRE prevention, drugs that were FDA-approved many years ago, it is important to emphasize the need to use bone-health agents appropriately, as there is potential evidence of an additive effect between these agents and the new prostate cancer therapies (22). Bone health is and will remain a driving factor in this disease, both in terms of morbidity and mortality. As the era of new drug approvals that extended OS continues, it is equally important to balance this excitement with the reminder of utilizing supportive care drugs to improve the overall outcomes and quality-of-life of our patients with advanced prostate cancer.

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Footnote

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