Editorial

Radium-223 for metastatic castration-resistant prostate cancer: results and remaining open issues after the ALSYMPCA trial

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Prostate cancer is the most common cancer in men and a leading cause of cancer death among men in developed countries (1). In recent years, several new targeted therapeutic agents become standard treatment options in metastatic castration-resistant prostate cancer (mCRPC) including androgen receptor targeting agents (abiraterone, enzalutamide) or taxane based chemotherapeutic agents (docetaxel, cabazitaxel) after showing prolongation of overall survival (OS) in corresponding phase III clinical studies compared with standard of care (2).

In a large phase III international multicenter study radium-223 (alpharadin) significantly prolonged OS for 3.6 months and reduced symptomatic skeletal event risk in bone metastasized mCRPC patients (ALSYMCA trial) compared to placebo. Based on the positive results of this ALSYMPCA study, radium-223 was approved for treatment of patients with mCRPC and symptomatic bone metastases without visceral metastases (3).

In general radium-223 is an alpha particle-emitting radiopharmaceutical with a physical half-life of 11.4 days. It is thought to have a unique dual mechanism of action via affecting tumor-induced pathologic bone activity and destroying bone-metastatic cancer cells (4). The most common treatment related adverse event (TRAE) reported in the initial phase III approval study included grade 3 or 4 myelosuppression (radium-223 *vs.* placebo: anemia, 13% *vs.* 13%; neutropenia, 2% *vs.* 1%; and thrombocytopenia, 7% *vs.* 2%) (3). Also a real-life study conducted by our working group presented at the AUA 2017 conference revealed similar TRAEs as well as response and OS rates in the daily routine (5). Interestingly, a recently published sub-analysis von ALSYMPCA showed that significantly fewer radium-223 versus placebo patients had at least one hospitalization event and also hospitalization days per patient for radium-223 (6).

In July 2017, Parker *et al.* reported follow up data on the safety of the ALSYMPCA trial investigating the impact of radium-223 in mCRPC patients up to three years. A total of 9 follow-up visits starting were performed (every second months for the first 0.5 year, every 4 months up to the third year) (7).

In line with the ALSYMPCA study protocol patients included in the study had a symptomatic and progressing mCRPC with at least two bone metastases but without any visceral metastases, a performance status 0 to 2, a life expectancy for at least 6 months as well as adequate baseline hematologic, renal, and liver functions. Patients were either pre-treated with docetaxel or were ineligible/unwilling to undergo chemotherapy. Median follow-up time from the first injection was 13 months (range, 0–36 months) for radium-223 patients and 9 months (range 0–36 months) for placebo patients.

Briefly data confirm at least one TRAE in 564/600 (94%) radium-223 and 292/301 (97%) placebo patients during the treatment period up to 12 weeks following the last injection. Grade 3/4 hematologic TRAEs in radium-223 and placebo groups included anemia in 13% and 13%, neutropenia in 2% and 1%, and thrombocytopenia in 7% and 2%, respectively. Grade 5 TRAEs occurred in 98/600 (16%) radium-223 and 68/301 (23%) placebo patients, among them malignant neoplasm progression was the most common cause of death, however in both the treatment and the placebo group. Of 901 patients in the ALSYMPCA safety population, 572 patients entered long-term safety follow-up. Twelve percent of patients in the radium-223 group and 7% of the placebo group completed the 3-year follow-up time whereof the primary reason for discontinuation was death (radium-223 70%, placebo 63%). Concerning those 572 patients (405 radium-223, 167 placebo) who entered in the long-term follow-up no newly diagnosed hematological malignancies like AML, MDS, or new primary bone cancer were observed, secondary non-treatment-related malignancies occurred in four radium-223 and three placebo patients. One radium-223 patient had aplastic anemia 16 months after the last injection. Interestingly during long-term safety follow-up, a higher percentage of placebo than of radium-223 patients died (7).

Generally, we congratulate the principal investigators to the robust data of this study, which is for sure an important milestone pushing the limits of mCRPC therapy. For sure, radium-223 is a potent treatment option for bone mCRPC patients with tolerable side effects. Concerning hematological TRAEs, recent ASYMPCA post hoc analyses of identified baseline risk factors associated with hematologic toxicities related to radium-223 treatment. Thereby they reported that prior docetaxel therapy and decreased platelet and hemoglobin levels are risk factors for grades 2–4 thrombocytopenia, moreover the baseline extent of disease (6–20 versus <6 bone metastases) as well as elevated PSA levels were risk factors for grades 2–4 anemia (8).

Despite of the excellent study protocol of the ASYMPCA several concerns have to be critically discussed:

Only 14% and 7% in the radium-223 and placebo group respectively, were still alive after the 3-year follow-up period, thereby reducing the explanatory and statistical power of the study. In our opinion 3 years of follow-up is even not an enough time frame for get a comprehensive overview about all side effects. Especially hematological malignancies can occur up to 20 years later after radiation, as we know from various previous radiation-oncology studies (9). Fortunately, also the principal investigators of the ALSYMPCA realized this problem, therefore an international prospective observational single-arm study is assessing the incidence of second primary malignancies after radium-223 treatment with a minimum follow-up of 7 years has been initiated (NCT02141438).

In the present study 80/167 patients (48%) underwent a subsequent therapy (mostly abiraterone and docetaxel) after radium-223 administration, which makes it difficult to argue that a certain long-term side effect is directly linked to previous radium-223 therapy. In addition, 44% of those patients received radiotherapy aggravating especially the evaluation of possible radium-223 caused secondary neoplasms. Further, a certain number of patient underwent concomitant treatment of denosumab, a monoclonal antibody against RANK-L also used in patients with osseous mCRPC. Another important point to discuss is that except for bisphosphonate use additional patients' medication beside radium-223 possibly also causing, potentiating or masking radium-223 side effects were not fully documented within this study.

A major general problem of the ALSYMPCA is the imaging used for detection of bone lesions (bone scan) as well as the exclusion of visceral metastases (computed tomography). Although still recommended by several guidelines we know that we have much better imaging options like PSMA PET- or Choline PET-CTs. Next, the number of metastases was high on average as almost 40% of included patients had 20 metastases. Is this a real-life situation?

Concerning response rates and side effects of radium-223 the ECOG performance status, skeletal tumor burden, alkaline phosphatase (ALP) as well as the Bone Scan Index have been reported to be promising biomarkers for both OS and hematological toxicities in patients with radium-223 therapy (2,10)

In our opinion, for the future especially the multimodal treatment concept integrating radium-223 in other mCRPC therapies are important, as it has been shown recently by Saad *et al.* (including also patients from our department) that radium-223 is also well tolerated and effective in combination with abiraterone or enzalutamide (11).

However, the best sequencing and/or combination of radium-223 with other agents have yet to be fully elucidated (12). Moreover, the role of radium-223 in

treating patients with hormone-sensitive metastatic prostate cancer who are candidates for chemotherapy should be clarified.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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