Early use of abiraterone and radium-223 in metastatic prostate cancer

The ALSYMPCA trial[1] previously showed that, in patients with castration-resistant prostate cancer and symptomatic bone metastases, treatment with the α-emitter radium-223 was associated with improvement in overall survival (hazard ratio 0·70, p=0·002) and in time to first symptomatic skeletal event (hazard ratio 0·66, p<0·001) compared with placebo. By contrast, the results from the ERA 223 trial, recently reported in *The Lancet Oncology*,[2] show that in patients with chemotherapy-naive, asymptomatic or mildly symptomatic, castration-resistant prostate cancer the addition of radium-223 to abiraterone acetate and prednisone (or prednisolone) did not improve symptomatic skeletal event-free survival, did not result in additive tumour control (eg, prostate-specific antigen [PSA] response or radiological progression-free survival), and was associated with an increased frequency of bone fractures when compared with the addition of placebos. As stated by Daniel E Spratt in his Comment,[3] it is plausible that the dual inhibitory effect on osteoblast function from abiraterone acetate and prednisone, combined with the osteoclastogenic effects of androgen deprivation, glucocorticoids, and radium-223, synergistically increased the risk of fracture.

However, the results also raise two fundamental questions. First, was there a strong rationale for using radium-223 in earlier stages of disease in ERA 223 than in ALSYMPCA (half of the patients in ERA 223 had asymptomatic disease and a third had less than six metastases)? The answer is probably no. Besides aspects related to bone fragility, radium-223 as a bone-seeking agent would be unable to halt growth of lymph node disease or occult visceral metastases. This result can only be expected with radioligands that target tumour cells. Radionuclide therapy targeting prostate-specific membrane antigen (PSMA) has shown great promise.[4] In patients with metastatic castration-resistant prostate cancer, who progressed after standard treatments, ^{177}Lu-PSMA-617 therapy was associated with improvements in pain, high PSA response, remarkable responses in measurable nodal and visceral disease, and low toxicity.[4] The use of ^{177}Lu-PSMA-617 therapy in earlier stages still needs to be investigated. Second, was there a strong rationale for combining radium-223 with abiraterone acetate? Although androgen deprivation sensitises prostate cancer to radiotherapy-induced death,[3] understanding how abiraterone acetate influences radionuclide uptake at tumour sites is important. Synergy would be expected if androgen deprivation with abiraterone further increases radionuclide uptake in bone lesions compared with normal bone. However, androgen deprivation is expected to reduce uptake of bone-seeking agents, although a transient paradoxical bone flare can be seen in healing lesions.[5] However, PSMA expression is high in castration-resistant prostate cancer and further increases with androgen deprivation.[4]

In conclusion, if radionuclide therapy is to be introduced earlier in castration-resistant prostate cancer, then PSMA-targeting radioligands rather than radium-223 would be the appropriate choice. Furthermore, synergy between PSMA-targeted radionuclide therapy and further androgen deprivation might be expected.

We declare no competing interests.

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1 Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; **369:** 213–23.
2 Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; **20:** 408–19.
3 Spratt DE. Combination therapies in prostate cancer: proceed with caution. *Lancet Oncol* 2019; **20:** 321–23.
4 Hofman MS, Violet J, Hicks RJ, et al. [^{177}Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol* 2018; **19:** 825–33.
5 Ryan CJ, Shah S, Efstathiou E, et al. Phase II study of abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. *Clin Cancer Res* 2011; **17:** 4854–61.