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Radium-223 in prostate cancer: emitting the right signals

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Five new treatments for metastatic castration resistant prostate cancer have shown improved overall survival.¹ Three of these therapies—abiraterone, enzalutamide, and cabazitaxel—have familiar methods of action and are more likely to produce decreases in prostate-specific antigen. The more ambiguous short-term findings with sipuleucel-T and radium-223 (no short term-changes in progression or prostate-specific antigen, but improved overall survival) have likely limited their clinical use. Radium-223 use is further complicated by the frequent requirement of a radiation oncologist or nuclear medicine radiologist for infusion. Furthermore, radium-223 is often relegated to late-stage metastatic castration resistant prostate cancer, consistent with the use of beta-emitting and gamma-emitting radionuclides.

Several years after radium-223 was shown to improve overall survival and delay symptomatic progression in metastatic castration resistant prostate cancer, emerging data is showing a clinical path forward for this well tolerated, alpha-emitting radiopharmaceutical.² Greater clinical experience with enzalutamide and abiraterone have defined their limitations, often mediated through overlapping mechanisms of resistance, including androgen receptor overexpression and androgen receptor splice variants.^{3,4} As clinical studies investigate strategies to overcome treatment resistance, the study by Fred Saad and colleagues⁵ in *The Lancet Oncology* provides intriguing preliminary data for the potential benefits involving radium-223-based combinations.

This phase 3b expanded access study enrolled patients with progressive bone-predominant metastatic castration resistant prostate cancer (excluding patients with visceral disease and lymph nodes >6 cm).⁵ The crucial difference between this study and the phase 3 ALSYMPCA trial² was the potential for concomitant use of anti-androgens and bone-targeting agents. This analysis reaffirmed the relative safety of radium-223 as a single treatment and strongly suggested its tolerability in combination with abiraterone, enzalutamide, and denosumab. In fact, the incidences of myelosuppression, gastrointestinal symptoms, and fatigue were substantially less than those reported in ALSYMPCA, though this could have been influenced by an ascertainment bias due to shorter follow-up in the present study, as the authors acknowledge. An additional contributing factor could have been the enrolment of less symptomatic patients (with potentially less advanced disease).^{2,5} As expected, patients with better prognostic features at baseline (haemoglobin >10 g/dL, normal alkaline phosphatase concentration, less pain, and better performance status) had improved overall survival compared with that in patients with worse prognostic features.⁵

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Although overall survival data are presented that suggest a greater benefit from radium-223 with concomitant enzalutamide, abiraterone, or denosumab, compared with radium-223 monotherapy, these data alone are not sufficient to warrant the use of combination therapy in all patients. Although this study does provide necessary safety data, as the authors assert, randomised trials are required to confirm the potential efficacy suggested by these findings. Such studies are ongoing, including a randomised study of abiraterone with or without radium-223 () and phase 2 trials with enzalutamide (including and). If radium-223 could extend the benefit of these anti-androgens beyond the emergence of resistant androgen receptor subclones, it could favourably impact disease progression and overall survival. Given the disparate mechanisms of action, combining radium-223 and anti-androgens seems to be a rational strategy to contend with androgen receptor-resistance.

Amidst the emergence of immune-based therapies, radium-223 could have additional relevance. Pre-clinical data suggest that radiopharmaceuticals can enhance immune recognition and immune killing of cancer cells via immunogenic modulation.⁶ A randomised clinical trial⁷ in metastatic castration resistant prostate cancer suggested the potential use of samarium-153 when combined with a therapeutic cancer vaccine. An ongoing study is also exploring the use of sipuleucel-T with or without radium-223 in metastatic castration resistant prostate cancer (). If radium-223 has confirmed immune-modulatory capabilities, interest might then focus on potential abscopal-like effects on non-bone targets, having profound implications on its utility in prostate cancer and other malignancies with bone metastasis. Patients with micrometastatic prostate cancer are another population that might benefit from radium-223. With emerging PET-imaging technologies identifying metastatic disease earlier, deployment of radium-223 in the micrometastatic setting could yield even greater clinical benefits given the smaller amount of tumour burden. Any immunological impact in addition to direct alpha-particle effects would enhance the likelihood of success in this setting. In addition, as more studies are investigating curative strategies in the newly diagnosed or oligometastatic setting, radium-223 could be investigated as a means to increase cure rates when combined with definitive radiation or surgery.

With various new treatments available for metastatic castration resistant prostate cancer, there is only a nascent understanding of the therapeutic potential in all stages of the disease. The potential of radium-223 appears unfulfilled, but perhaps the data presented by Saad and colleagues can provide the foundation for future therapeutic strategies employing this clinically active radiopharmaceutical.

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