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Research Letter

The Case Against the European Medicines Agency's Change to the Label for Radium-223 for the Treatment of Metastatic Castration-resistant Prostate Cancer

Joe M. O'Sullivan^{a,*}, Daniel Heinrich^b, Nicholas D. James^c, Sten Nilsson^d, Piet Ost^e, Christopher C. Parker^f, Bertrand Tombal^g

We write regarding a recent label change recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) and implemented by the European Medicines Agency (EMA) for the bone-targeted agent radium-223 (Xofigo) [1].

The EMA has concluded its review of the cancer medicine and has recommended restricting its use to patients who have had two previous treatments for metastatic castration-resistant prostate cancer (mCRPC) or who cannot receive other treatments. Depending on how these recommendations are interpreted, they might effectively restrict the use of this agent to the terminal phase of the illness. We believe that these restrictions are not justified on the basis of the available evidence and could result in fewer patients benefiting from this drug.

Radium-223 (Xofigo) has been licensed since 2013 for the treatment of patients with symptomatic mCRPC involving bone, with no visceral metastases. This licence was based on the improvement in overall survival (OS) demonstrated (hazard ratio [HR] 0.7) in the ALSYMPCA registration trial, which compared six cycles of radium-223 plus best standard of care to placebo plus best standard of care [2]. The trial also demonstrated a significant reduction in the risk of symptomatic skeletal events (HR 0.6). The benefits were similar whether or not men had received palliative chemotherapy with docetaxel, the only life-prolonging therapy approved for CRPC at the time of the trial. Further evidence of the benefit and safety of radium-223 has emerged over the past number of years [3,4].

The PRAC review of radium-223 was carried out in response to data from an unplanned interim analysis of a randomised trial comparing radium-223 plus abiraterone acetate and prednisolone versus placebo plus abiraterone acetate and prednisolone (ERA 223) in men with progressive mCRPC involving bone and no previous chemotherapy or abiraterone or enzalutamide. The agency's recommenda-

tions are based on an assessment of ERA 223 trial data that showed that for patients receiving radium-223 in combination with abiraterone/prednisolone, there was a higher incidence of bone fractures (28.6% vs 11.4%) and a possible reduction in OS (30.7 vs 33.3 mo; HR 1.195, 95% confidence interval [CI] 0.950–1.505; $p = 0.13$).

There was clearly a higher risk of fractures associated with use of radium-223 in ERA 223. This risk was reduced, but not abolished, when bone health agents (bisphosphonates or denosumab) were used. Routine imaging was not performed in ALSYMPCA and so it is not possible to know whether radium-223 also caused excessive asymptomatic fractures in that trial. Even if there were a higher risk of undetected asymptomatic fractures, ALSYMPCA does provide direct evidence of the lack of effect of radium-223 on clinically relevant fractures in the first- or second-line CRPC setting in the absence of exposure to abiraterone.

For agents such as radium-223 and abiraterone, which have both been shown to improve OS and quality of life, the associated risk of fractures is part of an acceptable risk-benefit profile. Indeed, of all the life-prolonging therapies for mCRPC, radium-223 has the most favourable toxicity profile, even accepting a risk of fracture. This led to the highest possible score on the ESMO Clinical Benefit Scale for radium-223, higher than for the other four life-prolonging therapies [5].

The PRAC has essentially suggested that the results of this combination trial should be extrapolated to patients treated under the previous label (symptomatic mCRPC involving bone and no evidence of visceral metastases). Combination of radium-223 with an effective therapy such as abiraterone is a very different clinical scenario to the standard use of radium-223 as monotherapy (along with androgen deprivation and supportive therapies).

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We strongly disagree with the PRAC interpretation of the ALSYMPCA data, in which they use the OS forest plot from the trial to claim that because the CI for the HR for OS crossed unity for patients with fewer than six bone metastases (HR 0.95, 95% CI 0.46–1.95) and for alkaline phosphatase <220 U/l (HR 0.82, 95% CI 0.64–1.07), such patients would not benefit in terms of OS and should not be offered radium-223.

The subgroup analyses in the forest plot tested for heterogeneity of effect and should not be used to test for treatment benefit in a particular subgroup. This topic is discussed in some depth in a recent article by one of the authors of this letter [6].

We agree that radium-223 should not be used in combination with abiraterone acetate and prednisolone/prednisone. However, we disagree with the recommendation that it should be reserved for third or later lines of therapy in mCRPC. We believe that the OS benefit from radium-223 plus best standard of care should not be in doubt as a result of the new data from ERA 223. Restricting the use of radium-223 to the third line in mCRPC will mean that many patients who could benefit will be denied access. In particular, patients with symptomatic bone metastases who are too frail to receive docetaxel or cabazitaxel or indeed who do not want cytotoxic chemotherapy may be denied access. For these patients who only have abiraterone or enzalutamide available as survival-prolonging options, the recommendation can be read as encouraging sequential use of abiraterone after enzalutamide, or vice versa, before an indication for radium-223. However, there is plenty of evidence that these sequences do not work, so this strategy would expose patients to useless expensive drugs [7].

For patients fit enough for docetaxel and/or cabazitaxel, the increasing likelihood of visceral metastases with increasing mCRPC duration [8] means that as these patients move on to third-line therapy, they are much less likely to be suitable for radium-223. If they do start radium-223, they are more likely to experience early visceral disease progression.

Of note, other drugs agencies including the US Food and Drug Administration, the Canadian Agency for Drugs and Technologies in Health, and the Japanese Pharmaceuticals and Medical Devices Agency have assessed the same data as the EMA and have decided on no change to the label for radium-223.

Conflicts of interest: Joe O'Sullivan: Advisory Board, Speakers Bureau: Astellas, Bayer, Janssen, Sanofi. Research funding (Institute) Bayer. Daniel Heinrich: Honoraria and consultancy: Astellas, Bayer, Janssen-Cilag, Roche. Nick James: Consultancy. Bayer, Astellas, Janssen, Merck, AstraZeneca, Clovis, Endocyte, Sanofi, Roche, Travel Janssen, Sanofi,

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^aCentre for Cancer Research and Cell Biology, Queen's University, Belfast City Hospital, Belfast, UK

^bAkershus University Hospital, Lørenskog, Norway

^cUniversity Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

^dKarolinska Hospital, Stockholm, Sweden

^eGhent University, Ghent, Belgium

^fInstitute of Cancer Research, Sutton, UK

^gUniversité Catholique de Louvain, Louvain, Belgium

*Corresponding author. Centre for Cancer Research and Cell Biology, Queen's University, Belfast City Hospital, Belfast BT9 7AB, UK. Tel. +44 28 95048549.

E-mail address: joe.osullivan@qub.ac.uk (Joe M. O'Sullivan).

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