available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Report – Editor's choice

Editorial by Ian D. Davis, Angelyn Anton, Edmond M. Kwan on pp. 289–291 of this issue

Decrease in Fracture Rate with Mandatory Bone-protecting Agents in the EORTC 1333/PEACE-3 Trial Comparing Radium-223 Combined with Enzalutamide Versus Enzalutamide Alone: A Safety Analysis

Silke Gillessen [a,b,], Bertrand Tombal [c], Fabio Turco [a], Ananya Choudhury [d], Alejo Rodriguez-Vida [e], Enrique Gallardo [f], Pedro Isaacsson Velho [g], Franco Nolè [h], Felipe Cruz [i], Yohann Loriot [j], Ray McDermott [k], Thierry Roumeguere [l], Gedske Daugaard [m], Rosley Yamamura [n], Emmanuelle Bompas [o], Pablo Maroto [p], Manuel Herrero Polo [q], Karine Martins da Trindade [r], Daniel D'Almeida Preto [s], Iwona Skoneczna [t], Frederic Lecouvet [c], Corneel Coens [u], Beatrice Fournier [u], Fred Saad [v]*

[a] *Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland;* [b] *Università della Svizzera Italiana, Lugano, Switzerland;* [c] *Cliniques Universitaires Saint Luc, Brussels, Belgium;* [d] *The Christie NHS Foundation Trust, Manchester, UK;* [e] *Hospital del Mar, Barcelona, Spain;* [f] *Hospital Universitari Parc Tauli, Sabadell, Spain;* [g] *Hospital Moinhos de Vento, Porto Alegre, Brazil;* [h] *Medical Oncology Division for Urogenital and Head & Neck Tumours, European Institute of Oncology IRCCS, Milan, Italy;* [i] *Instituto Brasileiro de Controle do Câncer, Sao Paulo, Brazil;* [j] *Institut Gustave Roussy, Paris, France;* [k] *St. Vincent's University Hospital, Dublin, Ireland;* [l] *Hôpital Universitaire de Bruxelles, Jules Bordet Institute and Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium;* [m] *Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark;* [n] *A Beneficência Portuguesa de São Paulo, São Paulo, Brazil;* [o] *Institut de Cancérologie de l'Ouest, Angers, France;* [p] *Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [q] *Hospital Universitario de Salamanca and Hospital Virgen De la Vega, Salamanca, Spain;* [r] *Instituto D'Or de Pesquisa e Ensino, Fortaleza, Brazil;* [s] *Hospital de Amor, Barretos, Brazil;* [t] *Maria Sklodowska Curie Memorial Cancer Centre, Warsaw, Poland;* [u] *European Organisation for Research and Treatment of Cancer, Brussels, Belgium;* [v] *Centre Hospitalier de l'Université de Montréal, Montreal, Canada*

Article info

Article history:
Accepted November 29, 2024

Associate Editor:
Gianluca Giannarini MD

Keywords:
Bone health;
Metastatic castration-resistant prostate cancer;
Enzalutamide;

EU ACME
www.eu-acme.org/europeanurology

Please visit www.eu-acme.org/europeanurology to answer questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Bone health is central to the management of patients with metastatic castration-resistant prostate cancer (mCRPC). International guidelines recommend giving a bone-protecting agent (BPA) to patients with mCRPC and bone metastases. However, the data supporting these recommendations were generated before androgen receptor pathway inhibitors (ARPIs) were available. Here we publish for the first time fracture rates from an interim safety analysis of the international prospective phase 3 PEACE-3 trial comparing radium-223 (^{223}Ra) combined with enzalutamide for first-line mCPRC to enzalutamide alone. After results from the ERA-223 trial (abiraterone ± ^{223}Ra) showed a high fracture rate in both arms, the independent data monitoring committee of PEACE-3 mandated BPA use during the trial, which increased BPA use from 46.1% to 97%. For patients who received BPA therapy, fracture rates significantly decreased in both study arms. At 1

* Corresponding author. Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland.
E-mail address: Silke.GillessenSommer@eoc.ch (S. Gillessen).

https://doi.org/10.1016/j.eururo.2024.11.027

Radium-223;
Safety analysis;
Bone-protecting agents;
Bone fractures

year, fractures decreased from 15.6% to 2.6% with a BPA in patients receiving enzalutamide monotherapy. The interim safety analysis of PEACE-3 underscores the high risk of fracture in patients with mCRPC and the necessity of complying with guidelines regarding BPA administration in the ARPI era.

The EORTC GUCG-1333 PEACE-3 trial is registered on ClinicalTrials.gov as NCT02194842 and on EudraCT as 2014-001787-36.

ADVANCING PRACTICE

What does this study add?
Results from this safety analysis of the PEACE-3 trial underline the importance of using a bone-protecting agent (BPA) in patients with metastatic castration-resistant prostate cancer and bone metastasis in the era of androgen receptor pathway inhibitors. These are new data from, to the best of our knowledge, the only trial for this indication that has made BPA use during trial treatment mandatory.

Clinical Relevance
Bone health plays a crucial role in managing the quality of life of patients with advanced prostate cancer, particularly in the metastatic castration-resistant phase, where there is an elevated risk of fractures due to bone metastases and treatment with androgen receptor pathway inhibitors. This interim safety analysis of the highly anticipated EORTC 1333 PEACE-3 trial demonstrates that bone-protecting agents, such as zoledronic acid or denosumab, administered at a monthly prophylactic dose, significantly reduce bone fracture rates in patients receiving radium-223 in combination with enzalutamide or enzalutamide alone. These findings underscore the importance of providing bone-protecting agents to patients with metastatic castration-resistant prostate cancer to prevent skeletal-related events and enhance their quality of life. Associate Editor: Gianluca Giannarini MD.

Patient Summary
Our study results show that patients with metastatic prostate cancer who have bone metastases and no longer respond to androgen deprivation therapy should receive a treatment for bone protection.

The standard of care treatment for most patients with metastatic castration-resistant prostate cancer (mCRPC) is one of the androgen receptor pathway inhibitors (ARPI) abiraterone or enzalutamide [1]. On the basis of abundant literature demonstrating a synergy between radiation therapy and hormone therapy, the combination of radium-223 (^{223}Ra) and an ARPI makes biological sense. The ERA-223 trial tested abiraterone combined with ^{223}Ra (NCT02043678) [2], while the PEACE-3 trial evaluated enzalutamide combined with ^{223}Ra (NCT02194842). Beyond the potential oncological benefit of these combinations, both studies highlight the importance of preventing bone complications in patients treated with an ARPI.

Bone loss induced by androgen deprivation therapy (ADT) was first described more than 25 years ago and has been confirmed in several prospective studies [3]. After 12 months of ADT, most patients will have lost 2–10% of their bone mass, leading to an increase in the risk of fractures [3]. Most international guidelines recommend monitoring bone loss via regular dual-energy X-ray absorptiometry (DEXA) scans and/or the use of algorithms that predict the risk of fractures, and treatment with low-dose/low-intensity bisphosphonates or denosumab (eg, zoledronic acid 5 mg once a year or denosumab 60 mg every 6 mo) in addition to calcium and vitamin D for patients at high risk. Later in the disease course, bone metastases will affect skeletal integrity, resulting in high skeletal-related event (SRE) rates, including pathological fractures, a need for bone radiotherapy or surgery, and spinal cord compression. On the basis of two historical randomized clinical trials, guidelines recommend a monthly dose of zoledronic acid 4 mg or denosumab 120 mg to reduce SREs for patients with mCRPC and bone metastases [4,5]. These studies were conducted in an era when few therapeutic options were available for mCRPC. Patients with advanced mCRPC were often included, with a significant proportion having already experienced one or more SREs [4,5]. Years after these studies, when abiraterone and enzalutamide became the standard of care for asymptomatic or mildly symptomatic mCRPC, physicians felt that BPAs could be postponed to later in the disease course; as a resulting, many patients did not receive adequate bone protection [6]. Post hoc analyses of clinical trial data suggested that addition of a BPA to ARPIs may provide further clinical benefits for patients with mCRPC [7].

In ERA-223, only 39% of patients in the combination arm and 42% in the placebo arm received a BPA, although all patients had skeletal metastases [2]. This had dramatic consequences. In November 2017, the Independent Data Mon-

itoring Committee (IDMC) recommended trial unblinding after observing more fractures in the abiraterone + ^{223}Ra arm than in the abiraterone + placebo arm (29% vs 11%). According to a post hoc analysis, the fracture rate was significantly lower for patients taking a BPA in both arms [2]. Following review of these results by the Pharmacovigilance Risk Assessment Committee, the European Medicines Agency formally warned against using ^{223}Ra in combination with abiraterone [8].

The EORTC GU-1333/PEACE-3 phase 3 trial is a collaboration involving Cancer Trials Ireland, the Canadian Urological Oncology Group, the Latin American Cooperative Oncology Group, and the French group UNICANCER-GETUG. The trial is evaluating the combination of enzalutamide plus ^{223}Ra versus enzalutamide alone in asymptomatic or mildly symptomatic patients with mCRPC and at least two metastases on bone scintigraphy. The main results from the trial have not yet been published.

Following release of the ERA-223 data, the PEACE-3 study was amended and an urgent safety letter was sent to investigators in March 2018 (Supplementary material). BPA administration (either zoledronic acid or denosumab) became mandatory at the monthly SRE-preventing dose. Patients had to receive at least two BPA doses before the first ^{223}Ra dose, with continuation of BPA administration during the study period. In addition, a DEXA scan became mandatory at entry to exclude pre-existing osteoporosis. The IDMC requested an additional safety analysis of the fracture rate. This created a unique continuum in a single trial, from an initial phase when BPA was left to the discretion of the treating physician, to a phase when it became mandatory.

Here, we report interim safety results for fracture incidence with and without BPA use in PEACE-3. The database lock date for this report was April 2021. At the time, 267 patients had been enrolled in the study, with treatment information available for 251 (122 in the combination arm and 129 in the enzalutamide arm). BPA use was defined as BPA administration during protocol treatment (regardless of use at the time of enrollment) but before any bone fracture. Of the 115 patients enrolled in the trial before the safety letter mandating BPA use, only 63 (54.8%) received a BPA. Of these 63 patients, eight received the BPA only after a fracture, and two received BPA at entry but stopped before protocol treatment. Thus, only 53 patients (46.1%) received a BPA during protocol treatment. Of the 251 patients in this safety analysis, BPA use was recorded for 184 (73%) patients. At the time of data cutoff for this analysis, 136 patients were treated after the urgent safety letter, of whom 131 (96%) received a BPA. Of these 131 patients, only one received the BPA after a fracture (Supplementary Table 1). A total of 40 fractures were reported. The cumulative fracture incidence and associated 95% confidence interval (CI) were estimated via the Fine-Gray method, with competing events taken into account (Supplementary material).

The impact of mandating BPA use is striking in both arms of the trial. After 1 year of treatment, the cumulative fracture incidence for patients without BPA use was 15.6% (95% CI 5.6–30.3%) in the enzalutamide arm and 37.1% (95% CI 21.3–53.0%) in the combination arm. The cumulative incidence of fractures at 1 year was dramatically lower for patients receiving a BPA, at 2.6% (95% CI 0.5–8.3%) in the enzalutamide alone and 2.7% (95% CI 0.5–8.5%) in the enzalutamide + ^{223}Ra arm (Fig. 1 and Supplementary Table 2). The high rate of fractures for patients on enzalutamide alone without BPA use (almost 16%) is in line with other

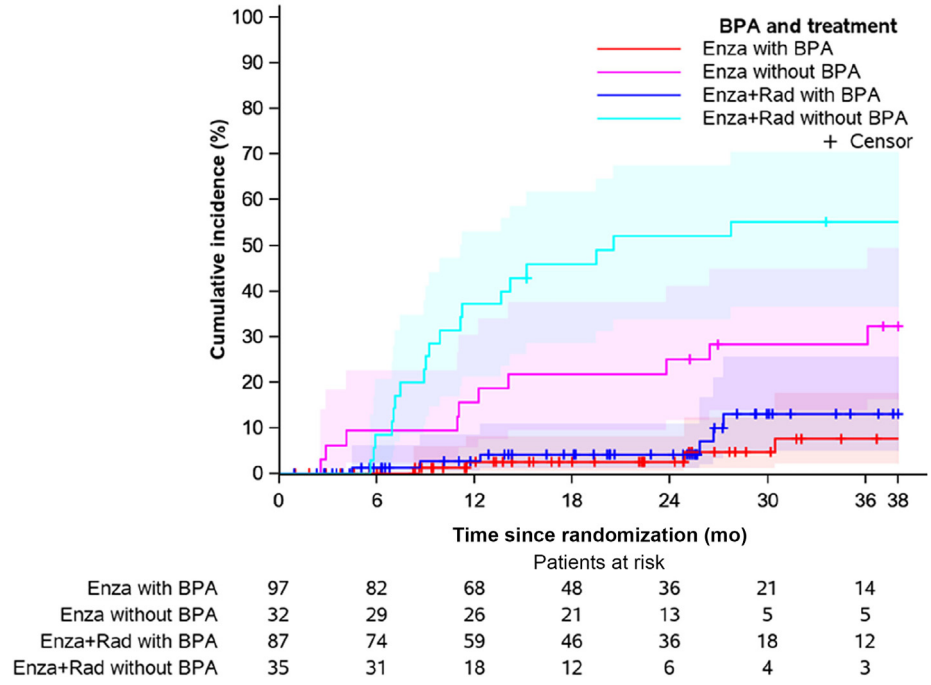

Fig. 1 – Fine-Gray cumulative incidence of fractures by treatment arm and BPA use. Shaded areas denote the 95% confidence interval. Enza = enzalutamide; RAD = radium-223; BPA = bone protecting agent.

studies; this issue is often overlooked despite being clinically relevant.

This interim safety analysis of PEACE-3 confirms the importance of complying with international recommendations to co-administer a BPA at the monthly SRE-prevention dose (eg, zoledronic acid 4 mg or denosumab 120 mg) when treating patients with mCRPC and bone metastases. Of note, this is the dosing scheme approved for this setting, but the optimal BPA dose and schedule and the optimal treatment duration are not known and need to be tested in further trials. Importantly, this is the first trial to prospectively demonstrate the impact of BPA use on fracture risk for men receiving an ARPI. Although prostate cancer bone metastases are predominantly osteoblastic, histological findings and analysis of bone turnover markers support the view that excess osteoclast activity induces bone destruction and thus bone fractures [9,10]. ^{223}Ra primarily targets osteoblasts, which may be the reason for the higher fracture rate in the combination arm. Thus, through their mechanism of action, both bisphosphonates and denosumab can reduce osteoporotic fractures and SREs in patients with mCRPC and bone metastases, as evidenced by our results.

Author contributions: Silke Gillessen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Gillessen, Tombal, Saad, Turco.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Coens.
Obtaining funding: Tombal, Gillessen.
Administrative, technical, or material support: None.
Supervision: Gillessen, Tombal, Saad.
Other: None.

Financial disclosures: Silke Gillessen certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Silke Gillessen reports personal honoraria from the Swiss Group for Clinical Cancer Research (SAKK), European Society of Medical Oncology (ESMO), and Meister ConCept; travel grants from Bayer, Gilead, and Intellisphere LLC; institutional honoraria for advisory board, independent data monitoring committee, or steering committee participation from Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Innomedica, Ipsen, Macrogenics, MSD, and Novartis; an invited speaker role for AdMeTech Foundation, SAKK, the American Society of Clinical Oncology, Meister ConCept, ESMO, PeerVoice, Pfizer, Silvio Grasso Consulting, EPG Health, and Intellisphere LLC; and patent royalties and other intellectual property interests in a research method for biomarker discovery (WO2009138392). Bertrand Tombal reports relevant financial relationships with Accord, Amgen, Astellas, AstraZeneca, Bayer, Curipum Ferring, Novartis, Janssen, Myovant, MSD, and Pfizer; and a relevant non-financial relationship with EORTC. Fabio Turco reports a travel grant from Bayer. Enrique Gallardo reports a consultant or advisory role for Advanced Accelerator Applications, Astellas, AstraZeneca, Bayer, BMS, Daiichi Sankyo, Eisai, GSK, Ipsen, Janssen, Lilly, Merck, Pfizer, Recordati, Roche, Sanofi, and Techdow; a speaking role for Advanced Accelerator Applications, Astellas, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, Eisai, GSK, Ipsen, Janssen, Leo Pharma, Menarini, Merck, MSD, Pfizer, Recordati/EUSA Pharma, Roche, Rovi, and Sanofi; grant support from Advanced Accelerator Applications, Astellas, AstraZeneca, Bayer, BMS, Ipsen, Janssen, Merck, MSD, Pfizer, Recordati, and Roche; and travel and accommodation expenses from Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Janssen, Leo Pharma, Pfizer, and Roche. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: We are grateful to Bayer HealthCare Pharmaceuticals for supporting this study through an educational grant and for providing Radium-223 for this study . We are also grateful to Astellas Pharma Europe Ltd for supporting this study through an educational grant and for providing Enzalutamide. The sponsors played no direct role in the study.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2024.11.027.

References

[1] Tilki D, van den Bergh RCN, Briers E, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer. Part II–2024 update: treatment of relapsing and metastatic prostate cancer. Eur Urol 2024;86:164–82.
[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] Butoescu V, Tombal B. Practical guide to bone health in the spectrum of advanced prostate cancer. Can J Urol 2014;21:84–92.
[4] Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377:813–22.
[5] Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004;96:879–82.
[6] Body JJ, von Moos R, Rider A, et al. A real-world study assessing the use of bone-targeted agents and their impact on bone metastases in patients with prostate cancer treated in clinical practice in Europe. J Bone Oncol 2019;14:100212.
[7] Saad F, Sternberg CN, Mulders PFA, Niepel D, Tombal BF. The role of bisphosphonates or denosumab in light of the availability of new therapies for prostate cancer. Cancer Treat Rev 2018;68:25–37.
[8] Gourd E. EMA guidance on radium-223 dichloride in prostate cancer. Lancet Oncol 2018;19:e190.
[9] Roudier MP, Morrissey C, True LD, Higano CS, Vessella RL, Ott SM. Histopathological assessment of prostate cancer bone osteoblastic metastases. J Urol 2008;180:1154–60.
[10] Brown JE, Cook RJ, Major P, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. J Natl Cancer Inst 2005;97:59–69.