Commentary to “Denosumab for bone health in prostate and breast cancer patients receiving endocrine therapy? A systematic review and a meta-analysis of randomized trials” (Galvano et al. J Bone Oncol 2019; 18:100252)

We read with great interest the systematic review and a meta-analysis of randomized trials on denosumab for bone health in cancer patients receiving endocrine therapy by Galvano A. et al. [1]. We disagree with the main conclusion of this review article, which is that denosumab administration can be considered effective and safe in this clinical situation.

In prostate cancer patients receiving androgen deprivation therapy, and in patients under adjuvant endocrine therapy for early-stage endocrine-sensitive breast cancer, denosumab is routinely discontinued when the hormonal treatment is interrupted, unless a diagnosis of osteoporosis persists. It is now well known that denosumab discontinuation is associated with a severe rebound effect that lasts 2 years, which combines an increase in bone turnover markers and a complete loss of bone density [2]. This rebound effect is associated, in post-menopausal osteoporosis, with multiple spontaneous vertebral fractures (MSVF) as described in several case series and in the post-hoc follow-up of the pivotal FREEDOM trial [3–7]. Cases have also been described in men [8]. It is a severe secondary effect, as patients present a median of five (1–11) vertebral fractures 7–20 months (median 11) after the last denosumab injection [7]. 1–10% of women with post-menopausal osteoporosis discontinuing denosumab suffer of MSVF, and although bisphosphonates given at denosumab discontinuation probably decrease the MVSF risk, cases of fracture despite bisphosphonate treatment have been described [7].

One could think that patients receiving denosumab for bone health preservation during hormonal therapies designed for breast and prostate tumors with a low fracture risk might be protected from MVSF. No case has been described including patients with prostate tumors under hormonal treatment. However, unpublished data from the off-treatment follow-up of the ABCSG-18 trial suggests the risk is increased similarly to post-menopausal women in those treated with aromatase-inhibitors [9]: in this study, the hazard ratio for MSVF was 3.52 (CI 0.98, 12.64) in women who stopped denosumab as compared to women who stopped placebo. Indeed, we just published data on a cohort of 15 women with early-stage breast cancer treated with aromatase inhibitors and denosumab for bone loss prevention [10]: they suffered 1–11 (mean 4.0 ± 1.9) clinical vertebral fractures within 7–16 months after last denosumab injection. Importantly, these fractures appeared earlier in patients without osteoporosis before denosumab (9.4 ± 2.0 vs. 13.0 ± 2.0 months; p = 0.005), suggesting low fracture risk does not protect from this adverse event.

We are aware that there is no published data on denosumab discontinuation in the targeted population to be included in the meta-analysis. However, this risk should be discussed, and the absence of off-denosumab solid data cited as an important limitation of the study, as the safety profile should also consider the significant post-treatment events.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References
Letter to Editor

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