



## Response to Letter

**Reply 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 the commentary by Gonzalez-Rodriguez E. et al and we would like to point out the followings. In our opinion, the crucial point is represented by the starting question from which the project of the metanalysis was born. The patient population included in our meta-analysis consists exclusively of patients suffering from early-stage breast or prostate cancer undergoing adjuvant hormone therapy in order to evaluate the efficacy in terms of vertebral and non-vertebral fracture risk reduction and densitometric improvement of Denosumab administered every six months for a duration of 24–36 months. In our analysis, what happens once treatment with Denosumab is discontinued is not taken into consideration, as no published data on the discontinuation of Denosumab was provided by randomized trials included in our pooling. It is certainly intuitive that stopping Denosumab could cause bone effects. Denosumab is a monoclonal antibody with high affinity and specificity for human RANKL. By binding to its target, it prevents RANKL from interacting with its RANK receptor on the surface of mature osteoclasts and their precursors and inhibits the bone resorption mediated by them. However, when the binding is exhausted, the initial state RANK-RANKL is restored [1]. The meta-analysis by Lamy et al. [2] studies the rebound effect of Denosumab and concludes that therapy can be suspended and could be replaced with a bisphosphonate due to the increased risk of new fractures, although this constitutes an opinion of the authors and not a consolidated strategy. In addition, study ABCSG-18 [3] has as its primary endpoint the time of appearance of the first fracture after starting Denosumab treatment in patients with non-metastatic breast cancer treated with aromatase inhibitors and as a secondary endpoint the disease-free survival; the conclusion of the same authors is that Denosumab has reduced the risk of fracture during treatment and was both effective and safe. Therefore, although it seems reasonable to consider the absence of post-treatment data as a limit to assess Denosumab long-term effects and clinical studies should be designed to investigate this situation, this aspect does not

appear as strong enough to invalidate the conclusions of the three phase III randomized trials [4–6] and our meta-analysis investigating the ability of Denosumab to reduce the risk of vertebral and non-vertebral fractures by improving the bone densitometric properties in patients with early-stage breast or prostate cancer treated with hormone therapy.

## References

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