of denosumab was present in all age groups, with no apparent interaction with age. At an overall hazard ratio of 0.5 for fracture reduction, denosumab should therefore be considered for patients receiving aromatase inhibitor irrespective of their age.

I agree that the relation between bone mineral density measurements and fracture risk needs to be further elucidated in these patients. Clearly, no such relation was apparent in patients with breast cancer who were randomly assigned to receive adjuvant aromatase inhibitor therapy in the ABCSG-18 trial, which might have affected their bone physiology differently compared to patients in the FREEDOM trial. In another trial, dual-energy x-ray absorptiometry scans were shown to be an imperfect surrogate parameter for the true magnitude of treatment-induced bone loss.

Longer durations (or more intense schedules) of denosumab treatment might indeed increase the risk of osteonecrosis of the jaw and atypical fractures, but as an adjuvant treatment, denosumab 60 mg given every 6 months for a limited duration is both highly effective and safe.

In response to Paul de Boissieu and Thierry Trenque, I can state that assessment and adjudication of potential cases of osteonecrosis of the jaw in the ABCSG-18 trial was done in accordance with the American Association of Oral and Maxillofacial Surgeons position paper about bisphosphonate-related osteonecrosis of the jaws, fully published first in 2007 and updated in 2009 and 2014. Because of the increased awareness of this rare but important side-effect, we have established a proactive system to screen for any potential osteonecrosis of the jaws in the ABCSG-18 study population (as outlined in detail in the appendix, p 60). In addition to reported cases of potential osteonecrosis of the jaw, the trial database was automatically checked every month by data management and additionally searched by a clinical safety officer for any of 42 predefined (candidate) terms of osteonecrosis. We found no statistical differences between the denosumab and placebo groups with respect to these identified database terms (five cases of periodontitis in the placebo group vs seven cases in the denosumab group; three cases of pain in jaw in the placebo group vs five cases in the denosumab group; one case of loose tooth in the placebo group vs two cases in the denosumab group; one case of oral abscess in the placebo group vs one case in the denosumab group; all other terms leading to adjudication occurred only in single cases in the database).

We stand firmly by our conclusion that denosumab 60 mg every 6 months, as used in the ABCSG-18 trial, is generally well tolerated and does not lead to relevant frequencies of osteonecrosis of the jaw. Unwarranted concerns about this adverse event should not preclude aromatase inhibitor-treated patients with breast cancer, with their significant risk of developing a treatment-induced fracture, from a beneficial treatment that reduces fracture incidence to 50%, at no added toxicity.

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