Denosumab in early-stage breast cancer

Authors' reply

We appreciate the comments of Elena Rodriguez and colleagues on our report[1] on the randomised, phase 3 ABCSG-18 trial showing that, in addition to reducing clinical fractures by 50%,[2] adjuvant denosumab 60 mg twice yearly improves disease-free survival in postmenopausal patients with early breast cancer receiving adjuvant aromatase inhibitors (AIs). We acknowledge and share their concerns about a potential rebound effect after discontinuation of the anti-RANK ligand therapy. However, patients with breast cancer receiving AIs causing treatment-induced bone loss might react differently to those without cancer in osteoporosis trials. We are currently working on a detailed analysis of post-treatment bone events in our trial, part of which has already been presented,[3] and showed that the incidence of rebound fractures is much lower in ABCSG-18 than in the FREEDOM trial. Although we agree that commencing other anti-resorptive therapies such as bisphosphonates after discontinuing denosumab treatment might be an interesting approach to prevent such a rebound effect, we strongly believe that such a strategy ultimately needs to be tested in a prospective randomised manner before being recommended for use in routine clinical practice.

We acknowledge the interest of Mariana Brandão and colleagues in the subject of adjuvant bone-targeted therapies for postmenopausal breast cancer; however, we disagree with their conclusions. We do not underestimate the importance of the meta-analysis[4] on adjuvant bisphosphonate trials to which we have contributed substantially in design, execution, and interpretation, but it does in no way contradict the results of a well designed, prospectively randomised, double-blind, placebo-controlled, 3425-patient phase 3 trial with a reasonable follow-up of more than 6 years. In fact, the reported hazard reductions for disease-free survival are very similar, as are long-term absolute gains both in ABCSG-18 and the meta-analysis.[1,4] Although the initial results of the D-CARE study[5] did not find a difference in its secondary endpoint disease-free survival, the trial is not entirely negative but showed positive signals in some interesting exploratory endpoints—eg, time to first bone metastasis (hazard ratio 0·82, 95% CI 0·66–1·02; p=0·068) and time to bone metastasis as first site of recurrence (0·76, 0·59–0·97; p=0·031). Also, as is very clear from Brandão and colleagues' valuable comparative table, patient populations differ massively between ABCSG-18 and D-CARE. In fact, the differences between these two trials both in design and outcomes are strikingly reminiscent of very similar differences between the ABCSG-12[6] and the AZURE[7] trial, both important large clinical trials from the bisphosphonate era, back then initiating controversial discussions but eventually helping to establish an accepted standard of care—and probably more importantly, creating highly valuable subsequent research and biomarker projects.[7]

In summary, we fully agree that adjuvant bisphosphonates are a valuable addition to the treatment algorithm of postmenopausal patients with early breast cancer on bone health-compromising adjuvant endocrine therapies, which has also most recently been strongly reiterated by the St Gallen Consensus Conference at its 2019 meeting in Vienna.[8] However, the better is the enemy of the good: to be able to make an informed choice, women should be empowered to choose between bisphosphonate therapy (with its well known side-effects often leading to early treatment discontinuation in clinical practice) and the adjuvant denosumab treatment as established in ABCSG-18, leading to a reduction of treatment-induced clinical fractures by half, conveying a benefit in disease-free survival similar to bisphophonates, and being applied by well tolerated subcutaneous injections twice yearly.

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1 Gnant M, Pfeiler G, Steger GG, et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; **20:** 339–51.

2 Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015; **386:** 433–43.

3 Pfeiler G, Steger GG, Egle D, et al. Fracture risk after stopping adjuvant denosumab in hormone receptor positive breast cancer patients on aromatase inhibitor therapy – an analysis of 3,425 postmenopausal patients in the phase III ABCSG-18 trial. *J Bone Miner Res* 2018; **33** (suppl 1)**:** LB-1167 (abstr).

4 Early Breast Cancer Trialists' Collaborative Group. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* 2015; **386:** 1353–61.

5 Coleman RE, Finkelstein D, Barrios CH, et al. Adjuvant denosumab in early breast cancer: first results from the international multicenter randomized phase III placebo controlled D-CARE study. *Proc Am Soc Clin Oncol* 2018; **36** (suppl 15)**:** 501 (abstr).

6 Gnant M, Mlineritsch B, Schippinger W. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009; **360:** 679–91.

7 Coleman RE, Collinson M, Gregory W, et al. Benefits and risks of adjuvant treatment with zoledronic acid in stage II/III breast cancer. 10 years follow-up of the AZURE randomized clinical trial (BIG 01/04). *J Bone Oncol* 2018; **13:** 123–35.

8 Balic M, Thomssen C, Würstlein R, Gnant M, Harbeck N. St. Gallen/Vienna 2019: a brief summary of the consensus discussion on the optimal primary breast cancer treatment. *Breast Care* 2019; published online April 4. DOI:10.1159/000499931.