Denosumab in early-stage breast cancer

It was with great interest that we read the survival results from the ABCSG-18 trial,[1] which randomly assigned postmenopausal patients with early-stage hormone receptor-positive breast cancer to denosumab or placebo. Results published in 2015 showed that denosumab significantly reduced clinical fractures, which was the primary endpoint of the study.[2] Now, Michael Gnant and colleagues report a modest improvement in disease-free survival with denosumab, a secondary endpoint, after a partial unmasking of the trial. Because of a variety of constraints, this analysis can only be considered descriptive, but it is implied that adjuvant denosumab or bisphosphonates should now be offered to postmenopausal women with hormone receptor-positive breast cancer. We have to disagree with this recommendation, since we believe that bisphosphonates remain the sole standard of care in this setting.

Ideally, the comparator in ABCSG-18 should have been a bisphosphonate and not placebo. Yet, in the absence of a direct head-to-head comparison, our clinical judgment must rely on the best available evidence. A meta-analysis[3] of adjuvant bisphosphonate treatment in early breast cancer showed that the use of bisphosphonates yielded an absolute reduction of 3·3% in breast cancer mortality in postmenopausal women (table). However, data on denosumab are contradictory, with the D-CARE trial[4] being negative for disease-free survival and overall survival and ABCSG-18 showing a modest benefit in disease-free survival, with no data reported on mortality. Notably, disease-free survival was a secondary endpoint of ABCSG-18, which was analysed on 3420 participants, whereas breast cancer recurrence and mortality were co-primary endpoints of the large meta-analysis,[3] analysed on 11 767 participants, thus making it a much more robust analysis.

In addition, the D-CARE trial[4] of 4509 participants had a similar follow-up time, a larger sample size, and used a more intense regimen of denosumab in higher-risk patients than did ABCSG-18. Hence, its negative results cannot be explained by suboptimal dosage or insufficient power, follow-up time, or number of disease-free survival events. Furthermore, ABCSG-18 showed that patients who started denosumab within 3 months of the start of aromatase inhibitors were the ones deriving more benefit from treatment.[1] In D-CARE,[4] it was mandatory to start treatment no later than 3 months after surgery, so patients had the ideal time window to receive denosumab.

Therefore, despite the promising role that denosumab might have in the adjuvant setting for postmenopausal patients with breast cancer, there

	ABCSG-18 trial[1,2]	D-CARE trial[4]	EBCTCG meta-analysis[3] (post-menopausal subgroup only)
Number of participants	3420	4509	11767
Recruitment period	2006–13	2010–12	Trials beginning before 2008
Key eligibility criteria	Postmenopausal patients with oestrogen receptor-positive early breast cancer receiving treatment with aromatase inhibitors	Patients with stage II or III breast cancer, any subtype	Patients with early breast cancer, any subtype
Population characteristics			
Lymph node-negative tumours	71%	6%	29%
Oestrogen receptor-positive and HER2-negative breast cancer	94%	65%	76%
HER2-positive breast cancer	6%	20%	Not reported
Triple-negative breast cancer	0	15%	Not reported
No previous chemotherapy	75%	4%	25%
Receiving aromatase inhibitors	100%	55% (within oestrogen receptor positive patients)	Not reported
Intervention	Denosumab 60 mg every 6 months, during aromatase inhibitor treatment	Denosumab 120 mg once every 3–4 weeks × 6 doses, followed by denosumab 120 mg once every 3 months for 54 months	Bisphosphonates, with mean scheduled treatment duration of 3·4 years
Comparator	Placebo	Placebo	Placebo
Timing of treatment initiation	<24 months after the beginning of aromatase inhibitor treatment	≤3 months after definitive surgery	Not specified

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	ABCSG-18 trial[1,2]	D-CARE trial[4]	EBCTCG meta-analysis[3] (post-menopausal subgroup only)
(Continued from previous page)			
Results			
Median follow-up	73 months (IQR 58–95)	67 months (IQR 55–74)	5·6 person-years (IQR 3·7–8·0)
Primary endpoints	Time to first clinical fracture: HR 0·50 (95% CI 0·39–0·65); first clinical fracture rates at 84 months: 11·1% with denosumab *vs* 26·2% with placebo	Bone metastasis-free survival rates: 87·1% with denosumab *vs* 86·5% with placebo (HR 0·97, 95% CI 0·82–1·14)	10-year recurrence of breast cancer: 15·4% with bisphosphonates *vs* 17·6% with placebo (RR 0·86, 95% CI 0·78–0·94); 10-year distant recurrence: 12·5% *vs* 14·8% (0·82, 0·74–0·92); 10-year breast cancer mortality: 14·7% *vs* 18·0% (0·82, 0·73–0·93)
Disease-free survival (secondary endpoint)	5-year disease-free survival: 89·2% with denosumab *vs* 87·3% with placebo; 8-year disease-free survival: 80·6% *vs* 77·5%; number of disease-free survival events: 240 (14·0%) *vs* 287 (16·8%), HR 0·82 (95% CI 0·69–0·98)	5·6 year disease-free survival: 80·4% with denosumab *vs* 80·8% with placebo; number of disease-free survival events: 442 (19·6%) *vs* 433 (19·2%), HR 1·04 (95% CI 0·91–1·19)	..
Absolute gain	In disease-free survival: 1·9% at 5 years; 3·1% at 8 years	No gain in disease-free survival	At 10 years: 2·2% in breast cancer recurrence, 2·3% in distant recurrence, 3·3% in breast cancer mortality
Subgroup analysis of disease-free survival	Oestrogen-receptor positive or HER2 negative 5-year disease-free survival: 89·1% with denosumab vs 87·4% with placebo (HR 0·83, 95% CI 0·69–0·98)	Oestrogen-receptor positive or HER2 negative: HR 0·95 (95% CI 0·79–1·14); postmenopausal: 1·12 (0·92–1·36)	..
Osteonecrosis of the jaw	0	5% with denosumab *vs* <1% with placebo	Not reported

HR=hazard ratio. RR=rate ratio. EBCGTCG=Early Breast Cancer Trialists' Collaborative Group.

Table: **Comparison of phase 3 trials testing adjuvant denosumab and the meta-analysis regarding the efficacy of adjuvant bisphosphonates in early-stage breast cancer**

are still uncertainties concerning its benefit on survival. In this clinical scenario, bisphosphonates should remain the standard of care, while denosumab can be recommended to patients who have contraindications for bisphosphonates and mostly with the goal of decreasing bone fracture risk.

MB and EdA declare travel expenses paid for by Roche-Genentech and research grants to their Institute from AstraZeneca, Novartis, Roche-Genentech, and Servier. EdA has also been a member of the advisory board for Roche-Genentech. MD declares no competing interests.

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