

Adjuvant denosumab in breast cancer (ABC SG-18): a multicentre, randomised, double-blind, placebo-controlled trial



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Summary

Background Adjuvant endocrine therapy compromises bone health in patients with breast cancer, causing osteopenia, osteoporosis, and fractures. Antiresorptive treatments such as bisphosphonates prevent and counteract these side-effects. In this trial, we aimed to investigate the effects of the anti-RANK ligand antibody denosumab in postmenopausal, aromatase inhibitor-treated patients with early-stage hormone receptor-positive breast cancer.

Methods In this prospective, double-blind, placebo-controlled, phase 3 trial, postmenopausal patients with early hormone receptor-positive breast cancer receiving treatment with aromatase inhibitors were randomly assigned in a 1:1 ratio to receive either denosumab 60 mg or placebo administered subcutaneously every 6 months in 58 trial centres in Austria and Sweden. Patients were assigned by an interactive voice response system. The randomisation schedule used randomly permuted block design with block sizes 2 and 4, stratified by type of hospital regarding Hologic device for DXA scans, previous aromatase inhibitor use, and baseline bone mineral density. Patients, treating physicians, investigators, data managers, and all study personnel were masked to treatment allocation. The primary endpoint was time from randomisation to first clinical fracture, analysed by intention to treat. As an additional sensitivity analysis, we also analysed the primary endpoint on the per-protocol population. Patients were treated until the prespecified number of 247 first clinical fractures was reached. This trial is ongoing (patients are in follow-up) and is registered with the European Clinical Trials Database, number 2005-005275-15, and with ClinicalTrials.gov, number NCT00556374.

Findings Between Dec 18, 2006, and July 22, 2013, 3425 eligible patients were enrolled into the trial, of whom 3420 were randomly assigned to receive denosumab 60 mg (n=1711) or placebo (n=1709) subcutaneously every 6 months. Compared with the placebo group, patients in the denosumab group had a significantly delayed time to first clinical fracture (hazard ratio [HR] 0.50 [95% CI 0.39–0.65], p<0.0001). The overall lower number of fractures in the denosumab group (92) than in the placebo group (176) was similar in all patient subgroups, including in patients with a bone mineral density T-score of –1 or higher at baseline (n=1872, HR 0.44 [95% CI 0.31–0.64], p<0.0001) and in those with a bone mineral density T-score of less than –1 already at baseline (n=1548, HR 0.57 [95% CI 0.40–0.82], p=0.002). The patient incidence of adverse events in the safety analysis set (all patients who received at least one dose of study drug) did not differ between the denosumab group (1366 events, 80%) and the placebo group (1334 events, 79%), nor did the numbers of serious adverse events (521 vs 511 [30% in each group]). The main adverse events were arthralgia and other aromatase-inhibitor related symptoms; no additional toxicity from the study drug was reported. Despite proactive adjudication of every potential osteonecrosis of the jaw by an international expert panel, no cases of osteonecrosis of the jaw were reported. 93 patients (3% of the full analysis set) died during the study, of which one death (in the denosumab group) was thought to be related to the study drug.

Interpretation Adjuvant denosumab 60 mg twice per year reduces the risk of clinical fractures in postmenopausal women with breast cancer receiving aromatase inhibitors, and can be administered without added toxicity. Since a main side-effect of adjuvant breast cancer treatment can be substantially reduced by the addition of denosumab, this treatment should be considered for clinical practice.

Funding Amgen.

Introduction

Adjuvant endocrine therapy is the treatment of choice for hormone receptor-positive early-stage breast cancer.¹ For postmenopausal patients, aromatase inhibitors have emerged as the standard of care because of their superior efficacy compared with tamoxifen, which has

been shown in several large clinical trials in upfront, sequencing, and extended adjuvant treatment settings (Early Breast Cancer Trialists' Collaborative Group, personal communication).

Aromatase inhibitors suppress the conversion of androgens to oestrogens, resulting in oestrogen

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See Online for appendix

Research in context

Evidence before this study

We searched the PubMed database on May 4, 2015, using "adjuvant denosumab" and "breast cancer" as keywords, with no date or language restrictions. Our search identified 37 reports, of which most were review articles and reports on the use of bisphosphonates for bone protection. Our search found one small series (n=252 patients) of adjuvant denosumab for breast cancer reported by Ellis and colleagues (2008), with beneficial effects of a 24-month intervention on bone mineral density, but no information about fractures. We also searched the ClinicalTrials.gov database on May 4, 2015, and found 17 studies registered for "denosumab" and "breast cancer". Most of these studies investigate the use of the anti-RANK ligand antibody in metastatic disease. When we confined our search to "adjuvant denosumab", we found only two randomised clinical trials registered there, of which ABCSG-18 is the first to report its results.

Added value of this study

Our findings show that adjuvant denosumab significantly reduces aromatase inhibitor-induced fractures in postmenopausal patients with breast cancer. The trial data also indicated that fracture rates might have been severely under-reported in previous large adjuvant aromatase

inhibitor trials; when bone health is the primary focus of a study (as in this trial), around 10% of all patients will have a new clinical fracture within 3 years, which is worrying. The trial data also indicate that fracture rates and adjuvant denosumab benefits are similar in patients with normal bone mineral density (T-score ≥ -1) at baseline and those starting their adjuvant breast cancer therapy when their T-score was already lower than -1 , suggesting that current bone-protection guidelines for postmenopausal breast cancer patients should be revisited.

Implications of all the available evidence

Our trial shows that for postmenopausal women with hormone receptor-positive breast cancer with their modest risk of cancer recurrence, state-of-the-art adjuvant endocrine therapy treatment with aromatase inhibitors poses a clinically significant risk of fracture that might numerically exceed the benefit of anticancer therapy. With adjuvant subcutaneous denosumab 60 mg every 6 months, the fracture risk can be reduced substantially and overall bone health improved, with no added toxicity. This intervention is in line with reports about denosumab benefits in non-oncology settings, and should be considered for postmenopausal patients with breast cancer in clinical practice.

depletion, which in turn leads to lower bone mineral density and increased fracture risk. Indeed, increased fracture rates and deterioration of bone health in patients with breast cancer have been reported both in clinical studies of aromatase inhibitors and in routine clinical practice.² Although the actual fracture risk can vary according to age, ethnic origin, body-mass index, and other factors, a major concern is that bone side-effects and their consequences on quality of life and health-care costs might even outweigh the benefits of adjuvant endocrine therapy.^{3,4}

Antiresorptive agents such as bisphosphonates have been used to successfully prevent and treat cancer treatment-induced bone loss in patients with breast cancer.^{5,6} Despite some controversy about whether or not this intervention actually reduces fracture risk,⁷ most breast cancer treatment guidelines recommend monitoring of bone mineral density and treatment with bisphosphonates when indicated.⁸

Denosumab is a fully human IgG2 monoclonal antibody that binds with high affinity and specificity to the RANK ligand, which is the essential mediator of osteoclast activity and bone resorption, produced by bone cells in the skeleton.⁹ In postmenopausal women with osteoporosis who do not have cancer, denosumab reduces the risk of vertebral, non-vertebral, and hip fractures.¹⁰

This prospective, randomised, placebo-controlled, double-blind phase 3 trial (ABCSG-18) was designed to investigate the effects of adjuvant denosumab on fractures and other bone health parameters, and on safety

outcomes, in postmenopausal patients with early-stage hormone receptor-positive breast cancer receiving treatment with aromatase inhibitors.

Methods

Study design and participants

The ABCSG-18 trial was a prospective double-blind placebo-controlled multicentre phase 3 study, in which postmenopausal women with histologically confirmed non-metastatic oestrogen receptor-positive or progesterone receptor-positive breast cancer receiving treatment with adjuvant non-steroidal aromatase inhibitors were randomly assigned in a 1:1 ratio to receive either denosumab 60 mg or placebo subcutaneously every 6 months. Women were defined as being of postmenopausal status if they had undergone a bilateral oophorectomy, were 60 years of age or older, or were younger than 60 years of age but had follicle-stimulating hormone and oestradiol levels in the postmenopausal range. The main exclusion criteria were: aromatase inhibitor therapy for longer than 24 months before trial inclusion; previous or concurrent treatment with selective oestrogen receptor modulators (eg, tamoxifen); evidence of metastatic disease; ongoing or previous intravenous bisphosphonate administration; oral bisphosphonate treatment if taken for 3 years or longer continuously or if taken for between 3 months and 3 years unless the patient had a washout period of at least 1 year before randomisation, or any use during the 3 months before randomisation; previous administration of denosumab;

known history of Paget's disease (bone), Cushing's disease, hyperprolactinaemia or other active metabolic bone disease, hypercalcaemia, or hypocalcaemia; and major surgery or substantial traumatic injury within the 4 weeks before randomisation. Daily supplements, containing 500 mg elemental calcium and at least 400 international units of vitamin D (cholecalciferol), were highly recommended throughout study treatment. The full study protocol, including amendments, study timelines, and the detailed statistical analysis plan, is available in the appendix.

The study was done in compliance with the good clinical practice guidelines defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The trial was approved by institutional review boards and ethics committees overseeing the study sites. All patients provided written informed consent before enrolment into this trial.

Randomisation and masking

Patients were randomly assigned to receive study medication (denosumab or placebo) by an interactive voice response system, using a randomly permuted block design with block sizes 2 and 4. Randomisation was stratified by: previous aromatase inhibitor use (yes/no), total lumbar spine bone mineral density score at baseline (T-score <-1.0 vs ≥ 1.0), and type of hospital (preselected bone mineral density centres vs others). All people involved in the trial conduct (patients, investigators, project manager, data management team, clinical research associates, and statisticians) were masked to the treatment group, which was achieved by denosumab and placebo being prepared in identical syringes and packaging by the study sponsor. Statisticians were unmasked to the treatment allocation on March 18, 2015, after database lock.

Procedures

To ensure that patients with metastatic disease were not erroneously enrolled at randomisation, routine staging procedures for patients with early-stage breast cancer, including a bone scan, were done at screening. Clinical follow-up, including fracture assessment and other diagnostic restaging procedures when indicated, was done at least every 6 months until the primary analysis data cutoff date on March 26, 2014, and annually thereafter. Patients remained on trial medication until up to 6 months after the primary analysis data cutoff date was reached. The assessments of the patients and the recording of adverse events followed the protocol-defined regular schedule (appendix pp 8–9).

Bone mineral density of the total lumbar spine, total hip, and femoral neck was measured by dual-energy x-ray absorptiometry (DXA) scans from baseline to 36 months and at the end of treatment visit in patients with evaluable DXA scans, and the same DXA scan device from the

same company (Hologic, Bedford, MA, USA) was used for all measurements. If the bone mineral density at the total hip or lumbar spine decreased by more than 10% during a 1-year period, an informed discussion took place between the investigators and the patient regarding the need for appropriate bone-specific treatment.

Fracture assessment was done by analysis of lateral radiographs of the thoracic and lumbar spine in a standardised procedure according to the Genant semiquantitative visual score.¹¹ The assessment was done independently by radiologists in peripheral centres and by a central reviewing committee of musculoskeletal radiologists at the Medical University of Vienna (Vienna, Austria) in a masked manner. In cases of discrepancies in assessments, an independent second review by another central reviewing committee radiologist was done for final judgment. Vertebral fractures were defined as height reductions of 20–25% or more on radiographs.

Adverse event severity was scored according to Common Terminology Criteria for Adverse Events version 3.0, and all adverse events were coded by the Medical Dictionary of Regulatory Activities version 17.1. The potential occurrence of any case of osteonecrosis of the jaw was monitored carefully during the trial because of the widespread concern about this side-effect of antiresorptive agents,¹² and suspected cases were adjudicated by an independent international expert panel. In addition to reported potential osteonecrosis of the jaw incidents, the trial database was automatically checked every month by data management and also searched by a clinical safety officer for any of 42 predefined terms of osteonecrosis (for the detailed workflow, see appendix p 60). Serial serum samples were collected for safety and translational purposes, such as the later assessment of bone markers and hormone levels.

Outcomes

The primary endpoint was time from randomisation until the date of the radiograph confirming the first clinical fracture. Clinical fractures were defined as clinically evident fractures with associated symptoms, except for those of the skull, face, fingers, and toes, which are typically not associated with osteoporosis. Secondary endpoints were divided into two categories. The bone-related secondary endpoints were: percentage change in total lumbar spine, total hip, and femoral neck bone mineral density from baseline to 36 months in patients with evaluable DXA scans using the same Hologic device; patient incidence of new vertebral fractures; and patient incidence of a new or worsening of pre-existing vertebral fractures (morphometric fractures identified from study radiographs and clinical vertebral fractures confirmed by radiographs) at month 36. Disease outcome-related secondary endpoints were: disease-free survival, bone-metastasis free survival, and overall survival; however, these findings are not presented here because of immature data. Exploratory

endpoints were the percentage change in bone mineral density at the aforementioned bone sites and new and new or worsening vertebral fractures at months 12 and 24. Results of vertebral fractures at months 12 and 24 are not presented here. Safety endpoints were patient incidence of treatment-emergent adverse events, clinically significant changes in laboratory values, and anti-denosumab antibody (binding and neutralising) formation.

Statistical analysis

Sample size calculations, reporting timelines, covariates, subgroups, and analysis sets were prespecified in a statistical analysis plan (appendix p 69). In brief, we planned to enrol around 3400 patients into the trial (1700 per treatment group). Based on a dropout rate of 3.6% per year, roughly 247 patients would need to have a clinical fracture for this study to have 80% power to detect a hazard ratio of 0.70 (denosumab vs control), with a two-sided significance level of 0.05, corresponding to a 30% decrease in fractures in the denosumab group compared with the control (placebo) group. Additionally, we planned to compare the percentage change in lumbar spine bone mineral density between the denosumab and placebo groups. To have 90% power to detect a mean 1.8% difference (SD 3.9%) between denosumab and placebo in the percentage of change of bone mineral density for the lumbar spine at 12 months, with a two-sided significance level of 0.05, we would need to have complete bone mineral density data from at least 102 patients per treatment group.

All analyses were based on the intention-to-treat principle. Hence, the full analysis set was defined as all patients who were randomly assigned. Every patient was analysed according to their randomised treatment. We analysed the time to first on-study clinical fracture using a Cox model¹³ including treatment groups as the independent variable and stratified by the randomisation stratification factors. Patients who died or withdrew from the study without experiencing a clinical fracture were censored at the date of final contact before the primary analysis cutoff date (including date of scheduled and unscheduled contact, clinic and telephone visits, of early study termination, and of deaths) or end-of-study visit, whichever occurred first. Summary statistics from the Cox model include the hazard ratio (HR) and the corresponding 95% CI of denosumab compared with placebo. We investigated the proportionality assumption of the Cox model with a time-dependent exploratory variable, defined as treatment multiplied by the logarithm of the time-to-event. We recorded no evidence against the proportionality assumption ($p=0.95$). Furthermore, we estimated clinical fracture rates with 95% CIs using the Kaplan-Meier method. As an additional sensitivity analysis, we analysed the primary endpoint on the per-protocol population, which included all patients who received at least one dose of study drug and did not violate

any inclusion or exclusion criteria. For this per-protocol analysis, patients were censored at the time when they deviated from their randomly assigned treatment or received bone-targeted prescription medication.

We calculated the percentage changes in lumbar spine, total hip, and femoral neck bone mineral density from baseline to 12, 24, and 36 months using ANCOVAs including treatment group as the independent variable and adjusted for baseline value and for the randomisation stratification factors. The bone mineral density analysis set included patients defined in the full analysis set with evaluable DXA scan values for the endpoint of interest (lumbar spine, total hip, or femoral neck) at baseline and the post-baseline timepoint under consideration (12, 24, or 36 months). DXA scans had to be done with the same Hologic device and be taken on the same side of the body as the baseline measurement. Summary statistics include the observed and estimated percentage changes, 95% CIs, and differences with 95% CI between the percentage changes in the two groups at the three timepoints.

We analysed the presence or absence of new and new or worsening vertebral fractures during a 36-month assessment period using logistic regression models that included treatment groups as the independent variable and were stratified by the randomisation stratification factors. The vertebral fracture analysis set included patients defined in the full analysis set who had a baseline assessment and at least one post-baseline evaluation of vertebral fracture at or before the timepoint under consideration.

Summary statistics include crude incidences, the odds ratio, and corresponding 95% CIs. We tested the primary and secondary null hypotheses using a hierarchical analysis strategy and the Hochberg procedure¹⁴ to control the overall significance level of 0.05. For safety analyses (adverse events, laboratory assessments, and anti-denosumab antibodies), which assess the safety profile of denosumab compared with placebo, descriptive summary tables and listings are provided.

In the original protocol, we had planned to do one formal interim analysis when 64 first clinical fractures had occurred. This interim analysis was dropped from the protocol in protocol amendment 2 on April 6, 2010, which was decided by the academic trial steering committee in accordance with the trial sponsor. There were no formal stopping rules because of safety data, but an independent data monitoring committee was established with at least annual meetings to review unmasked safety data. In case of severe safety issues, the committee was to recommend termination of the study.

SAS version 9.3 was used for all analyses. This trial is registered with the European Clinical Trials Database, number 2005-005275-15, and with ClinicalTrials.gov, number NCT00556374.

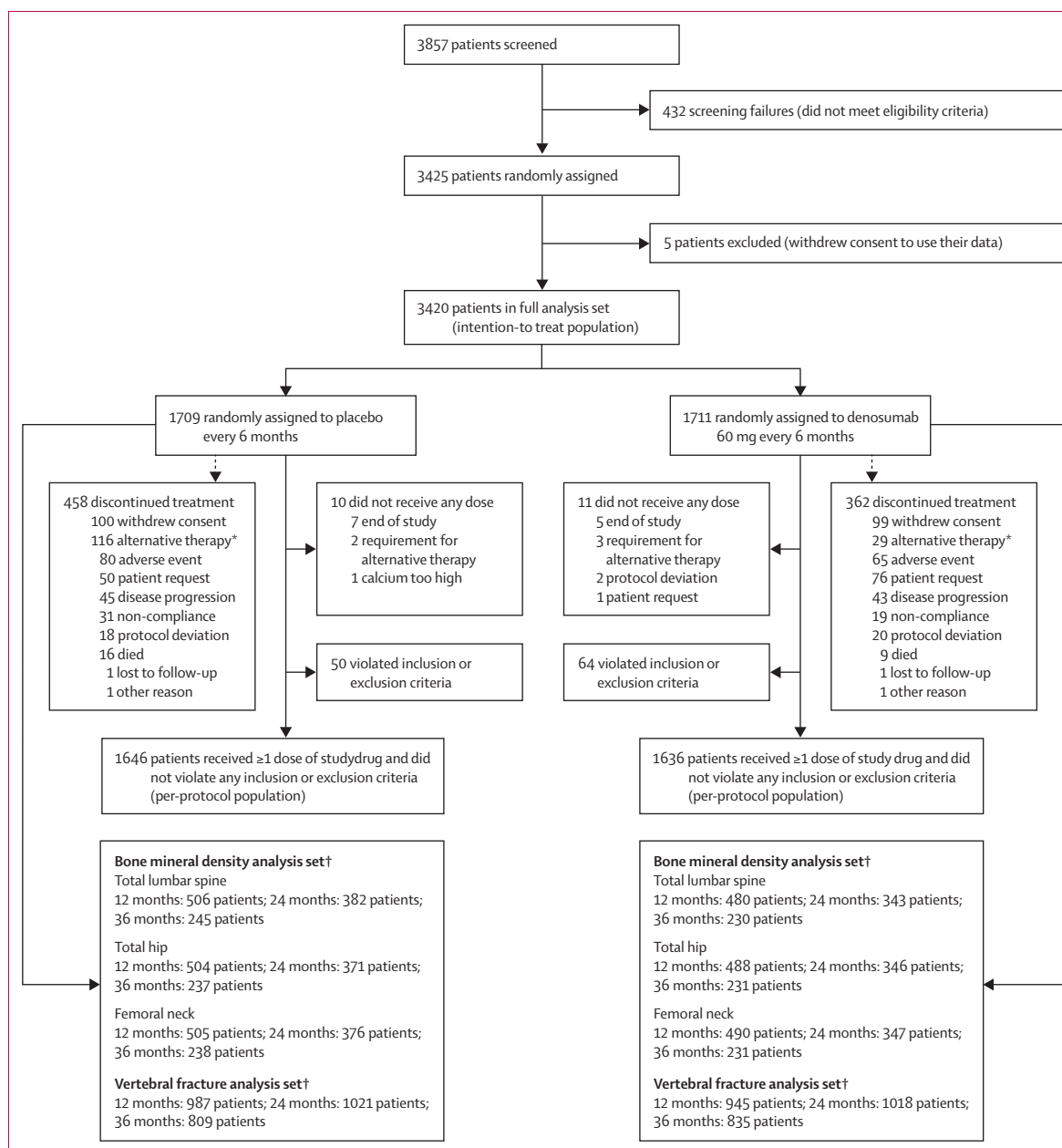


Figure 1: Trial profile

Treatment discontinuations refer to all patients who received at least one dose of study drug. Dashed arrows indicate special features of respective patients rather than an exclusion. *The difference between the groups in the numbers of patients who had alternative therapy can be explained by informed discussions that took place with patients who had a decrease in bone mineral density of more than 10% per year regarding the need for appropriate bone-specific treatment as described in the Methods. †The numbers of patients here indicate the number of patients in the analysis set at the analysed timepoint (12, 24, or 36 months).

Role of the funding source

An academic steering committee, consisting of the 50 trial investigators who designed the study, was responsible for the management and quality control of data collected by the clinical sites, and planned the analyses for the report before the unmasking of any data. Amgen was the legal funder of the study, and had 55 a role in protocol design and study design. The principal investigator (MG) wrote the first draft of the

report. Members of a publication committee approved the report for publication and guarantee the completeness and accuracy of the data. Analyses were done by the trial statistician (CF), and confirmed by statisticians of the trial funder. Throughout the conduct of the study, an international independent data monitoring committee reviewed unmasked safety data at least once per year, and provided guidance and advice. The principal investigator and the trial

	Placebo every 6 months (n=1709)	Denosumab 60 mg every 6 months (n=1711)
Ethnic origin		
White	1700 (99%)	1702 (99%)
Asian	7 (<1%)	5 (<1%)
Hispanic or Latino	1 (<1%)	3 (<1%)
Black or Afro-Caribbean	0	1 (<1%)
Unknown	1 (<1%)	0
Age group (years)		
<50	31 (2%)	34 (2%)
50–59	448 (26%)	473 (28%)
60–69	755 (44%)	782 (46%)
70–79	414 (24%)	372 (22%)
≥80	61 (4%)	50 (3%)
pT stage		
ypT0/ypTis/pT1	1236 (72%)	1232 (72%)
pT2/pT3/pT4	467 (27%)	479 (28%)
Unknown	6 (<1%)	0
pN stage		
Negative	1196 (70%)	1240 (73%)
Positive	506 (30%)	462 (27%)
Unknown	7 (<1%)	9 (<1%)
Tumour grade		
G1	338 (20%)	365 (21%)
G2/Gx	1028 (60%)	1038 (61%)
G3	339 (20%)	303 (18%)
Unknown	4 (<1%)	5 (<1%)
Primary tumour histology		
Ductal invasive	1275 (75%)	1261 (74%)
Lobular invasive	290 (17%)	312 (18%)
Other	140 (8%)	131 (8%)
Unknown	4 (<1%)	7 (<1%)
Hormone receptor status		
Oestrogen receptor negative and progesterone receptor positive, or oestrogen receptor positive and progesterone receptor negative	273 (16%)	305 (18%)
Oestrogen receptor positive and progesterone receptor positive	1434 (84%)	1405 (82%)
Unknown	2 (<1%)	1 (<1%)
Oestrogen receptor status		
Negative	16 (<1%)	20 (1%)
Positive	1693 (99%)	1691 (99%)

(Table 1 continues in next column)

statistician had access to all the study data, and all coauthors take responsibility for the decision to submit for publication.

Results

Between Dec 18, 2006, and July 22, 2013, 3425 postmenopausal women with early-stage hormone receptor-positive breast cancer were enrolled from 58 centres in Austria and Sweden (3302 patients from 53 centres in

	Placebo every 6 months (n=1709)	Denosumab 60 mg every 6 months (n=1711)
(Continued from previous column)		
Progesterone receptor status		
Negative	257 (15%)	286 (17%)
Positive	1450 (85%)	1424 (83%)
Unknown	2 (<1%)	1 (<1%)
HER2/neu status		
Negative	1592 (93%)	1605 (94%)
Positive	113 (7%)	103 (6%)
Unknown	4 (<1%)	3 (<1%)
Chemotherapy before randomisation		
None	1287 (75%)	1288 (75%)
Adjuvant	329 (19%)	338 (20%)
Neoadjuvant	93 (5%)	85 (5%)
Start of aromatase inhibitor treatment*		
With denosumab/placebo	269 (16%)	270 (16%)
Before denosumab/placebo	1440 (84%)	1441 (84%)
Total lumbar spine bone mineral density		
T-score <-1.0	775 (45%)	773 (45%)
T-score ≥-1.0	934 (55%)	938 (55%)

Data are n (%). pT stage=pathologic T stage. pN stage=pathologic N stage. *The protocol allowed administration of aromatase inhibitor for up to 2 years before randomisation. Median duration of aromatase inhibitor therapy before randomisation in 2881 patients was 1 month (IQR 1–4).

Table 1: Baseline characteristics

Austria and 123 patients from five centres in Sweden). Five patients subsequently prohibited any use of their data; therefore the full analysis set consists of 3420 patients, of whom 1711 were randomly assigned to the denosumab group and 1709 to the placebo group (figure 1).

Median patient age at randomisation was 64 years (range 38–91, IQR 58–70). Baseline demographics were well balanced between the two groups (table 1). 1872 (55%) of 3420 patients started the trial with normal total lumbar spine bone mineral density (T-score ≥-1.0), and 1548 patients (45%) had T-scores lower than -1.0 at baseline, indicating that they had low bone mineral density. 539 patients (16%) were randomly assigned at the time they started their adjuvant aromatase inhibitor treatment, whereas 2881 (84%) were already on aromatase inhibitor treatment (for a median duration of 1 month [IQR 1–4]) at randomisation). 845 (25%) patients had also received (neo)adjuvant chemotherapy, whereas 2575 (75%) patients had endocrine adjuvant therapy only.

21 patients (11 in the denosumab group and 10 in the placebo group) did not receive any study drug because of end of study (n=12), protocol deviation (n=2), requirement for alternative therapy (n=5), patient request (n=1), and one other reason (calcium was too high, and the patient never started the study). Of 3399 (99%) patients who actually received study treatment (denosumab or placebo), 2579 (76%) completed their treatment according

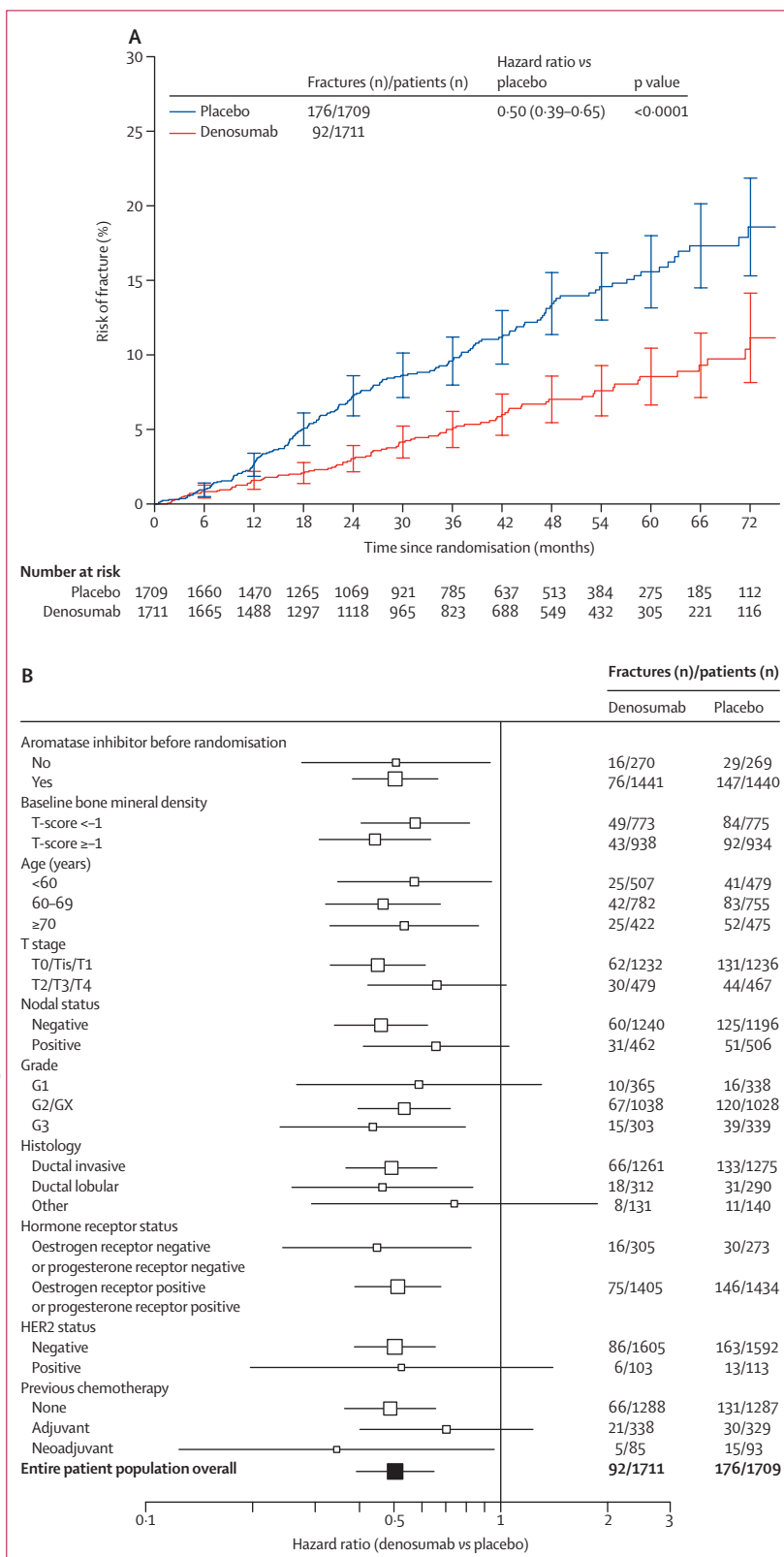
to the study plan. Figure 1 shows the reasons for treatment discontinuation. The median number of denosumab or placebo doses actually received (seven [range 1–16; IQR 4–10]) was almost identical between groups (denosumab seven [range 1–14, IQR 4–10]; placebo seven [range 1–16, IQR 4–9], as was median time on study (all patients: 38 months [IQR 21.2–57.6]; denosumab group: 38.2 months [21.0–58.0]; placebo group: 37.7 months [21.2–57.3]). At the time of analysis (March 16, 2015), the reasons for early study termination were death (93 [3%] patients), withdrawal of consent (362 [11%] patients), and loss to follow-up (12 [$<1\%$] patients). Therefore, 2953 patients (86%) continue the study in follow-up.

Based on 268 primary endpoint events (clinical fractures) at database lock, time to first clinical fracture was significantly delayed in the denosumab group compared with the placebo group (HR 0.5 [95% CI 0.39–0.65], $p<0.0001$; figure 2A). At 36 months after randomisation, an estimated 5.0% (95% CI 3.8–6.2) of patients in the denosumab group had experienced a fracture, compared with 9.6% (8.0–11.2) in the placebo group (estimated numbers of patients: 65 in the denosumab group vs 129 in the placebo group). Estimated first clinical fracture rates at 84 months are 11.1% (95% CI 8.1–14.1) in the denosumab group and 26.2% (15.6–36.8) in the placebo group (estimated numbers of patients: 92 in the denosumab group vs 176 in the placebo group). Most fractures occurred on the forearms or hands, followed by vertebrae, ribs, ankle or foot, humerus, pelvis or femur, lower leg or knee, and shoulder and sternum. Patient incidences of first clinical fractures by fracture location, by Common Terminology Criteria for Adverse Events grade and by trauma severity are available in appendix pp 10–12. Results from a preplanned sensitivity analysis based on the per-protocol population did not differ from those of the full intention-to-treat analysis dataset (HR 0.49 [95% CI 0.38–0.64], $p<0.0001$).

The recorded reduction in clinical fractures between the denosumab and placebo groups (overall cumulative incidence of first clinical fractures during the whole study period: 92 in the denosumab group vs 176 in the placebo group) was similar in all patient subgroups, including in the 1872 patients with normal bone mineral density (T-score ≥ -1) at baseline (HR 0.44 [95% CI 0.31–0.64], $p<0.0001$) and in the 1548 patients who had a T-score lower than -1 already when they started the trial (0.57 [0.40–0.82], $p=0.002$) (figure 2B and appendix p 61).

Figure 2: Effect of denosumab treatment on the occurrence of clinical fractures

Primary endpoint results, defined as the first clinical fracture per patient, are presented for women with breast cancer who received denosumab or placebo. (A) Percentage risk of fracture based on Kaplan-Meier time-to-event analysis within each treatment group at 6-month intervals. The hazard ratio and p value were calculated from a Cox model including treatment groups as the independent variable and stratified by the randomisation stratification factors. Error bars are 95% CIs. (B) Forest plot based on hazard ratios indicates the treatment effect for all randomly assigned patients and separated for subgroups. Error bars are 95% CIs.



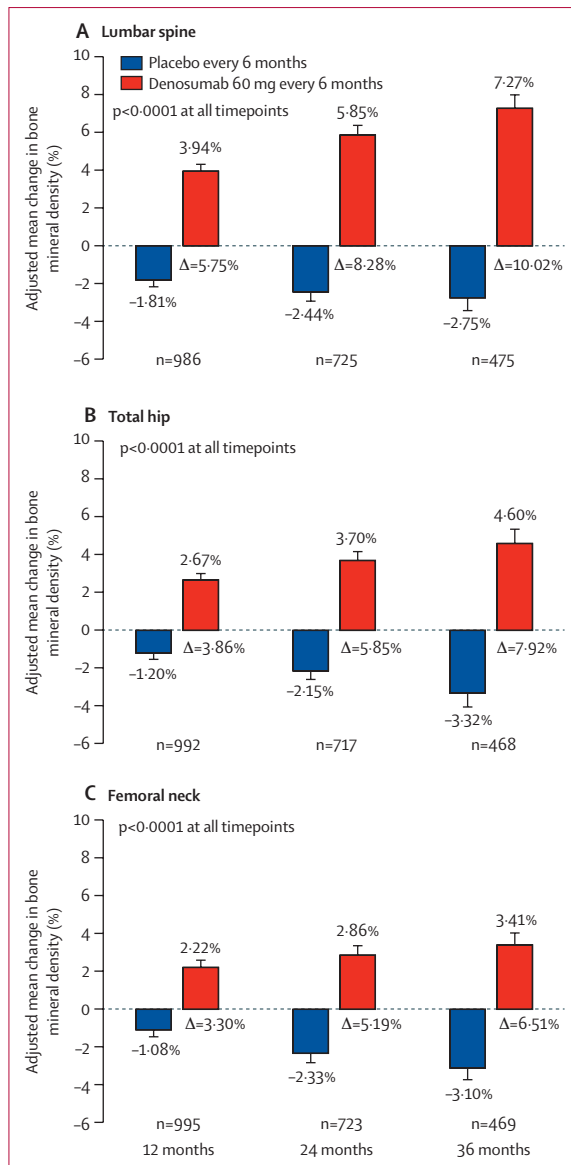


Figure 3: Bone mineral density changes
 Mean recorded percentages changes in bone mineral density at (A) total lumbar spine, (B) total hip, and (C) femoral neck for each treatment group at 12, 24, and 36 months. Differences between treatment groups at each timepoint and the corresponding p values are provided. Δ=percentage difference between denosumab and placebo values. Error bars are 95% CIs.

At 36 months, patients in the denosumab group had a relative increase in bone mineral density of 10.02% (95% CI 9.04–11.01) at the lumbar spine, 7.92% (6.87–8.97) at the total hip, and 6.51% (5.62–7.39) at the femoral neck, as compared with those in the placebo group (all adjusted p values <0.0001) (figure 3). Although bone mineral density decreased over time at all measurement sites in the placebo group, in the denosumab group bone mineral density increased substantially compared with baseline at all timepoints and measurement sites (figure 3). From baseline to 36 months,

only 24 (10%) of 230 patients in the denosumab group lost bone mineral density at the lumbar spine, whereas 181 (74%) of 245 patients in the placebo group experienced such reductions. Similar results were recorded for bone mineral density at the total hip (38 [17%] vs 185 [78%]) and femoral neck (51 [22%] vs 178 [75%]).

Denosumab treatment also significantly reduced the incidence of new vertebral fractures in the vertebral fracture analysis set (n=1644), with 27 fractures in 835 patients in the denosumab group compared with 49 in 809 patients in the placebo group (odds ratio 0.53 [95% CI 0.33–0.85], p=0.009) and the patient incidence of new or worsening vertebral fractures at 36 months (31 cases in 835 patients in the denosumab group vs 55 in 809 patients in the placebo group; odds ratio 0.54 [95% CI 0.34–0.84], p=0.007).

The total patient incidence of adverse events did not differ between patients who received denosumab (1366 episodes [80% of patients in the denosumab safety population]) or placebo (1334 episodes [79% of the placebo safety population]), nor did the patient incidence of serious adverse events (521 vs 511 episodes [30% of each group]; table 2, appendix pp 13–59). The recorded adverse events were mainly arthralgia and other aromatase inhibitor-related symptoms. 129 patients (80 in the denosumab group and 49 in the placebo group) had adverse events that were judged to be related to the study drug. In the entire study cohort, no neutralising anti-denosumab antibodies were identified in plasma samples at any timepoint. No atypical fracture was reported throughout the duration of the study. 93 patients (3% of the full analysis set) died during the study, of which one death (in the denosumab group) was recorded as related to the study drug.

35 potential dental problems were identified by proactive monitoring for osteonecrosis of the jaw during the trial, of which 31 suspected cases of this adverse event were assessed further in the predefined adjudication process. However, eventually no case was judged to meet the diagnostic criteria of osteonecrosis of the jaw.

Discussion

The results of the ABCSG-18 trial show that in postmenopausal patients with hormone receptor-positive early-stage breast cancer who receive adjuvant aromatase inhibitor therapy, the subcutaneous administration of denosumab every 6 months significantly reduced the rate of clinical fractures. Compared with placebo, time to first fracture was doubled, and denosumab also increased bone mineral density at total lumbar spine, total hip, and femoral neck. The observed bone-protective effect was also reported with respect to the incidence of new and the worsening of pre-existing vertebral fractures.

In view of the fact that aromatase inhibitors are the existing recommended standard of care for all postmenopausal women with hormone receptor-positive breast cancer (Early Breast Cancer Trialists' Collaborative Group, personal communication),¹⁵ and recommended durations of adjuvant endocrine therapy are increasing

beyond 5 years,¹⁶ these results are important for clinical practice. Since treatment-induced bone loss is essentially caused by aromatase inhibitor therapy, the findings of this study also unveil the underestimated magnitude of fracture risk. Although the reported incidence of treatment-induced fractures varies greatly between pivotal aromatase inhibitor trials, substantial concerns exist that fractures might have been severely under-reported in these oncology trials since they were recorded as adverse events rather than representing primary study endpoints.^{7,17} In this trial, with its focus on bone health, the recorded rate of fractures in the placebo group (estimated 10% at 3 years, 16% at 5 years, and 26% at 7 years) notably exceeds previous reports from large adjuvant aromatase inhibitor trials (Early Breast Cancer Trialists' Collaborative Group, personal communication) and is worrying.

Increased awareness about aromatase inhibitor treatment-induced bone loss¹⁸ has led to guidelines and recommendations that patients should be monitored for bone loss, and antiresorptive intervention considered when bone mineral density decreases during aromatase inhibitor therapy.⁸ However, the true consequences of aromatase inhibitors on bone strength might be substantially underestimated because bone mineral density measurements rely on DXA. In a nested safety substudy of a large breast cancer trial, 351 women were followed up for 2 years by DXA and more accurate high-resolution quantitative bone CT scans; the latter scans showed that both volumetric bone mineral density and cortical thickness deteriorated more dramatically than indicated by DXA.¹⁹ In fact, our data show that patients with apparently normal bone at baseline benefit to a similar extent from adjuvant denosumab as those who are already osteopenic.

At present, both oral and intravenous bisphosphonates are recommended to counteract aromatase inhibitor-induced bone loss, and have been shown to be cost effective.²⁰ In addition to the fact that none of the published trials of these agents have shown a clear effect on actual fractures so far, these agents are not without their side-effects. Compliance with oral bisphosphonates has been reported to be low in clinical practice, especially because of their gastrointestinal side-effects, and intravenous bisphosphonate therapy can be impeded by acute-phase reactions, ocular events, renal safety, and dental problems.²¹

Denosumab prevents the interaction of the RANK ligand with its receptor RANK and blocks the formation, function, and survival of osteoclasts. On the basis of this targeted mechanism of action and trial results of beneficial bone mineral density effects in women²² and men²³ with osteoporosis, denosumab 60 mg twice yearly has been established as effective therapy in women without cancer, and has also been shown to increase bone mineral density in a small trial of 252 patients with breast cancer receiving aromatase inhibitor treatment.²⁴ Moreover, denosumab improved bone mineral density

	Placebo every 6 months (n=1690)	Denosumab 60 mg every 6 months (n=1709)
Adverse events		
Musculoskeletal and connective tissue disorders	801 (47%)	832 (49%)
Arthralgia	437 (26%)	435 (26%)
Back pain	145 (9%)	151 (9%)
Bone pain	110 (7%)	137 (8%)
Pain in extremity	85 (5%)	106 (6%)
Vascular disorders	394 (23%)	472 (28%)
Hot flush	230 (14%)	263 (15%)
Hypertension	93 (6%)	111 (7%)
General disorders and administration site conditions	244 (14%)	277 (16%)
Fatigue	98 (6%)	108 (6%)
Serious adverse events		
Musculoskeletal and connective tissue disorders	120 (7%)	134 (8%)
Osteoarthritis	57 (3%)	62 (4%)
Invertebral disc protrusion	15 (<1%)	14 (<1%)
Injury, poisoning, and procedural complications	68 (4%)	55 (3%)
Meniscus injury	24 (1%)	23 (1%)
Nervous system disorders	57 (3%)	66 (4%)
Carpal tunnel syndrome	13 (<1%)	14 (<1%)
Eye disorders	32 (2%)	25 (2%)
Cataract	28 (2%)	16 (<1%)
Endocrine disorders	13 (<1%)	23 (1%)
Goitre	12 (<1%)	21 (1%)
All adverse events that occurred in more than 5% of all patients and all serious adverse events that occurred in more than 25 patients are listed.		
Table 2: Patient incidence of adverse events and serious adverse events in all patients who received at least one dose of study drug		

and reduced new vertebral fractures in men receiving androgen depletion therapy for prostate cancer.²⁵ By confirming and extending these data, ABCSG-18 is the first trial to show that denosumab can successfully prevent fractures in patients with breast cancer.

Patients with breast cancer are more likely to have reduced bone mineral density and subclinical vertebral fractures than are healthy people without the disease,²⁶ even before the occurrence of any additive detrimental treatment-related side-effect. Although the underlying mechanism is still not understood, the notable reduction in fractures—including new vertebral fractures and worsening of pre-existing fractures—in ABCSG-18 is of particular importance for the population of postmenopausal women with hormone receptor-positive breast cancer population with its constantly improving outcomes and low risk of disease recurrence. In addition to avoiding quality-of-life detriments, substantial health-care costs can be saved through the prevention of fractures in the increasing group of breast cancer survivors.²⁷

Adjuvant denosumab at a dose of 60 mg every 6 months proved to be virtually without added toxicity in our trial, with no relevant difference between the antibody and placebo groups in terms of adverse events or severe adverse events. On the basis of existing concerns that anti-resorptive treatments may cause osteonecrosis of the jaw, we established a proactive screening and monitoring system within our trial. Despite this approach and expert adjudication of suspected episodes of dental problems, we did not identify any cases of osteonecrosis of the jaw in this trial. This finding is in line with the experience with denosumab at this dose in the published literature on osteoporosis,⁹ and provides reassurance that this treatment is safe. Both bisphosphonates and denosumab at higher doses cause higher rates of osteonecrosis of the jaw,¹² which is a concern in the treatment of metastatic breast and other cancers. Furthermore, atypical fractures have been reported with anti-resorptive agents,²⁸ but were not seen in ABCSG-18.

Adjuvant bisphosphonates have been shown to reduce breast cancer recurrence and improve outcomes in several adjuvant breast cancer trials.²⁹ Although even large individual trials have reported conflicting results,^{30,31} a recent large meta-analysis³² showed convincing evidence that disease-free and overall survival are improved in postmenopausal patients who are treated with adjuvant bisphosphonates. When mature, survival data from the ABCSG-18 trial and from the D-CARE trial (ClinicalTrials.gov identifier NCT01077154) of a higher dose of denosumab will provide information as to whether or not this finding is also true for the anti-RANK ligand antibody.

In conclusion, subcutaneous denosumab 60 mg every 6 months substantially reduces fracture risk and improves bone health in postmenopausal patients with early-stage hormone receptor-positive breast cancer, with no added toxicity. For these patients with modest risk of disease recurrence, to effectively prevent the most serious side-effect of their aromatase inhibitor treatment is highly beneficial, and should be added to clinical practice.

Contributors

MG developed the idea for the study and was the principal investigator of the trial. MG, RG, RJ, CM, and GGS designed the study protocol. MG, GP, PCD, MH, RG, RJ, VW, MB, FH, EM, VB-R, SA-M, FF, PS, BM, DM, RE, DE, JB, and CFS gathered and managed the data. ST and CF developed the statistical analysis plan, DW supervised the statistical analyses, and CF and ST did the analyses. FK was responsible for central review of radiographs. MG wrote the final report, with major input from GP, PCD, JB, and CF. All authors interpreted the data and contributed to revisions of the report.

Declaration of interests

MG has received grants from Sanofi-Aventis, Novartis, Roche, GlaxoSmithKline, Pfizer, and Smith Medical, and personal fees from Novartis, Roche, GlaxoSmithKline, AstraZeneca, Nanostring Technologies, and Accelsiors. GP has received personal fees from Roche, Novartis, and Amgen. PCD has received personal fees from Roche, AstraZeneca, and Pfizer, and travel or accommodation expenses reimbursement from Novartis. MH has received grants from Roche, Amgen, and Novartis; serving personal fees from Celgene and Roche; and travel or accommodation expenses reimbursement from Roche, Celgen, and Amgen. RG has received grants and personal

fees from Roche and Celgene, personal fees from BMS, and grants from Amgen. CF is an employee of the ABCSG. MB has received grants from Amgen and Celgene; personal fees from Celgene, Novartis, Roche, and AstraZeneca; and travel or accommodation expenses reimbursement from Amgen, Celgene, and Roche. PS has received grants and personal fees from Amgen, Roche Austria, and AstraZeneca, and personal fees from Boehringer Ingelheim, Eisai, Amomed, Janssen Cilag, MSD, and Olympus Austria. GGS has received grants from Roche, personal fees from Amgen, Novartis, AstraZeneca, Celgene, Pfizer, TEVA, and Roche, and non-financial support from Novartis, AstraZeneca, Celgene, TEVA, and Roche. DE has received personal fees and non-financial support from Roche, Novartis, Pierre Fabre, and Ratiopharm. JB reports that Karolinska University Hospital and Karolinska Institutet have received payment for academic clinical studies and research grants for molecular biological studies or PET studies from the following companies: Amgen, AstraZeneca, Bayer, Merck, Pfizer, Roche, and Sanofi-Aventis. FK has received personal fees from Amgen and Abbvie. ST and DW are employees of Amgen. The other authors declare no competing interests.

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