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

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Summary

Background In postmenopausal women with hormone receptor-positive, early-stage breast cancer, treatment with adjuvant aromatase inhibitors is the standard of care, but it increases risk for osteoporosis and fractures. Results from the ABCSG-18 trial showed that use of denosumab as an adjuvant to aromatase inhibitor therapy significantly reduced clinical fractures. Disease-free survival outcomes from ABCSG-18 have not yet been reported.

Methods Postmenopausal patients with early, hormone receptor-positive, non-metastatic adenocarcinoma of the breast, who had completed their initial adjuvant treatment pathway (surgery, radiotherapy, or chemotherapy, or a combination) and were receiving adjuvant aromatase inhibitors, were enrolled at 58 trial centres in Austria and Sweden into this prospective, double-blind, placebo-controlled, phase 3 trial. With permuted block randomisation (block sizes 2 and 4, stratified by previous aromatase inhibitor use, total lumbar spine bone mineral density score at baseline, and type of centre), patients were assigned (1:1) to receive subcutaneous denosumab (60 mg) or matching placebo every 6 months during aromatase inhibitor therapy. The primary endpoint (previously reported) was the time to first clinical fracture after randomisation. The secondary endpoint reported here is disease-free survival (defined as time from randomisation to first evidence of local or distant metastasis, contralateral breast cancer, secondary carcinoma, or death from any cause) in the intention-to-treat population. This study is registered with EudraCT (number 2005–005275–15) and ClinicalTrials.gov (number NCT00556374), and is ongoing for long-term follow-up.

Findings Between Dec 18, 2006, and July 22, 2013, 3425 eligible patients were enrolled and randomly assigned; 1711 to the denosumab group and 1709 to the placebo group (with five others withdrawing consent). After a median follow-up of 73 months (IQR 58–95), 240 (14·0%) patients in the denosumab and 287 (16·8%) in the placebo group had disease-free survival events. Disease-free survival was significantly improved in the denosumab group versus the placebo group (hazard ratio 0·82, 95% CI 0·69–0·98, Cox p=0·0260; descriptive analysis, without controlling for multiplicity). In the denosumab group, disease-free survival was 89·2% (95% CI 87·6–90·8) at 5 years and 80·6% (78·1–83·1) at 8 years of follow-up, compared with 87·3% (85·7–89·0) at 5 years and 77·5% (74·8–80·2) and 8 years in the placebo group. No independently adjudicated cases of osteonecrosis of the jaw or confirmed atypical femoral fractures were recorded. The total number of adverse events was similar in the denosumab group (1367 [including 521 serious] adverse events) and the placebo group (1339 [515 serious]). The most common serious adverse events were osteoarthritis (62 [3·6%] of 1709 in the denosumab group *vs* 58 [3·4%] of 1690 in the placebo group), meniscus injury (23 [1·3%] *vs* 24 [1·4%]), and cataract (16 [0·9%] *vs* 28 [1·7%]). One (<0·1%) treatment-related death (due to pneumonia, septic kidney failure, and cardiac decompensation) occurred in the denosumab group.

Interpretation Denosumab constitutes an effective and safe adjuvant treatment for patients with postmenopausal hormone receptor-positive early breast cancer receiving aromatase inhibitor therapy.

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Introduction

For postmenopausal women with hormone receptor-positive, early-stage breast cancer, aromatase inhibitors are the preferred adjuvant therapy[1] for most patients because of their association with improved outcomes compared with tamoxifen.[2] Inhibition of the aromatase enzyme decreases oestrogen production by inhibiting the conversion of androgens to oestrogens.[3] By this mechanism, aromatase inhibitors reduce recurrences of breast cancer, breast cancer deaths, and all-cause mortality,[4] but at the cost of decreased bone mineral density and increased fracture risk.[2,5]

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed on Oct 19, 2018, using "adjuvant denosumab" and "breast cancer" as key words, with no date restrictions. The search identified 70 reports published between October, 2006, and September, 2018, of which most were review articles and reports on the use of bisphosphonates for bone protection. When searching with the key words "adjuvant denosumab" and "breast cancer" and "disease-free survival", only ten reports were found, which were published between September, 2009, and November, 2017, and were mostly reviews and reports related to bisphosphonates. To our knowledge, no paper has so far reported the effect of adjuvant denosumab on disease-free survival. We also searched ClinicalTrials.gov on Oct 19, 2018, and found 19 studies registered for "denosumab" and "breast cancer", most of which were investigating the use of an anti-RANK-ligand antibody in metastatic disease. When the search was confined to "adjuvant denosumab", only two other randomised clinical trials were found to be registered: one that had finished accrual (D-CARE), and one that started recruitment in September, 2017 (ENDEAVOR Trial, NCT03324932), although these studies used bone mineral density as an endpoint. To our knowledge, ABCSG-18 is the first prospective phase 3 trial to report disease-free survival data from patients with breast cancer treated with adjuvant denosumab.

Added value of this study

The previously reported primary endpoint data of the ABCSG-18 trial showed that adjuvant denosumab significantly reduces aromatase inhibitor-induced fractures in postmenopausal patients with breast cancer. In this Article, disease-free survival was shown to be significantly improved by adjuvant denosumab at a dosage of 60 mg every 6 months compared with placebo during adjuvant aromatase inhibitor therapy. A similar incidence of adverse events was observed between groups, indicating that denosumab treatment was associated with few additional side-effects.

Implications of all the available evidence

For postmenopausal patients with breast cancer with hormone receptor-positive disease, with a modest risk of cancer recurrence, the addition of 6-monthly denosumab to state-of-the-art adjuvant aromatase inhibitor therapy significantly improves disease-free survival. Given the negligible side-effect profile of denosumab, and the previously reported reduction in clinical fractures, adjuvant subcutaneous denosumab at 60 mg every 6 months should be offered to postmenopausal women with hormone receptor-positive breast cancer.

Antiresorptive agents such as bisphosphonates and denosumab have been successfully used in patients with early breast cancer to maintain bone health and counteract bone loss induced by cancer treatment.[3,6] In addition, bisphosphonates are beneficial for bone health and for increasing bone mineral density during aromatase inhibitor therapy, although a reduced fracture risk was not shown in all trials,[6] and compliance with oral bisphosphonate treatment is often suboptimal.[7] Furthermore, a meta-analysis[3] from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) indicated that the addition of bisphosphonates improved outcomes (recurrences, breast cancer-specific survival, and overall survival) in postmenopausal patients with hormone receptor-positive breast cancer.[3,8,9] However, despite many proposed theories,[10–12] how adjuvant bone-targeted therapies affect dormant tumour micrometastasis remains unknown.[13]

Denosumab is a human monoclonal antibody that targets the RANK ligand, with high affinity and specificity for the soluble and cell membrane-bound forms of human RANK ligand.[14] The RANK–RANK ligand system is an important mediator of signalling in osteoclastogenesis and bone resorption, and also influences biological processes beyond the skeletal system, including the immune system, and has been suggested to have a role in suppressing tumorigenesis.[9,15,16] Like bisphosphonates, denosumab is also a standard of care for the prevention of skeletal-related events in patients with solid tumours who have developed bone metastasis.[13]

The primary endpoint results of the prospective, randomised, placebo-controlled, double-blind trial ABCSG-18 (NCT00556374) showed that adjuvant denosumab at 60 mg twice-yearly significantly delayed time to first clinical fracture (hazard ratio [HR] 0·5, 95% CI 0·39–0·65, p<0·0001), increased bone mineral density in patients with aromatase inhibitor-treated postmenopausal early hormone receptor-positive breast cancer, and could be administered without added toxicity.[17] Whether or not the monoclonal antibody denosumab can also improve breast cancer outcomes, as has been shown for bisphosphonates, has been addressed in two large, phase 3 clinical trials: D-CARE (NCT01077154) and ABCSG-18, with disease-free survival as a secondary endpoint in both trials. Here, we present the disease-free survival results from the ABCSG-18 trial.

Methods

Study design and participants

In this prospective, double-blind, placebo-controlled, multicentre, phase 3 trial, postmenopausal women with non-metastatic breast cancer positive for oestrogen receptor, progesterone receptor, or both, and who received adjuvant aromatase inhibitor were enrolled at 58 centres in Austria and Sweden (appendix p 8).[17] The protocol allowed patients to be randomly allocated to the study groups right at the start or within the first 2 years of

standard adjuvant aromatase inhibitor therapy. Patients were included if they had histologically or cytologically confirmed non-metastatic adenocarcinoma of the breast positive for oestrogen receptor, progesterone receptor, or both; had completed locoregional treatment (surgery with or without radiotherapy); and were undergoing adjuvant aromatase inhibitor therapy. Laboratory tests, including the following, were required to assess eligibility: sodium, potassium, calcium, blood urea nitrogen or urea, creatinine, total bilirubin, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase, γ-glutamyltransferase, albumin, red blood cell count, haemoglobin, haematocrit, platelet count, white blood cell count, and denosumab antibody assay. Patients with known liver or renal deficiency (AST ≥2·5× upper limit of normal, ALT ≥2·5× upper limit of normal, and serum creatinine ≥2× upper limit of normal) as assessed by the investigator were excluded. Women were also required to have postmenopausal status (defined as having undergone bilateral oophorectomy, age ≥60 years, or [if aged <60 years] having follicle-stimulating hormone and oestradiol serum concentrations in the postmenopausal range), and an Eastern Cooperative Oncology Group performance status of 0 or 1. Women younger than 60 years of age were required to have a negative pregnancy test within 7 days before randomisation (unless they had had a hysterectomy). Key exclusion criteria were receipt of aromatase inhibitor therapy for more than 24 months before entering the trial; previous or concurrent treatment with selective oestrogen receptor modulators (eg, tamoxifen); evidence of metastatic disease; current or previous intravenous bisphosphonate administration; and receipt of oral bisphosphonate treatment for 3 or more years continuously, for more than 3 months but less than 3 years unless the participant had had a washout period of at least 1 year before randomisation, or if oral bisphosphonate was taken at all during the 3 months before randomisation. Patients with any previous administration of denosumab, known history of Paget's disease (bone), Cushing's disease, hyperprolactinaemia or other active metabolic bone disease, hypercalcaemia or hypocalcaemia, major surgery, or substantial traumatic injury occurring within 4 weeks before randomisation were also excluded. The full protocol is in the appendix, including amendments (p 11), a detailed statistical analysis plan (p 110), and the data sharing statement (p 8).

An academic steering committee, consisting of trial investigators who designed the trial, was responsible for the management and quality control of data collected by the clinical sites, and planned the analyses before the unmasking of any data. Throughout the conduct of the study, an international independent data monitoring committee (IDMC) reviewed unmasked safety data at least once per year, and provided guidance and advice to the trialists. The timing of the disease-free survival analyses was triggered by a recommendation of the IDMC evaluating an interim futility analysis for disease-free survival and the primary results of the ABCSG-18 trial.[17] On the basis of the substantial difference in the primary endpoint results and the non-futility of the secondary endpoint disease-free survival, the IDMC recommended that patients receiving placebo should be offered the option of unmasking (between May 10, 2016, and May 10, 2017, in Austria; and between June 2, 2016, and June 2, 2017, in Sweden). Eligible patients who opted for unmasking and turned out to have been in the placebo group were offered 3 years (ie, seven doses) of denosumab (60 mg every 6 months). Subsequently, a time-driven analysis for disease-free survival was recommended before any unmasking at the patient or investigator level, to protect the integrity of the secondary endpoints. The trial steering committee accepted this IDMC recommendation, and the trial protocol was subsequently amended on Feb 22, 2016.

The IDMC also recommended that, after unmasking and eventual crossover of patients who opted for unmasking, treatment, safety, and efficacy follow-up should be continued until the end of the study. Because of concerns about a potential dilution effect caused by treatment end or crossover, the steering committee decided to do a descriptive analysis of the secondary endpoint disease-free survival in early 2018, which is reported here. Technically, all analyses after the partial unmasking of the trial have to be considered descriptive.

This study was done in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, and was approved by institutional review boards and ethics committees overseeing the study sites. All patients provided written informed consent before randomisation.

Randomisation and masking

Patients were randomly allocated (1:1) to receive either 60 mg denosumab or placebo, subcutaneously once every 6 months. Medications were prepared in identical syringes and packaging by the study sponsor. Patients, treating physicians, investigators, data managers, and all study personnel were masked to treatment allocation. The study sponsor generated the randomisation schedule, which was designed by the steering committee, based on permuted block randomisation with block sizes of 2 and 4, and stratification by previous aromatase inhibitor use (yes or no), total lumbar spine bone mineral density score at baseline (T-score <–1·0 or ≥–1·0), and type of centre (pre-selected bone mineral density centres or others). The schedule was implemented by use of an interactive voice response system (ClinPhone), which was used to assign patients to the treatment groups.

Procedures

At screening, routine staging procedures for patients with early breast cancer, including a bone scan, were

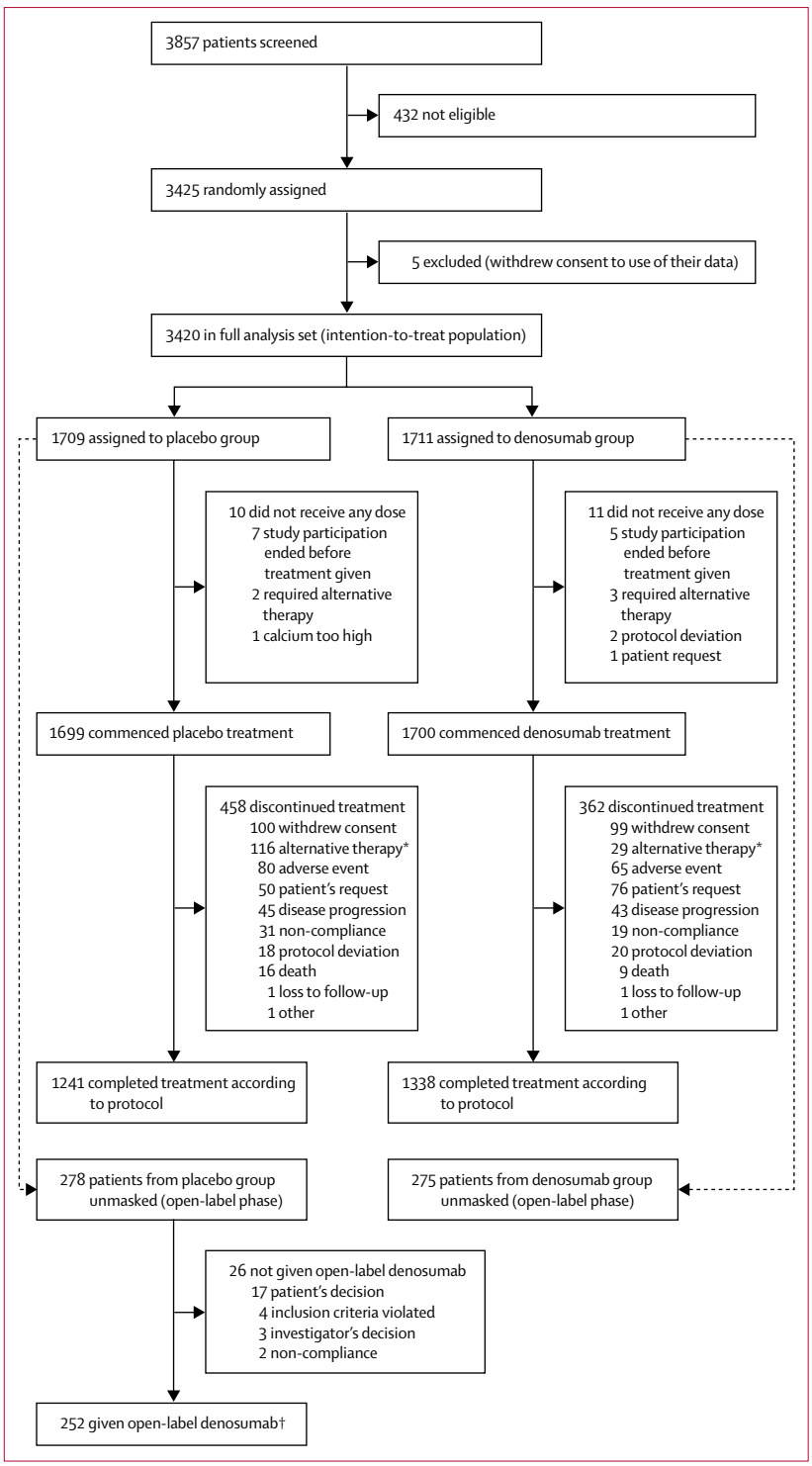

Figure 1: **Trial profile**

*The between-group difference in the numbers of patients who received alternative treatment can be explained by informed discussions regarding the need for appropriate bone-specific treatment that took place with patients who had a decrease in bone mineral density of more than 10% per year (appendix p 52). Alternative therapies mainly included recommendation of bisphosphonates or commercially available denosumab. †32 patients discontinued denosumab treatment as of Feb 19, 2018.

done to rule out the presence of metastases at randomisation. Postmenopausal status (according to the aforementioned criteria) was verified. Patients received 60 mg denosumab or placebo twice yearly. No dose reductions were permitted; however, interruption was possible (eg, if a patient missed the regular visit or had a grade 3 or 4 adverse event). Patients were advised to take daily supplements containing 500 mg of elemental calcium and at least 400 international units of vitamin D (cholecalciferol) during the study. Clinical follow-up, including clinical fracture assessment and other diagnostic re-staging procedures when indicated, was done at least semi-annually until the primary analysis data cutoff date, and annually thereafter. Vertebral fracture assessments were done by X-ray from baseline to 36 months and at the end of treatment, and analysed according to the Genant semiquantitative visual score and centrally reviewed, as previously described.[17] Bone mineral density of the lumbar spine, total hip, and femoral neck was measured annually by dual-energy X-ray absorptiometry scans from baseline to 36 months and at the end of treatment. Patients received trial medication until the primary analysis data cutoff date, which was defined when 247 first clinical fracture events were reached and all participants had had the opportunity to receive a minimum of at least two doses of the investigational product. Planned treatment duration was 5 years; however, because of the event-driven design, study duration varied for individual patients. The definition of end-of-treatment visit was based on the primary analysis data cutoff date and execution of the yearly radiological assessments; therefore, patients had their end-of-treatment visit either 6 months (plus a 45-day time window) before or 6 months after the primary analysis data cutoff date. Patients remained on trial medication until up to 6 months after the primary analysis data cutoff date was reached in March 26, 2014. Patients were allowed to remain on trial medication after ceasing adjuvant aromatase inhibitor therapy. The last patients received their final dose of study treatment in October, 2014.

Patient assessments, including laboratory tests (haematology, serum chemistry, and pregnancy test) and the recording of adverse events, were done before administration of each dose of the study medication until end of treatment, and followed the protocol-defined regular schedule (appendix p 83).

Adverse events were documented until 30 days after the last administration of investigational product or placebo. The potential occurrence of any case of osteonecrosis of the jaw was monitored carefully during the trial: suspected cases were adjudicated by an independent international expert panel (for the detailed workflow, see appendix of primary publication).[17] For the review of potential atypical femur fractures, the following criteria were applied: femur midshaft fracture, femur subtrochanteric fracture, or femur distal fracture with

	Placebo group (n=1709)	Denosumab group (n=1711)
Ethnicity		
White	1700 (99·5%)	1702 (99·5%)
Asian	7 (0·4%)	5 (0·3%)
Hispanic or Latino	1 (0·1%)	3 (0·2%)
Black	0	1 (0·1%)
Unknown	1 (0·1%)	0
Age, years		
<50	31 (1·8%)	34 (2·0%)
50–59	448 (26·2%)	473 (27·6%)
60–69	755 (44·2%)	782 (45·7%)
70–79	414 (24·2%)	372 (21·7%)
≥80	61 (3·6%)	50 (2·9%)
pT stage		
ypT0, ypTis, or pT1	1236 (72·3%)	1232 (72%)
pT2–pT4	467 (27·3%)	479 (28%)
Unknown	6 (0·4%)	0 (<0·1%)
pN stage		
Negative	1196 (70%)	1240 (72·5%)
Positive	506 (29·6%)	462 (27%)
Unknown	7 (0·4%)	9 (0·5%)
Tumour grade		
G1	338 (19·8%)	365 (21·3%)
G2 or Gx	1028 (60·2%)	1038 (60·7%)
G3	339 (19·8%)	303 (17·7%)
Unknown	4 (0·2%)	5 (0·3%)
Primary tumour histology		
Ductal invasive	1275 (74·6%)	1261 (73·7%)
Lobular invasive	290 (17%)	312 (18·2%)
Other	140 (8·2%)	131 (7·7%)
Unknown	4 (0·2%)	7 (0·4%)
Hormone receptor status		
Oestrogen receptor negative or progesterone receptor negative	273 (16%)	305 (17·8%)
Oestrogen receptor positive and progesterone receptor positive	1434 (83·9%)	1405 (82·1%)
Unknown	2 (0·1%)	1 (0·1%)
(Continued from previous column)		
Oestrogen receptor status		
Negative	16 (0·9%)	20 (1·2%)
Positive	1693 (99·1%)	1691 (98·8%)
Progesterone receptor status		
Negative	257 (15%)	286 (16·7%)
Positive	1450 (84·8%)	1424 (83·2%)
Unknown	2 (0·1%)	1 (0·1%)
HER2 status		
Negative	1592 (93·2%)	1605 (93·8%)
Positive	113 (6·6%)	103 (6%)
Unknown	4 (0·2%)	3 (0·2%)
Chemotherapy before randomisation		
None	1287 (75·3%)	1288 (75·3%)
Adjuvant	329 (19·3%)	338 (19·8%)
Neoadjuvant	93 (5·4%)	85 (5·0%)
Start of aromatase inhibitor therapy*		
With denosumab or placebo administration	269 (15·7%)	270 (15·8%)
Before denosumab or placebo administration	1440 (84·3%)	1441 (84·2%)
Total lumbar spine bone mineral density		
T-score <–1·0	775 (45·3%)	773 (45·2%)
T-score ≥–1·0	934 (54·7%)	938 (54·8%)

Data are n (%). *The protocol allowed administration of aromatase inhibitor for up to 2 years before randomisation (median duration before randomisation in 2881 patients was 1 month).

Table 1: **Baseline characteristics**

minimal or inadequate trauma (fall from standing height or less). Serial serum samples were collected for safety and translational research purposes.

Outcomes

Detailed study procedures and outcomes regarding the primary endpoint (time from randomisation to first clinical fracture) and the secondary fracture-related endpoints (percentage change in bone mineral density, incidence of new vertebral fractures, and incidence of new or worsening of pre-existing vertebral fractures) have been described previously.[17] Disease outcome-related secondary endpoints were disease-free survival, bone metastasis-free survival, and overall survival (the latter two are planned for analysis at the end of the study). For the assessment of disease-free survival (the secondary disease-related endpoint reported in this Article), occurrences of a disease-free survival event in all study participants—including invasive locoregional recurrence, invasive contralateral breast carcinoma, distant metastases (from breast cancer, histologically verified), second primary invasive non-breast carcinoma (histologically verified), distant metastases or second primary cancer (not histologically verified), ductal carcinoma in situ, or death—were carefully evaluated and documented during the study every 6 months at study visits, and centrally reviewed by the ABCSG Safety Department. During the follow-up phase, patients were further assessed for disease-free survival, bone-metastasis-free survival, and overall survival once every 12 months by clinic visits or telephone contacts, starting from their end-of-treatment visit. Disease-free survival time was calculated as interval (days) from randomisation date to date of first evidence of local or distant metastasis, contralateral breast cancer, secondary carcinoma, or death from any cause, whichever occurred first. Patients last known to be alive and who had not had recurrence of disease were censored at their last contact date (including clinic and telephone visits, whether scheduled or unscheduled [in instances of early study termination]),

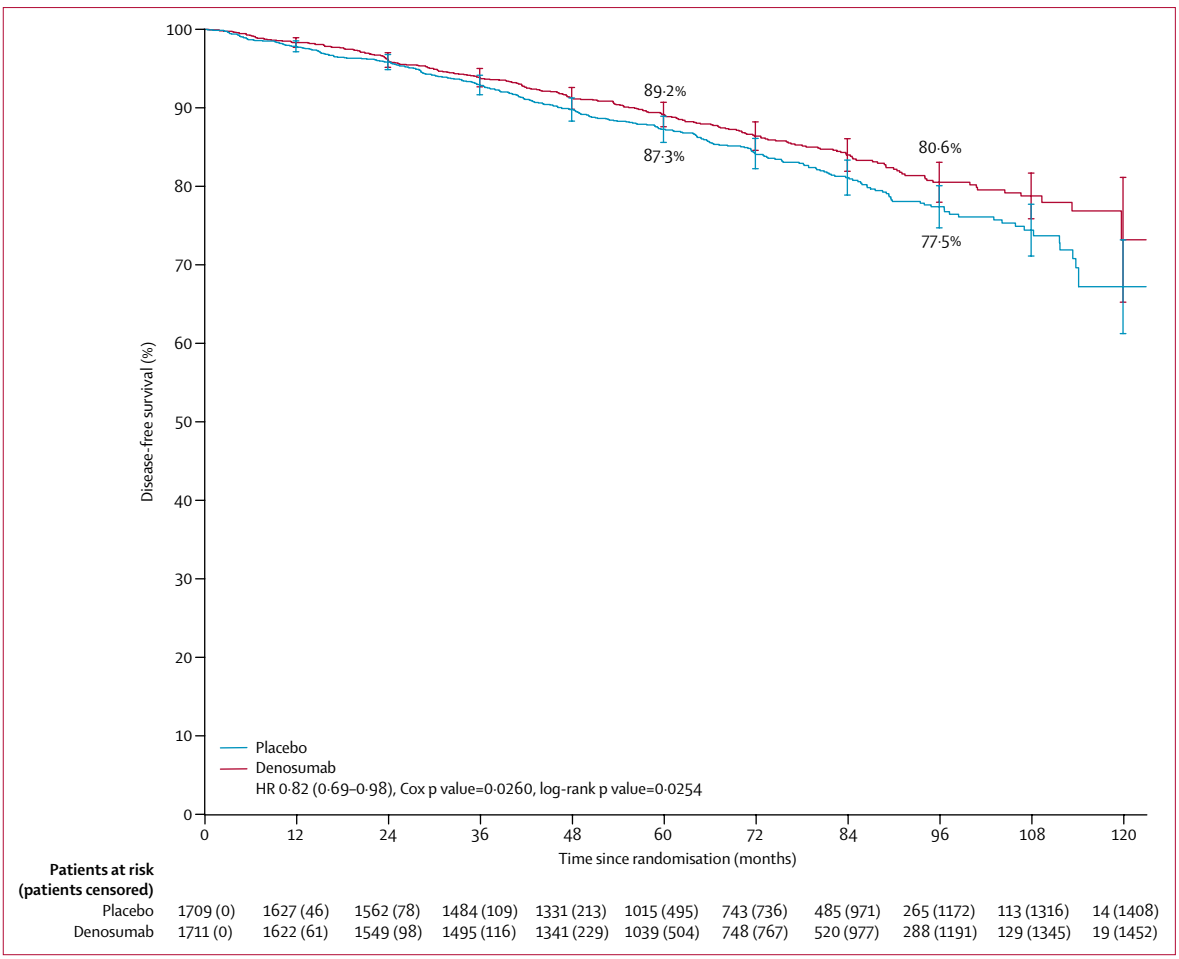

Figure 2: **Kaplan-Meier analysis of disease-free survival in the intention-to-treat population**
Disease-free survival in postmenopausal women with breast cancer who received denosumab or placebo, based on Kaplan-Meier time-to-event analysis within each treatment group at 12-month intervals. The HR and p value were calculated from a Cox model including treatment groups as the independent variable, and stratified by hospital type, previous use of aromatase inhibitor, and baseline lumbar spine bone mineral density. Error bars are 95% CIs. HR=hazard ratio.

or at the end of long-term follow-up or analysis data cutoff date (Sept 30, 2017), whichever came first.

Statistical analysis

Details of analyses (timelines, analysis sets, covariates, and subgroups) were prespecified in a statistical analysis plan (appendix p 110).

The analysis of disease-free survival was done on the full analysis set (defined as all participants who were randomly allocated to a treatment group) and all analyses were based on the intention-to-treat principle. Thus, every patient was analysed according to their randomised treatment group.

Summary statistics for disease-free survival time were based on the Cox proportional hazards model (stratified by randomisation stratification factors and after appropriate testing of the proportionality assumption) and log-rank test, and include the HR and 95% CI for denosumab compared with placebo. Disease-free survival rates with 95% CIs at the follow-up timepoints were estimated by the Kaplan-Meier method.

Additional exploratory analyses of subgroups included the following prespecified variables: previous aromatase inhibitor use (yes or no); total lumbar spine bone mineral density score at baseline (T-score <–1·0 or ≥–1·0); age (<50 years, 50–59 years, 60–69 years, 70–79 years, or ≥80 years); tumour stage (T0–T1 [including Tis] or T2–T4); lymph node status (positive or negative); histopathological grade of breast tumour (G1, G2 or Gx, or G3); tumour type (ductal invasive carcinoma, lobular invasive carcinoma, or other); hormone receptor status (oestrogen receptor positive and progesterone receptor positive, or other); and previous chemotherapy (adjuvant, neoadjuvant, or none). HER2 status (positive or negative) was added as a subgroup post hoc. A separate, descriptive post-hoc analysis was done for the time between aromatase inhibitor initiation and start of study treatment (<3 months or ≥3 months; grouped based on a medically meaningful and statistically feasible [with regard to group size] cutoff for the time variable). To verify subgroup results, we did a post-hoc analysis that used a

full Cox proportional hazards model including treatment, all baseline covariates, and all interaction terms between a single covariate and trial treatment, stratified by type of centre (pre-selected bone mineral density centres or other), use of aromatase inhibitor (yes or no), and baseline lumbar spine bone mineral density (T-score <–1·0 or ≥–1·0).

Several sensitivity analyses were done to account for treatment crossover: first, a rank-preserving, structured failure time model,[18] including a correction of treatment effect estimate for bias introduced by crossover; second, a model censoring participants at the date of first open-label phase denosumab administration; third, an analysis censoring participants who received any bisphosphonates or commercially available denosumab before the end of treatment (with end-of-treatment reason given as "requirements for alternative therapies"). Patients who received an alternative (bone-targeted) therapy and did not have a disease-free survival event before the analysis data cutoff date were censored at the end of treatment. Finally, a combination of the censoring done in the second and third sensitivity analyses was done post hoc.

The safety analysis set consisted of all participants who were randomly allocated to a treatment group and received at least one dose of study treatment. Safety analyses (treatment-emergent adverse events, and cases of potential osteonecrosis of the jaw or of atypical femoral fracture) were done to evaluate the safety profile of denosumab as compared with placebo, and descriptive summary tables and listings were provided. During the open-label phase, we only recorded serious adverse events for patients receiving open-label phase denosumab. Adverse event severity was scored using the Common Terminology Criteria for Adverse Events (version 3.0), and all adverse events were coded using the Medical Dictionary of Regulatory Activities (version 17.1). All analyses were done with SAS software (version 9.1 or higher).

The study is registered with EudraCT (number 2005–005275–15) and ClinicalTrials.gov (number NCT00556374), and is ongoing for long-term follow-up of secondary endpoints.

Role of the funding source

Amgen was the legal sponsor of the study and had a role in protocol and study design, and reviewed the manuscript, but was not involved in data collection, data interpretation, or writing of the manuscript. CF and SF had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

3425 postmenopausal women with early hormone receptor-positive breast cancer were enrolled into the trial between Dec 18, 2006, and July 22, 2013, at 53 centres in Austria (3302 patients) and five centres in Sweden (123 patients). Five patients later withdrew consent to use their data. The full analysis set therefore comprised 3420 patients: 1711 (50·0%) in the denosumab group and 1709 (50·0%) in the placebo group. From the full analysis set, 553 (16·2%) patients chose to be unmasked to treatment allocation following the protocol amendment, of whom 278 patients were originally in the placebo group. Of the unmasked placebo group, 252 (90·6%) patients actually received denosumab in the open-label phase, constituting a crossover of 14·7% of the original placebo group, and 7·4% of the total trial population (figure 1).

	Placebo group (n=1709)	Denosumab group (n=1711)	Total (n=3420)
All events	287 (16·8%)	240 (14·0%)	527 (15·4%)
Invasive locoregional recurrence	23 (1·3%)*†	22 (1·3%)†‡	45 (1·3%)*†‡
Ductal carcinoma in situ	9 (0·5%)	9 (0·5%)‡	18 (0·5%)‡
Invasive contralateral breast carcinoma	23 (1·3%)	18 (1·1%)	41 (1·2%)
Distant metastases (from breast cancer), histologically verified	18 (1·1%)*	19 (1·1%)	37 (1·1%)*
Distant metastases or second primary cancer, not histologically verified	68 (4·0%)†	56 (3·3%)†	124 (3·6%)†
Second primary invasive non-breast carcinoma, histologically verified	100 (5·9%)	80 (4·7%)	180 (5·3%)
Death as first event	48 (2·8%)	39 (2·3%)	87 (2·5%)

Data are n (%). In each category, an event was counted only if it was the first (or first simultaneous) event per patient. Distant metastases and second primary non-breast carcinomas that were not histologically verified were pooled. *Simultaneous occurrence of invasive locoregional recurrence and distant metastases (from breast cancer), histologically verified. †Simultaneous occurrence of invasive locoregional recurrence and distant metastases or second primary cancer, not histologically verified. ‡Simultaneous occurrence of invasive locoregional recurrence and ductal carcinoma in situ.

Table 2: **Disease-free survival events**

The study population is described in detail in our previous report of the primary endpoint of this study.[17] In brief, at the time of randomisation, median patient age was 64 years (IQR 58–70), and baseline demographics were well balanced between the groups (table 1). At baseline, 1872 (54·7%) of 3420 patients had normal total lumbar spine bone mineral density, and 1548 (45·3%) patients had T-scores of less than –1·0. Aromatase inhibitor treatment was started at randomisation in 539 (15·8%) patients, and 2881 patients (84·2%) had previously started aromatase inhibitor treatment (median duration before randomisation 1 month [IQR 0–4]; maximum 2 years as per protocol). Previous adjuvant or neoadjuvant chemotherapy was documented in 845 patients (24·7%), and 2575 patients (75·3%) had received adjuvant endocrine therapy only.

Of 3399 (99·4%) patients who received at least one dose of either denosumab or placebo, 2579 (75·9%) completed

	Events (n)/patients (N)		5-year disease-free survival, % (95% CI)		HR (95% CI) vs placebo
	Placebo	Denosumab	Placebo	Denosumab	
Previous aromatase inhibitor use					
No	58/269	36/270	86·8 (82·5–91·1)	91·7 (88·3–95·2)	0·58 (0·38–0·88)
Yes	229/1440	204/1441	87·4 (85·6–89·2)	88·7 (87·0–90·4)	0·89 (0·73–1·07)
Bone mineral density at baseline					
T score <–1	130/775	111/773	87·4 (84·9–89·8)	88·8 (86·4–91·2)	0·84 (0·65–1·08)
T score ≥–1	157/934	129/938	87·3 (85·0–89·5)	89·5 (87·5–91·6)	0·81 (0·64–1·02)
Age, years					
<60	72/479	49/507	89·0 (86·0–91·9)	92·8 (90·5–95·1)	0·64 (0·44–0·91)
60–69	117/755	109/782	88·7 (86·3–91·0)	88·8 (86·5–91·2)	0·89 (0·68–1·15)
>69	98/475	82/422	83·3 (79·7–86·9)	85·5 (81·9–89·1)	0·97 (0·72–1·31)
T stage					
T0, Tis, or T1	174/1236	147/1232	90·0 (88·3–91·8)	90·4 (88·7–92·2)	0·84 (0·67–1·04)
T2–T4	112/467	93/479	80·4 (76·7–84·2)	86·1 (82·8–89·3)	0·78 (0·59–1·03)
Nodal status					
Negative	173/1196	147/1240	89·1 (87·3–91·0)	90·8 (89·1–92·5)	0·82 (0·66–1·02)
Positive	113/506	92/462	83·1 (79·7–86·5)	84·9 (81·4–88·3)	0·89 (0·67–1·17)
Grade					
G1	41/338	31/365	91·8 (88·8–94·8)	93·4 (90·7–96·1)	0·69 (0·43–1·10)
G2 or GX	176/1028	161/1038	86·9 (84·7–89·1)	88·9 (86·9–90·9)	0·90 (0·73–1·12)
G3	70/339	48/303	84·0 (79·9–88·1)	84·9 (80·6–89·2)	0·76 (0·53–1·10)
Histology					
Ductal invasive	219/1275	176/1261	86·8 (84·8–88·7)	88·7 (86·8–90·5)	0·80 (0·65–0·97)
Lobular invasive	46/290	47/312	88·2 (84·3–92·1)	90·0 (86·5–93·5)	0·93 (0·62–1·40)
Other	21/140	17/131	90·9 (85·8–96·1)	91·7 (86·8–96·6)	0·82 (0·43–1·59)
Hormone receptor status					
ER negative or PgR negative	49/273	48/305	84·9 (80·4–89·5)	88·1 (84·4–91·9)	0·83 (0·55–1·24)
ER positive and PgR positive	238/1434	192/1405	87·7 (86·0–89·5)	89·4 (87·7–91·1)	0·81 (0·67–0·98)
HER2					
Negative	269/1592	227/1605	87·4 (85·7–89·1)	89·1 (87·5–90·7)	0·83 (0·69–0·98)
Positive	17/113	13/103	86·2 (79·5–93·0)	90·3 (84·3–96·4)	0·81 (0·39–1·69)
Previous chemotherapy					
None	204/1287	170/1288	88·4 (86·6–90·3)	89·8 (88·1–91·5)	0·83 (0·68–1·01)
Adjuvant	60/329	48/338	85·3 (81·3–89·3)	89·0 (85·5–92·6)	0·73 (0·50–1·08)
Neoadjuvant	23/93	22/85	79·3 (70·7–87·8)	80·7 (71·8–89·5)	1·04 (0·57–1·93)
Entire population	**287/1709**	**240/1711**	**87·3 (85·7–89·0)**	**89·2 (87·6–90·7)**	**0·82 (0·69–0·98)**

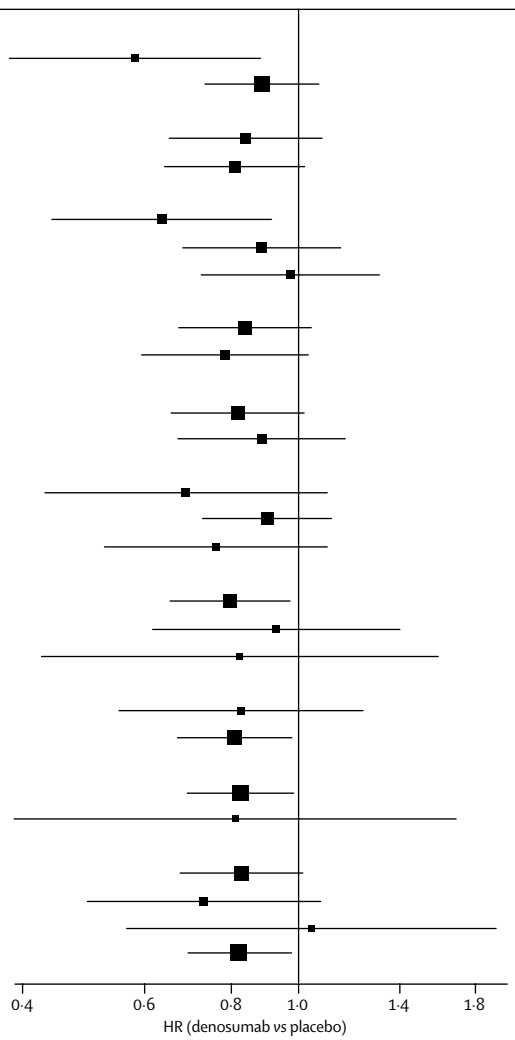

Figure 3: **Disease-free survival subgroup analysis in the intention-to-treat population**
Forest plot of HRs indicating treatment effect in all randomly assigned patients separated by subgroups. Error bars are 95% CIs. HR=hazard ratio. ER=oestrogen receptor. PgR=progesterone receptor.

their treatment according to protocol (figure 1). The median number of doses received (7 [IQR 4–10]) was identical in the denosumab and placebo groups. At the data cutoff date (Sept 30, 2017), the median duration of follow-up was 73 months (58–95) and the reasons for early study termination were death (207 [6·1%] of 3420 patients), consent withdrawal (428 [12·5%]), and loss to follow-up (19 [0·6%]), with no obvious differences between groups. Thus, 2766 patients (80·9%) completed follow-up to the cutoff date (1402 [81·9%] in the denosumab group and 1364 [79·8%] in the placebo group).

At data cutoff for this disease-free survival analysis, disease-free survival events had occurred in 287 (16·8%) of 1709 patients in the placebo group and 240 (14·0%) of 1711 patients in the denosumab group. Results from the denosumab group showed a significant disease-free survival benefit (HR 0·82 [95% CI 0·69–0·98]) compared with the placebo group in this descriptive analysis (figure 2). Disease-free survival at 5 years was 89·2% (95% CI 87·6–90·8) in the denosumab group and 87·3% (85·7–89·0) in the placebo group, and at 8 years was 80·6% (78·1–83·1) in the denosumab group and 77·5% (74·8–80·2) in the placebo group (figure 2). Thus, absolute differences in disease-free survival were roughly 2 percentage points at 5 years and 3 percentage points at 8 years.

The numbers of patients with locoregional or contralateral recurrences or ductal carcinoma in situ were similar between treatment groups, as were histologically

verified distant metastases from breast cancer. The disease-free survival difference between the groups appeared to be driven by distant metastases from breast cancer that were not histologically verified and new primary cancers (table 2).

Univariate descriptive subgroup analysis showed that denosumab significantly improved disease-free survival in postmenopausal patients younger than 60 years of age, patients who received no aromatase inhibitor treatment before randomisation, patients with ductal invasive tumours, patients with oestrogen receptor and progesterone receptor double-positive status, and patients with HER2-negative status (figure 3). However, scrutiny with a full interaction model could not verify a significant benefit for any subgroup (appendix p 6).

In subgroups of patients with different lead times of denosumab or placebo after aromatase inhibitor initiation, patients who started denosumab concomitantly or within 3 months after initiation of aromatase inhibitor therapy had a greater benefit from denosumab than did patients who started denosumab at 3 months or later after aromatase inhibitor treatment (figure 4).

1160 (67·8%) of 1711 patients in the denosumab group and 1139 (66·6%) of 1709 patients in the placebo group were still receiving adjuvant aromatase inhibitor therapy after 5 years from initiation of aromatase inhibitor therapy.

Although the disease-free survival analysis presented in this Article was based on the intention-to-treat principle (to remain highly conservative towards potential crossover bias), various sensitivity analyses were done to account for potential bias resulting from the partial crossover of some patients after unmasking. All analytical methods used showed results similar to those of the intention-to-treat analysis, substantiating a statistically significant increase in disease-free survival in the denosumab group (appendix p 5). Sensitivity disease-free survival analysis censoring for crossover at the date of first open-label phase denosumab showed an HR of 0·82 (0·69–0·98). A rank-preserving structural failure time model analysis, which corrects the treatment effect estimate for bias introduced by crossover, resulted in an HR of 0·82 (0·68–0·97). Further sensitivity analysis results are provided in the appendix (p 5).

The number of episodes of treatment-emergent adverse events was similar in each group: 1367 (including 521 serious adverse events) in the denosumab group, and 1339 (including 515 serious adverse events) in the placebo group. The most common adverse events of grade 3–5 are shown in table 3, and serious adverse events of all grades are shown in table 4. Grade 1–2 adverse events that occurred in at least 340 (10%) of the 3399 patients who received at least one dose of denosumab or placebo were arthralgia (424 [24·8%] patients in the denosumab group *vs* 431 [25·5%] in the placebo group) and hot flushes (265 [15·5%] *vs* 228 [13·5%]).[17] There were 11 treatment-related serious adverse events in the denosumab group (bronchitis, diarrhoea, dysphagia, hypersensitivity,

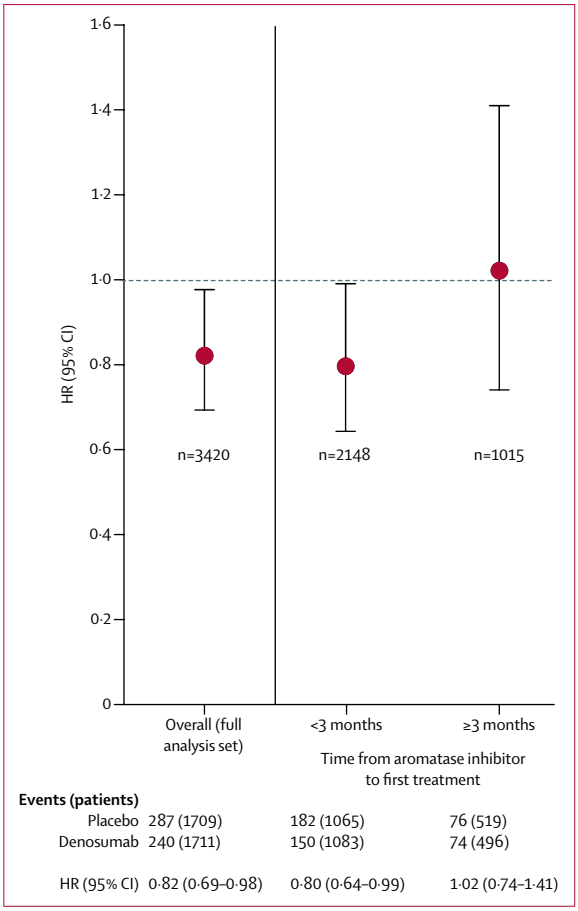

Figure 4: **Denosumab treatment effect by interval between start of aromatase inhibitor therapy and start of study treatment**
Effect of denosumab versus placebo in subgroups with different lead times of aromatase inhibitor therapy before the start of denosumab or placebo treatment. 257 patients are not included in the subgroup analysis: 236 patients received study treatment but no aromatase inhibitor therapy, and 21 patients did not receive study treatment (of whom four patients did not receive aromatase inhibitor). HR=hazard ratio.

hypertension, hypocalcaemia, osteoarthritis, pain, sinusitis, swollen tongue, and tenosynovitis stenosans, which occurred in one [0·1%] patient each) and five in the placebo group (amnesia, generalised tonic-clonic seizure, and Raynaud's phenomenon, in one [0·1%] patient each; and infection in two [0·1%] patients). The most common serious adverse events were osteoarthritis (62 [3·6%] of 1709 in the denosumab group *vs* 58 [3·4%] of 1690 in the placebo group), meniscus injury (23 [1·3%] *vs* 24 [1·4%]), and cataract (16 [0·9%] *vs* 28 [1·7%]).

15 (6·0%) of the 252 patients who received denosumab as part of the open-label phase had a serious adverse event, with the following occurring in more than one patient: infections and infestations (six [2·4%] patients); musculoskeletal and connective tissue disorders (three [1·2%]); neoplasms benign, malignant, and unspecified (including cysts and polyps; two [0·8%]); and renal and urinary disorders (two [0·8%]).

	Placebo group (n=1690)			Denosumab group (n=1709)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Musculoskeletal and connective tissue disorders	92 (5·4%)	1 (0·1%)	0	104 (6·1%)	2 (0·1%)	0
Osteoarthritis	39 (2·3%)	0	0	43 (2·5%)	2 (0·1%)	0
Vascular disorders	46 (2·7%)	3 (0·2%)	0	54 (3·2%)	2 (0·1%)	0
Hypertension	10 (0·6%)	1 (0·1%)	0	20 (1·2%)	0	0
Injury, poisoning, and procedural complications	38 (2·2%)	1 (0·1%)	0	37 (2·2%)	1 (0·1%)	0
Meniscus injury	14 (0·8%)	0	0	14 (0·8%)	0	0
Eye disorders	32 (1·9%)	0	0	27 (1·6%)	0	0
Cataract	28 (1·7%)	0	0	19 (1·1%)	0	0

Data are n (%). Events that occurred before the primary analysis data cutoff date in all patients who received at least one dose of denosumab or placebo in the double-blind phase of the trial are shown. Events are only listed if they occurred in a total of 25 patients or more at any grade in any group. Only the highest grade per patient, standard of care, and preferred term is included. Nine of the 1699 patients who commenced placebo treatment received denosumab treatment (mistakenly) at least once during the course of the study and were therefore included in the denosumab group for the safety analyses. Grade 5 events that occurred in less than 25 patients and events that occurred in the open-label phase of the trial are reported in the text.

Table 3: **Adverse events (grade 3–5)**

	Placebo group (n=1690)	Denosumab group (n=1709)
Musculoskeletal and connective tissue disorders	121 (7·2%)	134 (7·8%)
Osteoarthritis	58 (3·4%)	62 (3·6%)
Intervertebral disc protrusion	15 (0·9%)	14 (0·8%)
Injury, poisoning, and procedural complications	68 (4·0%)	56 (3·3%)
Meniscus injury	24 (1·4%)	23 (1·3%)
Nervous system disorders	57 (3·4%)	66 (3·9%)
Carpal tunnel syndrome	13 (0·8%)	14 (0·8%)
Eye disorders	32 (1·9%)	25 (1·5%)
Cataract	28 (1·7%)	16 (0·9%)
Endocrine disorders	13 (0·8%)	23 (1·3%)
Goitre	12 (0·7%)	21 (1·2%)

Data are n (%). Serious adverse events (any grade) that occurred in more than 25 patients in the double-blind phase of the trial, before the primary analysis data cutoff date, in all patients who received at least one dose of denosumab or placebo are shown. Nine of the 1699 patients who commenced placebo treatment received denosumab treatment (mistakenly) at least once during the course of the study and were therefore included in the denosumab group for the safety analyses. Adverse events that occurred in the open-label phase of the trial are reported in the text.

Table 4: **Serious adverse events**

207 (6·1%) of 3420 patients in the full analysis set (98 [5·7%] of 1711 patients in the denosumab group and 109 [6·4%] of 1709 patients in the placebo group) died during the course of the study. Causes of death were not breast cancer (117 [3·4%] patients), any breast cancer (63 [1·8%]), and unknown cause (27 [0·8%]; appendix p 7). One (<0·1%) of these deaths (in the denosumab group) was recorded as treatment-related (not breast cancer; pneumonia, septic kidney failure, and cardiac decompensation).

No neutralising anti-denosumab antibodies were found in any of the serum samples from the study cohort at any timepoint.

35 potential dental problems were identified by proactive monitoring for osteonecrosis of the jaw during the trial, of which 31 suspected cases of osteonecrosis (20 in the intervention group; 11 in the control group) of the jaw were considered via the predefined adjudication process. No case met the diagnostic criteria for osteonecrosis of the jaw. Four candidate cases of atypical femoral fractures (two in each treatment group) were recorded, but none were confirmed after review.

Discussion

In this analysis of disease-free survival outcomes from the ABCSG-18 trial, after a median follow-up of 73 months (IQR 58–95), adjuvant denosumab therapy at a dosage of 60 mg every 6 months significantly improved disease-free survival in postmenopausal patients with breast cancer receiving adjuvant aromatase inhibitor therapy. This difference translated into an approximate absolute disease-free survival difference of 3 percentage points at 8 years of follow-up. The tolerability profile of this novel adjuvant treatment approach was favourable.

In postmenopausal patients with hormone receptor-positive early breast cancer, tamoxifen and aromatase inhibitors are both valid therapeutic options.[19] Use of aromatase inhibitors for a total of 5 years has been established as the preferred choice for early hormone receptor-positive breast cancer in postmenopausal women, either in the upfront or in the sequential or extended adjuvant therapy setting, and such patients often have a very good prognosis.[20] The disadvantage of this treatment is bone loss and bone degradation, which are frequently observed in patients with breast cancer, leading to a higher risk of fracture.[21] Fractures are not only associated with decreased quality of life, but also with increased mortality.[22] Bisphosphonates[3] and denosumab[17] have been shown to counteract this cancer-treatment-induced bone loss and improve bone mineral density, but only denosumab significantly reduces clinical (and vertebral) fractures in postmenopausal patients with breast cancer treated with an aromatase inhibitor. Moreover, bisphosphonate therapy has an unfavourable side-effect profile (including acute-phase reactions, gastrointestinal sequelae, and renal toxicity), often leading to early discontinuation in clinical practice.[23]

After conflicting results from individual trials, the EBCTCG's meta-analysis showed that bisphosphonates improve outcomes in postmenopausal patients with breast cancer (rate ratio for recurrence 0·86 [95% CI 0·78–0·94], p=0·002).[3] The monoclonal anti-RANK ligand antibody denosumab has shown equal or better efficacy compared with bisphosphonates with respect to prevention of skeletal-related events and treatment of bone metastases in advanced cancer.[24] Therefore, it is logical to also test this tailored approach to osteoclast inhibition in the adjuvant setting. ABCSG-18 assessed 60 mg denosumab administered subcutaneously twice yearly versus placebo in postmenopausal patients with aromatase inhibitor-treated early hormone receptor-positive breast cancer.[17] The observed disease-free survival benefit of adjuvant denosumab in ABCSG-18 was

numerically similar to the effect of bisphosphonates on breast cancer recurrence in the EBCTCG meta-analysis.[3]

Adjuvant denosumab therapy at the dose used in the ABCSG-18 trial had very few measurable side-effects, as previously reported.[17] The updated serious adverse event data, including those of patients treated with open-label phase denosumab, shows that this adjuvant therapy is safe and highly tolerable. Although, in accordance with the protocol, adverse events were only recorded for up to 30 days after the last dose of study treatment in this trial, adverse event data for denosumab at a dosage of 60 mg every 6 months for up to 6 months after treatment are available from other settings (eg, the FREEDOM trial).[25] From a safety and tolerability perspective, adjuvant denosumab has a more favourable side-effect profile than that of adjuvant bisphosphonates.[26] Furthermore, the complications of osteonecrosis of the jaw and atypical femoral fracture, which have been observed in denosumab-treated patients with advanced cancer,[27,28] were not reported with the 6-monthly dosing in our trial.

There are two main limitations associated with these results of the secondary endpoint of disease-free survival in the ABCSG-18 trial. First, the unmasking of patients after the primary endpoint results became available (based on a recommendation by the IDMC) renders subsequent analyses more complex, and, technically, descriptive. However, the number of crossovers was relatively small, and we still observed a disease-free survival benefit of adjuvant denosumab in the conservative intention-to-treat analysis. Additional sensitivity analyses substantiated the significant benefit of adjuvant denosumab on disease-free survival. The size and power of this prospective placebo-controlled trial minimises the concern about play of chance, but the descriptive nature of this analysis precludes any final conclusion beyond hypothesis generation.

Second, the exact mechanism of action of adjuvant denosumab on disease-free survival remains to be understood. Details of the composite-endpoint analysis showed that non-histologically verified distant metastases and new primary cancers were reduced in the denosumab group, and there was no difference between the intervention and placebo groups in locoregional recurrences. However, if overall invasive breast cancer events had been used as an endpoint, the difference between groups might not have been significant. Overall survival will have to be assessed after very long-term follow-up in this cohort of patients with early breast cancer at moderate risk of relapse. Several hypotheses about the mechanism of action by which denosumab reduces disease recurrence have been proposed. Increased bone turnover after aromatase inhibition was shown to mobilise haemopoietic stem cells from the bone marrow endosteal niche, where dormant tumour cells are retained.[29] Such mobilisation contributes to the reactivation of dormant cancer cells, or might even condition premetastatic niches for disseminated tumour cells.[30] The RANK–RANK ligand pathway might also have direct, osteoclast-independent effects on tumour cells, and its activity has been associated with tumour progression and advanced disease in cancer cells.[16,31] RANK ligand expression has also been associated with epithelial-to-mesenchymal transition, a morphological switch in which cancer cells upregulate mesenchymal-associated genes that lead to loss of cell-to-cell adhesion, thereby increasing the migration capacity and invasive potential of cancer cells.[32]

Furthermore, the RANK–RANK ligand axis has been implicated in antitumor immunity (eg, via cross-modulation of the tumour microenvironment; and by alleviation of immunosuppression mediated by RANK-expressing myeloid or dendritic cells or by interruption of thymic central tolerance).[33] Therefore, treatment with an anti-RANK inhibitor might reverse this immuno-suppressive effect of RANK–RANK ligand signalling.[34]

It remains conceptually unclear why patients starting denosumab therapy in parallel with adjuvant aromatase inhibitor treatment appeared to benefit from a larger risk reduction than did patients who started aromatase inhibitor therapy earlier. However, a similar effect was seen in the ZO-FAST trial, where fewer recurrences were reported for women treated with aromatase inhibitor who received immediate bone protection compared with those in whom bisphosphonates were introduced months or years after changes in bone mineral density or manifest fractures.[35] Furthermore, the observed difference in disease-free survival between the ABCSG-12[36] and the AZURE trial[37] was also attributed to the different time courses of treatment-induced amenorrhoea in those trials. The bone marrow environment might be differently sensitive (or more receptive or susceptible) to anti-resorptive therapies early after locoregional treatment or at the beginning of oestrogen-depriving therapies as compared with later in follow-up.[38]

Further studies are warranted to elucidate the anti-cancer effect of denosumab in clinical settings. The final analysis of ABCSG-18, evaluating other secondary disease-related endpoints (bone-metastasis-free survival and overall survival), will take place after completion of the long-term follow-up after 2020. These data will show whether the observed disease-free survival benefit in patients receiving denosumab will translate into an overall survival benefit. With appropriate caution, our results might, in principle, support the use of denosumab for the prevention of breast cancer in women at high risk. This approach will be investigated in a worldwide trial of denosumab for breast cancer prevention in *BRCA*-mutation carriers (ABCSG-50, EudraCT number 2017–002505–35). The D-CARE trial[39] investigated the effects of adjuvant denosumab—of a higher dose and frequency than used in the current study—in women with high-risk early breast cancer receiving neoadjuvant or adjuvant therapy (NCT01077154). That study showed no difference in bone-metastasis-free-survival (primary

endpoint) or disease-free survival, but did show benefits with respect to time to bone metastasis as first recurrence, although with an increased incidence of osteonecrosis of the jaw in the denosumab group (5·4%, 122 patients) compared with the placebo group (0·2%, 4 patients).

Data from ABCSG-18 are also being used in translational research projects addressing bone turnover markers, hormone serum concentrations, tumour markers, RANK ligand pathway indicators, and patient-derived covariates such as body-mass index to help to clarify the anticancer mechanism of denosumab, and ultimately assist clinicians in optimum patient selection. One such project is investigating the *MAF* gene. Potential associations between *MAF* status (a putative biomarker for bone metastasis) and bone relapse were shown in a post-hoc analysis of the AZURE trial of standard adjuvant treatment with or without the addition of zoledronic acid,[40] in which the zoledronic acid group showed longer invasive-disease-free survival in patients with *MAF*-negative tumours than in those with *MAF*-positive tumours (HR 0·52 [95% CI 0·36–0·75]). Importantly, *MAF* positivity was associated with increased extraskeletal recurrence in the zoledronic acid group (HR 6·92 [95% CI 2·44–19·60]).

In general, even when statistically significant, the absolute benefits of new therapies in adjuvant early breast cancer trials are often modest in numbers considering the already good outcomes of this population with current standard treatment. In ABCSG-18, at 5 years, the difference in disease-free survival between groups was 1·9% (89·2% of patients without an event in the denosumab group *vs* 87·3% in the placebo group). These modest results are comparable with those of pivotal early breast cancer studies, such as the ATAC trial,[2] a 2008 study comparing anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer, which showed an absolute disease-free survival effect size at 5 years of 2·5% (13·9% patients with an event in the anastrozole group *vs* 16·4% in the tamoxifen group). Furthermore, the EBCTCG patient-level meta-analysis of aromatase inhibitor versus tamoxifen therapy in early breast cancer showed a 3·1% difference in recurrence between groups (9·0% with an event in the aromatase inhibitor group *vs* 12·1% in the tamoxifen group at 5 years).[4] The effect size at 5 years in the EBCTCG meta-analysis of bisphosphonates for postmenopausal patients was 2·4% (13·4% patients with an event in the bisphosphonates group *vs* 15·8% in the no bisphosphonates group).[3] All of these studies show an effect size of similar magnitude to that observed in ABCSG-18, and have defined a new standard of care in postmenopausal patients with early breast cancer.

In summary, subcutaneous administration of adjuvant denosumab at 60 mg twice yearly improved disease-free survival in patients with hormone receptor-positive breast cancer receiving aromatase inhibitor treatment, and was consistently well tolerated throughout the trial. On the basis of descriptive analyses for disease-free survival in ABCSG-18 and the previously reported reduction of fractures independent of baseline bone mineral density,[17] adjuvant denosumab constitutes an effective and safe treatment option for postmenopausal patients with hormone receptor-positive breast cancer who receive aromatase inhibitor therapy.

Contributors

MG developed the idea for the study, designed the study protocol, served as principal investigator of the trial, contributed to patient data collection and data acquisition, and analysis and interpretation of the data, and wrote the first draft of the manuscript. GP, RG, GGS, RJ, and CFS contributed to conception and design of the trial, patient data collection and data acquisition, and analysis and interpretation of the data. FF, DE, CM, and MB contributed to patient data collection and data acquisition, and analysis and interpretation of the data. VW, FH, VB-R, PS, BM, RE, and EM-Z contributed to patient data collection and data acquisition. CF and SF provided major writing input, developed the statistical analysis plan, and did the analyses. MG wrote the final report. All authors contributed to revisions of the report. Members of a publication committee approved the manuscript for publication and guarantee the completeness and accuracy of the data. Data preparation and analyses were done by the ABCSG statisticians and verified by statisticians of the trial sponsor.

Declaration of interests

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Data sharing

Because the study is still ongoing and other secondary endpoints will be analysed at the end of the study, data cannot be shared at this time.

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