Ther Adv Med Oncol

2023, Vol. 15: 1–20

DOI: 10.1177/
17588359231173180

Adjuvant denosumab in early breast cancer: a systematic review and meta-analysis of randomized controlled clinical trials

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Abstract

Background: In early breast cancer (BC) the impact of denosumab on survival outcomes is still unclear. We undertook a systematic review and meta-analysis to assess efficacy and safety of adjuvant denosumab in addition to standard anticancer therapy.

Methods: PubMed, CENTRAL, Scopus, Embase, and oncological meetings websites were screened to identify potentially eligible randomized controlled trials (RCTs). Survival outcomes were disease-free survival (DFS), bone-metastasis-free survival (BMFS), and overall survival (OS). Fracture incidence and time to first fracture were bone-health outcomes. Osteonecrosis of the jaw (ONJ), atypical femur fractures (AFF), and other adverse events were also evaluated. Pooled hazard ratios (HRs) and risk ratios (RR) with respective 95% confidence interval (95% CI) were computed using a random-effects model. Exploratory subgroup analyses were performed.

Results: Two phase III RCTs were included, the Austrian Breast & Colorectal Cancer Study Group-18 (ABCSG-18) and the D-CARE trials, for a total of 7929 patients. In the ABCSG-18 trial, denosumab was administered every 6 months during endocrine therapy (for a median of seven cycles) while the D-CARE trial used an intensive schedule for a total treatment duration of 5 years. Adjuvant denosumab showed no difference in DFS (HR: 0.932; 95% CI: 0.748–1.162), BMFS (HR: 0.9896; 95% CI: 0.751–1.070), and OS (HR: 0.917; 95% CI: 0.718–1.171) compared to placebo in the overall population. In hormone receptor positive/human epidermal growth factor receptor 2 (HER2) negative BC patients, a DFS (HR: 0.883; 95% CI: 0.782–0.996) and BMFS (HR: 0.832; 95% CI: 0.714–0.970) benefit was observed and BMFS was prolonged in all hormone receptor positive patients (HR: 0.850; 95% CI: 0.735–0.983). Fracture incidence (RR: 0.787; 95% CI: 0.696–0.890) and time to first fracture (HR: 0.760; 95% CI: 0.665–0.869) were also improved. No increase in overall toxicity was seen with denosumab and no differences were observed for ONJ and AFF between the 60-mg every 6-month schedule and placebo.

Conclusion: Denosumab addition to anticancer treatment does not improve DFS, BMFS, or OS in the overall population, although a DFS improvement was observed in hormone receptor positive/HER2 negative BC patients and a BMFS improvement in all hormone receptor positive patients. Bone-health outcomes were improved with no added toxicity with the 60-mg schedule.

Registration: PROSPERO identifier: CRD42022332787.

Keywords: adjuvant therapy, bone-health, denosumab, early breast cancer, meta-analysis

Received: 13 January 2023; revised manuscript accepted: 13 April 2023.

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Introduction

Breast cancer (BC) is the most common tumor in women worldwide[1] and bone is a typical site of distant recurrence, occurring as first metastatic relapse in 40% of patients.[2]

Among hormone receptor positive early BC patients, aromatase inhibitors (AIs) are the standard of care[3] in the postmenopausal setting and represent an option for high-risk premenopausal patients in addition to ovarian suppression.[4] AIs disrupt the conversion of androgens to estrogens as well as ovarian suppression and they induce a hypoestrogenic state that results in decreased bone mineral density (BMD) and increased fracture risk.[5]

Bisphosphonates increase BMD during endocrine therapy (ET) and reduce fracture risk[6,7] but compliance with these oral drugs tends to be suboptimal.[8] In terms of oncological outcomes, a meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) indicated that the addition of bisphosphonates to anticancer therapy reduces the risk of distant recurrence, bone recurrence, and BC mortality, but this positive effect was substantial only in postmenopausal patients.[9]

Denosumab is a human monoclonal antibody that selectively binds to and inhibits the receptor activator of nuclear factor κB ligand (RANKL), an important mediator of osteoclastogenesis signaling and bone resorption.[10] Like bisphosphonates, it is used in both early and metastatic BCs for the prevention of skeletal-related events.[11] In the adjuvant setting, randomized controlled trials (RCTs) showed that denosumab significantly increased BMD[12] and delayed the time to first clinical fracture, when compared with placebo.[13,14] Nevertheless, preclinical evidence has suggested that RANKL inhibition is capable of attenuating BC development,[15] preventing and reducing BC bone metastasis,[16] and dissemination of circulating BC cells from bone tissue.[17] However, the impact of denosumab on long-term outcomes is unclear, as the two randomized trials that tested this issue reported conflicting results.[18,19]

Herein, a systematic review and meta-analysis of survival and safety data of RCTs was conducted to evaluate denosumab *versus* placebo in association to standard anticancer treatment in early BC, to shed light on the potential benefit of such a therapeutic strategy.

Methods

This systematic review and meta-analysis has been performed in accordance with the Methodological Expectations of Cochrane Intervention Reviews standards and reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Statement (Supplemental Table S1).[20] The protocol was registered to PROSPERO (CRD42022332787).

Search strategy

PubMed, Cochrane Central Register of Controlled Trials, Embase, Scopus, and clinicaltrials.gov were systematically searched for RCTs of adjuvant denosumab in early BC published up to 14 December 2022.

Keywords used included 'denosumab', 'breast cancer', and 'trial'. Full search strategy is reported in Supplemental Table S2. Abstracts and presentations from the American Society of Clinical Oncology, the European Society for Medical Oncology, and the San Antonio Breast Cancer Symposium were also reviewed to identify unpublished studies or updates of published studies. Selected studies were also searched through reference section for other potentially eligible reports. Three investigators (LM, NM, and EDM) independently conducted a systematic literature search; disagreements were resolved through consensus or referring to a fourth author (GG).

Selection criteria

Based on the inclusion criteria, trials were considered eligible if they met the following criteria:

(P) Participants: pre- and postmenopausal women with early BC, regardless of hormone receptor and human epidermal growth factor receptor 2 (HER2) status.
(I) Intervention: adjuvant denosumab, either following or concomitant with standard of care anticancer therapy, including chemotherapy, anti-HER2 therapy, radiotherapy, and/or ET (AIs, tamoxifen, and/or ovarian suppression).
(C) Comparator: placebo.
(O) Outcomes: disease-free survival (DFS), bone-metastasis-free survival (BMFS), overall survival

(OS), fracture incidence, time to first clinical fracture, adverse events (AEs) and serious AEs (SAEs), osteonecrosis of the jaw (ONF), and atypical femur fractures (AFF).
(S) Study design: phase III RCTs.

All records were restricted to English language. Studies were excluded if they met one or more of the following: (1) reviews, meta-analysis, letters, editorials, case reports, comments, and expert opinions; (2) survival outcomes or AEs not reported.

Data extraction

Data were collected using a digital spreadsheet. The following information were extracted: title and trial name, first author, publication year, study design, total number of patients enrolled and allocated in each arm, median follow-up time, experimental and control arm, inclusion and exclusion criteria, denosumab administration schedule, primary and secondary endpoints, hazard ratios (HRs) with respective 95% confidence interval (95% CI) for pre-specified outcomes in the overall population and for subgroups of interest, AEs. Specific events concurring to the DFS endpoint were also collected. The following patients' characteristics were extracted: age, menopausal status, tumor size (T), lymph node status (N), pathological stage, histopathological grade, immunohistochemical subtype, hormone receptor and human epidermal growth factor receptor 2 (HER2) status, and previous and concomitant anticancer therapies (endocrine, anti-HER2, or cytotoxic therapy). When multiple reports from the same trial were available, the most recent and complete publication was included. Data not published in the original papers or in further updates were requested to the authors. Three reviewers independently extracted the data (LM, NM, and EDM) and disagreements were resolved through discussion or involving a fourth author (GG).

Endpoints

Survival endpoints were DFS (as reported by trialists), BMFS (time from randomization to first occurrence of bone metastasis or death from any cause), and OS (time from randomization to death from any cause). Fracture incidence and time to first clinical fracture (time from randomization to first vertebral or non-vertebral fracture) were bone-health endpoints, while AEs, SAEs, ONJ, AFF, discontinuations, and hypocalcemia were safety endpoints. Pre-specified subgroup analysis for DFS, BMFS, and OS were performed according to menopausal status (premenopausal *versus* postmenopausal), concomitant therapy (adjuvant or neoadjuvant), hormone receptor and HER2 status (positive *versus* negative), and immunophenotype. For bone-health-related outcomes, a subgroup analysis in relation to menopausal status was performed.

Study quality and risk-of-bias assessment

According to the Cochrane Handbook for Systematic Reviews of Interventions,[21] the risk of bias for eligible RCTs was assessed using the Cochrane Collaboration Risk of Bias Tool (RoB 2.0).[22] The risk for each domain was evaluated: bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result, and overall risk of bias. Studied were graded as low, moderate, or high risk of bias for each domain by three independent reviewers (LM, NM, and EDM). Any disagreement was resolved through consensus or referring to a fourth author (GG). The quality of evidence was evaluated using the grading of recommendations assessment, development and evaluation (GRADE) approach.

Statistical analysis

Natural logarithm for HRs and respective 95% CIs were calculated for time to event outcomes (DFS, BMFS, OS, and time to first clinical fracture) and risk ratios (RRs) for dichotomous outcomes (fracture incidence and safety) in the overall population and according to study-level patients' subgroups. Pooled estimates were calculated using a random-effects model, which was assumed to better represent trials' clinical and methodological differences. For time to event outcomes, the restricted maximum likelihood estimator was used to calculate τ^2 and the Q-profile method for CIs.[23] Cumulative RRs with 95% CIs were calculated according to the Mantel–Haenszel method for dichotomous events. When required, a standard continuity correction of 0.5 was applied. Inconsistency between studies was assessed with Cochran's Q and Higgins I^2 index was used to quantify heterogeneity. Pooled HRs with 95% CIs were calculated for each subgroup and presented with a forest plot. In view of the different DFS definitions between studies, a sensitivity analysis was conducted including only DFS events

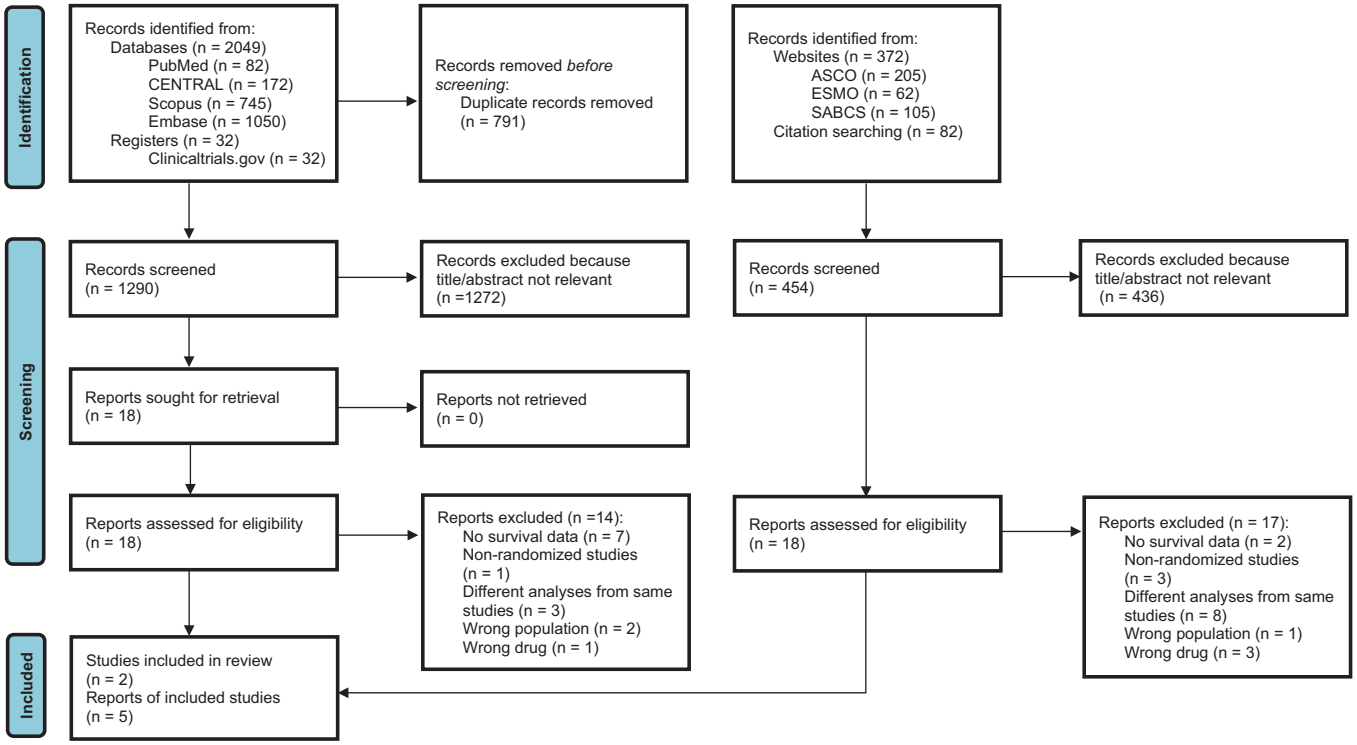


Figure 1. PRISMA flowchart.
ASCO, American Society of Clinical Oncology; CENTRAL, Cochrane Central Register of Controlled Trials; ESMO, European Society for Medical Oncology; n, number; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; SABCS, San Antonio Breast Cancer Symposium.

considered in all trials. Pooled curves for the cumulative incidence of fractures were generated with a random-effects model extracting data at specific time-points from the original papers using a digital software. Statistical analyses were conducted using R version 4.1.3 (package 'meta'). All tests were two-tailed and statistical significance was set at p-value < 0.05.

Results

Study selection

Overall, 2081 records were identified from databases and registers and 454 from websites and reference list of primary studies. After 791 duplicate records were removed, 1744 records were screened with title and abstract. Of these, 1708 were excluded and the 36 remaining reports were selected for full test reviews and assessed for eligibility. Finally, five reports from two RCTs, three for the ABCSG-18 trial,[19,24,25] and two for the D-CARE trial[14,18] fulfilled the inclusion criteria and were considered for the meta-analysis, for a total of 7929 patients. The PRISMA flowchart is shown in Figure 1.

Studies' characteristics, risk-of-bias assessment, and grading

Characteristics of the two eligible RCTs are summarized in Table 1 and patients' characteristics in Table 2.

The ABCSG-18 study was a double-blind, phase III trial, that evaluated adjuvant denosumab in 3420 postmenopausal, hormone receptor positive, BC patients treated with AIs. Patients were randomized to receive subcutaneous denosumab 60 mg every 6 months during ET ($n = 1711$) or matching placebo ($n = 1709$). Patients were randomly allocated at the start or within the first 2 years of adjuvant AI therapy. The median number of denosumab or placebo doses received was 7. Median follow-up was 8 years and median age was 64 years. All patients were hormone receptor positive and most women were node negative ($n = 2436$, 71.2%) and HER2 negative ($n = 3197$,

Table 1. Characteristics of the RCTs included in the meta-analysis.

Study	First author	Phase	Median follow-up	Denosumab treatment	Primary endpoint	Secondary and exploratory endpoints
ABCSG-18	Gnant *et al.*[13]	III	8 years	60 mg every 6 months	Time to first clinical fracture	DFS BMFS OS Percentage change in BMD Vertebral fractures
D-CARE	Coleman *et al.*[18]	III	5.6 years	120 mg every 4 weeks followed by 120 mg every 3 months up to 5 years	BMFS	DFS Distant recurrence-free survival OS Time to first bone metastasis Time to bone metastasis as site of first recurrence Time to first symptomatic bone metastasis Time to first on-study fracture Time to first on-study skeletal-related event

BMFS, bone-metastasis-free survival; DFS, disease-free survival; OS, overall survival; RCTs, randomized controlled trials.

93.8%). A total of 2575 (75.3%) patients received only ET, while 667 (19.5%) received adjuvant chemotherapy and 178 (5.2%) neoadjuvant chemotherapy. Patients receiving adjuvant chemotherapy or adjuvant ET only were included in the adjuvant subgroup. The primary endpoint was the time to first clinical fracture, which was significantly delayed with denosumab addition compared with placebo. DFS, BMFS, OS, and vertebral fractures were secondary endpoints. DFS was defined as time from randomization to first event of local or distant metastasis, contralateral BC, secondary non-breast carcinoma, or death from any cause. Following the protocol amendment that allowed crossover to denosumab after the primary endpoint was met, 252 (14.7%) patients from the original placebo group received open label denosumab.

The D-CARE study was a double-blind, phase III trial, that assessed whether denosumab could increase BMFS in 4509 early BC patients, regardless of immunophenotype, when combined with standard of care systemic and locoregional therapy. Patients were randomly assigned to an intensive dose schedule of denosumab 120 mg subcutaneously every 4 weeks for approximately 6 months followed by denosumab 120 mg every 3 months for a total duration of treatment of 5 years ($n = 2256$) or matching placebo ($n = 2253$). Patients were recruited at the time adjuvant or neoadjuvant systemic therapies were proposed. Median follow-up was 67 months and median age was 50 years. Both pre- ($n = 2360$, 52.3%) and postmenopausal women ($n = 2149$, 47.7%) were included. Most of the patients were hormone receptor positive ($n = 3492$, 77.4%) and HER2 negative ($n = 3602$, 79.9%). A total of 2918 (64.7%) women were hormone receptor positive/HER2 negative, 574 (12.7%) hormone receptor positive/HER2 positive, 331 (7.3%) hormone receptor negative/HER2 positive, and 684 (15.2%) triple negative. Almost all women received chemotherapy ($n = 4321$, 95.8%) and 119 (2.6%) ET only. Overall, 3105 (68.9%) patients received ET, 1898 (42.1%) AIs, 1961 (43.5%) tamoxifen, and 392 (8.7%) ovarian suppression. Patients received standard of care adjuvant or neoadjuvant chemotherapy, adjuvant ET if hormone receptor status was positive and HER2 targeted therapy if HER2 status was positive, or a combination. Primary endpoint was BMFS, with no significant difference between denosumab and placebo arm. DFS, OS, and time to first on-study fracture were secondary endpoints. DFS was defined as time from randomization to first observation of disease recurrence or death from any cause, while new primary non-breast malignancies were not included as DFS events.

Both studies were double-blind, phase III RCTs and the global quality of the studies was high, with an overall low risk of bias (Figure 2 and Supplemental Table S3). According to the GRADE scoring system, the global quality of evidence for DFS, BMFS, and OS is moderate, as

Table 2. Patients' characteristics.

Study	ABCSG-18	D-CARE
Number of patients	3420	4509
Denosumab	1711	2256
Placebo	1709	2253
Median age	64 years (range 38–91)	50 years (range 44–59)
Menopausal status		
Postmenopausal	3420 (100%)	2149 (47.7%)
Premenopausal	0 (0%)	2360 (52.3%)
Lymph nodes		
Lymph node negative	2436 (71.2%)	261 (5.8%)
Lymph node positive	968 (28.3%)	4215 (93.4%)
Unknown	16 (0.5%)	33 (0.8%)
Hormone receptor status		
Hormone receptor positive	3417 (100%)	3492 (77.4%)
Hormone receptor negative	0 (0%)	1015 (22.5%)
Unknown	3 (0%)	1 (0.1%)
HER2 status		
HER2 negative	3197 (93.5%)	3602 (79.9%)
HER2 positive	216 (6.3%)	905 (20%)
Unknown	7 (0.2%)	1 (0.1%)
Molecular subtype		
Hormone receptor positive/HER2 negative	3197 (93.5%)	2918 (64.7%)
Hormone receptor positive/HER2 positive	216 (6.3)	574 (12.7%)
Hormone receptor negative/HER2 negative	0 (0%)	331 (7.3%)
Hormone receptor negative/HER2 positive	0 (0%)	684 (15.2%)
Systemic therapy		
Chemotherapy	845 (24.7%)	4321 (95.8%)
ET only	2575 (75.3%)	119 (2.6%)
Therapy timing		
Adjuvant	3242 (94.8%)	3418 (75.8%)
Neoadjuvant	178 (5.2%)	1091 (24.2%)
ET		
Overall	3420 (100%)	3105 (68.9%)
AIs	3420 (100%)	1898 (42.1%)
Tamoxifen	0 (0%)	1961 (43.5%)
Ovarian suppression	0 (0%)	392 (8.7%)

In the D-CARE, among node-positive patients, 2750 (61%) were N1, 1011 (22.4%) N2, and 454 (10%) N3.
AI, aromatase inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2.

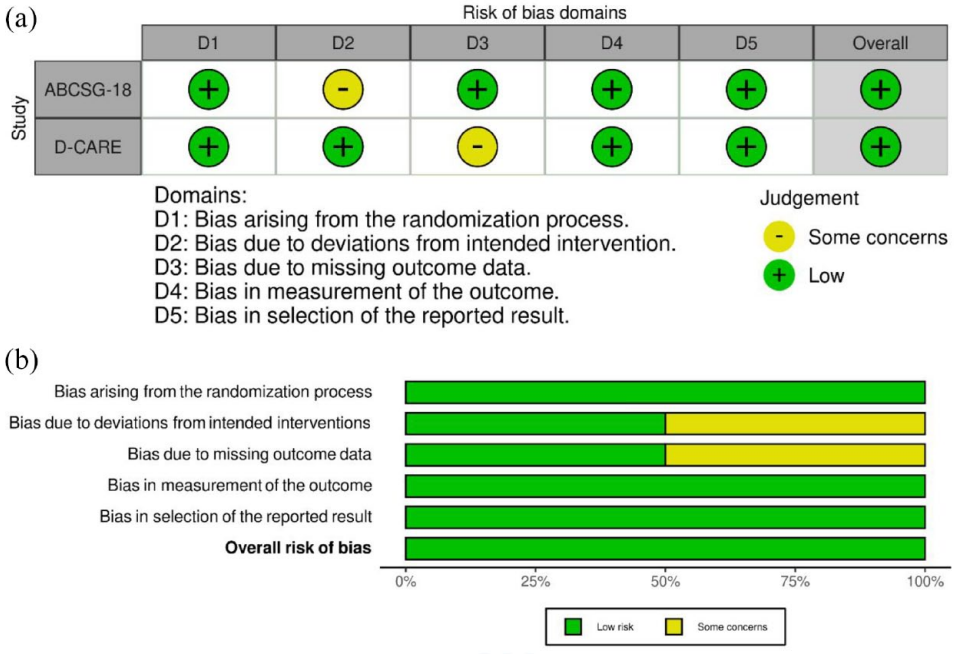


Figure 2. Risk-of-bias assessment for survival outcomes. Traffic lights plot (*a*), bar plot (*b*).

effect of a one level downgrade due to inconsistency. For bone-health outcomes, the quality of evidence is high and no downgrade was applied (Supplemental Table S4).

Survival outcomes

DFS. Overall, denosumab addition to standard of care anticancer treatment showed no DFS difference compared to placebo (HR: 0.932; 95% CI: 0.748–1.162) and heterogeneity among the studies was high ($I^2 = 79\%$, $p = 0.03$) [Figure 3(a)]. No DFS difference was observed between pre- (HR: 0.970; 95% CI: 0.807–1.166) and postmenopausal (HR: 0.958; 95% CI: 0.716–1.284) patients ($p = 0.96$). A significant benefit was observed in DFS in the hormone receptor positive/HER2 negative subtype (HR: 0.883; 95% CI: 0.782–0.996) and in patients receiving adjuvant therapy (HR: 0.877; 95% CI: 0.779–0.988). No difference was seen in other molecular subtypes or according to hormone receptor and HER2 status (Figure 4).

Despite DFS definitions being slightly different, sufficient homogeneity is retained to extract a meaningful estimate, and the sensitivity analysis revealed consistent results (Supplemental Figure S1).

BMFS. BMFS was not improved with denosumab in the overall population (HR: 0.896; 95% CI: 0.751–1.070), with moderate heterogeneity among the trials ($I^2 = 44\%$, $p = 0.18$) [Figure 3(b)]. No BMFS difference was observed between pre- (HR: 0.900; 95% CI: 0.713–1.135) and postmenopausal (HR: 0.913; 95% CI: 0.713–1.169) patients ($p = 0.95$). A statistically significant improvement was observed with denosumab in hormone receptor positive/HER2 negative subtype (HR: 0.832; 95% CI: 0.714–0.970), in all hormone receptor positive patients (HR: 0.850; 95% CI: 0.735–0.983) and in patients receiving adjuvant therapy (HR: 0.843; 95% CI: 0.714–0.994). No difference was observed for other molecular subtypes, in hormone receptor negative patients or according to HER2 status (Figure 5).

OS. Pooled OS analysis in the overall population showed no difference with denosumab addition compared with placebo (HR: 0.917; 95% CI: 0.718–1.171, $p = 0.34$), with high heterogeneity among the studies ($I^2 = 62\%$, $p = 0.10$) [Figure 3(c)]. No difference was observed between pre- (HR: 1.090; 95% CI: 0.815–1.458) and postmenopausal (HR: 0.882; 95% CI: 0.718–1.083) and patients ($p = 0.28$). A relationship of borderline significance was seen in hormone receptor

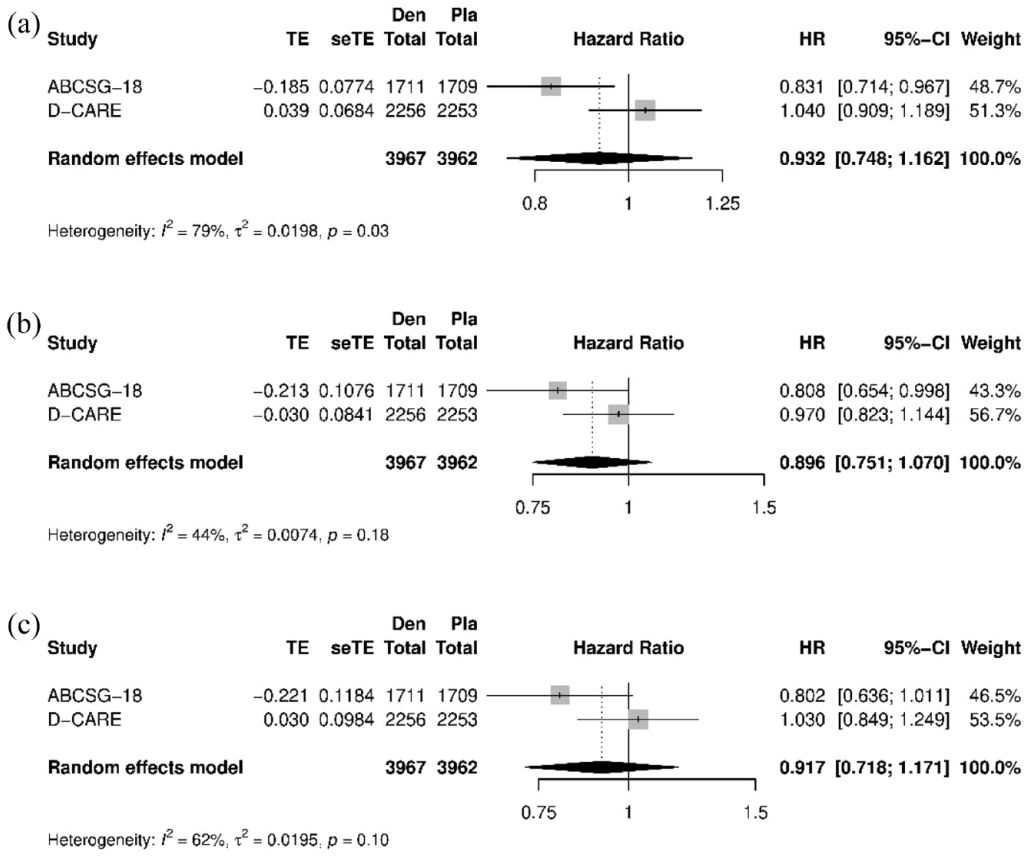


Figure 3. Intention to treat analysis for DFS (a), BMFS (b), and OS (c).
95% CI, 95% confidence interval; BMFS, bone-metastasis-free survival; Den, denosumab; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; Pla, placebo; seTE, treatment effect standard error; TE, treatment effect.

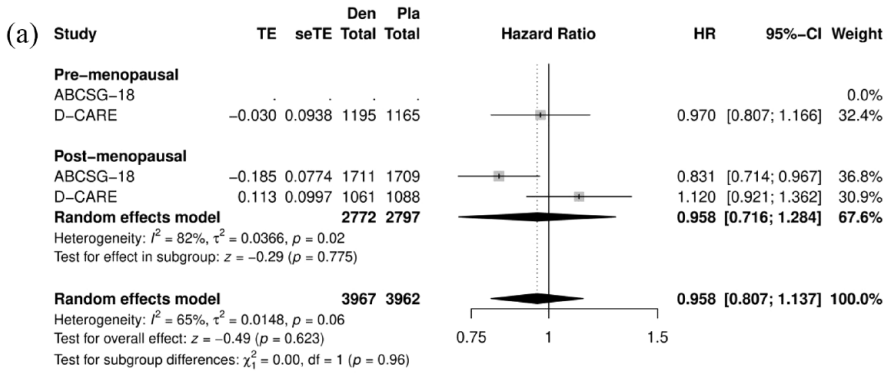
positive/HER2 negative subtype (HR: 0.839; 95% CI: 0.699–1.007). No significant difference was seen in other subgroups (Figure 6).

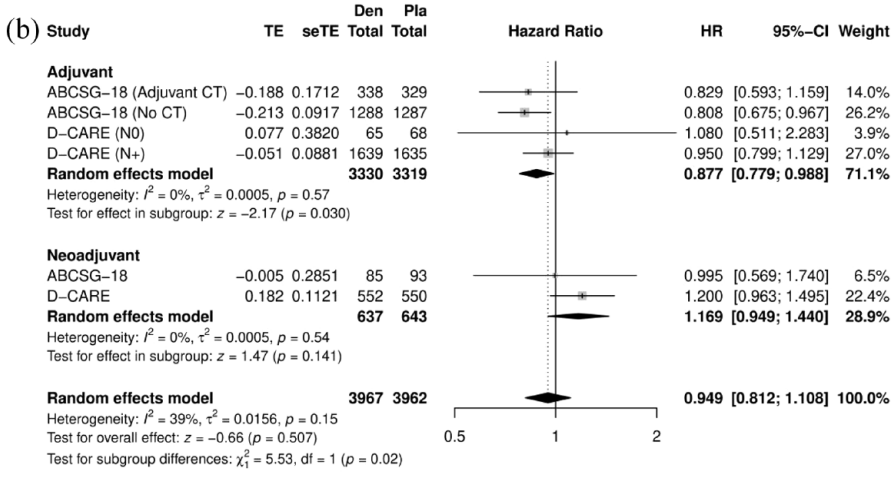
Bone-health outcomes

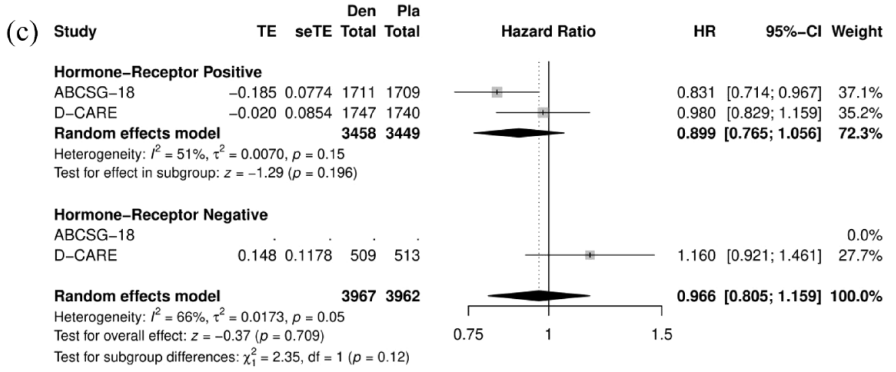
Denosumab addition to standard of care anticancer therapy significantly reduced fracture incidence in the overall population (RR: 0.787; 95% CI: 0.696–0.890) and in pre- (RR: 0.771; 95% CI: 0.589–1.009) and postmenopausal patients (RR: 0.794; 95% CI: 0.692–0.912) (Figure 7). Denosumab treatment also delayed the time to first fracture (HR: 0.760; 95% CI: 0.666–0.869), with a consistent treatment effect among pre- (HR: 0.740; 95% CI: 0.557–0.984, $p < 0.01$) and postmenopausal patients (HR: 0.764; 95% CI: 0.657–0.887) [Figure 8 (a) and (b)]. At 72 months, cumulative incidence of fractures was 14.2% for denosumab and 10.7% for placebo, with a 3.5% absolute difference [Figure 8(c)].

Safety outcomes

Overall, denosumab was generally well tolerated and no difference was observed between denosumab and placebo arms in terms of all AEs (RR: 1.003; 95% CI: 0.995–1.012) and SAEs (RR: 1.016; 95% CI: 0.951–1.086) (Supplemental Figure S2A and B). No ONJ cases occurred in the ABCSG-18 trial with the 60-mg every 6-month schedule, while 122 (5.4%) and 4 (0.2%) cases occurred, respectively, in denosumab and placebo arms in the D-CARE trial (RR: 30.187; 95% CI: 11.170–81.581). Only 1 (<0.1%) and 9 (0.4%) cases of AFF were recorded, respectively, in the ABCSG-18 (RR: 2.967; 95% CI: 0.121–72.772) and in the D-CARE study (RR: 18.805; 95% CI: 1.095–322.897), all in the denosumab arm (cumulative RR: 8.326; 95% CI: 0.994–69.743). Given the different denosumab dosing schedule in the two trials, it should be noted that denosumab was significantly associated with a higher incidence of AFF events only in the


(a)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
Pre−menopausal
ABCSG−18 . . . . 0.0%
D−CARE −0.030 0.0938 1195 1165 0.970 [0.807; 1.166] 32.4%
Post−menopausal
ABCSG−18 −0.185 0.0774 1711 1709 0.831 [0.714; 0.967] 36.8%
D−CARE 0.113 0.0997 1061 1088 1.120 [0.921; 1.362] 30.9%
Random effects model 2772 2797 0.958 [0.716; 1.284] 67.6%
Heterogeneity: I^2 = 82%, τ^2 = 0.0366, p = 0.02
Test for effect in subgroup: z = −0.29 (p = 0.775)
Random effects model 3967 3962 0.958 [0.807; 1.137] 100.0%
Heterogeneity: I^2 = 65%, τ^2 = 0.0148, p = 0.06
Test for overall effect: z = −0.49 (p = 0.623)
Test for subgroup differences: χ^2_1 = 0.00, df = 1 (p = 0.96)
0.75
1
1.5


(b)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
Adjuvant
ABCSG−18 (Adjuvant CT) −0.188 0.1712 338 329 0.829 [0.593; 1.159] 14.0%
ABCSG−18 (No CT) −0.213 0.0917 1288 1287 0.808 [0.675; 0.967] 26.2%
D−CARE (N0) 0.077 0.3820 65 68 1.080 [0.511; 2.283] 3.9%
D−CARE (N+) −0.051 0.0881 1639 1635 0.950 [0.799; 1.129] 27.0%
Random effects model 3330 3319 0.877 [0.779; 0.988] 71.1%
Heterogeneity: I^2 = 0%, τ^2 = 0.0005, p = 0.57
Test for effect in subgroup: z = −2.17 (p = 0.030)
Neoadjuvant
ABCSG−18 −0.005 0.2851 85 93 0.995 [0.569; 1.740] 6.5%
D−CARE 0.182 0.1121 552 550 1.200 [0.963; 1.495] 22.4%
Random effects model 637 643 1.169 [0.949; 1.440] 28.9%
Heterogeneity: I^2 = 0%, τ^2 = 0.0005, p = 0.54
Test for effect in subgroup: z = 1.47 (p = 0.141)
Random effects model 3967 3962 0.949 [0.812; 1.108] 100.0%
Heterogeneity: I^2 = 39%, τ^2 = 0.0156, p = 0.15
Test for overall effect: z = −0.66 (p = 0.507)
Test for subgroup differences: χ^2_1 = 5.53, df = 1 (p = 0.02)
0.5
1
2


(c)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
Hormone−Receptor Positive
ABCSG−18 −0.185 0.0774 1711 1709 0.831 [0.714; 0.967] 37.1%
D−CARE −0.020 0.0854 1747 1740 0.980 [0.829; 1.159] 35.2%
Random effects model 3458 3449 0.899 [0.765; 1.056] 72.3%
Heterogeneity: I^2 = 51%, τ^2 = 0.0070, p = 0.15
Test for effect in subgroup: z = −1.29 (p = 0.196)
Hormone−Receptor Negative
ABCSG−18 . . . . 0.0%
D−CARE 0.148 0.1178 509 513 1.160 [0.921; 1.461] 27.7%
Random effects model 3967 3962 0.966 [0.805; 1.159] 100.0%
Heterogeneity: I^2 = 66%, τ^2 = 0.0173, p = 0.05
Test for overall effect: z = −0.37 (p = 0.709)
Test for subgroup differences: χ^2_1 = 2.35, df = 1 (p = 0.12)
0.75
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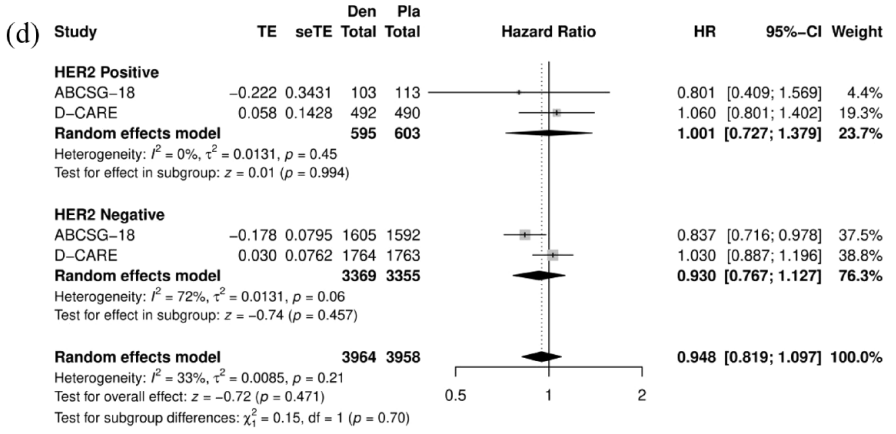
1.5


(d)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
HER2 Positive
ABCSG−18 −0.222 0.3431 103 113 0.801 [0.409; 1.569] 4.4%
D−CARE 0.058 0.1428 492 490 1.060 [0.801; 1.402] 19.3%
Random effects model 595 603 1.001 [0.727; 1.379] 23.7%
Heterogeneity: I^2 = 0%, τ^2 = 0.0131, p = 0.45
Test for effect in subgroup: z = 0.01 (p = 0.994)
HER2 Negative
ABCSG−18 −0.178 0.0795 1605 1592 0.837 [0.716; 0.978] 37.5%
D−CARE 0.030 0.0762 1764 1763 1.030 [0.887; 1.196] 38.8%
Random effects model 3369 3355 0.930 [0.767; 1.127] 76.3%
Heterogeneity: I^2 = 72%, τ^2 = 0.0131, p = 0.06
Test for effect in subgroup: z = −0.74 (p = 0.457)
Random effects model 3964 3958 0.948 [0.819; 1.097] 100.0%
Heterogeneity: I^2 = 33%, τ^2 = 0.0085, p = 0.21
Test for overall effect: z = −0.72 (p = 0.471)
Test for subgroup differences: χ^2_1 = 0.15, df = 1 (p = 0.70)
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2

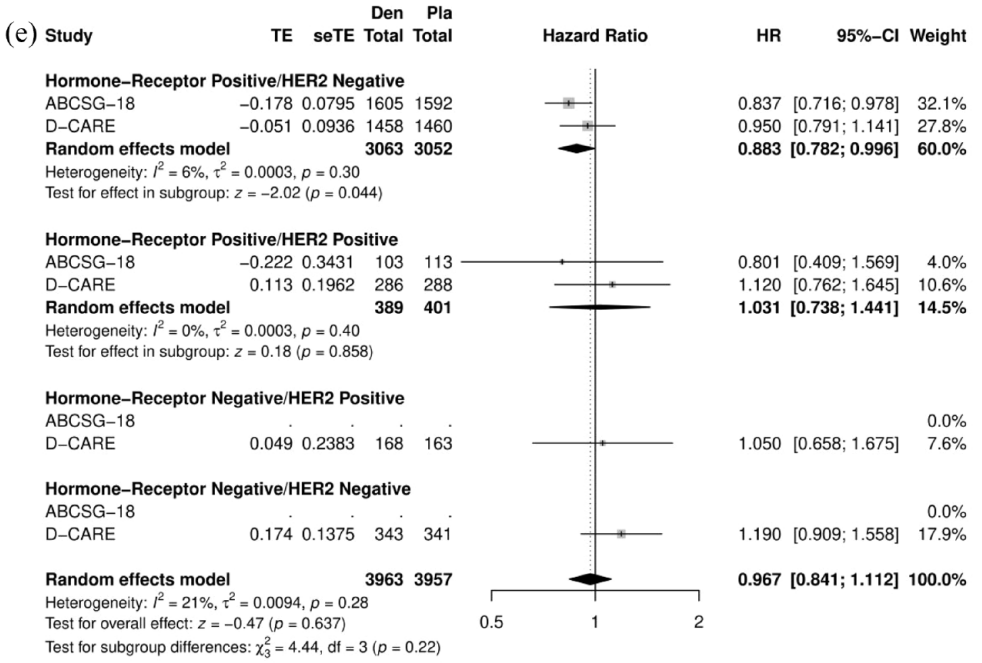


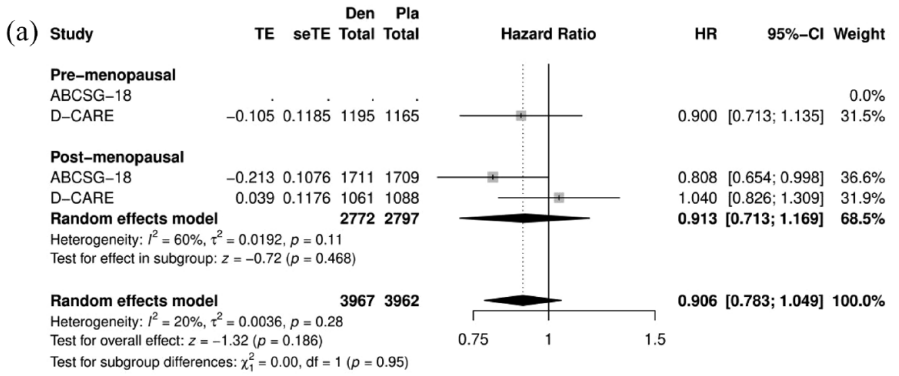
Figure 4. Subgroup analysis for DFS: menopausal status (a), concomitant therapy (b), hormone receptor status (c), HER2 status (d), molecular subtype (e).
95% CI, 95% confidence interval; CT, chemotherapy; Den, denosumab; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; N, lymph nodes; Pla, placebo; seTE, treatment effect standard error; TE, treatment effect.

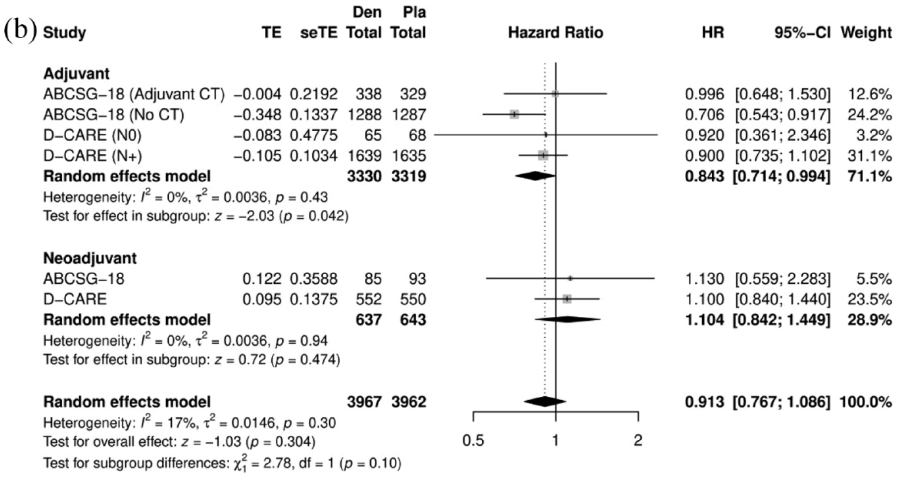
D-CARE trial (Supplemental Figure S2C and D). Only 1 case of hypocalcemia (<0.1%) was reported in the ABCSG-18 trial, compared to 226 in D-CARE trial, respectively, 146 (6.5%) and 80 (3.6%) in the denosumab and placebo arm. Pooled RR was 1.812 (95% CI: 1.390–2.363) but only the intensive schedule reached statistical significance (RR: 1.806; 95% CI: 1.384–2.357) (Supplemental Figure S2E). The ABCSG-18 schedule was generally well tolerated, with 65 (3.8%) discontinuation in the denosumab arm compared to 80 (4.7%) in the placebo arm, with a RR of 0.803 (95% CI: 0.583–1.107). The RR for discontinuation in the D-CARE trial was 1.325 (95% CI: 0.951–1.847) and pooled RR was 1.030 (95% CI: 0.631–1.682) (Supplemental Figure S2F).

Discussion

This meta-analysis tried to resolve the controversy of denosumab survival benefit in early BC patients treated with curative intent. Denosumab addition to standard (neo)adjuvant therapy did not result in a DFS, BMFS, and OS advantage in the overall population. Subgroup analyses suggest an advantage in DFS and BMFS in hormone receptor positive/HER2 negative BC patients and a BMFS improvement in all hormone receptor positive patients regardless of HER2 status. No DFS, BMFS, and OS benefit was instead observed in triple negative and HER2 positive BCs.

These results are consistent with the assumption that denosumab, as a bone-targeted agent, could have a primary impact on bone recurrence. The exact mechanism of action by which denosumab exerts antitumor effects still needs to be fully elucidated. Nevertheless, several hypotheses have been put forward. In BC, the host tissue chemokine milieu has been proposed to explain why some tumors preferentially metastasize to certain organs.[26] The cytokine RANKL, a critical osteoclastic differentiation factor highly expressed in the bone marrow microenvironment, has been shown to trigger the migration of RANK-expressing human epithelial cancer cells, including BC cells.[27] On the other hand, circulating tumor cells, attracted to the bone surface, are capable of colonizing so-called premetastatic niches, where they remain dormant even for long periods.[28] For reasons not well elucidated, these BC stem cells may begin to proliferate and


(a)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
Pre−menopausal
ABCSG−18 . . . . 0.0%
D−CARE −0.105 0.1185 1195 1165 0.900 [0.713; 1.135] 31.5%
Post−menopausal
ABCSG−18 −0.213 0.1076 1711 1709 0.808 [0.654; 0.998] 36.6%
D−CARE 0.039 0.1176 1061 1088 1.040 [0.826; 1.309] 31.9%
Random effects model 2772 2797 0.913 [0.713; 1.169] 68.5%
Heterogeneity: I^2 = 60%, τ^2 = 0.0192, p = 0.11
Test for effect in subgroup: z = −0.72 (p = 0.468)
Random effects model 3967 3962 0.906 [0.783; 1.049] 100.0%
Heterogeneity: I^2 = 20%, τ^2 = 0.0036, p = 0.28
Test for overall effect: z = −1.32 (p = 0.186)
Test for subgroup differences: χ^2_1 = 0.00, df = 1 (p = 0.95)
0.75
1
1.5


(b)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
Adjuvant
ABCSG−18 (Adjuvant CT) −0.004 0.2192 338 329 0.996 [0.648; 1.530] 12.6%
ABCSG−18 (No CT) −0.348 0.1337 1288 1287 0.706 [0.543; 0.917] 24.2%
D−CARE (N0) −0.083 0.4775 65 68 0.920 [0.361; 2.346] 3.2%
D−CARE (N+) −0.105 0.1034 1639 1635 0.900 [0.735; 1.102] 31.1%
Random effects model 3330 3319 0.843 [0.714; 0.994] 71.1%
Heterogeneity: I^2 = 0%, τ^2 = 0.0036, p = 0.43
Test for effect in subgroup: z = −2.03 (p = 0.042)
Neoadjuvant
ABCSG−18 0.122 0.3588 85 93 1.130 [0.559; 2.283] 5.5%
D−CARE 0.095 0.1375 552 550 1.100 [0.840; 1.440] 23.5%
Random effects model 637 643 1.104 [0.842; 1.449] 28.9%
Heterogeneity: I^2 = 0%, τ^2 = 0.0036, p = 0.94
Test for effect in subgroup: z = 0.72 (p = 0.474)
Random effects model 3967 3962 0.913 [0.767; 1.086] 100.0%
Heterogeneity: I^2 = 17%, τ^2 = 0.0146, p = 0.30
Test for overall effect: z = −1.03 (p = 0.304)
Test for subgroup differences: χ^2_1 = 2.78, df = 1 (p = 0.10)
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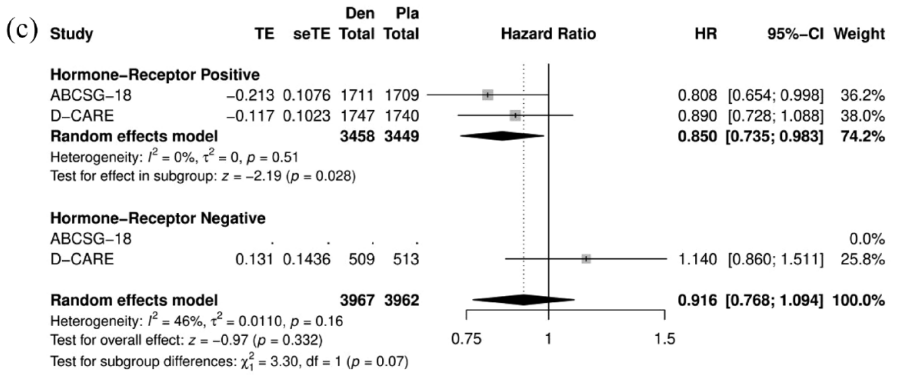
(c)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
Hormone−Receptor Positive
ABCSG−18 −0.213 0.1076 1711 1709 0.808 [0.654; 0.998] 36.2%
D−CARE −0.117 0.1023 1747 1740 0.890 [0.728; 1.088] 38.0%
Random effects model 3458 3449 0.850 [0.735; 0.983] 74.2%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.51
Test for effect in subgroup: z = −2.19 (p = 0.028)
Hormone−Receptor Negative
ABCSG−18 . . . . 0.0%
D−CARE 0.131 0.1436 509 513 1.140 [0.860; 1.511] 25.8%
Random effects model 3967 3962 0.916 [0.768; 1.094] 100.0%
Heterogeneity: I^2 = 46%, τ^2 = 0.0110, p = 0.16
Test for overall effect: z = −0.97 (p = 0.332)
Test for subgroup differences: χ^2_1 = 3.30, df = 1 (p = 0.07)
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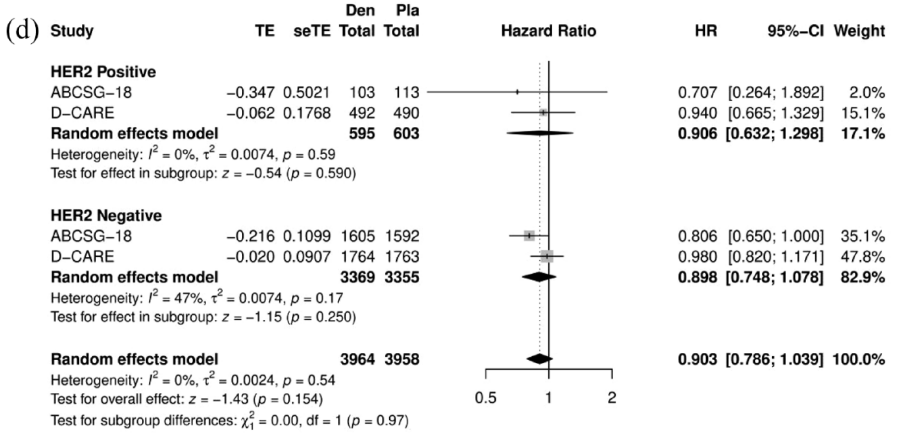
(d)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
HER2 Positive
ABCSG−18 −0.347 0.5021 103 113 0.707 [0.264; 1.892] 2.0%
D−CARE −0.062 0.1768 492 490 0.940 [0.665; 1.329] 15.1%
Random effects model 595 603 0.906 [0.632; 1.298] 17.1%
Heterogeneity: I^2 = 0%, τ^2 = 0.0074, p = 0.59
Test for effect in subgroup: z = −0.54 (p = 0.590)
HER2 Negative
ABCSG−18 −0.216 0.1099 1605 1592 0.806 [0.650; 1.000] 35.1%
D−CARE −0.020 0.0907 1764 1763 0.980 [0.820; 1.171] 47.8%
Random effects model 3369 3355 0.898 [0.748; 1.078] 82.9%
Heterogeneity: I^2 = 47%, τ^2 = 0.0074, p = 0.17
Test for effect in subgroup: z = −1.15 (p = 0.250)
Random effects model 3964 3958 0.903 [0.786; 1.039] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0.0024, p = 0.54
Test for overall effect: z = −1.43 (p = 0.154)
Test for subgroup differences: χ^2_1 = 0.00, df = 1 (p = 0.97)
0.5
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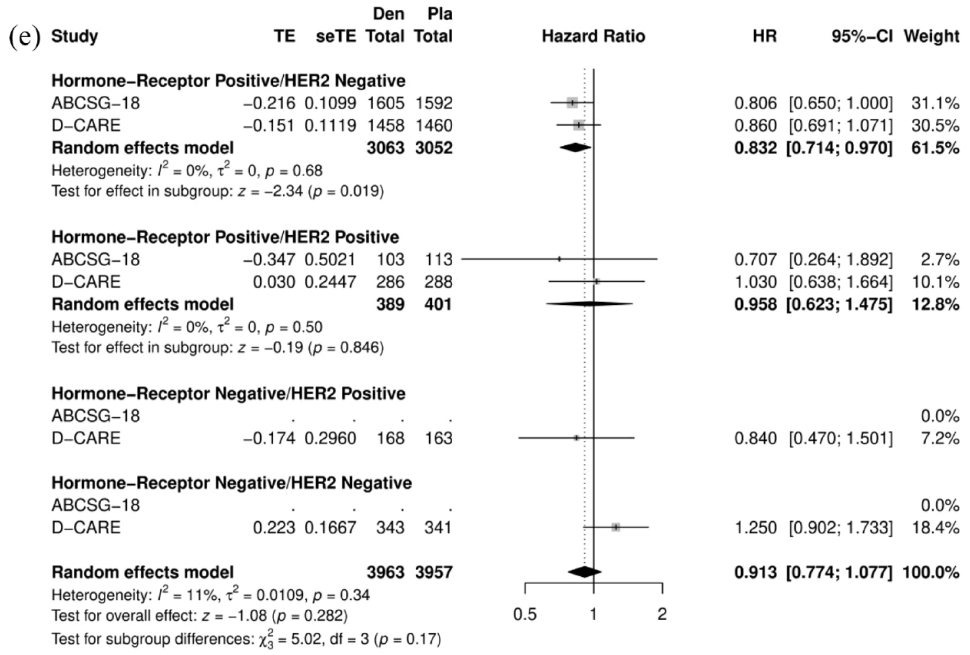
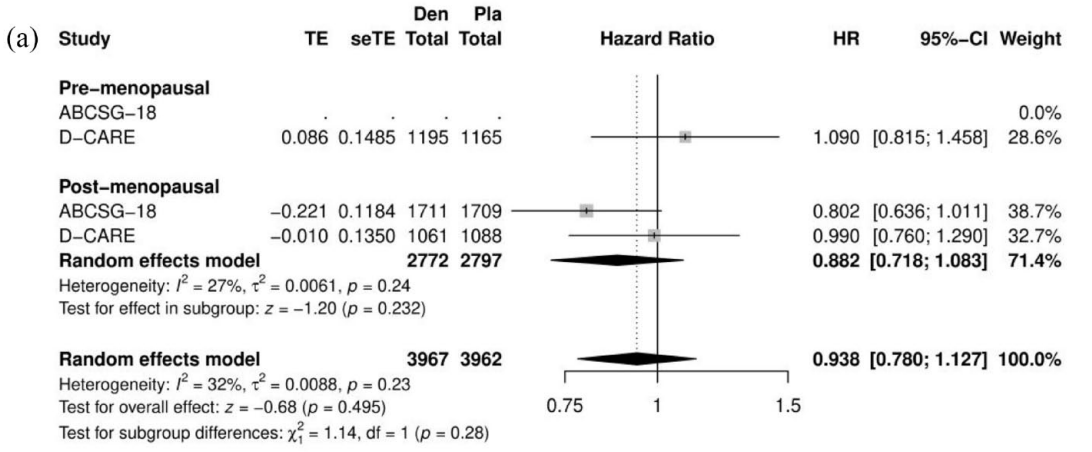


Figure 5. Subgroup analysis for BMFS: menopausal status (a), concomitant therapy (b), hormone receptor status (c), HER2 status (d), molecular subtype (e).
95% CI, 95% confidence interval; BMFS, bone-metastasis-free survival; CT, chemotherapy; Den, denosumab; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; N, lymph nodes; Pla, placebo; seTE, treatment effect standard error; TE, treatment effect.

establish macro-metastases in bone or other sites.[29] Increased bone turnover due to estrogen-reducing therapies releases growth factors that may both promote the development of premetastatic niches and the attachment of disseminated cancer cells and contribute to the reactivation of dormant cells.[30] Preclinical models have shown that, in addition to preventing bone resorption, RANKL inhibition can exert a direct, osteoclast-independent antitumor effect and an indirect, osteoclast-dependent, and immune-related antitumor effect.[31–33] In preclinical models, RANKL inhibition is capable of both blocking the direct effect of RANKL on tumor cells expressing RANK, including BC cells, and reducing regulatory T lymphocytes, enhancing antitumor immune responses. However, strong clinical evidence is lacking. More importantly, preclinical and clinical data showed that RANKL inhibition breaks the vicious cycle of cytokine release between osteoblasts, osteoclasts, and tumor cells, in which bone turnover and tumor cell proliferation mutually enhance each other. Thus, denosumab alters the bone microenvironment and makes it less attractive to cancer cells and, consequently, may prevent and reduce bone metastasis.[31,34]

In this regard, bone recurrences are known to occur more frequently in hormone receptor positive/HER2 negative patients, either as exclusive disease or in combination with other distant metastases, while less than 10% of triple-negative and HER2 positive patients develop bone metastases without other distant sites.[35] Based on this consideration, the results of the meta-analysis help resolve the discrepancy of the survival outcomes from denosumab addition in the two RCTs. The ABCSG-18 trial exclusively enrolled hormone receptor positive patients treated with AIs, with only 7% HER2 positive disease, while in the D-CARE trial only 65% were hormone receptor positive/HER2 negative and about 57% of hormone receptor positive patients were treated with tamoxifen – a selective estrogen receptor modulator – which has bone-protective effects.[13,18,36] The D-CARE study enrolled patients with higher risk of recurrence than ABCSG-18 trial, but not bone recurrence specifically. In addition, in the ABCSG-18 study, the DFS difference between the denosumab and placebo arms appeared to be driven by new primary non-breast tumors and histologically unproven distant metastases[19]; consistent with the bone recurrence hypothesis, BMFS was significantly improved with denosumab compared with


(a)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
Pre−menopausal
ABCSG−18 . . . . 0.0%
D−CARE 0.086 0.1485 1195 1165 1.090 [0.815; 1.458] 28.6%
Post−menopausal
ABCSG−18 −0.221 0.1184 1711 1709 0.802 [0.636; 1.011] 38.7%
D−CARE −0.010 0.1350 1061 1088 0.990 [0.760; 1.290] 32.7%
Random effects model 2772 2797 0.882 [0.718; 1.083] 71.4%
Heterogeneity: I^2 = 27%, τ^2 = 0.0061, p = 0.24
Test for effect in subgroup: z = −1.20 (p = 0.232)
Random effects model 3967 3962 0.938 [0.780; 1.127] 100.0%
Heterogeneity: I^2 = 32%, τ^2 = 0.0088, p = 0.23
Test for overall effect: z = −0.68 (p = 0.495)
Test for subgroup differences: χ^2_1 = 1.14, df = 1 (p = 0.28)
0.75
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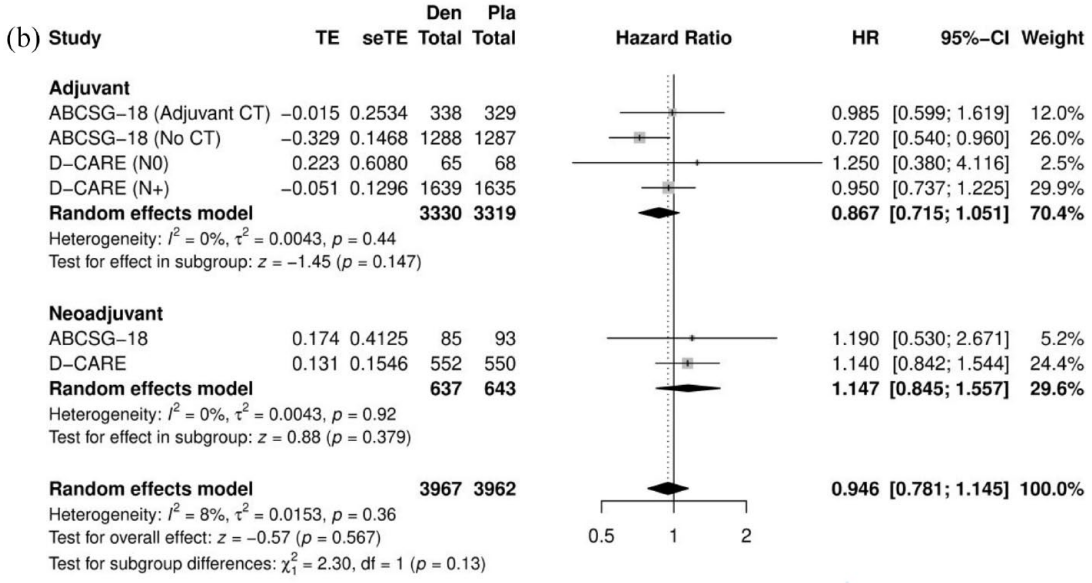
(b)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
Adjuvant
ABCSG−18 (Adjuvant CT) −0.015 0.2534 338 329 0.985 [0.599; 1.619] 12.0%
ABCSG−18 (No CT) −0.329 0.1468 1288 1287 0.720 [0.540; 0.960] 26.0%
D−CARE (N0) 0.223 0.6080 65 68 1.250 [0.380; 4.116] 2.5%
D−CARE (N+) −0.051 0.1296 1639 1635 0.950 [0.737; 1.225] 29.9%
Random effects model 3330 3319 0.867 [0.715; 1.051] 70.4%
Heterogeneity: I^2 = 0%, τ^2 = 0.0043, p = 0.44
Test for effect in subgroup: z = −1.45 (p = 0.147)
Neoadjuvant
ABCSG−18 0.174 0.4125 85 93 1.190 [0.530; 2.671] 5.2%
D−CARE 0.131 0.1546 552 550 1.140 [0.842; 1.544] 24.4%
Random effects model 637 643 1.147 [0.845; 1.557] 29.6%
Heterogeneity: I^2 = 0%, τ^2 = 0.0043, p = 0.92
Test for effect in subgroup: z = 0.88 (p = 0.379)
Random effects model 3967 3962 0.946 [0.781; 1.145] 100.0%
Heterogeneity: I^2 = 8%, τ^2 = 0.0153, p = 0.36
Test for overall effect: z = −0.57 (p = 0.567)
Test for subgroup differences: χ^2_1 = 2.30, df = 1 (p = 0.13)
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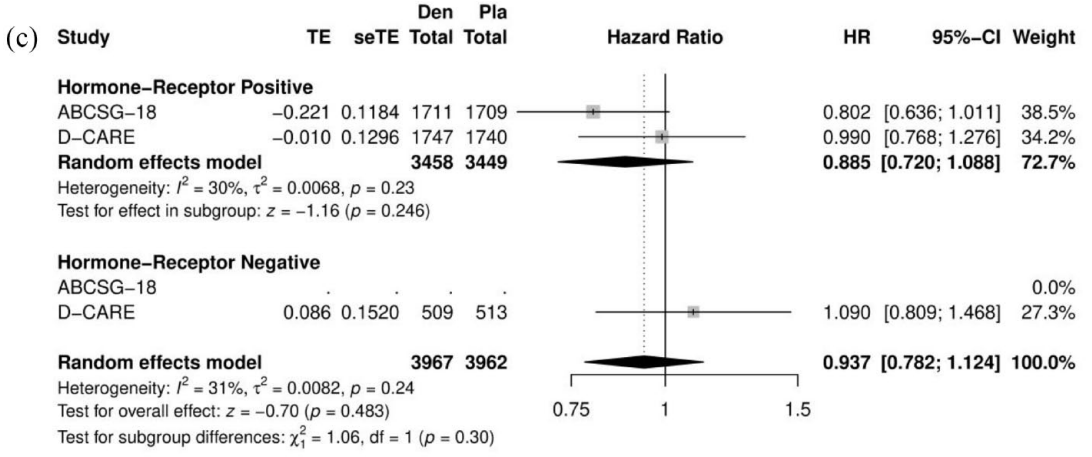
(c)
Study TE seTE Den Total Pla Total Hazard Ratio HR 95%−CI Weight
Hormone−Receptor Positive
ABCSG−18 −0.221 0.1184 1711 1709 0.802 [0.636; 1.011] 38.5%
D−CARE −0.010 0.1296 1747 1740 0.990 [0.768; 1.276] 34.2%
Random effects model 3458 3449 0.885 [0.720; 1.088] 72.7%
Heterogeneity: I^2 = 30%, τ^2 = 0.0068, p = 0.23
Test for effect in subgroup: z = −1.16 (p = 0.246)
Hormone−Receptor Negative
ABCSG−18 . . . . 0.0%
D−CARE 0.086 0.1520 509 513 1.090 [0.809; 1.468] 27.3%
Random effects model 3967 3962 0.937 [0.782; 1.124] 100.0%
Heterogeneity: I^2 = 31%, τ^2 = 0.0082, p = 0.24
Test for overall effect: z = −0.70 (p = 0.483)
Test for subgroup differences: χ^2_1 = 1.06, df = 1 (p = 0.30)
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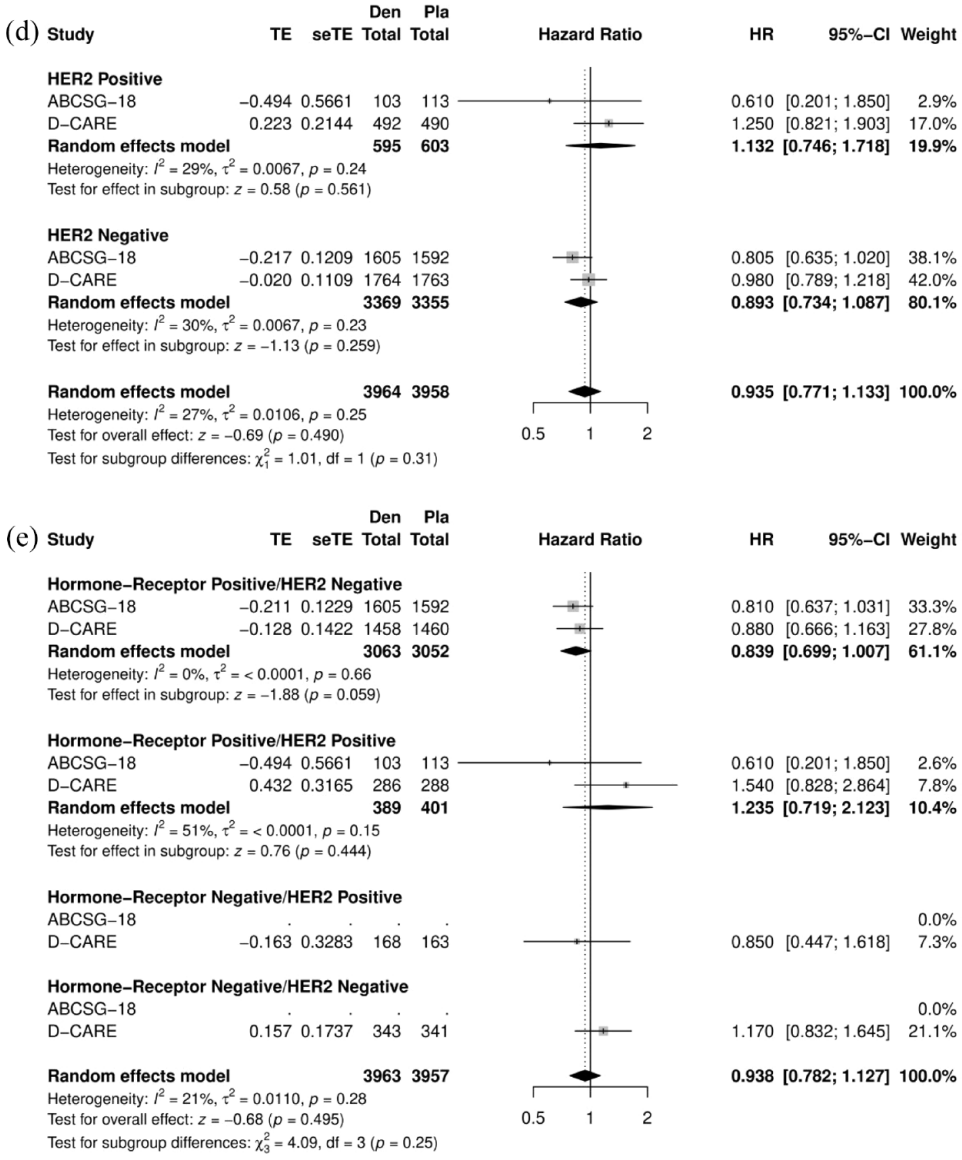

Figure 6. Subgroup analysis for OS: menopausal status (a), concomitant therapy (b), hormone receptor status (c), HER2 status (d), molecular subtype (e).
95% CI, 95% confidence interval; CT, chemotherapy; Den, denosumab; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; N, lymph nodes; OS, overall survival; Pla, placebo; seTE, treatment effect standard error; TE, treatment effect.

placebo.[24] In the D-CARE trial, denosumab addition reduced the incidence of bone metastasis as the first site of recurrence, but the effect on the BMFS endpoint may have been diluted by the fact that 40% of the events were non-cancer or not BC-related deaths, masking the clinical impact of such a bone-directed agent.[18,37] Thus, differences in patient characteristics, endocrine therapies and survival event composition may explain the apparent inconsistency in the benefit of adding denosumab to standard therapy in early-stage BC.

When considering menopausal status subgroups, a non-significant trend toward survival improvement was observed for DFS and BMFS with similar estimates in both pre- and postmenopausal subgroups. This highlights that a potential role for denosumab benefit regardless of menopausal status cannot be excluded. It should be noted that, as mentioned above, while all patients in the ABCSG-18 trial were postmenopausal and treated with AIs, in the D-CARE study 47.7% of patients were postmenopausal and not all received

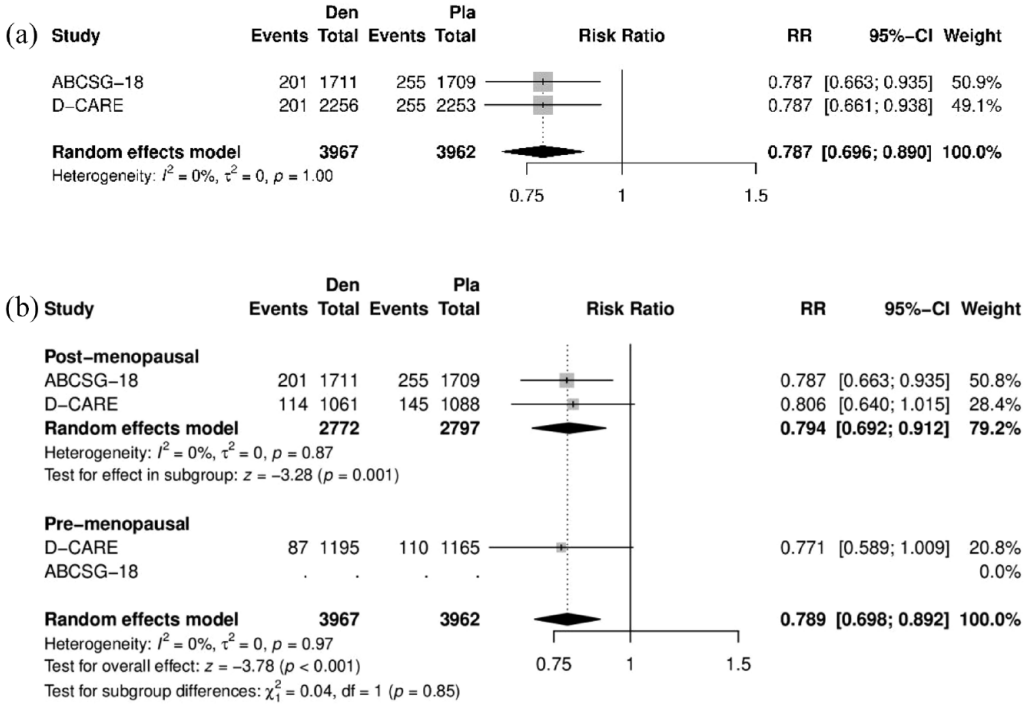

Figure 7. Fracture incidence in the overall population (a) and according to menopausal status (b).
95% CI, 95% confidence interval; Den, denosumab; Pla, placebo; RR, risk ratio.

AIs, whereas 52.3% were premenopausal and only 12% receiving ovarian suppression. Since AIs and ovarian suppression induce high bone turnover while tamoxifen has bone-protective effects in postmenopausal patients,[36] the inhibition of bone turnover and tumor cell attachment by denosumab might be greater when administered in combination with therapies that cause rapid bone loss. Therefore, statistical significance, at least in the postmenopausal subgroup, may not have been met since a proportion of these patients was receiving bone-protective ET.

As expected, in the present meta-analysis, we observed a 21% relative reduction in fracture risk, with a 3.5% absolute difference in the fracture incidence at 6 years, and 26% relative prolongation of time to first fracture for patients receiving denosumab compared with placebo. These results strengthen the already strong evidence supporting the role of denosumab as a highly effective antiresorptive agent. Interestingly, in the ABCSG-18 study, the first HR reported for time to first clinical fracture was 0.50 (95% CI: 0.39–0.65, $p < 0.0001$), while it was 0.76 (95% CI: 0.63–0.92) at the median follow-up of 8 years. Given that at the time of the study design the recommended duration of ET was increasing beyond 5 years and the median number of doses of denosumab was seven in both standard and experimental treatment arms, this could suggest that the fracture risk reduction from denosumab is maintained after discontinuation, albeit with a smaller effect size.

In terms of toxicity, no increase was noted for AEs and SAEs in patients receiving denosumab. A significant numerical increase in ONJ and AFF was shown only for the intensive denosumab schedule used in the D-CARE trial, while denosumab 60 mg twice a year was not different from placebo in terms of relative differences. This may be concerning in view of the curative treatment setting, and therefore the intensive denosumab schedule has no role in the management of early BC.

Beside denosumab, bisphosphonates are also adopted in patients with hormone receptor positive early BC to preserve bone health. Two meta-analyses of randomized trials compared the efficacy and safety of denosumab *versus* bisphosphonates in patients with osteoporosis or low BMD, showing that denosumab was more effective than bisphosphonates in improving BMD with similar safety profiles.[38,39] However,

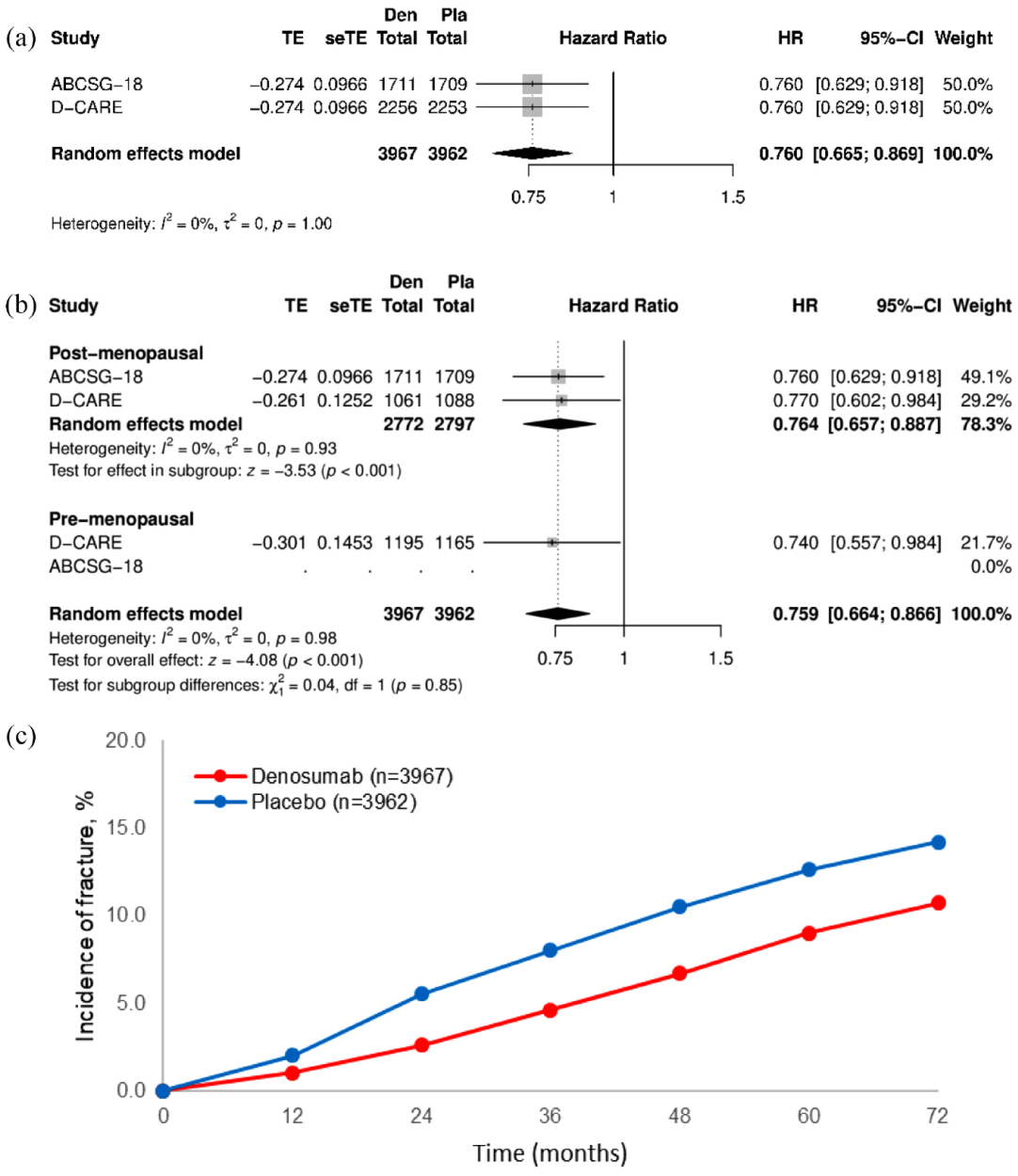

Figure 8. Time to first fracture in the overall population (a) and according to menopausal status (b). 95% CI, 95% confidence interval; Den, denosumab; HR, hazard ratio; *n*, total number of patients; Pla, placebo.

real-world studies report low adherence and poor persistence with bisphosphonates among postmenopausal women with osteoporosis, with less than 80% remaining on the prescribed treatment at 1 year, increasing their fracture risk.[40,41] In addition to osteoprotective effects, in the adjuvant setting bisphosphonates have been shown to have an impact on disease outcome, albeit with inconsistent results among trials. The EBCTCG meta-analysis suggested a benefit of adjuvant bisphosphonates on distant recurrences, particularly on bone metastases, and BC mortality.[9] However, the benefit in bone recurrence and BC mortality was limited only to postmenopausal women, whether natural or artificial and, based on the results, international guidelines recommend adjuvant bisphosphonate therapy for postmenopausal (natural or induced) patients receiving adjuvant ET.[3] The benefit of bisphosphonates therapy varies according to the underlying risk of recurrence and the OS improvement is modest. Although the type of ET in pre- and postmenopausal patients is

not reported, the meta-analysis also included patients with drug-induced menopause in the postmenopausal subgroup. Again, this suggests that denosumab may be more able to reduce and prevent bone metastasis in the presence of high bone turnover, where RANKL is upregulated as with estrogen-reducing therapies such as AIs and/or ovarian suppression.[42] Regarding subgroups by molecular subtype, in the hormone receptor positive population the EBCTCG meta-analysis reports a 15% reduction in the risk of bone recurrence (RR: 0.85; 95% CI: 0.70–1.04), similar to the 15% increase in the probability of BMFS observed in our meta-analysis. Although the EBCTCG meta-analysis adopted recurrence endpoints and not survival outcomes, making direct comparisons potentially misleading, this confirms the impact of bone-targeted agents in the BC molecular subtype with the highest risk of bone recurrence compared with HER2-positive and triple-negative tumors.

Like denosumab, zoledronic acid has also been shown to counteract cancer treatment-induced bone loss and to improve BMD during adjuvant ET,[43] although not all studies demonstrated a decreased incidence of fractures.[8,44,45] In terms of survival, two randomized studies found that adding zoledronic acid to tamoxifen or AI and ovarian suppression improved DFS in comparison to placebo,[8,45] while a meta-analysis suggested a potential DFS benefit only in the postmenopausal subgroup.[46] Following inconsistent findings from individual studies, two meta-analyses of randomized trials failed to support the impact of zoledronic acid in DFS, and no advantage was found in any subgroup analysis. Overall, the rate of ONF is reported to be around 0.5–1%.[6,47]

To the best of our knowledge, at the time of writing this manuscript, this is the first published meta-analysis on the survival impact of denosumab in early BC. Our results are in keeping with the published data of denosumab 60 mg every 6 months increasing DFS and BMFS in the hormone receptor positive/HER2 negative BC population as compared with placebo, without additional toxicity.

Although preclinical studies emphasize an immune-mediated antitumor effect of RANKL inhibition, evidence from randomized trials and our meta-analysis confirms the possible benefit of denosumab especially in preventing and reducing bone disease recurrence. In this regard, to further investigate the immune modulating role of denosumab, a randomized phase II trial, PERIDENO (NCT03532087), is evaluating the effect of denosumab on intratumoral and circulating immune cells in HER2 negative postmenopausal patients undergoing surgery and adjuvant chemotherapy. In addition, trial results are expected to expand current evidence in both reduction of disease recurrence and BC prevention. The randomized phase III ENDEAVOR trial (NCT03324932) is testing the efficacy of denosumab on BMD in early BC patients treated with adjuvant AIs, with DFS and OS as secondary endpoints. Another randomized phase III trial, BRCA-P (NCT04711109), is studying the effect of denosumab on BC preventing in women with a BRCA1 germline mutation.

This meta-analysis had some limitations. First, only two studies explored denosumab efficacy in this setting and were included in this analysis. Even if one might argue about pooling results with a low number two studies, the high number of patients enrolled can allow to retain meaningful trends and to better define the population for further randomized trials. Secondly, the analysis was based on published results rather than individual patients' data. This approach precluded exploring heterogeneity in terms of survival outcomes among patient' subgroups of interest and particularly depending on the ET adopted. Given the different bone effect of endocrine therapies in the hormone receptor positive/HER2 negative subtype, it would have been interesting to evaluate the pooled HRs for DFS, BMFS, and OS among patients treated with AIs and/or ovarian suppression *versus* tamoxifen. Bone turnover induced by AIs and ovarian suppression could help more than the menopausal status to identify patients' subgroups who benefit more from bone-targeted therapy. The lack of individual data prevented the analysis of different recurrence events according to patient characteristics (molecular subtype, menopausal status, ET). Second, the survival data from the meta-analyzed studies were obtained after a median follow-up of different duration, which affected the relative contribution to the pooled HR calculation. The median duration of the shortest follow-up among the two included studies was 67 months (in the D-CARE trial), a period long enough to detect recurrence events in HER2 positive and triple-negative BC subtypes. It should be noted that the ABCSG-18 study, including mostly exclusively hormone receptor positive/HER2 negative patients, has an

updated median follow-up of 8 years, making the analysis of recurrence events quite reliable, while the OS results should still be considered inconclusive. In addition, multiple subgroup analyses have been performed with results to be considered descriptive and hypothesis-generating, but consistent in identifying the best patients' subgroup likely to benefit from bone-targeted therapy.

In conclusion, besides the established role of denosumab in the management of early hormone receptor positive BC to preserve bone health and reduce fracture risk, the present meta-analysis suggested a significant DFS and BMFS benefit from denosumab addition in hormone receptor positive/HER2 negative BC patients, with a reduction of bone recurrences in all hormone receptor positive population and no added toxicities compared to placebo. No interaction was found between treatment effect and menopausal status, suggesting that denosumab added to standard anticancer therapy has no differential benefit in pre and postmenopausal patients. Based on these results, the implementation of denosumab use in combination with ET in the early BC setting could be reconsidered.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
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Acknowledgements
Special thanks to Professor Robert Coleman for sharing data that were missing. Thanks to our librarian Chiara Sanna for her support in the research strategy.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
LM, GG, EDM, NM, MP, LP, SP, MCC, and ADB declare no conflict of interest. AP has declared consulting fees/advisory role for Amgen, MSD, Novartis, travel and accommodation by Pfizer. AF has declared consulting fees/advisory role for AstraZeneca, Daiichi Sankyo, Eisai, Eli-Lilly. Epionpharma, exact science, MSD, Novartis, Pierre Fabre, Roche, Seagen. GT is supported by funds of Ministero della Salute (Ricerca Corrente 2022). EB is currently supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC) under Investigator Grant (IG) No. IG20583. EB is supported by institutional funds of Università Cattolica del Sacro Cuore (UCSC-project D1). EB is supported by funds of Ministero della Salute (Ricerca Corrente 2022). EB received speakers' and travels' fee from MSD, AstraZeneca, Pfizer, Eli-Lilly, BMS, Novartis, and Roche. EB received institutional research grants from AstraZeneca, Roche. AO has declared consulting fees/advisory role for Novartis, Roche, Eli-Lilly, Amgen, Daiichi Sankyo and travel and accommodation by Daiichi Sankyo, Novartis, Roche, and Pfizer.

Availability of data and materials

All the data supporting the conclusions are presented in the article or in supplemental material.

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Supplemental material

Supplemental material for this article is available online.

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