Adv Ther (2021) 38:4569–4580
https://doi.org/10.1007/s12325-021-01812-9

BRIEF REPORT

Bone Health Outcomes from the International, Multicenter, Randomized, Phase 3, Placebo-Controlled D-CARE Study Assessing Adjuvant Denosumab in Early Breast Cancer

Robert Coleman · Ying Zhou · Danielle Jandial · Benoit Cadieux · Arlene Chan

Received: April 28, 2021 / Accepted: May 28, 2021 / Published online: June 29, 2021

ABSTRACT

Introduction: D-CARE, an international, phase 3, randomized, double-blind, placebo-controlled study in women with early-stage breast cancer at high risk of disease recurrence, failed to meet its primary endpoint—improvement in bone metastasis-free survival (BMFS) with adjuvant denosumab vs placebo injections. As a result of the limitations of assessing BMFS, which includes relapse in bone with and without extraskeletal recurrences and deaths from any cause, the prespecified exploratory bone endpoints' analysis may provide a more clinically meaningful effect of denosumab in this disease setting.

Methods: The study enrolled women (aged $\geq$ 18 years) with histologically confirmed stage II/III breast cancer. Patients treated with adjuvant/neoadjuvant chemotherapy meeting inclusion criteria were randomly assigned 1:1 to receive either denosumab (120 mg) or placebo subcutaneously every 3–4 weeks for about 6 months and then every 3 months for a total treatment duration of 5 years. Five prespecified exploratory bone endpoints and post hoc subgroup analysis based on age (< 50 and ≥ 50 years) and menopause status (premenopausal and postmenopausal) were evaluated.

Results: Overall, 4509 women with early-stage breast cancer were assigned to receive denosumab ($N = 2256$) or placebo ($N = 2253$). The baseline demographics and clinical characteristics were comparable between the two arms. The hazard ratio (HR) for time to first bone metastasis was 0.82 (95% CI 0.66–1.02; $p = 0.068$), with HRs of 0.70 (95% CI 0.52–0.94; $p = 0.018$) for patients < 50 years old and 0.74 (95% CI 0.55–0.98; $p = 0.038$) for premenopausal patients, favoring the denosumab group. The HRs for time to first on-study fracture and time to first on-study skeletal-related event were 0.76 (95% CI 0.63–0.92; $p = 0.004$) and 0.52 (95% CI 0.35–0.78; $p = 0.001$), respectively, again favoring the denosumab group.

Conclusion: The exploratory bone endpoints indicate the benefits of denosumab treatment in patients with high-risk early breast cancer, supporting the expected bone health benefits contributed by denosumab.

R. Coleman
University of Sheffield, Sheffield, UK

Y. Zhou · D. Jandial · B. Cadieux
Amgen Inc., Thousand Oaks, CA, USA

A. Chan
Breast Cancer Research Centre-WA and Curtin University, Perth, WA, Australia

A. Chan (✉)
Perth Breast Cancer Institute, Hollywood Consulting Centre, Suite 406, 91 Monash Ave, Nedlands, WA 6009, Australia
e-mail: arlenechan@me.com

Trial Registration Number: NCT01077154

Keywords: Denosumab; Exploratory bone endpoints; High-risk early breast cancer; Post hoc analysis

Key Summary Points

Why carry out this study?

Although denosumab treatment reduces skeletal-related event (SRE) risk and delays the time to first SRE in patients with solid metastatic tumors, the benefits of denosumab to bone health have not been established in patients with early-stage breast cancer at high risk of disease recurrence.

Besides evaluating bone metastasis-free survival (BMFS), we further investigated the potential benefits of denosumab treatment by assessing the prespecified bone endpoints and the associated subgroup analysis in patients with high-risk early breast cancer receiving denosumab versus placebo.

What was learned from the study?

The hazard ratios of the prespecified exploratory bone endpoints mostly favored denosumab over placebo, suggesting a clinically meaningful effect of denosumab in these patients.

This study demonstrates that denosumab improves bone-related outcomes for women with high-risk early breast cancer.

INTRODUCTION

Female breast cancer is the most common form of cancer and the fourth leading cause of cancer deaths in the USA [1]. Distant relapse occurs most frequently in the bone, with 65–80% of patients with metastatic breast cancer developing bone metastases during the course of their disease [2, 3]. Metastatic bone disease is associated with pathologic fractures, bone pain, spinal cord compression, and hypercalcemia of malignancy [2].

Denosumab is a fully human monoclonal antibody that binds to and inhibits the receptor activator of nuclear factor-kappa B ligand [4]. Treatment with denosumab reduces the incidence of skeletal-related events (SREs) and delays the time to first SRE in patients with solid metastatic tumors, including breast cancer [5–7]. Denosumab was superior to zoledronic acid in delaying or reducing SREs in patients with breast cancer that had metastasized to the bone [5].

D-CARE (ClinicalTrials.gov, NCT01077154) is an international, phase 3, randomized, double-blind, placebo-controlled study in women with early-stage breast cancer at high risk of disease recurrence to assess whether denosumab with standard-of-care adjuvant/neoadjuvant chemotherapy would increase bone metastasis-free survival (BMFS) and disease-free survival. The study did not reach its primary endpoint because adjuvant denosumab did not significantly improve BMFS versus placebo [8]. Exploratory bone endpoints were assessed in D-CARE to determine the bone protective effects of denosumab in this setting, specifically pertaining to metastasis to bone, fractures, and on-study SREs occurring after bone recurrence. Here, we summarize the bone health outcomes of adjuvant denosumab in women with early breast cancer in the D-CARE study.

METHODS

Details of the D-CARE clinical study have been previously published [8]. Briefly, eligible women (≥ 18 years old) with histologically confirmed stage II/III or locally advanced disease were randomized to receive subcutaneous denosumab (120 mg) or matching placebo every 4 weeks with adjuvant/neoadjuvant systemic therapy for approximately 6 months followed by denosumab or placebo every 3 months for 4.5 years (total treatment

duration, 5 years). Patients were not required to undergo bone mineral density assessment and were not excluded on the basis of bone mineral density results. Written informed consent was provided by all patients before participation, and the study was approved by each study site's institutional review board and independent ethics committee. Participating investigators and institutions and ethics committees were in compliance with all applicable regulatory requirements and International Conference on Harmonisation and Good Clinical Practice (ICH GCP) guidelines.

Menopause status [i.e., postmenopausal (yes/no)] of patients was assessed by investigators at screening. Postmenopausal status was defined in the study as follows: having undergone bilateral oophorectomy, age $\geq$ 60 years, age 45–59 years with amenorrhea lasting more than 12 months plus an intact uterus and at least one intact ovary or with amenorrhea lasting no more than 12 months and follicle-stimulating hormone and estradiol in the postmenopausal range, and patients who had received adjuvant or neoadjuvant chemotherapy must have met at least one of the aforementioned criteria for postmenopausal status prior to that chemotherapy. Patients underwent mandatory imaging (mammography, full-body radioisotope bone scans, and computed tomography/magnetic resonance imaging of the chest, abdomen, and all other known or suspected sites of disease) at screening, at the end of year 1, and annually thereafter. Images and scans were assessed by blinded independent central review (BICR) and local investigators. An SRE was defined as any fracture (vertebral or nonvertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression following the development of bone metastasis. Prespecified exploratory bone endpoints (defined in Table 1) included 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 before bone metastasis, and time to first on-study SRE following bone metastasis.

Statistical Analyses

The full analysis set, which included all patients who were randomized to the study, was used for all efficacy endpoints, including exploratory bone endpoints. For time to bone metastasis as site of first recurrence and time to first symptomatic bone metastasis, a cumulative incidence function (CIF) [9] was estimated with non-bone site(s) of first recurrence and first asymptomatic bone metastasis, respectively, as competing events. Comparison of the CIF between denosumab and placebo was based on Gray [10] and Zhou et al. [11] and stratified by the randomization stratification factors. For other time to event endpoints, the Kaplan-Meier method was used to estimate the survival function for each treatment group. The hazard ratio (HR) of denosumab versus placebo and the corresponding two-sided 95% confidence interval (CI) were estimated using a Cox proportional hazards model stratified by the randomization stratification factors. A log-rank test, stratified by the randomization stratification factors, was performed to compare the treatment groups. Post hoc subgroup analyses for the exploratory bone endpoints were conducted by age group ($<$ 50 years vs $\geq$ 50 years) and menopause status (premenopausal vs postmenopausal). Post hoc sensitivity analyses were conducted for the exploratory bone endpoints. In the sensitivity analysis for each exploratory endpoint, patients who received on-study bisphosphonate therapy prior to their event/censoring time of the original analysis were censored at the start date of the bisphosphonate use.

RESULTS

Detailed study outcomes have been previously reported [8]. Overall, 4509 patients were randomized to receive either denosumab or placebo and were included in the primary analysis (Table 2). The median age was 51 years [569 (13%) aged 18–39, 1491 (33%) aged 40–49, and 2449 (54%) aged $\geq$ 50], 2360 (52%) patients were premenopausal, and 3492 (77%) patients had estrogen receptor-positive and/or

Table 1 Summary of prespecified exploratory bone endpoints

Exploratory endpoint	Description
Time to first bone metastasis	Determined by the time from randomization to the first observation of bone metastasis as site of first or subsequent disease recurrence, excluding death
Time to bone metastasis as site of first recurrence	Determined by the time from randomization to the first observation of bone metastasis as site of first disease recurrence, excluding death
Time to first symptomatic bone metastasis	Determined by the time from randomization to the first observation of bone metastasis, which is accompanied by symptom at the time of detection
Time to first on-study fracture (before bone metastasis)	Determined by the time from randomization to the first observation of on-study vertebral or nonvertebral fracture prior to the development of bone metastasis
Time to first on-study SRE (following bone metastasis)	Determined by the time from randomization to the first on-study SRE, defined as any fracture (vertebral or nonvertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression, following the development of bone metastasis

SRE skeletal-related event

progesterone receptor-positive status. Neoadjuvant and adjuvant therapies were received by a total of 1091 (24%) and 3418 (76%) patients, respectively. Of the 3424 patients with estrogen receptor-positive breast cancer, 1961 (57%) received tamoxifen, 1898 (55%) received aromatase inhibitors, and 392 (11%) underwent ovarian ablation as the prior and/or on-study hormonal therapy (excluding the usage after disease recurrence). Overall, 27/2256 (1%) patients in the denosumab arm and 70/2253 (3%) in the placebo arm used on-study bisphosphonate before bone metastasis or death. For patients with confirmed bone metastasis, 2/155 (1%) patients in the denosumab arm and 6/189 (3%) in the placebo arm used on-study bisphosphonate prior to the event. The median (range) time on study before the primary analysis cutoff was 67 (0–87) months in the denosumab arm and 67 (0–86) months in the placebo arm.

For the exploratory bone endpoints (Table 3), the time to first bone metastasis was similar for denosumab and placebo (HR 0.82; 95% CI 0.66–1.02; $p = 0.068$; Fig. 1a). Improvements in bone metastasis-related exploratory endpoints were seen with denosumab versus placebo for time to bone metastasis as site of first recurrence (non-bone site of first recurrence as a competing risk [HR 0.76; 95% CI 0.59–0.97; $p = 0.031$]; Fig. 1b) and time to first symptomatic bone metastasis (asymptomatic bone metastasis as a competing risk [HR 0.60; 95% CI 0.39–0.93; $p = 0.024$]; Fig. 1c). Subgroup analysis showed improvements in the bone metastasis-related exploratory endpoints for denosumab versus placebo in women < 50 years old and in premenopausal women, but not in women ≥ 50 years old or in postmenopausal women (Table 3).

Skeletal morbidity was reduced for time to first on-study fracture (before bone metastasis [HR 0.76; 95% CI 0.63–0.92; $p = 0.004$]; Fig. 1d) and time to first on-study SRE (after disease recurrence in bone [HR 0.52; 95% CI 0.35–0.78; $p = 0.001$]; Fig. 1e). Subgroup analysis (Table 3) revealed improvements in time to first on-study fracture for denosumab versus placebo in women ≥ 50 years old and in both premenopausal and postmenopausal women, with similar relative risk reduction. Improvements in time to first on-study SRE after disease recurrence in bone for denosumab versus placebo were seen in women < 50 years old and in premenopausal women, but not in women ≥ 50 years old or in postmenopausal women.

The sensitivity analysis in which patients who received on-study bisphosphonate therapy

Table 2 Baseline demographics and clinical characteristics

	Denosumab (*N* = 2256)	**Placebo (*N* = 2253)**	**All (*N* = 4509)**
Age, median (range), years	50 (25–88)	51 (20–85)	51 (20–88)
Age group, *n* (%), years			
< 50	1032 (46)	1028 (46)	2060 (46)
18–39	296 (13)	273 (12)	569 (13)
40–49	736 (33)	755 (34)	1491 (33)
≥ 50	1224 (54)	1225 (54)	2449 (54)
Menopause status, *n* (%)			
Premenopausal	1195 (53)	1165 (52)	2360 (52)
Postmenopausal	1061 (47)	1088 (48)	2149 (48)
Hormone receptor (ER/PR) status, *n* (%)			
ER and/or PR positive	1744 (77)	1748 (78)	3492 (77)
ER and PR negative	511 (23)	504 (22)	1015 (23)
Missing	1 (< 1)	1 (< 1)	2 (< 1)
IHC subtypes of breast cancer, *n* (%)			
Hormone receptor positive and HER2 positive	286 (13)	288 (13)	574 (13)
Hormone receptor positive and HER2 negative	1458 (65)	1460 (65)	2918 (65)
Hormone receptor negative and HER2 positive	168 (7)	163 (7)	331 (7)
Hormone receptor negative and HER2 negative	343 (15)	341 (15)	684 (15)
Missing	1 (< 1)	1 (< 1)	2 (< 1)
Systemic breast cancer therapy, *n* (%)			
Neoadjuvant	548 (24)	543 (24)	1091 (24)
Adjuvant	1708 (76)	1710 (76)	3418 (76)
Prior and on-study therapy for ER-positive breast cancer			
ER-positive breast cancer, *n*	1719	1705	3424
Hormonal therapy, *n* (%[a])	1554 (90)	1551 (91)	3105 (91)
Tamoxifen	991 (58)	970 (57)	1961 (57)
Aromatase inhibitors	934 (54)	964 (57)	1898 (55)
Ovarian ablation[b]	199 (12)	193 (11)	392 (11)

ER estrogen receptor, *HER2* human epidermal growth factor receptor 2 (also known as ERBB2), *IHC* immunohistochemical, *PR* progesterone receptor

[a] Based on the number of patients with ER-positive breast cancer

[b] Defined as bilateral oophorectomy in patients who were premenopausal at randomization

Table 3 Exploratory bone endpoints

	No. of patients with event, *n* (%)		HR (95% CI)	Descriptive *p* value
	Denosumab (*N* = 2256)	Placebo (*N* = 2253)		
Time to first bone metastasis	155 (6.9)	189 (8.4)	0.82 (0.66–1.02)	0.068
Age, years				
< 50	74/1029 (7.2)	107/1026 (10.4)	0.70 (0.52–0.94)	0.018
≥ 50	81/1227 (6.6)	82/1227 (6.7)	0.98 (0.72–1.33)	0.88
Menopause status				
Premenopausal	81/1195 (6.8)	108/1165 (9.3)	0.74 (0.55–0.98)	0.038
Postmenopausal	74/1061 (7)	81/1088 (7.4)	0.92 (0.67–1.27)	0.61
Time to bone metastasis as site of first recurrence[a]	110 (4.9)	145 (6.4)	0.76 (0.59–0.97)	0.031
Age, years				
< 50	50/1029 (4.9)	83/1026 (8.1)	0.61 (0.43–0.86)	0.005
≥ 50	60/1227 (4.9)	62/1227 (5.1)	0.97 (0.68–1.38)	0.85
Menopause status				
Premenopausal	54/1195 (4.5)	85/1165 (7.3)	0.62 (0.44–0.87)	0.006
Postmenopausal	56/1061 (5.3)	60/1088 (5.5)	0.96 (0.67–1.38)	0.83
Time to first symptomatic bone metastasis[b]	32 (1.4)	54 (2.4)	0.60 (0.39–0.93)	0.024
Age, years				
< 50	13/1029 (1.3)	30/1026 (2.9)	0.44 (0.23–0.85)	0.015
≥ 50	19/1227 (1.5)	24/1227 (2.0)	0.80 (0.44–1.46)	0.47
Menopause status				
Premenopausal	16/1195 (1.3)	31/1165 (2.7)	0.52 (0.28–0.95)	0.033
Postmenopausal	16/1061 (1.5)	23/1088 (2.1)	0.71 (0.38–1.36)	0.30
Time to first on-study fracture (before bone metastasis)	201 (8.9)	255 (11.3)	0.76 (0.63–0.92)	0.004
Age, years				
< 50	74/1029 (7.2)	90/1026 (8.8)	0.81 (0.59–1.10)	0.18
≥ 50	127/1227 (10.4)	165/1227 (13.4)	0.73 (0.58–0.93)	0.009
Menopause status				
Premenopausal	87/1195 (7.3)	110/1165 (9.4)	0.74 (0.56–0.99)	0.040
Postmenopausal	114/1061 (10.7)	145/1088 (13.3)	0.77 (0.60–0.98)	0.037
Time to first on-study SRE (following bone metastasis)	38 (1.7)	72 (3.2)	0.52 (0.35–0.78)	0.001
Age, years				
< 50	15/1029 (1.5)	39/1026 (3.8)	0.38 (0.21–0.69)	0.001
≥ 50	23/1227 (1.9)	33/1227 (2.7)	0.69 (0.41–1.18)	0.17

Table 3 continued

	No. of patients with event, *n* (%)		HR (95% CI)	Descriptive *p* value
	Denosumab (*N* = 2256)	Placebo (*N* = 2253)		
Menopause status				
Premenopausal	15/1195 (1.3)	38/1165 (3.3)	0.38 (0.21–0.69)	< 0.001
Postmenopausal	23/1061 (2.2)	34/1088 (3.1)	0.68 (0.40–1.16)	0.16

CI confidence interval, *HR* hazard ratio, *SRE* skeletal-related event

[a] Non-bone site of first recurrence as a competing risk

[b] Asymptomatic bone metastasis as a competing risk

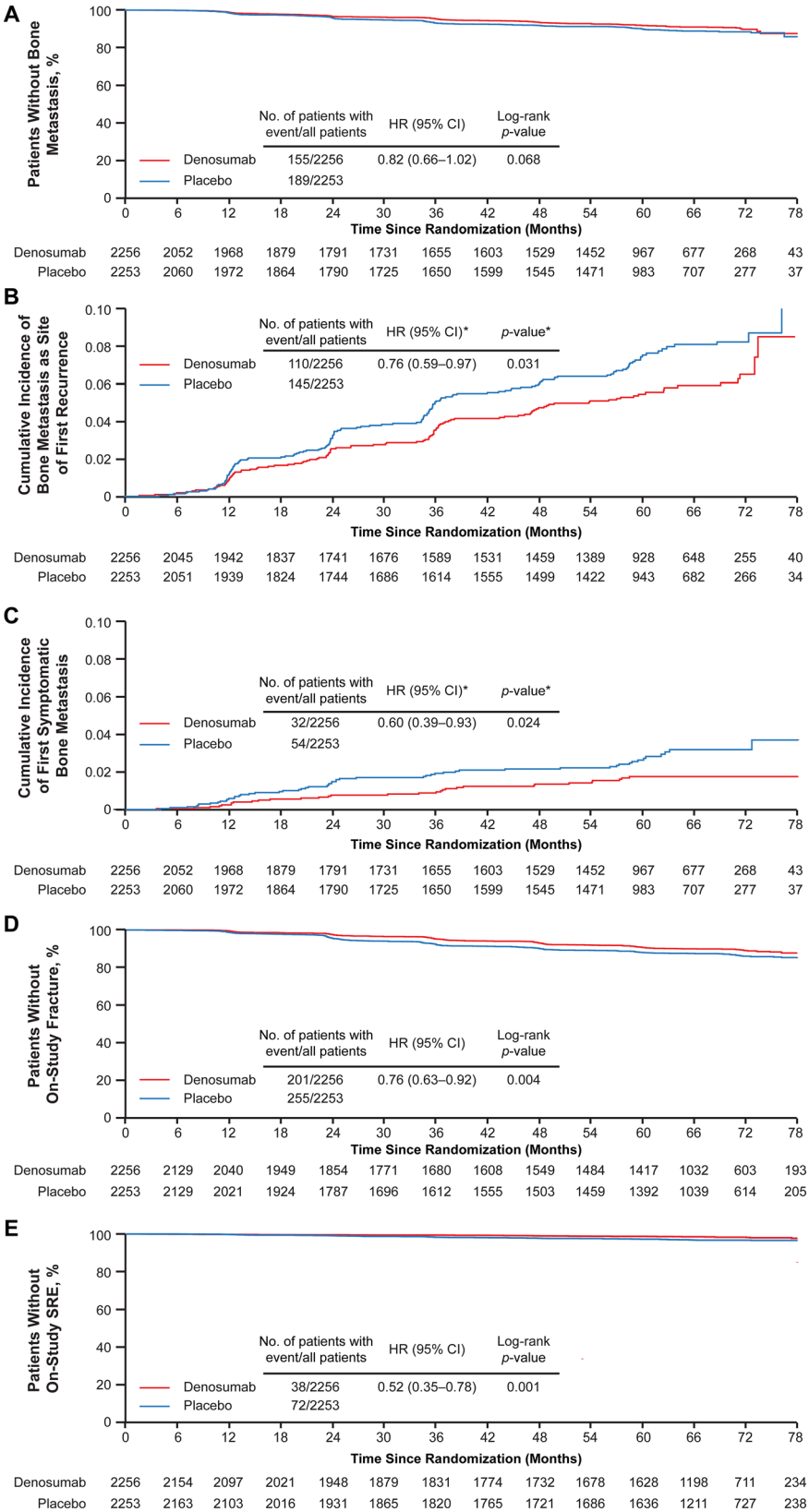
prior to their event/censoring time of the original analysis were censored at the start date of the bisphosphonate use and showed similar results to the original analysis, further confirming the observed results (Table 4).

DISCUSSION

No statistically significant improvements in the primary endpoint of BMFS were observed with denosumab treatment versus placebo overall or in any subgroup in the D-CARE study. However, BMFS is a composite endpoint that includes relapse in bone with and without recurrence at other anatomic sites and death from any cause. Approximately 40% of the patients died before experiencing bone metastasis. Thus, the composite BMFS endpoint may have limited the ability to identify a clinically meaningful effect of denosumab. However, for the exploratory bone endpoints, denosumab treatment was associated with a delay to bone metastasis as the site of first recurrence and first symptomatic bone metastasis, suggesting beneficial biological effects on the bone microenvironment. Additionally, bone events reflecting the expected structural benefits of denosumab on bone, such as time to first on-study SRE and time to first on-study fracture (before bone metastasis), were prolonged by denosumab when compared with placebo, and confirmed the expected bone health benefits of denosumab. As reported previously, our results indicate that denosumab, which functions within the bone microenvironment, was unable to modify the metastatic process if recurrences first occurred outside bone or in extraosseous sites, subsequently leading to bone involvement.

Subgroup analyses suggested improvements in time to first on-study fracture (before bone metastasis) in women who were premenopausal at study entry that were of similar magnitude to the expected reduction in fractures affecting postmenopausal women. As the risk of fragility fractures in premenopausal women is low, this appears somewhat counterintuitive. However, it may reflect the very rapid bone loss known to be associated with chemotherapy-induced menopause that would have occurred in many of the premenopausal women aged 40–49 years [12]. Unfortunately, information on chemotherapy-induced menopause was not collected in this trial; thus, this potential explanation cannot be explored further.

The benefit of exploratory bone endpoints is similar to that observed in other denosumab studies in breast cancer. In the phase 3 ABCSG-18 trial (NCT00556374) [7], 3425 postmenopausal women with early hormone receptor-positive breast cancer (breast cancer with lower relapse risk than in D-CARE) received twice-yearly denosumab (60 mg) or placebo with aromatase inhibitors. Denosumab significantly delayed the time to first clinical fracture (HR 0.50; 95% CI 0.39–0.65; $p < 0.001$) and reduced the incidence of new vertebral fractures (odds ratio, 0.53; 95% CI 0.33–0.85;


A
Patients Without Bone Metastasis, %
No. of patients with event/all patients
HR (95% CI)
Log-rank p-value
Denosumab 155/2256 0.82 (0.66–1.02) 0.068
Placebo 189/2253
Time Since Randomization (Months)
Denosumab 2256 2052 1968 1879 1791 1731 1655 1603 1529 1452 967 677 268 43
Placebo 2253 2060 1972 1864 1790 1725 1650 1599 1545 1471 983 707 277 37
B
Cumulative Incidence of Bone Metastasis as Site of First Recurrence
No. of patients with event/all patients
HR (95% CI)*
p-value*
Denosumab 110/2256 0.76 (0.59–0.97) 0.031
Placebo 145/2253
Time Since Randomization (Months)
Denosumab 2256 2045 1942 1837 1741 1676 1589 1531 1459 1389 928 648 255 40
Placebo 2253 2051 1939 1824 1744 1686 1614 1555 1499 1422 943 682 266 34
C
Cumulative Incidence of First Symptomatic Bone Metastasis
No. of patients with event/all patients
HR (95% CI)*
p-value*
Denosumab 32/2256 0.60 (0.39–0.93) 0.024
Placebo 54/2253
Time Since Randomization (Months)
Denosumab 2256 2052 1968 1879 1791 1731 1655 1603 1529 1452 967 677 268 43
Placebo 2253 2060 1972 1864 1790 1725 1650 1599 1545 1471 983 707 277 37
D
Patients Without On-Study Fracture, %
No. of patients with event/all patients
HR (95% CI)
Log-rank p-value
Denosumab 201/2256 0.76 (0.63–0.92) 0.004
Placebo 255/2253
Time Since Randomization (Months)
Denosumab 2256 2129 2040 1949 1854 1771 1680 1608 1549 1484 1417 1032 603 193
Placebo 2253 2129 2021 1924 1787 1696 1612 1555 1503 1459 1392 1039 614 205
E
Patients Without On-Study SRE, %
No. of patients with event/all patients
HR (95% CI)
Log-rank p-value
Denosumab 38/2256 0.52 (0.35–0.78) 0.001
Placebo 72/2253
Time Since Randomization (Months)
Denosumab 2256 2154 2097 2021 1948 1879 1831 1774 1732 1678 1628 1198 711 234
Placebo 2253 2163 2103 2016 1931 1865 1820 1765 1721 1686 1636 1211 727 238

◀**Fig. 1** Time to **a** first bone metastasis, **b** bone metastasis as site of first recurrence with non-bone site of first recurrence as a competing risk, **c** first symptomatic bone metastasis with asymptomatic bone metastasis as a competing risk, **d** first on-study fracture (before bone metastasis), and **e** first on-study SRE (following bone metastasis). CI confidence interval, HR hazard ratio, SRE skeletal-related event. *Based on subdistribution hazards (Gray [10] and Zhou et al. [11]) stratified by the randomization stratification factors

$p = 0.009$) versus placebo [7]. In the phase 3 AZURE trial (NCT00072020) [13] in 3360 women with stage II or III breast cancer (45% premenopausal), treatment with zoledronic acid (4 mg every 3–4 weeks for 6 doses, then every 3 months for 8 doses, followed by every 6 months for 5 doses) reduced the risk of fracture at 5 years (3.8% for zoledronic acid vs 5.9% for standard adjuvant systemic treatment; HR 0.69; 95% CI 0.53–0.90; $p = 0.005$), although most of the benefit was associated with fewer fractures after disease recurrence in bone rather than effects on the normal skeleton [13]. In AZURE, treatment with zoledronic acid also significantly reduced the incidence of bone metastases as the first recurrence (adjusted HR 0.78; 95% CI 0.63–0.96; $p = 0.020$) or at any time (adjusted HR 0.81; 95% CI 0.68–0.97; $p = 0.022$).

The benefit of denosumab for exploratory bone endpoints observed in breast, prostate, and other cancer studies may be explained by modification of the disease process in bone and suppression of bone resorption and osteoclastic activity. In a phase 2 trial [14], 111 patients with solid tumors (e.g., prostate, breast) or multiple myeloma were treated with a bisphosphonate every 4 weeks or denosumab (180 mg) every 4 or 12 weeks. The percentage of patients experiencing a first on-study SRE by week 25 was 8% (6/75) in the denosumab arm and 17% (6/35) in the zoledronic acid arm (odds ratio, 0.31; 95% CI 0.08–1.18). Denosumab treatment resulted in greater suppression of bone turnover markers and an osteoclast biomarker (TRAP-5b) than bisphosphonate treatment.

In a phase 3 trial [5], 2049 patients with breast adenocarcinoma that had metastasized to the bone were randomized to receive either denosumab 120 mg or zoledronic acid 4 mg every 4 weeks. Denosumab treatment was significantly more effective at delaying or reducing SREs and resulted in greater suppression of bone turnover markers compared with zoledronic acid. Specifically, denosumab versus zoledronic acid reduced the risk of developing multiple SREs (time to first and subsequent SREs) by 23% (rate ratio, 0.77; 95% CI 0.66–0.89; $p = 0.001$) and reduced the mean skeletal morbidity rate (i.e., the ratio of SREs per patient divided by the patient's time at risk) by 22%. By week 14, denosumab treatment resulted in an 80%

Table 4 Exploratory bone endpoints: sensitivity analysis—censoring at on-study bisphosphonate use

	No. of patients with event, *n* (%)		HR (95% CI)	Descriptive *p* value
	Denosumab (*N* = 2256)	Placebo (*N* = 2253)		
Time to first bone metastasis	153 (6.8)	183 (8.1)	0.83 (0.67–1.03)	0.083
Time to bone metastasis as site of first recurrence[a]	108 (4.8)	141 (6.3)	0.76 (0.59–0.98)	0.032
Time to first symptomatic bone metastasis[b]	32 (1.4)	52 (2.3)	0.62 (0.40–0.96)	0.033
Time to first on-study fracture (before bone metastasis)	199 (8.8)	247 (11.0)	0.77 (0.64–0.93)	0.006
Time to first on-study SRE (following bone metastasis)	35 (1.6)	67 (3.0)	0.51 (0.34–0.77)	0.001

CI confidence interval, *HR* hazard ratio, *SRE* skeletal-related event

[a] Non-bone site of first recurrence as a competing risk

[b] Asymptomatic bone metastasis as a competing risk

median decrease in urinary N-telopeptide for creatinine levels versus 68% with zoledronic acid ($p < 0.001$). Denosumab treatment also resulted in a 44% median decrease in bone-specific alkaline phosphatase levels versus 37% with zoledronic acid ($p < 0.001$). The authors hypothesized that the greater inhibition of osteoclast-induced bone resorption by denosumab, as suggested by the increased suppression of bone turnover markers, results in improved treatment outcomes for denosumab relative to zoledronic acid.

Limitations

Several limitations are present in the study. Our study results may have been limited by the high proportion of patients who withdrew consent (more than 10% of randomized patients), which possibly introduced bias in the clinical outcomes. Moreover, the favorable bone metastasis as site of first recurrence exploratory endpoint may have been diluted by the deaths that occurred before bone metastasis and/or preferential spread of tumor cells to other metastatic sites. Inclusion of patients with variable bone health and treatments may also have influenced our findings.

CONCLUSIONS

Overall, the benefits demonstrated by these exploratory D-CARE bone endpoints confirmed the expected bone health aspects of denosumab and probable effects on bone metastasis as a first site of metastasis. The lower rates of fractures and SREs with denosumab treatment likely reflect the structural benefits of suppression of osteoclast activity and change in the balance of bone remodeling in favor of bone formation.

ACKNOWLEDGEMENTS

Funding. This study was sponsored and funded by Amgen Inc., Thousand Oaks, CA, USA, including the Journal's Rapid Service and Open Access Fee.

Medical Writing Assistance. The authors thank Rick Davis, MS, RPh (Complete Healthcare Communications, a CHC Group company, North Wales, PA, USA), whose work was funded by Amgen Inc., and Yin C. Lin, PhD (Amgen Inc.), for medical writing assistance in the preparation of this manuscript.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Robert Coleman, Ying Zhou, Danielle Jandial, and Arlene Chan contributed to the study conception and design. Ying Zhou performed statistical analysis. All the authors analyzed the data. The first draft of the manuscript was written by Robert Coleman, Ying Zhou, Danielle Jandial, and Arlene Chan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosures. Robert Coleman has received steering committee fees and travel support from Amgen; has received funding for IME lectures from Amgen, ITM, and Novartis; has received consulting fees from Astellas, AstraZeneca, Boehringer Ingelheim, ITM, and Scancell; and has share options for a biomarker in development (Inbiomotion). Ying Zhou and Danielle Jandial are employees of Amgen and hold Amgen stock. Benoit Cadieux was an employee of Amgen. Arlene Chan has no relationships to disclose.

Compliance with Ethics Guidelines. Written informed consent was provided by all patients before participation, and the study was approved by each study site's institutional review board and independent ethics committee. Participating investigators and institutions and ethics committees were in compliance with all applicable regulatory requirements and

International Conference on Harmonisation and Good Clinical Practice (ICH GCP) guidelines.

Data Sharing. There is a plan to share data. This may include de-identified individual patient data for variables necessary to address the specific research question in an approved data-sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and (1) this product and indication (or other new use) have been granted marketing authorization in both the US and Europe, or (2) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labeling. A committee of internal advisor's reviews requests. If not approved, requests may be further arbitrated by a Data Sharing Independent Review Panel. Requests that pose a potential conflict of interest or an actual or potential competitive risk may be declined at Amgen's sole discretion and without further arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Further details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/

REFERENCES

1. National Institutes of Health. Cancer stat facts: female breast cancer. 2019. https://seer.cancer.gov/statfacts/html/breast.html. Accessed 25 Sep 2019.
2. Lipton A. Bone metastases in breast cancer. Curr Treat Options Oncol. 2003;4(2):151–8.
3. Coleman R. Potential use of bisphosphonates in the prevention of metastases in early-stage breast cancer. Clin Breast Cancer. 2007;7(suppl 1):S29–35.
4. XGEVA®. Denosumab. Thousand Oaks, CA: Amgen Inc.; 2018.
5. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol. 2010;28(35):5132–9.
6. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer. 2012;48(16):3082–92.
7. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2015;386(9992):433–43.
8. Coleman R, Finkelstein DM, Barrios C, et al. Adjuvant denosumab in early breast cancer (D-CARE):

an international, multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2020;21(1): 60–72.

9. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: Wiley; 1980.

10. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16:1141–54.

11. Zhou B, Latouche A, Rocha V, Fine J. Competing risks regression for stratified data. Biometrics. 2011;67(2):661–70.

12. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol. 2008;9(9):840–9.

13. Coleman R, Cameron D, Dodwell D, et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. Lancet Oncol. 2014;15(9):997–1006.

14. Fizazi K, Lipton A, Mariette X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol. 2009;27(10):1564–71.