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The development of denosumab for the treatment of diseases of bone loss and cancer-induced bone destruction

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Denosumab is a fully human monoclonal antibody against RANK ligand (RANKL), an essential cytokine for the formation, function, and survival of osteoclasts. The role of excessive RANKL as a contributor to conditions characterized by bone loss or bone destruction has been well studied. With its novel mechanism of action, denosumab offers a significant advance in the treatment of postmenopausal osteoporosis; bone loss associated with hormone ablation therapy in women with breast cancer and men with prostate cancer; and the prevention of skeletal-related events in patients with bone metastases from solid tumors by offering clinical benefit to these patients in need.

Keywords: denosumab; RANKL; postmenopausal osteoporosis; bone metastases

Introduction

Denosumab is a fully human monoclonal antibody against RANK ligand (RANKL). The RANKL pathway was identified in the late 1990s to play a central role in the regulation of both physiologic and pathologic bone resorption. RANKL binds to its receptor RANK on osteoclast precursors and mature osteoclasts and stimulates osteoclast differentiation and function, and promotes osteoclast survival.[1–5] The first component identified for this novel pathway regulating bone resorption and remodeling was osteoprotegerin (OPG), which was discovered through a genomics-based approach. OPG transgenic mice were born with high bone mass and marked reductions in osteoclast numbers and activity.[6] The ability of OPG to reduce bone resorption and increase bone mass was due to its ability to bind and inhibit RANKL, a cytokine produced by osteoblasts and other cell types. OPG functions as a soluble decoy receptor by binding to RANKL, thereby preventing RANKL from binding and activating RANK[4] and leading to the arrest of osteoclast formation, attachment to bone, and activation, and to osteoclast apoptosis.

The importance of the RANKL pathway in the regulation of bone resorption was further demonstrated in animal models whereby components of the pathway were either genetically ablated or overexpressed, or in some cases both. Ablation of OPG led to increased bone turnover and cortical porosity and reduced bone volume and density,[7] while OPG overexpression led to increased bone mass.[6] Ablation of either RANK or RANKL led to severe osteopetrosis,[1,8] while injections of soluble RANKL led to increased bone turnover and cortical porosity and reductions in bone volume, density, and strength.[9] Early gene knockout studies in mice revealed that ablation of the RANK or RANKL genes in developing embryos prevented the formation of lymph nodes and the early development of T and B cells.[1,8] In contrast, in studies in adult rodents, administration of exogenous RANKL inhibitors, or continuous RANKL inhibition through OPG overexpression did not reduce lymphocyte counts nor impair the host response to various immune system challenges.[10–12] Overall, the data in adult animals

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suggest that the role of RANKL in the adult immune system may be largely redundant with other pathways.[13]

The role of excessive RANKL as a contributor to conditions characterized by bone loss or bone destruction has been well studied.[14,15] A comprehensive clinical development program for denosumab resulted in a robust data set that supported global regulatory approvals of the RANKL-targeted antibody denosumab in the bone loss and cancer-induced bone destruction settings.

Denosumab for osteoporosis

Osteoporosis is a global health problem that affects an estimated 200 million women worldwide.[16] The condition is characterized by low bone mass and weakening of bone structure leading to compromised bone strength and an increased risk of fracture.[17] The World Health Organization defines osteoporosis as a bone mineral density (BMD) T-score of ≤ -2.5, meaning a BMD value at least 2.5 standard deviations below the mean for young, healthy individuals. In the United States, one in two Caucasian women will experience an osteoporotic fracture in her lifetime.[17] Fractures are associated with significant morbidity and an increased mortality risk that may extend for up to 10 years following hip fracture.[18,19] Despite the availability of effective treatment options, many women with osteoporosis remain at risk for fracture. Observational studies consistently show about 50% of patients discontinue osteoporosis treatments within the first year.[20–22] Complex dosing regimens and concerns about tolerability in the real world setting may contribute to the poor compliance and persistence with treatment regimens and the resultant loss of antifracture efficacy among patients who discontinue therapy.[23–25] Thus, despite the availability of generally tolerated and efficacious therapies, osteoporosis management is not optimal and an unmet need remains for affected patients.

To advance the care of osteoporosis, new therapies must have greater antiresorptive activity, which would lead to significant antifracture efficacy; must be well tolerated; and must be convenient to administer so that the efficacy observed in clinical trials can be realized when the product is used long-term in clinical practice. Advances in the understanding of bone biology permit the development of improved therapeutics for conditions that are driven by an excess of osteoclast activity such as osteoporosis. Denosumab's unique, targeted mechanism of action (modulation of the activity of RANKL, a key mediator of osteoclast bone resorption), which results in substantial reductions in bone resorption, and convenient dosing regimen (once every six months (Q6M) by SC injection) therefore have the potential to improve the effectiveness of osteoporosis treatment.

The effects of denosumab on bone mass and strength were tested in animal models of osteoporosis. In mature, ovariectomized cynomolgus monkeys, denosumab treatment for 16 months reduced bone turnover and increased bone mass at cortical and trabecular sites compared with vehicle-treated OVX controls (OVX-Veh).[26] Mechanical testing showed denosumab improved bone strength parameters including peak load (Fig. 1A and B), stiffness, and energy to failure while maintaining normal bone material properties.[26] Bone histomorphometry demonstrated that denosumab inhibited tissue-level bone remodeling at all sites compared with OVX-Veh animals.[27] Denosumab also reduced trabecular bone surface erosion by up to 86% and cortical porosity by up to 72% (Fig. 1C and D).[27]

Denosumab (60 mg administered Q6M) is approved for the treatment of postmenopausal women with osteoporosis at high/increased risk for fracture.[28,29] Denosumab was first evaluated in humans in a trial of 49 healthy postmenopausal women. A single dose of denosumab reduced bone turnover marker (BTM) levels by 77% within 12 hours, and this effect was maintained for up to six months at the higher doses studied.[30] A larger phase 2 trial in postmenopausal women with low bone mass evaluated multiple doses of denosumab given subcutaneously every three months (Q3M) or Q6M, with the primary outcome measure being the change in lumbar spine BMD at 12 months compared with placebo. The 60 mg Q6M dose was selected as the dose for phase 3 trials because no additional pharmacodynamic activity was demonstrated at doses higher than 60 mg Q6M, and the Q6M interval was selected for convenience and potentially increased patient compliance. Subjects receiving continued denosumab for eight years in the extension of this phase 2 trial had mean BMD gains of 16.5% at the lumbar spine and 6.8% at the total hip.[31]

Fracture risk reduction with denosumab was evaluated in a double-blind, placebo-controlled

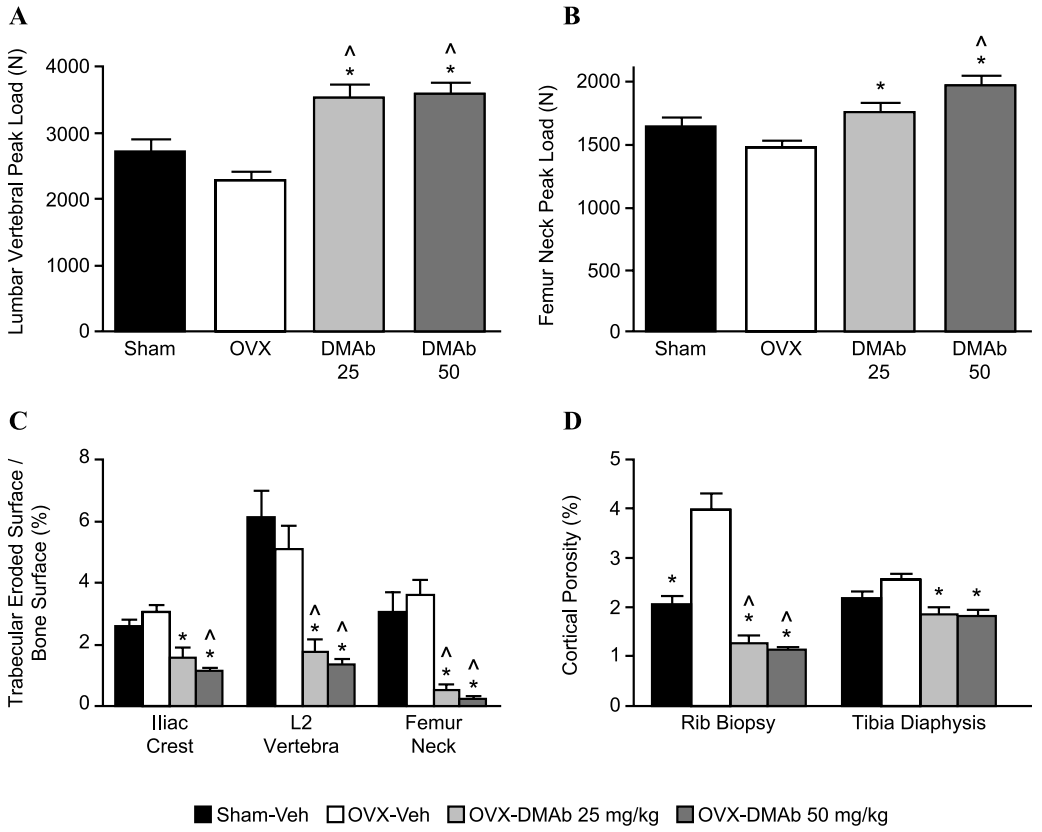

Figure 1. **In a study performed using adult female cynomolgus monkeys, sham operated or ovariectomized (OVX) animals were treated by subcutaneous injection with vehicle (Sham and OVX-Veh) or denosumab (Dmab) at 25 or 50 mg/kg every four weeks for 16 months beginning one month after surgery. Compared to OVX-Veh controls, denosumab-treated OVX animals exhibited significantly greater peak load at the (A) lumbar vertebrae and (B) femur neck, (C) significantly lower eroded bone surface, and (D) significantly lower cortical porosity in month six rib biopsies. Data are expressed as mean ± SE, $n = 14$–20 per group. *$P < 0.05$ versus OVX-Veh; ^$P < 0.05$ versus Sham. Figures reprinted from Ominsky *et al.*[26] and Kostenuik *et al.*[27] with permission from Elsevier.**

study in 7808 women with postmenopausal osteoporosis.[32] Denosumab treatment for three years significantly reduced the risk of new vertebral fracture by 68% compared with placebo ($P < 0.001$). Denosumab also significantly reduced hip fracture risk by 40% ($P = 0.04$) and nonvertebral fracture risk by 20% ($P = 0.01$) (Fig. 2A).

Reductions in fracture risk were accompanied by significant reductions in BTM levels and significant increases in BMD at the lumbar spine and total hip.[32] Data from this study showed that hip BMD changes at three years explained up to 51% of the new vertebral fracture risk reduction and up to 87% of the nonvertebral fracture risk reduction observed with denosumab treatment.[33] This is a larger proportion than what has been reported for other osteoporosis agents.[34–36]

Participants who missed no more than one dose of investigational product in the pivotal phase 3 fracture trial and completed the month 36 study visit were eligible to enter a seven-year, single-arm, open-label extension that will continue to evaluate denosumab 60 mg Q6M administration for up to a total of 10 years. Over the first two years of the extension, BMD continued to increase in the long-term treatment group (those subjects who received denosumab in the parent study and the extension, i.e., five years of continuous denosumab treatment) and vertebral and nonvertebral fracture rates remained low (Fig. 2B–D).[37]

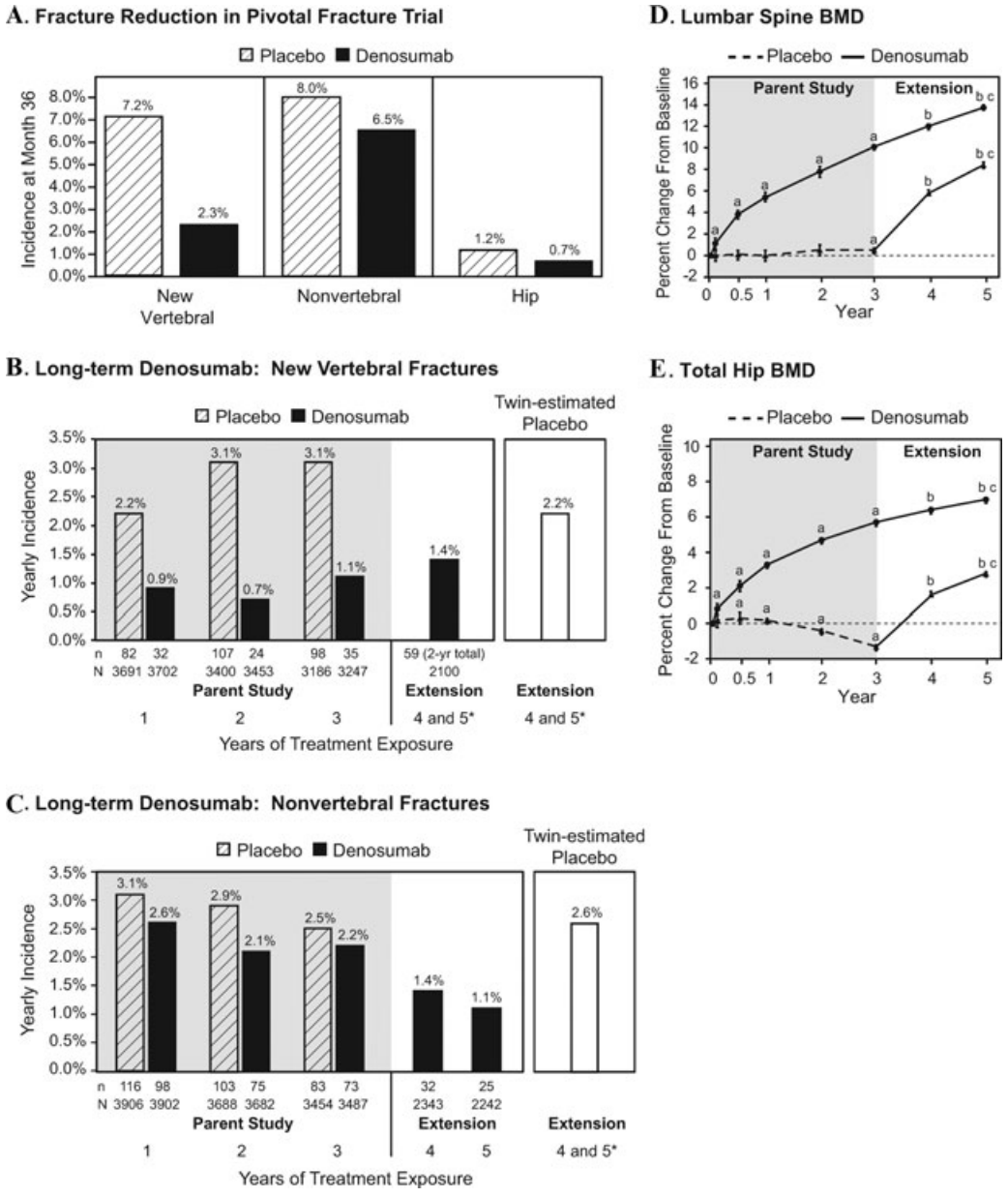

Figure 2. (A) Incidence of new vertebral, nonvertebral, and hip fractures with placebo and denosumab (60 mg Q6M) at 36 months in postmenopausal women with osteoporosis in the phase 3 pivotal fracture trial.[32] (B) New vertebral and (C) nonvertebral fractures by year for placebo and denosumab in the pivotal fracture trial and for the long-term denosumab group in the first two years of on open-label extension. Comparison to a twin-estimated placebo group in the extension phase is shown. ∗Annualized rate, i.e., (two-year rate)/2. Lateral radiographs (lumbar and thoracic) were not obtained at year four (year 1 of the extension). (D) Percent change from baseline in lumbar spine and (E) total hip BMD over time with placebo and/or denosumab treatment in the pivotal fracture trial and long-term extension. [a] $P < 0.05$ compared with parent study baseline; [b] $P < 0.05$ compared with parent study baseline and extension baseline. [c] $P < 0.05$ compared with year 4. Panels B–E originally published in Papapoulos *et al.*[37] © 2012 American Society for Bone and Mineral Research.

Two additional studies compared the effects of denosumab and the bisphosphonate alendronate on BMD. In postmenopausal women with low bone mass who were naive to bisphosphonate therapy and in those with prior bisphosphonate use, denosumab treatment led to significantly greater gains in BMD compared with alendronate at all measured skeletal sites.[38,39]

Both cortical and trabecular bone contribute to bone strength.[40] Analysis of the distal radius by high-resolution peripheral quantitative computed tomography (HR-pQCT)—an imaging technique that allows measurement of volumetric BMD and distinguishes between cortical and trabecular bone compartments—indicated that denosumab increased cortical, trabecular, and total BMD and improved polar moment of inertia, a surrogate for bone strength, to a greater extent than placebo or alendronate.[41] Denosumab also significantly reduced cortical porosity compared with placebo.[42]

The effects of denosumab are reversible upon discontinuation. In a four-year study in postmenopausal women with low BMD, two years of denosumab or placebo treatment were followed by two years without treatment. Significant increases in BMD and reductions in bone turnover were observed with denosumab during the treatment phase.[43] After denosumab cessation, BTM levels initially increased above study baseline transiently and returned to baseline levels by 24 months.[44] While BMD decreased after discontinuation of denosumab, it remained above the BMD levels in the placebo group at 24 months after discontinuation.[44] In a separate study, histomorphometric evaluation of bone biopsies from subjects who discontinued denosumab treatment for an average of 25 months showed that tissue-level bone remodeling and structural parameters were similar to those observed in a comparator group of postmenopausal women with osteoporosis not receiving treatment.[45]

The pivotal phase 3 fracture trial and its ongoing extension provide the largest body of available clinical trial data on the safety profile of denosumab in the osteoporosis setting. In the three-year double-blind phase, the overall incidence of adverse events and serious adverse events between the denosumab and placebo groups was similar.[32] All subjects received calcium and vitamin D supplements and the incidence of hypocalcemia was low. Certain skin conditions including eczema and serious adverse events of cellulitis occurred more frequently with denosumab than with placebo.[32,46] The overall incidence of serious adverse events of infection was not significantly different between the denosumab and placebo groups (4.1% vs 3.4%; $P = 0.14$).[32] In a smaller phase 3 trial in postmenopausal women with low bone mass, more subjects receiving denosumab than placebo were hospitalized for serious adverse events of infections (4.9% vs. 0.6%, $P = 0.02$);[43] however this has not been observed in other clinical trials with the 60 mg Q6M dose or with the higher 120 mg Q4W advanced cancer dose. In two years of the extension study, exposure-adjusted adverse event rates including serious adverse events of infections were similar to or lower than those observed in the double-blind phase.[37] Since denosumab inhibits bone resorption, certain adverse events that may be associated with reduced bone turnover, such as osteonecrosis of the jaw (ONJ) and atypical fractures of the femur were closely monitored in the denosumab studies. While ONJ was not reported in the pivotal phase 3 fracture trial, four cases of ONJ have been confirmed through adjudication in the study extension.[37] No cases of atypical femoral fractures were reported with denosumab in the double-blind phase of the pivotal trial; two cases of atypical femoral fractures have been reported in the extension study to date.[32,47]

Denosumab for cancer treatment-induced bone loss

Bone loss and fracture risk are also of concern in cancer patients receiving hormone ablation therapy. Adjuvant aromatase inhibitor (AI) therapy and androgen deprivation therapy (ADT) improve recurrence-free survival in patients with hormone-sensitive breast and prostate cancer, respectively, but these treatments increase bone resorption, leading to accelerated bone loss and increased fracture risk. The bone loss that results from hormone-ablation therapy may be the result of reduced estrogen levels. AI therapy reduces estrogen levels directly while evidence suggests ADT therapy reduces conversion of androgens to estrogens. In rodents, orchiectomy was associated with increased RANKL levels in bone marrow,[48,49] and conditional ablation of the androgen receptor increased RANKL mRNA expression by osteoblasts.[50] RANKL inhibition with OPG prevented orchiectomy-associated bone loss in rats.[48] In a recent metaanalysis of six phase 3 trials

of postmenopausal women with early stage breast cancer, the odds of fracture increased significantly with longer duration of AI use.[51] Similarly, fracture risk increases by about 70% in men receiving ADT therapy for prostate cancer compared to those not receiving ADT,[52,53] and the effect appears to be dose dependent.[54] As in the setting of postmenopausal osteoporosis, fractures in women with breast cancer and in men with prostate cancer are associated with increased morbidity and mortality.[54–58]

Denosumab (60 mg Q6M) is approved as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer and in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.[28] In a study of 252 women with hormone-receptor positive nonmetastatic breast cancer (all patients were to be supplemented with calcium and vitamin D), denosumab increased lumbar spine BMD by 4.8% compared with a change of −0.7% in the placebo group after 12 months ($P < 0.0001$). BMD continued to increase over 24 months when significant increases compared with placebo were observed at the lumbar spine and at all measured skeletal sites including the hip and 1/3 radius.[59]

Similarly, in men ($n = 1468$) receiving androgen-deprivation therapy for nonmetastatic prostate cancer, denosumab increased BMD at all measured skeletal sites.[60] In these men, who were all to receive daily calcium and vitamin D supplements, lumbar spine BMD at 24 months, the primary endpoint, increased by 5.6% in the denosumab group compared with a −1.0% decrease in the placebo group. Denosumab reduced the incidence of new vertebral fracture compared with placebo; at 36 months, the relative risk reduction was 62%, consistent with the vertebral fracture reduction observed in the pivotal fracture trial of postmenopausal women with osteoporosis. To date, denosumab is the only agent to achieve a fracture reduction benefit in men receiving ADT for prostate cancer.

Incidences of adverse events and serious adverse events were generally similar between the denosumab and placebo groups in these patients with cancer treatment-induced bone loss.[59,60] Hypocalcemia events were rare and similar between treatment groups. A greater incidence of cataracts was observed in men receiving denosumab compared with placebo;[60] this finding has not been observed in other studies, including those using greater and more frequent doses of denosumab in a similar patient population.[61]

Denosumab in advanced cancer

In patients with advanced cancer, bone metastases can have significant clinical consequences such as bone pain, pathological fractures, or spinal cord compression that may result in physical and functional impairment, and increased mortality.[62] About 70% of women with advanced breast cancer and over 80% of men with castration-resistant prostate cancer will develop bone metastases.[62–65]

The development of bone metastases is thought to result from complex interactions between cancer cells and the bone microenvironment. Tumor cell deposits that reach the bone secrete growth factors and other factors that result in a local increase in bone turnover. As increased bone resorption occurs, growth factors are released from the bone matrix that feed back to the cancer cells and further stimulate tumor growth. This interplay is referred to as the vicious cycle of bone metastasis.[66] Osteoclast-mediated bone resorption is thought to contribute not only to the bony destruction that occurs in bone metastases, but also the establishment and progression of skeletal tumors. Because RANKL is a key mediator of osteoclast formation, function, and survival,[3,4] inhibition of RANKL decreases osteoclast-driven bone resorption, interrupting the vicious cycle and curbing cancer-induced bone destruction. Furthermore, osteoclast suppression achieved with RANKL inhibition is a rational strategy to delay the establishment of bone metastases.

Experimental data and analysis of bone metastasis samples indicate that diverse signals (e.g., IL-1β, IL-6, IL-8, IL-11, IL-17, MIP1α, TNF-α, PTHrP, PGE2) generated by tumor cells converge on the local bone microenvironment to upregulate RANKL and/or downregulate OPG production.[67] The net increase in RANKL signal to osteoclasts leads to the focal bone destruction typical of bone metastases. RANKL inhibition has been shown to reduce tumor-induced bone destruction and skeletal tumor burden in preclinical models representing numerous tumor types including prostate cancer (Fig. 3).[67–69] In addition, RANKL inhibition has been shown to reduce pain[70] and increase survival[71] in animal models of bone metastases. As would be predicted by an approach targeting the bone microenvironment

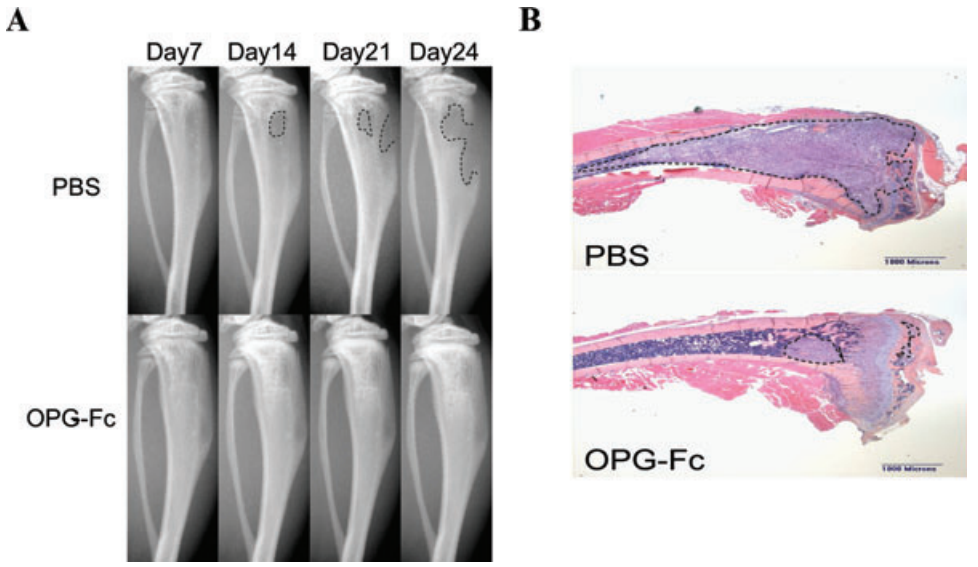

Figure 3. (A) OPG-Fc treatment inhibited progression of PC3 cell-induced osteolytic lesions relative to PBS treated mice. (B) PC3 intratibial tumor burden was decreased in OPG-Fc treated mice. Images from Armstrong *et al.*[68] © 2007 Wiley-Liss, Inc.

and disruption of the vicious cycle, the effects of RANKL inhibition to reduce tumor burden were additive when combined with other pharmacologic agents.[72,73] Through a mechanism distinct from its action in the bone and due rather to the intrinsic expression and function of RANK and RANKL within the mammary epithelium, the RANKL pathway is now known to mediate progestin-dependent mammary epithelial mitogenesis and expansion of mammary stem cells.[74–76] These data suggested the RANKL pathway may also be involved in promoting breast carcinogenesis and metastasis, which is supported by recent data. RANKL inhibition delayed incidence and time to onset of induced and spontaneous breast tumors in mouse models[77,78] and also prevented the metastasis of breast cancer cells to the lungs.[77,79]

Denosumab (120 mg SC Q4W) is approved for the prevention of skeletal-related events (SREs, including pathological fractures, radiation therapy to bone, surgery to bone, and spinal cord compression) in patients with bone metastases from solid tumors.[80] Intravenous bisphosphonates, predominantly zoledronic acid, are effective at reducing SREs. Nevertheless, nearly 40% of patients with advanced solid tumors and bone metastases still experience skeletal complications with zoledronic acid treatment.[81,82] In addition, zoledronic acid has a significant risk of renal toxicity, which can complicate care in cancer patients who are already at risk for renal complications due to underlying disease and critical treatments with nephrotoxic potential (e.g., chemotherapy or antibiotic therapy), and necessitates dose adjustment and continued monitoring of renal function.[83] Further, tolerability of IV zoledronic acid is affected by development of a flu-like syndrome in some patients, particularly after administration of the first dose. Consequently, more effective treatment options with an improved safety profile were needed.

Initially, two dose-ranging studies were conducted to evaluate the ability of denosumab versus zoledronic acid to reduce bone turnover in patients with advanced cancer.[84,85] In one study, patients were naive to bisphosphonate treatment whereas in the other study, patients had received prior treatment but BTM levels remained elevated. In both studies, denosumab reduced levels of the urinary BTM N-telopeptide to a significantly greater extent than zoledronic acid.[84,85]

The ability of denosumab to prevent the skeletal sequelae resulting from bone metastases in patients with advanced cancer was evaluated in three identically designed, randomized, blinded, phase 3 head-to-head studies versus zoledronic acid.[86–88] All patients were recommended to take daily calcium and vitamin D supplements and received standard of care antineoplastic therapies. Denosumab was

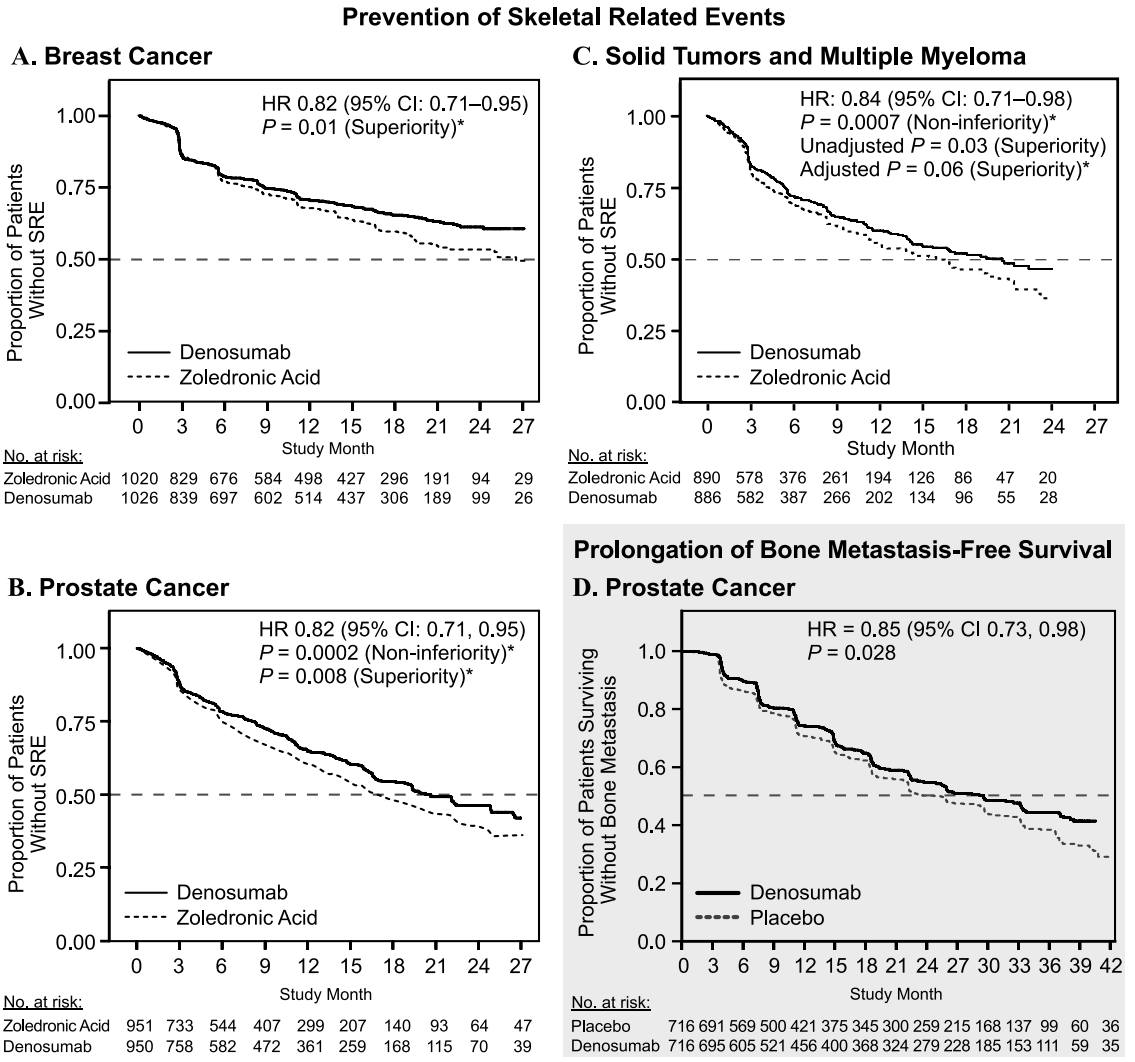

Figure 4. (A–C) Kaplan–Meier estimates showing time to first skeletal-related event for denosumab (120 mg Q4W) versus zoledronic acid in three identically designed phase 3 studies in patients with advanced cancer and bone metastases with the following populations: A, breast cancer, B, prostate cancer, and C, solid tumors (excluding breast or prostate cancer) or multiple myeloma. (D) Kaplan–Meier estimate showing prolongation of bone metastasis free survival for denosumab (120 mg Q4W) versus placebo in men with castrate-resistant prostate cancer without bone metastasis at baseline. *Adjusted for multiplicity. Panel A is reprinted from Stopeck *et al.*[88] Reprinted with permission. © 2010 American Society of Clinical Oncology. Panel B is reprinted from Fizazi *et al.*[86] © 2011, with permission from Elsevier. Panel C is reprinted from Henry *et al.*[87] Reprinted with permission. © 2011 American Society of Clinical Oncology. Panel D is reprinted from Smith *et al.*[61] © 2012, with permission from Elsevier.

superior to zoledronic acid in reducing the risk of a first (HR = 0.83 [95% CI: 0.76 to 0.90]; $P < 0.0001$) and multiple SREs (RR = 0.82 [95% CI: 0.75 to 0.89]; $P < 0.0001$) in a prespecificed combined analysis of data from the three studies.[89] Denosumab was also superior to zoledronic acid in reducing the risk of SREs in the breast cancer (HR = 0.82 [95% CI: 0.71, 0.95]; $P = 0.0101$ for superiority) and prostate cancer (HR = 0.82 [95% CI: 0.71, 0.95]; $P = 0.0085$ for superiority) studies (Fig. 4A and B). In the solid tumor/multiple myeloma study, denosumab was noninferior to zoledronic acid (HR = 0.84 [95% CI: 0.71, 0.98]; $P = 0.0007$ for noninferiority), with a trend toward superiority (Fig. 4C). Among patients with solid tumors in this study, denosumab significantly reduced the risk of first SREs by 19% (HR = 0.81 [95% CI: 0.68, 0.96]; $P < 0.02$).[90] In an ad hoc analysis from this study, denosumab increased

overall survival in patients with non-small-cell lung cancer by 21% (HR = 0.79 [95% CI: 0.65, 0.95])[87] while the hazard ratio for overall survival with denosumab was 2.26 (95% CI: 1.13, 4.50) for multiple myeloma and 1.08 (95% CI: 0.90, 1.30) for other solid tumors.

Adverse events were generally similar between the treatment groups in the SRE trials and the safety profile of denosumab was consistent with its mechanism of action as a potent inhibitor of bone resorption. In the three SRE studies, the incidence of events of hypocalcemia was higher for denosumab than for zoledronic acid (9.6% vs. 5.0%);[89] cases were usually mild to moderate in severity and no deaths related to hypocalcemia occurred. In the voluntary reporting postmarketing setting where adherence to labeled recommendations is unknown, symptoms associated with severe hypocalcemia have been reported with denosumab, including rare fatal cases.[80] In the SRE trials, ONJ was defined as a lesion in the oral cavity of exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found, associated with nonhealing after appropriate care for eight weeks in a patient without prior history of radiation to the head, face, or mouth.[91] Events of ONJ that were adjudicated positively occurred infrequently (1.8% denosumab, 1.3% zoledronic acid) and were usually managed with conservative treatment (e.g., mouthwashes, antibiotics, minimal dental/oral procedures) with resolution in up to 40% of cases in the denosumab group and up to 30% of cases in the zoledronic acid group.[91] Median time to resolution (i.e., complete mucosal coverage of exposed bone) was 8.0 months in the denosumab group and 8.7 months in the zoledronic acid group. In both treatment groups, most patients who had adverse events of ONJ had risk factors such as tooth extraction or oral infections, or systemic treatments with antiangiogenics or corticosteroids.[91] As expected, more patients had adverse events related to impaired kidney function and acute phase reactions in the zoledronic acid group than in the denosumab group.[86–88] No renal monitoring or dose adjustment for renal insufficiency is required with denosumab.

Denosumab in nonmetastatic castration resistant prostate cancer

The ability of denosumab to prevent bone metastases has also been investigated in a phase 3 double-blind, placebo-controlled study in men with nonmetastatic castration resistant prostate cancer.[61] Men in this study were at high risk for developing bone metastases based on their PSA level and/or PSA doubling time. Denosumab increased bone metastasis-free survival by 4.2 months compared with placebo (29.5 months versus 25.2 months; HR = 0.85 [95% CI: 0.73, 0.98]; $P = 0.028$) (Fig. 4D) and delayed the median time to a first bone metastasis by 3.7 months (HR = 0.84 [95% CI: 0.71, 0.98]; $P = 0.032$). Fewer patients in the denosumab group than the placebo group had symptomatic bone metastases (10% vs. 13%, $P = 0.03$). Overall survival was similar between the denosumab and placebo groups.[61] ONJ (5% vs. 0%) and hypocalcemia (2% vs. <1%) occurred with greater frequency with denosumab than with placebo, respectively. As in the SRE trials, ONJ could be managed conservatively (e.g., mouthwashes, antibiotics, minimal dental/oral procedures) in most cases, and 39% of cases resolved during the observation period.[61]

Denosumab in giant cell tumor of bone

Denosumab has also shown a benefit in the treatment of giant cell tumor of bone (GCTB), a rare bone tumor with high expression of RANKL. Currently there are no approved therapeutic agents for GCTB making surgery the only treatment option. In an open-label, single-arm study of adult patients with recurrent or unresectable GCTB, denosumab 120 mg administered every four weeks (with loading doses at days 8 and 15 of the first month) produced a tumor response in 30 of 35 evaluable patients by 25 weeks.[92] Additionally, in a second study of GCTB patients receiving denosumab, 72 of 73 (99%) evaluable patients with surgically unsalvageable disease had no disease progression and 15 of 23 patients (65%) with planned surgery at baseline had no surgery over a 12-month period.[93] Denosumab has shown a favorable tolerability profile and is being further studied in patients with GCTB.

Future directions

With its novel mechanism of action, denosumab offers a significant advance in the treatment of postmenopausal osteoporosis; bone loss associated with hormone ablation therapy in women with breast cancer and men with prostate cancer; and the prevention of SREs in patients with bone metastases from solid tumors by offering clinical benefit to these patients in need. The ability of denosumab

to treat other patient populations and conditions associated with excessive bone resorption or reliant on RANKL signaling continues to be explored. These include male osteoporosis, bone metastasis- and disease-free survival in adjuvant breast cancer, and hypercalcemia of malignancy (HCM). In a preliminary report, denosumab lowered serum calcium levels to normal levels in 12 of 15 patients with HCM who were refractory to IV bisphosphonates.[94] Additional studies in these disease states are ongoing.

Acknowledgments

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Conflict of interest

All authors are employees and shareholders of Amgen Inc.

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