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Responder Analysis of the Effects of Denosumab on Bone Mineral Density in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

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Abstract

Background—Men with prostate cancer are at risk of experiencing accelerated bone loss and fractures as a result of androgen deprivation therapy (ADT).

Objective—We evaluated the effects of denosumab, a fully human monoclonal antibody against RANKL, on preservation of BMD at 3 key skeletal sites (lumbar spine [LS], femoral neck [FN], and total hip [TH]) and the distal radius at 36 months both by responder category and individual responses in a waterfall plot analysis.

Design, Setting, and Participants—This phase 3, randomized, double-blind study of men with non-metastatic prostate cancer receiving ADT investigated the effects of denosumab on bone mineral density (BMD) and fractures. Patients were treated for 36 months.

Intervention—Subcutaneous denosumab 60 mg (n=734) or placebo (n=734) every 6 months for up to 36 months. Patients were instructed to take supplemental Calcium and vitamin D.

Measurements—Primary outcome measure: The percentage change from baseline to month 36 in LS, FN, and TH BMD was measured by dual energy x-ray absorptiometry. BMD at the distal 1/3 radius at 36 months was measured in a sub-study of 309 patients.

Results and Limitations—At 36 months, significantly more patients in the denosumab arm had increases of >3% BMD from baseline at each site studied compared with placebo (LS, 78% vs 17%; TH, 48% vs 6%; FN, 48% vs 13%; distal 1/3 radius, 40% vs 7%). The percentage of denosumab patients with bone loss at all 3 key BMD sites at month 36 was 1%, as opposed to

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42% in placebo arm. At 36 months 69% of denosumab-treated patients had BMD increases at all three sites (LS, TH or FN) compared with 8% of placebo-treated patients. Lower baseline BMD was associated with higher magnitude lumbar spine, femoral neck, and total hip BMD responses to denosumab.

Conclusions—In men with prostate cancer receiving ADT significantly higher BMD response rates were observed with denosumab vs. placebo.

Trial Registration—This study is registered with ClinicalTrials.gov with the identifier NCT00089674.

Keywords

androgen deprivation; bone mineral density; bone loss; antiresorptive therapy; responder analysis

Introduction

In the EU, prostate cancer is the most common malignancy in men with an annual incidence of 0.1% representing nearly one quarter of all cancer diagnoses in this population.[1] Following the adoption of prostate specific antigen (PSA) screening in 1987, the diagnosis of prostate cancer has markedly increased.[2] During 2000–2004 the mortality rate from prostate cancer in the EU was 14.3 per 100,000 men representing 65,000 deaths annually.[3] Androgen deprivation therapy (ADT), using GnRH agonists or bilateral orchiectomy to prevent hormone-dependent growth and metastasis of tumor cells, remains a mainstay of treatment for advanced prostate cancer.[4] A claims sample of US Medicare beneficiaries from 1993–2000 demonstrated an increase in use of ADT from 1.8% to 2.9%.[5] Whether by chemical castration or bilateral orchiectomy, ADT can result in marked bone loss and increased fracture risk.[6, 7] The treatment-induced loss in bone mineral density (BMD) is progressive: up to 4.8% of LS BMD and 3.9% of FN BMD is lost in the first year with an overall BMD loss reaching approximately 7% after two years of GnRH agonist therapy.[8, 9]

Denosumab is an investigational human monoclonal antibody against RANK ligand (RANKL), a key activator of osteoclast formation, function, and survival. Denosumab inhibits osteoclast function and bone resorption.[10] In this phase 3, randomized, double-blind study of men receiving ADT for non-metastatic prostate cancer, denosumab was associated with a 62% reduction in vertebral fractures (adjusted P=0.0125) at 36 months, with marked reduction evident within the first year.[11]. At 24 months in this study, denosumab produced a BMD increase at the lumbar spine of 6.7% compared with placebo (P<0.001); significant differences were also observed at the total hip, femoral neck, and distal 1/3 radius.[11]

Waterfall plots have become increasingly useful in oncology studies to evaluate the magnitude of patients' individual contributions to overall outcomes [12, 13] including PSA and bone turnover marker by prostate cancer treatment outcome.[14, 15] To our knowledge this type of analysis has not been used to demonstrate individual BMD responses. Herein, we report the results of a responder analysis comparing percent change in BMD from baseline between denosumab and placebo across 4 skeletal sites including the proportion of responders and magnitude of response.

Patients and Methods

This randomized, double-blind, placebo-controlled trial evaluated denosumab for treating bone loss in men undergoing androgen-deprivation therapy for nonmetastatic prostate

cancer. Men aged ≥70 years, or <70 years with a history of osteoporotic fracture or a BMD T-score at the lumbar spine, total hip, or femoral neck <−1.0, and who had histologically confirmed prostate cancer, were eligible. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 and to have undergone either bilateral orchiectomy or have begun ADT with a gonadotropin-releasing hormone (GnRH) agonist with therapy expected to continue for at least 12 months.

Men were excluded if they were receiving concurrent anti-neoplastic therapy or radiotherapy, a PSA greater than 5 mg/mL after being on ADT more than 1 month, or a BMD T-score less than −4.0 at lumbar spine, total hip, or femoral neck. Full eligibility criteria have been previously published.[16]

Patients were randomized to denosumab or placebo groups in a double blind fashion using an interactive voice response system (IVRS). Stratification at baseline was by age group (<70 vs ≥70 years old) and duration of ADT (≤6 vs >6 months); and patients were randomly assigned to receive placebo or denosumab 60 mg subcutaneously every 6 months for up to 36 months. All patients were instructed to take supplemental calcium, ≥1 g daily, and either ≥400 IU vitamin D daily (if screening 25[OH] vitamin D was >20 ng/mL) or ≥800 IU vitamin D daily (if screening 25[OH] vitamin D was 12 to 20 ng/mL).

Lumbar spine, total hip, and femoral neck BMD were measured during the 36 month treatment period.[11]. Within a sub-study, 309 patients also underwent BMD measurements at the distal 1/3 radius.

BMD assessments by dual x-ray absorptiometry (DXA) of the lumbar spine, hip (total hip, femoral neck, and trochanter), distal 1/3 radius, and total body were performed on GE Lunar or Hologic bone densitometers at baseline and at months 1, 3, 6, 12, 24, and 36. Men with BMD losses of more than 7% over a 12-month period or with a T-score <−4.0 at the total hip or lumbar spine were evaluated for alternative treatment options.

Statistical Analysis

All randomized patients with available baseline and at least 1 post-baseline measurement of BMD were included in the analysis.

BMD measures were analyzed employing an analysis of covariance (ANCOVA) model using last observation value carried forward (LOCF) imputation with treatment group, baseline BMD value, machine type (Lunar vs. Hologic), the interaction of baseline BMD value and machine type, age group (<70 versus ≥70 year old), and duration of ADT (≤6 versus >6 months) as covariates. Based on DXA scanner precision of 1%, the least significant change (LSC) in BMD at the 95% CL of 3% was chosen as the minimally clinically significant value to define responders in accordance with accepted standards.[17]

Results

Patient demographics and disease characteristics at baseline were well balanced between the two groups as recently described.[16] Briefly, most (83%) patients were white, with a mean age of 75 years, and most (76%) had more than 6 months duration of prior ADT therapy. Sixty-two percent of enrolled patients completed the 36-month study. Withdrawal of consent (18%) was the primary reason for discontinuation and most occurred when patients refused to participate for an additional year in the study when it was extended from 24 to 36 months. The 309 patients enrolled in the sub-study for distal 1/3 radius BMD analysis had baseline demographics and distribution by randomization strata that were qualitatively similar to patients enrolled in the full study.

Denosumab significantly increased BMD at the LS, TH and FN by 7.9%, 5.7%, and 4.9%, respectively, compared with placebo ($p<0.0001$ for each comparison at 36 months).[16] A significantly greater proportion of patients in the denosuamb group had BMD increases >0% at all 3 sites: at 36 months, 69% of denosumab patients vs 8% of placebo patients had gains of any magnitude in BMD at all three key sites ($p<0.0001$). Patients in the denosumab group had marked increases from baseline of >6% BMD at the three key sites: lumbar spine (56% vs 6% placebo), femoral neck (20% vs 4% placebo), and total hip (16% vs 2% placebo) and also had at least moderate gains of >3% BMD (defined as clinically meaningful response) from baseline at the lumbar spine (78% vs 17% placebo), femoral neck (48% vs 13% placebo), and total hip (48% vs 6% placebo; Figure 1). In the sub-study of patients evaluated for change from baseline in BMD at the distal 1/3 radius, 10% of patients in the denosumab group had >6% increases in BMD, compared with 0% of placebo patients ($P<0.0001$; Figure 1). Forty percent of patients receiving denosumab in the radius sub-study had BMD increases of >3% compared with 7% in the placebo group. Overall, at 36 months, 69% of denosumab patients vs 8% of placebo patients had gains of any magnitude in BMD at all three key sites.

Compared with placebo, significantly more patients in the denosumab group had BMD changes >0%: at the lumbar spine in 92% of patients, at the total hip in 87% of patients, at the femoral neck in 79% of patients, and at the distal 1/3 radius in 74% of patients (Figure 1).

BMD responses from individual patients are plotted as waterfall plots in Figure 2 showing the magnitude of individual responses. At 36 months 42% in the placebo group had BMD losses (defined as stable to significant bone loss with ≤0% BMD change) at all three key sites compared with 1% of patients in the denosumab group. At the distal radius a greater number of patients in the placebo group also experienced BMD losses compared with the denosumab group (75% vs 26%). BMD losses in the placebo group were greater in magnitude overall than losses experienced by patients receiving denosumab. Similarly, patients in the denosumab group overall had a greater magnitude of BMD gains.

We also examined the magnitude of BMD responses by different baseline strata. In the denosumab group the magnitude of response was dependent on the degree of osteopenia at baseline. In general, patients with lower baseline T-scores had greater BMD responses at all three key sites (Figure 3a). The association between low baseline T-score and BMD response was significant at the lumbar spine and total hip. In the placebo group, baseline T-scores were not correlated with BMD responses (Figure 3b).

Adverse events reported in this study have been described elsewhere.[18] Briefly, 87% of patients in each group experienced at least one adverse event; the most common events were arthralgia, back pain, and constipation. Treatment-related adverse events were reported for 0.4% of patients in the denosumab group and 0.6% of patients in the placebo group. No treatment-related serious adverse event was reported for more than 1 patient in either group.

Discussion

In this study of men undergoing ADT for nonmetastatic prostate cancer denosumab significantly improved BMD at the lumbar spine, total hip, femoral neck, and distal radius compared with placebo at 12, 24, and 36 months of treatment. The current responder analysis revealed that substantially higher proportions of patients treated with denosumab experienced gains in BMD at various body sites tested as compared to patients treated with placebo. The proportion of patients receiving placebo who experienced losses in BMD was substantial and significantly higher compared with denosumab despite daily calcium and

vitamin D supplementation in both study arms. This indicates that, while necessary, these supplements alone were not sufficient to prevent bone loss for most men in this at-risk population.

Clinically significant BMD improvements obtained at 12 months were maintained over the 36-month course of the study. The 12-month changes in BMD were comparable to those seen in a separate study by Greenspan et al of men with nonmetastatic prostate cancer given weekly oral alendronate treatment for one year resulting in a difference of 5.1% at the posterior-anterior spine compared with placebo.[19]

The BMD gains achieved by patients in this study were similar to those observed with the same denosumab regimen in other populations. In postmenopausal women with low BMD, treated with denosumab 60 mg every 6 months, comparable BMD improvements were reported after 24 months at the lumbar spine (7.0%), total hip (4.5%), and femoral neck (3.7%) relative to placebo.[20] Similarly, in a study of postmenopausal women receiving aromatase inhibitors for early stage breast cancer, a 7.6% gain in BMD at the lumbar spine relative to placebo was achieved after 24 months of denosumab treatment.[21] These responses, which exceed the predefined LSC of 3%, represent BMD gains that are likely to have impact on fracture outcomes.[22]

Individual patient data (Figure 2, **part D**) demonstrates that overall, placebo-treated patients had greater magnitudes of bone loss at the radius than at other skeletal sites with 75% of this group losing bone at this site. The denosumab group achieved a 6.9% increase in BMD at the distal 1/3 radius relative to placebo at 36 months with 74% of patients experiencing BMD gains. At 24 months BMD gains at the radius were greater (5.5%) than those observed in studies of denosumab in postmenopausal women with osteopenia at 24 months (3.5%) [20], and comparable to gains seen in women with non-metastatic breast cancer receiving aromatase inhibitors (6.1%).[21] Reversal of bone loss at the radius, composed of primarily cortical bone, has not previously been reported in patients with prostate cancer treated with bisphosphonates. In the Greenspan study patients receiving oral alendronate had a BMD loss of 0.9% from baseline at the radius, while placebo patients lost twice as much.[19]

The analysis of BMD response by baseline T-score suggests an augmented treatment benefit may be obtained in patients with lower baseline BMD, ie, in those patients who would be expected to benefit most from interventional measures to reduce fracture risk.

To our knowledge this represents the first such responder analysis for antiresorptives by skeletal site. In men receiving ADT, the risk of any fracture is increased [23] and BMD gains at key skeletal sites should translate into reduced fracture risk. Hip BMD has been suggested to be of paramount importance for prediction of hip and nonvertebral fractures in men [24] while spine BMD alone may be more critical in predicting vertebral fractures in women.[25] In this study, denosumab produced robust improvements in BMD at all skeletal sites tested, including the distal 1/3 radius, whereas in the aforementioned Greenspan study patients receiving oral alendronate had a 0.9% loss of BMD from baseline at the radius.[19] While there is unequivocal data to show that BMD improvements lead to reductions in fractures, the identification of skeletal sites most predictive of individual fracture types is still open to debate.

In summary, for men undergoing ADT for non-metastatic hormone-sensitive prostate cancer, a substantial proportion of patients experience bone loss despite calcium and vitamin D supplementation. Denosumab increased BMD at all measured sites compared to placebo. Moreover, for the overwhelming majority of men, denosumab not only prevented ADT-associated bone loss but improved bone density in a clinically meaningful way. Most

importantly, as previously reported, these changes in BMD were reflected in the statistically significant reduction of vertebral fractures in men treated with denosumab.

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References

1. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in europe in 2008. European Journal of Cancer. 2010; 46:765–81. [PubMed: 20116997]
2. Brawley OW. Prostate carcinoma incidence and patient mortality: The effects of screening and early detection. Cancer. 1997; 80:1857–63. [PubMed: 9351560]
3. La Vecchia C, Bosetti C, Lucchini F, Bertuccio P, Negri E, Boyle P, et al. Cancer mortality in europe, 2000–2004, and an overview of trends since 1975. Annals of Oncology. 2009
4. Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP, et al. Eau guidelines on prostate cancer. Eur Urol. 2008; 53:68–80. [PubMed: 17920184]
5. Barry MJ, Delorenzo MA, Walker-Corkery ES, Lucas FL, Wennberg DC. The rising prevalence of androgen deprivation among older american men since the advent of prostate-specific antigen testing: A population-based cohort study. BJU International. 2006; 98:973–8. [PubMed: 16879443]
6. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. 2005; 352:154–64. [PubMed: 15647578]

7. Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med. 2001; 345:948–55. [PubMed: 11575286]
8. Morote J, Orsola A, Abascal JM, Planas J, Trilla E, Raventos CX, et al. Bone mineral density changes in patients with prostate cancer during the first 2 years of androgen suppression. Journal of Urology. 2006; 175:1679–83. discussion 83. [PubMed: 16600728]
9. Maillefert JF, Sibilia J, Michel F, Saussine C, Javier RM, Tavernier C. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. Journal of Urology. 1999; 161:1219–22. [PubMed: 10081873]
10. Lacey DL, Timms E, Tan HL, Kelley MJ, Dunstan CR, Burgess T, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell. 1998; 93:165–76. [PubMed: 9568710]
11. Smith MR, Egerdie B, Hernandez Toriz N, Feldman R, Tammela TL, Saad F, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer [see comment]. New England Journal of Medicine. 2009; 361:745–55. [PubMed: 19671656]
12. Siegel AB, Cohen EI, Ocean A, Lehrer D, Goldenberg A, Knox JJ, et al. Phase ii trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. Journal of Clinical Oncology. 2008; 26:2992–8. [PubMed: 18565886]
13. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, et al. Phase ii placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma [see comment]. Journal of Clinical Oncology. 2006; 24:2505–12. [PubMed: 16636341]
14. Yu EY, Wilding G, Posadas E, Gross M, Culine S, Massard C, et al. Phase ii study of dasatinib in patients with metastatic castration-resistant prostate cancer. Clin Cancer Res. 2009; 15:7421–8. [PubMed: 19920114]
15. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the prostate cancer clinical trials working group. Journal of Clinical Oncology. 1148; 26:1148–59. [PubMed: 18309951]
16. Smith MR, Saad F, Egerdie B, Szwedowski M, Tammela TL, Ke C, et al. Effects of denosumab on bone mineral density in men receiving androgen deprivation therapy for prostate cancer. Journal of Urology. 2009; 182:2670–75. [PubMed: 19836774]
17. Bonnick SL, Johnston CC Jr, Kleerekoper M, Lindsay R, Miller P, Sherwood L, et al. Importance of precision in bone density measurements. Journal of Clinical Densitometry. 2001; 4:105–10. [PubMed: 11477303]
18. Egerdie, B.; Saad, F.; Smith, MR.; Tammela, TLJ.; Heracek, J.; Ke, C., et al. A responder analysis of the effects of denosumab on bone mineral density in men with prostate cancer receiving androgen deprivation therapy. Poster presented at the 2009 American Urological Association Meeting; Chicago, Illinois. April 28, 2009;
19. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: A randomized trial. Ann Intern Med. 2007; 146:416–24. [PubMed: 17371886]
20. Bone HG, Bolognese MA, Yuen CK, Kendler DL, Wang H, Liu Y, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab. 2008; 93:2149–57. [PubMed: 18381571]
21. Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for non-metastatic breast cancer. J Clin Oncol. 2008; 26:4875–82. [PubMed: 18725648]
22. Sebba AI. Significance of a decline in bone mineral density while receiving oral bisphosphonate treatment.[erratum appears in clin ther. 2008 jun;30(6):1177–8]. Clinical Therapeutics. 2008; 30:443–52. [PubMed: 18405784]
23. Smith MR, Boyce SP, Moyneur E, Duh MS, Raut MK, Brandman J. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. Journal of Urology. 2006; 175:136–9. discussion 39. [PubMed: 16406890]

24. Cummings SR, Cawthon PM, Ensrud KE, Cauley JA, Fink HA, Orwoll ES. Bmd and risk of hip and nonvertebral fractures in older men: A prospective study and comparison with older women. Journal of Bone and Mineral Research. 2006; 21:1550–56. [PubMed: 16995809]

25. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996; 312:1254–9. [PubMed: 8634613]

Take Home Message

Denosumab, a fully human monoclonal antibody against RANK ligand, significantly increased bone mineral density compared with placebo in men with non-metastatic prostate cancer. Lower baseline BMD was associated with higher magnitude lumbar spine, femoral neck, and total hip BMD responses to denosumab.

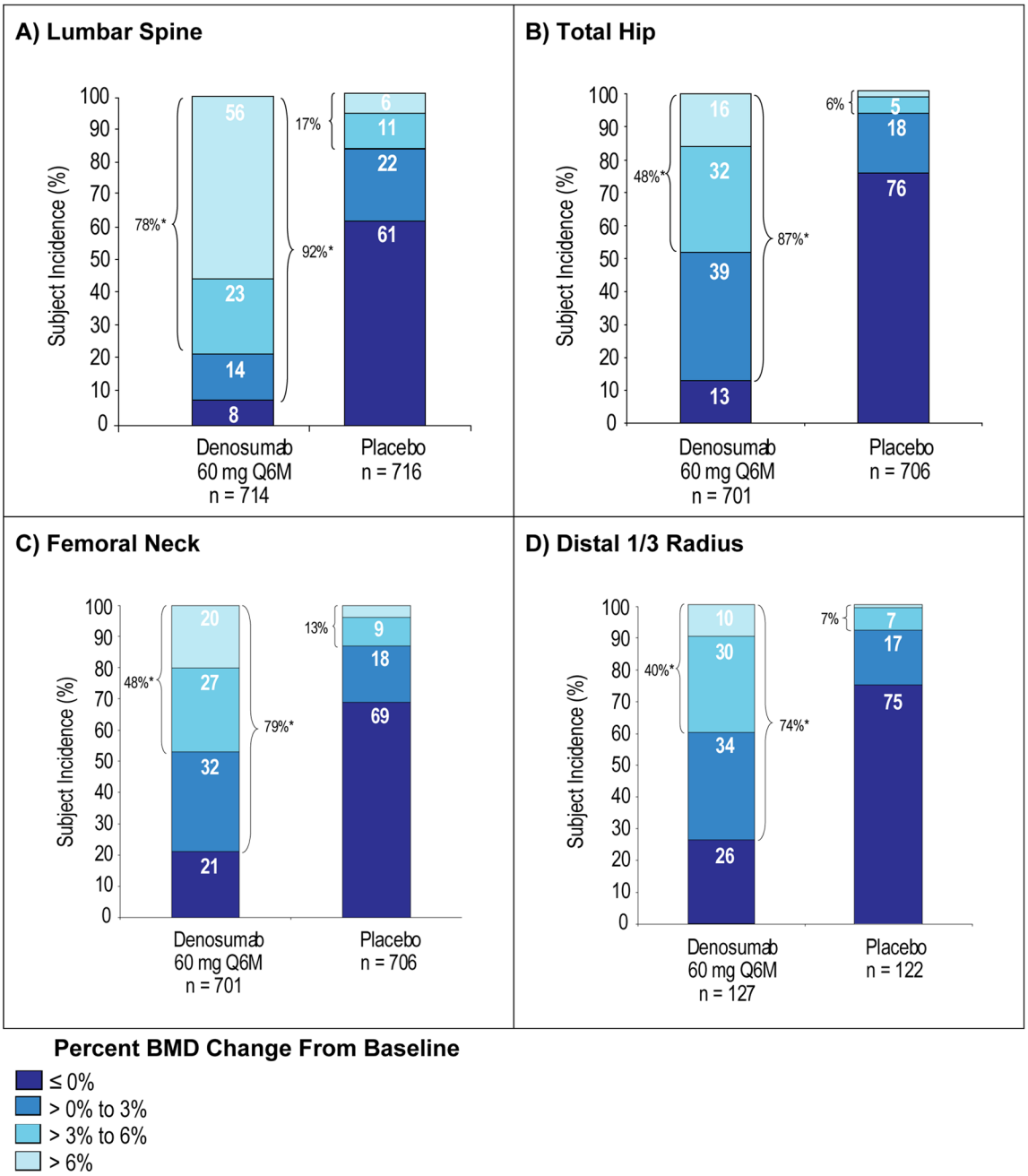

Figure 1. Responder Analysis: BMD Percent Change from Baseline at 36 Months

* $p < 0.0001$ vs placebo

n = number of patients evaluated

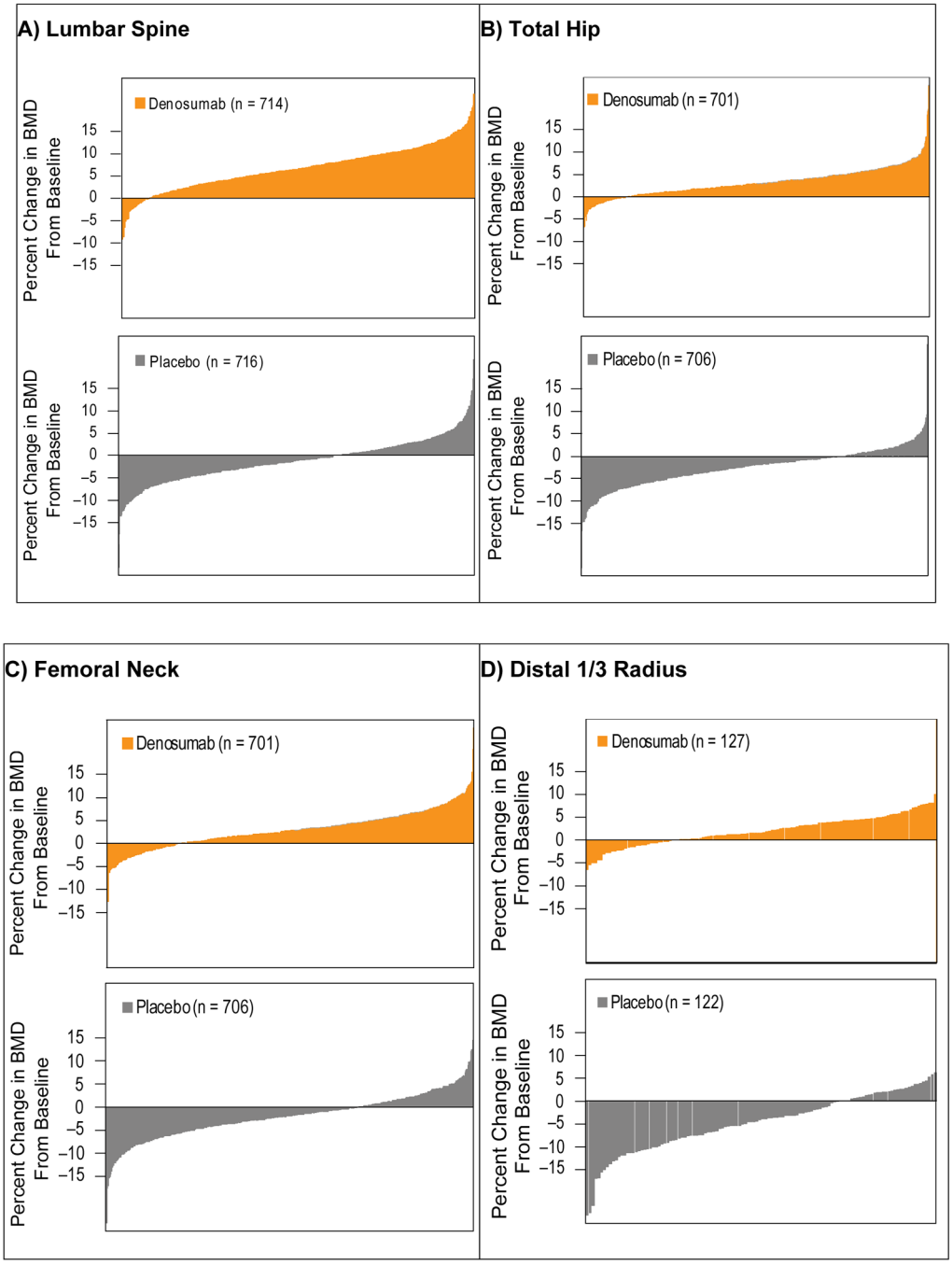

Figure 2.
Waterfall Analysis: Individual Percent Changes in BMD from Baseline at 36 Months

Figure 3a.

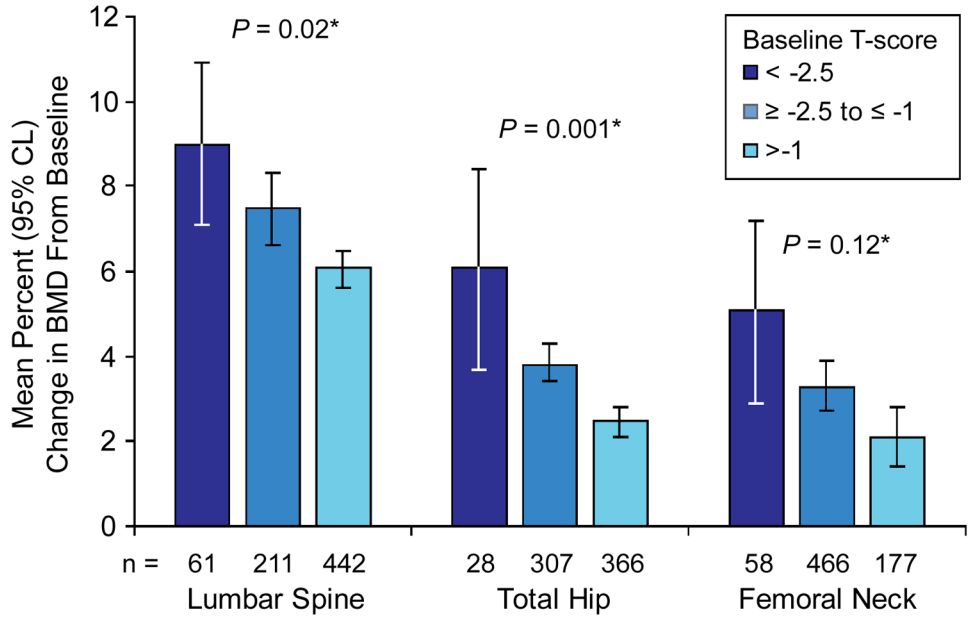

Figure 3b.

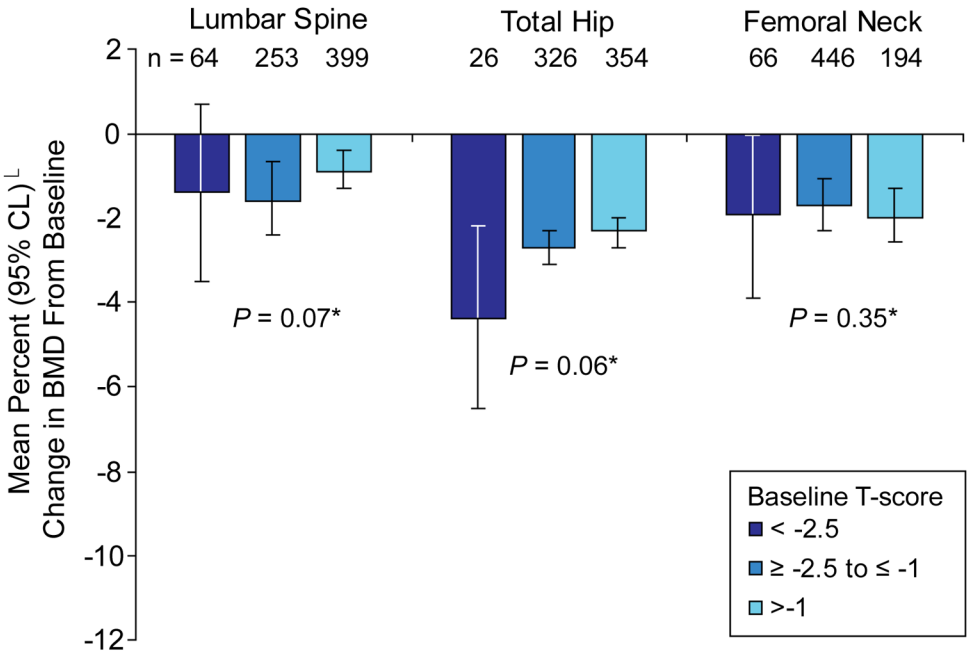

Figure 3.

Figure 3a. Mean change in BMD response in the denosumab group at 36 mo
*Within-group ANCOVA test for heterogeneity
Figure 3b. Mean change in BMD response in the placebo group
*Within-group ANCOVA test for heterogeneity