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Denosumab and Changes in Bone Turnover Markers During Androgen Deprivation Therapy for Prostate Cancer

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Abstract

Androgen deprivation therapy (ADT) for prostate cancer increases fracture risk, decreases bone mineral density, and increases bone turnover markers (BTMs) including serum type 1 C-telopeptide (sCTX), tartrate-resistant alkaline phosphatase 5b (TRAP-5b), and procollagen-1 N-terminal telopeptide (P1NP). In a pre-specified exploratory analysis of a phase 3, multicenter, double-blind study, we evaluated the effects of denosumab (60 mg subcutaneously every 6 months for 3 years) vs. placebo (1468 patients, 734 in each group) on BTM values. BTMs were measured at baseline, month 1, and pre-dose at months 6, 12, 24, and 36 in the overall population. BTMs at month 1 are also reported for subgroups based on age (<70 years vs. ≥ 70 years), prior duration of ADT (≤6 months vs. >6 months), and baseline BTM (≤ median vs. >median BTM values). Treatment with denosumab provided a rapid and sustained decrease of BTM values compared with placebo. The median change in sCTX levels at month 1 was −90% in the denosumab group and −3% in the placebo group (p <.0001). The median change in TRAP-5b levels at month 1 was −55% in the denosumab group and −3% in the placebo group (p <.0001). The maximal median change in P1NP was −64% in the denosumab group and −11% in the placebo group, (p <.0001). Significantly greater decreases in BTM for denosumab were also seen in subgroup analyses based on age, prior ADT treatment, and baseline BTM values. Suppression of bone turnover markers was consistent with marked increases in bone mineral density reported previously.

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Conflict of Interest Statement:
MRS has served as a consultant to Amgen.
FS is an investigator in this study and is a consultant and advisory board member, for Amgen, Novartis, and Sanofi Aventis
BE is an investigator in this study and is a consultant, advisory board member, and speaker for Amgen, Bayer, and Pfizer.
PS is an investigator in this study and a consultant and advisory board member for Amgen.
TLJT is an investigator in this study and is a consultant, advisory board member, and/or speaker for Amgen, Orion Pharma, AstraZeneca, Sanofi-Aventis, Astellas and GSK.
BZL is a consultant for Amgen and has received research funding from Amgen and Lilly.
CK and CG are employees of Amgen Inc. and have received Amgen stock/stock options.

Keywords

(5) denosumab; androgen deprivation therapy; bone turnover markers; prostate cancer

INTRODUCTION

In men with prostate cancer, androgen deprivation therapy (ADT) decreases bone mineral density (BMD) and increases the risk of clinical fractures.[1, 2] Treatment-related bone loss is accompanied by an increase in the markers of bone resorption (eg, serum concentration of type 1 C-telopeptide [sCTX]), tartrate-resistant alkaline phosphatase 5b [TRAP-5b]), and bone formation (eg, intact N-terminal propeptide of type I procollagen (P1NP).[3, 4] Significant evidence of bone resorption, as indicated by increases in sCTX and TRAP-5b, was reported in men with prostate cancer receiving ADT for 35 months.[5] In normal men receiving a GnRH agonist, P1NP levels initially decreased, but then increased at 12 weeks of treatment.[6] Current therapies for treatment-induced bone loss in men with early-stage prostate cancer include bisphosphonates such as intravenous zoledronic acid and oral alendronate, although none are approved for that indication.[7,8]

Denosumab is a fully human monoclonal antibody against RANK ligand (RANKL), a key activator of osteoclast formation, function, and survival. By binding and inactivating RANKL, denosumab inhibits osteoclast function and bone resorption. In two phase 2 studies of patients with breast cancer, prostate cancer, or other solid tumors and bone metastases, patients treated with denosumab every 4 weeks experienced a rapid reduction of the bone turnover markers (BTMs) sCTX, TRAP-5b, and P1NP, which was sustained over the 25 weeks of the studies.[9] Denosumab also suppressed bone turnover, indicated by decreased levels of sCTX and P1NP over 36 months, in a phase 3 study of denosumab administered every 6 months to postmenopausal women with osteoporosis.[10]

While elevated BTMs are associated with increased risk for skeletal complications in men with advanced prostate cancer,[11] a prognostic role for BTMs in men with early stage prostate cancer treated with ADT has yet to be established.[12] Among these men, those who are older and those with a longer duration of hormonal treatment have been shown to have a greater risk for skeletal events.[2, 13] While early decreases in BTMs have been shown to predict long term BMD responses to bisphosphonate therapy among women with osteoporosis,[14] similar data are lacking in men with early stage prostate cancer.

In a phase 3, randomized, double-blind study of men who were receiving ADT for non-metastatic prostate cancer, denosumab significantly increased BMD at all measured sites and significantly reduced new vertebral fractures by 62% over 3 years.[15] Adverse events in this study were representative of the study population and balanced between the study arms.[15] In this report, we describe results from a protocol-specified exploratory analysis of longitudinal changes in BTMs in the phase 3 clinical trial. In order to assess therapy outcomes using potentially predictive baseline demographic and clinical variables, the analysis includes results for the overall study population as well as subgroup analyses based on baseline age, duration of prior ADT, and baseline BTM values. Additionally, we performed a correlative analysis of lumbar spine and total hip BMD responses at 36 months with BTM measurements at 6 months was undertaken.

MATERIALS AND METHODS

Study Design

This was an international, multicenter, randomized, double-blind, placebo-controlled study. The study was conducted in accord with the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice. Complete eligibility criteria have been reported previously.[15] Briefly, eligible patients were men with histologically confirmed prostate cancer. They were aged ≥70 years old, or if <70 years of age, had a history of osteoporotic fracture or a BMD *T*-score <−1.0 at the lumbar spine, total hip, or femoral neck. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; had undergone bilateral orchiectomy or had initiated luteinizing hormone-releasing hormone (LHRH) treatment and were expected to continue therapy for ≥12 months. Patients with other concurrent anti-neoplastic therapy or radiotherapy; prostate specific antigen [PSA] >5 mg/mL after being on ADT for >1 month; or BMD *T*-score <−4.0 at the lumbar spine, total hip, or femoral neck were excluded.

Patients were stratified at baseline by age group (<70 vs ≥70 years old) and duration of ADT (≤6 vs >6 months) and were randomly assigned to receive placebo or denosumab 60 mg subcutaneously every 6 months for 36 months. All patients were advised to take ≥ 1000 mg supplemental calcium and ≥ 400 IU vitamin D daily. The primary endpoint of the study was the percentage change in lumbar spine BMD from baseline to month 24; results have been reported.[15] This report describes results for a pre-specified exploratory endpoint: the percentage change from baseline in the bone turnover markers sCTX, TRAP-5b, and P1NP at months 1, 6, 12, 24, and 36. It also describes the results of an ad hoc analysis evaluating the relationship between changes in these bone turnover markers at 6 months and changes in BMD at 36 months.

Laboratory Analyses

Bone turnover markers were assessed by a central laboratory at Amgen, Inc. (sCTX) or a specialty laboratory (P1NP, TRAP-5b: Covance Laboratories, Chantilly, VA.) sCTX was evaluated using the Serum CrossLaps® enzyme-linked immunosorbent assay (ELISA, Nordic Bioscience Diagnostics A/S, Denmark; interassay coefficient of variation [CV] = 4% to 12%). P1NP assessments used the P1NP RIA kit (Orion Diagnostica, Finland; CV = 9% to 18%). The BoneTRAP® Assay Kit (IDS, Inc., UK; CV = 9% to 13%) was used for TRAP 5b assessments.

Statistical Analysis

The analyses of bone turnover markers included all patients who were randomized and for whom baseline and at least one post-baseline measurement of the endpoint of interest were available. Fasting values for sCTX, TRAP-5b, and P1NP were measured at baseline and 1 month post-dose, and pre-dose (trough level) at months 6, 12, 24, and 36. The limits of quantification for sCTX, TRAP-5b, and P1NP were 0.049 ng/mL, 1.3 U/L, and 10 μg/L respectively. Subgroup analyses evaluated bone turnover marker response at 1, 6, 12, 24, and 36 months according to age (<70 years vs. ≥ 70 years), prior duration of ADT (≤ 6 months vs. >6 months), and baseline marker values (≤ median vs. >median). The van Elteren stratified rank test[16] was used to compare treatment groups for percent change in bone turnover markers, using the stratification variables of age group and duration of ADT or time since orchiectomy at study entry. Spearman correlation coefficients were calculated to evaluate the relationship between changes in BTM values at 6 months (sCTX, TRAP-5b, and P1NP) with changes in BMD at 36 months for the lumbar spine and total hip.

RESULTS

A total of 1468 men receiving ADT for nonmetastatic prostate cancer were assigned randomly to denosumab (n=734) or placebo (n=734).[15] Sixty-two percent of patients (64% denosumab, 61% placebo) completed the 36-month study. The most frequently cited reason for discontinuation was withdrawal of consent (17% denosumab, 19% placebo), most of which occurred when patients declined to consent to an additional year in the study when it was extended from 24 to 36 months in a protocol amendment.

As described previously,[15] baseline demographic and disease characteristics were well balanced between the two groups. Mean age was 75 years; 83% in each treatment group were aged ≥ 70 years. Most men were white had received ADT for >6 months at study entry (median 20.4 months denosumab and 20.8 months placebo). Baseline BTMs for both treatment groups are summarized in Table 1.

Changes in Bone Turnover Markers in the Overall Study Population

In this population of men receiving ADT for nonmetastatic prostate cancer, denosumab treatment resulted in a rapid, sustained decrease of BTMs over time that was statistically significant compared with placebo for all markers. The median (Q1, Q3) change in sCTX at month 1 was −90% (−93%, −85%) in the denosumab group, compared with −3% (−21%, +19%) in the placebo group (p <.0001; Figure 1). At the end of the first dosing interval at 6 months, statistically significant suppression of sCTx continued, with median (Q1, Q3) changes in sCTX of −65% (−80%, −42%) for the denosumab group and −7% (−27%, +31%) for the placebo group. Significantly greater suppression of sCTX in the denosumab group than in the placebo group continued through the end of the last dosing interval at month 36 (p <.0001; Figure 1).

The median (Q1, Q3) change in TRAP-5b at month 1 was −55% (−63%, −45%) in the denosumab group and −3% (−12%, +6%) in the placebo group (p <.0001; Figure 2). As with sCTX, suppression of TRAP-5b continued through month 36 to a statistically significantly greater degree in the denosumab group than in the placebo group (P < .0001; Figure 2.)

Median (Q1, Q3) change in P1NP after 1 month of treatment was −27% (−36%, −15%) in the denosumab group, compared with a median change of 1% (−9%, +14%) in the placebo group (p <.0001; Figure 3). Maximal median suppression of P1NP was observed at month 12 and maintained to a statistically significant degree through month 36 (Figure 3).

Changes in Bone Turnover Markers in Patient Subgroups

At 1 month following the first dose, denosumab consistently reduced bone turnover markers across all subgroups studied, including subgroups based on age (Figure 4), prior duration of ADT (Figure 5), and bone turnover marker levels at baseline (Figure 6). Compared with placebo, these differences were statistically significant for all bone turnover markers and all subgroups (p <.0001). Similar statistically significant consistency of treatment effect was observed across all subgroups at 6, 12, 24, and 36 months (data not shown).

Changes in Bone Turnover Markers Related to Changes in BMD

Changes in BTMs at 6 months were associated with changes in BMD at 36 months. In general, correlations between BTM decreases and gains in BMD were stronger in the denosumab group compared with the placebo group (Table 2).

DISCUSSION

In this recently reported phase 3, randomized, double-blind study of men who were receiving ADT for non-metastatic prostate cancer, denosumab significantly increased BMD at all measured sites and significantly reduced new vertebral fractures.[15] In the current prespecified analysis of data from that study, denosumab induced rapid inhibition of bone turnover over time, with significant decreases in sCTX, TRAP-5b, and PINP evident at 1 month and thereafter. The consistency of the anti-resorptive effect is reflected by the narrow interquartile range around the 1-month bone resorption marker levels and indicates high pharmacodynamic response rates across patients (Figures 1 and 2). The rapid and substantial inhibition of bone turnover is consistent with the significant increases in BMD at all skeletal sites observed after 1 month of therapy–the earliest measured timepoint in the study. Reductions in BTMs at 6 months were also associated with BMD gains at the lumbar spine and total hip at 36 months (Table 2). Suppression of bone turnover was sustained throughout the 36 months study; this finding is also consistent with the continued gains in BMD at all measured time points.

sCTX and TRAP-5b decreased sharply from baseline to month 1 and then increased slightly at later timepoints. Peak marker inhibition at this early timepoint may reflect timing of measurements relative to drug dosing. The month 1 measurement was taken approximately 30 days after the first denosumab dose in an every-6-month dosing regimen, while the measurements at months 6, 12, 24, and 36 reflected trough levels of denosumab, measured at the end of the 6-month dosing cycle. Because BTMs were not evaluated between subsequent treatment cycles, we cannot determine whether each denosumab treatment resulted in similar sharp decreases in BTMs. Nevertheless, these findings suggest that the effects of denosumab on bone are reversible.[17]

In men receiving ADT for prostate cancer, two prior studies reported older age and longer ADT duration are associated with greater risk of clinical fractures.[2, 13] However, the effects on BTMs for these subgroups were not reported. In the current analyses, denosumab significantly decreased BTMs in all subgroups including men aged 70 years or older, men with an ADT duration at baseline longer than 6 months, and men with higher baseline BTM values (Figures 4–6). The significant treatment effects observed in each of these subgroups suggests that denosumab is effective in men at greatest risk for fracture. These results are congruent with previous findings that denosumab consistently increased BMD at all measured skeletal sites and all subgroups regardless of age, ADT duration, or baseline levels of BTMs.[15]

RANKL is essential for osteoclast formation, function, and survival. RANKL expression is increased in high bone turnover states. By binding to RANKL and thereby inhibiting osteoclast activity, denosumab significantly decreased bone turnover, as indicated by decreased levels of sCTX, TRAP-5b, and P1NP. Although marked inhibition was observed regardless of baseline levels of bone turnover and the differences between subgroups were small, the median decreases in BTM were greatest for subjects with the highest BTM values at baseline. These observations highlight the important role of RANKL in regulating osteoclast activity and the efficacy of RANKL inhibition in decreasing bone turnover, even in high bone turnover states.

Because patients were excluded from this study if they had received either 3 years continuous treatment with oral bisphosphonates or IV bisphosphonates within 5 years prior to enrollment, we were unable to assess the effect of prior antiresorptive therapy on subsequent BTM responses to denosumab. Although both bisphosphonates and denosumab have been shown to decrease BTMs and increase BMD in prostate cancer patients,[8,18,19]

denosumab has a distinct mechanism of action. In contrast to bisphosphonates, which accumulate in bone where they inhibit osteoclast recruitment, function, and survival,[20] denosumab prevents the formation, maturation, and survival of osteoclasts.[21] The recent comparison of results from two phase 2 studies suggested a potential treatment difference based on previous bisphosphonate exposure.[9] Responses to treatment among women with metastatic breast cancer who had no previous IV bisphosphonate treatment were compared with patients with advanced solid tumors or multiple myeloma who had elevated levels of the bone turnover marker urinary N-telopeptide at study entry despite at least 8 weeks of previous IV bisphosphonate treatment. Although both denosumab and zoledronic acid produced reductions in bone turnover, in patients who had been previously treated with bisphosphonates, suppression of TRAP-5b at study week 25 was substantially greater with denosumab than with zoledronic acid (73% vs 11%). This difference suggests that in some patients, osteoclast function can persist despite bisphosphonate treatment, and that identification of these patients through BTM assessment early in therapy could lead to improved treatment outcomes.

Conclusion

In men receiving ADT for nonmetastatic prostate cancer, denosumab resulted in a rapid and sustained decrease of BTMs, including the bone resorption markers sCTX and TRAP-5b and the bone formation marker P1NP, compared with placebo. The rapid and sustained suppression of BTMs was consistent with previously reported increases in BMD and reduction in new fractures in this population. Denosumab may provide a new therapeutic option to prevent fractures in men receiving ADT for prostate cancer.

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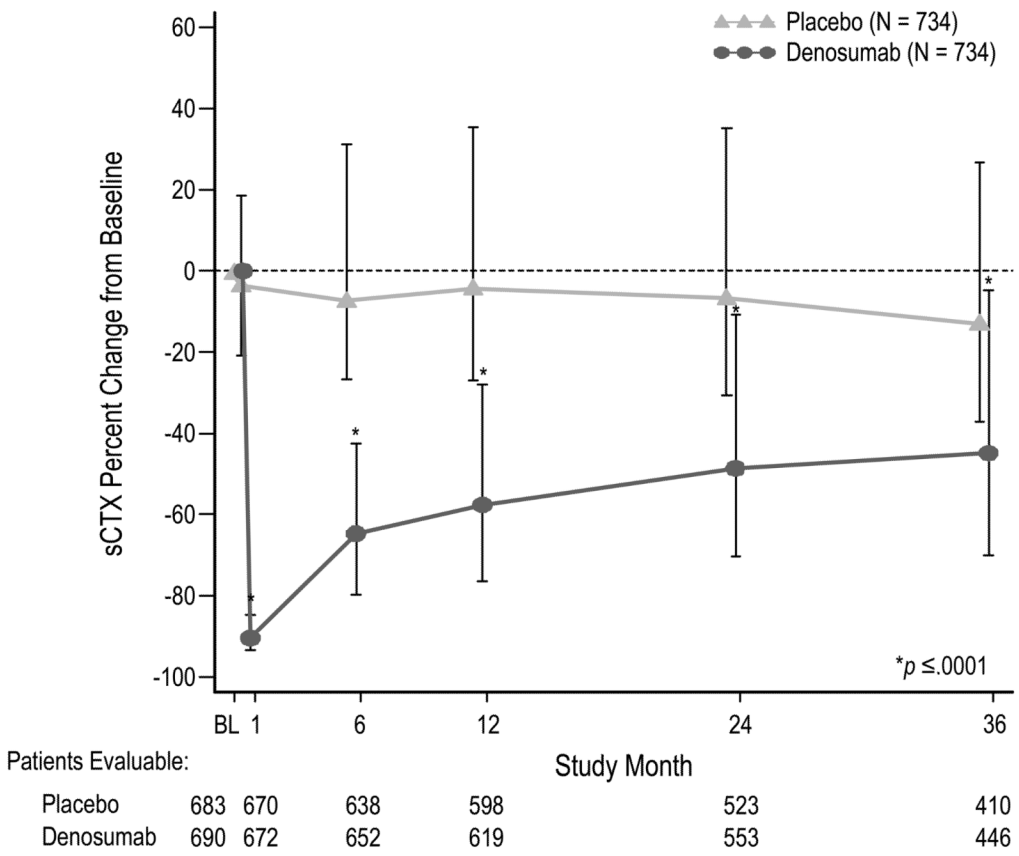

Figure 1.

Median percent change in sCTX values from baseline by study month. Measurements at months 6, 12, 24, and 36 were obtained pre-dose. N=number of subjects randomized; Q1: first quartile; Q3: third quartile; BL: baseline.

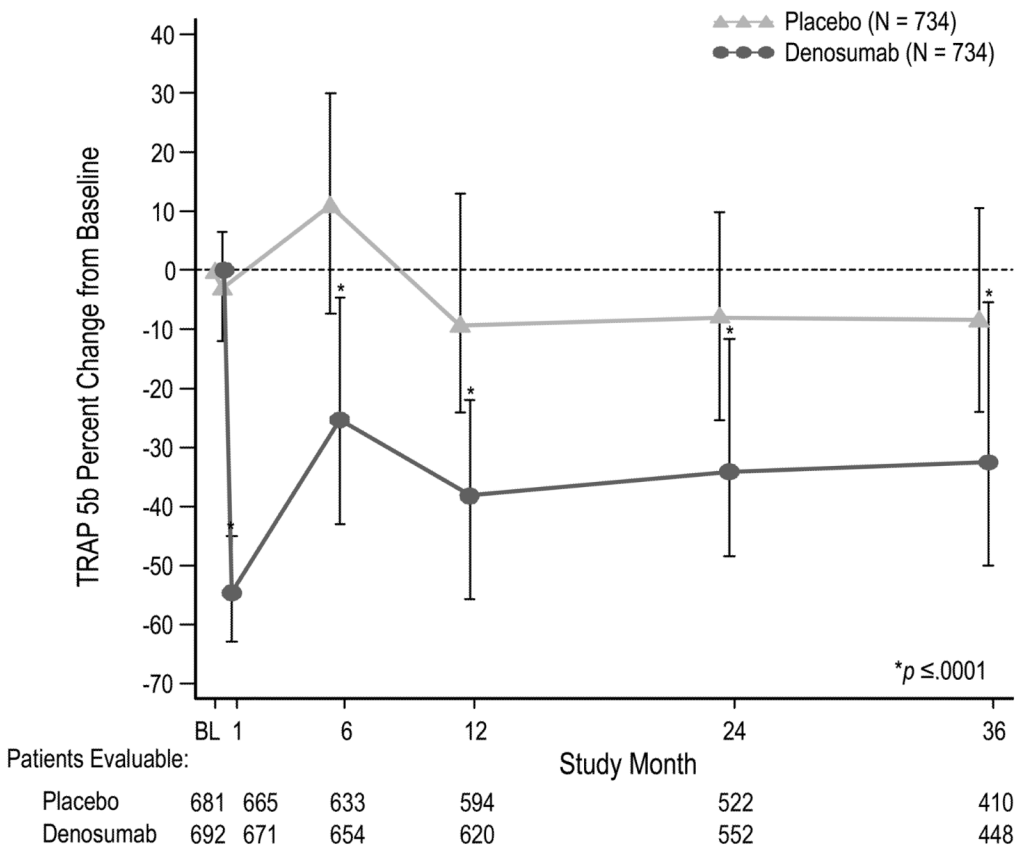

Figure 2.

Median percent change in TRAP-5b values from baseline by study month. Measurements at months 6, 12, 24, and 36 were obtained pre-dose. N=number of subjects randomized; Q1: first quartile; Q3: third quartile; BL: baseline.

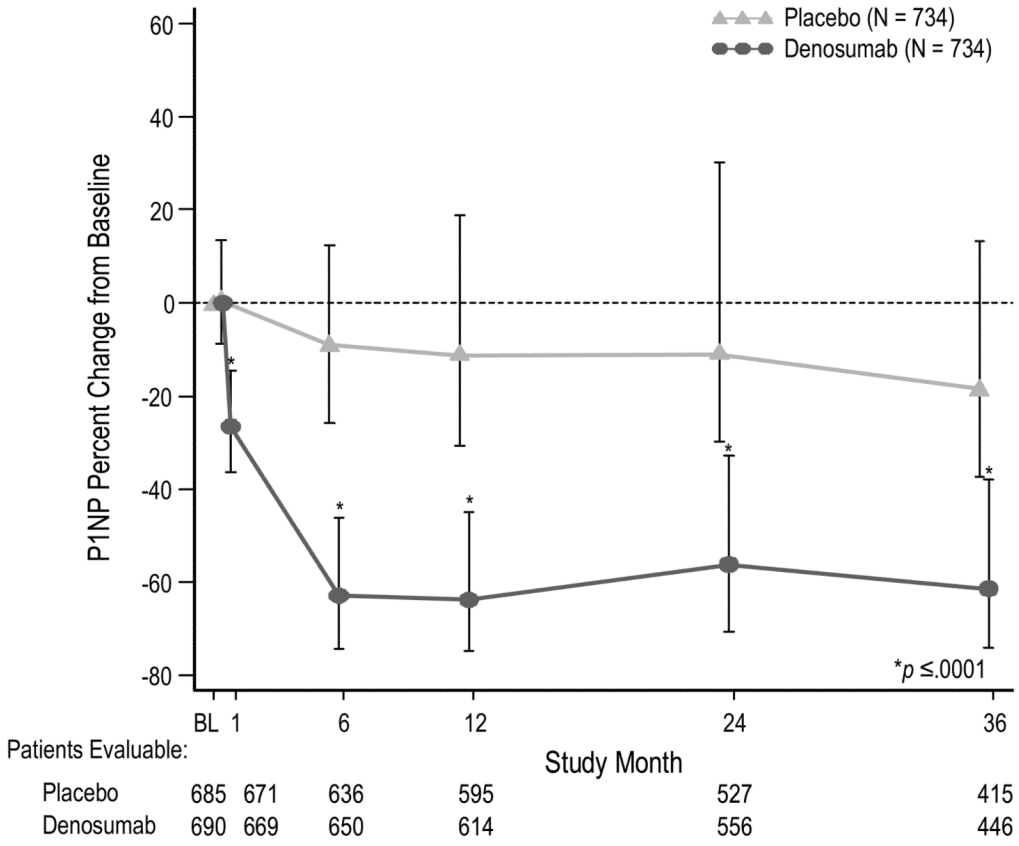

Figure 3.

Median percent change in P1NP values from baseline by study month. Measurements at months 6, 12, 24, and 36 were obtained pre-dose. N=number of subjects randomized; Q1: first quartile; Q3: third quartile; BL: baseline.

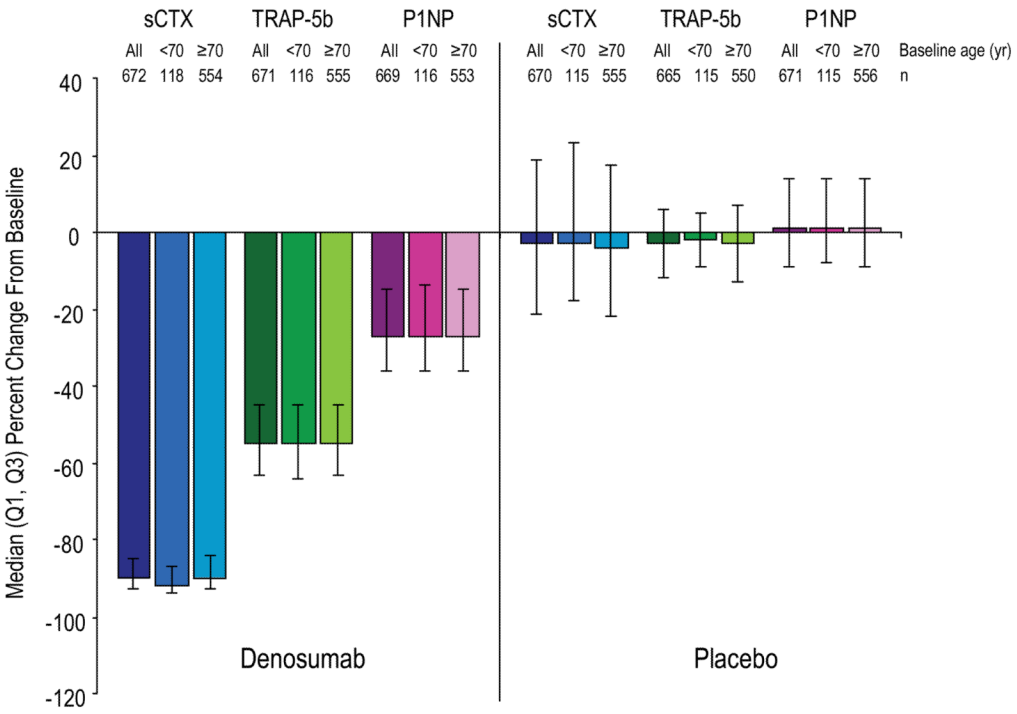

Figure 4.

Median BTM percent change at 1 month in patients aged <70 years and ≥ 70 years at baseline. n=number of patients with observed data.

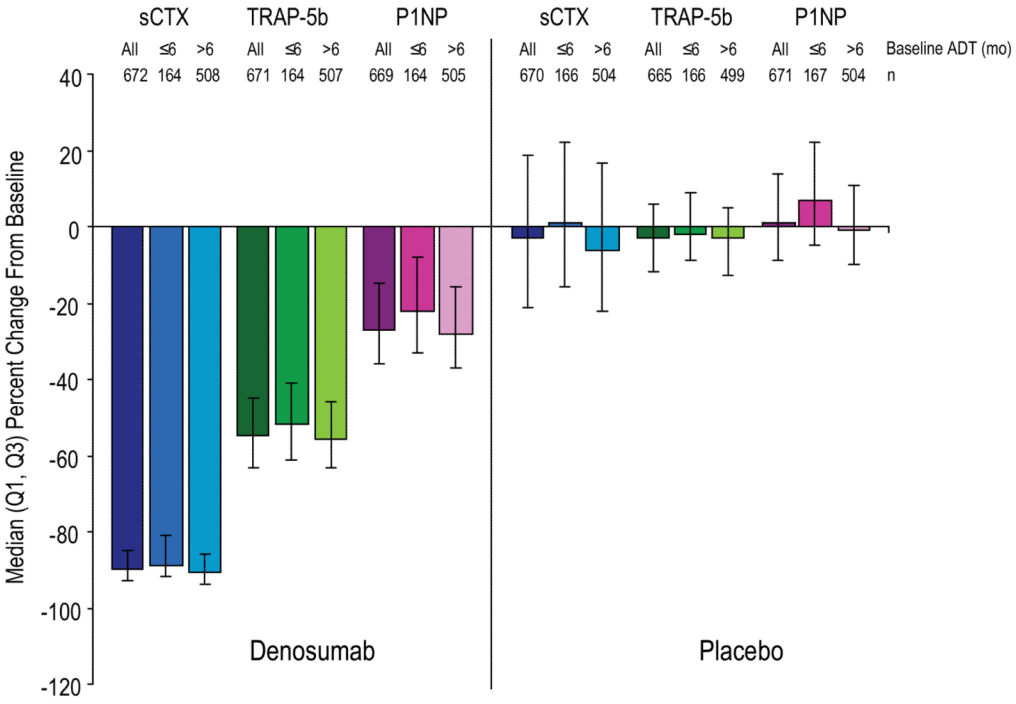

Figure 5.

Median BTM percent change at 1 month in patients in patients with <6 months ADT and ≥ 6 months ADT at baseline. n=number of patients with observed data.

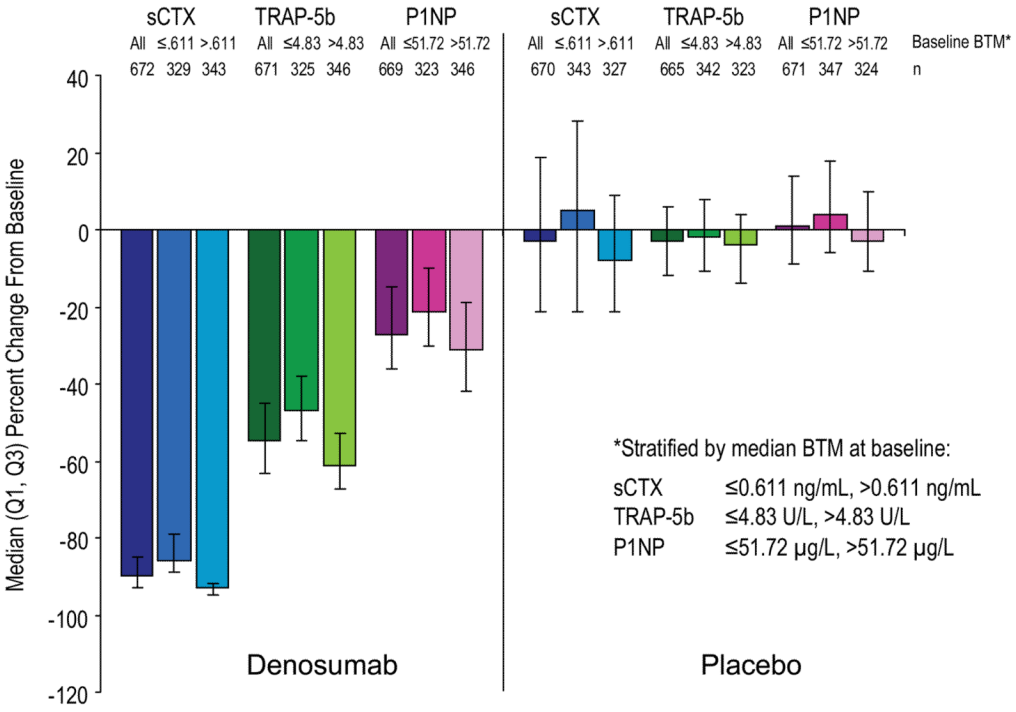

Figure 6.

Median BTM percent change at 1 month in patients in patients stratified by median BTM at baseline. n=number of patients with observed data.

Table 1

Baseline Bone Turnover Markers

Bone turnover markers at baseline, median (Q1, Q3)	Placebo (N=734)	Denosumab (N=734)
sCTX (ng/mL)[a]	0.61 (0.41, 0.83) (n = 683)	0.62 (0.42, 0.87) (n = 690)
TRAP-5b (U/L)[b]	4.80 (3.97, 5.95) (n = 681)	4.90 (3.98, 6.11) (n = 692)
P1NP (μg/L)[c]	50.86 (37.09, 68.05) (n = 685)	52.41 (38.45, 72.14) (n = 690)

N = Number of subjects randomized

n = Number of subjects with observed data

[a] Normal human serum range in men: below the lower limit of quantification (0.049 ng/mL) to 0.475 ng/mL

[b] Normal human serum range in men: 2.804 U/L to 5.196 U/L

[c] Normal human serum range in men: 36.305 μg/L to 97.531 μg/L

Table 2

Spearman Correlation Between BMD Change From Baseline at Month 36 and Change in sCTX, P1NP, and TRAP-5b at Month 6

	Lumbar spine		Total hip	
	r (n)	r (n)	r (n)	r (n)
	Placebo	Denosumab	Placebo	Denosumab
sCTX	−0.15 (390)[a]	−0.27 (410)[a]	−0.09 (375)[b]	−0.23 (400)[a]
TRAP-5b	−0.18 (387)[a]	−0.28 (412)[a]	−0.20 (372)[a]	−0.24 (402)[a]
P1NP	−0.23 (389)[a]	−0.24 (410)[a]	−0.15 (374)[a]	−0.29 (400)[a]

r = Spearman correlation

n = Number of randomized subjects

[a] $P < 0.05$

[b] $P = 0.09$