# Suppression of bone density loss and bone turnover in patients with hormone-sensitive prostate cancer and receiving zoledronic acid

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**OBJECTIVE**

To report a randomized, placebo-controlled study of treatment with zoledronic acid every 3 months in patients with hormone-sensitive prostate cancer, both with and without bone metastases, to assess the effect on bone mineral density (BMD) and markers of bone turnover.

**PATIENTS AND METHODS**

Eligible patients included those with prostate cancer and on androgen-deprivation therapy for <12 months. Patients received zoledronic acid 4 mg intravenously, or placebo, every 3 months for four treatments. BMD, urinary N-telopeptides of type I collagen (NTX), and serum bone alkaline phosphatase (BAP) were measured every 3 months. In all, 42 patients were randomized.

**RESULTS**

After excluding BMD data from sites of known metastases, patients receiving zoledronic acid had a relative increase in BMD compared with those receiving placebo, of 4.2% and 7.1% at the femoral neck and lumbar spine, respectively. NTX and BAP decreased significantly in patients receiving zoledronic acid. NTX and BAP levels were significantly higher at baseline in patients with bone metastases than in those without.

**CONCLUSIONS**

Treatment with zoledronic acid every 3 months preserved bone density and suppressed markers of bone turnover in patients with androgen-deprived prostate cancer, both with and without bone metastases.

**KEYWORDS**

prostate cancer, osteoporosis, bone density, zoledronic acid, androgen deprivation

**BACKGROUND**

Androgen-deprivation therapy (ADT) with a LHRH agonist, or orchidectomy, remains the primary and most effective treatment for advanced prostate cancer. Negative effects of ADT on the skeleton include loss of bone mineral density (BMD) and associated increased risk of fracture [1–3]. In men with bone metastases, the risk of skeletal complications is significant [4].

Bisphosphonates prevent BMD loss in patients with prostate cancer undergoing ADT [2,3,5]. Zoledronic acid (ZA), the most potent bisphosphonate clinically developed to date, reduces skeletal-related events in men with metastatic, hormone-refractory prostate cancer [4]. ZA increases the BMD in androgen-deprived patients with prostate cancer with no bone metastases [3,5].

Biochemical markers of bone turnover include urinary *N*-telopeptides of type I collagen (NTX), a highly specific marker of osteolysis and osteoclastic activity, and serum bone-specific alkaline phosphatase (BAP), a maker of osteoblastic activity. Recent studies suggested that biochemical markers of bone metabolism are highly predictive of the clinical outcome in patients with metastatic bone disease [6]. A significant association was reported between elevated levels of markers of bone turnover and risk of skeletal-related events, disease progression, and death in patients with metastatic, hormone-refractory prostate cancer [7,8]. Elevated levels of bone turnover markers in patients receiving ZA is associated with a worse clinical outcome, suggesting that suppression of bone markers is a potential therapeutic goal [9].

We conducted a randomized, placebo-controlled study of ZA given every 3-months to assess the effect on BMD and bone turnover markers in patients with hormone-sensitive prostate cancer; they were within the first year of ADT and included patients with and with no bone metastases, a distinguishing feature from other such studies of ZA [3,5]. The objectives of this trial were to assess the ability of ZA to preserve or improve BMD of the spine and hip, and to determine the effects of ZA on urinary NTX and serum BAP.

**PATIENTS AND METHODS**

Eligibility criteria included a histological diagnosis of adenocarcinoma of the prostate and a life-expectancy of ≥1 year. Patients must have been receiving ADT with an LHRH agonist or orchidectomy and must have received ADT for ≤1 year. Patients who were scheduled to start ADT at the time of study entry were also eligible. Patients must not have received previous bisphosphonate therapy. Written, informed consent, using an institutionally approved consent form, was obtained from all patients.

| Characteristics | ZA | Placebo |
|---|---|---|
| N | 22 | 20 |
| Mean (SD) age, years | 64.9 (10.8) | 65.2 (9.0) |
| range | 50–87 | 49–82 |
| Race, n | | |
| African American | 7 | 2 |
| White | 12 | 17 |
| unknown | 3 | 1 |
| Bone metastasis, n | | |
| Yes | 10 | 9 |
| No | 12 | 11 |
| ADT type, n | | |
| Orchidectomy | 2 | 1 |
| LHRH agonist | 20 | 19 |
| Time (months) on ADT, n | | |
| <6 | 19 | 18 |
| 6–12 | 3 | 2 |
| Anti-androgen, n | | |
| Yes | 15 | 14 |
| No | 6 | 6 |
| Unknown | 1 | |
| Previous therapy, n | | |
| Prostatectomy | 7 | 11 |
| Radiotherapy to prostate | 7 | 4 |
| Radiotherapy to bone | 0 | 2 |
| Chemotherapy | 1 | 2 |
| Bone scan results, metastasis at: | | |
| Hip/femoral neck | 6 | 2 |
| Lumbar spine | 3 | 2 |
| Mean (SD) BMI, kg/m$^2$, | 29.5 (7.1) | 31.4 (7.2) |
| Mean (SD) BMD, g/cm$^2$, at | | |
| Femoral neck | 0.978 (0.192) | 0.988 (0.126) |
| Lumbar spine | 1.337 (0.205) | 1.424 (0.274) |
| Geometric mean (95% CI) serum testosterone, ng/dL, at: | | |
| Baseline | 42 (18–97) | 79 (34–185) |
| 3 months | 10 (6–16) | 12 (9–15) |
| 6 months | 7 (5–10) | 14 (10–18) |
| 9 months | 10 (8–12) | 11 (9–14) |
| 12 months | 12 (8–17) | 11 (8–16) |

*TABLE 1*
*The patients' characteristics and clinical features*

*BMI, body mass index.*

Patients were randomized with equal probability, and in a double-blind fashion, to either ZA or placebo; randomization was stratified by duration on ADT (<6 or 6–12 months). Every 3 months for four treatments patients randomized to the ZA group received ZA 4 mg in 100 mL of sterile 0.9% NaCl, administered over 15 min. Patients randomized to the placebo group received an equal volume of sterile 0.9% NaCl administered in the same fashion. All patients were instructed to take calcium carbonate supplementation equivalent to 260 mg elemental calcium orally, four tablets daily. Patients were to remain on ADT throughout the 12-month study period.

A total-body $^{99}$Tc bone scan was taken within 4 weeks of study entry; patients had a physical examination and relevant medical history taken every 3 months while on the study. Dual-energy X-ray absorptiometry (DEXA; Lunar Prodigy densitometer, GE Medical Systems, Madison, WI, USA) was used to measure BMD of the lumbar spine and proximal femur at baseline and every 3 months for 1 year. The precision error was 1% for the lumbar spine, 1% for the total hip, and 1.5% for the femoral neck. Adverse events were retrospectively abstracted from patient charts.

Blood samples for BAP and testosterone, and urine samples for NTX, were obtained at baseline and every 3 months, and analysed at a central laboratory (Core Endocrine Laboratory, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA). Serum BAP levels were measured with a solid-phase, monoclonal antibody immunoenzymatic assay (Immunodiagnostic Systems Inc., Fountain Hills, AZ, USA), while urinary NTX levels were measured with a competitive-inhibition ELISA (Wampole Laboratories, Princeton, NJ, USA). The interassay precision for both assays was <10%. Serum testosterone levels were measured with a solid-phase radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA) using $^{125}$I-labelled testosterone. Interassay coefficients of variation were 9% at a mean testosterone value of 84 ng/dL.

A sample size of 40 patients in each arm was chosen to detect a mean difference in BMD between the ZA and placebo groups of ≥0.05 g/cm$^2$ by the end of 1 year. Based on a SD of 0.14 g/cm$^2$, and assuming that measurements at different times would have a correlation of 0.9, this sample size would have ≈94% power to detect a difference in BMD of 0.05 g/cm$^2$ at the end of a year and ≥90% power to detect a mean difference in each marker of bone turnover of 0.87 SDs at the end of a year. Power estimates were based on a two-sided test at the 0.05 level. Enrolment was closed after 42 patients were randomized because the trial was superseded by a multi-institutional effort, the Zometa US05 study [5]. To gain statistical power and fully use the data, all available BMD data (0, 3, 6, 9 and 12 months) were used. Based on the intent-to-treat principle, the efficacy analysis included all randomized patients whose BMD was measured at baseline and one of the follow-up visits, and the safety analysis included all randomized men who received at least one dose of study medication. A random-effects linear model was used to examine the difference in the rate of BMD change over time between the ZA and placebo groups. Absolute changes in BMD were converted to percentage change per year to facilitate interpretation. After log transformation, changes in biochemical markers (NTX, BAP and testosterone) were analysed using random-effects linear models. We transformed back the means of log-transformed values to obtain geometric means. To examine whether the effect of ZA was different in patients with and with no bone metastases, a three-way interaction of (treatment group × time × bone metastasis

*TABLE 2 BMD values and changes over 12 months*

| Site | ZA N | ZA Mean (SD) | Placebo N | Placebo Mean (SD) | Difference |
|---|---|---|---|---|---|
| **Femoral neck*** | | | | | |
| Baseline | 16 | 1.008 (0.158) | 16 | 0.975 (0.127) | |
| 3 months | 15 | 1.006 (0.164) | 15 | 0.997 (0.111) | |
| 6 months | 15 | 1.005 (0.158) | 14 | 0.987 (0.127) | |
| 9 months | 15 | 1.021 (0.166) | 15 | 0.967 (0.120) | |
| 12 months | 14 | 0.985 (0.143) | 14 | 0.964 (0.134) | |
| Slope (95% CI), g/cm$^2$/year | 0.009 (–0.007, 0.026) | | –0.032 (–0.049, –0.015) | | 0.041 (0.018–0.065) |
| % change/year (95% CI) | 0.9 (–0.87, 2.6) | | –3.2 (–5.0, –1.5) | | 4.2 (1.8–6.6) |
| *P* | 0.28 | | <0.001 | | 0.001 |
| **Lumbar spine†** | | | | | |
| Baseline | 19 | 1.306 (0.191) | 16 | 1.406 (0.285) | |
| 3 months | 17 | 1.383 (0.186) | 15 | 1.418 (0.236) | |
| 6 months | 16 | 1.362 (0.155) | 14 | 1.438 (0.299) | |
| 9 months | 16 | 1.376 (0.155) | 15 | 1.418 (0.303) | |
| 12 months | 15 | 1.351 (0.180) | 13 | 1.363 (0.227) | |
| Slope (95% CI), g/cm$^2$/year | 0.066 (0.032–0.101) | | –0.030 (–0.067, 0.008) | | 0.096 (0.045–0.147) |
| % change/year (95% CI) | 4.9 (2.3–7.5) | | –2.2 (–4.9, 0.6) | | 7.1 (3.3–10.8) |
| *P* | <0.001 | | 0.12 | | <0.001 |

**Excluded eight patients with bone metastases at the femoral neck; †excluded five patients with bone metastases at the lumbar spine.*

status) was tested in the framework of random-effects linear regression analysis. The baseline concentration of NTX and BAP was compared between patients with and with no bone metastases using a *t*-test, followed by multiple linear regression to adjust for duration on ADT and testosterone. Fisher's exact test was used to compare the proportions of adverse events between the groups, with $P < 0.05$ considered to indicate statistical significance in all tests.

## RESULTS

From January 2000 to December 2002, 42 patients were enrolled and randomized at the University of Chicago; their baseline characteristics are shown in Table 1, and none of the baseline characteristics were significantly different between the groups. About half of the patients had scintigraphic evidence of bone metastases; 88% had received ADT for <6 months at the time of study enrolment, and most received an LHRH agonist as their form of ADT.

Of men in the ZA and placebo groups, respectively, 40% and 50% had castrate levels of testosterone (<50 ng/dL) at study entry. The serum concentration of testosterone decreased significantly during follow-up in both groups ($P < 0.001$, Table 1) and the reduction did not differ between the groups ($P = 0.62$). All patients in both groups achieved castrate levels at all follow-up visits except that one in the ZA and one in the placebo group had testosterone levels slightly above 50 ng/dL at 3 and 6 months, respectively.

All enrolled patients received at least one dose of study medication, and 36 (86%) received all four doses of the assigned medication. Three patients in the ZA group discontinued treatment because they died before study completion, and one in the ZA group missed the treatment at 3 months; two in the placebo group withdrew consent after they received the baseline treatment.

Because of the confounding effect of bone metastases on DEXA measurements [10], the data were analysed after excluding the BMD data for patients with scintigraphic evidence of metastatic bone disease at the hip or lumbar spine (Table 2). After excluding these data, the difference in the mean change of BMD per year (slope, g/cm$^2$/year) between ZA and placebo was statistically significant at both the femoral neck ($P = 0.001$) and the lumbar spine ($P < 0.001$). Compared with patients receiving placebo, patients receiving ZA had a relative BMD increase of 4.2% per year at the femoral neck and 7.1% at the lumbar spine. Figure 1 shows the percentage change in BMD from baseline to each of follow-up visits. For the femoral neck, there was no difference between the treatment groups at 3 and 6 months but the difference was obvious at 9 and 12 months (both $P < 0.05$). By contrast, the effect of ZA on the lumbar spine was apparent at 3 months and persisted through the 1 year of the study (all $P < 0.05$).

The mean NTX and BAP levels were similar between the ZA and placebo groups at baseline ($P = 0.88$ and 0.26; Table 3). Over the 12-month study, NTX and BAP levels remained the same in the placebo group but decreased significantly in the ZA group (both $P < 0.001$; Table 3 and Fig. 2). To examine whether the effect of ZA was present in patients with or with no bone metastases, we used the three-way interaction in a random effects linear regression analysis. There was no significant interaction for either NTX ($P = 0.97$) or BAP ($P = 0.47$), indicating that

*TABLE 3 The geometric mean (95% CI) of NTX and BAP over time by treatment group and bone metastasis status*

| Biomarkers | Sample time, months: Baseline | 3 | 6 | 9 | 12 | P |
|---|---|---|---|---|---|---|
| **NTX, nmol BCE/mmol Cr** | | | | | | |
| All patients: | | | | | | |
| Placebo | 66 (39–114) | 61 (40–95) | 65 (40–108) | 63 (39–102) | 54 (41–71) | 0.92 |
| ZA | 69 (41–117) | 36 (21–62) | 28 (20–38) | 31 (21–46) | 23 (17–30) | <0.001 |
| No bone metastasis | | | | | | |
| Placebo | 42 (25–68) | 40 (30–53) | 44 (31–61) | 45 (34–60) | 51 (38–68) | 0.51 |
| ZA | 35 (26–47) | 23 (18–30) | 22 (17–29) | 24 (20–30) | 21 (16–26) | 0.001 |
| Bone metastasis | | | | | | |
| Placebo | 128 (45–363) | 95 (43–211) | 94 (38–234) | 88 (33–237) | 58 (31–111) | 0.60 |
| ZA | 146 (60–356) | 52 (18–146) | 39 (17–90) | 45 (15–133) | 28 (9–89) | <0.001 |
| **BAP, µg/L** | | | | | | |
| All patients | | | | | | |
| Placebo | 35 (23–53) | 34 (23–50) | 34 (23–49) | 32 (25–41) | 33 (27–42) | 0.28 |
| ZA | 44 (30–65) | 28 (18–43) | 25 (16–38) | 24 (17–36) | 22 (16–29) | <0.001 |
| No bone metastasis | | | | | | |
| Placebo | 25 (21–30) | 25 (20–30) | 26 (21–33) | 28 (22–35) | 32 (27–39) | 0.019 |
| ZA | 26 (23–29) | 18 (16–21) | 18 (16–21) | 17 (15–20) | 18 (15–21) | <0.001 |
| Bone metastasis | | | | | | |
| Placebo | 55 (21–146) | 47 (22–99) | 44 (21–91) | 37 (22–62) | 35 (20–60) | 0.34 |
| ZA | 85 (44–164) | 47 (19–117) | 37 (12–112) | 42 (16–109) | 31 (13–75) | 0.006 |

*BCE, bone collagen equivalent; Cr, creatinine.*

*FIG. 2. The geometric mean (95% CI) percentage change from baseline in all patients in: (A) urinary NTX and (B) serum BAP.*

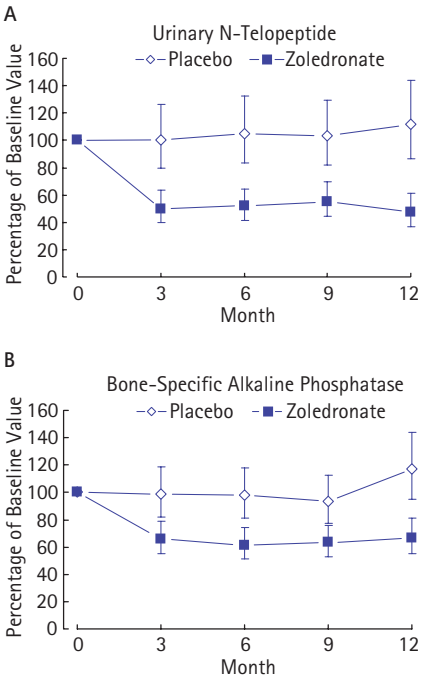



*FIG. 1. The mean (95% CI) percentage change from baseline in BMD at two sites in men treated with ZA or placebo. The scheduled measurements are the same for the two groups but a horizontal break was added for display purposes.*

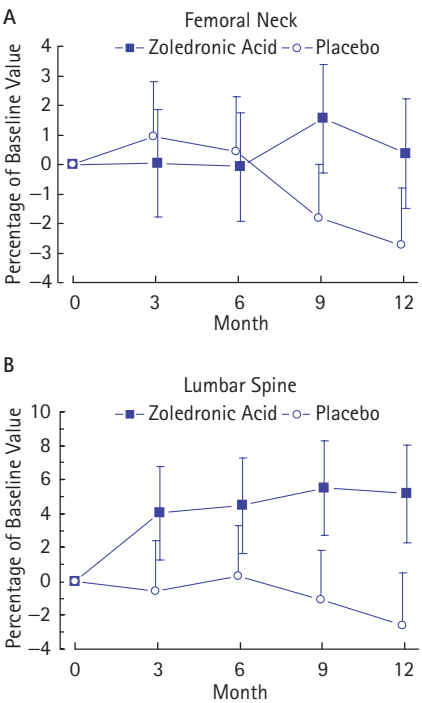



*FIG. 3. The geometric mean (95% CI) percentage change from baseline in men without and with bone metastases in: (A) urinary NTX and (B) serum BAP.*

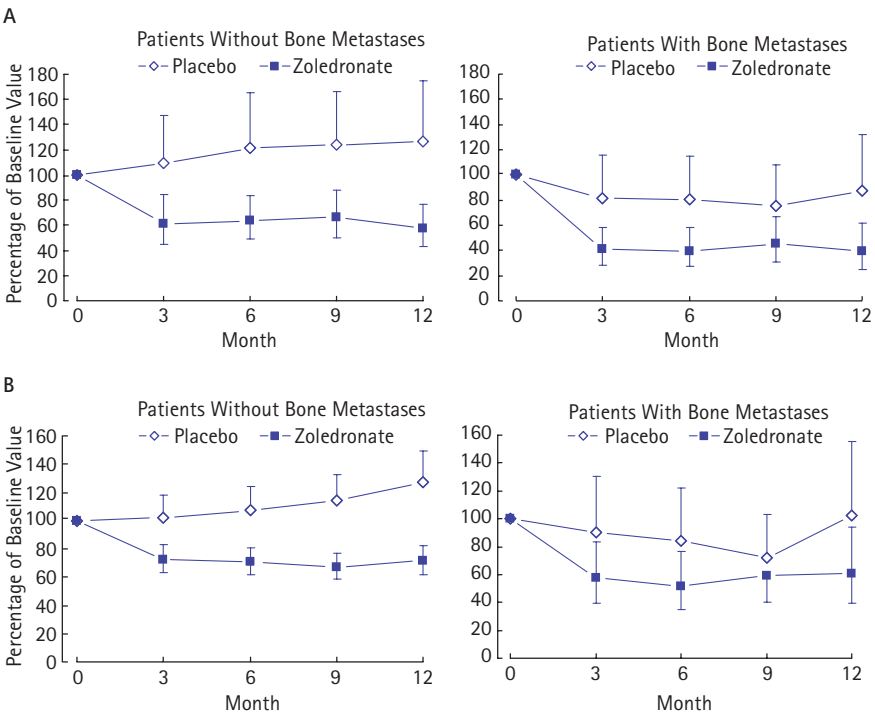
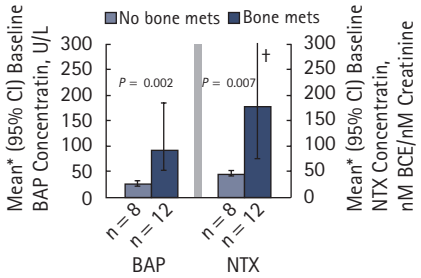


*FIG. 4. Baseline BAP and NTX concentrations in men receiving >0.5 months of ADT. Values are expressed as the geometric mean (95% CI). †CI truncated at 300 nM bone collagen equivalent per nmol creatinine.*




| Adverse event | ZA, n (%) | Placebo, n (%) |
|---|---|---|
| N | 19 | 16 |
| Pain | 12 (63) | 8 (50)* |
| Fatigue | 11 (58) | 8 (50) |
| Bone pain/arthralgia | 10 (53) | 6 (38)* |
| Genitourinary | 6 (32) | 2 (13) |
| Neurological | 3 (16) | 4 (25)* |
| Diarrhoea | 1 (5) | 4 (25) |
| Fever | 2 (11) | 2 (13) |
| Constipation | 2 (11) | 1 (6) |
| Anorexia | 2 (11) | 1 (6) |
| Nausea | 0 | 3 (19) |
| Vomiting | 0 | 2 (13) |
| Infection | 1 (5) | 0 |
| Respiratory | 1 (5) | 1 (6) |
| Alopecia | 0 | 1 (6) |

*TABLE 4*
*Adverse events by treatment group, available from 35 patients*

**Each includes one severe adverse event.*

the effect of ZA on bone marker changes was similar in men with bone metastases and those with no bone metastases (Fig. 3).

We also examined the effect of the presence of bone metastases on baseline bone turnover markers. The mean NTX level was 3.6 times higher and the mean BAP level 2.7 times higher (both $P < 0.001$) in men with bone metastases than in those without bone metastases. After adjusting for testosterone level, both NTX (2.9 times, $P = 0.006$) and BAP (2.8 times, $P = 0.001$) were still higher at baseline in men with bone metastases than in those without. To address whether the duration of testosterone suppression might have influenced the level of bone markers, we used a threshold of 0.5 months of ADT to differentiate hormone-naive from castrate patients. Levels of bone marker for patients on ADT for >0.5 months are shown in Fig. 4. In multiple linear regression analysis adjusting for the duration on ADT (≤ 0.5 or >0.5 months), both NTX (3.3 times, $P = 0.002$) and BAP (3.1 times, $P < 0.001$) were still higher in men with bone metastases than in men without bone metastases at baseline.

The commonly reported adverse events were similar between the treatment groups (Table 4). All reported adverse events were mild or moderate in severity, except for one patient in the placebo group who had severe adverse events.

## DISCUSSION

We showed that in patients with hormone-sensitive prostate cancer, treatment with ZA every 3 months had a suppressive effect on bone turnover. ZA suppressed both NTX and BAP, compared with placebo, over the 12-month study period. The effects of ZA on the primary endpoint, BMD, were less obvious because we included patients with bony metastatic disease, which can interfere with the accuracy of DEXA [10]. When data for men with scintigraphic evidence of bone metastases at the site of DEXA measurement were excluded, the benefit of ZA became apparent. In the analysis excluding these subjects, the SEM of the slope was actually reduced, even though the sample size was smaller, suggesting that the BMD measurements in these excluded patients were problematic (data not shown). The effect at the lumbar spine was statistically significant in analyses with or without men with bone metastases at the lumbar spine.

In men receiving ZA, both NTX and BAP concentrations were lower than with placebo, regardless of the presence of bone metastases. In hormone-refractory patients receiving ZA, an increase of NTX and BAP levels while on therapy has been associated with a significantly higher risk of skeletal complications, disease progression and death, suggesting that suppression of bone markers could serve as a surrogate goal of bisphosphonate therapy [9]. The present patients consisted of those with hormone-sensitive disease, both with and with no bone metastases. Studies investigating the effect of ZA on patients with hormone-sensitive prostate cancer and bone metastases have been limited. An open-label study of 3-weekly ZA for 1 year in such patients also detected a significant decrease in NTX and BAP over the study period [11]. The present study shows that infrequent (3-monthly) infusions of ZA are effective in suppressing NTX and BAP levels in these patients. Given that adverse effects such as osteonecrosis of the jaw might be associated with cumulative exposure to bisphosphonates [12], investigating less frequent infusion schedules such as ours, in patients with metastatic bone disease, should be pursued.

The NTX and BAP levels were significantly higher in patients with bone metastases than in those without. While this association was reported previously [13,14], a recent publication suggested that increased markers of osteoclastic activity in patients with prostate cancer and bone metastases might be due to the effects of ADT alone, rather than an effect of metastatic disease on the bone [15]. In the present study both markers were significantly higher in patients with bone metastases than in those without, after controlling for both testosterone level and duration of ADT.

In conclusion, 3-monthly ZA prevents bone loss and increases BMD in men with prostate cancer treated with ADT. This regimen also has a suppressive effect on markers of bone turnover in patients with hormone-sensitive prostate cancer, both with and with no bone metastases. Further studies investigating the association between bone markers and response to anti-resorptive therapy and clinical outcome are warranted.

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## CONFLICT OF INTEREST

Christopher Ryan, Walter Stadler and Nicholas Vogelzang have served as paid consultants to Novartis. Christopher Ryan and Walter Stadler are study investigators funded by the sponsor. Source of funding: Novartis.

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Abbreviations: **BMD**, bone mineral density; **ZA**, zoledronic acid; **ADT**, androgen-deprivation therapy; **NTX**, N-telopeptide; **BAP**, bone-specific alkaline phosphatase; **DEXA**, dual-energy X-ray absorptiometry.