Changes in Bone Turnover Marker Levels and Clinical Outcomes in Patients with Advanced Cancer and Bone Metastases Treated with Bone Antiresorptive Agents

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Abstract

Purpose: Bone antiresorptive agents can significantly reduce bone turnover markers (BTM) in patients with advanced cancer. We evaluated association of changes in BTMs with overall survival (OS), disease progression (DP), and disease progression in bone (DPB) in patients with advanced cancer and bone metastases following denosumab or zoledronic acid treatment.

Experimental Design: This is an integrated analysis of patient-level data from three identically designed, blinded, phase III trials with patients randomized to subcutaneous denosumab or intravenous zoledronic acid. Levels of the BTMs urinary N-telopeptide (uNTx) and serum bone-specific alkaline phosphatase (sBSAP) measured at study entry and month 3 were analyzed. OS, DP, and DPB were compared in patients with BTMs ≥ median versus < median based on month 3 assessments.

Results: uNTx levels ≥ the median of 10.0 nmol/mmol at month 3 were associated with significantly reduced OS compared with levels < median (HR for death, 1.85; P < 0.0001). sBSAP levels ≥ median of 12.6 ng/mL were associated with significantly reduced OS compared with levels < median (HR, 2.44; P < 0.0001). uNTx and sBSAP levels ≥ median at month 3 were associated with significantly greater risk of DP (HR, 1.31; P < 0.0001 and HR, 1.71; P < 0.0001, respectively) and DPB (HR, 1.11; P = 0.0407 and HR, 1.27; P < 0.0001, respectively).

Conclusions: BTM levels ≥ median after 3 months of bone antiresorptive treatment were associated with reduced OS and increased risk of DP and DPB. Assessment of uNTx and sBSAP levels after bone antiresorptive therapy may add to identification of patients at risk for worse clinical outcomes.

Introduction

Bone is a frequent and often the only site of metastasis in patients with advanced solid tumors such as breast cancer, prostate cancer, or lung cancer (1–7), and bone metastases are often associated with significant morbidity and poor prognosis (3, 6, 8). Metastatic bone disease disrupts the homeostasis of osteoclast-mediated bone resorption and osteoblast-mediated bone formation, leading to dysregulation of normal bone remodeling processes (2, 3).

The loss of bone homeostasis compromises the structural integrity of the skeleton and leads to clinical complications including pathologic fractures, spinal cord compression, life-threatening hypercalcemia, or the need for radiation or surgery to bone to prevent or treat fractures (2, 5, 8–10). These clinical complications, collectively termed skeletal-related events (SRE; refs. 8, 11–13), often lead to severe pain and a significant decrease in quality of life (14–17).

Osteoblasts produce the cytokine receptor activator of nuclear factor kappa-B ligand (RANKL), which is an essential mediator of osteoclast function, formation, and survival (6, 18, 19). The presence of tumor cells in the bone stimulates osteoblasts to increase RANKL expression (6, 18, 19), which in turn induces osteoclast-mediated bone resorption and bone destruction, leading to SREs (20, 21).
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Translational Relevance

Patients with advanced cancer and bone metastases often have elevated levels of the bone turnover markers urinary N-telopeptide (uNTx) and serum bone-specific alkaline phosphatase (sBSAP). Bone antiresorptive agents such as denosumab and zoledronic acid can reduce uNTx and sBSAP levels. Our study demonstrated that uNTx and sBSAP levels ≥ median levels, compared with < median levels, after 3 months of treatment with denosumab or zoledronic acid were associated with reduced overall survival and increased risk of disease progression and disease progression in bone. These results suggest a potential utility for uNTx and sBSAP as easily measurable, noninvasive, early predictors for response and survival in patients with advanced cancer and bone metastases who are receiving bone antiresorptive agents. Evaluating uNTx and sBSAP levels could complement established prognostic markers based on disease stage factors.

Materials and Methods

Patients and treatments

Details of the three identically designed, blinded, phase III trials comparing denosumab and zoledronic acid in patients with breast cancer (ClinicalTrials.gov: NCT00321464; ref. 27), prostate cancer (ClinicalTrials.gov: NCT00321620; ref. 25), or solid tumors (excluding breast cancer and prostate cancer) or myeloma (ClinicalTrials.gov: NCT00330759; ref. 26) have been previously reported. In those three parent studies, eligible patients ≥ 18 years old had received either a subcutaneous injection of denosumab 120 mg (XGEVA, Amgen Inc.; ref. 29) and an intravenous infusion of placebo every 4 weeks or an intravenous infusion of zoledronic acid 4 mg (Zometa, Novartis; ref. 28) and a subcutaneous injection of placebo every 4 weeks (see Supplementary Fig. S1 for study design).

In the three parent studies, creatinine clearance ≥ 30 mL/minute and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 were required at study entry. Daily supplementation with calcium (≥ 2500 mg) and vitamin D (≥ 400 U) was strongly recommended. Exclusion criteria included prior treatment with intravenous bisphosphonates, planned radiation or surgery to bone, or unhealed dental or oral surgery.

Patients who participated in the studies had provided written, informed consent before any study-specific procedure was performed, except for 3 patients in the zoledronic acid group of the breast cancer study (27), who were excluded from analysis due to lack of proper documentation of informed consent. Study protocols were approved by the relevant institutional review boards and independent ethics committees for each site, and the studies were conducted in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki.

Assessments of outcomes

Levels of uNTx and sBSAP measured at baseline and after 3 months of treatment with either denosumab or zoledronic acid were analyzed. Urine was collected from the second void of the day, before noon. uNTx measurements (corrected for urine creatinine levels) were performed by Amgen Inc. or PPD Development using an ELISA (Osteomark). sBSAP measurements were performed by the University of Liege (Liege, Belgium) using a chemiluminescent assay (Access Ostase reagents on the Access immunoassay system, Beckman Coulter). OS, DP, and DPB were compared in patients who had uNTx and sBSAP levels ≥ or < the median levels at month 3. The time point of 3 months after antiresorptive treatment was selected to provide adequate time for response to therapy.

Statistical analysis

The integrated patient-level dataset from patients with solid tumors enrolled in the three phase III trials (25–27) was used for this analysis. This excludes the multiple myeloma patient population enrolled in the solid tumor and myeloma study (26). In this post hoc analysis on uNTx and sBSAP levels, respectively, Cox models were used to analyze the association between the level (≥ or < the median levels) at month 3 and OS, DP, and DPB by taking the level category as the independent variable and stratified by study, treatment, and the actual stratification factors based on month 3 assessments. To determine the impact of risk factors associated with a more advanced disease state, additional analyses that included the covariates of baseline visceral metastases (presence versus absence), baseline number of bone metastases (≤ 2 versus > 2), or baseline ECOG performance status category (0–1 versus ≥ 2) were performed.

For uNTx and sBSAP, the absolute value of levels at month 3 and percentage change from baseline were determined. OS, DP, and DPB were analyzed by month 3 BTM category (≥ or < median) as well as by percentage change category (≥ or < median percentage change). In addition, clinical outcomes
were analyzed by patients’ combined category of uNTx and sBSAP levels at month 3: HH (high-high: uNTx ≥ median and sBSAP ≥ median at month 3), HL (high-low: uNTx ≥ median and sBSAP < median at month 3), LH (low-high: uNTx < median and sBSAP ≥ median at month 3), LL (low-low: uNTx < median and sBSAP < median at month 3).

### Table 1. Baseline demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Denosumab 120 mg, Q4W (n = 2,775)</th>
<th>Zoledronic acid 4 mg, Q4W (n = 2,768)</th>
<th>All (N = 5,543)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1,286 (46.3)</td>
<td>1,310 (47.3)</td>
<td>2,596 (46.8)</td>
</tr>
<tr>
<td>Male</td>
<td>1,489 (53.7)</td>
<td>1,458 (52.7)</td>
<td>2,947 (53.2)</td>
</tr>
<tr>
<td><strong>Median (IQR) age, years</strong></td>
<td>63.0 (54.0–70.0)</td>
<td>63.0 (54.0–72.0)</td>
<td>63.0 (54.0–71.0)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2,352 (84.8)</td>
<td>2,320 (83.8)</td>
<td>4,672 (84.3)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>2,534 (90.6)</td>
<td>2,472 (89.3)</td>
<td>4,986 (90.0)</td>
</tr>
<tr>
<td>≥2</td>
<td>258 (9.3)</td>
<td>288 (10.4)</td>
<td>546 (9.9)</td>
</tr>
<tr>
<td><strong>Primary tumor type, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1,026 (37.0)</td>
<td>1,020 (36.8)</td>
<td>2,046 (36.9)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>950 (34.2)</td>
<td>930 (34.4)</td>
<td>1,880 (34.3)</td>
</tr>
<tr>
<td>Non–small cell lung cancer</td>
<td>350 (12.6)</td>
<td>352 (12.7)</td>
<td>702 (12.7)</td>
</tr>
<tr>
<td>Other</td>
<td>449 (16.2)</td>
<td>445 (16.1)</td>
<td>894 (16.1)</td>
</tr>
<tr>
<td><strong>Median (IQR) time from diagnosis of cancer to randomization, months</strong></td>
<td>26.5 (8.2–66.1)</td>
<td>27.0 (8.4–68.1)</td>
<td>26.7 (8.3–67.1)</td>
</tr>
<tr>
<td><strong>Median (IQR) time from diagnosis of bone metastases to randomization, months</strong></td>
<td>2.2 (1.0–7.2)</td>
<td>2.3 (1.1–7.8)</td>
<td>2.3 (1.0–7.4)</td>
</tr>
<tr>
<td><strong>Presence of visceral metastases, n (%)</strong></td>
<td>2,185 (42.7)</td>
<td>1,352 (41.6)</td>
<td>2,337 (42.2)</td>
</tr>
<tr>
<td><strong>Number of metastatic lesions in bone, n (%)</strong></td>
<td>2,070 (75.7)</td>
<td>684 (24.7)</td>
<td>1,358 (24.5)</td>
</tr>
<tr>
<td><strong>Bone turnover markers, median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uNTx (nmol/mmol)</td>
<td>44.2 (24.8–82.9)</td>
<td>45.5 (25.1–81.8)</td>
<td>45.7 (25.0–82.4)</td>
</tr>
<tr>
<td>sBSAP (ng/mL)</td>
<td>211 (14.0–41.5)</td>
<td>211 (13.6–41.1)</td>
<td>211 (13.8–41.3)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; Q4W, every 4 weeks.

*Excludes the myeloma patient population.
Results

Patients

A total of 5,543 patients with advanced solid tumors and bone metastases from the three parent phase III studies (25–27) were included in this integrated analysis (denosumab, n = 2,775; zoledronic acid, n = 2,768). The myeloma patient population (n = 180) from the solid tumor and myeloma study (26) was excluded from this analysis. Data on BTM levels were available for most of the patients: uNTx, n = 4,299 (breast cancer, n = 1,705; prostate cancer, n = 1,527; and non-small cell lung cancer [NSCLC], n = 461) and sBSAP, n = 4,316 (breast cancer, n = 1,708; prostate cancer, n = 1,512; and NSCLC, n = 480).

Patient demographics and baseline clinical characteristics were generally balanced between the treatment groups (Table 1). Both groups had a median age of 63.0 years. Most (90.0%) patients had an ECOG performance status of 0–1. A total of 2,337 (42.2%) patients had visceral metastases, 4,185 (75.5%) patients had an ECOG performance status of 0 (26). Table 2. Covariate analysis of OS, DP, and DPB at month 3, overall and by tumor type

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tumor types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uNTx</td>
<td>2,775</td>
<td>1.85 (1.67–2.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>2,768</td>
<td>1.31 (1.21–1.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DP</td>
<td>2,775</td>
<td>1.21 (1.01–1.41)</td>
<td>0.0407</td>
</tr>
<tr>
<td>DPB</td>
<td>2,775</td>
<td>1.41 (1.01–1.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>sBSAP</td>
<td>2,768</td>
<td>2.44 (2.20–2.71)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>2,775</td>
<td>1.71 (1.57–1.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DP</td>
<td>2,775</td>
<td>1.27 (1.14–1.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Breast cancer</td>
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<td></td>
</tr>
<tr>
<td>uNTx</td>
<td>1,527</td>
<td>1.54 (1.21–1.87)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>1,512</td>
<td>1.21 (1.07–1.38)</td>
<td>0.0024</td>
</tr>
<tr>
<td>DP</td>
<td>2,775</td>
<td>1.25 (1.05–1.44)</td>
<td>0.0087</td>
</tr>
<tr>
<td>sBSAP</td>
<td>1,527</td>
<td>2.97 (2.42–3.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>1,512</td>
<td>1.67 (1.47–1.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DP</td>
<td>2,775</td>
<td>1.56 (1.34–1.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uNTx</td>
<td>1,705</td>
<td>2.12 (1.82–2.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>1,763</td>
<td>1.32 (1.17–1.50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DP</td>
<td>2,149</td>
<td>0.86 (0.75–1.02)</td>
<td>0.0911</td>
</tr>
<tr>
<td>sBSAP</td>
<td>1,705</td>
<td>2.81 (2.39–3.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>1,763</td>
<td>1.83 (1.61–2.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DP</td>
<td>2,149</td>
<td>1.07 (0.90–1.27)</td>
<td>0.4234</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>uNTx</td>
<td>461</td>
<td>1.83 (1.44–2.33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>480</td>
<td>1.30 (1.03–1.63)</td>
<td>0.0249</td>
</tr>
<tr>
<td>DP</td>
<td>461</td>
<td>1.41 (0.97–2.03)</td>
<td>0.0691</td>
</tr>
<tr>
<td>sBSAP</td>
<td>461</td>
<td>1.66 (1.31–2.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>480</td>
<td>1.37 (1.09–1.71)</td>
<td>0.0061</td>
</tr>
<tr>
<td>DP</td>
<td>461</td>
<td>1.35 (1.09–2.21)</td>
<td>0.0152</td>
</tr>
</tbody>
</table>

aNumber of patients included in the analysis.

bExcludes the myeloma patient population.

1 OS is measured by death of all cause. An HR >1 indicates an increased risk of death and decreased OS.

n = 2,775 for patients with uNTx levels ≤ median and n = 2,159 for patients with uNTx levels > median.

n = 2,768 for patients with sBSAP levels ≤ median and n = 2,159 for patients with sBSAP levels > median.

n = 853 for patients with sBSAP levels ≤ median and n = 853 for patients with sBSAP levels < median.

n = 764 for patients with uNTx levels ≤ median and n = 763 for patients with uNTx levels < median.

n = 754 for patients with sBSAP levels ≤ median and n = 754 for patients with sBSAP levels < median.

n = 231 for patients with uNTx levels ≤ median and n = 230 for patients with uNTx levels < median.

n = 239 for patients with sBSAP levels ≤ median and n = 234 for patients with sBSAP levels < median.

Changes in BTM levels at month 3 of bone antiresorptive treatment

After 3 months of treatment with either denosumab or zoledronic acid, median levels of uNTx for all patients decreased from 43.7 to 10.0 nmol/mmol (Supplementary Table S1). This decrease was consistent across tumor types, with month 3 median levels of 10.4 nmol/mmol for patients with breast cancer and 9.6 nmol/mmol for patients with prostate cancer or NSCLC. Median levels of sBSAP decreased from 21.1 to 12.6 ng/mL for all patients (Supplementary Table S1). By tumor type, median levels of sBSAP at month 3 were higher in patients with prostate cancer (21.4 ng/mL) than in patients with breast cancer or NSCLC (10.9 and 10.1 ng/mL, respectively).

Association of BTM levels with OS, DP, and DPB at month 3 of bone antiresorptive treatment

In the integrated analysis, patients with uNTx levels ≥ median at month 3 had significantly reduced OS compared with patients with uNTx levels < median [HR, 1.85; 95% confidence interval (CI), 1.67–2.04; P < 0.0001; Fig. 1A; Table 2]. Similarly, patients with sBSAP levels ≥ median at month 3 had significantly reduced OS compared with those who had sBSAP levels < median [HR, 1.85; 95% CI, 1.75–1.95; P < 0.0001; Fig. 1B; Table 2].

The risk of DP significantly increased for patients with uNTx and sBSAP levels ≥ median at month 3 (HR, 1.31; 95% CI, 1.21–1.41; P < 0.0001 and HR, 1.71; 95% CI, 1.57–1.85; P < 0.0001, respectively; Fig. 2A and B; Table 2). Similarly, the risk of DPB significantly increased for patients with uNTx and sBSAP levels ≥ median at month 3 (HR, 1.11; 95% CI, 1.01–1.24; P = 0.0407 and HR, 1.27, 95% CI, 1.14–1.41; P < 0.0001, respectively; Fig. 3A and B; Table 2).

Clinical outcomes were also assessed by tumor type. In patients with breast cancer, uNTx and sBSAP levels ≥ median at month 3 were associated with significantly reduced OS and a significantly increased risk of DP and DPB (Table 2), consistent with results seen for the combined patient population. In patients with prostate cancer, uNTx and sBSAP levels ≥ median at month 3 were associated with a significantly reduced OS and significantly increased risk of DP; however, nonsignificant changes in the risk of DPB were seen with levels ≥ median at month 3 for uNTx (HR, 0.86; 95% CI, 0.73–1.02; P = 0.0911) and sBSAP (HR, 1.07, 95% CI, 0.90–1.27; P = 0.4234) compared with those with levels < median (Table 2). In patients with NSCLC, uNTx and sBSAP levels ≥ median at month 3 were associated with significantly reduced OS and significantly increased risks of DP and DPB (Table 2).
increased risk of DP. In addition, sBSAP levels ≥ median at month 3 were associated with a significantly increased risk of DP. Although uNTx levels ≥ median at month 3 showed an association with increased risk of DPB, this association did not reach statistical significance (HR, 1.41; 95% CI, 0.97–2.03; \( P = 0.0691 \)).

**OS, DP, and DPB adjusted for baseline visceral metastases, bone metastases, or ECOG performance status category**

Significant associations of uNTx and sBSAP levels with OS, DP, and DPB were observed even after adjusting for factors associated with advanced cancer such as baseline visceral metastases, baseline multiple metastatic bone lesions, and baseline ECOG performance status category (Supplementary Table S2). After adjusting for baseline visceral metastases, uNTx levels ≥ median, compared with uNTx levels < median, were associated with reduced OS (HR, 1.81; 95% CI, 1.64–2.00; \( P < 0.0001 \)), greater risk of DP (HR, 1.29; 95% CI, 1.19–1.39; \( P < 0.0001 \)), and also greater risk of DPB (HR, 1.11; 95% CI, 1.00–1.23; \( P = 0.0469 \)). Similarly, sBSAP levels ≥ median, compared with sBSAP levels < median, were associated with reduced OS (HR, 2.41; 95% CI, 2.17–2.68; \( P < 0.0001 \)), greater risk of DP (HR, 1.69; 95% CI, 1.56–1.83; \( P < 0.0001 \)), and also greater risk of DPB (HR, 1.26; 95% CI, 1.14–1.41; \( P < 0.0001 \)). Similar results were observed after adjusting for baseline multiple metastatic bone lesions and baseline ECOG performance status category; that is, month 3 BTM levels ≥ median, compared with BTM levels < median, were associated with significantly reduced OS and a significantly increased risk of DP and DPB (Supplementary Table S2).

**Outcomes by category (≥ or < median) of month 3 BTM percentage change from baseline**

Overall, sBSAP level is reduced from baseline to month 3, with the median percentage change in sBSAP from baseline to month 3 of −35.6%. Patients who achieved a smaller reduction from baseline in sBSAP levels (i.e., percentage change from baseline ≥ −35.6%) had improved OS and decreased risk of DP and DPB. On the other hand, patients who achieved further reduction in sBSAP levels (i.e., percentage change from baseline < −35.6%) had improved OS and decreased risk of DP and DPB (Supplementary Fig. S2A–S2C). An association of outcomes and percentage change in uNTx levels was not observed (data not shown).

**Outcomes by uNTx and sBSAP combined category (≥ or < median) at month 3**

Assessment of patients’ month 3 combined uNTx and sBSAP levels demonstrated reduced OS for the HH group (uNTx and sBSAP both ≥ median at month 3) and LH group (uNTx < median and sBSAP ≥ median at month 3) compared with the HL (uNTx ≥ median and sBSAP < median at month 3) and LL groups (uNTx and sBSAP both < median at month 3; Fig. 4A). The risk of DP increased in the HH and LH groups compared with the LL and HL groups (Fig. 4B). A similar trend, though less pronounced, was also observed for DPB (Fig. 4C).

**Discussion**

In this retrospective study, we analyzed patient-level data from a total of 5,543 patients with advanced solid tumors and bone metastases who had participated in three identically designed phase III trials and had received the bone antiresorptive agents...
denosumab or zoledronic acid. Overall, our analysis demonstrated that ≥ median levels of the BTMs uNTx and sBSAP after 3 months of bone antiresorptive treatment were associated with significantly reduced OS and significantly increased risk of DP and DPB.

Across tumor types (breast cancer, prostate cancer, and NSCLC), month 3 uNTx and sBSAP levels ≥ median were associated with significantly reduced OS and a significantly increased risk of DP, consistent with data observed for all tumor types combined. However, the pattern of association of BTM levels ≥ median with DPB appeared to vary by tumor type. Month 3 levels of both uNTx and sBSAP ≥ median were associated with a significantly increased risk of DPB in patients with breast cancer but were not associated with an increased risk of DPB in patients with prostate cancer. In patients with breast cancer, whereas uNTx is an emerging marker (20, 38–40), sBSAP has been known to be a potential prognostic marker in bone metastases that are secondary to advanced cancer, whereas uNTx is an emerging marker (20, 38–40). However, to date, neither has been shown to be a definitive prognostic marker in this patient population. As such, an approach that includes assessing levels of both uNTx and sBSAP might provide combined uNTx and sBSAP levels at month 3 (Fig. 4A–C). Patients with high levels of both uNTx and sBSAP at month 3 (≥ median levels) had substantially reduced OS and an increased risk of DP and, to a lesser extent, an increased risk of DPB. A similar negative correlation was also observed in patients with high sBSAP (≥ median level) but low uNTx (< median level) at month 3.

Previous studies have shown the potential prognostic value of uNTx and sBSAP levels in patients with solid tumors and bone metastases. A recent study in patients with prostate cancer showed low baseline uNTx and sBSAP levels to be prognostic and to be associated with longer OS (35). Low uNTx and sBSAP levels were also shown to be associated with positive clinical outcomes in patients with bone metastases secondary to prostate cancer, NSCLC, or other solid tumors (20, 21, 36, 37), independent of whether patients had received bone antiresorptive agents. Similar to findings from our current study, Coleman and colleagues 2005 (20) reported significantly reduced OS and significantly increased risk of DPB in patients with persistently high uNTx levels (≥100 nmol/mmol creatinine) to moderate uNTx levels (50–99 nmol/mmol creatinine) versus patients with low uNTx levels (<50 nmol/mol creatinine). Also, that study reported significantly reduced OS and significantly increased risk of DPB in patients with persistently high sBSAP levels (≥146 U/L) versus patients with low sBSAP levels (<146 U/L).

Historically, sBSAP has been known to be a potential prognostic marker in bone metastases that are secondary to advanced cancer, whereas uNTx is an emerging marker (20, 38–40). However, to date, neither has been shown to be a definitive prognostic marker in this patient population. As such, an approach that includes assessing levels of both uNTx and sBSAP might provide

Figure 3.
DPB stratified by uNTx (A) and sBSAP (B) levels at month 3.

Excludes the myeloma patient population.
additional information regarding potential clinical outcomes in patients with advanced cancer and bone metastases.

Tumor growth in the bone is typically associated with increased rates of bone resorption and formation that might be reflected by increased levels of the biochemical markers of bone metabolism such as uNTx and sBSAP (20, 21). Therefore, modalities that reduce bone turnover rates might impact tumor growth, thus limiting DPB and improving survival (20, 21). Denosumab and zoledronic acid are potent bone antiresorptive agents that have been shown to significantly reduce the levels of BTMs such as uNTx and sBSAP (35, 34). As such, decreased levels of uNTx and sBSAP after treatment with denosumab or zoledronic acid might be an indicator of reduced tumor growth in the bone due to reduced bone turnover rates, whereas high levels of these BTMs might indicate continued tumor growth. However, data from our study do not address the reason for the observed associations between uNTx or sBSAP levels ≥ median at month 3 of antiresorptive therapy and worse clinical outcomes. Possible explanations for this observed association include the possibility that patients responding to therapy targeted at their primary tumors may have lower uNTx and sBSAP levels than those not responding to therapy, the possibility of involvement of bone antiresorptive agents, or reasons unrelated to the primary tumor or bone antiresorptive agents.

Other baseline variables shown to be associated with improved OS, mostly in patients with prostate cancer, include low alkaline phosphatase levels (35, 40, 41), absence of prior SREs (35, 42, 43), absence of visceral metastases (35, 40, 44), better ECOG performance status (35, 37, 40), low levels of PSA (35, 40), and high hemoglobin levels (35, 37, 40, 44). Monitoring PSA levels is limited to the prostate cancer setting, and even within this setting, challenges have been encountered with accurate interpretation of PSA levels following treatment with new therapies that may have novel mechanisms of action. As an example, sipuleucel-T was reported to improve survival with no impact on early PSA levels (45). In other cases, PSA values have been shown to first rise and then decline following effective systemic treatment, thus making timing of sampling an important factor (45, 46). As such, additional variables are needed for predicting clinical outcomes, especially markers that show prognostic value across tumor types.

Several limitations of our study must be noted. This study analyzed data from patients originally recruited for clinical trials in which individuals with poor performance (ECOG performance status >2) or serious medical illnesses were excluded from enrollment, thereby limiting the generalizability of our findings to real world settings. In our study, we defined high uNTx or sBSAP as ≥ median at month 3 of antiresorptive therapy, and these levels were used as cutoffs to determine association with clinical outcomes. However, these cutoff levels may not necessarily reflect definitive categorizations for these biochemical markers, and it is possible that different results could be obtained by choosing different cutoff levels. In addition, the three parent phase III studies were not prospectively designed to collect all potential covariates for OS, DP, and DPB as the objective of the original studies was to evaluate risk reduction for time to first SRE between denosumab and zoledronic acid. Another limitation is tumor heterogeneity in the analyzed patient population.

While the results of this study do not establish a causal link between decreased levels of sBSAP and uNTx and clinical outcomes, they suggest a potential utility for these BTMs as easily measurable, noninvasive, early predictors for response and survival in patients with advanced cancer and bone metastases who are receiving bone antiresorptive agents such as denosumab or zoledronic acid. In this patient population, changes in BTM levels to higher than or lower than levels at baseline might provide insights into potential clinical outcomes. Taken together, our findings and the findings from earlier studies appear to point to...
the gross prognostic value of sBSAP and uNTx levels, either at baseline or after treatment with bone antiresorptive agents. In conclusion, patients with BTM levels > median at month 3 of antiresorptive therapy had significantly worse clinical outcomes including OS, DP, and DPB than patients whose BTM levels were < median. Therefore, assessment of BTM levels after antiresorptive therapy may add to the identification of patients most at risk for decreased OS and increased DP and DPB in this patient population.

Disclosure of Potential Conflicts of Interest
K. Fizazi is a consultant/advisory board member for Amgen. A.T. Stopeck reports receiving a commercial research grant and speakers bureau honoraria from, and is a consultant/advisory board member for Amgen and Novartis. F. Saad is a consultant/advisory board member for Amgen. L. Zhu and D.J. Warner hold stock in Amgen Inc. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

References
Bone Turnover Markers in Patients with Advanced Cancer


Clinical Cancer Research

Changes in Bone Turnover Marker Levels and Clinical Outcomes in Patients with Advanced Cancer and Bone Metastases Treated with Bone Antiresorptive Agents

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