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Original Research

Effect of denosumab versus zoledronic acid in preventing skeletal-related events in patients with bone metastases by baseline characteristics

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Abstract ***Background:*** Analyses of phase III trials showed that denosumab was superior to zoledronic acid (ZA) in preventing skeletal-related events (SREs) irrespective of age, history of SREs, or baseline pain status. This analysis assessed the risk of SREs across additional baseline characteristics.

Patients and Methods: Patients (N = 5543) from three phase III trials who had breast cancer, prostate cancer, or other solid tumours and one or more bone metastasis were included. Superiority of denosumab versus ZA in reducing risk of first SRE and first and subsequent SREs was assessed in subgroups defined by the Eastern Cooperative Oncology Group performance

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status (ECOG PS), bone metastasis location, bone metastasis number, visceral metastasis presence/absence, and urinary N-telopeptide (uNTx) level using Cox proportional hazards and Anderson–Gill models. Subgroups except bone metastasis location were also assessed for each solid tumour type.

Results: Compared with ZA, denosumab significantly reduced the risk of first SRE across all subgroups (hazard ratio [HR] ranges: ECOG PS, 0.79–0.84; bone metastasis location, 0.78–0.83; bone metastasis number, 0.78–0.84; visceral metastasis presence/absence, 0.80–0.82; uNTx level, 0.73–0.86) and reduced the risk of first and subsequent SREs in all subgroups (HR ranges: ECOG PS, 0.76–0.83; bone metastasis location, 0.78–0.84; bone metastasis number, 0.79–0.81; visceral metastasis presence/absence, 0.79–0.81; uNTx level, 0.74–0.83). Similar results were observed in subgroups across tumour types.

Conclusion: Denosumab was superior to ZA in preventing SREs in patients with bone metastases from advanced cancer, regardless of ECOG PS, bone metastasis number, baseline visceral metastasis presence/absence, and uNTx level.

1. Introduction

Patients with bone metastases are at increased risk for skeletal complications, including pathologic fracture, spinal cord compression, and radiation or surgery to the bone, collectively termed skeletal-related events (SREs) [1]. SREs are associated with not only substantial morbidity but also greater mortality, increased pain, decreased quality of life, and increased treatment costs [2–6].

Bone-targeting agents have been shown to reduce SREs associated with bone metastases/lesions in patients with advanced solid tumours or multiple myeloma [6–11]. Denosumab is a fully human monoclonal antibody against RANK ligand (RANKL), an important regulator of osteoclast-mediated bone resorption [12]. In a prespecified combined analysis of three identically designed phase III randomised clinical trials, denosumab was superior to zoledronic acid (ZA) in reducing the risk of first on-study SRE (17% risk reduction; $P < 0.001$) and the risk of first and subsequent on-study SREs (18% risk reduction; $P < 0.001$) in patients with bone metastases/lesions from breast cancer, prostate cancer, or other solid tumours and multiple myeloma [13].

Previous publications have reported a variety of potential risk factors for the occurrence of SREs in patients with bone metastases from lung, breast, or prostate cancer, including history of SREs, Eastern Cooperative Oncology Group performance status (ECOG PS), extent of bone disease, pain status, and urinary N-telopeptide (uNTx) level, a frequently used bone turnover marker [14–19]. However, it is unknown whether such risk factors could be used to identify patients most likely to benefit from treatment with bone-targeted agents. Previous analyses of the phase III trials of denosumab described above have shown that denosumab was superior to ZA in preventing SREs regardless of patient age, SRE history, or baseline pain status [13]. In the current combined analysis of these three trials, we assessed the ability of denosumab every 4 weeks (Q4W) versus ZA Q4W to reduce the risk of SREs across a larger group of baseline characteristics, including ECOG PS, location of bone metastases, number of bone metastases, presence or absence of visceral metastases, and uNTx level, both in the overall population and by tumour type. These characteristics are typically considered by clinicians when evaluating patients for bone-targeted therapy.

2. Materials and methods

2.1. Patients

This was a post hoc analysis of three identically designed, double-blind, double-dummy phase III trials in patients with breast cancer (NCT00321464) [8], prostate cancer (NCT00321620) [9], or other solid tumours (NCT00330759) [10]. Patients with multiple myeloma were excluded (ZA, n = 93; denosumab, n = 87; Fig. 1). Eligible patients had radiographic evidence of at least one bone metastasis, adequate organ function, and ECOG PS ≤2. Exclusion criteria included creatinine clearance <30 ml/min (per ZA prescribing information) [20], life expectancy <6 months, and oral or intravenous bisphosphonate for treatment of bone metastases. Patients provided written informed consent; the trial protocols were approved by each site's ethics committee.

2.2. Trial design and treatment

Patients were randomised to receive subcutaneous denosumab 120 mg or intravenous ZA 4 mg Q4W (or equivalent creatinine clearance–adjusted dose of ZA per the prescribing information). Randomisation was

stratified by prior SRE and other factors specific to the cancer type (breast cancer, prostate cancer, or other solid tumours and multiple myeloma) in each trial. The other factors were prior oral bisphosphonate use, current chemotherapy, and geographic region in the breast cancer trial [8]; prostate-specific antigen and chemotherapy for prostate cancer within 6 weeks before randomisation in the prostate cancer trial [9]; and tumour type, previous SRE, and systemic anticancer therapy at enrolment in the trial for other solid tumours and multiple myeloma [10]. All patients, investigators, and trial sponsor personnel remained blinded to treatment.

2.3. Statistical analysis

The primary end-point of the phase III trials was time to first on-study SRE (assessed as noninferiority or superiority) [8–10]. SREs were defined as radiation therapy to bone (including radioisotopes), pathologic fracture (excluding trauma), surgery to bone, or spinal cord compression. Time to first and subsequent on-study SREs (assessed for superiority) was a secondary end-point. Radiologic assessments included skeletal surveys (i.e. radiographs) performed every 12 weeks and unscheduled radiographic examinations performed for symptoms. All radiographic evidence was assessed by blinded centralised image review. For each subgroup defined by the baseline characteristics investigated, time to first on-study SRE was assessed using a Cox proportional hazards model with treatment as a covariate and stratified by study and the randomisation stratification factors for the analysis in the overall population, as well as the analysis by tumour type. Similarly, time to first and subsequent on-study SREs was assessed using an Anderson–Gill model with treatment as a covariate and stratified by study and the randomisation stratification factors. Subgroups by treatment interactions were tested for each of the baseline characteristics in the models described above in the overall group by adding the subgroup and subgroup by treatment interaction in the model. All statistical comparisons were two-sided with a 0.05 level of significance. *P* values were not adjusted for multiplicity.

2.4. Analysis by baseline characteristics

The analysis of baseline characteristic subgroups included all trial patients except those with multiple myeloma (i.e. those with breast cancer, prostate cancer, or other solid tumours; Fig. 1). In the overall pooled analysis population, the superiority of denosumab versus ZA in reducing the risk of first on-study SRE and first and subsequent on-study SREs was assessed in patient subgroups defined by ECOG PS (0 versus ≥1), location of bone metastases per central imaging review (axial skeleton only [skull, vertebral column, ribs, and sternum] versus appendicular skeleton only [limbs and thoracic and pelvic girdles] versus both axial and appendicular skeleton), number of bone metastases per central imaging review (<2 versus ≥2), presence or absence of visceral metastases (yes versus no), and uNTx level (≥43.7 nmol/mmol [the median uNTx level observed across the three phase III trials] versus <43.7 nmol/mmol).

Among patients with each of the solid tumour types reported in the original trials except multiple myeloma (breast cancer, prostate cancer, or other solid tumours), the superiority of denosumab compared with ZA in reducing the risk of first on-study SRE and first and subsequent on-study SREs was assessed in subgroups based on ECOG PS (0 versus ≥1), number of bone metastases (<2 versus ≥2), presence or absence of

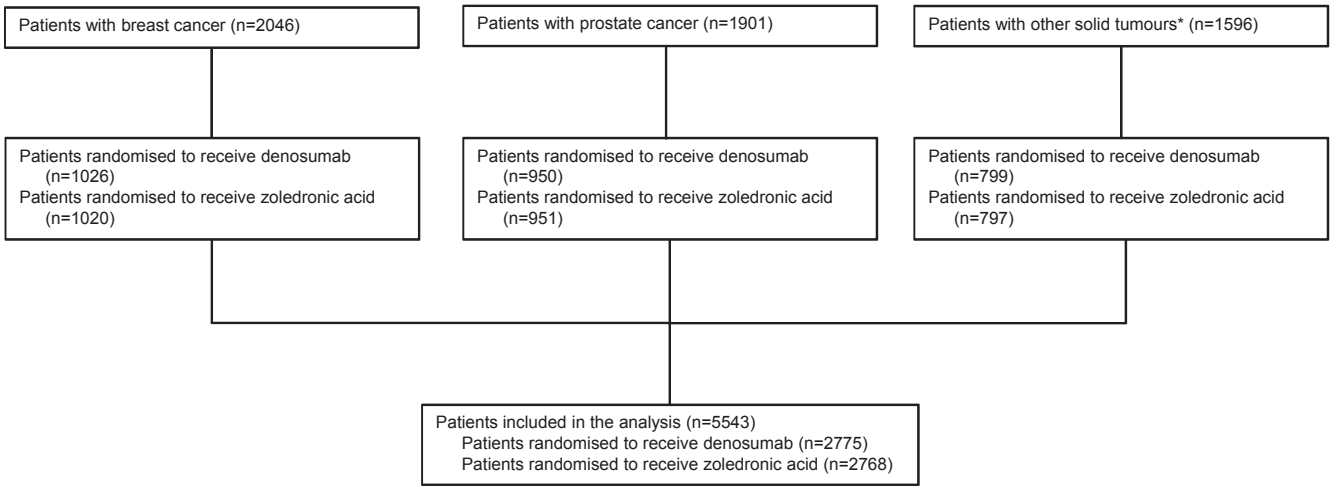

Fig. 1. Flowchart of patients included in the overall population analysis of baseline characteristic subgroups and in the analysis of baseline characteristic subgroups by solid tumour type. '*', Indicates that patients with multiple myeloma (zoledronic acid, n = 93; denosumab, n = 87) were excluded from this analysis.

visceral metastases (yes versus no), and uNTx level (≥43.7 nmol/mmol [median] or <43.7 nmol/mmol). When baseline characteristics were assessed by solid tumour type, there were insufficient data for the assessment of location of bone metastases.

3. Results

3.1. Patients

Of the 5732 patients enrolled in the three trials between April 2006 and October 2009, 5543 were included in the efficacy analysis (Fig. 1). Patient disposition for the three combined trials has been previously published [13]. Patient demographics and baseline disease characteristics were similar between treatment groups (Table 1).

3.2. Assessment of efficacy across baseline characteristics in overall population

The percentages of risk reduction for first on-study SRE and for first and subsequent on-study SREs with denosumab compared with ZA in the overall population (breast cancer, prostate cancer, or other solid tumours) are shown in Figs. 2 and 3, respectively. For time to first on-study SRE and time to first and subsequent on-study SREs, none of the subgroup by treatment interaction tests were statistically significant, indicating the consistency of treatment effects across the subgroups. Treatment with denosumab significantly reduced the risk of first on-study SRE compared with ZA across all baseline subgroups, including ECOG PS (0 versus ≥1) at baseline, location of bone metastases (axial versus appendicular versus both), number of bone metastases (<2 versus ≥2), presence or absence of visceral metastasis (yes versus no), and uNTx level (≥43.7 nmol/mmol [median] or <43.7 nmol/mmol) (Fig. 2). Similarly, treatment with denosumab significantly reduced the risk of first and subsequent on-study SREs compared with ZA across all the baseline subgroups, with the exception of the appendicular skeleton subgroup (the smallest subgroup assessed), which failed to meet nominal statistical significance ($P = 0.072$) despite having a point estimate that was similar to the other metastasis locations (Fig. 3).

Median time to first on-study SRE was longer with denosumab compared with ZA across all baseline subgroups (Supplemental Table 1).

3.3. Assessment of efficacy across baseline characteristics by solid tumour type

Further analysis of four baseline characteristic subgroups (ECOG PS, number of bone metastases, presence or absence of visceral metastasis, and uNTx level) showed a reduced risk of first on-study SRE with denosumab versus ZA among patients with each solid tumour type (breast cancer, prostate cancer, and other solid tumours). Sample size was limited for some subgroups in the analysis by tumour type, which may limit interpretation of these data (Fig. 4). Similar outcomes were observed for first and subsequent SREs (Fig. 5). Consistent with the assessment in the overall population, none of the subgroup treatment interaction tests by tumour type were statistically significant.

4. Discussion

Several risk factors for the occurrence of SREs have been identified in patients with bone metastases from lung, breast, or prostate cancer, including history of SREs, ECOG PS, extent of bone disease, pain status, and uNTx level [14–19]. In this combined analysis of three identically designed trials, we assessed whether denosumab Q4W was superior to ZA Q4W in reducing the risk of SREs across patient subgroups by the baseline characteristics that have been identified as potential risk factors for SREs and that are among those commonly considered by clinicians when considering bone-targeted therapy. We found that denosumab Q4W was superior to ZA Q4W in reducing the risk of first on-study SRE and first and subsequent on-study SREs, irrespective of key patient baseline characteristics such as ECOG PS, number of bone metastases, presence or absence of visceral metastases, and baseline uNTx level. These results were consistent across solid tumour types (breast cancer, prostate cancer, and other solid tumours).

Table 1
Patient demographics and baseline characteristics.

Characteristic	Zoledronic acid (n = 2768)	Denosumab (n = 2775)
Tumour type, n (%)		
Breast	1020 (37)	1026 (37)
Prostate	951 (34)	950 (34)
Other solid tumours	797 (29)	799 (29)
ECOG performance status,[a] n (%)		
0	1120 (41)	1141 (41)
≥1	1640 (59)	1631 (59)
Location of bone metastases,[b,c] n (%)		
Axial only	672 (24)	706 (25)
Appendicular only	345 (13)	387 (14)
Axial and appendicular	833 (30)	804 (29)
Number of bone metastases, n (%)		
<2	1696 (61)	1689 (61)
≥2	1072 (39)	1086 (39)
Presence or absence of visceral metastasis, n (%)		
Yes	1152 (42)	1185 (43)
No	1616 (58)	1590 (57)
Median uNTx level,[d] n (%)		
≥43.7 nmol/mmol	1222 (44)	1254 (45)
<43.7 nmol/mmol	1246 (45)	1229 (44)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; uNTx, urinary N-telopeptide.
[a] n = 2760 for zoledronic acid; n = 2772 for denosumab.
[b] n = 1850 for zoledronic acid; n = 1897 for denosumab.
[c] Per central imaging review.
[d] n = 2468 for zoledronic acid; n = 2483 for denosumab.

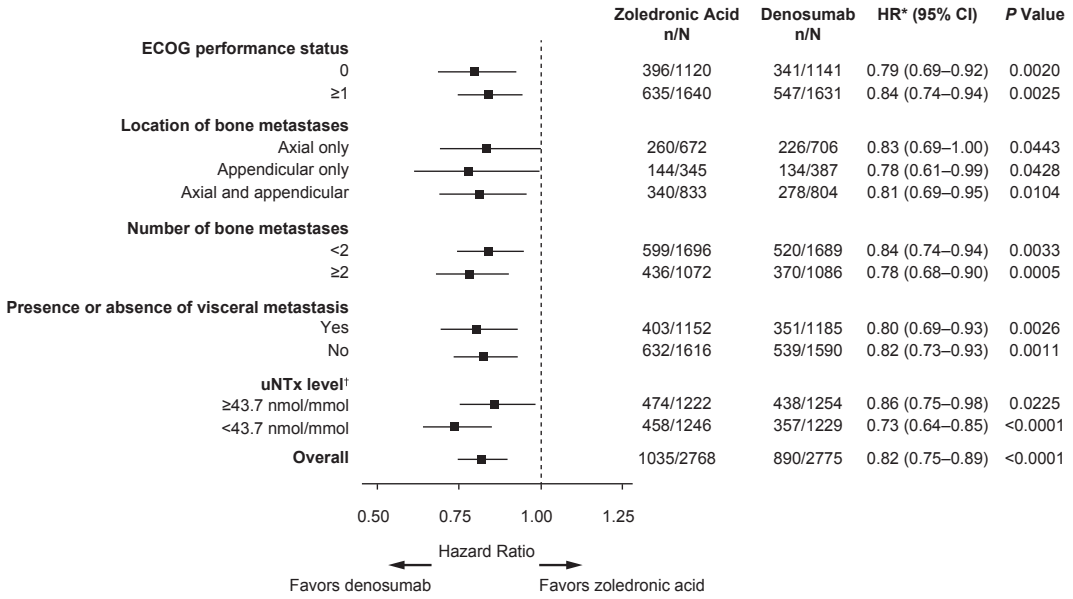

Fig. 2. Risk of first on-study SRE by baseline characteristic subgroups in the overall analysis population. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; SRE, skeletal-related event; uNTx, urinary N-telopeptide; n, number of patients with events; N, number of randomised patients. '*', Based on a Cox proportional hazards model with treatment groups as the independent variable stratified by the randomisation stratification factors. '†', Median = 43.7 nmol/mmol.

Consistent with the results of this analysis, Lipton et al [13] found that denosumab Q4W reduced the risk of SRE compared with ZA Q4W in patients with a previous SRE (16% risk reduction; $P = 0.01$), in those without a previous SRE (18% risk reduction; $P < 0.001$), and in patients <65 and ≥65 years of age (18% risk reduction for both groups; $P < 0.01$). In another analysis of these trials, von Moos et al [21] reported that denosumab Q4W significantly delayed time to first SRE compared with ZA Q4W in patients with no/mild baseline pain at trial entry (16% risk reduction; $P = 0.01$) and in those with moderate/severe pain at trial entry (17% risk reduction; $P = 0.003$). The risk reductions achieved in these

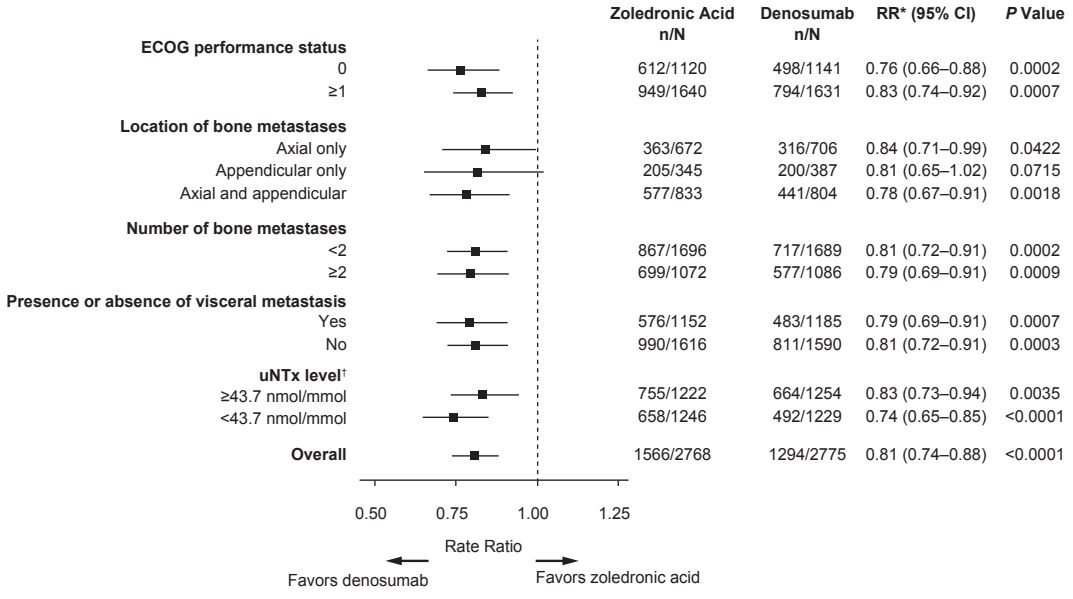

Fig. 3. Risk of first and subsequent on-study SREs by baseline characteristic subgroups in the overall analysis population. ECOG, Eastern Cooperative Oncology Group; RR, rate ratio; SRE, skeletal-related event; uNTx, urinary N-telopeptide; n, the number of patients with events; N is the number of randomised patients. '*', Based on an Andersen–Gill model stratified by the randomisation stratification factors. '†', Median = 43.7 nmol/mmol.

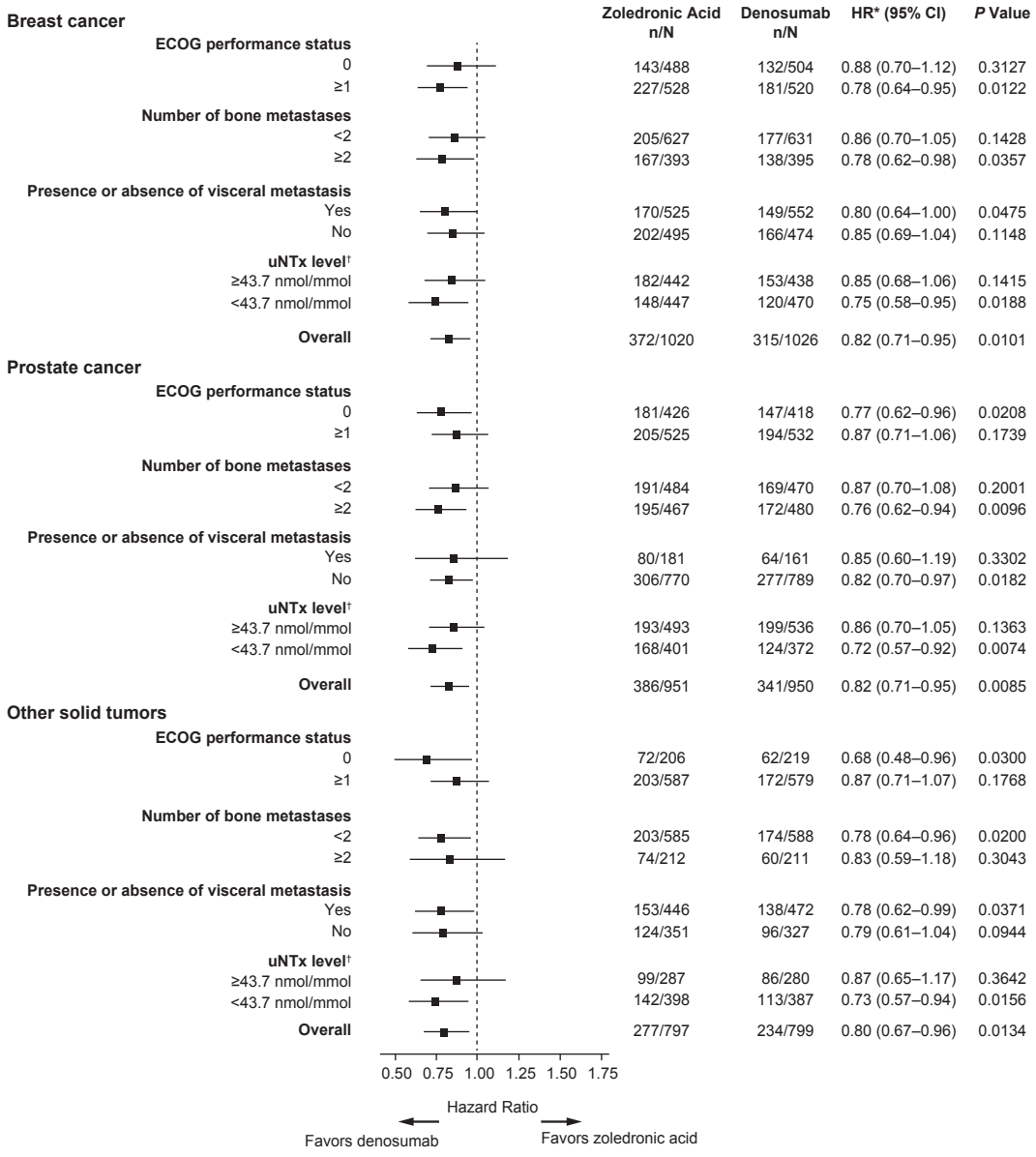

Fig. 4. Risk of first on-study SRE by baseline characteristic subgroups in patients with breast cancer, prostate cancer, or other solid tumours. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; SRE, skeletal-related event; uNTx, urinary N-telopeptide; n, the number of patients with events; N is the number of randomised patients. '*', Based on a Cox proportional hazards model with treatment groups as the independent variable stratified by the randomisation stratification factors. '†', Median = 43.7 nmol/mmol.

subgroups were of a similar magnitude to those in the current subgroup analysis. In the proof-of-concept randomised phase II trial in patients with bone metastases/lesions from breast cancer, prostate cancer, or other neoplasms and multiple myeloma who had elevated uNTx levels and prior exposure to intravenous bisphosphonates, treatment with denosumab resulted in a greater reduction in osteolysis and a lower incidence of on-study SREs compared with intravenous bisphosphonate [22–24].

A strength of this study was its use of a patient-level combined analysis approach, which allowed for the evaluation of clinical characteristics. Our results suggest that in all subgroups of patients, denosumab provided superior protection against the development of SREs, confirming the importance of the RANK/RANKL pathway in SRE pathophysiology in patients with bone metastases from solid tumours. Previous analyses have also shown a greater treatment effect of denosumab versus ZA in preventing SREs regardless of prior SREs [13] and increased baseline pain [21]. As with previous analyses assessing baseline characteristics and SRE risk, this study was limited by its post hoc design and the analyses of multiple end-points by multiple subgroup variables that were not corrected for in the statistical design. In addition, small sample sizes in several

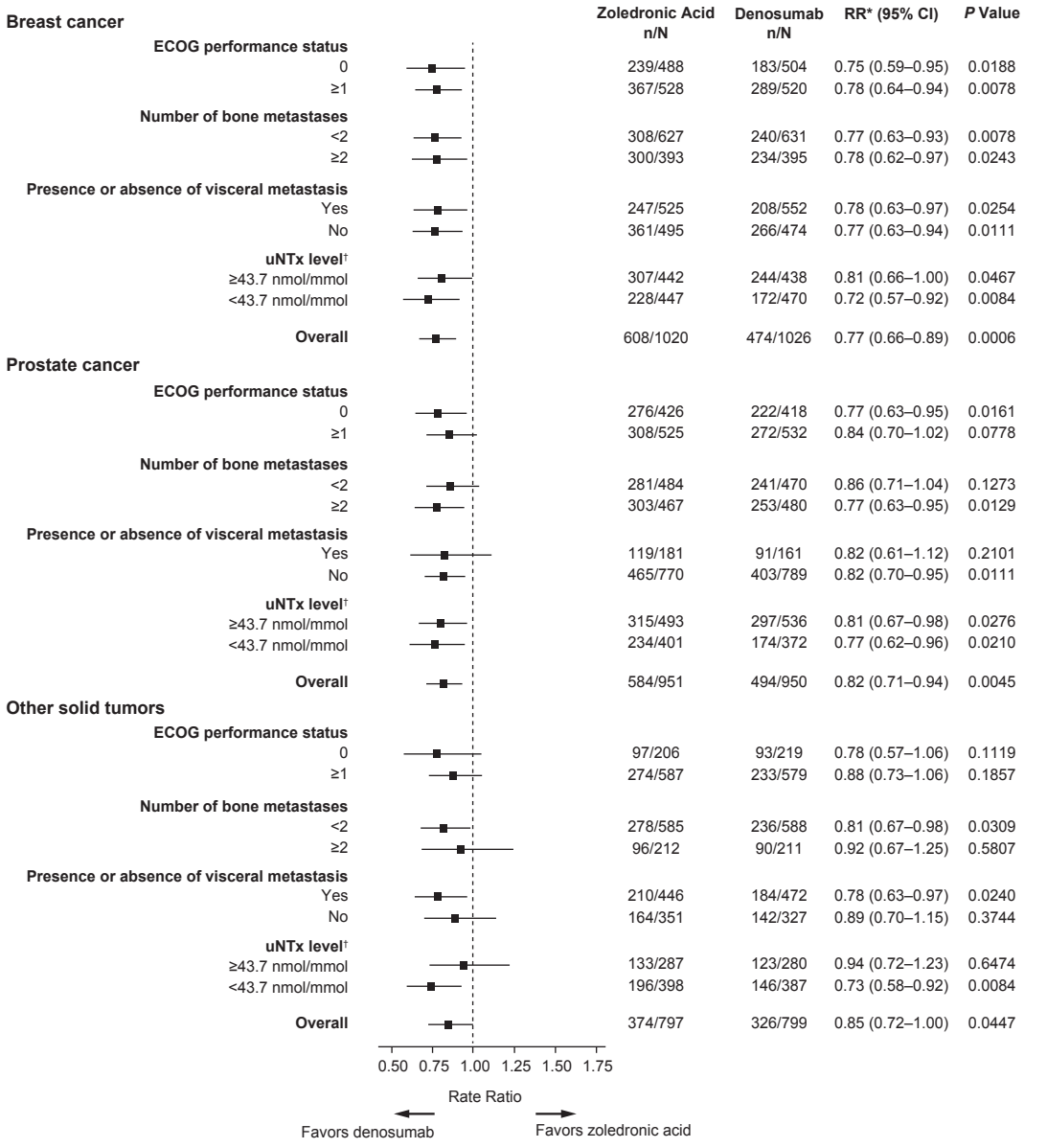

Fig. 5. Risk of first and subsequent on-study SREs by baseline characteristic subgroups in patients with breast cancer, prostate cancer, or other solid tumours. ECOG, Eastern Cooperative Oncology Group; RR, rate ratio; SRE, skeletal-related event; uNTx, urinary N-telopeptide; n, number of patients with events; N, number of randomised patients. '*', Based on an Andersen–Gill model stratified by the randomisation stratification factors. '†', Median = 43.7 nmol/mmol.

subgroups may limit interpretation of subgroup analyses by specific tumour types.

In conclusion, this analysis showed that denosumab Q4W is superior to ZA Q4W in preventing SREs in all patients with metastatic bone disease, regardless of the baseline characteristics of ECOG PS, number of bone metastases, presence or absence of visceral metastases, and uNTx level.

Conflict of interest statement

AL has received honoraria from, has served as a consultant/advisor for, has received research funding from and provided expert testimony for Amgen Inc. and Novartis. KF received honoraria from and has served as a consultant/advisor for Amgen Inc. and Novartis. ATS has received honoraria from Amgen Inc., GlaxoSmithKline, and Genentech, has served as a consultant/advisor for Amgen Inc., Clovis, Pfizer, CSL Behring, and Bayer, has participated in speakers' bureau for Genomic Health, and received research funding from Amgen Inc., Novartis, Bayer, and Puma. DHH has served as a consultant/advisor for and has received research funding and travel expenses from Amgen Inc. MRS has served as a consultant/advisor for and has received research funding from Amgen Inc. NS has served as a consultant/advisor for Astellas, Bayer, Dendreon, Janssen, Medivation, and Sanofi. MM has

received honoraria from and has served as a consultant/advisor for Amgen Inc. SV-R has received honoraria from, has served as a consultant/advisor for, and has received research funding from Amgen Inc. JEB has received honoraria from Amgen Inc., has served as a consultant/advisor for Amgen Inc., Novartis, and Bristol Myers Squibb, has participated in speakers' bureau for GlaxoSmithKline, and holds patents. GER has received research funding from the Cabrini Institute. FS has received honoraria from and served as a consultant/advisor for Amgen Inc. DAY declared no conflict of interest. KZ is an employee for and owns stock in Amgen Inc. AB is an employee for and owns stock in Amgen Inc. and Merck. AB is an employee of and owns stock in Amgen Inc. and Biothera.

Role of the funding source

This work and the included studies were sponsored by Amgen Inc. The study sponsor, in collaboration with the investigators, designed the protocols of the included studies and analysed and interpreted the data. The authors made the final decision to submit the manuscript for publication. All authors contributed to the writing and/or editing of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2015.09.011.

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