# Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study

*Karim Fizazi, Michael Carducci, Matthew Smith, Ronaldo Damião, Janet Brown, Lawrence Karsh, Piotr Milecki, Neal Shore, Michael Rader, Huei Wang, Qi Jiang, Sylvia Tadros, Roger Dansey, Carsten Goessl*

## Summary

**Background** Bone metastases are a major burden in men with advanced prostate cancer. We compared denosumab, a human monoclonal antibody against RANKL, with zoledronic acid for prevention of skeletal-related events in men with bone metastases from castration-resistant prostate cancer.

**Methods** In this phase 3 study, men with castration-resistant prostate cancer and no previous exposure to intravenous bisphosphonate were enrolled from 342 centres in 39 countries. An interactive voice response system was used to assign patients (1:1 ratio), according to a computer-generated randomisation sequence, to receive 120 mg subcutaneous denosumab plus intravenous placebo, or 4 mg intravenous zoledronic acid plus subcutaneous placebo, every 4 weeks until the primary analysis cutoff date. Randomisation was stratified by previous skeletal-related event, prostate-specific antigen concentration, and chemotherapy for prostate cancer within 6 weeks before randomisation. Supplemental calcium and vitamin D were strongly recommended. Patients, study staff, and investigators were masked to treatment assignment. The primary endpoint was time to first on-study skeletal-related event (pathological fracture, radiation therapy, surgery to bone, or spinal cord compression), and was assessed for non-inferiority. The same outcome was further assessed for superiority as a secondary endpoint. Efficacy analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00321620, and has been completed.

**Findings** 1904 patients were randomised, of whom 950 assigned to denosumab and 951 assigned to receive zoledronic acid were eligible for the efficacy analysis. Median duration on study at primary analysis cutoff date was 12·2 months (IQR 5·9–18·5) for patients on denosumab and 11·2 months (IQR 5·6–17·4) for those on zoledronic acid. Median time to first on-study skeletal-related event was 20·7 months (95% CI 18·8–24·9) with denosumab compared with 17·1 months (15·0–19·4) with zoledronic acid (hazard ratio 0·82, 95% CI 0·71–0·95; p=0·0002 for non-inferiority; p=0·008 for superiority). Adverse events were recorded in 916 patients (97%) on denosumab and 918 patients (97%) on zoledronic acid, and serious adverse events were recorded in 594 patients (63%) on denosumab and 568 patients (60%) on zoledronic acid. More events of hypocalcaemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 [6%]; p<0·0001). Osteonecrosis of the jaw occurred infrequently (22 [2%] *vs* 12 [1%]; p=0·09).

**Interpretation** Denosumab was better than zoledronic acid for prevention of skeletal-related events, and potentially represents a novel treatment option in men with bone metastases from castration-resistant prostate cancer.

**Funding** Amgen.

*Lancet* 2011; 377: 813–22

Published Online February 25, 2011 DOI:10.1016/S0140-6736(10)62344-6

See Comment page 785

**Institut Gustave Roussy, University of Paris Sud, Villejuif, France** (Prof K Fizazi MD); **Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA** (M Carducci MD); **Massachusetts General Hospital Cancer Center, Boston, MA, USA** (M Smith MD); **Hospital Universitario Pedro Ernesto, Rio de Janeiro, Brazil** (Prof R Damião MD); **Cancer Research UK Clinical Centre, Leeds, UK** (J Brown MD); **Urology Center of Colorado, Denver, CO, USA** (L Karsh MD); **Wielkopolskie Centrum Onkologii, Poznań, Poland** (P Milecki MD); **Carolina Urologic Research Center, Myrtle Beach, SC, USA** (N Shore MD); **Union State Bank Cancer Center, Nyack Hospital, Nyack, NY, USA** (M Rader MD); **and Amgen, Thousand Oaks, CA, USA** (H Wang PhD, Q Jiang PhD, S Tadros MPH, R Dansey MD, C Goessl MD)

Correspondence to: Prof Karim Fizazi, Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Sud, 39 rue Camille Desmoulins, Villejuif 94805, France
**fizazi@igr.fr**

## Introduction

In western countries, prostate cancer is the most common non-dermatological malignant disease in men. An estimated 217730 new cases will have been diagnosed in 2010 in the USA[1] and 382250 cases were diagnosed in 2008 in Europe,[2] accounting for 28% and 22% of new non-cutaneous cancer diagnoses, respectively. Bone metastases often develop in patients with advanced prostate cancer; the associated complications present a substantial disease and economic burden.[3]

Since the late 1990s, the assessment of bone-targeted agents for treatment of bone metastases has been based on the endpoint of skeletal-related events, a composite of local skeletal complications consisting of pathological fracture, spinal cord compression, and radiotherapy or surgery to bone. This composite endpoint was the primary endpoint in a phase 3 study in which intravenous zoledronic acid was better than placebo for prevention of skeletal-related events in patients with bone metastases from castration-resistant prostate cancer.[4,5]

Although bone metastases from prostate cancer have a predominantly osteoblastic appearance, histological findings[6] and analysis of bone turnover markers[7,8] support the view that excess osteoclastic activity induces bone destruction in these metastases.[9] RANKL is the main driver of osteoclast formation, function, and

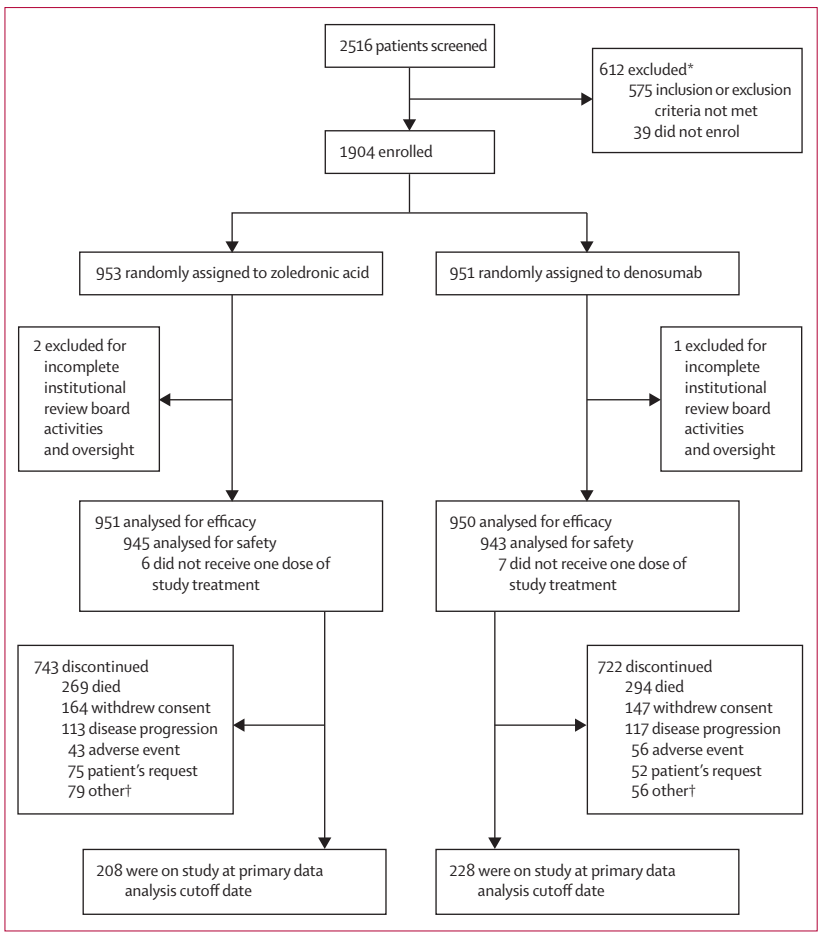


***Figure 1:*** **Trial profile**
*Most common reasons for exclusion were evidence of bone metastasis (n=124 patients), serum testosterone of 1·72 nmol/L or higher (n=54), and informed consent not given (n=52); two patients were excluded because they did not meet inclusion or exclusion criteria and because they did not enrol. †Includes six terms with less than 5% occurrence: miscellaneous, lost to follow-up, non-compliance, protocol deviation, ineligibility established, and administrative decision.

survival.[10] In-vitro co-culture of prostate cancer cells with osteoblasts produced upregulation of RANKL and downregulation of the endogenous RANKL inhibitor OPG.[11] In-vivo inhibition of RANKL in an osteoblastic prostate cancer model also decreased sclerotic changes in the bone.[12] Denosumab is a human monoclonal antibody against RANKL; it inhibits osteoclast-mediated bone destruction and is being investigated in clinical studies in men with advanced prostate cancer,[13] including for prevention of bone metastases. We undertook a phase 3 study to compare the efficacy and safety of denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer.

## Methods

### Patients

In this phase 3 study undertaken between May, 2006, and October, 2009, men aged 18 years or older were enrolled from 342 centres in 39 countries worldwide. Eligible patients had histologically confirmed prostate cancer, existing or previous radiographic evidence of at least one bone metastasis, and documented failure of at least one hormonal therapy, indicated by a rising prostate-specific antigen concentration, with a final concentration of 0·4 μg/L or higher within 8 weeks of randomisation in the setting of castrate serum testosterone concentrations (<1·72 nmol/L by chemical or surgical castration). Other inclusion criteria were adequate organ function, an albumin-adjusted serum calcium concentration of 2·0–2·9 mmol/L, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Key exclusion criteria included current or previous treatment with intravenous bisphosphonate or oral bisphosphonate for bone metastasis (although previous oral bisphosphonate use for osteoporosis was allowed provided treatment was stopped before the first dose of investigational drug), planned radiation therapy or surgery to bone, life expectancy of less than 6 months, current or previous osteonecrosis or osteomyelitis of the jaw, any planned invasive dental procedure during the study, a malignant disease other than prostate cancer within the past 3 years, or creatinine clearance of less than 0·5 mL/s (because zoledronic acid is contraindicated in such patients).[14]

The study was done according to the Declaration of Helsinki and the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice. Approvals from appropriate research ethics committees were obtained from each study centre. All patients provided written informed consent before any study-specific procedure. An external independent Data Monitoring Committee (DMC) convened twice yearly to monitor patient safety and efficacy throughout the study.

### Randomisation and masking

The computer-generated randomisation schedule was prepared by an individual independent of the study team. An interactive voice response system was used to assign patients (1:1 ratio) to receive subcutaneous denosumab (XGEVA, Amgen, Thousand Oaks, CA, USA) plus intravenous placebo, or subcutaneous placebo plus intravenous zoledronic acid (Zometa, Novartis, East Hanover, NJ, USA). Randomisation was stratified by previous skeletal-related event (yes *vs* no), prostate-specific antigen concentration (<10 *vs* ≥10 mg/mL), and chemotherapy for prostate cancer within 6 weeks before randomisation (yes *vs* no). Patients, study staff, and investigators were masked to treatment assignment throughout the primary analysis period; DMC members were unmasked to treatment assignment.

### Procedures

Patients received 120 mg denosumab or 4 mg zoledronic acid (or equivalent creatinine clearance-adjusted dose

of zoledronic acid in patients with baseline creatinine clearance of ≤1·0 mL/s) every 4 weeks, until the primary analysis cutoff date. In this double-dummy study, the volume of intravenous or subcutaneous placebo was equivalent to that of the active drug given in the opposite treatment group. Intravenous treatments were given for at least 15 min. As per the prescribing information for zoledronic acid, dose adjustments of intravenous treatments (zoledronic acid or placebo) were made at baseline by use of the Cockcroft-Gault formula, and intravenous treatments were withheld for any patient with renal deterioration until recovery to within 10% of the baseline creatinine value.[14] No dose adjustments or withholding were required for subcutaneous treatments (denosumab or placebo). We strongly recommended that all patients take daily supplemental calcium (≥500 mg) and vitamin D (≥400 IU).

The primary endpoint was time to first on-study skeletal-related event, and was assessed for non-inferiority. If testing of the primary endpoint showed non-inferiority, then the same outcome was further tested as a secondary endpoint, together with the secondary endpoint of time to first and subsequent on-study skeletal-related events (multiple events), for superiority. Because this study was event-driven, time on study was from enrolment to discontinuation for individual patients, or until the primary analysis cutoff date, whichever occurred first. Protocol-specified treatment discontinuation occurred when patients received open-label intravenous or oral bisphosphonates.

Key exploratory endpoints were overall survival, investigator-assessed overall disease progression (encompassing visceral distant metastatic disease, loco-regional progression, and biochemical progression, and excluding skeletal-related events), prostate-specific antigen concentration during the study, and change in bone turnover markers from baseline. Safety endpoints included frequency of treatment-emergent adverse events, changes in routine chemistry and haematology laboratory values, and presence of neutralising anti-denosumab antibodies.

Safety assessments for adverse events, routine chemistry and haematology laboratory studies, and concomitant drug treatments were done at baseline and every 4 weeks thereafter. Skeletal surveys done at baseline and every 12 weeks included radiographs of the skull, spine, chest, pelvis, arm from shoulder to elbow, and leg from hip to knee. A skeletal-related event was defined as a pathological fracture (excluding fractures from severe trauma), radiation therapy to bone (including use of radioisotopes), surgery to bone, or spinal cord compression. Two central imaging readers confirmed all site-reported skeletal-related events of pathological fracture and spinal cord compression by masked radiological assessment, and a third reviewer adjudicated differences. As in previous trials of zoledronic acid,[4,5,14] new bone metastases (symptomatic or asymptomatic) were not included in the definition of skeletal-related events. ECOG performance status and prostate-specific antigen were assessed at baseline and every 12 weeks. Prostate-specific antigen and routine laboratory values were assessed by a central laboratory. Bone turnover markers of urinary N-telopeptide adjusted for creatinine (uNTx/Cr) and serum bone-specific alkaline phosphatase were measured at baseline and week 13. Adverse events potentially associated with renal toxicity were identified by use of a list of 49 predefined terms in the Medical Dictionary for Regulatory Activities (MedDRA). Similarly, adverse events potentially associated with acute phase reactions were compiled from a list of 37 predefined MedDRA terms.

Potential cases of osteonecrosis of the jaw were identified by oral examinations, review of reported adverse events with 36 predefined MedDRA terms potentially indicating osteonecrosis of the jaw, and clinical review of all other adverse events. Each potential event was reviewed by an independent, masked external expert adjudication committee.

| | Zoledronic acid (n=951) | Denosumab (n=950) |
|---|---|---|
| Age (years) | 71 (66–77) | 71 (64–77) |
| <65 | 216 (23%) | 253 (27%) |
| ≥65 | 735 (77%) | 697 (73%) |
| Race | | |
| White | 810 (85%) | 829 (87%) |
| Other | 141 (15%) | 121 (13%) |
| ECOG performance status 0–1 | 886 (93%) | 882 (93%) |
| Time from diagnosis of prostate cancer to randomisation (months) | 41·2 (18·3–82·0) | 37·5 (18·1–75·4) |
| Time from diagnosis of bone metastases to randomisation (months) | 5·19 (1·31–16·10) | 3·94 (1·22–15·67) |
| Presence of visceral metastases | 181 (19%) | 161 (17%) |
| Recent chemotherapy*† | 132 (14%) | 132 (14%) |
| Haemoglobin concentration (g/L) | 126 (16) | 125 (16) |
| Creatinine clearance of ≥1·5 mL/s | 333 (35%) | 331 (35%) |
| PSA at randomisation (μg/L)* | 60·0 (19·8–202·2) | 58·5 (18·2–225·6) |
| <10 | 145 (15%) | 145 (15%) |
| ≥10 | 806 (85%) | 805 (85%) |
| Gleason score at diagnosis | | |
| 2–6 | 180 (19%) | 175 (18%) |
| 7 | 280 (29%) | 273 (29%) |
| 8–10 | 408 (43%) | 394 (41%) |
| Missing | 83 (9%) | 108 (11%) |
| Bone turnover markers | | |
| Bone-specific alkaline phosphatase (μg/L) | 31·8 (17·2–82·2) | 34·3 (17·5–90·0) |
| Urinary N-telopeptide (nmol/mmol) | 49·7 (27·4–112·0) | 53·9 (28·4–111·9) |
| Previous skeletal-related event* | 231 (24%) | 232 (24%) |

Data are median (IQR), number (%), or mean (SD). ECOG=Eastern Cooperative Oncology Group. PSA=prostate-specific antigen. *Based on stratification at randomisation. †Within 6 weeks before randomisation.

***Table 1:*** **Baseline demographic and clinical characteristics**

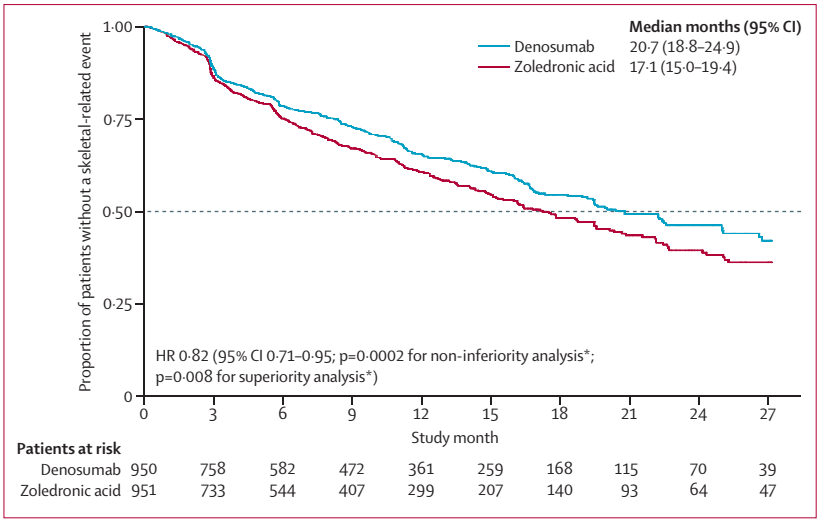


***Figure 2:*** **Kaplan-Meier estimates of time to first on-study skeletal-related event**
Patients were assessed from baseline to the primary analysis cutoff date. HR=hazard ratio. *p values were adjusted for multiplicity.

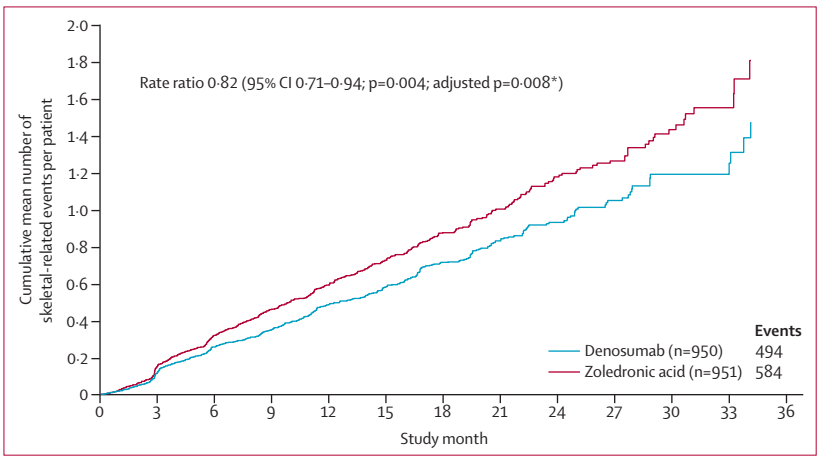


***Figure 3:*** **Time to first and subsequent on-study skeletal-related events**
Events occurred at least 21 days apart. *Adjusted for multiplicity.

| | Zoledronic acid (n=951) | Denosumab (n=950) |
|---|---|---|
| Total confirmed events | 386 (41%) | 341 (36%) |
| Radiation to bone | 203 (21%) | 177 (19%) |
| Pathological fracture | 143 (15%) | 137 (14%) |
| Spinal cord compression | 36 (4%) | 26 (3%) |
| Surgery to bone | 4 (<1%) | 1 (<1%) |

Data are number (%).

***Table 2:*** **Patients with first on-study skeletal-related events by type**

## Statistical analysis

The main analysis of both primary and secondary efficacy endpoints included all randomised patients, irrespective of administration of study treatments (intention to treat). To assess the time to first skeletal-related event (primary endpoint), the hazard ratio (HR, 95% CI) of denosumab compared with zoledronic acid was estimated by use of a Cox proportional hazards model with treatment group as the independent variable stratified by the randomisation factors of previous skeletal-related event, prostate-specific antigen concentration, and chemotherapy within 6 weeks before randomisation.

On the basis of Saad and colleagues study,[5] the estimated HR of zoledronic acid versus placebo was 0·677 (95% CI 0·505–0·908).[5] In our study, we calculated that if the true HR was 0·90, 745 patients with one or more skeletal-related events would provide 90% power to detect non-inferiority of denosumab to zoledronic acid. This hypothesis was based on a synthesis approach[15] designed to show that denosumab preserves at least 50% of the effect of zoledronic acid. Assuming a true HR of 0·80 for both secondary endpoints and a correlation coefficient of 0·6 between the two secondary endpoints, 745 patients with one or more skeletal-related events would provide 90% power to detect superiority of denosumab to zoledronic acid for at least one of the two secondary endpoints after adjustment for multiplicity.

For time-to-event variables, the Kaplan-Meier method was used to estimate the median time and associated 95% CI. For time to first and subsequent on-study skeletal-related events, an Andersen-Gill model with robust variance estimate, stratified by the randomisation factors, was used to test for superiority of denosumab to zoledronic acid.[16] The significance level for the primary endpoint of non-inferiority was 0·05. Once the primary endpoint of non-inferiority was confirmed, secondary endpoints were tested simultaneously by use of the Hochberg procedure at a signficance level of 0·05.[17] No formal interim analyses were planned.

For exploratory endpoints of overall survival and investigator-reported disease progression, the HR (95% CI) of denosumab versus zoledronic acid was estimated in all randomised patients by use of a proportional hazards model stratified by randomisation factors and baseline covariates, including age, time from primary diagnosis of prostate cancer to metastatic disease, time from initial diagnosis of prostate cancer to initial bone metastatic disease, visceral metastasis, Gleason score, and ECOG performance status. The overall survival analysis included all patients on study from baseline up to the primary analysis cutoff date or in survival follow-up. Bone turnover markers were compared between treatment groups for patients who had assessments at both baseline and week 13 by use of the van Elteren test stratified by the randomisation factors.

The safety dataset included all patients from the full analysis set who received at least one dose of study treatment. Patients were analysed according to the treatment received. Descriptive statistics were used for most safety analyses. All treatment-emergent adverse

events were coded according to MedDRA (version 12.1) and Common Terminology Criteria for Adverse Events (version 3.0), and were characterised by assessment of frequency and severity of events. We measured changes in routine chemistry and haematology laboratory values, and number (%) of patients who developed anti-denosumab antibodies. Prespecified analyses of positively adjudicated osteonecrosis of the jaw compared event rates between denosumab and zoledronic acid by use of Fisher's exact test. Comparisons in adverse events between treatment groups were done ad hoc by use of Fisher's exact test and unadjusted p values were reported.

This study is registered with ClinicalTrials.gov, number NCT00321620, and has been completed.

### Role of the funding source

The corresponding author collaborated with the sponsor to design the protocol. Data collection and analysis were done by the sponsor. The authors had full access to the data for interpretation. All authors, including those employed by the sponsor, participated in the drafting and critical review of the article for important intellectual content, with the assistance of a medical writer provided by the sponsor. The corresponding author was responsible for the final decision to submit the report for publication.

## Results

1904 patients were randomly assigned to treatment between May 12, 2006 and Dec 18, 2008, of whom 951 assigned to receive zoledronic acid and 950 assigned to receive denosumab were eligible for efficacy analyses (figure 1). A protocol amendment on May 5, 2008, increased the sample size by 10% from 1700 to 1870 patients to account for slower than projected enrolment. By the primary analysis cutoff on Oct 30, 2009, about 41 months from the start of enrolment, we expected that about 745 first skeletal-related events would have occurred. At this date, median time on study was 12·2 months (IQR 5·9–18·5) for the denosumab group and 11·2 months (IQR 5·6–17·4) for the zoledronic acid group.

Age, race, ECOG performance status, bone turnover markers, and Gleason score were balanced between treatment groups at baseline (table 1). Patients in the zoledronic acid group had a slightly longer median time from diagnosis of bone metastases to randomisation, but the IQRs were similar. Previous oral bisphosphonate use was reported by 24 patients (3%) on denosumab and 33 patients (3%) on zoledronic acid. On-study use of calcium and vitamin D was reported by 850 patients (90% of 943) in the denosumab group and 822 patients (87% of 945) in the zoledronic acid group.

942 patients (99%) assigned to receive denosumab were exposed to denosumab for a median of 11·9 months (IQR 5·6–18·2, maximum 40·5), and 946 patients (99%) assigned to receive zoledronic acid were exposed to zoledronic acid for a median of 10·2 months (IQR 4·9–16·6, maximum 37·4). Of patients on zoledronic acid, 213 (22%) needed protocol-mandated dose adjustments for baseline creatinine clearance, and

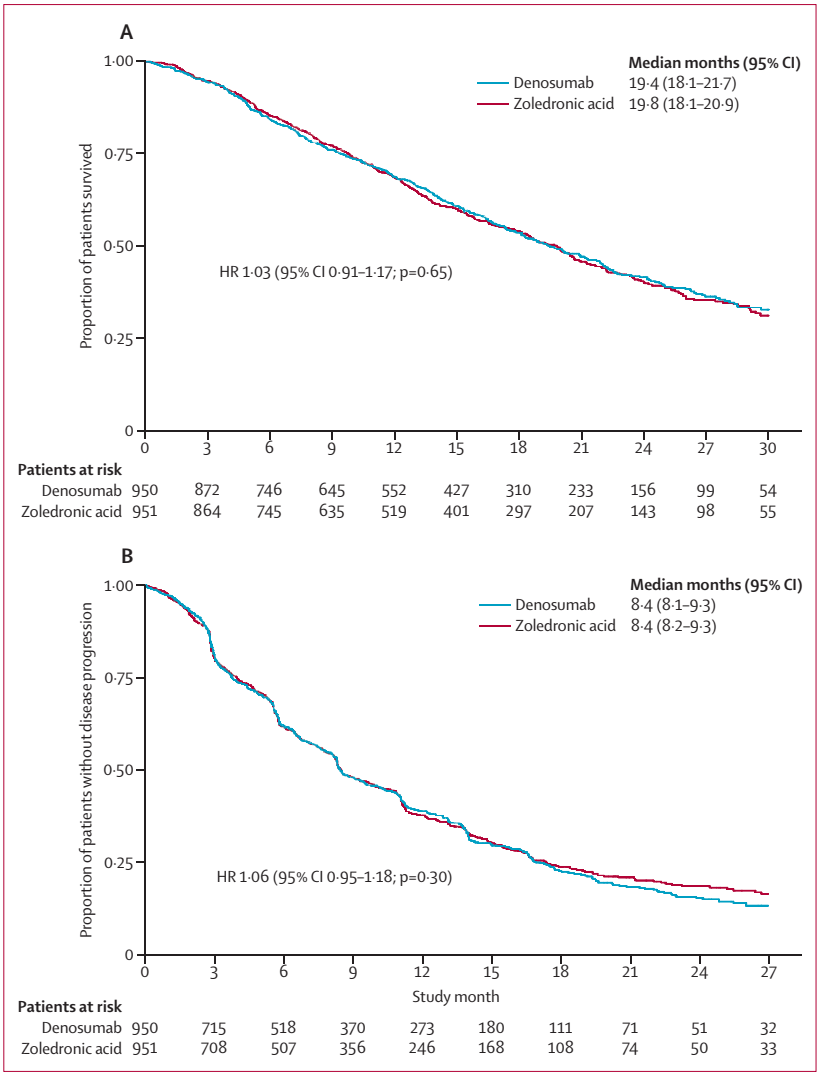


***Figure 4:*** **Kaplan-Meier estimates of (A) overall survival and (B) time to disease progression**
Patients who were no longer on study, but who were still in the survival follow-up, were included along with those remaining on study in the risk set for the survival analysis. HR=hazard ratio.

| | Zoledronic acid | | Denosumab | | p value |
|---|---|---|---|---|---|
| | Patients | Median absolute change (%, IQR) | Patients | Median absolute change (%, IQR) | |
| uNTx/CR (nmol/mmol) | 719 | −28·4 (−69%, −83 to −43) | 738 | −40·3 (−84%, −92 to −66) | p<0·0001 |
| Bone-specific alkaline phosphatase (μg/L) | 739 | −4·8 (−27%, −47 to 16) | 755 | −7·9 (−35%, −54 to −3) | p<0·0001 |

Data are presented for patients who had assessments at both baseline and week 13. uNTx/Cr=urinary N-telopeptide adjusted for creatinine.

***Table 3:*** **Median change in bone turnover markers from baseline to study week 13**

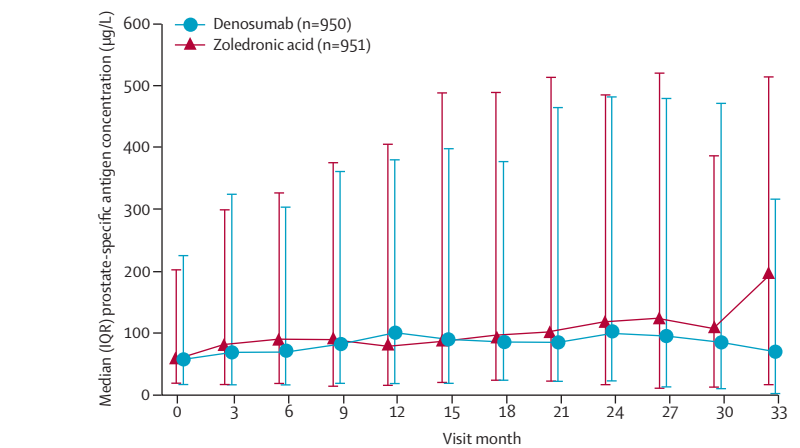


***Figure 5:*** **Median prostate-specific antigen concentrations during the study**
Prostate-specific antigen was measured every 3 months in all patients remaining on study. Data are presented by visit months, where an assessment within each 3-month period was captured at the end of the window between visits.

| | Zoledronic acid (n=945) | Denosumab (n=943) | p value* |
|---|---|---|---|
| **Overall safety summary** | | | |
| Any adverse event | 918 (97%) | 916 (97%) | 1·00 |
| Adverse events occurring with ≥20% frequency in either treatment group | | | |
| Anaemia | 341 (36%) | 337 (36%) | 0·89 |
| Back pain | 287 (30%) | 304 (32%) | 0·40 |
| Decreased appetite | 274 (29%) | 267 (28%) | 0·76 |
| Nausea | 245 (26%) | 272 (29%) | 0·16 |
| Fatigue | 222 (23%) | 257 (27%) | 0·06 |
| Constipation | 251 (27%) | 236 (25%) | 0·46 |
| Bone pain | 245 (26%) | 235 (25%) | 0·63 |
| Asthenia | 239 (25%) | 239 (25%) | 1·00 |
| Arthralgia | 202 (21%) | 194 (21%) | 0·69 |
| Pain in extremity | 196 (21%) | 197 (21%) | 0·95 |
| Peripheral oedema | 174 (18%) | 192 (20%) | 0·30 |
| Adverse events leading to treatment discontinuation | 138 (15%) | 164 (17%) | 0·10 |
| CTCAE grade 3 or 4 adverse events | 628 (66%) | 678 (72%) | 0·01 |
| Serious adverse events | 568 (60%) | 594 (63%) | 0·20 |
| Fatal adverse events | 276 (29%) | 283 (30%) | 0·72 |
| **Adverse events of interest** | | | |
| Infectious adverse events† | 375 (40%) | 402 (43%) | 0·21 |
| Cumulative osteonecrosis of the jaw (total) | 12 (1%) | 22 (2%) | 0·09 |
| Year 1 | 5 (1%) | 10 (1%) | .. |
| Year 2 | 8 (1%) | 22 (2%) | .. |
| Hypocalcaemia | 55 (6%) | 121 (13%) | <0·0001 |
| New primary malignant disease | 10 (1%) | 18 (2%) | 0·13 |

Data are number (%). CTCAE=Common Terminology Criteria For Adverse Events (version 3.0). *Calculated by Fisher's exact test. †Based on Medical Dictionary for Regulatory Activities (MedDRA; version 12.1) system organ class categorisation of infections and infestations.

***Table 4:*** **Adverse events and adverse events of interest in patients receiving at least one dose of study treatment**

143 (15%) needed zoledronic acid doses to be withheld on study to allow serum creatinine to decrease. Per protocol, no subcutaneous dose adjustments or subcutaneous doses were withheld for renal function. Major reasons for study discontinuation were balanced between groups (figure 1). During the study, docetaxel use was reported in 292 patients (31%) on denosumab and 326 patients (34%) on zoledronic acid.

Denosumab significantly delayed the time to first on-study skeletal-related event by 18% compared with zoledronic acid, with a between-group difference of 3·6 months (figure 2). Between-group divergence was evident from 3 months after start of treatment. Denosumab also significantly delayed the time to first and subsequent on-study skeletal-related events (figure 3). 727 patients (38%) had first on-study skeletal-related events, 341 in the denosumab group and 386 in the zoledronic acid group, most of which were radiation to bone or pathological fracture (table 2).

Overall survival (figure 4A) and investigator-reported disease progression (figure 4B) were not significantly different between treatment groups. At week 13, median decreases in concentrations of uNTx and serum bone-specific alkaline phosphatase were significantly greater with denosumab than with zoledronic acid (table 3). Median prostate-specific antigen concentrations were similar between treatment groups during the study (figure 5). No neutralising antibodies to denosumab were detected.

Overall, occurrences of adverse events and serious adverse events were similar between groups (table 4). The most common adverse events were anaemia, back pain, decreased appetite, nausea, fatigue, constipation, and bone pain. 176 patients had hypocalcaemia (table 4), of whom most reported events of mild-to-moderate severity (70 patients [58%] on denosumab *vs* 38 patients [69%] on zoledronic acid), and had only one event (79 [65%] *vs* 40 [73%]). Hypocalcaemia tended to occur within the first 6 months of treatment (82 patients [68%] on denosumab, 31 patients [56%] on zoledronic acid), and most events were asymptomatic. No adverse events of hypocalcaemia were fatal. Calcium decreases of grade 3 or higher, assessed by the central laboratory, occurred in 48 patients (5%) receiving denosumab and 13 patients (1%) receiving zoledronic acid.

Positively adjudicated osteonecrosis of the jaw occurred in 34 patients (table 4), of whom 17 (77%) on denosumab and ten (83%) on zoledronic acid had a history of tooth extraction, poor oral hygiene, or use of a dental appliance. On-study chemotherapy use in patients with osteonecrosis of the jaw was reported by 14 patients (64%) on denosumab and nine (75%) on zoledronic acid. By April, 2010, surgical treatment for osteonecrosis of the jaw had been done in ten patients (45%) on denosumab who had limited surgery (debridement, sequestrectomy, or curettage) and two (9%) who had bone resection, whereas three patients (25%) on zoledronic acid had

limited surgery and one (8%) had bone resection. Overall, resolution of osteonecrosis of the jaw, as defined by mucosal coverage, was recorded in four patients (18%) on denosumab and one patient (8%) on zoledronic acid.

New primary malignant diseases occurred during the blinded treatment phase in 18 patients (2%) receiving denosumab and ten patients (1%) receiving zoledronic acid, of whom 16 and nine, respectively, had the disease identified in the first year on study. The range of tumour types was as expected for this elderly population and included bladder, lung, colorectal, and skin cancers, with no more than two cases reported for any individual type.

During the first 3 days of treatment, adverse events potentially associated with acute phase reactions occurred in 79 patients (8%) on denosumab and 168 patients (18%) on zoledronic acid. Adverse events potentially associated with renal impairment occurred in 139 patients (15%) in the denosumab group and 153 patients (16%) in the zoledronic acid group.

### *Panel:* Research in context

**Systematic review**

A comprehensive review of treatment and prevention of prostate cancer-induced bone complications was published in July, 2010.[18] As part of the review, Lee and colleagues provided a summary of three contemporary randomised trials of bone-targeted therapies for skeletal complications arising from castrate-resistant prostate cancer (table 5). Results from these three trials investigating zoledronic acid, pamidronic acid, and clodronic acid, respectively, established intravenous zoledronic acid as the standard of care and the only agent approved for this indication.

**Interpretation**

Denosumab is a monoclonal antibody against RANKL, the key activator of osteoclastic bone resorption. In our phase 3 trial, 120 mg subcutaneous denosumab every 4 weeks was better than 4 mg intravenous zoledronic acid every 4 weeks for prevention of skeletal complications in patients with castrate-resistant prostate cancer.

## Discussion

We have shown that denosumab is better than the established therapy, zoledronic acid, for the delay or prevention of skeletal-related events in patients with advanced prostate cancer (panel). Zoledronic acid is the standard of care, and is better than placebo,[5,18] for prevention of skeletal-related events in men with castration-resistant prostate cancer.[5,18] However, skeletal-related events continue to occur despite treatment with zoledronic acid, albeit at a reduced rate. Zoledronic acid use also has limitations and inconveniences: need for intravenous access and administration; monitoring of renal function, with dose adjustments and withholding to prevent renal injury in patients who develop renal impairment during treatment; and management of the influenza-like syndrome associated with acute phase reactions that might occur, mostly after the first dose.[20] Renal issues can be particularly important in elderly patients with castration-resistant prostate cancer who frequently have renal dysfunction caused by urinary tract obstruction. These limitations do not apply to denosumab, which is given subcutaneously, has no effect on renal function and no need for renal monitoring, and is not known to be associated with acute phase reactions.[13,21–23]

We expected changes in serum calcium because of the mechanism of action of antiresorptive agents, and changes were seen more frequently with denosumab than with zoledronic acid. Hypocalcaemia is a side-effect manageable with appropriate supplementation with a combination of oral calcium and vitamin D. Osteonecrosis of the jaw occurred infrequently in both treatment groups, and was usually associated with previously reported risk factors, such as tooth extraction.[24] Most patients received conservative treatment with only three patients needing surgical resection. Resolution was documented in a few cases, and we are continuing to monitor the outcomes of osteonecrosis of the jaw in this population.

In a recent review of treatment and prevention of bone complications in prostate cancer,[18] Lee and colleagues identified only one phase 3 study of

| | Drugs studied | Study duration (months) | Patients with skeletal-related events | Median time to first skeletal-related event (months) | Time to first and subsequent skeletal-related events |
|---|---|---|---|---|---|
| Saad et al (2004)[5] | Zoledronic acid (n=214) *vs* placebo (n=208) | 24* | 81 (38%) *vs* 101 (49%); p=0·028 | 16·0 *vs* 10·5; p=0·009 | HR 0·64 (95% CI 0·485–0·845); p=0·002 |
| Small et al (2003)[19] | Pamidronic acid (n=169) *vs* placebo (n=181) | 6·8† | 42 (25%) *vs* 46 (25%); p value not reported | Not tested | Not tested |
| Fizazi et al (2011) | Denosumab (n=950) *vs* zoledronic acid (n=951) | 41‡ | 341 (36%) *vs* 386 (41%) | 20·7 (95% CI 18·8–24·9) *vs* 17·1 (15·0–19·4); p=0·0002 (non-inferiority), p=0·008 (superiority)§ | RR 0·82 (95% CI 0·71–0·94); p=0·008§ |

n=number of patients. HR=hazard ratio. RR=rate ratio. *Fixed interval study with maximum of 24 months' treatment duration. †Fixed interval study with maximum of 27 weeks' treatment duration. ‡Event-driven study with maximum of 41 months' treatment duration. §All randomised patients; p values were adjusted for multiplicity.

***Table 5:*** **Studies of antiresorptive drugs for the prevention of skeletal-related events in castration-resistant prostate cancer**

bisphosphonate therapy for metastatic prostate cancer in which skeletal-related events were assessed as the primary endpoint. Saad and colleagues[5] showed that zoledronic acid significantly reduced the proportion of patients with skeletal-related events and increased the median time to first skeletal-related event compared with placebo (table 5). In a combined analysis of two trials in which skeletal-related events were assessed as a secondary endpoint, the intravenous bisphosphonate pamidronic acid was ineffective in patients with bone metastases from castration-resistant prostate cancer (table 5).[19] The role of clodronic acid, another bisphosphonate, is unclear in patients with prostate cancer.[25] In our study, the monoclonal antibody denosumab provided significant improvements in time to both first skeletal-related events and subsequent skeletal-related events compared with zoledronic acid (table 5). The frequency of types of skeletal-related event recorded in our trial was consistent with the findings of a previous phase 3 study of zoledronic acid.[4] We noted that patients treated with denosumab also had significantly greater suppression of uNTx/Cr and bone-specific alkaline phosphatase, paralleling the reduction in skeletal-related events. In both groups, the median overall survival of about 20 months was as expected for the study population. On the basis of the similarity between the survival curves, any survival benefit attributed to the active comparator, zoledronic acid,[4,26] seems to be similar for denosumab. Disease progression reported by investigators was also not significantly different between treatment groups; however, the challenges and complexities of identification of disease progression in castration-resistant prostate cancer are well recognised.[27]

Two limitations were apparent in our study. The double-dummy design did not allow us to objectively measure the benefits of subcutaneous versus intravenous administration. Additionally, the protocol-specified requirement to exclude patients with creatinine clearance of less than 0·5 mL/s, for whom the comparator drug is not approved, prevented assessment of treatment benefit in patients with severe renal dysfunction at baseline.

Our study adds to growing evidence showing that bone-targeting strategies in castration-resistant prostate cancer are an important part of integrated treatment.[28] Other agents under investigation for targeted therapy of bone metastases from prostate cancer include novel endothelin-1 inhibitors[29] and radiopharmaceuticals.[30,31] Therapeutic intervention targeting the RANKL pathway is a recent strategy in the management of skeletal complications of metastatic disease: denosumab is the first monoclonal antibody to be investigated for this purpose. Our study is one of three identically designed phase 3 studies comparing the effect of denosumab versus zoledronic acid on skeletal-related events in patients with advanced malignant diseases from different tumour types involving the bone. The results from all three studies showed a consistent effect in prevention of skeletal-related events with denosumab versus zoledronic acid.[32,33] Denosumab represents a novel potential treatment option for the prevention of skeletal complications in patients with metastatic castration-resistant prostate cancer.

**Contributors**

KF, MS, HW, QJ, ST, RD, and CG designed the study. KF, MC, MS, RD, JB, LK, PM, NS, and MR enrolled patients. KF, MC, MS, RD, JB, LK, PM, NS, MR, ST, RD, and CG collected and interpreted data. KF, LK, RD, and CG searched for published articles; and KF, MC, MS, RD, JB, LK, PM, NS, MR, HW, QJ, RD, and CG wrote the report.

**20050103 prostate cancer skeletal-related event study group**

*Argentina* C Alasino, P Alvarez, C Bas, A Bechara, E F Becher, C Blajman, E Bogado, M A Brown Arnold, M Cuevas, CA Delfino, J J Garcia, C R Giudice, G Jankilevich, J A Lacava, G L Lerzo, S Metrebian, J M O'Connor, E Richardet, E Rodriguez, J Rozanec, R L Santos, A E Stagnaro, A Tomadoni, S A Vigo, M I Viniegra. *Australia* W Babington, B Chern, I Davis, P De Souza, V Ganju, D Kotasek, R Lowenthal, R Lynch, P Mainwaring, G Marx, S Ng, K Pittman, S Sewak, J Shapiro, R Stanley, B Stein, S Troon, S Wong, C Wynne. *Austria* K Fink, W Horninger, M Krainer, W Loidl, N Schmeller. *Belgium* T Besse Hammer, J-J Body, J C Goeminne, L Hoekx, W Oosterlinck, T Roumeguère, C Schulman, H Van Poppel. *Brazil* BMHR Adam van Eyll, A Anelli, A Arrieira Azambuja, K Assunção, C Emerenciano, G Atta, C H E Barrios, C Cabral, S Cabral, F M Carcano, V Da Silva Teixeira, G De Castro Junior, A Del Giglio, G Delgado, A Faccio, M H H Federico, U Ferreira, F A Franke, S Glina, F Hahn Souza, W Koff, M Liberatti, A Malzyner, M A Marques Portella, J Matos-Neto, A A Moraes, Y V Neron do Nascimento, A Notari, F A M Oliveira, S Padiha, M Perez, H Pinczowski, G Pinheiro, P E Pizao, C F Rego, J A Rinck, A Rocha Lima, A Silva, A G Silva Netto, C Teloken, L Tinoco, L F A Vieiralves. *Bulgaria* P Chilingirov, K Guenova, H Markova, M Racheva, S Stratev, A Tomova, V Tzekova, G D Yaycarova. *Canada* L Aaron, C Andreou, M Carmel, R Casey, K Chi, J Chin, R B Egerdie, B Goldfarb, E Hirshberg, K Jansz, A Kapoor, T Kinahan, L Klotz, L Lacombe, W Leung, M Liquornik, W Love, R Pahil, P Pommerville, F Saad, G Steinhoff, J Trachtenberg, P Venner, J Zadra. *Chile* O R Aren Frontera, C Del Castillo Santa Maria, L Soto Diaz. *Costa Rica* D Otero Reyes. *Czech Republic* L Domes, P Hesoun, J Jansa, M Lukes, K Odrazka, J Pernicka, M Sincl, M Urban, F Zatura. *Denmark* M Borre, P Klarskov, P Mogensen. *Estonia* J Kahu, T Tamm, G Timberg. *Finland* P Hellström, T Tammela. *France* S Abadie Lacourtoisie, P Beuzeboc, M Colombel, G Deplanque, C El Kouri, P Fargeot, J M Ferrero, F Goldwasser, S Ladoire, E Lechevallier, X Muracciole, S Oudard, E Raymond, D Spaeth, C Theodore, J M Tourani, E Voog. *Germany* B Gaede, M-S Michel, K Miller, A Stenzl. *Greece* K Konstantinidis, P Perimenis, D Radopoulos, A Thanos, A Zervas. *Hungary* G Boszormenyi-Nagy, J M Feher, P Fel, P Tenke. *India* G Adams, A Kapadia, B Kashyapi, P Keechilat, A Maru, J Puthuveettil, S K Rawal, T Sahoo. *Israel* F Barak, R Ben-Yosef, A Neuman, R Pfeffer, E Rosenbaum. *Italy* A Falcone, D Gramaglia, M C Locatelli, C Sternberg, A Tubaro. *Latvia* M Bitina, E Grincuka, S Plate, G Purkalne, M Skrodele. *Lithuania* M Jievaltas, A Ulys. *Mexico* D Calvo Dominguez, G Gaxiola Meza, J Jaspersen Gastelum, M Jimenez-Rios, F E Leon Arellano, C Martinez Martinez, A Orozco Bravo, M Ramirez Marquez. *Netherlands* R J Davits, K P J Delaere, F M J A Froeling, J A F Leenarts, A H P Meier, P Verhagen. *New Zealand* A Beaven, P Gilling, F Kueppers, I Mundy, A Nixon. *Panama* G Garcia, A Jimenez. *Peru* S Falcon Lizaraso, C Lozada Zingoni, M J Philco Salas, J F Salas Sanchez. *Poland* K Bar, T Borkowski, T Dmowski, P Jarzemski, K Sacha, A Sikorski, K Szkarlat, R Szwedowski, P Trypens. *Romania* T-E Ciuleanu, S Curescu, A C Grigorescu, M Patran, D Smeianu, L Vata. *Russia* A Arkhipov, M Biyakhov,

V Borisov, S Cheporov, A Garin, O Gladkov, A Kaprin, O Karyakin, E Kopyltsov, M Lichinitser, V Lubennikov, A Makhson, L Roman, V Ruchkin. *Slovakia* V Balaz, J Beniak, F Goncalves, J Kliment, J Mikulas, L Valansky. *South Africa* G L Cohen, J P Jordaan, R A Mall. *Spain* L M Antón Aparicio, D Castellano, R Garcia, A González Martín, V Guillem Porta, M Lopez, J P Maroto, M Martin, B Mellado, J L Perez Garcia. *Sweden* T Björk, A Laurell. *Switzerland* U Huber, G Thalmann. *Turkey* L Turkeri. *Ukraine* L Chybisov, Y Hotko, I Kostinskyy, R Senyutovich, I Sokur. *UK* D Bottomley, P Carter, P Hoskin, P Kirkbride, H Newman, A Patel, M Sokal. *USA* G Adams, A Al-Janadi, J Bailen, W Berry, M Bidair, D Bilhartz, S Chang, V Charu, R Clark, A Dincer, B Ebrahimi, M Efros, J Figueroa, H Fisher, J Frankel, B Halibey, J Hays, E Heath, C Henderson, S Hopkins, A Hussain, B Kashyap, L Keeler, D Keiller, S Koukol, D Laber, S Lacy, K Liem, A Lipton, E Loizides, J MacNeill, Y Manalo, J Marion, S McKenney, B Mehlhaff, E Meiri, A Meluch, P Monk, R Moss, J Mullen, M Murdock, D Perry, A Perzin, W Pittman, S Richardson, P Rosen, W Schiff, M Schreeder, F Senecal, A Sidhom, P Sieber, F Smith, F Snoy, S Tannenbaum, G Thomas, J Thropay, P Van Veldhuizen, W Waterfield, J Weick, R G Wiggans, R Wurzel.

#### Conflicts of interest

KF has received consultancy fees and travel support from Amgen for this study and from Novartis; participated in speakers' bureaux and advisory boards for Amgen and Novartis; and provided expert testimony for Amgen. MC has received consultancy fees from Amgen for this study and for other agents in development, and from Novartis; and received research funding from Amgen. MS has received consultancy fees from Amgen; and participated in sponsored clinical research with Amgen and Novartis. RDam has received research funding from Amgen and the Center of Research in Urology Sergio Aguinaga (CEPUSA). JB has received travel support and payment for lectures from Amgen and Novartis; JB has received payment for membership of advisory boards from Amgen, Novartis, and GlaxoSmithKline; and JB and JB's institution have received consultancy fees from Amgen. LK has received consultancy fees, travel support, and honoraria for lectures and development of educational presentations from Amgen; and LK's institution has received research funding from Amgen. PM has received research funding from Amgen; and been a board member and principal investigator for, and received travel support from, Amgen. NS has received consultancy fees and travel support from Amgen for this study; and received research funding and honoraria from Amgen. MR has received travel support and honoraria for membership of advisory boards and lectures from Amgen; and MR's institution has received research funding from Amgen for this study. HW, Q J, ST, RDan, and CG are employees of Amgen, and have received stock or stock options from Amgen.

#### Acknowledgments

We thank the patients and investigators at all participating sites who made important contributions to this study; Geoffrey Smith, supported by Amgen, for medical writing assistance in preparation of this report; and the DMC for its diligence in monitoring of the study. The DMC wishes to remain anonymous because it is monitoring other trials of denosumab. This report is presented in memory of study investigator Lina Barbosa Cassol and study coordinator Carla Fioratti. This study was funded by Amgen, Thousand Oaks, CA, USA. Primary results of the data in this report were presented on June, 6, 2010, at the American Society of Clinical Oncology Annual Meeting in Chicago, IL, USA.

#### References

1 Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60:** 277–300.

2 Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010; **46:** 765–81.

3 Schulman KL, Kohles J. Economic burden of metastatic bone disease in the U.S. *Cancer* 2007; **109:** 2334–42.

4 Saad F, Gleason DM, Murray R, et al, and for the Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002; **94:** 1458–68.

5 Saad F, Gleason DM, Murray R, et al, and for the Zoledronic Acid Prostate Cancer Study Group. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004; **96:** 879–82.

6 Roudier MP, Morrissey C, True LD, Higano CS, Vessella RL, Ott SM. Histopathological assessment of prostate cancer bone osteoblastic metastases. *J Urol* 2008; **180:** 1154–60.

7 Brown JE, Cook RJ, Major P, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. *J Natl Cancer Inst* 2005; **97:** 59–69.

8 Demers LM. Bone markers in the management of patients with skeletal metastases. *Cancer* 2003; **97:** 874–79.

9 Percival RC, Urwin GH, Harris S, et al. Biochemical and histological evidence that carcinoma of the prostate is associated with increased bone resorption. *Eur J Surg Oncol* 1987; **13:** 41–49.

10 Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature* 2003; **423:** 337–42.

11 Fizazi K, Yang J, Peleg S, et al. Prostate cancer cells-osteoblast interaction shifts expression of growth/survival-related genes in prostate cancer and reduces expression of osteoprotegerin in osteoblasts. *Clin Cancer Res* 2003; **9:** 2587–97.

12 Zhang J, Dai J, Yao Z, Lu Y, Dougall W, Keller ET. Soluble receptor activator of nuclear factor κB Fc diminishes prostate cancer progression in bone. *Cancer Res* 2003; **63:** 7883–90.

13 Fizazi K, Lipton A, Mariette X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *J Clin Oncol* 2009; **27:** 1564–71.

14 Novartis. Zometa (zoledronic acid) package insert. East Hanover, NJ: Novartis, 2009. http://www.pharma.us.novartis.com/product/pi/pdf/Zometa.pdf (accessed Feb 7, 2011).

15 James Hung HM, Wang SJ, Tsong Y, Lawrence J, O'Neil RT. Some fundamental issues with non-inferiority testing in active controlled trials. *Stat Med* 2003; **22:** 213–25.

16 Anderson PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Statistics* 1982; **10:** 1100–20.

17 Westfall PH, Tobias RD, Rom D, Wolfinger RD, Hochberg Y. Multiple comparisons and multiple tests, using the SAS system. Cary, NC: SAS Institute, 1999.

18 Lee RJ, Saylor PJ, Smith MR. Treatment and prevention of bone complications from prostate cancer. *Bone* 2011; **48:** 88–95.

19 Small EJ, Smith MR, Seaman JJ, Petrone S, Kowalski MO. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with metastatic prostate cancer. *J Clin Oncol* 2003; **21:** 4277–84.

20 Olson K, Van Poznak C. Significance and impact of bisphosphonate-induced acute phase responses. *J Oncol Pharm Pract* 2007; **13:** 223–29.

21 Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol* 2008; **26:** 4875–82.

22 Lipton A, Steger GG, Figueroa J, et al. Randomized active-controlled phase II study of denosumab efficacy and safety in patients with breast cancer-related bone metastases. *J Clin Oncol* 2007; **25:** 4431–37.

23 Smith MR, Egerdie B, Hernández Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009; **361:** 745–55.

24 Walter C, Al-Nawas B, Grötz KA, et al. Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate. *Eur Urol* 2008; **54:** 1066–72.

25 Dearnaley DP, Mason MD, Parmar MKB, Sanders K, Sydes MR. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. *Lancet Oncol* 2009; **10:** 872–76.

26 Saad F. New research findings on zoledronic acid: survival, pain, and anti-tumour effects. *Cancer Treat Rev* 2008; **34:** 183–92.

27 Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the prostate cancer clinical trials working group. *J Clin Oncol* 2008; **26:** 1148–59.

28 Fizazi K, Sternberg CN, Fitzpatrick JM, Watson RW, Tabesh M. Role of targeted therapy in the treatment of advanced prostate cancer. *BJU Int* 2010; **105:** 748–67.

29 James ND, Caty A, Borre M, et al. Safety and efficacy of the specific endothelin-A receptor antagonist ZD4054 in patients with hormone-resistant prostate cancer and bone metastases who were pain free or mildly symptomatic: a double-blind, placebo-controlled, randomised, phase 2 trial. *Eur Urol* 2009; **55:** 1112–23.

30 Fizazi K, Beuzeboc P, Lumbroso J, et al. Phase II trial of consolidation docetaxel and samarium-153 in patients with bone metastases from castration-resistant prostate cancer. *J Clin Oncol* 2009; **27:** 2429–35.

31 Nilsson S, Franzén L, Parker C, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. *Lancet Oncol* 2007; **8:** 587–94.

32 Henry D, Costa L, Goldwasser F, et al. A randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol* (in press).

33 Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010; **28:** 5132–39.