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

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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.

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Introduction

In western countries, prostate cancer is the most common non-dermatological malignant disease in men. An estimated 217 730 new cases will have been diagnosed in 2010 in the USA[1] and 382 250 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 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.

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 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 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 castrationresistant prostate cancer.

20050103 prostate cancer skeletal-related event study group

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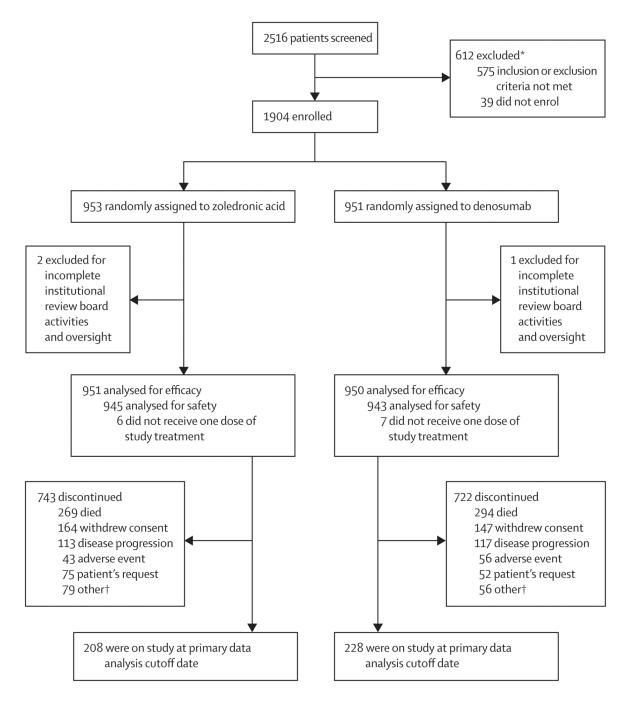
Figure 1. Trial profile

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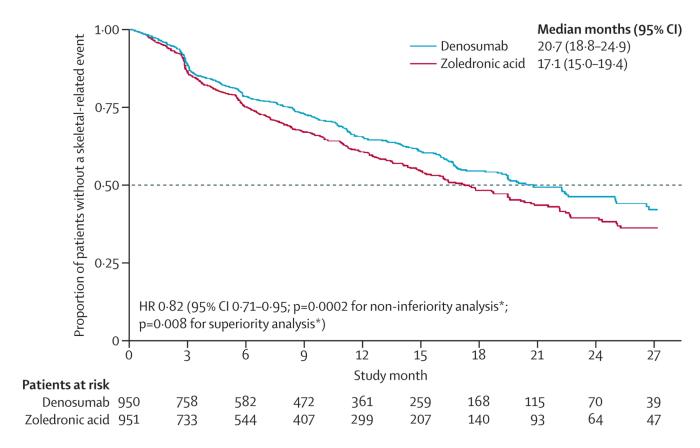
Figure 2. Kaplan-Meier estimates of time to first on-study skeletal-related event
Patients were assessed from baseline to the primary analysis cutoff date. HR=hazard ratio.
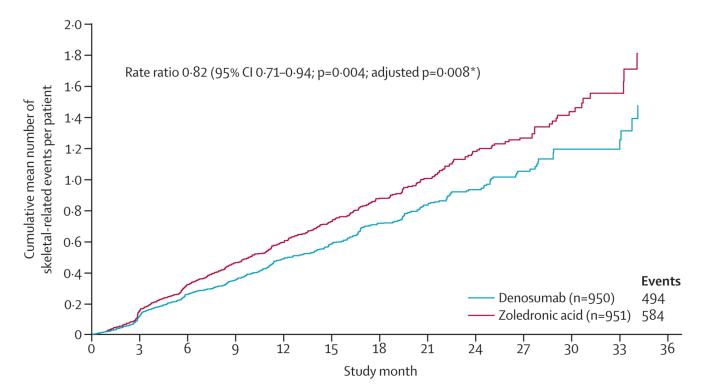*p values were adjusted for multiplicity.

Figure 3. Time to first and subsequent on-study skeletal-related events
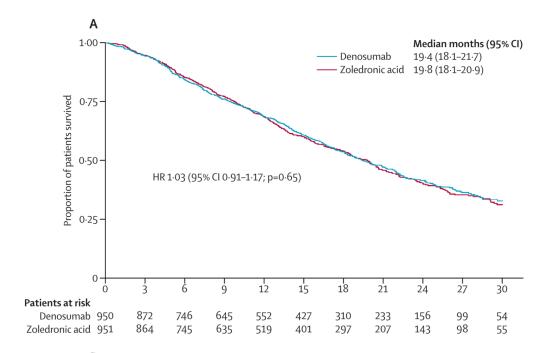Events occurred at least 21 days apart. *Adjusted for multiplicity.
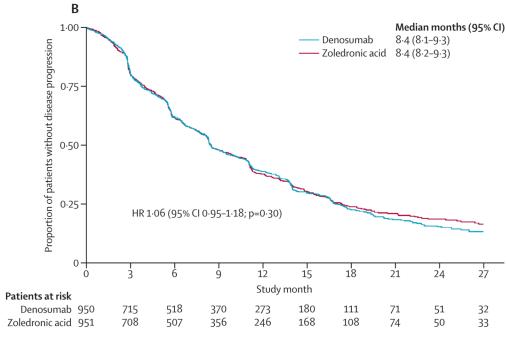
Figure 4. Kaplan-Meier estimates of (A) overall survival and (B) time to disease progression
Patients who were no longer on study, but who were still in the survival follow-up, were
included along with those remaining on study in the risk set for the survival analysis.
HR=hazard ratio.
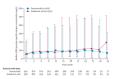
Figure 5. Median prostate-specific antigen concentrations during the study
Prostate-specific antigen was measured every 3 months in all patients remaining on study.
Data are presented by visit months, where an assessment within each 3-month period was
captured at the end of the window between visits.

Table 1

Baseline demographic and clinical characteristics

|	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 2

Patients with first on-study skeletal-related events by type

	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 3

Median change in bone turnover markers from baseline to study week 13

	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 4

Adverse events and adverse events of interest in patients receiving at least one dose of study treatment

	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 5

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

	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.