Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial

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Summary

Background Bone metastases are a major cause of morbidity and mortality in men with prostate cancer. Preclinical studies suggest that osteoclast inhibition might prevent bone metastases. We assessed denosumab, a fully human anti-RANKL monoclonal antibody, for prevention of bone metastasis or death in non-metastatic castration-resistant prostate cancer.

Methods In this phase 3, double-blind, randomised, placebo-controlled study, men with non-metastatic castration-resistant prostate cancer at high risk of bone metastasis (prostate-specific antigen [PSA] ≥8·0 μg/L or PSA doubling time ≤10·0 months, or both) were enrolled at 319 centres from 30 countries. Patients were randomly assigned (1:1) via an interactive voice response system to receive subcutaneous denosumab 120 mg or subcutaneous placebo every 4 weeks. Randomisation was stratified by PSA eligibility criteria and previous or ongoing chemotherapy for prostate cancer. Patients, investigators, and all people involved in study conduct were masked to treatment allocation. The primary endpoint was bone-metastasis-free survival, a composite endpoint determined by time to first occurrence of bone metastasis (symptomatic or asymptomatic) or death from any cause. Efficacy analysis was by intention to treat. The masked treatment phase of the trial has been completed. This trial was registered at ClinicalTrials.gov, number NCT00286091.

Findings 1432 patients were randomly assigned to treatment groups (716 denosumab, 716 placebo). Denosumab significantly increased bone-metastasis-free survival by a median of 4·2 months compared with placebo (median 29·5 [95% CI 25·4–33·3] *vs* 25·2 [22·2–29·5] months; hazard ratio [HR] 0·85, 95% CI 0·73–0·98, p=0·028). Denosumab also significantly delayed time to first bone metastasis (33·2 [95% CI 29·5–38·0] *vs* 29·5 [22·4–33·1] months; HR 0·84, 95% CI 0·71–0·98, p=0·032). Overall survival did not differ between groups (denosumab, 43·9 [95% CI 40·1–not estimable] months *vs* placebo, 44·8 [40·1–not estimable] months; HR 1·01, 95% CI 0·85–1·20, p=0·91). Rates of adverse events and serious adverse events were similar in both groups, except for osteonecrosis of the jaw and hypocalcaemia. 33 (5%) patients on denosumab developed osteonecrosis of the jaw versus none on placebo. Hypocalcaemia occurred in 12 (2%) patients on denosumab and two (<1%) on placebo.

Interpretation This large randomised study shows that targeting of the bone microenvironment can delay bone metastasis in men with prostate cancer.

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Introduction

Bone metastases are a major cause of morbidity and mortality in men with prostate cancer.[1,2] Nearly all men with fatal prostate cancer develop bone metastases and, for most of these men, bone is the dominant or only site of metastases.[3–5] Bone metastases pose a substantial health and economic burden because they are associated with skeletal-related events including pathological fractures, spinal cord compression, pain, and need for radiation therapy or surgery to bone.[6–8] Prevention of bone metastasis is an important unmet medical need.

Reciprocal interactions between tumour cells and bone seem to explain the bone-dominant pattern of metastases in prostate cancer.[9–11] In the bone microenvironment, growth factors secreted by tumour cells induce stromal cells and osteoblasts to express RANKL, an essential mediator of osteoclast formation, function, and survival.[12–14] Activation of osteoclasts by RANKL results in increased bone turnover and release of growth factors from bone matrix that might promote establishment of prostate cancer in the skeleton.[15] In preclinical models of prostate cancer, osteoclast inhibition prevents bone metastasis.[16,17] RANK expression on prostate cancer cells might also increase metastatic behaviour of tumour cells, with RANKL serving as a potential homing signal to bone marrow.[18]

Androgen deprivation therapy (ADT) through bilateral orchiectomy or treatment with gonadotropin-releasing hormone (GnRH) agonists or antagonist is standard first-line therapy for metastatic prostate cancer.[19,20] ADT is also often used to treat men with non-metastatic prostate

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cancer.[21] Although initial ADT is uniformly effective, nearly all men with prostate cancer eventually develop castration-resistant disease.[22] In men with progressive non-metastatic castration-resistant prostate cancer, high baseline prostate-specific antigen (PSA) and short PSA doubling time are consistently associated with reduced time to first bone metastasis and death.[23,24]

Denosumab is a fully human monoclonal antibody that specifically binds and inactivates RANKL. On the basis of superiority to zoledronic acid in breast and prostate cancer,[25,26] denosumab was approved in the USA for the prevention of skeletal-related events in patients with solid tumours and bone metastases.[27] We aimed to evaluate the effects of denosumab on bone-metastasis-free survival in men with castration-resistant prostate cancer, no evidence of bone metastases at baseline, and a high risk of progression based on raised PSA or short PSA doubling time.

Methods

Study design and patients

We undertook a phase 3, double-blind, randomised, placebo-controlled study in patients enrolled at 319 centres in 30 countries. Eligible patients were men aged 18 years or older with histologically confirmed prostate cancer, Eastern Cooperative Oncology Group performance status of 1 or less, and adequate organ function. Patients had to have received a bilateral orchiectomy or continuous ADT with a GnRH agonist or antagonist for at least 6 months when entering the study. Patients had to have a total serum testosterone lower than 1·72 nmol/L (50 ng/dL), and were to be castration-resistant with three consecutive increasing PSA tests separated by at least 2 weeks and the last two PSA measurements of 1·0 μg/L or higher. High risk for bone metastasis was also required, characterised by PSA of 8·0 μg/L or higher within 3 months before randomisation or PSA doubling time of 10 months or less, or both. Baseline renal function was not an eligibility criterion.

Key exclusion criteria included previous or present evidence of radiographically detectable bone metastasis, evidence of metastasis to other organs (except lymph nodes), history or evidence of osteomyelitis or osteonecrosis of jaw, previous secondary malignant disease within the past 5 years, previous administration of denosumab, intravenous bisphosphonate administration, and use of oral bisphosphonates for 3 or more years continuously (<3 years acceptable with washout of ≥1 year before randomisation). Antineoplastic therapies and concomitant treatments deemed necessary were allowed both before enrollment and on study.

All patients had a radioisotope bone scan during screening with subsequent imaging by CT, MRI, or plain radiograph if needed to exclude bone metastases. All screening images were assessed by a central imaging reader (CoreLab Partners, Princeton, NJ, USA) in a masked fashion, with double-reader confirmation and third-reader adjudication in case of disagreement. Patients with imaging results that were either equivocal or consistent with bone metastases at screening were excluded. The study was approved by the institutional review board or ethics committee for each site. Patients provided written informed consent before any study-specific procedure.

Randomisation and masking

Patients were randomly assigned (1:1) to denosumab or placebo. Masked allocation of patients to treatment occurred via interactive voice response system. An individual independent of the study team prepared the computer-generated randomisation schedule; all patients, investigators, and persons involved in study conduct remained masked to treatment allocation throughout the study. Randomisation was stratified by PSA criteria (both ≥8·0 μg/L and doubling time ≤10·0 months *vs* either one of these criteria) and previous or ongoing chemotherapy for prostate cancer (yes or no). A randomly permuted block design with a block size of four was applied.

Procedures

Patients received either subcutaneous denosumab 120 mg or subcutaneous placebo (sterile saline) every 4 weeks until the target number of study events was reached. Daily supplementation with calcium (≥500 mg) and vitamin D (≥400 IU) was strongly recommended, unless hypercalcaemia (albumin-adjusted serum calcium ≥2·9 mmol/L or ionised calcium >1·5 mmol/L) developed. Patients were discontinued from treatment when bone metastasis occurred so that they could receive standard treatment for bone metastasis per investigator discretion. These patients were followed up for survival in a masked fashion for up to an additional 3 years after discontinuation of investigational product.

Study procedures included medical history and physical examination, vital signs, radioisotope bone scans (every 4 months), radiographic skeletal surveys (yearly), haematological tests, serum chemistry, denosumab concentration and antidenosumab antibody assays, urine collection, central laboratory PSA measurement, and testosterone assessments. Investigators were also trained to undertake oral examinations (every 6 months). Bone scans were done every 4 months to detect bone metastases; a confirmed diagnosis of bone metastases required a second imaging modality (CT, MRI, or plain radiograph). All radiographic assessments were also done by the central reader in a masked fashion with double-reader confirmation and adjudication by a third reader in case of disagreement. Extraskeletal progression of prostate cancer and concomitant drugs were recorded by investigators. Potential cases of osteonecrosis of the jaw were identified with a predefined list of oral-related Medical Dictionary for Regulatory Activities preferred terms in addition to clinical review, and adjudicated by an independent, masked panel of experts. A data monitoring committee reviewed safety and efficacy data roughly twice yearly.

The primary efficacy endpoint was bone-metastasis-free survival, as determined by time to first occurrence of bone metastasis (symptomatic or asymptomatic) or death from any cause. Secondary endpoints were time to first bone metastasis (symptomatic or asymptomatic, excluding deaths) and overall survival (including deaths on study and during follow-up). Key exploratory prostate cancer endpoints included overall prostate cancer progression (ie, centrally confirmed bone metastasis and investigator-determined extraskeletal prostate cancer progression), prostate cancer progression-free survival (ie, progression as defined above or death), proportion of patients with symptomatic bone metastasis (bone metastases that were symptomatic at the time of radiological detection), and change from baseline in PSA concentration. Changes from baseline in bone turnover markers were also assessed. Safety was assessed at regular intervals and included adverse events graded by Common Terminology Criteria for Adverse Events (CTCAE) version 3. Safety endpoints included incidence of treatment-emergent adverse events, changes in laboratory values, and incidence of antidenosumab antibodies.

Statistical analysis

On the basis of the assumption that the hazard ratio (HR) for denosumab versus placebo was 0·8, a sample size of 1400 men was projected to provide sufficient study events (660 events) at about 80% power and significance level of 0·025 using a one-sided maximum likelihood test, which is equivalent to 0·05 using a two-sided test. Only two-sided p values are presented. SAS (version 9.1.3) was used for all analyses.

In this intention-to-treat analysis, the primary and secondary endpoints were assessed hierarchically. The secondary endpoint of time to first bone metastasis was tested only if the primary endpoint of bone-metastasis-free survival was significant in favour of denosumab. If time to first bone metastasis was also significant in favour of denosumab, overall survival was tested. The Cox proportional hazards model, stratified by the randomisation stratification factors, with treatment groups as independent variables was used to compare primary and secondary endpoints between treatment groups for all patients randomly assigned to treatment groups, providing HR, 95% CI, and two-sided p value based on the Wald test. Descriptive statistics were used for PSA concentrations and for change in bone turnover markers from baseline to 2 years. Safety analyses were done for all patients randomly assigned to treatment groups who received one or more doses of investigational drug. No formal statistical testing was done for safety analyses.

This study is registered at ClinicalTrials.gov, number NCT00286091.

Role of the funding source

Amgen provided the study drug and collaborated with investigators on protocol design, data analysis and interpretation, and preparation of this report. All authors had access to pertinent study data; the corresponding author (MRS) had full access to the study data for interpretation and drafting of the report. A medical writer provided by Amgen assisted authors in drafting and finalising the report. The corresponding author was responsible for the final decision to submit for publication.

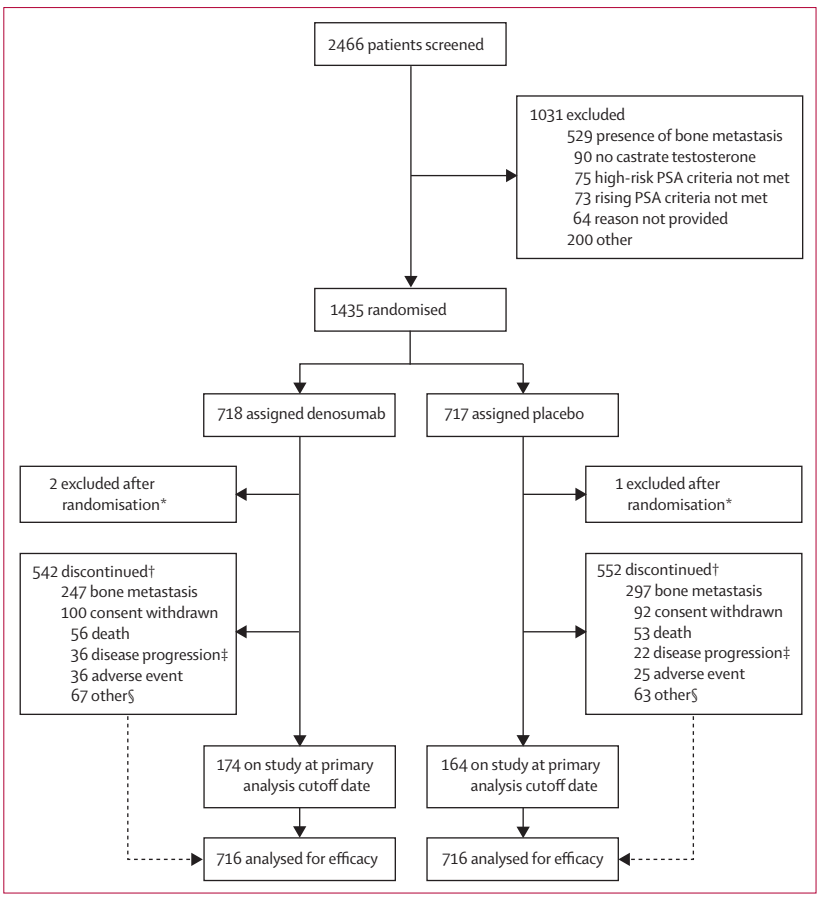

Figure 1: **Trial profile**
*Review activities and oversight of institutional review board not ensured. †Patients who no longer participated in monthly assessments; patients who withdrew consent or were lost to follow-up were not followed for survival. ‡Not in bone. §Administrative decision, noncompliance, lost to follow-up, protocol deviation, or ineligibility established.

Results

Between Feb 3, 2006, and July 23, 2008, 1432 patients were randomly assigned to treatment groups (716 denosumab, 716 placebo; figure 1). The event-driven date of the primary analysis cutoff was July 30, 2010. Thus, all enrolled patients had a chance to receive investigational product for at least 24 months. The database was locked on Dec 7, 2010, to allow time for radiological confirmation of newly detected bone-scan lesions up to July, 2010, and for data collection and cleaning. Baseline demographics and disease characteristics were generally balanced between treatment groups (table 1). Use of secondary hormone treatments

	Placebo (n=716)	Denosumab (n=716)
Race		
White	604 (84%)	606 (85%)
Black	35 (5%)	41 (6%)
Hispanic	37 (5%)	32 (4%)
Other	40 (6%)	37 (5%)
Region		
North America	237 (33%)	228 (32%)
Europe	309 (43%)	299 (42%)
Rest of world	170 (24%)	189 (26%)
Age		
Median (years)	74·0 (67·5–80·0)	74·0 (67·0–80·0)
≥65 years	600 (84%)	598 (84%)
Time from diagnosis to study entry (years)	6·1 (3·6–9·5)	6·1 (3·5–9·1)
PSA concentration (μg/L)	12·5 (4·9–28·5)	12·2 (4·7–27·5)
PSA dual risk factors*†‡	346 (48%)	346 (48%)
PSA single risk factor*†§	370 (52%)	370 (52%)
Previous chemotherapy*†	55 (8%)	55 (8%)
Duration of previous ADT (months)	47·1 (27·5–77·5)	47·2 (27·0–74·9)
Local therapy (prostatectomy or radiation, or both)	331 (46%)	313 (44%)
Current lymphatic disease	88 (12%)	93 (13%)
Gleason score at diagnosis		
≤7	432 (60%)	404 (56%)
8–10	214 (30%)	237 (33%)
Missing	70 (10%)	75 (10%)
ECOG status		
0	514 (72%)	505 (71%)
1	199 (28%)	210 (29%)
2	3 (<1%)	1 (<1%)
Urinary N-telopeptide corrected for urine creatinine (nmol/mmol)	25·4 (16·0–39·2)	23·2 (15·7–39·9)
Bone-specific alkaline phosphatase (μg/L)	13·5 (10·4–17·7)	13·1 (10·5–17·6)

Data are n (%) or median (IQR). PSA=prostate-specific antigen. ADT=androgen deprivation therapy. ECOG=Eastern Cooperative Oncology Group. *Per randomisation. †Stratification factor. ‡PSA 8·0 μg/L or higher within 3 months before randomisation and PSA doubling time 10·0 months or less. §PSA less than 8·0 μg/L within 3 months before randomisation and PSA doubling time 10 months or less or PSA 8·0 μg/L or higher within 3 months before randomisation and PSA doubling time greater than 10 months.

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

during the study was reported for 275 (38%) patients on denosumab and 302 (42%) patients on placebo, and of chemotherapy or biological agents for 198 (28%) patients on denosumab and 176 (25%) on placebo, with no notable differences in individual treatment types. Median absolute values of PSA at baseline (table 1) and change from baseline over time (data not shown) were similar in the denosumab and placebo groups.

705 events occurred, of which 605 were bone metastases and 100 were deaths. Of the 605 patients with bone metastases, 165 were denoted by the investigator as symptomatic and 440 as asymptomatic. Median time on study was 20·2 (IQR 10·2–31·3) months with denosumab and 19·0 (9·2–30·4) months with placebo. The most common reasons for study discontinuation were bone metastasis, consent withdrawal, and death (figure 1). 338 (24%) patients were on-study at the time of the primary analysis. Patients were exposed to denosumab for a median 19 (IQR 9–30) months and to placebo for a median 18 (9–30) months.

Denosumab treatment prolonged bone-metastasis-free survival (time to first occurrence of bone metastasis or death from any cause) by 4·2 months compared with placebo. Median bone-metastasis-free survival was 29·5 (95% CI 25·4–33·3) months with denosumab and 25·2 (22·2–29·5) months with placebo, representing a decrease in risk of 15% (HR 0·85, 95% CI 0·73–0·98, p=0·028; figure 2). Denosumab was also associated with increased time to first bone metastasis (either symptomatic or asymptomatic, excluding deaths) and increased time to symptomatic bone metastasis. Median time to first bone metastasis was 33·2 (95% CI 29·5–38·0) months with denosumab and 29·5 (22·4–33·1) months with placebo (HR 0·84, 95% CI 0·71–0·98, p=0·032; figure 2). Symptomatic bone metastases were reported in 69 (10%) patients on denosumab and 96 (13%) on placebo (p=0·03), and risk of symptomatic bone metastasis was decreased with denosumab by 33% (HR 0·67, 95% CI 0·49–0·92, p=0·01; figure 2).

Median time to overall prostate cancer progression, an exploratory endpoint defined as confirmed bone metastasis and investigator-determined prostate cancer progression, was 22·3 (95% CI 19·5–25·9) months with denosumab and 21·9 (18·6–25·1) months with placebo (HR 0·90, 95% CI 0·78–1·03, p=0·13). Overall survival (including deaths on study and during follow-up) did not differ between groups. Median overall survival was 43·9 (95% CI 40·1–not estimable) months with denosumab and 44·8 (40·1–not estimable) months with placebo (HR 1·01, 95% CI 0·85–1·20, p=0·91; figure 2). Median progression-free survival (an exploratory endpoint defined as confirmed bone metastasis, investigator-determined prostate cancer progression, or death) was 21·7 (95% CI 18·7–23·7) months with denosumab and 19·3 (18·3–22·1) months with placebo (HR 0·89, 95% CI 0·78–1·02, p=0·09).

Biochemical markers of bone turnover decreased significantly with denosumab treatment compared with placebo (data not shown; p<0·001 for each comparison). In patients with bone turnover assessments at baseline and month 22, concentrations of urinary N-telopeptide corrected for urine creatinine decreased from baseline by a median of 68% (IQR –82 to –48) for patients on denosumab (n=305) and increased by 1% (–37 to 88) for those on placebo (n=284) at month 22. Concentrations of bone-specific alkaline phosphatase decreased from baseline by 49% (–61 to –35) in the denosumab group (n=345) and by 7% (–25 to 16) in the placebo group (n=340) at month 22.

In the safety analysis, all patients who received at least one dose of study drug were analysed according to treatment received, irrespective of treatment assigned. Thus, four patients who were randomly assigned to placebo, but received denosumab in error, were included in the denosumab group, providing group sizes of

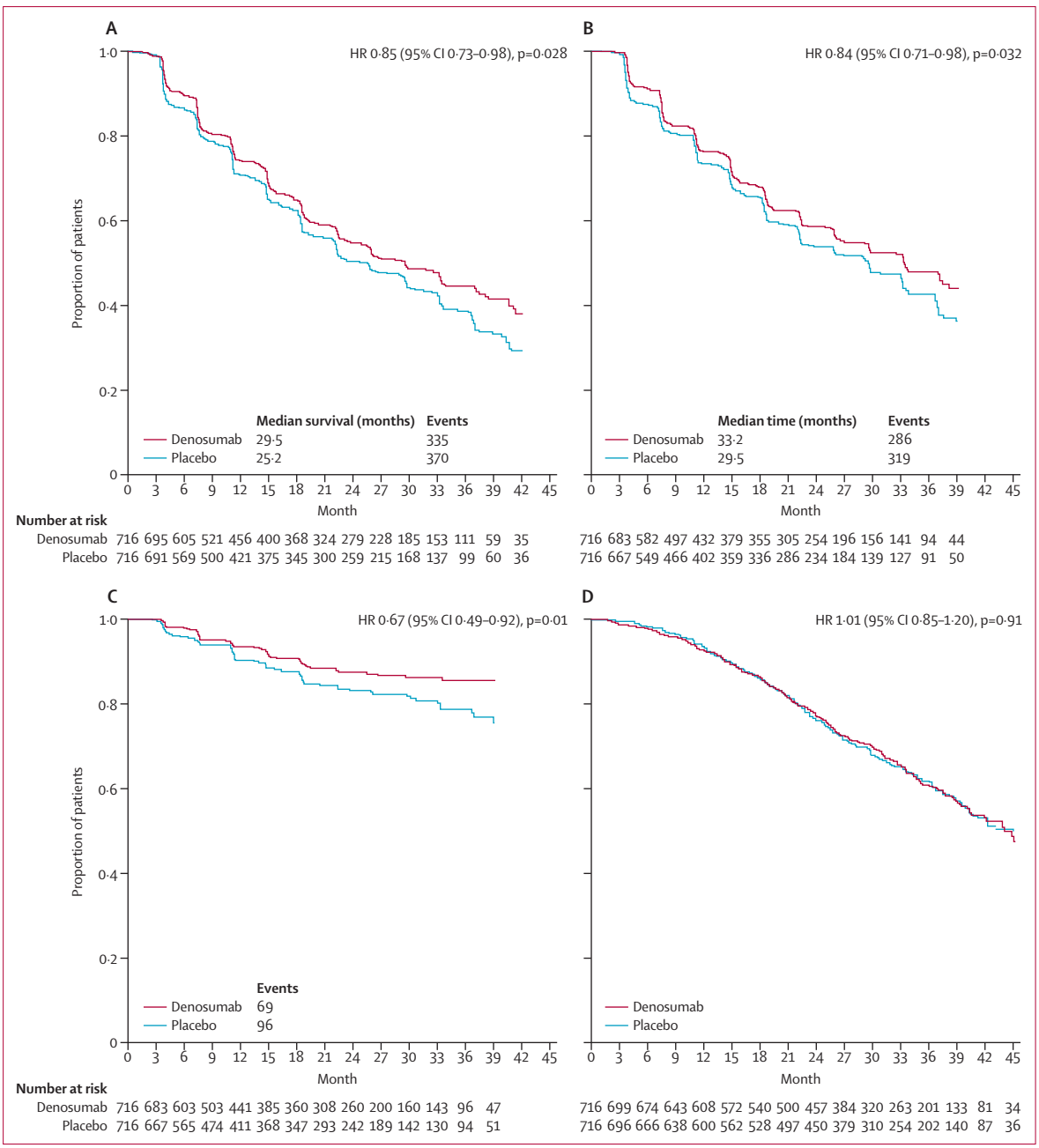

***Figure 2*: Kaplan-Meier curves of key efficacy endpoints**
(A) Bone-metastasis-free survival (primary endpoint). (B) Time to bone metastases (asymptomatic or symptomatic). (C) Time to symptomatic bone metastasis. (D) Overall survival. All curves were truncated when the combined risk sets dropped to less than 3·5% of the total risk set (ie, when there were 50 patients or fewer in the combined risk sets).

705 patients on placebo and 720 on denosumab. The most common adverse events were back pain, constipation, arthralgia, diarrhoea, and urinary tract infection, which occurred at similar rates in both treatment groups (table 2). Adverse events leading to study discontinuation occurred in 79 (11%) patients on denosumab and 67 (10%) on placebo. Rates of serious adverse events were 46% with both denosumab (n=329) and placebo (n=323). Denosumab was associated with increased incidence of osteonecrosis of the jaw and hypocalcaemia. Osteonecrosis of the jaw occurred in 33 (5%) men receiving denosumab at rates of 1% (n=8), 3% (n=21), and 4% (n=30) at end of years 1, 2, and 3, respectively; this adverse event did not occur in patients on placebo. Oral risk factors were noted in 31 (94%) patients with osteonecrosis of the jaw, including tooth extraction

	Placebo (n=705)	Denosumab (n=720)
Any adverse event	655 (93%)	676 (94%)
Most common adverse events		
Back pain	156 (22%)	168 (23%)
Constipation	119 (17%)	127 (18%)
Arthralgia	112 (16%)	123 (17%)
Diarrhoea	102 (14%)	111 (15%)
Urinary tract infection	96 (14%)	108 (15%)
Serious adverse events	323 (46%)	329 (46%)
Most common serious adverse events		
Urinary retention	31 (4%)	54 (8%)
Haematuria	24 (3%)	35 (5%)
Prostate cancer	21 (3%)	15 (2%)
Anaemia	12 (2%)	22 (3%)
Urinary tract infection	14 (2%)	15 (2%)
Grade 3, 4, or 5 adverse events	353 (50%)	381 (53%)
Adjudicated positive osteonecrosis of the jaw	0	33 (5%)
Hypocalcaemia	2 (<1%)	12 (2%)

Data are n (%).

Table 2: **Adverse events**

(n=23, 70%), poor oral hygiene (n=18, 55%), and dental appliance use (n=16, 48%). Limited interventions (ie, curettage and debridement) were needed in 21 (64%) patients with this adverse event and two (6%) patients underwent bone resection; in the remaining ten (30%) patients, the adverse event was managed with oral rinses or antibiotics. As of Feb 1, 2011, resolution (mucosal healing) had occurred in 13 (39%) patients.

Hypocalcaemia occurred more often with denosumab than with placebo (table 2); grade 3 or 4 hypocalcaemia (central laboratory) was reported in nine (1%) patients on denosumab and in no patients on placebo. Symptomatic hypocalcaemia was reported in one patient receiving denosumab; he was not taking calcium and vitamin D at the time of the event. No differences in creatinine profiles were noted between denosumab and placebo on study (data not shown). Neutralising antidenosumab antibodies were not detected in patient blood samples.

Discussion

In this global placebo-controlled randomised trial of men with high-risk castration-resistant prostate cancer, treatment with denosumab was associated with improved bone-metastasis-free survival. Treatment with denosumab was also associated with prolonged time to first bone metastasis and with fewer symptomatic bone metastases than was placebo. Several randomised controlled trials have evaluated the effects of other drugs on development of metastases in men with prostate cancer (panel), but have not shown a benefit.

This study has several major strengths. Although there are no evidence-based guidelines or established standards of care for salvage therapy in men with non-metastatic castration-resistant prostate cancer, other treatments were allowed during the study to increase the generalisability of the study results and to improve patient and clinician acceptance of the randomised design. Study treatment was discontinued at diagnosis of bone metastases because other therapies are approved for treatment of metastatic disease.[30] Bone scans were done every 4 months to detect bone metastases and were confirmed by a second imaging modality. Readers who were masked to treatment assignments centrally reviewed all radiographic studies. The primary efficacy analysis of bone-metastasis-free survival was based on a large number of informative events.

The study design required that patients discontinue investigational product after development of bone metastasis so they could receive standard treatment for prevention of skeletal-related events once bone metastasis had occurred. This requirement restricted our ability to evaluate overall survival with denosumab, since about 80% of the deaths occurred in patients who

Panel: **Research in context**

Systematic review

We searched the PubMed database up to April 20, 2011, without language restriction, for full papers reporting randomised controlled trials with the search terms "prostate cancer" and "bone metastases". Our search identified three randomised controlled trials of prevention of bone metastases in men with prostate cancer. In a study of 508 men with high-risk hormone-naive or hormone-sensitive non-metastatic prostate cancer, clodronate did not improve symptomatic bone-metastasis-free survival compared with placebo.[28] In a study of 941 men with castration-resistant prostate cancer and no bone metastases, atrasentan (an endothelin-1 receptor antagonist) did not significantly improve time to disease progression or time to first bone metastasis compared with placebo.[5] A randomised placebo-controlled trial of zoledronic acid in men with castration-resistant non-metastatic prostate cancer was stopped early because the event rate was lower than expected;[24] there was no difference in bone-metastasis-free survival between the groups.[29] Analyses of that study suggested that only high prostate-specific antigen (PSA) concentration and short PSA doubling time were independently associated with bone-metastasis-free survival. Those findings informed the eligibility criteria and event rate assumptions for our study.

Interpretation

Improvement in bone-metastasis-free survival and time to first bone metastasis with denosumab treatment in our study shows that a bone-targeted agent can delay time to bone metastasis in men with prostate cancer. Our findings also provide the first direct clinical evidence for the important role of the bone microenvironment and RANKL signalling in the development of bone metastases in men with prostate cancer.

had discontinued investigational product. With a median time from bone metastasis to death of 19 months, a treatment effect of denosumab on overall survival would be difficult to identify, particularly in the context of all other prostate cancer therapies used during that period that could affect survival. This same requirement also limited our ability to establish when asymptomatic bone metastases became symptomatic, since patients were removed from the study once a bone metastasis was detected and symptoms might not yet have occurred.

Denosumab was associated with increased incidence of osteonecrosis of the jaw and hypocalcaemia. The rate of osteonecrosis of the jaw in this study was similar when adjusted for exposure to that previously reported for denosumab, at the same dose and schedule, in another large trial[26] in patients with bone metastasis in prostate cancer. Median exposure to denosumab in the present study was longer than in the trial of skeletal-related events.[26] In the present study, most cases of osteonecrosis of the jaw were managed conservatively and 39% resolved. Grade 3 or 4 hypocalcaemia occurred in 1% of patients and only one patient developed symptomatic hypocalcaemia.

In 1889, Stephen Paget first proposed the so-called seed and soil hypothesis of interactions between tumour cells and the host microenvironment to explain why some cancers preferentially spread to specific anatomic sites.[9] Extensive contemporary preclinical research suggests a vicious cycle of complex bidirectional interactions between prostate cancer cells and the bone microenvironment, and tumour–bone interactions have been advanced as the foremost mechanism for the bone-dominant pattern of metastases in prostate cancer.[10] Our finding that denosumab increases bone-metastasis-free survival provides clinical evidence for the important role of the bone microenvironment and RANKL signalling in development of bone metastases in men with prostate cancer.

Contributors

All authors had access to pertinent study data, contributed to data analysis and interpretation, and reviewed and commented on multiple drafts of the report.

Conflicts of interest

MRS, RC, KF, and FS have been consultants for Amgen and Novartis. LK, BT, HVP, JC, JM, KM, PS, TLT, and NS have been consultants for Amgen. KF, FS, RC, and BT have participated in speakers' bureaus for Amgen and Novartis. NS, KM, PS, TB, and JM have participated in speakers' bureaus for Amgen. KF has received travel funds from Amgen and Novartis. BE, LK, BT, JC, KM, TB, and NS have received travel funds from Amgen. MRS, FS, LK, TLT, and NS have received research funding from Amgen. RC has received research funding from Novartis and honoraria from Amgen and Novartis. MRS, LK, and NS have received honoraria from Amgen. RC has provided expert testimony for Novartis. FG-V and RD declare that they have no conflicts of interest. ZY, AK, RD, and CG are employees of Amgen and have received stock or stock options from Amgen.

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