

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: 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. DOI: 10.1056/NEJMoa0809003.

Online Appendix 1: Methods

Inclusion and Exclusion Criteria

Eligible patients were ≥ 70 years old with non-metastatic, histologically confirmed prostate cancer; or adults < 70 years old with non-metastatic, histologically confirmed prostate cancer and evidence of bone loss (i.e., history of osteoporotic fracture or a BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0). All patients had undergone bilateral orchiectomy or had initiated androgen deprivation therapy with GnRH agonists and were expected to continue therapy for ≥ 12 months. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Patients were excluded from the study if they had evidence of distant metastases or a diagnosis of any other non-prostate malignancy within 5 years of study entry, with the exception of previously treated basal cell or squamous cell cancer. Patients also were excluded if they were taking any anti-neoplastic therapy or radiotherapy besides androgen deprivation therapy or anti-androgen therapies; had PSA > 5 ng/mL after being on androgen deprivation therapy > 1 month; had serum 25-hydroxyvitamin D deficiency (< 12 ng/mL); had serum calcium or albumin-adjusted serum calcium levels < 2.0 mmol/L (8.0 mg/dL) or ≥ 2.9 mmol/L (11.5 mg/dL); had a BMD T-score < -4.0 at the lumbar spine, total hip, or femoral neck; had height, weight, or girth that precluded accurate dual x-ray absorptiometry (DXA) measurements or less than 2 evaluable lumbar vertebrae (L1–L4); had Paget's disease, Cushing's disease, chronic liver disease, rheumatoid arthritis, human immunodeficiency virus, hepatitis C, or chronic hepatitis B; had unstable systemic disease (e.g., active infection, heart disease) within 6 months of study entry; had major surgery or traumatic injury within 4 weeks of study entry; hyperprolactinemia, hyper- or hypothyroidism, or any serum chemistry or hematology abnormality or inadequate organ function as determined by standard laboratory assessments; known sensitivity to mammalian cell derived biotechnology products; currently using oral

bisphosphonates or had been exposed to oral bisphosphonates for ≥ 3 years (patients who had used oral bisphosphonates previously for 3 months to 3 years were eligible if they had been oral bisphosphonate-free for ≥ 1 year prior to enrollment); had any exposure to intravenous bisphosphonates, fluoride, strontium ranelate, and gallium nitrate within 5 years of study entry; or had been exposed to parathyroid hormone (PTH) or PTH derivatives, anabolic steroids or testosterone, glucocorticoids, selective estrogen receptor modulators (SERMs), calcitonin, and calcitriol within 6 weeks of study entry. Current users of chronic oral glucocorticoids, but not inhaled or nasal glucocorticoids, also were excluded.

Statistical Analysis

The primary analysis was the comparison of percentage change in lumbar spine BMD from baseline to month 24 between the denosumab and placebo groups. The planned sample size was 1226 patients (613 patients per group). The planned sample size provided a 95% power to detect a 2% difference between the groups in percentage change in lumbar spine BMD from baseline to month 24 assuming $\alpha = 0.05$, a 6.4% standard deviation of change from baseline,^{10,15} and 10% annual dropout rate. Assuming a 12% incidence of new vertebral fractures at 36 months^{24,25} and fracture rates similar to those reported in a population-based study of men with prostate cancer,¹¹ the study had 80% power to detect a 45% reduction in risk of new vertebral fractures and a 45% reduction in risk of fractures at any site over 36 months.

Analysis of percentage changes in BMD included all randomized patients who had a baseline and ≥ 1 post-baseline BMD measurements, and was performed using analysis of covariance (ANCOVA) adjusting for stratification factors, baseline BMD value, machine type (Lunar or Hologic), and baseline value-by-machine type interaction. Missing BMD values were imputed using last observation carried forward (LOCF). Similar results to the LOCF method were observed in a pre-specified sensitivity analysis using a mixed-effects model for repeated

measures. Analysis of the incidence of new vertebral fracture included all randomized patients who had a baseline and ≥ 1 post-baseline evaluation of vertebral fracture. Analysis of incidence of fracture at any site included all randomized patients. Incidence of fracture at any site and new vertebral fracture were compared using a logistic regression model adjusting for stratification factors. Treatment effect was presented as the odds ratio and 95% 2-sided confidence interval (CI), with *P* values calculated using a score test. Absolute risk difference and risk ratio were also presented using the Mantel-Haenszel method adjusting for the stratification factors. All exploratory analyses were conducted using available patients' data at time of analysis. All statistical testing was 2-sided. Analyses of the primary and secondary endpoints were conducted hierarchically. Secondary endpoints were tested in a stepwise fashion to adjust for multiplicity at a significance level of 0.05. Patient incidence of fracture at any site and new vertebral fracture were tested within the same step, using the Hochberg procedure as within-step multiplicity adjustment for the two null hypotheses.

The safety dataset included all patients who received ≥ 1 dose of investigational product. Patients were analyzed according to the actual treatment received; patients who received ≥ 1 dose of denosumab were analyzed in the denosumab arm. Adverse events were coded using the Medical Dictionary for Regulatory Activities, Version 9 or higher. The incidence of anti-denosumab antibodies were tabulated by study visit. No formal statistical testing was done for safety analyses.

Early Stopping Rule

An external Data Monitoring Committee (DMC) monitored patient efficacy and safety throughout the 36-month treatment period. A pre-specified rule allowed the DMC to stop the study early for efficacy if the results of the new vertebral fracture or fracture at any site endpoints achieved a *P* value of < 0.0005 .

**Online Appendix 2: Number of Patients Who Contributed to the Analyses in Figure 2
Using Last Observation Carried Forward (LOCF) Imputation, and In Parentheses, The
Number of Patients Who Had Complete Data at Each Visit**

		M1	M3	M6	M12	M24	M36
Lumbar spine	Placebo (N = 734)	678 (678)	714 (679)	714 (666)	715 (633)	716 (537)	716 (422)
	Denosumab (N = 734)	674 (674)	710 (686)	714 (677)	714 (646)	714 (560)	714 (435)
Femoral Neck	Placebo (N = 734)	671 (671)	703 (666)	706 (654)	706 (619)	706 (523)	706 (406)
	Denosumab (N = 734)	655 (655)	695 (669)	699 (657)	700 (628)	701 (543)	701 (424)
Total Hip	Placebo (N = 734)	671 (671)	703 (666)	706 (654)	706 (619)	706 (523)	706 (406)
	Denosumab (N = 734)	655 (655)	695 (669)	699 (657)	700 (628)	701 (543)	701 (424)
Distal 1/3 Radius	Placebo (N = 148)	-	-	-	120 (120)	122 (93)	122 (84)
	Denosumab (N = 161)	-	-	-	127 (127)	127 (109)	127 (85)

N = number of randomized patients for lumbar spine, femoral neck, and total hip; number of randomized patients enrolled in the DXA substudy for distal 1/3 radius.

Online Appendix 3: Demographics and Baseline Characteristics of Overall Population and 36-Month Completers

	Overall Population		36-Month Completers	
	Placebo (N = 734)	Denosumab (N = 734)	Placebo (N = 445)	Denosumab (N = 467)
Mean (SD) age, years	75.5 (7.1)	75.3 (7.0)	74.4 (7.0)	74.7 (6.9)
Median (minimum, maximum) BMI, kg/m ²	27.6 (18, 42)	27.9 (15, 45)	27.7 (19, 42)	28.0 (15, 45)
ECOG status 0-1, n (%)	712 (97)	706 (96)	438 (98)	456 (98)
Median (minimum, maximum) PSA level, ng/mL	0.15 (0.01, 57.30)	0.13 (0.01, 33.70)	0.12 (0.01, 19.40)	0.10 (0.01, 33.70)
Mean (SD) lumbar spine BMD T-score	-0.41 (1.80)	-0.31 (1.78)	-0.42 (1.82)	-0.36 (1.81)
Mean (SD) total hip BMD T-score	-0.88 (1.03)	-0.87 (1.00)	-0.88 (1.01)	-0.83 (1.00)
Prevalent vertebral fracture, n (%)	174 (24)	155 (21)	98 (22)	94 (20)

BMI = body mass index; BMD = bone mineral density; ECOG = Eastern Cooperative Oncology Group; SD = standard deviation; PSA = prostate-specific antigen

Online Appendix 4: Serious Adverse Events of Infection

	Placebo (N = 725)	Denosumab (N = 731)
Serious adverse events of infection	33 (5)	43 (6)
Type of serious adverse events of infection*		
Pneumonia	11 (1.5)	11 (1.5)
Diverticulitis	0 (0)	5 (0.7)
Lobar pneumonia	0 (0)	3 (0.4)
Urosepsis	2 (0.3)	3 (0.4)
Bronchitis	2 (0.3)	2 (0.3)
Pseudomembranous colitis	0 (0)	2 (0.3)
Cystitis	0 (0)	2 (0.3)
Cellulitis	4 (0.6)	2 (0.3)
Gastroenteritis	2 (0.3)	1 (0.1)
Sepsis	4 (0.6)	0 (0)
Septic shock	4 (0.6)	0 (0)
Urinary tract infection	3 (0.4)	0 (0)
Deaths due to serious adverse events of infection	6 (0.8)	0 (0)

* For events that occurred in more than 1 patient

N = number of patients who received ≥ 1 dose of investigational product