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Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer

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Abstract

BACKGROUND—Androgen-deprivation therapy is well-established for treating prostate cancer but is associated with bone loss and an increased risk of fracture. We investigated the effects of denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor-κB ligand, on bone mineral density and fractures in men receiving androgen-deprivation therapy for nonmetastatic prostate cancer.

METHODS—In this double-blind, multicenter study, we randomly assigned patients to receive denosumab at a dose of 60 mg subcutaneously every 6 months or placebo (734 patients in each group). The primary end point was percent change in bone mineral density at the lumbar spine at 24 months. Key secondary end points included percent change in bone mineral densities at the femoral neck and total hip at 24 months and at all three sites at 36 months, as well as incidence of new vertebral fractures.

RESULTS—At 24 months, bone mineral density of the lumbar spine had increased by 5.6% in the denosumab group as compared with a loss of 1.0% in the placebo group ($P<0.001$); significant differences between the two groups were seen at as early as 1 month and sustained through 36 months. Denosumab therapy was also associated with significant increases in bone mineral density at the total hip, femoral neck, and distal third of the radius at all time points. Patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5%, vs. 3.9% with placebo) (relative risk, 0.38; 95% confidence interval, 0.19 to 0.78; $P = 0.006$). Rates of adverse events were similar between the two groups.

CONCLUSIONS—Denosumab was associated with increased bone mineral density at all sites and a reduction in the incidence of new vertebral fractures among men receiving androgen-deprivation therapy for nonmetastatic prostate cancer. (ClinicalTrials.gov number, NCT00089674.)

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Prostate cancer is the most common newly diagnosed cancer in men worldwide.1 In the United States, prostate cancer accounts for approximately 25% of all new cancer diagnoses and 10% of all deaths from cancer.[2] Androgen-deprivation therapy, through bilateral orchiectomy or treatment with gonadotropin-releasing hormone (GnRH) agonists, is the standard first-line therapy for metastatic prostate cancer.[3,4] GnRH agonists are also frequently used to treat men with nonmetastatic prostate cancer.5 Androgen-deprivation therapy improves disease-free and overall survival in various clinical settings, such as when used as adjuvant treatment in men with locally advanced prostate cancer who are undergoing radiation therapy 6,7 or in men with lymph node–positive prostate cancer treated with radical prostatectomy and pelvic lymphadenectomy.[8] Androgen-deprivation therapy is also commonly used in patients with an increasing prostate-specific antigen (PSA) level after primary therapy.

Androgen-deprivation therapy increases bone resorption, reduces bone mineral density, and increases the risk of fracture in men with prostate cancer.[9–13] The risk of fracture increases with increasing duration of androgen-deprivation therapy and is an important contributor to the morbidity associated with this therapy.[11,12] Although several drugs, including bisphosphonates and selective estrogen-receptor modulators, have been shown to prevent bone loss associated with androgen-deprivation therapy, published trial results showing an effect on fracture prevention are lacking. [10,14–18]

Denosumab is a fully human monoclonal antibody that specifically binds to the receptor activator of nuclear factor-κB ligand, a key mediator of osteoclast formation, function, and survival.[19] Denosumab use was associated with increased bone mineral density at multiple skeletal sites in women receiving aromatase-inhibitor therapy for breast cancer.[20] Similarly, in postmenopausal women with low bone mass, denosumab therapy was associated with increased bone mineral density at all measured skeletal sites and with decreased levels of markers of bone turnover.[21,22] In this randomized, phase 3 trial, we evaluated the effects of denosumab on bone mineral density and fractures in men receiving androgen-deprivation therapy for prostate cancer.

METHODS

STUDY DESIGN

This was a multicenter, randomized, double-blind, placebo-controlled study of men undergoing androgen-deprivation therapy for nonmetastatic, hormone-sensitive prostate cancer. Patients were enrolled in 156 study centers in North America and Europe and randomly assigned (by means of an interactive voice-response system) to receive denosumab, 60 mg subcutaneously through a 1-ml injection, or placebo every 6 months. In July 2006, the study protocol was amended to extend the period for safety and fracture evaluation from 2 to 3 years. Patients were stratified according to age (<70 vs. ≥70 years) and duration of androgen-deprivation therapy (≤6 months vs. >6 months). All patients were instructed to take daily supplements of calcium, 1 g or more, and vitamin D, 400 IU or more. Data were collected from April 2004 to June 2008.

The primary end point was the percent change in the baseline bone mineral density of the lumbar spine at 24 months; the percent change at 36 months was a secondary end point, as were percent changes in the baseline bone mineral density of the total hip and femoral neck at 24 and 36 months, the incidence of newly diagnosed vertebral fractures at 36 months, fracture at any site (morphometric or clinical vertebral or nonvertebral fracture), time to first clinical fracture, and safety events. For the end point of fracture at any site, we excluded fractures associated with severe trauma, pathologic fractures, and fractures of the skull, face, mandible, metacarpals, fingers, and toes.[23] This end point was based on published data that

showed a correlation between androgen-deprivation therapy and the risk of fracture across multiple skeletal sites.[11,12] Exploratory end points included the percent changes in bone mineral densities of the whole body and distal third of the radius and changes over time in levels of PSA and markers of bone turnover.

Institutional review boards at each center approved the protocol. All patients provided written informed consent before participating. An external data monitoring committee monitored patients' safety and efficacy throughout the 36-month study period. Early stopping rules are described in the Supplementary Appendix (available with the full text of this article at NEJM.org).

The study was codesigned by the principal (academic) investigator and the sponsor. The sponsor gathered the data and conducted the statistical analyses. The investigators had full access to the study data and were permitted to publish without undue delay. All authors contributed to the interpretation of the data, the decision to publish the results, and the writing of the manuscript and vouch for the accuracy and completeness of the data. The principal investigator wrote the first draft of the manuscript with assistance from the sponsor.

PATIENTS

The full inclusion and exclusion criteria are described in the Supplementary Appendix. Briefly, eligible patients had histologically confirmed prostate cancer and were receiving androgen-deprivation therapy (bilateral orchiectomy or GnRH-agonist therapy) with an expected duration of such treatment for 12 or more months of the study period. Men were 70 years of age or older or were younger than 70 years of age but had either a low bone mineral density (T score at the lumbar spine, total hip, or femoral neck of less than −1.0) at baseline or a history of an osteoporotic fracture. Bone mineral density T scores were calculated based on the third National Health and Nutrition Examination Survey (NHANES III) normative database. Patients had an Eastern Cooperative Oncology Group performance status score of 2 or less. Key exclusion criteria included concurrent receipt of antineoplastic therapy or radiotherapy, PSA level of more than 5 ng per milliliter after receiving androgen-deprivation therapy for more than 1 month, current use of oral bisphosphonates or previous exposure to oral bisphosphonates for 3 or more years (although patients who had used oral bisphosphonates previously for more than 3 months to less than 3 years were eligible if they had been free of oral bisphosphonates for ≥1 year before enrollment), and any exposure to intravenous bisphosphonates within 5 years before study entry. Patients with a bone mineral density T score of less than −4.0 at the lumbar spine, total hip, or femoral neck or who were currently receiving treatment for osteoporosis were also excluded.

STUDY PROCEDURES

Bone mineral densities of the lumbar spine, femoral neck, and total hip were measured by means of dual x-ray absorptiometry at baseline and at months 1, 3, 6, 12, 24, and 36. In a substudy of 309 patients, bone mineral densities of the whole body and distal third of the radius were measured every 12 months. Investigators were unaware of the bone mineral density results but were alerted about, and had the discretion of stopping the study drug in, patients who lost more than 7% of the bone mineral density at the lumbar spine or total hip within any 12-month period or who had a T score of less than −4.0 at the total hip or lumbar spine at any point during the study. Markers of bone turnover (serum C-telopeptide, procollagen type I N-terminal peptide, and tartrate-resistant acid phosphatase) were measured at baseline and at 1, 6, 12, 24, and 36 months. Routine laboratory values, PSA levels, and testosterone levels were measured at baseline and every 6 months during the

study. Antidenosumab antibody levels were assessed with the use of screening methods described previously.[21]

All bone mineral density and fracture results were assessed in a blinded fashion by a reader at a central facility (Synarc). Assessments of vertebral fractures were based on readings of lateral spine radiographs (of T4 to L4) at baseline and at 12, 24, and 36 months; nonvertebral fractures were also confirmed by the reader. To avoid unintentional unblinding of study-group assignments, serum calcium levels (unless grade 3 or above, as assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events) and results of bone-marker tests were not reported to the sites.

All adverse events were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA) system. An independent, external committee of cardiologists who were unaware of the study-group assignments adjudicated all deaths and serious adverse events that met a predefined set of MedDRA terms possibly related to cardiovascular events. All cases of osteonecrosis of the jaw were adjudicated by an independent external committee of experts in dental disease, in a blinded manner.

STATISTICAL ANALYSIS

The primary analysis was the comparison of percent change in bone mineral density at the lumbar spine between baseline and 24 months in the denosumab group and the placebo group. The planned sample size was 1226 patients (613 patients per group), which was calculated to provide a statistical power of 95% to detect an absolute difference of 2 percentage points between the two study groups in the percent change in bone mineral density at the lumbar spine between baseline and 24 months, assuming an alpha value of 0.05, a standard deviation of the mean change from baseline of 6.4%,[10,15] and an annual dropout rate of 10%. The study had a statistical power of 80% to detect a 45% reduction in the risk of new vertebral fracture and a 45% reduction in the risk of fracture at any site at 36 months with denosumab as compared with placebo, 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]

Full statistical methods are described in the Supplementary Appendix. Analysis of the percent changes in bone mineral density included data for all patients who had been randomly assigned to a study group and had a bone mineral density measurement at baseline, and one or more post baseline (the modified intention-to-treat population). This analysis consisted of an analysis of covariance, with adjustment for stratification factors (age and duration of previous androgen-deprivation therapy), baseline bone mineral density, densitometer type (Lunar or Hologic), and interaction between baseline bone mineral density and densitometer type. Missing values were imputed according to the last-observation-carried-forward method. The numbers of patients whose data were included in analyses of the bone mineral density are listed in the Supplementary Appendix. Analysis of the incidence of new vertebral fracture included data for all patients who had been randomly assigned to a study group and had a baseline evaluation and one or more postbaseline evaluations of vertebral fracture. Analysis of incidence of fracture at any site included data for all patients who had been randomized to a study group. All exploratory analyses were conducted using all data available at the time of analysis. All statistical testing was two-sided, with an alpha value of 0.05. Analysis of safety included data for all patients who had received at least one dose of a study drug. No formal statistical testing was performed for safety analysis.

RESULTS

STUDY POPULATION

The study included a total of 1468 patients (734 in the denosumab group and 734 in the placebo group) (Fig. 1). In all, 912 patients (62.1%) completed the 36-month study. The primary reason for study discontinuation was withdrawal of consent (18.4%), the majority of cases of which occurred when the blinded period was extended from 24 to 36 months. Baseline characteristics of the patients who participated throughout the 36-month study period were similar to those of the overall population (see the Supplementary Appendix).

Baseline characteristics were generally well balanced between the two groups (Table 1). The mean age was 75 years; 83.0% of patients were 70 years of age or older. Most patients were white and had received androgen-deprivation therapy for more than 6 months. Mean bone mineral density T scores were −0.4 at the lumbar spine, −0.9 at the total hip, and −1.4 at the femoral neck. Approximately 77.9% of patients had a T score of less than −1.0 at the spine or hip at baseline; 63.1% had a T score from −1.0 to −2.5, and 14.7% had a T score of less than −2.5. The median serum 25-hydroxy vitamin D level was similar in the two groups at baseline (24.4 ng per milliliter with denosumab and 24.9 ng per milliliter with placebo) and remained so at 36 months (31.4 and 31.0 ng per milliliter, respectively).

EFFICACY

Bone Mineral Density—Denosumab was associated with increased bone mineral density at all measured sites (Fig. 2). In the denosumab group, the bone mineral density at the lumbar spine was increased by 6.7 percentage points over that in the placebo group at 24 months (5.6% vs. −1.0%, P<0.001) (Fig. 2A). Bone mineral density at the lumbar spine was significantly increased with denosumab at 1 month, and continued to increase through 36 months, as compared with placebo (P<0.001 at all measured time points).

At 24 months, denosumab therapy was associated with significantly increased bone mineral density of the total hip, femoral neck, distal third of the radius, and whole body (absolute difference vs. value for placebo, 4.8, 3.9, 5.5, and 4.0 percentage points, respectively) (P<0.001 for all comparisons) (Fig. 2B, 2C, and 2D and data not shown, respectively). The between-group differences were significant at all measured time points (P≤0.001 for all comparisons). Denosumab use was also associated with significant increases in bone mineral density at all measured skeletal sites for every subgroup of patients, including older men and those with lower baseline values of bone mineral density, higher levels of serum C-telopeptide and tartrate-resistant acid phosphatase, and a history of vertebral fracture at baseline (data not shown).

FRACTURES

New Vertebral Fracture—Denosumab therapy was associated with decreases in the incidence of new vertebral fracture at 12, 24, and 36 months (Fig. 3). The cumulative incidence of new vertebral fracture at 36 months was 3.9% in the placebo group and 1.5% in the denosumab group, a significant decrease of 62% (relative risk, 0.38; 95% confidence interval [CI], 0.19 to 0.78; P = 0.006) (Fig. 3). This decrease was significant even after adjustment for multiple comparisons.

Fracture at Any Site—Fracture at any site developed in fewer patients in the denosumab group (38 [5.2%]) than in the placebo group (53 [7.2%]) during the 36-month period, although this difference was not significant (relative risk, 0.72; 95% CI, 0.48 to 1.07; P = 0.10). More than one fracture at any site developed in significantly fewer patients in the denosumab group (5 [0.7%]) than in the placebo group (18 [2.5%]) (relative risk, 0.28; 95%

CI, 0.10 to 0.74; P = 0.006). No significant differences were found between the groups in the time to first clinical fracture (any nonvertebral or clinically evident vertebral fracture).

Markers of Bone Turnover—At 36 months (6 months after the last dose of the study drug), levels of biochemical markers of bone turnover decreased significantly with denosumab treatment as compared with placebo (P<0.001 for each comparison). Serum levels of serum C-telopeptide, procollagen type I N-terminal peptide, and TRAP-5b were decreased from the baseline values by a median of 45%, 61%, and 33%, respectively, in the denosumab group as compared with 13%, 18%, and 8%, respectively, in the placebo group.

SAFETY

Rates of adverse events were approximately 87% for both the denosumab group and the placebo group (Table 2). Cataracts developed in more patients receiving denosumab (4.7%, vs. 1.2% receiving placebo), though none of these cases were considered related to the study drug. One patient receiving denosumab had hypocalcemia (0.1%), whereas none receiving placebo did. New primary cancer was reported in approximately 5% of patients in each group. A similar proportion of patients in each group discontinued the study drug (6.7% in the denosumab group and 6.5% in the placebo group) because of adverse events.

Rates of serious adverse events were 34.6% with denosumab and 30.6% with placebo (Table 2). Serious adverse events related to infection were reported in 5.9% of patients receiving denosumab and 4.6% of those receiving placebo (see the Supplementary Appendix). Adjudicated cardiovascular events were reported in approximately 11% of patients in each group. A total of 6% of patients died in each group (44 [6.0%] in the denosumab group and 46 [6.3%] in the placebo group). One death from a cardiovascular disorder in the placebo group was considered possibly treatment-related. None of the deaths in the denosumab group were considered treatment-related.

There were no changes in the serum chemical values (including serum creatinine) or hematologic values in association with denosumab therapy, other than the expected transient decreases in serum calcium, phosphorus, and total alkaline phosphatase levels. The incidence of Common Terminology Criteria grade 2 hypocalcemia (changes in laboratory values of albumin-adjusted serum calcium) was less than 1% in each of the two groups. PSA levels over time were unaffected by either study drug (data not shown).

There were no delays in healing of nonvertebral fractures in either group. No neutralizing antidenosumab antibodies were detected. No cases of osteonecrosis of the jaw were reported.

DISCUSSION

In this study of men receiving androgen-deprivation therapy for prostate cancer, a significant increase in bone mineral density was seen with denosumab at all measured skeletal sites, including the lumbar spine, hip, and radius. Denosumab was associated with significant decreases, as compared with placebo, in the cumulative incidence of new vertebral fractures at 12, 24, and 36 months.

Several randomized, controlled trials have evaluated the effects of other drugs on bone mineral density and bone turnover in men with prostate cancer. Bisphosphonates (e.g., pamidronate, zoledronic acid, and alendronate) and selective estrogen- receptor modulators (e.g., raloxifene and toremifene) have been associated with increases in bone mineral density of the hip and spine and decreases in bone turnover in men receiving androgen-deprivation therapy for prostate cancer. [10,14–18,26] In the present study, the beneficial effects in the

denosumab group appeared robust, as they were found as early as 1 month after therapy was begun and were sustained for 3 years. Denosumab was associated with significant increases in bone mineral density of the distal third of the radius, a site of predominantly cortical bone,[27] for which neither bisphosphonates nor selective estrogen-receptor modulators have been reported to have a positive effect. In a randomized, controlled trial of men receiving androgen-deprivation therapy for prostate cancer, for example, bone mineral density of the distal radius decreased, despite treatment with alendronate.[16]

There are limited data about fracture prevention in men with osteoporosis, and more specifically, in men receiving androgen-deprivation therapy. Several small studies have suggested that both oral bisphosphonates and teriparatide may reduce the risk of fracture in men with osteoporosis, unrelated to androgen-deprivation therapy. [28–31] In a preliminary report of a 2-year, placebo-controlled trial involving men receiving androgen-deprivation therapy for prostate cancer, toremifene use decreased the risk of new vertebral fractures by approximately 50%.[32]

We used a placebo-control design in our study for several reasons. First, there are limited data about fracture prevention in men in any context, including in men receiving androgen-deprivation therapy for prostate cancer. Second, no approved therapy is indicated for reduction of the risk of fracture in men receiving androgen-deprivation therapy for prostate cancer. Third, the natural history of bone loss and fractures has not been prospectively described in such men. Fourth, there are no evidence-based guidelines or established standards of care for fracture prevention in men receiving androgen-deprivation therapy for prostate cancer. Lastly, a study to evaluate the risk of fracture associated with denosumab in comparison with an active drug would have been impractical because of the large sample required.[33–36]

In conclusion, twice-yearly administration of denosumab was associated with increases in bone mineral density at all skeletal sites and reduction in vertebral fractures in men receiving androgen-deprivation therapy for prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

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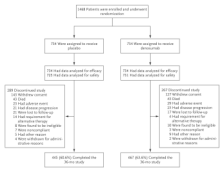

Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients

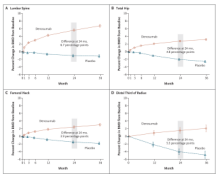

Figure 2. Mean Percent Changes from Baseline Bone Mineral Density (BMD) Values during the Study Period, According to Skeletal Site and Study Group

Results are presented as least-squares means of the BMDs of the lumbar spine (Panel A), the total hip (Panel B), the femoral neck (Panel C), and the distal third of the radius (Panel D). All values shown were significantly higher in the denosumab group than in the placebo group ($P \leq 0.001$). The means were estimated with the use of analysis-of-covariance models adjusting for study group, stratification variables, baseline BMD value, densitometer type, and the interaction between baseline BMD value and densitometer type. The means are based on data for 734 patients in each of the two groups except for the distal third of the radius, for which data were available for 161 patients in the denosumab group and 148 patients in the placebo group. I bars indicate 95% confidence intervals.

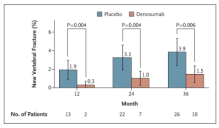

Figure 3. Cumulative Incidence of New Vertebral Fracture at 12, 24, and 36 Months, According to Study Group

The relative risk for vertebral fracture among 679 patients in the denosumab group as compared with 673 patients in the placebo group was 0.15 at 12 months, 0.31 at 24 months, and 0.38 at 36 months.

Table 1

Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Denosumab (N = 734)	Placebo (N = 734)
Age — yr		
Mean ±SD	75.3±7.0	75.5±7.1
Range	48 to 92	50 to 97
<70 yr — no. (%)	125 (17.0)	124 (16.9)
≥70 yr — no. (%)	609 (83.0)	610 (83.1)
Race or ethnic group — no. (%)†		
White	615 (83.8)	609 (83.0)
Black	36 (4.9)	32 (4.4)
Hispanic	77 (10.5)	81 (11.0)
Other	6 (0.8)	12 (1.6)
BMI — median (range)‡	27.9 (15 to 45)	27.6 (18 to 42)
ECOG performance status score — no. (%)		
0	552 (75.2)	538 (73.3)
1	154 (21.0)	174 (23.7)
2	28 (3.8)	21 (2.9)
Unknown	0	1 (0.1)
PSA — ng/ml		
Median	0.13	0.15
Range	0.01 to 33.70	0.01 to 57.30
Total testosterone — nmol/liter		
Median	0.28	0.28
Range	0.14 to 35.19	0.14 to 33.66
Serum C-telopeptide — ng/ml		
Median	0.62	0.61
Range	0.05 to 2.48	0.05 to 2.49
T score below −2.5 at any site — no. (%)§	105 (14.3)	111 (15.1)
Lumbar spine BMD, according to densitometer type — absolute value in g/cm^2		
Hologic		
Median	1.0	1.0
Range	0.6 to 1.9	0.6 to 1.9
Lunar		
Median	1.2	1.2
Range	0.4 to 2.0	0.6 to 2.0
Lumbar spine BMD T score		
Median (range)	−0.5 (−6.8 to 7.3)	−0.6 (−4.8 to 7.6)
Mean ±SD	−0.3±1.8	−0.4±1.8

Characteristic	Denosumab (N = 734)	Placebo (N = 734)
Total hip BMD, according to densitometer type — absolute value in g/cm^2		
Hologic		
Median	0.9	0.9
Range	0.6 to 1.5	0.6 to 1.4
Lunar		
Median	1.0	1.0
Range	0.6 to 1.4	0.6 to 1.6
Total hip BMD T score		
Median (range)	−0.9 (−3.6 to 3.3)	−1.0 (−3.6 to 3.1)
Mean ±SD	−0.9±1.0	−0.9±1.0
Femoral neck BMD, according to densitometer type — absolute value in g/cm^2		
Hologic		
Median	0.8	0.8
Range	0.4 to 1.3	0.5 to 1.2
Lunar		
Median	0.9	0.9
Range	0.5 to 1.3	0.6 to 1.4
Femoral neck BMD T score		
Median (range)	−1.5 (−3.8 to 3.0)	−1.5 (−3.5 to 1.9)
Mean ±SD	−1.4±0.9	−1.4±0.9
Duration of previous androgen-deprivation therapy — mo		
Calculated median (range)	20.8 (0.0 to 195.3)	20.4 (0.0 to 354.6)
0–6 mo — no. (%)	175 (23.8)	175 (23.8)
>6 mo — no. (%)	559 (76.2)	559 (76.2)
Previous bisphosphonate therapy — no. (%)	10 (1.4)	9 (1.2)
Vertebral fracture at baseline — no. (%)	155 (21.1)	174 (23.7)
History of osteoporotic fracture — no. (%)	163 (22.2)	196 (26.7)

*BMD denotes bone mineral density, ECOG Eastern Cooperative Oncology Group, and PSA prostate-specific antigen.

†Race was self-reported.

‡The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§"Any site" refers to the lumbar spine, total hip, or femoral neck.

Table 2

Summary of Adverse Events.*

Event	Denosumab (N = 731)	Placebo (N = 725)
	no. (%)	
Adverse event	638 (87.3)	627 (86.5)
Most common: ≥5% in either group		
Arthralgia	92 (12.6)	80 (11.0)
Back pain	81 (11.1)	74 (10.2)
Constipation	73 (10.0)	75 (10.3)
Pain in extremity	66 (9.0)	51 (7.0)
Hypertension	57 (7.8)	51 (7.0)
Peripheral edema	53 (7.3)	48 (6.6)
Nasopharyngitis	47 (6.4)	45 (6.2)
Fatigue	44 (6.0)	45 (6.2)
Dizziness	41 (5.6)	31 (4.3)
Musculoskeletal pain	41 (5.6)	26 (3.6)
Diarrhea	40 (5.5)	39 (4.4)
Hot flush	38 (5.2)	32 (4.4)
Urinary tract infection	37 (5.1)	32 (4.4)
Possibly treatment-related	62 (8.5)	65 (9.0)
CTC grade 3, 4, or 5	269 (36.8)	244 (33.7)
Serious adverse event	253 (34.6)	222 (30.6)
Adjudicated cardiovascular	80 (10.9)	80 (11.0)
Cardiovascular death	19 (2.6)	21 (2.9)
Acute coronary syndrome	18 (2.5)	27 (3.7)
Stroke or transient ischemic attack	21 (2.9)	17 (2.3)
Congestive heart failure	8 (1.1)	11 (1.5)
Other vascular	18 (2.5)	12 (1.7)
Arrhythmia	19 (2.6)	15 (2.1)
Most common other serious adverse event: ≥1% in either group		
Pneumonia	11 (1.5)	11 (1.5)
Syncope	8 (1.1)	5 (0.7)
Dyspnea	8 (1.1)	3 (0.4)
Metastasis to bone	3 (0.4)	10 (1.4)
Possibly treatment-related	3 (0.4)	4 (0.6)
Death	44 (6.0)	46 (6.3)

*CTC denotes Common Terminology Criteria of the National Cancer Institute (version 3).