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ORIGINAL REPORT

Denosumab and Bone Metastasis–Free Survival in Men With Nonmetastatic Castration-Resistant Prostate Cancer: Exploratory Analyses by Baseline Prostate-Specific Antigen Doubling Time

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A B S T R A C T

Purpose

Denosumab, an anti–RANK ligand monoclonal antibody, significantly increases bone metastasis–free survival (BMFS; hazard ratio [HR], 0.85; $P = .028$) and delays time to first bone metastasis in men with nonmetastatic castration-resistant prostate cancer (CRPC) and baseline prostate-specific antigen (PSA) ≥ 8.0 ng/mL and/or PSA doubling time (PSADT) ≤ 10.0 months. To identify men at greatest risk for bone metastasis or death, we evaluated relationships between PSA and PSADT with BMFS in the placebo group and the efficacy and safety of denosumab in men with PSADT ≤ 10, ≤ 6, and ≤ 4 months.

Patients and Methods

A total of 1,432 men with nonmetastatic CRPC were randomly assigned 1:1 to monthly subcutaneous denosumab 120 mg or placebo. Enrollment began February 2006; primary analysis cutoff was July 2010, when approximately 660 men were anticipated to have developed bone metastases or died.

Results

In the placebo group, shorter BMFS was observed as PSADT decreased below 8 months. In analyses by shorter baseline PSADT, denosumab consistently increased BMFS by a median of 6.0, 7.2, and 7.5 months among men with PSADT ≤ 10 (HR, 0.84; $P = .042$), ≤ 6 (HR, 0.77; $P = .006$), and ≤ 4 months (HR, 0.71; $P = .004$), respectively. Denosumab also consistently increased time to bone metastasis by PSADT subset. No difference in survival was observed between treatment groups for the overall study population or PSADT subsets.

Conclusion

Patients with shorter PSADT are at greater risk for bone metastasis or death. Denosumab consistently improves BMFS in men with shorter PSADT and seems to have the greatest treatment effects in men at high risk for progression.

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INTRODUCTION

Development of bone metastases represent a key event in the progression of castration-resistant prostate cancer (CRPC). Bone is the dominant and often only site of distant disease for most men with metastatic prostate cancer. A majority of men with fatal prostate cancer have bone metastases,[1] and the median survival for men with CRPC metastatic to bone is approximately 1.5 to 2 years.[2-4] Bone metastases are life altering, often painful, and associated with progressive morbidities, such as skeletal-related events (eg, pathologic fractures, surgery or irradiation of bone, and spinal cord compression) and ineffective hematopoiesis.[5] Bone metastases are frequently a trigger for the initiation of other systemic treatments for metastatic disease, including chemotherapy.[6-9] Prevention of bone metastases remains an important unmet medical need for men with CRPC.

In men with nonmetastatic CRPC, both baseline absolute prostate-specific antigen (PSA) and PSA kinetics are associated with risk of disease progression and mortality.[10,11] In analyses of 201 men with progressive CRPC and no detectable metastases, higher baseline PSA and shorter PSA doubling time (PSADT) were associated with decreased time

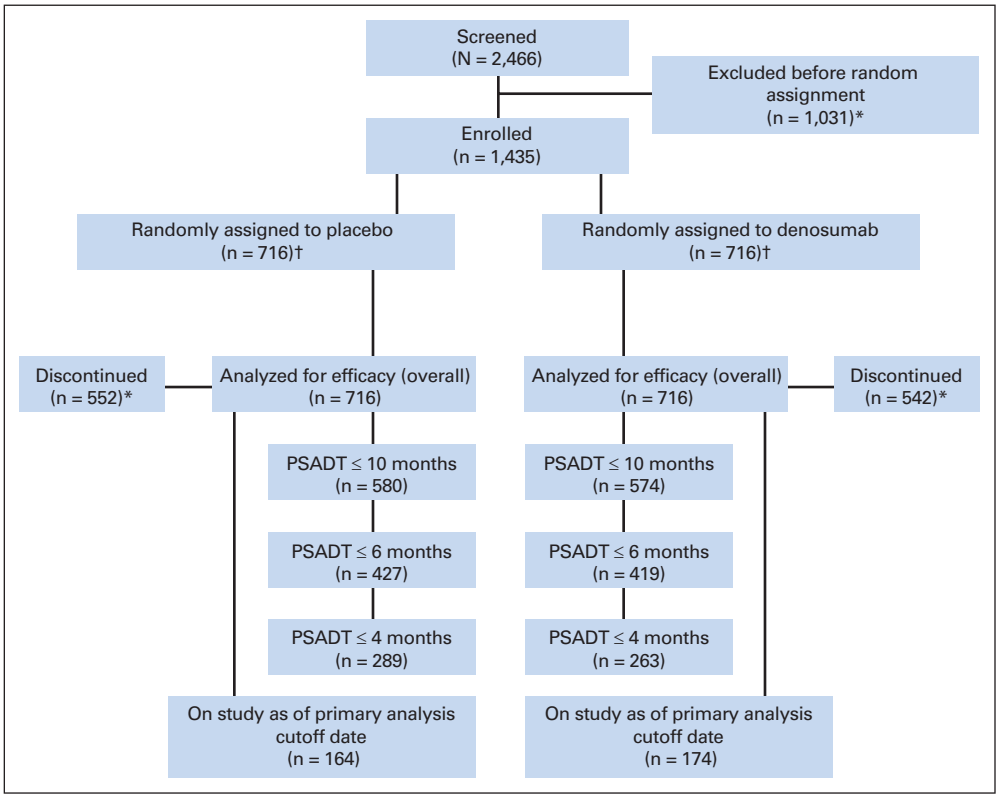

Fig 1. CONSORT diagram. PSADT, prostate-specific antigen doubling time. (*) Data published previously.[18] (†) One additional patient assigned to placebo and two patients assigned to denosumab were excluded after random assignment because review activities and oversight of institutional review board were not ensured.

to first bone metastasis and death.[11] In a different study of 331 men with nonmetastatic CRPC, higher baseline PSA and PSA velocity, another descriptor of PSA kinetics, were significantly associated with shorter overall (OS) and bone metastasis–free survival (BMFS).[10] In both studies, other baseline covariates were not consistently associated with clinical outcome.

In animal models, increased bone turnover has been shown to promote the development of bone metastases, and inhibition of RANK ligand (RANKL), an essential mediator of osteoclast formation, function, and survival, can prevent the development of de novo bone metastases and progression of existing bone metastases.[12-15] Furthermore, because some prostate cancers express RANK,[16] RANKL produced by osteoblasts and bone marrow stromal cells may contribute to homing of RANK-positive prostate cancer cells to bone.[17]

Denosumab is a fully human monoclonal antibody that specifically binds and blocks RANKL activation and is currently approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors. In a recently reported randomized, placebo-controlled, phase III study of men with nonmetastatic CRPC and high risk for progression (based on baseline PSA ≥ 8 ng/mL or PSADT ≤ 10 months), denosumab significantly improved BMFS (as determined by time to first bone metastasis or death resulting from any cause), time to first bone metastasis, and time to symptomatic bone metastasis, with no differences observed in OS or progression-free survival.[18] We now report results of exploratory analyses on the relationship between baseline PSADT and BMFS, time to first bone metastasis, and OS in the placebo group. We also report the effects of denosumab on these clinical outcomes in men at particularly high risk for progression based on shorter baseline PSADT.

PATIENTS AND METHODS

Patients

Patients included men age ≥ 18 years with histologically confirmed, nonmetastatic CRPC at high risk for developing bone metastasis, as characterized by PSA ≥ 8.0 ng/mL within 3 months before random assignment, PSADT ≤ 10 months at baseline, or both. Castration resistance was defined as three consecutive increasing PSA tests separated by a minimum of 2 weeks and PSA ≥ 1.0 ng/mL for the last two measurements. Patients with extraskeletal metastases (except regional lymph nodes) or who received previous intravenous bisphosphonate therapy were excluded. Concomitant treatments and antineoplastic therapies judged necessary by the study investigator before enrollment and during study were allowed. Patients were enrolled from 319 centers in 30 countries and were required to provide written informed consent before any study-specific procedure. Complete eligibility criteria have been reported previously.[18] This study was approved by the institutional review board or ethics committee at each site.

Study Design

In this randomized, phase III, double-blind, placebo-controlled study, patients were randomly assigned 1:1 to receive treatment every 4 weeks with either subcutaneous denosumab 120 mg or subcutaneous placebo (sterile saline; Fig 1). Treatment assignment was conducted by interactive voice response system using permuted blocks with a block size of four. Random assignment was stratified based on PSA criteria (PSA level ≥ 8.0 ng/mL and PSADT ≤ 10.0 months [yes *v* no] and previous or current chemotherapy for prostate cancer [yes *v* no]). Patient enrollment occurred between February 2006 and July 2008. Daily calcium (≥ 500 mg) and vitamin D (≥ 400 IU) supplementation was strongly encouraged, unless hypercalcemia (albumin-adjusted serum calcium > 2.9 mmol/L [> 11.5 mg/dL] or ionized calcium > 1.5 mmol/L) developed. Patients discontinued treatment when bone metastasis occurred to receive standard treatment for bone metastasis per investigator discretion; these patients were observed (in a blinded fashion) for up to an

additional 3 years to assess survival. Bone metastases detected by bone scans or skeletal surveys were confirmed through central review (x-ray, computed tomography, or magnetic resonance imaging) by two readers, with subsequent adjudication by a third reader in case of disagreement. During the treatment phase, bone scans were scheduled every 4 months and a skeletal survey every year. Blinding to treatment allocation was maintained for the study duration among all patients, investigators, central readers, and others involved in the study conduct.

Statistical Analysis

The primary end point of BMFS (determined by time to first occurrence of bone metastasis [symptomatic or asymptomatic] or death resulting from any cause, whichever occurred first) and secondary end points of time to first bone metastasis (symptomatic or asymptomatic), excluding deaths, and OS (including deaths during study and follow-up), along with safety and tolerability of denosumab in this population, have been previously reported.[18] Results for overall prostate cancer progression, prostate cancer progression–free survival, proportion of patients with symptomatic bone metastases, and change from baseline in PSA concentration and levels of urinary *N*-telopeptide have also been reported previously.[18]

Exploratory analyses were performed to understand the relationship between baseline PSA and PSADT with respect to clinical outcome and confirm that short PSADT was a predictor of risk for bone metastasis. The longest PSADT observed in this study was used to set the baseline risk for the remainder of the population.

We then evaluated the treatment effect of denosumab in subsets at higher risk to identify patients who could benefit most from denosumab, starting with PSADT ≤ 10 months, one of the high-risk eligibility criteria for the trial. These included analysis of the risk of BMFS plotted by PSADT as a continuous variable in the placebo group and between-treatment differences in BMFS, time to bone metastasis, OS, time to overall prostate cancer progression (centrally confirmed bone metastasis and investigator-determined extraskeletal prostate cancer progression), and adverse events by PSADT subsets.

For time-to-event variables, all randomly assigned patients (intention to treat) in the PSADT subsets were included in efficacy analyses. The Kaplan-Meier method was used to estimate the median, first and third quartiles, and 95% CIs. The Cox proportional hazards model, stratified by the randomization stratification factors, with treatment groups as independent variables, was used to estimate hazard ratios (HRs) and associated two-sided 95% CIs.[19] Safety analyses of adverse events were conducted for all patients in the PSADT subsets randomly assigned to treatment groups who received ≥ one doses of investigational drug. No formal statistical testing was performed for the safety analyses.

Number-needed-to-treat (NNT) analyses for BMFS were conducted to quantitatively assess the benefit of denosumab treatment by PSADT subset. NNT calculations were based on event rates adjusted per patient year according to the following calculation: NNT = 1/([No. of placebo events/placebo patient years] − [No. of denosumab events/denosumab patient years]).

RESULTS

Analysis of the placebo arm demonstrated that the risk of bone metastasis or death increased as PSADT decreased below 8 months (Fig 2A). Compared with the overall placebo arm study population, time to bone metastasis or death was approximately 3 months shorter in patients with PSADT ≤ 10 months and 7 months shorter in patients with PSADT ≤ 6 months (Fig 2B). In contrast to PSADT, baseline PSA was not associated with BMFS (data not shown). Notably, OS was shorter in subsets of men with shorter PSADT in the placebo group (overall, 44.8 months; PSADT ≤ 10 months, 42.2 months; PSADT ≤ 6 months, 40.7 months; and PSADT ≤ 4 months, 39.5 months).

After observing a strong relationship between shorter PSADT and reduced BMFS in the placebo group (HR, 1.30; 95% CI, 1.04 to 1.63; $P = .022$), we next evaluated the treatment effect of denosumab in subgroups of men with PSADT ≤ 10 months, one of the high-risk eligibility criteria for the trial (representing 81% [n = 1,154] of enrolled patients), and men with PSADT ≤ 6 months, the subgroup demonstrated in previous studies to represent increased risk[10,11] (representing approximately 60% of enrolled patients [n = 846]). We also evaluated the treatment effect of denosumab in men with PSADT ≤ 4 months to assess the consistency of treatment effect, although this subgroup represented < 40% of enrolled patients (n = 552).

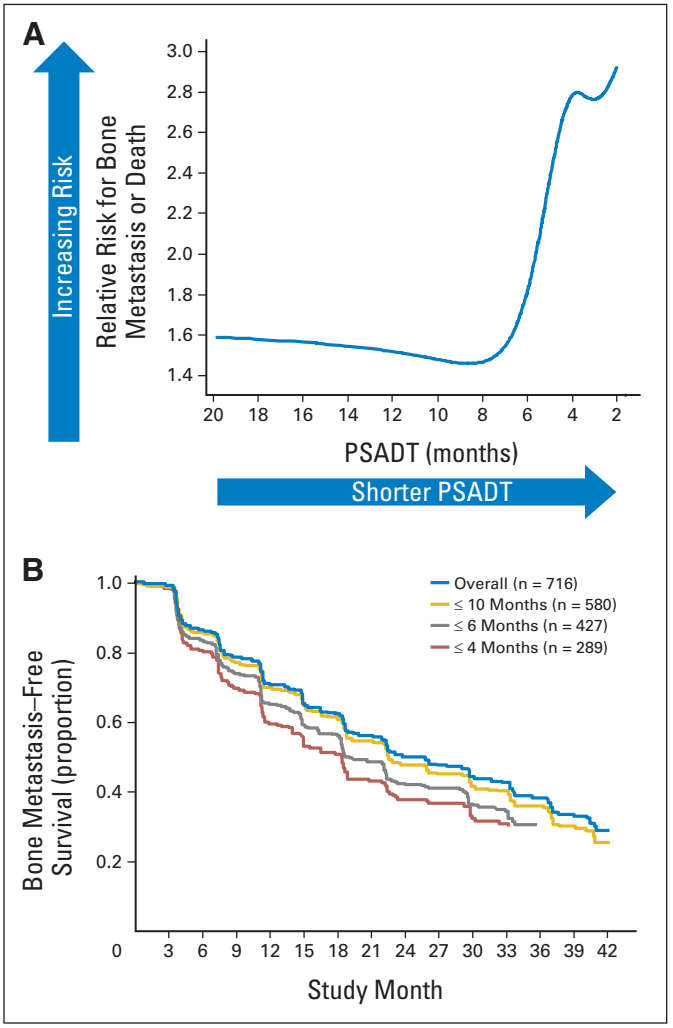

Fig 2. (A) Relative risk for bone metastasis–free survival (BMFS) over prostate-specific antigen doubling time (PSADT) in placebo group. Cox proportional hazards model was used with natural cubic spline of 6 *df* for inverse of PSADT. The *y*-axis represents increasing risk; *x*-axis represents PSADT at study entry expressed as continuous variable. For practical purposes, *x*-axis begins at 20 months at origin and goes to doubling time of 2 months. (B) Proportion of patients with BMFS in placebo group among overall population and by PSADT subgroup.

A total of 1,432 patients were randomly assigned to receive treatment: 716 patients to denosumab and 716 patients to placebo. At baseline, PSA was 12.3 ng/mL, PSADT was 5.1 months, and doubling time duration was 47.1 months (median values) for the treatment groups combined. Details on enrollment, discontinuation, and baseline demographic and disease characteristics by treatment group for the overall population have been previously reported.[18] Discontinuation rates among patients who did not meet the primary end point of

Table 1. Baseline Characteristics

Characteristic	Overall		PSADT (months) ≤ 10		≤ 6		≤ 4	
	Placebo (n = 716)	Denosumab (n = 716)	Placebo (n = 580)	Denosumab (n = 574)	Placebo (n = 427)	Denosumab (n = 419)	Placebo (n = 289)	Denosumab (n = 263)
Median age, years	74.0	74.0	73.0	73.0	73.0	73.0	73.0	71.0
Median time from diagnosis to study entry, years	6.1	6.1	6.0	5.8	5.6	5.5	5.2	5.0
Median duration of prior ADT, years	3.9	3.9	3.7	3.8	3.4	3.7	3.1	3.1
Median PSA, ng/mL	12.5	12.2	10.5	10.3	12.5	12.3	14.3	15.9
Median PSADT, months	5.1	5.2	4.0	4.2	3.1	3.2	2.5	2.4
Gleason score 8 to 10 at diagnosis								
No.	214	237	180	201	137	155	97	108
%	30	33	31.0	35.0	32.1	37.0	33.6	41.1

Abbreviations: ADT, antigen doubling time; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

on-study bone metastasis or death were 30.2% (n = 216) for the denosumab group and 26.1% (n = 187) for the placebo group. The most common reasons for discontinuation were consent withdrawal (12.8% [n = 92] denosumab *v* 12.2% [n = 87] placebo), adverse event (4.9% [n = 35] denosumab *v* 3.5% [n = 25] placebo), and disease progression (3.9% [n = 28] denosumab *v* 2.5% [n = 18] placebo). As previously reported, median time on study was 1.2 months longer with denosumab than with placebo.[18] Among patients who had at least one postbaseline image, there was 12% (n = 170) discordance between central reader assessment.

Baseline characteristics by PSADT subset were generally balanced (Table 1). Extraskeletal progression was similar between study arms after adjustment for baseline covariates in the overall population (HR, 1.03; 95% CI, 0.85 to 1.25; $P = .78$) and also similar by PSADT subsets of ≤ 10, ≤ 6, and ≤ 4 months ($P > .1$ for each subset). On-study use of cancer chemotherapy and hormonal therapy was also balanced between study arms for the overall population and by PSADT subsets (data not shown).

Denosumab and BMFS

Among men with PSADT ≤ 10 months, median BMFS was 6.0 months longer in the denosumab group compared with the placebo group (28.4 *v* 22.4 months). Denosumab reduced the risk of bone metastasis or death by 16% (HR, 0.84; 95% CI, 0.72 to 0.99; $P = .042$; Table 2; Fig 3A). Among men with PSADT ≤ 6 months, median BMFS was 7.2 months longer in the denosumab group than in the placebo group (25.9 *v* 18.7 months). Denosumab reduced the risk of bone metastasis or death by 23% (HR, 0.77; 95% CI, 0.64 to 0.93; $P = .006$; Fig 3B). Among men with PSADT ≤ 4 months, median BMFS was 7.5 months longer in the denosumab group than in the placebo group (25.8 *v* 18.3 months). Denosumab reduced the risk of bone metastasis or death by 29% (HR, 0.71; 95% CI, 0.56 to 0.90; $P = .004$; Fig 3C). Results by nonoverlapping PSADT subgroups are shown in Appendix Figure A1 (online only). Additionally, NNT for BMFS was 20 for PSADT ≤ 10 months, 11 for PSADT ≤ 6 months, and 8 for PSADT ≤ 4 months.

Denosumab and Time to First Bone Metastasis

Among men with PSADT ≤ 10 months, time to first bone metastasis was 6.4 months longer in the denosumab group than in the placebo group (32.4 *v* 26 months). Denosumab reduced the risk of first bone metastasis by 15% (HR, 0.85; 95% CI, 0.71 to 1.01; $P = .065$; Table 2; Fig 4A). Among men with PSADT ≤ 6 months, time to first bone metastasis was 4.4 months longer in the denosumab group than in

Table 2. BMFS and Time to First Bone Metastasis by Baseline PSADT

Population	Median Time for Denosumab (months)	Median Time for Placebo (months)	Median Delay (months)	HR	Crude Incidence Reduction (%)	*P*
BMFS						
Overall (n = 1,432)	29.5	25.2	4.2	0.85	4.9	.028
PSADT, months						
≤ 10 (n = 1,154)	28.4	22.4	6.0	0.84	5.7	.042
≤ 6 (n = 846)	25.9	18.7	7.2	0.77	9.7	.006
≤ 4 (n = 552)	25.8	18.3	7.5	0.71	10.7	.004
Time to first bone metastasis						
Overall (n = 1,432)	NE*	40.8	NE*	0.76	4.9	.0107
PSADT, months						
≤ 10 (n = 1154)	32.4	26	6.4	0.85	4.9	.0647
≤ 6 (n = 846)	26.5	22.1	4.4	0.80	7.6	.0257
≤ 4 (n = 552)	26.4	18.5	7.95	0.71	9.4	.0075

Abbreviations: BMFS, bone metastasis–free survival; HR, hazard ratio; NE, not estimable; PSADT, prostate-specific antigen doubling time.
*At the time of primary analysis, > one half of patients had not reached the end point.

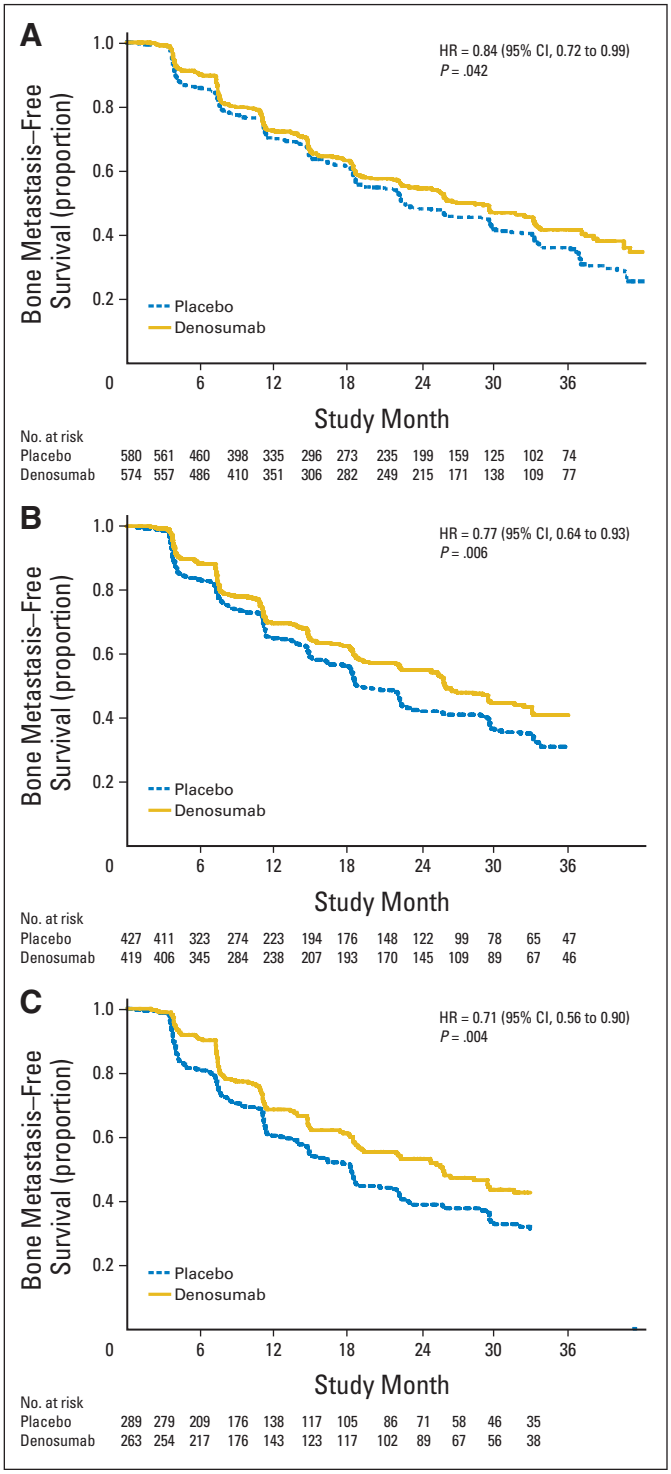

Fig 3. Bone metastasis–free survival by prostate-specific antigen doubling time (A) ≤ 10, (B) ≤ 6, and (C) ≤ 4 months. HR, hazard ratio.

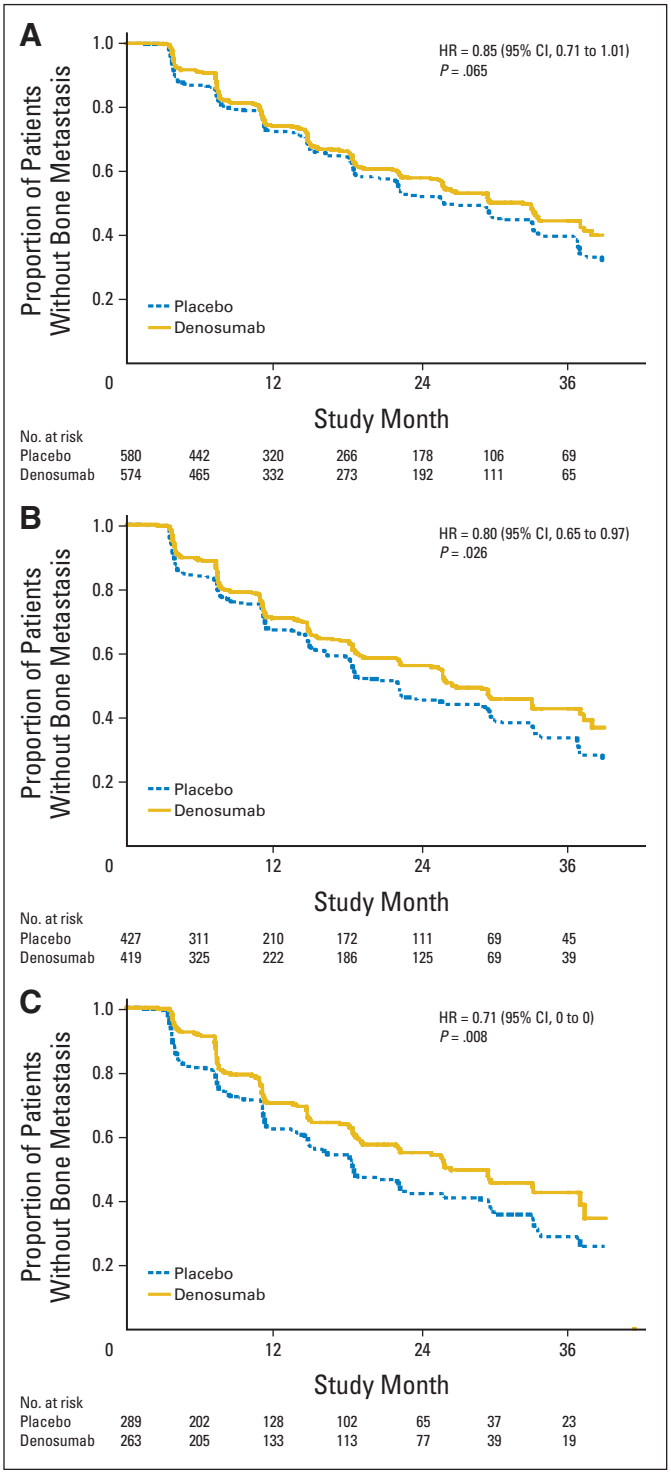

Fig 4. Time to first bone metastasis by prostate-specific antigen doubling time (A) ≤ 10, (B) ≤ 6 months, and (C) ≤ 4 months. HR, hazard ratio.

the placebo group (26.5 *v* 22.1 months). Denosumab reduced the risk of first bone metastasis by 20% (HR, 0.80; 95% CI, 0.65 to 0.97; $P = .026$; Fig 4B). Among men with PSADT ≤ 4 months, time to first bone metastasis was 8 months longer in the denosumab group than in the placebo group (26.4 *v* 18.5 months). Denosumab reduced the risk of first bone metastasis by 29% (HR, 0.71; 95% CI, 0.55 to 0.91; $P = .008$; Fig 4C).

Denosumab and OS and Overall Prostate Cancer Progression

OS was assessed through the follow-up phase after patients discontinued investigational treatment when bone metastasis occurred. No difference in OS was observed by treatment group in men in the overall population or by PSADT subset of ≤ 10 months (HR, 1.00;

Table 3. Adverse Events

Variable	Total No. of Patients		Adverse Events				Serious Adverse Events				Hypocalcemia				Adjudicated Positive ONJ			
			Placebo		Denosumab		Placebo		Denosumab		Placebo		Denosumab		Placebo		Denosumab	
	Placebo	Denosumab	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Overall	705	720	655	93	676	94	323	46	329	46	2	< 1	12	2	0	0	33	5
PSADT, months																		
≤ 10	572	578	526	92	541	94	258	45	262	45	2	< 1	11	2	0	0	26	5
≤ 6	421	423	380	90	394	93	177	42	190	45	2	< 1	10	2	0	0	18	4
≤ 4	283	267	255	90	249	93	110	39	121	45	2	< 1	5	2	0	0	14	5

Abbreviations: ONJ, osteonecrosis of the jaw; PSADT, prostate-specific antigen doubling time.

95% CI, 0.83 to 1.22; $P = .960$), ≤ 6 months (HR, 0.99; 95% CI, 0.79 to 1.23; $P = .895$), or ≤ 4 months (HR, 0.97; 95% CI, 0.75 to 1.26; $P = .829$).

Statistically significant differences were not observed in time to overall prostate cancer progression by treatment group in men in the overall population or by PSADT subset of ≤ 10 months (HR, 0.90; 95% CI, 0.77 to 1.05; $P = .179$), ≤ 6 months (HR, 0.87; 95% CI, 0.73 to 1.03; $P = .110$), or ≤ 4 months (HR, 0.82; 95% CI, 0.66 to 1.02; $P = .073$).

Adverse Events

The safety results in patients with shorter PSADT were similar to those in the overall patient population (Table 3). The incidence of adverse events and serious adverse events was generally similar between treatment groups in each of the PSADT subsets, as was the incidence of hypocalcemia and osteonecrosis of the jaw (ONJ), both of which are known risks associated with denosumab treatment.

DISCUSSION

In this global, randomized, placebo-controlled trial of men with high-risk CRPC, denosumab increased BMFS and time to first bone metastasis. OS and overall prostate cancer progression were similar between the placebo and denosumab groups. In the placebo group, PSADT was significantly associated with BMFS. In subset analyses, the efficacy of denosumab for men with shorter baseline PSADT was more pronounced than that observed in the overall population for the end points of BMFS and time to first bone metastasis, whereas OS and overall prostate cancer progression remained similar between treatment arms in the subgroups.

To our knowledge, this was the first large phase III study to use continuous PSA kinetics to identify patients at higher risk for disease progression. The similarity of the estimated and observed BMFS in the placebo group (29.5 *v* 25.2 months) supports the use of PSADT to select high-risk patients in this setting. Furthermore, the increase in risk for bone metastasis and death for men with shorter PSADT may inform the design of future clinical trials and facilitate the selection of particularly high-risk patients.

The results of these analyses extend the evidence linking PSA kinetics to clinical outcome in men with nonmetastatic CRPC and confirm that short PSADT is a predictor of risk for bone metastasis. PSA kinetics were associated with BMFS and OS in two earlier prospective studies of men with nonmetastatic CRPC.[10,11] However, in contrast to earlier studies of nonmetastatic CRPC,[11,20,21] baseline PSA in our analyses was not associated with treatment effect, which might reflect differences in the inclusion criteria among the various studies. Our study included only patients with baseline PSA ≥ 8.0 ng/mL or PSADT ≤ 10.0 months, whereas earlier studies included patients with lower PSA values and without requirements for PSADT.

Our analyses demonstrate that denosumab consistently increased BMFS and reduced the risk in each of the high-risk PSADT subgroups, suggesting greater clinical benefit in these patients. In men with PSADT ≤ 6 months, the subgroup that may represent the best clinical cutoff for increasing risk of development of bone metastasis, denosumab significantly increased BMFS by 7.2 months compared with placebo, representing a decrease in risk of 23% ($P = .006$). This is in contrast to the overall enrolled population, in whom denosumab significantly prolonged BMFS by 4.2 months, representing a decrease in risk of 15% ($P = .028$).

ONJ was observed in 5% of men who received denosumab, with rates of 1%, 3%, and 4% after 1, 2, and 3 years, respectively. Notably, the safety profile including the adverse event of ONJ remained unchanged in the subgroups with shorter PSADT, resulting in an improved benefit-risk profile for those patients with the highest medical need.

In summary, faster PSADT was associated with shorter BMFS in men with nonmetastatic CRPC. In the overall study population, denosumab significantly increased BMFS and time to first bone metastasis. The effects of denosumab on these clinical outcomes were greater in subsets of men at even higher risk for progression based on baseline PSADT.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: Zhishen Ye, Amgen (C); Carsten Goessl, Amgen (C) **Consultant or Advisory Role:** Matthew R. Smith,

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Appendix

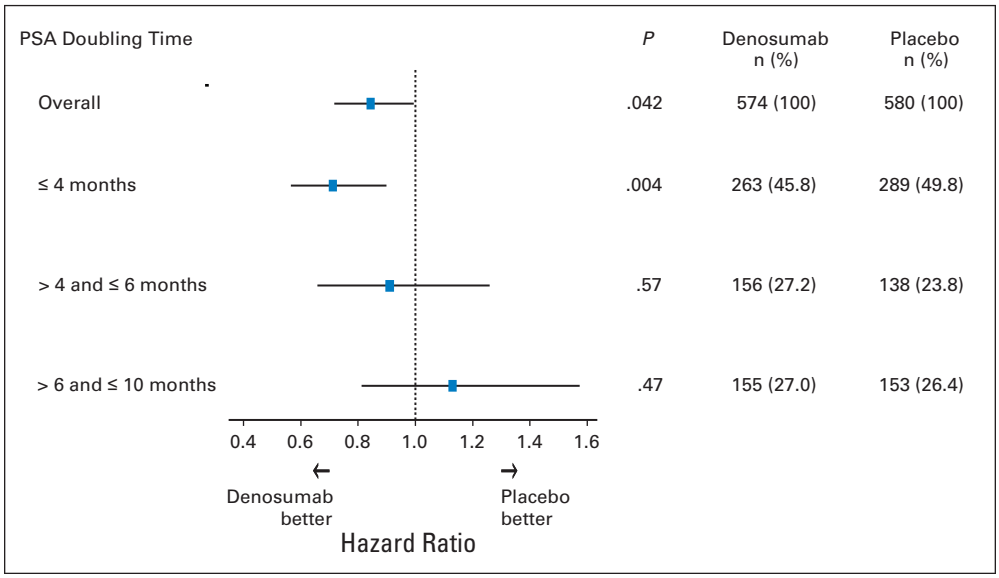

Fig A1. Results by nonoverlapping prostate-specific antigen (PSA) doubling time subgroups; hazard ratios and 95% CIs from Cox proportional hazards model stratified by random assignment stratification variables.