SUPPLEMENTAL MATERIALS

METHODS

Study conduct

The ALSYMPCA study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation, and was approved by the institutional review board of each participating site. All participating patients provided written informed consent.

Patients

Eligible patients had histologically confirmed and symptomatic progressive castration-resistant prostate cancer with ≥2 metastases detected by skeletal scintigraphy, and no visceral metastases (malignant lymphadenopathy ≤3 cm in short-axis diameter allowed). Patients had previously received docetaxel, were not fit enough or willing to receive docetaxel, or did not have docetaxel available to them. Symptomatic disease was defined as regular use of nonopioid or opioid analgesia for cancer-related bone pain or treatment with external beam radiation therapy for bone pain within the last 12 weeks.

Treatment regimen

At randomization, patients were stratified by prior use or no prior use of docetaxel, baseline alkaline phosphatase level (<220 U/L vs ≥220 U/L), and current use or non-use of bisphosphonates. Patients were randomized 2:1 to receive 6 intravenous injections of radium-223 at a dose of 50 kBq/kg body weight plus standard of care (SOC) or matching placebo plus SOC; one injection was administered every 4 weeks. Best SOC was defined as the routine care provided at each center (e.g. local external beam radiation therapy or treatment with glucocorticoids, antiandrogens, ketoconazole, or estrogens such as diethylstilbestrol or estramustine).

Health-related quality of life assessments

The FACT-P (version 4) is a validated 39-item questionnaire with 4 subscales related to physical well-being (PWB; 7 items, score range 0-28), social/family well-being (SWB; 7 items, score range 0-28), emotional well-being (EWB; 6 items, score range 0-24), functional well-being (FWB; 7 items, score range 0-28), and a prostate cancer subscale (PCS 12 items, score range

0-48) [Cella et al. Value Health 2009; 12: 124-129; Esper et al. Urology 1997; 50: 920-928]. Collectively, these subscales make up a total score (score range 0-156). In addition, a pain-related score (PRS, score range 0-16) is derived from 4 pain-related questions from the PCS [Cella et al. Value Health 2009; 12: 124-129]. A higher score indicates improved QOL; a clinically meaningful change (minimally important difference; MID) in a specific score has been estimated as 6-10 for FACT-P total score, 2-3 for PCS and FACT-P subscales, and 1-2 for the PRS (**Table S1**). For the EQ-5D utility score, the MID values are country specific (e.g. 0.09 for the United Kingdom, 0.06 for the United States). For this analysis, the EQ-5D utility score MID was estimated to be a change of ≥0.1 [Pickard et al. Health Qual Life Outcomes 2007; 5: 70].

Table S1. Estimated minimally important differences (MID) for FACT-P scores and subscales

FACT-P Score	Source	Range of MID	MID used in analyses
FACT-P total	Cella et al. Value Health 2009; 12: 124-129	6-10	10
Physical well-being (PWB)	Cella et al. Qual Life Res 2002; 11: 207-221; Yost et al. Eval Health Prof 2005; 28: 172-191	2-3	3
Social well-being (SWB)	Yost et al. Eval Health Prof 2005; 28: 172-191	2-3	3
Emotional well-being (EMB)	Yost et al. Eval Health Prof 2005; 28: 172-191	2-3	3
Functional well-being (FWB)	Cella et al. Qual Life Res 2002; 11: 207-221; Yost et al. Eval Health Prof 2005; 28: 172-191	2-3	3
Prostate cancer subscale (PCS)	Cella et al. Value Health 2009; 12: 124-129	2-3	3
Pain-related score (PRS)	Cella et al. Value Health 2009; 12: 124-129	1-2	2

RESULTS

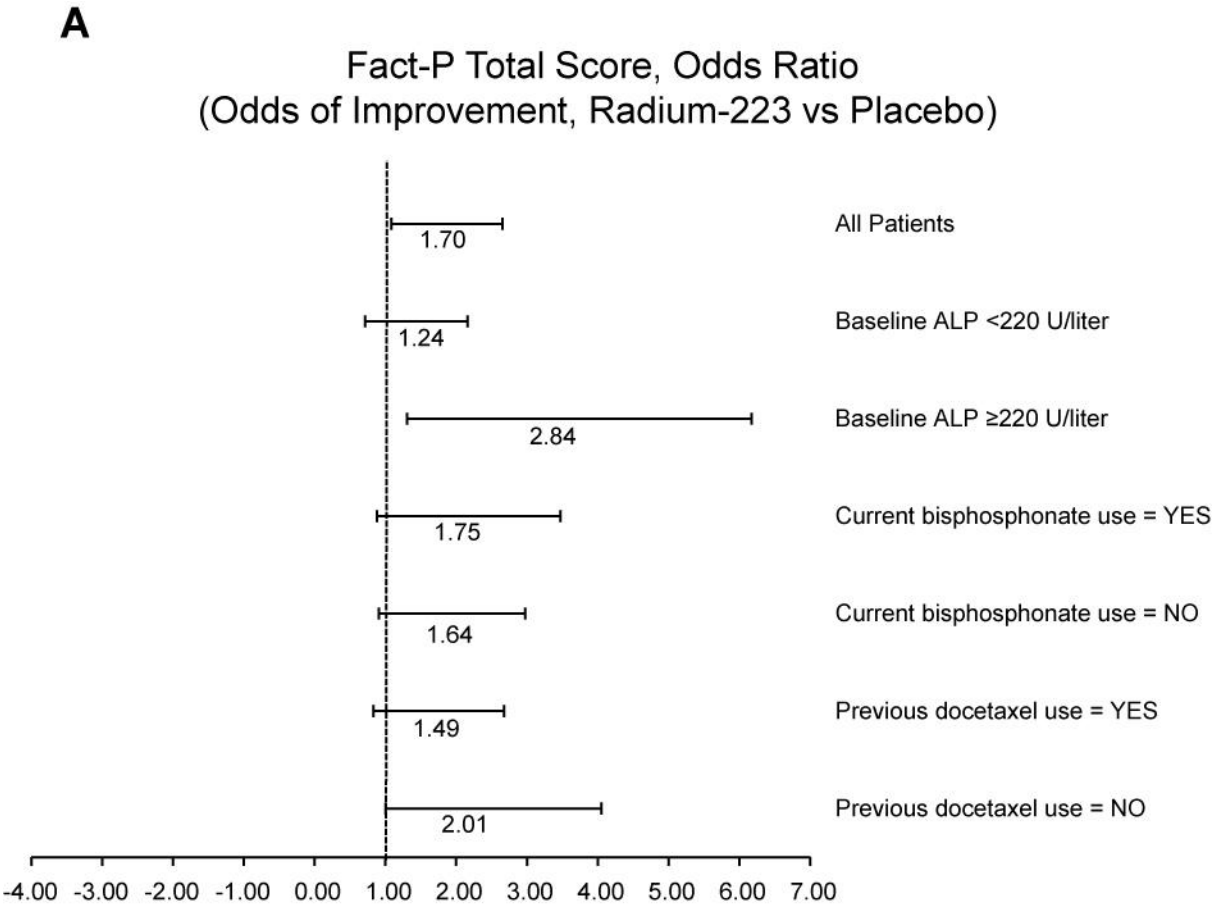
Table S2. Completion rates for Functional Assessment of Cancer Therapy—Prostate (FACT-P) total score and EuroQOL 5D (EQ-5D) utility score

	Observed		Expected[a]		Completion rate (%)	
	Radium-223	**Placebo**	**Radium-223**	**Placebo**	**Radium-223**	**Placebo**
FACT-P						
Baseline	574	288	614	307	93.5	93.8
Week 16	463	198	576	276	80.4	71.7
Week 24	354	131	536	244	66.0	53.7
Week 44 (follow-up visit 2)	211	84	418	180	50.5	46.7
EQ-5D[b]						
Baseline	589	293	614	307	95.9	95.4
Week 16	472	202	576	276	81.9	73.2
Week 24	354	134	536	244	66.0	54.9
Week 36 (follow-up visit 1)	310	107	456	201	68.0	53.2
Week 44 (follow-up visit 2)	226	87	418	180	54.1	48.3

[a]For each treatment arm, the number of expected assessments was calculated by subtracting the number of patients who had died prior to the scheduled assessment from the total number of randomized patients.

[b]EQ-5D was also measured at additional follow-up visits (weeks 36, 52, 68, 84, 100, 116, and 132).

Figure S1. Forest plots for the responder analysis showing odds ratio (95% CI) for all patients and by ALSYMPCA trial stratification factors (baseline alkaline phosphatase [ALP], current bisphosphonate use, and previous docetaxel use) for (A) Functional Assessment of Cancer Therapy—Prostate (FACT-P) total score, (B) pain-related score (PRS) from FACT-P prostate cancer symptoms (PCS), and (C) EQ-5D utility score.



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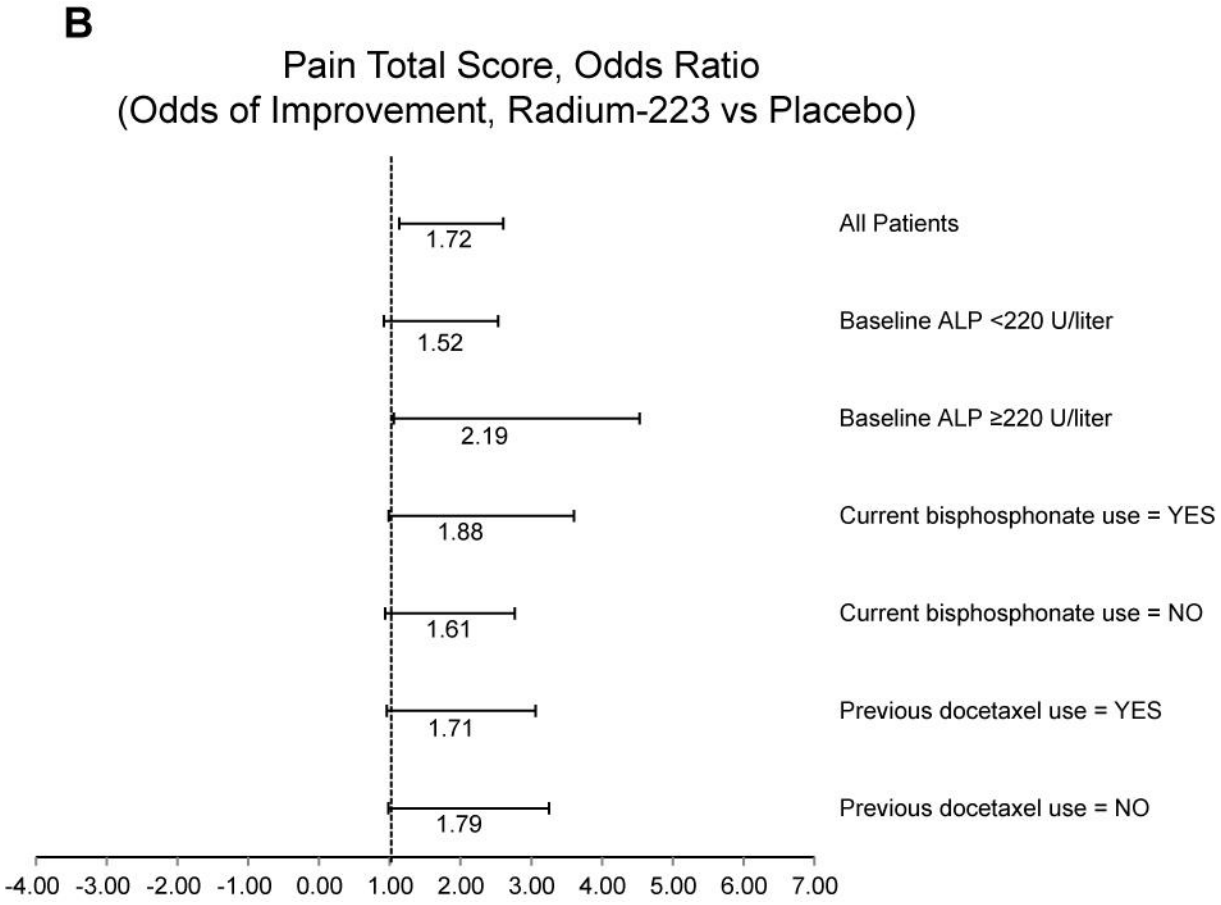

Pain Total Score, Odds Ratio
(Odds of Improvement, Radium-223 vs Placebo)
1.72
All Patients
1.52
Baseline ALP <220 U/liter
2.19
Baseline ALP ≥220 U/liter
1.88
Current bisphosphonate use = YES
1.61
Current bisphosphonate use = NO
1.71
Previous docetaxel use = YES
1.79
Previous docetaxel use = NO
-4.00 -3.00 -2.00 -1.00 0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00

C

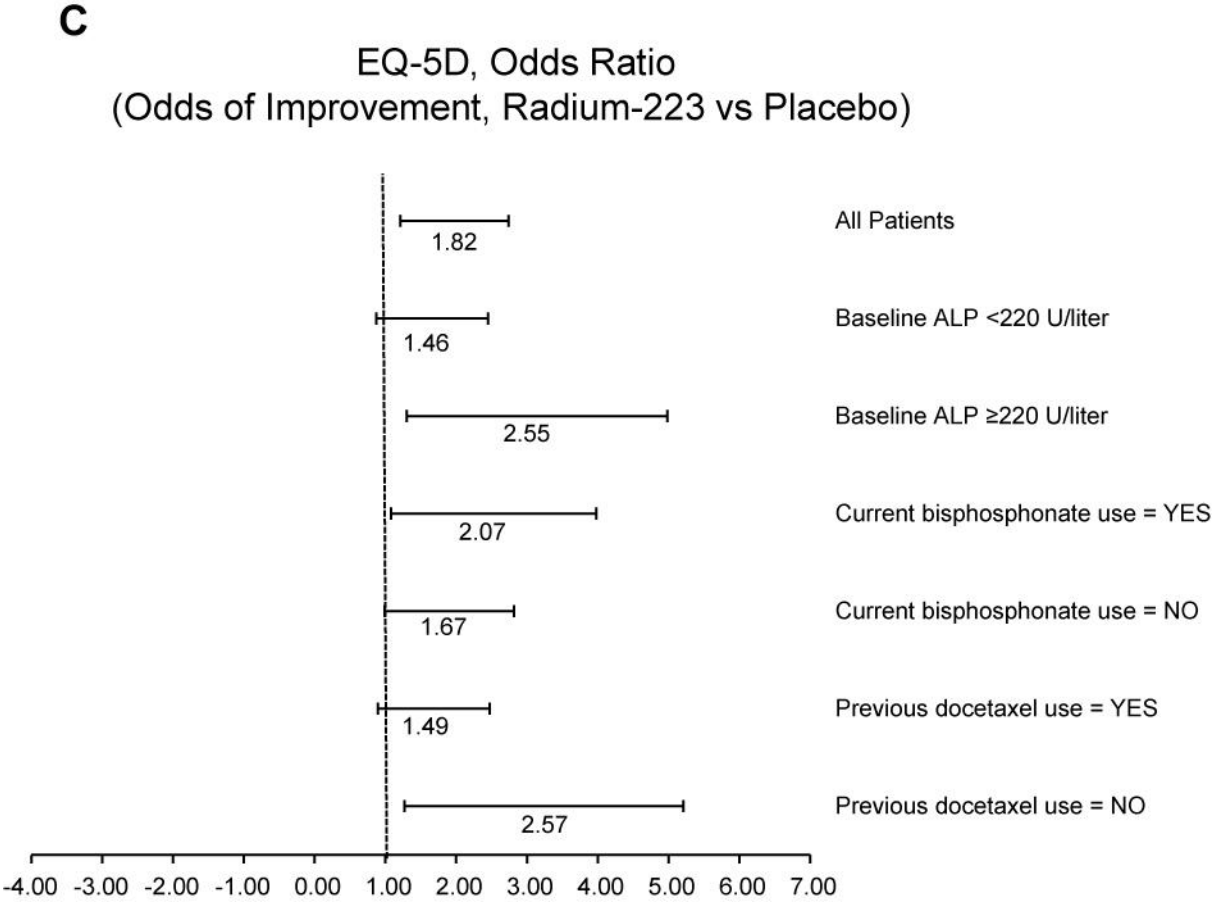
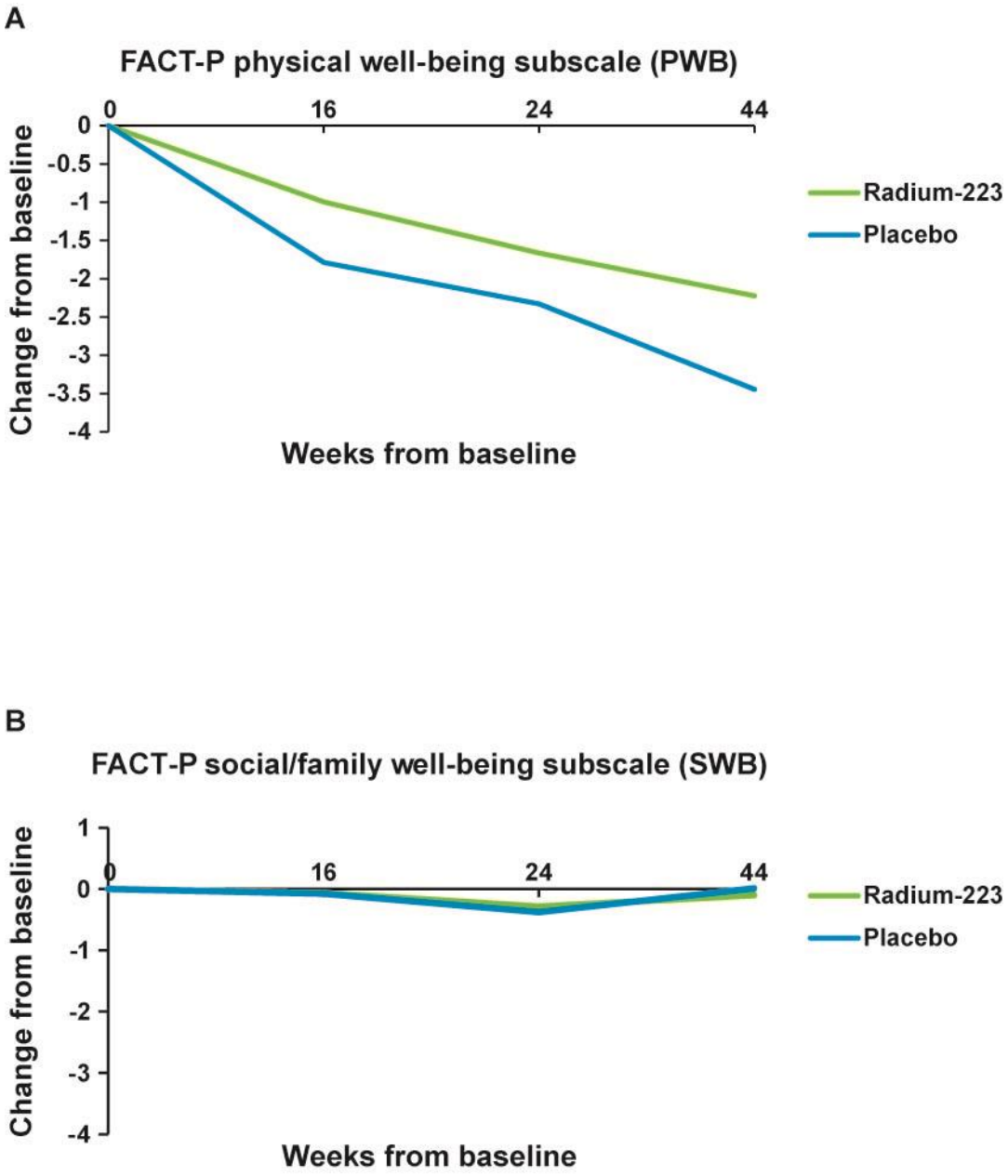

EQ-5D, Odds Ratio
(Odds of Improvement, Radium-223 vs Placebo)
1.82
All Patients
1.46
Baseline ALP <220 U/liter
2.55
Baseline ALP ≥220 U/liter
2.07
Current bisphosphonate use = YES
1.67
Current bisphosphonate use = NO
1.49
Previous docetaxel use = YES
2.57
Previous docetaxel use = NO
-4.00 -3.00 -2.00 -1.00 0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00

Figure S2. Mean changes from baseline in FACT-P subscales for the radium-223 and placebo groups (ANCOVA analysis)



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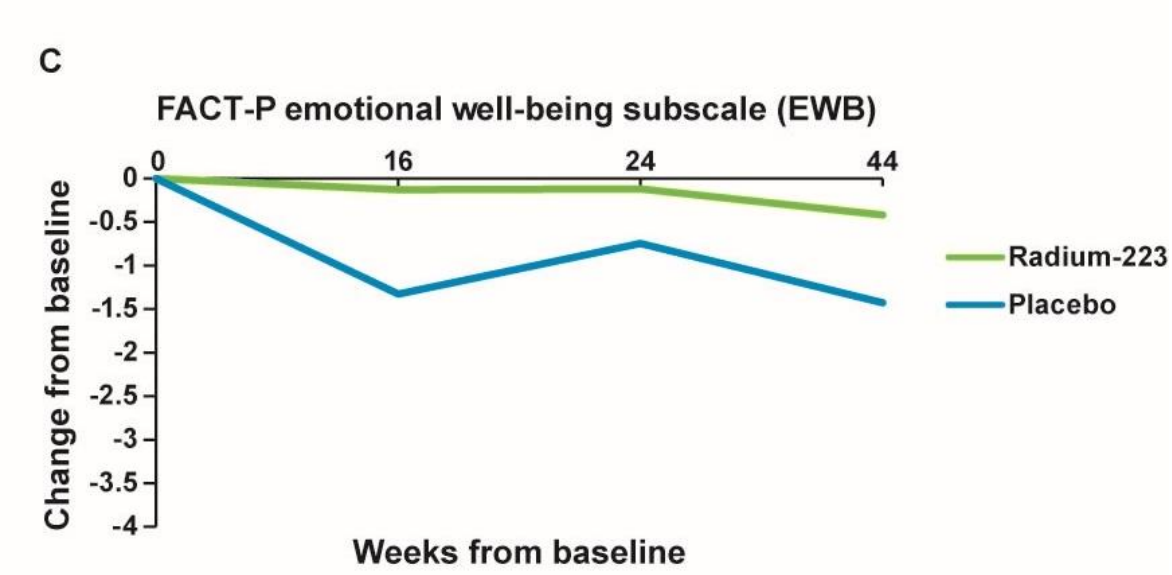
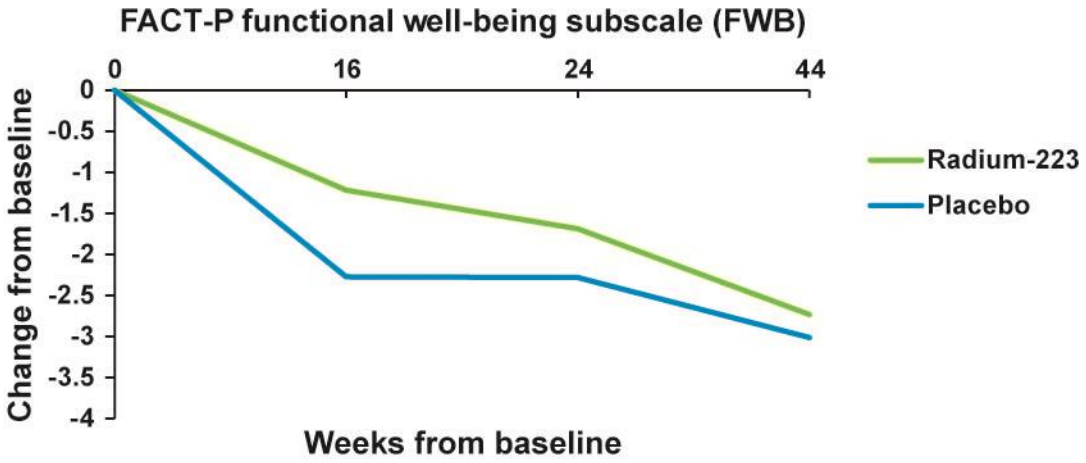

FACT-P emotional well-being subscale (EWB)
0
16
24
44
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
Change from baseline
Weeks from baseline
Radium-223
Placebo

D


FACT-P functional well-being subscale (FWB)
0
16
24
44
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
Change from baseline
Weeks from baseline
Radium-223
Placebo

E

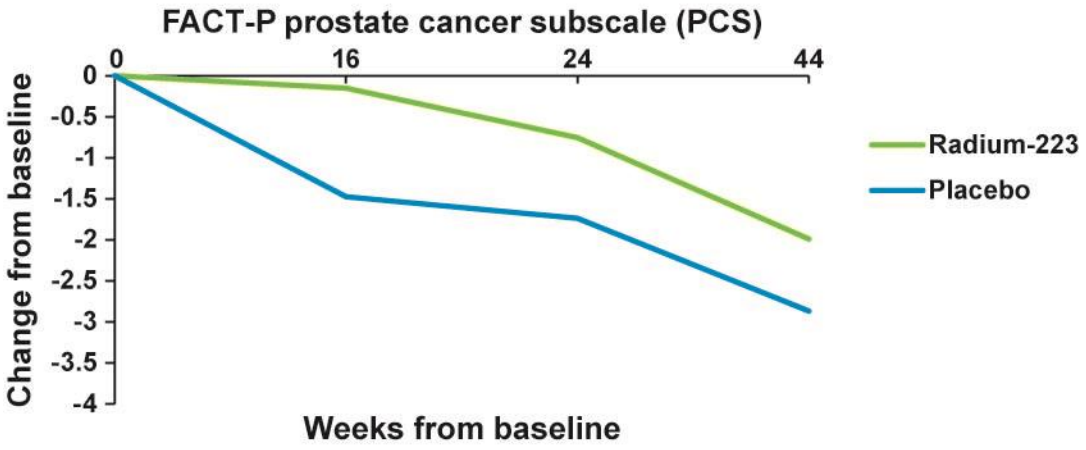
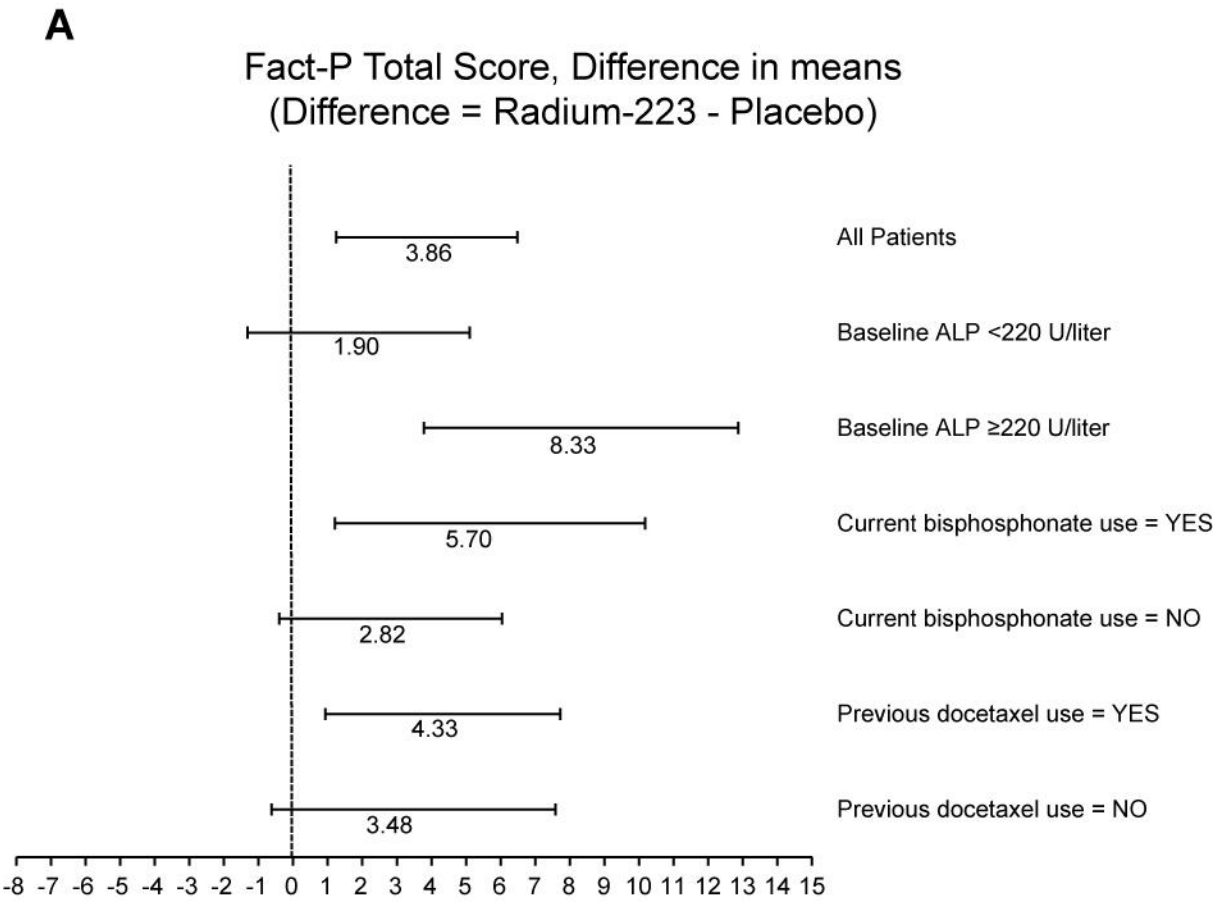

FACT-P prostate cancer subscale (PCS)
0
16
24
44
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
Change from baseline
Weeks from baseline
Radium-223
Placebo

Figure S3. Forest plots for difference in mean score (difference = radium-223 – placebo with 95% CI) for all patients and by ALSYMPCA trial stratification factors (baseline alkaline phosphatase [ALP], current bisphosphonate use, and previous docetaxel use) for (A) Functional Assessment of Cancer Therapy—Prostate (FACT-P) total score, (B) pain-related score (PRS) from FACT-P prostate cancer symptoms (PCS), and (C) EQ-5D utility score. Difference in mean score between radium-223 and placebo treatment arms was calculated from an ANCOVA regression model adjusting for baseline score.



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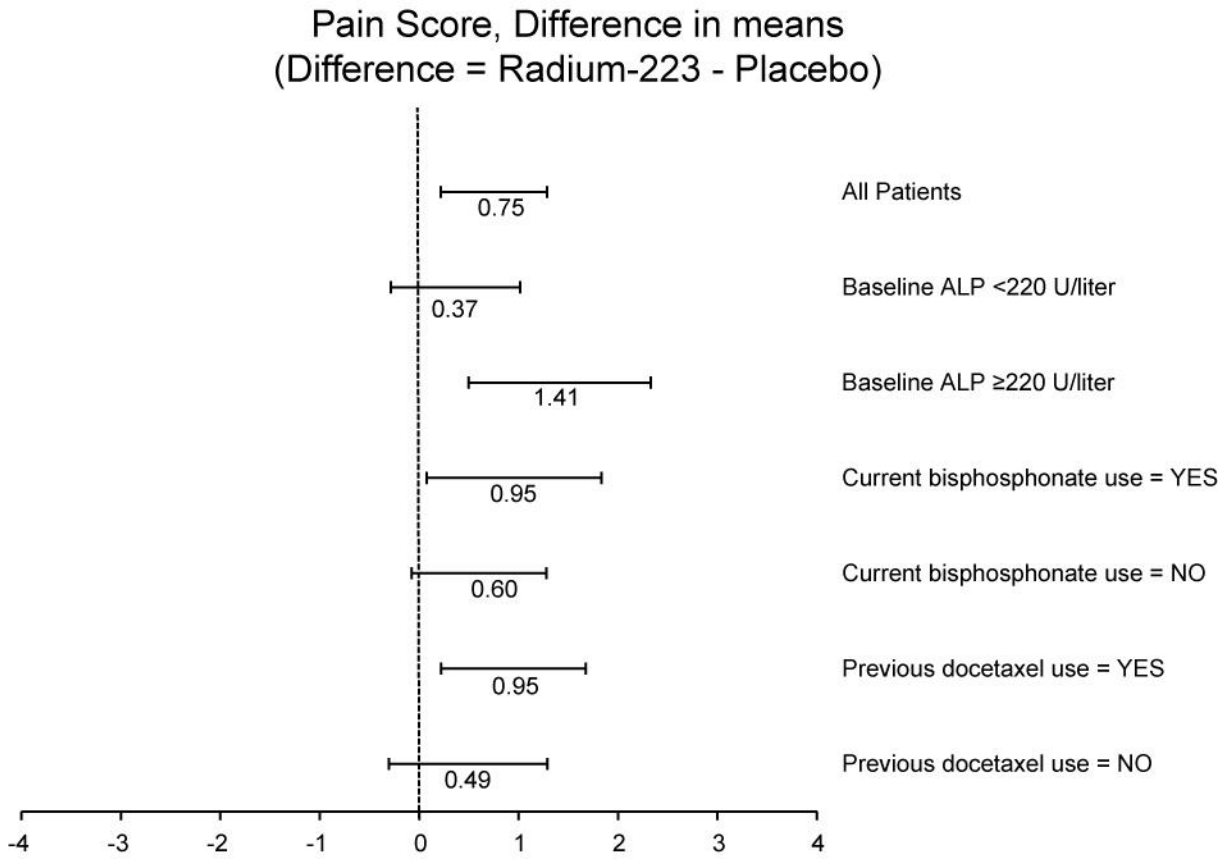
Pain Score, Difference in means
(Difference = Radium-223 - Placebo)
0.75
All Patients
0.37
Baseline ALP <220 U/liter
1.41
Baseline ALP ≥220 U/liter
0.95
Current bisphosphonate use = YES
0.60
Current bisphosphonate use = NO
0.95
Previous docetaxel use = YES
0.49
Previous docetaxel use = NO
-4
-3
-2
-1
0
1
2
3
4

C

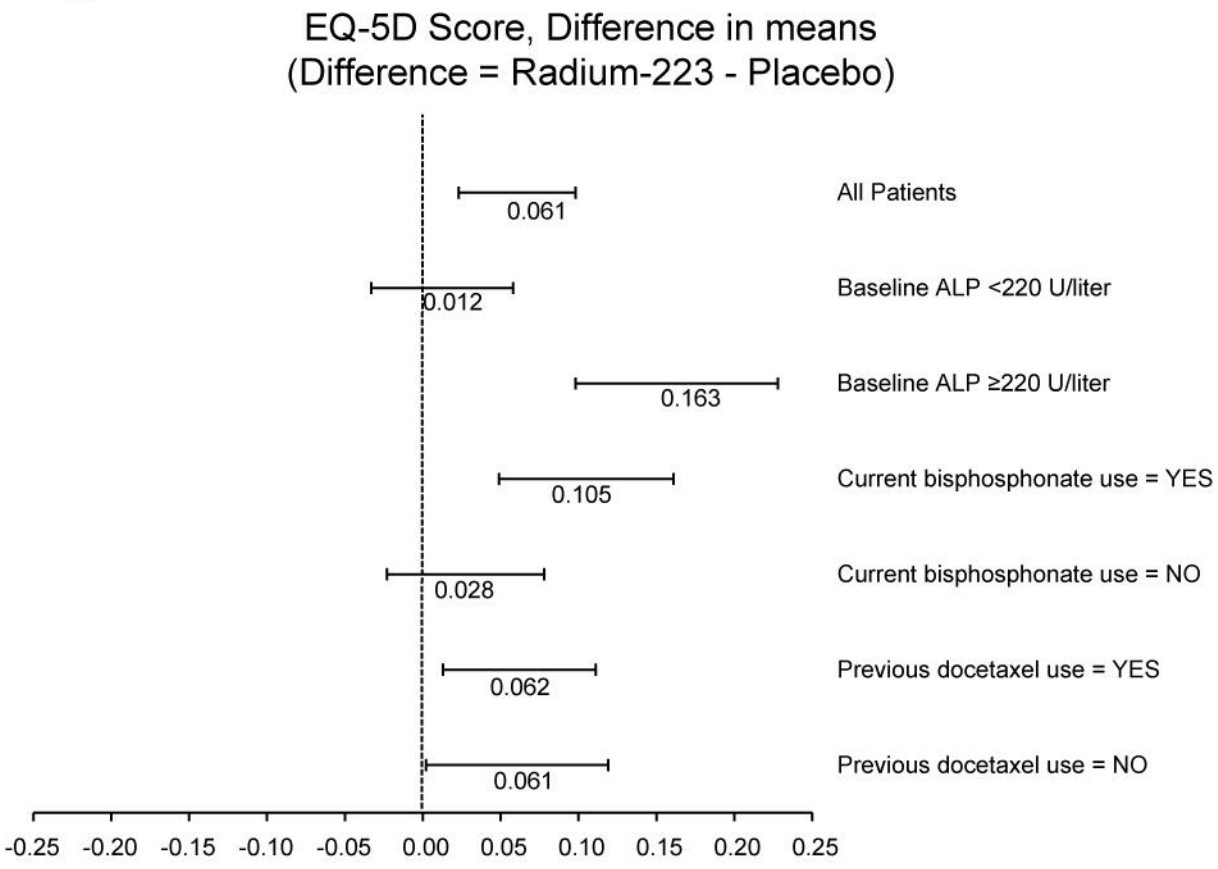
EQ-5D Score, Difference in means
(Difference = Radium-223 - Placebo)
All Patients
0.061
Baseline ALP <220 U/liter
0.012
Baseline ALP ≥220 U/liter
0.163
Current bisphosphonate use = YES
0.105
Current bisphosphonate use = NO
0.028
Previous docetaxel use = YES
0.062
Previous docetaxel use = NO
0.061
-0.25 -0.20 -0.15 -0.10 -0.05 0.00 0.05 0.10 0.15 0.20 0.25

Table S3. Least-squares (LS) mean change from baseline in EQ-5D utility score per visit

Analysis	Treatment group	n	EQ-5D utility score			
			LS mean	SE	LS mean difference (RA–PL)	95% CI for difference
Change from baseline to week 16	Radium-223 (RA) Placebo (PL)	460 194	-0.03 -0.09	0.01 0.02	0.07	0.02, 0.11
Change from baseline to week 24	Radium-223 (RA) Placebo (PL)	343 131	-0.04 -0.11	0.02 0.03	0.06	0, 0.12
Change from baseline to follow-up visit 1	Radium-223 (RA) Placebo (PL)	300 105	-0.08 -0.12	0.02 0.03	0.04	-0.03, 0.10
Change from baseline to follow-up visit 2	Radium-223 (RA) Placebo (PL)	220 84	-0.14 -0.13	0.02 0.03	-0.01	-0.08, 0.06
Change from baseline to follow-up visit 3	Radium-223 (RA) Placebo (PL)	164 62	-0.11 -0.12	0.02 0.04	0.01	-0.07, 0.09
Change from baseline to follow-up visit 4	Radium-223 (RA) Placebo (PL)	93 32	-0.13 -0.24	0.03 0.05	0.10	-0.01, 0.22
Change from baseline to follow-up visit 5	Radium-223 (RA) Placebo (PL)	45 22	-0.12 -0.17	0.05 0.07	0.05	-0.11, 0.21
Change from baseline to follow-up visit 6	Radium-223 (RA) Placebo (PL)	21 10	-0.15 -0.26	0.09 0.13	0.11	-0.14, 0.36
Change from baseline to follow-up visit 7	Radium-223 (RA) Placebo (PL)	7 3	0.02 -0.15	0.10 0.20	0.18	-0.38, 0.73

EQ-5D, EuroQoL 5D utility score; SE, standard error.

Note: If the follow-up visits occurred on schedule, follow-up visits 1 through 7 occurred 36, 44, 52, 68, 84, and 100 weeks after baseline, respectively.

Table S4. Least-squares (LS) mean change from baseline in FACT-P total score per visit for the radium-223 and placebo groups (ANCOVA analysis)

Analysis	Treatment group	n	FACT-P score			
			LS mean	SE	LS mean difference (RA–PL)	95% CI for difference
Change from baseline to week 16	Radium-223 (RA) Placebo (PL)	407 177	-2.69 -6.81	0.86 1.28	4.12	1.18, 7.07
Change from baseline to week 24	Radium-223 (RA) Placebo (PL)	314 120	-4.28 -7.27	1.03 1.65	3.00	-0.70, 6.68
Change from baseline to follow-up visit 2 (week 44)	Radium-223 (RA) Placebo (PL)	186 75	-7.36 -11.08	1.43 2.25	3.73	-1.32, 8.77

Note: Model adjusted for baseline score, treatment, total ALP <220, current use of bisphosphonates, prior use of docetaxel.

ALP, alkaline phosphatase; ANCOVA, analysis of covariance; FACT-P, Functional Assessment of Cancer Therapy—Prostate; SE, standard error.