Optimizing the sequence of metastatic castration-resistant prostate cancer treatment options

Badrising, S.K.

Chapter 6

Integrated Analysis of Pain, Health-Related Quality of Life and Analgesic use in Patients with Metastatic Castration-Resistant Prostate Cancer Treated with Radium-223

Sushil K Badrising[#], Rebecca D Louhanepessy[#], Vincent van der Noort, Jacobien Kieffer, Jules LLM Coenen, Paul Hamberg, Aart Beeker, Nils Wagenaar, Marnix Lam, Filiz Celik, Olaf J.L Loosveld, Ad Oostdijk, Hanneke Zuetenhorst, Jeantine M de Feijter, Vincent O Dezentjé, Suzan Ras-van Spijk, Erik Vegt, John B Haanen, Lonneke V van de Poll-Franse, Wilbert Zwart, Andries M Bergman on behalf of the ROTOR investigators and the Dutch Uro-Oncology Study group (DUOS15102).

#These authors contributed equally

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ABSTRACT

Background

First line- or post docetaxel Radium-223 (Ra-223), an alpha-emitting radiopharmaceutical, treatment established an improved overall survival and Health-Related Quality of Life (HRQoL) in symptomatic metastatic castration-resistant prostate cancer (mCRPC) patients. However, effects on pain were not specifically evaluated. Here we assess integrated HRQoL, pain and opioid use in a contemporary, more extensively pretreated, symptomatic and asymptomatic mCRPC population.

Patients and methods

mCRPC patients scheduled for Ra-223 treatment were included in a real-life cohort and analyzed for HRQoL, pain and opioid use, using FACT-P and BPI-SF questionnaires and recording of opioid use and dosage, respectively. Primary outcome measure was the percentage of patients experiencing a complete pain response, while a complete- or partial pain response (better BPI-SF score and decrease of opioid use) and a better- or no change in HRQoL was evaluated as an integrated overall clinical response (IOCR)

Results

This registry included 300 patients, of whom 105 (35%) were evaluable for FACT-P and BPI-SF during Ra-223 treatment. Forty-five (43%) patients had PAB (BPI-SF worst pain score 5-10 points) and 60 (57%) had no-PAB (BPI-SF worst pain score 0-4 points). Complete pain response was achieved in 31.4% of the patients, while 58% had an IOCR. The median time to pain progression was 5.6 months, and the median time to deterioration of FACT-P scores was 5.7 months, the difference between PAB and no-PAB patients was not significant.

Conclusions

In contemporary, extensively pretreated mCRPC patients, Ra-223 treatment induced complete pain responses while Integrated analysis of HRQoL, pain response and opioid use, demonstrated that the majority of patients derive clinical benefit.

INTRODUCTION

Each year, over 1.2 million men are diagnosed with prostate cancer worldwide and approximately 350.000 patients succumb to the consequences of this disease, rendering it the most common non-cutaneous cancer in males and the second-largest cause of cancer-related death in men.[1] Metastatic castration-resistant prostate cancer (mCRPC) is the end stage of this disease with high morbidity and mortality as hallmarks.[2] Up to 90% of mCRPC patients develop bone metastases, which are not only associated with a shorter life expectancy, but also with cancer-related pain and skeletal-related events, including pathological fractures, compression of the spinal cord, vertebral instability and hypercalcemia, which all affect Health-Related Quality of Life (HRQoL).[3] Symptoms and complications of bone metastases can be treated with analgesics, external beam-radiation therapy (EBRT), bisphosphonates, RANK-ligand inhibitors, surgery and radiopharmaceuticals.[4]

In the ALSYMPCA study, the alpha-emitter Radium-223 dichloride (Ra-223) showed a 3.6 month overall survival (OS) benefit and a favorable HRQoL in symptomatic mCRPC patients.[4] However, the effect of Ra-223 on pain was not evaluated using pain-specific questionnaires, and changes in the dosages of analgesics were not considered in the evaluation of pain.[5] Another study showed that asymptomatic mCRPC patients treated with Ra-223 had better treatment outcomes than symptomatic patients, but HRQoL and pain were not assessed.[6] Since the introduction of Ra-223 into the clinic in 2013, the number of treatment options for mCRPC patients has expanded significantly.[7] Consequently, contemporary patients treated with Ra-223 are more extensively pretreated, questioning the present relevance of HRQoL results from the ALSYMPCA study.[8] Given the paucity of knowledge on the effect of Ra-223 on pain and HRQoL in contemporary symptomatic and asymptomatic mCRPC patients, there is a need for a reevaluation.[8] In this observational study we evaluated and integrated the effect of Ra-223 on patient-reported pain, analgesic use and HRQoL in a real-life cohort. Patients with pain at baseline (PAB) and no pain at baseline (no-PAB) were assessed separately.

METHODS

Study population and design

A non-interventional, multicenter, prospective observational registry was initiated to evaluate clinical outcomes, HRQoL, pain and analgesic use in a real-life mCRPC population treated with Ra-223. The study design is fully described elsewhere.[8] In short, patients aged 18 years or older with progressive mCRPC and scheduled for Ra-223 treatment were included prospectively in 20 hospitals in the Netherlands (intention-to-treat population). There were no other in- and exclusion criteria or stopping rules. Paper questionnaires were sent to the patients one week before each

treatment and monthly in follow-up, which were returned by mail to the data management office. Clinical data was collected from the medical records after completion of Ra-223 treatment. This registry was approved by local medical ethics committees. Obtaining signed informed consent for the study was not required, but patients had to provide oral consent and written approval for registration and use of their identifiers.

Procedures

Patients were treated with Ra-223 at 4 week intervals, according to the manufacturer's guidelines. Number of treatments was at the physician's discretion, who provided the motivation for discontinuation. Patients were evaluated at the outpatient clinic prior to each treatment, where Eastern Cooperative Oncology Group performance and clinical lab assessments were documented. Radiological evaluation during and after Ra-223 treatment and frequency of follow-up visits were at the physician's discretion. Patients' baseline characteristics within 14 days prior to the first Ra-223 treatment were recorded. Baseline characteristics, efficacy assessments and patient reported outcome measures (PROMs) were stored in an electronic case-report form. Follow-up was continued until start of subsequent treatment or death.

Patient reported outcomes measures

HRQoL and pain were assessed using the validated patient self-reported measures Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory-Short Form (BPI-SF), respectively. [9–11] Furthermore, patients were asked to list all analgesic drugs (free text: name, dose, frequency and period of use) used in the previous 4 weeks. Patients were requested to complete all questionnaires at baseline and every 4 weeks during and after Ra-223 treatment until start of subsequent treatment or death. Patients were considered evaluable for pain, opioid use and HRQoL analysis when baseline questionnaires and at least one set of questionnaires during treatment were returned. According to published algorithms, scale scores were calculated when at least 50% of the items in that scale had been completed.[9–11]. An overview of the questionnaires and their use and interpretation is provided in Supplementary Table 1.

Brief Pain Inventory-Short Form

The BPI-SF contains 4 items on pain severity (worst pain, least pain, Average pain and pain now) and 7 items on pain interference (*e.g.:* during sleep, walking, daily activities).[9] Every question is scored from 0 to 10, where 0 is no pain/interference and 10 is the worst imaginable pain/interference (Supplementary Table 1). The clinically meaningful change of BPI-SF score (CMC-BPI) was defined as a change of score of at least 30% from baseline score, with a minimum of 2 points.[9, 10] Two groups in the cohort were separately analyzed; no-PAB patients were defined as a Worst Pain score at baseline between 0 and 4 points, and PAB patients were defined as a Worst Pain score between 5-10. This division is in line with the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) recommendations.[12]

Functional Assessment of Cancer Therapy-Prostate

The FACT-P is a validated 39-item questionnaire, including the FACT-General original subscales: Physical Well-being (PWB), Social/Family Well-being (SWB), Emotional Well-being (EWB), and Functional Well-being (FWB), and a prostate cancer subscale (PCS).[11] Items are rated on a five-point scale ranging from 0 (not at all) to 4 (very much). Subscales as well as the total score can be calculated by the sum of the items. When not all subscales are evaluable, the total score cannot be calculated. The range of these scores is (0–156) for the FACT-P total score, (0–28) for the PWB, SWB, and FWB, (0–24) for EWB, and (0–48) for PCS. (Supplementary Table 1). The clinically meaningful change of FACT-P (CMC-FACT) was defined as a minimal change of 10 points from baseline for the Total FACT-P score, 3 points from baseline for the subscales and 2 points from baseline for pain. A higher score indicates a better HRQoL.[13]

Analgesic use

Patients were asked to fill out a list of all analgesics, dosages and frequencies used in the past 4 weeks (Supplementary Table 1). Dosages of the various opioid drugs and formulations were converted to oral morphine equivalents in mg per day (Supplementary Table 2). Non-opioids and on-demand opioids were not included in our analysis.

Endpoints and statistical analyses

The primary endpoint of the study was the percentage of patients experiencing a complete pain response. The International Bone Metastases Consensus Working Party (IBMCWP) has defined criteria for evaluating results of these types of studies.[14] In this classification, the use of opioid drugs was integrated into the PROMs as follows: A complete pain response was defined as a score of 0 on the BPI-SF Worst pain item and no increase in daily use of analgesics; a partial response was defined as a pain reduction of at least 2 points on the BPI-SF Worst pain item or a reduction of at least 25% of daily use of analgesics; pain progression was defined as an increase in pain of at least 2 points on the BPI-SF Worst pain item or an increase of at least 25% of daily analgesic use. Indeterminate response was defined as all pain decreases, not captured by complete response or partial response. Patients were categorized according to their best response.[14] Secondary endpoints included the percentage of patients experiencing a partial and an indeterminate pain response. Moreover, patients were categorized by their Total FACT-P response, which was “improved HRQol” (better score meeting CMC-FACT), “no change in HRQoL” (no change or changes not meeting CMC-FACT), or “worse HrQoL” (deteriorated score meeting CMC-FACT). A complete or partial pain response and an improved HRQoL or no change in HRQoL were evaluated as an Integrated Overall Clinical Response (IOCR).

Moreover, secondary outcomes included Time to Total FACT-P Deterioration (TTFD), Time to Pain Progression (TPP), Progression Free Survival (PFS) and OS. Definitions of the secondary endpoints are listed In Supplementary Table 3,. All time-to-event endpoints were estimated using the Kaplan-

Meier product limit method. Patients who did not experience an event of interest were censored at their last day of follow-up for OS and PFS and at the time of their last questionnaire for TTFD or TPP.

Sample size calculation

The sample size was chosen to ensure enough power to detect a meaningful increase (compared to historical placebo) of the number of Ra-223 treated patients with a complete pain response. From the placebo arm of the ALSYMPCA trial we estimated that, without treatment, up to 20% of patient will have a complete or partial pain response.[4] Our interest is in the power to find a one-sided 95% confidence interval around our observed pain response rate that lies entirely above the 'placebo rate' of 20%, under the assumption of a true pain response rate of 30% or more. We computed this power under various assumptions on the percentage of patients returning at least two PROMs forms. Of the scenarios presented in the Supplementary Table 4, we considered the number of 120 evaluable patients the most realistic. We estimated a 40% response rate based on the reported 10-70% response rates in previous studies on self-reported outcome measures in real-life populations .[15–17] As shown in Supplementary Table 4, the power at this percentage of evaluable patients is 81%.

Software

TENALEA, an online service, was used to collect data. IBM SPSS statistics for iOS, version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for iOS, Version 25.0. Armonk, NY: IBM Corp.) and Statistical Analysis System (SAS) statistical software were used for statistical analysis and for conducting graphs. Additional graphs and analyses were made and performed using GraphPad Prism version 8.00 for Mac OS X, GraphPad Software, La Jolla California USA, www.graphpad.com.

RESULTS

Baseline characteristics and survival

Between April 2015 and March 2018, 305 mCRPC patients from 20 Dutch hospitals, scheduled for Ra-223 treatment were included. Five patients were excluded because written approval to use identifiers (name, address, residence) could not be retrieved or was not stored according to guidelines (Figure 1). This registry included 300 patients (registry sample), of whom 121 (40%) completed the baseline questionnaires, and 105 (35%) completed a baseline and at least one follow-up BPI-SF and FACT-P questionnaire and were therefore evaluable for the individual questionnaires (evaluable sample). One hundred and three patients were evaluable for pain response analysis, because 2 patients provided insufficient data on analgesics use.

The registry sample and the evaluable sample were comparable on most baseline and survival characteristics and treatment outcomes (Table 1, Supplementary table 5). However, patients in the

evaluable sample used calcium/vitamin D suppletion more often (52% and 41.0%, respectively, p=0.02), and bisphosphonates less often (10% and 16.7%, respectively, p=0.03) than patients in the registry sample. Moreover, evaluable patients less often received EBRT in the 12 weeks prior to Ra-223 (2% and 8%, respectively, p=0.01). Although there was no significant difference in PFS, OS was significantly shorter in the registry sample than in the evaluable sample (15.2 and 19.6 months, respectively, p=0.04).

Of the 105 evaluable patients, 45 had pain at baseline (PAB) and 60 had no pain at baseline (no-PAB) (Figure 1, Table 1). The baseline characteristics of the two groups were comparable, however, as expected, more PAB patients used opioids (51.2% and 16.7%. respectively, p<0,001). After a median follow-up of the evaluable sample of 13.2 months, PAB patients had a significantly shorter OS than no-PAB patients (13.5 and 20.3 months, respectively, p=0.05) (Table 2, Supplementary Figure 1A).

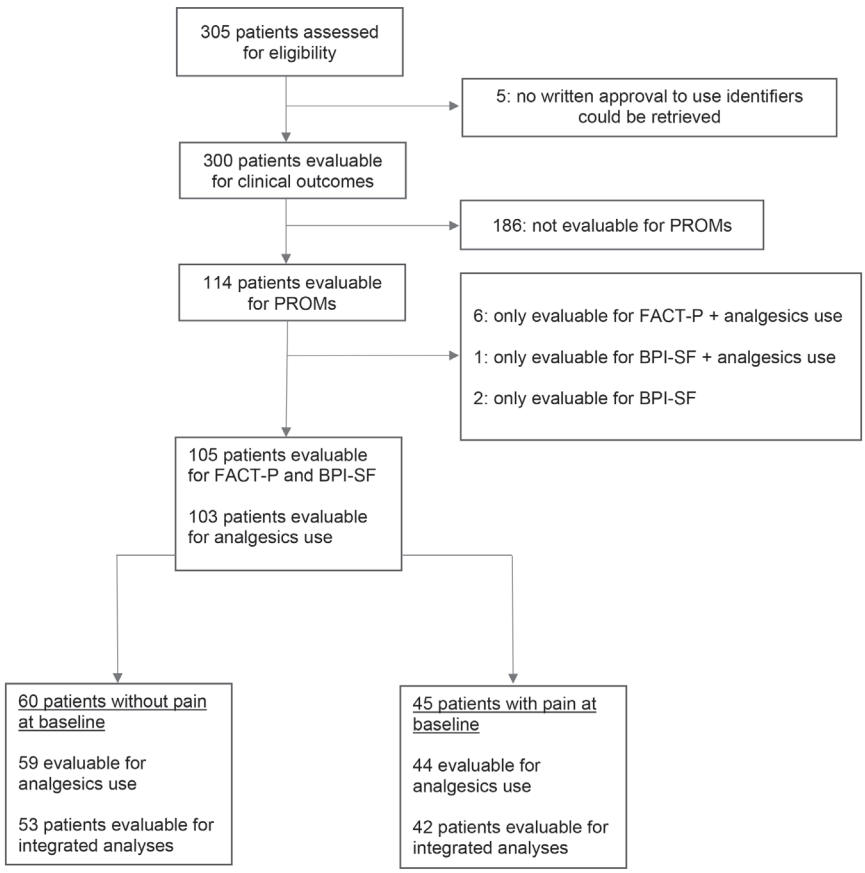

Figure 1. Consort diagram.

Health-related Quality of Life

Questionnaires completion rates per time point are listed in Supplementary Table 6.

BPI-SF

BPI-SF baseline values are reported in Supplementary table 7. PAB patients scored significantly higher on all baseline BPI-SF subscales compared to no-PAB patients ($p<0.001$), while the Worst pain subscale was used to define PAB and no-PAB patients. Median and mean times to deterioration of the BPI-SF subscales are reported in Table 3. The median TPP was 5.6 months in the evaluable sample (Table 3, Figure 2A). PAB patients had a significantly longer median time to deterioration of the BPI-SF subscale Average pain than no-PAB patients (12.6 and 5.5 months, respectively, $p=0.03$). (Table 3, Supplementary Figure 2). PAB patients also had a longer TPP than no-PAB patients (11.1 and 4.1 months, respectively; $p=0.001$)(Figure 2A). Changes in time of the BPI-SF Worst pain and Average pain subscales are displayed in Figure 2A and B, respectively, and the other BPI-SF subscales in Supplementary Figure 3. During treatment, 49.5% of the evaluable sample had a clinically meaningful improvement of the BPI-SF Worst pain subscale (Table 3; Figure 2B).

Table 1. Baseline characteristics of the registry sample and symptomatic and asymptomatic evaluable patients

Patient demographics	**Median or value [IQR], Number of Patients (%)**					
	Registry sample (*n*=300)	**Evaluable sample (*n*=105)**	***p***	**Pain at Baseline (*n=45*)**	**No Pain at Baseline (*n=60*)**	***p***
Age, years	73 [67-78]	73 [68–77]	ns	73 [68-77]	72 [66-78]	ns
ECOG performance status, no. of patients (%)			ns			ns
0-1	264 (88.0)	94 (90)		39 (87)	55 (92)	
2	15 (5.0)	3(3)		2 (4)	1 (2)	
≥3	0	0		0	0	
Missing data	21 (7.0)	8 (8)		4 (9)	4 (7)	
Gleason score, no. of patients (%)			ns			ns
≤7	87 (29.0)	27 (26)		10 (22)	17 (28)	
8	67 (22.3)	32 (30)		12 (27)	20 (33)	
≥9	95 (31.7)	27 (26)		14 (31)	13 (22)	
Missing data	51 (17.0)	19 (18)		9 (20)	10 (17)	
Metastatic sites, no. of patients (%)						
Bone	297 (99.0)	100 (95)	ns	44 (98)	56 (93)	ns
Lymph nodes	84 (29.0)	22 (21)	ns	10 (22)	12 (20)	ns
Visceral organs	0	1 (1)	ns	0	1 (2)	ns
Missing data	3 (1)	3 (3)		0	3 (5)	

No. of bone metastases, no. of patients (%)			ns			ns
0-1	0	2 (2)		1 (2)	1 (2)	
2-6	21 (7.0)	12 (11)		5 (11)	7 (2)	
>6	246 (82.0)	87 (83)		37 (82)	50 (80)	
Super scan	5 (1.7)	2 (2)		0	2 (3.1)	
Missing data	28 (9.3)	6 (6)		3 (7)	3 (5)	
Laboratory values						
PSA, mg/l	72.3 [25.0-175.0]	72 [22-179]	ns	73 [16-225]	72.0 [23-172]	ns
Hemoglobin, mmol/l	12.6 [11.3-13.4]	12.6 [11.6-13.4]	ns	12.3 [11.6-13.4]	12.7[11.6-13.4]	ns
ALP, U/l	138 [85-248]	118 [75-242]	ns	136 [85-330]	102 [73-186]	ns
ALP ^{3}220 U/l, *n (%)*	81 (27.0)	28 (27)	ns	15 (33)	13 (22)	ns
LDH, U/l	225.0 [192-296]	213 [183-280]	ns	237 [190-298]	206 [179-237]	0.07
Albumin, g/l	42 [38-44]	42 [40-44]	ns	42 [39-44]	42 [40-44]	ns
Calcium, mmol/l	2.4 [2.3-2.4]	2.4 [2.3-2.4]	ns	2.3 [2.2-2.4]	2.4 [2.3-2.4]	0.06
Testosterone, nmol/l	0.5 [0.45-0.50]	0.5 [0.5-0.5]	ns	0.5 [0.5-0.5]	0.5 [0.3-0.5]	ns
Previous lines of systemic treatments (%)			ns			ns
0	34 (11.3)	10 (10)		5 (11)	5 (8)	
1	104 (34.7)	34 (32)		10 (22)	24 (40)	
2	96 (32.0)	35 (33)		21 (47)	14 (23)	
3	50 (16.7)	19 (18)		4 (9)	15 (25)	
4	13 (4.3)	5 (5)		4 (9)	1 (2)	
5	3 (1.0)	1 (1)		1 (2)	0	
Missing data	0	1 (1)		0	1 (2)	
Specific previous treatments, no. of patients (%)						
Abiraterone and or Enzalutamide	214 (71.3)	75 (71)	ns	31 (69)	44 (73)	ns
Docetaxel	197 (65.7)	73 (71)	ns	35 (78)	38 (63)	ns
Cabazitaxel	52 (17.3)	18 (17)	ns	10 (22)	8 (13)	ns
Radiotherapy 12 weeks prior to treatment	23 (8)	2 (2)	0.01	2 (4)	0	ns
Concomitant medication, no. of patients (%)						
Bisphosphonates	49 (16.7)	11 (10)	0.03	3 (7)	8 (13)	ns
Denosumab	63 (24.4)	25 (24)	ns	14 (31)	11 (18)	ns
Calcium/Vitamin D	123 (41.0)	55 (52)	0.02	25 (56)	30 (50)	ns
Analgesics use		*n=103*		*n=44*	*n=59*	
Non-opioids	NA	3 (2.9)		0 (0)	3 (6.7)	
Opioids	NA	38 (36)		25 (56)	13 (22)	<0.001
Dose (mg/day) *	NA	44.4 [18.8-111.6]		60 [15-118.8]	30 [30-75]	ns

Data are n (%), median or value [IQR]. Abbreviations: ECOG Eastern Cooperative Oncology Group; PSA serum Prostate Specific Antigen; ALP serum Alkaline Phosphatase; LDH Lactate Dehydrogenase; mg milligram; *oral morphine equivalent; ns, not significant; NA, not available.

Table 2. Clinical outcomes of Radium-223 treatment

Outcome variables		Median [IQR or 95% CI], No. of Patients (%)			*p* *
		Evaluable sample (*n*=105)	Pain at baseline (*n*=45)	No-Pain at baseline (*n*=60)	
Follow-up, months		13.2 (11.4-15)	13.4 (10.1-17.5)	13.2 (11.3-16.3)	ns
No. of Radium-223 cycles, median		5 [4-6]	5 [3-6]	6 [4-6]	0.003
ALP decline, no. of patients (%)					
³30%		39 (37)	17 (38)	22 (37)	ns
³50%		18 (17)	11 (24)	7 (12)	ns
³90%		1 (1)	1 (2)	0 (0)	ns
Missing		3 (3)	2 (4)	1 (2)	ns
Time to ALP progression, months					ns
	Median	6.8 (6.2-NR)	7.4 (6.0-NR)	6.6 (6.2-NR)	
	Mean	8.0 (6.7-9.2)	7.7(5.9 – 9.5)	7.5 (6.3 – 8.7)	
PSA decline , no. of patients (%)					
³30%		7 (7)	2 (4)	5 (8)	ns
³50%		2 (2)	0 (0)	2 (3)	ns
³90%		2 (1.8)	0	2 (3.1)	ns
Missing		3 (3)	2 (4)	1 (2)	ns
Reason for Radium-223 discontinuation, no. of patients (%)					
Six cycles completed		55 (52)	16 (36)	39 (65)	0.003
Symptomatic progression		32 (30)	19 (42)	13 (22)	0.03
PSA progression		27 (26)	15 (33)	12 (20)	ns
Radiological progression		14 (13)	7 (16)	7 (12)	ns
Intolerance		12 (11)	6 (13)	6 (10)	ns
Death		3 (3)	3 (7)	0	ns
Other		1 (1)	1 (2)	0	ns
Time to first SSE, months					ns
	Median	6.8 (6.2-NR)	NR	NR	
	Mean	23.7 (21.9-25.4)	19.5 (16.6-22.3)	22.4 (20.7-24.1)	
Progression free survival, months		5.2 (4.8-6)	4.8 (3.6-5.5)	5.7 (4.9-7)	ns
Overall Survival, months		19.6 (16.6-NR)	13.5 (9.5-NR)	20.3 (19.2-NR)	0.05
Time to subsequent treatment, months					ns
	Median	3.7 (2.7-8.8)	3.1 (2.1-NR)	4.1 (3.2-NR)	
	Mean	6.5 (5.2-7.8)	5.9 (3.9-7.9)	6.8 (5.2-8.4)	
Hospital admission during Radium-223 treatment, no. of patients (%)		24 (23)	13 (29)	11 (18)	ns

* Pain at baseline *vs* No-pain at baseline

Abbreviations: 95% CI: 95% confidence interval; PAB: Pain at Baseline, No-PAB: No Pain At Baseline, ALP: alkaline phosphatase, PSA: serum Prostate Specific Antigen, SSE: Symptomatic Skeletal Event, NR: Not reached; ns: Not significant.

The percentage of patients in the evaluable sample experiencing a complete pain response for the duration of Ra-233 treatment, as defined by IBMCWP was 31.4% (Table 3).

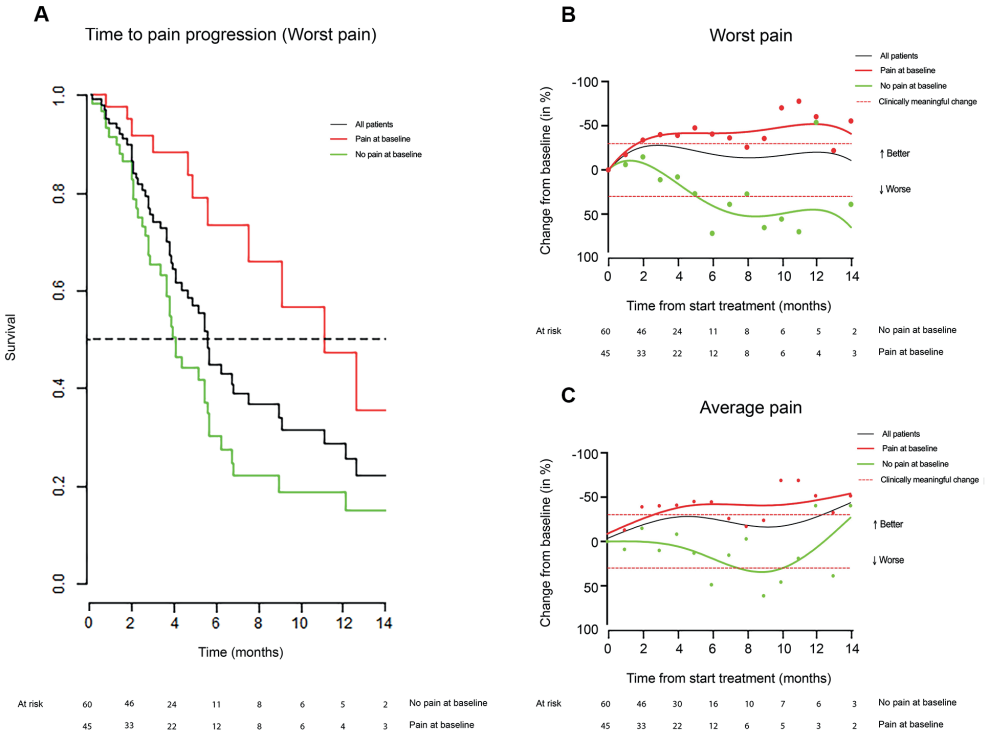

Figure 2. Brief Pain Inventory (BPI).

A: Kaplan-Meier estimates of time to clinically meaningful BPI– Worst pain subscale score deterioration for the evaluable sample (black line), patients with pain at baseline (red line) and patients without pain at baseline (green line). The horizontal dotted line represents 50% events. **B:** Change in Brief Pain Inventory (BPI) – Worst pain and **C:** Average pain subscales scores over time in the evaluable sample (black line), patients with pain at baseline (red line) and patients without pain at baseline (green line). Data points show average scores at time points, while the lines are made to fit the trend of change of score in time. The horizontal dotted lines represent the threshold for clinically meaningful change from baseline.

FACT-P

FACT-P baseline values are reported in Supplementary Table 7. PAB patients had a significantly lower baseline total FACT-P score than no-PAB patients (95.2 and 107.6, respectively, $p<0.001$), suggesting a worse HRQoL. Moreover, PAB patients had significantly lower baseline FACT-P subscale scores, suggesting a poorer performance on PCS (26.2 and 31.6, respectively, $p<0.001$), PWB (19.8 and 22, respectively, $p<0.001$), EWB (12.5 and 14.1, respectively,

p=0.031), FWB (16.5 and 18.2, respectively, p=0.039) and pain (5.9 and 11.5, respectively, p<0.001) than no-PAB patients.

Median and mean TTFD and other deteriorations of FACT-P subscales are reported in Table 3. The median TTFD was 5.7 months in the evaluable sample, while there was no significant difference between PAB and no-PAB patients (Table 3; Figure 3A). There were also no significant differences in all other time to FACT-P subscale deteriorations between PAB and no-PAB patients (Table 3; Supplementary Figure 4). During treatment, 31.4% of the evaluable sample had a clinically meaningful improvement of Total FACT-P, with no significant difference between PAB and no-PAB patients (Table 3; Figure 3B). Changes in time of the FACT-P subscales are displayed in Supplementary Figure 5.

Table 3. Patient-reported outcomes: Median time to BPI-SF and FACT-P deterioration and pain response

Outcome variables		**Median [IQR], No. of Patients (%) [IQR or 95% CI]**			***p* ***
		Evaluable sample (*n*=105)	**Pain at baseline (*n*=45)**	**No pain at baseline (*n*=60)**	
Time to BPI-SF deterioration, months					
Worst pain					0.001
	Median	5.6 (4.7-9)	11.1 (7.6-NR)	4.1 (3.6-5.7)	
	Mean	7.9 (6.4-9.4)	11.2 (8.5-13.8)	6.1 (4.6-7.7)	
Least pain					ns
	Median	7.1 (6.2-NR)	14.1 (6.9-NR)	6.5 (5.8-NR)	
	Mean	10.7 (8.5-12.9)	11.5 (8.3-14.7)	9.6 (7.3-11.9)	
Average pain					0.03
	Median	6.1 (5.5-NR)	12.6 (6.2-NR)	5.5 (4.1-6.8)	
	Mean	9.4 (7.8-11)	11.5 (8.8-14.2)	8 (6.1-9.8)	
Pain now					ns
	Median	6.2 (4.7-NR)	NR (10-NR)	5.7 (4.1-7.2)	
	Mean	9 (7.3-10.6)	11.9 (9.1-14.6)	7.7 (5.8-9.6)	
Overall pain interference					ns
	Median	8.3 (6.5-13.5)	10.6 (7.2-NR)	6.7 (5.7-NR)	
	Mean	10.4 (8.2-12.5)	9.9 (7.1-12.8)	9.8 (7.5-12.1)	
Clinically meaningful improvement of BPI-Worst Pain during treatment, No of patients (%)		52 (49.5)	35 (77.7)	17 (28.3)	< 0.0001
Pain response, no. of patients (%)					0.004
Complete		33 (31.4)	9 (20.0)	24 (40.0)	0.03
Partial		28 (26.7)	21 (46.7)	7 (11.7)	0.0001
Indeterminate		35 (33.3)	11 (24.4)	24 (40.0)	ns
Progressive pain		6 (5.7)	3 (6.7)	3 (5.0)	ns
Not evaluable		3 (2.8)	1 (2.2)	2 (1.7)	

Time to FACT-P deterioration, months					
Total					ns
	Median	5.7 (3.3-NR)	13.7 (2.5-NR)	5.5 (3.1-NR)	
	Mean	7.8 (6.2-9.3)	8.4 (6.4-10.5)	7 (5.4-8.6)	
Prostate cancer subscale					ns
	Median	9.8 (7-NR)	NR (6.4-NR)	9.8 (7-NR)	
	Mean	11.1 (8.9-13.2)	12.4 (9.6-15.2)	9.9 (7.5-12.3)	
Physical well-being					ns
	Median	NR (7.2-NR)	12.6 (6.4-NR)	NR (NR-NR)	
	Mean	12.4 (10.4-14.4)	10.2 (7-13.5)	12.8 (10.7-14.9)	
Social well-being					ns
	Median	13.2 (11.2-NR)	NR (NR-NR)	13.2 (10.4-NR)	
	Mean	13.2 (11.1-15.3)	14.6 (12.3-17)	12.3 (10-14.6)	
Emotional well-being					ns
	Median	NR (NR-NR)	NR (12.6-NR)	NR (NR-NR)	
	Mean	13.6 (12.1-15.2)	14.4 (12-16.8)	13.1 (11.2-15)	
Functional well-being					ns
	Median	NR (12.7-NR)	12.7 (7.6-NR)	NR (NR-NR)	
	Mean	13.9 (12-15.9)	12.4 (9.2-15.6)	14.2 (12.2-16.2)	
Pain					ns
	Median	10.7 (9-NR)	12.6 (12.6-NR)	9 (5.8-NR)	
	Mean	9.6 (7.9-11.3)	11 (8.9-13.1)	8.3 (6.9-9.7)	
Clinically meaningful improvement of Total FACT-P during treatment, No of patients (%)		33 (31.4)	17 (37.7)	16(26.7)	ns

* Pain at baseline *vs* No-pain at baseline.

Abbreviations: BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate; NR: Not reached. ns: Not significant. Clinically meaningful improvement of total Fact-P was defined as a minimal change of 10 points from baseline for the Total FACT-P score, 3 points from baseline for the subscales and 2 points from baseline for pain. ; The Clinically Meaningful improvement of BPI-SF score (CMC-BPI) was defined as a change of score of at least 30% from baseline score, with a minimum of 2 points.

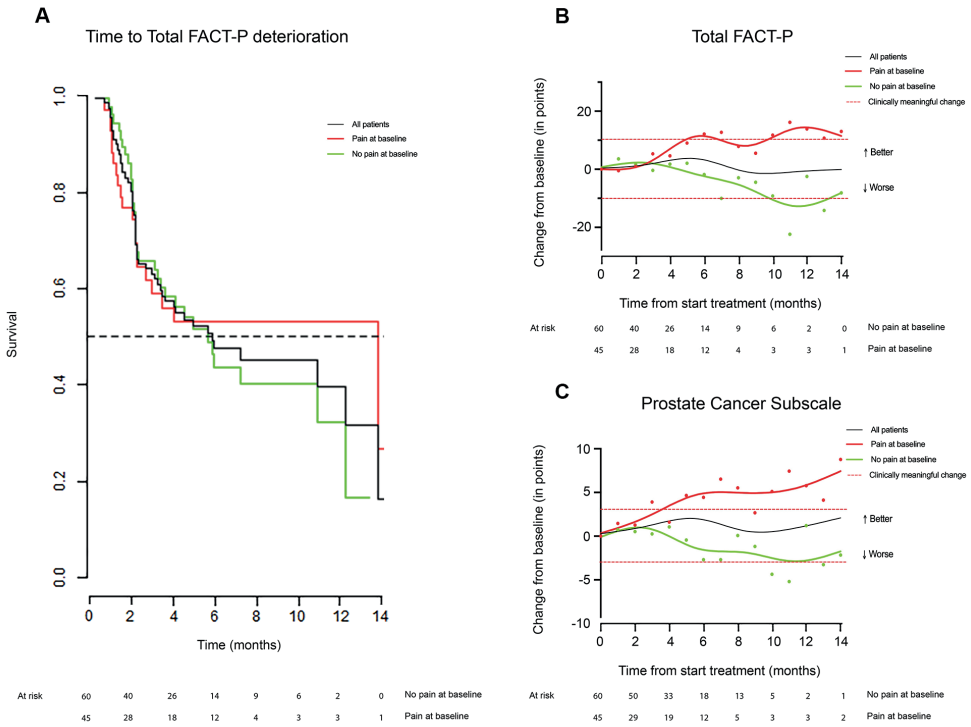

Figure 3. Functional Assessment of Cancer Therapy–Prostate (FACT-P)

A: Kaplan-Meier estimates of time to clinically meaningful Total Functional Assessment of Cancer Therapy–Prostate (FACT-P) score deterioration for the evaluable sample (black line), patients with pain at baseline (red line) and patients without pain at baseline (green line). The horizontal dotted line represents 50% events. **B:** Change in Total FACT-P and **C:** Prostate cancer subscale scores in time for the evaluable sample (black line), patients with pain at baseline (red line) and patients without pain at baseline (green line). Data points show average score at time points, while the lines are made to fit the trend of change of score in time. The horizontal dotted lines represent the threshold for clinically meaningful change from baseline.

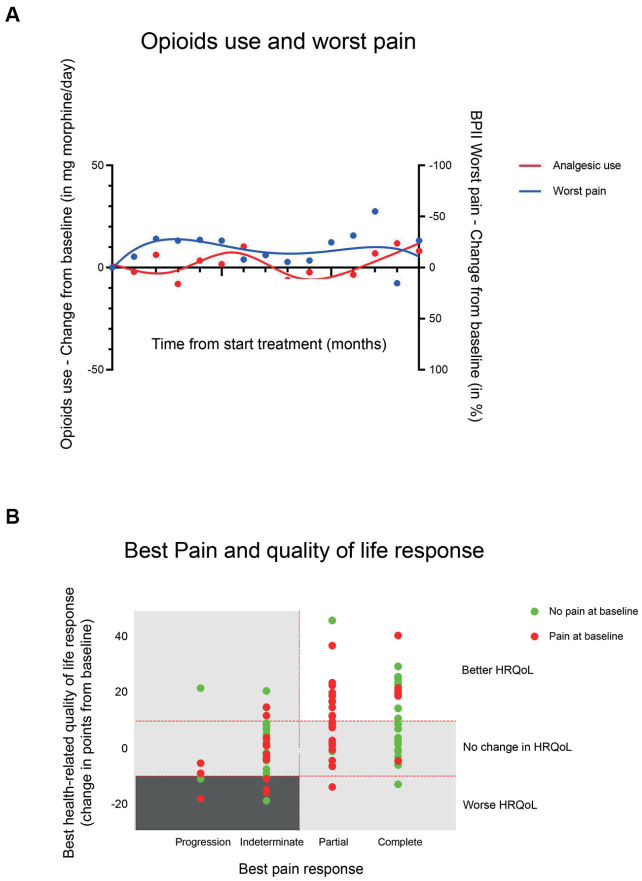

Figure 4. Integrated pain and Health related quality of life response.

A: Percentage change in Brief Pain Inventory (BPI) – Worst pain subscale scores from baseline in time (blue line) and change in average analgesics use from baseline in mg morphine equivalents per day (red line). **B:** Patients were categorized for their best pain response (Worst pain subscale) integrated with opioid drugs use according to IBMCWP recommendations (Horizontal axis: Progression, Indeterminate, Partial and Complete response) and for their best health-related quality of life response (Vertical axis: Total FACT-P clinically meaningful better or worse or not meeting these criteria and therefore considered as No change). The red, horizontal dotted lines represent the threshold for clinically meaningful Total FACT-P change (10 points), while the vertical dotted line separates progression and indeterminate pain responses from partial and complete pain responses. Red dots represent Pain at baseline patients and green dots no-Pain at baseline patients.

Analgesics use and integration of PROMs results

Use of analgesics in the evaluable sample decreased during Ra-223 treatment and remained low during follow-up (Figure 4A; Supplementary Figure 6). The score of the BPI-SF subscale Worst pain did not clinically meaningfully change during Ra-223 treatment and in follow-up. Ninety-five patients had sufficient data to be categorized for best pain response and total-FACT-P response. Fifty-five (57.9%) had an IOCR, of whom 27 (49.1%) were PAB and 28 (50.9%) were no-PAB patients (Figure 4B).

DISCUSSION

In this prospective study, 31.4% of mCRPC patients treated with Ra-223 had a complete pain response, which was the primary outcome. In the ALSYMPCA study, pain was evaluated using the non-pain-specific questionnaires FACT-P and EQ-5D.[5] Evaluation of opioids use was limited to baseline opioid use and 3 monthly assessment of opioid use in patients without baseline use. A non-significant reduction in pain was found between Ra-223 and placebo treated patients at 16 and 24 weeks of treatment.[4, 5] The percentages of patients experiencing a clinically meaningful improvement of total FACT-P in our cohort was comparable with ALSYMPCA (31.4% and 24.6%, respectively).[5] However, there are critical differences between the ALSYMPCA population and the population in the current cohort. The ALSYMPCA trial was conducted in a time when there was no other treatment for mCRPC patients then docetaxel. Consequently, in ALSYMPCA, patients received Ra-223 after docetaxel or as a first line mCRPC treatment. Contemporary mCRPC patients have multiple treatment options. In this study more than half of the patients received at least 2 treatments prior to Ra-223 treatment. It can be assumed that the extensively pretreated patients in this study are prone to poorer performance, while strict patient selection might compensate for that. Moreover, in ALSYMPCA patients were symptomatic, while in this study the majority of patients had no pain at baseline. Unfortunately, baseline Total FACT-P scores of patients included in ALSYMPCA have not been made available.[5, 18]

In this study, outcomes of the different PROMs were integrated into an IOCR, which was established in 58% of patients. Cancer related pain and HRQoL are not mutually exclusive, as was reported previously.[19, 20] However, some patients had more pain but a better HRQoL, while others experienced less pain and a worse HRQoL. In part this can be explained by inclusion of the best pain response and best HRQoL change for establishing the IOCR. Moreover, HRQoL can also be affected by other domains than pain, including fatigue, psychological distress, financial problems or social problems.[21] Another possible explanation is that this is caused by response shift, where patients accommodate to their pain by cognitive reframing and re-prioritizing of previously held values, internal standards and expectations to help cope with high levels of pain. [22]

The strength of this study lies in the inclusion of a contemporary real-world population, pretreated with multiple mCRPC treatment options. Moreover, both symptomatic and asymptomatic patients were included, as this inclusion criterium of the ALSYMPCA study is generally not considered in daily practice. This makes the results of this study directly applicable to current prostate cancer patients' treatment.

Limitations of this study include its non-randomized nature and the likelihood of survival and selection bias. Another limitation is the lower than expected questionnaires completion rates. The percentage of patients evaluable was within the previously reported 10-70% range of response rates in studies on self-reported outcome measures in real-life populations[15–17], but lower than the 40% we assumed for the power calculation. It was previously reported that a higher frailty score was a strong predictor for non-completion. [23] The older age and more advanced disease and with that a presumably higher frailty score of patients in our cohort compared with similar studies in patients with other cancers, might explain the lower than expected completion rates. Despite the above, the evaluable sample seemed to be representative for the registry sample since there were no major differences in baseline characteristics.

In conclusion, our study shows that a significant proportion of Ra-223 treated symptomatic and asymptomatic, extensively pretreated mCRPC patients experience an improved HRQoL and a pain response. These results suggest that the majority of contemporary mCRPC patients derives clinical benefit from Ra-223 treatment.

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DISCLOSURE STATEMENT

Bergman participated in Advisory Boards of Janssen Pharma, Bayer, Sanofi and Astellas, received speaking fees from Jansen Pharma, Bayer and Astellas and received a research grants from Sanofi and Astellas. Feijter participated in advisory boards of Janssen Pharma, Merck and Pfizer. Haanen has provided consultation, attended advisory boards, and/or provided lectures for: AIMM, Amgen, BioNTech, BMS, GSK, Ipsen, Merck Serono, Molecular Partners, MSD, Novartis, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics, Third Rock ventures. He is on the scientific advisory boards of IMM, BioNTech US, Gadeta, Immunocore, T-Knife and Neogene Therapeutics. He received grant support from Amgen, BioNTech US, BMS, MSD, Novartis. He also has stock options in Neogene Therapeutics. All remaining authors have declared no conflicts of interest.

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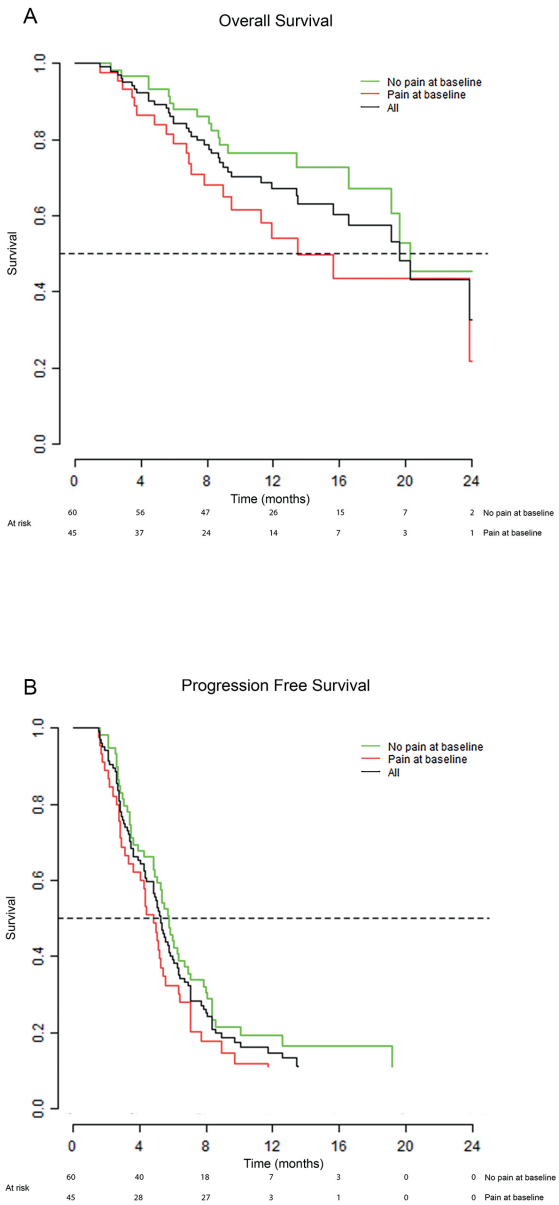
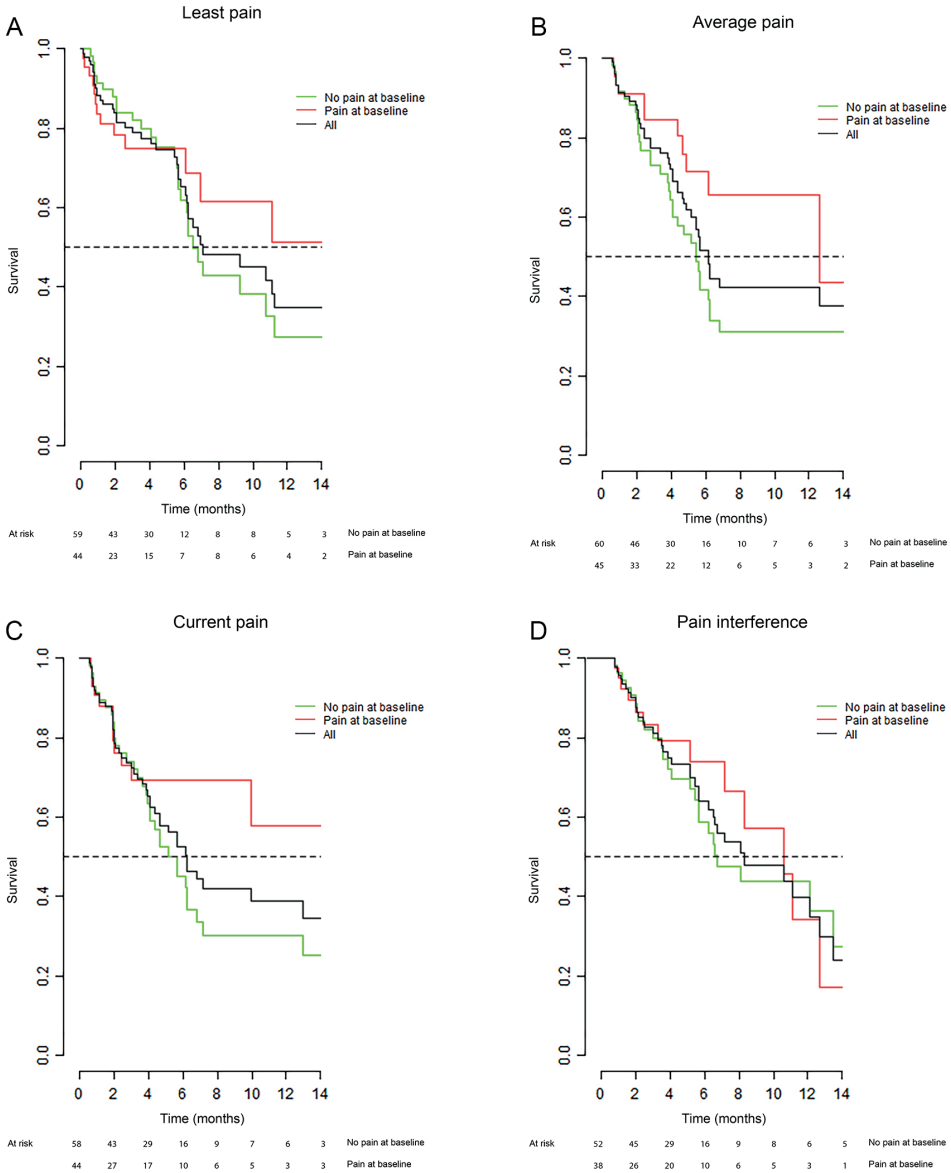
SUPPLEMENTARY MATERIALS



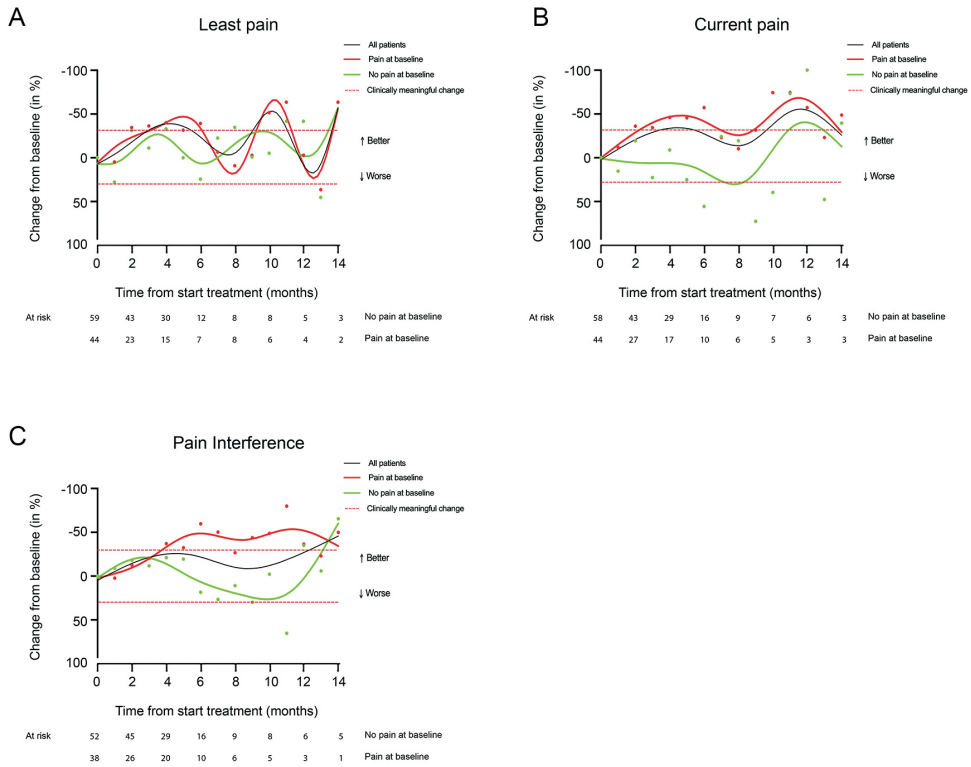
Supplementary Figure 1. Kaplan-Meier estimates of survival in the evaluable sample.

A. Overall survival, **B.** Progression free survival. Black lines represent the evaluable sample, red lines patients with pain at baseline and green lines patients without pain at baseline. The horizontal dotted lines represent 50% events.



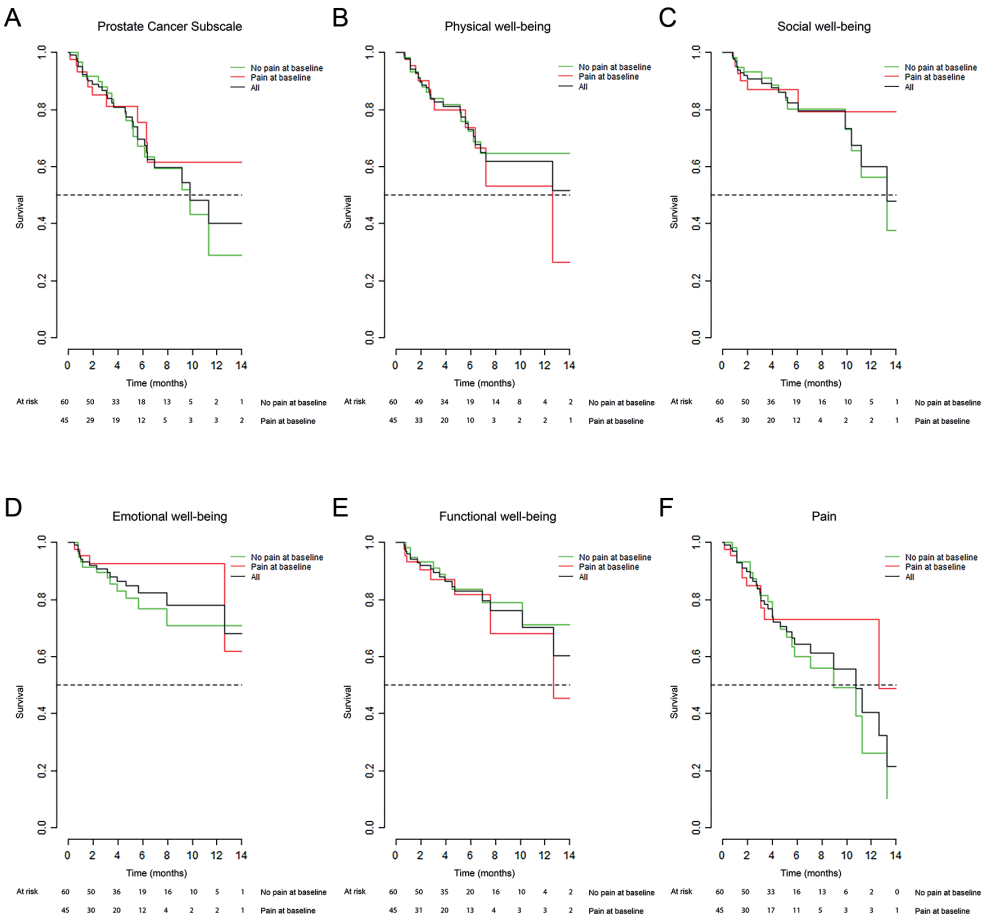
Supplementary Figure 2. Kaplan-Meier estimates of time to clinically meaningful Brief Pain Inventory (BPI) subscales score deteriorations.

A: BPI - Least pain subscale, **B:** BPI – Average pain subscale, **C:** BPI – Current pain subscale, **D:** BPI – Pain interference subscale. Black lines represent the evaluable sample, red lines patients with pain at baseline and green lines patients without pain at baseline. The horizontal dotted lines represent 50% events.



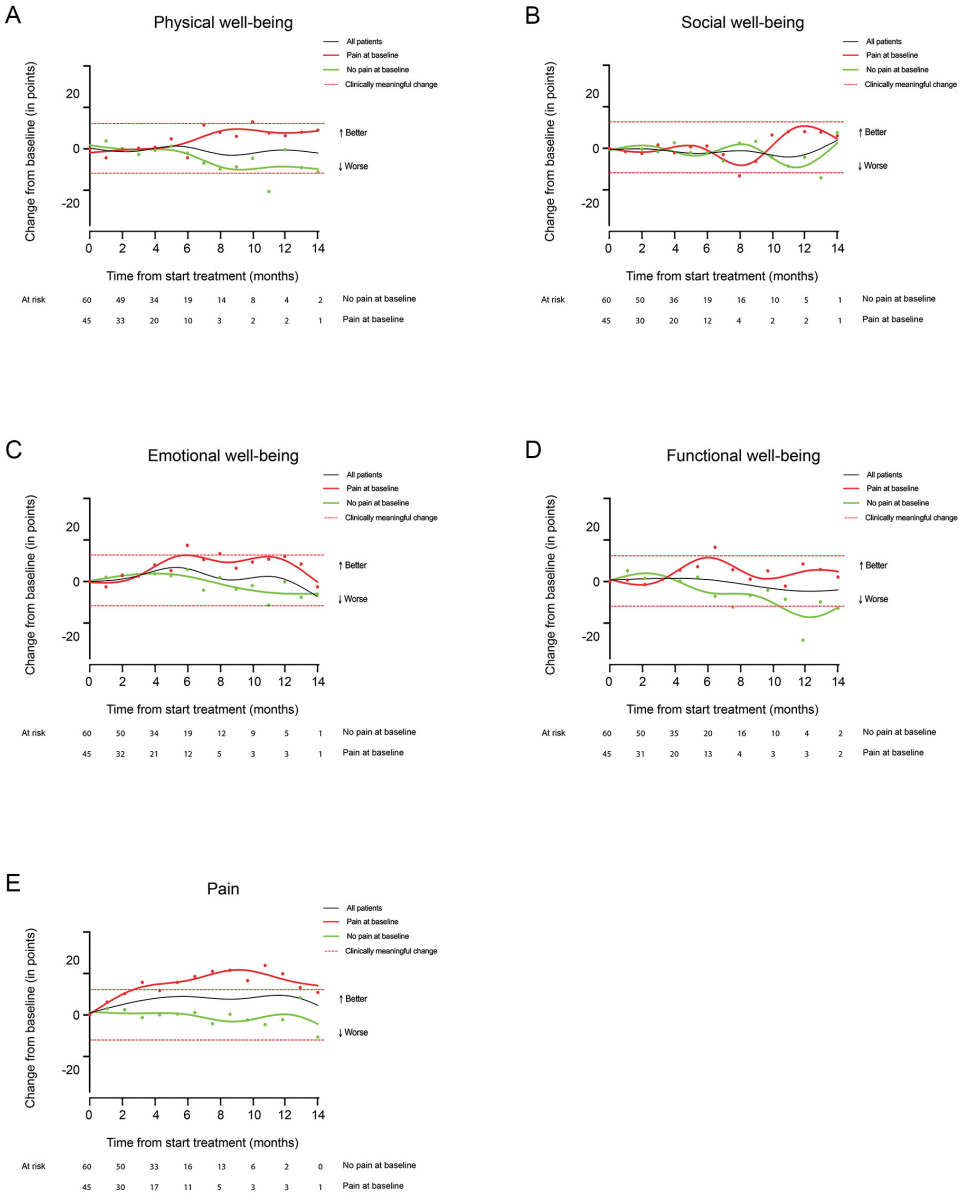
Supplementary Figure 3. Change of Brief Pain Inventory (BPI) subscale scores in time.

A: BPI – Least pain subscale, **B:** BPI – Current pain subscale, **C:** BPI - Pain interference subscale. Data points show average scores at time points, while the lines are made to fit the trend of change of score in time. The black lines represent the evaluable sample, the red line patients with pain at baseline and the green line patients without pain at baseline. The horizontal dotted lines represent the threshold for clinically meaningful change from baseline for BPI.



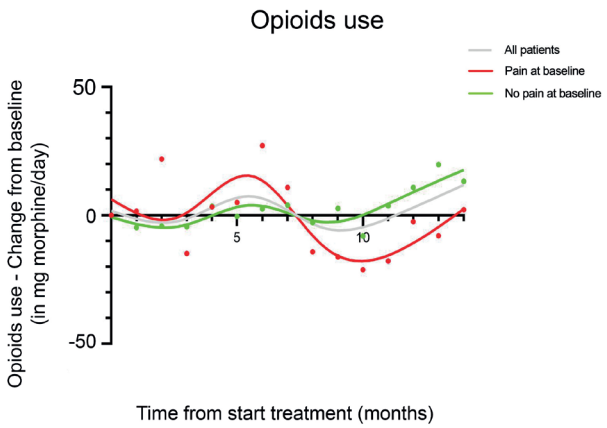
Supplementary Figure 4. Kaplan-Meier estimates of time to clinically meaningful Functional Assessment of Cancer Therapy–Prostate (FACT-P) subscales score deteriorations.

A: FACT-P – Prostate cancer subscale, **B:** FACT-P – Physical well-being subscale, **C:** FACT-P – Social well-being subscale, **D:** FACT-P –Emotional well-being subscale, **E:** FACT-P – Functional well-being subscale, **F:** FACT-P – Pain subscale. Black lines represent the evaluable sample, red lines patients with pain at baseline and green lines patients without pain at baseline. The horizontal dotted lines represent 50% events.



Supplementary Figure 5. Change of Functional Assessment of Cancer Therapy–Prostate (FACT-P) subscale scores in time.

A: FACT-P – Physical well-being subscale, **B:** FACT-P – Social well-being subscale, **C:** FACT-P –Emotional well-being subscale, **D:** FACT-P – Functional well-being subscale, **E:** FACT-P – Pain subscale. Data points show average scores at time points, while the lines are made to fit the trend of change of score in time. The black lines represent the evaluable sample, the red lines patients with pain at baseline and the green lines patients without pain at baseline. The horizontal dotted lines represent the threshold for clinically meaningful change from baseline for FACT-P.



Supplementary Figure 6. Average change in opioids use from baseline in mg morphine equivalents per day. The grey line represents the evaluable sample, the red line patients with pain at baseline and the green line patients without pain at baseline.

Supplementary Table 1. Questionnaires used to assess health-related quality of life, pain and analgesics use.

	Number of items	Score range	Clinically meaningful change	Description	Completion dates
Functional Assessment of Cancer Therapy-Prostate (FACT-P)				A validated questionnaire used to evaluate HRQol in mCRPC patients. A higher FACT-P total score represents better HRQoL	Baseline, once every 4 weeks until start of subsequent treatment or death
Total score	39	0-156	10 points from baseline		
Prostate cancer subscale	12	0-48	3 points from baseline		
Physical well-being	7	0-28	3 points from baseline		
Functional well-being	7	0-28	3 points from baseline		
Emotional well-being	6	0-24	3 points from baseline		
Social well-being	7	0-28	3 points from baseline		
Pain	4	0-16	2 points from baseline		
Brief Pain Inventory-Short Form (BPI-SF)				A commonly used validated questionnaire used to evaluate pain in cancer trials. This questionnaire assesses several aspects of pain. Each aspect is assessed with an individual score on a scale of 0-10, with higher scores representing more pain.	Baseline, once every 4 weeks until start of subsequent treatment or death
Worst pain	1	0-10	Increase ≥ 30% and ≥ 2 point from baseline		
Least Pain	1	0-10	Increase ≥ 30% and ≥ 2 point from baseline		
Average pain	1	0-10	Increase ≥ 30% and ≥ 2 point from baseline		
Current Pain	1	0-10	Increase ≥ 30% and ≥ 2 point from baseline		
Pain interference	7	0-10	Increase ≥ 30% and ≥ 2 point from baseline	Described as pain during daily activities (*e.g.:* sleep, mood)	
List of opioid drugs used				Free text list of all opioid drugs used in the previous 4 weeks	Baseline, once every 4 weeks until start of subsequent treatment or death

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; HRQoL, health-related quality of life;

Supplementary Table 2. Conversion of opioid drugs to oral morphine

Morphine		**Fentanyl**	**Oxycodon**		**Hydromorphine**		**Tramadol**	**Buprenophine**	**Tapentadol**
Oral	S.C./I.V	Patch	Oral	S.C./I.V.	Oral	S.C/I.V.	Oral	Patch	Oral
mg/24h	mg/24h	μg/h	mg/24h	mg/24h	mg/24h	mg/24h	mg/24h	μg/h	mg/24h
30	10	12	20	10	8	2	150	-	75-100
60	20	25	40	20	12	4	300	-	150
120	40	50	80	40	24	8	-	52.2	300
180	60	75	120	60	36	12	-	-	450
240	80	100	160	80	48	16	-	105	-
360	120	150	240	120	72	24	-	-	-
480	160	200	320	160	96	32	-	-	-

Abbreviations: S.C., subcutaneously; I.V., intravenously; mg/h, milligrams per hour; μg/h, microgram per hour;

Supplementary Table 3. Definitions of time-to-event secondary endpoints

Endpoint	Definition
Time to Total FACT-P Deterioration (TTFD)	Time from the date of first Ra-223 course to the first moment of a decrease in Total FACT-P score of at least 10 points from baseline
Time to Pain Progression (TPP)	Time from the date of first Ra-223 treatment to the moment of an increase in worst pain score fulfilling the CMC-FACT criteria*
Progression Free Survival (PFS)	Date of first Ra-223 treatment to the date of confirmed disease progression. Progression was defined as, clinical progression (defined as clinical signs of progression), radiological progression (according to RECIST v. 1.1)†, onset of a subsequent treatment or death, all in line with PCWG3 recommendations††.
Overall Survival (OS)	Date of the first Ra-223 cycle to the date of death

Abbreviations: CMC-FACT-P, clinically meaningful change of Functional Assessment of Cancer Therapy–Prostate. Defined as a minimal change of 10 points from baseline for the Total FACT-P score, 3 points from baseline for the subscales and 2 points from baseline for pain

†Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur. J. Cancer 2009; 45(2):228–247.

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Supplementary Table 4. Power calculations

Number of evaluable patients (out of 300)	300	200	150	120	100	50
Power to find significant increase in proportion of pain responses compared to 20%	99%	95%	88%	81%	70%	43%

Supplementary Table 5. Comparison of treatment outcomes of the registry sample and the evaluable sample for pain and quality of life

	Median [IQR], Number of Patients (%) or value (n=patients evaluable)		
	Registry sample (*n=300*)*	**Evaluable sample (*n=105*)**	***P***
Treatment outcomes			
Follow-up, months	13.2 (12.1-14.4)	13.2 (11.4-15)	Ns
No. of Radium-223 cycles			Ns
Median no. of cycles	5.0 [3.0-6.0]	5 [4-6]	
ALP decline	*(n=255)*	*(n=102)*	
≥30%	122 (47.8)	39 (37%)	Ns
≥50%	56 (22.0)	18 (17%)	Ns
≥90%	1 (0.4)	1 (1%)	Ns
Time to ALP progression, months			Ns
Median	6.7 (6.4 – 7.4)	6.8 (6.2-NR)	
Mean	7.9 (6.7 – 9.2))	8.0 (6.7-9.2)	
PSA decline	*n=256*	*n=103*	
≥30%	16 (6.3)	7 (7%)	Ns
≥50%	11 (4.3)	2 (2%)	Ns
≥90%	3 (1.2)	2 (1.8%)	Ns
Time to first SSE, months	Median not reached	Median not reached	
Progression free survival, months	5.1 (4.5-5.8)	5.2 (4.8-6)	Ns
Overall Survival, months	15.2 (12.8-17.6)	19.6 (16.6-NR)	0.04
Time to subsequent treatment, months	5.9 (4.1-7.7)	3.7 (2.7-8.8)	Ns
Hospital admission during Radium-223 treatment	82 (28.1)	24 (23%)	Ns

Abbreviations: ECOG: Eastern Cooperative Oncology Group; PSA: serum Prostate Specific Antigen; ALP: serum Alkaline Phosphatase; LDH: Lactate Dehydrogenase; SSE: Symptomatic Skeletal Event. Ns:Not significant; Base-line characteristics of the whole population was previously described (Badrising *et al*, Int. J Cancer 2020).

Supplementary Table 6. Completion rates for questionnaires

Radium cycle	Number of patients	At least one completed questionnaire (%)	All three questionnaires completed (%)	All three questionnaires completed including baseline (%)
Baseline	300	126 (42)	121 (40)	121 (40)
Cycle 1	290	184 (63)	181 (62)	66 (23)
Cycle 2	272	182 (67)	181 (67)	80 (29)
Cycle 3	250	170 (68)	168 (67)	74 (30)
Cycle 4	210	130 (62)	130 (62)	58 (28)
Cycle 5	164	110 (67)	109 (67)	55 (34)
Cycle 6	140	108 (77)	108 (77)	46 (33)

Supplementary Table 7. Baseline scores of Patient Reported Outcomes

Outcome variables	Mean (SD)			
	Evaluable sample (*n*=105)	Pain at baseline (*n*=45)	No pain at baseline (*n*=60)	*p**
BPI-SF				
Worst pain	4.2 (2.8)	7.0 (1.1)	2.1 (1.4)	
Least pain	1.8 (1.7)	2.8(1.8)	1.1 (1.1)	<0.001
Average pain	3.1 (2.1)	5.0 (1.5)	1.6 (1.2)	<0.001
Pain now	2.4 (2.3)	4.0 (2.4)	1.2 (1.3)	<0.001
Overall pain interference	3.0 (2.2)	4.1 (1.9)	2.2 (2.0)	<0.001
FACT-P				
Total score	102.0 (17.4)	95.2 (13.0)	107.6 (18.6)	<0.001
Prostate cancer subscale	29.2 (6.6)	26.2 (4.5)	31.6 (6.9)	<0.001
Physical well- being	21.1 (4.3)	19.8 (3.3)	22.0 (4.7)	<0.001
Social well-being	21.0 (4.4)	20.5 (4.5)	21.5 (4.3)	0.59
Emotional well-being	13.4 (3.5)	12.5 (3.5)	14.1 (3.4)	0.031
Functional well-being	17.5 (5.2)	16.5 (4.1)	18.2 (5.8)	0.039
Pain	9.1 (4.1)	5.9 (2.7)	11.5 (3.3)	<0.001

*Pain at baseline vs no pain at baseline

Abbreviations: SD: Standard deviation ; BPI-SF: Brief Pain Inventory-Short Form; FACT-P: Functional Assessment of Cancer Therapy-Prostate;