Original Study

Health-related Quality of Life and Pain in a Real-world Castration-resistant Prostate Cancer Population: Results From the PRO-CAPRI Study in the Netherlands

Malou C.P. Kuppen,[1] Hans M. Westgeest,[2] Alphonsus J.M. van den Eertwegh,[3] Jules L.L.M. Coenen,[4] Reindert J.A. van Moorselaar,[5] Pieter van den Berg,[6] Maud M. Geenen,[7] Niven Mehra,[8] Mathijs P. Hendriks,[9] Menuhin I. Lampe,[10] Addy C.M. van de Luijtgaarden,[11] Frank P.J. Peters,[12] Ton A. Roeleveld,[13] Tineke J. Smilde,[14] Ronald de Wit,[15] Inge M. van Oort,[16] Winald R. Gerritsen,[8] Carin A. Uyl-de Groot[1]

Abstract

In castration-resistant prostate cancer (CRPC), several life-prolonging drugs have been registered, but patient-reported outcomes in daily practice are scare. In our study, 151 patients with CRPC completed quality of life (QoL) questionnaires. Although the majority received life-prolonging drugs, QoL deteriorated during the course of CRPC. Supportive care should be timely thought of to maintain QoL as long as possible.

Background: The purpose of this study was to determine generic, cancer-specific, and prostate cancer-specific health-related quality of life (HRQoL), pain and changes over time in patients with metastatic castration-resistant prostate cancer (mCRPC) in daily practice. **Patients and Methods:** PRO-CAPRI is an observational, prospective study in 10 hospitals in the Netherlands. Patients with mCRPC completed the EQ-5D, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and Brief Pain Inventory-Short Form (BPI-SF) every 3 months and European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module (EORTC QLQ-PR25) every 6 months for a maximum of 2 years. Subgroups were identified based on chemotherapy pretreatment. Outcomes were generic, cancer-specific, and prostate cancer-specific HRQoL and self-reported pain. Descriptive statistics were performed including changes over time and minimal important differences (MID) between subgroups. **Results:** In total, 151 included patients answered 873 questionnaires. The median follow-up from the start of the study was 19.5 months, and 84% were treated with at least 1 life-prolonging agent. Overall, patients were in good clinical condition (Eatern Cooperative Oncology Group performance status 0-1 in 78%) with normal baseline hemoglobin, lactate dehydrogenase, and alkaline phosphatase. At

M.C.P.K. and H.M.W. contributed equally to this article.

[1]Institute for Medical Technology Assessment, Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, the Netherlands
[2]Department of Internal Medicine, Amphia Hospital, Breda, the Netherlands
[3]Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands
[4]Department of Oncology, Isala, Zwolle, the Netherlands
[5]Department of Urology, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands
[6]Department of Internal Medicine, TerGooi Ziekenhuizen, Hilversum, the Netherlands
[7]Department of Internal Medicine, OLVG, Amsterdam, the Netherlands
[8]Department of Medical Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
[9]Department of Internal Medicine, Northwest Clinics, Alkmaar, the Netherlands
[10]Department of Urology, Medical Center Leeuwarden, Leeuwarden, the Netherlands
[11]Department of Internal Medicine, Reinier de Graaf Gasthuis and Reineir Haga Prostate Cancer Center, Delft, the Netherlands
[12]Department of Internal Medicine, Zuyderland Medical Center, Heerlen-Sittard-Geleen, the Netherlands
[13]Department of Urology, Northwest Clinics, Alkmaar, the Netherlands
[14]Department of Internal Medicine, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands
[15]Department of Medical Oncology, Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, the Netherlands
[16]Department of Urology, Radboud University Medical Center, Nijmegen, the Netherlands

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Address for correspondence: Malou C.P. Kuppen, MD, Institute for Medical Technology Assessment, Erasmus School of Health Policy and Management, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, the Netherlands
E-mail contact: kuppen@ehspm.eur.nl

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inclusion, generic HRQoL was high with a mean EQ visual analog score of 73.2 out of 100. The lowest scores were reported on role and physical functioning (mean scores of 69 and 76 of 100, respectively), and fatigue, pain, and insomnia were the most impaired domains. These domains deteriorated in > 50% of patients. **Conclusion:** Although most patients were treated with new treatments during follow-up, mCRPC has a negative impact on HRQoL with deterioration in all domains over time, especially role and physical functioning. These domains need specific attention during follow-up to maintain HRQoL as long as possible by timely start of adequate supportive care management.

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Introduction

The survival of patients with metastatic castration resistant prostate cancer (mCRPC), that is progression of disease on androgen deprivation therapy, is not likely to extend beyond 14 months with only best supportive care.[1] Several life-prolonging drugs (LPDs), such as chemotherapy (ie, docetaxel, cabazitaxel), androgen-receptor targeting treatments (ie, abiraterone, enzalutamide), and radionuclide therapy (ie, radium-223), have shown a survival benefit compared with placebo.[2-8] In a contemporary cohort with access to these new LPDs, we observed a median overall survival of 26 months.[9]

mCRPC has a negative impact on health-related quality of life (HRQoL) with a decline in HRQoL over time.[1,10-17] Deterioration occurs in general domains as well as specific symptoms such as pain, fatigue, and appetite loss.[12] However, these results are derived from trials performed in the era before the registration of new LPDs.[1,12,15,16] In the pivotal phase III trials, the LPDs showed a delay in HRQoL deterioration and pain progression in both chemotherapy-naive (CTx-naive) and post-chemotherapy (post-CTx) disease phases,[18-21] but adverse events of new agents can also add to the symptom burden in mCRPC.

There remains a paucity of data concerning treatment sequencing and direct comparisons of LPDs in randomized trials. Moreover, cumulating evidence on real-world data points toward the fact that trials utilize highly selected populations with significantly better outcomes that are commonly not generalizable to an oncology practice.[9] Benefits of LPDs in trials are comparable and economic costs are in the same range, making patient-reported outcomes (PROs) of special interest in order to determine the best treatment. The use of PROs in daily practice can also inform physicians on efficacy and tolerability, increase patient satisfaction, and improve symptom control and supportive care measures.[22]

The high proportion of patients experiencing HRQoL deterioration owing to either disease- or treatment-related symptoms, the lack of discriminative results from trials, and the gap between these trials and real-world practice underline the necessity for PROs in daily practice. The objective of this study is therefore to determine generic, cancer-specific, and prostate cancer-specific HRQoL and changes over time in patients with mCRPC using data from a patient registry in the Netherlands.

Patients and Methods

Study Design and Setting

PRO-CAPRI is a prospective observational cohort study in 10 hospitals in the Netherlands. The study aimed to evaluate HRQoL, pain, and resource use outside the hospital in daily practice using validated questionnaires. The study was approved by a central and local medical ethics committee and hospital board before the start of inclusion. The PRO-CAPRI study is registered in the Dutch Trial Registry as NL3934 (NTR4096). PRO-CAPRI is a side study of the CAstration-resistant Prostate cancer RegIstry (CAPRI) registered as NL3440 (NTR3591). The methods of the CAPRI registry have been described in depth previously.[9]

Objectives

The objectives are to determine generic, cancer-specific, and prostate cancer-specific HRQoL, pain, and changes over time in patients with mCRPC in daily practice.

Participants

Patients diagnosed with mCRPC between January 1, 2010 and December 31, 2015 were eligible for inclusion, conforming to the CAPRI inclusion criteria.[9] Patients were eligible for the PRO-CAPRI study from diagnosis of CRPC to 4 weeks after the start of the first post-docetaxel treatment. Eligible patients provided written informed consent to the treating physician at the hospital site. All PRO-CAPRI patients were also included in the CAPRI registry.

Subgroups were created based on the disease state at inclusion, namely chemotherapy-naive state (CTx-naive [ie, no prior docetaxel treatment]) and (post-) chemotherapy state (post-CTx [ie, current docetaxel or post-docetaxel treatment]).

Study Size

In PRO-CAPRI, 167 participants were included out of the total of 3616 patients with mCRPC that were included in the CAPRI registry.

Follow-up and Data Collection

PRO-CAPRI started in June 2013 with 4 participating hospitals, but because of slow accrual, the protocol was amended after 1 year to include an additional 6 hospitals and prolong the inclusion period for 6 months. This amendment also included the addition of the pain-specific questionnaire, the Brief Pain Inventory-Short Form (BPI-SF).

The baseline evaluation of consenting patients consisted of 4 questionnaires (EQ-5D, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire [EORTC

QLQ-C30], European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module [EORTC QLQ-PR25], and after the amendment, BPI-SF) and commonly used demographic items, namely age, socioeconomic status, marital status, and educational level. After baseline measurement, EQ-5D, EORTC QLQ-C30, and BPI-SF were repeated every 3 months, and EORTC QLQ-PR25 every 6 months. All patients were followed until death, withdrawal of consent, or end of study duration (either a total follow-up period of 2 years from the start of the study or December 31, 2017).

A case record form linked the participating patient to the CAPRI database, combining HRQoL with the clinical characteristics.

Outcome

The primary outcome was generic HRQoL, measured with EQ-5D. The first part of the EQ-5D is a generic 5-dimensional questionnaire on a 5-point Likert scale, which was transformed into utility or EQ-5D index value based on Dutch population norms.[23] The second part is a visual analogue scale (VAS).[24]

The secondary outcomes were cancer-specific HRQoL, prostate cancer-specific HRQoL, and pain. The EORTC QLQ-C30 (cancer-specific HRQoL) and EORTC QLQ-PR25 (prostate cancer-specific HRQoL) include 55 questions in different HRQoL domains, including functional scales, symptom scales, and a global health status. For the majority of items, a 4-point Likert-type response scale was used. Exception is the global health status, where a 7-point scale was used. All EORTC QLQ-C30 and EORTC QLQ-PR25 scales were linearly transformed to a scale from 0 to 100 according to the scoring manual.[25,26] The BPI-SF assesses severity of pain (4 items), impact of pain on daily function (7 items), location of pain, pain medication, and amount of pain relief in the past 24 hours or the past week. The areas were measured on a scale from 0 to 10, with 0 indicating "no pain" and 10 indicating "worst possible pain."[27] Clinically relevant pain was defined as a score of ≥ 4 on pain severity. Supplemental Table 1 (in the online version) shows an overview of the used questionnaires.

Both the primary and secondary outcomes are measured at baseline (ie, inclusion) and over time. A minimally important difference (MID) was used to assess clinically relevant changes.[27-30] The thresholds for MIDs are also shown in Supplemental Table 1 (in the online version). Time to first MID deterioration was calculated in months from the date of first questionnaire to the date of first MID deterioration.

Missing Values

Missing values were handled based on the scoring manual for the specific questionnaires. In EQ-5D, the index value and VAS were calculated if all domains were present.[24] For EORTC QLQ-C30, EORTC QLQ-PR25, and BPI-SF, averages were calculated if more than one-half of the questions were completed per scale.[25-27]

Statistical Analysis

The compliance rate was calculated as the number of patients returning a questionnaire divided by the total number of evaluable patients per questionnaire. Baseline characteristics were measured in the period of 3 months prior to 3 months after inclusion. Descriptive statistics were used to describe the study population with subgroups per disease state at inclusion. Data on HRQoL were presented as mean changes from baseline and proportion with MID. The McNemar test was used for differences in proportion with MID between 6 and 12 months for subgroups. The independent sample t test, Mann-Whitney U test, or χ^2 test were used to compare parametric continuous, nonparametric continuous, and categorical variables, respectively, between CTx-naive and post-CTx patients. A P-value of .05 or less was considered statistically significant. IBM SPSS Statistics Version 24.0 (IBM, Armonk, NY) was used for all analyses.

Results

In total, 167 patients were included in the PRO-CAPRI study. Nine patients were excluded for failing to meet the inclusion criteria (n = 7) or missing informed consent (n = 2). Seven of the 158 patients who were sent the first questionnaire did not respond, either owing to death (n = 4), withdrawal of consent (n = 2), or inability to answer (n = 1). Baseline questionnaires were evaluable for 151 patients (Figure 1).

In total, 873 questionnaires were completed, and the median number of questionnaires per patient was 6 (range, 1-9). The median follow-up from the first questionnaire was 19.5 months (IQR, 13-25 months). Thirty-eight (25%) patients completed all 9 questionnaires. Termination of the study before the maximum follow-up of 2 years occurred in 113 (75%) patients, owing to death (n = 56; 37%), lost-to-follow-up (n = 22; 15%), withdrawal of informed consent (n = 9; 6%), or database cutoff (n = 26; 17%). The compliance rate ranged from 94% to 100% per questionnaire, except for BPI-SF, which was added during the study after a protocol amendment (see Supplemental Table 2 in the online version).

Treatment Characteristics

At inclusion, 112 (74%) patients were in the CTx-naive state, and 39 (26%) patients were in the post-CTx state. At the time of the first questionnaire, 37 (33%) patients in the CTx-naive state were treated with LPD, mainly enzalutamide (n = 27; 24%), whereas in the post-CTx state, most patients were treated with docetaxel (n = 17; 44%). During follow-up, 84% of patients were treated with at least 1 LPD, mainly enzalutamide (n = 89; 59%) or docetaxel (n = 65; 43%) (Table 1).

Patient and Disease Characteristics

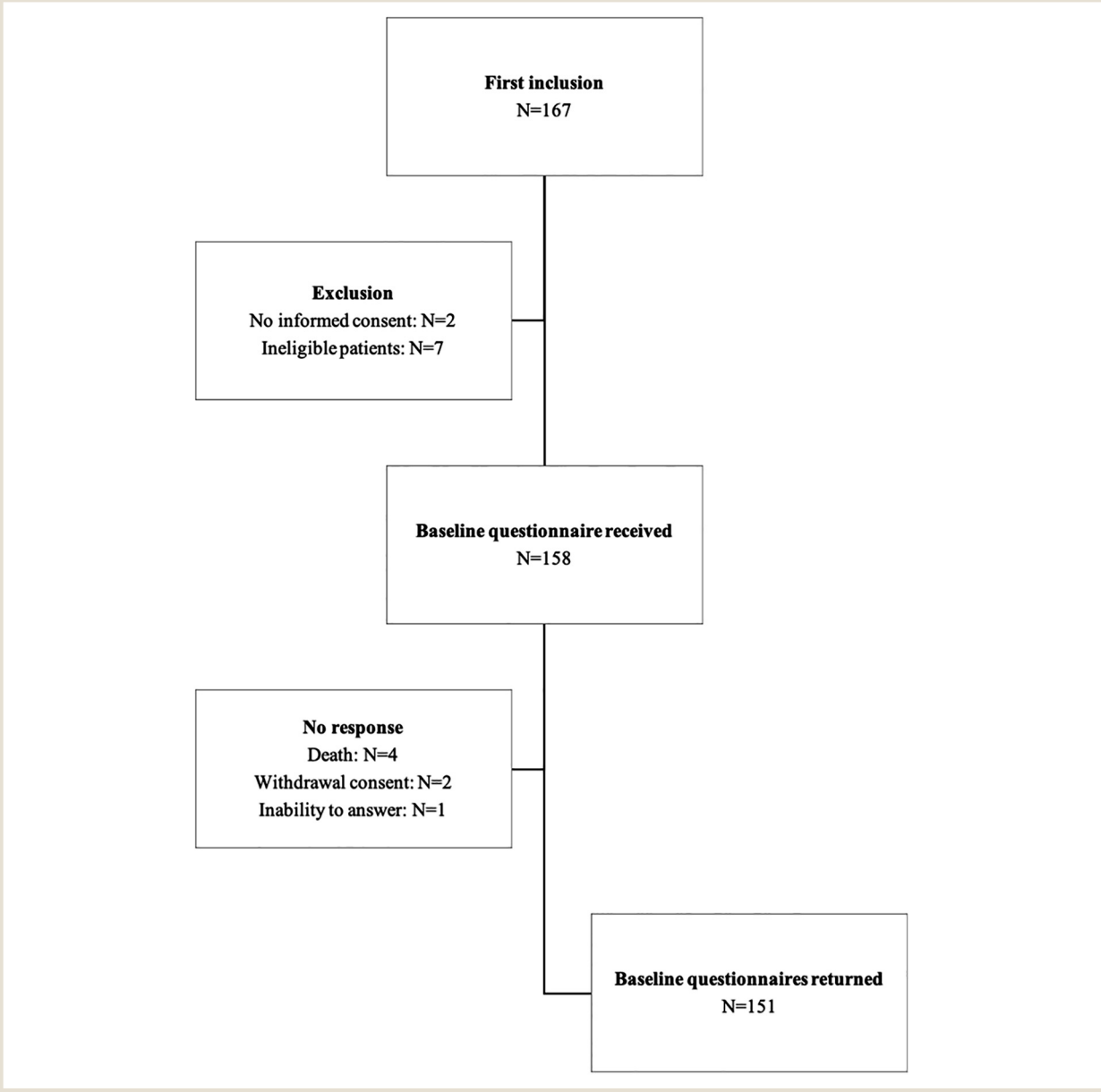
At mCRPC diagnosis, patients included in the PRO-CAPRI study were younger (72 vs. 75 years; $P < .01$) and had higher hemoglobin (8.3 vs. 8.0 mmol/L; $P = .01$) compared with the total mCRPC population in the CAPRI registry (see Supplemental Table 3 in the online version).

CTx-naive patients were older (median 75 vs. 71 years; $P = .02$), had less prevalent bone metastases (73% vs. 82%; $P = .03$), and had lower educational level ($P = .03$) at inclusion than post-CTx patients (Table 1). PSA tended to be lower in CTx-naive patients (median, 36 vs. 86 μg/L; $P = .06$).

Generic HRQoL (EQ-5D)

Generic HRQoL was high, with a mean EQ VAS of 73.2 of 100 and EQ-5D index value of 0.82 of 1 at inclusion. Most problems were reported on pain/discomfort (55%) and mobility (48%). No

Figure 1 Flowchart of Patient Inclusion



differences between disease state were observed in generic HRQoL (Figure 2A, Supplemental Table 4 [in the online version]).

EQ VAS deteriorated over time, but changes were small, and the mean change did not reach MID during 24 months of follow-up (Figure 3A). There were no differences in proportion with MID deterioration at 6 and 12 months (Table 2, Supplemental Table 5 [in the online version]). The median time to MID deterioration on generic HRQoL was 10.8 months for EQ VAS, without differences between CTx-naive and post-CTx patients (Table 3, Supplemental Table 6 [in the online version]).

Cancer-specific HRQoL (EORTC QLQ-C30)

Figure 2A and B show cancer-specific HRQoL at inclusion. Role (ie, patient's ability to perform daily activities, leisure time activities, and/or work) and physical functioning were most affected in cancer-specific HRQoL (mean scores of 69 and 76 of 100, respectively). CTx-naive patients had significant but not relevant lower levels of emotional functioning compared with post-CTx patients (mean scores of 81 vs. 88; $P = .02$). Most symptoms were measured on scales of fatigue, pain, and insomnia, without differences in subgroups per disease state (Figure 2A and B).

Deterioration was seen on all functioning domains of EORTC QLQ-C30, except for emotional functioning (Figures 3B-G). The proportion of CTx-naive patients with MID after 12 months was higher compared with after 6 months in global health status (32% vs. 18%; $P = .03$), physical functioning (44% vs. 27%; $P = .02$), role functioning (45% vs. 27%; $P = .02$), and social functioning (35% vs. 19%; $P = .01$). In post-CTx patients, no differences in proportion

Table 1 Patient and Disease Characteristics per Disease State

	Total N = 151	CTx-naive N = 112	Post-CTx N = 39	*P* Value
Age, y				.020
Median (IQR)	74 (68-80)	75 (68-81)	71 (68-75)	
Range	54-95	54-95	58-84	
ECOG performance status, %				.235
0	38	39	36	
1	40	35	54	
>1	9	10	5	
Unknown	13	16	5	
Gleason score, %				.431
≤7	34	35	31	
8-10	56	53	64	
No histology	3	5	0	
Metastasis biopsy	1	1	3	
Unknown	6	7	3	
Charlson comorbidity index, %				.565
6	69	66	77	
7-8	25	27	21	
9-10	5	6	3	
>10	1	1	0	
Unknown	0	0	0	
Disease state, %				
N1/N0/Nx	49/13/38	44/13/44	64/15/21	.749
M1/M0/Mx (bone)	76/8/17	73/5/22	82/18/0	.031
M1/M0/Mx (visceral)	9/31/60	5/25/70	18/49/33	.387
Period from castration to mCRPC, mos				.105
Median (IQR)	15.1 (9-28)	16.5 (9-32)	13.0 (7-22)	
Unknown, %	0	0	0	
Period from mCRPC to inclusion PRO-CAPRI, mos				<.001
Median (IQR)	7.0 (2.0-21.0)	4.7 (1-14)	19.4 (10-29)	
Unknown, %	0	0	0	
Hemoglobin, mmol/L				.479
Median (IQR)	8.0 (7.3-8.5)	8.1 (7.5-8.5)	8.0 (7.1-8.4)	
Unknown, %	2.6	3	3	
Lactate dehydrogenase, U/L				.341
Median (IQR)	213 (185-261)	211 (182-259)	218 (187-281)	
Unknown, %	7	7	5	
Alkaline phosphatase, U/L				.421
Median (IQR)	103 (72-173)	102 (72-168)	113 (76-254)	
Unknown, %	2	3	0	
Prostate-specific antigen, μg/L				.061
Median (IQR)	40.4 (12-121)	36.0 (11-106)	86.0 (14-180)	
Unknown, %	2	3	0	
Marital state, %				.210
Married/living together	85	83	90	
Single/not living together	5	4	8	
Divorced	3	4	0	
Widowed	8	10	3	

Table 1 Continued

	Total N = 151	CTx-naive N = 112	Post-CTx N = 39	*P* Value
Educational level, %[a]				.030
None	1	1	0	
Low	39	45	23	
Middle	15	11	26	
High	38	35	46	
Other/unknown	8	9	5	
Current profession, %				.395
Employed	8	7	10	
Entrepreneur	7	10	0	
Incapacitated	3	2	5	
Retired/early retired	79	78	82	
Other/unknown	3	4	3	
Treatment at inclusion, %[b]				
None	24	32	0	<.001
No LPD	26	35	0	<.001
LPD	50	33	100	<.001
Docetaxel	11	0	44	<.001
Cabazitaxel	1	0	3	.089
Abiraterone acetate	12	9	18	.125
Enzalutamide	27	24	36	.001
Radium-223	0	0	0	–
Study drug	0	0	0	–
Treatment during follow-up, %[c]				
None	6	9	0	.053
No LPD	15	18	8	.128
LPD	84	80	97	.008
Docetaxel	43	44	41	.767
Cabazitaxel	19	14	31	.023
Abiraterone acetate	25	23	28	.533
Enzalutamide	59	59	59	.996
Radium-223	11	11	10	.936
Study drug	3	4	3	.762

All baselines measured are measured within 3 months prior or after the start of study. Percentages may exceed 100% owing to rounding.
P values calculated for differences in time to first minimally important difference between CTx-naive and post-CTx patients.
Abbreviations: ADT = androgen deprivation therapy; CTx-naive = no or no prior docetaxel chemotherapy at inclusion; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LPD = life prolonging drug (either docetaxel, cabazitaxel, abiraterone, enzalutamide or radium-223); mCRPC = metastastic castration-resistant prostate cancer; post-CTx = current or post-docetaxel chemotherapy at inclusion.
[a]Educational level converted to classes according to the Dutch Central Bureau of Statistics (CBS).[31]
[b]Any systemic treatment at time of first questionnaire.
[c]Any systemic treatment at time of second or later questionnaires.

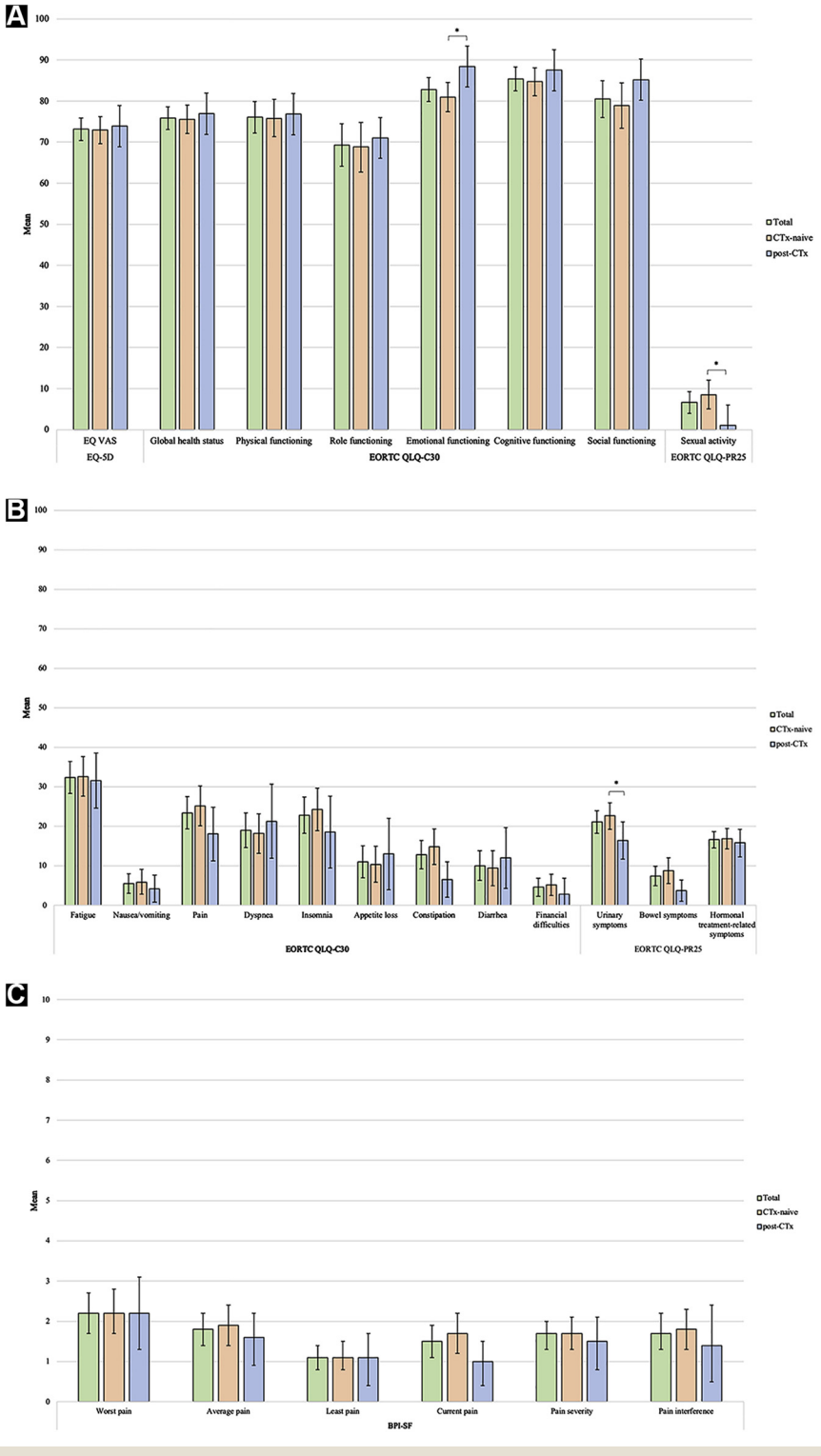
with MID deterioration after 6 and 12 months was seen. Symptoms increased over time, with the highest proportion of patients with MID in fatigue and appetite loss. The proportion of patients with MID after 12 months was higher than after 6 months for pain (22% vs. 36%; $P < .01$), which was only present in the CTx-naive subgroup (see Supplemental Table 5 in the online version).

All functioning domains of EORTC QLQ-C30 deteriorated approximately 1 year after inclusion, except for emotional functioning (median, 26.6 months) (Table 3). The median time to deterioration of the symptoms fatigue and pain were, respectively, 8.2 and 15.3 months.

Prostate Cancer-specific HRQoL (EORTC QLQ-PR25)

At inclusion, 31 (21%) patients reported any sexual activity measured with EORTC QLQ-PR25, with higher activity levels in CTx-naive patients than in post-CTx patients (mean, 8.5 vs. 1.4; $P = .02$). Prostate cancer-specific symptoms were mostly present as urinary symptoms at inclusion. CTx-naive patients reported more bowel symptoms than post-CTx patients (mean 8.9 vs. 3.7; $P = .04$). During follow-up, sexual activity and prostate cancer-specific symptoms remained stable, and no clinically relevant deterioration was observed.

Figure 2 Health-related Quality of Life Measured at Study Inclusion. A, Mean Scores of Functioning Scales. High Scores Indicate High Level of Functioning. B, Mean Scores of Symptom Scales. High Scores Indicate High Symptom Burden. C, Mean Scores of Pain. High Scores Indicate High Pain Severity or Interference. Error Bars Represent 95% Confidence Intervals. *Significant Differences at Level $P < .05$



Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; CTx-naive = no or no prior docetaxel chemotherapy at inclusion; post-CTx = current or post-docetaxel chemotherapy at inclusion; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PR25 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module; VAS = visual analog scale.

Pain (BPI-SF)

The mean pain severity and interference were low at inclusion, without differences between subgroups (Figure 2C). Sixteen percent (17 of 108 patients with baseline BPI-SF) reported clinically relevant pain at inclusion.

Thirty-six percent of patients without clinical meaningful pain at inclusion had MID deterioration during follow-up. Eight (47.1%) of 17 patients with clinical meaningful pain at inclusion had evaluable follow-up questionnaires, with 4 (23.5%) reporting MID improvement of pain. In CTx-naive patients, the proportion of patients with MID after 12 months was higher for "worst" (29% vs. 18%; $P = .04$) and "average" (24% vs. 13%; $P = .02$) pain and pain interference on daily functioning (26% vs. 11%; $P < .01$) than after 6 months (see Supplemental Table 5a in the online version).

No differences between CTx-naive and post-CTx patients were found in time to deterioration except for "worst" pain (see Supplemental Table 6 in the online version). CTx-naive patients had a significantly longer time to deterioration on "worst" pain than post-CTx patients (24.5 vs. 9.9 months, respectively; $P = .04$).

Discussion

To our knowledge, this is the largest contemporary real-world longitudinal analysis of HRQoL during mCRPC. Previous research mainly focused on patients treated in randomized controlled trials, but results from these trials cannot be easily generalized to the real-world practice.[9] The absence of complicated inclusion and exclusion criteria in our study warrants the reflection of a real-world population in current daily practice.

In this study, we showed that at inclusion, baseline HRQoL was relatively high. Most of our patients were in an early disease phase, with 75% of patients without docetaxel pretreatment and a short interval from diagnosis of castrate-resistance to inclusion into the study. Previously published mCRPC cohorts reported lower HRQoL.[12,32] For example, the mean EQ-5D index value was 0.82 in our study, compared with 0.64 to 0.74 in other reports.[12,32] However, differences between our study and previous reports can be explained by differences in patient selection, the availability of life-prolonging therapeutic options, and international valuation of HRQoL measurement.[33,34] This contemporary cohort indicates that in Dutch daily practice, generic HRQoL is high in the early mCRPC state.[12,14,15,32] Most baseline symptoms were identified in role (ie, patient's ability to perform daily activities, leisure time activities, and/or work) and physical functioning, with high symptom burden on pain, fatigue, and insomnia.

Deterioration was seen in almost all domains of HRQoL. Deterioration in HRQoL is part of the normal aging process, and scores on cognitive, emotional, and social functioning are comparable to the European population norms of the same age group ($\geq$ 70 years).[35] However, we found low scores on role and physical functioning at inclusion, probably showing the impact of mCRPC on these domains.[35] Role and physical functioning were also prone to deterioration. Therefore, specific attention for these domains at the start of new systemic treatment and during follow-up of patients with mCRPC is needed to maintain HRQoL as long as possible.

A delay in HRQoL and pain progression has been reported in randomized controlled trials of new LPDs.[18-21] Eighty-four percent of patients in our study were also treated with LPDs during follow-up. Owing to small sample sizes, we were not able to calculate differences between treated and untreated patients, and more specifically between treatments. In our total mCRPC population, the median time to pain deterioration ("worst" pain) was 24.5 months in CTX-naive and 9.9 months in post-CTX patients. This time to progression on "worst" pain is in agreement with the chemotherapy-naive COU-AA-302 treatment arm (25.8 months)[36] and in the post-chemotherapy COU-AA-301 treatment arm (7.4 months).[37] Comparison with clinical trials, however, warrants caution owing to differences in patient selection, outcome measures, and the definition of MID compared with our real-world population.

In prostate cancer-specific HRQoL, we found low sexual activity and mostly urinary symptoms at baseline. A population-based survey in the United Kingdom showed that sexual activity was low among all stages of prostate cancer.[38] Although younger patients were concerned about the lack of sexual activity, less than one-half of the patients were offered treatment to improve sexual health.[38] The baseline assessment in individual patients with mCRPC can address problems and concerns about sexual health and guide individual treatment. However, similar to other research, no trends in prostate-cancer specific HRQoL were observed during follow-up.[14] Therefore, the EORTC QLQ-PR25 seems of low additional value when it comes to monitoring treatment effects and tolerability.

An important limitation of this study was the relatively small sample size. Only 4 percent of all patients included in the CAPRI-registry were included in the PRO-CAPRI study. At baseline mCRPC diagnosis, patients in the PRO-CAPRI study tended to be in better clinical condition than patients in the CAPRI-registry. Therefore, results are possibly not generalizable for the total Dutch population. The second limitation of this study was the non-randomized study design that made it impossible to compare the individual new treatments. Subgroups per treatment were too small for reliable analyses of changes in HRQoL.

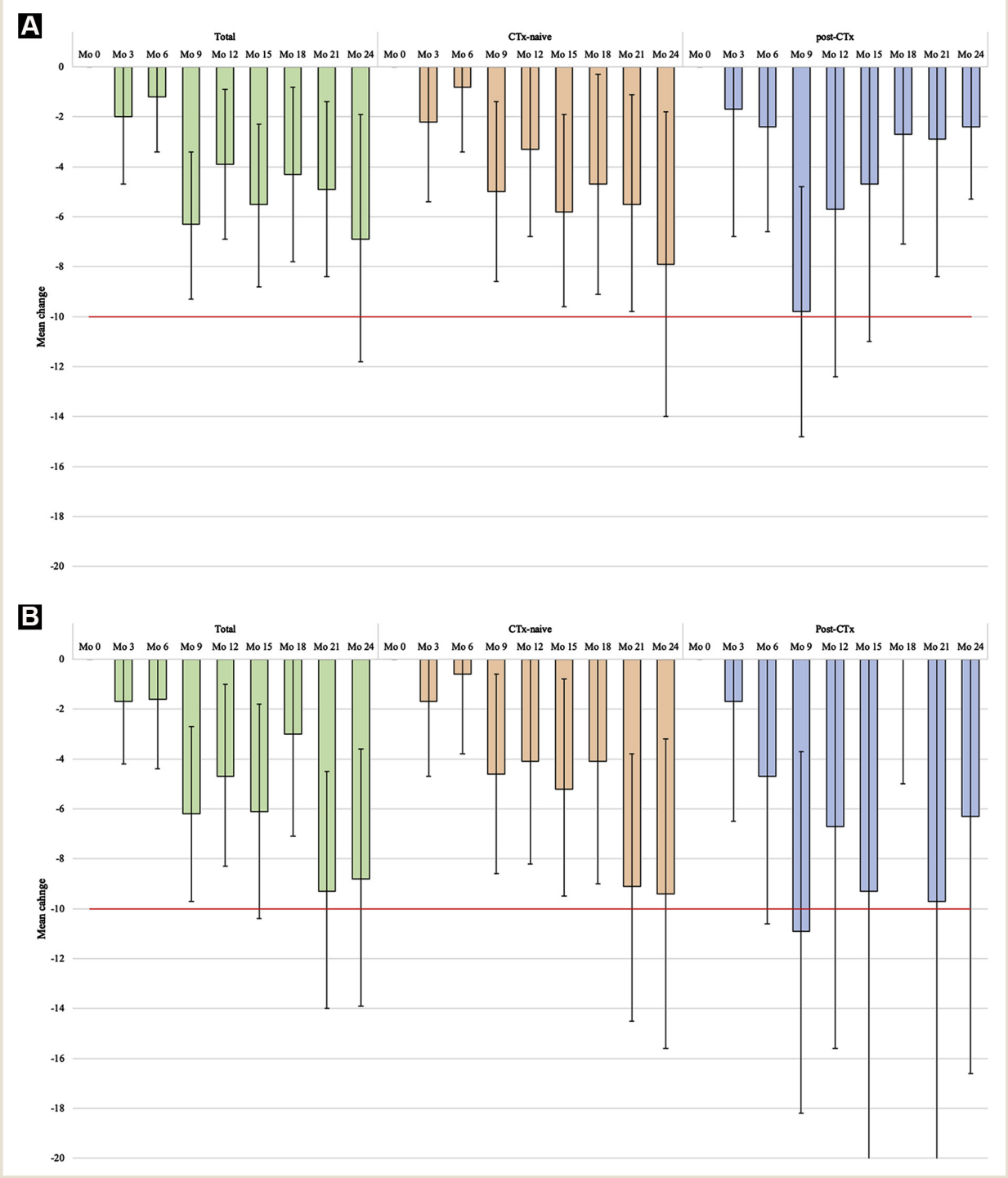
Conclusion

To conclude, in spite of the availability of LPDs, deterioration was seen in almost all domains of HRQoL with the domains role and physical functioning especially prone to deterioration. Therefore, specific attention during follow-up is needed in order to maintain HRQoL as long as possible by timely starting supportive care management. Incorporating individual PRO assessment in daily clinical practice can possibly aid physicians in treatment decisions, monitoring treatment effects and tolerability, and improving symptom control.

Clinical Practice Points

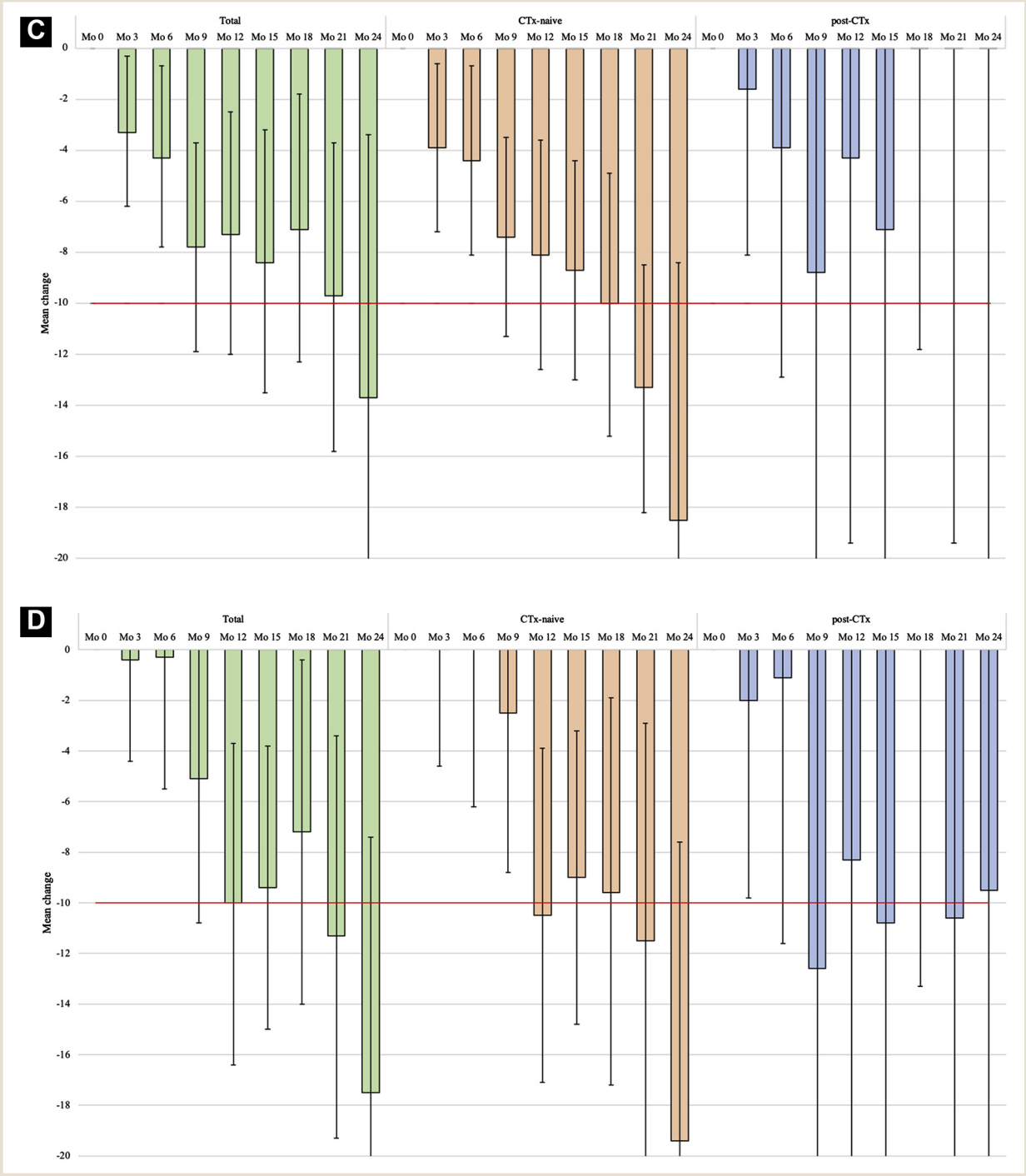
- Patients with mCRPC experience a decline in HRQoL over time. Several drugs, registered for mCRPC based on a survival benefit, also show a delay in HRQoL deterioration and pain progression. However, there is a paucity of data on HRQoL in a real-world population with mCRPC treated with these new drugs.

Figure 3 Changes in HRQoL Over Time per Disease State. A, Mean Changes of EQ-VAS (Generic HRQoL). B, Mean Changes of Global Health Status (Cancer-specific HRQoL). C, Mean Changes of Physical Functioning (Cancer-specific HRQoL). D, Mean Changes of Role Functioning (Cancer-specific HRQoL). E, Mean Changes of Emotional Functioning (Cancer-specific HRQoL). F, Mean Changes of Cognitive Functioning (Cancer-specific HRQoL). G, Mean Changes of Social Functioning (Cancer-specific HRQoL). Mean Changes From Inclusion. Error Bars Represent 95% Confidence Interval and Red Line Represents MID



Abbreviations: CTx-naive = No or no prior docetaxel chemotherapy at inclusion; post-CTx = current or post-docetaxel chemotherapy at inclusion; HRQoL = health-related quality of life; MID = minimally important difference; VAS = visual analog scale.

Figure 3 continued



- We have shown that patients experienced most problems in role (ie, patient's ability to perform daily activities, leisure time, and/or work) and physical functioning with pain, fatigue, and insomnia. Although 80% of our real-world population was treated with new drugs, HRQoL deteriorated over time, mainly on role and physical functioning.
- These results show the changes in HRQoL during mCRPC and highlight specific domains prone to deterioration. The start of

Figure 3 continued

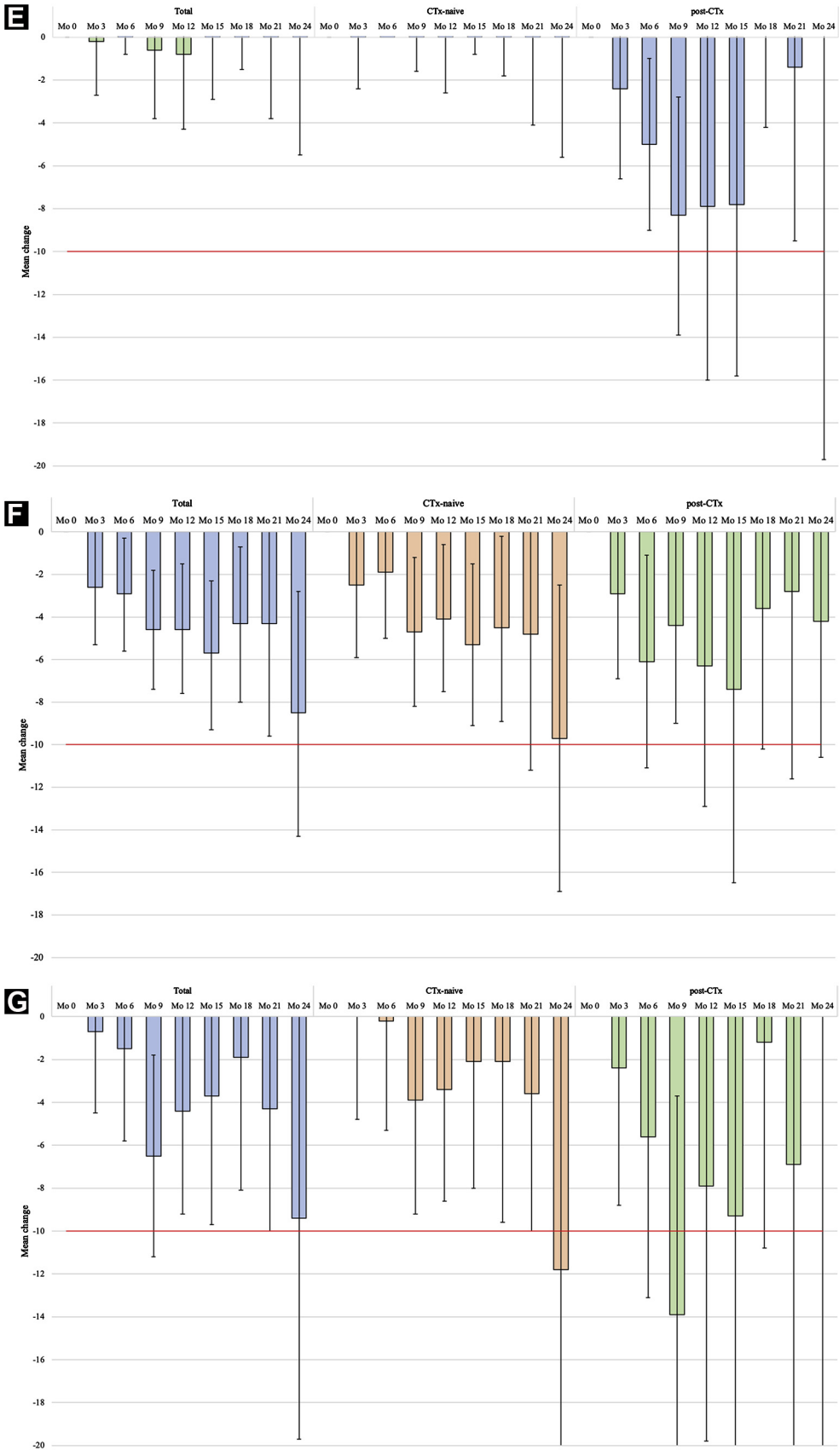


Table 2 Proportion of Patients With a Clinically Relevant Deterioration in HRQoL at Month 6 and Month 12

		Month 6	Month 12	*P* Value
Generic HRQoL (EQ-5D)	EQ VAS	31/115 (27.0)	31/95 (32.6)	.281
Cancer-specific HRQoL (EORTC QLQ-C30)	Global health status	27/120 (22.5)	32/96 (33.3)	.023
	Physical functioning	38/115 (33.0)	37/90 (41.1)	.170
	Role functioning	36/117 (30.8)	43/93 (46.2)	.009
	Emotional functioning	15/119 (12.6)	19/95 (20.0)	.092
	Cognitive functioning	37/119 (31.1)	33/95 (34.7)	.664
	Social functioning	28/119 (23.5)	33/95 (34.7)	.015
	Fatigue	53/116 (45.7)	50/94 (53.2)	.064
	Nausea/vomiting	15/119 (12.6)	19/95 (20.0)	.359
	Pain	26/119 (21.8)	34/95 (35.8)	.002
	Dyspnea	26/116 (22.4)	16/93 (17.2)	.267
	Insomnia	16/116 (13.8)	20/94 (21.3)	.118
	Appetite loss	24/118 (20.3)	26/93 (28.0)	.286
	Constipation	17/118 (14.4)	17/94 (18.1)	.664
	Diarrhea	20/117 (17.1)	24/95 (25.3)	.152
	Financial difficulties	8/118 (6.8)	6/95 (6.3)	.688
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	Sexual activity	14/117 (12.0)	16/93 (17.2)	.180
	Urinary symptoms	21/115 (18.3)	22/94 (23.4)	.332
	Bowel symptoms	11/93 (11.8)	10/71 (14.1)	.508
	Hormonal therapy related symptoms	19/118 (16.1)	24/94 (25.5)	.052
Pain (BPI-SF)	Pain severity	9/75 (12.0)	13/65 (20.0)	.039
	Worst pain	15/76 (19.7)	21/65 (32.3)	.003
	Average pain	10/74 (13.5)	18/63 (28.6)	<.001
	Least pain	9/73 (12.3)	14/64 (21.9)	.118
	Current pain	9/75 (12.0)	9/63 (14.3)	.289
	Pain	7/61 (11.5)	14/51 (27.5)	.004

Data are presented as n/N (%) for total population (N = 151).
P values calculated for differences percentage of patients with MID at month 6 and month 12.
Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; CTx-naive = no or no prior docetaxel chemotherapy at inclusion; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PR25 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module; HRQOL = health-related quality of life; MID = minimal important difference; post-CTx = current or post-docetaxel chemotherapy at inclusion; VAS = visual analog scale.

best supportive care targeting these specific domains should be thought of in order to maintain HRQoL as long as possible.

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Disclosure

W. Gerritsen and C. Uyl-de Groot had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 3 Time to Clinical Relevant Deterioration in Months of HRQoL for Total Population

		No. Events, %	Time to MID, mos
Generic HRQoL (EQ-5D)	EQ VAS	59.6	10.8 (6-NR)
Cancer-specific HRQoL (EORTC QLQ-C30)	Global health status	54.3	14.7 (7-26)
	Physical functioning	58.9	13.1 (6-26)
	Role functioning	60.3	12.2 (4-28)
	Emotional functioning	33.8	26.6 (10-NR)
	Cognitive functioning	53.6	12.2 (6-28)
	Social functioning	55.6	12.8 (7-NR)
	Fatigue	66.2	8.2 (4-20)
	Nausea/vomiting	47.0	19.0 (9-NR)
	Pain	56.3	15.3 (6-26)
	Dyspnea	43.0	22.6 (7-NR)
	Insomnia	41.1	22.6 (9-NR)
	Appetite loss	48.3	17.0 (9-NR)
	Constipation	38.4	24.5 (10-NR)
	Diarrhea	36.4	NR (9-NR)
	Financial difficulties	17.9	NR (26-NR)
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	Sexual activity	13.9	NR (NR-NR)
	Sexual functioning	2.0	NR (NR-NR)
	Urinary symptoms	26.5	NR (15-NR)
	Bowel symptoms	17.2	NR (26-NR)
	Incontinence aid	5.3	NR (NR-NR)
	Hormonal therapy related symptoms	27.8	26.3 (13-NR)
Pain (BPI-SF)[a]	Pain severity	34.2	NR (10-NR)
	Worst pain	46.8	15.9 (7-NR)
	Average pain	36.9	NR (10-NR)
	Least pain	38.7	NR (10-NR)
	Current pain	32.4	NR (10-NR)
	Pain interference	31.5	NR (13-NR)

Data are presented as percentages for number of events (ie, number of patients with MID) and median (IQR) for time to first MID in total population (N = 151).
Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; CTx-naive = no or no prior docetaxel chemotherapy at inclusion; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PR25 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module; HRQoL = health-related quality of life; IQR = interquartile range; MID = minimal important differences; NR = not reached; post-CTx = current or post-docetaxel chemotherapy at inclusion; VAS = visual analog scale.
[a]Only patients with BPI-SF measurement at inclusion (N = 111).

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Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2019.11.015.

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Supplemental Data

Supplemental Table 1 Overview of Used Questionnaires and MID

	No. Items	No. Items Needed[a]	Scale	MID
EQ-5D[28,29]	–		–	–
EQ VAS	1	1	0-100	7-11
EQ-5D index value	5	5	−0.594 to 1	–
EORTC QLQ-C30[29,30]				
Physical functioning[b]	5	3	0-100	10
Role functioning[b]	2	1	0-100	10
Emotional functioning[b]	4	2	0-100	10
Cognitive functioning[b]	2	1	0-100	10
Social functioning[b]	2	1	0-100	10
Fatigue[c]	3	2	0-100	10
Nausea/vomiting[c]	2	1	0-100	10
Pain[c]	2	1	0-100	10
Dyspnea[c]	1	1	0-100	10
Insomnia[c]	1	1	0-100	10
Appetite loss[c]	1	1	0-100	10
Constipation[c]	1	1	0-100	10
Diarrhea[c]	1	1	0-100	10
Financial difficulties[c]	1	1	0-100	10
EORTC QLQ-PR25[29]				
Sexual activity[b]	2	1	0-100	10
Sexual functioning[b]	4	2	0-100	10
Urinary symptoms[c]	8	4	0-100	10
Bowel symptoms[c]	4	2	0-100	10
Hormonal therapy-related symptoms[c]	6	3	0-100	10
Use of incontinence aid[c]	1	1	0-100	10
BPI-SF[27,29]				
Pain severity	4	4	0-10	≥30% and ≥ 2 points from baseline
Worst pain	1	1	0-10	≥30% and ≥ 2 points from baseline
Least pain	1	1	0-10	≥30% and ≥ 2 points from baseline
Average pain	1	1	0-10	≥30% and ≥ 2 points from baseline
Current pain	1	1	0-10	≥30% and ≥ 2 points from baseline
Pain interference	7	4	0-10	≥50% of baseline standard deviation and ≥2 points

Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PR25 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module; MID = minimally important difference; VAS = visual analog scale.
[a]The number of items per domain needed to be completed to adequately calculate the score per domain.
[b]Functional scales (high scores indicate high level of functioning).
[c]Symptom scales (high scores indicate high symptom burden).

Supplemental Table 2 Compliance Rate With HRQoL Questionnaires

Months After Inclusion	Total	EQ-5D	EORTC QLQ-C30	EORTC QLQ-PR25	BPI-SF[a]
0	151	150 (99)	146 (97)	145 (96)	111 (74)
3	136	133 (98)	134 (99)	—	107 (79)
6	124	122 (98)	123 (99)	120 (97)	99 (80)
9	119	118 (99)	118 (99)	—	103 (87)
12	101	98 (97)	98 (97)	96 (95)	85 (84)
15	83	81 (98)	82 (99)	—	71 (86)
18	70	70 (100)	70 (100)	66 (94)	57 (81)
21	55	55 (100)	55 (100)	—	50 (91)
24	39	39 (100)	39 (100)	38 (97)	34 (87)

Compliance rate = the number of patients completing at least one question divided by the total number of available patients per time point (ie, alive and still on study).
All data are presented as n (%).
Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PR25 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module; HRQoL = health-related quality of life.
[a]BPI-SF was added 1 year after study start through protocol amendment: 27% of patients was enrolled before protocol amendment.

Supplemental Table 3 Representativeness of PRO-CAPRI Population Based on Baseline Characteristics

	PRO-CAPRI, N = 151	CAPRI, N = 3616	*P* Value
Age, y			
Median (range)	72 (54-94)	75 (46-99)	.002
≥75 y, %	41	52	.006
ECOG performance score, %			.078
0	30	18	
1	21	18	
>1	3	5	
Unknown	46	60	
Gleason score, %			.602
≤7	34	34	
8-10	56	51	
No histology	3	3	
Metastasis biopsy	1	1	
Unknown	6	10	
Charlson comorbidity index, %			.211
6	70	62	
7-8	26	32	
9-10	4	5	
>10	1	2	
Unknown	0	0	
Disease state, %			
N1/N0/Nx	5/46/49	7/28/65	.020
M1/M0/Mx (bone)	6/62/33	9/53/39	.144
M1/M0/Mx (visceral)	14/3/83	16/4/81	1.000
Period from castration to mCRPC, mos			.986
Median (IQR)	15.1 (9-28)	15.1 (8-29)	
Unknown, %	0	<1	
Hemoglobin, mmol/L			.014
Median (IQR)	8.3 (7.6-8.8)	8.0 (7.3-8.6)	
Unknown, %	30	34	
Lactate dehydrogenase, U/L			.058
Median (IQR)	212 (184-249)	223 (188-294)	
Unknown, %	47	59	
Alkaline phosphatase, U/L			.041
Median (IQR)	97 (75-150)	106 (78-192)	
Unknown, %	30	37	
Prostate-specific antigen, μg/L			.247
Median (IQR)	15.0 (5-44)	16.7 (6-62)	
Unknown, %	1	3	
Treatment during follow-up, %			<.001
None	1	12	
No LPD	5	25	
LPD	94	63	
Docetaxel	66	43	<.001
Cabazitaxel	25	13	<.001
Abiraterone	38	32	.106
Enzalutamide	72	30	<.001
Radium-223	17	8	<.001

All baseline measurements were included if they were measured in the period of 3 months prior or 3 months after mCRPC diagnosis.
Tested for statistical significance between the PRO-CAPRI subgroup and the rest of CAPRI-population (N = 3465).
Abbreviations: ADT = Androgen deprivation therapy; CTx-naive = no or no prior docetaxel chemotherapy at inclusion; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; LPD = life prolonging drug (either docetaxel, cabazitaxel, abiraterone, enzalutamide or radium-223); mCRPC = metastastic castration-resistant prostate cancer; post-CTx = current or post-docetaxel chemotherapy at inclusion.

Supplemental Table 4 Assessment of HRQoL With Subgroups per Disease State at Inclusion

		Total N = 151	CTx-naive N = 112	Post-CTx N = 39	*P* Value
Generic HRQoL (EQ-5D)	Mobility, %[a]	48	47	49	.775
	Self-care, %[a]	15	16	10	.404
	Usual activities, %[a]	43	43	44	.774
	Pain/discomfort, %[a]	55	46	51	.698
	Anxiety/depression, %[a]	27	28	23	.630
	EQ VAS	73.2 (17)	72.9 (17)	73.9 (16)	.848
	EQ-5D index value	0.82 (0.17)	0.82 (0.16)	0.82 (0.16)	.796
Cancer-specific HRQoL (EORTC QLQ-C30)	Global health status	75.9 (17)	75.5 (18)	76.9 (12)	.954
	Physical functioning	76.1 (23)	75.8 (24)	76.8 (23)	.972
	Role functioning	69.3 (32)	68.8 (32)	71.0 (30)	.853
	Emotional functioning	82.8 (18)	80.9 (19)	88.4 (14)	.022
	Cognitive functioning	85.4 (18)	84.7 (18)	87.5 (17)	.455
	Social functioning	80.5 (27)	78.9 (29)	85.2 (21)	.405
	Fatigue	32.3 (25)	32.6 (26)	31.6 (21)	.963
	Nausea/vomiting	5.5 (15)	5.9 (17)	4.2 (10)	.770
	Pain	23.4 (25)	25.2 (26)	18.1 (20)	.243
	Dyspnea	18.9 (27)	18.2 (26)	21.3 (28)	.516
	Insomnia	22.8 (28)	24.3 (28)	18.5 (27)	.235
	Appetite loss	11.0 (25)	10.4 (24)	13.0 (27)	.490
	Constipation	12.8 (22)	14.8 (24)	6.5 (13)	.083
	Diarrhea	10.0 (23)	9.4 (23)	12.0 (23)	.260
	Financial difficulties	4.6 (14)	5.2 (14)	2.8 (12)	.203
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	Sexual activity	6.7 (16)	8.5 (18)	1.4 (5)	.016
	Sexual functioning[b]	55.2 (22)	58.3 (18)	45.0 (33)	.246
	Urinary symptoms	21.1 (17)	22.7 (18)	16.4 (14)	.057
	Bowel symptoms	7.4 (14)	8.9 (16)	3.7 (8)	.038
	Incontinence aid[c]	13.3 (29)	14.7 (23)	9.1 (22)	.407
	Hormonal therapy related symptoms	16.6 (13)	16.9 (14)	15.8 (10)	.980
Pain (BPI-SF)	Pain severity				
	Worst pain	2.22 (2)	2.21 (3)	2.24 (2)	.530
	Average pain	1.82 (2)	1.89 (2)	1.58 (2)	.960
	Least pain	1.11 (2)	1.12 (2)	1.08 (2)	.858
	Current pain	1.52 (2)	1.67 (2)	0.96 (1)	.407
	Pain interference	1.73 (2)	1.82 (2)	1.42 (2)	.492

All data are presented as mean (SD) unless listed otherwise.
Percentages can exceed 100% owing to rounding.
P values calculated for differences in time to first MID between CTx-naive and post-CTx patients.
Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; CTx-naive = no or no prior docetaxel chemotherapy at inclusion; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PR25 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module; HRQOL = health-related quality of life; post-CTx = current or post-docetaxel chemotherapy at inclusion; SD = standard deviation; VAS = visual analog scale.
[a]Percentage of patients reporting any problems (level 2 to 5).
[b]Mean scores of patients reporting any sexual activity.
[c]Mean scores of patients reporting any use of incontinence aid.

Supplemental Table 5a **Proportion of CTx-naive Patients With a Clinically Relevant Deterioration and Time to Deterioration in HRQoL at Month 6 and Month 12**

		Month 6	Month 12	*P* Value
Generic HRQoL (EQ-5D)	EQ VAS	22/85 (25.9)	23/73 (31.5)	.556
Cancer-specific HRQoL (EORTC QLQ-C30)	Global health status	16/90 (17.8)	24/75 (32.0)	.027
	Physical functioning	23/85 (27.1)	30/69 (43.5)	.019
	Role functioning	24/88 (27.3)	33/73 (45.2)	.017
	Emotional functioning	8/89 (9.0)	13/74 (17.6)	.096
	Cognitive functioning	27/89 (30.3)	27/74 (36.5)	.302
	Social functioning	17/89 (19.1)	26/74 (35.1)	.007
	Fatigue	38/86 (44.2)	39/73 (53.4)	.096
	Nausea/vomiting	12/89 (13.5)	13/74 (17.6)	.791
	Pain	18/89 (20.2)	25/74 (33.8)	.019
	Dyspnea	20/86 (23.3)	14/72 (19.4)	.549
	Insomnia	13/86 (15.1)	16/73 (21.9)	.227
	Appetite loss	19/88 (21.6)	21/72 (29.2)	.302
	Constipation	14/88 (15.9)	15/73 (20.5)	.648
	Diarrhea	15/87 (17.2)	20/74 (27.0)	.238
	Financial difficulties	6/88 (6.8)	6/74 (8.1)	.688
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	Sexual activity	12/86 (14.0)	16/71 (22.5)	.070
	Urinary symptoms	16/83 (19.3)	18/71 (25.4)	.424
	Bowel symptoms	10/66 (15.2)	8/52 (15.4)	.688
	Hormonal therapy related symptoms	11/87 (12.6)	18/72 (25.0)	.035
Pain (BPI-SF)	Pain severity	6/56 (10.7)	9/52 (17.3)	.219
	Worst pain	10/57 (17.5)	15/52 (28.8)	.039
	Average pain	7/56 (12.5)	12/51 (23.5)	.016
	Least pain	7/54 (13.0)	11/51 (21.6)	.267
	Current pain	6/57 (10.5)	5/50 (10.0)	1.000
	Pain interference	5/46 (10.9)	11/42 (26.2)	.008

Data are presented as n/N (%) for total population (N = 112).
P values calculated for differences between proportion of patients with MID at month 6 and month 12.
Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; CTx-naive = no or no prior docetaxel chemotherapy at inclusion; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PR25 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module; HRQoL = health-related quality of life; MID = minimal important difference; VAS = visual analog scale.

Supplemental Table 5b **Proportion of Post-CTx Patients With a Clinically Relevant Deterioration and Time to Deterioration in HRQoL at Month 6 and Month 12**

		Month 6	Month 12	*P* Value
Generic HRQoL (EQ-5D)	EQ VAS	9/30 (30.0)	8/22 (36.4)	.375
Cancer-specific HRQoL (EORTC QLQ-C30)	Global health status	11/30 (36.7)	8/21 (38.1)	1.000
	Physical functioning	15/30 (50.0)	7/21 (33.3)	.453
	Role functioning	12/29 (41.4)	10/20 (50.0)	.453
	Emotional functioning	7/30 (23.3)	6/21 (28.6)	.688
	Cognitive functioning	10/30 (33.3)	6/21 (28.6)	.688
	Social functioning	11/30 (36.7)	7/21 (33.3)	1.000
	Fatigue	15/30 (50.0)	11/21 (52.4)	.688
	Nausea/vomiting	3/30 (10.0)	6/21 (28.6)	.375
	Pain	8/30 (26.7)	9/21 (42.9)	.063
	Dyspnea	6/30 (20.0)	2/21 (9.5)	.500
	Insomnia	3/30 (10.0)	4/21 (19.0)	.625
	Appetite loss	5/30 (16.7)	5/21 (23.8)	1.000
	Constipation	3/30 (10.0)	2/21 (9.5)	1.000
	Diarrhea	5/30 (16.7)	4/31 (19.0)	.688
	Financial difficulties	2/30 (6.7)	0/21 (0.0)	1.000
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	Sexual activity	2/31 (6.5)	0/22 (0.0)	1.000
	Urinary symptoms	5/32 (15.6)	4/23 (17.4)	1.000
	Bowel symptoms	1/27 (3.7)	2/19 (10.5)	1.000
	Hormonal therapy related symptoms	8/31 (25.8)	6/22 (27.3)	1.000
Pain (BPI-SF)	Pain severity	3/19 (15.8)	4/13 (30.8)	.250
	Worst pain	5/19 (26.3)	6/13 (46.2)	.125
	Average pain	3/18 (16.7)	6/12 (50.0)	.063
	Least pain	2/19 (10.5)	3/13 (23.1)	.500
	Current pain	3/18 (16.7)	4/13 (30.8)	.250
	Pain interference	2/15 (13.3)	3/9 (33.3)	1.000

Data are presented as n/N (%) for CTx-naive population (N = 39).
P values calculated for differences between proportion of patients with MID at month 6 and month 12.
Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PR25 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module; HRQoL = health-related quality of life; MID = minimal important difference; post-CTx = current or post-docetaxel chemotherapy at inclusion.

Supplemental Table 6 Time to Clinical Relevant Deterioration in Months of HRQoL per Disease State

		CTx-naive N = 112		Post-CTx N = 39		*P* Value
		No. Events, %	Time to MID, mos	No. Events, %	Time to MID, mos	
Generic HRQoL (EQ-5D)	EQ VAS	56.3	12.3 (6-NR)	69.2	10.0 (4-21)	.299
Cancer-specific HRQoL (EORTC QLQ-C30)	Global health status	55.4	15.1 (7-26)	51.3	13.4 (7-NR)	.978
	Physical functioning	58.9	14.7 (6-26)	59.0	6.8 (4-NR)	.490
	Rolefunctioning	63.4	12.3 (5-22)	51.3	12.1 (4-NR)	.521
	Emotional functioning	31.3	26.6 (12-NR)	41.0	NR (6-NR)	.167
	Cognitive functioning	52.7	12.6 (6-28)	56.4	10.0 (6-NR)	.847
	Social functioning	53.6	14.2 (9-NR)	61.5	9.5 (6-NR)	.276
	Fatigue	64.3	8.6 (4-23)	71.8	6.5 (4-13)	.381
	Nausea/vomiting	44.6	19.9 (9-NR)	53.8	15.3 (9-25)	.279
	Pain	52.7	15.8 (6-NR)	66.7	10.2 (6-24)	.200
	Dyspnea	42.9	22.6 (8-NR)	43.6	20.1 (7-NR)	.805
	Insomnia	43.8	21.8 (9-NR)	33.3	NR (10-NR)	.356
	Appetite loss	50.9	16.5 (8-NR)	41.0	NR (9-NR)	.459
	Constipation	39.3	24.5 (9-NR)	35.9	24.1 (12-NR)	.672
	Diarrhea	35.7	NR (10-NR)	38.5	21.7 (8-NR)	.696
	Financial difficulties	20.5	NR (24-NR)	10.3	NR (NR-NR)	.205
Prostate cancer-specific HRQoL (EORTC QLQ-PR25)	Sexual activity	17.0	NR (NR-NR)	5.1	NR (NR-NR)	.092
	Sexual functioning	2.7	NR (NR-NR)	0	NR (NR-NR)	.353
	Urinary symptoms	28.6	25.6 (15-NR)	20.5	NR (19-NR)	.571
	Bowel symptoms	18.8	NR (25-NR)	12.8	NR (NR-NR)	.783
	Incontinence aid	5.4	NR (NR-NR)	5.1	NR (NR-NR)	.941
	Hormonal therapy related symptoms	26.8	26.3 (16-NR)	30.8	NR (12-NR)	.242
Pain (BPI-SF)[a]	Pain severity	32.6	NR (11-NR)	40.0	NR (9-NR)	.408
	Worst pain	41.9	24.5 (8-NR)	64.0	9.9 (7-16)	.042
	Average pain	32.6	NR (11-NR)	52.0	12.5 (10-NR)	.072
	Least pain	39.5	NR (10-NR)	36.0	NR (11-NR)	.833
	Current pain	30.2	NR (11-NR)	40.0	NR (9-NR)	.349
	Pain interference	31.4	NR (15-NR)	32.0	NR (10-NR)	.633

Data are presented as percentages for number of events (ie, number of patients with MID) and median (IQR) for time to first MID.
P values calculated for differences in time to first MID between CTx-naive and post-CTx patients.
Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; CTx-naive = no or no prior docetaxel chemotherapy at inclusion; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ-PR25 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Prostate Cancer Module; HRQoL = health-related quality of life; IQR = interquartile range; MID = minimal important differences; NR = not reached; post-CTx = current or post-docetaxel chemotherapy at inclusion; VAS = visual analog scale.
[a]Only patients with BPI-SF measurement at inclusion (CTx-naive, N = 86 and post-CTx, N = 25).