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# Post Hoc Health-Related Quality of Life Analysis According to Response Among Patients with Prostate Cancer in the PROSELICA and FIRSTANA Studies

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

**Key Words.** Prostate • Metastatic castration-resistant prostate cancer • Cabazitaxel • Docetaxel • Pain • Health-related quality of life

## Abstract

***Background.*** The phase III PROSELICA (NCT01308580) and FIRSTANA (NCT01308567) trials investigated taxane chemotherapy among men with postdocetaxel metastatic, castration-resistant prostate cancer (mCRPC) or chemotherapy-naïve mCRPC, respectively. We present a post hoc analysis of patient-reported health-related quality of life (HRQL) among patients with or without a clinical (pain, tumor, or prostate-specific antigen [PSA]) response.

***Materials and Methods.*** PROSELICA and FIRSTANA HRQL and pain data were collected and analyzed using protocol-defined Functional Assessment of Cancer Therapy-Prostate (FACT-P) and McGill-Melzack (Present Pain Intensity scale) questionnaires. Outcomes included definitive FACT-P Total Score (TS) improvements and longitudinal assessment of FACT-P TS.

***Results.*** In PROSELICA and FIRSTANA, the proportion of patients receiving taxane chemotherapy with a definitive FACT-P TS improvement was significantly higher among patients with versus without a pain or PSA response (pain: PROSELICA: 67% vs. 33.5%; $p < .001$; FIRSTANA: 75.2% vs. 45.8%; $p < .001$; PSA: PROSELICA: 50.3% vs. 34.2%; $p < .001$; FIRSTANA: 49.8% vs. 38.9%; $p = .001$). In PROSELICA, the proportion of patients receiving taxane chemotherapy with a definitive FACT-P TS improvement was significantly higher among patients with versus without a tumor response; the proportion was numerically higher in FIRSTANA (PROSELICA: 54.4% vs. 36.7%; $p = .001$; FIRSTANA: 50.6% vs. 45.3%). FACT-P TS was significantly improved or maintained for the majority of treatment cycles analyzed.

***Conclusion.*** In PROSELICA and FIRSTANA, HRQL improvements were significantly higher among patients with a pain, tumor, or PSA response versus those without, with the exception of patients with a tumor response in FIRSTANA.

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**Implications for Practice:** Using data from the FIRSTANA and PROSELICA phase III clinical trials, this study demonstrated that patients with metastatic, castration-resistant prostate cancer (mCRPC) receiving docetaxel or cabazitaxel who exhibited a response (pain, tumor, prostate-specific antigen), often experienced significantly greater improvements in health-related quality of life (HRQL) compared with patients without a response. For patients with a pain response, significant HRQL improvements occurred early and were maintained. This study provides further insight into the impact of taxane chemotherapy on the HRQL of patients with mCRPC and allows for a better understanding of the relationship between treatment, response, and HRQL, supporting therapeutic decision making.

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## Introduction

Prostate cancer often presents as early-stage disease, which is well managed with expectant management, radiotherapy, and surgery [1]. For some patients, their disease will advance and metastasize, whereas others may present with metastatic disease at diagnosis; prognosis and treatment for these patients are more challenging. There are a range of treatment options available for patients with advanced disease. Docetaxel, cabazitaxel, abiraterone, enzalutamide, olaparib, rucaparib, radium-223, denosumab, zoledronic acid, and sipuleucel-T are all approved for the treatment of metastatic, castration-resistant prostate cancer (mCRPC) following successful phase III trials [2–11].

In the TAX-327 trial, docetaxel chemotherapy demonstrated a significant improvement in overall survival (OS) compared with mitoxantrone plus prednisone in patients with mCRPC [3]. Cabazitaxel was developed to overcome resistance to docetaxel and is approved for the treatment of patients with mCRPC previously treated with docetaxel, after demonstrating OS benefits over mitoxantrone in the phase III TROPIC trial [12]. More recently, the phase III PROSELICA trial demonstrated cabazitaxel 20 mg/m$^2$ (C20) maintained ≥50% of the OS benefit of cabazitaxel 25 mg/m$^2$ (C25) versus mitoxantrone, reported in TROPIC, in patients with mCRPC previously treated with docetaxel [13]. In the phase III FIRSTANA trial, no significant difference in OS was reported for patients receiving first-line C20 or C25 versus docetaxel 75 mg/m$^2$ (D75) for chemotherapy-naïve mCRPC [14].

Typically, response to prostate cancer treatment is assessed by radiological and prostate-specific antigen (PSA) assessment. Patient-reported outcomes (PROs), obtained through self-reported patient questionnaires, provide a more patient-centric view of response to treatment (i.e., how a patient feels and functions) as well as the associated health-related quality of life (HRQL). The publishing of PRO and HRQL data continues to have an increasing impact on routine clinical practice. The value of including PRO endpoints, alongside clinical response endpoints, in clinical trials is reflected by its inclusion in regulatory guidelines [15].

Bone metastases are a significant and common problem in patients with mCRPC; up to 90% of patients with mCRPC have radiographically detectable bone metastases [16]. The extent of bone metastases has been shown to associate with survival and often results in a variety of skeletal-related problems including pain, which can negatively impact a patient's HRQL [17–19]. In patients receiving treatment for mCRPC, PROs have an important role in monitoring HRQL and pain responses, which ultimately may impact treatment outcomes and survival [20].

The current study presents the results of a post hoc analysis describing the HRQL of patients enrolled in the PROSELICA and FIRSTANA phase III trials. Specifically, we investigate Functional Assessment of Cancer Therapy-Prostate (FACT-P) Total Score (TS) improvements and change from baseline in FACT-P TS over the study duration in patients with or without a pain, tumor, or PSA response.

## Materials and Methods

### Study Population and Design

PROSELICA and FIRSTANA trial designs are summarized in Figure 1. The phase III PROSELICA study enrolled patients with mCRPC who had previously received docetaxel [13]. FIRSTANA was a phase III study that enrolled patients with mCRPC who had not previously received chemotherapy [14]. Full study details have been published previously [13, 14]. Written informed consent was provided by all patients and the study was conducted in compliance with the guidelines for Good Clinical Practice.

### Assessment of HRQL and Pain

HRQL assessments were prospectively performed using the FACT-P questionnaire (version 4), a disease-specific instrument that measures the concerns of patients with prostate cancer [21, 22]. The FACT-P scale consists of five subscales: physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate-specific concerns. The FACT-P TS sums all five subscales to give a score in the range of 0–156, in which higher values represent better HRQL. Questionnaires were completed by patients within 3 days prior to the first administration (baseline), after each subsequent cycle (prior to the next infusion), and 30 days after last treatment.

Pain was assessed using the Present Pain Intensity (PPI) scale from the McGill-Melzack questionnaire [23]. Patient-reported pain was collected for seven consecutive days prior to each scheduled cycle start, on day 1 of each treatment cycle and 30 days after last treatment.

### Statistical Analysis

Patients who completed the FACT-P questionnaire at baseline and at least once after baseline were included in the analysis (FACT-P population). Patients who did not complete the FACT-P questionnaire at baseline and at least once after baseline were defined as the non-FACT-P population. The FACT-P TS was evaluable when >80% of the questions were answered. For the individual FACT-P subscales, a score was evaluable when >50% of the questions in the subscale domain were answered [21]. If <50% of the questions were missing in any FACT-P subscale, the subscale score could be imputed by prorated subscale scores using the following formula: prorated subscale score = [sum of question scores] × [number of questions in subscale] ÷ [number of questions answered]. Median PPI and mean analgesic score (AS) were calculated only if five of the seven expected values were available in the patient records.

Definitive improvement or ''maintained or improved'' FACT-P TS data were analyzed among patient subgroups defined by their clinical response to treatment, including those with (responder) and without (nonresponder) a pain, tumor, and PSA response (definitions are summarized in Table 1). A definitive HRQL improvement was defined as a ≥ 7-point improvement from baseline in FACT-P TS, confirmed at two time points that were ≥ 3 weeks apart [22]. ''Maintained or improved'' HRQL was defined as not

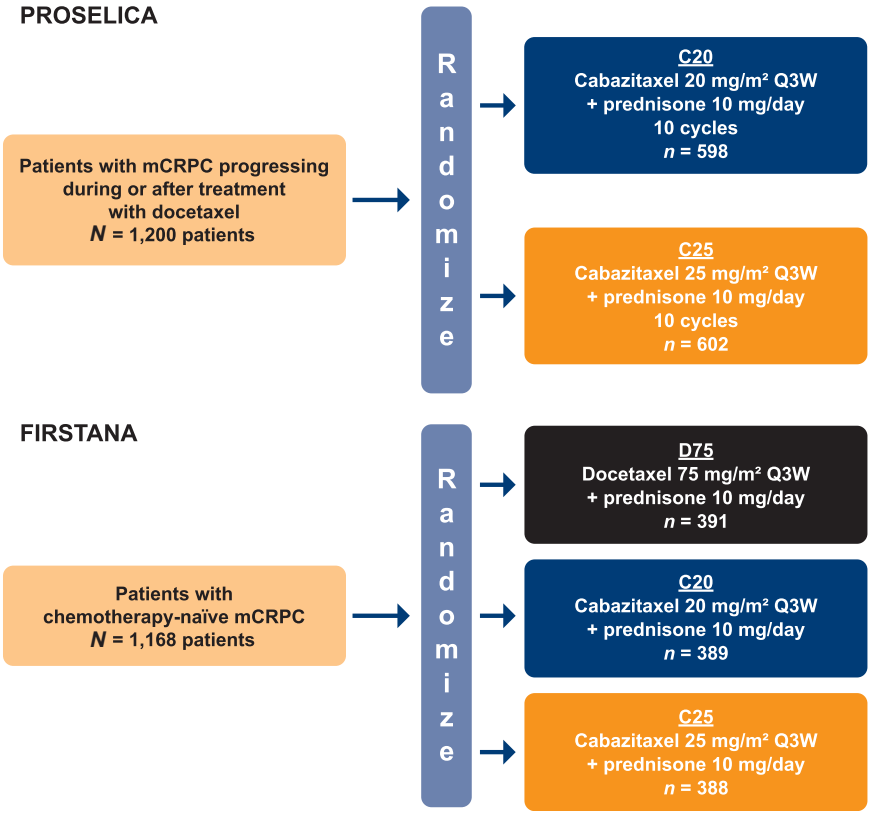


**Figure 1.** PROSELICA and FIRSTANA study designs [13, 14].
Abbreviations: C20, cabazitaxel 20 mg/m$^2$; C25, cabazitaxel 25 mg/m$^2$; D75, docetaxel 75 mg/m$^2$; mCRPC, metastatic castration-resistant prostate cancer; Q3W, every 3 weeks.

meeting the criteria for definitive deterioration; determined as a ≥ 10% decrease from baseline in FACT-P TS, confirmed at two time points that were ≥ 3 weeks apart. Pain responders were defined by a ≥ 2-point improvement from baseline median PPI score with no concomitant increase in AS *or* a reduction of ≥50% in analgesic use from baseline mean AS (only in patients with baseline mean AS ≥10) with no concomitant increase in pain. Tumor responders were defined by measurable disease at baseline and a partial or complete response according to RECIST 1.1 criteria. PSA responders were defined by a PSA >10 ng/dL at baseline and a PSA decline of ≥50% confirmed by a second PSA assessment ≥3 weeks later. Comparisons of definitive FACT-P TS improvements between responders and nonresponders were performed using a Score Test.

Mean change from baseline in FACT-P TS after each treatment cycle is reported; data are presented over 10 and 16 treatment cycles for PROSELICA and FIRSTANA, respectively. For these analyses, a clinically meaningful FACT-P TS improvement was defined as a ≥ 7-point increase in the FACT-P TS mean change from baseline. In PROSELICA, treatment was limited to 10 cycles per protocol. In FIRSTANA, treatment was not limited per protocol but over time analyses were limited to 16 treatment cycles because of data availability. For analyses over the entire on-treatment period, additional cycles in FIRSTANA (up to 42) were also included. Comparisons of "maintained or improved" across treatment groups were performed via unadjusted logistic regression. Nominal *p* values are provided for comparisons.

## Results

### Baseline Characteristics

Results from the PROSELICA and FIRSTANA phase III trials have been reported previously [13, 14]. In PROSELICA, 1,200 patients with mCRPC previously treated with docetaxel were randomized; 598 received C20, and 602 received C25. In FIRSTANA, 1,168 patients with chemotherapy-naïve mCRPC were randomized (1:1:1); 391 received D75, 389 received C20, and 388 received C25. In each study baseline characteristics between treatment arms were well balanced (supplemental online Tables 1 and 2).

In PROSELICA and FIRSTANA, questionnaires were completed at each visit by over 89% and 92% of patients, respectively. In PROSELICA, a total of 557 patients (93.1%) receiving C20 and 543 (90.2%) receiving C25 were eligible for HRQL evaluation; in FIRSTANA 376 (96.2%) receiving D75, 372 (95.6%) receiving C20, and 361 (93.0%) receiving C25 were eligible. Baseline PROs for patients with or without a pain, tumor, or PSA response in the PROSELICA and FIRSTANA studies are presented in supplemental online Tables 3 and 4; mean FACT-P TS at baseline was slightly higher in responder versus nonresponder subgroups.

### HRQL in Patients with a Pain Response

In PROSELICA, 248 patients (41.5%) in the C20 arm and 284 (47.2%) in the C25 arm were evaluable for pain response. The number of patients who experienced a

**Table 1.** Definitions of definitive HRQL improvement, "maintained or improved" HRQL, and pain, tumor, and PSA responders

| Term | Measure | Definition |
|---|---|---|
| HRQL | | |
| Definitive improvement | FACT-P TS | ≥7-point improvement from BL, confirmed at two time points ≥ 3 weeks apart [22] |
| Maintained or improved | FACT-P TS | Did not meet the criteria for definitive deterioration[a] |
| Clinical responder subgroups | | |
| Pain responders | PPI score | Patients with a ≥2-point improvement from BL median PPI score with no concomitant increase in AS *or* a reduction of ≥50% in analgesic use from BL mean AS (only in patients with BL mean AS ≥10) with no concomitant increase in pain |
| Tumor responders | RECIST 1.1 | Patients with measurable disease at BL and a partial or complete response according to RECIST 1.1 criteria, as assessed by the investigator |
| PSA responders | PSA | Patients with PSA >10 ng/dL at BL and a PSA decline of ≥50% confirmed by a second PSA assessment ≥3 weeks later |

[a]≥10% decrease from BL, confirmed at two time points ≥ 3 weeks apart, for FACT-P TS, functional subscales, fatigue and PCS-Pain; ≥1-point deterioration from BL, confirmed at two time points ≥ 3 weeks apart, for PPI.

Abbreviations: AS, analgesic score; BL, baseline; FACT-P TS, Functional Assessment of Cancer Therapy-Prostate Total Score; HRQL, health-related quality of life; PCS-Pain, prostate cancer subscale pain-related score; PPI, Present Pain Intensity; PSA, prostate-specific antigen.

pain response did not differ between the two treatment groups (C20, 86/248; 34.7%; C25, 106/284; 37.3%; $p = .4785$) [13]. The proportion of patients receiving cabazitaxel (C20, C25) with a definitive FACT-P TS improvement was significantly higher among patients with a pain response (67.0%) compared with those without (33.5%, $p < .0001$; Table 2). FACT-P TS was "maintained or improved" in 86.7% and 84.8% of patients with a pain response receiving C20 and C25, respectively (supplemental online Table 5). Among patients with a pain response, a clinically meaningful improvement in FACT-P TS mean change from baseline was observed after cycle 2 (9.7, $n = 80$) and cycle 1 (11.1, $n = 81$) in patients receiving C20 and C25, respectively; improvements were consistently observed after each subsequently analyzed cycle (Fig. 2A) [22]. Among patients without a pain response, there was

**Table 2.** PROSELICA: Definitive Functional Assessment of Cancer Therapy-Prostate Total Score improvements in patients with or without a response

| Treatment arm | Pain | | | | Tumor | | | | PSA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Response[a] *n* (%) | No response *n* (%) | OR (95% CI) | *p* value | Response[b] *n* (%) | No response *n* (%) | OR (95% CI) | *p* value | Response[c] *n* (%) | No response *n* (%) | OR (95% CI) | *p* value |
| C20[d] | 54 (65.1) | 55 (35.3) | 3.42 (1.96–5.97) | <.0001 | 24 (53.3) | 77 (36.5) | 1.99 (1.04–3.81) | .0359 | 84 (54.9) | 115 (32.9) | 2.49 (1.69–3.67) | <.0001 |
| C25[d] | 68 (68.7) | 54 (32.0) | 4.67 (2.74–7.97) | <.0001 | 32 (55.2) | 67 (37.0) | 2.09 (1.15–3.81) | .0146 | 103 (47.0) | 100 (35.8) | 1.59 (1.11–2.28) | .0117 |
| C20 + C25[d] | 122 (67.0) | 109 (33.5) | 4.03 (2.74–5.92) | <.0001 | 56 (54.4) | 144 (36.7) | 2.05 (1.32–3.18) | .0012 | 187 (50.3) | 215 (34.2) | 1.95 (1.50–2.53) | <.0001 |

[a]Patients with a ≥ 2-point improvement from BL median Present Pain Intensity score with no concomitant increase in *AS or* a reduction of ≥50% in analgesic use from BL mean AS (only in patients with BL mean AS ≥10) with no concomitant increase in pain.

[b]Patients with measurable disease at BL and a partial or complete response according to RECIST 1.1 criteria, as assessed by the investigator.

[c]Patients with PSA >10 ng/dL at BL and a PSA decline of ≥50% confirmed by a second PSA assessment ≥3 weeks later.

[d]Calculated from the number of evaluable patients, defined as patients with BL assessment and at least one post-BL assessment.

Abbreviations: AS, analgesic score; BL, baseline; C20, cabazitaxel 20 mg/m$^2$; C25, cabazitaxel 25 mg/m$^2$; CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.

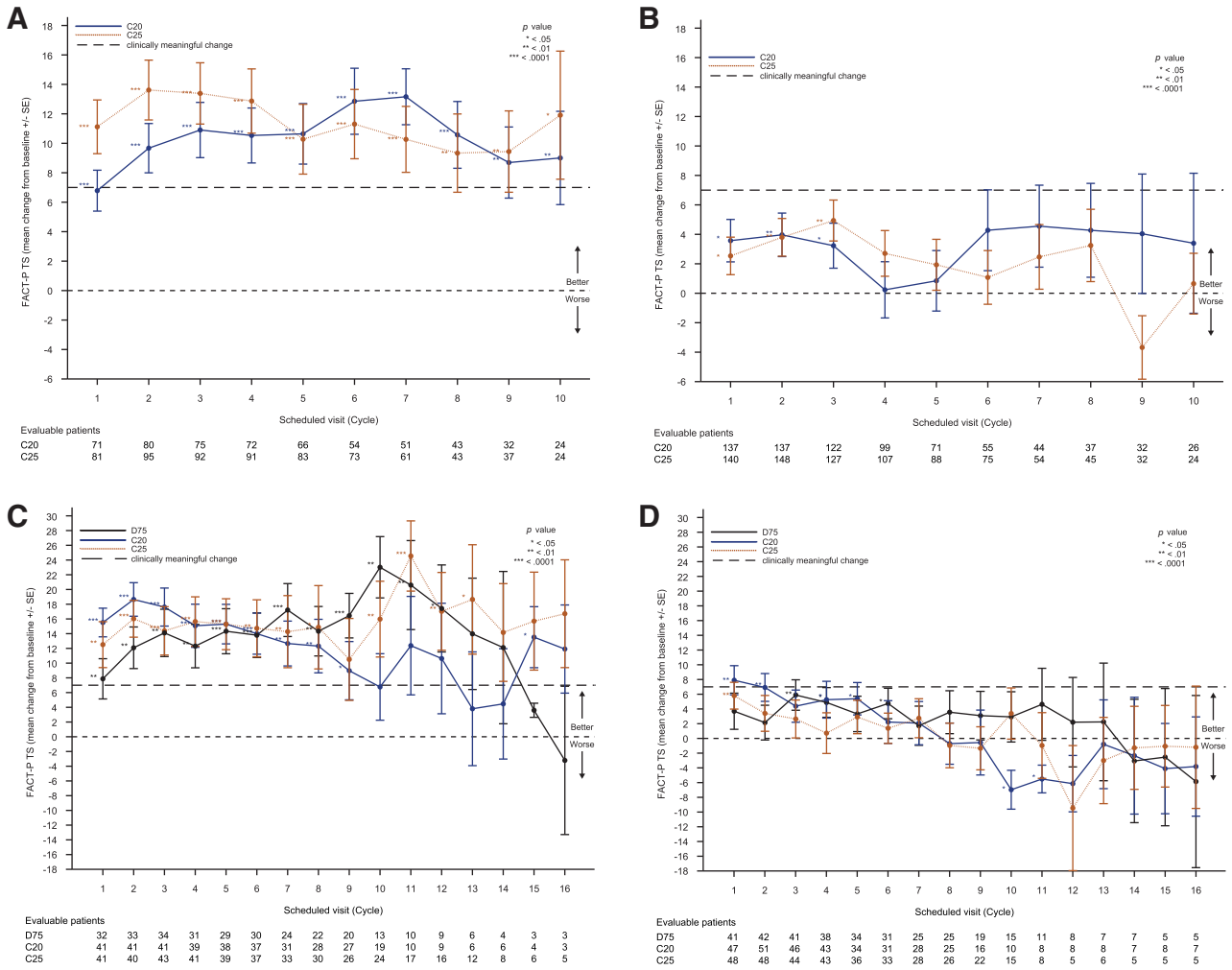


**Figure 2.** FACT-P TS mean change from baseline over time in patients with or without a pain response for PROSELICA **(A)** and **(B)** and FIRSTANA **(C)** and **(D)**. **(A):** PROSELICA: Patients with a pain response. **(B):** PROSELICA: Patients without a pain response. **(C):** FIRSTANA: Patients with a pain response. **(D):** FIRSTANA: Patients without a pain response.
Abbreviations: C20, cabazitaxel 20 mg/m$^2$; C25, cabazitaxel 25 mg/m$^2$; D75, docetaxel 75 mg/m$^2$; FACT-P TS, Functional Assessment of Cancer Therapy-Prostate Total Score

no clinically meaningful improvement in the FACT-P TS mean change from baseline after any treatment cycle in both treatment groups (Fig. 2B).

In FIRSTANA, 82 (21.0%), 99 (25.4%), and 104 (26.8%) patients receiving D75, C20, and C25, respectively, were evaluable for a pain response. The number of patients who experienced a pain response did not differ between the docetaxel and cabazitaxel treatment groups (D75, 35/82; 42.7%; C20, 45/99; 45.5%; $p = .6038$; C25, 45/104; 43.3%; $p = .7374$) [14]. The proportion of patients receiving taxane chemotherapy (D75, C20, C25) with a definitive FACT-P TS improvement was significantly higher among patients with a pain response (75.2%) compared with those without (45.8%, $p < .0001$; Table 3). FACT-P TS was "maintained or improved" in 85.3%, 88.4%, and 84.1% of patients with a pain response receiving D75, C20, and C25, respectively (supplemental online Table 6). Among patients with a pain response, a clinically meaningful improvement in the FACT-P TS mean change from baseline was observed after cycle 1 (D75 7.9, $n = 32$; C20 15.5, $n = 41$; C25 12.5, $n = 41$); this improvement was consistently observed at each subsequent cycle until cycle 15, 9, and > 16 in the D75, C20, and C25 treatment groups, respectively (Fig. 2C). Among patients without a pain response, a clinically meaningful improvement in the FACT-P TS mean change from baseline was observed after cycle 1 (7.9, $n = 47$) in patients receiving C20; in the other treatment groups, there was no clinically meaningful improvement in the FACT-P TS mean change from baseline after any subsequently analyzed cycle (Fig. 2D).

## HRQL in Patients with a Tumor Response

In PROSELICA, 271 (45.3%) patients in the C20 arm and 256 (42.5%) in the C25 arm had evaluable tumor responses. Tumor response rates were 18.5% (50/271) and 23.4% (60/256) for C20 and C25, respectively, with no difference between treatments groups observed (nominal $p = .1924$) [13]. The proportion of patients receiving cabazitaxel (C20, C25) with a definitive FACT-P TS improvement was significantly higher among patients with a tumor response (54.4%) compared with those without (36.7%, $p = .0012$; Table 2). FACT-P TS was "maintained or improved" in 73.3% and 69.0%

**Table 3.** FIRSTANA: Definitive Functional Assessment of Cancer Therapy-Prostate Total Score improvements in patients with or without a response

| Treatment arm | Pain | | | | Tumor | | | | PSA | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Response[a] *n* (%) | No response *n* (%) | OR (95% CI) | *p* value | Response[b] *n* (%) | No response *n* (%) | OR (95% CI) | *p* value | Response[c] *n* (%) | No response *n* (%) | OR (95% CI) | *p* value |
| D75[d] | 24 (70.6) | 23 (48.9) | 2.50 (0.98–6.37) | .0513 | 28 (53.8) | 47 (41.2) | 1.66 (0.86–3.22) | .1297 | 113 (49.1) | 32 (31.3) | 2.14 (1.31–3.50) | .0021 |
| C20[d] | 35 (81.4) | 24 (45.3) | 5.29 (2.07–13.53) | .0003 | 33 (55.9) | 59 (49.2) | 1.31 (0.70–2.45) | .3946 | 108 (53.7) | 56 (45.2) | 1.41 (0.90–2.21) | .1333 |
| C25[d] | 32 (72.7) | 24 (43.6) | 3.44 (1.47–8.07) | .0037 | 30 (43.5) | 44 (45.4) | 0.93 (0.50–1.73) | .8099 | 107 (47.1) | 37 (39.4) | 1.37 (0.84–2.24) | .2025 |
| C20 + C25[d] | 67 (77.0) | 48 (44.4) | 4.19 (2.24–7.84) | <.0001 | 63 (49.2) | 103 (47.5) | 1.07 (0.69–1.66) | .7529 | 215 (50.2) | 93 (42.7) | 1.36 (0.98–1.88) | .0684 |
| All 3 arms[d] | 91 (75.2) | 71 (45.8) | 3.59 (2.13–6.03) | <.0001 | 91 (50.6) | 150 (45.3) | 1.23 (0.86–1.77) | .2572 | 328 (49.8) | 125 (38.9) | 1.56 (1.19–2.04) | .0013 |

[a]Patients with a ≥ 2-point improvement from BL median Present Pain Intensity score with no concomitant increase in AS *or* a reduction of ≥50% in analgesic use from BL mean AS (only in patients with BL mean AS ≥10) with no concomitant increase in pain.
[b]Patients with measurable disease at BL and a partial or complete response according to RECIST 1.1 criteria, as assessed by the investigator.
[c]Patients with PSA >10 ng/dL at BL and a PSA decline of ≥50% confirmed by a second PSA assessment ≥3 weeks later.
[d]Calculated from the number of evaluable patients, defined as patients with BL assessment and at least one post-BL assessment.
Abbreviations: AS, analgesic score; BL, baseline; C20, cabazitaxel 20 mg/m$^2$; C25, cabazitaxel 25 mg/m$^2$; CI, confidence interval; D75, docetaxel 75 mg/m$^2$; OR, odds ratio; PSA, prostate-specific antigen.

of patients, receiving C20 and C25, respectively (supplemental online Table 5). Among patients with a tumor response, a clinically meaningful improvement in the FACT-P TS mean change from baseline was observed after cycle 3 (7.1, $n = 40$) and after cycles 1–4 (7.1–9.0, $n = 53$–$54$) in patients receiving C20 and C25, respectively (Fig. 3A). Among patients without a tumor response, there was no clinically meaningful improvement in the FACT-P TS mean change from baseline after any analyzed treatment cycle in the C20 and C25 treatment groups (Fig. 3B).

In FIRSTANA, 175 (44.8%), 188 (48.3%), and 173 (44.6%) patients in the D75, C20, and C25 arms, respectively, were evaluable for tumor response. Tumor response rate for patients receiving C20 was 32.4% ($n = 61/188$), which did not differ significantly from the response rate in patients receiving D75 (30.9%; $n = 54/175$; nominal $p = .7313$) [14]. The tumor response rate was significantly higher in the C25 ($n = 72/173$; 41.6%) compared with the D75 treatment group (nominal $p = .0370$). The proportion of patients receiving taxane chemotherapy (D75, C20, C25) with a definitive FACT-P TS improvement was slightly higher among patients with a tumor response (50.6%) compared with those without (45.3%; $p = .2572$; Table 3). FACT-P TS was "maintained or improved" in 71.2%, 78.0%, and 63.8% of patients receiving D75, C20, and C25, respectively (supplemental online Table 6). Among patients with a tumor response, a clinically meaningful improvement in the FACT-P TS mean change from baseline was observed after cycle 2 (7.7, $n = 49$) and cycle 10 (7.0, $n = 38$) in patients receiving D75 (Fig. 3C). For patients receiving C20 and C25, there was no clinically meaningful improvement in the FACT-P TS mean change from baseline after any analyzed treatment cycle. Among patients without a tumor response, a clinically meaningful improvement in the FACT-P TS mean change from baseline was observed after cycle 1 (7.3, $n = 105$) and cycle 2 (7.0, $n = 114$) in patients receiving C20 and after cycle 11 (10.5, $n = 19$) in patients receiving C25. In patients without a tumor response receiving D75, there was no clinically meaningful improvement in FACT-P TS mean change after any analyzed treatment cycle (Fig. 3D).

## HRQL in Patients with a PSA Response

In PROSELICA, 543 (90.8%) patients receiving C20 and 538 (89.4%) receiving C25 had evaluable PSA responses. PSA response rates were 29.5% (160/543) and 42.9% (231/538) for C20 and C25, respectively. The PSA response rate was significantly higher in the C25 versus C20 arm ($p < .0001$) [13]. The proportion of patients receiving cabazitaxel (C20, C25) with a definitive FACT-P TS improvement was significantly higher among patients with a PSA response (50.3%) compared with patients without a PSA response (34.2%, $p < .0001$; Table 2). FACT-P TS was "maintained or improved" in 78.4% and 74.9% of patients with a PSA response receiving C20 and C25, respectively (supplemental online Table 5). Among patients with or without a PSA response, there was no clinically meaningful improvement in the FACT-P TS mean change from baseline after any analyzed treatment cycle in both treatment groups (Fig. 4A, B).

In FIRSTANA, 354 (90.5%), 346 (88.9%), and 342 (88.1%) patients receiving D75, C20, and C25, respectively, had

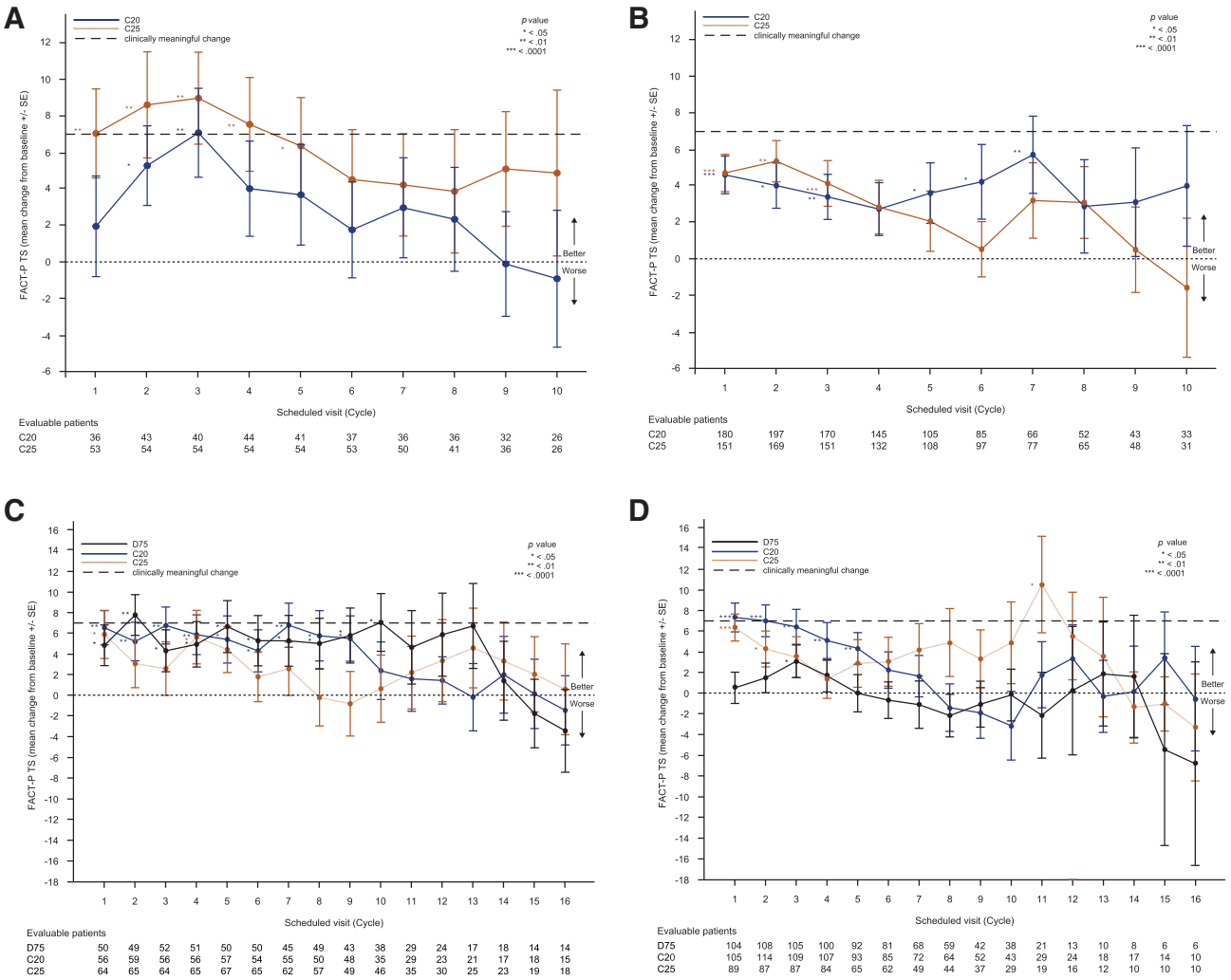


**Figure 3.** FACT-P TS mean change from baseline over time in patients with or without a tumor response for PROSELICA **(A)** and **(B)** and FIRSTANA **(C)** and **(D)**. **(A):** PROSELICA: Patients with a tumor response. **(B):** PROSELICA: Patients without a tumor response. **(C):** FIRSTANA: Patients with a tumor response. **(D):** FIRSTANA: Patients without a tumor response.
Abbreviations: C20, cabazitaxel 20 mg/m$^2$; C25, cabazitaxel 25 mg/m$^2$; D75, docetaxel 75 mg/m$^2$; FACT-P TS, Functional Assessment of Cancer Therapy-Prostate Total Score.

evaluable PSA responses. PSA response rates were 68.4% (242/354), 60.7% (210/346), and 68.7% (235/342) for D75, C20, and C25, respectively, with no difference between treatment groups observed (C20 vs. D75 $p = .0524$; C25 vs. D75 $p = .9993$) [14]. The proportion of patients receiving taxane chemotherapy (D75, C20, C25) with a definitive FACT-P TS improvement was significantly higher among patients with a PSA response (49.8%) compared with patients without a PSA response (38.9%; $p = .0013$; Table 3). FACT-P TS was "maintained or improved" in 76.1%, 71.6%, and 70.0% of patients, receiving D75, C20, and C25, respectively (supplemental online Table 6). Among patients with a PSA response, there was no clinically meaningful improvement in the FACT-P TS mean change from baseline after any analyzed treatment cycle in any treatment groups (Fig. 4C). Among patients without a PSA response receiving D75, there was no clinically significant improvement in the FACT-P TS mean change from baseline after any analyzed treatment cycle. A clinically meaningful improvement in the FACT-P TS mean change from baseline was observed after cycle 1 (7.8, $n = 117$) and cycle 2 (7.9, $n = 112$) in patients receiving C20 and after cycle 5 (7.2, $n = 50$) and cycles 7–11 (7.1–14.3, $n = 35$–12) in patients receiving C25 (Fig. 4D).

## Discussion

Bone is the most common site of metastases in patients with mCRPC, resulting in significant morbidity, primarily through skeletal-related events [16]. Bone metastases often cause intermittent or constant pain for the patient, which results in a significant reduction in their HRQL [24]. In PROSELICA and FIRSTANA, the majority of patients had bone metastases at baseline (PROSELICA: C20, 93.5%; C25, 94.5%; FIRSTANA: D75, 91.0%; C20, 88.7%; C25, 88.9%) reflecting a large patient population with advanced disease. Our findings from the PROSELICA and FIRSTANA studies suggest that patients with mCRPC receiving docetaxel or cabazitaxel who have a pain response also have an increase

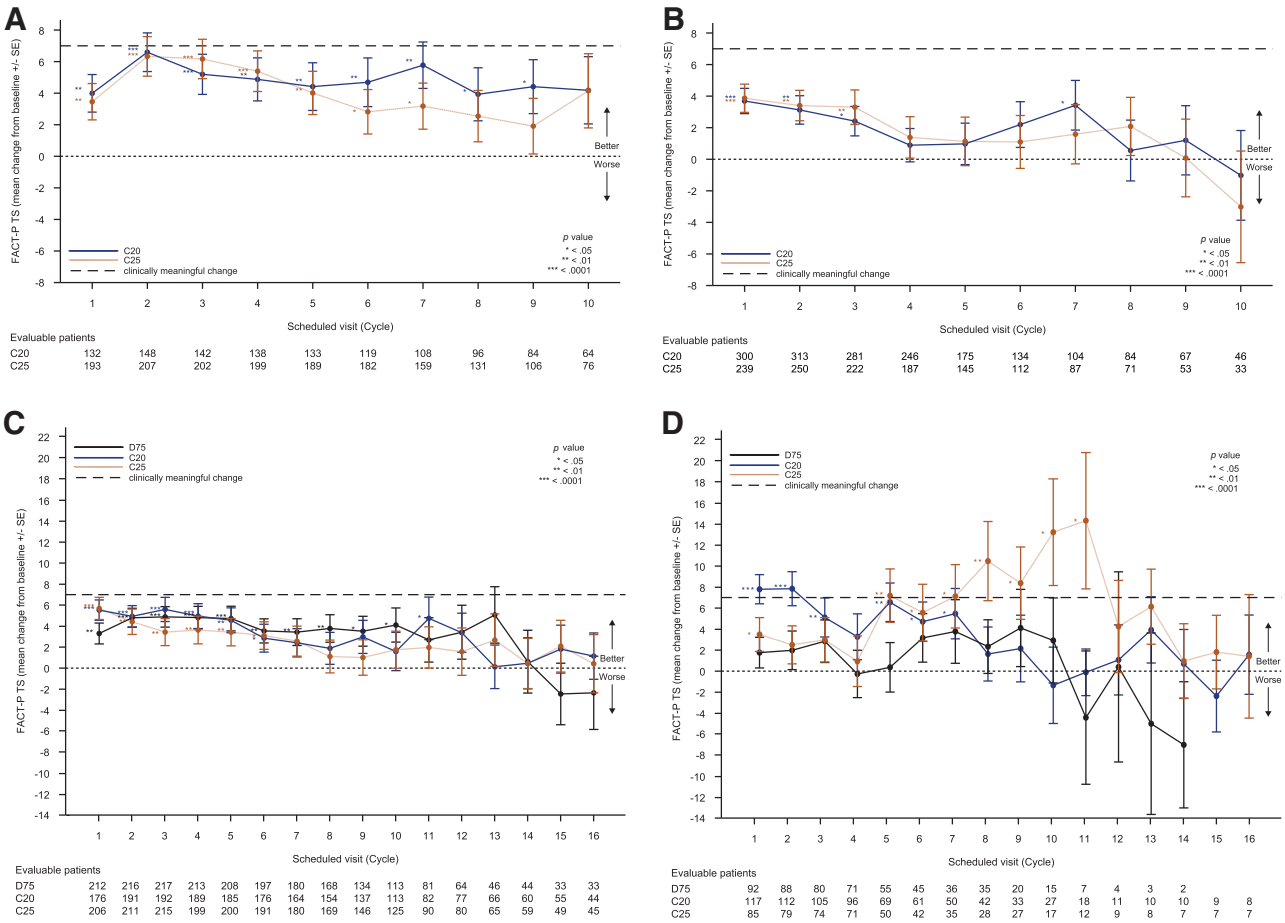


**Figure 4.** FACT-P TS mean change from baseline over time in patients with or without a prostate-specific antigen (PSA) response for PROSELICA **(A)** and **(B)** and FIRSTANA **(C)** and **(D)**. **(A):** PROSELICA: Patients with a PSA response. **(B):** PROSELICA: Patients without a PSA response. **(C):** FIRSTANA: Patients with a PSA response. **(D):** FIRSTANA: Patients without a PSA response.
Abbreviations: C20, cabazitaxel 20 mg/m$^2$; C25, cabazitaxel 25 mg/m$^2$; D75, docetaxel 75 mg/m$^2$; FACT-P TS, Functional Assessment of Cancer Therapy-Prostate Total Score.

in their HRQL. The kinetics of this HRQL benefit is noteworthy, with clinically meaningful improvements observed after one treatment cycle for the majority of treatment arms that were maintained. Furthermore, patients with a pain or PSA response had superior HRQL improvements compared with those without. These data suggest that pain and PSA responses are associated with HRQL improvements. Importantly, an increase in a patient's HRQL has been demonstrated to positively impact a patient's survival in both the mCRPC chemotherapy-naïve and postchemotherapy setting [25]. HRQL improvements observed in patients with versus without a clinical response appeared more pronounced in the PROSELICA study compared with the FIRSTANA study. This could be due to patients in PROSELICA having more advanced disease in terms of prior treatment, bone metastases, and PSA levels at baseline, compared with the chemotherapy-naïve patients in FIRSTANA, consequently making HRQL improvements more challenging to detect in the FIRSTANA study.

Limitations of this study include the inherent variability that arises from the tumor response being determined at multiple sites. Additionally, the number of patients with evaluable clinical responses and HRQL assessments is low, reducing the statistical power of the analyses. PSA has historically been a widely used biomarker to track disease burden but does not always accurately indicate a patient's response to a given treatment [26]. Circulating tumor cells are increasingly being used as a more accurate measure of efficacy [27–29]. Finally, data providing evidence suggesting that clinical responses are positively correlated with HRQL improvements might be considered as relatively intuitive, but demonstration of this relationship is underreported and perhaps assumed.

In the phase III COU-AA-301 trial, abiraterone plus prednisone increased OS in the mCRPC postdocetaxel setting and shortened time to palliation of pain intensity in patients with clinically significant pain at baseline compared with patients receiving prednisone alone [30, 31]. Similarly, in the phase III COU-AA-302 trial, patients with chemotherapy-naïve mCRPC receiving abiraterone plus prednisone had an improvement in radiographic progression-free survival and reported a delay in time to pain progression compared with patients receiving prednisone alone [32, 33]. Patients with mCRPC receiving enzalutamide in the first-line (PREVAIL, NCT01212991) or second-line (AFFIRM, NCT00974311) setting demonstrated both increased OS and reduced risk of skeletal-related events compared with patients receiving placebo [4, 34]. Importantly, HRQL improvements were reported

in the COU-AA-302, PREVAIL, and AFFIRM studies for patients with mCRPC receiving abiraterone or enzalutamide. This suggests that patients with mCRPC receiving chemotherapy, abiraterone, or enzalutamide who have a pain response, may also have improved HRQL.

Overall, our data are the first to our knowledge to demonstrate that patients with mCRPC receiving taxane chemotherapy who exhibit a pain, PSA, or tumor response are more likely to have an improvement in their HRQL. This information is of importance to allow a more informed assessment of the benefits of each anticancer treatment among patients with mCRPC.

## Conclusion

In the PROSELICA and FIRSTANA clinical trials, the proportion of patients receiving taxane chemotherapy with an improvement in their HRQL (definitive FACT-P TS improvement) was significantly higher among patients with versus without a pain or PSA response. Longitudinal studies demonstrated that clinically meaningful improvements in HRQL (FACT-P TS mean change from baseline) occurred early and were durable in patients with a pain response. For the PSA and tumor response analysis in both studies, the HRQL (FACT-P TS) of patients was maintained for the majority of treatment cycles regardless of clinical response. Overall, among patients with mCRPC who received taxane chemotherapy and had a pain, tumor, or PSA response, HRQL (FACT-P TS) improvements were significantly higher compared with those patients without a pain, tumor, or PSA response (with the exception of tumor response in FIRSTANA).

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## Disclosures

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