ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

ORIGINAL RESEARCH

An analysis of health-related quality of life in the phase III PROSELICA and FIRSTANA studies assessing cabazitaxel in patients with metastatic castration-resistant prostate cancer

A. Thiery-Vuillemin[1*], K. Fizazi[2], O. Sartor[3], S. Oudard[4], D. Bury[5], K. Thangavelu[6], A. Ozatilgan[5], E. M. Poole[7], M. Eisenberger[8] & J. de Bono[9]

[1]Centre Hospitalier Régional Universitaire, Besançon; [2]Cancer Medicine, Institut Gustave Roussy, University of Paris Saclay, Villejuif, France; [3]Tulane University School of Medicine, New Orleans, USA; [4]George Pompidou European Hospital, René Descartes University, Paris, France; [5]Sanofi US, Cambridge; [6]MeDaStats LLC, Billerica; [7]Bluebird Bio, Cambridge; [8]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, USA; [9]Royal Marsden and The Institute of Cancer Research, Sutton, UK

Available online xxx

Background: Men with metastatic castration-resistant prostate cancer (mCRPC) are living longer, therefore optimizing health-related quality of life (HRQL), as well as survival outcomes, is important for optimal patient care. The aim of this study was to assess the HRQL in patients with mCRPC receiving docetaxel or cabazitaxel.

Patients and methods: PROSELICA (NCT01308580) assessed the non-inferiority of cabazitaxel 20 mg/m^2 (C20) versus 25 mg/m^2 (C25) in patients with mCRPC after docetaxel. FIRSTANA (NCT01308567) assessed the superiority of C25 or C20 versus docetaxel 75 mg/m^2 (D75) in patients with chemotherapy-naive mCRPC. HRQL and pain were analyzed using protocol-defined, prospectively collected, Functional Assessment of Cancer Therapy—Prostate (FACT-P) and McGill-Melzack questionnaires. Analyses included definitive improvements in HRQL, maintained or improved HRQL, and HRQL over time.

Results: In total, 2131 patients were evaluable for HRQL across the two studies. In PROSELICA, 38.8% and 40.5% of patients receiving C20 and C25, respectively, had definitive FACT-P total score (TS) improvements. In FIRSTANA, 43.4%, 49.7%, and 44.9% of patients receiving D75, C20, and C25, respectively, had definitive FACT-P TS improvements. In both trials, definitive improvements started after cycle 1 and were maintained for the majority of subsequent treatment cycles. More than two-thirds of patients maintained or improved their FACT-P TS.

Conclusions: In PROSELICA and FIRSTANA, >40% of the 2131 evaluable patients with mCRPC had definitive FACT-P TS improvements; improvements occurred early and were maintained. More than 75% of patients maintained or improved their FACT-P TS.

Key words: cabazitaxel, docetaxel, health-related quality of life, metastatic castration-resistant prostate cancer, patient-reported outcomes

INTRODUCTION

Worldwide, prostate cancer is the most frequently occurring cancer in men, with 1.6 million cases and 366 000 deaths reported in 2015.[1] In the USA, it is estimated that there will be 174 650 new cases and 31 620 deaths from the disease in 2019.[2]

Several new treatment approaches are currently available for patients with metastatic castration-resistant prostate cancer (mCRPC) including two chemotherapies, two androgen-signaling-targeted inhibitors, sipuleucel-T, radium-223, and olaparib.[3-9] Docetaxel is approved for the treatment of mCRPC based on the outcome of the phase III TAX-327 trial, which demonstrated significantly increased overall survival (OS) and health-related quality of life (HRQL) compared with mitoxantrone.[10] Cabazitaxel, a second-generation taxane, is approved for patients with mCRPC previously treated with docetaxel.[11,12] Approval followed the phase III TROPIC study, where cabazitaxel 25 mg/m^2 (C25) led to improved OS versus mitoxantrone ($P < 0.0001$).[13] In the subsequent PROSELICA non-inferiority trial (NCT01308580), cabazitaxel 20 mg/m^2 (C20) maintained ≥50% of the OS benefit of C25 versus

*Correspondence to: Dr Antoine Thiery-Vuillemin, MCU-PH Medical Oncology, CHRU Minjoz, Boulevard Flemming, 25030 Besançon, France. Tel: +33-3-8147-9999; Fax: +33-3-7063-2214

E-mail: antoine.thieryvuillemin@oncologyfc2.onmicrosoft.com (A. Thiery-Vuillemin).

mitoxantrone that was previously reported in TROPIC, in patients with mCRPC previously treated with docetaxel.[14] In PROSELICA, the number of patients who experienced a pain response and the risk of pain progression was similar between treatment groups; furthermore, median time to definitive deterioration in the Functional Assessment of Cancer Therapy—Prostate (FACT-P) subscales did not differ between cohorts.[14] In the FIRSTANA trial (NCT01308567), similar OS was seen in patients with chemotherapy-naive mCRPC receiving docetaxel 75 mg/m^2 (D75), C20, and C25.[15] Overall, the median time to definitive deterioration in the FACT-P subscales did not differ between cohorts, with the exception of physical well-being which showed a longer median time to definitive deterioration in the C20 versus D75 arm.[15]

Patients with mCRPC may suffer from a range of symptoms, including, but not limited to, bone pain and fatigue, which impede a patient's functional, social, and emotional well-being.[16] Assessing patient-reported outcomes (PROs), including HRQL, has become an important part of clinical trials, including those in mCRPC.

With the exception of the observational study CAPRISTANA (189 patients), which demonstrated that HRQL was maintained (40.3%) or improved (32.2%) in 72.5% of patients with mCRPC receiving cabazitaxel in the post-docetaxel setting (based on FACT-P), there is a need for further HRQL analyses of patients receiving cabazitaxel.[17] In this paper we present PRO results, including detailed HRQL data, for patients with mCRPC receiving cabazitaxel or docetaxel from the PROSELICA and FIRSTANA clinical trials. Pain progression data have been published previously.[14,15]

PATIENTS AND METHODS

Trial design

PROSELICA and FIRSTANA trial designs are summarized in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100089, and have been previously described.[14,15] In PROSELICA, 1200 patients with mCRPC who had previously received docetaxel were randomly assigned (1 : 1) to C20 or C25, plus prednisone 10 mg.

In FIRSTANA, 1168 patients with chemotherapy-naive mCRPC were randomly assigned (1 : 1 : 1) to receive D75, C20, or C25, plus prednisone 10 mg.

Written informed consent was provided by all patients and the studies were conducted in compliance with the guidelines for Good Clinical Practice.

Assessment of HRQL, fatigue, and pain

Protocol-driven HRQL assessments were prospectively carried out using the FACT-P questionnaire (version 4), a validated, self-administered PRO used to assess HRQL in patients with prostate cancer.[18,19] 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 five subscales were combined for the FACT-P total score (TS; 0-156). The Trial Outcome Index (TOI), which is responsive to changes in functional and physical outcomes, was calculated by summing physical well-being, functional well-being, and prostate-specific concern (0-104).[20] To provide a general functional assessment of cancer therapy, the Functional Assessment of Cancer Therapy—General (FACT-G) was calculated by summing physical well-being, social/family well-being, emotional well-being, and functional well-being (0-108).[21] For FACT-P TS, TOI, and FACT-G, higher values represent better HRQL/functioning. Questionnaires were completed within 3 days before the first administration (baseline), after each subsequent cycle (before the next infusion), and 30 days after last administration. Post-treatment questionnaires were completed every 6 weeks for the first 6 months and every 12 months thereafter in PROSELICA, and every 12 weeks in FIRSTANA.

Fatigue was assessed via the FACT-P questionnaire based on one question regarding lack of energy (0-4), where higher values represent an increased level of fatigue.[22]

A prostate cancer subscale pain-related subscale score (PCS-pain) was derived from four questions on the FACT-P questionnaire specifically related to pain (0-16), where higher values represent increased pain levels.

Pain was also assessed using the Present Pain Intensity (PPI) scale from the McGill-Melzack questionnaire.[23] Median PPI and mean Analgesic Score were calculated if five of the seven expected values were available in the patient records. Patient-reported pain was collected for 7 consecutive days before each scheduled cycle, on day 1 of each treatment cycle and 30 days after last treatment.

Definitions for changes in PRO measures

Definitive improvement and 'maintained or improved' PRO data are reported. A definitive improvement in FACT-P TS was defined as a $\geq$7-point improvement from baseline; for subscale improvements a $\geq$3-point improvement was used.[19] A definitive improvement in fatigue was defined as a $\geq$1-point improvement from baseline, derived from a single item regarding lack of energy (per the FACT Advanced Prostate Symptom Index, FAPSI-6 and FAPSI-8).[20,22,24-26] A definitive improvement in PCS-pain was defined as a $\geq$2-point improvement from baseline.[19] A definitive improvement in PPI was defined as a $\geq$2-point improvement from baseline median PPI score.[23] Furthermore, all definitive improvements required confirmation at two time points that were $\geq$3 weeks apart. Thresholds for definitive improvements were selected because they are considered clinically meaningful.[19,20,22,24-26]

A patient was defined as having 'maintained or improved' when they did not meet the criteria for definitive deterioration; determined as a $\geq$10% decrease from baseline, confirmed at two time points $\geq$3 weeks apart. Thresholds were prespecified in the protocol and statistical analysis plan. Definitions for definitive improvement in FACT-P, fatigue, and pain are summarized in Table 1, along with the definition for 'maintained or improved'.[23]

At each visit, the observed FACT-P TS change from baseline was classified as a transient improvement or

Table 1. Definitions for definitive improvement and 'maintained or improved'

	Definitive improvement	Maintained or improved
FACT-P		
FACT-P TS	≥7-point improvement from BL, confirmed at two time points ≥3 weeks apart[19]	Did not meet the criteria for definitive deterioration[b]
Functional subscales[a]	≥3-point improvement from BL, confirmed at two time points ≥3 weeks apart[19]	
Fatigue	≥1-point improvement from BL, confirmed at two time points ≥3 weeks apart[20]	
Pain		
PCS-pain	≥2-point improvement from BL, confirmed at two time points ≥3 weeks apart[19]	
PPI	≥2-point improvement from BL, confirmed at two time points ≥3 weeks apart[23]	

BL, baseline; FACT-P TS, Functional Assessment of Cancer Therapy—Prostate total score; PCS, prostate cancer subscale; PPI, present pain intensity.
[a] Physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate-specific concerns.
[b] ≥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.

deterioration based on the change being ≥7 or ≤−10%, respectively, for each individual patient. A patient was considered to have a transient maintenance if they did not meet the criteria for either transient improvement or deterioration. Total count and overall percentage for each category across all visits for all eligible patients is reported. Thresholds were prespecified in the protocol and statistical analysis plan. Definitions for FACT-P TS transient improvement, maintenance, and deterioration are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100089.

FACT-P population definition

For HRQL, patients who completed the FACT-P questionnaire at baseline and at least once after baseline were included (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.[18] 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] × [*N* of questions in subscale]/[*N* of questions answered].

Statistical analysis

Patient baseline characteristics for the intention-to-treat, FACT-P, and non-FACT-P populations are summarized by treatment arm using descriptive statistics (median and range or mean and standard deviation for continuous characteristics and number and percent for categorical characteristics). Median OS in these populations was estimated using the Kaplan—Meier approach. Baseline PRO and HRQL assessments are summarized using mean and standard deviation. Comparisons of definitive improvement or 'maintained or improved' PRO measures between treatment groups were carried out using unadjusted logistic regressions. Longitudinal FACT-P TS change from baseline analyses are summarized using mean and standard error at each cycle; statistical significance was assessed using paired *t*-tests.

In PROSELICA, treatment was limited to 10 cycles; no limits were defined in the FIRSTANA protocol. When analyses are presented by visit, data are presented over 10 and 16 treatment cycles, respectively. For analyses over the entire on-treatment period, additional cycles in FIRSTANA (up to 42) were also included. For comparisons between treatment arms within the studies, nominal *P* values are provided.

RESULTS

Baseline characteristics

In PROSELICA, a total of 1200 patients with mCRPC previously treated with docetaxel were randomized (1 : 1) to receive C20 ($n = 598$) or C25 ($n = 602$). In FIRSTANA, 1168 patients with chemotherapy-naive mCRPC were randomized (1 : 1 : 1) to receive D75 ($n = 391$), C20 ($n = 389$), and C25 ($n = 388$).

In PROSELICA and FIRSTANA, questionnaires were completed at each visit by more than 89% and 92% of patients, respectively (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100089). Overall, baseline characteristics and PROs were well balanced between treatment arms within each study, although certain adverse disease characteristics were more frequent in the non-FACT-P population compared with the FACT-P population. For example, there were more patients with Eastern Cooperative Oncology Group performance status 2 and liver metastases in the non-FACT-P population (Table 2; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100089). In PROSELICA, the median OS was 4.4 and 3.9 months in the non-FACT-P population compared with 14.1 and 15.0 months in the FACT-P population, for patients who received C20 or C25, respectively. In FIRSTANA, the median OS was 20.6, 23.4, and 6.1 months in

Table 2. Baseline PROs and HRQL assessments: FACT-P population

Mean (SD)	PROSELICA		FIRSTANA		
	C20 ($n = 557$)	C25 ($n = 543$)	D75 ($n = 376$)	C20 ($n = 372$)	C25 ($n = 361$)
FACT-P TS	102.7 (21.7)	101.4 (21.8)	106.4 (21.8)	106.2 (21.1)	105.5 (21.1)
PWB	20.2 (5.59)	19.6 (6.1)	22.1 (5.0)	21.9 (5.2)	21.5 (5.3)
SWB	20.6 (5.0)	20.7 (4.9)	20.5 (5.6)	20.4 (5.1)	20.6 (5.2)
EWB	16.9 (4.4)	16.6 (4.8)	16.8 (4.4)	16.8 (4.3)	17.0 (4.4)
FWB	16.0 (6.0)	16.0 (5.9)	17.1 (6.3)	16.8 (6.0)	16.9 (6.0)
PSC	29.5 (7.7)	28.6 (7.7)	30.3 (7.2)	30.4 (7.6)	29.9 (7.5)
TOI	65.5 (16.8)	64.3 (17.1)	69.5 (16.2)	68.9 (16.5)	68.2 (16.2)
FACT-G TS	73.3 (15.5)	72.8 (15.9)	76.1 (16.3)	75.8 (15.2)	75.9 (15.2)
PPI pain score	1.3 (1.1)	1.4 (1.2)	1.0 (1.0)	1.2 (1.1)	1.2 (1.1)
PCS-pain	9.5 (4.5)	9.2 (4.6)	10.7 (4.0)	10.3 (4.5)	10.1 (4.5)
Fatigue	2.2 (1.1)	2.2 (1.2)	2.7 (1.1)	2.7 (1.1)	2.7 (1.1)

C20/C25, cabazitaxel 20/25 mg/m^2; D75, docetaxel 75 mg/m^2; EWB, emotional well-being; FACT-G TS, Functional Assessment of Cancer Therapy—General total score; FACT-P TS, Functional Assessment of Cancer Therapy—Prostate total score; FWB, functional well-being; HRQL, health-related quality of life; PCS, prostate cancer subscale; PPI, present pain intensity; PRO, patient-reported outcome; PSC, prostate-specific concerns; PWB, physical well-being; SD, standard deviation; SWB, social/family well-being; TOI, Trial Outcome Index.

the non-FACT-P population compared with 24.5, 24.6, and 25.8 months in the FACT-P population, for patients who received D75, C20, or C25, respectively (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100089). In PROSELICA, among the intention-to-treat population, 557 patients (93.1%) receiving C20 and 543 (90.2%) receiving C25 were eligible for HRQL evaluation; in FIRSTANA, 376 patients (96.2%) receiving D75, 372 (95.6%) receiving C20, and 361 (93.0%) receiving C25 were eligible.

Improvements in HRQL, pain, and fatigue

In PROSELICA, 38.8% (209/539) and 40.5% (212/524) of evaluable patients in the C20 and C25 groups, respectively, had a definitive improvement in FACT-P TS. In FIRSTANA, 43.4% (157/362), 49.7% (177/356), and 44.9% (157/350) of evaluable patients in the D75, C20, and C25 treatment arms, respectively, had a definitive improvement in FACT-P TS. In PROSELICA and FIRSTANA, there was no significant difference in the proportion of patients with a definitive improvement in FACT-P TS between treatment groups (PROSELICA: C20 versus C25, $P = 0.5750$; FIRSTANA: D75 versus C20, $P = 0.0884$; D75 versus C25, $P = 0.6895$).

The FACT-P subscales, fatigue and pain measurements, and the proportion of patients who 'maintained or improved' are presented in Supplementary Tables S5 and S6, available at https://doi.org/10.1016/j.esmoop.2021.100089. In PROSELICA, FACT-P TS was 'maintained or improved' in 80.1% and 78.4% of patients receiving C20 and C25, respectively. Physical well-being was 'maintained or improved' in 71.6% and 65.5% of patients receiving C20 and C25, respectively. PPI, PCS-pain, and fatigue were 'maintained or improved' in >60% of patients receiving C20 or C25. In FIRSTANA, FACT-P TS was 'maintained or improved' in 76.5%, 73.9%, and 74.0% of patients receiving D75, C20, and C25, respectively. Physical well-being was 'maintained or improved' in 61.0%, 66.7%, and 59.8% of patients receiving D75, C20, and C25, respectively. In >70% of patients receiving D75, C20, or C25, PCS-pain was 'maintained or improved'; PPI score and fatigue were 'maintained or improved' in at least 40%.

Longitudinal FACT-P TS

The mean change from baseline in FACT-P TS among evaluable patients after each cycle is presented in Figure 1. In PROSELICA and FIRSTANA, study treatment did not influence the overall mean change from baseline in FACT-P TS to a magnitude that was clinically meaningful; FACT-P TS was maintained for 10 cycles in PROSELICA and ≥16 cycles in FIRSTANA.

The mean change from baseline in FACT-P TS at each cycle among patients with a definitive improvement in FACT-P TS is presented in Figure 2. In PROSELICA, for patients with a definitive improvement in FACT-P TS, a ≥7-point increase in the FACT-P TS mean change from baseline was observed after cycle 1 (C20 12.3, $n = 179$; C25 13.1, $n = 190$) and was consistently observed after each subsequent cycle (Figure 2A). FACT-P TS was 'maintained or improved' in 80.1% (432/539) and 78.4% (411/524) of patients receiving C20 and C25, respectively (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2021.100089). In FIRSTANA, for patients with a definitive improvement in FACT-P TS, a ≥7-point increase in the FACT-P TS mean change from baseline was observed after cycle 1 (D75 11.7, $n = 146$; C20 13.8, $n = 161$; C25 14.6, $n = 143$); improvements were consistently observed after each subsequently analyzed cycle, with the exception of cycles 15 and 16 in the D75 treatment group, and cycle 16 in the C20 treatment group (Figure 2B). FACT-P TS was 'maintained or improved' in 76.5% (277/362), 73.9% (263/356), and 74.0% (259/350) of patients receiving D75, C20, and C25, respectively (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2021.100089). In PROSELICA and FIRSTANA, there was no difference in the proportion of patients with 'maintained or improved' FACT-P TS between treatment groups (PROSELICA: C20 versus C25, $P = 0.4907$; FIRSTANA: D75 versus C20, $P = 0.4124$; D75 versus C25, $P = 0.4361$).

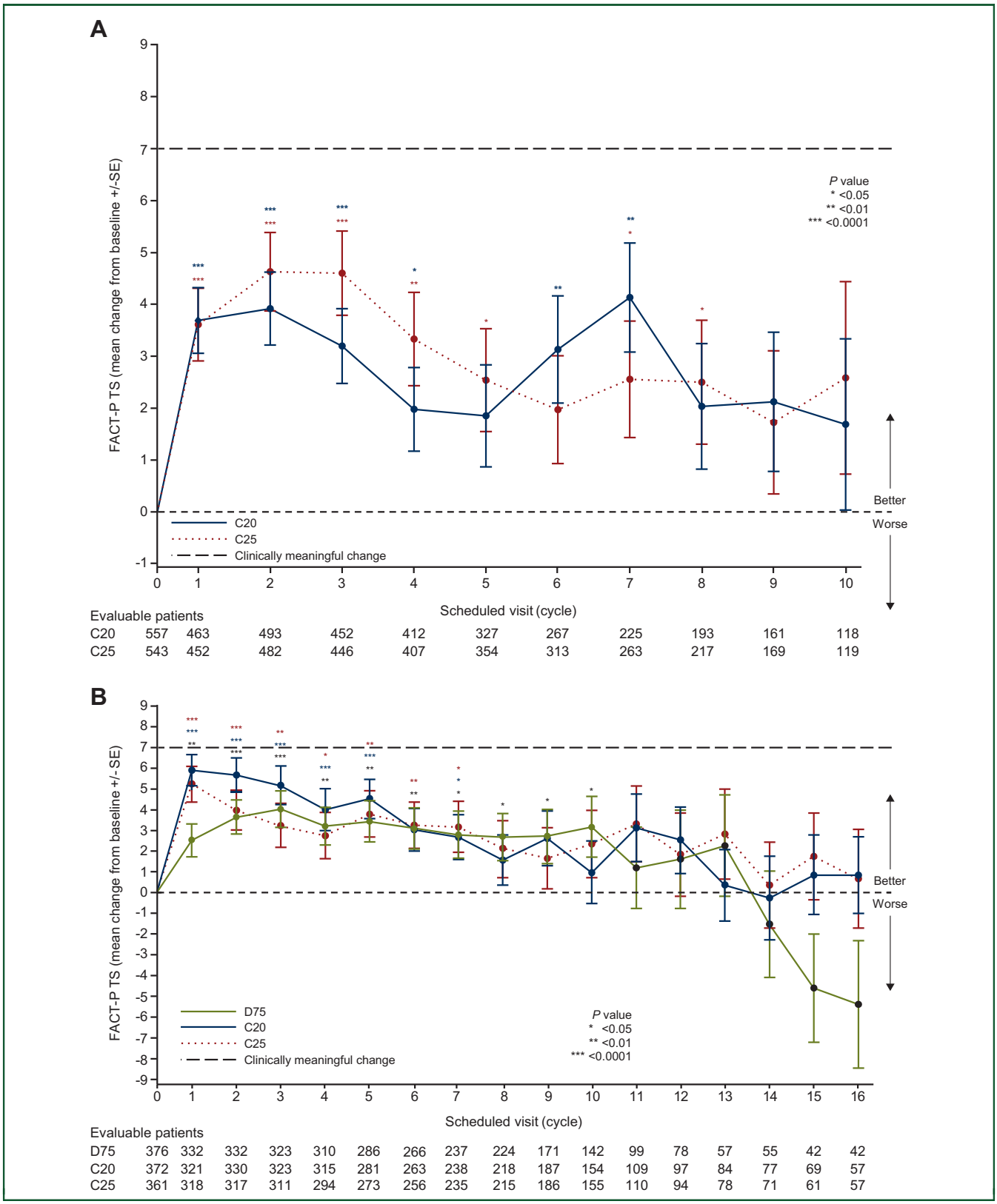

Figure 1. Change in mean FACT-P TS from baseline at each cycle among the overall population for (A) PROSELICA and (B) FIRSTANA.
Significant *P* values are shown by asterisks. C20/C25, cabazitaxel 20/25 mg/m^2; D75, docetaxel 75 mg/m^2; FACT-P TS, Functional Assessment of Cancer Therapy—Prostate total score; SE, standard error.

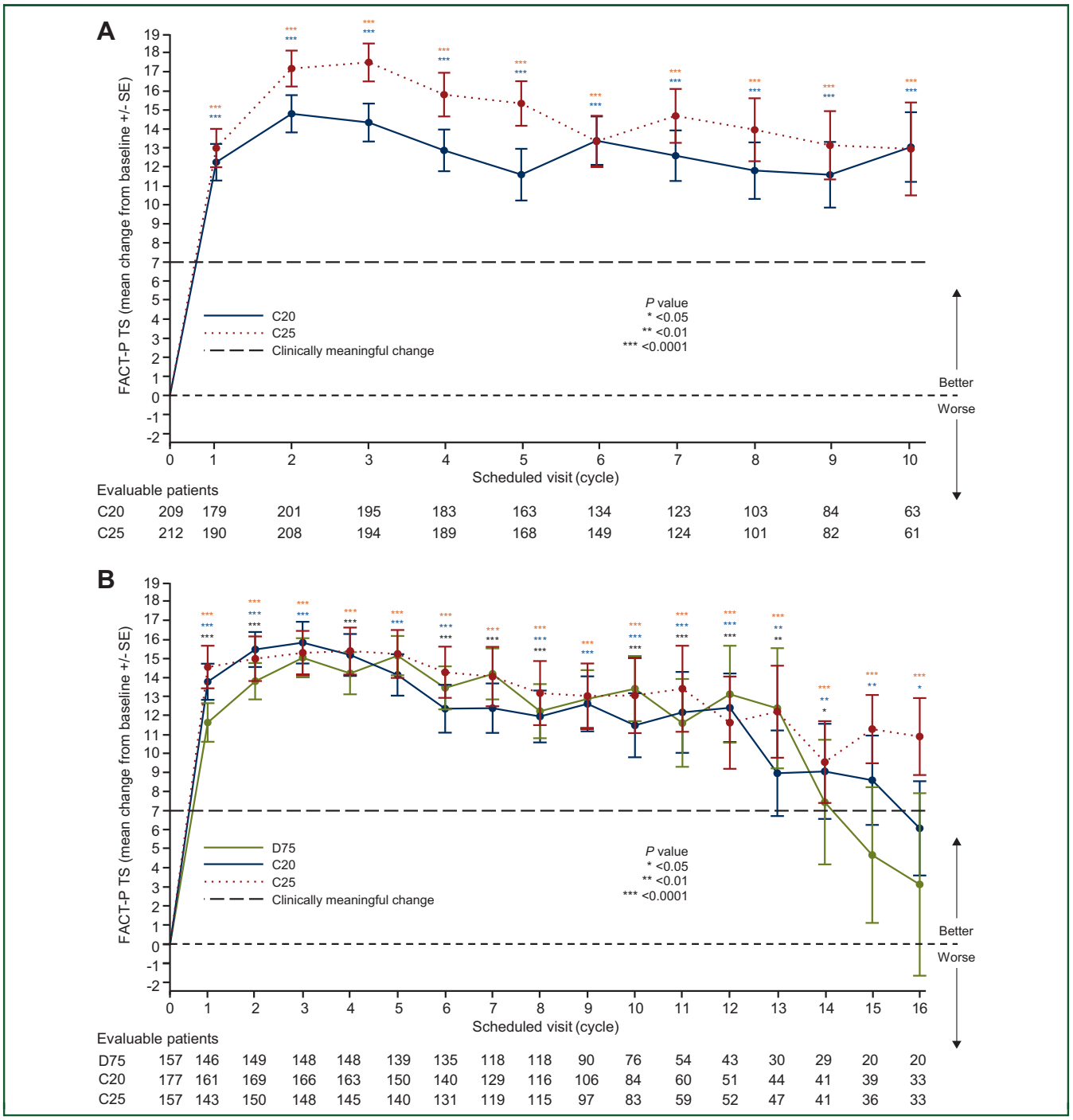

Figure 2. Change in mean FACT-P TS from baseline at each cycle in patients with a definitive improvement in FACT-P TS for (A) PROSELICA and (B) FIRSTANA. C20/C25, cabazitaxel 20/25 mg/m^2; D75, docetaxel 75 mg/m^2; FACT-P TS, Functional Assessment of Cancer Therapy—Prostate total score; SE, standard error.

Transient changes in FACT-P TS

The overall proportion of patient assessments with transiently 'maintained or improved' FACT-P TS among all available assessments is presented in Figure 3. In PROSELICA, the FACT-P TS change from baseline was transiently improved or maintained in 83.3% and 81.7% of available assessments in patients receiving C20 and C25, respectively. In FIRSTANA, the FACT-P TS change from baseline was transiently 'maintained or improved' in 80.9%, 82.4%, and 82.2% of available assessments in patients receiving D75, C20, and C25, respectively.

The overall proportion of patient assessments with transiently 'maintained or improved' FACT-P TS among available assessments in patients with a definitive improvement in FACT-P TS is presented in Figure 3. In PROSELICA, FACT-P TS change from baseline was transiently 'maintained or improved' in 95.8% and 97.0% of all available assessments in patients with a definitive improvement

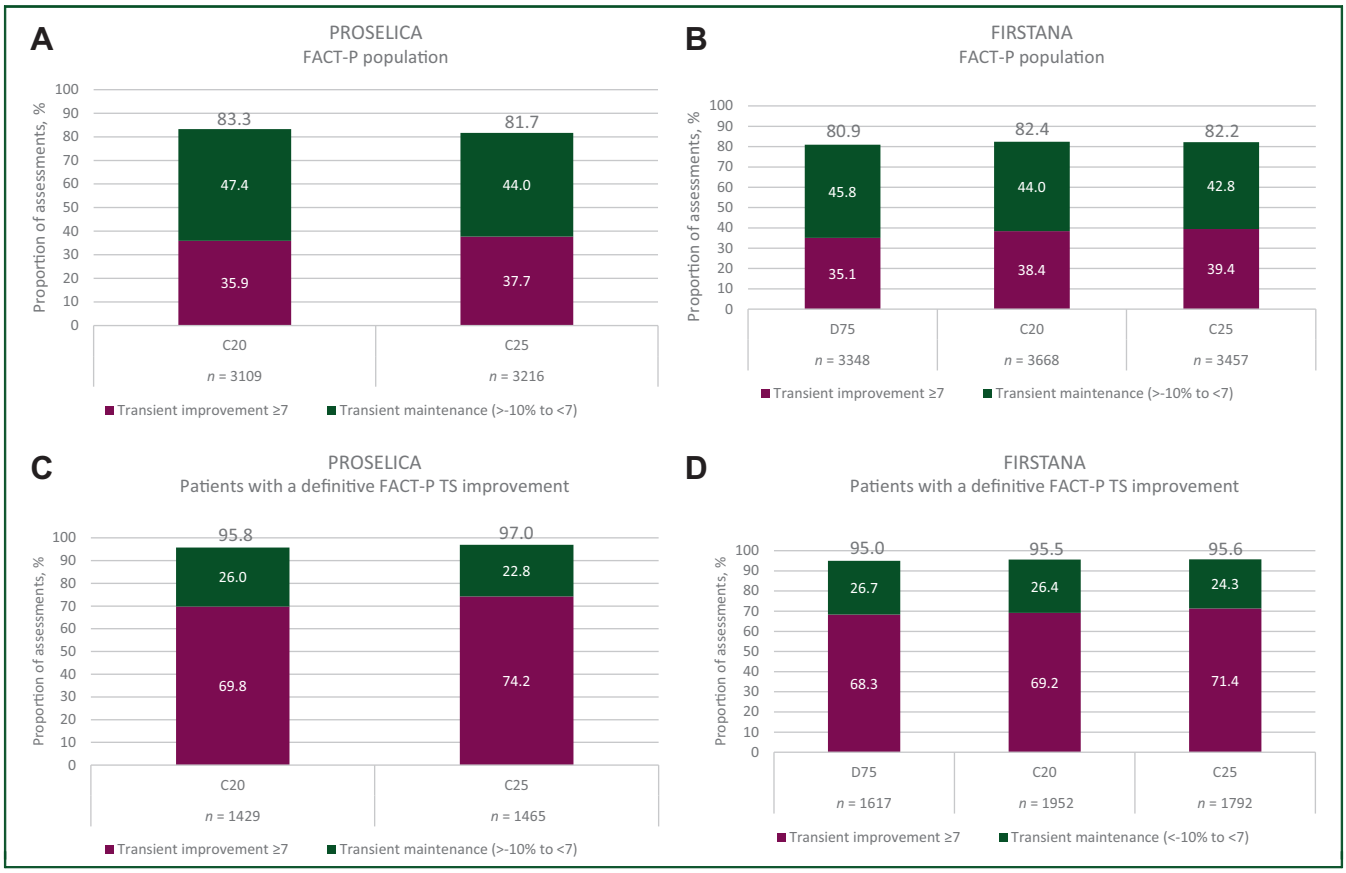

Figure 3. Proportion of patients with a transient maintenance or improvement in FACT-P TS among all available patient HRQL assessments for the overall FACT-P population in (A) PROSELICA and (B) FIRSTANA and the subgroup of patients with a definitive improvement in FACT-P TS in (C) PROSELICA and (D) FIRSTANA.
n = total evaluable patient HRQL assessments. A patient was considered to have a transient improvement in FACT-P TS if they had a ≥7-point change from baseline. A patient was considered to have a transient deterioration in FACT-P TS if they had a ≤-10% change from baseline. A patient was considered to have a transient maintenance in FACT-P TS if they did not meet the criteria for either transient improvement or transient deterioration. Transient FACT-P TS changes were determined for each evaluable HRQL assessment.
C20/C25, cabazitaxel 20/25 mg/m^2; D75, docetaxel 75 mg/m^2; FACT-P TS, Functional Assessment of Cancer Therapy—Prostate total score; HRQL, health-related quality of life.

in FACT-P TS receiving C20 and C25, respectively. In FIRSTANA, FACT-P TS change from baseline was transiently 'maintained or improved' in 95.0%, 95.5%, and 95.6% of all available assessments in patients with a definitive improvement in FACT-P TS receiving D75, C20, and C25, respectively.

DISCUSSION

Patients with mCRPC who present with disease-related symptoms impacting on HRQL often have the perception that chemotherapy will negatively impact their HRQL.[27,28] The findings from this study suggesting HRQL, pain, and fatigue are often 'maintained or improved' in men with mCRPC receiving docetaxel or cabazitaxel will support informed treatment decision making between patient and physician. HRQL benefits for patients with mCRPC are important, as several studies have suggested that PROs significantly impact clinical outcomes.[29] For example, in the COU-AA-302 trial, for patients with chemotherapy-naive mCRPC receiving abiraterone plus prednisone, worsening of PROs was associated with a greater risk of radiographic progression.[30]

A limitation of the current analysis is that the number of patients and HRQL assessments decrease over time, which reduces the statistical power of the HRQL analysis in later cycles. In addition, the effect of a patient's disease progression on their HRQL cannot be separated from the impact of the type and duration of treatment received. Another limitation is that although the analysis thresholds selected for this study are stringent, derived results and conclusions are ultimately subject to them, and further standardization could promote more effective cross-comparisons. Finally, bias can occur regarding the HRQL of patients who complete the questionnaire versus those who do not. Even if baseline characteristics were quite similar within PROSELICA and FIRSTANA, median OS in the non-FACT-P population (<10% of patients) appeared lower compared with that in the FACT-P population. Questionnaire completion was high for both studies (>89%).

HRQL and FACT-P TS have been evaluated in other studies in mCRPC. After 25 weeks of treatment in the phase III AFFIRM trial, the mean FACT-P TS decreased by 1.52 points in post-chemotherapy patients who received enzalutamide compared with 13.73 points in patients who received placebo.[31] In the PROSELICA study, we demonstrate that the

FACT-P TS was often 'maintained or improved' in patients receiving cabazitaxel. In the phase III COU-AA-301 trial, post-chemotherapy patients who received abiraterone had significantly improved FACT-P TS (48% versus 32%) and a longer time to FACT-P TS deterioration (59.9 weeks versus 36.1 weeks) compared with patients who received placebo.[32] In PROSELICA, 38.8% and 40.5% of post-docetaxel patients receiving C20 or C25 had definitive improvements in their FACT-P TS. Of note, patients had a higher mean FACT-P TS at baseline in AFFIRM (enzalutamide arm 108.7) and COU-AA-301 (abiraterone arm 108.2) compared with PROSELICA (C20 arm 102.7; C25 arm 101.4). In the CARD study, which compared cabazitaxel with abiraterone or enzalutamide in patients with mCRPC who had received prior docetaxel and had previously progressed within 12 months while receiving the alternative androgen-signaling-targeted inhibitor (abiraterone or enzalutamide), the median time to FACT-P TS deterioration was 14.8 months [95% confidence interval (CI) 6.3 to not estimable (NE)] with cabazitaxel versus 8.9 months (95% CI 6.3 to NE) with abiraterone or enzalutamide (hazard ratio 0.72, 95% CI 0.44-1.20; log-rank $P = 0.21$).[33] The median radiographic progression-free survival was significantly longer (8.0 months versus 3.7 months) among patients who received cabazitaxel compared with abiraterone or enzalutamide, which may explain why the time to FACT-P TS deterioration was shorter among patients who received abiraterone or enzalutamide.[34]

In the phase III COU-AA-302 and PREVAIL trials in chemotherapy-naive mCRPC, HRQL data have been reported.[35,36] In COU-AA-302, the median time to deterioration in FACT-P TS was 12.7 months (95% CI 11.1-14.0) in patients who received abiraterone plus prednisone compared with 8.8 months (95% CI 7.4-10.6) in patients who received prednisone. Similarly, in PREVAIL, the median time to deterioration in FACT-P TS was 11.3 months (95% CI 11.1-13.9) in patients who received enzalutamide compared with 5.6 months (95% CI 5.5-5.6) in patients who received placebo. In FIRSTANA, we demonstrate that the FACT-P TS is 'maintained or improved' in more than two-thirds of all patients. Of note, patients had a higher mean FACT-P TS at baseline in COU-AA-302 (abiraterone arm 122.1) and PREVAIL (enzalutamide arm 119.6) compared with FIRSTANA (D75 arm 106.4; C20 arm 106.2; C25 arm 105.5). It is also of note that patients included in the PREVAIL and COU-AA-302 studies were asymptomatic or mildly symptomatic (a score of 0-3 for item 3 of the Brief Pain Inventory short form) and the control arm in these studies was placebo or prednisone with placebo. In CABA-DOC, a more recent cross-over trial assessing patient preference between cabazitaxel and docetaxel in the chemotherapy-naive mCRPC setting, cabazitaxel was preferred; the most common factors for influencing preference were fatigue, HRQL, hair loss, and pain.[37] In the phase III CHAARTED trial investigating androgen deprivation therapy (ADT) versus ADT plus docetaxel for patients with metastatic hormone-sensitive prostate cancer, both study arms reported a similar minimal change in HRQL over time.[38] Regarding fatigue, in the AQUARiUS study, fatigue outcomes were more favorable in chemotherapy-naive patients with mCRPC who received abiraterone compared with enzalutamide.[39] In STAMPEDE, a multi-arm, multi-stage trial, that in part investigated docetaxel and abiraterone in patients with metastatic hormone-sensitive prostate cancer, HRQL was higher among patients who received abiraterone compared with docetaxel in the first 2 years of treatment, although this difference did not meet the predefined clinically meaningful threshold.[40] Direct comparison of patients who received docetaxel or abiraterone in STAMPEDE showed no evidence of a difference in OS.[41] However, safety profiles of androgen-signaling-targeted inhibitors differ from taxane chemotherapies, which may explain why the HRQL was different between patients who received docetaxel compared with abiraterone.

Overall, our data suggest that the HRQL improvements seen with docetaxel and cabazitaxel are similar to those observed with various other mCRPC treatments and suggest that disease control with an active anticancer treatment improves HRQL.

Conclusions

In PROSELICA and FIRSTANA collectively, >40% of the 2131 evaluable patients with mCRPC had a definitive improvement in FACT-P TS, which occurred early and was maintained, and >75% 'maintained or improved' their FACT-P TS. Our analysis was carried out using stringent FACT-P TS improvement criteria on data from two clinical trials where questionnaire compliance rates were >89%; a rate reflective of oncology randomized, controlled trials.[42] In PROSELICA, FACT-P TS was 'maintained or improved' in 80.1% and 78.4% of patients receiving C20 and C25 after docetaxel, respectively. In FIRSTANA, FACT-P TS was 'maintained or improved' in 76.5%, 73.9%, and 74.0% of chemotherapy-naive patients receiving D75, C20, and C25, respectively. In both studies pain was often 'maintained or improved' in patients receiving chemotherapy, although in FIRSTANA the PPI score was only 'maintained or improved' for >40% of patients receiving chemotherapy. Overall, our data suggest that patients with mCRPC receiving chemotherapy often have 'maintained or improved' HRQL.

ACKNOWLEDGEMENTS

The authors received editorial support from Mark Cockerill of MediTech Media, funded by Sanofi.

FUNDING

This study was supported by Sanofi (no grant number).

DISCLOSURE

AT: AstraZeneca (employment), Novartis, Sanofi, Astellas Pharma, Pfizer, Janssen, Ipsen (consulting or advisory role), Pfizer (research funding), and Novartis, Sanofi, Pfizer (travel, accommodations, expenses). KF: Janssen, Sanofi, Astellas Pharma (honoraria), Janssen Oncology, Bayer, Astellas Pharma, Sanofi, Orion Pharma GmbH, Curevac, AstraZeneca

(consulting or advisory role), and Amgen, Janssen (travel, accommodations, expenses). OS: Bayer, Bellicum Pharmaceuticals, Johnson & Johnson, Medivation, Oncogenex, Sanofi, Tokai Pharmaceuticals, AstraZeneca (Inst), Progenics (Inst), Dendreon (consulting or advisory role), Bayer (Inst), Johnson & Johnson (Inst), Sanofi (Inst), Dendreon (Inst), Endocyte (Inst), Innocrin Pharma (Inst), Progenics (Inst) (research funding), Bayer, Johnson & Johnson, Medivation, Oncogenex, Sanofi, Tokai Pharmaceuticals, AstraZeneca, Progenics (travel, accommodations, expenses). SO: Sanofi, Janssen, Bayer, and Astellas (advisory board or board of directors). DB, KT, AO, and EMP: Sanofi employees. ME: VERU Inc. (board of directors). JB: Sanofi (honoraria), Sanofi, AstraZeneca, GlaxoSmithKline, Genentech, Roche, Merck (consulting or advisory role), AstraZeneca/MedImmune (speakers' bureau), AstraZeneca/MedImmune (Inst), GlaxoSmithKline (Inst), Sanofi (Inst), Merck Sharp & Dohme (Inst), Genmab (Inst), Genentech (Inst) (research funding) and patent on abiraterone acetate with prednisone.

REFERENCES

1. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Allen C, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncol*. 2017;3:524-548.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7-34.
3. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2012;13:983-992.
4. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368:138-148.
5. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367:1187-1197.
6. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369:213-223.
7. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411-422.
8. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer: extended analysis of the Phase 3 PREVAIL study. *Eur Urol*. 2017;71:151-154.
9. de Bono JS, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382:2091-2102.
10. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351:1502-1512.
11. National Comprehensive Cancer Network I. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Prostate Cancer Version 2. 2018*. 2018. Available at: https://www.nccn.org/professionals/physician_gls/default.aspxref. Accessed March 12, 2021.
12. Sanofi. *Jevtana (cabazitaxel) Prescribing Information*. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/201023s025lbl.pdf. Accessed March 12, 2021.
13. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376:1147-1154.
14. Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m^2) and the currently approved dose (25 mg/m^2) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. *J Clin Oncol*. 2017;35:3198-3206.
15. Oudard S, Fizazi K, Sengelov L, et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: a randomized Phase III trial-FIRSTANA. *J Clin Oncol*. 2017;35:3189-3197.
16. Thompson JC, Wood J, Feuer D. Prostate cancer: palliative care and pain relief. *Br Med Bull*. 2007;83:341-354.
17. Carles J, Pichler A, Korunkova H, et al. An observational, multicentre study of cabazitaxel in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel (CAPRISTANA). *BJU Int*. 2019;123:456-464.
18. Adam S, Afifi H, Thomas M, et al. Quality of life outcomes in a pediatric thalassemia population in Egypt. *Hemoglobin*. 2017;41:16-20.
19. Cella D, Nichol MB, Eton D, et al. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy–Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health*. 2009;12:124-129.
20. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes*. 2003;1:79.
21. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11:570-579.
22. Yount S, Cella D, Banik D, et al. Brief assessment of priority symptoms in hormone refractory prostate cancer: the FACT Advanced Prostate Symptom Index (FAPSI). *Health Qual Life Outcomes*. 2003;1:69.
23. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain*. 1975;1:277-299.
24. McLeod LD, Coon CD, Martin SA, et al. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11:163-169.
25. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003;41:582-592.
26. Revicki D, Hays RD, Cella D, et al. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol*. 2008;61:102-109.
27. Sullivan PW, Mulani PM, Fishman M, et al. Quality of life findings from a multicenter, multinational, observational study of patients with metastatic hormone-refractory prostate cancer. *Qual Life Res*. 2007;16:571-575.
28. Lorusso D, Bria E, Costantini A, et al. Patients' perception of chemotherapy side effects: expectations, doctor-patient communication and impact on quality of life - An Italian survey. *Eur J Cancer Care (Engl)*. 2017;26:e12618.
29. Thiery-Vuillemin A, Hvid Poulsen M, Lagneau E, et al. Impact of abiraterone acetate plus prednisone or enzalutamide on patient-reported outcomes in patients with metastatic castration-resistant prostate cancer: final 12-mo analysis from the observational AQUARiUS study. *Eur Urol*. 2019;77:380-387.
30. Traina S, Li T, Johnson K, et al. Analysis of the relationship between patient-reported outcomes (Pros) and clinical outcomes in metastatic castration-resistant prostate cancer (Mcrpc) patients without prior chemotherapy. *Value Health*. 2015;18:A335-A336.
31. Cella D, Ivanescu C, Holmstrom S, et al. Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate cancer after chemotherapy: additional analyses from the AFFIRM randomized clinical trial. *Ann Oncol*. 2015;26:179-185.
32. Harland S, Staffurth J, Molina A, et al. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy. *Eur J Cancer*. 2013;49:3648-3657.
33. Fizazi K, Kramer G, Eymard JC, et al. Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study. *Lancet Oncol*. 2020;21:1513-1525.

34. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med*. 2019;381:2506-2518.
35. Basch E, Autio K, Ryan CJ, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. *Lancet Oncol*. 2013;14:1193-1199.
36. Loriot Y, Miller K, Sternberg CN, et al. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. *Lancet Oncol*. 2015;16:509-521.
37. Baciarello G, Delva R, Gravis G, et al. Final results from the randomized CABADOC trial: patient preference between cabazitaxel and docetaxel for first-line chemo. *J Clin Oncol*. 2019;37:5017.
38. Morgans AK, Chen YH, Sweeney CJ, et al. Quality of life during treatment with chemohormonal therapy: analysis of E3805 chemohormonal androgen ablation randomized trial in prostate cancer. *J Clin Oncol*. 2018;36:1088-1095.
39. Thiery-Vuillemin A, Poulsen MH, Lagneau E, et al. Impact of abiraterone acetate plus prednisone or enzalutamide on patient-reported outcomes in patients with metastatic castration-resistant prostate cancer: final 12-mo analysis from the observational AQUARiUS study. *Eur Urol*. 2020;77:380-387.
40. Rush HL, Cook AD, Brawley CD, et al. Comparative quality of life in patients randomized contemporaneously to docetaxel or abiraterone in the STAMPEDE trial. *J Clin Oncol*. 2020;38:14.
41. Sydes MR, Spears MR, Mason MD, et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. *Ann Oncol*. 2018;29:1235-1248.
42. Roydhouse JK, King-Kallimanis BL, Howie LJ, et al. Blinding and patient-reported outcome completion rates in US Food and Drug Administration Cancer Trial Submissions, 2007-2017. *J Natl Cancer Inst*. 2019;111:459-464.