# Quality of Life and Pain During Treatment of Metastatic Castration-resistant Prostate Cancer With Cabazitaxel In Routine Clinical Practice

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Original Study



# Quality of Life and Pain During Treatment of Metastatic Castration-resistant Prostate Cancer With Cabazitaxel In Routine Clinical Practice

Florence Joly,[1] Stéphane Oudard,[2] Karim Fizazi,[3] Florence Tubach,[4] Jérémy Jove,[5] Clémentine Lacueille,[5] Stéphanie Lamarque,[5] Estelle Guiard,[5] Aurélie Balestra,[5] Cécile Droz-Perroteau,[5] Annie Fourrier-Reglat,[5,6] Magali Rouyer,[5] Nicholas Moore[5,6]

## Abstract

**In a real-life prospective patient outcomes study in 60 patients with metastatic castration-resistant prostate cancer, cabazitaxel in the second line or beyond was associated with stable or improved quality of life, and stable or reduced pain in at least one-third of patients, during and beyond treatment.**

**Background:** This prospective study collected quality of life (QoL) and pain data during cabazitaxel treatment in patients with advanced metastatic or castration-resistant prostate cancer (mCRPC). **Patients and Methods:** Functional Assessment of Cancer Therapy-Prostate (QoL) and Brief Pain Inventory-Short Form (pain) questionnaires were collected over 6 months. **Results:** In 61 patients with mCRPC (median age, 72 years) from 22 centers, metastatic sites were bones (97%), lymph nodes (36%), and visceral (20%); 25% received cabazitaxel in the second line, 29% in the third line, and 46% in the fourth line or beyond. All had been previously treated with docetaxel, except one with paclitaxel, and 75% also with abiraterone, enzalutamide, or both. The median cabazitaxel duration was 3.4 months. Forty-nine patients were evaluable for QoL and 44 for pain. QoL was improved in 37%, maintained in 35%, and deteriorated in 37%. In 27%, pain decreased $\geq$ 1 level and remained stable in 52%. A total of 34% lowered analgesic drug level. Prostate-specific antigen response $\geq$ 50% was observed in 11 (32.6%) patients, of whom 7 improved QoL and 1 was stable. At 6 months, 83.6% survived (95% confidence interval, 71.7%-90.8%). A total of 46% had $\geq$ 1 grade $\geq$ 3 adverse events, mainly anemia and neutropenia. **Conclusion:** Although cabazitaxel was given as the third line and beyond for three-quarters of patients, over one-third had improved QoL and/or decreased pain during treatment.

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**Keywords:** FACT-P scores, Pain score BPI-S, Prospective observational study, Real-world information, Survival

## Introduction

Despite initial local treatment, prostate cancer can become castration-resistant and develop metastases. Additionally, around 10% of patients with prostate cancer are metastatic at diagnosis.[1] Docetaxel in combination with prednisone was approved for first-line treatment of metastatic castration-resistant prostate cancer (mCRPC) in 2004, improving overall survival (OS) mainly in symptomatic patients.[2] Cabazitaxel,[3] abiraterone acetate (abiraterone),[4] and enzalutamide[5]

[1]Medical Oncology Department, Centre François Baclesse, CHU Côte de Nacre, Caen, France
[2]Medical Oncology Department, Hôpital Européen Georges Pompidou, Paris Descartes University, Paris, France
[3]Medical Oncology Department, Institut Gustave Roussy, Villejuif, France
[4]Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP.Sorbonne Université, Hôpital Pitié Salpêtrière, Département de Santé Publique Centre de Pharmacoépidémiologie (Cephepi), Paris, France
[5]Bordeaux PharmacoEpi, University of Bordeaux, Bordeaux, France
[6]Inserm CIC1401 & U1219, Bordeaux, France

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Address for correspondence: Nicholas Moore, MD, PhD, Bordeaux PharmacoEpi - CIC1401, Université de Bordeaux - CHU de Bordeaux, Bâtiment Le Tondu - Case 41, 146, rue Léo Saignat, 33076 Bordeaux Cedex, France
E-mail contact: nicholas.moore@u-bordeaux.fr


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have been licensed for second-line treatment of mCRPC after failure of docetaxel. The latter 2 have subsequently been approved also for first-line treatment. The usual treatment of advanced prostate cancer is now based on docetaxel and one of these hormonal therapies, in indifferent order, followed by cabazitaxel when these treatments fail,[6,7] as confirmed by the CARD trial.[8]

Cabazitaxel was approved based on the results of the Phase III TROPIC trial, which compared cabazitaxel with mitoxantrone in 755 patients with mCRPC who progressed during or after docetaxel.[9] Patients receiving cabazitaxel 25 mg/m$^2$ had significantly better survival (15.1 vs. 12.7 months) than patients on mitoxantrone. The PROSELICA study showed the non-inferiority of cabazitaxel 20 mg/m$^2$ (C20) versus 25 mg/m$^2$ (C25) in 1200 post docetaxel patients with mCRPC.[10] Similar findings were reported in the first-line setting when C20 and C25 were compared with docetaxel.[11] A more recent trial, CARD, found superiority of cabazitaxel over abiraterone or enzalutamide in the third line, on a number of clinical outcomes.[8] In a real-life study in France where 82% of patients were in third line or more, we found a median OS of 12 months.[12] This was comparable to the 13.2 months in the CAPRISTANA observational study, where 85% of patients were in second line.[13]

Beyond survival, QoL and pain are major issues in these often elderly patients with advanced metastatic disease. In CAPRISTANA, QoL was maintained or improved in 72.5% of patients, and 53.6% of patients reported pain improvement.[13]

At the time of market approval of cabazitaxel in France in October 2011, the French Health Authorities requested a post-authorization study in real life to evaluate the impact of cabazitaxel on survival, QoL, pain, and analgesic use in patients with mCRPC. A first study confirmed survival characteristics of patients with mCRPC treated with cabazitaxel.[12] The present prospective study was set up to study QoL and pain, using real-world patient-reported data over 6 months.

## Materials and Methods

### *Study Design*

FUJI (Follow-Up of Jevtana in real life) is a French multicenter observational cohort study of patients with mCRPC starting treatment with cabazitaxel. A first historical study of 18-month survival in patients starting cabazitaxel in 2013 to 2015 has been reported elsewhere.[12] In the present study, FUJI-QoL, data on QoL and pain were collected prospectively over a 6-month treatment period in patients starting cabazitaxel between March 1, 2016 and February 28, 2017.

### *Participants*

Oncologists having participated in the first part of the study[12] were invited to include prospectively all patients with mRCPC who were to be newly treated with cabazitaxel, fulfilled the eligibility criteria, and consented to the study. All patients were informed about the goals and procedures of the study and provided written informed consent. Patients participating in clinical trials or who could not read or understand the study information or the patient questionnaires were not eligible.

Enrollment continued until the target sample size of 60 patients had been achieved.

### *Data Collection*

Baseline data were collected from patient files into an electronic case report form by a dedicated clinical research assistant and validated by the participating physician. These included the date of first prescription of cabazitaxel, patient demographics, medical and treatment history, cabazitaxel treatment modalities, clinical, biological (prostate-specific antigen [PSA]) and radiologic outcome (response, progression or death), analgesic consumption, and adverse events (AEs) reported during cabazitaxel treatment. AEs were coded using the current MedDRA classification, and their severity was coded according to the grading system of the National Cancer Institute's Common Terminology for the Classification of Adverse Events (NCI-CTCAE v4.0). AEs requiring hospitalization were identified.

Patients were asked to complete the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire (Version 4.0)[14] and the Brief Pain Inventory-Short Form (BPI-SF)[15] at inclusion, before every cabazitaxel infusion, and in the month following the last cabazitaxel administration (for patients moving to a new line of treatment). The FACT-P questionnaire consists of 39 items distributed across 5 dimensions. Each item is rated for impact over the previous 7 days on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much). The total score can thus range from 0 (no impact anywhere) to 156 (major impact on all aspects of QoL). The BPI-SF is a 15-item questionnaire. Four items measure pain intensity (worst, least, average, and current pain severity) on a 10-point ordinal scale. The mean score on these 4 scales was used for the analysis.

### *Outcome Variables*

The primary outcome variables were FACT-P and BPI-SF scores over the 6 months of the study and during the different treatment periods (before, during, and after cabazitaxel). Changes in QoL were defined as clinically meaningful improvement with changes from baseline $\geq +10$ points and deterioration with changes from baseline $\leq -10$ points.[16] Three categories of pain level at baseline were defined based on the plain intensity score of the BSI-SF: a mild pain for pain severity score (0-3), a moderate pain for pain severity score (4-6), and a severe pain for pain severity score (7-10).[16] The changes in pain during treatment were defined as an improvement for at least a decrease of 1 pain level, and deterioration for at least an increase of 1 pain level.

Secondary outcomes were OS, progression-free survival (PFS), and PSA response. PSA response was defined by a PSA decrease of at least 50% from baseline. Biological progression was defined as a confirmed increase in PSA of at least 25% and of at least 2 ng/mL compared to the lowest post-treatment value (PSA nadir) after initiation of cabazitaxel treatment, confirmed by a second PSA value at least 3 weeks later. Radiologic progression was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[17] Clinical progression was defined according to the opinion of the treating physician. Secondary outcomes were essentially defined to compare this study with the previous study of cabazitaxel.

In addition, patient characteristics, treatment modalities, occurrence of AEs, and use of analgesics were analyzed.

### *Statistical Analysis*

The target sample size in the QoL cohort (60 subjects) was determined to estimate the FACT-P score with a precision of 3.3

points and the BPI-SF with a precision of 10.5%. QoL and pain were analyzed from raw data. Sensitivity analyses tested multiple imputation of missing values using the Monte Carlo Markov Chain method. OS and PFS were estimated using Kaplan-Meier survival analysis. All statistical analyses were performed with SAS (SAS Institute, version 9.4, Cary, NC).

### *Ethics*

The study was done in accordance with all relevant national legislation and guidelines for observational studies, with approval from the French national data protection agency (CNIL). The study protocol was submitted and approved by the French health authorities as part of the post-marketing commitments of the manufacturer of cabazitaxel (Sanofi-Aventis). All patient data in the study database were rendered anonymous. Written informed consent was obtained from all patients prior to inclusion. The study was registered with the European Union PAS registry (ENCEPP/SDPP/10391).

## Results

### *Study Population*

A total of 56 physicians agreed to participate in this prospective QoL and pain study. Of these, 22 invited 63 patients who were starting cabazitaxel treatment to participate in the study. Two patients refused. The remaining 61 patients were included and provided with the questionnaires. Complete evaluable FACT-P and BPI-SF data (ie, questionnaire at inclusion and at least 1 during follow-up) were available for 49 (80.3%) and 44 (72.1%) patients, respectively. The patient recruitment process is illustrated in Figure 1, and baseline characteristics are in Table 1. There was no difference in patient characteristics between patients who were analyzable and those who were not because of missing data.

The median time from prostate cancer diagnosis to cabazitaxel initiation was 6.8 years. The median time from diagnosis to metastasis was 35 months. All patients but 1, treated with paclitaxel, had been previously treated with docetaxel. Cabazitaxel was prescribed in the second-, third-, and fourth-line or beyond in 24.6%, 29.5%, and 45.9% of patients, respectively. Three-quarters (75%) of the patients had been previously treated with enzalutamide and/or abiraterone.

### *Treatment With Cabazitaxel*

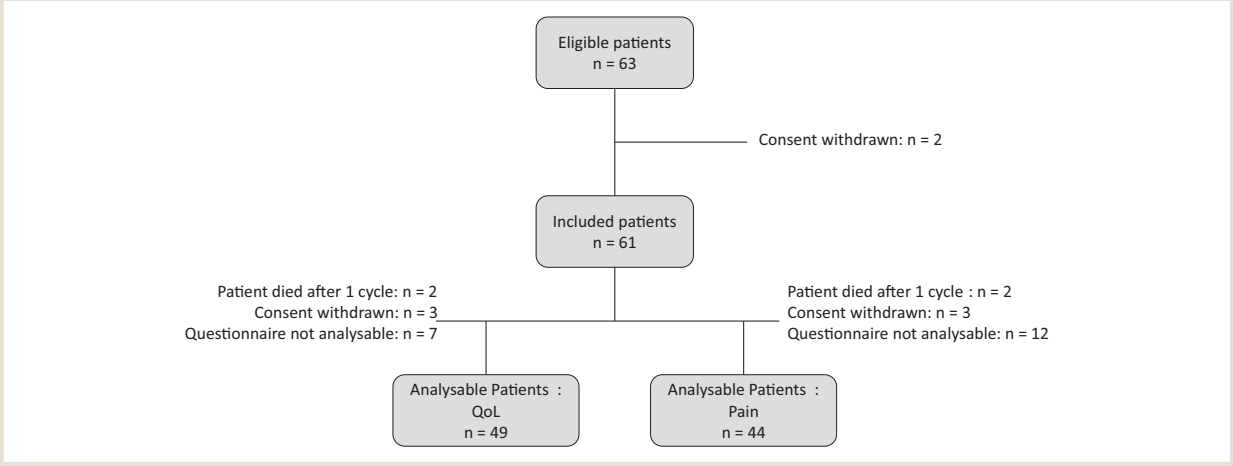
Cabazitaxel was given every 3 weeks in 52 (85.2%) patients with a starting dose of 25 mg/m$^2$ in 25 (48.1%) patients. Nine patients had different schedules. Twenty-seven patients had a standard schedule but a lower starting dose. The median duration of cabazitaxel treatment was 3.4 months with a median of 5 cycles.

*Quality of Life.* At inclusion, the mean total FACT-P score was 93.3 in the 49 evaluable patients of the QoL cohort (Table 2). The most affected FACT-P dimension was functional well-being. During treatment, total FACT-P scores remained stable in 34.4% of patients, improved by at least 10 points in 36.7%, and decreased by at least 10 points in 36.7% (Figure 2). These results were globally similar after multiple imputation of missing data, with improvement in QoL of 10 points or higher in 41.1% of patients, maintenance in QoL in 28.6% of patients, and a deterioration in QoL of at least −10 points in 37.5% of patients. With regard to individual sub-scores, the highest proportion of patient improvement was observed for the functional well-being score (46.9% of patients improved) and the prostate cancer score (61.2%). There was no consistent difference in QoL based on previous lines of treatment, but with small numbers of patients on each line.

### *Pain*

At inclusion, the mean BPI-SF "Pain Severity" score in the 44 evaluable patients was 3.1, with around two-thirds of patients reporting mild pain (Table 2). During treatment, pain intensity remained stable in 52.3% of patients, improved in 27.3%, and deteriorated in 20.5%. The change of "Pain Severity" score is illustrated in Figure 3. Many patients initially improved, then

**Figure 1** Patient Flow diagram




Abbreviation: QoL = Quality of life.

**Table 1** Patient Characteristics at Inclusion

| | QoL Cohort n = 61 (%) |
|---|---|
| Median age at cabazitaxel initiation, y [IQR] | 72.0 [69-78] |
| Median time from prostate cancer diagnosis to cabazitaxel initiation, y [IQR] | 6.8 [3.3-11.6] |
| Gleason score at diagnosis | |
| 6-7 | 30 (49.2) |
| 8-10 | 24 (39.3) |
| Missing data | 7 (11.5) |
| Median time from primary diagnosis to metastases, mos [IQR] | 35 [0.4-100.8] |
| Status of metastases | |
| Synchronous | 23 (37.7) |
| Metachronous | 38 (62.3) |
| Visceral metastases at cabazitaxel initiation | 12 (19.7) |
| > 5 bone metastases at cabazitaxel initiation | 48 (81.4) |
| ECOG PS score at cabazitaxel initiation | |
| 0-1 | 23 (37.7) |
| ≥ 2 | 9 (14.8) |
| Not available | 29 (47.5) |
| Median PSA value at cabazitaxel initiation, ng/mL [IQR] | 109.5 [24-272] |
| Polypharmacy, > 5 drugs (excluding cancer treatments) | 16 (26.2) |
| Number of cancer treatments* before cabazitaxel initiation | |
| 1 | 15 (24.6) |
| 2 | 18 (29.5) |
| 3 | 16 (26.2) |
| 4 or 5 | 12 (19.7) |
| Docetaxel before cabazitaxel initiation | 60 (98.4) |
| Abiraterone acetate before cabazitaxel initiation | 37 (60.7) |
| Enzalutamide before cabazitaxel initiation | 37 (60.7) |
| Abiraterone acetate and/or enzalutamide before cabazitaxel initiation | 46 (75.4) |
| Previous medical history | |
| Cardiovascular disorders | 44 (72.1) |
| Digestive disorders | 36 (59.0) |
| Musculoskeletal disorders | 30 (49.2) |
| Metabolism and nutrition disorders | 29 (47.5) |
| Urogenital disorders | 26 (42.6) |
| Respiratory and ENT disorders | 18 (29.5) |
| Nervous disorders | 14 (23.0) |
| Hepatic disorders | 8 (13.1) |
| Other cancer | 7 (11.5) |

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; ENT = ear, nose, and throat; IQR = interquartile range; PSA = prostate-specific antigen; QoL = quality of life.

**Table 2** Quality of Life (FACT-P) and Pain (BPI-FS) Scores

| Characteristics | Data |
|---|---|
| Quality of life (FACT-P) | n = 49 |
| Total FACT-P score at inclusion (mean ± SD) | 93.3 ± 18.3 |
| FACT-P dimension scores at inclusion (mean ± SD) | |
| Physical well-being (range, 0-28) | 18.0 ± 5.9 |
| Social/family well-being (range, 0-28) | 19.8 ± 3.8 |
| Emotional well-being (range, 0-24) | 16.0 ± 4.8 |
| Functional well-being (range, 0-28) | 12.9 ± 5.0 |
| Prostate cancer (range, 0-48) | 26.6 ± 6.6 |
| Trial outcome index[a] (range, 0-96) | 57.5 ± 15.0 |
| FACT-G[b] (range, 0-108) | 66.7 ± 13.5 |
| Change during treatment (total FACT-P score) | |
| Stable | 17 (34.7) |
| Improvement of ≥ 10 points | 18 (36.7) |
| Median time to change, d | 42.5 |
| Deterioration of ≤ 10 points | 18 (36.7) |
| Median time to change, d | 45.5 |
| Pain (BPI-FS) scores | n = 44 |
| Pain severity at inclusion (mean ± SD) | 3.1 ± 2.0 |
| Mild pain (pain severity score, 0-3) | 30 (68.2) |
| Moderate pain (pain severity score, 4-6) | 12 (27.3) |
| Intense pain (pain severity score, 7-10) | 2 (4.5) |
| Mean pain interference at i nclusion (±SD) | 3.4 ± 2.5 |
| Change during treatment | |
| Stable | 23 (52.3) |
| Improvement of ≥ 1 pain level | 12 (27.3) |
| Median time to change, d | 21 |
| Deterioration of ≥ 1 pain level | 9 (20.5) |
| Median time to change, d | 42 |

Data presented as n (%) or median ± standard deviation.
Abbreviations: BPI-SF = Brief Pain Inventory - Short Form; FACT-G = Functional Assessment of Cancer Therapy-General; FACT-P = Functional Assessment of Cancer Therapy-Prostate.
[a]Calculated as the sum of the functional well-being, physical well-being, and prostate cancer dimension scores.
[b]Calculated as the sum of the of the 4 well-being dimension scores.

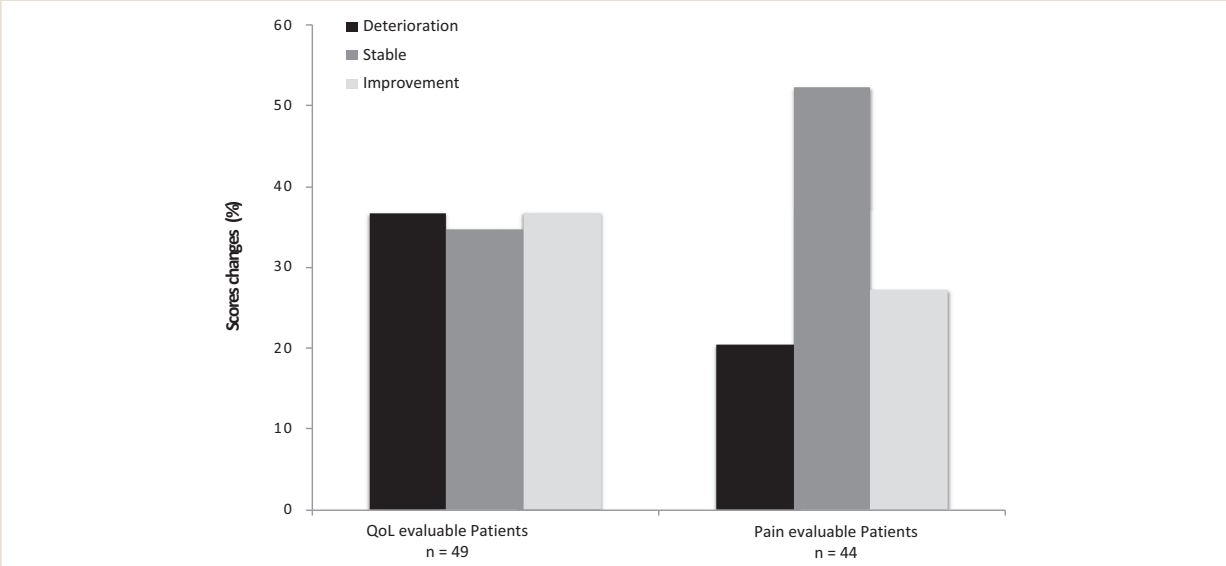
worsened as the disease progressed. The median time to improvement (21 days) was shorter than the median time to deterioration (42 days). Mean intensity scores remained essentially unchanged over the treatment period.

QoL was higher in patients with slight or moderate pain than in patients with severe pain (Figure 3) (test for trend $R^2$ 0.44; $P < .001$).

### *Analgesic Use*

Analgesic use at initiation and during treatment with cabazitaxel was collected from 2 data sources: medical records (~40%-60% of patients) and self-questionnaires (>90%), with a good concordance between the 2 sources for level II and III analgesic use, which concerned about 20% of patients for each level. From medical records, 27

**Figure 2** Change in Functional Assessment of Cancer Therapy-Prostate (FACT-P) Total Score and Pain Severity Scores During Cabazitaxel treatment




Abbreviation: QoL = Quality of life.

(44.3%) patients were using an analgesic before initiation of cabazitaxel and 40 (65.6%) patients during cabazitaxel treatment. Approximately one-third (34.4%) of patients reported decreased analgesic level during cabazitaxel, and approximately two-thirds (65.6%) of patients reported no increase. The introduction of a level II or III analgesic was observed in 8% to 10% of patients.

### *Other Outcomes*

*Overall and Progression-Free Survival.* OS at 6 months was 83.6% (95% CI, 71.7%-90.8%). The median OS had not been reached at the end of the observation period. The median PFS was 3.7 months (95% CI, 3.0-4.5 months).

*PSA ≥ 50% Response.* Information on PSA response was available for 43 (70.5%) patients. In 14 (32.6%) patients, a response was noted within a median time of 3.7 months. Among the latter, 42.9% had a decreased level of analgesic use during cabazitaxel. Of the 11 patients with PSA response and evaluable QoL, 7 improved the QoL score and 1 was stable. The median time to PSA progression was 3.6 months.

*Adverse Events.* Among the 61 patients, 46% of patients had at least 1 grade ≥ 3 AE. The most common AEs were anemia (21%) and neutropenia (13%). Among the 8 patients with neutropenia, 25% received granulocyte-colony stimulating factor at each cabazitaxel infusion. Two patients developed febrile neutropenia despite having granulocyte-colony stimulating factor at each cabazitaxel infusion. A total of 85% of patients had all 3 recommended preventive medications (H1 and H2 antihistamines and steroids). Two deaths occurred, 1 owing to cardiac arrest and the other to hypoglycemic coma. Neither was considered by the physician to be related to cabazitaxel.

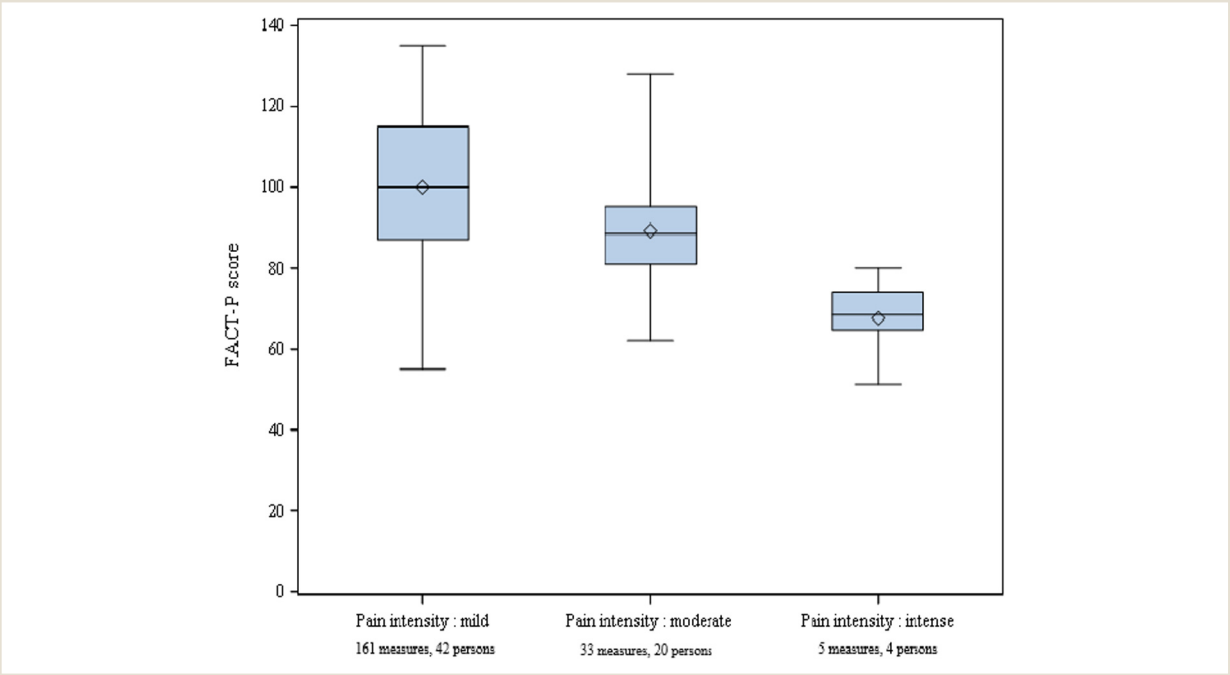
The AEs did not differ from what was expected from clinical trials and previous observational studies, by nature or by frequency.

## Discussion

The main objective of this study was to evaluate QoL and pain scores in patients starting cabazitaxel for mCRPC. These remained stable or improved over the cabazitaxel treatment period for three-quarters of the patients. Similar numbers of patients reported improvement or deterioration during treatment. These results support the benefit and tolerability of cabazitaxel at an advanced stage of the disease, after failure of docetaxel and abiraterone and/or enzalutamide. In these circumstances, QoL becomes of primary importance. The proportion (36.7%) of patients with a clinically significant improvement in QoL of ≥ +10 points on the FACT-P total score was comparable to that previously reported in studies of abiraterone and enzalutamide following docetaxel.[18,19] In the CAPRISTANA study of patients with mCRPC treated by cabazitaxel, 84.7% of whom received cabazitaxel as second-line therapy, QoL was maintained in 40.3% of patients or improved in 32.2%.[13] Here, these proportions were similar, maintained for 34.4% and improved for 36.7%, indicating that this benefit on QoL is maintained even when cabazitaxel is administered later: in our cohort cabazitaxel was given in the third line or beyond for 75% of patients.

Based on the BPI-SF pain severity score, 27% of patient in FUJI reported pain improvement (pain decrease ≥ 1 level), and 52%

**Figure 3** Quality of Life in Different Pain groups




Abbreviation: FACT-P = Functional Assessment of Cancer Therapy-Prostate.

were stable. These results remain comparable to those found in CAPRISTANA that indicated approximately 75% of patients with stable or improved pain measured with a FACT-P PCS pain score.[13] The stability of pain ratings during treatment is consistent with the observation that < 50% of patients increased the intensity of analgesic use over the course of the study and < 25% required initiation of a Level II or Level III analgesic. In the PROSELICA trial, comparing 20 mg/m$^2$ with 25 mg/m$^2$ cabazitaxel as initial dose, about 40% of patients in either group experienced pain progression. Health-related QoL indices were not different between groups, with a median time to deterioration of 7 to 11 months.[10]

### *Weaknesses and Strengths*

This is a prospective study using primary patient data and specific questionnaires for mCRPC. Data for death and progression were abstracted from the clinical files. Patients came from various cancer treatment centers in France, and appear to be typical of the population of patients with prostate cancer in terms of age, previous cancer therapy lines, or concomitant illnesses. In a previous historical cohort study of cabazitaxel users in 401 patients with mCRPC in France, the mean age was 70, and clinical characteristics were similar. The median PFS was 3.9 months in that population, compared with 3.7 months here.[12] The median OS was 11.9 months, whereas it was not measurable here owing to the shorter follow-up. In PROSELICA,[10] comparing 20 mg/m$^2$ with 25 mg/m$^2$ as initial dose, the median time to progression (PFS) was 2.9 months for C20 and 3.5 months for C25.[10] The short follow-up in the present study was related to the objectives of the study, which were patient reported outcomes of QoL and pain, over the first 6 months of treatment and follow-up.

Only 44 (Pain) to 49 (QoL) patients out of the 61 recruited provided analyzable data, resulting in potential selection bias, even though the patient characteristics of the responders were the same as those of the complete initial cohort. We have experience in another study that non-responders do not necessarily alter results.[20] The results of these questionnaires were consistent with other studies in similar settings.

## Conclusion

In conclusion, 37% of patients initiating cabazitaxel had improved QoL during treatment, and 35% did not worsen. This is consistent with cabazitaxel's reported effectiveness and manageable tolerability, including in heavily pretreated patients. Pain, which is correlated to QoL, appeared stable over the treatment period. This is important at such an advanced stage of cancer, especially considering the often very painful nature of bone metastases. Quality as well as quantity of life is increasingly important in daily practice, and treatments which do not alter QoL because of side effects are crucial in late-stage prostate cancer.

### *Clinical Practice Points*

- In patients with mCRPC, the use of cabazitaxel, as indicated, is susceptible of improving QoL, decreasing pain, and limiting the use of major analgesia.

## CRediT authorship contribution statement

**Florence Joly:** Conceptualization, Methodology, Supervision, Validation, Visualization, Writing - review & editing. **Stéphane**

**Oudard:** Conceptualization, Methodology, Supervision, Validation, Visualization, Writing - review & editing. **Karim Fizazi:** Conceptualization, Methodology, Supervision, Validation, Visualization, Writing - review & editing. **Florence Tubach:** Conceptualization, Methodology, Supervision, Validation, Visualization, Writing - review & editing. **Jérémy Jove:** Data curation, Formal analysis, Resources, Software, Supervision, Writing - review & editing. **Clémentine Lacueille:** Data curation, Formal analysis, Resources, Software, Supervision, Writing - review & editing. **Stéphanie Lamarque:** Investigation, Project administration, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing. **Estelle Guiard:** Investigation, Project administration, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing. **Aurélie Balestra:** Investigation, Project administration, Resources, Validation, Writing - original draft, Writing - review & editing. **Cécile Droz-Perroteau:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Annie Fourrier-Reglat:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - review & editing. **Magali Rouyer:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Nicholas Moore:** Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

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## Disclosure

N.M. has received fees from Sanofi-Aventis for training in pharmacoepidemiology, independent from and before this study. He has received training or consulting fees from other pharmaceutical companies not involved in this study or in the treatment of prostate cancer. Bordeaux PharmacoEpi has several dozen ongoing studies financed by pharmaceutical companies outside the scope of this study. The salaries of Bordeaux PharmacoEpi employees (M.R., J.J., C.L., S.L., E.G., A.B., C.dP.) are derived in part from the funding of this study, but they have no direct conflict of interest. S.O. declares honoraria from Sanofi, Astellas, Janssen, Bayer, Pfizer, Novartis, Ipsen, MSD, BMS, and Astra Zeneca. F.J. declares scientific board, consulting, or lecture during symposium for Pfizer, Sanofi, Novartis, Bayer, Ipsen, Roche, Astra Zeneca, Tesaro, Astellas, Janssen, BMS, and MSD; travel from Tesaro, Janssen, Astra-Zeneca, BMS, and Roche. K.F. declares participation to advisory boards/honorarium for Astellas, AAA, Bayer, Clovis, Curevac, Incyte, Janssen, MSD, Orion, and Sanofi. F.T. is head of the Centre de Pharmacoépidémiologie (Cephepi) of the Assistance Publique — Hôpitaux de Paris and of the Clinical Research Unit of Pitié-Salpêtrière Hospital. Both these structures have received research funding, grants, and fees for consultant activities from a large number of pharmaceutical companies, which have contributed indiscriminately to the salaries of its employees. F.T. did not receive any personal remuneration from these companies. The remaining authors have stated that they have no conflicts of interest.

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