Use of cabazitaxel in treatment of metastatic Castration-Resistant Prostate Cancer (mCRPC): patient characteristics, safety and effectiveness in the FUJI cohort

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Background

Prostate cancer is the most common cancer in men in France; it evolves slowly but its prognosis is poor at the metastatic stage. Several therapeutic strategies are available for patients with metastatic castration-resistant prostate cancer (mCRPC). Since 2004, docetaxel has been the first-line treatment of mCRPC. Since 2011, cabazitaxel (CAB), abiraterone acetate, and enzalutamide have obtained an European marketing authorization as second-line treatment, then as a first-line treatment for the latter two. Little data on CAB use in real-life practice is available. French Health Authorities have requested a post-authorization study to assess the performance of CAB in a real-life setting.

Objectives

- To evaluate the overall survival (OS) and PSA response in mCRPC patients treated by CAB.
- To evaluate the safety profile during CAB treatment.
- To evaluate prospectively quality of life (QoL) and pain during CAB treatment.

Declaration of Interest Statement

FUJI study obtained an ENCePP study seal (ENCEPP/SDPP/10391), performed by BPE platform with an unconditional grant from Sanofi-Aventis and supervised by a scientific committee.

Methods

➢ **Study design**
- French multicenter cohort study including a main cohort (401 patients in 42 centers) and a QoL cohort (61 patients in 22 centers).

➢ **Recruitment process and follow-up**
- Identification of potential centers based on drug sales.
- Main cohort: retrospective identification of patients initiating CAB from nominative hospital pharmacy registries between Sept. 2013 and Aug. 2015, with 18-months follow-up.
- QoL cohort: prospective identification of patients by physicians between Mar. 2016 and Mar. 2017, with 6-month follow-up.

➢ **Data collection**
- Data were collected from medical files using a standardized electronic Case **R**eport **F**orm.
- For QoL cohort, specific questionnaires were completed by patients: FACT-P questionnaire for QoL and Brief Pain Questionnaire - Short form (BPI-SF) for pain to be filled in before each CAB infusion, and up to 45 days after the last CAB infusion.

➢ **Clinical outcomes and data analysis**
- Adverse events (AE), based on the data collected through the medical files, coded using NCI-CTCAE v4.0 and MedDRA thesaurus.
- OS estimated using Kaplan-Meier method (time from first CAB infusion to death of any cause).
- Multivariate Cox regression analysis of factors associated with death in main cohort.
- QoL and pain were analyzed from raw data and after multiple imputation of missing data (Monte Carlo Markov Chain method).

Results

Characteristics of patients and real-life use of treatment

Table 1. Baseline characteristics of patients and CAB use for main and QoL cohorts

	Main cohort n = 401	QoL cohort n = 61
Baseline characteristics		
Median age at CAB initiation, years	70.0	72.0
Median time of cancer history before CAB initiation, years	5.5	6.8
ECOG performance status at CAB initiation		
Missing data	237 (59.1)	29 (47.5)
0 or 1	101 (25.2)	23 (37.7)
≥ 2	63 (15.7)	9 (14.8)
Visceral metastases at CAB initiation, n (%)	79 (19.7)	12 (19.7)
> 5 bone metastases at CAB initiation, n (%)	269 (67.1)	48 (78.7)
Median PSA value at CAB initiation, ng/ml	112.5	109.5
Polypharmacy, > 5 drugs (excluding cancer treatments), n (%)	83 (20.7)	16 (26.2)
Number of cancer treatments* before CAB initiation, n (%)		
1 treatment	72 (18.0)	15 (24.6)
2 treatments	155 (38.7)	18 (29.5)
3 treatments	91 (22.7)	16 (26.2)
4 or 5 treatments	83 (20.7)	12 (19.7)
Docetaxel before CAB initiation, n (%)	401 (100.0)	60 (98.4)
Abiraterone acetate before CAB initiation, n (%)	307 (76.6)	37 (60.7)
Enzalutamide before CAB initiation, n (%)	134 (33.4)	37 (60.7)
Cabazitaxel use		
Starting dose of CAB 25 mg/m^2	185 (46.1)	24 (39.3)
CAB perfusion every 3 weeks, n (%)	364 (90.8)	52 (85.2)
Median CAB use, months	3.4	3.4

** apart from 1st generation hormonotherapies*

➢ In the main cohort, 95% had discontinued CAB within 18-month follow-up; the main reasons were disease progression or disease-related death (83.2%) and AE (15.2%). In the QoL cohort, 63.9% had discontinued CAB within 6-month follow-up; the main reasons were disease progression or related-death (89.7%) and AE (25.6%).

Survival outcomes

➢ The 18-month OS rate was 32.4% [95%CI, 27.8-37.1] and median OS was 11.9 months [95%CI, 10.1-12.9] for main cohort (**Figure 1**). Factors associated with the risk of death are presented in **Table 2**.

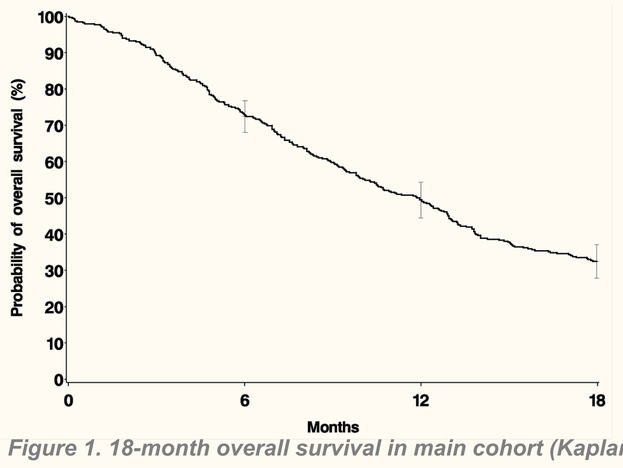

Figure 1. 18-month overall survival in main cohort (Kaplan-Meier method)

Table 2. Factors associated with the risk of death in the main cohort

	212 *vs* 113 HR [95%CI]	p
At least one grade ≥ 3 adverse event during CAB use	2.05 [1.53 – 2.73]	<0.0001
Visceral metastases at CAB initiation	1.98 [1.40 – 2.80]	0.0001
Polypharmacy, number of drugs > 5 (excluding cancer treatments)	1.74 [1.23 – 2.45]	0.0016
> 5 bone metastases at CAB initiation	1.74 [1.20 – 2.53]	0.0038
Time to disease progression after docetaxel		0.0198
Within 3 months of last docetaxel infusion	1.51 [1.07 – 2.14]	
Disease progression during docetaxel	1.69 [1.13 – 2.53]	
≥ 3 drugs with OS impact (docetaxel, abiraterone acetate, enzalutamide before CAB)	1.39 [1.00 – 1.92]	0.0488
PSA ≥ 135 ng/ml at CAB initiation	1.36 [1.01 – 1.82]	0.0404
≥ 10-years since primary cancer diagnosis	0.66 [0.46 – 0.96]	0.0297
≥ 6 months from last docetaxel dose to CAB initiation	0.71 [0.52 – 0.97]	0.0325

Results adjusted for the following covariates "Evolution of analgesics prescription over time" (non significant covariate but confounding factor with "Number of drugs excluding cancer treatment > 5") and "age"

PSA Response

➢ After at least 3-month of CAB use, a PSA decrease ≥ 50% from baseline concerned 39.9% of 258 patients with evaluable PSA in main cohort and 32.6% of 43 evaluable patients in QoL cohort (**Figure 2**).

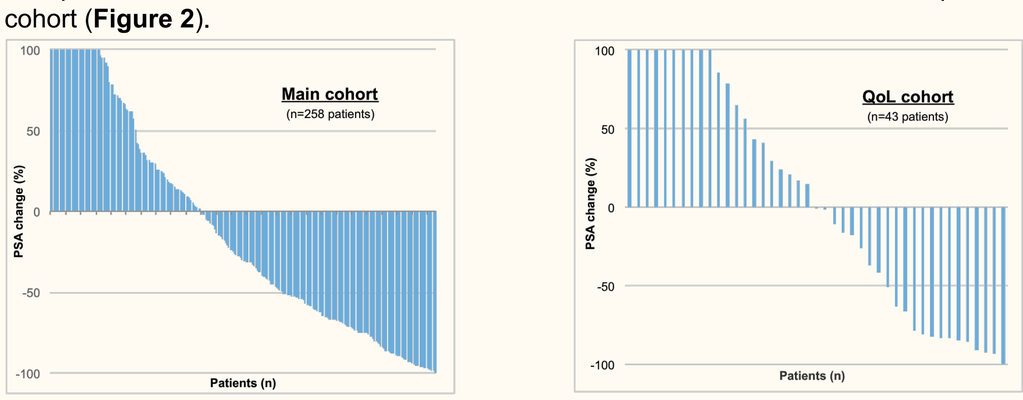

Figure 2. Waterfall plot showing maximum PSA change from baseline in main and QoL cohorts

Safety

Table 3. Safety profile according to grade NCI-CTCAE in main and QoL cohorts

	Main Cohort, n=401		QoL Cohort, n=61	
Adverse event (AE)	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
≥ 1 AE, n (%)	**397 (99.0)**	**222 (55.4)**	**61 (100.0)**	**28 (45.9)**
≥ 1 haematologic AE, n (%)	**371 (92.5)**	**160 (39.9)**	**57 (93.4)**	**19 (31.1)**
Anemia	363 (90.5)	108 (26.9)	56 (91.8)	13 (21.3)
Thrombopenia	116 (28.9)	21 (5.2)	20 (32.8)	3 (4.9)
Neutropenia	108 (26.9)	60 (15.0)	17 (27.9)	8 (13.1)
Leucopenia	100 (24.9)	38 (9.5)	22 (36.1)	5 (8.2)
Febrile neutropenia	32 (8.0)	32 (8.0)	2 (3.3)	2 (3.3)
General disorders, n (%)	**331 (82.5)**	**17 (4.2)**	**46 (75.4)**	**3 (4.9)**
Fatigue and asthenia	279 (69.6)	13 (3.2)	38 (62.3)	2 (3.3)
Gastrointestinal disorders, n (%)	**274 (68.3)**	**17 (4.2)**	**39 (63.9)**	-
Diarrhea	160 (39.9)	10 (2.5)	17 (27.9)	-
Nausea	120 (29.9)	4 (1.0)	20 (32.8)	-
Vomiting	79 (19.7)	5 (1.2)	11 (18.0)	-
Renal and urinary disorders, n (%)	**152 (37.9)**	**37 (9.2)**	**17 (27.9)**	**3 (4.9)**
Hematuria	81 (20.2)	6 (1.5)	10 (16.4)	-
Renal failure	30 (7.5)	29 (7.2)	3 (4.9)	3 (4.9)
Urinary retention	24 (6.0)	2 (0.5)	-	-
Infections and infestations, n (%)	**124 (30.9)**	**20 (5.0)**	**14 (23.0)**	**3 (4.9)**
Septicemia and septic shock	20 (5.0)	20 (5.0)	3 (4.9)	3 (4.9)

Quality of life and Pain evaluation

➢ **QoL**: 49 patients were evaluable for QoL. At CAB initiation, total FACT-P score was 93.3 on a scale of 0 to 156. QoL changes from baseline during CAB use are presented in **Table 4**.

Table 4. QoL changes from baseline during CAB use in QoL cohort

	QoL evaluable Patients (Raw data) n = 49	QoL evaluable Patients (Imputed data) n = 56
Total FACT-P score (Changes from baseline - 10 points)		
Stable QoL, n (%)	**17 (34.7)**	**16 (28.6)**
Improved QoL (≥ +10), n (%)	**18 (36.7)**	**23 (41.1)**
Median time to 1st QoL improvement (days)*	42.5	42.0
Deterioration of QoL (≤ -10), n (%)	**18 (36.7)**	**21 (37.5)**
Median time to 1st deterioration of QoL (days)*	45.5	42.0

** Concerned patients*

➢ **Pain**: 44 patients were evaluable for pain. At CAB initiation, 68.2% of patients had a mild pain ("Pain severity" score [0-3]), 27.3% of patients an moderate pain (score [4-6]) and 4.5% had a severe pain (score [7-10]). QoL changes from baseline during CAB use are presented in **Table 5**.

Table 5. Pain changes from baseline during cabazitaxel use in QoL cohort

	Pain evaluable Patients (Raw data) n = 44	Pain evaluable Patients (Imputed data) n = 56
Stable « Pain severity », n (%)	**23 (52.3)**	**28 (50.0)**
Improved (≥ 1 decrease of level « Pain severity »), n (%)	**12 (27.3)**	**14 (25.0)**
Median time to decreased « Pain severity », (days) *	21.0	21.0
Deterioration (≥ 1 increase of level « Pain severity »), n (%)	**9 (20.5)**	**14 (25.0)**
Median time to increased « Pain severity », (days) *	42.0	42.0

** Concerned patients*

Conclusion

- Real-life median OS at 18-month in the FUJI cohort was slightly lower as regards what was reported in the TROPIC trial (11.9 *vs.* 15.1 months). However, at baseline TROPIC patients were younger than FUJI patients, had a good ECOG and normal hematologic, hepatic, renal and cardiac functions (Bono et al., 2010). In addition, 82% of FUJI patients received CAB in 3rd-line or beyond, reflecting the changes in prostate cancer medical care.
- Safety profile in FUJI cohort was similar to that reported for TROPIC trial (AE grade ≥ 3: 55.4% *vs.* 57.4%).
- QoL and pain were improved/stable in respectively 70% and 75% of patients treated by CAB. These results are similar to those observed in the literature with patients treated by 2nd-generation hormonotherapies.

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