Evaluation of cabazitaxel in metastatic castration-resistant prostate cancer with real-life use, effectiveness, safety, and quality of life in the FUJI cohort

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Abstract

Background: Cabazitaxel (CAB) was marketed in March 2012 in France, based on overall survival (OS) benefit in metastatic castration-resistant prostate cancer (mCRPC) in 2nd-line (2L) post-docetaxel (DOC). FUJI is a post-authorisation study of the real-life performance of CAB. **Objectives:** To evaluate OS, safety, quality of life (QoL) and pain using specific patient questionnaires (FACT-P for QoL and BPI-SF for pain). **Methods:** FUJI is a multicentre (n=42) cohort study in mCRPC CAB initiators in real-life, included from Sept 2013 to Aug 2015 in a retrospective cohort (follow-up (FU) 18 months (mths)), and from March 2016 to March 2017 in a prospective cohort (FU 6 mths). OS was analyzed using Kaplan-Meier method. A multivariate Cox analysis, adjusted on prognostic factors, evaluated the risk of death. **Results:** The retrospective cohort included 401 patients (median age 70) with CAB in 2L (18%), 3L (39%), 4L (23%), or >4L (20%). Treatments before CAB included DOC (100%), abiraterone acetate (ABI 77%), enzalutamide (ENZ 33%). Median CAB use was 3.4 mths. Median OS was 11.9 mths [95%CI, 10.1-12.9]. In multivariate analyses, factors associated with a shorter OS were: grade ≥ 3 adverse event (AE) (HR=2.05 [1.53-2.73]), visceral metastases (HR=1.98 [1.40-2.80]), polymedication >5 drugs (HR=1.74 [1.23-2.45]), >5 bone metastases (HR=1.74 [1.20-2.53]), disease progression during DOC (HR=1.69 [1.13-2.53]) or within 3 mths of last DOC cycle (HR=1.51 [1.07-2.14]), ≥3 drugs such as DOC, ABI, ENZ before CAB (HR=1.39 [1.00-1.92]), and PSA ≥ 135 ng/ml (HR=1.36 [1.01-1.82]). Factors associated with better OS were ≥ 10-yr cancer history before CAB (HR=0.66 [0.46-0.96]), ≥ 6 mths from last DOC dose to CAB initiation (HR=0.71, [0.52-0.97]). Grade ≥ 3 AEs occurred in 55%, mainly anaemia (27%), neutropenia (15%), febrile neutropenia (8%), renal failure (7%), septicaemia/septic shock (5%). The prospective cohort included 61 patients (median age 72) previously treated with DOC (98%), ABI (61%) and ENZ (61%). 49 patients were evaluable for QoL and 44 for pain. QoL improved in 41%, was maintained in 29%, and deteriorated in 38%. 25% had pain decrease ≥ 1 level, 50% were stable and 25% increase ≥ 1 level. **Conclusions:** Real-life median OS in FUJI was lower than in TROPIC (11.9 *vs.* 15.1 mths), but very few FUJI patients would have satisfied TROPIC inclusion criteria. There were no new safety issues. Improved/stable QoL and pain were reported by 70% and 75% of patients treated by CAB, respectively.

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). Cabazitaxel (CAB) was marketed in March 2012 in France, based on an overall survival (OS) benefit in mCRPC in 2nd-line post-docetaxel. Little data on CAB use in real-life practice are 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) and is carried out by the Bordeaux PharmacoEpi platform with an unconditional grant from Sanofi-Aventis, supervised by a scientific committee.

Methods

- **Study design**
  French multicentre cohort study including:
  - a **main cohort** with patients identified from Sept 2013 to Aug 2015 and followed 18 months,
  - a **Quality of Life (QoL) cohort** with patients identified from Mar 2016 to Mar 2017 and followed 6 months.
- **Data collection**
  - Data were collected from medical files using a standardized electronic Case Report Form.
  - For QoL cohort, specific questionnaires were completed by patients: FACT-P for QoL and 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 from any cause).
  - Multivariate Cox regression analysis of factors associated with death in the main cohort.
  - QoL and pain were analyzed from raw data and after multiple imputation of missing data (Monte Carlo Markov Chain method).

Results

Recruitment process and follow-up

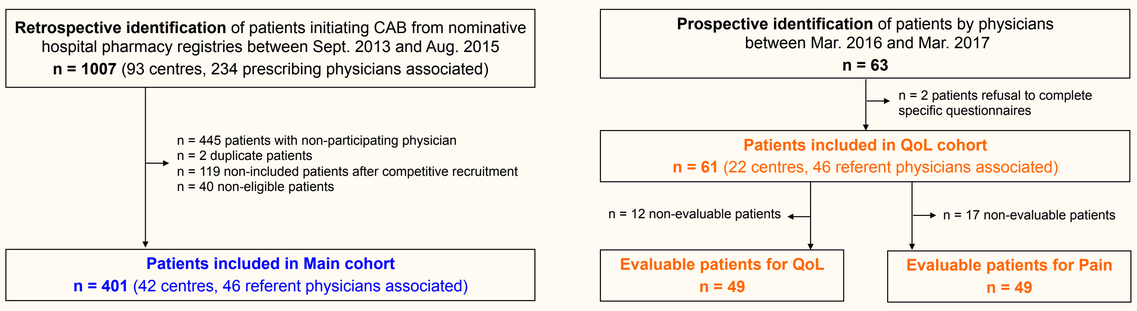

Figure 1. Study populations for main and QoL cohorts

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	59.1	47.5
0 or 1	25.2	37.7
≥ 2	15.7	14.8
Visceral metastases at CAB initiation (%)	19.7	19.7
> 5 bone metastases at CAB initiation (%)	67.1	78.7
Median PSA value at CAB initiation, ng/ml	112.5	109.5
Polypharmacy, > 5 drugs (excluding cancer treatments) (%)	20.7	26.2
Number of cancer treatments [a] before CAB initiation (%)		
1 treatment	18.0	24.6
≥ 2 treatments	82.0	75.4
Docetaxel before CAB initiation (%)	100.0	98.4
Abiraterone acetate before CAB initiation (%)	76.6	60.7
Enzalutamide before CAB initiation (%)	33.4	60.7
Cabazitaxel use		
CAB perfusion every 3 weeks (%)	90.8	85.2
Starting dose of CAB 25 mg/m^2 (%)	46.1	39.3
Median CAB use, months	3.4	3.4
Discontinuation of CAB [b] (%)	95.0	63.9
Main reasons of discontinuation [c] (%)		
Progression disease or disease-related death	83.2	89.7
Adverse events	15.2	25.6

[a] apart from 1st generation hormonotherapies; [b] at 18 months of follow-up for the main cohort and at 6 months of follow-up for the QoL cohort; [c] among patients who had discontinued CAB

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 2**). Factors associated with the risk of death are presented in **Table 2**.

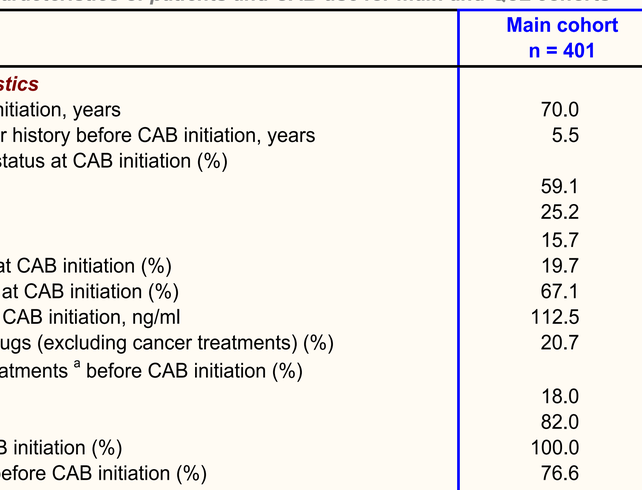

Figure 2. 18-month overall survival in main cohort (Kaplan-Meier method)

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 AE 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, > 5 drugs (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			
At least 6 months after last docetaxel dose	0.71	[0.52 – 0.97]	0.0325
Within 3 months of last docetaxel dose	1.51	[1.07 – 2.14]	0.0198
Disease progression during docetaxel	1.69	[1.13 – 2.53]	0.0198
≥ 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

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"
**212 dead patients and 113 alive patients*

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 3**).

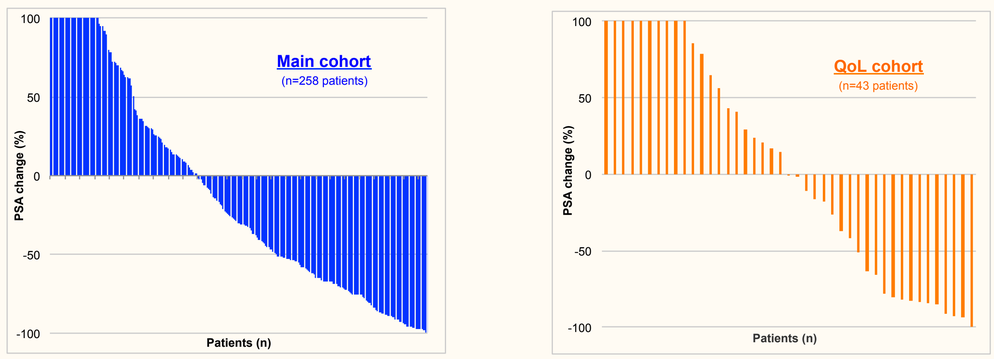

Figure 3. Waterfall plot showing maximum PSA change from baseline in main and QoL cohorts

Safety

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

	Main Cohort, n=401		QoL Cohort, n=61	
Adverve event (AE)	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
≥ 1 AE (%)	**99.0**	**55.4**	**100.0**	**45.9**
≥ 1 haematologic AE (%)	**92.5**	**39.9**	**93.4**	**31.1**
Anemia	90.5	26.9	91.8	21.3
Thrombopenia	28.9	5.2	32.8	4.9
Neutropenia	26.9	15.0	27.9	13.1
Leucopenia	24.9	9.5	36.1	8.2
Febrile neutropenia	8.0	8.0	3.3	3.3
General disorders (%)	**82.5**	**4.2**	**75.4**	**4.9**
Fatigue and asthenia	69.6	3.2	62.3	3.3
Gastrointestinal disorders (%)	**68.3**	**4.2**	**63.9**	-
Diarrhea	39.9	2.5	27.9	-
Nausea	29.9	1.0	32.8	-
Vomiting	19.7	1.2	18.0	-
Renal and urinary disorders (%)	**37.9**	**9.2**	**27.9**	**4.9**
Hematuria	20.2	1.5	16.4	-
Renal failure	7.5	7.2	4.9	4.9
Urinary retention	6.0	0.5	-	-
Infections and infestations (%)	**30.9**	**5.0**	**23.0**	**4.9**
Septicemia and septic shock	5.0	5.0	4.9	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 **Figure 4**.
- **Pain**: 44 patients were evaluable for pain. At CAB initiation, 68.2% of patients had a mild pain, 27.3% a moderate pain and 4.5% a severe pain. QoL changes from baseline during CAB use are presented in **Figure 5**.

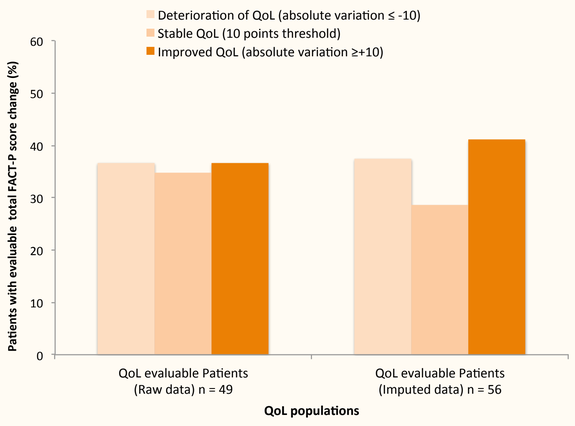

Figure 4. QoL changes from baseline during CAB use in QoL cohort

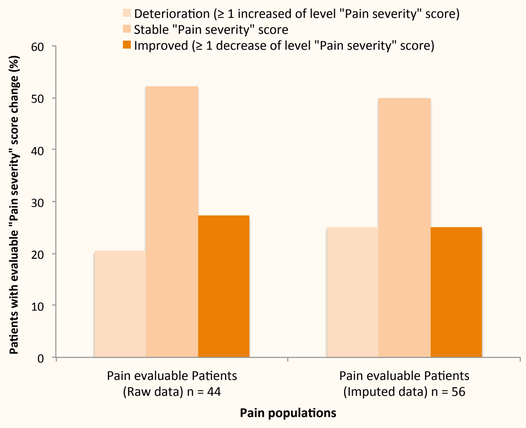

Figure 5. Pain changes from baseline during CAB use in QoL cohort

Conclusion

- Real-life median OS at 18-month in the FUJI cohort was slightly lower than 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 better 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.

34th ICPE International Society for Pharmacoepidemiology
August 22-26, 2018, Prague, Czech Republic