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Bordeaux Pharmacoépi
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FUJI study: **F**ollow-**U**p of **J**evtana® in real l**l**fe

English version of the synopsis

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TITLE	FUJI study: **F**ollow-**U**p of **J**evtana® in real l**l**fe.
SPONSOR	Sanofi-Aventis France
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COORDINATING CENTRE AND CO-SPONSOR	Service de Pharmacologie, Pharmaco-épidémiologie CIC Bordeaux CIC1401 INSERM - Université de BORDEAUX – CHU de Bordeaux – ADERA Bâtiment Le Tondu – case 41 146 rue Léo Saignat – 33076 Bordeaux Cedex
RATIONALE & BACKGROUND	Prostate cancer is the most common cancer in France; it evolves slowly but there is a poor prognosis at the metastatic stage. Several therapeutic strategies are available such as hormonal therapies and chemotherapies. Cabazitaxel (Jevtana®) is a new taxane that has a European marketing authorisation since March 2011 in combination with prednisone/prednisolone for the treatment of metastatic hormone-resistant prostate cancer (mHRPC) in patients previously treated with docetaxel. Two androgen receptor (AR) targeted agents, have also obtained a European marketing authorisation: abiraterone in September 2011 and enzalutamide in June 2013 in the same indication. Radium-223, a solution for injection containing alpha radiation emitters, obtained a European marketing authorisation in November 2013. The availability of cabazitaxel is recent (December 2012) and there is only limited data on the use, safety, and effectiveness of cabazitaxel in real-life practice.
RESEARCH QUESTION	In September, 2013, the French Health Authorities asked Sanofi, the holder of the marketing authorisation for Jevtana® (cabazitaxel), to perform a study to assess, in a real-life setting, the survival, safety, and quality of life of patients treated with Jevtana®, taking into account previous treatments.

OBJECTIVES	• **Primary objective:** - To evaluate the overall survival (OS) of patients treated with a cabazitaxel-containing regimen in the whole population and by treatment-line. • **Secondary objectives:** - To evaluate the safety profile during cabazitaxel treatment. - To evaluate the quality of life (QoL) and pain in patients starting cabazitaxel treatment in the prospective part of the study. - To describe the characteristics of the treated study population and the conditions of cabazitaxel use in a real-life setting (indications, previous treatments, dose-intensities received, etc.). - To evaluate the Progression-free survival (PFS) of patients receiving cabazitaxel.
STUDY DESIGN	A national cohort study will be implemented with a retrospective and prospective identification of patients treated by cabazitaxel from September 2013 to February 2016. The study will be conducted with participation of hospital pharmacists and physicians. Each patient will be followed for a minimum of 18 months after treatment initiation. For a sub-group of patients, the QoL will be assessed using the FACT-P QoL questionnaire and pain will be evaluated by the Brief Pain Questionnaire - Short form (BPI-SF); these questionnaires will be completed by patients before each cabazitaxel infusion, up to the last cabazitaxel cycle.
POPULATION	• **Procedure of centre recruitment and patient identification:** All centres prescribing cabazitaxel in France will be defined as potential centres for participation in the study. Identification of these potential centres will be based on drug sales between September 2013 and December 2014, provided by the marketing authorization holder. At least 45 centres are expected to participate. In each centre, the source population of the cohort will be all patients initiating cabazitaxel treatment between 1 September 2013 and 28 February 2016. In France, cabazitaxel prescriptions are nominative and confined to hospitals. A retrospective identification of patients will be performed by pharmacists from hospital pharmacy registers in order to avoid influencing prescription and to offer exhaustive coverage for each centre, irrespective of indication. Medical files of patients will be selected chronologically and consecutively according to the date of cabazitaxel treatment initiation, from September 2013 and until February 2016 to obtain the required number of patients, *i.e.* 400 patients treated for prostate cancer. From the time of participating centre opening, physicians are to inform patients about data collection and obtain their participation consent. They are to propose QoL and pain evaluation for a sub-group of patients before treatment initiation.

Verification of inclusion criteria and data collection will be performed by clinical research assistants (CRAs) of the coordinating centre, using medical files provided by the prescribing physicians.

- **Inclusion criteria:**
  - Patients who have initiated cabazitaxel therapy from 1 September 2013 until 28 February 2016,
  - Patients who have been informed of the study, and who have given written informed consent to participate.
- **Exclusion criteria:**
  - Patient participating in a clinical trial,
  - Patient concerned by a language barrier (unable to read the patient information letter or to complete the questionnaires to evaluate QoL and pain).

VARIABLES

1. Identification data

- Initials, date of birth,
- Date of cabazitaxel initiation,

2. Baseline demographic and clinical characteristics at study inclusion for eligible patients

- Gender, date of birth,
- Weight and height at cabazitaxel initiation,
- Date of initial disease diagnosis, as well as TNM stage, PSA values, and Gleason score at initial diagnosis,
- Date of metastases diagnosis, localisation (bone, lymph nodes, visceral) and number of bone metastases at cabazitaxel initiation.
- Previous treatments for the primary cancer and metastatic cancer before initiation of cabazitaxel: surgery, radiotherapy, curietherapy, HIFU, hormonotherapy such as LHRH agonists and/or LHRH antagonists and/or anti-androgen agents (including abiraterone or enzalutamide), chemotherapy such as docetaxel +/- estramustine, mitoxantrone, and radium-223 with:
  - date of treatment start
  - date of treatment end
  - reason for discontinuation (*e.g.* disease progression, unacceptable toxicities, patient choice…).

  A special emphasis will be put on documenting previous use of docetaxel, abiraterone, and enzalutamide.
- Previous medical or surgical history,
- Biological data (date and results) before cabazitaxel initiation: haematological parameters, urea, creatinine, creatinine clearance, serum calcium, albumin, gamma GT, transaminases, bilirubin, LDH, alkaline phosphatase
- Presence of cancer pain and analgesic treatment,
- ECOG performance status.

3. Data related to cabazitaxel use

- Date of infusion,
- Administration regimen (every 3 weeks or other),
- Administered dose,
- Dose changes, postponement of infusion, and reasons for these,
- Other treatment associated (notably prophylaxis treatment and growth factors): name of drug, dates of treatment initiation and discontinuation.

4. Other data collected during cabazitaxel infusion

- ECOG performance status,
- Biological data: PSA, LDH
- Radiological evaluation: date, type of exam
- Tumour response as per investigator judgement
- Investigator's decision for treatment following tumour evaluation
- Reasons for cabazitaxel treatment discontinuation
- QoL: each patient planned to receive cabazitaxel treatment in participating centres after opening, will be proposed a QoL and pain evaluation. Those who give written informed consent, will fill-in the FACT-P (QoL) and BPI-SF (pain) questionnaires at baseline and before each of the cabazitaxel infusions during the treatment period.
- Safety data
  - Biological data: haematology at each cycle (Hb, WBC, neutrophils, platelets), transaminases, alkaline phosphatases, bilirubin, creatinine.
  - All adverse events (AEs) reported as from the first administration of cabazitaxel, for each treatment cycle, and during the 18 months of follow-up. The NCI-CTCAE grade and hospitalization associated with each event will be collected. These AEs are coded according to the MedDRA dictionary.

End of treatment-line

- Date of first and last treatment cycle,
- Reason for treatment-line discontinuation,
- Biological data at the end of treatment: PSA.

Survival outcomes and subsequent treatments

- Date and cause of death, (with CepiDC, Inserm procedure whenever needed)
- Date of disease progression, as per investigator's judgement
- All patients will be followed from initial inclusion to death or end of study, irrespective of treatment. Follow-up will be at least 18 months for all patients.

DATASOURCE

Coordinating centre CRAs will collect the necessary information from patient medical files using an electronic CRF, in close collaboration with a member of the department concerned in each participating centre.

DATA-MANAGEMENT AND QUALITY CONTROL

Data-management

A data validation plan will be developed and will describe in detail the controls to be made for each variable (coherence of dates and intervals, coherence of conditional variables, invalid values, boundaries, missing data, respect of criteria predefined in the protocol, *etc.*). After verification and resolution of incoherencies, the database will be locked for extraction and statistical analysis.

Data quality control

Data quality control will be performed on active sites (which have enrolled at least one patient). Quality control will be performed by the sponsor CRA. This on-site quality control will concern mainly: existence of the included patients and accuracy of a limited number of major variables collected. The methodology of data quality control and appropriate consecutive corrective actions will be detailed in the study report.

STUDY SIZE

The analyses of this study will be descriptive; the sample size is determined in terms of precision (half the width of 95% CI).
The median overall survival was 15.1 months in the TROPIC study[1], the pivotal RCT. The present study plans to enrol 400 patients; based on the assumptions of exponentially distributed OS and a median OS of 15 months, the survival rate would be 50% at 15 months, 57.4% at 12 months, and 43.5% at 18 months. The 95% CI around these OS rates is given in the following table:

95% CI (precision)		
OS rate at 12 months 57.4%	OS rate at 15 months 50%	OS rate at 18 months 43.5%
[52.2 ; 62.5]	[44.9 ; 55.1]	[38.1 ; 48.8 %]

Greenwood's formula around the overall survival rates (Kaplan-Meier estimates) -Lost to Follow-up distribution is presumed exponential and the rate is assumed to be 15% at 18 months.

The precision (half the width of 95% CI) with 400 included patients to describe the OS rate is about 5%.

The number of subjects in sub-populations defined according to previous treatment will be less than in the whole cohort, the width of 95% CI will therefore be larger. For example, for a sub-population of 150 patients the precision will be about 8.0%-to-8.5% and for a sub-population of 100 patients, the precision will be about 9.6%-to-10.5%.

Taking into account patients who would be treated for an indication other

[1] *de Bono J. S. 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: 1147–54*

	than prostate cancer, those lost to follow-up, and withdrawing their participation agreement, to include 400 patients treated for prostate cancer a total of 440 patients treated with cabazitaxel is required. Regarding the QoL study, 60-80 evaluable patients at each visit, accuracy is around 3 and 3.5 points that is acceptable. For the BPI-SF pain score, with 60 to 80 evaluable patients the accuracy to describe an improvement of 30% to 50% at the different evaluation time varies between 10.5% and 11.7%.
EVALUATION CRITERIA	• Primary criterion: OS, that is defined as the interval between date of first cabazitaxel administration and the date of death, irrespective of cause, for the total population and according to treatment line. • Treatment toxicity, based on the data collected through the medical files and using the NCI-CTCAE v4.0. All AEs will be coded (MEDdRA). • Progression-free survival, defined as time from first day of cabazitaxel until progression as per physician judgement indicated in the medical file or death. Progression date and parameters (Radiological, biological clinical…) used by the investigator to judge progression will be investigated by the CRA and will be documented in the CRF. • QoL will be assessed using the FACT-P questionnaire and pain using the BPI-SF questionnaire. These questionnaires will be filled-in before each cabazitaxel infusion.
STATISTICAL ANALYSIS	The statistical analysis will be performed using the SAS software (current version), following a detailed statistical analysis plan validated by the Scientific Committee. Qualitative variables (dichotomous or categorical) will be described in terms of number and frequency. Quantitative variables will be described in terms of mean, standard deviation, median, first and third quartiles, and range (min, max). The following analyses will be performed for the study population: • Description of prescriber characteristics • Description of the baseline demographic clinical characteristics and, previous treatment at study inclusion date, • Description of treatment pattern during follow-up after study inclusion date, Descriptive analyses will also be performed according to previous sequence of treatment (*i.e.* the antineoplastic treatments: docetaxel, abiraterone, enzalutamide, received since diagnosis of mCRPC). Overall and progression-free survival outcomes will be analysed using Kaplan Meier estimate (including curve), median survival and the survival rate at 12 and 18 months will be reported with 95%CI. These analyses will also be performed according to treatment line.

	The multivariate analysis will be performed using the Cox proportional hazard risk model to assess the factors associated with mortality and disease progression. The total score and the subscale scores assessed by FACT-P for the QoL and BPI-SF for pain will be descriptively summarized and 95% CI of the difference from baseline at each time point will be given. The safety will be described. The representativeness of the centres and the actual patient population included in this study will be investigated by comparing the characteristics of centres and patients in the study with available national data.
MILESTONE	Approval of protocol from the Health Authority (*Commission de Transparence* / CEPS) Apr 2015 Regulatory submission Q2-Q3 2015 Regulatory approval (CNIL) Q4 2015 Recruitment of centres Q4 2015 First patient to sign the informed consent form (prospective and retrospective part) Q4 2015 Last patient to sign the informed consent form Q1 2016 End of patient follow-up Q1 2017 Data-management and statistical analysis Q2-Q3 2017 Final report Sept 2017