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Sponsor: Sanofi **Drug substance(s):** XRP6258	**Study Identifiers:** U1111-1131-3161, NCT02074137 **Study code:** CABAZ_L_06499

Title of the study: Multicentre, single arm, open label, non controlled phase IV clinical trial to evaluate safety of cabazitaxel (Jevtana®) in combination with oral prednisone (or prednisolone) for the treatment of patients with metastatic hormone refractory prostate cancer previously treated with a docetaxel-containing regimen.

Study center(s): This study was conducted at 3 centres across India.

Study period:

Date first patient enrolled: 21/Jun/2014

Date last patient completed: 25/Mar/2016

Phase of development: Phase 4

Objectives:

Primary objective:

- To evaluate safety of cabazitaxel (Jevtana®) in patients with metastatic hormone refractory prostate cancer (mHRPC)

Secondary objectives:

- To describe the use of cabazitaxel (Jevtana®) in combination with oral prednisolone for treatment of patients with mHRPC
- To describe clinical profile of patients with mHRPC in terms of demography, disease characteristics, and prior treatment history
- To describe efficacy outcomes: radiological response (if available) using Response Evaluation Criteria In Solid Tumours (RECIST) criteria V 1.1 and prostate-specific antigen (PSA) response

Methodology:

This was a multicentre, single arm, open label, non-controlled, Phase 4 clinical trial. At the end of the 1-week screening period, patients eligible for the study were treated with Jevtana® (cabazitaxel) 25 mg/m^2 intravenous (IV) in combination with oral prednisone (or prednisolone) 10 mg/day until disease progression, death, unacceptable toxicity, investigator's decision or withdrawal of consent. The patients were followed up during treatment with cabazitaxel and for 30 days after last administration. The study was considered completed for a patient when he completed end of study visit, which was 30 days after the last administration of Jevtana®.

Number of patients:

Planned: 10

Randomized: Not applicable

Treated: 10

Evaluated:

Efficacy for radiological assessment: 2

Efficacy for change in PSA response: 8

Safety: 10

Diagnosis and criteria for inclusion:

Inclusion criteria

- mHRPC previously treated with a docetaxel containing regimen
- Disease progression during or after docetaxel-containing regimen for mHRPC
- Surgical or medical castration
- Patients who were ≥ 18 years and ≤ 75 years of age
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2
- Adequate bone marrow, liver, and renal function: neutrophils > 1500 /mm^3; haemoglobin > 10 g/dL; platelets > 100×10^9/L; bilirubin < upper limit of normal (ULN); aspartate aminotransferase (AST) < 1.5 × ULN; alanine aminotransferase (ALT) < 1.5 × ULN; creatinine < 1.5 × ULN. In case of creatinine 1.0 × ULN and ≤ 1.5 × ULN, calculated creatinine clearance according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was to be ≥ 60 mL/min
- Written informed consent was to be obtained prior to any study related procedures

Exclusion criteria

- Prior radiotherapy to ≥ 40% of bone marrow
- Previous treatment with cabazitaxel
- Prior surgery, radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to enrolment
- Active Grade ≥ 2 peripheral neuropathy
- Active Grade ≥ 2 stomatitis
- Active infection requiring systemic antibiotic or anti-fungal medication
- Active cancer (other than mHRPC) including prior malignancy from which the patient has been disease-free for ≤ 5 years
- Known brain or leptomeningeal involvement
- History of severe hypersensitivity reaction (≥ Grade 3) to docetaxel
- History of severe hypersensitivity reaction (≥ Grade 3) to polysorbate 80 containing drugs
- History of severe hypersensitivity reaction (≥ Grade 3) or intolerance to prednisone or prednisolone
- Uncontrolled severe illness or medical condition (including uncontrolled diabetes mellitus)
- Concurrent or planned treatment with strong inhibitors or strong inducers of cytochrome P450 (CYP) 3A4/5 (a 2 weeks wash-out period was necessary for patients who were already on these treatments)
- Participation in any other clinical trial with any investigational drug
- Patient with reproductive potential not implementing accepted and effective method of contraception

Study treatments

Investigational medicinal product: Jevtana® (cabazitaxel)

Formulation: Concentrate for solution for infusion

Route of administration: IV

Dose regimen: 25 mg/m^2 every 3 weeks

Noninvestigational medicinal product: Prednisolone

Formulation: Oral tablet

Route of administration: Oral

Dose regimen: 10 mg/day

Duration of treatment: Jevtana® 25 mg/m^2 was administered by 1 hour IV infusion given once in 3 weeks. Treatment was continued until disease progression, death, unacceptable toxicity, investigator's decision to discontinue treatment, or the withdrawals of consent of the patients were reported over the course of the study.

Duration of observation: During treatment and 30 days after last administration of Jevtana®

Criteria for evaluation:

Primary endpoints:

- Number of patients with treatment-related serious adverse events (SAEs)

Secondary endpoints:

- Dose administration of Jevtana® and duration of exposure and total number of cycles received from the initiation of cabazitaxel therapy, dose modifications
- Patient profile in terms of demography, disease characteristics and prior treatment history
- Safety Analysis will be done by summarizing AEs, SAE regardless of relationship to cabazitaxel and laboratory data. Summarization of adverse events (AEs) and SAEs regardless of the relationship to cabazitaxel and laboratory data analysis
- Radiological overall response (if radiological tumour assessment was done) using RECIST criteria
- Number of patients with at least 50% decrease in PSA level

Statistical methods:

Sample size justification: No formal statistical calculation for sample size was conducted. The sample size was decided after reviewing the disease incidence, study timelines, and the recruitment rates in the previous studies for this drug. This study enrolled 10 patients across 3 centres.

All statistical analyses were descriptive (no formal statistical tests were performed).

The safety population was defined as patients who have signed the informed consent form and who have received at least a part of a dose of cabazitaxel.

The per protocol population was defined as patients who fulfil all inclusion criteria and none of the exclusion criteria and have no other critical protocol deviations through the study period and used for baseline data analysis. The safety population was defined as patients who have signed the informed consent form and who have received at least a part of a dose of Jevtana® and used for safety data analysis.

Efficacy data were analysed for 2 separate efficacy populations as below:

Efficacy population:

- For best radiological response = patients with radiological tumour assessment done at baseline and with at least one further radiological tumour assessment
- For PSA response = patients with PSA value at baseline ≥ 10 ng/mL

Summary:

Baseline data:

In all, 14 patients were screened and 10 patients were enrolled. Of the 4 patients who were screen failures, 1 patient did not meet inclusion criterion number 1 (patient with mHRPC previously treated with a docetaxel containing regimen) and 3 patients did not meet inclusion criterion number 6 (patient with adequate bone marrow, liver, and renal function).

All 10 patients were included in both the per protocol and safety populations. Two patients were included in the efficacy population to analyze radiological data and 8 patients were included in the efficacy population to study change in PSA response.

For the 10 enrolled patients, the mean (SD) age was 59.9 (4.7) years. The mean (SD) weight was 76.2 (16.8) kg. The mean (SD) height was 161.6 (5.3) cm.

The mean (SD) duration from initial diagnosis of prostate cancer was 3.9 (2.4) years. The mean (SD) duration of mHRPC was 2.0 (1.6) years.

All 10 patients had disease progression at baseline, which was evident by increased PSA levels (n = 10), clinical progression (n = 2), and new bone metastases on bone scan (n = 5). For all patients, there was metastasis to bone. Cancer was metastasized to pelvis in 2 patients.

All patients had received a docetaxel regimen previously. Other anti-cancer therapies administered prior to inclusion in the study were bicalutamide (n = 5), fosfestrol (n = 3), and 1 patient each received abiraterone, dexamethasone, and stilboestrol. Eight patients had undergone surgery and 3 patients had received radiotherapy prior to inclusion in the study.

Seven patients had undergone surgical castration, and 5 patients had undergone medical castration. Two patients had undergone both medical and surgical castration.

All the patients had ECOG PS scores ≤2 (capable of self-care) at baseline.

Table T-1: Eastern Cooperative Oncology Group performance status at baseline

Eastern Cooperative Oncology Group Performance Status Score	Number of Patients
0	1
1	8
2	1
3	0
4	0
5	0

Jevtana Treatment:

All patients completed first 3 cycles of treatment. Eight patients completed ≥ 4 cycles of treatment. One patient completed 29 cycles of treatment (Table T-2). The mean (SD) duration of dosing was 27.5 (23.2) weeks. The mean (SD) dose received by each patient was 401.6 (253.9) mg/m^2. Dose was delayed for 3 patients, and it was reduced for 3 patients to 20 mg/m^2 during the study. Reasons for dose reduction included haematological toxicity (febrile neutropenia and anaemia) in 2 patients and non-haematological toxicity (diarrhoea) in 1 patient; all events were related to Jevtana®.

Table T-2: Summary of maximum number of cycles completed by patients

Maximum number of cycles	Number of patients (n)
3	2
5	2
8	1
9	1
10	2
16	1
29	1

All patients received prophylactic granulocyte-colony stimulating factor (G-CSF) and 4 patients also received curative G-CSF.

Safety results:

Nine patients completed the study and one patient discontinued due to death not related to Jevtana®. All 10 patients had at least 1 AE. A total of 92 AEs, including 2 pre-treatment AEs and 1 post-treatment AE, were reported in all 10 patients. System organ classes (SOCs) in which AEs were reported were gastrointestinal disorders (9 out of 10 patients, 90%), general disorders and administrative site conditions (7 out of 10 patients, 70%), blood and lymphatic system disorders (6 out of 10 patients, 60%), musculoskeletal and connective tissue disorders (5 out of 10 patients, 50%), and nervous system disorders (5 out of 10 patients, 50%).

More than 10 AEs were reported in the following SOCs: 19 AEs in the SOC of gastrointestinal disorders (13 events of diarrhoea, 3 of vomiting and 1 event each of abdominal pain lower, haemorrhoids and constipation); 18 AEs in the SOC of general disorders and administration site conditions (10 events of fatigue, 5 of pyrexia, 2 of pain and 1 of oedema peripheral); and 11 AEs in the SOC of blood and lymphatic system disorders (6 of anaemia, 4 of neutropenia and 1 of febrile neutropenia). In all other SOCs, fewer than 10 AEs were reported.

Jevtana®-related AEs were reported in the following SOCs: 12 AEs in the SOC of gastrointestinal disorders (11 events of diarrhoea and 1 of vomiting), 9 AEs in the SOC of general disorders and administration site conditions (7 events of fatigue and 2 of pyrexia), 9 AEs in the SOC of blood and lymphatic system disorders (4 events each of anaemia and neutropenia and 1 of febrile neutropenia), 1 AE in the SOC of metabolism and nutrition disorders (hypoalbuminaemia), 2 events in the SOC of infections and infestations (1 event each of UTI and oral candidiasis), 1 AE in the SOC of nervous system disorders (neuropathy peripheral), 5 AEs in the SOC of investigations (1 event each of ALT increased, AST increased, blood alkaline phosphatase increased, blood bilirubin increased and gamma glutamyl transferase [GGT] increased), 1 AE in the SOC of skin and subcutaneous tissue disorders (rash).

Jevtana®-related Grade 3 AEs were as follows: 2 events of diarrhoea and 1 event each of anaemia, neutropenia, febrile neutropenia, UTI, GGT increased). Jevtana® unrelated Grade 3 events were as follows: 1 event each of anaemia, hyponatraemia, UTI, pain in extremity and joint range of motion decreased. Jevtana® related Grade 4 event was neutropenia. No Jevtana® unrelated Grade 4 event was reported.

No Grade 5 Jevtana®-related AE was reported.

There was one Grade 5 Jevtana® unrelated AE. This patient died due to UTI during the 30-day follow up period. The fatal event was not related to Jevtana® or prednisolone. Patient 3 was a 63-year-old man with a history of hypertension. He underwent right subcapsular orchidectomy on 07 December 2012 and received docetaxel 10 mg/kg (cumulative dose 750 mg/kg) until 27 November 2013. He received his first dose of Jevtana® on 29 July 2014. His baseline ECOG PS was 1. Dose was delayed at cycle 3 by 7 days (abscess not related to Jevtana, detected 09 September 2014) and cycle 5 by 13 days (UTI related to Jevtana® detected on 29 October 2014), and reduced to 20 mg/m^2 at cycle 5 (anaemia related to Jevtana detected, diarrhoea not related to Jevtana®). The last full dose was given on 08 October 2014 at cycle 4. On 22 October 2014, he was diagnosed with anaemia (haemoglobin 6.5 g/dL) which was considered related to Jevtana®. For anaemia, the patient received 1 unit of peripheral red blood cells on 22 October 2014. On 27 October 2014, the patient was hospitalized because of diarrhoea, which had developed on 26 October 2014. The diarrhoea stopped on 29 October 2014; diarrhoea was not considered related to Jevtana®. On 29 October 2014, he was diagnosed with UTI and was treated with cefoperazone, sulbactam and amikacin. The follow-up urine culture showed no bacterial growth and the UTI was considered resolved on 05 November 2014. The anaemia detected on 22 October 2014 was considered resolved on 06 November 2014. The patient received cycle 5 of Jevtana® on 11 November 2014 at a reduced dose of 20 mg/m2. Investigations revealed that the patient had UTI with haematuria on 21 November 2014 and was hospitalized on 22 November 2014 and treated with tranexemic acid. UTI was treated with antibiotics. Associated hypokalaemia and hyponatraemia were corrected with adequate supportive treatment. The haematuria persisted. The patient died on 26 November 2014 due to urosepsis with shock and multiorgan failure. Reason for death was mentioned as UTI. The investigator considered the fatal AE of UTI to be not related to Jevtana®.

Overall 7 SAEs were reported in 4 patients. The reported SAEs were UTI (3 SAEs), anaemia (1 SAE), febrile neutropenia (1 SAE), diarrhoea (1 SAE), pyrexia (1 SAE). Three Jevtana®-related SAEs, which were reported, were febrile neutropenia, anaemia and UTI. These all resolved/recovered.

None of the patients had prednisolone-related AEs or SAEs during the study.

Study treatment was permanently discontinued in 4 patients due to AEs as mentioned below:

- Patient 1: body pain, vomiting, fever (study treatment discontinued because of all these AEs)
- Patient 2: joint range of motion decreased, oedema limbs (study treatment discontinued because of all these AEs)
- Patient 3: UTI
- Patient 4: increase in ALT, AST, alkaline phosphatase, GGT, and blood bilirubin with hypoalbuminaemia (study treatment discontinued because of all these AEs).

Efficacy results:

Radiological assessment was not mandated by the protocol. If the Investigator performed radiological assessment within 21 days prior to enrolment, then these assessments were done during the study treatment. Only 2 patients had radiological evaluation performed at baseline. During the study treatment, 1 subject had stable disease at cycle 2, and the other subject had stable disease at cycle 6 and cycle 9. Radiological evaluation was not done at any other cycles.

Per protocol, PSA was evaluated at the screening visit and at the end of the study. Eight patients had PSA testing performed at the screening visit and at the end of the study. None of the patients showed a greater than 50% decrease in PSA response at the end of the study (mean [SD] 770.51 [1721.0] ng/mL at baseline vs. 826.48 [1777.4] ng/mL at the end of the study).

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