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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** Cabazitaxel (Jevtana®)	**Study Identifiers:** U1111-1155-8055, NCT02441894 **Study code:** CABAZL07239
Title of the study: Cabazitaxel in combination with prednisolone with primary prophylaxis with PEG-G-CSF for the treatment of patients with metastatic castration-resistant prostate cancer (PEGAZUS)	
Study center(s): 8 sites in Japan	
Study period: Date first patient enrolled: 27/Apr/2015 Date last patient completed: 21/Nov/2016	
Phase of development: Phase IV	
Objectives: Primary: • To assess the tolerability of cabazitaxel 25 mg/m^2 every 3 weeks for patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with chemotherapy including docetaxel with primary prophylactic polyethylene glycol granulocyte colony-stimulating factor (PEG-G-CSF) in terms of the incidence rate of febrile neutropenia (FN) (defined: absolute neutrophil count [ANC] < 1000/mm^3 and a single temperature of > 38.3ºC or a sustained temperature of ≥ 38ºC for more than 1 hour) during cycle 1. Secondary: • To assess overall rate of FN and grade ≥ 3 neutropenia and diarrhea; the number of patients with dose delay due to adverse events (AEs) and dose reduction due to AEs; relative dose intensity (RDI); incidences of FN-related hospitalization and use of intravenous anti-infectives; tolerability (Common Terminology Criteria for Adverse Events [CTCAE] version 4.0); prostatic specific antigen (PSA) response (50% decrease); and tumor response according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.	
Methodology: This was a multicenter, non-controlled, single-arm, open-label study in patients with mCRPC treated by cabazitaxel 25 mg/m^2 every 3 weeks combination of prednisolone 10 mg daily and PEG-G-CSF that were injected at least 24 hours after completion of the cabazitaxel infusion (i.e., on Day 2) for primary prophylaxis for FN in first and subsequent cycles. The study period included the screening phase (14 days), the study treatment period (21 days/cycle, maximum 10 cycles), and the follow-up period (maximum 30 days).	
Number of patients**:**	Planned: Approximately 25 Registered: 21 Treated: 21
Evaluated:	Safety: 21 FN evaluable: 21 PSA evaluable: 21 Tumor evaluable: 4

Diagnosis and criteria for inclusion:

- Patient with mCRPC previously treated with chemotherapy including docetaxel.
- Patient must have either measurable or non-measurable disease, or documented rising PSA levels.
- Patient signed informed consent.

Study treatments

Investigational medicinal product(s): Cabazitaxel

Formulation: Cabazitaxel was yellowish to brownish yellow viscous solution, and contained in a 15 mL clear glass vial containing a total of 60 mg/1.5 mL of cabazitaxel and polysorbate 80 (1.56 g) as an additive. For injection, 4.5 mL of 13% (w/w) ethanol in water was attached as solvent.

Route(s) of administration: Cabazitaxel was administered as a 1-hour intravenous infusion.

Dose regimen: The individual dosage of cabazitaxel was 25 mg/m^2 administered as a 1-hour intravenous infusion every 3 weeks in combination with oral prednisone 10 mg administered daily.

Adaptation of doses: Every effort was made to administer the full dose regimen to maximize dose-intensity.

If possible, toxicities were managed symptomatically. If toxicity occurred, the appropriate treatment was used to improve signs and symptoms including antiemetics for nausea and vomiting, anti-diarrheals for diarrhea, and antipyretics, and/or antihistamines for drug fever.

Dose delays/Modifications:

A maximum of a 2-week delay was allowed between 2 study cycles. If the treatment delay was more than 2 weeks, patients were withdrawn from the study. Patients were monitored closely for toxicity. In addition to optimizing supportive care, cabazitaxel doses could be adjusted after cycle 1 or recovery from AEs to grade ≤ 1. Each patient was treated until disease progression, death, unacceptable toxicity, or up to the 10th cycle.

Dose reduction:

The doses of cabazitaxel could be reduced level by level, i.e., from 25 mg/m^2 to 20 mg/m^2 or from 20 mg/m^2 to 15 mg/m^2* if the patients experienced unacceptable toxicity. However, when dose reduction led to a dose to be administered below 15 mg/m^2, patients were to be withdrawn from the study treatment. When the patients resumed the study treatments, they had to meet the criteria for retreatment. No dose escalation was allowed after dose reduction.

*The dosage could be reduced up to 15 mg/m^2 according to physician's decision.

Noninvestigational medicinal product(s):

- PEG-G-CSF: Pegfilgrastim (Genetical Recombination)
- Prednisolone

Formulation:

PEG-G-CSF:

PEG-G-CSF was supplied in 0.36 mL prefilled syringes containing 3.6 mg pegfilgrastim (recombinant) in a clear, colorless solution. Each syringe contained D-sorbitol (18 mg), glacial acetic acid (0.216 mg), sodium hydroxide (adequate dose), and polysorbate 20 (0.0144 mg) as additives.

Prednisolone:

Commercial prednisolone tablet was used.

Route(s) of administration: PEG-G-CSF was administered subcutaneously.

Prednisolone was administered orally.

Dose regimen:

PEG-G-CSF:

One dose per cycle of cabazitaxel (3.6 mg/body [fixed dose] of pegfilgrastim [KRN125] subcutaneously).

It started at least 24 hours after completion of the cabazitaxel infusion, i.e. on Day 2.

Prednisolone:

Patients received prednisolone 5 mg oral tablet twice daily (10 mg daily) orally in morning and noon, or 10 mg orally in morning.

Duration of treatment: 21 days/cycle (maximum 10 cycles)

Duration of observation: Up to 30 days after the last treatment

Criteria for evaluation:

Primary analysis:

The incidence of FN (all grades) during cycle 1.

Secondary endpoint(s):

- Overall incidence of FN (all grades) through the treatment period.
- Overall incidence of neutropenia with grade ≥ 3 through the treatment period.
- Overall incidence of diarrhea with grade ≥ 3 through the treatment period.
- The numbers of patients with delay in the start of drug administration, dose reduction due to AEs through the treatment period, and RDI.
- Incidences of FN-related hospitalization and use of intravenous anti-infective drugs through the all treatment period.
- PSA response (defined as at least 50% decrease from baseline confirmed by a second PSA decline at least 3 weeks later).
- Overall Response Rate (in patients with measurable disease): The best of objective responses (complete response [CR] and partial response [PR]) for measurable disease as assessed by investigators or sub-investigators according to RECIST (version 1.1).
- AEs and event severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0, classified by Medical Dictionary for Regulatory Activities (MedDRA).

Safety analysis:

Adverse events, Clinical laboratory tests, vital signs

Statistical methods:

Determination of the sample size:

The sample size calculations were based on the primary variable, incidence of FN (in cycle 1), with the following assumptions:

- Null hypothesis proportion, P0 of 0.43 that was assumed based on the proportion of patients who experienced FN during cycle 1 in the cabazitaxel Phase 1 study in Japan (TED11576).
- The alternative proportion, PA of 0.10 that was expected proportion of patients who experienced FN during cycle 1 with primary prophylaxis of PEG-G-CSF in this study.

An exact binomial test with a nominal 0.05 2-sided significance level had more than 90% power to detect the difference between P0 and PA when the sample size was 21. Considering the possibility to have patients who were not evaluable for primary analysis, 25 patients were to be enrolled. The patient enrollment was stopped when 21 patients were registered in this study because all 21 enrolled patients were eligible for the FN evaluable population.

Analysis Population:

- Safety population: All registered patients exposed to cabazitaxel, regardless of the amount of treatment administered.
- FN evaluable population: The subset of patients from the all treated population with the evaluation of FN during cycle 1. The patient who (1) received PEG-G-CSF administration during cycle 1, (2) had at least 1 scheduled hematological laboratory test during cycle 1 and (3) 1 body temperature measurement during cycle 1.
- PSA evaluable population: The subset of patients from the all treated population that had a detectable PSA at baseline (i.e., the value of more than lower limit of quantitation) and at least once scheduled PSA measurement during on-treatment period.
- Tumor evaluable population: The subset of patients from the all treated population that have had a measurable disease at baseline and at least once scheduled the tumor assessment during on-treatment period.

Primary Analysis:

- The number of FN occurrence during cycle 1 was summarized using the number and percentage of patients and its 95% confidence interval (CI).

Secondary Analysis

- FN occurrence, neutropenia and diarrhea, and FN related hospitalization was summarized using the numbers and percentages of patients and the 95% CIs for each study cycle and entire period of the study.
- FN related administration of intravenous anti-infectives was summarized as with concomitant medications.
- The number and percentage of patients with PSA response and its 95% CI were presented. Maximum PSA change from baseline, and median time and the 95% CIs on time to progression were plotted.
- The numbers and percentages of patients in each best overall response status and the 95% CIs were presented.

Safety Analysis:

- AEs were coded using MedDRA version 19.0 at the time of database lock.
- The numbers and percentages of patients reporting AEs were calculated about the categories for every system organ class (SOC)/preferred term (PT). The same analysis was performed for the categorized AEs as follows: treatment-emergent adverse event (TEAE), TEAE of grade 3 or 4, serious TEAE, TEAE leading to death, TEAE leading to permanent treatment discontinuation, and adverse event with special interest (AESI).
- Laboratory parameters were summarized.
- Vital signs were plotted for each parameter.

Analyses on cycle 1:

An analysis was performed when all patients completed the study cycle 1 treatment just for data analysis. The data cutoff date was the last date before cycle 2 after all patients completed cycle 1.

Summary:

Population characteristics:

A total of 21 patients were registered and treated with cabazitaxel in this study. Of these, 9 patients (42.9%) completed the study treatment and 12 patients (57.1%) discontinued the study treatment. The reasons for treatment discontinuation were disease progression in 9 patients (42.9%) and AEs in 3 patients (14.3%). All 21 patients completed the study cycle 1.

In the safety population, median age was 70.0 years (range, 56 to 82 years), with 4 patients (19.0%) below 65 years and 17 patients (81.0%) at or above 65 years. Median of baseline body surface area (BSA) was 1.720 m^2 (range, 1.51 to 1.87 m^2). The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was rated at 0 in 17 patients (81.0%) and at 1 in 4 patients (19.0%). Thirteen (13) patients (61.9%) had received enzalutamide and 10 patients (47.6%) had received abiraterone acetate as prior therapy.

Primary results:

FN occurred in 2 of 21 patients (9.5%, 95%CI = 1.17 to 30.38) during cycle 1.

Secondary results:

A total of 2 patients (9.5%) experienced FN during the study; all FN occurred during cycle 1 and FN was not observed during the subsequent cycles. These 2 patients (9.5%) were hospitalized due to FN during cycle 1.One (1) patient (4.8%) was treated with intravenous anti-infectives related to FN.

Grade 3 or 4 neutropenia was observed in 20 patients (95.2%) during the study.

No patients had grade 3 or 4 diarrhea during the study.

The median number of cycles was 7.0 (range, 3 to 10). The median RDI of cabazitaxel, pegfilgrastim, and prednisolone was 67.41% (range, 53.2% to 91.3%), 76.36% (range, 68.2% to 91.3%), and 100.00% (range, 88.7% to 100.0%), respectively. The dose of cabazitaxel was reduced in 17 patients (81.0%). Of these, the dose was reduced once in 14 patients (66.7%), and twice in 3 patients (14.3%). Dose delay was reported in all 21 patients and in 104 of 128 cycles (81.3%).

In the PSA evaluable population, PSA response was observed in 6 patients (28.6%) during the study. Fourteen (14) patients (66.7%) had PSA progression. Seven (7) patients (33.3%) were censored due to any reasons and, of them, 2 censored patients were still in PSA response at cycle 10. Median estimated time to PSA progression was 182 days (95%CI = 71.00 to 255.00).

For the best overall response evaluated in the tumor evaluable population (4 patients), 3 patients had stable disease (SD) and 1 patient had progressive disease (PD).

Safety results:

All 21 patients (100.0%) reported at least 1 TEAE as well as TEAE related to cabazitaxel. Common TEAEs were neutropenia in 20 patients (95.2%), fatigue in 16 patients (76.2%), diarrhoea in 14 patients (66.7%), decreased appetite in 9 patients (42.9%), nausea in 8 patients (38.1%), back pain in 8 patients (38.1%), and constipation in 7 patients (33.3%). Among these TEAEs, neutropenia in 20 patients (95.2%), fatigue in 15 patients (71.4%), diarrhoea in 11 patients (52.4%), and decreased appetite in 7 patients (33.3%) were considered as related to cabazitaxel.

Grade 3 or 4 TEAEs occurred in 21 patients (100.0%). Common grade 3 or 4 TEAEs were neutropenia in 20 patients (95.2%), thrombocytopenia in 5 patients (23.8%), leukopenia in 3 patients (14.3%), FN in 2 patients (9.5%), and decreased appetite in 2 patients (9.5%).

No TEAE leading to death was reported. A total of 8 serious TEAEs were reported in 5 of 21 patients (23.8%). Serious TEAEs were FN in 2 patients (9.5%), and decreased appetite, atrial fibrillation, gastrointestinal haemorrhage, nausea, cholecystitis acute, and haemoglobinuria in 1 patient each (4.8%). Among them, decreased appetite, atrial fibrillation, cholecystitis acute, and haemoglobinuria in 1 patient each (4.8%) were judged as not related to cabazitaxel. A total of 7 TEAEs leading to permanent treatment discontinuation were reported in 6 patients (28.6%). TEAEs leading to permanent treatment discontinuation were neuropathy peripheral in 2 patients (9.5%), and decreased appetite, pleural effusion, cholecystitis acute, haemoglobinuria, and fatigue in 1 patient each (4.8%). Among them, pleural effusion, cholecystitis acute, and haemoglobinuria in 1 patient each (4.8%) were judged as not related to cabazitaxel. No AESI was reported during the study.

Hematology and biochemistry data were summarized at each planned time point. Unscheduled data were not included in the analyses and thus, the frequency of laboratory abnormalities could be fewer than that of AEs related to laboratory tests. Therefore, summaries of hematology and biochemistry data were presented for reference. Leukocytes level (including lymphocytes, monocytes, and neutrophils levels) decreased at Day 8 in cycle 1, increased at Day 15 in cycle 1 compared with the baseline level and subsequently returned to around the baseline level by Day 1 in cycle 2. During cycle 1, median ANC at the nadir, time to nadir and time to recover were 176.0/mm^3 (range, 0–1740/mm^3), 8.0 days (range, 7–9 days) and 4.0 days (range, 3–8 days), respectively. Other laboratory parameters showed no consistent pattern of change during the study.

Vital signs showed no consistent pattern of change during the study.

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