

Original Article

# Impact of pegfilgrastim as primary prophylaxis for metastatic castration-resistant prostate cancer patients undergoing cabazitaxel treatment: an open-label study in Japan

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## Abstract

**Background:** Cabazitaxel is an efficacious treatment for patients with metastatic castration-resistant prostate cancer who have previously progressed on docetaxel, but febrile neutropenia during the first cycle is a frequent complication. Asian patients are at increased risk of febrile neutropenia. Although primary prophylaxis with granulocyte colony-stimulating factor can reduce the incidence, its efficacy has not been prospectively demonstrated in Japanese patients with cabazitaxel treatment.

**Methods:** PEGAZUS, a prospective, single-arm study conducted at eight clinical sites in Japan, enrolled 21 heavily pretreated patients with metastatic castration-resistant prostate cancer. Patients received cabazitaxel 25 mg/m<sup>2</sup> every 3 weeks, up to 10 cycles. Oral prednisolone 10 mg was taken daily. Pegfilgrastim 3.6 mg was administered at least 24 h after the cabazitaxel infusion. The primary endpoint was the incidence of febrile neutropenia in the first cycle.

**Results:** The median number of treatment cycles was seven. The relative dose intensity of cabazitaxel was 67.4% (range, 53.2–91.3%). Two of 21 patients (9.5%) experienced febrile neutropenia in the first cycle. This rate was lower than the rate (43%) previously observed without prophylactic granulocyte colony-stimulating factor in a similar patient population. Six patients showed a prostate-specific antigen response (28.6%). Three of four patients evaluable for tumor response had stable disease and one had progressive disease. Grade  $\geq 3$  diarrhea was not observed. Primary prophylaxis with granulocyte colony-stimulating factor significantly reduced the incidence of febrile neutropenia in this study.

**Conclusions:** Cabazitaxel plus granulocyte colony-stimulating factor is safe and effective for Japanese patients with metastatic castration-resistant prostate cancer who have previously progressed on docetaxel.

**Clinical trial registration:** ClinicalTrials.gov (NCT02441894).

**Key words:** Asian, febrile neutropenia, taxane, pegylated granulocyte colony-stimulating factor, prostate-specific antigen

## Introduction

Cabazitaxel is a taxane approved by the Food and Drug Administration in 2010 for the treatment of castration-resistant prostate cancer (CRPC). Cabazitaxel was selected for clinical development among ~400 compounds for its ability to overcome docetaxel resistance as shown in *in vitro* studies (1–4). In the TROPIC study (NCT00417079, a large, multicenter, multinational trial), cabazitaxel treatment significantly improved survival in men with metastatic castration-resistant prostate cancer (mCRPC) who had progressive disease after docetaxel treatment (5). Febrile neutropenia (FN) is a major dose-limiting toxicity in patients treated with chemotherapy (6,7), and complications from neutropenia are the most frequent cause of death among patients taking cabazitaxel (5). FN in the first cycle of chemotherapy is associated with early termination of treatment and increased mortality (7–9). Therefore, effective treatment strategies are needed to prevent the development of FN. Japanese and other Asian patients treated with taxanes may have a higher incidence of FN than Caucasian patients (10). In a phase I trial in Japanese patients with CRPC treated with cabazitaxel, the overall incidence of FN was 54.5% (11). In contrast, in the phase III TROPIC study of primarily Caucasian men with mCRPC treated with cabazitaxel, the overall incidence of FN (no prophylactic granulocyte colony-stimulating factor [G-CSF] in the first cycle and it was allowed in subsequent cycles) was only 8% (5).

G-CSF stimulates the production of granulocytes and promotes the survival and proliferation of neutrophil precursors (12). Pegfilgrastim is a recombinant form of G-CSF that has been pegylated to extend its half-life. In pivotal trials testing the efficacy of pegfilgrastim, the incidence of FN was reduced by 94% (13). Prophylactic G-CSF is recommended in the package insert for cabazitaxel (14) and is included in the current Japanese guidelines for the treatment of patients with prostate cancer (15). The American Society of Clinical Oncology (ASCO) recommends primary prophylaxis with G-CSF whenever the risk of FN is above 20% (16).

Primary prophylaxis with G-CSF has been demonstrated to reduce the incidence of FN in adults with solid tumors or lymphoma undergoing chemotherapy (17). In Japan, some retrospective studies have assessed risk factors and predictors of FN among patients with urological cancer, including prostate cancer (18) and mCRPC (19) treated with docetaxel. However, prospective clinical studies have not been conducted to evaluate the benefit of primary prophylaxis with G-CSF in Japanese patients with mCRPC treated with cabazitaxel. We conducted a single-arm, open-label study (PEGAZUS) at eight clinical sites in Japan. The goal of the study was to examine whether preventative administration of pegfilgrastim reduced the incidence of FN in patients with mCRPC previously treated with chemotherapy.

## Materials and Methods

### Patients

The PEGAZUS study (NCT02441894) enrolled Japanese patients with mCRPC treated with cabazitaxel plus prednisolone. Eligible

subjects were men at least 20 years old (with no upper age limit) with mCRPC previously treated with chemotherapy including docetaxel. Patients meeting the following criteria were excluded: Eastern Cooperative Oncology Group performance status (ECOG-PS)  $\geq 2$ ; life expectancy  $< 3$  months; inadequate organ/bone marrow function; prior surgery, radiation or chemotherapy within 4 weeks before enrollment; history of severe hypersensitivity reaction to polysorbate 80-containing drugs, prednisolone, pegfilgrastim, G-CSF or their components; or unwillingness to use an effective method of contraception during the study period. Ethical approval was granted by the institutional review boards of each institution, and all patients provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Study design

This single-arm, open-label study was conducted between April 2015 and November 2016 at eight treatment centers in Japan. After informed consent, 21 patients were enrolled in the study and followed until disease progression, appearance of unacceptable toxicity, withdrawal of informed consent or completion of 10 treatment cycles (Supplementary Fig. S1). A post-treatment follow-up period lasted 30 days after the last study treatment.

For each treatment cycle, cabazitaxel 25 mg/m<sup>2</sup> was administered as a 1-h intravenous infusion every 3 weeks. Oral prednisolone 10 mg was administered daily. Pegfilgrastim (3.6 mg) was administered subcutaneously at least 24 hours (i.e. on day 2) after completion of the cabazitaxel infusion. Patients were treated for up to 10 cycles. The doses of cabazitaxel could be reduced stepwise (i.e. by increments of 5 mg/m<sup>2</sup>) if a patient experienced unacceptable toxicity. However, when dose reduction required a dose below 15 mg/m<sup>2</sup>, study treatment was discontinued. To resume the study treatment, patients had to meet the criteria for retreatment outlined in the protocol. Treatment with cabazitaxel could be delayed no more than 2 weeks to allow recovery from acute toxicity. If a treatment delay was longer than 2 weeks, the patient discontinued cabazitaxel. No dose escalation was allowed after dose reduction. Data were recorded by each investigator in case report forms, which were designed by the sponsor to record all observations and data relevant to the clinical investigation. All study drugs were provided by the sponsor.

### Study objectives and endpoints

The primary objective was to assess tolerability of cabazitaxel 25 mg/m<sup>2</sup> every 3 weeks in this patient population receiving primary prophylaxis with pegfilgrastim. The primary endpoint was the incidence of FN in cycle 1. FN was defined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (20), as an absolute neutrophil count  $< 1000/\text{mm}^3$  and a single temperature of  $> 38.3^\circ\text{C}$  or a sustained temperature of  $\geq 38^\circ\text{C}$  for  $\geq 1$  h. The

secondary objectives included the overall rates of FN and grade  $\geq 3$  neutropenia and diarrhea, the number of patients with dose delay due to adverse events (AEs) or dose reduction due to AEs, relative dose intensity, incidences of FN-related hospitalization and use of intravenous anti-infectives, prostate-specific antigen (PSA) response (50% decrease) and tumor response according to Response Evaluation Criteria in Solid Tumors version 1.1. Tolerability (AEs) was assessed by the CTCAE v4.0 and classified by system organ class/preferred term according to MedDRA version 19.0. Laboratory safety variables included hematology tests, biochemistry, clinical examinations and urinalysis assessed during each cycle and at the follow-up examination.

### Statistical considerations

Sample size calculations relied on data from a previous phase I study in Japan in which the incidence of FN was 43% in the first treatment cycle. Data from 21 patients were determined to provide over 90% power to detect a significant reduction in FN incidence compared with the phase I study if 43% of the patients in this study experienced FN, against the expected FN incidence of 10%.

For the primary and secondary analyses, incidences of each endpoint were calculated along with a 95% confidence interval (CI) using data from all treated patients. A cut-off analysis for the primary analysis of the incidence of FN was planned for when all patients completed the first study cycle, then the final analysis on all data was conducted after all patients completed the study treatment. Continuous variables were summarized using descriptive statistics, and categorical variables were summarized using the numbers and percentages of patients. The data were analyzed using SAS<sup>®</sup> software (version 9.2 or later).

### Results

Twenty-one patients were enrolled in the PEGAZUS study (Table 1). The median age was 70 years (range, 56–82 years). All patients had an ECOG-PS of 0 or 1 and were of Asian descent; 61.9% had prior treatment with enzalutamide (median duration, 3.1 months; range, 0.5–10.8 months) and 47.6% with abiraterone acetate (median duration 2.4 months; range, 0.9–5.9 months). All patients had prior treatment with docetaxel for a median of 8.5 months (range, 1.0–60.3 months).

All patients completed at least one study treatment cycle. Nine patients (42.9%) completed all 10 cycles of treatment, and 12 patients (57.1%) discontinued the treatment (Fig. 1). The median number of cycles completed was seven (range, 3–10). Nine of the patients who discontinued treatment had disease progression, and three experienced AEs.

The median relative dose intensity of cabazitaxel was 67.4% (range, 53.2–91.3%). 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 primary endpoint analysis, two patients (9.5%, 95% CI 1.17–30.38%) experienced FN in cycle 1. Both patients were hospitalized, and one was treated with intravenous anti-infectives. There were no additional episodes of FN in the study.

In the secondary endpoint analysis, there were no incidents of grade 3 or 4 diarrhea during the study. Grade  $\geq 3$  neutropenia was observed in 20 patients (95.2%) over the course of the study. PSA response was observed in six patients (28.6%), and PSA increased in

7 (33.3%) (Fig. 2). The median time to PSA progression was 182 days (95% CI, 71–255). Four patients had measurable tumors and were evaluable for tumor response. Three had stable disease and one had progressive disease.

All patients presented with at least one grade  $\geq 3$  treatment-emergent adverse event (TEAE) (Table 2). TEAEs included neutropenia, thrombocytopenia, leukopenia, FN and decreased appetite. Eight serious TEAEs occurred in five of 21 patients (23.8%). There were no treatment-related deaths, and no FN was observed after cycle 1. During cycle 1, median absolute neutrophil count at nadir was  $176.0 \text{ mm}^3$  (range, 0–1740/ $\text{mm}^3$ ), time to nadir was 8.0 days (range, 7–9 days), and time to recovery was 4.0 days (range, 3–8 days).

### Discussion

The PEGAZUS study was designed to evaluate whether primary prophylaxis with G-CSF would lower the incidence of FN in Japanese patients with mCRPC being treated with cabazitaxel. In the PEGAZUS trial, the incidence of FN was 9.5%. The upper confidence limit, 30%, is lower than the previously observed rate of 43%. Thus, preventative administration of G-CSF is beneficial for patients treated with cabazitaxel.

ASCO and other organizations have recognized the benefit of primary prophylaxis with G-CSF in patients at high risk for FN. The ASCO guidelines list age, advanced disease and prior chemotherapy as potential risk factors (16). The high-risk population has not been completely defined. Nonetheless, several studies have reported that taxane-induced myelosuppression and risk of developing FN are higher among Asian populations compared with non-Asian populations (10,21). Yano et al. studied the toxicity profile of docetaxel according to dose and ethnicity and found that the risk of grade 3/4 neutropenia was almost 19 times higher in studies conducted in Asia than non-Asian studies (21).

Although the safety of cabazitaxel has not been directly compared in Asian and Western populations in a single trial, studies such as the TROPIC trial suggest that FN among Western patients is typically  $<10\%$ , much lower than that of Asian populations (5). The frequency of bone marrow suppression with taxanes is reported to be high in Japanese and other Asian patients (10,21), and it is therefore worthwhile to examine preventative administration of G-CSF when taxanes, such as cabazitaxel, are administered to patients at risk of FN (10,11,22). This study provides evidence that Asian populations are among the high-risk groups that should routinely undergo primary prophylaxis with G-CSF.

The inclusion criteria for this study were similar to those used for the phase I trial; however, there were some differences in the patient groups (11). The phase I trial included patients who had failed to respond to docetaxel, but the PEGAZUS study included many patients treated with novel hormone therapies, such as abiraterone acetate and enzalutamide. Thus, the patients in this study had been treated with more lines of therapy. Lastly, there was no upper age limit in the current study; however, the phase I study enrolled patients up to 74 years old.

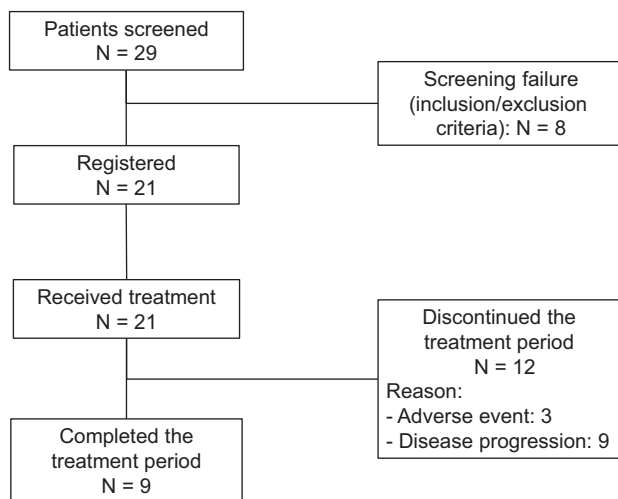
Although the patients in the PEGAZUS study were potentially at high risk of FN, FN was manageable with prophylactic peg-G-CSF administration. The median actual dose intensity and relative dose intensity for cabazitaxel were  $5.62 \text{ mg/m}^2/\text{week}$  and 67.4% in this study, respectively. In the phase I study, the actual dose intensity and relative dose intensity were slightly higher,  $6.83 \text{ mg/m}^2/\text{week}$

**Table 1.** Baseline patient demographics

Characteristic	All patients (N = 21)
Age, median (years)	70.0 (range, 56–82)
Body weight, median (kg)	62.3 (range, 48.8–74.8)
BMI, median (kg/m <sup>2</sup> )	23.2 (range, 18.1–28.2)
eGFR, median (ml/min/1.73 m <sup>2</sup> )	90.2 (range, 61–106)
ECOG-PS [n (%)]	
0	17 (81.0)
1	4 (19.0)
Gleason score [n (%)]	
≤7	5 (23.8)
>7	15 (71.4)
Unknown	1 (4.8)
Serum PSA concentration, median (ng/ml)	89.1 (range, 4.44–737.0)
Metastatic organs involved, n (%)	
Bone	19 (90.5)
Lymph nodes	5 (23.8)
Prostate	4 (19.0)
Pelvis	2 (9.5)
Bladder	1 (4.8)
Liver	1 (4.8)
Prior radiation therapy [n (%)]	
Palliative radiation therapy	3 (14.3)
Curative radiation therapy	3 (14.3)
Both	0
No radiation therapy	15 (71.4)
Prior hormonal therapy [n (%)]	
LHRH agonist	20 (95.2)
LHRH antagonist	3 (14.3)
Antiandrogen	21 (100.0)
Estramustine	10 (47.6)
Enzalutamide	13 (61.9)
Abiraterone acetate	10 (47.6)
Other	8 (38.1)
Number of prior hormonal therapies, median [n (%)]	4.0 (2–7)
Prior chemotherapy	
Prior docetaxel therapy [n (%)]	21 (100)
Treatment duration, median (months)	8.51 (range, 1.0–60.3)
Total prior docetaxel dose, <sup>a</sup> median (mg/m <sup>2</sup> )	611.97 (range, 222.5–2946.2)
Docetaxel dose intensity, <sup>a</sup> median (mg/m <sup>2</sup> /week)	16.54 (range, 10.0–28.3)

BMI, body mass index; eGFR, estimated glomerular filtration rate; ECOG-PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen; LHRH, luteinizing hormone-releasing hormone.

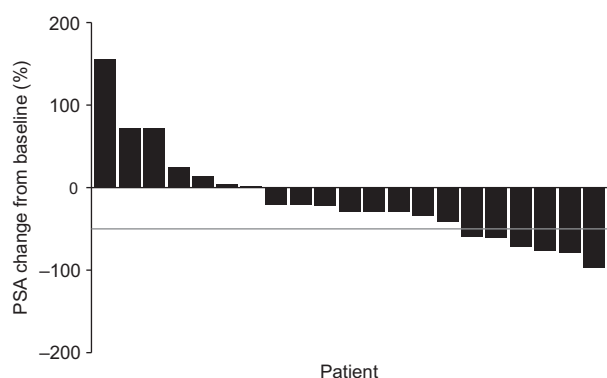
<sup>a</sup>Calculated based on the body surface area at baseline.



**Figure 1.** Patient disposition.

and around 80%, respectively (11). Dose delays were also more frequent in the PEGAZUS study (81.3% of cycles) than in the phase I study (37.4%). Although the dose intensity was relatively lower than the previous phase I study, incidence of FN in cycle 1 as the primary endpoint of this study was not influenced by the low dose intensity because all 21 patients received the 25-mg/m<sup>2</sup> dose in cycle 1. The PSA response rate in this study was similar to the response rate in the Japanese phase I study, and the median time to PSA progression of about 6 months in this study was longer than that of 3.7 months in the phase I study. This result was consistent with results of the TROPIC and PROSELICA studies (5,23).

Taxanes are generally associated with gastrointestinal events (nausea, vomiting, and diarrhea), hair loss, and peripheral neuropathy, all of which can reduce patient quality of life. Grade 3 diarrhea (observed in the Japanese phase I study) was not observed in the current study. The frequency of other gastrointestinal symptoms was low, and two cases (9.5%) of grade 1 hair loss were reported.



**Figure 2.** Maximum percent change in prostate-specific antigen (PSA) from baseline for each patient. PSA response, defined as at least a 50% reduction in PSA from baseline, is indicated by the horizontal line.

**Table 2.** Grade  $\geq 3$  TEAEs by primary system organ class and preferred term

	All patients (N = 21)
Any TEAE	21 (100.0)
Blood and lymphatic system disorders	20 (95.2)
Neutropenia	20 (95.2)
Thrombocytopenia	5 (23.8)
Leukopenia	3 (14.3)
Febrile neutropenia	2 (9.5)
Anemia	1 (4.8)
Metabolism and nutrition disorders	3 (14.3)
Decreased appetite	2 (9.5)
Hypokalemia	1 (4.8)
Nervous system disorders	1 (4.8)
Neuropathy peripheral	1 (4.8)
Cardiac disorders	1 (4.8)
Atrial fibrillation	1 (4.8)
Vascular disorders	1 (4.8)
Hypertension	1 (4.8)
Gastrointestinal disorders	2 (9.5)
Gastrointestinal hemorrhage	1 (4.8)
Nausea	1 (4.8)
Hepatobiliary disorders	1 (4.8)
Cholecystitis acute	1 (4.8)
Renal and urinary disorders	1 (4.8)
Hemoglobinuria	1 (4.8)
General disorders and administration site conditions	1 (4.8)
Fatigue	1 (4.8)

Data are reported as n (%).

TEAE, treatment-emergent adverse event.

The number of adverse reactions observed in this trial was similar to that of the phase I trial.

This study had some limitations. The study was conducted without a control arm at a limited number of selected study centers. In addition, overall survival was not assessed because the follow-up period ended within 30 days from the last cabazitaxel cycle.

## Conclusions

The results of the PEGAZUS study showed that primary prophylaxis with PEG-G-CSF for Japanese patients with mCRPC reduced the

frequency of FN to <10%. A therapeutic regimen of cabazitaxel plus G-CSF has a good safety profile and is an effective treatment option for Japanese patients with mCRPC who have previously received docetaxel.

## Abbreviations

AE, adverse event; ASCO, American Society of Clinical Oncology; BMI, body mass index; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; LHRH, luteinizing hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PEG-G-CSF, pegylated granulocyte colony-stimulating factor; PSA, prostate-specific antigen; TEAE, treatment-emergent adverse event.

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## Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

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## Conflict of interest statement

H. Uemura received consultancy fees from Janssen Pharmaceutical K.K., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd, Bayer Yakuhin, Ltd, and Daiichi Sankyo Co., Ltd; and lecture fees from AstraZeneca K.K., Sanofi K.K., Fujifilm Corporation, Kyowa Hakko Kirin Co., Ltd, and Kissei Pharmaceutical Co. M. Sumitomo received consultancy fees from Sanofi K.K., Janssen Pharmaceutical K.K., Ono Pharmaceutical Co., Ltd, Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd, and Kissei Pharmaceutical Co.; lecture fees from Sanofi K.K., Pfizer Japan Inc., Takeda Pharmaceutical Co., Ltd, and AstraZeneca K.K.; and research funding from Ono Pharmaceutical Co., Ltd, Sanofi K.K., Astellas Pharma Inc., AstraZeneca K.K., and Takeda Pharmaceutical Co., Ltd., M. Sugimoto received manuscript writing/editing fees from Janssen Pharmaceutical K.K., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd, and AstraZeneca K.K. Y. Sunaga is an employee of Sanofi K.K. and owns stock of Sanofi K.K. M. Oya received consultancy fees from Astellas Pharma Inc.; lecture fees from Astellas Pharma Inc., Janssen Pharmaceutical K.K., AstraZeneca, Sanofi, and Takeda; research funding from Astellas Pharma Inc. and Takeda Pharmaceutical Co., Ltd. E. Ecstein-Fraisse is an employee of Sanofi.

T. Kosaka, N. Hayashi, K. Yoshimura, and S. Fukasawa have no conflicts of interest to declare.

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