

# Phase I dose-escalation study of cabazitaxel administered in combination with gemcitabine in patients with metastatic or unresectable advanced solid malignancies

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Taxane–gemcitabine combinations have demonstrated antitumor activity. This phase I study (NCT01001221) aimed to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of cabazitaxel plus gemcitabine and to assess the preliminary efficacy of this combination. The patients included had metastatic or unresectable solid tumors and had exhausted standard treatment. Cohorts of three to six patients received cabazitaxel (15–20 mg/m<sup>2</sup>) before (part 1a) or after (part 1b) gemcitabine (700–1000 mg/m<sup>2</sup>) on Day 1 and gemcitabine alone on Day 8. Prophylactic growth factors were not allowed in cycle 1. In part 1a ( $n = 12$ ), five patients received 20 mg/m<sup>2</sup> cabazitaxel plus 1000 mg/m<sup>2</sup> gemcitabine (20/1000), five received 15/900, two received 15/700. In part 1b, all six patients received the lowest dose (700/15). At all doses, two or more patients experienced a DLT, regardless of administration sequence, including febrile neutropenia ( $n = 4$ ), grade 4 neutropenia ( $n = 2$ ), grade 4 thrombocytopenia ( $n = 2$ ), and grade 3 aspartate transaminase increase ( $n = 1$ ). The MTD was not established as all cohorts exceeded the MTD by definition. All patients experienced an adverse event; the most frequent all-grade nonhematologic events were fatigue (66.7%), decreased appetite (50.0%), and diarrhea (44.4%). The most frequent grade 3–4 hematologic abnormalities were

neutropenia (83.3%), leukopenia (77.8%), and lymphopenia (72.2%). Toxicity was sequence-independent but appeared worse with gemcitabine followed by cabazitaxel. Durable partial responses were observed in three patients (prostate cancer, appendiceal cancer, and melanoma). The unacceptable DLTs with cabazitaxel plus gemcitabine, at doses reduced more than 25% from single-agent doses, preclude further investigation. *Anti-Cancer Drugs* 26:785–792 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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## Introduction

Cabazitaxel, a second-generation taxane, is a semisynthetic derivative of 10-deacetylbaicatin III [1]. It was identified from a preclinical screen of ~450 different candidate molecules, examined for their effects on microtubule stabilization, in-vitro activity in taxane-sensitive and taxane-resistant cell lines, and in-vivo activity in a tumor model of induced docetaxel resistance [2]. Cabazitaxel differs from docetaxel by the replacement of two hydroxyl groups with

methoxy groups at the C7 and C10 positions of the baccatin moiety [1]. Compared with docetaxel, cabazitaxel exhibits greater activity and a different cytotoxicity profile against murine and human cell lines, in addition to demonstrating a significant antitumor effect in multiple tumor xenograft models showing acquired or intrinsic resistance to docetaxel [2]. Furthermore, unlike docetaxel, cabazitaxel has been shown to cross the blood–brain barrier, with greater exposure in the brain than in plasma in rodents [3]. Following the results of the TROPIC trial (NCT00417079) [4], 25 mg/m<sup>2</sup> cabazitaxel administered as a 1-h intravenous infusion every 3 weeks was approved by regulatory authorities for the treatment of patients with ‘hormone-refractory’ metastatic prostate cancer, now termed metastatic castration-resistant prostate cancer, previously treated with a docetaxel-containing treatment regimen [5,6]. In this pivotal study, the most frequent significant side effects were grade 3–4 neutropenia and febrile neutropenia, which occurred in 82 and 8% of the treated patients, respectively [4–6].

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Gemcitabine is a 2-difluoro-substituted pyrimidine nucleoside analog that inhibits DNA synthesis. It is cytotoxic in cells undergoing DNA synthesis (S-phase) and also prevents cells from progressing through the G1/S-phase boundary, thereby inhibiting cell division [7]. Gemcitabine is approved for the treatment of patients with various malignancies, including metastatic breast cancer, advanced pancreatic adenocarcinoma, and advanced non-small-cell lung cancer (NSCLC) [7].

As they have differing targets and act at different phases of the cell cycle [8,9], combination treatment with a taxane and gemcitabine has previously been explored in clinical trials, with positive results reported for the docetaxel–gemcitabine combination in several tumor types including NSCLC [10], metastatic breast cancer [11], and soft-tissue sarcomas [12]. Notably, studies have shown that the activity of this combination in cell lines is schedule dependent, with drug synergy varying according to the sequence of treatment administration [13]. These results, and the superior activity of cabazitaxel compared with docetaxel in sarcoma mouse xenograft models [3], suggest a unique activity and toxicity profile for this combination. Therefore, we explored the activity of the cabazitaxel–gemcitabine combination in a phase I trial in patients with advanced solid tumors. A prior dose-escalation study, ongoing at the time of initiation of our study [14], had defined the maximum tolerated dose (MTD) of cabazitaxel in combination with capecitabine as 20 mg/m<sup>2</sup> cabazitaxel administered intravenously on Day 1 with 1000 mg/m<sup>2</sup> capecitabine administered twice daily on Days 1–14, cycled every 3 weeks. Therefore, the planned starting dose for this study was 20 mg/m<sup>2</sup> of cabazitaxel on Day 1 and 1000 mg/m<sup>2</sup> gemcitabine on Days 1 and 8, administered every 3 weeks, using a similar regimen to that used for gemcitabine in combination with docetaxel [15–17].

## Patients and methods

### Study design

This phase I clinical trial comprised two parts. In part 1 (dose-escalation phase), the MTD and dose-limiting toxicities (DLTs) of cabazitaxel administered in combination with gemcitabine in 21-day cycles were to be determined. A standard 3+3 study design was to be used, with cohorts of three to six patients receiving cabazitaxel on Day 1, followed by gemcitabine on Day 1 and Day 8 (part 1a). The administration sequence of the drugs on Day 1 was to be reversed in part 1b. A 7-day gap between enrollment of the first patient and enrollment of the subsequent two patients was to be incorporated to allow toxicity to be evaluated. If none of the three patients experienced a DLT during cycle 1, the dose was to be escalated to the next higher dose level. If one of the three patients experienced a DLT during cycle 1, up to three more patients were to be enrolled at the same dose level. If two or more patients experienced a DLT, no

further dose escalation was to be performed and additional patients were to be enrolled at a lower dose to confirm the MTD. The MTD was defined as the highest dose at which none of the first three patients or one of up to six total patients experienced a DLT during cycle 1.

In part 2 of the study (dose-expansion phase), 15 additional patients were to be treated at the MTD determined in the dose-escalation phase, with the objective of examining the antitumor activity of the cabazitaxel–gemcitabine combination.

The study protocol and all amendments were approved by the Institutional Review Boards and Independent Ethics Committees at each participating institution. All patients gave written informed consent. The study was conducted according to good clinical practice and the Declaration of Helsinki and its amendments. The trial is registered at <http://www.ClinicalTrials.gov> as NCT01001221.

### Dose-limiting toxicities

DLTs were defined [according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0] [18] as any non-hematologic grade 3 or higher event except: fever without infection; inadequately treated nausea, vomiting, mucositis, or stomatitis; or grade 3 fatigue, anorexia, and aspartate aminotransferase/alanine aminotransferase elevations that returned to baseline before next cycle or hypersensitivity reaction in the absence of required premedication. Grade 2 peripheral neuropathy that had not resolved before the initiation of the next treatment cycle was also considered a DLT. Hematologic DLTs were febrile neutropenia, grade 4 neutropenia lasting for more than 7 days, or grade 4 thrombocytopenia. Any life-threatening toxicity that was thought to be drug related was also considered a DLT.

### Patient population

Adult patients with a histologically or cytologically confirmed advanced, refractory solid malignancy that was metastatic or unresectable, and for which standard treatment did not exist, were eligible for this study. Exclusion criteria included: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of at least 2, anticipated need for a major surgical procedure or radiation therapy during the study, prior cabazitaxel treatment within 2 years, or a history of grade 3–4 hypersensitivity to taxanes, polysorbate-80, or their derivatives. Patients with any clinically significant toxic effect (excluding alopecia) of prior therapy that had not resolved to grade 1 or lower according to NCI-CTCAE version 3.0 [18], those who had not completed prior chemotherapy, biologic therapy, targeted noncytotoxic therapy for at least 3 weeks, or radiotherapy for at least 4 weeks before registration; and those who had inadequate organ function (bone marrow, hepatic, renal) were also excluded.

Prior receipt of taxane treatment other than cabazitaxel was permissible.

### Treatment

Cabazitaxel and gemcitabine were administered as 60-min and 30-min intravenous infusions, respectively. In the dose-escalation phase, cabazitaxel was administered followed by gemcitabine on Day 1 of each 3-week cycle. Premedication consisting of an antihistamine, a steroid, and a H2 antagonist was administered at least 30 min before each cabazitaxel dose. On Day 8 of each cycle, gemcitabine was administered alone. The starting dose was 20 mg/m<sup>2</sup> cabazitaxel and 1000 mg/m<sup>2</sup> gemcitabine, with one planned higher dose level (25/1000 mg/m<sup>2</sup>) and two lower dose levels, one planned (15/900 mg/m<sup>2</sup>) and one added following a protocol amendment (15/700 mg/m<sup>2</sup>). On the basis of the emerging toxicity profile observed in the first part of the study (part 1a), a protocol amendment was applied, such that the schedule of cabazitaxel and gemcitabine administration was reversed (part 1b; gemcitabine followed by cabazitaxel on Day 1 with a 60-min interval between the two treatments, and gemcitabine alone on Day 8, every 21 days). In part 1b, the starting dose was 700 mg/m<sup>2</sup> gemcitabine and 15 mg/m<sup>2</sup> cabazitaxel, with three planned higher dose levels (900/15, 900/20, and 1000/20 mg/m<sup>2</sup>). Patients received treatment until disease progression, unacceptable toxicity, withdrawal of consent, or until the investigator decided to withdraw the patient. Prophylactic and therapeutic use of hematopoietic growth factors was not permitted during the first cycle of study treatment but was permitted after the patient had developed a hematologic DLT.

### Evaluations

Safety was assessed in terms of vital signs, medical history, physical examinations, ECOG PS, electrocardiograms, laboratory safety tests (including complete blood count, serum chemistry analysis, and urinalysis), and incidence and severity of adverse events (AEs; graded using NCI-CTCAE v. 3.0 [18]). Vital signs, medical history, physical examinations, and ECOG PS were all assessed at screening/baseline and Day 1 and Day 8 of each cycle. Laboratory safety tests and incidence and severity of AEs were assessed at baseline/screening, Day 1, Day 8, and Day 15 of each cycle, and at the end of study treatment. The period of observation for collection of AEs extended from the day of the first study drug administration until 30 days after the final dose of study drugs. Antitumor activity was assessed according to RECIST 1.1 [19] by imaging (computed tomography or MRI) of the chest, abdomen, and pelvis performed every 6 weeks and whenever disease progression was suspected. Disease control was defined as complete response, partial response (PR), or stable disease (SD).

### Pharmacokinetic analysis

In part 1, blood samples for the cabazitaxel assay were taken before infusion, 5 min before the end of infusion (EOI), and at various time points up to 168 h after the EOI. For gemcitabine and 2',2'-difluorodeoxyuridine (dFdU; the major metabolite of gemcitabine) assays, blood samples were taken before infusion, immediately before the EOI, and at various time points up to 22.5 h after the EOI for part 1a and up to 23.5 h after the EOI for part 1b, on both Day 1 and Day 8. Plasma concentrations of cabazitaxel, gemcitabine, and dFdU were determined by validated liquid chromatography/tandem mass spectrometry techniques, with a lower limit of quantification of 1 ng/ml for cabazitaxel and 50 ng/ml for gemcitabine and dFdU. A noncompartmental pharmacokinetic (PK) analysis was carried out to estimate the following PK parameters: maximum observed concentration ( $C_{max}$ ), time to maximum concentration ( $t_{max}$ ), area under the concentration–time curve extrapolated to infinity (AUC), area under the concentration–time curve from time 0 to the time of the last measurable concentration (AUC<sub>last</sub>), terminal half-life ( $t_{1/2z}$ ), total plasma clearance (CL), and volume of distribution at steady state ( $V_{ss}$ ). CL and  $V_{ss}$  normalized to body surface area (BSA) were also calculated ( $V_{ss}/BSA$  and  $CL/BSA$ ).

### Statistical analysis

For the dose-escalation phase, a sample size of 31 patients was calculated for each of the two administration sequences on the basis of four planned dose levels (three to six patients per dose level). The treated population was defined as all patients who took at least part of a dose of cabazitaxel or gemcitabine. Descriptive statistics were used to summarize the PK parameters of cabazitaxel, gemcitabine, and dFdU. For gemcitabine and dFdU, the ratios from Day 1 to Day 8 for AUC<sub>last</sub> and AUC were calculated for each dose level, where possible.

## Results

### Patients

A total of 19 patients were enrolled in the dose-escalation phase (13 in part 1a and six in part 1b). One patient assigned to 15 mg/m<sup>2</sup> cabazitaxel and 700 mg/m<sup>2</sup> gemcitabine in part 1a was not treated because of elevated blood creatinine levels between registration and first treatment, exceeding that permitted by the protocol. The majority of patients were heavily pretreated (three or more prior treatment regimens, 78.9%; Table 1). All patients discontinued treatment. Reasons for discontinuation included disease progression (11 patients, 57.9%), AEs (five patients, 26.3%), or other reasons (two patients, 10.5%; poor PS and patient decision, each  $n = 1$ ). In total, 14 patients received granulocyte colony-stimulating factor (treatment and prophylaxis) during the study.

**Table 1 Patient demographics and baseline characteristics**

	Part A (cabazitaxel followed by gemcitabine) (n = 13)	Part B (gemcitabine followed by cabazitaxel) (n = 6)	Total (N = 19)
Race (%)			
White	76.9	100	84.2
Black	7.7	0	5.3
Asian	7.7	0	5.3
Other (Filipino)	7.7	0	5.3
Sex (%)			
Male	61.5	50.0	57.9
Age (years)			
Mean (SD)	58.4 (9.5)	56.3 (16.1)	57.7 (11.5)
ECOG PS (%)			
0	23.1	16.7	21.1
1	76.9	83.3	78.9
Primary tumor site (%)			
Lung	30.8	0	21.1
Pancreas	15.4	16.7	15.8
Bladder	7.7	16.7	10.5
Head/neck	15.4	0	10.5
Prostate	15.4	0	10.5
Other <sup>a</sup>	15.4	66.7	31.6
Number of prior anticancer regimens (%)			
1	15.4	0	10.5
2	15.4	0	10.5
≥ 3	69.2	100	78.9

ECOG PS, Eastern Cooperative Oncology Group performance status.

<sup>a</sup>Colon, muscle/soft tissue, ovaries, pelvis, skin, and appendix (n = 1 each).

### Dose escalation

In the dose-escalation phase, the investigators observed multiple instances of patients with grade 2 and 3 uncomplicated neutropenia who could not receive subsequent cycles on time. Although this was not defined as a formal DLT criterion, to more fully characterize hematologic toxicities, the protocol allowed expansion of the first dose cohort with additional patients.

In part 1a of the dose-escalation phase (cabazitaxel followed by gemcitabine on Day 1), the first three patients treated at dose level 0 (20 mg/m<sup>2</sup> cabazitaxel and 1000 mg/m<sup>2</sup> gemcitabine) were not evaluable for DLT; one patient received granulocyte colony-stimulating factor in violation of the protocol, and two patients had a treatment delay because of grade 2 and 3 neutropenia. As treatment delay was not a formal DLT criterion, two additional patients were enrolled. Of these patients, two experienced a DLT (grade 4 febrile neutropenia and grade 4 neutropenia lasting for more than 7 days; each n = 1). As the initial dose level exceeded the MTD, five additional patients were enrolled and treated at the next lower dose level (-1; 15 mg/m<sup>2</sup> cabazitaxel/900 mg/m<sup>2</sup> gemcitabine), and all were evaluable for DLTs. Two DLTs were reported (grade 3 elevated aspartate aminotransferase and grade 4 neutropenia lasting for more than 7 days; each n = 1), indicating that 15 mg/m<sup>2</sup> cabazitaxel/900 mg/m<sup>2</sup> gemcitabine was also higher than the MTD. Following a protocol amendment, two patients were treated at a lower dose level (-2; 15 mg/m<sup>2</sup> cabazitaxel/700 mg/m<sup>2</sup> gemcitabine); both patients reported DLTs (grade 3 febrile neutropenia and grade 4

thrombocytopenia, n = 1; grade 4 febrile neutropenia, n = 1). Therefore, it was decided not to proceed further with dose escalation for this sequence of administration, and no MTD was defined. Neutropenia with or without fever was the predominant DLT for this sequence.

On the basis of preclinical data evaluating the combination of docetaxel and gemcitabine [13], we hypothesized that administration of gemcitabine before cabazitaxel might potentially lessen myelosuppression. In part 1b of the dose-escalation phase, in which gemcitabine was followed by cabazitaxel on Day 1, one DLT (grade 4 thrombocytopenia) was reported in the first three patients treated at dose level 0 (700 mg/m<sup>2</sup> gemcitabine/15 mg/m<sup>2</sup> cabazitaxel). Of three additional patients enrolled at this dose level, one patient did not receive Day 8 treatment because of grade 3 neutropenia, and one patient developed a DLT (grade 3 neutropenic fever). The initial dose level in part 1b also exceeded the MTD, with neutropenia as a limiting hematologic toxicity. On the basis of these results, the study was stopped without investigating a lower dose level in part 1b or performing the planned dose-expansion phase.

### Safety

A median of four treatment cycles was administered per patient [mean 7.7 (SD 7.1), range 1–22], and the median duration of treatment was 13.4 weeks (Table 2). The median relative dose intensities were 97% for cabazitaxel and 79% for gemcitabine. Of 14 patients evaluable for DLT, seven experienced a hematologic DLT and one experienced a nonhematologic DLT. The most frequent DLT was febrile neutropenia (grade 3, n = 1; grade 4, n = 2). All patients experienced an AEs. The most frequent AEs of any grade were typical of cytotoxic chemotherapies and included fatigue (66.7%), decreased appetite (50%), diarrhea (44.4%), and nausea (38.9%; see Table 1, Supplemental digital content 1, <http://links.lww.com/ACD/A110>, which shows the most frequent nonhematologic AEs). Hematologic abnormalities were observed in all patients (Table 3), and the rates of grade 3–4 hematologic abnormalities were: neutropenia (83.3%), leukopenia (77.8%), lymphopenia (72.2%), thrombocytopenia (50.0%), and anemia (27.8%). Seventeen patients (94.4%) experienced a treatment-related grade 3–4 AE. Thirteen patients (72.2%) experienced a serious AE, which was treatment related in 10 patients (55.6%; febrile neutropenia in 22.2%, and neutropenia, pancytopenia, and thrombocytopenia in 11.1% each).

As a result of AEs, 11 patients (61.1%) required a dose delay and 13 patients (72.2%) required a dose reduction, which in both cases were most frequently due to neutropenia (38.9% for each; see Table 2, Supplemental digital content 1, <http://links.lww.com/ACD/A110>, which shows AEs leading to dose delay or reduction). Four patients died, one of whom died during the study treatment period (within 30 days of the last dose of study

**Table 2 Study treatment exposure for cabazitaxel and gemcitabine**

	Part A (cabazitaxel followed by gemcitabine) (n = 12)	Part B (gemcitabine followed by cabazitaxel) (n = 6)	Total (N = 18)
Median number of cycles administered per patient (range) (n)	4.0 (1–22)	5.0 (1–16)	4.0 (1–22)
Median duration of treatment (range) (weeks)	12.14 (3–68)	16.29 (3–56)	13.43 (3–68)
Median cumulative dose (range) (mg/m <sup>2</sup> )			
Cabazitaxel	62.30 (14.9–333.5)	75.31 (14.6–240.8)	62.30 (14.6–333.5)
Gemcitabine	6007 (1260–30001)	5962 (701–16184)	6007 (701–30001)
Median relative dose intensity (range)			
Cabazitaxel	0.986 (0.85–1.00)	0.876 (0.69–1.00)	0.968 (0.69–1.00)
Gemcitabine	0.844 (0.5–1.00)	0.518 (0.44–0.88)	0.794 (0.44–1.00)

**Table 3 Hematologic abnormalities, including all-grade and grade 3–4 abnormalities**

Preferred term	Part A (cabazitaxel followed by gemcitabine) (%)						Part B (gemcitabine followed by cabazitaxel) (%)		All (N = 18) (%)			
	20/1000 mg/m <sup>2</sup> (n = 5)		15/900 mg/m <sup>2</sup> (n = 5)		15/700 mg/m <sup>2</sup> (n = 2)		All levels (n = 12)		700/15 mg/m <sup>2</sup> (n = 6)		All (N = 18) (%)	
	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4
Anemia	100	20.0	100	0	100	50.0	100	16.7	100	50.0	100	27.8
Leukopenia	100	80.0	100	80.0	100	100	100	83.3	100	66.7	100	77.8
Lymphopenia	100	60.0	100	60.0	100	100	100	66.7	83.3	83.3	94.4	72.2
Neutropenia	100	80.0	80.0	80.0	100	100	91.7	83.3	100	83.3	94.4	83.3
Thrombocytopenia	100	40.0	100	20.0	100	50.0	100	33.3	100	83.3	100	50.0

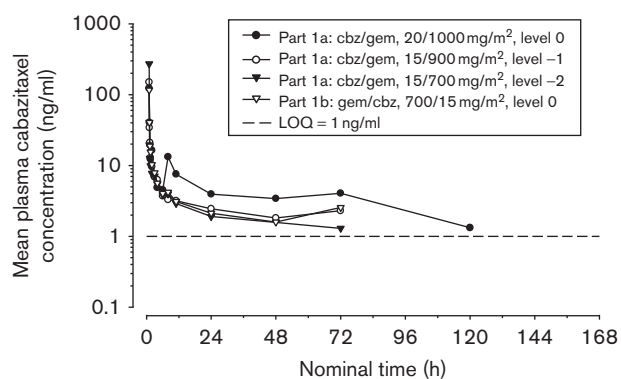
Frequencies do not include toxicity grade value of 0 or missing. Abnormalities are based on laboratory values not adverse events.

drug). Of the other three patients, one died 33 days after the last dose of study drug and the other two died more than 80 days after the last dose of study drug. All deaths were attributed to disease progression.

### Pharmacokinetics

All patients were included in the cabazitaxel PK analysis except for one patient from part 1a who received 15/900 mg/m<sup>2</sup>. PK samples for gemcitabine and dFdU assays were not collected on Day 8 in two patients at 20/1000 mg/m<sup>2</sup> and two patients at 15/700 mg/m<sup>2</sup> in part 1a and two patients in part 1b. Because of sampling errors, some patients were excluded for gemcitabine (one patient on Day 1 and two patients on Day 8 in part 1a, and one patient in part 1b) and dFdU (one patient on Day 8 in part 1a, and one patient in Part 1b) PK analysis.

The mean cabazitaxel plasma concentration–time curves after 1 h intravenous infusion of 20 and 15 mg/m<sup>2</sup> doses are shown in Fig. 1, and the descriptive statistics for cabazitaxel PK parameters are reported in Table 3 of Supplemental digital content 1 (<http://links.lww.com/ACD/A110>). Cabazitaxel CL/BSA pooled across part 1a dose levels appeared similar to the values reported previously for cabazitaxel in combination with capecitabine after noncompartmental analysis [14]. Over the study, CL/BSA values (33.7 l/h/m<sup>2</sup> for part 1a and 49.6 l/h/m<sup>2</sup> for part 1b) were in the range of those reported in monotherapy studies (44.7 and 27.3 l/h/m<sup>2</sup>) after individual

**Fig. 1**

Mean plasma concentrations of 20 or 15 mg/m<sup>2</sup> cabazitaxel (semi-log scale) after a 1-h intravenous infusion (cycle 1). Cbz, cabazitaxel; gem, gemcitabine; LOQ, limit of quantification.

modeling [20,21]. Therefore, neither gemcitabine nor its major metabolite, dFdU, appeared to have an effect on cabazitaxel. However, because of the limited data available, this apparent lack of effect of gemcitabine when administered before cabazitaxel needs to be confirmed.

The ratios of AUC<sub>last</sub> and AUC from Day 1 to Day 8 for gemcitabine and dFdU were close to 1 in both parts of the study (Table 4), suggesting no alteration in PK with coadministration of cabazitaxel. Therefore, cabazitaxel

**Table 4** Effect of cabazitaxel on the pharmacokinetics of gemcitabine and 2',2'-difluorodeoxyuridine at cycle 1

PK parameter ratio Day 1/Day 8 (min–max)	Plasma gemcitabine			Plasma dFdU		
	Part A (cabazitaxel followed by gemcitabine)		Part B (gemcitabine followed by cabazitaxel) (700/15 mg/m <sup>2</sup> )	Part A (cabazitaxel followed by gemcitabine)		Part B (gemcitabine followed by cabazitaxel) (700/15 mg/m <sup>2</sup> )
	20/1000 mg/m <sup>2</sup>	15/900 mg/m <sup>2</sup>		20/1000 mg/m <sup>2</sup>	15/900 mg/m <sup>2</sup>	
<i>N</i>	1	3	3	2	5	3
AUC <sub>last</sub>	1.15	1.17 (0.661–2.49)	1.11 (0.994–1.25)	0.948 (0.898–1.00)	0.829 (0.670–1.15)	0.911 (0.847–1.03)
AUC	1.15	1.24 (0.660–2.47)	1.11 (0.994–1.25)	0.950 (0.904–1.00)	0.854 (0.673–1.23)	0.889 (0.763–1.01)

AUC, area under the concentration–time curve extrapolated to infinity; AUC<sub>last</sub>, area under the concentration–time curve from time 0 to the time of the last measurable concentration; dFdU, 2',2'-difluorodeoxyuridine; PK, pharmacokinetic.

appeared to have no major effect on gemcitabine or dFdU, regardless of drug administration sequence. Descriptive statistics for gemcitabine and dFdU PK parameters are reported in Table 4 of Supplemental digital content 1 (<http://links.lww.com/ACD/A110>), and the mean plasma concentration–time curves for gemcitabine and dFdU are shown in Fig. 1 of Supplemental digital content 1 (<http://links.lww.com/ACD/A110>).

### Efficacy

Disease control (SD or better for at least 12 weeks) was achieved in 11 patients (61.1%; see Table 5, Supplemental digital content 1, <http://links.lww.com/ACD/A110>, which shows antitumor responses). Nine patients (50%) experienced durable disease control (PR or SD for at least six cycles of treatment). Three patients (16.7%) achieved a PR as the best overall response (none of whom had been exposed to gemcitabine or taxanes previously): a patient with prostate cancer that had metastasized to the bone, liver, lung, and lymph nodes treated with 20 mg/m<sup>2</sup> cabazitaxel/1000 mg/m<sup>2</sup> gemcitabine achieved a PR after cycle 2 and completed 12 treatment cycles; a patient with appendiceal carcinoma previously exposed to several chemotherapy regimens treated with 15 mg/m<sup>2</sup> cabazitaxel/900 mg/m<sup>2</sup> gemcitabine achieved a PR after cycle 8 and completed 19 treatment cycles; and a patient with melanoma of the scalp with metastasis to the lung and lymph nodes treated with 700 mg/m<sup>2</sup> gemcitabine/15 mg/m<sup>2</sup> cabazitaxel achieved a PR after cycle 4 and completed 16 treatment cycles. All three patients who achieved PR discontinued treatment because of subsequent disease progression. Of note, treatment-related AEs of any grade experienced by more than one of the responding patients included anemia, neutropenia, diarrhea, fatigue, alopecia, and decreased appetite, each occurring in two of the three patients. Grade 3–4 treatment-related AEs in the three responding patients included neutropenia (*n* = 2) and bronchiolitis (*n* = 1). Eight patients (44.4%) achieved SD as the best overall response, and durable SD was observed in six patients who received between six and 22 cycles of treatment. One patient with pancreatic cancer treated with cabazitaxel followed by gemcitabine, who had

disease progression on prior gemcitabine treatment, achieved SD at cycle 2 and at each subsequent assessment up to and including cycle 22. Six patients (33.3%) had progressive disease as the best overall response, and one patient was nonevaluable.

### Discussion

Cabazitaxel, a second-generation taxane, is an approved treatment for metastatic castration-resistant prostate cancer [4–6]. Cabazitaxel and gemcitabine are cytotoxic agents with different mechanisms of action [5–7]. In this study, we aimed to evaluate combined treatment with cabazitaxel and gemcitabine in patients with advanced solid tumors in terms of safety, PK, and antitumor activity.

Preclinical studies of combinations of cytotoxic agents have demonstrated that treatment administration sequence can profoundly influence activity, with results that vary along a continuum including antagonistic, additive, and/or synergistic effects [22,23]. In a study performed on NSCLC cell lines, administering gemcitabine followed by docetaxel produced a weak synergistic effect that could be eliminated with a 48-h washout between agents. However, the reverse sequence (docetaxel followed by gemcitabine) resulted in a marked synergistic effect that was increased with a 48-h washout between the two treatment administrations [13]. This may be explained by the fact that docetaxel causes arrest at the G2-M premitotic stage of the cell cycle [9]; after 48 h, a large fraction of the recovered, synchronized cells would be at the G1/S boundary, where gemcitabine is most active [13].

On the basis of these results, we designed the current study to investigate the sequence of cabazitaxel followed by gemcitabine in the clinical setting. The starting dose and sequence of cabazitaxel in combination with gemcitabine were based on previous studies describing the safety and dosing of cabazitaxel as a monotherapy and in combination with other agents [4,20,21]. At both of the initial planned dose levels, however, at least two patients experienced a hematologic DLT. To further investigate this combination while attempting to mitigate the observed toxicity,

a protocol amendment introduced a lower dose level for the cabazitaxel–gemcitabine sequence. Unfortunately, both patients treated at the amended dose level also experienced a hematologic DLT. In a further attempt to mitigate hematologic toxicity, a protocol amendment was put in place that allowed reversal of the sequence of administration (gemcitabine followed by cabazitaxel on Day 1 of each cycle; part 1b). The rationale behind this amendment was that gemcitabine followed by cabazitaxel may at least be additive and/or synergistic on the basis of the results from in-vitro data suggesting similar findings for combinations of antimetabolites and taxanes [22,23]. In addition, clinical studies of similar drugs (e.g. docetaxel and gemcitabine) have shown that these treatment sequences are reasonably well tolerated, with low incidences of grade 3–4 hematologic AEs [24–26]. In our study, however, two of six patients treated at the first dose level for the gemcitabine followed by cabazitaxel sequence (which included the same doses as for dose level –2 in the preceding cohort) experienced hematologic DLTs. As the MTD was exceeded with all treatment sequences and dose levels, the study was terminated and the dose-expansion phase did not commence.

No relevant PK interactions between gemcitabine or dFdU and cabazitaxel were observed, regardless of the sequence of administration. Cabazitaxel had no effect on gemcitabine and dFdU exposure, which is in contrast to other studies that report a potential effect of docetaxel [27] or paclitaxel [28] on the PK parameters of gemcitabine. Population-based PK analyses suggest minor differences between the cabazitaxel and the docetaxel PK profiles [29–31]. Despite the absence of an obvious PK drug–drug interaction, the combination of cabazitaxel and gemcitabine had more hematologic toxicity than expected, on the basis of the individual tolerability profiles of these drugs, suggesting that an interaction cannot be ruled out. Excessive hematologic toxicity is not universal; for example, this effect was not observed in a phase I study investigating cabazitaxel in combination with the cytotoxic agent cisplatin (NCT00925743; unpublished results).

We saw preliminary indications of efficacy for combination treatment with cabazitaxel and gemcitabine in this heavily pretreated population, with three patients (16.7%) experiencing PRs and eight patients (44.4%) experiencing SD, even when both agents were administered at a nonoptimal dose. However, the efficacy of the combination versus that of cabazitaxel monotherapy is unclear. Given that studies investigating cabazitaxel in combination with other agents are underway, attempts at further defining a safe margin for the administration of gemcitabine and cabazitaxel had little priority. The use of prophylactic growth factors could be considered to support what proved to be a highly myelosuppressive regimen, but this intervention would add significant expense to the regimen. In summary, we observed an excessive incidence of DLTs with both treatment

sequences of cabazitaxel and gemcitabine, even at markedly reduced doses for both agents, predominantly characterized by myelosuppression. We therefore conclude that this combination does not warrant further investigation at the doses tested in this study.

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## Conflicts of interest

P.M.L.: consultant to Novartis, Genentech, Astex. R.B.C.: consultant to Sanofi; research grant to Fox Chase Cancer Center to support the conduct of the trial. L.S., J.Y.Y., S.D.: Sanofi employees. A.J.O.: consultant to BMS, Genentech, Takeda, and Santaris. For the remaining authors, there are no conflicts of interest.

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