

RESEARCH ARTICLE

A phase 1/2 dose-finding, safety, and activity study of cabazitaxel in pediatric patients with refractory solid tumors including tumors of the central nervous system

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Abstract

Background: This phase 1/2 study (NCT01751308) evaluated cabazitaxel in pediatric patients. Phase 1 determined the maximum tolerated dose (MTD) in patients with recurrent/refractory solid tumors, including central nervous system (CNS) tumors. Phase 2 evaluated activity in pediatric recurrent high-grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG).

Procedure: In phase 1, a 3 + 3 dose-escalation study design was followed. Cabazitaxel was administered at a starting dose of 20 mg/m². Dose-limiting toxicities (DLTs) during cycle 1 were assessed to determine the MTD. Tumor response and cabazitaxel pharmacokinetics were also assessed. In phase 2, patients received cabazitaxel at the MTD determined in phase 1. Tumor responses were assessed every 9 weeks (modified Response Assessment in Neuro-oncology criteria). Progression-free survival and cabazitaxel pharmacokinetics were evaluated, and overall survival was estimated.

Results: In phase 1, 23 patients were treated, including 19 with CNS tumors. One patient had a partial response; five had stable disease for >3 cycles. Common adverse events included fatigue, diarrhea, nausea and vomiting, febrile neutropenia, and hypersensitivity reactions. Two of three DLTs (febrile neutropenia) occurred with a dose of 35 mg/m²; the MTD was 30 mg/m². Slightly higher cabazitaxel clearance was observed compared with adult trials. In phase 2, 16 patients (eight HGG and eight DIPG) were enrolled; 11 were evaluable for response and five withdrew (three due to anaphylaxis). All 11 patients progressed within four cycles. No responses were observed; the study was stopped due to futility.

Conclusions: The safety profile of cabazitaxel was consistent with previous studies. The MTD (30 mg/m²) was higher than the adult MTD. Cabazitaxel did not demonstrate activity in recurrent/refractory HGG or DIPG.

KEYWORDS

cabazitaxel, pediatric, solid tumors

1 | INTRODUCTION

Central nervous system (CNS) tumors are the main cause of cancer-related death in children.^{1,2} High-grade gliomas (HGGs) represent approximately 8–12% of all pediatric CNS tumors and the prognosis is poor.³ There is no effective chemotherapy for the treatment of children with HGG or diffuse intrinsic pontine glioma (DIPG); surgery and/or radiation therapy (alone or in combination with an experimental agent) constitute the most common treatment options.^{3,4}

Taxane chemotherapies are widely used in adult patients with solid tumors, eliciting antitumor activity by inducing mitotic block.^{5–8} Taxanes have also been used to treat extracranial solid tumors in pediatric patients.^{9,10} Their potential in the treatment of tumors of the CNS is, however, disputed due to poor penetration into the brain. Clinical studies of paclitaxel have demonstrated partial responses (PR) and stable disease (SD) in adult and pediatric patients with recurrent CNS tumors.^{11–14} In one study using intratumoral convection enhanced delivery, paclitaxel demonstrated activity in 11/15 patients, including five complete responses (CR) and six PRs (giving a response rate of 73%) in adult patients with glioblastoma.¹⁵ Conversely, in a phase 2 trial, docetaxel failed to demonstrate activity in adult patients with recurrent malignant glioma.¹⁶ In another phase 2 trial, paclitaxel concentrations fell to undetectable levels soon after systemic bolus administration.¹¹ In a separate study, although tumor concentrations of paclitaxel were in the therapeutic range for three patients with recurrent glioma, measurement of drug concentration in normal brain tissue suggested that paclitaxel does not cross the intact blood–brain barrier (BBB).¹⁶ Taxanes are therefore considered to have limited utility in the treatment of CNS tumors due to poor penetration of the BBB. The P-glycoprotein (P-gp) efflux pump may play a role in limiting taxane availability in the brain, as exemplified by a study that demonstrated paclitaxel antitumor activity in an orthotopic glioblastoma model when P-gp was inhibited by a cyclosporine analogue.¹⁷ Penetration of the BBB remains a challenge in improving the efficacy of taxanes and other chemotherapies for CNS tumors. Moreover, while disruption of the BBB may lead to increased exposure to taxane chemotherapy, it must also be noted that use of concomitant medications, such as corticosteroids, would have the opposite effect due to increased clearance.¹⁵

Cabazitaxel, a second-generation taxane, is characterized by stronger suppression of microtubule dynamics, faster drug uptake, and better intracellular retention compared with docetaxel, and has demonstrated activity in cell lines resistant to docetaxel and paclitaxel.^{7,18,19} Cabazitaxel is indicated for patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel.^{20,21} The greater ability of cabazitaxel to penetrate the BBB may be due to its higher lipophilicity or differences in interaction with efflux transporters. Thus, cabazitaxel showed high permeability in

cells expressing high levels of P-gp, and higher intracellular accumulation than first-generation taxanes in multidrug-resistant ABCB1(+) cell lines.^{22,23} Cabazitaxel penetrates BBB both in non-tumor bearing and orthotopic glioma models, with similar exposure patterns observed in mice, rats and dogs.^{18,22,24–26}

Recently, De Placido et al. described three case reports of patients with mCRPC and brain metastases who were treated with cabazitaxel plus whole-brain radiotherapy.²⁷ Although the role of radiotherapy in the treatment of brain metastases in mCRPC is considered only palliative, the combination of cabazitaxel with whole-brain radiotherapy has shown activity in this setting.²⁷

Taken together, these results suggest that antitumor activity may be achieved with taxanes in CNS tumors if sufficient concentrations could be delivered to the tumor. This phase 1–2 study assessed cabazitaxel in pediatric patients with recurrent/refractory solid tumors, including CNS tumors.

2 | METHODS

2.1 | Study design

This was an open-label, multicenter, phase 1/2 study conducted through the Pediatric Oncology Experimental Therapeutics Investigators' Consortium. The phase 1 study enrolled patients with refractory/recurrent solid tumors, including CNS tumors, between February 2013 and August 2014. The primary objective was to assess dose-limiting toxicities (DLTs) and determine the maximum tolerated dose (MTD). The starting cabazitaxel dose was 20 mg/m² (80% of the MTD in adults)²⁸ and, if tolerated, the dose would be escalated to 25, 30, 35, and 40 mg/m². If DLTs were observed at 20 mg/m², the dose would be decreased to 15 mg/m². Pharmacokinetics, safety, and preliminary antitumor activity were assessed. In the phase 2 study, patients with recurrent, measurable HGG or DIPG received cabazitaxel at the MTD determined in phase 1. Patients were enrolled between September 16, 2014 and March 5, 2015. The primary objective was to evaluate the objective response (OR) rate of cabazitaxel (as per modified Response Assessment in Neuro-oncology [RANO] criteria²⁹). During initial phase 2 enrolment, 10 patients were planned to be enrolled and evaluated for response. If ≥ 2 ORs were observed, 19 additional patients would be enrolled in a second stage of enrolment; and if ≤ 1 OR was observed, accrual would cease. Secondary endpoints included overall survival (OS), progression-free survival (PFS), pharmacokinetics, and safety.

2.2 | Treatment

Cabazitaxel was administered intravenously over 1 hr on day 1 of every 21-day cycle. Patients received treatment until progressive disease or unacceptable toxicity. As part of a protocol amendment to manage infusion-related reactions, dexamethasone (0.05–0.10 mg/kg; 10 mg maximum) was administered 24 and 12 hrs before each cabazitaxel dose. Additional steroids, antihistamines, and H2 blockers were administered 30–60 mins before each cabazitaxel dose. Prophylactic granulocyte-colony stimulating factor (G-CSF) was administered daily, including during cycle 1, beginning at least 24 hrs post-cabazitaxel and

Abbreviations: AE, adverse event; AUC, area under curve; BBB, blood–brain barrier; BSA, body surface area; CI, confidence interval; CNS, central nervous system; CR, complete response; DIPG, diffuse intrinsic pontine glioma; DLT, dose-limiting toxicity; G-CSF, granulocyte-colony stimulating factor; HGG, high-grade glioma; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; P-gp, P-glycoprotein; PR, partial response; RANO, Response Assessment in Neuro-oncology; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event

continuing daily until the absolute neutrophil count was $\geq 1.0 \times 10^9/l$; a single dose of pegylated G-CSF per cycle was also permitted.

2.3 | Patients

Eligible patients were 2–18 years old, had acceptable performance status (Lansky ≥ 60 for patients ≤ 10 years of age; Karnofsky $\geq 60\%$ for patients > 10 years of age), adequate organ function and a body surface area (BSA) $< 2.1 \text{ m}^2$. Patients must have recovered from acute toxic effects of all prior therapy to grade ≤ 1 before study entry. Patients were excluded if they had systemic anticancer therapy within ≤ 3 weeks of study entry; investigational agents or small field radiotherapy ≤ 4 weeks; craniospinal (or other large-field) radiation therapy ≤ 6 months prior to the first cabazitaxel dose; prior systemic radioisotope therapy or total body irradiation; prior bone marrow or stem cell transplant; or any clinically significant illness that could not be controlled with appropriate therapy, would compromise cabazitaxel tolerability, or result in an inability to assess toxicity. Patients requiring concomitant treatment with strong inhibitors/inducers of CYP3A4 or enzyme-inducing anti-epileptic drugs 14 days prior to the first cabazitaxel dose were excluded.

2.4 | Safety

Adverse events (AEs) were assessed continuously and graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.³⁰ DLTs during cycle 1 were considered when determining dose escalation and MTD. Hematologic DLTs were AEs or laboratory abnormalities considered related to the treatment as follows: grade 4 hematologic toxicity (excluding grade 4 neutropenia lasting ≤ 7 days); grade 3/4 febrile neutropenia (except grade 3/4 febrile neutropenia in the absence of G-CSF prophylaxis); and grade 4 thrombocytopenia (excluding grade 4 thrombocytopenia lasting < 7 days). Non-hematologic DLTs included any grade ≥ 3 non-hematologic toxicity, excluding grade 3 nausea, grade 3/4 vomiting or grade 3/4 diarrhea that, in the investigator's opinion, occurred in the setting of poor compliance with supportive care measures; grade 3/4 dehydration that, in the investigator's opinion, occurred in the setting of inadequate treatment of other toxicities; grade 3 fatigue lasting ≤ 7 days; inadequately treated hypersensitivity reactions; elevated transaminases $< 10\times$ the upper limit of normal, lasting ≤ 7 days; and retreatment delay of > 2 weeks due to delayed recovery from a toxicity related to the study treatment to baseline grade or $\leq$ Grade 1 (except for alopecia). If there was a treatment delay > 2 weeks before the start of cycle 2, the patient was to discontinue the study treatment. Platelet transfusions during cycle 1 and treatment delays of > 2 weeks before cycle 2 due to a treatment-related toxicity were considered DLTs.

2.5 | Tumor response

Responses were assessed as per Response Criteria in Solid Tumors version 1.1³¹ (phase 1) and modified RANO criteria²⁹ for patients with CNS tumors (phase 1 and 2). Patients were evaluated every 9 weeks after the first cabazitaxel dose. OR rate (ORR) was

calculated as the proportion of patients with CR and PR after three cabazitaxel cycles, maintained for ≥ 4 weeks. Responses were assessed in patients with measurable disease at baseline and ≥ 1 post-baseline tumor evaluation. All patients were followed until progression.

2.6 | Statistical considerations

MTD was defined, using a traditional 3 + 3 dose-escalation design, as the dose where no more than one of six patients experienced a DLT. ORR was assessed using a Simon's two-stage design which tested the null hypothesis that the true ORR would be $\leq 10\%$ versus the alternative hypothesis that the true ORR would be $\geq 30\%$, assuming a one-sided significance level of 5% and power of 80%. If two or more ORs were observed in the initial stage, a further 19 patients would be enrolled in the second stage. If six or more ORs were observed in the initial and second stages combined, the null hypothesis could be rejected. PFS and OS were assessed using the Kaplan–Meier method.

2.7 | Pharmacokinetics

Blood samples were obtained during cycle 1. Cabazitaxel plasma concentrations were analyzed by liquid chromatography/tandem mass spectrometry with a lower limit of quantification of 1 ng/ml. Pharmacokinetic parameters were calculated using Bayesian estimation from a BSA-scaled population non-linear mixed effect model. A population pharmacokinetic model developed in adults was adapted in order to appropriately adjust pharmacokinetic parameters for this pediatric population of patients.³²

2.8 | Role of the funding source

This study was sponsored by Sanofi. Sanofi contributed to the study design, data analysis and interpretation, and critically reviewed the manuscript. All authors had full access to study data and were responsible for the decision to submit for publication.

3 | RESULTS

3.1 | Phase 1

3.1.1 | Patients and treatment

Twenty-three patients were enrolled and received cabazitaxel at four dose levels. The median age was 9 years (range: 4–18 years). All patients had disease refractory to standard therapy or for which no standard therapy exists. Of 23 patients, 19 (82.6%) had CNS tumors and four (17.4%) had other solid tumors (Table 1). The patients received a median of three cabazitaxel cycles, with 78.3% receiving > 1 cycle. Ten patients (43.5%) had ≥ 1 dose modification (including four dose reductions), five (21.7%) had ≥ 1 dose interruption, and four (17.4%) had ≥ 1 treatment cycle delayed (Table 2).

TABLE 1 Baseline patient characteristics

	Phase 1					Phase 2
	20 mg/m ² n = 6	25 mg/m ² n = 3	30 mg/m ² n = 7	35 mg/m ² n = 7	All n = 23	30 mg/m ² n = 16
Age, years						
Mean (SD)	10.8 (5.7)	10.0 (4.0)	9.7 (4.9)	9.1 (4.1)	9.9 (4.5)	9.6 (4.5)
Median (range)	11.0 (5–17)	10.0 (6–14)	10.0 (4–17)	7.0 (6–18)	9.0 (4–18)	9.5 (3–16)
Age groups, years, n (%)						
2–4	0	0	2 (29)	0	2 (8.7)	2 (13)
5–6	2 (33)	1 (33)	0	1 (14)	4 (17)	4 (25)
7–11	1 (17)	1 (33)	3 (43)	5 (72)	10 (44)	4 (25)
12–18	3 (50)	1 (33)	2 (29)	1 (14)	7 (30)	6 (38)
Sex, n (%)						
Male	1 (17)	3 (100)	6 (86)	5 (71)	15 (65)	8 (50)
Race, n (%)						
Caucasian/White	4 (67)	2 (67)	6 (86)	3 (43)	15 (65)	11 (69)
Black	1 (17)	0	1 (14)	3 (43)	5 (22)	2 (13)
Asian	0	1 (33)	0	1 (14)	2 (9)	2 (13)
Other	1 (17)	0	0	0	1 (4.3)	1 (6.3)
Primary tumor site, n (%)						
Brain/CNS	4 (67)	3 (100)	5 (71)	7 (100)	19 (83)	16 (100)
Other	2 (33)	0	2 (29)	0	4 (17)	0
Histology, n (%)						
HGG	0	0	1 (14)	0	1 (4.3)	8 (50) ^a
DIPG	2 (33)	0	0	2 (29)	4 (17)	8 (50)
Medulloblastoma	0	0	1 (14)	1 (14)	2 (8.7)	0
Ependymoma	2 (3)	2 (67)	2 (29)	3 (43)	9 (39)	0
Brain, other ^b	0	1 (33)	1 (14)	1 (14)	3 (13)	0
Osteosarcoma	0	0	2 (29)	0	2 (8.7)	0
Other ^c	2 (33)	0	0	0	2 (8.7)	0
Extent of disease, n (%)						
Metastatic	4 (67)	3 (100)	3 (43)	1 (14)	11 (48)	2 (13)
Locally advanced	2 (33)	0	3 (43)	4 (57)	9 (39)	11 (69)
Locoregional	0	0	1 (14)	2 (29)	3 (13)	3 (19)
Prior anticancer regimens ^d						
Patients, n (%)	6 (100)	3 (100)	7 (100)	4 (57)	20 (87)	15 (94)
Median, n (range)	3.5 (1–9)	4.0 (2–5)	2.0 (1–7)	1.0 (1–2)	2.0 (1–9)	1.0 (1–2)
Other prior therapy, n (%)						
Radiation therapy	5 (83)	1 (33)	4 (57)	7 (100)	17 (74)	16 (100)
Cancer-related surgery	4 (67)	3 (100)	7 (100)	5 (71)	19 (83)	8 (50)

^aFour patients had anaplastic astrocytoma and four patients had glioblastoma.

^bBrain, other category includes anaplastic astrocytoma (one patient), fibrillary astrocytoma (one patient), and pilomyxoid astrocytoma (one patient).

^cOther category includes grade III teratoma with yolk sac component (one patient) and Wilms' tumor (one patient).

^dAnticancer regimens include biologicals, chemotherapy, cryotherapy, gene therapy, hormonotherapy, immunotherapy, and other therapies. Prior radiotherapy and cancer-related surgery are excluded.

CNS, central nervous system; DIPG, diffuse intrinsic pontine glioma; HGG, high-grade glioma; SD, standard deviation.

TABLE 2 Treatment characteristics

	Phase 1					Phase 2
	20 mg/m ²	25 mg/m ²	30 mg/m ²	35 mg/m ²	All	30 mg/m ²
	n = 6	n = 3	n = 7	n = 7	n = 23	n = 16
Time from initial diagnosis to first cabazitaxel dose, months						
Mean (SD)	52.7 (52.9)	48.7 (25.8)	28.9 (16.0)	29.3 (21.6)	37.8 (31.9)	16.1 (11.2) ^a
Median (range)	26.1 (6.9–134.6)	42.1 (26.7–771.1)	25.5 (6.1–51.0)	20.3 (7.8–62.9)	26.7 (6.1–134.6)	11.4 (6.4–39.1) ^a
Time from last progression to cabazitaxel dose, months						
Mean (SD)	1.2 (1.1)	1.2 (1.0)	1.7 (1.4)	1.2 (0.4)	1.3 (1.0)	0.8 (0.4)
Median (range)	0.6 (0.3–2.9)	0.7 (0.7–2.3)	1.3 (0.3–4.4)	1.2 (0.7–1.6)	1.1 (0.3–4.4)	0.7 (0.1–1.8)
Duration of study treatment, weeks						
Median (range)	8.9 (3.0–54.9)	9.4 (8.9–47.4)	9.0 (3.0–79.3)	9.0 (3.0–21.0)	9.0 (3.0–79.3)	6.0 (3.0–12.1)
Cabazitaxel cycles received, n						
Total	34	21	46	19	120	29
Median (range)	3 (1–18)	3 (3–15)	3 (1–25)	3 (1–7)	3 (1–25)	2 (1–4)

SD, standard deviation.

^an = 15.

3.1.2 | Dose-limiting toxicities

Twenty patients were evaluable for DLTs. Patients excluded from the DLT evaluable population included one patient who started treatment after the establishment of the MTD, one patient who exhibited progressive disease on Day 8, and one patient whose infusion was stopped after 3 mins in the first cycle due to an acute reaction. At the 20 mg/m² dose level, one out of six DLT-evaluable patients had a DLT (grade 3 febrile neutropenia). No DLTs were reported in patients receiving 25 or 30 mg/m². At the 35 mg/m² dose level, two out of the five DLT-evaluable patients experienced a DLT (grade 3 febrile neutropenia). The MTD was established as 30 mg/m².

3.1.3 | Antitumor activity

Of 23 patients, 22 were evaluable for antitumor assessment. One patient (a 15-year-old female with ependymoma) achieved a PR, resulting in an ORR of 4.5% (95% confidence interval [CI]: 0.1–22.8%). At cycle 3, this patient's target lesion showed a 27.5% reduction in size. Assessment at cycle 4 indicated a PR, which was maintained until cycle 15; progressive disease was noted at cycle 18. SD was achieved in five patients (22.7%; with DIPG, grade 3 teratoma with yolk sac, osteosarcoma, fibrillary astrocytoma, and pilomyxoid astrocytoma) (Table 3).

3.1.4 | Safety

The most frequent all-grade treatment-emergent AEs (TEAEs) were fatigue (39.1%), headache, diarrhea, nausea (all 34.8%), vomiting (30.4%), cough (26.1%), and constipation (26.1%) (Table 4). Treatment-emergent serious AEs (SAEs) of grade ≥3 were reported in 12 patients (52.2%), including febrile neutropenia (n = 5; 21.7%). No patient discontinued treatment due to TEAEs. Infusion-related/hypersensitivity reactions occurred in five patients (21.7%). Fifteen deaths (65.2%) were reported on-study (≤30 days of the last cabazitaxel dose; n = 1) and during post-study follow-up (>30 days after the last cabazitaxel dose; n = 14). Causes of death included disease progression (n = 14)

and reasons unknown (n = 1); no deaths were considered related to treatment.

3.2 | Phase 2

3.2.1 | Patients and treatment

Sixteen patients were enrolled and received cabazitaxel at the phase 1 MTD. Patients were 3–16 years of age (median: 9.5 years). Eight patients (50%) had DIPG and eight (50%) had non-DIPG HGG (Table 1). Patients received a median of two cabazitaxel cycles with 56.3% receiving >1 cycle. Nine patients (56.3%) had ≥1 dose modification (including three dose reductions), six (37.5%) had ≥1 dose interruption, and no patient had a treatment cycle delayed (Table 2).

3.2.2 | Antitumor activity

Tumor response was assessed in the initial 10 evaluable patients. As recruitment continued until there were ≥10 evaluable patients, this resulted in an additional patient being assessed before assessment of the first 10 patients was performed. Therefore, of the 16 patients enrolled, 11 were evaluable for tumor response (five excluded due to the termination of treatment prior to the first tumor assessment for reasons other than disease progression) (Table 3). There were no ORs observed in the first 10 evaluable patients. As per the planned study design, no further patients were enrolled and the null hypothesis could not be rejected. Median OS was 2.7 months (95% CI: 1.7–4.5 months) and median PFS was 1.3 months (95% CI: 0.6–2.1 months).

3.2.3 | Safety

In the phase 2 part of the study, the most frequent all-grade TEAEs were diarrhea (43.8%), dysphagia (37.5%), nausea (31.3%), vomiting (25.0%), and headache (25.0%) (Table 4). TEAEs of grade ≥3 were reported in 11 patients (68.8%). Treatment-emergent SAEs of grade ≥3 were reported in 10 patients (62.5%), including febrile neutropenia (n = 3). Infusion-related/hypersensitivity reactions were seen in

TABLE 3 Best objective responses as per Response Criteria in Solid Tumors and modified RANO criteria (CNS tumors) in the evaluable population^a

	Phase 1					Phase 2
	20 mg/m ²	25 mg/m ²	30 mg/m ²	35 mg/m ²	All patients	30 mg/m ²
Patients, n (%)	n = 5	n = 3	n = 7	n = 7	n = 22 ^a	n = 11 ^a
ORR (confirmed CR + confirmed PR)	1 (20)	0	0	0	1 (4.5)	0
Complete response	0	0	0	0	0	0
Partial response	1 (20)	0	0	0	1 (4.5)	0
Stable disease	1 (20)	1 (33)	2 (29)	1 (14)	5 (23)	1 (9.1)
Progressive disease	3 (60)	2 (67)	4 (57)	6 (86)	15 (68)	10 (91)
Not assessed	0	0	1 (14)	0	1 (4.5)	0

One patient in phase 1 and five patients in phase 2 were not included in the efficacy analysis because they permanently terminated treatment prior to the first tumor evaluation at the end of cycle 3 for a reason other than disease progression. One patient met the definition of evaluable, but was not assessed after three cycles.

CR, complete response; ORR, objective response rate; PR, partial response.

^aEvaluable population = patients who were treated and for whom at least the post-treatment tumor assessment at the end of cycle 3 is available.

five patients. Four patients discontinued the treatment due to TEAEs (SAE of anaphylactic reaction: $n = 3$; grade 2 elevated liver transaminases: $n = 1$). There were 12 deaths (75.0%) on-study (≤ 30 days of the last cabazitaxel dose; $n = 4$) and during post-study follow-up (> 30 days after the last cabazitaxel dose; $n = 8$), all due to disease progression; no deaths were considered treatment related.

After the Study Committee had analyzed the three SAEs of anaphylaxis, the protocol was amended to provide additional steroid premedication prior to the infusion of cabazitaxel. Across both phases, of the 33 patients who were treated prior to the protocol amendment, 10 patients (30.3%) had anaphylactic reactions ($n = 3$), hypersensitivity ($n = 2$), or infusion-related reactions ($n = 5$). After this amendment, the number of reactions significantly decreased. Of the eight additional patients treated after the protocol amendment, only one had an infusion-related reaction (12.5%).

3.3 | Pharmacokinetics

Thirty-one patients were evaluable for pharmacokinetic assessment. Cabazitaxel pharmacokinetic parameters were consistent across the different doses. Overall, cabazitaxel exhibited a very large volume of distribution at steady state, high plasma clearance, and a long third half-life (Table 5), as already described in adults. However, mean cabazitaxel clearance was 37.5 l/hr/m²; 39% higher than that reported in adults (27.0 l/hr/m²).³² At 30 mg/m² ($n = 20$), the mean area under the curve (AUC) was 877 ng·h/ml, which is slightly lower than that reported in adults (991 ng·h/ml at 25 mg/m²).³²

4 | DISCUSSION

Preclinical evaluation suggested that cabazitaxel may be able to penetrate the BBB, providing rationale for the evaluation of cabazitaxel in pediatric patients with CNS tumors.^{18,22,24–26} In the phase 1 study, cabazitaxel was assessed in pediatric patients with recur-

rent/refractory solid tumors, including CNS tumors. Under guidance and request from the US Food and Drug Administration, the phase 2 study assessed cabazitaxel in pediatric patients with recurrent/refractory HGG and DIPG tumors.

The MTD of cabazitaxel in pediatric patients with recurrent/refractory solid tumors was 30 mg/m². This is higher than the MTD previously observed in adults and may be a result of the increased cabazitaxel clearance observed in the pediatric population compared with adult populations.^{28,32,33} Clinical studies of paclitaxel in adult and pediatric patients with CNS tumors suggest that common concomitant medications, such as enzyme-inducing anti-epileptic agents and corticosteroids, may increase taxane clearance.^{11–14,34} In this study, dexamethasone administration did not impact cabazitaxel clearance in the pediatric population, based on the analysis of only five patients who received dexamethasone. Our results agree with studies showing no effect of CYP inducers (prednisolone or methyl prednisolone) on the pharmacokinetics of cabazitaxel in adults.³² Pediatric patients in this study required higher cabazitaxel doses to match the AUC observed in previous studies of cabazitaxel in adult patients with mCRPC.

Four patients discontinued cabazitaxel treatment due to TEAEs, and three due to SAEs (anaphylactic reaction). After the protocol amendment to provide additional steroid premedication, incidence of infusion-related hypersensitivity/anaphylactic reactions decreased, suggesting that these effects can be mitigated with steroids. Interestingly, patients who had been treated with steroids prior to study entry experienced fewer infusion-related/hypersensitivity reactions on-study compared with patients who had not. Overall, the safety profile of cabazitaxel appeared manageable and, aside from the infusion-related/hypersensitivity, aligned with that observed in adult patients.³³ In studies of paclitaxel and docetaxel, hypersensitivity reactions have been observed in both adult (docetaxel: 15%; paclitaxel: 33%)^{35,36} and pediatric patients (docetaxel: 3%; paclitaxel: 33%),^{9,37} with shorter infusion times of paclitaxel (1–3 hrs) associated with an increase in hypersensitivity reactions.^{35,37,38} Rates of hypersensitivity reactions observed in the pediatric population receiving cabazitaxel in

TABLE 4 Summary of treatment-emergent adverse events

	Phase 1					Phase 2
Patients, n (%)	20 mg/m ²	25 mg/m ²	30 mg/m ²	35 mg/m ²	All patients	30 mg/m ²
	n = 6	n = 3	n = 7	n = 7	n = 23	n = 16
Any TEAE	6 (100)	3 (100)	7 (100)	7 (100)	23 (100)	16 (100)
Grade 3/4 TEAE	4 (67)	1 (33)	5 (71)	3 (43)	13 (57)	11 (69)
Grade 5 TEAE	1 (17)	0	0	0	1 (4.3)	5 (31)
Any grade SAE	4 (67)	1 (33)	5 (71)	3 (43)	13 (57)	12 (75)
Grade ≥3 SAE	4 (67)	1 (33)	4 (57)	3 (43)	12 (52)	10 (63)
TEAE related to study treatment	4 (67)	3 (100)	4 (57)	6 (86)	17 (74)	12 (75)
TEAE leading to permanent treatment discontinuation	0	0	0	0	0	4 (25)
TEAEs occurring in ≥20% of all patients						
	All grade n = 23	Grade ≥3		All grade n = 16	Grade ≥3	
Febrile neutropenia	5 (22)	5 (22)		3 (19)	3 (19)	
Headache	8 (35)	0		4 (25)	0	
Cough	6 (26)	0		0	0	
Diarrhea	8 (35)	1 (4.3)		7 (44)	3 (19)	
Nausea	8 (35)	0		5 (31)	0	
Vomiting	7 (30)	0		4 (25)	0	
Constipation	6 (26)	0		3 (19)	0	
Abdominal pain	5 (22)	0		2 (13)	0	
Fatigue	9 (39)	2 (8.7)		3 (19)	0	
Dysphagia	0	0		6 (38)	1 (6.3)	
Laboratory abnormalities occurring during TEAE period in ≥20% of all patients						
	All grade	Grade ≥3		All grade n = 15	Grade ≥3	
Neutropenia	16 (70)	15 (65)		10 (67)	8 (53)	
Anemia	22 (96)	3 (13)		14 (93)	1 (6.7)	
Thrombocytopenia	13 (57)	3 (13)		8 (53)	2 (13)	
Leukopenia	15 (65)	14 (61)		11 (73)	8 (53)	
Lymphopenia	16 (70)	7 (30)		n = 14		
				11 (79)	4 (29)	
Hypocalcemia	7 (30)	0		n = 15		
				6 (40)	0	
Hypokalemia	6 (26)	0		4 (27)	2 (13)	
Hyponatremia	8 (35)	0		4 (27)	1 (6.7)	
Hypophosphatemia	7 (30)	1 (4.3)		5 (33)	2 (13)	
Hypoalbuminemia	8 (35)	0		7 (47)	0	
Hyperglycemia	14 (61)	0		8 (53)	0	
Elevated ALT	8 (35)	0		7 (47)	1 (6.7)	
Elevated AST	7 (30)	0		5 (33)	0	

ALT, alanine transaminase; AST, aspartate transaminase; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

this study (phase 1: 21.7%; phase 2: 31.3%) were similar to the levels reported for paclitaxel, and higher than those observed in adults receiving cabazitaxel. The prescribing information for paclitaxel, docetaxel, and cabazitaxel carry a warning for hypersensitivity and rec-

ommend premedication with either corticosteroids alone (docetaxel) or corticosteroids, antihistamines, and H2 antagonists (paclitaxel, cabazitaxel) to mitigate these effects; discontinuation of treatment is advised if hypersensitivity is observed.^{21,36,39}

TABLE 5 Pharmacokinetic parameters for all patients in phase 1 and phase 2 studies combined

	20 mg/m ²	25 mg/m ²	30 mg/m ²	35 mg/m ²
Mean (geometric mean) (CV %)	n = 6	n = 3	n = 20	n = 2
C _{max} , ng/ml	205 (159) (92.7)	284 (226) (85.7)	257 (226) (49.8)	233 (233) (0.1)
AUC, ng·h·ml	700 (591) (64.3)	879 (822) (47.2)	877 (820) (41.1)	1,003 (983) (27.7)
CL/BSA, l/hr/m ²	36 (33) (35.8)	33 (31) (38.8)	39 (36) (33.5)	37 (35.92) (27.27)
V _{ss} /BSA, l/m ²	3,391 (3,334) (20.3)	3,302 (3,290) (10.7)	3,371 (3,255) (29.0)	1,489 (1,233) (79.2)
t _{1/2} , hr	121 (107) (57.6)	132 (114) (68.9)	105 (97) (38.7)	36 (32) (66.9)

AUC, area under the concentration–time curve; CL/BSA, plasma clearance normalized to body-surface area; C_{max}, maximal concentration; CV, coefficient of variance; t_{1/2}, third half-life; V_{ss}, volume of distribution at the steady state normalized to body-surface area.

During phase 1, there was one PR (in a patient with ependymoma) and five patients with SD (with both non-CNS and CNS tumors). At the time of study cut-off, one patient from phase 1 was continuing treatment, with SD reported as the best response. During phase 2, there were no ORs in patients with HGG or DIPG, and one instance of SD in a patient with DIPG. Therefore, the primary objective of demonstrating the activity of cabazitaxel in pediatric patients with HGG or DIPG was not met. Prior to and during both phases of the study, all patients received concomitant corticoid medication. Concomitant corticosteroids may have reduced the levels of cabazitaxel penetrating the BBB to therapeutically insufficient concentrations, limiting the exposure of the HGG and DIPG tumors to cabazitaxel. Unfortunately, cerebrospinal fluid was not collected during the study, and it was not possible to estimate the concentrations of cabazitaxel crossing the BBB. It has been previously suggested that steroids can reduce chemotherapy penetration of the BBB by altering transporter levels.^{40–42} Treating patients with HGG or DIPG after the completion of radiation therapy and prior to recurrent disease may be a more optimal treatment approach, as we would expect such patients to receive minimal corticosteroids during this period.

Taxanes are not routinely used in the treatment of CNS tumors due to poor BBB penetration; however, the phase 1 responses in this study and preclinical data suggest that cabazitaxel can penetrate the BBB. Multiple drugs have failed to show clinical efficacy in pediatric patients with HGG or DIPG, which are aggressive brain tumors; it must, therefore, be considered that cabazitaxel may not be effective as a single agent for the treatment of HGG or DIPG. This study selected tumors resistant to a wide variety of chemotherapeutics, small molecule inhibitors, and monoclonal antibodies. It may be possible that cabazitaxel is active in other brain tumor types not tested in this study. Assessing ways to deliver taxanes and other chemotherapies across the BBB will be important for the future design of effective trials and the development of treatments for pediatric patients with CNS tumors.

This study established the MTD of cabazitaxel in pediatric patients with recurrent/refractory solid tumors, including CNS tumors. Compared with adults, pediatric patients had higher cabazitaxel clearance and increased infusion-related/hypersensitivity reactions; the latter were mitigated with steroid premedication. The study did not demonstrate the activity of cabazitaxel in the pediatric population with HGG or DIPG. Cabazitaxel was generally safe and tolerable at the established MTD.

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CONFLICT OF INTEREST

J.P.B., E.B., J.D., and F.F. are full-time employees of Sanofi; all the other authors have no relevant conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

P.E.M. contributed to the study design, as well as data acquisition, analysis, and interpretation. T.T., A.A.S., M.E.M., S.E.S.L., J.B., K.J.C., S.G., L.B.K., G.D., J.D., C.E.H., and S.P. contributed to data acquisition, analysis, and interpretation. F.F. contributed to data analysis and interpretation. E.B. and J.P.B. contributed to the study design, as well as data analysis and interpretation. S.N.C. contributed to the study design, as well as data acquisition, analysis, and interpretation. All authors critically reviewed each draft of the manuscript, provided their approval of the final draft, and agreed to submit the manuscript to Pediatric Blood and Cancer.

ETHICS COMMITTEE APPROVAL

The protocol and the amendments were submitted to independent ethics committees and/or institutional review boards for review and written approval. The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol also complied with the laws and regulations, as well as any applicable guidelines, of the countries where the study was conducted. All patients provided written informed consent prior to participation.

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