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A phase I dose-escalation and pharmacokinetic study of a micellar nanoparticle with entrapped docetaxel (CPC634) in patients with advanced solid tumours

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ABSTRACT

Background: CPC634 is docetaxel entrapped in core-cross linked polymeric micelles. In preclinical studies, CPC634 demonstrated enhanced pharmacokinetics and improved therapeutic index. This phase I dose escalation study is the first-in-human study with CPC634.

Methods: adult patients with advanced solid tumours received CPC634 intravenously either 3-weekly (Q3W) (part 1, dose range 15–100 mg/m^2), 2-weekly (Q2W) (part 2, 45 mg/m^2) or Q3W with dexamethasone premedication (part 3, 60 mg/m^2).

Results: thirty-three patients were enrolled. Skin toxicity was dose limiting (DLT) at ≥ 60 mg/m^2 in part 1 and at 45 mg/m^2 in part 2 and was the most common CPC634 related grade ≥ 3 adverse event (24%). With dexamethasone premedication no DLTs were observed at 60 mg/m^2 Q3W. CPC634 exhibited a dose-proportional pharmacokinetic profile. At 60 mg/m^2, the plasma area under the curve was 4067.5 ± 2974.0 ng/h/mL and the peak plasma level 217.3 ± 91.9 ng/mL with a half-life of 39.7 ± 9.4 h for released docetaxel.

Conclusion: CPC634 could be administered safely upon pretreatment with dexamethasone. Cumulative skin toxicity was the main DLT. The recommended phase 2 dose was determined at 60 mg/m^2 Q3W with dexamethasone premedication.

1. Background

Docetaxel is an antimicrotubule agent registered for multiple indications and is usually administered 3-weekly (Q3W) at doses ranging from 60 to 100 mg/m^2 [1–3]. Important limitations of docetaxel are acute hypersensitivity reactions, neutropenia, neuropathy, fatigue, nausea, vomiting and nail toxicity [2–4].

Nanotechnology is a novel drug delivery method to improve the pharmacokinetic behaviour of cytotoxic drugs through the so-called enhanced permeability and retention effect [5]. This enhanced permeability effect is a unique phenomenon in solid tumours and is related to high vascular density and large endothelium fenestrations enabling selective extravasation and accumulation of nanomedicines within the tumour interstitium. As a result, intratumoural drug concentrations can be several-fold higher than those in normal tissues [6]. Several nanoparticles have been developed that are physical assemblies like liposomes and traditional micelles. These physical assemblies are often prone to premature drug release and/or rapid disintegration upon entry into the circulation [7]. This poor pharmacokinetic profile is presumably the reason why most of the current nanoformulations in clinical trials show a comparable toxicity profile to the native drug and only a few show improved efficacy [5,8,9]. CPC634 is a novel nanomedicine consisting of docetaxel covalently entrapped in a stabilized, 65 nm sized core-cross linked polymeric micelles (CCL-PMs) [10,11]. CCL-PMs are composed of poly (ethylene glycol)-b-poly[N-(2-hydroxypropyl) methacrylamidelactate] copolymers, partially derivatised with methacrylate moieties to enable crosslinking after micelle formation. Docetaxel is covalently crosslinked to CCL-PMs via a hydrolysable ester

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linker (see **supplementary file 1** for structure formula) to enable initially good stability upon administration, a prolonged circulation and thereby increased intratumoural drug accumulation as well as a controlled drug release from the CCL-PMs [12]. In preclinical studies, CPC634 demonstrated this prolonged systemic circulation and enhanced tumour uptake resulting in improved antitumour activity [11]. In MDA-MB-231 breast cancer xenograft mice, CPC634 single-dose administration resulted in complete tumour free survival at a dose of 125 mg/kg which exceeded the 98 mg/kg maximum tolerated dose (MTD) for generic docetaxel. At a dose level of 60 mg/kg, conventional docetaxel showed less efficacy and a significantly worse toxicity profile [11]. Additionally, in a 5-day repeated dose toxicity study in healthy rats, CPC634 toxicities were substantially reduced compared to conventional docetaxel, despite a 45% higher dose. In addition, haematological toxicities were significantly lower in rats that received CPC634 [11]. Recently, CPC634 demonstrated an improved circulation and target site accumulation in a clinical head-to-head comparison with conventional docetaxel [13]. This first-in-human phase 1 dose escalation study evaluated the safety and determined the recommended phase 2 dose (RP2D), pharmacokinetic profile, and preliminary antitumour activity of CPC634 in patients with various types of solid tumours.

2. Methods

2.1. Study design and dose escalation

This was a three-part, open label, dose escalation study in patients with solid tumours conducted at two sites in the Netherlands and one site in Belgium (Clinicaltrials.gov number NCT02442531). Dose escalation followed a standard 3 + 3 design. According to a 3 + 3 design at least 3 patients are treated at each dose level, by applying the following rules; 1. dose escalation to the next dose level if no dose limiting toxicity (DLT) occurs, 2. if 1 out of 3 patients experiences a DLT, treat 3 additional patients at this dose level, 3. stop dose escalation if ≥2 out of 3 or ≥ 2 out of 6 patients experience a DLT [14]. In part 1 and in part 2 CPC634 was administered without premedication. CPC634 was administered every three weeks (Q3W) in part 1. In part 2, CPC634 was administered once every two weeks (Q2W) to explore if the tolerability of CPC634 could be improved by this dosing schedule. In part 3, CPC634 was administered once Q3W with oral dexamethasone premedication (8 mg 12, 3 and 1 h before infusion). In part 1 and in part 3, one treatment cycle was three weeks and comprised of one drug infusion followed by three weeks of rest. In part 2 the duration of one treatment cycle was set at four weeks and thus comprised of two drug administrations, each followed by two weeks of rest. A minimum of three patients were enrolled at each dose level. The starting dose of 15 mg/m^2 was calculated as a safe starting dose using one-tenth of the MTD observed in the single dose acute toxicity study in rats. Preplanned dose escalation levels were set at 30, 60, 100, 150, and 210 mg/m^2. Part 2 was started after completion of part 1. The starting dose in part 2 was based on the MTD reached in part 1. The DLT observation period was one treatment cycle. All dose escalation decisions were made following completion of the DLT observation period and after consultation with all the investigators.

Upon completion of treatment cycle 1, patients could receive additional treatment cycles, with ongoing safety monitoring. This study was conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles that have their origin in the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics committee of all participating centres. All patients provided written informed consent before participation in the trial.

Table 1
Patient characteristics at baseline.

	No (%)
Patients	
Screened	49
Enrolled	33
Age (years)	
Median	61
Range	48–77
Performance status[a]	
0	5 (15)
1	28 (85)
Gender	
Female	13 (39)
Male	20 (61)
Tumour type	
Prostate cancer	7 (21)
Adenocarcinoma of unknown primary origin	3 (9)
Colorectal cancer	3 (9)
Adenoid cystic carcinoma	3 (9)
Small cell lung cancer	2 (6)
Other	15 (45)
Previous systemic treatment	
Yes	31 (94)
No	2 (6)
> 2 lines of chemotherapy	15 (46)
Yes	
No	18 (55)
Previous treatment with taxanes	
Yes	12 (36)
No	21 (64)

[a] Eastern Cooperative Oncology performance status.

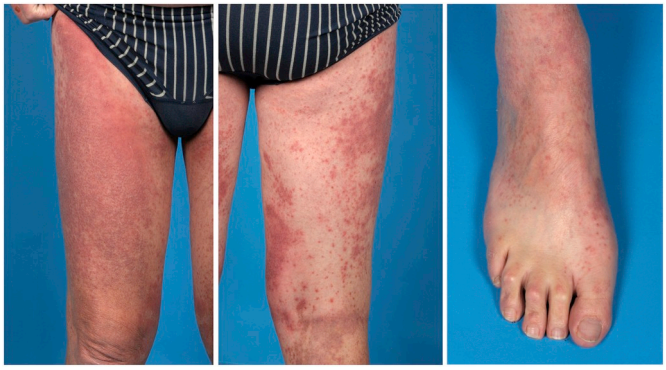

Fig. 1. Appearance of cumulative skin toxicity; presence of maculopapular rash with erythema on the lower limb and foot in a patient in the 70 mg/m^2 cohort.

2.2. Definition of DLT

Safety assessments were done according to Common Terminology Criteria for Adverse Events (version 4.03). Haematological DLT was defined as drug-related grade > 3 neutropenia lasting more than 1 week; grade ≥ 3 febrile neutropenia; grade 4 thrombocytopenia, or grade 3 thrombocytopenia with bleeding requiring platelet transfusion; grade ≥ 4 anaemia. Non-haematological DLT was defined as any drug related grade ≥ 3 toxicity with the exception of inadequately treated nausea, vomiting or diarrhoea. Delayed administration of the study drug for more than two weeks and any other toxicity which in the view of the investigator represented a clinically significant hazard to the patient - even outside the DLT window- also qualified as DLT. The RP2D was determined by the rate of the DLTs and overall tolerability of repeated CPC634 administrations.

2.3. Patients

Eligible patients had a pathologically confirmed diagnosis of an

Table 2
Overview of all the dose levels with the number of patients experiencing dose limiting toxicities (DLTs).

CPC634 dose (mg/m^2)	DLT ratio	DLT	Received > 2 cycles	Median number of received cycles	AE leading to dose reduction	CPC634 related grade ≥ 3 AE	Off-study due to CPC634 related toxicity
Part 1 (without dexamethasone)							
15	0/3	–	2	6 (2 − 23)	0	1	0
30	0/3	–	1	2 (2–3)	0	0	0
60	0/3	–	1	3 (1–4)	0	0	0
100	3/3	Skin rash grade 2 and grade 3, PPE grade 3	2	3 (2–3)	3	7	3
80	2/3	Fatigue grade 3; skin rash grade 3	1	2 (2–3)	1	1	2
70	1/6	Skin rash grade 3	2	2 (1–4)	2	5	1
60	2/3	Colitis grade 3; skin rash grade 3	2	3 (2–7)	2	7	1
Part 2 (without dexamethasone)							
45	2*/3	Hypomagnesemia grade 3; skin rash grade 3; PPE grade 3	0	3 (3–4)	0	3	2
Part 3 (with dexamethasone premedication)							
60	0/6	–	5	5.5 (2–9)	0	3	2

Abbreviations; AE, adverse event; PPE, palmar-plantar erythrodysaesthesia; * one patient in part 2 experienced 2 DLTs; hypomagnesemia grade 3 and rash grade 3.

advanced solid tumour with no standard therapy options, with measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Eligible patients were ≥ 18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and had adequate haematological, liver and renal function (extended inclusion and exclusion criteria are described in **supplementary file 2A**).

2.4. Treatment

CPC634 was provided by Cristal Therapeutics (Maastricht, The Netherlands). Preparation of CPC634 before administration included thawing for 16–24 h in a 2–8 °C refrigerator. On the day of administration CPC634 vials were placed at room temperature (18–25 °C) for 1.0 h to reach ambient temperature before administration. CPC634 was administered intravenously over 60 min.

2.5. Pharmacokinetic assessments

In part 1, plasma samples for docetaxel measurement were collected at the following time points during treatment cycles 1 and 2: 0, 5, 15, 30 min, 1, 1.5, 2, 4, 6, 24 h, 2–4 and 7 days after drug infusion. In part 2, pre-dose plasma samples were taken during treatment cycles 1 to 3 and one sample after administration of CPC634 in cycle 1. In part 3, only pre-dose plasma samples were taken during treatment cycles 1 to 4 to demonstrate the absence of any drug accumulation upon repeated administration. The bioanalytical validation and sample measurement was conducted by BioClin Research Laboratories Ltd. (Athlone, Ireland). Total and released docetaxel human plasma samples were analysed by high-pressure liquid chromatography with tandem mass spectrometric detection using turbo ion spray (**supplementary file 2B**). The lower limit of quantification was 100 ng/mL for total and 1 ng/mL for released docetaxel. Determination of the relevant pharmacokinetic parameters included the maximum plasma concentration (C_{max}) and its corresponding time (T_{max}), area under the curve (AUC) from time of dosing extrapolated to infinity (AUC_{inf}), the elimination half-life (T½), total plasma clearance (CL/m^2) and the volume of distribution (Vd L/m^2) (**supplementary file 2B**).

2.6. Antitumour activity

Antitumour activity was assessed by the investigators using RECIST version 1.1. In part 1 and in part 3, response evaluation was performed at the end of treatment cycles 2, 4, and 6 and subsequently after every 3 cycles; and at end of treatment. In part 2, response evaluation was performed every eight weeks and at the end of study participation. The duration of response was defined as the number of days from the date of first response to the earliest documentation of radiographic progressive disease (PD) or death of all causes.

2.7. Statistical analyses

Patients who received at least one dose of CPC634 were included in the safety assessment. Descriptive statistics were used for patient characteristics, pharmacokinetic parameters of CPC634, safety and efficacy data. All the pharmacokinetic descriptive statistics were calculated using Phoenix® WinNonlin® Version 7 (Certara USA, Inc., Princeton, NJ, USA). The data cut-off for analysis of safety and antitumour activity was July 23, 2018. The non-parametric Mann Whitney test was used to compare the pharmacokinetic profile of patients experiencing DLT with patients without DLT.

3. Results

3.1. Patient characteristics

Thirty-three patients (part 1; $n = 24$, part 2; $n = 3$, part 3; $n = 6$) with various solid tumours were included between July 2015 and June 2018 (Table 1).

3.2. Dose escalation and DLTs

In part 1, dose escalation could be pursued from 15 up to 100 mg/m^2. No DLTs were observed at 15, 30 and 60 mg/m^2 during treatment cycle 1. Therefore, CPC634 dose was escalated to 100 mg/m^2. At 100 mg/m^2, one patient developed neutropenia grade 4 lasting < 7 days. Treatment cycle 2 for this patient was therefore reduced to 80 mg/m^2. During treatment cycle 2 the patient was admitted to hospital due to bullous skin rash grade 3 and a coinciding pneumonia grade 4. Both events were considered potentially related to CPC634. The second patient at 100 mg/m^2 developed bullous skin rash grade 2 and neutropenia grade 3 lasting < 7 days in cycle 1. Treatment cycles 2 and 3 were therefore reduced to 80 mg/m^2. The third patient at 100 mg/m^2 developed maculopapular skin rash grade 2 during treatment cycle 1, and received cycle 2 and 3 at 80 mg/m^2. During treatment cycle 3, this patient developed palmar-plantar erythrodysesthesia syndrome (PPE)

Table 3
Treatment-related adverse events of all-grades which occurred in ≥10% of all patients.

N (%)	Part 1												Part 2		Part 3		Total (n = 33)	
	15 mg/m^2(n = 3)		30 mg/m^2(n = 3)		60 mg/m^2(n = 6)		70 mg/m^2(n = 6)		80 mg/m^2(n = 3)		100 mg/m^2(n = 3)		45 mg/m^2(n = 3)		60 mg/m^2(n = 6)			
	All grade	G3/4	All grade	G3/4	All grade	G3/4	All grade	G3/4	All grade	G3/4	All grade	G3/4	All grade	G3/4	All grade	G3/4	All grade	G3/4
Skin rash	0	0	0	0	4	1	6	1	2	0	3	1	2	1	2	1	19 (58%)	5 (15%)
Fatigue	2	0	2	0	3	1	2	0	2	1	3	0	1	1	3	0	18 (55%)	3 (9%)
Decreased appetite	1	0	0	0	1	0	3	1	2	0	1	0	2	0	1	0	11 (33%)	1 (3%)
Nausea	1	0	0	0	2	0	2	0	1	0	1	0	2	0	2	0	11 (33%)	0
Vomiting	1	0	1	0	0	0	2	0	0	0	0	0	0	0	3	1	7 (21%)	1 (3%)
IRR	1	0	0	0	1	0	1	0	1	0	2	0	0	0	1	0	7 (21%)	0
PPE	0	0	0	0	1	0	0	0	1	0	2	2	1	1	1	0	6 (18%)	3 (9%)
PSN	0	0	0	0	1	0	1	0	1	0	1	0	0	0	2	1	6 (18%)	2 (6%)
Diarrhoea	1	0	1	0	1	1	0	0	1	0	2	0	0	0	0	0	6 (18%)	1 (3%)
Stomatitis	0	0	0	0	0	0	2	0	1	0	2	1	0	0	1	0	6 (18%)	1 (3%)
Alopecia	0	0	0	0	0	0	1	0	1	0	1	0	0	0	2	0	5 (15%)	0
PMN	1	0	0	0	1	1	1	0	0	0	0	0	0	0	1	0	4 (12%)	1 (3%)
Dyspnoea	0	0	0	0	1	1	2	0	0	0	0	0	0	0	1	0	4 (12%)	1(3%)

Abbreviations; IRR, infusion related or allergic reaction; PPE, palmar-plantar erythrodysaesthesia; PSN, peripheral sensory neuropathy; PMN, peripheral motor neuropathy.

grade 3.

Following the observation of possible cumulative (and potentially dose-limiting) skin toxicity beyond treatment cycle one, the DLT observation period, with particular emphasis on skin toxicity, was extended beyond treatment cycle 1 to better assess the clinical toxicity. Next, a lower dose level of 80 mg/m^2 was explored in 3 patients. One patient experienced intermittent fatigue grade 3 during treatment cycle 1. Treatment cycle 2 was given at 80 mg/m^2. The second patient received CPC634 at a dose of 80 mg/m^2 during treatment cycle 1 and 2. During treatment cycle 2 the patient developed skin rash grade 2 which impeded further administrations of CPC634. The skin toxicity was considered as DLT. The third patient received two treatment cycles at 80 mg/m^2. Due to skin PPE grade 2 during treatment cycle 2, the third cycle was given at a reduced dose of 60 mg/m^2. Subsequently, a lower dose level of 70 mg/m^2 was evaluated in 3 patients. The first patient developed skin rash grade 2 during treatment cycle 2. During treatment cycle 3 which was given at 60 mg/m^2 the skin rash worsened to grade 3 (Fig. 1) which confirmed the need for an extended DLT observation period as described above. Three additional patients were included at this dose level. Although no formal DLTs were observed during treatment cycle 1 in these patients, the gradual onset of drug-related skin rash up to grade 2 during additional treatment cycles hampered timely administration of CPC634 beyond treatment cycle 2. Therefore, the 60 mg/m^2 dose level was expanded with an additional 3 patients. Of these, one patient developed diarrhoea grade 3 during treatment cycle 1 due to colitis confirmed on endoscopy with biopsy and one patient developed skin rash grade 3 during treatment cycle 3. It was concluded from part 1, that 60 mg/m^2 should be considered for further exploration in part 3. Overall, skin rash was an important adverse event (AE) with various presentation such as erythema, maculopapular, bullous lesions affecting all parts of the body, localized rash near the injection sites or PPE. After treatment cessation the skin rash recovered gradually in the majority of the patients. Treatment of skin rash included cutaneous application of chlorhexidine 0,5%, clobetasol propionate 0,05% or menthol 0,5% in cetomacrogol creme.

In part 2, 3 patients were enrolled at the 45 mg/m^2. One patient developed PPE grade 3 during treatment cycle 1. A second patient experienced a combination of hypomagnesemia grade 3 during treatment cycle 1 and skin rash grade 3 during treatment cycle 2. Because 2 out of 3 patients enrolled in the first dose level of part 2 developed DLTs, further dose exploration was not pursued.

In part 3, 6 patients received 60 mg/m^2 CPC634 after dexamethasone premedication according to the schedule described. One patient developed skin toxicity consisting of skin fissures and erythema grade 4 during treatment cycle 5 which recovered after cessation of treatment. Because the other 5 patients did not experience skin toxicity that hampered repeated administrations, the RP2D for part 3 of the study was determined at 60 mg/m^2. Based on part 1 the MTD of CPC634 was determined at 70 mg/m^2 Q3W. An overview of all the dose levels with the corresponding DLTs is summarized in Table 2.

Serious AEs observed in the study population were gastrointestinal disorders (1 out of 9 related to CPC634), infection (1 out of 6 related to CPC634), skin toxicities (5, all related to CPC634), neutropenia (2, both related to CPC634), peripheral sensory neuropathy (1, related to CPC634), pain (3, none related to CPC634), tumour bleeding (1, not related to CPC634), pericardial tamponade (1, not related to CPC634), hyperglycaemia (1, not related to CPC634), edema (1, related to CPC634) and 1 case of death (related to progressive disease).

Adverse events related to CPC634 occurring in > 10% of patients with the corresponding prevalence of grade ≥ 3 AE during therapy are summarized in Table 3. Grade ≥ 3 AEs related to CPC634 were skin toxicity (24%), neutropenia (6%), infection (6%), vertigo (3%), swollen tongue (3%), increased aspartate aminotransferase (3%), increased gamma-glutamyl transferase (3%), hypotension (3%) and hypomagnesaemia (3%).

Table 4
Summary of noncompartmental pharmacokinetic parameters of cycle 1, mean ± SD (% coefficient of variation) values by each dose level in part 1. *Abbreviations; C_{max}, maximum concentration; T_{max}, peak time; AUC_{inf}, area under the curve from time 0 to infinity; $T_{1/2}$ elimination half-life; CL, total clearance; V_z, volume of distribution.*

Released docetaxel

Dose mg/m^2 (N)	C_{max} (ng/ml)	T_{max} (hr)	AUC_{inf} (ng/h/ml)	$T_{½}$ (h)	CL (liter/h/m^2)	V_z (liter/m^2)
15 (3)	62.0 ± 13.5 (21.8)	2.5 ± 1.3 (50.8)	1214.2 ± 492.8 (40.6)	26.6 ± 10.9 (41.1)	13.6 ± 4.6 (34.0)	451.3 ± 121.2 (26.9)
30 (3)	67.4 ± 17.6 (26.1)	1.2 ± 0.3 (23.3)	3231.6 ± 2959.1 (91.6)	33.6 ± 1.4 (4.3)	14.7 ± 9.0 (61.3)	659.4 ± 339.4 (51.5)
60 (5)	217.3 ± 91.9 (41.6)	1.4 ± 0.4 (29.9)	4067.5 ± 2974.0 (24.8)	39.7 ± 9.4 (23.6)	15.3 ± 3.6 (23.6)	737.5 ± 201.0 (27.3)
70 (6)	341.0 ± 170.0 (49.8)	1.8 ± 1.2 (67.0)	6213.1 ± 1938.9 (31.2)	41.0 ± 2.9 (7.0)	12.3 ± 3.9 (31.6)	647.3 ± 170.4 (26.3)
80 (2)	325.5 ± 20.9 (6.4)	1.5 ± 0.7 (47.1)	5479.0 ± 424.0 (7.7)	39.60 ± 0.05 (0.1)	14.6 ± 1.2 (8.4)	685.1 ± 57.1 (8.3)
100 (3)	321.9 ± 120.6 (37.5)	1.8 ± 0.3 (15.7)	8424.4 ± 562.5 (6.7)	44.9 ± 9.9 (22.1)	12.0 ± 0.7 (5.6)	690.9 ± 176.2 (25.5)

Total docetaxel

Dose mg/m^2 (N)	C_{max} (ng/ml)	T_{max} (hr)	AUC_{inf} (ng/h/ml)	$T_{½}$ (h)	CL (liter/h/m^2)	V_z (liter/m^2)
15 (3)	7793.8 ± 1106.7 (14.2)	1.8 ± 0.3 (15.5)	309,676.9 ± 22,012.7 (7.1)	33.2 ± 2.6 (7.8)	0.05 ± 0.00 (6.0)	2.2 ± 0.1 (3.6)
30 (3)	17,729.6 ± 3407.0 (19.2)	1.6 ± 0.6 (33.9)	514,212.9 ± 167,829.0 (32.6)	29.9 ± 2.7 (9.2)	0.06 ± 0.02 (31.0)	2.5 ± 0.5 (21.8)
60 (5)	27,144.4 ± 7999.3 (29.5)	1.5 ± 0.4 (23.5)	973,986.6 ± 246,491.0 (25.3)	31.6 ± 1.3 (4.2)	0.06 ± 0.02 (26.3)	2.9 ± 0.8 (28.2)
70 (6)	29,711.8 ± 13,361.5 (45.0)	2.6 ± 1.5 (60.2)	1,179,287.4 ± 500,045.7 (42.4)	32.9 ± 3.6 (11.0)	0.07 ± 0.02 (33.5)	3.2 ± 1.2 (37.5)
80 (2)	28,685.4 ± 5327.1 (18.6)	1.3 ± 0.4 (28.3)	1,116,310.7 ± 119,844.0 (10.7)	41.1 ± 10.2 (24.9)	0.07 ± 0.01 (9.9)	4.1 ± 10.2 (17.5)
100 (3)	44,116.1 ± 8645.3 (19.6)	3.3 ± 2.3 (67.9)	1,836,280.0 ± 385,084.5 (21.0)	35.0 ± 3.2 (9.2)	0.06 ± 0.01 (23.0)	2.7 ± 0.8 (28.7)

3.3. Pharmacokinetics

Of the 24 patients enrolled in part 1, 22 patients contributed to complete pharmacokinetic analysis for cycle 1. A summary of the pharmacokinetic parameters of treatment cycle 1 is shown in Table 4. There was a rank order increase in the AUC_{inf} and C_{max} with an increase in dose for both released and total docetaxel.

Plasma concentration-time profile of released and total docetaxel at 60 mg/m^2 are illustrated in Fig. 2A and B. The mean T½ of released docetaxel ranged from 26.6 ± 10.9 h to 44.9 ± 9.9 h. The T½ of total docetaxel across the cohorts varied from 29.9 ± 2.7 h to 41.0 ± 10.2 h. The Vd and CL were broadly consistent over the dose range for both released and total docetaxel. The plasma AUC_{inf} of released docetaxel levels did not differ between the patients who experienced DLT and those who did not (p = .1229, Fig. 2C). On the other hand, the plasma AUC_{inf} of total docetaxel was significantly higher in patients experiencing a DLT (p = .0021, Fig. 2D).

3.4. Antitumour activity

Thirty patients (n = 21 in part 1, n = 3 in part 2, n = 6 in part 3) were evaluable for tumour response. In part 1, 11 patients showed stable disease and 1 patient had an unconfirmed partial response with a duration of 77 days as best response. This patient had an adenocarcinoma of unknown origin without any previous systemic therapy and received CPC634 at 60 mg/m^2. The total tumour burden measured in this patient decreased from 129 mm at screening to 109 mm in cycle 2, 90 mm in cycle 4, 86 mm in cycle 6 and 85 mm at EOT. The median duration of stable disease was 58 days (range, 27–482). One patient received treatment up to 23 cycles (at 15 mg/m^2). In part 2, all patients showed progressive disease as best response. In part 3, five patients had stable disease with a median duration of 125 days (range, 35–195). One prostate cancer patient showed a 60% decrease in prostate-specific antigen plasma concentration. This patient was not evaluable for radiological response evaluation.

4. Discussion

Taxanes are frequently used in oncology but are known for their narrow therapeutic index [2,4,15–17]. Taxanes are water-insoluble and therefore have a relatively short circulation time and low tumour exposure [2,4,15–17]. Nanotechnology can serve to improve target delivery of water-insoluble drugs while preserving healthy tissues. CPC634 is such a novel nanomedicine and consists of docetaxel covalently entrapped in a stabilized, 65 nm sized core-cross linked polymeric micelles (CCL-PMs). In this first in human study, the RP2D of CPC634 was established at 60 mg/m^2 administered Q3W with dexamethasone premedication. Other nanoparticles containing docetaxel resulted in comparable RP2D's ranging between 60 and 75 mg/m^2 [5,9,18]. The most important DLT of CPC634 observed in this study was cumulative skin toxicity. We could demonstrate a pharmacokinetic/toxicity relationship with higher plasma AUC for total docetaxel in patients experiencing this DLT. Docetaxel is known to induce similar skin toxicities [19,20]. Nanomedicines can induce the hypersensitivity syndrome called C activation-related pseudoallergy (CARPA) which is likely due to interaction with circulating serum proteins [21,22]. The clinical manifestation of CARPA usually occurs during the first infusion of the nanomedicine [21,22]. CPC634 is known to have a very low protein affinity in human blood plasma [23] and the skin DLTs related to CPC634 were observed after repeated administrations. We therefore hypothesize that the mechanism of the skin DLTs is not due to CARPA effect but rather related to the prolonged systemic exposure and different biodistribution of docetaxel released by CPC634. A head− to head comparison of the systemic, intratumoural and skin pharmacokinetics of CPC634 with conventional docetaxel has been investigated in the so-called CriTax study (Netherlands Trial Register number NTR6474, www.trialregister.nl).). The published intratumoural pharmacokinetic data showed that CPC634 resulted in a higher intratumoural total docetaxel and comparable released docetaxel levels relative to conventional docetaxel [13]. Although the RP2D of CPC634 is lower than that of conventional docetaxel, the increased intratumoural exposure to docetaxel presumably compensates for that. Thus, CPC634 has the potential to reduce the number of cycles needed for clinical activity.

Neutropenia is a frequently occurring AE of conventional docetaxel. The incidence of grade ≥ 3 neutropenia is approximately 50% with Q3W docetaxel at 60–100 mg/m^2[19,20]. In our study grade ≥ 3 neutropenia only occurred in two patients and only, short lasting, at the highest dose level of 100 mg/m^2. This is in contrast with other phase 1 studies with docetaxel-containing nanoparticles where neutropenia was an important DLT [5,14,15]. In a pharmacodynamics analysis of conventional docetaxel monotherapy, greater C_{max} of unbound plasma docetaxel was correlated with higher risk of grade 4 neutropenia [24]. Presumably, the unbound docetaxel reaches the bone marrow resulting in neutropenia. Albumin and a1-acid glycoprotein are the main carriers of docetaxel in the plasma [25]. The measured released docetaxel

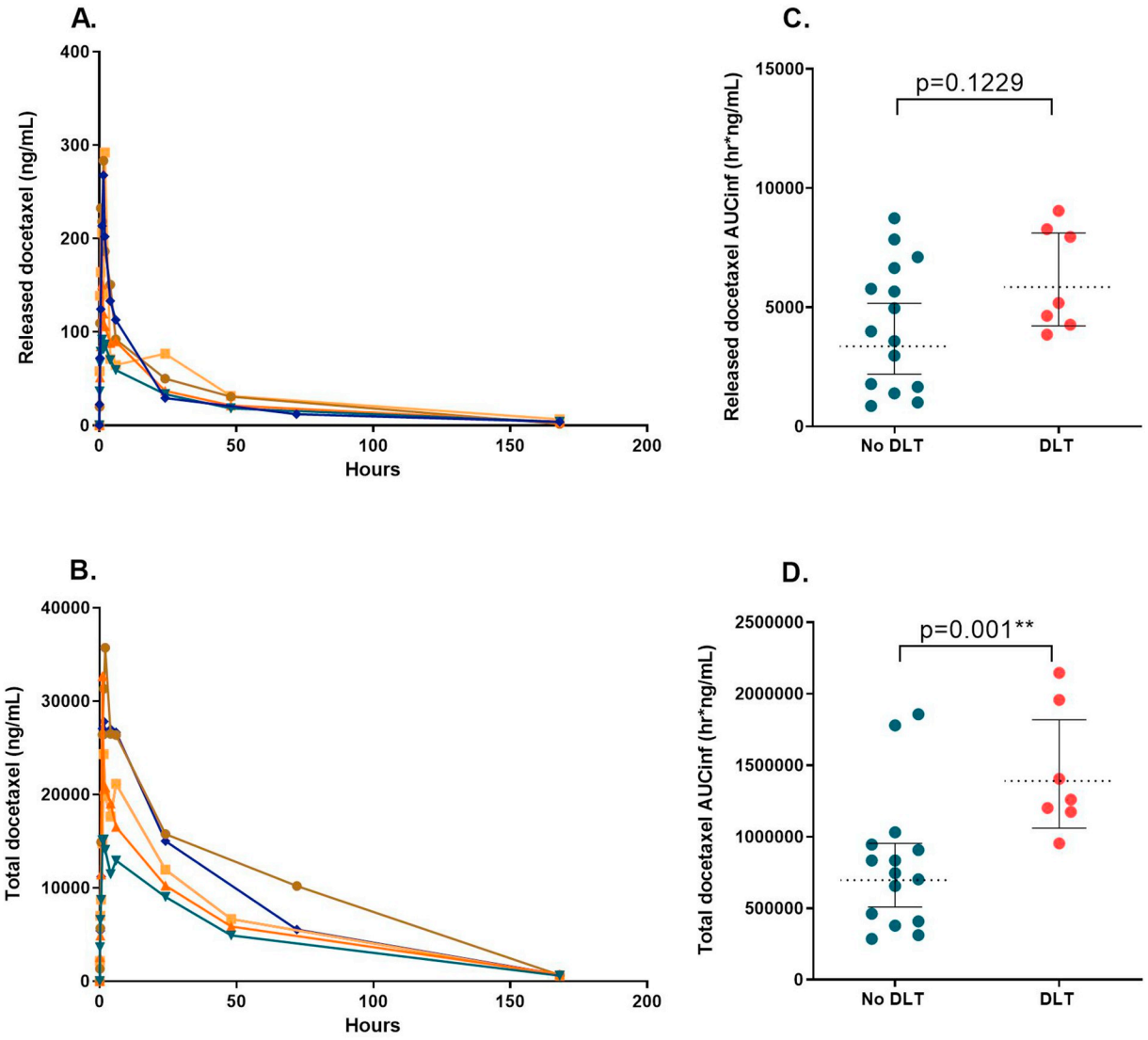

Fig. 2. Plasma concentration-time profile of released (A) and total docetaxel (B) at the 60 mg/m^{2}dose ($n = 5$). Plasma AUC_{inf} of released (C) and total (D) docetaxel in patients with (red dots) and without (blue dots) DLTs in part 1 (22 patients contributed to complete pharmacokinetic analysis for cycle 1). AUC_{inf} of total docetaxel was higher in patients with DLT ($p = .001$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

concentration in this study includes both protein bound and unbound docetaxel. A plausible explanation for the low incidence of neutropenia in this study could be the lower C_{max} of released docetaxel from CPC634 compared to conventional docetaxel and other docetaxel-containing nanoparticles [1,21]. The CCL-PMs in CPC634 enable a stable and slow release of docetaxel from the nanoparticles that could explain this low C_{max}. The pharmacokinetic profile of CPC634 compared to published data of conventional docetaxel (100 mg/m^2 dose as a comparison) demonstrate a 7 fold lower C_{max}, 2 fold longer half-life and comparable CL and AUC for released docetaxel, whereas in our aforementioned CriTax study [13] CPC634 has a lower C_{max} of released docetaxel compared to conventional docetaxel. The 309 fold higher AUC of total docetaxel in combination with 2 fold longer half-life and 283 fold lower CL indicate a high retention of docetaxel in the nanoparticles which supports a prolonged systemic exposure to docetaxel [1,19]. A PET imaging of the intratumoural docetaxel exposure by CPC634 is studied in the PICCOLO trial (Clinicaltrials.gov number NCT03712423).

Conventional docetaxel is often administered as a part of combinational chemotherapeutic regimens which all have a high risk of developing febrile neutropenia [20]. Using CPC634 instead of conventional docetaxel in any of these regimens could have the potential to reduce this AE. Further studies are therefore indicated to explore safety and efficacy of CPC634 as monotherapy and in combination with any of these regimens.

In conclusion this phase 1 study has demonstrated that Q3W administration of CPC634 at 60 mg/m^2 is feasible with manageable toxicity and a small risk of neutropenia. The pharmacokinetic profile of CPC634 is dose-proportional with prolonged systemic exposure to docetaxel in accordance with preclinical data. A phase II efficacy study (the CINOVA trial) of CPC634 monotherapy is ongoing (Clinicaltrials.gov number NCT03742713).

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