A phase I dose-finding and pharmacokinetic study of CPC634 (nanoparticle entrapped docetaxel) in patients with advanced solid tumors

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BACKGROUND

- Important limitation of docetaxel is its narrow therapeutic window with lack of selectivity resulting in side effects and drug resistance[1]
- Nanomedicine-based drugs aim to improve the pharmacokinetic (PK) profile, biodistribution and efficacy/safety balance of the native drug via the enhanced permeability and retention (EPR) effect[2]
- CPC634 is a novel nanomedicine consisting of docetaxel entrapped in 65 nm sized core crosslinked polymeric micelles
- CPC634 is designed to have a prolonged circulation and improved biodistribution profile with enhanced tumor uptake aiming to enhance the therapeutic index of docetaxel

OBJECTIVES

Primary objectives

- To assess safety and establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for CPC634
- To evaluate the PK profile of CPC634

Secondary objective

- To evaluate preliminary signs of anti-tumor activity of CPC634

METHODS

STUDY DESIGN

- European multicenter phase 1 study with 3+3 dose escalation design (NCT02442531)
- Patients with solid tumors with no treatment options were included
- CPC634 was administered IV Q3W (part 1), Q2W (part 2) or Q3W with dexamethasone premedication (part 3)
- One cycle was defined 3 weeks in part 1 and 3, and 4 weeks in part 2

DOSE LIMITING TOXICITY (DLT) CRITERIA

- Grade ≥4 anemia
- Grade ≥3 thrombocytopenia requiring transfusion
- Grade >3 neutropenia lasting >7 days
- Grade ≥3 febrile neutropenia of any duration
- Grade ≥3 non-haematological toxicity
- Missing of study drug due to drug-related toxicity lasting > 14 days
- Any other toxicity that represented a clinically significant hazard to the patient, even outside the DLT window

ASSESSMENTS

- RP2D was determined based on DLT rate and overall tolerability of repeated CPC634 administrations
- Objective response was assessed using RECIST 1.1 criteria
- PK sampling for CPC634 was done during cycle 1-2 in part 1

RESULTS

Table 1. Demographics and clinical characteristics

Characteristics, n (%)		Total, n=33
Age, years	Median [range]	61 [48-77]
Gender	Female	13 (39)
	Male	20 (61)
ECOG[1] status	Grade 0	5 (15)
	Grade 1	28(85)
Tumor site	Prostate	7 (21)
	ACUP[2]	3 (9)
	Colorectal cancer	3 (9)
	Other	20 (61)

[1]Eastern Cooperative Oncology performance status, [2]adenocarcinoma of unknown primary origin

Table 2. Overview of the DLT ratio and CPC634 tolerability

CPC634 dose mg/m²	DLT ratio[1]	Dose reduction due to TEAEs[2]	Off-study due to TEAEs	Median number of cycles (range)
Part 1				
15	0/3	-	-	6 (2-23)
30	0/3	-	-	2 (2-3)
60	2/6	-	-	3 (1-7)
100	3/3	3	3	3 (2-3)
80	2/3	1	1	2 (2-3)
70	1/6	2	2	2 (1-4)
Part 2				
45	2[3]/3	-	2	3 (3-4)
Part 3				
60	0/6	-	2	5.5 (2-9)

[1]Number of patients with DLT in each cohort, [2]treatment emergent adverse events(TEAEs), [3]one patient experienced 2 DLTs

Table 3. Overview of the DLTs

	Part 1				Part 2
DLT	60 mg/m²	70 mg/m²	80 mg/m²	100 mg/m²	45 mg/m²
Skin rash	1	1	1	2	1
PPE[1]	-	-	-	1	1
Hypomagnesemia	-	-	-	-	1
Fatigue	-	-	1	-	-
Colitis	1	-	-	-	-

[1]Palmar-plantar erythrodysaesthesia

Figure 1. Skin rash in a patient at 70mg/m² cohort

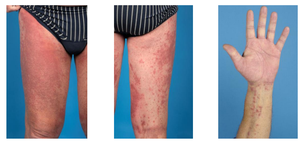


Table 4A. CPC634 related adverse events (AEs) of all-grades occurred in ≥3 of the patients

All-grade	Part 1 mg/m²						Part 2 mg/m²	Part 3 mg/m²	Total N(%)
	15	30	60	70	80	100	45	60	
Skin rash	-	-	4	6	2	3	2	2	19 (58)
Fatigue	2	2	3	2	2	3	1	3	18 (55)
Anorexia	1	-	1	3	2	1	2	1	11 (33)
Nausea	1	-	2	2	1	1	2	2	11 (33)
Vomiting	1	1	-	2	-	-	-	3	7 (21)
IRR[1]	1	-	1	1	1	2	-	1	7 (21)
PPE	-	-	1	-	1	2	1	1	6 (18)
Diarrhea	1	1	1	-	1	2	-	-	6 (18)
Stomatitis	-	-	-	2	1	2	-	1	6 (18)
PSN[2]	-	-	1	1	1	1	-	2	6 (18)
Alopecia	-	-	-	1	1	1	-	2	5 (15)
PMN[3]	1	-	1	1	-	-	-	1	4 (12)
Dyspnoea	-	-	1	2	-	-	-	1	4 (12)
Infection	1	-	1	-	-	1	1	-	4 (12)
Neutropenia	-	-	-	-	-	3	-	-	3 (9)

Table 4B. All CPC634 related grade ≥3 AEs

Grade ≥ 3 AEs	Part 1 mg/m²						Part 2 mg/m²	Part 3 mg/m²	Total N(%)
	15	30	60	70	80	100	45	60	
Skin rash	-	-	1	1	-	1	1	1	5 (15)
Fatigue	-	-	1	-	1	-	1	-	3 (9)
PPE	-	-	-	-	-	2	1	-	3 (9)
Neutropenia	-	-	-	-	-	2	-	-	2 (6)
Infection	1	-	-	-		1	-	-	2 (6)
PSP	-	-	1	-	-	-	1	1	2 (6)
Anorexia	-	-	-	1	-	-	-	-	1 (3)
Vomiting	-	-	-	-	-	-	-	1	1 (3)
Hypo-Mg[4]	-	-	-	-	-	-	1	-	1 (3)
Diarrhoea	-	-	1	-	-	-	-	-	1 (3)
Stomatitis	-	-	-	-	-	1	-	-	1 (3)
PMN	-	-	1	-	-	-	-	-	1 (3)
Dyspnoea	-	-	1	-	-	-	-	-	1 (3)
GGT[5]	-	-	-	1	-	-	-	-	1 (3)
AST[6]	-	-	-	1	-	-	-	-	1 (3)
Vertigo	-	-	1	-	-	-	-	-	1 (3)
Hypotension	-	-	-	1	-	-	-	-	1 (3)
Swollen tong	-	-	-	-	-	1	-	-	1 (3)

[1]Infusion related reaction, [2]peripheral sensory neuropathy, [3]peripheral motor neuropathy, [4]hypomagnesemia, [5]gamma-glutamyltransferase elevation, [6]aspartate aminotransferase elevation

DOSE ESCALATION

- MTD of CPC634 was 70 mg/m² Q3W
- Cumulative skin toxicity was the most frequent occurring DLT hampering repeated CPC634 administrations at 60-100 mg/m²
- Dexamethasone premedication in part 3 permitted repeated administration of CPC634 at 60 mg/m²

Table 5. Pharmacokinetic parameters mean ± SD in cycle 1 part 1

Dose mg/m² (N)	C_{max} (ng/mL)	T_{max} (hr)	Half-life (h)	AUC_{inf} (ng/h/mL)	CL (L/h/m²)
Released docetaxel					
15 (3)	62.0 ± 13.5	2.5± 1.3	26.6 ± 10.9	1214.2 ± 492.8	13.6 ± 4.6
30 (3)	67.4 ± 17.6	1.2 ± 0.3	33.6 ± 1.4	3231.6 ± 2959.1	14.7 ± 9.0
60 (5)	217.3 ± 91.9	1.4 ± 0.4	39.7 ± 9.4	4067.5 ± 2974.0	15.3 ± 3.6
70 (6)	341.0 ± 170.0	1.8 ± 1.2	41.0 ± 2.9	6213.1 ± 1938.9	12.3 ± 3.9
80 (2)	325.5 ± 20.9	1.5 ± 0.7	39.60 ± 0.05	5479.0 ± 424.0	14.6 ± 1.2
100 (3)	321.9 ± 120.6	1.8 ± 0.3	44.9 ± 9.9	8424.4 ± 562.5	12.0 ± 0.7
Total docetaxel					
15 (3)	7793.8 ± 1106.7	1.8 ± 0.3	33.2 ± 2.6	309676.9 ± 22012.7	0.05 ± 0.00
30 (3)	17729.6 ± 3407.0	1.6 ± 0.6	29.9 ± 2.7	514212.9 ± 167829.0	0.06 ± 0.02
60 (5)	27144.4 ± 7999.3	1.5 ± 0.4	31.6 ± 1.3	973986.6 ± 246491.0	0.06 ± 0.02
70 (6)	29711.8 ± 13361.5	2.6 ± 1.5	32.9 ± 3.6	1179287.4 ± 500045.7	0.07 ± 0.02
80 (2)	28685.4 ± 5327.1	1.3 ± 0.4	41.1 ± 10.2	1116310.7 ± 119844.0	0.07 ± 0.01
100 (3)	44116.1 ± 8645.3	3.3 ± 2.3	35.0 ± 3.2	1836280.0 ± 385084.5	0.06 ± 0.01

Figure 2. Plasma released (A) and total docetaxel (B) concentration versus time of patients in 60mg/m² cohort (n=4)

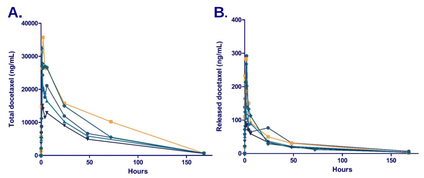
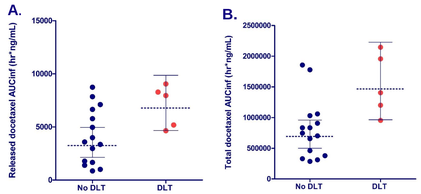


Figure 3. AUC_{inf} of released (A) and total docetaxel (B), in patients with (red dots) and without DLT (blue dots)



ANTI-TUMOR RESPONSE

- One patient with ACUP with no treatment history had partial response
- 16 cases of stable disease were confirmed in part 1 and in part 3 as best response.

CONCLUSION

RP2D

- CPC634 60 mg/m² Q3W with dexamethasone was determined as RP2D based on long term skin tolerability

PHARMACOKINETCS

- CPC634 exhibited a linear plasma PK profile
- A clear PK/DLT relation was seen;
  - AUC_{inf} of released and total docetaxel were higher in patients with DLT(p=0.036 and p=0.011, respectively) (**Figure 3**)

COMPARISON WITH CONVENTIONAL DOCETAXEL[1,3]

- CPC634 resulted in:
  - Lower incidence of neutropenia; 6% versus 36.6%
  - Lower incidence of alopecia; 15% versus 87%
  - Longer half-life

FUTURE IMPLICATIONS

- CPC634 might reduce the number of cycles needed if a prolonged exposure of docetaxel is also observed in the tumor
- Additional studies assessing intratumoral exposure of CPC634 are presented at the ASCO 2019 (abstract number 3039 and 3096).
- A phase II efficacy study of CPC634 in patients with platinum resistant ovarian cancer is ongoing (NCT03742713)

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