# Nanoparticle entrapped docetaxel (CPC634) enhances intratumoral docetaxel exposure compared to conventional docetaxel (Cd) in patients with solid tumors

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## BACKGROUND

- Failure or resistance to chemotherapy may be caused by sub-therapeutic intratumoral drug levels[1]
- Nanomedicine-based drugs aim to improve the pharmacokinetic (PK) profile and thereby the efficacy/safety profile of the native drug[2]
- CPC634 is a novel nanomedicine consisting of docetaxel entrapped in 65 nm sized core crosslinked polymeric micelles
- Preclinical data have shown that CPC634 results in higher intratumoral docetaxel concentration compared to conventional docetaxel (Cd)[3]
- This is the first study to investigate intratumoral docetaxel concentration in a clinical setting

## OBJECTIVES

### PRIMARY OBJECTIVE

- To demonstrate a 25% increase in intratumoral docetaxel concentration of CPC634 compared to Cd.

### SECONDARY OBJECTIVES

- To compare the systemic pharmacokinetic (PK) profile of CPC634 with Cd
- To evaluate the safety profile of CPC634 and compare this with Cd

## METHODS

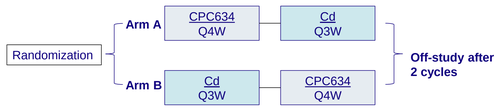
### STUDY DESIGN

- Randomized cross-over study (NCT02442531)
- Patients with solid tumors without treatment options were included
- Patients were randomized to receive 75 mg/m$^2$ CPC634 in cycle 1 and 75 mg/m$^2$ Cd in cycle 2 or *vice versa* (**figure 1.**)
- Patients went off-study after completing two cycles

### ASSESSMENTS

- Tumor biopsies were taken 24, 48, 72 and 96 hours after administration of CPC634 and Cd
- For each biopsy time point 4 patients were included
- Plasma PK sampling was done during both cycles
- Total docetaxel was determined for both drugs and released docetaxel for CPC634 in tumor tissue and in plasma using a validated LC-MS/MS method[4]

**Figure 1. Schematic view of the study design**




## RESULTS

**Table 1. Demographics, clinical characteristics and randomization results of all the patients.**

| Characteristics | | Total n=19 (%) |
|---|---|---|
| Age, years | Median [range] | 60 [38-74] |
| Gender | Female | 5 (26.3) |
| | Male | 14 (73.7) |
| ECOG[1] status | Grade 0 | 4 (21) |
| | Grade 1 | 15 (78.9) |
| Tumor type | Esophagus | 4 (21) |
| | Panreatic | 4 (21) |
| | Bile duct | 3 (15.7) |
| | Cervix | 2 (10.5) |
| | ACUP[2] | 2 (10.5) |
| | Other | 4 (21) |
| Randomization | Arm A | 9 (47.4) |
| | Arm B | 10 (52.6) |
| Patients evaluable for primary endpoint | Yes | 16 (84.2) |
| | No | 3 (15.8) |
| Number of patients receiving treatment | CPC634 + Cd | 16 (84.2) |
| | CPC634 | 2 (10.5) |
| | Cd | 1 (5.3) |

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

**Table 2. Treatment emergent adverse events (TEAEs) occurring in ≥ 2 patients during treatment with Cd or CPC634.**

| TEAE | Cd (n=17) | | CPC634 (n=18) | |
|---|---|---|---|---|
| | Grade 1-2 (%) | Grade 3-4 (%) | Grade 1-2 (%) | Grade 3-4 (%) |
| Nausea | 6 (35.3) | - | 7 (38.9) | 1[1] (5.6) |
| Vomiting | 3 (17.6) | 1[1] (5.9) | 4 (22.2) | - |
| Anorexia | 6 (35.3) | - | 6 (33.3) | 1 (5.6) |
| Stomatitis | 7 (41.2) | 1 (5.9) | 5 (27.8) | - |
| Constipation | 4 (23.5) | 1 (5.9) | 3 (16.7) | - |
| Diarrhea | 6 (35.3) | 1 (5.9) | 3 (16.7) | - |
| Abdominal pain | 3 (17.6) | - | 1 (5.6) | - |
| Heartburn | - | - | 3 (16.7) | - |
| Rash | 3 (17.6) | 1 (5.9) | 13 (72.2) | - |
| Pain | 4 (23.5) | 2[1] (11.8) | 7 (38.9) | 2 (11.1) |
| Fatigue | 7 (41.2) | 1 (5.9) | 4 (22.2) | 3 (16.7) |
| Fever | 4 (23.5) | - | 1 (5.6) | - |
| Infection | 1 (5.9) | 2 (11.8) | - | - |
| Ototoxicity | 5 (29.4) | - | 4 (22.2) | 1 (5.6) |
| Sens neuro | 1 (5.9) | - | 3 (16.7) | - |
| Dyspnea | 4 (23.5) | - | 5 (27.8) | - |
| Alopecia | 5 (29.4) | - | 2 (11.1) | - |
| Edema | 2 (11.8) | - | 1 (5.6) | - |
| Dizziness | 1 (5.9) | - | 4 (22.2) | - |
| Headache | 1 (5.9) | - | 2 (11.1) | - |
| Neutropenia | 1 (5.9) | 12 (70.6) | 1 (5.6) | 1 (5.6) |
| Febrile neutropenia | - | 2[2] (11.8) | - | - |

[1]One and [2]two patients with this TEAE was admitted to hospital which was classified as a serious adverse event (SAE)

**Figure 2. Neutrophil count after administration of Cd (n=17) or CPC634 (n=18).**

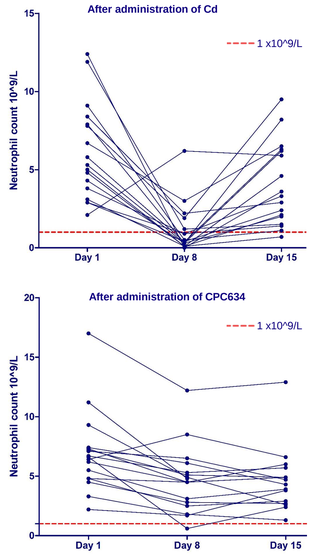
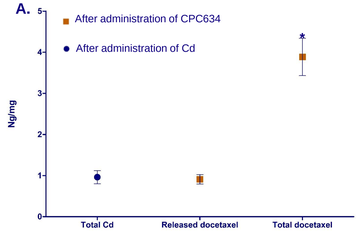



**Figure 3. Intratumoral docetaxel concentration after administration of Cd and CPC634 in all patients (n=16) (A), at 24h (B), 48h (C), 72h (D), and 96h (E), post-dose (n=4 for each cohort).**




* 323% (95% CI: 148,621) higher total docetaxel level compared to Cd, p<0.001

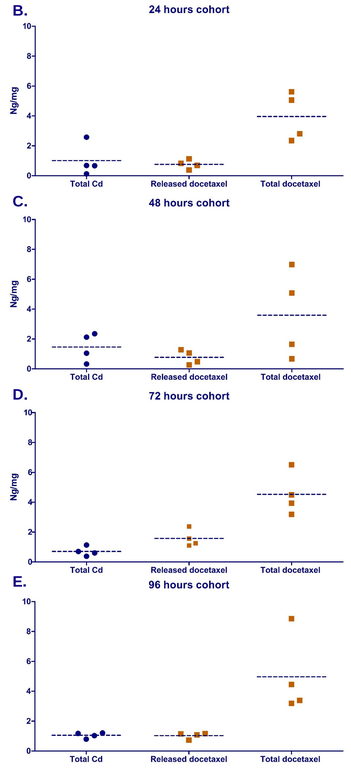



**Table 3. Relative difference (RD) in plasma PK of released docetaxel (CPC634) compared to Cd (n=16)**

| | RD | 95% CI | P value |
|---|---|---|---|
| $C_{max}$ | -90.40% | -91.97 to -88.51 | < 0.001 |
| $AUC_{inf}$ | 34.88% | 16.07 to 56.72 | = 0.001 |
| CL | -25.86% | -36.19 to -13.85 | = 0.001 |
| Vz | -99.78% | -99.84 to -99.70 | < 0.001 |

## CONCLUSION

### PHARMACOKINETCS

- Comparison of the PK profile of CPC634 with Cd revealed:
  - Higher (+323%) intratumoral total docetaxel levels
  - Higher (+34,88%) plasma AUC
  - Lower (-90,40%) plasma $C_{max}$
  - Lower (-25,86%) plasma clearance

### SAFETY

- CPC634 resulted in lower incidence of grade ≥ 3 neutropenia compared to Cd; 5.6%, versus 70.6%, respectively

### FUTURE IMPLICATIONS

- A phase 1 study of CPC634 is presented at this meeting (abstract number 3026)
- Another study noninvasively assessing intratumoral docetaxel exposure of CPC634 is presented at this meeting (abstract number 3093)
- A phase II study of CPC634 in patients with platinum resistant ovarian cancer is ongoing (NCT03742713)

## REFERENCES

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