A population PK analysis of docetaxel after IV administration of CPC634 (CriPec® docetaxel) and generic docetaxel in plasma and tumor

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Introduction

- CPC634 is a CriPec® polymeric nanoparticle entrapping docetaxel (DTX), conjugated via a biodegradable ester bond, developed to improve the tolerability and tumor accumulation as compared to generic docetaxel.
- Over time after intravenous (IV) administration, DTX bound to the nanoparticle is released via linker cleavage. The latter is defined as released DTX, whilst the nanoparticle conjugated is defined as unreleased DTX, and total = released + unreleased.

Objectives

- Characterize the PK of released and unreleased docetaxel after IV administration of CPC634.
- Determine the correlation between in *vivo* and *in vitro* release of DTX from CPC634 in plasma and pH 7.4 buffer.

Model

- The *in vitro* release of DTX from CPC634 in pH 7.4 buffer was described by a one compartment model with time-dependent release and linear elimination.
- A plasma population PK model for unreleased and released DTX was developed in three steps:
  1. A PK model (*DTX model*) for generic DTX was developed that served as disposition model for released DTX.
  2. A PK model (*CPC model*) was developed for unreleased DTX based on data from the CriTax and Piccolo studies. Elimination of CPC634 was described by linear kinetics whereas release of DTX was found to be time-dependent.
  3. The two models were combined to a *DTX-CPC* model that simultaneously described released and un-released DTX (Fig. 1, left-hand side). The release of DTX served as uptake of released DTX in the *DTX model*. The estimated *in vivo* and *in vitro* release profiles were compared.
- Assumptions plasma PK model:
  - The distribution of unreleased DTX is independent of the amount of DTX in the CriPec such that the distribution of [89Zr]-Df-CriPec is similar to the distribution of unreleased DTX.
  - Released DTX follows the same kinetics as generic DTX.
  - The depletion of (entrapped) DTX in CPC634 takes place by release of DTX and elimination of intact CPC634 nanoparticles.

Data

- CriTax study: a randomized cross-over study including 24 patients with solid tumors.
  - Patients received a 1-hour IV administration of 75 mg/m^2 CPC634 in cycle 1 and 75 mg/m^2 generic DTX in cycle 2 or *vice versa* [1].
  - Total and released DTX were measured in plasma and tumor tissue, unreleased concentrations were derived.
- Piccolo study: an open-label, non-invasive PET study with [89Zr]-Df-CPC634 DTX (CPC634 labelled with zirconium-89 (89Zr)) performed in five patients with solid tumors [2].
  - As a first dose, participants received 0.1 – 2 mg of [89Zr]-Df-CPC634 tracer. Two weeks later, patients were administered 60 mg/m^2 of CPC634 followed by a second [89Zr]-tracer injection.
  - Total and [89Zr]-Df-CPC634 DTX were determined in plasma and tumor tissue.

- The integrated plasma *DTX-CPC* PK model was linked to a tumor PK model for released and unreleased DTX:
  - Distribution of released and unreleased DTX in tumor was described by two effect compartments with linear release of DTX from CPC634 (right-hand side in Fig. 1).

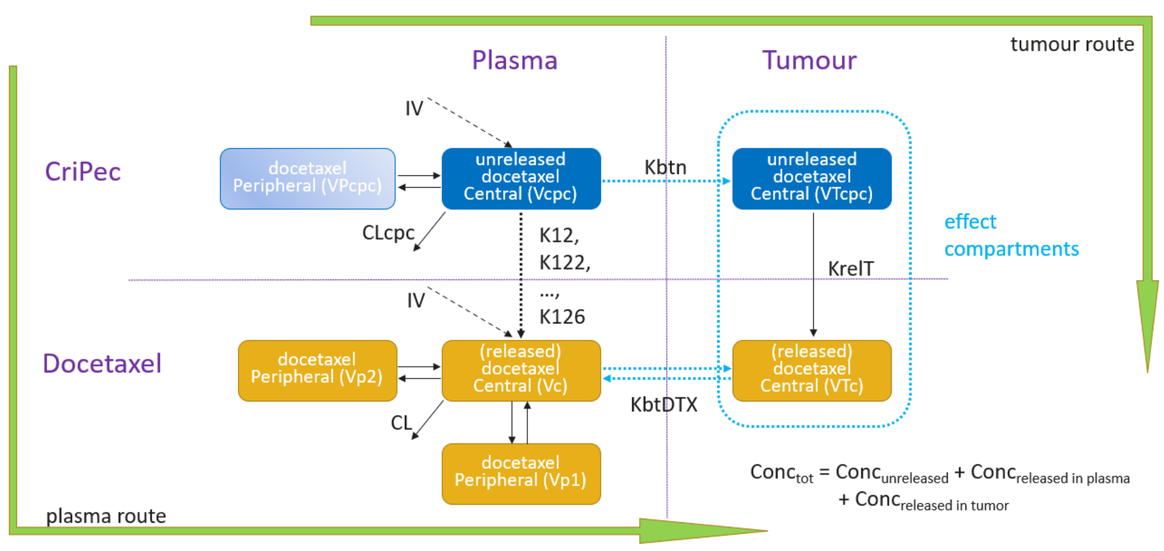

Figure 1 Schematic Plasma-Tumor *DTX-CPC model*. Upper part describes PK of CPC634 in plasma (left-hand side) and tumour (right-hand side). Lower part describes PK of docetaxel in plasma (left-hand side) and tumour (right-hand side). Concentrations of docetaxel in tissue originate from the plasma and the tumour route.

Results

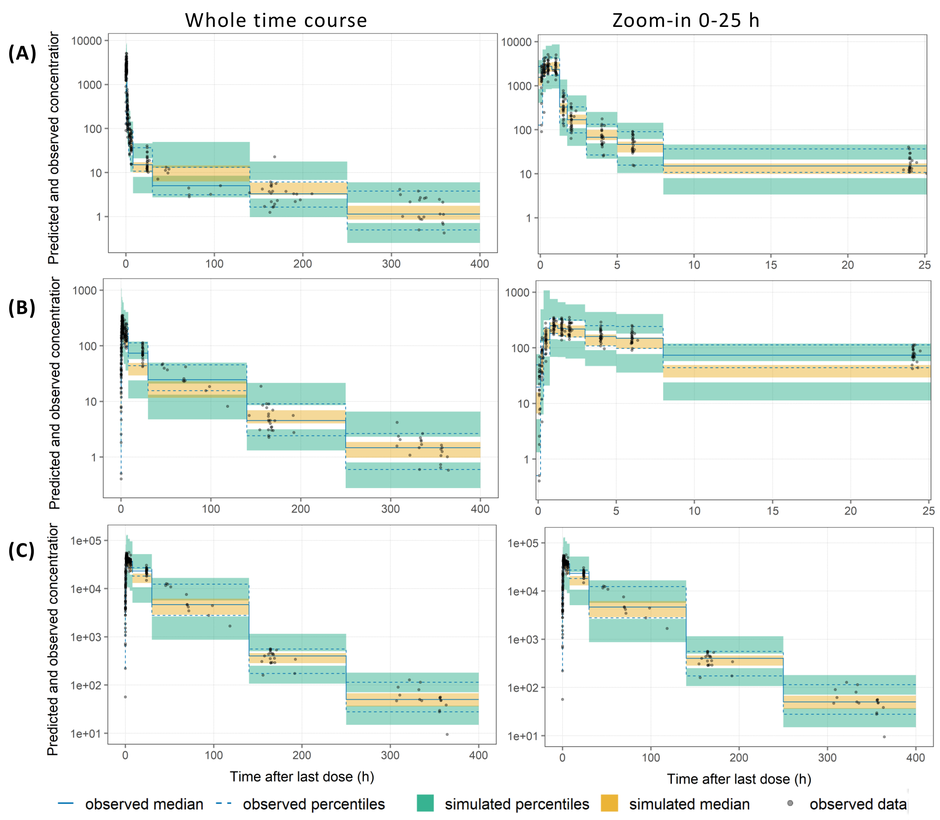

Figure 2 VPCs for (A) generic, (B) released, and (C) unreleased docetaxel concentrations (ng/mL) in plasma.

- The integrated plasma-tumour *DTX-CPC model* (Fig. 1) adequately described the disposition of generic DTX (Fig. 2A) (CL = 26.9 L/h, Vc = 7.18 L), and released (Fig. 2B) and unreleased (Fig. 2C) DTX in plasma after administration of CPC634 and higher dose levels of [89Zr]-Df-CriPec (CLcpc = 0.0229 L/h, Vcpc = 3.44 L).
- Some remaining bias can be seen at time points around 24 and 168 h, which indicates that PK of DTX and CPC634 might exhibit more complex behaviour (e.g., Hooker et al. [3]).

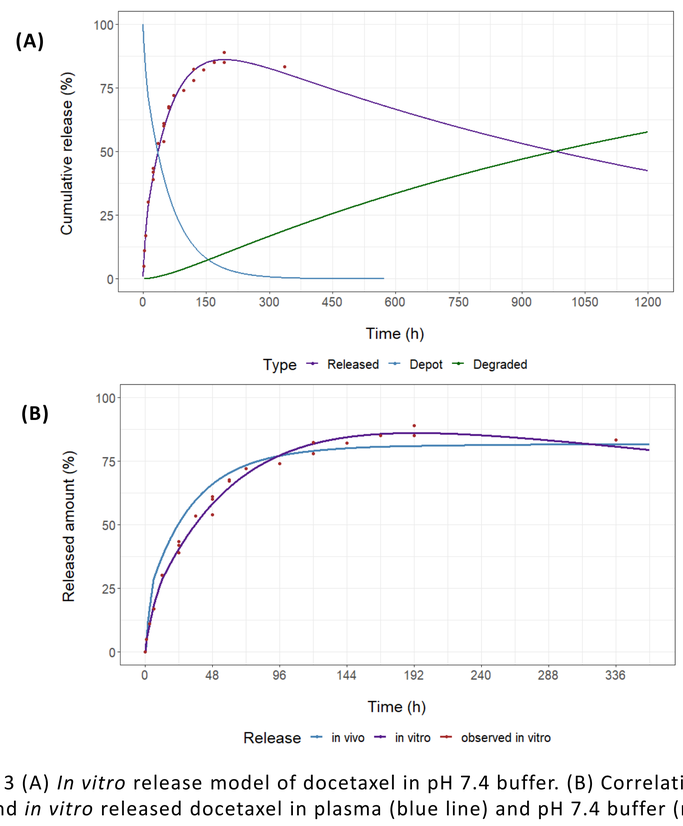

Figure 3 (A) *In vitro* release model of docetaxel in pH 7.4 buffer. (B) Correlation between *in vivo* and *in vitro* released docetaxel in plasma (blue line) and pH 7.4 buffer (red), respectively.

- *In vitro*, around 95% of DTX was released from the nanoparticles after 192 h (Fig. 3A). The Predicted *in vivo* and *in vitro* cumulative release profiles were similar based on visual comparison (Figure 3B).
- In tumour, the PK of docetaxel was adequately described by two effect tumour compartments for unreleased and released docetaxel, connected by a linear release rate constant.
  - IVIVC of the release in tumour was further assessed by Rietveld et al. [4].

Conclusion

- Released and unreleased docetaxel after IV administration of generic docetaxel, CPC634 and [89Zr]-Df-CPC634 were adequately described by an integrated plasma-tumour *DTX-CPC model* with time-dependent release rates and linear distribution and elimination.
- *In vitro* release of docetaxel was adequately described by a one compartment model with a first order degradation and simplified time dependent release process. Predicted *in vitro* and *in vivo* cumulative release were similar, indicating that the *in vitro* release at pH 7.4 buffer is predictive for *in vivo* release of docetaxel in plasma.

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[2] Miedema et al. First-in-human imaging of nanoparticle entrapped docetaxel (CPC634) in patients with advanced solid tumors using 89Zr-Df-CPC634 PET/CT. Journal of Clinical Oncology, Volume 37, Number 15_suppl,2019.
[3] Hooker et al. Population pharmacokinetic model for docetaxel in patients with varying degrees of liver function: Incorporating cytochrome P450 3A activity measurements. Clinical Pharmacology & Therapeutics, 2008; 84: 111-118.
[4] Rietveld et al. The effect of pH on intratumoural docetaxel release from polymeric nanoparticle CPC634. PAGE 2024 - Rome, Italy.