The effect of pH on intratumoural docetaxel release from polymeric nanoparticle CPC634

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INTRODUCTION

- Docetaxel (DTX) is a widely used anti-mitotic chemotherapeutic agent
- Docetaxel has a high inter-patient variability
- Nanocarrier systems may improve DTX delivery
- CPC634 is a polymeric nanoparticle containing DTX temporarily covalently bound to core-cross linked polymeric micelles via a biodegradable linker
- DTX is released via a pH-responsive ester sulfone linker

MATERIALS & METHODS

- Combined PK data from NAPOLY, CRITAX, and PICCOLO studies.
- NAPOLY (n=23): Phase I dose escalation study with CPC634 [1]
- CRITAX Study (n=24): tumor uptake of CPC634 via invasive biopsies [2]
- PICCOLO Study (n=5): radiolabelled zirconium-89-desferal CPC634 for non-invasive tumor accumulation imaging [3]
- In vitro release studies: examined release of CPC634 across pH values (5, 6, 6.5, 7, 7.4)
- NONMEM v7.5 with FO estimation for pH-specific models and FOCE+I for concentration-time data analysis
- The population PK model was based on a combined plasma-tumour model for released and unreleased DTX by Zeiser S. et al [4].

PK Measurements	NAPOLY (n=23)	CRITAX (n=24)	PICCOLO (n=5)
Plasma			
Total	455	255	
Released	463	271	
Conventional		270	
Zr-Df-Cripec			51
Tumor			
Total		24	
Released		24	
Conventional		24	
Zr-Df-Cripec			39

AIM

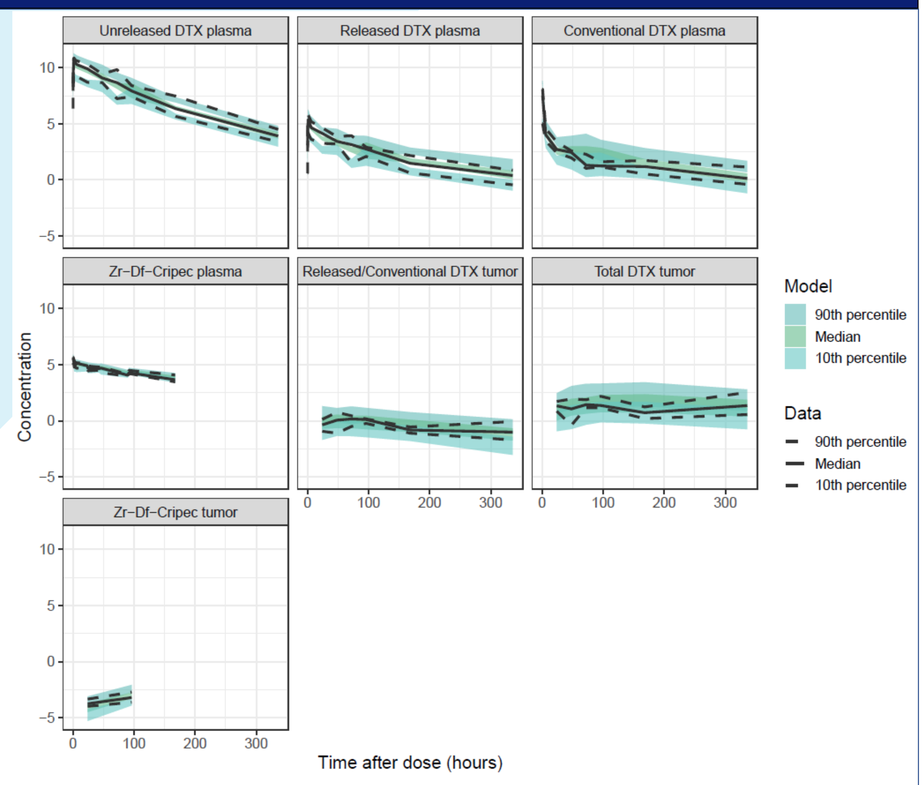
- **Predict intratumoral PK of CPC634**
- **Assess the impact of pH on DTX release from CPC634**

CONCLUSION

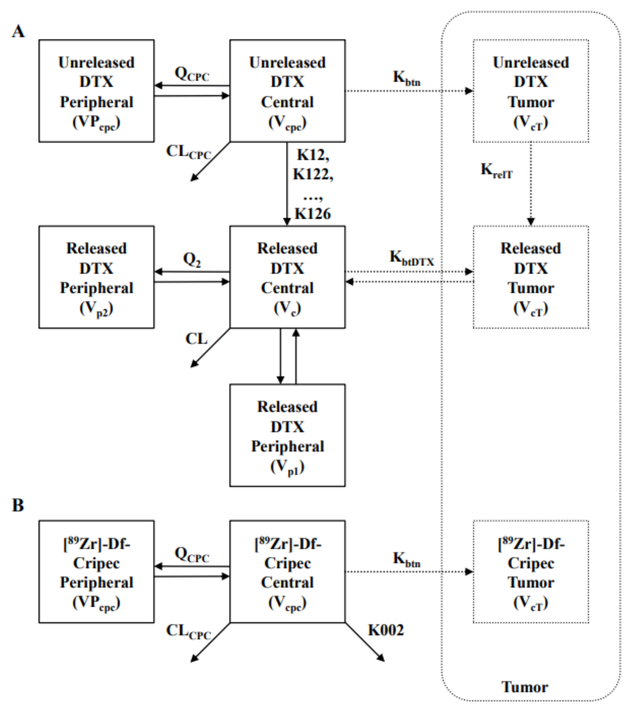
- DTX release from CPC634 increases at higher pH as predicted by the in vitro model
- In vivo release: low release rate within the tumor. Indicates a pH between 5 and 6

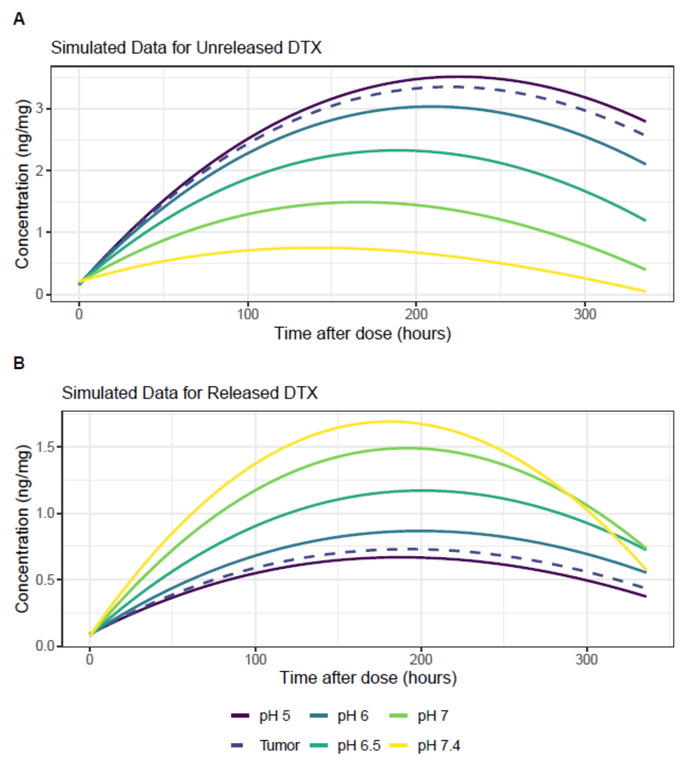
RESULTS

- PopPK Model: Described PK of total, released, and unreleased DTX in plasma and tumor tissue
- pH-dependent in vitro release rates: Increased release rates with higher pH, from 0.9610^-3 h^-1 at pH 5 to 16.910^-3 h^-1 at pH 7.4
- Tumor release rate estimated at 1.29 *10^-3 h^-1, corresponding to a pH between 5 and 6



Visual Predictive Check for various forms of DTX (unreleased, released, conventional, total, and Zr−Df−Cripec) in plasma and tumor tissue. Plasma concentrations are presented as log(ng/ml), and tumor tissue concentrations as log(ng/mg).





In vivo simulation of unreleased (A) and released (B) DTX concentrations in tumor tissue, based on in vitro release rates and estimated release in vivo

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