DEVELOPMENT OF A TUMOUR GROWTH INHIBITION MODEL TO ELUCIDATE THE EFFECTS OF RITONAVIR ON INTRATUMOURAL METABOLISM AND ANTI-TUMOUR EFFECT OF DOCETAXEL IN A MOUSE MODEL FOR HEREDITARY BREAST CANCER

Huixin Yu, Jeroen J.M.A. Hendrikx, Alfred H. Schinkel, Sven Rottenberg, Jan H.M. Schellens, Jos H. Beijnen, Alwin D.R. Huitema

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Docetaxel (DOC)

- An anticancer agent for several types of cancer, such as lung, breast, gastric and prostate cancer
- It acts by the inhibition of cell mitosis
- Oral ingestion of docetaxel increases convenience for patients comparing to intravenous administration
- One major limitation for oral docetaxel is its low bioavailability due to its affinity for P-glycoprotein (Pgp) and Cytochrome P450 (CYP) 3A

Docetaxel (DOC)

- An anticancer agent for several types of cancer, such as lung, breast, gastric and prostate cancer
- It acts by the inhibition of cell mitosis
- Oral ingestion of docetaxel increases convenience for patients comparing to intravenous administration
- One major limitation for oral docetaxel is its low bioavailability due to its affinity for P-glycoprotein (Pgp) and Cytochrome P450 (CYP) 3A

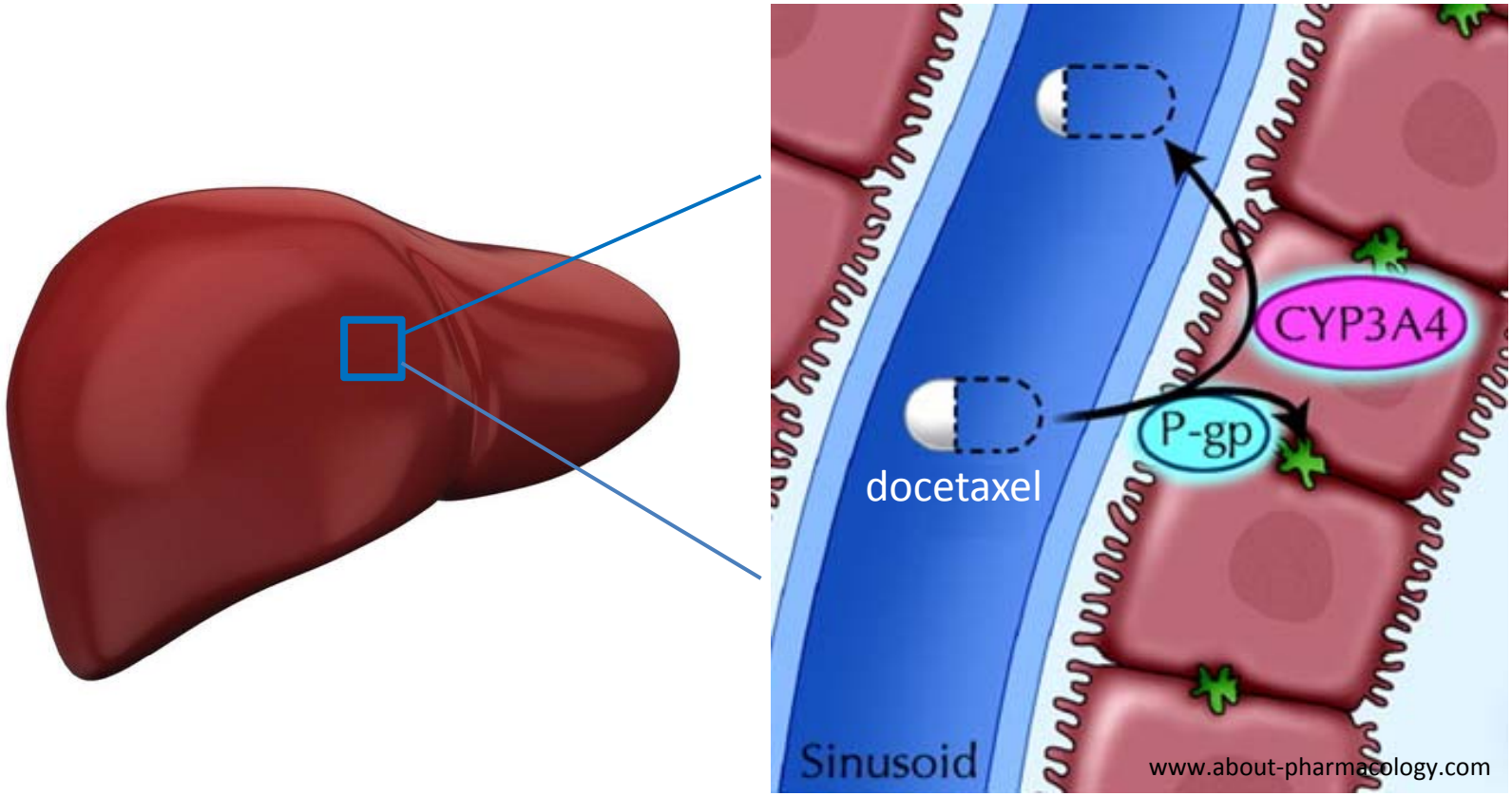
Ritonavir (RTV)

- An HIV protease inhibitor and also a strong CYP3A4 inhibitor
- It has been suggested to have an anti-cancer effect

Gaedicke S et al. Cancer Res. 2002,62(23):6901–8; Kariya R et al.Cancer Lett. 2014,342:52–9; Srirangam A et al. Clin cancer Res. 2006,12(6):1883–96

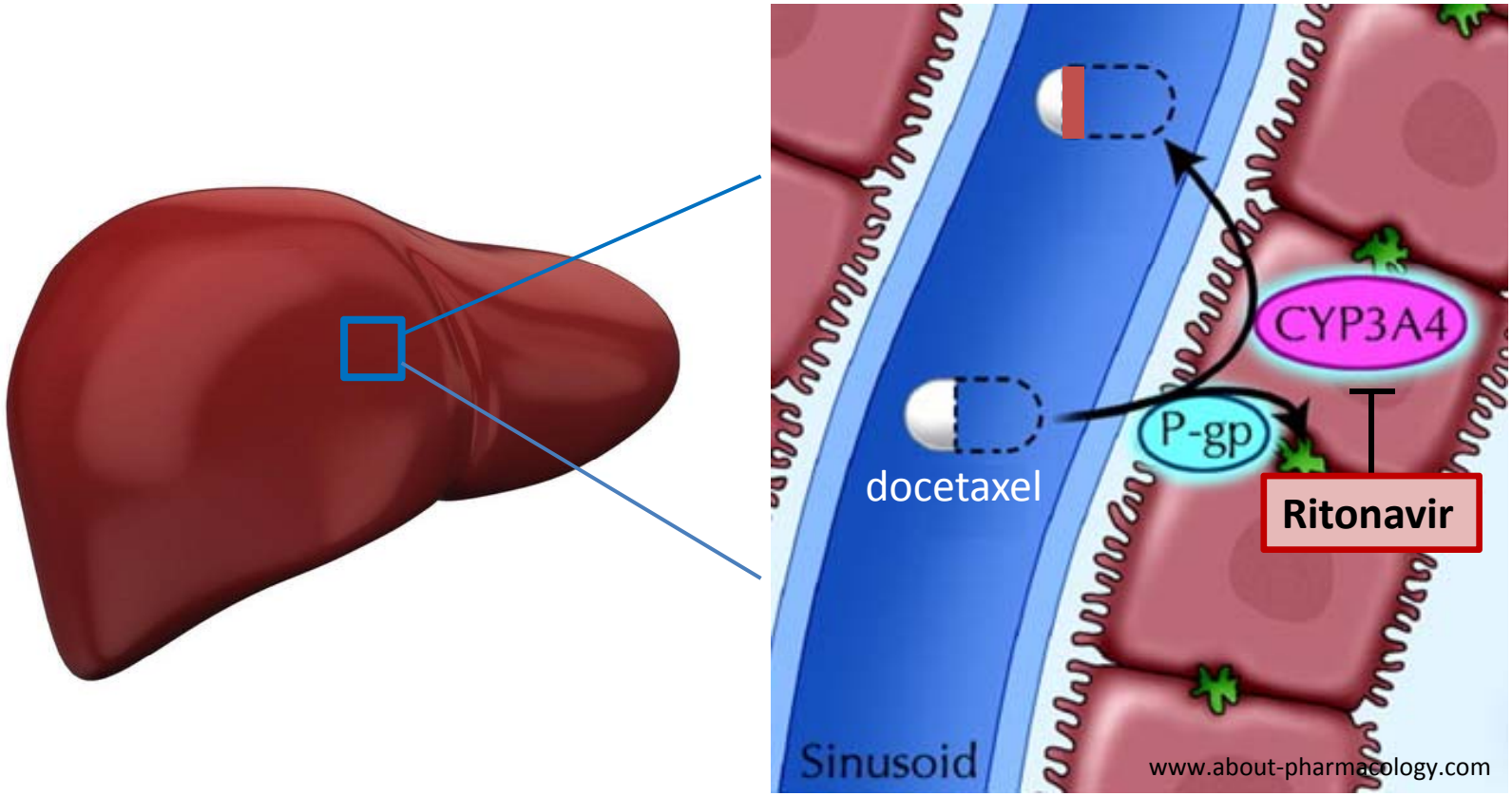
Co-administration of docetaxel and ritonavir

- PK: In both mice and humans, co-administration results in an enhanced docetaxel plasma concentration by CYP3A4 inhibition



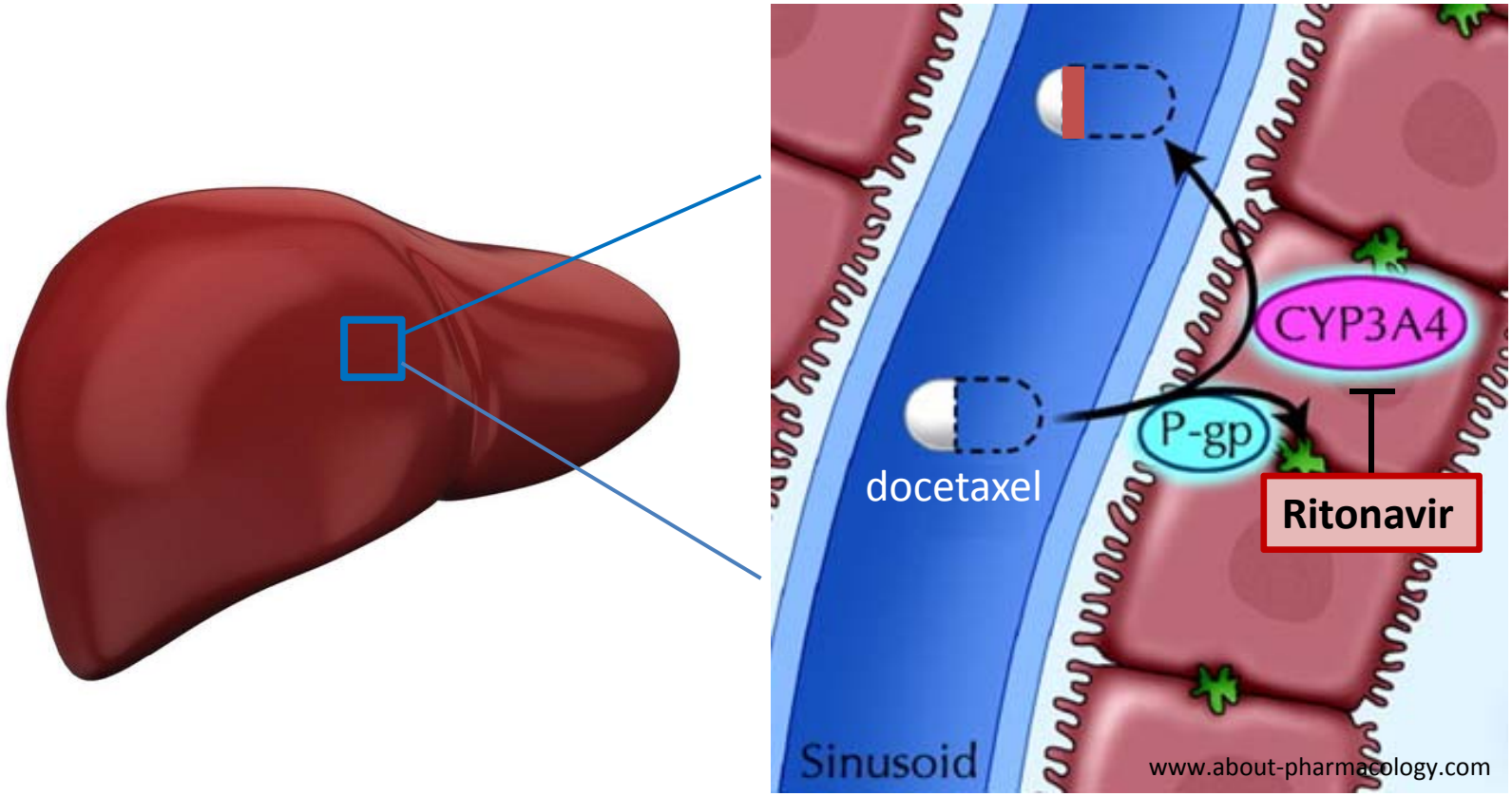
Co-administration of docetaxel and ritonavir

- PK: In both mice and humans, co-administration results in an enhanced docetaxel plasma concentration by CYP3A4 inhibition



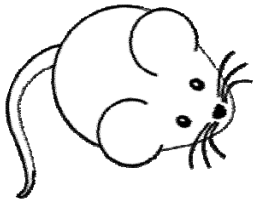
Co-administration of docetaxel and ritonavir

- PK: In both mice and humans, co-administration results in an enhanced docetaxel plasma concentration by CYP3A4 inhibition



- PK: Will ritonavir inhibit docetaxel intratumoural metabolism?
- PD: Will co-administration enhance anticancer effect?

Preclinical experiment – study design



Host: Cyp3a knock-out

+

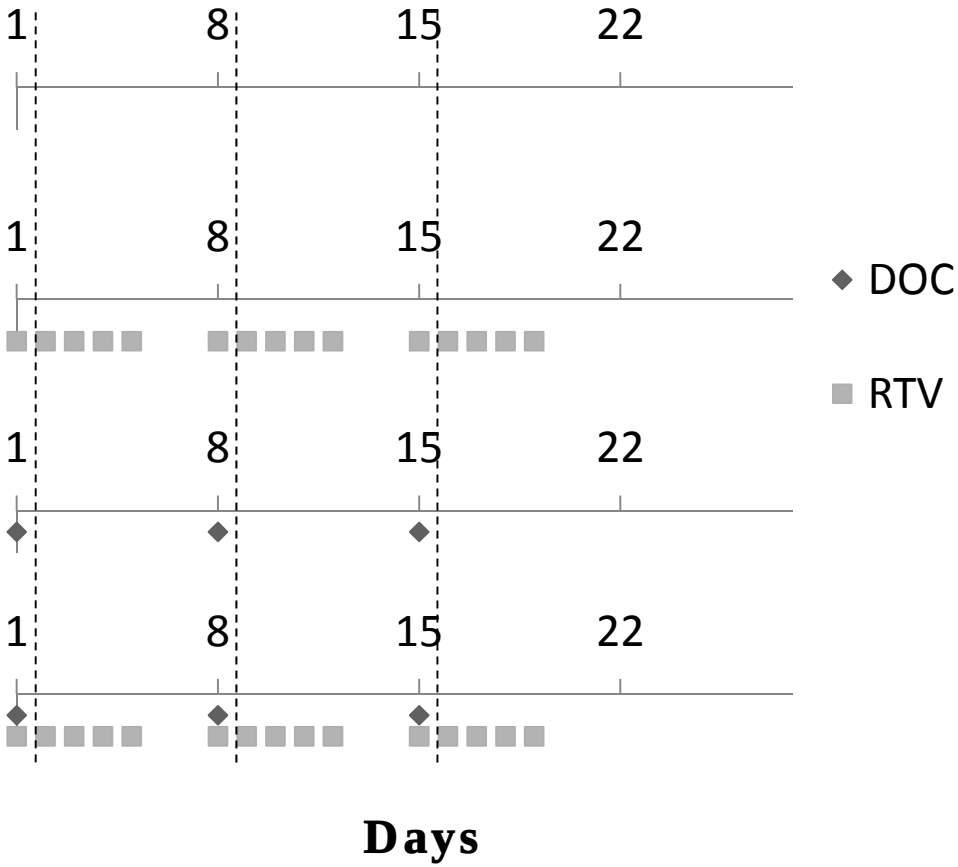
Tumour: inherent Cyp3a expression

Arm1: Control
(n=15)

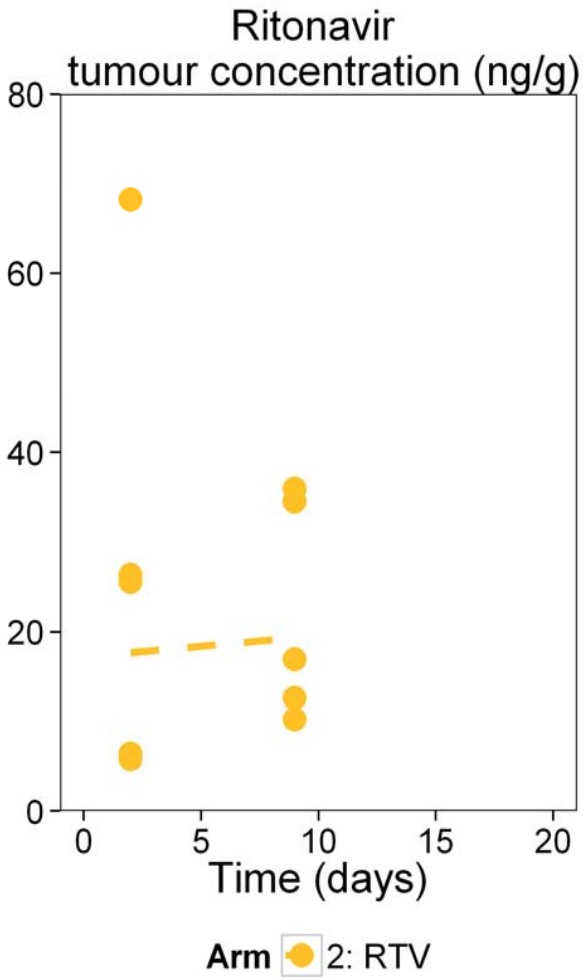
Arm2: RTV (p.o.)
(n=15)

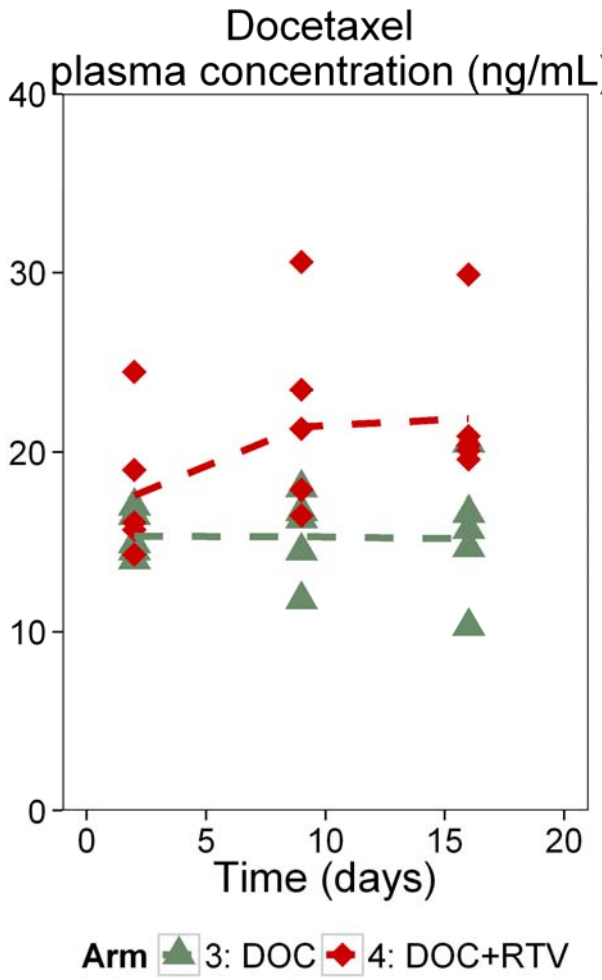
Arm3: DOC (i.v.)
(n=20)

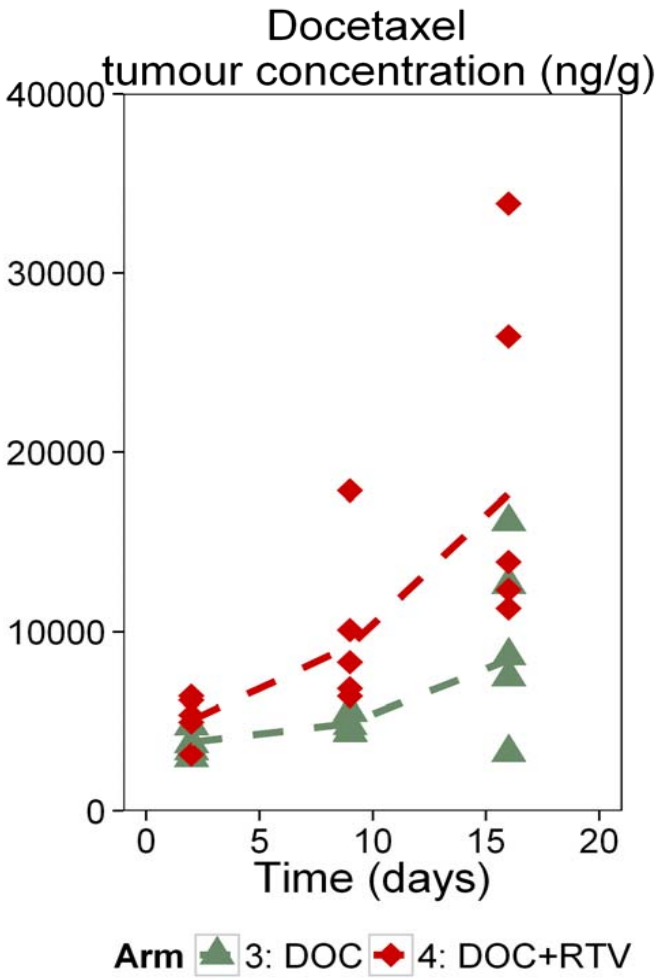
Arm4: DOC+RTV
(n=20)



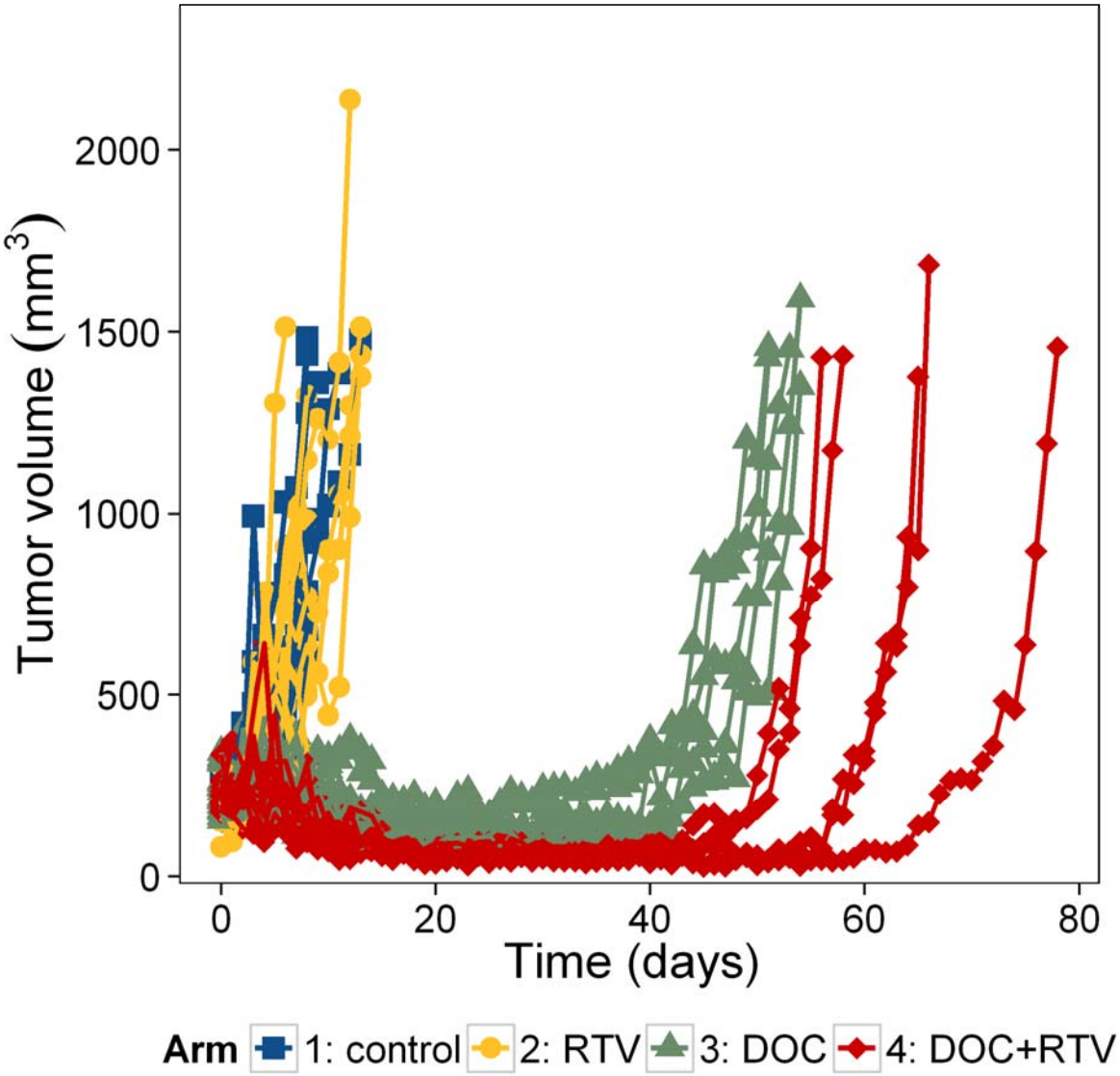
Preclinical experiment – PK data



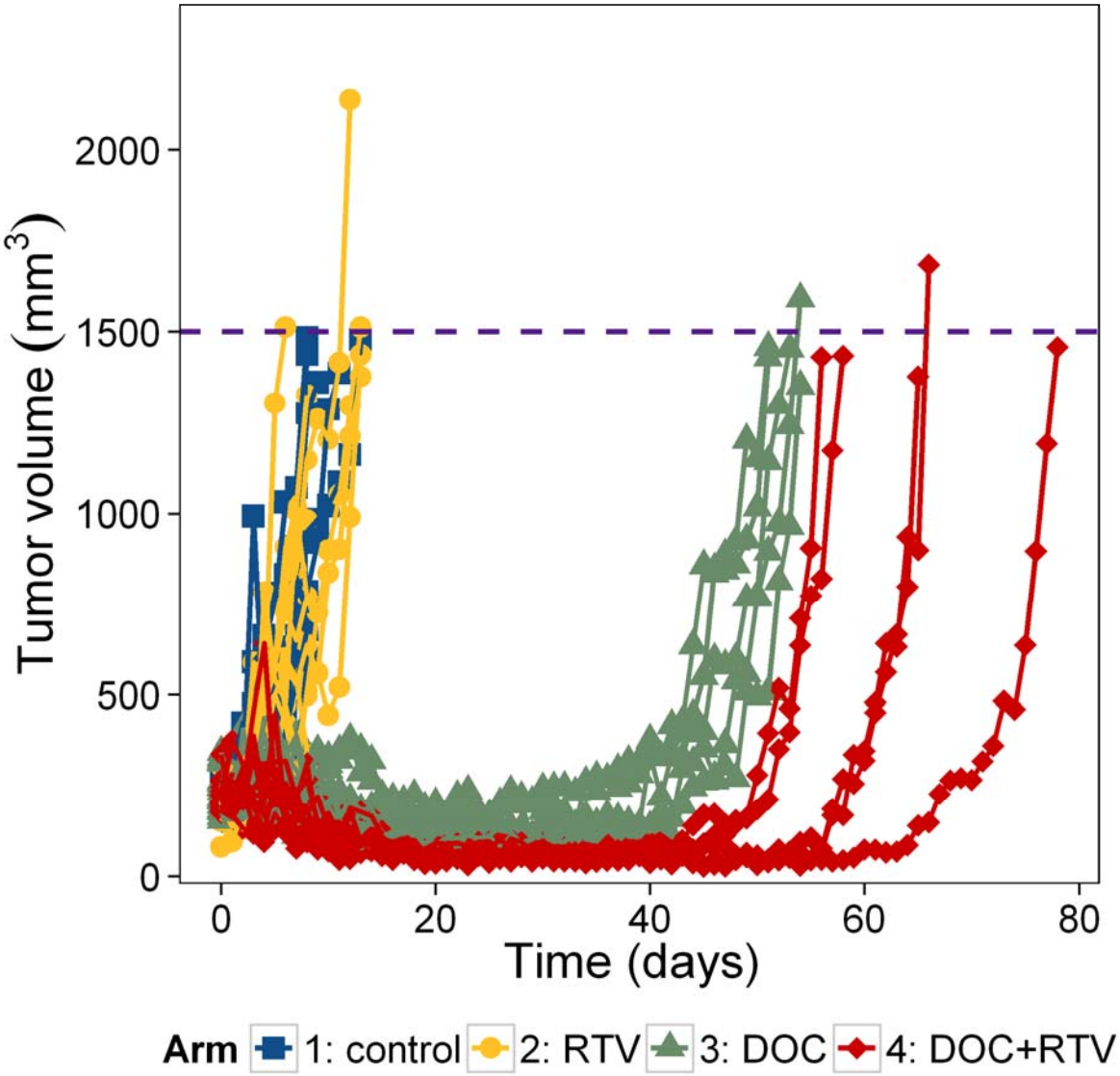




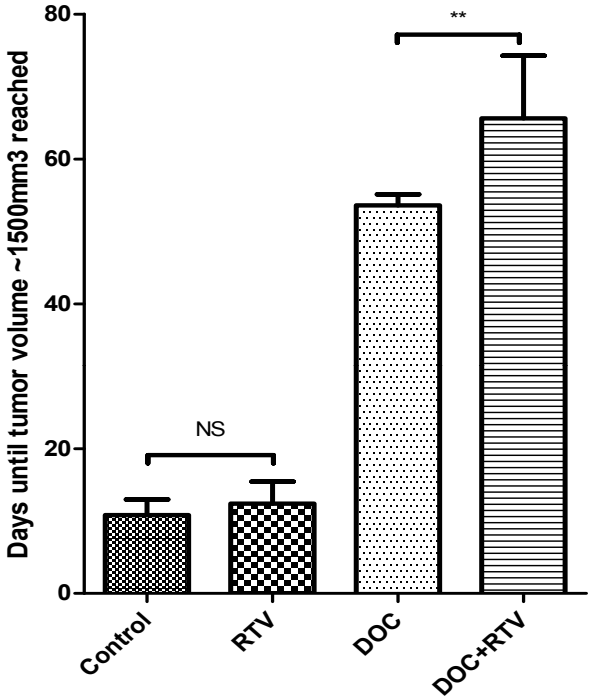
Preclinical experiment – PD data



Preclinical experiment – PD data



Days to reach 1500 mm3



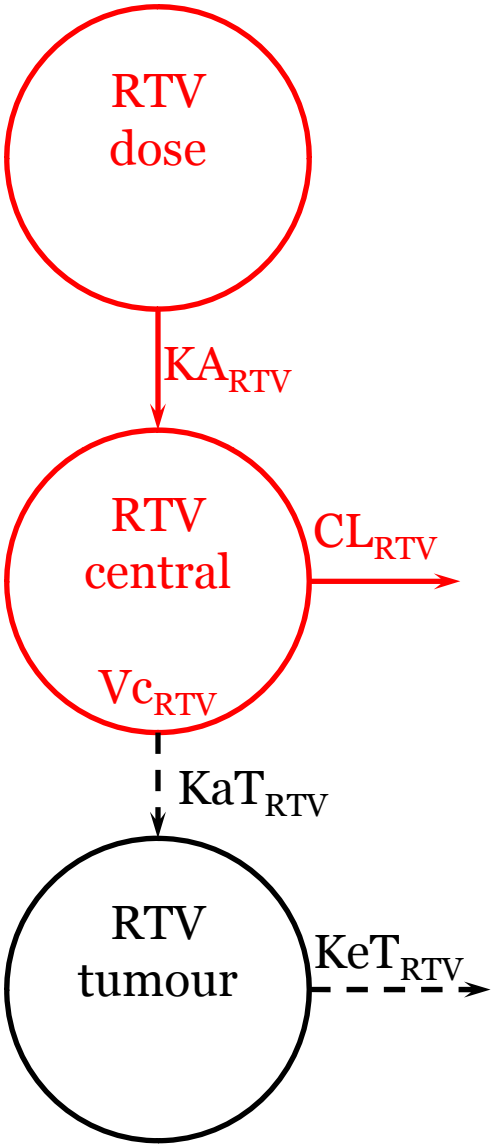
Arm	Median	Mean ± SD
Control	10	10.8 ± 2.2
RTV	14	12.4 ± 3.1
DOC	54	53.6 ± 1.1
DOC+RTV	66	65.6 ± 8.6

Objectives

- To develop a PK- PD model based on docetaxel concentration and tumour sizes from preclinical study

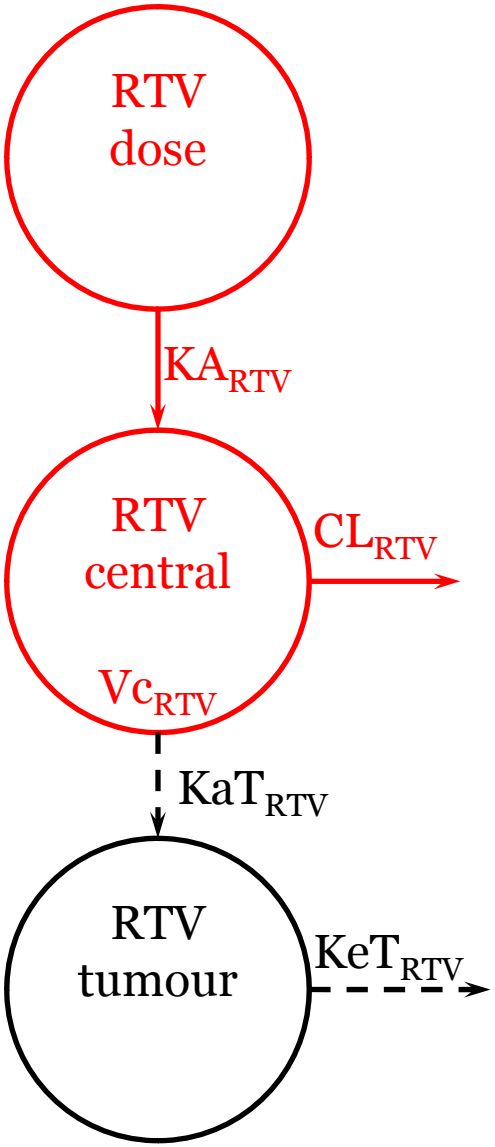
- To further evaluate and quantify the effects of ritonavir on systemic and intratumoral concentration and anti-tumour effects of docetaxel when co-administered

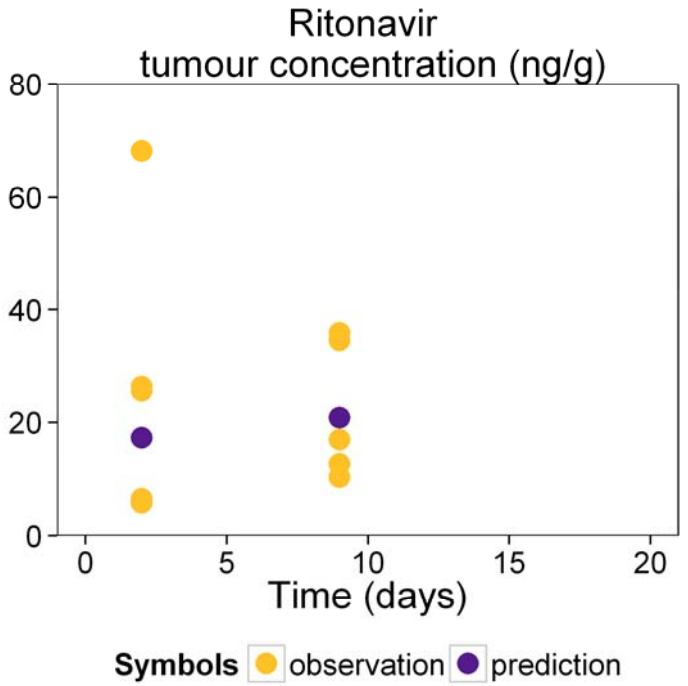
PK model – ritonavir



Koolen SLW, et al. J Clin Pharmacol. 2012,52(3):370–80

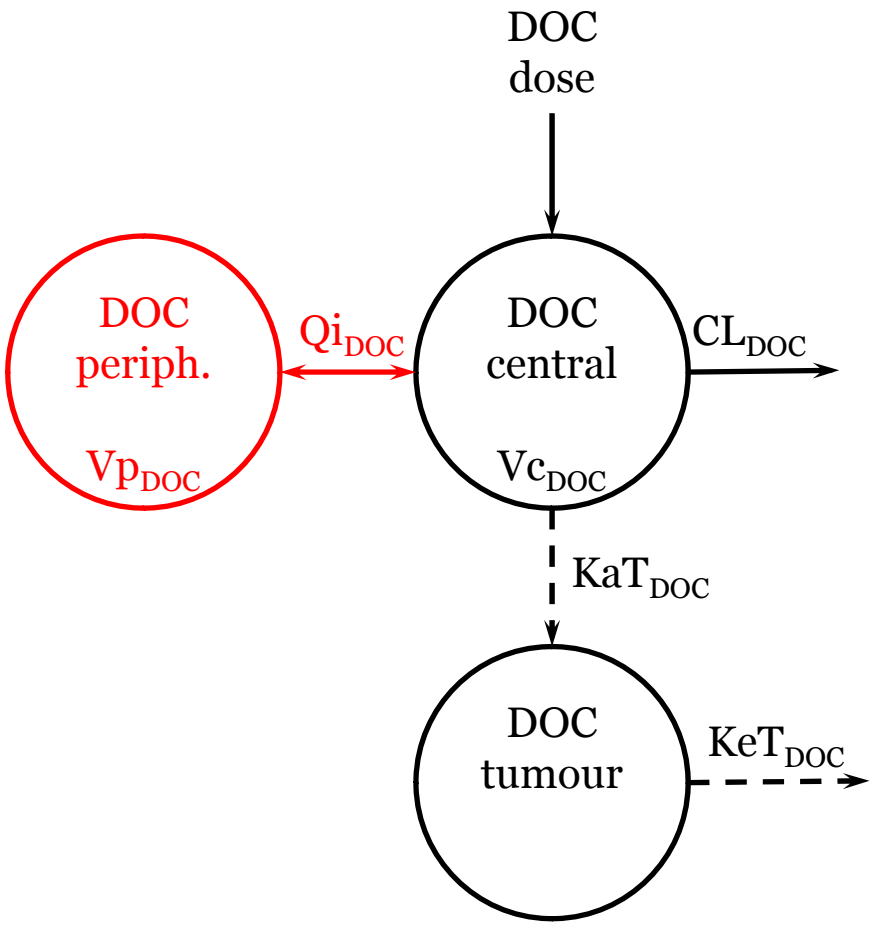
PK model – ritonavir





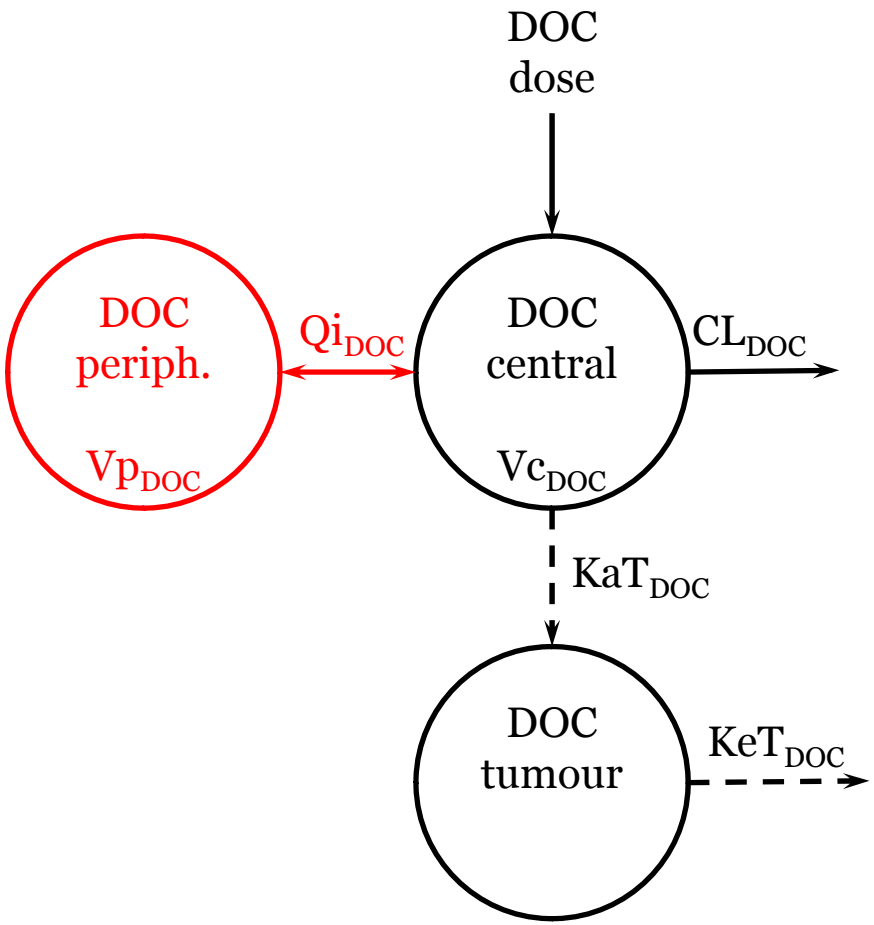
Koolen SLW, et al. J Clin Pharmacol. 2012,52(3):370–80

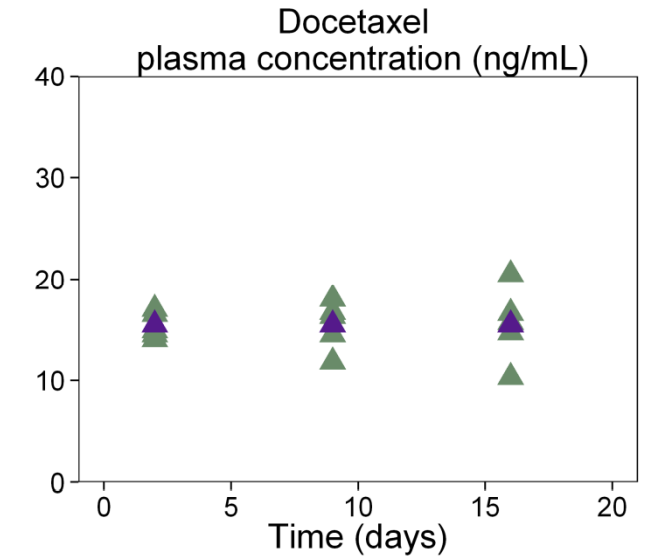
PK model – docetaxel

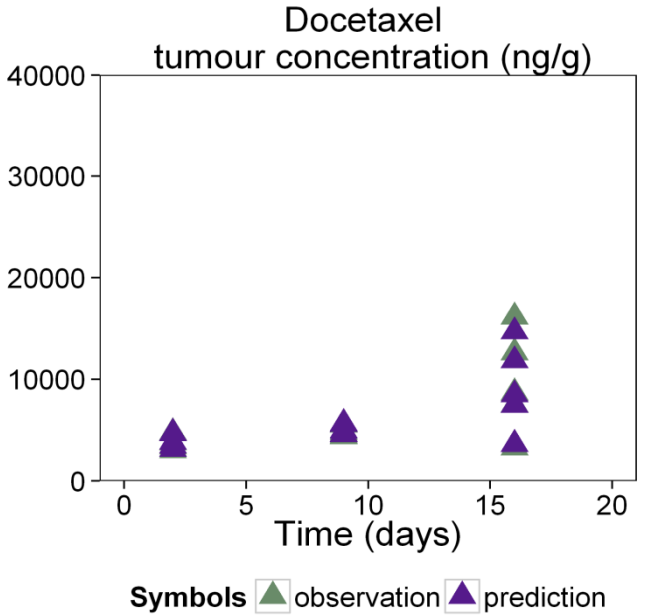


Koolen SLW, et al. J Clin Pharmacol. 2012,52(3):370–80

PK model – docetaxel

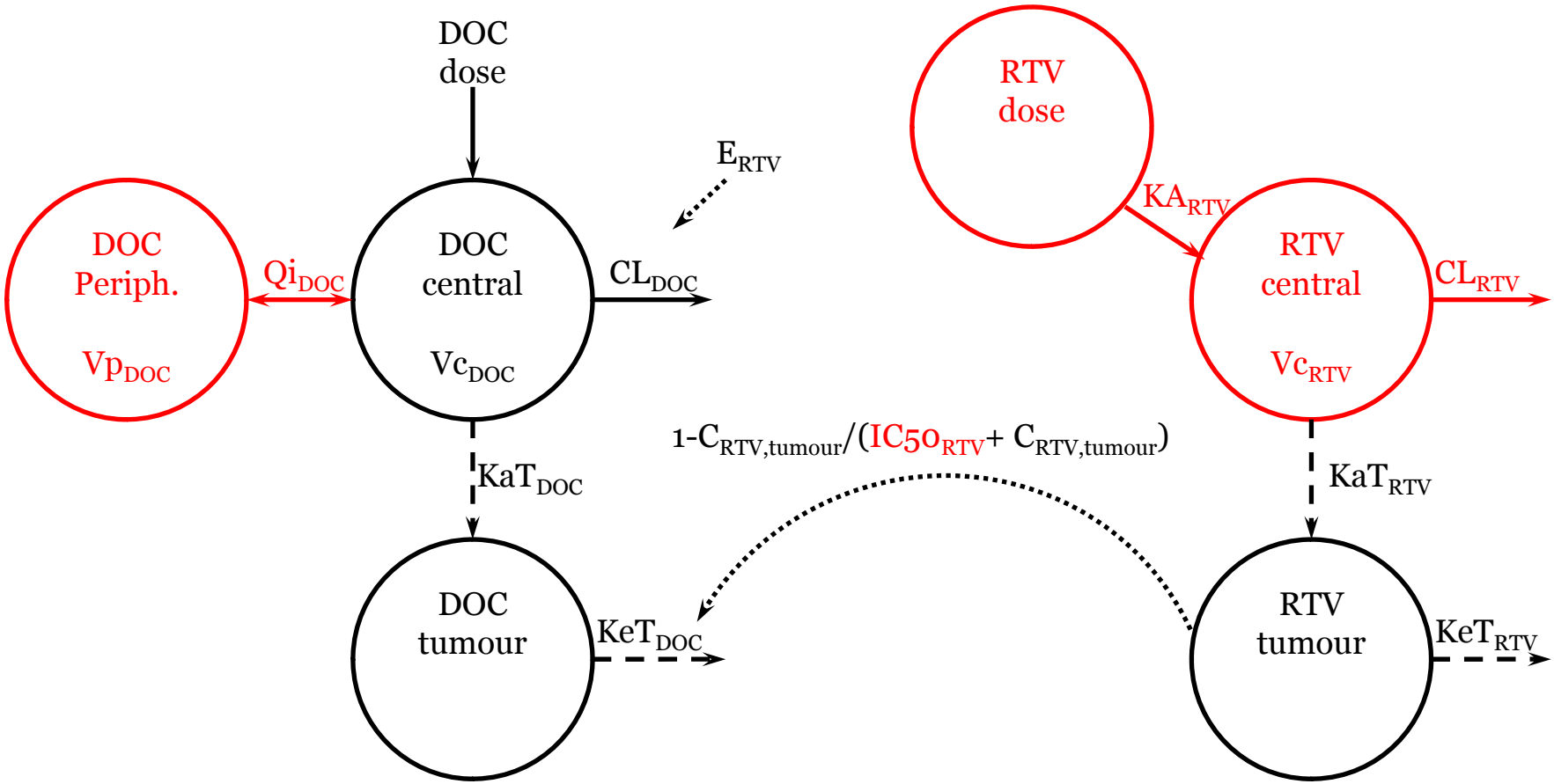






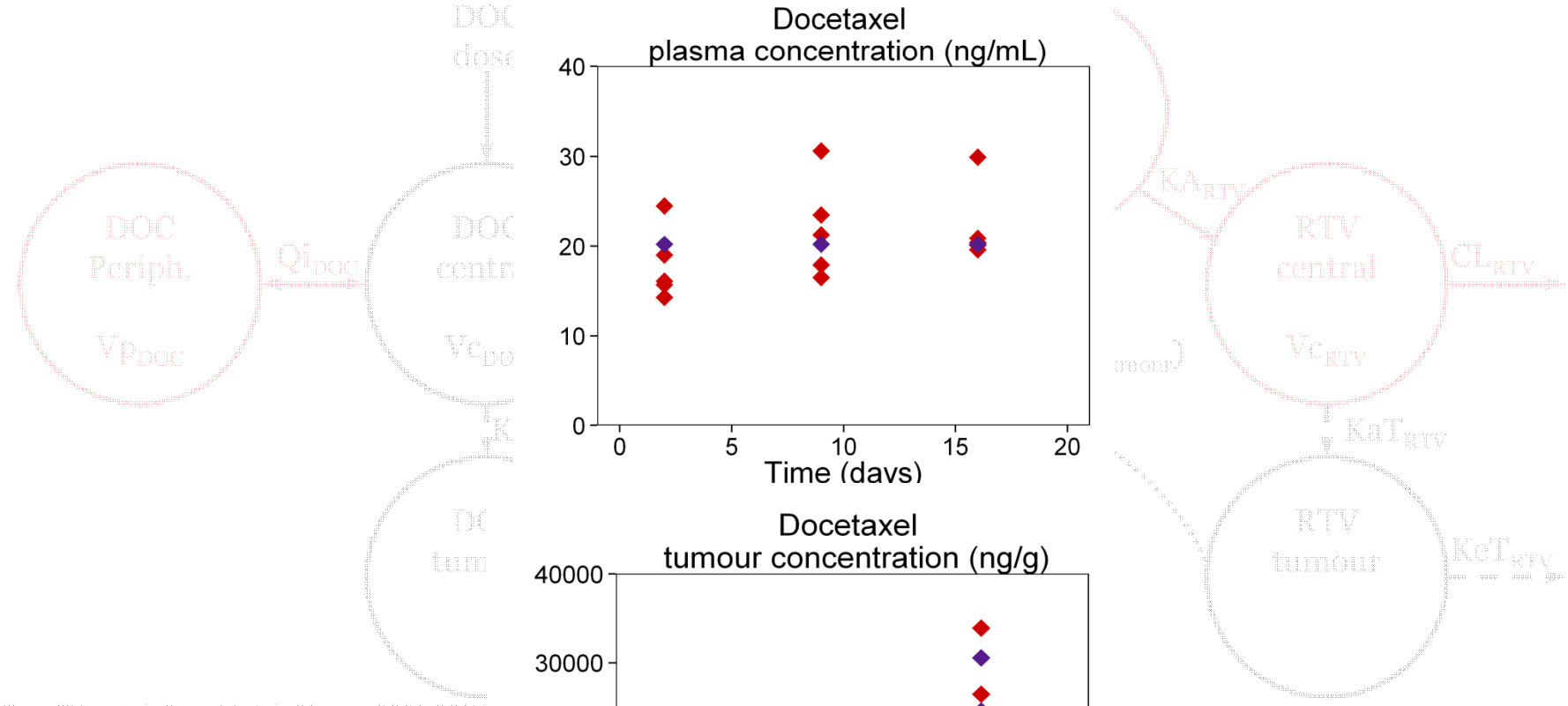
Koolen SLW, et al. J Clin Pharmacol. 2012;52(3):370–80

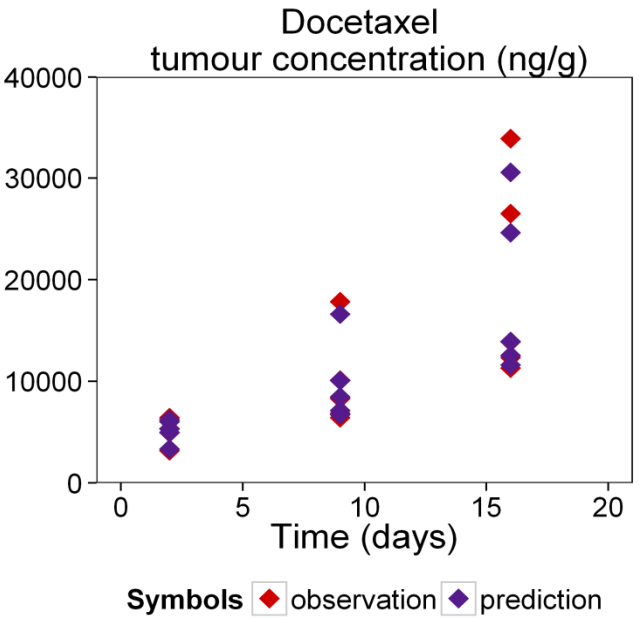
PK model – co-administration of docetaxel and ritonavir



Tran TH, et al. Drug Metab Dispos. 2002,30(12):1441–5

PK model – co-administration of docetaxel and ritonavir



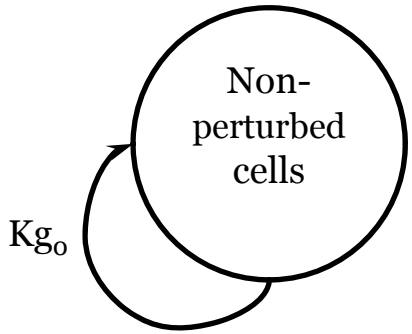


PK model – conclusions

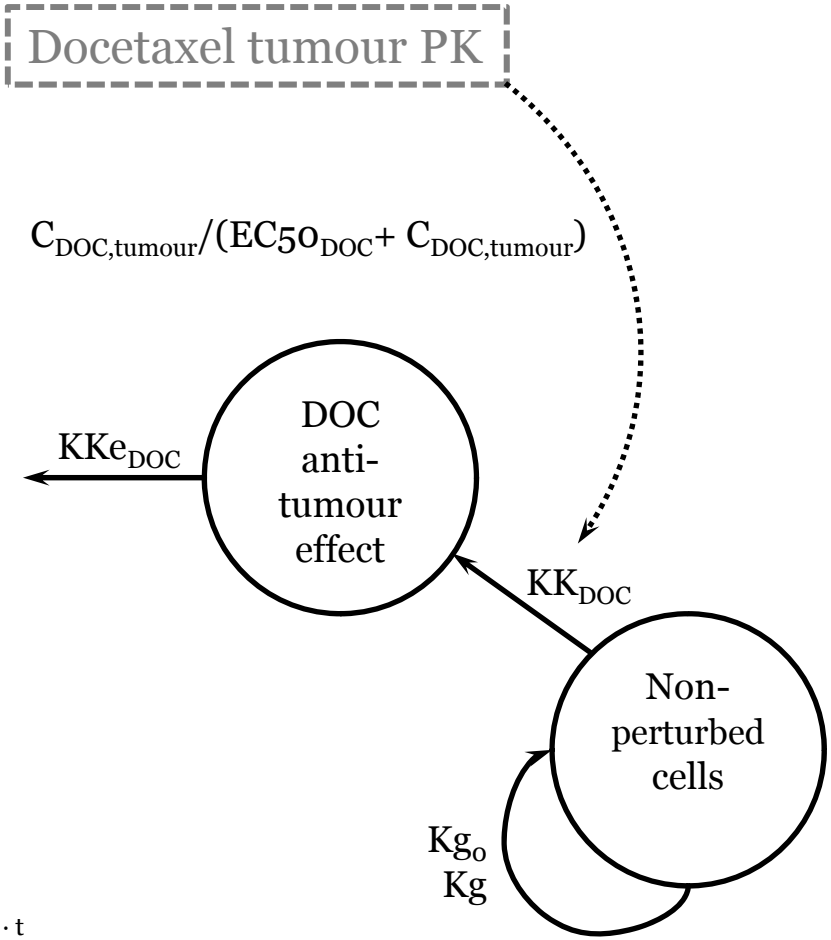
- In Cyp3a knock-out host, ritonavir slightly decreased docetaxel systemic clearance by 8% when co-administered

- In tumour with inherent Cyp3a expression, ritonavir inhibited docetaxel metabolism resulting in docetaxel tumour AUC 2.5-fold higher when co-treated with ritonavir

PK-PD model – Exponential tumour growth model

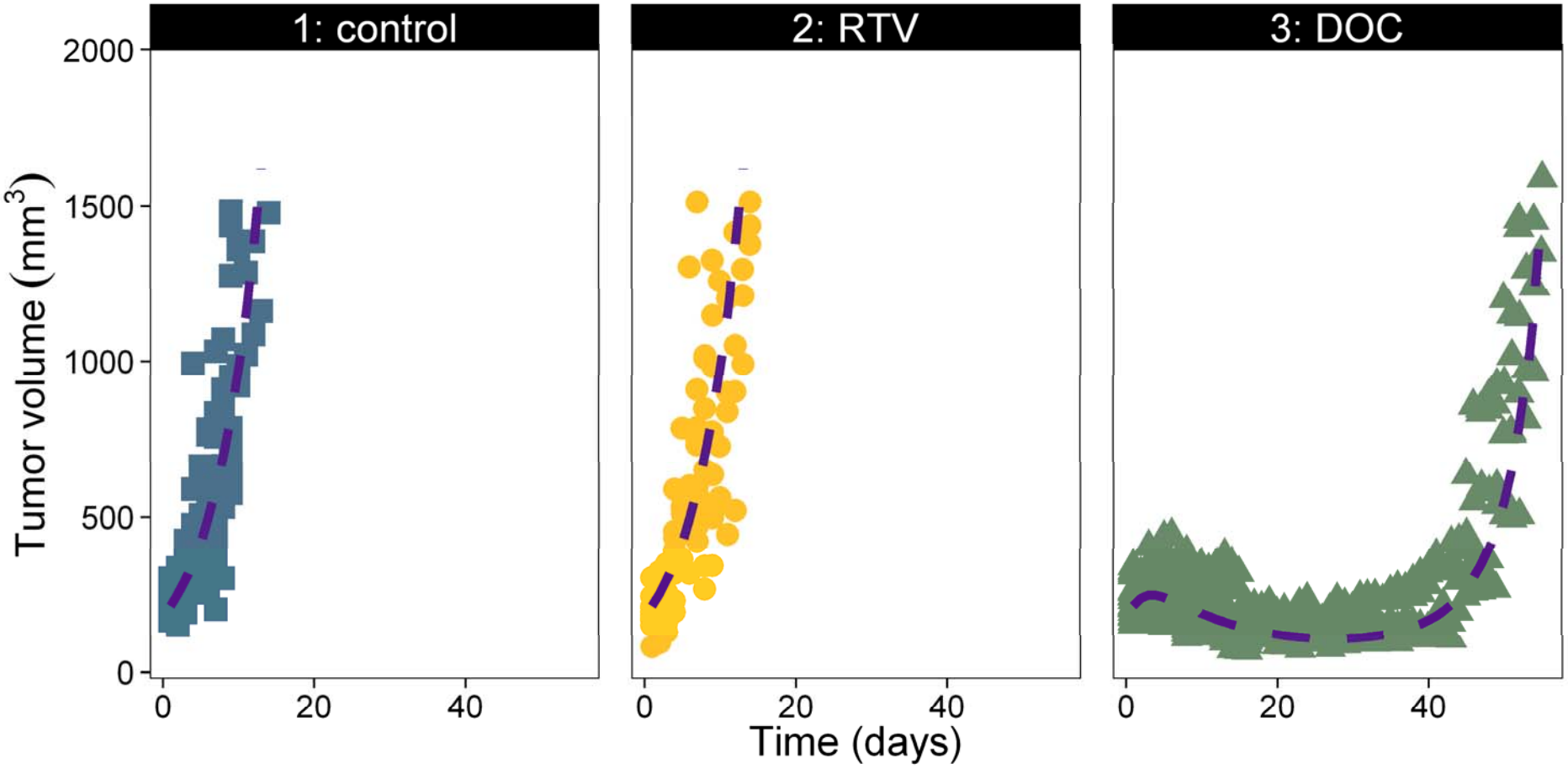


PK-PD model – docetaxel-treated tumour growth inhibition (TGI) model

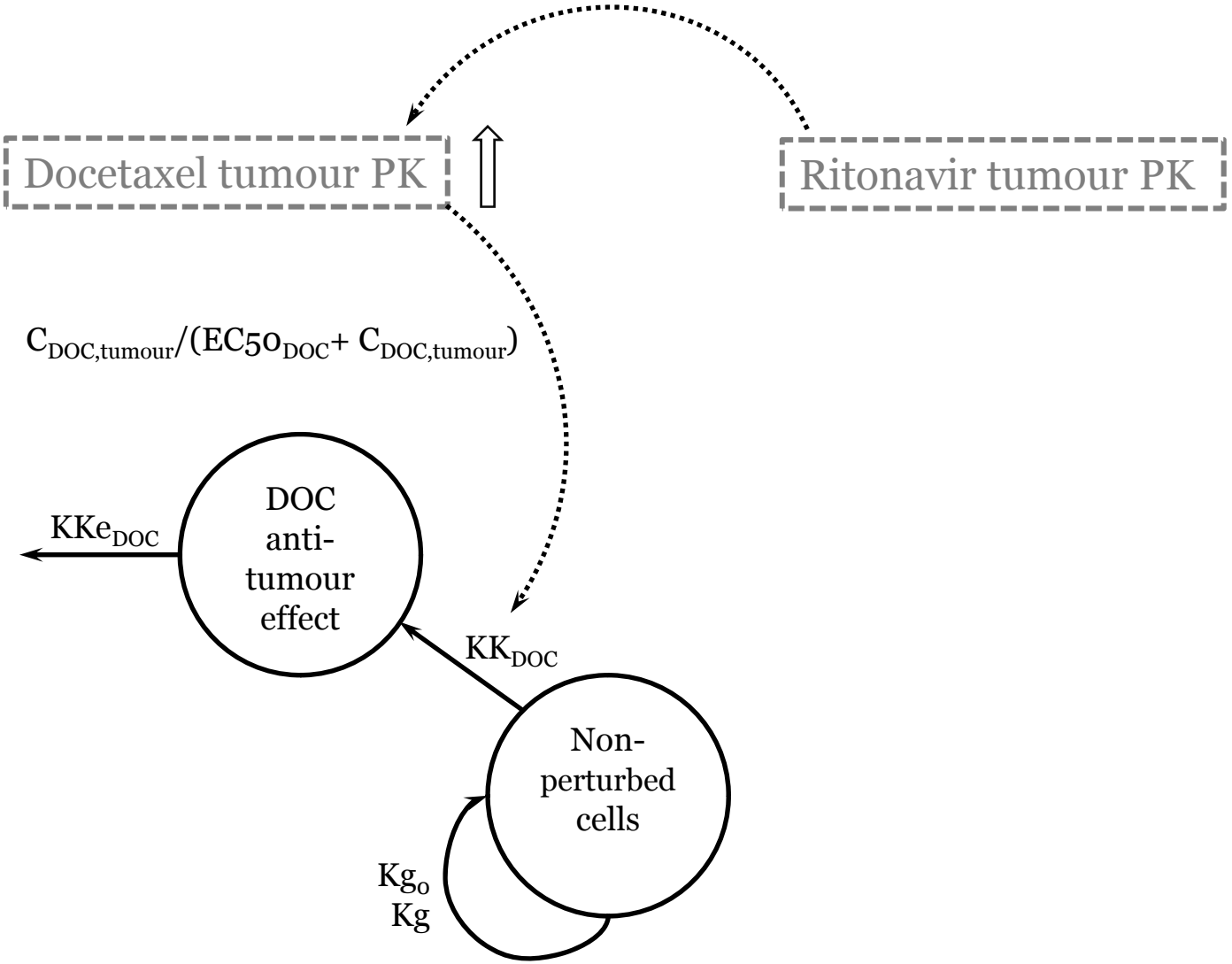


$Kg=Kg_0 \cdot e^{\lambda \cdot t}$
(λ= 0.061 $week^{-1}$)

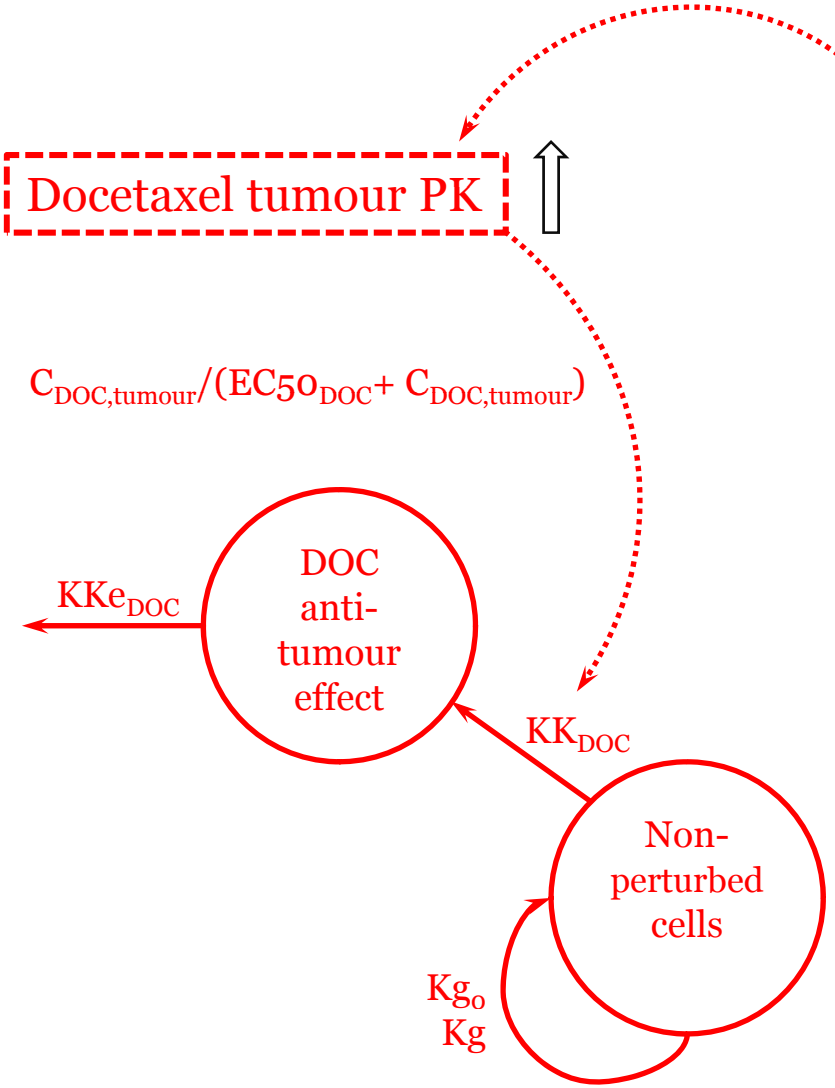
PK-PD model – docetaxel-treated tumour growth inhibition (TGI) model

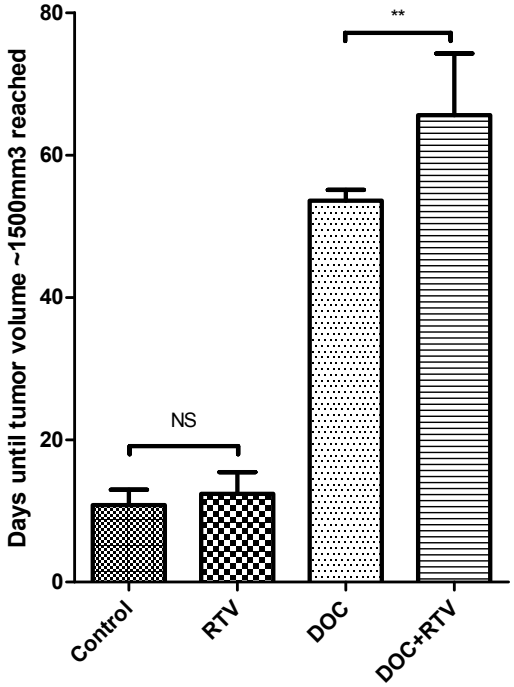


PK-PD model – ritonavir co-treated TGI model

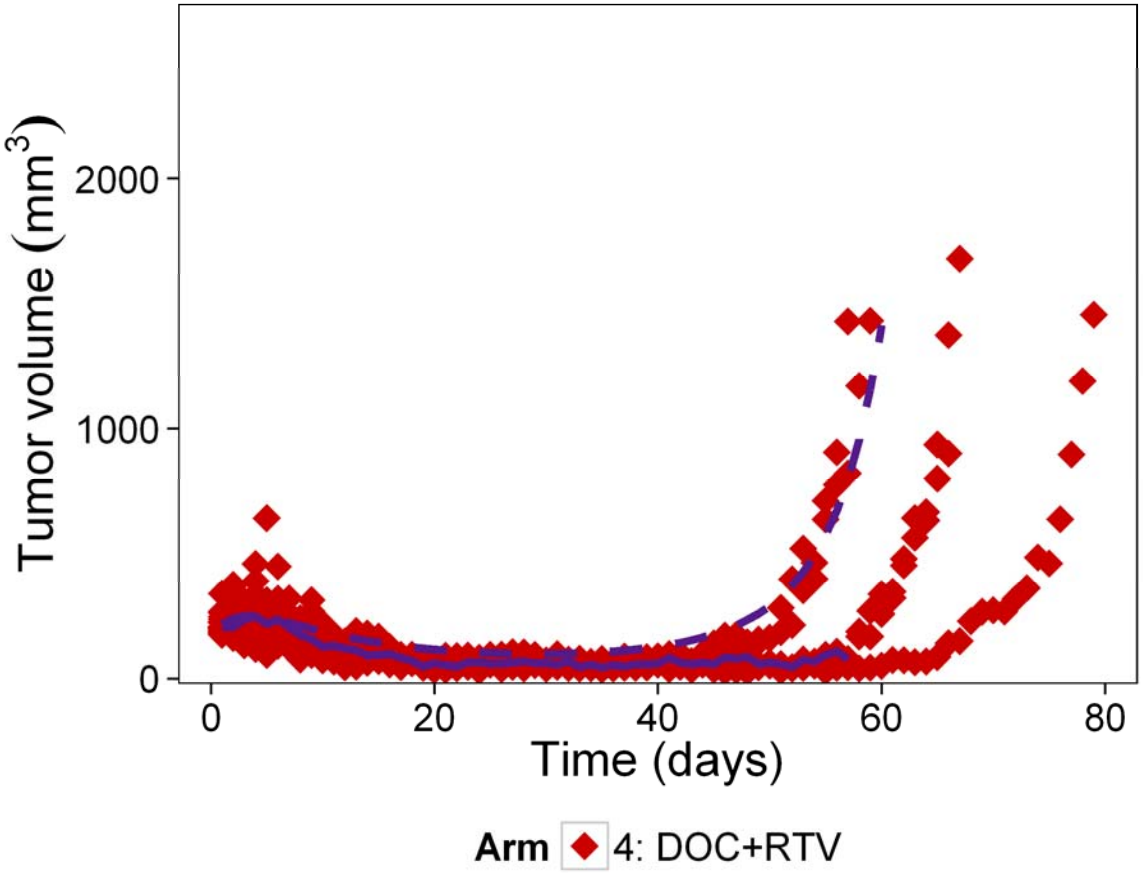


Hypothesis test –TGI model with docetaxel-treated TGI and PK parameters



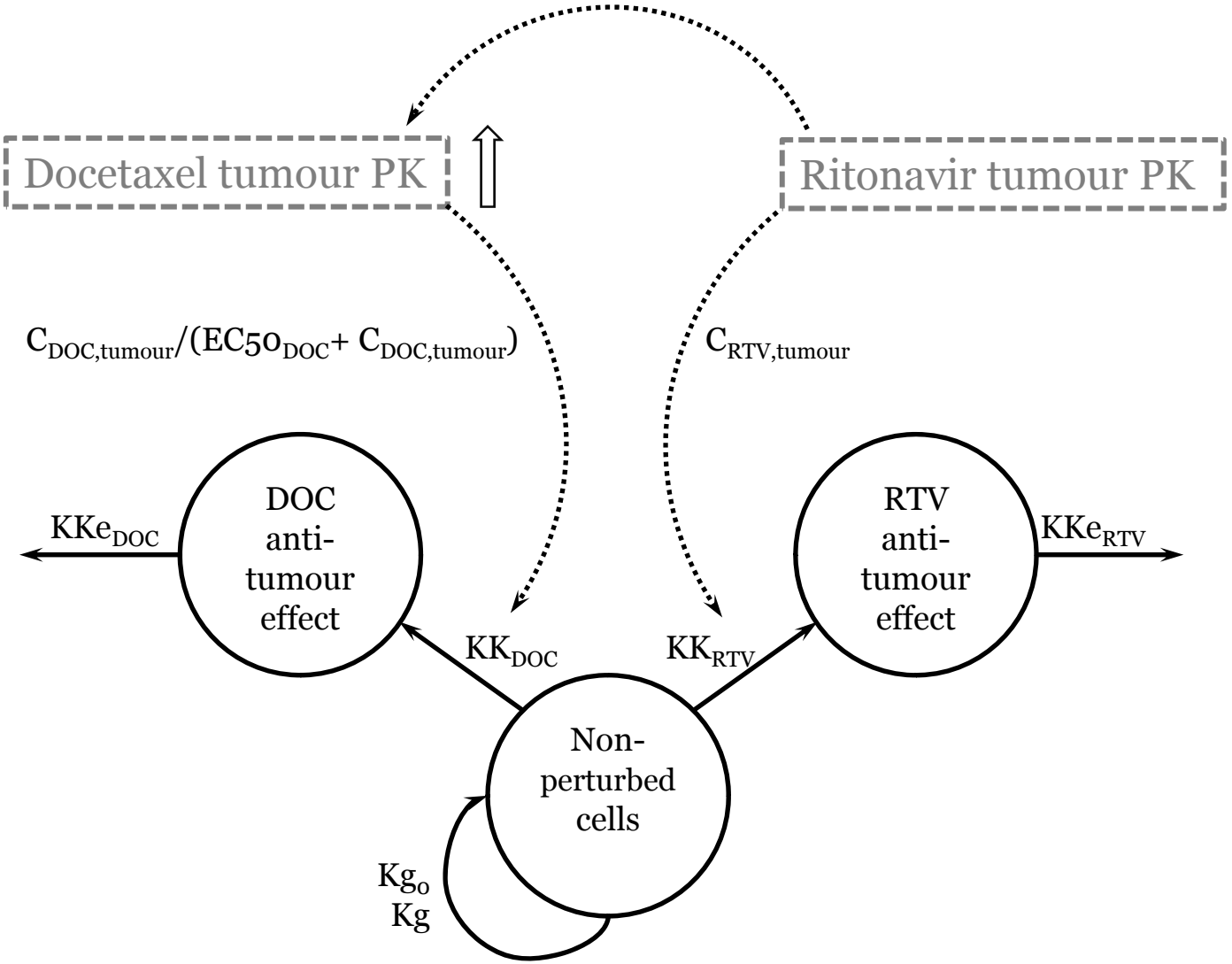


Hypothesis test –TGI model with docetaxel-treated TGI and PK parameters

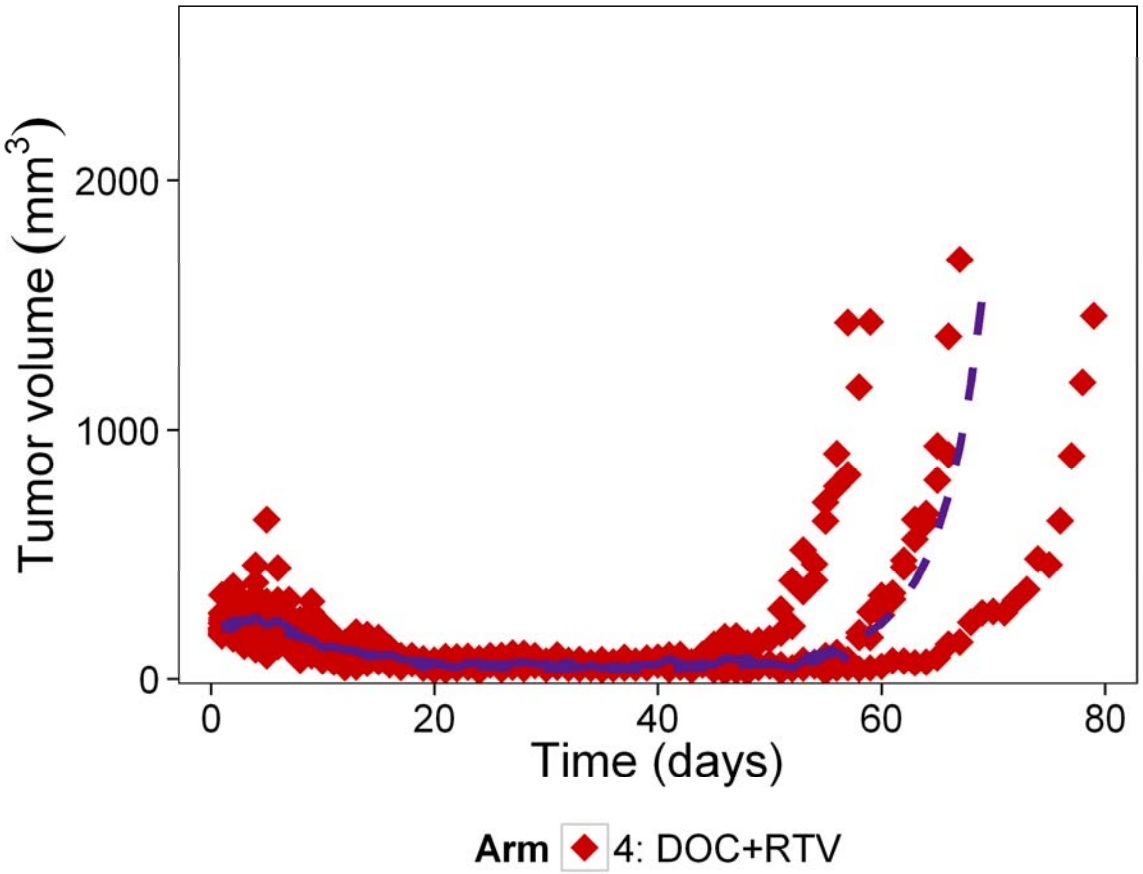


- Slight underestimation of anti-tumour effect in early phase of treatment
- Underestimation of the time to tumour re-growth

Hypothesis test – estimation of ritonavir anti-tumour effect

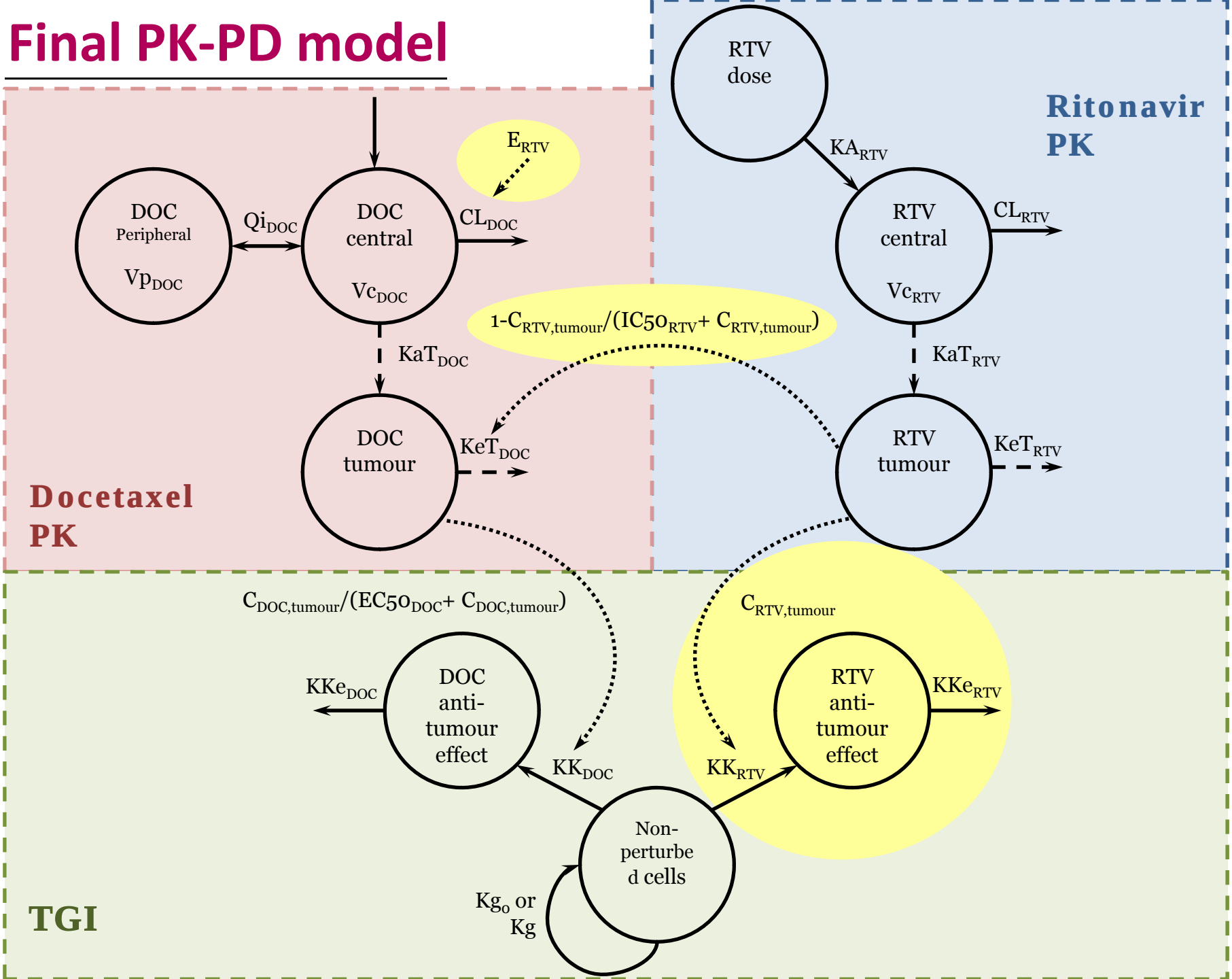


Hypothesis test – estimation of ritonavir anti-tumour effect

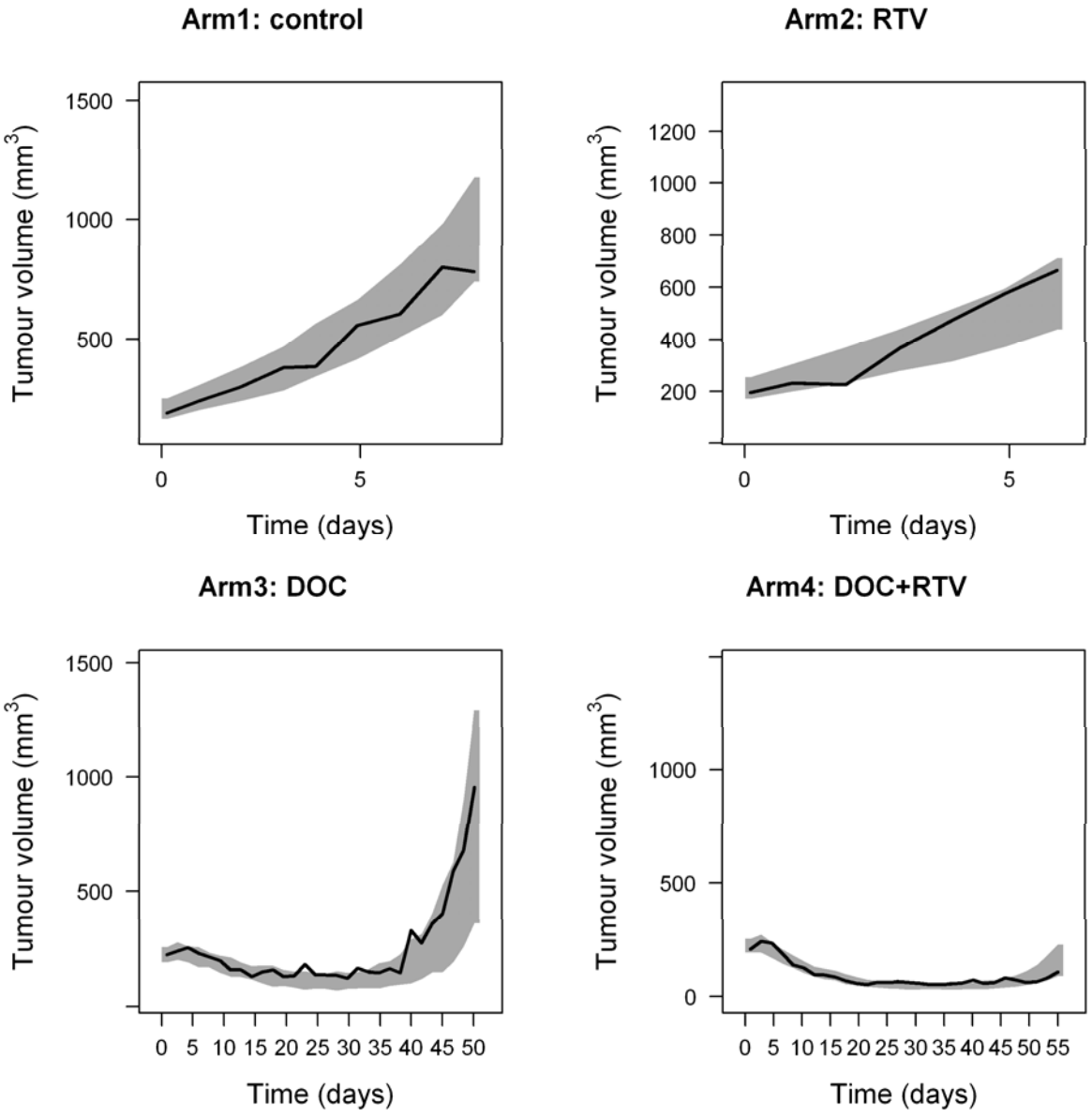


- Bias in the model prediction of tumour volume in the co-administration disappeared
- Objective function value dropped 59 points comparing to the model estimation without ritonavir anti-tumour effect

Final PK-PD model



Final PK-PD model – visual predictive check



Conclusions

- A PK-PD model has been successfully developed describing the complex interaction between docetaxel and ritonavir when co-administered in a mouse model for hereditary breast cancer

- We showed that the enhanced tumour growth inhibition observed in the co-administration of docetaxel with ritonavir is mainly caused by boosting the tumour concentration of docetaxel and to a minor extent by a direct tumour growth inhibitory effect of ritonavir

Acknowledgement

the Netherlands Cancer Institute

Dept. Pharmacy & Pharmacology

Jeroen J.M.A. Hendrikx

Alwin D.R. Huitema

Jos H. Beijnen

Jan H.M. Schellens

Alfred H. Schinkel

Sven Rottenberg

Coen van Hasselt

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

PAGE committee &

PAGE student sponsorship

PAGE