

PK Study and Proof-Of-Concept Animal Studies

- BCRP: Important role in drug absorption, distribution and elimination Anticancer drugs resistance (irinotecan, SN-38)
- MBLI-98: New BCRP inhibitor → **Efficacy in-vitro and in-vivo^{1,2}**
- M&S useful in drug development³

PK study

- 1 single dose administered IP (irinotecan ± MBLI-98, MBLI-98 ± irinotecan)
- Plasma concentration measured during 24h
- 5 animals per time point

Proof-Of-Concept Animal Studies

- SCID mice xenografted with HEK293 tumour cells overexpressing BCRP
- 4 treatment groups: Control, irinotecan, MBLI-98, irinotecan+MBLI-98
- Irinotecan and MBLI-98 administered IP
- POC1:** 2 weeks of treatment+2 weeks of wash-out+2 weeks of treatment
1st drug administration on day 2
- POC2:** 4 weeks of treatment
1st drug administration on day 7

	POC 1 (N=41)	POC 2 (N=19)
Total amount (irinotecan) (mg)	6.6	6.4
Total amount (MBLI-98) (mg)	0.87	1.14
Treatment duration (d)	74	41
Treatment intensity (irinotecan) (mg.d ⁻¹)	0.14	0.16
Treatment intensity (MBLI-98) (mg.d ⁻¹)	0.018	0.028

Table 1: Dosing Regimens comparison

- Characterizing the 2 levels of interaction between irinotecan, SN-38 and MBLI-98
- Finding key factors for treatment efficacy
- Applying M&S to early preclinical development

Multi-Scale Semi-Mechanistic PKPD Model

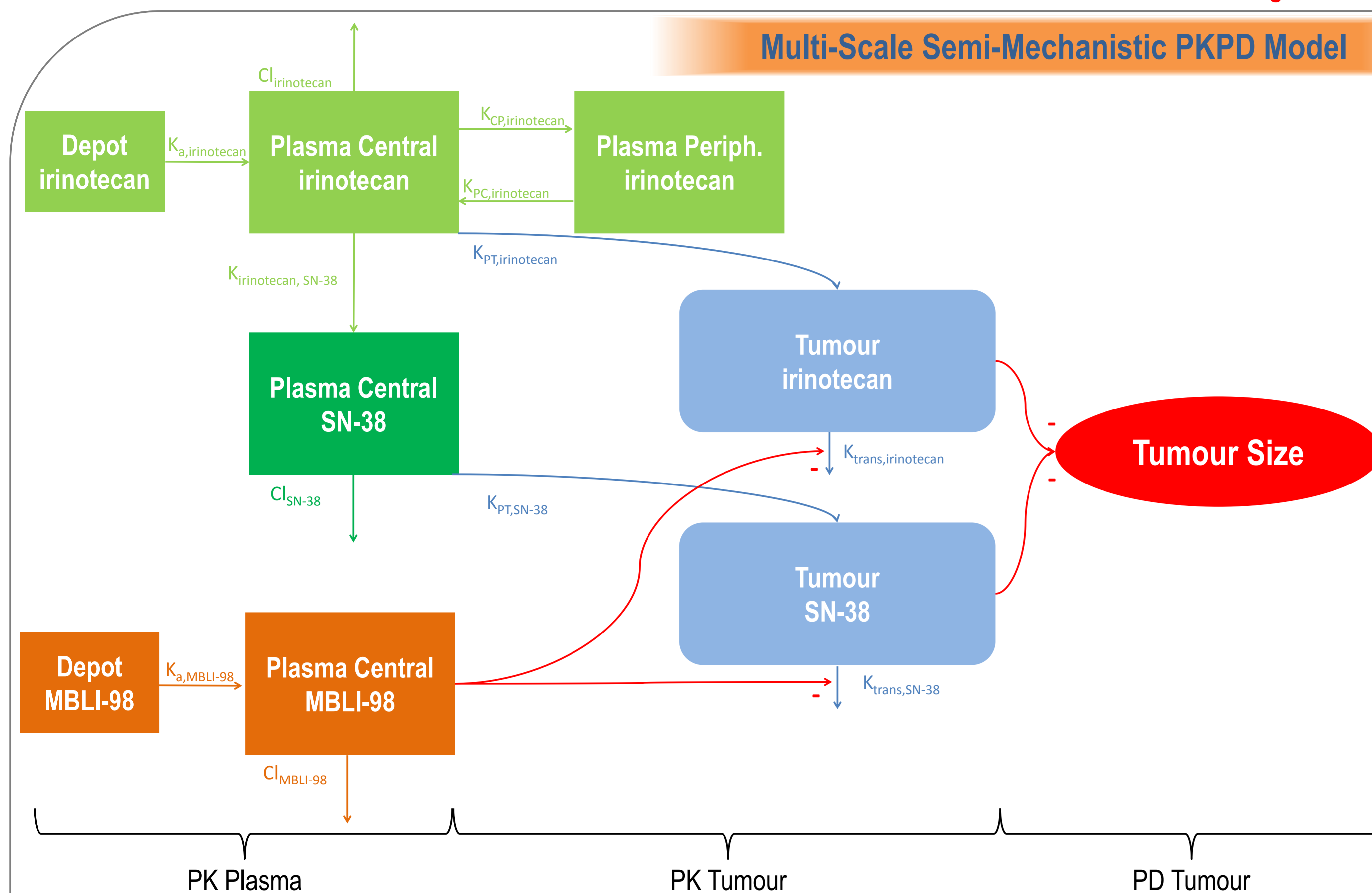


Figure 1: Multi-scale semi-mechanistic model

$K_{a,irinotecan}$	Absorption rate irinotecan	$K_{CP,irinotecan}$	Distribution rate central, peripheral
$K_{a,SN-38}$	Absorption rate SN-38	$K_{PC,irinotecan}$	Distribution rate peripheral, central
$K_{a,MBLI-98}$	Absorption rate MBLI-98	$K_{PT,irinotecan}$	Tumour accumulation rate due to passive diffusion
$Cl_{irinotecan}$	Clearance irinotecan	$K_{PT,SN-38}$	Tumour accumulation rate due to passive diffusion
Cl_{SN-38}	Clearance SN-38	$K_{trans,irinotecan}$	Active efflux rate irinotecan
$Cl_{MBLI-98}$	Clearance MBLI-98	$K_{trans,SN-38}$	Active efflux rate SN-38
$K_{irinotecan,SN-38}$	Metabolization rate irinotecan, SN38		

PK data

irinotecan, SN-38 data fitted together
M2 method for BQL data

Assessment of PK interaction

- 1st interaction level** based on mechanistic model developed on *in-vitro* study⁴

Drug influx: Passive diffusion

Drug efflux: Active transport (Michaelis-Menten)

Competitive interaction with MBLI-98
(MBLI-98 inhibits active efflux)

$$K_{trans} = \frac{V_{max}}{K_m \times \left(1 + \frac{[MBLI98]_{pl}}{K_i}\right) + [irinotecan/SN38]_{pl}}$$

Description of intracellular drug disposition

Quantification of : irinotecan, SN-38 K_m value
MBLI-98 K_i value

- 2nd interaction level**

Irinotecan, SN-38 both active compounds

Cooperative interaction on tumour growth⁵

Quantification of irinotecan, SN-38 cytotoxic potencies

$$\text{Drug Effect} = \alpha \times \left(\frac{[irinotecan]_{tum}}{K_{i,irinotecan}} + \frac{[SN38]_{tum}}{K_{i,SN38}} \right)$$

- PK model fitted separately and then fixed in final model
- Natural tumour growth modelled with Simeoni *et al.* model⁶
- K_m , K_i values corrected to take into account plasma protein binding**
- 4 submodels (intracellular, PK, tumour growth and drug effect) combined and fitted separately to POC1 and POC2

- Model parameters estimated in NonMem 7.1.2 software with FOCEI method
- Model validated with VPC (Figure 2)
- Based on plasma concentration, **no plasma-PK interaction found between the 3 compounds**
- Based on *in-vitro* data, **BCRP affinity greater for SN38 than for irinotecan**
- MBLI-98 BCRP-inhibitory constant (K_i) estimated at 2.5 μM

	POC 1	POC 2		POC 1	POC 2
$K_{PT,irinotecan}$ (d ⁻¹)	0.93 (-)	3.86 (30.4%)	λ_1 (d ⁻¹)	0.99 (0.5%)	0.99 (247.8%)
$K_{PT,SN-38}$ (d ⁻¹)	1.15 (28.1%)	9.94 (33.6%)	α/K_i ($\mu\text{mol.d}^{-1}$)	0.169 (18.1%)	0.0877 (3.3%)
$K_{trans,irinotecan}$ (d ⁻¹)	0.001 (-)	0.0126 (30.3%)	Baseline	1* (21.9%)	1* (14.7%)
$K_{trans,SN-38}$ (d ⁻¹)	0.001 (-)	0.0116 (31.7%)	Residual error	0.199	0.168
λ_0 (d ⁻¹)	0.0503 (22.9%)	0.0605 (24.6%)			

Table 2: Parameters estimates
Typical value (%IV)
* Fixed values

Parameter Estimates Comparison

- Treatment intensity** POC2 > POC1
- Treatment delay** POC2 > POC1
- K_{PT} POC2 > POC1 equilibration plasma / tumour faster in POC2
- K_{trans} POC2 > POC1 active efflux greater in POC2
- α/K_i POC2 < POC1 treatment less efficient in POC2

→ **Tumour vasculature / Proportion of quiescent cells: POC2 > POC1**
Treatment delay: Key factor for irinotecan + MBLI-98 efficacy

Model gets adequate predictive performances

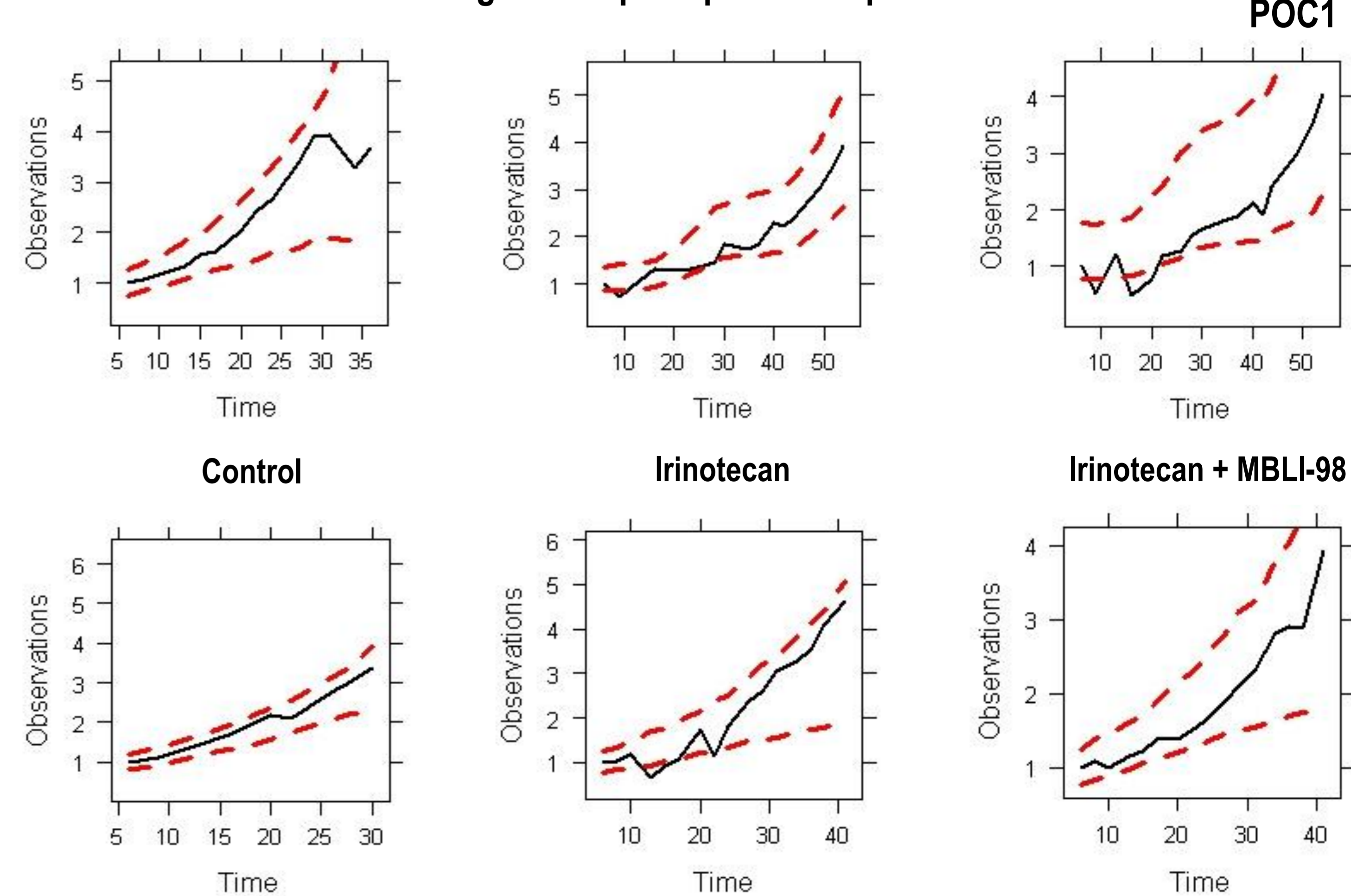


Figure 2: VPC

Red lines: 90% non-parametric confidence interval for the median
Black lines: Observed median

- Development of a NLME model quantifying tumour growth and the 2 levels of interaction between irinotecan, SN-38 and MBLI-98
- Model developed on Proof-Of-Concept studies and *in-vitro* studies
- **M&S successfully applied to early preclinical drug development**
- Treatment delay, tumour development stage: factors contributing to treatment efficacy