

Preclinical Pharmacokinetic/Pharmacodynamic modeling to evaluate combination efficacy and the modification effect of oncology compounds with anti-angiogenic drugs (Sunitinib, Axitinib)

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Objectives

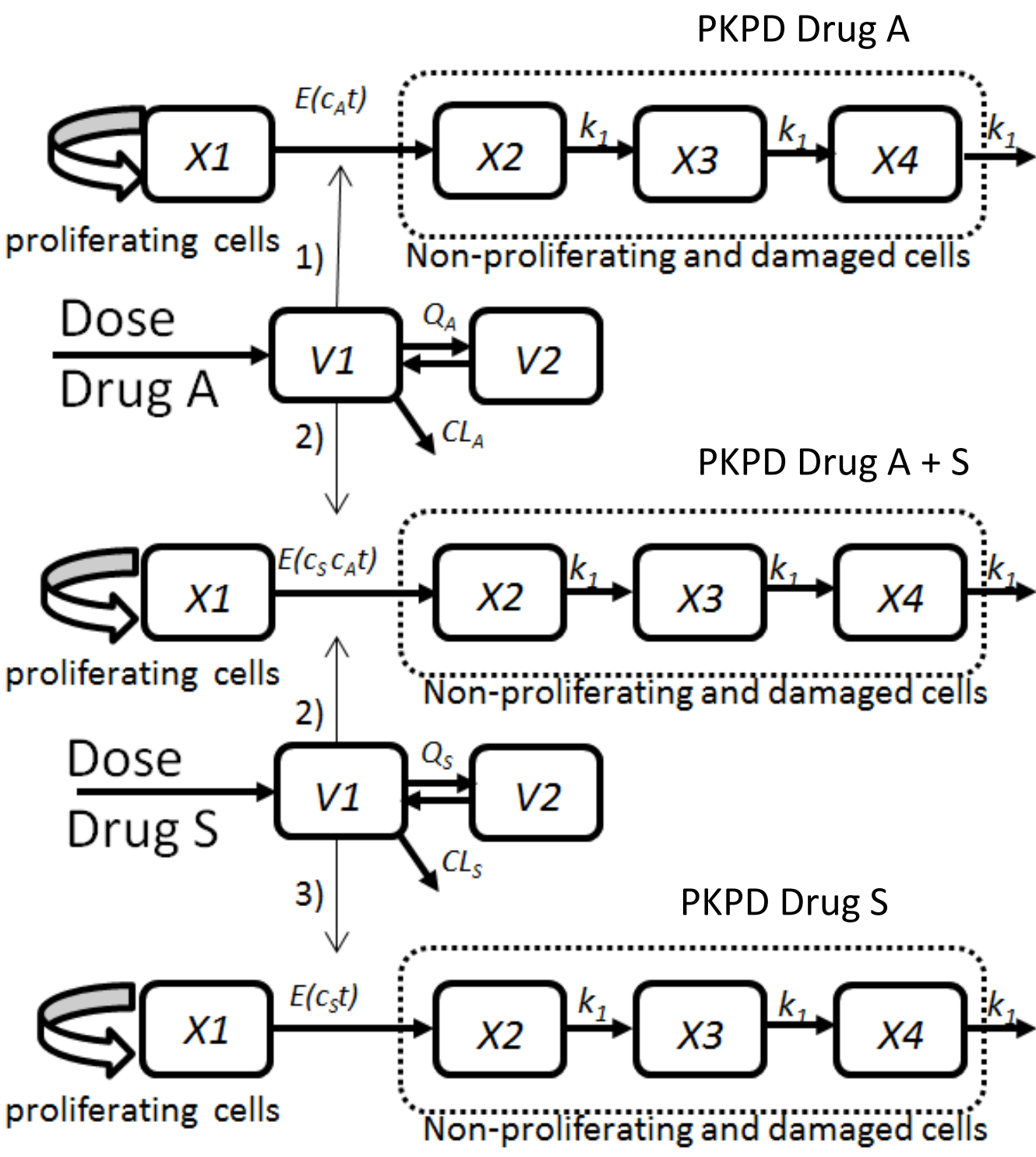
Combination therapies may dramatically improve the outcome for cancer patients, and it is expected that such Therapies will eventually become the standard of care for cancer treatment (Morrissey et al., 2016). However, the increasing complexity of combination therapies presents a substantial challenge in the clinical stages of drug development for oncology. Thus, preclinical data evaluation has been emerged as key for the success in cancer combination therapy. Using PK/PD modeling, we were able to support study design in xenografted mice models as well as to evaluate and quantify the combination efficacy and the modification effect of these compounds through a model selection and multi-experimental fit approach.

Methods

Population PK analysis was performed with a pre-selected PDX model to assess inter-individual and between-treatment variability in combination. A multi-experimental fit approach was conducted in order to assess the PK/PD relationship. Model proposed by Li et al. 2016 was used to analyze the combination efficacy. In order to assess the modification effect, we investigated several factors on the different drug effects and used model selection to uncover the compounds which profits or non-profits from combination. Parameter estimation was performed using NONMEM version 7.3 with interaction (FOCE-I) method and data analysis using R version 3.4.0.

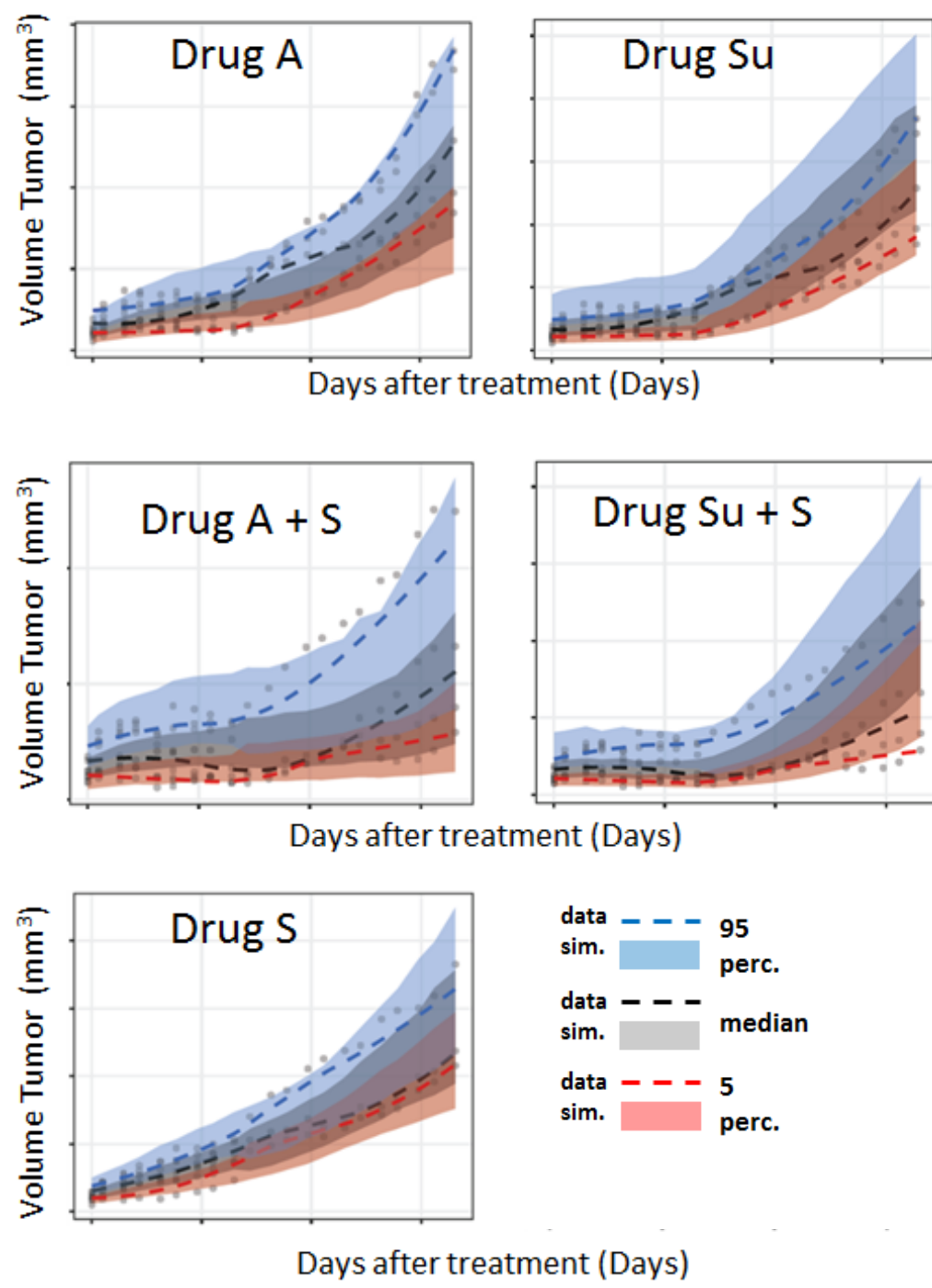
Multi-experimental fit approach

- System describing combination treatment

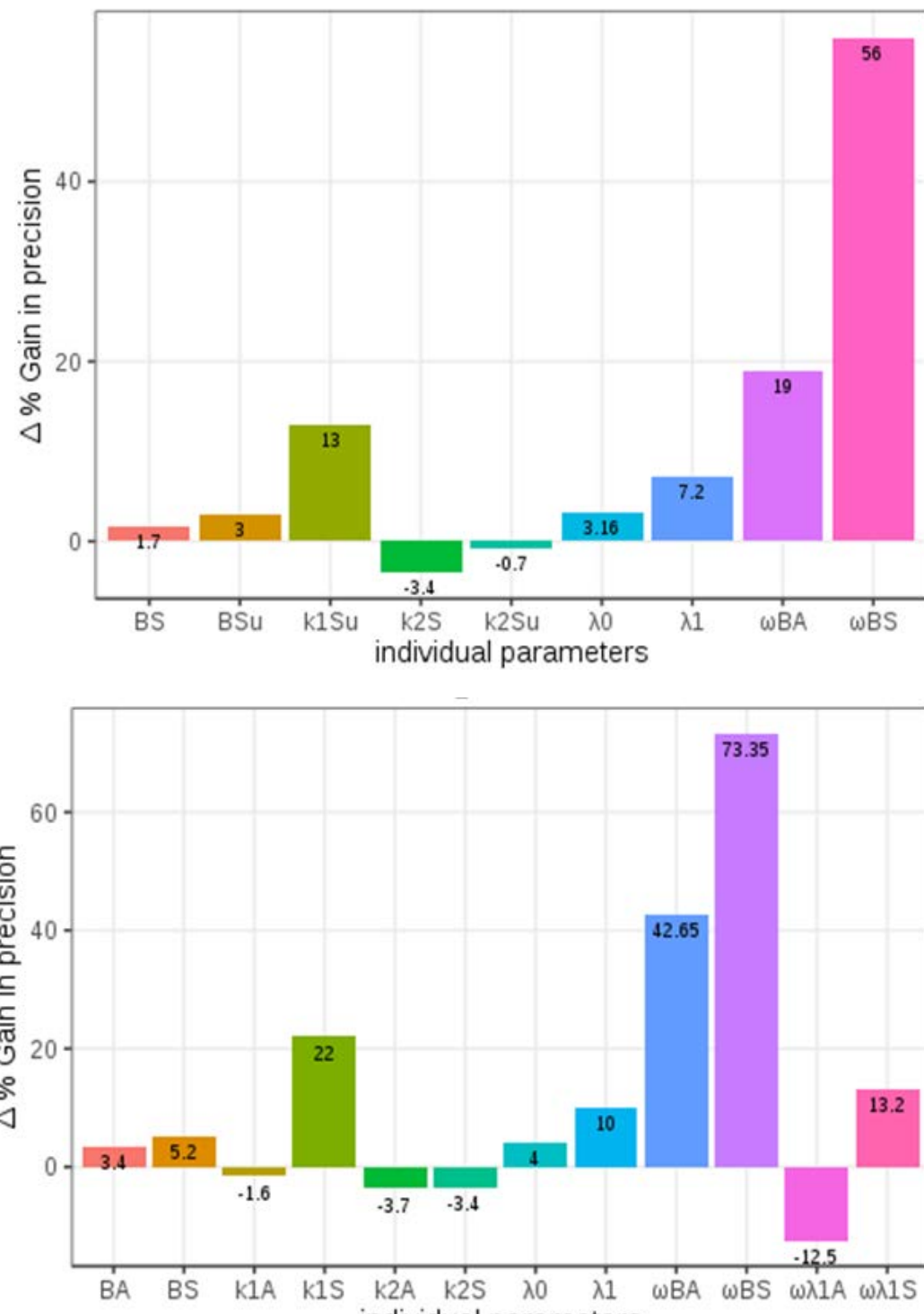


- A tumor growth model proposed by Simeoni et al. 2004 was used.

- Resulting VPC plots after multi-experimental fit



- Gain in precision based on RSE % : Multi-experimental vs. single fit approach



- Multi-experimental fit approach reduces uncertainty on most estimates

PK/PD parameters DrugS + DrugA		
Parameter [unit]	Population estimate	RSE (%)
λ_0 [h ⁻¹]	$3.91 \cdot 10^{-3}$	6.3
λ_1 [mm ³ h ⁻¹]	1.58	10.4
ρ	20	-
k_2 drug S [mL·ng ⁻¹ h ⁻¹]	$4.19 \cdot 10^{-5}$	10.4
k_2 drug A [mL·ng ⁻¹ h ⁻¹]	$1.27 \cdot 10^{-4}$	9.2
k_1 [h ⁻¹]	$4.95 \cdot 10^{-6}$	4.9
k_3 [h ⁻¹]	$7.05 \cdot 10^{-5}$	23.4
w_0 [mm ³]	131	6.5
ωw_0	0.2	0.25
$\omega \lambda_1$	0.32	37
ϕ	0.224	9.15

PK/PD parameters DrugS + DrugSu		
Parameter [unit]	Population estimate	RSE (%)
λ_0 [h ⁻¹]	$2.32 \cdot 10^{-3}$	7.2
λ_1 [mm ³ h ⁻¹]	1.62	13.2
ρ	20	-
k_2 drug S [mL·ng ⁻¹ h ⁻¹]	$2.0 \cdot 10^{-5}$	7
k_2 drug Su [mL·ng ⁻¹ h ⁻¹]	$1.47 \cdot 10^{-7}$	7.7
k_1 [h ⁻¹]	$1.1 \cdot 10^{-6}$	-
k_3 [h ⁻¹]	2.67	38
k_3 [h ⁻¹]	0.085	21.8
w_0 [mm ³]	168	10
ωw_0	0.52	17
ϕ	0.46	4.9

Model selection strategy

$$\frac{E_{max1} \cdot C_1^{Y1}}{EC_{501}^{Y1} + C_1^{Y1}} + \frac{E_{max2} \cdot C_2^{Y2}}{EC_{502}^{Y2} + C_2^{Y2}} \cdot \phi$$

Drug1 Potency Drug2 Potency Combination Factor

- Magnitude and position of the combination factor determines compounds which profits or non-profits from combination

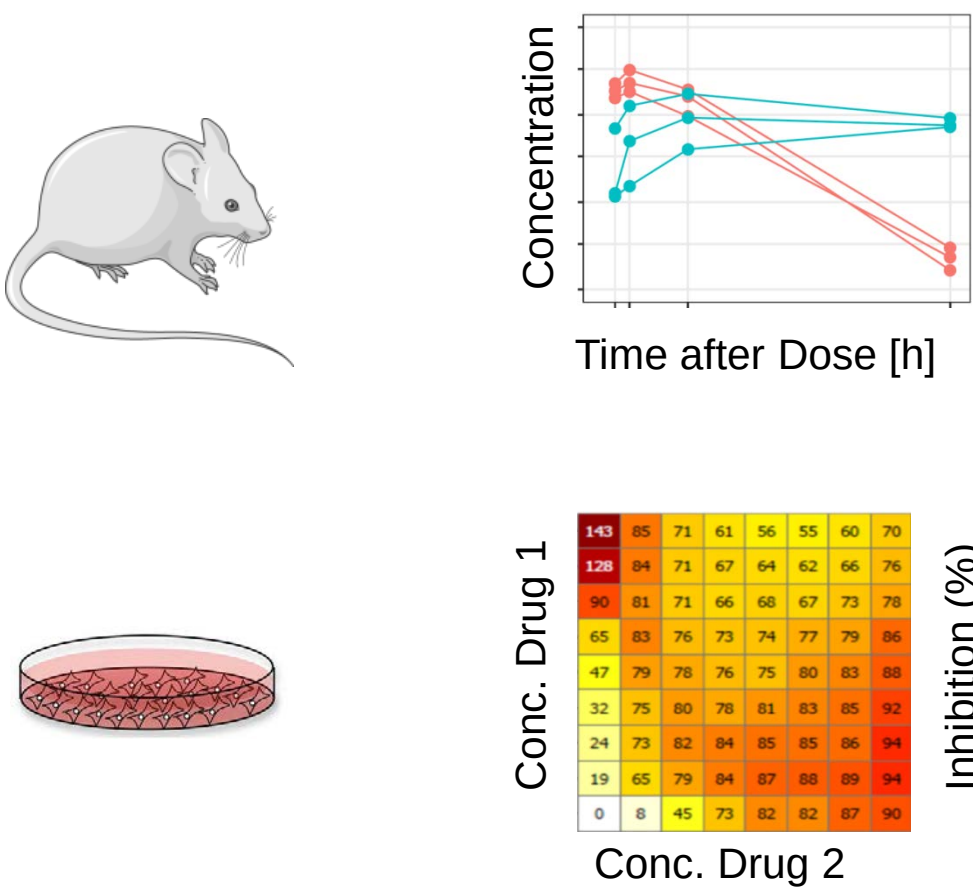
- $\phi = 1$ additive effect 1. (Drug1 Potency + Drug2 Potency) · ϕ
- $\phi < 1$ antagonistic effect 2. Drug1 Potency + (Drug2 Potency · ϕ)
- $\phi > 1$ synergistic effect 3. (Drug1 Potency · ϕ) + Drug2 Potency

- Based on the goodness of fit, we identified which compound is modified in combination and quantify the modification effect

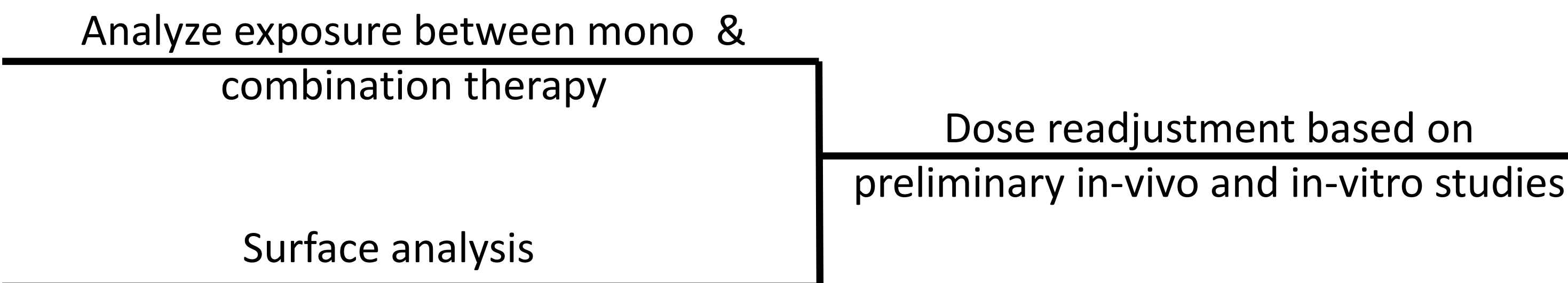
- In combination mainly Axitinib potency was impaired to approx. 80%
 $\text{Drug}_S \text{ Potency} + (\text{Drug}_A \text{ Potency} \cdot \phi)$ $\phi = 0.23$ $\phi < 1$ antagonistic effect
- Both DrugS & Sunitinib potency was impaired to approx. 50%, with main effect on Sunitinib
 $(\text{Drug}_S \text{ Potency} + \text{Drug}_{Su} \text{ Potency}) \cdot \phi$ $\phi = 0.46$ $\phi < 1$ antagonistic effect

Preclinical re-design study

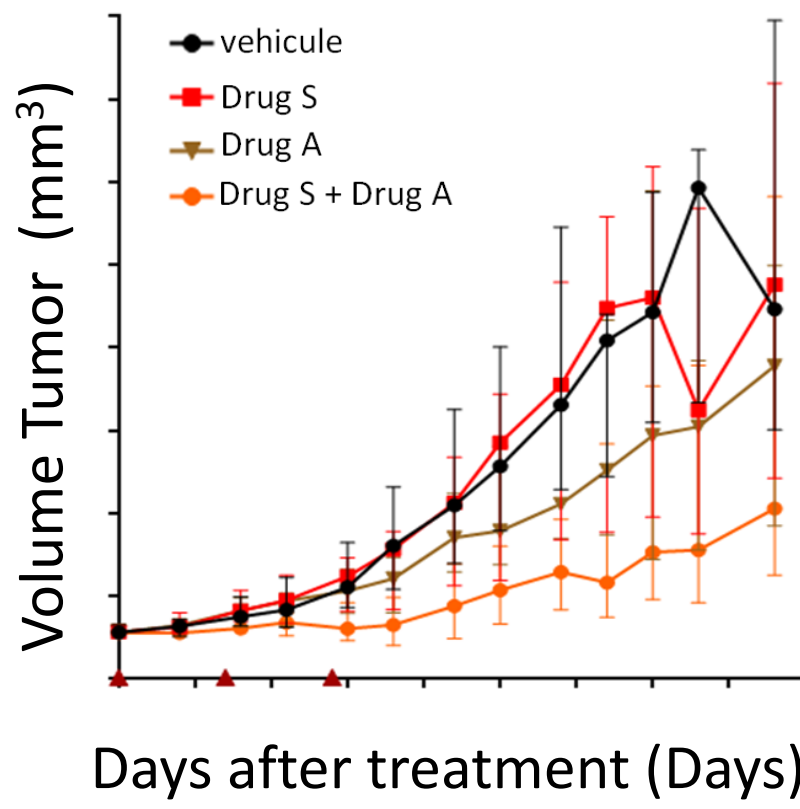
- Opportunity to redesign a new study with the same drugs



- Counterintuitive findings are in good agreement with PK modulation in combination



- Model-based design results in a more pronounced discrepancy between treatment groups



- Six treatments groups of 8 mice were used to compare drug combination potency.
- Tumor volume in mm³ was observed until 69 days and measured twice a week.

Conclusions

The present study shows the benefit of a preliminary dose adjustment design to support preclinical studies avoiding misinterpretation and reducing resources. This benefit can be only achieved through PK modeling. A PK/PD analysis allowed comparing combination efficacy of the compounds when administered in combination. Moreover, the evaluation of the modification effect in combination confirmed interference of Drug S with anti-angiogenic compounds affecting potency of the anti-angiogenic drugs. We conclude that the evaluation of the modification effect improves the characterization of drug activity in combination. Finally, identifying the modified potency of compounds can guide dose adaptation reducing synergistic toxicity and antagonistic efficacy effects in combination therapy.

References:

[1] Morrissey KM et al., (2016). Immunotherapy and Novel Combinations in Oncology: Current Landscape, Challenges, and Opportunities. Clin Transl Sci. 9:89-104.
[2] Simeoni M et al., (2004). Predictive pharmacokinetic- pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. Cancer Res. 1;64(3):1094-101.
[3] Li J et al., (2016). Preclinical PK/PD model for combined administration of erlotinib and sunitinib in the treatment of A549 human NSCLC xenograft mice. Acta Pharmacologica Sinica, 37(7), 930-940.