

Modeling and simulation for improving the efficacy of the combination between antiangiogenic and chemotherapy in NSCLC

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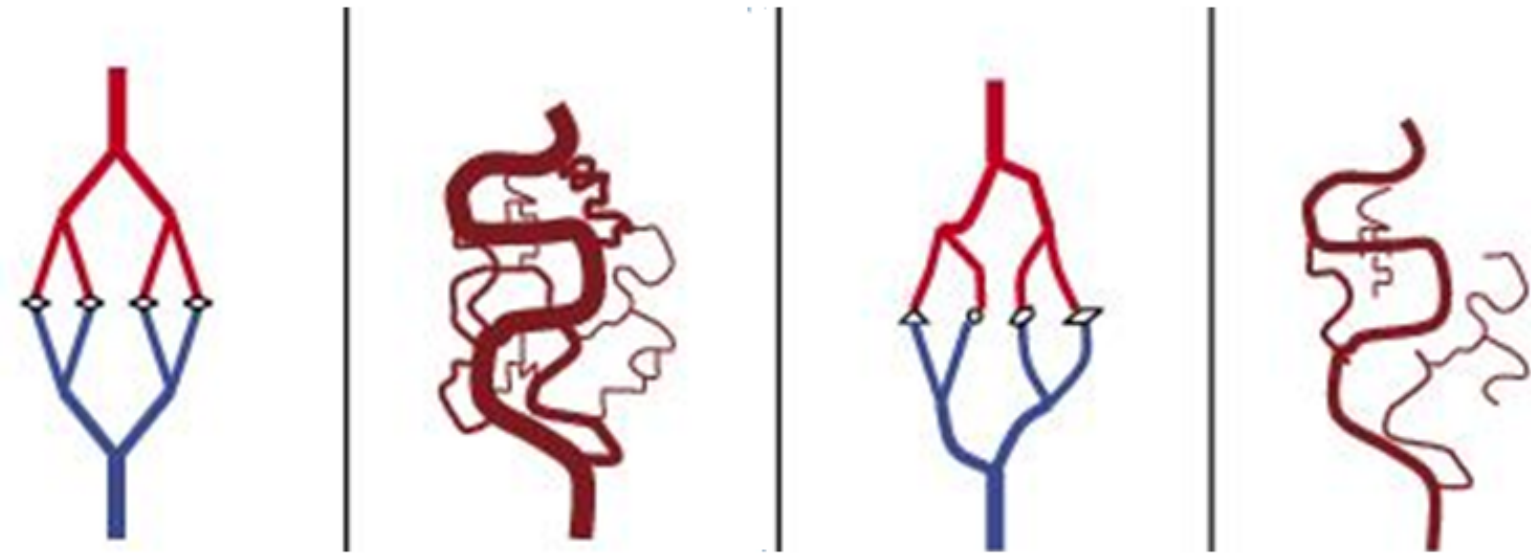
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Objectives

- Validate a biologically-based mathematical model describing the effect of anti-VEGF on tumor vasculature and the combination with cytotoxics
- Identify the best scheduling for the combination of bevacizumab (B) and pemetrexed-cisplatin (C) in non small cell lung cancers (NSCLC)

Background

- Bevacizumab could trigger transient **normalization** of the vascular architecture [1]

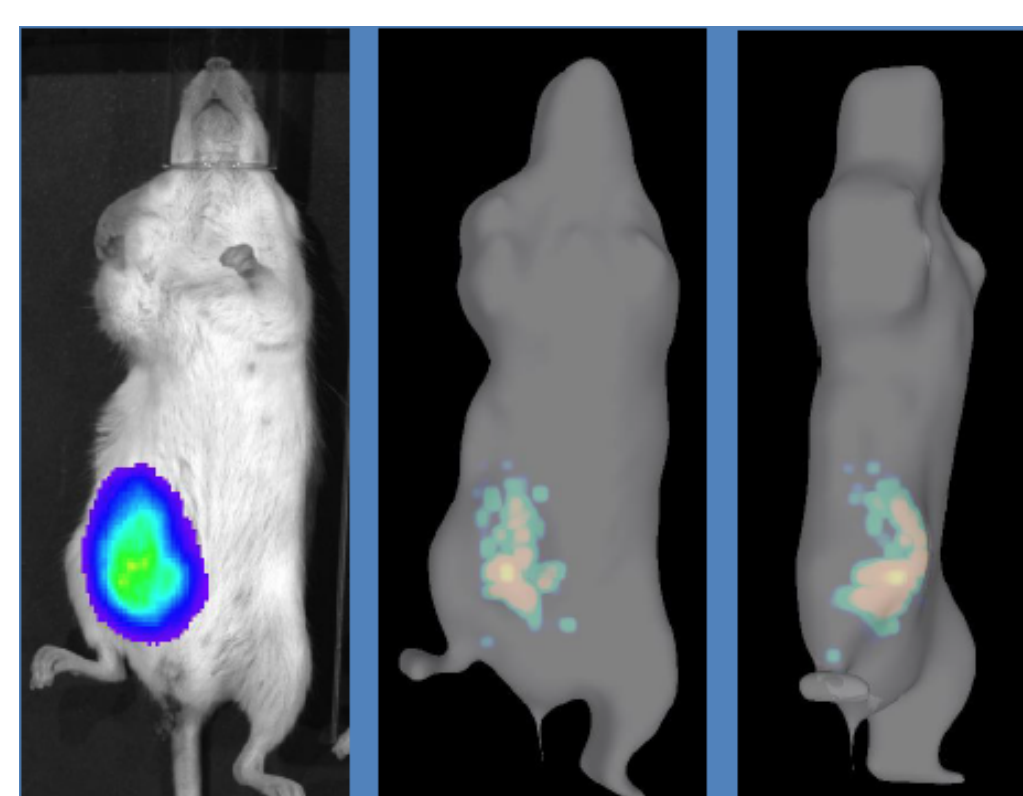


- Suggests an **optimal time window** for improving delivery of cytotoxic drugs [1]
- Sequential use** of bevacizumab associated with chemotherapy could achieve better efficacy [1]

Materials

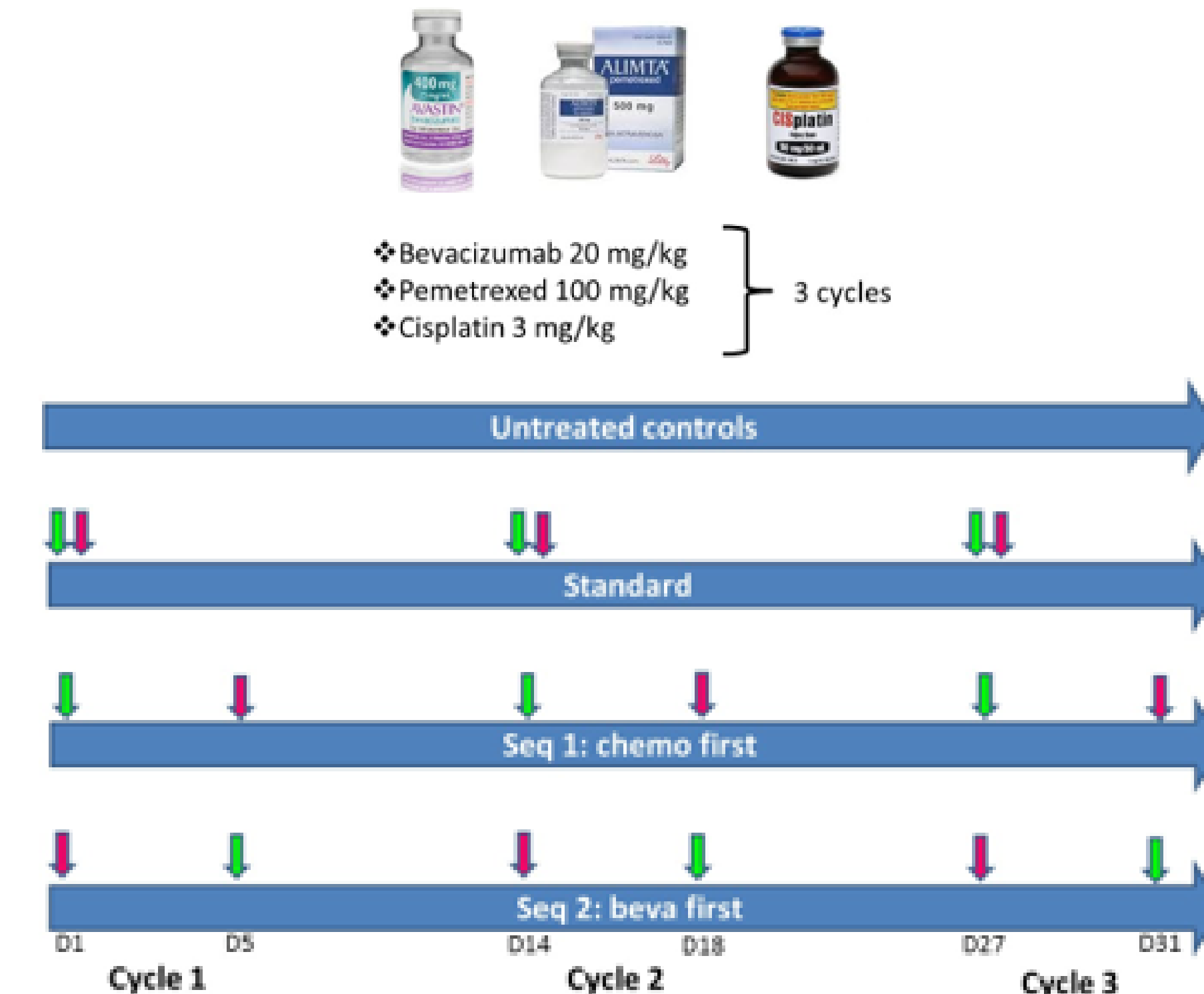
Animal model

- Immunocompromised mice, subcutaneous xenograft with Human NSCLC H460 Luciferase +
- Tumor growth follow-up by **bioluminescence**



Treatment scheduling

- 4 groups : Control vs B+C, C/B, B/C



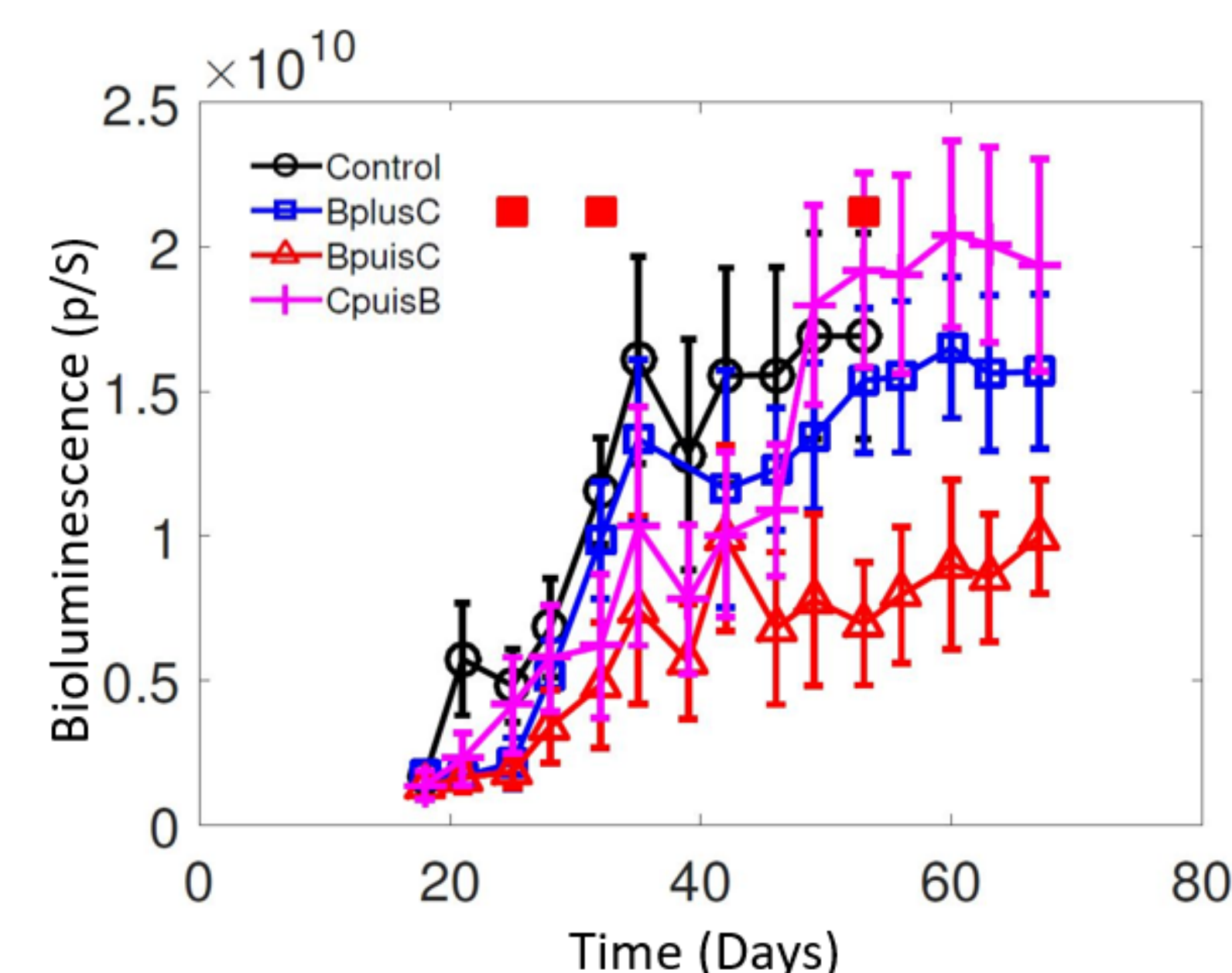
Important Results

- Preclinical POC has shown **superiority of sequential administration B/C** over the standard B+C schedule
- Modeling and simulation identified an **optimal lag-time of 3 days** between B and C

Results

Experimental data (Proof of Concept study (POC))

- Mean tumor mass of **beva-first** sequence was **42% lower** compared to other treatment groups



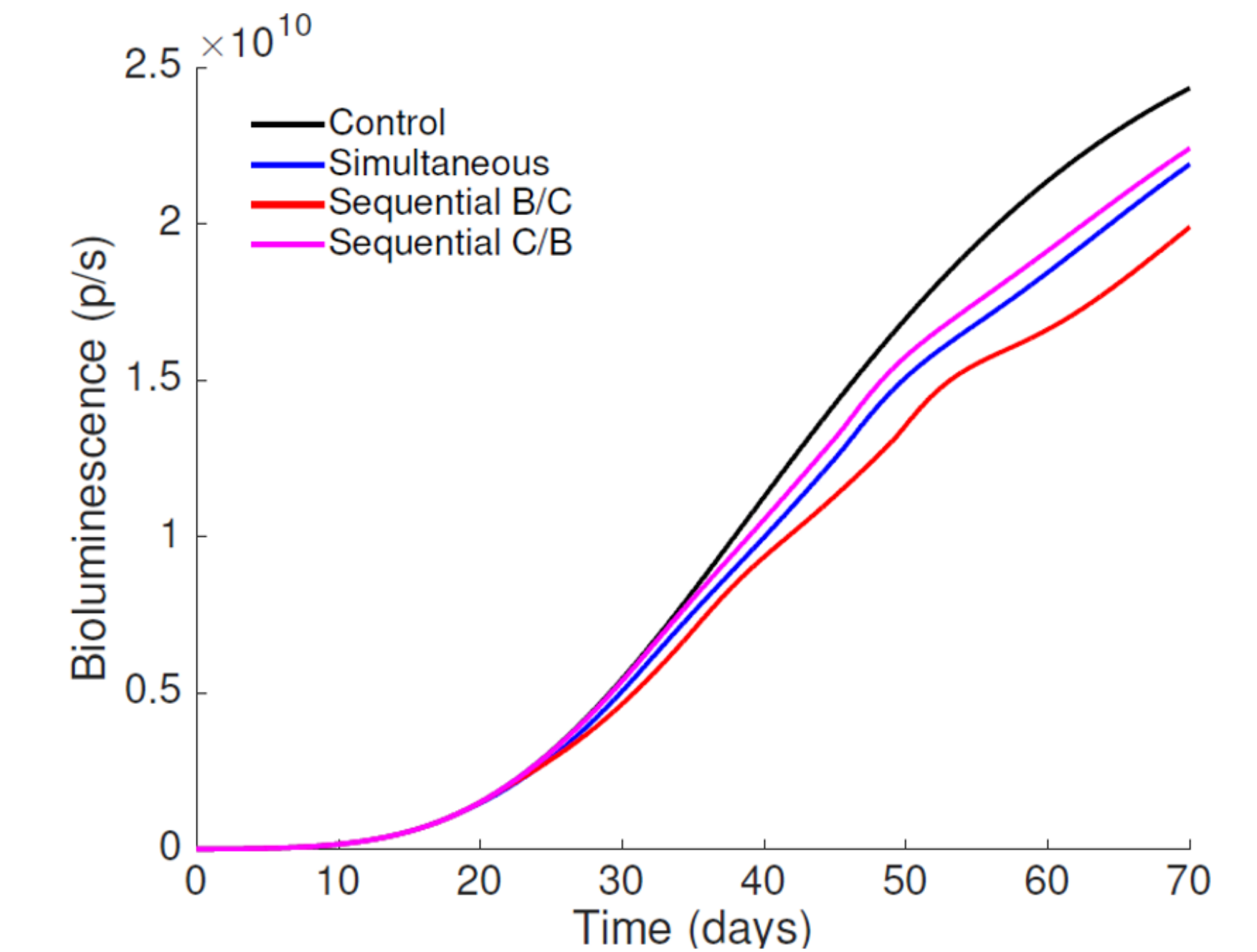
- No significant difference between control and the concomitant or the reversed sequence (i.e., chemo first) was observed.

Methods

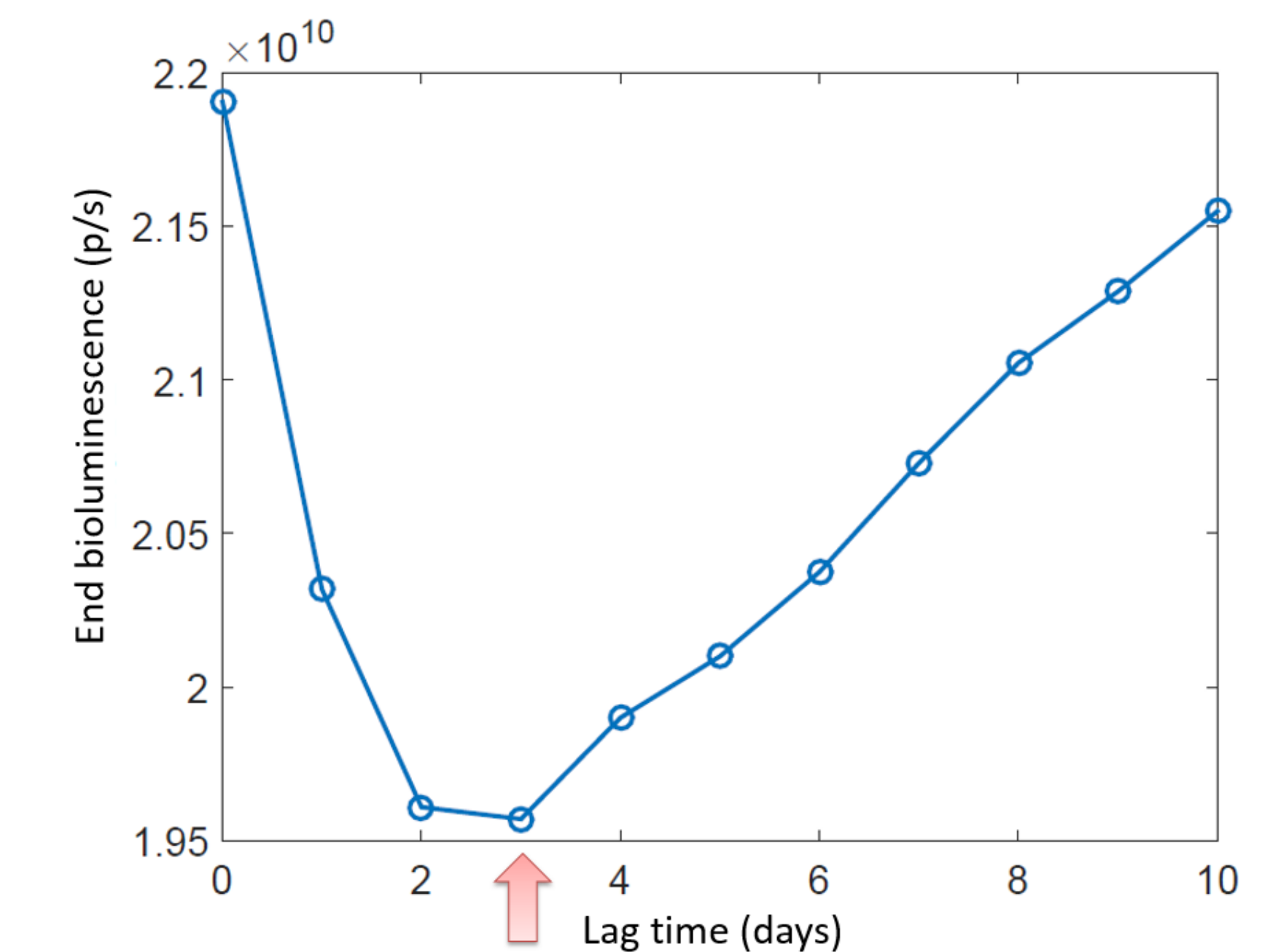
- Fit of experimental data according to a **population approach** (non-linear mixed effects models) using Monolix 4.3.3 Lixoft.
- Mathematical model** [2]

$$\begin{cases} \frac{dV}{dt} = aV \ln\left(\frac{K}{V}\right) - e_{CT}QC(t)V \\ \frac{dK}{dt} = bN - dN^{2/3}K - e_{AA}QA(t)K \\ \frac{dQ}{dt} = A(t) - gQ \\ \frac{dZ_1}{dt} = e_{CT}QC(t)V - kZ_1 \\ \frac{dZ_2}{dt} = kZ_1 - kZ_2 \\ \frac{dZ_3}{dt} = kZ_2 - kZ_3 \\ N = V + Z_1 + Z_2 + Z_3 \end{cases}$$

- Median curves of tumor growth



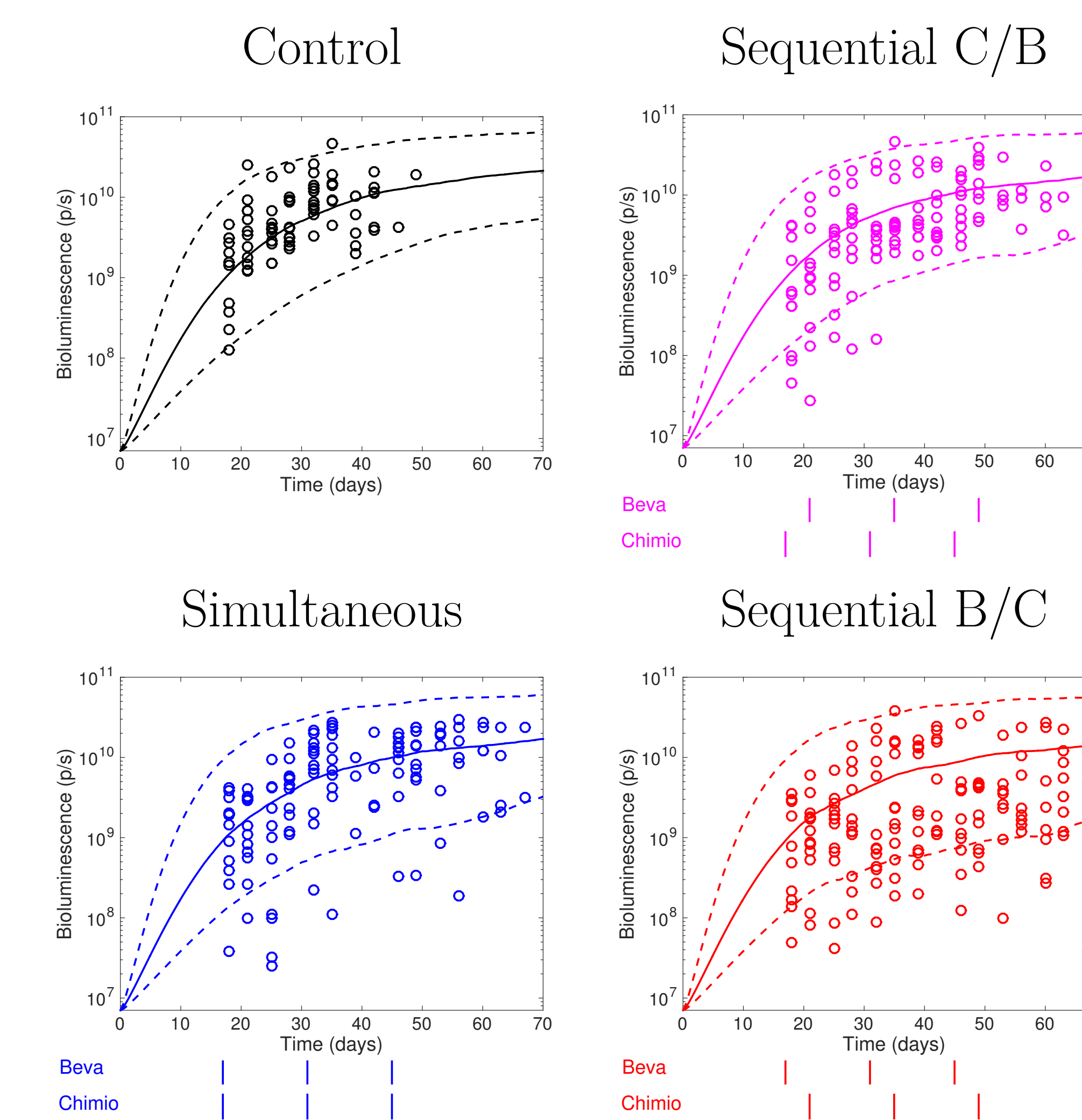
- Optimal lag time between B and C



Results

Model prediction

- Goodness of fit plots : Visual predictive check



References

- Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med. sept 2001.
- Benzekry S, Chapuisat G, Ciccolini J, Erlinger A, Hubert F. A new mathematical model for optimizing the combination between antiangiogenic and cytotoxic drugs in oncology. Comptes Rendus Math. janv 2012.

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