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# Mathematical modeling of differential effects of neo-adjuvant Sunitinib on primary tumor and metastatic growth

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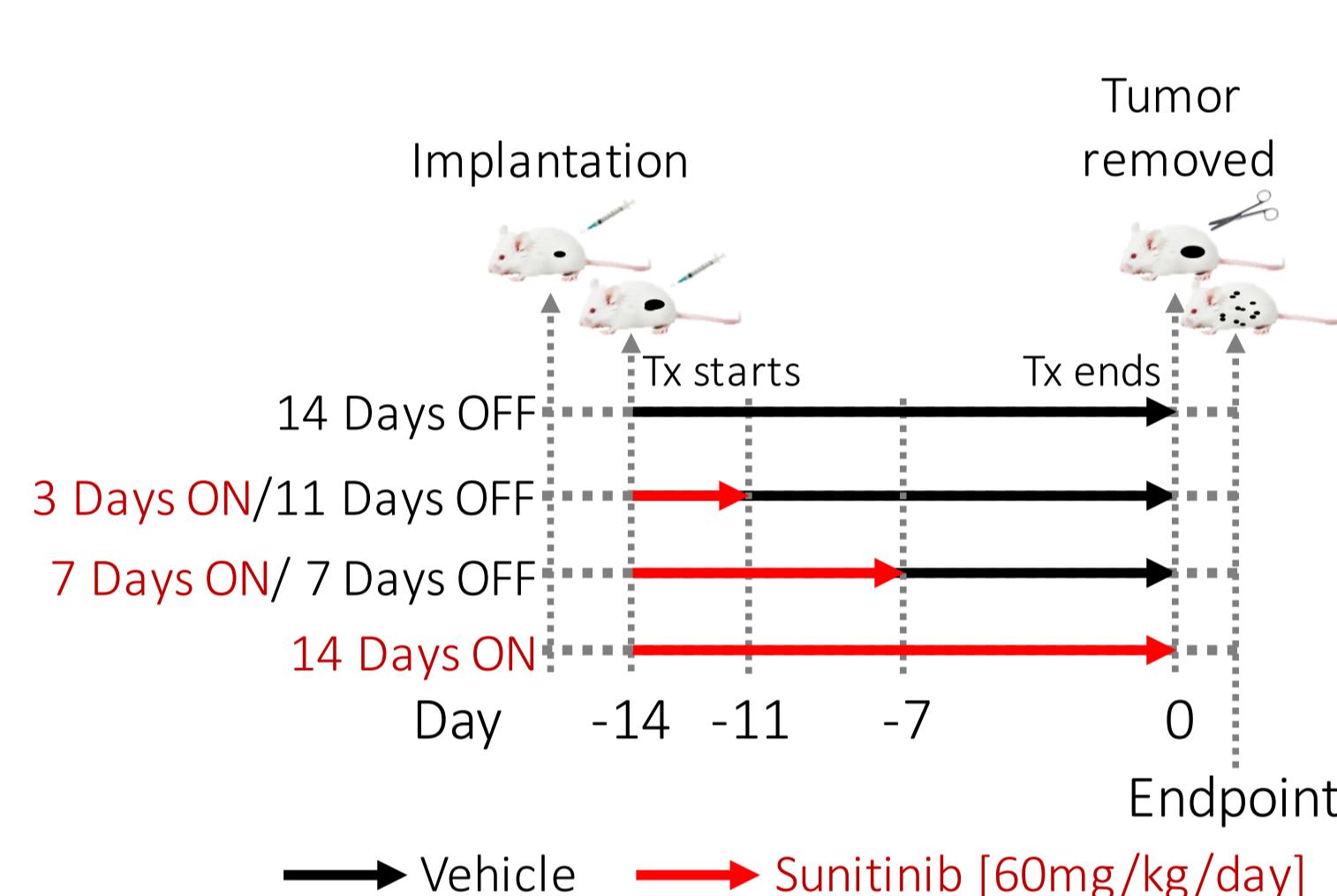
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## BACKGROUND

- Sunitinib is a drug with anti-angiogenic activity used in the treatment of patients with metastases from renal cell carcinoma or gastrointestinal tumors.
- It is currently evaluated in clinical trials in the neo-adjuvant setting.
- Despite clear efficacy in reducing established tumor growth, recent preclinical studies have shown limited, or even opposing, efficacies in preventing metastatic spread.
- In this work, we evaluated a mathematical model of the metastatic process to describe primary tumor and metastatic dynamics in response to sunitinib in a clinically relevant ortho-surgical mouse model of spontaneous metastatic breast cancer.

## EXPERIMENTAL DATA

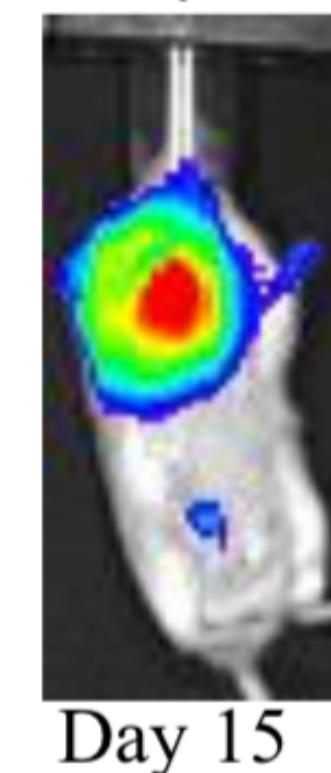


Measurements of

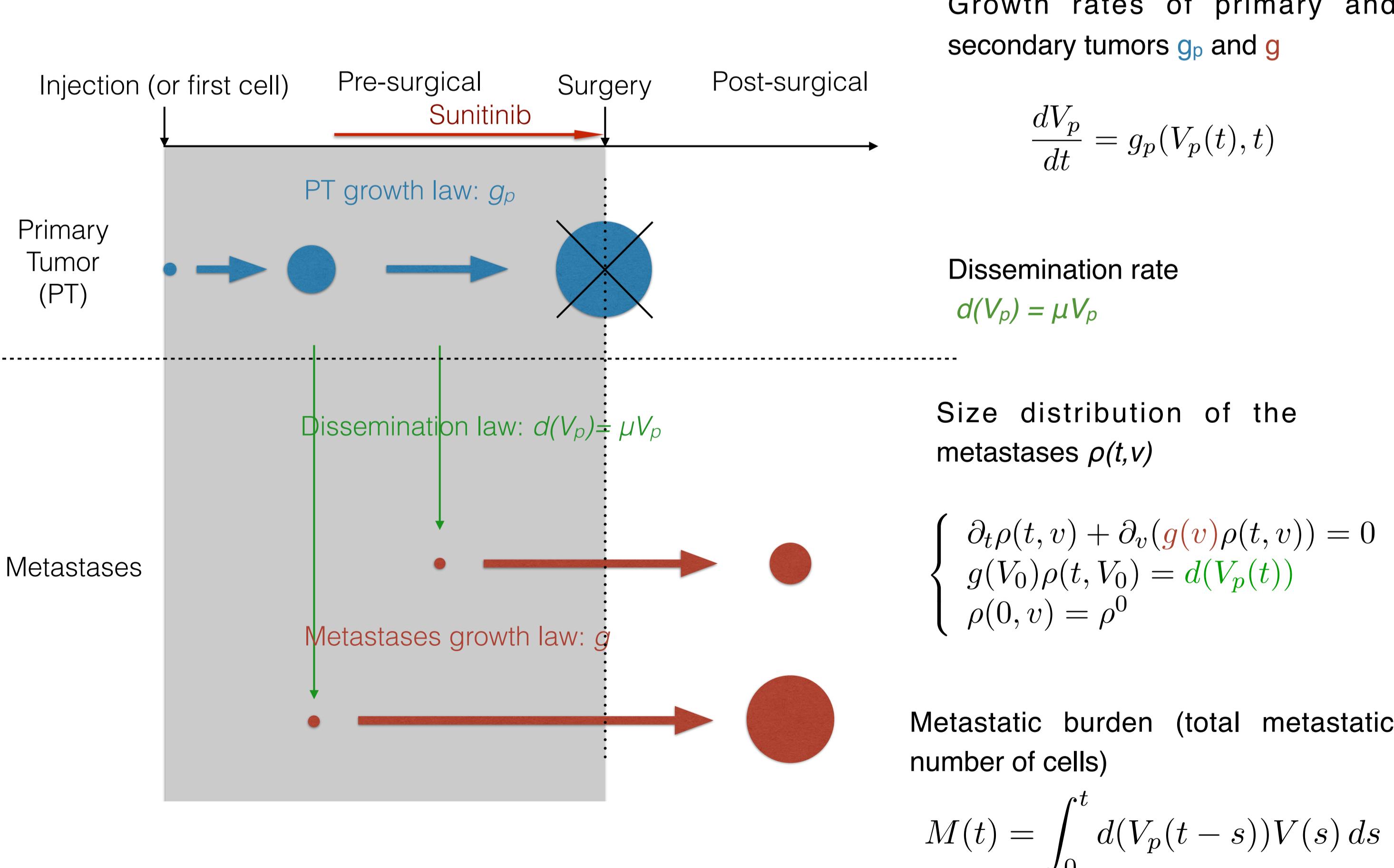
- primary tumor kinetics,
- metastatic burden (bioluminescence)
- pre-surgical molecular and cellular biomarkers, including Ki67 and CD31 expression, circulating tumor cells (CTCs) and myeloid derived suppressor cells (MDSCs).

Orthotopic xenograft breast model:  
LM2-4<sup>LUC+</sup> human metastatic breast carcinoma cells.

Bioluminescence monitoring of post-surgical metastasis



## AN ELEMENTARY THEORY OF METASTATIC DYNAMICS: DISSEMINATION + GROWTH



## REFERENCES

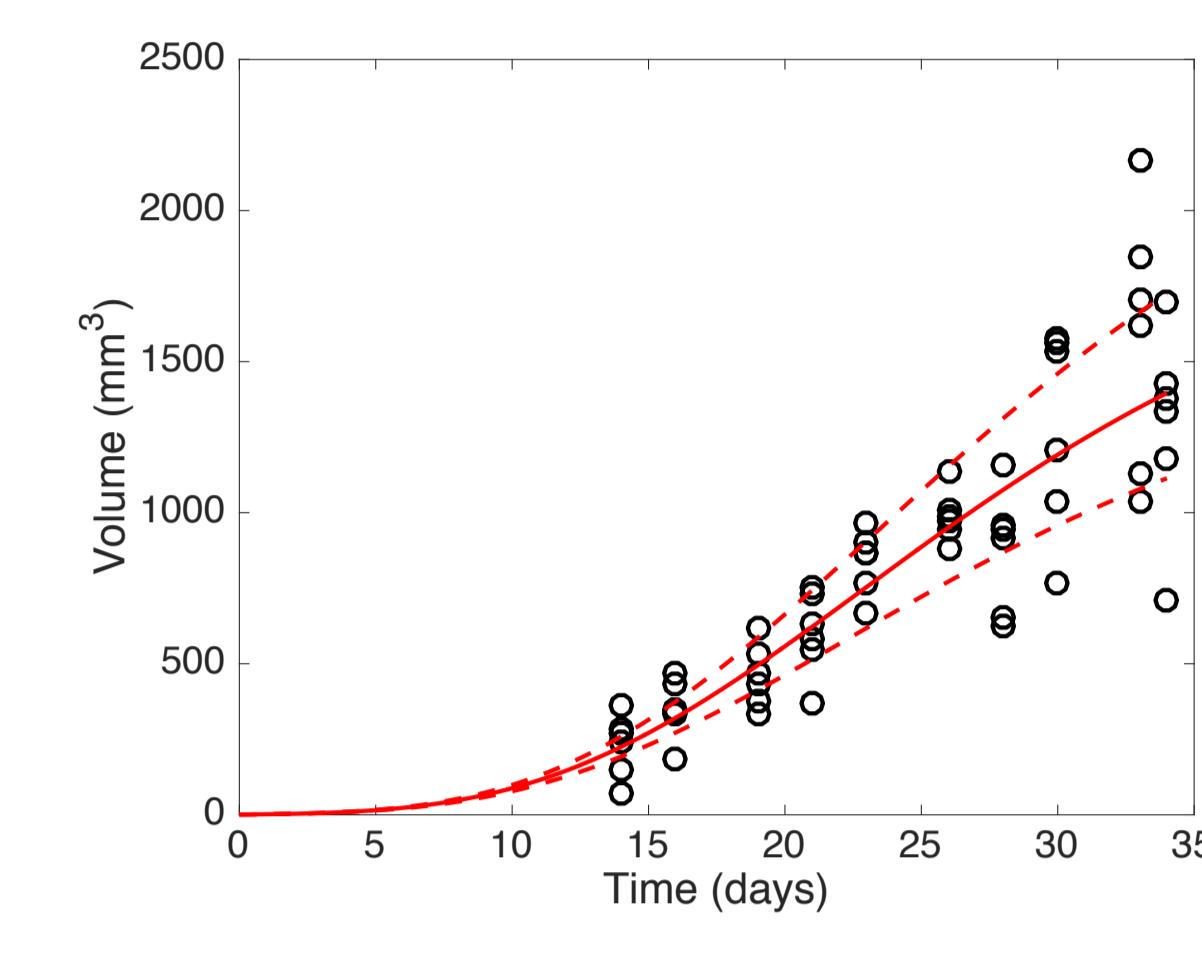
[1] Ebos, J. M. L., Mastri, M., Lee, C. R., Tracz, A., Hudson, J. M., Attwood, K., Cruz-Munoz, W. R., Jedeszko, C., Burns, P., and Kerbel, R. S. (2014). Neoadjuvant antiangiogenic therapy reveals contrasts in primary and metastatic tumor efficacy. *EMBO Mol Med*, 6(12):1561–1576

[2] Benzekry, S., Tracz, A., Mastri, M., Corbelli, R., Barbolosi, D., and Ebos, J. M. L. (2016). Modeling spontaneous metastasis following surgery: an in vivo-in silico approach. *Cancer Res*, 76(3):535–547.

## DIFFERENTIAL EFFECTS OF SUNITINIB ON PRIMARY TUMOR AND METASTASIS

### Primary tumor growth:

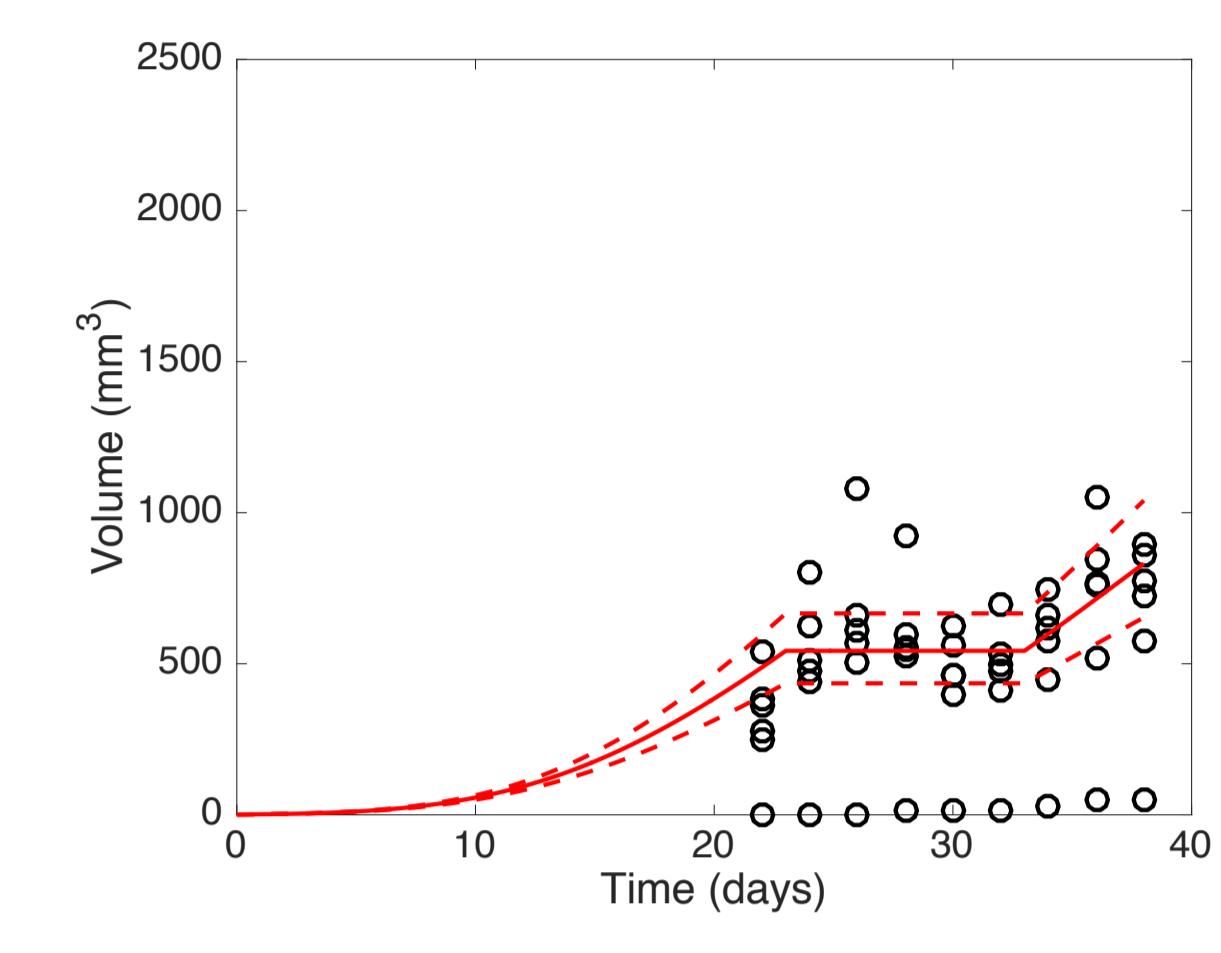
Untreated group



Gomp-Exp model

$$g_p(V) = \min \left( \lambda V, \left( \alpha_0 - \beta \ln \left( \frac{V}{V_c} \right) \right) V \right)$$

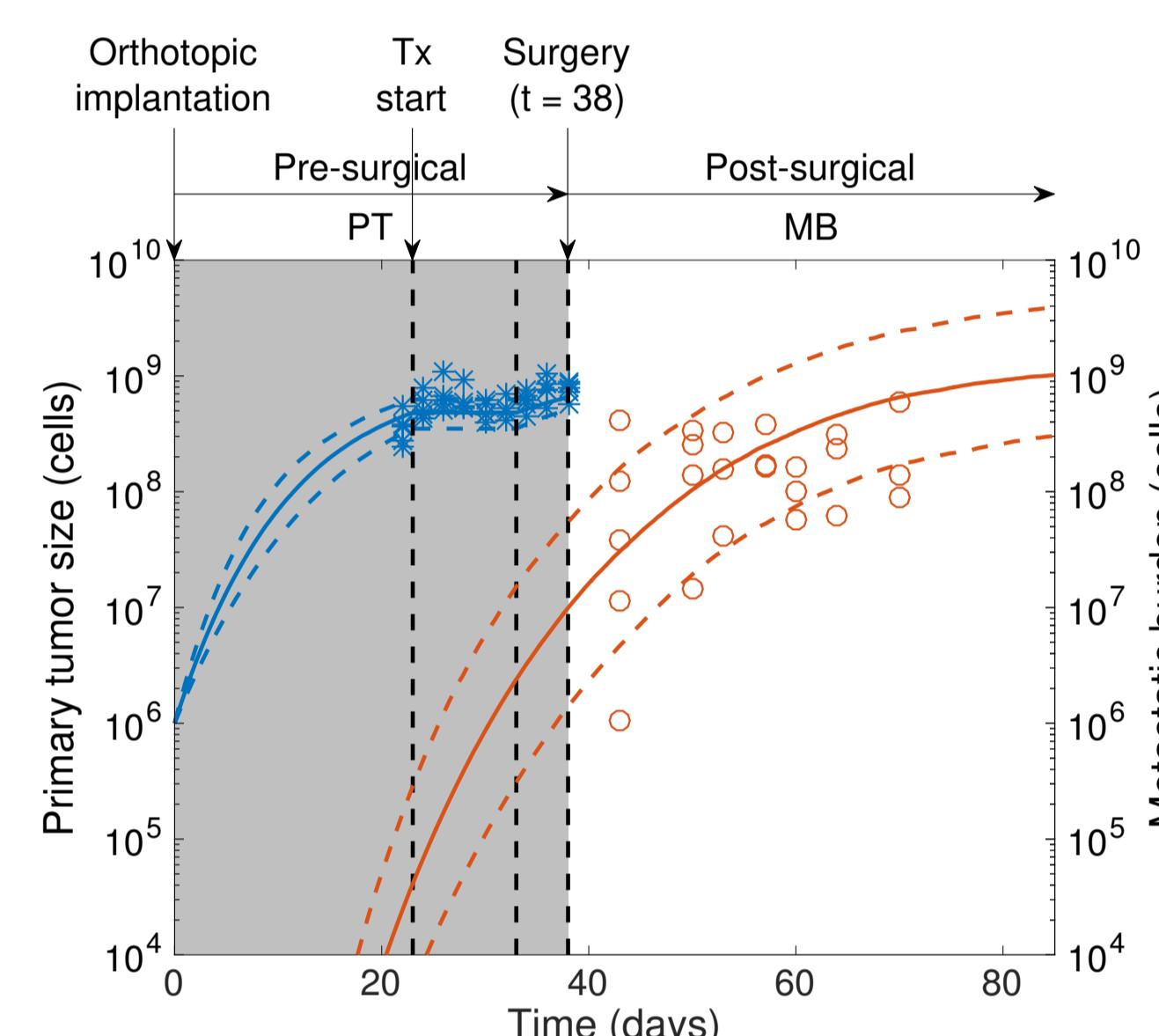
Treated group (11 days)



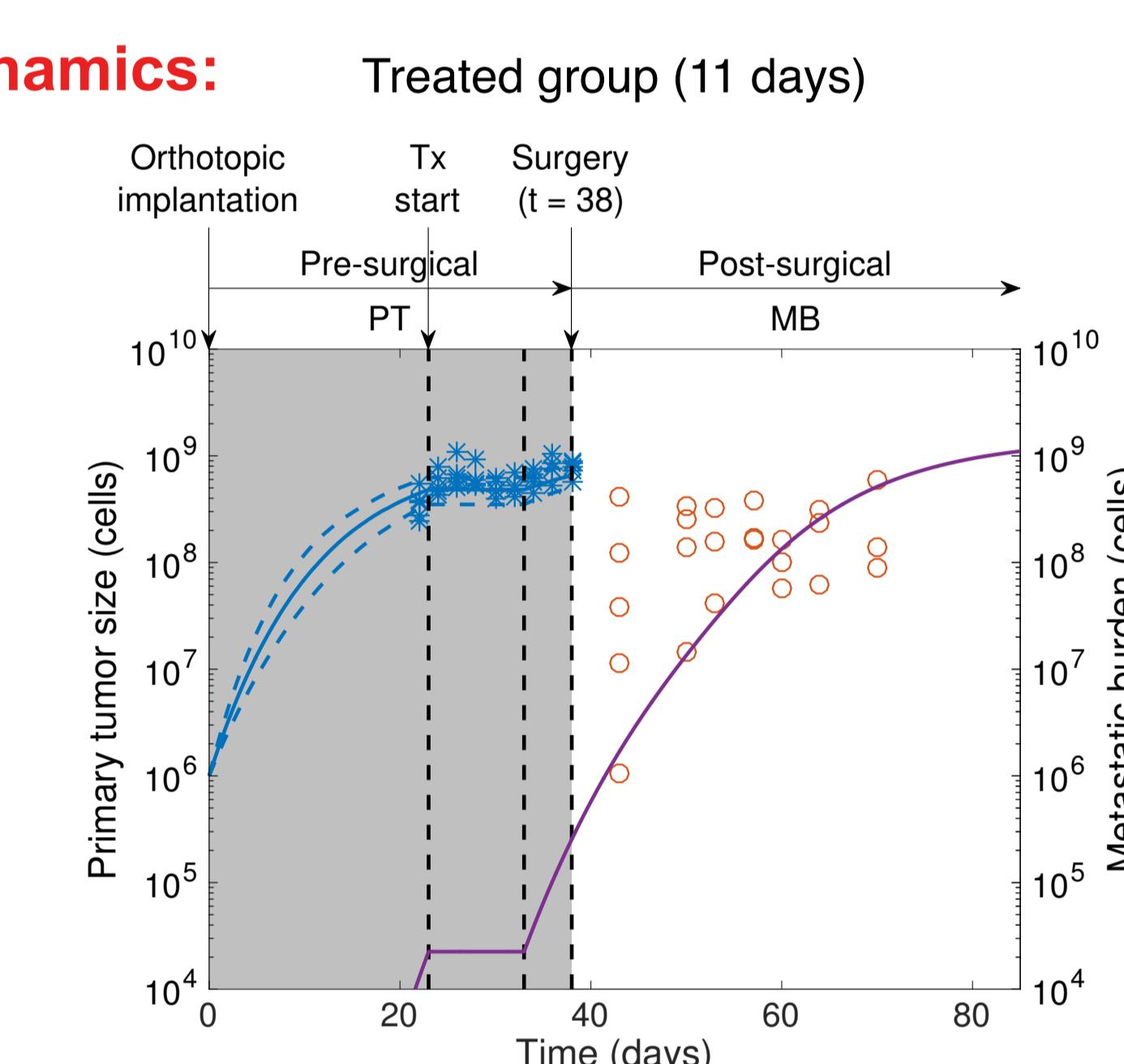
Gomp-Exp model with therapy

$$g_p(V, t) = 0 \quad \text{during the phase of treatment}$$

### Primary tumor - metastatic growth dynamics:



Population fit assuming no effect of treatment on metastasis



Simulation of treatment also on metastasis

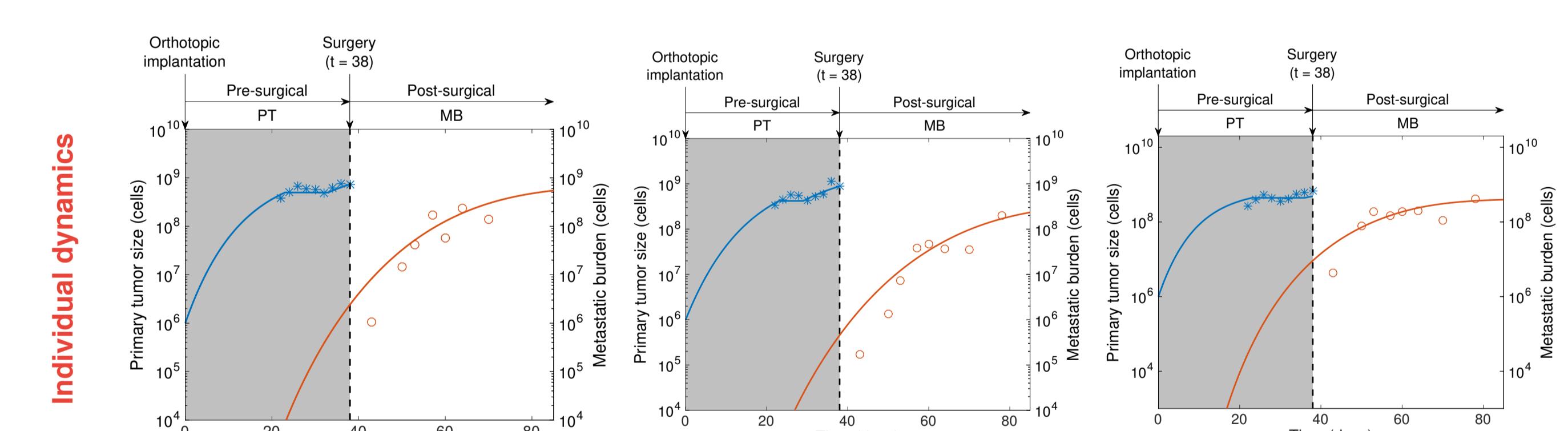
Treatment acts differently on primary and secondary tumor growth

Mixed-effects population approach.

Log-normal distribution for the individual parameters:

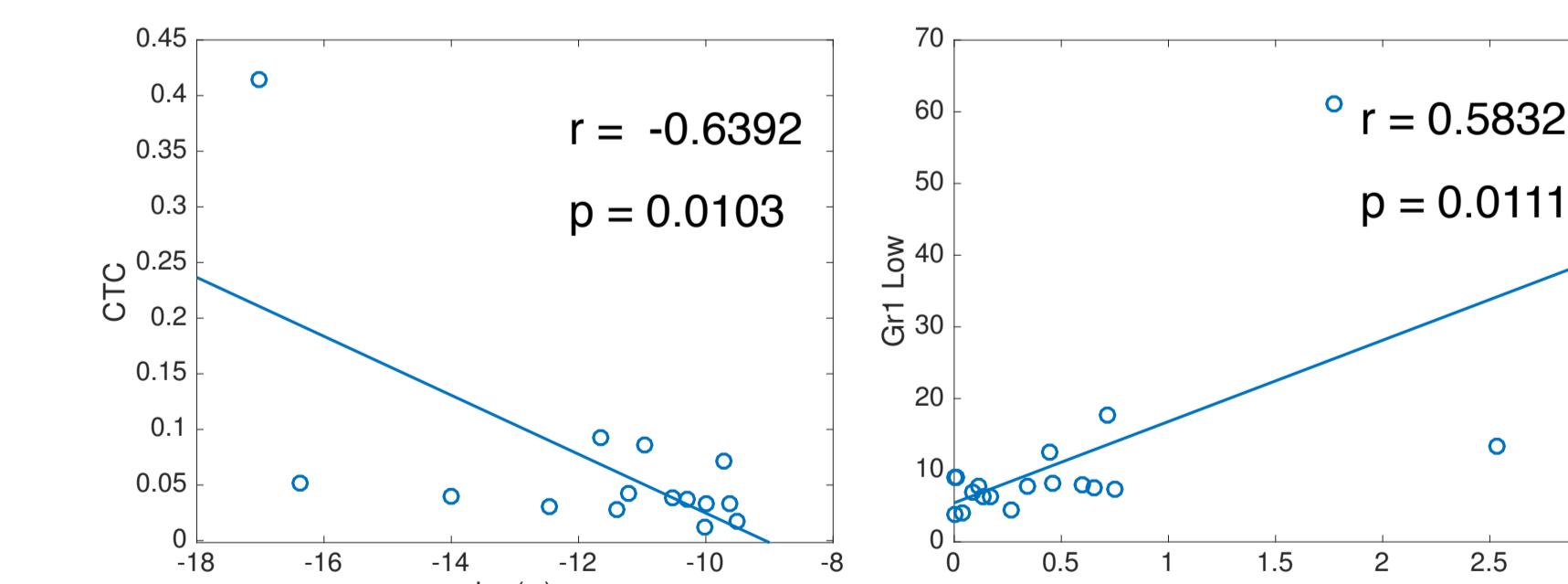
$$\log(\psi_i) \sim \log(\psi_{pop}) + \eta_i, \quad \eta_i \sim \mathcal{N}(0, \omega^2)$$

MLE of  $\psi_{pop}$  through the SAEM algorithm.



## COVARIATES ANALYSIS

### Biomarkers VS individual parameters



• Biomarkers can be included in the model as covariates in order to explain part of the variability in the individual parameters

$x_i$  : individual covariate

$$\log(\mu_i) = \log(\mu_{pop}) + \beta x_i + \eta_i, \quad \eta_i \sim \mathcal{N}(0, \omega^2)$$

## CONCLUSIONS

These results confirm a differential effect of sunitinib on primary (localized) tumors compared to secondary (metastatic) disease. Our results suggest that Ki67+/CD31+, CTCs and MDSCs measurements might help in personalized prediction of metastatic potential and thus aid in predicting benefit in overall survival for preoperative antiangiogenic treatments.