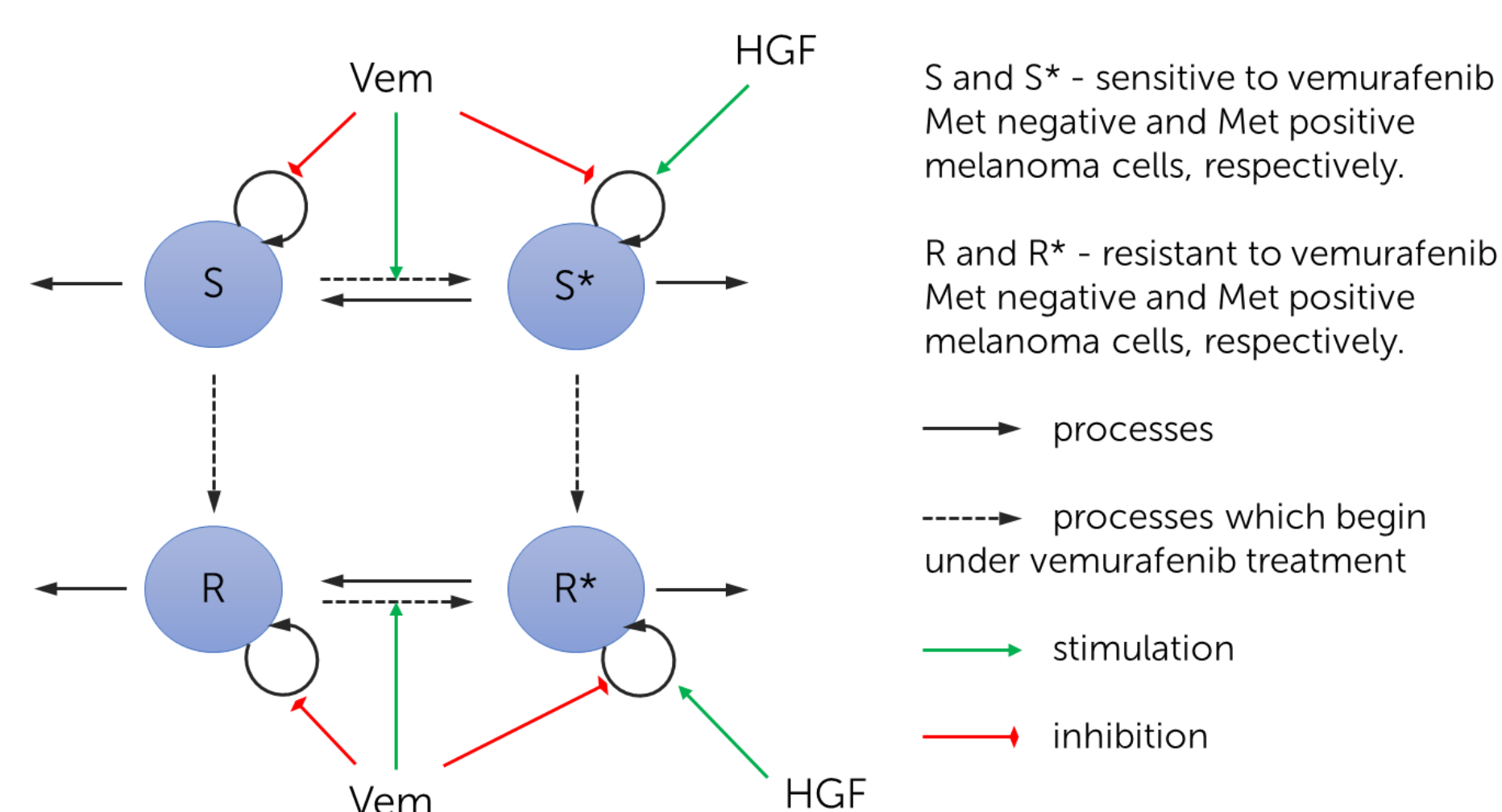


INTRODUCTION

Targeted therapy with BRAF inhibitors has resulted in significant progress in the treatment of metastatic melanoma bearing BRAF V600E mutation. Despite the initial success of clinical outcomes, most patients ultimately develop drug resistance and relapse. The recent studies evidence that HGF/c-MET pathway plays a crucial role in the development of drug resistance mediated by tumor microenvironment. The aim of this study is to develop a semi-mechanistic model of targeted therapy for melanoma (using vemurafenib as an example) which is able to describe the emergence of drug resistance during therapy, to describe inter-patient variability in response to vemurafenib treatment, and to explore the effect of c-MET inhibitors in combination with BRAF inhibitor vemurafenib for different types of virtual patients.

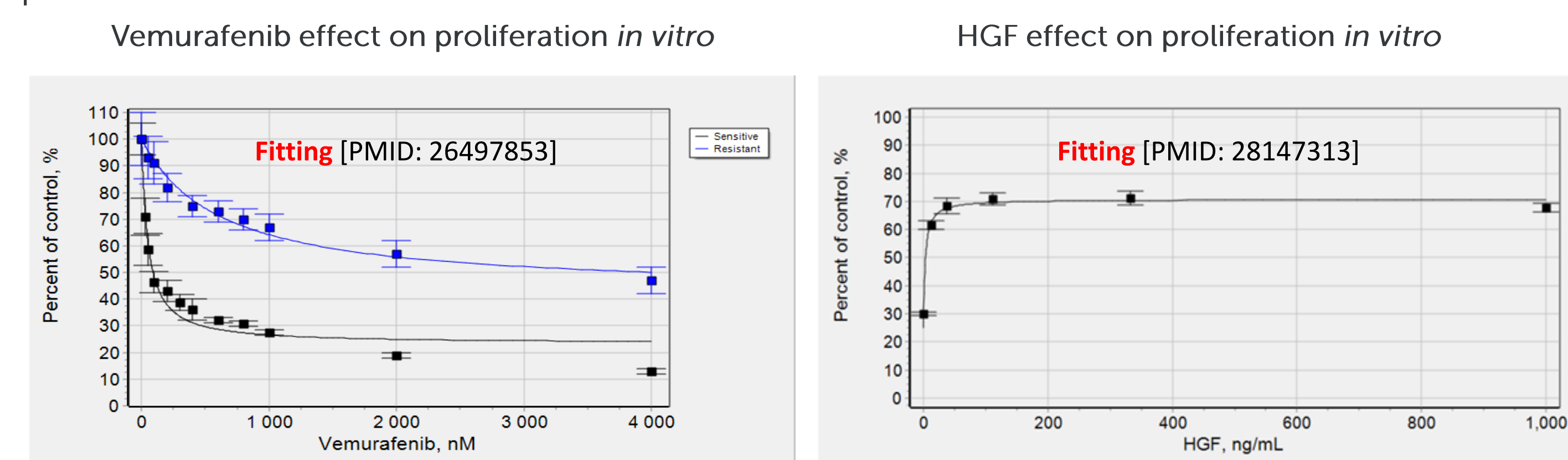
MODEL DESCRIPTION

The model comprises of 6 ordinary differential equations (ODEs): 4 of them describe cellular dynamics and other 2 describe pharmacokinetics (PK) of the drug. PK model and parameters for vemurafenib were taken from FDA clinical pharmacology and biopharmaceutics review. The cellular block of the model includes 4 various cell states (c-MET negative/positive and sensitive/resistant to BRAF inhibitor melanoma cells) and describes proliferation, apoptosis, and transition between cell states, as well as effects of vemurafenib and HGF on the rate of proliferation. An effect of c-MET inhibitors was simulated by decreasing parameter Emax of HGF stimulatory effect on proliferation of c-MET positive cells. Tumor volume was defined as an explicit function of a total number of melanoma cells and used to measure change from baseline during the therapy.

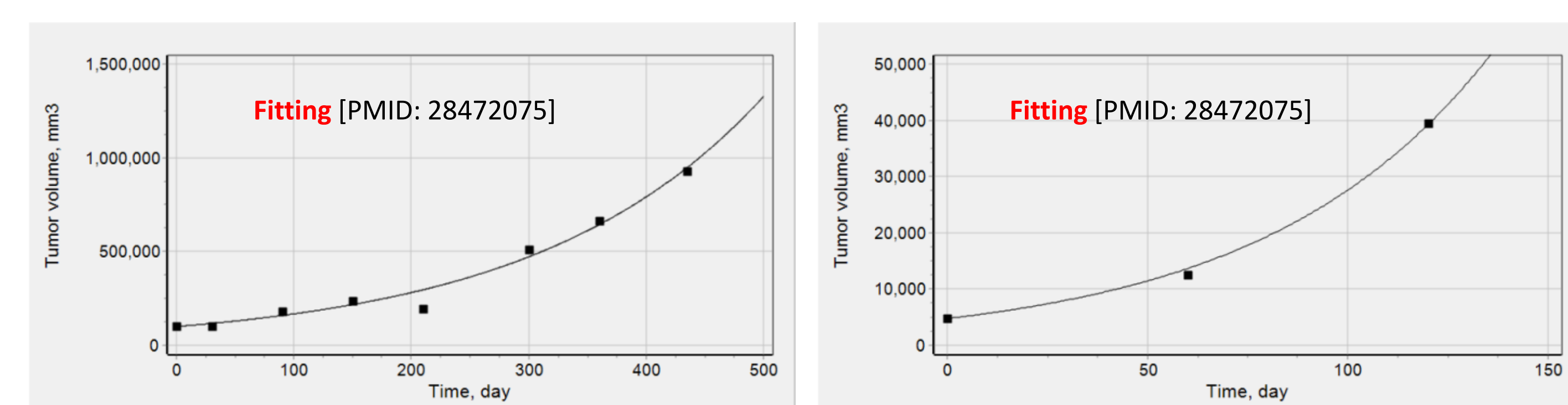


MODEL CALIBRATION

Parameters of the model were calculated or fitted on the basis of available published data.



Parameters of the melanoma growth were fitted on the basis of available published data on changes in total tumor volume along the course of the disease.



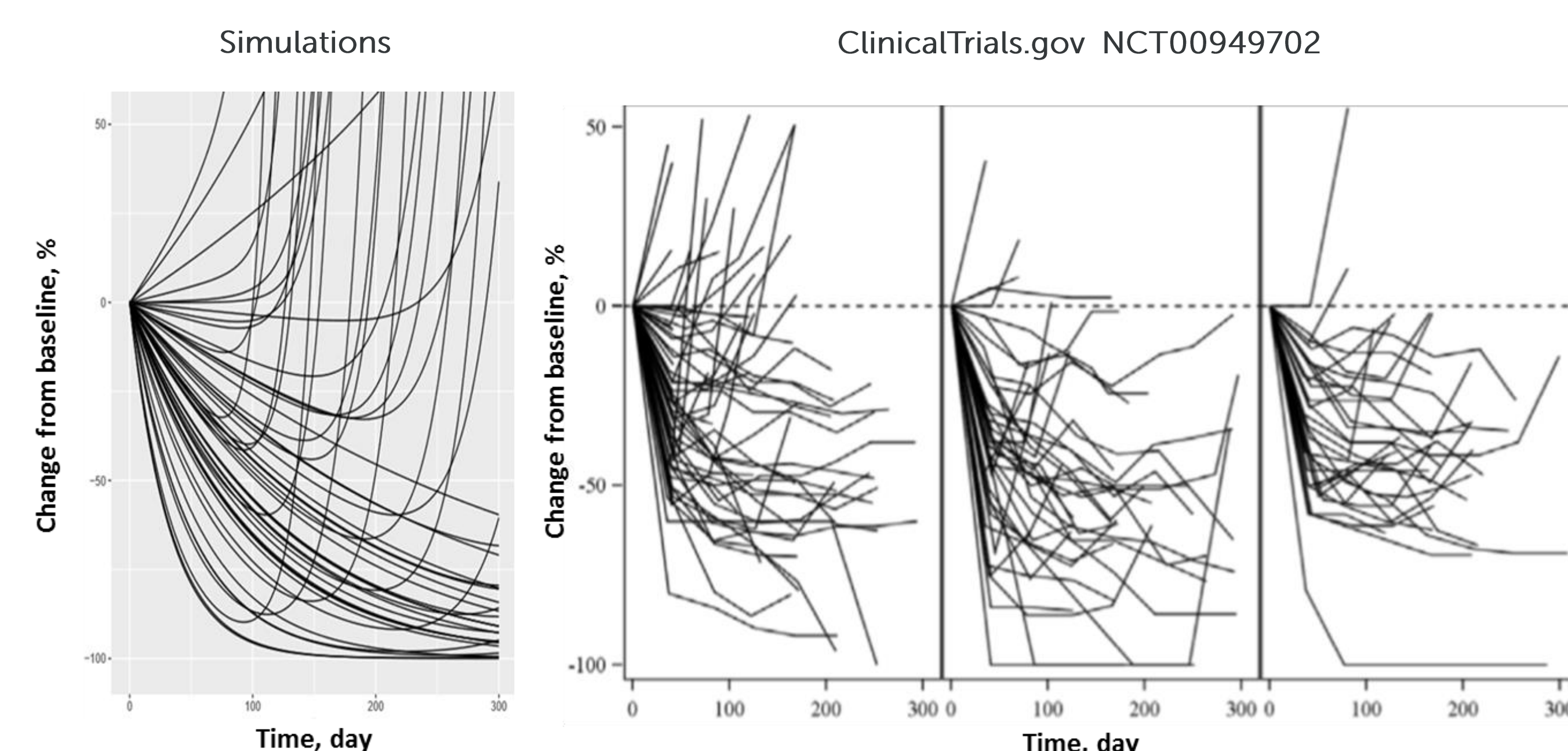
INTER-PATIENT VARIABILITY

To introduce an inter-patient variability in the model for further multiple simulations we compiled available published data and tried to estimate variability for several numbers of parameters. Also, we tried to estimate the amount of pre-existing drug-resistant cells in the tumor on the basis of clinical data on time to progression. It is important to note due to the lack of data we are able only to assume the probability distribution of each parameter and approximately to estimate mean and variance. The R package 'stats' were used for random generation of parameters sets according to their function of distribution (R v3.2.1).

Parameter	Description	Source
k_apo	Rate constant of apoptosis/death of melanoma cells	PMID: 22356324
k_growth	Rate constant reflecting real growth of melanoma cells	PMID: 23805382; 28472075; 26105199
Imax_pro_sen_vem	Imax of vemurafenib inhibitory effect on proliferation of sensitive to vemurafenib melanoma cells	PMID: 22763439; 22763448; 26497853
IC50_pro_sen_vem	IC50 of vemurafenib inhibitory effect on proliferation of sensitive to vemurafenib melanoma cells	PMID: 23658559
IC50_pro_res_vem	IC50 of vemurafenib inhibitory effect on proliferation of relatively resistant to vemurafenib melanoma cells	PMID: 23658559
Emax_pro_meL_hgf	Emax of HGF stimulatory effect on proliferation of melanoma cells expressing Met (HGF receptor)	PMID: 28147313; 22763448
Frequency	Frequency of mutations related to development of drug resistance in melanoma cell	PMID: 3567893
HGF_plasma_pg_mL	HGF level in plasma	PMID: 27206057
PK parameters	PK parameters for vemurafenib (k_abs, CL, Vd)	FDA report
MeL_sen_met_neg	Initial number of sensitive to vemurafenib melanoma cells in tumor at the starting time of therapy	PMID: 22356324
MeL_res_met_neg	Initial number of resistant to vemurafenib melanoma cells in tumor at the beginning of therapy	PMID: 22356324

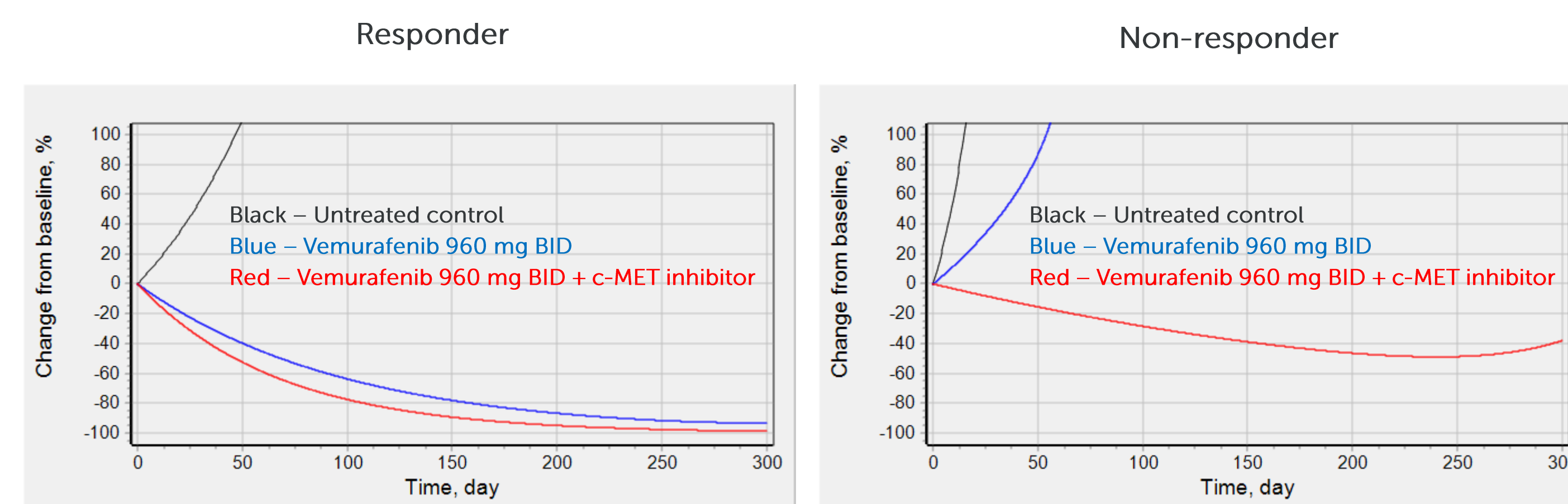
SIMULATIONS: VEMURAFENIB MONOTHERAPY

The developed model is able to adequately reproduce all possible types of tumor response to vemurafenib monotherapy according to RECIST criteria. An overall response rate predicted by the model was 70% versus 53% (95% CI, 44 to 62) observed in phase 2 clinical trial (NCT00949702). However, the model tends to overestimate the treatment effect possibly due to we did not take into account an intermittent administration and dose reduction in case of adverse events.



SIMULATIONS: POTENTIAL ROLE OF C-MET INHIBITORS

The results obtained predict that usage of c-MET inhibitors in combination with BRAF inhibitors for treatment of metastatic melanoma patients could improve response and overall response rate, as well as delay or avoid BRAF-inhibitors resistance development and relapse.



CONCLUSIONS

The developed model was able to satisfactory predict the variability in response to vemurafenib treatment on the basis of published data only. The model could be used as a tool for optimization of new targeted therapies and their combinations for melanoma treatment.

CONTACTS

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