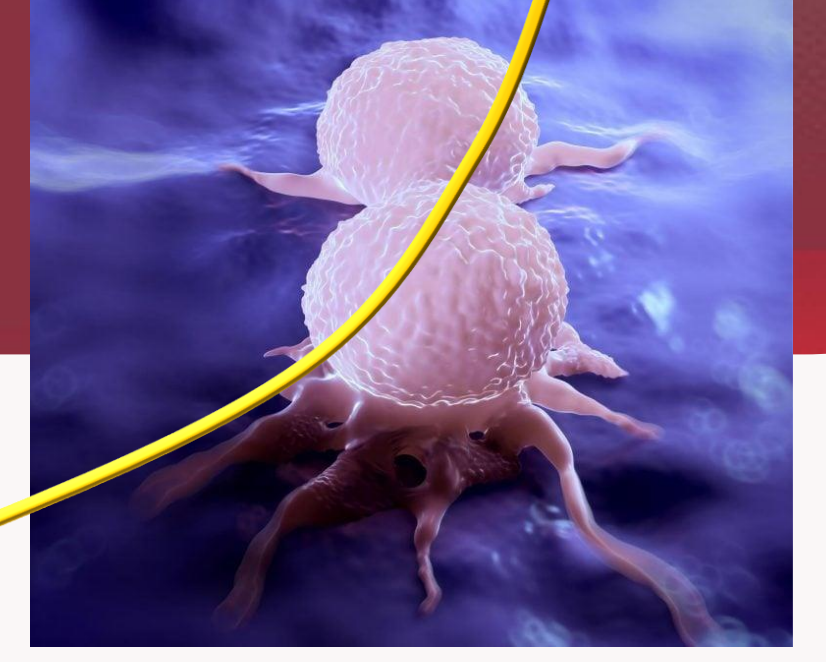


# A new model of Tumor Growth Inhibition for pseudo-progression in Immuno-Oncology<sup>1</sup>



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## Background and Objective

Modelling of longitudinal tumor size metrics has gained traction in Oncology to complement traditional endpoints. Several models have been developed to model Tumor Growth Inhibition (TGI) but none appear to be tailored to Immuno-oncology (IO) trials in which a few patients (typically 5-10%) pseudo-progress, a phenomenon where tumour size initially increases prior to decreasing. Well capturing TGI in these patients is essential (often a substantial fraction of responders), particularly if attempting to predict overall survival (OS) [1]. **We developed and tested a new TGI model that can be used to analyse clinical trials where pseudo-progression is present.**

## Methods

A new model has been developed by introducing a pseudo-progression term in the standard model developed by Stein et al [2]. The regular Stein model incorporates two components, a growing term ( $\exp(k_g t)$ ) and a shrinking term ( $\exp(k_k t)$ ). These combine into an analytical solution that can capture either tumor growth only, or shrinkage and growth, or only shrinkage ( $TS = TS_0 (\exp(k_g t) + \exp(k_k t) - 1)$ ). The model was adapted by introducing an initial phase with a linear growth ( $G \cdot t$ ) into the analytical solution. This initial phase is activated for a duration  $t$  such that  $0 \leq t \leq d_{ps}$ . Profiles are automatically classed into pseudo-progression vs. non-pseudo-progression by inference of  $d_{ps}$  and a population  $d_{ps}$  cut-off.

The model was initially explored in parameters space. It was then used to model a TGI dataset for an undisclosed IO drug. The dataset was composed of TGI data for approximately 600 patients. In this dataset, approximately 10% of patients displayed pseudo-progression or steep changes in tumor size. Both the Stein and the new models were used to model the data via the Stochastic Approximation Expectation Minimization (SAEM) algorithm by Monolix 2024R1 (<https://monolixsuite.slp-software.com/>). Observations were censored to account for lower limit of quantification and early drop-out. An exponential random-effect model was used for each parameter, assuming a normal distribution with mean 0 and variance  $\omega^2$ . A correlation was also modelled between  $k_g$  and  $k_k$  while residual errors were modelled as a combination of proportional and additive errors.

## Results

Exploring the model in parameters space confirmed its ability to capture pseudo-progression. When the regular Stein model and our new model were applied to the IO TGI dataset, the new model was able to capture all atypical or pseudo-progression cases which could not be captured by the regular Stein model. In all other cases, the same profile was obtained with the two approaches (Figure 1). The fixed effects for  $k_g$  and  $k_k$  and standard deviation obtained with the two methods can be seen in Table 1.

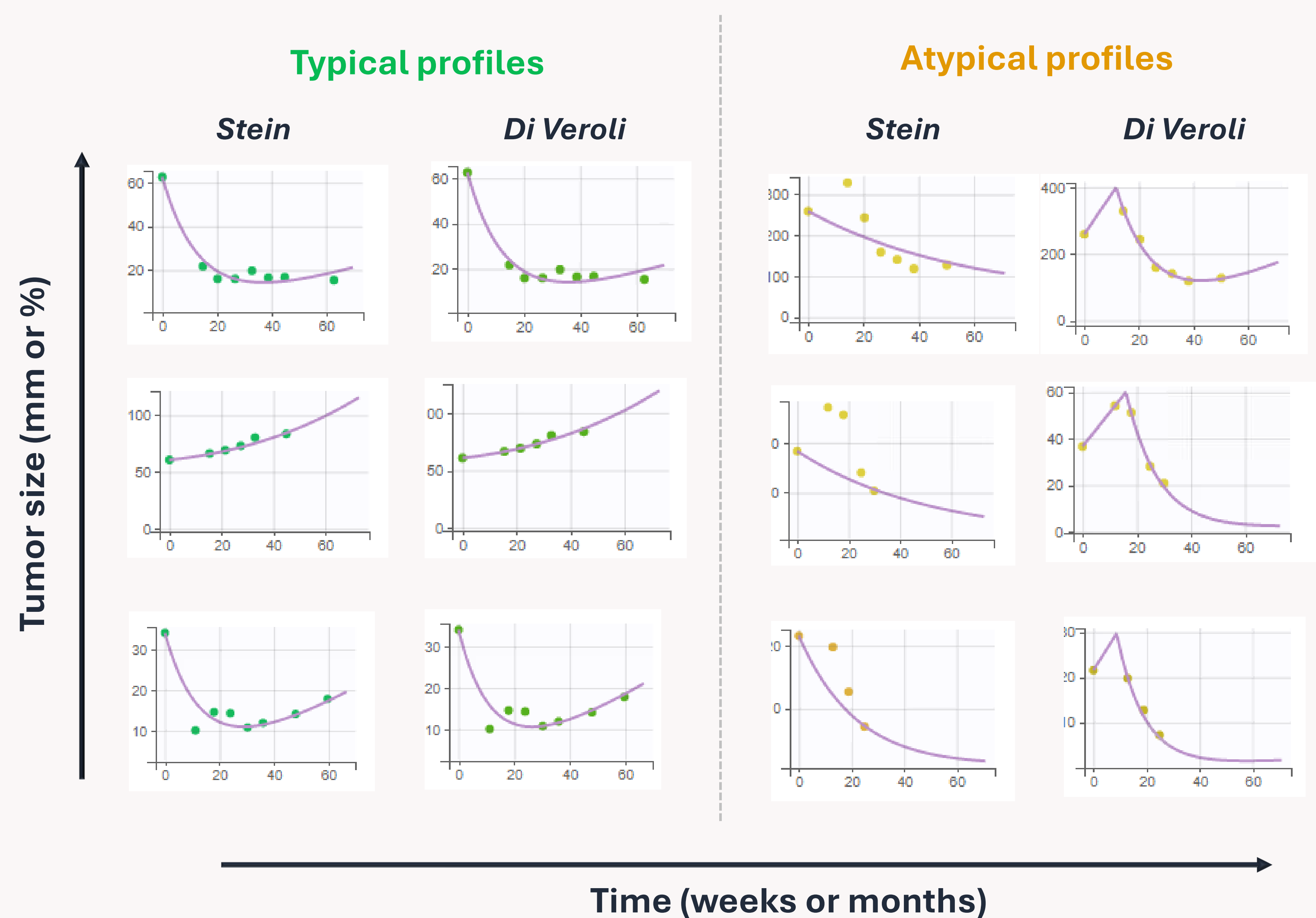
The parameters  $k_g$  and  $k_k$  were found to be similar for both models for patients that did not pseudo-progress. For patients that displayed pseudo-progression, the new model provided parameters that better reflected the post-pseudo-progression phase of tumor longitudinal changes. Visual predictive checks (VPC) were similar for the two models while goodness-of-fit and individual weighted residuals (IWRES) over time plots, as well as Bayesian information criterion (BIC; 7438.4 vs. 8346.6 for Di Veroli and Stein respectively) all favoured the new model.

**Table 1:** The fixed effects for  $k_g$  and  $k_k$  and their standard deviations

Models	$\omega k_g$ (%R.S.E.)	$\omega k_k$ (%R.S.E.)
Stein	1.8 (6.9%)	1.4 (6.1%)
Di Veroli	1.4 (6.8%)	1.2 (6.8%)

Models	$k_g$ [/week] (%R.S.E.)	$k_k$ [/week] (%R.S.E.)
Stein	$3.8 \cdot 10^{-3}$ (15.2%)	$1.5 \cdot 10^{-2}$ (11.8%)
Di Veroli	$4.8 \cdot 10^{-3}$ (11.2%)	$3.4 \cdot 10^{-2}$ (9.2%)

**Figure 1:** Examples of typical and atypical profiles models



## Conclusions

We have developed a new mathematical model to support TGI modelling in Immuno-Oncology trials where pseudo-progression is observed. The model can be applied to all patients independently of their response type, and its parameters can be easily interpreted in terms of the various phases of tumor progression: pseudo-progression (if present), shrinkage and (re)growth.

## References

- [1] Bruno R, Bottino D, De Alwis DP, Fojo AT, Guedj J, Liu C, et al. Progress and opportunities to advance clinical cancer therapeutics using tumor dynamic models. Clin Cancer Res 2020;26:1787–95.
- [2] Stein WD, Gulley JL, Fojo T, Schlom J, Madan RA, Dahut W, Figg WD, Ning Y-M, Arlen PM, Price D, Bates SE. Tumor Regression and Growth Rates Determined in Five Intratumoral NCI Prostate Cancer Trials: The Growth Rate Constant as an Indicator of Therapeutic Efficacy. Clin Cancer Res (2011) 17 (4): 907–917

