Different ODE models of tumor growth can deliver similar results

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Abstract

Background: Simeoni and colleagues introduced a compartmental model for tumor growth that has proved quite successful in modeling experimental therapeutic regimens in oncology. The model is based on a system of ordinary differential equations (ODEs), and accommodates a lag in therapeutic action through delay compartments. There is some ambiguity in the appropriate number of delay compartments, which we examine in this note.

Methods: We devised an explicit delay differential equation model that reflects the main features of the Simeoni ODE model. We evaluated the original Simeoni model and this adaptation with a sample data set of mammary tumor growth in the FVB/N-Tg(MMTVneu)202Mul/J mouse model.

Results: The experimental data evinced tumor growth heterogeneity and inter-individual diversity in response, which could be accommodated statistically through mixed models. We found little difference in goodness of fit between the original Simeoni model and the delay differential equation model relative to the sample data set.

Conclusions: One should exercise caution if asserting a particular mathematical model uniquely characterizes tumor growth curve data. The Simeoni ODE model of tumor growth is not unique in that alternative models can provide equivalent representations of tumor growth.

Keywords: Tumor growth, Cancer chemotherapy, Mathematical model, Ordinary differential equations, Delay differential equations

Background

Simeoni and colleagues [1–3] introduced and developed a pharmacokinetic/pharmacodynamic (PK/PD) model of tumor growth from in vivo animal studies, which could be summarized mathematically by a system of ordinary differential equations (ODEs). The model, and adaptations, have proved quite successful in predicting or modeling tumor growth and efficacy of cancer treatments [4–9].

A distinguishing characteristic of the Simeoni tumor growth model is that under chemotherapy, a drug’s action is not instantaneous: rather, tumor cells pass through progressive stages of damage because of the drug’s mechanism of action. This delay in drug action is modeled through a series of delay compartments through which the cells transit before elimination. In this note, we propose an alternative mathematical formulation of the Simeoni model using delay differential equations, without recourse to a series of delay compartments. We describe the two models in the next section, and then compare their performances with experimental data relating to mammary tumor growth in a mouse model. We conclude that one should be cautious if asserting that a particular tumor growth model uniquely characterizes experimental data.

Methods

The Simeoni model

The Simeoni model is depicted in Fig. 1. The central compartment $Z_1$ represents the actively growing tumor, which increases according to a growth function $TGF_c(t)$. $c(t)$ denotes the concentration of a chemotherapeutic or
immunotherapeutic agent in the central compartment $Z_1$ at time $t$. In turn, $c(t)$ induces a fraction of tumor cells to commit to cell death with a killing constant $k_1$. Tumor cells damaged by pharmacological treatment are shunted off successively into the peripheral compartments $Z_2, Z_3, Z_4$ with a rate constant $k_2$, followed by elimination representing cell death. The observed tumor volume is the sum of cells in compartments $Z_1, Z_2, Z_3, Z_4$. The system of differential equations prescribing the Simeoni model is as follows:

\[
\begin{align*}
\frac{dZ_1}{dt}(t) &= TGF(t) - k_1 c(t) Z_1(t) \\
\frac{dZ_2}{dt}(t) &= k_1 c(t) Z_1(t) - k_2 Z_2(t) \\
\frac{dZ_3}{dt}(t) &= k_2 Z_2(t) - k_2 Z_3(t) \\
\frac{dZ_4}{dt}(t) &= k_2 Z_3(t) - k_2 Z_4(t)
\end{align*}
\]  

(1)

with initial conditions $Z_1(0) = V_0$, $Z_2(0) = Z_3(0) = Z_4(0) = 0$. Total tumor volume is

\[ V(t) = Z_1(t) + Z_2(t) + Z_3(t) + Z_4(t), \]  

(2)

and the tumor growth function $TGF(t)$ is given by

\[ TGF(t) = \frac{\lambda_0 Z_1(t)}{1 + \left(\frac{V(t)}{C_16/C_17}\right)^{1/\psi}} \]  

(3)

Although we have depicted the Simeoni model with 3 peripheral compartments, we note that the number of peripheral compartments is in general arbitrary.

The model incorporating a delay differential equation is conceptually similar to the Simeoni model, the only difference being that the compartments $Z_2, Z_3, Z_4$ are replaced by a single compartment that incorporates a delay in elimination (Fig. 2). The system of differential equations describing this model is:

\[
\begin{align*}
\frac{dZ_1}{dt}(t) &= TGF(t) - k_1 c(t) Z_1(t) \\
\frac{dZ_2}{dt}(t) &= k_1 c(t) Z_1(t) - k_2 delay(Z_2, t_2);
\end{align*}
\]  

(4)

where

\[ delay(Z_2, t_2) = Z_2(t-t_2), \]

TGFr(t) and c(t) are as before, $V(t) = Z_1(t) + Z_2(t)$, and initial conditions are $Z_1(0) = V_0$, $Z_2(0) = 0$, and $Z_2(t) = 0$.
for $t < 0$. The variable $t_2$ represents the time delay before elimination.

In the absence of chemotherapeutic or immunotherapeutic intervention (i.e., $c(t) = 0$), tumor growth in the Simeoni formulation reduces to the biphasic process $TGF(t)$, characterized by initial exponential growth followed by linear growth. In particular, in contrast to more classic models of tumor growth, e.g. logistic, Gompertz, Von Bertalanffy, there is no plateau or upper limit of tumor size. One of these alternative models might credibly be more appropriate than $TGF$ in certain experimental settings. The generalized logistic model is defined by

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**Fig. 3 a, b** Time course of tumor growth in 21 untreated tumor-bearing mice over the course of the experiment. The X-axis (time) denotes days, and the Y-axis (volume) denotes mm$^3$. 
\[
d\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right)^\gamma
\]
(5)

the Gompertz model is given by
\[
d\frac{dV}{dt} = aV\ln(\beta V)
\]
(6)
and the Von Bertalanffy model is
\[
d\frac{dV}{dt} = aV^\gamma - bV
\]
(7)

These three models have analytic solutions [10], which might aid in nonlinear fitting to experimental data.

**In vivo tumor growth experiments**

A series of experiments was undertaken at PRISM, the goal being to establish a viable and reproducible mouse model for mammary tumors. The FVB/N-Tg(MMTVneu)202Mul/J model was used for this purpose (Jackson stock #002376). All mice were bred at PRISM, with female mice genotyped by polymerase chain reaction to confirm transgene expression. In vivo tumor growth experiments were recorded using the approximating formula
\[
V(t) = V(0) + \int_0^t f(t)\,dt,
\]
where \( f(t) \) is the structural model, expressed from the rotation of a semi-ellipsis around its larger axis
\[
\frac{x^2}{a^2} + \frac{y^2}{b^2} = 1,
\]
and \( (x, y) \) are the coordinates of the tumor. The term \( f \) is the structural model, expressed from the systems of ordinary differential equations shown earlier. The residual error is \( \varepsilon_i = f(t_{ij}, \phi_i) + g(t_{ij}, \phi_i, \zeta)\varepsilon_{ij} \), where \( \varepsilon_{ij} \sim N(0, \sigma^2) \) and \( \zeta = (a, b) \) is a p-vector of random effects, \( W \) is the p x p variance-covariance matrix of the random effects, and \( h \) is a fixed transformation. We assume that all of the model parameters are log-normally distributed.

**In vivo tumor growth experiments**

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\[
V = \frac{L\times W^2}{2},
\]
where \( L > W \). [In this approximating formula, tumor shape is taken as an ellipsoid generated from the rotation of a semi-ellipsis around its larger axis (length), and a multiplicative constant involving \( p \) is ignored.] Mice were euthanized when tumors reached a volume of \( \sim 2500 \mathrm{mm}^3 \) (or measured 17 mm in length + width + height), or for complications, e.g., interference, ulceration. The method of euthanization was \( \mathrm{CO}_2 \) narcosis followed by cervical dislocation, a method consistent with the 2013 recommendations of the American Veterinary Medical Association Panel on Euthanasia. The protocol for this study was approved by the Institutional Animal Care and Use Committee of Prism, confirmed by the National Institutes of Health Office of Laboratory Animal Welfare Assurance, #D16–00819. Animals were housed in Prism’s animal care facility.

All 40 animals initially randomized to the untreated and the cisplatin-treated groups were included in the subsequent analyses. There were a total of 386 observations among the 21 control animals, and 545 observations among the 19 treated animals.

**Statistical methods**

A nonlinear mixed effects (NLME) model was used to fit growth curves to the longitudinal tumor size data. In our context, a general form for NLME models would be:
\[
y_{ij} = f(t_{ij}, \phi_i) + g(t_{ij}, \phi_i, \zeta)\varepsilon_{ij}, \quad 1 \leq i \leq N, \quad 1 \leq j \leq n_i,
\]
where \( N \) is the number of individuals, \( n_i \) is the number of observations for individual \( i \), \( t \) is the regression variable time, and \( y \) are the observations (tumor volumes). The term \( f \) is the structural model, expressed from the systems of ordinary differential equations shown earlier. The residual error is \( \varepsilon_{ij} = g(t_{ij}, \phi_i, \zeta)\varepsilon_{ij} \), where \( \varepsilon_{ij} \sim N(0, \sigma^2) \) in our modeling.

The individual parameters \( \phi_i \) are defined as follows:
\[
\phi_i = h(\mu, \lambda_1, ..., \lambda_l; \Omega, \zeta),
\]
where \( m \) is a p-dimensional vector of fixed population parameters, \( l \) is a p-vector of random effects, \( \Omega \) is the p x p variance-covariance matrix of the random effects, and \( h \) is a fixed transformation. We assume that all of the model parameters are log-normally distributed.

**Table 1** Summary statistics relating to growth curve models fit to the control data

| model       | −2LL  | AIC   | AICc  | AICc_0 | w(AICc)  | w(AICc_0) | BIC   | w(BIC)   |
|-------------|-------|-------|-------|--------|----------|-----------|-------|----------|
| generalized logistic | 5159.69 | 5179.69 | .0037 | 5180.07 | .0038 | 5190.13 | .0038 |
| Gompertz    | 5182.79 | 5198.79 | 2.66E-07 | 5199.01 | 2.88E-07 | 5207.15 | 7.72E-07 |
| von Bertalanffy | 5189.97 | 5209.97 | 9.94E-10 | 5210.35 | 9.95E-10 | 5226.42 | 5.05E-11 |
| Simeoni     | 5148.52 | 5168.52 | .9963 | 5168.90 | .9963 | 5179.01 | .9962 |

**Notes**

LL log likelihood, AIC Akaike information criterion, w(AIC) weights derived from candidate model AIC values, AICc corrected Akaike information criterion, w(AICc) weights derived from candidate model AICc values, BIC Bayesian information criterion, w(BIC) weights derived from candidate model BIC values.
Fig. 4 Observed tumor sizes and fitted values of the 21 untreated tumor-bearing mice over the course of the experiment. The Simeoni tumor growth function was fit to the tumor size data from the entire cohort of animals, and individual fits were then derived from the mixed model analysis undertaken in Monolix.
among the individuals in each cohort, so that $h(x) = \exp(x)$.

Parameter estimation of the typical population values and the interindividual variability of each model parameter were estimated using Monolix 2019R1 (Lixoft, Antony, France).

The Monolix suite of programs implements a stochastic approximation expectation maximization (SAEM) algorithm [11, 12] for maximum likelihood estimation of the model parameters. With the treated animals, following a single bolus injection of cisplatin we took $c(t)$ to represent first order

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**Fig. 5 a, b** Time course of tumor growth in 19 treated tumor-bearing mice over the course of the experiment. Treatment consisted of a single dose of cisplatin (5 mg/kg) on day 0. The X-axis (time) denotes days, and the Y-axis (volume) denotes mm$^3$. 
elimination, that is, a constant proportion of the drug is eliminated per unit time.

Model selection and comparison was based on the Akaike information criterion (AIC), the corrected Akaike information criterion (AICc), and the Bayesian information criterion (BIC). AICc is a modified version of the AIC, and includes a correction term for small sample sizes [13–15]:

$$AIC_c = AIC + \frac{2k(k + 1)}{n-k-1}$$ (8)

where $k$ denotes the number of free parameters, and $n$ is the number of observations. In our setting, we also included variance components from the random effects in the parameter count.

Given a set of candidate models, each with a specific IC (AIC, AICc, BIC) value, we calculate IC model weights [15–17] for comparative purposes. We first compute for each model $j$ the difference in IC relative to the IC of the best candidate model: $\Delta j = IC_j - \min IC$. We then obtain the model weights by transforming to the likelihood scale and normalizing:

$$w_j = \frac{\exp(-\Delta j/2)}{\sum_{m=1}^{M} \exp(-\Delta m/2)}$$ (9)

These weights are measures of the strength of evidence. They sum to one, and reflect the probability of each model $j$ given the data and the $M$ candidate models [15, 17].

**Results**

In the experiment outlined above, a total of 21 tumor-bearing mice were untreated. Tumor growth over time in this group of animals is shown in Fig. 3.

We use this cohort of controls to investigate various tumor growth functions, namely, generalized logistic, Gompertz, Von Bertalanffy, and Simeoni. We present summary data relative to these fits in Table 1. It turns out that the Simeoni tumor growth function provides the best fit to these data, with minimal AIC, AICc, and BIC. The weights convey the overwhelming preference for the Simeoni tumor growth function among the candidate functions.

Plots of the individual fits with the Simeoni tumor growth function are shown in Fig. 4. Although the individual growth curves are quite heterogeneous (Fig. 3), the fitted curves quite nicely represent the observed data.

Nineteen tumor-bearing mice were treated with cisplatin. Their individual growth patterns are shown in Fig. 5.

We used the Simeoni tumor growth function, and proceeded to fit the Simeoni model with varying numbers of peripheral delay compartments as well as the delay model to these data. Summary statistics are given in Table 2. Among the candidate models, the delay model evinces minimal AIC and AICc values, whereas the Simeoni model with 2 delay compartments minimizes the BIC. The weights reflect this model uncertainty: one might deem the delay model preferable to the Simeoni - 2 and Simeoni - 3 models relative to AIC or AICc, but this order is reversed with BIC. Regardless, the Simeoni - 1 model appears inferior to the other candidate models.

Plots of the individual fits with the delay model are shown in Fig. 6. Again, inter-animal variability is quite high, especially in terms of tumor response to treatment, with the individual fits modeling the observed data appropriately.

**Discussion**

The Simeoni tumor growth function switches between exponential and linear growth, but without a plateau phase, in contrast to the classic tumor growth functions. It works quite well in our experimental setting, in which tumor-bearing mice were euthanized for ethical reasons when tumor volume reached the maximum allowable tumor mass, and this generally occurred before a plateau phase was reached. We caution, however, that in other experimental or clinical settings, the Simeoni tumor growth function might be supplanted by a more biologically realistic growth law [10, 18]. And, as a reviewer has pointed out, even the classical growth curve models logistic, Gompertz, and von Bertalanffy (our eqs. 5–7)

| Table 2 | Summary statistics relating to growth curves models fit to the treated data |
|---------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| model   | -2*LL | AIC  | w(AIC) | AICc | w(AICc) | BIC  | w(BIC) |
| Simeoni -1 | 6786.12 | 6818.12 | .015 | 6818.91 | .016 | 6833.23 | .020 |
| Simeoni -2 | 6780.10 | 6812.10 | .310 | 6812.89 | .325 | 6827.21 | .410 |
| Simeoni -3 | 6780.32 | 6812.32 | .278 | 6813.11 | .291 | 6827.44 | .366 |
| delay     | 6775.61 | 6811.61 | .397 | 6812.64 | .368 | 6828.61 | .204 |

Notes

1, 2, and 3 in the Simeoni model designations refer to the number of delay compartments incorporated into these models (Fig. 1). The delay model has one peripheral compartment, with an explicit delay in elimination (Fig. 2).

LL log likelihood, AIC Akaike information criterion, w(AIC) weights derived from candidate model AIC values, AICc, corrected Akaike information criterion, w(AICc) weights derived from candidate model AICc values, BIC Bayesian information criterion, w(BIC) weights derived from candidate model BIC values.
Observed tumor sizes and fitted values of the 19 treated tumor-bearing mice over the course of the experiment. A system of delay differential equations incorporating the Simeoni tumor growth function was fit to the tumor size data from the entire cohort of animals, and individual fits were then derived from the mixed model analysis undertaken in Monolix.
enjoy many variations, specializations, and extensions, which might be judiciously employed to good effect in experimental settings.

The original Simeoni model essentially is a transit compartment model: tumor cells pass through progressive stages of damage because of the drug’s mechanism of action. Dying tumor cells stop proliferating and pass through several stages of dying (depicted by n delay compartments) before eventual death. However, there is some ambiguity over the exact number of delay compartments. With our experimental data, the appropriate number of delay compartments remains somewhat uncertain, relative to goodness of fit. Moreover, we have found that the delay compartments can effectively be replaced by a model incorporating a single peripheral compartment with a delay in elimination; that is, explicit incorporation of a delay term in the Simeoni tumor growth model can operationally replace the multiple transit compartments originally proposed, and effectively model the duration of the death process subsequent to drug action. Delay differential equation models have often been successfully investigated in tumor growth studies [19–24], and seem especially applicable in settings where tumor volume decrease appears delayed with respect to observed drug concentrations. With agents such as cisplatin, the delay in cell kill relative to the time course of extracellular exposure likely reflects the kinetics of cellular drug uptake and binding to intracellular targets [25]. Alternatively, more physiologically based models can ameliorate the ambiguity inherent with an arbitrary number of transit compartments [25–28].

With regard to model selection, we are more interested in the relative performances of the models rather than their absolute AIC, AICc, or BIC values. In this regard, the weights derived from the information criterion values quantify the probabilities of each model being optimal, given the data and the set of candidate models, hence provide useful criteria for model comparisons. There is little uncertainty about the suitability of the Simeoni growth function in Table 1, whereas the identifiability of the best approximating model in Table 2 is not incontrovertible. Regardless, the delay model is certainly competitive with the Simeoni model, and does provide excellent agreement with the experimental data, even with substantial tumor growth heterogeneity and inter-animal diversity in response.

Conclusions
One should exercise caution if asserting a particular mathematical model uniquely characterizes tumor growth curve data. The Simeoni ODE model of tumor growth is not unique in that alternative models can provide equivalent representations of tumor growth.

Abbreviations
AIC: Akaike information criterion; AICc: Corrected Akaike information criterion; BIC: Bayesian information criterion; nlme: Nonlinear mixed effects; ODEs: Ordinary differential equations; pk/pd.: Pharmacokinetic/pharmacodynamic; PRISM: Proteogenomics Research Institute for Systems Medicine; SAEM: Stochastic approximation expectation maximization

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Author contributions
JES conceived and designed the underlying animal studies, and directed the project. TJF assisted with planning the animal studies and carried out the implementation and data acquisition. JAK performed the mathematical analysis and drafted the manuscript. All authors read, edited, and approved the final manuscript.

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Availability of data and materials
The datasets analysed in this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Institutional Animal Care and Use Committee of PRISM.

Consent for publication
Not applicable.

Competing interests
The authors declare they have no competing interests.

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References
1. Simeoni M, Magni P, Cammia C, De Nicolao G, Croci V, Pesenti E, Germani M, Poggesi I, Rocchetti M. Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. Cancer Res. 2004;64:1094–11.
2. Magni P, Simeoni M, Poggesi I, et al. A mathematical model to study the effects of drug administration on tumor growth dynamics. Math Biosci. 2006;200:127–51.
3. Simeoni M, De Nicolao G, Magni P, et al. Modeling of human tumor xenographs and dose rationale in oncology. Drug Discov Today Technol. 2013;10:e365–72.
4. Rocchetti M, Del Bene F, Germani M, Fiorentini F, Poggesi I, Pesenti E, Magni P, De Nicolao G. Testing additivity of anticancer agents in pre-clinical studies: a PK/PD modelling approach. Eur J Cancer. 2009;45:3336–46.
5. Zhou R, Maozuchuk RV, Tamburlin JJ, Harrold JM, Mager DE, Straubinger RM. Differential pharmacodynamic effects of paclitaxel formulations in an intracranial rat brain tumor model. J Pharmacol Exp Ther. 2010;332:479–88.
6. Terranova N, Germani M, Del Bene F, Magni P. A predictive pharmacokinetic-pharmacodynamic model of tumor growth kinetics in xenograft mice after administration of anticancer agents given in combination. Cancer Chemother Pharmacol. 2013;72:471–82.
7. Li J, Ren J, Yuan Y, Ji SM, Zhou SP, Wang LJ, Mou ZZ, Li L, Li W, Zhou TY. A preclinical PK/PD model for combined administration of erlotinib and sunitinib in the treatment of A549 human NSCLC xenograft mice. Acta Pharmacol Sin. 2016;37:930–40.
8. Pigatto MC, Roman RM, Carrara L, Buffon A, Magni P, Dalla CT. Pharmacokinetic/pharmacodynamic modeling of etoposide tumor growth increase.
inhibitory effect in Walker −256 tumor-bearing rat model using free intratumoral drug concentrations. Eur J Pharm Sci. 2017;97:70–8.

9. Yates JWT, Holt SV, Armelie Logie A, et al. A pharmacokinetic–pharmacodynamic model predicting tumour growth inhibition after intermittent administration with the mTOR kinase inhibitor AZD8055. Br J Pharmacol. 2017;174:2652–61.

10. Benzekry S, Lamont C, Beheshti A, et al. Classical mathematical models for description and prediction of experimental tumor growth. PloS Comput Biol. 2014;10:e1003800.

11. Delion B, Lavielle M, Moulines E. Convergence of a stochastic approximation version of the EM algorithm. Ann Stat. 1999;27:94–128.

12. Comets E, Lavenu A, Lavielle M. Parameter estimation in nonlinear mixed effect models using saemix an R implementation of the SAEM algorithm. Journal of Statistical Software. 2017. https://doi.org/10.18637/jss.v080.i03.

13. Sugiuira N. Further analysis of the data by Akaike's information criterion and the finite corrections. Communications in Statistics, Theory and Methods. 1978;7:11–26.

14. Hurvich CM, Tsai C-L. Model selection for extended quasi-likelihood models in small samples. Biometrics. 1995;51:1077–84.

15. Burnham KP, Anderson DR. Model selection and multi model inference: A practical information-theoretic approach. New York: Springer-Verlag; 2002.

16. Akaike H. On the likelihood of a time series model. The Statistician. 1974;27:217–35.

17. Wagenmakers E-J, Farrell S. AIC model selection using Akaike weights. Psychon Bull Rev. 2004;11:192–6.

18. Mould DR, Walz A-C, Lave T, Gibbs JP, Frame B. Developing exposure/response models for anticancer drug treatment: special considerations. CPT Pharmacometrics Syst Pharmacol. 2015;4:12–27.

19. Villasana M, Radunskaya A. A delay differential equation model for tumor growth. J Math Biol. 2003;47:270–94.

20. Cui S, Xu S. Analysis of mathematical models for the growth of tumors with time delays in cell proliferation. J Math Anal Appl. 2007;336:523–41.

21. Bodnar M, Piotrowska M, Forus U. Gompertz model with delays and treatment: mathematical analysis. Math Biosci Eng. 2013;10:551–63.

22. Xu S, Wei X, Zhang F. A time-delayed mathematical model of tumor growth with the effect of a periodic therapy. Comput Math Methods Med. 2016;2016:3643019.

23. Mazlan MSA, Rosli N, Azmi NS. Modelling the cancer growth process by stochastic delay differential equations under Verhults and Gompertz’s law. Jurnal Teknologi. 2016;78:77–82.

24. Kim PS, Lee PP. Modeling protective anti-tumor immunity via preventable cancer vaccines using a hybrid agent-based and delay differential equation approach. PLoS Comput Biol. 2012;8:e1002742.

25. El-Kareh AW, Secomb TW, A mathematical model for cisplatin cellular pharmacodynamics. Neoplasia. 2003;5:161–9.

26. Ribba B, Watkin E, Tod M, et al. A model of vascular tumour growth in mice combining longitudinal tumour size data with histological biomarkers. Eur J Cancer. 2011;47:479–90.

27. Ribba B, Kaloshi G, Peyre M, et al. A tumor growth inhibition model for low-grade glioma treated with chemotherapy or radiotherapy. Clin Cancer Res. 2012;18:5071–80.

28. Ribba B, Holford NH, Magni P, et al. A review of mixed-effects models of tumor growth and effects of anticancer drug treatment used in population analysis. CPT Pharmacometrics Syst Pharmacol. 2014;3:e113.

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