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ORIGINAL ARTICLE

Preclinical Modeling of Tumor Growth and Angiogenesis Inhibition to Describe Pazopanib Clinical Effects in Renal Cell Carcinoma

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The objective was to leverage tumor size data from preclinical experiments to propose a model of tumor growth and angiogenesis inhibition for the analysis of pazopanib efficacy in renal cell carcinoma (RCC) patients. We analyzed tumor data in mice with RCC CAKI-2 cell line treated with pazopanib. Clinical tumor size data obtained in a subset of patients with RCC were also analyzed. A model accounting for the processes of tumor growth, angiogenesis, and drug effect was developed. The final tumor model was composed of two variables: the tumor and its vasculature. Our results show that, both in mice and in humans, pazopanib exhibits a dual mechanism of action, and parameter estimation values highlight the inherent difference between mice and humans on the time scale of tumor size response. We developed a semimechanistic tumor growth inhibition model that takes into account tumor angiogenesis in order to describe the effects of pazopanib in mice. Analyzing rich preclinical data with a semimechanistic model may be a relevant approach to facilitate the description of sparse clinical longitudinal tumor size data and to provide insights for the understanding of the drug mechanisms of action in patients.
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC? ☑ Pazopanib is a tyrosine kinase inhibitor with multiple targets including angiogenesis. Existing pharmacokinetic-pharmacodynamic models are based on an empiric representation of tumor shrinkage due to treatment, and this representation does not specifically capture the compound's antiangiogenic action. • WHAT QUESTION DID THIS STUDY ADDRESS? ☑ The study focuses on the analysis of tumor size time course data from preclinical studies to lead to the development of a mechanistic model to predict pazopanib clinical efficacy. • WHAT THIS STUDY ADDS TO OUR KNOWLEDGE ☑ Our analysis supports the use of complete tumor dynamics in mice to build an angiogenesis-dependent tumor growth model that describes the antiangiogenic effects of pazopanib in phase II patients. Our work concludes that, both in mice and in humans, pazopanib exhibits a dual mechanism of action, and that the scaling of preclinical to clinical parameters shows a correspondence with allometric ratios that needs to be investigated in a future work. • HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS ☑ For a compound with a mechanism of action similar to that of pazopanib, an interesting avenue of research would be to compare clinical tumor response to the response predicted by scaling the preclinical model parameters for the new compound with the rate ratios estimated for pazopanib. Our model suggests that PD might be identified prematurely as a potential long-term tumor shrinkage due to the antiangiogenic effect of pazopanib that is likely to occur in some patients. If this statement is validated in future work, it will help to build new trial protocols in order to better assess efficacy.

Targeted therapy with tyrosine kinase inhibitors (TKI) such as pazopanib (VOTRIENT; GlaxoSmithKline, UK) is widely used in the treatment of renal cell carcinoma (RCC). Pazopanib has multiple targets, including the vascular endothelial growth factor (VEGF) receptors 1, 2, and 3; the platelet-derived growth factor receptors (PDGFR) α and β, and the stem cell factor receptor c-KIT.[1] The mechanisms of action of pazopanib, like those of other multitarget inhibitors, are complex and not fully understood. The underlying complexity of multitarget inhibitors makes the development of these drugs challenging, especially when translating from mice to humans.[2] For this purpose, many compounds that showed excellent antitumor properties in animals did not perform as well in patients, which resulted in drug development failure. This was the case for the compounds SU5416, TNP-470, and IM862, for example.[3]

Population modeling is recognized as a relevant method for characterizing tumor response to anticancer drugs. Tumor growth and inhibition (TGI) models have been used to leverage data on early tumor size dynamics with the aim of optimizing the design of late-phase trials.[4,5] Several models have been published that describe the time course of tumor size in RCC. Maitland *et al.*[6] successfully applied the model of Wang *et al.* to analyze tumor size time course in RCC patients treated with sorafenib. Houk *et al.*[7] used the model of Claret *et al.*[8] to describe the efficacy of sunitinib in metastatic RCC patients,

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and Stein *et al.*[9] proposed another model to describe tumor size kinetics in metastatic RCC patients treated with everolimus in a phase III trial. Bonate and Suttle developed a model that specifically addresses tumor size response in RCC patients treated with pazopanib.[10] Their model relies on an empiric representation of tumor shrinkage due to treatment, and this representation does not specifically capture the compound's antiangiogenic action. Like the models reviewed above, this model was developed on the basis of tumor size data.

The models described above bear high resemblance to one another, despite considering drugs with different mechanisms of action. This similarity may be due to the fact that in most cases longitudinal tumor size measurements in treated patients are characterized by an initial decrease eventually followed by a tumor regrowth. The designs of the clinical trials, as well as the need to remove patients from the study when tumor size increases, are significant constraints for the development of detailed mechanistic models.

To develop more accurate mechanistic models of tumor response, it is necessary to take advantage of any available complementary data associated with the clinical dataset analyzed. In previous work, carried out in a preclinical setting, we used histological data to complement tumor size records and proposed a multiscale model for tumor growth and angiogenesis.[11] The use of data on circulating biomarkers can also supplement the information encompassed in tumor size measurements to better predict patients' outcomes in response to treatment (see refs. 12–14 as examples). Challenges in translating data from animal models in oncology are frequently cited as a critical impediment to drug development efforts,[15] yet herein we propose that preclinical tumor size data can provide sufficient insights to facilitate the development of a more detailed mechanistic model of clinical tumor size response. Specifically, we show that the analysis of tumor size time course data from preclinical studies can be used to obtain a more detailed description of pazopanib effect in patients and can lead to the development of a mechanistic model to predict pazopanib clinical efficacy.

METHODS

Preclinical data

Female CB-17 SCID mice, aged 8–10 weeks, were housed in specific-pathogen-free environments and subcutaneously injected with a suspension of RCC CAKI-2 tumor cells. Once their tumors had grown to a size between 100 and 250 mm^3, mice were randomly distributed into dosing groups (8 mice per group) and received vehicle control, or 10, 30, or 100 mg/kg of pazopanib. The drug was administered once daily by oral gavage for 24 days. Twice weekly for the duration of the experiment, mice were weighed and tumor volumes were evaluated (eight observations of each type per mouse). The length and width of tumors were measured by handheld calipers, and tumor volume was calculated according to the following formula: tumor volume $= (\text{Length} \times \text{Width}^2)/2$.

Clinical data

Clinical data were obtained from a multicenter, open-label phase II study (NCT00244764).[16] We had access to a subset of 47 patients, aged 43 to 79 years, with advanced and/or metastatic RCC of predominantly clear-cell histology and obviousness of measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST). Patients were included in the dataset if they were treatment-naïve or had previously undergone a single treatment with systemic immunotherapy by cytokines, and/or had benefited from prior surgery (nephrectomy) and/or radiotherapy. Additional eligibility criteria included an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and adequate hematologic, hepatic, and renal function. The clinical trial was conducted according to the International Conference on Harmonization Guidelines for Good Clinical Practice and the amended Declaration of Helsinki. Patients were administered a dose of 800 mg of pazopanib once daily that was reduced in case of intolerance. Treatment was stopped because of unacceptable toxicity, withdrawal of consent for any reason, or disease progression (PD) assessed through RECIST 1.1.[17] No dose interruptions were reported within the dataset despite the events listed above. Disease assessments (sum of longest tumor diameter (SLD)) using computed tomography or magnetic resonance imaging were scheduled prior to initiation of pazopanib treatment (at baseline), at weeks 8 and 12 following treatment commencement, and every 8 weeks thereafter until progression.

Mixed effect modeling of tumor growth and effects of drug treatment

Nonlinear mixed-effect modeling (NLME) enables variability among individuals to be integrated into the description of any given process.[18] In our case, the structural part of the model corresponds to the solution of a system of ordinary differential equations (ODEs). In modeling tumor growth and effects of drug treatment, ODEs are generally written as a balance between the net growth and the drug-induced decay of the tumor size. Net growth can be represented by several types of functions, for example, linear, exponential, or logistic. The term representing drug-induced decay can be constant or exponential, driven by drug exposure, and it can incorporate a resistance term or a delay term to accommodate a wide range of tumor response shapes (see refs. 8,9,19–24 for reviews).

To develop the statistical component of the model, we considered additive, proportional, and combined residual error models for both preclinical and clinical data and assumed that the individual parameters were log-normally distributed.

The preclinical and clinical data were analyzed using the First Order Conditional Estimation with Interaction method (FOCEI with NONMEM 7.2). The value of Bayesian information criterion (BIC) was used to drive the process of model selection. Validity of candidate models was also evaluated through the percent of relative standard error (RSE) of the parameters and goodness of fit plots such as visual predictive check (VPC). VPC was performed by simulating 500 studies from where the 95% confidence intervals for the 5th, 50th, and 95th percentiles were calculated. For the preclinical data, VPC plots were stratified according to the doses administered. For the clinical data, we performed

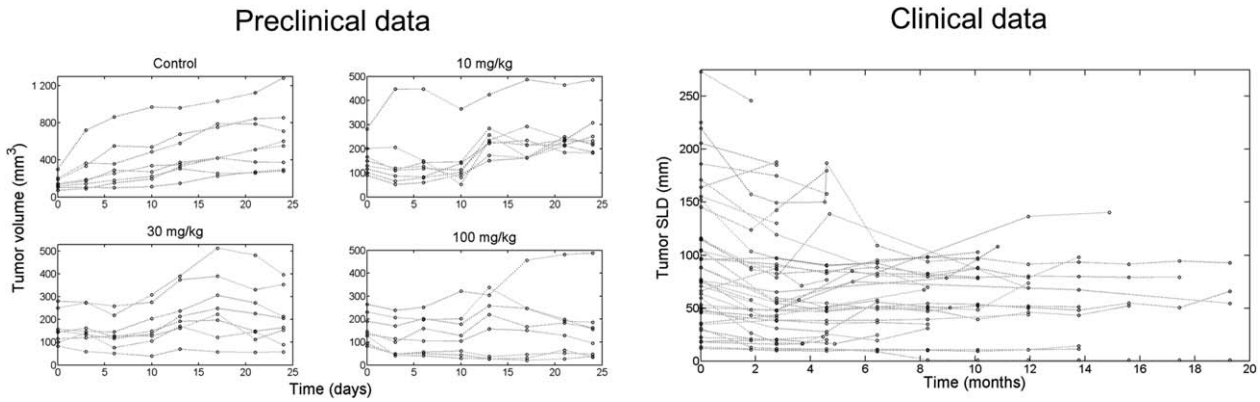

Figure 1 Left: Tumor volume time course in CAKI-2 xenograft mice treated with vehicle or pazopanib 10, 30, or 100 mg/kg given from time 0 to the end of the experiment. Right: Individual time course of tumor size, expressed as the sum of longest diameters, in the subset of 47 patients included in the analysis. Dashed lines are the individual tumor dynamics.

prediction-corrected VPC, as most of the patients experienced dose reduction (see ref. 25 for further details).

RESULTS

Figure 1 (left panel) presents tumor volume time course data in mice treated with vehicle or pazopanib 10, 30, or 100 mg/kg.

In a first stage, we analyzed the data from animals (both control and treated). Testing models of increasing complexity resulted in a final model composed of a system of two ordinary differential equations (see **Supplementary Table S1** for the full list of tested models). One equation represents the tumor volume (P) while the other describes the tumor carrying capacity (K), which is defined as the maximal tumor volume or mass supported by the current level of tumor vascularization. We suppose that the tumor, through proangiogenic factors such as vascular endothelial growth factor (VEGF), is capable of extending its carrying capacity (K). Thereby the capacity (K) is expected to always increase. This hypothesis is consistent with RCC growth as it overexpresses proangiogenic factors due to the von Hippel Lindau (VHL) gene mutation leading to a continuous and anarchic tumor angiogenesis.[26] Tumor vasculature can be seen as a growth-limiting factor supporting the concept of tumor carrying capacity. We assume that tumor angiogenesis is dependent on the tumor volume (P) as more proangiogenic factors are synthesized when the quantity of tumor cells increases. To modulate the relationship between the carrying capacity (K) and the tumor volume (P), we introduce an empirical parameter n.

The tumor growth and angiogenesis inhibition model can be written as follows:

$$\frac{dp}{dt} = \lambda \cdot P \cdot \left(1 - \frac{P}{K}\right) - \alpha \cdot e^{-\delta t} \cdot P$$
$$\frac{dk}{dt} = b \cdot P^{n} - \gamma \cdot K \quad (1)$$

where P is the tumor volume in mm^3 and λ its growth rate constant (in 1/day). The parameter b is the capacity rate constant (in 1/day). It regulates how quickly the carrying capacity grows. The parameter n was not identifiable but was tested using likelihood profiling with different arbitrary values. Specifically, we varied the value of n between 0.5 and 3 to cover a sufficient range of angiogenesis potency (tested values: 0.5, 2/3, 1, 1.5, 2, 2.5, and 3).

As proposed by Hahnfeldt *et al.*,[27] when $n = 2/3$ the model assumes that the tumor angiogenesis (represented by the carrying capacity term K) depends on a surface area of the tumor volume. We evaluated the fit of the model by analyzing changes in the BIC and individual fits. The best results were obtained with an n value of 1. γ (1/day), α (1/day), and δ (1/day) are constants representing the antiangiogenic effect, the putative cytotoxic effect, and the resistance on the cytotoxic effect of pazopanib, respectively.

Based on the individual fits, goodness of fit plots, and BIC values (**Table S1**), assumption of a single effect of pazopanib on the tumor carrying capacity K (representing its antiangiogenic action) was not sufficient to optimally describe the tumor data, since both observed initial and long-term tumor shrinkage could not be fitted by the model. The final model integrated a second direct effect on the tumor volume P, which can be attributed to a cytotoxic effect of the drug. In addition, in line with previous suggestions,[8] we added a resistance term (δ) that decreases the cytotoxic effect on tumor volume with time (Eq. 1). A resistance on the cytotoxic effect depending on the drug exposure was tested but resulted in worse BIC values and individual fits. This is probably due to the fact that the variability of patients' drug exposures was small and not sufficient to discriminate an effect on drug resistance.

Drug exposure (area under the curve (AUC)) was also included in the model; we used the following covariate models to describe its effect on the drug efficacy parameters α and γ:

$$\alpha = \alpha_0 \cdot AUC^{\beta_\alpha} \quad (2)$$

$$\gamma = \gamma_0 \cdot AUC^{\beta_\gamma} \quad (3)$$

where AUC is treated as a continuous variable with values of 220.2, 656.8, and 1140.8 μg·h/mL for the doses of 10,

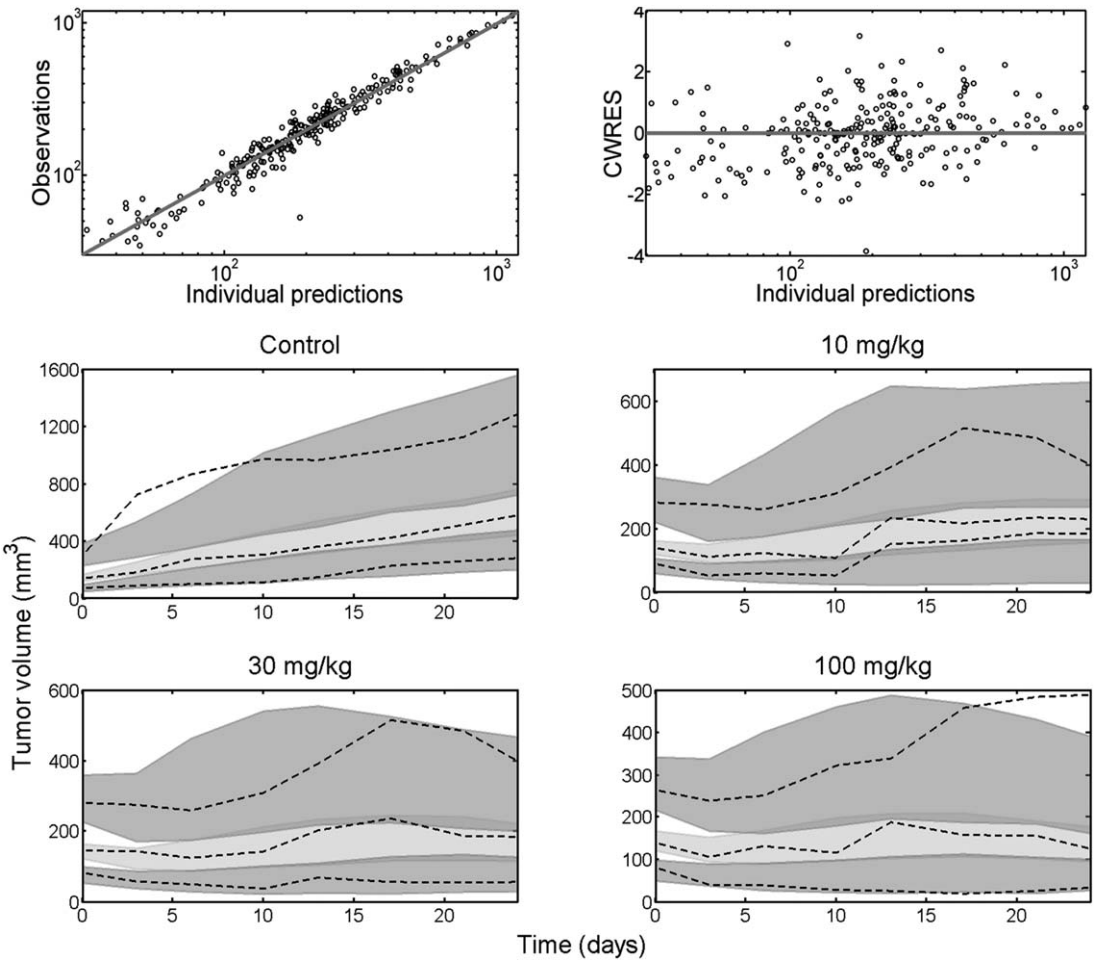

Figure 2 Up, left: Observed vs. predicted tumor volumes for individual mice across treatment groups (vehicle, 10, 30, 100 mg/kg). Up, right: Conditional weighted residuals (CWRES) vs. individual predictions. VPC stratified by the dose for the preclinical analysis ($n = 8$ mice per group). Middle, left: VPC for the vehicle group. Middle, right: 10 mg/kg. Bottom, left: 30 mg/kg. Bottom, right: 100 mg/kg. The dashed lines represent the 5%, 50%, and 95% percentiles of the observed data. The colored areas represent the 95% prediction areas for the respective percentiles. VPC should be interpreted carefully, as the number of mice for each group is small. Therefore, observed 5th and 95th percentiles are equals to the smallest and biggest tumor dynamic respectively. Nevertheless, the model is describing well the median observed tumor dynamic for each group.

30, and 100 mg/kg, respectively, as reported in separate preclinical pharmacokinetic studies (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000_PharmR.pdf). α_0 and γ_0 stand respectively for the "baseline" population values of α and γ; and β_α and β_γ represent the two covariate model parameters to be estimated. As an assumption, no interindividual variability (IIV) was associated with these two parameters. Pazopanib displays a nonlinear pharmacokinetics, which mechanism seems to be due to the drug absorption process. Overall, the model contains seven structural parameters (λ, b, α, δ, γ, P_0, K_0). The initial tumor volume (P_0) was set to the observed value so that only six model parameters were estimated. To avoid bias due to sampling errors, we took into account the values of the residual error parameters in the initial condition of tumor size. Random effects were assumed for all model parameters except for parameter b, as its estimation was associated with numerical instabilities. Data were not log-transformed, as this transformation did not result in any improvement of the estimation.

In contrast to other tumor models, the proposed model (Eq. 1) can assume for certain parameter values a finite, nonzero equilibrium, i.e., represent prolonged stable disease. To understand this long-term behavior of the model, note that asymptotically (i.e., for large values of t), in the particular case of $n = 1$, an infinite set of equilibrium $P = K > 0$ can be reached if $b = \gamma$. For n values other than 1, the model can also assume a unique nonzero equilibrium:

$$P = K = \left(\frac{\gamma}{b}\right)^{\frac{1}{n-1}} \tag{4}$$

$P = K = 0$ defines an equilibrium given that n is strictly greater than 0.

The combination of both antiangiogenic and cytotoxic effects led to the best diagnostics. Overall, the proposed

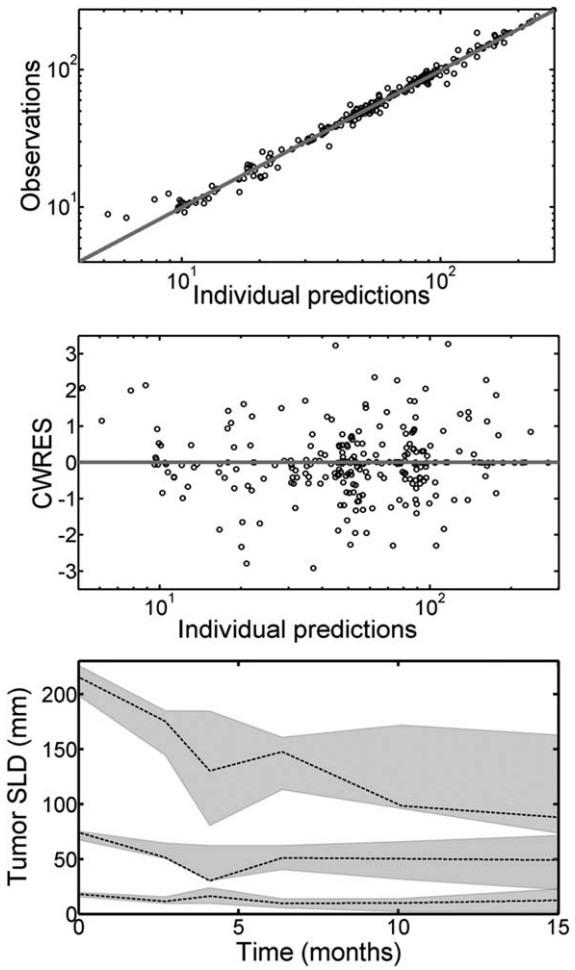

Figure 3 Up: Observed tumor size expressed as sum of the longest diameters vs. the model's individual predictions. Middle: CWRES vs. individual predictions. Bottom: prediction-corrected VPC for the clinical analysis. The dashed lines represent the 5%, 50%, and 95% percentiles of the observed data, and the colored areas stand for the 95% prediction areas for the respective percentiles.

model provided an adequate description of the tumor volume data within the four treatment groups (see **Figure 2** for basic goodness of fit plots and VPCs stratified by dose).

The same model was applied to the analysis of the clinical data presented in **Figure 1** (right panel). For this analysis, it was necessary to apply a correction on the empirical parameter *n*, which was set in this case to the value 0.5. This value allows the model to better predict the tumor regrowth, as well as the second decrease due to the long-term antiangiogenic effect, by reducing the potency of the tumor angiogenesis. Therefore, this new value of *n* significantly improved the fits of the model's predictions to the tumor size dynamics of individual patients. For this analysis, IIV of the parameters K_0 and *b* was fixed to 0; we verified that increasing the IIV of K_0 and *b* did not improve the objective function. The model also incorporated mean exposure at each dose level (800 mg daily and at reduced doses). To identify these mean exposure levels in the absence of pharmacokinetic data, we fitted an E_{max} model to mean AUC values reported in previous clinical trials; this approach enabled us to account for the less-than-dose-proportional increase in AUC. Data from five clinical trials that investigated pazopanib doses of 5 mg to 2,000 mg administered once daily were pooled for the analysis.[28–32] According to the E_{max} model, mean exposure was 771.6 μg·h/mL (range, 629.4–802.4 μg·h/mL) corresponding to a mean dose of 727 mg (range: 473–800 mg) through the population of 47 patients. Predicting patients' exposures from the E_{max} model may certainly introduce a degree of uncertainty that complicates the comparison of tumor and drug-specific parameters between mice and humans.

As in the case of the preclinical data, we ruled out the possibility that simpler including models assuming a single (antiangiogenic or cytotoxic) effect of the drug would be sufficient to describe the clinical data (**Table S1**). Basic goodness of fit plots and VPC plots (**Figure 3**) indeed indicated that a model that assumes both effects is more appropriate. Individual plots were much better with our model, as it could describe the initial and long-term tumor shrinkage due to pazopanib effects. Nevertheless, regarding BIC values, no significant improvement was observed between the dual effect model and the single cytotoxic effect model or the model described in ref. 8 (**Supplementary Table S1**). The values of the parameter estimated by the final model in both preclinical and clinical settings are summarized in **Table 1**. Both studies were analyzed separately, as a simultaneous analysis did not improve parameter identifiability. **Figure 5** shows individual data and their corresponding model's predictions for 3 mice per group (control, 10, 30, and 100 mg/kg pazopanib) selected according to their residual error values that are increasing from the first row to the third one. The same graphs for nine patients are shown in **Figure 6**.

DISCUSSION

Most models developed so far have been indifferently applied to cytotoxic and cytostatic drugs, including angiogenesis inhibitors such as pazopanib. Our model takes into account the role of tumor vasculature in tumor growth and shrinkage, and therefore is well suited to pazopanib, as it is an angiogenesis inhibitor. The use of preclinical data, obtained through a rich experimental design (characterized by a high number of longitudinal observations, in addition to an accelerated course of disease), enabled us to build a simple mechanistic model that would probably not have been possible given clinical data alone. **Figure 4** illustrates the typical dynamics of tumor size over time (the data shown are outcomes of a simulation using the population parameters reported in **Table 1**). The typical response to pazopanib in both humans and mice displays an unusual pattern: tumor burden decreases as soon as treatment starts. After some time, the tumor regrows before shrinking again. In light of the model's assumptions, the observed shape can be explained in the following terms: The initial decrease is due to a direct cytotoxic effect of the drug. Reducing vasculature could potentially

Table 1 Model parameter estimates for the preclinical and clinical data analysis

			Preclinical results		Clinical results	
	Parameters	**Unit**	**Estimates (RSE %)**	**IIV (RSE %)**	**Estimates (RSE %)**	**IIV (RSE %)**
Model parameters	λ	day^{-1}	0.166 (24)	53 (108)	0.0021 (6)	82 (35)
	K_0	mm^3 I mm	543 (15)	36 (77)	329 (25)	Fixed to 0
	b	day^{-1}	0.0183 (58)	Fixed to 0	0.0392 (22)	Fixed to 0
	γ	day^{-1}	0.007 (29)	19 (127)	0.0023 (9)	31 (51)
	β_γ		0.332 (15)		0.142 (7)	
	α	day^{-1}	0.251 (13)	24 (96)	0.0032 (2)	62 (29)
	β_α		Fixed to 0		0.125 (14)	
	δ	day^{-1}	0.196 (26)	42 (103)	0.0153 (3)	101 (45)
Residual error	ε_1 (proportional)	%	14 (23)		8 (2)	
	ε_2 (additive)	mm^3 I mm	3 (17)		1 (3)	

Interindividual variability (IIV) is approximated by the square root of the variance (omega) estimated by NONMEM and expressed as a percentage together with standard errors of estimates (RSE). In both preclinical and clinical settings, the best error model was a combination of proportional (ϵ_1) and additive (ϵ_2) parameters. They are both expressed as standard deviations that are calculated from variances (sigma) estimated by NONMEM. ϵ_1 is presented as a percentage, whereas ϵ_2 is the standard deviation in the unit of the observed variable (mm^3 and mm for preclinical and clinical tumor size, respectively).

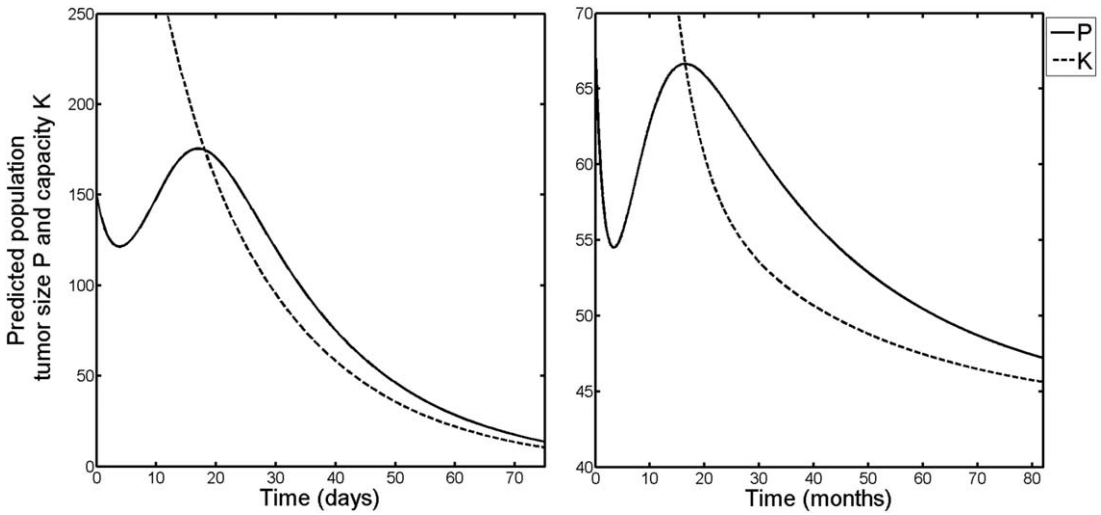

Figure 4 Model simulation of tumor size (*P*) and carrying capacity (*K*) time course using the population parameter estimates of the preclinical (left) and clinical (right) data. Tumor size is expressed as volume (mm^3) for mice and SLD (mm) for patients.

translate into tumor shrinkage, but with a delay in time. This delay allows *K* to go below the tumor size variable and corresponds in reality to the time needed for the cells to respond to lack of oxygen supply. This delay is not observed in mice and patients. However, because of the resistance term, this effect disappears with time and, consequently, tumor size once again increases as disease progresses. This regrowth occurs until the antiangiogenic effect leads to a decrease in the carrying capacity (*K*) below the tumor size (*P)* so that the tumor shrinks again. Simulations show that if the treatment is administered for a sufficiently long period of time, the tumor size (*P*) and the carrying capacity (*K*) will decrease exponentially to reach a steady state. Interestingly, model simulations with typical (population) parameter values produce this unusual shape in both mice and humans even if only 13% of the population presents these tumor size dynamics. In patients whose tumors followed such a pattern, the initial short decrease in tumor size and the subsequent, longer-term decrease appeared after about 3 and 17 months of treatment, respectively (see **Figure 4**). A large majority of patients, however, did not show this behavior. This may have been a result of the schedule of assessments (we note that dose interruptions were not reported for any of our analyzed patients). The model is still capable of reproducing the behavior, as the second decrease is observed among tumors whose initial carrying capacity K_0 is relatively high, indicating high vascularization.

In mice, the level of pazopanib exposure had no impact on the cytotoxic effect (β_α was initially estimated at 0.0002 then fixed to 0). However, the impact of exposure level on the antiangiogenic effect parameter was significant, meaning that, in mice, higher doses of pazopanib are associated with greater long-term tumor shrinkage, due to the destruction of the tumor vasculature. In humans, the impact of drug exposure on both antiangiogenic and cytotoxic efficacy was found to be significantly different from 0, although the range of exposure levels was narrow.

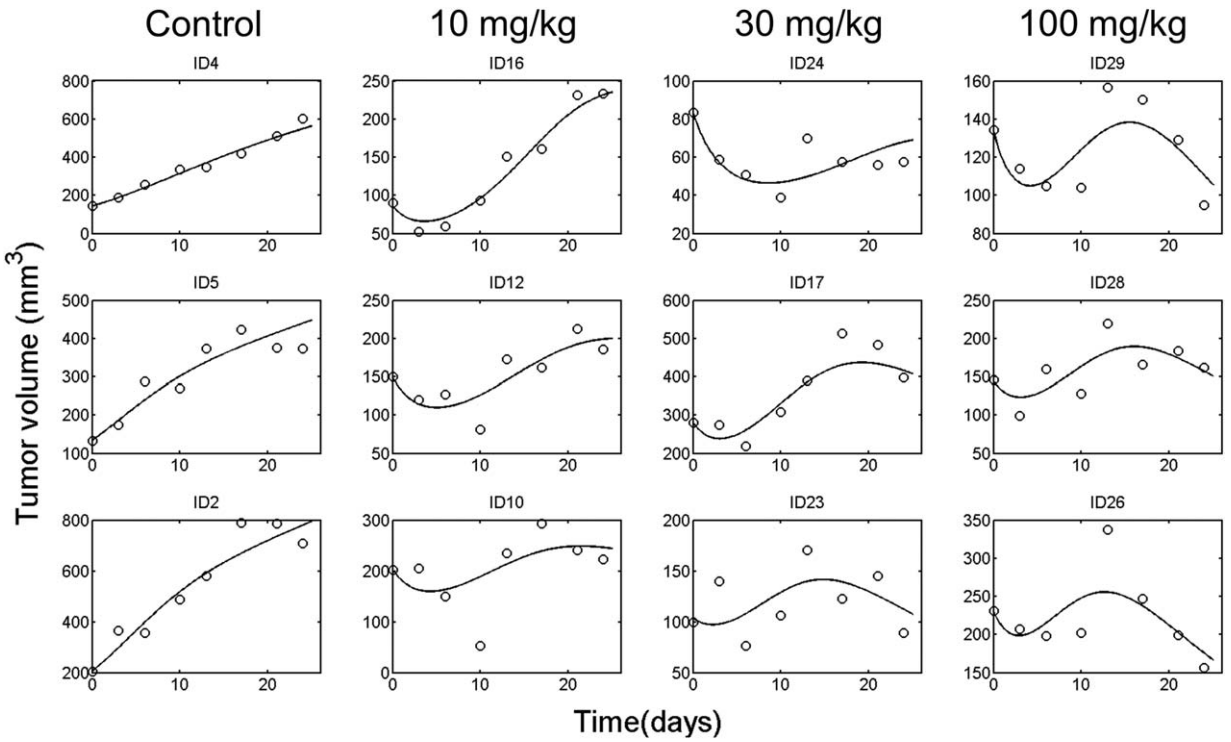

Figure 5 Observed tumor volume (circles) and individual predictions (solid line) for 3 mice per group (from left to right: control, 10, 30, and 100 mg/kg pazopanib) selected on the basis of their typical residual error magnitude (top row: best; middle row: median; bottom row: worst).

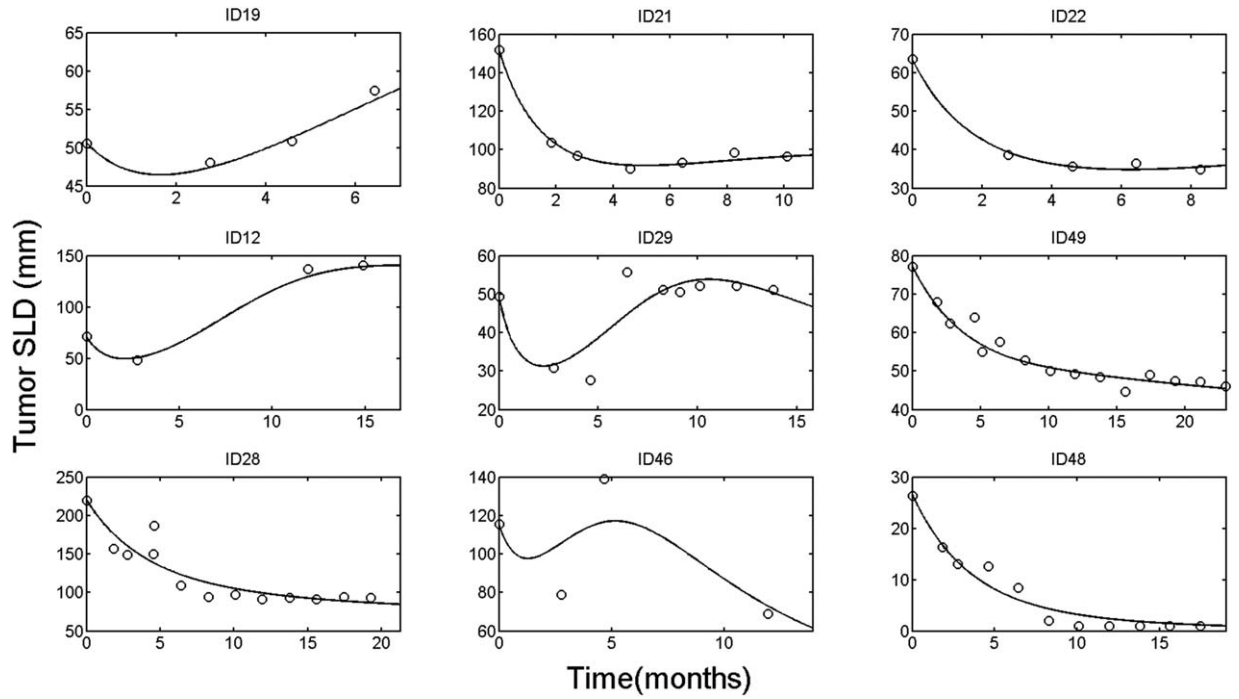

Figure 6 Observed SLD (circles) and individual predictions (solid line) for nine individuals selected on the basis of their typical residual error magnitude (top row: best; middle row: median; bottom row: worst).

Our model, incorporating an indirect effect of the drug on the tumor size through inhibition of the vasculature, is based on plausible biological phenomena. Indeed, pazopanib's effect on tumor size is likely to be partially attributable to the drug's antiangiogenic action, as RCC is characterized by high tumor vascularization, due to the overexpression of proangiogenic factors by the cells displaying the mutation of the *VHL* gene. By inhibiting the pathways activated by VEGF and PDGF in endothelial cells, pazopanib could lead to a transient normalization of the blood vessels and subsequent destruction of the tumor vasculature, thus depriving tumor cells of oxygen and nutrients needed for growth. The modeled cytotoxic effect is supported by several mechanisms documented in the literature. A cytotoxic effect may plausibly occur through pazopanib's effect on the VEGF pathway, a pathway known to promote proliferation and resistance to apoptosis.[33,34] Pazopanib is also a potent inhibitor of the stem cell factor receptor c-KIT ($IC_{50} = 0.074$ μmol/L; for comparison, $IC_{50} = 0.010$, 0.030, and 0.047 μmol/L for VEGFR1, 2, and 3, respectively. $IC_{50} = 0.071$ and 0.084 μmol/L for PDGFR-α and β, respectively[1]), which is responsible for the proliferation, differentiation, migration, and survival of concerned cells.[35] Finally, emergence of resistance to the cytotoxic effect of pazopanib can be plausibly attributed to acquired polymorphisms and mutations of TKI receptors.[36]

Herein, by using preclinical tumor size time course information as input data in a model-building procedure, we were able to propose a new semimechanistic model of tumor size response to pazopanib in RCC patients. The model could describe the full unusual tumor dynamics in both mice and patients better than previously published tumor growth inhibition models. This preliminary work opens up many opportunities. In a future work it would be of interest to translate preclinical results into clinical predictions by using new scaling methods or allometry. To this end, we computed ratios between the preclinical and clinical rate parameter values (**Supplementary Table S2**). While these ratios do not provide exact matches to allometric ratios (e.g., unadjusted physiologic time ratio of $7.3 = (70/0.025\ \text{kg})^{0.25}$ for drug half-life, or the maximum life-span potential ratio of about 30 between humans and mice), they show a rough correspondence in terms of order of magnitude.[37] More specifically, for a compound with a mechanism of action similar to that of pazopanib, an interesting avenue of research would be to compare clinical tumor response to the response predicted by scaling the preclinical model parameters for the new compound with the rate ratios estimated for pazopanib. Another field of investigation concerns the improvement of the evaluation of clinical TKI efficacy. Indeed, our model is able to predict a long-term antiangiogenic effect following tumor regrowth. Therefore, it may be possible that some patients who dropped out due to PD, assessed through RECIST criteria, might have experienced a second tumor shrinkage thanks to the antiangiogenic effect of pazopanib. This suggests that a longer follow-up and/or treatment could be beneficial to better assess efficacy in phase II. Actual data cannot support this statement, which needs to be investigated in a future work.

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Author Contributions. B.R., A.O., H.S., A.B.S., and D.O. wrote the article; B.R., A.O., H.S., A.B.S., and D.O. designed the research; B.R., A.O., H.S., A.B.S., and D.O. performed the research; B.R., A.O., H.S., A.B.S., and D.O. analyzed the data.

Conflict of Interest. D.O., H.S., and A.B.S. were employees of GlaxoSmithKline at the time of planning, analysis, and publication development.

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