

Optimisation of the dose and schedule of everolimus and sorafenib combination therapy in patients with solid tumors using a PKPD/time-to-event model

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Introduction

Defining the optimal doses and schedules of combined targeted drugs in oncology is challenging. The objective of this study was to develop a pharmacokinetic-pharmacodynamic (PKPD) model for everolimus (EVE), sorafenib (SOR) and serum biomarkers linked with a time-to-event (TTE) analysis based on data from EVESOR phase I trial in solid tumor patients in order to propose an optimised dosing schedule of EVE and SOR association.

Methods

Treatment arms Forty-three patients were assigned into four treatment arms:

A (n = 7) and B (n = 7)	C (n = 16)	D (n = 13)
Continuous SOR 200 mg BID Continuous EVE 5 mg QD	1 week on/1 week off SOR 200-400 mg BID and EVE 5-10 mg QD	3 days/week SOR 200-400 mg BID Continuous EVE 5-10 mg QD

Pharmacokinetics SOR and EVE PK data were described by a one- and two-compartment model, respectively, with linear absorption and elimination [1].

Biomarker data Serum vascular endothelial growth factor receptor 2 (sVEGFR2) levels during 1st treatment cycle were measured in 39 patients (n = 169 concentrations). Data were described by an indirect response model.

TTE model Parametric TTE model was developed in NONMEM 7.5 to describe the baseline hazard of disease progression. The individual model-predicted relative change in sVEGFR2 from baseline at day 21 ($RCFB_{sVEGFR2,Day21}$) and the baseline tumor MAPK pathway activity score [2] were tested in the TTE model as predictors of progression-free survival (PFS).

Simulations sVEGFR2 kinetics under different SOR doses and schedules were simulated with the final PKPD model (n=1000 PD profiles for each). The median PFS (CI90%) for each dosing schedule were calculated using TTE model.

Results

sVEGFR2 model An indirect-response model best described the time course of sVEGFR2 with SOR inhibiting production rate constant (K_{in}) in an I_{max} manner (Table 1). The model was validated by a prediction-corrected visual predictive check (pcVPC, Figure 1).

TTE model Weibull models were used to describe the baseline hazard of disease progression (PFS) and of dropout (D):

$$h_{PFS}(t) = \lambda_{PFS} \cdot \alpha_{PFS} \cdot t^{\alpha_{PFS}-1} \cdot e^{\beta_1 \cdot RCFB_{sVEGFR2,Day21} + \beta_2 \cdot MAPKScore}$$
$$h_D(t) = \lambda_D \cdot \alpha_D \cdot t^{\alpha_D-1}$$

Patients exhibiting higher decrease in sVEGFR2 at day 21 and those with higher baseline activation of MAPK pathway had lower risk of disease progression. The final model was validated by Kaplan Meier VPCs (Figure 2).

Simulations The kinetics of SOR under different dosing schedules and the corresponding sVEGFR2 profiles over 21 days of treatment are presented on Figure 3a. As presented on Figure 3b, SOR 200 mg BID 5 days/week (+EVE 5 mg QD continuous) was associated with improved PFS (median=4.1 months, CI95%=2.0-12.3) compared to the median PFS in the EVESOR trial (3.6

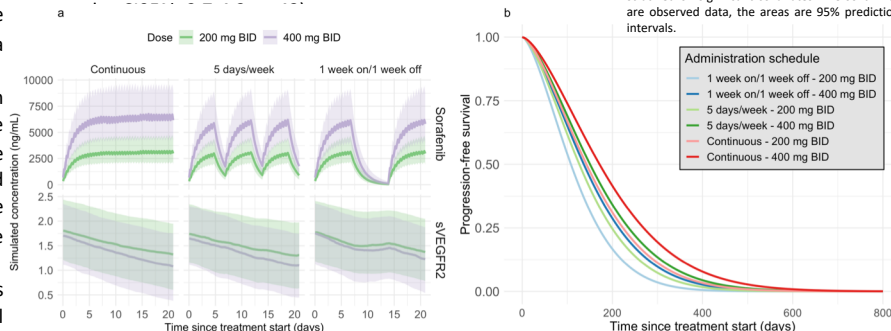


Figure 3. (a) Simulated profiles of SOR plasma concentrations and sVEGFR2 levels under different dosing schedules. The solid lines represent the median and the areas represent the 25th-75th percentiles of the simulated data (n = 1000). (b) Progression-free survival calculated for each of the simulated dosing schedule (median MAPK pathway activity score was considered in the simulations). The solid lines represent median of 1000 simulations for each schedule.

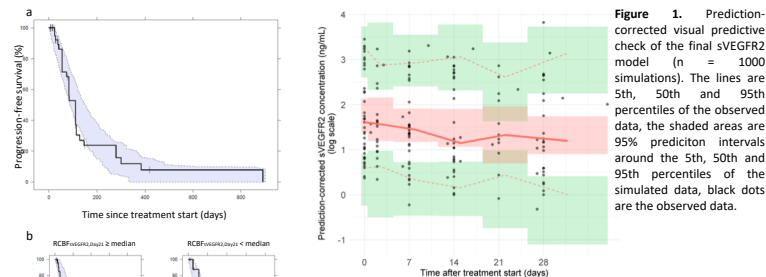


Figure 1. Prediction-corrected visual predictive check of the final sVEGFR2 model (n = 1000 simulations). The lines are 5th, 50th and 95th percentiles of the observed data, the shaded areas are 95% prediction intervals around the 5th, 50th and 95th percentiles of the simulated data, black dots are the observed data.

Table 1. Final estimates of the sVEGFR2 and TTE models. (relative standard error, RSE%) [shrinkage]

Parameter	Mean estimate
sVEGFR2 model	
Baseline sVEGFR2 (ng/mL)	5.75 (15%)
Mean Residence Time (hours)	704 (30%)
Imax sorafenib	1 FIXED
IC50 sorafenib (ng/mL)	1060 (33%)
IIV on baseline sVEGFR2 (CV%)	111.6 (7%) [1%]
IIV on MRT (CV%)	134.2 (22%) [38%]
Proportional residual error (CV%)	27.8 (9%)
Time-to-event model	
λ_{PFS} (day ⁻¹)	0.0035 (13%)
α_{PFS}	1.54 (12%)
λ_D (day ⁻¹)	0.0126 (13%)
α_D	0.691 (16%)
β_1 $RCFB_{sVEGFR2,Day21}$ on PFS	4.58 (37%)
β_2 Baseline MAPK score on PFS	-0.352 (50%)

Conclusions

Based on simulations and on the toxicity of SOR 400 mg BID dose observed in EVESOR trial (in all arms), SOR 200 mg BID 5 days/week (+EVE 5 mg QD continuous) was selected for clinical evaluation in the extension of EVESOR trial to confirm its superior benefit-risk ratio over the previously tested treatment arms. EVE dose was not optimised since EVE PK was not related to PFS in this study.

References

[1] El Madani et al. Future Oncol. 2017. [2] Wagle et al. Precision Oncology 2018.