PKPD Modeling of Predictors for Adverse Effects and Overall Survival in Sunitinib-Treated Patients With GIST

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A modeling framework relating exposure, biomarkers (vascular endothelial growth factor (VEGF), soluble vascular endothelial growth factor receptor (sVEGFR)-2, -3, soluble stem cell factor receptor (sKIT)), and tumor growth to overall survival (OS) was extended to include adverse effects (myelosuppression, hypertension, fatigue, and hand–foot syndrome (HFS)). Longitudinal pharmacokinetic–pharmacodynamic models of sunitinib were developed based on data from 303 patients with gastrointestinal stromal tumor.

Myelosuppression was characterized by a semiphysiological model and hypertension with an indirect response model. Proportional odds models with a first-order Markov model described the incidence and severity of fatigue and HFS. Relative change in sVEGFR-3 was the most effective predictor of the occurrence and severity of myelosuppression, fatigue, and HFS. Hypertension was correlated best with sunitinib exposure. Baseline tumor size, time courses of neutropenia, and relative increase of diastolic blood pressure were identified as predictors of OS. The framework has potential to be used for early monitoring of adverse effects and clinical response, thereby facilitating dose individualization to maximize OS.

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RESULTS

The analysis included data pooled from four clinical trials8–11 in phases I–III, which comprised 303 patients with imatinib-resistant malignant GIST treated with sunitinib and/or placebo (Table 1). Available data were biomarker candidates (VEGF, sVEGFR-2, sVEGFR-3, and sKIT), OS, and the most commonly reported treatment-related adverse effects, fatigue, HFS, neutropenia, and hypertension (diastolic blood pressure, dBP).

Longitudinal information on dose, sunitinib daily area under the concentration–time curve (AUC), and biomarkers

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were evaluated as predictors for adverse effects. The time courses of the biomarker (BM(t)) concentrations were characterized by indirect response models, as described in the study by Hansson et al. The predicted value of the different biomarkers for adverse effects was assessed by investigating how descriptive measures of the individual model–predicted biomarker time courses were, alone or in addition to drug exposure. The model-predicted baselines (BM0), absolute and relative change from baseline (BM REL), or the complete biomarker time courses were evaluated as predictors.

**Myelosuppression model**

A semiphysiological myelosuppression model using Box–Cox-transformed data adequately described the extent and time course of the change in absolute neutrophil count (ANC) following sunitinib treatment. A more pronounced reduction in ANC was observed during the first treatment cycle, with partial recovery to baseline levels during the subsequent off-treatment period. A smaller decline in ANC was subsequently observed during the second treatment cycle and thereafter. Placebo-treated patients did not show any systematic alterations in ANC levels.

All of the investigated biomarkers were statistically significantly correlated with the changes in ANC levels when assessed at a fixed time point (landmark). However, the longitudinal model–predicted relative change in sVEGFR-3 from baseline (sVEGFR-3 REL) was the better descriptor of the myelosuppression time course (change in the objective function value, $\Delta$OFV = 170.8, compared with AUC). No further improvement in the description of the data was observed when any of the other biomarkers or sunitinib AUC was added to the univariate model.

An $E_{\text{max}}$ function most appropriately characterized the biomarker–ANC relationship. A separate baseline parameter (ANC0) was estimated to account for lower ANC levels in Study 45, which was conducted in Japanese patients. The final model included interindividual variability in ANC0, mean transit time (MTT) through the nonsensitive compartments, $E_{\text{max}}$ and EC50 ($\text{Table 2}$), with a correlation between ANC0 and $E_{\text{max}}$ of 90%. For a typical patient receiving a daily 50-mg sunitinib dose (4/2 schedule) and an ANC0 of $4.94 \cdot 10^9/l$, the model predicted a 62% decrease in ANC corresponding to a nadir of $1.9 \cdot 10^9/l$.

The predictive performance of the final myelosuppression model, as illustrated by a prediction-corrected visual

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**Table 1** Data summary of the analyzed studies

| Study number | Study 1004 | Study 1047 | Study 1045 | Study 013 |
|--------------|------------|------------|------------|-----------|
| Reference    | Demetri et al.12 | George et al.13 | Shiaro et al.14 | Maki et al.15 |
| N            | 202 active | 13 | 36 | 52 |
| Placebo      | 47 | | | |
| Study design | Double-blind, randomized, placebo-controlled, phase III | Nonrandomized, evaluating continuous treatment regimen, phase II | Nonrandomized, dose-escalating study in Japanese patients, phase I/II | Nonrandomized, dose-escalating study, phase I/II |
| Dosing schedule (weeks on/weeks off) | 0, 50mg q.d. 6-week cycles (4/2) | 37.5mg q.d. 4-week cycles, continuous treatment | 25, 50, 75mg q.d. 6-week cycles (4/2) | 25, 50, 75mg q.d. 6-week cycles (4/2) |
| Fatigue (%)a | 0: 30 | 0: 54 | 0: 31 | 0: 11 |
| Hand–foot syndrome (%)a | 0: 83 | 0:100 | 0: 14 | 0: NA |
| Absolute neutrophil counts ($10^9/l$), median (range) | 3.1 (0.080–20) | 1.8 (0.010–7.5) | 2.1 (0.28–12) | 2.6 (0.16–15) |
| Diastolic blood pressure (mmHg), median (range) | 80 (20–120) | 78 (40–120) | 79 (40–120) | 80 (50–130) |
| Survival (weeks), median (range) | 61 (4–226) | 31 (81–15) | 37 (27–48) | 39 (4–96) |

NA, not available; q.d., once daily.

aHighest observed severity score within an individual (%). bObserved median (range) response during the treatment period.
Table 2  Final model parameter estimates (relative SE, %)

| Parameter                     | Estimate | RSE, % | IIV CV, % | RSE, % |
|-------------------------------|----------|--------|-----------|--------|
| Myelosuppression model        |          |        |           |        |
| ANC₀ (10⁹/l)                  | 4.94     | 2.8    | 42        | 5.6    |
| ANCᵡ (Study 45 (10⁹/l))      | 3.69     | 6.9    | 42        | 5.6    |
| MTT (hours)                  | 248      | 3.6    | 17        | 19     |
| ANC Eₜₕₑₓ                   | 0.520    | 9.1    | 13        | 36     |
| ANC ECₜ₀ (pg·hour/l)         | 0.552    | 17     | 46        | 16     |
| λ                            | 0.362    | 7.4    | —         | —      |
| Residual error*              | 0.406    | 4.3    | —         | —      |
| Blood pressure model          |          |        |           |        |
| dBP₀ placebo (mmHg)          | 77.6     | 1.6    | 12        | 6.7    |
| dBPslope (l/mg·hour)         | 0.119    | 9.4    | 65        | 11     |
| Residual error (%)           | 0.362    | 9.1    | 13        | 36     |
| Survival model               |          |        |           |        |
| λ / (week)                   | 0.0079   | 55     | —         | —      |
| α                            | 1.15     | 9.1    | —         | —      |
| α₀sea                       | 1.27     | 44     | —         | —      |
| β₁ ANC/10⁹                   | 4.76     | 31     | —         | —      |
| β₂ dBPSREL                   | −1.29    | 27     | —         | —      |
| β₃ tumor size (mm)            | −0.00172 | 46     | —         | —      |
| λ₀sea / (week)               | 0.0019   | 6.6    | —         | —      |

ANC₀ : baseline absolute neutrophil count; CV, coefficient of variation; dBP₀, baseline diastolic blood pressure (DBP); dBPSREL, parameter relating drug exposure to the change in DBP; IIV, interindividual variability; MRT, mean residence time; MTT, mean transit time; RSE, relative standard error; α, shape factor in Weibull probability density function; α₀sea, shape factor in Weibull probability density function for censoring; β₁ ANC, Parameter relating ANC(t) to the hazard; β₂ dBPSREL, parameter relating the relative change in DBP to hazard; β₃ tumor size, parameter relating observed baseline tumor size to the hazard; γ, feedback factor; λ, scale factor in the Weibull probability density function; λ₀sea scale factor in the Weibull probability density function for censoring.

*Residual error on Box–Cox-transformed scale.

predictive check (VPC; Figure 1), shows a good description of the ANC data.

Blood pressure model
An indirect response model with stimulation of the production rate (Kᵢ) as proposed by Keizer et al. for another angiogenic drug, described the observed elevated DBP during sunitinib treatment periods and the return to near baseline during off-treatment periods (Eq. 1). No increase in DBP could be identified for placebo patients. However, this group had a significantly higher baseline DBP (dBP₀) when estimated separately.

\[
\frac{ddBP}{dt} = K_in \cdot (1 + dBP_{Drug\ effect} \cdot AUC) - K_out \cdot dBP(t) \quad (1)
\]

\[
K_{in} = dBP_0 \cdot K_{out}
\]

Sunitinib AUC was linked to the production rate (Kᵢ) by a linear slope factor (dBP_{Drug\ effect}). None of the evaluated biomarkers were found to be significantly related to the dBP time course. Interindividual variability was estimated for dBP₀, the mean residence time MRT (=1/kᵢ), and dBP_{Drug\ effect} and a combined additive and proportional residual error model was used. A correlation between dBP₀ and dBP_{Drug\ effect} (65%) was estimated. The final model predicted a drug-induced increase in dBP by 10 mmHg for the typical patient with a baseline dBP of 71.8 mmHg treated with 50 mg sunitinib receiving a 4/2 schedule.

The relative standard errors (RSEs, %) for the estimated parameters were low to intermediate, showing an adequate precision in the estimates (Table 2). The prediction-corrected VPC shows a good predictive performance of the final blood pressure model (Figure 2).

Fatigue and HFS models
The data were treated as ordered categorical (grades 0, 1, 2, ≥3), and an extension of the proportional odds model was used to describe the probability and severity of fatigue and HFS over time. The extension included a first-order Markov model to condition the probability of transition between different severities based on the preceding one, thereby accounting for that the severity of the adverse effects is not independent from one time point to another. Logit transformations were used to constrain the estimated probabilities to values between 0 and 1, and the function describing the probability of transition from grade a to grade b for the fth patient at the fth observation was given the structure shown in Eq. 2.

\[
\text{Logit}(P_{ij|a}) = \ln \frac{P_{ij|a}}{1 - P_{ij|a}} = f_{ij|a} + \eta_i \quad (2)
\]

\[
f_{ij|a} = B_{ij|a} + g(x_i)
\]

where fᵢ|ᵢ is a function of baseline transition probabilities (Bᵢ|ᵢ), and g(x) is a linear function on the logit scale relating explanatory factors, such as time, drug exposure (dose and AUC), and absolute/relative changes in biomarker concentrations over time, to the probability of developing fatigue and HFS. The interindividual random effect for patient i (ηᵢ) was assumed to be normally distributed with a mean of zero and a variance of ω².

All of the biomarkers were significantly related to the probability and severity of fatigue and HFS. However, the relative change over time for sVEGFR-3 (sVEGFR-3 REL) showed the most profound relationship (ΔOFV = −103 for fatigue, ΔOFV = −159 for HFS, compared with AUC), and no further improvement in the description of the data was observed when AUC or the other biomarkers were also incorporated. No significant trend over time was identified. Increasing sVEGFR-3 REL, i.e., a more pronounced reduction in sVEGFR-3, was associated with increased probability and severity of fatigue and HFS. Incorporation of an effect compartment into the model |ke₂| = 0.424/hour (fatigue) and
0.347/hour (HFS) significantly improved both the fatigue and HFS models (Table 3). The parameters were estimated with acceptable precision and are reported on the logit scale in Table 3. The simulation-based model evaluation described well the time course for the probability and severity of fatigue and HFS (Table 3, Figure 3). Furthermore, the simulated numbers of transitions between different severity grades were consistent with the observed values (results not shown).

**OS model**
A Weibull model described the underlying baseline hazard for the observed survival data ($\lambda$; hazard coefficient, $\alpha$; shape factor; Eq. 3, Table 2). The time course of neutropenia [ANC(t)] was the most significant predictor of OS (ΔOFV = −42.6). Additionally, dBP$_{REL}(t)$ was significantly related to OS (ΔOFV = −25.4), whereas fatigue and HFS were not related. A more pronounced decrease in ANC over time and/or a larger relative increase in dBP decreased the hazard risk of death.

To be able to compare our model with the previously reported survival model from that in our companion article, which included sVEGFR-3$_{REL}$ and tumor size at start of treatment as predictors, these two predictors were also included and reevaluated for significance, in addition to the presence of the adverse events. The model including ANC and dBP...
Table 3 Time course for the probability and severity of HFS and fatigue

| Parameter | HFS model | Fatigue model |
|-----------|-----------|---------------|
| $B_{10}$  | -10.4     | -16.3         |
| $B_{20}$  | -0.974    | -0.834        |
| $B_{30}$  | -1.59     | -2.04         |
| Slope$_{30}$ | -8.00  | -9.02         |
| $\omega_{10}$ | 3.07 | 3.07          |
| $\omega_{20}$ | 2.29 | 2.46          |
| $\omega_{30}$ | -9.53 | -8.00         |

The developed first-order mixed-effects Markov models characterized the dynamics of longitudinal fatigue and HFS data. The model provides an alternative approach to traditional analysis of toxicity data, which often only reports the highest severity during the study for a patient and thereby discards the evolution of toxicity over time. An increased sunitinib exposure or sVEGFR-3 response was related to a higher
risk and severity of adverse effects. The proposed models with sVEGFR-3 as a descriptor are empirical and provide limited contribution to the understanding of the mechanism for development of HFS and fatigue but could be of prognostic value.

The relative change in sVEGFR-3 over time is predictive of OS (ref 2) and the adverse event dynamics for myelosuppression, fatigue, and HFS. Therefore, monitoring sVEGFR-3 has the potential to identify the patients at highest risk of toxicity and to enhance dose optimization. Efficient dose individualization could minimize the occurrence of severe adverse events and improve the treatment efficacy. A maintained dose intensity is of importance because higher exposures have been shown to be associated with longer OS and time to progression in a previously reported exposure–response analysis.16

The relative change in dBP, myelosuppression time course, and tumor size at start of treatment were predictive of OS. The model predicted that patients with a greater relative change in blood pressure and ANC, together with a smaller tumor size at baseline, displayed the longest OS. Cutoff values of blood pressure and neutropenia have previously been identified as predictors in sunitinib treatment using traditional statistical analysis. ANC < 1.5×10^9/l or dBP > 90 mmHg at any time during treatment were associated with longer OS.5–7

ANC and dBP measurements from the first treatment cycle can predict OS. The developed survival model may guide intrapatient dose escalation based on dBP and neutropenia and explore the effectiveness of alternate dosing strategies. The potential impact on the augmented incidence and severity of HFS and fatigue due to the increased dose adjustments can be considered. A future simulation study will evaluate a dose individualization approach to ultimately optimize the use of sunitinib in GIST. These factors will require confirmation in larger prospective trials.

Figure 3 Visual predictive check of the final model for the time course of the probability and severity of fatigue (left) and hand–foot syndrome (HFS) (right) for actively treated patients stratified by severity grade. The solid lines (—) represent the observed time course of each severity grade, and the shaded areas are the 95% confidence intervals generated from simulations.

Figure 4 Kaplan–Meier plot of the observed survival data (solid line) and the 95% confidence interval (shaded area) based on the simulated data (n = 200) for the final survival model (left). A Weibull model (λ = 0.0019, α = 1.3) was applied in the simulations to describe censoring. The right panel illustrates the predictive properties of the model when only using data from the first 6 weeks of treatment.
conclusion, this analysis proposed the relative change in sVEGFR-3 over time as a predictor of the occurrence and severity of myelosuppression, fatigue, and HFS following sunitinib treatment. Furthermore, sunitinib-induced hypertension and neutropenia were identified as predictors of OS in GIST. The developed framework, including adverse effects as biomarkers, has a potential to be used for early monitoring of response, thereby facilitating effective dose individualization.

METHODS

Patients and study design. The analyzed data were from four clinical trials8–11 in phases I–III, which comprised patients with imatinib-resistant malignant GIST treated with sunitinib. Only patients with biomarker and survival data reported were included in the analysis, totaling 303 patients. Sunitinib was administered in one of four different treatment schedules, including the 4/2, 2/2, and 2/1 (weeks on/weeks off) schedule, and continuous treatment, with doses ranging from 0 to 75 mg orally once daily (Table 1). Patients randomized to receive placebo treatment (n = 47) in the placebo-controlled trial (study 1004) were offered sunitinib on disease progression as defined by the Response Evaluation Criteria in Solid Tumors (RECIST).19 The studies were approved by local ethics committees and were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Data analysis. This population PK/PD analysis was performed sequentially using the nonlinear mixed-effects modeling approach. The first-order conditional estimation method with interaction (FOCEI) and the Laplacian estimation method implemented in the software NONMEM (version 7.2, gFortran version 4.5.0, Gnu compiler collection; Supplementary Data) were used for parameter estimation. The R-based software Xpose (version 4)20 was used for model diagnostics and graphical visualization of the results, and the PsN toolkit (version 3)21,22 was used for the postprocessing of results.

Model selection was based on assessment of graphical diagnostics and comparison of the OFV, provided by NONMEM, in the log-likelihood ratio test. The difference in OFV for two nested models is proportional to minus twice the log likelihood of the data and is approximately χ² distributed. A significance level of P < 0.01 was used in this analysis, which corresponds to a decrease in OFV of at least 6.63 for the addition of one extra parameter. Evaluation of model robustness was based on relative standard errors (RSEs, %) of the model parameter estimates determined by nonparametric bootstrapping (n = 200). Prediction-corrected VPCs23 were also assessed to judge the predictive performance of the developed models.

Pharmacokinetics. Dose or daily area under the concentration–time curve (AUC) was calculated as Dose/(CL/F), with AUC = 0 during off-treatment periods, was used as the exposure measure for sunitinib (no data for the equipotent metabolite SU1266 were available). Total oral plasma clearance (CL/F) was described by the individual parameter estimates or population values [(when no PK data were available (n = 57)] obtained from a population PK model.24

Biomarker models. The time courses of the biomarkers were characterized by individual parameter estimates obtained from previously developed biomarker models.2 The models described the changes in biomarker concentrations [BM(t)] through indirect response models assuming a decreased production of the zero-order rate constant (kₚ) for sVEGFR-2, sVEGFR-3, and sKIT and an inhibited degradation of VEGF (kₑ). A linear disease progression model characterized the increase of VEGF and sKIT over time. Data on sVEGFR-3 were not available for two of the studies (n = 69), but the high correlation between sVEGFR-2, sVEGFR-3, and VEGF to sVEGFR-3 enabled derivation of information on sVEGFR-3 in individuals with missing data.2

Myelosuppression model. The time course of sunitinib-related changes in ANC was described by a semimechanistic model for myelosuppression.12 The model is composed of a compartment representing drug-sensitive proliferating progenitor cells in the bone marrow, a compartment of systemic circulating neutrophils, and a link between them through three transit compartments reflecting cell maturation. The model also includes a feedback function mimicking the effect of endogenous growth factors, e.g., granulocyte colony stimulating factor (G-CSF), which increases the proliferation rate when neutrophil levels in the blood are low. The half-life of circulating neutrophils in blood was fixed to the literature value of 7 hours25 to enhance the physiological interpretation of the model. Estimated system-specific parameters were
ANC0, MTT, and the feedback factor ($\gamma$). Furthermore, the drug effect—which is assumed to act by reducing the proliferation rate and inducing cell loss—was estimated. Herein, linear, $E_{\text{max}}$, and sigmoid $E_{\text{max}}$ models were evaluated to link drug exposure (dose and AUC) and biomarkers (baseline, absolute, and relative change) to cell death.

Modeling was performed on Box–Cox-transformed neutrophil data ($\text{ANC}_{\text{transformed}} = \text{ANC}^\lambda - 1/\lambda$), with $\lambda = 0.2$, as this previously has been shown to result in approximately normally distributed residuals.26,27 Interindividual variability was assumed to be log-normally distributed with a mean of zero and a variance of $\omega^2$ and was evaluated for ANC0, MTT, and the drug effect parameters. Residual variability was described by an additive (on Box–Cox scale) error model. The predictive performance of the myelosuppression model was evaluated by prediction-corrected VPCs (500 simulations).23

Blood pressure model. The sunitinib-induced hypertension was reported in terms of increase in dBP. The actual times of the day for blood pressure measurements were not available and were therefore assumed to occur in the morning for all observations. The increase in dBP following sunitinib treatment was described using (i) an indirect response model with stimulation of $K_c$, or (ii) the alternative model with inhibition of $k_{\text{sat}}$, dBP, and $K_c$ (reported as MRT = 1/$k_{\text{sat}}$) were estimated, and $K_c$ was derived as dBP$_0 \times k_{\text{sat}}$. Linear, $E_{\text{max}}$, and sigmoid $E_{\text{max}}$, drug effect relationships to sunitinib exposure (dose and AUC) and biomarkers (baseline, absolute, and relative changes over time) were evaluated. Interindividual variability was assumed to be log-normally distributed with a mean of zero and a variance of $\omega^2$. Additive, proportional, or combined additive and proportional residual error models were evaluated.

The predictive properties of the final blood pressure model were evaluated using prediction-corrected VPCs ($n = 500$).23

Fatigue and HFS model. Fatigue and HFS were assessed daily throughout treatment. They were reported according to the National Cancer Institute common toxicity criteria (version 3.0) as different grades, where grade 0 corresponds to no adverse event and grade 4 refers to a life-threatening event. However, grade 4 was only reported in a few patients (for fatigue: 1%; and for HFS: 0%), and these occurrences were consequently grouped with grade 3 into a single category.

Models for ordered categorical data (grades 0, 1, 2, and $\geq 3$) with a first-order Markov model were applied. Transitions between all the different severity grades were considered in the analysis, totaling 16 different possible transitions. The sum of the associated probabilities for each grade ($P_{\text{in}10}$, $P_{\text{in}20}$, $P_{\text{in}30}$ and $P_{\text{in}02}$) is one, and therefore three probabilities for each grade were directly estimated and the fourth probability ($P_{\text{in}00}$, $P_{\text{in}10}$, $P_{\text{in}20}$, and $P_{\text{in}30}$) was expressed as one minus the sum of the associated probabilities. Linear and nonlinear models for the explanatory factors were assessed, and the addition of an effect compartment to account for a delay in the drug effect was tested.28

The fatigue and HFS models were evaluated by categorical VPCs, where 95% confidence intervals were generated from 500 simulations and overlaid with the observed time course of fatigue and HFS stratified by severity. In addition, predictive checks were created by comparing the simulated and observed numbers of transitions between different toxicity grades.

OS model. A parametric survival (time-to-event) model was developed to evaluate whether any of the studied treatment-related adverse effects were predictive of OS. The underlying distribution of the observed survival data was evaluated by exponential, Weibull, log-logistic, extreme value, and Gompertz probability density functions. The individual predicted time courses, using AUC as predictor, for neutropenia and hypertension were extrapolated based on the developed models assuming dosing and schedule according to protocol until time of censoring/death. For neutropenia and hypertension baseline levels, absolute time course and absolute and relative change from baseline over time were evaluated as predictors of OS. For fatigue and HFS, the observed severity scores (last observation carried forward) were evaluated as predictors of OS by including each observed score as a predictor. To be able to compare our model with the previously reported survival model, which included sVEGFR–sREL and tumor size at start of treatment as predictors,4 these two predictors were also included and reevaluated for significance, in addition to the presence of the adverse events.

The predictive properties of the survival model were assessed by Kaplan–Meier plots of the observed survival data compared with a 95% confidence interval generated from simulations of 200 replicates of the data sets. Censoring because of, e.g., a short follow-up period was described as a Weibull model, which was applied in the simulations.

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Author contributions. E.K.H., M.A.A., P.A.M., J.F., L.E.F., and M.O.K. wrote the manuscript. E.K.H., G.M., M.A.A., P.A.M., J.F., L.E.F., and M.O.K. designed the research. E.K.H., G.M., M.A.A., J.F., L.E.F., and M.O.K. performed the research. E.K.H. and G.M. analyzed the data.

Conflict of interest. G.M., M.A.A., and P.A.M. are employees of Pfizer Ltd. At the time the work was carried out, G.M. was supported by a research grant from Pfizer Ltd. and J.F. was an employee at Pfizer Ltd. M.O.K. and L.E.F. have acted as paid consultants to Pfizer Ltd. As Deputy Editor-in-Chief of CPT: Pharmacometrics & Systems Pharmacology, L.E.F. was not involved in the review or decision process for this article. E.K.H. declared no conflict of interest.

E.K.H., G.M., M.A.A., J.F., L.E.F., and M.O.K. performed the research. E.K.H. and G.M. analyzed the data.
Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Sunitinib-induced change in the angiogenic biomarker soluble vascular endothelial growth factor receptor (sVEGFR)-3 was a predictor of overall survival (OS) in a modeling framework evaluating exposure–biomarker–tumor size–OS relationships for gastrointestinal stromal tumor (GIST).

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ In a population PKPD analysis, exposure and the changes in angiogenic biomarkers over time were investigated as predictors for sunitinib-induced adverse effects. The time courses of the adverse effects were tested for their predictive capacities for OS.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ The framework was expanded to integrate adverse effects. The relative change in sVEGFR-3 over time was a predictor of myelosuppression, fatigue, and hand–foot syndrome. The relative increase in diastolic blood pressure (dBP) was positively correlated with sunitinib AUC. Neutrophil count and dBP REL were identified to predict OS equally well as sVEGFR-3.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ Models of four common adverse effects of sunitinib were added to the developed framework on integrated PKPD models. Neutrophil counts and blood pressure measurements show promise to be applied in feedback individualization to increase OS in GIST.

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