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ORIGINAL ARTICLE

Development of a modeling framework to simulate efficacy endpoints for motesanib in patients with thyroid cancer

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Abstract
Purpose To develop a modeling framework that simulates clinical endpoints (objective response rate and progression-free survival) to support development of motesanib. The framework was evaluated using results from a phase 2 study of motesanib in thyroid cancer.
Methods Models of probability and duration of dose modifications and overall survival were developed using data from 93 patients with differentiated thyroid cancer and 91 patients with medullary thyroid cancer, who received motesanib 125 mg once daily. The models, combined with previously developed population pharmacokinetic and tumor growth inhibition models, were assessed in predicting dose intensity, tumor size over time, objective response rate, and progression-free survival. Dose–response simulations were performed in patients with differentiated thyroid cancer.
Results The predicted objective response rate and median progression-free survival in patients with differentiated thyroid cancer was 15.0% (95% prediction interval, 7.5%–23.7%) and 40 weeks (95% prediction interval, 32–49 weeks), respectively, compared with the observed objective response rate of 14.0% and median progression-free survival of 40 weeks. The simulated median objective response rate increased with motesanib starting dose from 13.5% at 100 mg once daily to 38.0% at 250 mg once daily. However, simulated median progression-free survival was independent of starting dose, ranging from 40.5 weeks (95% prediction interval, 38.6–46.9 weeks) at 100 mg once daily to 40.0 weeks (95% prediction interval, 38.6–46.8 weeks) at 250 mg once daily.
Conclusions Dose–response simulations confirmed the appropriateness of 125-mg once-daily dosing; no clinically relevant improvement in progression-free survival would be obtained by dose intensification. This modeling framework represents an important tool to simulate clinical response and support clinical development decisions.

Keywords Simulation · Clinical endpoints · Motesanib · Thyroid cancer

Introduction

There has been significant debate regarding the design and interpretation of phase 2 oncology studies [1–3]. It has been suggested that quantitative approaches to the analysis of phase 2 data may provide useful information to guide clinical development decisions [4]. Recently, a modeling framework comprising longitudinal exposure–response tumor growth inhibition (TGI) and drug-independent survival models has been proposed to assess drug effect in phase 2 studies and to predict expected survival in phase 3 trials of metastatic breast and colorectal cancer [5, 6]. The TGI model is used to quantify antitumor effect based on longitudinal tumor size measurements, and the survival model uses change in tumor size at the end of cycle 2 as the main predictor for survival together with prognostic factors. A similar modeling framework has also been proposed in non-small-cell lung cancer [7].

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Motesanib is an orally administered small-molecule antagonist of vascular endothelial cell growth factor receptors 1, 2, and 3; platelet-derived growth factor receptor; and Kit receptors [8] that has demonstrated antitumor activity as a monotherapy [9] and in combination with chemotherapy [10, 11]. In a phase 2 study of patients with progressive or advanced medullary thyroid cancer (MTC) or differentiated thyroid cancer (DTC), treatment with motesanib 125 mg once daily (QD) was tolerable and demonstrated evidence of clinical benefit [12, 13]. The objective response rate (ORR) was 14% in the DTC cohort. In the MTC cohort, the ORR was 2%, and a further 48% of patients had durable (≥24 weeks) stable disease. Using data from this study, Lu et al. [14] recently developed a population pharmacokinetic (PK)/TGI model for motesanib and assessed various exposure metrics to drive drug effect, as described in the companion manuscript [14].

To support end-of-phase 2 development decisions, the TGI model was used to simulate the clinical endpoints of ORR and progression-free survival (PFS). We developed a model to simulate dose intensity over long-term motesanib treatment and a survival model. These models, combined with the previously developed population PK/TGI model reported in the companion manuscript [14], were used to simulate longitudinal tumor size data and survival at different initial doses of motesanib in patients with DTC (Fig. 1). The ORR and PFS (per Response Evaluation Criteria in Solid Tumors [RECIST]) [15] were derived from the simulated data.

Methods

Data

Data were obtained from a phase 2 study of motesanib monotherapy conducted among 184 patients with advanced DTC ($n = 93$) [12] or MTC ($n = 91$) [13]. The primary endpoint was to evaluate ORR as assessed by independent central review according to RECIST. Patients received motesanib 125 mg QD for up to 48 weeks or until unacceptable toxicity, disease progression, or death precluded further treatment. If necessitated by the emergence of a treatment-related grade 3 adverse event that could not be controlled with supportive care, any grade 4 adverse event, or symptomatic hypertension, doses of motesanib could be reduced or withheld until the adverse event resolved. Administration of motesanib could then be resumed at a dose of 100 mg QD, or at a dose of 75 mg QD after a second treatment interruption. Plasma samples for intensive assessment of motesanib PK were obtained after the first dose of motesanib on study day 1. Additional samples for assessment of motesanib trough concentrations were obtained before the daily dose of motesanib at 4-week intervals up to study week 24.

Pharmacokinetic/tumor growth inhibition model

As reported in the companion manuscript [14], a longitudinal exposure–tumor response model of drug effect on tumor growth dynamics was developed using PK parameter estimates from the phase 2 motesanib thyroid cancer study.

Dose-modification models

Three models were developed to simulate dose intensity over time: one model for the probability of dose-reduction events and two models for the duration of dose-reduction and dose-interruption events.

Model for the probability of dose-reduction events

An ordered categorical model was developed to describe the probability of dose-reduction events as a function of

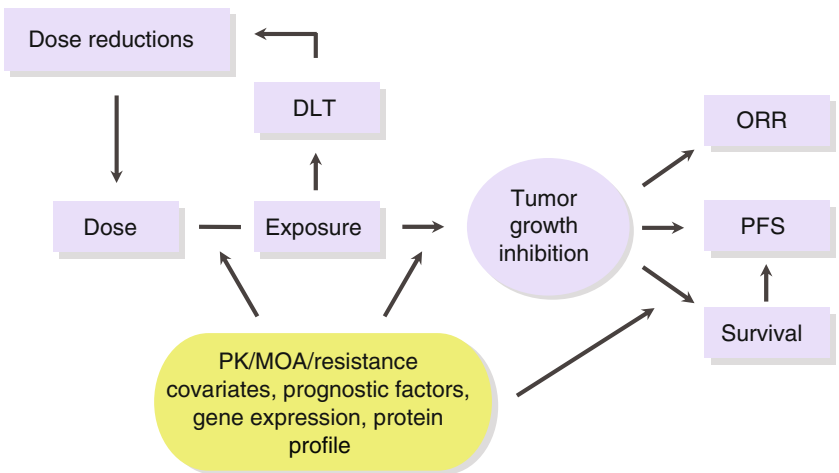

Fig. 1 A drug-disease causal modeling framework to simulate clinical endpoints in oncology. *DLT* dose-limiting toxicity, *MOA* mechanism of action, *ORR* objective response rate, *PFS* progression-free survival, *PK* pharmacokinetic. Adapted by permission from Macmillan Publishers Ltd: Clin Pharmacol Ther [3], copyright 2009

time and exposure. Four ordered categories of dosing events were considered, including starting dose (125 mg), daily dose reduction to 100 mg, daily dose reduction to 75 mg, and daily dose interruption (0 mg). We used a "biophase kinetic approach" [16] in which a measure of exposure (i.e., AUC) is introduced into and eliminated from a virtual biophase compartment, and the exposure (AUC(t)) in the compartment drives drug effect. This implementation allows modeling of exposure–response-time data without requiring a full pharmacokinetic/pharmacodynamic approach. In this model, the dynamics of drug exposure in the biophase is given by the following equation expressing the AUC intensity model:

$$\frac{\mathrm{dAUC}(t)}{\mathrm{d}t} = u(t) - k_p \cdot \mathrm{AUC}(t) \quad \mathrm{AUC}(0) = 0 \tag{1}$$

where k_p is a first-order rate constant, $u(t)$ is the input function of daily AUC = *Dose*/CL, CL was estimated for individual patients using the previously developed population PK model [14], and *Dose* may be one of 125, 100, 75, or 0 mg.

For patient (i), the drug effect $E_i(t)$ at time t responsible for the dose modification is:

$$E_i(t) = S_{\mathrm{drug}} \cdot \mathrm{AUC}(t) + \eta_i \tag{2}$$

In this model, S_{drug} is the slope of drug effect, and η_i are the random effects for patient (i). The η_i are normally distributed with mean zero and variance ω^2.

The logit transformation of the probabilities of dose-reduction events are assumed to depend on the drug effect as follows:

$$\begin{aligned}
&\mathrm{logit}[P(100\ \mathrm{mg},\ t)] = \mathrm{int}_1 + E_i(t)\\
&\mathrm{logit}[P(100\ \mathrm{or}\ 75\ \mathrm{mg},\ t)] = \mathrm{int}_1 + \mathrm{int}_2 + E_i(t)\\
&\mathrm{logit}[P(100\ \mathrm{or}\ 75\ \mathrm{or}\ 0\ \mathrm{mg},\ t)] = \mathrm{int}_1 + \mathrm{int}_2 + \mathrm{int}_3 + E_i(t)
\end{aligned} \tag{3}$$

where int_1, int_2, and int_3 are intercepts. Intercepts are used together with $E_i(t)$ to calculate at time, t, the probability to the 100 mg reduction event, $P(100\ \mathrm{mg},\ t)$, the cumulative probabilities to the 100 or 75 mg reduction events, $P(100$ or 75 mg, $t)$, and to the 100 or 75 or 0 mg reduction events, $P(100$ or 75 or 0 mg, $t)$. From the cumulative probabilities, the probabilities at time t to the 75 mg reduction, $P(75$ mg, $t)$, to the dose interruption, $P(0$ mg, $t)$, and the probability to maintain the starting dose $P(125$ mg, $t)$ are calculated as follows:

$$\begin{aligned}
&P(75\ \mathrm{mg},\ t) = P(100\ \mathrm{or}\ 75\ \mathrm{mg},\ t) - P(100\ \mathrm{mg},\ t)\\
&P(0\ \mathrm{mg},\ t) = P(100\ \mathrm{or}\ 75\ \mathrm{or}\ 0\ \mathrm{mg},\ t) - P(100\ \mathrm{or}\ 75\ \mathrm{mg},\ t)\\
&P(125\ \mathrm{mg},\ t) = 1 - P(100\ \mathrm{or}\ 75\ \mathrm{or}\ 0\ \mathrm{mg},\ t)
\end{aligned} \tag{4}$$

Model parameters, k_p, S_{drug}, int_1, int_2, int_3 and ω^2 were estimated by using the nonlinear mixed-effect modeling software program NONMEM (version VI, level 1.0; ICON Development Solutions, Ellicott City, MD) [17]. The first-order conditional estimation with Laplace method (FOCEI) was used. The NONMEM control stream for this model is provided in the Appendix.

Models for the duration of dose reduction and interruption events

The event duration was described by a time-to-event model considering the event duration T as a random variable. The model computed the probability $P(T > t)$ that T was longer than t as follows:

$$P(T > t) = \exp\left[\int_0^t h(a)\mathrm{d}a\right] \tag{5}$$

In this expression, the hazard function $h(a)$ may be selected as corresponding to one among the normal, log-normal, Weibull, logistic, log-logistic, and exponential probability density functions [18]. The selection criterion was based on the difference in log-likelihood and goodness-of-fit plots of alternative density functions. If the probability density is Weibull, the above relationship becomes:

$$P(T > t) = \exp[-(\lambda \cdot t)^p] \tag{6}$$

Two time-to-event models were used to describe the duration of dose reductions and the duration of dose interruptions. For both models, parameters were λ and p, the scale and shape parameters of the Weibull distribution, respectively. Parameters were estimated by using the CensorReg function in S-plus (version 6.1; Insightful, Seattle, WA).

Overall survival model

Survival time was defined as the time from study entry to the time of death for whatever reason. Data were censored when death was not observed. A model was proposed to describe the survival time distribution as a function of the following predictors:

1. A disease characteristic; the tumor size at baseline,
2. A patient characteristic; the baseline Eastern Cooperative Oncology Group (ECOG) performance status, and
3. A measure of treatment effect; the relative change $[y(0) - y(\mathrm{week8})]/y(0)$ in tumor size from baseline, $y(0)$, at the first posttreatment visit at approximately week 8, y(week8). Week 8 was selected because data were available for all patients at this time and y(week8) is predicted by the TGI model [14].

As described previously, a time-to-event model associated with a Weibull hazard function was selected. The

scale parameter for the patient (i), λ_i, was regressed against the three predictors z_{ij} as follows:

$$-\log(\lambda_i) = \text{int} + b_j \cdot z_{ij} \quad j = 1:3 \tag{7}$$

where int is the intercept and b_j is the coefficient for the covariate j. The model parameters int, b_j and p. Parameters were estimated by using the CensorReg function in S-plus (version 6.1; Insightful, Seattle, WA). Of note, the survival model can be considered as a drug-independent model relating a biomarker response (relative change in tumor size) and prognostic factors (baseline tumor size, ECOG performance status) to a clinical endpoint (survival time). Similar models have been described previously [5–7].

Modeling framework assessment

Performance of the dose-modification models and of the full modeling framework was assessed using visual posterior predictive checks (PPCs). The models and the study design were used to simulate statistics of interest for many hypothetical trial replicates across model parameter uncertainty (for different replicates), interindividual variability (within replicates), and residual error. Statistics of interest included

1. For the dose-modification models:

   a. Median daily AUC intensity (AUC intensity was calculated as the mean of daily AUCs for each patient).
   b. Mean dose-reduction and dose-interruption event durations.

2. For the full modeling framework (dose modification, TGI, and survival models): ORR and PFS. The models were used to predict:

   a. Daily AUC up to end of study (48 weeks),
   b. Longitudinal tumor size profiles (based on daily AUC and tumor size at baseline) using the model described in the companion manuscript [14],
   c. Survival (based on ECOG, tumor size at baseline, and relative change from baseline at week 8).
   d. Predicted patient data were limited to tumor progression (≥20% increase from baseline sum of the longest diameters) and/or death (i.e., PFS events). Patients without a PFS event at 48 weeks were considered censored at the time of last disease measurement. The ORR and PFS were determined for each of the replicates based on the simulated data (i.e., the longitudinal tumor size data and the death events) according to RECIST [15]. Distributions of ORR and PFS across replicates (posterior distributions) were compared with observed endpoints from the phase 2 study [12, 13].

Models were considered qualified if the observed statistics fell within the posterior 95% prediction interval [PI] determined in the simulated trials.

Simulations

To explore dose–response relationships, simulations of clinical endpoints were performed for once-daily motesanib starting doses of 100, 125, 150, and 250 mg. Simulations were performed as described for the PPC. Patient characteristics were sampled in the original data set, and AUC was extrapolated for the different starting doses, assuming linear PK. The predictive distributions (95% PI) of clinical endpoints (ORR, PFS, and proportion of patients without a PFS event at end of study) across 100 replicates of 500 patients were provided as a function of starting dose.

Results

Dose-modification models

Among 184 patients from the phase 2 study, individual PK parameters were estimated through post hoc step in the population PK model for those with at least one evaluable PK concentration ($n = 156$); typical PK parameters were used for those patients without any PK data ($n = 28$). The exploratory analysis using AUC and dose modification indicated that the proportion of motesanib dose modifications increased with time and drug exposure (AUC). For example, at the end of the study (approximately week 48), the proportion of patients with a reduced daily dose (<125 mg) was 5, 22, 43, and 55% in the first, second, third, and fourth quartiles of exposure, respectively. The mean durations of dose reductions for the 100-mg and 75-mg doses were 64 and 53 days, respectively. The mean duration of dose interruptions was much shorter (6.5 days).

Parameter estimates of models of dose reduction, duration of dose reductions, and duration of dose interruptions are shown in Table 1. The parameters appeared to be well estimated except for k_p, a measure of the time dynamics for the dose-reduction events, which was estimated with a large uncertainty (relative standard error, 64%). The point estimate translates into a half-life of 247 days (~35 weeks), indicating that a steady state in the probability of dose-reduction event was not reached by the end of the study (48 weeks), thereby explaining the uncertainty in the estimates. The parameter estimates of Weibull distributions (Table 1) demonstrated a longer duration for dose reductions compared with that of dose interruptions (about 50 vs. 6 days). Simulated distributions were in agreement

Table 1 Parameter estimates for the dose-modification models

Parameter (units)	Estimate	RSE (%)
Probability of dose-reduction events		
int_1	−14.3	16
int_2	0.866	24
int_3	0.755	11
k_p (days^{-1})	0.0028	64
S_{drug} (mg h l^{-1})	0.0372	30
log(ω)	2.22	9
Duration of dose interruptions		
−log(λ)	1.85	4.3
log(p)	1.03	
Duration of dose reductions		
−log(λ)	4.03	2.8
log(p)	1.16	

int intercept for cumulative probabilities, k_p first-order rate constant, *RSE* relative standard error, S_{drug} slope of drug effect, ω interpatient standard deviation, λ scale parameter, p shape parameter

with the distributions of observed durations (data not shown).

The ability of the dose-modification models to simulate AUC intensity at various times during treatment was assessed. The model predictive performance (Fig. 2) indicated that the observed AUC intensity at 24 weeks was consistent with the PI (across 100 replicates). The median exposure at the starting dose appeared to be substantially reduced at 24 weeks, and the combination of the models correctly predicted the reduction in exposure due to modifications in the dose intensity (Fig. 2).

Survival model

Median survival could not be estimated, because only 51 deaths occurred among the 184 patients before the end of the study (48 weeks). A total of 161 patients could be included in the survival analysis (patients with baseline and at least one post baseline measurement). Exploratory analyses (Kaplan–Meier and Cox regression) demonstrated that survival time distribution was not significantly different between patients with DTC and patients with MTC ($P = 0.86$) and was significantly related to baseline tumor size ($P = 0.0017$) and ECOG performance status ($P < 0.0001$). A trend was also observed in the ability of relative change in tumor size from baseline at week 8 to predict survival, although this did not reach statistical significance ($P = 0.089$). The association between relative change in tumor size and survival (Fig. 3) suggests that a longer follow-up might reveal a stronger trend.

In the parametric analysis, the Weibull distribution best described the survival distribution (data not shown). Parameter estimates of the Weibull model are shown in Table 2. Baseline tumor size and ECOG performance status were found to be significant independent predictors of survival ($P = 0.014$ and $P = 0.0007$, respectively). There was a trend toward relative change in tumor size predicting overall survival ($P = 0.089$). However, it is important to note that the covariate effect estimates of these parameters are limited by the relatively small size of the study population from this phase 2 study. Thus, this model should be regarded as a preliminary one and will be used as a tool for simulation of PFS events.

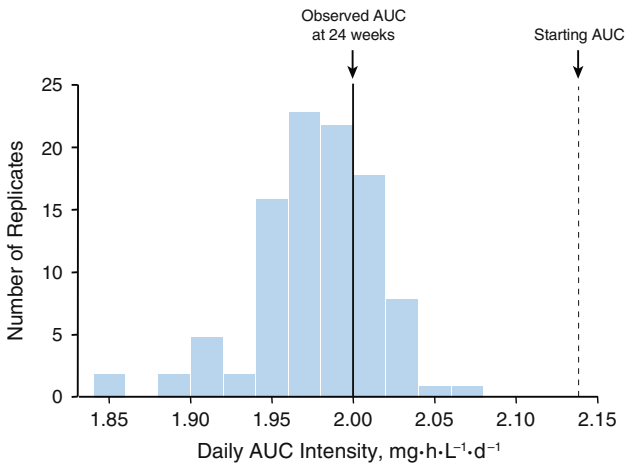

Fig. 2 Distribution of model-predicted median daily AUC intensity up to 24 weeks for 100 replicates compared with observed in the phase 2 motesanib thyroid cancer study. The *dotted line* indicates the area under the concentration vs. time curve (AUC) at the starting dose

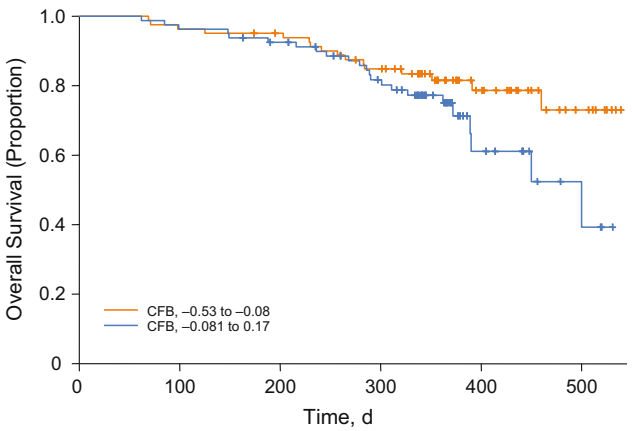

Fig. 3 Overall survival as a function of fractional change in tumor size stratified at the median value (−0.08). *CFB* fractional change in tumor size from baseline

Table 2 Parameter estimates for the survival model

Parameter	Estimate	RSE (%)	P^a
int	6.98	3.2	<0.0001
b_1	−0.429	29	0.0007
b_2	−0.0018	41	0.014
b_3	−1.23	59	0.089
log(p)	0.466		

Survival time in days, *int* intercept, p shape parameter, *RSE* relative standard error, b_1 baseline Eastern Cooperative Oncology Group performance status coefficient, b_2 tumor size at baseline coefficient, b_3 relative change in tumor size from baseline coefficient

[a] Probability calculated using Wald test

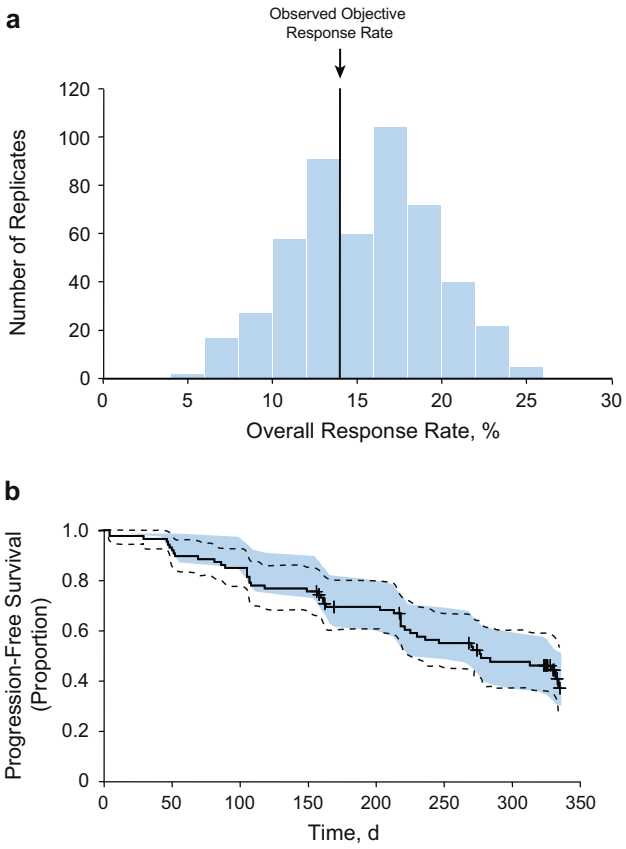

Fig. 4 Distribution of, **a** model-predicted objective response rate (*ORR*) and, **b** model-predicted median progression-free survival (*PFS*) for 500 replicates compared with observed Kaplan–Meier estimates. The *vertical black line* in panel **a** indicates the observed ORR. The *black lines* in panel **b** indicate the observed Kaplan–Meier estimate of median PFS and its 95% CI at each time point

Qualification of the modeling framework

The full modeling framework, comprising the dose-modification models (to simulate dose and AUC intensity), the TGI model [14], and the preliminary survival model, was used to simulate multiple replicates ($n = 500$) of the phase 2 study. The observed data were well within the predictive distributions for ORR and PFS in patients with DTC as illustrated in Fig. 4. The predicted ORR in patients with DTC was 15.0% (95% PI, 7.5–23.7%) compared with the observed ORR of 14.0% (95% CI, 7.7–22.7%). The predicted median PFS was 40 weeks (95% PI, 32–49 weeks) compared with the observed median PFS of 40 weeks (95% CI, 32–50 weeks).

Simulations

The mean simulated relative AUC intensities decreased with motesanib starting dose (from 0.89 at 125 mg to 0.85 at 250 mg) in patients with DTC. The simulated median ORR across replicates increased with starting dose and ranged from 13.5% (95% PI, 10.2–18.2%) at 100 mg QD to 38.0% (95% PI, 30.9–45.7%) at 250 mg QD. However, simulated median PFS was independent of the motesanib starting dose, ranging from 40.5 weeks (95% PI, 38.6–46.9 weeks) at 100 mg QD to 40.0 weeks (95% PI, 38.6–46.8 weeks) at 250 mg QD (Table 3).

Table 3 Simulated median objective response rate and progression-free survival

Dose (mg)	ORR [% (95% PI)[a]]	Median PFS [week (95% PI)[a]]
100	13.5 (10.2–18.2)	40.5 (38.6–46.9)
125	17.9 (12.8–23.4)	42.2 (38.6–46.9)
150	23.5 (18.8–30.0)	43.3 (38.9–46.9)
250	38.0 (30.9–45.7)	40.0 (38.6–46.8)

ORR objective response rate, *PI* prediction interval, *PFS* progression-free survival

[a] Prediction intervals calculated across 100 replicates

Discussion

The purpose of this study was to develop a modeling framework to simulate the clinical endpoints of ORR and PFS to aid further clinical development of motesanib. The modeling framework, comprising the dose modification models, a survival model, and a previously developed PK and tumor growth inhibition model [14], was assessed for its ability to predict AUC intensity, tumor size over time, ORR, and PFS, compared with the results of a phase 2 study of motesanib monotherapy in patients with progressive or advanced MTC or DTC [12, 13].

Dose-modification models were developed to calculate the probability and duration of motesanib dose-reduction and dose-interruption events as a function of time and dose. The model correctly predicted the motesanib AUC

intensity until the end of study at 48 weeks. Dose reductions and dose modifications can often be attributed to adverse events. Our approach of modeling the probability and duration of dose modifications is a pragmatic approach to the simulation of dose or AUC intensity that avoids the need to develop multiple exposure–response models for different dose-limiting toxicities. This modeling approach was previously used to predict that dose reductions in capecitabine would result in a reduction in median dose intensity, reduced tumor shrinkage, and small decreases in survival in patients with colorectal cancer [19]. A specific model to simulate dose intensity is particularly valuable if there is a significant proportion of dose modifications and when it is necessary to perform simulations of tumor size up to progressive disease and to investigate dose response.

Median survival time could not be estimated because of the limited number of events. However, using the survival model, baseline tumor size and ECOG performance status were identified as significant predictors of survival distribution. Drug effect (model-predicted relative change in tumor size at week 8) showed a trend to predict survival and was incorporated in the model. The data indicated that tumor shrinkage might have a stronger impact on longer-term survival. The preliminary model developed here was only used to simulate death events for the determination of PFS. Change in tumor size at the end of cycle 2 (weeks 6 or 8) has been shown to predict overall survival in phase 3 studies of other solid tumor types, such as metastatic breast cancer [5], colorectal cancer [6], and non-small-cell lung cancer [7].

The full modeling framework, consisting of the models above coupled with population PK and tumor growth inhibition models reported in the companion manuscript [14], was qualified to perform simulations of motesanib clinical endpoints (ORR and PFS) following a starting dose of motesanib 125 mg QD. The predicted ORR and PFS among patients with DTC was 15% and 40 weeks, respectively, compared with the observed ORR of 14% and the observed PFS of 40 weeks in the phase 2 study [12]. Simulations of dose response up to 250 mg QD were performed for patients with DTC. High-dose simulations implied some extrapolation (twofold from 125 to 250 mg) of the models and assumed that motesanib PK was linear and the dose reduction model was able to simulate dose intensity for higher starting doses. Of note, drug effect in the models was driven by AUC estimated by a population PK model [14], and the interpatient variability in exposure supported the dose–response simulations. Individual post hoc estimates of AUC ranged from 1.66 to 9.28 ng h/ml (i.e., a 5.6-fold range) for a 125-mg starting dose in patients with DTC. These simulations suggested that ORR depends on starting dose and that higher doses (e.g., 250 mg QD) may provide a better response. However, the clear dose response seen in ORR would not translate into a benefit in PFS (as assessed by both median PFS and the proportion of patients without a PFS event at 48 weeks). Thus, the dose–response simulations do not support any motesanib dose intensification in DTC, because no clinically relevant improvement in PFS would be expected.

Tumor growth inhibition models, combined with drug-independent survival models, have previously been used to predict survival in phase 3 studies based on results from phase 2 studies [5, 6]. In these simulations, individual dose intensities were resampled from those observed in the clinical studies, i.e, models to simulate dose intensity were not developed, and tumor size simulations were limited to first assessment (week 8). The approach we are presenting here is, to the best of our knowledge, the first attempt to simulate long-term (48 weeks) dose intensity, longitudinal tumor size data, and survival, as well as the first use of simulated data to derive the clinical endpoints ORR and PFS. The results suggest that this modeling framework is a useful tool for simulating expected clinical response in phase 2 trials and may therefore be useful in supporting early development decisions in oncologic drug development (e.g., go/no go, phase 3 study design), consistent with US Food and Drug Administration recommendations [4].

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Conflict of interest LC and RB are employees of Pharsight and contractors to Amgen Inc. J-FL, and Y-NS are employees of and stockholders in Amgen Inc.

Appendix

The NONMEM control stream for the model for probability of dose reduction events is as follows:

```
$PROB KPD model for dose reductions

$INPUT ID TIME DV MDV DOSE=AMT
;ID   patient identifier
;TIME day from first dose
;DV   daily dose categories 0:125mg, 1:100mg, 2:75mg, 3:0mg
;MDV  missing dependent variable (1: yes, 0: no)
;AMT  Daily AUC (daily dose/clearance)

$DATA dose1.csv  IGNORE=C

$SUBROUTINE ADVAN6 TOL=5

$MODEL COMP = (KPD,DEFDOSE)

$PK
INT3 = THETA(3)
INT2 = THETA(2)
INT1 = THETA(1)
KP   = THETA(4) ; KP (day-1)
SDRG = THETA(5) ; Sdrug (mg·h·L-1)
LSTD = THETA(6) ; log(standard deviation of ETA1)

$DES
DADT(1) = -KP * A(1); KPD model
A1=A(1)

$ERROR
E = SDRG*(A(1)/3)+EXP(LSTD)*ETA(1)
E1=INT1+E
E2=INT2+E1
E3=INT3+E2
IF(E1.GE.100) E1=100
IF(E2.GE.100) E2=100
IF(E3.GE.100) E3=100

; probabilities
P1=EXP(E1)/(1+EXP(E1)) ; P(100 mg,t)
P2=EXP(E2)/(1+EXP(E2)) ; P(100 mg or 75 mg,t)
P3=EXP(E3)/(1+EXP(E3)) ; P(100 mg or 75 mg or 0 mg,t)

PR0= 1-P3        ; P(125 mg,t)
PR1= P1          ; P(100 mg,t)
PR2= P2-P1       ; P(75 mg,t)
PR3= P3-P2       ; P(0,t)

IF(DV .GT. 2.5) Y=PR3
IF(DV .LE. 2.5 .AND. DV .GT. 1.5) Y=PR2
IF(DV .LE. 1.5 .AND. DV .GT. 0.5) Y=PR1
IF(DV .LT. 0.5) Y=PR0

$THETA
1     ; int1
1     ; int2
1     ; int3
0.01  ; KP (day-1)
0.001 ; Sdrug (mg·h·L-1)
-3    ; log(standard deviation of ETA1)

$OMEGA 1 FIXED

$EST MAXEVALS=3000 PRINT=10 POSTHOC NOABORT METHOD=COND LAPLACE
LIKE
$COV
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