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ORIGINAL ARTICLE

Population pharmacokinetic/pharmacodynamic modeling for the time course of tumor shrinkage by motesanib in thyroid cancer patients

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Abstract
Objective To develop a population pharmacokinetic/pharmacodynamic model describing the relationship between motesanib exposure and tumor response in a phase 2 study of motesanib in patients with advanced differentiated thyroid cancer or medullary thyroid cancer.
Methods Data from patients ($n = 184$) who received motesanib 125 mg once daily were used for population pharmacokinetic/pharmacodynamic modeling. Motesanib concentrations were fitted to a 2-compartment population pharmacokinetic model. Observed change in tumor size was the drug response measure for the pharmacodynamic model. Exposure measures in the pharmacokinetic/pharmacodynamic model included dose, plasma concentration profile, or steady-state area under the concentration versus time curve (AUC_{ss}). A longitudinal exposure–tumor response model of drug effect on tumor growth dynamics was used.
Results Motesanib oral clearance in patients with medullary thyroid cancer was 67% higher than in patients with differentiated thyroid cancer patients (73.7 vs. 44 L/h). Patients' disease type (medullary thyroid cancer vs. differentiated thyroid cancer) was the most important covariate for explaining interpatient variability in clearance. The objective response rates were 14 versus 2% for differentiated thyroid cancer and medullary thyroid cancer, respectively. Motesanib exposure measures (AUC_{ss} or concentration profile) were better predictors of tumor response than motesanib dose. The estimated motesanib concentration yielding tumor stasis (1.9 ng/mL) was lower than the observed trough concentrations in differentiated thyroid cancer and medullary thyroid cancer patients.
Conclusions Differences in motesanib pharmacokinetics likely explain the difference in tumor response observed between differentiated thyroid cancer and medullary thyroid cancer patients. The population pharmacokinetic/pharmacodynamic model provides a tool for predicting tumor response to the drug to support the dosing regimen of motesanib in thyroid cancer patients.

Keywords Population pharmacokinetics/pharmacodynamics · Tumor response · Motesanib · Thyroid cancer

Introduction

Objective response (an assessment of changes in tumor dimensions) is a commonly used endpoint in phase 2 oncology studies. Recent studies have shown that tumor shrinkage as a continuous rather than a categorical variable can be used to describe the time course of tumor response, improve study design, dose, and dose regimen selection and, more importantly, that it can predict outcomes such as survival [1–6]. These data are especially significant in the era of targeted therapeutics, when many compounds are available for clinical testing and the incidence of toxicity is

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no longer the primary criterion defining dose selection in phase 3 studies.

However, although pharmacokinetic (PK)/pharmacodynamic (PD) modeling has been utilized to assess drug effect in preclinical tumor xenograft studies [7, 8], the use of PK/PD modeling of longitudinal data in clinical development is limited and has yet to gain widespread application as an endpoint for drug-effect simulation in clinical trials. Notably, longitudinal exposure–tumor response models based on data from phase 2 studies have been developed to simulate drug effect on tumor size changes over time in studies of metastatic breast cancer, colorectal cancer, and metastatic non–small-cell lung cancer [6, 9]. Clinically relevant covariates can be incorporated into such models to reduce unexplained variability and increase the power to detect a treatment effect and identify populations of responders.

Motesanib is an orally administered small-molecule antagonist of vascular endothelial growth factor receptors 1, 2, and 3; platelet-derived growth-factor receptor; and Kit receptors [10]. In a phase 1 study, treatment with motesanib 125 mg once daily (QD) resulted in antitumor activity in patients with advanced solid cancers, including 5 patients with differentiated thyroid cancer (DTC) [11]. In a phase 2 study, treatment with motesanib 125 mg QD resulted in an objective response rate (ORR, per RECIST and independent review) of 14% among DTC patients [12] and 2% among patients with medullary thyroid cancer (MTC) [13]. Forty-eight percent of MTC patients and 35% of DTC patients achieved durable (≥24 weeks) stable disease. Motesanib exposure, estimated as area under the concentration versus time curve (AUC) and maximum (C_{max}) and minimum (C_{min}) observed plasma concentrations, was lower in the MTC cohort than in the DTC cohort [12, 13]. Additionally, the median trough concentrations at different sampling time points were 33–74% lower in MTC patients than in DTC patients [13]. The goals of the present study were to develop a population PK/PD model to describe the difference in drug exposure between MTC and DTC patients and its potential contribution to the difference in tumor response, and to support dose selection decisions for future motesanib studies.

Methods

Study design

As described previously [12, 13], this was a phase 2 open-label study that enrolled patients with progressive or symptomatic (MTC only), locally advanced or metastatic DTC ($n = 93$) and MTC ($n = 91$). The study was conducted at 42 centers in 10 countries. The primary endpoint was the ORR, which was assessed by centralized independent radiologic review according to modified RECIST [14]. Secondary endpoints included duration of tumor response, tumor-related symptoms (incidence and severity of diarrhea and flushing occurrences; MTC cohort only), and progression-free survival time. Other endpoints included time to response, overall survival time, motesanib PK, and adverse events. Patients self-administered motesanib (Amgen Inc., Thousand Oaks, CA) 125 mg QD for up to 48 weeks or until unacceptable toxicity, disease progression, or death. Doses of motesanib could be reduced or withheld if necessary according to protocol-specified rules. Following a dose reduction, treatment could resume at a dose of 100 mg QD (75 mg QD after a second treatment interruption).

For the assessment of tumor response, computed tomographic or magnetic resonance imaging of the neck, chest, and abdomen was performed every 8 weeks and when disease progression was suspected [12, 13]. The sums of the longest diameters of the target lesions were used as the drug-response measure for pharmacodynamic modeling.

Pharmacokinetic sample collection

Plasma samples for the assessment of motesanib PK were collected from a subgroup of patients (DTC, $n = 9$; MTC, $n = 10$) at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after the first dose of motesanib on study day 1. Plasma samples for the assessment of motesanib trough concentrations were collected from all patients immediately before the daily dose of motesanib once every 4 weeks during the first 24 weeks of the study. Plasma motesanib concentrations were assayed using a validated liquid chromatography/tandem mass spectroscopy method (CEDRA Clinical Research LLC, Austin, TX). The lower limit of quantitation was 0.2 ng/mL.

Population pharmacokinetic model

One- and two-compartment models with first-order elimination and first-order absorption with a lag time were fitted to the plasma concentration versus time data. An exponential interindividual variability error term, which assumes a log-normal distribution, was included with all PK parameters (K_a, lag-time, CL, Q, V_c, and V_p) in the model. Due to the oral administration, clearances and volumes of distribution are actually overestimated as much as the inverse of the bioavailability F. Residual intra-individual random error was modeled with combined additive and proportional components.

Other than disease type and baseline diarrhea effect on CL, no formal covariate analysis was undertaken with the population PK analysis.

A sequential PK/PD modeling approach was used. Individual PK parameters were first obtained as post hoc estimates from the final population model. Concentration profiles or the steady-state AUC (AUC_{ss}) were then calculated and subsequently used as exposure measures in the PK/PD model.

Population pharmacokinetic/pharmacodynamic model

A mechanism-based PK/PD model was applied to describe the underlying disease progression and exposure-driven drug effect on tumor size over time [6]:

$$\begin{aligned} &\frac{\mathrm{d}(Y(t))}{\mathrm{d}t} = k_g \cdot Y(t) - k_k \cdot Exposure(t) \times R(t) \times Y(t) \\ &R(t) = \exp(-\lambda t) \\ &Y(0) = Y_0 \end{aligned} \quad (1)$$

where Y is the sum of longest diameters of all target lesions; k_g and k_k are the tumor growth rate and drug constant-cell-kill rate, respectively; $R(t)$ is a resistance function that incorporates a rate constant of resistance appearance (λ); Y_0 is the observed tumor size as baseline; and *Exposure* is drug exposure measured by dose, AUC_{ss}, or the full plasma drug concentration profile in the central compartment.

The empirical resistance function is required to explain the observed biphasic decrease in tumor response with a fast reduction in tumor size followed by relatively slow reduction or regrowth after long-term treatment. The motesanib exposure yielding tumor stasis (ie, $\mathrm{d}Y(t)/\mathrm{d}t = 0$), a measure of tumor sensitivity to drug, was calculated as the ratio of k_g to k_k at baseline assuming no resistance.

An exponential interindividual variability error term was included with all the pharmacodynamic parameters in the model. An additive residual error model was used. Patient and disease covariates tested in the PK/PD model included patients' disease type (MTC vs. DTC) and Eastern Cooperative Oncology Group (ECOG) performance status.

Population pharmacokinetic and pharmacodynamic data analysis

Samples from patients with at least 1 evaluable PK sample were included. Data were analyzed using the nonlinear mixed-effect modeling software program NONMEM (version V or VI, level 1.0; ICON Development Solutions, Ellicott City, MD) with the Digital Fortran Compiler Comparq Visual FORTRAN 6 [15]. Graphical and all other statistical analyses, including evaluation of NONMEM outputs, were performed using S-PLUS 7.0 for Windows (Insightful, Seattle, WA, USA). The first-order and first-order conditional estimation with interaction (FOCEI) methods were used for population PK and PK/PD analyses, respectively. PK parameters were derived using the POSTHOC step in NONMEM. When comparing alternative models, the main criterion used was the difference in the NONMEM minimal value of objective function (MVOF), which has an approximately chi-square distribution with n degrees of freedom, where n is the difference in the number of parameters between the hierarchical models (likelihood ratio test). For both population PK and PK/PD analyses, model discrimination was based on changes of MOFV of NONMEM. A decrease in OFV of >7.88 corresponds approximately to a P value of <0.005 for nested models differing in one variable. The goodness of fit of each model was evaluated using diagnostic scatter plots that included predicted and observed motesanib plasma concentrations or tumor size, residual and weighted residual plots versus time, and predicted plasma concentrations or tumor size.

In addition to diagnostic plots, a posterior predictive check was performed to evaluate the final PK/PD model. A total of 200 replicates using the original study design were simulated. Quartiles of relative tumor change (from baseline) at week 8 were computed, and the distribution of quartiles across replicates was compared with the observed quartiles. Tumor size change was assessed at week 8 because it was the first date of assessment in the study and has been shown to be a good predictor of clinical endpoints in non–small-cell lung cancer and metastatic colorectal cancer [4, 6].

Results

Patients

The study enrolled a total of 184 patients. The final database for PK analysis consisted of a total of 853 plasma concentration assessments from 156 patients (85% of the study population) who had at least 1 evaluable sample (MTC, $n = 76$; DTC, $n = 80$). Of these patients, 19 (MTC, $n = 10$; DTC, $n = 9$) were included in the intensive PK sampling portion of the study. Approximately 5 samples were available per patient (range, 1–36), with collection times of more than 1 year for some patients (97.5th percentile, 382 days). The patient incidence rate of diarrhea at baseline, which is a frequent symptom of MTC [16], was notably higher in the MTC cohort (68%) than in the DTC cohort (6%). Complete baseline and demographic characteristics, as well as the results of the primary and secondary endpoints, have been published previously [12, 13].

Population pharmacokinetic analysis

A statistically significant ($P < 0.005$) improvement in the model fit was observed when a 2-compartment model was used to fit the plasma concentration data compared with a 1-compartment model. The mean CL value in DTC patients was approximately one-half of that observed in MTC subjects (Fig. 1). Between weeks 4 and 24, median trough concentrations at each sampling time point were between 33 and 74% lower in MTC patients compared with DTC patients treated with the same once-daily dose [13].

In an initial analysis, incorporating baseline diarrhea as a covariate in the CL model resulted in a significant improvement in the model fit; however, after incorporating patients' disease type (DTC vs. MTC) as a covariate, baseline diarrhea no longer significantly affected model fit. After accounting for patients' disease type, neither the presence (Fig. 2a) nor the severity (Fig. 2b) of diarrhea in the population model significantly affected mean CL in the MTC cohort. However, estimation of separate CL values for MTC and DTC patients resulted in a significant ($P < 0.005$) improvement in the model fit as measured by the reduction in the minimum value of objective function by 93 units. The population CL estimate for the MTC cohort was approximately 67% higher than that for the DTC cohort. Indeed, there was no statistically significant difference in the volume of distribution between the MTC and DTC cohorts. Evaluation of plasma concentration profiles revealed a clear trend toward lower exposure in the MTC cohort compared with the DTC cohort, especially during the terminal phase (Fig. 1), suggesting that the effect is likely related to differences in CL.

Patients' disease type (DTC vs. MTC) was the only covariate included in the population PK model for derivation of individual PK parameters. Overall, the population model adequately fitted the plasma concentration–time data, PK parameters were estimated with acceptable accuracy (Table 1), and no obvious bias in the fit was observed (data not shown).

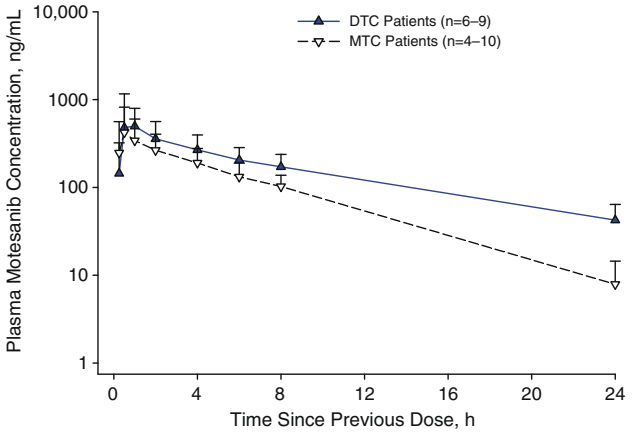

Fig. 1 Mean plasma motesanib concentration versus time profiles after 125-mg oral dosing in patients with differentiated and medullary thyroid cancer. The *n* values represent the total number of concentration points at each time point (and consequently vary from point to point)

Population pharmacokinetic/pharmacodynamic analysis

A total of 700 tumor size measurements from 163 patients (MTC, $n = 82$; DTC, $n = 81$) from the total study population of 184 patients (89%) were used to establish the PD model for tumor response. Among these 163 patients, 156 had at least one evaluable plasma sample.

Population PK parameters were assigned for the 7 patients without evaluable data. The mean ± standard deviation (SD) of time for the follow-up tumor evaluations was 132.9 ± 113.1 days. The observed relative reduction in the sum of the longest diameters of target lesions up to week 48 in the study was lower in the MTC cohort compared with the DTC cohort (Fig. 3).

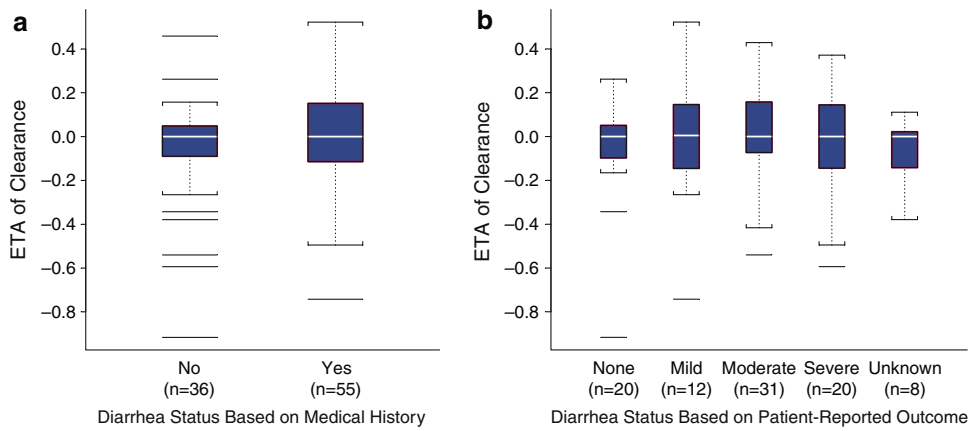

Fig. 2 Effect of **a** baseline diarrhea status and **b** diarrhea severity on motesanib clearance in medullary thyroid cancer patients. ETA: interpatient variability

Table 1 Population pharmacokinetic parameters of motesanib in patients with differentiated or medullary thyroid cancer

Parameter, units	Population estimate (RSE% of estimate)[a]
k_a, h^{-1}	1.72 (69)
Typical CL, L/h	44 (8.32)
Effect of patients' disease type on CL (MTC vs. DTC)	1.67 vs. 1 (11.5)
V_c, L	39.6 (26.3)
V_p, L	346 (12.6)
Q, L/h	171 (30)
Lag time, h	0.2 (0.33)
ω_{Ka}, %	68.6 (184)
ω_{CL}, %	48.6 (26.3)
ω_{Vc}, %	38.1 (322)
ω_{Vp}, %	88.3 (43.2)
ω_{Q}, %	101.0 (32.2)
σ_{prop}, %	38.3 (10.5)
σ_{add}, ng/mL	11.7 (70.9)

CL clearance, *DTC* differentiated thyroid cancer, k_a absorption rate constant, *MTC* medullary thyroid cancer, Q distribution clearance, *RSE* relative standard error, V_c volume of distribution for the central compartment, V_p volume of distribution for the peripheral compartment, ω intersubject variability, σ_{prop} proportional intrapatient variability, σ_{add} additive intrasubject variability

[a] RSE% = (SE/parameter estimate) × 100

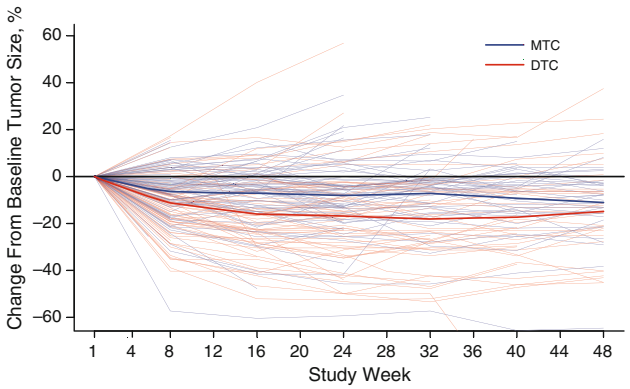

Fig. 3 Observed change in tumor size (sum of longest diameters) from baseline in (*red*) differentiated thyroid cancer (DTC) and (*blue*) medullary thyroid cancer (MTC)

Dose, daily AUC_{ss}, and concentration profile were compared in the PK/PD model as exposure measures for drug efficacy. Among these, the model including dose as an exposure measure displayed the highest NONMEM objective function (Table 2). The objective functions were comparable when AUC_{ss} or concentration versus time profiles were included in the model. The model incorporating AUC_{ss} as a measure of drug exposure was selected for the final PK/PD analysis mainly owing to the much shorter run time in NONMEM compared with using the concentration profile (30 min vs. 74 h, respectively).

The incorporation of patients' disease type (DTC vs. MTC) as a covariate in either k_g or k_k did not result in any significant improvement in the fit of the model. None of the tested patient factors or disease covariates were significant predictors of motesanib effect on tumor size.

The final PK/PD model, which incorporated AUC_{ss} as a measure of systemic motesanib exposure, was used to simulate change in tumor size over time in multiple replicates ($n = 200$) of the phase 2 study. The model adequately predicted change in tumor size from baseline over time observed in the phase 2 study, as indicated by the goodness-of-fit plots (Fig. 4) and the posterior predictive check (Fig. 5), where the observed quartiles are consistent with the predictive distribution from the model. Using the PK/PD model, the motesanib concentration or exposure yielding tumor stasis, a measure of tumor sensitivity to the drug, was estimated to be 1.9 ng/mL or 750 ng h/mL using concentration profile or AUC_{ss}, respectively.

Discussion

In this study, a population PK/PD model was developed to describe the plasma concentrations of motesanib versus time and the relationship between motesanib exposure (dose, AUC_{ss}, and concentration profile) and the time course of change in tumor size in a phase 2 study of motesanib monotherapy patients with DTC or MTC. The population PK analysis confirmed the difference in motesanib PK between the DTC and MTC cohorts previously reported with noncompartmental analysis [12, 13]. Oral clearance in the MTC cohort (73.7 L/h) was approximately 67% higher than in the DTC cohort (44 L/h), with no meaningful differences in *Vc*.

Among all covariates tested, patients' disease type (DTC vs. MTC) was best able to account for interpatient variability in CL. Although the mechanistic basis for the difference in CL between DTC and MTC patients remains unclear, the most likely explanation for the faster CL in MTC patients was the higher patient incidence rate of diarrhea at baseline in the MTC cohort (68%) compared with the DTC cohort (6%). However, the results of the current study suggest that incidence of diarrhea may not explain the difference in CL. First, incorporating diarrhea into the population model, after accounting for the patients' disease type, did not result in any significant improvement in the model fit. In addition, there was no difference in CL among MTC patients with severe, moderate, and mild diarrhea (Fig. 2). Most importantly, the effect of diarrhea on absorption, if any, likely resulted in a reduction in oral bioavailability of motesanib, which would have been

Table 2 Summary of pharmacodynamic model parameters using dose, AUC_{ss}, or concentration profile as the driver for drug effect on tumor growth inhibition

Parameter	Population estimate by models with different drug exposure measure[a]		
	Dose	AUC_{ss}	Plasma concentration
Objective function	3,605.9	3,582.5	3,583.9
k_g (RSE%)[b,c]	0.00117 (30.0)	0.00125 (27.6)	0.000958 (34)
k_k (RSE%)[d]	0.000188 (14.8)	0.00167 (13.7)	0.000515 (19.4)
λ (RSE%)	0.182 (14.1)	0.174 (13.2)	0.278 (22.8)
ω_{KG} (%)	150.3 (25.4)	144.6 (26.8)	158.4 (27.2)
ω_{KA} (%)	106.8 (18.7)	94.3 (21.1)	61.6 (59.5)
ω_{λ} (%)	45.2 (56.1)	42.4 (52.9)	77.6 (45.0)
σ_{add} (mm)	4.5 (14.5)	4.6 (14.9)	4.6 (14.8)

AUC_{ss} steady-state area under the concentration versus time curve, k_g rate constant of tumor inhibition, k_k rate constant of tumor growth rate constant, *RSE* relative standard error, λ rate constant of resistance appearance, ω intersubject variability, σ_{add} additive intrasubject variability

[a] A total of 700 tumor size assessments were used in the pharmacodynamic model

[b] The time unit for k_g is adjusted to 1 week

[c] RSE% = (SE/parameter estimate) × 100

[d] The unit for k_k is 1/(mg wk), 1/(μg h/mL wk), or 1/(ng/mL wk) for the dose, AUC, and concentration driven models, respectively

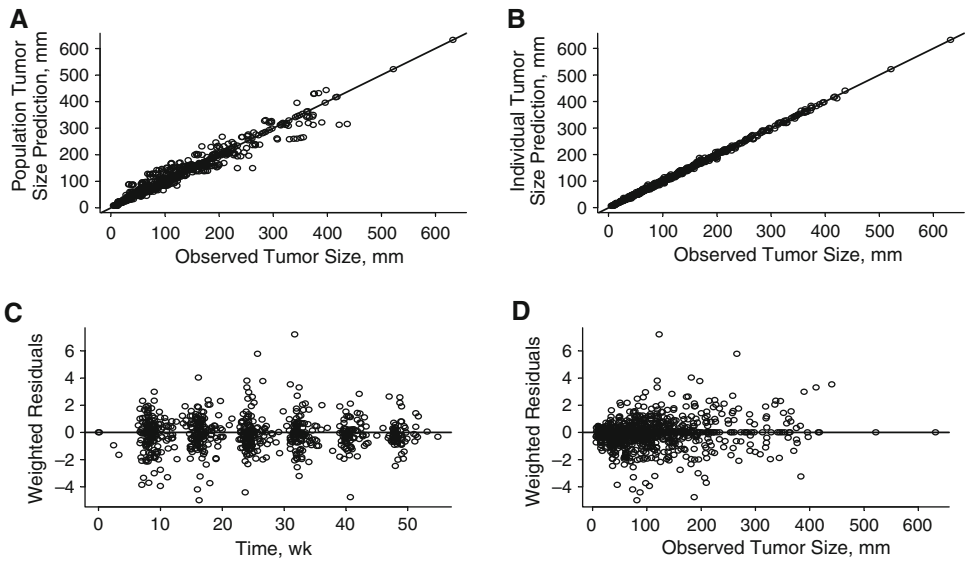

Fig. 4 Diagnostic plots for the final PK/PD model. **a** Population prediction versus observed tumor size; **b** individual prediction versus observed tumor size; **c** population weighted residual versus population prediction; **d** individual weighted residual versus individual prediction

manifested as increases in both CL and V_c. However, careful evaluation of the scatter plot of the plasma motesanib concentration versus time data (Fig. 1) suggests that the effect on V_c was minimal, because the plasma concentrations around the time to $C_{\max}$ were comparable in the MTC and DTC cohorts.

Another potential explanation for the differences in CL between the MTC and DTC cohorts is suggested by clinical studies investigating the metabolism of motesanib. In human hepatocyte incubations, more than 90% of motesanib was metabolized via conjugation (N-glucuronidation) [17]. Diarrhea may have hindered enterohepatic recirculation of motesanib-glucuronide, thereby affecting motesanib reabsorption. However, because enterohepatic circulation of motesanib-glucuronide would have occurred later than absorption, hindering the reabsorption of motesanib would have been expected to alter only the terminal phase, with limited effects on V_c.

Differences in metabolic rate between the MTC and DTC cohorts may also have accounted for the observed difference in CL. Studies with cultured human cells have demonstrated that thyroid hormones can regulate the expression of the cytochrome P450 (CYP) enzymes, which play a central role in phase II drug metabolism [18], thereby potentially altering the metabolism and the effects of a variety of drugs. Because motesanib is partially metabolized by CYP3A4 [17], induction of CYP3A4 expression by thyroid hormones could potentially have

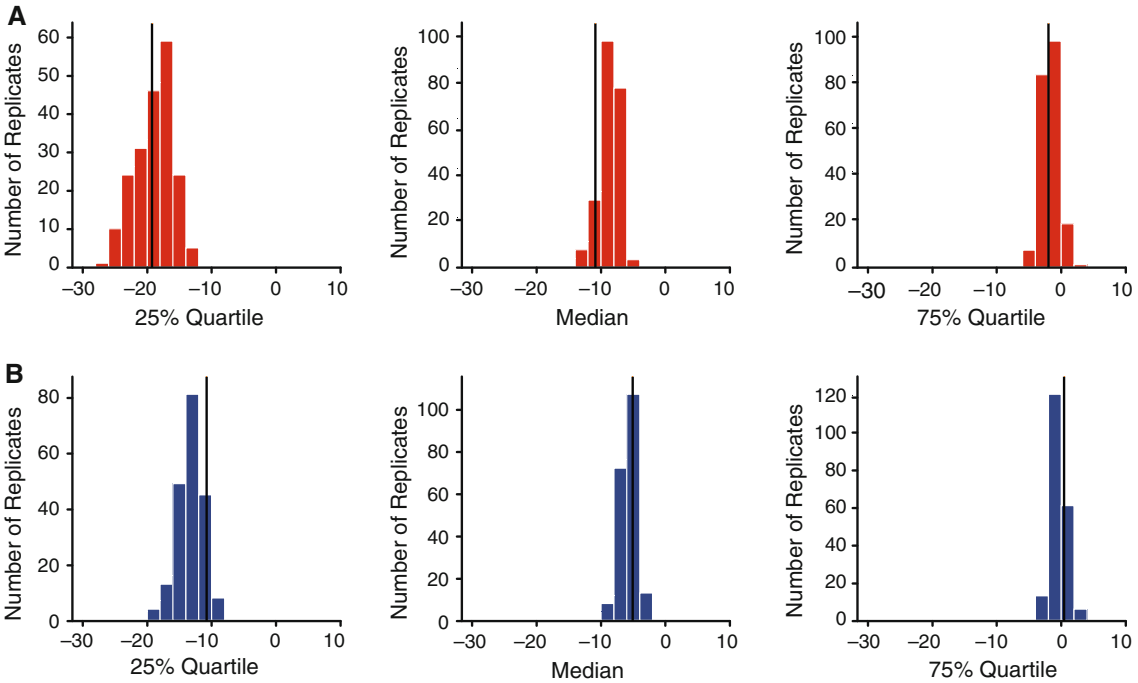

Fig. 5 Final pharmacokinetic/pharmacodynamic model qualification. Posterior distribution of relative tumor change quartiles at week 8 compared with observed quartiles (**a** differentiated thyroid cancer, **b** medullary thyroid cancer)

resulted in increased motesanib CL, with limited effect on V_c. Additionally, thyroid hormones have been shown to regulate the expression of cell membrane transporters and alter basal-to-apical drug transport [19].

In the motesanib thyroid cancer phase 2 study, the ORR in the DTC and MTC cohort was 14 and 2%, respectively, despite treatment with the same dose (125 mg QD) of motesanib [12, 13]. However, the clinical benefit rate (complete response + partial response + durable [≥24 weeks] stable disease) was similar among the 2 cohorts (DTC, 49%; MTC, 51%). The population PK/PD model was developed to provide a framework for investigation of the effect of systemic motesanib exposure on tumor growth dynamics and assess the effect of potential covariates on tumor response. Dose was the least predictive measure of the correlation of drug exposure with tumor response. The exposure (assessed as AUC_{ss} or predicted concentration profile after dose)–tumor dynamics model adequately predicted the time course of tumor response in both cohorts. The observation that systemic exposure measures such as AUC_{ss} or concentration profiles were better in fitting tumor size data than dose is in contrast to the report by Tham et al. [9], which did not demonstrate an improvement in using AUC to describe the tumor size data in patients with non–small-cell lung cancer treated with gemcitabine. The similar goodness-of-fit and MOFV of AUC_{ss} or plasma concentration profiles in driving motesanib drug effect are unsurprising because the ratio of the mean steady-state plasma concentrations and AUC_{ss} is constant. The patients' disease type effect (MTC vs. DTC) did not result in any further improvement in the model fit, suggesting that the lower systemic exposure observed in MTC patients is sufficient to account for the lower tumor response compared with DTC patients. None of the patient factors or disease covariates tested were significant predictors of motesanib effect on tumor size.

The motesanib concentration or AUC_{ss} yielding tumor stasis was estimated to be 1.9 ng/mL or 750 ng h/mL using concentration profile or AUC_{ss} as an exposure measure, respectively, in the PK/PD model. In the phase 2 study, the observed median trough concentrations ranged from 8.5 to 26.3 ng/mL for the DTC cohort and from 4.9 to 6.8 ng/mL for the MTC cohort [13]. The median AUC_{ss} based on the population model estimate was 1,700 and 2,840 ng h/mL, respectively. These results suggest that at a dose of 125 mg QD, motesanib should have antitumor activity in both MTC and DTC patient populations, which is consistent with the similar clinical benefit rate in the DTC and MTC cohorts. However, an exposure greater than that required to yield tumor stasis may be necessary to produce an ORR in MTC patients similar to that observed in the DTC cohort.

In summary, the PK of motesanib was best described using a linear 2-compartment model. The observed difference in motesanib exposure between the DTC and MTC patients could only be explained by disease status. The incorporation of the incidence or severity of diarrhea did

not improve the fit of the model. The change in tumor size in DTC and MTC patients was described by a tumor PD model. The larger ORR and tumor reduction observed in the DTC patients compared with MTC patients can be partly explained by the difference in motesanib exposure, which confirmed the appropriateness of the 125-mg QD dose for DTC patients. Population PK/PD modeling encompassing dose-exposure-effect relationships can provide useful information for the determination of rational dosing strategies and may thereby help to improve the likelihood of late-phase clinical study success.

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

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