ARTICLE

Tumor growth inhibition modeling to support the starting dose for dacomitinib

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Abstract

Dacomitinib is a second-generation, irreversible EGFR tyrosine kinase inhibitor for first-line treatment of patients with metastatic non-small cell lung cancer and EGFR-activating mutations. A high rate of dose reductions in the pivotal trial led to an observed inverse exposure-response (ER) relationship with the primary end points. Three ER models were developed to determine if the starting dose from the pivotal trial, 45 mg once daily (q.d.) dose, is appropriate: a longitudinal logistic regression model for adverse event-related dose changes, a Claret tumor growth inhibition (TGI) model, and a Cox model for progression-free survival (PFS) based on the TGI model predictions. This analysis included 266 patients taking dacomitinib with a starting dose of 45 mg ($N = 250$) or 30 mg ($N = 16$) q.d. The ER relationships with the time-varying exposure metrics, most recent maximum plasma concentration (C_{max}) and average concentration (C_{avg}) from the first dose, were established for the dose reduction and TGI models, respectively. The TGI model characterized the tumor inhibition over time with constant growth rate ($k_L = 0.0012$ years^{-1}) and highly variable kill rate ($k_D = 1.002$ years^{-1}/[µg/L]$^{\theta cavg}$, coefficient of variation [CV] = 89%) and drug resistance ($\lambda = 14.47$ years^{-1}, CV = 96%) leading to prolonged tumor shrinkage. The ER relationship was characterized using an exposure parameter with a power parameterization ($\theta cavg = 0.454$, $p < 0.0001$). The Cox model found that baseline tumor size ($p = 0.0166$) and week 8 tumor shrinkage rate ($p = 0.0726$) were the best predictors of PFS. Simulations of dose reductions and drug interruptions on tumor shrinkage over time showed greater and more prolonged tumor shrinkage with a starting dose of 45 mg q.d.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Lung cancer is the leading cause of cancer-related deaths in the United States and continues to be an area with unmet medical need for patients. Determining an appropriate dose recommendation is a primary consideration and one in which

exposure-response (ER) modeling plays a key role. Tumor growth inhibition (TGI) models are an established ER methodology that is frequently used to evaluate the efficacy of a new treatment. Because oncology programs typically only study a single dose, the use of TGI models can be a key consideration during the design of clinical trials, particularly with respect to the dose selection.

WHAT QUESTION DID THIS STUDY ADDRESS?
Absent a direct ER relationship with the primary end point (e.g., progression-free survival) in a pivotal phase III study, how can TGI models be used to support the dose regimen?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
When there is an observed inverse ER relationship using a time-invariant exposure metric, TGI models that account for dose interruptions and reductions can adequately characterize an ER relationship and provide support for the dose recommendations.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
Modeling and simulation based on a direct measure of tumor size over time may be an acceptable alternative efficacy end point for establishing an ER relationship. A TGI model using a time-varying exposure metric was a valuable tool in characterizing the benefit of a higher starting dose because the tumor shrinkage is fastest at the beginning of treatment and the higher initial exposures resulted in a greater reduction in tumor size, despite the risk of dose reductions.

INTRODUCTION

The life-threatening nature of cancer creates development issues that few other disease areas face. It is rare that more than one dose level is studied in the pivotal trial or more than one pivotal study is performed to evaluate efficacy. During the trial, patients are willing to tolerate more severe adverse events (AEs) as they may benefit from investigational treatments and usually do not have alternative treatment options. Although the gold standard for efficacy is overall survival (OS), it takes time for OS data to be mature, especially if a drug works well, leading to the use of surrogate clinical end points, such as progression-free survival (PFS) and objective response rate (ORR) as primary end points in phase II/III trials and for registration.

The standard approach for determining ORR is to use the Response Evaluation Criteria in Solid Tumors (RECIST) in which tumor size is the key component with a confirmed reduction in tumor size of greater than 30% considered a response (using the sum of the longest diameters [SLDs] in target lesions).[1] Although tumor size is the primary driver of determining response or disease progression, explicit exposure-response (ER) modeling of the tumor size as a measure of efficacy is not typically expected with new drug applications. When tumor modeling is performed, it is usually part of a model with PFS or OS where the predicted tumor size after a given time (e.g., 4, 6, or 8 weeks) is a predictor of the PFS or OS. These tumor growth inhibition (TGI)-efficacy models commonly

are developed as part of designing clinical trials, predicting efficacy, and calculating the probability of success, just to name a few applications.[2–8]

The frequent practice in oncology of proceeding into late-stage development studying a single dose can make it difficult to establish dose–response or ER relationships, particularly when the percentage of dose reductions is higher than expected.[9–11] When the patients who experience frequent or permanent dose reductions stay on treatment the longest, an inverse relationship between exposure and efficacy end points may be observed. One approach is to evaluate the first dose exposure, but when most patients have the same first dose, it may not be possible to characterize an ER relationship. The assumption of a time-invariant exposure measure having a constant effect on the hazard function over time, which is inherent to many parametric survival models, is likely to be violated when the number of dose reductions is high resulting in biased estimates of the ER relationship. Whereas these models can be extended to incorporate the effect of time-varying exposures and non-constant hazard functions, other approaches, such as tumor modeling and Cox proportional hazard modeling, are frequently used to explicitly account for time effects.[12,13]

The use of TGI models for justifying a starting dose after a pivotal trial has confirmed that efficacy or clinical benefit is uncommon, as regulators expect ER analyses for the primary end points (eg PFS). There are a few notable examples where TGI modeling was used rather

than a primary end point to support dosing recommendations. After establishing efficacy in a phase III trial for metastatic renal cell carcinoma, a TGI model was developed for everolimus to support 10 mg as the preferred dose while also confirming antitumor activity for patients taking 5 mg daily, which is the recommend dose for patients needing a dose reduction.[14] Motesanib established efficacy in a phase II trial for thyroid cancer, but dose-limiting toxicities (DLTs) required dose interruptions, many of which resulted in permanent dose reductions. A pharmacokinetic (PK)/TGI model was developed that included a dose-modification component (for both dose interruptions and dose reductions), which was subsequently used to predict PFS/OS for several potential starting doses.[15] An additional PK-TGI model for motesanib was developed to evaluate dose selection considering the dose reductions.[16] A TGI model of vismodegib in patients with metastatic basal cell carcinoma showed that a dosing holiday of up to 8 weeks, after an initial 12 weeks of treatment, did not have a clinically relevant effect on efficacy.[17] Capecitabine is another example where TGI models were developed to evaluate dose reductions and efficacy.[18] In the case of lenvatinib (combined with everolimus), 89% of patients required a dose modification during the pivotal trial, suggesting that the starting dose was too high.[19] The US Food and Drug Administration (FDA) recommended a longitudinal TGI model with time-varying exposure to assess the ER relationship. Simulations from the TGI model suggested that a lower starting dose, with the option for upward titrations, would provide comparable efficacy.[20] These examples all show the value of tumor modeling for supporting dose recommendations, particularly when dose interruptions or reductions were more frequent than expected.

Dacomitinib (Vizimpro) is a second-generation, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR-activating mutations.[21] In an open-label phase II trial, 89 patients were enrolled, including 45 with EGFR-activating mutations.[22] In the randomized, open-label, pivotal phase III trial, PFS was significantly improved with dacomitinib versus gefitinib. Median PFS was 14.7 months (95% confidence interval [CI] 11.1–16.6) in the dacomitinib group and 9.2 months (95% CI 9.1–11.0) in the gefitinib group (hazard ratio 0.59, 95% CI 0.47–0.74; $p < 0.0001$).[23,24] Based on these results, dacomitinib was approved by the FDA in 2018 with a recommended dose of 45 mg once daily (q.d.), with dose reductions of 30 mg q.d. and then 15 mg q.d. for adverse-reaction management.[21,25]

A high rate of AE-related dose reductions or interruptions were observed in the phase III trial (66%). The protocol allowed for study treatment to be interrupted for grade 3, grade 4, or intolerable grade 2 toxicity (using National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.0). Upon recovery to grade 2 or baseline, and in the clinical judgment of the investigator with the agreement of the patient, treatment could be resumed at the same dose level or a new dose level. As many of the patients with long periods of sustained response to dacomitinib experienced at least one dose reduction, there was a lowering of the average exposure in patients with the best response to treatment resulting in an inverse ER relationship with PFS.[25] The subgroup analysis of the phase III results found that patients who never reduced the dose from 45 mg q.d. had shorter median PFS and OS—similar to the gefitinib control arm—than patients who reduced the dose at least once (PFS 9.1 vs. 16.6 months; OS 22.0 vs. 36.7 months). The PK analysis showed that patients who did not reduce the dose tended to have lower initial plasma exposures at cycle 2, day 1 compared to patients who reduced at least once. Discontinuations due to AEs in the dacomitinib arm were also low (<10%).[26] This suggested there was an ER relationship with efficacy, but the time-varying nature of the exposure needed to be considered.

The FDA review of dacomitinib also identified the inverse relationship with PFS determining that dose interruptions and reductions were the most likely cause. Their exploratory analysis considered the first dose exposure and found "a flat/slightly positive ER relationship" with PFS.[25] To better characterize the ER relationship, three additional models were developed: (1) an empirical model describing the probability of dose-altering AEs using the time-varying maximum concentration from the most recent dose (maximum plasma concentration [C_{max}]) calculated on a weekly basis. (2) A TGI model considering the timing and duration of the AE-related dose reductions, to evaluate the impact of the dose reductions on tumor size, using the time-varying average exposure from time zero up until the day of each tumor assessment (average concentration [C_{avg}]). (3) A Cox proportional hazards model was developed to evaluate PFS with the tumor shrinkage rate predicted from the TGI model as a covariate. The models together helped characterize the ER relationship with both safety and efficacy over time to support the dosing regimen for dacomitinib with a starting dose of 45 mg q.d.

METHODS

Dose-altering AE model

A longitudinal logistic regression model was developed to provide an empirical characterization of the occurrence

of dose-altering AEs (yes or no within each week). AEs leading to either temporary or permanent dose reduction were included in the model. The model was fit using the glmer() function in R. Within each week, the drug exposure was time-varying and predicted from the population PK model using the post hoc estimates for each patient and their dosing history. The C_{max} in the week prior to the dose reduction, the C_{avg} since the most recent dose prior to the day of the AE, and the running C_{avg} (area under the curve divided by time since the first dose) were considered as potential exposure metrics in the model. As the probability of a dose-altering AE is not time-invariant, a parameter was included to account for the decreased probability of experiencing a dose-altering AE over time. The square root of time was selected as it was considered to adequately characterize the effect of time. The linear form of the model is presented below.

$$\text{logit}(p) = \theta_{int} + (\theta_{Exposure} + \eta_{1i}) \cdot \text{Exposure} + \theta_{time} \cdot \sqrt{\text{time}} + \theta_{interaction} \cdot \left(\text{Exposure} \cdot \sqrt{\text{time}}\right)$$

where θ_{int} is an intercept, $\theta_{Exposure}$ represents the effect of a one-unit increase in the exposure during a given week on the risk of experiencing a dose reduction, θ_{time} is a linear effect to account for systematic changes in the mean as a function of time (included as the square root of the time [in number of weeks] since the start of treatment). An interaction parameter $\theta_{interaction}$ was included to allow for changes in the effect on treatment over time. The parameter η_{1i} represents intersubject variability in the effect of the exposure and was assumed to be normally distributed with mean 0 and variance ω^2.

Tumor model

Several semimechanistic TGI models were explored in the development of a structural model. The general form was a change over time modeled as a net growth effect and a drug-induced decay effect. The Simeoni (2004), Stein and Wang (2012), and Claret (2009) models were considered.[2,14,27] The Claret model was selected as the primary tumor dynamic model based on the visual evaluation of the model fit which best captured the rapid decrease and sustained suppression of tumor growth. This model utilizes longitudinal tumor-size data to estimate a drug-specific cell-kill rate constant (k_D), a drug-resistance rate constant (λ), and a disease-specific growth rate constant (k_L). The effect of exposure was added as an effect on the kill rate constant along with the drug resistance parameter that decreases the killing rate over time (λ). The initial value of the tumor compartment, $y(t)$ at time zero, was

set to the observed baseline tumor size for each subject, which may have been collected up to 28 days prior to the first dose of active treatment. The form of the derivative is provided below:

$$\frac{dy}{dt} = k_L \cdot y(t) - k_D \cdot \text{Exposure} \cdot \exp(-\lambda \cdot t) \cdot y(t)$$

In this model, the effect of drug exposure over time was tested using a linear, maximum effect (E_{max}), and power parameterization. The parameterization was the exposure metric to the power of θ using the metric C_{avg} from time zero up until the tumor collection day, which was simulated using the previously developed population PK model. The power parameterization was selected based on model stability, precision of model estimates, and goodness of fit diagnostics. A covariate search using forward selection ($p = 0.05$) followed by backward elimination ($p = 0.001$) was used to assess age, sex, baseline tumor size, smoking status, and baseline Eastern Cooperative Oncology Group performance score (ECOG PS) as potential covariates on k_D, k_L, and λ.

Variability was included in the model with random effects for k_D and λ, assumed to be lognormal. The residual error was adequately described using an additive error following a normal distribution. Although simulations in theory could predict some negative values with the additive normal error, the central tendency was well-estimated and the visual predictive checks (VPCs) looked good with the observed 5th, 50th, and 95th percentiles all within the bands in each of the bins.

PFS model

After the tumor model was developed, the PFS was modeled with a Cox proportional hazard model using the predicted rate of tumor size reduction at week 8 relative to the observed baseline SLD as a covariate on the hazard function. The predicted tumor size was calculated using the individual post hoc estimates from the TGI model. To account for differences in the timing of the observed tumor size measurements, the rate of change was standardized by the time, in days, since the first dose of dacomitinib. This was calculated as ($y(0)$ − y(week 8))/$y(0)$/Time where $y(0)$ is the observed baseline SLD, y(week 8) is the model-predicted tumor size at week 8, and Time is the actual number of days from the first dose and the observed day of the tumor assessment for each patient. For patients that discontinued prior to week 8, the per-day rate of change at the time of the last tumor measurement (most commonly week 4) was used. The baseline tumor size and the predicted

tumor size rate of change at week 8 were included in the model. An additional covariate search was performed evaluating age, sex, body weight, and baseline ECOG using a $p = 0.05$ inclusion criterion.

Simulations of dose modifications

Simulations were performed to assess the relationship of exposure with tumor growth and dose-altering AEs considering the effect of dose interruptions and permanent dose reductions during treatment. A total of 500 simulations were performed with 2000 subjects randomly sampled, with replacement, from the original analysis dataset to maintain any correlation structure among patients. Post hoc random effects were simulated for each subject from the distributions specified in the population PK model, the TGI model, and the dose-altering AE model. Dosing records were simulated out to 120 weeks (~27.6 months), which was considered sufficient as the median PFS was 14.7 months in the phase III trial. The simulations tested for a dose-altering AE every 7 days (once a week). If a dose-altering AE was not simulated to occur that week, the patient continued at the same dose. If a dose-altering AE was simulated to occur, it was assumed the patient would require a 1-week dosing holiday (no doses for 7 days) before resuming at a lower dose. Seven days was considered a reasonable length of time for dose-interruption to resolve the AE sufficiently before a patient resumes treatment. Dose reductions were in 15-mg decrements with a maximum of two dose reductions (maximum of one dose reduction if starting at 30 mg).

The estimated C_{avg} that resulted under each of the different dose-reduction scenarios was used to predict tumor size.

Tumor response was calculated as at least a 30% reduction from baseline. Tumor progression was based on the RECIST criteria (increase of >20% from nadir) and evaluated once every 2 months (matching the frequency of the clinical trials). Because the TGI model cannot capture extended complete remission, progression was calculated relative to the individual predicted nadir. If the time was prior to the nadir, a 20% increase from the previous measurement as well as 20% greater than the individual prediction (IPRED) at that time was required for progression. From the simulations, response rates, dropout rates due to AEs, dropout rates from disease progression, and the survival probabilities (accounting for censoring due to AEs) were calculated and plotted with 90% prediction intervals. Visual predictive checks used 16 and 250 subjects, resampled with replacement from the 2000 simulated subjects, for 30 mg and 45 mg q.d. starting doses, respectively.

RESULTS

Patient disposition

The data used in this analysis were collected from two studies conducted in patients with cancer: the phase II study A7471017 (Clinicaltrials.gov ID: NCT00818441, January 8, 2019) and the phase III study ARCHER1050 (Clinicaltrials.gov ID: NCT01774721, April 17, 2019). Both studies were conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonization Guidelines for Good Clinical Practice. Each study was approved by the institutional review board of each study center. Written informed consent was obtained from all individual patients included in each study. All mandatory laboratory health and safety procedures were complied with when conducting any experimental work reported.

The phase II study evaluated the safety and efficacy of dacomitinib. Patients were administered dacomitinib at either 30 mg q.d. or 45 mg q.d. The phase III study compared the efficacy of dacomitinib 45 mg q.d. versus gefitinib 250 mg q.d. Patients in these studies who had EGFR-activating mutations (exon 19 deletions or exon 21 L858R mutation) and who had at least one tumor measurement were included in the analysis. There were 270 patients that met the disease and mutation criteria. Four of these patients did not have any tumor measurements in the source dataset and were excluded from the analysis. In total, 266 patients were used in the modeling, of which 16 patients from study A7471017 started at 30 mg q.d. and the remaining patients receiving 45 mg q.d. ($n = 29$ for 1017 and $n = 221$ for study ARCHER1050; see Table 1). The baseline tumor size relative to the last dose and age as well as the observed individual time course of the tumor sizes are provided in Figures S1 and S2.

Analysis data

The exposure metrics C_{max} and C_{avg} were calculated for all patients in the pooled analysis dataset using a previously developed population PK model developed for dacomitinib (description in Supplemental Materials). The reasons for dose interruptions or permanent reductions were recorded in the case report forms (CRFs) for each subject in the studies. Dose-altering AEs were determined based on this information. The tumor sizes were calculated following RECIST using the SLD (cm) from up to five target lesions. The measurements and determination of progression were based on the evaluation from an independent reviewer for all patients in study ARCHER1050; however, in study A7471017, the investigator made the

TABLE 1 Background, demographic, and dose reduction summaries

Variable	Level	Study A7471017	Study ARCHER1050	Total
Sample size		45 (100%)	221 (100%)	266 (100%)
Starting dose	30 mg q.d.	16 (36%)	0	16 (6%)
	45 mg q.d.	29 (64%)	221 (100%)	250 (94%)
Smoker	Never	36 (80%)	143 (65%)	179 (67%)
	Current	0	14 (6%)	14 (5%)
	Former	9 (20%)	64 (29%)	73 (27%)
Baseline ECOG	0	21 (47%)	74 (33%)	95 (36%)
	1+	24 (53%)	147 (67%)	171 (64%)
Dose reductions	None	16 (36%)	75 (33%)	91 (34%)
	One	22 (49%)	84 (37%)	106 (39%)
	Two	7 (16%)	66 (27%)	73 (27%)
Age, years	Mean (SD)	62.2 (10.6)	61.1 (11.3)	61.3 (11.2)
	Median	62	62	62
	Min; Max	39; 84	28; 87	28; 87
Baseline SLD, cm	Mean (SD)	7.5 (6.3)	5.3 (2.9)	5.7 (3.8)
	Median	6	4.7	4.8
	Min; Max	1.3; 28	1.0; 21.5	1.0; 28
Time of first dose reduction, days				
Starting dose 30 mg q.d.	Median	113	–	113
	Min; Max	64; 896	–	64; 896
Starting dose 45 mg q.d.	Median	70.5	74	74
	Min; Max	10; 362	9; 617	9; 617
Second dose reduction, days	Median	141	143	141
	Min; Max	43; 701	11; 617	11; 701

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Max, maximum; Min, minimum; q.d., once daily; SLD, sum of the longest diameter.

determinations. Across the 266 patients in the analysis dataset, 67% experienced at least one dose reduction with the median time to the first dose reduction of 71 days for patients assigned to the 45 mg q.d. starting dose. Dose interruptions and dose reductions were primarily driven by AEs with skin toxicities being the most common. All AEs were reversible by stopping or reducing the dose. The timing of dose reductions and the proportion of patients with a dose reduction to 30 mg and/or 15 mg q.d. are shown in Figure 1 out to 2 years postdose. Assumptions and limitations are provided in the Supplementary Material. R, NONMEM, and PsN were used for the analyses,[28–31] libraries, and software versions.[32,33] The model estimates from the three models presented are provided in Table 2.

Dose-altering AE model

The empirical model for dose-altering AEs established an ER relationship with the C_{max} in the previous week, which was selected based on the log-likelihood. The square root of time was found to adequately characterize the effect of time. The model showed that the probability of a dose-altering AE was higher with a 45 mg dose compared with a 30 mg dose (see Figure 2). The greatest period of dose reductions was during the first 2 months of treatment. A posterior predictive check is provided in Figure S3.

TGI model

The TGI model was found to adequately characterize the tumor inhibition over time, accounting for time-varying exposures, with a growth rate ($k_L = 0.012 \, \text{years}^{-1}$), cell death rate ($k_D = 1.002 \, \text{years}^{-1}/[\mu g/L]^{\theta cavg}$ coefficient of variation [CV] = 89%) with drug resistance ($\lambda = 14.47 \, \text{years}^{-1}$, CV = 96%) leading to prolonged tumor shrinkage. The estimated exposure effect, θ_{cavg}, using a power parameterization, was 0.454 ($p < 0.0001$), indicating a greater tumor death rate associated with increased dacomitinib exposure. Although the rate of disease resistance was estimated to be relatively fast, the variability for the resistance
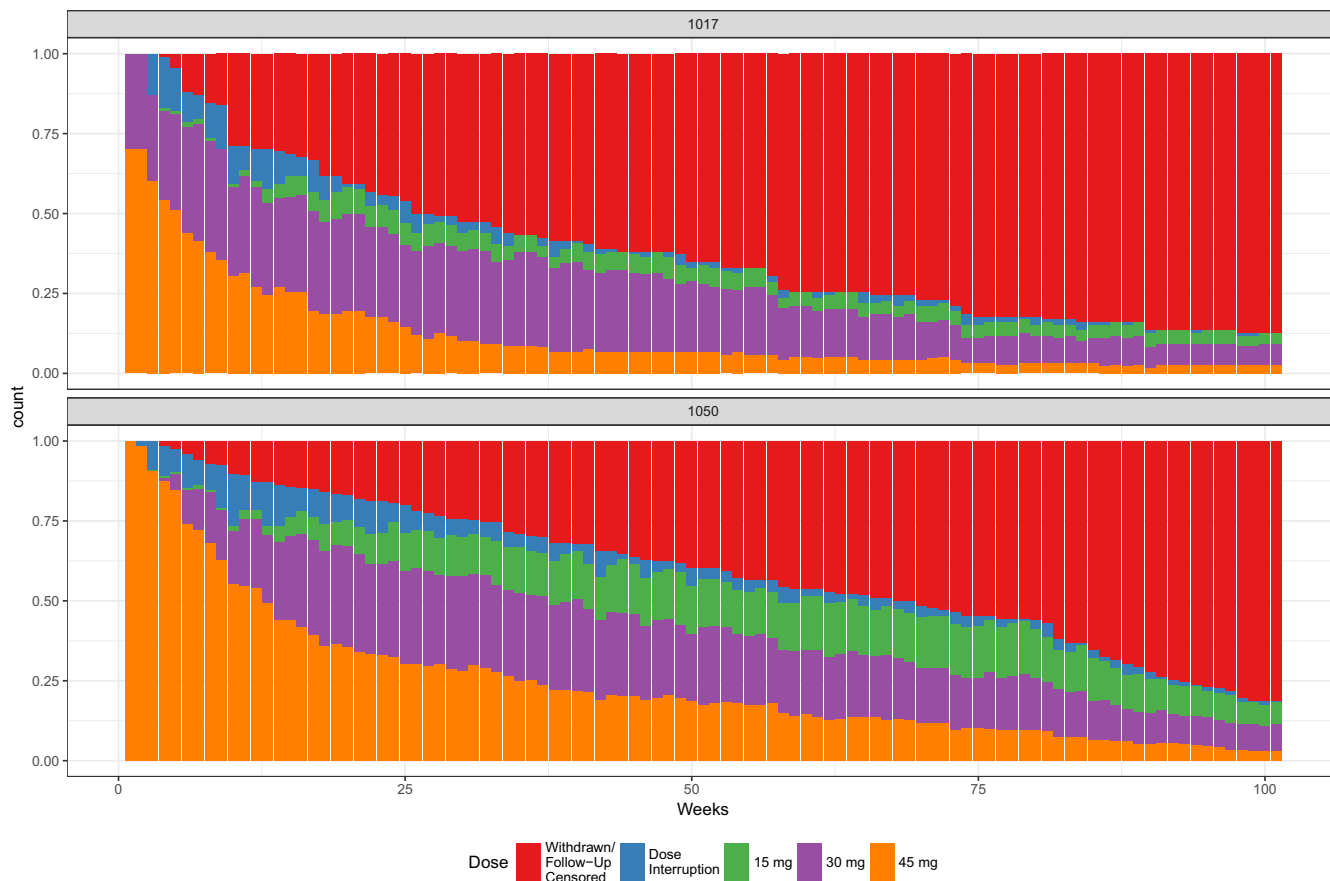
FIGURE 1 Observed relative frequency of patients receiving each of the dosages. The proportion of patients receiving 45 mg (orange), 30 mg (purple), 15 mg (green), dose interruptions (blue), or withdrawn/follow-up/censored (red) is shown over time. Each vertical bar represents 1 week of time. To create this graphic, each patient was categorized into one of the five groups. If on treatment, the lowest dose during the 1-week interval was used. If a patient missed at least one dose during the week, the patient was considered to be in the dose interruption category.

parameter was substantial with the CV of 96% resulting in many patients experiencing sustained periods of TGI. Shrinkage of k_D and λ were 20% and 22%, respectively, which is considered acceptable.[34] None of the covariates met the selection criterion and were not included in the final model. Although no covariates were included in the TGI model, covariate effects were accounted for in the exposure simulations using the population PK model. The VPC does not show any issues with the predictive ability of the model (see Figure S4). The diagnostic plots are provided in Figure S5. The sharp rise seen in the last tumor measurement for some patients is assumed to be partially explained by the residual error, which would affect the ability to predict the time of progression.

PFS model

The final Cox proportional hazards model included baseline SLD and the relative rate of change of the tumor size at week 8, predicted from the TGI model. No other covariates met the inclusion criterion. The estimated effect for baseline SLD on the hazard function corresponded to a larger baseline SLD associated with an increased hazard ($p < 0.05$). The relative rate of tumor shrinkage predictor was found to have a negative estimate, indicating that a faster rate of reduction of tumor size is associated with a lower hazard ($p < 0.1$). The effect of the rate of change of the tumor size at week 8 on the hazard function for PFS is evidence of an ER relationship with efficacy.

Simulations of tumor shrinkage with different dosing regimens

Simulations were performed to evaluate the timing of dose reductions as well as their effect on the tumor size over time. Following the schema described in the Methods section, the exposures were simulated based on the dose reductions; dose escalation was not considered. The percent of subjects who dropped out of the study due to AE are provided in Figure S6. Due to fewer dose reductions

TABLE 2 Model parameter estimates for both dose-altering AEs, TGI, and PFS models

	Estimates	90% CI[a]	RSE (%)	p value[*]	Shrinkage (%)
AE model					
Intercept (θ_{int})	−4.174	(−4.921 to 3.427)	−10.9	<0.001	
C_{max} (θ_{Cmax})	12.012	(4.21, 19.81)	39.5	0.011	
sqrt (week) (θ_{time})	−0.522	(−0.685 to −0.359)	−19.0	<0.001	
C_{max}-sqrt (week) interaction ($\theta_{time.Cmax}$)	3.823	(1.78, 5.87)	32.5	0.002	
Omega (C_{max}) (ω_{Cmax})	6.333				54
TGI model					
k_L, years^{-1}	0.012	(0.0082, 0.0145)	20.4	<0.001	
k_D, years^{-1}/(µg/L)$^{\theta cavg}$	1.002	(0.763, 1.273)	24.4	<0.001	
λ, years^{-1}	14.47	(12.82, 16.11)	9.7	<0.001	
C_{avg} (θ_{Cavg})	0.454	(0.386, 0.522)	9.1	<0.001	
Residual variance (σ)	0.431	(0.404, 0.460)	9.6		
ω_{k_L}	0 Fixed				0
ω_{k_D} (%CV)	0.788 (89%)	(0.582, 0.995)			20
ω_{λ} (%CV)	0.926 (96%)	(0.636, 1.253)			22
PFS model					
Baseline SLD	1.0409	(1.012, 1.069)		0.0166	
Week 8 tumor change rate	0.9867	(0.975, 0.998)		0.0726	

Abbreviations: %CV, percent coefficient of variation; AE, adverse event; C_{avg}, average exposure from time 0 up until the day of each tumor assessment; CI, confidence interval; C_{max}, maximum concentration from the most recent dose; PFS, progression-free survival; RSE, relative standard error; SLD, sum of the longest diameter; TGI, tumor growth inhibition.

[a]Confidence intervals for the AE model and PFS we calculated using the profile likelihood approach, while for the TGI model they were estimated using SIR.

[*]The *P*-value was calculated using the assumption of normality. The coefficient of variation (CV) was calculated as CV = 100 % · $\sqrt{\omega^2}$.
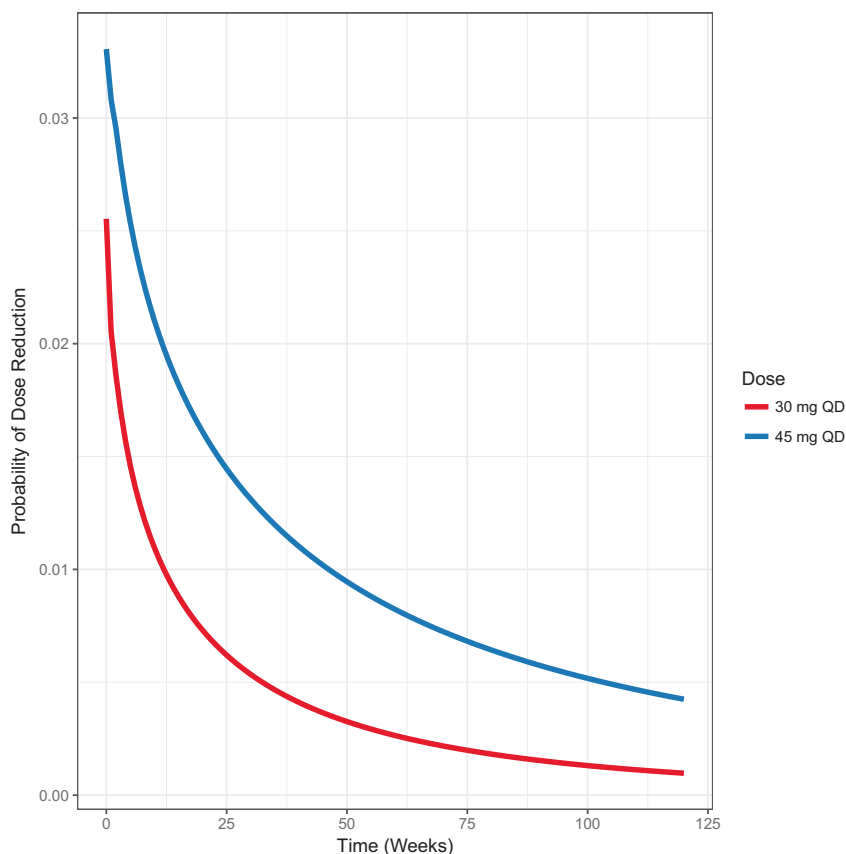

FIGURE 2 Probability of a dose-altering AE over time. The estimated probability of a dose-altering AE is provided for both 45 mg q.d. and 30 mg q.d. AE, adverse event.

being possible, the simulations for the 30 mg starting dose do not adequately represent the rates observed in patients. The 45 mg starting dose underestimates the dropout rates. When considering only observed dropouts who had at least one dose reduction, the simulations better capture the observed rates, although the dropout early in treatment is still underestimated.

Using the exposure from these simulations, the predicted percentage of subjects with shrinkage of at least 30% was calculated at each month and compared to the observed rates (see Figure 3). The simulations for the 45 mg starting dose match the observed rates, along with the quick onset of the response, very well. The predictions for the 30 mg starting dose seem to overestimate the rates as well as the onset rates, which appears to be slower than in patients starting at 45 mg, although there were only 16 observed subjects with the lower starting dose. Tumor progression was predicted based on the simulations (see Figure S7). Together with the dropouts due to AEs, the Kaplan–Meier survival probabilities for PFS were calculated for each of the simulations and shown in Figure S8.

The predicted median PFS (90% prediction intervals) based on the simulations was 15.0 months (12.6, 18.8) for 45 mg q.d and 15.1 months (7.8, 27.8) for 30 mg q.d. In general, the simulations overpredict the response rates for the 16 subjects who started with 30 mg q.d.

The time course of the tumor size was also simulated for a typical individual based on preset times for the dose reductions (see Figure 4). The simulations of the typical exposures show that when starting at 45 mg q.d., the expected tumor size is expected to reach the RECIST definition with greater shrinkage compared to the 30 mg starting dose with no dose reductions. Additional considerations regarding defining disease progression and the predictive performance of the simulations are discussed in the Supplementary Materials.

DISCUSSION

Dacomitinib showed a statistically significant improvement in PFS (the primary endpoint) in the pivotal phase
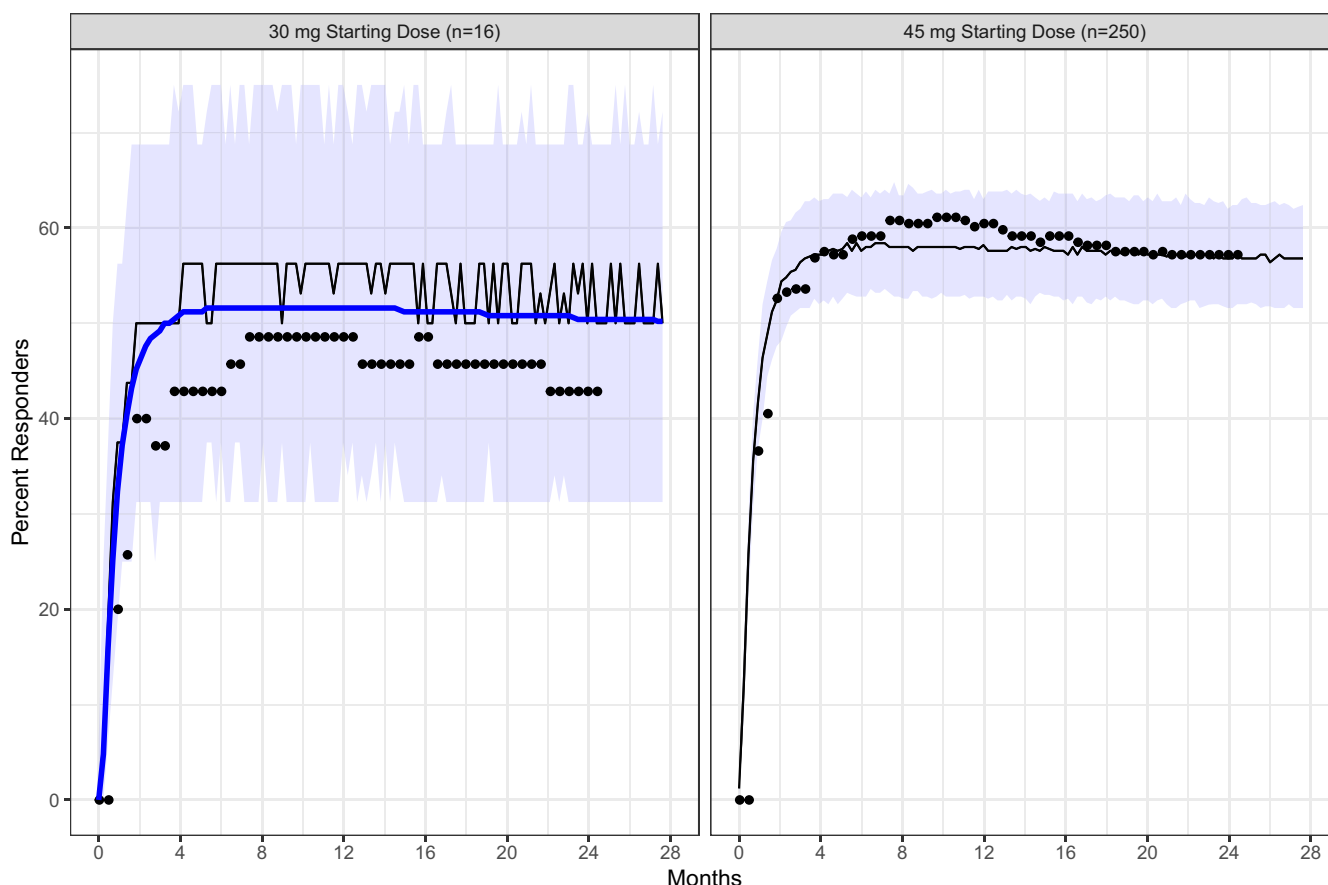

FIGURE 3 Predicted response rate of at least 30% over time. The points represent the observed rates of subjects with at least 30% shrinkage from their baseline tumor measurement during each 1 month period. The shaded areas represent the 90% prediction interval for the rates of responders from the 500 simulations accounting for dose reductions. The 90% prediction intervals are based on $n = 16$ patients for 30 mg q.d. and 250 patients for 45 mg q.d. The solid blue line for the 30 mg starting dose panel shows the typical response calculated from a simulated sample size of 250 subjects to help with comparisons to the 45 mg q.d. starting dose.
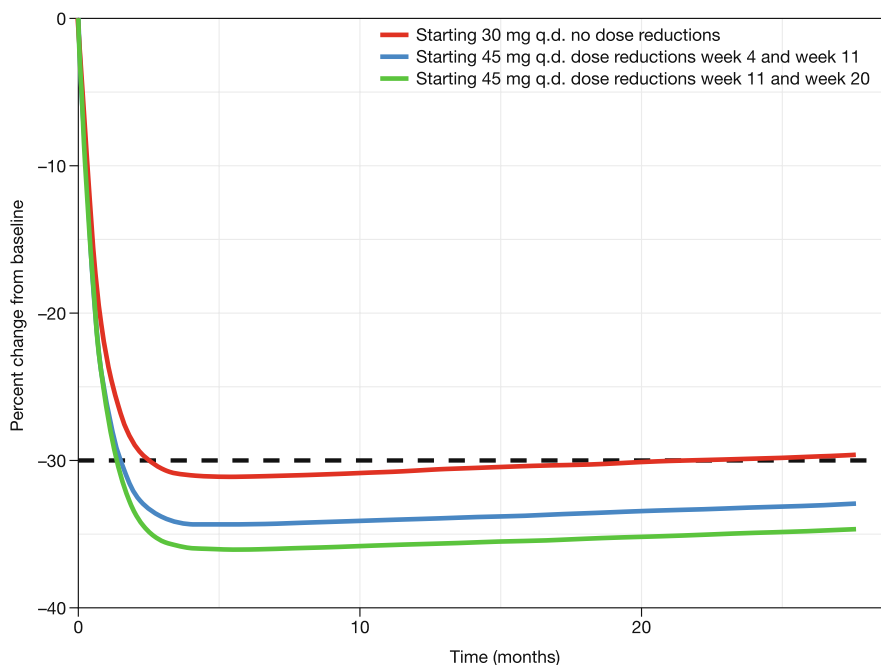
FIGURE 4 Simulated tumor size for selected dosing schemes. The time course for three different starting dose and dose reduction scenarios are presented for a typical patient. The red line (top) is the typical tumor size for a starting dose of 30 mg q.d. with no dose reductions. The blue line (middle) represents the typical tumor size over time for a starting dose of 45 mg q.d. with dose reductions at week 4 and week 11. The green line (bottom) represents the typical tumor size over time for a starting dose of 45 mg q.d. with dose reductions at week 11 and week 20. The black dotted line represents the RECIST criteria of 30% shrinkage, which is used to determine if a patient responds. RECIST, Response Evaluation Criteria in Solid Tumors; q.d., once daily.

III study over the positive control (gefitinib). However, permanent dose reductions together with a single tested starting dose resulted in an observed inverse ER relationship with PFS as well as other end points for safety and efficacy (data not provided). With a high rate of dose reductions and no formal dose ranging study, a natural question is whether the starting dose is appropriate. The three models and the simulations presented together support the conclusion that despite the risk of permanent dose reductions, 45 mg q.d. is an appropriate starting dose for the indicated patient population.

The dose-altering AE model found that a higher C_{max} was associated with a higher probability of grade greater than or equal to 3 AEs, which resulted in a dose modification. In addition, patients who never required a dose reduction tended to have lower cycle 2 day 1 plasma. The patients who never required a dose reduction also experienced lower rates of grade greater than or equal to 3 AEs.[23,26] For the 33% of patients without a dose reduction, a lower starting dose would mean even lower exposures with no expected safety benefits. For the patients who did require permanent dose reduction, characterizing the ER relationship was essential to evaluate the benefit of the higher starting dose.

The Claret TGI model adequately characterized the tumor sizes over time with a power parameterization for

the effect of exposure. The exposure parameter was less than one and indicates diminishing returns with higher exposures. Because patients who required permanent dose reductions tended to have higher exposures, the shape of the ER curve may have a bias, which is a plausible reason for the diminishing benefits at higher exposures. Nonetheless, the effect was statistically significant establishing an ER relationship with an efficacy measure having accounted for the dose reductions. This was subsequently linked to PFS, including the tumor shrinkage rate as a predictor.

The model for dose-altering AEs illustrated that considering events on a weekly basis adequately characterized the ER relationship over time. The simulations of the dropout rate based on AEs underestimated the initial discontinuations due to AEs, but, over time, the VPCs show that the rates are contained within the prediction bands for 45 mg q.d. (see Figure S6). The dropout rates due to AEs are overpredicted for the 30 mg q.d. group because only one dose reduction is allowed. In the observed subjects, only one discontinued due to an AE.

The overall efficacy for any combination of dose reductions was the main concern irrespective of the timing. Figure 3 shows that with the 45 mg q.d. starting dose, the tumor response rates (shrinkage of at least 30%) are greater with a faster onset rate than with 30 mg q.d. The

predictions for the 45 mg group are well-characterized by the models accounting for dose reductions. The simulations overpredict the response rates for the 30 mg group with the predicted response rates at each time markedly better than the observed rates. The predicted median PFS for the 45 mg q.d. starting dose was consistent with the clinical trials, but the initial disease progression rate was overestimated. There were too few PFS events for a reliable estimate of median PFS for the 30 mg q.d. group. As shown in Figure 4, the expected tumor size time course for three potential dosing scenarios were 45 mg q.d. starting dose with a dose reduction at week 11 and a second dose reduction at week 20; 45 mg q.d. starting dose with a dose reduction at week 4 and a second dose reduction at week 11; and 30 mg q.d. starting dose with no dose reductions. The timing of the dose reductions was selected based on the median values in Table 1. These specific cases, along with the response rates prediction in Figure 3, show that even with dose reductions, a starting dose of 45 mg q.d. has greater tumor shrinkage than a starting dose of 30 mg q.d.

The evaluation of the recommended starting dose of dacomitinib benefited in several ways. There was a small cohort of patients in the target population from study A7471017 who initially received 30 mg q.d., which provided a second starting dose to characterize the ER relationship with tumor size (efficacy). The percentage of patients with at least one dose reduction was high (66%) but was still sufficient to characterize an ER curve (unlike the case with lenvatinib). In addition, the known AEs were all reversible and manageable by dose interruption/reduction. The percentage of AE-related discontinuations was small (<10% in the phase III study). With ER relationships characterized for both efficacy and safety, modeling and simulation were able to illustrate the beginning of treatment is the time in which the greatest tumor shrinkage is expected, and, as a result, the higher starting dose (45 mg q.d.) is associated with the benefit in patients.

AUTHOR CONTRIBUTIONS

L.K.F., D.J.N., W.T., and K.P. wrote the manuscript, designed the research, and performed the research. L.K.F. and D.J.N. analyzed the data.

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CONFLICT OF INTEREST

All authors are all shareholders and employees of Pfizer Inc. The authors declared no additional competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.