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ARTICLE

Brigatinib Dose Rationale in Anaplastic Lymphoma Kinase–Positive Non-Small Cell Lung Cancer: Exposure–Response Analyses of Pivotal ALTA Study

Neeraj Gupta[1,*], Xiaohui Wang[2], Elliot Offman[2], Benjamin Rich[2], David Kerstein[1,3], Michael Hanley[1], Paul M. Diderichsen[2], Pingkuan Zhang[1] and Karthik Venkatakrishnan[1,4]

Brigatinib is a kinase inhibitor indicated for patients with advanced anaplastic lymphoma kinase–positive non-small cell lung cancer who progressed on or are intolerant to crizotinib. Approval was based on results from a randomized, dose-ranging phase II study (ALK in Lung Cancer Trial of AP26113 (ALTA)). Despite an apparent dose–response relationship for efficacy in ALTA, an exposure–response relationship was not discernable using static models driven by time-averaged exposure. However, exposure–response modeling using daily time-varying area under the concentration curve as the predictor in time-to-event models predicted that increasing the dose of brigatinib (range, 30 mg once daily (q.d.) to 240 mg q.d.) would result in clinically meaningful improvements in progression-free survival (PFS), intracranial PFS, and overall survival. Grade ≥ 2 rash and amylase elevation were predicted to significantly increase with brigatinib exposure. These results provided support for a favorable benefit-risk profile with the approved dosing regimen (180 mg q.d. with 7-day lead-in at 90 mg) versus 90 mg q.d.

STUDY HIGHLIGHTS

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Brigatinib was approved at 180 mg once daily (q.d.) after 7-day lead-in at 90 mg q.d. for anaplastic lymphoma kinase–positive non-small cell lung cancer based on results from a randomized dose-ranging study.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Do the underlying exposure–response relationships for efficacy and safety support selection of the 180-mg dose?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Exposure–response analyses predicted clinically meaningful improvements in progression-free survival (PFS), intracranial PFS, and overall survival with increasing brigatinib doses up to 240 mg q.d.

☑ Although the incidences of some adverse events (grade ≥ 2 amylase increase and rash) are expected to increase with dose, they would not exceed 10%.

☑ Dynamic models with time-varying exposure predictors enable better characterization of exposure–response relationships than models using static metrics of time-averaged exposure.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These analyses provided clinical pharmacology support for the benefit-risk profile associated with the currently approved brigatinib dosing regimen (180 mg q.d. with 7-day lead-in at 90 mg q.d.).

Brigatinib is an orally active inhibitor of oncogenic variants of the anaplastic lymphoma kinase gene (*ALK*), including ALK fusions (e.g., EML4-ALK) found in non-small cell lung cancer (NSCLC).[1–3] Brigatinib received accelerated approval in the United States (2017) and approval in the European Union and Canada (2018) based on a randomized, multicenter phase II trial (ALK in Lung Cancer Trial of AP26113 (ALTA), NCT02094573) in adult patients with locally advanced or metastatic *ALK*-positive NSCLC that progressed on crizotinib.[4] In ALTA, 222 patients were randomly assigned to receive brigatinib 90 mg once daily (q.d.) or 180 mg q.d. (with 7-day lead-in at 90 mg q.d.).[4] At the 2-year follow-up, compared with the 90 mg arm, the 180 mg arm had numerically higher independent review committee-assessed confirmed systemic objective response rate (ORR; 51%; 95% confidence interval, CI: 41%–61% vs. 56%; 95% CI, 47%–66%) and intracranial ORR (iORR) in patients with measurable baseline brain metastases (50%; 95% CI, 30%–70% vs. 67%; 95% CI, 41%–87%).[5] The median duration of response was 12.0 months (95% CI, 9.2–17.7) in the 90 mg arm and 13.8 months (95% CI, 10.2–19.3) in the 180 mg arm.[5] Median systemic progression-free survival (PFS; 90 mg: 9.2 months (95% CI, 7.4–12.8); 180 mg: 16.7 months (95% CI, 11.6–21.4)) and intracranial PFS (iPFS; 90 mg: 12.8 months (95% CI, 9.2–18.3); 180 mg: 18.4 months (95% CI, 12.6–23.9)) were numerically longer with 180 mg than

[1]Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts, USA; [2]Certara, Princeton, New Jersey, USA; [3]Present address: Anchiano Therapeutics, Cambridge, Massachusetts, USA; [4]Present address: EMD Serono, Inc., Billerica, Massachusetts, USA. *Correspondence: Neeraj Gupta (Neeraj.Gupta@takeda.com)
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with 90 mg.[5] However, the trial was not powered to demonstrate superiority of the 180-mg dosing regimen versus the 90-mg dose.

Brigatinib is well tolerated in most patients; the most common adverse events (AEs) are gastrointestinal symptoms and increased blood creatine phosphokinase and alanine aminotransferase (ALT) levels.[3,4,6] However, moderate to severe pulmonary AEs in a small subset of patients within the first 7 days after brigatinib initiation were initially identified in a phase I/II trial.[3,4] In the single-arm, open-label, phase I/II dose-escalation trial, these early-onset pulmonary events (EOPEs) occurred in 8% (11/137) of patients, and incidence generally increased with the starting dose.[3] None of the 32 patients who escalated to 180 mg after 7 days at 90 mg experienced an EOPE after dose escalation. The recommended dosing regimen for brigatinib (180 mg q.d. with a 7-day lead-in at 90 mg q.d.) was selected because it appeared to mitigate the risk of EOPEs while allowing for optimal long-term PFS and intracranial efficacy associated with the higher dose.[3,4,7] Results of an ongoing phase III trial (ALTA-1L) in ALK–tyrosine kinase inhibitor naive patients with *ALK*-positive NSCLC showed that PFS was significantly longer among patients who received brigatinib 180 mg q.d. (with 90-mg lead-in) than those who received crizotinib (2-year PFS, 48% vs. 26%; hazard ratio, 0.49 (95% CI, 0.35–0.68); $P < 0.0001$) at the second interim analysis.[6,8]

A population pharmacokinetics (PK) model for brigatinib was developed based on data from phase I and II trials.[9] The PK of brigatinib in both healthy volunteers and patients with cancer was best described by a three-compartment model with a transit compartment for absorption. Albumin was the only predictor of apparent oral clearance. Body weight, sex, age, race, mild or moderate renal impairment, and mild hepatic impairment did not meaningfully explain variability in apparent oral clearance, suggesting that no dose adjustment is required based on these covariates.

Although assessment of dose–response relationships for efficacy is not commonly conducted in oncology drug development, the randomized design of ALTA allowed for characterization of dose–response for efficacy and safety in the determination of an optimal dose.[10–13] In addition, the first-in-human brigatinib phase I/II study provided data over a wide dose range in adults with advanced malignancies (30 mg–300 mg/day) and in 79 patients with *ALK*-positive NSCLC (60 mg–240 mg/day).[3] As pharmacological exposure–response relationships are typically nonlinear and saturable, use of the totality of data across these trials was expected to provide the opportunity for more comprehensive exposure–response analyses across a broader dose range. The purpose of the current analyses was to discern potential exposure–response relationships and provide supportive evidence of the superior risk-benefit ratio of the 180 mg dose relative to 90 mg. These results informed brigatinib dose selection for clinical use and further development in the first-line setting.[6,8] In the exposure–efficacy analyses, outcomes of PFS, iPFS, overall survival (OS), confirmed ORR, and iORR were assessed in relation to brigatinib exposure estimates. The exposure–safety analyses assessed the relationship between brigatinib exposure and AEs of interest, including pulmonary events.

METHODS

Study design and patient population

All data were from two clinical trials of brigatinib: the phase I/II trial (NCT01449461) and ALTA. The phase I/II trial was a single-arm, open-label trial in adults with advanced malignancies, including *ALK*-rearranged NSCLC.[3] Patients received oral brigatinib (30–300 mg/day) in a 3 + 3 design in phase I and regimens of 90, 180, and 180 mg with lead-in in phase II. In the ALTA trial, adults with locally advanced or metastatic *ALK*-positive NSCLC that progressed on crizotinib were randomized to brigatinib 90 mg q.d. or 180 mg q.d. (with lead-in).[4] Study design and methodology of each trial have been published.[3,4] The blood sampling schedule for each trial is shown in **Table S1**. The study protocols were approved by relevant local review boards or ethics committees. Patients with *ALK*-positive NSCLC were included in the efficacy exposure–response population if they had received at least one brigatinib dose, had been included in the population PK analysis population, and had at least one postbaseline efficacy measurement ($N = 279$). The safety exposure–response population included all patients enrolled in the phase I/II and ALTA trials who had received at least one brigatinib dose, had been included in the population PK analysis population, and had at least one postbaseline safety measurement ($N = 337$).

Efficacy exposure–response analysis

The population PK model[9] was used to derive brigatinib exposure metrics over the treatment course. Individual daily time-varying brigatinib exposures were derived using simulated rich PK profiles based on actual dosing history and individual *post hoc* (empirical Bayes) PK parameter estimates from the population PK model. Specifically, for time t in days and $C(t)$, the predicted drug concentration at time t,

$$\mathrm{AUC}(t) = \int_{\lceil t-1 \rceil}^{\lceil t \rceil} C(u)\,du$$

denotes the area under the concentration-time curve (AUC) on day $\lceil t \rceil$ of treatment (e.g., $\mathrm{AUC}(t)$ = AUC on day 1 for $0 < t \leq 1$). Using 90 mg q.d. as a reference regimen, a reference exposure $\mathrm{AUC}_{\mathrm{REF}}(t)$ was defined by simulating a rich PK profile for a "typical" individual (all covariates set to reference values and all random effects set to zero) under this regimen.

For time-to-event analyses (PFS, iPFS, OS), time-varying exposures until the time of the event or censoring were considered. For logistic regression of binary efficacy (ORR, iORR) and safety end points, the average exposure to an event was used. Exposure metrics (time-averaged AUC until progression or daily time-varying AUC) were derived from the individual-predicted brigatinib concentration-time profile over the treatment duration (or to the event). Other exposure metrics (e.g., AUC per treatment cycle or weekly AUC) were not considered since these metrics are not proximal to an event.

Analysis of PFS, iPFS, and OS by daily time-varying AUC. Kaplan-Meier plots were generated and stratified by brigatinib exposure quartiles. A parametric time-to-event (TTE) survival model was developed to describe the hazard

function of PFS/iPFS/OS as a function of time, daily time-varying exposure until the event (or censoring), and other potential or known risk factors.

The hazard function was modeled as:

$$h(t) = h_0(t) \times \exp\left\{\beta_{AUC}\log_2\left(AUC(t) / AUC_{REF}(t)\right) + \beta_{cov_1}\left(cov_1\right) + \ldots + \beta_{cov_n}\left(cov_n\right)\right\} \quad (1)$$

where $AUC(t)$ is the daily time-varying AUC of brigatinib at time t, $AUC_{REF}(t)$ is a reference exposure used for centering as defined previously, $cov_1, \ldots, cov_n$ are potential or known risk factors, the coefficients (β) are log hazard ratios, and $h_0(t)$ is the parametric baseline hazard function. Based on this model, $\exp(\beta_{AUC})$ was interpreted as the hazard ratio associated with a twofold increase in brigatinib exposure. A saturating maximum effect (E_{max}) model for the effect of daily time-varying AUC was also considered. The reference exposure $AUC_{REF}(t)$ was defined as the daily time-varying AUC for a typical patient under a 90-mg q.d. dosing regimen. For the baseline hazard, model discrimination primarily based on Akaike information criterion was performed, considering exponential, Weibull, log-logistic, log-normal, gamma, generalized gamma, and Gompertz parametric forms (**Section S1**).

Performance of the final models was evaluated using visual predictive checks (VPCs). The final TTE models of PFS, iPFS, and OS were used in simulations performed to predict outcomes under different brigatinib dosing regimens (**Table S1, Section S2**). Logistic regression analyses of ORR and iORR by time-averaged AUC are also described in **Table S2**.

Safety exposure–response analysis

Development of logistic regression model. Exposure–safety relationships were quantitatively assessed using logistic regression according to:

$$\text{logit}\left(P_{i,\text{event}}\right) = \log\left(\frac{P_{i,\text{event}}}{1 - P_{i,\text{event}}}\right) = \beta_0 + \beta_1(\text{Exposure}) + \beta^T X_i \quad (2)$$

where β_0 represents the baseline logit; and β_1 and β are scalar and vector parameters that represent the effect of exposure and possible predictor variables X_i (e.g., age and sex) on the logit, respectively. If exposure was identified as a significant predictor of event occurrence ($P < 0.05$) in the base model, a covariate model was evaluated. The predicted logistic regression curve and the observed event rate in each brigatinib exposure quartile (along with the associated 95% CI) were plotted. Relationships between exposure and the occurrence of EOPEs were evaluated graphically and using logistic regression models relating time-averaged AUC to the probability of event occurrence.

Concentration-QTcF interval, -PR interval, and -heart rate models. Relationships between brigatinib plasma concentrations and the change from baseline in QTcF interval (QT interval corrected using Fridericia's formula), PR interval, and heart rate (HR) were modeled using PK time-matched triplicate electrocardiogram data collected in the phase I/II study. In all three models (QTcF, PR, HR), the observed response (change from baseline, Δ) was described by a linear mixed effects model with random slope and intercept (Eq. 3). The effect of concentration was implemented based on a normalized concentration using time-matched observed concentration ($CONC_{NORM} = \frac{CONC}{10{,}000}$) defined in:

$$\Delta = INTC_i + CONC_{NORM} \cdot SLP_i + \varepsilon \quad (3)$$

$$INTC_i = INTC_{TV} + \eta_1, SLP_i = SLP_{TV} + \eta_2$$

The epsilon(ε), individual intercept ($INTC_i$) and slope (SLP_i) parameters were defined based on corresponding typical estimates ($INTC_{TV}$ and SLP_{TV}) and multivariate normal random effects, η_1 and η_2, with a mean of zero and variance of ω_1^2 and ω_2^2, respectively. Normalization of concentration by a factor of 10,000 helped with model stability. Models with and without the factor were identical, and the resulting estimate for the slope parameter was unaffected by this change. The covariance between the random effects, ρ, was only estimated if including it resulted in a statistically significant improvement of model fit based on the likelihood ratio test. The unexplained residual variability was described by an additive error model with variance σ^2.

Data set construction (**Table S2**) was performed using SAS (version 9.2, SAS Institute, Cary, NC). Parametric TTE modeling and PR, QTcF, and HR analyses were performed using NONMEM (version 7.3.0, ICON Development Solutions, Hanover, MD). Exposure–response analyses of ORR, iORR, and safety end points using logistic regression were performed using R (version 3.3.1, R Core Team, Vienna, Austria).

RESULTS

Efficacy exposure–response analysis

The exposure–efficacy analysis population included 279 patients with *ALK* positive NSCLC (phase I/II trial[3]: $n = 78$, doses: 60–240 mg/day; ALTA trial[4]: $n = 201$; doses: 90 mg q.d. or 180 mg q.d. (with lead-in)) who had received brigatinib and had at least one postbaseline scan (**Table 1**).

Initial modeling using time-averaged AUC did not demonstrate significant relationships between time-averaged exposure and PFS. Therefore, a parametric TTE survival model was developed using daily time-varying AUC values as a predictor to describe the probability of PFS as a function of time and other potential or known risk factors. Use of a log-logistic distribution as the baseline hazard in this parametric TTE model provided adequate fit to the observed data (**Figure 1a,b, Table 2**) and demonstrated that daily time-varying AUC was a significant predictor of PFS. The log sum of baseline target lesions was the only covariate retained from a stepwise covariate search and was associated with a hazard ratio of 1.80 (95% CI, 1.39–2.35;

Table 1 Demographics and baseline characteristics of the exposure–response populations

Covariate	Efficacy population, *n* = 279	Safety population, *n* = 337
Continuous covariates, median (range)		
Age, years	54 (18–83)	55 (18–83)
Log sum target lesion at baseline, mm	3.69 (2.30–5.48)[a]	—
Categorical covariates, n (%)		
Sex		
Female	154 (55.2)	194 (57.6)
Male	125 (44.8)	143 (42.4)
Race		
White	197 (70.6)	242 (71.8)
Asian	74 (26.5)	81 (24.0)
Black	4 (1.4)	7 (2.1)
ECOG status		
0	103 (36.9)	110 (32.6)
1	163 (58.4)	213 (63.2)
2	13 (4.7)	14 (4.2)
3	0 (0.0)	0 (0.0)
Received prior chemotherapy	206 (73.8)	250 (74.2)
Brain metastases present at baseline	55 (19.7)	—
Current or prior smoker	93 (33.5)[b]	—
Received prior crizotinib	—	279 (82.8)

ECOG, Eastern Cooperative Oncology Group.
[a]*n* = 275.
[b]*n* = 278.

$P < 0.001$), indicating that a doubling in the sum of target lesions would be associated with a 50% increase in the rate of death or progression at any time. The hazard ratio estimate for the effect of time-varying daily AUC ($\log_2$ (AUC/AUC under the reference regimen of 90 mg q.d.)) was 0.812 (95% CI, 0.747–0.883), which indicates that doubling brigatinib exposure is associated with an 18.8% reduction in the rate of death or progression at any given time. Simulations from the final model predicted median (95% CI) PFS values at 90 mg q.d. and 180 mg q.d. of 12.0 (11.6–12.3) months and 14.7 (14.2–15.2) months, respectively (**Figure 1c,d**).

The iPFS end point was adequately described by the parametric TTE model (**Figure 2a**). Daily time-varying AUC was a significant predictor of iPFS. Based on this model, the hazard ratio estimate for the effect of $\log_2$ (AUC/AUC under the reference regimen of 90 mg q.d. (AUC_{REF})) on iPFS was 0.782 (95% CI, 0.737–0.829), indicating that doubling brigatinib exposure (daily AUC) would be associated with a 21.8% reduction in the likelihood of intracranial progression or death at any time. No additional covariates were significant predictors of iPFS. Simulations based on the final TTE model estimated that the predicted median (95% CI) iPFS values at exposures associated with the 90-mg q.d. and 180-mg q.d. regimens were 15.1 (14.8–15.5) months and 19.2 (18.7–19.7) months, respectively (**Figure 2b,c**).

OS was adequately described by the parametric TTE model (**Figure 3a,Table 2**). The model produced a hazard ratio estimate of 0.784 (95% CI, 0.729–0.843) for the effect of $\log_2$ (AUC/AUC_{REF}) on OS, indicating that doubling brigatinib exposure (daily AUC) would be associated with a 21.6% reduction in the rate of death at any time. The log sum of baseline target lesions was the only covariate retained in the OS model, with a hazard ratio of 1.92 (95% CI, 1.40–2.63; $P < 0.001$), indicating that doubling the sum of baseline target lesions would increase the rate of death at any time by 21.7%. Simulations predicted that the 20th percentile (95% CI) of OS (i.e., the time at which 80% of patients are expected to remain alive) was 12.4 (12.0–13.0) months with the 90 mg q.d. dosing regimen and 15.8 (15.2–16.5) months with the 180 mg q.d. regimen (**Figure 3b,c**).

Probability plots of time-averaged AUC until an event for ORR did not suggest a relationship between exposure and the likelihood of a response (**Figure S1**). Logistic regression modeling showed that time-averaged AUC was not a significant predictor of ORR (**Table 2**). Although not statistically significant, there was a graphical trend toward a greater probability of an intracranial objective response with increasing time-averaged exposure (**Figure S2, Table 2**).

Safety exposure–response analysis

The relationship between time-averaged exposure until the occurrence of a grade ≥ 2 AE (or until end of treatment in patients without an AE of interest) and clinical safety events of interest (**Table 3**) was explored. The safety exposure–response population consisted of 337 patients (phase I/II study, *n* = 136; ALTA, *n* = 201; **Table 1**). Of the AEs of interest evaluated, only grade ≥ 2 rash and amylase elevation were found to be associated with time-averaged brigatinib exposure.

The logistic regression model for log-transformed time-averaged AUC until grade ≥ 2 rash with the covariates of interest (i.e., sex, prior chemotherapy, Eastern Cooperative Oncology Group status, race, presence of brain metastases, smoking status, age at study entry, log sum baseline target lesions, and time since initial diagnosis) indicated a statistically significant exposure–response relationship for this AE (intercept β (SD): –9.49 (3.14), $P = 0.002$; log

Figure 1 Parametric time-to-event final model for PFS. Visual predictive check of the final model for the overall efficacy population (**a**) and by ALK in Lung Cancer Trial of AP26113 treatment arm (**b**) and simulated Kaplan-Meier plots of PFS (**c**) and median PFS (**d**) under different brigatinib dosing regimens (*N* = 10,000 simulated patients). In **a** and **b**, the blue shaded area represents the spread (5th to 95th percentiles) of the simulated Kaplan-Meier curve based on the 500 simulated replicates from the final model; the blue solid line represents the median of the values of the simulated Kaplan-Meier curves. The gray solid lines represent the actual Kaplan-Meier curves, with the gray dashed lines representing the corresponding 95% CIs. The visual predictive check evaluated the model by taking the individual survival function values, $S(t_j, x_i)$, at time (t_j) of all events and predicting PFS status for each patient by time point based on the final model estimates and each patient's daily exposure.[36] A survival time (T) for patient i was generated by the inverse cumulative distribution function method.[37–39] Survival times were randomly simulated based on survival probabilities on a grid of time points using the algorithm of Rich *et al*.[39] In **c**, the red line represents the median survival with the tan shaded area representing the 95% CI for the median PFS. CI, confidence interval; PFS, progression-free survival; q.d., once daily.

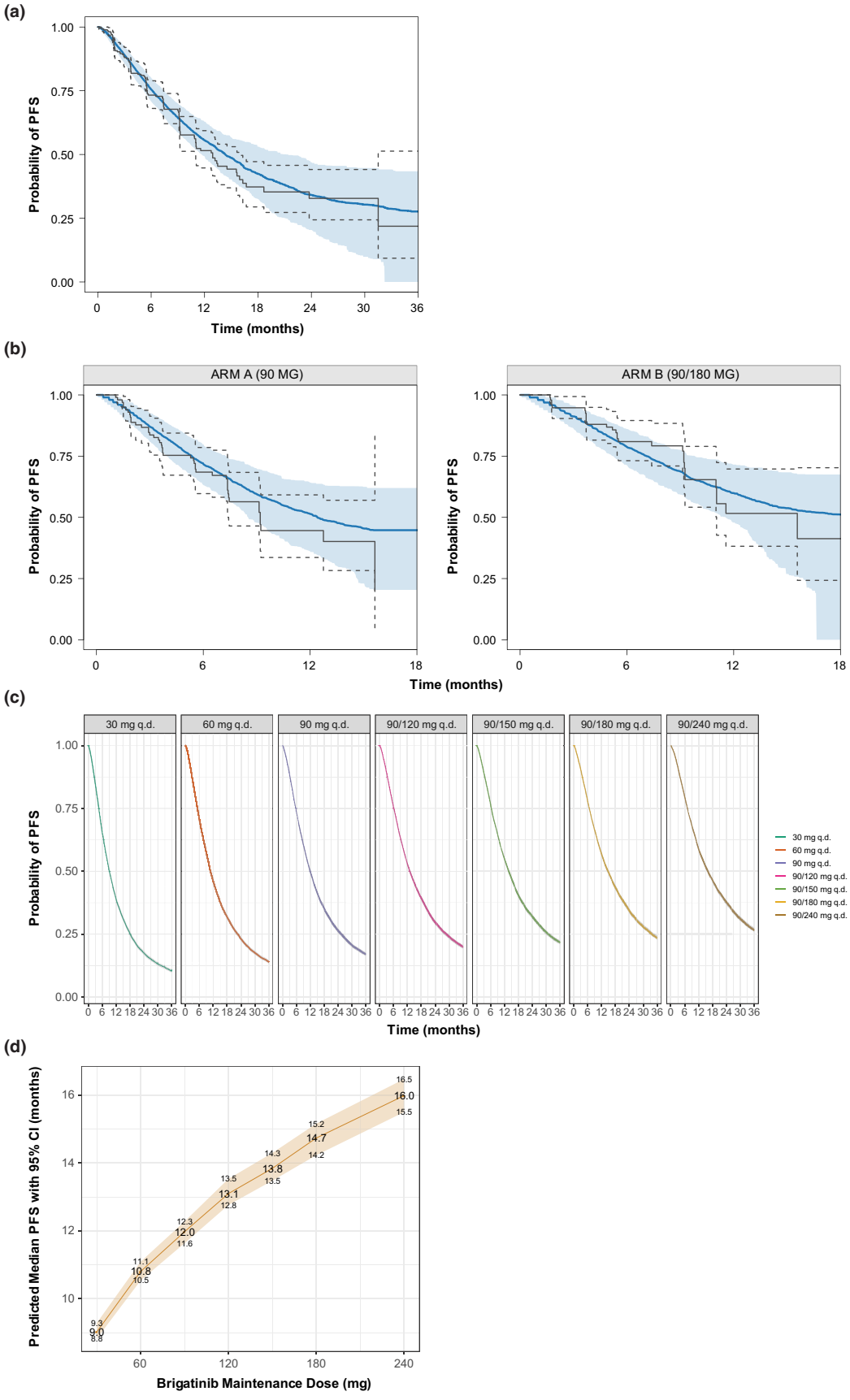

(a)
Probability of PFS
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
Time (months)
(b)
ARM A (90 MG)
ARM B (90/180 MG)
Probability of PFS
Time (months)
(c)
30 mg q.d.
60 mg q.d.
90 mg q.d.
90/120 mg q.d.
90/150 mg q.d.
90/180 mg q.d.
90/240 mg q.d.
Probability of PFS
Time (months)
(d)
Predicted Median PFS with 95% CI (months)
Brigatinib Maintenance Dose (mg)
9.3
9.0
8.8
11.1
10.8
10.5
12.3
12.0
11.6
13.5
13.1
12.8
14.3
13.8
13.5
15.2
14.7
14.2
16.5
16.0
15.5

Table 2 TTE modeling and logistic regression results

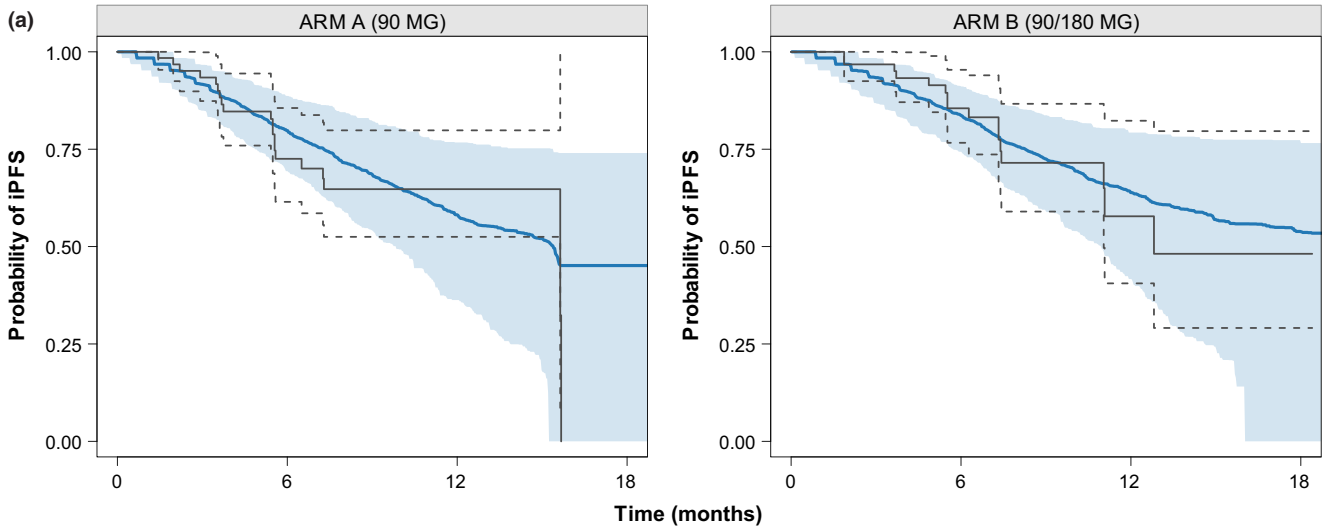
Parametric TTE models for PFS, iPFS, and OS with time-varying daily AUC			
TTE model, coefficient	**Hazard ratio (95% CI)**		
PFS			
$Log_2(AUC/AUC_{REF})$	0.81 (0.75–0.88)		
Log sum baseline target lesions	1.80 (1.39–2.35)		
iPFS			
$Log_2(AUC/AUC_{REF})$	0.78 (0.74–0.83)		
OS			
$Log_2(AUC/AUC_{REF})$	0.78 (0.73–0.84)		
Log sum baseline target lesions	1.92 (1.40–2.63)		
Logistic regression estimates for ORR and time-averaged AUC			
Exposure metric, covariate	**β**	**SD**	***P* value**
Time-averaged AUC until best response			
Intercept	2.0544	1.8669	0.271
Log (time-averaged AUC until best response)	−0.1717	0.1968	0.383
Time-averaged AUC until end of treatment			
Intercept	2.2875	1.8889	0.226
Log (time-averaged AUC during treatment)	−0.1956	0.1983	0.324
Logistic regression estimates for iORR and time-averaged AUC			
	β	**SD**	***P* value**
Time-averaged AUC until best intracranial response			
Intercept	−4.7783	3.4094	0.161
Log (time-averaged AUC until best intracranial response)	0.5605	0.3615	0.121
Time-averaged AUC until end of treatment			
Intercept	−4.868	3.489	0.163
Log (time-averaged AUC during treatment)	0.567	0.368	0.123

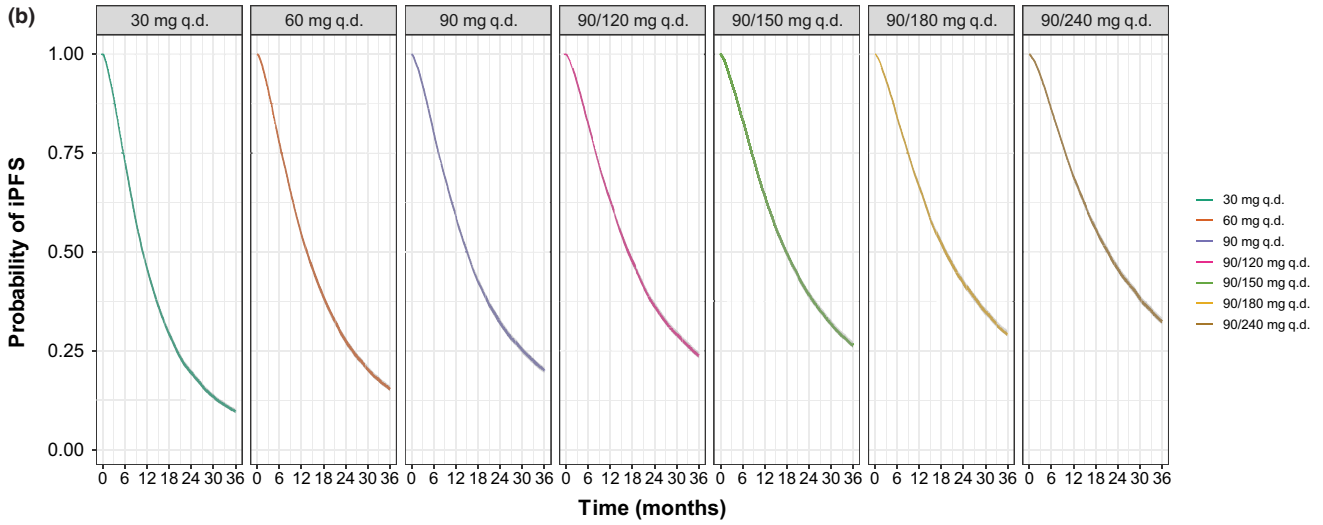
AUC, area under the concentration-time curve; AUC_{REF}, AUC under the reference regimen of 90 mg once daily; CI, confidence interval; iORR, intracranial objective response rate; iPFS, intracranial progression-free survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SD, standard deviation; TTE, time to event.

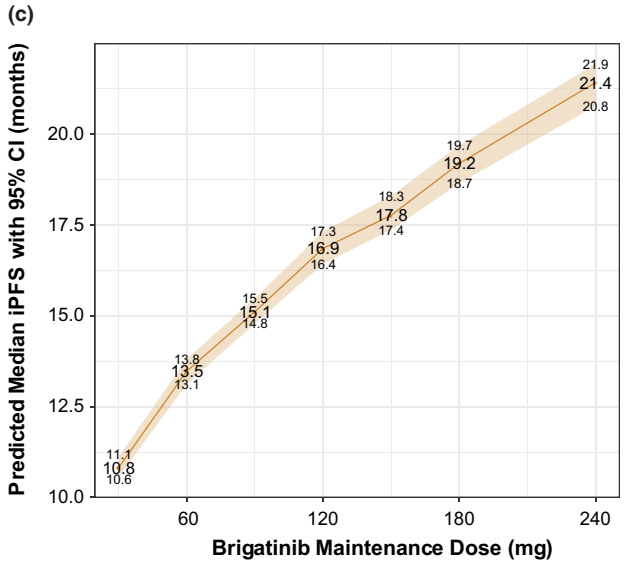
of time-averaged exposure until grade 2 rash β (SD): 0.74 (0.32), $P = 0.021$). Time-averaged AUC until the occurrence of a grade ≥ 2 rash is shown in **Figure S3a**. The VPC showed good agreement between the predicted and observed rates of grade ≥ 2 rash (**Figure 4a**). Model-based simulations for a typical patient with albumin levels (the only predictor of brigatinib PK in the population PK model[9]) set to 38 g/L estimated the predicted probability of experiencing a grade ≥ 2 rash was 5.92% (95% CI, 3.38–10.17) for a typical patient taking brigatinib 90 mg q.d. and 9.53% (95% CI, 6.72–13.35) for a patient taking brigatinib 180 mg q.d.

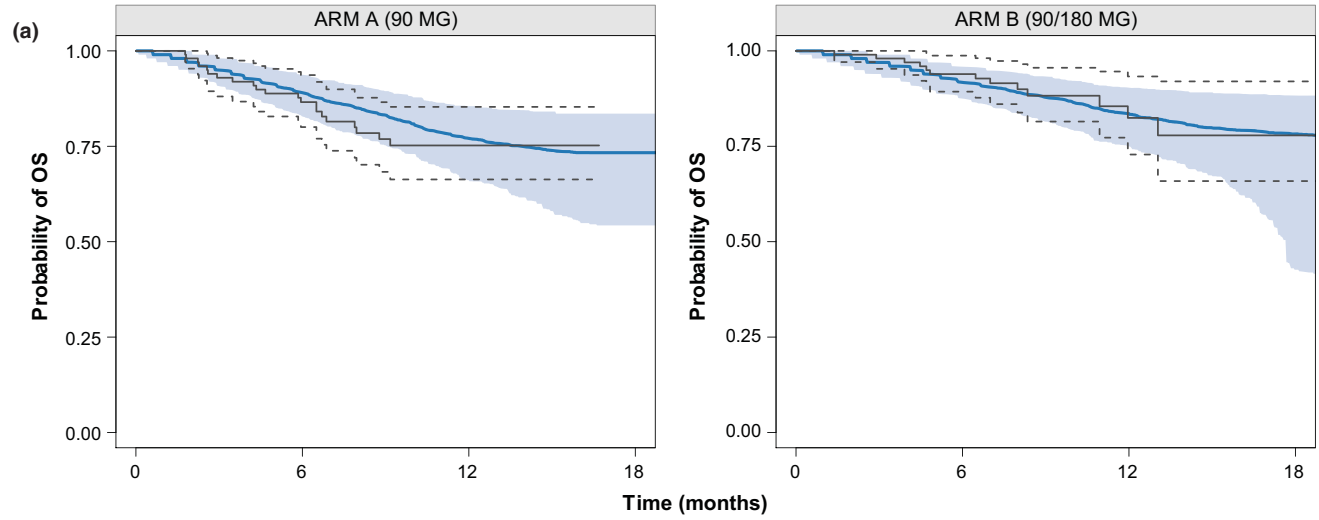
A logistic regression model with log-transformed time-averaged daily AUC until grade ≥ 2 amylase elevation with covariates of interest indicated a statistically significant exposure–response relationship (intercept β (SD): −9.2568 (3.38), $P = 0.006$; log time-averaged exposure until event β (SD): 0.6990 (0.3466), $P = 0.044$). Time-averaged AUC until the occurrence of a grade ≥ 2 AE of increased amylase is illustrated in **Figure S3b**. The VPC showed good agreement between the predicted and observed rates of grade ≥ 2 amylase increase (**Figure 4b**). Model-based simulations estimated the probability of experiencing a grade ≥ 2 amylase increase would

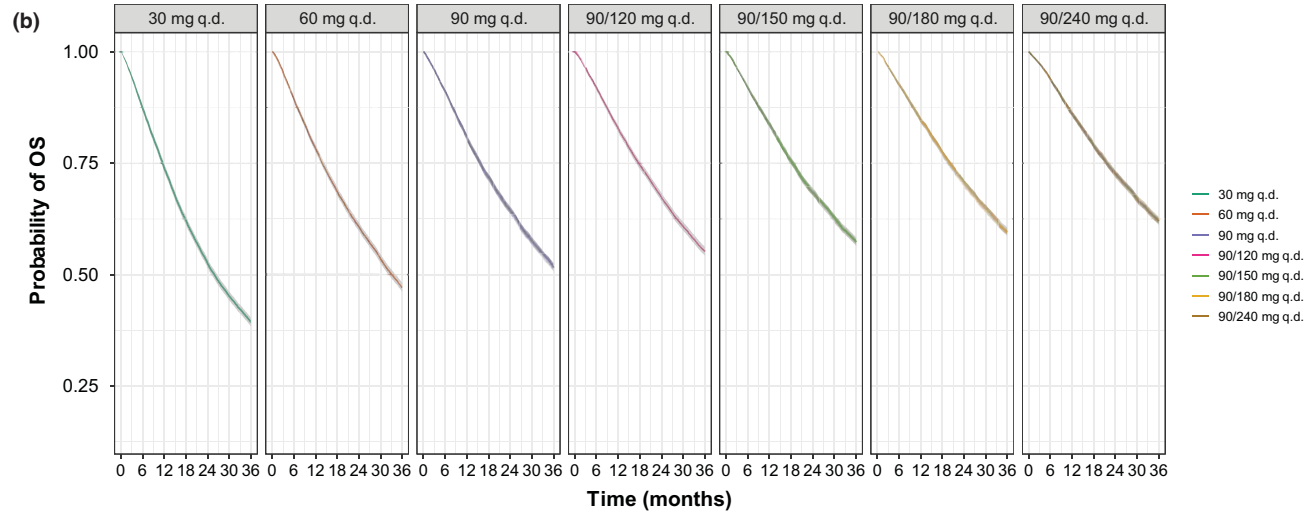
Figure 2 Parametric time-to-event final model for iPFS. Visual predictive check by ALK in Lung Cancer Trial of AP26113 treatment arm (**a**) and simulated Kaplan-Meier curves (**b**) and median iPFS (**c**) calculated using the final model for seven different brigatinib dosing regimens ($N = 10{,}000$ simulated patients). In **a**, the blue shaded area represents the spread (5th to 95th percentiles) of the simulated Kaplan-Meier curve based on the 500 simulated replicates from the final model; the blue solid line represents the median of the values of the simulated Kaplan-Meier curves. The gray solid lines represent the actual Kaplan-Meier curves, with the gray dashed lines representing the corresponding 95% CI. The visual predictive check evaluated the model by taking the individual survival function values, $S(t_j, x_i)$, at time (t_j) of all events and predicting iPFS status for each patient by time point based on the final model estimates and each patient's daily exposure.[36] A survival time (T) for patient i was generated by the inverse cumulative distribution function method.[37–39] Survival times were randomly simulated based on survival probabilities on a grid of time points using the algorithm of Rich *et al*.[39] In **b**, the solid line represents the point estimate for the probability of iPFS at different levels of brigatinib maintenance dose in 10,000 simulated patients. In **c**, the solid line and shaded region represent the point estimate and 95% CI, respectively, for the median iPFS at different levels of brigatinib maintenance dose in the simulated patients. CI, confidence interval; iPFS, intracranial progression-free survival; q.d., once daily.


(a)
ARM A (90 MG)
ARM B (90/180 MG)
Probability of iPFS
1.00
0.75
0.50
0.25
0.00
0
6
12
18
Time (months)


(b)
30 mg q.d.
60 mg q.d.
90 mg q.d.
90/120 mg q.d.
90/150 mg q.d.
90/180 mg q.d.
90/240 mg q.d.
Probability of iPFS
1.00
0.75
0.50
0.25
0.00
0 6 12 18 24 30 36
Time (months)


(c)
Predicted Median iPFS with 95% CI (months)
20.0
17.5
15.0
12.5
10.0
21.9
21.4
20.8
19.7
19.2
18.7
18.3
17.8
17.4
17.3
16.9
16.4
15.5
15.1
14.8
13.8
13.5
13.1
11.1
10.8
10.6
60
120
180
240
Brigatinib Maintenance Dose (mg)


(a)
ARM A (90 MG)
ARM B (90/180 MG)
Probability of OS
1.00
0.75
0.50
0.25
0.00
0
6
12
18
Time (months)


(b)
30 mg q.d.
60 mg q.d.
90 mg q.d.
90/120 mg q.d.
90/150 mg q.d.
90/180 mg q.d.
90/240 mg q.d.
Probability of OS
1.00
0.75
0.50
0.25
0 6 12 18 24 30 36
Time (months)

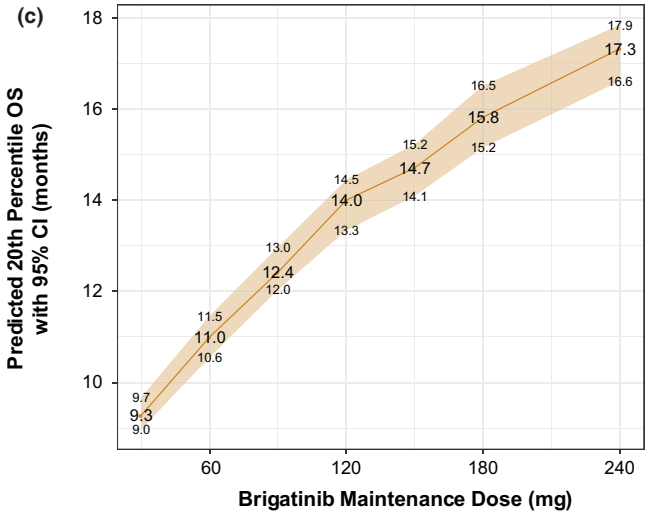

(c)
Predicted 20th Percentile OS with 95% CI (months)
18
16
14
12
10
9.7
9.3
9.0
11.5
11.0
10.6
13.0
12.4
12.0
14.5
14.0
13.3
15.2
14.7
14.1
16.5
15.8
15.2
17.9
17.3
16.6
60
120
180
240
Brigatinib Maintenance Dose (mg)

Figure 3 Parametric time-to-event final model for OS. Visual predictive check by ALK in Lung Cancer Trial of AP26113 treatment arm (**a**), simulated Kaplan-Meier curves (**b**), and median OS (**c**) for seven different brigatinib dosing regimens (N = 10,000 simulated patients). In **a**, the blue shaded area represents the spread (5th to 95th percentiles) of the simulated Kaplan-Meier curve based on the 500 simulated replicates from the final model; the blue solid line represents the median of the values of the simulated Kaplan-Meier curves. The gray solid lines represent the actual Kaplan-Meier curves, with the gray dashed lines representing the corresponding 95% CI. In **b**, the solid line represents the point estimate for the probability of OS over time at different levels of brigatinib maintenance dose in 10,000 simulated patients. In **c**, the solid line and shaded region represent the point estimate and 95% CI, respectively, for the 20th percentile of OS at different levels of brigatinib maintenance dose in the simulated patients (the 20th percentile of OS is the time at which 80% of patients are expected to remain alive). CI, confidence interval; OS, overall survival; q.d., once daily.

be 5.05% (95% CI, 2.76–9.09) with brigatinib 90 mg q.d. and 7.95% (95% CI, 5.41–11.54) with brigatinib 180 mg q.d.

Owing to the limited number of pulmonary events at any time and EOPEs (occurring on or before day 14 of treatment), an exposure–response relationship could not be estimated for EOPEs. For patients treated in ALTA, the contribution of washout time following discontinuation of prior treatment with crizotinib (a moderate cytochrome P450 (CYP) 3A inhibitor) until initiation of brigatinib (i.e., crizotinib washout time) and its potential relationship with the occurrence of EOPEs was assessed by relating crizotinib washout time to brigatinib exposure metrics. When evaluated graphically, the duration of crizotinib washout time prior to the first brigatinib dose did not appear to be related to brigatinib exposure metrics (**Figure S4**), suggesting that the likelihood of EOPEs is not driven by higher brigatinib exposure due to shorter crizotinib washout.[14]

Concentration-QTc, -PR, and -HR relationships. The relationships between brigatinib concentration and observed changes from baseline in the QTcF interval (**Figure 4c**), PR interval (**Figure 4d**), and HR (**Figure 4e**) were described by a linear mixed effects model with uncorrelated random effects on intercept and slope versus brigatinib concentration. The QTcF interval model predicted an increase of the QTcF interval of 0.134 milliseconds (95% CI, –1.94 to 2.19) at a brigatinib plasma concentration of 1452 ng/mL, corresponding to the typical steady-state maximum plasma concentration (C_{max}) at the 180 mg dose. The PR model predicted an increase of the PR interval of 9.36 milliseconds (95% CI, 7.64–11.1), and the HR model predicted a decrease in HR of 3.86 beats per minute (95% CI, 1.48–6.27) at the steady-state brigatinib C_{max} (1452 ng/mL).

DISCUSSION

To better understand the relationship between brigatinib exposure and efficacy outcomes, exposure–response analyses were performed using exposure metrics derived from a published population PK model[9] and pooled efficacy data from 279 patients with *ALK* positive NSCLC treated in two clinical trials.[3,4] Use of a static metric (i.e., time-averaged brigatinib exposure) in exposure–response analyses did not permit estimation of an exposure–efficacy relationship for PFS that could explain the dose–PFS relationship observed in the ALTA study. Although a static exposure measure (log average concentration at steady state ($C_{avg,\,ss}$)) was found to be a significant predictor of PFS and ORR in an exposure–efficacy model of crizotinib,[15] these measures have not been found to be predictive of efficacy outcomes in models of other *ALK* inhibitors, including alectinib and ceritinib.[16,17] Exposure–efficacy modeling of alectinib in patients with crizotinib-resistant *ALK* positive NSCLC found that the static metric of log steady-state concentrations at trough ($C_{trough,SS}$) was not a significant predictor of OS.[17] Analyses of ceritinib in previously untreated patients with *ALK* positive NSCLC in the ASCEND-4 study also found that a static exposure metric (average C_{trough}) was not predictive of improved PFS with increasing ceritinib exposure.[16] Instead, a pharmacologically implausible

Table 3 Incidence of grade ≥ 2 adverse events of interest evaluated in the safety exposure–response analysis

Safety outcomes	Phase I/II study, 30–300 mg (n = 136), n (%)	ALTA, 90–180 mg (n = 201), n (%)	Total (N = 337), n (%)
Hypertension	17 (12.5)	27 (13.4)	44 (13.1)
Increased lipase	16 (11.8)	15 (7.5)	31 (9.2)
Rash	15 (11.0)	15 (7.5)	30 (8.9)
Increased CPK	0 (0.0)	28 (13.9)	28 (8.3)
Increased amylase	14 (10.3)	11 (5.5)	25 (7.4)
Pulmonary event	11 (8.1)	8 (4.0)	19 (5.6)
EOPE[a]	9 (6.6)	5 (2.5)	14 (4.2)
Increased AST	6 (4.4)	5 (2.5)	11 (3.3)
Increased ALT	5 (3.7)	4 (2.0)	9 (2.7)
Hyperglycemia	4 (2.9)	5 (2.5)	9 (2.7)
Bradycardia	1 (0.7)	1 (0.5)	2 (0.6)

ALT, alanine aminotransferase; ALTA, ALK in Lung Cancer Trial of AP26113; AST, aspartate aminotransferase; CPK, creatine phosphokinase; EOPE, early-onset pulmonary event.
[a]Occurred on or before day 14 of brigatinib treatment.

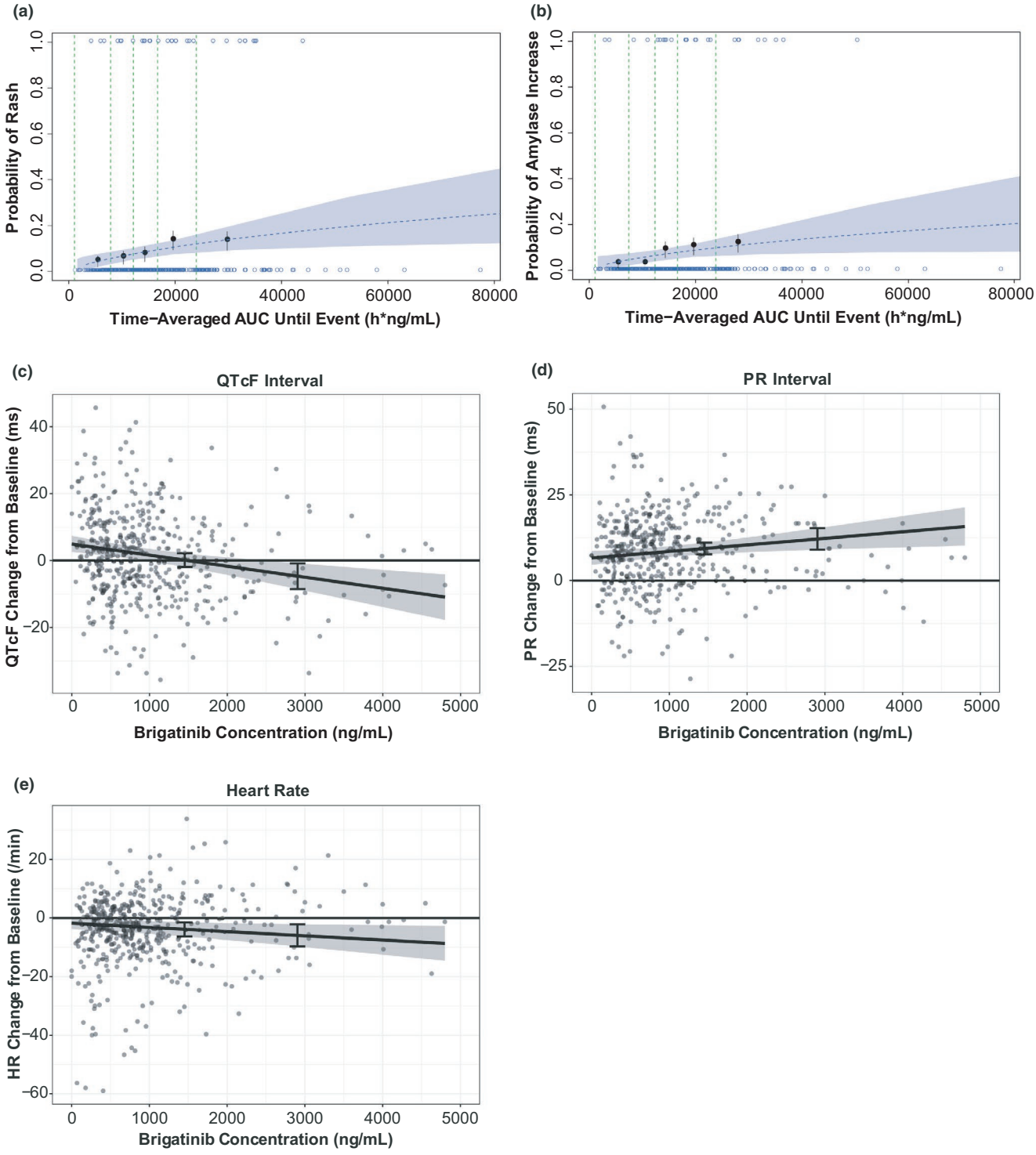


Figure 4 Visual predictive check of a logistic regression model for grade ≥ 2 rash (**a**) and grade ≥ 2 amylase increase (**b**) based on time-averaged brigatinib exposure, scatterplots of QTcF interval (**c**), PR interval (**d**), and HR responses (**e**) versus brigatinib concentrations with model-predicted typical responses and 90% CIs. In **a** and **b**, the open blue circles reflect the observed events. The filled black symbols are the observed probability of an event, and the error bars are SE (sqrt (P*(1-P)/N)) for quantiles at (100 × 1/5th) percentiles (vertical dotted lines) of exposures (plotted at the median value within each quantile). The blue dashed lines are the predicted probabilities based on the final models. The blue shaded areas represent the 95% confidence band based on 1000 bootstrap samples. In **c**, **d**, and **e**, the dots represent brigatinib concentrations, and the line and gray area represent the model-predicted typical responses and 90% CIs. Error bars show the response at 1452 ng/mL (C_{max} at 180 mg q.d.) and 2904 ng/mL (C_{imp}, corresponding to twice C_{max}). AUC, area under the concentration versus time curve; CI, confidence interval; C_{imp}, maximum plasma concentration for patients with impaired elimination; C_{max}, geometric mean steady-state maximum plasma concentration; HR, heart rate; QTcF, QT interval corrected using Fridericia's formula; SE, standard error; sqrt, square root.

inverse exposure–efficacy relationship suggestive of shorter PFS at higher ceritinib exposures was observed.[16] Implementation of a model based on a dynamic time-varying exposure metric eliminated inverse relationships between ceritinib exposure and PFS.

In the current brigatinib analyses, a range of doses and associated exposures were represented in the combined data set across the phase I/II and dose-ranging ALTA trials.[3,4] A time-varying (nonstatic) exposure metric (i.e., daily time-varying AUC) was shown to be significantly associated with time to PFS, iPFS, and OS in the longitudinal parametric TTE models. The utility of parametric TTE modeling in exposure–efficacy modeling of oncology therapies has been previously described.[18]

In the models for PFS and OS, both brigatinib exposure and baseline tumor burden were significant predictors of PFS. The observed relationship between baseline tumor burden and survival outcomes is consistent with results of the alectinib exposure–response analysis in crizotinib-refractory patients.[17] Baseline tumor size is an established prognostic factor in NSCLC. An analysis of the Surveillance, Epidemiology, and End Results (SEER) registry database of more than 50,000 patients with NSCLC showed that a doubling in primary tumor size relative to the median tumor size in the population (3.2 cm) was associated with significantly worse survival (hazard ratio, 1.35; 95% CI, 1.33–1.38).[19]

Simulations using the TTE model demonstrated a nonlinear increase in predicted median PFS up to brigatinib doses of 240 mg per day. The model-predicted median PFS values of 12.0 months for 90 mg q.d. and 14.7 months for 180 mg q.d. generally aligned with observed median dose–response PFS in the ALTA trial, where the median PFS was 9.2 months in the 90 mg q.d. arm and 16.7 months in the 180 mg q.d. arm (with a 7-day 90 mg lead-in).[4,20] The recommended clinical dose range (90–180 mg q.d.) is associated with brigatinib concentrations that exceed *in vitro* estimates of the concentrations of drug producing 50% and 90% inhibition for inhibition of native EML4-ALK and mutants associated with resistance to *ALK* inhibitors (e.g., G1202R).[21] Previously reported simulations based on the population PK model showed that approximately 95% of patients receiving brigatinib 180 mg q.d. would achieve trough concentrations that exceed the concentration of drug producing 50% and 90% inhibition for native EML4-ALK by more than eightfold. Of note, the fifth percentile of average concentration (C_{av}) concentrations at 180 mg q.d. was 1.7-fold higher than the adjusted concentration of drug producing 50% inhibition for the G1202R mutant.[21,22] The predicted advantage for the 240 mg dose compared with the 180 mg dose for median PFS was 16.0 vs. 14.7 months, for median iPFS was 21.4 vs. 19.2 months, and for the time to 20th percentile OS was 17.3 vs. 15.8 months. These results suggest a potential benefit of increasing the daily brigatinib dose to 240 mg, albeit with higher probability of grade ≥ 2 rash and grade ≥ 2 amylase increase, warranting further clinical exploration. An ongoing clinical trial (NCT03535740) is evaluating the efficacy, safety, and tolerability of escalation to brigatinib 240 mg after progression on 180 mg in patients with *ALK* positive NSCLC refractory to alectinib or ceritinib.

Similar to PFS, model-predicted median iPFS exhibited nonlinear increases with increasing brigatinib dose up to 240 mg per day. Predicted median iPFS was 15.1 and 19.2 months for the 90 and 180 mg q.d. doses, respectively, compared with 12.8 and 18.4 months, respectively, in ALTA.[4,20] The observed relationship between increasing exposure and iPFS indirectly supports the central nervous system (CNS) penetration of brigatinib in patients with *ALK* positive NSCLC, an important drug characteristic in this patient population for whom brain metastases are common and associated with poor prognosis.[23] Brigatinib has consistently demonstrated high CNS activity, significantly decreasing the risk of CNS progression compared with crizotinib in *ALK*–tyrosine kinase inhibitor naive patients with and without baseline brain metastases in the phase III ALTA-1L trial (hazard ratio for iPFS in the intention-to-treat population, 0.42; 95% CI, 0.24–0.70).[6]

For OS, the model-predicted 20th percentile increased in a nonlinear manner with increasing brigatinib dose up to 240 mg per day. For the 90 mg and 180 mg regimens, the predicted times at which 80% of patients would remain alive were 12.4 and 15.8 months, respectively. Increasing the daily dose to 240 mg per day is predicted to result in 80% of patients surviving at 17.3 months. Although an impact of subsequent anticancer therapies on OS outcomes cannot be ruled out, there is no indication that access to subsequent anticancer therapies was imbalanced.

In the safety exposure–response analysis, the only events found to have a higher probability of occurrence with increasing brigatinib exposure were grade ≥ 2 rash and grade ≥ 2 amylase increase. Rash has been reported with other *ALK* inhibitors[24–27] and is the most commonly reported treatment-related AE with ensartinib (56%).[28] Increased amylase AEs have also been reported with other *ALK* inhibitors, occurring at higher rates with ceritinib than with crizotinib or alectinib.[29]

There was no statistically significant relationship between brigatinib concentration and change in QTcF interval. The estimated coefficient of the concentration effect suggested that brigatinib does not prolong the QT interval to a clinically relevant extent, unlike the *ALK* inhibitors crizotinib and ceritinib.[30,31] The model describing PR interval versus brigatinib concentration predicted an increase in the PR interval of 12.1 milliseconds at concentrations equivalent to twice the steady-state C_{max} for brigatinib at 180 mg q.d. (2904 ng/mL). However, simulations based on the model showed fewer than 0.1% of patients would have absolute PR interval values > 200 milliseconds and a > 25% increase in PR relative to baseline at the same brigatinib concentration. The magnitudes of these effects of brigatinib on the PR interval are not considered clinically meaningful. The HR model predicted an HR decrease of 4.86 beats per minute at steady-state C_{max} for brigatinib 180 mg (1452 ng/mL). Bradycardia is a class effect among *ALK* inhibitors and has been observed with brigatinib.[32]

The etiology of EOPEs with brigatinib remains unknown.[14,33] One hypothesis is that a short crizotinib washout time may reduce metabolic clearance of brigatinib and increase exposure following the initial doses of brigatinib because crizotinib is a time-dependent inhibitor of CYP3A4,[34] the primary metabolizing enzyme for brigatinib.[35] However, the current analyses found no relationship between brigatinib exposure after the first dose and the duration of crizotinib washout, suggesting that EOPEs are not driven by higher brigatinib exposure due to shorter crizotinib washout.

CONCLUSIONS

Exposure–response modeling supports a dose-related increase in brigatinib efficacy for PFS, iPFS, and OS over 30–240 mg q.d. These relationships could be discerned using dynamic models driven by time-varying exposure metrics, but not using static models driven by time-averaged exposure metrics. While the incidences of some AEs (i.e., rash and amylase elevation) are expected to increase at the higher dose, they remained less than or equal to 10%. Taken together, these analyses demonstrate superior benefit to risk associated with the 180 mg q.d. dose (with 7-day lead-in at 90 mg q.d.) compared with 90 mg q.d., thereby providing support for the currently approved brigatinib dosing regimen. In addition, the observed exposure–response relationships for rash and amylase increase are supportive of the recommended dose reductions for patients experiencing treatment-emergent toxicities.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

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Conflict of Interest. N.G., M.H., and P.Z. report employment with Millennium Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. X.W., E.O., B.R., and P.M.D. are employees of Certara, a consulting firm under contract with Takeda. D.K. is a former employee and stock owner of Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. K.V. is a former employee of Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Author Contributions. N.G. and K.V. wrote the manuscript. N.G., K.V., X.W., E.O., B.R., D.K., M.H., P.Z., and P.M.D. designed the research. N.G., K.V., X.W., E.O., B.R., D.K., M.H., P.Z., and P.M.D. performed the research. X.W., E.O., B.R., and P.M.D. analyzed the data.

Data Availability Statement. The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participant data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after deidentification in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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