ARTICLE

Pharmacometric analyses of alectinib to facilitate approval of the optimal dose for the first-line treatment of anaplastic lymphoma kinase–positive non-small cell lung cancer

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Abstract

Alectinib is an anaplastic lymphoma kinase (ALK) inhibitor approved for treatment of *ALK*-positive non-small cell lung cancer. Population pharmacokinetic (PK) models were developed for alectinib and its major active metabolite M4 using phase I/II PK data in crizotinib-failed patients ($N = 138$). The PK profiles were best described by two separate models with similar structure for both entities: open one-compartment models with sequential zero/first-order input and first-order elimination rate. Body weight with fixed allometric scaling factor on clearance and volume of both entities was the only significant covariate. Bayesian feedback analyses of the PK data collected from Japanese and global treatment-naïve patients in phase III studies ($N = 334$) confirmed the body weight effect. Landmark Cox proportional hazards analyses of progression-free survival in treatment-naïve patients identified the average molar concentrations of both entities alectinib and M4 during the first 6 weeks of treatment as a significant covariate, with an optimal response achieved for concentrations above 1040 nmol/L. With 600 mg twice daily (b.i.d.), 92% of global patients are above this threshold concentration, compared with only 43% of patients with 300 mg b.i.d. In Japan, where the body weight distribution is lower, the approved 300 mg b.i.d. dose brings about 70% of Japanese patients above this threshold. Logistic regression analyses found no significant relationship between the combined alectinib–M4 molar concentration and first occurrence of adverse events. These pharmacometric results were used to expedite and facilitate regulatory approvals of 600 mg b.i.d. for first-line *ALK*-positive NSCLC in the United States and European Union in 2017 and in China in 2018.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Alectinib 300 mg twice daily (b.i.d.) received approval in Japan in 2014 for the first-line treatment of patients with *ALK*-positive NSCLC. Subsequently, alectinib 600 mg b.i.d. received approval in the United States and European Union in 2017 and in China in 2018 for the first-line treatment of *ALK*-positive NSCLC, having previously been approved for second-line use in patients who failed treatment with crizotinib.

WHAT QUESTION DID THIS STUDY ADDRESS?
This analysis confirms that alectinib 600 mg b.i.d. is the optimal dosing regimen for the treatment of advanced *ALK*-positive NSCLC in the global patient population.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Pharmacometric approaches were instrumental in confirming the optimal dosing regimen of alectinib for the treatment of advanced *ALK*-positive NSCLC in the global patient population.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
The outcomes of these pharmacometric analyses expedited and facilitated regulatory approval of alectinib by health authorities in the United States, European Union, and China.

INTRODUCTION

Approximately 5% of patients with non-small cell lung cancer (NSCLC) have oncogenic anaplastic lymphoma kinase (*ALK*) rearrangements.[1] Alectinib is a tyrosine kinase inhibitor that targets ALK and rearranged during transfection (RET), inhibiting intracellular signaling pathways involved in tumor cell proliferation and survival.[2,3] It can penetrate the blood–brain barrier and is active in the central nervous system (CNS).[4,5] Alectinib and M4, its major active metabolite, are equipotent.[6–8]

Alectinib was first approved in Japan in July 2014 at 300 mg twice daily (b.i.d.) for the treatment of ALK inhibitor–naïve patients with *ALK*-positive, unresectable, recurrent, or advanced NSCLC, based on one single-arm, open-label, phase I/II study (AF-001JP).[9] The approved 300 mg b.i.d. dose was the highest dose that could be tested due to the maximum amount of excipient, sodium lauryl sulfate (SLS), allowed by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.[10] Subsequently, a phase III study (J-ALEX) was conducted in ALK inhibitor–naïve Japanese patients with *ALK*-positive NSCLC to directly compare the efficacy and safety of alectinib 600 mg b.i.d. versus crizotinib.[11] Results of the second interim analysis for J-ALEX demonstrated superior progression-free survival (PFS) for alectinib versus crizotinib (hazard ratio [HR], 0.37; 95% confidence interval [CI], 0.26–0.52).[12]

Alectinib 600 mg b.i.d. was approved in the United States and European Union in 2017 for treatment-naïve patients with *ALK*-positive NSCLC based on the primary analysis of the global phase III ALEX study, having previously been approved for second-line use in patients who failed treatment with crizotinib.[13,14] These results showed that PFS was prolonged with alectinib 600 mg b.i.d. compared with crizotinib (HR, 0.47; 95% CI, 0.34–0.65; *p* < 0.0001; 12-month event-free survival rate 68.4% [95% CI, 61.0%–75.9%] with alectinib and 48.7% [95% CI, 40.4%–56.9%] with crizotinib).[15] The safety profile of alectinib in the ALEX study was consistent with that observed in previous studies and compared favorably with that of crizotinib.[15]

Based on the ALEX results, alectinib 600 mg b.i.d. was approved in China in August 2018 for the first-line treatment of advanced *ALK*-positive NSCLC.[16] Subsequently, results of the phase III ALESIA study, conducted in Asian patients with treatment-naïve, *ALK*-positive advanced NSCLC, demonstrated a consistent PFS increase versus crizotinib (HR, 0.22; 95% CI, 0.13–0.38; *p* < 0.0001) and a consistent safety profile.[11,15,17]

This article describes the pharmacometric analyses that confirmed alectinib 600 mg b.i.d. as the optimal dose regimen and expedited and facilitated its approval in the United States, European Union, and China.

METHODS

Studies and data

To investigate the pharmacokinetic (PK) characteristics, exposure–efficacy and exposure–safety relationships of

alectinib and its major active metabolite, M4 in the target population, available data from the following open-label, multicenter studies were analyzed:

- NP28673 (NCT01801111): single-arm, multicenter phase I/II study of alectinib in patients with *ALK*-positive NSCLC who failed crizotinib treatment[18]
- J-ALEX (JapicCTI-132316): randomized phase III study of alectinib versus crizotinib in ALK inhibitor–naïve Japanese patients with *ALK*-positive advanced or recurrent NSCLC[11]
- ALEX (NCT02075840): randomized phase III study of alectinib versus crizotinib in treatment-naive patients with *ALK*-positive advanced NSCLC[15]
- ALESIA (NCT02838420): randomized phase III study of alectinib versus crizotinib in treatment-naïve Asian patients with *ALK*-positive advanced NSCLC.[17]

Study protocols were approved by the institutional review board or ethics committee at each participating center, and the studies were conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice Guidelines, and local laws. Written informed consent was obtained from all patients before enrollment.

A detailed summary of the PK, efficacy, and safety data included in the analyses is provided in Table 1.

Population PK analyses of alectinib and M4

Population PK models for alectinib and M4 developed using phase I/II data in crizotinib-failed patients[19-21]

Attempts were undertaken to develop a joint parent–metabolite model to simultaneously describe the PK of alectinib and M4. However, no acceptable goodness-of-fit plots could be obtained, mainly due to limited correlation between the PK profiles of the two entities (only about 40% of the variability in M4 was explained by variability in alectinib). Subsequently, two separate models were investigated. Key objectives were to adequately characterize the PK properties of the two active entities and to assess the exposure–response relationships. Separate models with one and two open compartments were tested for both alectinib and M4. The assumed oral dose of M4 was the dose of alectinib adjusted by the difference in molecular weight. Previous studies suggest limited first-pass metabolism of alectinib by cytochrome P450 (CYP) 3A.[22] For the absorption phase of alectinib and formation rate of M4, first-order, zero-order, or sequential zero-order and first-order rates were tested, with or without a lag time. Compartmental models were parameterized in terms of clearance(s) and volume(s) of distribution. The differences

in PK parameters between individuals were assumed to be normally distributed random quantities with a mean of zero and a variance that could be estimated. For residual error models, additive, multiplicative, and a combination of additive and multiplicative models were tested.

Covariate analyses were conducted to evaluate and quantify factors that contribute significantly to between-patient variability in PK parameters of alectinib and M4. Demographic-related, laboratory-related, and disease-related individual baseline covariates (Supplement 1) were first screened against individual post hoc parameters estimated by the basic population PK model using generalized additive modeling (GAM) and bootstrap of the GAM. As most of the PK data collected were trough concentrations and only sparse samples were collected during the absorption phase, covariate effects were investigated on the apparent clearances and volumes for alectinib and M4. Covariates identified by GAM were then tested in NONMEM using a forward inclusion ($p < 0.005$) followed by a backward deletion process ($p < 0.001$). The PK model that included statistically significant covariates was referred to as the final population PK model.

The adequacy of the model to describe alectinib and M4 data was assessed through the evaluation of objective function values and standard diagnostic and graphical assessments as well as precision of parameter estimates. In addition, predictive performance was evaluated using a visual predictive check (VPC) simulating the phase I/II NP28673 study 300 times.

Application of population PK models of alectinib and M4 to phase III data in ALK inhibitor–naïve patients[23,24]

As PK data subsequently became available from phase III studies in ALK inhibitor–naïve patients (J-ALEX, ALEX, and ALESIA), Bayesian feedback analyses were conducted to assess whether the PK characteristics of alectinib and M4 were consistent across different treatment lines, races, and studies. For Bayesian feedback analyses, population PK parameter values from the alectinib and M4 models developed using phase I/II data from crizotinib-failed patients were fixed, and the number of maximal evaluation (i.e., MAXEVAL) was fixed to 0 in the estimation subroutine (i.e., $ESTIMATION) in the NONMEM control streams. Individual PK parameters (i.e., post hoc) for alectinib and M4 were derived using individual observed concentration-time profiles, population parameters, and interindividual variabilities.

All diagnostic plots used during the development of the alectinib and M4 models and simulation-based diagnostics (VPCs) were used to assess the performance of the population PK models in describing alectinib and M4 data for patients across treatment lines, races, and studies.

TABLE 1 Summary of PK, efficacy, and safety data by study

Study	Patient population and dose	Analysis	Data
NP28673, phase I/II	Crizotinib-failed patients	Population PK	• Plasma samples obtained from all patients on Day 1 and Day 21 of Cycle 1 at predose and 2, 4, 6 and 8 h postdose, and sparse predose plasma samples were obtained throughout the study • 138 patients treated with alectinib 600 mg b.i.d., with a total of 2080 alectinib and 2080 M4 plasma concentrations
J-ALEX, phase III	Treatment-naïve Japanese patients, 300 mg b.i.d.	Population PK	• Sparse plasma samples obtained from all patients before first dosing on Days 1, 57, and 113 • 96 patients with 187 alectinib and 188 M4 plasma concentrations
		Exposure–efficacy for PFS	• PFS by IRF (data cutoff: December 3, 2015) • 96 patients treated with alectinib 300 mg b.i.d. (PK population) • 104 patients treated with crizotinib 250 mg b.i.d.
		Exposure–safety for SAE and Grade ≥3 AEs	• Safety was assessed and graded according to NCI CTCAE (Version 4.03) throughout the study
ALEX, phase III	Treatment-naïve global patients, 600 mg b.i.d.	Population PK	• Intensive plasma PK samples obtained from a subset of patients ($n = 10$) randomized to receive alectinib on Day 1 and at Week 4 • Sparse plasma samples obtained from all patients before first dosing on Day 1, Weeks 4 and 8, and every 8 weeks thereafter until progressive disease or death/treatment discontinuation • 143 patients with 1486 alectinib and 1486 M4 plasma concentrations
		Exposure–efficacy for PFS	• PFS by IRC (data cutoff: February 9, 2017) • 143 patients treated with alectinib 600 mg b.i.d. (PK population) • 151 patients treated with crizotinib 250 mg b.i.d.
		Exposure–safety for SAE and Grade ≥3 AEs	• Safety was assessed and graded according to NCI CTCAE (Version 4.03) throughout the study
ALESIA, phase III	Treatment-naïve Asian patients in China, South Korea, and Thailand; 600 mg b.i.d.	Population PK	• Following the same sampling schedule as in the global ALEX study, with intensive plasma PK obtained from 20 patients • 95 Asian patients with 624 alectinib and 624 M4 plasma concentrations • Chinese patients: $n = 85$
		Exposure–efficacy for PFS	• PFS by IRC (data cutoff: May 31, 2018) • 95 patients treated with alectinib 600 mg b.i.d. (PK population) • 62 patients treated with crizotinib 250 mg b.i.d.
		Exposure–safety for SAE and Grade ≥3 AEs	• Safety was assessed and graded according to NCI CTCAE (Version 4.03) throughout the study

Abbreviations: AE, adverse event; b.i.d., twice daily; IRC, independent review committee; IRF, independent review facility; M4, alectinib major active metabolite; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PFS, progression-free survival; PK, pharmacokinetic; SAE, serious adverse event.

Exposure–efficacy analyses in ALK inhibitor–naïve patients

Initial Cox proportional hazards (CPH) analysis of J-ALEX PFS data following alectinib 300 mg b.i.d.[21,23,24]

Initial investigation of whether variability in alectinib exposure could partly explain variability in efficacy was conducted using data from J-ALEX, a phase III study of alectinib in patients with *ALK*-positive NSCLC. To avoid immortal time bias, a landmark CPH analysis was performed to characterize the relationship between alectinib exposure and PFS.[25–27] Individual $C_{average\_6\ week}$, defined as the cumulative area under the molar concentration curve of both alectinib and M4 for the first 6 weeks on treatment derived from population PK models divided by 6 weeks, was used as a surrogate for exposure for each patient. This time frame was selected as no patient in

the alectinib treatment arm progressed during the first 6 weeks. Because M4 has a metabolite/parent ratio of 0.4 and similar *in vitro* potency and plasma protein binding to alectinib,[8] both entities are expected to contribute to overall alectinib efficacy and safety. $C_{average\_6 week}$ was computed as the sum of molar concentrations of alectinib and M4 (molecular weights of 482.6 and 456.6 g/mol, respectively). Exposure was tested as a continuous covariate and as a categorical covariate using two categories. The optimal cutoff concentration and its 95% CI that defined low and high exposure categories were identified as the value yielding the lowest CPH log likelihood using a log likelihood profiling (LLP) method.

In addition to exposure, the impact on PFS of demographic-related and disease-related baseline covariates was investigated (Supplement 1). Covariates were assessed in the CPH model by univariate addition and ranked in descending order according to change in log likelihood ratio test. Variables were then tested by stepwise addition. Covariates were included at a significance level of $p < 0.05$. When no further significant covariates could be included at this significance level, backward deletion was carried out at $p < 0.01$, where the relative influence of each covariate was re-evaluated by deleting it individually. Kaplan-Meier plots and log-rank statistics were used to graphically confirm exposure–efficacy relationships between alectinib and M4 exposure and PFS for patients in J-ALEX.

Subsequent CPH analyses by sequentially including ALEX and ALESIA PFS data following 600 mg b.i.d.

As PFS data from ALEX became available, the CPH analysis was repeated by pooling patients from J-ALEX and ALEX to further assess the relationship between alectinib and M4 exposure and PFS across the dose range 300–600 mg b.i.d. in ALK inhibitor–naïve and treatment-naïve patients. Previously investigated demographic and disease status covariates were assessed. The CPH analysis was further updated when PFS data from ALESIA became available by pooling data from J-ALEX, ALEX, and ALESIA. In addition, Kaplan-Meier plots and log-rank statistics were used to graphically confirm exposure–efficacy relationships between alectinib and M4 exposure and PFS.

Exposure–safety analyses in ALK inhibitor–naïve patients

Logistic regressions were performed to investigate whether the first occurrence of safety events following alectinib 300 and 600 mg b.i.d. in ALK inhibitor–naïve patients could be attributed to alectinib and M4 exposure.[19,24] The first occurrence of serious adverse events (SAEs) and adverse events (AEs) Grade ≥3 in each patient were the safety parameters analyzed for J-ALEX, ALEX, and ALESIA.

Individual $C_{average}$, defined as the average molar concentration (for the sum of alectinib and M4) from the first dose to the time of the first safety event derived by the population PK model, was used as a surrogate for exposure. For patients without a safety event, individual $C_{average}$ was defined as the average concentration from the first dose to the time of the last dose received on record.

Software

Population PK analyses and all simulations were performed using NONMEM version 7.2.0. SAS System for Windows version 9.4 TS Level 1M0 was used to create all analysis data sets and for the graphical analyses. RStudio version 0.97.551 (with R version 3.1.2) was used for the graphical analyses.

RESULTS

Population PK and exposure–efficacy and exposure–safety analyses were conducted in 334 ALK inhibitor–naïve patients to support the regulatory approval for the first-line treatment of NSCLC in the United States, European Union, and China. Patient demographic data and disease status at baseline for NP28673, J-ALEX, ALEX, and ALESIA is summarized in Table 2. The distribution of continuous covariates was fairly homogenous across studies. As expected, the lowest median body weight was in J-ALEX (56.9 kg); the highest median body weight (71.1 kg) was in NP28673. Among the three studies conducted in ALK inhibitor–naïve patients, J-ALEX had the lowest median tumor size at baseline (38.0 mm), and ALEX had the highest (70.0 mm). Although all patients in J-ALEX and ALESIA were Asian, 47% in ALEX were Asian and 48% were White, whereas 26% in NP28673 were Asian and 67% were White. In ALEX and ALESIA, 31% and 37% of patients, respectively, had CNS metastases at baseline compared with only 15% in J-ALEX.

Population PK analyses of alectinib and M4

Population PK models for alectinib and M4 developed using phase I/II data in crizotinib-failed patients[19,24]

A total of 2080 alectinib and 2080 M4 plasma concentrations measured from 138 patients with *ALK*-positive

TABLE 2 Summary of patient demographic data and disease status at baseline by study

Continuous covariates	NP28673, median (min/max)	J-ALEX, median (min/max)	ALEX, median (min/max)	ALESIA, median (min/max)	All patients, median (min/max)
Age, years	52.0 (21.0/79.0)	61.5 (27.0/85.0)	57.0 (25.0/81.0)	52.0 (21.0/78.0)	54.0 (21.0/85.0)
Body weight, kg	71.1 (41.0/122)	56.9 (37.2/99.3)	65.2 (40.4/131.5)	61.0 (35.0/92.0)	63.4 (35.0/131.5)
Baseline tumor size, mm	40.0 (10.0/238)	38.0 (10.1/180.8)	70.0 (10.1/206)	49.0 (12.0/196)	48.7 (10.0/238)

Categorical covariates	NP28673, n (%)	J-ALEX, n (%)	ALEX, n (%)	ALESIA, n (%)	All patients, n (%)
Ethnicity					
Non-Hispanic	130 (94)	96 (100)	135 (94)	96 (100)	457 (97)
Hispanic	8 (6)	0 (0)	8 (6)	0 (0)	16 (3)
Race					
White	93 (67)	0 (0)	69 (48)	0 (0)	162 (34)
Black	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Asian	36 (26)	96 (100)	67 (47)	96 (100)	295 (62)
American Indian	1 (1)	0 (0)	4 (3)	0 (0)	5 (1)
Other	7 (5)	0 (0)	3 (2)	0 (0)	10 (2)
Sex					
Female	77 (56)	57 (59)	82 (57)	49 (51)	270 (56)
Male	61 (44)	39 (41)	61 (43)	47 (49)	208 (44)
Smoking status					
Nonsmoker	96 (70)	51 (53)	87 (61)	69 (72)	265 (61)
Past smoker	39 (28)	43 (45)	47 (33)	23 (24)	152 (35)
Active smoker	3 (2)	2 (2)	9 (6)	4 (4)	18 (4)
CNS metastases					
No	104 (75)	82 (85)	90 (63)	66 (69)	342 (72)
Yes	34 (25)	14 (15)	53 (37)	30 (31)	131 (28)
ECOG PS					
0	44 (32)	52 (54)	42 (29)	14 (15)	153 (32)
1	81 (59)	43 (45)	95 (66)	79 (82)	298 (63)
2	13 (9)	1 (1)	6 (4)	3 (3)	23 (5)

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; max, maximum; min, minimum.

NSCLC in NP28673 were available for the development of the population PK model for each of these two entities. The two final models that best described the plasma concentration-time profiles of alectinib and M4 are both one-compartment open models with first-order elimination and sequential zero-order and first-order rates for both input phases, that is, an absorption phase for alectinib and a formation phase for M4 (Tables S1 and S2 in Supplement 2).

A significant body weight effect, following allometric scaling principles, was found on clearance and volume for both alectinib and M4. No other covariates tested had a significant effect on the variability in PK for alectinib and M4.

Population PK parameters for both entities were precisely estimated and diagnostic plots for both models did not present any major unexpected deficiencies (Figures S1–S4 in Supplement 2). Proportional errors were less than 20% for both alectinib and M4. Additive errors (41.9 ng/ml for alectinib; 10.9 ng/ml for M4) were higher than the limit of quantification for both analytes (1.5 ng/ml); however, they remained low compared with concentrations at steady state. This reflected residual variability was contributed by the large collection of sparse predose PK samples. The quality of the goodness-of-fit plots and adequate precision of parameter estimates showed that the models were able to describe PK profiles well for both alectinib and M4, indicating that the final population PK models could be used to estimate individual exposure parameters for exposure–efficacy and exposure–safety analyses. The VPC also demonstrated that these models could be used for simulations (Figures S5 and S6 in Supplement 2).

Application of population PK models of alectinib and M4 to phase III data in ALK inhibitor–naïve patients[19,23,24]

Results from Bayesian feedback analyses conducted on three phase III studies ($n = 334$; 2297 alectinib and 2298 M4 concentrations) confirmed that the population PK models, developed using phase I/II data from patients who failed on crizotinib, were robust in describing the PK characteristics of alectinib and M4 across treatment lines, races, and studies where body weight was considered. Body weight was confirmed as the only significant covariate following allometric scaling principles on clearance and volume for both alectinib and M4. Of the 27 patients (8.1%) who had dose reductions in the phase III studies, similar empirical Bayes estimates were obtained compared with those who did not have dose reductions. Results also confirmed that the relationship between body weight and PK of alectinib and M4 remained consistent across treatment lines, races, and studies (Figure 1). The population half-life computed from the estimated apparent clearances and volumes are 34 h for alectinib and 32 h for M4. The mean metabolite-to-parent ratio computed from the individual $C_{average}$ exposures was 0.38, with an estimated between-patient variability of 30%. A summary of the $C_{average\_6\ week}$ exposure derived for alectinib and M4 is available in Table S3 in Supplement 2.

Diagnostic plots for the Bayesian feedback analyses conducted for alectinib and M4 did not present any major unexpected deficiencies. In additionally, covariates that were not significant in previous analyses remained not significant. Comparison of empirical Bayes estimates of posterior individual PK parameters per dose confirmed that the PK of alectinib and M4 was dose proportional from 300 mg to 600 mg b.i.d. The external VPC showed that the predictive performance of the population PK models for both alectinib and M4 was satisfactory and that they could be used to derive individual exposure parameters for exposure–efficacy and exposure–safety analyses (Figure S7 in Supplement 2).

Exposure–efficacy relationships in ALK inhibitor–naïve patients

Initial CPH analysis of J-ALEX PFS data following alectinib 300 mg b.i.d.[19,21,24]

In total, 200 patients (alectinib 300 mg b.i.d. $n = 96$, crizotinib 250 mg b.i.d. $n = 104$) from J-ALEX were included in the CPH analysis. Exposure to alectinib, when split in two categories, was the only significant covariate. An optimal $C_{average\_6\ week}$ cutoff of 1040 nmol/L (95% CI, 965–1120 nmol/L) was identified by LLP, and two exposure categories (low, high) were created. Both categories were associated with longer PFS compared with crizotinib, and high alectinib exposure was associated with a greater decrease in the risk of progression (low alectinib exposure versus crizotinib: HR, 0.55 [95% CI, 0.28–1.07]; high alectinib exposure versus crizotinib: HR, 0.18 [95% CI, 0.09–0.36]; Figure S1 and Table S1 in Supplement 3).

Subsequent CPH analyses by sequentially including ALEX and ALESIA PFS data following 600 mg b.i.d.

A total of 294 patients from ALEX (alectinib 600 mg b.i.d. $n = 143$, crizotinib 250 mg b.i.d. $n = 151$) and 157 patients from ALESIA (alectinib 600 mg b.i.d. $n = 95$, crizotinib 250 mg b.i.d. $n = 62$) were added sequentially to the J-ALEX
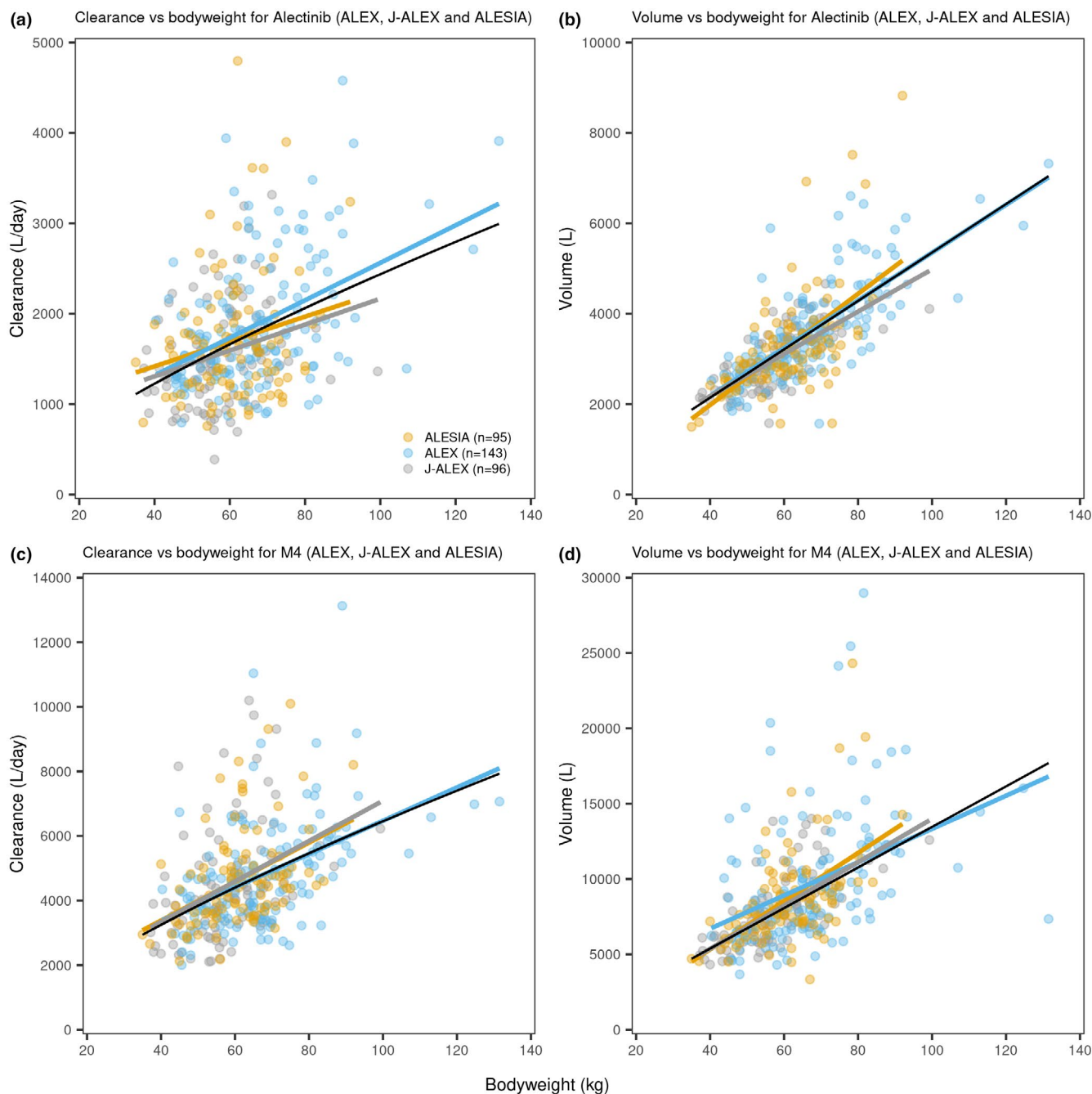
FIGURE 1 Relationship between body weight and the individual pharmacokinetic parameters (post hoc) apparent clearance and apparent volume of distribution for alectinib and M4. (a) Clearance and (b) volume of distribution versus body weight for alectinib, and (c) clearance and (d) volume of distribution versus body weight for M4. Orange line, regression line through the ALESIA data; blue line, regression line through the ALEX data; gray line, regression line through the J-ALEX data; black line, pharmacokinetic model, population prediction from the population PK model. M4, alectinib major active metabolite

data set, and the CPH analysis was repeated each time. In each case, alectinib exposure was confirmed to be significant, and the same optimal $C_{average\_6\,week}$ cutoff (1040 nmol/L; 95% CI, 990–1130 nmol/L) was identified by LLP (Figure S2 and Tables S2–S3 in Supplement 3). In the latest analysis, patients above the optimal $C_{average\_6\,week}$ cutoff had a lower risk of PFS (HR, 0.36; 95% CI, 0.28–0.46) compared with those

below the cutoff (HR, 0.76; 95% CI, 0.46–1.25). Both exposure categories were associated with longer PFS compared with crizotinib, and high alectinib exposure was associated with a greater decrease in the risk of progression (Figures 2 and 3). For concentrations above the optimal threshold value, the two exposure groups tended to have similar HRs (Figure S3 in Supplement 3). Baseline tumor size was also identified as
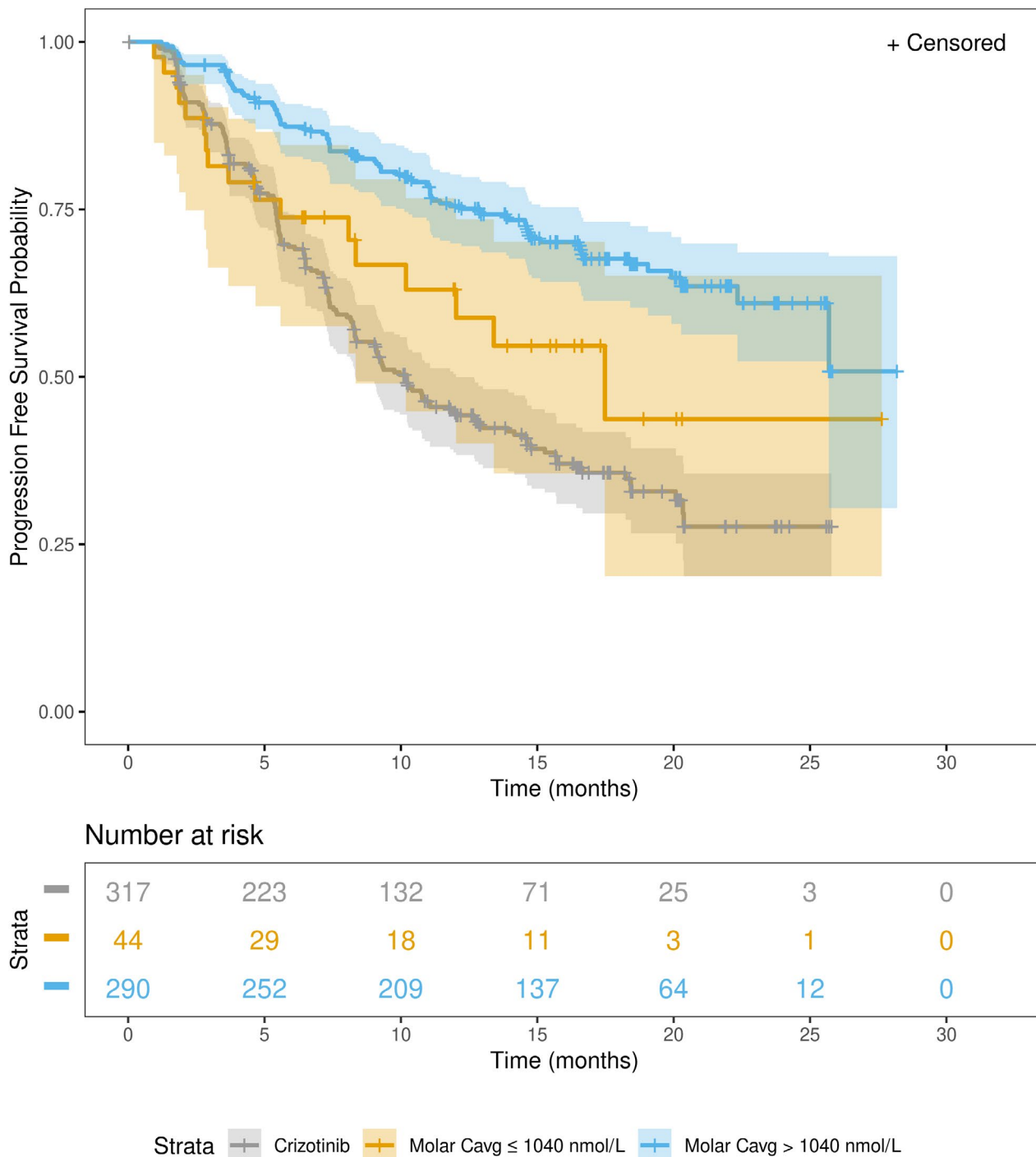
FIGURE 2 Progression-free survival (independent review committee) by exposure category following alectinib 300 mg b.i.d. in J-ALEX and 600 mg b.i.d. in ALEX and ALESIA or crizotinib treatment. b.i.d., twice daily; Cavg, average molar concentration from the first dose to the time of the first safety event

a significant covariate on PFS and was retained in the latest CPH model (Table S3 in Supplement 3). Compared with a patient with a baseline tumor size of 52 mm, a patient with a baseline tumor size of 15 mm had a lower risk of progression (HR, 0.75; 95% CI, 0.69–0.81) and a patient with baseline tumor size of 155 mm had a higher risk (HR, 2.24; 95% CI, 1.79–2.80; Figure 3).

Rationale for the optimal alectinib dose for the treatment of ALK-positive advanced NSCLC in the global patient population

For each patient in the PK database, $C_{average\_6\ week}$ of alectinib and M4 following 600 mg b.i.d. dose was computed using the individual post hoc estimates. This dosing
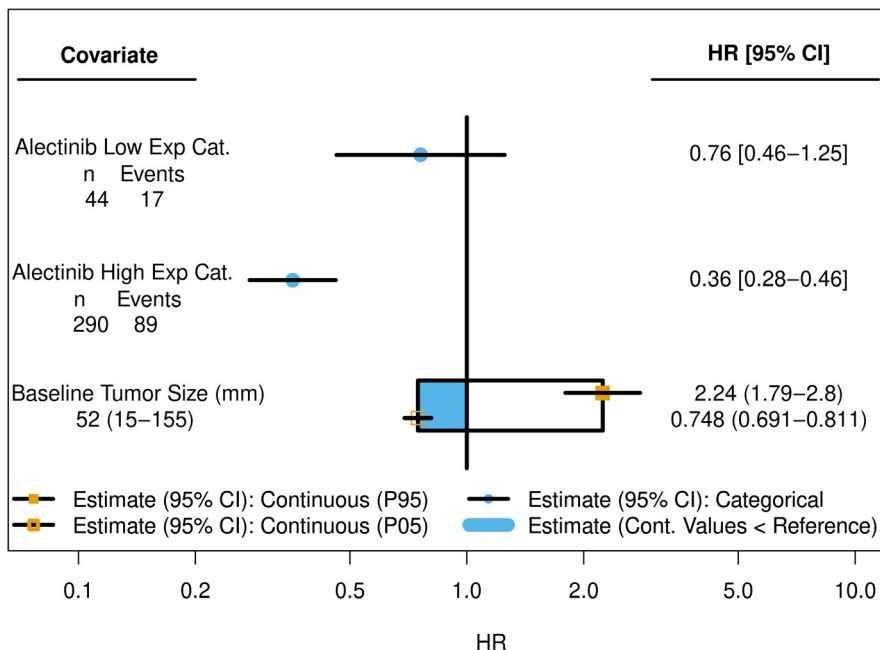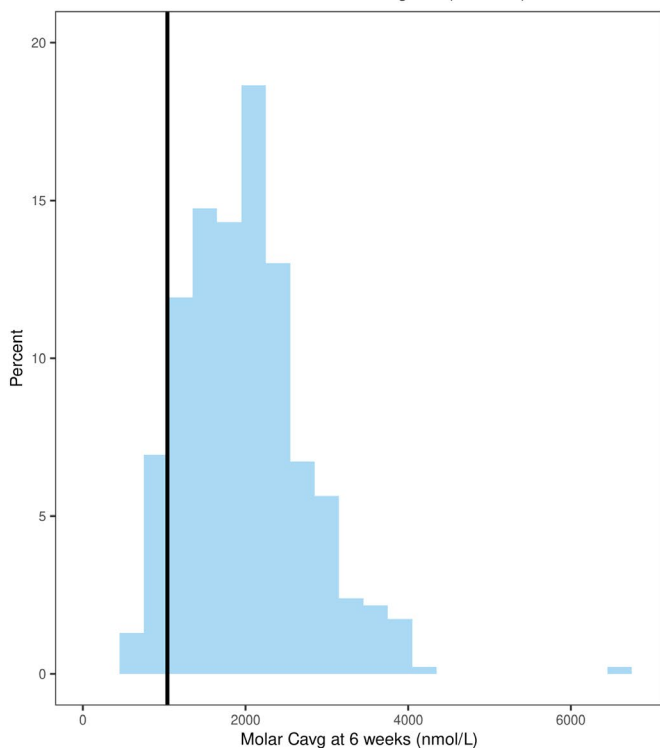
FIGURE 3 Covariate effects of the Cox proportional hazards model for progression-free survival by independent review committee assessment (J-ALEX, ALEX, and ALESIA). CI, confidence interval; Cat., category; Cont., continuous; Exp, exposure; HR, hazard ratio

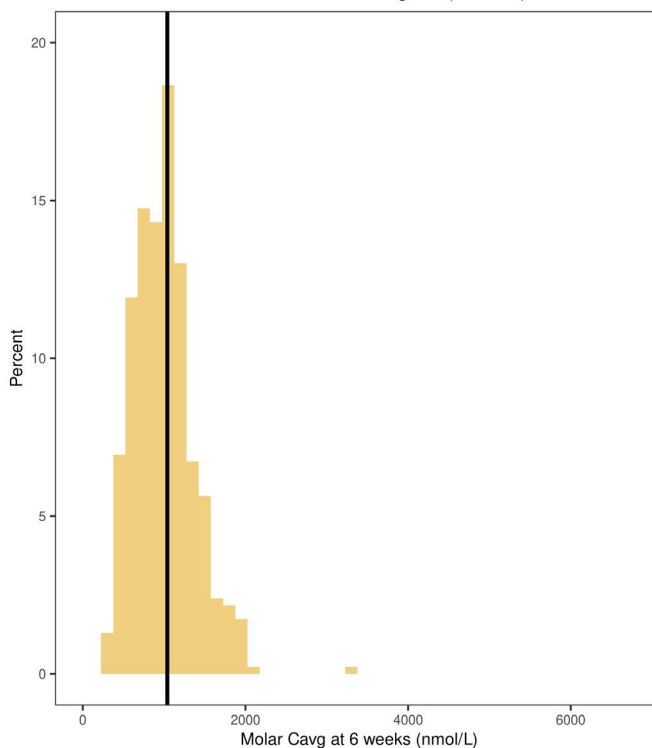**FIGURE 4** Distribution of alectinib exposure ($C_{average\_6\ week}$) following (a) 600 mg or (b) 300 mg b.i.d. for all alectinib-treated patients. The black vertical line indicates the optimal cutoff of $C_{average\_6\ week}$ identified. b.i.d., twice daily; Cavg, average molar concentration from the first dose to the time of the first safety event; ITT, intent to treat

regimen was found to ensure that 92%, 100%, and 96% of patients in ALEX, J-ALEX, and ALESIA, respectively, would fall into the high-exposure category (Figure 4).

Conversely, with 300 mg b.i.d., only 43%, 69%, and 51% of patients, respectively, would fall into the high-exposure category.
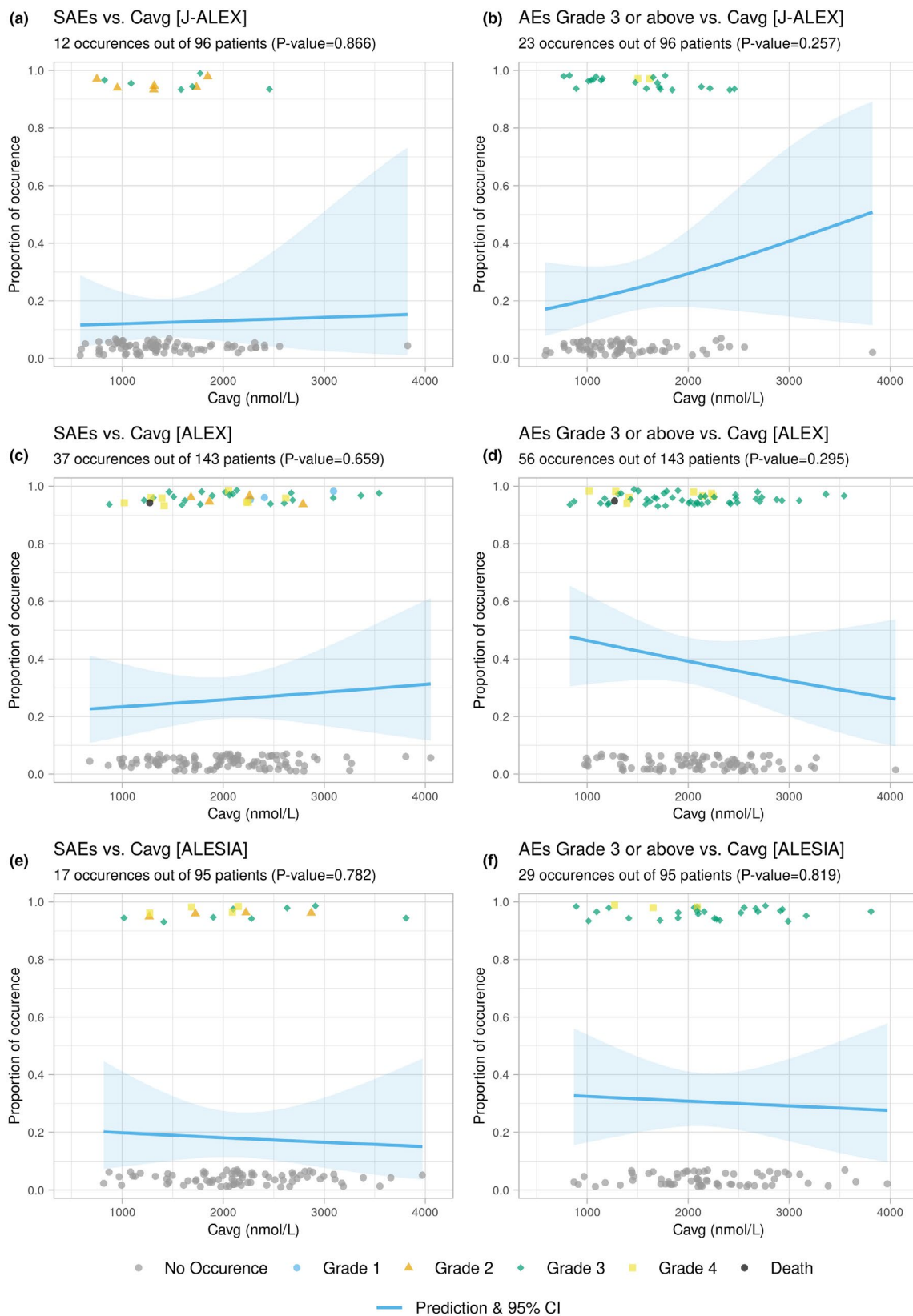
FIGURE 5 SAEs and Grade ≥3 AEs versus combined alectinib and M4 exposure following alectinib 300 mg b.i.d. in J-ALEX and 600 mg b.i.d. in ALEX and ALESIA. (a) SAEs and (b) Grade ≥3 AEs versus Cavg in J-ALEX, (c) SAEs and (d) Grade ≥3 AEs versus Cavg in ALEX, and (e) SAEs and (f) Grade ≥3 AEs versus Cavg in ALESIA. AE, adverse event; b.i.d., twice daily; Cavg, average molar concentration from the first dose to the time of the first safety event; CI, confidence interval; M4, alectinib major active metabolite; SAE, serious adverse event

Exposure–safety relationships in ALK inhibitor–naïve patients

For patients receiving alectinib 300 or 600 mg b.i.d., logistic regression analyses showed no significant relationship the combined molar concentration of alectinib and M4 ($C_{average}$) and the first occurrence of SAEs (Figure 5).[19,21,24] There was no significant relationship between $C_{average}$ and the first occurrence of Grade ≥3 AEs (Figure 5). In addition, there was no apparent effect of $C_{average}$ on severity of the first event for SAEs or Grade ≥3 AEs.

DISCUSSION

Alectinib is a potent and selective ALK inhibitor that demonstrated superiority versus crizotinib in patients with *ALK*-positive NSCLC. Alectinib was first approved in Japan for *ALK*-positive, unresectable, recurrent, or advanced NSCLC at the dose of 300 mg b.i.d.,[9] the highest dose that could be tested due to the maximum amount of SLS excipient permitted by PMDA. Alectinib 600 mg b.i.d. was subsequently approved in the United States, European Union, and China for treatment-naïve patients, having previously been approved in patients who failed treatment with crizotinib.[7,8,16] To support these filings, population PK and exposure–response analyses were conducted. Key objectives of these analyses were to characterize the PK properties of alectinib and its major active metabolite, M4, following oral administration in the target population and to investigate the relationship between exposure to alectinib, M4, and PFS.

PK data collected in phase I/II from patients with *ALK*-positive NSCLC previously treated with crizotinib were used to build population PK models for alectinib and M4. A correlation between the two entities was limited, and consequently their PK profiles were better described with two separate one-compartment open models with sequential zero-order and first-order input rates and a first-order elimination. Body weight with a fixed allometric scaling factor on both clearance and volume was identified as the only significant covariate partially explaining the variability in alectinib PK. As CYP3A is the main enzyme involved in alectinib and M4 metabolism and there is a correlation between liver size and body size, a significant body weight effect on the clearance of alectinib and M4 was expected.[8,28] Similarly, a significant effect of body weight on the volume of distribution of alectinib and M4 was expected as both entities are lipophilic.[29] Once the influence of body weight was taken into account in the model, no differences between races were found, and the PK characteristics of alectinib and M4 appeared similar in Asian and White patients.

These two population PK models were used to analyze PK data collected in the three phase III studies conducted in treatment-naïve patients with *ALK*-positive advanced NSCLC (i.e., J-ALEX in Japanese patients, ALEX in global patients, and ALESIA in Asian patients) by fixing the population parameters and estimating the individual PK parameters. These analyses confirmed that the PK of alectinib and M4 were similar across races once body weight was accounted for and showed that the PK of the two entities is similar between ALK inhibitor–naïve and previously ALK inhibitor–treated patients.

Estimated individual PK parameters were used to investigate the PK exposure–PFS relationship starting with J-ALEX data and sequentially adding ALEX and ALESIA data. To avoid immortal time bias, a landmark analysis was conducted using a PK exposure parameter before any PFS event occurred (i.e., average molar concentration of both alectinib and M4 during the first 6 weeks of treatment [$C_{average\_6\ week}$]).[25–27] In three consecutive CPH analyses, conclusions were consistent, and the same $C_{average\_6\ week}$ threshold value of 1040 nmol/L was identified. In patients with $C_{average\_6\ week}$ above this threshold, the risk of progression was reduced by about 40% compared with those with $C_{average\_6\ week}$ below this threshold. By conducting simulations using the population PK models, the 600 mg b.i.d. dose was shown to bring more than 90% of all global patients, across the entire body weight range, above the $C_{average\_6\ week}$ threshold, whereas the 300 mg b.i.d. dose would only bring approximately 40% of them above the threshold. Due to the lower body weight distribution of Japanese patients in J-ALEX compared with White patients, alectinib 300 mg b.i.d. would bring approximately 70% of Japanese patients above the threshold. For Chinese patients in the ALESIA study ($n = 85$), body weight distribution was between that of Japanese and White patients; the 600 mg b.i.d. dose was shown to bring more than 95% of Chinese patients above the $C_{average\_6\ week}$ threshold, whereas the 300 mg b.i.d. dose would only approximately 50% to achieve the threshold. As distribution of body weight differs among White, Japanese, and Chinese patients, this difference in percentage of patients above the threshold was expected.

Alectinib consistently showed a favorable safety profile compared with crizotinib in the head-to-head phase III studies, J-ALEX, ALEX, and ALESIA and was consistent with that reported in phase I/II studies.[12,17,30–33] In the ALEX study, Grade ≥3 AEs and SAEs were more frequent with crizotinib than alectinib; discontinuation rates and dose interruptions due to AEs were similar between treatment arms despite longer treatment duration for alectinib.[33]

No significant trend was observed between alectinib exposure and the first occurrence of safety events, indicating that variability in alectinib exposure at 600 mg b.i.d. was not associated with the probability of a safety event. Despite the

identified effect of body weight on PK exposure, no dose adjustment by body weight was considered necessary due to the lack of significant exposure–safety relationships following administration of alectinib 600 mg b.i.d.

Pharmacometrics played a critical role in supporting alectinib 600 mg b.i.d. as an effective, well-tolerated optimal dose regimen in treatment-naïve patient populations.[27] Based on population PK analyses, the PK characteristics of alectinib and M4 were confirmed to be consistent across age, sex, race, treatment lines, and disease status when body weight is taken into consideration. Exposure–efficacy analyses demonstrated that alectinib exposure is significant in partially explaining the variability in the risk of progression, that is, higher exposure is associated with lower risk compared with crizotinib.

Pharmacometric analyses presented herein expedited the approval of alectinib 600 mg b.i.d. for treatment-naïve patients with *ALK*-positive NSCLC in the United States[27] and European Union in 2017. They also enabled approval in China in 2018 before initial efficacy results from the phase III ALESIA study became available.

CONFLICT OF INTEREST
Joy C. Hsu, Felix Jaminion, Elena Guerini, Walter Bordogna, and Bogdana Balas are employees of and hold stocks/shares in F. Hoffmann-La Roche Ltd. Peter N. Morcos is a previous employee and holds stocks/shares in F. Hoffmann-La Roche Ltd. Nicolas Frey is an employee of and holds stocks/shares in F. Hoffmann-La Roche Ltd.

AUTHOR CONTRIBUTIONS
J.C.H., F.J., E.G., B.B., W.B., P.N.M., and N.F. wrote the manuscript. E.G. and B.B. designed the research. E.G., B.B., W.B., P.N.M., and N.F. performed the research. J.C.H., F.J., and P.N.M. analyzed the data.

REFERENCES
1. Barlesi F, Mazieres J, Merlio J-P, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). *Lancet*. 2016;387:1415-1426.

2. Kodama T, Tsukaguchi T, Satoh Y, et al. Alectinib shows potent antitumor activity against RET-rearranged non-small cell lung cancer. *Mol Cancer Ther*. 2014;13:2910-2918.

3. Kodama T, Tsukaguchi T, Yoshida M, Kondoh O, Sakamoto H. Selective ALK inhibitor alectinib with potent antitumor activity in models of crizotinib resistance. *Cancer Lett*. 2014;351:215-221.

4. Kodama T, Hasegawa M, Takanashi K, Sakurai Y, Kondoh O, Sakamoto H. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. *Cancer Chemother Pharmacol*. 2014;74:1023-1028.

5. Gadgeel S, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann Oncol*. 2018;29:2214-2222.

6. European Medicines Agency (EMA). Alectinib prescribing information. https://www.ema.europa.eu/en/documents/product-information/alecensa-epar-product-information_en.pdf. Published 2017. Accessed October 29, 2020.

7. Food & Drug Administration (FDA). Alectinib highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208434s004lbl.pdf. Published 2018. Accessed October 29, 2020.

8. Sato-Nakai M, Kawashima K, Nakagawa T, et al. Metabolites of alectinib in human: their identification and pharmacological activity. *Heliyon*. 2017;3:e00354.

9. Pharmaceuticals and Medical Devices Agency (PMDA). Report on the deliberation results (alectinib). https://www.pmda.go.jp/files/000208811.pdf. Published 2014. Accessed October 29, 2020.

10. Seto T, Kiura K, Nishio M, et al. CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1–2 study. *Lancet Oncol*. 2013;14:590-598.

11. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet*. 2017;390:29-39.

12. Nakagawa K, Hida T, Nokihara H, et al. Final progression-free survival results from the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. *Lung Cancer*. 2020;139:195-199.

13. F. Hoffmann-La Roche, L. Press release. European Commission approves Roche's Alecensa (alectinib) as first-line treatment in ALK-positive lung cancer. https://www.roche.com/media/releases/med-cor-2017-12-21.htm. Published 2017. Accessed October 29, 2020.

14. Food & Drug Administration (FDA). Press release. Alectinib approved for (ALK) positive metastatic non-small cell lung cancer (NSCLC). https://www.fda.gov/drugs/resources-information-approved-drugs/alectinib-approved-alk-positive-metastatic-non-small-cell-lung-cancer-nsclc. Published 2017. Accessed October 29, 2020.

15. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377:829-838.

16. F. Hoffmann-La Roche, L. Press release. China National Drug Administration grants rapid approval of Roche's Alecensa (alectinib) as a treatment for ALK-positive lung cancer. https://www.roche.com/media/releases/med-cor-2018-08-20.htm. Published 2018. Accessed October 29, 2020.

17. Zhou C, Kim SW, Reungwetwattana T, et al. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study. *Lancet Respir Med*. 2019;7:437-446.

18. Gadgeel SM, Shaw AT, Govindan R, et al. Pooled analysis of CNS response to alectinib in two studies of pretreated patients

with ALK-positive non-small-cell lung cancer. *J Clin Oncol*. 2016;34:4079-4085.

19. Hsu JC, Carnac R, Henschel V, et al. Population pharmacokinetics (popPK) and exposure-response (ER) analyses to confirm alectinib 600 mg BID dose selection in a crizotinib-progressed or intolerant population. *J Clin Oncol*. 2016;34:e20598.

20. Hsu JC, Carnac R, Bogman K, et al. Population pharmacokinetics and exposure-efficacy and safety analyses of alectinib in crizotinib-progressed or intolerant population (Abstract W-41). *J Pharmacokinet Pharmacodyn*. 2016;43:S104.

21. Hsu JC, Jaminion F, Guerini E, et al. Population pharmacokinetic and exposure-efficacy/safety analyses for bridging J-ALEX to global population with alectinib 600mg BID dose regimen. Poster W-078 presented at ACoP8. https://isop.memberclicks.net/assets/Legacy_ACOPs/ACOP8/Abstracts/W-078.pdf. Published 2016. Accessed October 29, 2020.

22. Morcos PN, Cleary Y, Guerini E, et al. Clinical drug-drug interactions through cytochrome P450 3A (CYP3A) for the selective ALK inhibitor alectinib. *Clin Pharmacol Drug Dev*. 2017;6:280-291.

23. Hsu JC, Jaminion F, Guerini E, et al. Population pharmacokinetics (popPK) and exposure-response (ER) analyses bridge J-ALEX to the global population with an alectinib (ALC) 600mg bid dosing regimen. *J Clin Oncol*. 2017;35:e20616.

24. Hsu JC, Jaminion F, Guerini E, et al. Population pharmacokinetics and exposure-response analyses confirm the alectinib 600 mg BID dose in the global ALK inhibitor-naïve population. *Clin Pharmacol Ther*. 2018;103:S5-S97.

25. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087.

26. Gleiss A, Oberbauer R, Heinze G. An unjustified benefit: immortal time bias in the analysis of time-dependent events. *Transplant Int*. 2018;31:125-130.

27. Morcos PN, Liu J, Blumenthal GM, Zhao H. Model-informed drug development approach to expedite approval: Case of alectinib in first-line anaplastic lymphoma kinase + non-small cell lung cancer. *Clin Pharmacol Ther*. 2019;105:826-828.

28. Nakagawa T, Fowler S, Takanashi K, et al. In vitro metabolism of alectinib, a novel potent ALK inhibitor, in human: contribution of CYP3A enzymes. *Xenobiotica*. 2018;48:546-554.

29. Morcos PN, Yu L, Bogman K, et al. Absorption, distribution, metabolism and excretion (ADME) of the ALK inhibitor alectinib: results from an absolute bioavailability and mass balance study in healthy subjects. *Xenobiotica*. 2017;47:217-229.

30. Novello S, Mazières J, Oh IJ, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. *Ann Oncol*. 2018;29:1409-1416.

31. Ou SH, Ahn JS, De Petris L, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. *J Clin Oncol*. 2016;34:661-668.

32. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol*. 2016;17:234-242.

33. Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol*. 2020;31:1056-1064.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.