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CLINICAL TRIALS

Global population pharmacokinetics of the investigational Aurora A kinase inhibitor alisertib in cancer patients: rationale for lower dosage in Asia

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AIMS

This population pharmacokinetic analysis was conducted to describe quantitatively the regional differences and sources of interpatient variability on the apparent oral clearance of alisertib.

METHODS

A population pharmacokinetic analysis was performed on data from 671 cancer patients in Western countries and in Japan/East Asia to whom alisertib 5–150 mg once or twice daily (b.i.d.) was administered in multiple dosing schedules. The final model was used to simulate alisertib pharmacokinetics in patients in the West and East Asian regions in the single-agent schedule of 7 days of dosing in a 21-day cycle. Exposure–safety relationships for mechanism-related antiproliferative toxicities (neutropenia, mucositis and diarrhoea) were estimated by logistic regression.

RESULTS

Alisertib pharmacokinetics were described by a two-compartment model with four-transit compartment absorption and linear elimination. The final model included a covariate effect of region on relative bioavailability, with patients in the East Asian region estimated to have a 52% higher bioavailability compared with Western patients. Population simulated exposure at 30 mg b.i.d. in patients in Asia was similar to that at 50 mg b.i.d. in Western patients [geometric mean (coefficient of variation) steady state area under the concentration-time curve over the dosing interval ($AUC_{(0-\tau)}$): 21.4 μM.h (52.3%) and 24.1 μM.h (53.6%), respectively]. Exposure–AE relationships could be described for neutropenia, stomatitis and diarrhoea, supporting the lower dosage of alisertib in Asia for global clinical development.

CONCLUSIONS

Model-based simulations support the achievement of similar alisertib exposures in patients in Asia who are administered a 40% lower dose compared with the Western population, thereby providing a quantitative clinical pharmacology bridging and regional dosing rationale for global drug development.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Alisertib is an Aurora kinase A inhibitor in development for haematological and nonhaematological malignancies.
- Ethnic differences may affect a medication's pharmacokinetics and benefit–risk profile, making quantitative clinical pharmacological characterization of these effects important, to optimize dosage in global drug development.
- The maximum tolerated dose of alisertib is 50 mg twice daily and 30 mg twice daily, respectively, in Western and East Asian patients.

WHAT THIS STUDY ADDS

- This study provided a global population pharmacokinetic model for alisertib that quantitatively describes the sources of interpatient variability in pharmacokinetics and estimates the effect of the East Asian region on the apparent oral clearance of this agent, to support appropriate dosing recommendations for global drug development.

Introduction

The **Aurora kinases** are key regulators of mitosis and multiple signalling pathways. Alterations in Aurora kinase signalling are associated with mitotic errors and have been closely linked to chromosomal aneuploidy in cancer cells [1, 2]. Several studies have shown amplification and/or overexpression of **Aurora kinase A** (AAK) in haematological malignancies and solid tumours. AAK regulates several cell cycle events, including centrosome maturation, mitotic entry, centrosome separation, bipolar spindle assembly, alignment of chromosomes on the mitotic spindle, cytokinesis and mitotic exit. Inhibition of AAK results in mitotic spindle defects and delayed/abnormal mitotic progression, leading ultimately to apoptosis or senescence, making AAK a potential target in anticancer therapy [3–5]. **Alisertib** (MLN8237; Takeda Pharmaceuticals International Co., Cambridge, MA, USA), an investigational, oral, selective AAK inhibitor, is in clinical development for haematological and nonhematological malignancies [6].

In a phase I US study in adults with advanced solid tumours, the 50 mg twice-daily (b.i.d.) dose of alisertib, administered for 7 days in a 21-day cycle, was determined to be the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) for single-agent development [7]. A concurrent phase I study conducted in Spain in adults with metastatic and/or advanced solid tumours also concluded that the MTD and RP2D were 50 mg b.i.d. for 7 days [8]. Additional phase I studies conducted in Western countries have supported this dose regimen as MTD/RP2D [9, 10]. A phase I/II study conducted in four Western countries (the Czech Republic, France, Poland and the USA) in patients with breast cancer, small-cell lung cancer, nonsmall-cell lung cancer, head and neck squamous cell carcinoma, or gastro-oesophageal adenocarcinoma, utilizing the recommended phase II dose of alisertib, 50 mg twice daily for 7 days in a 21-day cycle, demonstrated a generally manageable toxicity profile and preliminary description of antitumour activity [11]. This alisertib dose regimen has since been tested in phase II Western studies, in which it was generally well tolerated and its clinical activity was demonstrated [12–14]. The most common treatment-emergent AEs of grade 3 or higher severity observed in ≥5% of patients treated with alisertib in this dosing regimen include stomatitis, diarrhoea, neutropenia, anaemia, thrombocytopenia, leukopenia, febrile neutropenia and fatigue. These AEs predominantly reflect the antiproliferative effects of alisertib on epithelial cells (e.g. stomatitis, diarrhoea) and bone marrow progenitor cells (e.g. neutropenia).

Initial clinical development of alisertib utilized a powder-in-capsule (PIC) immediate-release formulation, with subsequent transition to an enteric-coated tablet (ECT) which is currently used in ongoing clinical development. In Western patients, alisertib absorption is fast, with a median time from dosing to first occurrence of maximum serum concentration (T_{max}) of 2–3 h postdose and a mean steady-state half-life following multiple dosing of approximately 19–23 h [7–10]. A population pharmacokinetic (PK), pharmacodynamic (PD) and PK–safety analysis was performed to support phase II/III dose and regimen selection using data from these Western phase I and early phase II studies [7–10, 12–14]. Population PK analyses supported dose-linear and time-linear PK without identification of clinically meaningful covariates or a discernible difference in the bioavailability (F) of the PIC and ECT formulations. Exposure–safety analyses supported a low predicted incidence of dose-limiting toxicity at 50 mg b.i.d. [15].

In order to enable future globalization of alisertib development, consistent with the principles of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E5 (ICH E5) regulatory guidelines regarding ethnic differences in a medicine's safety, efficacy, dosage or dose regimen [16], a phase I study was conducted to determine the MTD and RP2D of oral alisertib in East Asian patients (in Singapore, Taiwan, Hong Kong and South Korea) with advanced solid tumours or lymphomas. Alisertib was administered b.i.d. for 7 days in 21-day cycles, with escalation proceeding from a starting dose of 30 mg b.i.d. and planned escalations to 40 mg b.i.d. and 50 mg b.i.d., dependent on tolerability. The 30 mg b.i.d. dose was defined as the MTD and the RP2D in East Asian patients. This lower dose in East Asian patients (30 mg b.i.d. *vs*. 50 mg b.i.d. in Western patients) was consistent with higher systemic exposures observed in the East Asian population and could be explained by the lower apparent oral clearance (CL/F) and higher dose-normalized systemic exposure of alisertib in East Asian patients. Alisertib was also generally well tolerated in East Asian patients;

commonly reported adverse events (AEs) included alopecia, diarrhoea, neutropenia and stomatitis [17].

Similar to what has been observed in Western patients, alisertib absorption in East Asian patients is fast following b.i.d. dosing, with a median T_{max} of 2–3 h postdose and a half-life of 15–17 h. Dose-normalized geometric mean steady-state exposures [area under the plasma concentration–time curve over the dosing interval ($AUC_{0-\tau}$)] were similar at the 30 mg b.i.d. and 40 mg b.i.d. dose levels, consistent with dose-linear PK. The mean CL/F of alisertib in East Asian patients (2.65 l h^{-1}) was approximately 40% lower than that in Western patients (4.39 l h^{-1}), which resulted in an approximately 70% higher geometric mean steady-state systemic exposure in East Asian patients. More than 75% of East Asian patients had dose-normalized systemic exposures that exceeded the median value of the Western population and >75% of Western patients had dose-normalized systemic exposures that were below the median value of the East Asian population [17].

The current global population PK analysis was conducted to describe quantitatively the sources of interpatient variability in alisertib PK based on data collected across 10 clinical trials of alisertib in multiple geographical regions (USA, Europe, Japan and other East Asian countries). A specific objective of the analysis was to estimate the effect of the Asian region/race on the CL/F of alisertib using a model-based approach, in order to support appropriate dosing recommendations for global drug development. Estimates of systemic exposures in individual patients from the present population PK analysis were used subsequently to explore potential relationships with the key AEs of alisertib reflecting its antiproliferative mechanism of action (incidence of grade ≥3 neutropenia, grade ≥2 stomatitis and grade ≥2 diarrhoea) in this global dataset comprising Western and Asian patients. These exposure-safety analyses were performed to describe the pharmacological relevance of the observed regional differences in alisertib PK in support of the Asian dose.

Methods

Patients and data collection

A summary of the phase I and phase I/II clinical studies in the current analysis is presented in Table 1. Alisertib was administered as a single agent at doses of 5–150 mg once daily (QD) or b.i.d. in these studies. In all studies, alisertib was administered under nil per os conditions, with patients advised to not eat from 2 h before until 1 h after dosing. Multiple dosing schedules (7, 14 or 21 days of dosing in 21-, 28- or 35-day treatment cycles, respectively) were evaluated in early phase I studies [7–9], whereas all other studies evaluated the current

Table 1

Studies contributing to population PK analysis

STUDY	Region	Cancer type	Data use	*n*	Form	Doses (mg)	Dose regimen	Max occasions#	Average PK samples/patient
C14001 (NCT00500903)[a]	West	Nonhaematological	Analysis	87	PIC, ECT	5 to 150	b.i.d., QD	3	21
C14002 (NCT00651664)[a]	West	Nonhaematological	Analysis	59	PIC	5 to 150	b.i.d., QD	3	18
C14003 (NCT00697346)[a]	West	Haematological	Analysis	58	PIC, ECT	25 to 90	b.i.d., QD	3	12
C14004 (NCT00807495)[b]	West	Haematological	Analysis	48	PIC	25, 50	b.i.d.	3	4
C14005 (NCT00830518)[b]	West	Haematological	Analysis	57	PIC	50	b.i.d.	2	4
C14006 (NCT00853307)[b]	West	Nonhaematological	Analysis	31	PIC	25, 40, 50	b.i.d.	3	5
C14007 (NCT01045421) phase 1[a]	West	Nonhaematological	Analysis	24	ECT	10 to 60	b.i.d.	3	21
C14013 (NCT01512758)[a]	East Asia	Haematological and nonhaematological	Analysis	36	ECT	30,40	b.i.d.	2	22
TB-MA010030 (JapicCTI-101 320)[a]	Japan	Nonhaematological	Analysis	14	ECT	20, 30, 40	b.i.d.	2	22
TB-MA010033 (JapicCTI-121 841)[a]	Japan	Haematological	Analysis	9	ECT	20, 30	b.i.d.	2	23
C14007 (NCT01045421) phase 2[b]	West	Nonhaematological	Validation	249	ECT	50	b.i.d.	1	4

b.i.d., twice daily; ECT, enteric-coated tablet; PIC, powder-in-capsule; PK, pharmacokinetic; QD, once daily

[a]Rich PK data from serial PK sampling in phase I studies

[b]Sparse PK data from phase II studies

recommended single-agent dosing schedule of 7 days of dosing in 21-day treatment cycles. The clinical protocols were approved by the Institutional Review Board or Independent Ethics Committee for each site, and informed consent was obtained from all patients prior to enrolment. The current population PK analysis consisted of data from 671 patients enrolled in six phase I clinical studies, one phase I/II clinical study and three phase II clinical studies of alisertib [seven studies in Western countries; two studies in Japan; and one study in other East Asian countries (Singapore, Taiwan, Hong Kong and South Korea)]. The data were separated into an analysis set consisting of rich and sparse PK data (n = 422) for model development and an external validation set consisting of sparse data (n = 249) for model validation (Table 1) [18].

Most patients received multiple-dose oral administration of alisertib over multiple treatment cycles, with PK data collected on up to three different occasions in each patient. Patients' baseline continuous covariate data are summarized by data set in Table 2. Patients' categorical covariate data are summarized by data set in Table 3. Genotyping was performed for the UDP glucuronosyltransferase 1 family, polypeptide A1 (*UGT1A1*) gene variant alleles *28 and *6 on DNA isolated from whole-blood samples using previously described polymerase chain reaction methods [15].

PK sampling and sample analysis

Plasma PK sampling schemes were dense in phase I studies and sparse in the phase II studies. In the phase I studies, serial PK samples were collected following the first dose of alisertib in cycle 1 and following repeat dose administration (e.g. over the day 7 dosing interval), including the washout (disposition) phase during the rest period after cessation of multiple-dose treatment. Sparse PK sampling schemes varied across the phase II studies and typically included a limited number of samples collected over 3 h following the first dose of alisertib on cycle 1, day 1 and a combination of trough (predose) samples and random samples collected at the time of clinic visits during multiple-dose treatment in cycles 1–3. Actual dosing and sampling times were recorded and utilized in the population PK analysis. Additional details of the PK sampling schedules in each study are summarized in Table 1. Plasma concentrations of alisertib were measured using a previously described validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay [7]. The dynamic range of the alisertib LC/MS/MS method was 5–2500 ng ml^{-1}. Across these studies, the assay precision ranged from 2.6% to 11%, and accuracy ranged from −1.0% to 2.0%.

Population PK modelling

Population modelling was performed using NONMEM Version VII level 2 (Icon Development Solutions, Dublin, Ireland) with Intel® Visual Fortran Intel® 64 Compiler XE, Version 12.0.0.104 Build 20 101 006 (Santa Clara, CA, USA). The R data analysis language (Version 2.15.1 or greater) was used for most graphical output and data manipulation. The remaining graphical output and data manipulation were performed using Microsoft® Excel 2003 or later. A log-transform-both-sides approach was used and parameter estimation was performed using the stochastic approximation expectation-maximization (SAEM) estimation method. Importance sampling was used to estimate final objective function values and parameter precision. One-, two- and three-compartment PK models with first-order absorption (with and without lag time) or transit compartment oral absorption models were evaluated. Interpatient population parameter variability was described using an exponential error model, and a combined proportional and additive residual error model was used. Structural PK model selection was guided by the results of a previous population PK analysis [15]. Goodness of fit was judged by diagnostic plots and changes in the minimum objective function value and the Akaike information criterion (AIC) for comparing structural models. A reduction in AIC of 2 or more was used to declare a model being a substantially better fit of the data. Continuous covariate–parameter relationships [e.g. body surface area (BSA), age] were modelled as power functions referenced to a median/standard value, and

Table 2

Patient characteristics: baseline continuous covariates

Covariate	Combined data set (n = 671) Median (min, max)	Analysis data set (n = 422)	Validation data set[a] (n = 249)
Age, years	62 (21, 88)	62 (21, 85)	61 (30, 88)
Body weight, kg	74.0 (40.8, 205.0)	73.3 (42.6, 175.0)	74.1 (40.8, 205.0)
BSA, m^2	1.84 (1.34, 3.28)	1.84 (1.36, 2.97)	1.87 (1.34, 3.28)
BMI, kg m^{-2}	25.7 (14.9, 61.0)	25.8 (17.1, 61.0)	25.5 (14.9, 57.5)
Creatinine clearance, ml min^{-1}	85.3 (24.7, 409.0)	83.2 (27.1, 241.0)	89.7 (24.7, 409.0)
Bilirubin, mmol l^{-1}	7.0 (1.71, 345.0)	7.0 (1.71, 38.0)	7.0 (2.0, 345.0)
ALT, U l^{-1}	21.0 (5.0, 342.0)	22.0 (5.0, 229.0)	19.0 (5.0, 342.0)
AST, U l^{-1}	25.0 (7.0, 384.0)	26.0 (9.0, 341.0)	23.0 (7.0, 384.0)
Plasma albumin, g l^{-1}	40.0 (20.0, 51.4)	40 (20.0, 51.4)	40.0 (25.0, 48.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area
[a]Validation data set comprises the phase II portion of study C14007

Table 3

Patient characteristics: categorical covariates

Covariate	Category	Combined data set (*n* = 671) *n* (%)	Analysis data set (*n* = 422)	Validation data set[a] (*n* = 249)
Gender	Male/female	367 (55) / 304 (45)	226 (54)/196 (46)	141 (57)/108 (43)
Race	Asian – All East	59 (8)	59 (14)	0
	Asian – Chinese	22 (3)	22 (5)	0
	Asian – Japanese	23 (3)	23 (5)	0
	Asian – Korean	13 (2)	13 (3)	0
	Asian – Other	1 (<1)	1 (<1)	0
	Asian – West	8 (1)	5 (1)	3 (1)
	White	556 (83)	326 (77)	230 (92)
	Black	33 (5)	21 (5)	12 (5)
	Missing	8 (1)	7 (2)	1 (<1)
	Other	7 (1)	4 (1)	3 (1)
Region	West	612 (91)	363 (86)	249 (100)
	East	59 (9)	59 (14)	0
Region (race)	East (Asian)	59 (9)	59 (14)	0
	West (Asian)	8 (1)	5 (1)	3 (1)
	West (Non-Asian)	604 (90)	358 (85)	246 (99)
Alisertib formulation	PIC	299 (45)	299 (71)	0
	ECT	372 (55)	123 (29)	249 (100)
Ethnicity	Hispanic	93 (14)	84 (20)	9 (4)
	Non-Hispanic	578 (86)	338 (80)	240 (96)
UGT1A1*28 alleles, n	Not known	293 (44)	44 (10)	249 (100)
	0	203 (30)	203 (48)	0
	1	138 (21)	138 (33)	0
	2	37 (6)	37 (9)	0
UGT1A1*6* alleles, *n	Not known	621 (93)	372 (88)	249 (100)
	0	36 (5)	36 (9)	0
	1	11 (2)	11 (3)	0
	2	3 (<1)	3 (1)	0
Cancer type	Nonhaematological	490 (73)	241 (57)	249 (100)
	Haematological	181 (27)	181 (43)	0

East (Asian): patients of Asian race living in East Asia region; West (Asian): patients of Asian race living in Western region; West (Non-Asian): patients of non-Asian race living in Western region. ECT, enteric-coated tablet; PIC, powder-in-capsule; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1

[a]Validation data set comprises the phase II portion of study C14007

categorical covariate effects (e.g. region, race, gender) were modelled as dichotomous/multichotomous relationships. Covariate selection was performed by forward addition (P = 0.01) and backward deletion (P = 0.001). The addition of parameters and covariates was also assessed by their ability to reduce interindividual variability terms. Various diagnostic plots were used to assess model performance. Inclusion of a covariate in the final model was guided additionally by precision of the estimated covariate effect on the parameter (relative standard error of the estimate <51.2% required to justify inclusion, to ensure that only covariates that were estimated with reasonable precision were carried forward into the final model), and clinical relevance was assessed by its contribution to overall parameter variability (i.e. decrease in interpatient variance by >5% required to justify inclusion). Other considerations used to guide final model selection included model stability and shrinkage of the empirical Bayes estimates of key model parameters (e.g. CL/F). Model stability was first tested by the ability of the models to pass the covariance step of NONMEM 7.2, with the failure to pass the covariance step taken as an indication that the model had parameters estimated with poor precision. Models that passed the covariance step were further tested through evaluation of the model condition number, which was calculated as the square root of the ratio of the largest to the smallest eigenvalue of the correlation matrix. A condition number ≤20 suggested that the degree of collinearity between the parameter estimates was acceptable. A condition number ≥100 indicated potential instability due to high collinearity, implying difficulties with independent estimation of highly collinear parameters.

Base models were developed in two stages. First models used the basic form of the structural model (one-, two- or three-compartment), including oral absorption models (stage 1). In addition, the between-subject variability (BSV) structure was assessed. BSV was included on all parameters by default. The effect of removing BSV from apparent intercompartmental clearance (Q/F) was examined. Models were ranked by AIC and the most suitable model was carried forward at each stage, as determined by the model selection criteria.

The best base model was carried forward for an analysis of the effects of covariates (stage 2). A set of clinically important covariate relationships for evaluation were specified *a priori* and were examined systematically, and covariate analysis proceeded by examining separately the influence of each covariate alone on each model parameter (Table 4). The resulting univariate covariate models were ranked by the *P*-value for the likelihood ratio test comparison with the base model (adjusted for the number of additional parameters in the covariate model). Those with a *P*-value of less than 0.01 were considered in more detail.

Multivariate models with all covariate relationships were then examined. The model with all selected candidate covariate relationships was declared the 'full' model, and was subjected to a backward elimination process using a *P*-value of 0.001. A covariate was therefore considered significant if the *P*-value for removing it from the full model was less than 0.001. The choice of the final covariate model was based on models that had a statistically significant improvement in the objective function value, passed the covariance step and had a condition number less than 20, had precise estimates of the covariate parameter (asymptotic standard error [se%] <51.2%), and reduced the BSV of the associated population parameters to a clinically important extent (e.g. >5% reduction in BSV).

The predictive performance of the final model was evaluated using visual predictive checks (VPCs; based on simulations of 200 versions of the analysis data set, representing 84 600 virtual patients) of dose-normalized concentration–time profiles stratified by region, and concentration–time profiles stratified by dose and region. The predictive performance of the model was considered to be acceptable if the time courses of the median simulated and observed data were similar, with no important systematic deviations, and the majority of the original data points lay inside the prediction intervals. Parameter precision estimates [95% confidence intervals (CIs)] were derived by nonparametric bootstrapping (n = 1000).

The final model (Figure 1) included a covariate effect of region on F, with patients in the East Asian region estimated to have a 52% higher F compared with Western patients. Therefore, simulations were performed using the final population PK model to evaluate the appropriateness of a reduced dose of alisertib in achieving systemic exposures that approximately matched those achieved upon dosing at the recommended phase III dose of 50 mg b.i.d. in Western patients. The final model was used to simulate the dosing of Western patients (50 mg b.i.d.) and patients in the East Asian region (30 mg b.i.d.) for 7 days followed by 14 days off.

Exposure–safety analyses

Alisertib exposure–safety relationships were evaluated for three toxicities of interest: grade ≥3 neutropenia, grade ≥2 stomatitis and grade ≥2 diarrhoea, which were among the most common treatment-emergent AEs and representative of mechanism-related antiproliferative toxicities. Alisertib time-averaged systemic exposures (AUC per day) were calculated for each patient from the start of alisertib dosing up to the start of the worst grade of the toxicity of interest while on treatment. The calculation of overall time-average exposure (AUC per day) for each patient was based on the actual administered doses (i.e. considering dose modifications) and individual estimates of CL/F from the population PK model. Logistic regression (TIBCO Spotfire S + ® Version 8.1, Palo Alto, CA, USA) was used to evaluate relationships between the log-transformed time-averaged alisertib AUC and incidence of grade ≥3 neutropenia (n = 591), grade ≥2 stomatitis (n = 593) and grade ≥2 diarrhoea (n = 594) following alisertib administration in the 7-day schedule.

Nomenclature of targets and ligands

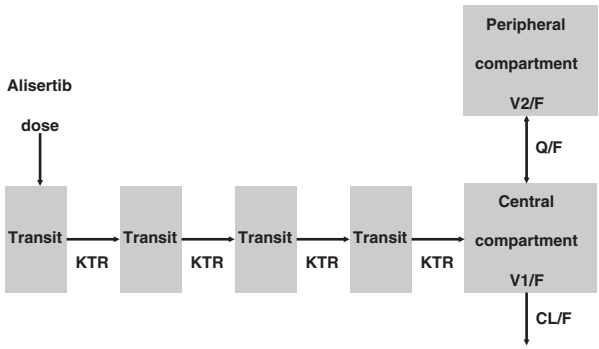
Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [19], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [20].

Table 4

Planned covariate evaluations

Parameter	Covariates
CL/F	Age, weight, BSA, bilirubin, ALT, AST, ALB, CCL, BILI, use of strong or moderate CYP3A inhibitors, *UGT1A1* genotype (number of *28 or *6 alleles), gender, race (particularly Asian), region (East *vs*. West)
V1/F	Weight, BSA, ALB, gender
V2/F	Weight, BSA, ALB, gender
Ka, Lag or KTR	Formulation
F	Formulation, region, race

ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; BSA, body surface area; CCL, creatinine clearance; CL/F, apparent clearance; CYP3A, cytochrome P450 3A4/5; F, bioavailability; Ka, first-order absorption rate constant; KTR, transit compartment rate constant; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1; V1/F, apparent central volume; V2/F, apparent peripheral volume



CL/F = Population (CL/F) x $e^{IIV(CL/F)}$ x (1+f)

V1/F = Population (V1/F) x$e^{IIV(V1/F)}$ x (1+f) x (BSA/1.84)^{BSAV1}

Q/F = Population (Q/F) x (1+f)

V2/F = Population (V2/F) x $e^{IIV(V2/F)}$ x (1+f)

KTR = Population (KTR) x $e^{IIV(KTR)}$

if Region = West, f = 0;

if Region = East (i.e. Asia/Japan), f=RGNF

Figure 1

Schematic representation of the population pharmacokinetic model of alisertib. BSA, body surface area; BSAV, effect of BSA on V1/F; CL/F apparent clearance; KTR, transit compartment rate constant; Q/F, apparent intercompartment clearance; V1/F, apparent central volume; V2/F, apparent peripheral volume; RGNF, effect of region

Results

Population PK model

Alisertib PK was described by a two-compartment model [CL/F 4.11 l h^{-1}; interpatient coefficient of variation (CV): 51.8%] with four-transit-compartment absorption and linear elimination (Table 5). The overall population PK model is summarized in Figure 1. BSV was used on the parameters CL/F, apparent central distribution volume (V1/F), apparent peripheral distribution volume (V2/F) and absorption transit compartment rate constant (KTR) with a full omega block. There was a covariate effect of BSA on V1/F and region (West/East) on F. The population alpha and beta half-lives of alisertib were 1.71 h and 15.1 h, respectively. The absorption transit rate constant was 4.17 1 h^{-1}. The net mean transit time for oral absorption was 0.96 h. All model parameters, including BSV values, were estimated with acceptable precision (Table 5). The VPCs of the time course of dose-normalized alisertib concentrations demonstrated that the model was able to simulate the observed data with acceptable accuracy and could therefore be used for simulation of alisertib PK and exposure metrics.

The post-hoc CL/F values estimated for the validation data using the final model had a bias of 10.9% and a precision of 23.7%, with CL/F being lower for the validation data than predicted from the analysis data. This suggests that CL/F was 10.9% lower, or F 10.9% higher, for the patients in the validation set than for those in the analysis data set. The CL/F value corresponding to peak density was lower than population CL/F, consistent with the 10.9% bias identified. This difference was considered unimportant, given the 52% BSV for CL/F in the population. There were no substantial differences in the density distributions when conditioned on the covariate values, suggesting that there were no major covariate influences on CL/F for the validation data that were not identified during the modelling of the analysis data. The parameter values for this model (designated the updated final model; Table S1) were not substantially different from those of the final model from the model development phase (Table 5), with the fixed and random-effect parameters differing by no more than 10%.

In the final population PK model, region (East Asia *vs.* West) was identified as a statistically significant covariate on all apparent clearance (CL/F, Q/F) and volume (V1/F, V2/F) parameters, indicating a 51.7% (95% CI 36.5%, 70.1%) higher F in the East Asian region.

The effects of BSA on V1/F and the region effect on F (i.e. CL/F, V1/F and V2/F) are adequately accounted for in the final model (Figure 2). Figure 3 presents the VPCs of dose-normalized alisertib concentration by region, in the West region at the Western MTD, and in the East Asian region at the MTD in Asia. All 1000 bootstrap model runs converged successfully. There was general agreement between parameter estimates obtained from the model fit and covariance matrix, and by the bootstrap analysis.

Effects of BSA on alisertib PK

BSA was a statistically significant covariate on V1/F but not on CL/F. As BSA was not found to affect alisertib CL/F, the overall systemic exposure of alisertib (AUC) is not impacted by BSA. However, patients with a lower BSA were predicted to have modestly higher maximum serum concentration (C_{max}) values and a wider fluctuation in concentration between doses (Figure 4). The population peak-to-trough ratios for the steady-state interdose interval were 2.08, 1.88 and 1.68 for the 2.5th, 50th, and 97.5th percentile BSA,

Table 5

Final model parameters

Parameter	Description	Pop value	SE, %	IIV, ratio	SE, %	ETA shrinkage, %
CL/F	Apparent clearance, l h^{-1}	4.11	3.1	0.518	10.3	6.8
V1/F	Apparent central volume, l	54.3	3.9	0.412	15.8	26.9
Q/F	Apparent intercompartment clearance, l h^{-1}	7.07	10.9	–	–	–
V2/F	Apparent peripheral volume, l	28.7	10	1.044	11.6	25.3
KTR	Transit compartment rate constant, 1 h^{-1}	4.17	3	0.54	17.5	18.0
RGNF	Effect of region	−0.341[a]	11	–	–	–
BSAV1	Effect of BSA on V1/F	0.899	26.3	–	–	–
CCV	Proportional residual error, ratio	0.491	3.5	–	–	–
ADD	Additive residual error, nmol l^{-1}	0[b]	FIXED	–	–	–

Correlation	CL/F	V1/F	V2/F	KTR
CL/F	1			
V1/F	0.582			
V2/F	0.509	0.085		
KTR	0.116	0.255	−0.025	1

BSA, body surface area; ETA, empirical Bayes estimate of the interindividual random effect; IIV: interindividual variability; SAEM, stochastic approximation expectation maximization; SE, standard error

[a]0.341 indicates that the affected parameters were multiplied by (1–0.341) for the East Asian region (i.e. CL/F, V1/F, V2/F and Q/F were 34.1% lower in the East Asian region, reflecting 52% higher bioavailability)

[b]Automatically set to zero by the SAEM estimation algorithm

respectively. As BSA was not identified as a covariate on alisertib CL/F, the effect of region (Asia *vs*. West) in the final model is not explained by a lower BSA distribution in Asian patients. Importantly, when viewed in the context of overall variability in alisertib steady-state peak (45–52% CV) and trough concentrations (59–77% CV), simulations showed no clinically meaningful differences (<15% differences in steady-state peak and trough alisertib concentrations) between the 2.5th and 97.5th percentile BSA groups (Figure 4).

Effects of region and race on alisertib PK

The dose-normalized steady-state alisertib $AUCs_{(0-\tau)}$ in patients in East Asia were 65% higher than those in Western patients (Table 6).

As summarized in Table 6, GM (CV) dose-normalized alisertib $AUC_{(0-\tau)}$ (nM.h) in Asian patients in the West [475 (43%); n = 8] were comparable to those in non-Asian patients in the West [482 (43%); n = 604], but not to Asian patients in Asia [797 (45%); n = 59]. This is consistent with the lower CL/F of alisertib in East Asia compared with patients in the West, and a similar distribution of CL/F in Asian and non-Asian patients in the West (Figure 5, panel A). These observations suggest a contribution of extrinsic factor(s) to the higher bioavailability observed in Asian patients in East Asia. The distributions of alisertib CL/F were similar across Japanese, Chinese and Korean patients in Asia (Figure 5, panel B), consistent with similar dose-normalized exposures in these Asian races (Table 6).

Simulation of exposure-matched regional dosing

Population simulated alisertib concentrations (for a dose regimen of b.i.d. dosing for 7 days in a 21-day cycle) showed that 30 mg b.i.d. for patients in the East Asian region produced a time course of alisertib concentrations and AUC substantially similar to patients in the West who were given 50 mg doses (Figure 6). One thousand virtual patients in the West (geometric mean BSA: 1.88 m^2, BSA log standard deviation: 0.135, 50 mg b.i.d.) and 1000 patients in East Asia (geometric mean BSA: 1.63 m^2, BSA log standard deviation: 0.0862, 30 mg b.i.d.) were simulated using the final parameter values of the final PK model. Population simulated exposure at 30 mg b.i.d. in patients in East Asia was similar to that at 50 mg b.i.d. in Western patients [GM (CV) steady-state $AUC_{(0-\tau)}$: 21.4 μM.h (52.3%) and 24.1 μM.h (53.6%), respectively]. Therefore, dosing at a 40% lower dose of 30 mg b.i.d. in East Asia/Japan can be expected adequately to match systemic exposures achieved at the 50 mg b.i.d. Western MTD (Figure 6).

Exposure–safety relationships

Common treatment-emergent AEs of alisertib include neutropenia, stomatitis and diarrhoea, reflecting its antiproliferative effects as a cytotoxic agent [11, 13]. The time-averaged alisertib AUC was a statistically significant predictor (P < 0.0001) of the probability of grade ≥3 neutropenia, grade ≥2 stomatitis and grade ≥2 diarrhoea, following administration of 5–200 mg day^{-1} alisertib in the 7-day

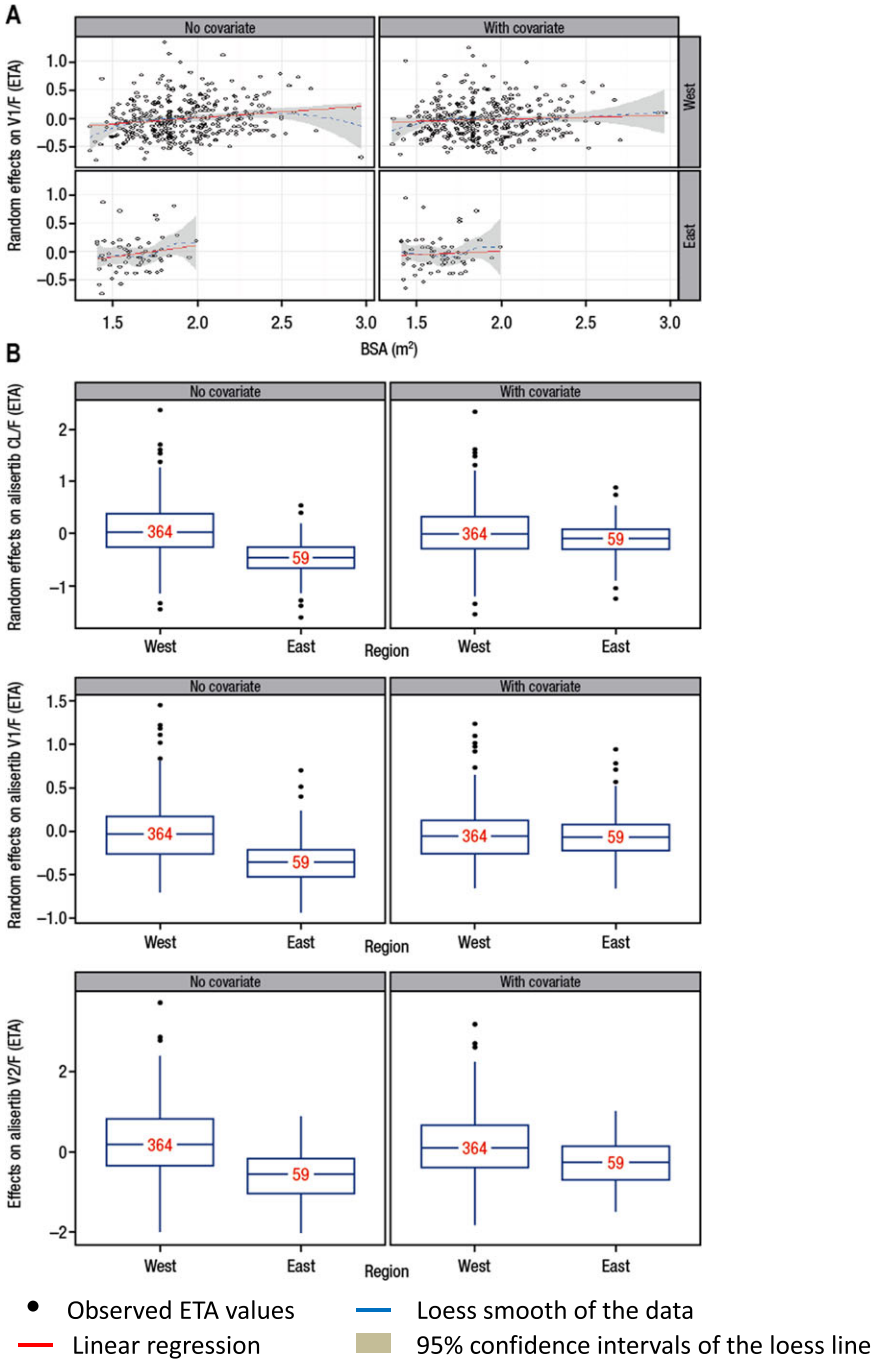


Figure 2

Evaluation of covariate effects in the final population pharmacokinetic model of alisertib. (A) Relationships between empirical Bayes estimates of the interindividual random effect (ETA) for apparent central volume (V1/F) and body surface area (BSA) in the final model without (left) and with (right) the covariate relationship, with the upper and lower panels for Western countries and East Asian regions, respectively. (B) Relationships between empirical Bayes estimates of the interindividual random effect (ETA) for apparent clearance (CL/F), apparent central volume (V1/F) and apparent peripheral volume (V2/F), and region in the final model. Left and right panels show boxplots of ETA for each covariate category for the final model without and with the covariate, respectively. Numbers in the boxplots show the number of patients in each category. The region 'East' refers to East Asian countries (Taiwan, Hong Kong and South Korea) and Japan

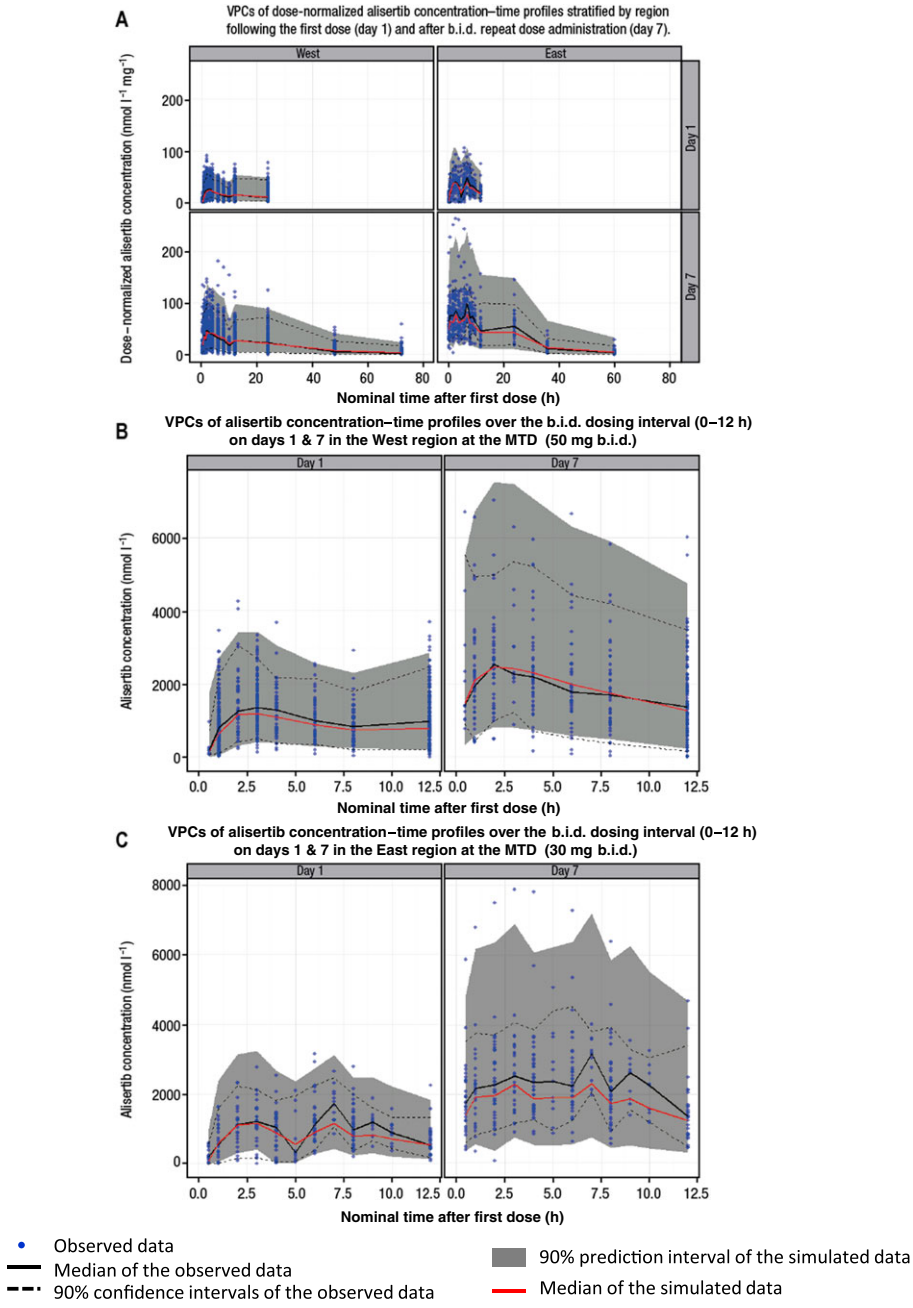
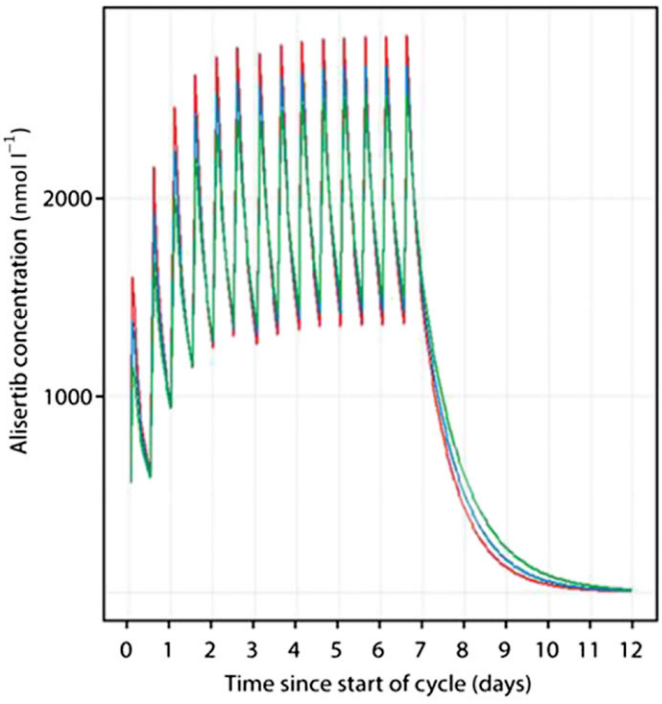


Figure 3

Visual predictive checks (VPCs) of alisertib concentration–time data following b.i.d. administration in 7-day dosing schedules. (A) VPCs of dose-normalized concentrations stratified by region and day. (B and C) VPCs of concentrations at the maximum tolerated doses (MTDs) of 50 mg b.i.d. in the West and 30 mg b.i.d. in Asia, respectively.

dosing schedule (Figure 7) [15]. At the Western RP2D of 50 mg b.i.d. (estimated population mean time-averaged AUCs of 15.63 μM*h day^{-1} and 23.72 μM*h day^{-1} for patients in the West and in East Asia, respectively), the predicted probabilities of experiencing grade ≥3 neutropenia in patients in the West *vs*. East Asia were 39% (95% CI 34%, 44%) and 46% (95% CI 41%, 50%), respectively. At the RP2D of 50 mg b.i.d., the estimated probabilities of experiencing grade ≥2 stomatitis in patients in the West *vs*. East Asia were 7% (95% CI 5%, 10%) and 13% (95% CI 10%, 16%), respectively. The estimated probabilities of grade ≥2 diarrhoea in patients in the West *vs*. East Asia were 13% (95% CI 10%, 17%) and 17% (95% CI 14%, 20%), respectively. However, at the RP2D of alisertib of 30 mg b.i.d. determined for patients in East Asia (estimated population mean time-averaged AUC of 14.23 μM*h day^{-1}), the estimated probabilities of these AEs (37% for grade ≥3 neutropenia, 6.5% grade ≥2 stomatitis, 12% grade ≥2 diarrhoea) were comparable with those estimated for Western patients at the 50 mg b.i.d. dose.



BSA	Geometric mean $C_{max,ss}$, nmol l^{-1} (CV, %)	Geometric mean $C_{min,ss}$, nmol l^{-1} (CV, %)
2.5 pct (1.44 m^2)	2740 (51)	1270 (77)
50 pct (1.84 m^2)	2550 (52)	1340 (70)
97.5 pct (2.43 m^2)	2420 (45)	1370 (59)

Figure 4

Effect of body surface area (BSA) on alisertib concentration–time profiles as assessed using simulations from the final population pharmacokinetic model (n = 200 Western patients each at the 2.5th, 50th and 97.5th percentiles (pct) of the BSA distribution). The inset shows the geometric mean (% CV) of steady-state peak ($C_{max,ss}$) and trough ($C_{min,ss}$) alisertib plasma concentrations in the three BSA groups

Table 6

Alisertib dose-normalized exposure by region and race

Region	Race	n	Geometric mean (%CV) dose-normalized alisertib $AUC_{0-\tau,ss}$ (nM.h mg^{-1})
East	All (Japanese, Korean, Chinese)	59	797 (45)
	Japanese	23	799 (34)
	Korean	13	885 (53)
	Chinese	22	752 (48)
West	All	612	482 (43)
	All non-Asian races	604	482 (43)
	White	556	482 (43)
	Black	33	462 (57)
	Asian	8	475 (43)

$AUC_{0-\tau,ss}$, area under the concentration–time curve from time zero to end of the dosing period at steady state; CV, coefficient of variation

Discussion

Globalization of clinical development inclusive of Asia is on the rise, especially for investigational anticancer agents, in an effort to decrease the lag in access to drugs in the Asian region and improve drug development efficiency through broader access to patients worldwide [21]. However, ethnic, racial and/ or regional differences in intrinsic and/or extrinsic factors may affect a medication's safety, efficacy, dosage and dose regimen in a new, previously untested region. This makes characterization of the effects of race/region on PK/PD and safety crucial ahead of clinical trial globalization [16, 22–25]. This is especially important for anticancer agents associated with a narrow therapeutic range as modest differences in systemic exposures between Asian and Western patient populations can translate to

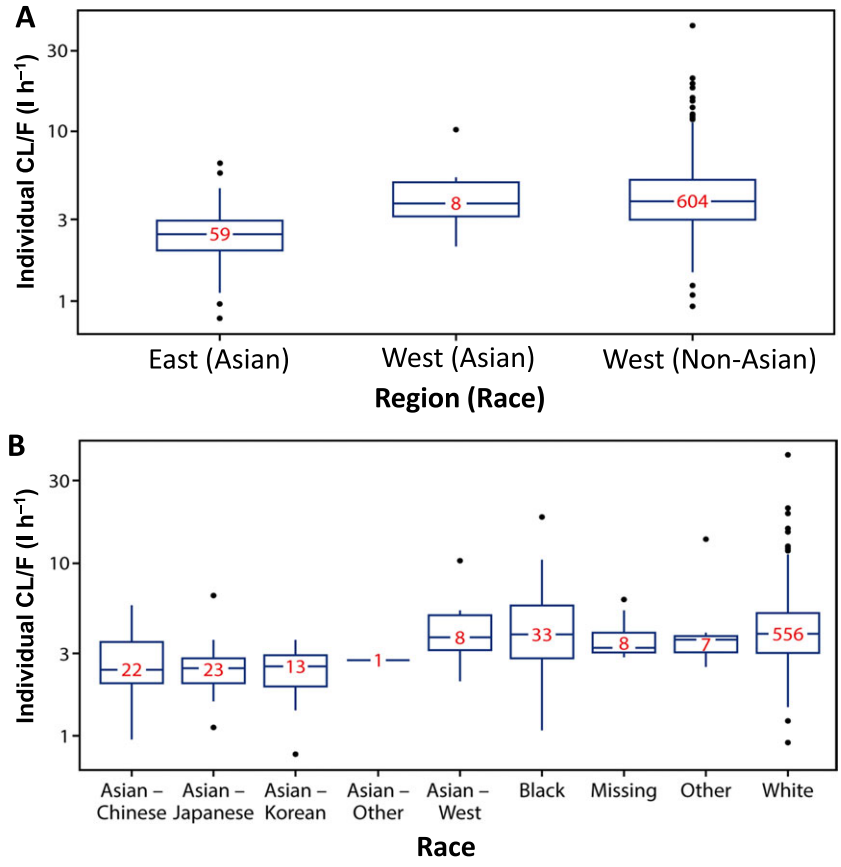


Figure 5

Effects of region and race on alisertib apparent clearance (CL/F) based on the updated final model (analysis and validation data sets combined). (A) Box plots of CL/F distributions by region and race. (B) Box plots of CL/F distributions by race. The 'West (Asian)' category in (A) and 'Asian – West' category in (B) refer to the eight patients in the data set that were of Asian race in the Western region

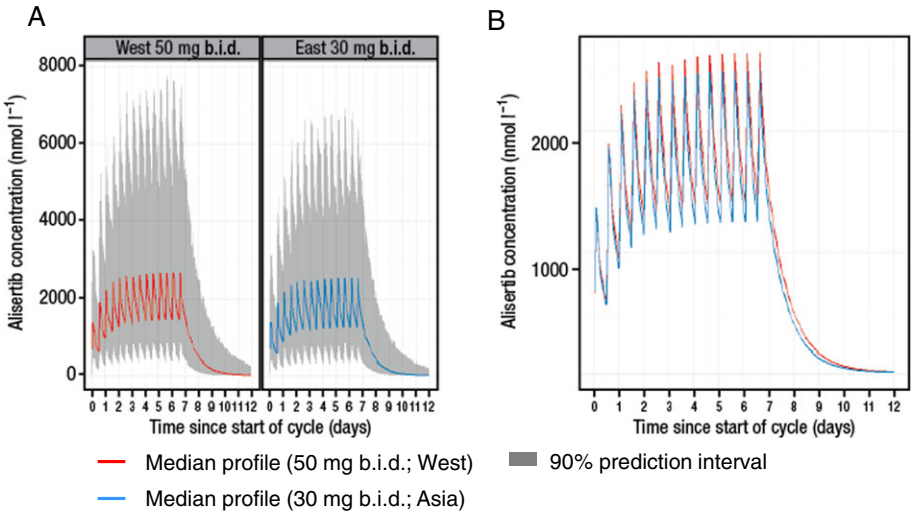


Figure 6

Qualification of 30 mg twice-daily (b.i.d.) alisertib in Asia/Japan as an exposure-matching dose regimen to 50 mg b.i.d. in the West, based on simulations from the final population pharmacokinetic model (n = 1000 per region administered on a 7-day dosing schedule).

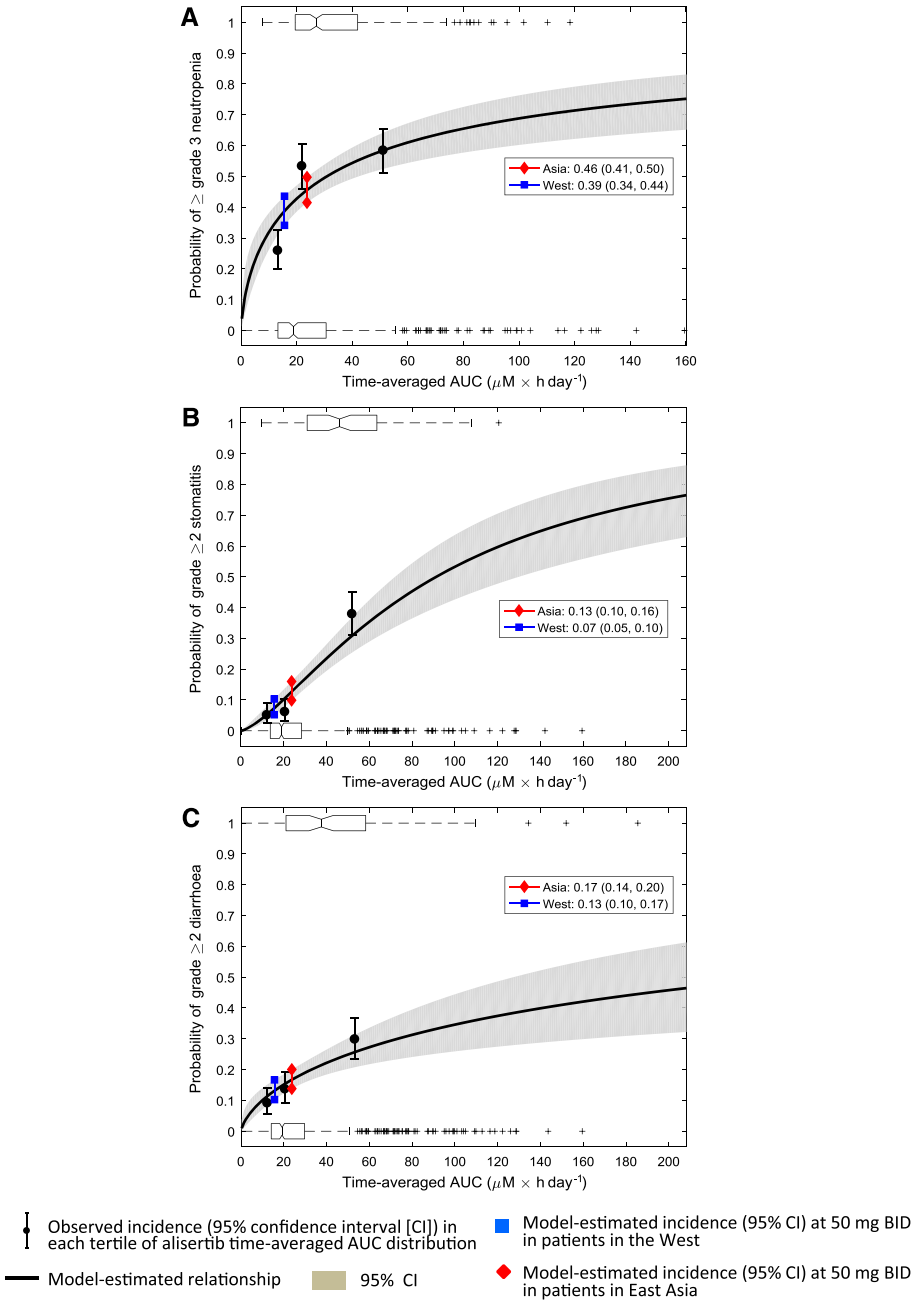


Figure 7

Alisertib exposure–safety relationships estimated using logistic regression analyses. (A–C) Relationships between alisertib time-averaged exposure and the incidence of grade ≥3 neutropenia ($n = 591$ patients, $P < 0.001$), grade ≥2 stomatitis ($n = 593$ patients, $P < 0.001$) and grade ≥2 diarrhoea ($n = 594$ patients, $P < 0.001$). The box plots show the distributions of alisertib time-averaged area under the curve (AUC) in patients who experienced (Yes = 1) or did not experience (No = 0) the toxicity of interest. The notches in the boxes mark the 95% confidence intervals of the medians of the alisertib time-averaged AUC in each group, and the whiskers represent the 10th and 90th percentiles

meaningful differences in the safety profile in the setting of a steep exposure–toxicity relationship [26]. The sources of potential differences in drug exposure between Asian and Western patient populations can be multi-factorial, including intrinsic (e.g. differences in body weight, genetic polymorphisms in drug metabolizing enzymes) and extrinsic (e.g. dietary/environmental) factors [27]. A quantitative characterization of sources of PK variability and assessment of the clinical significance of any observed effects of race/region on systemic exposure are crucial in order to underwrite appropriate dosing of investigational anticancer agents in global clinical trials.

Alisertib is an investigational orally administered selective AAK inhibitor in clinical development for the

treatment of haematological and nonhaematological malignancies. An MTD/RP2D of 50 mg b.i.d. administered for 7 days in 21-day treatment cycles was determined in the phase I single-agent setting in the USA and Europe [7–10]. Population PK, exposure–PD and exposure–safety analyses conducted using data obtained across the Western clinical development programme supported achievement of bioactive exposures associated with robust PD effects of decreased chromosome alignment and spindle bipolarity in mitotic tumour cells, while providing acceptable tolerability [15]. A subsequent dose-escalation phase I PK and safety study was conducted in Korean and Chinese cancer patients in South Korea, Taiwan, Hong Kong and Singapore, to enable the globalization of clinical development of this molecule, including Asia [17]. The MTD in the East Asia phase I study was determined to be 30 mg b.i.d. [17]. The safety profile of the East Asia MTD/RP2D (30 mg b.i.d.) was similar to that of the Western MTD (50 mg b.i.d.), with the differences in MTD between the regions explained by higher dose-normalized systemic exposures of alisertib observed in the East Asia phase I study compared with historical Western phase I PK data [17].

Given the regional differences in alisertib PK and MTD that were discovered during phase I clinical evaluation in East Asia, the objectives of the current population PK analysis were to quantitatively evaluate the sources of PK variability in the global dataset acquired during the phase I and phase II clinical development programme of alisertib. A population PK model was developed and evaluated to investigate the differences in kinetics between geographical regions and for patients who were Asian *vs*. those of other races, utilizing data from 10 clinical trials that included PK assessments of alisertib from Western countries (seven trials) and from the East Asian region (three trials).

The PK of alisertib were described by a two-compartment model with linear elimination kinetics and a four-transit-compartment absorption model. Body weight, BSA, UGT1A1 genotype, creatinine clearance, gender, age, race, and alanine aminotransferase, aspartate aminotransferase and bilirubin levels were not important in explaining the variability in the apparent oral clearance of alisertib. The predominant covariate effect identified in the analysis was an effect of region on alisertib relative bioavailability. Region (East Asia *vs* Western countries) was a covariate on all apparent clearance and volume parameters, consistent with a 52% higher relative bioavailability in patients in East Asia relative to Western patients.

The observed differences could have been attributed to differences in race (Asian *vs*. non-Asian) or differences due to region (East Asia *vs*. the West) itself, such as diet or other extrinsic factors. Data from the Asian patients from the West were important for differentiating between these possibilities. Using a multivariate covariate model selection process, it was concluded that the difference in bioavailability in the East Asian patients was not directly attributable to the characteristics of patients identifying as being of the Asian race. This conclusion is supported by the post-hoc CL/F values when plotted by region and race, where the Asian patients in Western countries appeared to group better with Western non-Asians than Asians in East Asia and Japan (Figure 5, panel A). It should be noted that this analysis included only eight patients of Asian race living in the West. As such, the available data preclude a conclusive attribution of race *vs*. region effects to the observed difference in F for alisertib. Additional data from global populations, ideally including patients of non-Asian race (e.g. Caucasian) living in East Asia, will be valuable to definitively characterize the relative contributions of race *vs*. other region-related extrinsic factors on alisertib PK. The factors contributing to the difference in relative bioavailability of alisertib by region are not readily determined from the present data set. Nevertheless, the identification of a region effect on F in this population PK analysis is entirely consistent with the observed higher steady-state AUC of alisertib in the East Asian *vs*. Western regions without observation of a correspondingly longer terminal half-life.

There was a covariate effect of BSA on V1/F but the CL/F of alisertib was unaffected by body weight or BSA, suggesting that interpatient variability in body size in an adult patient population would have minimal impact on exposure following administration of fixed doses of alisertib, supporting the use of fixed dosing in any ongoing or future clinical studies. Further, the lack of a body size/weight effect on CL/F supports the conclusion that the observed difference in F between regions is not explainable by the lower BSA/body weight distribution in patients in East Asian countries compared with Western countries. Additionally, the lack of an effect of creatinine clearance ($\geq$ 27 ml min^{-1}) on alisertib CL/F supports the conclusion of the lack of clinically meaningful effects of mild or moderate renal impairment on alisertib exposure.

The metabolism of alisertib in human liver microsomes is mediated through a combination of oxidative and glucuronidation pathways of metabolism, with the glucuronidation occurring via multiple UGT enzyme isoforms, including UGT1A1. The observed frequency of *UGT1A1* genotypes in the analysis dataset utilized for development of this population PK model were consistent with the reported population frequency of the *28 allele of 0.32 to 0.34 in Caucasian/Western populations and distributions of the homozygous and heterozygous *UGT1A1*28* genotypes [28, 29]. *UGT1A1*28* genotype status was not identified as an important covariate in the univariate covariate analysis. Of note, genotyping was performed for not only the *UGT1A1*28* allele, but also the *UGT1A1*6* allele in the phase I studies conducted in Japan and other East Asian countries, given the importance of the *UGT1A1*6* genotype in Asian populations. The distribution density of alisertib CL/F did not substantially differ by *UGT1A1* genotype, supporting the use of a common starting dose of alisertib independent of *UGT1A1* genotype status. This is consistent with *UGT1A1* being one of several enzymes identified *in vitro* as being able to glucuronidate alisertib and the knowledge that the *UGT1A1*28* allelic variant results in only a partial decrease in the expression of the enzyme rather than a complete abrogation of expression or enzyme activity [30]. Although the representation of patients with the *UGT1A1*6* genotype in the analysis population is small, with only 14 patients that had at least one copy of this variant allele, analogous covariate models using combined data on the number of *6 and *28 alleles did not indicate significant effects of these variants on alisertib clearance.

Based on evaluation of goodness-of-fit plots, model metrics such as shrinkage, condition number and parameter precision, and on the performance of model evaluation and inspection of VPCs, it was concluded that the model was able to simulate the observed data with acceptable accuracy and could therefore be used for simulation of alisertib PK and exposure metrics. The agreement between the model predictions and external data was considered acceptable, given the potential inherent differences in the analysis and validation data due to the predominance of phase II data with sparser PK sampling in the validation data set.

The simulated alisertib concentrations for 200 patients in the West who were administered a 50 mg b.i.d. 7-day dosing regimen show that BSA did not affect alisertib CL/F and exposure, but that patients with a lower BSA were predicted to have modestly higher C_{max} values and a wider fluctuation in concentration between doses (Figure 4). The simulation showed that 30 mg b.i.d. doses for patients in East Asia produced a time course of alisertib concentrations and AUC substantially similar to that of patients in the West who were given 50 mg b.i.d. doses (Figure 6), providing PK support for the observed differences in MTD between the regions (50 mg b.i.d. in the West, and 30 mg b.i.d. in Asia).

Alisertib exposures were significantly related to the incidence of grade ≥3 neutropenia, grade ≥2 stomatitis and grade ≥2 diarrhoea, the most common treatment-emergent

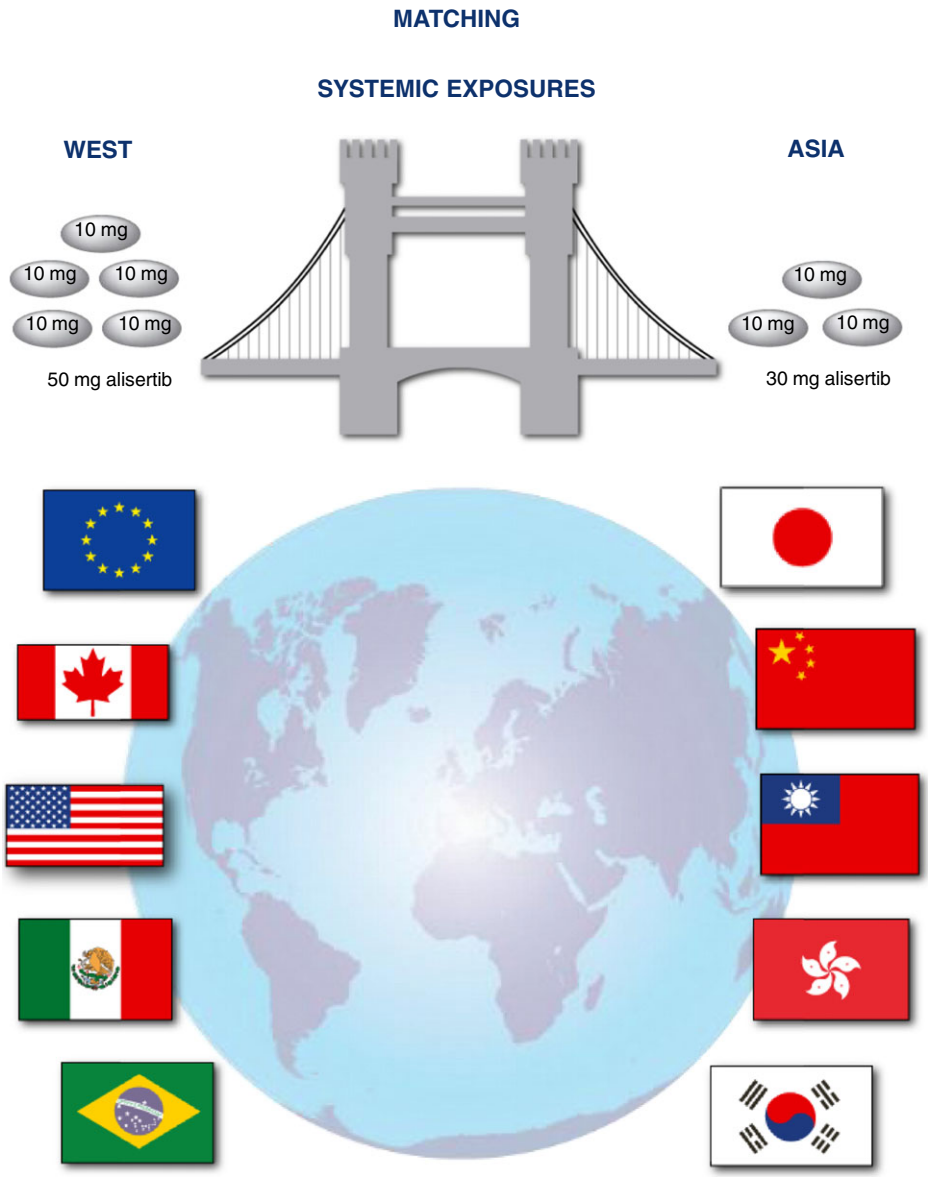


Figure 8

Model-based support for alisertib dose for global drug development. Despite alisertib pharmacokinetic differences in Asia *vs.* the West, dosing at a 40% lower dose of 30 mg twice daily (b.i.d.) in Asia/Japan can be expected adequately to match systemic exposures achieved at the Western dose of 50 mg b.i.d.

toxicities reflecting alisertib's antiproliferative effects resulting from its mechanism of action as an antimitotic agent. The selection of grade cut-offs for these evaluations (i.e. grade ≥3 for neutropenia and grade ≥2 for stomatitis and diarrhoea) was based on the differential clinical relevance of these AEs in relation to their impact on patient tolerability and quality of life. When these exposure–safety relationships were viewed in the context of population predicted exposures of alisertib in patients in East Asia *vs*. those in the West, it was readily apparent that the former would be expected to have a higher incidence of neutropenia, stomatitis and diarrhoea if treated at the Western MTD of 50 mg b.i.d. However, the estimated incidence of these AEs in patients in Asia who are administered 30 mg b.i.d. alisertib was comparable to those in Western patients who are administered 50 mg b.i.d. doses. These observations are consistent with a lower MTD/RP2D of 30 mg b.i.d. that was determined in the East Asian phase I study compared with the Western MTD of 50 mg b.i.d.

At the recommended phase II doses of 50 mg b.i.d. and 30 mg b.i.d. in the Western and East Asian patient populations, respectively, alisertib has been generally well tolerated, with treatment-emergent AEs manageable through protocol-specified dose modifications. In a multi-arm Western phase II trial [11] that enrolled patients across five solid tumour indications, only 26 (10%) of 249 patients experienced at least one AE that resulted in discontinuation of alisertib treatment. The mean (CV) relative dose intensity was 91.7% (16.2%). These observations are similar to the corresponding statistics for the 30 mg b.i.d. recommended dose in East Asian patients [17]. Specifically, only two (6.7%) of 30 patients discontinued alisertib owing to treatment-emergent AEs, and the mean (CV) relative dose intensity was 91.6% (12%). Taken together, these data support qualification of 50 mg b.i.d. and 30 mg b.i.d. starting doses as the recommended doses for alisertib clinical development in Western and East Asian populations, respectively.

In summary, model-based simulations support the achievement of similar alisertib exposures in patients in East Asia administered at a 40% lower dose compared with the Western population (i.e. 30 mg b.i.d. *vs*. 50 mg b.i.d.), thereby providing quantitative clinical pharmacology bridging and a regional dosing rationale for global drug development (Figure 8). Viewed from a broader perspective, this example highlights the importance of timely clinical pharmacological evaluation of investigational anticancer agents in Asian patient populations and model-based integration of the data, to help to define doses that optimize benefit–risk in Asian patient populations ahead of Asia-inclusive globalization of clinical development.

Competing Interests

X.Z., E.S.-W., D.H. and K.V. are employees of Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. T.T. is an employee of Takeda Pharmaceutical Company Limited. D.R.M. is President, Projections Research Inc., and a paid consultant for Takeda. A.M. is an employee of Boston Pharmaceuticals.

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Contributors

X.Z., D.R.M., T.T., E.S.-W., D.H., A.M. and K.V. contributed to the study design, data analyses, data interpretation and manuscript development and review.

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Supporting Information

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Table S1 Parameter values for the updated final model