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PHASE I STUDIES

Mass balance, routes of excretion, and pharmacokinetics of investigational oral [^{14}C]-alisertib (MLN8237), an Aurora A kinase inhibitor in patients with advanced solid tumors

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Summary

Aims This two-part, phase I study evaluated the mass balance, excretion, pharmacokinetics and safety of the investigational aurora A kinase inhibitor, alisertib, in three patients with advanced malignancies. *Methods* Part A; patients received a single 35-mg dose of [^{14}C]-alisertib oral solution (~80 μCi total radioactivity [TRA]). Serial blood, urine, and fecal samples were collected up to 336 h post-dose for alisertib mass balance and pharmacokinetics in plasma and urine by liquid chromatography–tandem mass spectrometry, and mass balance/recovery of [^{14}C]-radioactivity in urine and feces by liquid scintillation counting. Part B; patients received non-radiolabeled alisertib 50 mg as enteric-coated tablets twice-daily for 7 days in 21-day cycles. *Results* In part A, absorption was fast (median plasma T_{max}, 1 h) for alisertib and TRA. Mean plasma $t_{1/2}$ for alisertib and TRA were 23.4 and 42.0 h, respectively. Mean plasma alisertib/TRA $AUC_{0–inf}$ ratio was 0.45, indicating presence of alisertib metabolites in circulation. Mean TRA blood/plasma $AUC_{0–last}$ ratio was 0.60, indicating preferential distribution of drug-related material in plasma. On average, 87.8% and 2.7% of administered radioactivity was recovered in feces and urine, respectively (total recovery, 90.5% by 14 days post-dose). In part B, patients received a median 3 cycles of alisertib. The most common any-grade adverse events were fatigue and alopecia. *Conclusions* Findings suggest that alisertib is eliminated mainly via feces, consistent with hepatic metabolism and biliary excretion of drug-related material. Further investigation of alisertib pharmacokinetics in patients with moderate-severe hepatic impairment is warranted to inform dosing recommendations in these patient populations.

Keywords Alisertib · Mass balance · Pharmacokinetics · Aurora A kinase

Introduction

Aurora A kinase (AAK) plays an important role in centrosome function and maturation, mitotic spindle assembly, chromosome alignment, and mitotic entry [1, 2]. AAK is amplified and/or overexpressed, or both, in a variety of tumor types, including colon, breast, pancreatic, and bladder cancers, as well as in certain lymphomas, leukemias, and multiple myeloma [3–10]. Inhibition of AAK leads to mitotic spindle defects, and ultimately to mitotic arrest and cell death [11]; as such, this enzyme is a rational target for anti-cancer therapy.

Alisertib (MLN8237; sodium 4-{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoate hydrate) is an investigational, orally administered, selective inhibitor of AAK [12, 13]. Single-agent alisertib has been evaluated as a powder-in-capsule (PIC) formulation or enteric-coated tablet (ECT) formulation in several phase I and II clinical studies of patients with advanced non-hematologic [14–18] and hematologic malignancies [19–21]. These studies have assessed the pharmacokinetics, tolerability, and anti-tumor activity of alisertib and defined the recommended dose and schedule for single agent alisertib in adult Western patients to be 50 mg twice daily (b.i.d.) for 7 days in 21-day cycles [14–16, 21, 22].

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Alisertib is currently being evaluated as a monotherapy or in combination with other agents across multiple advanced solid tumors and lymphomas.

This study (NCT01714947) was conducted to quantitatively characterize the mass balance, routes of excretion, pharmacokinetics, and safety of a single oral dose of [^{14}C]-alisertib in patients with advanced malignancies.

Methods

Patients

Eligible patients were adults with histologically or cytologically confirmed metastatic and/or advanced solid tumors or lymphomas, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate bone marrow or other organ function as evidenced by: absolute neutrophil count (ANC) ≥1500/mm^3; platelet count ≥75,000/mm^3 (and no requirement for platelet transfusion to maintain platelet levels ≥75,000/mm^3); calculated creatinine clearance ≥30 mL/min (Cockcroft–Gault formula); total bilirubin ≤1.5 x the upper limit of normal (ULN) or aspartate aminotransferase/alanine aminotransferase ≤2.5 x ULN (≤5 x ULN if the elevation could be reasonably attributed to the presence of metastatic disease to the liver). Patients were required to have a radiographically or clinically evaluable tumor, although measurable disease by Response Evaluation Criteria In Solid Tumors v1.1 (for solid tumors) or 2007 International Working Group criteria (for lymphomas) was not mandated. Recovery from the reversible effects of prior antineoplastic treatment (with the exception of alopecia and grade 1 neuropathy) was also required.

Key exclusion criteria were: ongoing grade ≥ 2 nausea or vomiting; grade ≥ 2 diarrhea (or use of antimotility agents to control diarrhea to grade ≤ 1); treatment with investigational products, systemic antineoplastic agents, or glucocorticoids within 21 days of the first alisertib dose; receipt of nitrosoureas, mitomycin C, or unconjugated therapeutic antibodies within 42 days of the first alisertib dose; receipt of radioimmunoconjugates or toxin immunoconjugates within 56 days of the first alisertib dose; treatment with clinically significant enzyme inducers within 14 days of the first dose of alisertib and during the study; known gastrointestinal disease or gastrointestinal procedures that could interfere with the oral absorption, excretion, or tolerance of alisertib; radiotherapy involving <25% of the hematopoietically active bone marrow within 21 days and ≥ 25% within 42 days preceding the first alisertib dose; and a history of urinary and/or fecal incontinence.

The trial protocol was reviewed and approved by an institutional review board at each participating center. The study was conducted in accordance with the ethical principles founded in the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable regulatory requirements (including International Conference on Harmonisation guidelines). All patients provided written informed consent.

Study design and treatment

This was a two-part, open-label, phase I study conducted between January and June 2013 at 2 centers in the United States. In part A, patients received a single 35 mg dose of [^{14}C]-alisertib oral solution (Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited,) for assessment of the mass balance, excretion, and pharmacokinetics of alisertib. In part B, patients received non-radiolabeled alisertib 50 mg ECT b.i.d. for 7 days in 21-day cycles and safety/tolerability was assessed. The treatment schema is summarized in Fig. 1.

Part A Eligible patients were admitted to the clinical facility on the morning of day −1 (the day prior to the first dose of alisertib). Following the collection of pre-dose assessments on day 1, patients received a single 35 mg dose of [^{14}C]-alisertib oral solution containing approximately 80 μCi of total radioactivity (TRA; 1.19 mCi/mmol). The actual amount of administered radioactivity was documented for each patient. The 35 mg dose of [^{14}C]-alisertib was expected to produce systemic exposures (area under the plasma concentration–time curve [AUC]) similar to those observed following administration of alisertib 50 mg ECT (i.e., the unit dose of the clinical dosing regimen) based on results of two previous relative bioavailability studies (ECT in reference to PIC [15] and a prototype oral solution in reference to PIC) [23].

During part A only, alisertib was given on an empty stomach, with patients not permitted to eat or drink anything except for water and prescribed medications, for 2 h before and 1 h after dosing. Patients drank the [^{14}C]-alisertib oral solution directly from the vial. This was followed by 3 × 10 mL rinses with water directly from the vial and ingestion of approximately 200 mL of water. To ensure collection of fecal samples before discharge from the clinical facility, patients received 2 × 15 mL doses of oral Milk of Magnesia (magnesium hydroxide) approximately 2 h apart, on the evening of day 7; the second dose was withheld if the first dose was not tolerated. Patients were discharged from the clinic on day 11 (maximum day 17) provided that ≥80% of the total dose of radioactivity had been collected or the excretion of radioactivity in the urine and feces combined had declined to ≤1% of the total administered radioactivity per day for at least two consecutive days. Patients entered part B of the study immediately after or within 2 weeks after discharge from part A.

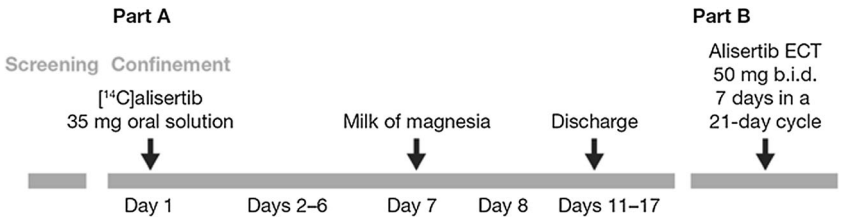

Fig. 1 Treatment schema

Part B Patients received non-radiolabeled alisertib 50 mg ECT (5 × 10 mg tablets with 240 mL water) b.i.d. for 7 days in 21-day cycles until disease progression or unacceptable toxicity. Prior to commencing a new treatment cycle, patients were required to have an ANC ≥1500/mm^3, platelet count ≥75,000/mm^3, and all toxicities considered to be related to alisertib must have resolved to grade ≤ 1, to the patient's baseline (day 1) values, or to a level considered acceptable to the investigator. If these criteria were not met, then the start of the next cycle was delayed for up to 1 week. For treatment delays of ≥1 week due to incomplete recovery from alisertib-related toxicity, the alisertib dose was reduced by one dose level (10 mg) for commencement of the next cycle.

Alisertib dose adjustment and interruption guidelines for this study are generally in line with those reported in previously published studies [19, 21, 24]. Alisertib dose re-escalation was not permitted during part B. A maximum of two dose reductions for toxicity management were allowed; study drug was discontinued in patients requiring more than two dose reductions unless there was evidence of clinical benefit as agreed by the investigator and sponsor.

In parts A and B, the use of antacids or calcium-containing supplements from 2 h before alisertib dosing until up to 2 h after dosing was not permitted. Anti-emetic agents were administered at the investigator's discretion. Although not prohibited, the use of benzodiazepines for the prophylaxis or treatment of nausea or vomiting was discouraged due to the potential benzodiazepine-like effects of alisertib. Patients did not receive prophylactic therapy with loperamide, but were instructed to take loperamide at the occurrence of the first loose stool, per standard oncology practice.

Objectives

The primary objectives of this study were to evaluate the mass balance of alisertib (i.e. cumulative excretion of TRA in urine and feces) and characterize the pharmacokinetics of alisertib in plasma and urine, and of TRA in plasma and whole blood, following a single 35 mg dose of [^{14}C]-alisertib oral solution in part A. Secondary objectives were to collect samples for characterization of the metabolic profile of alisertib in plasma, urine, and feces, following a single 35 mg dose of [^{14}C]-alisertib oral solution in part A, and to assess the safety and tolerability of multiple-dose administration of alisertib in part B. Alisertib metabolic profiling data collected during part A of the study are the subject of a separate report and are not described herein.

Assessments

Serial blood samples for analysis of whole blood and plasma alisertib pharmacokinetics and TRA were collected over a 10-day period, starting at pre-dose on day 1 and then at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 h post-dose (or until discharge from the study). Urine and fecal samples for analysis of TRA were collected pre-dose on day 1, in intervals of 0–12 and 12–24 h post-dose, and thereafter in 24-h collection intervals until discharge from the study. The blood, plasma, urine and feces collected at pre-dose were used for the determination of background radioactivity levels for the respective matrices for each individual patient.

Safety was assessed by monitoring adverse events (AEs), vital signs, physical examinations, electrocardiograms, and clinical laboratory tests. Treatment-emergent AEs were recorded from the first dose until 30 days after the last dose of alisertib, and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 [25]. Blood samples for laboratory assessments were collected prior to dosing on day 1 of each treatment cycle and at the end of study visit for part A, and on days 1 (pre-dose), 8, and 15 and at the end of study visit for part B.

Analysis of alisertib concentrations in plasma and urine

Alisertib concentrations in plasma and urine samples were analyzed using a validated liquid chromatography–tandem mass spectrometry method, as described previously [15].

Analysis of total radioactivity in blood, plasma, feces, and urine

TRA of [^{14}C]-alisertib-related material was measured in whole blood, plasma, fecal homogenates, and urine by liquid scintillation counting (Perkin Elmer Tri-Carb Model 3100 TR). Aliquots of plasma (200 μL) and urine (500 μL) were mixed directly with liquid scintillation fluid prior to measurement of radioactivity. In contrast, aliquots of whole blood (300 μL) and fecal homogenates (0.4 g) were first combusted

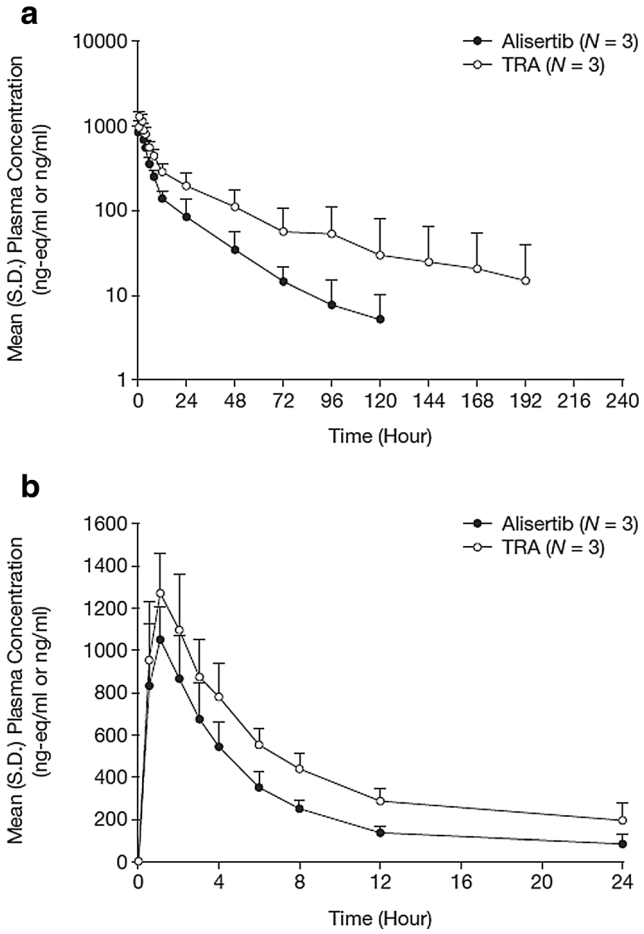

Fig. 2 Mean (SD) plasma concentration–time profiles of alisertib and total radioactivity (TRA) following a single 35 mg dose of [^{14}C]-alisertib oral solution (**a** semilogarithmic scale; **b** linear scale for the first 24 h)

(PerkinElmer Model 307 Sample Oxidizer) and the combustion products, trapped as $^{14}CO_2$, were then mixed with liquid scintillation fluid for radioactivity measurement.

Pharmacokinetic analysis

Non-compartmental analysis using Phoenix™ WinNonlin® version 6.1 (Pharsight Corp., Mountain View, California, USA) was used for estimation of pharmacokinetic parameters for alisertib in plasma and urine, and for TRA in whole blood, plasma, urine, and feces. The following single-dose pharmacokinetic parameters were derived: maximum plasma concentration (C_{max}), time to reach first maximum observed plasma concentration (T_{max}), area under the concentration–time curve from time 0 extrapolated to infinity ($AUC_{0–inf}$), AUC from time 0 to the last quantifiable concentration ($AUC_{0–last}$), terminal disposition phase half-life ($t_{1/2}$), renal clearance (CL_R), and apparent oral clearance (CL/F).

Results

Patients

Three patients, all with solid tumors (stage IV ovarian cancer, stage IV bladder cancer, and mesothelioma of unknown stage; each $n = 1$), were enrolled and treated with alisertib during Parts A and B of the study. Two of the three patients were male. Two patients were white and the other was black. Mean age was 64 years (50, 66, and 76 years, respectively). Mean weight was 80.3 ± 20.8 kg (range, 63.0–103.3 kg) and mean body mass index was 26.9 ± 8.3 kg/m^2 (range, 21.6–36.5 kg/m^2). There were no clinically relevant findings with regard to medical history, previous medication, serology, or physical examination at screening. All three patients had received prior therapy and undergone prior surgery for their solid tumors, and two patients (with bladder cancer and mesothelioma, respectively) had received prior radiation therapy.

Pharmacokinetic profile of alisertib

In part A, the actual doses of [^{14}C]-alisertib received by the three patients were 80.4, 81.5, and 80.3 μCi, respectively (mean, 80.7 μCi). All three patients were evaluable for pharmacokinetic analysis. Plasma concentration–time profiles for alisertib and TRA (drug-related material) after a single 35 mg dose of [^{14}C]-alisertib oral solution are shown in Fig. 2 and plasma pharmacokinetic parameters are summarized in

Table 1 Plasma pharmacokinetic parameters of alisertib and total radioactivity following a single 35 mg dose of [^{14}C]-alisertib oral solution ($N = 3$)

Parameter[a]	Alisertib	Total Radioactivity
C_{max}, nmol/L or nmol-eq/L	2179.4 (7.4)	2599.8 (8.8)
T_{max}, hour	1.0 (0.5–2.0)	1.0 (0.5–2.0)
$AUC_{0\text{-last}}$, nmol*hour/L or nmol-eq*hour/L	16,359.7 (29.4)	33,635.4 (55.5)
$AUC_{0\text{-inf}}$, nmol*hour/L or nmol-eq*hour/L	16,803.0 (29.8)	38,386.8 (55.2)
$t_{1/2}$, hour	23.4 (7.0)	42.0 (25.3)
CL/F, L/h	4.1 (25.6)	N/A
CL_R, L/h	Negligible	N/A

[a] Values are geometric means (coefficient of variation %) for C_{max}, AUC parameters, CL/F and CL_R, Median (range) for T_{max}, arithmetic mean (standard deviation) for $t_{1/2}$

Table 2 Mean (SD) plasma alisertib/total radioactivity ratios and whole blood/plasma total radioactivity ratios

Plasma alisertib/Total radioactivity ratios			Whole blood/plasma Total radioactivity ratios		
C_{max}	$AUC_{0–last}$	$AUC_{0–inf}$	C_{max}	$AUC_{0–last}$	$AUC_{0–inf}$
0.84 (0.059)	0.50 (0.136)	0.45 (0.120)	0.66 (0.067)	0.60 (0.101)	0.68 (0.017)

Table 1. Following a single 35 mg dose of [^{14}C]-alisertib oral solution, absorption was fast with a median T_{max} of 1 h for alisertib and TRA. The mean $t_{1/2}$ for alisertib and TRA in plasma was 23.4 and 42.0 h, respectively. The geometric mean plasma CL/F for alisertib was 4.1 L/h.

Table 2 summarizes the ratio of alisertib versus TRA in plasma and the ratio of TRA in whole blood versus plasma. The mean plasma $AUC_{0\text{-}inf}$ ratio of alisertib versus TRA was 0.45, indicating the presence of alisertib metabolites in circulation. These findings are consistent with the observed mean concentration–time profiles of alisertib and TRA shown in Fig. 2. The time course of TRA was comparable between plasma and whole blood with slightly lower concentrations in whole blood, suggesting preferential distribution of drug-related material in plasma (Fig. 3). The mean TRA blood versus plasma $AUC_{0–last}$ ratio was 0.60 (Table 2).

Mass balance and excretion of alisertib

Figure 4 shows the mean time course of the cumulative excretion of drug-related material in urine and feces. After a single 35 mg dose of [^{14}C]-alisertib oral solution containing approximately 80 μCi of TRA, a mean of 2.7% of the administered radioactivity was recovered in urine (Table 3). The majority of the drug-related material was cleared via the fecal route, with a mean of 87.8% of the administered radioactivity excreted in feces (Table 3). In total, a mean of 90.5% of the administered radioactivity was recovered in excreta by 14 days post-dose (Fig. 4; Table 3).

Safety

The safety of multiple-dose alisertib (50 mg ECT b.i.d. for 7 days in 21-day cycles) was assessed during part B of the study; all three patients were evaluable for safety. One patient received 2 cycles of alisertib and two patients received 3 cycles. All three patients experienced at least one treatment-emergent AE. Fatigue and alopecia were the only AEs reported in more than one patient (each $n = 2$). Most AEs were grade 1 in intensity as assessed by the investigator. Grade 2 AEs included headache, musculoskeletal pain, and back pain (each $n = 1$). Grade 3 AEs of neutrophil count decreased and neutropenia occurred in one patient. All three patients experienced at least one drug-related treatment-emergent AE, of which fatigue was the most common ($n = 2$). There were no reported discontinuations due to AEs, serious AEs, or on-study deaths. No clinically significant changes in laboratory assessments, vital signs measurements, electrocardiogram tests, or physical examinations were recorded.

Discussion

This phase I study assessed the mass balance, routes of excretion, and pharmacokinetics of the investigational AAK inhibitor alisertib, administered as an oral [^{14}C]-alisertib solution, in three patients with advanced solid tumors. The absorption of [^{14}C]-alisertib was fast with peak plasma concentrations of alisertib and TRA achieved at a median of 1 h following administration of the oral solution. The mean $t_{1/2}$ of alisertib in plasma was approximately 23 h (consistent with that

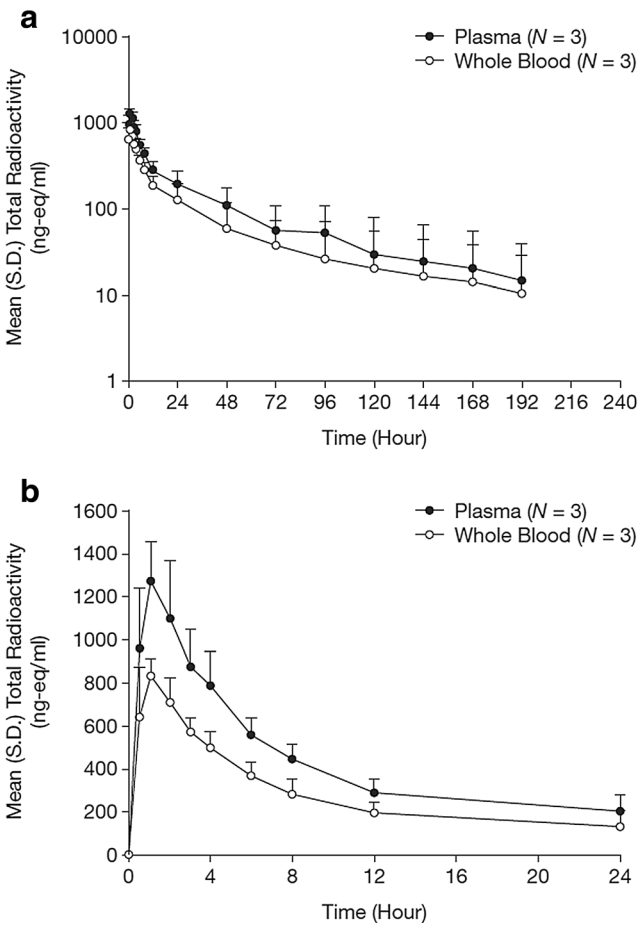

Fig. 3 Mean (SD) plasma and whole blood total radioactivity (TRA)–time profiles following a single 35 mg dose of [^{14}C]-alisertib oral solution (**a** semilogarithmic scale; **b** linear scale for the first 24 h)

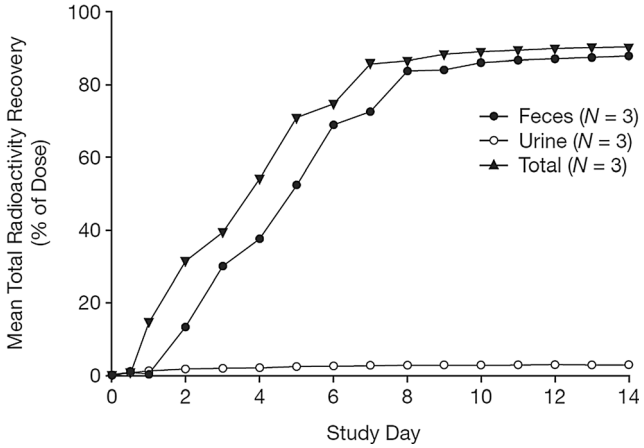

Fig. 4 Mean time course of cumulative excretion of drug-related material in urine and feces

previously reported for alisertib ECT 50 mg in patients with non-hematologic malignancies) [16] and the mean $t_{1/2}$ of drug-related material in plasma was 42 h. The time course of TRA was comparable between plasma and whole blood, with lower concentrations in whole blood, suggesting preferential distribution of drug-related material in plasma. The mean TRA blood versus plasma $AUC_{0–last}$ ratio was 0.60, which is similar to previously determined values for in vitro blood/plasma ratio of 0.57 for the parent drug (alisertib) (Millennium Pharmaceuticals, Inc., data on file). The mean plasma $AUC_{0–inf}$ ratio of alisertib versus drug-related material was 0.45, indicating the presence of alisertib metabolite(s) in circulation. Following a single 35 mg dose of [^{14}C]-alisertib oral solution, 90.5% of the administered radioactivity was recovered, on average, in excreta by 14 days post-dose. Approximately 88% of administered radioactivity was recovered in feces over the 14-day period, indicating that the predominant route of elimination for drug-related material was fecal, consistent with hepatic metabolism and biliary excretion. Renal clearance of unchanged alisertib was found to be negligible, as previously reported in studies of alisertib in patients with advanced solid tumors [15] or non-hematologic malignancies [16].

The safety of multiple-dose alisertib administered as an ECT formulation (50 mg b.i.d. for 7 days in 21-day cycles) was also evaluated in this study. Under the conditions of this study, alisertib appeared to be well-tolerated, although patients only received 2 or 3 cycles of alisertib before study drug was discontinued due to progressive disease. Treatment-emergent AEs, the most common of which were fatigue and alopecia, were consistent with the known safety profiles for alisertib as established in previous phase I and II studies [14–17, 20, 21]. No new safety signals for alisertib were noted.

In conclusion, characterization of the mass balance, excretion, and pharmacokinetics of alisertib, helps guide understanding of metabolic and elimination pathways for alisertib. Such characterization also allows us to predict patient-specific (e.g. renal or hepatic impairment) or extrinsic (e.g. concomitant medications with potential to affect drug metabolism) factors that may affect the metabolism and elimination of alisertib. This type of study is therefore important to inform strategies to manage potential drug–drug interactions and facilitate use of alisertib in special patient populations. Specifically, the results of this mass balance study suggest a major role of hepatic metabolism and/or biliary excretion to the overall clearance of alisertib based on the predominantly fecal pattern of excretion of drug-related material and the presence of circulating metabolites (based on the observed alisertib/TRA AUC ratio). Accordingly, evaluation of the effect of hepatic impairment on alisertib pharmacokinetics will be important to inform dosing recommendations in this special patient population. A population pharmacokinetics analysis of data from phase I and II clinical studies of alisertib has shown that mild hepatic impairment (bilirubin ≤2.22 mg/dL reflecting the inclusion criterion of bilirubin ≤1.5 X ULN in the clinical program) did not produce clinically meaningful effects on alisertib pharmacokinetics [22]. To further evaluate the effects of moderate and severe hepatic impairment on alisertib pharmacokinetics and inform dosing in these special patient sub-populations, a hepatic impairment study in patients with advanced cancer (NCT02214147) is currently ongoing.

Table 3 Total radioactivity recovery in urine and feces by 14 days post-administration of 35 mg [^{14}C]-alisertib oral solution

	Urine		Feces		Total recovery
	Ae, μg (eq)	Fe, %	Ae, μg (eq)	Fe, %	Fe, %
Patient 1	1655	4.7	30,378	86.0	90.7
Patient 2	711	2.0	31,186	87.1	89.1
Patient 3	453	1.3	31,906	90.4	91.7
Mean (SD)	939 (633)	2.7 (1.8)	31,157 (764)	87.8 (2.3)	90.5 (1.3)
Geometric mean (% CV)	811 (67.4)	2.3 (67.7)	31,150 (2.5)	87.8 (2.6)	90.5 (1.4)
Median (range)	711 (453–1655)	2.0 (1.3–4.7)	31,186 (30,378–31,906)	87.1 (86.0–90.4)	90.7 (89.1–91.7)

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Compliance with ethical standards

Conflict of interests X Zhou, S Pusalkar, S K. Chowdhury, Y Li, and K Venkatakrishnan are employees of Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Ltd.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent All participants provided written informed consent prior to any study-related procedures.

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