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PHARMACOKINETICS

Pharmacokinetics of ixazomib, an oral proteasome inhibitor, in solid tumour patients with moderate or severe hepatic impairment

Correspondence Dr Neeraj Gupta, Clinical Pharmacology, Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, 40 Landsdowne Street, Cambridge, MA, 02139, USA. Tel.: +1 617 444 2119; Fax: +1 617 551 7817; E-mail: neeraj.gupta@takeda.com

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Neeraj Gupta[1], Michael J. Hanley[1], Karthik Venkatakrishnan[1], Raymond Perez[2], Robin E. Norris[3], John Nemunaitis[4], Huyuan Yang[1], Mark G. Qian[1], Gerald Falchook[5], Richard Labotka[1] and Siqing Fu[6]*

[1]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, [2]University of Kansas Clinical Research Center, Fairway, KS, USA, [3]University Hospitals of Cleveland, Cleveland, OH, USA, [4]Mary Crowley Cancer Research Centers, Dallas, TX, USA, [5]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA and [6]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

*Principal investigator.

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AIM

The aim of the present study was to characterize the pharmacokinetics of the oral proteasome inhibitor, ixazomib, in patients with solid tumours and moderate or severe hepatic impairment, to provide posology recommendations.

METHODS

Eligible adults with advanced malignancies for which no further effective therapy was available received a single dose of ixazomib on day 1 of the pharmacokinetic cycle; patients with normal hepatic function, moderate hepatic impairment or severe hepatic impairment received 4 mg, 2.3 mg or 1.5 mg, respectively. Blood samples for single-dose pharmacokinetic characterization were collected over 336 h postdose. After sampling, patients could continue to receive ixazomib on days 1, 8 and 15 in 28-day cycles.

RESULTS

Of 48 enrolled patients (13, 15 and 20 in the normal, moderate and severe groups, respectively), 43 were pharmacokinetics-evaluable. Ixazomib was rapidly absorbed (median time to reach peak concentration was 0.95–1.5 h) and highly bound to plasma proteins, with a similar mean fraction bound (~99%) across the three groups. In patients with moderate/severe hepatic impairment (combined group), the geometric least squares mean ratios (90% confidence interval) for unbound and total dose-normalized area under the plasma concentration *vs.* time curve from time zero to the time of the last quantifiable concentration in reference to the normal hepatic function group were 1.27 (0.75, 2.16) and 1.20 (0.79, 1.82), respectively. Seven (15%) of the 48 patients experienced a grade 3 drug-related adverse event; there were no drug-related grade 4 adverse events.

CONCLUSIONS

In patients with moderate/severe hepatic impairment, unbound and total systemic exposures of ixazomib were 27% and 20% higher, respectively, *vs.* normal hepatic function. A reduced ixazomib starting dose of 3 mg is recommended for patients with moderate or severe hepatic impairment.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Ixazomib is an oral proteasome inhibitor (recommended starting dose: 4 mg, administered on days 1, 8 and 15 in 28-day cycles).
- Metabolism appears to be the major mechanism of ixazomib clearance; accordingly, hepatic impairment may increase ixazomib exposures.
- Mild hepatic impairment does not affect ixazomib pharmacokinetics but the effect of moderate or severe hepatic impairment on ixazomib disposition is unknown. The present study was undertaken to characterize ixazomib pharmacokinetics in these patient populations, to inform dosing recommendations.

WHAT THIS STUDY ADDS

- Moderate and severe hepatic impairment have a similar impact on the pharmacokinetics of ixazomib.
- Unbound and total systemic exposures of ixazomib were 27% and 20% higher, respectively, in patients with moderate/severe hepatic impairment (combined group) *vs.* those observed in patients with normal hepatic function.
- A reduced starting ixazomib dose of 3 mg is recommended for patients with moderate or severe hepatic impairment.

Introduction

In November 2015, the oral proteasome inhibitor, ixazomib, was approved by the United States Food and Drug Administration for use in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy [1]. Ixazomib may also have utility in other oncology/haematology settings [2, 3]. Although the clearance mechanisms of ixazomib in humans have not been fully elucidated [2, 4], data from preclinical *in vitro* metabolic studies and drug disposition studies indicate that metabolism is expected to be the major route of elimination for ixazomib [5]. Further, the renal clearance of ixazomib has been reported to be 0–0.51 l h^{-1} [2]. Given the role of metabolism in the clearance of ixazomib [4], plasma exposures may be altered in patients with hepatic impairment.

In clinical studies, ixazomib was rapidly absorbed, with a median time to reach peak concentration (T_{max}) of 0.5–2.0 h, and exhibited a long terminal half-life [6, 7]. The pharmacokinetic (PK) characteristics of ixazomib were similar in patients with different cancer types (such as solid tumours, lymphoma and MM) [8]. Data from a population PK analysis of ixazomib that included cancer patients with mild hepatic impairment, as defined by National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG) criteria [total bilirubin less than or equal to the upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin > 1–1.5 × ULN with any AST level] [9], indicated that there were no clinically relevant PK changes in patients with mild hepatic impairment [4]. These findings suggest that no ixazomib dose adjustment is required for patients with mild hepatic impairment and, as a result, patients with mild hepatic impairment have been enrolled in all pivotal studies without any dose adjustment. However, the effects of more severe liver dysfunction on the PK of ixazomib are unknown. Consequently, the present study (registered at clinicaltrials.gov as NCT01912222) was performed to characterize the PK of ixazomib in patients with advanced malignancies and moderate or severe hepatic impairment, in order to develop dosing recommendations for these specific patient populations.

Methods

Patients

Adults (aged ≥18 years) with advanced malignancies for which no further effective therapy was available were eligible to enrol in the study. Three patient cohorts with varying degrees of liver dysfunction (based on assessment of blood levels of total bilirubin and AST, as defined by NCI ODWG criteria [9]) were enrolled, including patients with: (i) normal hepatic function (total bilirubin and AST ≤ ULN); (ii) moderate hepatic impairment (total bilirubin >1.5–3 × ULN, with any AST level); and (iii) severe hepatic impairment (total bilirubin >3 × ULN, with any AST level). To ensure stable hepatic function, total bilirubin and AST were measured in two or three blood samples taken at least 48 h apart, with one sample obtained within 48 h prior to the day 1 dose of ixazomib; the two most recent measurements had to be in agreement (i.e. indicate the same hepatic function category) for the patient to be eligible for enrolment. All patients had adequate haematological (absolute neutrophil count ≥1000 μl^{-1}, platelet count >100 000 μl^{-1}, and haemoglobin ≥8 g dl^{-1}) and renal [measured or calculated (by the Cockcroft–Gault formula) creatinine clearance >30 ml min^{-1}] function, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. The renal function entrance criteria were supported by the results of a previously reported population PK analysis showing that mild and moderate renal impairment (creatinine clearance ≥30 ml min^{-1}) did not alter ixazomib PK [4].

Patients were excluded from the trial if they had: received systemic treatment with strong or moderate inhibitors of cytochrome P450 (CYP) 1A2 or CYP3A or strong inducers of CYP3A within 14 days before the first dose; undergone major surgery, received radiotherapy or systemic antineoplastic therapy, used any nicotine-containing products or had an infection requiring systemic antibiotic therapy or other serious infection within 14 days before the first dose; been treated with any investigational products within 21 days, therapeutic monoclonal antibodies or antibody–drug conjugates within 60 days, or nitrosoureas or mitomycin C within 6 weeks before the first dose; any uncontrolled cardiovascular conditions within the past 6 months; a corrected QT interval (QTc) >500 ms on a 12-lead electrocardiogram; symptomatic brain metastasis or

central nervous system (CNS) involvement; peripheral neuropathy (PN) of grade ≥2, or grade 1 with pain; uncontrolled hyperglycaemia; a life-threatening illness, or severe CNS, pulmonary or renal disease unrelated to the underlying cancer; or known HIV infection. Systemic treatment with strong or moderate inhibitors of CYP1A2 or CYP3A, and strong inducers of CYP3A was prohibited during the PK study.

All patients provided written informed consent prior to the initiation of any study-specific procedures and could withdraw from the trial at any time. Institutional review boards (IRBs) and/or independent ethics committees at all four sites approved the protocol [The University of Texas MD Anderson Cancer Center IRB, Houston, TX, USA (centre number: 58004); Mary Crowley Medical Research Center IRB, Dallas, TX, USA (centre number: 58008); University Hospitals Case Medical Center IRB, Cleveland, OH, USA (centre number: 58007); KU Medical Center Human Subjects Committee, Kansas City, KS, USA (centre number: 58002)]. The study was conducted according to the ethical provisions of the Declaration of Helsinki, Good Clinical Practice, the International Conference on Harmonisation guideline (1996) and federal regulations.

Study design

The present open-label, non-randomized, three-arm phase 1 study was conducted at four sites in the United States between 27 August 2013 (first patient enrolled) and 5 February 2015 (data cut-off). After assignment into one of the three hepatic function groups, patients received a single oral dose of ixazomib on day 1 of the PK cycle on an empty stomach (no food or fluids, except water and prescribed medications, were permitted for 2 h before and for 1 h after dosing) [10]. Patients in the normal hepatic function, moderate hepatic impairment or severe hepatic impairment groups received ixazomib at a dose of 4 mg (the established starting dose for phase 2/3 clinical trials [4], and also the recommended starting dose when administered in combination with lenalidomide and dexamethasone for the treatment of MM [1]), 2.3 mg or 1.5 mg, respectively (Figure 1).

After completion of PK sampling on day 15 of the PK cycle (Part A), patients could continue on the study and receive ixazomib on days 1, 8 and 15 of 28-day cycles (Part B). Patients could receive up to 12 cycles of ixazomib, unless it was determined by the investigator and the sponsor that a patient would derive clinical benefit from continued therapy beyond 12 cycles, or until patients were no longer considered to be deriving clinical benefit, or until they experienced unacceptable toxicity. In Part B, patients continued on the same dose of ixazomib as in Part A, unless a dose adjustment was needed for safety/tolerability or a change in hepatic function. If patients with moderate or severe hepatic impairment tolerated their respective starting doses for ≥1 cycle during Part B, the dose of ixazomib could be escalated (up to a maximum dose of 4 mg).

Assessments

Blood samples (3 ml) for the measurement of plasma ixazomib concentrations were collected before dosing and at the following time points after the day 1 dose of ixazomib in Part A: 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 8 h, 24 h, 48 h, 72 h, 96 h, 120 h, 144 h, 168 h, 240 h, 264 h and 336 h. An additional predose blood sample was collected for the estimation of ixazomib plasma protein binding.

Plasma ixazomib concentrations were measured using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay. A reverse-phase gradient method, running at a flow rate of 0.3 ml min^{-1} on a Fortis Phenyl, 2.1 × 50 mm, 5-μm column (Fortis Technologies Ltd, Neston, UK), provided sample stacking and separation for the analyte. Ixazomib and the internal standard ($^{13}C_9$-ixazomib) were ionized in the positive ion spray mode and detected through multiple reaction monitoring of mass transition pairs at 343.1 → 109.0 m/z and 352.1 → 115.0 m/z, respectively. Assay linearity was achieved over a concentration range of 0.5–500 ng ml^{-1} for ixazomib. Assay precision for ixazomib in plasma samples ranged from 1.7% to 6.1% coefficient of variance (CV), with a bias of −4.0% to 2.3%.

The protein binding assay was conducted in triplicate using rapid equilibrium dialysis. Predose plasma samples were spiked with ixazomib at concentrations of 70 ng ml^{-1} or 280 ng ml^{-1} and then dialysed against isotonic sodium

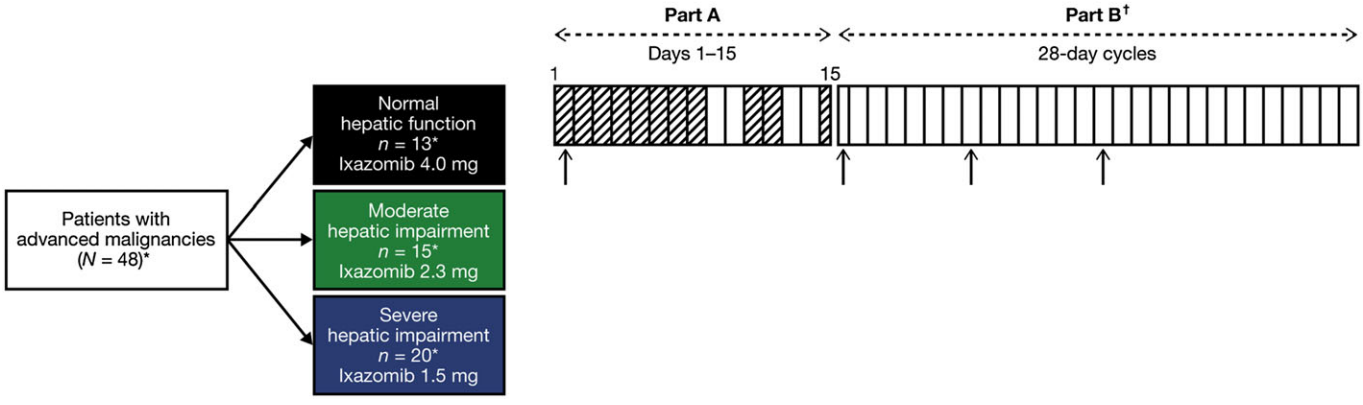

Figure 1

Study design overview. PK, pharmacokinetics. *Patient numbers are for the safety population. A total of 43 patients were PK-evaluable (normal hepatic function, $n = 12$; moderate hepatic impairment, $n = 13$; severe hepatic impairment, $n = 18$). The five patients who were excluded from the PK-evaluable population had received an excluded concomitant medication during Part A of the study. †Started on day 15 after PK collection in Part A. ↑ Ixazomib dose, ▨ PK sampling

phosphate buffer (120 mM, pH 7.5) at 37 °C using a dialysis membrane with an 8000-Da mass cut-off. Following 3 h of dialysis (the time for reaching equilibrium was selected from a pretest in human plasma), the plasma sample from the donor side was collected and mixed with an equal volume of dialysis buffer. Similarly, the receiver-side buffer samples were collected and mixed with equal volumes of blank human plasma. The concentration of ixazomib in the plasma : buffer (50:50 v/v) samples was determined by LC/MS/MS. The cross-mixed donor- and receiver-side samples had the same matrix composition [50:50 (v/v) plasma:buffer], which minimized the potential matrix effect associated with the sample analysis using the LC/MS/MS-based assay.

Adverse events (AEs) were monitored throughout the study, from first dosing until 30 days after the last dose of ixazomib, and were graded according to NCI Common Terminology Criteria for Adverse Events v4.03.

Statistical analyses

A minimum of 12 PK-evaluable patients were planned to be enrolled to each of the normal hepatic function, moderate hepatic impairment and severe hepatic impairment groups in order to have adequate data to characterize the PK of ixazomib in each hepatic function group. PK-evaluable patients included patients who received the protocol-specified single dose of ixazomib, did not receive any excluded concomitant medications during Part A of the study, and for whom there was sufficient concentration–time data to estimate PK parameters. For PK-evaluable patients without reportable unbound fraction (f_u) values (i.e. one patient in the normal hepatic function group and one patient in the severe hepatic impairment group), the mean value from the hepatic function group to which the patient belonged was used for calculating unbound PK parameters because protein binding was similar across the hepatic function groups.

PK parameters were calculated using noncompartmental methods (WinNonlin® software v6.2; Pharsight, St Louis, MO, USA) and summarized using descriptive statistics. The primary PK endpoints were the unbound dose-normalized maximum observed plasma concentration (C_{max}) and area under the plasma concentration *vs*. time curve from time zero to the time of the last quantifiable concentration ($AUC_{0–last}$) of ixazomib. Unbound and total dose-normalized PK parameters were natural log-transformed and geometric mean ratios and 90% confidence intervals (CIs) for the hepatic impairment *vs*. normal hepatic function groups were calculated using a mixed-effects analysis of variance (ANOVA) model with hepatic function group as a fixed effect.

Safety/tolerability was another primary endpoint. The safety population included all patients who received ≥1 dose of ixazomib.

Results

Patients

Forty-eight patients were enrolled and received at least one dose of ixazomib (safety population): 13 were enrolled into the normal hepatic function group, 15 into the moderate hepatic impairment group and 20 into the severe hepatic impairment group (Figure 1). Of these patients, 43 had reportable PK parameters (C_{max} or AUC) and were PK evaluable, including 12 with normal hepatic function, 13 with moderate hepatic impairment and 18 with severe hepatic impairment. All five patients who were excluded from the PK-evaluable population had received an excluded concomitant medication during Part A of the study; however, as these excluded concomitant medications were not expected to alter the binding of ixazomib to plasma proteins, the predose samples from these five patients were included in the plasma protein binding analysis.

Baseline characteristics are summarized in Table 1. Median age was 56.5 years (range, 24–83) and 28 patients (58%) were male. The most common cancers were colorectal (27%) and hepatocellular carcinoma (21%). Apart from baseline total bilirubin, AST levels, and time from initial diagnosis, baseline characteristics were generally well matched among the three groups (Table 1). All patients enrolled into the moderate or severe hepatic impairment groups had liver dysfunction due to primary or metastatic tumours.

Treatment exposure

Forty-three patients (90%) completed Part A of the study. As of the data cut-off date (5 February 2015), 46 patients had discontinued the study, 36 owing to progressive disease (PD), five owing to AEs and five owing to withdrawal of consent; two patients were ongoing.

Forty-seven patients (98%) received ≤3 cycles of ixazomib and one patient (2%) continued on study for >3 cycles (a 66-year-old woman with endometrial carcinoma and normal hepatic function, 10 cycles). The median number of cycles received was one (range, 1–10) and the median overall treatment duration was 15 days (range, 1–273). The extent of exposure to ixazomib was similar across the three hepatic function groups; the median number of cycles received was one in all three groups, and the median relative dose intensity ranged from 83% to 86% across the groups. Two patients in the severe hepatic impairment group had dose increases from 1.5 mg to 2.3 mg, and a third had two sequential dose increases from 1.5 mg to 2.3 mg to 3.0 mg. No patient had a dose increase to 4.0 mg.

PK

In vitro plasma protein binding assays using predose samples showed that ixazomib was highly bound to plasma proteins in all three hepatic function groups. The mean ± standard deviation f_u was 0.84 ± 0.35% in the normal hepatic function group (n = 12), 0.93 ± 0.37% in the moderate hepatic impairment group (n = 15) and 0.98 ± 0.46% in the severe hepatic impairment group (n = 19); plasma protein binding data are reported for all patients except two patients for whom samples were not available (one in the normal hepatic function group and one in the severe hepatic impairment group). The respective bound fractions were 99.2 ± 0.34%, 99.1 ± 0.37% and 99.0 ± 0.45%.

Key PK parameters are reported in Table 2 and the mean dose-normalized ixazomib plasma concentration *vs*. time profiles are shown in Figure 2. After oral administration, ixazomib was rapidly absorbed in all three hepatic function groups examined, with a median T_{max} of 0.95–1.5 h. In agreement with the ixazomib doses received, geometric mean total and unbound systemic PK parameters

Table 1

Patient demographics and baseline disease characteristics, by hepatic function group (safety population)

Characteristic	Hepatic function group			
	Normal function (*n* = 13)	Moderate impairment (*n* = 15)	Severe impairment (*n* = 20)	Total (*N* = 48)
Median age, years (range)	62 (24–83)	55 (28–79)	56 (25–74)	56.5 (24–83)
Male, *n* (%)	6 (46)	8 (53)	14 (70)	28 (58)
Race, *n* (%)				
White	11 (85)	8 (53)	13 (65)	32 (67)
Black or African-American	2 (15)	2 (13)	6 (30)	10 (21)
Asian	0	1 (7)	1 (5)	2 (4)
Other	0	4 (27)	0	4 (8)
ECOG performance status, *n* (%)				
0	1 (8)	0	1 (5)	2 (4)
1	12 (92)	15 (100)	19 (95)	46 (96)
Median time from initial diagnosis, months (range)	61.5 (6–149)	22.0 (4–66)	23.0 (5–108)	26.7 (4–149)
Disease type at diagnosis, *n* (%)				
Colorectal cancer	2 (15)	4 (27)	7 (35)	13 (27)
Hepatocellular carcinoma	0	5 (33)	5 (25)	10 (21)
Sarcoma	1 (8)	1 (7)	2 (10)	4 (8)
Pancreatic cancer	0	1 (7)	2 (10)	3 (6)
Renal cell carcinoma	2 (15)	0	0	2 (4)
Melanoma	0	2 (13)	0	2 (4)
Other solid tumours*	8 (62)	2 (13)	4 (20)	14 (29)
Prior anticancer therapy, *n* (%)	13 (100)	15 (100)	20 (100)	48 (100)
Prior radiation, *n* (%)	6 (46)	6 (40)	11 (55)	23 (48)
Prior surgery, *n* (%)	12 (92)	14 (93)	18 (90)	44 (92)
Mean total bilirubin, μmol l^{-1} (SD)†	7.43 (3.09)	40.25 (5.59)	108.61 (78.37)	59.85 (66.25)
Mean AST, U l^{-1} (SD)†	21.04 (6.88)	169.97 (147.43)	197.48 (198.21)	141.09 (167.26)

AST, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation. *Other solid tumour types were endometrial, oesophageal, gall bladder, head and neck, mesothelioma, non-small cell lung, ovarian, prostate, cholangiocarcinoma, malignant fibrous histiocytoma, metastatic poorly differentiated squamous cell carcinoma of the pelvis, moderately differentiated adenocarcinoma compatible with intrahepatic cholangiocarcinoma, an unknown primary with liver metastasis and peritoneal adenocarcinoma (all *n* = 1). †For total bilirubin and AST, ≥2 baseline measurements for each patient were required to verify enrolment status. The average of the measurements was summarized.

(C_{max} and AUC values) were higher in patients with normal hepatic function (4 mg dose) than in patients with moderate hepatic impairment (2.3 mg dose), which in turn were higher than in patients with severe hepatic impairment (1.5 mg dose) (Table 2).

By contrast, total and unbound dose-normalized PK parameters were higher in patients with moderate or severe hepatic impairment than in patients with normal hepatic function (Table 2 and Figure 3). Unbound dose-normalized C_{max} was 27% and 21% higher in patients with moderate hepatic impairment or severe hepatic impairment, respectively, than in patients with normal hepatic function (Table 3). Likewise, unbound dose-normalized $AUC_{0–last}$ was 32% and 23% higher in patients with moderate hepatic impairment or severe hepatic impairment, respectively, than in patients with normal hepatic function (Table 3). As these analyses suggested a similar effect of moderate and severe hepatic impairment on the unbound dose-normalized PK parameters of ixazomib, a combined analysis was performed by pooling data from the moderate and severe hepatic impairment groups to estimate the ratio of geometric least squares means for the combined group in reference to patients with normal hepatic function. The corresponding geometric least squares mean ratios (90% CI) for unbound dose-normalized C_{max} and $AUC_{0\text{-last}}$ were 1.24 (0.79, 1.95) and 1.27 (0.75, 2.16), respectively (Table 3). The geometric least squares mean ratios (90% CI) for total dose-normalized C_{max} and $AUC_{0–last}$ were 1.17 (0.77, 1.78) and 1.20 (0.79, 1.82), respectively.

Safety and tolerability

The most common treatment-emergent AEs (TEAEs) were nausea, fatigue, peripheral oedema, vomiting, dyspnoea, decreased appetite and hyperbilirubinaemia (Table 4). In general, a lower proportion of patients with hepatic impairment, who were treated with lower doses of ixazomib, experienced AEs (excluding those relating to underlying liver disease) compared with patients with normal hepatic function (Table 4). Drug-related AEs, which were observed in 22 patients (46%), included nausea (17%), vomiting (10%),

Table 2

Ixazomib plasma PK parameters following single-dose administration, by hepatic function group (PK-evaluable population)

Parameter	Hepatic function group		
	Normal function 4 mg (n = 12)	Moderate impairment 2.3 mg (n = 13*)	Severe impairment 1.5 mg (n = 18†)
Total PK parameters			
T_{max}, h‡	0.95 (0.48–4)	1.50 (0.5–2.5)	1.21 (0.5–4)
C_{max}, ng ml^{-1}	61.0 (54)	42.5 (63)	26.1 (70)
AUC_{0-last}, h·ng ml^{-1}	1160 (41)	846 (49)	489 (50)
Dose-normalized C_{max}, ng ml^{-1} mg^{-1}	15.3 (54)	18.5 (63)	17.4 (70)
Dose-normalized AUC_{0-last}, h·ng ml^{-1} mg^{-1}	289 (41)	368 (49)	326 (49)
Unbound PK parameters			
C_{max}, ng ml^{-1}	0.509 (47)	0.372 (80)	0.232 (84)
AUC_{0-last}, h·ng ml^{-1}	9.65 (50)	7.33 (61)	4.44 (63)
Dose-normalized C_{max}, ng ml^{-1} mg^{-1}	0.127 (47)	0.162 (80)	0.154 (84)
Dose-normalized AUC_{0-last}, h·ng ml^{-1} mg^{-1}	2.41 (50)	3.19 (61)	2.96 (63)

Values shown are geometric mean (% coefficient of variation) unless otherwise specified. AUC_{0-last}, area under the plasma ixazomib concentration *vs.* time curve from time 0 to the time of the last quantifiable concentration; C_{max}, maximum observed plasma concentration; PK, pharmacokinetic; T_{max}, time to reach C_{max}. *n = 10 for AUC_{0-last}, dose-normalized AUC_{0-last}, unbound AUC_{0-last} and unbound dose-normalized AUC_{0-last}. †n = 11 for AUC_{0-last}, dose-normalized AUC_{0-last}, unbound AUC_{0-last} and unbound dose-normalized AUC_{0-last}. ‡Values are median and range.

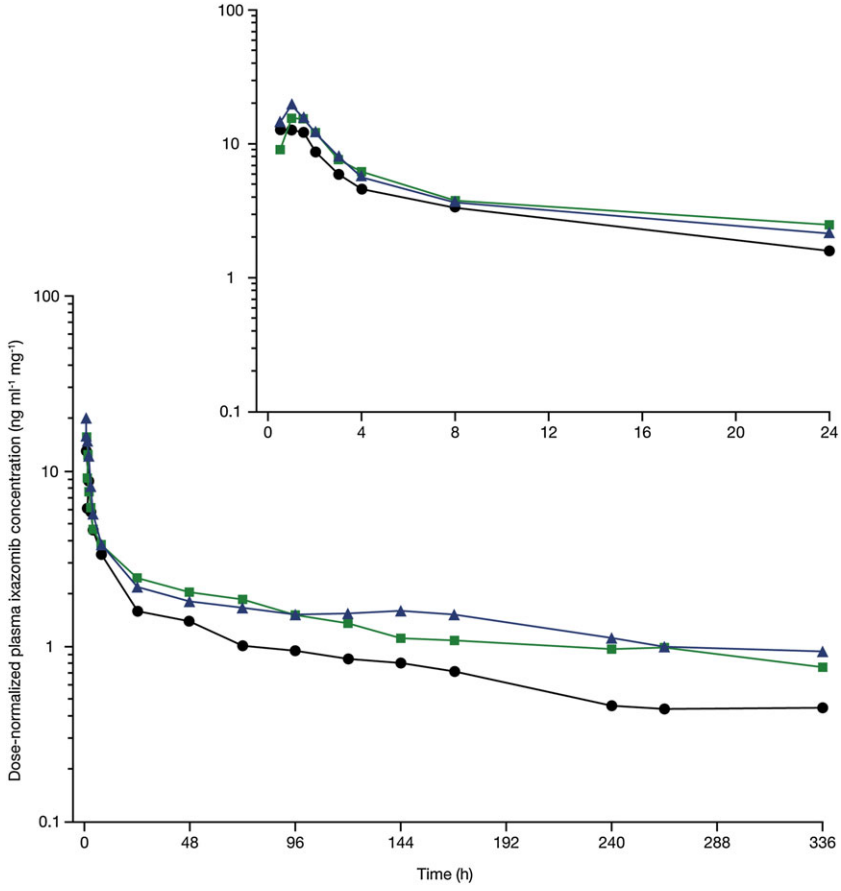

Figure 2

Mean dose-normalized plasma concentration *vs.* time profiles for ixazomib after single-dose administration in patients with normal hepatic function (4 mg), moderate hepatic impairment (2.3 mg) or severe hepatic impairment (1.5 mg). The inset shows the plasma concentrations over the first 24 h postdose. —● Normal (n = 12), —■ moderate impairment (n = 13), —▲ severe impairment (n = 18)

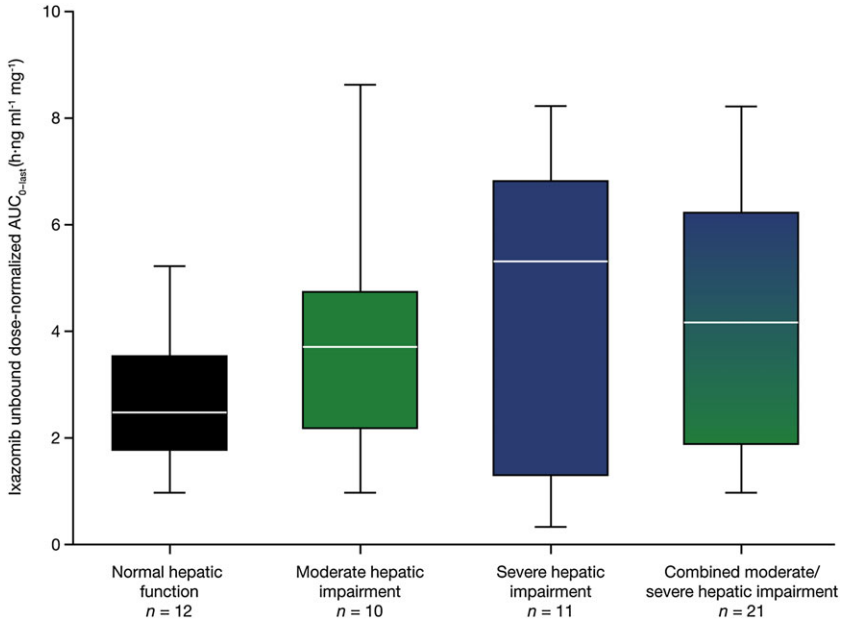

Figure 3

Comparison of ixazomib unbound dose-normalized $AUC_{0–last}$ values by hepatic function group. $AUC_{0–last}$, area under the plasma ixazomib concentration *vs.* time curve from time 0 to the time of the last quantifiable concentration. The box lines denote the 25th, 50th and 75th percentiles. Whiskers represent the 10th and 90th percentiles for each hepatic function group

Table 3

Geometric least squares mean ratios (90% CI) for unbound and total dose-normalized C_{max} and $AUC_{0–last}$ for ixazomib following single-dose administration in patients with moderate or severe hepatic impairment as compared with patients with normal hepatic function

Parameter	Geometric least squares mean ratio (90% CI)		
	Moderate impairment *vs.* normal function	**Severe impairment *vs.* normal function**	**Moderate/severe impairment* *vs.* normal function**
Unbound			
Dose-normalized C_{max}, ng ml^{-1} mg^{-1}	1.27 (0.74, 2.18)	1.21 (0.74, 2.01)	1.24 (0.79, 1.95)
Dose-normalized $AUC_{0–last}$, h·ng ml^{-1} mg^{-1}	1.32 (0.70, 2.50)	1.23 (0.66, 2.29)	1.27 (0.75, 2.16)
Total			
Dose-normalized C_{max}, ng ml^{-1} mg^{-1}	1.21 (0.74, 2.00)	1.14 (0.72, 1.82)	1.17 (0.77, 1.78)
Dose-normalized $AUC_{0–last}$, h·ng ml^{-1} mg^{-1}	1.27 (0.77, 2.11)	1.13 (0.69, 1.84)	1.20 (0.79, 1.82)

$AUC_{0–last}$, area under the plasma ixazomib concentration *vs.* time curve from time 0 to the time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration. *Patients with moderate or severe hepatic impairment combined.

decreased appetite (8%), fatigue (8%), diarrhoea (6%) and dehydration (6%). The overall incidence of drug-related AEs was higher in the normal hepatic function patients compared with those in the moderate and severe hepatic impairment groups (77%, 47% and 25%, respectively). This was likely to have been due to the lower doses received in the hepatic impairment groups and also to the shorter treatment duration.

Approximately three-quarters of patients (77%) experienced a grade ≥3 AE, which included hyperbilirubinaemia, acute renal failure, anaemia, ascites, dehydration, fatigue, hypotension and leukocytosis (Table 4). Fifteen percent of patients developed a grade 3 study drug-related AE [dehydration (6%), fatigue (4%), anaemia (2%) and fall (2%)]; no patient had a grade 4 drug-related AE. Similar to the overall AE incidence, the incidence of drug-related grade ≥3 AEs was higher in the normal hepatic function patients compared with the moderate and severe hepatic impairment patients (23%, 20% and 5%, respectively).

Six patients (13%) had an AE resulting in discontinuation of ixazomib [peritoneal haemorrhage, axillary pain/groin pain, acute hepatic failure, progression of pancreatic carcinoma, confusional state and acute renal failure; all n = 1 (2%)]; none of these AEs were attributed by the investigator to ixazomib. Serious AEs were reported in 31 patients (65%).

Table 4

Most common any-grade (≥10% of patients overall) and grade ≥3 (≥5% of patients overall) TEAEs of any cause, by hepatic function group (safety population)

	Hepatic function group			
	Normal function 4 mg (*n* = 13)	Moderate impairment 2.3 mg (*n* = 15)	Severe impairment 1.5 mg (*n* = 20)	Total (*N* = 48)
Any-grade AE, *n* (%)	13 (100)	15 (100)	20 (100)	48 (100)
Nausea	9 (69)	4 (27)	5 (25)	18 (38)
Fatigue	6 (46)	4 (27)	5 (25)	15 (31)
Peripheral oedema	2 (15)	9 (60)	4 (20)	15 (31)
Vomiting	7 (54)	2 (13)	4 (20)	13 (27)
Dyspnoea	4 (31)	3 (20)	4 (20)	11 (23)
Decreased appetite	7 (54)	2 (13)	1 (5)	10 (21)
Hyperbilirubinaemia	0	5 (33)	5 (25)	10 (21)
Dehydration	3 (23)	2 (13)	3 (15)	8 (17)
Anaemia	2 (15)	3 (20)	3 (15)	8 (17)
Pyrexia	1 (8)	2 (13)	4 (20)	7 (15)
Acute renal failure	0	1 (7)	6 (30)	7 (15)
Abdominal pain	2 (15)	2 (13)	2 (10)	6 (13)
Ascites	0	3 (20)	3 (15)	6 (13)
Cough	1 (8)	2 (13)	3 (15)	6 (13)
Diarrhoea	4 (31)	1 (7)	1 (5)	6 (13)
Insomnia	3 (23)	2 (13)	1 (5)	6 (13)
Upper abdominal pain	2 (15)	1 (7)	2 (10)	5 (10)
Hyperkalaemia	1 (8)	2 (13)	2 (10)	5 (10)
Back pain	2 (15)	0	3 (15)	5 (10)
Hypotension	0	1 (7)	4 (20)	5 (10)
Grade ≥3 AE, *n* (%)	6 (46)	13 (87)	18 (90)	37 (77)
Hyperbilirubinaemia	0	5 (33)	5 (25)	10 (21)
Acute renal failure	0	1 (7)	5 (25)	6 (13)
Anaemia	1 (8)	1 (7)	2 (10)	4 (8)
Ascites	0	2 (13)	2 (10)	4 (8)
Dehydration	0	2 (13)	2 (10)	4 (8)
Fatigue	2 (15)	1 (7)	1 (5)	4 (8)
Hypotension	0	1 (7)	2 (10)	3 (6)
Leukocytosis	0	1 (7)	2 (10)	3 (6)

AE, adverse event; TEAE, treatment-emergent adverse event.

Five serious AEs in four patients were considered by the investigator to be drug related (8%); these events included dehydration (4%) and oesophageal ulcer, fall and dyspnoea (2% each). Other than the temporal proximity to ixazomib administration, no additional rationale for study drug relatedness was provided by the investigators. There were 14 on-study deaths (six in the moderate hepatic impairment group and eight in the severe hepatic impairment group). All on-study deaths were considered to be related to progressive disease, and none were considered to be related to treatment with ixazomib.

Five patients had a total of seven rash-related AEs. All cases were grade 1 or 2 in intensity, and none were considered serious. In addition, one patient (2%) developed PN (grade 2), which was considered to be treatment-related; however, this patient had a history of neuropathy.

Discussion

Liver disease is known to be associated with multiple pathophysiological changes (e.g. alterations in hepatic blood flow, changes in liver enzyme activity, decreased binding of drug to plasma proteins and impaired biliary excretion) that can alter the PK of a drug [11, 12]. As hepatic metabolism appears to be the major clearance mechanism for ixazomib [2, 5], the present phase 1 study was conducted to explore the effect of moderate or severe hepatic impairment on the PK of ixazomib in patients with advanced cancers. Patients with mild hepatic impairment were not included in the study based on the results of a prior population PK analysis of ixazomib phase 1 data which showed no relationship between total bilirubin (>1–1.5 × ULN; which constitutes the definition of mild hepatic impairment by NCI ODWG criteria

[9, 13]) and ixazomib clearance or AUC [4], thereby supporting a common dose for patients with mild hepatic impairment and normal hepatic function (4 mg fixed starting dose on days 1, 8 and 15 in 28-day cycles [4]). In addition, all clinical studies conducted during the development of ixazomib, including ongoing phase 3 trials, have included patients with mild hepatic impairment [2–4, 7, 14–20].

Ixazomib is cytotoxic and cannot be administered to healthy volunteers. Accordingly, the present study was conducted in cancer patients and was designed primarily as a single-dose PK study to inform dosing recommendations in patients with moderate and severe hepatic impairment. As ixazomib has a long half-life (4–9 days after oral dosing [8]), the PK samples in the present study were collected over 15 days after administration of the single dose in Part A to meet the primary objective of the study. As the study was conducted in patients with advanced malignancies for whom there were no other approved treatment options, it was necessary to balance the primary PK objective with an opportunity to provide potential benefit to patients with a dose on days 1, 8, and 15 of 28-day cycles during Part B of the study. For this reason, PK characterization over a longer period in Part A of the study was not feasible.

In Part A of the study, patients received a single oral dose of ixazomib based on their hepatic function status. Patients with normal hepatic function received a 4 mg dose of ixazomib, patients with moderate hepatic impairment received 2.3 mg and patients with severe hepatic impairment received 1.5 mg. This design was implemented to ensure patient safety and was supported by the previously demonstrated dose-proportional and time-independent PK of ixazomib after oral dosing [7, 8, 20]. This also permitted analysis of the effect of hepatic impairment on ixazomib PK to be based on comparisons of dose-normalized PK parameters, as precedented by hepatic impairment studies of other anticancer agents such as imatinib [21] and bortezomib [9].

As hepatic impairment can alter the extent of binding of a drug to plasma proteins [11, 12], a predose sample was collected from patients for the purpose of measuring the unbound fraction of ixazomib, which was subsequently used to calculate unbound PK parameters. Ixazomib was highly protein bound, with a mean bound fraction of approximately 99% among all three hepatic function groups. As a result, hepatic impairment does not appear to alter the extent to which ixazomib binds to plasma proteins.

In the present study, analysis of unbound dose-normalized PK parameters following single-dose administration indicated that the PK of ixazomib are similar in patients with moderate or severe hepatic impairment when viewed in relation to the overall variability in these groups. This provided the rationale for pooling data from the moderate and severe hepatic impairment groups. Median unbound dose-normalized exposures in the moderate or severe hepatic impairment groups were higher than the 75th percentile of the corresponding distribution in the normal hepatic function group (Figure 3), indicating higher systemic exposures of ixazomib in the setting of moderate or severe hepatic impairment. Estimation of geometric least squares mean ratios using combined data from the two hepatic impairment groups showed that moderate/severe hepatic impairment was associated with unbound dose-normalized C_{max} and $AUC_{0–last}$ values that were 24% and 27% higher, respectively, than those observed in patients with normal hepatic function. Similarly, geometric least squares mean ratios indicated that total dose-normalized C_{max} and $AUC_{0–last}$ values were 17% and 20% higher, respectively, for the combined moderate/severe hepatic impairment group as compared to those observed in patients with normal hepatic function. Accordingly, a 3 mg starting dose of ixazomib administered to patients with moderate or severe hepatic impairment would be expected to provide systemic exposures of ixazomib that are comparable with those observed in patients with normal hepatic function (or mild hepatic impairment) after a 4 mg dose.

The AE profile of ixazomib was consistent with prior reports [2–4, 7, 14–16, 18–20, 22]. The most commonly reported TEAEs were nausea, fatigue, peripheral oedema, vomiting, dyspnoea, decreased appetite and hyperbilirubinaemia. With the exception of AEs relating to liver dysfunction (e.g. hyperbilirubinaemia), most individual AEs occurred more commonly in patients with normal hepatic function. This observation of a lower incidence of nonhepatic TEAEs in the moderate and severe hepatic impairment groups compared with the normal hepatic function group is consistent with the reduced doses conservatively used in these groups (2.3 mg and 1.5 mg, respectively) than would be necessary (i.e. 3 mg) based on the observed 20–27% increase in geometric mean AUC in patients with moderate/severe hepatic impairment. A notable observation across all three hepatic function groups was the low incidence of PN (2%), a common and sometimes dose-limiting side effect of the first-generation proteasome inhibitor, bortezomib [23, 24].

Following completion of Part A of the study, most patients received one or two additional cycles of ixazomib, and only one patient, who was enrolled in the normal hepatic function group, received >3 cycles (10 cycles). This short duration of treatment was anticipated, given that all patients had advanced malignancies and were heavily pretreated. In addition, by the nature of the study, many patients had underlying liver disease (a known adverse prognostic factor in patients with solid tumours [25–27]) owing to their primary malignancy or metastases to the hepatobiliary system. Hence, most patients in the present trial were at a very advanced stage of their illness, with a short life expectancy. This was likely to have been a contributory factor to the high rate of on-study deaths (29%), all of which involved patients with hepatic impairment who died from causes related to the disease under study or complications thereof.

In summary, the results of the present phase 1 study showed that patients with moderate/severe hepatic impairment have approximately 27% and 20% higher unbound and total systemic ixazomib exposures, respectively, compared with exposures observed in patients with normal hepatic function. A reduced ixazomib starting dose of 3 mg is therefore recommended for patients with moderate or severe hepatic impairment.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available

on request from the corresponding author) and declare: NG, MJH, KV, HY, MGQ and RL are current employees of the sponsor, Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; RP has received research funding from Agensys, Bristol Meyers Squibb, Dompe, Eli Lilly, Incyte, Medimmune, Novartis, Pfizer, Takeda/Millennium, Immunogen and Tetralogics, and has acted as a consultant for PRA; REN has acted as a consultant for Nektar Pharmaceuticals; GF received research funding and travel reimbursement for a research presentation at ESGO 2013, from Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; and JN and SF have received no support from any organization for the submitted work.

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