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ORIGINAL ARTICLE

Phase 1 dose-escalation study of IV ixazomib, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma

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Ixazomib is an investigational proteasome inhibitor that has shown preclinical activity in lymphoma models. This phase 1 study assessed the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics, pharmacodynamics and preliminary activity of intravenous (IV) ixazomib in relapsed/refractory lymphoma patients who had received ⩾2 prior therapies. Thirty patients with a range of histologies received ixazomib 0.125 – 3.11 mg/m^2 on days 1, 8 and 15 of 28-day cycles. Patients received a median of two cycles (range 1 – 36). MTD was determined to be 2.34 mg/m^2. Most common drug-related adverse events (AEs) included fatigue (43%), diarrhea (33%), nausea, vomiting and thrombocytopenia (each 27%). Drug-related grade ⩾3 AEs included neutropenia (20%), thrombocytopenia (13%) and diarrhea (10%). Drug-related peripheral neuropathy occurred in four (13%) patients; no grade ⩾3 events were reported. Plasma exposure increased dose proportionally from 0.5 – 3.11 mg/m^2; terminal half-life was 4 – 12 days after multiple dosing. Of 26 evaluable patients, five achieved responses: 4/11 follicular lymphoma patients (one complete and three partial responses) and 1/4 peripheral T-cell lymphoma patients (partial response). Sustained responses were observed with ⩾32 cycles of treatment in two heavily pretreated follicular lymphoma patients. Results suggest weekly IV ixazomib is generally well tolerated and may be clinically active in relapsed/refractory lymphoma.

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INTRODUCTION

There is an ongoing need for additional therapeutic options for patients with lymphoma. In the United States, in 2014, there will be an estimated 70 800 new cases of non-Hodgkin lymphoma and 9190 cases of Hodgkin lymphoma diagnosed, and an estimated 18 990 and 1180 deaths from non-Hodgkin lymphoma and Hodgkin lymphoma, respectively.[1] For various lymphoma subtypes a high proportion of patients relapse following initial therapy, and require multiple subsequent lines of treatment.[2,3] For indolent subtypes in particular, these new treatment options need to be tolerable and amenable for long-term dosing.

The validity of proteasome inhibition as an effective therapeutic approach in lymphoma has been demonstrated by the first-in-class proteasome inhibitor bortezomib. Bortezomib is approved in the United States for the treatment of mantle cell lymphoma in patients who have received at least one prior therapy.[4] Clinical data suggest that bortezomib as a single agent and in combination may be clinically active in various other non-Hodgkin lymphoma subtypes, including follicular lymphoma,[5,6] peripheral T-cell lymphoma,[2,7] cutaneous T-cell lymphoma[2,8] and the non-germinal-center B-cell subtype of diffuse large B-cell lymphoma.[9,10]

Ixazomib is an investigational, orally bioavailable, small molecule inhibitor of the 20S proteasome inhibitor.[11] Like bortezomib, ixazomib binds to the β5 site of the 20S proteasome.[11] However, ixazomib has structural and physicochemical properties distinct from those of bortezomib, which may result in differences in activity and safety profiles.[11] Ixazomib (MLN2238) refers to the biologically active boronic acid form of ixazomib citrate (MLN9708). The drug substance is administered as a stable citrate ester, designated as ixazomib citrate. Under physiological conditions ixazomib citrate undergoes rapid hydrolysis to the biologically active boronic acid, ixazomib.[11] Ixazomib has shown improved preclinical activity compared with bortezomib in several lymphoma models, including a primary xenograft model derived from tissue of a bortezomib-refractory patient with activated B-cell subtype-diffuse large B-cell lymphoma.[11,12] Correlated with stronger antitumor activity, greater proteasome inhibition in tumor was also demonstrated in these models, suggesting improved tissue distribution and target engagement with ixazomib.

The preclinical findings with ixazomib and the clinical data relating to bortezomib in various lymphoma subtypes provided the rationale for the investigation of ixazomib in patients with lymphoma. Clinical development of ixazomib has involved investigation of both intravenous (IV) and oral formulations in various tumor types.[13–17] Here we report the final results of the first phase 1 study of IV ixazomib in patients with relapsed/refractory lymphoma, including dose-limiting toxicities (DLTs), the MTD, the safety profile, pharmacokinetic/pharmacodynamic characteristics and preliminary antitumor activity.

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PATIENTS AND METHODS

Patients

Patients aged 18 years or older with a pathologically confirmed diagnosis of lymphoma (including non-Hodgkin lymphoma or Hodgkin lymphoma), who had relapsed and/or refractory disease after at least two prior chemotherapeutic regimens, and for whom no curative option existed, were eligible. Patients were required to have: an Eastern Cooperative Oncology Group performance status of 0–2; radiographically or clinically measurable disease by International Working Group criteria;[18] and adequate hepatic, renal and hematologic function.

Patients were excluded if they had: Waldenström's macroglobulinemia; grade $\geqslant 2$ peripheral neuropathy (PN); received an autologous stem cell transplant within 6 months before day 1 of cycle 1, or prior allogeneic stem cell transplant; grade >1 diarrhea; received antineoplastic therapy including radiotherapy within 21 days, rituximab therapy within 2 months, or systemic treatment with strong inhibitors of CYP1A2, strong inhibitors of CYP3A or strong CYP3A inducers within 14 days of first dose of ixazomib; ongoing corticosteroid therapy; clinically uncontrolled central nervous system involvement; or evidence of uncontrolled cardiovascular conditions.

All patients provided written informed consent. Review boards at all participating institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki, the International Conference on Harmonization, and the Guidelines for Good Clinical Practice.

Study design

This was an open-label, phase 1, dose-escalation study, registered with ClinicalTrials.gov (NCT00893464). Patients were enrolled from 20 August 2009 to 14 September 2012 at seven sites in the United States and Canada. The primary objectives were to evaluate the safety and tolerability of weekly IV ixazomib and determine the MTD and/or the recommended phase 2 dose. The secondary objectives were to characterize the pharmacokinetics of ixazomib in plasma and urine, to characterize the pharmacodynamic effects of IV ixazomib on 20S proteasome inhibition in whole blood as a marker of target inhibition, and to assess preliminary disease response.

Ixazomib was administered as an IV bolus on days 1, 8 and 15 of 28-day cycles for up to 12 months or until disease progression or unacceptable toxicity occurred. Prolonged therapy beyond 12 months was permitted whether it was determined that a patient would derive benefit from continued therapy. Dose escalation initially proceeded with one patient per dose level and dose doubling from 0.125 to 1.0 mg/m^2. Dose escalation then occurred in 26–40% increments (that is, 1.0–1.4, 1.4–1.76, 1.76–2.34 and 2.34–3.11 mg/m^2) using a standard 3+3 schema based on the occurrence of DLTs in cycle 1. DLTs were defined as any of the following during cycle 1, considered by the investigator to be related to ixazomib: grade 4 thrombocytopenia or neutropenia lasting >7 days, or platelets $<10\,000$ mm^3 at any time; grade 3 neutropenia with fever and/or infection, or grade 3 thrombocytopenia with clinically significant bleeding; grade $\geqslant 3$ nonhematologic toxicity; grade 2 PN with pain or grade $\geqslant 3$ PN; and a delay of more than 1 week in the initiation of cycle 2 due to a lack of adequate recovery of ixazomib-related hematologic or nonhematologic toxicities. The MTD was defined as the highest dose resulting in DLTs during cycle 1 in 0/3 or 1/6 patients.

Assessments

Adverse events (AEs) were monitored throughout the study and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) v3.0. Blood samples were collected for analyses of ixazomib pharmacokinetics prior to dosing (within 1 h) on days 1 and 15 of cycle 1 and day 1 of cycle 2, and at the following time points after the administration of ixazomib on days 1 and 15 of cycle 1: 5, 15 and 30 min, and 1, 2, 4, 8, 24, 48, 96 and 168 h (prior to next dose). Pharmacokinetic parameters were calculated using noncompartmental methods (WinNonlin v5.3), and included the maximum plasma concentration, C_{max}, and the area under the plasma concentration versus time curve. Urine was collected following administration of ixazomib on days 1 and 15 from 0 to 4 h. Urine pharmacokinetic parameters such as fraction excreted and renal clearance were also calculated.

Blood samples were collected for pharmacodynamic analysis (20S proteasome activity) at the same sampling points described above for pharmacokinetic evaluation. Whole blood 20S proteasome activity was measured using a fluorogenic assay, as previously reported.[19] Pharmacodynamic parameters were estimated using noncompartmental analysis methods. Pharmacodynamic parameters calculated for individual whole blood 20S proteasome inhibition-time data following ixazomib administration on days 1 and 15 of cycle 1 included the maximum observed percent inhibition of blood 20S proteasome activity (E_{max}), the time of occurrence of E_{max} and the area under the effect versus time curve.

Response was assessed at the end of cycle 2, every 2 cycles thereafter up to cycle 12, and then every 4 cycles using International Working Group criteria for lymphoma.[18] At screening, all patients were imaged by computed tomography and positron-emission tomography; patients with a positive positron-emission tomography scan at screening received subsequent positron-emission tomography scans at the end of cycle 2 and cycle 4, and then as indicated based on standard clinical practice.

Statistical analysis

The safety population included patients who received at least one dose of ixazomib. The response-evaluable population included patients who received at least one dose of ixazomib, had measurable disease at baseline, and at least one post-baseline disease assessment. The pharmacokinetic/pharmacodynamic populations included patients who received ixazomib per protocol during cycle 1 without dose reductions or interruptions, did not receive any excluded concomitant medications through the completion of pharmacokinetic/pharmacodynamic sampling, and had sufficient concentration-time and effect-time data to permit reliable estimation of pharmacokinetic and pharmacodynamic parameters. Descriptive statistics were used to summarize the pharmacokinetic parameters.

RESULTS

Patients

A total of 31 patients were enrolled, and 30 were treated with ixazomib at eight dose levels: one each at 0.125, 0.25, 0.5 and 1.0 mg/m^2; four at 1.4 mg/m^2; seven at 1.76 mg/m^2; 10 at 2.34 mg/m^2; and five at 3.11 mg/m^2. The demographics and baseline characteristics of these 30 patients are summarized in Table 1. The median age was 57 years (range 23–78), 63% were male, and the most common histologies were follicular lymphoma (37%), diffuse large B-cell lymphoma (17%) and peripheral T-cell lymphoma (13%). Patients had received a median of five prior lines of therapy (range 2–11); prior procedures included radiation in 27%, stem cell transplant in 23% and surgery or other non-radiation procedure in 23%.

DLTs and MTD

Twenty-eight patients were included in the DLT-evaluable population; two patients (one at 2.34 mg/m^2 and one at 3.11 mg/m^2) did not receive all cycle 1 doses of ixazomib due to nontreatment-related AEs and were excluded. Four patients reported DLTs: one grade 4 neutropenia at 1.76 mg/m^2; one grade 3 neutropenia at 2.34 mg/m^2 that caused a >1 week delay in starting cycle 2; one grade 3 acute renal failure at 3.11 mg/m^2, a pre-renal condition due to dehydration as a result of grade 3 diarrhea and grade 3 vomiting; and a DLT at 3.11 mg/m^2 of grade 2 fatigue, grade 2 nausea, grade 2 vomiting and grade 3 diarrhea despite best supportive care. All DLTs resolved after ixazomib dose modification or delay, and the use of supportive care (such as growth factor support, anti-emetics and hydration). One patient who experienced grade 3 neutropenia at 2.34 mg/m^2 permanently discontinued ixazomib treatment, whereas the other three patients continued at a reduced dose level.

As two DLTs occurred in four DLT-evaluable patients treated in the 3.11 mg/m^2 cohort, enrollment to this cohort was stopped and the MTD was determined as 2.34 mg/m^2, at which DLTs occurred in one of six DLT-evaluable patients. The MTD cohort was expanded to enroll an additional four patients and no further DLTs were observed.

Table 1. Patient demographics and baseline characteristics

Characteristic	*Ixazomib dose (mg/m²)*					
	0.125–1.0 (n = *4*)	*1.4* (n = *4*)	*1.76* (n = *7*)[a]	*2.34* (n = *10*)	*3.11* (n = *5*)	*Total* (n = *30*)
Median age, years (range)	52 (43–65)	69 (63–78)	45 (23–73)	69.5 (47–75)	56 (27–72)	57 (23–78)
Male, *n* (%)	3	3	4	5	4	19 (63)
Race, n *(%)*[b]						
White	2	4	5	9	4	24 (83)
African American	2	0	1	0	0	3 (10)
Other	0	0	1	0	1	2 (7)
Histology, (%)						
FL	2	2	2	3	2	11 (37)
DLBCL	0	1	2	1	1	5 (17)
PTCL	0	0	0	4	0	4 (13)
HL	0	0	3	0	0	3 (10)
Mycosis fungoides	1	0	0	0	1	2 (7)
MCL	0	0	0	1	1	2 (7)
Others[c]	1	1	0	1	0	3 (10)
Ann Arbor stage at diagnosis, n *(%)*						
I	0	1	0	1	0	2 (7)
II	2	1	1	1	1	6 (20)
III	0	1	1	2	0	4 (13)
IV	1	1	4	4	0	10 (33)
Unknown	1	0	0	1	2	4 (13)
Not applicable	0	0	1	1	2	4 (13)
Lines of prior therapy, n *(%)*						
2	0	0	1	3	0	4 (13)
3	1	0	1	2	0	4 (13)
4	0	2	1	1	1	5 (17)
5	2	0	0	2	2	6 (20)
⩾6	1	2	4	2	2	11 (37)
Prior procedures, n *(%)*						
Radiation	0	1	3	2	2	8 (27)
Stem cell transplant	0	1	4	1	1	7 (23)
Surgery or other non-radiation	2	0	1	2	2	7 (23)
Median time since primary diagnosis, months (range)	64 (50–82)	88 (8–236)	37 (19–122)	40 (14–230)	117 (34–254)	49.5 (8–254)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL Hodgkin lymphoma; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma. [a]Seven patients were enrolled to the 1.76 mg/m^2 dose group as one patient had a delay in cycle 1 due to an upper respiratory tract infection; an additional patient was enrolled but the delayed patient subsequently completed cycle 1. [b]Data missing for one patient. [c]Malignant lymphoma (unspecified site), refractory composite lymphoma, chronic lymphocytic leukemia, each $n = 1$.

Safety

Thirty patients received at least one dose of ixazomib and were included in the safety population. At formal data cut-off for this report (1 March 2013), patients had received a median of 2 cycles of ixazomib (range 1–34); 10 patients received ⩾4 cycles and three patients received >12 cycles. At data cut-off, treatment was ongoing in five patients, including three patients at the time of reporting (31 December 2013), in cycles 16, 26 and 42, respectively. Reasons for discontinuation of ixazomib included disease progression (63%), AEs (10%) and symptomatic deterioration (10%; defined as a global deterioration of health status without objective evidence of disease progression).

All 30 treated patients experienced at least one drug-related AE. At data cut-off, the most common drug-related AEs included fatigue (43%), diarrhea (33%), nausea, thrombocytopenia and vomiting (each 27%), as summarized in Table 2. A total of 22 (73%) patients experienced grade ⩾3 AEs, with 14 (47%) experiencing drug-related grade ⩾3 AEs; the most common included neutropenia (20%), thrombocytopenia (13%) and diarrhea (10%), as summarized in Table 3. Two of the six cases of grade ⩾3 neutropenia were DLTs. Of those experiencing grade ⩾3 AEs, 2/6 patients with neutropenia required growth factor support, and 0/4 with thrombocytopenia required platelet transfusions; 3/3 patients with diarrhea were administered with anti-emetics (5-HT3 antagonists) or anti-diarrheal agents. Four (13%) patients had grade 1 or 2 drug-related PN, and no patient had grade ⩾3 PN; onset of PN ranged from cycle 1 to cycle 5. Among patients reporting AEs of Skin and subcutaneous tissue disorders (MedDRA System Organ Class; $n = 8$, 27%), five (17%) experienced drug-related rash, including two grade 1 (rash pruritic, acneiform rash), two grade 2 (rash papular, rash maculopapular) and one grade 3 (rash pruritic). Three patients discontinued due to AEs of drug-related grade 3 neutropenia (DLT at 2.34 mg/m^2), drug-related grade 3 asthenia plus unrelated grade 3 acute renal failure, and unrelated grade 3 thrombocytopenia (both at 3.11 mg/m^2).

Eight patients experienced serious AEs. In the 1.4 mg/m^2 dose group, one patient had grade 3 increased serum creatinine, and one patient had grade 2 pyrexia, both of which were considered unrelated to ixazomib. In the 2.34 mg/m^2 dose group, one patient had grade 1 pyrexia, considered related to ixazomib, one had grade 3 dyspnea that was considered unrelated to ixazomib, and

Table 2. Most common drug-related AEs (⩾10% of patients in total)

AE, n *(%)*	*Ixazomib dose (mg/m²)*					
	0.125–1.0 (n = *4*)	*1.4* (n = *4*)	*1.76* (n = *7*)	*2.34* (n = *10*)	*3.11* (n = *5*)	*Total* (n = *30*)
Any AE	4	4	7	10	5	30 (100)
Fatigue	3	2	4	2	2	13 (43)
Diarrhea	1	0	3	2	4	10 (33)
Nausea	1	1	3	1	2	8 (27)
Skin/SC tissue disorders[a]	1	1	2	4	0	8 (27)
Thrombocytopenia	1	2	2	2	1	8 (27)
Vomiting	0	0	4	1	3	8 (27)
Decreased appetite	1	1	1	0	3	6 (20)
Headache	2	0	2	1	1	6 (20)
Neutropenia	0	1	1	3	1	6 (20)
Abdominal pain	0	0	1	2	2	5 (17)
Pyrexia	0	0	3	2	0	5 (17)
Chills	0	0	2	1	1	4 (13)
Cough	0	0	2	1	1	4 (13)
Dysgeusia	0	1	2	1	0	4 (13)
Hypokalemia	1	0	1	0	2	4 (13)
Lymphopenia	0	1	0	2	1	4 (13)
Oral herpes	0	1	1	1	1	4 (13)
Peripheral edema	0	0	1	2	1	4 (13)
PN NEC[b]	1	0	2	0	1	4 (13)
Arthralgia	0	0	0	1	2	3 (10)
Constipation	0	0	0	0	3	3 (10)
Pain in extremity	0	0	0	2	1	3 (10)
Paresthesia	1	1	0	1	0	3 (10)
Decreased platelet count	0	0	1	0	2	3 (10)

Abbreviations: AE, adverse events; PN, peripheral neuropathy; SC, subcutaneous. [a]Skin/SC tissue disorders includes all AEs within this MedDRA System Organ Class (SOC); overall rate includes rash pruritic ($n = 2$), dermatitis acneiform, dry skin, erythema, rash maculo-papular, rash papular, skin fibrosis, skin induration and skin ulcer (each $n = 1$)—patients may have experienced more than one AE within this SOC. [b]NEC, not elsewhere classified; high-level term, including 'neuropathy peripheral' and 'peripheral sensory neuropathy'.

Table 3. Drug-related grade ⩾3 AEs (⩾2 patients in total)

AE, n *(%)*	*Ixazomib dose (mg/m²)*					
	0.125–1.0 (n = *4*)	*1.4* (n = *4*)	*1.76* (n = *7*)	*2.34* (n = *10*)	*3.11* (n = *5*)	*Total* (n = *30*)
Any grade ⩾3 AE[a]	1	3	3	4	3	14 (47)
Neutropenia	0	1	1	3	1	6 (20)
Thrombocytopenia	0	1	1	1	1	4 (13)
Diarrhea	0	0	0	0	3	3 (10)
Dehydration	0	0	0	0	2	2 (7)
Lymphopenia	0	0	0	1	1	2 (7)
Renal failure[b]	0	0	0	0	2	2 (7)
Skin/SC tissue disorders[c]	1	0	0	1	0	2 (7)

Abbreviations: AE, adverse effects; SC, subcutaneous. [a]Asthenia, increased blood creatinine phosphokinase, fatigue, hypokalemia, hyponatremia, hypophosphatemia, leukopenia, nausea, decreased platelet count, pruritic rash, skin ulcer, and vomiting (each $n = 1$). [b]Includes 'renal failure' and 'renal failure acute'. [c]Skin/SC tissue disorders includes all AEs within this MedDRA System Organ Class (SOC); overall rate includes rash pruritic and skin ulcer (each $n = 1$).

one patient died due to respiratory failure 28 days after receiving their last dose in cycle 2. This latter event, in a peripheral T-cell lymphoma patient, was considered unrelated to ixazomib and due to disease progression. Three patients had serious AEs in the 3.11 mg/m^2 dose group. One patient experienced treatment-related grade 3 renal failure due to dehydration (DLT) secondary to grade 3 nausea and grade 3 vomiting, one patient experienced grade 3 acute renal failure considered related to ixazomib, which was accompanied by grade 3 dehydration preceded by low grade anorexia and vomiting, and one patient experienced grade 4 septic shock considered unrelated to ixazomib.

Pharmacokinetics and pharmacodynamics

Thirty patients were included in the pharmacokinetics-evaluable population. Concentration-time profiles for these 30 patients are shown in Figures 1a and b; the disposition of ixazomib following IV administration of ixazomib was multi-phasic, with a rapid initial phase that was over by 4 h. Pharmacokinetic parameters are shown in Table 4. Mean ixazomib C_{max} and AUC_{0-168h} on days 1 and 15 are plotted by ixazomib dose level in Figures 1c and d, respectively. Dose-proportionality analysis was conducted by examining the relationship between ixazomib $AUC_{0-168hr}$ and absolute ixazomib dose (in mg) using linear regression. The

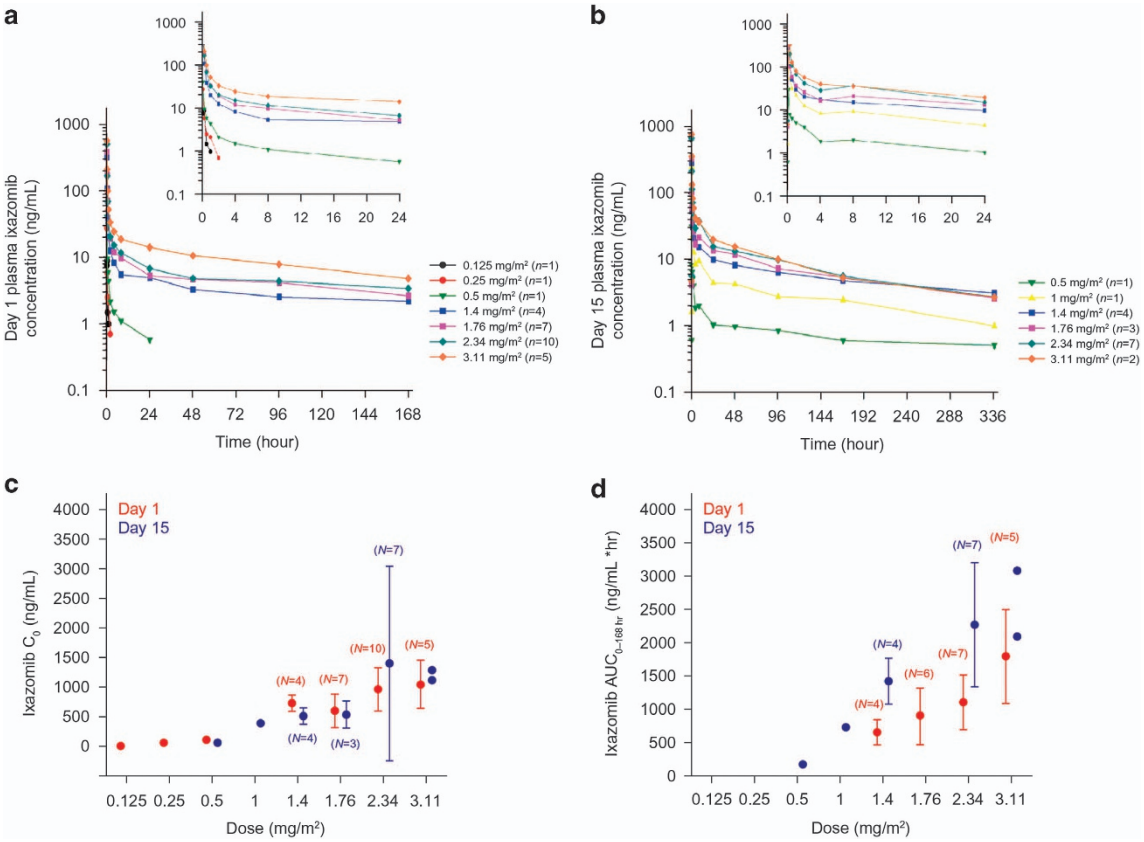

Figure 1. Days 1 (**a**) and 15 (**b**) plasma concentration-time profiles of ixazomib following IV ixazomib administration (inserts show 0–24 h), and mean ± s.d. ixazomib (**c**) C_{max} and (**d**) $AUC_{0-168\,h}$ on days 1 and 15 according to ixazomib dose.

calculated slope (95% confidence interval) of the linear regression line using log-transformed data was 0.8 (0.1 – 1.5) on day 1 and 1.3 (0.7 – 1.9) on day 15. As both the 95% confidence intervals contain 1.0, these data support the conclusion of dose-proportionality of ixazomib exposure over the ixazomib dose range of 0.5–3.11 mg/m^2 (absolute dose 2.5–6.8 mg). The terminal half-life was 4–12 days after multiple dosing. Accumulation of ixazomib increased approximately twofold between the day 1 and day 15 doses (Figure 1d). Urine pharmacokinetic data were available for 25 patients; the fraction of ixazomib excreted unchanged in urine was $<1\%$ of the administered dose. The renal clearance of ixazomib was 0–0.51 l/h.

A total of 23 patients were included in the pharmacodynamics population. Pharmacodynamic parameters are shown in Table 4. There was a dose-dependent increase in maximal whole blood 20S proteasome inhibition. At the MTD of 2.34 mg/m^2, the maximal 20S proteasome inhibition on day 1 was 82%, observed 5 min after administration, and on day 15 was 80%, observed after 10 min. The effect-time curves across ixazomib dose levels on days 1 and 15 are shown in Figure 2.

Preliminary responses

Twenty-six of the 30 patients were evaluable for response; four patients were excluded due to not having a post-baseline disease assessment ($n=3$) or having disease not measurable by International Working Group criteria ($n=1$; protocol exception permitted). At data cutoff, four patients (three follicular lymphoma, one peripheral T-cell lymphoma) had achieved a complete (CR) or partial response (PR); by the time of reporting, a fifth response (PR) had occurred in a follicular lymphoma patient.

One patient with follicular lymphoma treated at 1.76 mg/m^2 achieved a PR at cycle 4, which improved to a CR at cycle 20; at the time of reporting (31 December 2013), the patient remained in CR and was ongoing at cycle 42. Progressive scans from this patient, showing lesions pre-ixazomib and after achieving a CR at cycle 20, are shown in Figure 3. One patient with follicular lymphoma treated at 1.4 mg/m^2 achieved a PR at cycle 8 but progressed at cycle 32; the duration of response was 24.1 months. One patient with follicular lymphoma treated at 3.11 mg/m^2 achieved a PR at cycle 2 but progressed at cycle 6, with a response duration of 3.5 months. Another patient with follicular lymphoma treated at 2.34 mg/m^2, who was in cycle 5 at data cutoff, achieved a PR at cycle 8 but progressed at cycle 10, with a response duration of 2 months.

One patient with peripheral T-cell lymphoma treated at 2.34 mg/m^2 achieved a PR at cycle 4 but progressed at cycle 8 at one nodal site only, and discontinued study per protocol; the affected nodal site was irradiated but no other systemic antineoplastic therapy was offered to this patient while off study. In the 3 months following discontinuation of ixazomib treatment, it was observed that all other non-irradiated measurable lesions either disappeared or had significant reductions in lesion size. The patient was considered to have experienced probable delayed response and was allowed back on ixazomib treatment. At the time of reporting, the patient had received 18 retreatment cycles and had a PR at the last scan at retreatment cycle 8.

The treatment histories of the five responding patients are shown in Table 5. They were all heavily pretreated with 4–6 prior therapies, including both standard immuno- and chemotherapies, and targeted investigational agents such as idelalisib.

A further six patients (with malignant lymphoma unspecified site; refractory composite lymphoma; diffuse large B-cell lymphoma; Hodgkin lymphoma; follicular lymphoma; mantle cell lymphoma; each $n=1$) had stable disease, with a median duration of 3.6 months (range 1.7–5.4).

Table 4. Ixazomib geometric mean (percent coefficient of variation)[a] plasma pharmacokinetic parameters and mean (± s.d.)[a] pharmacodynamic (20S) parameters on days 1 and 15

Parameter	*Dose of ixazomib, mg/m²*							
	0.125	*0.25*	*0.5*	*1*	*1.4*	*1.76*	*2.34*	*3.11*
Pharmacokinetic parameters								
Day 1								
n	1	1	1	0	4	7[b]	10[c]	5
C_0, ng/ml	7.43	59.4	106	–	714 (21)	542 (48)	898 (39)	961 (39)
$AUC_{0-168\,h}$, hr/ng/ml	NC	NC	NC	–	637 (30)	821 (48)	1060 (37)	1680 (39)
DN C_0, ng/ml/mg	32.3	126	91.4	–	248 (18)	172 (50)	211 (47)	159 (44)
DN $AUC_{0-168\,h}$, hr/ng/ml/mg	NC	NC	NC	–	221 (41)	259 (49)	257 (50)	278 (46)
Day 15								
n	0	0	1	1	4	3	7[d]	2
C_0, ng/ml	–	–	56.3	383	497 (27)	499 (45)	803 (119)	1110, 1280
$AUC_{0-168\,h}$, hr/ng/ ml	–	–	175	732	1390 (24)	NC	2110 (41)	2090, 3080
DN C_0, ng/ml/mg	–	–	48.5	202	173 (31)	154 (45)	190 (135)	163, 225
DN $AUC_{0-168\,h}$, hr/ng/ml/mg	–	–	151	385	481 (34)	NC	500 (55)	307, 540
t½, h	–	–	292	146	209 (31)	146 (37)	108 (19)	97.9, 120
Accumulation ratio	–	–	NC	NC	2.17 (7)	NC	2.27 (15)	2.02, 2.21
Pharmacodynamic parameters								
Day 1								
n	1	1	1	1	3	7[e]	5	4
E_{max}, % inhibition	5.15	18.5	33.2	50.5	66.3 (±14.8)	72.2 (±8.1)	81.9 (±3.2)	80.2 (±3.6)
Time to E_{max}, h[f]	0.25	0.083	0.1	0.083	0.117 (0.1–0.133)	0.083 (0.083–0.1)	0.083 (0.083–0.25)	0.109 (0.083–0.533)
$AUE_{0-168\,h}$, % inhibition/h	NC	NE	888	NE	2000 (±1160)	1050 (±1000)	850 (±3100)	4530 (±1000)
Day 15								
n	0	1	1	1	3	3	4	2
E_{max}, % inhibition	–	64.3	19.2	44.4	69.8 (±10.6)	74.8 (±4.5)	79.6 (±4.9)	82.3, 85
Time to E_{max}, h[f]	–	0.1	0.1	0.083	0.083 (0.083–0.083)	0.083 (0.033–0.083)	0.167 (0.083–0.25)	0.083, 0.117
$AUE_{0-168\,h}$, % inhibition/h	–	NE	NE	NE	732 (±1160)	NC	2280 (±3640)	4280, 5360

Abbreviations: $AUC_{0-168\,h}$, area under the plasma ixazomib concentration versus time curve from 0 to 168 h post-dose; $AUE_{0-168hr}$, area under the 20S inhibition versus time curve from 0 to 168 h post-dose; C_0, extrapolated immediate post-bolus concentration of ixazomib; DN, dose normalized; NC, not calculated; NE, no effect; t½, terminal disposition phase half-life. [a]Individual values are reported in $n < 3$. [b]$n = 6$ for AUC_{0-168h} and DN AUC_{0-168h}. [c]$n = 7$ for AUC_{0-168h} and DN AUC_{0-168h}. [d]$n = 6$ for accumulation ratio. [e]$n = 5$ for AUE_{0-168h}. [f]Values shown are median (range).

DISCUSSION

The phase 1 data presented here suggest that weekly IV ixazomib is generally well tolerated in patients with relapsed/refractory lymphoma, with the MTD established as 2.34 mg/m^2. The safety profile comprised generally manageable toxicities, with infrequent PN and no grade $\geqslant 3$ PN is reported to date. These data also indicate that ixazomib may be clinically active in heavily pretreated relapsed/refractory lymphoma patients; in particular, 4 of 11 FL patients responded to treatment, with one CR and three PRs (2 of these 11 follicular lymphoma patients received ixazomib at doses $\leqslant 1$ mg/m^2). Durable responses were observed despite prior exposure to multiple chemotherapeutic regimens. These findings are important in the context of lymphoma, especially indolent subtypes, due to the relapsing disease course and the need for additional active treatment options, which need to be tolerable and amenable for long-term dosing.

The DLTs reported with ixazomib in this phase 1 study included neutropenia, gastrointestinal toxicities and acute renal failure secondary to gastrointestinal toxicities. Gastrointestinal DLTs and acute renal failure were only reported in patients receiving ixazomib at doses above the MTD of 2.34 mg/m^2. All DLTs resolved following ixazomib dose modification or discontinuation, or with the use of supportive care following standard clinical practice. Three of the four patients who experienced DLTs continued on therapy at a reduced dose level.

Ixazomib has also been evaluated in other phase 1 dose-escalation studies using different dosing schedules (weekly or twice-weekly), different routes of administration (IV or oral), and in different patient populations (multiple myeloma (MM), systemic light-chain amyloidosis, or solid tumors).[13–17] The safety profile of IV ixazomib in the present study appears generally similar to that reported in other ixazomib studies.[13–17] In all studies, the most common drug-related AEs included fatigue, gastrointestinal toxicities (diarrhea, nausea and vomiting) and hematologic toxicities (thrombocytopenia, neutropenia), and all treatment-emergent AEs observed to date appear clinically manageable with standard supportive care.

In the present study, 27% of patients were reported to have dermatologic AEs of Skin and subcutaneous tissue disorders (MedDRA System Organ Class); 17% were reported as drug-related rash. Similar rates have been reported in studies of weekly oral ixazomib; for example, in a study in relapsed or refractory MM the rate of drug-related AEs in the Skin and subcutaneous tissue disorders System Organ Class was 22%,[13] and in a study in relapsed or refractory light-chain amyloidosis the rate of all-cause rash/maculopapular rash was 18%.[16] By contrast, in a study of twice-weekly oral ixazomib in relapsed or refractory MM, there was a higher rate (40%) of drug-related skin and subcutaneous tissue disorders, including a 28% rate of drug-related rash.[15] These AEs of rash associated with ixazomib have proven manageable with the administration of primarily oral or topical anti-histamines and steroids.[15,16]

The low rate of PN reported in the present study is consistent with findings from other studies of single-agent oral ixazomib to date. In the study of weekly oral ixazomib in MM, one patient (2%) experienced drug-related grade 3 PN, with 12 (20%) patients experiencing any-grade drug-related PN.[13] This is in contrast to the higher rates of PN seen with IV bortezomib in lymphoma, with

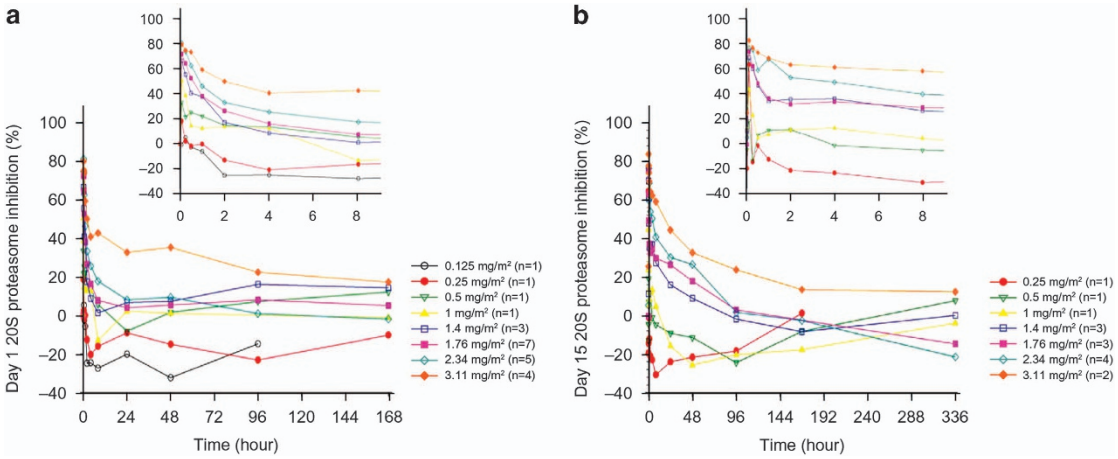

Figure 2. Mean whole blood 20S proteasome inhibition versus time (inserts show 0–8 h) according to ixazomib dose on (**a**) days 1 and (**b**) 15.

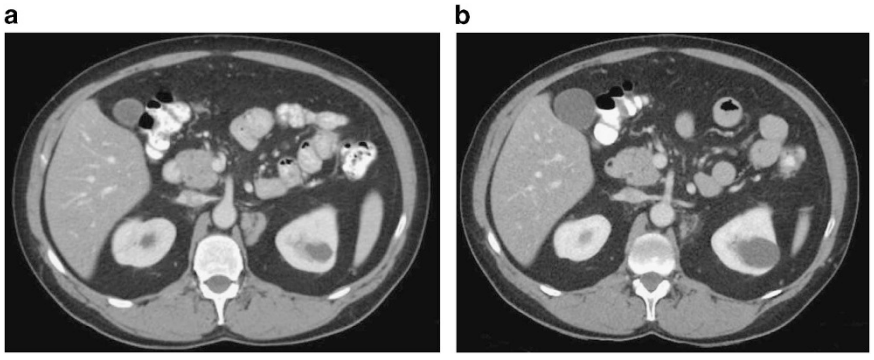

Figure 3. Screening (**a**) and post-treatment (**b**) scans from the patient with follicular lymphoma treated with ixazomib 1.76 mg/m^2 who achieved a CR at cycle 20; at the time of reporting this patient remained in CR and was ongoing at cycle 42.

Table 5. Lines of prior therapy for responding patients ($n = 5$)

Patient, response and duration of treatment	*Prior therapies,* n	*Regimen*	*Duration, months*[a]
FL	4	Chlorambucil, vincristine, prednisone	54.0
1.4 mg/m^2		Investigational agent: hA20 anti- CD20 antibody (veltuzumab)	19.1
PR		Investigational agent: hLL1 (anti-CD74 antibody)	4.0
32 cycles		Rituximab, lenalidomide	22.9
FL	4	R-CHOP	3.0
1.76 mg/m^2		R-DICE plus Mesna	4.1
CR		Tositumomab	15.0
42+ cycles		Investigational agent: idelalisib	7.6
FL	4	R-CHOP	11.1
3.11 mg/m^2		R-DICE	8.0
PR		Bortezomib, tositumomab	10.0
6 cycles		Investigational agent: idelalisib	9.0
PTCL	4	CHOP	3.1
2.34 mg/m^2		ESHAP	2.0
PR		EPOCH	3.1
26+ cycles		Belinostat	3.5
FL	5	R-CVP	24.0
2.34 mg/m^2		Bendamustine	11.0
PR		Gemcitabine, dexamethasone, cisplatin	1.0
10 cycles		R-EPOCH	7.0
		Investigational agent: DCDS4501A	4.6

Abbreviatons: EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone; R-DICE, rituximab, dexamethasone, ifosfamide, cisplatin, etoposide; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin. [a]Time from start of therapy to start of next line of therapy (or from start of last line of prior therapy to the date of first ixazomib dose).

reported overall rates of 17–55% and grade 3 PN rates of 3–13%.[6,20–25] However, it is important to note that comparisons are confounded by between-study differences in patient baseline characteristics, dosing schedule (weekly vs twice-weekly), mode of administration (IV or subcutaneous) and duration of administration.[22,26]

The pharmacokinetics of ixazomib reported here support continued investigation of a weekly dosing schedule. Pharmacokinetics data from urine suggest that metabolism is the major mechanism of ixazomib clearance, with $< 1\%$ of the administered dose being excreted unchanged in the urine on both days 1 and 15. The pharmacokinetics reported here are comparable with pharmacokinetic data reported in other studies.[27] With weekly dosing of oral ixazomib in relapsed or refractory MM, there was a dose-proportional increase in plasma exposure with a terminal half-life of 4–12 days after multiple dosing.[13] Pharmacodynamic assessment showed that there was a dose-dependent increase in whole blood 20S proteasome inhibition.[27] Blood 20S proteasome inhibition is a marker of the pharmacodynamic effect of ixazomib in blood; however, it is not a marker for target engagement in tumor so it does not directly correlate with antitumor activity.

Preliminary antitumor activity of ixazomib was seen in this heavily pretreated relapsed/refractory lymphoma population, with five patients achieving an objective response, all of whom had received at least four lines of prior therapy. In particular, 4 of 11 patients with follicular lymphoma achieved responses, including one CR and three PRs. The 11 follicular lymphoma patients were enrolled to receive ixazomib doses from 0.25 mg/m^2 to 3.11 mg/m^2, with the CR occurring in a patient receiving 1.76 mg/m^2, and one PR reported in a patient receiving 1.4 mg/m^2, two dose levels below the MTD. The responses to ixazomib presented here appear to be durable, especially in two follicular lymphoma responders, who received more than 30 cycles of ixazomib treatment. Importantly, the drug was well tolerated in these two follicular lymphoma patients with no cumulative toxicities observed over the near-3-year treatment period. Two of the five responders are still on study receiving ixazomib, including the follicular lymphoma patient who achieved a CR and, at the time of reporting, is currently in treatment cycle 42. Interestingly, the patient with peripheral T-cell lymphoma responded to a rechallenge with ixazomib after a period of treatment discontinuation; such a phenomenon has been observed in patients with MM retreated with bortezomib.[28–30]

This first clinical study of IV ixazomib in patients with advanced lymphoma has demonstrated the general tolerability of this agent in heavily pretreated patients and the feasibility of long-term dosing, indicating that ixazomib may be clinically active in this population. These data provide the rationale for further investigation of ixazomib in lymphoma.

CONFLICT OF INTEREST

SE Assouline has received research funding from Roche and Novartis. BD Cheson has served as an advisory board member for Millennium: The Takeda Oncology Company. S Hamburg and R Reyes declare no potential conflicts of interest. J Chang has received research funding from Genentech and Celgene. R Rifkin has served as an advisory board member for Millennium: The Takeda Oncology Company, Onyx, and Celgene, and has received payment for lectures including service on speakers' bureaus for Millennium: The Takeda Oncology Company, Celgene, INCYTE, and Amgen. P Martin has received payment for lectures including service on speakers' bureaus for Millennium: The Takeda Oncology Company. A-M Hui, J Yu, N Gupta, A Di Bacco, and Y Shou are employed by Takeda Pharmaceuticals International Co., Cambridge, MA.

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