

A phase I/II dose-escalation study investigating all-oral ixazomib-melphalan-prednisone induction followed by single-agent ixazomib maintenance in transplant-ineligible newly diagnosed multiple myeloma

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SUPPLEMENTARY MATERIAL

Supplementary methods

Secondary endpoints

Secondary phase II endpoints included progression-free survival (PFS), time to progression (TTP), overall survival (OS), overall response rate, time to response, duration of response, and safety. PFS was defined as the time interval from the date of enrollment to the date of first documented disease progression (PD) or death. TTP was defined as the time interval from the date of enrollment to the date of first documented PD. OS was defined as the time from the date of enrollment to the date of death. Overall response rate was defined as the proportion of patients having achieved a partial response or better. Time to response was defined as the time interval from the date of first dose of any study drug to the date of first documented response during the induction period. Duration of response was defined for responders as the time interval from the date of first response to the date of PD.

Safety outcome measures included all adverse events (AEs), grade ≥ 3 AEs, serious AEs, AEs resulting in treatment discontinuation, and AEs resulting in dose reduction. Time to resolution (defined as the time from the initial onset date [inclusive] to the resolution date for resolved events) and time to improvement (defined as the time from the initial onset date [inclusive] of the maximum grade to the first onset date that the toxicity grade is below the maximum grade with no higher grade thereafter, or the resolution date, whichever occurred first) of peripheral neuropathy (PN; defined as treatment-emergent AEs in the high-level term of peripheral neuropathies not elsewhere classified according to the Medical Dictionary for Regulatory Activities) were exploratory safety endpoints.

While not permitted in cycle 1 (unless dose-limiting toxicity [DLT] was documented), dose modifications/treatment interruptions for all study drugs were allowed thereafter to manage toxicity.

Eligibility criteria

Male or female patients with previously untreated, symptomatic multiple myeloma (MM; or asymptomatic myeloma with myeloma-related organ damage; diagnosed according to standard criteria) who were ineligible to receive high-dose therapy and autologous stem cell transplant due to age (≥ 65 years) or a significant comorbidity (i.e. one that was likely to have a negative impact on the tolerability of high-dose therapy and autologous stem cell transplant), and for whom standard melphalan-prednisone treatment was indicated, were enrolled.

Further inclusion criteria included: measurable disease (defined as at least one of the following: serum M-protein ≥ 1 g/dL [≥ 10 g/L], urine M-protein ≥ 200 mg/24 hours, or an involved free light chain level ≥ 10 mg/dL with an abnormal serum free light chain ratio); an Eastern Cooperative Oncology Group performance status of 0-2; and adequate hematologic (absolute neutrophil count $\geq 1,000/\text{mm}^3$ and platelet count $\geq 75,000/\text{mm}^3$; platelet transfusions to help patients meet the eligibility criteria were not allowed), hepatic (total bilirubin $\leq 1.5 \times$ upper limit of normal and alanine/aspartate aminotransferase $\leq 3 \times$ upper limit of normal), and renal (calculated creatinine clearance ≥ 30 mL/min) function within the 3 days before the first dose of study treatment.

The following exclusion criteria were applied: grade ≥ 2 PN on clinical examination during screening, or grade > 1 diarrhea (according to National Cancer Institute Common Terminology Criteria for AEs grading) in the absence of antidiarrheal

therapy; female patients who were breast feeding or pregnant; major surgery (excluding kyphoplasty or vertebroplasty), serious infection (including infection requiring systemic antibiotic therapy), radiotherapy, systemic treatment with strong cytochrome P450 1A2 inhibitors or strong inhibitors/inducers of cytochrome P450 3A, or use of Ginkgo biloba or St. John's wort within 14 days of the first dose of study treatment; QTc interval of >470 ms on 12-lead electrocardiogram during screening; central nervous system involvement; uncontrolled cardiovascular conditions within the past 6 months; known or suspected HIV infection, hepatitis B surface antigen-positive status, or active hepatitis C infection; any serious medical or psychiatric illness that could potentially interfere with the completion of study treatment; known gastrointestinal disease or gastrointestinal procedure that could interfere with oral absorption or tolerance of study medication, including difficulty swallowing; known allergy to any of the study medications, their analogs, or excipients; a diagnosis of smoldering MM, Waldenström macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome; diagnosis of or treatment for another malignancy (excluding completely resected nonmelanoma skin cancer or carcinoma *in situ* of any type) within the past 2 years, or any evidence of residual disease related to a prior malignancy.

Prior systemic therapy for MM, including investigational drugs, was not permitted. However, patients who had received prior treatment with corticosteroids (<160 mg dexamethasone, or equivalent, over a 2-week dosing period) or localized radiotherapy were eligible.

Dose-limiting toxicities

DLTs were defined as any of the following occurring during cycle 1 of induction treatment: grade 4 thrombocytopenia or neutropenia lasting for >7 days, or platelets <10,000/mm³ at any time; grade 3 neutropenia with fever (temperature >38.3°C) and/or infection, or grade 3 thrombocytopenia with clinically significant bleeding (blood loss >100 mL or requirement for a red blood cell transfusion); grade 3 PN, or grade 2 PN with pain; grade ≥3 nausea and/or emesis despite optimal antiemetic prophylaxis, grade ≥3 diarrhea despite maximal supportive therapy, or any other grade ≥3 non-hematologic toxicity (except grade 3 arthralgia/myalgia or brief [<1 week] grade 3 fatigue); grade ≥2 study drug-related non-hematologic toxicity requiring discontinuation of all study drugs; or a treatment delay of >2 weeks due to inadequate recovery from combination study drug-related toxicity.

Pharmacokinetic assessment

Blood samples (3 mL) for determination of plasma concentrations of ixazomib were collected and measured using a good laboratory practice-validated liquid chromatography/tandem mass spectrometry assay. Sampling times for the twice-weekly ixazomib schedule were as follows: pre-dose (within 1 hour of dosing) and at multiple time points following the day 1 (0.25, 0.5, 1, 1.5, 2, 4, 8, and 24 hours) and day 11 (0.25, 0.5, 1, 1.5, 2, 4, 8, 24, 96, 120, and 144 hours) ixazomib doses, as well as prior to ixazomib dosing on days 4 and 8 in cycle 1; and prior to each ixazomib dose in cycles 2 and 3. For the once-weekly ixazomib schedule, sampling times were: pre-dose and at multiple time points following the day 1 (0.25, 0.5, 1, 1.5, 2, 4, 8, 24, 48, and 72 hours) and day 15 (0.25, 0.5, 1, 1.5, 2, 4, 8, 24, 48, 72, and 168

hours) ixazomib doses, as well as prior to ixazomib dosing on day 8 in cycle 1; and prior to the day 1 ixazomib dose in cycles 2 and 3.

Plasma pharmacokinetic parameters were estimated in the pharmacokinetic population using noncompartmental analysis methods and analyzed using Phoenix[®] WinNonlin[®] version 6.3 (Pharsight, St. Louis, MO, USA). The plasma pharmacokinetic parameters calculated for individual ixazomib plasma concentration-time data included maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration-time curve to 168 hours post dose (AUC_{168}), and terminal half-life ($t_{1/2}$). Only pharmacokinetic data for one relevant dose level for each of the 4 arms are presented. All pharmacokinetic parameters are summarized using descriptive statistics.

Minimal residual disease assessment

For MRD evaluation, bone marrow aspirates were obtained at the time of suspected CR. Aspirates were placed in a fixative (Streck Cell Preservative[™]; for maintaining cell surface expression of antigens) and were analysed within 72 hours of collection using a panel of antibodies against CD138, CD38, CD45, CD19, CD56, γ and κ on a FACSCanto[™] II flow cytometer.¹ An algorithmic gating strategy for CD38/CD138 was used for initial detection of plasma cells, followed by assessment of γ / κ expression on detected plasma cells, and finally CD56 and/or CD19 expression to detect aberrant plasma cells in the absence of light-chain restriction. If no clonal plasma cells were detected at thresholds of 20 events or 0.01% of total nucleated

events, the sample was considered MRD negative. The sensitivity of the assay was 10^4 . **Safety assessments**

AEs were monitored throughout the study until 30 days after cessation of study treatment or the start of subsequent antineoplastic therapy, and were graded using the National Cancer Institute Common Terminology Criteria for AEs, version 4.03. Additional regular safety assessments included physical examination, Eastern Cooperative Oncology Group performance status, 12-lead electrocardiogram, vital signs, weight, hematology, clinical chemistry, and urinalysis.

Analysis populations

The safety population (used for all safety analyses, and analysis of PFS, TTP, and OS) was defined as all patients receiving ≥ 1 dose of any study drug. The DLT-evaluable population (used to determine the maximum tolerated dose) was defined as phase I patients receiving $\geq 80\%$ of ixazomib and melphalan doses or experiencing a DLT in cycle 1. The response-evaluable population (used for the response analyses) was defined as patients receiving $\geq 5/8$ (Arm A), $\geq 2/3$ (Arm B), $\geq 4/5$ (Arm C), or $\geq 3/4$ (Arm D) doses of ixazomib during cycle 1 who had measurable disease at baseline and ≥ 1 post-baseline response assessment. The pharmacokinetic population was defined as all patients with sufficient dosing data and ixazomib concentration-time and effect-time data to permit estimation of pharmacokinetic parameters.

Results

Dose-limiting toxicities and recommended phase II dose

In Arm A, the MTD of ixazomib was determined to be 3.0 mg based on hematologic and dermal DLTs (at 3.7 mg, 1 of 3 patients experienced maculo-papular rash, and another patient experienced thrombocytopenia and neutropenia; at 3.0 mg, 1 of 6 patients experienced pruritic rash). In Arm B, the MTD of ixazomib was determined to be 4.0 mg, based primarily on non-hematologic DLTs (at 5.5 mg, 1 of 3 patients experienced ileus and neurogenic bladder, and another experienced hematemesis, vomiting, diarrhea, esophageal ulcer hemorrhage, and thrombocytopenia; at 4.0 mg, no patients experienced DLTs).

A safety review was conducted after 7 patients in Arm A and 9 patients in Arm B had been treated at the MTDs of 3.0 mg and 4.0 mg, respectively (data cut-off of November 27, 2012). The preliminary data indicated an overall improved safety and tolerability profile for patients in Arm B compared with patients in Arm A, while efficacy was similar between arms. Therefore, patient enrollment to Arm A was terminated, and the 4.0 mg group in Arm B was expanded to include 26 patients.

Two additional weekly ixazomib arms (Arms C and D) were introduced with alternative 6-week schedules. The MTD of ixazomib in Arm C was determined to be 3.0 mg, based largely on hematologic DLTs (at 4.0 mg, 1 of 3 patients experienced neutropenia and lymphopenia, and another experienced neutropenia; at 3.0 mg, 1 of 6 patients experienced neutropenia, thrombocytopenia, and respiratory tract infection). In Arm D, the MTD of ixazomib was determined to be 4.0 mg based on hematologic DLTs (at 4.0 mg, 1 of 6 patients experienced neutropenia and thrombocytopenia, and another experienced neutropenia). Once these MTDs had been determined, enrollment to Arms C and D was discontinued because the Arm B IMP regimen was considered to have a favorable benefit/risk profile.

Previous studies have suggested that, particularly for elderly patients, weekly ixazomib dosing may be slightly better tolerated than twice-weekly dosing,²⁻⁵ although this has not been verified in a comparative study. As response rates were similar across arms (Table S4), the lower incidence of DLTs and hematologic toxicity in Arm B compared with the total population (Table 6) supports these observations, and resulted in the selection of weekly 4.0 mg ixazomib dosing as the RP2D.⁶

Pharmacokinetics

Twenty patients who received the RP2D of ixazomib were evaluable for analysis of pharmacokinetics (Table S3). Ixazomib was rapidly absorbed (median T_{max} , 1 hour on day 1 and day 15) after weekly administration in combination with melphalan-prednisone at the RP2D. The geometric mean (% coefficient of variation [%CV]) ixazomib C_{max} and AUC_{168} values on day 1 were 43.3 (77) ng/mL and 709 (59) hr*ng/mL, respectively. After day 15 administration, the geometric mean (%CV) ixazomib C_{max} and AUC_{168} values were 63.4 (75) ng/mL and 1480 (48) hr*ng/mL, respectively.

Ixazomib exhibited a multi-exponential disposition profile that included a long terminal phase. After day 15 administration of the RP2D, the geometric mean (%CV) $t_{1/2}$ for ixazomib was 124 (35) hours. The geometric mean (%CV) accumulation ratio (day 15 AUC_{168} / day 1 AUC_{168}) was 2.21 (27), which was consistent with the weekly dosing regimen and the observed $t_{1/2}$.

The pharmacokinetics of ixazomib at the RP2D were consistent with previous studies of weekly ixazomib dosing.^{3, 7} Ixazomib was rapidly absorbed and exhibited a multi-exponential disposition profile that included a long terminal phase. Importantly,

and as seen for other ixazomib combination regimens,^{7, 8} the pharmacokinetic studies did not suggest any interactions between ixazomib and MP.

Supplementary tables

Table S1. Planned ixazomib dose levels.

Dose level	Arm A	Arm B	Arm C	Arm D
-1*	3.0 mg	3.0 mg	-	-
1	3.0 mg [†]	3.0 mg [†]	3.0 mg [†]	4.0 mg [‡]
2	3.7 mg	4.0 mg	4.0 mg	-
3	5.5 mg	5.5 mg	-	-
4	-	7.0 mg	-	-
5+	-	Prior dose x1.33	-	-

*It was planned that the melphalan dose at dose level -1 in Arm A and Arm B would be reduced to 6.75 mg/m² (from 9 mg/m²) and 4.5 mg/m² (from 6 mg/m²), respectively; [†]The starting dose of ixazomib 3.0 mg in Arms A, B, and C was based on population pharmacokinetic models and clinical data available at study initiation.¹⁻³ [‡]As cohort recruitment was sequential, a 4.0 mg fixed dose of ixazomib was selected for Arm D based on the maximum tolerated dose determined for Arm B.

Table S2. Treatment exposure.

	Total (N=61)	RP2D 4.0 mg Arm B (N=26)
Median number of ixazomib cycles, n (range)	16 (1-61)	12.5 (1-61)
Median duration of ixazomib treatment, months (range)	16.8 (0.3-58.0)	11.3 (0.3-58.0)
Number of patients proceeding to maintenance, n (%)	36 (59)	13 (50)
Median number of maintenance cycles received, n (range)	12 (2-49)	10 (2-49)
Number of patients remaining on treatment for >2 years, n (%)	15 (25)	5 (19)
Mean relative dose intensity, % (SD)		
Ixazomib	82.8 (16.7)	87.1 (14.9)
Melphalan	90.6 (10.6)	91.2 (10.6)
Prednisone	95.6 (6.0)	95.6 (5.9)

RP2D, recommended phase II dose; SD, standard deviation.

Table S3. Plasma pharmacokinetic parameters for ixazomib by relevant dose level for each study arm (pharmacokinetic analysis population).

	Arm A	Arm B	Arm C	Arm D
Ixazomib dose, mg	3.0	4.0 (RP2D)	3.0	4.0
Day	1	1	1	1
Patients, n	7	18*	6	5
Median T _{max} , hr (range)	1.02 (0.617-4)	1 (0.5-2.17)	1.56 (0.483-4)	0.567 (0.417-2.15)
C _{max} , ng/mL (%CV)	21.8 (68)	43.3 (77)	43.4 (79)	60.1 (75)
AUC ₇₂ , hr × ng/mL (%CV)	304 (33)	NA	NA	NA
AUC ₁₆₈ , hr × ng/mL (%CV)	NA	709 (59)	576 (63)	859 (42)
DN C _{max} , ng/mL/mg (%CV)	7.27 (68)	10.8 (77)	14.5 (79)	15.0 (75)
DN AUC ₇₂ , hr × ng/mL/mg (%CV)	101 (33)	NA	NA	NA
DN AUC ₁₆₈ , hr × ng/mL/mg (%CV)	NA	177 (59)	192 (63)	215 (42)

Day	11	15	29	29
Patients, n	7	14[†]	5[§]	4
Median T _{max} , hr (range)	1.05 (0.5-4)	1 (0.5-4)	1.5 (0.5- 4.03)	0.76 (0.3- 1.43)
C _{max} , ng/mL (%CV)	63.8 (44)	63.4 (75)	50.4 (62)	125 (62)
AUC ₇₂ , hr × ng/mL (%CV)	1180 (28)	NA	NA	NA
AUC ₁₆₈ , hr × ng/mL (%CV)	NA	1480 (48)	1360 (64)	2210 (45)
DN C _{max} , ng/mL/mg (%CV)	21.3 (44)	15.9 (75)	16.8 (62)	31.3 (62)
DN AUC ₇₂ , hr × ng/mL/mg (%CV)	393 (28)	NA	NA	NA
DN AUC ₁₆₈ , hr × ng/mL/mg (%CV)	NA	370 (48)	453 (64)	553 (45)
t _{1/2} , hr (%CV)	NR	124 (35)	134 (35)	113 (38)
Accumulation ratio (%CV)	3.90 (28)	2.21 (27)	2.55 (26)	2.54 (8)

AUC_x, area under the plasma ixazomib concentration-time curve from time 0 to x hours post dose; C_{max}, maximum observed plasma concentration; CV, coefficient of

variation; DN, dose normalized; NA, not applicable; NR, not reported; RP2D, recommended phase II dose; $t_{1/2}$, terminal half-life; T_{max} , time to first C_{max} . *n=17 for AUC_{168} and DN AUC_{168} . †n=13 for $t_{1/2}$ and 12 for the accumulation ratio. §n=4 for $t_{1/2}$.

Table S4. Response rates after induction and at end of study (response-evaluable population), by treatment arm.

n (%)	Arm A, N=10	Arm B (all), N=31	Arm B (RP2D), N=23	Arm C, N=8	Arm D, N=4
<i>Response after</i>					
<i>induction</i>					
ORR (≥PR)	8 (80)	21 (68)	15 (65)	4 (50)	2 (50)
CR (confirmed)	1 (10)	4 (13)	3 (13)	1 (13)	1 (25)
sCR (confirmed)	0	2 (6)	1 (4)	1 (13)	0
VGPR	4 (40)	10 (32)	7 (30)	1 (13)	1 (25)
CR+VGPR (confirmed)	5 (50)	14 (45)	10 (43)	2 (25)	2 (50)
<i>Response at end</i>					
<i>of study</i>					
ORR	8 (80)	21 (68)	15 (65)	4 (50)	2 (50)
CR (confirmed)	4 (40)	7 (23)	5 (22)	2 (25)	2 (50)
sCR (confirmed)	1 (10)	5 (16)	4 (17)	2 (25)	2 (50)
VGPR	1 (10)	8 (25)	6 (26)	0	0
CR+VGPR	5 (50)	15 (48)	11 (48)	2 (25)	2 (50)

(confirmed)

≥50% reduction in	8 (80)	26 (84)	18 (82)	7 (88)	2 (50)
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M-protein

100% reduction in	5 (50)	16 (52)	11 (48)	2 (25)	1 (25)
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M-protein

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