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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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ABSTRACT

This phase I/II dose-escalation study investigated the all-oral ixazomib-melphalan-prednisone regimen, followed by single-agent ixazomib maintenance, in elderly, transplant-ineligible patients with newly diagnosed multiple myeloma. Primary phase I objectives were to determine the safety and recommended phase II dose of ixazomib-melphalan-prednisone. The primary phase II objective was to determine the complete plus very good partial response rate. In phase I, patients were enrolled to 4 arms investigating weekly or twice-weekly ixazomib (13 28-day cycles or nine 42-day cycles) plus melphalan-prednisone. In phase II, an expansion cohort was enrolled at the recommended phase II ixazomib dose. Of the 61 patients enrolled, 26 received the recommended phase II dose (ixazomib 4.0 mg [days 1, 8, 15] plus melphalan-prednisone 60 mg/m^2 [days 1-4], 28-day cycles). Of the 61 enrolled patients, 36 (13 of 26 in the recommended phase II dose cohort) received single-agent ixazomib maintenance (days 1, 8, 15; 28-day cycles). In phase I, 10/38 patients reported dose-limiting toxicities in cycle 1, including grade 3 and/or 4 neutropenia (n=6) and thrombocytopenia (n=4). Complete plus very good partial response rate was 48% (48% at recommended phase II dose), including 28% (22%) complete response or better; responses deepened during maintenance in 34% (33%) of evaluable patients. After median follow up of 43.6 months, median progression-free survival was 22.1 months. Adverse events were mainly hematologic events, gastrointestinal events, and peripheral neuropathy. This study demonstrates the feasibility, tolerability, and activity of ixazomib-melphalan-prednisone induction and single-agent ixazomib maintenance in transplant-ineligible newly diagnosed multiple myeloma patients. *clinicaltrials.gov identifier 01335685.*

Introduction

Although multiple myeloma (MM) remains, for most patients, an incurable hematologic malignancy, recent advances in treatment and diagnosis have led to substantial improvements in both progression-free survival (PFS) and overall survival (OS).[1-4] As with many malignancies, younger, fitter patients usually achieve the best outcomes with initial treatment, while outcomes for elderly patients and those with comorbidities, who are unable to tolerate high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT), have traditionally lagged behind.[3-8] For these elderly and frail patients, active, novel, frontline combination regimens are needed to achieve the best long-term outcomes. However, tolerability can be an issue for some patients,[5,6] particularly in the case of long-term, continuous therapy, which is associated with improved outcomes.[9-13]

Following demonstration of favorable efficacy and tolerability in phase III trials,[14-17] the combination of the proteasome inhibitor (PI) bortezomib plus melphalan and prednisone (VMP) is now, in many geographies, a standard-of-care regimen for the first-line treatment of elderly patients with newly diagnosed MM (NDMM) who are not eligible to receive HDT/ASCT because of age-related frailty and/or comorbidity.[3,4] VMP represents an active, feasible frontline treatment option, including for patients with high-risk cytogenetic abnormalities (due to the activity of PI-based regimens in this population) and patients with renal impairment (as no starting dose adjustment is required), and offers a suitable option for patients in whom immunomodulatory drug-containing therapy is contraindicated.[18-22]

However, despite being a standard of care, the parenteral administration of bortezomib may create a burden for elderly patients, limiting its feasibility for long-term use. The combination of another parenterally administered PI, carfilzomib, and melphalan-prednisone (MP) was recently compared with VMP and demonstrated no statistically significant difference in PFS in transplant-ineligible NDMM; however, carfilzomib-MP was associated with a higher number of specific grade ≥3 adverse events (AEs), notably acute renal failure, cardiac failure, dyspnea, and hypertension, and fewer incidences of peripheral neuropathy (PN) than VMP.[23]

Therefore, there remains a need for a tolerable, efficacious, and convenient PI option for elderly patients with transplant-ineligible NDMM. Ixazomib is an oral PI with a safety profile amenable to extended dosing.[24-26] Based on the results of the TOURMALINE-MM1 study, which led to its first approval in 2015, ixazomib has been approved in more than 50 countries worldwide, including the US, EU, and Japan, for use in combination with lenalidomide-dexamethasone (IRd) for the treatment of MM patients who have received at least one prior therapy.[26-28] Recent phase I/II studies have demonstrated the activity and tolerability of ixazomib-based induction (IRd) and long-term ixazomib maintenance therapy in NDMM, demonstrating the feasibility of this approach.[29,30] This phase I/II trial *(clinicaltrials.gov identifier 01335685)* was undertaken to evaluate the all-oral ixazomib-MP (IMP) induction regimen, followed by long-term maintenance with single-agent ixazomib, in predominantly elderly, transplant-ineligible patients with NDMM.

Methods

Study design

This was a phase I/II, open-label, multicenter, dose-escalation study. The primary phase I objectives were to determine safety, maximum tolerated dose (MTD), and recommended phase II dose (RP2D) of ixazomib in combination with MP. A secondary objective was to characterize ixazomib pharmacokinetics. The primary phase II objective was to determine the complete response plus very good partial response (CR+VGPR) rate. Secondary objectives included overall response rate (ORR), time to response, duration of response, PFS, time to progression, OS, and safety (for details, see the *Online Supplementary Material*).

Patients

Patients with previously untreated MM who were ineligible for HDT/ASCT due to age (≥65 years) or comorbidity, and for whom standard MP treatment was indicated, were enrolled. Detailed eligibility criteria are presented in the *Online Supplementary Material.*

The study complied with regulatory requirements, the Declaration of Helsinki, and Good Clinical Practice standards. Independent review boards/ethics committees approved the study. Patients gave written informed consent.

Treatment

In phase I, patients were enrolled into one of four arms, as assigned by investigators under direction of the sponsor (Figure 1). In Arm A, patients received up to 9 42-day cycles of twice-weekly ixazomib (days 1, 4, 8, 11, 22, 25, 29, 32). In Arm B, patients received up to 13 28-day cycles of weekly ixazomib (days 1, 8, 15). In Arms C and D, patients received up to 9 42-day cycles of weekly ixazomib (days 1, 8, 15, 22, 29 for Arm C and days 1, 8, 22, 29 for Arm D). Patients also received melphalan 6 mg/m^2 (Arm B) or 9 mg/m^2 (Arms A, C, D) on days 1-4 and prednisone 60 mg/m^2 (days 1-4) in each cycle.

Ixazomib dose-escalation proceeded via a standard 3+3 design based on cycle 1 dose-limiting toxicities (DLTs; as defined in the Online Supplementary Material). The MTD required no more than 1 out of 6 DLT-evaluable patients to have a first-cycle DLT. Planned dose levels for ixazomib are shown in *Online Supplementary Table S1*. In phase II, an expansion cohort was enrolled at the RP2D, which was established by considering all available phase I toxicity (grade 3/4 AEs, serious AEs [SAEs], all-grade PN, and treatment discontinuation) and ORR over multiple cycles.

After induction, patients with stable disease or better could receive single-agent ixazomib maintenance (at the dose tolerated for induction) on days 1, 8, 15 for up to 12 28-day cycles, or until disease progression or unacceptable toxicity (Figure 1).

Assessments

Responses were assessed by investigators on day 1 of each cycle, at the end of induction, every 2 cycles during maintenance, and every 16 weeks during follow up until progression or start of subsequent antineoplastic therapy, according to International Myeloma Working Group criteria.[31] AEs were monitored throughout and graded using the National Cancer Institute-Common Terminology Criteria for AEs, version 4.03. Details of the pharmacokinetic, minimal residual disease (MRD), and safety assessments are provided in the *Online Supplementary Material.*

Analyses

Analysis populations are defined in the *Online Supplementary Material.* Time-to-event endpoints were analyzed using survival

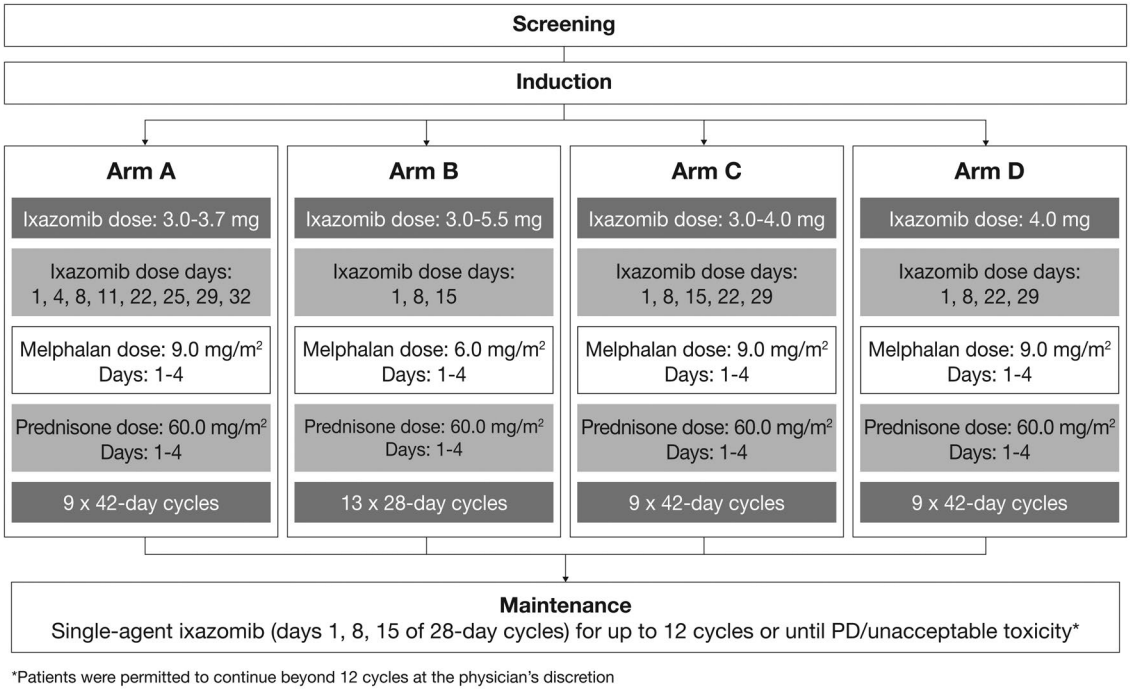

Figure 1. Phase I study design. PD: progressive disease.

analysis techniques based on Kaplan-Meier estimates. All data were summarized using descriptive statistics.

Results

Patient disposition and baseline characteristics

A total of 61 patients were enrolled: 11, 34, 10, and 6 to Arms A, B, C, and D, respectively (Tables 1 and 2). All patients received ≥1 dose of any study drug and were included in the safety population; 26 of these patients received ixazomib at the RP2D (Tables 1 and 2). The baseline demographics and disease characteristics of the safety population are shown in Table 1. Seven patients had high-risk cytogenetics; all were enrolled in Arm B.

Dose-limiting toxicities and recommended phase II dose

During phase I, 38 patients (9, 14, 9, and 6 in Arms A, B, C, and D, respectively) were evaluable for assessment of DLTs. Among these patients, 10 (26%) experienced a total of 16 DLTs in cycle 1. All DLTs were grade 3 or grade 4 in intensity.

The RP2D was determined as weekly ixazomib 4.0 mg (days 1, 8, and 15 of 28-day cycles) based on the Arm B MTD, ORR (*Online Supplementary Table S4*), and observed rates of toxicity across multiple cycles. Baseline characteristics for this RP2D cohort were similar to those for the total study population (Table 1). Detailed descriptions of DLTs and determination of the RP2D can be found in the *Online Supplementary Material.*

Treatment exposure

At final analysis, 4 patients remained on treatment. Primary reasons for discontinuation were progressive disease, patient withdrawal, and completion of protocol-specified treatment (Table 2). After a median fol-

Table 1. Patient demographics and disease characteristics at baseline (safety population).

Characteristic	Total (N=61)	RP2D 4.0 mg Arm B (N=26)
Median age, years (range)	74 (63-90)	74 (67-84)
Male, n (%)	23 (38)	10 (38)
Race, n (%)		
White	57 (93)	24 (92)
Black / African American	1 (2)	1 (4)
Asian	1 (2)	0
Other	2 (3)	1 (4)
ECOG performance status, n (%)		
0	17 (28)	7 (27)
1	33 (54)	13 (50)
2	11 (18)	6 (23)
ISS stage, n (%)		
I	13 (21)	5 (19)
II	31 (51)	14 (54)
III	17 (28)*	7 (27)
Type of myeloma at initial diagnosis, n (%)		
IgG	36 (59)	20 (77)
IgA myeloma	20 (33)	5 (19)
Light-chain disease	5 (8)	1 (4)
Extramedullary disease, n (%)	6 (10)	2 (8)
High-risk cytogenetics, n (%)†	7 (12)	5 (21)
Median β_2M, mg/L (range)	4.3 (2.1-14.0)	4.6 (2.4-14.0)
CrCl ≤60 mL/min, n (%)	34 (56)	13 (50)

β_2M: beta-2 microglobulin; CrCl: creatinine clearance; ECOG: Eastern Cooperative Oncology Group; Ig: immunoglobulin; ISS: International Staging System; RP2D: recommended phase II dose. The safety population was defined as all patients receiving ≥1 dose of any study drug. *Unknown for two patients; †High-risk cytogenetics includes del17p, t(4:14), and t(14:16) abnormalities.

Table 2. Ixazomib dose received and primary reason for discontinuation by study arm (safety population).

	Arm A		Arm B			Arm C		Arm D	Total*
Ixazomib dose received, mg	3.0	3.7	3.0	4.0 (RP2D)	5.5	3.0	4.0	4.0	
Patients, N	7	4	3	26	5	6	4	6	61
Primary reason for discontinuation, n (%)									
PD	5 (71)	2 (50)	2 (67)	11 (42)	3 (60)	3 (50)	1 (25)	2 (33)	29 (48)
AEs	0	0	0	8 (31)	2 (40)	0	1 (25)	2 (33)	13 (21)
Patient withdrawal	1 (14)	2 (50)	0	2 (8)	0	0	1 (25)	0	6 (10)
Completion of protocol-specified treatment	1 (14)	0	1 (33)	2 (8)	0	0	1 (25)	1 (17)	6 (10)
Unsatisfactory therapeutic response	0	0	0	1 (4)	0	1 (17)	0	0	2 (3)
Preference for immunomodulatory therapy given the PR	0	0	0	1 (4)	0	0	0	0	1 (2)
Study terminated by sponsor	0	0	0	1 (4)	0	2 (33)	0	1 (17)	4 (7)

AE: adverse event; PD: progressive disease; PR: partial response; RP2D: recommended phase II dose. *Discontinuation due to – PD: 8 during induction, 21 during maintenance; AEs: 11 during induction, 2 during maintenance; patient withdrawal: 3 during induction, 3 during maintenance; completion of protocol-specified treatment: all 6 during induction; unsatisfactory therapeutic response: both during induction; preference for immunomodulatory therapy: during induction; study terminated: all 4 during maintenance.

low up for OS of 43.6 months, patients had received a median of 16 cycles of ixazomib (12.5 cycles in the RP2D cohort; *Online Supplementary Table S2*). A total of 36 patients entered the maintenance phase (n=13 at the RP2D), and received a median number of maintenance cycles of 12, with a maximum duration of ixazomib treatment of 58 months (*Online Supplementary Table S2*). Thirteen patients (36%) remained on maintenance therapy for ≥13 cycles (≥1 year), and 5 patients (14%) remained on maintenance for ≥25 cycles (≥2 years). Mean relative dose intensity over the whole study for ixazomib was 82.8% (87.1% at the RP2D), and ≥90% for both melphalan and prednisone (*Online Supplementary Table S2*).

Pharmacokinetic analyses are shown in *Online Supplementary Table S3*.

Efficacy

Fifty-three patients were evaluable for response, including 23 at the RP2D. Among response-evaluable patients, the confirmed CR+VGPR rate at the end of study was 48%, including 28% ≥CR (Table 3). The confirmed ORR at end of study was 66%, with 86% of patients achieving a ≥50% reduction in serum M-protein. In both the total population and at the RP2D, 48% of patients demonstrated a 100% reduction in their serum M-protein (Table 3). Median time to ≥VGPR and CR was 3.7 and 11.6 months, respectively (Table 4). Of the 7 high-risk patients, 1 patient achieved a CR and 3 patients achieved a PR; 2 patients were not evaluable for response.

Responses deepened during maintenance with single-agent ixazomib: in 11/32 (34%) response-evaluable patients overall (CR to sCR in 2 patients; VGPR to sCR in 5 patients; VGPR to CR in 3 patients; and PR to VGPR in 1 patient); and in 4/12 (33%) response-evaluable patients who received the RP2D (CR to sCR in 1 patient; VGPR to sCR in 2 patients; and PR to VGPR in 1 patient). The confirmed CR rate was 13% after induction, rising to 28% at the end of treatment (Table 3).

Thirteen of 53 (24%) response-evaluable patients were assessed for minimal residual disease (MRD) by flow cytometry, 5 of whom were in the RP2D cohort. Of these 13 patients, 12 had a best confirmed response of ≥CR and one had a best confirmed response of VGPR. MRD results in 9 of the 12 patients with ≥CR (75%) (3 at the RP2D) were found to be negative. Therefore, in the total study population, 9 of 53 response-evaluable patients (17%; 3 of 23 [13%] in the RP2D cohort) were MRD-negative.

Evaluation of time-to-event data demonstrated the durability of responses (Table 4). Median time to best response (≥PR) was 4.6 months in the total study population and at the RP2D. Median duration of response was 22.6 months overall and 25.4 months in patients achieving ≥VGPR (Table 4). Median PFS was 22.1 months overall and 18.4 months at the RP2D after median follow up for PFS of 18.0 and 10.2 months, respectively (Figure 2A and Table 4). For patients who entered the maintenance phase, median PFS was 27.5 months (38.7 months at the RP2D) (Figure 2A and Table 4); median PFS for standard-risk patients who entered the maintenance phase was similar, at 28.8 months (38.7 months at the RP2D). Median OS was 54.4 months overall and not reached at the RP2D after median follow up of 43.6 months in the total population and 48.6 months in Arm B, respectively (Figure 2B and Table 4).

Safety

Safety profiles during induction and maintenance are shown in Table 5, and the most common toxicities are shown in Table 6. The most common grade ≥3 AEs (≥10% incidence) were thrombocytopenia, neutropenia, lymphopenia, leukopenia, anemia, and diarrhea (Table 6). Hematologic toxicities were less common at the RP2D than in the total population. The most common SAE was pneumonia (n=6 [10%]; n=2 [8%] at the RP2D). The only AE to result in discontinuation of study treatment in more than one patient was thrombocytopenia (n=3, 5%). None of the 3 on-study deaths (all in the RP2D cohort; attributed to pneumonia, septic shock, and worsening of end-stage MM, respectively) were considered by investigators to be related to study treatment.

There was a limited incidence of new-onset toxicities during single-agent ixazomib maintenance compared with IMP induction. Any-grade AEs with a ≥15% difference between patients who entered the maintenance period and those who did not were thrombocytopenia (64% for

Table 3. Response rates after induction and at end of study (response-evaluable population).

n (%)	Total	RP2D 4.0 mg Arm B
Response after induction	N=53*	N=23
ORR (≥PR)	35 (66)	15 (65)
CR (confirmed)	7 (13)	3 (13)
sCR (confirmed)	3 (6)	1 (4)
VGPR	16 (30)	7 (30)
CR+VGPR (confirmed)	23 (43)	10 (43)
≥50% reduction in M-protein	41 (82)	17 (77)
Response at end of study	N=53*	n=23
ORR	35 (66)	15 (65)
CR (confirmed)	15 (28)	5 (22)
sCR (confirmed)	10 (19)	4 (17)
VGPR	9 (17)	6 (26)
CR+VGPR (confirmed)	24 (48)	11 (48)
≥50% reduction in M-protein	43 (86)	18 (82)
100% reduction in M-protein	24 (48)	11 (48)

CR: complete response; ORR: overall response rate; PR: partial response; R2PD: recommended phase II dose; sCR: stringent complete response; VGPR: very good partial response. Response-evaluable population was defined as patients receiving ≥5/8 (Arm A), ≥2/3 (Arm B), ≥4/5 (Arm C), or ≥3/4 (Arm D) doses of ixazomib during cycle 1 with measurable disease at baseline and 1 post-baseline response assessment. *Eight patients were not evaluable for response due to: no measurable disease (two patients); no post-baseline assessment (one patient); and incomplete dosing in cycle 1 (5 patients).

Table 4. Time-to-event outcomes with IMP induction and single-agent ixazomib maintenance.

Outcome (in months unless otherwise stated)	Total (N=61)	RP2D 4.0 mg Arm B (n=26)
Median time to first response (range)*	1.7 (1-7)	1.9 (1-7)
Median time to first ≥VGPR (range)*	3.7 (1-13)	3.7 (1-13)
Median time to first CR (range)*	11.6 (1-23)	9.5 (5-22)
Median DOR (95% CI)*†	22.6 (15.9, 32.4)	25.2 (4.6, NR)
Median DOR in patients achieving ≥VGPR (95% CI)*	25.4 (15.0, 29.5)	29.5 (2.8, NR)
Median PFS (95% CI)†‡	22.1 (18.0, 30.0)	18.4 (8.3, 38.7)
Median PFS in patients who entered maintenance phase (95% CI)‡	27.5 (18.7, 37.8)	38.7 (15.6, NR)
Median time to progression (95% CI)†‡	23.5 (18.0, 30.0)	22.1 (8.8, NR)
Median OS (95% CI)†‡	54.4 (39.7, NR)	NR (35.0, NR)
Estimated 3-year OS rate, %†‡	73	68

CI: confidence interval; CR: complete response; DOR: duration of response; NR: not reached; OS: overall survival; PFS: progression-free survival; RP2D: recommended phase II dose; VGPR: very good partial response. *Response-evaluable population (total, N=53; RP2D 4.0 mg Arm B, n=23); †Median follow up: 18.4 (total) and 16.6 (RP2D) months for DOR; 18.0 (total) and 10.2 (RP2D) months for PFS and time to progression; and 43.6 (total) and 48.6 (RP2D) months for OS. ‡Safety population.

induction-only patients *vs.* 86% for maintenance patients), lymphopenia (28% *vs.* 44%), anemia (60% *vs.* 36%), constipation (52% *vs.* 33%), and rash (16% *vs.* 33%).

Any-grade PN (classified by the high-level term peripheral neuropathies not elsewhere classified) considered to be study drug-related was reported in 24 patients (39%) (Table 6). PN was primarily low grade, with 12 patients (20%; 5 [19%] at the RP2D) and 19 patients (15%; 5 [19%] at the RP2D) reporting grade 1 and grade 2 PN, respectively. Three patients (5%) had grade 3 PN events. No patient had grade 4. Overall, 8 patients (13%) received dose reductions and 7 patients (11%) had study drug held due to PN. Twenty of the 24 patients (83%) who developed PN events during induction or maintenance had improved symptoms by the end of the study, with 17 (71%) having complete resolution of symptoms. Median time to resolution of PN events was 4.6 months (95% confidence interval: 1.6–14.3). Median time to resolution or improvement of PN events was 1.7 months (95% confidence interval: 1.1–6.4).

Discussion

A PI, namely bortezomib, combined with MP has been shown to be an effective frontline treatment approach for NDMM patients unable to undergo HDT/ASCT due to advanced age and/or significant comorbidities, including those for whom immunomodulatory drugs are not an option.[16,17,23] Most studies of the VMP regimen have utilized a fixed duration of treatment (often approximately 1 year) rather than extended or continuous therapy.[17,19,32,33] Furthermore, in the real-world clinical practice setting, early discontinuations due to toxicities are common.[34] As long-term, continuous therapy is associated with improved outcomes,[9-13] a tolerable, more convenient treatment regimen suitable for long-term use is needed, especially in elderly patients.

The data from this study suggest that all-oral IMP induction followed by single-agent ixazomib maintenance is an active and well-tolerated frontline regimen in transplant-ineligible patients with NDMM. The regimen showed encouraging tolerability over a prolonged treatment period, with ≥50% of patients proceeding to maintenance, including at the RP2D, and duration of therapy of up to 4.8 years. The regimen also demonstrated high response rates, with an overall CR+VGPR rate of 48%, including 28% ≥CR. Additionally, lengthy outcomes were reported, with an overall median PFS of 22.1 months, and an overall median OS of 54.4 months.

Differences in outcomes between the overall and RP2D populations should be interpreted with caution due to the relatively small numbers of patients involved and differences in patient characteristics (for example, 5 of the 7 patients with high-risk cytogenetic abnormalities were in the RP2D cohort). Additionally, the median follow up for PFS in the RP2D cohort was shorter than in the overall population, which also included patients who received more dose-intense regimens that may have resulted in improved short-term efficacy (ORR).

While the efficacy data reported here were obtained in a relatively small number of patients within the context of a non-comparative early-phase trial, they appear similar to those seen with VMP or carfilzomib plus MP in phase III studies in transplant-ineligible patients with

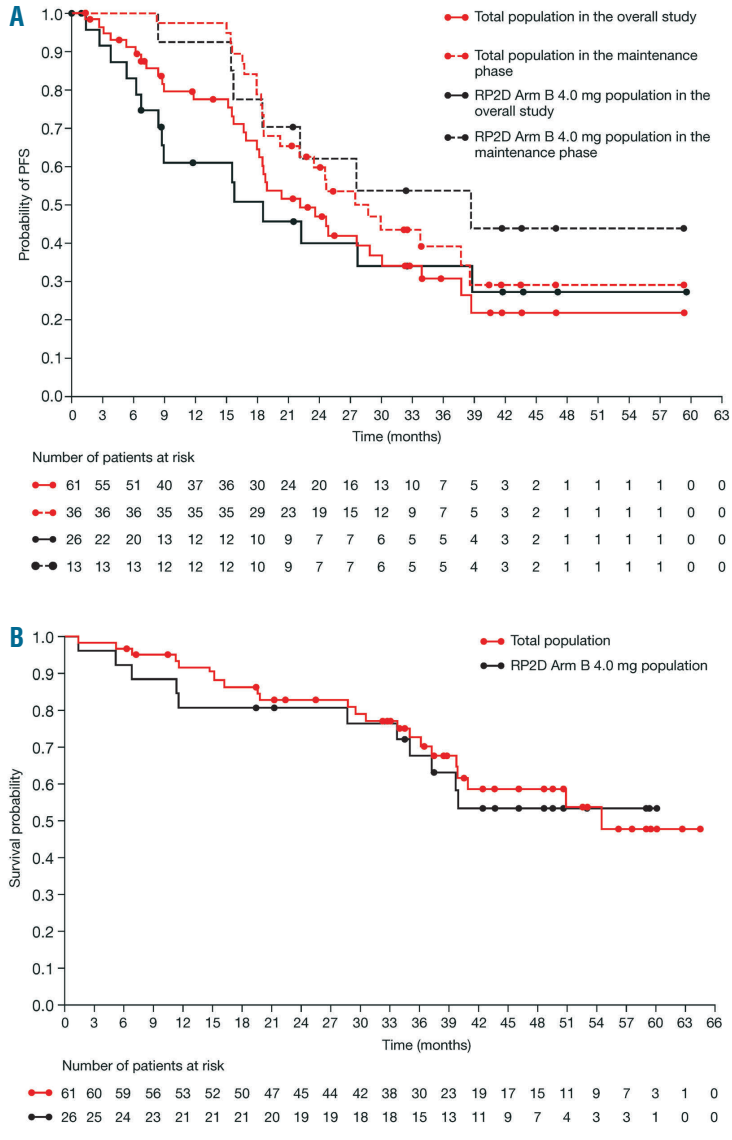

Figure 2. Kaplan-Meier analysis of PFS and OS. (A) PFS for the total patient population in the overall study (induction and maintenance phases) and in patients who went on to receive maintenance, and (B) OS in the overall study, for the total safety population and the subset of patients treated at the RP2D (4.0 mg) in Arm B. OS: overall survival; PFS: progression-free survival; RP2D: recommended phase II dose. Figure 2A, one patient in the RP2D group with PD entered maintenance, the patient was identified later following reassessment of the data.

NDMM.[14,16,17,19,23,32,33] The CR+VGPR rates post-IMP (43%) and overall (48%) are comparable to rates reported for VMP (41–50% in the phase III VISTA, GIMEMA-MM-03-05, and ALCYONE trials[17,19,33]), and median PFS (22.1 months) also appeared similar to that reported with VMP and carfilzomib-MP (18.1–27.3 months).[17,19,23,33] Similar CR+VGPR rates (47–49%) and median PFS (21–26 months) were seen with fixed-duration and continuous lenalidomide-dexamethasone (Rd) in the FIRST phase III trial in transplant-ineligible NDMM,[35] and while responses and outcomes appeared better with daratumumab-VMP in ALCYONE (71% CR+VGPR, 18-month PFS 71.6%),[33] and with IRd (58–63%, median PFS 29.4–35.4 months)[29] and bortezomib-Rd (44%, median PFS 43 months) in NDMM patients,[36] these differences should be considered in the context of the addition of daratumumab as a fourth induction agent and as maintenance therapy in ALCYONE, and the inclusion of a high proportion of transplant-eligible patients in the IRd (35%)[29] and VRd (69%) studies.[36] The overall CR rate (28%) seen with IMP plus ixazomib maintenance was also comparable to those reported for VMP without maintenance (24–33%[17,19,23,33]). Although the post-IMP induction CR rate was lower than that reported for VMP in the VISTA study (13% *vs.* 31%), the CR rate increased to 28% during maintenance. This difference may simply reflect the longer median time to CR observed with IMP (11.6 months, compared with 4.2 months for VMP in the VISTA study).[17] Indeed, the time to first response with IMP (1.7 months) was similar to that seen in the VISTA study (1.4 months). These findings together suggest that the response with IMP may mature over a longer period compared with VMP and similar response rates can be achieved with IMP followed by ixazomib maintenance and VMP without maintenance.[17,19,23,33] It should also be noted that the weekly IMP regimen used at the RP2D was similar to the less-intense weekly VMP regimen used in the PETHEMA/GEM05 study, followed by bortezomib-based maintenance.[14] In the overall study, the CR rate

Table 5. Safety profile with IMP induction and single-agent ixazomib maintenance (safety population).

n (%)	Overall		New-onset AE during induction		New-onset AE during maintenance	
	Total (N=61)	RP2D 4.0 mg Arm B (N=26)	Total (N=61)	RP2D 4.0 mg Arm B (N=26)	Total (N=36)	RP2D 4.0 mg Arm B (N=13)
Grade ≥3 AE	54 (89)	21 (81)	54 (89)	21 (81)	18 (50)	5 (38)
Serious AE	31 (51)	12 (46)	28 (46)	11 (42)	8 (22)	2 (15)
AE leading to discontinuation of any study drug	15 (25)	8 (31)	13 (21)	6 (23)	2 (6)	2 (15)
AE leading to dose reduction of any study drug	32 (52)	13 (50)	31 (51)	12 (46)	3 (8)	3 (23)
On-study death	3 (5)	3 (12)	3 (5)*	3 (12)*	0	0

AE: adverse event; IMP: ixazomib-melphalan-prednisone; RP2D: recommended phase II dose. *On-study deaths: disease progression in 1 patient, and pneumonia and septic shock in 1 patient each (not considered drug related).

Table 6. Most common (≥30% incidence in either population) any-grade and grade ≥3 AEs (safety population).

n (%)	Any-grade AE		Grade ≥3 AE	
	Total (N=61)	RP2D 4.0 mg Arm B (n=26)	Total (N=61)	RP2D 4.0 mg Arm B (n=26)
Thrombocytopenia	47 (77)	16 (62)	30 (49)	7 (27)
Diarrhea	38 (62)	17 (65)	7 (11)	4 (15)
Neutropenia	38 (62)	12 (46)	27 (44)	6 (23)
Nausea	33 (54)	11 (42)	0	0
Anemia	31 (51)	9 (35)	9 (15)	4 (15)
Vomiting	28 (46)	11 (42)	2 (3)	0
Constipation	25 (41)	6 (23)	1 (2)	0
PN NEC*	24 (39)	11 (42)	3 (5)	1 (4)
Lymphopenia	23 (38)	8 (31)	18 (30)	5 (19)
Asthenia	22 (36)	9 (35)	4 (7)	1 (4)
Decreased appetite	22 (36)	8 (31)	0	0
Pyrexia	20 (33)	6 (23)	1 (2)	0
Leukopenia	19 (31)	7 (27)	12 (20)	3 (12)
Rashes, eruptions and exanthems NEC*	18 (30)	6 (23)	4 (7)	1 (4)
Fatigue	17 (28)	9 (35)	2 (3)	2 (8)

AE: adverse event; NEC: not elsewhere classified; PN: peripheral neuropathy; RP2D: recommended phase II dose. *Higher-level terms including multiple preferred terms: PN NEC includes peripheral sensory neuropathy, neuropathy peripheral and polyneuropathy; rashes eruptions and exanthems NEC includes rash macular, rash maculo-papular, rash, rash papular, rash generalized.

post-VMP induction was 20%,[14] and in a matched-pairs analysis comparing the PETHEMA/GEM05 and VISTA regimens, the CR rate in PETHEMA/GEM05 patients improved from 19% post-induction to 30% overall, following maintenance.[32] As shown by the improved responses in >30% of patients during extended treatment with single-agent ixazomib maintenance, patients continued to derive clinical benefit from long-term single-agent ixazomib maintenance, an observation consistent with results from other early-phase ixazomib studies.[29,30]

The overall safety profile was as expected based on previous studies of ixazomib regimens and MP,[24,26,37-41] with most AEs being hematologic and gastrointestinal, which are among the common AEs reported with melphalan and proteasome inhibitors, including ixazomib.[42] Dose reductions or discontinuations of any study drug were required in approximately half and a quarter of patients, respectively. The incidence of PN was comparable to that reported in studies of IRd in NDMM,[25,30] and appeared limited when compared with that reported with a VMP regimen incorporating twice-weekly intravenous bortezomib (13% grade ≥3).[43] Importantly, >80% of reported PN events in the present study resolved or improved by study end. As suggested for IRd,[26] the all-oral IMP regimen would be expected to be convenient for patients, and the number of planned visits to the clinic for administration of the regimen would be expected to be lower than with the VMP regimen, resulting in a lower patient burden. Our experience with regards to weekly and twice-weekly ixazomib dosing and dose level is in line with experience with IRd,[44] which suggests that twice-weekly ixazomib may be associated with some additional toxicity, notably an increase in PN and rash.[29,30]

Importantly, the continued clinical benefit demonstrated with weekly single-agent ixazomib maintenance therapy was complemented by a favorable tolerability profile. The majority of AEs were observed during the induction period, only 6% of patients discontinued ixazomib maintenance because of AEs, and no on-study deaths occurred during maintenance. The number of patients who continued on long-term single-agent ixazomib maintenance therapy further emphasizes the tolerability of this regimen. Based on the efficacy and tolerability of single-agent maintenance seen in this and other trials, weekly ixazomib is under phase III

investigation as MM maintenance therapy following ASCT (*TOURMALINE-MM3; clinicaltrials.gov identifier 02181413*). A second phase III study is also investigating weekly ixazomib as maintenance therapy after initial induction therapy without ASCT (*TOURMALINE-MM4; clinicaltrials.gov identifier 02312258*). Phase III investigation of IMP followed by ixazomib maintenance therapy is not currently planned.

In conclusion, this study demonstrates the feasibility, tolerability, and antimyeloma activity of the all-oral IMP induction regimen followed by long-term maintenance with single-agent oral ixazomib in elderly, transplant-ineligible patients with NDMM. Oral dosing, coupled with a favorable safety profile at the RP2D, make ixazomib particularly suitable for long-term continuous therapy and may offer a more convenient, active, and well-tolerated alternative to a parenterally administered PI in this setting.

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