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Original Research

All-oral ixazomib, cyclophosphamide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma

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KEYWORDS
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Abstract ***Background:*** Novel efficacious treatments with long-term tolerability are needed for transplant-ineligible, newly diagnosed multiple myeloma (NDMM) patients. This phase 2 study evaluated the safety and efficacy of all-oral ixazomib-cyclophosphamide-dexamethasone (ICd) followed by single-agent ixazomib maintenance.
Patients and methods: Patients were randomised (1:1) to receive 4.0 mg of ixazomib, 300 (Arm A) or 400 (Arm B) mg/m^2 of cyclophosphamide (days 1, 8, and 15), and 40 mg of

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dexamethasone (days 1, 8, 15, and 22) as induction (up to 13 × 28-day cycles), followed by single-agent ixazomib maintenance (28-day cycles) until progressive disease, death, or unacceptable toxicity. Primary end-point was complete response (CR) + very good partial response (VGPR) rate for ICd induction.

Results: Seventy patients were enrolled (n = 36 Arm A; n = 34 Arm B); median age was 73 years (range, 61–87). At data cut-off, 66% of patients had completed 13 induction cycles followed by ixazomib maintenance. Median overall treatment duration was 19 cycles (range, 1–29); 21% of patients discontinued treatment during induction and 3% during maintenance due to adverse events (AEs). During induction, among 67 response-evaluable patients, CR+VGPR rate was 25%, and overall response rate (ORR) was 73%. Including the maintenance phase, CR+VGPR rate was 33%, and ORR was 76%. Median progression-free survival was 23.5 months (median follow-up: 26.1 months). The most common all-grade AE was neutropenia (31%). Grade ≥3 AEs were reported by 73% of patients. Five on-study deaths occurred (not treatment-related).

Conclusions: ICd treatment followed by ixazomib maintenance is tolerable and active in elderly, transplant-ineligible NDMM patients.

Trial registration number: NCT02046070.

1. Introduction

Multiple myeloma (MM) commonly affects elderly patients: the median age at diagnosis is 69 years, and 33% of patients are aged ≥75 years [1]. Many elderly patients with newly diagnosed MM (NDMM) are frail and present with comorbidities; these patients are generally ineligible for autologous stem cell transplantation (ASCT) and are currently underrepresented in NDMM clinical trials [1]. New, active, first-line treatment options for elderly and frail MM patients represent an ongoing unmet need [2].

Current therapeutic approaches in MM are shifting towards extended treatment, with maintenance therapy frequently being incorporated into treatment schedules, to further improve clinical outcomes [3–6]. However, elderly and/or frail patients with NDMM are more susceptible to drug-related complications and adverse events (AEs), which may lead to early treatment discontinuations or dose reductions [1]. Hence, new efficacious regimens that are easy to administer for prolonged periods of time, have limited late-onset or long-term toxicity, and can sustain or deepen responses while maintaining quality of life (QoL) are needed for these patients.

Ixazomib, the first orally administered proteasome inhibitor (PI), is approved in the US and Europe, in combination with lenalidomide and low-dose dexamethasone (Rd), for patients with MM who have received one or more prior therapy [7,8], based on the phase 3 TOURMALINE-MM1 study [9]. Combinations of weekly ixazomib and immunomodulatory drugs have also demonstrated feasibility and efficacy in patients with NDMM [10–12]. Triplet regimens including PIs and immunomodulatory drugs are commonly used for patients with NDMM [13]. However, there may be patients for whom immunomodulatory drugs are not preferred; for example, in patients with severe renal impairment (RI) or undergoing dialysis, lenalidomide treatment may not be recommended or may require dose adjustments and close monitoring of haematological toxicity [14]. Patients with MM have an increased baseline risk of venous thromboembolism, which can further increase with immunomodulatory drug-based therapies [15], and randomised clinical trial data suggest that lenalidomide maintenance post-transplant is associated with increased incidence of second primary malignancies [16]. Therefore, for some patients, a PI-based, immunomodulatory drug-free triplet regimen may represent a necessary and less costly alternative treatment option.

Combinations of bortezomib or carfilzomib with cyclophosphamide-dexamethasone (VCd or KCd) or melphalan-prednisone (VMP, KMP), as well as ixazomib-MP, are efficacious in NDMM patients [17–25]. However, in the real-world setting, some regimens may have limited feasibility due to the potential for peripheral neuropathy (PN; bortezomib-based regimens), renal or cardiac failure (carfilzomib-based therapy), or the requirement for regular intravenous or subcutaneous administration of the PI [17,20,21]. An all-oral ixazomib-based triplet combination may represent a more tolerable and convenient initial treatment option for MM. This randomised, multicentre, phase 2 study (NCT02046070) investigated the efficacy and toxicity of weekly oral ixazomib plus cyclophosphamide and low-dose dexamethasone (ICd) as induction, followed by single-agent ixazomib maintenance, in elderly, transplant-ineligible NDMM patients.

2. Patients and methods

2.1. Patients

Patients aged ≥18 years with previously untreated, symptomatic MM, who were ineligible for ASCT due to age (≥65 years) or comorbidities, were enrolled. Additional eligibility criteria are described in the Appendix. All patients provided written informed consent. Review boards at all participating institutions approved the study, which was conducted according to the Declaration of Helsinki, the International Conference on Harmonisation guidelines, and the Guidelines for Good Clinical Practice.

2.2. Study design and objectives

This open-label phase 2 study was part of a 3-arm study that evaluated the safety, tolerability, and efficacy of ICd in adult patients with MM. Two arms of the study enrolled patients with NDMM, and one arm enrolled patients with relapsed/refractory multiple myeloma (RRMM). Here, we report only on the patients with NDMM, and results for patients with RRMM will be reported separately. The study was conducted at 23 sites in Australia, Greece, Sweden, Poland, and the United States between March 5, 2014 and June 29, 2016. Patients were randomised (1:1) to receive 4.0 mg of oral ixazomib plus 300 mg/m^2 (Arm A) or 400 mg/m^2 (Arm B) of oral cyclophosphamide on days 1, 8, and 15, and 40 mg of dexamethasone (20 mg for patients aged >75 years) on days 1, 8, 15, and 22, for up to 13 28-day cycles as induction.

Patients with stable or responding disease who tolerated therapy entered the maintenance phase and received single-agent ixazomib (at the dose tolerated at the end of induction) on days 1, 8, and 15, in 28-day cycles, until progressive disease (PD), death, or unacceptable toxicity. The primary study objective was to determine the combined rate of complete response (CR; including stringent CR [sCR]) plus very good partial response (VGPR) after ICd induction. Secondary objectives are listed in the Appendix.

2.3. Assessments

Responses were assessed by the investigators at the end of each cycle during induction and at the end of every other cycle during maintenance, based on the International Myeloma Working Group uniform criteria [26]. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, and recorded from the first dose of study treatment until 30 days after the last dose. Patient demographic and medical history data, including comorbidities, were collected by investigators at screening.

2.4. Statistical analyses

Kaplan–Meier methodology was used to evaluate time to first response, time to VGPR or better, duration of response (DOR), and progression-free survival (PFS). Definitions of patient populations, time to response, DOR, time to progression, PFS, and relative dose intensity (RDI) are reported in the Appendix. No formal interim analyses or statistical comparisons between the treatment arms were planned; use of cyclophosphamide at two different doses was not for statistical comparison but instead to guide selection of the more appropriate dose.

3. Results

3.1. Patients and disposition

Overall, 70 patients with NDMM were enrolled, 36 in Arm A (cyclophosphamide 300 mg/m^2) and 34 in Arm B (cyclophosphamide 400 mg/m^2). Demographic and baseline disease characteristics were generally similar between the arms (Table 1). Overall, median age was 73 years, with 12 (17%) patients aged >80 years. A proportion of 51% of patients had cardiovascular or pulmonary pre-existing conditions, and 34% had moderate RI (creatinine clearance 30 to <60 mL/min); 11 patients aged >80 years had moderate RI.

At protocol-specified data cut-off (June 29, 2016), 46 (66%) patients, including 24 (67%) in Arm A and 22 (65%) in Arm B, had completed 13 ICd induction cycles and proceeded to ixazomib maintenance. Among the 12 patients aged >80 years, 5 (42%) completed ICd induction and started ixazomib maintenance therapy. Overall, 24 (34%) patients (12 in each arm) discontinued treatment during ICd induction because of AEs (21%), PD (4%), patient withdrawal (1%), or other reasons (7%). During ixazomib maintenance, 13 (19%) patients (6 in Arm A and 7 in Arm B) discontinued treatment; the most common reason for discontinuation was PD (11%), followed by AEs and other reasons (3% each), and patient withdrawal (1%). At data cut-off, 33 (47%) patients were continuing on ixazomib maintenance, including 18 (50%) in Arm A and 15 (44%) in Arm B. Among the 12 patients aged >80 years, 6 (50%) discontinued treatment due to AEs, and one (8%) patient withdrew from the study during ICd induction; during maintenance, 5 (42%) patients discontinued treatment because of PD.

3.2. Efficacy

Confirmed responses during induction and overall of 67 response-evaluable patients are summarised in Table 2. During induction, the rate of CR+VGPR was 25%; the ORR was 73%. Of 46 response-evaluable patients who

Table 1
Demographics and baseline characteristics of patients receiving ICd, by treatment arm and for the two treatment arms combined.

Characteristic	Arm A (N = 36)	Arm B (N = 34)	Arm A + Arm B (N = 70)
Age (years)	72.5 (65–87)	75.5 (61–84)	73.0 (61–87)
Age ≥75 years	12 (33)	18 (53)	30 (43)
Male	15 (42)	18 (53)	33 (47)
White	35 (97)	34 (100)	69 (99)
ECOG PS			
0	12 (33)	10 (29)	22 (31)
1	18 (50)	17 (50)	35 (50)
2	6 (17)	7 (21)	13 (19)
ISS stage at diagnosis			
I	11 (31)	11 (32)	22 (31)
II	13 (36)	10 (29)	23 (33)
III	10 (28)	10 (29)	20 (29)
Unknown	2 (6)	3 (9)	5 (7)
Myeloma disease type			
IgG	21 (58)	18 (53)	39 (56)
IgA	9 (25)	10 (29)	19 (27)
Kappa light chain only	4 (11)	4 (12)	8 (11)
Biclonal	0 (0)	1 (3)	1 (1)
Other[a]	2 (6)	1 (3)	3 (4)
High-risk cytogenetics[b]	5 (14)	6 (18)	11 (16)
CrCl category (mL/min)			
30 to <60	10 (28)	14 (41)	24 (34)
60 to <90	18 (50)	14 (41)	32 (46)
≥90	8 (22)	6 (18)	14 (20)
Cardiovascular/pulmonary comorbidity	17 (47)	19 (56)	36 (51)
Lytic bone disease	26 (72)	24 (71)	50 (71)
Extramedullary disease	0 (0)	3 (9)	3 (4)

Data are n (%) or median (range).
Abbreviations: CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; Ig, immunoglobulin; ISS, International Staging System; PS, performance status.
[a] IgM, IgD or IgE.
[b] Includes: t(4; 14), t(14; 16) and del(17p).

received ixazomib maintenance, 6 improved their response (1 CR to sCR, 1 VGPR to CR, and 4 partial response [PR] to VGPR), and 1 patient experienced a *de novo* response (stable disease to PR). Across induction and maintenance treatment, the CR+VGPR rate was 33%, and ORR was 76%, indicating deepening of responses during maintenance. Among the 12 patients aged >80 years, 10 were evaluable for response; among these, the ORR across induction and maintenance was 90% (n = 9), and the rate of CR+VGPR was 60% (n = 6). Of the 3 non-responding patients, 2 discontinued treatment during cycle 1 (and were not evaluable for response) and one during cycle 2 because of AEs.

Time to first response and time to VGPR or better are shown in Fig. 1. Among 49 patients who had a response during induction (26 in Arm A; 23 in Arm B), 17 progressed (4 VGPR, 13 PR) during induction. The median DOR for responding patients was not estimable (NE; 95% confidence interval [CI], 19.8 months–NE); the maximum DOR was 31.5 months in 1 patient ongoing on treatment (Arm A) at data cut-off. M-protein reductions in 59 patients with measurable M-protein at baseline are shown in Fig. 2.

A later data cut-off (April 17, 2017; median follow-up of 26.1 months [95% CI, 24.9–27.2]) was used to provide an updated PFS analysis. The combined median PFS was 23.5 months (95% CI, 19.8–NE) (Fig. 3); Kaplan–Meier estimates of 1-year PFS and TTP for patients receiving ixazomib maintenance were 59% and 61%, respectively (Fig. S1). PFS results by age group (<75 vs ≥75 years) are reported in the Appendix (Fig. S2).

Table 2
Confirmed best response by investigator assessment to ICd induction therapy and overall (ICd induction plus ixazomib maintenance) in response-evaluable patients, by treatment arm and for the two treatment arms combined.

Response	Arm A (N = 33)[a]		Arm B (N = 34)[a]		Arm A + Arm B (N = 67)[a]	
	Induction	Overall[b]	Induction	Overall[b]	Induction	Overall[b]
CR	4 (12)	5 (15)	3 (9)	4 (12)	7 (10)	9 (13)
sCR	1 (3)	2 (6)	0 (0)	0 (0)	1 (1)	2 (3)
VGPR	5 (15)	7 (21)	5 (15)	6 (18)	10 (15)	13 (19)
PR	17 (52)	15 (45)	15 (44)	14 (41)	32 (48)	29 (43)
SD	4 (12)	6 (18)	7 (21)	6 (18)	11 (16)	12 (18)
PD	0 (0)	0 (0)	1 (3)	2 (6)	1 (1)	2 (3)
CR+VGPR	9 (27)	12 (36)	8 (24)	10 (29)	17 (25)	22 (33)
ORR (≥PR)	26 (79)	27 (82)	23 (68)	24 (71)	49 (73)	51 (76)

Data are n (%).
Abbreviations: CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.
[a] Of 67 response-evaluable patients, 46 completed induction and proceeded to maintenance (Arm A, n = 24; Arm B, n = 22). Three patients did not have ≥1 post-baseline response assessment and were therefore not included in the response-evaluable population. Among the response-evaluable population, data for best response were not available/collected for 3 patients in each arm during induction and for 2 patients in Arm B during the entire treatment period.
[b] Entire treatment period: ICd induction (cycles 1–13) and single-agent ixazomib maintenance phases combined.

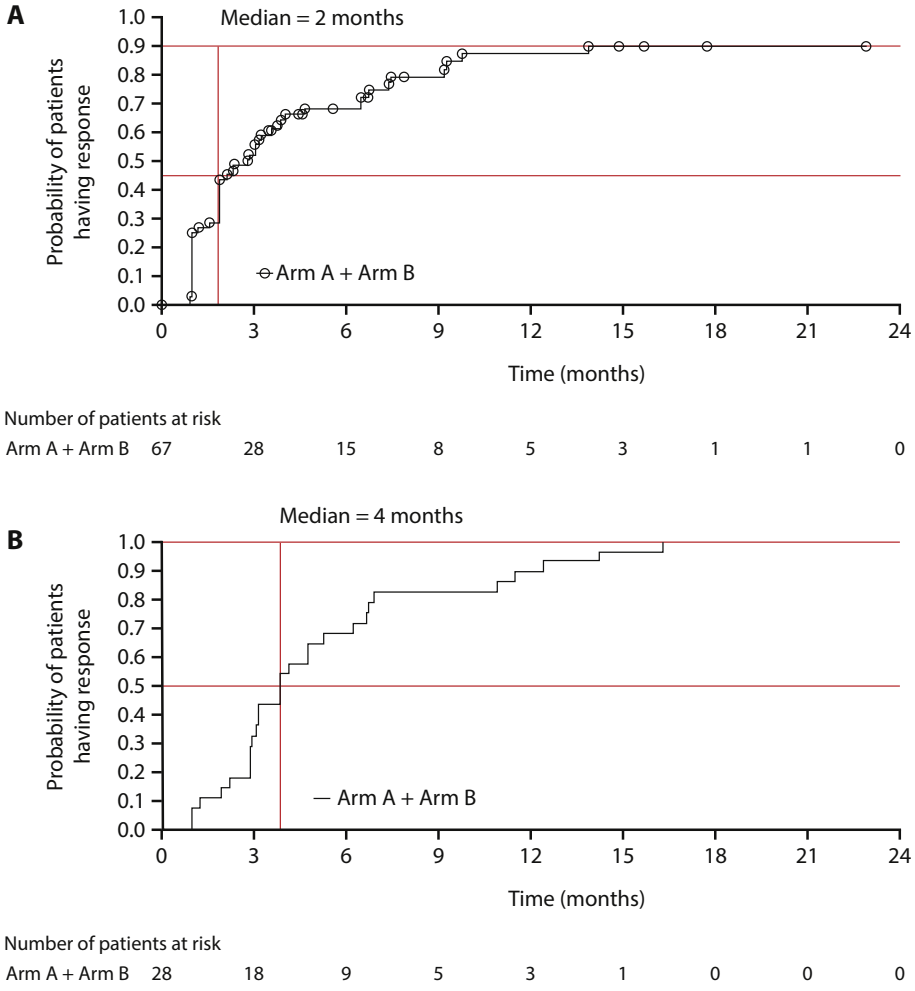


Fig. 1. **Time to first response (A) and time to VGPR or better (B) (Arm A + Arm B).** Time to first response data are calculated as the time from the first dose of study treatment to the first documented confirmed response of PR or better in patients who responded during the induction phase. Data for time to VGPR or better are reported for responding patients and calculated as the time from the first dose of study treatment to the first documentation of a confirmed response of VGPR or better. PR, partial response; VGPR, very good partial response.

3.3. Treatment exposure and safety

Across induction and maintenance, patients received a median of 19 treatment cycles (range, 1–29); median time on treatment was ~1.4 years. Among 46 patients who proceeded to ixazomib maintenance, median treatment duration was 8 cycles (range, 1–16). During induction, the median RDI of all 3 study drugs was ≥96% overall and was similar in both arms (Table 3).

Among all 70 patients, 68 (97%) reported AEs of any grade (34 in each arm) during the entire treatment period (Table 3). The most common any-grade AEs were neutropenia, anaemia, diarrhoea, nausea, and peripheral oedema (Table 4). Any-grade peripheral sensory neuropathy occurred more frequently in Arm B (24%) than in Arm A (8%). Grade ≥3 AEs were reported in 26 (72%) patients in Arm A and in 25 (74%) in Arm B (Table 5). One patient (Arm B) reported grade ≥3 PN, 4 (2 in each arm) had grade ≥3 heart failure, 2 (1 in each arm) had grade ≥3 acute renal failure, and 3 in Arm A reported grade ≥3 rashes. Serious AEs (SAEs), AEs resulting in treatment discontinuation or dose reduction, and on-study deaths are summarised in Table 3.

The types and patterns of AEs observed were similar during ICd induction and single-agent ixazomib maintenance (Tables 4 and 5). Among patients who entered maintenance, a lower percentage of patients had AEs of any grade during maintenance (87%) than during ICd induction (96%). Fewer patients experienced grade ≥3 AEs and SAEs during maintenance (39% and 15%, respectively) than during ICd induction (63% and 41%). Safety data by age and QoL results are summarised in the Appendix.

4. Discussion

This phase 2 study is the first to indicate that all-oral ICd induction followed by single-agent ixazomib maintenance is tolerable and active in transplant-ineligible

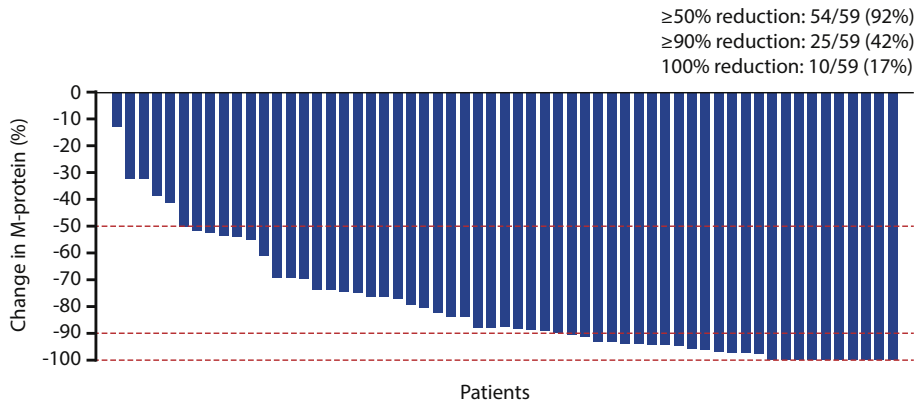
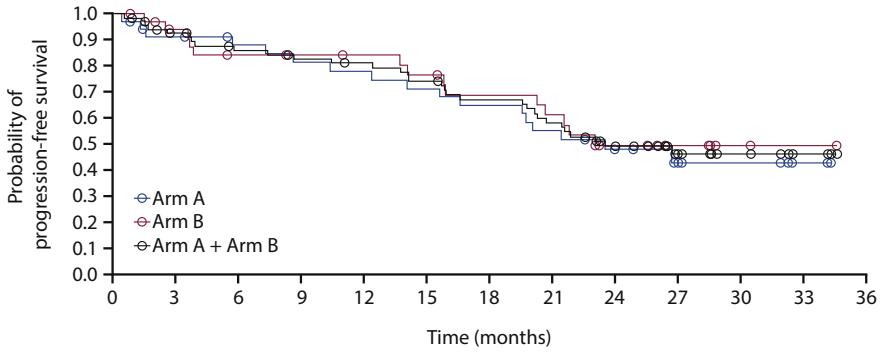


Fig. 2. **Waterfall plot of best change from baseline M-protein levels (Arm A + Arm B).** Fifty-nine patients had measurable M-protein at baseline; 11 patients had disease measurable by free light chain only.



Number of patients at risk

Arm A	36	30	27	25	24	22	20	17	13	6	5	2	0
Arm B	34	29	25	24	23	21	18	16	11	6	2	1	0
Arm A + Arm B	70	59	52	49	47	43	38	33	24	12	7	3	0

Fig. 3. **Progression-free survival (PFS) by treatment arm and for the two treatment arms combined.** PFS rates at 12, 18, and 24 months were, 81%, 67%, and 49%, respectively. In Arm A and Arm B, respectively, after a median follow-up of 26.8 months (95% CI 24.0–31.9) and 25.6 months (95% CI 23.1–28.6), the median PFS was 23.5 months (95% CI 15.7–not estimable) and 23.0 months (95% CI 15.9–not estimable). CI, confidence interval.

NDMM patients, many of whom are elderly and have multiple comorbidities. The ORR after ICd induction was 73%, with a CR+VGPR rate of 25%, improving to 76% and 33%, respectively, after maintenance; responses deepened during treatment and were sustained, with median DOR currently not reached. Elderly patients aged >80 years had an ORR of 90% and a rate of CR+VGPR of 60%. The median treatment duration was 19 cycles, indicating the long-term tolerability of this regimen. After a median follow-up of 26.1 months, median PFS was 23.5 months. ICd demonstrated a manageable safety profile, with no new-onset toxicity during single-agent ixazomib maintenance and with an overall incidence of grade ≥3 AEs and SAEs of 73% and 51%, respectively, across all treatment. Furthermore, QoL scores were maintained throughout treatment, suggesting that this therapy is tolerable in elderly NDMM patients.

KCd and VCd are active and feasible in elderly, transplant-ineligible NDMM patients, with high ORRs (95%) in phase 2 studies [20,27,28]. It is important to note that in this clinical setting, heterogeneity in patients' demographic and disease characteristics is commonly observed; therefore, cross-trial comparisons should be interpreted with caution. Other PI-alkylator combinations are also active in these patients. In phase 3 studies, VMP and KMP showed comparable efficacy in this setting, with median PFS of ~22 months and ORR >70% [21,22]. Although limited conclusions can be drawn from comparisons between phase 2 and phase 3 trials, the median PFS of 23.5 months observed with ICd plus ixazomib maintenance suggests comparable benefit to a current standard-of-care treatment, VMP, in elderly, ASCT-ineligible NDMM patients [24]. The estimated PFS rates at 18 and 24 months in patients aged >75 years (62% and 41%, respectively) were similar to those in the overall population (67% and 49%, respectively), suggesting that ICd plus single-agent ixazomib maintenance may be associated with clinical benefits in elderly transplant-ineligible NDMM patients.

Table 3
Relative dose intensity during the ICd induction period and summary of safety profile for the entire treatment period (ICd induction plus ixazomib maintenance). Data are presented by treatment arm and for the two treatment arms combined.

RDI and safety	Arm A (N = 36)	Arm B (N = 34)	Arm A + Arm B (N = 70)
RDI during ICd induction[a]			
Ixazomib	97.4 (33.3–100.0)	94.9 (66.7–100.0)	97.4 (33.3–100.0)
Cyclophosphamide	96.2 (34.4–124.0)	94.8 (54.8–102.5)	96.0 (34.4–124.0)
Dexamethasone	97.1 (25.0–101.9)	97.1 (37.5–101.9)	97.1 (25.0–101.9)
Safety profile for ICd induction + ixazomib maintenance			
Any AEs	34 (94)	34 (100)	68 (97)
Drug-related AEs	26 (72)	31 (91)	57 (81)
Grade ≥3 AEs	26 (72)	25 (74)	51 (73)
Drug-related grade ≥3 AEs	15 (42)	23 (68)	38 (54)
Serious AEs[b]	17 (47)	19 (56)	36 (51)
Drug-related serious AEs	5 (14)	7 (21)	12 (17)
AEs resulting in treatment discontinuation of any study drug[c]	7 (19)	11 (32)	18 (26)
Ixazomib[d,e]	4 (11)	5 (15)	9 (13)
Cyclophosphamide[d]	3 (8)	3 (9)	6 (9)
Dexamethasone[d]	5 (14)	6 (18)	11 (16)
AEs resulting in dose reduction of any study drug[f]	11 (31)	10 (29)	21 (30)
Ixazomib	7 (19)	9 (26)	16 (23)
Cyclophosphamide	5 (14)	9 (26)	14 (20)
Dexamethasone	5 (14)	5 (15)	10 (14)
On-study deaths[g]	3 (8)	2 (6)	5 (7)

Data are n (%) or median (range), %.
Abbreviations: AE, adverse event; ICd, ixazomib, cyclophosphamide, dexamethasone; RDI, relative dose intensity; SAE, Serious AE.
[a] Dose received divided by dose prescribed.
[b] No individual SAE was reported in >3 patients in either arm.
[c] Fatigue (4%) was the most common AE.
[d] Permanent treatment discontinuation.
[e] During ixazomib maintenance, in the 2 treatment arms combined, 2 (3%) of patients discontinued treatment because of AEs.
[f] Neutropenia (6%) was the most frequent AE.
[g] 3 patients in Arm A (respiratory failure, upper gastrointestinal haemorrhage, and pulmonary oedema) and 2 in Arm B (pulmonary oedema and pneumonia); none were considered related to treatment.

In our study, ICd induction plus ixazomib maintenance was well tolerated, no late-onset toxicity was observed, and the overall safety profile was in line with toxicities reported for KCd or VCd in similar NDMM patient cohorts [20,27]. The rates of the most common AEs across induction and maintenance (neutropenia, anaemia, diarrhoea, nausea, and peripheral oedema) were consistent with the established toxicity profile of ixazomib plus lenalidomide and low-dose dexamethasone (IRd) [9–11], suggesting that use of cyclophosphamide instead of lenalidomide does not cause increased toxicity. As expected, ICd plus ixazomib maintenance was associated with a low rate of grade ≥3 PN, a toxicity commonly observed with bortezomib-based combinations [22,27]. Furthermore, the incidence of PN was consistent with that reported with KCd in elderly NDMM patients [20]. Any-grade or grade ≥3 haematological toxicities were generally less frequent than with KMP or VMP in elderly, transplant-ineligible NDMM patients [22,23].

Elderly patients with NDMM often present with comorbidities and so can be more susceptible to AEs and treatment complications [1]. For elderly patients with pre-existing conditions such as prothrombotic disorders or prior history of thromboembolic, cardiovascular, renal, or pulmonary disease, lenalidomide-based regimens may not be desirable, and alternative treatment options are needed. The median age in our study was 73 years, with 51% of patients presenting with pulmonary or cardiovascular comorbidities. In this context, 66% of patients completed ICd induction and proceeded to ixazomib maintenance therapy, emphasising the efficacy, tolerability, and feasibility of this regimen. Furthermore, low rates of AEs leading to treatment discontinuations or dose reductions were reported throughout induction and maintenance, in line with results from studies of bortezomib-based regimens in elderly NDMM patients [22,27].

This study evaluated two doses of cyclophosphamide, 300 mg/m^2 (Arm A) and 400 mg/m^2 (Arm B), in combination with ixazomib and dexamethasone. Although PFS was similar, ORR was higher in Arm A, and AE rates were higher in Arm B. These efficacy and safety data indicate that further evaluation of ICd induction in this patient population should use cyclophosphamide 300 mg/m^2.

In conclusion, ICd induction plus single-agent ixazomib maintenance is associated with high response rates, deepening responses, and a notable PFS benefit, and is well tolerated, with no unexpected safety concerns and low treatment discontinuation rates in elderly, transplant-ineligible NDMM patients. This regimen may represent a new potential therapeutic

Table 4
Most common any-grade AEs, occurring in ≥10 of patients during ICd induction and during the entire treatment period. Data are presented by treatment arm and for the two treatment arms combined.

AE	Arm A (N = 36)	Arm B (N = 34)	Arm A + Arm B (N = 70)
ICd induction			
Patients with ≥1 most common any-grade AE	29 (81)	31 (91)	60 (86)
Neutropenia	6 (17)	16 (47)	22 (31)
Anaemia	10 (28)	9 (26)	19 (27)
Nausea	8 (22)	9 (26)	17 (24)
Peripheral oedema	9 (25)	8 (24)	17 (24)
Diarrhoea	8 (22)	7 (21)	15 (21)
Constipation	9 (25)	5 (15)	14 (20)
Fatigue	8 (22)	6 (18)	14 (20)
Vomiting	6 (17)	8 (24)	14 (20)
Upper respiratory tract infection	5 (14)	5 (15)	10 (14)
Peripheral neuropathy	6 (17)	3 (9)	9 (13)
Peripheral sensory neuropathy	2 (6)	7 (21)	9 (13)
Bronchitis	5 (14)	3 (9)	8 (11)
Herpes zoster	5 (14)	3 (9)	8 (11)
Pneumonia	5 (14)	3 (9)	8 (11)
Thrombocytopenia	4 (11)	4 (12)	8 (11)
Pyrexia	3 (8)	4 (12)	7 (10)
ICd induction + ixazomib maintenance			
Patients with ≥1 most common any-grade AE	30 (83)	31 (91)	61 (87)
Neutropenia	6 (17)	16 (47)	22 (31)
Anaemia	10 (28)	9 (26)	19 (27)
Diarrhoea	11 (31)	7 (21)	18 (26)
Peripheral oedema	9 (25)	9 (26)	18 (26)
Nausea	8 (22)	10 (29)	18 (26)
Vomiting	6 (17)	9 (26)	15 (21)
Constipation	9 (25)	5 (15)	14 (20)
Fatigue	8 (22)	6 (18)	14 (20)
Upper respiratory tract infection	7 (19)	5 (15)	12 (17)
Peripheral sensory neuropathy	3 (8)	8 (24)	11 (16)
Pyrexia	5 (14)	5 (15)	10 (14)
Bronchitis	5 (14)	4 (12)	9 (13)
Arthralgia	4 (11)	5 (15)	9 (13)
Thrombocytopenia	4 (11)	4 (12)	8 (11)
Respiratory tract infection	3 (8)	4 (12)	7 (10)

Data are n (%).
Abbreviations: AE, adverse event; ICd, ixazomib, cyclophosphamide, dexamethasone.

Table 5
Most common grade ≥3 AEs, occurring in ≥2 patients, during ICd induction and during the entire treatment period. Data are presented by treatment arm and for the two treatment arms combined.

AE	Arm A (N = 36)	Arm B (N = 34)	Arm A + Arm B (N = 70)
ICd induction			
Patients with ≥1 grade ≥3 AE	19 (53)	22 (65)	41 (59)
Neutropenia	5 (14)	15 (44)	20 (29)
Anaemia	4 (11)	6 (18)	10 (14)
Pneumonia	5 (14)	3 (9)	8 (11)
Atrial fibrillation	3 (8)	2 (6)	5 (7)
Thrombocytopenia	2 (6)	2 (6)	4 (6)
Diarrhoea	2 (6)	1 (3)	3 (4)
Fatigue	2 (6)	1 (3)	3 (4)
Hypertension	0 (0)	3 (9)	3 (4)
Constipation	1 (3)	1 (3)	2 (3)
Muscular weakness	1 (3)	1 (3)	2 (3)
Nausea	2 (6)	0 (0)	2 (3)
Pancytopenia	0 (0)	2 (6)	2 (3)
Pulmonary embolism	0 (0)	2 (6)	2 (3)
Upper respiratory tract infection	0 (0)	2 (6)	2 (3)
ICd induction + ixazomib maintenance			
Patients with ≥1 grade ≥3 AE	26 (72)	25 (74)	51 (73)
Neutropenia	5 (14)	15 (44)	20 (29)
Anaemia	4 (11)	6 (18)	10 (14)
Pneumonia	5 (14)	3 (9)	8 (11)
Atrial fibrillation	3 (8)	2 (6)	5 (7)
Thrombocytopenia	2 (6)	2 (6)	4 (6)
Fatigue	2 (6)	2 (6)	4 (6)
Hypertension	0 (0)	4 (12)	4 (6)
Nausea	2 (6)	1 (3)	3 (4)
Diarrhoea	2 (6)	1 (3)	3 (4)
Arthralgia	0 (0)	2 (6)	2 (3)
Cardiac failure	0 (0)	2 (6)	2 (3)
Constipation	1 (3)	1 (3)	2 (3)
Muscular weakness	1 (3)	1 (3)	2 (3)
Pancytopenia	0 (0)	2 (6)	2 (3)
Pulmonary embolism	0 (0)	2 (6)	2 (3)
Pulmonary oedema	1 (3)	1 (3)	2 (3)
Syncope	1 (3)	1 (3)	2 (3)
Upper respiratory tract infection	0 (0)	2 (6)	2 (3)

Data are n (%).
Abbreviations: AE, adverse event; ICd, ixazomib, cyclophosphamide, dexamethasone.

algorithm in this setting; head-to-head phase 3 trials comparing ICd vs the current standard-of-care treatments VMP and Rd [6,22,24,29] may be valuable and have the potential to guide treatment decisions in these patients. The non-ASCT NDMM treatment landscape is rapidly evolving as novel regimens including ixazomib in combination with lenalidomide-dexamethasone (Rd; NCT01850524) and daratumumab plus Rd (NCT02252172) are currently being investigated in large phase 3 trials in transplant-ineligible NDMM patients. In addition, within the emerging paradigm of long-term therapy in MM, ixazomib is currently being evaluated as maintenance therapy vs placebo in non-ASCT patients who responded to initial therapy (NCT02312258). In this context, all-oral ICd plus ixazomib maintenance therapy may be particularly valuable for patients for whom the use of immunomodulatory drugs is contraindicated due to RI or increased venous thromboembolism risk or in patients who do not have access to triplet regimens that include a PI/monoclonal antibody and an immunomodulatory drug. Although the numbers are small, ICd was well tolerated and effective among patients aged >80 years and with moderate RI. In addition, the all-oral ICd regimen offers patients the flexibility of at-home administration of medication, an important advantage for patients with limited mobility and access to medical facilities and can offer reduced treatment burden during long-term therapy compared

with therapies requiring regular parenteral administration. Furthermore, oral ICd also represents a less-expensive and thus potentially more accessible treatment option than triplet combinations including a PI/monoclonal antibody and an immunomodulatory drug [30], emphasising the potential value of prolonged ixazomib treatment in transplant-ineligible NDMM patients.

Contributors

M.A.D., S.K., C.B., R.L., Z.T., and H.Y. were involved in study conception and design. All authors were involved in the collection and assembly of data. M.A.D., S.K., C.B., R.L., Z.T., and H.Y. were responsible for data analysis and interpretation. Patients were recruited by M.A.D., S.K., S.G., W.W.J., H.N., A.G., M.H., and N.Gr. All authors contributed to manuscript preparation and revisions as well as reviewed and approved the final version of the manuscript.

Conflict of interest statement

M.A.D. reports personal fees from Celgene, Janssen, Amgen, and Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA. W.W.J. reports research grants from Roche, Celgene, Janssen, Amgen, Novartis, and Millennium Pharmaceuticals, Inc., personal fees from Roche, Novartis, Janssen, Abbvie, BMS, and Amgen, and non-financial support from Roche, Novartis, and Pierre Fabre. C.B., R.L., Z.T., N.Gu., and H.Y. are employees of Millennium Pharmaceuticals, Inc. H.Y. and Z.T. report an ownership interest in Millennium Pharmaceuticals, Inc. N.Gr. reports honoraria from Amgen, Celgene, Janssen, Mundipharma, and Millennium Pharmaceuticals, Inc. S.K. reports research funding from Abbvie, Celgene, Novartis, Janssen, Merck, Sanofi, Roche, KITE, and Takeda, and consultancy for Oncopeptides. M.H. reports personal fees from Amgen, Celgene, Janssen, and Millennium Pharmaceuticals, Inc. H.N., S.G., and A.G. declare no competing interests.

Role of the funding source

The trial was designed by the lead and senior authors (M.A.D. and S.K.) in collaboration with the sponsor, Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA. The sponsor funded collection, analysis, and interpretation of data. Manuscript preparation, approval, and the final decision to submit were led by the authors. FireKite, an Ashfield company, part of UDG Healthcare plc, provided writing support funded by the sponsor. All authors had full access to all study data, including the raw data, and agreed to be accountable for the accuracy and integrity of the data and analyses. The corresponding author had final responsibility for the decision to submit for publication.

Data-sharing statement

Takeda makes patient-level, de-identified data sets and associated documents available after applicable marketing approvals and commercial availability have been received, an opportunity for the primary publication of the research has been allowed, and other criteria have been met as set forth in Takeda's data-sharing policy (see https://www.takedaclinicaltrials.com for details). To obtain access, researchers must submit a legitimate academic research proposal for adjudication by an independent review panel, who will review the scientific merit of the research and the requestor's qualifications and conflict of interest that can result in potential bias. Once approved, qualified researchers who sign a data-sharing agreement are provided access to these data in a secure research environment.

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Appendix A. Supplementary data

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