original reports

Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial

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abstract

PURPOSE Maintenance therapy prolongs progression-free survival (PFS) in patients with newly diagnosed multiple myeloma (NDMM) not undergoing autologous stem cell transplantation (ASCT) but has generally been limited to immunomodulatory agents. Other options that complement the induction regimen with favorable toxicity are needed.

PATIENTS AND METHODS The phase III, double-blind, placebo-controlled TOURMALINE-MM4 study randomly assigned (3:2) patients with NDMM not undergoing ASCT who achieved better than or equal to partial response after 6-12 months of standard induction therapy to receive the oral proteasome inhibitor (PI) ixazomib or placebo on days 1, 8, and 15 of 28-day cycles as maintenance for 24 months. The primary endpoint was PFS since time of randomization.

RESULTS Patients were randomly assigned to receive ixazomib (n = 425) or placebo (n = 281). TOURMALINE-MM4 met its primary endpoint with a 34.1% reduction in risk of progression or death with ixazomib versus placebo (median PFS since randomization, 17.4 *v* 9.4 months; hazard ratio [HR], 0.659; 95% CI, 0.542 to 0.801; $P < .001$; median follow-up, 21.1 months). Ixazomib significantly benefitted patients who achieved complete or very good partial response postinduction (median PFS, 25.6 *v* 12.9 months; HR, 0.586; $P < .001$). With ixazomib versus placebo, 36.6% versus 23.2% of patients had grade ≥ 3 treatment-emergent adverse events (TEAEs); 12.9% versus 8.0% discontinued treatment because of TEAEs. Common any-grade TEAEs included nausea (26.8% *v* 8.0%), vomiting (24.2% *v* 4.3%), and diarrhea (23.2% *v* 12.3%). There was no increase in new primary malignancies (5.2% *v* 6.2%); rates of on-study deaths were 2.6% versus 2.2%.

CONCLUSION Ixazomib maintenance prolongs PFS with no unexpected toxicity in patients with NDMM not undergoing ASCT. To our knowledge, this is the first PI demonstrated in a randomized clinical trial to have single-agent efficacy for maintenance and is the first oral PI option in this patient population.

J Clin Oncol 38:4030-4041. © 2020 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on August 26, 2020 and published at ascopubs.org/journal/jco on October 6, 2020: DOI https://doi.org/10.1200/JCO.20.02060

INTRODUCTION

Treatment for multiple myeloma (MM) is shifting increasingly to maintenance and continuous therapy, which improves outcomes versus fixed-duration treatment followed by a remission period.[1-3] Real-world data suggest that, at relapse, approximately one third of patients never receive second-line treatment,[4,5] highlighting the importance of maximizing progression-free survival (PFS) with initial therapy and the need for tolerable, active treatment options for long-term administration.[6] Proteasome inhibitors (PIs), immunomodulatory drugs, and monoclonal antibodies are backbones of therapy for MM.[7] However, there are no approved maintenance or continuous therapy options with PIs for initial therapy.[8,9]

Maintenance therapy prolongs PFS in the post-transplantation and nontransplantation settings, and overall survival (OS) when used post-transplantation.[10-12] To date, only lenalidomide is approved as post-transplantation maintenance therapy.[13] There are currently no agents specifically approved as maintenance after any standard-of-care induction therapy

CONTEXT

Key Objective

Does the oral proteasome inhibitor ixazomib improve progression-free survival (PFS) in patients with newly diagnosed multiple myeloma (NDMM) not undergoing autologous stem cell transplantation when used as maintenance therapy after best response to any standard-of-care induction?

Knowledge Generated

Treatment with weekly ixazomib maintenance resulted in a statistically significant and clinically meaningful improvement in PFS since randomization, with an 8-month increase in the median, and demonstrated PFS benefits in prespecified patient subgroups, including a statistically significant benefit in patients who achieved complete or very good partial responses to initial therapy, and benefits in patients with stage IIII disease, patients aged ≥ 75 years, and patients with expanded high-risk cytogenetics. Ixazomib maintenance had a tolerable safety profile with no increase in health care use or impact on patients' self-reported quality of life as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-Core 30 and EORTC QLQ-MY20 questionnaires.

Relevance

To our knowledge, ixazomib is the first induction-agnostic maintenance option investigated for transplantation-ineligible patients with NDMM and represents a valuable treatment option in this setting.

for patients not undergoing autologous stem cell transplantation (ASCT). These patients may receive continuous treatment with one or more agents received as induction, such as lenalidomide[9,14,15] and/or daratumumab.[8,16] In routine clinical practice, treatment duration may be limited because of toxicity and route of administration.[6,17] More tolerable and convenient options are required for this generally elderly population, who may not be eligible for transplantation because of age or presence of comorbidities.[18]

The oral PI ixazomib is approved in combination with lenalidomide-dexamethasone for the treatment of patients with MM who have received one prior therapy.[19] Ixazomib as post-transplantation maintenance therapy prolongs PFS versus placebo,[20] with limited cumulative toxicity or impact on quality of life (QoL).[20,21] We report the efficacy and safety of ixazomib as maintenance therapy in transplantation-ineligible patients after standard-of-care induction therapy.

PATIENTS AND METHODS

Trial Design and Patients

In this randomized, double-blind, placebo-controlled, phase III trial, patients were randomly assigned from April 23, 2015, through October 8, 2018, at 187 sites in 34 countries (Data Supplement, online only). The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and appropriate regulatory requirements. Local independent ethics committees or institutional review boards at each site approved the protocol, which is available in the Data Supplement. All patients provided written informed consent.

Adults with a confirmed diagnosis of symptomatic MM per International Myeloma Working Group (IMWG) criteria[22] who were ineligible for, or did not wish to receive, ASCT and who achieved at least a partial response (PR) as their best response after 6-12 months of any standard-of-care induction therapy, were eligible. Patients required an Eastern Cooperative Oncology Group performance status of 0 to 2 and documented initial disease state, initial therapy and response, and cytogenetics and International Staging System (ISS) disease stage assessments at diagnosis (Data Supplement). Eligible patients were required to be randomly assigned ≤ 60 days after the last dose of induction therapy.

Procedures

Using centralized randomization through an interactive voice/web response system (Data Supplement), patients were randomly assigned 3:2 to receive either oral ixazomib 3 mg or matching placebo on days 1, 8, and 15 of 28-day cycles. The dose was increased to 4 mg from cycle 5 if tolerated during cycles 1-4 (Data Supplement). Randomization was stratified by induction regimen (PI-containing *v* non-PI therapy); preinduction ISS disease stage (I or II *v* III); age at randomization (< 75 *v* ≥ 75 years); and response to initial therapy at screening (complete response [CR] or very good partial response [VGPR] *v* PR). Patients continued treatment for approximately 24 months (if no treatment delays, equivalent to 26 cycles, to the nearest complete cycle) or until progressive disease (PD) or unacceptable toxicity, whichever occurred first. Dose adjustments for toxicities were permitted using protocol-specified dose-modification guidelines.

Outcomes and Assessments

The primary endpoint was PFS, defined as time since random assignment to first documentation of PD (per independent review committee [IRC] evaluation) or death as a result of any cause. The key secondary endpoint was OS.

Secondary and exploratory endpoints are listed in the Data Supplement.

Patient evaluations and follow-up are summarized in the Data Supplement. Response was assessed on day 1 of every treatment cycle and every 4 weeks during the PFS follow-up period until PD. Response and PD were evaluated by an IRC blinded to both treatment assignment and investigator assessment of response; assessments were based on central laboratory M-protein results, plus local bone marrow and imaging data, using IMWG 2011 criteria.[23] Adverse events (AEs) were assessed throughout the treatment period and through 30 days after the last dose of the study drug and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03. For more details on assessments, see the Data Supplement.

Statistical Analysis

The study used a closed sequential testing procedure for the primary (PFS) and key secondary (OS) endpoints, in this order. Two interim analyses (IAs), plus a final analysis, were planned to test OS; the first IA, reported here, was the

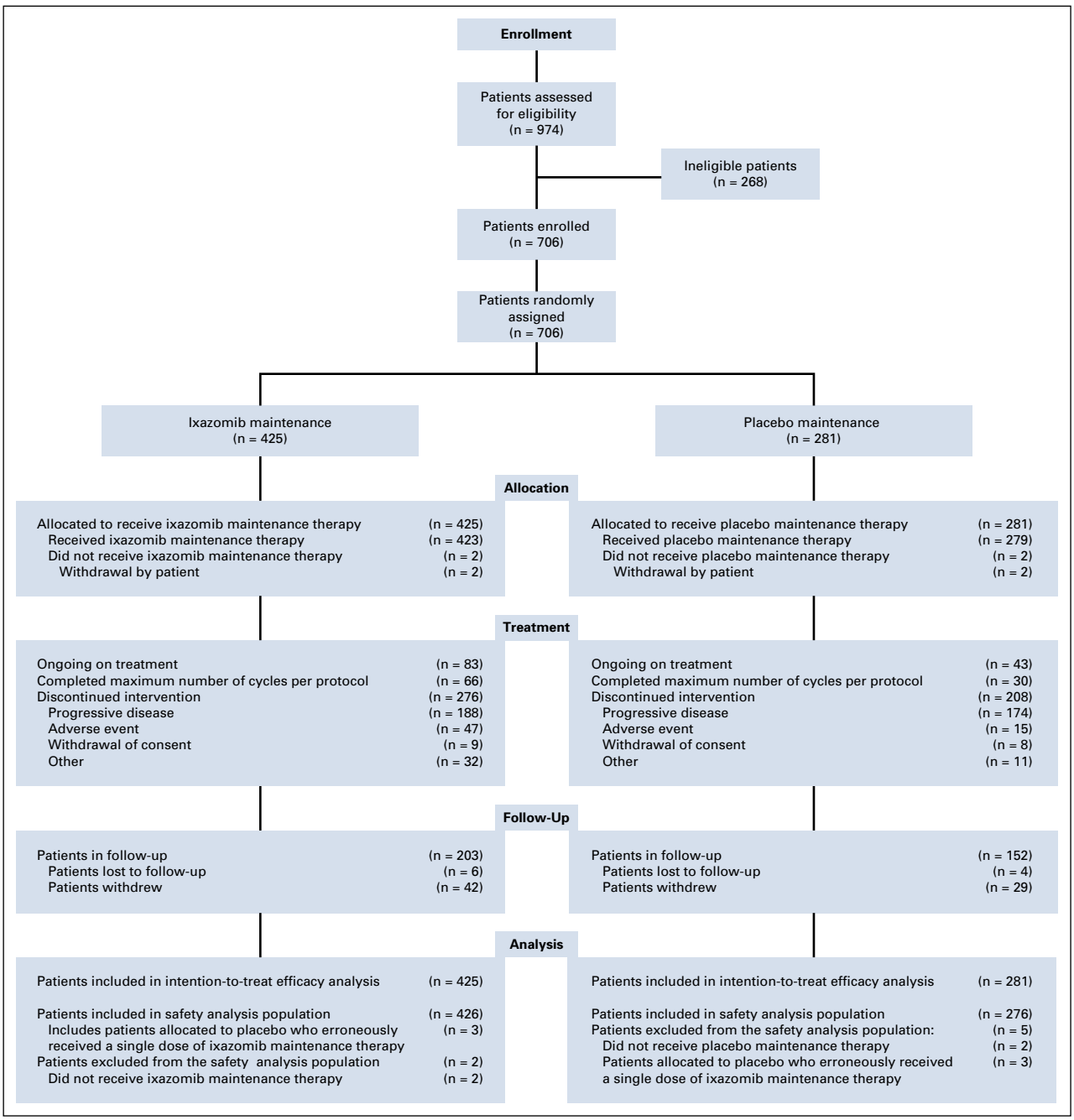

FIG 1. CONSORT diagram.

TABLE 1. Baseline Characteristics of Patients in the Intention-to-Treat Population

Characteristic	Ixazomib (n = 425)	Placebo (n = 281)
Age, years		
Median (range)	72 (42-89)	73 (52-90)
< 65	39 (9.2)	29 (10.3)
≥ 65 and < 75	226 (53.2)	142 (50.5)
≥ 75	160 (37.6)	110 (39.1)
Male sex	222 (52.2)	155 (55.2)
Race[a]		
White	330 (77.6)	227 (80.8)
Asian	63 (14.8)	39 (13.9)
Black or African American	15 (3.5)	5 (1.8)
Type of myeloma at initial diagnosis		
Immunoglobulin G	252 (59.3)	174 (61.9)
Immunoglobulin A	102 (24.0)	67 (23.8)
Light chain	62 (14.6)	36 (12.8)
Other[b]	9 (2.1)	4 (1.4)
ISS disease stage at initial diagnosis[c]		
I	112 (26.4)	66 (23.5)
II	165 (38.8)	114 (40.6)
III	148 (34.8)	101 (35.9)
ECOG PS at study entry[d]		
0	213 (50.1)	147 (52.3)
1	193 (45.4)	120 (42.7)
2	18 (4.2)	14 (5.0)
Frailty status[e]		
Fit	172 (40.5)	112 (39.9)
Unfit	147 (34.6)	98 (34.9)
Frail	102 (24.0)	68 (24.2)
Creatinine clearance at study entry (mL/min)[f]		
< 30	8 (1.9)	3 (1.1)
30 to < 60	148 (34.8)	104 (37.0)
60 to < 90	184 (43.3)	108 (38.4)
≥ 90	85 (20.0)	65 (23.1)
Cytogenetic features		
High-risk cytogenetic abnormalities[g]	74 (17.4)	48 (17.1)
Expanded high-risk cytogenetic abnormalities[h]	150 (35.3)	91 (32.4)
Elevated lactate dehydrogenase at study entry	57 (13.4)	38 (13.5)
Evidence of lytic bone disease at study entry	203 (47.8)	141 (50.2)

(continued on following page)

primary and only analysis of PFS. See the Data Supplement for detailed statistical analysis methodology. At this analysis, the study had 90% power to detect a hazard ratio (HR) of 0.71 (two-sided log-rank test, two-sided alpha of .04) for PFS in the intention-to-treat-population. Additionally, PFS was tested in parallel in three prespecified subgroups per stratification variables: patients with preinduction ISS stage III disease, patients aged ≥ 75 years, and patients who achieved CR or VGPR with initial therapy. Subgroup testing for PFS was conducted using the remaining alpha (.01) and the Hochberg procedure for multiplicity correction (Data Supplement). The study was not powered for statistical testing in other prespecified subgroups. The O'Brien-Fleming alpha spending function (Lan-Demets method[24]) was used to calculate the significance boundary for OS on the basis of the observed number of deaths at each IA. All other efficacy endpoints were tested at a two-sided alpha level of .05. Analysis populations are defined in the Data Supplement.

RESULTS

Patients

A total of 706 patients with newly diagnosed MM (NDMM) were enrolled (Fig 1), 425 in the ixazomib arm and 281 in the placebo arm. Baseline patient demographics and disease characteristics, including prior induction treatment, were well balanced between groups (Table 1; Data Supplement). Overall median age at study entry was 73 years, with 38.2% of patients aged ≥ 75 years; 35.3% of patients had ISS stage III disease, 82.3% received a PI and 32.7% received an immunomodulatory drug as part of their induction regimen, and 62.0% were in CR or VGPR at study entry.

Efficacy

At data cutoff (August 12, 2019), with a median overall follow-up for PFS of 21.1 months, there was a significant 34.1% reduction in risk of progression or death in the ixazomib versus placebo group (HR, 0.659; 95% CI, 0.542 to 0.801; $P < .001$); median PFS since randomization was 17.4 months (95% CI, 14.8 to 20.3 months) versus 9.4 months (95% CI, 8.5 to 11.5 months; Fig 2A). When landmarked to the date of induction therapy, median total PFS time since start of induction was 26.3 versus 20.3 months in the ixazomib versus placebo group (Table 2). In the prespecified subgroups, there was a statistically significant improvement in PFS since randomization with ixazomib versus placebo in patients who achieved CR or VGPR with initial therapy (HR, 0.586; 95% CI, 0.449 to 0.765; $P < .001$). Clinical benefits were observed in patients with ISS stage III disease (HR, 0.695; 95% CI, 0.499 to 0.967; $P = .030$) and patients

TABLE 1. Baseline Characteristics of Patients in the Intention-to-Treat Population (continued)

Characteristic	Ixazomib (n = 425)	Placebo (n = 281)
Induction regimen containing[i]		
PI	351 (82.6)	230 (81.9)
Bortezomib	346 (81.4)	228 (81.1)
Immunomodulatory drug	137 (32.2)	94 (33.5)
Thalidomide	92 (21.6)	63 (22.4)
Lenalidomide	47 (11.1)	32 (11.4)
PI plus immunomodulatory drug	66 (15.5)	44 (15.7)
Common regimens (≥ 5% overall)		
VMP	117 (27.5)	88 (31.3)
VCd	112 (26.4)	75 (26.7)
VTd	27 (6.4)	14 (5.0)
Rd	20 (4.7)	16 (5.7)
CTd	21 (4.9)	14 (5.0)
Response at study entry[i]		
CR	96 (22.6)	62 (22.1)
VGPR	168 (39.5)	112 (39.9)
PR	161 (37.9)	107 (38.1)
Median time from start of induction to first maintenance dose (range), months	9.5 (5.6-15.0)	9.4 (6.3-14.8)

NOTE. Data are No. (%) unless otherwise indicated. See the Data Supplement for detailed baseline characteristics.

Abbreviations: CR, complete response; CTd, cyclophosphamide-thalidomide-dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; PI, proteasome inhibitor; PR, partial response; Rd, lenalidomide-dexamethasone; VCd, bortezomib-cyclophosphamide-dexamethasone; VGPR, very good partial response; VMP, bortezomib-melphalan-prednisone; VTd, bortezomib-thalidomide-dexamethasone.

[a]Additional categories reported for race are summarized in a footnote in the Data Supplement.

[b]Other categories are summarized in a footnote in the Data Supplement.

[c]Data shown are per patient-level data and not per data reported for randomization stratification.

[d]Data missing for one patient in the ixazomib arm.

[e]Patients' frailty status was classified as fit, unfit, or frail on the basis of four components: age, the Katz Index of Independence in Activities of Daily Living, the Lawton Instrumental Activities of Daily Living Scale, and the Charlson Comorbidity Index Scoring System. Frailty status was reported as missing in four patients (0.9%) in the ixazomib arm and three patients (1.1%) in the placebo arm.

[f]Data missing for one patient in the placebo arm.

[g]High-risk cytogenetic abnormalities were del(17p), t(4;14), and t(14;16). If all three abnormalities were unknown, indeterminate, or missing, the patient was called unclassifiable. There was no cutoff for defining the presence of del(17p). All cytogenetic evaluations were performed locally according to local standards. See the Data Supplement for additional details.

[h]Expanded high-risk cytogenetic abnormalities comprised the high-risk cytogenetic abnormalities plus amplification of 1q21. See the Data Supplement for additional details.

[i]Per investigator.

aged ≥ 75 years (HR, 0.738; 95% CI, 0.537 to 1.014; P = .060; Table 2). PFS benefit in other patient subgroups is summarized in Figure 2B.

Median time to progression was 17.8 versus 9.6 months with ixazomib versus placebo, and response improvements during maintenance were seen in 14.6% versus 8.2% of patients (Table 2). PFS2 and OS data were not mature at the time of this analysis. The study remains blinded; follow-up for PFS2 and OS continues.

Treatment Exposure and Safety

The safety population included 426 and 276 patients in the ixazomib and placebo groups, respectively (Fig 1). Treatment exposure data are summarized in Table 3. At data cutoff, patients had received a median of 13 (1 to 26) and 12 (1 to 26) treatment cycles in the ixazomib and placebo groups, respectively, 16.0% and 10.1% of patients had completed all protocol-specified cycles, and 19.5% and 15.3% were ongoing; 70.7% and 78.3% of patients dose-escalated from the starting dose of 3 mg to 4 mg, respectively.

In the ixazomib versus placebo group, 36.6% versus 23.2% of patients had grade ≥ 3 treatment-emergent AEs (TEAEs), 22.1% versus 16.7% had serious TEAEs, and 30.8% versus 5.1% had a dose reduction and 12.9% versus 8.0% discontinued because of TEAEs (Table 3). TEAEs for which the incidence was ≥ 5% higher with ixazomib versus placebo included nausea (26.8% *v* 8.0%), rash (25.6% *v* 10.5%), vomiting (24.2% *v* 4.3%), diarrhea (23.2% *v* 12.3%), peripheral neuropathy (19.5% *v* 10.9%), and pyrexia (11.3% *v* 5.1%; Table 4). Most TEAEs were grade 1 or 2 severity, with rates of grade ≥ 3 events being ≤ 3% for all individual TEAEs except pneumonia (3.8% grade 3; n = 16; ixazomib group). There was no evidence of cumulative toxicity over the course of treatment. Rates of cardiac arrhythmias, heart failure, hypotension, liver impairment, and renal impairment were all low and similar between groups (Table 4). Nine patients (2.1%) in the ixazomib group had grade ≥ 3 events of renal impairment (considered unrelated to the study drug in six); three events resolved (two without drug interruption, one after dose delay), three resulted in discontinuation, and the one grade 5 event was considered unrelated to the study drug. Of these patients, three had preexisting kidney disease, including the patient who died. The overall rate of herpes zoster was 3.1% with ixazomib and 0.7% with placebo; in patients receiving antiviral prophylaxis, rates were 0.4% and 0%, respectively (Table 4). At a median follow-up of 2 years, there was no difference in the rate of new primary malignancies (Table 4).

Changes in mean Global Health Status/QoL score on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 are shown in the Data Supplement. Scores were similar between groups

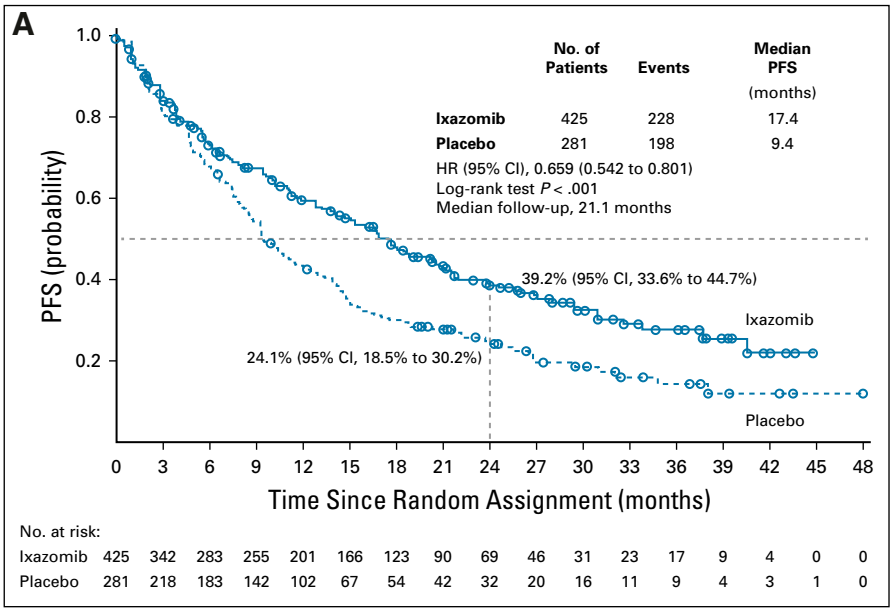

FIG 2. Kaplan-Meier analysis of progression-free survival (PFS) by independent review (A) in the intention-to-treat population and (B) by prespecified patient subgroups. Stratified log-rank tests and Cox models were used for interarm comparisons. Some subgroup data are not shown because of small patient numbers. (*) Data per stratification variables. (†) Data per individual patient-level clinical data after medical review. (‡) High-risk cytogenetic abnormalities were del(17p), t(4;14), and t(14;16). See the Data Supplement for additional details. (¶) Expanded high-risk cytogenetic abnormalities comprised the high-risk cytogenetic abnormalities plus amplification of 1q21. See the Data Supplement for additional details. CR, complete response; HR, hazard ratio; IMiD, immunomodulatory drug; ISS, International Staging System; PI, proteasome inhibitor; PR, partial response; VGPR, very good partial response.

at study entry and were maintained in both groups during the protocol-defined treatment period.

Health care resource use (HRU) during treatment is summarized in the Data Supplement. Ixazomib did not result in additional HRU (hospitalizations, emergency room stays, and outpatient visits).

DISCUSSION

Ixazomib maintenance after standard-of-care induction treatment resulted in a statistically significant and clinically meaningful[25] 34.1% reduction in the risk of progression or death since the time of randomization compared with placebo, with an 8-month increase in median PFS. Additionally, a statistically significant benefit was demonstrated in patients who achieved CR or VGPR with initial therapy. Outcomes since randomization favoring ixazomib were seen in patients with ISS stage III disease and patients aged ≥ 75 years. In the prespecified subgroups of patients with no prior PI exposure and patients with prior immunomodulatory drug exposure, notable PFS benefits since randomization (based on HRs) were seen with ixazomib versus placebo. Although no PFS benefit was seen in the small subgroup of patients with conventional high-risk cytogenetics [t(4;14), t(14;16), del(17p)], ixazomib showed a PFS benefit in the larger subgroup with expanded high-risk cytogenetics, incorporating patients with amp1q21 in line with the current IMWG definition of high-risk cytogenetics.[26] The benefits of ixazomib maintenance were realized in the context of a well-tolerated safety profile and no adverse impact on patients' QoL or HRU, important considerations in this generally elderly, transplantation-ineligible population; similar and consistent findings have been reported from other phase III studies of ixazomib-based therapy in different treatment settings.[21,27,28] TOURMALINE-MM4 (ClinicalTrials.gov identifier: NCT02312258) findings also support the significant PFS benefit seen with ixazomib versus placebo as post-transplantation maintenance therapy in the TOURMALINE-MM3 trial.[20] Together, these studies demonstrate the utility and prolonged activity of oral, once-weekly ixazomib maintenance.

In the context of current therapy, the comparison versus placebo is a limitation of TOURMALINE-MM4; however, at the time of study design, there were no approved or standard-of-care maintenance therapies in non-transplantation NDMM and thus no clear comparator to use instead of placebo. Furthermore, current standard-of-care maintenance may vary among regions. Nevertheless, it is well established that lenalidomide provides a significant improvement in PFS after induction therapy in transplantation-ineligible patients. In the Myeloma XI trial,[10] lenalidomide improved PFS since maintenance randomization versus observation.[10] This study differs from TOURMALINE-MM4 in that patients received maintenance after thalidomide- (48%) or lenalidomide-containing (52%) induction[10]; that is, approximately half the patients received continuous lenalidomide through induction and maintenance. Lenalidomide maintenance after lenalidomide-based induction also demonstrated a PFS benefit, overall and since the start of maintenance, versus placebo or no maintenance in the MM-015[12] and GIMEMA RV-MM-PI-209[29] trials. In the FIRST trial of transplantation-ineligible patients with NDMM, continuous lenalidomide-dexamethasone since the start of therapy demonstrated improved PFS versus fixed-duration lenalidomide-dexamethasone, further highlighting the benefit of maintaining long-term lenalidomide therapy.[15] However, no significant OS benefits were reported in these

B

Subgroup	No. of Patients with PFS Events (of total patients) Ixazomib	Placebo	Median PFS (months) Ixazomib	Placebo	HR (95% CI)
All patients (n = 706)	228 of 425	198 of 281	17.4	9.4	0.659 (0.542 to 0.801)
Age at time of random assignment					
< 75 years (n = 432)*	141 of 261	123 of 171	17.7	9.3	0.615 (0.480 to 0.788)
≥ 75 years (n = 274)*	87 of 164	75 of 110	16.7	10.6	0.738 (0.537 to 1.014)
Prior PI exposure					
Yes (n = 566)*	187 of 342	152 of 224	16.8	11.1	0.743 (0.597 to 0.924)
No (n = 140)*	41 of 83	46 of 57	24.1	7.7	0.395 (0.251 to 0.622)
Preinduction ISS stage					
I or II (n = 465)*	144 of 281	128 of 184	17.4	10.6	0.641 (0.503 to 0.816)
III (n = 241)*	84 of 144	70 of 97	16.6	7.8	0.695 (0.499 to 0.967)
Response to initial therapy					
CR or VGPR (n= 438)*	116 of 263	112 of 175	25.6	12.9	0.586 (0.449 to 0.765)
PR (n= 268)*	112 of 162	86 of 106	10.2	6.5	0.756 (0.566 to 1.010)
Age					
< 65 years (n = 68)†	25 of 37	24 of 31	11.5	8.3	0.569 (0.297 to 1.090)
≥ 65 years and < 75 years (n = 365)†	116 of 224	100 of 141	17.9	9.3	0.632 (0.480 to 0.833)
≥ 75 years (n = 273)†	87 of 164	74 of 109	16.7	10.2	0.742 (0.539 to 1.021)
Sex					
Male (n = 377)	129 of 222	113 of 155	15.3	8.3	0.700 (0.539 to 0.909)
Female (n = 329)	99 of 203	85 of 126	20.3	12.5	0.620 (0.457 to 0.842)
Race					
White (n = 557)	178 of 330	167 of 227	16.9	9.2	0.602 (0.483 to 0.751)
Asian (n = 102)	31 of 63	23 of 39	20.3	14.8	0.826 (0.458 to 1.491)
Other or not reported (n = 27)	9 of 17	5 of 10	22.0	18.7	3.152 (0.356 to 27.875)
Region					
Asia-Pacific (n = 118)	36 of 70	32 of 48	18.7	10.7	0.793 (0.471 to 1.337)
Europe/Middle East/Africa (n = 505)	164 of 304	143 of 201	16.9	9.3	0.635 (0.503 to 0.801)
Other (n = 83)	28 of 51	23 of 32	17.4	9.2	0.672 (0.337 to 1.343)
Frailty status					
Fit (n = 284)	91 of 172	83 of 112	18.6	8.5	0.530 (0.387 to 0.727)
Unfit (n = 245)	80 of 147	67 of 98	17.6	10.6	0.746 (0.526 to 1.058)
Frail (n = 170)	54 of 102	47 of 68	15.4	11.1	0.733 (0.481 to 1.117)
Prior IMiD exposure					
Yes (n = 231)	72 of 137	73 of 94	18.9	8.7	0.498 (0.350 to 0.708)
No (n = 475)	156 of 288	125 of 187	16.6	10.6	0.734 (0.575 to 0.936)
ISS stage at initial diagnosis					
I (n = 178)†	52 of 112	43 of 66	20.3	14.5	0.741 (0.479 to 1.148)
II (n = 279)†	90 of 165	84 of 114	15.7	9.4	0.555 (0.403 to 0.765)
III (n = 249)†	86 of 148	71 of 101	17.7	7.9	0.712 (0.510 to 0.993)
Revised ISS stage at initial diagnosis					
I (n = 86)	21 of 54	22 of 32	21.8	8.0	0.531 (0.278 to 1.015)
II (n = 347)	121 of 204	107 of 143	15.4	9.3	0.667 (0.508 to 0.876)
III (n = 92)	36 of 58	24 of 34	15.3	7.8	0.966 (0.544 to 1.714)
Unclassifiable (n = 181)	50 of 109	45 of 72	18.6	14.2	0.644 (0.407 to 1.019)
Response at study entry					
CR (n = 163)†	31 of 98	29 of 65	40.5	26.7	0.760 (0.434 to 1.332)
VGPR (n = 306)†	97 of 175	102 of 131	17.6	8.7	0.550 (0.410 to 0.737)
PR (n = 194)†	82 of 121	60 of 73	11.1	7.4	0.702 (0.491 to 1.004)
Cytogenetic risk‡					
High risk (n = 122)	51 of 74	36 of 48	10.1	9.6	1.011 (0.631 to 1.621)
Standard risk (n = 465)	142 of 275	139 of 190	17.9	9.2	0.617 (0.484 to 0.787)
Unclassifiable (n = 119)	35 of 76	23 of 43	22.0	14.3	0.735 (0.401 to 1.347)
Cytogenetic risk¶					
Expanded high risk (n = 241)	101 of 150	72 of 91	10.8	8.3	0.765 (0.550 to 1.063)
Standard risk (n = 256)	70 of 148	77 of 108	18.7	9.3	0.550 (0.388 to 0.780)
Unclassifiable (n = 209)	57 of 127	49 of 82	26.7	14.2	0.645 (0.424 to 0.983)
Reason for transplantation ineligibility					
Age (n = 617)	195 of 373	170 of 244	17.6	9.9	0.651 (0.526 to 0.805)
Other (n = 70)	28 of 43	20 of 27	14.8	9.3	0.783 (0.413 to 1.484)

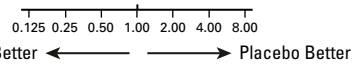

FIG 2. (Continued).

TABLE 2. PFS in Patient Subgroups Prespecified for Testing for Statistical Significance, Time to Progression, and Response Improvements Seen With Ixazomib Versus Placebo as Postinduction Maintenance Therapy in the Intention-to-Treat Population

Endpoint	Ixazomib (n = 425)	Placebo (n = 281)	Hazard Ratio (95% CI)	*P*
Median PFS in prespecified subgroups, months[a,b]				
Patients with a CR or VGPR with initial therapy (n = 263 *v* n = 175)	25.6	12.9	0.586 (0.449 to 0.765)	< .001
Patients with preinduction ISS stage III disease (n = 144 *v* n = 97)	16.6	7.8	0.695 (0.499 to 0.967)	.030
Patients aged ≥ 75 years (n = 164 *v* n = 110)	16.7	10.6	0.738 (0.537 to 1.014)	.060
Median total PFS landmarked from start of induction, months[b]	26.3	20.3	0.650 (0.534 to 0.791)	< .001
Median time to progression, months[b]	17.8	9.6	0.655 (0.537 to 0.799)	< .001
Response improvements during maintenance				
VGPR/PR patients with deepening response during treatment, No. (%)	62 (14.6)	23 (8.2)	—	.004[c]
VGPR patients converting to CR during study, No. (%)	41 (9.6)	16 (5.7)	—	—
PR patients converting to VGPR or better during study, No. (%)	21 (4.9)	7 (2.5)	—	—

Abbreviations: CR, complete response; ISS, International Staging System; PFS, progression-free survival; PR, partial response; VGPR, very good partial response.

[a]Subgroup testing for PFS was conducted using an alpha of .01 and the Hochberg procedure for multiplicity correction. There was a significant difference with ixazomib versus placebo in patients who had CR or VGPR with initial therapy, and there were benefits in patients with ISS stage III disease and in patients aged ≥ 75 years, although these did not meet the significance test.

[b]Kaplan-Meier methodology was used to estimate time-to-event distributions, with stratified log-rank tests and Cox models used for interarm comparisons of time-to-event endpoints.

[c]Per the Cochran-Mantel-Haenszel test stratified by response at study entry (PR *v* VGPR).

four studies.[10,12,15,29] Similarly, bortezomib-based maintenance after bortezomib-based induction has contributed to notable overall outcomes in transplantation-ineligible patients in the GEM05MAS65,[30] GIMEMA-MM-03-05,[31] and UPFRONT studies[32]; however, the specific impact of bortezomib-based maintenance or PI-based maintenance more broadly has not been determined in a randomized, placebo-controlled phase III trial.

Patients in TOURMALINE-MM4 received induction therapy with a PI-containing and/or immunomodulatory drug–containing regimen at the discretion of their treating physicians. No patients received prior ixazomib, although 82.6% received PI-based induction, resulting in continuous PI-based therapy and a median total PFS of approximately 26 months. Evaluation of this overall median in the context of other data in transplantation-ineligible patients with NDMM is confounded by the immortal time bias arising from TOURMALINE-MM4 requiring patients to have achieved greater than or equal to PR at enrollment after 6-12 months of standard-of-care induction therapy. Comparisons among studies are also confounded by various patient- and disease-related factors, and should be avoided.

To our knowledge, TOURMALINE-MM4 is the first randomized phase III trial to specifically investigate an induction-agnostic maintenance approach—randomly assigning patients to ixazomib versus placebo regardless of the standard-of-care induction therapy received—in transplantation-ineligible NDMM. The feasibility of maintaining long-term PI-based therapy and convenience of oral administration with ixazomib are valuable attributes for treatment of the nontransplantation population, particularly for elderly patients, and this unique approach may be of value when considering tailoring treatment to specific patients. Given the disease heterogeneity of MM, physicians require options that enable them to amend and individualize first-line therapy. Prolongation of PFS with ixazomib regardless of the standard-of-care induction therapy is of potential value as an additional treatment option, along with continuous therapy approaches[15,16] with lenalidomide[12,29,33,34] or daratumumab[8] after lenalidomide-based or daratumumab-based induction.

An alternative approach to long-term PI-based therapy is to use ixazomib in a continuous manner similar to that used with lenalidomide[12,29,33,34] or daratumumab.[8] A recent analysis of four phase II studies of ixazomib maintenance after ixazomib-based induction demonstrated the feasibility and activity of this approach.[35] The phase III, placebo-controlled TOURMALINE-MM2 trial in transplantation-ineligible patients with NDMM compared ixazomib-lenalidomide-dexamethasone versus placebo-lenalidomide-dexamethasone for 18 cycles, followed by reduced-dose ixazomib-lenalidomide versus placebo-lenalidomide from cycle 19 onward. At the time of publication, a PFS benefit with ixazomib-based therapy, with a lengthy median, has been reported[36] and the publication of the full study results is awaited. Transplantation-ineligible patients with NDMM are highly heterogeneous—one treatment approach does not fit all. An induction-agnostic maintenance or continuous therapy option may be of value for optimizing therapy in individual patients.

TABLE 3. Treatment Exposure and Overall Safety Profile in the Safety Population

Variable	Ixazomib (n = 426)[a]	Placebo (n = 276)[a]
Treatment cycles, median No. (range)	13 (1-26)	12 (1-26)
Dose escalated to 4 mg at cycle ≥ 5	301 (70.7)	216 (78.3)
Median duration of treatment at a dose/placebo equivalent of 4 mg, months (range)	6.0 (0-21)	7.8 (0-21)
Completed protocol-specified 26 cycles	68 (16.0)	28 (10.1)
Ongoing on treatment[b]	83 (19.5)	43 (15.3)
Mean (SD) relative dose intensity, %[c]	90.4 (12.63)	96.6 (7.63)
Mean (SD) relative dose intensity in patients escalated to 4 mg at cycle 5, %[c]	93.7 (8.36)	98.6 (3.99)
Any TEAE	389 (91.3)	226 (81.9)
Any drug-related TEAE	284 (66.7)	111 (40.2)
Any grade ≥ 3 TEAE	156 (36.6)	64 (23.2)
Any drug-related grade ≥ 3 TEAE	76 (17.8)	12 (4.3)
Any serious TEAE	94 (22.1)	46 (16.7)
Any drug-related serious TEAE	22 (5.2)	3 (1.1)
TEAE resulting in discontinuation of the study drug	55 (12.9)	22 (8.0)
TEAE resulting in dose reduction of the study drug	131 (30.8)	14 (5.1)
Death during the treatment period[d]	11 (2.6)	6 (2.2)

NOTE. Data are No. (%) unless otherwise indicated.

Abbreviation: SD, standard deviation; TEAE, treatment-emergent adverse event.

[a]Two patients in the ixazomib group and two patients in the placebo group never received the study drug and were excluded from the safety population. Three patients assigned to the placebo group erroneously received a single dose of ixazomib and were therefore analyzed as part of the ixazomib group in the safety population.

[b]Percentages determined in the intention-to-treat-population (n = 425; n = 281) instead of the safety population.

[c]Relative dose intensity is defined as 100 × (total amount of dose taken) / (total prescribed dose of treated cycles). Total prescribed dose of treated cycles is calculated as: dose prescribed (3 mg, cycles 1-4, 3 mg or 4 mg, cycle 5 onward) × prescribed doses per cycle × number of treated cycles (calculated separately for cycles 1-4 and cycle 5 onward in patients who escalated to 4 mg at cycle 5 onward).

[d]Death during the treatment period was recorded through 30 days after receiving the last dose of the study drug or placebo.

TOURMALINE-MM4 demonstrated the tolerability of ixazomib maintenance in this elderly population of transplantation-ineligible patients; 70.7% of patients tolerated the 3-mg dose of ixazomib sufficiently well to escalate to 4 mg. Overall rates of TEAEs were similar between groups, and TEAEs were mostly grade 1-2 severity. Rates of serious TEAEs and discontinuations because of TEAEs appeared slightly higher with ixazomib versus placebo, whereas rates of on-study death and new primary malignancies appeared similar. Common TEAEs that were more frequent with ixazomib included GI toxicities, rash, and peripheral neuropathy; however, rates of grade 3 events were low in both groups. No new safety signals were seen, reflecting the findings of TOURMALINE-MM3.[20] In the Myeloma XI trial of lenalidomide as maintenance post-transplantation or postinduction, with a median duration of therapy of eighteen 28-day cycles, 28% of patients who had discontinued lenalidomide did so because of AEs.[10] Furthermore, lenalidomide appeared to be associated with higher rates of dose modifications (69%) and serious AEs (45%)[10] than seen in TOURMALINE-MM4 (dose reductions, 30.8%; serious TEAEs, 22.1%) or TOURMALINE-MM3 (19% and 27%, respectively),[20] and an elevated risk of new primary malignancies.[10] The tolerable safety profile of ixazomib maintenance in TOURMALINE-MM4 was reflected in similar HRU data between arms and in patient-reported QoL, which was maintained since study entry in both arms and was generally similar throughout the treatment period, indicating that active treatment with ixazomib did not have a negative impact on patient-reported QoL versus placebo in this double-blind trial.

In TOURMALINE-MM4, treatment duration was fixed at 2 years, based on the duration of bortezomib-based maintenance in prior phase III trials.[31,37] At the time of trial design, PI-based treat-to-progression approaches had not been studied in a phase III trial, and, to date, the optimal duration of PI-based maintenance remains to be determined. Longer-term therapy may have resulted in improved outcomes in some patients in TOURMALINE-MM4; however, because median PFS was less than 24 months, the median would be unlikely to be affected. With the favorable tolerability of ixazomib, it was felt that this treatment duration could be achieved with minimal discontinuations because of toxicity and a reduced risk of developing resistant disease. Nevertheless, because median treatment duration was 13 cycles and 16.0% of patients completed protocol-specified therapy, treat-to-progression therapy is unlikely to have resulted in prolonged treatment except in a few patients.

TABLE 4. Common TEAEs in the Safety Population (≥ 10% in either group or rate difference of ≥ 5% between ixazomib and placebo groups) Plus Other TEAEs of Clinical Interest

	Ixazomib Group (n = 426)			Placebo Group (n = 276)		
Adverse Event	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Common hematologic TEAEs of any cause						
Thrombocytopenia[a]	20 (4.7)	9 (2.1)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Neutropenia[a]	10 (2.3)	8 (1.9)	1 (0.2)	9 (3.3)	4 (1.4)	0 (0.0)
Common nonhematologic TEAEs of any cause						
GI disorders (MedDRA SOC)	222 (52.1)	22 (5.2)	0 (0.0)	93 (33.7)	7 (2.5)	0 (0.0)
Nausea	114 (26.8)	2 (0.5)	0 (0.0)	22 (8.0)	0 (0.0)	0 (0.0)
Vomiting	103 (24.2)	7 (1.6)	0 (0.0)	12 (4.3)	2 (0.7)	0 (0.0)
Diarrhea	99 (23.2)	8 (1.9)	0 (0.0)	34 (12.3)	2 (0.7)	0 (0.0)
Infections and infestations (MedDRA SOC)[b]	206 (48.4)	28 (6.6)	0 (0.0)	104 (37.7)	12 (4.3)	0 (0.0)
Upper respiratory tract infection	67 (15.7)	2 (0.5)	0 (0.0)	30 (10.9)	1 (0.4)	0 (0.0)
Rash[a]	109 (25.6)	12 (2.8)	0 (0.0)	29 (10.5)	0 (0.0)	0 (0.0)
Peripheral neuropathy[a]	83 (19.5)	7 (1.6)	0 (0.0)	30 (10.9)	0 (0.0)	0 (0.0)
Back pain	61 (14.3)	1 (0.2)	0 (0.0)	31 (11.2)	1 (0.4)	0 (0.0)
Arthralgia	49 (11.5)	2 (0.5)	0 (0.0)	20 (7.2)	2 (0.7)	0 (0.0)
Pyrexia	48 (11.3)	1 (0.2)	0 (0.0)	14 (5.1)	0 (0.0)	1 (0.4)
Fatigue	46 (10.8)	6 (1.4)	0 (0.0)	28 (10.1)	1 (0.4)	0 (0.0)
Other TEAEs of clinical interest						
Cardiac arrhythmias[a,c]	18 (4.2)	6 (1.4)	0 (0.0)	13 (4.7)	2 (0.7)	0 (0.0)
Heart failure[a,d]	5 (1.2)	2 (0.5)	0 (0.0)	4 (1.4)	1 (0.4)	1 (0.4)
Hypotension[a]	10 (2.3)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)
Liver impairment[a]	19 (4.5)	6 (1.4)	0 (0.0)	7 (2.5)	3 (1.1)	0 (0.0)
Myocardial infarction[a,e]	1 (0.2)	0 (0.0)	1 (0.2)	4 (1.4)	1 (0.4)	0 (0.0)
Renal impairment[a,f]	16 (3.8)	4 (0.9)	4 (0.9)	5 (1.8)	0 (0.0)	0 (0.0)
Herpes zoster	13 (3.1)	1 (0.2)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
In patients receiving antiviral prophylaxis	1/274 (0.4)	0 (0.0)	0 (0.0)	0/167 (0.0)	0 (0.0)	0 (0.0)
In patients not receiving prophylaxis	12/152 (7.9)	1/152 (0.7)	0 (0.0)	2/109 (1.8)	0 (0.0)	0 (0.0)
New primary malignant tumor	22 (5.2)	—		17 (6.2)	—	

NOTE. Data are No. (%).

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; TEAEs, treatment-emergent adverse events.

[a]Data were based on a standardized MedDRA query that incorporated pooled preferred terms or multiple preferred terms. Preferred terms included within each standardized MedDRA query are summarized in the Data Supplement.

[b]Seven patients (1.6%) in the ixazomib group and one patient (0.4%) in the placebo group had grade 5 infections and infestations events, including septic shock (n = 6), sepsis (n = 2), and viral pneumonia (n = 1) in the ixazomib group and septic shock (n = 1) in the placebo group.

[c]One patient (0.2%) in the ixazomib group had a grade 5 event of cardiac arrest, and one (0.4%) in the placebo group had a grade 5 event of sudden death.

[d]One patient (0.2%) in the ixazomib group had grade 5 acute pulmonary edema.

[e]One patient (0.4%) in the placebo group had grade 5 myocardial infarction.

[f]One patient (0.2%) in the ixazomib group had grade 5 acute kidney injury.

In conclusion, to our knowledge, ixazomib is the first induction-agnostic maintenance option investigated for transplantation-ineligible patients with NDMM. These results indicate that ixazomib is well tolerated and provides a PFS benefit in this setting, thereby representing a valuable treatment option for patients. Subgroup analyses suggest PFS benefit across this population, including in elderly patients, those with preinduction ISS stage III disease, and patients achieving CR or VGPR postinduction. Furthermore, ixazomib may provide a valuable maintenance option in combination with other agents, such as immunomodulatory drugs and monoclonal antibodies. TOURMALINE-MM4 continues in a double-blind fashion for long-term evaluation of PFS2 and OS.

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PRIOR PRESENTATION

Poster presented at the ASCO20 Virtual Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 29-31, 2020; paper presented at the virtual 25th Annual Congress of the European Hematology Association, The Hague, Netherlands, June 11-21, 2020.

SUPPORT

Sponsored by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

CLINICAL TRIAL INFORMATION

NCT02312258

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.02060

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ACKNOWLEDGMENT

This study was sponsored by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. The trial was designed by the authors in collaboration with the sponsor. Data were gathered by the investigators and sponsor, and analyzed by the sponsor. The sponsor funded professional medical writing support to prepare the manuscript. We thank the patients and their families, as well as the physicians, nurses, study coordinators, and research staff for participation in the trial; Dasha Cherepanov, PhD, and Lauren Cain, PhD, of Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, for their contributions to health-related quality of life and health care resource use analyses and interpretations; Renda Ferrari, PhD, of Millennium Pharmaceuticals, Inc., for editorial assistance; and Steve Hill, PhD, of FireKite, an Ashfield company, part of UDG Healthcare, for professional medical writing assistance, which was funded by Millennium Pharmaceuticals, Inc.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.