ORIGINAL ARTICLE

Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

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ABSTRACT

BACKGROUND

Ixazomib is an oral proteasome inhibitor that is currently being studied for the treatment of multiple myeloma.

METHODS

In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned 722 patients who had relapsed, refractory, or relapsed and refractory multiple myeloma to receive ixazomib plus lenalidomide–dexamethasone (ixazomib group) or placebo plus lenalidomide–dexamethasone (placebo group). The primary end point was progression-free survival.

RESULTS

Progression-free survival was significantly longer in the ixazomib group than in the placebo group at a median follow-up of 14.7 months (median progression-free survival, 20.6 months vs. 14.7 months; hazard ratio for disease progression or death in the ixazomib group, 0.74; P=0.01); a benefit with respect to progression-free survival was observed with the ixazomib regimen, as compared with the placebo regimen, in all prespecified patient subgroups, including in patients with high-risk cytogenetic abnormalities. The overall rates of response were 78% in the ixazomib group and 72% in the placebo group, and the corresponding rates of complete response plus very good partial response were 48% and 39%. The median time to response was 1.1 months in the ixazomib group and 1.9 months in the placebo group, and the corresponding median duration of response was 20.5 months and 15.0 months. At a median follow-up of approximately 23 months, the median overall survival has not been reached in either study group, and follow-up is ongoing. The rates of serious adverse events were similar in the two study groups (47% in the ixazomib group and 49% in the placebo group), as were the rates of death during the study period (4% and 6%, respectively); adverse events of at least grade 3 severity occurred in 74% and 69% of the patients, respectively. Thrombocytopenia of grade 3 and grade 4 severity occurred more frequently in the ixazomib group (12% and 7% of the patients, respectively) than in the placebo group (5% and 4% of the patients, respectively). Rash occurred more frequently in the ixazomib group than in the placebo group (36% vs. 23% of the patients), as did gastrointestinal adverse events, which were predominantly low grade. The incidence of peripheral neuropathy was 27% in the ixazomib group and 22% in the placebo group (grade 3 events occurred in 2% of the patients in each study group). Patient-reported quality of life was similar in the two study groups.

CONCLUSIONS

The addition of ixazomib to a regimen of lenalidomide and dexamethasone was associated with significantly longer progression-free survival; the additional toxic effects with this all-oral regimen were limited. (Funded by Millennium Pharmaceuticals; TOURMALINE-MM1 ClinicalTrials.gov number, NCT01564537.)

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*A complete list of TOURMALINE-MM1 study investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Outcomes of multiple myeloma have improved substantially over the past 15 years with the introduction of proteasome inhibitors and immunomodulatory drugs,[1,2] and these agents now form the backbone of therapy for multiple myeloma.[3] In phase 3 studies, triplet regimens based on these agents were shown to be more efficacious than doublet regimens when these regimens were used as a first-line treatment[4-6] and in relapsed disease.[7,8] In addition, there has been a shift in treatment patterns toward the use of extended treatment to further improve long-term outcomes,[9] and this shift highlights the need for additional effective agents with acceptable side-effect profiles that will enable patients to continue receiving therapy for prolonged periods.

Ixazomib is a peptide boronic acid proteasome inhibitor that is administered orally and that has a chemical structure and pharmacologic properties that are distinct from those of bortezomib.[10,11] Ixazomib was shown to have synergy with lenalidomide in preclinical studies.[12] In an early-phase study, ixazomib was administered orally once weekly in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma and was shown to have encouraging efficacy (58% of patients who could be evaluated had a complete response or a very good partial response) and manageable adverse events that included some peripheral neuropathy; the results from this study showed that long-term treatment could be continued for more than 4 years.[13,14]

These early-phase data provided the rationale for the phase 3, randomized, double-blind, placebo-controlled trial reported here. We compared the efficacy and safety of ixazomib, administered weekly, plus lenalidomide–dexamethasone (an all-oral triplet regimen containing a proteasome inhibitor and an immunomodulatory drug, together with dexamethasone) with those of placebo plus lenalidomide–dexamethasone in patients with relapsed, refractory, or relapsed and refractory multiple myeloma.

Methods

Patients

Adult patients were eligible for enrollment if they had relapsed, refractory, or both relapsed and refractory multiple myeloma; had measurable levels of disease (even if measurable by serum free light-chain assay only); had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2 (on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability); had received one to three prior therapies; and had adequate hematologic and hepatic function. Patients with mild-to-moderate impairment of renal function (i.e., patients with a calculated creatinine clearance of at least 30 ml per minute per 1.73 m^2 of body-surface area) were eligible. Patients were not eligible if they had peripheral neuropathy of grade 1 with pain or grade 2 or higher or had disease that was refractory to prior lenalidomide therapy or proteasome inhibitor–based therapy; however, patients with primary refractory disease (defined as no response to prior therapy) were eligible. Eligibility criteria are described in detail in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Study Design

Patients were randomly assigned, in a 1:1 ratio, to receive, in 28-day cycles, either 4 mg of oral ixazomib or matching placebo on days 1, 8, and 15; in addition, all patients received 25 mg of oral lenalidomide on days 1 through 21 (10 mg for patients with a creatinine clearance of ≤60 or ≤50 ml per minute per 1.73 m^2, with the cutoff point determined according to the local prescribing information) and 40 mg of oral dexamethasone on days 1, 8, 15, and 22. Randomization was stratified according to the number of prior therapies (1 vs. 2 or 3), previous exposure to proteasome inhibitors (not exposed vs. exposed), and International Staging System disease stage (I or II vs. III, with higher stages indicating more advanced disease) (Table S1 in the Supplementary Appendix). Treatment was continued until disease progression or the development of unacceptable toxic effects. Thromboprophylaxis was required in all patients (97% of the patients in the ixazomib group and 98% of the patients in the placebo group received thromboprophylaxis); prophylactic medications and permitted concomitant treatments are listed in the Supplementary Appendix. Dose adjustments for toxic effects were permitted according to established dose-adjustment guidelines specified in the protocol or prescribing information for each study drug.

The primary end point was progression-free survival, which was defined as the time from the

date of randomization to the date of first documentation of disease progression or death from any cause, as assessed by an independent review committee, whose members were unaware of the study-group assignments. Prespecified key secondary end points were overall survival in the intention-to-treat population and overall survival in patients with chromosome 17p deletion [del(17p)]. Other secondary end points included the overall rate of response, the rate of complete response plus very good partial response, the duration of response, the time to disease progression, progression-free survival in patients with high-risk cytogenetic abnormalities, safety, and change in global health status. Additional end points are listed in the Supplementary Appendix.

STUDY OVERSIGHT

The trial was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and appropriate regulatory requirements. Local ethics committees or institutional review boards approved the protocol, which is available at NEJM.org. All patients provided written informed consent.

The trial was designed by the first, last, and other authors in collaboration with the sponsor, Millennium Pharmaceuticals, a subsidiary of Takeda Pharmaceuticals. Data were gathered by the investigators and the sponsor and were analyzed by the sponsor; all the authors had access to the data. The initial draft of the manuscript was written by the first and last authors and two other authors, along with a professional medical writer who was funded by the sponsor. All the authors contributed to subsequent drafts, all the authors and the sponsor reviewed the drafts, and all the authors made the decision to submit the manuscript for publication. The investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data. All the authors vouch for the integrity, accuracy, and completeness of the data and analyses and for the fidelity of the study to the protocol.

ASSESSMENTS

Assessments of the response to the study regimen were performed every cycle until disease progression. Assessments of response and disease progression were based on central laboratory results and International Myeloma Working Group 2011 criteria (Table S2 in the Supplementary Appendix),[15] as evaluated by an independent review committee whose members were unaware of the study group assignments and investigator assessments. All patients were followed for survival after disease progression (every 12 weeks until death or termination of the study). Cytogenetic abnormalities were assessed by a central laboratory at screening, with high-risk abnormalities defined as del(17p), translocation between chromosomes 4 and 14 [t(4;14)], or translocation between chromosomes 14 and 16 [t(14;16)]. Health-related quality of life was evaluated with the use of patient self-reported instruments that included the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 module (EORTC QLQ-C30) and the myeloma-specific module (EORTC QLQ-MY20) (for additional information on assessments, see the Supplementary Appendix).

STATISTICAL ANALYSIS

The primary end point of progression-free survival and the key secondary end points of overall survival and overall survival in patients with del(17p) were evaluated with the use of a closed sequential testing procedure to control for the type 1 error rate at a two-sided alpha level of 0.05; the test for overall survival was to be conducted on its own alpha-spending functions only if progression-free survival was significant. Three sequential interim analyses and a final analysis were planned. We calculated the total sample size such that the study would have 80% power to detect a 30% difference in overall survival (hazard ratio for death with ixazomib, 0.77), at a two-sided alpha level of 0.05. The study was powered to detect the superiority of ixazomib over placebo with respect to progression-free survival (hazard ratio of 0.74). An O'Brien–Fleming stopping boundary for efficacy was calculated with the use of a Lan–DeMets alpha-spending function[16] on the basis of the number of events observed at the time of data cutoff. An interim analysis was planned when approximately 36% of the patients had an event of progression or death.

At the first prespecified analysis at a median follow-up of approximately 15 months, the progression-free survival results crossed the prespecified O'Brien–Fleming boundary and showed that the ixazomib regimen was associated with a significant benefit as compared with the placebo regimen; therefore, in accordance with the statistical analysis plan in the protocol and the

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

Characteristic	Ixazomib Group (N=360)	Placebo Group (N=362)	Overall (N=722)
Age			
Median (range) — yr	66 (38–91)	66 (30–89)	66 (30–91)
>65 yr — no. (%)	192 (53)	186 (51)	378 (52)
Male sex — no. (%)	207 (58)	202 (56)	409 (57)
White race — no. (%)†	310 (86)	301 (83)	611 (85)
ECOG performance status score — no./total no. (%)‡			
0	180/354 (51)	170/358 (47)	350/712 (49)
1	156/354 (44)	164/358 (46)	320/712 (45)
2	18/354 (5)	24/358 (7)	42/712 (6)
ISS disease stage at study entry — no. (%)§			
I	226 (63)	233 (64)	459 (64)
II	89 (25)	87 (24)	176 (24)
III	45 (12)	42 (12)	87 (12)
Median creatinine clearance (range) — ml/min per 1.73 m^2	78.4 (20–233)	78.4 (27–233)	78.4 (20–233)
Creatinine clearance — no. (%)			
<30 ml/min per 1.73 m^2	5 (1)	5 (1)	10 (1)
30 to <60 ml/min per 1.73 m^2	74 (21)	95 (26)	169 (23)
60 to <90 ml/min per 1.73 m^2	155 (43)	129 (36)	284 (39)
≥90 ml/min per 1.73 m^2	126 (35)	132 (36)	258 (36)
Median time since initial diagnosis of multiple myeloma (range) — mo	44.2 (3–281)	42.2 (4–306)	42.8 (3–306)
Cytogenetic features — no. of patients (%)¶			
Standard-risk cytogenetic abnormalities	199 (55)	216 (60)	415 (57)
High-risk cytogenetic abnormalities	75 (21)	62 (17)	137 (19)
Data not available	86 (24)	84 (23)	170 (24)
No. of prior therapies — no. of patients (%)‖			
1	224 (62)	217 (60)	441 (61)
2	97 (27)	111 (31)	208 (29)
3	39 (11)	34 (9)	73 (10)
Prior stem-cell transplantation	212 (59)	199 (55)	411 (57)
Disease category — no./total no. (%)			
Relapsed	276/359 (77)	280/362 (77)	556/721 (77)
Refractory	42/359 (12)	40/362 (11)	82/721 (11)
Relapsed and refractory	41/359 (11)	42/362 (12)	83/721 (12)
Primary refractory	24/359 (7)	22/362 (6)	46/721 (6)
Prior proteasome inhibitor therapy — no. (%)	249 (69)	253 (70)	502 (70)
Bortezomib	248 (69)	250 (69)	498 (69)
Carfilzomib	1 (<1)	4 (1)	5 (1)
Disease refractory to any prior proteasome inhibitor therapy — no. (%)**	4 (1)	8 (2)	12 (2)

Table 1. (Continued.)

Characteristic	Ixazomib Group (N=360)	Placebo Group (N=362)	Overall (N=722)
Prior immunomodulatory drug therapy — no./total no. (%)	193/360 (54)	204/362 (56)	397/722 (55)
Lenalidomide	44/360 (12)	44/362 (12)	88/722 (12)
Thalidomide	157/360 (44)	170/362 (47)	327/722 (45)
Disease refractory to any prior immunomodulatory drug therapy††	41/193 (21)	50/204 (25)	91/397 (23)

* There were no significant differences at baseline between the two groups in the characteristics shown.
† Race was self-reported.
‡ Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability related to tumor.
§ The International Staging System (ISS) consists of three stages: stage I, serum β_2-microglobulin level lower than 3.5 mg per liter (300 nmol per liter) and albumin level 3.5 g per deciliter or higher; stage II, neither stage I or III; and stage III, serum β_2-microglobulin 5.5 mg per liter or higher (470 nmol per liter). Higher stages indicate more severe disease.
¶ High-risk cytogenetic abnormalities were detected by fluorescence in situ hybridization (FISH) analysis and were defined as chromosome 17p deletion [del(17p)], translocation between chromosomes 4 and 14 [t(4;14)], and translocation between chromosomes 14 and 16 [t(14;16)]. A total of 36 patients in the ixazomib group and 33 patients in the placebo group had del(17p) alone or in combination with either t(4;14) or t(14;16) or both; 36 and 25 patients, respectively, had t(4;14) alone; and 3 and 4 patients, respectively, had t(14;16) alone. Standard-risk cytogenetic abnormalities were defined as the absence of high-risk abnormalities in the samples that were available for evaluation; samples from some patients were not available for testing because the sample was missing or clotted or for other reasons. In accordance with the protocol, the cutoff values for defining the presence of high-risk cytogenetic abnormalities were established by the central diagnostic laboratory on the basis of the false positive rates (or technical cutoff values) of the FISH probes that we used. These cutoff points were 5% positive cells for del(17p), 3% positive cells for t(4;14), and 3% positive cells for t(14;16).
‖ The number of prior therapies was determined by the sponsor in a blinded medical review of data on prior therapy.
** Refractoriness to any prior proteasome inhibitor therapy was determined by the sponsor in a blinded medical review.
†† All the patients had disease that had been refractory to prior therapy with thalidomide, except for one patient in the placebo group, who, on further blinded medical review by the sponsor, was determined to have disease that had been refractory to prior therapy with lenalidomide. Percentages are shown are those patients who received prior therapy with immunomodulatory drugs.

principle of group sequential design, this was the final statistical analysis of progression-free survival. According to the protocol, the study continued in a double-blind manner to gain more mature data on overall survival; a second prespecified analysis at a median follow-up of approximately 23 months was conducted to assess survival.

The intention-to-treat population, which included all patients who underwent randomization, was evaluated for all primary and secondary efficacy analyses. The safety population included all patients who received at least one dose of a study drug or placebo. Additional details regarding the populations included in our analyses are provided in the Supplementary Appendix. The Kaplan–Meier method was used to estimate time-to-event distributions, and stratified log-rank tests and Cox models, at a two-sided alpha level of 0.05, were used for between-group comparisons of time-to-event end points. We performed prespecified subgroup analyses of progression-free survival, including in subgroups defined according to cytogenetic characteristics. A stratified Cochran–Mantel–Haenszel chi-square test was used to assess between-group differences in response rates.

RESULTS

PATIENTS

A total of 722 patients at 147 sites in 26 countries were enrolled in the study from August 28, 2012, to May 27, 2014 (Fig. S1 in the Supplementary Appendix). Baseline characteristics of the patients in the intention-to-treat population were well balanced between the study groups (Table 1). The results of cytogenetic analysis were available for 76% of the patients and showed that 19% of the intention-to-treat population had high-risk cytogenetic abnormalities, including 10% with del(17p).

EFFICACY

At the time of data cutoff for the first analysis (October 30, 2014), the median follow-up was 14.8 months in the ixazomib group and 14.6 months in the placebo group. As assessed by an independent review committee, 129 events of disease progression or death occurred in the ixazomib group and 157 in the placebo group. The median progression-free survival was 20.6 months in the ixazomib group and 14.7 months in the placebo group and the hazard ratio for disease progression or death was 0.74 (95% confidence interval [CI], 0.59 to 0.94; P=0.01), representing a 35% longer progression-free survival with ixazomib plus lenalidomide–dexamethasone as compared with placebo plus lenalidomide–dexamethasone. Because the primary end point of progression-free survival was significantly longer in the ixazomib group than in the placebo group, no further statistical testing of this end point was performed.

The benefit with respect to progression-free survival was consistent in all key prespecified patient subgroups (Fig. 1B), including patients with a poor prognosis, such as those with high-risk cytogenetic abnormalities, those with International Staging System stage III disease, those older than 75 years of age, and those who had received two or three prior therapies; no significant interactions were observed between these subgroups and study-group assignment. The median progression-free survival among the patients with high-risk cytogenetic abnormalities (75 patients in the ixazomib group and 62 patients in the placebo group) was 21.4 months and 9.7 months, respectively (hazard ratio for disease progression or death in the ixazomib group, 0.54; 95% CI, 0.32 to 0.92; P=0.02); the median progression-free survival among the patients with del(17p) (36 patients in the ixazomib group and 33 in the placebo group) was 21.4 months and 9.7 months, respectively (hazard ratio, 0.60; 95% CI, 0.29 to 1.24), and, among the patients with t(4;14) without del(17p) or t(14;16) (36 patients in the ixazomib group and 25 in the placebo group), was 18.5 months and 12.0 months, respectively (hazard ratio, 0.65; 95% CI, 0.25 to 1.66).

Overall rates of response were 78.3% in the ixazomib group and 71.5% in the placebo group (P=0.04) (Table 2). The responses were rapid and durable (Table 2) and deepened with increasing duration of treatment (i.e., more people had a response and the type of response also got better over time, with more people having a very good partial response or a complete response) (Fig. S2 in the Supplementary Appendix).

Figure 1 (facing page). Kaplan–Meier Analysis of Progression-free Survival.

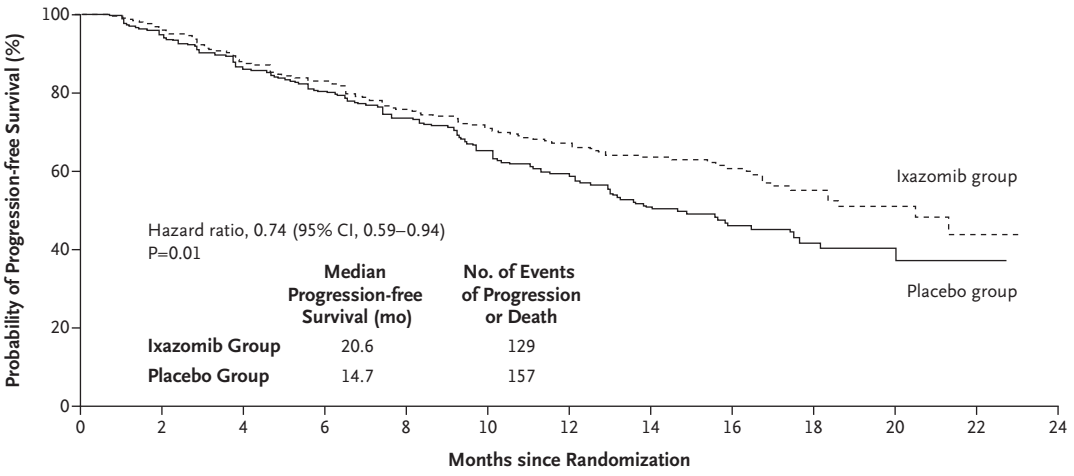
Data are from the final statistical analysis for progression-free survival. ISS denotes International Staging System (stage I, serum β_2-microglobulin level <3.5 mg per liter [300 nmol per liter] and albumin level ≥3.5 g per deciliter; stage II, neither stage I nor III; and stage III, serum β_2-microglobulin ≥5.5 mg per liter [470 nmol per liter] — higher stage indicates more advanced disease) and NE could not be estimated.

Because the primary end point of progression-free survival was significantly longer in the ixazomib group than in the placebo group and because the groups did not differ significantly with respect to overall survival at the first analysis, a subsequent analysis of overall survival at a data-cutoff date of July 12, 2015, was performed; the median follow-up was 23 months. The median overall survival had not yet been reached in either study group; 171 deaths had occurred by the 23-month analysis (81 in the ixazomib group and 90 in the placebo group), which represents 35% of the prespecified number of deaths required for final analysis of overall survival, and follow-up is ongoing (for additional details regarding the subsequent analysis, see the Supplementary Appendix).

SAFETY

Safety data were evaluated at both the first and second analyses. The safety profile with the longer duration of exposure (second analysis) was consistent with the safety profile with the shorter duration of exposure (first analysis). At the 23-month analysis, the safety population included 361 patients in the ixazomib group and 359 in the placebo group (Fig. S1 in the Supplementary Appendix). Patients in the ixazomib group received treatment for a median of 17 cycles (range, 1 to 34), and those in the placebo group received treatment for a median of 15 cycles (range, 1 to 34) (48% and 43% of patients in the respective study groups received treatment for ≥18 cycles, and 20% and 19% received treat-

A Progression-free Survival in the Intention-to-Treat Population



No. at Risk

Ixazomib group	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo group	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

B Subgroup Analysis

Subgroup	Ixazomib Group	Placebo Group	Ixazomib Group	Placebo Group	Hazard Ratio (95% CI)
	no. of patients		*median progression-free survival (mo)*		
All patients	360	362	20.6	14.7	0.74
Age					
≤65 yr	168	176	20.6	14.1	0.68
>65–75 yr	145	125	17.5	17.6	0.83
>75 yr	47	61	18.5	13.1	0.87
ISS stage (stratification factor)					
I or II	314	318	21.4	15.7	0.75
III	46	44	18.4	10.1	0.72
Cytogenetic risk					
Standard risk	199	216	20.6	15.6	0.64
High risk	75	62	21.4	9.7	0.54
No. of prior therapies					
1	224	217	20.6	15.9	0.83
2	97	111	17.5	14.1	0.75
3	39	34	NE	10.2	0.37
Proteasome inhibitor					
Exposed	250	253	18.4	13.6	0.74
Not exposed	110	109	NE	15.7	0.75
Prior immunomodulatory drug therapy					
Exposed	193	204	NE	17.5	0.74
Not exposed	167	158	20.6	13.6	0.70
Refractory to last prior therapy					
Yes	59	55	NE	NE	0.71
No	301	307	20.6	14.1	0.74
Relapsed or refractory					
Relapsed	276	280	18.7	15.6	0.77
Refractory	42	40	NE	13.0	0.78
Relapsed and refractory	41	42	NE	13.1	0.51

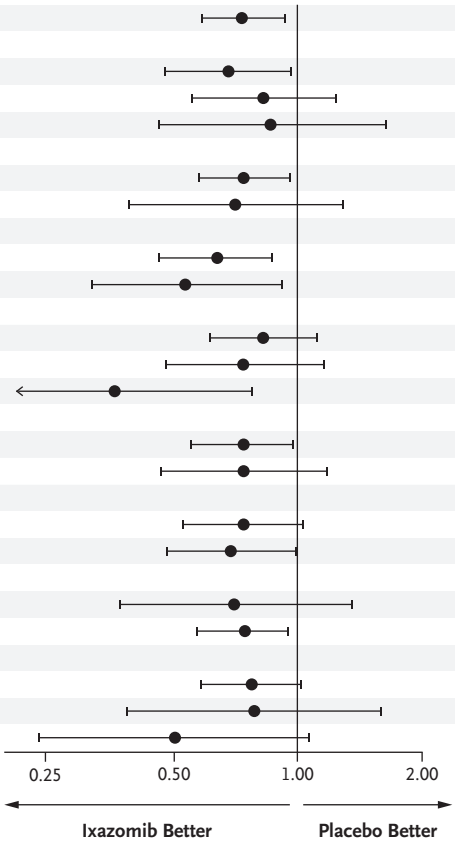


Table 2. Best Confirmed Responses to Study Regimen and Time to Progression in the Intention-to-Treat Population.*

Variable	Ixazomib Group (N=360)	Placebo Group (N=362)	P Value
Overall response rate			0.04
Patients with response — no. (%)	282 (78)	259 (72)	
Response rate, 95% CI — %	74–83	67–76	
≥Very good partial response			0.01
Patients with response — no. (%)	173 (48)	141 (39)	
Response rate, 95% CI — %	43–53	34–44	
Best response			
Complete response			0.02
Patients with response — no. (%)	42 (12)	24 (7)	
Response rate, 95% CI — %	9–15	4–10	
Stringent complete response†‡			—
Patients with response — no. (%)	9 (2)	3 (<1)	
Response rate, 95% CI — %	1–5	<1–2	
Partial response			—
Patients with response — no. (%)	240 (67)	235 (65)	
Response rate, 95% CI — %	62–72	60–70	
Very good partial response†			—
Patients with response — no. (%)	131 (36)	117 (32)	
Response rate, 95% CI — %	31–42	28–37	
Stable disease			—
Patients with response — no. (%)	40 (11)	59 (16)	
Response rate, 95% CI — %	8–15	13–21	
Median time to response — mo§	1.1	1.9	0.009
Median duration of response (≥partial response) — mo	20.5	15.0	—
Median time to disease progression — mo¶	21.4	15.7	0.007

* The best confirmed responses to the study regimen were assessed by an independent review committee in a blinded manner at the 15-month analysis. P values were calculated for protocol-defined end points.
† Stringent complete response is a subset of complete response, and very good partial response is a subset of partial response.
‡ Criteria for a stringent complete response include the criteria for a complete response plus a normal free light-chain ratio and absence of clonal plasma cells as assessed by immunohistochemical analysis or by two-color to four-color flow cytometry (details on the criteria for disease responses are provided in the Supplementary Appendix).
§ The median time to response in patients who had a response was 1.0 month in the ixazomib group and 1.1 month in the placebo group.
¶ For median time to disease progression, the hazard ratio in the ixazomib group was 0.71 (95% CI, 0.56 to 0.91). A Kaplan–Meier analysis of time to disease progression is provided in Figure S3 in the Supplementary Appendix.

ment for ≥25 cycles). The assigned study regimen was discontinued in 62% of the patients in the ixazomib group and in 63% of the patients in the placebo group (Table S3 in the Supplementary Appendix). The main reasons for discontinuation of the study regimen were disease progression, which was the reason for discontinuation in 34% of the patients in the ixazomib group and in 40% of the patients in the placebo group, and adverse events, which were the reason for discontinuation in 17% and 14% of the patients, respectively. The median relative dose intensity for lenalidomide and dexamethasone was similar in the two study groups; the median relative dose intensity for ixazomib was 97.4% and for placebo was 98.8% (Table S4 in the Supplementary Appendix).

The safety profiles at the 23-month analysis

Table 3. Overall Safety Profile at the 23-Month Analysis in the Safety Population.*

Variable	Ixazomib Group (N=361)	Placebo Group (N=359)
Median follow-up — mo†	23.3	22.9
Median treatment cycles (range) — no.	17 (1–34)	15 (1–34)
Any adverse event — no. (%)	355 (98)	357 (99)
Any grade ≥3 adverse event — no. (%)	267 (74)	247 (69)
Any serious adverse event — no. (%)	168 (47)	177 (49)
Adverse event resulting in dose reduction of any drug — no. (%)	203 (56)	181 (50)
Adverse event resulting in discontinuation of any agent — no. (%)‡	91 (25)	73 (20)
Adverse event resulting in discontinuation of the study regimen — no. (%)§	60 (17)	50 (14)
Death during the treatment period — no. (%)¶	15 (4)	23 (6)

* The safety population included all patients who received at least one dose of a study drug or placebo. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
† Among the 360 patients who were randomly assigned to the ixazomib group, 2 did not receive any study regimen, and at the first interim analysis, 2 of the 362 patients who were randomly assigned to the placebo group received limited dosing of ixazomib by mistake and were therefore conservatively included in the ixazomib group for analyses of exposure and safety. At the second interim analysis, a third patient from the placebo group who received limited dosing of ixazomib by mistake was included in the ixazomib group for analyses of exposure and safety.
‡ Discontinuation of any agent was defined as discontinuation of one or more of the three agents in the assigned study regimen.
§ Discontinuation of the study regimen was defined as discontinuation of the full study regimen and included discontinuation because of disease progression.
¶ Death during the treatment period was recorded through 30 days after receiving the last dose of the study drug or placebo.

are summarized in Table 3; the rates of serious adverse events, discontinuation of the study regimen because of adverse events, and death during the treatment period (recorded through 30 days after receiving the last dose of the study drug or placebo) were similar in the ixazomib group and the placebo group. The most common hematologic and nonhematologic adverse events are summarized in Table 4.

Thrombocytopenia, an overlapping adverse event that is seen with ixazomib and lenalidomide–dexamethasone,[14,17-19] was reported in 31% of the patients in the ixazomib group and in 16% of the patients in the placebo group; thrombocytopenia of grade 3 and of grade 4 occurred more frequently in the ixazomib group (12% and 7%, respectively) than in the placebo group (5% and 4%, respectively). Transient and cyclical decreases in platelet count were observed in both study groups. The rate of platelet transfusion was similar in the two groups (8% in the ixazomib group and 6% in the placebo group), as were the rates of serious adverse events of thrombocytopenia (2% in each group) and discontinuation of the study regimen because of thrombocytopenia (1% in each group).

Nonhematologic adverse events that have been observed to occur both with the use of ixazomib and with the use of lenalidomide–dexamethasone include gastrointestinal events and rash.[14,17-19] Gastrointestinal events were more common in the ixazomib group than in the placebo group, but they were observed primarily within the first 3 months after initiation of therapy and were low grade and manageable with supportive therapy; 22% of the patients in the ixazomib group and 19% in the placebo group received antidiarrheal agents, and 21% and 13%, respectively, received antiemetic drugs. The medical management of diarrhea included the use of antidiarrheal agents (primarily loperamide) and dose adjustment of lenalidomide or ixazomib. The incidence of rash (data were based on a standardized *Medical Dictionary for Regulatory Activities* [MedDRA] query) was 36% in the ixazomib group and 23% in the placebo group; the difference between groups was driven primarily by grade 1 and grade 2 events. The rash events occurred primarily in the first 3 months after initiation of the study regimen and were frequently self-limiting; 21% of the patients in the ixazomib group and 12% in the placebo group

reported that the events had resolved without intervention. The medical management of rash included the use of antihistamines (primarily cetirizine) or topical glucocorticoids and dose adjustment to manage symptoms.

Peripheral neuropathy is a known side effect of bortezomib, a first-in-class proteasome inhibitor.[20] The incidence of peripheral neuropathy was 27% in the ixazomib group (15% had grade 1 events and 10%, grade 2 events) and 22% in the placebo group (14% had grade 1 events and 6%, grade 2 events); 2% of patients in each study group had grade 3 events, and no grade 4 or 5 events or serious adverse events of peripheral neuropathy were reported. The incidence of peripheral neuropathy with pain was 4% in the ixazomib group and 3% in the placebo group.

No between-group differences were observed with respect to the rates of heart failure (4% in each study group) and arrhythmias (16% in the

Table 4. Common Adverse Events and Other Adverse Events of Clinical Importance in the Safety Population at the 23-Month Analysis.*

Adverse Event	Ixazomib Group (N=361)			Placebo Group (N=359)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Common hematologic adverse events of any cause†						
Neutropenia‡	118 (33)	64 (18)	17 (5)	111 (31)	63 (18)	22 (6)
Thrombocytopenia‡	112 (31)	43 (12)	26 (7)	57 (16)	19 (5)	13 (4)
Anemia	103 (29)	34 (9)	0	98 (27)	48 (13)	0
Common nonhematologic adverse events of any cause†						
Diarrhea	164 (45)	23 (6)	0	139 (39)	9 (3)	0
Rash§						
Standardized MedDRA query	131 (36)	18 (5)	0	82 (23)	6 (2)	0
High-level term	72 (20)	9 (2)	0	45 (13)	6 (2)	0
Constipation	126 (35)	1 (<1)	0	94 (26)	1 (<1)	0
Fatigue	106 (29)	13 (4)	0	102 (28)	10 (3)	0
Nausea	104 (29)	6 (2)	0	79 (22)	0	0
Peripheral edema	101 (28)	8 (2)	0	73 (20)	4 (1)	0
Peripheral neuropathy‡	97 (27)	9 (2)	0	78 (22)	6 (2)	0
Back pain	87 (24)	3 (<1)	0	62 (17)	9 (3)	0
Vomiting	84 (23)	4 (1)	0	42 (12)	2 (<1)	0
Upper respiratory tract infection	83 (23)	2 (<1)	0	70 (19)	3 (<1)	0
Nasopharyngitis	81 (22)	0	0	73 (20)	0	0
Insomnia	73 (20)	7 (2)	0	98 (27)	11 (3)	0
Muscle spasms	66 (18)	0	0	95 (26)	2 (<1)	0
Other adverse events of clinical interest						
Arrhythmias‡¶	56 (16)	17 (5)	3 (<1)	53 (15)	10 (3)	1 (<1)
Thromboembolism‡¶	29 (8)	9 (2)	2 (<1)	38 (11)	11 (3)	1 (<1)
Liver impairment‡	26 (7)	7 (2)	0	21 (6)	4 (1)	0
Hypertension						
Any	22 (6)	11 (3)	0	18 (5)	4 (1)	0
Hypertensive crisis	1 (<1)	0	0	0	0	0
Hypotension‡¶	22 (6)	4 (1)	0	21 (6)	1 (<1)	0

Table 4. (Continued.)

Adverse Event	Ixazomib Group (N=361)			Placebo Group (N=359)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Heart failure‡¶	16 (4)	7 (2)	2 (<1)	14 (4)	4 (1)	2 (<1)
Acute renal failure‡	31 (9)	7 (2)	2 (<1)	41 (11)	12 (3)	4 (1)
Myocardial infarction‡¶	5 (1)	0	3 (<1)	8 (2)	2 (<1)	2 (<1)
Encephalopathy‡	2 (<1)	2 (<1)	0	4 (1)	0	0
Interstitial lung disease‡	4 (1)	1 (<1)	1 (<1)	7 (2)	2 (<1)	0
New primary malignant tumor‡‖	17 (5)	NA	NA	14 (4)	NA	NA

* Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Among the 360 patients who were randomly assigned to the ixazomib group, 2 did not receive any study regimen, and at the second interim analysis, 3 of the 362 patients who were randomly assigned to the placebo group received limited dosing of ixazomib by mistake and were therefore conservatively included in the ixazomib group for analyses of exposure and safety. NA denotes not applicable.

† This adverse event was reported in at least 20% of the patients in either group.

‡ Data were based on a standardized *Medical Dictionary for Regulatory Activities* (MedDRA) query that incorporated pooled preferred terms or multiple preferred terms. "Thrombocytopenia" was coded according to the preferred terms of thrombocytopenia and decreased platelet count. "Neutropenia" was coded according to the preferred terms of neutropenia and decreased neutrophil count. "Peripheral neuropathy" represents the high-level term peripheral neuropathies not elsewhere classified, excluding neuritis; preferred terms included peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

§ Data for the "standardized MedDRA query" for rash were based on a standardized MedDRA query that pooled 27 preferred terms; data for the "high-level term" for rash were taken from the high-level term of rashes, eruptions, and exanthems not elsewhere classified, according to the data on rash reported in the U.S. prescribing information.

¶ In addition, grade 5 arrhythmia was reported in two patients in the ixazomib group and in three patients in the placebo group; grade 5 thromboembolism was reported in one patient in each group; grade 5 hypotension was reported in one patient in the ixazomib group; grade 5 heart failure was reported in one patient in the ixazomib group and in three patients in the placebo group; and grade 5 myocardial infarction was reported in one patient in the ixazomib group and in two patients in the placebo group.

‖ New primary malignant tumor was an event of special interest; the data shown include adverse-event data and data from the follow-up period of the study.

ixazomib group and 15% in the placebo group), as well as in the rates of hypertension (6% and 5%, respectively) and myocardial infarction (1% and 2%). At the 23-month analysis there was no significant difference in the rate of new primary malignant tumor (5% in the ixazomib group and 4% in the placebo group). At the 23-month analysis, EORTC QLQ-C30 and QLQ-MY20 scores indicated similar patient-reported quality of life in the ixazomib group and the placebo group over the course of the follow-up (Fig. S4 in the Supplementary Appendix).

DISCUSSION

This study showed that in patients with relapsed, refractory, or relapsed and refractory myeloma, treatment with oral ixazomib plus lenalidomide–dexamethasone was associated with significantly longer progression-free survival — by a median duration of approximately 6 months — than the progression-free survival observed with the use of placebo plus lenalidomide–dexamethasone. An overall survival benefit has not yet been shown. On the basis of the data from this study, the Food and Drug Administration approved the use of ixazomib in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy.[21]

The benefit of the ixazomib regimen with respect to progression-free survival was observed consistently in all key prespecified subgroups, including in the subgroups of patients with a poor prognosis, such as elderly patients, those who have received two or three prior therapies, those with advanced-stage disease, and those with high-risk cytogenetic abnormalities, for whom lenalidomide–dexamethasone has been shown to be a less effective treatment on the basis of emerging data.[22] Data on median progression-free survival suggest that an ixazomib regimen may improve the prognosis for patients with high-risk cytogenetic features, which have tradi-

tionally been associated with a poor prognosis, by lengthening the progression-free survival to a point that is similar to that among patients with standard-risk cytogenetic features.[23] In accordance with the protocol, the cutoff values for defining the presence of these cytogenetic abnormalities were established by the central diagnostic laboratory on the basis of the false positive rates (or technical cutoff values) of the fluorescence in situ hybridization probes we used. These cutoff values differed from those used in other studies[8,24,25]; standard clinical cutoff values remain an area of investigation.

The reported clinical benefit in our trial is consistent with findings from previous reports that have shown triplet regimens to be more efficacious than doublet regimens[4-8] — particularly two previous studies of lenalidomide–dexamethasone plus a third agent versus lenalidomide–dexamethasone in patients with early relapsed multiple myeloma.[8,24] However, the results with respect to response rates and median progression-free survival differ among the studies. In our study, the median progression-free survival was 20.6 months in the ixazomib group and 14.7 months in the placebo group; in the study by Stewart et al.,[8] the median progression-free survival was 26.3 months in the group that received carfilzomib plus lenalidomide–dexamethasone and 17.6 months in the group that received lenalidomide–dexamethasone alone, and in the study by Lonial et al.,[24] the median progression-free survival was 19.4 months in the group that received elotuzumab plus lenalidomide–dexamethasone and 14.9 months in the group that received lenalidomide–dexamethasone alone. However, cross-trial comparisons are confounded by differences in study designs, methods, and patient populations (e.g., differences in the inclusion of patients with renal impairment, primary refractory disease, and measurable levels of disease as measured by serum free light-chain assay only). Nevertheless, the relative benefit of these triplet regimens over lenalidomide–dexamethasone, as evaluated by hazard ratios, appeared to be consistent, with hazard ratios of 0.74 (current study), 0.69,[8] and 0.70.[24]

An increased focus on continuous therapy[8,9,17,26,27] has heightened the need for regimens that have acceptable side-effect profiles, that allow quality of life to be maintained, and that are easy to administer. The duration of therapy with the ixazomib regimen was notable; almost half the patients had received treatment for at least 18 cycles at the 23-month analysis. The rates of adherence to the ixazomib regimen and the placebo regimen appeared to be high and were similar in the two groups, a finding that is consistent with the observed side-effect profiles; these findings suggest that the all-oral ixazomib regimen was as simple and convenient for patients to follow as the placebo regimen. No adverse effect on quality of life was reported by the patients in the ixazomib group in this double-blind study. In considering this finding in the context of quality-of-life data from other studies, it should be noted that there is a tendency to overestimate the benefit on quality of life in open-label studies.[28] This finding should also be considered in the context of the limitations of existing instruments.[29,30]

The rates of serious adverse events, discontinuation of the study regimen because of adverse events, and death during the study period were similar in the two groups, and the only adverse event of grade 3 or higher for which there was at least a 5% difference between the ixazomib and placebo groups was thrombocytopenia, a known side effect of bortezomib and carfilzomib,[31,32] for which there were no apparent clinical sequelae. No cardiac, renal, or respiratory safety signals were associated with the use of ixazomib. The addition of ixazomib to a regimen of lenalidomide–dexamethasone resulted in a higher rate of peripheral neuropathy (27% in the ixazomib group and 22% in the placebo group), and 2% of patients in the ixazomib group had grade 3 events, as compared with 6% of patients who received subcutaneous bortezomib[33] and 3% of patients who received carfilzomib[8] in other studies.

In conclusion, the addition of ixazomib to a regimen of lenalidomide–dexamethasone led to significantly longer progression-free survival in patients with relapsed, refractory, or relapsed and refractory multiple myeloma, with limited additional toxic effects; in consideration of its adverse-event profile and efficacy, this all-oral regimen provides an additional therapeutic option for patients with relapsed, refractory, or relapsed and refractory multiple myeloma.[34]

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APPENDIX

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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This Supplementary Appendix has been provided by the authors to give the readers additional information about their work. It's content may not have undergone peer review.

Supplementary Appendix

Supplement to: Moreau P, Masszi T, Grzasko N, et al. Oral Ixazomib, Lenalidomide and Dexamethasone for Relapsed Multiple Myeloma

Contents

This Supplementary Appendix has been provided by the authors to give the readers additional information about their work. It's content may not have undergone peer review.

TOURMALINE-MM1 Collaborators

Patients were recruited from 180 centers across 26 countries in 4 continents. The following investigators (listed by country) enrolled patients into the study:

Australia: Andrew Spencer, Andrew Grigg (Simon He), Douglas Joshua; **Austria**: Richard Greil, Thomas Kühr, Werner Linkesch (Siegfried Sormann), Heinz Ludwig; **Belgium:** Valérie Robin, Henri Schots, Marie-Christiane Vekemans, Ka Lung Wu, Chantal Doyen; **Canada**: Kevin Song, Anthony Reiman, Chaim Shustik, Nizar Bahlis, Irwindeep Sandhu; **China**: Yan Xu, Jie Jin; **Czech Republic**: Luděk Pour, Vlastimil Ščudla, Evžen Gregora, Roman Hájek, Vladimir Maisnar; **Denmark**: Niels Andersen, Peter Gimsing, Henrik Gregersen; **France**: Thierry Facon, Philippe Moreau, Laurent Garderet, Anne-Marie Stoppa, Martine Escoffre-Barbe, Gerald Marit, Lotfi Benboubker, Guillaume Cartron, Michel Attal, Arnaud Jaccard, Bertrand Arnulf; **Germany**: Roland Fenk, Christian Langer, Hans-Jürgen Salwender, Burkhard Schmidt; **Hungary**: Árpád Illés, Tamás Masszi, János Jakucs; **Israel**: Dina Ben-Yehuda, Andrei Braester, Irit Avivi (Noam Benyamini), Izhar Hardan, Arnon Nagler, Olga Shvetz, Svetlana Trestman, Hila Magen-Nativ; **Italy**: Franco Aversa, Alberto Bosi, Michele Cavo, Felicetto Ferrara, Anna Marina Liberati, Antonio Palumbo, Paolo De Fabritis, Pier Paolo Fattori; **Japan**: Takaaki Chou, Hiroshi Handa, Tohru Izumi, Morio Matsumoto, Takuya Komeno, Kenshi Suzuki, Masahiro Kizaki, Chiaki Nakaseko, Nobuyuki Aotsuka, Koji Miyazaki, Shinichiro Okamoto, Hirokazu Nagai, Shinsuke Iida, Mitsuru Tsudo (Hitomi Kaneko), Kazutaka Sunami (Shiro Kubonishi), Toru Kiguchi, Shuji Ozaki, Naokuni Uike, Tadao Ishida; **Korea**: Jae Hoon Lee, Kihyun Kim; **The Netherlands**: Marie José Kersten, Sonja Zweegman, Edo Vellenga, Monique Christina Minnema; **New Zealand**: Peter Stephen Ganly, David Robert Simpson, Leanne Carol Berkahn, Kenneth Robert Romeril, Bartrum William

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Baker, Gillian Corbett, Sharon Jackson; **Poland**: Sebastian Grosicki, Norbert Grząsko, Andrzej Hellmann, Andrzej Pluta, Tadeusz Robak; **Portugal**: Catarina Geraldes, Luísa Viterbo; **Romania**: Gabriela Borșaru, Horia Bumbea, Emanuil Gheorghita; **Russia**: Alexander Shmidt, Julia Alexeeva, Alexander Korobkin, Elleonora Podoltseva, Alexander Pristupa, Olga Samoilova, Larisa Mendeleeva, Kamil Kaplanov; **Singapore**: Wee Joo Chng, Yeow Tee Goh; **Spain**: María Casanova Espinosa, María Asunción Echeveste, Jorge Gayoso, Miguel Granell, Maria Victoria Mateos, Laura Rosiñol; **Sweden**: Cecilie Blimark, Astrid Gruber, Markus Hansson, Hareth Nahi; **Turkey**: Meral Beksaç; **United Kingdom**: Supratik Basu, Matthew William Jenner, Gordon Marron, Catherine Williams, Hamdi Sati, Jane Tighe, James Cavet; **USA**: William Bensinger, Mehdi Hamadani (Abraham Kanate), Paul Richardson, Parameswaran Hari, Veena Charu, Shaji Kumar, Jan S Moreb, David Siegel, David H Irwin, Robert Stuart, Gustavo Fonseca, Tariq Nazir, Raul Oyola, (Robert Hermann), Rosalind Catchatourian, Martin Hyzinski, Hong Liu (Sarah Holstein)

Additional Methodology

Key Inclusion and Exclusion Criteria

Adult patients with relapsed and/or refractory multiple myeloma, measurable disease (defined by at least one of the following: serum protein electrophoresis [serum M-protein ≥1 g/dL], urine protein electrophoresis [urine M-protein ≥200 mg / 24 hours], serum free light chain assay [involved free light chain level ≥100 mg/dL, provided that serum free light chain ratio was abnormal]), and ECOG performance status 0–2 (a scale from 0 to 5 where 0 is asymptomatic and increasing numbers indicate increasing tumor-related disability) who had received 1–3 prior lines of therapy were enrolled. Patients refractory to prior lenalidomide or proteasome inhibitor-based therapy at any time were not eligible (refractoriness was defined as disease progression on treatment or within 60 days after last dose of therapy); patients refractory to thalidomide were eligible. Patients with primary refractory disease (defined as no response to prior therapy) were included.

Patients had adequate hematologic (absolute neutrophil count ≥1,000/mm^3, platelet count ≥75,000/mm^3) and hepatic (total bilirubin ≤1.5 x the upper limit of the normal range [ULN], alanine aminotransferase and aspartate aminotransferase ≤3 x ULN) function. Platelet transfusions to help patients meet eligibility criteria were not allowed within 3 days prior to randomization. Patients with mild-to-moderate renal function impairment (calculated creatinine clearance ≥30 mL/min) were eligible Patients with a low creatinine clearance of ≤60 mL/min (or ≤50 mL/min, according to local prescribing information) received a reduced lenalidomide dose of 10 mg once daily on Days 1 through 21 of each 28-day cycle. The lenalidomide dose could be escalated to 15 mg once daily after 2 cycles if the patient was not responding to

treatment and was tolerating the treatment. If renal function normalized (i.e., creatinine clearance >60 mL/min or >50 mL/min, according to local prescribing information) and the patient continued to tolerate this treatment, lenalidomide could be escalated to 25 mg once daily.

Patients were excluded if they had failed to recover (≤grade 1 toxicity) from the effects of prior chemotherapy (except for alopecia) regardless of the interval since last treatment, or had any of the following within 14 days before randomization: had undergone major surgery or received radiotherapy, had an infection requiring systemic antibiotic therapy or other serious infection, had received systemic treatment with strong CYP1A2 inhibitors (fluvoxamine, enoxacin, ciprofloxacin), strong CYP3A inhibitors (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole), or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or had used Ginkgo biloba or St John's wort. Patients with any central nervous system involvement were excluded. Patients with evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months were also ineligible. Those with any comorbid systemic illness or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into the study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens (e.g., peripheral neuropathy that was grade 1 with pain or grade 2 or higher of any cause), or who had been diagnosed or treated for another malignancy within 2 years before

randomization or previously diagnosed with another malignancy and had evidence of residual disease were also excluded.

Prophylactic Medications and Permitted Concomitant Treatments

Thromboprophylaxis according to the American Society of Clinical Oncology (ASCO) guidelines or institutional standard of care was required to prevent thromboembolic complications that may occur with lenalidomide-based regimens, e.g., aspirin (81–325 mg PO once daily) or low-molecular weight heparin (equivalent to enoxaparin 40 mg subcutaneous [SQ] per day) depending on patient risk factors. Prophylactic antiviral therapy was permitted as clinically indicated.

All necessary supportive care consistent with optimal patient care per local standards was available to patients. Use of myeloid growth factors (e.g., granulocyte colony stimulating factor, granulocyte macrophage-colony stimulating factor) and erythropoietin was allowed, with use of erythropoietin to be minimized as much as possible given potential risk of deep vein thrombosis with lenalidomide. Red blood cell and platelet transfusions were given as clinically indicated. Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor (5-HT3) antagonists were recommended for emesis if it occurred once treatment was initiated; prophylactic anti-emetics were also permitted at the physician's discretion. Topical, intravenous, or oral antihistamines or steroids were permitted to manage rash. Concomitant treatment with bisphosphonates was also permitted.

Systemic treatment with strong CYP1A2 inhibitors (fluvoxamine, enoxacin, and ciprofloxacin) or strong CYP3A inhibitors (clarithromycin, telithromycin, itraconazole,

voriconazole, ketoconazole, nefazodone, and posaconazole), or use of Ginkgo biloba or St John's wort was not permitted. Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital) was to be avoided. Radiation therapy or any antineoplastic treatment with activity against multiple myeloma, other than the study drugs, was not permitted.

Pre-Specified Secondary Endpoints

Key secondary endpoints were: overall survival (OS), measured as the time from the date of randomization to the date of death and OS in high-risk patients with del(17p). Additional secondary endpoints included: overall response rate (complete response [CR] + very good partial response [VGPR] + partial response [PR]); CR + VGPR rate; duration of response, measured as the time from the date of first documentation of response to the date of first documented progression; time to progression, measured as the time from randomization to the date of first documented progression; progression-free survival in patients with high-risk cytogenetic abnormalities; comparison of change in global health status between baseline and each post-baseline assessment, as measured by the global health scale, functioning, and symptoms of the EORTC QLQ-C30 and MY-20.

Laboratory Assessments including Cytogenetic Evaluations

Laboratory assessments for disease status were performed at a central laboratory, except bone marrow assessments for plasma cell percentage and absence of clonal plasma cells by immunohistochemistry or cytometry which were done locally. High-risk cytogenetic abnormalities (del(17p); t(4:14) and t(14:16)) were assessed by a Clinical Laboratory Improvement Amendment (CLIA)-certified central laboratory.

situ hybridization (FISH) testing using Kreatech probes. 97% of the cytogenetics results were from the central laboratory, the remaining 3% from local laboratories. Cut-off values for defining the presence of high-risk cytogenetic abnormalities were, per protocol, established by the central diagnostic laboratory based on the false-positive rates, or technical cut-offs, of the FISH probes used. These cut-offs were 5% positive cells for del(17p), 3% for t(4;14), and 3% for t(14;16).

Patient-Reported Quality of Life Assessments

EORTC-QLQ-C30 and MY-20 questionnaires were obtained every 2 cycles until disease progression. Patients were blinded to treatment assignment, which is particularly noteworthy given the tendency to overestimate quality of life benefit in open-label studies (Food and Drug Administration. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009). The EORTC QLQ-C30 questionnaire comprises five functional scales, three symptom scales, and a global health/quality of life scale. Scale scores range from 0 to 100, with higher scores representing a better health state for the functional scores and lower scores representing a better health state for the symptom scores. The EORTC QLQ-MY-20 consists of a 20-item questionnaire grouped into four scales: disease symptoms, treatment adverse effects, social support, and future perspective. Scale scores range from 0 to 100, with higher scores representing higher levels of symptomatology or problems.

Definition of Analysis Populations

A total of approximately 703 patients were planned to be randomized in a 1:1 ratio. The intent-to-treat population was defined as all patients who were randomized. Patients were analyzed according to the treatment they were randomized to receive, regardless of any errors in dosing. The safety population was defined as all patients who received at least 1 dose of any study drug. Patients were analyzed according to the treatment actually received, regardless of which treatment they were randomized to receive. Patients who received any dose of ixazomib were included in the ixazomib group and patients who did not receive any dose of ixazomib were included in the placebo group, regardless of their randomized treatment.

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Additional Results

Subsequent Analysis at a Median Follow-up of 23 Months

As the primary objective was met, and with overall survival not statistically significantly different at the first analysis, a subsequent analysis for overall survival was conducted with a data cut-off date of 12 July 2015; the median follow-up was 23 months. Based on 171 deaths (81 in the ixazomib group, 90 in the placebo group), which represents 35% of the pre-specified number of deaths required for final analysis of overall survival, median overall survival was not reached in either group and follow-up is ongoing. Due to the sequential testing of the primary and key secondary endpoints, formal statistical analysis of overall survival in del(17p) patients was not conducted in the absence of statistical significance for overall survival (at the time of the analysis, 9 of 36 patients in the ixazomib group and 15 of 33 patients in the placebo group who had del(17p) had died). At the same time point, a non-inferential analysis of progression-free survival was conducted with 372 progression-free survival events (177 events in the ixazomib group, 195 in the placebo group). The hazard ratio for progression-free survival was 0.82 (95% confidence interval: 0.67, 1.0) for the ixazomib regimen versus the placebo regimen, and the estimated median progression-free survival was 20 months with the ixazomib regimen and 15.9 months with the placebo regimen.

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Supplementary Figures

Figure S1. CONSORT diagram

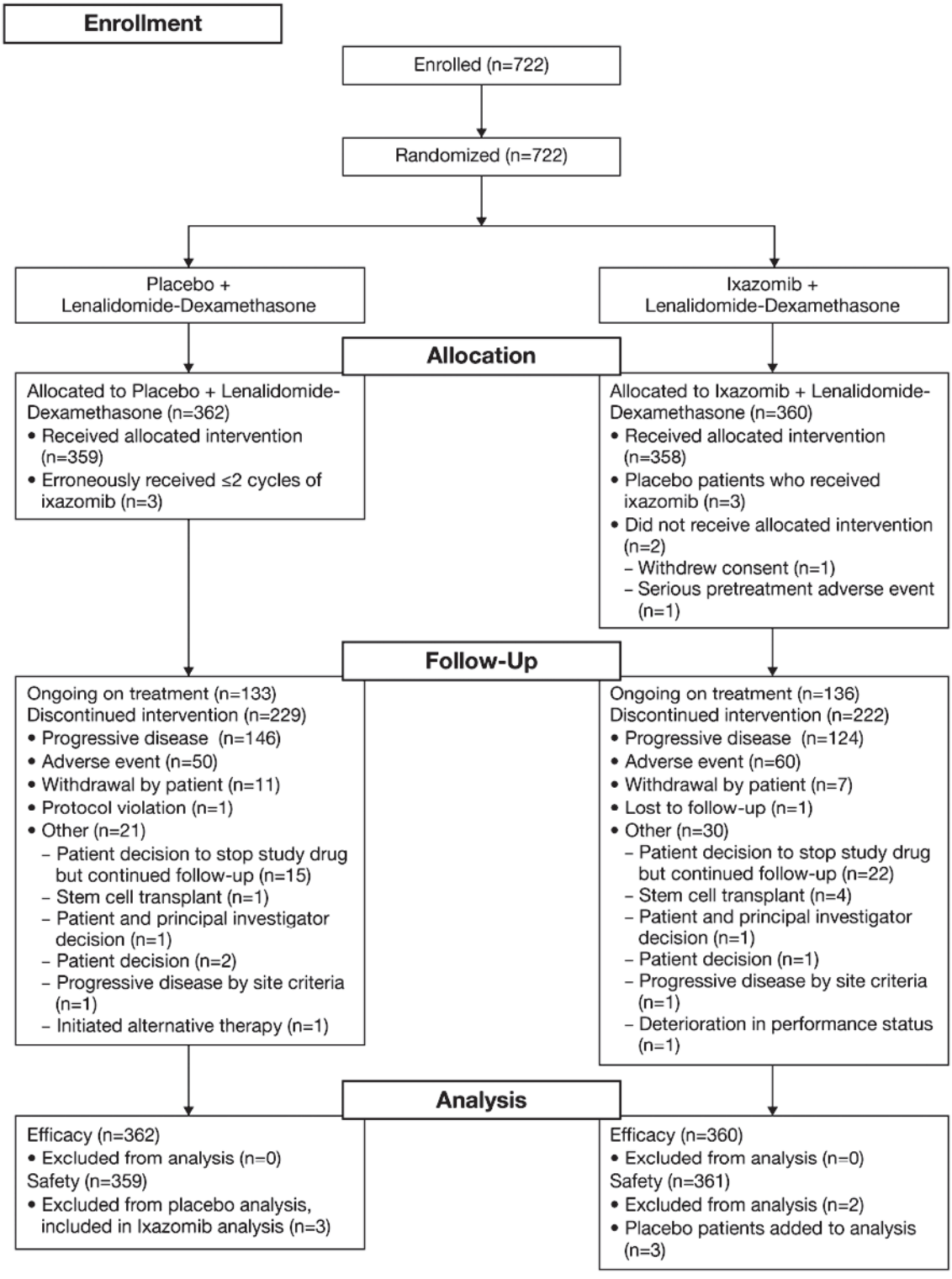

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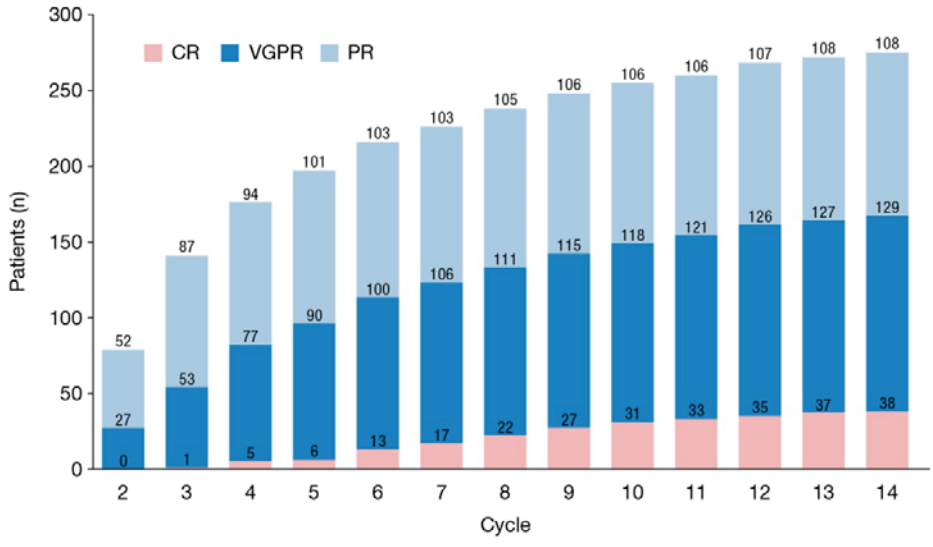
Figure S2. Cumulative best responses over time in the intent-to-treat population. A. Ixazomib group, B. Placebo group.

A



B

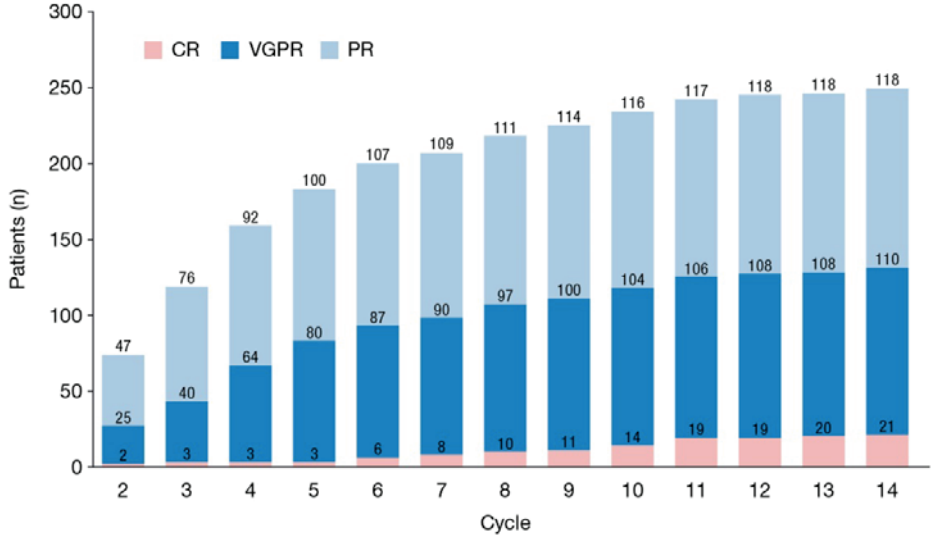


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Figure S3. Kaplan-Meier plot of time to progression in the ITT population. (Data from final statistical analysis for progression-free survival)

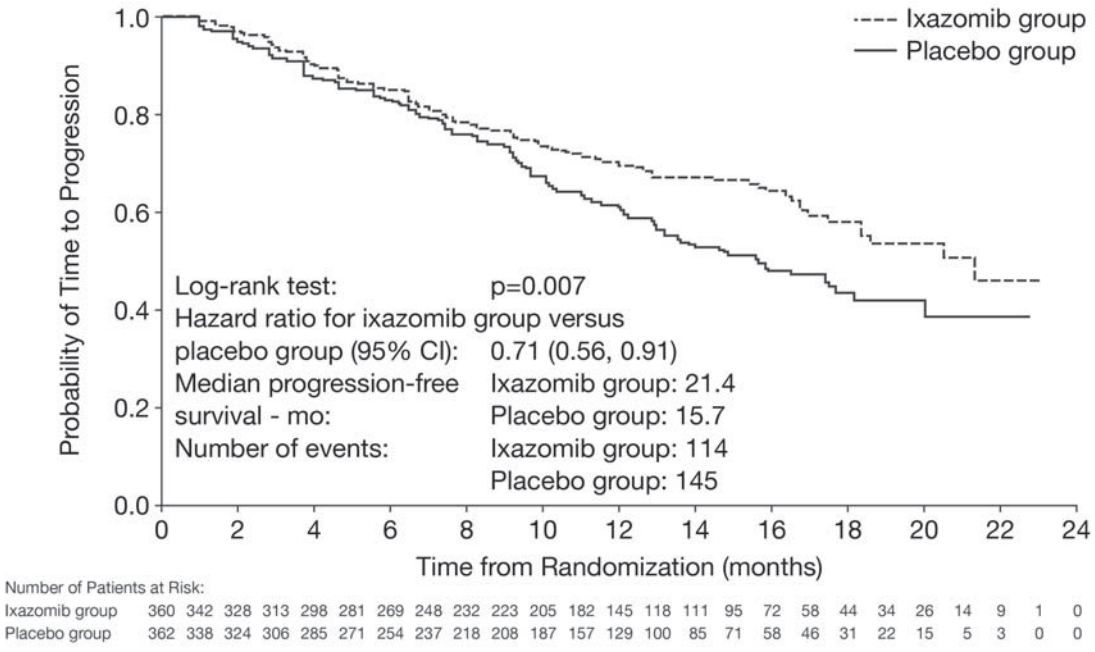

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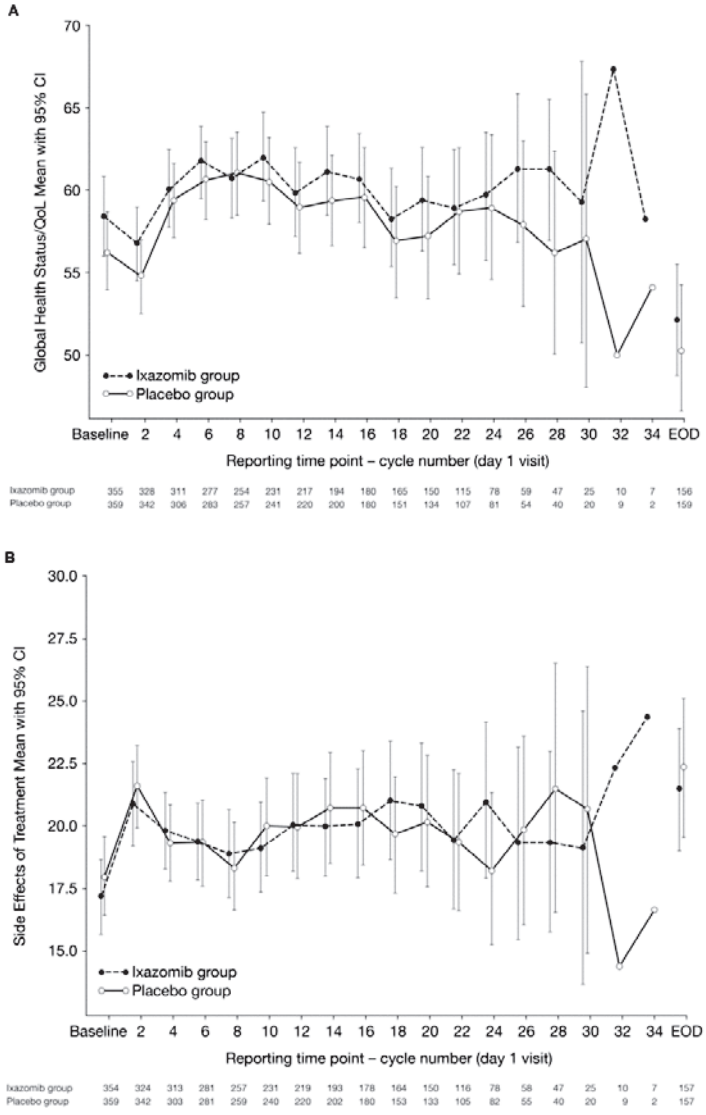
Figure S4. EORTC-QLQ-C30 mean global health status score (A) and MY-20 score for side effects of treatment (B) over time. (ITT population; median follow-up of ~23 months). Patient-reported quality of life was maintained with the addition of a third agent to lenalidomide-dexamethasone. Additionally, there was a trend for better physical functioning, emotional functioning, and fatigue scores for the ixazomib regimen compared with the placebo regimen. Symptoms of nausea and vomiting were similar in the two regimens and were stable across treatment; diarrhea appeared to worsen in the ixazomib regimen in later cycles (data not shown). (EOT, end of treatment.)



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Supplementary Tables

Table S1. International Staging System disease stage criteria

Stage	Criteria
Stage I	Serum β_2-microglobulin <3.5 mg/L Serum albumin ≥3.5 g/dL
Stage II	Neither Stage I nor Stage III: • Serum β2-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL; or, • Serum β2-microglobulin 3.5 to <5.5 mg/L irrespective of serum albumin level
Stage III	Serum β_2-microglobulin ≥5.5 mg/L

Greipp PR, et al. J Clin Oncol 2005;23:3412–3420.

Table S2. International Myeloma Working Group Uniform Response Criteria

Disease response	Criteria
Stringent complete response (sCR)	CR as defined below, plus: • Normal free light chain ratio, and • Absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry
Complete response (CR)	• Negative immunofixation of serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • <5% plasma cells in bone marrow Additional criterion in patients with measurable disease by serum free light chain levels only: • Normal free light chain ratio of 0.26 to 1.65
Very good partial response (VGPR)	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, or • ≥90% reduction in serum M-component plus urine M-component <100 mg/24 h Additional criterion in patients with measurable disease by serum free light chain levels only: • >90% decrease in difference between involved and uninvolved free light chain levels
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 h If serum and urine M-protein are not measurable: • Decrease of ≥50% in difference between involved and

	uninvolved free light chain levels If serum and urine M-protein and serum free light assay are not measurable: • ≥50% reduction in bone marrow plasma cells, provided baseline percentage was ≥30% In addition to the above criteria, if present at baseline: • ≥50% reduction in size of soft tissue plasmacytomas
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR, or PD
Progressive disease (PD) / relapse	Any one or more of the following: • Increase of 25% from lowest response value in any of: o Serum M-component (absolute increase ≥0.5 g/dL), and/or o Urine M-component (absolute increase ≥200 mg/24 h), and/or o Difference between involved and uninvolved free light chain levels (absolute increase >10 mg/dL) (only in patients without measurable serum and urine M-protein levels), and/or o Bone marrow plasma cell percentage (absolute percentage ≥10%) (only in patients without measurable serum and urine M-protein levels and without measurable disease by free light chain levels) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of

	existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All response categories and relapse require 2 consecutive assessments made at any time before the institution of any new therapy. If radiographic studies were performed, sCR, CR, VGPR, PR, and SD require no known evidence of progressive or new bone lesions. CR and VGPR require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of ≥1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL. For PD, definite increase of plasmacytoma defined as a 50% (at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion).

Rajkumar SV, et al. Blood 2011;117:4691–4695.

Durie BG, et al. Leukemia 2006;20:1467–73.

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Table S3. Reasons for treatment discontinuation (median follow-up of ~23 months)

Reason for treatment discontinuation	Ixazomib group (N=360)*	Placebo group (N=362)
Any — no. (%)	222 (62)	229 (63)
Progressive disease — no. (%)	124 (34)	146 (40)
Adverse event — no. (%)	60 (17)	50 (14)
Common adverse events resulting in treatment discontinuation — no. (%)†		
Diarrhea	6 (2)	1 (<1)
Peripheral neuropathy NEC	7 (2)	2 (<1)
Fatigue	4 (1)	2 (<1)
Thrombocytopenia	4 (1)	4 (1)
Cardiac failure	1 (<1)	3 (<1)
Neutropenia	3 (<1)	3 (<1)
Decreased platelet count	1 (<1)	3 (<1)
Withdrawal by patient — no. (%)	7 (2)	11 (3)
Protocol violation — no. (%)	0	1 (<1)
Lost to follow-up — no. (%)	1 (<1)	0
Other — no. (%)	30 (9)	21 (6)

*Two patients did not receive the allocated intervention (see Figure S1).

†Reported for at least 3 patients.

NEC, not elsewhere classified.

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Table S4. Relative dose intensity of study drugs (median follow-up of ~23 months)

Median relative dose intensity	Ixazomib group (N=361)	Placebo group (N=359)
Ixazomib — %	97.4	Not applicable
Placebo — %	Not applicable	98.8
Lenalidomide — %	93.8	96.6
Dexamethasone — %	92.2	94.9

Relative dose intensity determined as the percentage of the total amount of dose taken divided by the total amount of planned dose over treated cycles