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Final Overall Survival Analysis of the TOURMALINE-MM1 Phase III Trial of Ixazomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma

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abstract

PURPOSE The double-blind, placebo-controlled, phase III TOURMALINE-MM1 study demonstrated a statistically significant improvement in progression-free survival with ixazomib-lenalidomide-dexamethasone (ixazomib-Rd) versus placebo-Rd in patients with relapsed or refractory multiple myeloma. We report the final analyses for overall survival (OS).

PATIENTS AND METHODS Patients were randomly assigned to ixazomib-Rd (n = 360) or placebo-Rd (n = 362), stratified by number of prior therapies (1 *v* 2 or 3), previous proteasome inhibitor (PI) exposure (yes *v* no), and International Staging System disease stage (I or II *v* III). OS (intent-to-treat population) was a key secondary end point.

RESULTS With a median follow-up of 85 months, median OS with ixazomib-Rd versus placebo-Rd was 53.6 versus 51.6 months (hazard ratio, 0.939; $P = .495$). Lower hazard ratios, indicating larger magnitude of OS benefit with ixazomib-Rd versus placebo-Rd, were seen in predefined subgroups: refractory to any (0.794) or last (0.742) treatment line; age > 65-75 years (0.757); International Staging System stage III (0.779); 2/3 prior therapies (0.845); high-risk cytogenetics (0.870); and high-risk cytogenetics and/or 1q21 amplification (0.862). Following ixazomib-Rd versus placebo-Rd, 71.7% versus 69.9% of patients received ≥ 1 anticancer therapy, of whom 24.7% versus 33.9% received daratumumab and 71.8% versus 76.9% received PIs (next-line therapy: 47.5% *v* 55.8%). Rates of new primary malignancies were similar with ixazomib-Rd (10.3%) and placebo-Rd (11.9%). There were no new or additional safety concerns.

CONCLUSION Median OS values in both arms were the longest reported in phase III studies of Rd-based triplets in relapsed or refractory multiple myeloma at the time of this analysis; progression-free survival benefit with ixazomib-Rd versus placebo-Rd did not translate into a statistically significant OS benefit on intent-to-treat analysis. OS benefit was greater in subgroups with adverse prognostic factors. OS interpretation was confounded by imbalances in subsequent therapies received, especially PIs and daratumumab.

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ASSOCIATED CONTENT

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Data Supplement

Protocol

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

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INTRODUCTION

An increasing number of treatment options are becoming available for patients with relapsed or refractory (RR) multiple myeloma (MM).[1,2] Although these advances have led to marked improvements in overall survival (OS),[3] there remains a need for effective and tolerable therapies for patients who continue to relapse or are refractory to treatment, as well as for hard-to-treat subgroups such as the elderly and/or frail, and those with high disease burden or high-risk cytogenetics.[2]

Proteasome inhibitors (PIs) are an established backbone of therapy in newly diagnosed MM and RRMM.[1,4] Data in newly diagnosed MM have shown that progression-free survival (PFS) and OS may be prolonged with long-term versus shorter-duration PI-based therapy.[5,6] In RRMM, a retrospective observational study demonstrated that increasing duration of second-line therapy is associated with improved OS.[7] The same study found that treatment duration was shorter than time to next treatment (TTNT), suggesting that patients were not being treated to progression.[7]

CONTEXT

Key Objective

Does the significant improvement seen in progression-free survival with ixazomib-lenalidomide-dexamethasone (ixazomib-Rd) versus placebo-Rd in patients with relapsed or refractory multiple myeloma (RRMM) after 1-3 prior therapies translate into an overall survival (OS) benefit?

Knowledge Generated

The global, phase III TOURMALINE-MM1 trial did not meet the key secondary end point of demonstrating a significant OS improvement with ixazomib-Rd versus placebo-Rd in patients with RRMM, although median OS values (53.6 *v* 51.6 months) were the longest reported to date in phase III studies of Rd-based combinations in this setting, and greater OS benefit was observed in subgroups of patients with adverse prognostic factors. OS interpretation was confounded by imbalances between arms in receipt of subsequent proteasome inhibitors and daratumumab.

Relevance

While the evolving treatment landscape has increased OS for patients with RRMM, the availability of multiple active salvage therapies may limit the ability to demonstrate OS benefit in clinical trials in the early-relapse setting.

Other studies have shown that premature discontinuation of antimyeloma therapy may negatively affect outcomes, being associated with reduced duration of response[8] and poorer OS.[9] Notably, longer-term use of parenteral PIs, particularly in routine clinical practice, may be limited because of the associated treatment burden, including toxicities and the need for patients to visit the clinic or hospital for treatment.[10,11] There remains a need for all-oral regimens with manageable toxicity that can delay progression in patients with RRMM.

Ixazomib, the first oral PI,[12] is approved in combination with lenalidomide-dexamethasone (Rd) for the treatment of patients with MM who have received ≥ 1 prior therapy.[13] Approval was based on the results of the international, multicenter, randomized, double-blind, placebo-controlled, phase III TOURMALINE-MM1 study.[14] TOURMALINE-MM1 demonstrated a statistically significant improvement in PFS with ixazomib-Rd versus placebo-Rd in patients with RRMM (median PFS 20.6 *v* 14.7 months; hazard ratio [HR] 0.74; 95% CI, 0.59 to 0.94; $P = .01$), with limited additional toxicity.[14] Here, we report the final OS analysis from TOURMALINE-MM1.

PATIENTS AND METHODS

Patients

Full details of the TOURMALINE-MM1 trial have been reported previously.[14] Briefly, adult patients with relapsed, refractory, or relapsed and refractory MM after 1-3 prior therapies were eligible. Patients were enrolled at 147 sites in 26 countries between August 28, 2012, and May 27, 2014, and randomly assigned (1:1) to receive ixazomib-Rd or placebo-Rd, stratified according to number of prior therapies (1 *v* 2 or 3), previous PI exposure, and International Staging System disease stage (I or II *v* III) (Data Supplement, online only).[14] Cytogenetic abnormalities were assessed at screening by a central laboratory; high-risk cytogenetic abnormalities were defined as del(17p), t(4;14), and t(14;16), with the addition of 1q21 amplification for expanded high-risk cytogenetics.[14,15]

The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and appropriate regulatory requirements. The Protocol (online only) was approved by local ethics committees or institutional review boards. All patients provided written informed consent.

Treatment

Patients received ixazomib 4 mg or matching placebo on days 1, 8, and 15, plus lenalidomide 25 mg on days 1-21 and dexamethasone 40 mg on days 1, 8, 15, and 22, in 28-day cycles until disease progression or unacceptable toxicity (Data Supplement). Treatments received in subsequent lines of antimyeloma therapy were also recorded. Per Protocol, patients were to remain blinded throughout subsequent therapy; however, unblinding was permitted to properly treat an adverse event (AE) or safety issue and for the treating physician to choose subsequent therapy.

Outcomes and Assessments

The primary end point was PFS, as assessed by blinded independent review. Prespecified key secondary end points were OS from random assignment in the intent-to-treat (ITT) population and the subgroup of patients with del(17p). Other secondary end points included OS in patients with high-risk and expanded high-risk cytogenetics, safety, and comparison of changes in patient-reported quality of life (QoL) between baseline and each post-baseline assessment, assessed using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 and myeloma-specific module instruments. Exploratory ad-hoc analyses were conducted to assess TTNT in the ITT

population and OS according to subsequent therapies received.

Response was assessed each cycle until disease progression per International Myeloma Working Group 2011 criteria.[16] Patients were followed for subsequent therapy and survival every 12 weeks from disease progression. Patients were assessed for new primary malignancies from the start of study treatment until death or study termination. See the Data Supplement for additional details of assessments, including schedule of QoL instrument completion.

Statistical Analysis

The study used a closed sequential testing procedure to evaluate the primary (PFS) and key secondary (OS) end points (Data Supplement). Testing for OS was conducted using an alpha-spending function (O'Brien-Fleming) following demonstration of a significant PFS difference.[14] The significance threshold for testing OS in the ITT population at this final analysis was $\alpha = .0462$ per the Lan-DeMets alpha-spending function.[17] OS was evaluated using Kaplan-Meier methodology and compared between treatment arms using a stratified Cox model to estimate the HR and 95% CIs for the treatment effect and two-sided, stratified log-rank tests for *P* values. OS was evaluated within prespecified patient subgroups defined by the stratification factors and other patient and disease characteristics. To adjust for the potential effects of subsequent therapies after patients discontinued study treatment, two prespecified sensitivity analyses of OS were conducted (Data Supplement).[18,19]

For the exploratory ad-hoc analyses of TTNT and OS according to subsequent therapy, patients were analyzed according to treatment random assignment. Kaplan-Meier methodology was used, and comparisons between arms or groups were done using the statistical methodology described above. These analyses were not prespecified, and the study was not powered to test for statistical significance—all statistics are descriptive.

Data cutoff for this final analysis was on September 28, 2020.

RESULTS

Patients and Disposition

Patient demographics and disease characteristics for the 360 and 362 patients who were enrolled and randomly assigned to receive ixazomib-Rd or placebo-Rd, respectively (ITT population), have been reported previously.[14] Key baseline characteristics (Table 1) were well balanced between arms.

Patient disposition at this final analysis is presented in Figure 1. At data cutoff, 16 (4.4%) and 15 (4.1%) patients in the ixazomib-Rd and placebo-Rd arms, respectively, remained on study treatment. In the ITT population, 257 (71.4%) and 253 (69.9%) patients had received subsequent therapy; 236 (91.8%) in the ixazomib-Rd arm and 216 (85.4%) in the placebo-Rd arm remained blinded at the time of next-line therapy.

Final OS Analysis: ITT Population

At data cutoff, median follow-up for OS was 85.0 and 85.1 months in the ixazomib-Rd and placebo-Rd arms, respectively; 484 (67.0% of ITT population) patients had died, 240 (66.7%) and 244 (67.4%) in the ixazomib-Rd and placebo-Rd arms, respectively, and 113 (31.4%) and 116 (32.0%) were known to be alive at the date of last contact. Median OS was 53.6 months (95% CI, 49.25 to 62.95) in the ixazomib-Rd arm and 51.6 months (95% CI, 44.78 to 59.14) in the placebo-Rd arm; OS was not statistically significantly different between arms (HR, 0.939; 95% CI, 0.784 to 1.125; $P = .495$) (Fig 2A).

The two prespecified OS sensitivity analyses, using Marginal Structural Models and Inverse Probability of Censoring Weighted methods to adjust for the confounding effect of subsequent therapies, are summarized in the Data Supplement (Table A1). OS HRs were 0.68 and 0.70, respectively.

Final OS Analysis: Prespecified Subgroups

Ixazomib-Rd showed a treatment benefit in patients with del(17p) (HR 0.916; 95% CI, 0.516 to 1.626), high-risk cytogenetics (HR 0.870; 95% CI, 0.580 to 1.305), or expanded high-risk cytogenetics (HR 0.862; 95% CI, 0.660 to 1.124) (Figs 3A-3C) as evidenced by OS HRs < 1. In other prespecified patient subgroups (Fig 2B), ixazomib-Rd versus placebo-Rd showed a positive trend in patients who were refractory to any (HR 0.794; 95% CI, 0.538 to 1.172) or to their last (HR 0.742; 95% CI, 0.460 to 1.198) prior line of treatment; were refractory to thalidomide (HR 0.781; 95% CI, 0.461 to 1.322); were $>$ 65-75 years of age (HR 0.757; 95% CI, 0.559 to 1.027); had International Staging System stage III disease at study entry (HR 0.779; 95% CI, 0.487 to 1.247); had received 2-3 prior therapies (HR 0.845; 95% CI, 0.642 to 1.114); or had standard-risk cytogenetics (HR 0.875; 95% CI, 0.684 to 1.118).

Exploratory Ad Hoc Analysis: Subsequent Therapy

Median TTNT (ITT population) was 29.7 (95% CI, 24.51 to 32.85) and 26.9 (95% CI, 22.34 to 30.52) months in the ixazomib-Rd and placebo-Rd arms, respectively (HR 0.917; 95% CI, 0.769 to 1.094). Subsequent therapies received in any line and as next-line therapy are shown in Table 2. In the safety population, 259 (71.7%) and 251 (69.9%) patients in the ixazomib-Rd and placebo-Rd groups, respectively, received $\geq$ 1 subsequent therapy; subsequent therapies with $\geq$ 5% rate differences between groups included daratumumab (24.7% *v* 33.9%), bortezomib (56.8% *v* 61.8%), and carfilzomib (27.0% *v* 33.5%). There was an 8.3-percentage-point difference (47.5% *v* 55.8%) in the rates of patients receiving PI-based next-line therapy.

TABLE 1. Key Baseline Characteristics (intent-to-treat population)

Characteristic	Ixazomib-Rd (n = 360)	Placebo-Rd (n = 362)
Age		
Median, years (min-max)	66 (38-91)	66 (30-89)
> 65 years, No. (%)	192 (53.3)	186 (51.4)
Male, No. (%)	207 (57.5)	202 (55.8)
White race, No. (%)	312 (86.7)	303 (83.7)
ECOG PS, No. (%)		
0	180 (50.0)	170 (47.0)
1	156 (43.3)	164 (45.3)
2	18 (5.0)	24 (6.6)
Missing	6 (1.7)	4 (1.1)
ISS stage at study entry, No. (%)		
I	226 (62.8)	233 (64.4)
II	89 (24.7)	86 (23.8)
III	45 (12.5)	43 (11.9)
CrCL, median (min-max), mL/min/1.73 m^2	78.4 (20-233)	78.4 (27-233)
Cytogenetic risk, No. (%)[a]		
Standard risk	200 (55.6)	216 (59.7)
High risk	75 (20.8)	62 (17.1)
Not available	85 (23.6)	84 (23.2)
Expanded high risk[a]	155 (43.1)	154 (42.5)
No. of prior therapies, No. (%)[b]		
1	224 (62.2)	217 (59.9)
2	97 (26.9)	111 (30.7)
3	39 (10.8)	34 (9.4)
Prior stem-cell transplant, No. (%)	212 (58.9)	199 (55.0)
Prior PI therapy, No. (%)	249 (69.2)	253 (69.9)
Prior bortezomib	248 (68.9)	250 (69.1)
Prior IMiD therapy, No. (%)	193 (53.6)	204 (56.4)

Abbreviations: CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IMiD, immunomodulatory drug; ISS, International Staging System; PI, proteasome inhibitor; Rd, lenalidomide and dexamethasone.

[a]High-risk cytogenetic features were detected by FISH and defined as at least one of del(17p), t(4;14), and t(14;16). Standard-risk cytogenetics were defined as the absence of high-risk features in evaluable samples. Expanded high-risk cytogenetics included at least one of del(17p), t(4;14), t(14;16), and 1q21 amplification. Cutoff values for defining the presence of cytogenetic abnormalities were based on the false-positive rates (technical cutoffs) of the FISH probes that were used. Cutoff points were 5% positive cells for del(17p), and 3% positive cells for t(4;14), t(14;16), and 1q21 amplification.[14,15]

[b]Number of prior therapies was determined by the sponsor in a blinded medical review of data on prior therapy.

Exploratory Ad Hoc Analysis: OS According to Subsequent Therapy

Median OS from random assignment in the 510 patients who received subsequent therapy was 54.3 (95% CI, 49.84 to 62.95) versus 58.1 (95% CI, 50.30 to 60.94) months in the ixazomib-Rd and placebo-Rd arms, respectively (HR 0.985; 95% CI, 0.800 to 1.213); in the 212 patients who did not receive subsequent therapy, median OS was 50.4 (95% CI, 26.97 to 76.94) versus 31.5 (95% CI, 22.70 to 50.17) months (HR 0.877; 95% CI, 0.603 to 1.275). Among patients receiving daratumumab in any subsequent line, median OS was 78.9 versus 83.4 months in the ixazomib-Rd versus placebo-Rd arms (HR 1.15); in those not receiving subsequent daratumumab, median OS was 49.2 versus 35.5 months (HR 0.83) (Appendix Fig A1, online only). Timing of subsequent daratumumab is summarized in Appendix Figure A2 (online only).

Figure 4 shows OS in patients in the ixazomib-Rd versus placebo-Rd arms who received PI-based next-line therapy (median 52.0 *v* 56.9 months, HR 1.04) and in the

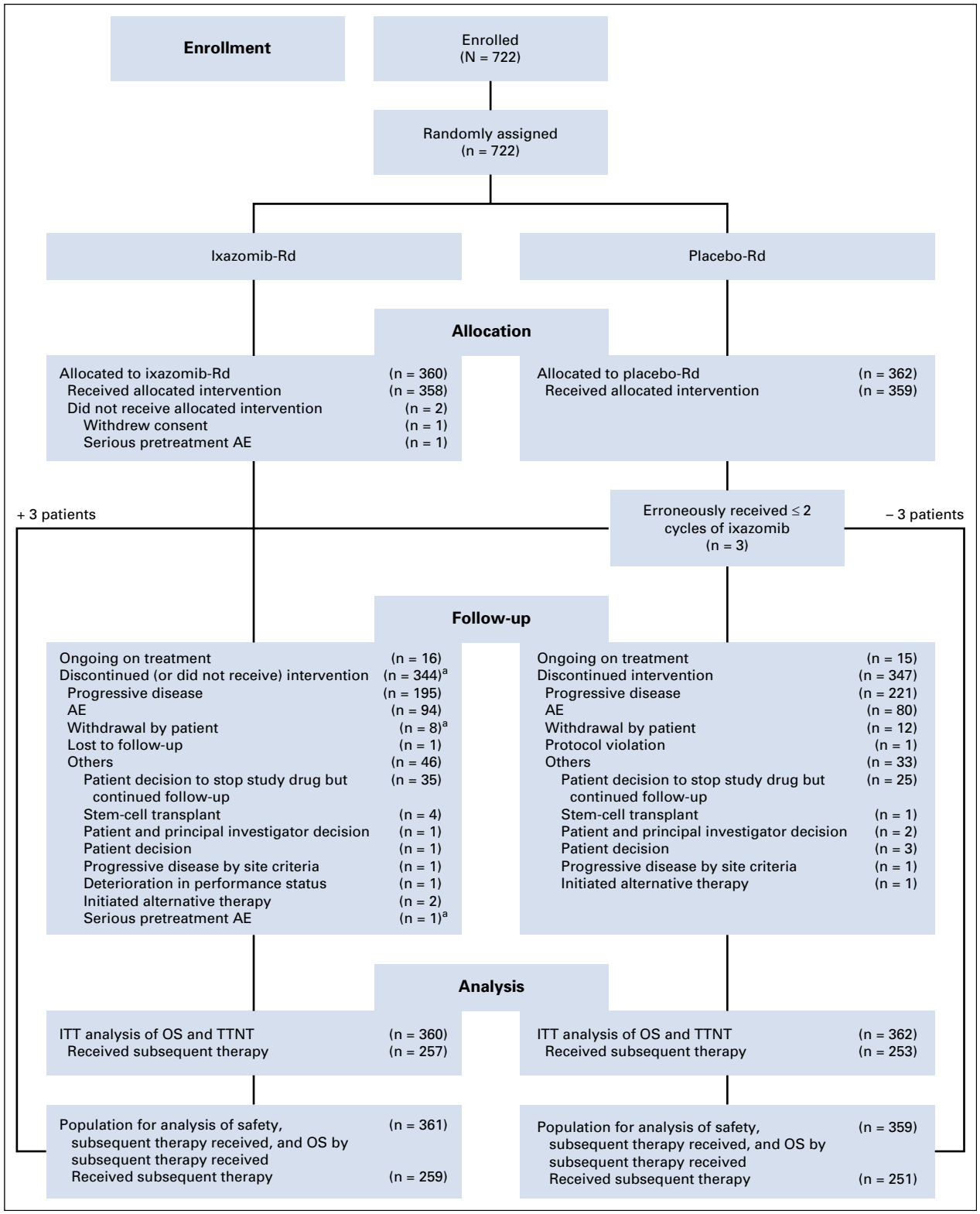
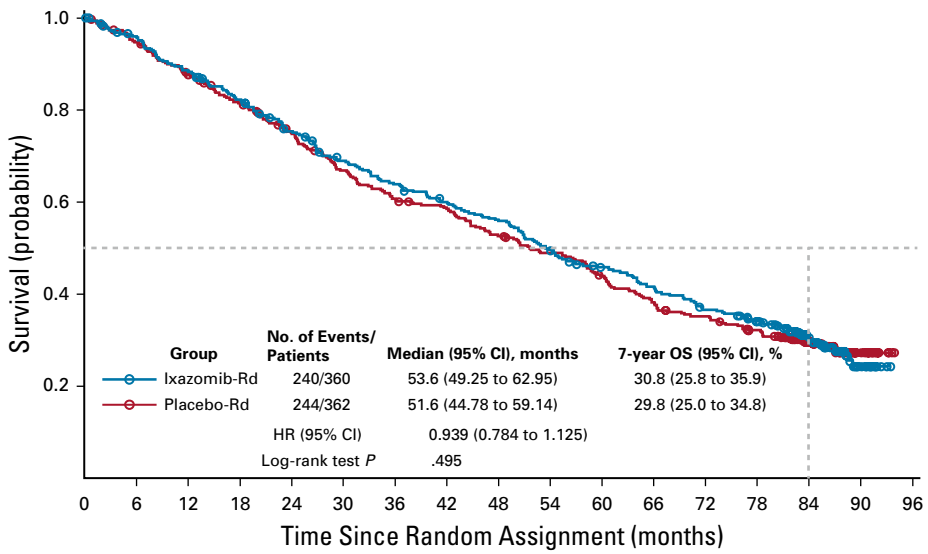


FIG 1. CONSORT diagram of patient disposition at the final analysis. [a]Two patients listed as having discontinued ixazomib-Rd did not receive the allocated intervention (withdrawal by patient, n = 1; serious pretreatment AE, n = 1); see also Allocation. AE, adverse event; ITT, intent-to-treat; OS, overall survival; Rd, lenalidomide and dexamethasone; TTNT, time to next treatment. Copyright © (2021) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[14]

A



No. at risk:

Ixazomib-Rd	360	340	314	288	259	233	216	201	188	165	149	135	118	104	59	15	0
Placebo-Rd	362	340	315	286	260	230	209	199	179	165	147	128	116	100	60	17	0

B

Variable	Subgroup	Events, n/N Ixazomib-Rd	Events, n/N Placebo-Rd	Median Survival (months) Ixazomib-Rd	Median Survival (months) Placebo-Rd	HR	95% CI
All patients	All (N = 722)	240/360	244/362	53.6	51.6	0.939	0.784 to 1.125
Age, years	≤ 65 (n = 344)	106/168	111/176	54.9	60.4	1.079	0.822 to 1.416
	> 65-75 (n = 270)	93/145	85/125	56.7	46.9	0.757	0.559 to 1.027
	> 75 (n = 108)	41/47	48/61	36.9	37.9	1.068	0.670 to 1.704
ISS stage	I or II (n = 632)	202/314	207/318	59.5	57.7	0.970	0.798 to 1.178
	III (n = 90)	38/46	37/44	27.6	23.6	0.779	0.487 to 1.247
Cytogenetic risk	High risk (n = 137)	57/75	48/62	46.9	30.9	0.870	0.580 to 1.305
	Standard (n = 416)	123/200	140/216	56.9	55.8	0.875	0.684 to 1.118
	Expanded high risk (n = 309)	112/155	117/154	44.6	33.4	0.862	0.660 to 1.124
Prior therapies (IVRS)	1 (n = 425)	136/212	140/213	54.3	58.3	1.016	0.801 to 1.287
	2 or 3 (n = 297)	104/148	104/149	53.0	43.0	0.845	0.642 to 1.114
Prior therapies (EDC)	1 (n = 437)	141/223	143/214	54.3	58.3	0.976	0.773 to 1.233
	2 (n = 211)	71/98	78/113	52.4	42.0	0.926	0.669 to 1.282
	≥ 3 (n = 74)	28/39	23/35	54.3	47.1	0.883	0.498 to 1.564
PI	Exposed (n = 503)	173/250	169/253	53.0	55.8	0.994	0.803 to 1.231
	Naive (n = 219)	67/110	75/109	55.4	50.4	0.817	0.585 to 1.142
Prior IMiD therapy	Exposed (n = 397)	130/193	138/204	52.4	50.5	0.918	0.717 to 1.176
	Naive (n = 325)	110/167	106/158	54.3	56.6	0.945	0.721 to 1.240
Relapsed or refractory	Relapsed (n = 557)	186/278	188/279	53.9	57.7	1.000	0.815 to 1.227
	Refractory (n = 80)	21/40	30/40	51.0	32.0	0.680	0.375 to 1.236
	Relapsed and refractory (n = 85)	33/42	26/43	54.3	44.2	0.920	0.531 to 1.593
Refractory to any prior line	Yes (n = 165)	54/82	56/83	52.2	35.5	0.794	0.538 to 1.172
	No (n = 557)	186/278	188/279	53.9	57.7	1.000	0.815 to 1.227
Refractory to last prior line	Yes (n = 117)	36/59	40/58	49.0	35.5	0.742	0.460 to 1.198
	No (n = 605)	204/301	204/304	54.3	56.9	1.003	0.824 to 1.221
Thalidomide refractory	Yes (n = 89)	26/39	36/50	42.2	31.7	0.781	0.461 to 1.322
	No (n = 633)	214/321	208/312	54.3	57.7	0.975	0.804 to 1.183

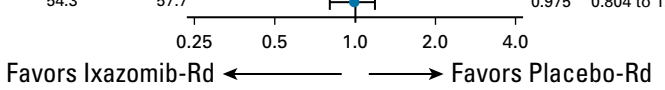


FIG 2. OS in (A) the ITT population and (B) by patient subgroup (ITT population). EDC, electronic data capture (electronic case report form); HR, hazard ratio; IMiD, immunomodulatory drug; ISS, International Staging System; ITT, intent-to-treat; IVRS, interactive voice response system (random assignment stratification); OS, overall survival; PI, proteasome inhibitor; Rd, lenalidomide and dexamethasone.

remaining patients in the ITT population (median 54.6 *v* 48.8 months, HR 0.90). Of the patients who received next-line therapy, 21/257 (8.2%) and 37/253 (14.6%) patients in the ixazomib-Rd and placebo-Rd arms, respectively, were unblinded before next-line treatment selection. Among unblinded patients treated with ixazomib-Rd versus placebo-Rd, next-line therapy was PI-based in 5 (23.8%) versus 30 (81.1%) patients, and non–PI-based in 16 (76.2%) versus 7 (18.9%) patients. Among patients who remained blinded, 117/236 (49.6%) versus 111/216 (51.4%) received PI-based next-line therapy.

Treatment Exposure, Safety, and QoL

Patients received a median of 18 and 16 cycles of ixazomib-Rd and placebo-Rd, respectively (Table 3). The overall safety profiles and rates of grade ≥ 3 treatment-emergent AEs (TEAEs) and TEAEs of clinical importance indicated no new or additional safety concerns during the 7-year follow-up period (Table 3, Data Supplement Table A2) beyond those reported previously.[14,20] Thrombocytopenia (pooled term; 21.3% *v* 10.3%) and diarrhea (10.0% *v* 3.1%) were the only two grade ≥ 3 TEAEs occurring with a ≥ 5% higher incidence with ixazomib-Rd versus placebo-Rd (Table 3). The rate of new primary malignancies was 10.3% and 11.9% in the ixazomib-Rd and placebo-Rd groups, respectively (Table 3).

There were no apparent differences in QoL measures between arms. Approximately half the patients in each arm reported increases of ≥ 10 points (minimally important difference) in the EORTC Quality of Life Questionnaire Core-30 global health status or QoL domain over the course of treatment (ixazomib-Rd, 49.2% *v* placebo-Rd 52.2%); similar rates of ≥ 10-point improvements between arms were seen for the EORTC Quality of Life Questionnaire, myeloma-specific module domains of Disease Symptoms (65.6% *v* 60.8%) and Side Effects of Treatment (28.9% *v* 30.4%) (Appendix Fig A3, online only).

DISCUSSION

This final analysis of the TOURMALINE-MM1 study, after a median follow-up of > 7 years, reports the longest median OS data seen to date in phase III studies of Rd-based combinations in RRMM,[21-24] with median OS approaching 4.5 years in both arms. Although the slight trend (OS HR 0.939) in favor of ixazomib-Rd in the ITT population was not statistically significant, greater magnitudes of OS benefit (lower HRs) were observed in predefined patient subgroups with adverse-risk characteristics, including more heavily pretreated patients, patients refractory to prior treatment, patients with stage III MM, and those with high-risk or expanded high-risk cytogenetics.

OS has improved in MM associated with the introduction of multiple, active novel agents over the past decade[25]; improvements in median OS in clinical trials of Rd-based regimens for RRMM correspond with the increasing availability of new treatment options at the time these studies were conducted.[21-24] Consequently, translation of PFS benefit into OS benefit and interpretation of OS has become increasingly confounded by more extensive use of subsequent therapies with optimized sequencing.[2] In TOURMALINE-MM1, approximately 70% of patients received subsequent therapy, and imbalances were seen between arms. Patients progressed earlier on placebo-Rd, received a higher number of subsequent therapies than those on the ixazomib-Rd arm (median 3 *v* 2), and received subsequent PIs, daratumumab, and other treatments more frequently. Together, these imbalances may have contributed to the significant PFS benefit seen with ixazomib-Rd at the previous interim analysis[14] not translating to a significant OS benefit at this final analysis. The findings of our two protocol-specified sensitivity analyses for OS support this hypothesis; these analyses used statistical methodologies to adjust for the impact of subsequent therapies on OS.[18,19] Both methodologies resulted in HRs (0.68 and 0.70) supportive of a more substantial benefit with ixazomib-Rd versus placebo-Rd than demonstrated in the unadjusted primary OS analysis (0.939). Additionally, our analysis of OS in patients not receiving subsequent therapy also favored ixazomib-Rd more strongly (HR 0.877).

The double-blind nature of TOURMALINE-MM1 also contributed to confounding interpretation of OS. The majority of patients in each arm remained blinded at the time of next-line therapy, and equal proportions of blinded patients received PI or non-PI treatment as next-line therapy in each arm. PI sensitivity was required at study entry,[14] and approximately 70% of patients in each arm had received prior PI therapy. However, patients progressing on placebo-Rd had had a PI-free interval or may still have been PI-naive (30% of the placebo-Rd ITT population had not received prior PI therapy), and thus were more likely to remain PI-sensitive and therefore benefit from PI-based next-line therapy—representing a de facto crossover. Conversely, for patients progressing on ixazomib-Rd, subsequent PI-based therapy was potentially their third exposure to a PI; additionally, they were likely to have become PI-refractory. Thus, PI-based next-line therapy would potentially be less effective, as well as being inconsistent with treatment sequencing guidelines, which state that for patients in second

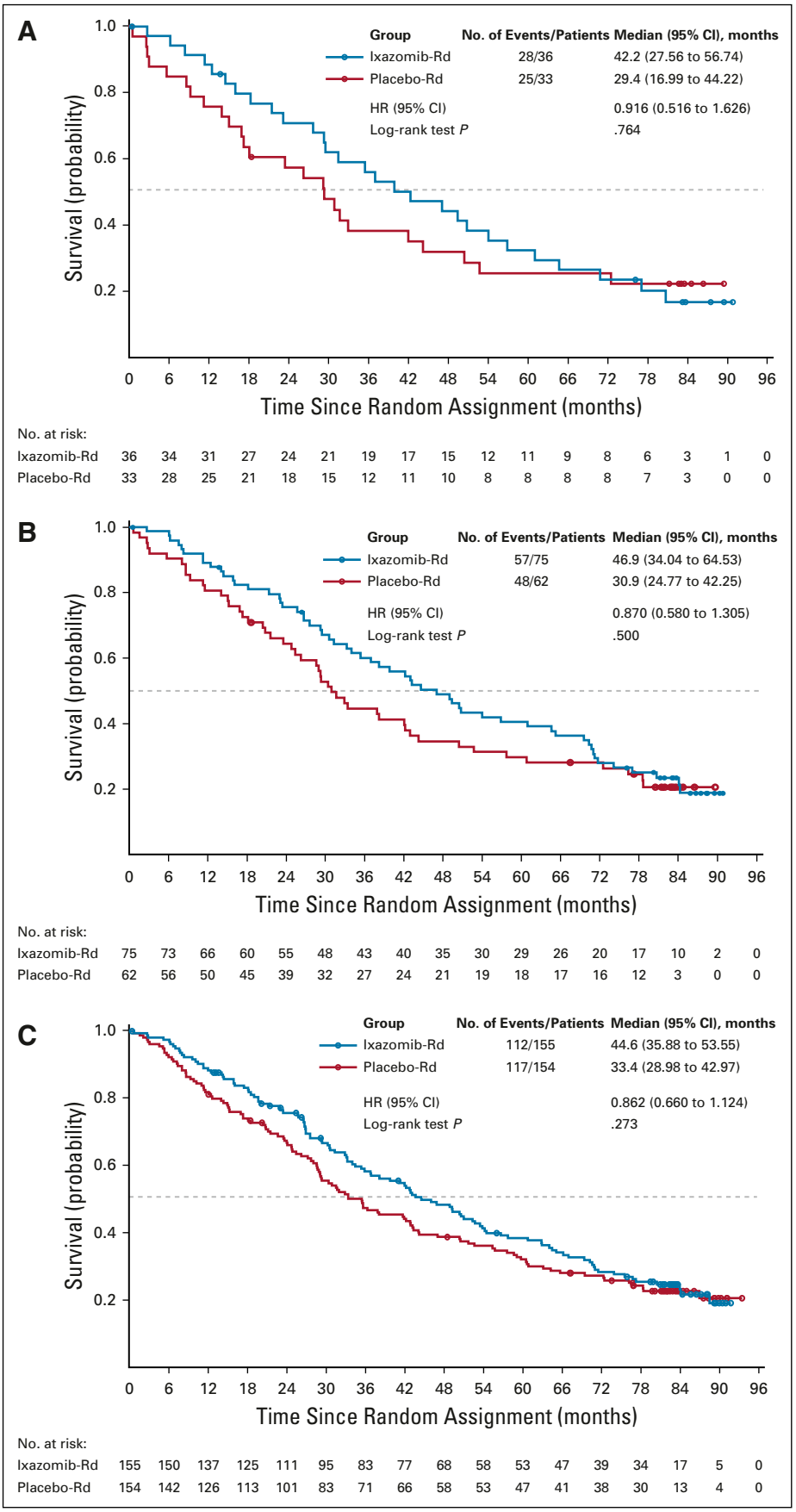


FIG 3. Overall survival in patients with (A) del(17p), (B) high-risk cytogenetics, and (C) expanded high-risk cytogenetics (intent-to-treat population). High-risk cytogenetic features were detected by FISH and defined as at least one of del(17p), t(4;14), and t(14;16). Standard-risk cytogenetics were defined as the absence of high-risk features in evaluable samples. Expanded high-risk cytogenetics included at least one of del(17p), t(4;14), t(14;16), and 1q21 amplification. Cutoff values for defining the presence of cytogenetic abnormalities were based on the false-positive rates (technical cutoffs) of the FISH probes that were used. Cutoff points were 5% positive cells for del(17p), and 3% positive cells for t(4;14), t(14;16), and 1q21 amplification.[14,15] FISH, fluorescence in situ hybridization; HR, hazard ratio; Rd, lenalidomide and dexamethasone.

or higher relapse, preferred treatment choices include any first relapse options that have *not* already been tried.[2] In this context, the extensive use of PIs as next-line therapy (47.5% ixazomib-Rd, 55.8% placebo-Rd) may have specifically affected the OS findings. Predictably, unblinding strongly influenced next-line therapy decisions; 76.2% of unblinded ixazomib-Rd patients received a non–PI-based next-line therapy, whereas 81.1% of unblinded placebo-Rd patients received PI-containing next-line therapy.

The imbalance in rates of subsequent daratumumab treatment (24.7% *v* 33.9% in any subsequent line in the ixazomib-Rd versus placebo-Rd groups) is another notable confounding factor. Daratumumab became clinically available for the treatment of RRMM shortly after

TABLE 2. Subsequent Therapies Received in Any Line and as Next Line of Treatment (safety population[a])

	Ixazomib-Rd (n = 361)		Placebo-Rd (n = 359)	
Patients	**Any Line**	**Next Line**	**Any Line**	**Next Line**
Any subsequent therapy, No. (%)	259 (71.7)	259 (71.7)	251 (69.9)	251 (69.9)
Median No. of lines of subsequent therapy received, No. (min-max)	2 (1-9)	NA	3 (1-12)	NA
	n = 259		**n = 251**	
Corticosteroid, No. (%)	235 (90.7)	213 (82.2)	240 (95.6)	220 (87.6)
Dexamethasone	226 (87.3)	192 (74.1)	228 (90.8)	195 (77.7)
Prednisone	27 (10.4)	14 (5.4)	34 (13.5)	16 (6.4)
Immunomodulatory drug, No. (%)	200 (77.2)	109 (42.1)	179 (71.3)	104 (41.4)
Pomalidomide	133 (51.4)	53 (20.5)	131 (52.2)	50 (19.9)
Lenalidomide	75 (29.0)	34 (13.1)	70 (27.9)	39 (15.5)
Thalidomide	47 (18.1)	23 (8.9)	49 (19.5)	15 (6.0)
PI, No. (%)	186 (71.8)	123 (47.5)	193 (76.9)	140 (55.8)
Bortezomib	147 (56.8)	106 (40.9)	155 (61.8)	110 (43.8)
Carfilzomib	70 (27.0)	16 (6.2)	84 (33.5)	22 (8.8)
Alkylating agent, No. (%)	159 (61.4)	94 (36.3)	172 (68.5)	98 (39.0)
Cyclophosphamide	128 (49.4)	67 (25.9)	125 (49.8)	63 (25.1)
Bendamustine	40 (15.4)	14 (5.4)	47 (18.7)	15 (6.0)
Melphalan	35 (13.5)	15 (5.8)	49 (19.5)	20 (8.0)
Monoclonal antibody, No. (%)				
Daratumumab	64 (24.7)	16 (6.2)	85 (33.9)	13 (5.2)
Anthracycline, No. (%)	29 (11.2)	17 (6.6)	34 (13.5)	13 (5.2)
Doxorubicin	24 (9.3)	13 (5.0)	30 (12.0)	12 (4.8)
Stem-cell transplant, No. (%)	13 (5.0)	5 (1.9)	28 (11.2)	5 (2.0)
Autologous	10 (3.9)	3 (1.2)	24 (9.6)	4 (1.6)
Allogenic	3 (1.2)	2 (0.8)	4 (1.6)	1 (0.4)

NOTE. Subsequent treatments with ≥ 10% incidence (any line) and stem-cell transplant are shown.

Abbreviations: NA, not applicable; PI, proteasome inhibitor; Rd, lenalidomide and dexamethasone.

[a]Of the intent-to-treat population, two patients in the ixazomib-Rd arm did not receive treatment and three patients in the placebo-Rd arm erroneously received ≤ 2 doses of ixazomib and were included in the ixazomib-Rd group in the safety population.

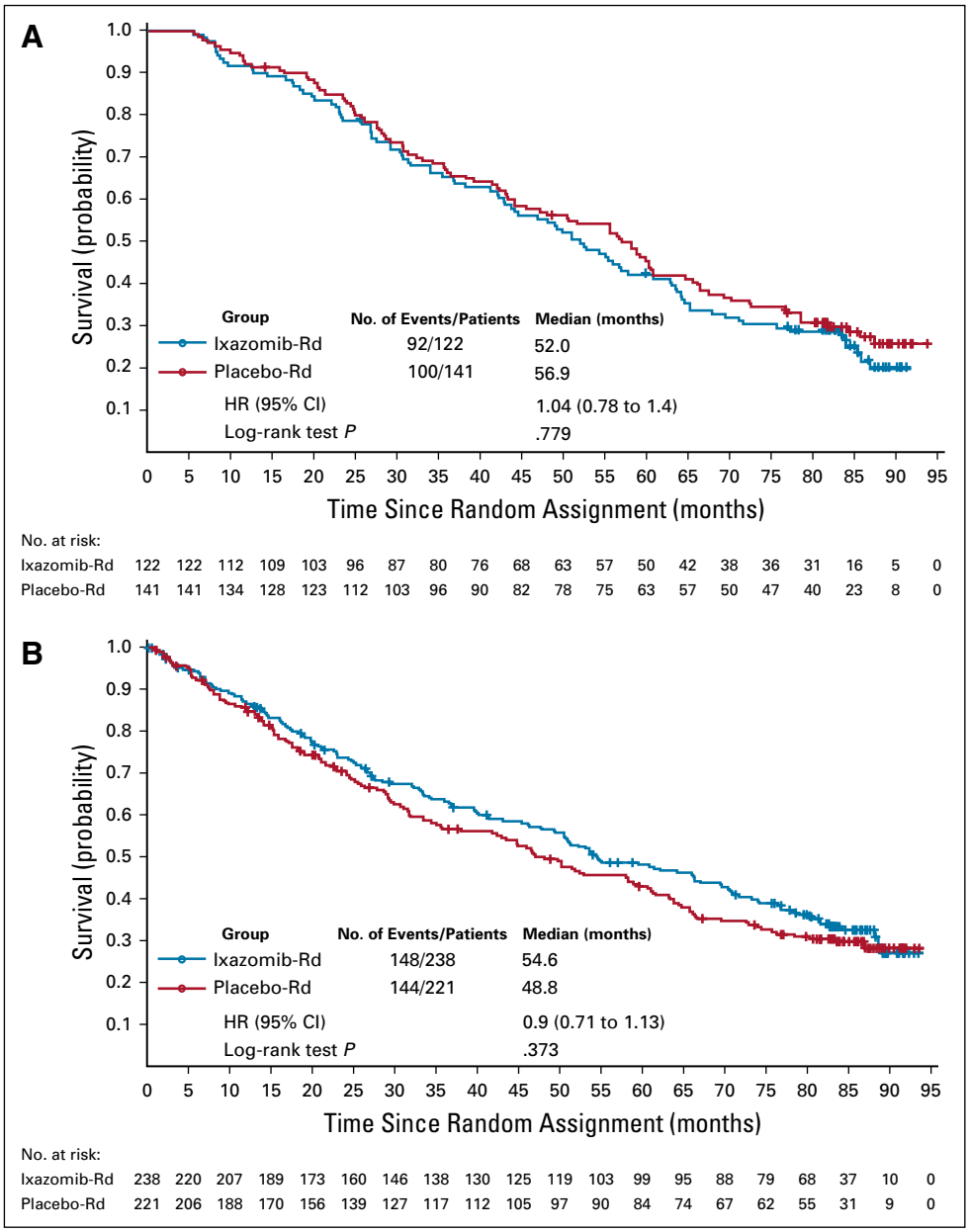


FIG 4. Overall survival in patients (A) receiving a PI as next-line therapy and (B) not receiving a PI as next-line therapy (intent-to-treat population). HR, hazard ratio; PI, proteasome inhibitor; Rd, lenalidomide and dexamethasone.

completion of enrollment to TOURMALINE-MM1.[26,27] Among TOURMALINE-MM1 patients receiving subsequent daratumumab, there was an OS trend in favor of placebo-Rd (HR 1.15). We hypothesize that this could be because of placebo-Rd patients receiving daratumumab earlier and in larger numbers (Appendix Fig A2) than ixazomib-Rd patients, with some later-progressing ixazomib-Rd patients yet to receive subsequent daratumumab. In patients who did not receive subsequent daratumumab therapy, there was a trend in favor of ixazomib-Rd (HR 0.83). The China Continuation study, a separate regional expansion of TOURMALINE-MM1, demonstrated significantly improved PFS (HR 0.598) and OS (HR 0.419) with ixazomib-Rd versus placebo-Rd.[28] However, only approximately 50% of patients received subsequent therapy, and patients in China did not have access to the broader range of approved or investigational agents and regimens available to patients in North America and Europe.[28] Thus, PFS benefit translated into OS benefit in these patients with limited subsequent therapy options.

TABLE 3. Summary of Treatment Exposure and Safety (safety population[a]) and New Primary Malignancies (intent-to-treat population)

Exposure/Safety Parameter	Ixazomib-Rd	Placebo-Rd
No. of treated cycles	n = 361	n = 359
Median (min-max)	18 (1-99)	16 (1-100)
Summary of safety profile	n = 361	n = 359
Any AE	359 (99.4)	357 (99.4)
Drug-related AE	339 (93.9)	333 (92.8)
Grade ≥ 3 AE	289 (80.1)	266 (74.1)
Drug-related grade ≥ 3 AE	240 (66.5)	203 (56.5)
Serious AE	205 (56.8)	201 (56.0)
Drug-related serious AE	115 (31.9)	108 (30.1)
AE resulting in study drug dose reduction	218 (60.4)	195 (54.3)
AE resulting in study drug dose modification	290 (80.3)	265 (73.8)
AE resulting in any study drug discontinuation	140 (38.8)	116 (32.3)
AE resulting in all study drug discontinuation	91 (25.2)	78 (21.7)
On-study deaths	21 (5.8)	30 (8.4)
Grade ≥ 3 AEs occurring in ≥ 5% of all patients	n = 361	n = 359
Neutropenia[b]	94 (26.0)	96 (26.7)
Thrombocytopenia[b]	77 (21.3)	37 (10.3)
Pneumonia	52 (14.4)	43 (12.0)
Anemia	41 (11.4)	53 (14.8)
Diarrhea	36 (10.0)	11 (3.1)
Cataract	19 (5.3)	28 (7.8)
NPMs	n = 360	n = 362
Any NPM	37 (10.3)	43 (11.9)
Hematologic	2 (0.6)	4 (1.1)
Nonhematologic—nonmelanoma skin	19 (5.3)	23 (6.4)
Nonhematologic—melanoma skin	1 (0.3)	0
Nonhematologic—other	17 (4.7)	19 (5.2)

NOTE. Data are presented as No. (%) unless otherwise stated.

Abbreviations: AE, adverse event; NPM, new primary malignancy; Rd, lenalidomide and dexamethasone.

[a]Of the intent-to-treat population, two patients in the ixazomib-Rd arm did not receive treatment and three patients in the placebo-Rd arm erroneously received ≤ 2 doses of ixazomib and were included in the ixazomib-Rd group in the safety population.

[b]Data were based on a standardized Medical Dictionary for Regulatory Activities 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.

These findings support the idea that with greater numbers of options available for subsequent therapies, the ability to translate PFS benefit into OS benefit in RRMM clinical studies is diminished. Indeed, in the context of this expanding range of active salvage therapies, the utility of OS as an end point in phase III trials in the early-relapse RRMM setting may be increasingly limited, albeit remaining important to evaluate to confirm no adverse impact. With median OS from diagnosis now exceeding 10 years in some reports,[29] and patients typically receiving multiple lines of therapy,[2,30] PFS and sustained measurable residual disease–negative status[31] may be more appropriate end points.

Survival improvements seen in clinical trials are not always reflected in real-world findings.[10,11] This discrepancy between clinical trial efficacy and real-world effectiveness may be because of various factors, including those affecting patients' QoL and the feasibility of long-term treatment, such as the burden of repeated parenteral administration, access to treatment centers, and treatment convenience.[10,11] A recent real-world evaluation in Czech registry patients with RRMM reported median PFS for ixazomib-Rd of 17.5 months,[32] comparable to the 20.6 months reported in TOURMALINE-MM1.[14] Furthermore, the significant PFS improvement with ixazomib-Rd versus Rd in this real-world analysis (median 17.5 *v* 11.5 months; $P = .005$) translated into a significant OS improvement (median 36.6 *v* 26.0 months; $P = .008$),[32] demonstrating the survival benefit of ixazomib-Rd in real-world patients with RRMM, for whom subsequent treatment options may have been more limited than for patients in TOURMALINE-MM1. Given these observations, further real-world evaluation of the effectiveness of ixazomib-Rd in patients with RRMM across diverse geographies is warranted.

In conclusion, although the slight favorable trend in OS seen with ixazomib-Rd versus placebo-Rd at this final analysis of TOURMALINE-MM1 was not significant, these results were obtained in the context of the longest median OS reported to date in phase III studies of Rd-based therapy in RRMM. Furthermore, greater OS benefit was observed in subgroups of patients with adverse prognostic factors. Interpretation of OS was confounded by the blinded nature of the study and the extent of, and imbalances in, subsequent therapies received. The impact of the evolving RRMM treatment landscape on the ability to demonstrate OS benefit in clinical trials warrants further consideration regarding randomized trial design and the utility of OS as an end point. Nonetheless, with a demonstrated PFS benefit, limited additional toxicity versus placebo-Rd, and the convenience of an all-oral triplet regimen, ixazomib-Rd continues to represent an important treatment option for patients with RRMM.

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DATA SHARING STATEMENT

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Final Overall Survival Analysis of the TOURMALINE-MM1 Phase III Trial of Ixazomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma

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APPENDIX

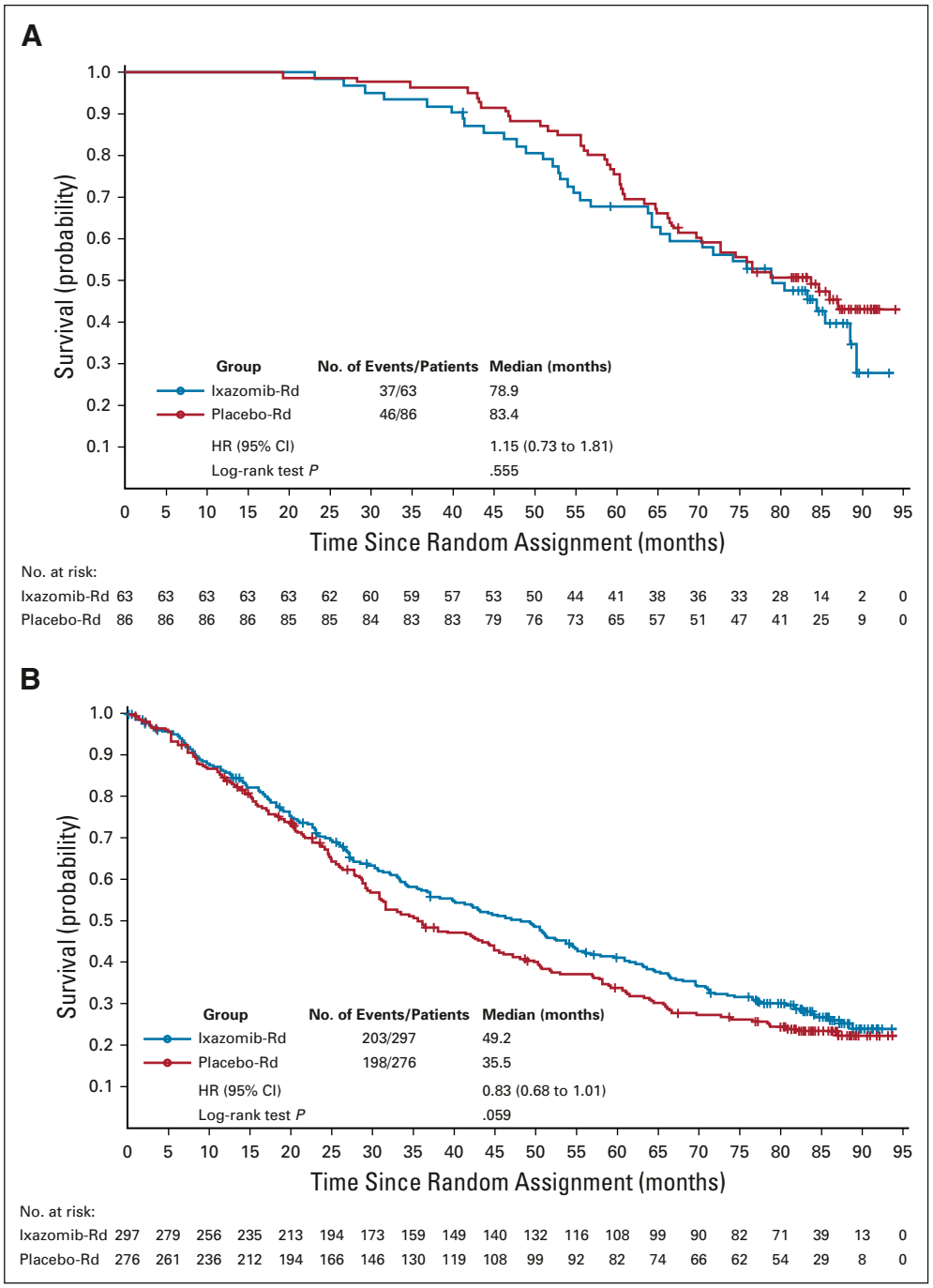

FIG A1. Overall survival in patients (A) receiving daratumumab or (B) not receiving daratumumab in any subsequent line of therapy (intent-to-treat population). HR, hazard ratio; Rd, lenalidomide and dexamethasone.

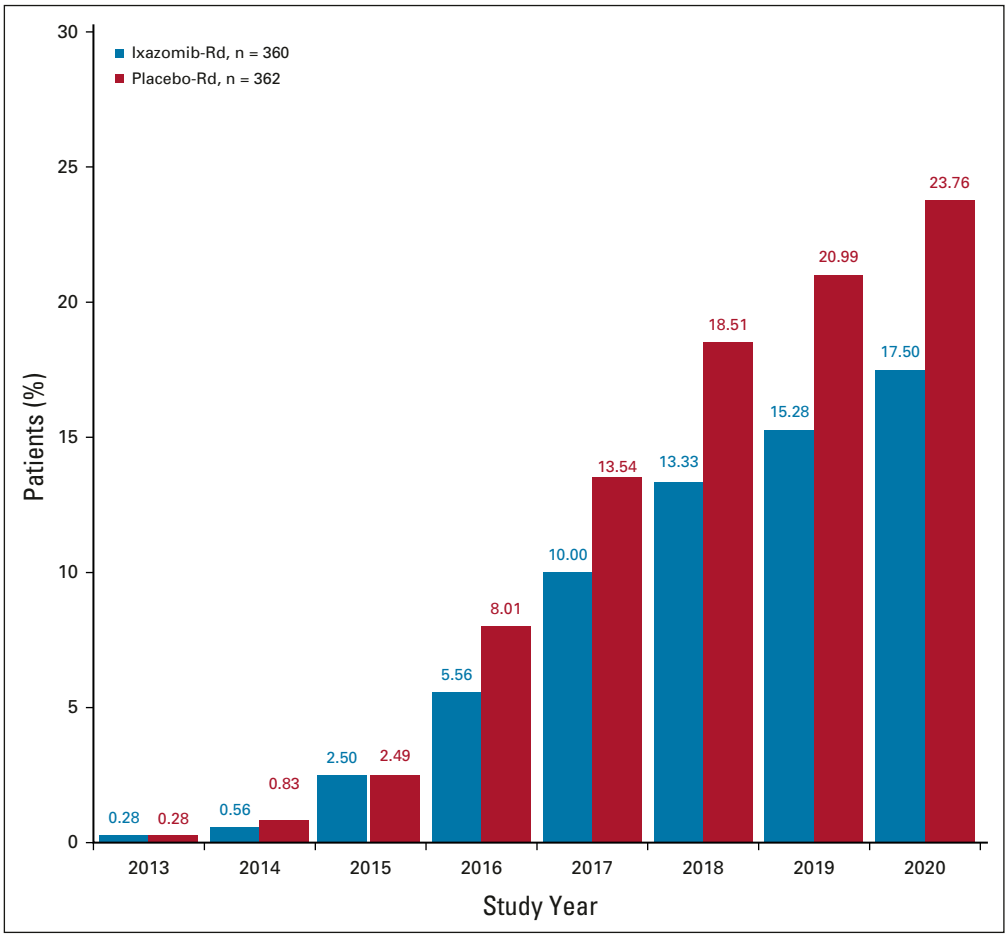

FIG A2. Cumulative proportions of patients to receive subsequent daratumumab by study year (intent-to-treat population). Rd, lenalidomide and dexamethasone.

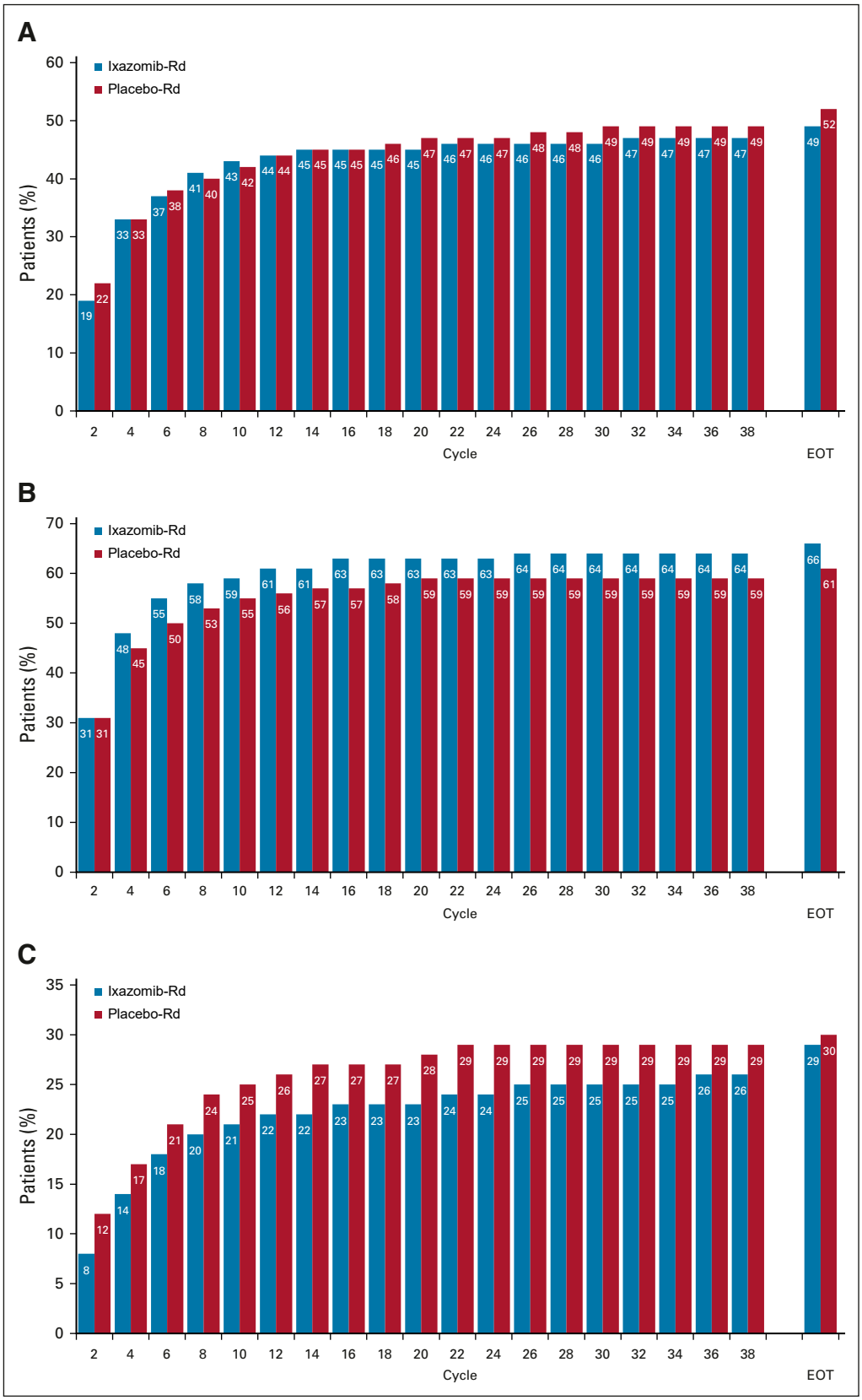

FIG A3. Cumulative proportions of patients with a minimally important difference improvement in European Organization for the Research and Treatment of Cancer (A) QLQ-C30 Global Health Status/QoL, (B) QLQ-MY20 Disease Symptoms, and (C) QLQ-MY20 Side Effects of Treatment domain scores in the ixazomib-Rd and placebo-Rd arms. EOT, end of treatment; QLQ-C30, Quality of Life Questionnaire Core-30; QLQ-MY20, Quality of Life Questionnaire, myeloma-specific module; QoL, quality of life; Rd, lenalidomide and dexamethasone.