Supplemental Data

Supplemental Tables

Supplemental Table 1. Patients by MRD range level and geographical region in the ixazomib and placebo arms

	Americas		Europe		Asia-Pacific		Overall	
	Ixazomib n = 64	**Placebo n = 36**	**Ixazomib n = 610**	**Placebo n = 413**	**Ixazomib n = 146**	**Placebo n = 93**	**Ixazomib n = 820**	**Placebo n = 542**
Total samples, N	68	31	980	649	217	132	1265	812
Patients, n (n/N*)								
LOD $<10^{-6}$	0	0	2 (0.2)	1 (0.2)	1 (0.5)	1 (0.8)	3 (0.2)	2 (0.2)
LOD $\geq 10^{-6}$ and $<10^{-5}$	22 (32.3)	8 (25.8)	803 (81.9)	534 (82.2)	184 (84.8)	111 (84.1)	1009 (79.8)	653 (80.4)
LOD $\geq 10^{-5}$ and $<10^{-4}$	43 (63.2)	21 (67.7)	168 (17.1)	111 (17.1)	30 (13.8)	17 (12.9)	241 (19.1)	149 (18.3)
LOD $\geq 10^{-4}$	3 (4.4)	2 (6.5)	7 (0.7)	3 (0.5)	2 (0.9)	3 (2.3)	12 (0.9)	8 (1.0)

LOD, limit of detection; MRD, measurable residual disease.

*n/N = patients/total samples.

Supplemental Table 2. MRD data imputation, overall and by study

Patients, n (%)	TOURMALINE-MM3 N = 656	TOURMALINE-MM4 N = 706	Total N = 1362
MRD available at baseline (with imputation)	**630 (96.0)**	**650 (92.1)**	**1280 (94.0)**
MRD imputed at baseline	76 (12.1)	286 (44.0)	362 (28.3)
MRD available at 14 months (with imputation)	**396 (60.4)**	**221 (31.3)**	**617 (45.3)**
MRD imputed at 14 months	69 (17.4)	103 (46.6)	172 (27.9)
MRD available at 28 months (with imputation)	**162 (24.7)**	**45 (6.4)**	**207 (15.2)**
MRD imputed at 28 months	15 (9.3)	18 (40.0)	33 (15.9)

MRD, measurable residual disease.

Supplemental Table 3. Change in MRD dynamics over time in TOURMALINE-MM3 and -MM4 by MRD status at randomization

Patients, n (%)	TOURMALINE-MM3 N = 656	TOURMALINE-MM4 N = 706
MRD– at randomization	**192 (29.3)**	**70 (9.9)**
MRD– at 14 months	92 (47.9)	22 (31.4)
MRD+ at 14 months	38 (19.8)	12 (17.1)
MRD N/A at 14 months	62 (32.3)	36 (51.4)
MRD– at 28 months	44 (22.9)	4 (5.7)
MRD+ at 28 months	21 (10.9)	4 (5.7)
MRD N/A at 28 months	127 (66.1)	62 (88.6)
MRD+ at randomization	**438 (66.8)**	**580 (82.2)**
MRD– at 14 months	41 (9.4)	17 (2.9)
MRD+ at 14 months	211 (48.2)	154 (26.6)
MRD N/A at 14 months	186 (42.5)	409 (70.5)
MRD– at 28 months	24 (5.5)	5 (0.9)
MRD+ at 28 months	67 (15.3)	28 (4.8)
MRD N/A at 28 months	347 (79.2)	547 (94.3)
MRD N/A at randomization	**26 (4.0)**	**56 (7.9)**

N/A, not available; MRD, measurable residual disease.

Supplemental Table 4. MRD conversions from randomization to the 14-month landmark by treatment group

Patients, n (%)	Ixazomib n = 820	Placebo n = 540	*P* value*
MRD– at randomization	**161 (19.6)**	**101 (18.7)**	
MRD available or PD by 14 months	**96 (59.6)**	**68 (67.3)**	
MRD+ or PD by 14 months	23 (24.0)	27 (39.7)	.04
MRD– and no PD by 14 months	73 (76.0)	41 (60.3)	
MRD+ at randomization	**606 (73.9)**	**412 (76.3)**	
MRD available or PD by 14 months	**278 (45.9)**	**145 (23.8)**	
MRD+ or PD by 14 months	242 (87.1)	123 (84.8)	0.72
MRD– and no PD by 14 months	36 (12.9)	22 (15.2)	

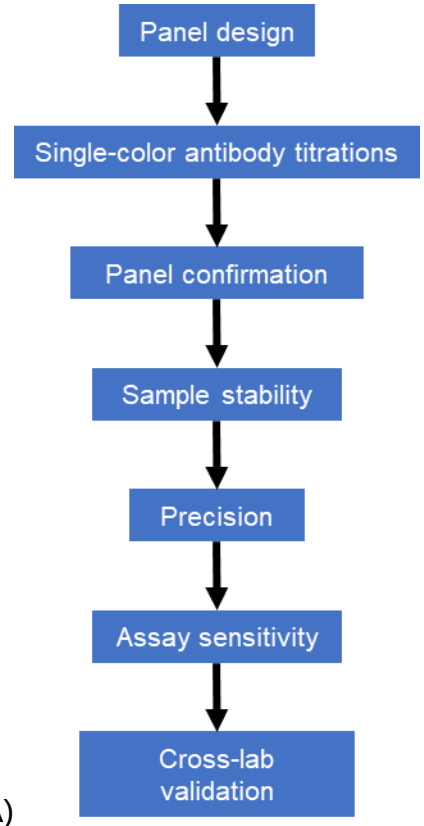
MRD, measurable residual disease; PD, progressive disease.

**P* value based on an exact conditional test stratified by study (TOURMALINE-MM3 vs -MM4).

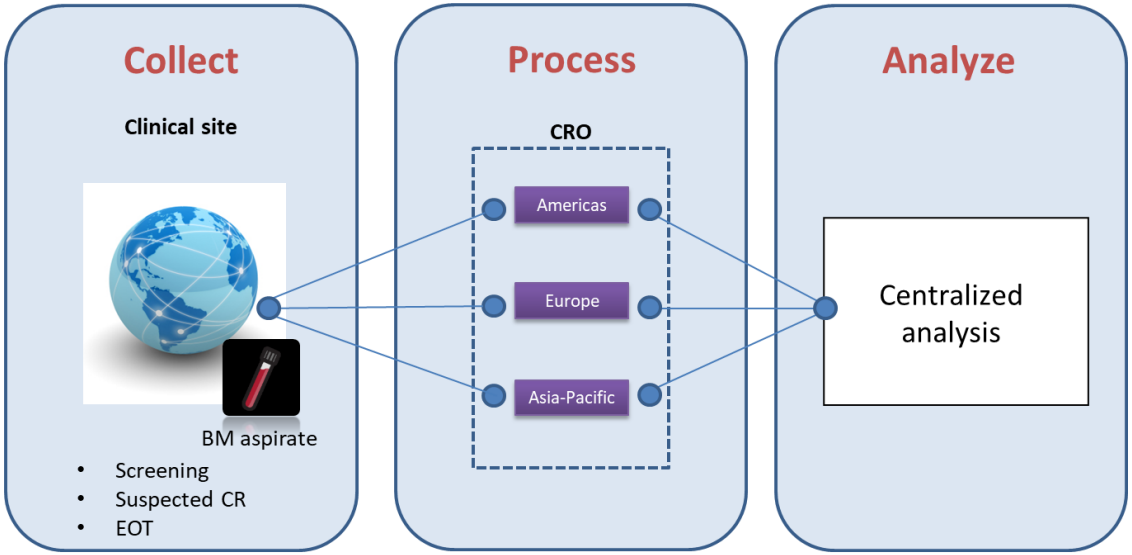
Supplemental Figures

Supplemental Figure 1. Validation and standardization of BM aspirate samples. A) Key steps in validating the MRD assay, and B) the process flow for testing and reporting data in a standardized fashion.

A)



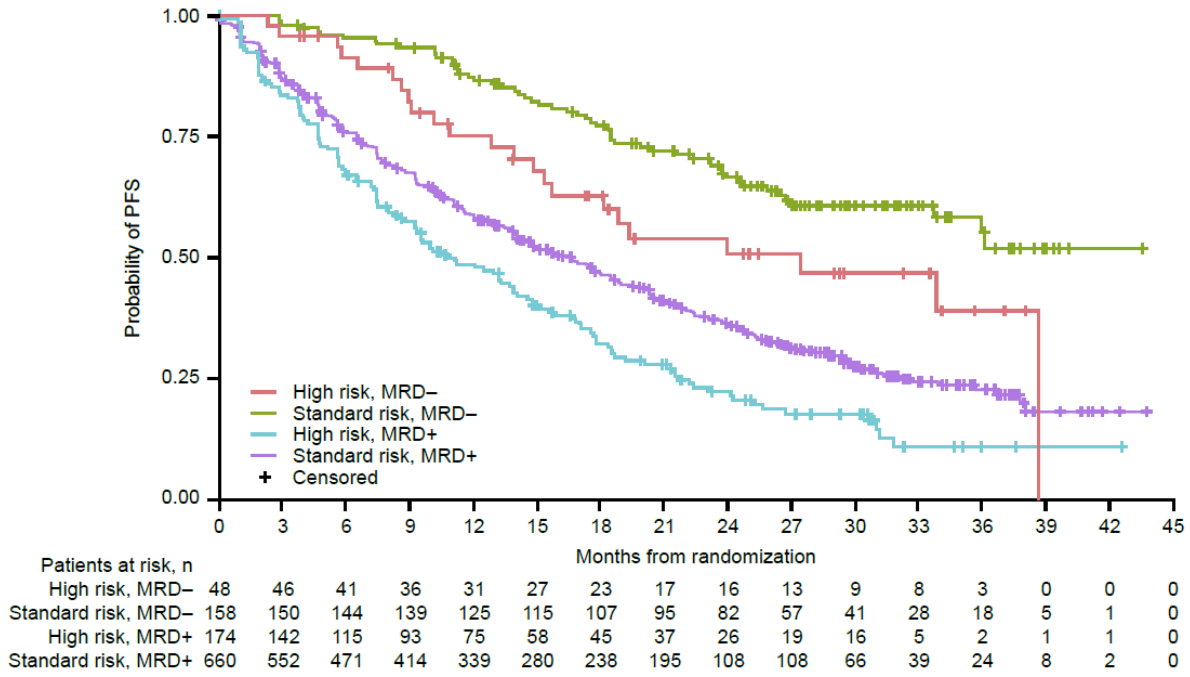
B)



BM, bone marrow; CR, complete response; CRO, contract research organization; EOT, end of treatment; MRD, measurable residual disease.

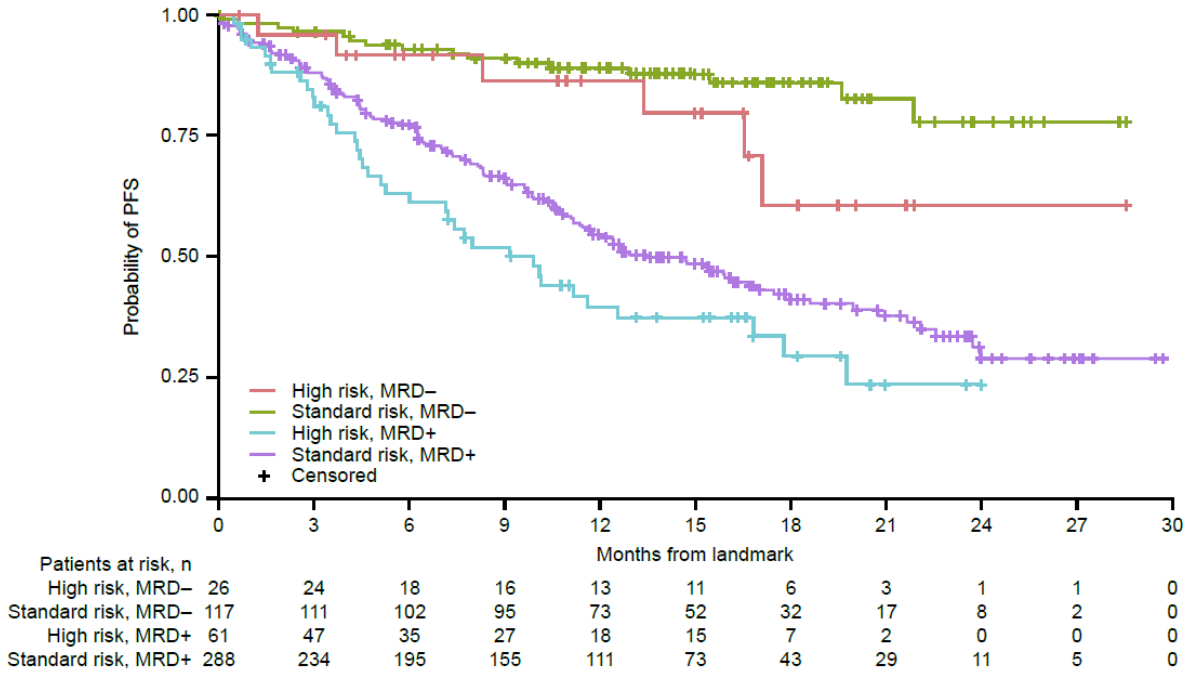
Supplemental Figure 2. PFS according to cytogenetic risk group at diagnosis and MRD status (A) at randomization and (B) the 14-month landmark analysis. Kaplan-Meier analysis of PFS for patients with MRD+ or MRD– status at randomization who received ixazomib or placebo in the TOURMALINE-MM3 and -MM4 trials. Cytogenetic assessments were performed locally and interpreted centrally by a board-certified hematopathologist. High-risk cytogenetics were defined as the presence of any of the following 3 individual abnormalities: del(17), t(4;14), t(14;16).

A



Patients		n	Events	Median follow-up, months (95% CI)	Median PFS, months (95% CI)	2-year PFS rate, % (95% CI)	HR (95% CI)	*P* value
MRD–	High risk	48	23	29.0 (19.6-33.5)	27.4 (15.7-NR)	50.8 (37.2-69.4)	1.55 (0.87-2.74)	.133
	Standard risk	158	56	29.0 (27.0-30.9)	NR (33.7-NR)	66.6 (59.1-74.9)		
MRD+	High risk	174	132	30.2 (25.1-30.9)	10.8 (9.2-14.5)	22.3 (16.4-30.3)	1.48 (1.20-1.82)	<.001
	Standard risk	680	415	27.6 (26.5-28.9)	16.6 (14.2-18.5)	36.2 (32.4-40.5)		

B



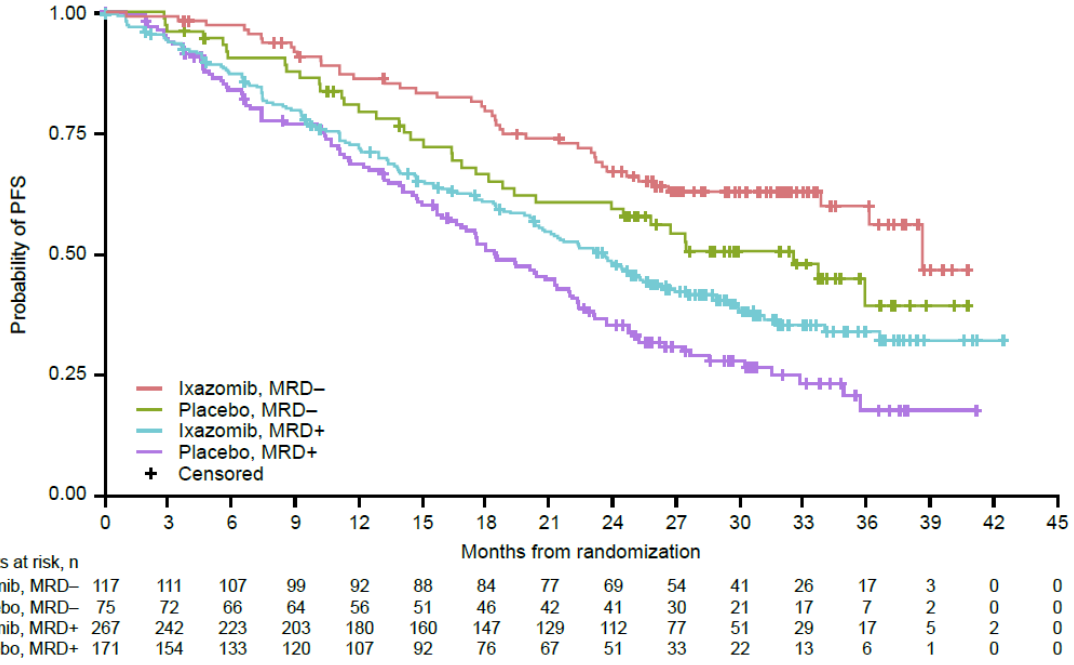
Patients at risk, n											
High risk, MRD–	26	24	18	16	13	11	6	3	1	1	0
Standard risk, MRD–	117	111	102	95	73	52	32	17	8	2	0
High risk, MRD+	61	47	35	27	18	15	7	2	0	0	0
Standard risk, MRD+	288	234	195	155	111	73	43	29	11	5	0

Patients		n	Events	Median follow-up, months (95% CI)	Median PFS, months (95% CI)	1-year PFS rate, % (95% CI)	HR (95% CI)	*P* value
MRD–	High risk	26	6	15.2 (10.7-19.5)	NR (17.1-NR)	86.4 (73.1-100)	2.06 (0.67-6.17)	.189
	Standard risk	117	16	15.2 (13.8-16.8)	NR (NR-NR)	89.1 (83.5-95.1)		
MRD+	High risk	61	37	16.3 (13.8-19.6)	9.9 (6.1-17.8)	39.7 (28.4-55.4)	1.50 (1.01-2.24)	.043
	Standard risk	288	142	15.3 (13.9-16.3)	13.4 (11.7-17.5)	54.7 (48.8-61.3)		

CI, confidence interval; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; PFS, progression-free survival.

Supplemental Figure 3. PFS with ixazomib vs placebo according to MRD status at randomization in (A) TOURMALINE-MM3 and (B) TOURMALINE-MM4. Kaplan-Meier analysis of PFS for patients with MRD+ or MRD– status at randomization who received ixazomib or placebo in the TOURMALINE-MM3 and -MM4 trials.

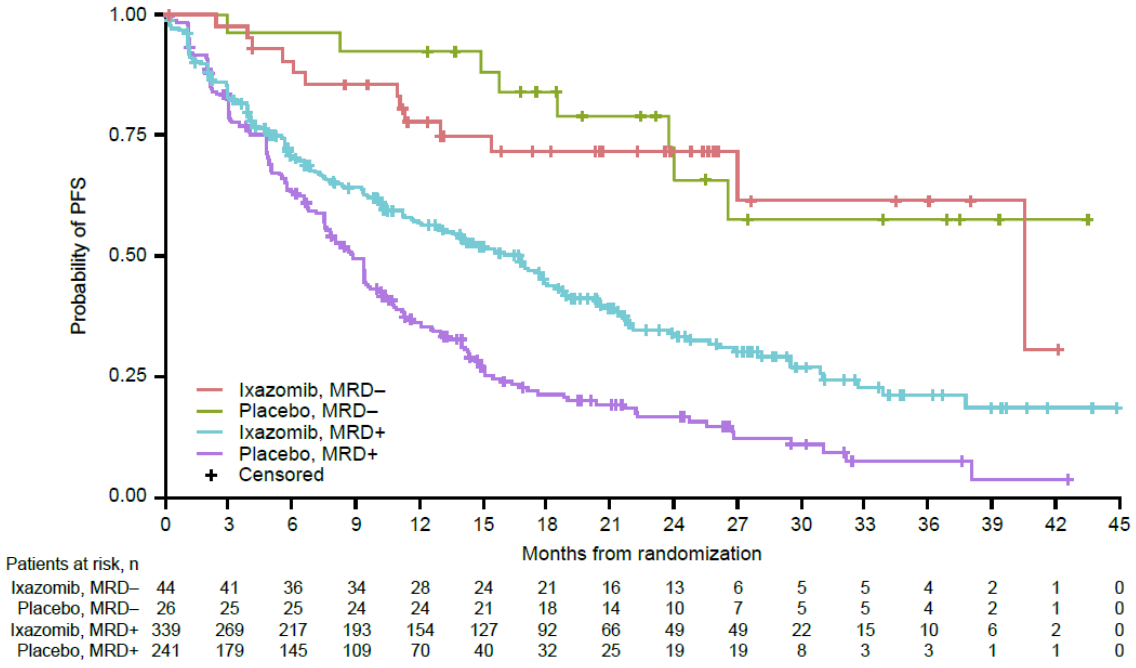
A



Patients at risk, n																
Ixazomib, MRD–	117	111	107	99	92	88	84	77	69	54	41	26	17	3	0	0
Placebo, MRD–	75	72	66	64	56	51	46	42	41	30	21	17	7	2	0	0
Ixazomib, MRD+	267	242	223	203	180	160	147	129	112	77	51	29	17	5	2	0
Placebo, MRD+	171	154	133	120	107	92	76	67	51	33	22	13	6	1	0	0

Patients		n	Events	Median follow-up, months (95% CI)	Median PFS, months (95% CI)	2-year PFS rate, % (95% CI)	HR (95% CI)	*P* value
MRD–	Ixazomib	117	42	31.2 (29.5-32.4)	38.6 (36.1-NR)	67.1 (58.7-76.7)	0.61 (0.39-0.97)	.034
	Placebo	75	37	32.7 (29.2-34.5)	32.5 (23.9-NR)	59.2 (48.8-71.9)		
MRD+	Ixazomib	267	153	30.1 (28.4-30.9)	23.5 (20.5-26.2)	48.2 (42.4-54.9)	0.74 (0.58-0.94)	.014
	Placebo	171	114	29.5 (27.4-30.8)	18.5 (16.4-22.1)	35.3 (28.5-43.8)		

B



Patients at risk, n

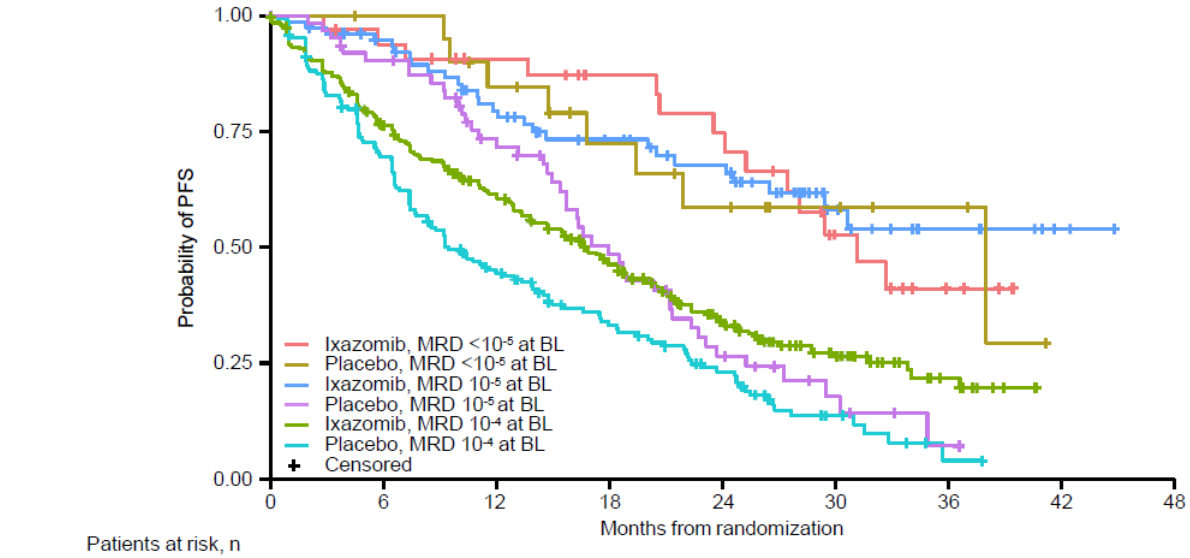
Ixazomib, MRD–	44	41	36	34	28	24	21	16	13	6	5	5	4	2	1	0
Placebo, MRD–	26	25	25	24	24	21	18	14	10	7	5	5	4	2	1	0
Ixazomib, MRD+	339	269	217	193	154	127	92	66	49	49	22	15	10	6	2	0
Placebo, MRD+	241	179	145	109	70	40	32	25	19	19	8	3	3	1	1	0

Patients		n	Events	Median follow-up, months (95% CI)	Median PFS, months (95% CI)	2-year PFS rate, % (95% CI)	HR (95% CI)	*P* value
MRD–	Ixazomib	44	13	22.2 (18.1-25.3)	40.5 (26.9-NR)	71.7 (58.7-87.6)	1.54 (0.56-4.19)	.398
	Placebo	26	8	25.4 (19.6-33.8)	NR (23.7-NR)	65.8 (47.4-91.4)		
MRD+	Ixazomib	339	198	21.0 (19.5-24.1)	16.6 (12.8-17.8)	34.0 (28.4-40.8)	0.60 (0.49-0.74)	<.001
	Placebo	241	184	21.2 (19.4-26.3)	8.7 (7.4-9.5)	16.7 (11.9-23.5)		

CI, confidence interval; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; PFS, progression-free survival.

Supplemental Figure 4. Landmark analysis of PFS according to MRD+ logarithmic levels at randomization with ixazomib maintenance vs placebo.

Kaplan-Meier analysis of PFS for patients with MRD+ status at randomization who received ixazomib or placebo in the TOURMALINE -MM3 and -MM4 trials.

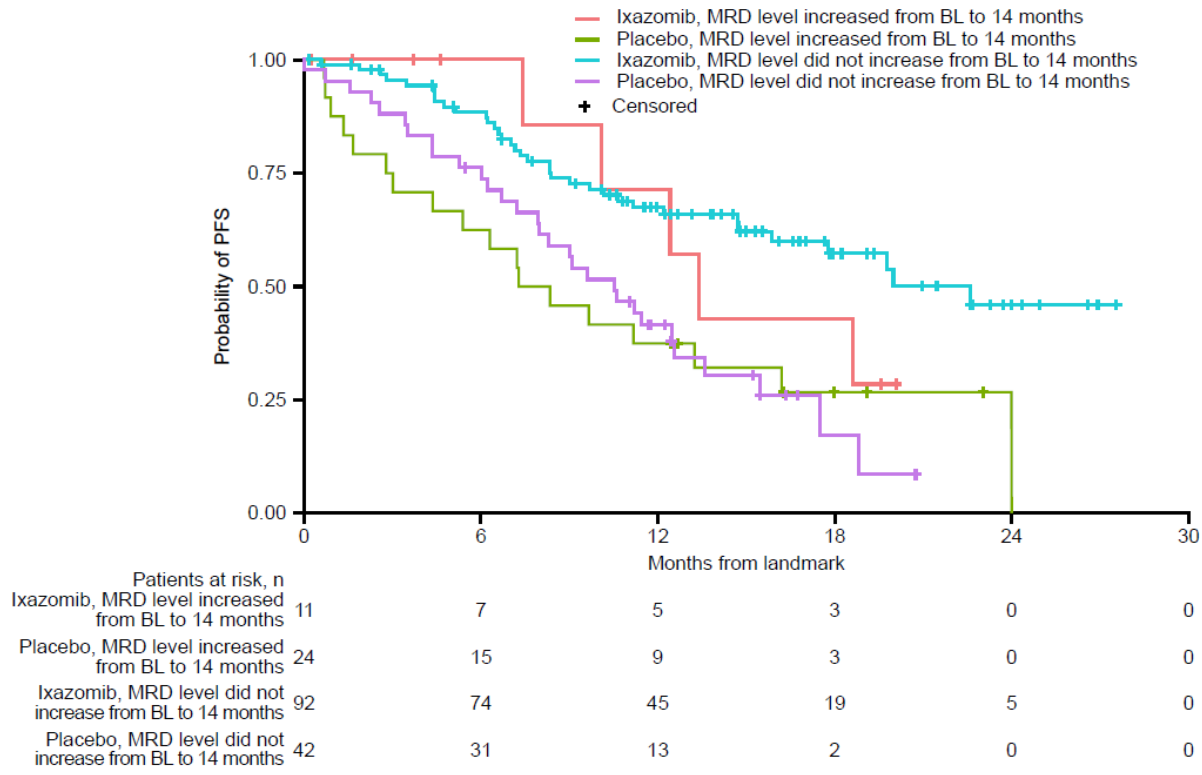


Patients at risk, n									
Ixazomib, MRD <10-5 at BL	33	30	26	21	18	9	3	0	0
Placebo, MRD <10-5 at BL	21	20	16	11	8	5	3	0	0
Ixazomib, MRD 10-5 at BL	82	70	54	43	36	15	8	3	0
Placebo, MRD 10-5 at BL	66	56	39	25	13	5	1	0	0
Ixazomib, MRD 10-4 at BL	279	201	152	107	65	31	10	0	0
Placebo, MRD 10-4 at BL	177	115	69	45	28	8	1	0	0

Patients		n	Events	Median follow up, months (95% CI)	Median PFS, months (95% CI)	2-year PFS rate, % (95% CI)	HR (95% CI)	*P* value
MRD <10-5	Ixazomib	33	14	33.0 (29.2-35.9)	31.3 (27.4-NR)	74.8 (60.0-93.2)	0.96 (0.35-2.62)	.936
	Placebo	21	8	26.3 (21.5-32.0)	38.0 (19.4-NR)	58.6 (38.7-88.6)		
MRD 10-5	Ixazomib	82	27	27.2 (24.7-29.0)	NR (29.4-NR)	67.8 (57.4-80.1)	0.45 (0.27-0.78)	.003
	Placebo	66	45	26.8 (25.8-33.1)	18.0 (15.7-22.4)	26.5 (16.8-41.8)		
MRD 10-4	Ixazomib	279	181	27.2 (26.1-30.1)	16.8 (13.9-19.2)	33.5 (28.0-40.2)	0.66 (0.52-0.84)	< .001
	Placebo	177	135	26.5 (25.7-29.5)	9.5 (7.6-13.9)	23.1 (17.2-31.2)		

BL, baseline; CI, confidence interval; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; PFS, progression-free survival.

Supplemental Figure 5. Landmark analysis of PFS according to MRD logarithmic levels at randomization to 14 months with ixazomib maintenance vs placebo. Kaplan-Meier analysis of PFS for patients whose MRD levels had increased or not increased from randomization to 14 months with ixazomib or placebo in the TOURMALINE -MM3 and -MM4 trials.



Patients		n	Events	Median follow up, months (95% CI)	Median PFS, months (95% CI)	2-year PFS rate, % (95% CI)	HR (95% CI)	*P* value
MRD level increased	Ixazomib	11	5	19.6 (3.71-NR)	13.4 (10.1-NR)	28.6 (8.9-92.2)	0.67 (0.22-2.07)	.487
	Placebo	24	18	18.0 (16.3-23.0)	7.8 (5.4-NR)	0 (NR-NR)		
MRD level did not increase	Ixazomib	92	35	16.1 (13.9-17.9)	22.6 (15.9-NR)	45.9 (33.1-63.8)	0.39 0.22-0.68	< .001
	Placebo	42	30	15.4 (12.2-NR)	10.5 (8.0-15.4)	8.7 (1.6-47.9)		

BL, baseline; CI, confidence interval; HR, hazard ratio; MRD, measurable residual disease; NR, not reached; PFS, progression-free survival.