Oral ixazomib maintenance following autologous stem cell transplant in patients with newly diagnosed multiple myeloma: Final overall survival analysis from the TOURMALINE-MM3 study

P943

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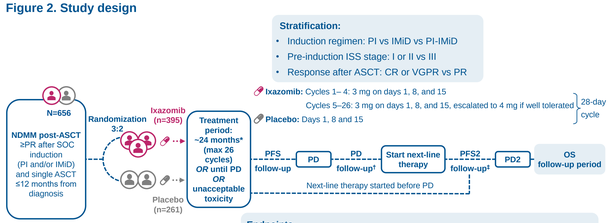
Background

- The increasing number of treatment options available for patients with multiple myeloma (MM) has been associated with improvement in overall survival (OS);[1] however, effective and tolerable therapies are still required, particularly for hard-to-treat groups, such as elderly patients, and those with high-risk cytogenetic abnormalities
- Considering the guideline-recommended use of lenalidomide in earlier lines of therapy, and the approval of lenalidomide as post-autologous stem cell transplantation (ASCT) maintenance in MM, the population of lenalidomide-exposed and -refractory patients is increasing[2]
- Proteasome inhibitors (PIs) provide an alternative to lenalidomide due to their different mechanism of action; however, prolonged use of parenteral PIs as maintenance therapy may be limited due to treatment burden[3]
- The double-blind TOURMALINE-MM3 study (NCT02181413) included patients with newly diagnosed MM (NDMM) who had achieved at least a partial response (PR) following induction therapy, high-dose melphalan conditioning, and single ASCT within 12 months of diagnosis
  - This study previously demonstrated a statistically significant and clinically meaningful improvement in its primary endpoint of progression-free survival (PFS) with ixazomib versus placebo (5.2 months, median 26.5 vs 21.3 months; hazard ratio [HR] 0.72, 95% confidence interval (CI) 0.58–0.89, *P*=0.002)[4]
  - However, an interim analysis showed no statistically significant difference in the key secondary endpoint of OS[5]
- Here, we report the final OS analysis in the TOURMALINE-MM3 intent-to-treat (ITT) population and patient subgroups of interest

Methods

- Full methods for the phase 3, double-blind, placebo-controlled TOURMALINE-MM3 study have been published previously[4] (**Figure 2** and **Summary panel**)

Figure 2. Study design



*After the first 4 cycles of treatment, eligible patients had their dose of ixazomib (or matching placebo) escalated from 3 mg to 4 mg. †If a physician chose to start next-line therapy before PD, the patient skipped the PD follow-up period and entered directly into the PFS2 follow-up period. ‡After the first occurrence of PD, the date and characteristics of PD2, PFS2, and disease status were assessed by the treating physician/investigator only. All disease response and PD assessments were performed according to the International Myeloma Working Group uniform response criteria, version 2011.[6]

CR, complete response; IMiD, immunomodulatory drug; IRC, independent review committee; ISS, International Staging System; MRD, minimal residual disease; PD, progressive disease; PD2, PD on next line of treatment; PFS2, PFS on next-line therapy; SOC, standard of care; TTNT, time to next treatment; VGPR, very good partial response.

Results

Patients

- At data cutoff (September 8, 2023), 194/395 (49%) patients in the ixazomib arm vs 151/261 (58%) patients in the placebo arm had discontinued study treatment prior to completion of 24 months of therapy, mostly due to PD (**Table 1**)

Table 1. Patient disposition (ITT population)

n (%)	Ixazomib (n=395)	Placebo (n=261)
Completed 26 cycles of study regimen	**199 (50)**	**109 (42)**
Discontinued study regimen	**194 (49)**	**151 (58)**
PD	143 (36)	121 (46)
AE	25 (6)	7 (3)
Other	20 (5)	19 (7)
Withdrawal by patient	6 (2)	4 (2)

AE, adverse event.

- Demographics and baseline characteristics have been published[4]
  - In the ixazomib and placebo arms, respectively, median age was 58 and 60 years, and 15% and 21% of patients had high-risk cytogenetic abnormalities [del(17p) and/or t(4;14) and/or t(14;16)]
  - Of 585/656 patients tested for MRD at study entry, 225/357 (63%) vs 139/228 (61%) were MRD-positive in the ixazomib vs placebo arms, and 117/357 (33%) vs 75/228 (33%) were MRD-negative in the ixazomib vs placebo arms

Question Does oral ixazomib fixed duration maintenance improve long-term OS compared with placebo among patients with NDMM who have undergone ASCT?

Study design

Patients with NDMM and ≥PR following PI and/or IMiD induction therapy prior to receiving ASCT

3:2 — Ixazomib (n=395) / Placebo (n=261)

Treatment period: ~24 months (max 26 cycles) *OR* until progression or unacceptable toxicity*

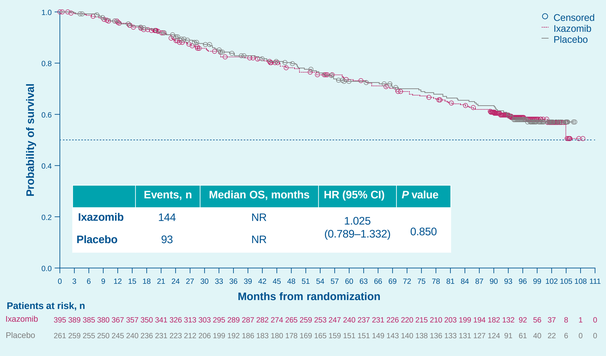
*whichever occurs first

Primary endpoint: PFS by IRC assessment

Key secondary endpoint: OS

Results

Figure 1A: Overall survival (ITT population)



	Events, n	Median OS, months	HR (95% CI)	*P* value
Ixazomib	144	NR	1.025 (0.789–1.332)	0.850
Placebo	93	NR		

Patients at risk, n

Ixazomib	395	389	385	380	367	357	350	341	326	313	303	295	289	282	274	265	259	253	247	240	237	231	226	220	215
Placebo	261	259	255	250	245	240	236	231	223	212	206	199	192	186	183	180	178	169	165	159	151	151	149	143	140

Ixazomib	210	203	199	194	182	132	92	56	37	8	1	0													
Placebo	138	136	133	131	127	124	91	61	40	22	6	0	0												

Figure 1B: Overall survival by subgroup (ITT population)

Variable	Subgroup	Events; n / Median survival (months) Ixazomib	Placebo	HR	95% CI
All patients	All (N=656)	144; 395 / NE	93; 261 / NE	1.025	0.789–1.332
Age	<60 years (n=356)	80; 229 / NE	34; 127 / NE	1.295	0.862–1.944
	≥60 and <75 years (n=300)	64; 166 / 105.0	59; 134 / 94.2	0.907	0.629–1.307
Induction regimen	PI-exposed (n=585)	132; 352 / 105.0	83; 233 / NE	1.060	0.804–1.396
	PI-naïve (n=71)	12; 43 / NE	10; 28 / 90.2	0.746	0.322–1.731
Response at study entry	CR (n=225)	43; 132 / NE	32; 93 / NE	0.922	0.579–1.469
	VGPR (n=294)	72; 179 / 105.0	42; 115 / NE	1.049	0.712–1.544
	PR (n=137)	29; 84 / NE	19; 53 / NE	1.239	0.677–2.267
Cytogenetic risk	High risk (n=115)	33; 61 / 64.2	30; 54 / 69.0	0.970	0.583–1.613
	Standard-risk (n=404)	77; 252 / NE	48; 152 / NE	0.960	0.666–1.385
	Unclassifiable (n=137)	34; 82 / NE	15; 55 / NE	1.609	0.861–3.007
MRD status at study entry	MRD- (n=192)	34; 117 / NE	27; 75 / NE	0.700	0.414–1.184
	MRD+ (n=364)	86; 225 / 105.0	53; 139 / NE	0.966	0.682–1.368
	Unknown (n=100)	24; 53 / 91.4	13; 47 / NE	2.026	0.991–4.142

NE, not estimable.

0.25 0.5 0.75 1.0 3.0 5.0

Favors ixazomib — Favors placebo

Key take aways Despite meeting its primary endpoint of PFS, the final OS analysis of the TOURMALINE-MM3 study demonstrated no statistically significant difference between ixazomib fixed duration maintenance and placebo in patients with NDMM who had achieved ≥PR post-ASCT.

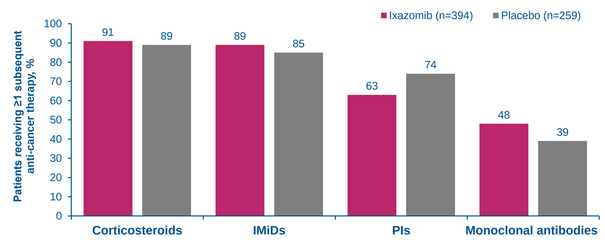
OS in the ITT population and subgroups

- At data cutoff, at the median follow-up of 94.4 months for ixazomib and 94.5 months for placebo, 144 patients (36%) and 93 patients (36%) had died, respectively
- Median OS was not reached (NR) in either treatment group (HR, 1.025; 95% CI: 0.789–1.332; *P*=0.850) (**Summary Panel**, **Figure 1A**)
- In patient subgroups, there were no significant differences in median OS for ixazomib versus placebo (**Summary Panel**, **Figure 1B**)
  - There was a trend favouring ixazomib among patients who were PI-naïve (HR, 0.746; 95% CI: 0.322–1.731) or MRD-negative at study entry (HR, 0.700; 95% CI 0.414–1.184)

TTNT, PFS2, and subsequent therapies

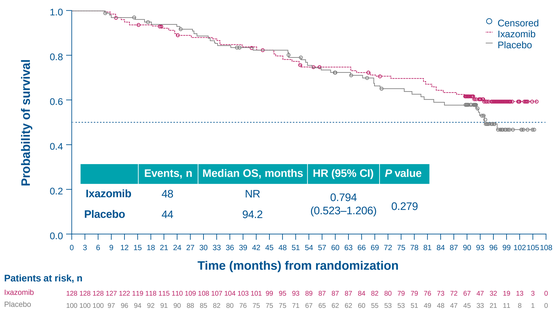
- Median TTNT was 33.1 months (ixazomib) vs 27.6 months (placebo); HR, 0.849; 95% CI: 0.704–1.022
- Median PFS2 was 84.0 months (ixazomib) vs 80.4 months (placebo); HR, 1.015; 95% CI: 0.795–1.298
- In both treatment arms, 73% of patients received ≥1 subsequent anti-cancer therapy (**Figure 3**)

Figure 3. Patients receiving subsequent anti-cancer therapy (safety population)



- For patients who received a PI in their next-line therapy, median OS was NR (ixazomib) vs 94.2 months (placebo); HR, 0.794; 95% CI: 0.523–1.206 (**Figure 4**)
- For patients whose next-line therapy did not include a PI, median OS was 74.9 months (ixazomib) vs 90.3 months (placebo); HR, 1.310; 95% CI: 0.901–1.904 (**Figure 5**)

Figure 4. OS in patients whose next-line therapy included a PI



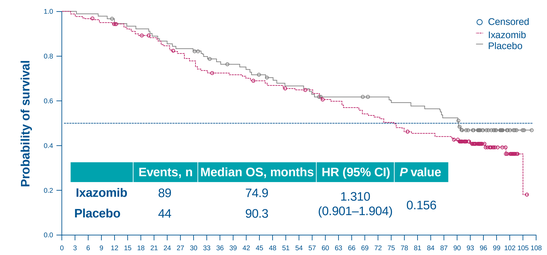
	Events, n	Median OS, months	HR (95% CI)	*P* value
Ixazomib	48	NR	0.794 (0.523–1.206)	0.279
Placebo	44	94.2		

Patients at risk, n

Ixazomib	128	128	128	127	122	119	118	115	110	109	108	107	104	103	101	99	95	93	89	87	87	87	84	82	80
Placebo	100	100	100	97	96	94	92	91	90	88	85	82	80	76	75	75	75	71	67	65	62	62	60	55	53

Ixazomib	79	79	76	73	72	67	47	32	19	13	3	0													
Placebo	53	51	49	48	47	45	33	21	11	8	1	0													

Figure 5. OS in patients whose next-line therapy did not include a PI



	Events, n	Median OS, months	HR (95% CI)	*P* value
Ixazomib	89	74.9	1.310 (0.901–1.904)	0.156
Placebo	44	90.3		

Patients at risk, n

Ixazomib	158	156	153	150	147	141	136	132	127	120	115	109	106	105	104	100	97	94	93	92	85	82	79	76	73
Placebo	90	90	89	88	85	83	82	79	76	74	73	69	66	64	62	59	57	54	54	51	48	48	48	47	46

Ixazomib	69	65	62	62	60	56	39	27	17	9	1	0													
Placebo	44	44	43	42	39	39	28	21	14	7	2	0													

New primary malignancies (NPM) and quality of life (QoL)

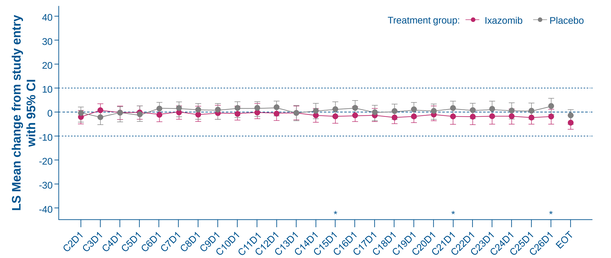
- The incidence of NPMs was 7% in the ixazomib arm vs 8% in the placebo arm (**Table 2**)

Table 2. Incidence of NPMs (safety population)

n (%)	Ixazomib (n=394)	Placebo (n=259)
Patient with ≥1 NPM	**28 (7)**	**21 (8)**
NPM type		
Hematologic	6 (2)	8 (3)
Non-hematologic	12 (3)	8 (3)
Non-hematologic (skin)	12 (3)	5 (2)

- Patients' global health-related QoL (HRQoL) was maintained in both arms over the course of treatment (**Figure 6**)

Figure 6. Change from study entry in EORTC QLQ-C30 scores – global health status/QoL



Ixazomib	372	357	360	349	345	334	328	325	314	296	290	286	280	274	261	257	246	243	243	233	229	222	213	202	182	349
Placebo	247	240	239	231	220	214	205	203	194	193	190	176	180	168	162	153	145	139	134	132	127	120	116	114	108	237

Patient-reported outcomes were measured at study entry and at least once post-study entry. Score changes from baseline were assessed using linear mixed models (visits). **P*≤0.05.

C, cycle; D, day; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30; EOT, end of treatment (visit); LS, least squares.

Conclusions

- Although TOURMALINE-MM3 study met its primary endpoint of PFS, the final OS analysis of the study demonstrated no significant differences between ixazomib fixed duration maintenance and matching placebo in patients with NDMM who had achieved ≥PR post-ASCT
- Despite nearly 8 years of follow-up, median OS had not been reached in either arm, supporting the concept that the growing number of available, highly effective salvage treatments with novel mechanisms of action make demonstrating an OS advantage in front-line myeloma studies increasingly challenging
- Most patients who progressed in the ixazomib treatment group had done so after completing study treatment (median PFS, 26.5 months), suggesting that they had benefitted from ixazomib maintenance treatment but, once stopped, the disease progressed
- Ixazomib fixed duration maintenance did not appear to have an adverse effect on subsequent therapies, NPM incidence remained low in both treatment arms, and patient HRQoL was maintained

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Disclosures

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