Ixazomib maintenance in transplant-ineligible patients with newly diagnosed multiple myeloma: Final overall survival analysis from the TOURMALINE-MM4 study

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Question Does oral ixazomib maintenance improve long-term OS compared with placebo among a cohort of patients with NDMM who have not undergone ASCT?

Study design

Transplant ineligible patients
NDMM enrolled at 187 sites in 34 countries (N = 706)

3:2

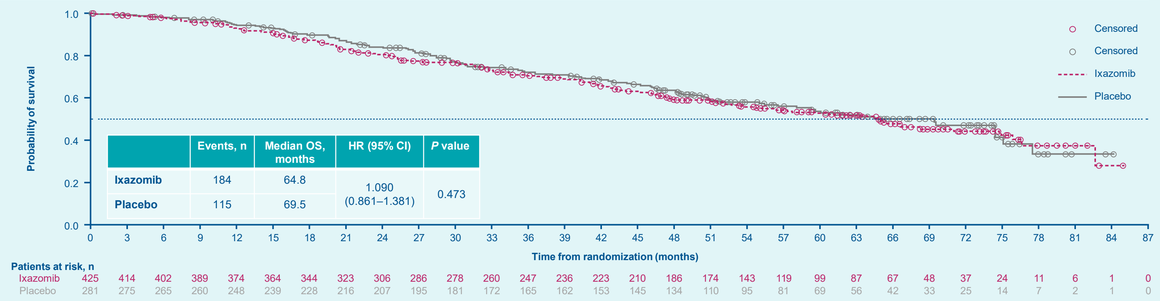
- Ixazomib (n = 425)
- Placebo (n = 281)

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

Primary endpoint: PFS (based on IRC assessment)
Key secondary endpoints included: OS

Results

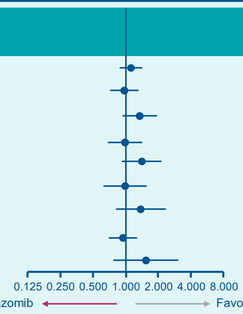
Figure 1A: Overall survival (ITT population)



	Events, n	Median OS, months	HR (95% CI)	*P* value
Ixazomib	184	64.8	1.090 (0.861–1.381)	0.473
Placebo	115	69.5		

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

Variable	Subgroup	Events; n / Median OS, months: Ixazomib	Placebo	HR	95% CI
All subjects	All (N = 706)	184; 425 / 64.8	115; 281 / 69.5	1.090	0.861–1.381
Age at time of randomization	<75 years (n = 432)	105; 261 / 74.8	71; 171 / 64.4	0.953	0.702–1.295
	≥75 years (n = 274)	79; 164 / 54.6	44; 110 / 69.6	1.317	0.909–1.909
Frailty status	Fit (n = 283)	68; 171 / 74.8	45; 112 / 64.4	0.965	0.655–1.422
	Unfit (n = 246)	65; 148 / 61.1	36; 98 / 69.6	1.381	0.900–2.119
	Frail (n = 170)	50; 102 / 55.7	33; 68 / 44.1	0.975	0.613–1.549
Cytogenetic risk	High risk (n = 122)	45; 74 / 37.3	26; 48 / 48.3	1.357	0.799–2.306
	Standard risk (n = 465)	105; 275 / 66.7	76; 190 / 69.6	0.923	0.681–1.250
	Unclassifiable (n = 119)	34; 76 / 76.0	13; 43 / 69.5	1.516	0.753–3.052



Key take aways Despite meeting its primary endpoint, the final OS analysis of the TOURMALINE-MM4 study demonstrated no statistically significant difference between ixazomib and placebo including in high-risk patients (aged ≥75 years, frail, and high-risk cytogenetics at baseline)

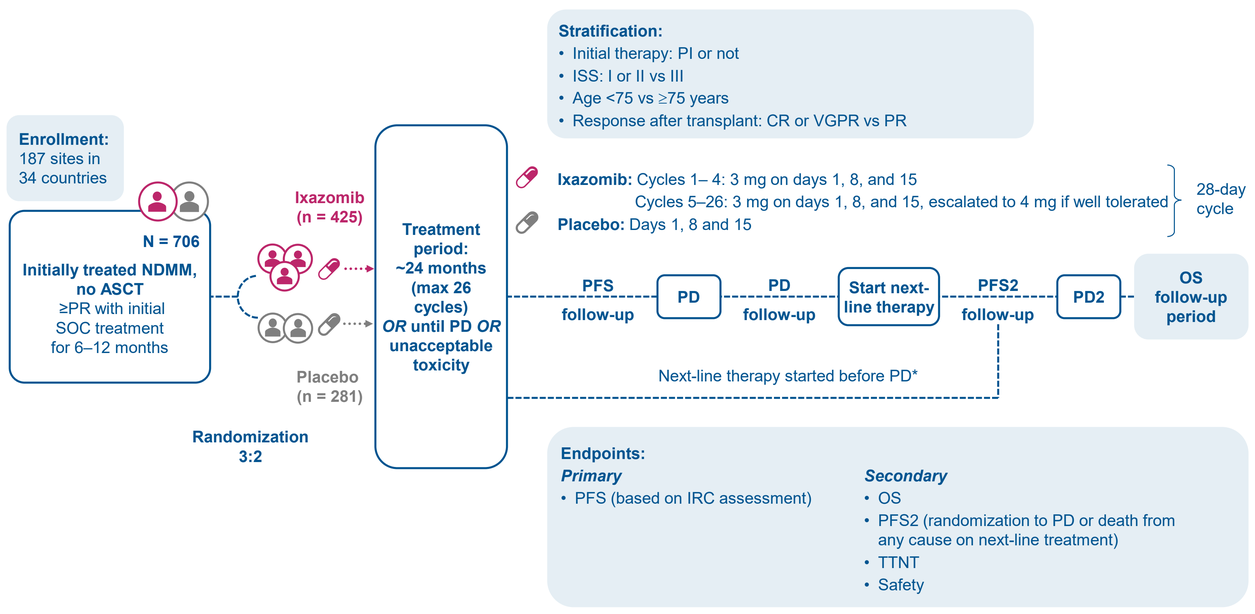
Background

- 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 subgroups, such as elderly or frail patients, and those with high-risk cytogenetic abnormalities
- There is currently no single agent specifically approved as maintenance after any standard-of-care (SOC) induction therapy for patients with newly diagnosed multiple myeloma (NDMM) not undergoing autologous stem cell transplantation (ASCT)[2]
- The TOURMALINE-MM4 study was designed to investigate ixazomib maintenance following any SOC induction in non-ASCT patients with NDMM (NCT02312258)[2]
- The study has previously demonstrated a statistically significant and clinically meaningful improvement in its primary endpoint of progression-free survival (PFS) for ixazomib maintenance versus placebo[2]
  - Ixazomib demonstrated a 34.1% reduction in risk of progression or death versus placebo (median PFS: 17.4 months versus 9.4 months, respectively; hazard ratio [HR], 0.659; 95% confidence interval [CI]: 0.542–0.801; *P* <0.001)[2]
- However, an interim analysis of the key secondary endpoint of OS reported no statistically significant difference between study arms[3]
  - After a median follow-up of 36 months, the median OS had not yet been reached in either the ixazomib or placebo arm (HR, 1.136; 95% CI: 0.853–1.514; *P* = 0.382)[3]
- Here we report the final OS analysis for the TOURMALINE-MM4 study

Methods

- Full methods for the phase 3, double-blind, placebo-controlled TOURMALINE-MM4 study have been published previously;[2] the study design is shown in **Figure 2**

Figure 2: Study design[2]



*If a physician chose to start a patient on next-line therapy before PD, the patient skipped the PD follow-up period and entered directly into the PFS2 follow-up period. All disease response and PD assessments were performed according to the International Myeloma Working Group uniform response criteria, version 2011.
CR, complete response; IRC, independent review committee; ISS, International Staging System; PD, progressive disease; PD2, progressive disease on next line of treatment; PFS2, time from the date of randomization to the date of objective PD on next line treatment or death from any cause, whichever occurs first; PR, partial response; TTNT, time to next treatment; VGPR, very good PR

Results

Patients

- At data cutoff (October 29, 2022), 307/425 (72%) patients in the ixazomib arm versus 226/281 (80%) patients in the placebo arm had discontinued study treatment prior to completion of 24 months of therapy, most commonly due to PD (**Table 1**)
- Patient demographics and baseline disease characteristics have been published previously[2]
  - In the ixazomib and placebo arms, respectively, 38% and 39% of patients were aged ≥75 years, 24% and 24% were classified as frail,[4,5,6] and 17% and 17% had high-risk cytogenetic abnormalities [del(17p) and/or t(4;14) and/or t(14;16)][2]

Table 1: Patient disposition

	Ixazomib (n = 425)	Placebo (n = 281)
Completed study regimen, %	28	20
Discontinued study regimen, %	72	80
PD	50	68
AE	12	5
Other	8	4
Withdrawal by subject	2	3
Protocol violation	<1	0
Lost to follow-up	<1	0

AE, adverse event

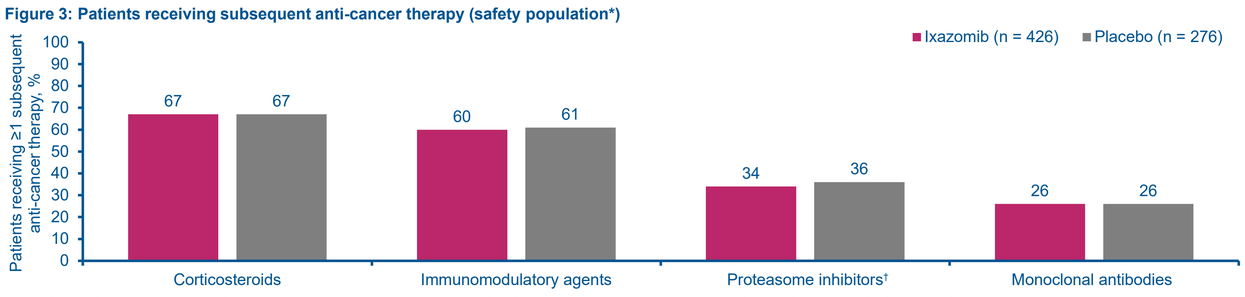
OS

- At data cutoff, median follow-ups were 57 and 58 months for the ixazomib and placebo arms, respectively, and OS events had occurred in 43% and 41% of patients
- Median OS for ixazomib versus placebo was 65 months versus 70 months (HR, 1.090; 95% CI 0.861–1.381); the difference was not statistically significant (**Summary Panel, Figure 1A**)
- In high-risk patient subgroups, there were no significant differences in median OS for ixazomib versus placebo (**Summary Panel, Figure 1B**):
  - Patients aged ≥75 years at randomization: 55 months versus 70 months (HR, 1.317; 95% CI: 0.909–1.909)
  - Frail patients: 56 months versus 44 months (HR, 0.975; 95% CI: 0.613–1.549)
  - Patients with baseline high-risk cytogenetic abnormalities [del(17p) and/or t(4;14) and/or t(14;16)]: 37 months versus 48 months (HR, 1.357; 95% CI: 0.799–2.306)

TTNT, PFS2, and subsequent therapies

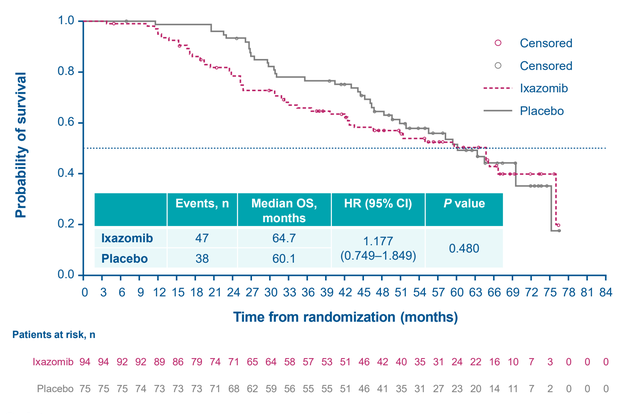
- Median TTNT in the ixazomib arm compared with the placebo arm was 22 months versus 17 months (HR, 0.881; 95% CI: 0.734–1.058)
- Median PFS2 with ixazomib versus placebo was 51 months versus 50 months (HR, 0.984; 95% CI: 0.777–1.246)
- In both treatment arms, 72% of patients received ≥1 subsequent anti-cancer therapy (**Figure 3**)
- For patients who received a PI in their next line of therapy, median OS was 64.7 months versus 60.1 months in the ixazomib versus placebo arms (HR, 1.177; 95% CI: 0.749–1.849) (**Figure 4**)
- For patients whose next line of therapy did not include a PI, median OS was 57.1 months versus 55.1 months in the ixazomib versus placebo arms (HR, 0.928; 95% CI: 0.672–1.283) (**Figure 5**)

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



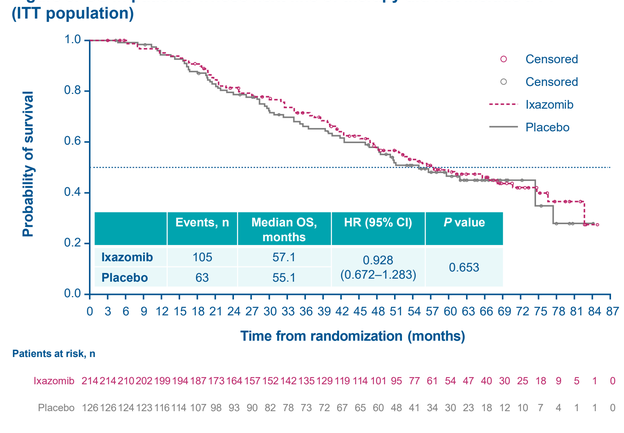
*Two patients in the ixazomib group and two patients in the placebo group never received the study drug and were excluded from the safety population. Three patients assigned to the placebo group erroneously received a single dose of ixazomib and were therefore analyzed as part of the ixazomib group in the safety population. †Patients could receive a proteasome inhibitor as a subsequent anti-cancer therapy regardless of whether they were refractory to ixazomib due to the double-blind nature of this trial.
ITT, intent-to-treat

Figure 4: OS in patients receiving a PI as next-line therapy (ITT population)



	Events, n	Median OS, months	HR (95% CI)	*P* value
Ixazomib	47	64.7	1.177 (0.749–1.849)	0.480
Placebo	38	60.1		

Figure 5: OS in patients whose next line of therapy did not include a PI (ITT population)



	Events, n	Median OS, months	HR (95% CI)	*P* value
Ixazomib	105	57.1	0.928 (0.672–1.283)	0.653
Placebo	63	55.1		

Safety

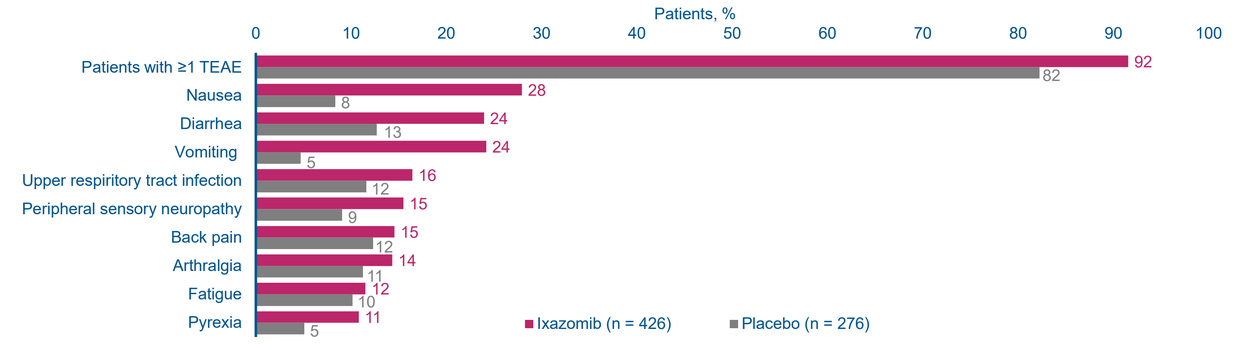
- No new safety signals with ixazomib were identified (**Table 2**)
- For patients receiving ixazomib and placebo, nausea and diarrhea were the most common treatment-emergent adverse events (TEAEs), respectively (**Figure 6**)
- The incidence of new primary malignancies (NPMs) in each treatment arm was 3%, with <1% incidence of hematological NPMs in either arm

Table 2: Overall safety summary (safety population*)

Patients, n (%)	Ixazomib (n = 426)	Placebo (n = 276)
Any TEAE	390 (92)	227 (82)
Grade ≥3	166 (39)	68 (25)
Treatment-related	286 (67)	113 (41)
Treatment-related grade ≥3	78 (18)	12 (4)
SAE	101 (24)	48 (17)
Treatment-related SAE	24 (6)	3 (1)
TEAE resulting in dose modification of ixazomib or placebo†	210 (49)	66 (24)
Resulting in dose reduction	133 (31)	14 (5)
1 reduction	89 (21)	11 (4)
≥2 reductions	44 (10)	3 (1)
Resulting in discontinuation	62 (15)	22 (8)
On-study deaths‡	11 (3)	6 (2)

*Two patients in the ixazomib group and two patients in the placebo group never received the study drug and were excluded from the safety population. Three patients assigned to the placebo group erroneously received a single dose of ixazomib and were therefore analyzed as part of the ixazomib group in the safety population. †Dose modification includes dose reduction, dose delay, and discontinuation of ixazomib or placebo. ‡On-study deaths are defined as deaths that occured within 30 days of the last dose of ixazomib or placebo; on-study deaths were related to MM in 45% and 50% of ixazomib and placebo patients, respectively.
SAE, serious adverse event

Figure 6: TEAEs occurring in ≥10% of patients in either arm (safety population*)



*Two patients in the ixazomib group and two patients in the placebo group never received the study drug and were excluded from the safety population. Three patients assigned to the placebo group erroneously received a single dose of ixazomib and were therefore analyzed as part of the ixazomib group in the safety population. A patient who experienced the same adverse event more than once had that event counted only once within each preferred term.

Conclusions

- Despite meeting its primary endpoint of improved PFS,[2] the final OS analysis for TOURMALINE-MM4 demonstrated no statistically significant difference between ixazomib and placebo
- Additionally, there was no statistically significant difference observed between ixazomib and placebo among high-risk patients (aged ≥75 years, frail status, and high-risk cytogenetics)
- However, showing an OS advantage in myeloma trials is becoming increasingly difficult due to confounding effects of expanding numbers of effective treatment options with novel mechanisms of action for subsequent therapies, and imbalances between treatment arms[7,8,9]
- Due to the double-blind nature of this study, following progression, 34% of patients who received ixazomib received another PI to which they were likely already refractory
- For patients who received a PI as next-line therapy, a slight OS benefit with placebo was observed (HR, 1.177), and for patients whose next line of therapy did not include a PI, a slight OS benefit with ixazomib was observed (HR, 0.928)
- Ixazomib had a tolerable safety profile with no new safety signals observed, and incidence of NPM remained low
- In the appropriate setting, ixazomib could be a viable alternative for non-ASCT NDMM patients who are refractory to common maintenance options such as lenalidomide

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Disclosures

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