The 7th World Congress on CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

IXAZOMIB VERSUS PLACEBO AS MAINTENANCE THERAPY IN TRANSPLANT-INELIGIBLE, NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS DEMONSTRATES PROGRESSION-FREE SURVIVAL BENEFIT AND MAINTAINED QUALITY OF LIFE ACROSS AGE AND FRAILTY SUBGROUPS

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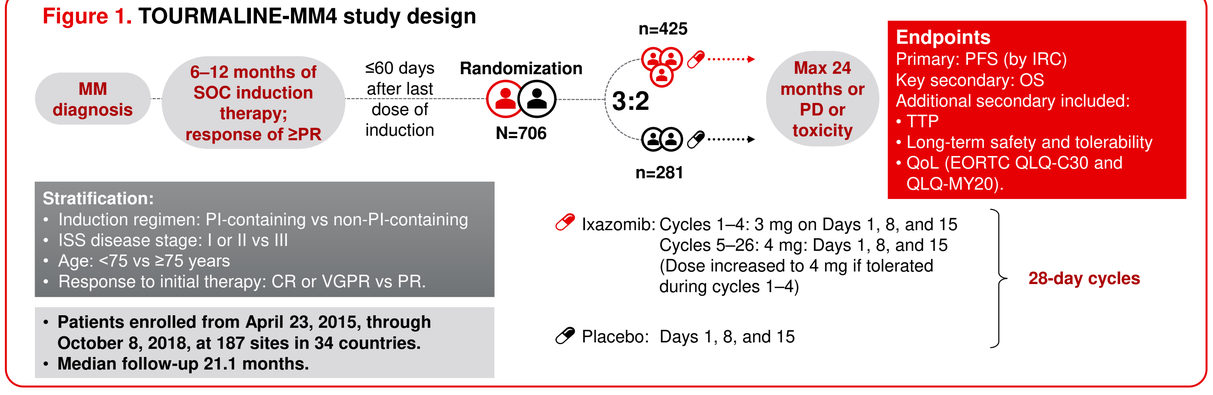
INTRODUCTION AND METHODS

- Maintenance therapy following initial treatment delays disease progression in transplant-ineligible NDMM patients.[1,2]
  - Additional active, well-tolerated treatment options that are suitable for long-term administration are required.[3]
- The Phase 3 TOURMALINE-MM4 trial (NCT02312258) demonstrated that maintenance with the oral PI ixazomib following standard-of-care induction resulted in a statistically significant and clinically meaningful 8-month increase in median PFS vs placebo.[4]
  - The benefits were realized in the context of a well-tolerated safety profile and with no adverse impact on patients' QoL.
- Feasible, tolerable options for long-term therapy are particularly important in this setting, as patients are often elderly and/or frail.
  - The feasibility of long-term PI-based therapy and the convenience of oral administration with ixazomib are valuable attributes, particularly for elderly and frail patients.

TOURMALINE-MM4

- TOURMALINE-MM4 is a multicenter, double-blind, placebo-controlled Phase 3 trial in non-transplant NDMM[4] (**Figure 1**).
- In this subgroup analysis, efficacy and safety were assessed by age (<65, 65–74, and ≥75 years) and frailty per IMWG frailty score[5] (fit, unfit, and frail).
- QoL was assessed using the EORTC QLQ-C30 and QLQ-MY20 instruments.
  - Covariate-adjusted changes in QoL subscales from baseline were estimated at each cycle using repeated measures linear mixed models stratified by age or frailty status.

Figure 1. TOURMALINE-MM4 study design



RESULTS

PATIENTS

- Baseline disease and treatment characteristics were generally balanced across age and frailty subgroups, with the exception of the following numerical differences (**Table 1**):
  - In patients aged <65 years, higher rates of ISS stage III disease, a higher proportion of fit patients, and a lower rate of CR or VGPR post-induction were seen for ixazomib vs placebo
  - Across frailty subgroups for ixazomib vs placebo, a higher rate of ≥VGPR post-induction was seen in fit patients, a lower rate of ISS stage III disease was seen in unfit patients, and a higher rate of ISS stage III disease and a lower rate ≥VGPR post-induction were seen in frail patients
- In each arm, the proportion of unfit and frail patients increased with age.

Table 1. Patients' key characteristics by age and frailty subgroups.

Age subgroup	<65 years		65–74 years		≥75 years	
	Ixazomib (n=39)	Placebo (n=29)	Ixazomib (n=226)	Placebo (n=142)	Ixazomib (n=160)	Placebo (n=110)
% of patients in treatment arm*	9	10	53	51	38	39
Prior PI exposure,† %	82	90	81	80	84	83
ISS stage III at diagnosis,† %	38	31	32	33	38	41
Post-induction ≥VGPR / PR,† %	59 / 41	79 / 21	68 / 32	63 / 37	55 / 45	55 / 45
Fit / Unfit / Frail, %	72 / 26 / 3	55 / 38 / 7	65 / 27 / 8‡	68 / 25 / 7#	0 / 48 / 53	1 / 48 / 51¶
Frailty subgroup	**Fit**		**Unfit**		**Frail**	
	Ixazomib (n=172)	Placebo (n=112)	Ixazomib (n=147)	Placebo (n=98)	Ixazomib (n=102)	Placebo (n=68)
% of patients in treatment arm§	41	40	35	35	24	24
Prior PI exposure,† %	80	79	87	84	80	82
ISS stage III at diagnosis,† %	33	33	35	41	40	34
Post-induction ≥VGPR / PR,† %	67 / 33	60 / 40	63 / 37	62 / 38	53 / 47	65 / 35
Age <65 / 65–74 / ≥75 years,† %	16 / 84 / 0	14 / 85 / 1	7 / 41 / 52	11 / 36 / 53	1 / 17 / 82	3 / 15 / 82

*N=425 for ixazomib, N=281 for placebo. †Randomization stratification factor (age: <75 vs ≥75 years). ‡N=222. #N=140. ¶N=109. §N=421 for ixazomib, N=278 for placebo.

EFFICACY

- PFS benefit with ixazomib vs placebo was seen across age subgroups, with hazard ratios of 0.576 for patients aged <65 years, 0.615 for patients aged 65–74 years, and 0.740 for patients aged ≥75 years (**Figure 2**).
- PFS benefit with ixazomib vs placebo was also seen across frailty subgroups, with hazard ratios of 0.530 for fit patients, 0.746 for unfit patients, and 0.733 for frail patients (**Figure 3**).
- Similar results were obtained for TTP.

Figure 2. PFS from randomization by age subgroup

Age subgroup	Median PFS, months	Events, n / N	HR (95% CI)	p-value
<65 years – Ixazomib	11.0	27 / 39	0.576 (0.299–1.108)	0.095
<65 years – Placebo	9.3	23 / 29		
65–74 years – Ixazomib	17.9	117 / 226	0.615 (0.467–0.810)	<0.001
65–74 years – Placebo	9.3	101 / 142		
≥75 years – Ixazomib	16.7	84 / 160	0.740 (0.537–1.019)	0.064
≥75 years – Placebo	10.2	74 / 110		

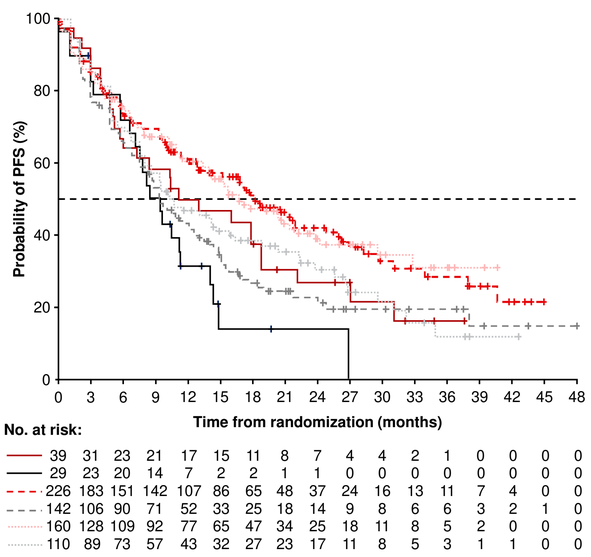
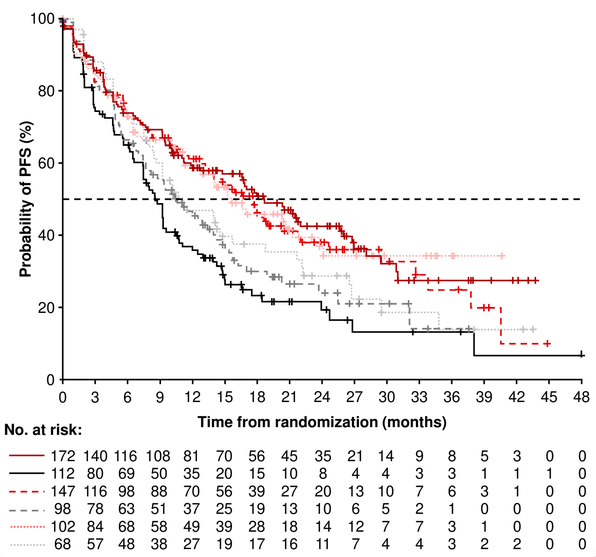


Figure 3. PFS from randomization by frailty subgroup

Frailty subgroup	Median PFS, months	Events, n / N	HR (95% CI)	p-value
Fit – Ixazomib	18.6	91 / 172	0.530 (0.387–0.727)	<0.001
Fit – Placebo	8.5	83 / 112		
Unfit – Ixazomib	17.6	80 / 147	0.746 (0.526–1.058)	0.098
Unfit – Placebo	10.6	67 / 98		
Frail – Ixazomib	15.4	54 / 102	0.733 (0.481–1.117)	0.147
Frail – Placebo	11.1	47 / 68		



RESULTS (CONTINUED)

SAFETY

- Rates of grade ≥3 TEAEs, serious TEAEs, and discontinuation due to TEAEs were higher or similar with ixazomib vs placebo across age (**Figure 4**) and frailty (**Figure 5**) subgroups.
- Rates were generally higher in older age and unfit and frail subgroups in both arms.
- Rates of discontinuation due to TEAEs were <20% across subgroups.

Figure 4. Safety profile by age subgroup

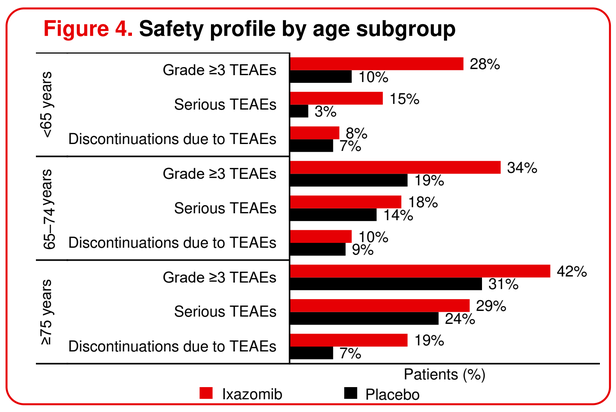
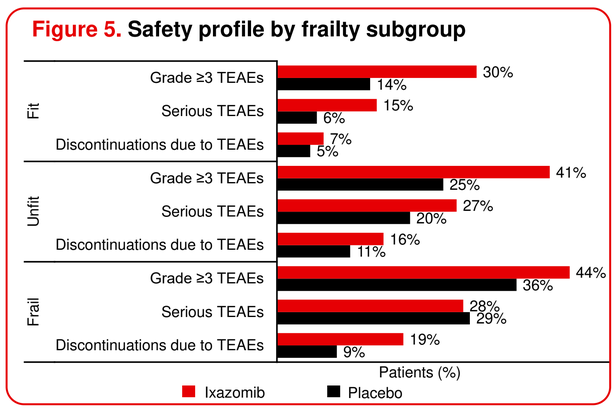


Figure 5. Safety profile by frailty subgroup



- With ixazomib, rates of common gastrointestinal TEAEs were similar across age and frailty subgroups, while rates of rash were similar across frailty subgroups.
- In older and frail patients, liver impairment appeared less common, while peripheral neuropathy was more frequent.

QoL

- Mean covariate-adjusted changes from baseline in the EORTC QLQ-C30 Global Health Status/QoL (**Figure 6**) and QLQ-MY20 Side Effects of Treatment scores (**Figure 7**) were in general <10 points (instrument scale range 0–100; change scale range -100–100) in both treatment arms across frailty subgroups.
  - These results indicate that continued treatment with ixazomib vs placebo maintenance did not adversely affect patients' QoL.
- Analyses by age were generally consistent with the results by frailty for both instruments.

Figure 6. EORTC QLQ-C30 Global Health Status/QoL scores by frailty subgroup

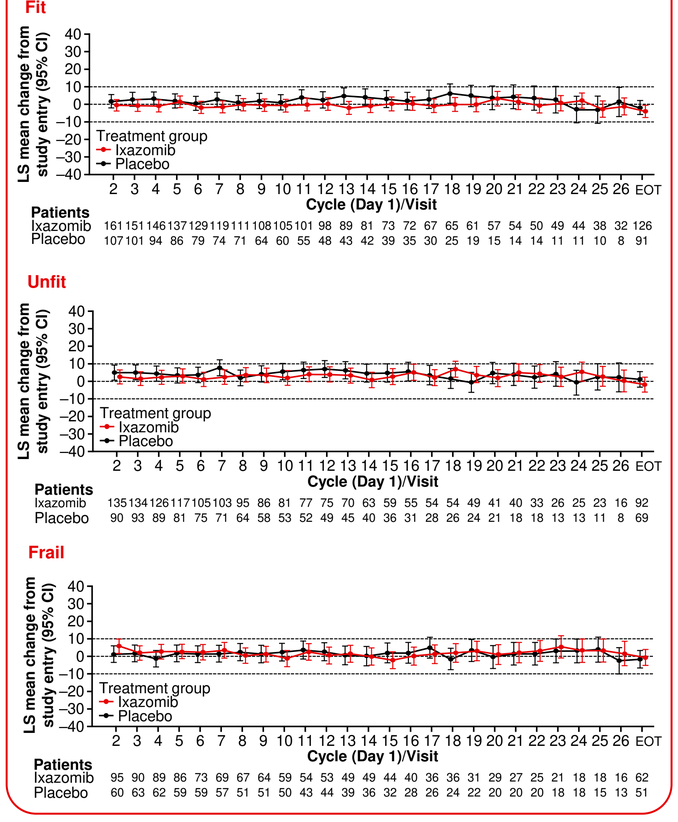
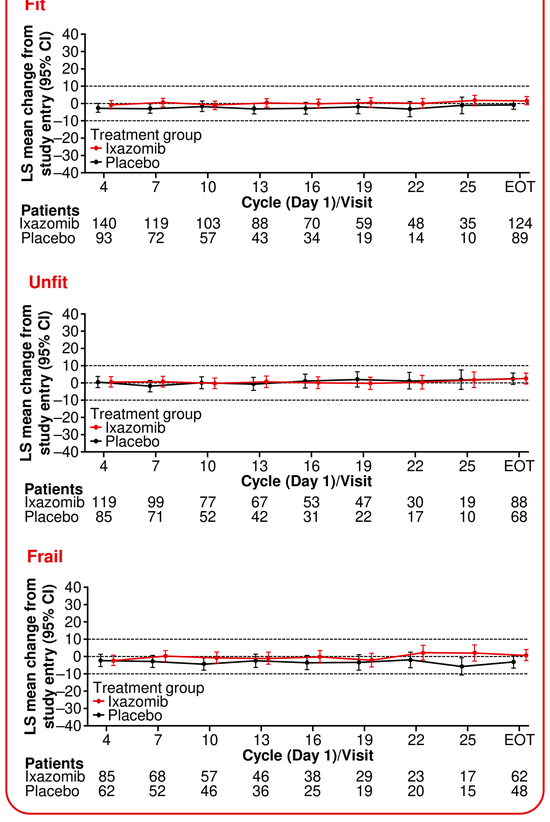


Figure 7. EORTC QLQ-MY20 Side Effects of Treatment scores by frailty subgroup



CONCLUSIONS

- Ixazomib as post-induction maintenance therapy in non-transplant NDMM patients resulted in PFS benefits vs placebo regardless of age or frailty status.
- Ixazomib appeared generally well tolerated across subgroups, with TEAE rates in both arms generally elevated in elderly/frail vs younger/fit patients.
- Maintenance treatment with ixazomib vs placebo did not adversely affect patients' QoL across frailty or age subgroups.
- Ixazomib is a feasible and effective maintenance option for prolonging PFS across this heterogeneous population of transplant-ineligible NDMM patients.

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ABBREVIATIONS

CI, confidence interval; CR, complete response; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; HR, hazard ratio; IMWG, international myeloma working group; IRC, independent review committee; ISS, International Staging System; Max, maximum; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; QLQ-C30, quality of life questionnaire core module 30; QLQ-MY20, quality of life questionnaire multiple myeloma module 20; QoL, quality of life; SOC, standard of care; TEAE, treatment-emergent adverse event; TTP, time to progression; VGPR, very good partial response.

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