Measurable residual disease (MRD) dynamics during maintenance with ixazomib vs placebo in 1280 newly diagnosed multiple myeloma (NDMM) patients: A pooled analysis of the TOURMALINE-MM3 and -MM4 trials

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Background

- MRD is one of the most powerful prognostic factors in multiple myeloma (MM)[1,2]
- There are promising, yet scarce, data on the clinical value of MRD assessment during continuous[3–5] or fixed-duration maintenance therapy[6]
- By contrast, there is virtually no information on patients' MRD status during observation[5]
- Paradoxically, maintenance and observation are the settings where MRD status is anticipated to help tailor treatment duration[7,8]
- Interest is growing in the use of serial assessments to improve risk stratification based on MRD dynamics[9]
  - Patients attaining sustained MRD negativity for ≥1 year show superior outcomes when compared to those with shorter durations of MRD remission[3,4,6,10]

Aim

- To investigate the prognostic value of MRD dynamics over time in patients with NDMM receiving ixazomib or placebo maintenance

Methods

- Full methodologies for TOURMALINE-MM3 and -MM4 have been published previously[11,12]

Study designs

- Randomized, double-blind, placebo-controlled, phase 3 TOURMALINE-MM3 (transplant-eligible patients) and TOURMALINE-MM4 (transplant-ineligible patients) trials of 2-year ixazomib maintenance vs placebo[11,12]

Patients

- Patients were randomized 3:2 to receive maintenance therapy with oral ixazomib 3 mg or matching placebo on days 1, 8, and 15 of 28-day cycles for up to 2 years (26 cycles). The dose was increased to 4 mg from cycle 5 if tolerated during cycles 1–4[11,12]

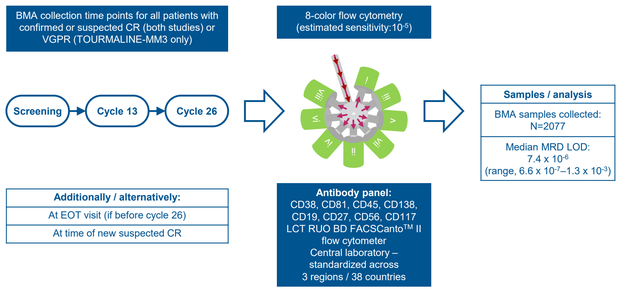
Endpoints

- Primary endpoint: progression-free survival (PFS; progressive disease or death per independent review committee [IRC] evaluation) from randomization
- Pre-specified secondary endpoints included the frequency of conversion from MRD+ to MRD– status, sustained MRD negativity, and the correlation between MRD status and survival[11,12]

MRD assessment

- The details of bone marrow aspirate (BMA) collection time-points and MRD assessment are shown in **Figure 2**

Figure 2: BMA collection and MRD assessment[11,12]



CR, complete response; EOT, end of treatment; LOD, limit of detection; VGPR, very good partial response

Results

Patient disposition

- Of the 1362 patients in this analysis, MRD status was available at randomization in 1280 (94%)
  - Of these, 262 (20%) had undetectable (MRD–) and 1018 (80%) detectable MRD (MRD+)
- Patient disposition according to MRD status, is shown in **Figure 3**

Question

Are MRD dynamics correlated with PFS in patients with NDMM, and is there a PFS benefit with ixazomib vs placebo according to MRD status during maintenance?

Study design

TOURMALINE-MM3 and -MM4: Randomized, double-blind, placebo-controlled, phase 3 trials of 2-year ixazomib maintenance vs placebo

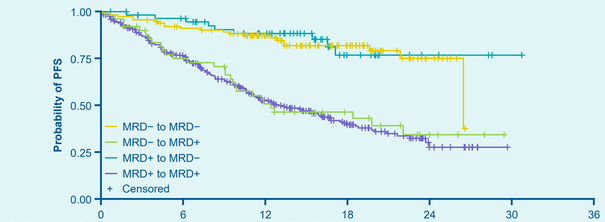
Patients (N=1362): TOURMALINE-MM3: Transplant-eligible (n=656) TOURMALINE-MM4: Transplant-ineligible (n=706)

Primary endpoint: PFS from randomization
Secondary endpoints included: Frequency of conversion from MRD+ to MRD–; sustained MRD– status; correlation between MRD status and PFS

Current analysis (n=1280): PFS based on MRD dynamics over time, landmarked at 14 and 28 months

Results

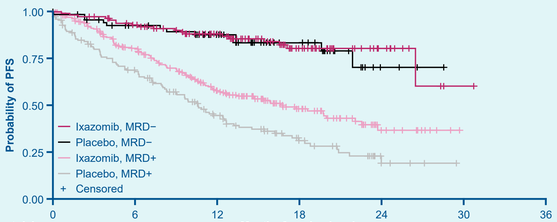
Figure 1A: Landmark analysis of PFS at 14 months based on MRD kinetics, regardless of treatment received



Patients at risk, n

MRD− to MRD−	114	97	70	40	9	0	0
MRD− to MRD+	50	35	23	14	4	0	0
MRD+ to MRD−	58	52	40	14	4	1	0
MRD+ to MRD+	365	241	129	50	10	0	0

Figure 1B: Landmark analysis of PFS at 14 months based on MRD status with ixazomib vs placebo



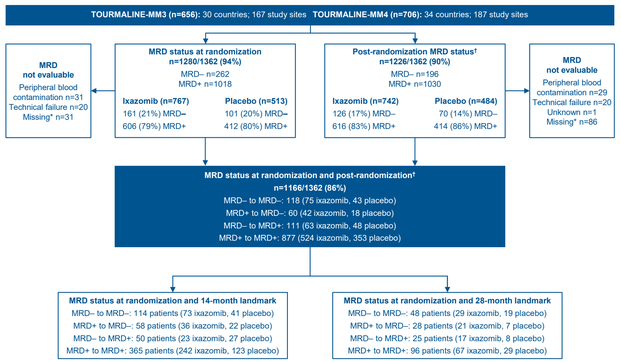
Patients at risk, n

Ixazomib, MRD−	116	102	74	35	11	1	0
Placebo, MRD−	72	58	44	23	3	0	0
Ixazomib, MRD+	274	188	106	46	11	0	0
Placebo, MRD+	155	97	52	22	4	0	0

Key take aways

1) MRD status is dynamic, and its prognostic value increased considerably with periodic vs single assessment; 2) the favorable prognosis of undetectable MRD was similar if achieved before or during maintenance, and thus it can become a relevant endpoint in this setting; 3) loss of MRD– status vs sustained MRD– status markedly increases the risk of progression; 4) patients who lost MRD– status had a poor PFS similar to patients with persistent MRD; and 5) treatment with ixazomib vs placebo improves the PFS in patients who were MRD+ at randomization or at the 14-month landmark in these studies but not in patients who were MRD– at these timepoints, suggesting lower efficacy of maintenance in MRD– patients.

Figure 3: Patient disposition according to MRD status



*Patients with <CR and missing MRD data were imputed as MRD+; ongoing patients in CR and missing MRD data were classified as 'missing'. †Post-randomization is at any time-point from randomization until EOT.

MRD evaluation and patient characteristics

- Patient demographics, except age, were generally well balanced between MRD– vs MRD+ patients (**Table 1**)
  - Of those with MRD– vs MRD+ status at randomization, 90% vs 77% were aged <75 years, which was likely a consequence of the greater MRD– rates observed in patients who received autologous stem cell transplant (MM3) vs those who did not (MM4)
  - There were no notable differences between patients who were MRD– and MRD+ at baseline in terms of pre-induction International Staging System (ISS) stage, cytogenetic risk at diagnosis, or prior treatment

Table 1: Patient demographics and baseline characteristics by MRD status and treatment arm at randomization

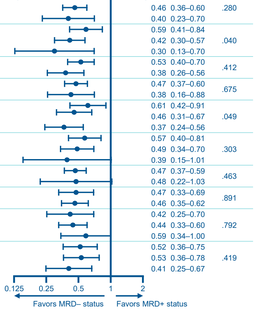
	MRD–			Known MRD+		
	Ixazomib n=820	Placebo n=542	All N=1362	Ixazomib n=820	Placebo n=542	All N=1362
Patients, n	161	101	262	606	412	1018
Age at randomization, n (%)						
<75 years	145 (90.1)	91 (90.1)	236 (90.1)	470 (77.6)	314 (76.2)	784 (77.0)
Sex, n (%)						
Male	94 (58.4)	60 (59.4)	154 (58.8)	352 (58.1)	243 (59.0)	595 (58.4)
Race, n (%)						
White	124 (77.0)	80 (79.2)	204 (77.9)	486 (80.2)	339 (82.3)	825 (81.0)
Asian	30 (18.6)	17 (16.8)	47 (17.9)	83 (13.7)	51 (12.4)	134 (13.2)
Other or not reported	7 (4.3)	4 (4.0)	11 (4.2)	37 (6.1)	22 (5.3)	59 (5.8)
Cytogenetic abnormalities at diagnosis, n (%)*						
High-risk‡	21 (13.0)	27 (26.7)	48 (18.3)	104 (17.2)	70 (17.0)	174 (17.1)
Corresponding standard risk	103 (64.0)	55 (54.5)	158 (60.3)	395 (65.2)	265 (64.3)	660 (64.8)
Unclassifiable	37 (23.0)	19 (18.8)	56 (21.4)	107 (17.7)	77 (18.7)	184 (18.1)
Expanded high-risk‡	42 (26.1)	37 (36.6)	79 (30.2)	204 (33.7)	135 (32.8)	339 (33.3)
Corresponding standard risk	65 (40.4)	35 (34.7)	100 (38.2)	223 (36.8)	149 (36.2)	372 (36.5)
Unclassifiable	54 (33.5)	29 (28.7)	83 (31.7)	179 (29.5)	128 (31.1)	307 (30.2)
Pre-induction ISS stage, n (%)						
I or II	108 (67.1)	69 (68.3)	177 (67.6)	415 (68.5)	277 (67.2)	692 (68.0)
III	53 (32.9)	32 (31.7)	85 (32.4)	191 (31.5)	135 (32.8)	326 (32.0)
PI exposed, n (%)§	145 (90.1)	90 (89.1)	235 (89.7)	511 (84.3)	342 (83.0)	853 (83.8)
IMiD exposed, n (%)¶	64 (39.8)	44 (43.6)	108 (41.2)	208 (34.3)	144 (35.0)	352 (34.6)
Response after transplant / induction, n (%)						
CR or VGPR	153 (95.0)	93 (92.1)	246 (93.9)	370 (61.1)	262 (63.6)	632 (62.1)
PR**	8 (5.0)	8 (7.9)	16 (6.1)	236 (38.9)	150 (36.4)	386 (37.9)

*Cytogenetic assessments were performed locally and interpreted centrally by a board-certified hematopathologist. †Defined as the presence of any of the following 3 individual abnormalities: del(17), t(4;14), t(14;16). ‡Defined as the presence of any of the following 4 individual abnormalities: del(17), t(4;14), t(14;16), amp1q. §Patients who had a prior PI during induction with or without an IMiD; not additive. ¶Patients who had a prior IMiD during induction with or without a PI; not additive. **Patients with PR based on M-protein levels from flow cytometry assay output; patients with PR were not included in the final MRD analyses. IMiD, immunomodulatory drug; PI, proteasome inhibitor; PR, partial response

Prognostic impact of MRD status at randomization

- Median PFS from randomization was reached and differed by 23 months between MRD– vs MRD+ patients: 38.6 vs 15.6 months (hazard ratio [HR] 0.47, 95% confidence interval [CI] 0.37–0.58)
- MRD– status was associated with prolonged PFS vs MRD+ status in nearly all patient subgroups, regardless of demographics, disease features at diagnosis, prior treatment, conventional response, or geographical region of MRD testing
- Univariate analysis of PFS based on IRC assessment is shown in **Figure 4**

Figure 4: Univariate analysis of PFS according to MRD status based on IRC assessment



Variable / subgroup		Events: N / Median PFS, months MRD+	Events: N / Median PFS, months MRD−	HR	95% CI	Interaction p value
All subjects	All (N=1280)	649; 1018 / 15.6	100; 262 / 38.6	0.47	0.37–0.58	
Study	MM3 (n=630)	267; 438 / 21.3	79; 192 / 36.1	0.52	0.40–0.68	.019
	MM4 (n=650)	382; 580 / 11.1	21; 70 / 40.5	0.35	0.22–0.55	
Region	America (n=87)	46; 75 / 14.0	5; 12 / 26.5	0.54	0.14–2.13	
	Europe (n=972)	491; 774 / 15.7	74; 198 / 38.6	0.46	0.36–0.60	.280
	Asia-Pacific (n=221)	112; 169 / 15.7	21; 52 / 35.9	0.40	0.23–0.70	
Age category	<60 years (n=365)	160; 264 / 20.7	43; 101 / NR	0.59	0.41–0.84	
	60–<75 years (n=659)	343; 524 / 14.3	51; 135 / 38.6	0.42	0.30–0.57	.040
	≥75 years (n=256)	146; 230 / 12.9	6; 26 / NR	0.30	0.13–0.70	
Sex	Male (n=749)	388; 595 / 14.7	66; 154 / 33.8	0.53	0.40–0.70	.412
	Female (n=531)	261; 423 / 17.1	34; 108 / 40.5	0.38	0.26–0.56	
Response after transplant / to initial treatment	CR or VGPR (n=878)	369; 632 / 18.8	94; 246 / 38.6	0.47	0.37–0.60	.675
	PR (n=402)	280; 386 / 11.1	6; 16 / NR	0.38	0.16–0.88	
Pre-induction ISS stage	I (n=402)	176; 312 / 20.3	35; 90 / 35.9	0.61	0.42–0.91	
	II (n=467)	256; 380 / 14.2	36; 87 / 36.1	0.46	0.31–0.67	.049
	III (n=411)	217; 326 / 12.5	29; 85 / NR	0.37	0.24–0.56	
Response at study entry	CR (n=347)	94; 195 / 23.1	55; 152 / NR	0.57	0.40–0.81	
	VGPR (n=538)	280; 442 / 17.0	40; 96 / 38.6	0.49	0.34–0.70	.303
	PR (n=395)	275; 381 / 10.7	5; 14 / NR	0.39	0.15–1.01	
Prior PI exposure	Yes (n=1088)	542; 853 / 15.7	89; 235 / 38.6	0.47	0.37–0.59	.463
	No (n=192)	107; 165 / 14.2	11; 27 / NR	0.48	0.22–1.03	
Prior IMiD exposure	Yes (n=460)	229; 352 / 15.1	40; 108 / NR	0.47	0.33–0.69	.891
	No (n=820)	420; 666 / 15.7	60; 154 / 38.6	0.46	0.35–0.62	
Cytogenetics	High-risk (n=222)	132; 174 / 10.8	23; 48 / 27.4	0.42	0.25–0.70	
	Corresponding standard-risk (n=818)	415; 660 / 16.6	56; 158 / NR	0.44	0.33–0.60	.792
	Unclassifiable (n=240)	102; 184 / 18.5	21; 56 / 40.5	0.59	0.34–1.00	
Expanded cytogenetics	Expanded high-risk (n=418)	255; 339 / 11.1	40; 79 / 23.9	0.52	0.36–0.75	
	Corresponding standard-risk (n=472)	215; 372 / 18.5	38; 100 / 36.1	0.53	0.36–0.78	.419
	Unclassifiable (n=390)	179; 307 / 18.4	22; 83 / NR	0.41	0.25–0.67	

Prognostic impact of MRD status at randomization (cont'd)

- Ixazomib maintenance improved PFS vs placebo in patients who were MRD+ at randomization (median 18.8 vs 11.6 months; HR 0.65; p<0.001)
- Pre-induction ISS stage, cytogenetic risk at diagnosis, response at randomization, treatment with ixazomib vs placebo, and MRD status showed independent prognostic value (**Table 2**)

Table 2: Multivariate analyses of PFS in the ITT population* based on IRC assessment

Factor	Parameter estimate (SE)	HR	95% CI	p value
Imputed MRD status at randomization (MRD– vs MRD+)	–2.08 (0.203)	0.13	(0.08–0.19)	<0.001
Prior response after transplant / induction (VGPR or CR vs PR)	–0.47 (0.080)	0.62	(0.53–0.73)	<0.001
Pre-induction ISS stage (I vs III)	–0.41 (0.098)	0.67	(0.55–0.81)	<0.001
Pre-induction ISS stage (II vs III)	–0.13 (0.088)	0.88	(0.74–1.04)	0.136
Cytogenetic group at initial diagnosis (unclassifiable vs standard-risk)	–0.08 (0.106)	0.93	(0.75–1.14)	0.461
Cytogenetic group at initial diagnosis (standard-risk vs high-risk)	–0.35 (0.097)	0.71	(1.17–1.71)	<0.001
Prior exposure to a PI (no vs yes)	–0.12 (0.106)	0.88	(0.92–1.39)	0.245
Treatment assigned at randomization (ixazomib vs placebo)	–0.36 (0.076)	0.70	(0.60–0.81)	<0.001

*Patients in ITT population with non-missing information. ITT, intent-to-treat; SE, standard error

- To address the immortal time-bias, the PFS analyses were landmarked at the end of 14 and 28 months. These landmarks were chosen based on the distribution of evaluable post-treatment MRD samples
- **Figure 1A, Summary Panel** shows dynamic MRD status and risk of progression
  - Median follow up was 16.8, 20.4, 16.1, and 15.2 months in patients with MRD– to MRD–, MRD– to MRD+, MRD+ to MRD–, and MRD+ to MRD+ status, respectively
  - The 14-month landmark analysis demonstrated prolonged PFS in patients converting from MRD+ to MRD– status vs those with persistent MRD+ status (median 16.1 vs 15.2 months; HR 3.72; p<0.001), with 2-year PFS rates of 76.8% vs 27.6%
  - PFS was also prolonged in patients with sustained MRD– status vs those converting from MRD– to MRD+ status (median 16.8 vs 20.4 months; HR 3.31; p<0.001), with 2-year PFS rates of 75.0% vs 34.2%
  - Similar results were noted in the 28-month landmark analysis
- **Figure 1B, Summary Panel** shows the impact of ixazomib maintenance vs placebo in MRD– and MRD+ patients
  - Median follow up was 16.6, 15.2, 14.8, and 17.8 months in patients with MRD– (ixazomib), MRD– (placebo), MRD+ (ixazomib), and MRD+ (placebo) status, respectively
  - Ixazomib maintenance improved PFS vs placebo in patients who were MRD+ at the 14-month landmark (median 16.8 vs 10.6 months; HR 0.65; p=0.003), with 2-year PFS rates of 36.7% vs 19.1%
  - No difference was observed in patients who were MRD–
    - Findings were similar for the 28-month landmark analysis

Conclusions

- This is the largest multiple myeloma dataset ever reported evaluating yearly MRD status during maintenance
- Five main conclusions emerged from this study:
  - MRD status is dynamic, its prognostic value increased considerably with periodic vs single assessment
  - The favorable prognosis for patients with undetectable MRD was similar if achieved before or during maintenance, and thus MRD can become a relevant endpoint in this setting
  - Loss of MRD– status vs sustained MRD– status markedly increased the risk of progression
  - Patients who lost MRD– status had a poor PFS similar to patients with persistent MRD
  - Treatment with ixazomib vs placebo improved the PFS in patients who were MRD+ at randomization or at the 14-month landmark in these studies but not in patients who were MRD– at these timepoints, suggesting lower efficacy of maintenance in MRD– patients

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