Final analysis of the phase 3 TOURMALINE-MM1 study investigating ixazomib + lenalidomide-dexamethasone (Rd) vs placebo-Rd in relapsed and/or refractory multiple myeloma patients

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Background

- An increasing number of treatment options are becoming available for RRMM,[1,2] resulting in marked improvements in OS.[3]
- However, there remains a need for effective and tolerable therapies for:
  - Patients who continue to relapse or are refractory to treatment
  - Hard-to-treat subgroups, e.g., elderly/frail, patients with high disease burden, patients with high-risk cytogenetics.[2]
- PIs are an established backbone of therapy;[1,4] longer- vs shorter-term PI-based therapy may prolong PFS and OS.[5]
  - Longer-term use of parenteral PIs may be limited by treatment burden and the need for clinic/hospital visits.[6,7]
  - Thus, there remains a need for all-oral regimens with manageable toxicity that can delay progression in RRMM patients.

Ixazomib

- Ixazomib, the first oral PI,[8] is approved in combination with Rd for the treatment of MM patients who have received ≥1 prior therapy.[9,10]
  - The phase 3 TOURMALINE-MM1 study demonstrated a statistically significant improvement in PFS with ixazomib-Rd vs placebo-Rd in RRMM patients (median 20.6 vs 14.7 months; HR 0.74; p=0.01), with limited additional toxicity.[11]

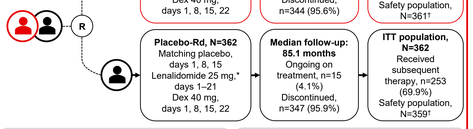
Objective

- Here we report the final analysis for OS in the ITT population of TOURMALINE-MM1 (a key secondary endpoint), and OS in subgroups of interest.

Methods and disposition

- TOURMALINE-MM1 (NCT01564537) was a randomized, double-blind, phase 3 study of ixazomib-Rd vs placebo-Rd in adult patients with RRMM (**Figure 1**).

Figure 1. TOURMALINE-MM1 study design and patient disposition at final OS analysis



Key eligibility criteria:
- RRMM
- Measurable disease
- 1–3 prior therapies
- ECOG PS 0–2

Stratification:
- Prior therapies: 1 vs 2/3
- Prior PI exposure: yes vs no
- ISS disease stage: I/II vs III

Key endpoints	Exploratory ad-hoc analyses
Primary: PFS	Subsequent therapy
Key secondary:	TTNT
OS (ITT, α=0.0462)	OS according to subsequent therapy
OS in patients with del(17p)	

*10 mg for patients with reduced CrCl according to local prescribing information. †Two patients in the ixazomib-Rd arm did not receive treatment and 3 in the placebo-Rd arm erroneously received ≤2 doses of ixazomib and were included in the ixazomib-Rd arm in the safety population.

Results

Patient characteristics

- Patient demographics and baseline characteristics were well balanced between arms (**Table 1**).

Table 1. Key baseline characteristics (ITT population)

Characteristic	Ixazomib-Rd (N=360)	Placebo-Rd (N=362)
Median age, years (range)	66 (38–91)	66 (30–89)
Male, n (%)	207 (58)	202 (56)
White, n (%)	312 (87)	303 (84)
ISS stage I / II / III at study entry, n (%)	226 (63) / 89 (25) / 45 (13)	233 (64) / 86 (24) / 43 (12)
Cytogenetics, n (%)		
High risk – del(17p), t(4;14), t(14;16)	75 (21)	62 (17)
Standard risk	200 (56)	216 (60)
Not available	85 (24)	84 (23)
Expanded high risk – del(17p), t(4;14), t(14;16), amp1q21	155 (43)	154 (43)
1 / 2 / 3 prior therapies, n (%)*	224 (62) / 97 (27) / 39 (11)	217 (60) / 111 (31) / 34 (9)
Prior stem cell transplant, n (%)	212 (59)	199 (55)
Prior PI therapy, n (%)	249 (69)	253 (70)
Prior bortezomib	248 (69)	250 (69)
Prior IMiD therapy, n (%)	193 (54)	204 (56)

*Number of prior therapies determined by the sponsor in a blinded medical review of data.

Final OS analysis: ITT population

- After a median follow-up for OS of 85 months:
  - 484 (67%) patients had died
  - 229 (32%) were alive at last OS follow-up.
- Median OS was 53.6 vs 51.6 months with ixazomib-Rd vs placebo-Rd (**summary panel**).
- OS was not statistically significantly different between arms (HR 0.939, p=0.495).
- On two prespecified sensitivity analyses for OS, to adjust for the confounding effect of subsequent therapies (MSM and IPCW methods), HRs were 0.68 and 0.70, respectively.

Final OS analysis: Prespecified subgroups

- Lower HRs, indicating a larger magnitude of OS benefit with ixazomib-Rd vs placebo-Rd, were seen in various prespecified subgroups of patients with adverse-risk characteristics as shown in **Figure 2** (patients with high-risk cytogenetics) and **Figure 3** (shaded subgroups plus patients with del(17p) [HR 0.916; data not shown in figure]).
- OS benefit was also seen in patients with standard-risk cytogenetics (**Figure 3**).

QUESTION

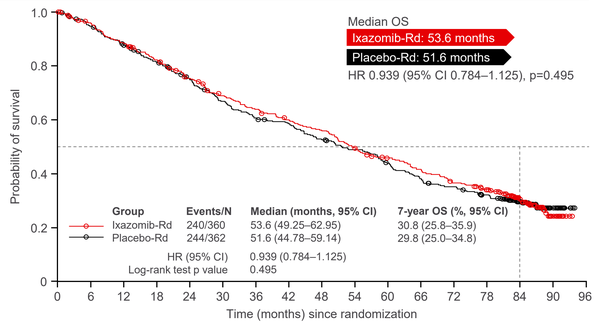
Does the significant improvement seen in PFS with ixazomib-Rd vs placebo-Rd in patients with RRMM after 1–3 prior therapies translate into an OS benefit?

INVESTIGATION

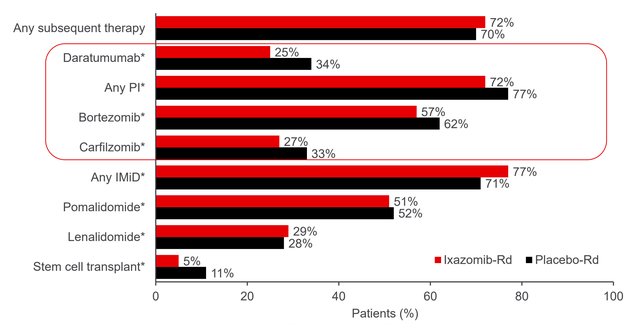
Randomization (1:1) N=722 → Stratified by prior PI exposure; ISS disease stage; lines of prior therapy → Ixazomib-Rd (N=360) / Placebo-Rd (N=362) → Treat in 28-day cycles until PD or unacceptable toxicity

RESULTS

Key secondary endpoint: OS



Exploratory ad-hoc analysis: Any subsequent therapy

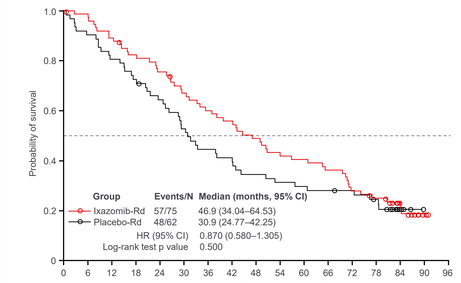


*Number of patients with ≥1 subsequent therapy (ixazomib-Rd, n=259; placebo-Rd, n=251) used as the denominator for percentages.

CONCLUSIONS

The slight OS trend in favor of ixazomib-Rd in the ITT population was not statistically significant, but OS interpretation was confounded by imbalances between arms in subsequent therapies

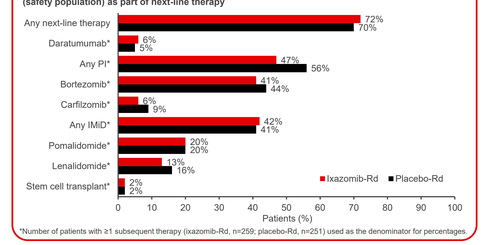
Figure 2. OS with ixazomib-Rd vs placebo-Rd in patients with high-risk cytogenetics



Exploratory ad-hoc analysis: Next-line and subsequent therapy

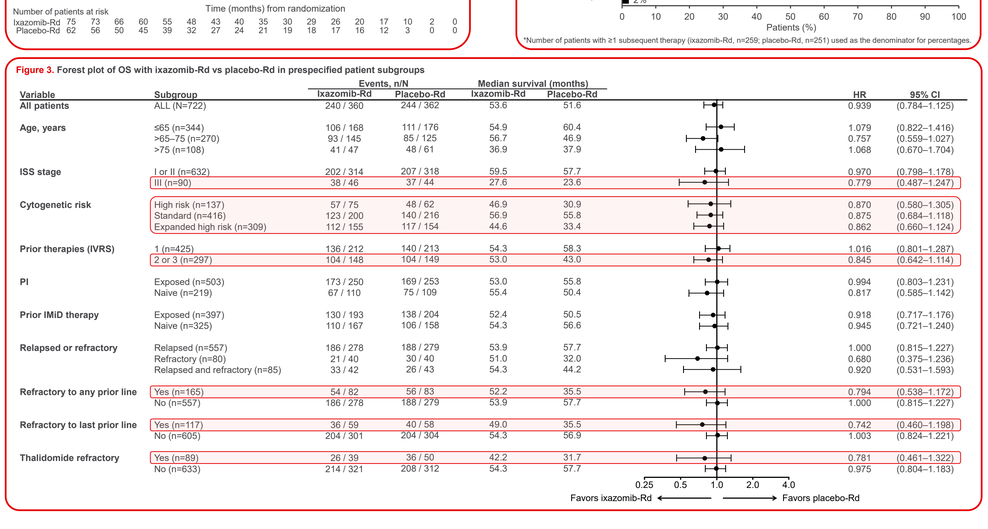
- Median TTNT (ITT population) was 29.7 and 26.9 months in the ixazomib-Rd and placebo-Rd arms, respectively (HR 0.917).
  - 72% and 70% of patients, respectively, received subsequent therapy.
- There were imbalances between groups in subsequent therapies received; patients progressed earlier on placebo-Rd (shorter PFS/TTP)[11], received a higher number of subsequent therapies than those on ixazomib-Rd (median 3 vs 2), and received subsequent PIs, daratumumab, and other treatments more frequently (**summary panel** and **Figure 4**).

Figure 4. Subsequent therapies received by patients in the ixazomib-Rd and placebo-Rd groups (safety population) as part of next-line therapy



*Number of patients with ≥1 subsequent therapy (ixazomib-Rd, n=259; placebo-Rd, n=251) used as the denominator for percentages.

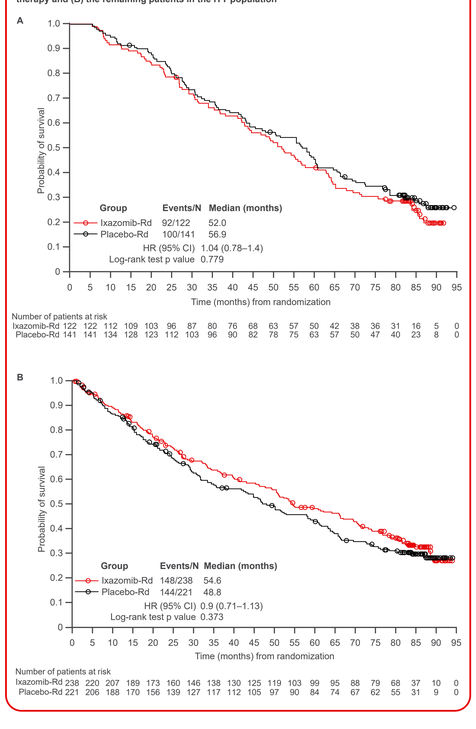
Figure 3. Forest plot of OS with ixazomib-Rd vs placebo-Rd in prespecified patient subgroups



Exploratory ad-hoc analysis: OS according to subsequent therapy

- Patients in the ixazomib-Rd vs placebo-Rd arms received subsequent daratumumab less frequently and later in the course of the study.
  - Among patients receiving daratumumab in any subsequent line, median OS was 78.9 vs 83.4 months (HR 1.15); in those not receiving subsequent daratumumab, median OS was 49.2 vs 35.5 months (HR 0.83).
- A similar differential OS benefit was seen between patients who received a PI as next-line therapy and those who did not (**Figure 5**).

Figure 5. OS with ixazomib-Rd vs placebo-Rd in (A) patients who received a PI-based next-line therapy and (B) the remaining patients in the ITT population



- The double-blind nature of TOURMALINE-MM1 confounded OS interpretation.
- Choice of next-line therapy was affected by blinding (**Table 2**).
  - Similar proportions of patients who remained blinded received next-line PI-based and non-PI-based therapy in both arms.
  - In the small number of patients unblinded at PD, PI-based therapy was less likely to be selected following ixazomib-Rd vs placebo-Rd.
- Next-line PI-based therapy was potentially less effective in patients progressing on ixazomib-Rd vs placebo-Rd.

Table 2. Next-line therapy received following ixazomib-Rd and placebo-Rd according to whether patients were unblinded or not

Blinding status at next-line therapy	Ixazomib-Rd (N=257)	Placebo-Rd (N=253)
Patients remaining blinded, n	236	216
PI-based next-line therapy, n (%)	117 (50)	111 (51)
Non-PI-based next-line therapy, n (%)	119 (50)	105 (49)
Patients who were unblinded, n	21	37
PI-based next-line therapy, n (%)	5 (24)	30 (81)
Non-PI-based next-line therapy, n (%)	16 (76)	7 (19)

Treatment exposure, safety, and QoL

- Patients received a median of 18 (range 1–99) and 16 (range 1–100) cycles of ixazomib-Rd and placebo-Rd, respectively.
- No new or additional safety concerns were evident during the 7-year follow-up period, beyond those reported previously.[11,12]
- The rate of new primary malignancies was similar in both arms: ixazomib-Rd 10%, placebo-Rd 12%.
- There were no apparent differences in QoL measures between arms; addition of ixazomib to Rd did not negatively impact patients' QoL.
- Approximately half the patients in each arm reported ≥10-point (MID) increases in the EORTC QLQ-C30 GHS/QoL domain over the course of treatment: ixazomib-Rd 49%, placebo-Rd 52%.

Conclusions

- This final analysis of TOURMALINE-MM1, after a median follow-up of >7 years, reports the longest median OS data seen to date in phase 3 studies of Rd-based combinations in RRMM.[13–16]
  - Median OS approached 4.5 years in both arms.
- Although the slight trend (OS HR 0.939) in favor of ixazomib-Rd in the ITT population was not statistically significant, greater magnitudes of OS benefit (lower HRs) were seen in prespecified subgroups with adverse prognostic factors, including high-risk cytogenetics.
- OS interpretation was confounded by the double-blind nature of the study and by imbalances between arms in subsequent therapies, including extensive use of PIs and daratumumab.
  - Prespecified sensitivity analyses for OS, to adjust for the impact of subsequent therapies, resulted in HRs (0.68, 0.70) supportive of a more substantial OS benefit with ixazomib-Rd.
- The evolving treatment landscape has increased OS for RRMM patients,[1–3] but the availability of multiple active salvage therapies may limit the ability to demonstrate an OS benefit in clinical trials in early-relapse RRMM.
- These findings show that ixazomib-Rd continues to represent an important option for patients with RRMM.
- **These findings are now published in the *Journal of Clinical Oncology*.**
  - **The paper is freely available via the following link: https://ascopubs.org/doi/abs/10.1200/JCO.21.00972**

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Abbreviations

CI, confidence interval; CrCl, creatinine clearance; Dex, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organization for the Research and Treatment of Cancer; GHS, Global Health Status; HR, hazard ratio; IMiD, immunomodulatory drug; IPCW, inverse probability of censoring weighted; ISS, International Staging System; ITT, intention-to-treat; IVRS, interactive voice response system (randomization stratification); MID, minimal important difference; MM, multiple myeloma; MSM, marginal structural models; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; QLQ-C30, Quality of Life Questionnaire Core-30; QoL, quality of life; Rd, lenalidomide-dexamethasone; RRMM, relapsed/refractory MM; TTNT, time to next therapy; TTP, time to progression.

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