Impact of prior therapy on the efficacy and safety of oral ixazomib-lenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma in TOURMALINE-MM1

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ABSTRACT

Prior treatment exposure in patients with relapsed/refractory multiple myeloma may affect outcomes with subsequent therapies. We analyzed efficacy and safety according to prior treatment in the phase 3 TOURMALINE-MM1 study of ixazomib-lenalidomide-dexamethasone (ixazomib-Rd) versus placebo-Rd. Patients with relapsed/refractory multiple myeloma received ixazomib-Rd or placebo-Rd. Efficacy and safety were evaluated in subgroups defined according to type (proteasome inhibitor [PI] and immunomodulatory drug) and number (1 vs. 2 or 3) of prior therapies received. Of 722 patients, 503 (70%) had received a prior PI, and 397 (55%) prior lenalidomide/thalidomide; 425 patients had received 1 prior therapy, and 297 received 2 or 3 prior therapies. At a median follow up of ~15 months, PFS was prolonged with ixazomib-Rd vs. placebo-Rd regardless of type of prior therapy received; HR 0.739 and 0.749 in PI-exposed and –naïve patients, HR 0.744 and 0.700 in immunomodulatory-drug-exposed and -naïve patients, respectively. PFS benefit with ixazomib-Rd vs. placebo-Rd appeared greater in patients with 2 or 3 prior therapies (HR 0.58) and in those with 1 prior therapy without prior transplant (HR 0.60) versus those with 1 prior therapy and transplant (HR 1.23). Across all subgroups, toxicity was consistent with that seen in the intent-to-treat population. In patients with relapsed/refractory multiple myeloma, ixazomib-Rd was associated with a consistent clinical benefit vs. placebo-Rd regardless of prior treatment with bortezomib or immunomodulatory drugs. Patients with 2 or 3 prior therapies, or 1 prior therapy without transplant seemed to have greater benefit than patients with 1 prior therapy and transplant. TOURMALINE-MM1 registered at clinicaltrials.gov identifier: 01564537.

Introduction

Novel agents such as proteasome inhibitors (PIs) and immunomodulatory drugs have revolutionized multiple myeloma (MM) treatment, with significant improvements in overall survival (OS) evident over the past 15 years.1-8 Despite the use of
These novel agents, MM follows a relapsing course, with many patients receiving multiple lines of therapy and ultimately becoming refractory to some agents, possibly due to the development and selection of increasingly treatment-resistant clones.\(^7\) Long-term outcomes, including progression-free survival (PFS) and OS, also become progressively shorter with increasing number of prior therapies,\(^8,9,10\) as rates of medical comorbidities and complications increase.\(^12\) Prior therapies are therefore often considered when selecting a therapy at relapse, with prior therapies shown to affect the outcomes of subsequent lines of treatment. For example, outcomes for thalidomide-exposed patients have been shown to be worse than for thalidomide-naive patients following treatment with bortezomib\(^13\) and with lenalidomide-dexamethasone.\(^15\)

Until 2012, bortezomib was the only PI available so subsequent treatment with other drugs of the same class was not possible outside of a clinical trial. However, treatment with bortezomib has been shown to be effective\(^14-17\) and, following the introduction of carfilzomib, the feasibility of retreatment with a different agent of the same class and with a similar mechanism of action has been demonstrated.\(^17\) Similarly, for the immunomodulatory drugs, lenalidomide plus dexamethasone improved responses, time to progression (TTP), and PFS compared with dexamethasone alone in patients with or without prior thalidomide exposure.\(^15\)

The phase 3, randomized, placebo-controlled, double-blind TOURMALINE-MM1 study in 722 patients with relapsed/refractory MM (RRMM) demonstrated a significant 35% improvement in PFS with the all-oral combination of ixazomib plus lenalidomide-dexamethasone (Rd) compared with placebo-Rd (median PFS 20.6 vs. 14.7 months; hazard ratio 0.74; P=0.01).\(^18\) On the basis of these data, ixazomib, in combination with lenalidomide and dexamethasone (ixazomib-Rd), was approved in 2015 by the US Food and Drug Administration, and in 2016 by the European Medicines Agency, for the treatment of patients with MM who have received at least one prior line of therapy. Given the widespread use of PIs and immunomodulatory drugs as first-line therapy, it is important to determine their impact on the overall and relative efficacy of new agents for the treatment of RRMM. The TOURMALINE-MM1 study included patients with prior exposure to PIs and the immunomodulatory drugs thalidomide and lenalidomide, and patients with and without prior transplant. Here we present a subgroup analysis of efficacy and safety data for ixazomib-Rd compared with placebo-Rd according to the number and type of prior therapies received.

### Methods

#### Study design and participants

Adult patients with measurable relapsed, refractory, or relapsed and refractory MM who had received 1-3 prior lines of therapy were eligible. Full eligibility criteria have been reported previously.\(^18\) Patients who had received prior PI- and thalidomide/lenalidomide (thal/R)-based regimens were eligible, as were primary refractory patients and patients refractory to thalidomide; patients who were refractory to prior PI- or lenalidomide-based therapy were not eligible. Study endpoints have been reported previously.\(^18\) The primary endpoint was PFS as assessed by a blinded independent review committee (IRC). The study was performed in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and appropriate regulatory requirements, and with approval of Institutional Review Boards at individual enrolling institutions. All patients provided written informed consent. A total of 722 patients were randomized 1:1 to receive oral ixazomib 4 mg (ixazomib-Rd arm, N=360) or placebo (placebo-Rd arm, N=362) on days 1, 8, and 15 of 28-day cycles, with oral lenalidomide 25 mg on days 1–21 and oral dexamethasone 40 mg on days 1, 8, 15 and 22, until disease progression or unacceptable toxicity. Stratification factors were number of prior therapies per investigator assessment (1 vs. 2 or 3), International Staging System disease stage (I or II vs. III), and prior thal/R exposure or thalidomide-refractoriness. A prior line of therapy was defined as 1 or more cycles of a planned treatment program, as determined by the investigator. Overall patient baseline demographics and disease characteristics were well balanced between ixazomib-Rd and placebo-Rd arms.\(^16\) Responses were assessed per International Myeloma Working Group 2011 criteria\(^19\) every cycle until disease progression, using a central laboratory. Adverse events (AEs) were assessed per National Cancer Institute’s Common Terminology Criteria for Adverse Events version 4.03 during treatment and until 30 days after the last dose of study medication was administered.

#### Analyses by prior treatment exposure

Subgroup analyses were performed for efficacy and safety outcomes relative to type of prior regimen. Patient subgroups were defined according to prior exposure to the PIs bortezomib and carfilzomib, and the immunomodulatory drugs lenalidomide and thalidomide. Outcomes were also assessed according to number of prior lines of therapy (1 vs. 2/3, per study stratification) and, within those subgroups, according to components of prior therapies, including transplant.

#### Statistical analysis

At a pre-planned analysis (median follow up of ~15 months), the study met the primary endpoint of a significant PFS benefit

| Prior therapy type, n (%) | Ixazomib-Rd (N=360) | Placebo-Rd (N=362) |
|--------------------------|----------------------|---------------------|
| PI naïve                 | 110 (31)             | 109 (30)            |
| Bortezomib naïve         | 112 (31)             | 112 (31)            |
| Pl exposed               | 250 (69)             | 253 (70)            |
| Bortezomib exposed       | 248 (69)             | 250 (69)            |
| Carfilzomib exposed      | 1 (<1)               | 4 (1)               |
| Immunomodulatory drug naïve | 167 (46)       | 158 (44)            |
| Thalidomide naïve        | 203 (56)             | 192 (53)            |
| Lenalidomide naïve       | 316 (88)             | 318 (88)            |
| Immunomodulatory drug exposed | 193 (54)      | 204 (56)            |
| Thalidomide exposed      | 137 (44)             | 170 (47)            |
| Lenalidomide exposed     | 44 (12)              | 44 (12)             |
| Thalidomide refractory   | 40 (11)              | 49 (14)             |

Pl: proteasome inhibitor; Rd: lenalidomide-dexamethasone.
with ixazomib-Rd vs placebo-Rd. Consistent with the statistical methodology, this was therefore the final statistical analysis for PFS. Per protocol, the study continued in a double-blind, placebo-controlled manner to gain more mature OS data; a second preplanned analysis (median follow up of ~23 months) was conducted for safety and survival. Time-to-event distributions were estimated using Kaplan-Meier methodology, with stratified log-rank tests and Cox models (alpha=0.05, two-sided) used for comparisons of time-to-event endpoints. A stratified Cochrans-Mantel-Haenszel $\chi^2$ test was used to assess inter-arm differences in response rates. The subgroup analyses were not powered for formal statistical testing.

**Results**

**Patients**

Of the 722 patients in the ITT population, 70% had received a prior PI (250 [69%] in the ixazomib arm, and 253 [70%] in the placebo arm). The majority of PI-exposed patients had received bortezomib (1 patient in the ixazomib arm and 4 patients in the placebo arm had received prior carfilzomib). Over half (55%) had received prior thalidomide or lenalidomide (193 [54%] in the ixazomib arm and 204 [56%] in the placebo arm) (Table 1). Of these, in the ixazomib and placebo arms, respectively, 157 (44%) and 170 (47%) patients had received prior thalidomide, and 44 (12%) and 44 (12%) patients had received prior lenalidomide; there was no prior pomalidomide therapy. A total of 425 patients had received 1 prior therapy (212 in the ixazomib arm and 213 in the placebo arm) and 297 had received 2 or 3 prior therapies (148 in the ixazomib arm and 149 in the placebo arm).

**Efficacy according to type of prior therapies received**

At a median follow up of ~15 months (14.8 months in the ixazomib-Rd group and 14.6 months in the placebo-Rd group), there was a clinical benefit in terms of pro-

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**Table 1.** Forest plot of progression-free survival (PFS) according to number and type of prior therapies (A), and forest plot of PFS according to type of prior therapy in patients who have received 1 versus 2 or 3 prior therapies (B). CI: confidence interval; HR: hazard ratio; PI: proteasome inhibitor; Rd: lenalidomide-dexamethasone.

**Figure 1.** Forest plot of progression-free survival (PFS) according to number and type of prior therapies (A), and forest plot of PFS according to type of prior therapy in patients who have received 1 versus 2 or 3 prior therapies (B). CI: confidence interval; HR: hazard ratio; PI: proteasome inhibitor; Rd: lenalidomide-dexamethasone.
longed PFS with ixazomib-Rd vs. placebo-Rd regardless of prior therapy received (Figure 1A, Figure 2); median PFS was 18.4 vs. 13.6 months (HR 0.74) in PI-exposed patients, not reached vs. 15.7 months (HR 0.749) in PI-naïve patients, not reached vs. 17.5 months (HR 0.744) in thal/R-exposed, and 20.6 vs. 13.6 months (HR 0.70) in thal/R-naïve patients. PFS was also prolonged with ixazomib-Rd versus placebo-Rd in patients refractory to thalidomide (HR 0.726; median PFS 16.6 vs. 13.0 months).

TTP was also longer with ixazomib-Rd than placebo-Rd regardless of type of prior therapy received. When analyzed by prior PI exposure, median TTP with ixazomib-Rd vs. placebo-Rd was 18.5 vs. 13.9 months (HR 0.702, 95% CI 0.526, 0.936) in PI-exposed patients, and not estimable vs. 17.5 months (HR 0.741, 95% CI 0.456, 1.203) in PI-naïve patients (Figure 3). For immunomodulatory drug exposure, median TTP was not estimable vs. 18.3 months (HR 0.727, 95% CI 0.515, 1.026) in exposed patients, and 20.6 vs. 13.6 months (HR 0.651, 95% CI 0.449, 0.945) in naïve patients.

Overall response rates (ORR) with ixazomib-Rd and placebo-Rd appeared generally similar across most subgroups (PI-naïve: 81% vs. 74%; PI-exposed: 77% vs. 70%; thal/R-naïve: 80% vs. 77%; R-naïve: 78% vs. 73%; Table 2) but were slightly lower in thalidomide-refractory patients (70% vs. 57%). Complete response plus very good partial response (CR+VGPR) rates with ixazomib-Rd vs. placebo-Rd by patient subgroup are shown in Table 2;

Figure 2. Kaplan-Meier analysis of progression-free survival (PFS) with ixazomib-Rd vs. placebo-Rd according to prior therapy. (A) PI-exposed patients; (B) PI-naïve patients; (C) immunomodulatory drug-exposed patients; (D) immunomodulatory drug-naïve patients; (E) patients with 1 prior therapy; (F) patients with 2/3 prior therapies. CI: confidence interval; Rd: lenalidomide-dexamethasone.
again, there was a consistent benefit with ixazomib-Rd vs. placebo-Rd.

**Efficacy according to number of prior therapies**

The benefit of ixazomib-Rd vs. placebo-Rd was seen when assessed by number of prior therapies, with prolonged PFS and TTP and improved response rates seen with ixazomib-Rd versus placebo-Rd in patients with 1 prior therapy and in those with 2 or 3 prior therapies (Figures 1A and 2, Table 2). However, the benefit seemed less pronounced in patients with 1 prior therapy versus those with 2 or 3 prior therapies: the hazard ratio for PFS was 0.88 (95% CI: 0.65–1.20) vs. 0.58 (95% CI: 0.40–0.84) in patients with 1 vs. 2 or 3 prior therapies, respectively, and the hazard ratio for TTP was 0.842 (95% CI 0.614, 1.156) vs. 0.550 (95% CI 0.370, 0.819) in patients with 1 vs. 2 or 3 prior therapies, respectively (Figures 1A and 3).

To investigate this further, PFS was analyzed in patients with 1 prior therapy and patients with 2 or 3 prior therapies according to type of prior therapy received and other clinical characteristics (Figure 1B). In patients with 2 or 3 prior therapies, the PFS benefit was consistent across all subgroups, regardless of type of prior therapy received or cytogenetic risk status. In patients with 1 prior therapy, the magnitude of PFS benefit was consistent regardless of prior exposure to PI or immunomodulatory drugs (HR ~0.7 across all subgroups; Figure 1A), but was greater in patients with high-risk cytogenetics (HR for PFS 0.64 vs. 0.81 for those with standard-risk cytogenetics) and those who did not have a prior transplant (HR for PFS 0.60 vs. 1.23 for those who did have a prior transplant) (Figure 1B).

**Safety**

Of the 722 patients randomized, 720 received at least one dose of study drug and were included in the safety population (ixazomib-Rd N=361, placebo-Rd N=359). Per the primary study report, safety data are reported from a pre-specified analysis at a median follow up of approximately 23 months. Rates of all-grade AEs, grade ≥3 AEs, and serious AEs for the overall population and by patient subgroup are shown in Table 3. Rates of all-grade AEs, grade ≥3 AEs, and serious AEs for the overall population and by patient subgroup are shown in Table 3. Rates of all-grade AEs, grade ≥3 AEs, and serious AEs for the overall population and by patient subgroup are shown in Table 3. Rates of all-grade AEs, grade ≥3 AEs, and serious AEs for the overall population and by patient subgroup are shown in Table 3. Rates of all-grade AEs, grade ≥3 AEs, and serious AEs for the overall population and by patient subgroup are shown in Table 3. Rates of all-grade AEs, grade ≥3 AEs, and serious AEs for the overall population and by patient subgroup are shown in Table 3. Rates of all-grade AEs, grade ≥3 AEs, and serious AEs for the overall population and by patient subgroup are shown in Table 3. Rates of all-grade AEs, grade ≥3 AEs, and serious AEs for the overall population and by patient subgroup are shown in Table 3. Rates of all-grade AEs, grade ≥3 AEs, and serious AEs for the overall population and by patient subgroup are shown in Table 3.

### Table 2. Response with ixazomib-Rd vs. placebo-Rd by type and number of prior therapies.

|                | ORR (N=360) | Placebo-Rd (N=362) | ≥VGPR (N=360) | Placebo-Rd (N=362) | ≥CR (N=360) | Placebo-Rd (N=362) |
|----------------|-------------|--------------------|--------------|--------------------|-------------|--------------------|
| Overall population | 282 (78)    | 259 (72)           | 173 (48)     | 141 (39)           | 42 (12)     | 24 (7)             |
| Prior PI Exposed | 193/250 (77) | 178/253 (70)       | 114/250 (46) | 101/253 (40)       | 22/250 (9)  | 15/253 (6)         |
| Naive           | 89/110 (81) | 81/109 (74)        | 59/110 (54)  | 40/109 (37)        | 20/110 (18) | 9/109 (8)          |
| Prior immunomodulatory drug Exposed | 148/193 (77) | 137/204 (67)       | 87/193 (45)  | 71/204 (35)        | 22/193 (11) | 13/204 (6)         |
| Naive           | 133/167 (80) | 122/158 (77)       | 86/167 (51)  | 70/158 (44)        | 20/167 (12) | 11/158 (7)         |
| Prior thalidomide Exposed | 122/157 (78) | 114/167 (67)       | 73/157 (46)  | 58/167 (34)        | 20/157 (13) | 10/167 (6)         |
| Naive           | 160/203 (79) | 145/192 (76)       | 100/203 (49) | 83/192 (43)        | 22/203 (11) | 14/192 (7)         |
| Prior lenalidomide Exposed | 34/44 (77)   | 26/44 (59)         | 20/44 (45)   | 16/44 (36)         | 4/44 (9)    | 3/44 (7)           |
| Naive           | 248/316 (78) | 233/313 (73)       | 153/316 (48) | 125/313 (39)       | 38/316 (12) | 21/313 (7)         |
| Thalidomide-refractory Yes | 28/40 (70)    | 28/49 (57)         | 12/40 (30)   | 13/49 (27)         | 2/40 (5)    | 2/49 (4)           |
| No              | 254/320 (79) | 231/313 (74)       | 161/320 (50) | 128/313 (41)       | 40/320 (13) | 22/313 (7)         |
| Number of prior therapies 1 | 163/212 (77) | 159/213 (75)       | 95/212 (45)  | 93/213 (44)        | 19/212 (9)  | 17/213 (8)         |
| 2 or 3         | 119/148 (80) | 100/149 (67)       | 78/148 (53)  | 48/149 (32)        | 23/148 (16) | 7/149 (5)          |

CR: complete response; ORR: overall response rate; PI: proteasome inhibitor; Rd: lenalidomide-dexamethasone; VGPR: very good partial response.

### Table 3. Overall summary of adverse events (AEs) according to number and type of prior therapies.

| n / N (%) | All-grade AEs | Grade ≥3 AEs | Serious AEs | On-study deaths |
|-----------|---------------|--------------|-------------|-----------------|
|           | ixazomib-Rd   | Placebo-Rd   | ixazomib-Rd | Placebo-Rd |
| Overall population | 355/361 (98) | 357/359 (99) | 267/361 (74) | 247/359 (69) |
| PI-naive | 108/109 (99)  | 109/109 (100) | 86/109 (79) | 72/109 (66) |
| PI-exposed | 247/252 (98) | 248/250 (99) | 181/252 (72) | 175/250 (70) |
| Immuno-modulatory drug-naive | 161/166 (97) | 156/158 (99) | 125/166 (75) | 112/158 (71) |
| Immuno-modulatory drug-exposed | 194/195 (99) | 201/201 (100) | 142/195 (73) | 135/201 (67) |
| 1 prior therapy | 208/212 (98) | 209/211 (99) | 153/212 (72) | 134/211 (64) |
| 2-3 prior therapies | 147/149 (99) | 148/148 (100) | 114/149 (71) | 113/149 (76) |

PI: proteasome inhibitor; Rd: lenalidomide-dexamethasone; VGPR: very good partial response.
grade ≥3 AEs, and serious AEs by patient subgroup were largely consistent with those seen for the overall population, the only exception being slightly higher rates of grade ≥3 AEs and serious AEs with placebo-Rd in patients with 2-3 prior therapies (76% and 56%, vs. 69% and 49% in the overall population, respectively).

Rates of AEs of clinical interest, including neutropenia, thrombocytopenia, peripheral neuropathy, rash, diarrhea, nausea, and vomiting, are shown in Table 4; common grade ≥3 AEs are shown in Online Supplementary Table S1. Rates of AEs were largely consistent across patient subgroups (Online Supplementary Table S1).

Across patient subgroups, the incidence of peripheral neuropathy, a known side effect of the first-in-class PI bortezomib, was largely consistent with the overall population (27% vs. 22% for ixazomib-Rd vs. placebo-Rd), including in PI-naïve (29% vs. 23%) and PI-exposed (26% vs. 21%) patients. Rates of grade ≥3 peripheral neuropathy with ixazomib-Rd vs. placebo-Rd were also similar across patient subgroups: 5% vs. <1% of PI-naïve, 2% vs. 2% of PI-exposed, 1% vs. 3% of immunomodulatory drug-naïve, 4% vs. <1% of immunomodulatory drug-exposed patients, 2% vs. 2% of patients with 1 prior therapy, and 3% vs. 1% of patients with 2-3 prior therapies (Online Supplementary Table S1). As with the overall population, the incidence of cardiac, thrombocytopenia, and renal failure toxicities were consistently low and similar in both treatment groups regardless of prior therapy (Table 4).

Discussion

This subgroup analysis demonstrated that, as with the overall TOURMALINE-MM1 study population,20 the addition of ixazomib to Rd was associated with prolonged PFS versus placebo-Rd across the patient subgroups analyzed, regardless of prior bortezomib or immunomodulatory drug exposure or number of prior therapies received. This PFS benefit was accompanied by improved response rates and a prolonged TTP versus placebo-Rd across all prior therapy subgroups. Reflecting the findings in the overall study population, the addition of ixazomib to lenalidomide-dexamethasone was consistently associated with limited additional toxicity regardless of prior therapy subgroup.18 These efficacy and safety data are particularly important given both the widespread use of PIIs and immunomodulatory drugs as front-line therapy in MM and the relapsing nature of the disease.20

Retreatment with bortezomib has previously been shown to be feasible,14-17 as has the benefit of carfilzomib-dexamethasone in patients with prior bortezomib exposure.21 However, the median PFS with carfilzomib-dexamethasone in bortezomib-exposed patients was less than that in bortezomib-naïve patients (15.6 months vs. not estimable), suggesting some effect of prior PI exposure on the efficacy of carfilzomib-dexamethasone.22 In the present study, ixazomib-Rd was associated with prolonged PFS and TTP and improved response rates vs. placebo-Rd in bortezomib-naïve and –exposed patients. Median PFS with ixazomib-Rd appeared longer in bortezomib-naïve vs. bortezomib-exposed patients (not estimable vs. 18.5 months), but the associated hazard ratios vs. placebo-Rd were similar (0.746 vs. 0.747), suggesting a similar PFS benefit with ixazomib-Rd in bortezomib-naïve and -exposed patients. Although no conclusions can be drawn regarding patients refractory to bortezomib, these similar hazard ratios also suggest that the adverse impact of prior bortezomib exposure on PFS and OS seen in a previous study of Rd22 may not be the case when ixazomib is added to the Rd regimen.

The clinical benefit of ixazomib-Rd versus placebo-Rd was also consistent regardless of prior exposure to immunomodulatory drugs. Ixazomib-Rd was associated with prolonged PFS vs. placebo-Rd in both immunomodulatory drug-naïve and –exposed patients (with HR of approximately 0.7 for both subgroups). Although only 12% of patients in each arm had received prior lenalidomide, ixazomib-Rd was associated with a clinical benefit versus placebo-Rd in patients with prior lenalidomide exposure (median PFS, not estimable vs. 17.5 months; HR 0.582), highlighting the benefit of adding a drug with a different mechanism of action for these patients. Of note, the clinical benefit of ixazomib-Rd was also seen in thalidomide-refractory patients; as lenalidomide-refractory patients were not eligible for the study, no conclusions can be drawn regarding these patients.

Patients with MM who have received multiple prior

| Variable                | Subgroup       | Median TTP, months (events/n) | HR 95% CI |
|-------------------------|----------------|-------------------------------|----------|
| Overall population      | All (N=722)    | 21.4 (114/360)               | 0.712 (0.556, 0.912) |
| Prior PI                | Exposed (n=503)| 18.5 (84/250)                 | 0.702 (0.528, 0.938) |
|                         | Naïve (n=219)  | NE (30/110)                   | 0.741 (0.456, 1.203) |
| Prior bortezomib        | Exposed (n=498)| 18.7 (84/248)                 | 0.702 (0.525, 0.938) |
|                         | Naïve (n=224)  | NE (30/112)                   | 0.764 (0.465, 1.254) |
| Prior immunomodulatory  | Exposed (n=397)| 18.3 (70/204)                 | 0.727 (0.515, 1.028) |
| drug                     | Naïve (n=235)  | 20.6 (53/167)                 | 0.651 (0.449, 0.945) |
| Thalidomide refractory   | Yes (n=89)     | 16.6 (14/49)                  | 0.794 (0.394, 1.598) |
|                          | No (n=633)     | 21.4 (100/220)                | 0.712 (0.545, 1.209) |
| Prior therapies          | 1 (n=425)      | 20.6 (73/213)                 | 0.842 (0.614, 1.156) |
|                          | 2 or 3 (n=297)| 16.6 (84/213)                 | 0.550 (0.370, 0.819) |

Favors Ixazomib-Rd  
Favors Placebo-Rd  
CI: confidence interval; PI: proteasome inhibitor; Rd: lenalidomide-dexamethasone.
therapies are a particularly difficult-to-treat population, with patient outcomes becoming progressively worse with increasing prior therapies.6,9,20 This may be in part due to clonal evolution, with multiple rounds of treatment with different agents exerting selection pressure on mutant plasma cells, leading to both the development of increasingly treatment-resistant clones and the re-emergence of original clones not completely suppressed.11 It is therefore important that effective and tolerable treatments are available for this heterogeneous patient population. Importantly, ixazomib-Rd was associated with a particular clinical benefit vs. placebo-Rd in patients with multiple prior therapies (HR 0.580; median PFS not estimable with ixazomib-Rd vs. 12.9 months with placebo-Rd), and this

Table 4. Adverse events (AEs) of clinical interest according to number and type of prior therapies.

| Common AEs of clinical interest | Overall population | PI-naive | PI-exposed | Immuno-modulatory drug-naive | Immuno-modulatory drug-exposed | 1 prior therapy | 2-3 prior therapies |
|---------------------------------|--------------------|----------|------------|-----------------------------|-------------------------------|----------------|------------------|
| Neutropenia*                   |                    |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 118/361 (33)       | 39/109 (36) | 79/252 (31) | 52/166 (31)                 | 66/195 (34)                  | 62/212 (29)   | 41/149 (28)      |
| Placebo-Rd                    | 115/359 (31)       | 31/109 (28) | 80/250 (32) | 46/158 (29)                 | 63/201 (32)                  | 53/211 (25)   | 39/148 (26)      |
| Thrombocytopenia†              |                    |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 112/361 (31)       | 37/109 (34) | 75/252 (30) | 49/166 (30)                 | 63/195 (32)                  | 49/212 (23)   | 37/149 (25)      |
| Placebo-Rd                    | 57/359 (16)        | 13/109 (12) | 44/250 (18) | 31/158 (20)                 | 26/201 (13)                  | 21/211 (10)   | 20/148 (14)      |
| Peripheral neuropathy‡         |                    |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 97/361 (27)        | 32/109 (29) | 65/252 (26) | 40/166 (24)                 | 57/195 (29)                  | 61/212 (29)   | 36/149 (24)      |
| Placebo-Rd                    | 78/359 (22)        | 25/109 (23) | 53/250 (21) | 30/158 (19)                 | 48/201 (24)                  | 44/211 (21)   | 34/148 (23)      |
| Diarrhea                      |                    |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 164/361 (45)       | 53/109 (49) | 111/252 (44) | 74/166 (45) | 90/195 (46)                  | 96/212 (45) | 68/149 (46)      |
| Placebo-Rd                    | 139/359 (39)       | 47/109 (43) | 92/250 (37) | 56/158 (35) | 83/201 (41)                  | 92/211 (44) | 47/148 (32)      |
| Rash‡                         |                    |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 72/361 (20)        | 25/109 (23) | 47/252 (19) | 33/166 (20) | 39/195 (20)                  | 34/212 (16) | 38/149 (26)      |
| Placebo-Rd                    | 45/359 (13)        | 13/109 (12) | 32/250 (13) | 23/158 (15) | 22/201 (11)                  | 28/211 (13) | 17/148 (11)      |
| Nausea                        |                    |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 104/361 (29)       | 29/109 (27) | 75/252 (30) | 46/166 (28) | 58/195 (30) | 53/212 (25) | 51/149 (34) |
| Placebo-Rd                    | 79/359 (22)        | 24/109 (22) | 55/250 (22) | 29/158 (18) | 50/201 (25) | 45/211 (21) | 34/148 (23) |
| Vomiting                      |                    |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 84/361 (23)        | 20/109 (18) | 64/252 (25) | 42/166 (25) | 42/195 (22) | 47/212 (22) | 37/149 (25) |
| Placebo-Rd                    | 42/359 (12)        | 12/109 (11) | 80/250 (12) | 20/158 (15) | 22/201 (11) | 21/211 (10) | 21/148 (14) |
| Other AEs of clinical interest |                    |          |            |                             |                               |                |                  |
| Acute renal failure*           |                    |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 31/361 (9)         | 9/109 (8) | 22/252 (9) | 17/166 (10) | 14/195 (7) | 5/212 (2) | 4/149 (3) |
| Placebo-Rd                    | 41/359 (11)        | 10/109 (9) | 31/250 (12) | 18/158 (11) | 23/201 (11) | 8/211 (4) | 6/148 (4) |
| Venous embolic and thrombotic events* |                  |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 29/361 (8)         | 10/109 (9) | 19/252 (8) | 16/166 (10) | 13/195 (7) | 17/212 (8) | 12/149 (8) |
| Placebo-Rd                    | 38/359 (11)        | 11/109 (10) | 27/250 (11) | 19/158 (12) | 19/201 (9) | 22/211 (10) | 16/148 (11) |
| Heart failure*                |                    |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 16/361 (4)         | 8/109 (7) | 8/252 (3) | 7/166 (4) | 9/195 (5) | 12/212 (6) | 4/149 (3) |
| Placebo-Rd                    | 14/359 (4)         | 3/109 (3) | 11/250(4) | 6/158 (4) | 8/201 (4) | 7/211 (3) | 7/148 (5) |
| Myocardial infarction*         |                    |          |            |                             |                               |                |                  |
| Ixazomib-Rd                   | 5/361 (1)          | 3/109 (3) | 2/252 (<1) | 1/166 (<1) | 4/195 (2) | 5/212 (2) | 0 |
| Placebo-Rd                    | 8/359 (2)          | 3/109 (3) | 5/250 (2) | 4/158 (3) | 4/201 (2) | 3/211 (1) | 5/211 (3) |

*Data based upon standardized MedDRA query, including neutropenia and neutrophil count decreased. †Data based upon standardized MedDRA query, including thrombocytopenia and platelet count decreased. ‡High-level term including peripheral neuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, and peripheral motor neuropathy. High-level term including acute febrile neutrophilic dermatosis, acriform dermatitis, allergic dermatitis, drug eruption, erythema multiforme, exfoliative rash, interstitial granulomatous dermatitis, pruritus, generalised pruritus, purpura, rash, erythematous rash, follicular rash, generalised rash, macular rash, maculo-papular rash, maculovesicular rash, morbilliform rash, papular rash, pruritic rash, papular rash, vesicular rash, red man syndrome, Stevens-Johnson syndrome, Toxic epidermal necrolysis, urticaaria, urticarial papular, and vasculitic rash. §Data based upon standardized MedDRA query, incorporating pooled preferred terms, or multiple preferred terms. PI, proteasome inhibitor. Rd, lenalidomide-dexamethasone.
was seen regardless of the type of prior therapies received. While there was a clinical benefit with ixazomib-Rd vs. placebo-Rd in patients with 1 prior therapy, the magnitude of benefit appeared reduced when compared to that in patients with multiple prior therapies (HR vs. placebo-Rd 0.88). These results appear to differ from those seen with carfilzomib-Rd versus Rd alone, in which there was a consistent benefit in patients with 1 prior therapy and in those with ≥2 prior therapies (HR 0.694 and 0.688). The further analysis of patients with 1 prior therapy in TOURMALINE-MM1 suggests this difference may, in part, be driven by effects in the subgroup of patients with prior transplant (HR 1.232, vs. 0.604 in those with no prior transplant). Across other subgroups of patients with 1 prior therapy there was a clear PFS benefit with ixazomib-Rd vs. placebo-Rd, including those with high-risk cytogenetics. One possibility suggested by preliminary findings is that tumors relapsed post-transplant may have a distinct biology with a less differentiated phenotype and lower expression of c-myc. The benefit (HR 0.44) in patients with no prior transplant but prior melphalan-containing therapy suggests that the difference is not driven by prior alkylator therapy but possibly due to the transplant itself or, although speculative, due to the myeloablative dose of melphalan administered before the transplant. Several published data have previously suggested a link between c-myc levels and the sensitivity to proteasome inhibitors. Immumomodulatory drugs and proteasome inhibitors appear to target different clones (less versus more differentiated phenotypes, respectively), which might explain in part their synergistic action and the increased benefit observed with ixazomib-Rd. As the study was not powered to detect a statistical difference between the subgroups, and the transplant vs. non-transplant analysis was retrospective and post-hoc rather than a prespecified subgroup analysis, this finding is hypothesis-generating and further investigations to characterize the tumor biology are ongoing.

As seen in the overall population, the addition of ixazomib was associated with limited additional toxicity when compared with placebo-Rd across all patient subgroups. Overall, the safety profile of ixazomib-Rd was similar regardless of number and type of prior therapies and was consistent with that reported for the overall patient population. Rates of all-grade AEs, grade ≥3 AEs and SAEs were similar between subgroups and were aligned with the rates seen in the overall study population. Peripheral neuropathy and the hematologic AEs neutropenia and thrombocytopenia are known side effects of PIs. There were no consistent differences in all-grade or grade ≥3 AEs in patients with 1 or 2-3 prior therapies. This is in contrast to results with carfilzomib-dexamethasone, where rates of AEs were generally higher in patients with 2-3 prior therapies vs. 1 prior therapy.

There are a number of limitations associated with subgroup analyses of this type. The subgroup analyses were not powered for formal statistical testing, some were not prespecified, and analyses did not use a multivariate approach, hence there may be confounding factors, such as an imbalance between some subgroups in terms of other prognostic factors. In conclusion, ixazomib plus lenalidomide-dexamethasone demonstrated a clear PFS, TTP, and response rate benefit compared to lenalidomide-dexamethasone alone, with limited additional toxicity, in patients with RRMM, regardless of prior therapy received. The findings in patients with 1 prior therapy and transplant are hypothesis-generating and further investigations are ongoing. Together, these findings support the results from the primary analysis of TOURMALINE-MM1, further demonstrating that the all-oral regimen of ixazomib, lenalidomide, and dexamethasone represents an effective and tolerable treatment option for patients with RRMM.

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References
1. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood. 2008;111(5):2521-2526.
2. Kastritis E, Zervas K, Symeonidis A, et al. Improved survival of patients with multiple myeloma after the introduction of new agents and the applicability of the International Staging System (ISS): an analysis of the Greek Myeloma Study Group (GMSG). Leukemia. 2009;23(6):1152-1157.
3. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Bjorkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1975 to 2003. J Clin Oncol. 2007;25(15):1993-1999.
4. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28(8):1122-1128.
5. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516-2520.
6. Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc. 2004;79(7):867-874.
7. Brioli A, Melchor L, Cavo M, Morgan GJ. The impact of intra-clonal heterogeneity on the treatment of multiple myeloma. Br J Haematol. 2014;165(4):441-454.
8. Jagannath S, Roy A, Kish J, et al. Real-world treatment patterns and associated progression-free survival in relapsed/refractory multiple myeloma among US community oncology practices. Expert Rev Hematol. 2016;9(7):707-717.
9. Kumar SK, Lee JH, Labuerba JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia. 2012;26(1):149-157.
10. San Miguel J, Weinkel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-008): a randomized, open-label, phase 3 trial. Lancet Oncol. 2015;16(14):1055-1066.
11. Willenbacher E, Weger B, Rochau U, Siebert U, Willenbacher W. Real-world use of 3rd line therapy for multiple myeloma in Austria: an Austrian Myeloma Registry
(AMR) analysis of the therapeutic landscape and clinical outcomes prior to the use of next generation myeloma therapeutics. PLoS One. 2016;11(5):e0147381.

12. Vogl DT, Stadtmueller EA, Richardson PG, et al. Impact of prior therapies on the relative efficacy of bortezomib compared with dexamethasone in patients with relapsed/refractory multiple myeloma. Br J Haematol. 2009;147(4):531-534.

13. Wang M, Dimopoulos MA, Chen C, et al. Lenalidomide plus dexamethasone is more effective than dexamethasone alone in patients with relapsed or refractory multiple myeloma regardless of prior thalidomide exposure. Blood. 2008;112(12):4445-4451.

14. Conner TM, Doan QD, Walters JB, LeBlanc AL, Beveridge RA. An observational, retrospective analysis of retreatment with bortezomib for multiple myeloma. Clin Lymphoma Myeloma. 2008;8(3):140-145.

15. Oriol A, Giraldo P, Kotsianidis I, et al. Efficacy and safety of bortezomib-based retreatment at the first relapse in multiple myeloma patients: A retrospective study. Hematology. 2015;20(7):405-409.

16. Petrucci MT, Giraldo P, Corradini P, et al. A prospective, international phase 2 study of bortezomib retreatment in patients with relapsed multiple myeloma. Br J Haematol. 2013;160(5):649-659.

17. Wolf J, Richardson PG, Schuster M, LeBlanc A, Walters JB, Battlemen DS. Utility of bortezomib retreatment in relapsed or refractory multiple myeloma patients: a multicenter case series. Clin Adv Hematol Oncol. 2008;6(10):755-760.

18. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;374(17):1621-1634.

19. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.

20. Sonneveld P, Brojil A. Treatment of relapsed and refractory multiple myeloma. Haematologica. 2016;101(4):596-406.

21. Moreau P, Joshua D, Chung WJ, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. Leukemia. 2016;31(1):115-122.

22. Avet-Loiseau H, Soulier J, Fermand JP, et al. Impact of high-risk cytogenetics and prior therapy on outcomes in patients with advanced relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone. Leukemia. 2010;24(5):623-628.

23. Dimopoulos MA, Stewart AK, Rajkumar SV, et al. Effect of carfilzomib, lenalidomide, and dexamethasone (KRd) vs lenalidomide and dexamethasone (Rd) in patients with relapsed multiple myeloma (RMM) by line of therapy: Secondary analysis from an interim analysis of the phase III study ASPIRE (NCT01080391). J Clin Oncol. 2015;33(15_suppl):abstract 8525.

24. Di Bacco A, Bahlis NJ, Munshi NC, et al. Higher c-MYC expression is associated with ixazomib-lenalidomide-dexamethasone (IRd) progression-free survival (PFS) benefit versus placebo-Rd: biomarker analysis of the phase 3 tournamé-MM1 study in relapsed/refractory multiple myeloma (RMM). Blood. 2016;128(22):abstract 245.

25. Chen S, Blank JL, Peters T, et al. Genomewide siRNA screen for modulators of cell death induced by proteasome inhibitor bortezomib. Cancer Res. 2010;70(11):4318-4326.

26. Chung WJ, Gertz MA, Chung TH, et al. Correlation between array-comparative genomic hybridization-defined genomic gains and losses and survival: identification of 1p31-32 deletion as a prognostic factor in myeloma. Leukemia. 2010;24(4):833-842.

27. Ravi D, Beheshti A, Abermil N, et al. Proteasomal inhibition by ixazomib induces CHK1 and MYC-dependent cell death in T-cell and Hodgkin lymphoma. Cancer Res. 2016;76(11):3319-333.