Management of adverse events associated with ixazomib plus lenalidomide/dexamethasone in relapsed/refractory multiple myeloma

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Summary

The oral proteasome inhibitor ixazomib is approved in the United States, European Union and other countries, in combination with oral lenalido-mide and dexamethasone (Rd), for the treatment of patients with multiple myeloma who have received at least one prior therapy. Approval was based on the global, randomised, double-blind, placebo-controlled Phase III TOURMALINE-MM1 study of ixazomib-Rd (IRd) versus placebo-Rd in patients with relapsed/refractory multiple myeloma. IRd resulted in a significant improvement in progression-free survival versus placebo-Rd (median: 20·6 vs. 14·7 months; hazard ratio 0·74). Common toxicities observed more commonly with IRd versus placebo-Rd were thrombocy-topenia, nausea, vomiting, diarrhoea, constipation, rash, peripheral neu-ropathy, peripheral oedema and back pain; these were generally grade 1/2 in severity except for thrombocytopenia (19% vs. 9% grade 3/4), which appeared manageable and reversible, with no differences between arms in significant bleeding or dose discontinuations. No cumulative toxicities were observed, indicating the potential feasibility of long-term IRd treatment. Safety data from TOURMALINE-MM1 are reviewed and guidance for managing clinically relevant adverse events associated with IRd is provided. Most toxicities were manageable with supportive care and dose delays or reductions as needed. Clinicians should be aware of and understand these potential side effects to optimise and prolong patient benefit.

Keywords: multiple myeloma, ixazomib, toxicity, proteasome inhibitor, dosing.

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Treatment options available for patients with newly diagnosed and relapsed/refractory multiple myeloma (RRMM) have increased over the past decade, resulting in improved outcomes (Kumar et al, 2014a; Moreau & Touzeau, 2015; Cornell & Kassim, 2016). Combinations of proteasome inhibitors (PIs) and immunomodulatory drugs are among the most effective regimens, but historically, the parenteral route of PI administration and their associated toxicities have limited duration of therapy (Rajkumar, 2012; Moreau & Touzeau, 2015). Ixazomib is the first oral PI to enter the clinic (Kumar et al, 2014b, 2015a; Richardson et al, 2014). Phase I/II results for the combination of ixazomib, lenalidomide and dexamethasone (IRd) demonstrated encouraging efficacy with this all-oral PI/immunomodulatory drug-based regimen and showed the feasibility of long-term therapy (Kumar et al, 2014c,d), providing support for the subsequent pivotal Phase III study.

Ixazomib was approved, in combination with lenalidomide and dexamethasone, by the United States Food and Drug Administration in 2015, Health Canada in 2016, and the European Commission in 2016, as well as in other countries worldwide, for the treatment of patients with MM who have received at least one prior therapy (http://www.ninlaro.com/downloads/prescribing-information.pdf), based on outcomes from the TOURMALINE-MM1 trial. TOURMALINE-MM1 was a global, randomised, double blind, placebo-controlled Phase III clinical study of IRd versus placebo plus lenalidomide and dexamethasone (placebo-Rd) in adult patients with RRMM (Moreau et al, 2016). Progression-free survival (PFS) was significantly improved with IRd versus placebo-Rd (median: 20·6 vs. 14·7 months; hazard ratio 0·74; $P = 0·012$) at a median follow-up of ~15 months; overall survival (OS) data were not mature at a subsequent analysis with a median follow-up of ~23 months (Moreau et al, 2016). Herein we perform an in-depth analysis of the adverse events (AEs) associated with IRd at the 23-month analysis, and review AE management with a view to delivering optimal therapeutic outcomes.

Methods

TOURMALINE-MM1 (NCT01564537) has been previously reported (Moreau et al, 2016). Briefly, adult RRMM patients who had received 1–3 prior therapies were eligible. Patients were excluded if refractory to PI or lenalidomide, had failed to recover (grade ≤1 toxicity) from effects of prior chemotherapy (except alopecia), had peripheral neuropathy (PN) of grade 1 with pain or grade ≥2 or evidence of uncontrolled cardiovascular conditions.

Patients were randomised 1:1 to receive oral ixazomib 4 mg ($n = 360$) or matching placebo ($n = 362$) on days 1, 8 and 15, plus oral lenalidomide 25 mg on days 1–21 (dose reduced for renal impairment per local prescribing information) and oral dexamethasone 40 mg on days 1, 8, 15 and 22, in 28-day cycles. The primary endpoint was PFS; key secondary endpoints were OS and OS in patients with del(17).

Information regarding toxicity was graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Attribution of toxicities to one or more drugs was at the investigator's discretion. Drug doses were omitted for significant attributable toxicity and could be restarted with dose reductions, once the toxicity resolved, per protocol. Ixazomib (or placebo, in this double-blind study) dose was reduced to 3 mg, 2·3 mg and then discontinued for persistent toxicity. Lenalidomide dose was reduced to 15 mg, 10 mg, 5 mg and then discontinued if toxicities did not resolve or recurred. Dexamethasone dose-reduction steps included 20 mg, 12 mg and 4 mg, followed by discontinuation. Patients completed quality-of-life (QoL) questionnaires at pre-specified intervals.

Blood samples (3 ml) were collected on day 1 of cycle 2 for measurement of ixazomib trough plasma concentrations, using a validated liquid chromatography/tandem mass spectrometry assay (Gupta et al, 2016a). Graphical analyses were used to evaluate exposure-safety relationships. Observed proportions of AEs were defined as the number of events/number of observations and were plotted for each exposure (C_{trough}) quartile. Three haematological AEs (anaemia, neutropenia, thrombocytopenia) and six non-haematological AEs (diarrhoea, fatigue, nausea, PN, rash, vomiting) were analysed. The dependent variable was the presence or absence of an AE during the study, specifically grade ≥3 events for haematological AEs and grade ≥2 events for non-haematological AEs.

Results

A total of 722 patients were enrolled (Figure S1); baseline demographic and disease characteristics were well balanced between groups (Moreau et al, 2016). With a median follow-up of ~23 months (data cut-off 12 July, 2015), the median number of treatment cycles was 17·0 (range: 1–34 cycles) for IRd and 15·0 (range: 1–34 cycles) for placebo-Rd. Dose intensity was high (median relative dose intensity, defined as percentage of total dose taken divided by total planned dose over treated cycles, for lenalidomide and dexamethasone was 93·8% and 92·2% in the IRd group, and 96·6% and 94·9% in the placebo-Rd group; median relative dose intensity for ixazomib was 97·4%, and for placebo was 98·8%) suggesting that addition of ixazomib did not compromise the background Rd regimen (Moreau et al, 2016).

The most common AEs are shown in Table I (Moreau et al, 2016). Differences between groups were mostly due to higher frequencies of low-grade events with IRd. The frequency of grade ≥3 AEs was higher with IRd versus placebo-Rd (74% vs. 69%) primarily due to the higher incidence of thrombocytopenia; the frequency of grade 4 AEs (18% vs. 15%) was similar between groups. Frequencies of serious AEs (47% vs. 49%), on-study deaths (4% vs. 6%), dose discontinuation of any agent due to an AE (25% vs. 20%) and discontinuation of the treatment regimen due to an AE (17% vs. 14%) were similar with IRd versus placebo-Rd (Moreau et al, 2016).

Haematological events

Thrombocytopenia. Thrombocytopenia is an overlapping toxicity of ixazomib and lenalidomide (Benboubker et al, 2014; http://www.revlimid.com/wp-content/uploads/2013/11/PI.pdf.; Kumar et al, 2014b,c; Lonial et al, 2005; Reece et al, 2012; Richardson et al, 2014). It was reported nearly twice as frequently with IRd versus placebo-Rd (31% vs. 16%; including 12% vs. 5% grade 3, 7% vs. 4% grade 4), but platelet counts of $\leq 10 \times 10^9$/l and $\leq 5 \times 10^9$/l were infrequently reported (IRd: 2% and <1%; placebo-Rd: 1% and <1%). Despite the higher incidence of grade 3/4 thrombocytopenia with IRd versus placebo-Rd, rates of platelet transfusions (8% vs. 6%) and haemorrhage events of any grade (20% vs. 19%) were similar. First occurrence of thrombocytopenia was highest during the first 3 months of treatment in the IRd (68/112; 61%) and placebo-Rd (29/57; 51%) groups and the incidence generally declined over time. Platelet counts showed a cyclical pattern, dropping after each ixazomib dose, with nadirs around day 14–21, and returning to baseline levels prior to initiation of the subsequent cycle, with no long-term cumulative effect (Fig 1). Thrombocytopenia leading to discontinuation of any drug occurred in five patients (1%) in the IRd group (associated with disease progression in two patients) and seven patients (2%) in the placebo-Rd group.

Neutropenia. Neutropenia is a relatively common side effect with many drugs used for MM treatment and increases the risk of infectious complications, especially if severe and prolonged (Palumbo et al, 2012; Dimopoulos et al, 2015a; Valkovic et al, 2015). The incidence of neutropenia was similar with IRd and placebo-Rd (33% vs. 31%; including 18% vs. 18% grade 3, 5% vs. 6% grade 4), and was transient and cyclical in nature. The median time to documented recovery was 8·0 and 12·0 days with IRd and placebo-Rd, respectively.

Table I. AEs of clinical importance occurring in at least 20% of patients in either arm.

AE category, n (%)	Placebo-Rd (n = 359)				IRd (n = 361)			
	AE	Gr ≥3	SAE	D/C	AE	Gr ≥3	SAE	D/C
Haematological events*								
Thrombocytopenia†	57 (16)	32 (9)	6 (2)	7 (2)	112 (31)	69 (19)	7 (2)	5 (1)
Neutropenia	111 (31)	85 (24)	2 (<1)	5 (1)	118 (33)	81 (22)	2 (<1)	3 (<1)
Non-haematological events*								
Nausea	79 (22)	0	0	0	104 (29)	6 (2)	2 (<1)	0
Vomiting	42 (12)	2 (<1)	0	0	84 (23)	4 (1)	2 (<1)	0
Diarrhoea	139 (39)	9 (3)	2 (<1)	3 (<1)	164 (45)	23 (6)	9 (2)	6 (2)
Constipation	94 (26)	1 (<1)	1 (<1)	1 (<1)	126 (35)	1 (<1)	1 (<1)	0
Rash†	82 (23)	6 (2)	1 (<1)	1 (<1)	131 (36)	18 (5)	1 (<1)	3 (<1)
PN†	78 (22)	6 (2)	0	2 (<1)	97 (27)	9 (2)	0	9 (2)
Peripheral oedema‡	73 (20)	4 (1)	1 (<1)	0	101 (28)	8 (2)	1 (<1)	0
Back pain	62 (17)	9 (3)	7 (2)	1 (<1)	87 (24)	3 (<1)	2 (<1)	0

AE, adverse event; D/C, discontinued; Gr, grade; IRd, ixazomib, lenalidomide and dexamethasone; Placebo-Rd, placebo plus lenalidomide and dexamethasone; PN, peripheral neuropathy; SAE, serious adverse event.

*Grade 4 thrombocytopenia reported in 13 (4%) and 26 (7%) patients in the placebo-Rd and IRd groups, respectively; grade 4 neutropenia reported in 22 (6%) and 17 (5%) patients, respectively. No grade 4 events reported for the non-haematological AEs listed here.

†Pooled preferred terms (broad pooling of standardized Medical Dictionary for Regulatory Activities query [SMQ] preferred terms).

‡An association between oedema and cardiac failure was similar between the two regimens (IRd: 1%; placebo-Rd: <1%).
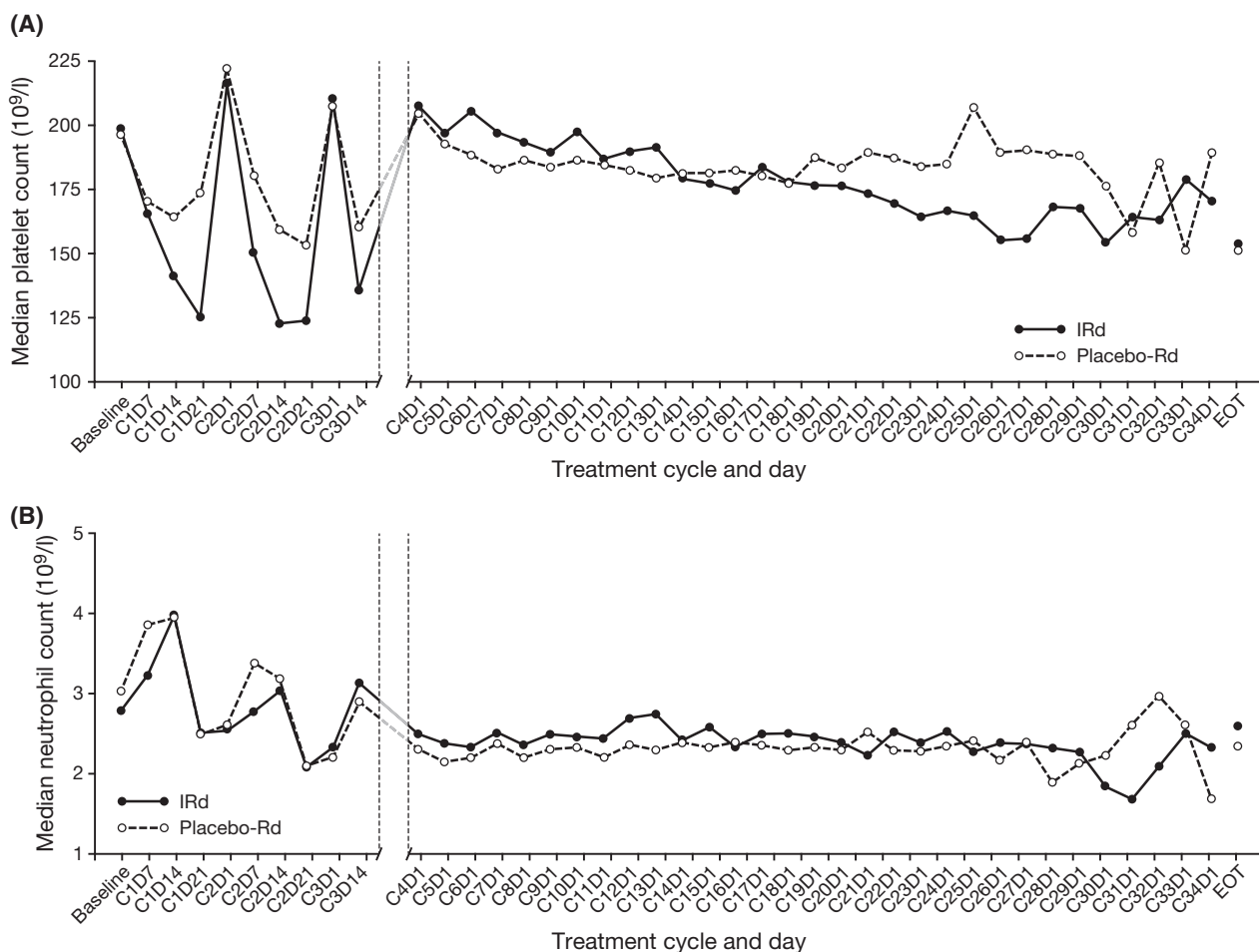
(A)

(B)

Fig 1. Median platelet and absolute neutrophil counts. (A) Median platelet count over cycles. (B) Median absolute neutrophil count over cycles. C, cycle; D, day; IRd, ixazomib, lenalidomide, and dexamethasone; Placebo-Rd, placebo plus lenalidomide and dexamethasone.

Neutropenia was reported most frequently within the first three cycles, with no cumulative effect seen. Lenalidomide was dose-reduced most frequently and similarly in the two regimens (IRd: 8%; placebo-Rd: 7%); ixazomib or placebo was reduced less frequently (4% in each regimen). The incidence of patients with grade ≥3 neutropenia and AEs within the 'infections and infestations' system organ class (SOC) was also similar (IRd: 2%; placebo-Rd: 3%). Febrile neutropenia was similarly infrequent with both regimens (<1% and 2%, respectively). Colony-stimulating factors were used by 21% and 20% of patients in the IRd and placebo-Rd groups.

Non-haematological events

Nausea/vomiting. Nausea and vomiting are reported with both lenalidomide and ixazomib (http://www.revlimid.com/wp-content/uploads/2013/11/PI.pdf; http://www.ninlaro.com/downloads/prescribing-information.pdf), but are more common with ixazomib, as seen with the single-agent trials (Kumar *et al*, 2014b, 2015a). Rates of nausea and vomiting were higher with IRd than placebo-Rd (nausea: 29% vs. 22%; vomiting: 23% vs. 12%) (Moreau *et al*, 2016). Differences were primarily due to higher frequencies of low-grade events with IRd (Table II). Individual agents were dose-reduced for nausea in ≤2% and ≤1% of patients in the IRd and placebo-Rd groups, respectively. There were no discontinuations due to nausea or vomiting, and no apparent differences between the IRd and placebo-Rd groups in incidences of potential complications, such as dehydration (2% vs. 1%) and weight loss (AE: 7% vs. 6%; mean change in actual weight over time: −2·4 kg vs. −2·7 kg). In both groups, the incidence of first occurrence of nausea was highest during the first 3 months of treatment, particularly in the first cycle. Time to onset with IRd was primarily the day of or after (12–48 h) ixazomib dosing. Nausea in the placebo-Rd group was also reported each week.

Use of anti-emetics was at the physician's discretion. Use of prophylactic anti-emetics starting prior to the first dose of study drugs was similar in both groups (IRd: 5%; placebo-Rd: 2%), while 11% versus 5% reported starting these agents for prophylactic use only after the first dose of study

Table II. Gastrointestinal toxicities with IRd and placebo-Rd.

	Placebo-Rd (n = 359)	IRd (n = 361)
Nausea		
Grade 1 (%)	15	22
Grade 2 (%)	7	5
Grade 3 (%)*	0	2
Time to documented recovery (days)	7	12
Vomiting		
Grade 1 (%)	8	17
Grade 2 (%)	3	6
Grade 3 (%)*	<1	1
Time to documented recovery (days)	1	1
Diarrhoea		
Grade 1 (%)	22	24
Grade 2 (%)	14	15
Grade 3 (%)*	3	6
Time to documented recovery (days)	5	4

IRd, ixazomib, lenalidomide, and dexamethasone; Placebo-Rd, placebo plus lenalidomide and dexamethasone.
*No grade 4 or 5 events were reported.

treatment. The most commonly prescribed anti-emetics were ondansetron and metoclopramide.

Diarrhoea and constipation. Diarrhoea has been reported with both lenalidomide and ixazomib, alone or in combination with dexamethasone (http://www.revlimid.com/wp-content/uploads/2013/11/PI.pdf; Kumar *et al*, 2014b, 2015a,b; Lonial *et al*, 2015; http://www.ninlaro.com/downloads/prescribing-information.pdf; Moreau *et al*, 2016; Pawlyn *et al*, 2014). The increased frequency of diarrhoea with IRd versus placebo-Rd (45% vs. 39%) was primarily due to a higher frequency of low-grade events (Table II). The incidence of diarrhoea was consistent with the lenalidomide prescribing information (reported frequency of 40–46%) (http://www.revlimid.com/wp-content/uploads/2013/11/PI.pdf). No apparent differences were noted between the IRd and placebo-Rd groups in the incidence of potential complications of diarrhoea, such as hypokalaemia (13% vs. 10%), dehydration, weight loss (per nausea/vomiting section), hyponatraemia (2% vs. 2%) and hypomagnesaemia (4% vs. 5%).

The incidence of the first occurrence of diarrhoea was highest during the first 3 months of treatment in both groups and generally declined over time. With IRd, onset was primarily on the day of or after ixazomib dosing, while it was reported at a consistent rate each week in the placebo-Rd group. Antidiarrhoeal medications were used to manage diarrhoea at the physician's discretion; loperamide was the most commonly prescribed medication (IRd: 19%; placebo-Rd: 15%). Discontinuation of individual drugs occurred in ≤2% and <1% of patients in the IRd and placebo-Rd groups, respectively. Across both regimens, lenalidomide was the agent most frequently dose-reduced for diarrhoea, followed

by dexamethasone and ixazomib/placebo. The incidence of constipation was 35% with IRd and 26% with placebo-Rd, which was all grade 1–2 (Table I); narcotic pain medications for myeloma-related bone pain as a confounding factor cannot be excluded. Use of laxatives was similar in the IRd and placebo-Rd groups (38% vs. 35%).

Rash. The incidence of rash was 36% vs. 23% with IRd versus placebo-Rd (Table I) (Moreau *et al*, 2016). The rash observed with IRd typically ranged from limited erythaematous, macular and/or papular lesions that could be pruritic over a few areas of the body, to a more generalised eruption predominantly on the trunk or extremities, and as such is described best using the high-level term of 'rashes, eruptions and exanthems', which includes the preferred terms of rash maculo-papular, rash macular, rash and rash generalized. The incidence of such rashes (pooled terms) was 20% and 13% with IRd and placebo-Rd, respectively, with the difference primarily due to a higher frequency of low-grade events; grade 3 events were reported in 5% and 2%, respectively.

The incidence of first occurrence of rash was highest during the first 3 months of treatment and generally declined over time in both groups. The median time to documented recovery was 12 days in both groups. The rash events were frequently self-limiting, with 21% and 12% of patients in the IRd and placebo-Rd groups, respectively, reporting events that resolved without intervention. Management approaches included antihistamines (primarily cetirizine) or topical glucocorticoids. Dose modification was also used, often with lenalidomide being dose-modified first (IRd: dose reduced in 7%, held in 9%; placebo-Rd: dose reduced in 3%, held in 2%), and then ixazomib (IRd: dose reduced in 4%; held in 3%) and dexamethasone (IRd: dose reduced in 2%, held in 1%; placebo-Rd: dose reduced in <1%, held in <1%) subsequently as needed. Rash leading to discontinuation of at least one agent occurred in three patients (<1%) in the IRd group (of lenalidomide in all three patients, and of ixazomib and dexamethasone in two patients) and one patient (<1%) in the placebo-Rd group (of lenalidomide).

Peripheral neuropathy. PN is a common finding in patients with RRMM, either related to the underlying disease process or due to prior treatment, usually thalidomide or bortezomib (Richardson *et al*, 2012). At study entry, 26% of patients (IRd: 23%; placebo-Rd: 30%) had either a medical history of PN or reported PN at baseline. Additionally, more than 50% of patients in both groups reported at least a little tingling in their hands or feet on the European Organization for Research and Treatment of Cancer Multiple Myeloma Module (EORTC QLQ-MY20) questionnaire at baseline even if the physician did not document a medical history of PN. Overall incidence of PN (including peripheral sensory neuropathy, neuropathy peripheral, and peripheral motor neuropathy) was 27% and 22% in the IRd and placebo-Rd

groups, respectively. This was mainly sensory neuropathy (IRd: 19%; placebo-Rd: 14%), with <1% in both arms experiencing peripheral motor neuropathy. Most PN was grade 1/2 (IRd: 24%; placebo-Rd: 20%), with only 2% in each group reporting grade 3 PN (there was no grade 4 PN).

Among 175 patients who reported PN, 14% and 17% in the IRd and placebo-Rd groups, respectively, had worsening of PN during treatment. The overall incidence of PN with pain was 3% and 2% in the IRd and placebo-Rd groups, respectively. Most events were grade 1 or grade 2 in both the IRd (five and seven patients, respectively) and placebo-Rd (one and six patients, respectively) groups; one patient in each group experienced grade 3 PN with pain. Of the 21 patients who experienced PN with pain, seven (IRd: three; placebo-Rd: four) had PN at baseline.

In both groups, most PN occurred during the first 3 months of treatment and the incidence generally declined over time, suggesting a lack of cumulative toxicity. Among patients who reported new onset or worsening of PN, the median time to onset was similar between the IRd and placebo-Rd groups (128 days and 125 days). Among patients who reported PN, resolution was recorded in 36% in each group. Median time to documented recovery was 53·5 days and 48·5 days in the IRd and placebo-Rd groups, respectively.

Infrequent clinically important AEs

Venous thromboembolism. The risk of venous thromboembolism (VTE) is increased in patients with cancer (~7% incidence), with higher rates (8–16%) reported in patients with RRMM treated with Rd (Palumbo *et al*, 2008; Chen *et al*, 2013). Thromboprophylaxis was required per protocol as all patients were receiving lenalidomide; 98% of patients reported use of aspirin or an anticoagulant (IRd: 97%; placebo-Rd: 98%). A review of venous thrombosis in aggregate identified a thromboembolism event in 29 patients (8%) in the IRd group and 38 patients (11%) in the placebo-Rd group. Arterial thromboembolic events were reported infrequently (2% in each group), consistent with rates of VTE events previously reported for patients with RRMM treated with Rd (Palumbo *et al*, 2008). Overall, the addition of ixazomib to Rd did not increase the VTE risk.

Herpes zoster virus. Herpes zoster virus (HZV) was reported in 5% and 2% of patients treated with IRd and placebo-Rd, respectively. Among patients who started HZV prophylaxis at study entry (*n* = 431), <1% and 1% in the IRd and placebo-Rd groups, respectively, reported HZV infection. This is in contrast to those that did not start HZV prophylaxis (*n* = 291; frequency of 8% and 3% in the IRd and placebo-Rd groups, respectively). Given this information, HZV prophylaxis should be considered for patients receiving ixazomib.

Other AEs of interest

Cardiac function. Cardiac toxicity has been a focus of several trials including PIs (San Miguel *et al*, 2013; Atrash *et al*, 2015; Mikhael, 2016). There were no safety concerns with respect to cardiac toxicity for ixazomib. There were similar frequencies of cardiac arrhythmia in the two groups (IRd: 16%; placebo-Rd: 15%). The incidences of heart failure (4% for both) and myocardial infarction (1% and 2%, respectively) were similar in the IRd and placebo-Rd groups. In particular, no increase in cardiac events was demonstrated in patients with pre-existing heart disease or cardiac risk factors (defined as myocardial infarction, cardiac ischaemia, angina, arrhythmia, congestive heart failure, valvular diseases, hypertension, diabetes, hyperlipidaemia or obesity).

Renal and hepatic dysfunction. There were no safety concerns regarding renal impairment; the incidence of the standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for acute renal failure, which captures a broad range of related individual preferred terms, was low and similar between the IRd and placebo-Rd groups (9% vs. 11%). Similarly, there were no safety concerns with respect to AEs associated with liver impairment (7% vs. 6%). Based on pharmacokinetic and safety data, a reduced ixazomib starting dose of 3·0 mg is recommended in patients with severe renal impairment or end-stage renal disease, and in patients with moderate-to-severe hepatic impairment (Gupta *et al*, 2016a,b).

Ocular events. The incidence of AEs in the eye disorders SOC was 32% and 23% in the IRd and placebo-Rd groups, respectively. The higher frequency with IRd was accounted for by differences in rates of low-grade events within individual preferred terms associated with conjunctival irritation, such as blurred vision (7% vs. 4%), conjunctivitis (7% vs. 2%) and dry eye (5% vs. 2%). Considering the similar frequencies between regimens, no safety concerns were noted with regards to these ocular events.

Secondary primary malignancies. No difference in the occurrence of secondary primary malignancies was observed with IRd versus placebo-Rd (5% vs. 4%, respectively); 31 patients (14 in the IRd group and 11 in the placebo-Rd group) were diagnosed with a new malignancy. Haematological new primary malignancies included myelodysplastic syndrome (1 patient in each group) and T-cell acute lymphoblastic leukaemia (1 patient in the placebo-Rd group). Solid tumours of heterogeneous types occurred in 8 and 2 patients in the IRd and placebo-Rd groups, respectively. Non-haematological skin malignancies occurred in 8 and 10 patients in the IRd and placebo-Rd groups, respectively. A clinically relevant medical history (prior history of adenomas and/or smoking) or prior treatment history (melphalan with or without autologous stem cell transplantation) was noted in 7 of 17 and 3

of 14 patients diagnosed with a new malignancy in the IRd and placebo-Rd groups, respectively.

Quality of life. QoL, as measured by the EORTC QLQ-C30 and MY-20 questionnaires, was similar in the two groups and was maintained throughout treatment (Leleu *et al*, 2016).

Exposure-safety analysis

The graphical exposure-safety analysis used data from 328 patients with safety and ixazomib trough concentration data at cycle 2, day 1. The analyses included selected haematological and non-haematological AEs. There appeared to be a relationship between ixazomib concentration and higher incidences of selected AEs, suggesting the appropriateness of dose modifications for these AEs (Figure S2).

Discussion

The TOURMALINE-MM1 results clearly demonstrate the overall safety profile of adding ixazomib to Rd. The toxicity profile of the triplet is favourable and appears comparable to that of the Rd doublet; this represents a beneficial efficacy-toxicity relationship given the PFS improvements seen. The toxicities that increased in incidence with addition of ixazomib appear to include thrombocytopenia, nausea, vomiting, diarrhoea, constipation, rash, PN, peripheral oedema and back pain. The haematological toxicity is predictable from prior experience with PIs, with transient, cyclical thrombocytopenia appearing to be a class effect (Lonial *et al*, 2005; Nooka, 2013). The increased gastrointestinal toxicity also reflects experience with bortezomib (Richardson *et al*,

2005; San Miguel *et al*, 2008), while the PN rate was lower than reported with bortezomib (Moreau *et al*, 2011). Rash was reported with single-agent ixazomib (Kumar *et al*, 2014b; Richardson *et al*, 2014); however, the feasibility of reliable comparison versus other PIs is limited due to differences in AE reporting, e.g., based on individual preferred terms or pooled terms/MedDRA queries. Notably, toxicities seen with the addition of ixazomib were mostly grade 1/2, except for thrombocytopenia, for which grade 3/4 AEs were also seen more frequently.

The increased incidence of grade 3/4 thrombocytopenia did not have any clinical consequence in terms of significant bleeding or dose discontinuations. No cumulative effect on platelet counts was seen and thrombocytopenia appeared to be manageable with no lasting consequences. If dose modification is considered warranted (Table III), alternating dose reduction of lenalidomide and ixazomib is recommended, given that thrombocytopenia is reported with both agents. Platelet counts should be monitored at least monthly during ixazomib treatment, and more frequent monitoring (weekly) should be considered during the first three cycles until steady dosing is achieved. Neutropenia was similar in both arms; management should follow dose-modification guidelines (http://www.revlimid.com/wp-content/uploads/2013/11/PI.pdf; http://www.ninlaro.com/downloads/prescribing-information. pdf) with use of colony-stimulating factors per standard medical guidelines (Smith *et al*, 2015) (Table III).

Management of gastrointestinal toxicity is particularly important given the oral nature of IRd. Considering the emetogenic potential of ixazomib, adequate anti-emetic therapy based on patients' needs and prophylactic anti-emetics, where appropriate, should be considered (Hesketh *et al*, 2016). Use of serotonin receptor antagonists prior to

Table III. Dose modifications guidelines for ixazomib in combination with lenalidomide and dexamethasone: haematological toxicities.

Haematological toxicities	Recommended actions*
Thrombocytopenia Platelet count <30 × 10^9/l	• Withhold ixazomib and lenalidomide until platelet count is ≥30 × 10^9/l • Following recovery, resume lenalidomide at the next lower dose according to its prescribing information and resume ixazomib at its most recent dose • If platelet count falls <30 × 10^9/l again, withhold ixazomib and lenalidomide until platelet count is ≥30 × 10^9/l • Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose†
Neutropenia ANC <0·5 × 10^9/l	• Withhold ixazomib and lenalidomide until ANC is ≥0·5 × 10^9/l. Consider adding G-CSF as per clinical guidelines • Following recovery, resume lenalidomide at the next lower dose according to its prescribing information and resume ixazomib at its most recent dose • If ANC falls to <0·5 × 10^9/l again, withhold ixazomib and lenalidomide until ANC is ≥0·5 × 10^9/l • Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose†

ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor.
*Per NINLARO® prescribing information (http://www.ninlaro.com/downloads/prescribing-information.pdf).
†For additional occurrences, alternate dose modification of lenalidomide and ixazomib.

ixazomib dosing effectively ameliorates nausea and should be considered in patients who develop nausea. Delayed-onset nausea has been uncommon. Although diarrhoea was reported more frequently with IRd versus placebo-Rd, management should be similar to that in patients receiving Rd (Reece *et al*, 2012). Prophylactic anti-diarrhoeal medication is not recommended, although anti-diarrhoeal medications (primarily loperamide) and dose modification of lenalidomide or ixazomib should be used as needed. Diarrhoea was generally manageable and did not appear to have clinical implications. The incidence of constipation was higher with IRd and was manageable with routine measures including diet and laxative adjustments (Tariman, 2007).

Rash was seen with IRd, reflecting the overlapping nature of this toxicity that has been seen with ixazomib alone (Kumar *et al*, 2014b) and with lenalidomide (Reece *et al*, 2012; Tinsley *et al*, 2015). Most lenalidomide-related rash is of mild-to-moderate severity and presents as patchy, raised macular skin lesions, sometimes with localised urticaria and/or pruritus (Reece *et al*, 2012; Tinsley *et al*, 2015). Although serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with lenalidomide (http://www.revlimid.com/wp-content/uploads/2013/11/PI.pdf) and SJS has been reported with IRd previously (Richardson *et al*, 2013), there were no occurrences of SJS or TEN. In the Phase I/II trial of IRd, skin rash was manageable with standard medical treatment and dose withholding/reductions as needed (Kumar *et al*, 2014c). Alternating dose modification of the potentially causative agents, lenalidomide and ixazomib, was utilised in TOURMALINE-MM1 and in line with the lenalidomide prescribing information (http://www.revlimid.com/wp-content/uploads/2013/11/PI.pdf), and appears to be an acceptable strategy (Table IV). As with lenalidomide-induced rash, symptomatic management with oral/topical antihistamines and/or topical corticosteroids should be employed as needed (Tariman, 2007; Reece *et al*, 2012; Tinsley *et al*, 2015). As other medications commonly used in the management of MM patients may cause rash, consideration of this alternative aetiology is important and discontinuation of such agents (e.g., antimicrobial agents, allopurinol) should be considered (Stern, 2012).

Patients receiving IRd should be monitored continuously for symptoms of PN. In one analysis, 36–83% of patients had either a medical history of PN or PN at baseline in RRMM clinical trials (Dimopoulos *et al*, 2015b); contemporary studies have reported PN rates of 17–22% for Rd (Chen *et al*, 2009; Stewart *et al*, 2015; Moreau *et al*, 2016). Patients

Table IV. Dose modifications guidelines for IRd: non-haematological toxicities.

Non-haematological toxicities and severity*	Recommended actions†
Rash	
Grade 2 or 3	• Withhold lenalidomide until rash recovers to grade ≤1 • Following recovery, resume lenalidomide at the next lower dose according to its prescribing information • If grade 2 or 3 rash occurs again, withhold ixazomib and lenalidomide until rash recovers to grade ≤1 • Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose‡
Grade 4	• Discontinue treatment regimen
Peripheral neuropathy	
Grade 1 with pain or grade 2	• Withhold ixazomib until peripheral neuropathy recovers to grade ≤1 without pain or patient's baseline • Following recovery, resume ixazomib at its most recent dose
Grade 2 with pain or grade 3	• Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or grade ≤1 prior to resuming ixazomib • Following recovery, resume ixazomib at the next lower dose
Grade 4	• Discontinue treatment regimen
Other toxicities	
Grade 3/4	• Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or grade ≤1 prior to resuming ixazomib • If attributable to ixazomib, resume ixazomib at the next lower dose following recovery

IRd, ixazomib, lenalidomide, and dexamethasone; PN, peripheral neuropathy.
*Grading based on National Cancer Institute Common Terminology Criteria v4.03.
†Per NINLARO® prescribing information (http://www.ninlaro.com/downloads/prescribing-information.pdf).
‡For additional occurrences, alternate dose modification of lenalidomide and ixazomib.

experiencing new or worsening PN require dose modification (Table IV). Additionally, management of PN symptoms, e.g., with the anti-seizure drugs gabapentin and pregabalin, tricyclic antidepressants and opioid analgesics, should be considered. Drug-induced PN may be irreversible; hence, careful attention to symptoms, prevention and appropriate dose modification/discontinuation remain the most effective strategies (Delforge et al, 2010).

The majority of peripheral oedema was independent of cardiac function, low-grade, and probably related to fluid retention induced by dexamethasone and vascular permeability effects described for proteasome inhibition (Tamura et al, 2010). Notably, the frequency of peripheral oedema for both lenalidomide (26·3%) and dexamethasone (21·1%) described in the lenalidomide prescribing information is consistent with frequencies in TOURMALINE-MM1 (http://www.revlimid.com/wp-content/uploads/2013/11/PI.pdf). Patients should be evaluated for underlying causes and provided with supportive care as necessary, including adjustment of dexamethasone or ixazomib dosing per prescribing information for grade 3/4 symptoms (http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/11664slr062_decadron_lbl.pdf; http://www.ninlaro.com/downloads/prescribing-information.pdf).

The relationships between ixazomib concentration and AEs suggest the appropriateness of dose modifications for these AEs (e.g., rash, PN, diarrhoea, nausea, vomiting, thrombocytopenia, anaemia). The results of these exposure-safety analyses, together with the overall safety profile, support management of AEs via dose modification and supportive care.

Therapy-related AEs, plus the multiple difficulties in managing complex MM-related symptoms, have a negative impact on patients' QoL (Osborne et al, 2012, 2014; Baz et al, 2015). In the context of the feasibility of long-term therapy, tolerability and QoL are important factors for RRMM patients. Over a median follow-up of 23 months, QoL was maintained with IRd compared to placebo-Rd (Moreau et al, 2016), and there was limited additional toxicity to add to the patient burden, as well as no additional physician office visits with IRd versus Rd. This is notable in the context of other PI-Rd or monoclonal antibody-Rd regimens, for which frequent physician visits for subcutaneous or lengthy intravenous administration of the PI or monoclonal antibody are required.

In conclusion, the IRd safety profile was generally manageable and added limited toxicity to the Rd background regimen. The observed toxicities were familiar for lenalidomide and reported in the literature (http://www.revlimid.com/wp-content/uploads/2013/11/PI.pdf; Dimopoulos et al, 2007; Reece et al, 2012; Weber et al, 2007) and generally consistent with those in studies of single-agent ixazomib (Kumar et al, 2014b; Richardson et al, 2014) and IRd (Kumar et al, 2014c; Gupta et al, 2015). Toxicities were manageable with routine supportive care and dose delays or reductions (Moreau et al, 2016). The most common haematological toxicity heightened by ixazomib was thrombocytopenia. Non-haematological AEs, such as nausea/vomiting, diarrhoea, rash and PN were generally grade 1/2. No cumulative toxicities were observed, and specifically no evidence of cumulative haematological toxicity or PN, indicating the potential feasibility of long-term IRd treatment. Ongoing patient/caregiver education is necessary and reinforces the importance of symptom awareness in order to maximise patient self-reporting so that toxicities can be appropriately managed with prompt standard medical interventions. Based on the efficacy and favourable toxicity profile observed in this study, IRd represents an appropriate regimen for patients with RRMM.

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Author contributions

SK, PM, HL, MCM, SL, DB, JL, NG, DLE and PGR conceived and designed the study; SK, PM, PH, MVM, HL, CS, TM, AS, RH, KR, IA, AML, MCM, HE, SL and PGR provided study materials or patients; SK, PM, MVM, HL, TM, IA, AML, DB, JL, NG and DLE collected and assembled the data; SK, PM, PH, HL, IA, MCM, HE, SL, DB, JL, NG, DLE and PGR analysed and interpreted the data; JL and NG performed statistical analysis; DB provided administrative support; SK, PM, PH, MVM, HL, CS, TM, AS, RH, IA, AML, MCM, HE, SL, DB, JL, NG, DLE and PGR wrote and reviewed the manuscript; all authors approved the manuscript. As corresponding author, SK had full access to the data in the study and final responsibility for the decision to submit for publication.

Conflict of interests

attended advisory boards for Janssen, Celgene, Amgen BMS, and Takeda. HL has received research funding from Takeda, and has received honoraria from Takeda, Amgen, Janssen Cilag, Celgene, BMS, Onyx and Novartis. CS has received honoraria from and attended advisory boards for Takeda, Janssen and Celgene. TM has attended advisory boards for BMS, Janssen Cilag, Takeda and Novartis. AS has received honoraria and research funding from Takeda and Celgene. RH has received honoraria from Amgen, Takeda, Celgene and Janssen, and has attended advisory boards for Amgen. KR has received honoraria from and attended advisory boards for Celgene and Janssen. MCM has attended advisory boards for Takeda, Celgene, Janssen Cilag and BMS. HE has received research funding and honoraria from, and attended advisory boards for Janssen Cilag, Celgene, Amgen and Novartis. SL has received honoraria for scientific advisory boards for Millennium, Celgene, Novartis, BMS, Onyx and Janssen. DB, JL, NG and D-LE are employees of Millennium Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. PGR has attended advisory boards for Celgene, Janssen, and Takeda. IA and AML declare no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig S1. CONSORT diagram.

Fig S2. Ixazomib C_{trough} *versus* individual AEs of clinical importance (grade ≥ 2 for non-haematological and grade ≥ 3 for haematological AEs). Ixazomib exposure range in each quartile is denoted by the horizontal black line. Black dots (vertical lines) represent the observed proportion of patients (95% CI) in each quartile. n/N is the number of patients with events/total number of patients in each quartile. The exposure metric for ixazomib in the exposure-safety analyses was trough concentration data at cycle 2, day 1 ($n = 328$ evaluable patients). The analyses were conducted on selected haematological and non-haematological AEs. Three haematological AEs (defined as grade ≥ 3 anaemia, neutropenia and thrombocytopenia) and six non-haematological AEs (defined as grade ≥ 2 diarrhoea, fatigue, nausea, peripheral neuropathy, rash and vomiting) were analysed. There appeared to be a visual relationship between ixazomib concentration and higher incidences of the AEs examined (rash, diarrhoea, nausea, vomiting and thrombocytopenia); these were primarily low-grade, manageable AEs without major clinical complications (see Discussion of AEs in main text). Decreasing exposure from an ixazomib dose of 4 mg to 3 mg corresponded to a decrease in the risk of developing the examined AEs. Therefore, the results of these analyses support management of AEs via dose modifications and supportive care in maintaining patients on ixazomib for as long as clinically indicated.

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