A phase I/II study of twice-weekly ixazomib plus pomalidomide and dexamethasone in relapsed and refractory multiple myeloma

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Abstract

Triplet therapies incorporating proteasome inhibitors, immunomodulatory drugs, and dexamethasone are active regimens for patients with relapsed/refractory multiple myeloma (RRMM). All oral regimens may offer greater real-world feasibility and convenience than other options. This phase I/II dose escalation and expansion study evaluated the oral proteasome inhibitor ixazomib at a dose of 3 or 4 mg on a twice-weekly schedule (days 1, 4, 8, and 11) in 21-day cycles, plus pomalidomide at a dose of 2, 3, or 4 mg (days 1-14) and dexamethasone 12 or 8 mg (days of/after ixazomib dosing), in 50 patients with RRMM. Patients had received a median of 2 prior lines, with 98.0% and 88.0% having received prior lenalidomide and bortezomib, respectively. The highest dose level investigated (ixazomib 4 mg, pomalidomide 4 mg) was the recommended phase II dose (RP2D). Patients received a median of 11 cycles. Common toxicities were neutropenia (76.0%; grade 3: 22.0%, grade 4: 4.0%), thrombocytopenia (70.0%; grade 3: 8.0%, grade 4: 8.0%), leukopenia (68.0%; grade 3: 22.0%, grade 4: 0%), fatigue (52.0%; grade 3: 4.0%, grade 4: 0%), and anemia (46.0%; grade 3: 2.0%, grade 4: 0%). During dose escalation, two dose-limiting toxicities (grade 3 upper respiratory tract infection; grade 3 neutropenia) were reported. The overall response rate was 60.0%: 24.0% ≥very good partial response (VGPR) in all 50 patients and 65.8% (28.9% ≥VGPR) in the 38 patients who received the RP2D. The median duration of response was 18.0 and 19.3 months, median progression-free survival was 13.9 and 17.8 months, and 3-year overall survival rates were 85.2% and 80.3%, respectively. Twice-weekly ixazomib plus pomalidomide-dexamethasone is a well-tolerated, efficacious all oral regimen with real-world utility in RRMM.

Introduction

Outcomes have improved substantially over the past two decades for patients with multiple myeloma (MM), with median overall survival (OS) in excess of ten years in transplant-eligible patients with newly diagnosed MM (NDMM)[1] and increasing OS in the setting of relapsed/refractory MM (RRMM).[2] These improvements have been associated with a rapidly expanding therapeutic armamentarium, with multiple novel agents and regimens becoming available to clinicians, particularly in the past ten years.[3,4] Nevertheless, despite these treatment advances, the majority of patients with MM experience relapse and progressively shorter outcomes,[5] and become refractory to multiple therapies. Furthermore, MM patients and their disease characteristics are highly heterogeneous,[6] resulting in differing treatment approaches, preferences, and outcomes.[2,7-9] These factors underscore the ongoing need for additional effective and well-tolerated treatment options for patients with RRMM.

In the current treatment algorithm, proteasome inhibitors (PI), immunomodulatory drugs (IMiD), and CD38 monoclonal antibodies (mAb) are the backbones of therapy, with quadruplet regimens comprising bortezomib or carfilzomib, lenalidomide, and daratumumab or isatuximab, plus dexamethasone, the standards of care in the NDMM setting.[3,4] For patients with RRMM, triplet/quadruplet regimens made up of these agents are among the key standard-of-care options, along with therapies incorporating different PI and

IMiD *versus* those used in first-line treatment, as well as novel immune-based approaches with the antibody-drug conjugate belantamab mafodotin, chimeric antigen receptor (CAR) T-cell therapies, and bispecific antibodies.[3,4] However, although there is this wealth of treatment options, clinicians must take into account numerous real-world factors when considering options for patients with RRMM, who may be being treated primarily in the community setting rather than at academic or specialist centers.[10] Such factors may include challenges associated with geography (distance to treatment center), convenience of therapy, patient preferences for their treatment, issues associated with immune status, and other criteria that may restrict eligibility for certain options.[7-9,11,12] Accessibility of some treatments, notably CAR T-cell therapies, may also present challenges.[13] Treatment options that remain viable in this real-world context are therefore important, such as active all oral combination regimens.

Ixazomib is the only oral PI available for the treatment of RRMM; it is approved in the US in combination with lenalidomide-dexamethasone (Rd) for patients with MM who have received ≥1 prior therapy[14] based on the findings of the TOURMALINE-MM1 study, which demonstrated superior progression-free survival (PFS) with weekly ixazomib plus lenalidomide-dexamethasone (Rd) *versus* Rd alone.[15-17] Ixazomib was initially evaluated as a single agent in patients with RRMM using both twice-weekly[18] and weekly[19] dosing schedules, and twice-weekly[20] and weekly[21-23] dosing of ixazomib has also been evaluated in combination with Rd for patients with NDMM.

Combinations incorporating the IMiD pomalidomide are among the standards of care for RRMM. Many patients receive lenalidomide-based therapy until disease progression as part of first-line therapy; they are thus lenalidomide-exposed or lenalidomide-refractory in the RRMM setting and require alternative options, such as regimens including a different IMiD. Pomalidomide is a highly potent IMiD that, in combination with dexamethasone, has demonstrated activity in patients with RRMM who are lenalidomide-exposed/refractory.[24] In the US, it has been approved in combination with dexamethasone for patients with MM who have received ≥2 prior therapies including lenalidomide and a PI, and have demonstrated disease progression on or within 60 days of completing their last therapy.[25]

Triplet combinations of a PI plus pomalidomide-dexamethasone (Pom-dex) have demonstrated substantial efficacy, with improved PFS, in RRMM,[26-29] including in patients with lenalidomide-refractory disease as in the OPTIMISMM phase III trial of bortezomib-Pom-dex *versus* bortezomib-dexamethasone.[28,29] Weekly ixazomib plus Pom-dex has also shown notable activity in the RRMM setting,[30-33] including in lenalidomide-refractory patients in the Alliance A061202 study.[32,33] Based on the promising activity seen with twice-weekly ixazomib-Rd in NDMM[20] and the twice-weekly bortezomib dosing regimen used in combination with Pom-dex in OPTIMISMM,[28,29] and in the context of the potential utility of a twice-weekly regimen in patients with high-risk features requiring more intensive therapy for rapid disease control, we conducted this phase I/II open-label, single-arm study to evaluate twice-weekly ixazomib plus Pom-dex in patients with RRMM.

Methods

Study design and patients

The study comprised a dose-escalation phase and an expansion phase at the maximum tolerated dose (MTD)/recommended phase II dose (RP2D). The study protocol and all amendments (DF/HCC Protocol #19-291; Takeda Protocol: X16117) were approved by institutional review boards or ethics committees at all participating sites. The study was conducted in accordance with the principles of the Declaration of Helsinki and as per International Council for Harmonization Good Clinical Practice guidelines and all applicable laws and regulations. Eligible patients had MM with measurable disease, as per International Myeloma Working Group (IMWG) criteria,[34] and required further treatment following disease progression (PD) on ≥2 prior therapies (or PD on/within 60 days of last therapy, after having received an IMiD plus a PI as first-line therapy). Patients were excluded if they had prior ixazomib exposure, were pomalidomide-refractory, or had received IMiD or PI within 14 days. Other eligibility criteria are listed in the *Online Supplementary Methods*. Written informed consent was provided by all patients prior to study participation.

Study treatment

Patients received treatment in 21-day cycles comprising ixazomib 3 or 4 mg on days 1, 4, 8, and 11, pomalidomide 2, 3, or 4 mg on days 1–14, and dexamethasone 12 mg (8 mg for patients aged ≥75 years) on the days of and after ixazomib dosing. Dose-escalation levels are shown in Table 1. Dose escalation proceeded per a standard 3+3 design, with 3-6 patients treated at each dose level; the MTD was the highest dose level at which <2 of 6 patients had a dose-limiting toxicity (DLT) during cycle 1 of treatment. DLT are defined in the *Online Supplementary Methods*.

Concomitant medications are detailed in the *Online Supplementary Methods*. Treatment continued until PD, occurrence of unacceptable adverse events (AE), patient withdrawal, or other reasons such as intercurrent illness that prevented further treatment. Patients who discontinued treatment for reasons other than PD were followed every four weeks until PD or initiation of subsequent therapy. Following PD, patients were followed every three months for two years for OS.

Objectives and assessments

The primary objectives were to determine the MTD in the dose-escalation phase I component, determine overall

Table 1. Planned dose levels and study enrollment in phase I and phase II.

Cohort/dose level	Ixazomib mg	Pomalidomide mg	Phase I enrollment N	Phase II enrollment N	Total
–1	2.3	2	0	0	0
0	3	2	3	0	3
1	3	3	3	0	3
2	3	4	6	0	6
3 (RP2D)	4	4	6	32	38
Total	–	–	18	32	50

RP2D: recommended phase II dose.

response rate (ORR; ≥partial response) and clinical benefit rate (CBR; ≥minimal response) in phase II, and evaluate safety in both phases. Disease response/progression was assessed using the 2011/2016 IMWG criteria.[35,36] AE were assessed throughout treatment and until 30 days after last dose of study drug. Secondary objectives and assessment details are provided in the *Online Supplementary Methods*.

Statistical analysis

Up to 24 patients were to be enrolled in the dose-escalation phase, and in phase II, at the MTD/RP2D, additional patients were to be enrolled to give a total of 37 treated at the MTD/RP2D across both phases. The phase II component used a Simon optimal two-stage design, with 19 patients enrolled in the first stage; with a null hypothesis of a 40% ORR and an alternative hypothesis of a 60% ORR, the study had 85% overall power with α=0.093. Analysis populations and additional statistical analysis details are provided in the *Online Supplementary Methods*.

The study was registered at clinicaltrials.gov (identifier: NCT04094961).

Results

Patient characteristics and organization

Between September 26, 2019, and June 18, 2024, a total of 51 patients were enrolled at four study sites in the United States. One patient was a screen failure and was not treated; the other 50 patients were treated, and were evaluable for safety and efficacy.

Patient demographics and disease characteristics in the overall population, according to study phase and cohort, and in patients who received the RP2D are summarized in Table 2. Among all 50 patients, the median age was 68 years, with 60% of patients aged ≥65 years. Adverse prognostic characteristics included International Staging System (ISS) disease stage III in 26.0% of patients, high-risk cytogenetics in 42.0% (with del(17p) in 16.0% and gain 1q in 30.0%), and refractory disease in 60.0%. Patients had received a median of 2 prior lines of treatment, including lenalidomide in 98.0% and bortezomib in 88.0%, as well as stem cell transplantation in 32.0%. Overall, 56.0% and 20.0% of patients were refractory to lenalidomide and bortezomib, respectively.

At data cut-off (September 15, 2025), 5 (10.0%) patients were ongoing on study treatment and a further 10 (20.0%) remained on study in follow-up. Reasons for discontinuing study treatment included PD in 31 patients (62.0%), toxicity or side-effects in 5 (10.0%), physician or patient decision in 4 (8.0%), consent withdrawal in one (2.0%), death in one (2.0%, following sudden cardiac arrest during dialysis), and other reasons in 3 (6.0%; cardiac comorbidities, adenocarcinoma, clinical deterioration). Median follow-up, determined on the basis of inverse Kaplan-Meier analysis of OS, was 30.8 months (95%CI: 28.4-36.3).

Dose escalation and recommended phase II dose

During the dose-escalation phase, there were no DLT reported in 3 patients treated in cohort 0 (ixazomib 3 mg, pomalidomide 2 mg) or in 3 patients treated in cohort 1 (ixazomib 3 mg, pomalidomide 3 mg). In cohort 2 (ixazomib 3 mg, pomalidomide 4 mg), one of the first 3 patients enrolled experienced a DLT of grade 3 upper respiratory tract infection, which was considered probably related to dexamethasone and was also a serious AE (SAE); no dose reduction was required. A further 3 patients were enrolled to cohort 2; no other DLT were reported, and dose escalation proceeded to cohort 3. In cohort 3 (ixazomib 4 mg, pomalidomide 4 mg), one of the first 3 patients experienced a DLT of grade 3 neutropenia, which was considered probably related to ixazomib and pomalidomide, and possibly related to dexamethasone; no dose reduction was required. A further 3 patients were enrolled to cohort 3; no other DLT were reported. As further dose escalation was not planned per protocol, the cohort 3 dose level was determined to be the MTD/RP2D.

Treatment exposure and safety

At data cut-off, patients had received a median of 13 cycles

of treatment (range 1-79); 20 patients (40.0%) had received ≥18 cycles (approx. 1 year) of treatment, including the 5 patients ongoing on study treatment. Table 3 summarizes the safety profile in the overall population, in the phase I dose escalation cohort (patients who received <RP2D), and in patients who received the RP2D (Cohort 3 in phase I, plus phase II cohort), together with the relative dose intensity of each agent. All patients reported at least one AE of any grade and at least one treatment-related AE (TRAE), with 78.0% and 64.0% having at least one grade 3/4 AE or grade 3/4 TRAE, respectively. The proportions of patients who had grade 3/4 AE and grade 3/4 TRAE were numerically higher in the RP2D cohort than in the phase I (<RP2D) cohort (81.6% and 66.7%; 73.7% and 33.3%, re-

Table 2. Patient demographics and disease characteristics, overall, in the phase I dose escalation cohort, including in individual cohorts, in the phase II cohort, and at the recommended phase II dose (RP2D).

Characteristic	All N=50	Phase I					Phase II N=32	RP2D N=38
		All N=18	Cohort 0 N=3	Cohort 1 N=3	Cohort 2 N=6	Cohort 3 N=6		
Age								
Median, years (range)	68 (49-83)	68 (57-83)	71 (57-76)	61 (58-70)	70 (59-74)	64 (57-83)	68 (49-80)	67 (49-83)
≥65 years, N (%)	30 (60.0)	11 (61.1)	2 (66.7)	1 (33.3)	5 (83.3)	3 (50.0)	19 (59.4)	22 (57.9)
Sex, N (%)								
Male	26 (52.0)	9 (50.0)	2 (66.7)	2 (66.7)	3 (50.0)	2 (33.3)	17 (53.1)	19 (50.0)
Female	24 (48.0)	9 (50.0)	1 (33.3)	1 (33.3)	3 (50.0)	4 (66.7)	15 (46.9)	19 (50.0)
Race, N (%)								
White	39 (78.0)	15 (83.3)	3 (100)	3 (100)	4 (66.7)	5 (83.3)	24 (75.0)	29 (76.3)
Asian	4 (8.0)	2 (11.1)	0	0	2 (33.3)	0	2 (6.3)	2 (5.3)
African American	1 (2.0)	0	0	0	0	0	1 (3.1)	1 (2.6)
Other	6 (12.0)	1 (5.6)	0	0	0	1 (16.7)	5 (15.6)	6 (15.8)
ECOG PS, N (%)								
0	17 (34.0)	6 (33.3)	0	1 (33.3)	3 (50.0)	2 (33.3)	11 (34.4)	13 (34.2)
1	32 (64.0)	12 (66.7)	3 (100)	2 (66.7)	3 (50.0)	4 (66.7)	20 (62.5)	24 (63.2)
2	1 (2.0)	0	0	0	0	0	1 (3.1)	1 (2.6)
ISS disease stage, N (%)								
I	17 (34.0)	4 (38.9)	0	1 (33.3)	1 (16.7)	2 (33.3)	13 (40.6)	15 (39.5)
II	18 (36.0)	8 (44.4)	2 (66.7)	1 (33.3)	3 (50.0)	2 (33.3)	10 (31.3)	12 (31.6)
III	13 (26.0)	5 (27.8)	1 (33.3)	0	2 (33.3)	2 (33.3)	8 (25.0)	10 (26.3)
Missing	2 (4.0)	1 (5.6)	0	1 (33.3)	0	0	1 (3.1)	1 (2.6)
Cytogenetic risk, N (%)								
High risk	21 (42.0)	8 (44.4)	1 (33.3)	0	4 (66.7)	3 (50.0)	13 (40.6)	16 (42.1)
t(4;14)	1 (2.0)	1 (5.6)	0	0	0	1 (16.7)	0	0
del(17p)	8 (16.0)	1 (5.6)	0	0	1 (16.7)	0	7 (21.9)	7 (18.4)
t(14;16)	5 (10.0)	2 (11.1)	0	0	0	2 (33.3)	3 (9.4)	5 (13.2)
Gain 1q	15 (30.0)	8 (44.4)	1 (33.3)	0	4 (66.7)	3 (50.0)	7 (21.9)	20 (52.6)
Standard risk	18 (36.0)	3 (16.7)	0	1 (33.3)	2 (33.3)	0	15 (46.9)	15 (39.5)
Missing	11 (22.0)	7 (38.9)	2 (66.7)	2 (66.7)	0	3 (50.0)	4 (12.5)	7 (18.4)
Hyperdiploidy	11 (22.0)	3 (16.7)	1 (33.3)	1 (33.3)	1 (16.7)	0	8 (25.0)	8 (21.1)
Disease status, N (%)								
Refractory	30 (60.0)	9 (50.0)	3 (100)	3 (100)	3 (50.0)	0	21 (65.6)	21 (55.3)
Relapsed	20 (40.0)	9 (50.0)	0	0	3 (50.0)	6 (100)	11 (34.4)	17 (44.7)
Median prior lines, N (range)	2 (1-6)	2 (1-4)	2 (1-3)	2 (1-2)	2 (1-3)	2 (1-4)	2 (1-6)	2 (1-6)
Prior therapies, N (%)								
SCT	16 (32.0)	11 (61.1)	2 (66.7)	2 (66.7)	3 (50.0)	4 (66.7)	5 (15.6)	9 (23.7)
Lenalidomide*	49 (98.0)	18 (100)	3 (100)	3 (100)	6 (100)	6 (100)	31 (96.9)	37 (97.4)
Refractory	28 (56.0)	8 (44.4)	1 (33.3)	1 (33.3)	3 (50.0)	3 (50.0)	20 (62.5)	23 (60.5)
Bortezomib	44 (88.0)	17 (94.4)	3 (100)	2 (66.7)	6 (100)	6 (100)	27 (84.4)	33 (86.8)
Refractory	10 (20.0)	5 (27.8)	1 (33.3)	0	2 (33.3)	2 (33.3)	5 (15.6)	7 (18.4)
Daratumumab	6 (12.0)	1 (5.6)	0	0	0	1 (16.7)	5 (15.6)	6 (15.8)
Refractory	2 (4.0)	0	0	0	0	0	2 (6.3)	2 (5.3)

*Of the 49 patients who had prior lenalidomide, 17 and 23 received full-dose and maintenance lenalidomide, respectively, as part of their most recent prior therapy. ECOG PS: Eastern Cooperative Oncology Group performance status; ISS: International Staging System; N: number; SCT: stem cell transplantation.

spectively), but the differences between cohorts in AE/TRAE maximum severity grades were not nominally significant (test for trend in proportions, *P*=0.60 and *P*=0.11, respectively).

The most common AE (unrelated or related), reported in at least 20% of the total population, are summarized by severity grade in Figure 1A, with the corresponding rates of these events in patients who received the RP2D shown in Figure 1B. The most common AE overall were neutropenia (76.0%), thrombocytopenia (70.0%), leukopenia (68.0%), fatigue (52.0%), and anemia (46.0%). The most common grade 3/4 AE were neutropenia (22.0%/4.0%), leukopenia (22.0%/0%), and thrombocytopenia (8.0%/8.0%). Other grade 3 AE included syncope in 3 patients (6.0%), glucose intolerance and lung infection in each of 2 patients (4.0%), and atrial fibrillation, catheter-related infection, dehydration, fall, fever, generalized muscle weakness, heart failure, hypertension, hyponatremia, localized edema, lymphopenia, non-cardiac chest pain, pneumonitis, sinusitis, thromboembolic event, treatment-related secondary malignancy, urinary tract infection, and vascular disorders in one patient each (2.0%). There were no other grade 4 AE reported on treatment; one patient (2.0%) had a grade 4 cardiac arrest while on study but off treatment. Peripheral sensory neuropathy was seen in 32.0% of patients overall, with one patient (2.0%) having a grade 3 event.

The incidence of SAE was numerically lower in the RP2D cohort than in the phase I (<RP2D) cohort (28.9% and 50.0%, respectively; Cochran-Armitage test, *P*=0.32), whereas the incidence of dose reductions due to AE was numerically higher (86.8% and 58.3%; Cochran-Armitage test, *P*=0.11). Overall, 5 patients (10.0%), all of whom were treated at the RP2D (5/38, 13.2%), discontinued treatment due to AE (peripheral sensory neuropathy within pain: N=2; peripheral sensory neuropathy: N=1) or reported side effects ("significant side effects": N=1; "edema": N=1).

Table 3. Summary of safety profile and dose intensity overall, in the phase I dose-escalation cohort, and at the recommended phase II dose (RP2D).

Adverse events	All N=50	Phase I <RP2D N=12	Phase II/RP2D N=38
Any AE, N (%)	50 (100)	12 (100)	38 (100)
Max grade 1	1 (2.0)	0	1 (2.6)
Max grade 2	10 (20.0)	4 (33.3)	6 (15.8)
Max grade 3	31 (62.0)	7 (58.3)	24 (63.2)
Max grade 4	8 (16.0)	1 (8.3)	7 (18.4)
Any related AE, N (%)	50 (100)	12 (100)	38 (100)
Max grade 1	3 (6.0)	1 (8.3)	2 (5.3)
Max grade 2	15 (30.0)	7 (58.3)	8 (21.1)
Max grade 3	27 (54.0)	4 (33.3)	23 (60.5)
Max grade 4	5 (10.0)	0	5 (13.2)
Any SAE, N (%)	17 (34.0)	6 (50.0)	11 (28.9)
Discontinuation due to AE, N (%)	5 (10.0)	0	5 (13.2)
Dose reduction (any drug) due to AE, N (%)	40 (80.0)	7 (58.3)	33 (86.8)
Ixazomib*	27 (54.0)	2 (16.7)	25 (65.8)
Pomalidomide†	26 (52.0)	4 (33.3)	22 (57.9)
Dexamethasone‡	35 (70.0)	6 (50.0)	29 (76.3)
Median relative dose intensity, % (range)#			
Ixazomib	94 (32-100)	100 (44-100)	89 (32-100)
Pomalidomide	96 (54-100)	100 (76-100)	92 (54-100)
Dexamethasone	76 (36-100)	95 (39-100)	70 (36-100)

*Protocol-specified ixazomib dose reductions were from 4.0 to 3.0 to 2.3 mg, twice-weekly, and then to 2.3 mg once-weekly. Overall, 5 patients (10%) switched to weekly dosing of ixazomib. †Protocol-specified pomalidomide dose reductions were from 4 to 3 to 2 to 1 mg. ‡Protocol-specified dexamethasone dose reductions were from 12 to 8 to 4 mg for patients aged <75 years and from 8 to 4 mg and then to 4 mg on the day of ixazomib dosing only. #Relative dose intensity calculated as the actual dose received in each cycle (accounting for dose reductions) relative to the assigned dose, averaged over all cycles, x 100. AE: adverse event; N: number; SAE: serious adverse event.

Efficacy

In all 50 patients, the ORR (partial response or better) was 60.0% (95%CI: 45.2-73.6), with 24.0% (95%CI: 13.1-38.2) having a very good partial response or better (≥VGPR) (Figure 2). In the phase II/RP2D cohort (N=38), the ORR was 65.8% (95%CI: 48.6-80.4; N=25 responding patients), with 11 patients (28.9%; 95%CI: 15.4-45.9) having ≥VGPR (Figure 2). CBR in all 50 patients and the phase II/RP2D cohort was 62.0% (95%CI: 47.2-75.3) and 68.4% (95%CI: 51.3-82.5), respectively. In patients who received lenalidomide in their most recent prior therapy (N=40), ORR was 55.0%. Among the 17 and 23 patients who received full-dose and maintenance lenalidomide, respectively, in their most recent prior therapy, ORR were 47.1% and 60.9%. In lenalidomide-refractory (N=28) and bortezomib-refractory (N=10) patients, ORR were 57.1% and 50.0%, respectively. A total of 6 patients had samples taken to confirm achievement of complete response and for minimal residual disease (MRD) analysis; one patient was not evaluable due to lack of a clonality sample, and samples are still under analysis for the other 5.

The median duration of response (DOR) in all 30 responding patients was 18.0 months (95%CI: 12.3-46.0) and in the 19 responding patients treated at the RP2D was 19.3 months (95%CI: 11.6-not evaluable [NE]) (Figure 3A). DOR appeared similar between responding patients with refractory or relapsed disease status (N=19 and 11, median 19.3 and 22.5 months, respectively, *P*=0.38), with lenalidomide-refractory and lenalidomide-non-refractory disease (N=16 and 14, median 18.0 and 22.5 months, respectively, *P*=0.37), and with or without 1q amp (N=9 and 13, median 12.6 months and not reached, *P*=0.20), but shorter in responding patients who were bortezomib-refractory compared with those who were not (N=5 and 25, median 12.6 and 22.5 months, *P*=0.0082). Comparisons of DOR in other subgroup pairs

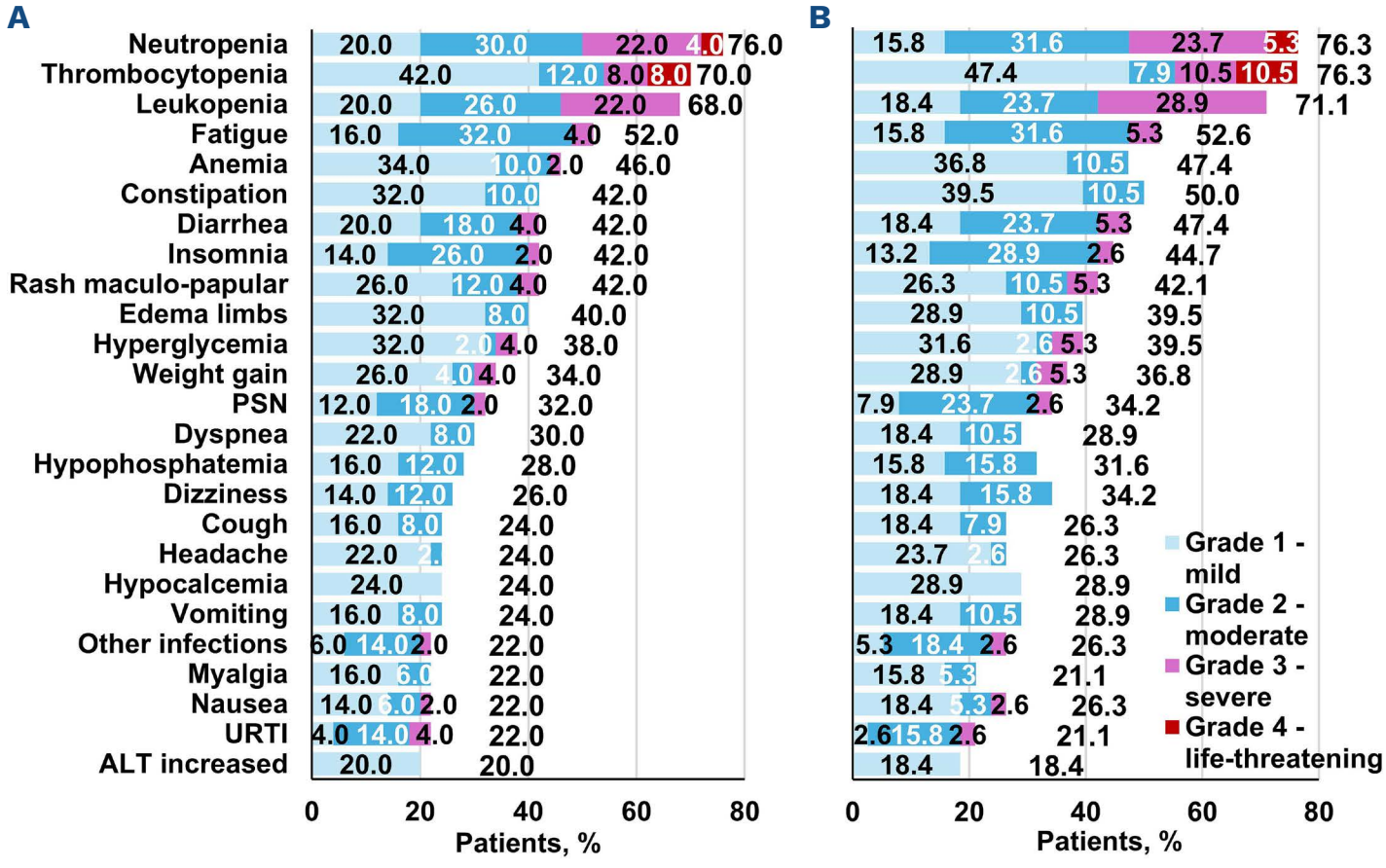


Figure 1. Most common toxicities reported on treatment with twice-weekly ixazomib plus pomalidomide and dexamethasone. Figures show all adverse events (AE) reported in ≥20% of patients in (A) the overall population (N=50) and (B) those treated at the RP2D (N=38). ALT: alanine aminotransferase; PSN: peripheral sensory neuropathy; RP2D: recommended phase II dose; URTI: upper respiratory tract infection.

were limited by small numbers of responding patients in one of the subgroups (N<5).

At data cut-off, PFS events had occurred in 30 patients (60.0%), including 27 who had PD and 3 who had died in the absence of PD. The median PFS in all 50 patients was 13.9 months (95%CI: 11.6-20.6) and in patients treated at the RP2D was 17.8 months (95%CI: 12.2-24.5) (Figure 3B), with respective 2-year PFS rates of 28.3% (95%CI: 14.3-44.0) and 33.6% (95%CI: 16.1-52.1). PFS in select patient subgroups is shown in Figure 4. PFS appeared similar between patients with refractory or relapsed disease status (Figure 4A), patients who were lenalidomide-refractory or non-refractory (Figure 4B), and those with high-risk and standard-risk cytogenetics (Figure 4D), including patients with/without del(17p) (Figure 4E) and patients with/without 1q amp (Figure 4F). Patients who were bortezomib-refractory (N=10) had shorter PFS than those who were not (N=40), with median PFS of 9.7 and 16.4 months, respectively (Figure 4C). Patients who had a response of ≥VGPR (N=12) had longer PFS than those who had <VGPR (N=38), with medians of 29.7 and 12.4 months, respectively (Figure 4G).

The median time to progression (TTP) in all 50 patients was 13.9 months (95%CI: 11.6-20.6) and in patients treated at the RP2D was 17.8 months (95%CI: 12.2-46.8), with respective 2-year TTP rates of 27.6% (95%CI: 13.2-44.2) and 33.2% (95%CI: 14.7-53.0). With 10 patients (20.0%) having died in total, median OS was not reached in all 50 patients

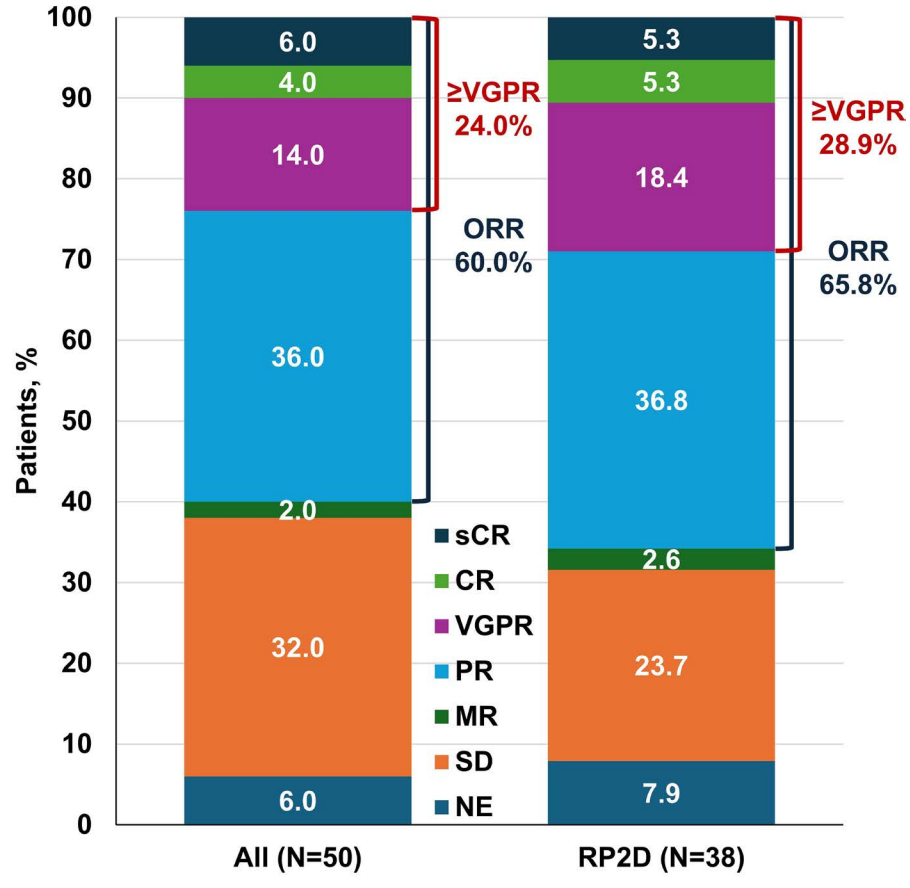


Figure 2. Best responses to twice-weekly ixazomib plus pomalidomide and dexamethasone. Best response to study treatment in (A) the overall population (N=50) and (B) those treated at the recommended phase II dose (RP2D) (N=38). CR: complete response; MR: minimal response; NE: not evaluable; ORR: overall response rate; PR: partial response; RP2D: recommended phase II dose; sCR: stringent complete response; SD: stable disease; VGPR: very good partial response.

or in patients treated at the RP2D (Figure 3C); 3-year OS rates were 85.2% and 80.3%, respectively.

Discussion

This phase I/II, multicenter study incorporated community sites and thereby reflected real-world treatment practice within the rigor of a clinical study. It demonstrated the real-world feasibility, safety, and efficacy of the all oral triplet regimen of twice-weekly ixazomib plus Pom-dex. The regimen was well tolerated in an elderly RRMM patient population (60% aged ≥65 years; although 98% had Eastern Cooperative Oncology Group performance status 0 or 1, and all required creatinine clearance ≥45 mL/min) with substantial prior exposure to lenalidomide and bor-

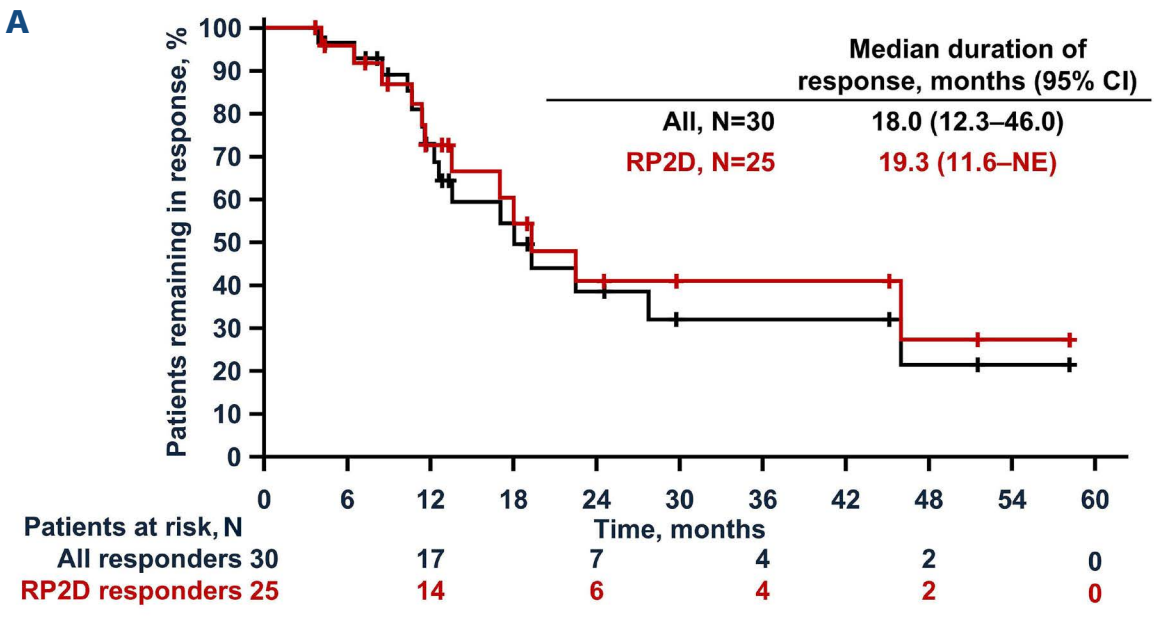


Figure 3. Kaplan-Meier analysis of time-to-event outcomes. (A) Duration of response in all responding patients (N=30) and in responding patients treated at the RP2D (N=25). (B) Progression-free survival and (C) overall survival in the overall population (N=50) and in those treated at the RP2D (N=38). CI: confidence interval; NE: not evaluable; NR: not reached; RP2D: recommended phase II dose.

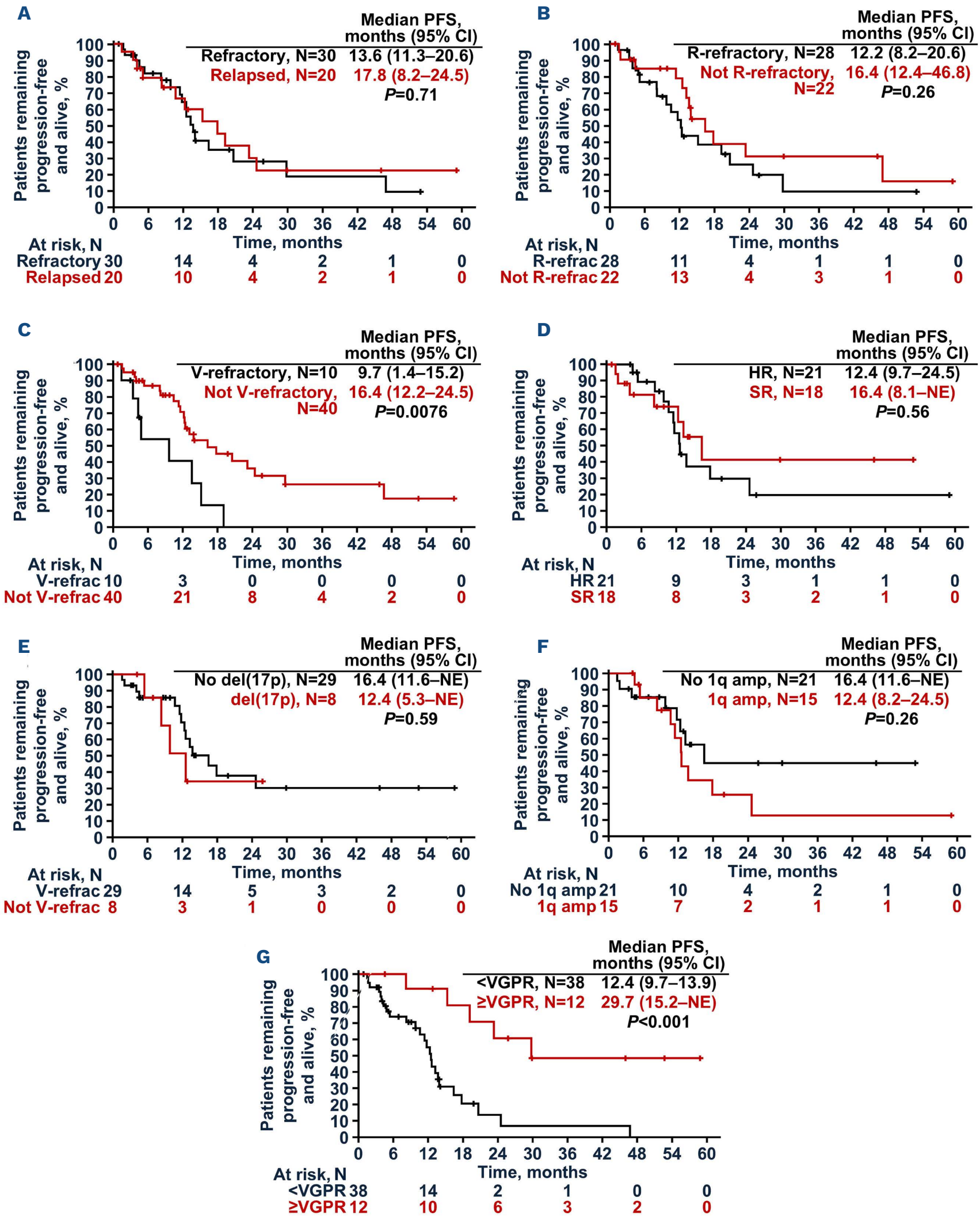


Figure 4. Kaplan-Meier analysis of progression-free survival in patient subgroups. Progression-free survival in patient subgroups defined by (A) baseline disease status (relapsed or refractory), (B) lenalidomide refractoriness, (C) bortezomib refractoriness, (D) cytogenetics risk, (E) presence of del(17p), (F) presence of 1q amp, and (G) best response to treatment. CI: confidence interval; HR: high-risk; NE: not evaluable; PFS: progression-free survival; refract: refractory; RP2D: recommended phase II dose; SR: standard-risk; V: bortezomib; VGPR: very good partial response.

tezomib and in which more than half of the patients were lenalidomide-refractory, with a lengthy median duration of treatment and a limited rate of discontinuation due to toxicity. The MTD/RP2D reflected the approved doses of ixazomib (4.0 mg) and pomalidomide (4.0 mg) in other regimens; common toxicities reflected the known safety profiles of the agents in the triplet regimen,[15,18-20,22-24,29,37] with no new or unexpected AE. The triplet regimen was efficacious, with an ORR of 65.8% at the RP2D, including 28.9% of patients with ≥VGPR, and notable long-term outcomes including durable responses and a median PFS of 17.8 months.

Together with other studies in RRMM and real-world analyses, the findings of our study demonstrate the efficacy/effectiveness of triplet therapy with ixazomib-Pom-dex. Our data specifically support the feasibility and activity of using twice-weekly ixazomib dosing in combination with Pom-dex in patients with RRMM, without appearing to substantively increase toxicity relative to previously published data with once-weekly ixazomib in combination with Pom-dex,[32] and suggest an additional ixazomib dosing schedule option for this regimen. Furthermore, these findings also suggest the feasibility of utilizing twice-weekly ixazomib in other combination regimens, such as with daratumumab-dexamethasone,[38] selinexor-dexamethasone,[39] or iberdomide-dexamethasone.[40]

Weekly ixazomib plus Pom-dex has shown substantial activity in RRMM in a number of other studies. The Alliance A061202 phase I/II randomized trial in lenalidomide-refractory patients at first relapse showed that ixazomib-Pom-dex significantly improved PFS *versus* Pom-dex alone (median 20.3 *vs*. 7.5 months, hazard ratio 0.437) and resulted in a higher ORR rate (63.2% *vs*. 43.6%) and ≥VGPR rate (28.9% *vs*. 5.1%).[32,33] These improvements were also seen in patients with high-risk cytogenetics,[32] reflecting the benefit seen in our study in terms of DOR and PFS in patients with 1q amp and del(17p). Direct cross-trial comparisons are confounded by differences in the patient populations receiving twice-weekly ixazomib in our study and weekly ixazomib in the Alliance trial, such as the higher proportion of patients with ISS stage III disease in our study and their greater exposure to prior therapies but lower rate of lenalidomide-refractory status.[32] Nonetheless, efficacy data at the RP2D in our study suggested similar ORR, ≥VGPR rate, median DOR, and median PFS with twice-weekly compared to weekly ixazomib,[32] despite including a population with somewhat more advanced-stage disease. A study of weekly ixazomib-Pom-dex plus clarithromycin in 32 PI- and lenalidomide-exposed patients with RRMM resulted in an ORR of 75% and a lengthy median PFS of 22.2 months, with similar outcomes in patients with high-risk features such as del(17p).[41] Additionally, an all-oral quadruplet regimen comprising weekly ixazomib-Pom-dex plus selinexor has shown promising preliminary activity in functionally high-risk patients with MM.[42]

Twice-weekly ixazomib dosing, as used in our study, may have specific utility in settings in which greater therapeutic intensity is required, such as in patients with high-risk features associated with more aggressive and rapidly progressive disease, who require rapid and maintained disease control. Such features may include specific high-risk cytogenetic abnormalities such as del(17p), t(4;14), and amp/gain 1q, more advanced disease stage with greater disease burden, and functional high-risk features such as early relapse[43] (potentially associated with high-risk gene-expression profiles and/or molecular features[44]). This is supported by findings from the IFM 2014-01 study, in which twice-weekly ixazomib 3.0 mg plus pomalidomide 4.0 mg and dexamethasone resulted in a >3-fold improvement in median TTP (10.2 months) compared to Pom-dex alone (3.0 months in the IFM 2010-02 study) in high-risk patients with adverse cytogenetics (del(17p) and/or t(4;14)) who were refractory to lenalidomide.[45] Our subgroup data offer additional support in this regard, indicating no or limited differences in PFS in the presence or absence of high-risk features. Furthermore, the twice-weekly regimen with 21-day treatment cycles used in our study may also be beneficial for patients in whom it would be preferable to limit the duration of continuous pomalidomide exposure (i.e., 14 days instead of 21 days in a standard 28-day cycle), such as those at potentially increased risk of pomalidomide-associated toxicities.

As noted, our study demonstrates the real-world feasibility and effectiveness of an all oral triplet regimen of twice-weekly ixazomib plus Pom-dex. Promising findings with weekly ixazomib plus Pom-dex have also been reported from a multicenter study in China that included 30 real-world and 20 clinical trial patients with RRMM after 1-3 prior lines; an ORR of 70% and a median time to next therapy of 9.5 months were reported.[31] These findings reflect the real-world feasibility and activity seen with the all oral triplet combination of ixazomib-Rd in patients with RRMM,[46-48] which represents a convenient, active option in this setting.[17] For example, although carfilzomib-Rd appears to offer somewhat better efficacy than ixazomib-Rd in clinical trials, the Korean KMM2004 study (a retrospective, real-world, multicenter analysis) showed similar response rates with the regimens and prolonged outcomes with the all oral triplet.[49] Additionally, another retrospective cohort study utilizing the TriNetX platform and real-world electronic health records showed a significantly lower risk of cardiac toxicities with ixazomib-Rd.[50]

It should be acknowledged that other triplet and quadruplet regimens incorporating a different PI, with or without a mAb, plus Pom-dex provide notable efficacy in the lenalidomide-refractory RRMM setting[26,27] and this efficacy may potentially exceed that achieved with ixazomib-Pom-dex. However, convenience, tolerability, and other real-world issues may impact the feasibility and effectiveness of such regimens compared to an all oral treatment option.

Indirect comparison of the safety profile of twice-weekly and weekly ixazomib dosing in combination with Pom-dex is confounded by differences in the patient population between our study and the Alliance trial,[32] as well as in the median number of doses of ixazomib and pomalidomide received (median 11 x 3-week cycles, compared to 9.5 x 4-week cycles[32]) and in the dexamethasone dosing schedule. Rates of hematologic toxicities showed no consistent pattern between our study (at the RP2D) and the Alliance trial,[32] with grade 2-4 neutropenia in 60.5% and 71.1%, thrombocytopenia in 28.9% and 13.2%, leukopenia in 52.6% and 42.1%, and anemia in 10.5% and 34.2% of patients, respectively. Gastrointestinal toxicities of grade 2-4 constipation (10.5% and 7.9%) and diarrhea (29.0% and 21.1%) were broadly similar, as were the rates of grade 2-4 peripheral sensory neuropathy (26.3% and 23.7%). These findings reflect the broadly similar safety profiles reported with twice-weekly ixazomib (MTD 2.0 mg/m^2)[18] and weekly ixazomib (MTD 2.97 mg/m^2)[19] in phase I monotherapy studies in heavily pretreated patients with RRMM; however, safety data for twice-weekly[20] and weekly ixazomib[22] plus Rd in patients with NDMM suggested greater toxicity with the more intensive regimen. Careful monitoring for key side effects is, therefore, important to ensure the tolerability of twice-weekly ixazomib plus Pom-dex.

Limitations of our study include the single-arm, non-comparative design, preventing direct evaluation of efficacy and safety against other regimens, and the small numbers of patients in some subgroup analyses, precluding interpretation of similar/differential efficacy. Our study also enrolled a limited number of patients with previous exposure to daratumumab, which may affect the broader representativeness of these findings in the context of widespread first-line use of CD38 monoclonal antibodies.[3,4] Nevertheless, in this context, it is interesting to note that weekly ixazomib in combination with the cereblon E3 ligase modulator iberdomide and dexamethasone has shown promising activity in elderly patients with RRMM at first relapse, including patients refractory to lenalidomide and daratumumab.[40]

In conclusion, our study has demonstrated the feasibility, tolerability, and efficacy of an all-oral triplet regimen of twice-weekly ixazomib plus Pom-dex in patients with RRMM. These findings suggest the utility of twice-weekly ixazomib dosing in this combination regimen, including its tolerability in an elderly population and its potential for use in patients with high-risk features. The results also indicate that the triplet may, therefore, represent a valuable real-world treatment option in this setting. Taken together, our findings suggest it may have a high likelihood of translation from these promising clinical trial results to clinical practice, not least given its outpatient use and all oral administration, which in turn can further improve patient outcome.[7,11]

Disclosures

ON reports advisory boards for Johnson and Johnson, BMS, Kite, AstraZeneca, GPCR Therapeutics, and Sanofi; and research funding from BMS, Takeda, and Johnson & Johnson. PMB is an employee of and reports personal financial interests in GlaxoSmithKline. GB reports honoraria from Alexion/AstraZeneca, Prothena, Janssen, and Pfizer; research funding from Pfizer; and advisory boards for Alexion/AstraZeneca, Prothena, and Prothego. CCM reports research funding from BMS. SM reports advisory board for BMS. AS reports consulting for Janssen. YL reports advisory board for OPNA Bio; and consultancy for Sanofi. MAH-B reports consultancy for IMF, GSK, Amgen, Alliance, Pfizer, MMRF, BMS/Celgene, and Sanofi; research funding from Karyopharm, GSK, Amgen, Johnson & Johnson, Pfizer, MMRF, BMS/Celgene, and Sanofi; and honoraria from IMF, GSK, Amgen, Alliance, Pfizer, MMRF, BMS/Celgene, and Sanofi. NCM reports consultancy for BMS, Janssen, Oncopep, Amgen, Karyopharm, Legend, AbbVie, Takeda, and GSK; and is a member of the board of directors and owner of stock holdings in Oncopep. KCA reports advisory boards for Johnson & Johnson, Astrazeneca, Pfizer, and Genentech-Roche; and founder/on the board of Oncopep, C4 Therapeutics, Dynamic Cell Therapies, Window, Starton, and Predicta. IMG reports consultancy for Bristol-Myers Squibb, AstraZeneca, Amgen, Curio Science, Sanofi, Janssen, Pfizer, Menarini Silicone Biosystems, Aptitude Health, GlaxoSmithKline, AbbVie, Adaptive Biotechnologies, Window Therapeutics, and Regeneron; honoraria or speaker fees from Vor Biopharma, Janssen, MJH Life Sciences, Novartis, Takeda, Amgen, Regeneron, Curio Science, Standard Biotools, and Physicians' Education Resource; founder and executive board member of and private equity ownership in Predicta Biosciences; and her spouse is chief medical officer of and holds private equity in Disc Medicine. PGR reports grants to the institution for clinical trials from Karyopharm, and Oncopeptides; and advisory committees for Bristol Myers Squibb / Celgene, GSK, Karyopharm, Oncopeptides, Regeneron, and Sanofi. All the other authors have no conflicts of interest to disclose.

Contributions

ON and PGR designed the study, enrolled and treated patients, oversaw the study, collected, analyzed and interpreted study data, and wrote the original draft of the paper. RAR and EJB oversaw the study and collected, analyzed and interpreted study data, and wrote the original draft of the paper. KCA interpreted study data. PMB, TJB, JPL, GB, CCM, JLR, SM, AS, YL, MAH-B, MPC, TN, AD, ER, AMVH, AJD, RG, NCM, KM, IMG and KCA enrolled and treated patients. MPC, TN, ER, AMVH, AJD, RG, KM, AL and RP oversaw the study and collected data. All authors critically reviewed and revised the draft manuscript and approved the final version of the manuscript for publication.

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Data-sharing statement

Access to anonymized clinical data might be granted upon reasonable request to the corresponding author.

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