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Phase I/II trial of the oral regimen ixazomib, pomalidomide, and dexamethasone in relapsed/refractory multiple myeloma

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Abstract

In this phase I/II trial, a triplet regimen of ixazomib (Ixa: 3 or 4 mg), pomalidomide (Pom: 4 mg), and dexamethasone (Dex: 40 mg) was administered to 32 lenalidomide-refractory multiple myeloma (MM) patients; 31 were evaluable for response and toxicity. At dose level 1 (DL1, 3 mg Ixa), 1/3 patients experienced grade 3 fatigue, grade 3 lung infection, grade 4 neutropenia, and grade 4 thrombocytopenia; all were considered dose limiting. Per 3+3 phase I design, an additional 3 patients were enrolled to DL1, with no further dose limiting toxicity (DLT). At dose level 2 (DL2, 4 mg Ixa), 1/3 patients had dose-limiting febrile neutropenia, neutropenia, and thrombocytopenia (grade 4 each). DL2 was expanded to enroll 3 additional patients with no further DLT, establishing the recommended phase II dose (RP2D). In phase II, 19 additional patients were treated at RP2D. With a median follow-up of 11.9 months, 48% achieved ≥partial

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response (PR), with 5 patients (20%) achieving very good partial response (VGPR) and 76% experiencing ≥stable disease. The most common adverse events (≥grade 2) were anemia, neutropenia, thrombocytopenia, and infections. Peripheral neuropathy was infrequent. In summary, Ixa/Pom/Dex is a well-tolerated and effective oral combination therapy for patients with relapsed/refractory MM.

Introduction

The treatment of multiple myeloma (MM) has been marked in recent years with the introduction of new drugs, often combined as doublet or triplet regimens, that have yielded improved outcomes. However, when patients do relapse, their disease is often refractory to these new therapeutic agents. Outcomes for these patients, especially those refractory to the proteasome inhibitor bortezomib and the immunomodulatory drug lenalidomide, are particularly discouraging.[1] Furthermore, as patients are living progressively longer with MM, both efficacy in advanced disease as well as a favorable toxicity profile are needed goals.[2]

Proteasome inhibition has become a valuable mainstay for MM since the availability of bortezomib.[3-5] However, two initial limitations were the need for parenteral administration and the risk of peripheral neuropathy.[6] The latter concern of neuropathy has been alleviated by use of subcutaneous bortezomib[7, 8] as well as the introduction of carfilzomib.[9, 10] Regardless, the cardiovascular toxicities seen with carfilzomib have raised concerns, and the twice weekly intravenous administration are potentially limiting for elderly or frail patients.[11]

Ixazomib is an orally available peptide boronic acid that preferentially binds to the β_5 subunit of the 20S proteasome and the β_1 and β_2 subunits at high concentrations.[12] Ixazomib as a single agent or in combination with other agents has demonstrated antitumor activity and tolerable safety profiles.[13-17] In a phase III trial, an entirely oral triplet regimen containing ixazomib, lenalidomide, and dexamethasone was associated with a significantly longer progression-free survival in comparison with placebo plus lenalidomide-dexamethasone. This finding led to the approval of this combination for relapsed myeloma.[18] Because ixazomib can be safely combined with an immunomodulatory drug, it would be of benefit to leverage the effectiveness and tolerability of an all-oral triplet regimen in a combination suitable for patients refractory to lenalidomide. The immunomodulatory drug pomalidomide is an appealing alternative to lenalidomide on the basis of its tumoricidal and immune-stimulatory effects in the relapsed/refractory setting, including in patients refractory to lenalidomide[19], and its use with dexamethasone.[19-26] In this phase I/II study, we report the safety and efficacy of ixazomib-pomalidomide-dexamethasone for patients with relapsed/refractory, lenalidomide-resistant multiple myeloma.

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Methods

Study design

This open-label, multi-center phase I/II study was designed to assess the safety, tolerability, and activity of weekly oral ixazomib combined with pomalidomide and dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma. Pomalidomide and dexamethasone were administered at 4 mg and 40 mg, respectively, with the exception of patients >75 years of age who received 20 mg dexamethasone. For the phase I portion, two doses of ixazomib, 3 mg and 4 mg, were tested. Patients were enrolled at four sites in the United States. The study was performed in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonization, and the Guidelines for Good Clinical Practice, and was approved by the institutional review boards at each of the individual enrolling institutions. All participants gave written informed consent. The study was conducted through the Multiple Myeloma Research Consortium. The study is registered at www.clinicaltrials.gov as #NCT02119468.

Drug administration

For both the phase I and phase II studies, patients received ixazomib on days 1, 8, and 15 of a 28-day cycle; in addition, all patients were given pomalidomide daily on days 1-21 of the cycle and dexamethasone on days 1, 8, 15, and 22. The study proceeded with a standard 3+3 design, and dose escalation decisions were based on the dose-limiting toxicities (DLTs) occurring in cycle 1. DLTs were defined as 1 or more of the following toxicities that were at least possibly related to ixazomib or pomalidomide: grade 4 neutropenia or grade 3 with fever ≥38.5°C, grade 4 thrombocytopenia or grade 3 with bleeding, delay in starting cycle 2 for >7 days because of treatment related toxicity, and any dose modification or delay of ixazomib or pomalidomide during cycle 1, except when caused by hypo/hyperthyroidism (grade ≤2) or herpes zoster infection. Also, DLTs included any grade ≥3 non-hematological toxicity except for diarrhea, fatigue, nausea, and vomiting recovering to grade <3 within 48 hours, and allergic reaction/hypersensitivity or electrolyte/metabolic toxicity correcting to grade <1 within 48 hours. Antithrombotic prophylaxis was mandatory for all patients. Antiviral prophylaxis against herpes zoster was also mandatory.

Study objectives

The primary objective of the phase I portion of the study was to determine the recommended phase II dose (RP2D) of ixazomib when given in combination with pomalidomide and dexamethasone. The secondary objective was to evaluate the safety of ixazomib at each dose level when given as part of this three-drug regimen.

The primary objectives of the phase II portion were to estimate the overall response rate and to evaluate the antitumor activity of the three drug combination (ixazomib at the RP2D, pomalidomide, and dexamethasone). The secondary objectives were to characterize and evaluate toxicities, and to obtain estimates of response duration, depth of response, clinical benefit response, and survival (overall and progression-free).

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Study methods

Inclusion/exclusion criteria

The study enrolled patients 18 years of age or older diagnosed with relapsed or relapsed and refractory multiple myeloma and treated with a minimum of 1 prior regimen and maximum of 5 prior regimens. Patients must have had therapy with a proteasome inhibitor and lenalidomide and have been refractory to lenalidomide according to the International Myeloma Working Group (IMWG) definition of refractory disease (progressive disease on or within 60 days of stopping lenalidomide). Patients were required to have measurable disease (serum M protein ≥ 0.5 g/dL, urine M protein ≥ 200 mg/24 hours, or serum free light chain ≥ 10 mg/dL provided the free light chain ratio is abnormal), Eastern Cooperative Oncology Group performance status of 0 to 2, and adequate hematologic (absolute neutrophil count ≥1000/mm^3, platelets ≥75,000/mm^3), hepatic (total bilirubin ≤1.5 × upper limit of normal, alanine/aspartate aminotransferase ≤3 × upper limit of normal), and renal (creatinine clearance ≥45 mL/minute) function.

Key exclusion criteria were grade >2 peripheral neuropathy; gastrointestinal disease or history of a procedure that could interfere with oral absorption and tolerance of ixazomib or pomalidomide; systemic treatment with strong CYP1A2 inhibitors or strong inhibitors/inducers of CYP3A within 14 days before the first dose of ixazomib; evidence of current uncontrolled cardiovascular conditions; and ongoing/active systemic infection, active hepatitis B or C virus infection, or known HIV positivity. Prior treatment with a multidrug regimen containing pomalidomide was disallowed except for the two-drug combination of pomalidomide and dexamethasone. Patients must not have been refractory to pomalidomide (progression on or within 60 days of stopping pomalidomide). Prior ixazomib was allowed provided that patients were not refractory.

Toxicity and disease assessments

Adverse events (AEs) were monitored throughout the study and were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute v4.03. Responses were assessed using the IMWG uniform criteria, incorporating minimal response (MR) per the European Group for Blood and Marrow Transplantation criteria. Responses were assessed by the investigators.

Statistical considerations

The phase I portion followed a standard 3+3 dose escalation design, to evaluate toxicities associated with ixazomib when given in combination with pomalidomide and dexamethasone. The primary endpoint for the phase I portion was toxicity. Two doses of ixazomib, 3mg and 4 mg, were to be tested in two dose levels. In the phase II portion, a Gehan two-stage design was implemented to estimate the response rate and evaluate the activity of ixazomib when given in combination with pomalidomide and dexamethasone. Patients were considered evaluable for response if they had baseline disease assessments, received at least 75% of pomalidomide and 100% of ixazomib planned doses during the first cycle of therapy, and had their disease re-evaluated. At stage 1, 9 patients were entered on the study. Note: Because patients treated during the phase I portion of the trial at the dose

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selected for the phase II trial (n=6) were brought forward, only 3 additional patients were to be enrolled at stage 1. Under this design, if the study regimen is >30% effective, there would be a 96% chance of at least one success. If 0 responses in the first 9 patients were observed, the study would be terminated and the true regimen response would be declared ≤30%. If at least 1 patient responded, the trial would continue to the second stage.

At stage 2, 16 additional patients were to be enrolled. This accrual provides for estimation of the response rate with no more than 10% standard error. The primary activity endpoint, overall response rate (confirmed stringent complete response/complete response/very good partial response or partial response [sCR/CR/VGPR or PR]), based on the International Myeloma Working Group (IMWG) criteria, was calculated as the number of responders divided by the number of evaluable patients. Confirmation of sCR/CR/VGPR or PR was assessed by IMWG criteria. Secondary activity endpoints were as follows: duration of response (defined as the time interval from the date of first documented response [sCR/CR/VGPR or PR] to documented disease relapse, progression, or death, whichever occurs first); clinical benefit rate (also based on the IMWG criteria, calculated as the number of responders plus those with a minimal response [MR] or stable disease [SD] divided by the number of evaluable patients); overall survival (defined as the time interval from date of first dose of study drug to date of death from any cause); and progression-free survival (defined as the time interval from date of first dose of study drug to first documented disease relapse, progression, or death from any cause, whichever occurs first). Exact 95% confidence intervals were calculated for these estimates. Response rates were also evaluated on the basis of number and type of prior therapy(ies). Time to response, duration of response, and survival were estimated using the product limit method of Kaplan and Meier.

Results

Patients

A total of 32 patients were enrolled between July 2014 and March 2016; 7 patients were treated at dose level 1 (DL1) (3 mg ixazomib, 4 mg pomalidomide, 40 mg dexamethasone). One patient treated on DL1 was declared inevaluable for dose limiting toxicity evaluation/response given that the patient received less than 75% of both pomalidomide and ixazomib because of the development of a respiratory syncytial virus infection, which was considered unrelated to study treatment. 25 patients were treated at dose level 2, the RP2D, (4 mg ixazomib, 4 mg pomalidomide, 40 mg dexamethasone), including 6 and 19 patients in the phase I and II portions, respectively. Patient demographics and baseline characteristics are summarized in Table 1. Patients received a median of 2 prior therapies (range 1-5), which included bortezomib (100%) and carfilzomib (19%). No patients were previously administered ixazomib, and approximately two-thirds were refractory to bortezomib (progressive disease on or within 60 days of stopping bortezomib). All patients were lenalidomide-refractory (see Table 2 for prior lenalidomide doses and the associated number of patients). Eight patients were 70 years of age or older at the start of study treatment, and 75% had previously undergone an autologous stem cell transplant.

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Dose limiting toxcities/ Recommended phase II dose

At DL1 (3 mg Ixa, 4 mg Pom, 40 mg Dex), 1 of the 3 patients initially enrolled experienced grade 3 fatigue, grade 3 lung infection, grade 4 neutropenia, and grade 4 thrombocytopenia; all were considered dose limiting (Table 3). Given that 1 of 3 patients experienced a DLT, an additional 3 patients were enrolled at this dose level; no further DLT was observed. Following a review of toxicities on DL1, authorization to escalate to DL2 (4 mg Ixa, 4 mg Pom, 40 mg Dex) was granted, and 3 patients were enrolled on DL2. In the first 3 patients treated, 1 patient experienced grade 4 febrile neutropenia, grade 4 neutropenia, and grade 4 thrombocytopenia (Table 3). Per the 3+3 design, DL2 was expanded to enroll/treat 3 additional patients; again, no further DLTs were reported. As this dose level was the highest planned, DL2 was declared the recommended phase II dose (RP2D).

Response

A total of 31 patients were evaluable for response and secondary endpoints; the median follow-up was 12.0 months (range 1.9 – 32.1), and median number of cycles received was 4.5 (range 1 – 28). One patient, treated on DL1 in the phase I portion, did not meet criteria for dose limiting toxicity assessment, for reasons unrelated to study drug and was replaced. Although this patient was also considered inevaluable for response per protocol evaluability definition, the patient ultimately received 7 cycles of therapy. The best response for this patient was PR after two cycles of treatment. Another patient withdrew from study because of disease progression before receiving ≥75% of both ixazomib and pomalidomide in the first cycle. On the basis of the protocol evaluability definition, this patient was evaluable for response. A total of 48% of patients at the RP2D (12/25) (95% CI: 27.8 – 68.7) achieved ≥partial response (PR), with 5 patients (20%) (95% CI: 6.8 – 40.7) achieving a very good partial response (VGPR) and 76% (19/25) (95% CI: 54.9 – 90.6) experiencing stable disease or better. The median PFS was 8.6 months (95% CI, 1.8 – not reached); 1-year OS was 82% (95% CI, 59 – 93) and median OS was not reached. The duration of response (≥PR among patients treated at the RP2D) was 9.2 months (range: 0.9 -13.9). In the 14 patients also refractory to bortezomib, 29% achieved PR or better, and the clinical benefit rate was 71% (95% CI: 41.9 – 91.6). (See also Supplementary Tables 1 -2 for additional response data.)

Cytogenetic abnormalities

Of the 31 evaluable patients, 12 patients had the following cytogenetic abnormalities: 5 (16%) 1q amplification, 5 (16%) 17p deletion, and 2 (6%) t(4,14) and 1q amplification. (Although gains in chromosome 1q have been identified as a poor prognostic marker by several studies,[27-30] the IMWG classification of cytogentically high-risk disease does not currently encompass this abnormality.) Six patients had normal cytogenetics, and the cytogenetic profile is unknown or was not done for 13 patients. Two (17%, 95% CI: 2.1 – 48.4) patients achieved a VGPR. 50% (95% CI: 21.1 – 78.9) and 92% (95% CI: 61.5 – 99.8) achieved an overall response rate and clinical benefit rate, respectively. (See also Supplementary Table 3 for responses by category.)

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Adverse events

An AE of any grade that was considered at least possibly related to the treatment was reported in 97% of patients at both DLs (Table 4). There were no treatment-related deaths. A grade 3 or 4 AE considered at least possibly related to the drug combination was observed in 23 (74%) patients overall, with 6 (100%) at DL1 and 17 (68%) at DL2. The most common grade 2 or higher AEs were anemia, neutropenia, thrombocytopenia, and infections. Figure 1 provides the distribution of all grades of selected toxicities deemed to be at least possibly related to administering the drug combination. Two patients withdrew from treatment because of an AE (1 from a grade 3 lung infection possibly related to study treatment, and 1 from grade 4 treatment-related febrile neutropenia), and in one patient treatment was delayed because of a serious adverse event, grade 3 treatment-related heart failure. This patient had a prior history of atrial fibrillation and congestive heart failure several years earlier while on lenalidomide, bortezomib and dexamethasone. On study she was admitted with shortness of breath that responded to diuretics; given her prior history it was deemed possibly treatment related. There was one case of disseminated zoster that required hospitalization; this patient had stopped acyclovir prophylaxis on his own accord two weeks prior. Another AE of note was gastrointestinal bleeding in one patient during cycle 14. Colonoscopy revealed a nonbleeding rectal ulcer, and the patient was given a presumptive diagnosis of colitis. We also noted one case of grade 3 tumor lysis that resolved within 48 hours with supportive care. Interestingly, peripheral neuropathy at least possibly related to the treatment was not frequently observed: 3 patients had peripheral sensory neuropathy at DL1 (all grade 1); 7 patients had this AE at DL2 (5 at grade 1, 2 at grade 2). One patient at DL2 had grade 1 peripheral motor neuropathy.

Ten patients died on the study; the most common cause of death was disease progression (9), followed by hypertensive disease that was determined to be unrelated to treatment (1).

Discussion

Myeloma therapy has evolved from the original paradigm of a fixed number of cycles of chemotherapy to one that recognizes that prolonged treatment can deepen response and prolong remission. In earlier years even in the era of novel agents such as intravenous bortezomib or thalidomide, prolonged treatment was not possible because of toxicity. In the relapsed setting the challenges are compounded by the need to find drugs active against disease that is refractory to the agents used upfront, and balancing toxicity in heavily pretreated patients. In addition, one cannot underscore the importance of quality of life and convenience if we are to commit patients to long term therapy.

This study supports the clinical utility of the entirely oral triplet regimen of ixazomib, pomalidomide, and dexamethasone for patients with relapsed or relapsed/refractory multiple myeloma who are specifically refractory to lenalidomide. Responses were promising in the context that patients had 1-5 prior lines of therapy. A number of studies of pomalidomide-dexamethasone doublet regimens have indicated no cross-resistance between pomalidomide and lenalidomide,[21, 22, 24, 25] justifying the use of pomalidomide for patients refractory to lenalidomide. Less is known about the therapeutic efficacy of ixazomib for patients who are bortezomib resistant; however, preclinical experiments point toward activity of ixazomib on

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cells from patients resistant to bortezomib,[31] and several studies have shown activity even in bortezomib refractory patients,[14, 32] although responses may be infrequent.[33, 34] Response and survival rates in this trial were lower than in a study of bortezomib/pomalidomide/dexamethasone,[35] possibly reflecting the modest response rate for bortezomib-refractory patients. Other possible approaches include optimizing the dose and schedule of the ixazomib, especially for bortezomib-refractory patients. For instance, the twice-weekly schedule at an MTD of 2.0mg/m^2 showed no severe neuropathy and a 76% stable disease or better rate.[13] The biweekly dosing at a flat dose of 3.0 or 3.7 mg has also been done in conjunction with an immunomodulatory drug in newly diagnosed patients and yielded high response rates.[36]

The other challenge in the relapsed setting is biologically high risk disease and the presence of clonal evolution. Hence, we were encouraged by the responses appearing in the 12 patients that were known to have cytogenetic abnormalities. It has been shown that the pomalidomide-dexamethasone regimen may partially surmount the poor prognosis of the 17p deletion in relapsed/refractory MM, but the t(4;14) translocation was not similarly overcome.[26] Further investigation is required to determine the extent to which ixazomib affects high risk cytogenetics when combined with pomalidomide and dexamethasone. The response and survival rates are favorable compared to the NIMBUS and STRATUS pomalidomide/dexamethasone trials (31% and 32.6% ORR, and median PFS of 4.0 and 4.6 months, respectively).[19, 37] A phase 1b trial of pomalidomide and daratumumab yielded an improved ORR (60%); however, infusion-related reactions occurred in 50% of patients. Similarly, the CD38 antibody isatuximab in conjunction with pomalidomide in a phase I trial demonstrated an ORR (PR or better) of 62% but with similar rates of infusional toxicity.[38] The lack of risk for such reactions is an advantage of all-oral regimens, together with patient convenience and independence. On the other hand, patient compliance may be suboptimal, although interventions such as pill diaries may alleviate this concern. It should be noted that all subjects in this study were refractory to lenalidomide, as many were in fact double refractory (59%) and even triple refractory (lenalidomide/bortezomib/carfilzomib) (9%), and every patient had received multiple lines of prior therapies.

Furthermore, toxicities were manageable and were in line with previous experience with the drug, including hematologic events. Notably, few patients experienced peripheral neuropathy that was at least possibly related to treatment. Previous studies have shown a low to moderate association between ixazomib use and increased incidence of peripheral neuropathy.[13-18] A relatively modest rate of gastrointestinal disturbance in this trial of three oral drugs is also part of the favorable toxicity profile, which is particularly noteworthy as other novel oral agents for multiple myeloma, such as selenixor and oprozamib, are associated with high rates of nausea and vomiting when used as monotherapy.[39, 40] Moreover, the tolerability of this regimen allows its use for extended durations as evidenced by several patients who are still on study for over two years. The tolerability of the combination allows for each individual drug to be given at its recommended single agent dose. Of note, the dose might be further increased, beyond 4 mg ixazomib (the study's RP2D) as in a randomized phase 2 trial of ixazomib and dexamethasone, where 5.5 mg ixazomib yielded a superior ORR over 4 mg ixazomib (54% vs. 31%).[16] However, in that two-drug regimen, toxicities were more frequent, and 40% of patients required a dose

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reduction by the fourth cycle, suggesting that the increase in the ixazomib dose may ultimately affect the ability to achieve dose intensity of pomalidomide without undue toxic effects.

On the basis of the promising efficacy and manageable toxicity resulting from the use of the ixazomib-pomalidomide-dexamethasone regimen for lenalidomide-refractory patients, we believe that the findings justify further study of this combination for relapsed patients with myeloma who are refractory to lenalidomide, preferably with randomized comparisons to specifically identify clinical benefit. In addition, this combination may be an ideal backbone for future studies in conjunction with the anti-CD38 monoclonal antibody daratumumab or isatuximab,[41-43] given the favorable safety profile and entirely oral route.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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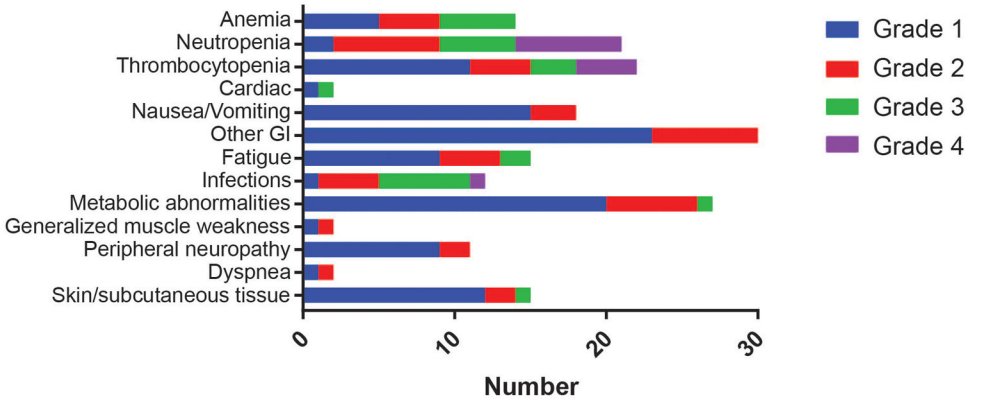

Figure 1. Distribution of selected toxicities by grade

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Table 1

Patient characteristics.

Variable (All:N=32, DL2:N=25)	Median (range) or N(%), All	Median (range) or N(%), DL2
Female/Male	12 (38%) / 20 (62%)	10 (40%) / 15 (60%)
Age at enrollment (years)	62 (38 - 84)	63 (38 - 84)
Time from diagnosis (years)	3.6 (1.0 - 8.9)	3.5 (1.0 – 8.9)
Number of prior lines of therapy	2 (1 - 5)	2 (1 - 5)
Bortezomib		
exposure	32 (100%)	25 (100%)
refractory	19 (59%)	14 (56%)
Lenalidomide		
exposure	32 (100%)	25 (100%)
refractory	32 (100%)	25 (100%)
Carfilzomib		
exposure	6 (19%)	5 (20%)
refractory	3 (50%) (N=6)	2 (40%) (N=5)
Double refractory (BOR/LEN)	19 (59%)	14 (56%)
Triple refractory (BOR/LEN/CFZ)	3 (9%)	2 (8%)
Prior autologous transplant	24 (75%)	18 (72%)

Abbreviations: DL, dose level; BOR, bortezomib; LEN, lenalidomide; CFZ, carfilzomib.

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Table 2

Prior lenalidomide doses

Lenalidomide dose	Number of patients treated
5 mg	2
10 mg	11
15 mg	4
20 mg	1
25 mg	14

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Table 3

Phase I: Dose-limiting toxicities.

	Number of patients treated	Number of patients with DLTs	Adverse events associated with the DLT
DL1 Ixa 3 mg, Pom 4 mg, Dex 40 mg	6	1	Fatigue (Gr 3), lung infection (Gr 3), neutropenia (Gr 4), thrombocytopenia (Gr 4)
DL2 Ixa 4 mg, Pom 4 mg, Dex 40 mg	6	1	Febrile neutropenia (Gr 4), neutropenia (Gr 4), thrombocytopenia (Gr 4)

Abbreviations: DLT, dose limiting toxicity; DL, dose level; Gr, grade.

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Table 4

Adverse events, by dose level.

	Dose Level 1 Ixa 3 mg, Pom 4 mg, Dex 40 mg		Dose Level 2 Ixa 4 mg, Pom 4 mg, Dex 40 mg	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Hematologic AEs				
Neutropenia	5	2	16	10
Anemia	4	1	10	4
Thrombocytopenia	5	1	17	6
Leukopenia	6	2	15	7
Lymphopenia	6	5	14	7
Nonhematologic AEs				
Fatigue	4	1	11	1
Sinus bradycardia	1	0	0	0
Diarrhea	2	0	7	1
Nausea	2	0	10	0
Vomiting	1	0	5	0
Edema	2	0	3	0
Infections and infestations	4	3	8	4
Increased ALT/AST	4	0	2	0
Increased blood creatinine/bilirubin	4	0	2	0
Metabolism/nutrition disorders	8	1	19	0
Peripheral sensory neuropathy	3	0	7	0
Peripheral motor neuropathy	0	0	1	0
Dizziness	2	0	6	1
Pruritus/rash	5	0	9	0
Hypertension	2	0	4	0
Hypotension	0	0	4	1

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Dex, dexamethasone; Ixa, ixazomib; Pom, pomalidomide