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ORIGINAL REPORT

Selective Inhibition of Nuclear Export With Oral Selinexor for Treatment of Relapsed or Refractory Multiple Myeloma

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ABSTRACT

Purpose

Selinexor, a first-in-class, oral, selective exportin 1 (XPO1) inhibitor, induces apoptosis in cancer cells through nuclear retention of tumor suppressor proteins and the glucocorticoid receptor, along with inhibition of translation of oncoprotein mRNAs. We studied selinexor in combination with low-dose dexamethasone in patients with multiple myeloma refractory to the most active available agents.

Patients and Methods

This phase II trial evaluated selinexor 80 mg and dexamethasone 20 mg, both orally and twice weekly, in patients with myeloma refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide (quad-refractory disease), with a subset also refractory to an anti-CD38 antibody (penta-refractory disease). The primary end point was overall response rate (ORR).

Results

Of 79 patients, 48 had quad-refractory and 31 had penta-refractory myeloma. Patients had received a median of seven prior regimens. The ORR was 21% and was similar for patients with quad-refractory (21%) and penta-refractory (20%) disease. Among patients with high-risk cytogenetics, including t(4;14), t(14;16), and del(17p), the ORR was 35% (six of 17 patients). The median duration of response was 5 months, and 65% of responding patients were alive at 12 months. The most common grade ≥ 3 adverse events were thrombocytopenia (59%), anemia (28%), neutropenia (23%), hyponatremia (22%), leukopenia (15%), and fatigue (15%). Dose interruptions for adverse events occurred in 41 patients (52%), dose reductions occurred in 29 patients (37%), and treatment discontinuation occurred in 14 patients (18%).

Conclusion

The combination of selinexor and dexamethasone has an ORR of 21% in patients with heavily pretreated, refractory myeloma with limited therapeutic options.

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INTRODUCTION

Survival of patients with multiple myeloma has improved over the past 15 years as a result of the introduction of several novel therapeutic agents and high-dose chemotherapy with autologous stem-cell transplantation. In particular, five new medications with proven single-agent antimyeloma efficacy have been introduced, including the proteasome inhibitors bortezomib and carfilzomib, the cereblon-binding drugs lenalidomide and pomalidomide, and the anti-CD38 monoclonal antibody daratumumab.[1-5] In addition, the histone deacetylase inhibitor panobinostat and pegylated liposomal doxorubicin have been approved in combination with bortezomib, and both the oral proteasome inhibitor ixazomib and the anti-SLAMF7 monoclonal antibody elotuzumab have been approved in combination with lenalidomide. However, none of these agents are curative, and patients with myeloma eventually develop disease refractory to all available therapies.[6] Myeloma progression is accompanied by complex cytogenetic and epigenetic alterations, which include overexpression of

ASSOCIATED CONTENT

Appendix
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oncoproteins and mutation or functional inactivation of tumor suppressor proteins.[7] Novel medicines that overcome or bypass these resistance mechanisms are needed to improve the outcomes of patients with multiple myeloma.

The nuclear export system is an attractive target for anticancer therapy. Of the eight known mammalian proteins that mediate the export of macromolecules from the nucleus to the cytoplasm, exportin 1 (XPO1; also known as CRM1) is the sole exporter for most tumor suppressor proteins, the glucocorticoid receptor, and several eIF4A-bound oncoprotein mRNAs.[8,9] Increasing expression of XPO1 accompanies the progression from monoclonal gammopathy of undetermined significance to smoldering multiple myeloma to active multiple myeloma.[10] Overexpression of XPO1 in multiple myeloma correlates with poor survival and leads to the functional inactivation of tumor suppressor proteins and the glucocorticoid receptor, as well as elevated oncoprotein expression.[10-15] Knockdown of XPO1 with RNA interference or targeted inhibition with small molecules is selectively lethal to myeloma cells compared with normal cells.[10,16]

Selinexor (KPT-330) is a first-in-class, orally bioavailable, selective inhibitor of XPO1-mediated nuclear export.[17,18] In preclinical studies, selective inhibitor of nuclear export compounds showed marked antimyeloma activity largely independent of genotype, as well as synergistic activity with glucocorticoids, proteasome inhibitors, and immunomodulatory drugs.[11,19] In a phase I study, selinexor alone or in combination with low-dose dexamethasone showed broad activity against hematologic malignancies, including multiple myeloma.[20] On the basis of these results, we evaluated the combination of selinexor and low-dose dexamethasone in patients with myeloma refractory to all of the most effective and currently available antimyeloma agents.

PATIENTS AND METHODS

Study Design and Oversight

This multicenter, open-label, phase II study was designed to assess selinexor and low-dose dexamethasone in patients with myeloma refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide (quad-refractory disease) and, in a subset, also refractory to anti-CD38 monoclonal antibody therapy (penta-refractory disease). The primary objective of the study was to evaluate the overall response rate (ORR). The secondary objectives were to evaluate duration of response, progression-free survival, overall survival, and the safety profile of selinexor and dexamethasone. The study protocol was approved by the institutional review board or an independent ethics committee at each participating center and is in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and local laws.

Patients

Patients were eligible if they had myeloma that was measurable based on International Myeloma Working Group (IMWG) guidelines,[21,22] provided written informed consent, and had been previously treated with at least three prior antimyeloma regimens, including an alkylating agent, glucocorticoids, bortezomib, carfilzomib, lenalidomide, and pomalidomide. Patients were required to have disease refractory (defined as $\leq$ 25% response to therapy or progression during or within 60 days of completion of therapy) to their most recent regimen and be refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide alone or in combination. In addition, a subset of patients was enrolled with disease refractory to an anti-CD38 monoclonal antibody. As a result of the difficulty obtaining specific progression dates on prior therapies and because some patients had toxicity on prior therapy that precluded re-treatment, we permitted enrollment of 15 patients with disease that was not documented to be refractory to one or more agents. Thus, although all patients were previously treated with lenalidomide, pomalidomide, bortezomib, and carfilzomib, three patients had clear documentation of disease refractory to only one of lenalidomide or pomalidomide, six patients had clear documentation of disease refractory to only one of carfilzomib or bortezomib, and four patients had clear documentation of disease refractory to only one of bortezomib or carfilzomib and only one of lenalidomide or pomalidomide. Documentation of refractoriness to proteasome inhibitors was not available for two patients who were included in the analysis. A full listing of inclusion and exclusion criteria can be found in Appendix Table A1 (online only).

Treatment

Oral selinexor was given as an 80-mg dose twice weekly on days 1, 3, 8, 10, 15, and 17 (six doses) of each 28-day cycle, and oral dexamethasone was given at 20 mg with each dose of selinexor. The dose and schedule were selected based on data from a phase I study of selinexor in hematologic malignancies, which identified a recommended phase II dose of selinexor of 45 mg/m^2 (approximately 80-mg flat dose) with dexamethasone 20 mg, given on days 1, 3, 8, 10, 15, and 17 of each 28-day cycle. After 23 patients were enrolled, it was noted that many patients would have met laboratory criteria for continued dosing in week 4 of cycle 1, including some patients who had treatment held during the first 3 weeks and had recovered sufficiently to resume dosing by week 4. Therefore, the protocol was modified to allow for continuous dosing of twice-weekly selinexor and dexamethasone on days 1, 3, 8, 10, 15, 17, 22, and 24 of each 28-day cycle (eight doses), with no weeks off therapy. For patients with at least stable disease and good tolerance of treatment, the dose of selinexor could be increased to 100 mg twice weekly. All patients received a 5-hydroxytryptamine-3 antagonist (ondansetron 8 mg or equivalent) before the first dose of selinexor and two to three times daily, as needed. Patients were also allowed to receive other antiemetics, appetite stimulants, hematopoietic growth factors, thrombopoietin receptor agonists (eltrombopag or romiplostim), and sodium chloride supplementation as needed.

Assessments

The primary end point was ORR (partial response or better), evaluated by an independent review committee using modified IMWG criteria.[21,22] Safety was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. All patients who received at least one dose of selinexor were considered evaluable for safety. Fluorescent in situ hybridization methods are described in the Appendix (online only).

Statistics

We had prespecified that a response rate $>$ 15% would demonstrate sufficient activity to justify further development of selinexor and dexamethasone for refractory myeloma. Our planned sample size of 79 patients provided 90% power, using a one-sided t test and α = .025, to detect a response rate of 30% or higher in comparison with the 15% reference rate. Progression-free survival, overall survival, and duration of response were analyzed using the Kaplan-Meier method. We conducted a landmark analysis[23] of patients surviving without progression after one cycle (28 days) and compared progression-free and overall survival using the log-rank test, estimating hazard ratios and 95% CIs with a Cox regression model.

RESULTS

Patients and Treatment

Of the 79 total patients enrolled (median age, 63 years), 48 had quad-refractory myeloma and 31 had penta-refractory myeloma

(Table 1). The median time from diagnosis was 4 years (range, < 1 to 35 years), and patients had received a median of seven prior regimens (range, three to 17 regimens). In addition to being quad- or penta-refractory, all patients had received prior glucocorticoid therapy, 97% had received prior alkylating agents, 41% had received anthracyclines, and 77% had undergone an autologous stem-cell transplantation. All patients had myeloma refractory to their most recent regimen (listed in Appendix Table A2, online only). Of the 31 patients who had received prior anti-CD38 antibody therapy, 25 (81%) had received single-agent daratumumab (n = 15) or isatuximab (n = 10), and six patients (19%) had received an anti-CD38 antibody combination (with either lenalidomide or pomalidomide). Among the 14 patients who received an anti-CD38 antibody in the immediate prior line of therapy, the median time between last dose of anti-CD38 antibody and first dose of selinexor was 3.5 weeks (range, 2 to 6 weeks). At the start of the study, 14 patients (18%) had hemoglobin levels < 8.5 g/dL, seven patients (9%) had platelet counts < 50,000/μL, and five patients (6%) had creatinine clearance rates < 30 mL/min. Of the 39 patients with cytogenetic assessments performed at the time of enrollment onto the study, 44% (17 patients) had high-risk abnormalities, including del(17p), t(4;14), and t(14;16). Because of the timing of enrollment, 83% of the patients with quad-refractory myeloma received six doses per cycle (40 of 48 patients), whereas 65% of the patients with penta-refractory disease were treated after study amendment and received eight doses per cycle (20 of 31 of patients).

Efficacy

Efficacy was evaluated in 78 patients (Table 2), excluding one patient assessed by the independent review committee as not having measurable myeloma at baseline according to IMWG criteria.[21,22] The ORR was 21% (95% CI, 13% to 31%), which was numerically higher than the prespecified minimally acceptable threshold of 15%, although the difference was not statistically significant ($P = .17$). Responses included 5% of patients with a very good partial response and 15% of patients with a partial response. An additional 13% of patients had a minimal response, yielding a clinical benefit rate of 33% (95% CI, 24% to 44%). Stable disease was observed in 35% of patients, with a median duration of stable disease of 2.0 months (range, 0.9 to 7.6 months). Responses were rapid, with 22 (85%) of 26 patients who achieved a minimal response or better responding within the first cycle of treatment. The median duration of response for patients with a partial response or better was 5 months, with at least one response lasting as long as 8.4 months (Fig 1). The ORR was 21% in patients with quad-refractory disease and 20% for patients with penta-refractory disease. The ORR in the 17 patients with high-risk cytogenetic abnormalities was 35%, and among the 12 patients with a 17p abnormality, there was one very good partial response and two partial responses (ORR, 25%). A waterfall plot (Fig 2) shows that the quality of responses was similar for patients with quad-refractory and penta-refractory myeloma.

The median progression-free and overall survival times were 2.3 and 9.3 months, respectively (Fig 3). Patients who achieved at least a minimal response after one cycle of therapy had significantly

Table 1. Demographic and Clinical Characteristics

Characteristic	All Patients (n=79)	Quad-Refractory (n=48)	Penta-Refractory (n=31)
Median age, years (range)	63 (34-78)	62 (41-78)	68 (34-78)
Age, years, No. (%)			
≤ 65	45 (57)	34 (71)	11 (35)
65-74	30 (38)	12 (25)	18 (58)
≥ 75	4 (5)	2 (4)	2 (6)
Male, No. (%)	37 (47)	24 (50)	13 (42)
Median No. of years since diagnosis (range)	4 (< 1-35)	4 (1-16)	4 (< 1-35)
Median No. of prior regimens (range)	7 (3-17)	7 (3-16)	7 (5-17)
Refractory to prior therapies,* No. (%)			
Bortezomib	68 (86)	43 (90)	25 (81)
Carfilzomib	76 (96)	46 (96)	30 (97)
Lenalidomide	75 (95)	46 (96)	29 (94)
Pomalidomide	76 (96)	47 (98)	29 (94)
Anti-CD38 antibody	31 (39)	—	31 (100)
Additional prior therapies, No. (%)			
Glucocorticoid	79 (100)	48 (100)	31 (100)
Alkylating agent	77 (97)	47 (98)	30 (97)
Anthracycline	32 (41)	20 (42)	12 (39)
Stem-cell transplantation	61 (77)	37 (77)	24 (77)
Cytogenetics,† No. (%)			
Standard risk	22 (56)	15 (60)	7 (50)
High risk			
del(17p)‡	8 (21)	4 (16)	4 (29)
t(4;14)‡	4 (10)	4 (16)	—
t(14;16)‡	1 (3)	1 (4)	—
del(17p) and t(4;14)	3 (8)	1 (4)	2 (14)
del(17p) and t(14;16)	1 (3)	—	1 (7)

*Patients with confirmed refractoriness.
†Shown are percentages of the 39 patients with cytogenetic assessments (karyotyping or fluorescence in situ hybridization) performed at baseline.
‡Does not include patients with both del(17p) and t(4;14) or del(17p) and t(14;16).

Table 2. Overall Response Rate

Group	No. of Patients*	No. of Patients (%)							
		ORR	CBR	VGPR	PR	MR	SD	PD	NE
Overall	78	16 (21)	26 (33)	4 (5)	12 (15)	10 (13)	27 (35)	21 (27)	4 (5)
Quad-refractory disease	48	10 (21)	14 (29)	2 (4)	8 (17)	4 (8)	21 (44)	11 (23)	2 (4)
Penta-refractory disease	30	6 (20)	12 (40)	2 (7)	4 (13)	6 (20)	6 (20)	10 (33)	2 (7)
6 doses per cycle	51	10 (20)	15 (29)	3 (6)	7 (14)	5 (10)	21 (41)	12 (24)	3 (6)
8 doses per cycle	27	6 (22)	11 (41)	1 (4)	5 (19)	5 (19)	6 (22)	9 (33)	1 (4)
Standard risk	22	4 (18)	9 (41)	1 (5)	3 (14)	5 (23)	11 (50)	2 (9)	—
High risk	17	6 (35)	9 (53)	1 (6)	5 (29)	3 (18)	6 (35)	2 (12)	—
del(17p)	8	3 (38)	5 (63)	1 (13)	2 (25)	2 (25)	2 (25)	1 (12)	—
t(4;14)	4	2 (50)	2 (50)	—	2 (50)	—	2 (50)	—	—
t(14;16)	1	1 (100)	1 (100)	—	1 (100)	—	—	—	—
del(17p) and t(4;14)	3	—	1 (33)	—	—	1 (33)	2 (67)	—	—
del(17p) and t(14;16)	1	—	—	—	—	—	—	1 (100)	—

NOTE. Response rates are presented as assessed by the independent review committee.
Abbreviations: CBR, clinical benefit rate; MR, minimal response; NE, nonevaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.
*One patient did not have measureable myeloma at baseline and was, therefore, not included in the analysis of response.

better overall survival than patients with stable or progressive disease (median, not reached *v* 7.2 months, respectively; $P = .01$), as shown in a landmark analysis[23] of 60 patients who were alive and evaluable for response after one cycle of therapy.

Safety

Seventy-nine patients received at least one dose of selinexor and were evaluable for safety assessments (Table 3). The most frequently reported nonhematologic treatment-related adverse events were nausea (73%), anorexia (49%), fatigue (63%), vomiting (44%), and diarrhea (43%), which were mostly grade 1 or 2. Grade 3 and 4 nonhematologic events occurring in > 5% of patients included fatigue (15%), nausea (8%), and diarrhea (5%).

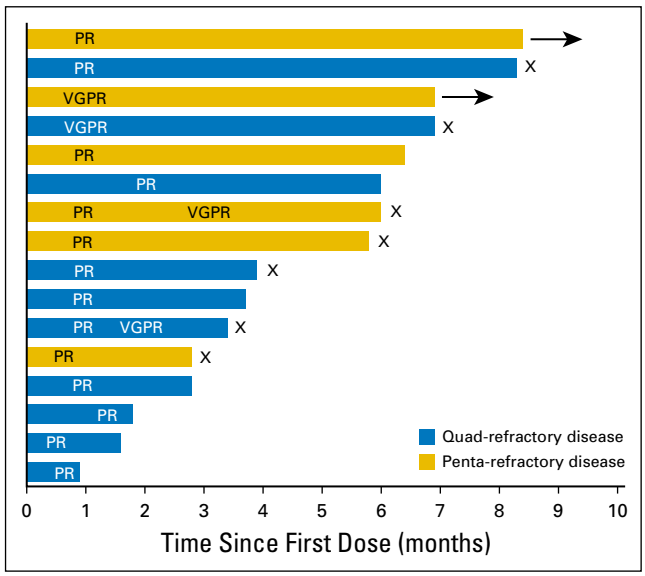

Fig 1. Time on study for patients with a partial response or better. In instances where two responses are given for a patient, the first indicates the first response and the second indicates best response. Arrows indicate that the patient is continuing on study as of the date of data cutoff. X indicates disease progression.

Grade 3 hyponatremia was reported in 22% of patients but was generally asymptomatic and reversible with supportive care. Commonly reported grade 3 or 4 hematologic adverse events included thrombocytopenia (59%), anemia (28%), and neutropenia (23%). Grade ≥ 3 bleeding occurred in two patients (3%). Febrile neutropenia occurred in one patient, and grade ≥ 3 infection occurred in 14 patients. We did not observe differences in toxicity between patients who received six or eight doses per cycle (Appendix Table A3, online only).

Dose interruptions for adverse events were required by 41 patients (52%), dose reductions occurred in 29 patients (37%), and treatment was discontinued in 14 patients (18%). Mean dose intensity in cycle 1 was higher for patients assigned to receive eight doses per cycle than six doses per cycle (475 *v* 412 mg, respectively; $P = .03$), although more patients in the eight-dose group required dose reductions or interruptions in cycle 1 (71%) than did patients in the six-dose group (43%). Three patients with at least stable disease after the first cycle and no dose-limiting adverse events received an increased dose of selinexor to 100 mg twice weekly. The higher dose was uniformly accompanied by increased adverse effects, and all three patients required dose interruptions or reductions. In addition to the low-dose dexamethasone that was part of the therapeutic regimen, all patients received a prophylactic 5-hydroxytryptamine-3 antagonist, with 11 patients (14%) receiving one additional antiemetic medication and four patients (5%) receiving two additional antiemetic medications. Eighteen patients (23%) received filgrastim, 10 patients (13%) received an additional appetite stimulant beyond their therapeutic dose of dexamethasone, 10 patients (13%) received eltrombopag or romiplostim, and five patients (6%) received salt tablets.

There were 22 serious adverse events deemed at least possibly related to study treatment reported in 19 patients, which are listed in Appendix Table A1 (online only). In general, serious adverse events were a result of cytopenias, sodium imbalance, infection, altered mental status, or nausea. One patient had fatal intracranial bleeding in the setting of severe thrombocytopenia attributed to myeloma, prior myelotoxic therapies, and possibly selinexor.

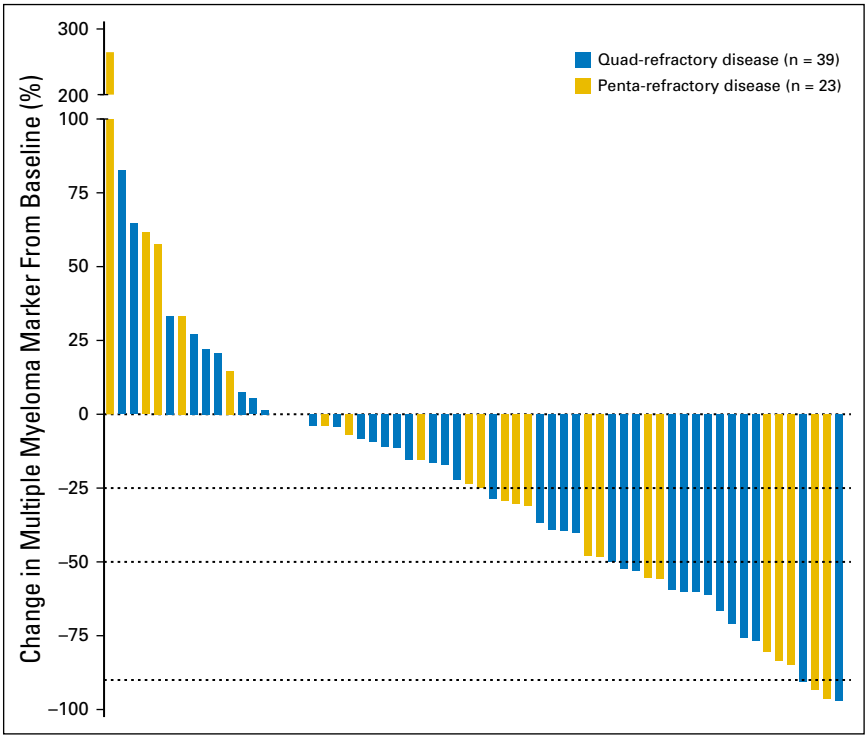

Fig 2. Depth of response to selinexor and dexamethasone among patients with refractory myeloma. Waterfall plot of best percent change in the primary myeloma marker (serum M-spike, urine M-spike, immunoglobulin, or serum free light chain) from baseline. Thirteen patients with clinical progression but no myeloma markers assessed after treatment are not included in the plot (seven quad-refractory patients and six penta-refractory patients). The dotted lines at −25%, −50%, and −90% indicate reductions that correspond to a minimal response, partial response, and very good partial response, respectively.

DISCUSSION

The trial data show that the combination of selinexor with low-dose dexamethasone has efficacy in heavily pretreated patients with myeloma refractory to all commonly used therapeutics. This prospective phase II trial enrolled patients who had received a median of seven prior treatment regimens and whose myeloma was refractory to both proteasome inhibitors and immunomodulators, as well as alkylating agents and corticosteroids. Furthermore, the relatively short median time since diagnosis (4 years) of the patients coupled with their quad- and penta-refractory status suggests that this population had particularly aggressive myeloma. Consistent with its novel mechanism of action, selinexor showed similar activity regardless of previous treatment history (including with an anti-CD38 antibody) and in patients with cytogenetically defined high-risk myeloma. Responses to selinexor and low-dose dexamethasone were of clinically meaningful depth and associated with improved overall survival compared with historic controls. Therefore, selinexor plus dexamethasone has significant potential to be a new treatment option for patients with refractory myeloma.

Selinexor is the first antimyeloma agent to show clear activity in penta-refractory myeloma, a patient population with a high unmet medical need. Although our observed overall response rate of 21% was not statistically significantly higher than our prespecified threshold of 15%, we believe that this evidence of efficacy is sufficient to warrant further study. In retrospect, a threshold response rate of 10% would have been more appropriate. Our observed response rate compares favorably to the low response rate to single-agent dexamethasone in this patient population[3] and to that of the recently approved anti-CD38 antibody daratumumab, which had a 21% ORR in the subset of patients with quad-refractory myeloma in a phase II study.[5] Therefore, we are proceeding with a confirmatory phase II trial, enrolling a uniform cohort of 122 patients with penta-refractory myeloma.

By inhibiting XPO1, selinexor forces the nuclear retention and functional activation of critical tumor suppressor proteins and limits the translation of oncoprotein mRNAs, leading to apoptosis in malignant cells. This novel mechanism of action was expected to be complementary to existing therapies for myeloma, as well as for other neoplasms. Combining selinexor with dexamethasone has a mechanistic rationale and is associated with higher response rates than single-agent selinexor. Specifically, selinexor potentiates glucocorticoid-mediated activation of the glucocorticoid receptor,[20] leading to increased glucocorticoid-mediated transcription and apoptosis induction in myeloma cells, even in cells previously resistant to glucocorticoids.[24] In a phase I study that included heavily pretreated patients with myeloma, the addition of dexamethasone increased the response rate to selinexor (given at various doses) from 5% to 35%.[20] All of the patients in the current study had received prior glucocorticoid therapy, with a median of six prior glucocorticoid-containing regimens. In addition, the ORR to single-agent dexamethasone in heavily pretreated myeloma is low; single-agent dexamethasone at a three-fold higher dose (40 mg/d on days 1 to 4, 9 to 12, and 17 to 20 of a 28-day cycle) in heavily pretreated, but pomalidomide-naïve myeloma had a response rate of 10%, and there was only a 6% response rate in the subset of patients refractory to both bortezomib and lenalidomide.[3] Therefore, it is improbable that the observed responses in our study are a result of dexamethasone alone.

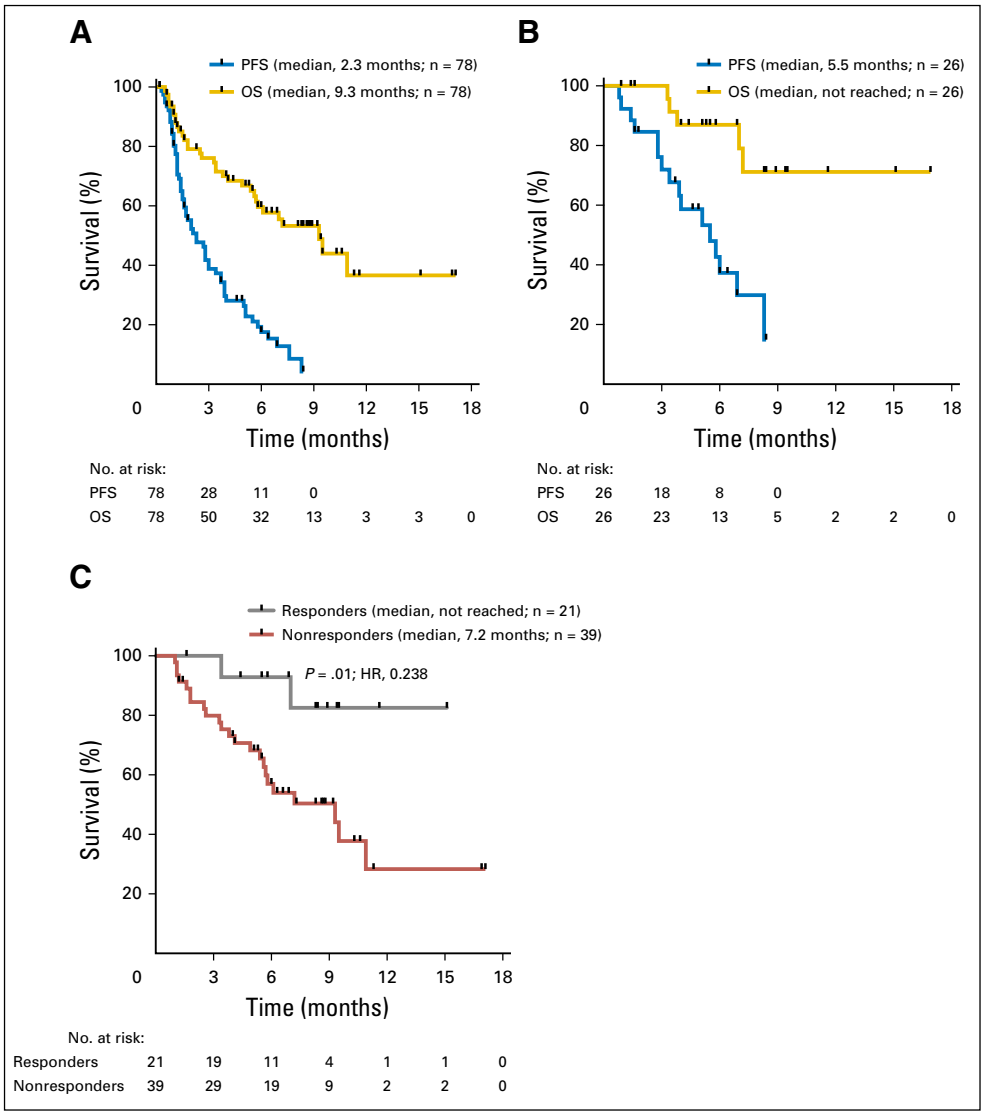

Fig 3. Kaplan-Meier analysis of progression-free survival (PFS) and overall survival (OS) for (A) all patients and (B) patients achieving at least a minimal response. (C) A landmark analysis comparing OS between patients with and without a minimal response or better who were alive and assessable for response at 1 month. HR, hazard ratio.

Multiple potential mechanisms may explain therapeutic resistance to selinexor in this highly refractory patient population, including acquired *XPO1* mutations,[25,26] upregulation of XPO1 expression,[17,27] activation of alternative signaling mechanisms,[28] and drug efflux pumps. Combining selinexor with other effective antimyeloma agents may help to reduce or overcome the emergence of therapeutic resistance. Combination regimens of selinexor with bortezomib, carfilzomib, or pomalidomide have shown preclinical synergy and evidence of response in early phase II clinical studies.[29-31] A randomized phase III trial comparing selinexor, bortezomib, and dexamethasone to bortezomib and dexamethasone is ongoing (ClinicalTrials.gov identifier: NCT03110562).

The adverse effect profile of selinexor and dexamethasone includes nausea, anorexia, fatigue, thrombocytopenia, hyponatremia, and anemia. These adverse effects are similar to those seen with selinexor therapy in patients with other heavily pretreated hematologic malignancies, although cytopenias are less prevalent in patients with solid tumors.[17,18] Over half of the patients in the study reported here required treatment interruptions or dose reductions for toxicity. Nevertheless, supportive care measures limited treatment discontinuation as a result of toxicity to 18% of patients. Effective supportive care recommended for patients receiving selinexor includes prophylactic antiemetics and, if required, sodium chloride supplementation and hematopoietic growth factors. We did not observe an increase in toxicity using eight doses of selinexor in each 28-day cycle compared with six doses and believe that the extended dosing schedule provides an appropriate balance between maximizing dosing intensity and allowing for individualized dose interruptions and reductions as needed. On the basis of our findings, a regimen of selinexor 80 mg and dexamethasone 20 mg on days 1, 3, 8, 10, 15, 17, 22, and 24 of each 28-day cycle is the recommended dose for further investigation. The effect of supportive care on both cost and quality of life needs to be balanced against the antimyeloma efficacy of this regimen.

In conclusion, selinexor is an oral agent with a novel mechanism of action and evidence of antimyeloma efficacy. In combination with low-dose dexamethasone, selinexor is an

Table 3. Treatment-Related Adverse Events Occurring in ≥ 10% of Patients

Adverse Event	No. of Patients (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
Nausea	32 (41)	20 (25)	6 (8)	—	58 (73)
Thrombocytopenia	5 (6)	6 (8)	20 (25)	27 (34)	58 (73)
Fatigue	12 (15)	26 (33)	12 (15)	—	50 (63)
Anemia	2 (3)	15 (19)	21 (27)	1 (1)	39 (49)
Decreased appetite	15 (19)	22 (28)	2 (3)	—	39 (49)
Vomiting	24 (30)	8 (10)	3 (4)	—	35 (44)
Diarrhea	27 (34)	3 (4)	4 (5)	—	34 (43)
Hyponatremia	16 (20)	—	17 (22)	—	33 (42)
Leukopenia	5 (6)	13 (16)	11 (14)	1 (1)	30 (38)
Weight decreased	15 (19)	10 (13)	1 (1)	—	26 (33)
Neutropenia	2 (3)	5 (6)	12 (15)	6 (8)	25 (32)
Lymphopenia	2 (3)	5 (6)	8 (10)	1 (1)	16 (20)
Dehydration	1 (1)	6 (8)	2 (3)	—	9 (11)
Dysgeusia	5 (6)	4 (5)	—	—	9 (11)
Creatinine increased	2 (3)	4 (5)	2 (3)	—	8 (10)
Dizziness	7 (9)	1 (1)	—	—	8 (10)
Pyrexia	5 (6)	2 (3)	1 (1)	—	8 (10)

NOTE. Treatment-related adverse events occurring in ≥ 10% of patients (n = 79). Additional grade 4 adverse events not listed in the table include one instance each of hypernatremia and increased lipase.

effective therapy for patients with refractory multiple myeloma for whom available treatments have been exhausted. Furthermore, XPO1 inhibition with either selinexor or a sister compound, verdinexor, has shown antitumor activity in other hematologic[27-32] and solid tumor malignancies.[17,18] Additional studies of selinexor alone or in combination are ongoing.

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Appendix

Assessments

Fluorescence in situ hybridization. A bone marrow aspirate was collected at screening from 39 patients who consented to exploratory karyotyping assessments. A central laboratory was used to isolate CD138-positive plasma cell fractions and perform fluorescent in situ hybridization assays to identify patients with high-risk cytogenetics, which included del(17p), t(4;14), and t(14;16). A certified hematopathologist scored the assay by counting 200 interphase cells from each slide and using a cutoff of $\geq$ 11% abnormal cells for del(17p) and $\geq$ 6% abnormal cells for t(4;14) and t(14;16).

Statistics. Differences were considered statistically significant when $P < .05$, without adjustment for multiple comparisons. Pairwise comparisons were conducted using the Mann-Whitney *U* test, and multiple group comparisons were conducted using one-way analysis of variance with Kruskal-Wallis post-test.

Table A1. Inclusion and Exclusion Criteria

Criteria
Inclusion Criteria
Patients must meet all of the following inclusion criteria to be eligible to enroll in this study:
1. Written informed consent in accordance with federal, local, and institutional guidelines.
2. Age ≥ 18 years.
3. Histologically confirmed diagnosis, measurable disease and evidence of disease progression of MM, as described below.
4. Symptomatic MM, based on IMWG guidelines. Patients must have measurable disease as defined by at least one of the following:
a. Serum M-protein ≥ 0.5 g/dL by serum electrophoresis (SPEP) or for IgA myeloma, by quantitative IgA; or
b. Urinary M-protein excretion at least 200 mg/24 hours; or
c. Serum free light chain (FLC) whereby the involved light chain measures ≥ 10 mg/dL and with an abnormal light chain ratio.
5. Patients must have received ≥ 3 prior anti-MM regimens including the following: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib and a glucocorticoid. There is no upper limit on the number of prior therapies provided that all other inclusion/exclusion criteria are met.
6. Quad-refractory MM: MM refractory to lenalidomide, pomalidomide, bortezomib, and carfilzomib. Refractory is defined as ≤ 25% response to therapy, or progression during therapy or progression within 60 days after completion of therapy.
7. Penta-refractory MM: 25% of patients must have MM refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and at least one anti-CD38 MAb (e.g., SAR 650984 or daratumumab).
8. Multiple myeloma refractory to the patient's most recent anti-MM regimen.
9. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2 (Appendix 1).
10. Resolution of non-hematological toxicities (if any) from previous treatments to ≤ grade 2
11. Adequate hepatic function within 21 days before Cycle 1 Day 1: total bilirubin < 2 × upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of < 3 × ULN), AST < 2.5 × ULN and ALT < 2.5 × ULN.
12. Adequate renal function within 21 days before cycle 1 day 1: estimated creatinine clearance of ≥ 20 mL/min, calculated using the formula of Cockroft and Gault: (140 − Age) • Mass (kg)/(72 • creatinine mg/dL). Multiply times 0.85 if the patient is female, or CrCl >20 mL/min as measured by 24-hour urine collection.
13. Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening. Male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post- ovulation methods) and withdrawal are not acceptable methods of contraception. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.
14. Adequate hematopoietic function within 21 days before cycle 1 day 1: total WBC count ≥ 1,500/mm^3, ANC ≥ 1000/mm^3, and platelet count ≥ 75,000/mm^3 (patients in whom < 50% of bone marrow nucleated cells are plasma cells) or ≥ 30,000/mm^3 (patients in whom > 50% of bone marrow nucleated cells are plasma cells. Patients receiving hematopoietic growth factor support, including erythropoietin (EPO), darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), and platelet stimulators (e.g. eltrombopag, romiplostim, or IL-11) may continue to do so.
Exclusion Criteria
Patients meeting any of the following exclusion criteria are not eligible to enroll in this study:
1. Smoldering MM.
2. Plasma cell leukemia.
3. MM that does not express M-protein or FLC (i.e., non-secretory MM is excluded; plasmacytomas without M-protein or FLC are excluded).
4. Documented systemic amyloid light chain amyloidosis.
5. Active CNS MM.
6. Pregnancy or breastfeeding.
7. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy ≤ 2 weeks before cycle 1 day 1, and radio-immunotherapy 6 weeks before cycle 1 day 1.
8. Not adequately recovered from the side effects of previous antineoplastic agents before dosing.
9. Active graft versus host disease after allogeneic stem cell transplantation.
10. Life expectancy of < 4 months.
11. Major surgery within four weeks before cycle 1 day 1.
12. Unstable cardiovascular function:
a. Symptomatic ischemia, or
b. Uncontrolled clinically-significant conduction abnormalities (e.g., patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree atrioventricular (AV) block or asymptomatic left anterior fascicular block/right bundle branch block (LAFB/RBBB) will not be excluded), or
c. Congestive heart failure (CHF) of New York Heart Association (NYHA) Class ≥ 3, or
d. Myocardial infarction (MI) within 3 months.
13. Uncontrolled hypertension.
14. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week before first dose.
15. Known HIV seropositive.
16. Known active hepatitis A, B, or C infection; or known to be positive for HCV RNA or HBsAg (HBV surface antigen).
17. Prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent > 5 years previously and without evidence of recurrence will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed unless approved by the medical monitor.
18. GI dysfunction interfering with the ability to swallow tablets, or any GI dysfunction that could interfere with absorption of study treatment.
19. Grade ≥ 2 peripheral neuropathy at baseline (within 21 days before Cycle 1 Day 1).
20. Serious psychiatric or medical conditions that, in the opinion of the investigator, could interfere with treatment.
21. Participation in an investigational anti-cancer study within 3 weeks before receiving first dose of study drug.

Abbreviations: FLC, free light chain; Ig, immunoglobulin; IMWG, International Myeloma Working Group; MM, multiple myeloma; ULN, upper limit of normal.

Table A2. Last Prior Therapy for All Patients and Time From CD38 Antibody

Patient No.	Last Prior Therapy
1	Bortezomib, dexamethasone, pomalidomide
2	Pomalidomide, dexamethasone, ixazomib
3	Pomalidomide, dexamethasone, cyclophosphamide
4	Daratumumab
5	Doxorubicin, cisplatin, dexamethasone, cyclophosphamide, etoposide
6	Daratumumab
7	Pomalidomide
8	Pomalidomide, dexamethasone, indatuximab ravtansine
9	Carfilzomib
10	Pomalidomide, dexamethasone, carfilzomib
11	Bortezomib, dexamethasone, cyclophosphamide
12	Bortezomib, thalidomide
13	Lenalidomide, dexamethasone, melphalan
14	Pomalidomide, dexamethasone, carfilzomib
15	Isatuximab
16	Pomalidomide, dexamethasone, cyclophosphamide
17	Pomalidomide, dexamethasone, carfilzomib
18	Bortezomib, dexamethasone, panobinostat
19	Carfilzomib, dexamethasone, cyclophosphamide, thalidomide
20	Carmustine, cytarabine, etoposide, melphalan, dexamethasone
21	Pomalidomide, dexamethasone, vorinostat
22	Isatuximab
23	Thalidomide, dexamethasone
24	Pomalidomide, dexamethasone, carfilzomib
25	Bortezomib, dexamethasone, lenalidomide
26	Bendamustine
27	Bortezomib, cisplatin, cyclophosphamide, etoposide, doxorubicin
28	Bendamustine
29	Bortezomib, bendamustine
30	Stem-cell transplantation (second)
31	Bortezomib, dexamethasone, thalidomide, cisplatin, cyclophosphamide, etoposide
32	Cyclophosphamide
33	Thalidomide, dexamethasone, melphalan
34	Carfilzomib, dexamethasone
35	Pomalidomide, dexamethasone, carfilzomib
36	Doxorubicin, vincristine, cyclophosphamide, prednisone
37	Bortezomib, dexamethasone, bendamustine
38	Pomalidomide, dexamethasone, carfilzomib
39	Doxorubicin, cyclophosphamide, etoposide
40	Pomalidomide, dexamethasone, carfilzomib
41	Bortezomib, dexamethasone, doxorubicin, cisplatin, cyclophosphamide, etoposide
42	Investigational therapy (venetoclax)
43	Pomalidomide, dexamethasone, carfilzomib, clarithromycin
44	Carfilzomib, dexamethasone
45	Lenalidomide, dexamethasone, daratumumab
46	Lenalidomide, dexamethasone, daratumumab
47	Daratumumab, dexamethasone
48	Carfilzomib, dexamethasone, cyclophosphamide
49	Cyclophosphamide
50	Pomalidomide, dexamethasone, carfilzomib
51	Daratumumab, dexamethasone
52	Carfilzomib, dexamethasone, cyclophosphamide
53	Pomalidomide, trametinib
54	Daratumumab, prednisone
55	Pomalidomide, dexamethasone, daratumumab
56	Bendamustine, prednisone
57	Lenalidomide, dexamethasone, isatuximab
58	Pomalidomide, dexamethasone, carfilzomib, clarithromycin
59	Bortezomib, dexamethasone, cyclophosphamide
60	Ibrutinib, dexamethasone
61	Investigational therapy (BET inhibitor, unknown agent)
62	Investigational therapy (CBP-839 glutaminase inhibitor)
63	Carfilzomib, dexamethasone, cyclophosphamide, panobinostat
64	Daratumumab
65	Daratumumab
66	Pomalidomide, dexamethasone, daratumumab
67	Bendamustine
68	Investigational therapy (JAK1 inhibitor INCB052793)
69	Carfilzomib, dexamethasone, cyclophosphamide
70	Pomalidomide, dexamethasone, carfilzomib
71	Doxorubicin, cisplatin, cyclophosphamide, etoposide
72	Pomalidomide, dexamethasone, carfilzomib
73	Lenalidomide, cyclophosphamide
74	Pomalidomide, dexamethasone, carfilzomib, cyclophosphamide
75	Daratumumab
76	Doxorubicin, cisplatin, cyclophosphamide, etoposide, thalidomide
77	Carfilzomib, dexamethasone, cyclophosphamide
78	Pomalidomide, dexamethasone, carfilzomib
79	Bortezomib, dexamethasone, panobinostat

(continued in next column)

Table A3. Adverse Events by Dose Schedule

Adverse Event	No. of Patients (%)			
	All Grades (6 doses per cycle)	Grades 3 and 4 (6 doses per cycle)	All Grades (8 doses per cycle)	Grades 3 and 4 (8 doses per cycle)
Nausea	35 (69)	3 (6)	23 (82)	3 (11)
Thrombocytopenia	38 (75)	31 (61)	20 (71)	16 (57)
Fatigue	30 (59)	8 (16)	20 (71)	4 (14)
Anemia	26 (51)	17 (33)	13 (46)	5 (18)
Decreased appetite	31 (61)	1 (2)	8 (29)	1 (4)
Vomiting	21 (41)	2 (4)	14 (50)	1 (4)
Diarrhea	20 (39)	1 (2)	14 (50)	3 (11)
Hyponatremia	18 (35)	10 (20)	15 (54)	7 (25)
Leukopenia	17 (33)	8 (16)	13 (46)	4 (14)
Weight decreased	19 (37)	1 (2)	7 (25)	—
Neutropenia	16 (32)	12 (24)	9 (33)	6 (21)
Lymphopenia	12 (24)	7 (14)	4 (14)	2 (7)
Dehydration	6 (12)	2 (4)	3 (11)	—
Dysgeusia	5 (10)	—	4 (14)	—
Creatinine increased	6 (12)	2 (4)	2 (7)	—
Dizziness	5 (10)	—	3 (11)	1 (4)
Pyrexia	5 (10)	1 (2)	3 (11)	—

NOTE. Treatment-related adverse events occurring in ≥ 10% of all patients as a function of dose group. Fifty-one patients received six doses per cycle, and 28 patients received eight doses per cycle.

Table A4. Treatment-Related Serious Adverse Events

Patient	Age (years)	Sex	Doses per Cycle	Serious Adverse Event
A	55	F	6	Pyrexia
A	55	F	6	Febrile neutropenia
B	64	M	8	Hyponatremia
C	64	M	6	Pyrexia and confusional state
D	57	M	8	Hyponatremia
E	55	F	6	Upper respiratory tract infection
F	64	M	6	Thrombocytopenia
G	69	M	6	Confusional state and delirium
G	69	M	6	Neutropenia and pyrexia
H	65	M	6	Pancreatitis
H	65	M	6	Anemia and thrombocytopenia
I	57	M	6	Anemia, dehydration, fatigue, nausea, and thrombocytopenia
J	59	F	6	Confusional state
K	69	M	8	Lung infection
L	65	F	8	Nausea and vomiting
M	41	F	6	Hematemesis
N	51	M	6	Dehydration and thrombocytopenia
O	54	M	6	Subdural hematoma
P	57	F	8	Hypernatremia
Q	73	F	8	Diarrhea
R	65	F	8	Syncope
S	57	F	8	Nausea

Abbreviations: F, female; M, male.