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A phase I study of selinexor combined with weekly carfilzomib and dexamethasone in relapsed/refractory multiple myeloma

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Abstract

We performed a phase I study of weekly selinexor, carfilzomib, and dexamethasone (wSKd) in patients with relapsed/refractory multiple myeloma (MM). The primary objective was to identify the maximum tolerated dose (MTD) of wSKd. Secondary endpoints included overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). Prior exposure/refractoriness to carfilzomib was permitted. Thirty patients were enrolled; 26 (87%) had triple-class exposed disease and 6 (20%) received chimeric antigen receptor (CAR) T-cell therapy. Dose level 2 (carfilzomib 70 mg/m^2 Intravenous [IV] on Days 1, 8, and 15; selinexor 100 mg PO on Days 1, 8, 15, 22; dexamethasone 40 mg on Days 1, 8, 15, 22 of 28-day cycles) was chosen as the MTD, with no DLTs having occurred. The most common hematologic adverse events (AE) were thrombocytopenia (83%), anemia (70%), lymphopenia (50%), and neutropenia (50%). The most common nonhematologic AE were fatigue (70%), nausea (70%), diarrhea (53%), and anorexia (47%). The ORR was 21/30 (70%) overall and 18/23 (78%) at the MTD. At a median follow-up of 12.3 months, the median PFS was 5.3 months and median OS 23.3 months. Responses were similar in carfilzomib naïve and exposed patients. Long-term efficacy of wSKd is modest; wSKd could be employed as a bridging strategy to immunotherapies.

KEYWORDS
clinical trial, multiple myeloma, phase I

What is the new aspect of this work?

This is the first study to our knowledge to evaluate the efficacy of weekly selinexor, carfilzomib, and dexamethasone in relapsed/refractory multiple myeloma with a high proportion of patients exposed and refractory to carfilzomib and/or prior chimeric antigen receptor (CAR) T-cell therapy.

What is the central finding of this work?

Weekly selinexor, carfilzomib, and dexamethasone (SKd) is safe with an overall response rate of 78% at the maximum tolerated dose; long-term efficacy was modest as evidenced by a median progression-free survival of 5.3 months.

What is (or could be) the specific clinical relevance of this work?

Weekly SKd may be a useful bridging strategy to immunotherapies in relapsed/refractory multiple myeloma.

1 | INTRODUCTION

The use of proteasome inhibitors (PIs: bortezomib, carfilzomib, ixazomib), immunomodulatory drugs (IMIDs: thalidomide, lenalidomide, pomalidomide), and monoclonal antibodies (mAbs: daratumumab, elotuzumab) has led to great advances in the treatment of multiple myeloma (MM). However, MM remains a disease characterized by a pattern of response and disease progression with shorter duration of response and higher attrition rates with each line of therapy.[1] Effective therapies for patients with triple-class refractory (refractory to at least one PI, IMiD, and anti-CD38 mAb) and/or penta-refractory MM (refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 mAb) remain an unmet need.

Selinexor is an oral selective inhibitor of nuclear export that targets Exportin 1 (XPO1), which is responsible for the export of hundreds of proteins including several tumor suppressors and cell-cycle regulators.[2] The inhibition of XPO1 causes accumulation of tumor suppressors in the nucleus, inhibits nuclear factor kappa-B, and decreases messenger RNA translocation of various oncoproteins.[3] Selinexor has shown activity in heavily pretreated MM; the phase IIb STORM trial evaluated the efficacy of twice-weekly selinexor and dexamethasone in 122 patients. Among a triple-class refractory population (68% penta-refractory), the overall response rate (ORR) was 26% (PR or better), with a median duration of response and progression-free survival (PFS) of 4.4 and 3.7 months, respectively.[4] Median overall survival (OS) was 8.6 months. Toxicities with the twice-weekly regimen were notable for asthenia, nausea, anorexia, and thrombocytopenia. Building on selinexor's activity, and drawing on the preclinical and clinical synergism of selinexor and PIs,[5,6] the randomized phase III BOSTON trial compared once-weekly selinexor, bortezomib, and dexamethasone (SVd) to twice-weekly bortezomib and dexamethasone (Vd) among patients with MM treated with 1–3 prior lines of therapy (19% received three).[7] In this less-heavily treated population, median PFS was nearly 14 months with SVd compared to 9.5 months with Vd. The frequency of grades 3–4 toxicities was lower in the SVd arm of the BOSTON study in comparison to what was observed in the STORM trial.

Given that most patients become refractory to bortezomib early in the course of disease, replacing bortezomib with a different PI carfilzomib may be more sensible. Carfilzomib is a modified epoxyketone that selectively and irreversibly inhibits the 20S proteasome, which leads to accumulation of intracellular proteins within myeloma cells and causes apoptosis.[8] Carfilzomib has activity in patients with MM who are refractory to bortezomib,[9] and preclinical data also suggested synergism between selinexor and carfilzomib.[10]

We previously reported on the safety and efficacy of twice-weekly selinexor, carfilzomib, and dexamethasone (twSKd) in a phase Ia study of 21 patients, identifying the recommended phase II dosing (RP2D) of selinexor 60 mg, carfilzomib 20/27 mg/m^2 and dexamethasone 20 mg twice weekly; further dose escalation in that study was not pursued based on the cumulative adverse event rates, dose reductions, and anti-myeloma activity seen at that dose level.[11] In a population with a median of four prior lines of therapy including 95% of whom were carfilzomib-refractory, the ORR was 48% with a median PFS and OS of 3.7 and 22.4 months, respectively.

We now report on the results of this multi-center, open-label phase Ib study investigating the safety and efficacy of weekly selinexor, carfilzomib, and dexamethasone (wSKd) to determine the maximum tolerated dose (MTD) and the recommended phase II dosing (RP2D).

2 | METHODS

2.1 | Study design

This is a phase Ib portion of a multi-center, open-label study (NCT02199665), with the same objectives as the phase Ia portion.[11]

Thirty patients were enrolled at one of three MM Research Consortium sites in the United States. Eligibility criteria included patients with measurable disease, having received at least two prior lines of therapy that included a PI and an IMiD, with an absolute neutrophil count ≥ 1.0 × 10^9/L, a hemoglobin ≥ 8 g/dL, and a platelet count ≥ 50 × 10^9/L along with adequate organ function (creatinine clearance ≥ 30 mL/min). Patients with amyloidosis or significant cardiac history (left ventricular ejection fraction <40%, New York Heart Association Class III/IV congestive heart failure, history of severe coronary artery disease, or uncontrolled hypertension) were excluded. A complete list of the inclusion and exclusion criteria can be found in the supplement (Data S1).

The study was approved by each center's institutional review board and was in accordance with the Declaration of Helsinki and the United States Food and Drug Administration and the International Conference on Harmonization Guidelines for Good Clinic Practice.

TABLE 1 Dose levels for selinexor, carfilzomib, and dexamethasone.

Selinexor-Kd dose level	No. of patients treated	Selinexor PO (weekly) (mg)	Carfilzomib IV (C1-8: Days 1, 8, 15 C9+: Days 1, 15) (mg/m^2)
−1	0	80	20/56
1	7	100	20/56
2	23	100	20/56/70

Note: Selinexor, carfilzomib, and dexamethasone were administered as above, starting with dose level 1. Carfilzomib 20 mg/m^2 Intravenous (IV) was administered on Days 1 and 2 of cycle 1 at all dose levels, and then weekly at the assigned dose level for the remainder of treatment. For dose level 2, carfilzomib 56 mg/m^2 IV was administered on Day 8 of cycle 1 and 70 mg/m^2 IV on Day 15 of cycle 1 and on Days 1, 8, and 15 for cycles 2+. Oral dexamethasone 40 mg was given weekly for cycles 1–4 and then 20 mg weekly for cycles 5+.

2.2 | Schedule and dosing

In the dose-escalation phase Ib portion, patients were assigned to each dose level as shown in Table 1. Selinexor, carfilzomib, and dexamethasone were administered in 28-day cycles. For dose level 1, oral selinexor 100 mg was given weekly; carfilzomib 20/56 mg/m^2 Intravenous (IV) on Days 1, 8, 15; oral dexamethasone 40 mg weekly for cycles 1–4, then 20 mg weekly for cycles 5 and thereafter. Selinexor 100 mg weekly was chosen based on the recommended phase II dose for selinexor in combination with a bortezomib and dexamethasone from the STOMP study.[6] For dose level 2, patients received the same dosing but with carfilzomib escalated to 70 mg/m^2. Once the MTD was established, that dose cohort was expanded. The RP2D was confirmed if the dose-limiting toxicity for this cohort was <30%.

All patients were provided with prophylaxis for venous thromboembolism (aspirin or prophylactic dose low molecular weight heparin), herpes simplex virus (acyclovir or valacyclovir), and nausea including a 5-HT3 antagonist and either olanzapine, megestrol acetate, or rolapitant during cycle 1 only.

2.3 | Endpoints

The primary objective was to determine the MTD for wSKd in patients with relapsed/refractory MM through a 3 + 3 dose escalation design and a subsequent expansion cohort to identify an RP2D. Secondary objectives were to determine the safety, tolerability, and efficacy of wSKd.

2.4 | Safety and response assessments

Dose-limiting toxicities (DLT) were pre-specified. Hematologic DLTs included: febrile neutropenia, grade 4 neutropenia >7 days, grade 4 thrombocytopenia >7 days even with a delay in dosing, and grades 3–4 thrombocytopenia with bleeding. Nonhematologic DLTs included: grade 2+ neuropathy, any grade 3+ toxicity despite appropriate supportive care, and any toxicities that delayed the start of cycle 2 for >7 days; notable exceptions included electrolyte abnormalities, hair loss, and elevation of liver enzymes.

Treatment-emergent adverse events were graded per the National Cancer Institute-Common Terminology Criteria for Adverse Events v4.0. Patients were followed for survival for up to 2 years after the end of treatment.

The response was measured per the International Myeloma Working Group (IMWG) consensus criteria.[12] PFS and OS endpoints were assessed by the Kaplan–Meier method and groups compared by the log–rank test using Stata version 16 (Stata Corp, TX).

2.5 | Statistical analysis

The initial plan called for a total of 40 patients, 20 in a carfilzomib naïve cohort and 20 in a carfilzomib-exposed/refractory cohort. The FDA approval of selinexor along with the difficulty in identifying carfilzomib naïve patients with two or more prior lines of therapy led to early discontinuation of the study due to slow accrual. A total of 30 patients ($n = 5$ carfilzomib naïve, $n = 16$ carfilzomib exposed but not refractory, and $n = 9$ carfilzomib refractory) were enrolled.

3 | RESULTS

A total of 30 patients were enrolled between March 2018 and July 2021. The data cut-off date was March 1, 2022. Baseline characteristics can be found in Table 2. The median age was 64 years (range 35–79); half of the patients were female, 10 (33%) identified as Black, and 4 (13%) identified as Hispanic. Ten (33%) patients were considered to have stage III disease by the International Staging System; high-risk cytogenetic abnormalities were detected by fluorescent in situ hybridization in 12 (40%) of patients, including 10 (33%) with t(4;14) and 4 (13%) with 17p deletion (Table 2). Patients had received a median of 5 prior lines of therapy, with 28 (93%) receiving three or more prior lines of therapy. Triple-class exposed disease was seen in 26 (87%) patients, penta-exposed disease in 14 (47%), and 6 (20%) received prior CAR T-cell therapy.

The median duration of treatment was 5 cycles (range 1–25), with 8 (27%) patients receiving 8 or more cycles. A total of 28 (93%) patients were off study at the time of data cutoff; 21 (70%) patients due to disease progression, 2 (7%) due to patient withdrawal, 2 (7%)

TABLE 2 Baseline characteristics.

	Subjects ($n = 30$)
Age (years), median (range)	64 (35–79)
>70 years	6 (20%)
Sex	
Male	15 (50%)
Female	15 (50%)
Race	
White	19 (63%)
Black	10 (33%)
Asian	1 (3%)
More than one race	1 (3%)
Ethnicity	
Hispanic	4 (13%)
Non-Hispanic	23 (77%)
Unknown	3 (10%)
ECOG PS	
0	12 (40%)
1	17 (57%)
Unknown	1 (3%)
ISS stage	
I	14 (47%)
II	6 (20%)
III	10 (33%)
High-risk cytogenetics[a]	
1+ abnormalities	12 (40%)
2+ abnormalities	2 (7%)
t(4;14)	10 (33%)
17p deletion	4 (13%)
t(14;16)	0 (0%)
Years since diagnosis, median (range)	5 (1–18)
Prior lines of therapy, median (range)[b]	5 (2–17)
Prior ASCT	26 (87%)
Lenalidomide exposed	29 (97%)
Pomalidomide exposed	24 (80%)
Bortezomib exposed	28 (93%)
Carfilzomib exposed/refractory	25 (83%)/9 (30%)
Daratumumab exposed	26 (87%)
Triple class exposed	26 (87%)
Penta exposed	14 (47%)
Prior CAR T-cell therapy	6 (20%)
Number of cycles of therapy, median (range)	5 (1–25)

Abbreviations: ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; ISS, International Staging System; Penta exposed, exposed to bortezomib, carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody; Triple class exposed, exposed to at least one proteasome inhibitor, immunomodulatory imide, and anti-CD38 monoclonal antibody.
[a]High-risk cytogenetics were determined by fluorescent in situ hybridization and included 17p deletion, *t*(4;14), and *t*(14;16).
[b]Refractoriness to therapies was only captured for carfilzomib and not other drug classes.

TABLE 3 Adverse events.

Adverse event	All grades, *n* (%) ($n = 30$)	Grade 3+, *n* (%) ($n = 30$)
Hematologic		
Thrombocytopenia	25 (83%)	13 (43%)
Anemia	21 (70%)	8 (27%)
Lymphopenia	15 (50%)	10 (33%)
Neutropenia	15 (50%)	5 (17%)
Nonhematologic		
Fatigue	21 (70%)	7 (23%)
Nausea	21 (70%)	3 (10%)
Diarrhea	16 (53%)	2 (7%)
Anorexia	14 (47%)	7 (23%)
Weight loss	13 (43%)	0 (0%)
Dyspnea	11 (37%)	0 (0%)
Insomnia	9 (30%)	2 (7%)
Acute kidney injury	8 (27%)	5 (17%)
Constipation	8 (27%)	0 (0%)
Dysgeusia	8 (27%)	0 (0%)
Electrolyte imbalances		
Hyponatremia	8 (27%)	1 (3%)
Hyperkalemia	5 (17%)	1 (3%)
Hypophosphatemia	5 (17%)	3 (10%)
Hypercalcemia	4 (13%)	0 (0%)
Hypokalemia	4 (13%)	1 (3%)
Hypomagnesemia	3 (10%)	0 (0%)
Hypocalcemia	3 (10%)	0 (0%)
Infection		
Upper respiratory	8 (27%)	0 (0%)
Lung	5 (17%)	3 (10%)
Bronchial	3 (10%)	1 (3%)
Nonpulmonary	3 (10%)	1 (3%)
Hyperglycemia	6 (20%)	4 (13%)
Left ventricular systolic dysfunction	3 (10%)	1 (3%)
Thromboembolic events	3 (10%)	1 (3%)
Myocardial Infarction	1 (3%)	1 (3%)[a]

[a]Grade 5 myocardial infarction, possibly related to study drugs. Patient was later found to have cardiac amyloidosis.

due to an adverse event, 2 (7%) for other reasons (patient relocation and investigator discretion), and 1 (3%) due to death. The cause of death was myocardial infarction possibly attributed to therapy in a patient who was found to have cardiac amyloidosis that was previously undiagnosed (amyloidosis was an exclusionary diagnosis for the study).

Among the 7 patients treated at dose level 1, 6 were evaluated for DLT. There was 1 (17%) DLT reported in dose level 1 (grade 3 acute kidney injury that resolved), allowing enrollment into dose level 2. No DLTs occurred in the first 3 evaluable patients in dose

TABLE 4 Response rates.

	All subjects ($n = 30$)	Triple-class Exposed ($n = 26$)	Penta exposed ($n = 14$)
Clinical benefit rate (%)	25 (83%)	21 (81%)	13 (93%)
Overall response rate (%)	21 (70%)	17 (65%)	12 (86%)
Best response (%)			
PD	5 (17%)	5 (19%)	1 (7%)
SD	4 (13%)	4 (15%)	1 (7%)
PR	13 (43%)	9 (35%)	8 (57%)
VGPR	6 (20%)	6 (23%)	4 (29%)
CR	0 (0%)	0 (0%)	0 (0%)
sCR	2 (7%)	2 (8%)	0 (0%)

Abbreviations: CR, complete response; PD, progressive disease; Penta exposed = exposed to two proteasome inhibitors, two immunomodulatory imides, and at least one anti-CD38 monoclonal antibody; PR, partial response; sCR, stringent complete response; SD, stable disease; Triple-class exposed, received at least one proteasome inhibitor, one immunomodulatory imide, and one anti-CD38 monoclonal antibody.

level 2. Therefore, dose level 2 was selected as the MTD for expansion. A total of 23 patients received treatment at this dose level.

Treatment-emergent adverse events (TEAEs) are shown in Table 3. The most common hematologic TEAEs of any grade were thrombocytopenia (83% all grades, 43% grade 3+), anemia (70%/27%), lymphopenia (50%/33%), and neutropenia (50%/17%). The most common (>50%) nonhematologic TEAEs were fatigue (70%/23%), nausea (70%/10%), diarrhea (53%/7%), and anorexia (47%/23%). Additional TEAEs of interest included dyspnea (37%/0%), acute kidney injury (27%/17%), hyponatremia (27%/3%), upper respiratory infections (27%/0%), and reduced left ventricular ejection fraction (10%/3%). One patient died from a myocardial infarction, which carried an attribution of being possibly related to therapy. Cessation of treatment for adverse events occurred in 2 (7%) patients. Delays in the initiation of a new cycle occurred in 4 (13%). Dose reductions occurred in 5 (17%) for selinexor, 1 (3%) for carfilzomib, and 1 (3%) for dexamethasone.

The ORR was 21/30 (70%, 95% CI 51%–85%): 43% partial response (PR), 20% very good PR (VGPR), 7% stringent complete response (sCR) (Table 4). Stable disease (SD) was observed in 4 (13%) and progressive disease (PD) in 5 (17%). Of the 5 patients with PD as the best response, 1 (20%) was carfilzomib-refractory and 2 (40%) received B-cell maturation antigen (BCMA)-directed CAR T-cell therapy. For patients treated at the MTD, the ORR was 18/23 (78%), 95% CI 57%–93%: 52% PR, 17% VGPR, 9% sCR, along with SD in 9% and PD in 13%. Among triple-class exposed and penta-exposed disease, the ORR was 17/26 (65%) and 12/14 (86%), respectively (Table 4). The ORR was 3/6 (50%) in patients who previously received BCMA-directed CAR T-cell therapy (median 7 lines of therapy, range 4–11).

The median follow-up was 12.3 months. Median PFS was 5.3 months (95% CI 3.8–10.8) and median OS was 23.3 months (95% CI 10.2-not estimable) (Figure 1); at the MTD, the median PFS and OS were 5.7 months and 26.9 months, respectively. One-year PFS was 24% and 1-year OS was 67%. When comparing patients with carfilzomib naïve/exposed and carfilzomib refractory disease, the PFS (median PFS 5.7 vs. 5.2 months, log–rank $p = .69$) and OS (median OS 23.3 vs. 20 months, $p = .96$) were similar. Of the 7 patients with a PFS of 12 or more months, 2 (29%) were carfilzomib-refractory, 3 (43%) were carfilzomib exposed, and 2 (29%) were carfilzomib-naïve. Among the 6 patients who previously received BCMA-directed CAR T-cell therapy, the median PFS was 2.3 months (vs. 6.4 months without prior BCMA-directed CAR T-cell therapy, log–rank $p = .2$).

4 | DISCUSSION

This phase Ib study demonstrated that the safety profile of wSKd is consistent with what has been previously reported for these agents singularly and in combination.[13] Despite concerns over the tolerability of selinexor, there were only a limited number of treatment holds, dose reductions, or withdrawals due to adverse events. While the rate of grade 3+ thrombocytopenia was 43%, there were a limited number of dose reductions owed to a strategy of continuing carfilzomib and holding selinexor until resolution of thrombocytopenia to grade 2 or less. The rate of grade 3+ infection was low overall, and there were no serious infections with COVID-19 in the patients treated since the onset of the pandemic. The weekly dosing may have served not only to improve patient convenience but also tolerability. The use of prophylactic anti-emetics early in treatment appears to have been instrumental in reducing high grade gastrointestinal adverse events (AEs) as was also seen in the BOSTON trial with once-weekly selinexor.[7] In light of these findings, dose level 2 was selected for dose expansion (selinexor 100 mg weekly, carfilzomib 70 mg/m^2 Days 1, 8, 15, and dexamethasone 40 mg weekly for cycles 1–4 followed by 20 mg weekly for cycles 5+). The RP2D from the study by Gasparetto et al.[13] included selinexor 80 mg weekly and carfilzomib 56 mg/m^2, although it should be noted that the definitions of DLT were different and this could account for differences in the RP2D.

Limitations of this study include its small sample size, along with under enrollment of the carfilzomib naïve cohort. We attribute this in part to the FDA approval of selinexor during the study which made the drug more widely available along with the difficulty in identifying

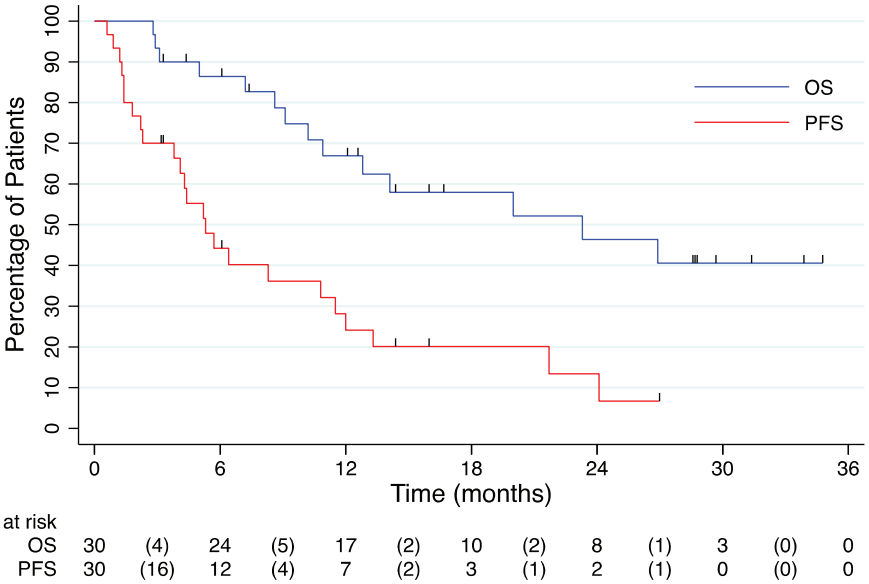

FIGURE 1 Kaplan–Meier analysis of progression-free (PFS) and overall survival (OS).

carfilzomib naïve patients for this study. The focus on carfilzomib-exposed patients and the inclusion of patients with prior BCMA-directed CAR T-cell therapy in this study is a strength, as it better reflects the patient population who would be considering use of selinexor. Additionally, with a third of patients identifying as Black and 10% identifying as Hispanic, this represents one of the highest rates of minority patient enrollment in a MM study to date.

In this heavily pre-treated population, the majority of whom were previously exposed to carfilzomib, 30% of whom were carfilzomib-refractory, and 20% of whom previously received prior BCMA-directed CAR T-cell therapy, wSKd led to an ORR of 70% (78% at the MTD). These response rates compare favorably with Sd in the STORM trial for heavily pretreated patients (ORR 26%), SVd in the BOSTON trial in much earlier lines of therapy (ORR 74.6%), and twSKd in the phase Ia portion of this study (ORR 48%).[4,7,11] In our study, the median PFS for all patients was 5.3 months and the median OS 23.3 months. Patients with prior BCMA-directed CAR T-cell therapy had a median PFS of 2.3 months compared to 6.4 months in those without prior BCMA-directed CAR T-cell therapy. These numbers fall short of a separate study investigating wSKd in 32 patients, which found an ORR of 78.1% with a median PFS of 15 months and a median OS not reached at 15 months of follow-up.[13] While ORR were similar between the two wSKd studies, PFS was not. Caution should be exercised when examining the PFS given that it was not the primary endpoint in either study and that only 3 (9%) patients in the Gasparetto, et al. study had previously received carfilzomib (vs. 83% in our study) and none had carfilzomib-refractory disease (vs. 30% in our study), 1 (3%) had received prior CAR T-cell therapy (vs. 20% in our study), and 72% underwent autologous stem cell transplant compared with 87% in our study.

That patients with carfilzomib refractory disease had similar responses and outcomes compared with carfilzomib naïve/exposed patients in our study suggests selinexor may help overcome resistance to carfilzomib, but that effect is not long lasting. This is evidenced by the fact that most of the durable responders were not carfilzomib refractory. The lack of a durable response in CAR T-cell recipients suggests a need for more effective therapies in the post-CAR T relapse setting. Preliminary data have shown that selective inhibitors of nuclear export may augment anti-tumor cytotoxicity when given prior to CD19-directed CAR T-cell therapy.[14] While the long-term efficacy of wSKd is modest in this cohort of primarily carfilzomib-exposed/refractory MM, these data suggest that wSKd could be employed as a bridging strategy to CAR T-cell therapy and provide rationale for selinexor in combination with other active anti-myeloma agents that may have already been utilized previously in a patient's care.

AUTHOR CONTRIBUTIONS

Andrzej Jakubowiak conceived and designed the trial. Benjamin A Derman, Theodore Karrison, and Andrzej Jakubowiak analyzed and interpreted the data. Benjamin A Derman and Andrzej Jakubowiak drafted the original manuscript. All authors collected and assembled the data, and critically reviewed and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Benjamin A Derman: Consultancy: Janssen, Sanofi, and COTA Healthcare. Honoraria: Plexus communications and MJH Life Sciences. Ajai

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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