Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial

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Summary

Background Selinexor combined with dexamethasone has shown activity in patients with heavily pre-treated multiple myeloma. In a phase 1b/2 study, the combination of oral selinexor with bortezomib (a proteasome inhibitor) and dexamethasone induced high response rates with low rates of peripheral neuropathy, the main dose-limiting toxicity of bortezomib. We aimed to evaluate the clinical benefit of weekly selinexor, bortezomib, and dexamethasone versus standard bortezomib and dexamethasone in patients with previously treated multiple myeloma.

Methods This phase 3, randomised, open-label trial was done at 123 sites in 21 countries. Patients aged 18 years or older, who had multiple myeloma, and who had previously been treated with one to three lines of therapy, including proteasome inhibitors, were randomly allocated (1:1) to receive selinexor (100 mg once per week), bortezomib (1·3 mg/m² once per week), and dexamethasone (20 mg twice per week), or bortezomib (1·3 mg/m² twice per week for the first 24 weeks and once per week thereafter) and dexamethasone (20 mg four times per week for the first 24 weeks and twice per week thereafter). Randomisation was done using interactive response technology and stratified by previous proteasome inhibitor therapy, lines of treatment, and multiple myeloma stage. The primary endpoint was progression-free survival in the intention-to-treat population. Patients who received at least one dose of study treatment were included in the safety population. This trial is registered at ClinicalTrials.gov, NCT03110562. The trial is ongoing, with 55 patients remaining on randomised therapy as of Feb 20, 2020.

Findings Of 457 patients screened for eligibility, 402 were randomly allocated—195 (49%) to the selinexor, bortezomib, and dexamethasone group and 207 (51%) to the bortezomib and dexamethasone group—and the first dose of study medication was given between June 6, 2017, and Feb 5, 2019. Median follow-up durations were 13·2 months [IQR 6·2–19·8] for the selinexor, bortezomib, and dexamethasone group and 16·5 months [9·4–19·8] for the bortezomib and dexamethasone group. Median progression-free survival was 13·93 months (95% CI 11·73–not evaluable) with selinexor, bortezomib, and dexamethasone and 9·46 months (8·11–10·78) with bortezomib and dexamethasone (hazard ratio 0·70 [95% CI 0·53–0·93], p=0·0075). The most frequent grade 3–4 adverse events were thrombocytopenia (77 [39%] of 195 patients in the selinexor, bortezomib, and dexamethasone group *vs* 35 [17%] of 204 in the bortezomib and dexamethasone group), fatigue (26 [13%] *vs* two [1%]), anaemia (31 [16%] *vs* 20 [10%]), and pneumonia (22 [11%] *vs* 22 [11%]). Peripheral neuropathy of grade 2 or above was less frequent with selinexor, bortezomib, and dexamethasone (41 [21%] patients) than with bortezomib and dexamethasone (70 [34%] patients; odds ratio 0·50 [95% CI 0·32–0·79], p=0·0013). 47 (24%) patients in the selinexor, bortezomib, and dexamethasone group and 62 (30%) in the bortezomib and dexamethasone group died.

Interpretation A once-per-week regimen of selinexor, bortezomib, and dexamethasone is a novel, effective, and convenient treatment option for patients with multiple myeloma who have received one to three previous lines of therapy.

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Research in context

Evidence before this study

We searched PubMed for articles published until Feb 18, 2020, with no language restrictions, using the search terms "multiple myeloma", "relapsed and refractory", "triplet therapy", and "combination treatment". Several phase 3 studies with novel agent-based triplet therapies showed improved response rates and progression-free survival times compared with doublet combinations in most patient subgroups with relapsed or refractory multiple myeloma. However, despite the success of combination therapies with established drugs, many of these regimens are cumbersome, requiring frequent or long clinic visits, and patients develop relapsed or refractory disease, necessitating the development of novel therapeutic options. Selinexor is an oral selective inhibitor of the nuclear export protein exportin 1. The efficacy and safety of selinexor in combination with other backbone treatments in patients with relapsed or refractory multiple myeloma has been investigated in a phase 1/2 study. The triplet combination of selinexor, bortezomib, and dexamethasone showed promising anti-myeloma activity with an overall response rate of 84% and median progression-free survival of 17·8 months (estimated on the basis of 25% of events) in patients with multiple myeloma not refractory to proteasome inhibitors. The triplet combination was well tolerated with low rates (10%) of peripheral neuropathy. These promising results led to the initiation of this phase 3 study to evaluate once-weekly selinexor, bortezomib, and dexamethasone compared with the standard twice-per-week combination of bortezomib and dexamethasone in patients who had received one to three previous lines of therapies for multiple myeloma.

Added value of this study

To our knowledge, this is the first large phase 3 trial to evaluate once-weekly dosing of bortezomib in a triplet combination. This regimen reduced the risk of progression or death by 30% and induced higher rates of overall response (partial response or better) and deep response (very good partial response or better) compared with the doublet therapy. Efficacy was consistent across various patient subgroups, including patients older than 65 years and those who are frail, those with one versus two to three previous lines of therapy, and patients who had received previous lenalidomide treatment. Moreover, efficacy was particularly noteworthy in patients who had not previously been treated with a proteasome inhibitor and in patients with high-risk cytogenetic abnormalities. Furthermore, the once-weekly combination was associated with lower rates and severity of bortezomib-induced peripheral neuropathy, with no new safety risks.

Implications of all the available evidence

The combination of selinexor, bortezomib, and dexamethasone is a novel and effective triplet therapy that uses 40% less bortezomib and 25% less dexamethasone during the first 24 weeks of treatment. The once-weekly regimen offers a convenient treatment option by reducing clinic visits by around 37% compared with standard bortezomib and dexamethasone doublet regimens and other commonly used triplet regimens containing bortezomib and dexamethasone. Finally, the lower frequency and severity of peripheral neuropathy could substantially improve patient quality of life.

Introduction

Although the number of treatment options has increased over the past 20 years, multiple myeloma remains largely an incurable disease. Most patients will relapse and develop refractory disease, underscoring an ongoing need for more efficacious and less toxic treatment strategies.[1,2] The combination of bortezomib, the first-in-class proteasome inhibitor, with low-dose dexamethasone is the standard therapy for patients with multiple myeloma.[3] However, the twice-per-week dosing regimen is associated with high rates of sensory, motor, and autonomic neuropathy, which can be irreversible and often limit long-term use.[4–6]

Exportin-1 (XPO1) is overexpressed in most cancer cells, including in multiple myeloma, and its levels are correlated with poor patient prognosis, treatment resistance, and aggressive disease.[7,8] XPO1 is an oncoprotein[9] that mediates the nuclear export and functional inactivation of the majority of tumour suppressor proteins and enhances the translation of certain oncoproteins, including Myc proto-oncogene protein, B-cell lymphoma 6 protein, and G1/S-specific cyclin-D1.[10] In addition, overexpression of XPO1 is associated with the development of resistance to proteasome inhibitors (including bortezomib)[11] and immunomodulatory agents.[12]

Selinexor is a potent, orally administered, selective inhibitor of nuclear export that binds to the Cys528 residue in the cargo-binding pocket of XPO1,[13] forcing the nuclear localisation and functional activation of tumour suppressor proteins, trapping NF-κB inhibitor α in the nucleus to suppress NF-κB activity, and preventing the translation of oncoprotein mRNAs.[8,14] The combination of selinexor (80 mg, twice per week) and dexamethasone has been approved in the USA for the treatment of patients who have received at least four previous therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody, based on the phase 2b STORM study wherein selinexor and dexamethasone produced an overall response rate (ORR) of 25·3% (95% CI 16·4–36·0) and a median progression-free survival time of 3·7 months (95% CI 3·0–5·3) in patients with myeloma refractory to currently available therapies (n=83).[15]

Nuclear export inhibitors and proteasome inhibitors have shown synergistic activity in preclinical models.[16] On this

basis, the combination of oral selinexor with subcutaneous bortezomib and dexamethasone in patients with multiple myeloma and at least one previous therapy was investigated in a phase 1b/2 study. Among 19 patients with multiple myeloma naive or not refractory to proteasome inhibitor treatment, selinexor, bortezomib, and dexamethasone induced an ORR of 84% (95% CI 62–94) and a median progression-free survival time of 17·8 months.[17] Given the encouraging activity against multiple myeloma and the low frequency of adverse events observed with once-per-week bortezomib combined with selinexor and dexamethasone, we designed a study to further evaluate the safety and efficacy of the triplet combination in comparison with bortezomib and dexamethasone (standard twice-per-week regimen) in patients with multiple myeloma who had received one to three previous lines of therapy.

Methods

Study design and participants

The Bortezomib, Selinexor, and Dexamethasone in Patients with Multiple Myeloma (BOSTON) trial was a phase 3, open-label, global, randomised, controlled trial. Patients were enrolled at 123 sites in 21 countries across Europe, North America, and the Asia-Pacific region. Patients were eligible if they were aged 18 years or older, had measurable myeloma according to the International Myeloma Working Group criteria[18] with documented evidence of progressive disease on or after their most recent treatment regimen, and had previously received treatment with at least one, but no more than three, different regimens for multiple myeloma. Patients who had previously received proteasome inhibitors (alone or as part of a combination treatment) were required to have had at least a partial response to the therapy and at least a 6-month interval since their last proteasome inhibitor therapy, with no history of discontinuation of bortezomib due to grade 3 or higher toxicity. Patients were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, and adequate hepatic, renal, and haematopoietic function. Patients were excluded if they had systemic light-chain amyloidosis, CNS involvement, or grade 2 painful or grade 2 or higher peripheral neuropathy (see appendix pp 3–4 for full inclusion and exclusion criteria).

The trial was done in accordance with the Declaration of Helsinki and the International Council for Harmonisation guidelines on Good Clinical Practice. The institutional review board or independent ethics committee of each centre approved the protocol. All patients provided written informed consent. A summary of the study protocol is provided in the appendix (pp 11–28).

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio and by permuted block randomisation to either the selinexor, bortezomib, and dexamethasone group or the bortezomib and dexamethasone group. Randomisation was done with use of interactive response technology and stratified by treatment with previous proteasome inhibitor therapies (yes *vs* no), number of previous lines of treatment (one *vs* two or more), and International Staging System stage (III *vs* I–II). There was no masking to treatment assignments.

Procedures

On the basis of the recommended phase 2 dose in the STOMP study,[17] patients allocated to the selinexor, bortezomib, and dexamethasone group received selinexor as a fixed oral 100 mg dose on days 1, 8, 15, 22, and 29 of each 5-week cycle; bortezomib once per week as a subcutaneous dose of 1·3 mg/m² on days 1, 8, 15, and 22 of each 5-week cycle; and dexamethasone as an oral 20 mg dose on days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 5-week cycle. In the bortezomib and dexamethasone group, for the first eight 3-week cycles, bortezomib was administered subcutaneously in accordance with the approved regimen of 1·3 mg/m² on days 1, 4, 8, and 11, and dexamethasone was given as an oral 20 mg dose on days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle. For cycles nine and above, bortezomib was administered subcutaneously once per week at a dose of 1·3 mg/m² on days 1, 8, 15, and 22, and dexamethasone was given as an oral 20 mg dose on days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 5-week cycle.

To minimise nausea, all patients received 5-hydroxytryptamine (8 mg or equivalent) before the first dose of study drug and two to three times daily on days 1 and 2 of each cycle, as needed. Additional supportive measures were provided at the discretion of the investigator and could include use of olanzapine, megestrol acetate, intravenous fluids, methylphenidate, thrombopoietin-stimulating agents, or transfusions. Treatment was administered until disease progression, physician decision, withdrawal of patient consent, or unacceptable side-effects. Dose reductions and treatment interruptions were permitted for the management of adverse events. If progressive disease was confirmed by the independent review committee, patients in the bortezomib and dexamethasone group could cross over to selinexor, bortezomib, and dexamethasone treatment if able to tolerate continued bortezomib treatment.

Fluorescence in-situ hybridisation was done at central laboratories and used to assess cytogenetic risk status.[19,20]

Frailty was measured as described by Facon and colleagues.[21]

Outcomes

The primary endpoint of progression-free survival was defined as time from randomisation until the first disease progression (determined by the independent review committee) per International Myeloma Working Group response criteria, or until death from any cause in the intention-to-treat population. Prespecified secondary endpoints included ORR (defined as the proportion of patients with a partial response or better); overall survival;

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See Online for appendix

duration of response; progression-free survival and ORR in patients who crossed over from the bortezomib and dexamethasone group to the selinexor, bortezomib, and dexamethasone group; progression-free survival on the subsequent line of therapy; time to next anti-multiple myeloma treatment; time to response; incidence of any grade 2 or higher peripheral neuropathy events; safety and tolerability of study treatment; and patient-reported peripheral neuropathy as measured by the Quality of Life–Chemotherapy-Induced Peripheral Neuropathy questionnaire (QLQ-CIPN20) from the European Organisation for Research and Treatment of Cancer. Definitions of efficacy endpoints and the protocol synopsis are provided in the appendix (pp 2, 11–28). Safety and tolerability were assessed by physical examination, laboratory assessments, ECOG performance status score, 12-lead electrocardiogram, and ophthalmic examination. Adverse events were graded in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03).

Statistical analysis

The sample size was designed to have 80% power to detect a median time to progression-free survival of 13·5 months for patients treated with selinexor, bortezomib, and dexamethasone versus 9·4 months for patients treated with bortezomib and dexamethasone,[22,23] using a one-sided α of 0·025, 15-month accrual, 18-month follow-up, and a 1:1 allocation to the two treatment groups, allowing

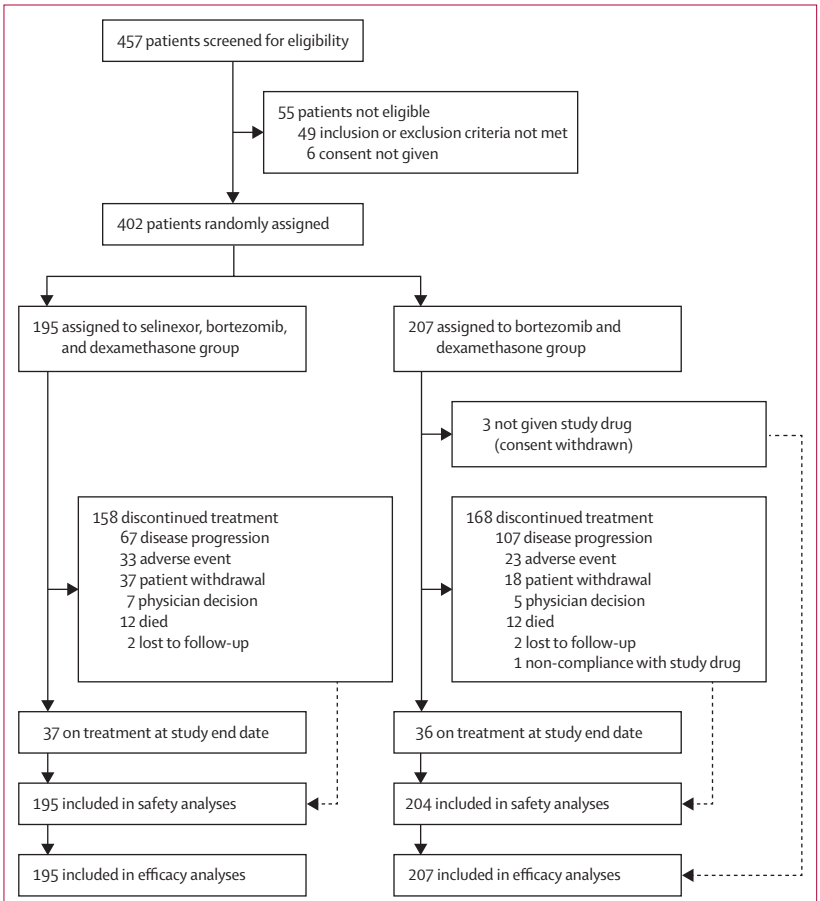


Figure 1: **Patient disposition**

	Selinexor, bortezomib, and dexamethasone group (n=195)	Bortezomib and dexamethasone group (n=207)
Age, years		
Median	66 (59–72)	67 (61–74)
18–50	15 (8%)	11 (5%)
51–64	71 (36%)	64 (31%)
65–74	75 (38%)	85 (41%)
≥75	34 (17%)	47 (23%)
Sex		
Male	115 (59%)	115 (56%)
Female	80 (41%)	92 (44%)
ECOG performance status*		
0	69 (35%)	77 (37%)
1	106 (54%)	114 (55%)
2	20 (10%)	16 (8%)
Cytogenetic abnormalities†		
del(17p)	21 (11%)	16 (8%)
t(14;16)	7 (4%)	11 (5%)
t(4;14)	22 (11%)	28 (14%)
1q21 amplification‡	80 (41%)	71 (34%)
Any of the above	97 (50%)	95 (46%)
Not assessed	15 (8%)	24 (12%)
R-ISS disease stage at screening		
I–II	173 (89%)	177 (86%)
III	12 (6%)	16 (8%)
Unknown	10 (5%)	14 (7%)
Time since initial diagnosis, years	3·8 (2·5–5·4)	3·6 (2·1–5·6)
Number of previous lines of therapy		
One	99 (51%)	99 (48%)
Two	65 (33%)	64 (31%)
Three	31 (16%)	44 (21%)
Previous stem-cell transplantation	76 (39%)	63 (30%)
Previous therapy		
Bortezomib	134 (69%)	145 (70%)
Carfilzomib	20 (10%)	21 (10%)
Ixazomib	6 (3%)	3 (1%)
Daratumumab	11 (6%)	6 (3%)
Lenalidomide	77 (39%)	77 (37%)
Pomalidomide	11 (6%)	7 (3%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. R-ISS=Revised International Staging System. *Scores range from 0 to 5, with higher scores reflecting greater disability. †Fluorescence in-situ hybridisation was done at central laboratories and used to assess cytogenetic risk status. ‡Required three or more copies.

Table 1: **Baseline demographic and clinical characteristics in the intention-to-treat population**

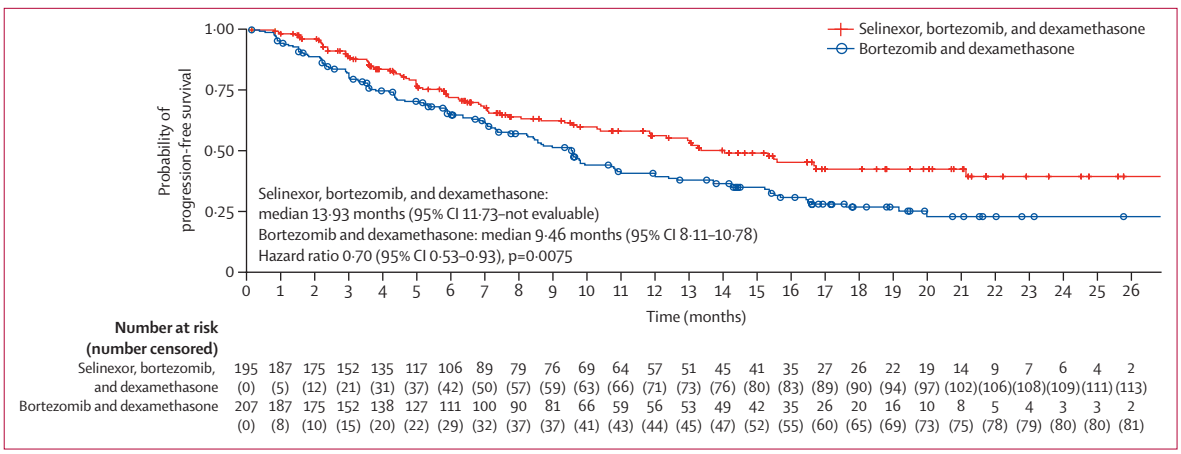


Figure 2: **Kaplan-Meier estimates of progression-free survival among patients in the intention-to-treat population**

for an interim analysis of progression-free survival for futility or superiority. The intention-to-treat population included all enrolled patients who met all eligibility criteria and was used for the primary efficacy analysis. The safety population included all patients who received at least one dose of study treatment. Progression-free survival was compared between the selinexor, bortezomib, and dexamethasone group and the bortezomib and dexamethasone group with a stratified log-rank test. Hazard ratios (HRs) and corresponding 95% CIs were estimated with use of a stratified Cox proportional-hazards model, with treatment as the single covariate. A stratified Cochran-Mantel-Haenszel χ^2 test was used to test differences in ORRs between the two groups. One-sided p values are presented for efficacy endpoints.

This trial is registered with ClinicalTrials.gov (NCT03110562).

Role of the funding source

The funder of the trial was involved in trial design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Of the 457 patients screened, 49 did not meet the selection criteria and six did not provide informed consent. The remaining 402 were randomly allocated—195 (49%) to the selinexor, bortezomib, and dexamethasone group and 207 (51%) to the bortezomib and dexamethasone group (figure 1)—and given the first dose of study medication between June 6, 2017, and Feb 5, 2019. Three patients from the bortezomib and dexamethasone group did not receive any dose of study drug and thus were not included in the safety population. Baseline demographic, disease, and clinical characteristics were balanced across the two treatment groups (table 1). Median age was 67 years (IQR 59–73) and 81 (20%) patients were aged 75 years or older. Median time since initial diagnosis of myeloma was 3·7 years (2·3–5·5). High-risk cytogenetic abnormalities were present in 192 (48%) patients. Median number of previous regimens was two (1–2), 75 (19%) patients had received three previous lines of therapy, and 139 (35%) patients had undergone stem-cell transplantation. Previous therapies included lenalidomide (154 [38%] patients) and proteasome inhibitors (307 [76%]), including bortezomib (279 [69%]). At data cutoff (Feb 18, 2020), 37 (19%) patients in the selinexor, bortezomib, and dexamethasone group and 36 (17%) in the bortezomib and dexamethasone group were still receiving treatment. The primary reason for treatment discontinuation was disease progression, which occurred in 67 (34%) patients in the selinexor, bortezomib, and dexamethasone group and 107 (52%) in the bortezomib and dexamethasone group.

After a median follow-up period of 13·2 months [IQR 6·2–19·8] for selinexor, bortezomib, and dexamethasone and 16·5 months [9·4–19·8] for bortezomib and dexamethasone, median progression-free survival time was significantly longer in the selinexor, bortezomib, and dexamethasone group (13·93 months [95% CI 11·73–not evaluable]) than in the bortezomib and dexamethasone group (9·46 months [8·11–10·78]; HR 0·70 [95% CI 0·53–0·93], p=0·0075; figure 2). Progression-free survival after the first subsequent therapy following study treatment is summarised in the appendix (p 6).

ORR was significantly higher in the selinexor, bortezomib, and dexamethasone group (76·4% [95% CI 69·8–82·2]) than in the bortezomib and dexamethasone group (62·3% [55·3–68·9]; odds ratio (OR) 1·96 [95% CI 1·3–3·1], p=0·0012; table 2). The proportion of patients with a very good partial response or better (ie, a ≥90% reduction in multiple myeloma markers) was 44·6% (95% CI 37·5–51·9) in the selinexor, bortezomib, and dexamethasone group and 32·4% (26·0–39·2) in the bortezomib and dexamethasone group (OR 1·66

	Selinexor, bortezomib, and dexamethasone group (n=195)	Bortezomib and dexamethasone group (n=207)
Overall response rate*	149 (76·4% [69·8–82·2])	129 (62·3% [55·3–68·9])
Best overall response†		
Stringent complete response	19 (10%)	13 (6%)
Complete response	14 (7%)	9 (4%)
Very good partial response	54 (28%)	45 (22%)
Partial response	62 (32%)	62 (30%)
Minimal response	16 (8%)	20 (10%)
Stable disease	25 (13%)	40 (19%)
Progressive disease	1 (1%)	10 (5%)
Non-evaluable	4 (2%)	8 (4%)
Negative status for minimal residual disease‡	9 (5%)	8 (4%)

Data are n (% [95% CI]) or n (%). *p=0·0012 for between-group comparison (Cochran-Mantel-Haenszel test). †Best overall response categories are mutually exclusive. ‡Minimal residual disease was assessed in patients with a stringent complete response or complete response; negative status was defined as an absence of malignant clones per 100 000 white blood cells.

Table 2: **Efficacy data**

[1·1–2·5], p=0·0082). Importantly, the proportion of patients who had stable disease or progressive disease as their best response was lower in the selinexor, bortezomib, and dexamethasone group (13·3% [8·9–18·9]) than in the bortezomib and dexamethasone group (24·2% [18·5–30·6]).

Outcomes in patients who crossed over from the bortezomib and dexamethasone group to selinexor, bortezomib, and dexamethasone treatment are summarised in the appendix (p 7).

Median time to first response in patients with a partial response or better was 1·1 months (IQR 0·8–1·6) in the selinexor, bortezomib, and dexamethasone group versus 1·4 months (0·8–1·6) in the bortezomib and dexamethasone group. Median duration of response was longer with selinexor, bortezomib, and dexamethasone (20·3 months [95% CI 12·5–not evaluable] *vs* 12·9 months [9·3–15·8]; HR 0·81 [95% CI 0·56–1·17], p=0·1364). In addition, the median time to next anti-multiple myeloma treatment was longer in the selinexor, bortezomib, and dexamethasone group (16·1 months [13·9–not evaluable]) than in the bortezomib and dexamethasone group (10·8 months [9·8–13·4]; 0·66 [0·50–0·86], p=0·0012).

As of the data cutoff date, 47 (24%) deaths had occurred in the selinexor, bortezomib, and dexamethasone group and 62 (30%) in the bortezomib and dexamethasone group. Median overall survival was not reached in the selinexor, bortezomib, and dexamethasone group (median follow-up 17·3 months [IQR 12·9–20·3]) and was 25 months (95% CI 23·5–not evaluable; median follow-up 17·5 months [14·4–20·5]) in the bortezomib and dexamethasone group (HR 0·84 [0·57–1·23], p=0·1852).

	Selinexor, bortezomib, and dexamethasone group (n=195)		Bortezomib and dexamethasone group (n=204)*	
	Any grade†	Grade 3–4	Any grade‡	Grade 3–4
Haematological adverse events				
Thrombocytopenia	117 (60%)	77 (39%)	55 (27%)	35 (17%)
Anaemia	71 (36%)	31 (16%)	47 (23%)	20 (10%)
Neutropenia	29 (15%)	17 (9%)	12 (6%)	7 (3%)
Non-haematological adverse events				
Fatigue	82 (42%)	26 (13%)	37 (18%)	2 (1%)
Nausea	98 (50%)	15 (8%)	20 (10%)	0
Diarrhoea	63 (32%)	12 (6%)	51 (25%)	1 (<1%)
Peripheral neuropathy§	63 (32%)	9 (5%)	96 (47%)	18 (9%)
Decreased appetite	69 (35%)	7 (4%)	11 (5%)	0
Weight loss	51 (26%)	4 (2%)	25 (12%)	2 (1%)
Asthenia	48 (25%)	16 (8%)	27 (13%)	9 (4%)
Constipation	33 (17%)	0	35 (17%)	3 (1%)
Cough	35 (18%)	1 (1%)	30 (15%)	0
Insomnia	31 (16%)	2 (1%)	32 (16%)	4 (2%)
Back pain	30 (15%)	1 (1%)	29 (14%)	2 (1%)
Pneumonia¶	35 (18%)	24 (12%)	34 (17%)	21 (10%)
Pyrexia	30 (15%)	3 (2%)	22 (11%)	2 (1%)
Cataract	42 (22%)	17 (9%)	13 (6%)	3 (1%)
Vomiting	40 (21%)	8 (4%)	9 (4%)	0
Peripheral oedema	23 (12%)	1 (1%)	26 (13%)	0
Dyspnoea	18 (9%)	1 (1%)	27 (13%)	5 (2%)
Bronchitis	24 (12%)	3 (2%)	20 (10%)	1 (<1%)
Upper respiratory tract infection	35 (18%)	5 (3%)	30 (15%)	1 (<1%)

Data are n (%). Events that occurred in <10% of patients are not shown. Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4·03). *Three patients from this group who did not receive any doses of study drug were excluded from the safety population. †Includes four grade 5 events: three (2%) cases of pneumonia and one (1%) case of bronchitis. ‡Includes four grade 5 events: three (1%) cases of pneumonia and one (<1%) case of anaemia. §Includes high-level MedDRA term "peripheral neuropathies NEC". ¶Includes pneumonia, lung infection, haemophilus infection, pulmonary sepsis, and pneumonia respiratory syncytial viral, pneumonia pneumococcal, pneumonia influenza viral, pneumonia parainfluenzae viral, pneumonia bacterial, and pneumonia fungal infections.

Table 3: **Most common treatment-emergent adverse events in the safety population**

The safety population included 195 patients from the selinexor, bortezomib, and dexamethasone group and 204 from the bortezomib and dexamethasone group. The most common grade 3–4 treatment-emergent adverse events (occurring in ≥10% of patients in either group) were thrombocytopenia, anaemia, pneumonia, and fatigue, all of which had higher incidence in the selinexor, bortezomib, and dexamethasone group than in the bortezomib and dexamethasone group (table 3).

Grade 3–4 thrombocytopenia was uncommonly associated with clinically relevant bleeding events (grade ≥3): in the selinexor, bortezomib, and dexamethasone group, two (1%) patients had epistaxis, one (1%) had upper

gastrointestinal haemorrhage, and one (1%) had cerebral haemorrhage; and in the bortezomib and dexamethasone group one (<1%) patient had epistaxis and one (<1%) had haematuria. Thrombopoietin receptor agonists were often used to mitigate thrombocytopenia (in 35 [18%] patients in the selinexor, bortezomib, and dexamethasone group and two [1%] in the bortezomib and dexamethasone group) and decreased the need for dose interruptions and reductions. 12 (6%) patients receiving selinexor, bortezomib, and dexamethasone and 13 (6%) receiving bortezomib and dexamethasone received platelet transfusions to manage thrombocytopenia. Neutropenic fever was rare, occurring in one patient in each group.

Among the grade 3–4 adverse events that occurred in less than 10% of patients, nausea, diarrhoea, decreased appetite, asthenia, cataract, vomiting, and neutropenia had higher incidence (>4% difference) in the selinexor, bortezomib, and dexamethasone than in the bortezomib and dexamethasone group (table 3).

The incidence of peripheral neuropathy was significantly lower in the selinexor, bortezomib, and dexamethasone group than in the bortezomib and dexamethasone group, whether considering any grade (62 [32%] *vs* 96 [47%] patients, respectively; OR 0·52 [95% CI 0·34–0·79], p=0·0010) or grade 2 or above (41 [21%] *vs* 70 [34%] patients; 0·50 [0·32–0·79], p=0·0013). Grade 3–4 peripheral neuropathy also had a numerically lower incidence in the selinexor, bortezomib, and dexamethasone group (4·6%) than in the bortezomib and dexamethasone group (8·8%; OR 0·48 (0·21–1·11), p=0·0828 [two-sided]). Patient scores on the sensory scale of the QLQ-CIPN20 showed a smaller mean change from baseline in the selinexor, bortezomib, and dexamethasone group than in the bortezomib and dexamethasone group, with an estimated mean between-group difference in weekly score change of –0·12 (SE 0·04; 95% CI –0·20 to –0·04], p=0·0038). The differences were most pronounced during the first 169 days of the study, when patients in the bortezomib and dexamethasone group received twice-per-week bortezomib, in contrast to the once-per-week bortezomib regimen in the selinexor, bortezomib, and dexamethasone group. Mean changes from baseline were similar in each group on the QLQ-CIPN20 motor scale (–0·06 [0·04; –0·14 to 0·02], p=0·1497) and autonomic scale (0·09 [0·06; –0·02 to 0·20], p=0·1228). Together, these findings indicate substantially lower rates of sensory peripheral neuropathy with once-per-week selinexor, bortezomib, and dexamethasone than with twice-per-week bortezomib and dexamethasone, consistent with the mostly sensory nature of bortezomib-induced peripheral neuropathy.[6]

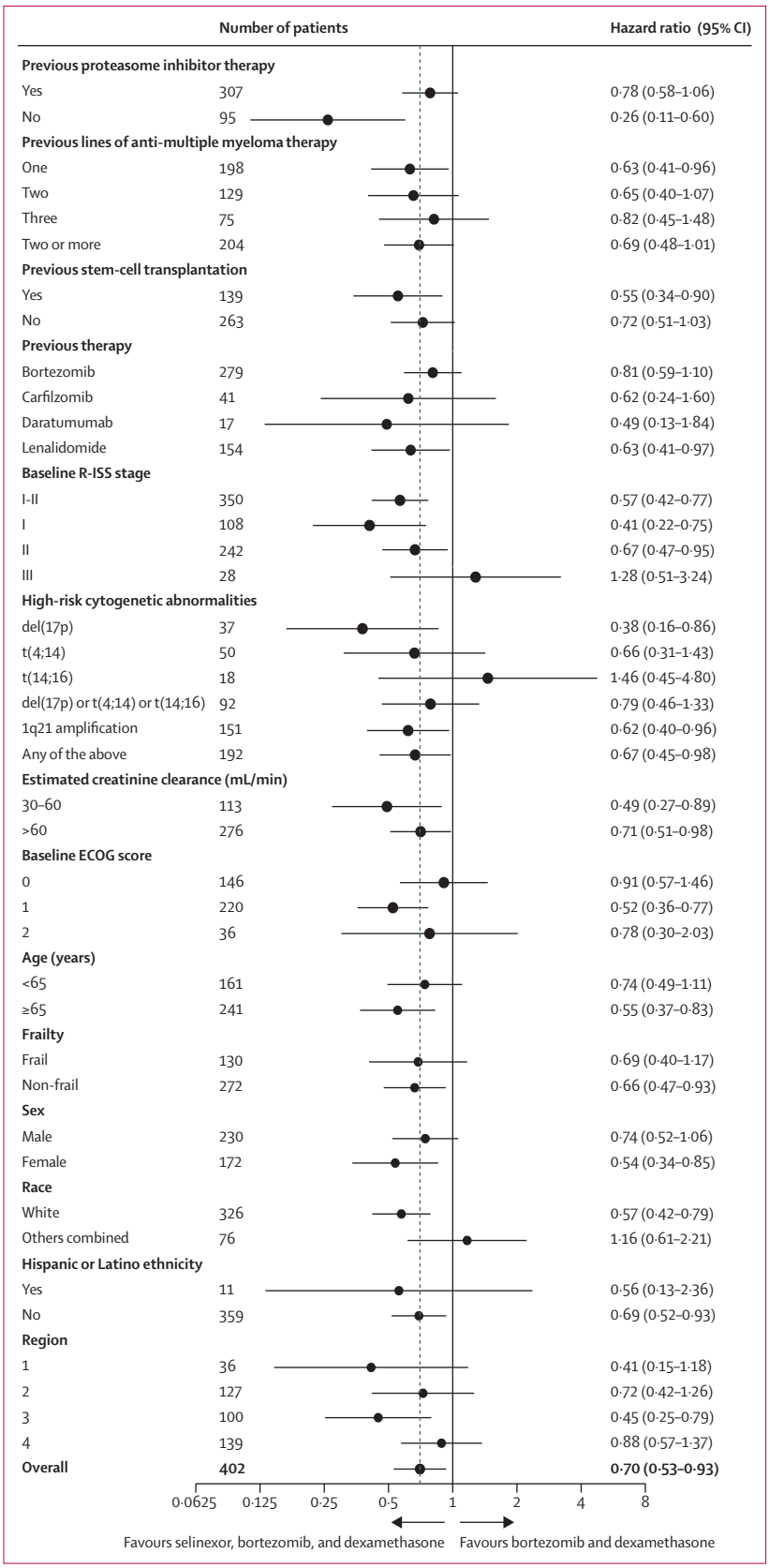
41 (21%) patients in the selinexor, bortezomib, and dexamethasone group and 32 (16%) in the bortezomib and dexamethasone group discontinued study treatment because of treatment-emergent adverse events. The most common reasons for discontinuation were peripheral neuropathy (nine [5%]), fatigue (seven [4%]), nausea (six [3%]), vomiting (four [2%]), decreased appetite (four [2%]), and thrombocytopenia (four [2%]) in the selinexor, bortezomib, and dexamethasone group, and peripheral neuropathy (15 [7%]) in the bortezomib and dexamethasone group. The median time to discontinuation of study treatment was 194 days (IQR 100–332) in the selinexor, bortezomib, and dexamethasone group and 184 days (106–276) in the bortezomib and dexamethasone group. Of the patients who discontinued treatment because of adverse events, 19 (46%) in the selinexor, bortezomib, and dexamethasone group and 16 (50%) in the bortezomib and dexamethasone group were older than 70 years.

Dose modifications (appendix p 5) were more common in the selinexor, bortezomib, and dexamethasone group (173 [89%] of 195 patients) than in the bortezomib and dexamethasone group (156 [76%] of 204). Most of the side-effects associated with selinexor were reversible and could be mitigated with standard supportive care.[24]

Serious adverse events were reported in 101 (52%) patients in the selinexor, bortezomib, and dexamethasone group and 77 (38%) in the bortezomib and dexamethasone group. Pneumonia was the most frequent serious adverse event, with the same incidence (12%) in both groups (appendix p 8). Most other serious adverse events were comparable in type and frequency across both groups. Infections occurred in 135 patients (69%) in the selinexor, bortezomib, and dexamethasone group and 119 (58%) in the bortezomib and dexamethasone group. The imbalance was due to a higher incidence of typically grade 1–2 upper respiratory tract infection, nasopharyngitis, or urinary tract infections in the selinexor, bortezomib, and dexamethasone group. Notably, the differences in incidence of sepsis between the selinexor, bortezomib, and dexamethasone group (4%) and the bortezomib and dexamethasone group (1%) were primarily due to four cases of sepsis in India that occurred early in the course of the study; there were no additional events after patient monitoring was increased in India. Outside of India, the rates of sepsis were similar in both groups. Importantly, rates of pneumonia were similar in the two groups (table 3).

The incidence of treatment-emergent adverse events was similar between patients aged 65 years or older and those aged less than 65 years (grade 3–4 adverse events 78% *vs* 80%, respectively; serious adverse events 56% *vs* 47%). Deaths due to adverse events were of similar frequency in the selinexor, bortezomib, and dexamethasone group (12 [6%]; of which eight [67%] were deemed to be unrelated to treatment) and the bortezomib and dexamethasone group (11 [5%]; ten [91%] unrelated to treatment). The most common treatment-emergent adverse events leading to death were pneumonia (three [2%]) and sepsis (three [2%]) in the selinexor, bortezomib, and dexamethasone group, and pneumonia (three [2%]) in the bortezomib and dexamethasone group.

Consistent with the overall population, risk of progression or death was significantly lower in the selinexor,



bortezomib, and dexamethasone group than in the bortezomib and dexamethasone group across a number of subgroups defined according to baseline characteristics, including patients aged 65 years and older (HR 0·55 [95% CI 0·37–0·83]), patients with high-risk cytogenetic abnormalities (0·67 [0·45–0·98]), those with one previous line of therapy (0·63 [0·41–0·95]), and those previously treated with lenalidomide (0·63 [0·41–0·97]; figure 3).

In addition, ORR was significantly higher in the selinexor, bortezomib, and dexamethasone group versus the bortezomib and dexamethasone group across key subgroups, including patients aged 65 years or older (76·1% [67·0–83·8] *vs* 64·4% [55·6–72·5]; OR 1·77 [1·1–2·5], p=0·0243), patients with high-risk cytogenetic abnormalities (77·3% [67·7–85·2] *vs* 55·8% [45·2–66·0]; 2·70 [1·4–5·0], p=0·0008), those with creatinine clearance between 30 mL/min and 60 mL/min (79·2% [65·9–89·2] *vs* 56·7% [43·2–69·4]; 2·92 [1·3–6·7], p=0·0055), patients with one previous line of therapy (80·8% [71·7–88·0] *vs* 65·7% [55·4–74·9]; 2·20 [1·2–4·2], p=0·0082), and patients previously treated with bortezomib (77·6% [69·9–84·4] *vs* 59·3% [50·8–67·4]; 2·38 [1·4–4·0], p=0·0005) or lenalidomide (67·5% [55·9–77·8] *vs* 53·2% [41·5–64·7]; 1·83 [0·9–3·5], p=0·035).

Discussion

In this randomised phase 3 trial, the combination of selinexor, bortezomib, and dexamethasone was associated with a significant increase in progression-free survival compared with bortezomib and dexamethasone in patients with previously treated multiple myeloma. Kaplan-Meier curves showed an early and sustained benefit, with a 30% reduction in the risk of death or disease progression for patients in the selinexor, bortezomib, and dexamethasone group compared with those in the bortezomib and dexamethasone group. This benefit was also seen across various subgroups, including patients older than 65 years, those who are frail, patients with high-risk cytogenetic abnormalities, and those who had previously received lenalidomide therapy. Notably, the improved efficacy was achieved during the first 24 weeks of treatment, when patients in the selinexor, bortezomib, and dexamethasone group were receiving 40% less bortezomib and 25% less dexamethasone than patients in the bortezomib and dexamethasone group. Selinexor, bortezomib, and dexamethasone also had the advantage of a significantly higher ORR, a higher proportion of patients with a deep response (very good

Figure 3: **Prespecified subgroup analysis for progression-free survival**
R-ISS=Revised International Staging System. ECOG=Eastern Cooperative Oncology Group. Region 1=Canada and the USA. Region 2=Australia, Austria, Belgium, France, Germany, Israel, Italy, Spain, and the UK. Region 3=Czech Republic, Greece, Hungary, and Poland. Region 4=Bulgaria, India, Romania, Russia, Serbia, and Ukraine.

partial response or better), and a significant and clinically meaningful increase of 5·3 months in the time to next anti-multiple myeloma treatment compared with the bortezomib and dexamethasone group. There were also numerically fewer deaths in the selinexor, bortezomib, and dexamethasone group (47 patients) than in the bortezomib and dexamethasone group (62 patients), although these data are immature given the patient population in the trial. Overall, these data reinforce the additive benefit of combining selinexor with bortezomib and dexamethasone that was previously observed in the phase 1/2 STOMP study.[17]

To our knowledge, selinexor, bortezomib, and dexamethasone is the first bortezomib-based triplet therapy evaluated in a large phase 3 trial in previously treated multiple myeloma that uses once-per-week bortezomib dosing and confers similar efficacy to that of other combination regimens used in the treatment of myeloma after at least one previous therapy. This regimen is also the simplest in terms of drug administration schedule (appendix p 9). Notably, bortezomib is most commonly administered once per week in clinical practice, and these results are therefore directly applicable to standard multiple myeloma therapies used outside of clinical trials. Furthermore, a 37% reduction in clinic visits facilitated by a once-per-week versus a twice-per-week dosing schedule would decrease the potential risks associated with such visits, especially in the setting of increased concern with regard to infections (eg, COVID-19).

The safety results in this study were consistent with the adverse event profile of selinexor, bortezomib, and dexamethasone in the phase 1/2 STOMP study,[17] as well as the known safety profile of selinexor and dexamethasone in multiple myeloma. No new risks were identified. Additionally, commonly reported grade 3–4 haematological adverse events were less frequent among patients in this study treated with selinexor, bortezomib, and dexamethasone following one to three previous lines of therapy (thrombocytopenia 39%; anaemia 16%; neutropenia 9%) than among more heavily pre-treated patients with advanced refractory disease who received selinexor and dexamethasone in the STORM study (thrombocytopenia 59%; anaemia 44%; neutropenia 22%; n=123).[15] A number of adverse events were reported more frequently in the selinexor, bortezomib, and dexamethasone group than in the bortezomib and dexamethasone group, including any-grade thrombocytopenia, anaemia, neutropenia, fatigue, nausea, diarrhoea, decreased appetite, weight loss, asthenia, cataract, and vomiting. In addition to the known side-effects of selinexor and dexamethasone, the triplet therapy might have contributed to the higher frequency and severity of adverse events; however, treatment discontinuations and deaths due to adverse events were similar between the two groups. Moreover, serious adverse events occurred at rates similar to those reported for other triplet bortezomib-containing regimens (appendix p 9). Finally, adverse events were generally self-limiting, reversible, and manageable with dose modifications and supportive care, as previously described for selinexor.[24]

BOSTON is the first phase 3 trial of a triplet bortezomib and dexamethasone regimen versus standard bortezomib and dexamethasone in which peripheral neuropathy was less frequent in patients receiving the triplet regimen than in those receiving bortezomib and dexamethasone only (appendix p 9). Peripheral neuropathy is the most important dose-limiting toxicity associated with bortezomib treatment, reported to occur in 35–55% of patients treated with doublet or triplet drug regimens, and was the most common adverse event that led to treatment discontinuation and dose reduction in BOSTON in both treatment groups.[25] Moreover, neuropathy, which is related to bortezomib-induced disturbances of calcium homoeostasis and inhibition of neuronal proteases, can persist for months or even the remainder of the patient's life and has a significant negative effect on activities of daily living, quality of life, and ability to receive subsequent therapies.[26,27] Cumulative treatment dose is the most significant predictor of bortezomib-induced peripheral neuropathy.[28] The substantial reduction in peripheral neuropathy with selinexor, bortezomib, and dexamethasone could be attributable to the once-per-week dosing of bortezomib in the selinexor, bortezomib, and dexamethasone regimen versus twice per week in the bortezomib and dexamethasone regimen. Additionally, based on the neuroprotective effects exerted by other XPO1 inhibitors, it might be that selinexor also reduces neurotoxicity.[29,30] Taken together, lower frequency and severity of peripheral neuropathy represent a crucial benefit to patients receiving selinexor, bortezomib, and dexamethasone, especially those with diabetes.

Although the combination of high doses of the second-generation proteasome inhibitor carfilzomib with dexamethasone is superior to standard bortezomib and dexamethasone, use of carfilzomib and dexamethasone warrants careful cardiovascular evaluation and management given the prominence of baseline cardiac dysfunction in patients with multiple myeloma.[31] The BOSTON study permitted treatment of patients with cardiac and other major organ dysfunction because selinexor is not generally associated with major organ toxicities. In addition, selinexor, bortezomib, and dexamethasone has a simpler dosing and clinic visit schedule than that of intravenous carfilzomib and dexamethasone or triplet bortezomib and dexamethasone combinations with antibody infusions or daily oral therapy. This simplicity is of particular importance in the context of real-world considerations, where new treatment strategies translate from the setting of well controlled studies to community practice.[32] The results in patients with high-risk cytogenetic abnormalities, particularly those with del(17p)—ie, deletion of the region encoding the tumour suppressor protein cellular tumour antigen p53—strongly support the early use of selinexor, bortezomib,

and dexamethasone in patients with high-risk chromosomal abnormalities. Selinexor, bortezomib, and dexamethasone also showed good efficacy in patients older than 65 years and frail patients, supporting its use outside of clinical trials where patients typically have higher numbers of comorbidities and associated concurrent medications. Finally, the selinexor, bortezomib, and dexamethasone regimen could have strong utility in the secondline setting—particularly following daratumumab, lenalidomide, and dexamethasone—because selinexor, bortezomib, and dexamethasone includes two novel mechanisms for the treatment of relapsed multiple myeloma that avoids repeated use of immunomodulatory agents or anti-CD38 monoclonal antibodies.

A limitation of this study is the open-label design, which was considered to be suitable given the different requirements for once-per-week versus twice-per-week subcutaneous bortezomib in the two groups of the study. Although physicians and patients were aware of their study treatments, to avoid bias, efficacy assessments were based solely on laboratory test results and were evaluated by an independent review committee that was masked to the treatment groups. In addition, few patients had received previous therapy with daratumumab (or other anti-CD38 antibodies) because of the timing of accrual into the study. The current US Food and Drug Administration approval of selinexor plus low-dose dexamethasone is for patients with penta-refractory multiple myeloma, which includes disease refractory to daratumumab, both lenalidomide and pomalidomide, bortezomib, and carfilzomib. Moreover, responses to the selinexor, carfilzomib, and dexamethasone regimen were not affected by previous therapy with daratumumab.[33] Therefore, it seems unlikely that previous daratumumab would significantly impair responses to the selinexor, bortezomib, and dexamethasone regimen.

In conclusion, selinexor, bortezomib, and dexamethasone is a potent and convenient treatment option for patients with previously treated multiple myeloma.

Contributors

SG, MS, IS, LP, IK, MGav, HP, HWA, XL, VD, GU, NJB, RH, RB, TKD, DKS, CPV, MGar, MGi, AJ, PR, MGal, CW-B, AR, GS, DAS, SB, AML, HQ, VSG-M, JB, EK, HO, SK, JK, SJ, PM, ML, DW, MEG, TF, MVM, MC, DR, LDA, MAD, PGR, and SD collected the data. SS, MGK, and NJB contributed to the study design. YC and LL analysed the data. All authors interpreted the data. AAJ drafted the manuscript. All authors edited and reviewed manuscript drafts, and approved the final version.

Declaration of interests

IS reports personal fees from Janssen-Cilag, Takeda, Sanofi Aventis, and Novartis; personal fees and non-financial support from Colgene, BMS, and Amgen. IK reports a consulting role, an advisory role, and a speaker's bureau role for Takeda, Janssen, Roche, AbbVie, and MSD; and travel support by Takeda, MSD, Roche, AbbVie, and Janssen. MGav reports receiving honoraria from Amgen, Karyopharm Therapeutics, Takeda, Genesis Pharma, and Janssen-Cilag. HWA reports an advisory role for Takeda and Karyopharm; a grant from Amgen; and a speaker's bureau role for Janssen. NJB reports grants and personal fees from Celgene; and personal fees from Janssen, Amgen, Takeda, AbbVie, GlaxoSmithKline, and Karyopharm. MGar reports support for attending conferences from Takeda; an advisory role for Amgen, Takeda, Jansen, Novartis, and Celgene; and a speaker's bureau role for Janssen. PR is a clinical trials investigator for Karyopharm. MGal reports honoraria from Bristol-Myers-Squibb, Celgene, Janssen, and Takeda. AR reports personal fees from Amgen, Takeda, Bayer, Janssen, Servier, AbbVie, Karyopharm, and Roche. AML reports personal fees from Incyte; sponsored research from Novartis, Janssen, AbbVie, Roche, Celgene, Amgen, BMS, Takeda, Incyte, Pfizer, Beigene, Oncopeptides, Verastem, Karyopharm, Archigen, Biopharma, Morphosys, Fibrogen, and Onconova; an advisory role for AbbVie, Amgen, and Takeda; and support for attending conferences from Janssen, Amgen, Bristol-Myers, Servier, Celgene, and Novartis. HQ reports grants from and an advisory board role for Amgen, Celgene, Karyopharm, GlaxoSmithKline; non-financial support and research drug supply from Sanofi; and an advisory board role for Janssen Cilag and Specialized Therapeutics. EK reports grants, personal fees, and non-financial support from Karyopharm. SJ reports consulting services for AbbVie, Bristol-Myers Squibb, Janssen Pharmaceuticals, and Merck. PM reports personal fees from Celgene, Amgen, Takeda, Janssen, and AbbVie. ML reports receiving consulting fees and lecture fees from Takeda, Celgene, Seattle Genetics, AbbVie, Jazz Pharmaceuticals, Gilead Sciences, Bristol-Myers Squibb, Amgen, Spectrum Pharmaceuticals, and Janssen. DW reports grants and personal fees from Amgen, Celgene, Janssen, Karyopharm, and Takeda; and personal fees from Antengene and Sanofi. TF reports an advisory board role for Karyopharm, Amgen, Roche, and Oncopeptides; and an advisory board role and a speaker's bureau role for Janssen, Celgene/BMS, and Takeda. DR reports an advisory board role for Karyopharm; a consultant role, an advisory board role, a speaker's bureau role, and an expert witness role for Celgene, Janssen, and Amgen; and a consultant role for Takeda. LA reports an advisory board role and a speaker's bureau role for Amgen and Celgene/BMS; an advisory board role for GlaxoSmithKline and Janssen; and a speaker's bureau role for Takeda. SS reports being employed by and owning stock in Karyopharm Therapeutics, holding patents (8999996, 9079865, 9714226, PCT/US12/048319, and I574957) on hydrazide-containing nuclear transport modulators and uses, and holding pending patents (PCT/US12/048319, 499/2012, PI20102724, and 2012000928) on hydrazide-containing nuclear transport modulators and uses. J-RS-M, JJ, YC, LL, VP, MA, JS, and MGK are employees of and stockholders of Karyopharm. AJ is a consultant to Karyopharm. PGR reports receiving grant support and honoraria from Oncopeptides, Celgene, and Takeda, grant support from Bristol-Myers Squibb, and honoraria from Amgen, Janssen, and Karyopharm Therapeutics. All other authors declare no competing interests.

Data sharing

Karyopharm Therapeutics agrees to share the individual participant data that underlie the results reported in this Article (after de-identification), including the study protocol. To gain access, data requestors should submit a request to medicalinformation@karyopharm.com.

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