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

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Summary

Background Selinexor with dexamethasone has demonstrated activity in patients with heavily pretreated multiple myeloma (MM). In a phase 1b/2 study, the combination of oral selinexor with the proteasome inhibitor (PI) bortezomib, and dexamethasone (SVd) induced high response rates with low rates of peripheral neuropathy, the main dose-limiting toxicity of bortezomib. The aim of this trial was to evaluate the clinical benefit of weekly SVd versus standard bortezomib and dexamethasone (Vd) in patients with previously treated MM.

Methods This phase 3, randomised, open label trial was conducted at 123 sites in 21 countries. Patients who were previously treated with one to three lines of therapy, including PIs were randomised (1:1) to selinexor (100 mg once-weekly) plus bortezomib (1·3 mg/m^2 once-weekly) and dexamethasone (20 mg twice-weekly) [SVd] or bortezomib (1·3 mg/m^2 twice-weekly) and dexamethasone (20 mg 4 times per week) [Vd]. Randomisation was done using interactive response technology and stratified by previous PI therapy, lines of treatment, and MM stage. The primary endpoint was progression-free survival (PFS) 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.

Findings Between June 2017 and February 2019, 402 patients were randomised: 195 to SVd and 207 to Vd. Median PFS was 13·93 (95% CI 11·73–NE) with SVd versus 9·46 months (8·11–10·78) with Vd; HR 0·70, [95% CI 0·53–0·93]; P=0.0075. Most frequent grade ≥3 adverse events (SVd *vs* Vd) were thrombocytopenia (77 [40%] *vs* 35 [17%]), fatigue (26 [13%] *vs* 2 [1%]), anaemia (31 [16%] *vs* 20 [10%]), and pneumonia (22 [11%] *vs* 22 [11%]). Peripheral neuropathy rates (overall, 32·3% *vs* 47·1%; OR 0·52, [95% CI 0·35-0·79]; P=0.0010 and grade

≥2, 21·0% *vs* 34·3%; OR 0·50, [95% CI 0·32-0·79]; P=0.0013) were lower with SVd. There were 47 (24%) deaths on SVd and 62 (30%) on Vd.

Interpretation Once-weekly SVd is a novel, effective, and convenient treatment option for patients with MM who have received 1-3 prior therapies**.**

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Research in context

Evidence before this study

We searched PubMed for articles published until February 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 demonstrated improved response rates and progression free survival 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 prolonged 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 (SVd) demonstrated promising antimyeloma activity with an overall response rate of 84% and median progression free survival of 17.8 months (estimated based on 25% of events) in patients with multiple myeloma not refractory to proteasome inhibitors. The triplet combination was well tolerated with low (10%) rates of peripheral neuropathy. These promising results led to the initiation of this phase 3 study to evaluate once-weekly SVd compared with the standard twice-weekly combination of bortezomib and dexamethasone (Vd) in patients who have received one to three prior lines of anti-myeloma therapies.

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 a higher rate of overall and deep responses compared with the doublet therapy. Efficacy was consistent across patient subgroups including those who are older and/or are frail, those with 1 versus 2-3 prior therapies and in patients who received prior 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 cytogenetics. 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

This study demonstrates that the combination of selinexor, bortezomib, and dexamethasone is a novel and effective triplet therapy while utilizing 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 approximately 37% as compared with standard Vd and commonly used Vd containing triplet regimens. Finally, the lower rates and severity of peripheral neuropathy may significantly improve patient quality of life.

Introduction

Although the number of treatment options has increased over the past 20 years, multiple myeloma (MM) 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 (PI), with low dose dexamethasone (Vd) is standard therapy for patients with MM.[3] However, the twice-weekly dosing regimen is associated with high rates of sensory, motor and autonomic neuropathy which can be irreversible and often limit prolonged use.[4-6]

Exportin 1 (XPO1) is overexpressed in most cancer cells including MM and its levels are correlated with poor patient prognosis, resistance and aggressive disease.[7-8] XPO1 is an oncoprotein,[9] mediating the nuclear export and functional inactivation of the majority of tumour suppressor proteins and enhancing the translation of certain oncoproteins including Myc, Bcl-6, and cyclin D1.[10] In addition, overexpression of XPO1 is associated with the development of resistance to PIs including bortezomib[11] and immunomodulatory agents (IMiDs).[12]

Selinexor is a potent, oral, selective inhibitor of nuclear export that binds to Cys528 in the cargo-binding pocket of XPO1,[13] forcing the nuclear localisation and functional activation of tumour suppressor proteins, trapping IκBα in the nucleus to suppress nuclear factor κB activity, and preventing oncoprotein mRNA translation.[8,14] Selinexor (80 mg twice weekly) in combination with dexamethasone (sel-dex) has been approved in the United States for the treatment of patients who have received at least four prior therapies and whose disease is refractory to at least two PIs, at least two IMiDs, and an anti-CD38 monoclonal antibody based on the phase 2b STORM study wherein, sel-dex demonstrated a response rate of 26·2% and median progression-

free survival (PFS) of 3·7 months in patients with myeloma refractory to currently available therapies.[15]

The combination of nuclear export inhibition with PIs showed synergistic activity in preclinical models.[16] Based on this, a phase 1b/2 study of the combination of oral selinexor with subcutaneous bortezomib and dexamethasone (SVd) in patients with MM and at least one prior therapy was conducted. Amongst 19 patients with PI non-refractory MM, SVd induced an overall response rate (ORR) of 84% and PFS of 17.8 months.[17] Based on the encouraging anti-MM activity and low rates of adverse events (AEs) observed with once weekly bortezomib regimen in combination with selinexor and dexamethasone, we conducted the BOSTON (Bortezomib, Selinexor, and Dexamethasone in Patients with Multiple Myeloma) trial to further evaluate the safety and efficacy of the triplet combination in comparison with Vd (standard twice-weekly) in patients with MM who had received one to three prior therapies.

Methods

Study design and participants

The BOSTON trial was a phase 3, randomised, controlled, open-label global trial. Patients were enrolled between June 2017 and February 2019 at 123 sites in 21 countries across Europe, North America and the Asia Pacific regions. The trial was performed 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. Patients aged ≥18 years with measurable myeloma according to the International Myeloma Working Group (IMWG) criteria[18] and previous treatment with at least one, but no more than three, prior anti-MM regimens were eligible. The study required patients who had received prior PI (alone or in combination), to have had at least a partial response and ≥6 months since last PI therapy, an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2, with adequate hepatic, renal, and haematopoietic function. Systemic light chain amyloidosis, central nervous system involvement, grade 2 painful or grade >2 peripheral neuropathy were exclusionary (appendix p 3-4). All patients provided written informed consent.

Randomisation and masking

Eligible patients were randomly assigned in a 1:1 ratio and by permuted block randomisation to either SVd or Vd. Randomisation was done using interactive response technology and stratified by treatment with prior PI therapies (yes *vs* no), number of previous lines of treatment (1 *vs* >1), and International Staging System stage (III *vs* I or II). There was no masking to treatment assignments.

Procedures

Based on the recommended phase 2 dose in the STOMP study[1], patients randomized to SVd received selinexor as a fixed oral 100 mg dose on days 1, 8, 15, 22, and 29 of each 5-week cycle; bortezomib was administered on the weekly schedule as a subcutaneous (SC) dose of 1·3 mg/m^2 on days 1, 8, 15, and 22 of each 5-week cycle; 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. In the Vd group, bortezomib was administered according to the approved regimen of 1·3 mg/m^2 SC on days 1, 4, 8, and 11; dexamethasone was given as an oral 20 mg dose on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 3-week cycle for the first 8 cycles. For cycles ≥9, bortezomib was administered on a weekly schedule at a dose of 1·3 mg/m^2 SC 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 minimize nausea, all patients received 5-hydroxytryptamine (8 mg or equivalent) before the first dose of study drug and 2-3 times daily on days 1 and 2, as needed. Additional supportive measures were provided at the discretion of the investigator and may have included use of olanzapine, megestrol acetate, intravenous fluids, methylphenidate, thrombopoietin stimulating agents, and/or transfusions. Treatment was administered until disease progression, discontinuation or unacceptable toxic effects. Dose reductions and treatment interruptions were permitted for the management of AEs. If PD was confirmed by the independent review committee, patients in the Vd group could cross over to SVd treatment, if able to tolerate continued bortezomib treatment.

Outcomes

The primary endpoint PFS was defined as time from randomisation until the first PD (determined by the independent review committee) per IMWG response criteria, or due to death from any

cause. Secondary endpoints included ORR, defined as any response ≥PR, overall survival (OS), duration of response, PFS and ORR in patients who crossed over from the Vd group to SVd treatment, PFS on the subsequent line of therapy, time to next anti-MM treatment, time to response, incidence of any grade ≥2 peripheral neuropathy events, and patient reported peripheral neuropathy as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy (EORTC QLQ-CIPN20). Definitions of efficacy endpoints are provided in the appendix p 2. Safety and tolerability were assessed by physical examination, laboratory assessments, ECOG performance status score, 12-lead electrocardiogram, and ophthalmic examination. AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs, version 4.03.

Statistical analysis

The sample size was designed to have 80% power to detect a median time to PFS for patients treated with SVd of 13·5 months versus patients treated with Vd of 9·4 months,[19,20] using a one-sided alpha of 0·025, 15 months accrual and 18 months follow-up, and a 1:1 allocation of treatment to SVd:Vd, and allowing for an interim analysis of PFS 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. PFS was compared between the SVd and Vd groups with the use of a stratified log-rank test. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were estimated with the use of a stratified Cox proportional-hazards model with treatment as the single covariate. A stratified Cochran–Mantel–Haenszel chi-square test was used to test differences in ORR between the two groups. One-sided p-values are presented for efficacy

endpoints. This trial is registered at ClinicalTrials.gov, number NCT03110562.

Role of funding source

The funder of the trial had a role 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

Between June 2017 and February 2019, 402 patients were randomly assigned to treatment: 195 and 207 to SVd and Vd groups, respectively (figure 1). Three patients from the Vd group were not included in the safety population. Baseline demographic, disease and clinical characteristics were balanced across the two treatment groups (table 1). The median age was 67 years (IQR 59-73) and 81 (20%) patients were ≥75 years. The median time since the initial diagnosis of myeloma was 3·7 years (IQR 2·3-5·5). High-risk cytogenetics were present in 192 (48%) patients. Median number of prior regimens was two (IQR 1-2). A total of 75 (19%) patients had received three previous lines and 139 (35%) patients received stem-cell transplant. Previous therapies included lenalidomide in 154 (38%) patients, PIs in 307 (76%) patients, including bortezomib in 279 (69%) patients. At data cut-off, 37 (19%) patients in the SVd group and 36 (17%) in the Vd group were still receiving treatment. The primary reason for treatment discontinuation was disease progression in 67 (34%) patients in the SVd group and 107 (52%) in the Vd group.

At the median follow-up of 13.2 months for SVd and 16.5 months for Vd, the median PFS was significantly longer in the SVd group compared with the Vd group (13·93 months [95% CI 11·73–not evaluable] *vs* 9·46 months [95% CI 8·11–10·78]; HR 0·70, 95% CI 0·53–0·93; p=0·0075; figure 2). The risk of progression or death was significantly lower with SVd versus Vd in a number of subgroups (figure 3). Progression-free survival after first subsequent therapy is summarized in the appendix (p 6).

Treatment with SVd was associated with a significantly higher ORR (76·4% [95% CI 69·8–82·2] *vs* 62·3% [55·3–68·9]; odds ratio (OR) 1·96 [1·3–3·1]; p=0·0012) (table 2). The rates of

≥VGPR (≥90% reduction in MM markers) were 44·6% [95% CI 37·5–51·9] with SVd versus 32·4% [26·0–39·2] with Vd (OR 1·66, 95% CI [1·1–2·5]; p=0·0082). Importantly, fewer patients on SVd had stable disease (SD) or PD as their best response as compared with Vd (13·3% [95% CI 8·9–18·9] *vs* 24·2% [18·5–30·6]). Consistent with the overall population, ORR was significantly higher with SVd compared with Vd across key subgroups including patients ≥65 years (76·1% [95% CI 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 cytogenetics (77·3% [95% CI 67·7–85·2] *vs* 55·8% [45·2–66·0]; OR 2·70, [1·4–5·0]; p=0·0008), those with creatinine clearance between 30–60 mL/min (79·2% [95% CI 65·9–89·2] *vs* 56·7% [43·2–69·4]; OR 2·92, [1·3–6·7]; p=0·0055), patients with one prior line of therapy (80·8% [95% CI 71·7–88·0] *vs* 65·7% [55·4–74·9]; OR 2·20, [1·2–4·2]; p=0·0082), with prior bortezomib treatment (77·6% [95% CI 69·9–84·4] *vs* 59·3% [50·8–67·4]; OR 2·38, [1·4–4·0]; p=0·0005) and prior lenalidomide treatment (67·5% [95% CI 55·9–77·8] *vs* 53·2% [41·5–64·7]; OR 1·83, [0·9–3·5]; p=0·035). Outcomes in patients who crossed over from the Vd group to SVd treatment are summarized in the appendix (p 7). Median time to first response in patients with a PR or better was 1·1 months with SVd versus 1·4 months with Vd. Median duration of response was longer with SVd (20·3 months [95% CI 12·5–not evaluable] *vs* 12.9 months [9·3–15·8]; HR 0·81[0·56-1·17]; p=0.1364). There was an increase in the time to the next anti-MM treatment on SVd compared with Vd (16·1 months [95% CI 13·9–not evaluable] *vs* 10·8 months [9·8–13·4]; HR 0·66 [0·50–0·86]; p=0·0012).

As of the data cut, there were 47 (24%) deaths with SVd versus 62 (30%) deaths with Vd. At a median follow-up of 17.3 months in the SVd group and 17.5 months in the Vd group, the median OS was not reached with SVd and was 25 months [95% CI 23·5–not evaluable] with Vd; HR 0.84 [95% CI 0·57-1·23]; p=0.1852.

The most common (≥10% of patients in either group) grade 3/4 treatment-emergent AEs by treatment (SVd *vs* Vd respectively) were thrombocytopenia (77 [40%] *vs* 35 [17%]), anaemia (31 [16%] *vs* 20 [10%]), pneumonia (24 [12%] *vs* 21 [10%]) and fatigue (26 [13%] *vs* 2 [1%]) (table 3). Thrombocytopenia (grade ≥3) was uncommonly associated with clinically relevant bleeding: four patients (2%) in the SVd group and two patients (1%) in the Vd group experienced grade ≥3 bleeding events. The bleeding events included epistaxis in two patients and upper gastrointestinal haemorrhage and cerebral haemorrhage in the SVd group; and epistaxis and haematuria in the Vd group. Thrombopoietin receptor agonists were often used to mitigate thrombocytopenia (35 patients [18%] on SVd and two patients [1%] on Vd) and led to reduced dose interruptions and reductions. Twelve patients (6%) on SVd and 13 patients (6%) on Vd received platelet transfusions to manage thrombocytopenia. Neutropenic fever was rare, with one patient in each group. Among less common (≤10%) grade 3/4 AEs, the incidence of nausea (15 [8%]), diarrhoea (12 [6%]), decreased appetite (7 [4%]), asthenia (16 [8%]), cataract (17 [9%]), and vomiting (8 [4%]) was higher with SVd compared with Vd (table 3).

Rates of overall (32·3% *vs* 47·1%, OR 0·52, [95% CI 0·34–0·79]; p=0·0010) and grade ≥2 (21·0% *vs* 34·3%, OR 0·50, [95% CI 0·32–0·79]; p=0·0013) peripheral neuropathy were significantly lower with SVd compared to Vd; rates of grade 3/4 peripheral neuropathy also trended lower with SVd (4·6 % *vs* 8·8%). A lower mean change from baseline score was observed with SVd compared to Vd for the EORTC QLQ-CIPN 20 sensory scale (-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 on Vd received twice-weekly bortezomib compared to once-weekly bortezomib on SVd. Mean changes from baseline scores were similar in both groups for motor (-0·06 (SE 0·04) [95% CI -0·14-0·02]; p=0·1497) and autonomic scales 0·09

(SE 0· 06) [95% CI -0·02-0·20]; p=0·1228). Together, these findings are consistent with the significantly lower rates of sensory peripheral neuropathy observed with once-weekly SVd in this study and the mostly sensory nature of bortezomib-induced peripheral neuropathy.

Discontinuation of study treatment due to treatment-emergent AEs occurred in 41 (21%) patients on SVd and 32 (16%) patients on Vd. The most common reasons for discontinuation were peripheral neuropathy (9 [5%]), fatigue (7 [4%]), nausea (6 [3%]), vomiting (4 [2%]), decreased appetite (4 [2%]), and thrombocytopenia (4 [2%]) on SVd, and peripheral neuropathy (15 [7%]) on Vd. The median time to discontinuation of study treatment was 194 days (IQR 100-332) in the SVd group and 184 days (IQR 106-276) in the Vd group. Nineteen (46%) of 41 patients in the SVd group and 16 (50%) of the 32 patients in the Vd group who discontinued treatment due to AEs were >70 years.

Dose modifications (appendix p 5) were more common on SVd than on Vd (173 [89%] *vs* 156 [77%]). Most of the side effects associated with selinexor were reversible and could be mitigated with standard supportive care.[21]

Serious AEs (SAEs) were reported in 101 (52%) patients on SVd and 77 (38%) patients on Vd; pneumonia was the most frequent SAE, occurring at the same rate (12%) in both groups (appendix p 6). The majority of the other SAEs were comparable in type and frequency across both groups. Infections occurred in 135 patients (69%) on SVd versus 119 (58%) on Vd. The imbalance was due to a higher incidence of typically low grade upper respiratory tract infection, nasopharyngitis and urinary tract infections on SVd. Of note, the difference in rates of sepsis between SVd (4%) versus Vd (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 once patient monitoring

was increased in India. Outside of India, the rates of sepsis were comparable in both groups. Importantly, rates of pneumonia, were comparable in the two arms.

The incidence of treatment-emergent AEs including grade 3/4 AEs (78% vs 80%) and SAEs (56% vs 47%) was comparable between patients ≥65 years and <65 years respectively. Deaths due to AEs were similar in the two groups: 12 (6%) on SVd and 11 (5%) on Vd; with 67% and 91% events deemed to be unrelated to treatment, respectively. The most common treatment-emergent AEs leading to death were pneumonia (3 [2%]), sepsis (3 [2%]) on SVd and pneumonia (3 [2%]) on Vd.

Discussion

In this randomised phase 3 trial, the combination of selinexor, bortezomib, and dexamethasone (SVd) was associated with a significant benefit on PFS in patients with previously treated MM. There was an early and sustained benefit as demonstrated by the Kaplan Meier curves corelating with a 30% reduction in the risk of death or progression for patients in the SVd group compared with Vd. This benefit was sustained across subgroups including patients older than 65 years, those who are frail, patients with high risk cytogenetics, and those who received prior lenalidomide therapy. It is noteworthy that the improved efficacy was achieved while using 40% less bortezomib and 25% less dexamethasone during the first 24-weeks of treatment. Patients on SVd had significantly higher ORR and deep (≥VGPR) response than those on Vd. There was also a significant and clinically meaningful increase in the time to next anti-MM treatment of 5·3 months on SVd. There were numerically fewer deaths on SVd (47) than on Vd (62), 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, SVd is the first bortezomib-based triplet evaluated in a large phase 3 trial in previously treated MM that utilizes once weekly bortezomib dosing, confers similar efficacy as other regimens and is the simplest regimen in terms of drug administration schedule (appendix p7). This is important because weekly bortezomib is most commonly used in clinical practice, and these results are therefore directly applicable to standard MM therapies used outside of clinical trials. Furthermore, 37% fewer clinic visits reduce potential risks associated with such visits, particularly in the setting of increased concerns of infections (e.g.,SARS-CoV-2).

The safety results were consistent with the AE profile of SVd in the phase 1/2 STOMP study [17] as well as the known safety profile of sel-dex in MM; no new risks were identified. Additionally, fewer commonly reported grade 3/4 haematological AEs were observed with SVd in these patients with one to three prior therapies as compared with sel-dex in the much more heavily pre-treated patients with advanced refractory disease in the STORM study: thrombocytopenia: 40% versus 59%; anaemia: 16% versus 44%; neutropenia: 9% versus 22%.[15] A number of AEs were reported more frequently in the SVd group compared to Vd, 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 sel-dex, the triplet therapy might have contributed to the higher frequency and severity of AEs; however, treatment discontinuations and deaths due to AEs were comparable between the two groups. Moreover, serious AEs occurred at rates similar to those reported for other triplet bortezomib-containing regimens (appendix p9). Finally, AEs were generally self-limiting, reversible, and manageable with dose modifications and supportive care as previously described for selinexor.[21]

BOSTON is the first phase 3 trial of a triplet-Vd regimen versus standard Vd where the rate of peripheral neuropathy is lower on the triplet regimen versus Vd (appendix p9). Peripheral neuropathy is the most important dose-limiting toxicity associated with bortezomib treatment, with rates of 35–55% reported in doublet and triplet drug regimens and is the most common AE leading to treatment discontinuation and dose reduction in BOSTON in both the SVd and Vd groups.[22] Moreover, neuropathy, which is related to bortezomib-induced disturbances of calcium homeostasis and inhibition of neuronal proteases, can persist for months or even the remainder of the patient's life and has significant negative impact on activities of daily living, quality of life and ability to receive subsequent therapies.[23,24] Cumulative treatment dose is the most significant

predictor of bortezomib-induced peripheral neuropathy.[25] The significant reduction in peripheral neuropathy with SVd can be attributable to once-weekly dosing of bortezomib in SVd vs twice-weekly in Vd. Additionally, based on the neuroprotective effects exerted by other XPO1 inhibitors, it may be that selinexor also reduces neurotoxicity.[26,27] Taken together, lower rates and severity of peripheral neuropathy represent a crucial patient benefit of the SVd treatment regimen especially in patients with diabetes mellitus.

While the combination of high doses of the second-generation PI, carfilzomib, and dexamethasone (Kd) is superior to standard Vd, use of Kd warrants careful cardiovascular evaluation and management given the prominence of baseline cardiac dysfunction in patients with MM.[28] The BOSTON study permitted treatment of patients with cardiac and other major organ dysfunction, as selinexor is not generally associated with major organ toxicities. In addition, SVd has a simpler dose and clinic visit schedule than intravenous Kd or triplet-Vd combinations with antibody infusions or daily oral therapy. This 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.[29] The results in patients with high risk cytogenetics, particularly those with del17p (i.e., the p53 tumour suppressor protein), strongly support the early use of SVd in patients with high risk chromosomal abnormalities. SVd also showed good efficacy in patients >65 years and frail patients, supporting its use outside of clinical trials where patients typically have higher number of comorbidities and associated concurrent medications. Finally, the SVd regimen may have strong utility in the second line setting, particularly following daratumumab, lenalidomide dexamethasone, as SVd includes two novel mechanisms for the treatment of relapsed MM that avoids repeated use of IMiDs or anti-CD38 monoclonal antibodies.

A limitation of this study is the open-label design. However, to avoid bias, efficacy assessments were based on laboratory test results and were evaluated by an independent review committee that was masked to the treatment groups. In addition, relatively few patients had received prior therapy with daratumumab (or other CD38 antibody) due to the timing of accrual into the study. The current US Food and Drug Administration approval of selinexor plus low dose dexamethasone is for patients that have penta-refractory MM, which includes disease refractory to daratumumab, both lenalidomide and pomalidomide, as well as bortezomib and carfilzomib. Moreover, responses to the selinexor, carfilzomib and dexamethasone regimen were not affected by prior therapy with daratumumab.[30] Therefore, it seems unlikely that prior daratumumab would significantly impair responses to the SVd regimen.

In conclusion, SVd is a potent and convenient treatment option for patients with previously treated MM.

Contributors

SG, MS, IS, LP, IK, MG (Maria Gavriatopoulou), HP, HWA, XL, VD, GU, NJB, RH, RB, TKD, DKS, CPV, MG (Mamta Garg), MG (Mercedes Gironella), AJ, PR, MG (Monica Galli), CWB, AR, GS, DAS, SB, AML, HQ, VGM, JB, EK, HO, SK, JK, SJ, PM, ML, DW, MEG, TF, MVM, MC, DR, LDA, MAD, PGR, SD collected the data. SS, MGK and NJB contributed to the study design. YC and LL analyzed 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; Travel support by Takeda, MSD, Roche, Abbvie and Janssen. MG reports (Maria Gavriatopoulou) receiving honoraria from Amgen, Karyopharm Therapeutics, Takeda, Genesis Pharma, and Janssen-Cilag; HA reports an advisory role for Takeda and Karyopharm; grant from Amgen; and a speaker's bureau role for Janssen. NB reports grants and personal fees from Celgene; personal fees from Janssen, Amgen, Takeda, Abbvie, GSK and Karyopharm. MG (Mamta Garg) 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. MG (Monica Galli) reports honoraria from Bristol-Myers-Squibb, Celgene, Janssen and Takeda. AR reports personal fees from Amgen, Takeda, Bayer, Janssen, Servier, Abbvie, Karyopharm and Roche. AL reports personal fees from Incyte; sponsored research from Novartis, Janssen, Abbvie, Roche, Celgene, Amgen, BMS, Takeda, Incyte, Pfizer, Beigene,

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Data sharing

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

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

Characteristic	SVd (n=195)	Vd (n=207)	Total (n=402)
Age (years), median (range)	66·0 (40, 87)	67.0 (38, 90)	67·0 (38, 90)
Distribution, n (%)			
18–50	15 (8)	11 (5)	26 (6)
51–64	71 (36)	64 (31)	135 (34)
65–74	75 (38)	85 (41)	160 (40)
≥75	34 (17)	47 (23)	81 (20)
Male sex, n (%)	115 (59)	115 (56)	230 (57)
ECOG performance-status, n (%)*			
0	69 (35)	77 (37)	146 (36)
1	106 (54)	114 (55)	220 (55)
2	20 (10)	16 (8)	36 (9)
Cytogenetic abnormalities, n (%)†			
del (17p)	21 (11)	16 (8)	37 (9)
t (14;16)	7 (4)	11 (5)	18 (4)
t (4;14)	22 (11)	28 (13)	50 (12)
amp 1q21††	80 (41)	71 (34)	151 (38)
del (17p) or t (14;16) or t (4;14) or 1q21	97 (50)	95 (46)	192 (48)
Unknown	15 (8)	24 (12)	39 (10)
R-ISS disease stage at screening, n (%)			
I or II	173 (89)	177 (85)	350 (87)
III	12 (6)	16 (8)	28 (7)
Unknown	10 (5)	14 (7)	24 (6)

Median time since initial diagnosis, range (year)	3·8 (0·4, 23·0)	3.6 (0·4, 22·0)	3.7 (0·4, 23·0)
Number of prior lines of therapy, n (%)			
1	99 (51)	99 (48)	198 (49)
2	65 (33)	64 (31)	129 (32)
3	31 (16)	44 (21)	75 (19)
Previous stem cell transplantation, n (%)	76 (39)	63 (30)	139 (35)
Previous therapy, n (%)			
Bortezomib	134 (69)	145 (70)	279 (69)
Carfilzomib	20 (10)	21 (10)	41 (10)
Ixazomib	6 (3)	3 (1)	9 (2)
Daratumumab	11 (6)	6 (3)	17 (4)
Lenalidomide	77 (39)	77 (37)	154 (38)
Pomalidomide	11 (6)	7 (3)	18 (4)

*Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores reflecting greater disability. †Fluorescence in-situ hybridisation were performed at central laboratories and used to assess cytogenetic risk status. ††amp 1q21 required ≥3

Table 2: Efficacy

Response category	SVd (n=195)	Vd (n=207)	p-value
Overall response rate			
Number with response	149	129	
Rate, % (95% CI)	76·4 (69·8, 82.2)	62·3 (55·3, 68·9)	0·0012*
Best overall response, n (%)			
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)	
Response could not be evaluated	4 (2)	8 (4)	
Negative status for minimal residual disease†	9 (5)	8 (4)	

*Calculated with the use of the Cochran–Mantel–Haenszel Test. †Minimal residual disease was assessed in patients with stringent complete response or complete response. Negative status for minimal residual disease was defined as absence of malignant clones per 100,000 white blood cells.

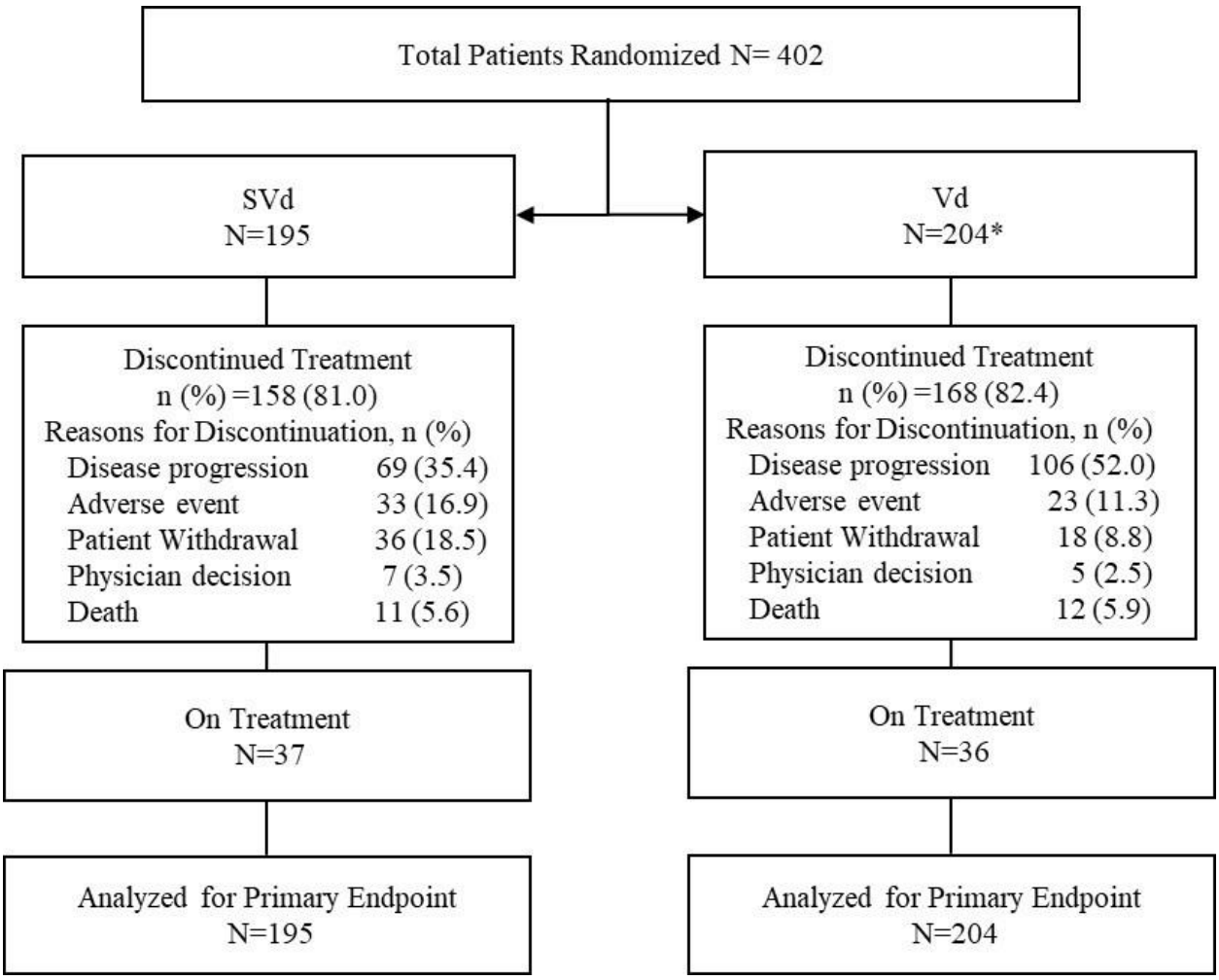
Table 3: Most common treatment emergent adverse Events* in the safety population

Event	SVd (n=195) n (%)		Vd (n=204) n (%)		Total (n=399) n (%)
	Any grade	grade 3 or 4	Any grade	grade 3 or 4	Any grade
Hematological adverse events					
Thrombocytopenia	117 (60)	77 (39)	55 (27)	35 (17)	172 (43)
Anaemia	71 (36)	31 (16)	47 (23)	20 (10)	118 (30)
Neutropenia	29 (15)	17 (9)	12 (6)	7 (3)	41 (10)
Non-haematological adverse events					
Fatigue	82 (42)	26 (13)	37 (18)	2 (1)	119 (30)
Nausea	98 (50)	15 (8)	20 (10)	0	118 (30)
Diarrhoea	63 (32)	12 (6)	51 (25)	1 (1)	114 (29)
Peripheral neuropathy†	63 (32)	9 (5)	96 (47)	18 (9)	159 (40)
Decreased appetite	69 (35)	7 (4)	11 (5)	0	80 (20)
Weight decreased	51 (26)	4 (2)	25 (12)	2 (1)	76 (19)
Asthenia	48 (25)	16 (8)	27 (13)	9 (4)	75 (19)
Constipation	33 (17)	0	35 (17)	3 (1)	68 (17)
Cough	35 (18)	1 (1)	30 (15)	0	65 (16)
Insomnia	31 (16)	2 (1)	32 (16)	4 (2)	63 (16)
Back pain	30 (15)	1 (1)	29 (14)	2 (1)	59 (15)
Pneumonia††	35 (18)	24 (12)	34 (17)	21 (10)	69 (17)
Pyrexia	30 (15)	3 (1)	22 (11)	2 (1)	52 (13)
Cataract	42 (21)	17 (9)	13 (6)	3 (1)	55 (14)
Vomiting	40 (20)	8 (4)	9 (4)	0	49 (12)

Oedema peripheral	23 (12)	1 (1)	26 (13)	0	49 (12)
Dyspnoea	18 (9)	1 (1)	27 (13)	5 (2)	45 (11)
Bronchitis	24 (12)	3 (1)	20 (10)	1 (1)	44 (11)
Upper respiratory tract infection	35 (18)	5 (3)	30 (15)	1 (1)	65 (16)

Note: *Shown are events that occurred in at least 10% of the patients. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. †Includes high-level term Peripheral Neuropathies NEC. ††Includes pneumonia, lung infection, haemophilus infection, pneumonia respiratory syncytial viral, pneumonia pneumococcal, pneumonia influenza, pneumonia parainfluenzae viral, pulmonary sepsis, pneumonia bacterial, and pneumonia fungal.

Figure 1: Patient Disposition



*Three patients in the Vd group withdrew consent prior to the first dose of study drug.

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

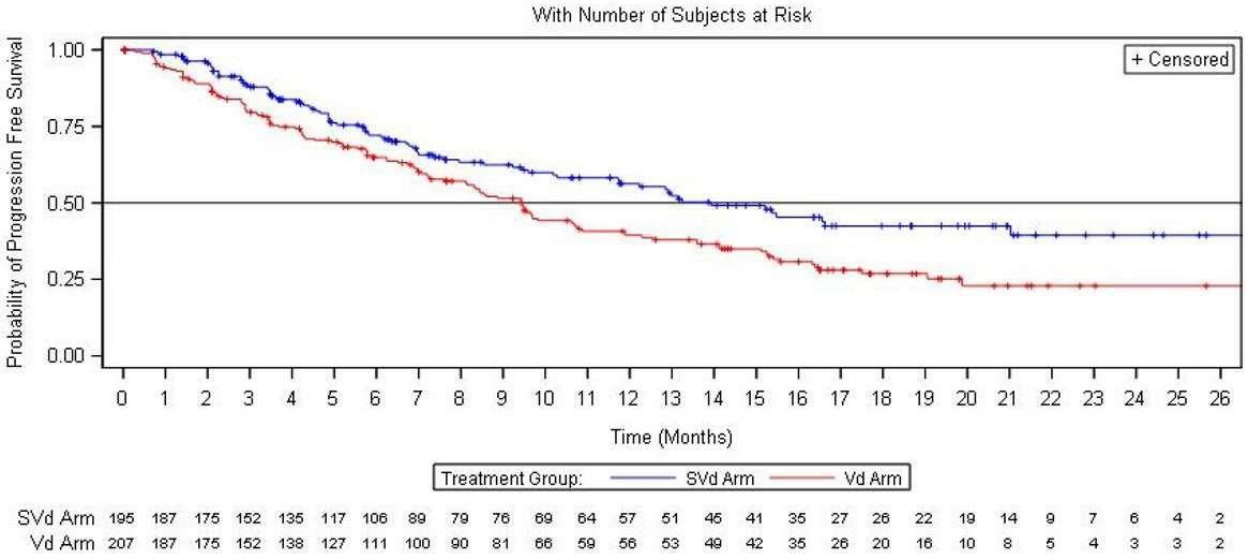


Figure 3: Analysis of progression-free survival in subgroups of the intention-to treat population defined according to baseline characteristics