LETTER TO THE EDITOR

Effect of prior treatments on selinexor, bortezomib, and dexamethasone in previously treated multiple myeloma

Maria V. Mateos1*, Maria Gavriatopoulou2, Thierry Facon3, Holger W. Auner4, Xavier Leleu5, Roman Hájek6, Meletios A. Dimopoulos7, Sosana Delimpasi8, Maryana Simonova9, Ivan Špička10, Luděk Pour11, Iryna Kriachok12, Halyna Pylypenko13, Vadim Doronin14, Ganna Usenko15, Reuben Benjamin16, Tuphan K. Dolai17, Dinesh K. Sinha18, Christopher P. Venner19, Mamta Garg20, Don A. Stevens21, Hang Quach22, Sundar Jagannath23, Philippe Moreau24, Moshe Levy25, Ashraf Z. Badros26, Larry D. Anderson Jr.27, Nizar J. Bahlis28, Michele Cavo29, Yi Chai30, Jacqueline Jeha30, Melina Arazy30, Jatin Shah30, Sharon Shacham30, Michael G. Kauffman30, Paul G. Richardson31† and Sebastian Grosicki32†

Abstract

Therapeutic regimens for previously treated multiple myeloma (MM) may not provide prolonged disease control and are often complicated by significant adverse events, including peripheral neuropathy. In patients with previously treated MM in the Phase 3 BOSTON study, once weekly selinexor, once weekly bortezomib, and 40 mg dexamethasone (XVd) demonstrated a significantly longer median progression-free survival (PFS), higher response rates, deeper responses, a trend to improved survival, and reduced incidence and severity of bortezomib-induced peripheral neuropathy when compared with standard twice weekly bortezomib and 80 mg dexamethasone (Vd). The pre-specified analyses described here evaluated the influence of the number of prior lines of therapy, prior treatment with lenalidomide, prior proteasome inhibitor (PI) therapy, prior immunomodulatory drug therapy, and prior autologous stem cell transplant (ASCT) on the efficacy and safety of XVd compared with Vd. In this 1:1 randomized study, enrolled patients were assigned to receive once weekly oral selinexor (100 mg) with once weekly subcutaneous bortezomib (1.3 mg/m²) and 40 mg per week dexamethasone (XVd) versus standard twice weekly bortezomib and 80 mg per week dexamethasone (Vd). XVd significantly improved PFS, overall response rate, time-to-next-treatment, and showed reduced all grade and grade ≥2 peripheral neuropathy compared with Vd regardless of prior treatments, but the benefits of XVd over Vd were more pronounced in patients treated earlier in their disease course who had either received only one prior therapy, had never been treated with a PI, or had prior ASCT. Treatment with XVd improved outcomes as compared to Vd regardless of prior therapies as well as manageable and generally reversible adverse events. XVd was associated with clinical benefit and reduced peripheral neuropathy compared to standard Vd in previously treated MM. These results suggest that the once weekly XVd regimen may be optimally administered to patients earlier in their course of disease, as their first bortezomib-containing regimen, and in those relapsing after ASCT.

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*Correspondence: mvmateos@usal.es
1 Paul G. Richardson and Sebastian Grosicki are co-senior authors
2 Hospital Universitario de Salamanca, Salamanca, Spain
Full list of author information is available at the end of the article

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To the Editor,

Therapeutic options have significantly advanced for patients with multiple myeloma (MM) including combination therapies employing complementary mechanisms or targeting mechanisms distinct from previous regimens [1, 2]. Selinexor is a first-in-class, orally-available, selective inhibitor of nuclear export (SINE) compound that has shown definitive activity with low dose dexamethasone in patients with triple class refractory MM in the STORM study [3] and synergistic activity with bortezomib and dexamethasone (XVd) in patients with 1–3 prior therapies in the BOSTON study [4].

Here we analyzed pre-specified subpopulations from the BOSTON study to determine the impact of prior lines of therapy and identify those who might optimally benefit from the XVd regimen.

Baseline characteristics were well balanced between treatment arms across subgroups (Additional file 1: Table S1). Median progression-free survival (PFS) was longer on XVd versus Vd in patients with 1 prior line ($P = 0.0148$) or 2–3 prior lines ($P = 0.0295$), lenalidomide-naïve ($P = 0.0150$) or lenalidomide-treated ($P = 0.0177$) patients, and PI-naïve patients ($P = 0.0003$), with a strong trend in PI-treated patients. Patients with IMiD-refractory MM had a significantly longer median PFS ($P = 0.0051$), as did patients with or without prior ASCT ($P = 0.0074$ and $P = 0.0341$). A post-hoc analysis showed a trend towards longer PFS with XVd in patients who received limited bortezomib induction prior to ASCT treatment (Table 1).

Treatment with XVd was associated with a significantly higher overall response rate including patients with 1 prior line, 2–3 prior lines, lenalidomide-naïve or treated, PI-naïve or treated, and prior ASCT (Fig. 1). Subgroups with 1 prior therapy, lenalidomide-naïve, and prior PI treatment had significantly higher rates of $\geq$ VGPR (Additional file 1: Table S2). Median time-to-next-treatment was significantly improved with XVd versus Vd: 1 prior line, 2–3 prior lines, lenalidomide-naïve or treated, PI-naïve or treated, and prior ASCT. Across the entire study, overall survival (OS) trended in favor of XVd over Vd (HR, 0.84 [95% CI 0.57–1.23]; $P = 0.19$). The median OS for lenalidomide-naïve and PI-naïve patients was not reached, but favored XVd over Vd (HR, 0.76 [95% CI 0.45–1.29] $P = 0.16$ and HR 0.63 [95% CI 0.25–1.61], $P = 0.16$, respectively) (Additional file 1: Table S3).

Overall grade $\geq 3$ adverse events (AEs) occurred more frequently with XVd and were generally well managed. Importantly, grade $\geq 2$ peripheral neuropathy occurred significantly less frequently across all XVd subgroups. The incidence of serious AEs and drug discontinuation due to AEs trended higher with XVd (Additional file 1: Table S4). There was no clear trend regarding AEs leading to a fatal outcome, although the slight excess number of deaths with XVd in the PI-treated subgroup were

| Patients (n, XVd vs Vd) | Median PFS, months (95% CI) | HR (95% CI) | P value |
|------------------------|-----------------------------|-------------|---------|
|                        | XVd | Vd            |                   |
| 1 prior line (99 vs 99) | 16.62 (13.24, NR) | 10.68 (7.26, 16.39) | 0.6295 (0.4133, 0.9586) | 0.0148 |
| 2–3 prior lines (96 vs 108) | 11.76 (7.39, NR) | 9.43 (6.83, 9.69) | 0.6949 (0.4760, 1.0147) | 0.0295 |
| Lenalidomide naïve (118 vs 130) | 16.62 (12.98, NR) | 10.61 (8.44, 15.41) | 0.6619 (0.4548, 0.9634) | 0.0150 |
| Lenalidomide treated (77 vs 77) | 9.59 (6.70, NR) | 7.23 (4.93, 9.69) | 0.6348 (0.4148, 0.9714) | 0.0177 |
| PI naïve (47 vs 48) | NR (NR, NR) | 9.69 (6.44, NR) | 0.2585 (0.1116, 0.5988) | 0.0003 |
| PI treated (148 vs 159) | 11.73 (7.95, 15.21) | 9.43 (7.06, 10.71) | 0.7839 (0.5791, 1.0612) | 0.0576 |
| IMiD refractory (74 vs 86) | 13.93 (6.70, NR) | 8.44 (5.78, 9.56) | 0.5752 (0.3753, 0.8816) | 0.0051 |
| Prior bortezomib only as induction for ASCT (37 vs 30) | 13.14 (11.73, NR) | 9.43 (5.75, NR) | 0.5807 (0.2860, 1.1791) | 0.0639 |
| ASCT (76 vs 63) | 16.56 (9.59, NR) | 9.43 (5.91, 10.87) | 0.5527 (0.3411, 0.8955) | 0.0074 |
| No ASCT (119 vs 144) | 13.24 (10.18, NR) | 9.56 (8.11, 13.60) | 0.7239 (0.5111, 1.0252) | 0.0341 |

ASCT autologous stem cell transplant, CI confidence interval, IMiD immunomodulatory drug, NR not reached, ORR overall response rate, PFS progression-free survival, PI proteasome inhibitor

Trial registration: ClinicalTrials.gov (NCT03110562). Registered 12 April 2017. https://clinicaltrials.gov/ct2/show/NCT03110562.

Keywords: Selinexor, Exportin-1, Multiple myeloma, SINE compound
restricted to India prior to the institution of increased monitoring, after which there were no additional deaths.

Our observations are particularly noteworthy as the once weekly XvD regimen utilizes ~40% less bortezomib and 25% less dexamethasone and requires ~37% fewer clinic visits for bortezomib injections than the standard Vd regimen. Despite the number of additional, subsequent therapies available to patients in this study, allowing patients on Vd with objective progressive disease to cross-over to a selinexor regimen, and the relatively short follow up, the results were accompanied by favorable trends on OS. Given its unique role in reactiving multiple tumor suppressor proteins and demonstrated synergy with PIs as well as other anti-MM drugs [5–9], these findings are consistent with the use of oral selinexor earlier in the MM treatment course. It is possible that some of the benefits of selinexor in those PI-treated patients may reflect the documented synergy between selinexor and PIs, even cells with marked PI refractoriness [5]. Moreover, benefits in duration and depth of response of XvD over Vd were most pronounced in patients who were PI-naïve, suggesting that selinexor could be an optimal partner for combining with weekly bortezomib as the first PI-containing MM regimen. Moreover, as daratumumab + lenalidomide/dexamethasone (DRd) is increasingly utilized in front-line MM treatment, the once weekly XvD regimen in second line could lead to a marked reduction in the development of prolonged or permanent bortezomib-associated neuropathy [10, 11]. Furthermore, the use of XvD following DRd allows for optimal mechanistic switching, thus preserving second generation agents (PIs, IMiDs and anti-CD38 mAbs) for subsequent lines of therapy where they may be more effective [1, 2, 12].

In conclusion, the earlier use of selinexor in treating MM may provide better, more durable outcomes with lower rates of peripheral neuropathy, using one of the simplest triplet regimens currently available for the treatment of patients with MM [4].

Abbreviations

ASCT: Autologous stem cell transplant; AE: Adverse event; CI: Confidence interval; DRd: Daratumumab plus lenalidomide/dexamethasone; HR: Hazard ratio; IMiDs: Immunomodulatory agents; MM: Multiple myeloma; NR: Not reached; ORR: Overall response rate; OS: Overall survival; PD: Progressive disease; PIs: Proteasome inhibitors; PFS: Progression-free survival; PN: Peripheral neuropathy; TTNT: Time-to-next-treatment; Vd: Bortezomib dexamethasone; VGPR: Very good partial response; XPO1: Exportin-1; XvD: Selinexor bortezomib dexamethasone.
Supplementary Information
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Additional file 1. Supplementary material.

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MVM, MG (Maria Gavriatopoulou), TF, HWA, XL, RH, MAD, SD, MS, IS, LP, IK, HP, GD, GU, RB, TKD, DKS, CV, MG (Mamta Garg), DAS, HQ, SJ, PM, ML, AZB, LDA, NJB, MC, YC, JJ, MA, JS, SS, MGK, PGR, SG collected the data. SS, MGK and NJB contributed to the study design. YC and JJ analyzed the data. All authors interpreted the data. All authors edited, and reviewed manuscript drafts, and approved the final version.

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Availability of data and materials
Karyopharm Therapeutics agrees to share individual participant data that underlie the results reported in this article (after deidentification), including the study protocol and statistical analysis plan. Data availability will begin 9 months after publication and will be available 36 months after publication. To gain access, data requestors should submit a proposal to medicalinformation@karyopharm.com. Proposals will be reviewed by an independent review committee identified for this purpose.

Declarations
Ethics approval and consent to participate
The study was approved and performed in accordance with the International Conference on Harmonization, the Guidelines for Good Clinical Practice, appropriate regulatory requirements, and with approval of institutional review boards at individual enrolling institutions. All patients provided written informed consent before study start.

Consent for publication
Not applicable.

Competing interests
M-VM has served as member of advisory boards or received honoraria from Janssen, BMS-Celgene, Takeda, Amgen, Sanofi, Oncopeptides, GSK, Adaptive, Pfizer, Regeneron, Roche and Sea-Gen. MG reports (Maria Gavriatopoulou) receiving honoraria from Amgen, Karyopharm Therapeutics, Takeda, Genesis Pharma, and Janssen-Cilag. TF reports an advisory board role for Karyopharm, Amgen, Roche and Oncopeptides; an advisory board role and a speaker bureau role for Janssen, Celgene/BMS, and Takeda. HWA reports an advisory role for Celgene, Karyopharm, Janssen-Cilag, Takeda, and Sanofi; and a speaker’s bureau role for Janssen. MGK reports grants and personal fees from Celgene; personal fees from Janssen, Amgen, Takeda, and AbbVie. MG (Mamta Garg) reports support for attending conferences from Takeda, an advisory role for Amgen, Takeda, Janssen, Novartis, and Celgene; and a speaker’s bureau role for Janssen.

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