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Impact of selinexor dose reductions on selinexor, bortezomib, dexamethasone (SVd) outcomes in patients (pts) with lenalidomide (LEN)-refractory multiple myeloma (MM): BOSTON trial subgroup analysis

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INTRODUCTION

- First-line treatment for patients with MM typically includes a combination of lenalidomide (LEN), dexamethasone, and daratumumab with or without bortezomib.[1]
- However, most patients relapse and develop LEN-refractory disease. Recommendations for relapsed/refractory MM (RRMM) include treatment with more than one drug and/or drug class switch to an agent that the patient has not had previous exposure.[2,3]
- Selinexor is a first-in-class, orally available XPO1 inhibitor with a unique mechanism of action that results in nuclear retention and functional activation of tumor suppressor proteins ultimately impacting cellular proliferation and tumor growth rates.
- Selinexor is approved by the EMA and US FDA in combination with bortezomib and dexamethasone (SVd) for adults with RRMM who have received at least one prior therapy, and in combination with dexamethasone (Sd) for adults with RRMM who have received at least four prior therapies and whose disease is refractory to at least two PIs, at least two IMiD agents, and an anti-CD38 monoclonal antibody.[4,5]
- In LEN-refractory patients, extended follow-up subgroup data from the phase 3 BOSTON trial showed a clinically meaningful improvement with SVd vs bortezomib and dexamethasone (Vd) in progression-free survival (PFS; 10.2 mo vs 7.1 mo), overall survival (OS; 26.7 mo vs 18.6 mo), and overall response rate (ORR; 68% vs 47%).[6]
- Moreover, results of a post hoc analysis of all patients in the BOSTON trial demonstrated that selinexor dose reductions (vs without dose reductions) were associated with longer progression-free survival (PFS; 16.6 mo vs 9.2 mo), duration of response (DOR; NR vs 12.0 mo), and time to next treatment (TTNT; 22.6 mo vs 10.5 mo).[7] In addition, this analysis showed that any-grade treatment-emergent adverse events (TEAEs) were lower and quality of life (QOL) was improved in the patients with selinexor dose reductions.
- The impact of selinexor dose reductions in LEN-refractory patients remains unknown.

OBJECTIVE

- In this subgroup analysis of the phase 3 BOSTON trial (NCT03110562), we analyzed LEN-refractory patients who received SVd to determine the clinical benefit of selinexor dose reductions on SVd efficacy.

METHODS

- In the BOSTON trial, patients randomized to the SVd arm (vs Vd) received the following during each five-week cycle: oral selinexor 100 mg (day [D] 1, 8, 15, 22, 29), bortezomib 1.3 mg/m^2 subcutaneously once weekly (D 1, 8, 15, 22), and oral dexamethasone 20 mg (D 1, 2, 8, 9, 15, 16, 22, 23, 29, 30).
- In this post-hoc subgroup analysis, efficacy (ORR, DOR, PFS, OS, TTNT), safety (TRAEs), and QOL (using the EORTC QLC-C30) were analyzed in LEN-refractory patients who received SVd with and without selinexor dose reductions.

RESULTS

Patients

- Fifty-three LEN-refractory patients were included in the SVd arm: 35 had selinexor dose reductions and 18 did not.
- Baseline characteristics and prior therapies are shown in **Table 1**.
- Patients with selinexor dose reductions had poorer performance status (PS) and more high-risk cytogenetic abnormalities.

Table 1. Baseline Characteristics and Prior Therapies

Characteristic	Patients With Selinexor Dose Reductions (n=35)	Patients Without Selinexor Dose Reductions (n=18)
Median age, years (range)	63 (44-87)	69 (40-77)
Sex, no. (%)		
Male	22 (63)	15 (83)
Female	13 (37)	3 (17)
IMWG frailty index score, no. (%)		
<2	26 (74)	13 (72)
≥2	9 (26)	5 (28)
ECOG PS, no. (%)		
0	11 (31)	12 (67)
1	21 (60)	5 (28)
2	3 (9)	1 (6)
High-risk cytogenetic abnormalities, no. (%)	21 (60)	8 (44)
R-ISS stage, no. (%)		
I	10 (29)	5 (28)
II	20 (57)	10 (56)
III	4 (11)	0
Not available	1 (3)	3 (17)
Median time since diagnosis, years (range)	3.5 (0.9-8.6)	4.0 (1.1-12.0)
Median prior lines of treatment, no. (range)	2 (1-3)	2 (1-3)
Prior line of treatments, no. (%)		
1	11 (31)	5 (28)
2	13 (37)	8 (44)
3	11 (31)	5 (28)
Prior SCT, no. (%)	13 (37)	10 (56)

RESULTS (continued)

Disposition and treatment

- **Table 2** summarizes patient disposition and treatment.
- Reasons for selinexor discontinuation were similar between groups.
- Patients who received dose reductions had a longer median duration of treatment (7.9 mo) than patients without dose reductions (2.5 mo).

Table 2. Disposition and Treatment

Parameter	Patients With Selinexor Dose Reductions (n=35)	Patients Without Selinexor Dose Reductions (n=18)
Primary reason for discontinuation		
Disease progression	16 (46)	8 (44)
Withdrawal by patient	8 (23)	5 (28)
Adverse events/toxicity to study drug	6 (17)	3 (17)
Death	2 (6)	1 (6)
Physician decision	1 (3)	1 (6)
Median selinexor dose/week, mg (range)	77.8 (44-98.6)	100 (70-108.2)
Median time to first dose reduction, days (range)	62 (15-808)	NA
Median duration of treatment, mo (range)	7.9 (0.5-33.2)	2.5 (0.1-10.9)
Median survival follow-up, mo (95% CI)	28.2 (23.4, 33.4)	27.2 (22.7, NE)

Selinexor dose reductions were associated with higher response rates, longer duration of response, longer duration of treatment, and extended time to next treatment

- ORR (74%) and very good partial response (VGPR) or better (49%) rates were higher in patients with dose reductions compared to patients without dose reductions (56% and 11%, respectively; **Figure 1**).
- Median DOR and median TTNT were longer for patients with dose reductions (**Table 3**).

Figure 1. Response to SVd in LEN-Refractory Patients by Dose Reduction Group

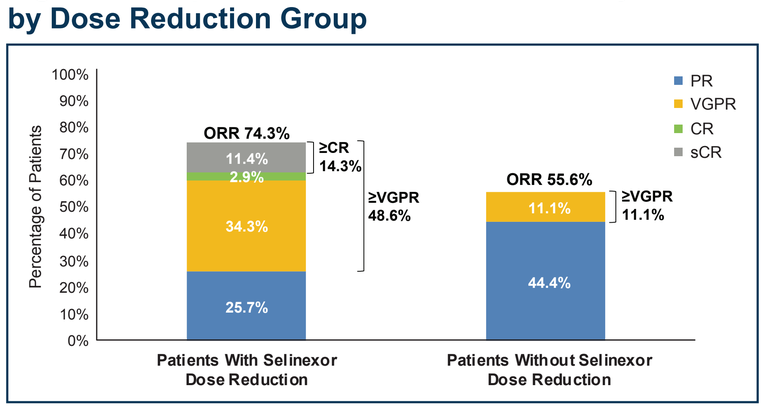


Table 3. Summary of Response Timing and Duration

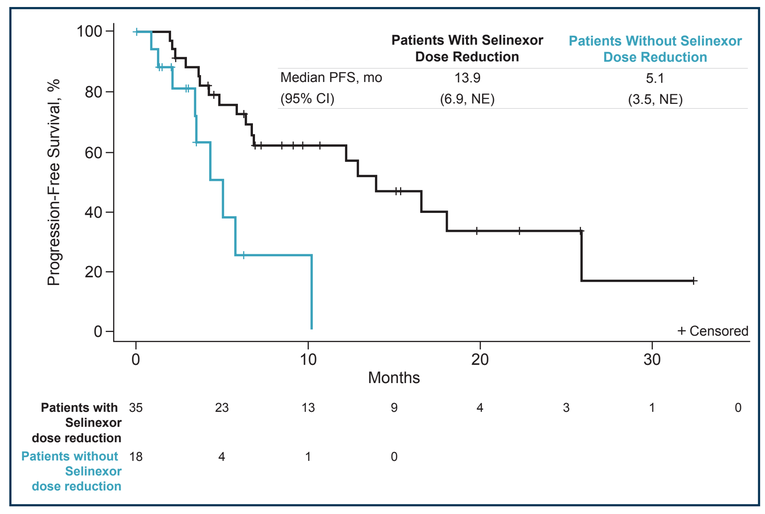
Parameter	Patients With Selinexor Dose Reductions (n=35)	Patients Without Selinexor Dose Reductions (n=18)
Median time to best response (PR or better), mo (range)	2.7 (0.7-11.7)	1.4 (0.7-2.1)
Median DOR, mo (95% CI)	15.3 (12.2, NE)	4.2 (4.2, NE)
Median TTNT*, mo (95% CI)	14.8 (13.4, 26.7)	4.8 (4.2, NE)

*TTNT was calculated as a time to event endpoint from date of randomization to the start of next anti-MM treatment or death, whichever occurred first.

Selinexor dose reductions correlated with longer progression free survival

- Median PFS was longer in patients with dose reductions (13.9 mo) compared to patients without dose reductions (5.1 mo; **Figure 2**).
- Median OS was slightly longer in patients with dose reductions (26.7 mo) compared to patients without dose reductions (24.6 mo) with a hazard ratio of 0.91 (95% CI 0.37,2.28).

Figure 2. PFS with SVd in LEN-Refractory Patients by Dose Reduction Group



Patients with selinexor dose reductions experienced greater improvements in quality of life compared to those without dose reductions

- Global health status QOL scores showed greater improvement in patients with dose reductions vs patients without (**Table 4**).

Table 4. EORTC QLC-C30 Global Health Status

Score Analysis	Patients With Selinexor Dose Reductions (n=35)	Patients Without Selinexor Dose Reductions (n=18)
Patients with non-missing baseline and at least one post-baseline score, no. (%)	32 (91)	16 (89)
Best change from baseline, mean ± SD (95% CI)	10.4 ± 23.2 (2.0, 18.8)	3.7 ± 26.9 (-10.7, 18.0)
Patients with at least one post-baseline score on or before first selinexor dose reduction and at least one post-baseline score after first dose reduction, no. (%)	24 (69)	NA
Change from last post-baseline score on or before first selinexor dose reduction to first post-baseline score after first dose reduction, mean ± SD (95% CI)	7.3 ± 20.5 (-1.4, 15.9)	NA
Change from last post-baseline score on or before first selinexor dose reduction to best post-baseline score after first selinexor dose, mean ± SD (95% CI)	18.1 ± 21.5 (9.0, 27.1)	NA
Best post-baseline score achieved after first selinexor dose reduction, mean ± SD (95% CI)	75.3 ± 16.7 (69.0, 81.5)	NA

Adverse events improved following the first dose reduction of selinexor

- The safety profile of SVd in patients with and without selinexor dose reductions remained consistent with the overall population in the BOSTON trial.
- In patients with selinexor dose reductions, a lower proportion of patients experienced any-grade treatment-related adverse events (TRAEs) after the first dose reduction, with the exception of thrombocytopenia, as shown in **Table 5**.

Table 5. Most Common All-Grade TRAEs Before and After Dose Reduction

All-Grade TRAEs, no. (%)	Pre-Selinexor Dose Reductions (n=35)	Post-Selinexor Dose Reductions (n=35)
Hematologic TRAEs in ≥10% of patients		
Thrombocytopenia	22 (63)	25 (71)
Anemia	8 (23)	6 (17)
Neutropenia	5 (14)	4 (11)
Nonhematologic TRAEs in ≥20% of patients		
Nausea	19 (54)	8 (23)
Fatigue	11 (31)	5 (14)
Diarrhea	10 (29)	7 (20)
Decreased appetite	8 (23)	4 (11)
Vomiting	8 (23)	6 (17)
Weight decreased	7 (20)	5 (14)

CONCLUSIONS

- In LEN-refractory patients, selinexor dose reductions were associated with improvements in safety, efficacy, and quality of life and were consistent with the analysis of selinexor dose reductions for the entire intent-to-treat population of the BOSTON trial. Specifically, selinexor dose reductions were associated with
  - higher response rates (ORR 74% vs 56%)
  - longer duration of response (15.3 vs 4.2 mo)
  - longer duration of treatment (7.9 vs 2.5 mo)
  - extended time to next treatment (14.8 vs 4.8 mo)
  - longer progression-free survival (13.9 vs 5.1 mo)
  - greater improvements in quality of life compared to those without dose reductions
  - a lower proportion of any-grade treatment-related adverse events after the first dose reduction including nausea (54% to 23%), diarrhea (29% to 20%), decreased appetite (23% to 11%), and vomiting (23% to 17%).
- These findings highlight the benefit of selinexor dose reductions in optimizing the treatment of LEN-refractory patients receiving SVd.

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ABBREVIATIONS: CI, confidence interval; CR, complete response; D, day; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; LEN, lenalidomide; MM, multiple myeloma; mo, months; NA, not applicable; NE, not estimable; no., number; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; PS, performance status; QOL, quality of life; R-ISS, Revised International Staging System; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; SCT, stem cell transplantation; SD, standard deviation; SVd, selinexor, bortezomib, dexamethasone; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TTNT, time to next treatment; US FDA, United States Food and Drug Administration; Vd, bortezomib, dexamethasone; VGPR, very good partial response.

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