Selinexor, Bortezomib, and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Updated Results of Boston Trial By Prior Therapies

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BACKGROUND

- While proteasome inhibitors (PI) formed the backbone of frontline treatment for multiple myeloma (MM) for many years, lenalidomide and daratumumab-based regimens are being administered following the approval of the combination of daratumumab, lenalidomide, and dexamethasone (DRd) in newly diagnosed MM.
- At early relapse, PI-based combinations are increasingly utilised.
- ESMO Guidelines endorse the use of a PI-based combination including selinexor, bortezomib, and dexamethasone (SVd) in MM pts with PI-naïve early relapse.[1]
- Selinexor is a first-in-class oral XPO1 inhibitor with a unique mechanism of action that results in nuclear retention and functional activation of tumour suppressor proteins ultimately impacting cellular proliferation and tumour growth rate.
- Selinexor in combination with bortezomib and dexamethasone (SVd) is indicated for relapsed and refractory MM (RRMM) in adults who have received at least one prior therapy.

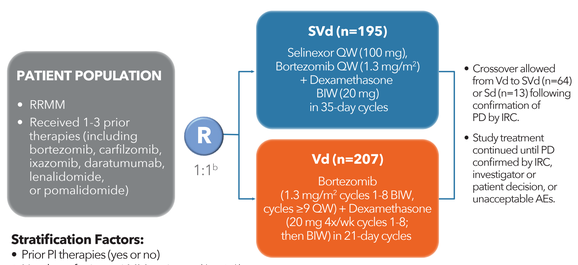
OBJECTIVE

- In this subgroup analysis of the phase 3 BOSTON trial (NCT03110562),[2] we analysed longer follow-up data to determine the impact of prior therapies, including PI, on SVd efficacy and safety.

METHODS

- SVd was compared with Vd in the Bortezomib, Selinexor, and Dexamethasone in Patients with Multiple Myeloma (BOSTON) pivotal, phase 3, open-label, global, randomized, controlled trial (**Figure 1**).
- This stratified analysis for PFS and response was performed in subgroups by prior PI therapy and number of prior regimens.
- Efficacy analyses were based on 15 Feb 2021 data cut and safety analyses on 15 Jun 2022 data extract.

Figure 1. BOSTON Study Design



AE, adverse event; BIW, twice weekly; IRC, independent review committee; ITT, intention to treat; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; QW, once weekly; R, randomized; RRMM, relapsed or refractory multiple myeloma;

REFERENCES

1. Dimopoulos MA, et al. *Ann Oncol.* 2021;32:309-322.
2. Grosicki S, et al. *Lancet.* 2020;396:1563-1573.

RESULTS

PATIENTS

- Baseline characteristics were generally balanced between the SVd and Vd groups (Table 1–3).

Table 1. Baseline Characteristics in 1 Prior Line of Treatment Group

	SVd (n=99)	Vd (n=99)
Median age (range)	67 (45-87)	69 (44-90)
Male patients, n (%)	55 (55.6%)	53 (53.5%)
Prior line of treatments, n (%)		
1	99 (100%)	99 (100%)
2		
3		
ECOG PS, n (%)		
0	39 (39.4%)	38 (38.4%)
1	52 (52.5%)	55 (55.6%)
2	8 (8.1%)	6 (6.1%)
R-ISS stage, n (%)		
I	33 (33.3%)	23 (23.2%)
II	52 (52.5%)	62 (62.6%)
III	9 (9.1%)	6 (6.1%)
Unknown	5 (5.1%)	8 (8.1%)
High-risk cytogenetic abnormalities*, n (%)	50 (50.5%)	48 (48.5%)
Prior SCT, n (%)	39 (39.4%)	23 (23.2%)
Creatinine clearance at baseline, n (%)		
< 30 mL/min	2 (2.0%)	4 (4.0%)
30-60 mL/min	27 (27.3%)	31 (31.3%)
> 60 mL/min	70 (70.7%)	64 (64.7%)
Median time since diagnosis (min-max), years	2.9 (0.41, 23.0)	2.8 (0.4, 18.4)

Table 2. Baseline Characteristics in PI-Naïve Group

	SVd (n=47)	Vd (n=48)
Median age (range)	68 (45-87)	67.5 (44-84)
Male patients, n (%)	26 (55.3%)	27 (56.2%)
Prior line of treatments, n (%)		
1	29 (61.7%)	25 (52.1%)
2	15 (31.9%)	14 (29.2%)
3	3 (6.4%)	9 (18.7%)
ECOG PS, n (%)		
0	15 (31.9%)	17 (35.4%)
1	26 (55.3%)	23 (47.9%)
2	6 (12.8%)	8 (16.7%)
R-ISS stage, n (%)		
I	15 (31.9%)	14 (29.2%)
II	30 (63.8%)	25 (52.1%)
III	1 (2.1%)	4 (8.3%)
Unknown	1 (2.1%)	5 (10.4%)
High-risk cytogenetic abnormalities*, n (%)	20 (42.5%)	19 (39.6%)
Prior SCT, n (%)	13 (27.7%)	10 (20.8%)
Creatinine clearance at baseline, n (%)		
< 30 mL/min	0 (0%)	3 (6.2%)
30-60 mL/min	15 (31.9%)	15 (31.3%)
> 60 mL/min	32 (68.1%)	30 (62.5%)
Median time since diagnosis (min-max), years	4.7 (0.4, 23.0)	3.4 (0.4, 17.8)

Table 3. Baseline Characteristics in Bortezomib-Naïve Group

	SVd (n=61)	Vd (n=62)
Median age (range)	68 (45-87)	68 (44-84)
Male patients, n (%)	36 (59.0%)	32 (51.6%)
Prior line of treatments, n (%)		
1	35 (57.4%)	34 (54.8%)
2	20 (32.8%)	18 (29.0%)
3	6 (9.8%)	10 (16.1%)
ECOG PS, n (%)		
0	19 (31.2%)	25 (40.3%)
1	34 (55.7%)	18 (29.0%)
2	8 (13.1%)	9 (14.5%)
R-ISS stage, n (%)		
I	17 (27.9%)	18 (29.0%)
II	41 (67.2%)	33 (53.2%)
III	1 (1.6%)	4 (6.5%)
Unknown	2 (3.3%)	7 (11.3%)
High-risk cytogenetic abnormalities*, n (%)	28 (45.90%)	26 (41.9%)
Prior SCT, n (%)	17 (27.9%)	14 (22.6%)
Creatinine clearance at baseline, n (%)		
< 30 mL/min	0 (0%)	4 (6.5%)
30-60 mL/min	18 (29.5%)	18 (29.0%)
> 60 mL/min	43 (70.5%)	40 (64.5%)
Median time since diagnosis (min-max), years	4.4 (0.4, 23.0)	4.2 (0.4, 17.8)

*High-risk cytogenetic abnormalities include any of the following: del(17p), t(4;14), t(14;16), amp 1q21.

EFFICACY

- SVd reduced the risk of disease progression or death in all subgroups (**Tables 4-6, Figures 2, 4, 6**).
- Time to next treatment (TTNT)* was prolonged with SVd vs Vd in all subgroups (**Tables 4-6**).
- Overall response rates and very good partial response or better rates were higher with SVd vs Vd in all subgroups (**Figures 3, 5, 7**).

*TTNT was calculated from the date of randomization to the start of next anti-MM treatment or death, whichever occurred first. Patients without an event were censored at the date of discontinuation from the study or last participating visit or database cut-off date, whichever occurred first.

EFFICACY in 1 Prior LOT Patients

Table 4. Outcomes in 1 Prior LOT Patients

	SVd (n=99)	Vd (n=99)
Median PFS, months (95% CI)	21.0 (13.2, NR)	10.7 (7.3, 16.4)
PFS HR (95% CI)	0.62 (0.41, 0.95)	
p-value	0.028	
Median TTNT, months (95% CI)	19.0 (15.3, 27.4)	12.9 (9.8, 16.2)
TTNT HR (95% CI)	0.70 (0.49, 1.01)	
p-value	0.056	
Overall response rate, %	80.8	66.7
OR (95% CI)	2.40 (1.22, 4.70)	
p-value	0.010	
VGPR or better, %	52.5	29.3
OR (95% CI)	2.65 (1.46, 4.78)	
p-value	0.001	

All p-values two sided

Figure 2. PFS in 1 Prior LOT Patients

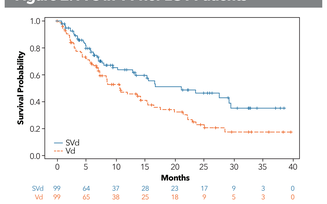
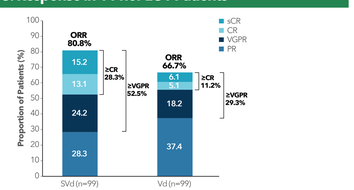


Figure 3. Response in 1 Prior LOT Patients



EFFICACY in PI-Naïve Patients

Table 5. Outcomes in PI-Naïve Patients

	SVd (n=47)	Vd (n=48)
Median PFS, months (95% CI)	29.5 (27.5, NR)	9.7 (8.4, 23.7)
PFS HR (95% CI)	0.29 (0.14-0.63)	
p-value	<0.001	
Median TTNT, months (95% CI)	30.2 (26.7, NR)	10.8 (10.1, 21.2)
TTNT HR (95% CI)	0.42 (0.23, 0.78)	
p-value	0.004	
Overall response rate, %	76.6	70.8
OR (95% CI)	1.30 (0.51, 3.33)	
p-value	0.581	
VGPR or better, %	53.2	41.7
OR (95% CI)	1.54 (0.68, 3.48)	
p-value	0.308	

All p-values two sided

Figure 4. PFS in PI-Naïve Patients

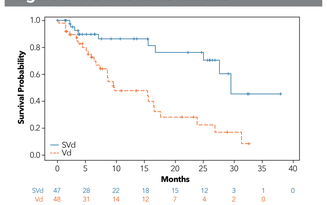
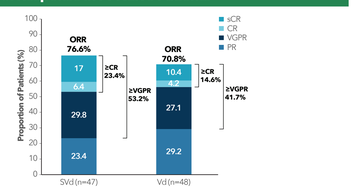


Figure 5. Response in PI-Naïve Patients



EFFICACY in Bortezomib-Naïve Patients

Table 6. Outcomes in Bortezomib-Naïve Patients

	SVd (n=61)	Vd (n=62)
Median PFS, months (95% CI)	29.5 (24.8, NR)	9.7 (8.4, 17.5)
PFS HR (95% CI)	0.35 (0.18, 0.68)	
p-value	0.002	
Median TTNT, months (95% CI)	29.8 (22.9, NR)	12.9 (10.4, 21.2)
TTNT HR (95% CI)	0.47 (0.28, 0.81)	
p-value	0.006	
Overall response rate, %	75.4	69.4
OR (95% CI)	1.57 (0.68, 3.64)	
p-value	0.295	
VGPR or better, %	49.2	41.9
OR (95% CI)	1.51 (0.73, 3.14)	
p-value	0.275	

All p-values two sided

HR=1 similar efficacy observed in SVd vs Vd; HR<1 higher efficacy observed in SVd vs Vd; HR>1 lower efficacy observed in SVd vs Vd. OR=1 similar efficacy observed in SVd vs Vd; OR<1 lower efficacy observed in SVd vs Vd; OR>1 higher efficacy observed in SVd vs Vd

Figure 6. PFS in Bortezomib-Naïve Patients

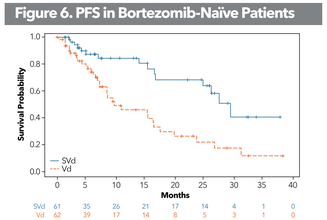
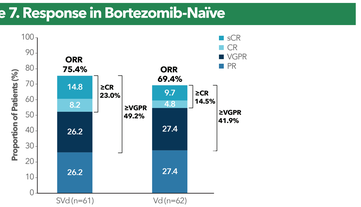


Figure 7. Response in Bortezomib-Naïve



CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; SVd, selinexor + bortezomib + dexamethasone; Vd, bortezomib + selinexor; VGPR, very good partial response.

SAFETY

- Safety findings were similar to those reported in the overall BOSTON population.
- Most common TEAEs (all grades) with SVd vs Vd in the three subgroups are summarized in **Figures 8-10**.

Figure 8. Most Common (≥25%) Treatment-Emergent Adverse Events (All Grades) in 1 Prior LOT Patients

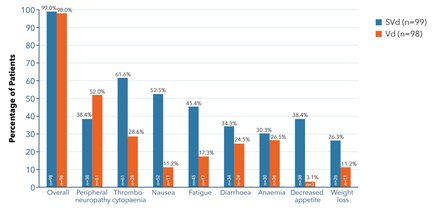


Figure 9. Most Common (≥25%) Treatment-Emergent Adverse Events (All Grades) in PI-Naïve Patients

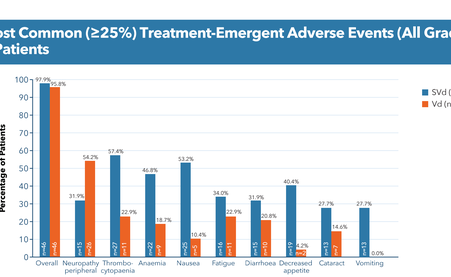
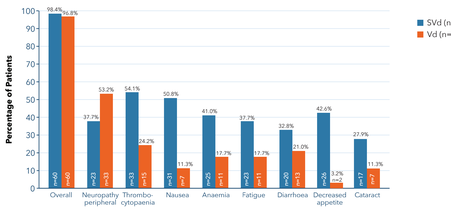


Figure 10. Most Common (≥25%) Treatment-Emergent Adverse Events (All Grades) in Bortezomib-Naïve Patients



CONCLUSIONS

- Findings of these stratified subgroup efficacy and safety analyses confirm the PFS benefit of SVd over Vd in patients without prior PI or bortezomib exposure as well as in patients who have received 1 prior line of therapy.
  - Statistically significant and clinically meaningful ~20-month median PFS improvement of SVd over Vd in RRMM patients that had no prior exposure to PI.
  - A similar PFS ~20-month median PFS improvement was observed in patients who were naïve to bortezomib.
  - A significant ~10-month PFS improvement with SVd vs Vd in patients who received one prior line of therapy.
- Overall response rates and very good partial response or better rates were higher with SVd vs Vd in all subgroups.
- Adverse events were generally manageable and aligned with the overall BOSTON population.
- These outcomes emphasize the combined effectiveness of selinexor plus bortezomib and the importance of a double mode of action switch.
- Findings show clinical utility of SVd in the following MM sub-populations:
  - PI-naïve RRMM
  - Bortezomib-naïve RRMM
  - First relapse