Once Weekly Selinexor, Bortezomib, and Dexamethasone (SVd) Versus Twice Weekly Bortezomib and Dexamethasone (Vd) in Relapsed or Refractory Multiple Myeloma: High-Risk Cytogenetic Risk Planned Subgroup Analyses from the Phase 3 BOSTON Study

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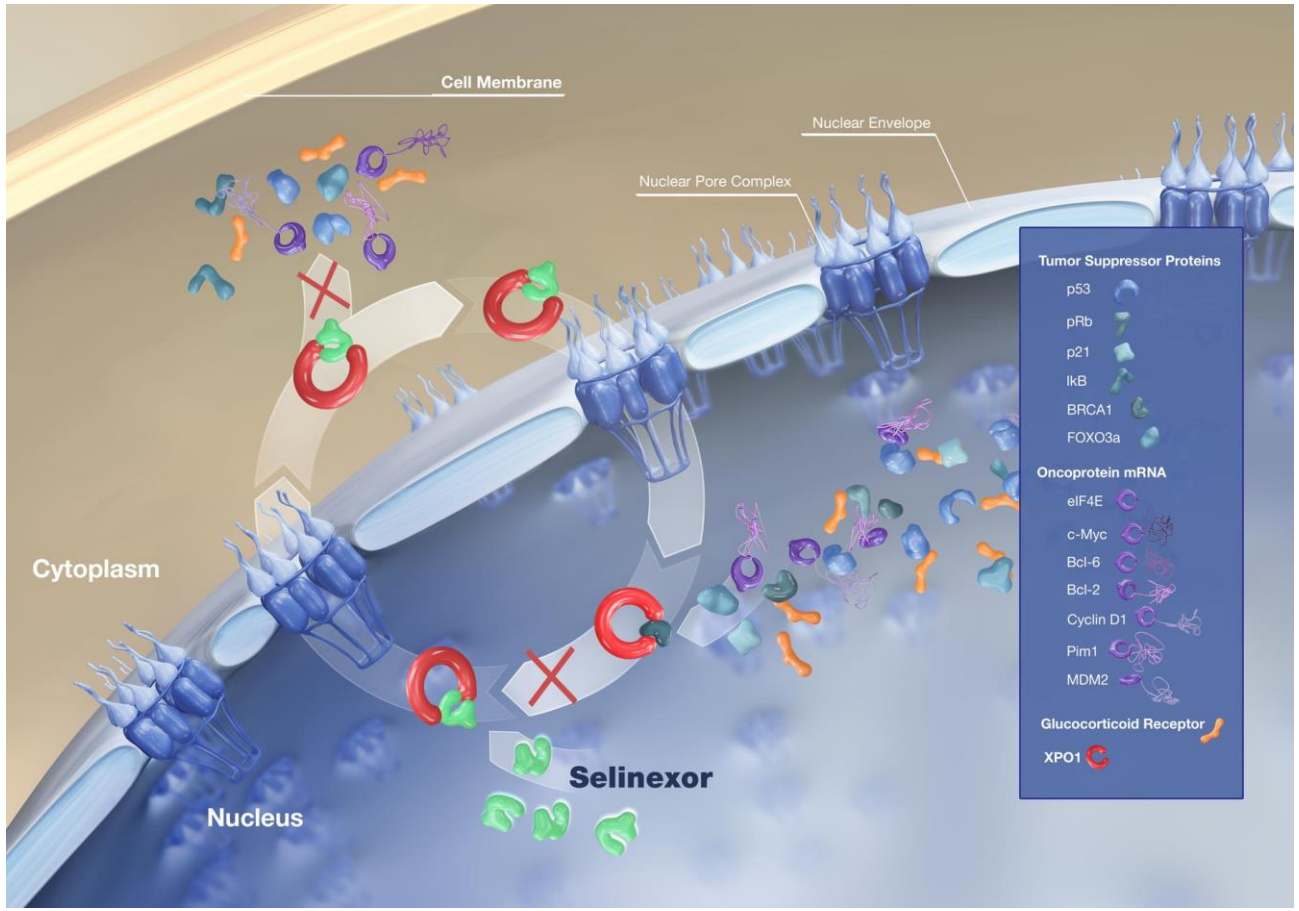
Conflict of Interest Disclosure

There are no relationships to disclose

Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export[1-8]

Demonstrates synergistic activity in combination with bortezomib *in vitro* and *in vivo*

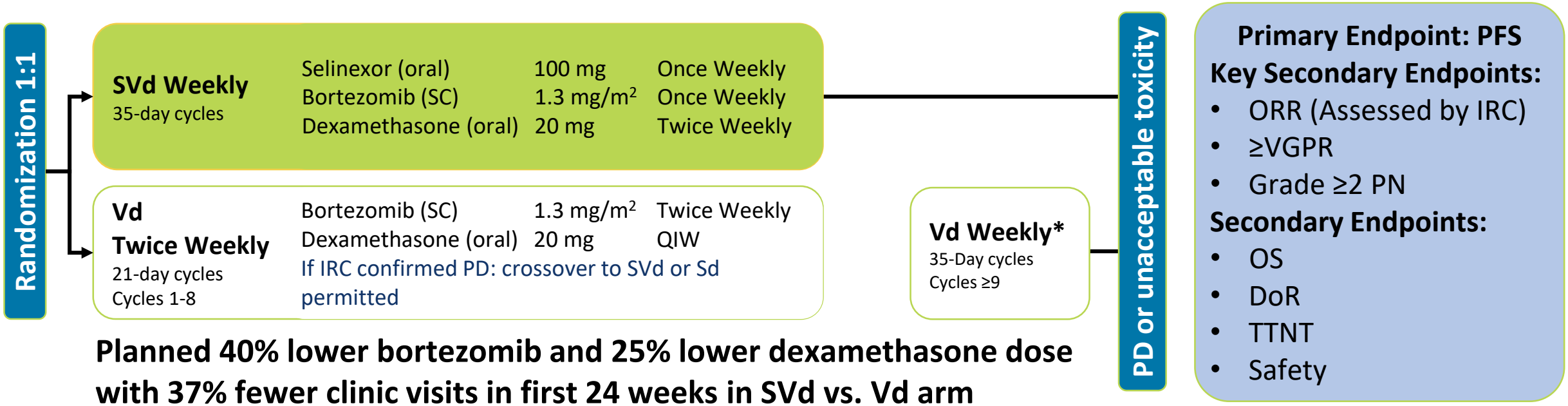


- **Exportin 1 (XPO1)** is overexpressed in MM and its levels correlate with poor prognosis and drug resistance
- **XPO1 Overexpression Causes:**
  - Tumor suppressor proteins (e.g., p53, IkB and FOXO) and glucocorticoid receptor inactivation and enhanced oncoprotein (e.g., c-Myc, Bcl-xL, cyclins) translation
- **Selinexor (S) is an oral selective XPO1 inhibitor that reactivates multiple TSPs and inhibits oncoprotein translation**
- **High Risk MM Cytogenetics:**
  - High-risk anomalies such as del(17p), t(4;14), and t(14;16) are associated with shorter PFS and overall survival relative to those with standard-risk cytogenetic features

1. Gupta A, et al. Therapeutic targeting of nuclear export inhibition in lung cancer. J Thorac Oncol. 2017;12(9):1446-1450. 2. Sun Q, et al. Inhibiting cancer cell hallmark features through nuclear export inhibition. Signal Transduct Target Ther. 2016;1:16010. 3. Gandhi UH, et al. Clinical implications of targeting XPO1-mediated nuclear export in multiple myeloma. Clin Lymphoma Myeloma Leuk. 2018;18(5):335-345. 4. Gravina GL, et al. Nucleo-cytoplasmic transport as a therapeutic target of cancer. J Hematol Oncol. 2014;7:85. 5. Fonseca, 2009; 6. Sonneveld, 2016 7. Avet-Loiseau, 2013; 8. Shah, 2018

BOSTON Study Trial Design

BOSTON Trial: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients with MM who had Received 1–3 Prior Therapies



Planned 40% lower bortezomib and 25% lower dexamethasone dose with 37% fewer clinic visits in first 24 weeks in SVd vs. Vd arm

Stratifications:

Prior PI therapies (Yes vs No); Number of prior anti-MM regimens (1 vs >1); R-ISS stage at study entry (Stage III vs Stage I/II)

5HT-3 prophylactic recommended in SVd arm

CR= complete response, DoR = duration of response, IMWG = International Myeloma Working Group, IRC = Independent Review Committee, OS = overall survival, PD = progressive disease, PFS = progression free survival, PR = partial response, PN = peripheral neuropathy, sCR = stringent complete response, TTNT = time to next therapy, VGPR = very good partial response. PFS defined as: Time from date of randomization until the first date of progressive disease, per IMWG response criteria, or death due to any cause, whichever occurred first, as assessed by IRC. ORR: Any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments. *Vd weekly dosing and schedule for cycles≥ 9 as per SVd arm description.

Overall Efficacy Results SVd vs. Vd

	SVd	Vd
PFS, median Hazard Ratio; (p value)	13.93 months 0.70 (*p=0.0075*)	9.46 months
ORR	76.6%	62.3%
≥VGPR	44.6%	32.4%
DOR	20.3 months	12.9 months

Methods

We performed post-hoc analyses of the BOSTON study to determine efficacy and safety among patients with high risk cytogenetics, defined as patients with at least 1 of the following abnormalities* in ≥10% of screened plasma cells: del 17p, t(4;14), t (14;16), or amplification of 1q21 (≥4 copies) vs standard risk patients

Total Patients Enrolled	SVd Arm (n=195)	Vd Arm (n=207)
High Cytogenetic Risk	SVd High Risk – 36% (n=70)	Vd High Risk – 34% (n=71)
Standard Risk	SVd Standard Risk – 64% (n=125)	Vd Standard Risk – 66% (n=136)

*Fluorescent in situ hybridization (FISH) was performed centrally on CD138+ cells, isolated from bone marrow aspirates collected at screening

Baseline and Disease Characteristics by Cytogenetic Risk Category

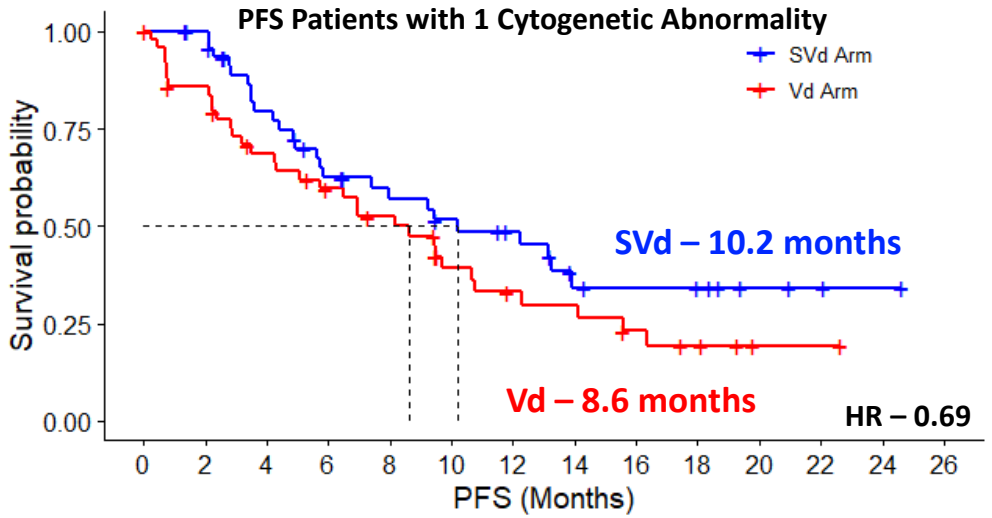
Categories	SVd – High Risk (n=70)	SVd – Standard Risk (n=125)	Vd – High Risk (n=71)	Vd – Standard Risk (n=136)
Median Age, Years (range)	**67** (45, 84)	**65** (40, 87)	**67** (49, 90)	**67** (38, 84)
Males, n (%)	**34** (48.6)	**81** (64.8)	**39** (54.9)	**76** (55.9)
Females, n (%)	**36** (51.4)	**44** (35.2)	**32** (45.1)	**60** (44.1)
Number of Prior Treatment Regimens, n (%) 1 2 3	 **35** (50.0) **22** (31.4) **13** (18.6)	 **64** (51.2) **43** (34.4) **18** (14.4)	 **32** (45.1) **20** (28.2) **19** (26.8)	 **67** (49.3) **44** (32.4) **25** (18.4)
Prior ASCT	**26** (37.1)	**50** (40.0)	**28** (39.4)	**35** (25.7)
Median Years Since Diagnosis to BOSTON Enrollment, (range)	**3.5** (1.1, 23.0)	**4.1** (0.4, 21.5)	**3.0** (0.6, 22.0)	**3.8** (0.4, 18.4)
High-Risk Chromosomal Abnormality Type, n (%) del(17p) / p53 t (14;16) t (4;14) amp 1q21 (≥4 copies) del(17p) ***or*** t(14;16) ***or*** t(4;14) ***or*** amp 1q21	 **21** (10.8) **7** (3.6) **22** (11.3) **43** (22.1) **70** (35.9)	 -- 	 **16** (7.7) **11** (5.3) **27** (13.0) **39** (18.8) **71** (34.3)	 --
Percentage of High Risk Patients Enrolled, n (%)	**70** (36%)		**71** (34%)	

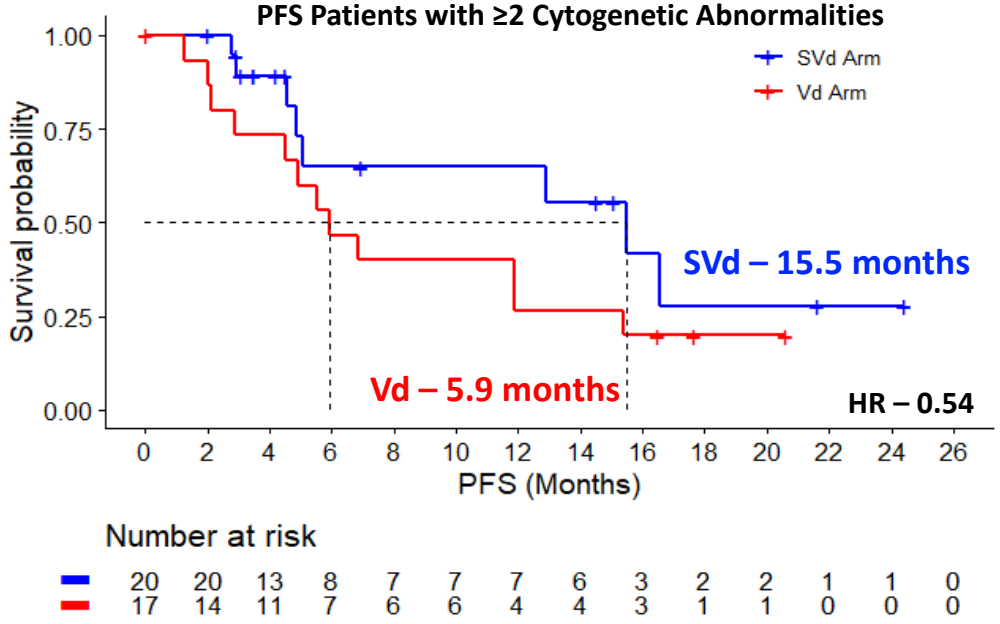
Related Adverse Events, All Grades, ≥10% Overall

AE Term	Cytogenetic Risk Categories			
	SVd – High (n=70)	SVd – Standard (n=125)	Vd – High (n=70)	Vd – Standard (n=134)
Thrombocytopenia	49 (70.0)	62 (49.6)	20 (28.6)	28 (20.9)
Neuropathy Peripheral	25 (35.7)	36 (28.8)	34 (48.6)	60 (44.8)
Nausea	34 (48.6)	59 (47.2)	2 (2.9)	10 (7.5)
Fatigue	27 (38.6)	42 (33.6)	6 (8.6)	13 (9.7)
Decreased appetite	19 (27.1)	44 (35.2)	1 (1.4)	7 (5.2)
Diarrhea	9 (12.9)	29 (23.2)	8 (11.4)	22 (16.4)
Anemia	13 (18.6)	31 (24.8)	6 (8.6)	12 (9.0)
Insomnia	14 (20.0)	15 (12.0)	10 (14.3)	17 (12.7)
Asthenia	15 (21.4)	23 (18.4)	--	11 (8.2)
Weight decreased	16 (22.9)	22 (17.6)	2 (2.9)	6 (4.5)
Constipation	5 (7.1)	13 (10.4)	11 (15.7)	13 (9.7)
Vomiting	10 (14.3)	24 (19.2)	--	5 (3.7)
Cataract	9 (12.9)	24 (19.2)	2 (2.9)	3 (2.2)
Neutropenia	14 (20.0)	12 (9.6)	4 (5.7)	2 (1.5)

- The safety profiles of SVd and Vd in the high-risk and standard-risk groups were consistent with the overall population. Rate of grade ≥2 peripheral neuropathy was lower with SVd compared with Vd in both the high-risk (25.7% vs 35.7%; p=0.100) and standard-risk groups (18.4% vs 33.6%; p=0.003).

SVd is Effective (PFS, ORR) in Patients with High or Standard Risk Cytogenetics





Abnormality Type	del(17p)		t(4;14)		t(14;16)	
Arm	SVd (n=21)	Vd (n=16)	SVd (n=22)	Vd (n=27)	SVd (n=7)	Vd (n=11)
PFS, months	12.22	5.91	13.24	8.33	4.57	11.89
HR, (p value)	0.38 (0.008)		0.70 (0.18)		1.46 (0.75)	
ORR%	76.2%	37.5%	90.9%	74.1%	85.7%	54.5%
(p value)	(0.0096)		(0.07)		(0.09)	

Abnormality Type	amp(1q21) ≥4 copies		All High Risk		Standard Risk	
Arm	SVd (n=43)	Vd (n=39)	SVd (n=70)	Vd (n=71)	SVd (n=125)	Vd (n=136)
PFS, months	12.91	8.15	12.91	8.61	16.62	9.46
HR, (p value)	0.63 (0.07)		0.73 (0.08)		0.61 (0.004)	
ORR%	76.7%	61.5%	78.6%	57.7%	75.2%	64.7%
(p value)	(0.07)		(0.004)		(0.03)	

- SVd significantly improved PFS relative to Vd in the high-risk (12.9 vs 8.6 months; HR, 0.73; 95% CI, 0.47-1.14; p=0.08) and standard-risk (16.6 vs 9.5 months; HR, 0.61; 95% CI, 0.42-0.88; p=0.004). Patients with 1 cytogenetic abnormality PFS (10.2 vs 8.6, HR 0.69, 95% CI (0.41–1.15); p=0.08). Patients with ≥2 cytogenetic abnormalities PFS (15.5 vs 5.9, HR 0.54, 95% CI (0.22-1.33) p=0.09)
- The ORR was significantly improved with SVd in the high-risk group (78.6% vs 57.7%; p=0.004) and in the standard-risk group (75.2% vs 64.7%; p=0.03). The ≥VGPR rate was 41.4% in patients on SVd versus 29.6% on Vd and 46.4% on SVd versus 33.8% on Vd in the high-risk and standard-risk groups, respectively.

Conclusions

- SVd is superior to Vd in patients with MM including high-risk disease:
  - Patients with high risk cytogenetics; PFS (12.9 vs 8.6, HR 0.73 p=0.08)
  - Patients with 1 cytogenetic abnormality; PFS (10.2 vs 8.6, HR 0.69, p=0.08)
  - Patients with ≥2 cytogenetic abnormalities; PFS (15.5 vs 5.9, HR 0.54, p=0.09)
  - Patients with del17p; PFS (12.2 vs 5.9, HR 0.38, p=0.009)
- Patients with high risk cytogenetics including del17p need new options with novel mechanism of action
- Selinexor's novel mechanism, reactivating TSP and reducing levels of oncoproteins may be particularly suited for high risk disease
- Non-PN AEs were higher with SVd and most of the AEs were reversible

Once weekly SVd is an effective and safe regimen and may be an important treatment option for patients with high risk MM