Impact of Prior Therapies on The Safety and Efficacy of Once-Weekly Selinexor, Bortezomib, and Dexamethasone Compared with Twice-Weekly Bortezomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Results from the BOSTON Study

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Conflict of Interest Disclosure

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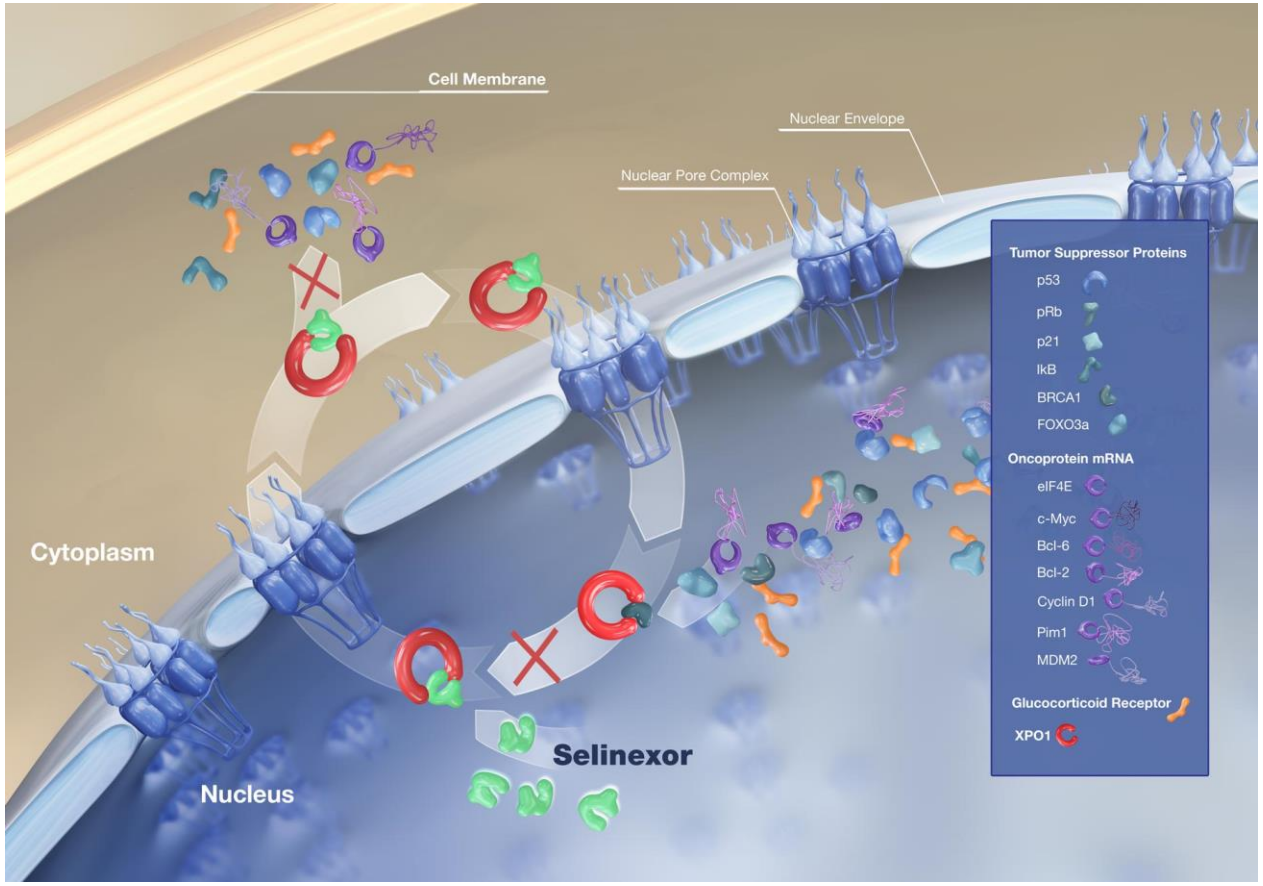
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export[1-7]

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

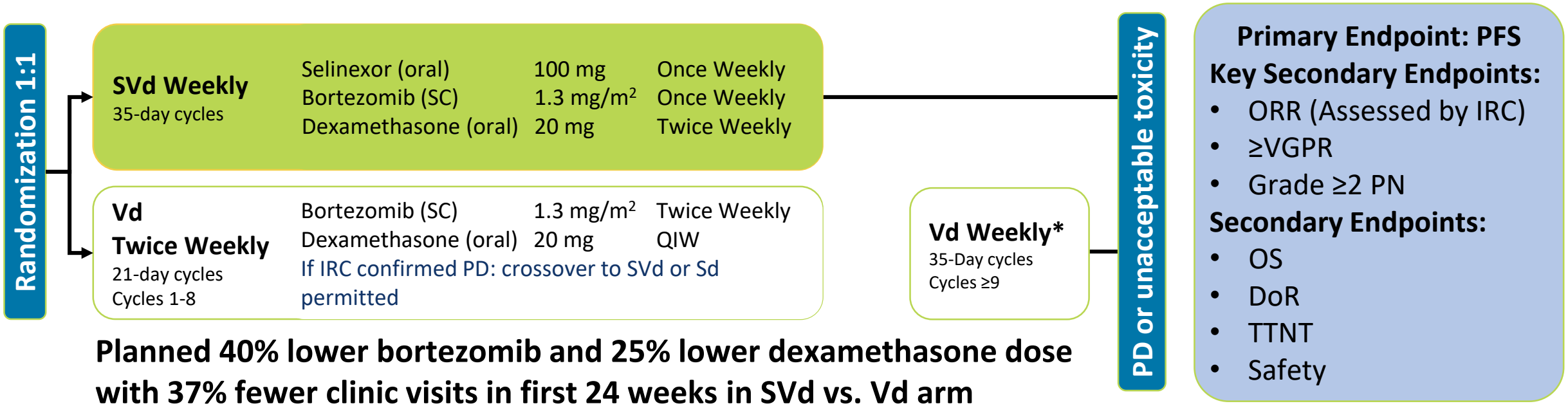


- **Exportin 1 (XPO1)** is overexpressed in MM and its levels correlate with poor prognosis and drug resistance
- **XPO1 Overexpression Causes:**
  - Tumor suppressor protein (e.g., p53, IκB and FOXO) and glucocorticoid receptor inactivation and enhanced oncoprotein (e.g., c-Myc, Bcl-xL, cyclins) translation
- **Selinexor (S) is an oral selective XPO1 inhibitor that reactivates multiple TSPs and inhibits oncoprotein translation**
- **Selinexor synergizes with proteasome inhibitors (PIs):**
  - In PI-sensitive cell lines and overcome resistance in PI resistant cell lines

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. Turner, Oncotarget 2016, 6. Bahlis, Blood 2018, 7.Jakubowiak, BJH 2019

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 treated with prior lenalidomide (Len) and based on number of prior regimens

	SVd Arm (n=195)		Vd Arm (n=207)	
Prior Lenalidomide	**SVd Len Treated** **39%** (n=77)	**SVd Len Naïve** **61%** (n=118)	**Vd Len Treated** **37%** (n=77)	**Vd Len Naïve** **63%** (n=130)
Prior Number of Treatment Regimens	**SVd 1 Prior** **51%** (n=99)	**SVd ≥2 Priors** **49%** (n=96)	**Vd 1 Prior** **48%** (n=99)	**Vd ≥2 Priors** **52%** (n=108)

Baseline Characteristics by Prior Len Treatment and Number of Prior Treatments

Len Categories	SVd – Len Treated (n=77)	SVd – Len Naïve (n=118)	Vd – Len Treated (n=77)	Vd – Len Naïve (n=130)
Median Age, Years (range)	**65** (40, 87)	**66** (45, 84)	**66** (45, 85)	**68** (38, 90)
Males, n (%) **Females, n (%)**	**53** (68.8) **24** (31.2)	**62** (52.5) **56** (47.5)	**40** (51.9) **37** (48.1)	**75** (57.7) **55** (42.3)
Number of Prior Regimens, n (%) 1 2 3	 **23** (29.9) **33** (42.9) **21** (27.3)	 **76** (64.4) **32** (21.7) **10** (8.5)	 **20** (26.0) **30** (39.0) **27** (35.1)	 **79** (60.8) **34** (26.2) **17** (13.1)

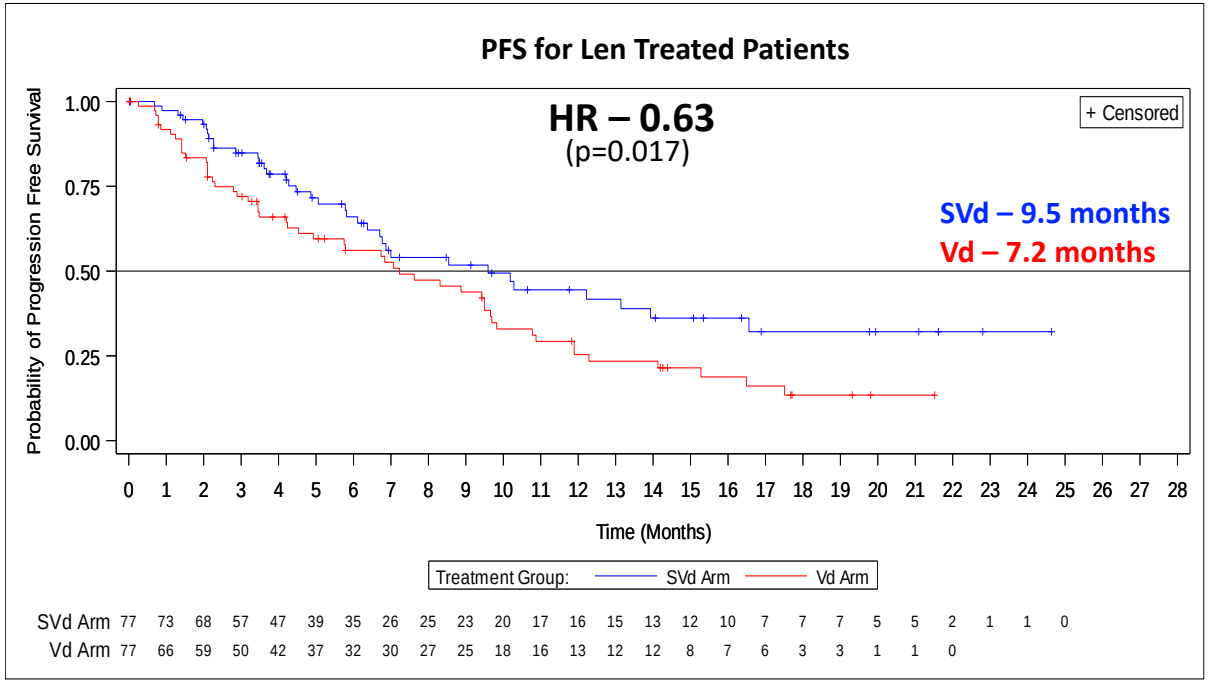
Prior Treatment Categories	SVd – 1 Prior (n=99)	SVd – ≥2 Priors (n=96)	Vd – 1 Prior (n=99)	Vd – ≥2 Priors (n=108)
Median Age, Years (range)	**67** (45, 87)	**65** (40, 84)	**69** (44, 90)	**65** (38, 85)
Males, n (%) **Females, n (%)**	**55** (55.6) **44** (44.4)	**60** (62.5) **36** (37.5)	**53** (53.5) **46** (46.5)	**62** (57.4) **46** (42.6)
Number of Prior Regimens, n (%) 1 2 3	 **99** (100.0) -- --	 -- **65** (67.7) **31** (32.3)	 **99** (100.0) -- --	 -- **64** (59.3) **44** (40.7)

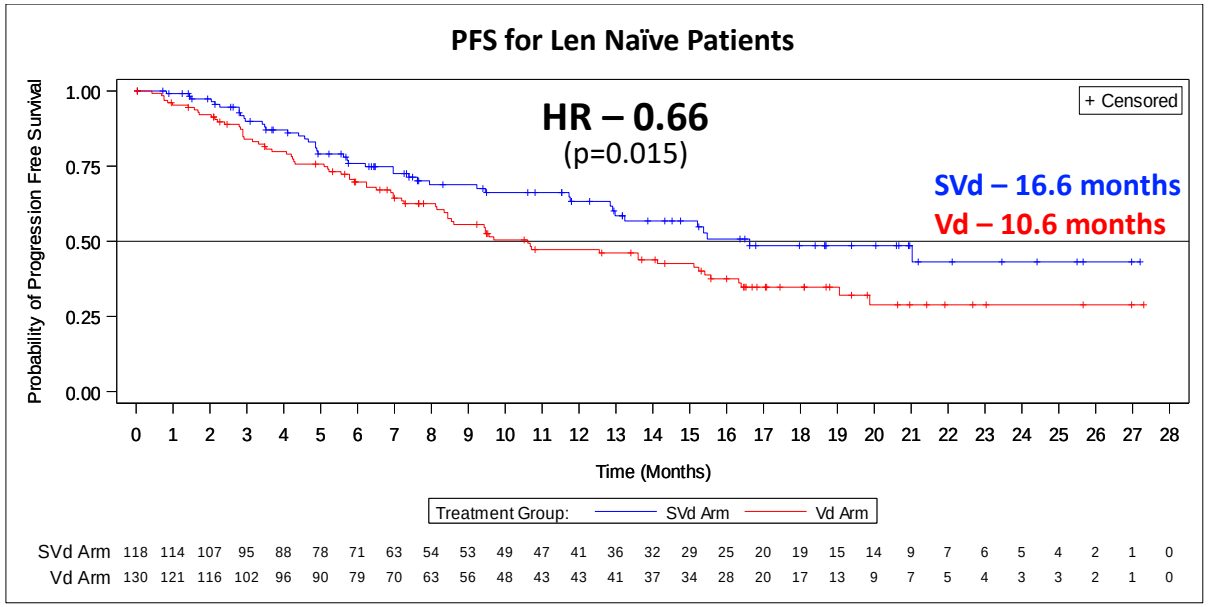
≥Grade 3 Adverse Events, ≥5% Overall

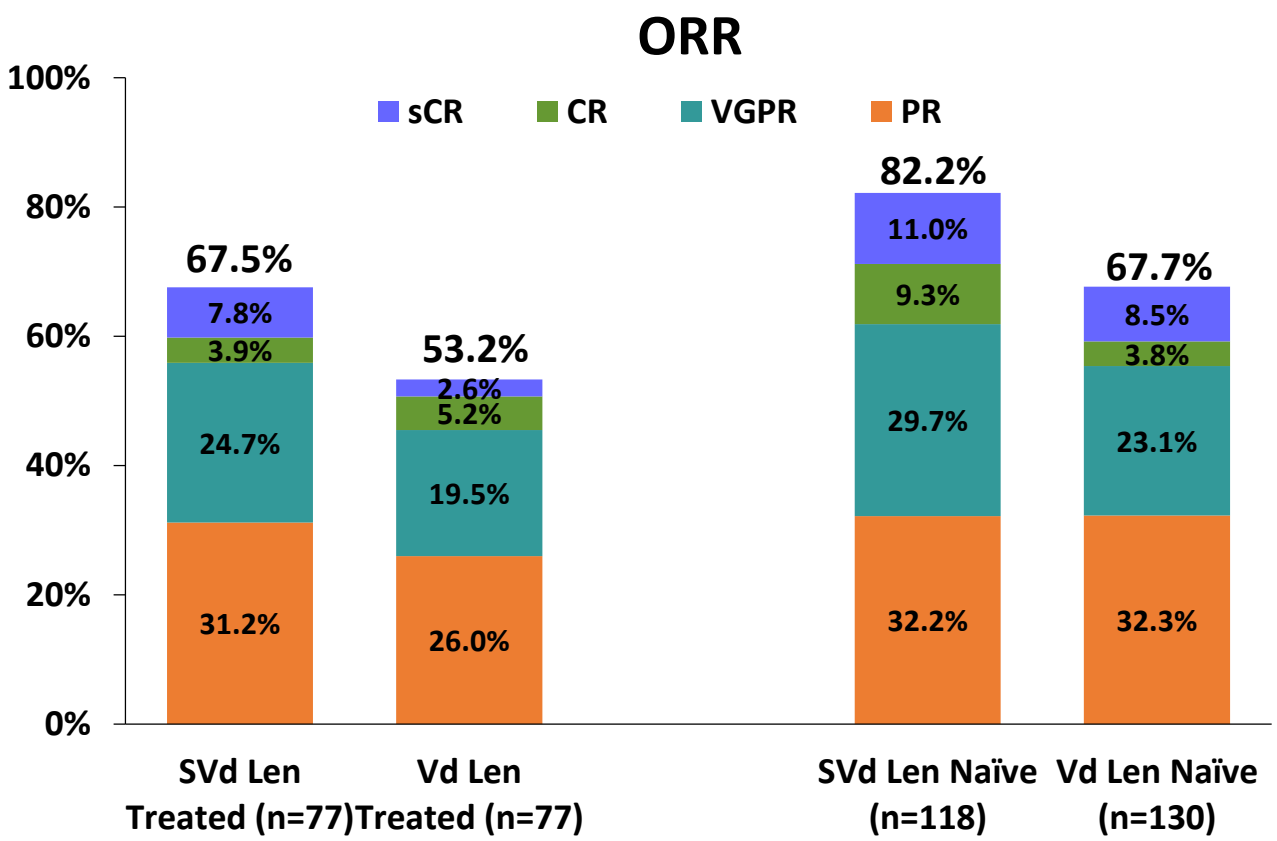
AE Term	SVd – Len Naïve (n=118)	SVd – 1 Prior (n=99)	Vd – Len Naïve (n=129)	Vd – 1 Prior (n=98)	SVd – Len Treated (n=77)	SVd – ≥2 Priors (n=96)	Vd – Len Treated (n=75)	Vd – ≥2 Priors (n=106)
Thrombocytopenia	40 (33.9)	39 (39.4)	17 (13.2)	17 (17.3)	37 (48.1)	38 (39.6)	18 (24.0)	18 (17.0)
Anemia	15 (12.7)	10 (10.1)	15 (11.6)	11 (11.2)	16 (20.8)	21 (21.9)	6 (8.0)	10 (9.4)
Pneumonia	13 (11.0)	9 (9.1)	15 (11.6)	10 (10.2)	9 (11.7)	13 (13.5)	7 (9.3)	12 (11.3)
Fatigue	14 (11.9)	12 (12.1)	1 (0.8)	1 (1.0)	12 (15.6)	14 (14.6)	1 (1.3)	1 (0.9)
Neuropathy Peripheral	7 (5.9)	6 (6.1)	13 (10.1)	9 (9.2)	2 (2.6)	3 (3.1)	5 (6.7)	9 (8.5)
Asthenia	14 (11.9)	11 (11.1)	5 (3.9)	6 (6.1)	2 (2.6)	5 (5.2)	4 (5.3)	3 (2.8)
Neutropenia	12 (10.2)	8 (8.1)	4 (3.1)	3 (3.1)	5 (6.5)	9 (9.4)	3 (4.0)	4 (3.8)
Cataract	7 (5.9)	8 (8.1)	2 (1.6)	1 (1.0)	10 (13.0)	9 (9.4)	1 (1.3)	2 (1.9)
Nausea	8 (6.8)	8 (8.1)	--	--	7 (9.1)	7 (7.3)	--	--
Hypertension	4 (3.4)	5 (5.1)	3 (2.3)	3 (3.1)	4 (5.2)	3 (3.1)	3 (4.0)	3 (2.8)
Diarrhea	5 (4.2)	5 (5.1)	1 (0.8)	--	7 (9.1)	7 (7.3)	--	1 (0.9)
Hypokalemia	6 (5.1)	6 (6.1)	1 (0.8)	3 (3.1)	2 (2.6)	2 (2.1)	4 (5.3)	2 (1.9)
Hypophosphatemia	5 (4.2)	4 (4.0)	1 (0.8)	--	5 (6.5)	6 (6.3)	2 (2.7)	3 (2.8)

- AEs of ≥Grade 3 were more commonly reported in the SVd treatment arm than in the Vd arm, LEN treated (83% SVd, 57% Vd), LEN-naïve (76% SVd, 55% Vd), 1 prior line (77% SVd, 56% Vd), 2-3 prior lines (81% SVd, 56% Vd), and were mostly managed with dose modification and/or supportive treatment. Grade ≥2 peripheral neuropathy occurred less frequently across all SVd subgroups compared with Vd: LEN treated (21% SVd, 37% Vd, p=0.0166); LEN-naïve (21% SVd, 33% Vd, p=0.0252), 1 prior line (21% SVd, 33% Vd, p=0.0501); 2-3 prior lines (21% SVd, 36% Vd, p=0.0107).

SVd is Effective (PFS, ORR) in Patients with or without Prior Len Treatment



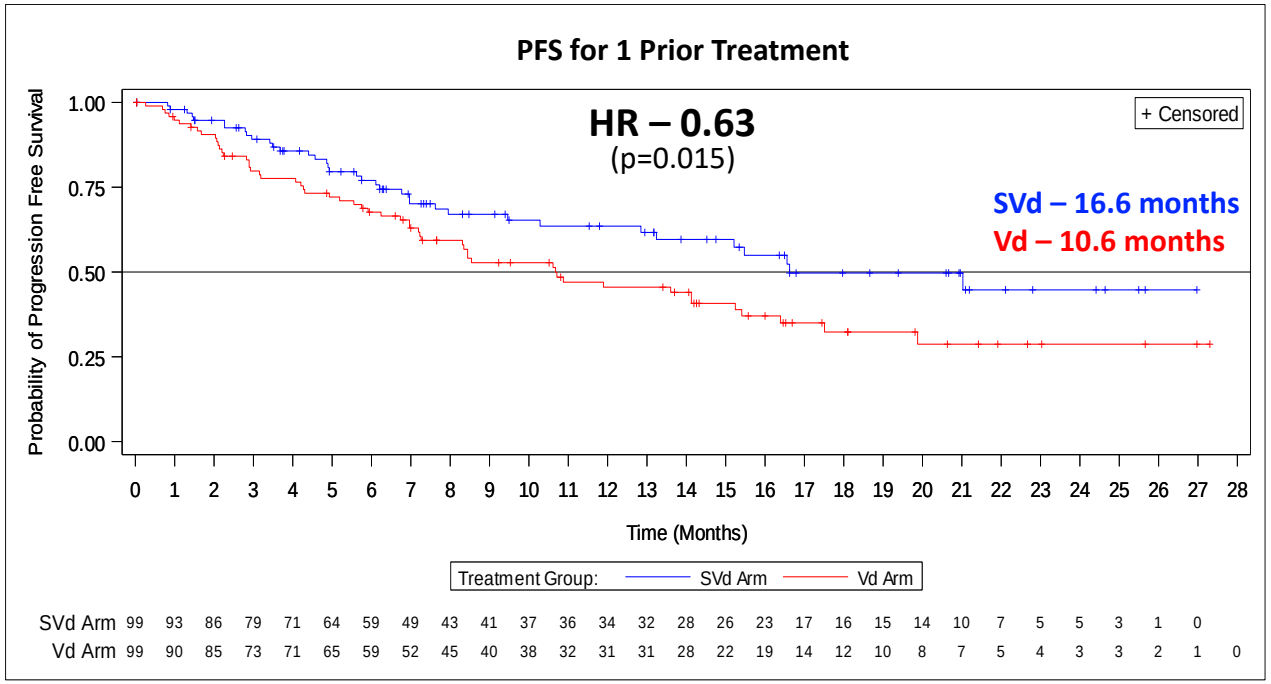


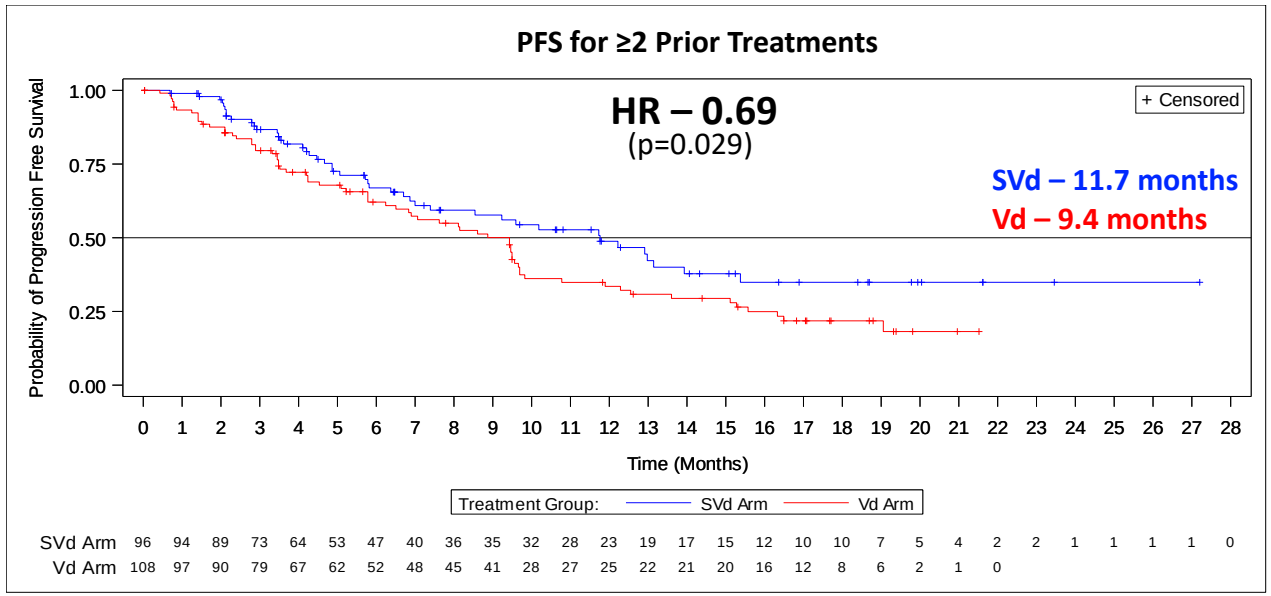


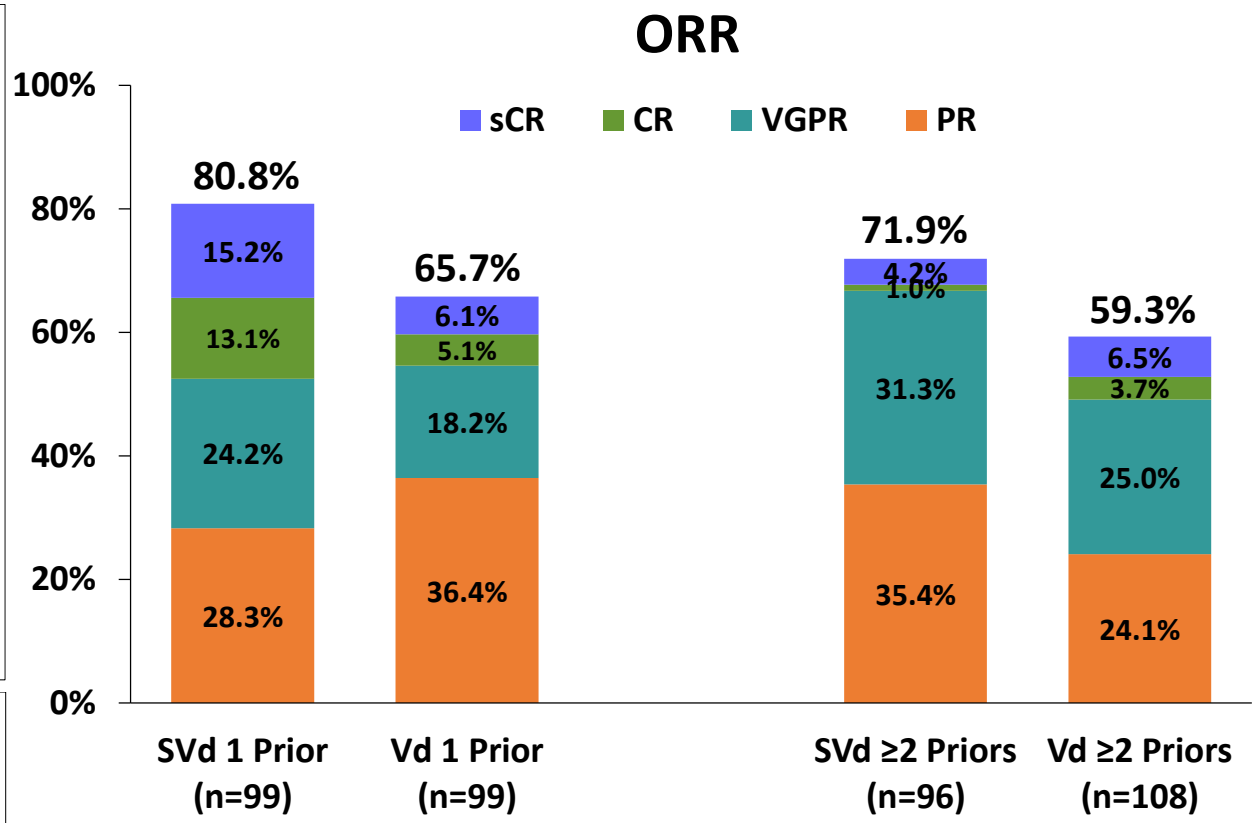
- PFS was significantly prolonged in both Len groups with SVd compared to Vd. In Len treated patients, PFS was 9.5 vs 7.2 months (HR, 0.63; 95% CI, 0.41-0.97; p=0.017) and in Len naïve, PFS was 16.6 vs 10.6 months (HR, 0.66; 95% CI, 0.45-0.96; p=0.015)

- The ORR significantly improved with SVd in Len treated (67.5% vs 53.2%; p=0.035) and Len naïve (82.2% vs 67.7%, p=0.004). The ≥VGPR rate was also higher in SVd compared to Vd.

SVd is Effective (PFS, ORR) in Patients with 1 Prior or ≥2 Prior Treatments







- PFS was significantly prolonged in both prior treatment groups with SVd compared to Vd. In patients with 1 prior, PFS was 16.6 vs 10.6 months (HR, 0.63; 95% CI, 0.41-0.96; p=0.015) and ≥2 priors, PFS was 11.7 vs 9.4 months (HR, 0.69; 95% CI, 0.48-1.01; p=0.029)

- The ORR significantly improved with SVd in patients with 1 prior (80.8% vs 65.7%; p=0.008) and ≥2 priors (71.9% vs 59.3%, p=0.029). The ≥VGPR rate was also higher in SVd compared to Vd.

Conclusions

- **Regardless of prior lenalidomide, the combination of SVd was active with a PFS HR of 0.63 among patients with prior lenalidomide treatment who received SVd compared to Vd**
- **Regardless of prior treatment, SVd treatment led to significantly improved ORR and PFS with the highest PFS of 16.6 months in first relapse**
- **Regardless of prior treatments SVd was associated with significantly reduced rates of ≥ grade 2 peripheral neuropathy (PN) compared with Vd**
- **AEs of ≥Grade 3 were more commonly reported in the SVd treatment arm than in the Vd arm, but most non-PN AEs were reversable and treatable; major organ toxicities were not common**

Once weekly SVd is effective and a convenient treatment option for patients with previously treated MM, including those who have been treated with Lenalidomide