Effect of Prior Treatment with Proteasome Inhibitors on the Efficacy and Safety of Once-Weekly Selinexor, Bortezomib, and Dexamethasone in Comparison with Twice-Weekly Bortezomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Subgroup Analysis from the BOSTON Study

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Conflict of Interest Disclosure

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Honoraria	Janssen, Celgene, Amgen, Takeda, Abbvie, GSK, Adaptive, Oncopeptides
Scientific Advisory Board	Janssen, Celgene, Amgen, Takeda, Abbvie, GSK, Pfizer, Regeneron, Adaptive, Oncopeptides, Roche, Seattle Genetics
Major Stockholder	--
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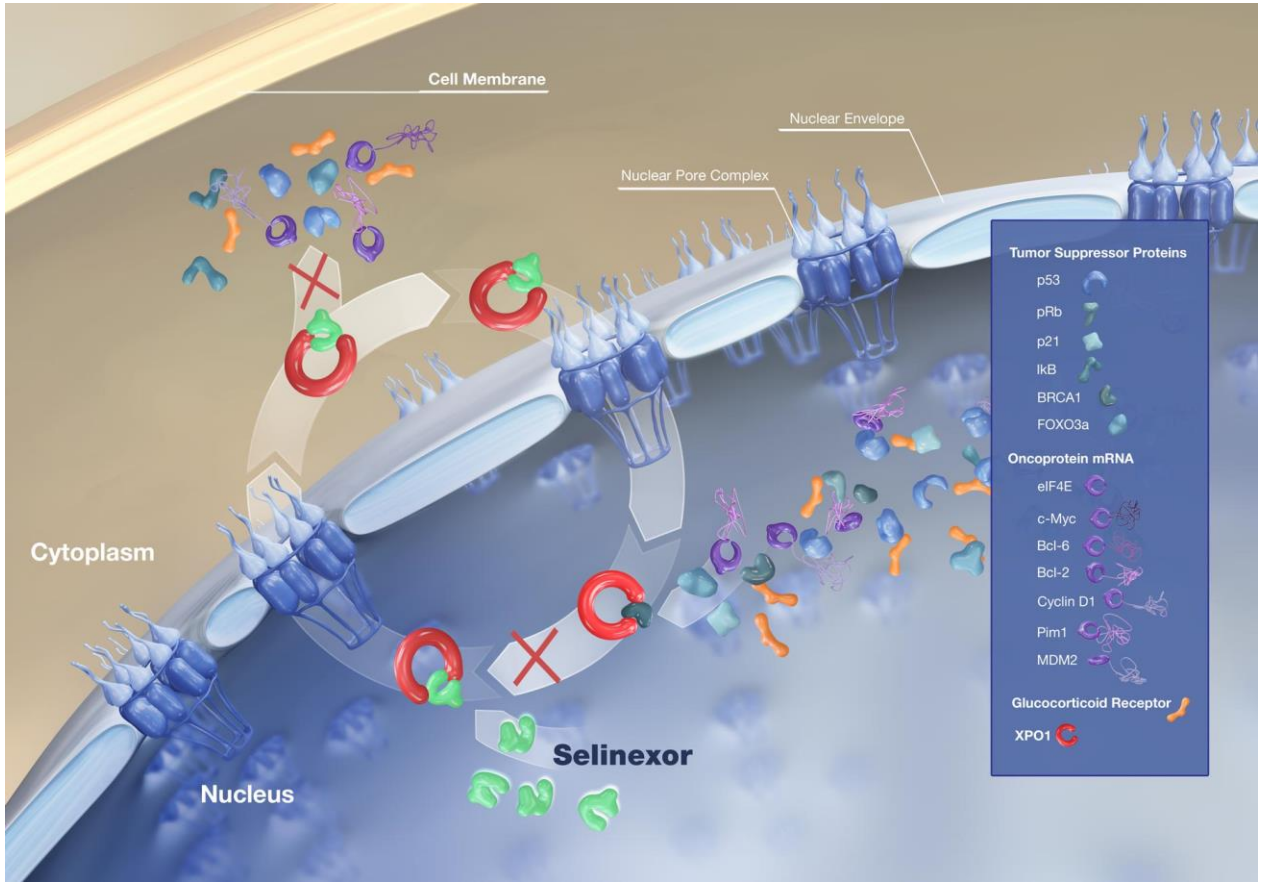
Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export[1-7]

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

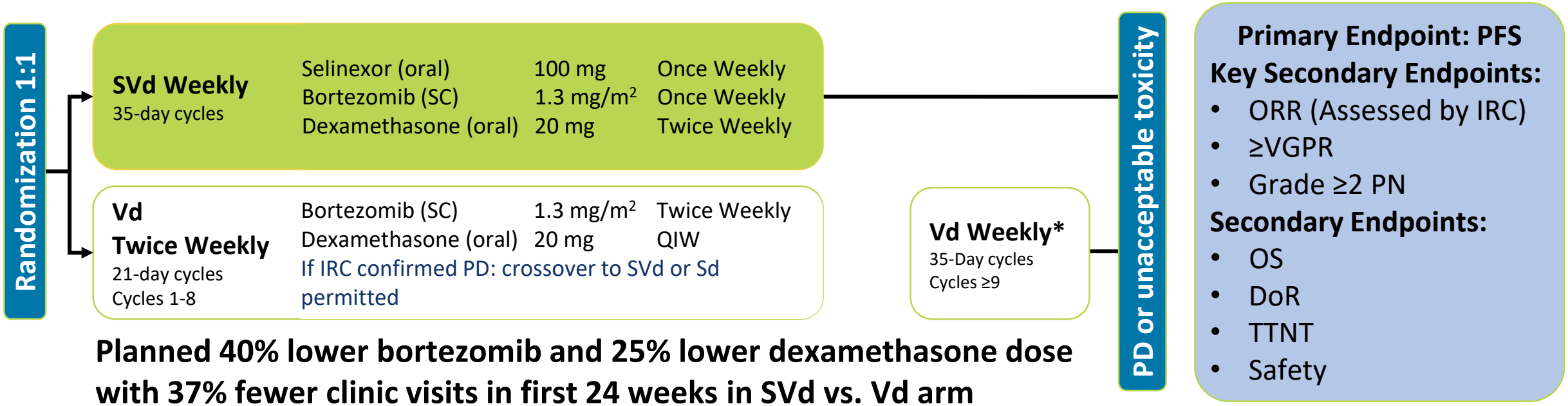


- **Exportin 1 (XPO1)** is overexpressed in MM and its levels correlate with poor prognosis and drug resistance
- **XPO1 Overexpression Causes:**
  - Tumor suppressor proteins (e.g., p53, IkB and FOXO) and glucocorticoid receptor inactivation and enhanced oncoprotein (e.g., c-Myc, Bcl-xL, cyclins) translation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

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

Conducted post-hoc analyses of the BOSTON study to determine the efficacy and safety among patients with prior proteasome inhibitor (PI) treatment

Total Patients Enrolled	SVd Arm (n=195)	Vd Arm (n=207)
Prior PI Treatment	**SVd Prior PI – 76%** (n=148)	**Vd Prior PI – 77%** (n=159)
PI Naïve	**SVd PI Naïve – 24%** (n=47)	**Vd PI Naïve – 23%** (n=48)

Baseline and Disease Characteristics by Prior PI Treatment Status

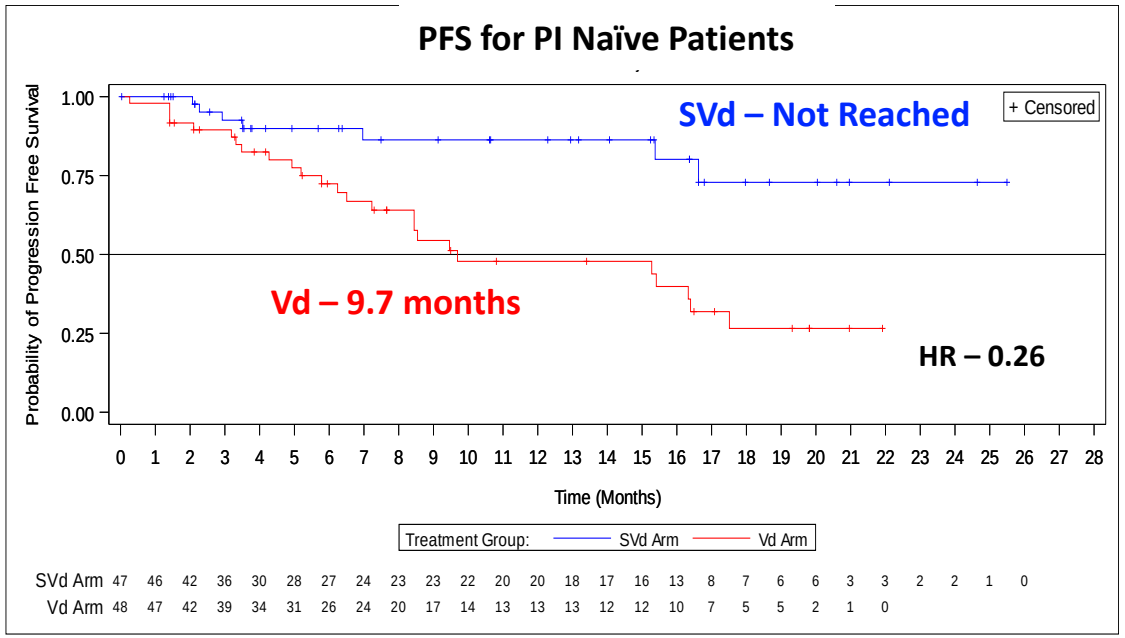
PI Treatment Category	SVd – Prior PI (n=148)	SVd – PI Naïve (n=47)	Vd – Prior PI (n=159)	Vd – PI Naïve (n=48)
Median Age, Years (range)	**65** (40, 84)	**68** (45, 87)	**67** (38, 90)	**68** (44, 84)
Males, n (%)	**89** (60.1)	**26** (55.3)	**88** (54.5)	**27** (56.3)
Females, n (%)	**59** (39.9)	**21** (44.7)	**71** (44.7)	**21** (43.8)
Number of Prior Treatment Regimens, n (%)				
1	**70** (47.3)	**29** (51.5)	**74** (46.5)	**25** (52.1)
2	**50** (33.8)	**15** (31.9)	**50** (31.4)	**14** (29.2)
3	**28** (18.9)	**3** (6.4)	**35** (22.0)	**9** (18.8)
Prior ASCT	**63** (42.6)	**13** (27.7)	**53** (33.3)	**10** (20.8)
Prior Treatment Exposure, n(%)				
Bortezomib	**134** (90.5)	--	**145** (91.2)	--
Carfilzomib	**20** (13.5)	--	**21** (13.2)	--
Ixazomib	**6** (4.1)	--	**3** (1.9)	--
Daratumumab	**11** (7.4)	--	**5** (3.1)	**1** (2.1)
Lenalidomide	**59** (39.9)	**18** (38.3)	**60** (37.7)	**17** (35.4)
Pomalidomide	**10** (6.8)	**1** (2.1)	**53** (33.3)	**1** (2.1)

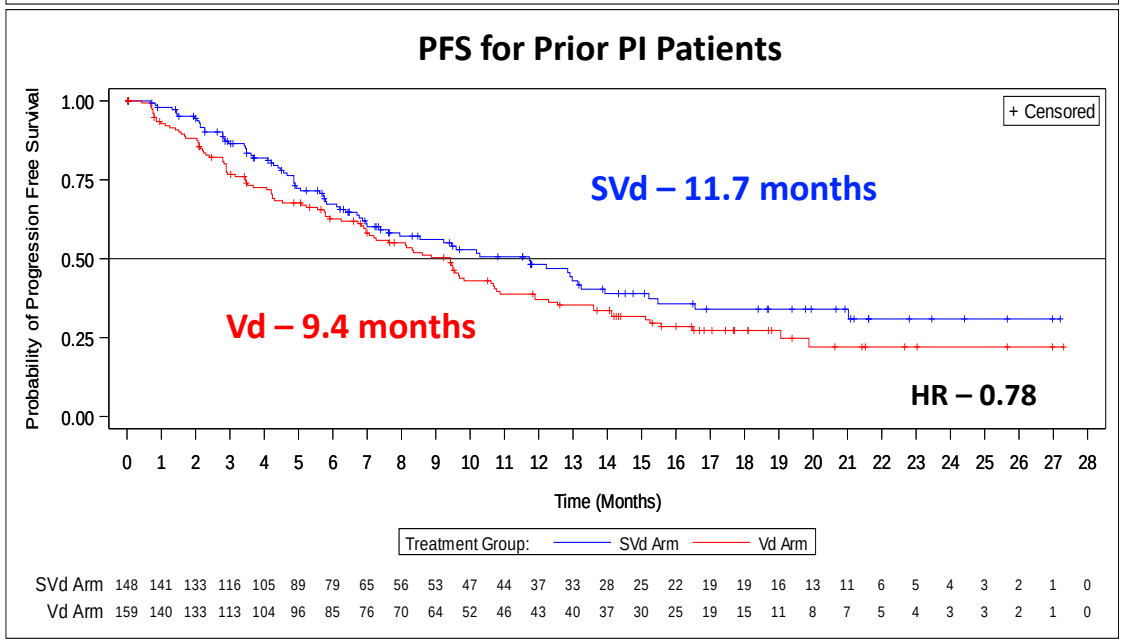
Related Adverse Events, All Grades, ≥10% Overall

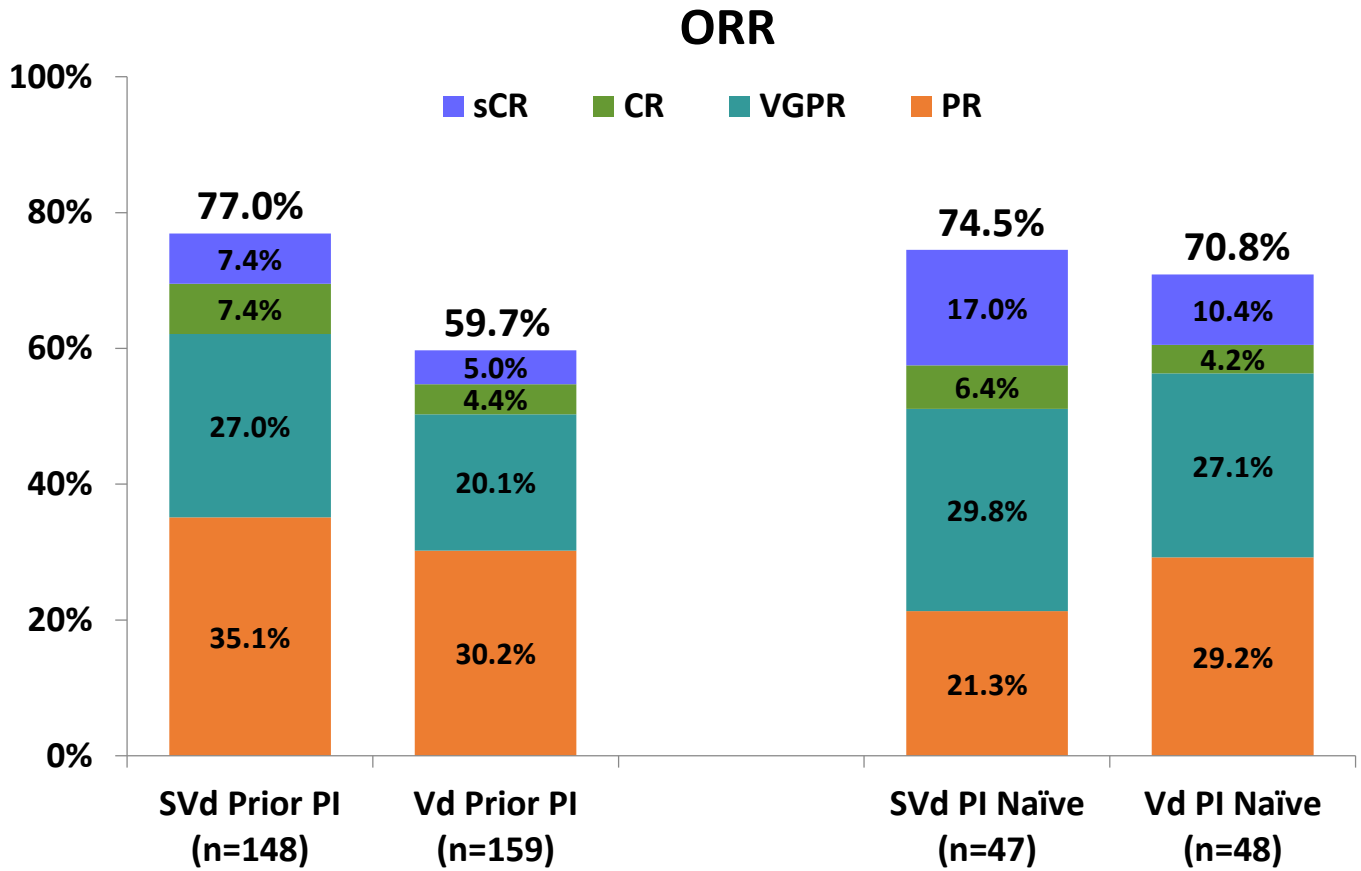
	Prior PI Treatment Categories			
	SVd – Prior PI (n=148)	SVd – PI Naïve (n=47)	Vd – Prior PI (n=156)	Vd – PI Naïve (n=48)
Thrombocytopenia	85 (57.4)	25 (53.2)	38 (24.4)	9 (18.8)
Neuropathy Peripheral	47 (31.8)	14 (29.8)	67 (42.9)	26 (54.2)
Nausea	69 (46.6)	24 (51.1)	10 (6.4)	2 (4.2)
Fatigue	56 (37.8)	13 (27.7)	10 (6.4)	9 (18.8)
Decreased Appetite	45 (30.4)	18 (38.3)	5 (3.2)	2 (4.2)
Diarrhea	26 (17.6)	11 (23.4)	21 (13.5)	8 (16.7)
Anemia	28 (18.9)	15 (31.9)	11 (7.1)	6 (12.5)
Insomnia	22 (14.9)	7 (14.9)	20 (12.8)	7 (14.6)
Asthenia	30 (20.3)	8 (17.0)	8 (5.1)	3 (6.3)
Weight Decreased	29 (19.6)	9 (19.1)	7 (4.5)	1 (2.1)
Constipation	14 (9.5)	4 (8.5)	17 (10.9)	7 (14.6)
Vomiting	23 (15.5)	11 (23.4)	5 (3.2)	--
Cataract	22 (14.9)	10 (21.3)	2 (1.3)	2 (4.2)

- AEs of ≥grade 3 occurred in 71% of patients in the PI naïve subgroup (SVd 77%, Vd 65%) and 74% of patients in the prior PI treatment subgroup (SVd 88%, Vd 60%). Thrombocytopenia was more frequent in patients in the SVd arms as was anemia and fatigue. Rate of grade ≥2 peripheral neuropathy was less frequent in the SVd than Vd treatment arms (PI naïve: 25.5%, Vd 43.8%, p=0.03; prior PI: SVd 19.6%, Vd 31.4%, p=0.009).

SVd is Effective (PFS, ORR) in Patients with Prior PI Treatment or PI Naïve



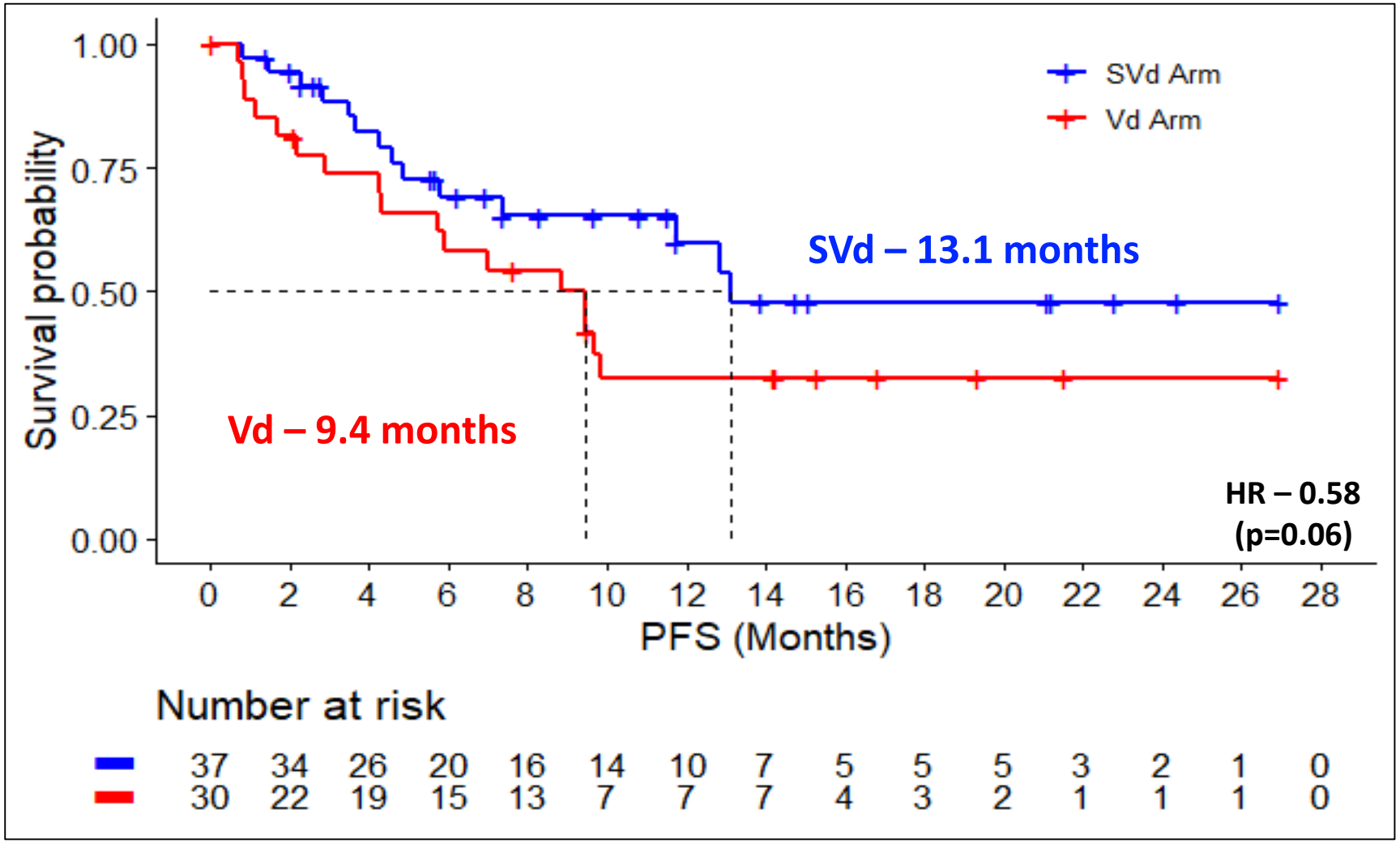




- PFS was prolonged in both PI groups with SVd compared to Vd. In prior PI, PFS was 11.7 vs 9.4 months (HR, 0.78; [95% CI, 0.58-1.06]; p=0.057) and in PI naïve, PFS was not reached vs 9.7 months (HR, 0.26; [95% CI, 0.11-0.60]; p=0.0003).
- The ≥VGPR rate was 41.9% in patients on SVd versus 29.6% on Vd (p=0.012) and 53.2% on SVd versus 41.7% on Vd (p=0.131) in the prior PI and PI naïve groups, respectively.

SVd is Effective Among Patients that Received Bortezomib Prior to ASCT as Induction Therapy – PFS, ORR

PFS for Bort-Treated Prior to ASCT



Conclusions

- **Patients who only had bortezomib based induction regimen prior to ASCT had a benefit with SVd**
  - **PFS improvement of 13.1 vs 9.4 months; HR 0.58, (p=0.06)**

- **Among patients who were PI treated or PI naïve, SVd improved PFS relative to Vd**
  - **PI Treated PFS; 11.7 months vs 9.4 months; HR 0.78, (p=0.057)**
  - **PI Naïve PFS; *Not Reached* vs 9.7 months; HR 0.26, (p=0.0003)**

- **ORR was significantly improved with SVd in patients with prior PI therapy (77.0% vs 59.7%; p=0.0006)**

- **Non-PN AEs were higher with in SVd than Vd therapy, but most of the AEs were reversible and treatable.**

Once weekly SVd is a active, convenient regimen and may be an important treatment option for patients with relapsed myeloma who had a bortezomib based induction or those who were PI naïve.