Once Weekly Selinexor, Bortezomib, and Dexamethasone Versus Twice Weekly Bortezomib and Dexamethasone in Relapsed or Refractory Multiple Myeloma: Age and Frailty Subgroup Analyses from the Phase 3 BOSTON Study

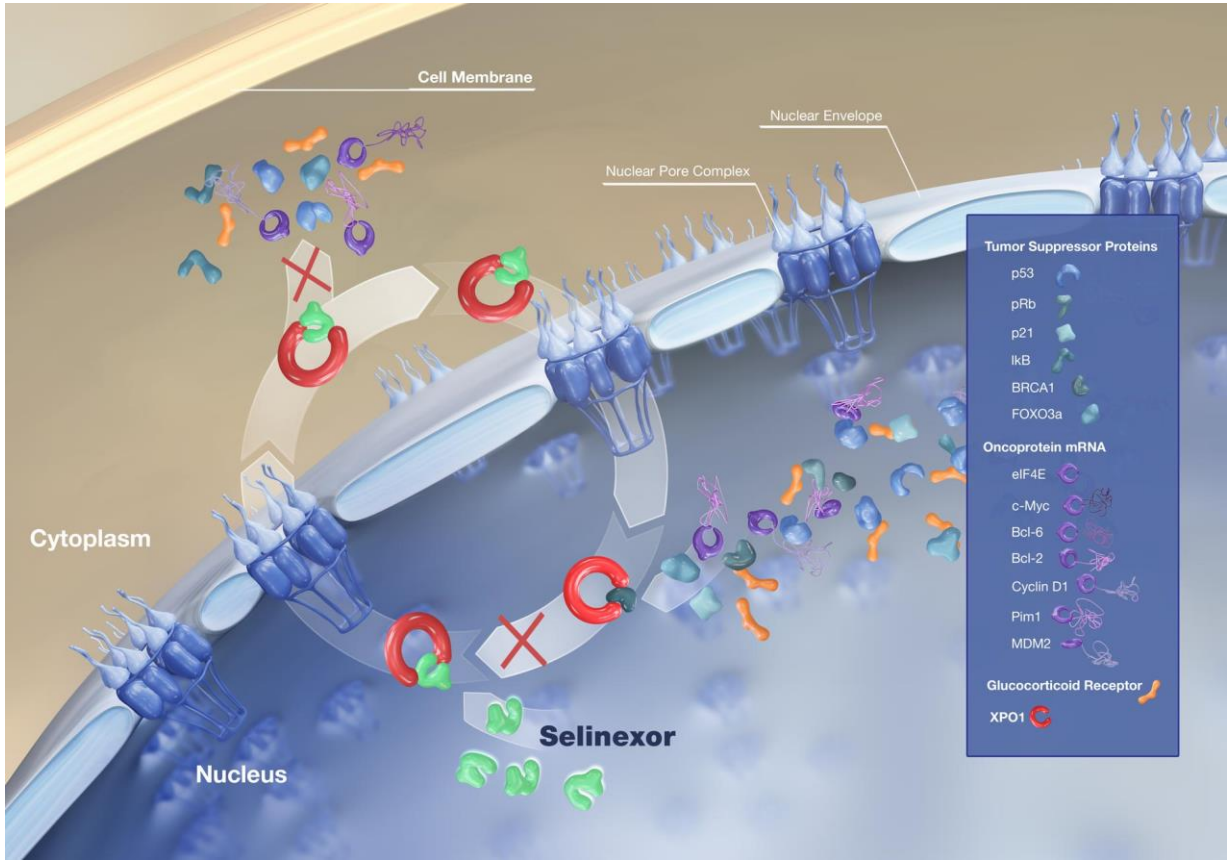
Holger W Auner[1], Maria Gavriatopoulou[2], Sosana Delimpasi[3], Maryana Simonova[4], Ivan Spicka[5], Ludek Pour[6], Meletios A. Dimopoulos[7], Iryna Kriachok[8], Halyna Pylypenko[9], Xavier Leleu[10], Vadim Doronin[11], Ganna Usenko[12], Roman Hajek[13], Reuben Benjamin[14], Tuphan Kanti Dolai[15], Dinesh Kumar Sinha[16], Christopher P Venner[17], Mamta Garg[18], Don Ambrose Stevens[19], Hang Quach[20] Sundar Jagannath[21], Phillipe Moreau[22], Moshe Levy[23], Ashraf Badros[24], Larry D. Anderson[25], Nizar J. Bahlis[26], Thierry Facon[27], Maria Victoria Mateos[28], Michele Cavo[29], Anita A Joshi[30], Yi Chai[30], Melina Arazy[30], Jatin Shah[30], Sharon Shacham[30], Michael G Kauffman[30], Paul G. Richardson[31], Sebastian Grosicki[32]

[1]**Imperial College London, London, United Kingdom**; [2]Alexandra Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; [3]General Hospital Evangelismos, Athens, Greece; [4]Institute of Blood Pathology & Transfusion Medicine of National Academy of Medical Sciences of Ukraine, Lviv, Ukraine; [5]Charles University and General Hospital, Prague, Czech Republic; [6]University Hospital Brno, Brno, Czech Republic; [7]National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [8]National Cancer Institute Ukraine, Kiev, Ukraine; [9]Department of Hematology, Cherkassy Regional Oncological Center, Cherkassy, Ukraine; [10]Department of Hematology, CHU la Miletrie and Inserm CIC 1402, Poitiers, France; [11]City Clinical Hospital #40, Moscow, Russian Federation; [12]City Clinical Hospital No. 4 of Dnipro City Council, Dnipro, Ukraine; [13]Department of Hemato-oncology, University Hospital Ostrava, University of Ostrava, Ostrava, Czech Republic; [14]Kings College Hospital NHS Foundation Trust, London, United Kingdom; [15]Nil Ratan Sircar Medical College and Hospital, Kolkata, India; [16]State Cancer Institute, Indira Gandhi Institute of Medical Sciences, Patna, India; [17]Cross Cancer Institute, University of Alberta, Edmonton, Alberta, Canada; [18]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [19]Norton Cancer Institute, St. Matthews Campus, Louisville, KY; [20]University of Melbourne, St. Vincent's Hospital, Melbourne, Victoria, Australia; [21]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [22]University Hospital, Hotel-Dieu, Nantes, France; [23]Baylor University Medical Center, Dallas, Texas; [24]University of Maryland, Greenebaum Comprehensive Cancer Center, Baltimore, MD; [25]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; [26]University of Calgary, Charbonneau Cancer Research Institute, Calgary, AB; [27]CHU Lille Service des Maladies du Sang F-59000, Lille, France; [28]Hospital Universitario de Salamanca, Salamanca, Spain; [29]Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [30] Karyopharm Therapeutics Inc., Newton, MA; [31]Dana Farber Cancer Institute, Boston, MA; [32]Medical University of Silesian, Katowice, Poland

Conflict of Interest Disclosure

Research Support	Amgen, Apollo
Consultant	--
Honoraria	--
Scientific Advisory Board	Karyopharm, Amgen, Takeda
Major Stockholder	--
Employee, Speakers Bureau	Janssen

Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export[1-6]
Demonstrates synergistic activity in combination with bortezomib *in vitro* and *in vivo*

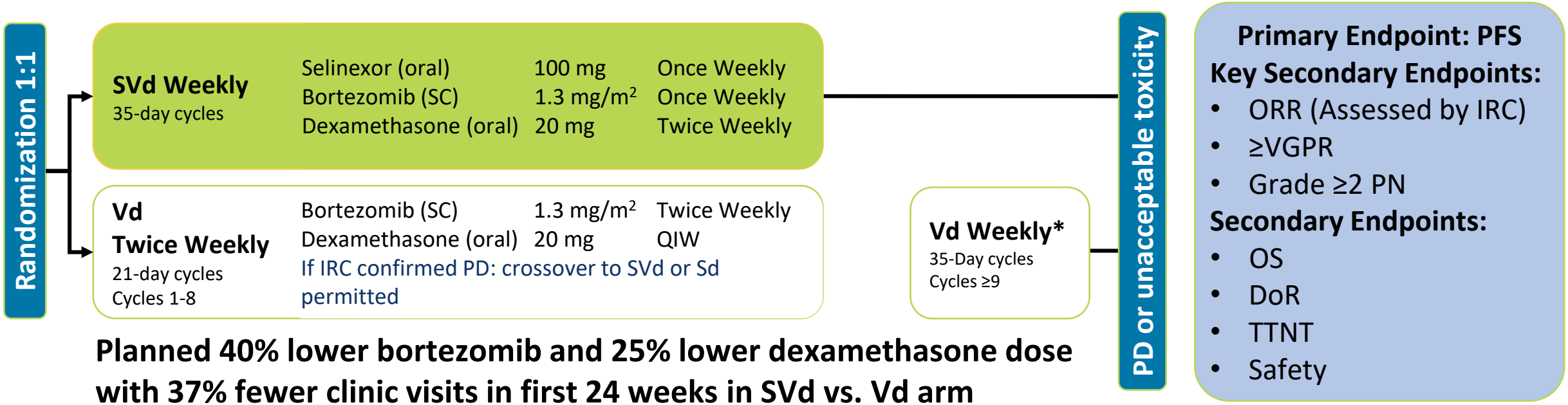


- **Exportin 1 (XPO1)** is overexpressed in MM and its levels correlate with poor prognosis and drug resistance
- **XPO1 Overexpression Causes:**
  - Tumor suppressor proteins (e.g., p53, IkB and FOXO) and glucocorticoid receptor inactivation and enhanced oncoprotein (e.g., c-Myc, Bcl-xL, cyclins) translation
- **Selinexor (S) is an oral selective XPO1 inhibitor that reactivates multiple TSPs and inhibits oncoprotein translation**
- **The BOSTON Trial Velcade-dex ± S (SVd vs Vd):**
  - Once weekly SVd significantly prolongs PFS (HR 0.70, *p*=0.0075) vs Vd, and was superior to Vd on ORR, TTNT, DoR
- **Older (≥65 years old) or Frail Patients with MM**
  - Multiple comorbid conditions contribute to the complexity of patients and exacerbation of side effects
  - Simple, well tolerated regimens required
  - Remains a challenging population to treat effectively

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. Chari NEJM 2019, 6. Gavriatopoulou IMW 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

Grosicki *et al*, The Lancet 2020;396(10262):1563-1573

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 <65 *vs* ≥65 years old or by Frailty score* (frail vs fit)

Total Patients Enrolled	SVd Arm (n=195)		Vd Arm (n=207)	
Age Categories	SVd <65 years **44%** (n=86)	SVd ≥65 years **56%** (n=109)	Vd <65 years **36%** (n=75)	Vd ≥65 years **64%** (n=132)
Frailty Categories	SVd Fit **66%** (n=129)	SVd Frail **34%** (n=66)	Vd Fit **69%** (n=143)	Vd Frail **31%** (n=64)

*Frailty Score was assessed using baseline characteristics including: Age, Charlson Comorbidity Index, and Eastern Cooperative Oncology Group Performance Status (Facon et al. Leukemia 2019)

Baseline and Disease Characteristics by Age Group and Frailty Category

Age Categories	SVd – <65 years (n=86)	SVd – ≥65 years (n=109)	Vd – <65 years (n=75)	Vd – ≥65 years (n=132)
Median Age, Years (range)	**57** (40, 64)	**71** (65, 87)	**58** (38, 64)	**71** (65, 90)
Males, n (%) **Females, n (%)**	**53** (61.6) **33** (38.4)	**62** (56.9) **47** (43.1)	**45** (60.0) **30** (40.0)	**70** (53.0) **62** (47.0)
Number of Prior Treatment Regimens, n (%) 1 2 3	 **43** (50.0) **28** (32.6) **15** (17.4)	 **56** (51.4) **37** (33.9) **16** (14.7)	 **29** (38.7) **26** (34.7) **20** (26.7)	 **70** (53.0) **38** (28.8) **24** (18.2)

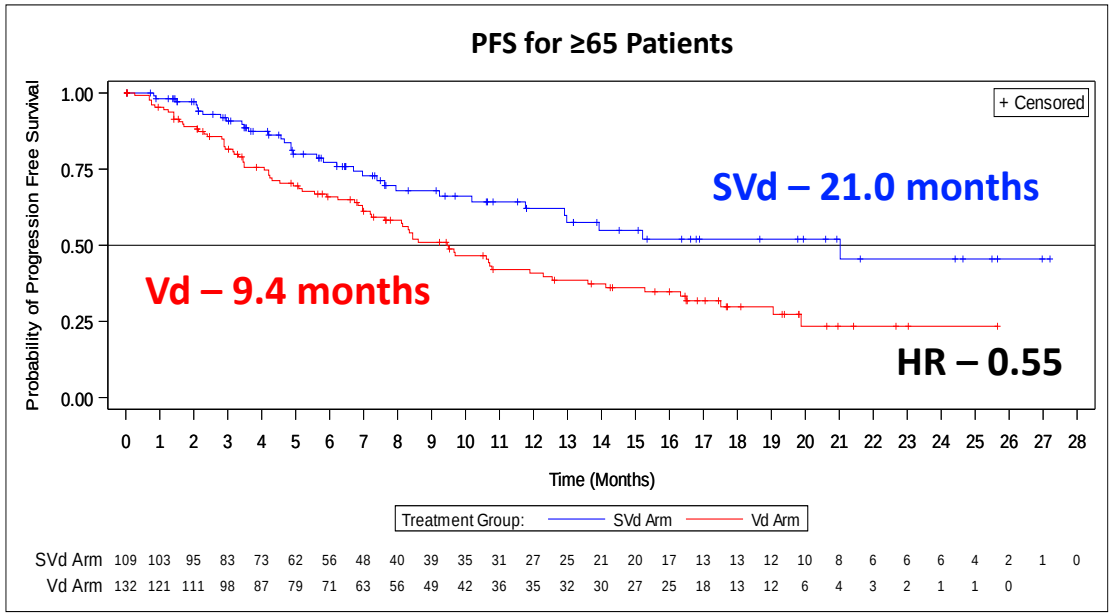
Frailty Categories	SVd – Fit (n=129)	SVd – Frail (n=66)	Vd – Fit (n=143)	Vd – Frail (n=64)
Median Age, Years (range)	**63** (40, 80)	**71** (47, 87)	**65** (38, 78)	**76** (48, 90)
Males, n (%) **Females, n (%)**	**78** (60.5) **51** (39.5)	**37** (56.1) **29** (43.9)	**83** (58) **60** (42)	**32** (50.0) **32** (50.0)
Number of Prior Treatment Regimens, n (%) 1 2 3	 **64** (49.6) **43** (33.3) **22** (17.1)	 **35** (53.0) **22** (33.3) **9** (13.6)	 **71** (49.7) **42** (29.4) **30** (21.0)	 **28** (43.8) **22** (34.4) **14** (21.9)

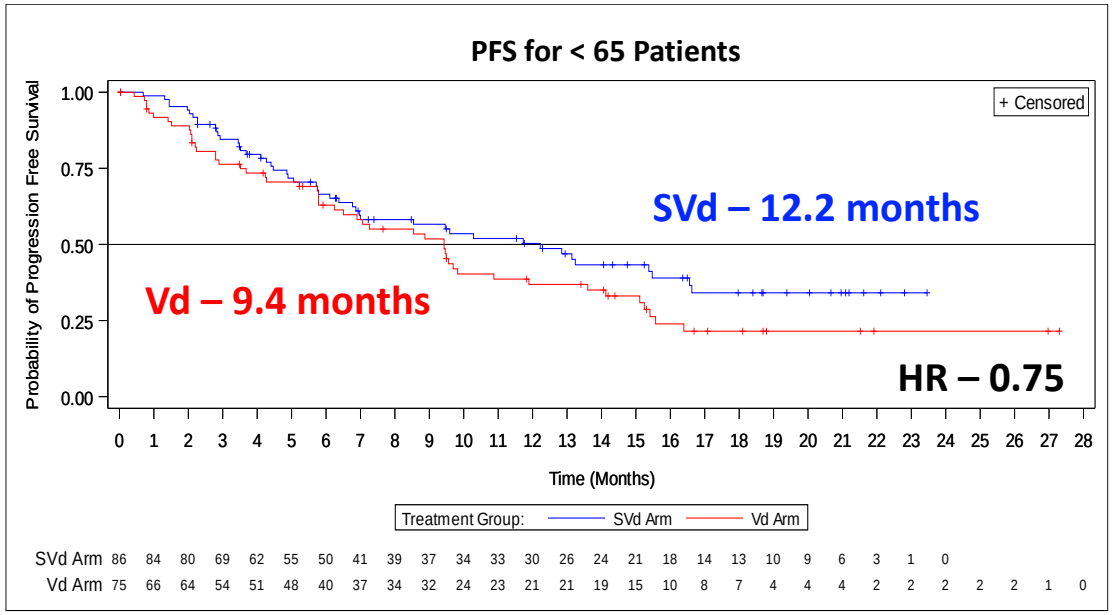
Related Adverse Events, All Grades, ≥10% Overall

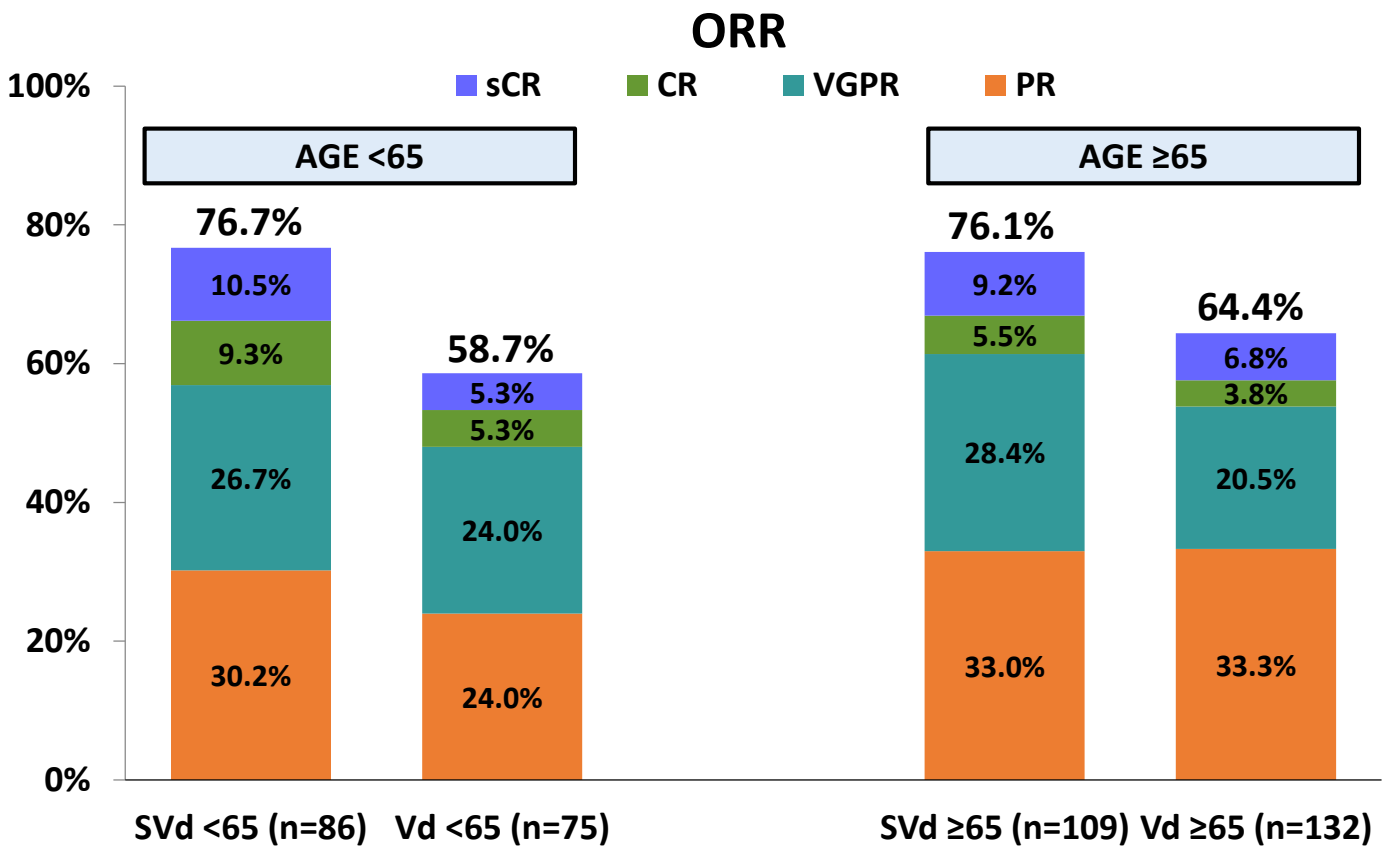
AE Term	SVd – <65 (n=86)	SVd – Fit (n=129)	Vd – <65 (n=75)	Vd – Fit (n=142)	SVd – ≥65 (n=109)	SVd – Frail (n=66)	Vd – ≥65 (n=129)	Vd – Frail (n=62)
Thrombocytopenia	47 (54.7)	78 (60.5)	18 (24.0)	33 (23.2)	63 (57.8)	32 (48.5)	29 (22.5)	14 (22.6)
Neuropathy Peripheral	27 (31.4)	45 (34.9)	35 (46.7)	62 (43.7)	34 (31.2)	16 (24.2)	58 (45.0)	31 (50.0)
Nausea	37 (43.0)	62 (48.1)	6 (8.0)	8 (5.6)	56 (51.4)	31 (47.0)	6 (4.7)	4 (6.5)
Fatigue	26 (30.2)	49 (38.0)	8 (10.7)	14 (9.9)	43 (39.4)	20 (30.3)	11 (8.5)	5 (8.1)
Decreased Appetite	27 (31.4)	44 (34.1)	6 (8.0)	7 (4.9)	36 (33.0)	19 (28.8)	1 (0.8)	--
Diarrhea	21 (24.4)	25 (19.4)	10 (13.3)	19 (13.4)	16 (14.7)	12 (18.2)	19 (14.7)	10 (16.1)
Anemia	18 (20.9)	30 (23.3)	6 (8.0)	12 (8.5)	25 (22.9)	13 (19.7)	11 (8.5)	5 (8.1)
Insomnia	9 (10.5)	20 (15.5)	14 (18.7)	26 (18.3)	20 (18.3)	9 (13.6)	13 (10.1)	1 (1.6)
Asthenia	17 (19.8)	20 (15.5)	5 (6.7)	7 (4.9)	21 (19.3)	18 (27.3)	6 (4.7)	4 (6.5)
Weight Decreased	15 (17.4)	23 (17.8)	5 (6.7)	7 (4.9)	23 (21.1)	15 (22.7)	3 (2.3)	1 (1.6)
Constipation	10 (11.6)	16 (12.4)	9 (12.0)	19 (13.4)	8 (7.3)	2 (3.0)	15 (11.6)	5 (8.1)
Vomiting	18 (20.9)	22 (17.1)	1 (1.3)	4 (2.8)	16 (14.7)	12 (18.2)	4 (3.1)	1 (1.6)
Cataract	21 (24.4)	29 (22.5)	2 (2.7)	3 (2.1)	11 (10.1)	3 (4.5)	2 (1.6)	1 (1.6)

- Similar to the overall population, the most common grade ≥3 AEs were thrombocytopenia, anemia, and fatigue. In the SVd arm, the incidence of AEs was comparable across subgroups except for a higher incidence of fatigue in ≥65 vs <65 (17% vs 8%) and pneumonia in the frail versus fit (19% vs 7%). There were more deaths in the ≥65 (30% [SVd 23%, Vd 36%]) and frail groups (35% [SVd 26%, Vd 44%]) compared with the <65 (23% [SVd 26%, Vd 20%]) and fit groups (24% [SVd 23%, Vd 24%]).

SVd is Effective (PFS, ORR) in Patients <65 and ≥65 Years



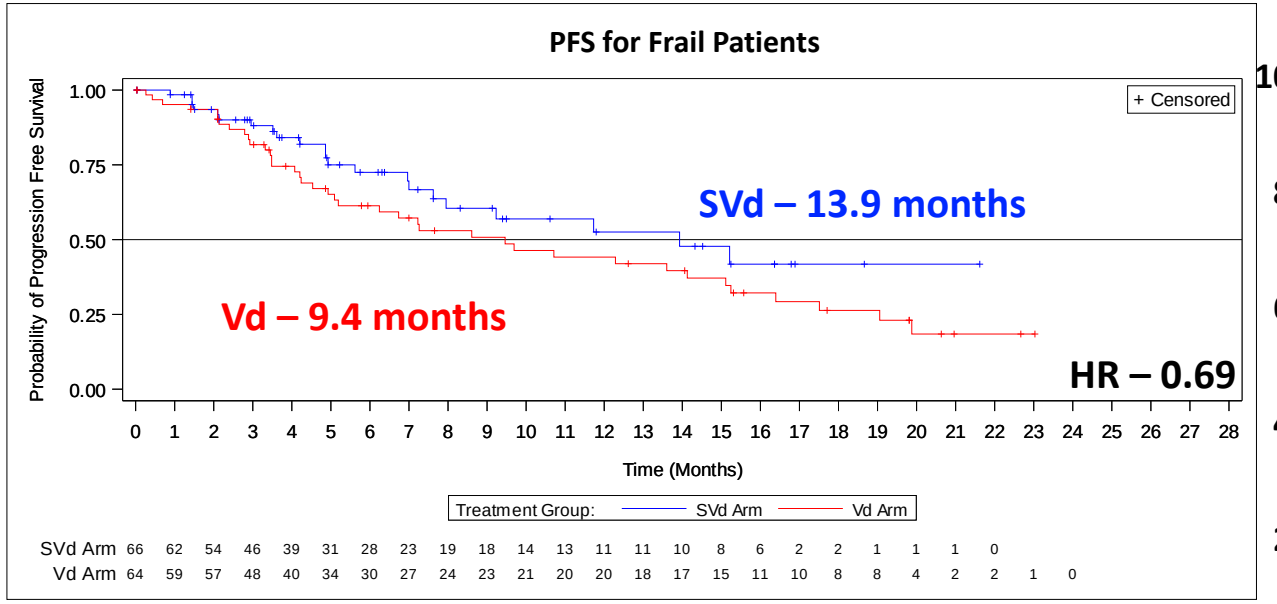


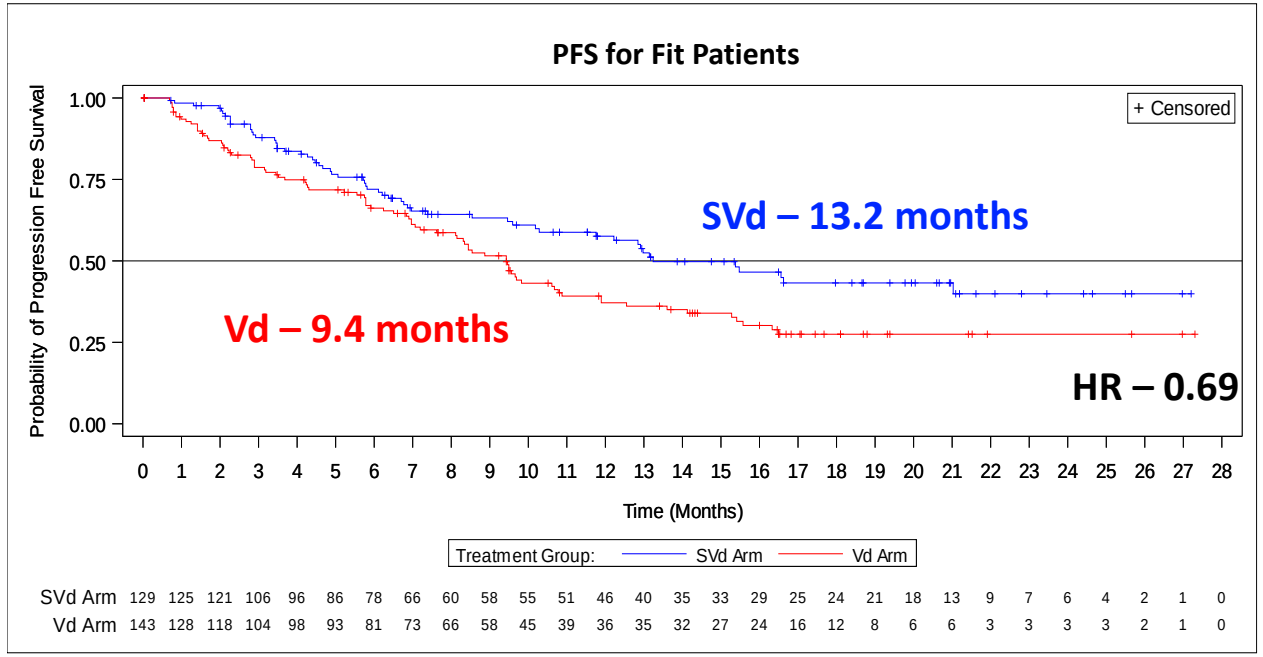


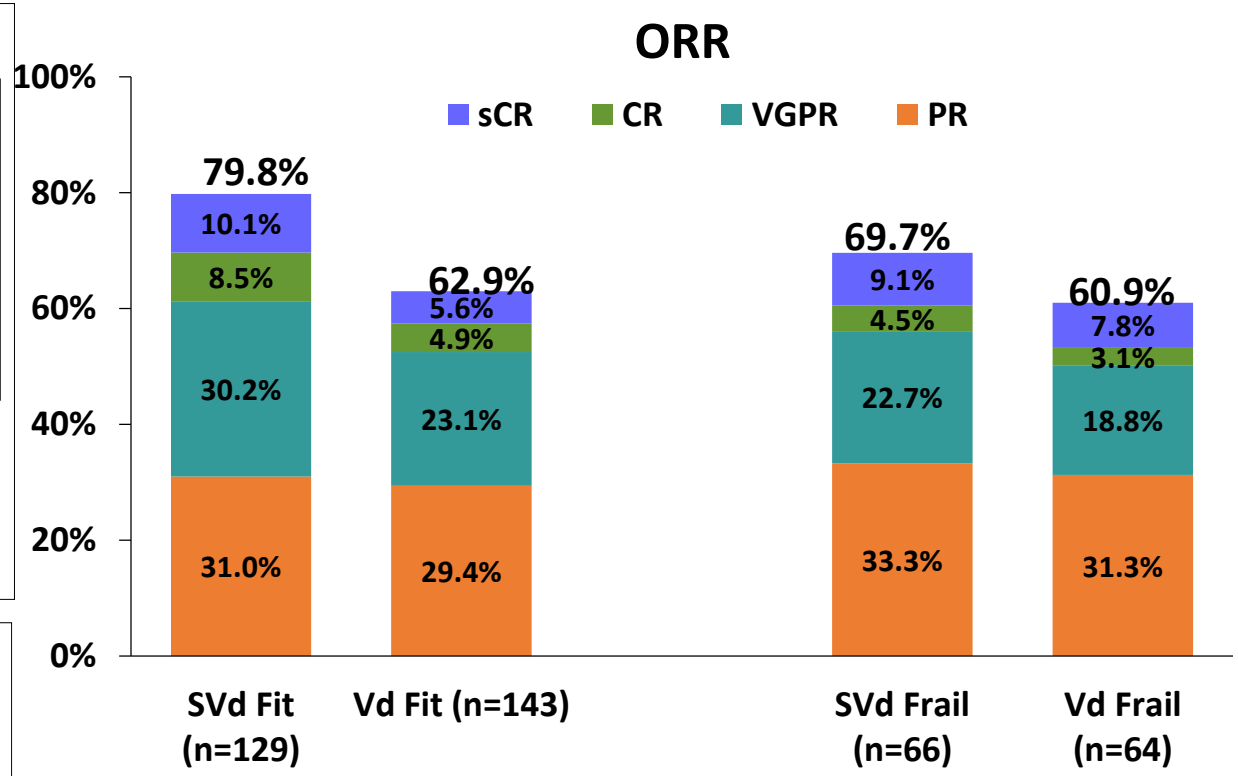
- PFS was prolonged in both age groups with SVd compared to Vd. In ≥65, PFS was 21.0 vs 9.4 months (HR, 0.55; 95% CI, 0.37-0.83; p=0.002) and in <65, PFS was 12.2 vs 9.4 months (HR, 0.74; 95% CI, 0.41-1.10; p=0.07).

- The ORR significantly improved with SVd in those ≥65 (76.1% vs 64.4%; p=0.0243) and <65 (76.7% vs 58.7%, p=0.0071). The ≥VGPR rate was also higher in SVd compared to Vd.

SVd is Effective (PFS, ORR) in Frail and Fit Patients







- The PFS benefit of SVd was sustained and comparable in the frail pts: 13.9 vs 9.4 months (HR, 0.69; 95% CI, 0.40-1.17; p=0.08); and in the fit pts: 13.2 vs 9.4 months (HR, 0.66; 95% CI, 0.47-0.93; p=0.008).

- The ORR were higher with SVd in frail (69.7% vs 60.9%; p=0.1479) and fit patients (79.8% vs 62.9%, p=0.001). The ≥VGPR rate was also higher in SVd compared to Vd.

Conclusions

- Both elderly and frail patients benefit from SVd compared to Vd
- Activity of SVd was preserved in patients ≥65 with a mPFS of 21 months and HR of 0.55
- SVd had similar PFS benefit in Fit vs Frail pts (13.2 vs 13.9 months with SVd)
- Once weekly SVd led to prolonged PFS, improved response rates and lower rates of PN regardless of age and frailty score compared to standard twice weekly Vd
- Non-PN AEs were higher with in SVd than Vd therapy, but most of the AEs were reversible and treatable

Once weekly SVd is an effective and safe treatment option for patients with previously treated MM, including those who are ≥65 years old or frail