Weekly Selinexor, Bortezomib and Dexamethasone (SVd) Versus Twice Weekly Bortezomib and Dexamethasone (Vd) in Patients with Multiple Myeloma (MM) After 1–3 Prior Therapies: Initial Results of the Phase 3 BOSTON Study

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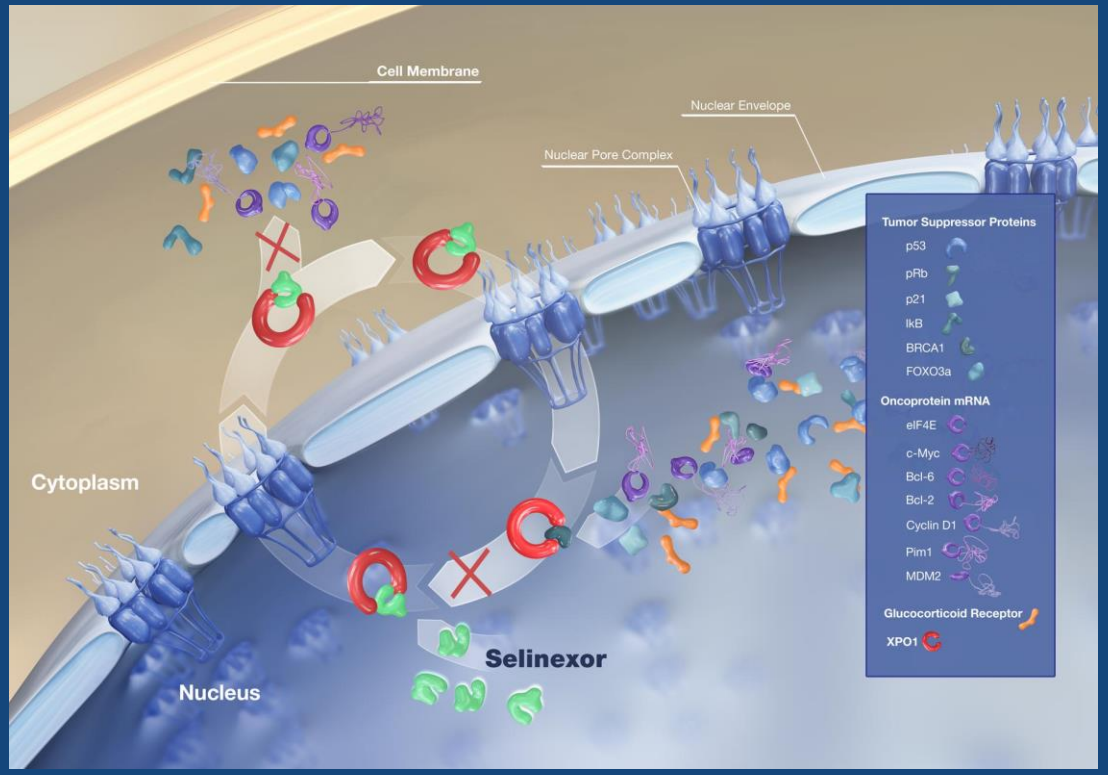
Selinexor:
First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)[1-4]

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

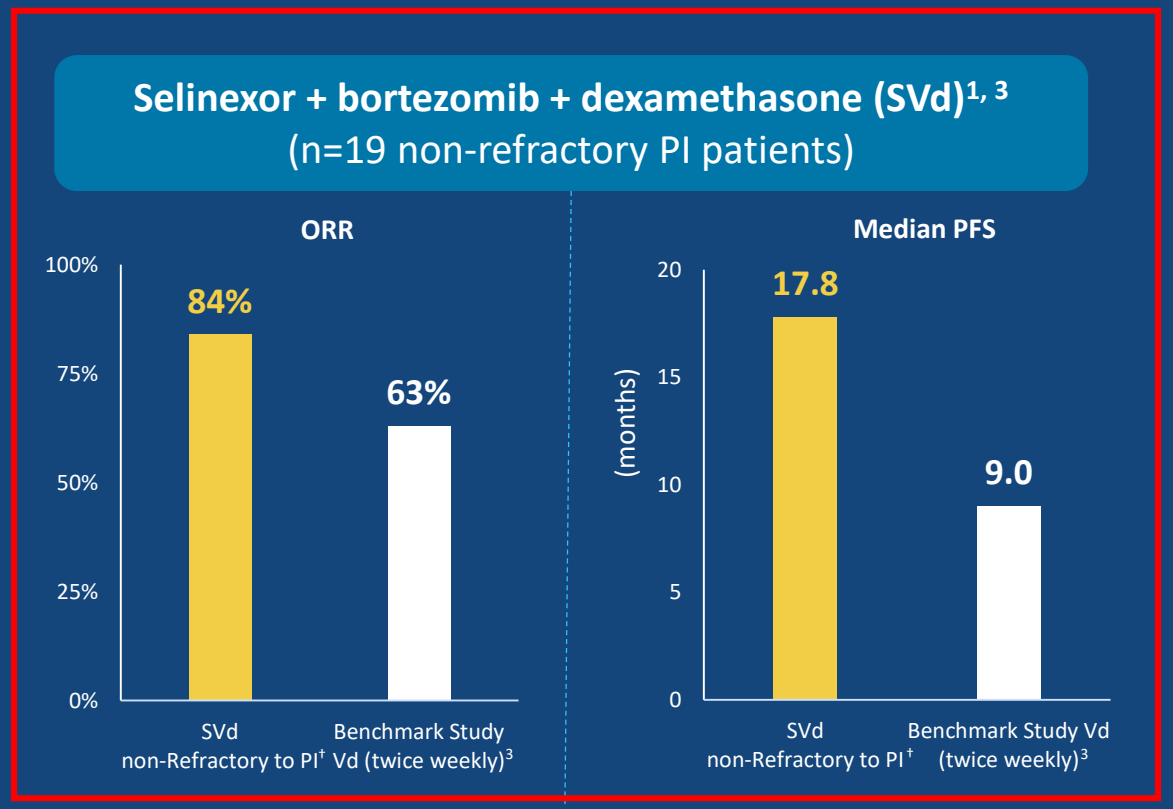


- **Exportin 1 (XPO1) is the major nuclear export protein for**
  - Tumor suppressor proteins (TSPs, e.g., p53, IkB and FOXO)
  - eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)
  - Glucocorticoid receptor (GR)
- **XPO1 is overexpressed in multiple myeloma (MM)**
  - High XPO1 levels enable cancer cells to escape TSP-mediated cell cycle arrest and apoptosis
  - XPO1 levels correlate with poor prognosis and drug resistance
- **Selinexor is an oral selective XPO1 inhibitor that:**
  - Reactivates multiple TSPs by preventing nuclear export
  - Inhibits oncoprotein translation
  - Reactivates GR signaling in presence of dexamethasone
- **Selinexor + dexamethasone is approved in the US for MM refractory to ≥4 therapies including ≥2 PIs,≥2 IMiDs and an anti-CD38 mAb**

IMiD = immunomodulatory imide drug, mAb = monoclonal antibody, PI = proteasome inhibitor. 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.

Selinexor + Bortezomib + Dexamethasone (SVd): ORR 84%, mPFS 17.8 months

STOMP*: A Phase 1b/2 Study in Patients With MM >1 Prior Therapy[1]



The STOMP study does not have a control/comparative arm.
The Vd Benchmark data are provided to contextualize the design of the BOSTON phase 3 trial.

*Selinexor and Backbone Treatments of Multiple Myeloma Patients. †Patient population eligible for Phase 3 BOSTON study.
AE = adverse event, mPFS = median progression-free survival, MTD = maximum tolerated dose,
PI = proteasome inhibitor, ORR = overall response rate, RP2D = recommended phase 2 dose.
1. Bahlis NJ, et al. Blood 2018. 2.Chari A et al., NEJM 2019 3.Dimopoulos MA et al., Lancet 2016.

STORM trial established single agent (ORR 26%) in triple class refractory MM[2]

RP2D: Once Weekly SVd (MTD not reached)[1]

- Selinexor: orally 100 mg once weekly
- Bortezomib: subcutaneous 1.3 mg/m^2 once weekly
- Dexamethasone: orally 40 mg per week

Safety[1]

- Most common Grade 1/2 AEs were constitutional symptoms (e.g., nausea, fatigue, anorexia)
- Most common Grade 3/4 AEs were cytopenias (e.g., thrombocytopenia, neutropenia, anemia)
- SVd reported peripheral neuropathy across all patients was Grade 1/2 only and limited to four patients (10%)

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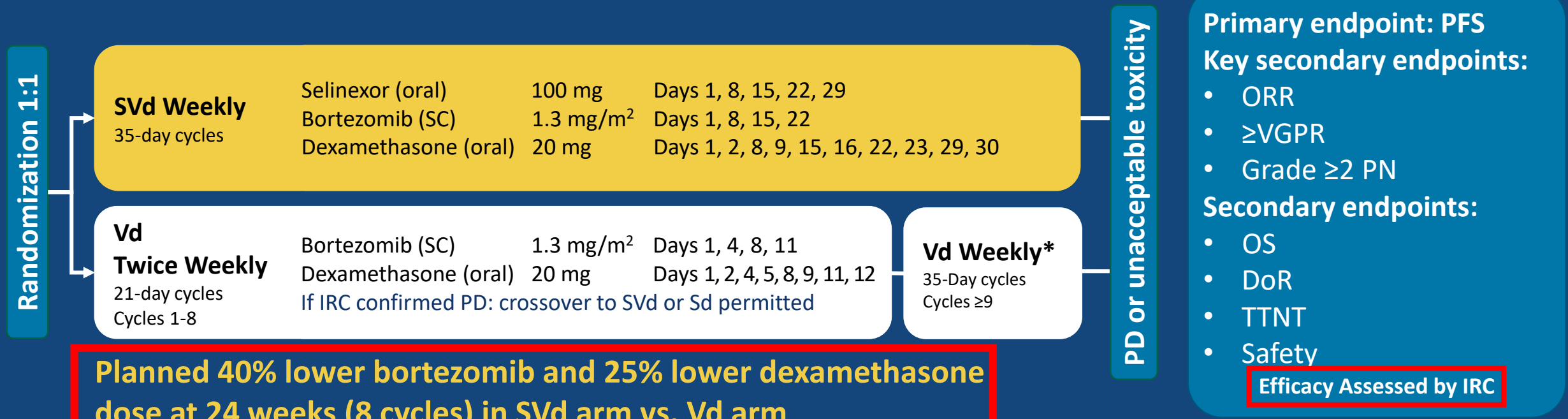
BOSTON Trial: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients With MM who Had Received 1–3 Prior Therapies



Primary endpoint: PFS

Key secondary endpoints:

- ORR
- ≥VGPR
- Grade ≥2 PN

Secondary endpoints:

- OS
- DoR
- TTNT
- Safety

Efficacy Assessed by IRC

Planned 40% lower bortezomib and 25% lower dexamethasone dose at 24 weeks (8 cycles) in SVd arm vs. Vd arm

Stratification:
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.

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BOSTON Trial: Inclusion/Exclusion Criteria

Key Inclusion Criteria

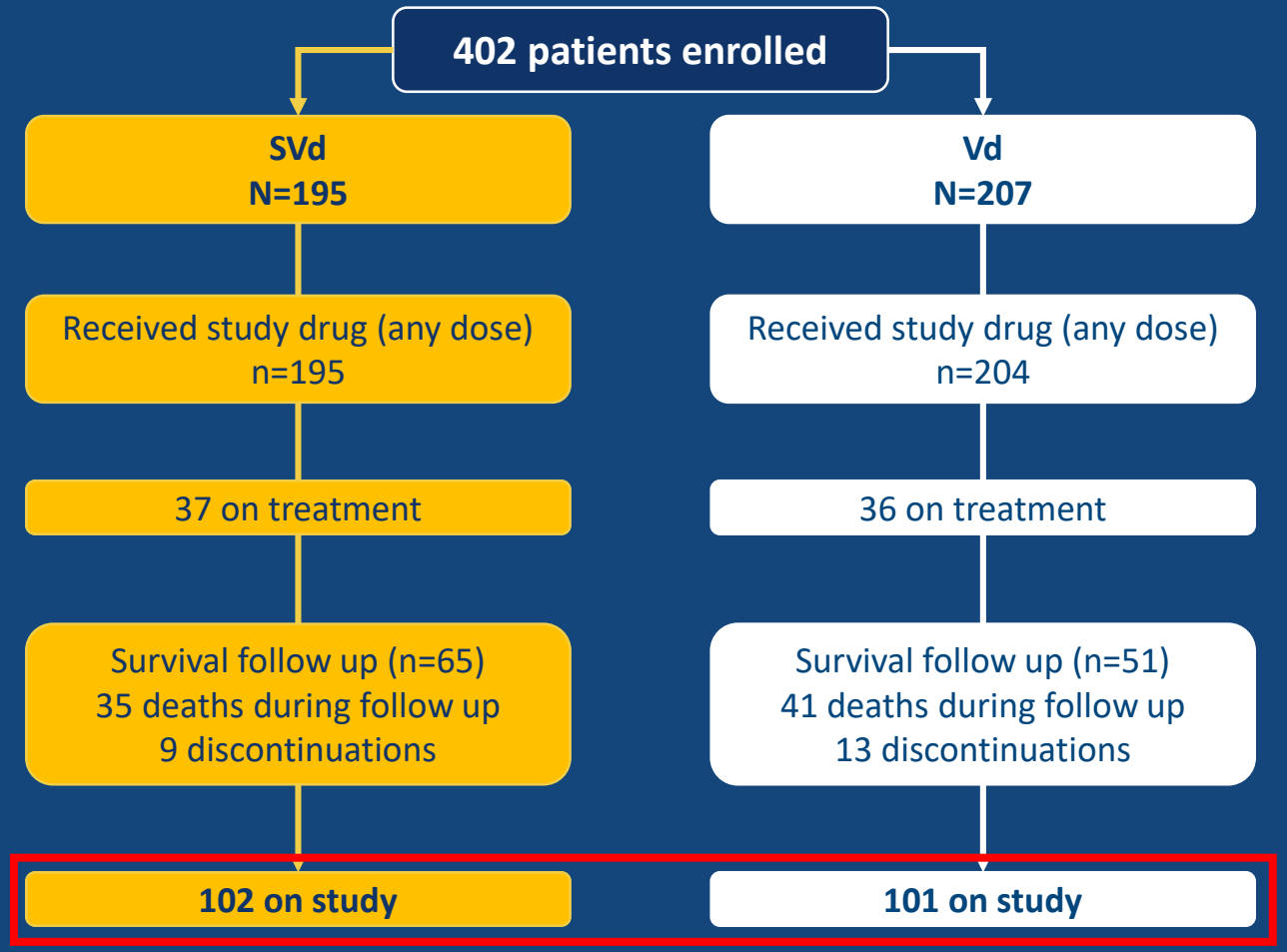
- Progressive measurable MM per IMWG criteria[1]
- 1–3 prior anti-MM regimens (at least a PR to a prior PI, if received)
- Patients with moderate or severe renal impairment (CrCl ≥ 20mL/min) allowed, patients requiring dialysis excluded
- ECOG status score 0–2
- Adequate hepatic and hematopoietic function
  - ANC > 1,000/μL
  - Platelets > 75,000/μL

Key Exclusion Criteria

- > Grade 2 neuropathy or ≥ Grade 2 neuropathy with pain at baseline
- Prior exposure to a SINE, including selinexor
- Prior malignancy that required treatment/had evidence of recurrence
- Concurrent medical condition/disease/active infection
- Active plasma cell leukemia
- MM involving the CNS

1. International Myeloma Working Group (IMWG) Criteria: Kumar S, et al. Lancet Oncology. 2016. Kumar et al. Leukemia 2017.
ANC = absolute neutrophil count, CNS = central nervous system, CrCl = creatinine clearance, ECOG = Eastern Cooperative Oncology Group.

BOSTON Trial: Patient Disposition



	SVd arm N=195	Vd arm N=204
Discontinued Treatment*	**158 (81%)**	**168 (82%)**
Disease progression	**67 (34%)**	**107 (52%)**
AEs/toxicity	**33 (17%)**	**23 (11%)**
Deaths	**12 (6%)**	**12 (6%)**
Patient withdrawal	**37 (19%)**	**18 (9%)**
No information reported	11 (6%)	5 (2%)
Related to AE	9 (5%)	6 (3%)
Other†	17 (9%)	7 (3%)
Discontinued Study	**93 (48%)**	**103 (50%)**
Patient withdrawal	37 (19%)	35 (17%)
Deaths	47 (24%)	61 (30%)
Lost to follow-up/Other	9 (5%)	7 (3%)

*In the SVd arm, 7 and 2 patients discontinued treatment due to physician decision and lost to follow up, respectively. In the Vd arm 5, 2 and 1 patients discontinued treatment due to physician decision, lost to follow up and noncompliance, respectively.
†Other: Logistic reasons (such as patient could not travel to site, patient relocated), hospice (poor health), assessment burden, IRC-approved PD . Data cut-off February 18, 2020.

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BOSTON Trial: Baseline Characteristics

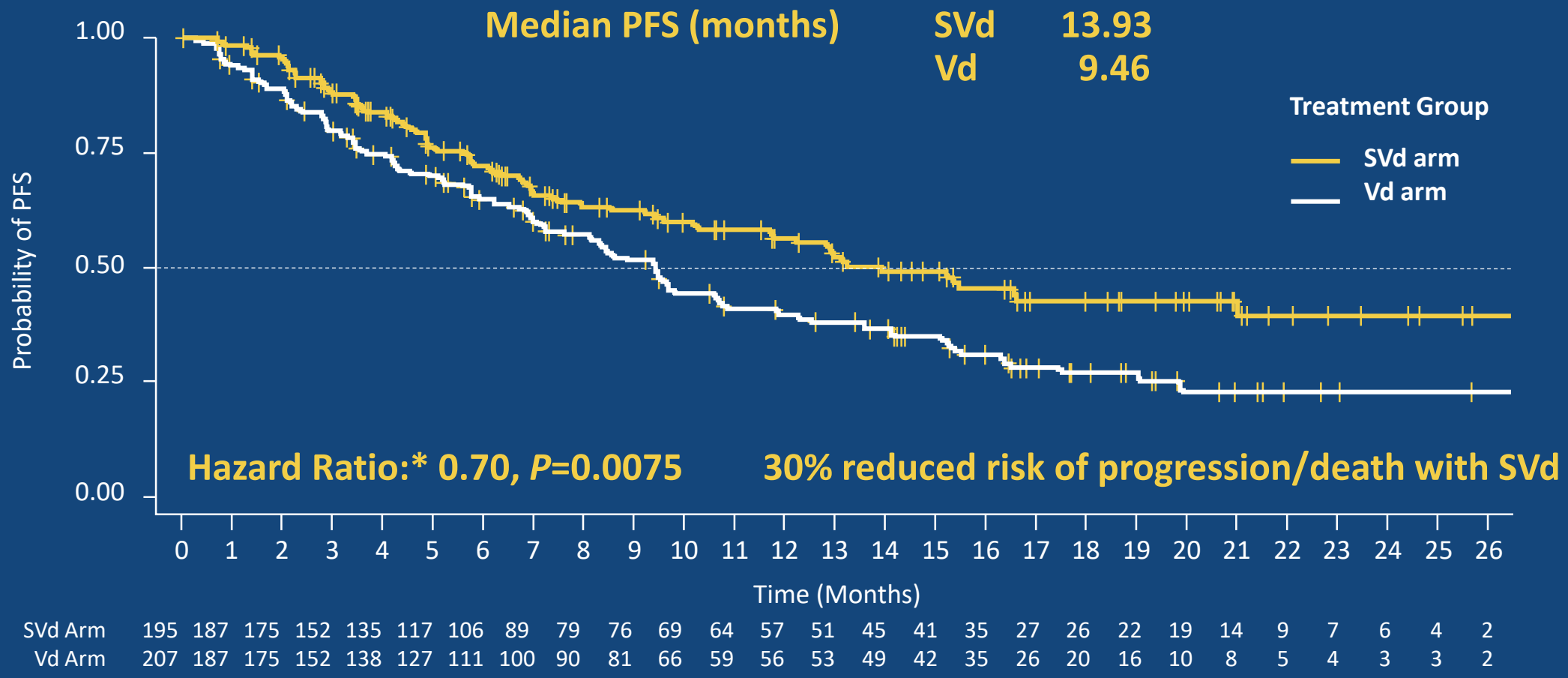
Patient and Disease Characteristics Well Balanced Between Treatment Arms

Characteristic	SVd arm (n=195)	Vd arm (n=207)	
Media Age, years (range)	66 (40, 87)	67 (38, 90)	
≥75 years, n (%)	34 (17)	47 (23)	
Male, n (%)	115 (59)	115 (56)	
Creatinine Clearance, mL/min, n (%)			
<30	3 (2)	10 (5)	
30-60	53 (27)	60 (29)	
Time since initial diagnosis, years, (range)	3.8 (0.4, 23.0)	3.6 (0.4, 22.0)	
High Risk Cytogenetic, [del (17p) or t (14;16) or t (4;14) or amp 1q21] n (%)*	97 (50)	95 (46)	
R-ISS disease stage at screening, n (%)			
I or II	173 (89)	177 (86)	
III	12 (6)	16 (8)	
Unknown	10 (5)	14 (7)	
Number of prior lines of therapy, n (%)			
1	99 (51)	99 (48)	
2	65 (33)	64 (31)	
3	31 (16)	44 (21)	
Prior Therapies, n (%)			
Bortezomib	134 (68.7)	145 (70.0)	
Carfilzomib	20 (10.3)	21 (10.1)	
	79.0%	80.1%	
Daratumumab	11 (5.6)	6 (2.9)	
Lenalidomide	77 (39.5)	77 (37.2)	

*Fluorescence in-situ hybridization was performed at a central laboratory and used to assess cytogenetic risk status. 1q21 required at least 3 copies.

BOSTON Trial: PFS Significantly Longer With SVd Compared to Vd

Early and Sustained PFS Benefit (Assessed by IRC)

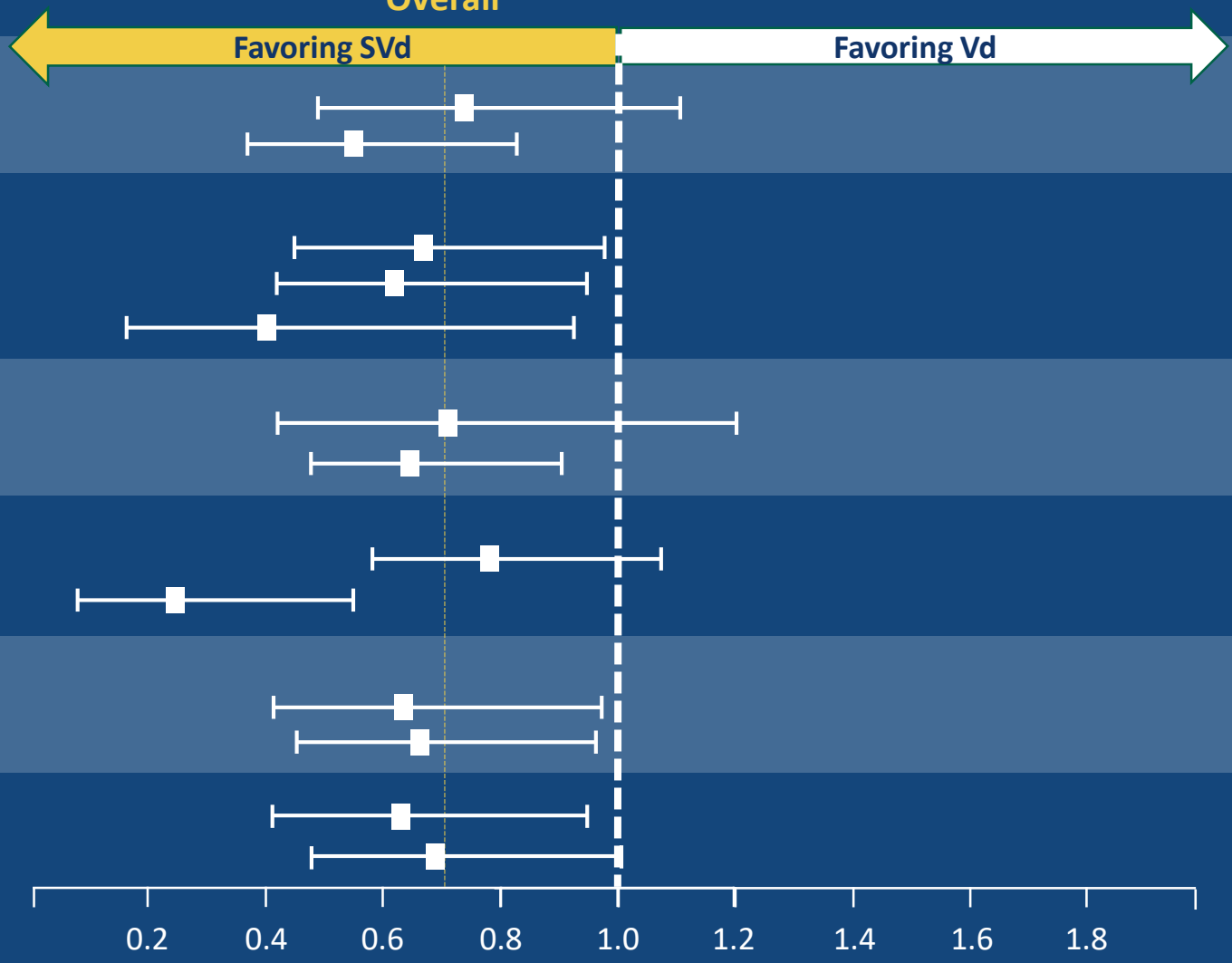


Intention-to-treat (ITT) population N=402, Data cut-off February 18, 2020
*Hazard Ratio 95% CI=0.53–0.93 one-sided *P* value.

Median follow-up: 13.2 and 16.5 months in SVd and Vd arms, respectively.

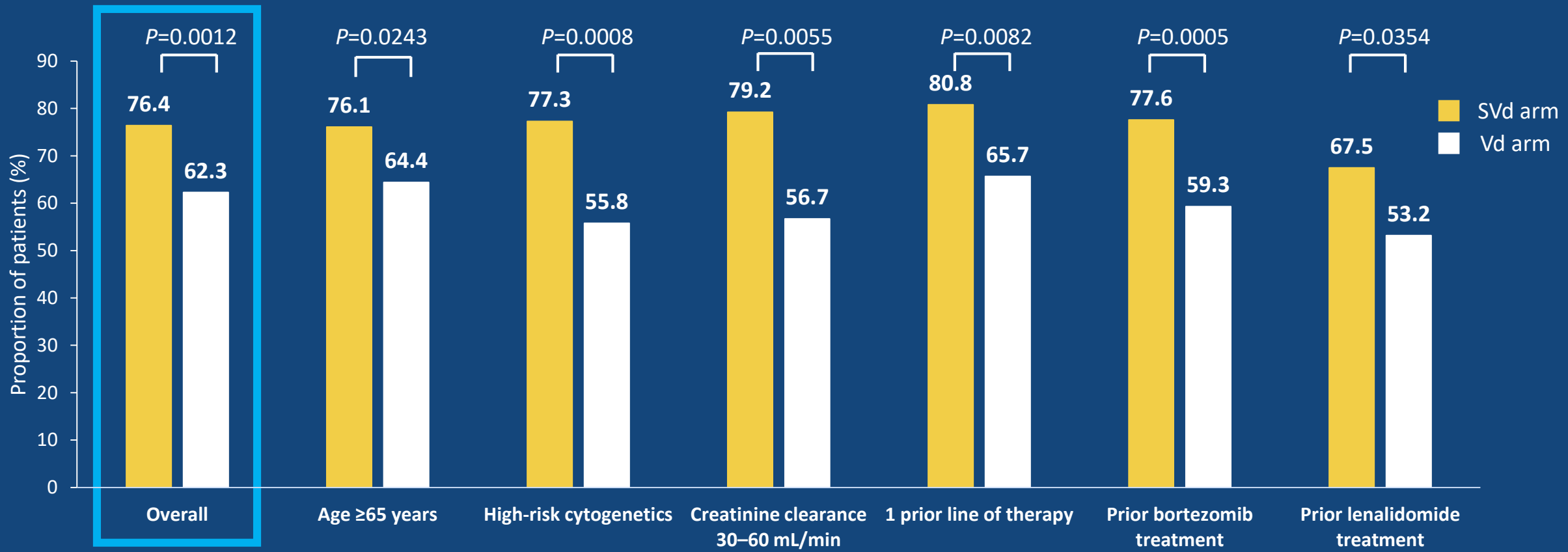
BOSTON Trial: Consistent PFS Benefit for SVd Across Subgroups

Subgroups	# Patients	HR (95% CI)
Age		
<65 years	161	0.74 (0.49–1.11)
≥65 years	241	0.55 (0.37–0.83)
High-risk Cytogenetics		
Yes Del[17p] or t[4;14] or t[14;16] or 1q21	192	0.67 (0.45–0.98)
No	210	0.62 (0.42–0.95)
Del[17p]	37	0.38 (0.16–0.86)
Frailty		
Frail	130	0.69 (0.40–1.17)
Fit	272	0.66 (0.47–0.93)
Previous PI Therapies		
Yes	307	0.78 (0.58–1.06)
No	95	0.26 (0.11–0.60)
Previous lenalidomide Therapy		
Yes	154	0.63 (0.41–0.97)
No	248	0.66 (0.45–0.96)
No. of Prior Lines of Therapy		
1	198	0.63 (0.41–0.95)
2–3	204	0.69 (0.48–1.01)



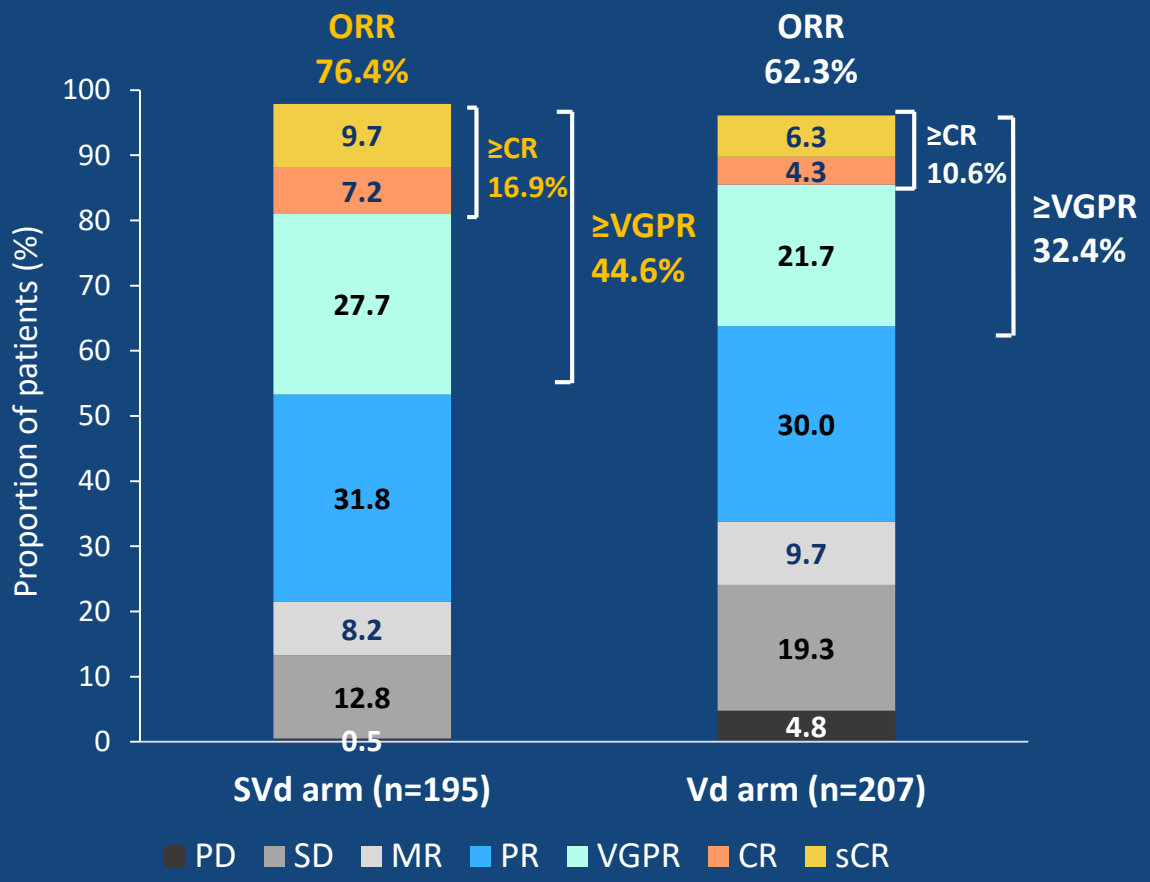
HR = Hazard Ratio, Data cut-off February 18, 2020.

SVd Was Associated With a Significantly Higher ORR Overall and Across Subgroups



One-sided *P* values for the Cochran-Mantel-Haenszel Test based on unstratified model. Data cut-off February 18, 2020.
Overall response, based on Independent Review Committee'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.

SVd: Significantly Higher Rate of Deep Responses (≥VGPR, *P*=0.0082)



Longer duration of response with SVd

	SVd arm (n=149)	Vd arm (n=129)
Median Time to Response (months)†	1.1	1.4
Median Duration of Response (months)*	20.3	12.9

Fewer patients with progressive disease: SVd (n=1, 0.5%) vs Vd (n=10, 4.8%)

CR= complete response, MR = minimal response, PD = progressive disease, PR = partial response, sCR = stringent complete response, SD = stable disease, VGPR = very good partial response. All Responses assessed by an Independent Review Committee (IRC), according to the IMWG criteria (Kumar et all. Lancet Oncology 2016) †Unadjusted Time from date of randomization until first response per IMWG response criteria.
*Duration of the time interval between the first IRC-confirmed PR or better response and the first IRC-confirmed PD or death due to any cause, whichever occurred first. Data cut-off February 18, 2020.

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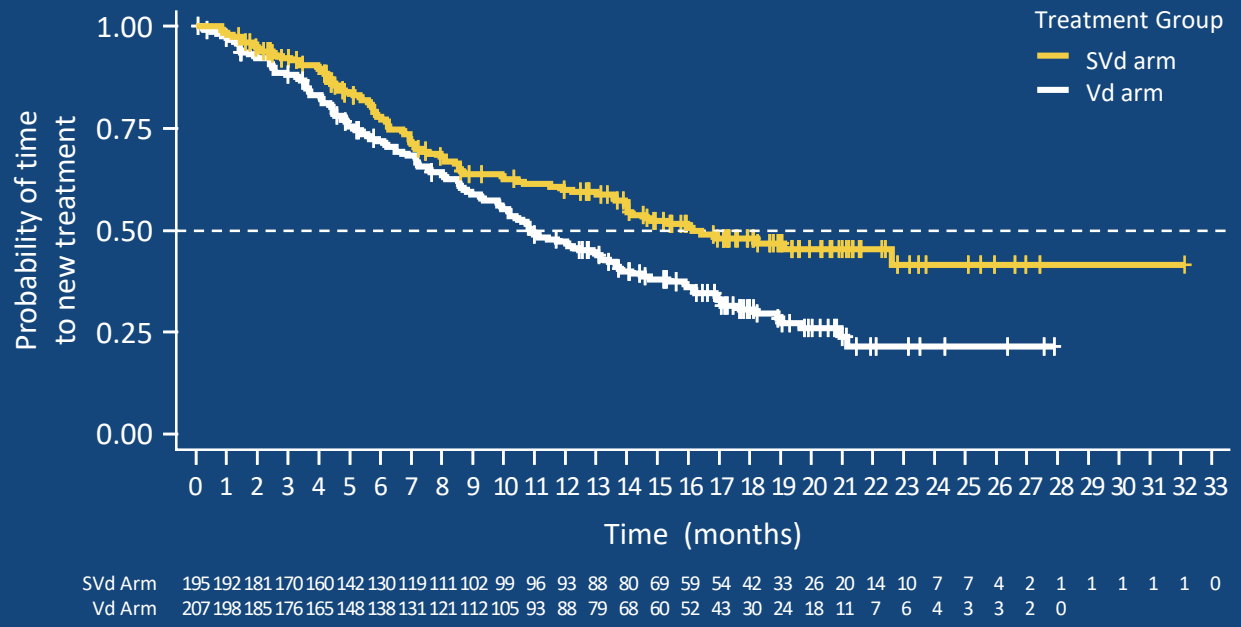
BOSTON Trial: Time to Next Therapy Analysis and Overall Survival Interim Analysis (109 Deaths [27%])

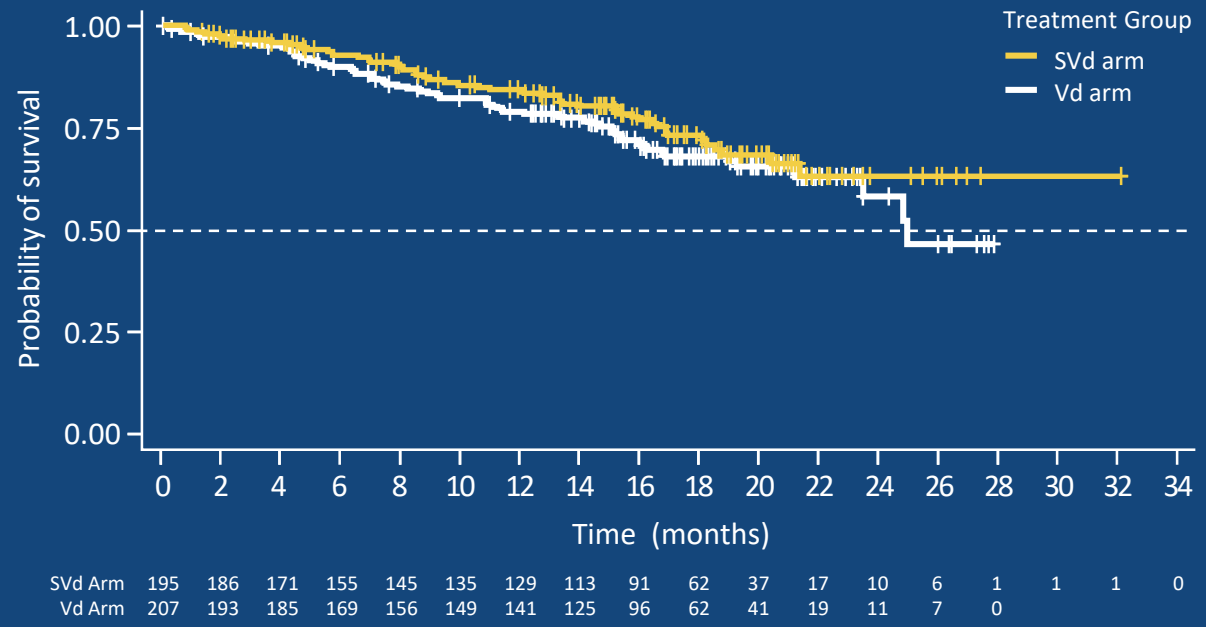
	SVd	Vd
Median TTNT (mos)	16.1	10.8

HR 0.66 (95% CI: 0.50, 0.86) *P=0.0012*



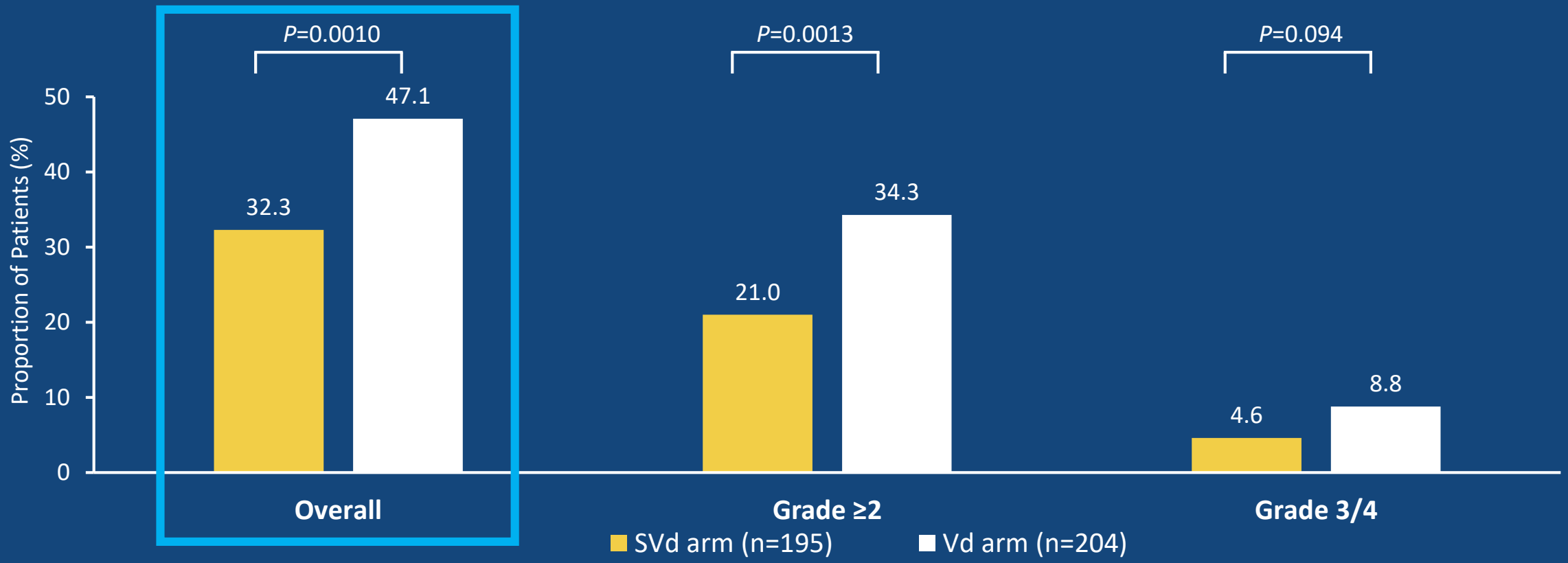
	SVd	Vd
# Death Events (n)	47	62
Median OS (mos)	Not Reached	25

HR 0.84 (95% CI: 0.57, 1.23) *P=0.19*



Intention-to-treat (ITT) population N=402, Median Follow up 17.4 months. HR = Hazard Ratio, OS = Overall Survival, TTNT = Time to Next Therapy. Data cut-off February 18, 2020.

Peripheral Neuropathy Rates Were Significantly Lower With SVd Than With Vd (Both Subcutaneous Bortezomib)



Peripheral neuropathy was the most common AE leading to treatment discontinuation: 4.6% on SVd, 7.4% on Vd

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Data cut-off February 18, 2020.

BOSTON Trial: Safety – Selected Hematological TEAEs*

	SVd (n=195)		Vd (n=204)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematological (%)				
Thrombocytopenia	60.0†	39.5	27.0	17.2
Grade ≥3 bleeding		2.1		1.0
Anemia	36.4	15.9	23.0	9.8
Neutropenia	14.9	8.7	5.9	3.4
Febrile neutropenia		0.5		0.5

- **Thrombopoietin receptor agonists were used to mitigate thrombocytopenia in 35 patients on SVd and 2 patients on Vd, and reduced dose interruptions and reductions**
- **Twelve patients on SVd and 13 patients on Vd received platelet transfusions to manage thrombocytopenia**

*Shown are events that occurred in at least 10% of patients and had a >5% difference between treatment arms. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. For patients who crossed over, adverse events that occurred after the crossover are not included. †Includes 3 fatal events. Data cut-off February 18, 2020.

BOSTON Trial: Safety – Selected Non-Hematological TEAEs*

	SVd (n=195)		Vd (n=204)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Non-hematological (%)				
Nausea	50.3	7.7	9.8	0
Fatigue	42.1	13.3	18.1	1.0
Decreased Appetite	35.4	3.6	5.4	0
Diarrhea	32.3	6.2	25.0	0.5
Peripheral Neuropathy†	32.3	4.6	47.1	8.8
Upper Respiratory Tract Infection‡	29.2	3.6	21.6	1.5
Weight decreased	26.2	2.1	12.3	1.0
Asthenia	24.6	8.2	13.2	4.4
Cataract§	21.5	8.7	6.4	1.5
Vomiting	20.5	4.1	4.4	0

*Shown are events that occurred in at least 15% of patients and had a >5% difference between treatment arms. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. For patients who crossed over, adverse events that occurred after the crossover are not included. †Includes high-level term Peripheral Neuropathies NEC. ‡Includes upper respiratory infection, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis and viral upper respiratory tract infection. §Per Ophthalmology exam during 24% patients on the SVd arm versus 8.5% patients on the Vd arm had new-onset cataracts and worsening of cataracts on study was noted in 20.5% patients on the SVd arm versus 7.9% on the Vd arm. Data cut-off February 18, 2020.

BOSTON Trial Conclusions

- **BOSTON is the first trial to assess a once-weekly triplet of the novel oral agent selinexor + subcutaneous bortezomib in MM (1–3 prior therapies) with a treat to progression plan**
- **Once-weekly SVd significantly prolongs PFS (mPFS improvement of 47%, HR 0.70, *P*=0.0075) vs Vd**
  - SVd was superior to Vd across all efficacy endpoints (PFS, ORR, ≥VGPR, TTNT, DoR) including in patients with prior lenalidomide and with del[17p]
  - Median OS not reached with SVd versus 25 months with Vd
- **Once-weekly dosing used in the SVd arm was associated with significantly lower rates and severity of bortezomib induced peripheral neuropathy compared with twice-weekly Vd**
- **Adverse events associated with SVd manageable and reversible**
  - Most common hematological and non-hematological AEs: cytopenia, infections, GI, weight decreased, fatigue, cataract
  - Discontinuation rate due to adverse events was 17% (SVd) and 11% (Vd)

In patients with MM who have received 1–3 prior therapies, including prior lenalidomide or PI

once-weekly oral selinexor + SC Vd offers patients an effective, convenient, IMiD free, novel triplet therapy

requiring ~40% less clinic visits and reduced rate of peripheral neuropathy

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- **Investigators, Co-investigators and Study Teams at each participating center**

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