TERAPIA DEL PAZIENTE TRIPLO REFRATTARIO

SELINEXOR

Sistema Socio Sanitario
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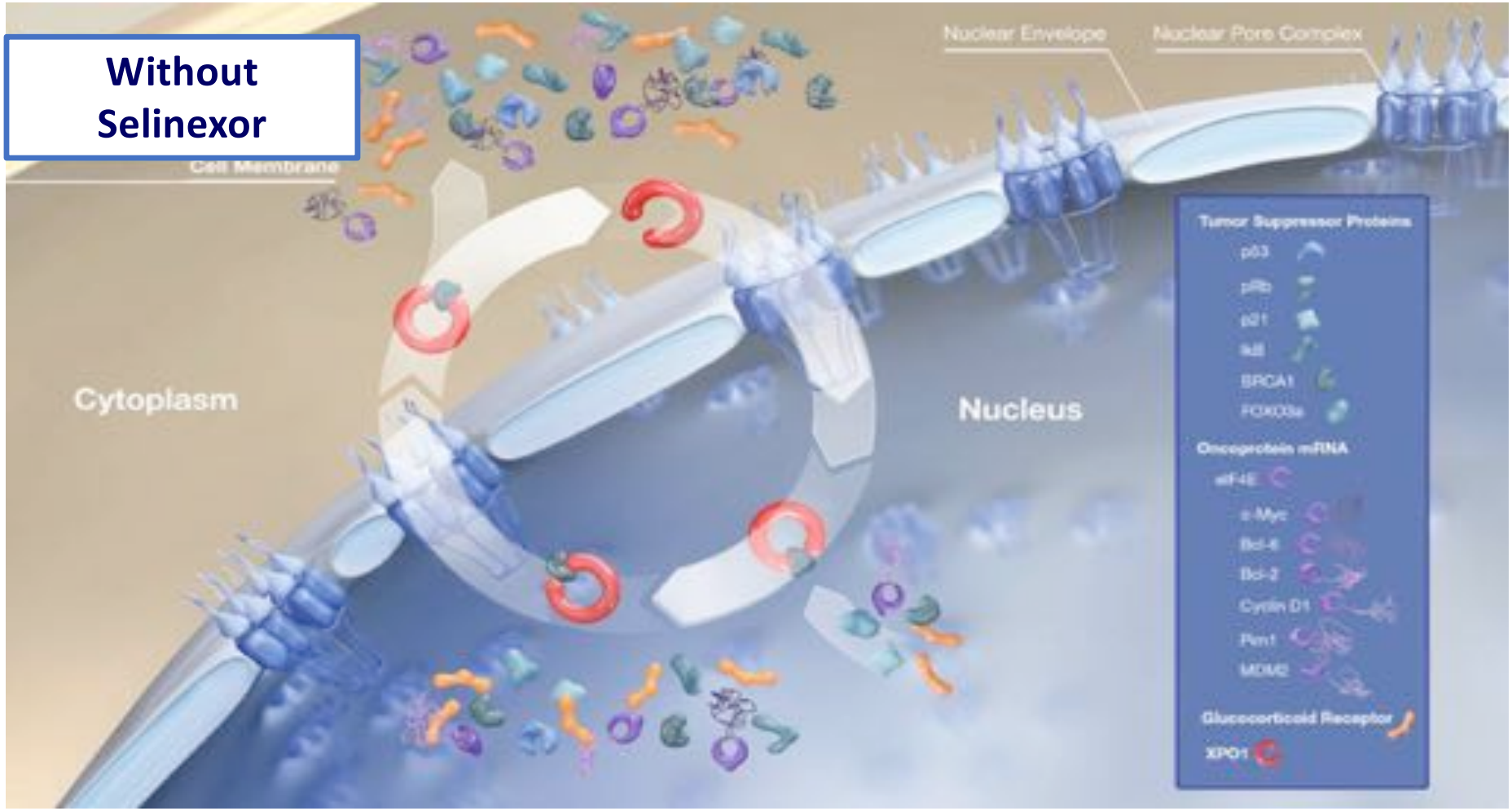
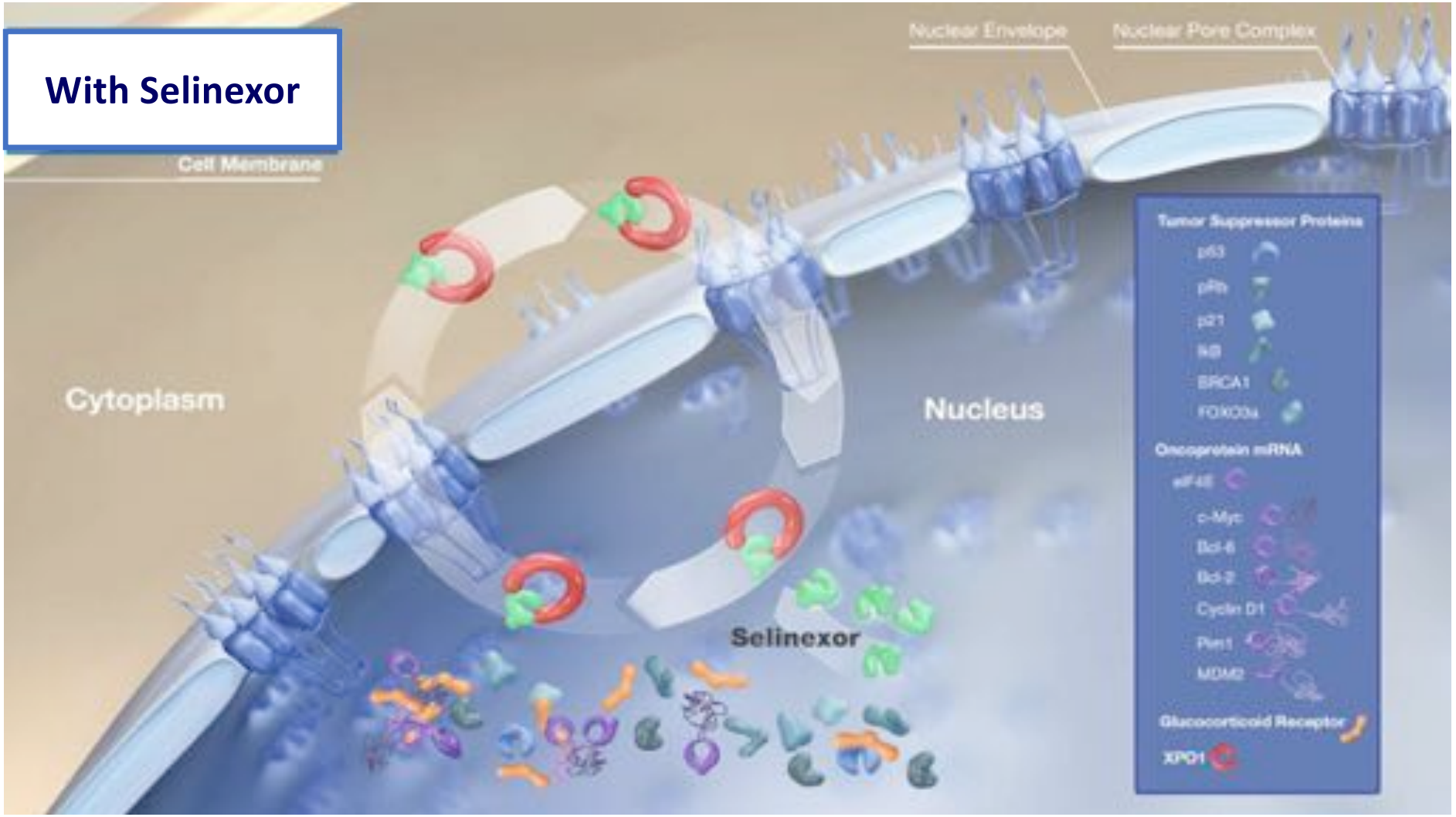
MECHANISM OF ACTION



Adapted from Theodoropulos et al. Targeted Oncology 2020

MECHANISM OF ACTION



Adapted from Theodoropulos et al. Targeted Oncology 2020

MECHANISM OF ACTION

Overexpression of XPO1 results in the mislocation of tumor suppressor proteins such as:

- **TP53**
- **IkBa**
- **Glucocorticoid receptor**
- APC/β-catenin
- FOXO3
- BRCA 1/2
- Survivin
- DNA topoisomerases I and IIa.

Bortezomib-resistant MM cell lines have a 4-fold increase of XPO1

Theodoropulos et al. Targeted Oncology 2020

STORM STUDY

Selinexor-Dex in penta-exposed, triple-refractory patients

Patients previously received ≥3 anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid.

TREATMENT

Oral selinexor (80 mg) plus dexamethasone (20 mg) twice weekly.

Chari et al. NEJM 2019

STORM STUDY

	N = 122
Median age, years (range)	65.2 (40-86)
18-50 years, n (%)	8 (7)
51-64 years, n (%)	52 (43)
65-75 years, n (%)	44 (36)
> 75 years, n (%)	18 (15)
Median time from diagnosis, years (range)	6.6 (1.1-23.4)
Males, n (%)	71 (58)
Creatinine Clearance, n (%)	
< 40 mL/min	14 (11)
< 60 mL/min	39 (32)
High risk cytogenetics, n (%)	65 (53)
Del(17p)	32 (26)
t(4;14)	17 (14)
t(14;16)	5 (4)
Amp 1q21 (> 2 copies)	40 (33)
ECOG Performance Status, n (%)	
0	36 (30)
1	71 (58)
2	11 (9)
Unknown	4 (3)

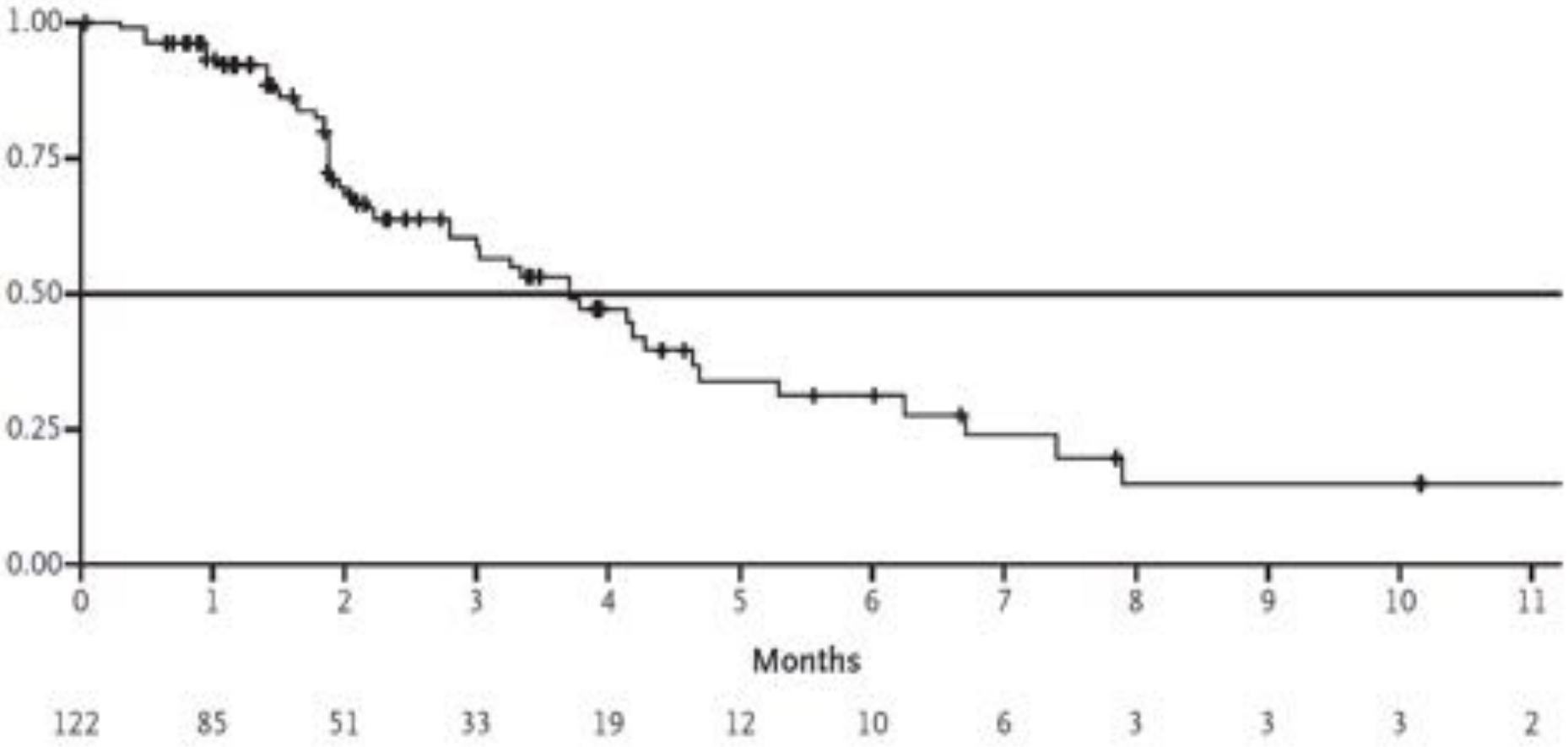
Chari et al. NEJM 2019

STORM STUDY – Primary Endpoint: ORR

Variable	Patients Included in Analysis	Patients with Partial Response or Better	Patients with Minimal Response or Better
	number	*number (percent)*	
Total	122	32 (26)	48 (39)
Previous therapies to which the disease was refractory			
Bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab	83	21 (25)	31 (37)
Carfilzomib, lenalidomide, pomalidomide, and daratumumab	101	26 (26)	37 (37)
Bortezomib, carfilzomib, pomalidomide, and daratumumab	94	25 (27)	36 (38)
Carfilzomib, pomalidomide, and daratumumab	117	31 (26)	45 (38)
R-ISS disease stage			
I	20	7 (35)	10 (50)
II	78	21 (27)	32 (41)
III	23	4 (17)	6 (26)
Measurable free light chains			
Yes	35	15 (43)	19 (54)
No	87	17 (20)	29 (33)
High-risk cytogenetic abnormality†	65	12 (18)	24 (37)

Chari et al. NEJM 2019

STORM STUDY – PFS



Chari et al. NEJM 2019

STORM STUDY – Safety

Most common (≥20%) TEAEs

- Thrombocytopenia* (74%)
- Fatigue† (73%)
- Nausea (72%)
- Anemia‡ (59%)
- Decreased appetite (53%)
- Decreased weight (47%)
- Diarrhea (44%)
- Vomiting (41%)
- Hyponatremia (39%)
- Neutropenia§ (34%)
- Leukopenia (28%)
- Constipation (25%)
- Dyspnea¶ (24%)
- URTI# (21%)

27% of patients permanently discontinued selinexor because of an AE

65% of patients had dose interruptions of selinexor due to AEs

53% of patients had dose reductions of selinexor due to AEs

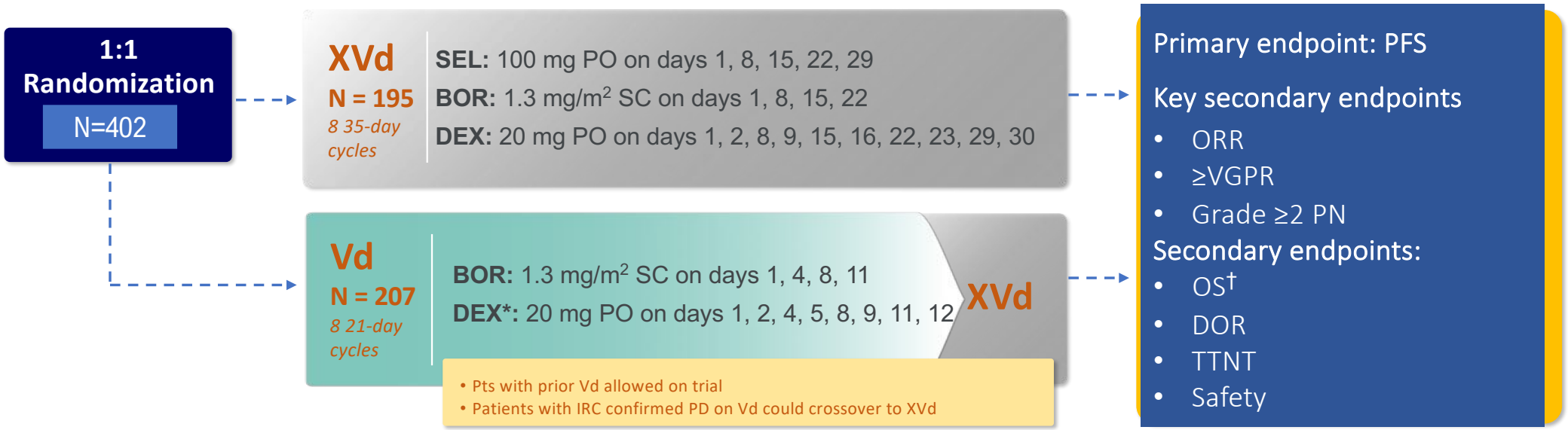
58% of patients receiving selinexor experienced serious AEs

9% of patients experienced fatal AEs

Chari et al. NEJM 2019

BOSTON STUDY

Selinexor-Vel-Dex vs Vel-Dex



Grosicki et al. Lancet 2020

BOSTON STUDY

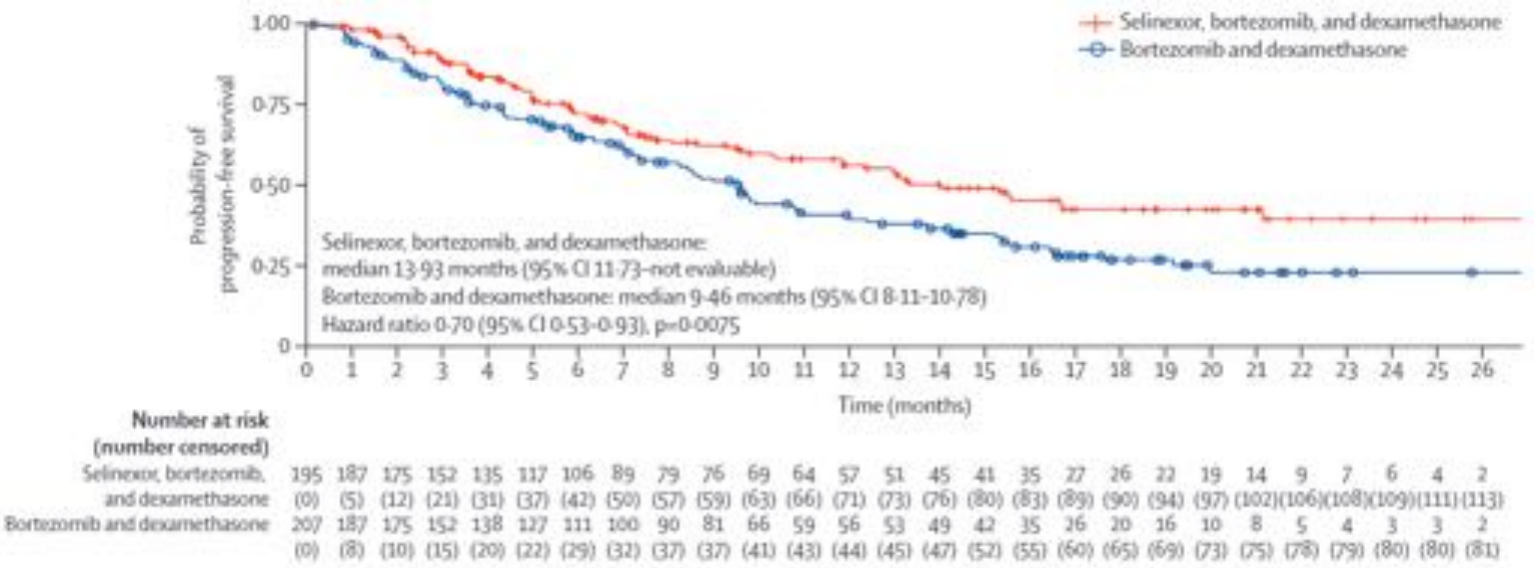
Characteristic	XVd arm (n = 195)	Vd arm (n = 207)
Median Age, years (range)[1]	66 (40, 87)	67 (38, 90)
≥75 years, n (%)	34 (17)	47 (23)
Creatinine Clearance, mL/min, n (%)[1]		
<30	3 (2)	10 (5)
30-60	53 (27)	60 (29)
Time since initial diagnosis, years, (range)[1]	3.8 (0.4, 23.0)	3.6 (0.4, 22.0)
High Risk Cytogenetics, [del (17p) or t (14;16) or t (4;14) or amp 1q21] n (%)[1*]	97 (50)	95 (46)
R-ISS disease stage at screening, n (%)[1]		
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]		
1	99 (51)	99 (48)
2	65 (33)	64 (31)
3	31 (16)	44 (21)
Prior Therapies, n (%)		
Bortezomib[1]	134 (68.7)	145 (70.0)
Carfilzomib[1]	20 (10.3)	21 (10.1)
Daratumumab[1]	11 (5.6)	6 (2.9)
Lenalidomide[1]	77 (39.5)	77 (37.2)
Thalidomide[2]	78 (40.0)	87 (42.0)
IMiD and PI[3]	60 (30.8)	64 (30.9)
Stem cell transplant[1]	76 (39.0)	63 (30.4)

Grosicki et al. Lancet 2020

BOSTON STUDY

PFS

	XVd arm (n = 195)	Vd arm (n = 207)
Median PFS, months (95% CI)	**13.93** (11.73, NE)	**9.46** (8.11, 10.78)
HR=0.70 (95% CI: 0.53, 0.93); one-sided *P* = .0075		



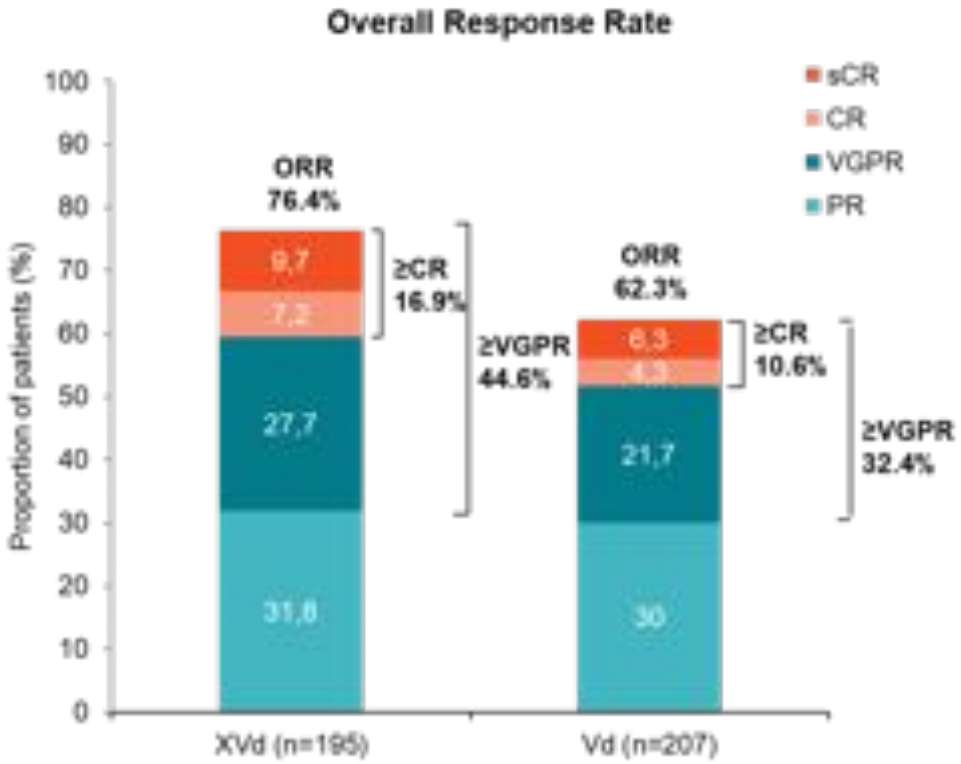
This data represents:

1. An increase of **4.47 months** in median PFS
2. A **30% reduction** in the risk of disease progression

Grosicki et al. Lancet 2020

BOSTON STUDY

ORR



- Key evidence of deep responses:
  - ≥VGPR $P = .0082^{*}$
  - 6% absolute difference in ≥CR
- Clinical benefit was evident in the XVd arm vs the Vd arm:
  - Proportion of patients with progressive disease: 0.5% in the XVd arm vs 5% in the Vd arm

	XVd arm (n = 195)	Vd arm (n = 207)
Median Time to Response, months	1.1	1.4
Median Duration of Response, months	20.3	12.9
Median Time to Next Treatment, months	16.1	10.8

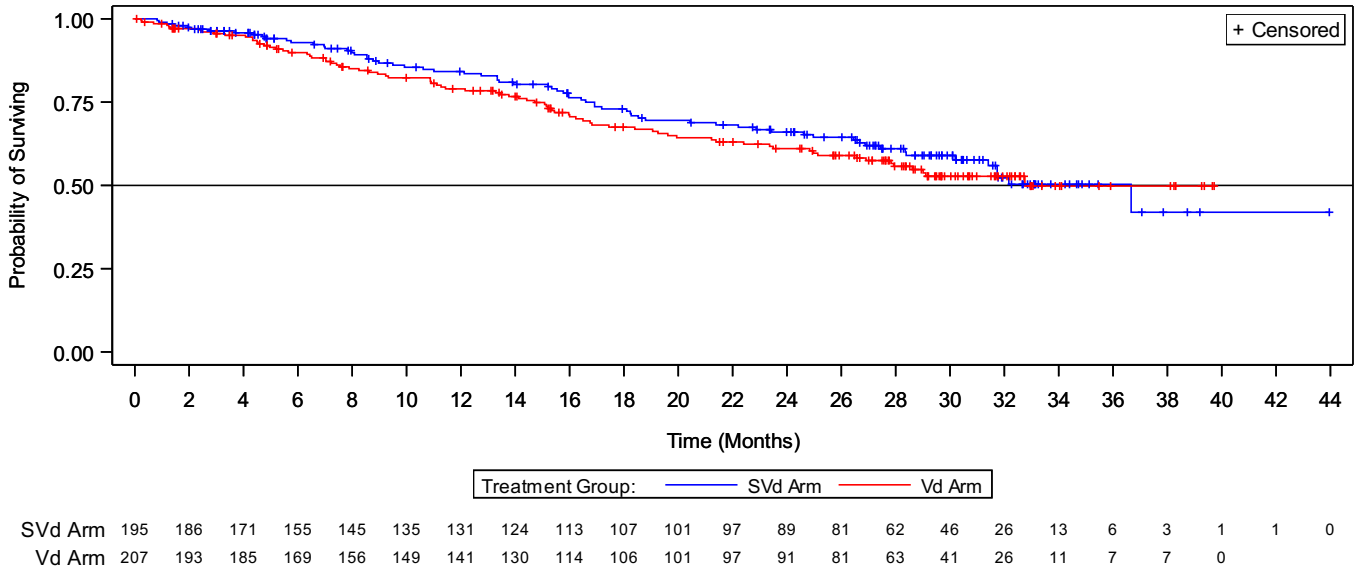
Grosicki et al. Lancet 2020

BOSTON STUDY

OS

Survival data is immature [148 deaths (36.8%)] (As of Data cutoff: Feb 15, 2021)

	XVd arm (n = 195)	Vd arm (n = 207)
Death events, n (%)	68 (34.9)	80 (38.6)
Median OS, mo (95% CI)	36.67 (30.19, NE)	32.76 (27.83, NE)
HR=0.87 (95% CI: 0.63, 1.21); one-sided *P* = .2152		



Grosicki et al. Lancet 2020

BOSTON STUDY

SAFETY

Most Common TEAEs (In ≥10% in either group), n %	XVd arm (n = 195)		Vd arm (n = 204)*	
	Any Grade†	Grade 3/4	Any Grade‡	Grade 3/4
Hematological adverse events				
Thrombocytopenia	117 (60)	77 (39)	55 (27)	35 (17)
Anemia	71 (36)	31 (16)	47 (23)	20 (10)
Neutropenia	29 (15)	18 (9)	12 (6)	7 (3)

Grosicki et al. Lancet 2020

BOSTON STUDY

SAFETY

Most Common TEAEs (In ≥10% in either group), n %	XVd arm (n = 195)		Vd arm (n = 204)*	
	Any Grade†	Grade 3/4	Any Grade‡	Grade 3/4
Non-hematological adverse events				
Fatigue	82 (42)	26 (13)	37 (18)	2 (1)
Nausea	98 (50)	15 (8)	20 (10)	0
Diarrhea	63 (32)	12 (6)	51 (25)	1 (<1)
Peripheral neuropathy§	63 (32)	9 (5)	96 (47)	18 (9)
Decreased appetite	69 (35)	7 (4)	11 (5)	0
Weight loss	51 (26)	4 (2)	25 (12)	2 (1)
Asthenia	48 (25)	16 (8)	27 (13)	9 (4)
Constipation	33 (17)	0	35 (17)	3 (1)
Cough	35 (18)	1 (1)	30 (15)	0
Insomnia	31 (16)	2 (1)	32 (16)	4 (2)
Back pain	30 (15)	1 (1)	29 (14)	2 (1)
Pneumonia¶	35 (18)	24 (12)	34 (17)	21 (10)
Pyrexia	30 (15)	3 (2)	22 (11)	2 (1)
Cataract	42 (22)	17 (9)	13 (6)	3 (1)
Vomiting	40 (21)	8 (4)	9 (4)	0
Peripheral edema	23 (12)	1 (1)	26 (13)	0
Dyspnea	18 (9)	1 (1)	27 (13)	5 (2)
Bronchitis	24 (12)	3 (2)	20 (10)	1 (<1)
URTI	35 (18)	5 (3)	30 (15)	1 (<1)

Grosicki et al. Lancet 2020

BOSTON STUDY

DISCONTINUATION DUE TO AEs

Event, %	XVd Arm (n = 195)	Vd Arm (n = 204)
Any TEAE	21.0	15.7
Peripheral Neuropathy	4.6	7.4
Fatigue/Asthenia	4.6	1.5
Nausea	3.1	0
Decreased appetite	2.1	0.5
Thrombocytopenia	2.1	0.5
Vomiting	2.1	0

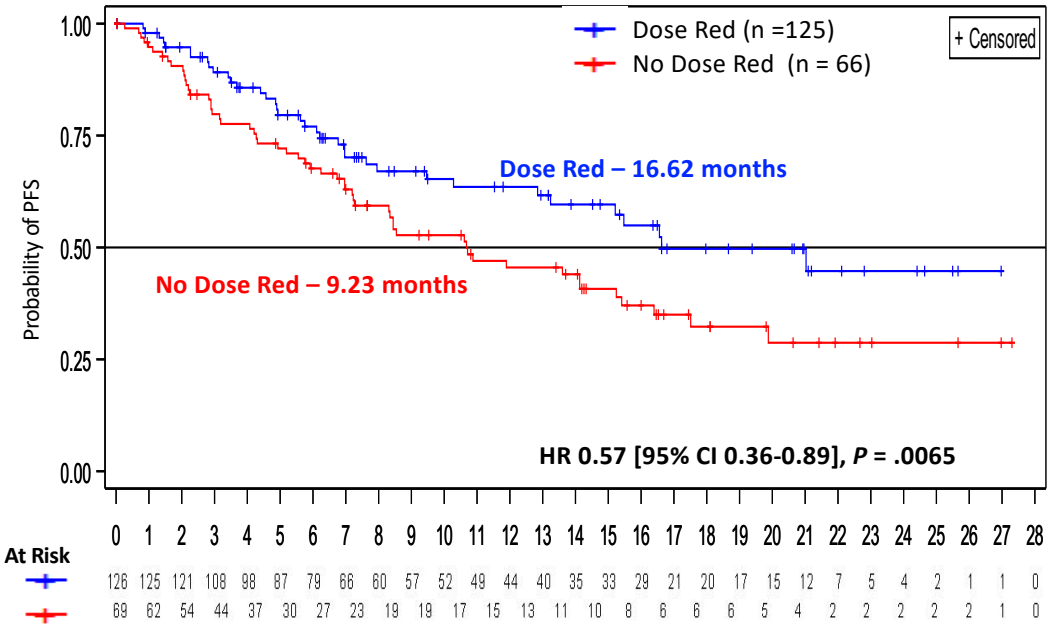
Grosicki et al. Lancet 2020

BOSTON STUDY

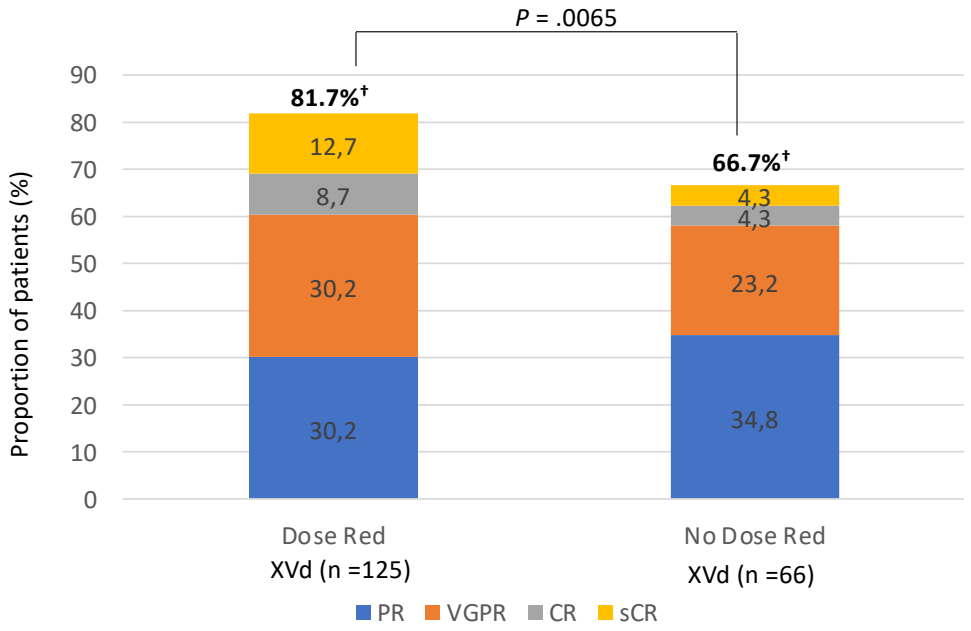
Dose Reductions due to AEs

XVd	Vd
72.3%	51.0%

PFS by Dose Reduction in Patients in the XVd arm



ORR Rates by Dose Reduction of Selinexor in the XVd arm



Grosicki et al. Lancet 2020

BOSTON STUDY – Subgroup Analisys

High Risk Cytogenetics

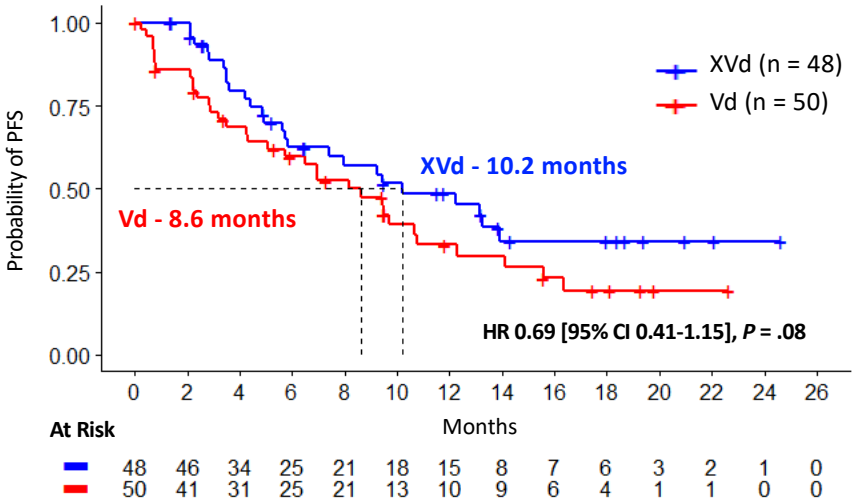
Characteristic	XVd		Vd	
	High Risk (n = 70)	Standard Risk (n = 125)	High Risk (n = 71)	Standard Risk (n = 136)
Median Age, years (range)	67 (45-84)	65 (40-87)	67 (49-90)	67 (38-84)
Years since diagnosis to enrollment, median (range)	3.5 (1.1-23.0)	4.1 (0.4 -21.5)	3.0 (0.6-22.0)	3.8 (0.4-18.4)
High Risk Cytogenetics, n (%)				
del(17p)	21 (10.8)	--	16 (7.7)	--
t(14;16)	7 (3.6)		11 (5.3)	
t(4;14)	22 (11.3)		27 (13.0)	
amp 1q21 (≥4 copies)	43 (22.1)		39 (18.8)	
del(17p) **or** t(14;16) **or** t(4;14) **or** amp 1q21	70 (35.9)		71 (34.3)	
Number of prior lines of therapy, n (%)				
1	35 (50.0)	64 (51.2)	32 (45.1)	67 (49.3)
2	22 (31.4)	43 (34.4)	20 (28.2)	44 (32.4)
3	13 (18.6)	18 (14.4)	19 (26.8)	25 (18.4)
Prior ASCT, n (%)	26 (37.1)	50 (40.0)	28 (39.4)	35 (25.7)

Grosicki et al. Lancet 2020

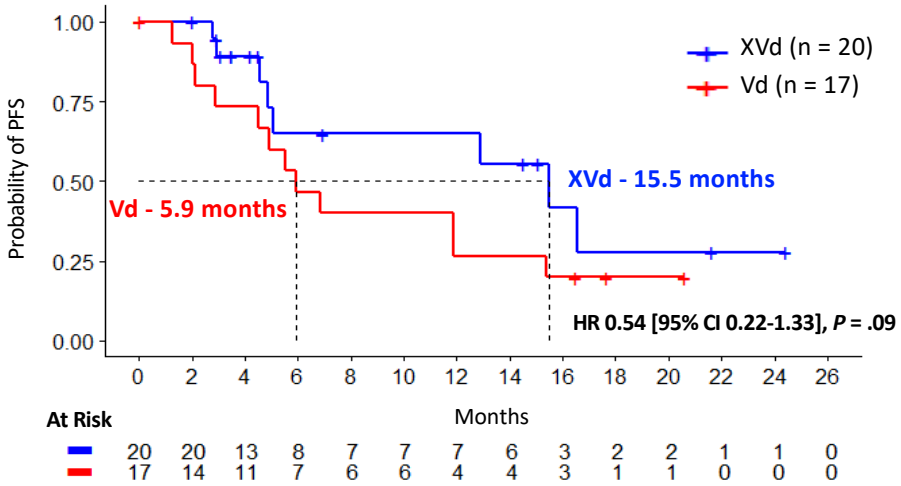
BOSTON STUDY – Subgroup Analisys

High Risk Cytogenetics

PFS in Patients With 1 Cytogenetic Abnormality



PFS in Patients With ≥2 Cytogenetic Abnormalities

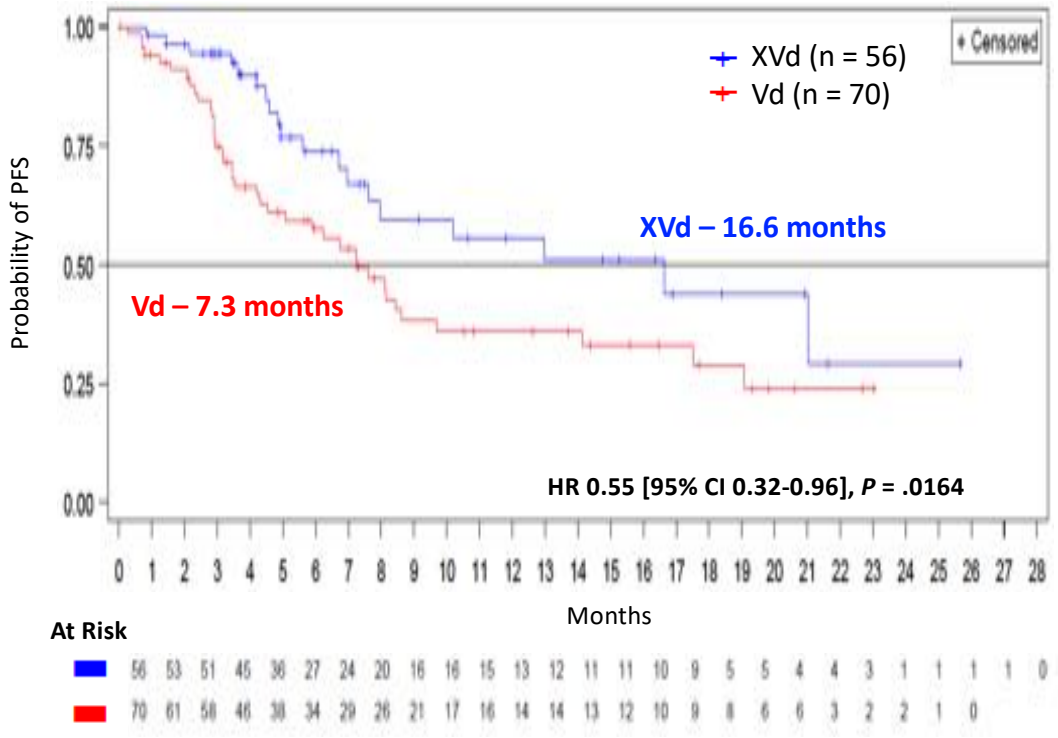


Grosicki et al. Lancet 2020

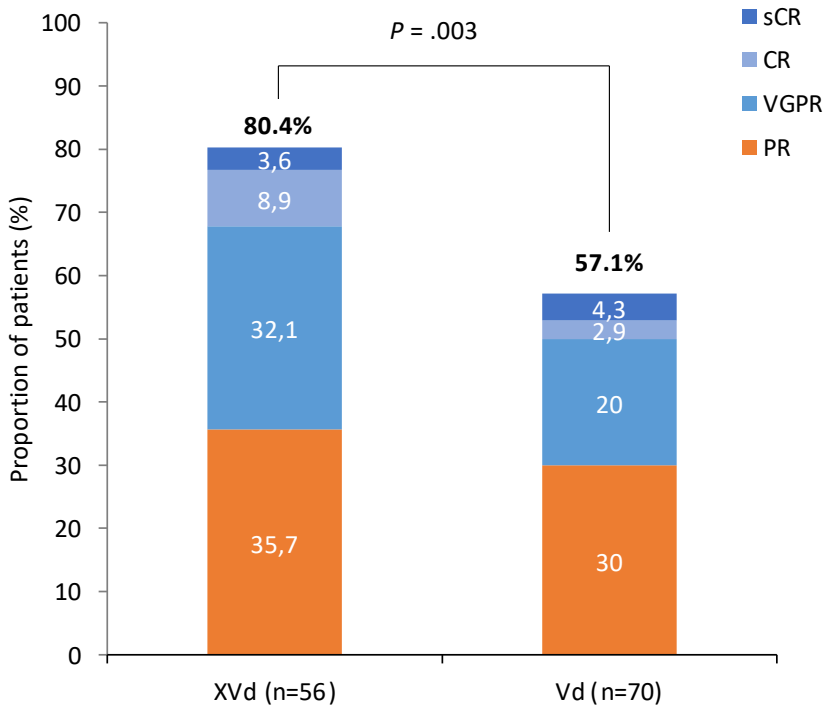
BOSTON STUDY – Subgroup Analisys

Renal Impairment

PFS in Patients with Creatinine Clearance ≤60 mL/min



Overall Response Rate in Patients with Creatinine Clearance ≤60 mL/min



Grosicki et al. Lancet 2020

BOSTON STUDY – Subgroup Analisys

Lenalidomide refractory

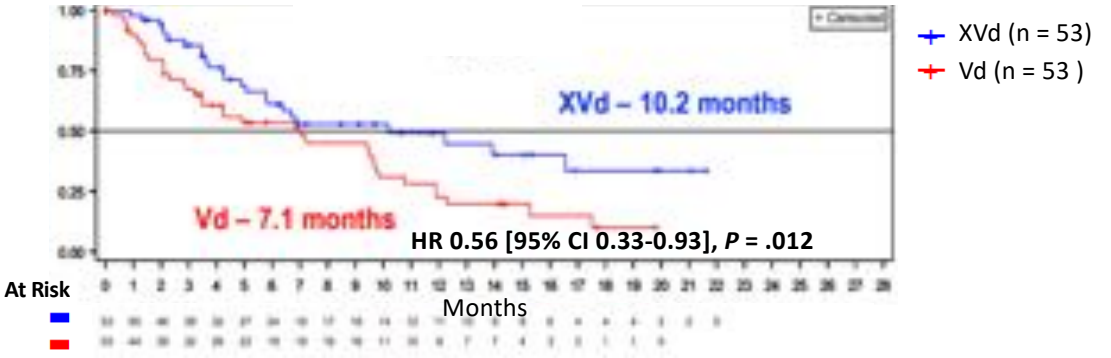
Characteristic	XVd		Vd	
	Len Ref (n = 53)	Not Len Ref (n = 142)	Len Ref (n = 53)	Not Len Ref (n = 154)
Age, median (range)	65 (40-87)	66 (42-84)	66 (45-85)	67 (38-90)
Males, n (%)	37 (69.8)	78 (54.9)	29 (54.7)	86 (55.8)
Number of prior regimens, n (%)				
1	16 (30.2)	83 (58.5)	14 (26.4)	85 (55.2)
2	21 (39.6)	44 (31.0)	20 (37.7)	44 (28.6)
3	16 (30.2)	15 (10.6)	19 (35.8)	25 (16.2)

Grosicki et al. Lancet 2020

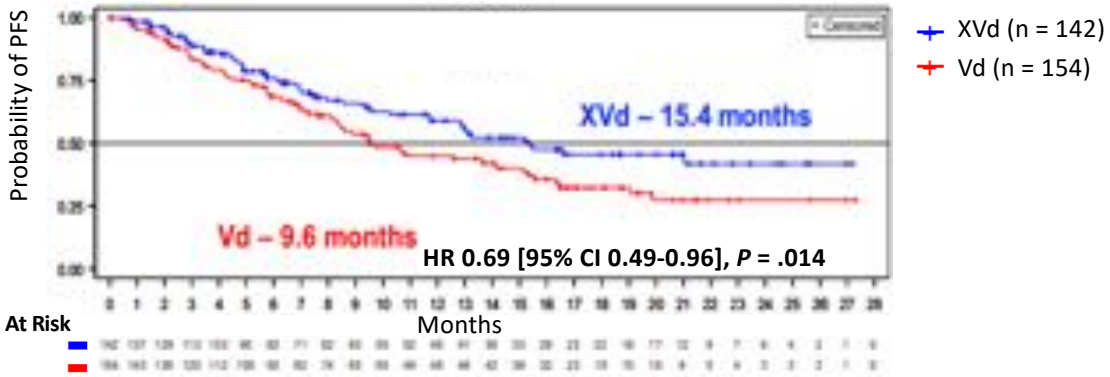
BOSTON STUDY – Subgroup Analisys

Lenalidomide refractory

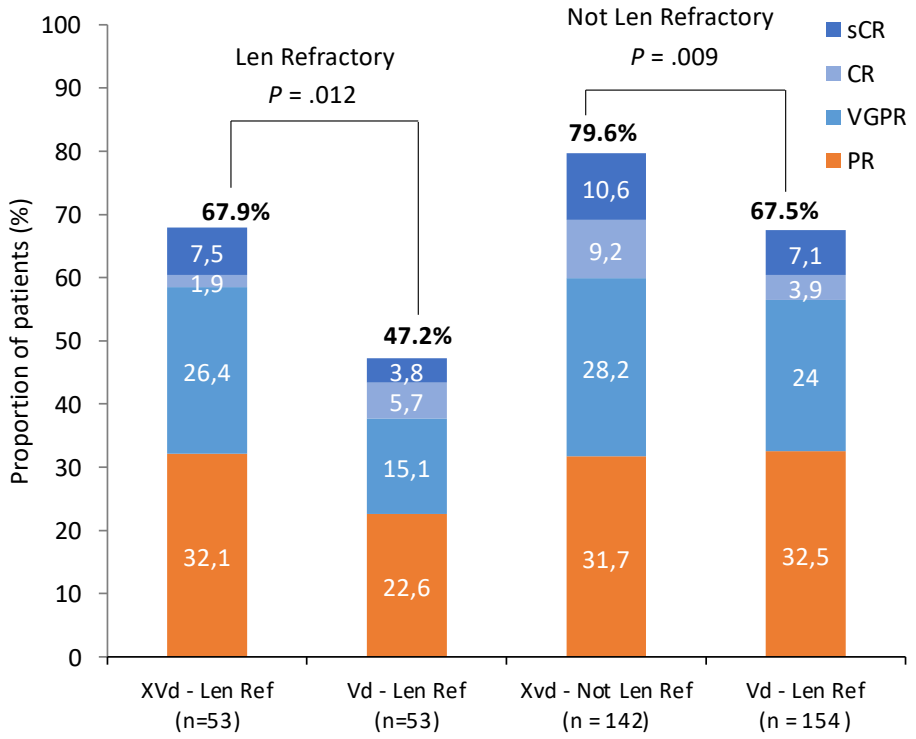
PFS in Patients Who Were Len Refractory



PFS in Patients Who Were Not Len Refractory



Overall Response Rate in Patients Based on Len-Refractory Status



Grosicki et al. Lancet 2020

STOMP STUDY – Phase 1b-2 Trial

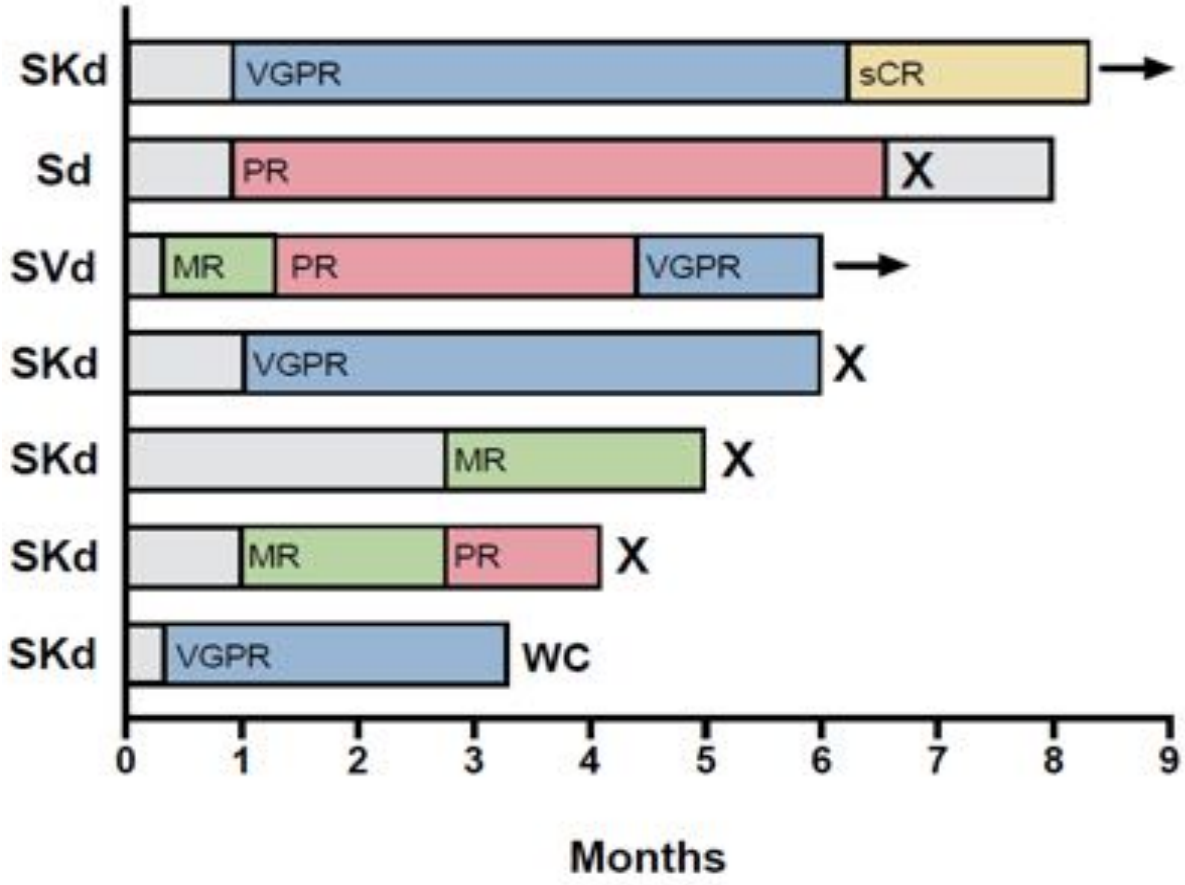
ARM 1	Selinexor	Dexamethasone	**Pomalidomide**	Relapsed/Refractory
ARM 2	Selinexor	Dexamethasone	**Bortezomib**	Relapsed/Refractory
ARM 3	Selinexor	Dexamethasone	**Lenalidomide**	Relapsed/Refractory
ARM 4	Selinexor	Dexamethasone	**Pomalidomide + Bortezomib**	Relapsed/Refractory
ARM 5	Selinexor	Dexamethasone	**Daratumumab**	Relapsed/Refractory
ARM 6	Selinexor	Dexamethasone	**Carfilzomib**	Relapsed/Refractory
ARM 7	Selinexor	Dexamethasone	**Lenalidomide**	Newly diagnosed
ARM 8	Selinexor	Dexamethasone	**Ixazomib**	Relapsed/Refractory
ARM 9	Selinexor	Dexamethasone	**Pomalidomide + Elotuzumab**	Relapsed/Refractory
ARM 10	Selinexor	Dexamethasone	**Belantamab Mafodotin**	Relapsed/Refractory
ARM 11	Selinexor	Dexamethasone	**Pomalidomide + Daratumumab**	Relapsed/Refractory

Selinexor-containing regimens for patients relapsed after anti-BCMA CAR-T cells

	1	2	3	4	5	6	7
Age	66	70	62	35	62	67	64
Sex	F	F	M	M	M	F	F
Ethnic Origin	White	White	White	White	White	White	White
ECOG Performance Status	1	0	1	1	1	1	1
ISS Staging at Diagnosis	III	II	I	II	I	II	Unknown
Time from Initial Diagnosis (Years)	6.3	15.9	9.8	8.9	10.0	4.8	8.0
Cytogenetics	t(14;16)	Gain (1q21), trisomy 3, 7, 9 plus IGH translocation	t(4; 14)	Hyperdiploidy with +1q and trisomy 9, 11, 15	t(4;14)	+1q, t(4;14), del 13	Complex hyperdiploid karyotype with del 1p
Extramedullary Plasmacytomas ≥ 1	No	Yes (2 sites)	No	Yes (2 sites)	Yes (2 sites)	Yes (3 sites)	Yes (1 site)
LDH at Baseline (U/L)	202	161	176	186	205	245	225
Prior Therapeutic Regimens (N)	10	15	7	5	11	6	12

Chari et al. ASH 2019

Selinexor-containing regimens for patients relapsed after anti-BCMA CAR-T cells



Chari et al. ASH 2019

CONCLUSIONS

Selinexor has a new and interesting mechanism of action, potentially effective in multi-refractory MM patients.

Safety is an issue, however, treatment of less advanced patients can show a better tolerability.

Selienexor needs to be combined with other drugs.

The real potentiality of Selinexor is object of active study.