Highlights from
IMS 20th meeting 2023

Massimo Gentile

Terapie del MM refrattario con nuovi agenti/classi di farmaci

Con inibitore di XPO1 (con/senza PI o IMiD)

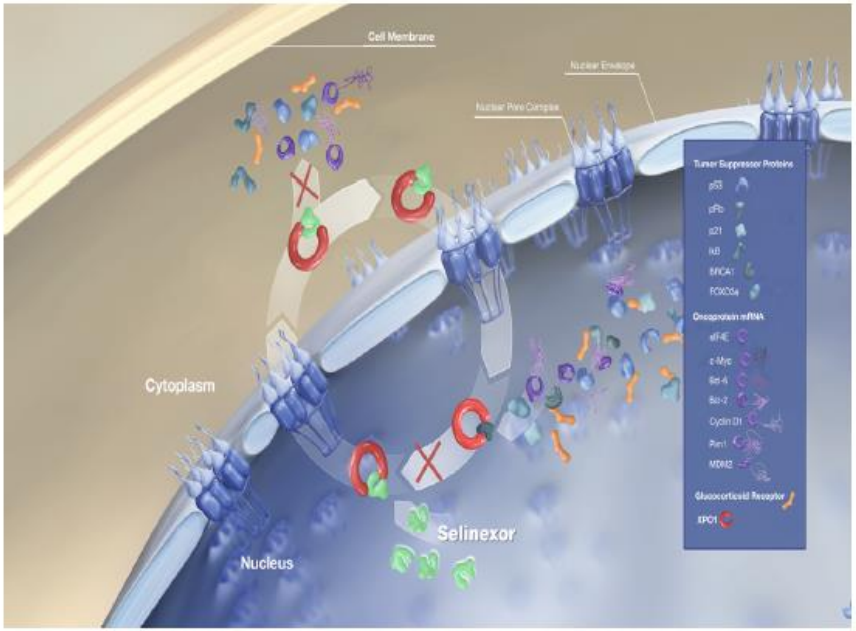
30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

Disclosures of Massimo Gentile

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BMS						x	
Menarini						x	
Janssen						x	

Selinexor:

First in Class, Oral Selective Inhibitor of Nuclear Export (SINE)[1-3]



[1]Schmidt et al., Leukemia, 2013, [2]Tai et al., Leukemia, 2013, [3]Argueta et al., Oncotarget, 2018

Exportin 1 (XPO1) is the major nuclear export protein for:

- Tumor suppressor proteins (TSPs, e.g p53, IκB and FOXO)
- Glucocorticoid receptor (GR)
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, BCL-xL, cyclins)

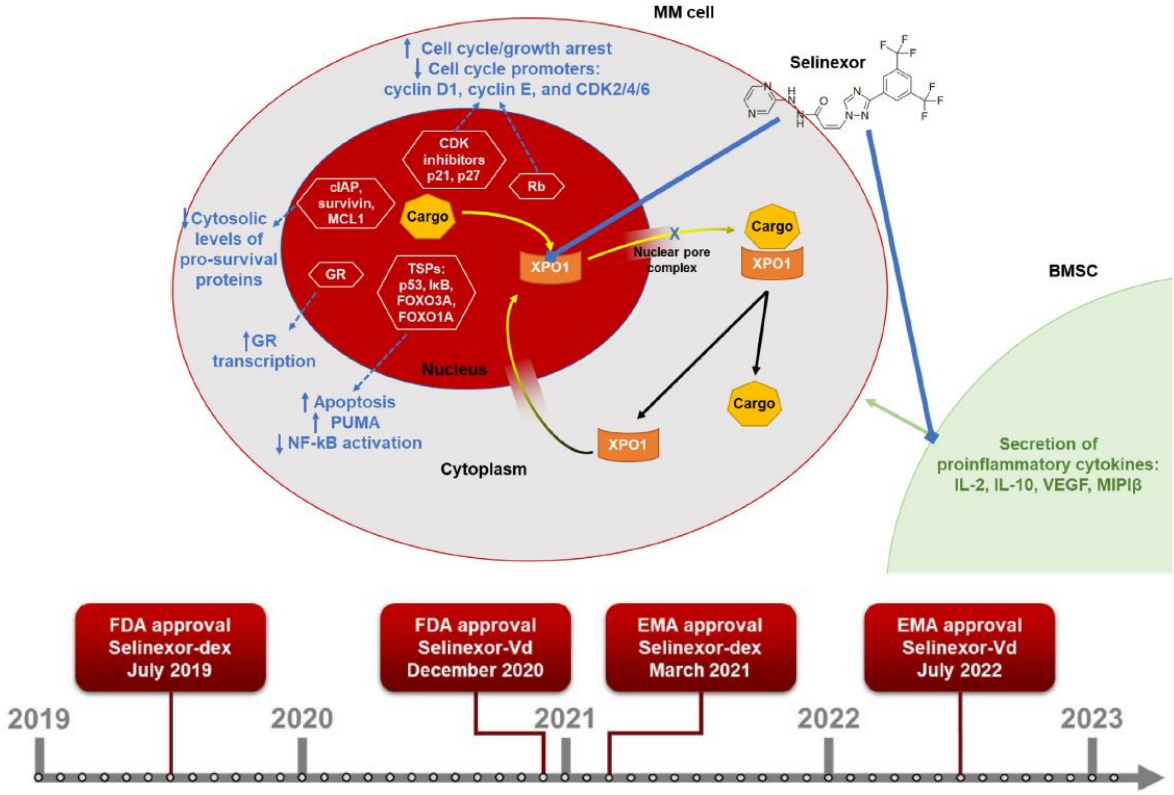
XPO1 is overexpressed in MM:

- High **XPO1** levels enable cancer cells to escape TSP mediated cell cycle arrest and induction of apoptosis
- **XPO1** levels correlate with poor prognosis and drug resistance

Selinexor is an oral selective **XPO1** inhibitor; preclinical data supports that selinexor :

- Reactivates multiple TSPs relevant to MM, inhibits NF-κB signaling and reduces c-Myc levels
- In combination with dexamethasone (dex) reactivates GR signaling

Schematic of the role of XPO1 in transporting various cargoes from the nucleus to the cytoplasm and the effects of XPO1 inhibition with selinexor



Mo CC et al EJHaem 2023

Selinexor + dexamethasone: Initial Clinical data for RRMM

Phase 1 Clinical Trial of Selinexor (Chen et al, Blood 2017) (N=81 patients):

- Enrolled patients with heavily pretreated MM
- R2PD was Selinexor 45 mg/m^2 (~80 mg) and dex (20 mg) given twice weekly
- The combination demonstrated an ORR of 50% (n=12 patients)

Phase 2b STORM Clinical Trial Part 1 (Vogl et al, JCO 2018) (N=79 patients)

- Enrolled both quad- (B,C,L,P) or penta-refractory (B,C,L,P, anti-CD38) MM
- Selinexor/dexamethasone was administered either 3/4 or 4/4 weeks
- Main side effects: nausea, anorexia, fatigue, thrombocytopenia, hyponatremia, and anemia
- Overall response rate (ORR) of 21%

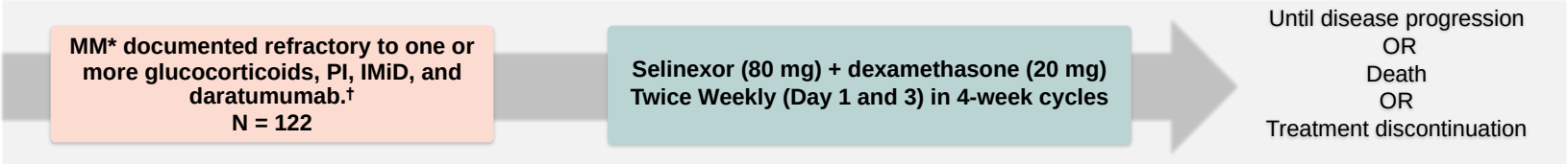
STORM Part 2: Expansion in Triple-class Refractory MM

Study Design

Phase 2b, multicenter, open-label study [NCT02336815]

Patient Population

Penta-refractory MM previously treated with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, an alkylating agent, and glucocorticoids



Key Inclusion Criteria

- Previously received ≥3 anti-MM regimens including: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid
- Adequate renal function: creatinine clearance ≥ 20 mL/min (Cockcroft/Gault); adequate hepatic function
- ECOG performance status ≤ 2
- Adequate hematopoietic function: ANC ≥ 1,000/mm^3, hemoglobin ≥ 8.5 g/dL, platelets ≥ 75,000/mm^3 (≥ 50,000/mm^3 if ≥ 50% of bone marrow nucleated cells are plasma cells)

Primary Endpoint

- ORR

Secondary Endpoints

- DOR
- CBR
- OS
- PFS
- Safety

Chari A, et al. *N Engl J Med*. 2019;381(8):727-738.

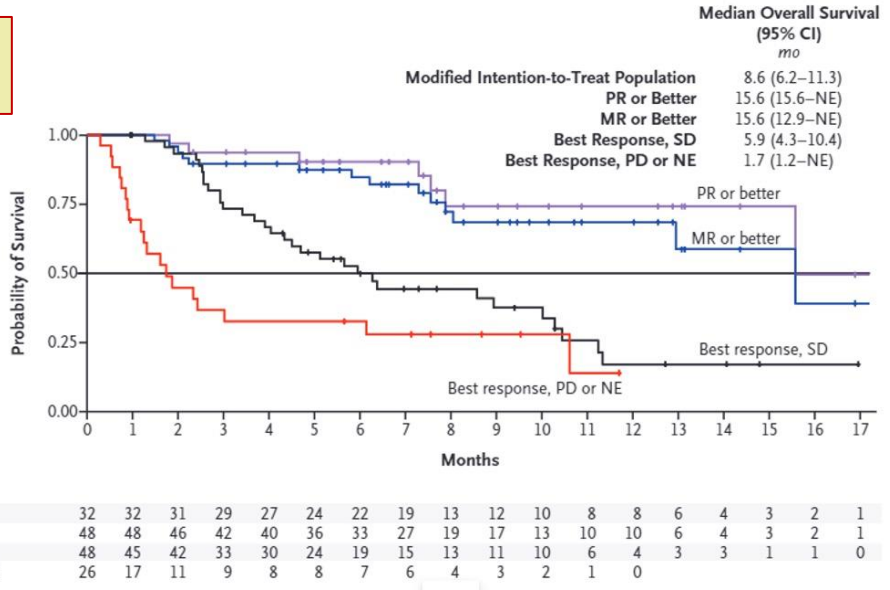
STORM Part 2: Expansion in Penta-Refractory MM

Activity

	N = 122
ORR, %	26
sCR	2
VGPR	5
PR	20
MR	13
SD	39
PD/NE	21
Median DOR, months	4.4
Median PFS, months	3.7

Penta-refractory
ORR 25.3%

Overall Survival by Best Response

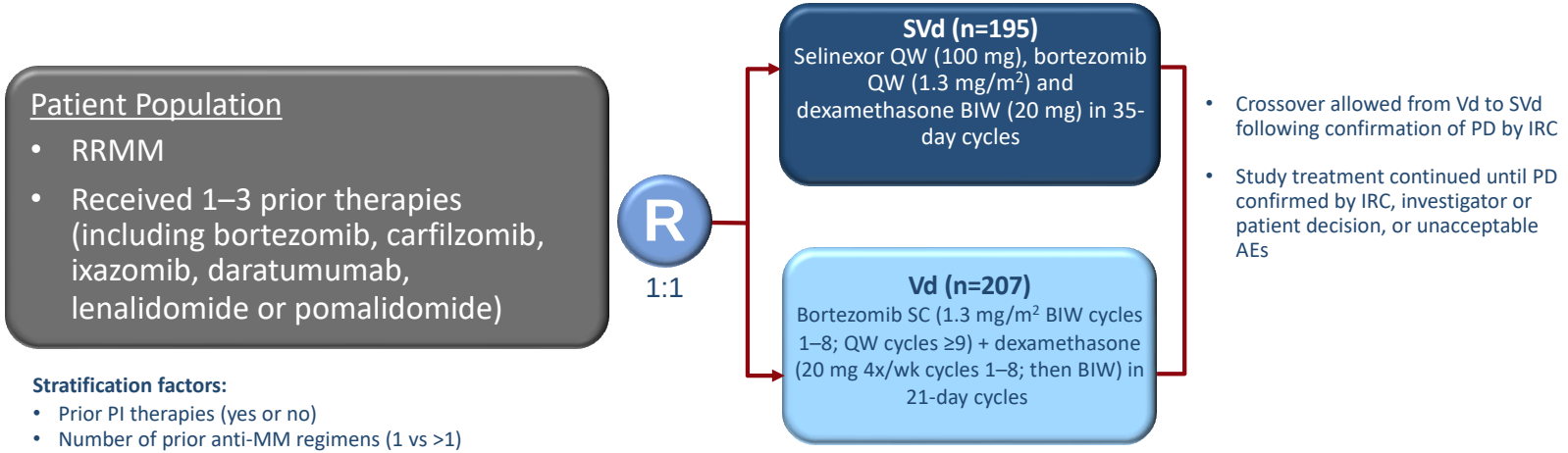


- The most common TEAEs were thrombocytopenia (73% of patients), fatigue (73%), nausea (72%), and anemia (67%); the most common SAEs were pneumonia and sepsis

Chari A, et al. *N Engl J Med*. 2019;381(8):727-738.

Selinexor plus bortezomib-dexamethasone

BOSTON study design



Stratification factors:
- Prior PI therapies (yes or no)
- Number of prior anti-MM regimens (1 vs >1)
- R-ISS stage at study entry (III vs I or II)

Primary endpoint: PFS in ITT population

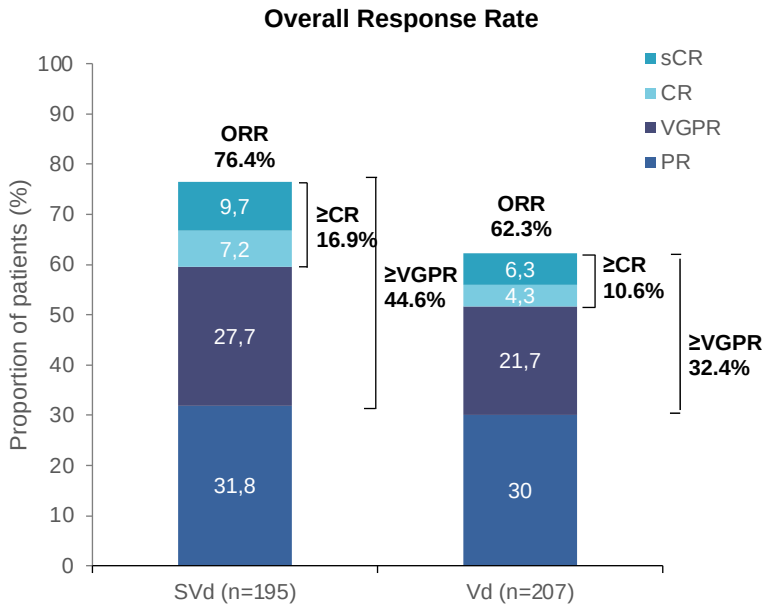
Grosicki S, et al. *Lancet*. 2020;396(10262):1563-1573

Baseline Patient Characteristics

Characteristic	SVd arm (n = 195)	Vd arm (n = 207)
Median Age, years (range)	66 (59-72)	67 (61-74)
≥75 years, n (%)	34 (17)	47 (23)
Male, n (%)	115 (59)	115 (56)
Time since initial diagnosis, years, (range)	3.8 (2.5-5.4)	3.6 (2.1-5.6)
High Risk Cytogenetics, [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 (69)	145 (70)
Carfilzomib	20 (10)	21 (10)
Daratumumab	11 (6)	6 (3)
Lenalidomide	77 (39)	77 (37)
Pomalidomide	11 (6)	7 (3)
Ixazomib	6 (3)	3 (1)
Stem cell transplant[1]	76 (39)	63 (30)

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

Treatment Responses With SVd vs Vd



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

	SVd 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

The most common grade 3-4 TEAEs (occurring in ≥10% of patients in either group) were **thrombocytopenia, anemia, pneumonia, fatigue and nausea**, all of which occurred more frequently in the SVd group than in the Vd group[1]

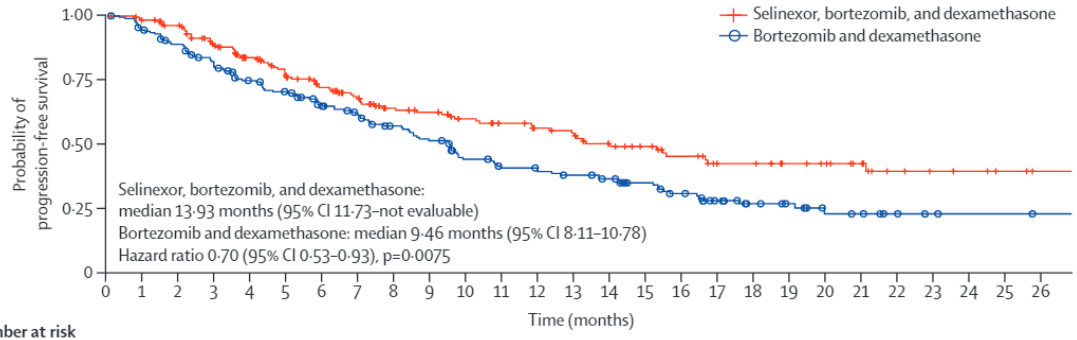
The incidence of **peripheral neuropathy** was significantly lower in the SVd arm vs the Vd arm: **32%** vs **47%**, respectively (OR 0.52 [95% CI 0.34-0.79], p=0.0010)[1]

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

Median PFS With SVd vs Vd

	SVd 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		

Kaplan-Meier estimates of progression-free survival among patients in the ITT population



Number at risk (number censored)

Selinexor, bortezomib, and dexamethasone	195 (0)	187 (5)	175 (12)	152 (21)	135 (31)	117 (37)	106 (42)	89 (50)	79 (57)	76 (59)	69 (63)	64 (66)	57 (71)	51 (73)	45 (76)	41 (80)	35 (83)	27 (89)	26 (90)	22 (94)	19 (97)	14 (102)	9 (106)	7 (108)	6 (109)	4 (111)	2 (113)
Bortezomib and dexamethasone	207 (0)	187 (8)	175 (10)	152 (15)	138 (20)	127 (22)	111 (29)	100 (32)	90 (37)	81 (37)	66 (41)	59 (43)	56 (44)	53 (45)	49 (47)	42 (52)	35 (55)	26 (60)	20 (65)	16 (69)	10 (73)	8 (75)	5 (78)	4 (79)	3 (80)	3 (80)	2 (81)	

This data represents:

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

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

Phase 3 BOSTON trial: sub-analyses

Population	N	ORR	mPFS (months)	HR
High risk cytogenetics	70 vs 71	79% vs 58%	12.9 vs 8.6	0.73
Renal impairment (CrCl 40-60 mL/min)	21 vs 26	80% vs 58%	16.6 vs 7.6	0.49
Renal impairment (CrCl <40 mL/min)	35 vs 44	81% vs 54%	7.6 vs 4.3	0.62
Age (>65 years)	109 vs 132	76% vs 64%	21 vs 9.5	0.55
Frail	66 vs 64	70% vs 61%	13.9 vs 13.1	0.75

Richard S, et al. Am J Hematol. 2021;
Delimpasi S, et al. Am J Hematol. 2022;
Auner HW, et al. Am J Hematol. 2021.

Phase 3 BOSTON trial: sub-analyses

Population	N	ORR	mPFS (months)	HR
1 prior line	99 vs 99	81% vs 66%	16.6 vs 10.7	0.63
2-3 prior lines	96 vs 108	72% vs 59%	11.8 vs 9.4	0.69
R-naive	118 vs 130	82% vs 68%	16.6 vs 10.6	0.66
R-exposed	77 vs 77	68% vs 53%	9.6 vs 7.2	0.63
PI-naive	47 vs 48	75% vs 71%	NR vs 9.7	0.26
PI-exposed	148 vs 159	77% vs 60%	11.7 vs 9.4	0.78
IMId-refractory	74 vs 86	69% vs 56%	13.9 vs 8.4	0.58
Prior ASCT	76 vs 63	82% vs 60%	16.6 vs 9.4	0.55
No prior ASCT	119 vs 144	73% vs 63%	13.2 vs 9.6	0.72

Mateos MV, et al. J Hematol Oncol. 2021.

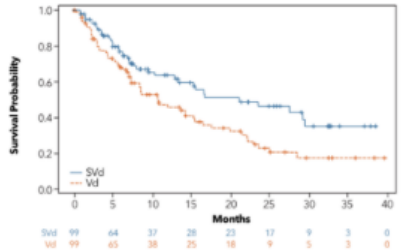
Selinexor, Bortezomib, and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Updated Results of Boston Trial By Prior Therapies

Maria-Victoria Mateos[1], Monika Engelhardt[2], Xavier Leleu[3], Mercedes Gironella Mesa[4], Michele Cavo[5], Meletios Dimopoulos[6], Martina Bianco[7], Giovanni Marino Merlo7, Charles la Porte[7], Philippe Moreau[8]

OBJECTIVE

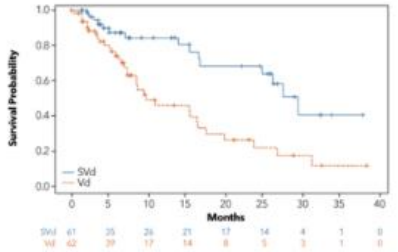
- In this subgroup analysis of the phase 3 BOSTON trial (NCT03110562),[2] we analysed longer follow-up data to determine the impact of prior therapies, including PI, on SVd efficacy and safety.

Figure 2. PFS in 1 Prior LOT Patients



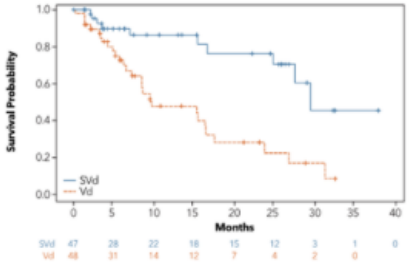
Median PFS:
21 vs 10.7 months
HR 0.68, P=0.028

Figure 6. PFS in Bortezomib-Naïve Patients



Median PFS:
29.5 vs 9.7 months
HR 0.35, P=0.002

Figure 4. PFS in PI-Naïve Patients



Median PFS:
29.5 vs 9.7 months
HR 0.29, P<0.001

CONCLUSIONS

- Findings of these stratified subgroup efficacy and safety analyses confirm the PFS benefit of SVd over Vd in patients without prior PI or bortezomib exposure as well as in patients who have received 1 prior line of therapy.
- Overall response rates and very good partial response or better rates were higher with SVd vs Vd in all subgroups.
- Adverse events were generally manageable and aligned with the overall BOSTON population.

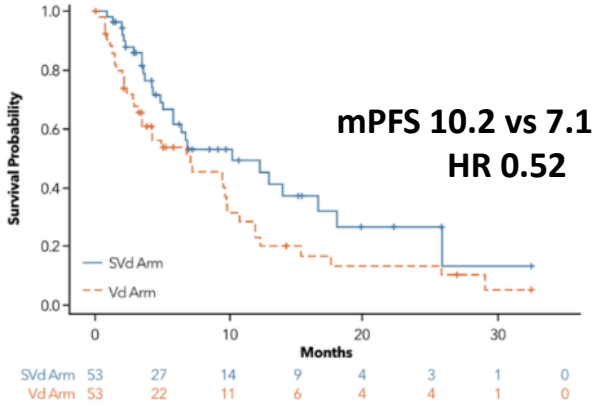
Efficacy, Survival and Safety of Selinexor, Bortezomib and Dexamethasone (SVd) in Patients with Lenalidomide-Refractory Multiple Myeloma: Subgroup Data from the Boston Trial

Maria-Victoria Mateos[1], Monika Engelhardt[2], Xavier Leleu[3], Mercedes Gironella Mesa[4], Michele Cavo[5], Meletios Dimopoulos[6], Martina Bianco[7], Giovanni Marino Merlo[7], Charles la Porte[7], Philippe Moreau[8]

OBJECTIVE

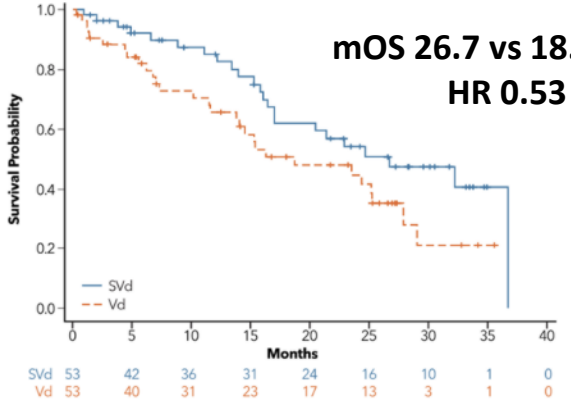
- In this subgroup analysis of the phase 3 BOSTON trial (NCT03110562), we analysed the subpopulation of patients with lenalidomide-refractory MM to determine the impact of lenalidomide refractoriness on the efficacy and safety of SVd.

Figure 2. PFS in Lenalidomide-Refractory Patients



mPFS 10.2 vs 7.1 mos; HR 0.52

Figure 3. OS in Lenalidomide-Refractory Patients



mOS 26.7 vs 18.6 mos; HR 0.53

CONCLUSIONS

- This subgroup analysis of the BOSTON trial confirms the benefit of SVd in patients with lenalidomide-refractory MM:
  - A statistically significant and clinically meaningful ~8 mo improvement in median OS (HR 0.53) as well as ~3 mo improvement in PFS (HR 0.52).
  - A statistically significant improvement in ORR (OR 2.59) and clinically meaningful improvement in VGPR (OR 1.74).
- The safety profile was similar to that observed in the overall BOSTON population.

GEM-SELIBORDARA trial

Study	Phase	Regimen	N	Population	Responses	Outcomes
SELIBOR-DARA	**2**	**Selinexor-V-Dara-dex (QW)**	**24 33**	**Parts 1/2: median 3/1 prior lines**	**sCR/CR 12%/24% ORR 50%/82%**	**NR**

Regarding adverse events (AEs) reported with longer f/u, hematological AEs were the most frequent ones [**thrombocytopenia** (70.1%; G 3-4 in 45%) and **neutropenia** (36.8%; G3-4 in 29.8%)]. Followed by GI-Tox [**diarrhea** (38.6%; G 3-4 in 2 pts) and **nausea** (35.1%; G3-4 in 5 pts]. 41 pts had **infections** during treatment (G3-4: 39%).

The dose of selinexor was the most frequently one modified (15 cases in part 1 and 23 in part 2) and discontinued in 8 pts (5 in part 1 and 3 in part 2). Only 1 pt discontinued the trial due to treatment toxicity.

Gonzalez-Calle V, et al. EHA 2023 (abstr 878).

Selinexor plus carfilzomib-dexamethasone

Regimens	Phase	N	Population	Responses	Outcomes
Selinexor-Kd (QW) [67]	1b/2	32	Median 4 prior therapies TCR 38%	• sCR/CR 16% • ≥VGPR 44% • ORR 78%	• mDOR 22.7 months • mPFS 15.0 months
		12	TCR [68]	• ≥VGPR 50% • ORR 67%	• mDOR 12.0 months • mPFS 13.8 months • mOS 33.0 months
Selinexor-Kd (QW)	1	30	Median 5 prior lines K-refractory 30% Prior CAR-T cell therapy 20%	• ≥VGPR 27% • ORR 70% • CBR 83%	• mPFS 5.3 months • mOS 23.3 months
Selinexor-Kd (BIW)	1	21	Median 4 prior lines TCR, penta-exposed 5%	• VGPR 14% • ORR 48% • CBR 71%	• mPFS 3.7 months • mOS 22.4 months

Gasparetto C, et al. Br J Cancer. 2022; Schiller GJ, et al. Blood. 2022;140(Suppl 1); Derman BA, et al. Eur J Haematol. 2023; Jakubowiak AJ, et al. Br J Haematol. 2019.

Selinexor plus carfilzomib-dexamethasone

Regimens	Phase	N	Population	Responses	Outcomes
Selinexor-Kd ($n = 23$) / Selinexor-Pom-dex ($n = 23$) (QW) [72]	1b/2	46	Median 4 prior regimens Selected for prior CD38 mAb; TCR 52%	• ORR 65%/52% • CBR 74%/76%	• mDOR 13.1 / 7.9 months • mPFS 15.0 / 8.7 months • mOS 33.0 / 21.8 months
Selinexor + Vd ($n = 3$), Kd ($n = 2$), Pom-dex ($n = 4$), V-Pom-dex ($n = 1$), Elo-Pom-dex ($n = 1$) [73]	1b/2	11	Median 6 prior lines Selected for prior anti-BCMA therapy	• VGPR 18% • ORR 64% • CBR 82%	• 6-month PFS 75.0%
Selinexor + dex (n = 1), Vd (n = 1), Kd (n = 5) (BIW/QW)	7	7	Median 10 prior regimens Selected for refractoriness to prior CAR T-cell therapy	• 1 sCR • 3 VGPR • 2 PR	• DOR 7.4+ months • DOR 3.4, 4.6+, 5.0 months • DOR 1.4, 5.6 months

Lentzsch S, et al. Blood. 2021;138(Suppl 1); Baljevic M, et al. EJHaem. 2022;
Chari A, et al. Br J Haematol. 2020

ABSTRACT/ POSTER 1546209

EFFECTIVENESS OF ANTI-B-CELL MATURATION ANTIGEN (BCMA)-TARGETING THERAPY AFTER SELINEXOR TREATMENT

Muhamed Baljevic[1], Philippe Moreau[2], Sascha A Tuchman[3], Natalie S Callander[4], Suzanne Lentzsch[5], Dane Van Domelen[6], Ohad S Benur[6], Jorge Monge[7], Noa Biran[8]

INTRODUCTION

- The influence of selinexor-based treatment on T-cell function, which may alter the efficacy of αBCMA therapies following selinexor treatment, is unknown.

METHODS

- We analyzed the effectiveness of non-cellular αBCMA (NCA) therapies in patients with MM treated in 4 clinical studies (STORM [NCT02336815]; STOMP [NCT02343042]; BOSTON [NCT03110562], XPORT-MM-028 [NCT04414475]) with selinexor + dexamethasone (Sd), with or without PIs, IMiDs, or αCD38 mAbs, followed by therapy with NCA.

Table 3. Non-cellular anti-BCMA therapies

	Patients with Non-CAR T-Cell Anti-BCMA Therapy After Selinexor (N = 37) n (%)
Belantamab mafodotin*	28 (75.7)
Teclistamab	2 (5.4)
SEA-BCMA	2 (5.4)
AMG 701	1 (2.7)
Elranatamab	1 (2.7)
MEDI2228	1 (2.7)
Investigational†	3 (8.1)

* One patient received 2 NCAs, belantamab and teclistamab.
† Two had αBCMA bispecific antibodies and 1 had αBCMA bispecific T-cell engager (BiTE).

Table 1. Patient characteristics and demographics*

	Patients with Non-CAR T-Cell Anti-BCMA Therapy After Selinexor (N = 37)
Age (Years)[1], median (range)	68.0 (40-87)
Sex, N (%)	
Male	21 (56.8)
Female	16 (43.2)
Duration from last dose of selinexor to first anti-BCMA therapy (weeks), median (range)	8.0 (2-117)
Baseline ECOG performance status, N (%)	
0	14 (37.8)
1	18 (48.6)
2	4 (10.8)
Missing	1 (2.7)
Number of prior lines of therapy, median (range)	5.0 (2-11)
Previously exposed to αCD38 mAb (daratumumab or isatuximab), n (%)	30 (81.1)
Refractory to, n (%):	
PI (bortezomib, carfilzomib, or ixazomib)	30 (81.1)
IMiD (thalidomide, lenalidomide, or pomalidomide)	29 (78.4)
αCD38 mAb (daratumumab or isatuximab)	27 (73.0)
αCD38 mAb, PI, and IMiD	21(56.8)
≥2 PIs, ≥2 IMiDs, and αCD38 mAb	8 (21.6)

Abbreviations: αCD38 mAb=anti-CD38 monoclonal antibody; ECOG=Eastern Cooperative Oncology Group; IMiD=immunomodulatory drug; PI=proteasome inhibitor; POM=pomalidomide; SEL=selinexor.
* Results are as of August 1, 2022 for ongoing studies STOMP and XPORT-MM-028.
†Age at screening.

Efficacy

- The median overall survival from initiation of NCA was 12.0 months (95% CI: 9.4, NE) with a median follow-up of 7.8 months (Figure 2 & Table 4).
- Median time to treatment discontinuation (TTD) with NCA was 3.1 months (95% CI: 2.1, NE) (Figure 3 & Table 4).
- A trend for longer overall survival and TTD was seen for the other NCAs compared with bela-maf (Table 4).

Table 4. Efficacy of NCAs after selinexor-based regimens

	Any NCA after selinexor (N = 37)	Bela-maf after selinexor (N=28)	NCA except bela-maf after selinexor (N=10)
OS, median (months) (95% CI)	12.0 (9.4, NE)	11.3 (6.6, NE)	NR (9.4, NE)
Median follow-up (months)	7.8	7.8	9.1
TTD, median (months) (95% CI)	3.1 (2.1, NE)	3.1 (1.4, NE)	8.7 (1.9, NE)

NE, not evaluable; NR, not reached; OS, overall survival; TTD, time to treatment discontinuation.

Safety

- The trials did not record treatment-emergent adverse events (TEAEs) that occurred when the patients started on αBCMA therapy.

CONCLUSIONS

- **In this cohort of heavily-pretreated patients with MM who received a selinexor regimen prior to NCA, overall survival was in the range of 1 year, akin to historical results seen with ADCs.**
- **The 8-week median time between administration of selinexor and NCAs suggests that selinexor, with various partner agents, did not negatively impact overall survival with subsequent NCA therapy, including bela-maf, bispecific antibodies, and BiTEs.**

Selinexor plus IMiDs

Regimen	Phase	N	Population	Responses	Outcomes
Selinexor-Rd (BIW/QW)	1b/2	24	Median 2 prior lines	≥VGPR 25% ORR 60% CBR 70%	NR
Selinexor-Pom-dex (QW)	1b/2	39	Median 2 prior lines TCR 26%	≥VGPR 23% ORR 54% CBR 74%	mPFS (RP2D) 8.9 mos

White DJ, et al. Blood. 2020;136(Suppl 1);
White DJ, et al. Blood. 2021;138(Suppl 1);

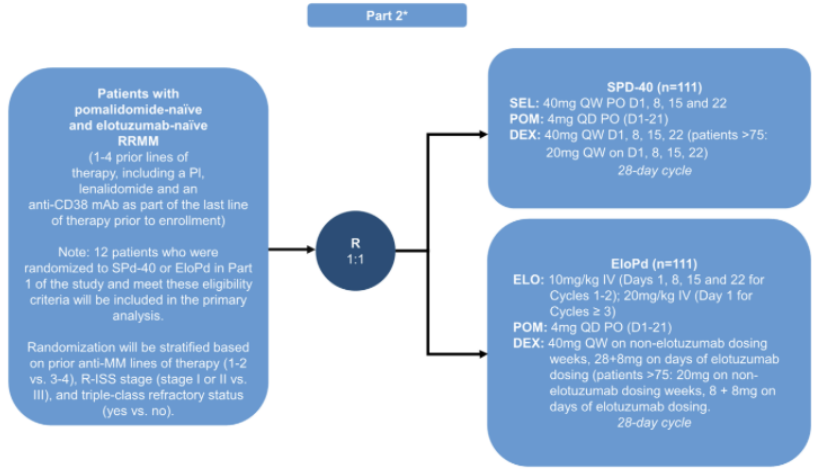
ABSTRACT/
POSTER
1552200

EMN29 A PHASE 3 RANDOMIZED, OPEN-LABEL TRIAL OF SELINEXOR, POMALIDOMIDE, AND DEXAMETHASONE VERSUS ELOTUZUMAB, POMALIDOMIDE, AND DEXAMETHASONE IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Katja Weisel[1], Ohad Bentur[2], Dane Van Domelen[2], Mario Boccadoro[3], Pieter Sonneveld[4]

STUDY DESIGN

EMN29 (NCT05028348)
A phase 3 randomized, open-label, multicenter trial of SPd versus EloPd in pts with RRMM.



Primary Objective: To compare the PFS of SPd and EloPd in patients with MM who have received 1 to 4 prior anti-MM lines of therapy, never received elotuzumab, pomalidomide, or selinexor, but who have been treated with an IMiD (lenalidomide) and a PI in the past and an anti-CD38 mAb in their immediate prior line of therapy.

ENDPOINTS

Primary Endpoint:
Investigator-determined PFS

Key secondary endpoints:
Overall response rate
Overall survival

Other secondary endpoints:
- Clinical benefit rate
- Duration of response
- Time to next treatment
- Time to initial response
- Time to best response
- Time to second disease progression
- Safety and tolerability
- Health-related quality of life
- Pharmacokinetic parameters

Exploratory endpoints:
- Cytogenetic and fluorescence in situ hybridization of prognostic biomarkers, including p53 abnormalities and other chromosomal aberrations*
- Genetic analysis including DNA and RNA sequencing of bone marrow samples*
- Relationships between selinexor exposure metrics such as C_{max} and AUC and efficacy and safety endpoints

* Part of correlative studies

ELIGIBILITY CRITERIA

Select inclusion criteria:
- ≥18 years of age
- Relapsed or refractory MM
- At least 1 and no more than 4 prior anti-MM lines of therapy that includes:
  - ≥2 consecutive cycles of lenalidomide and PI alone or in combination
  - Anti-CD38 mAb as part of their immediate last treatment prior to study entry
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤2
- Adequate hepatic, renal, and hematopoietic function

Select exclusion criteria:
- Prior treatment with selinexor, pomalidomide or elotuzumab
- Clinically significant cardiac disease
- Major surgery within 4 weeks prior to starting study drug
- Smoldering MM
- Plasma cell leukemia
- Active systemic amyloid light chain amyloidosis
- Uncontrolled infection requiring antibiotics, antivirals or antifungals within 1 week prior to starting study drug

PARTICIPATING LOCATIONS

- France
- Germany
- Greece
- Italy
- Netherlands
- Spain
- Turkey
- United States

STUDY INFORMATION

Study Contact:
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Key toxicities from clinical trials

Study	Regimen	Prior therapy	N	Grade 3/4 toxicities			
				Haematological (≥15%)	GI (≥5%)	Fatigue	Other[a]
STORM part 2 [54]	Selinexor-dex (BIW)	Median 7 lines	123	• Thrombocytopenia 59% • Anaemia 44% • Neutropenia 21%	• Nausea 10% • Diarrhoea 7% • Decreased appetite 5%	25%	• Hyponatremia 22% • Pneumonia 9%
STORM part 1 [53]	Selinexor-dex (BIW)	Median 7 lines	79[b]	• Thrombocytopenia 61%/57% • Anaemia 33%/18% • Neutropenia 24%/21%	• Nausea 6%/11% • Diarrhoea 2%/11%	16%/14%	• Hyponatremia 20%/25%
MARCH [57]	Selinexor-dex (BIW)	Median 5 lines	82	• Thrombocytopenia 51% • Anaemia 57% • Neutropenia 39%	• Nausea 7% • Vomiting 7%	10%	• Hyponatremia 29% • Lung infection 27% • Hypokalaemia 12% • Hyperglycaemia 10% • Hypocalcaemia 7% • AST increased 2% • ALT increased 4%
Chen et al. [52]	Selinexor±dex (BIW)	Median 6 therapies	81/84[c]	• Thrombocytopenia 45% • Anaemia 23% • Neutropenia 23%	• Diarrhoea 5%	13%	• Hyponatremia 26%
BOSTON [61]	Selinexor-Vd versus Vd (QW)	1–3 prior lines	195 versus 207	• Thrombocytopenia 39% versus 17% • Anaemia 16% versus 10%	• Nausea 8% versus 0 • Diarrhoea 6% versus <1%	13% versus 1%	• Pneumonia 12% versus 10%

Mo CC, et al. EJHaem. 2023.

Key clinical management recommendations for the use of selinexor-based therapy

	US PI [49]	Expert recommendations (for once-weekly selinexor) [97]
Patient selection	• Selinexor-Vd: patients who have received ≥1 prior therapy • Selinexor-dex: patients who have received ≥4 prior therapies; disease refractory to ≥2 PIs, ≥2 immunomodulatory drugs, an anti-CD38 mAb	• Weekly selinexor-based regimen with a PI or an immunomodulatory drug in patients progressing on an anti-CD38 mAb [97] • US: selinexor-Vd, selinexor-dara-dex, selinexor-Kd following 1–3 prior therapies; selinexor-pom-dex following 2 prior therapies including a PI and immunomodulatory drug (and refractory to last prior therapy) [9]
Baseline evaluations / actions	• Monitor weight, nutritional status and volume status • Monitor platelet counts • Obtain white blood cell counts with differential • Monitor sodium level	• Patient education regarding anticipated side-effects and duration, for example, nausea seen much less frequently beyond treatment cycle 2 • Highlight other known toxicities, for example, anorexia, fatigue • Suggest keeping daily record of symptoms for ≥1 cycle • Consider starting at lower dose (40–60 mg) and escalate to 100 mg as tolerated

Mo CC, et al. EJHaem. 2023.

Key clinical management recommendations for the use of selinexor-based therapy

Prophylaxis		
GI toxicity	• Provide prophylactic antiemetics; 5-HT3 receptor antagonist and other anti-nausea agents prior to treatment	• Combination of olanzapine, 5-HT3 receptor antagonists (ondansetron, granisetron) ± neurokinin 1 receptor antagonists (aprepitant, rolapitant, casopitant, fosaprepitant) • Low-dose olanzapine (2.5–5 mg), evenings, prior to/for 3 days post selinexor
Supportive care		
GI toxicity	• Administer 5-HT3 receptor antagonist and other anti-nausea agents during treatment • Provide standard anti-diarrheal agents • Provide IV fluids to prevent dehydration; replace electrolytes as clinically indicated • Monitor weight, nutritional status, and volume status throughout treatment, more frequently during first 3 months	• Comprehensive metabolic panel weekly (cycle 1) then at start of every cycle • Combination of olanzapine, 5-HT3 receptor antagonists ± neurokinin 1 receptor antagonists • Low-dose olanzapine (2.5–5 mg), evenings, prior to/for 3 days post selinexor • Taper anti-nauseants after cycle 2 as needed • Maintain hydration (2 L daily) – water, salt-containing drinks • IV fluids as required, for example, IV normal saline • Nutritional consultation, appetite stimulants • Consider dronabinol 2.5–5 mg PO BID for grade ≥2/3 anorexia • Initiate anti-diarrhoeal treatment for grade 1 diarrhoea
Fatigue	–	• Consider methylphenidate 5 mg PO BID for grade 4 fatigue

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Key clinical management recommendations for the use of selinexor-based therapy

Thrombocytopenia	• Monitor platelet counts throughout treatment, more frequently during first 3 months • Platelet transfusion and/or other treatments as clinically indicated	• Complete blood count weekly (cycle 1) then at start of every cycle • Romiplostim 10 μg/kg weekly for grade 3/4 toxicity
Neutropenia / Serious infections	• Monitor white blood cell counts with differential throughout treatment, more frequently during first 3 months • Consider antimicrobials and growth factors (e.g., G-CSF) • Monitor for signs and symptoms of infection, evaluate and treat promptly	• Complete blood count weekly (cycle 1) then at start of every cycle • Grade 4 or febrile neutropenia: G-CSF until ANC $>1.0 \times 10^9$/L
Hyponatremia	• Monitor sodium level throughout treatment, more frequently during first 2 months • Correct sodium levels for concurrent hyperglycemia and high serum paraprotein levels • Manage per clinical guidelines, including IV saline and/or salt tablets as appropriate and dietary review	• Maintain hydration (2 L daily) – water, salt-containing drinks • Consider addition of salt tablets, salty foods to diet
Neurological toxicity	• Optimize hydration, haemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status • Institute fall precautions	–

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Conclusions

- **Treatment strategies for MM have gained momentum in recent years, however, the prognosis for RRMM remains poor.**
- **Selinexor has shown encouraging results in RRMM.**
- **When combined with other medicines, selinexor displays superior therapeutic effects.**
- **Safety profile is well characterized and can be managed with appropriate supportive care, with particular attention to its GI toxicity.**
- **The mechanism of action provides an alternative approach for targeting MM, which is valuable in the context of patients commonly requiring multiple lines of therapy over their treatment course.**