Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

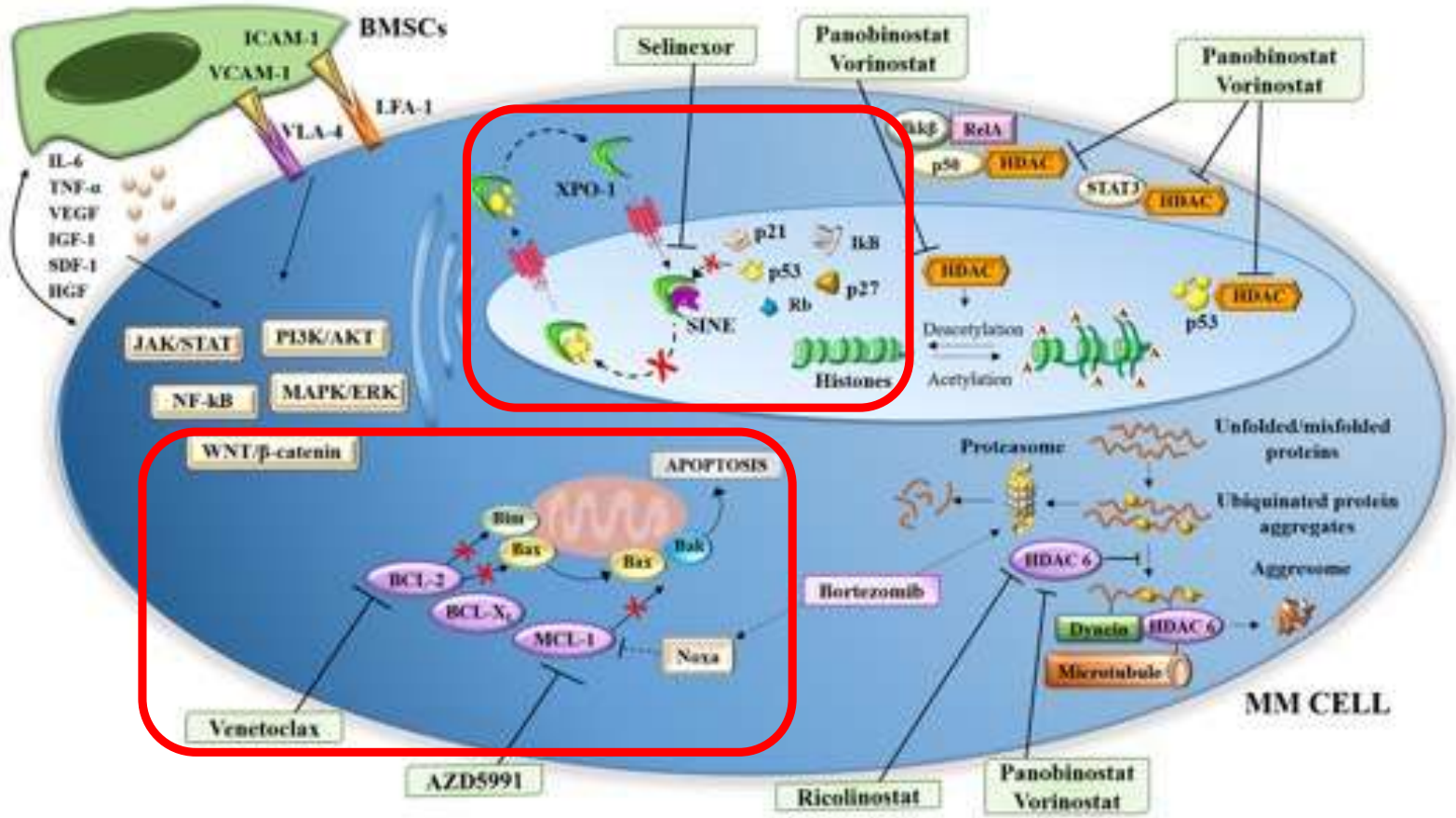
NICOLA GIULIANI

CON INIBITORE DELLE ESPORTINE O BCL-2.

Coordinatore Scientifico
Michele **CAVO**

Comitato Scientifico
Michele **CAVO**
Maria Teresa **PETRUCCI**

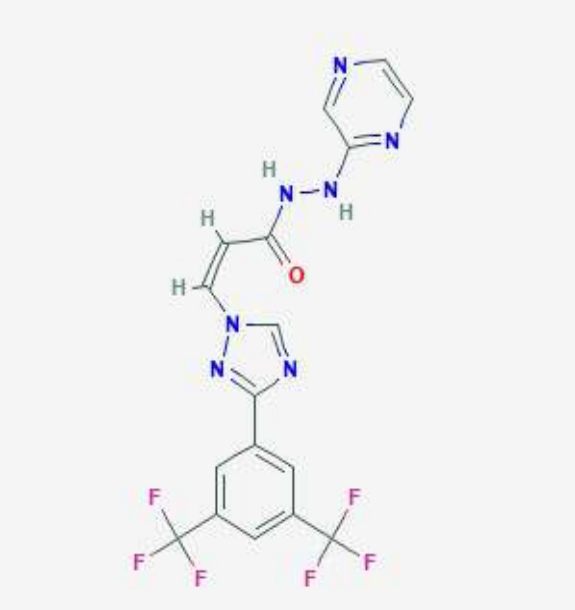
Potential targets for treatment in multiple myeloma (MM)



"Novel targets for the treatment of relapsing multiple myeloma", Giuliani et al., Expert Review of Hematology, 2019

Selinexor

- Selinexor (KPT-330) is a first-in-class, orally bioavailable, selective inhibitor of XPO1-mediated nuclear export.



Trade name: Xpovio
Other name: KPT-330

Roues of administration: by mouth

Metabolism: hepatic oxidation, glucuronidation and conjugation, by CYP3A4, UGT and GST

Elimination half-life: 6-8 hours

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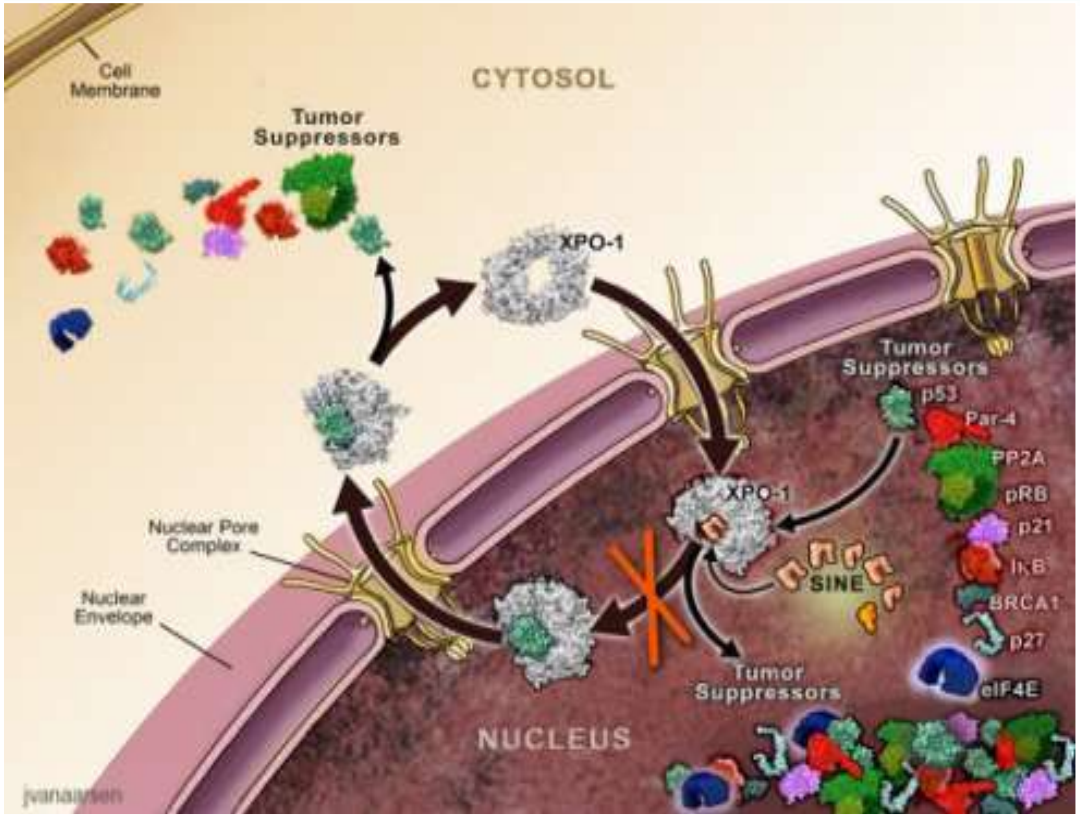
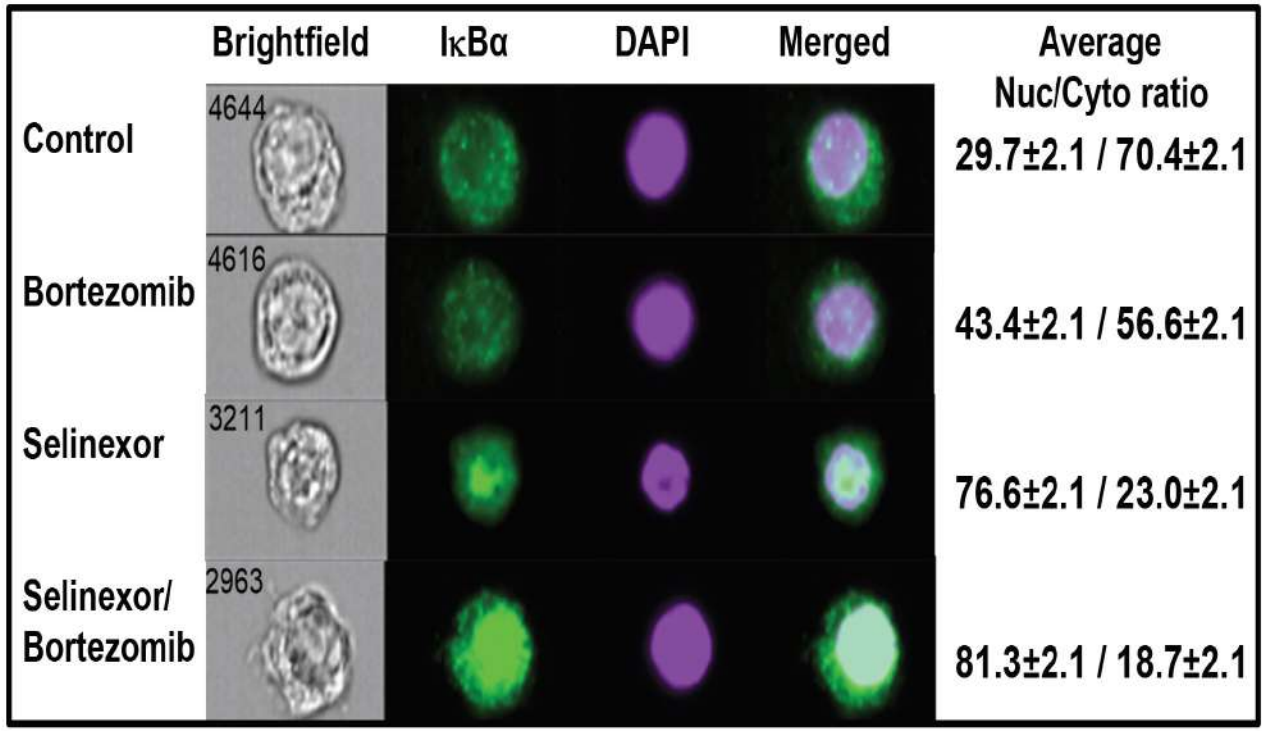


- Cancer cells (and MM) overexpress XPO1, causing increased export of tumor suppressors and growth of regulatory proteins from the nucleus
- Selinexor inhibits XPO1 mediated nuclear-cytoplasmic transport by transiently binding to XPO1 cargo binding site
- Accumulation of tumor suppressors in the nucleus amplifies the natural apoptotic function in cancer cells with damaged DNA

Tai YT et al. Leukemia 2014;28(1):155-65

- Evidence of synergistic anti-MM activity between selinexor and proteasome inhibitors (PI) through suppression of NF-kB signaling and nuclear retention of tumor suppressor proteins.
- Synergistic increase in IkBa expression by Selinexor and Bortezomib resulted in a strong anti-tumor effect.



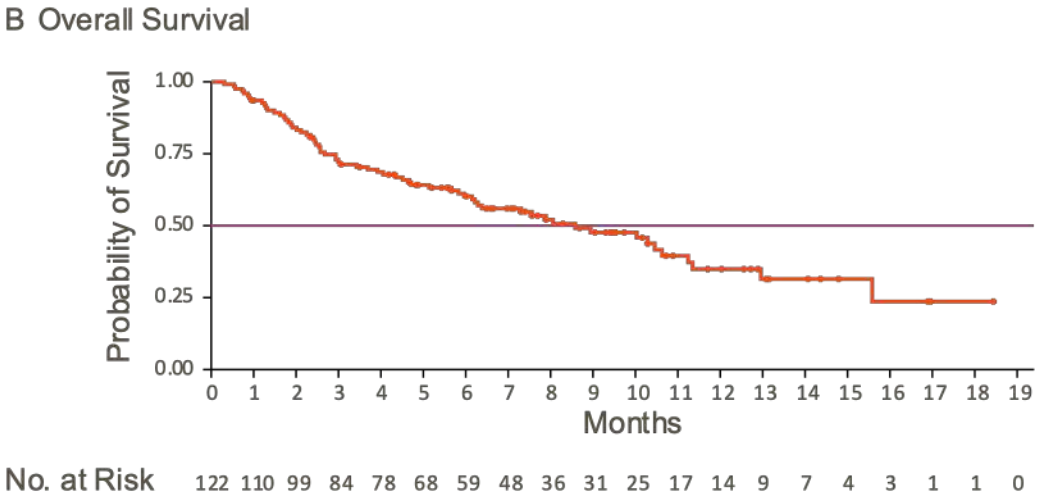
Turner et al., Oncotarget 2016

Selinexor in relapsed-refractory (RRMM) : Summary of phase 1/2 data

Single agent[1] (n=84)	+Dex[2] (n=79)	+Bort/dex[3] (n=40)	+Pom/dex[4] (n=24)	+ Dara/dex[5] (n=25)	+ Carf/Dex[6] (n=24)
15% MR	20% ORR (Penta-Refractory). Median PFS 2.3 m. OS: 9.3 m	ORR: 63% (43% in Btz Rfct), (PH III BOSTON trial ongoing)	ORR 29% in Pom/Len-R & ORR 65% in Pom-Naive/Len-R	ORR 79% (VGPR 29%)	ORR 71% (VGPR 40%)
Main AEs: nausea/vomiting 75%, fatigue 70%, anorexia 64%, thrombocytopenia 52% (G3-4 45%).	Main AEs: nausea 73%, anorexia 49%, fatigue 63%, vomiting 44%, thrombocytopenia 75% (G3-4 59%).	AEs: decreased appetite 60%, nausea 62%, thrombocytopenia 50%	AEs: gr 1/2: nausea 55%, anorexia 48%. Gr 3/4: neutropenia 48%, thrombocytopenia 31%	Gr 3/4 AEs: thrombocytopenia (44%), anemia (28%), neutropenia (24%)	Gr 3/4 AEs: thrombocytopenia (52%), anemia (20%), neutropenia (8%) GRADE 1-2 nausea 66%

1. Chen et al, Blood. 2018;131(8):855-863; 2. Chari et alJ Clin Oncol. 2018;36(9):859-86; 3. Bahlis NJ, Blood 2018;132(24):2546-2554; 4. Chen et al, ASH 2017, abstract 3136; 5. Gasparetto et al., ASH 2018, abstract 599.; Gasparetto ASCO 2020

STORM part 2
Selinexor + dex: PFS and OS



Population[1]	ORR (%)	sCR (%)	VGP R (%)	PR (%)	MR (%)
All patients (N=122)	**26.2**	**1.6**	**4.9**	**19.7**	**13.1**

mOS=8,6 months
mPFS= 3,7months
mDOR=4.4 months

1. Chari A et al. Results of the pivotal STORM study (part 2): deep and durable responses with oral selinexor plus low dose dexamethasone in patients with penta-exposed and triple class refractory MM. Presented at: 60th American Society of Hematology Annual Meeting (ASH); December 1-4, 2018; San Diego, CA. **2.** Chari A et al. *N Engl J Med*. 2019;381(8):727-738.

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BOSTON Study Design

Randomization 1:1

SVd Weekly
35-day cycles

Selinexor (oral)	100 mg	Days 1, 8, 15, 22, 29
Bortezomib (SC)	1.3 mg/m^2	Days 1, 8, 15, 22
Dexamethasone (oral)	20 mg	Days 1, 2, 8, 9, 15, 16, 22, 23, 29, 30

Vd Twice Weekly
21-day cycles
Cycles 1-8

Bortezomib (SC)	1.3 mg/m^2	Days 1, 4, 8, 11
Dexamethasone (oral)	20 mg	Days 1, 2, 4, 5, 8, 9, 11, 12

If IRC confirmed PD: crossover to SVd or Sd permitted

Vd Weekly*
35-Day cycles
Cycles ≥9

PD or unacceptable toxicity

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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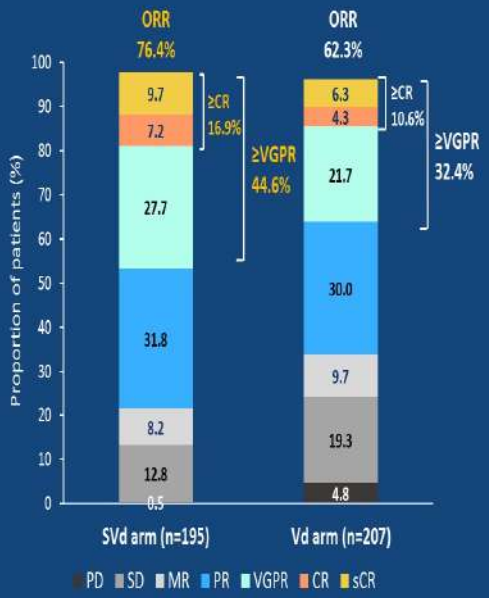
PFS for All Patients



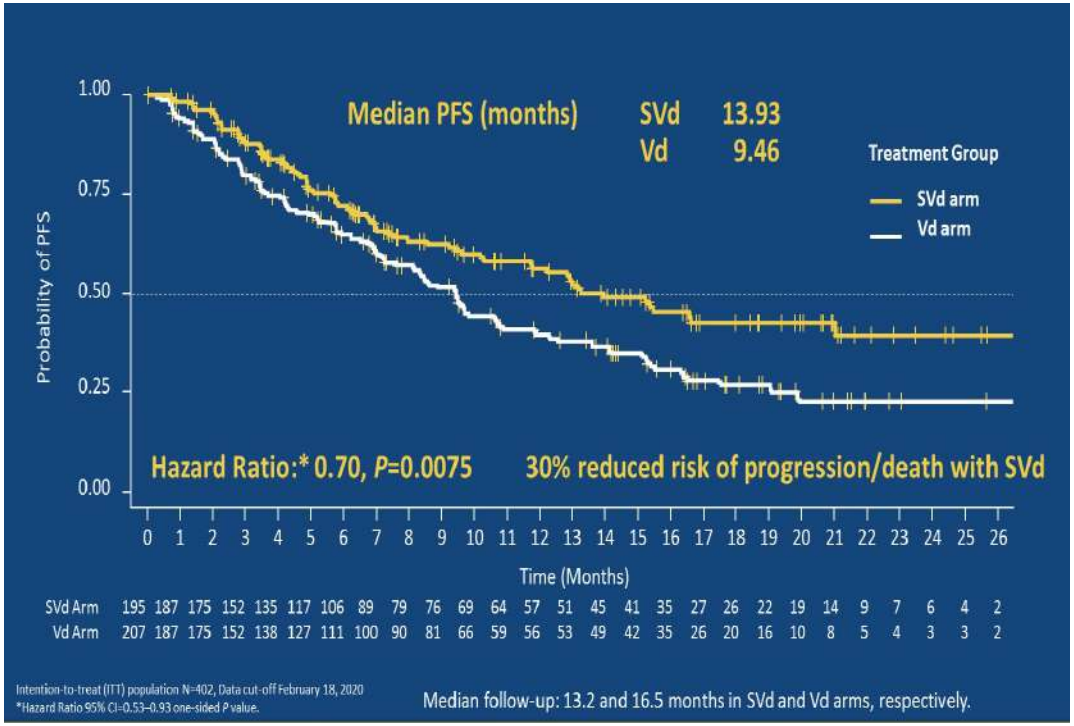
Longer duration of response with SVd

	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.

Response Rates in All Patients



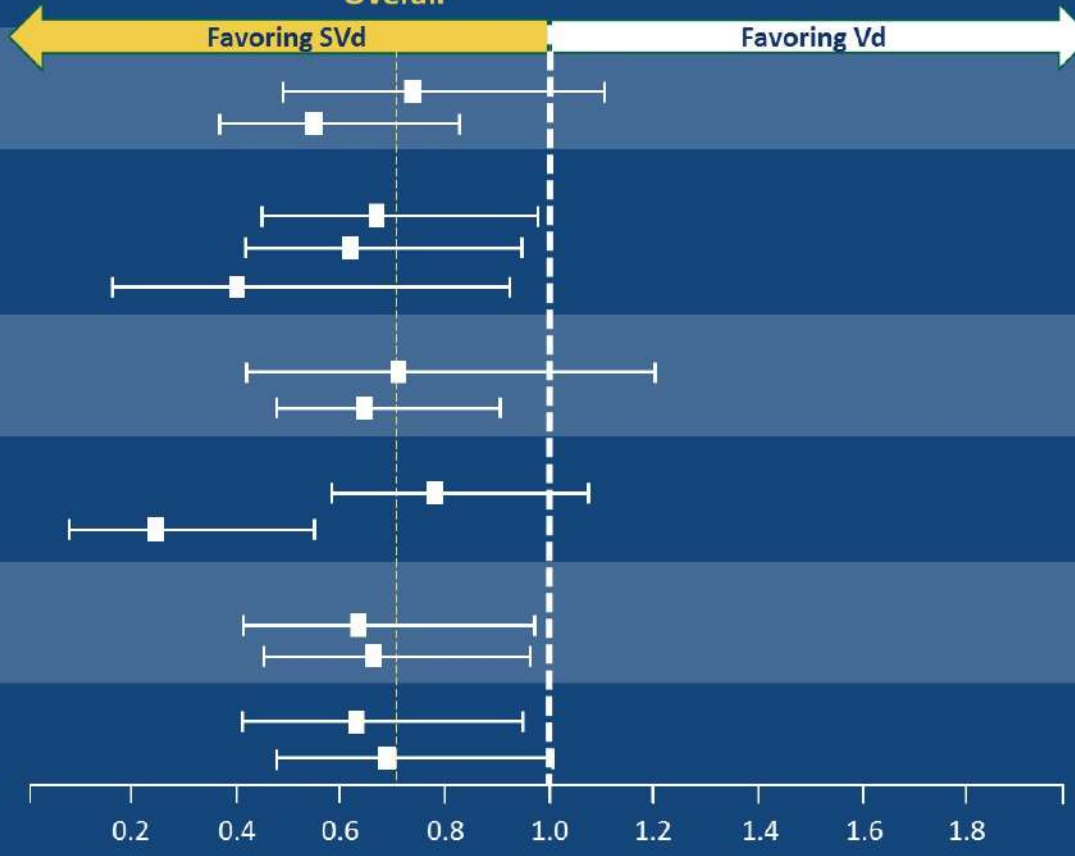
Intention-to-treat (ITT) population N=402, Data cut-off February 18, 2020
*Hazard Ratio 95% CI=0.53–0.93 one-sided *P* value.

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

Dimopoulus M, et al. ASCO 2020

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)

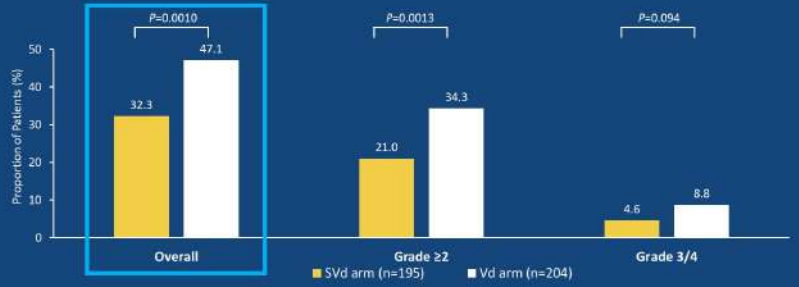


HR = Hazard Ratio, Data cut-off February 18, 2020.

Dimopoulus M, et al. ASCO 2020

Safety Overview

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, nasopharyngeal sinus infection, respiratory tract infection, rhinitis and viral upper respiratory tract infection. §Per Ophthalmology exam during 24% patients on the SVd arm versus 9.5% 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.

IMWG:
Selinexor in RRMM

P-211

Phase 2 MARCH study: ATG-010 (SELINEXOR) plus Dexamethasone in Chinese relapsed/refractory Multiple Myeloma (RRMM) patients previously treated with an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI)

Lugui Qiu et al.

METHODS

- MM patients previously treated with and refractory to PI, IMiD.
- The primary endpoint was overall response rate (ORR). The total planned 82 pts. This abstract includes data from the first 60 treated pts.

RESULTS

- Median follow-up was 9.5 months (mo) (range: 1.9-12.8).

- Pts had received a median of 5 (range 1-16) prior MM regimens, with the following baseline risk factors: 72% R-ISS II/III, 70% cytogenetic abnormalities, 22% del (17p13),20% renal impairment, 15% prior CAR-T therapy, and 25% pre-treated with daratumumab (considered 'triple-class exposed').

- **ORR was 26.7**% (95% CI: 16.1, 39.7). **ORR was 33.3% in triple-class-exposed pts**

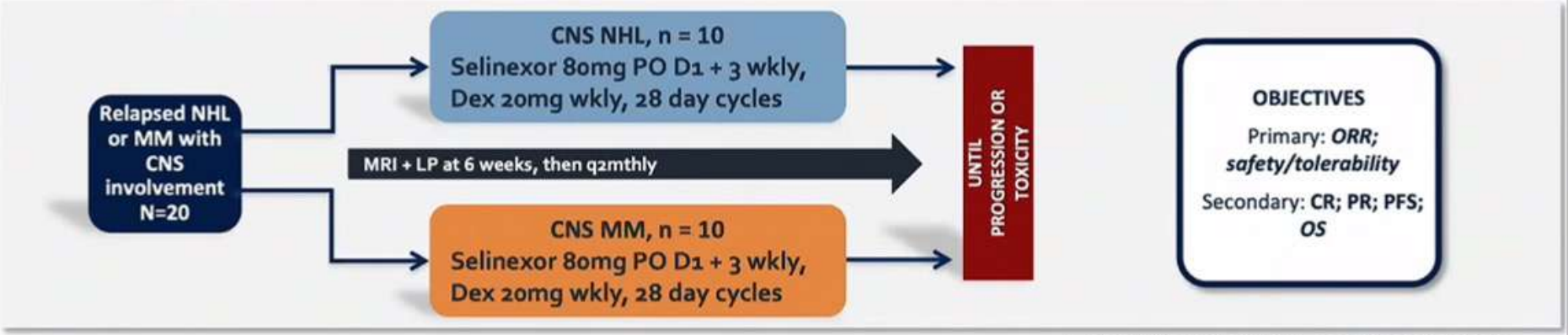
- Median duration of response (DOR) was 4.6 mo (95% CI: 1.42, NE).

- Median progression free survival was **3.7 mo** (95% CI: 1.92, 4.66). Median overall survival (OS) was not reached; 9-mo OS rate was 68.5%**..**

CNS MM

A single arm, multicentre, open label study of the Exportin 1 inhibitor Selinexor in relapsed/refractory CNS lymphoma and CNS myeloma (EXCLAIM) – AMaRC 20-01

CPI Matthew Ku

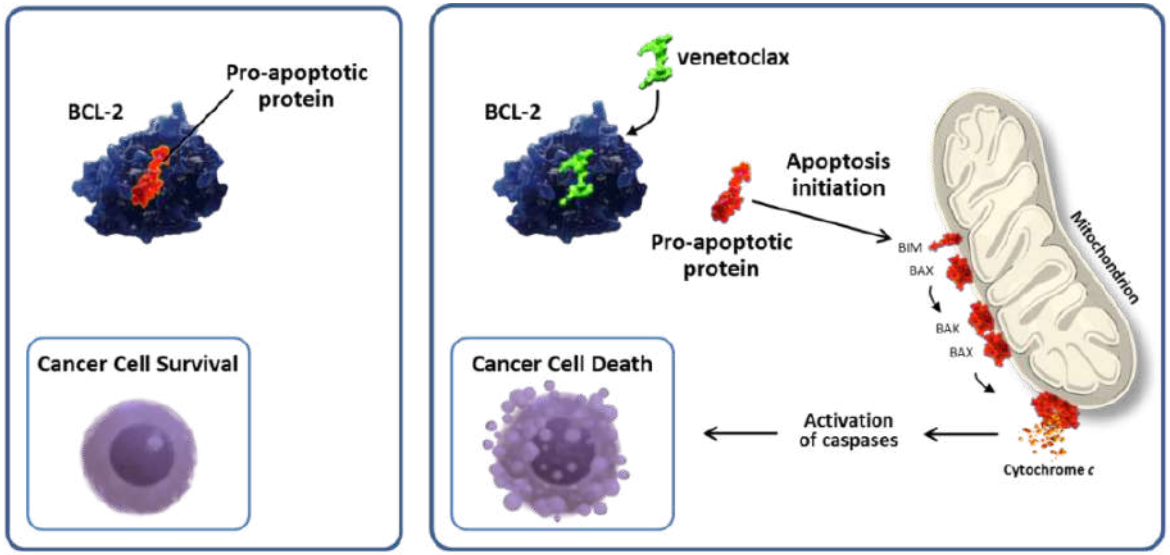


- Recruitment status: Accrual imminent.

AMaRC
AUSTRALASIAN MYELOMA RESEARCH CONSORTIUM

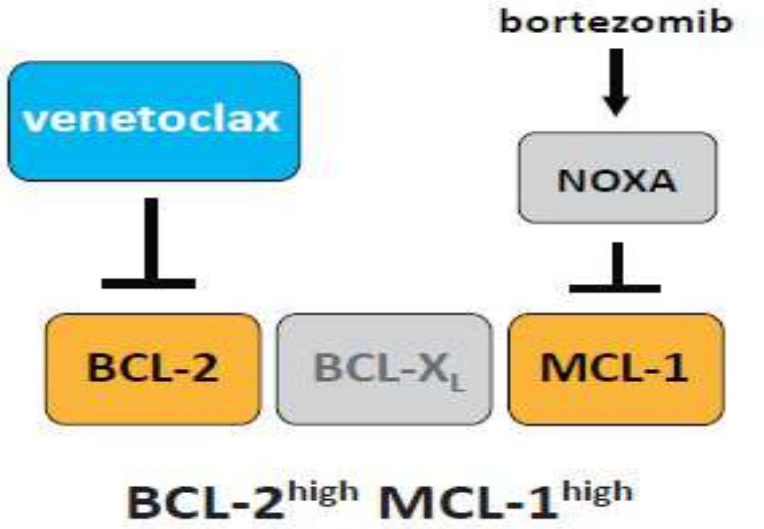
Targeting BCL-2 in MM

Venetoclax is a selective, orally available small molecule BCL-2 inhibitor induces cell death in MM cells, particularly those positive for the translocation t(11;14), which correlates with higher ratios of BCL2 to MCL1 and BCL2 to BCL2L1 (BCL-X_L) mRNA



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]

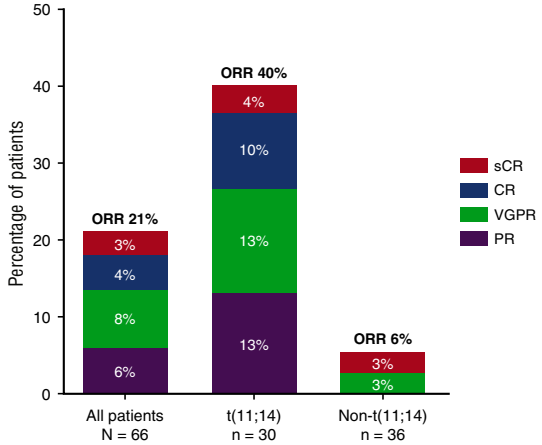
Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]

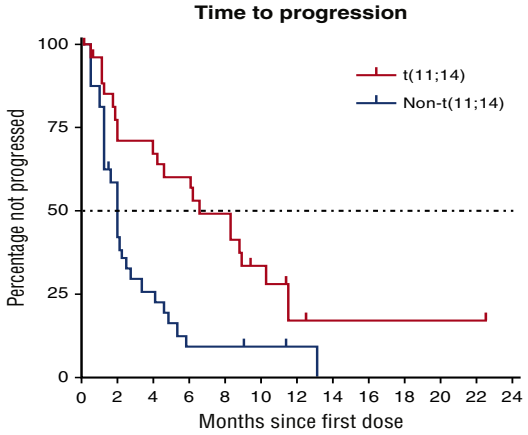


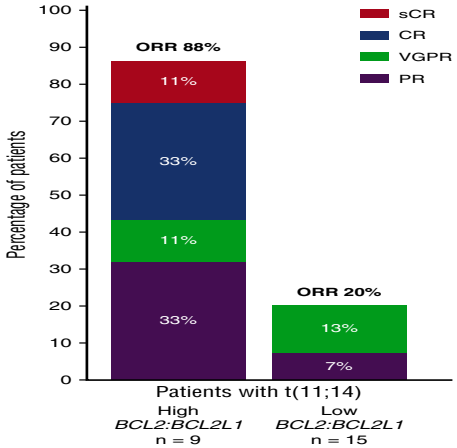
1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279ra40. 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Platt J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279–296. 4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.

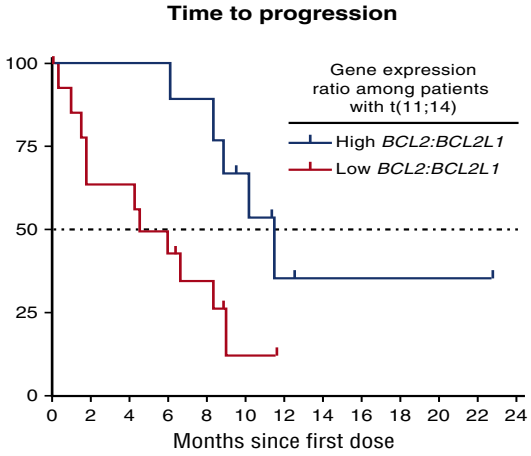
1. Roberts AW et al. *NEJM* 2015
2. Punnoose E et al. *Mol Cancer Ther* 2016

Targeting BCL-2 in RRMM









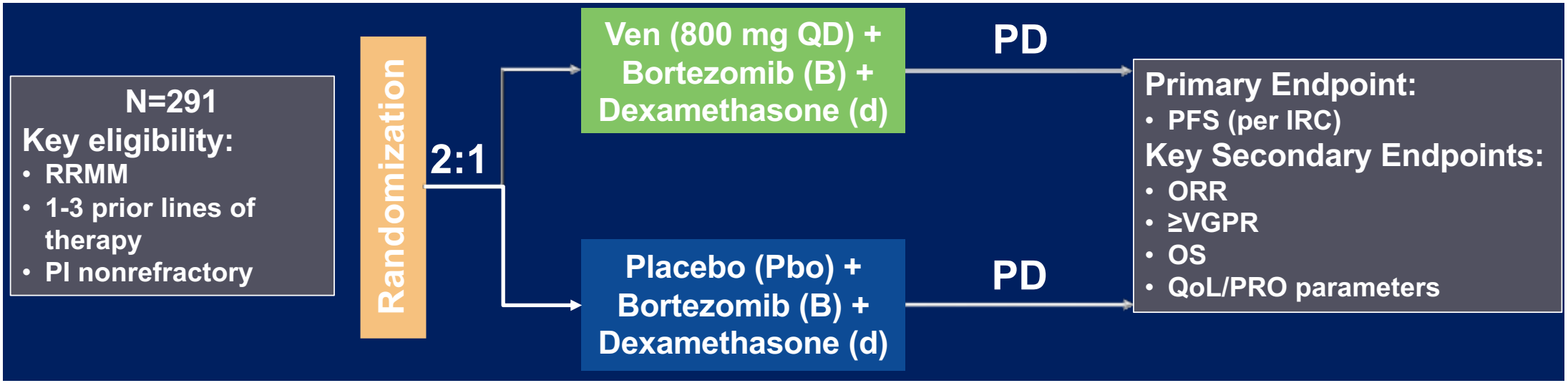
Venetoclax : clinical data in RRMM

Monotherapy (n=66)[1] (median 5 prior lines)	+ Dex in t(11;14) (n=20)[2]	+Bort-Dex (n=66)[3] (median 3 prior lines)	+K-dex (n=42)[4] (median 2 prior lines)	+Dara-Dex (n=24)[5] (median 2.5 prior lines)	+Bort-Dara-Dex (n=24)[5] (median 1 prior lines)
ORR 21% (40% in t(11;14))	ORR 65% (ORR 82% in Bort-R & 71% in Len-R)	ORR 67% (97% in Bort-sensitive & 94% in BCL2 high)	ORR 79% (≥CR 38%) (1-3 prior lines) non-t(11;14) (n=34): CR 32%; in t(11;14), n=8; CR 63%)	ORR 95% (≥CR 54%) All pts were t(11;14 pos)	ORR 92% (≥CR 42%) (1-3 prior lines) non-t(11;14) (n=34): CR 32%; in t(11;14), n=8; CR 63%)
G 3-4 AEs: Thrombocytopenia (26%), Neutropenia (21%), Anemia (14%), Leukopenia (14%), Lymphopenia (15%)	G3-4 AEs in ≥10% pts: Lymphopenia (15%), Hypophosphatemia (15%), Hyperuricemia (10%), Tumor lysis Sd (10%)	G3-4 AEs: Thrombocytopenia (29%), Anemia (15%), Neutropenia (14%)	G3/4 AEs: Lymphopenia 31%; Neutropenia 17%; Hypertension (14%); Thrombocytopenia (12%); Pneumonia (12%)	All grade AEs: Neutropenia 17%; Hypertension (25%); Thrombocytopenia (4%); Grade 3-4 Infections (21%)	All grade AEs: Neutropenia 4%; Hypertension (8%); Thrombocytopenia (13%); Grade 3-4 Infections (17%)

RRMM, relapsed/refractory multiple myeloma; ORR, overall response rate; K, carfilzomib; Len, lenalidomide; Bort, bortezomib; CR, complete response; Bort-R/Len-R, Bort/Len-refractory;

1. Kumar, et al. Blood 2017;130(22):2401-2409; 2. Kaufman et al, ASH 2017, abstract 3131; 3. Moreau, et al. Blood. 2017;130(22):2392-2400; 4. Costa et al. ASH 2018, abstract 303; 5. Kaufmann ASCO 2020.

BELLINI Study Design

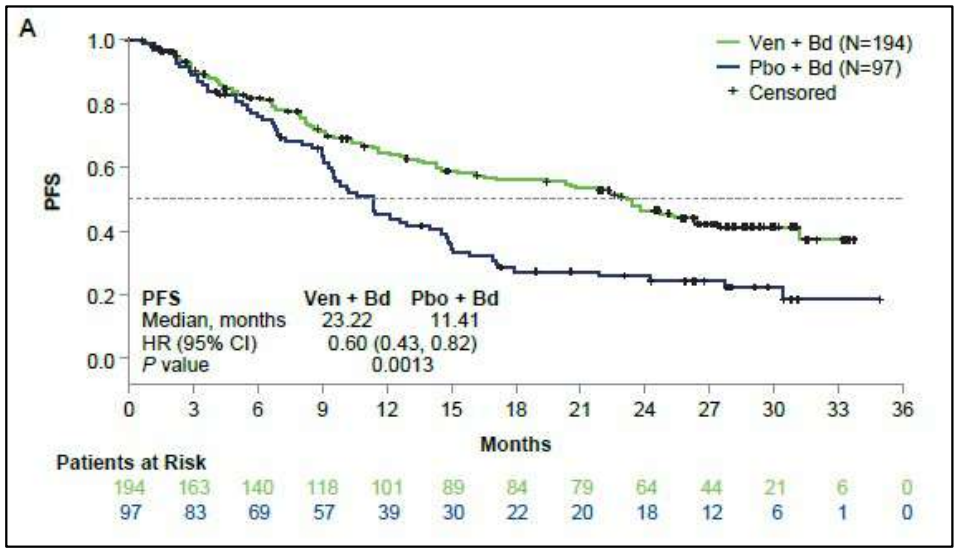


Cycles 1-8: 21-day, bortezomib 1.3 mg/m^2 days 1, 4, 8, 11 and dexamethasone 20 mg days 1, 2, 4, 5, 8, 9, 11, 12

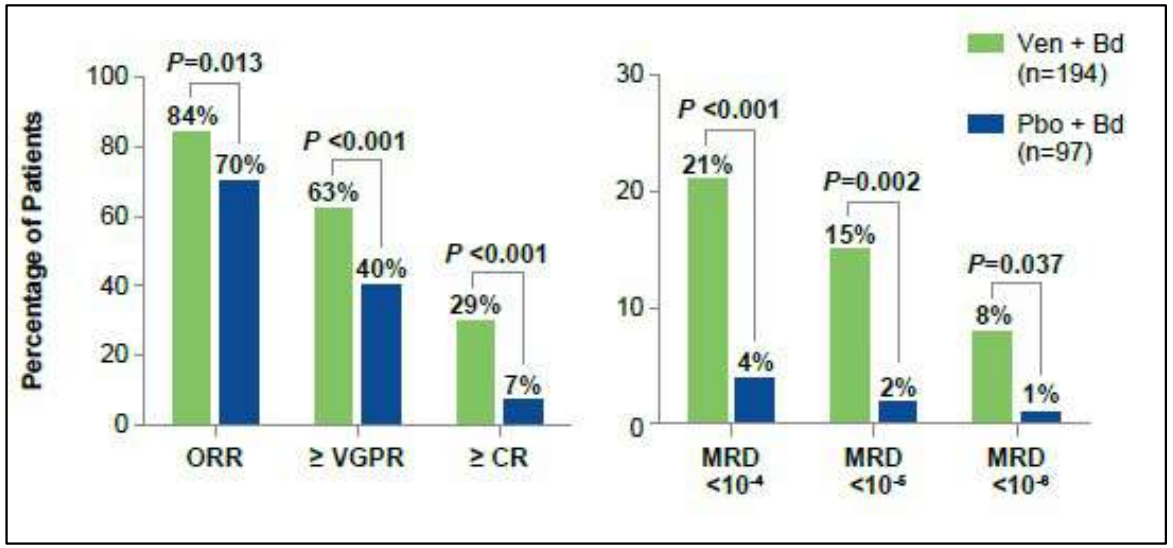
Cycles 9+: 35-day, bortezomib 1.3 mg/m^2 days 1, 8, 15, 22 and dexamethasone 20 mg days 1, 2, 8, 9, 15, 16, 22, 23

Stratification factors	• Bortezomib sensitive vs naïve • Prior lines of therapy: 1 vs 2–3
Nonranked secondary endpoints	PFS in BCL-2^{high} (IHC), DOR, TTP, MRD negativity rate, other PROs (GHS, fatigue)
Key subgroup analyses	t(11;14), high/standard-risk cytogenetics, and *BCL2* expression (gene expression)

PFS for All Patients



Response Rates in All Patients



- PFS and response rates favored the Ven + Bd arm
  - Median PFS was 23.2 months for patients receiving Ven + Bd and 11.4 months in the Pbo + Bd arm (HR, 0.60 [95% CI, 0.43-0.82]; *P=0.0013*)
  - The ORR was 84% in the Ven + Bd arm vs 70% in the Pbo + Bd arm (*P*=0.013)
- Minimal residual disease (MRD) negativity was more common in the venetoclax arm than the placebo arm at cutoffs of 10^{-4}, 10^{-5}, and 10^{-6}

PFS: subgroup analysis

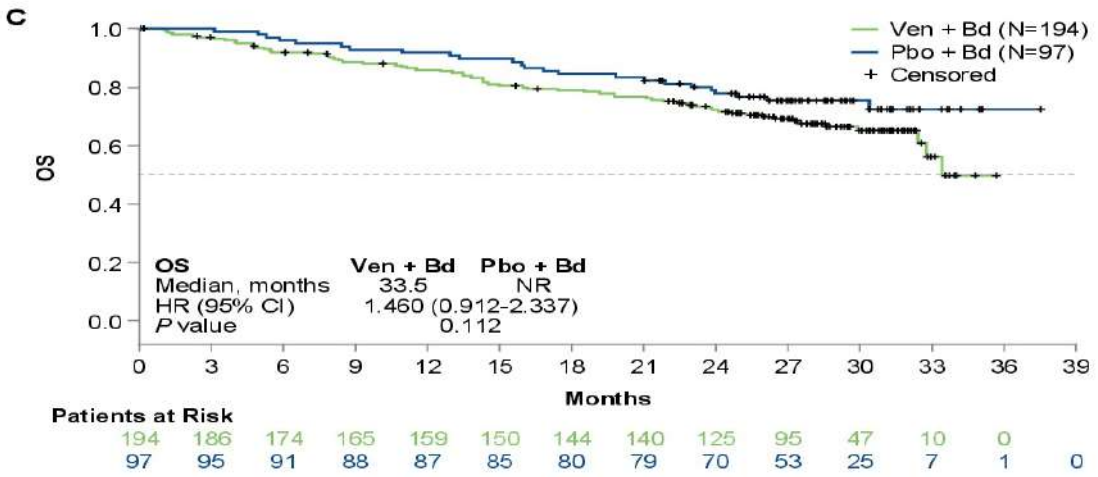
Table 3. Hazard Ratios for PFS and OS by *BCL2* Gene Expression and Cytogenetic Risk Status

Group		PFS HR (95% CI)	OS HR (95% CI)
A	t(11;14) or *BCL2*^{high} with standard-risk cytogenetics	0.32 (0.17-0.59)	0.90 (0.36-2.27)
B	t(11;14) or *BCL2*^{high} with high-risk cytogenetics	0.23 (0.04-1.21)	0.95 (0.12-7.49)
C	Non-t(11;14) and *BCL2*^{low} with standard-risk cytogenetics	0.71 (0.43-1.15)	1.35 (0.68-2.66)
D	Non-t(11;14) and *BCL2*^{low} with high-risk cytogenetics	1.88 (0.64-5.49)	6.01 (0.76-47.23)

HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

- **Importantly, outcomes in patients with high-risk cytogenetics were distinct based on t(11;14) status and *BCL2* gene expression**
  - **Trends in PFS and OS favored the venetoclax arm in patients with either t(11;14) or *BCL2*^{high} gene expression regardless of cytogenetics status**
  - **In contrast, patients with high-risk cytogenetics and *BCL2*^{low} gene expression in the absence of t(11;14) were most at risk when treated with venetoclax**

OS for All Patients



Bd, bortezomib + dexamethasone; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; Pbo, placebo; PFS, progression-free survival; Ven, venetoclax; VGPR, very good partial response.

Table 4. Treatment-Emergent AEs Leading to Death in the Safety Population

Deaths due to TEAEs in the safety population, n (%)	Ven + Bd (n=193)	Pbo + Bd (n=96)
Treatment-emergent deaths	12 (6)	1 (1)
Infection	9 (5)	0
Other[a]	3 (2)	1 (1)

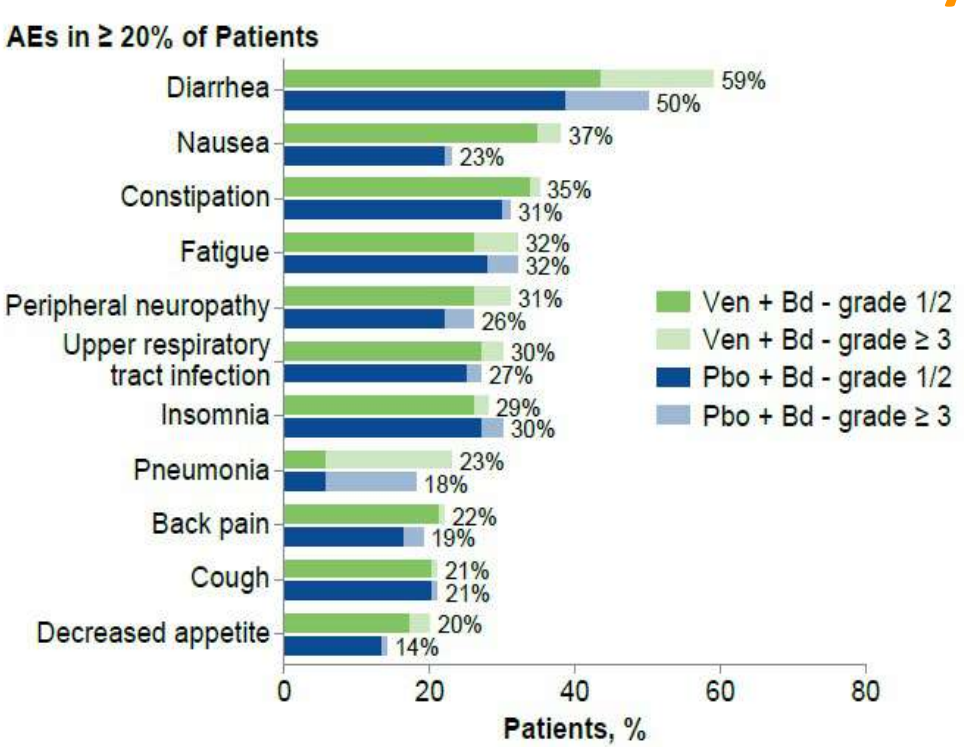
[a]Other included cardiac arrest (n=1), brain edema/coma (n=1), and multiple system organ dysfunction (n=2).
AE, adverse event; Bd, bortezomib + dexamethasone; Pbo, placebo; TEAE, treatment-emergent AE; Ven, venetoclax.

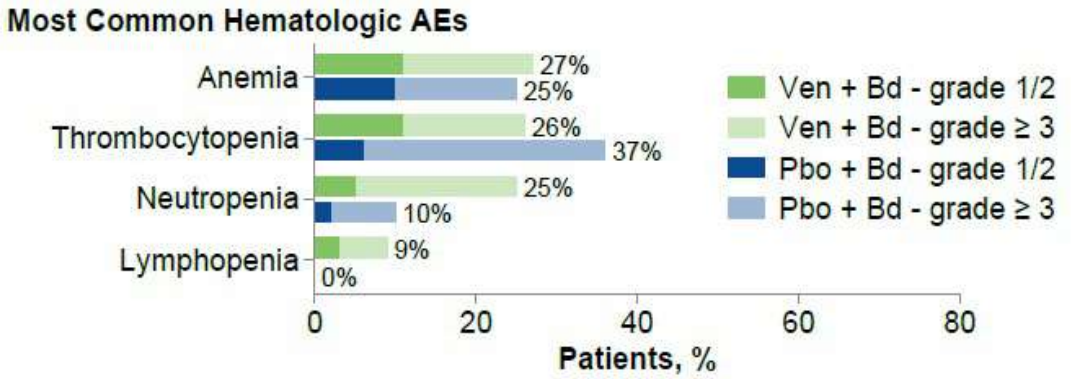
Table 5. Summary of Deaths by Treatment Group

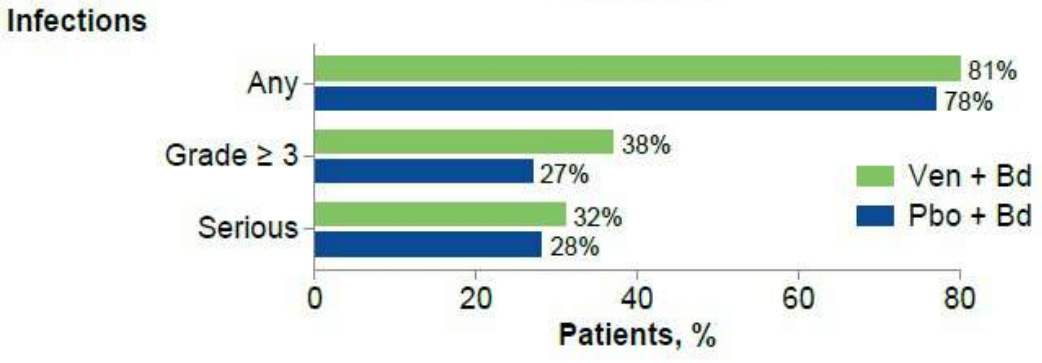
	Ven + Bd (n=193)	Pbo + Bd (n=96)	Total (N=289)
All Deaths	63 (33)	24 (25)	87 (30)
Deaths occurring while still receiving study drug	0	0	0
Death occurring off treatment within 30 days after last dose	14 (7)	1 (1)	15 (5)
Deaths occurring after 30 days of last dose	49 (25)	23 (24)	72 (25)

Bd, bortezomib + dexamethasone; Pbo, placebo; Ven, venetoclax.

Safety Overview







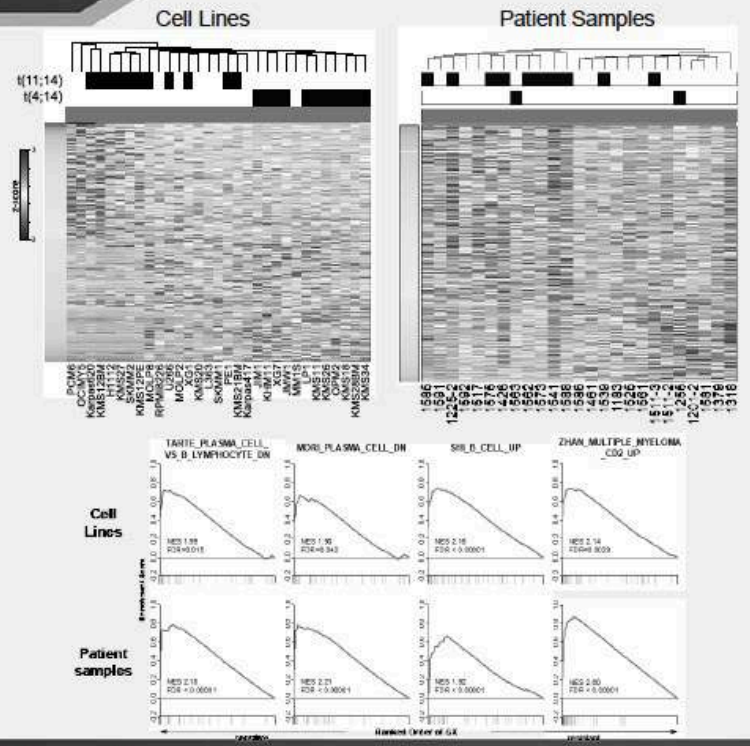
- The most common Gr3/4 AEs (in ≥15% of pts in the Ven + Pbo arms, respectively) were neutropenia (21% vs 8%), thrombocytopenia (15% vs 30%), anemia (16% vs 15%), diarrhea (15% vs 12%), and pneumonia (18% vs 13%)
- There were 12 treatment-emergent AEs (TEAEs) leading to death in the venetoclax arm and 1 in the placebo arm
  - Deaths attributed to infections were more common with Ven + Bd vs Pbo + Bd

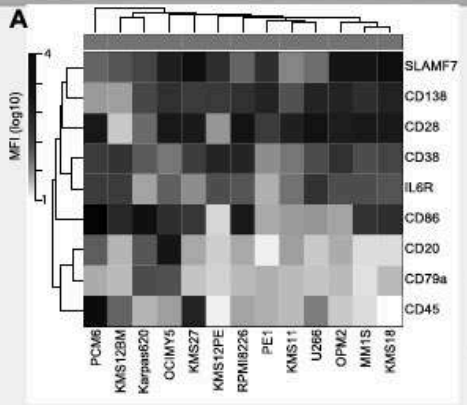
IMWG:
Venetoclax in RRMM

Personalized Treatment of Relapsed MM

Marc S. Raab, MD
Professor of Medicine,
Clinical Director, Heidelberg Myeloma Center
Department of Medicine V,
Heidelberg University Medical Center
&
German Cancer Research Center DKFZ
Heidelberg, Germany

Enrichment of B cell genes in venetoclax sensitive samples. Flow cytometry of cell surface markers predicts venetoclax sensitivity.

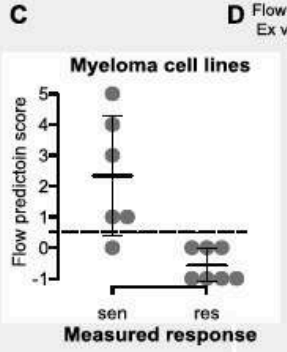


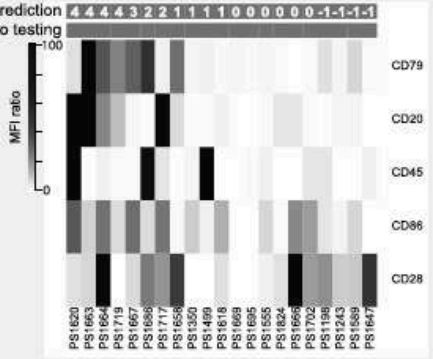


B

Marker	Score
CD79a	+2
CD20	+2
CD45	+1
CD86	+1
CD28	-1

Sensitive	Resistant
≥1	≤0

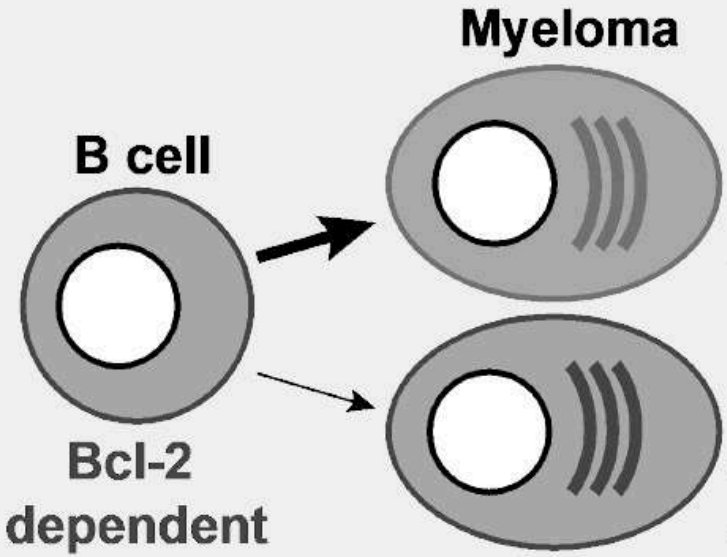




82% Sensitivity
80% Specificity
p=0.0089

Gupta et al., Blood, 2021

BH3-Mimetics require predictive markers for optimal use in MM



Plasma cell biology

Mcl-1 dependent

↑Proteasome Inhibitors

↑Immunomodulatory agents

B cell biology

Bcl-2 dependent

↓Proteasome Inhibitors

↓Immunomodulatory agents

Courtesy of L. Boise

P-051

Inferior outcomes for Multiple Myeloma (MM) patients (pts) harbouring t(11;14) and the promise of venetoclax, real-world Australian retrospective.

Kenneth Lim et al.

METHODS

- This was a retrospective, multicentre study conducted by members of the Australasian Leukaemia and Lymphoma Group, Myeloma Working Party. Cases were identified by interrogation of cytogenetics/FISH database.
- Here we aim to describe the historical outcomes of t(11;14) MM and response to Ven in a real-world cohort of Australian pts.

RESULTS

- The median progression free survival-1 (PFS-1) was 1.91 yrs (95% CI 1.73-2.56) [PI-based, n=60, PFS 1.84yrs (95% CI 1.61-2.41) vs IMiD-based, n=5, PFS 4.58yrs (95% CI 1.16-5.51), HR 0.68 p=0.45]. The median overall survival (OS) was 5.35 yrs (95% CI 4.12-6.56).
- Second and third line therapy was predominantly IMiD-based with recent introduction of anti-CD38 monoclonal antibodies (mAbs). Median PFS-2 was 0.77 yrs (95% CI 0.39-0.98) while median PFS-3 was 0.65 yrs (95% CI 0.34-1.16)

- Eleven pts (median 3 prior lines of therapy) were given Ven [Six pts in combination with PI, three with PI and mAbs and two with dexamethasone].
- **ORR to Ven was 55% with 45% ≥ VGPR. Median PFS with Ven was 0.54 yrs** (85% CI 0.05-2.17).
- Median PFS for patients with 1-4 lines (n=6) was 1.22 years and median PFS for patients with 5 lines or more (n=5) was 0.54 years, HR 0.56 (95% CI 0.12-2.5).

P-087

Real world efficacy and safety of venetoclax in t(11;14) multiple myeloma in Hungary

Virág Szita et al.

METHODS

- We retrospectively evaluated hematologic response, survival and safety after venetoclax treatment in t(11;14) myeloma patients in Hungary.
- Overall, 49 patients from seven clinical centers were reported. **32 relapsed/refractory patients**, who received venetoclax after multiple lines of therapy, often in an ultimate effort;

RESULTS

We observed remarkably good hematological response rates (ORR): 94% in the relapsed/refractory group. This translated into a median PFS of 9.6 months and a median OS of 14.6 months in the relapsed group;

P-084

Venetoclax monotherapy is feasible and efficient in patients with bcl-2 overexpressing relapsed/refractory multiple myeloma at high-risk sites: a case series.

David Cordas dos Santos et al.

METHODS

We report on three consecutive RRMM patients treated between 2019 and 2021. In all patients, IHC staining of MM cells in bone marrow biopsies demonstrated a **strong and homogeneous bcl-2 protein expression at relapse**, respectively. Venetoclax was dosed up to 800 mg daily and all patients remained on this dose level.

-Case 1: Penta-refractory RRMM patient; prior lines: 8

-Case 2: RRMM patient with CNS involvement; prior lines: 7

-Case 3: RRMM patient with extramedullary relapse after auto-allo-SCT

RESULTS

- First case: two months after venetoclax beginning, IgG levels dropped to normal range reaching a VGPR (Duration of response (DOR) is 7 months).
- Second case: a CR was achieved in PET-CT and MRI scans 5 months after beginning of venetoclax treatment (DOR 15 months
- Third case showed a CR of the previously described extramedullary manifestations three months after venetoclax dosing.

There were no hematological adverse events in any of the cases.

CONCLUSIONS

- The exportin1 inhibitor ***Selinexor*** can be a therapeutic option in MMRR patients after 1-2 lines of treatment in combination with Bor-Dex (previously treated with PI and IMiDs) including high-risk patients with a limited organ toxicity.

- The BCL-2 inhibitor ***Venetoclax*** can be considered a therapeutic option in selected RRMM patients as MM patients with t11,14 translocation but not all of them: *Biomarkers of response: BCL-2 overexpression by IHC, B cell genes overexpression by MM cells.*

Thanks for your attention…