BCL-2 and XPO1 inhibitors in Multiple Myeloma

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Disclosures

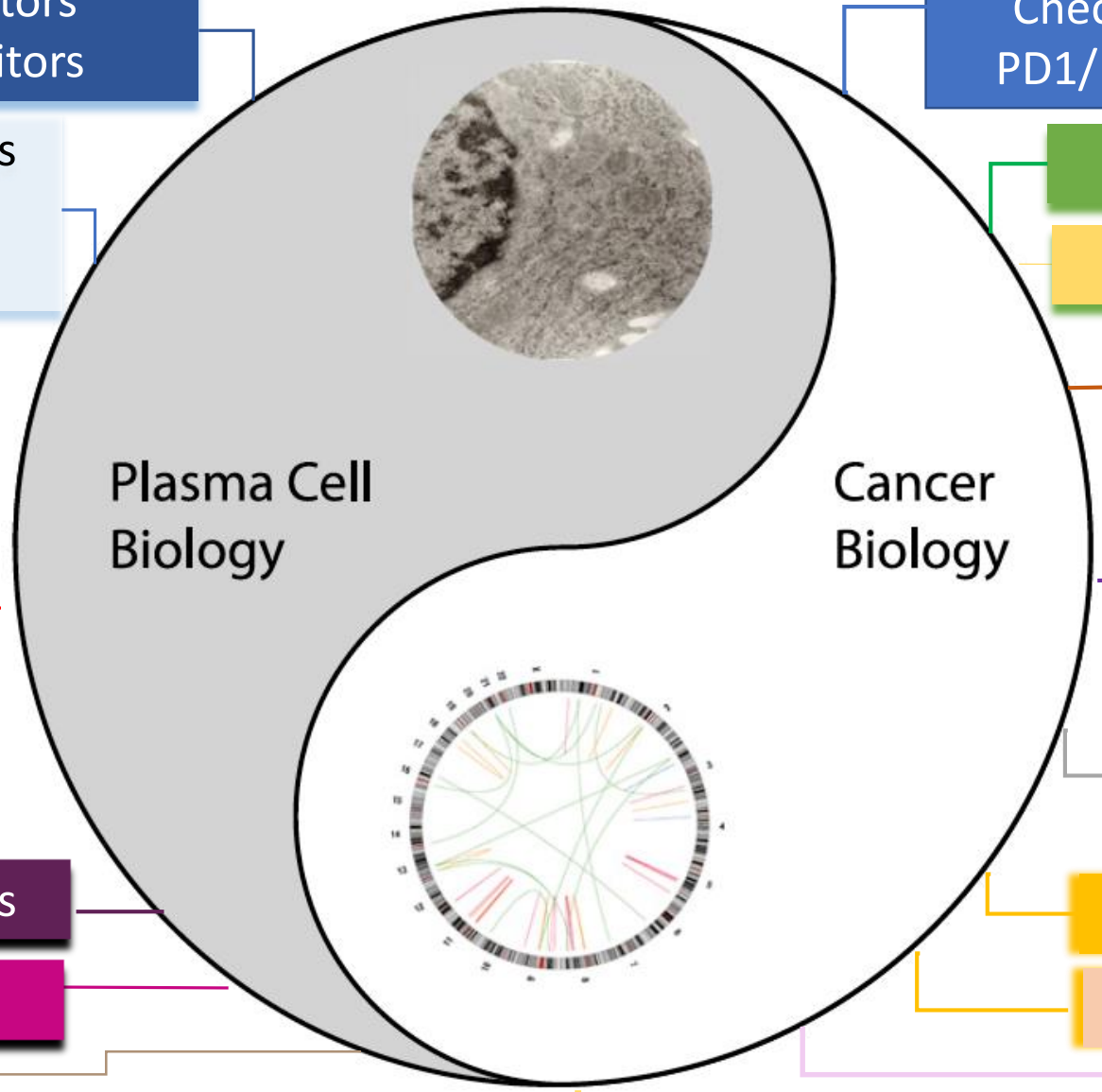
Honoraria & Speaker Bureau:

Abbvie, Amgen, BMS, Celgene, Genentech, Janssen, Karyopharm, Pfizer, Sanofi, Takeda

Research Funding: Pfizer

The Tao of Myeloma

Boise LH. Blood 2014



BCL2 Inhibitors
MCL1 inhibitors

Proteasome Inhibitors
DUBs inhibitors
VP/p97 inhibitors

Abs BiTES CARs
BCMA
SLAMF7
CD38
CD138
GPRC5D
FCRH5
CD56

BRD4 inh. /degraders

EP300 inhibitors

Steroids

DNA alkylating agents

CDK7,9 inhibitors

KSP inhibitors

PRMT5 inhibitors

HDAC inhibitors

FGFR3 inhibitors

AKT/mTORC
PIM2 kinase inhibitors

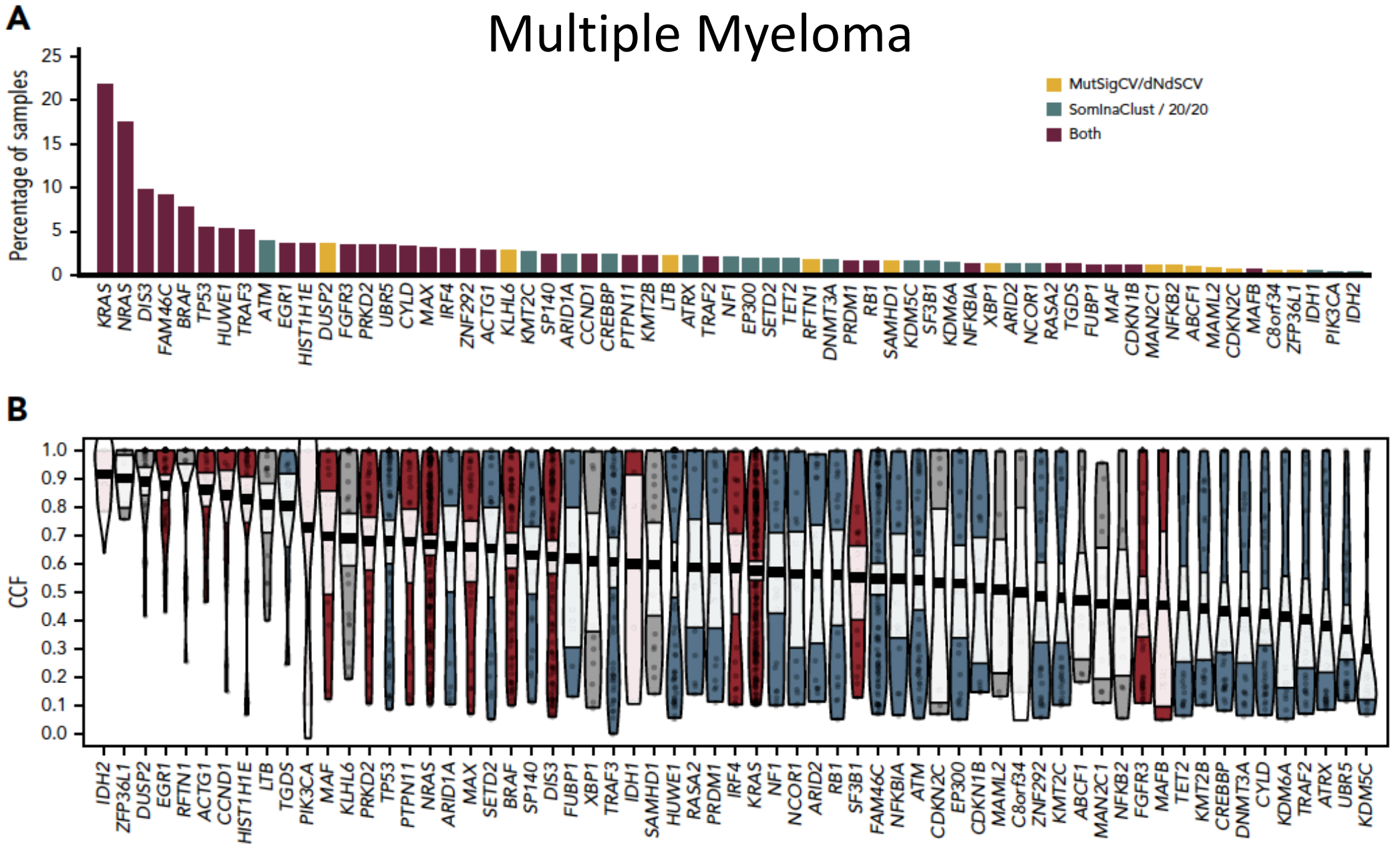
RAF/MEK/ERK inhibitors

XPO1 inhibitors

CELMODs (IMiDs)

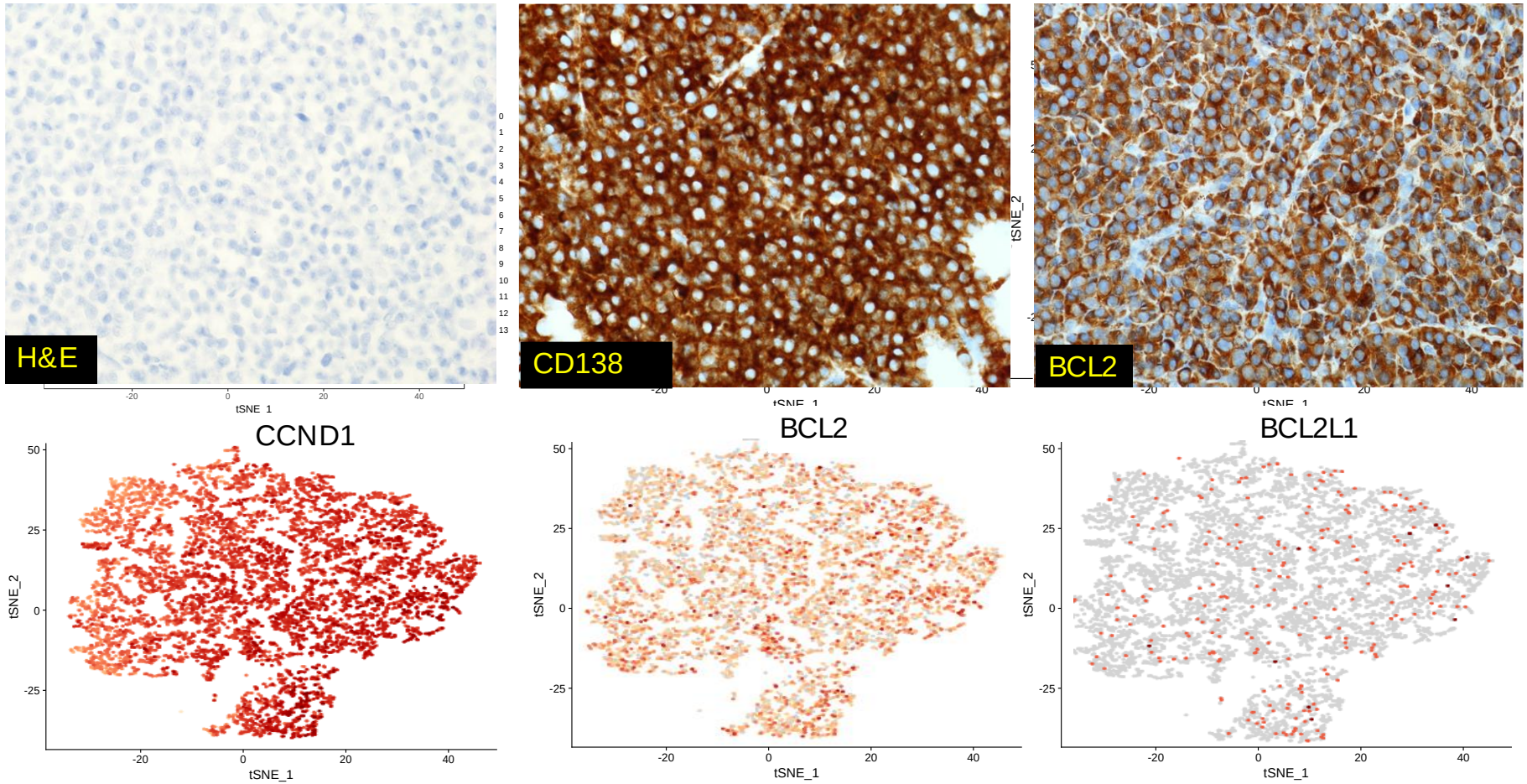
Checkpoint inhibitors
PD1/PDL1; LAG3; TIGIT

Oncogenic dependencies and molecular subgroups in Multiple Myeloma



Walker B et al Blood. 2018;132:587-597

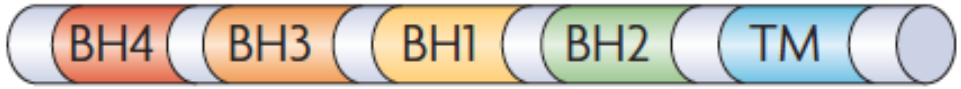
t(11;14) myeloma:
high CCND and BCL2 expression



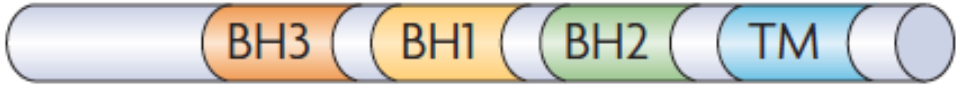
Neri P et al, unpublished work

BCL-2 family

Anti-apoptotic BCL-2 proteins:
BCL-2, BCL-W, BCL-XL, A1, MCL1

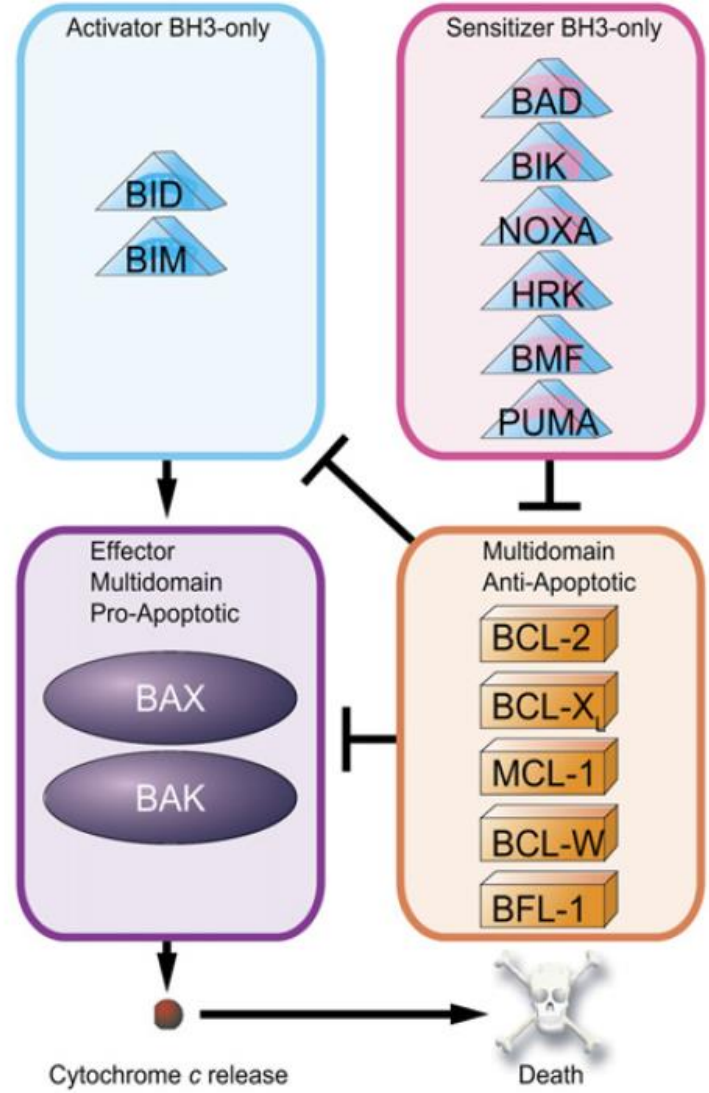


Pro-apoptotic BCL-2 proteins:
Effectors
BAX , BAK and BOK

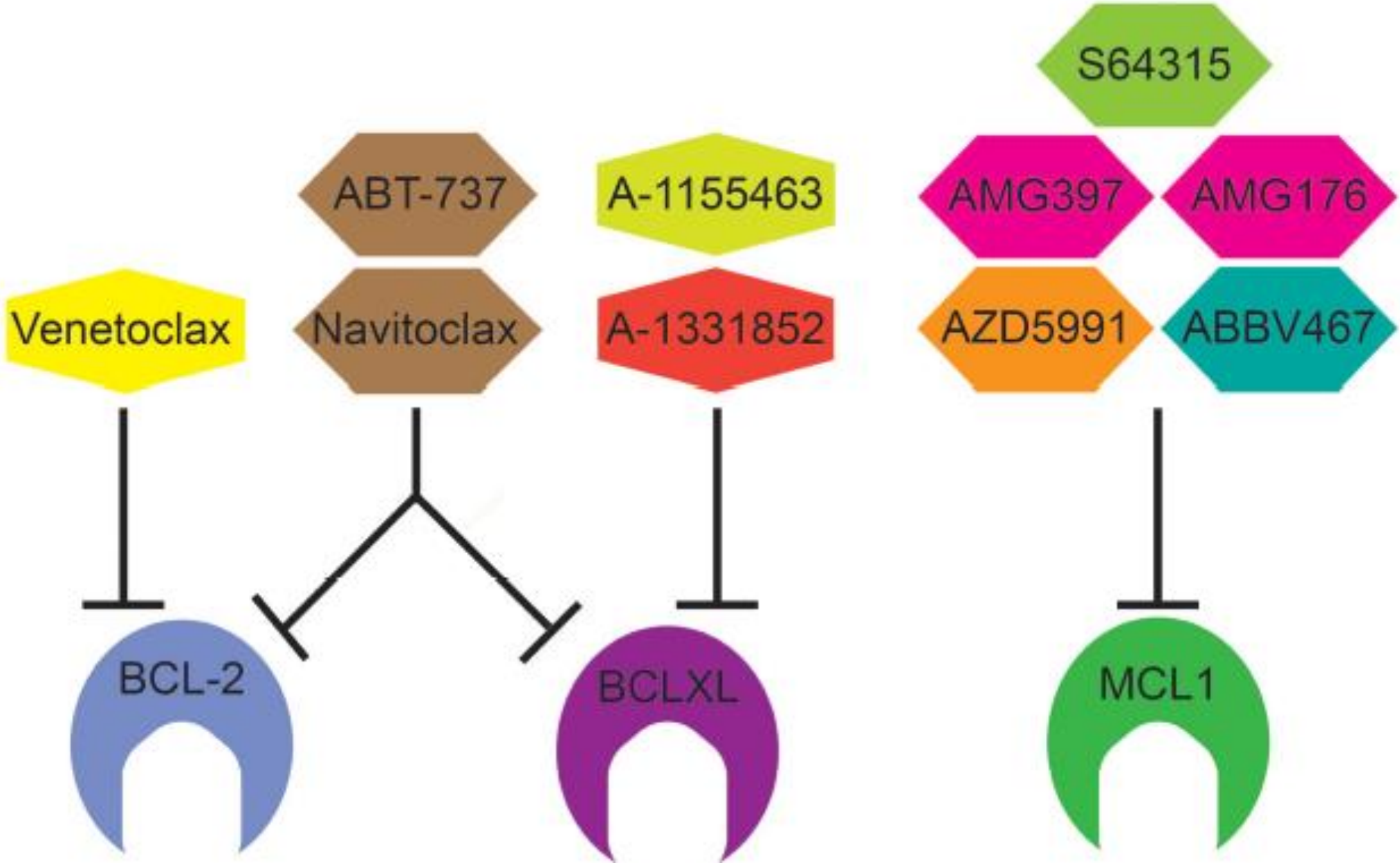


BH3-only proteins (Activators and sensitizers)
BID, BIM, BAD, BIK, BMF, BNIP3, HRK, NOXA and PUMA

Deng J et al, Cancer Cell 2007
Tait S et al, Mol Cell Biol 2010



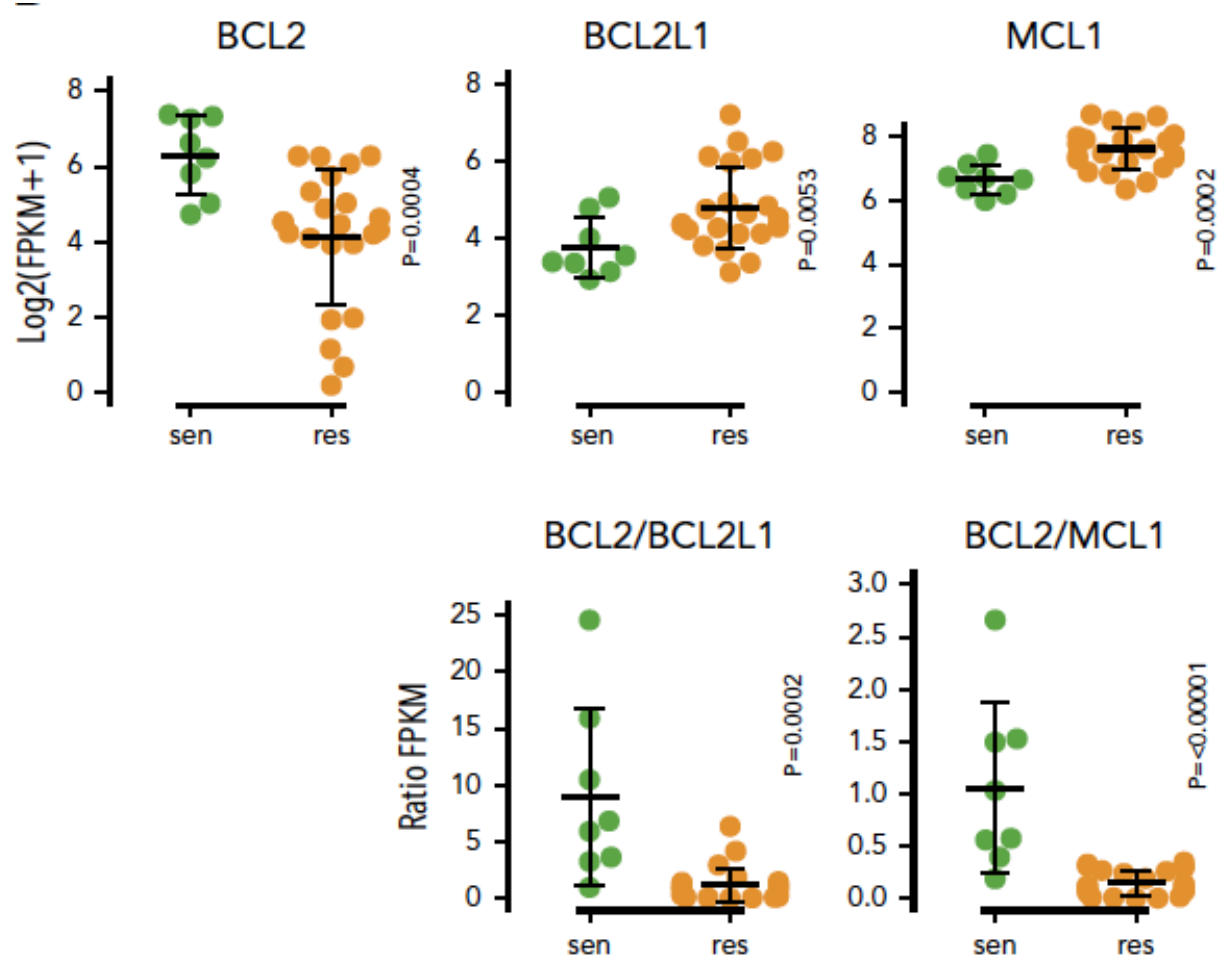
BCL-2 family



Gupta V et al Blood Lymphat Cancer 2021

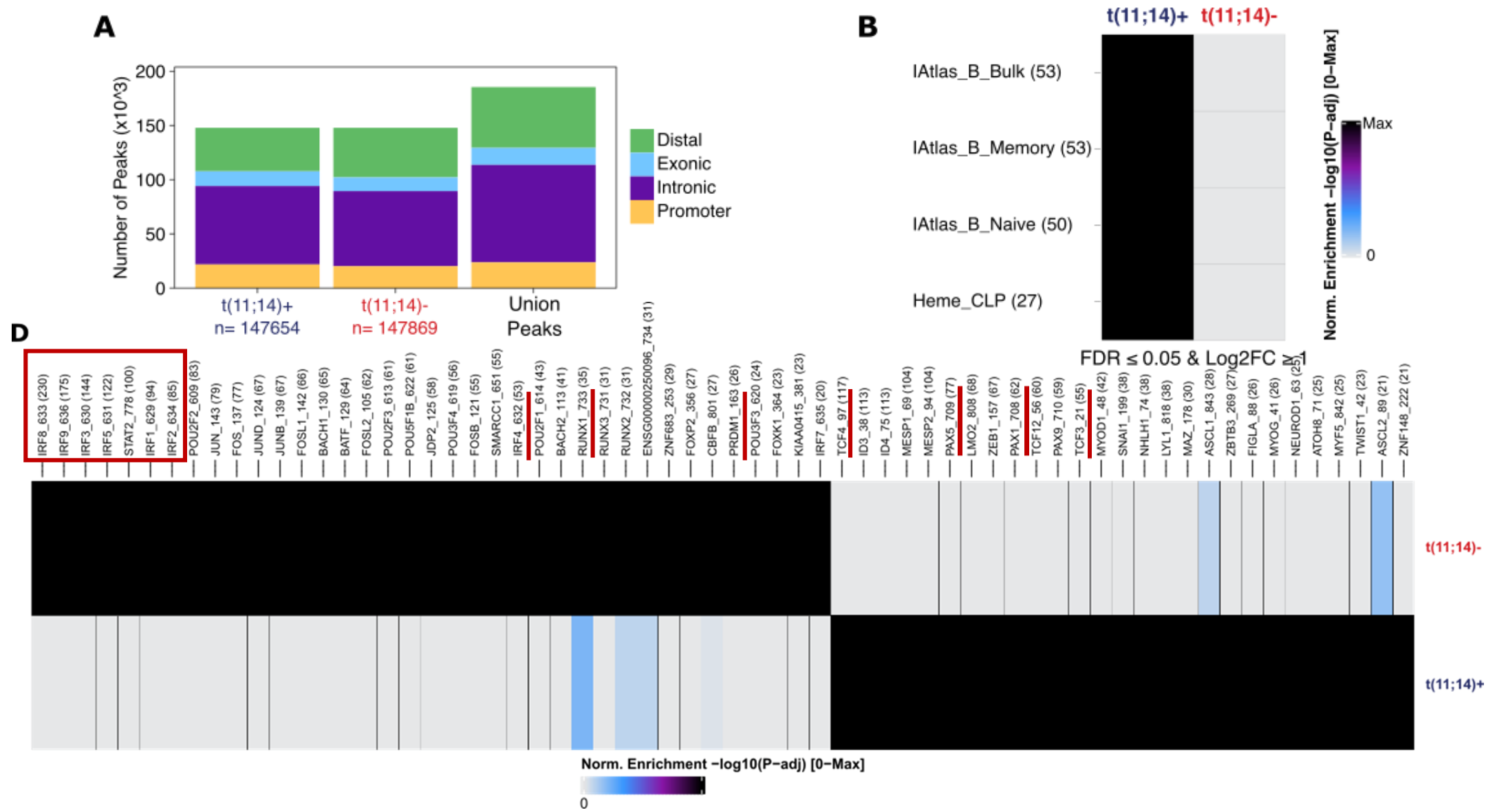
High Bcl-2 and B-cell genes expression in t(11;14) MM correlates with sensitivity to venetoclax

HMCL	LD_{50}, nM	Translocation	Target genes
SKMM2	7 ± 0.4	t(11;14)	CCND1
NAN-7	15 ± 3	t(11;14)	*CCND1*
XG-5	40 ± 12	t(11;14)	*CCND1*
Karpas-620	60 ± 13	t(11;14)	*CCND1*
KMS-12-PE	60 ± 17	t(11;14)	*CCND1*
KMS-12-BM	150 ± 7.5	t(11;14)	*CCND1*
JJN-3	2000 ± 315	t(14;16)	*c-MAF*
NAN-1	2000 ± 540	t(14;16)	*c-MAF*
KMS-11	2000 ± 660	t(4;14)	*MMSET/FGFR3*
XG-2	3000 ± 700	t(12;14)	unknown
RPMI 8226	4000 ± 760	t(14;16)	*c-MAF*
XG-6	5800 ± 112	t(16;22)	*c-MAF*
OPM-2	6000 ± 910	t(4;14)	*MMSET*
NCI-H929	7200 ± 840	t(4;14)	*MMSET/FGFR3*
L-363	7000 ± 620	t(20;22)	*MAFB*
BCN	8000 ± 566	t(14;16)	*c-MAF*
NAN-3	9200 ± 780	t(4;14)	*MMSET*
LP-1	10 000 ± 1 400	t(4;14)	*MMSET/FGFR3*
AMO-1	13 500 ± 1 600	t(12;14)	unknown
KMM-1	20 000 ± 740	t(6;14)	CCND3
XG-1	> 20 000	t(11;14)	*CCND1*
U-266	> 20 000	t(11;14)	*CCND1*
MM.1S	> 20 000	t(14;16)	*c-MAF*
JIM-3	> 20 000	t(4;14)	*MMSET/FGFR3*
XG-7	> 20 000	t(4;14)	*MMSET*



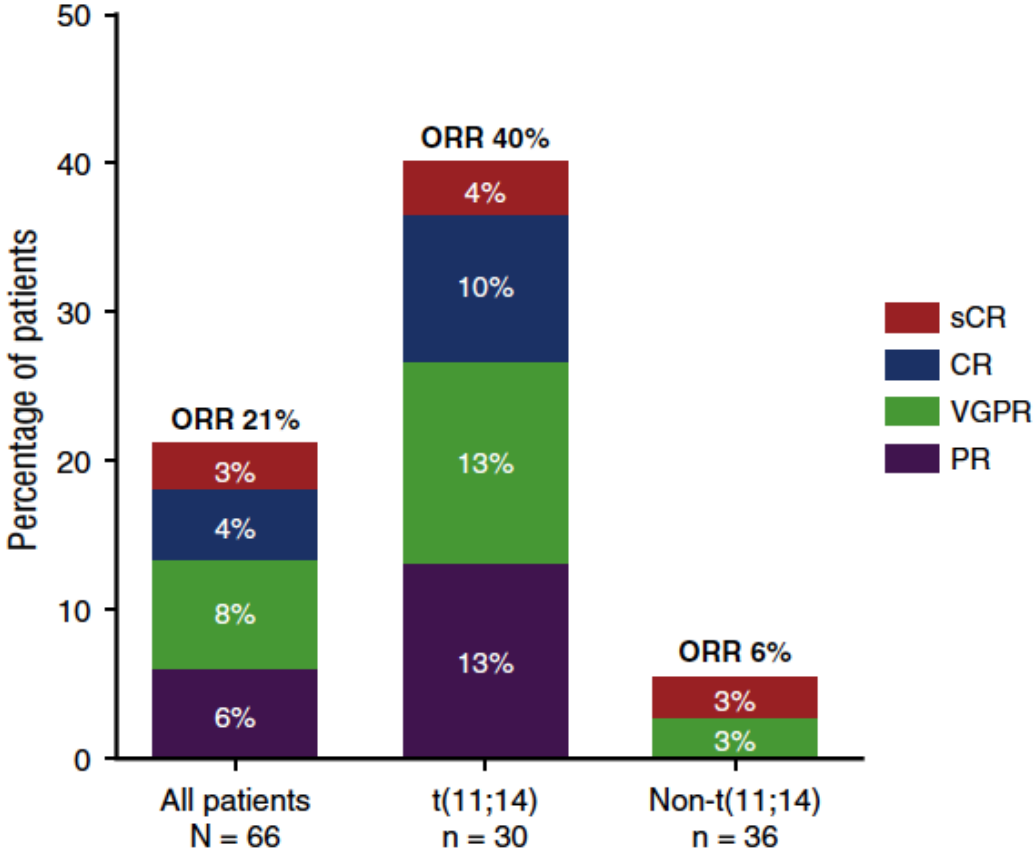
Bodet et al Blood 2011
Touzeau et al Leukemia 2013
Gupta et al Blood 2021

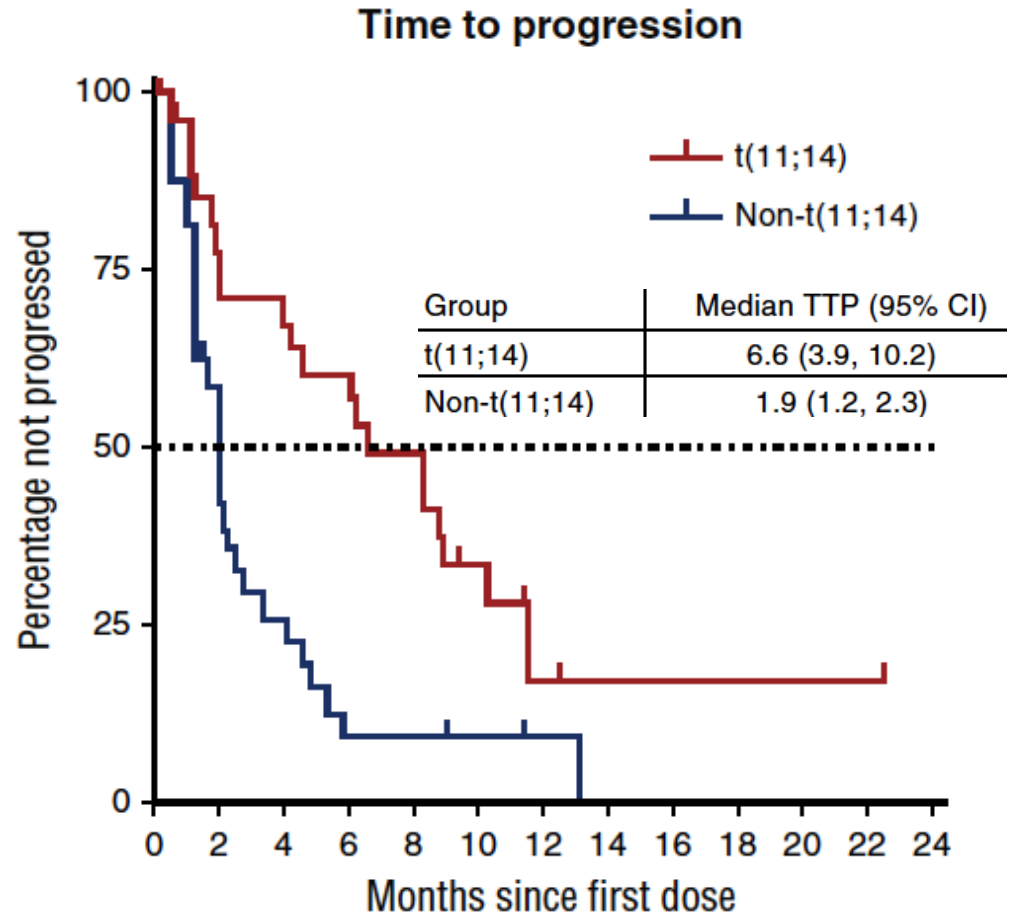
t(11;14) MM is characterized by a “B cell-like” epigenetic signature



Leblay N, Neri P et al. Blood 2021, abs # 725

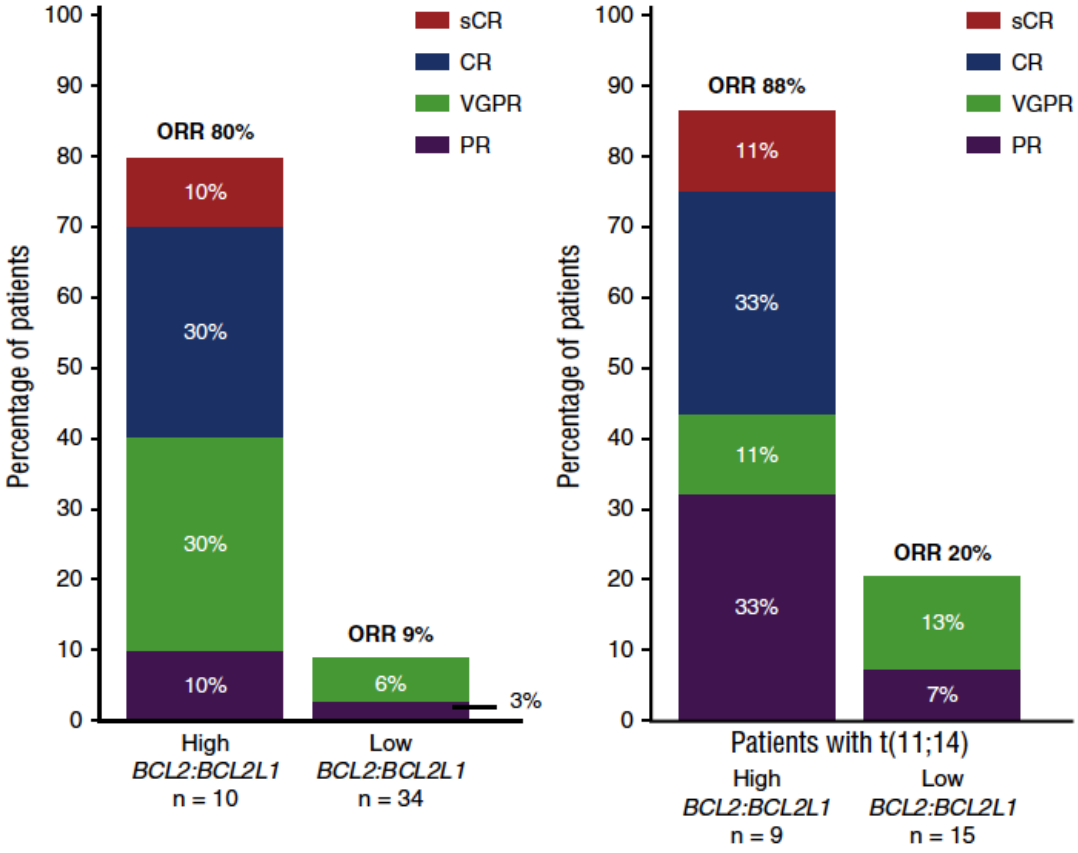
Venetoclax single agent activity in relapsed/refractory with t(11;14) multiple myeloma

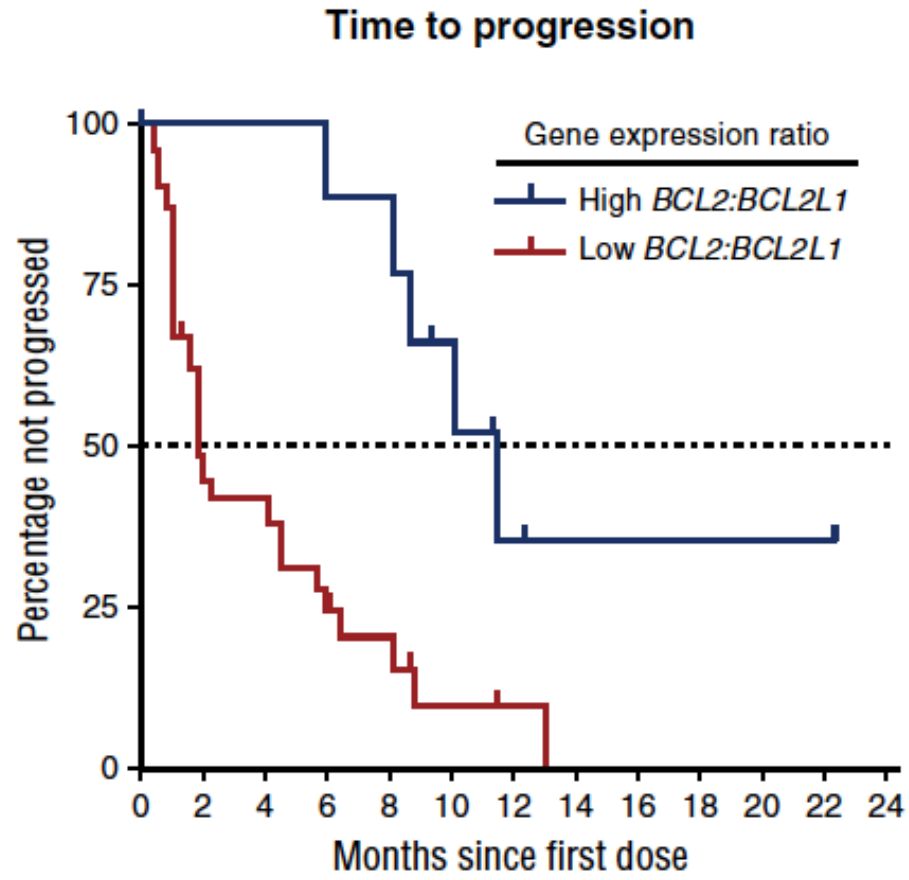




Kumar S et al Blood 2017

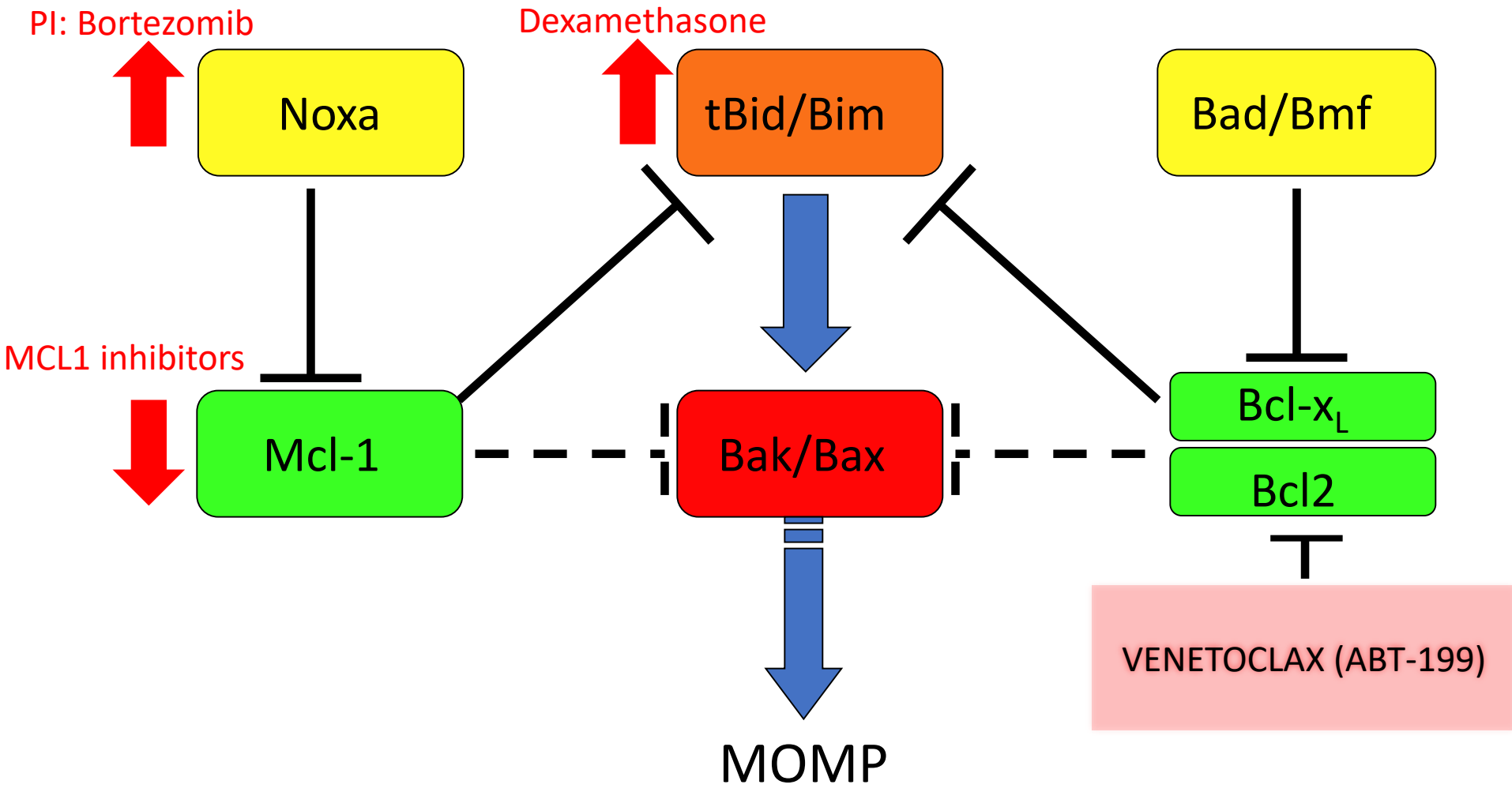
Venetoclax single agent activity in relapsed/refractory myeloma with high BCL2:BCL2L1 ratio





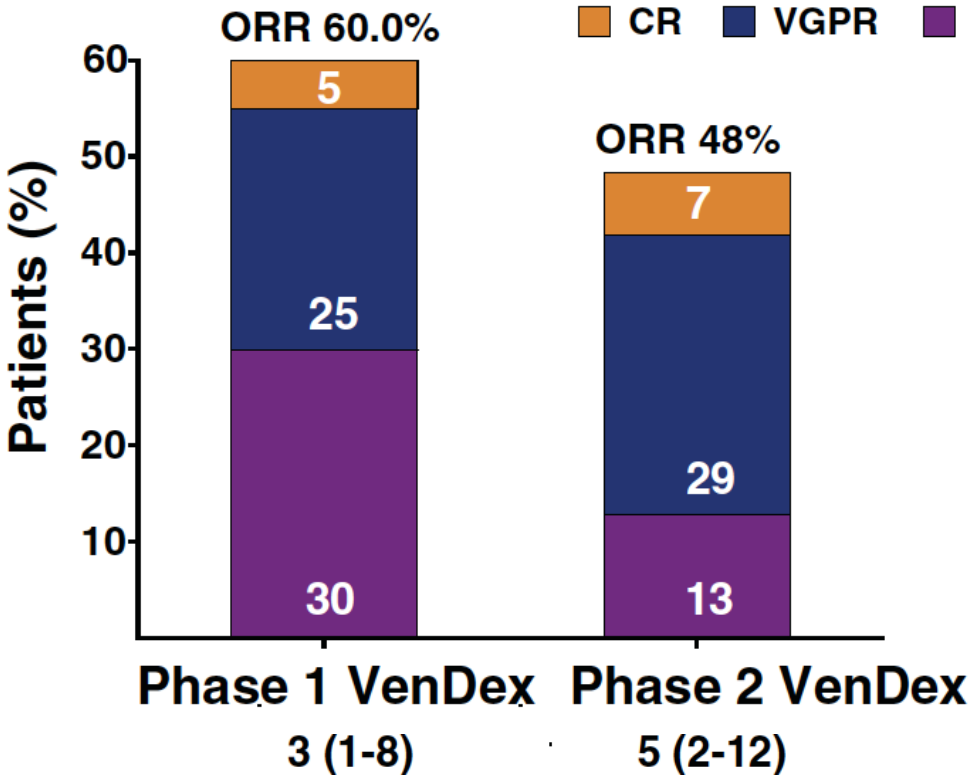
Kumar S et al Blood 2017

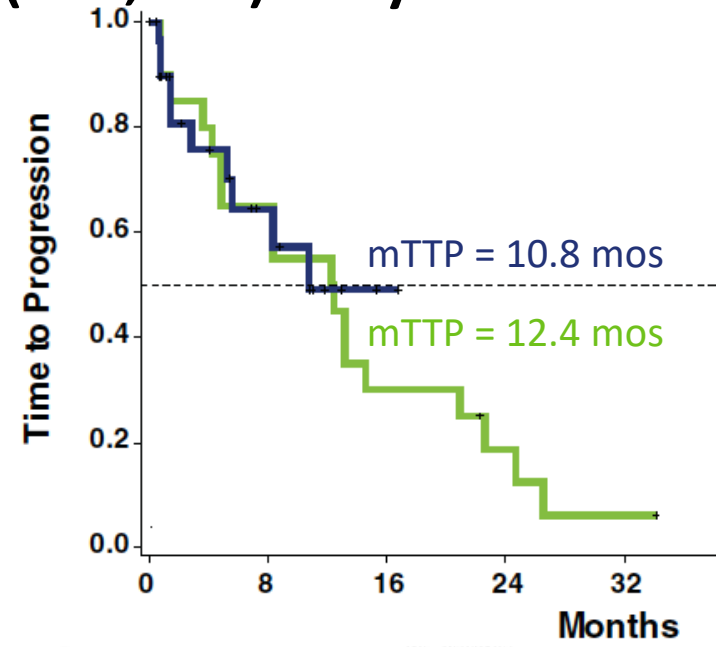
Strategies to enhance MM cells sensitivity to Venetoclax

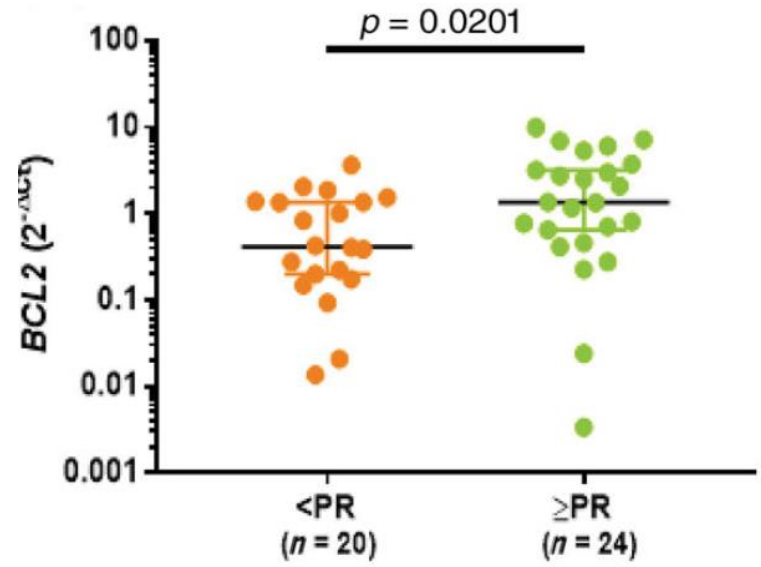


slide modified from original courtesy of Dr LH Boise

Venetoclax with dexamethasone in relapsed/refractory t(11;14) Myeloma

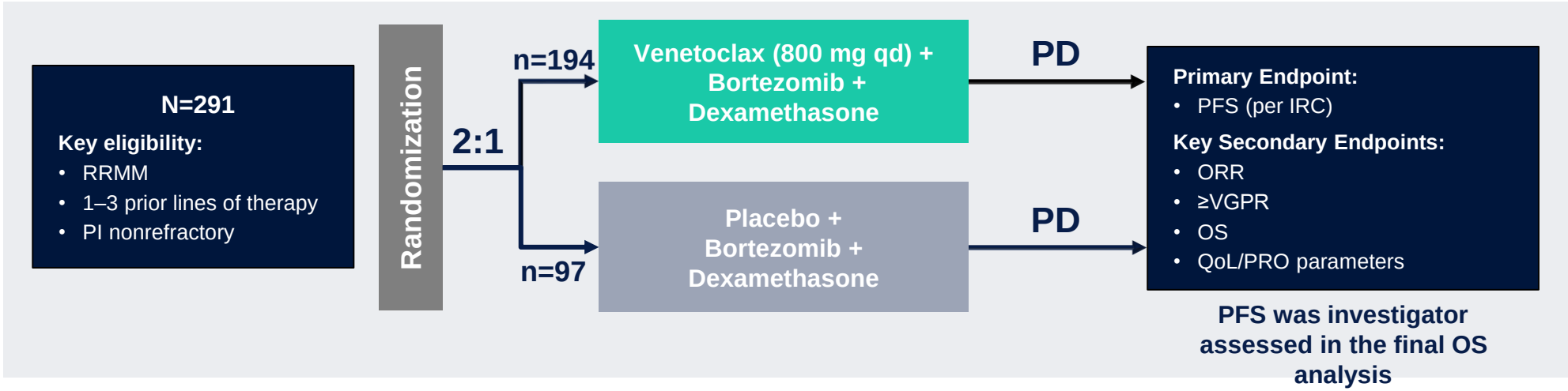






Kaufman J et al Am J Hematol 2021

BELLINI (NCT02755597) is a Phase 3, randomized, placebo-controlled, double-blind, multicenter study of patients with RRMM treated with Ven + Bd or Pbo + Bd



Cycles 1–8: 21-day cycle, 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 cycle, bortezomib 1.3 mg/m^2 Days 1, 8, 15, 22 and dexamethasone 20 mg Days 1, 2, 8, 9, 15, 16, 22, 23

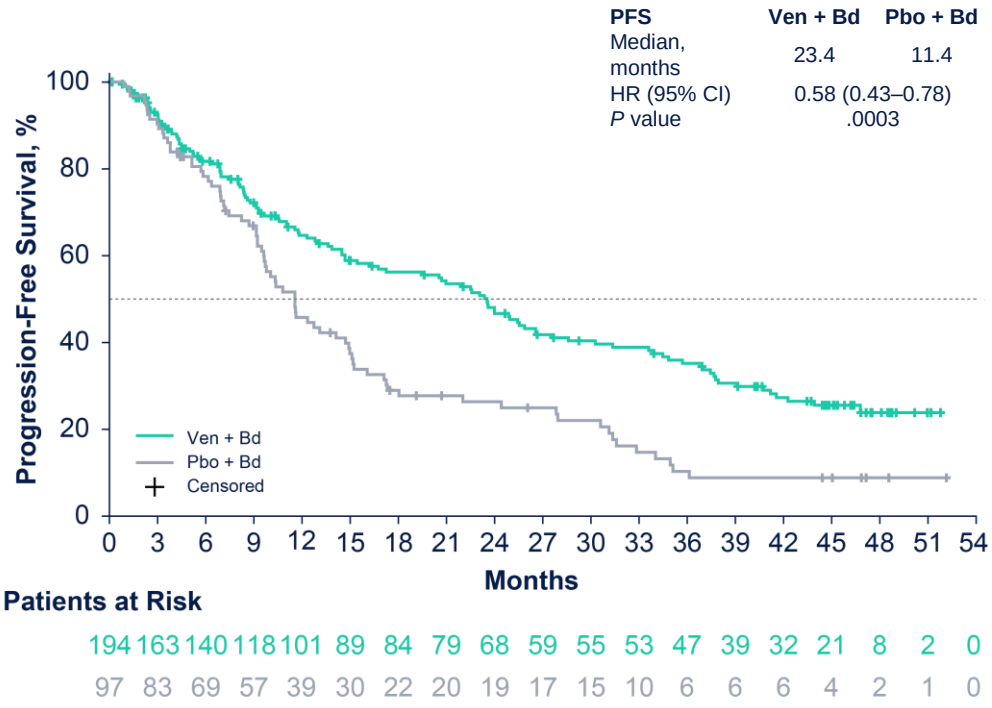
Stratification factors	• Bortezomib sensitive vs naïve • Prior lines of therapy: 1 vs 2 or 3
Non-ranked secondary endpoints	PFS in high BCL-2 (IHC), DOR, TTP, MRD negativity rate,[a] other PROs (GHS, fatigue)
Key subgroup analyses	t(11;14), high/standard-risk cytogenetics, and *BCL2* expression (gene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

[a]MRD negativity in bone marrow was measured by next-generation sequencing at the time of suspected CR/sCR and at 6 and 12 months post-confirmation of CR/sCR. Bd, bortezomib + dexamethasone; CR, complete response; DOR, duration of response; GHS, global health status; IHC, immunohistochemistry; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; Pbo, placebo; PFS, progression-free survival; PI, proteasome inhibitor; PRO, patient-reported outcome; qd, daily; QoL, quality of life; RRMM, relapsed/refractory multiple myeloma; sCR, stringent CR; TTP, time to progression; Ven, venetoclax; VGPR, very good partial response.

Kumar S et al, Lancet Oncol. 2020; 21:1630-1642.

PFS was significantly prolonged in the Ven + Bd arm compared with the Pbo + Bd arm; median OS was not reached in either treatment arm at a median follow-up of 45.6 months

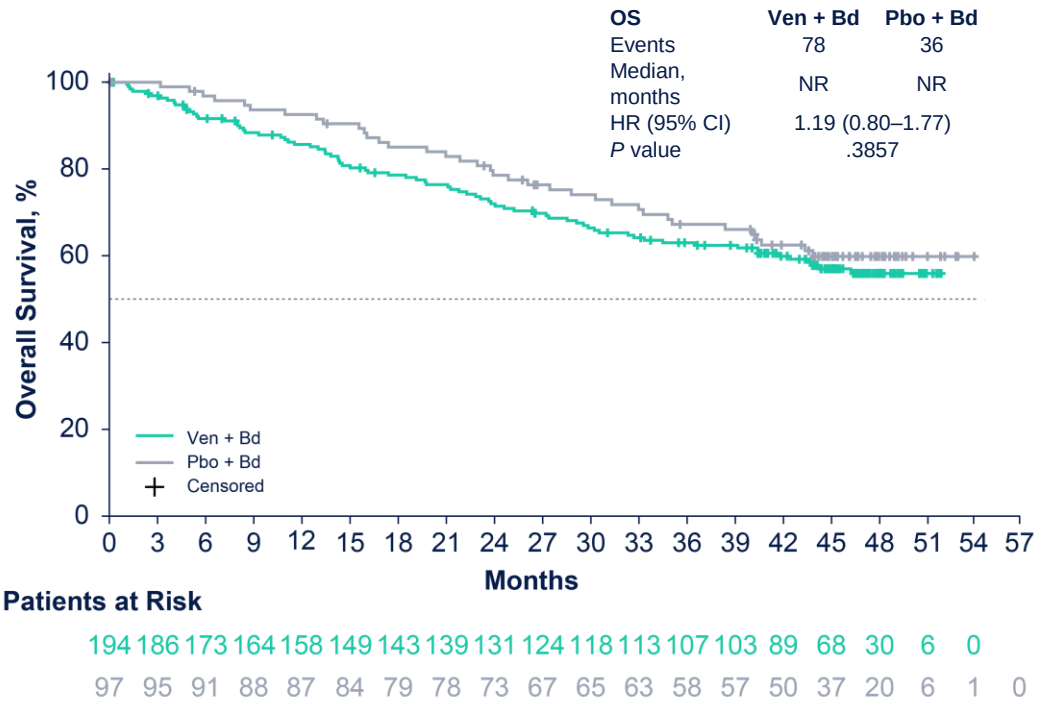
Investigator-Assessed PFS in All Patients



Patients at Risk

194	163	140	118	101	89	84	79	68	59	55	53	47	39	32	21	8	2	0
97	83	69	57	39	30	22	20	19	17	15	10	6	6	6	4	2	1	0

OS in All Patients



Patients at Risk

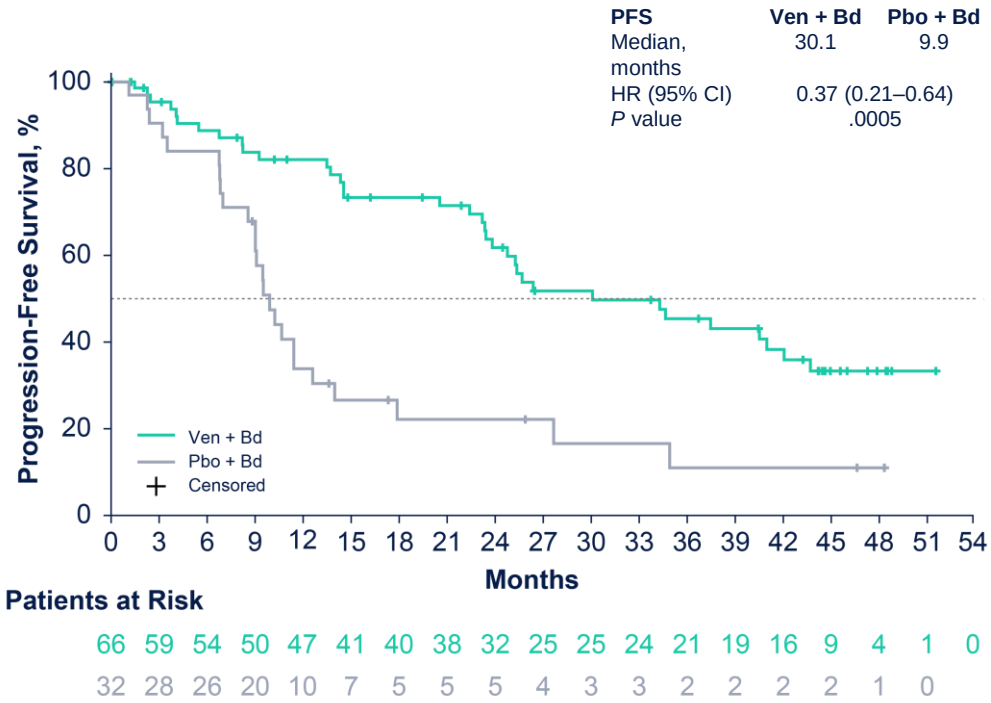
194	186	173	164	158	149	143	139	131	124	118	113	107	103	89	68	30	6	0
97	95	91	88	87	84	79	78	73	67	65	63	58	57	50	37	20	6	1	0

Bd, bortezomib + dexamethasone; HR, hazard ratio; NR, not reached; OS, overall survival; Pbo, placebo; PFS, progression-free survival; Ven, venetoclax.

Kumar S et al, Lancet Oncol. 2020; 21:1630-1642.

Among patients with *BCL2*^{high} expression, median PFS was 30.1 months in the Ven + Bd arm compared with 9.9 months in the Pbo + Bd arm (*P*=.0005)

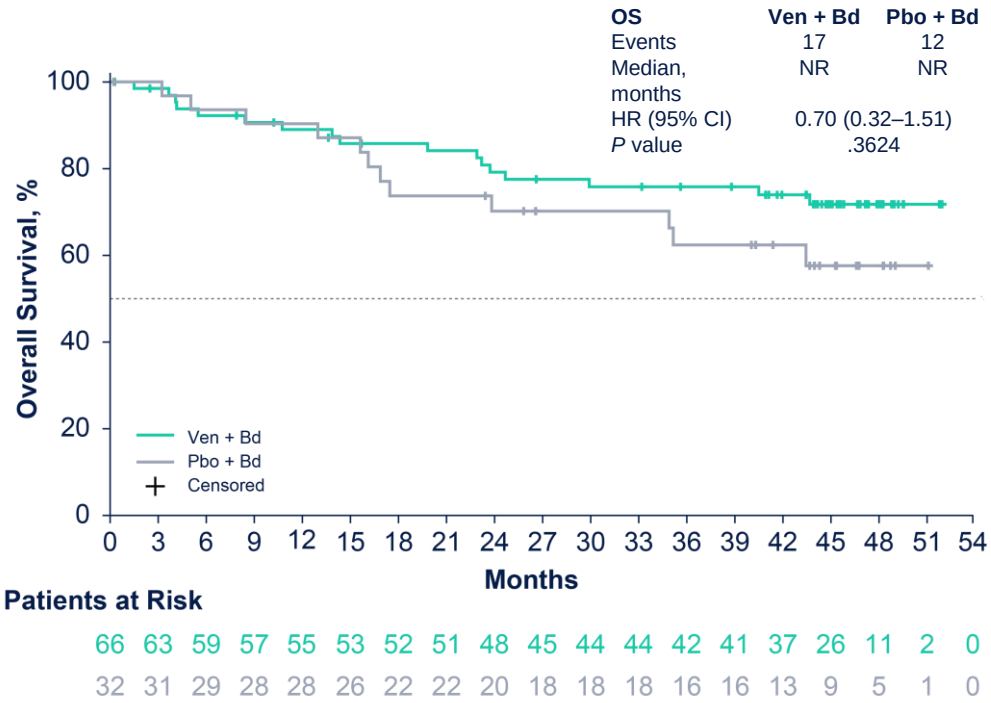
Investigator-Assessed PFS in Patients With *BCL2*^{high}



Patients at Risk

66	59	54	50	47	41	40	38	32	25	25	24	21	19	16	9	4	1	0
32	28	26	20	10	7	5	5	5	4	3	3	2	2	2	2	1	0	

OS in Patients With *BCL2*^{high}



Patients at Risk

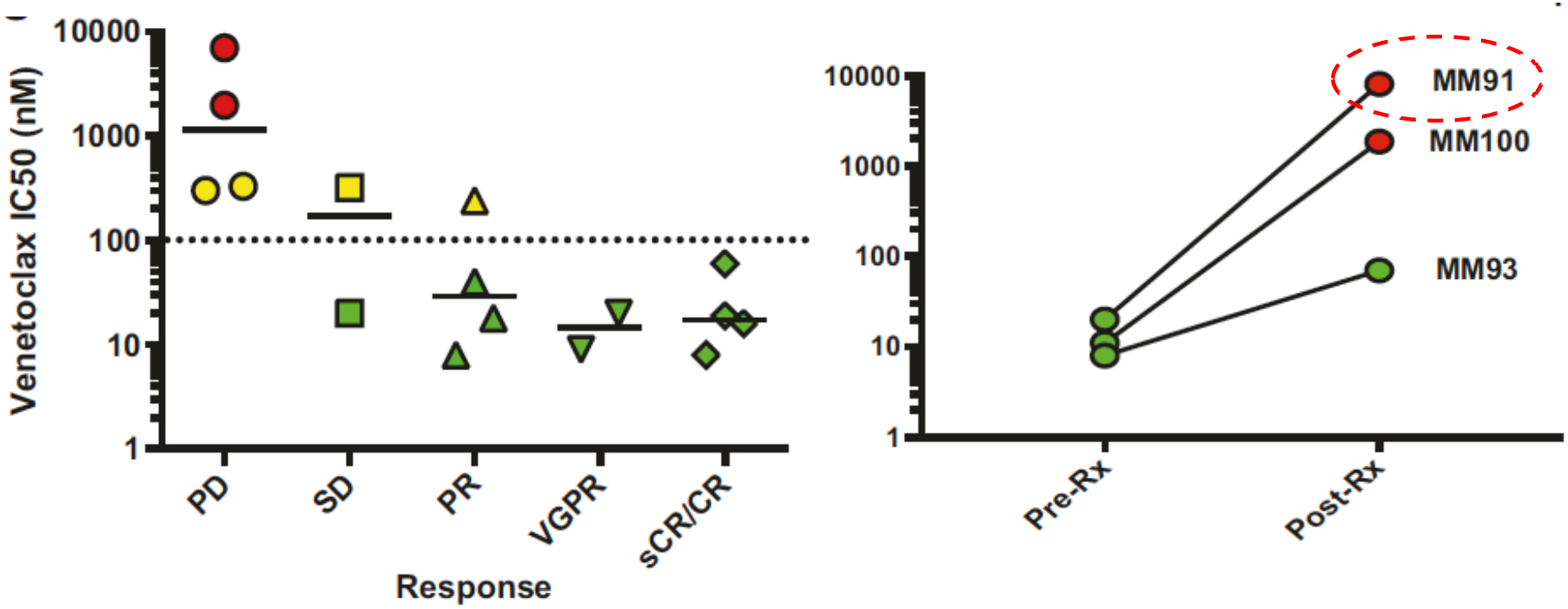
66	63	59	57	55	53	52	51	48	45	44	44	42	41	37	26	11	2	0
32	31	29	28	28	26	22	22	20	18	18	18	16	16	13	9	5	1	0

Bd, bortezomib + dexamethasone; HR, hazard ratio; NR, not reached; OS, overall survival; Pbo, placebo; PFS, progression-free survival; Ven, venetoclax.

Kumar S et al, Lancet Oncol. 2020; 21:1630-1642.

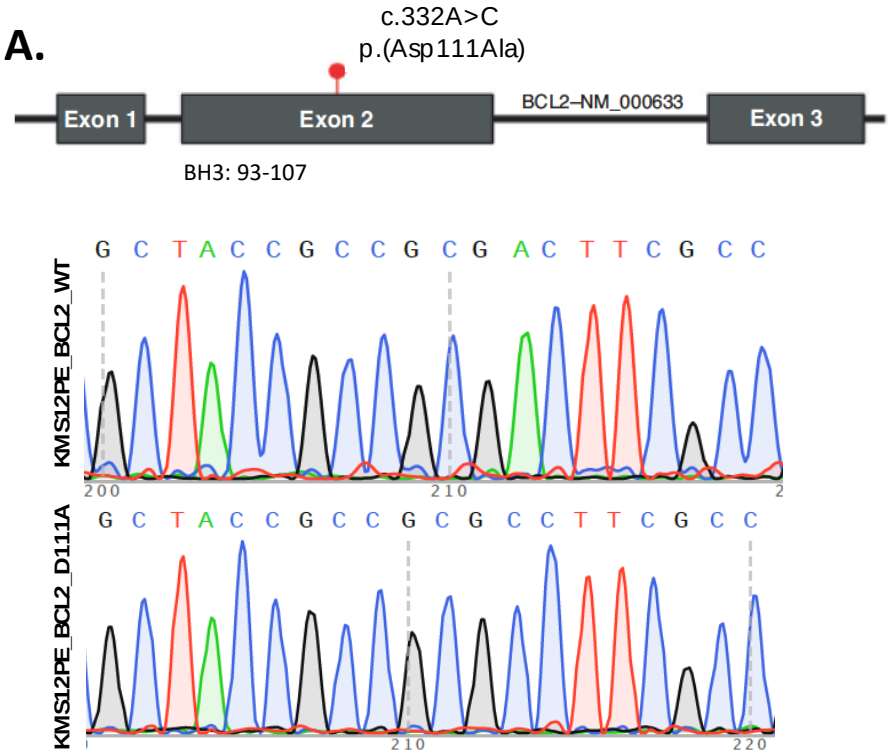
Ex-vivo sensitivity profiling strongly correlates with clinical response to venetoclax

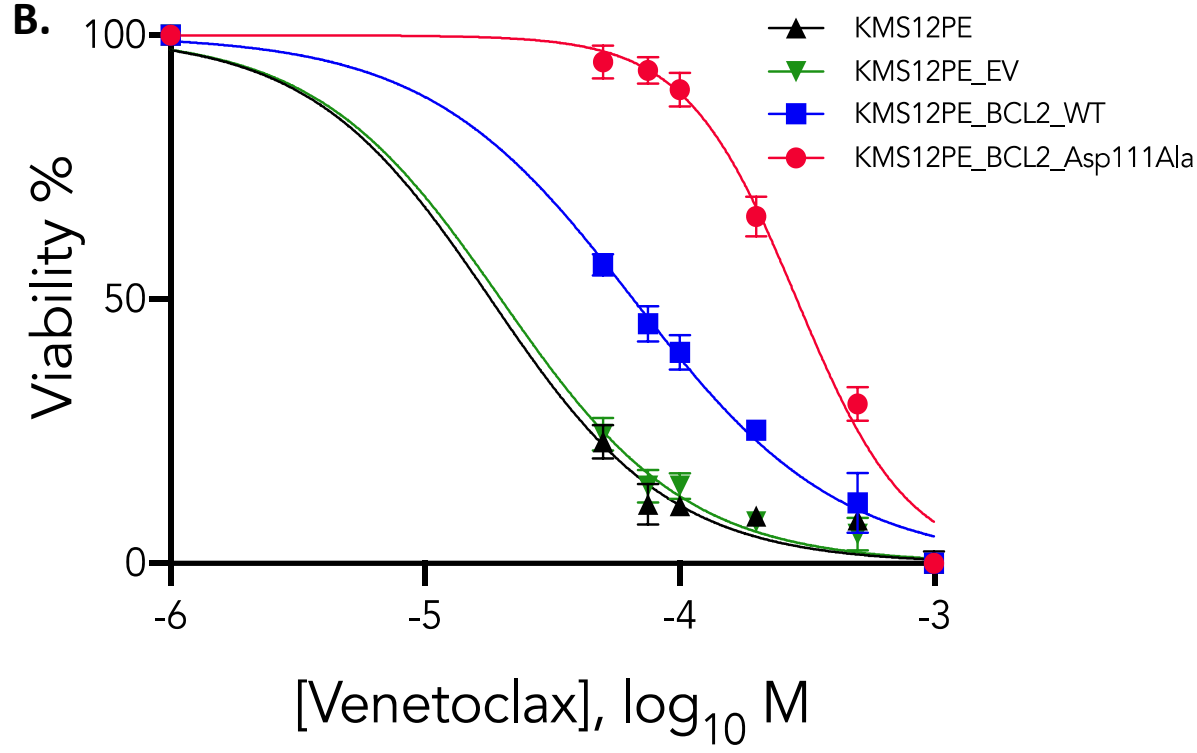
1000 folds increase in venetoclax IC50 at disease progression

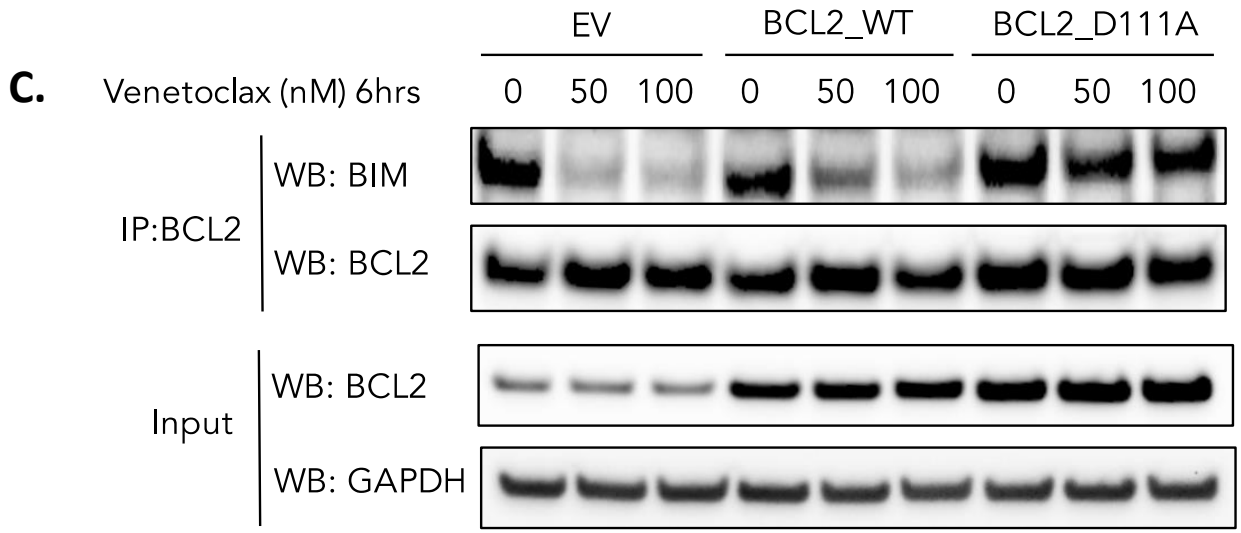


Matullis S et al Leukemia 2019 33:1291–1296

Acquired BCL2 D111A mutation induces resistance to Venetoclax





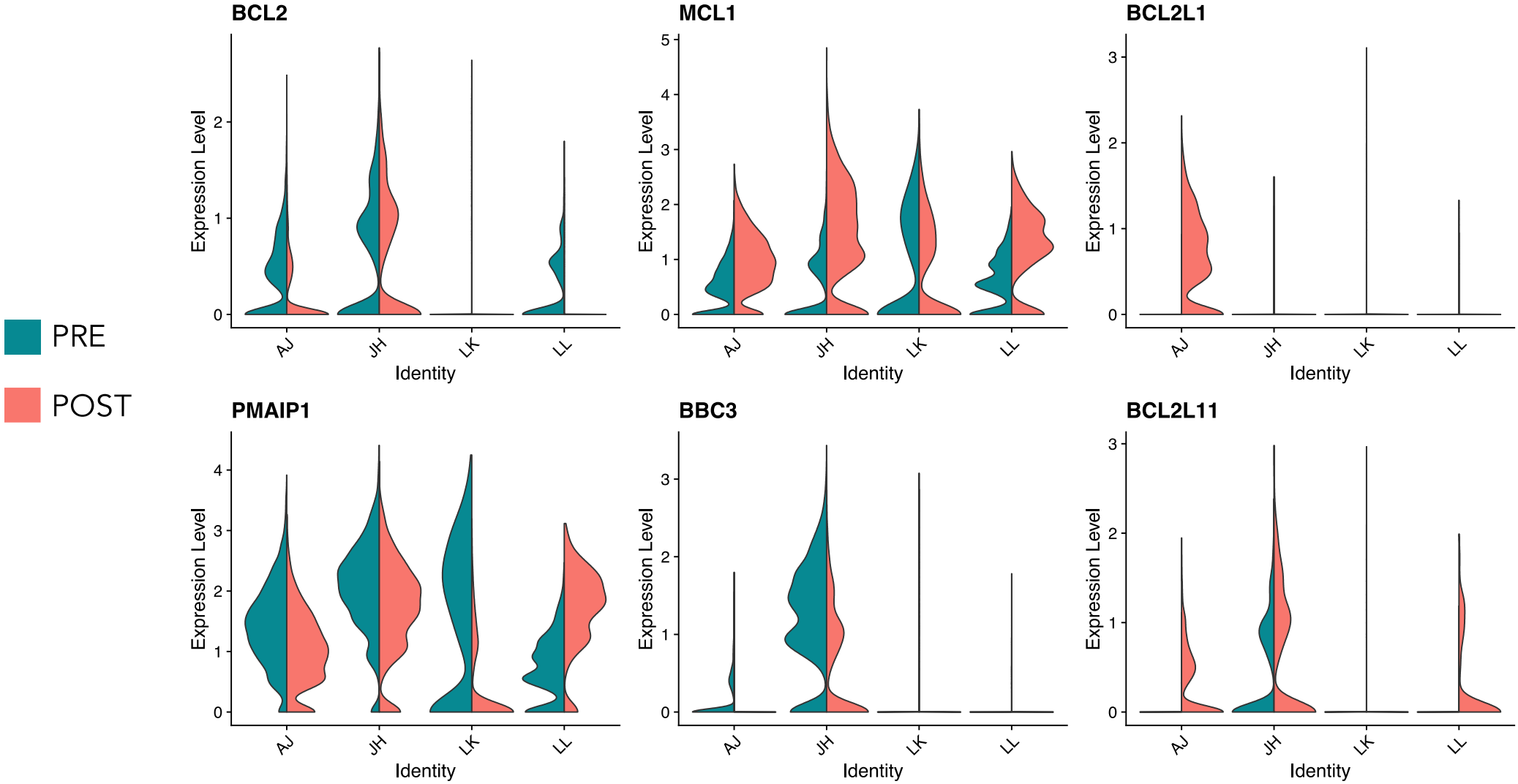


Neri P, Bahlis N et al Blood 2019 134 (S1): 572.

How do MM patients acquire resistance to BCL2 inhibition with venetoclax?

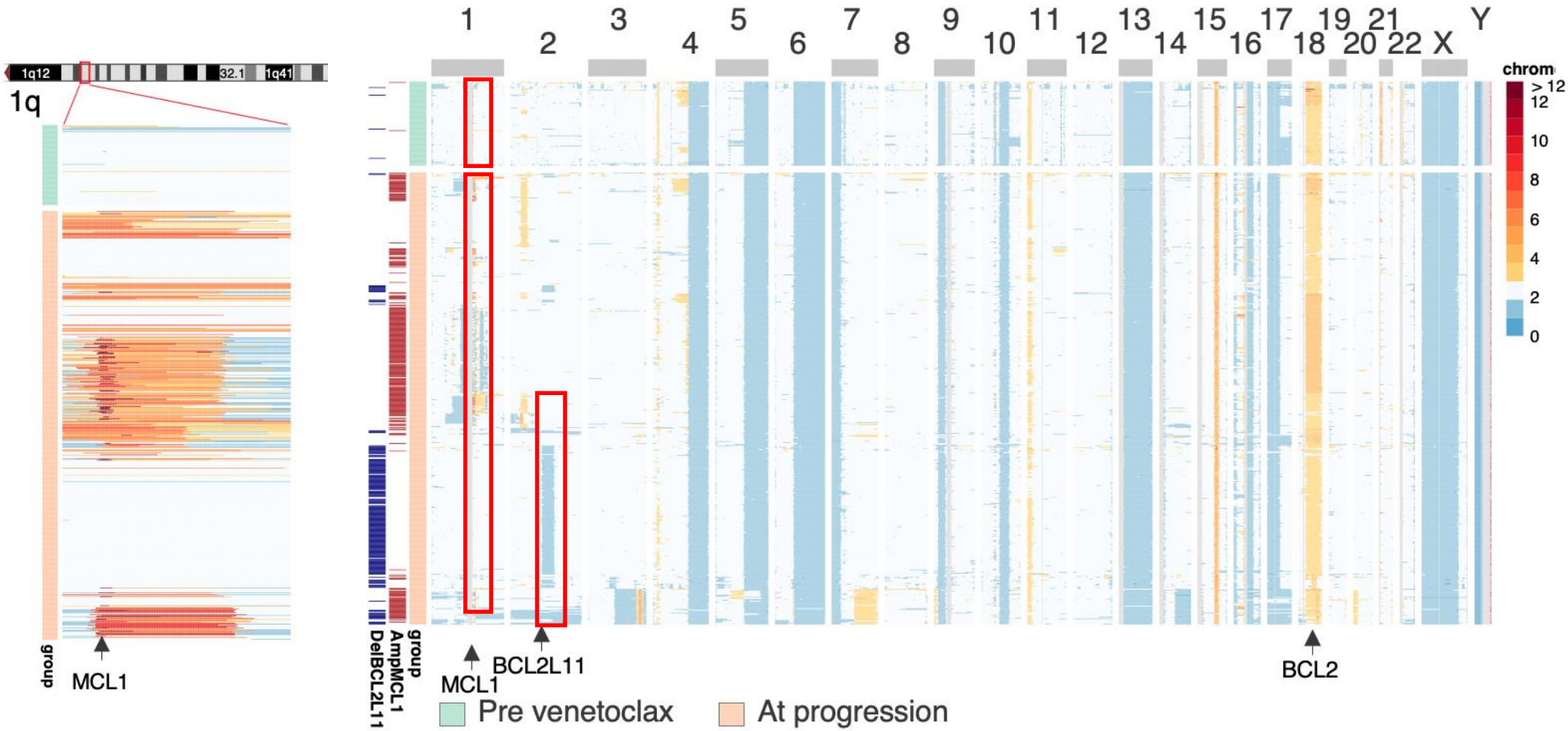
- BCL2 mutations impeding venetolax-mediated displacement of BIM and/or release of BAX/BAK
- 1q21 gain/amp: MCL1 dependency or co-dependency (BH3 priming)
- Upregulation of BCL2L1 (BH3 priming)
- Pro-apoptotic Bcl2 effector (BAX or BAK) or activators (BCL2L11) genes mutations

scRNA transcript mRNA expression levels of levels of BCL2 genes pre & post venetoclax



Neri P, Bahlis N et al Blood 2019 134 (S1): 572.

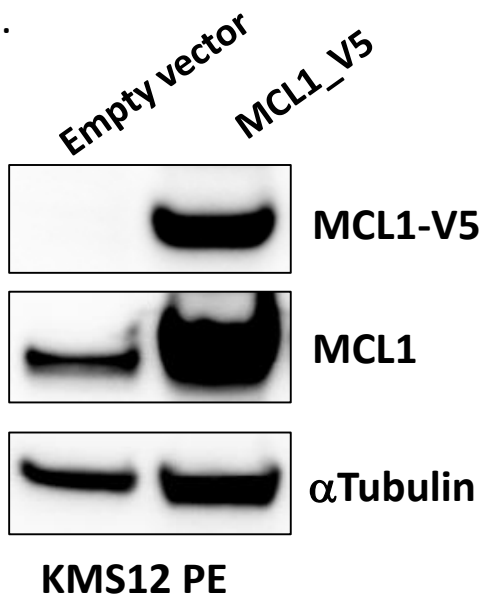
scCNV identified focal copy number gain at the MCL1 locus (1q21) with subclonal loss at the BCL2L11 locus at the time of acquired venetoclax resistance



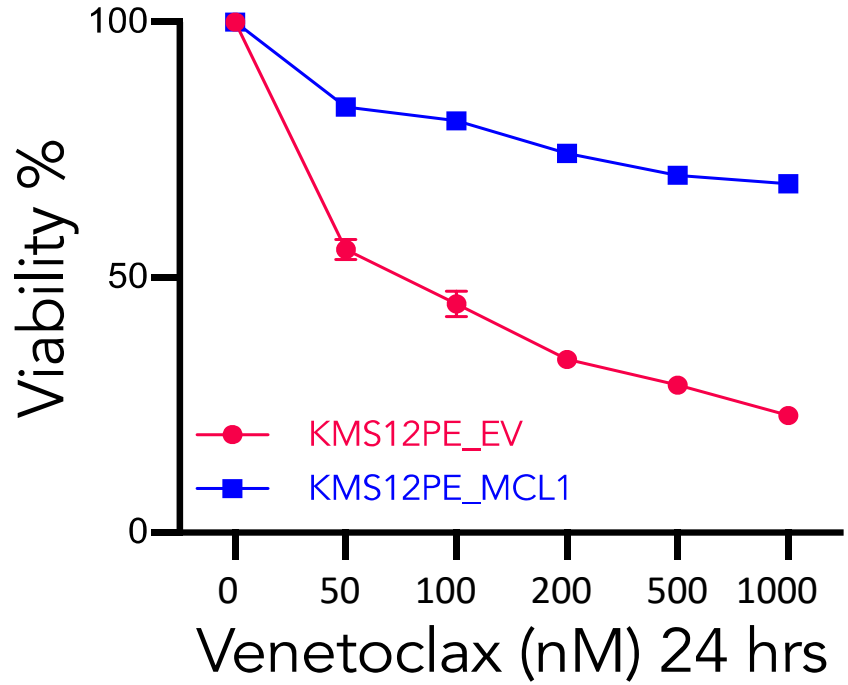
Neri P, Bahlis N et al Blood 2019 134 (S1): 572.

Does MCL1 overexpression lead to Venetoclax resistance in a BCL2 dependent cell line? YES

A.



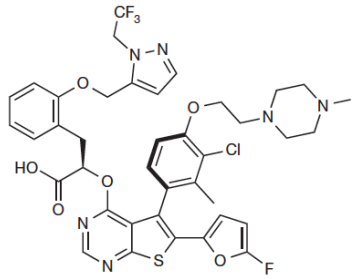
B.



Alberge JB, Neri P and Bahlis N et al, Manuscript in preparation

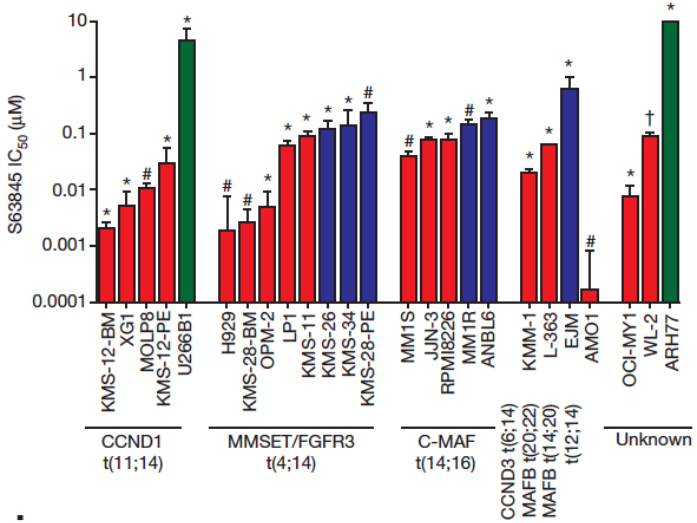
Halted clinical development of MCL1 inhibitors in multiple myeloma due to cardiac toxicity signal

MIK665



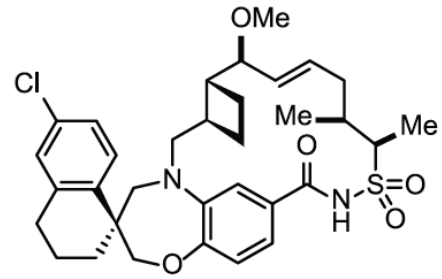
S63845

K_I (MCL1, FP) < 1.2 nM
K_D (MCL1, SPR) = 0.19 nM
K_I (BCL2, FP) > 10,000 nM
K_I (BCL-X_L, FP) > 10,000 nM

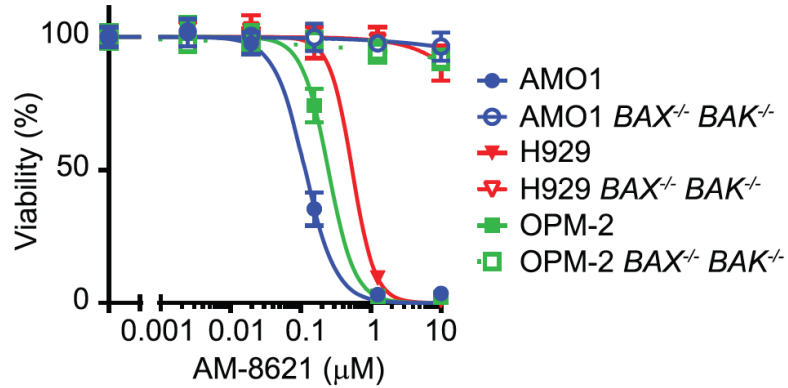


ClinicalTrials.gov: \NCT02992483)

AMG176

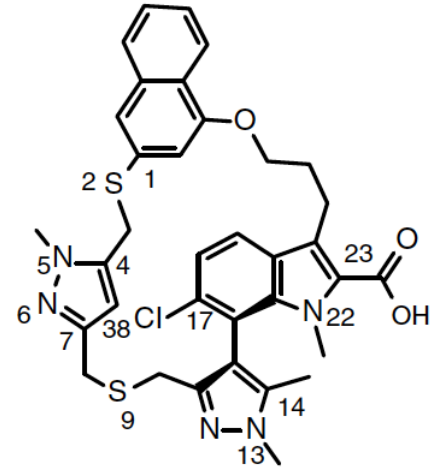


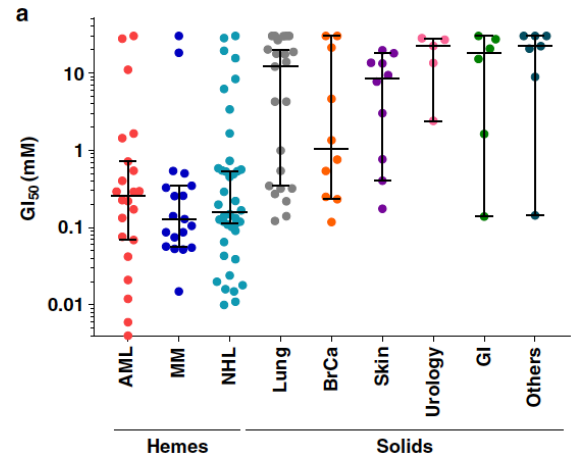
(AMG 176), Ki = 0.00006 μM
BCL-XL, Ki = 0.7 μM
BCL-2, Ki = 0.95 μM
Mouse MCL1, Ki = 0.044 μM
Dog MCL1, Ki = <0.001 μM



ClinicalTrials.gov:
NCT03797261

AZD5991

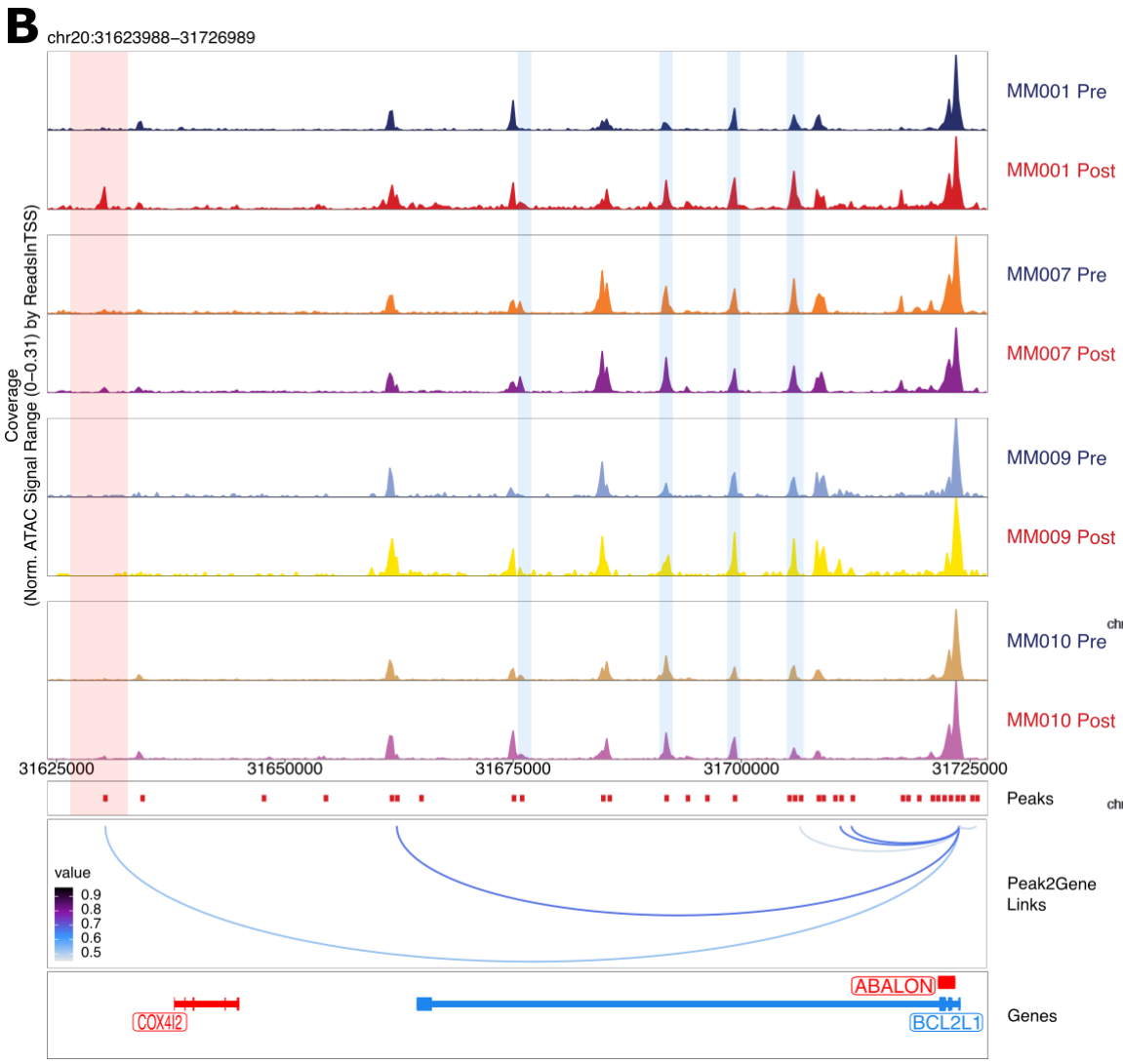


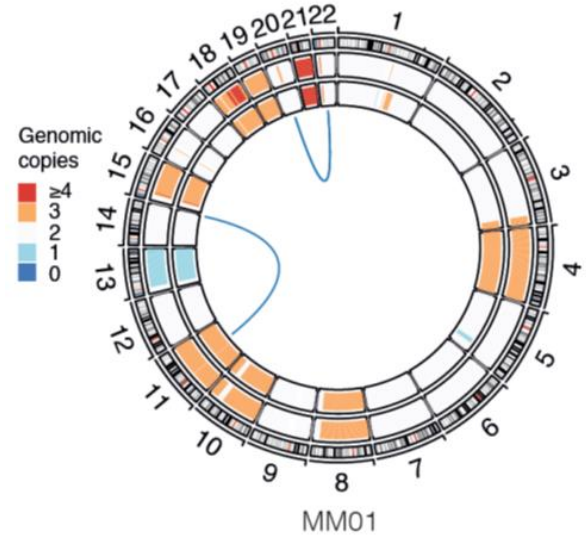


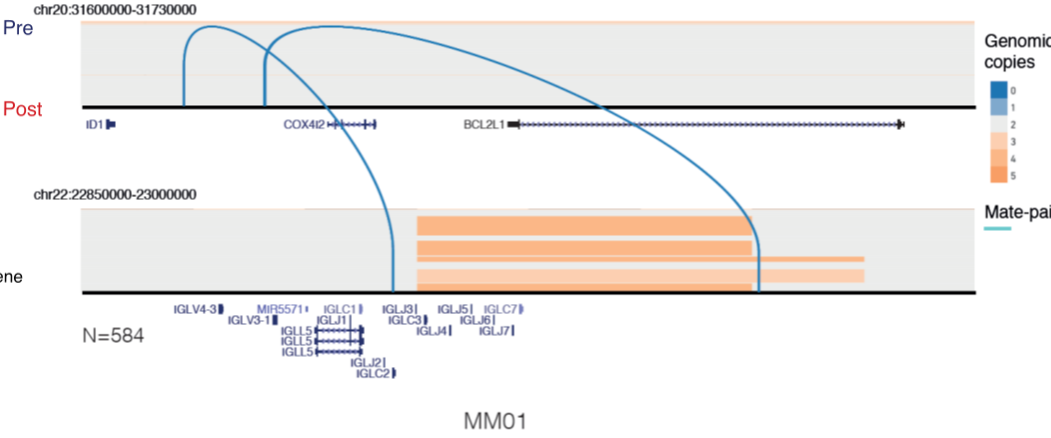
ClinicalTrials.gov:
NCT03218683

Kotschy et al Nature 2016
Tron A et al Nature Commun 2018

Acquired cis-regulatory elements at the BCL2L1 locus post venetoclax driven by IGLL5-BCL2L1 rearrangement

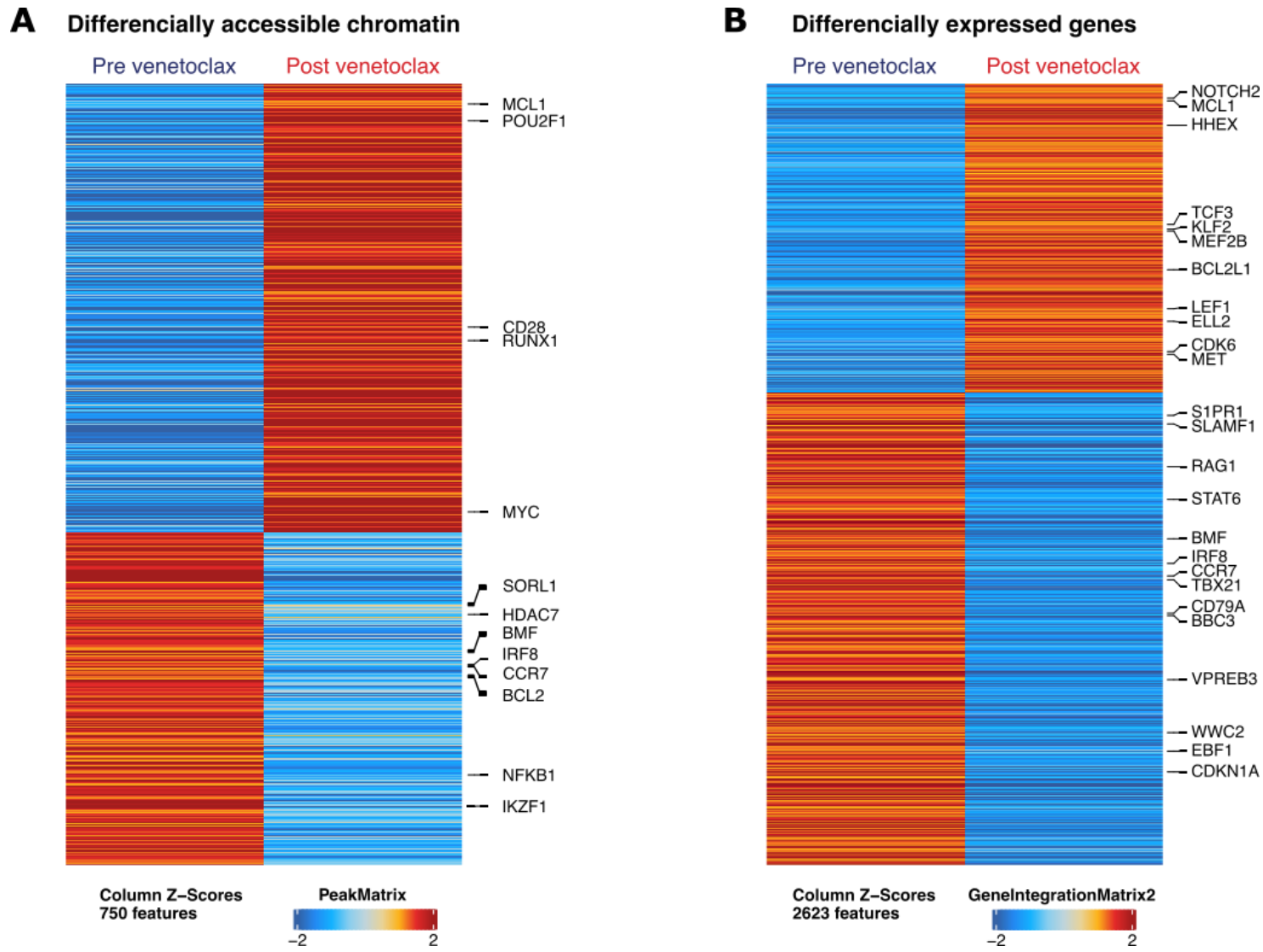






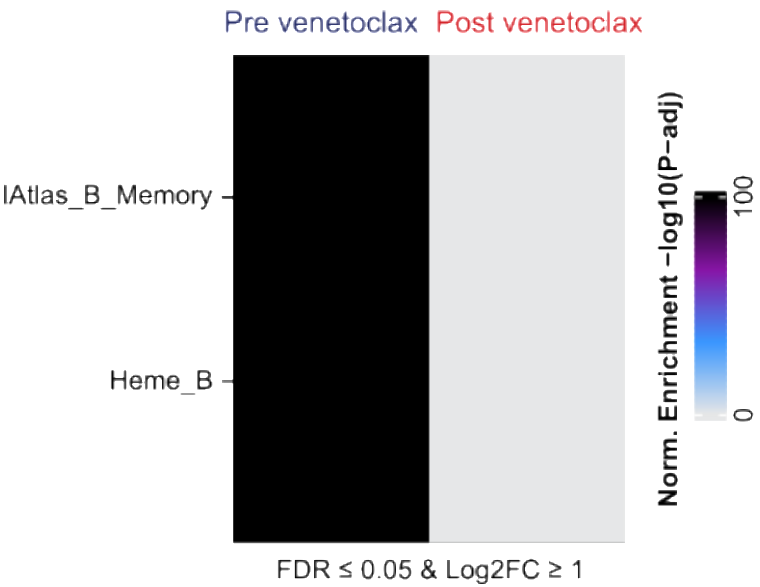
Alberge JB, Neri P and Bahlis N et al, Manuscript in preparation

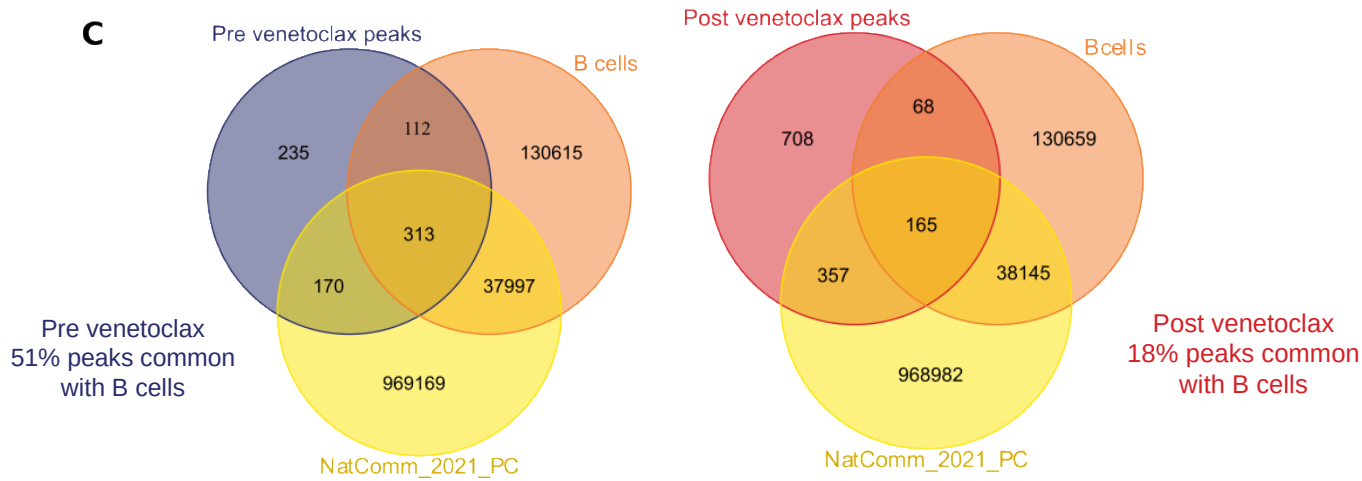
Divergence of epigenomic and transcriptomic profiles in Pre vs Post Venetoclax from B-cell to plasma cells



Leblay N, Neri P et al. Blood 2021, abs # 725

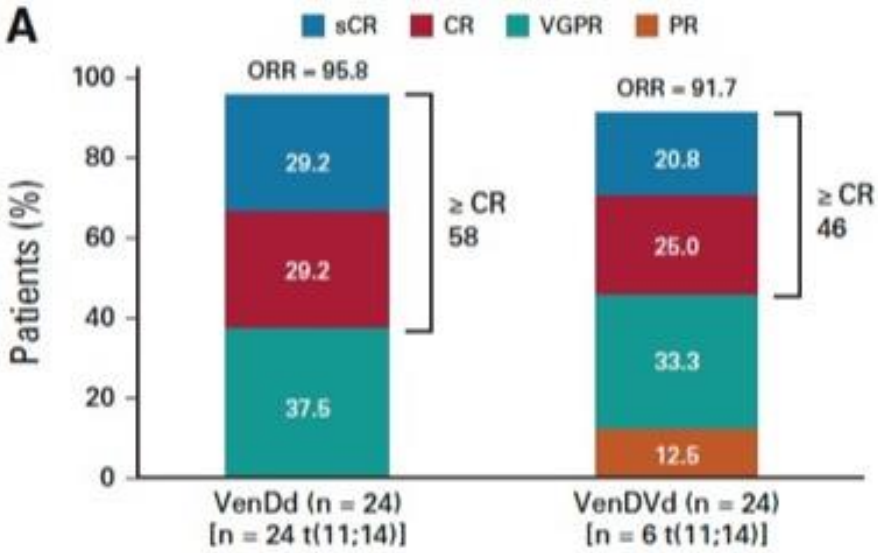
Loss of “B cell-like” epigenetic signature in post venetoclax resistant samples

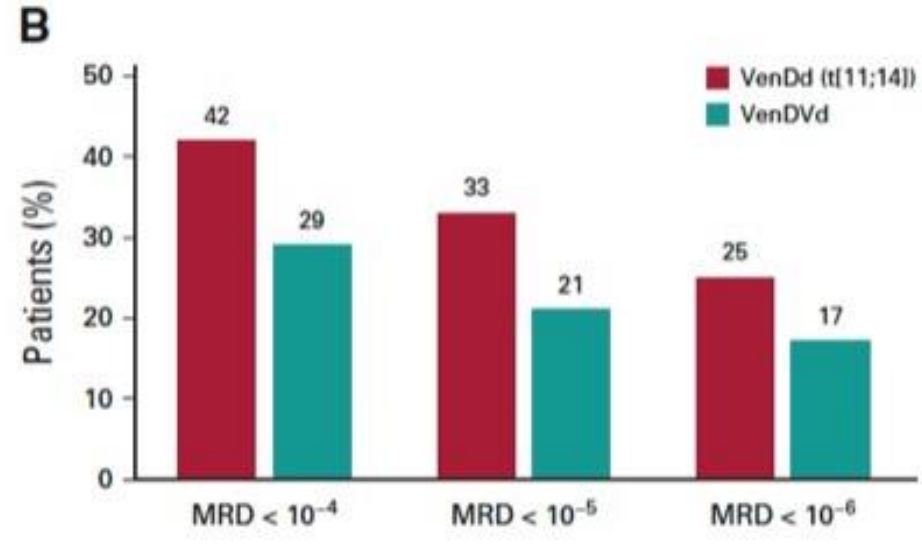


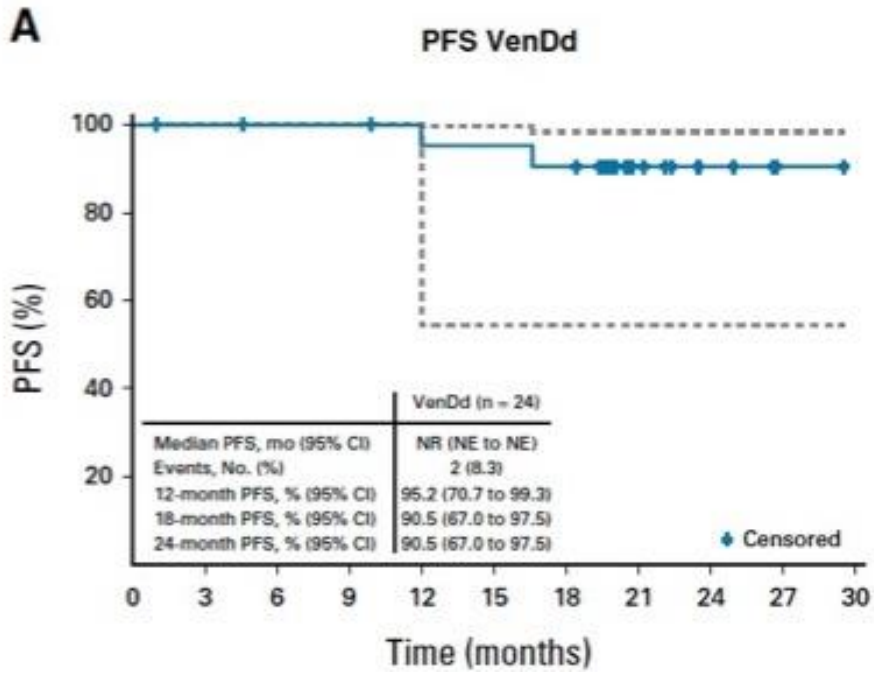


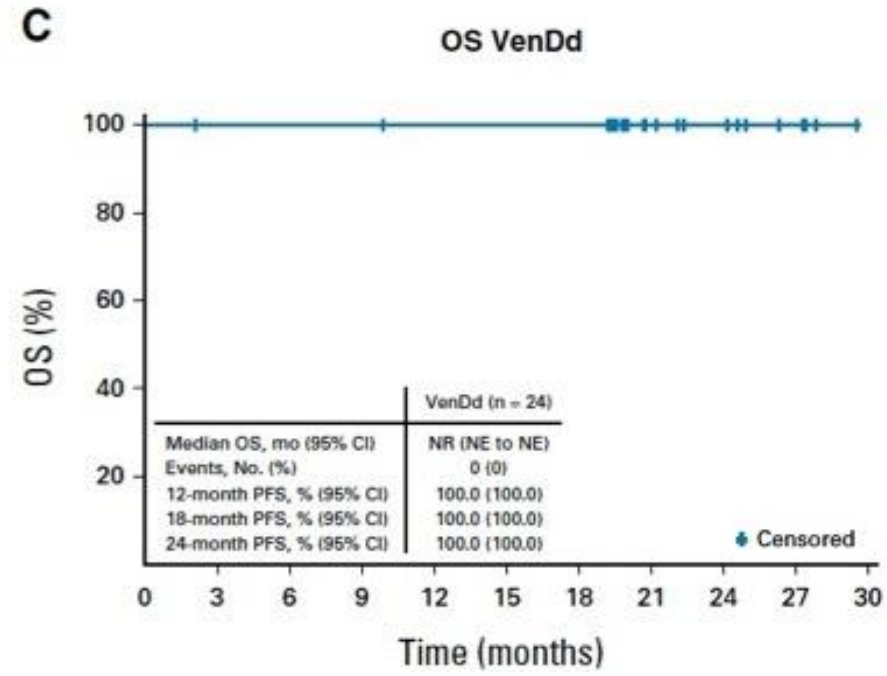
Leblay N, Neri P et al. Blood 2021, abs # 725

Combination of Venetoclax with Daratumumab in relapsed myeloma





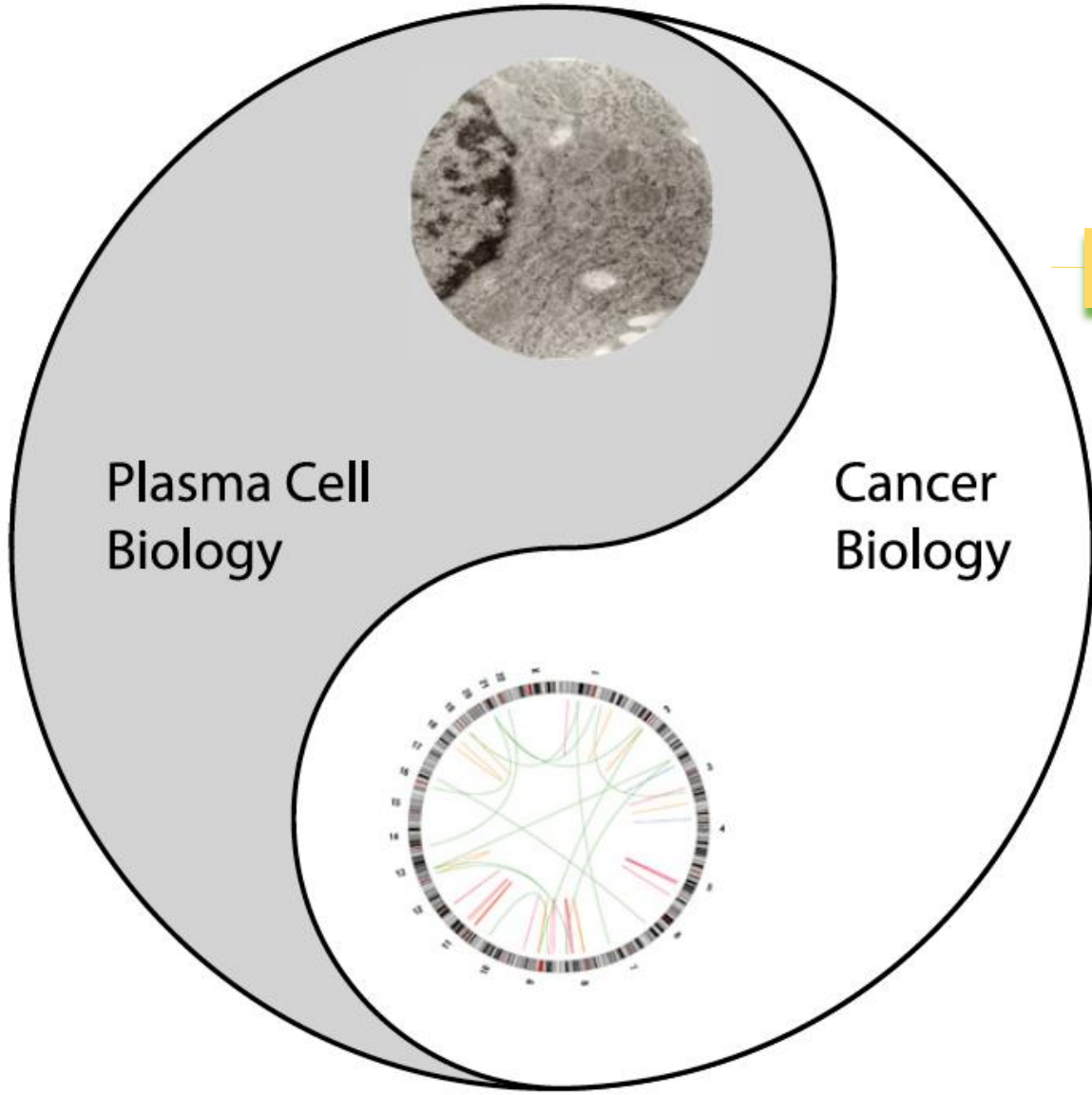




Bahlis N et al Clin Oncol 39:3602-3612.

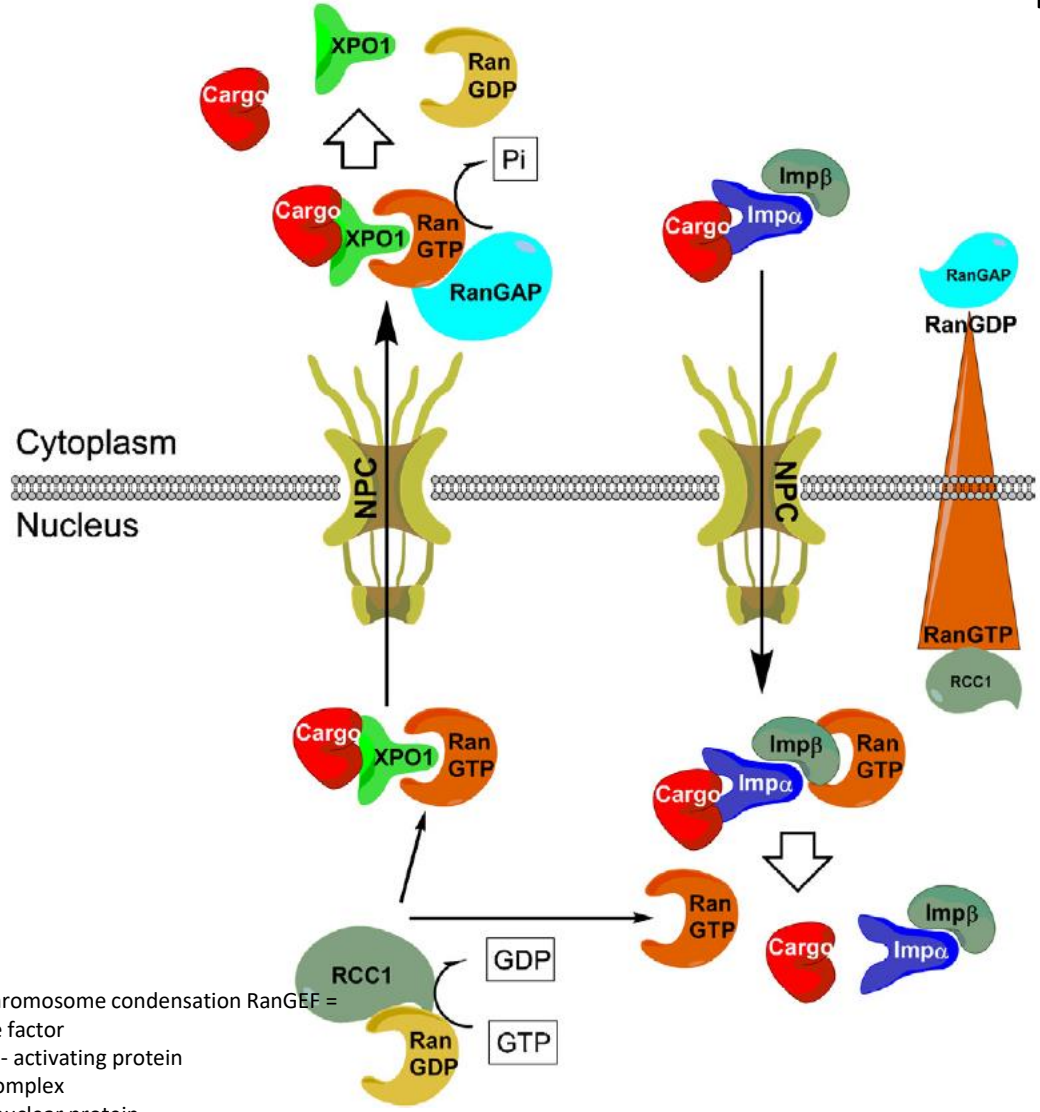
The Tao of Myeloma

Boise LH. Blood 2014



XPO1 inhibitors

The mammalian nuclear pore complex



RCC1 = regulator of chromosome condensation RanGEF = Ran guanine exchange factor
RanGAP = Ran GTPase- activating protein
NPC = Nuclear Pore Complex
Ran – Ras associated nuclear protein

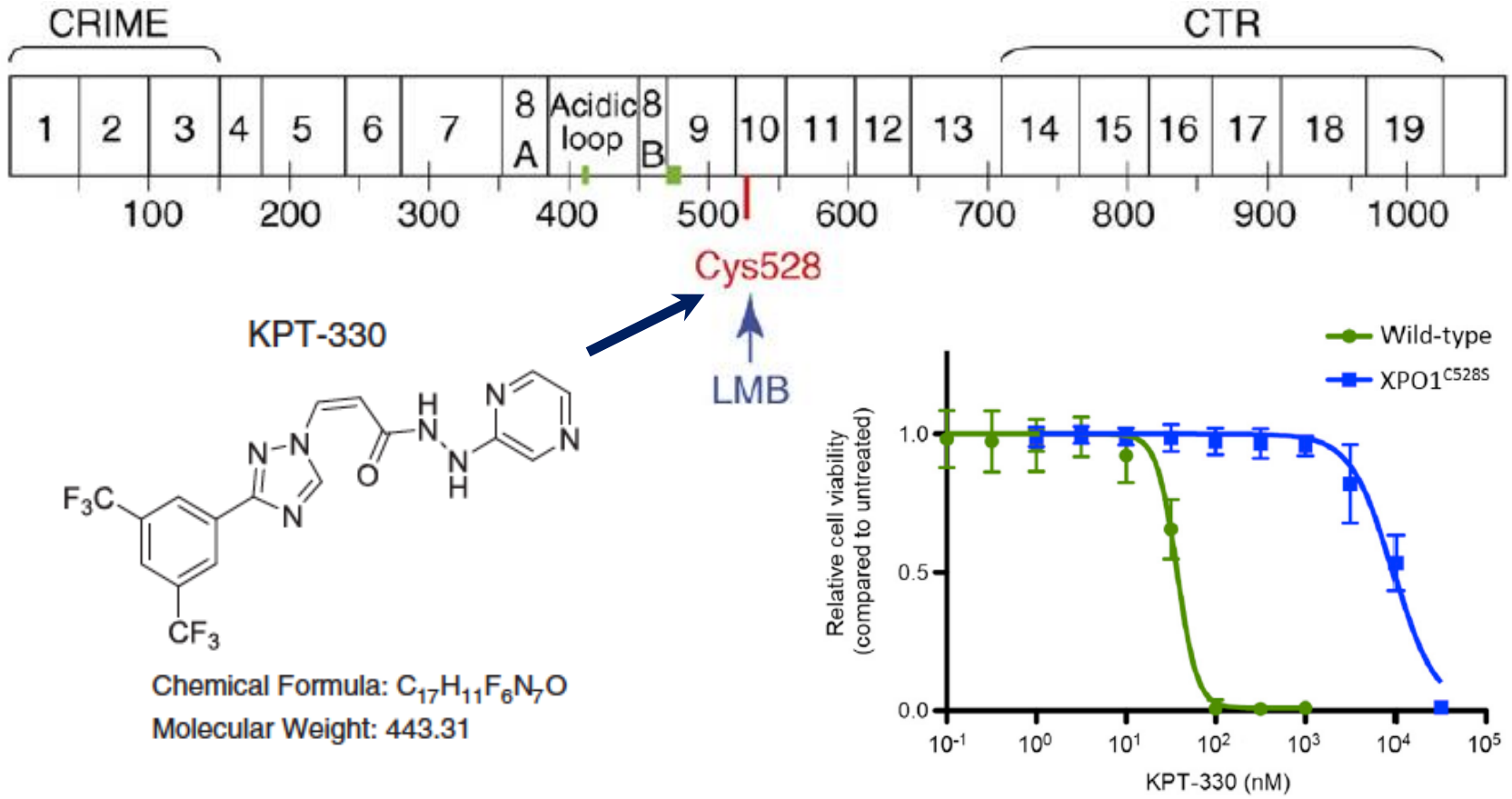
Karyopherin are the major family of nuclear transport proteins: Importins and Exportins.

CRM1 (Chromosomal Maintenance 1, Exportin 1 or XPO1) is the major mammalian export protein.

XPO1 facilitates the transport of large macromolecules (>40 kDa) including RNA and protein across the nuclear membrane to the cytoplasm.

Stade et al, Cell 1997
Adachi et al, The Journal of Cell Biol 1989
Hutten et al Trends in Cell Biology 2007
Azmi et al, Nat Rev Clin Oncol 2021

Small-molecule selective inhibitors of nuclear export (SINEs)

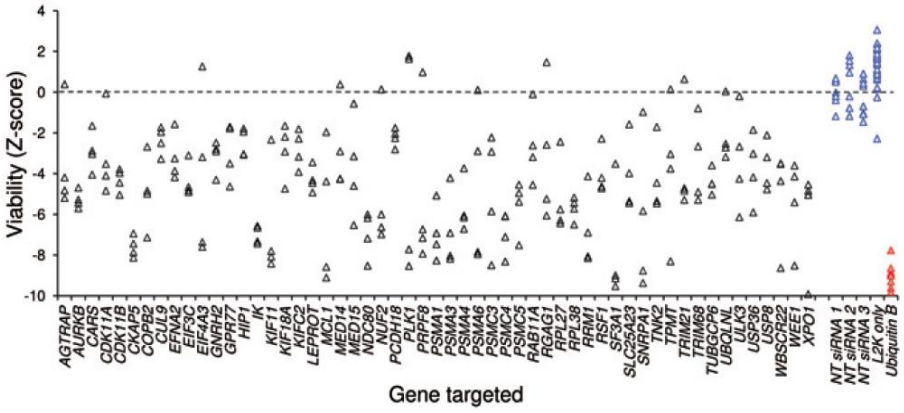


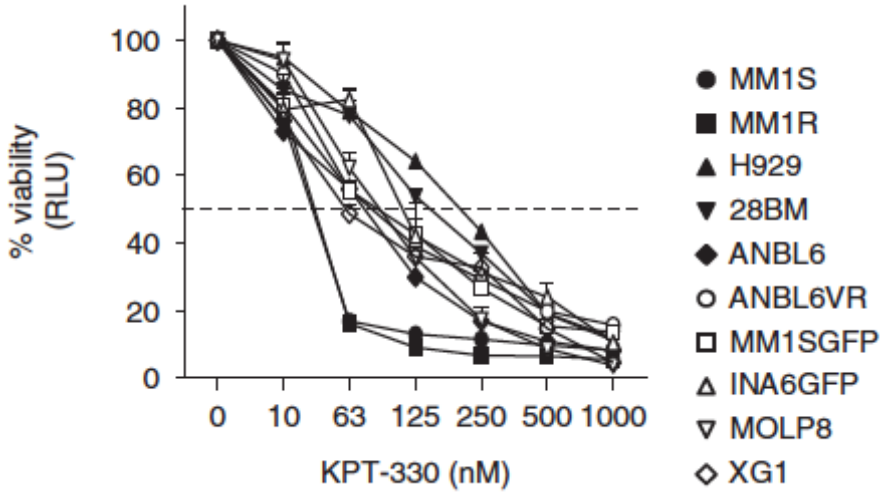
SINE compounds: KPT-185, KPT-251, KPT-276, selinexor, eltanexor and verdinexor

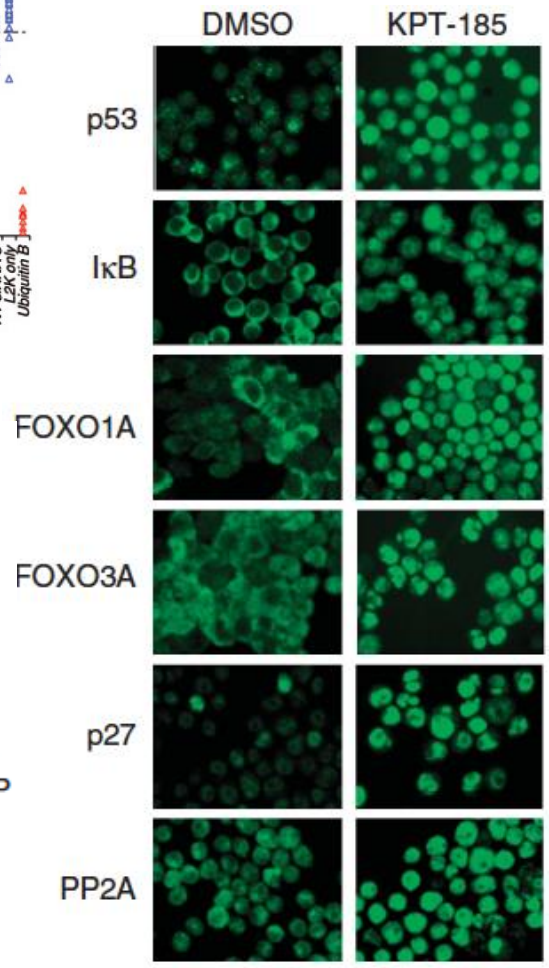
Kalid et al, J Comput Aided Mol Des 2012
Neggers et al, Chemistry & Biology 2015

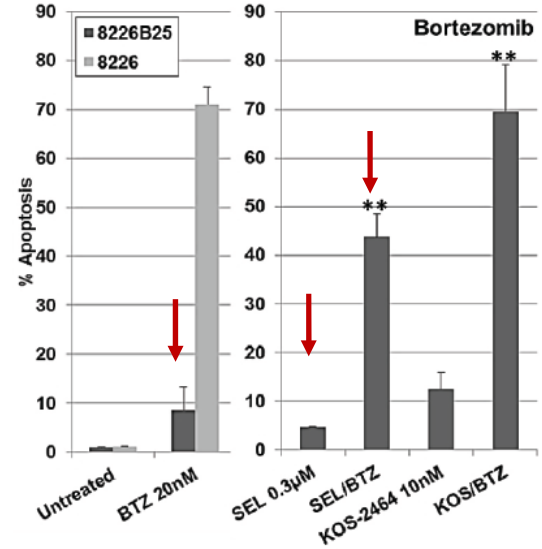
XPO1as therapeutic target in Myeloma

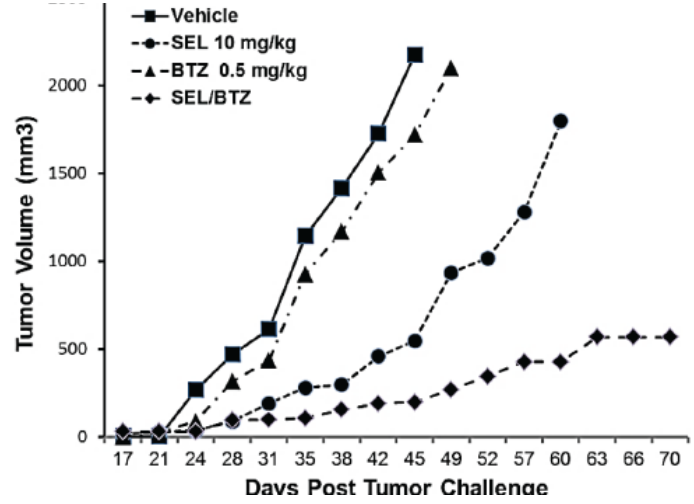
Synergy with Proteasome inhibitors







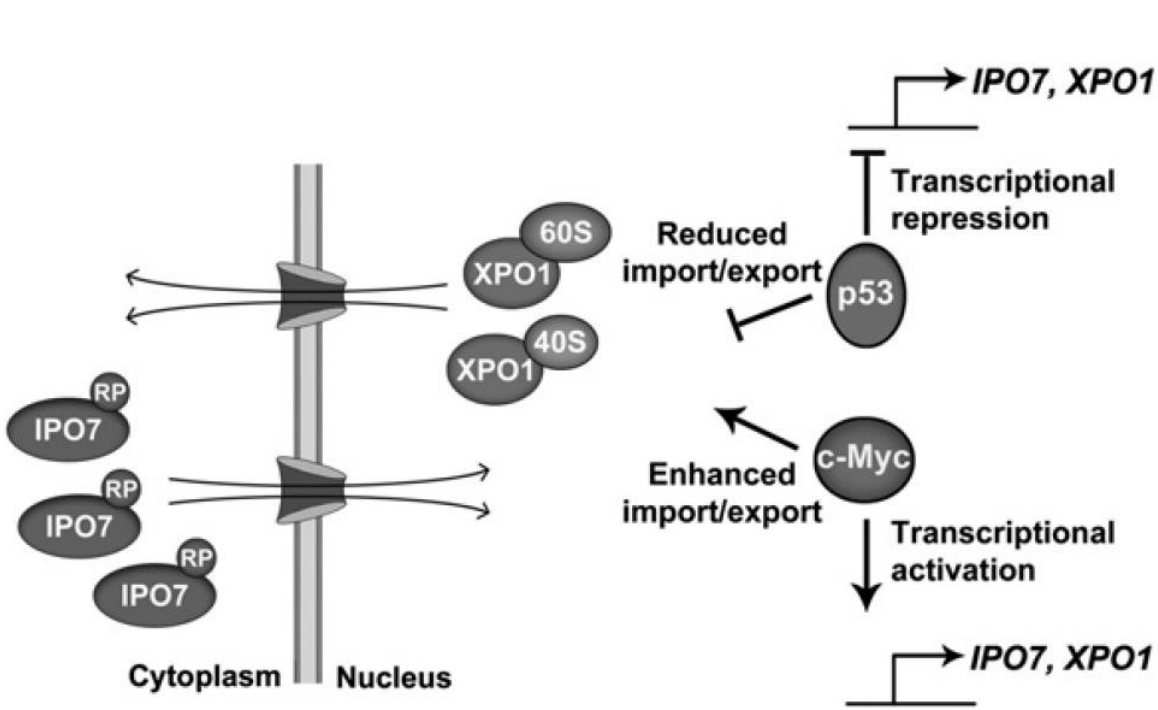


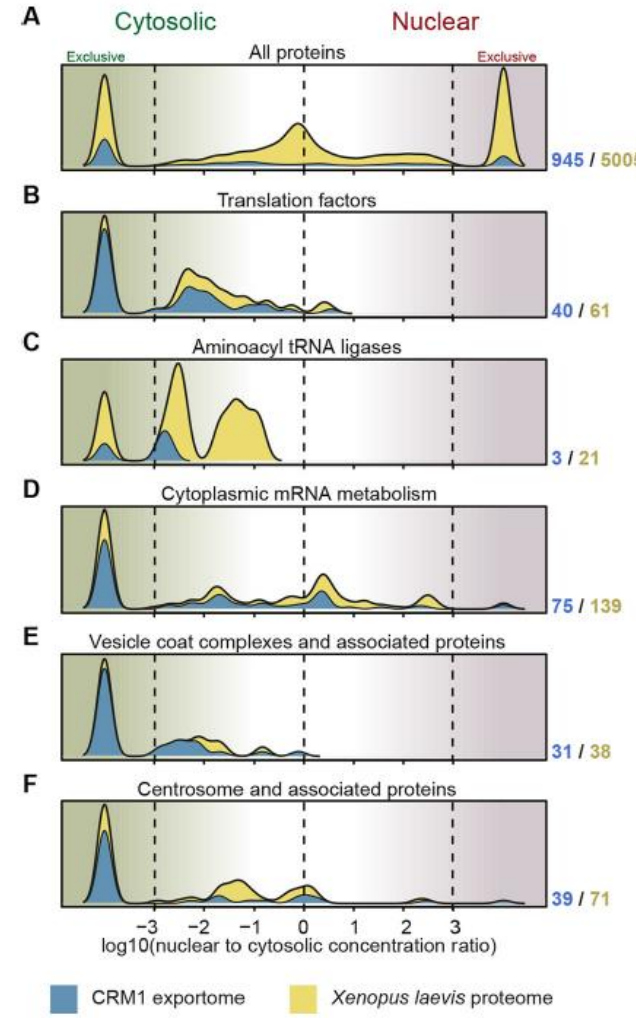


Tiedemann et al Cancer Research 2011
Schmidt et al, Leukemia 2013
Tai et al, Leukemia 2014

Turner et al, Oncotarget 2016
Rosebeck et al, Mol Cancer Ther 2016

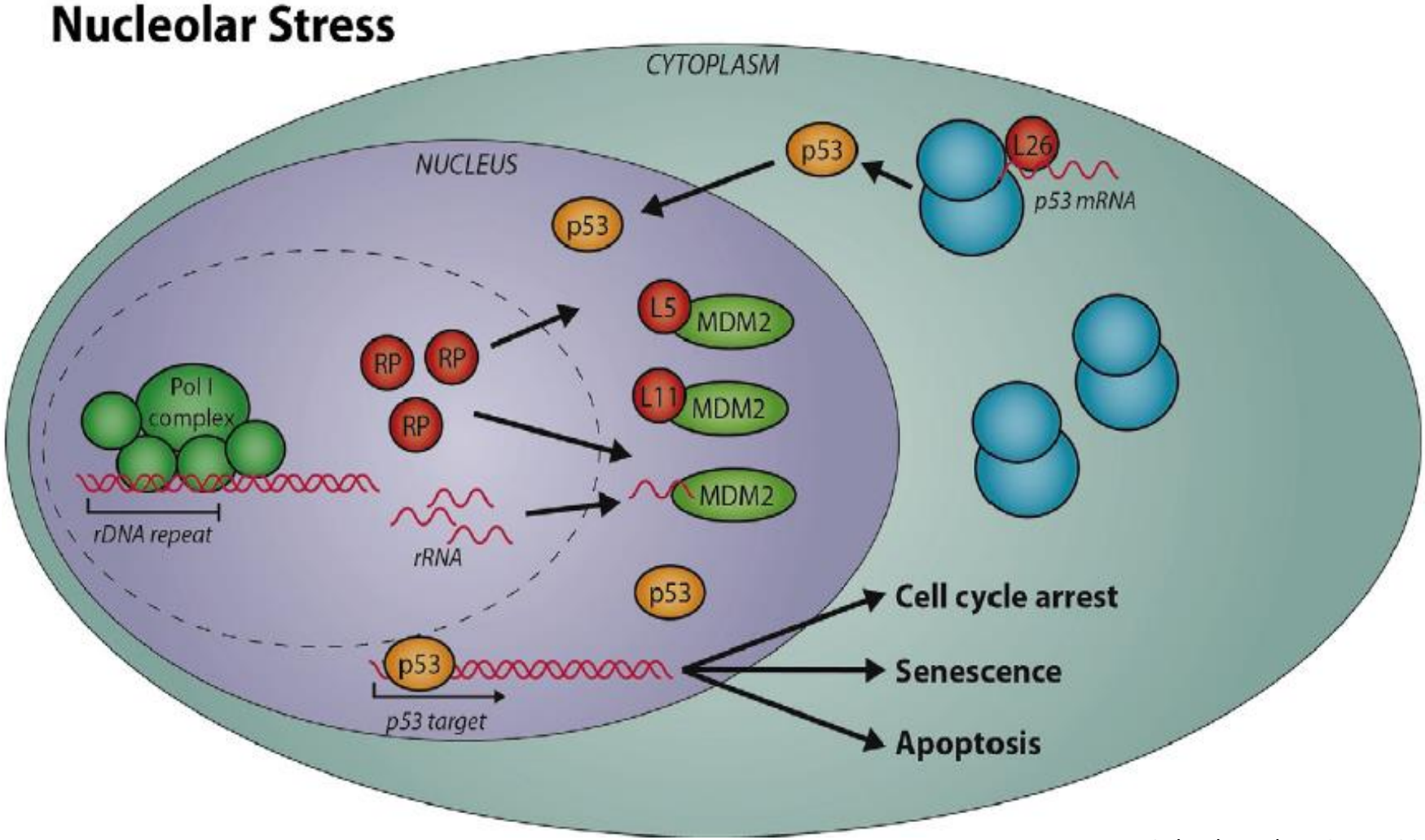
XPO1 regulates translation & Ribosomal biogenesis





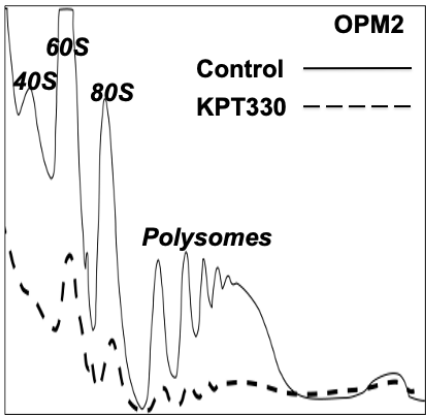
Golomb et al, Molecular Cell 2012
Kirli et al, eLife 2015
Fischer et al, eLife 2015
Moy et al, Genes and Development 1999
Rouquette et al, The EMBO Journal 2005

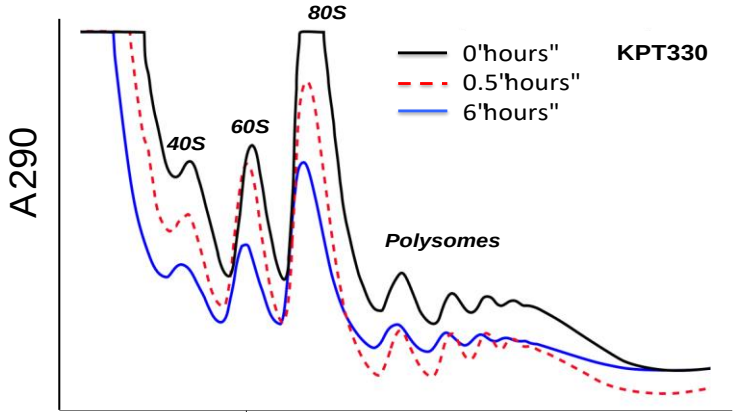
Ribosomal stress response

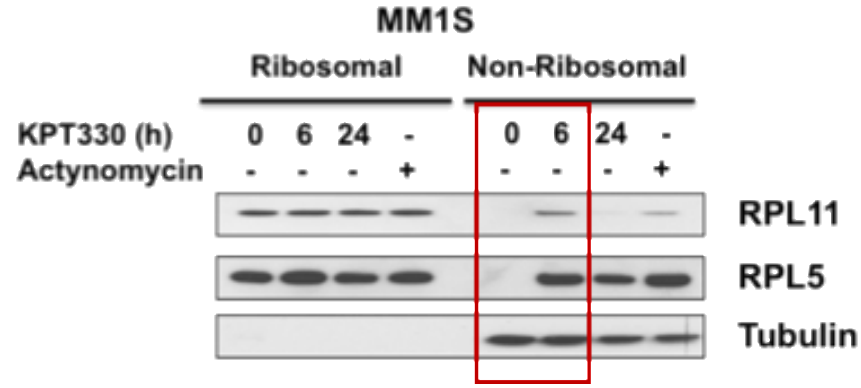


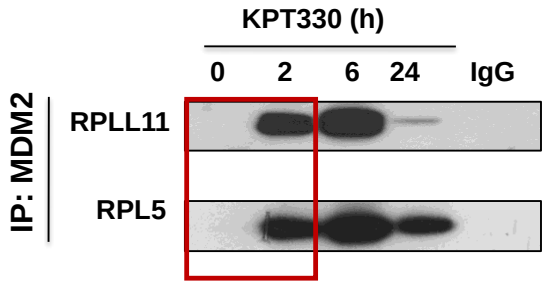
Golomb et al FEBS Lett. 2014
Quin et al Biochimica et Biophysica Acta 2014

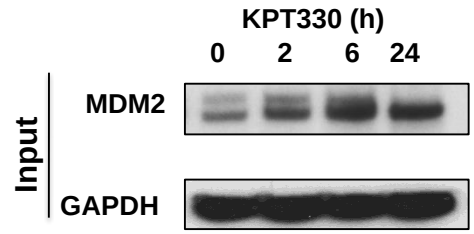
XPO1 inhibition induces ribosomal stress response in MM cells

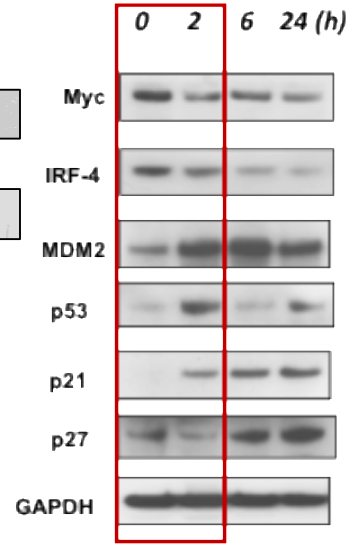


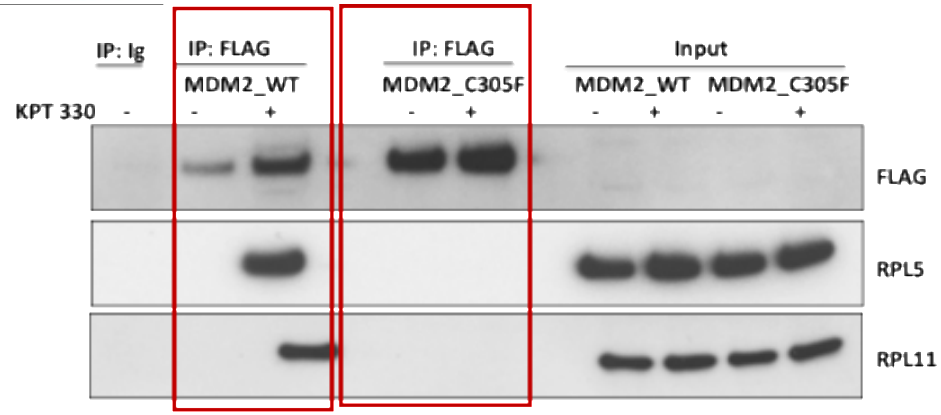


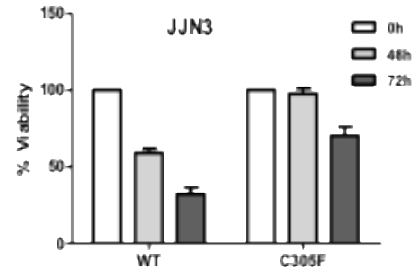


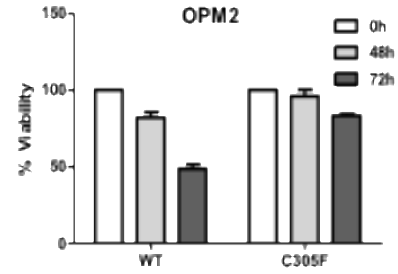






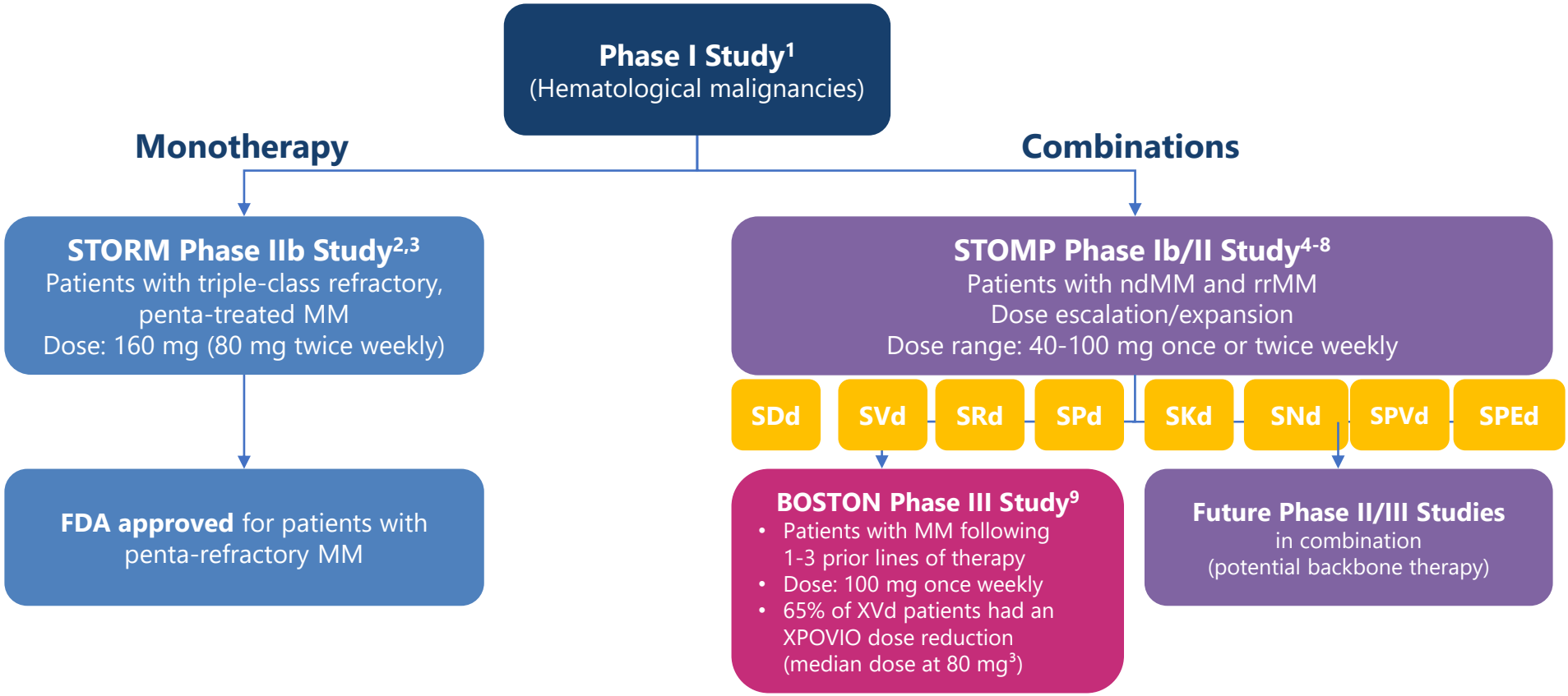






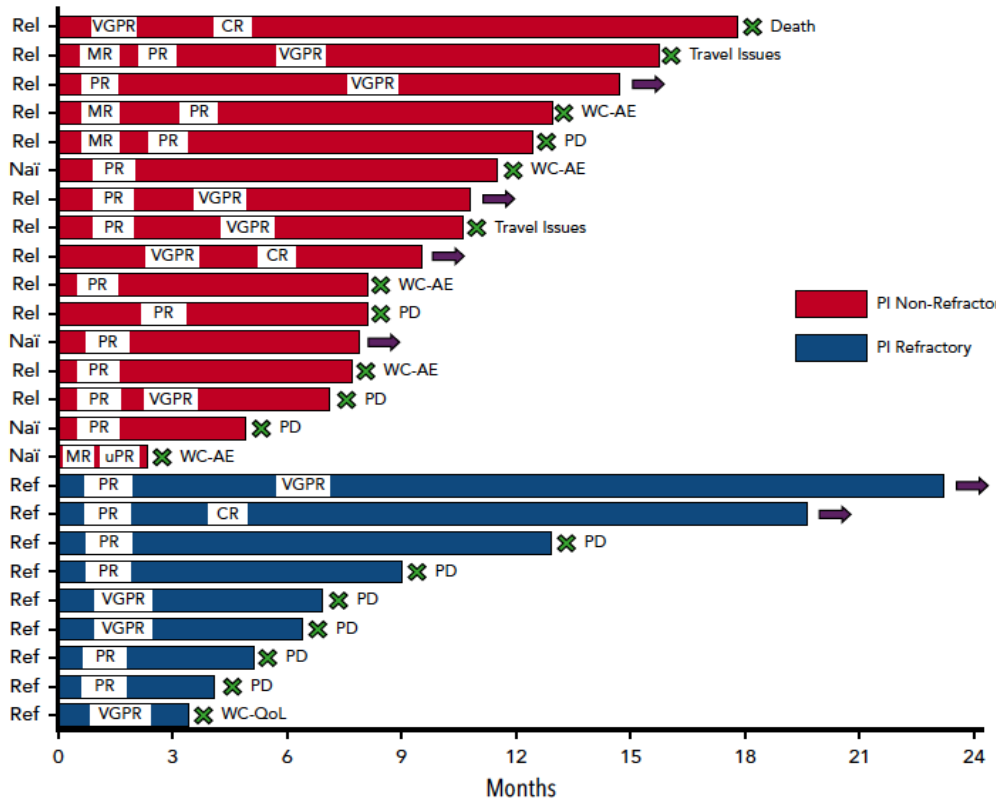
Tagoug I, Bahlis N et al Blood 2014

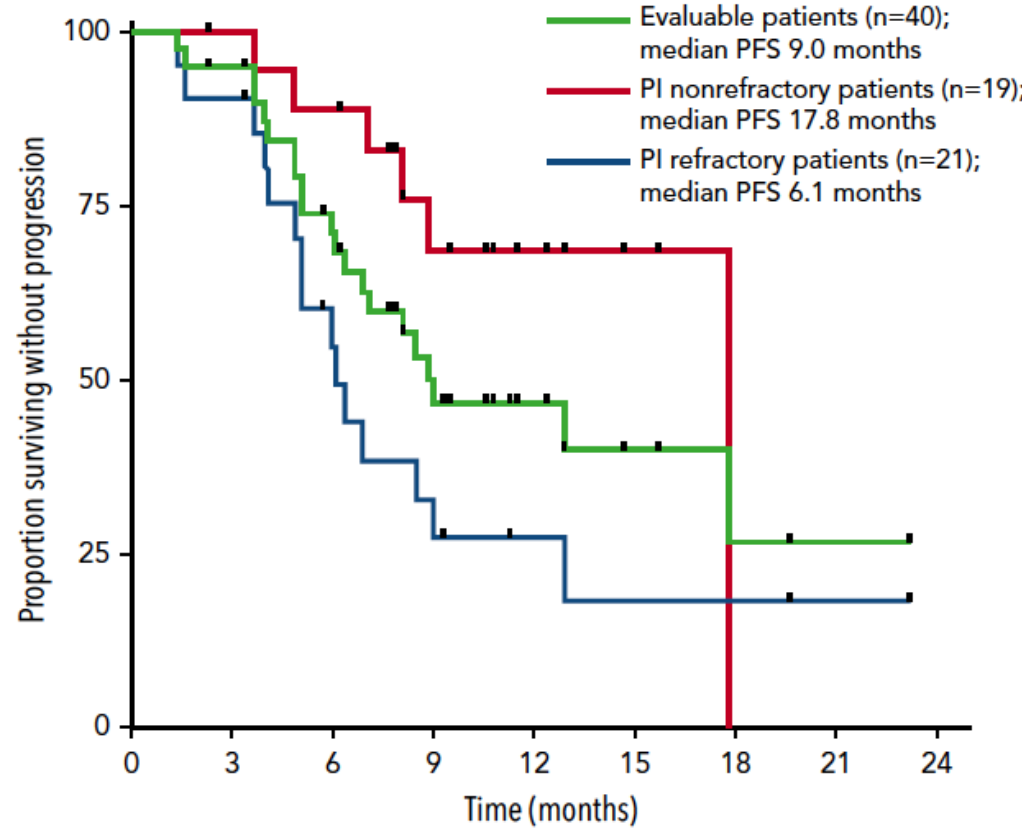
SELINEXOR Clinical Development in Relapse and Refractory MM



1. Chen et al. Blood. 2018;131:855-63; 2. Vogl et al. J Clin Oncol. 2018;36:859-66; 3. Chari et al. N Engl J Med. 2019;381:727-38; 4. Chen et al. Blood. 2019;134(supplement_1):141; 5. Bahlis et al. Blood. 2018;132:2546-54; 6. White et al. Blood. 2017;130(supplement_1):1861; 7. Gasparetto et al. Blood. 2018;134(supplement_1):3157; 8. Salcedo et al. Blood. 2019;20:198-200; 9. Grosicki et al. Lancet. 2020;396:1563-73.

Selinexor Bortezomib Dexamethasone (SVd) induces durable responses in relapsed /refractory Myeloma



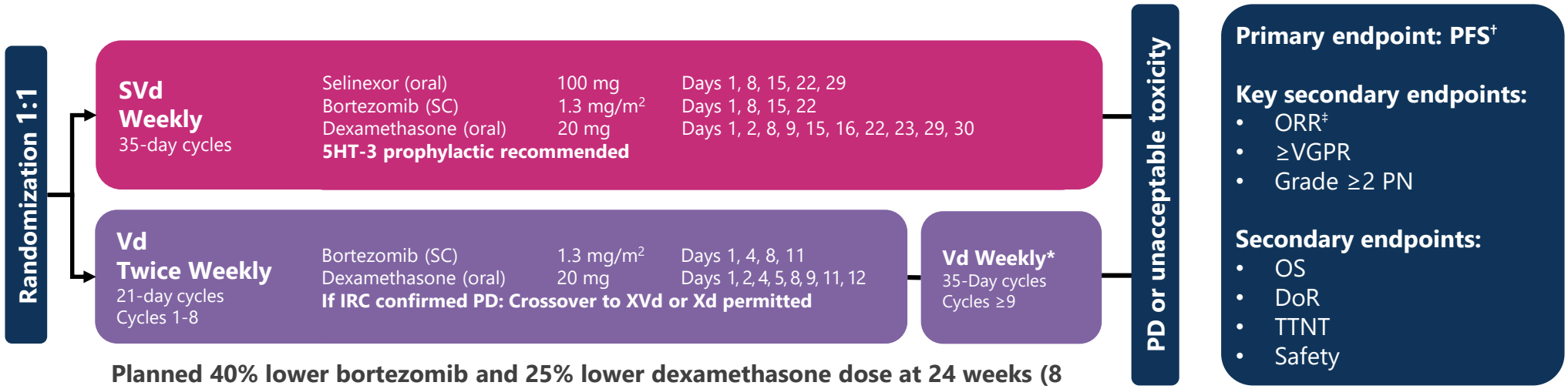


No. at Risk

All Eval	40	37	27	15	8	4	2	1	0
PI Nonref	19	18	16	9	5	2	0	0	0
PI Ref	21	19	11	6	3	2	2	1	0

Bahlis N. Blood 2018;132:2546-2554

BOSTON: Phase III, open-label, global, randomized, controlled trial



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

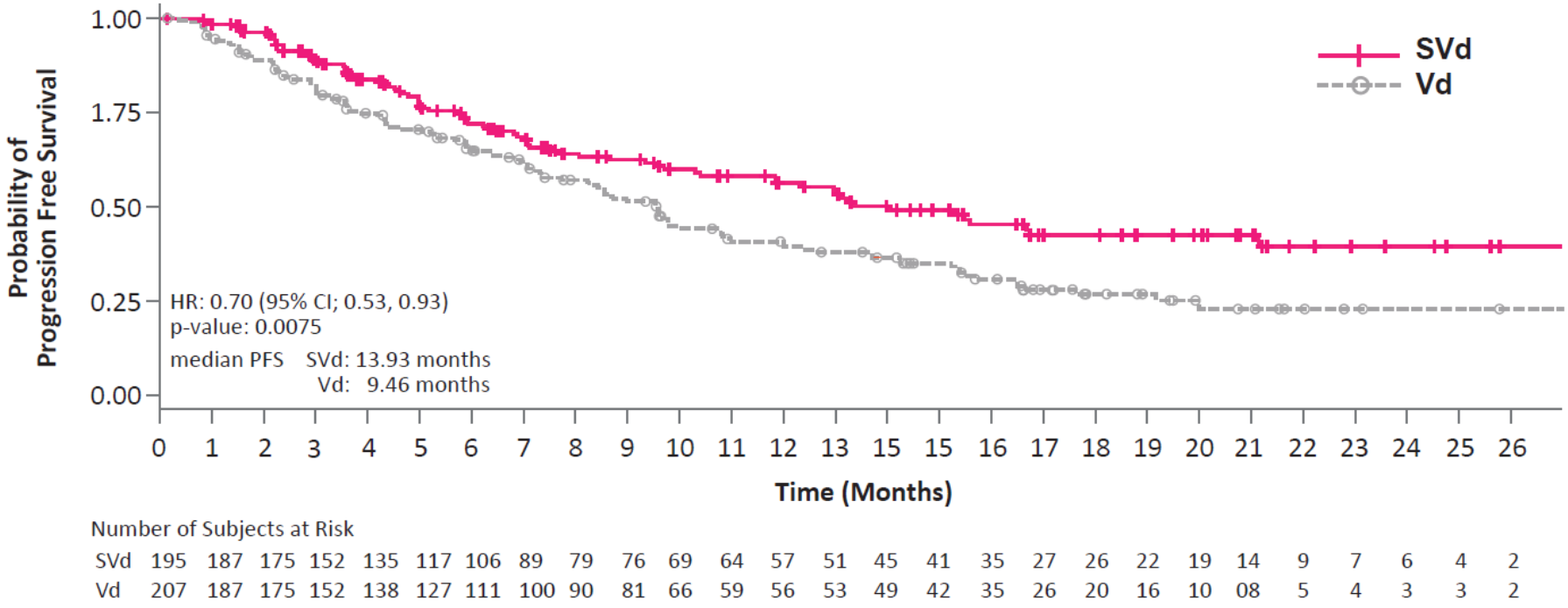
Stratification:
Prior PI therapies (Yes vs. No)
Number of prior anti-MM regimens (1 vs. >1)
R-ISS stage at study entry (Stage III vs. Stage I/II)

*Vd weekly dosing and schedule for cycles ≥9 as per XVd arm description; †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 defined as: Any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria. All changes in MM disease assessments were based on baseline MM disease assessments.

5-HT3: 5-hydroxytryptamine; d: dexamethasone; DoR: duration of response; IMWG: International Myeloma Working Group; IRC: Independent Review Committee; ORR: objective response rate; OS: overall survival; PD: progressive disease; PFS: progression free survival; PI: proteasome inhibitor; PN: peripheral neuropathy; PR: partial response; R-ISS: revised international staging system; SC: subcutaneous; sCR: stringent complete response; TTNT: time to next treatment; VGPR: very good partial response; V: Velcade (bortezomib); X: XPOVIO (selinexor).

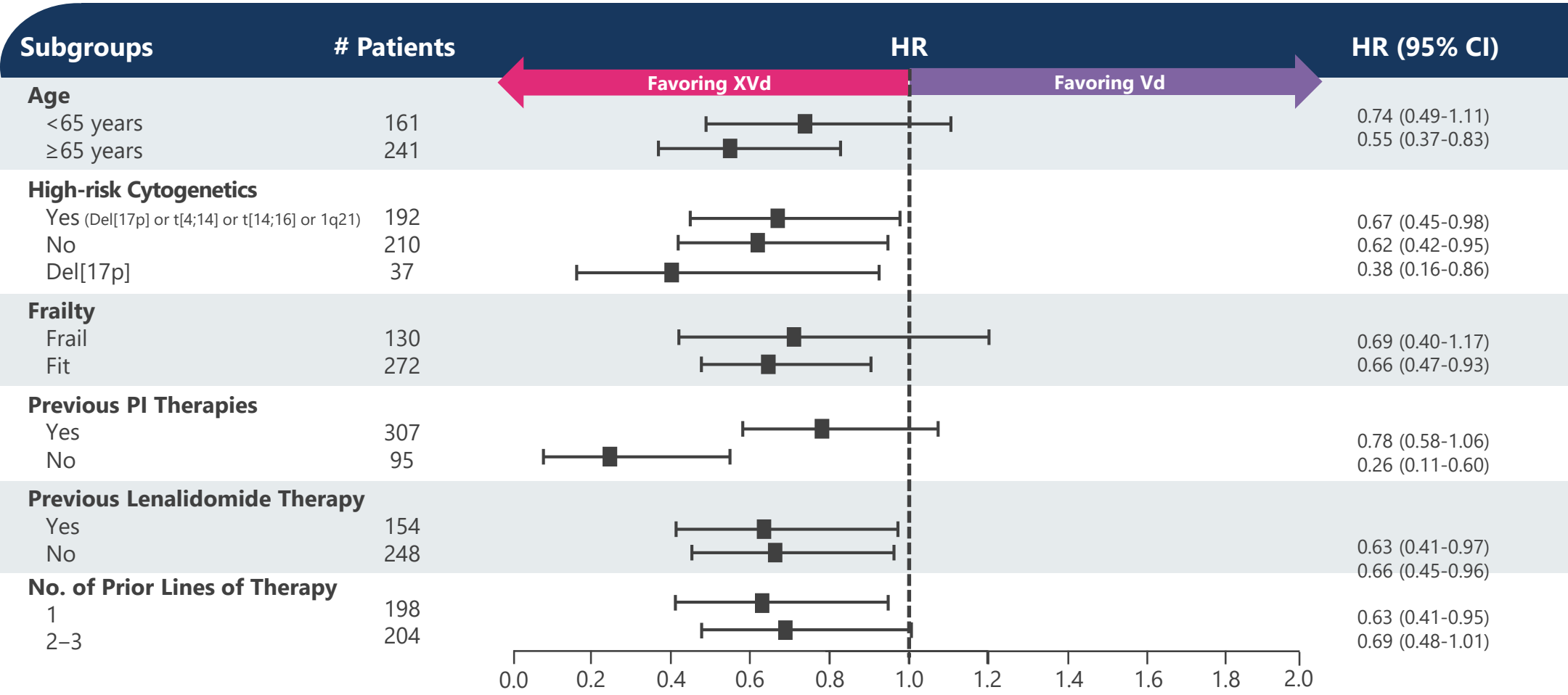
Grosicki et al. Lancet. 2020;396:1563-73.

SVd improved Progression-free Survival compared to Vd



1. Grosicki et al. Lancet. 2020;396:1563-73.

PFS Subgroup Analysis: Activity in high risk MM



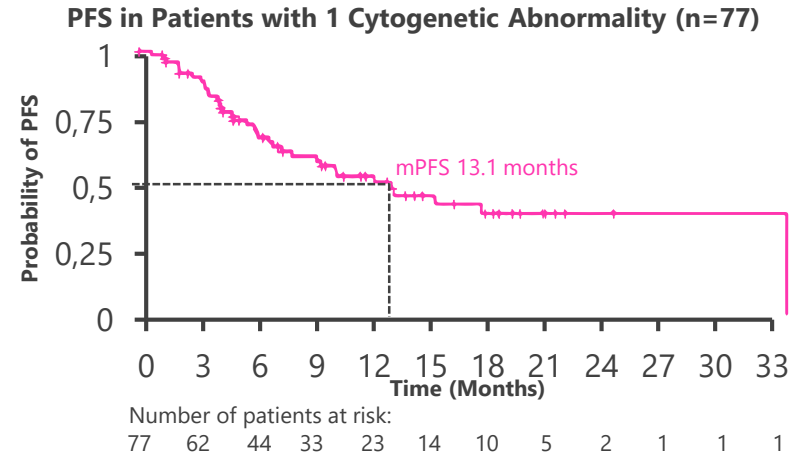
1. Grosicki et al. Lancet. 2020;396:1563-73.

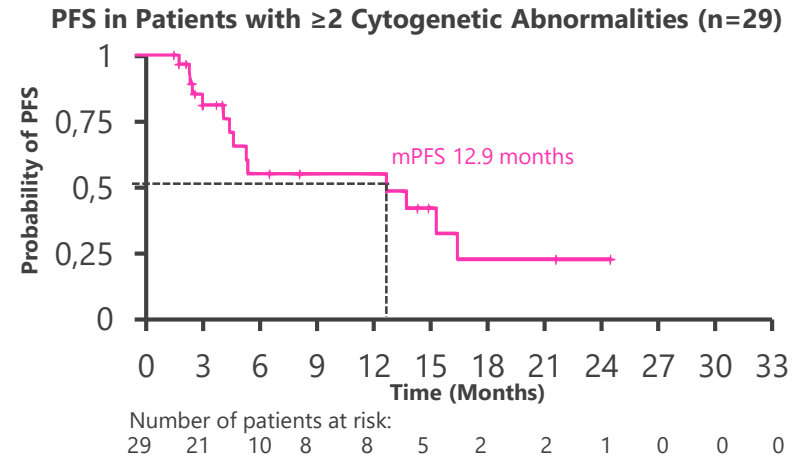
Efficacy in Patients with High-risk Cytogenetics in BOSTON & STOMP

Category	Any High-risk (n=106)	Standard-risk (n=131)
mPFS, months	12.9	16.6
mOS, months	Not Reached	Not Reached
ORR, %	76.4%	69.5%

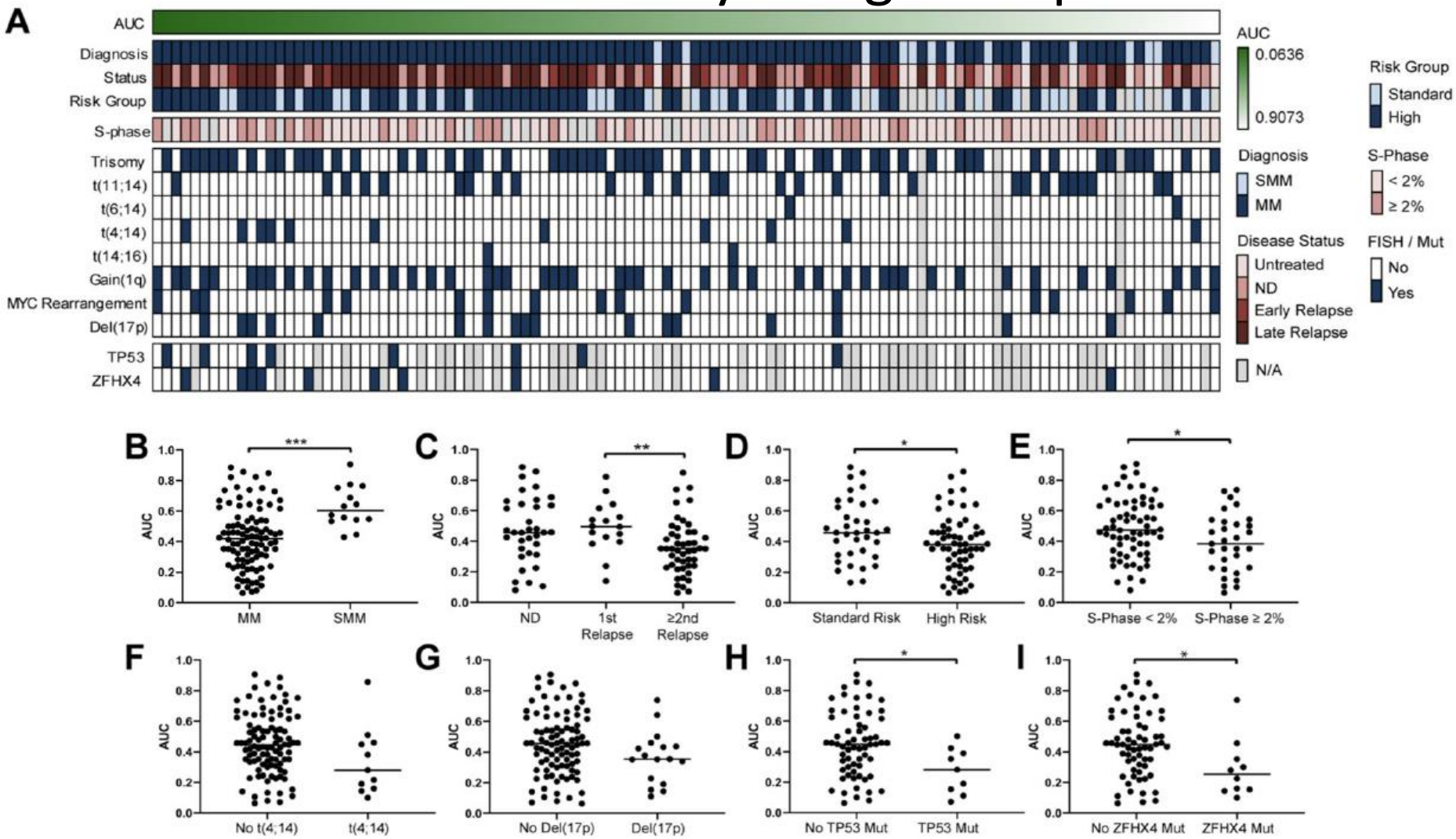
High-risk Abnormality	del (17p)	t(4;14)	t(14;16)	Amp 1q21
mPFS, months	12.2	13.2	5.3	13.9
mOS, months	Not Reached	20.44	16.43	Not Reached
ORR, %	72.0%	88.0%	90.0%	73.8%

1. Bahlis et al. ASH; 2021 Dec 11-14 [Abstract 1634]
2. Richard S et al. Am J Hematol 2021;96:1120-1130





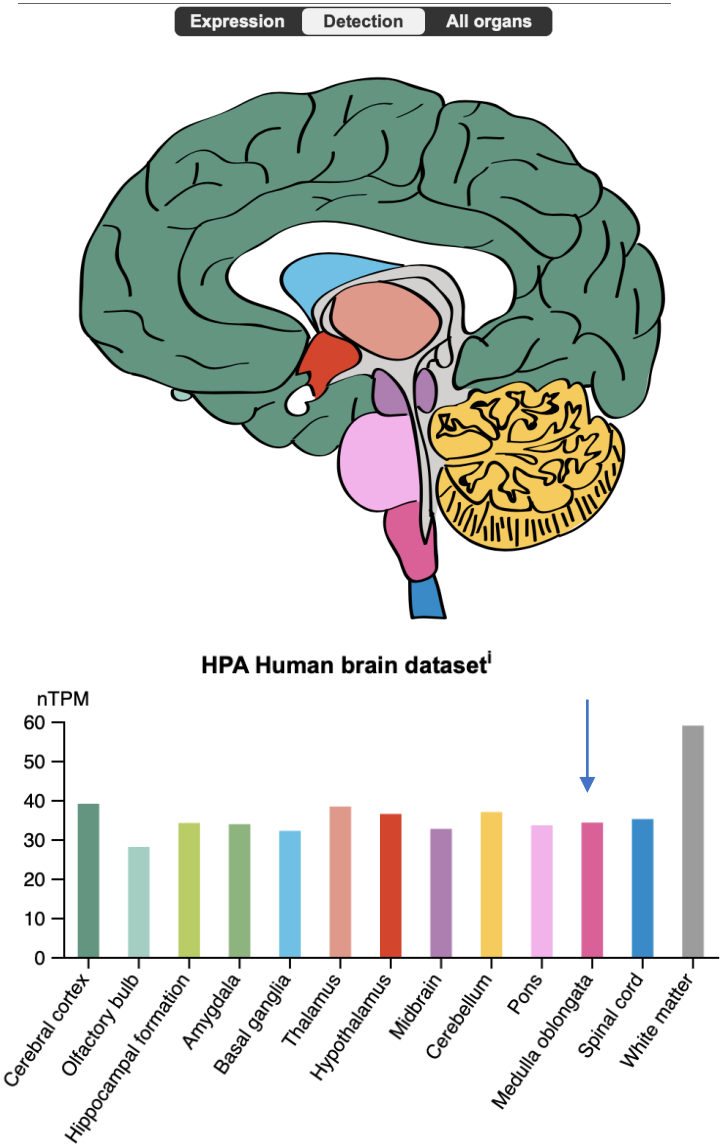
Selinexor sensitivity in high-risk patients



Bonolo de Campos et al Blood Cancer Journal 2020

Management of GI toxicity with Selinexor based regimen

Use of 5-HT3 or NK-1 receptor antagonist in combination with Olanzapine



Data from the Human Protein Atlas, https://www.proteinatlas.org

	XVd (N=195)			Vd (N=204)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Nausea	98 (50)	15 (8)	0 (0)	20 (10)	0 (0)	0 (0)
Fatigue	82 (42)	26 (13)	0 (0)	37 (18)	2 (1)	0 (0)
Decreased appetite	69 (35)	7 (4)	0 (0)	11 (5)	0 (0)	0 (0)
Diarrhea	63 (32)	11 (6)	1 (< 1)	51 (25)	1 (< 1)	0 (0)
Peripheral Neuropathy†	*63 (32)*	*8 (4)*	*1 (< 1)*	*96 (47)*	*18 (9)*	*0 (0)*
Upper Respiratory Tract Infection‡	57 (29)	7 (4)	0 (0)	45 (22)	4 (2)	0 (0)
Weight decreased	51 (26)	4 (2)	0 (0)	25 (12)	2 (1)	0 (0)
Asthenia	48 (25)	16 (8)	0 (0)	27 (13)	9 (4)	0 (0)
Cataract§	42 (22)	17 (9)	0 (0)	13 (6)	0 (0)	3 (2)
Vomiting	40 (21)	8 (4)	0 (0)	9 (4)	0 (0)	0 (0)

*Events that occurred in at least 15% of patients and had a >5% difference between treatment arms. AEs were graded according to the NCI CTCAE, V 4.03. For patients who crossed over, AEs 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 XVd 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 XVd arm versus 7.9% on the Vd arm. Data cut-off February 18, 2020.

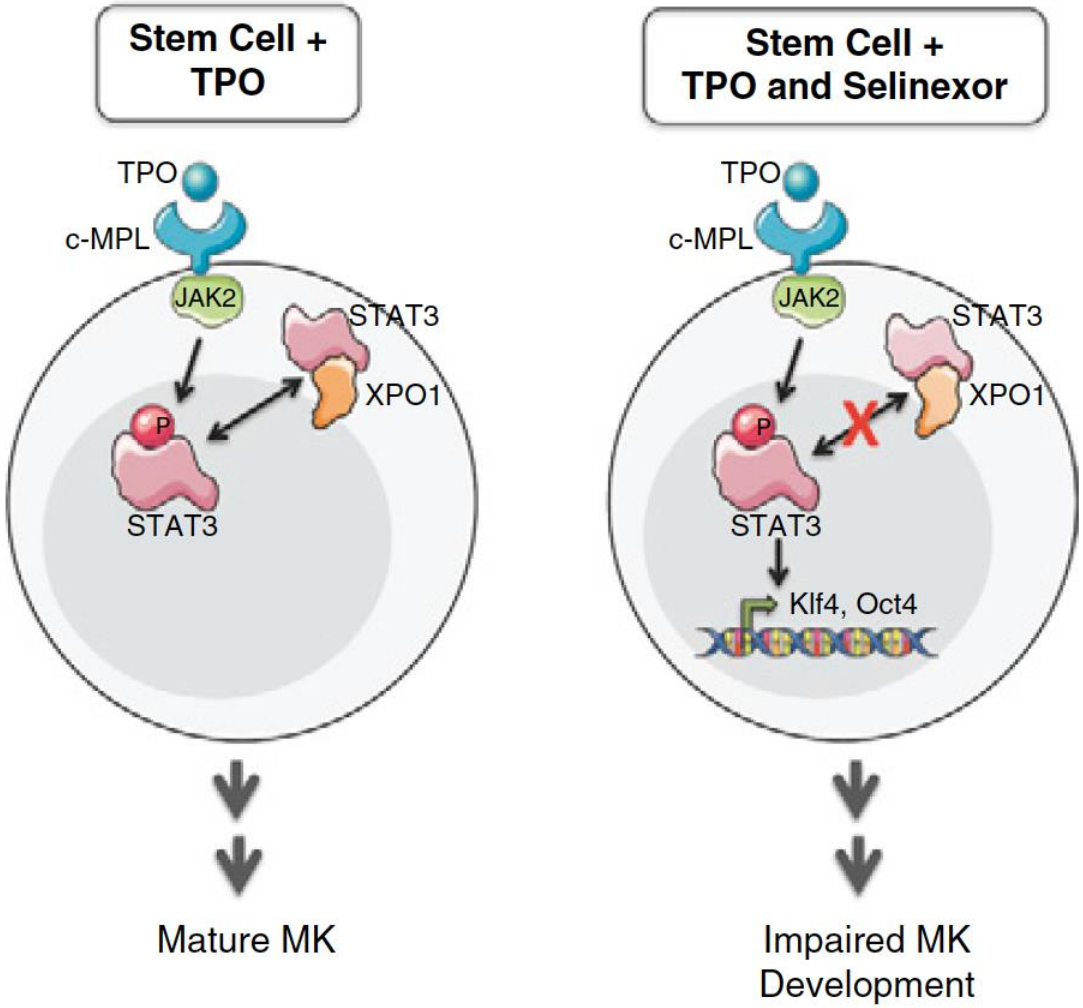
Grosicki et al. Lancet. 2020;396:1563-73

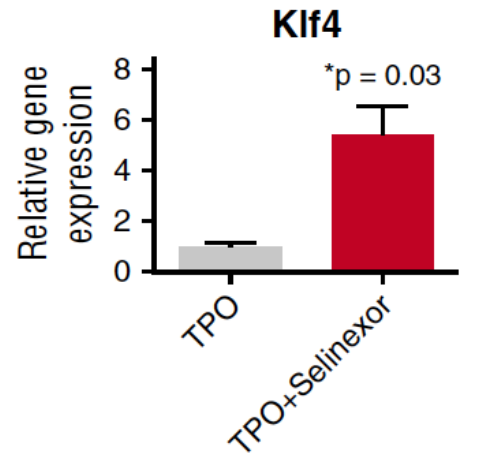
Selinexor induces transient and reversible thrombocytopenia

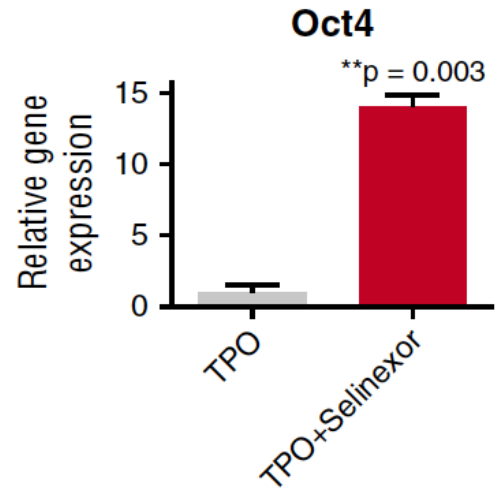
	Selinexor, bortezomib, and dexamethasone group (n=195)		Bortezomib and dexamethasone group (n=204)*	
	Any grade†	Grade 3–4	Any grade‡	Grade 3–4
Haematological adverse events				
Thrombocytopenia	117 (60%)	77 (39%)	55 (27%)	35 (17%)
Anaemia	71 (36%)	31 (16%)	47 (23%)	20 (10%)
Neutropenia	29 (15%)	17 (9%)	12 (6%)	7 (3%)

Grosicki et al. Lancet. 2020;396:1563-73

Selinexor-induced thrombocytopenia results from inhibition of thrombopoietin signaling in early megakaryopoiesis

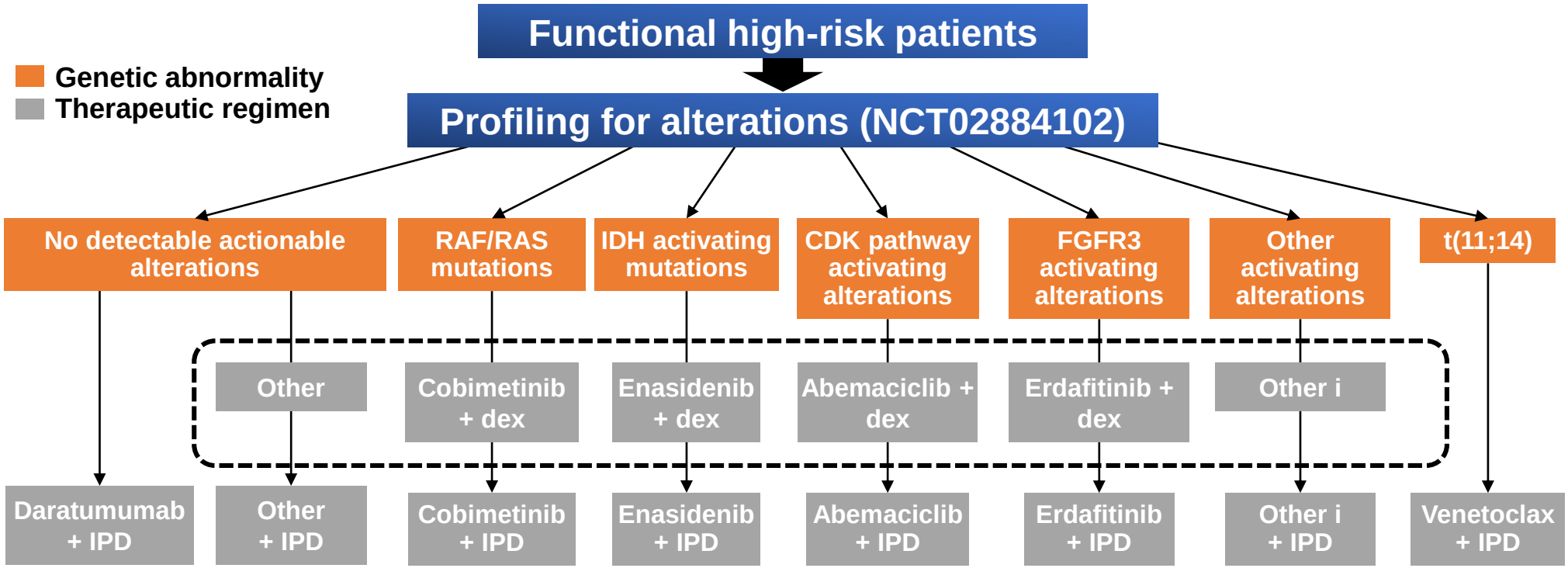






Machlus K et al Blood. 2017;130:1132-1143

Targeted therapy in Multiple Myeloma



i, inhibitor

Other targets in clinical trials:
BRD4 inhibitors, EP300 inhibitors, MMSET/NSD2 inhibitors, Sumoylation inhibitors

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