TREATMENT FOR RELAPSED TRANSLOCATION 11;14 MULTIPLE MYELOMA: THE ROLE OF BCL2 INHIBITORS

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EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

VENETOCLAX IN MYELOMA (NOT FDA APPROVED)

Biology of myeloma and t(11;14)

Role of BCL2 inhibition

Venetoclax

Venetoclax with dexamethasone

- Venetoclax with dexamethasone and bortezomib
- Venetoclax with daratumumab
- Venetoclax with carfilzomib

t(11;14) Myeloma

Myeloma and the t(11;14)(q13;q32); evidence for a biologically defined unique subset of patients

Rafael Fonseca, Emily A. Blood, Martin M. Oken, Robert A. Kyle, Gordon W. Dewald, Richard J. Bailey, Scott A. Van Wier, Kimberly J. Henderson, James D. Hoyer, David Harrington, Neil E. Kay, Brian Van Ness, and Philip R. Greipp

BLOOD, 15 MAY 2002 • VOLUME 99, NUMBER 10

TRANSLOCATION (11;14) MYELOMA

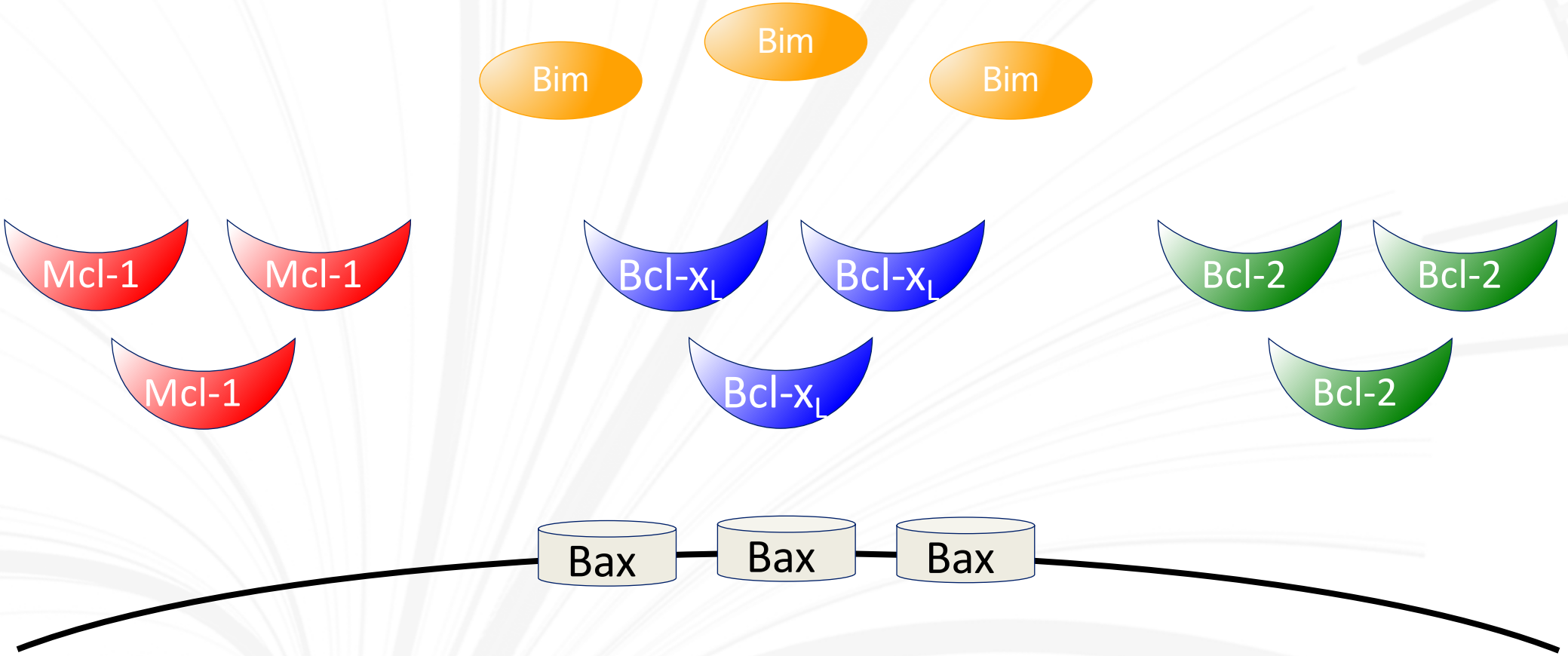
- approximately 15% of myeloma
- Characteristic lymphoplasmacytoid morphology
- Most common abnormality in primary plasma cell leukemia
- Prevalent in AL amyloidosis
- More likely light chain myeloma
- More common in rare variants: IgM; IgD; non secretory
- Expression of CD20 more common

Distribution of Bim determines Mcl-1 dependence or codependence with Bcl-x_L/Bcl-2 in Mcl-1–expressing myeloma cells

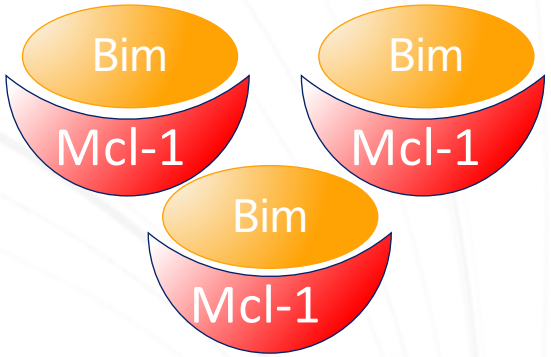
*Alejo A. Morales,[1] *Metin Kurtoglu,[2] *Shannon M. Matulis,[2] Jiangxia Liu,[2] David Siefker,[1] Delia M. Gutman,[1] Jonathan L. Kaufman,[2] Kelvin P. Lee,[3] Sagar Lonial,[2] and Lawrence H. Boise[2]

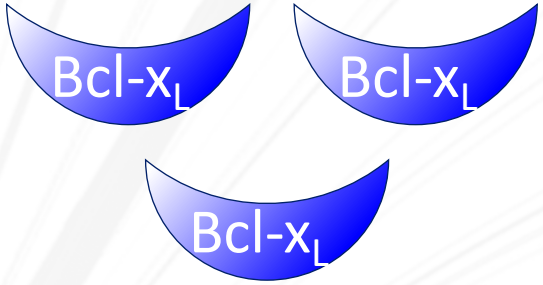
Bcl-2/Bcl-x_L–dependent and can be targeted with ABT-737. These data have several clinical implications, such as selecting the correct subset of patients to treat with ABT-737 as well as searching for agents that may synergize with this BH3-mimetic. Furthermore,

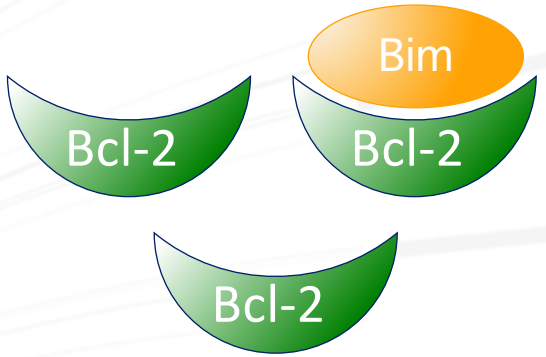
BLOOD, 4 AUGUST 2011 • VOLUME 118, NUMBER 5

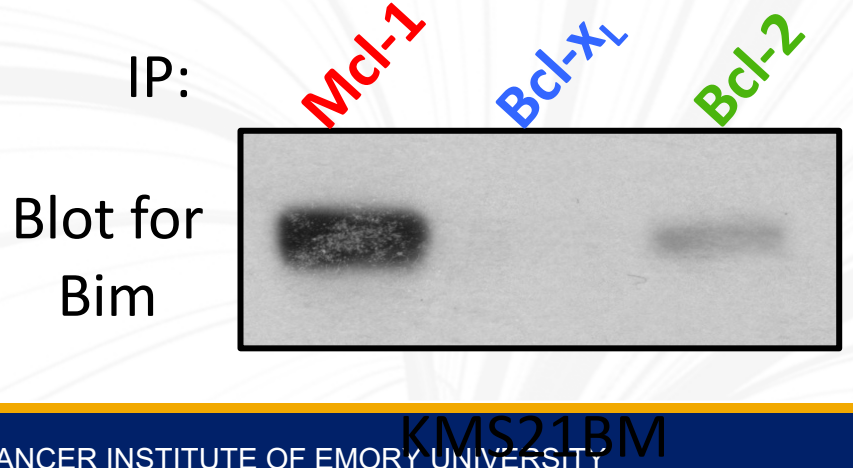

Bim
Bim
Bim
Mcl-1
Mcl-1
Mcl-1
Bcl-xL
Bcl-xL
Bcl-xL
Bcl-2
Bcl-2
Bcl-2
Bax
Bax
Bax
Mitochondria

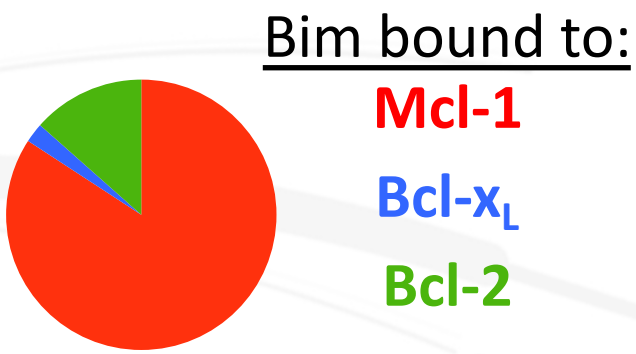
Mcl-1 Dependent



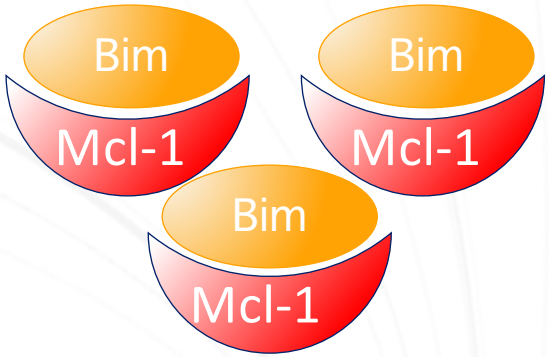


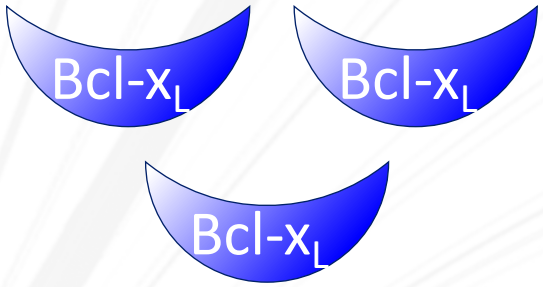


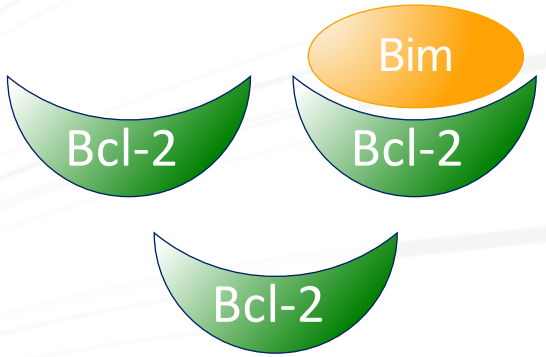


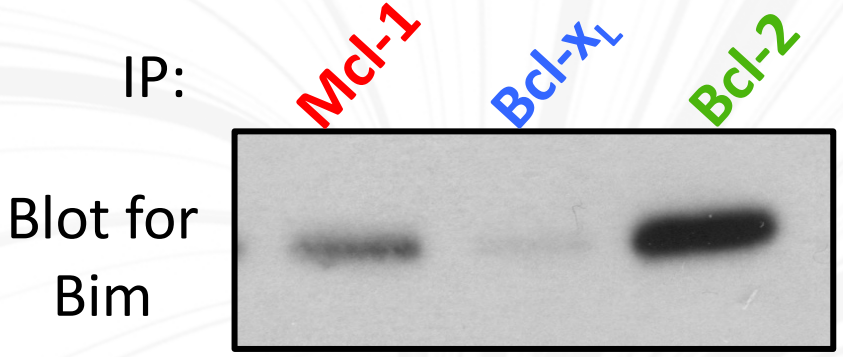


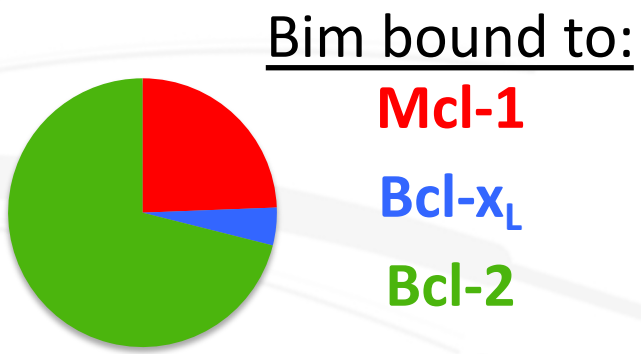
Bcl-2 Dependent



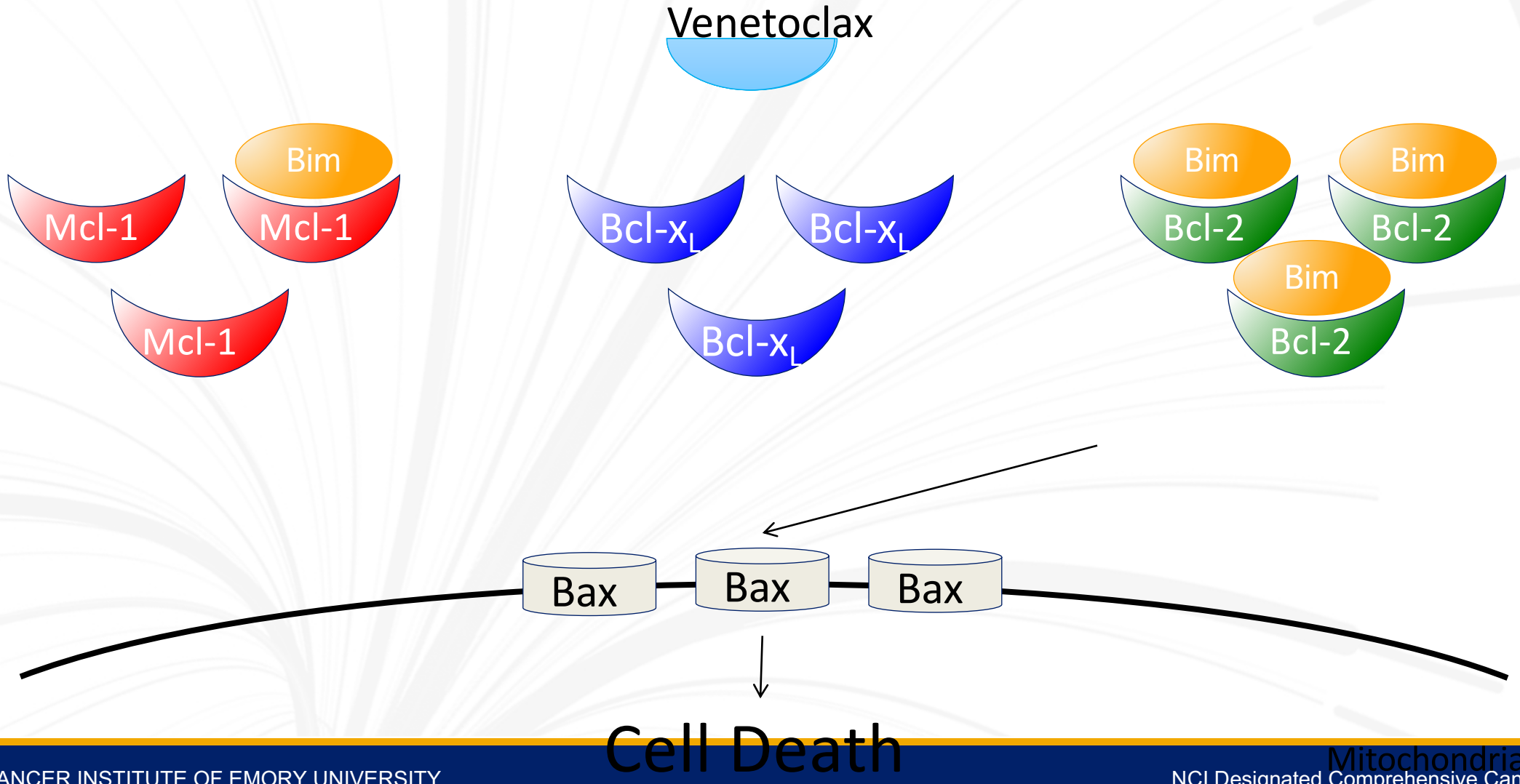




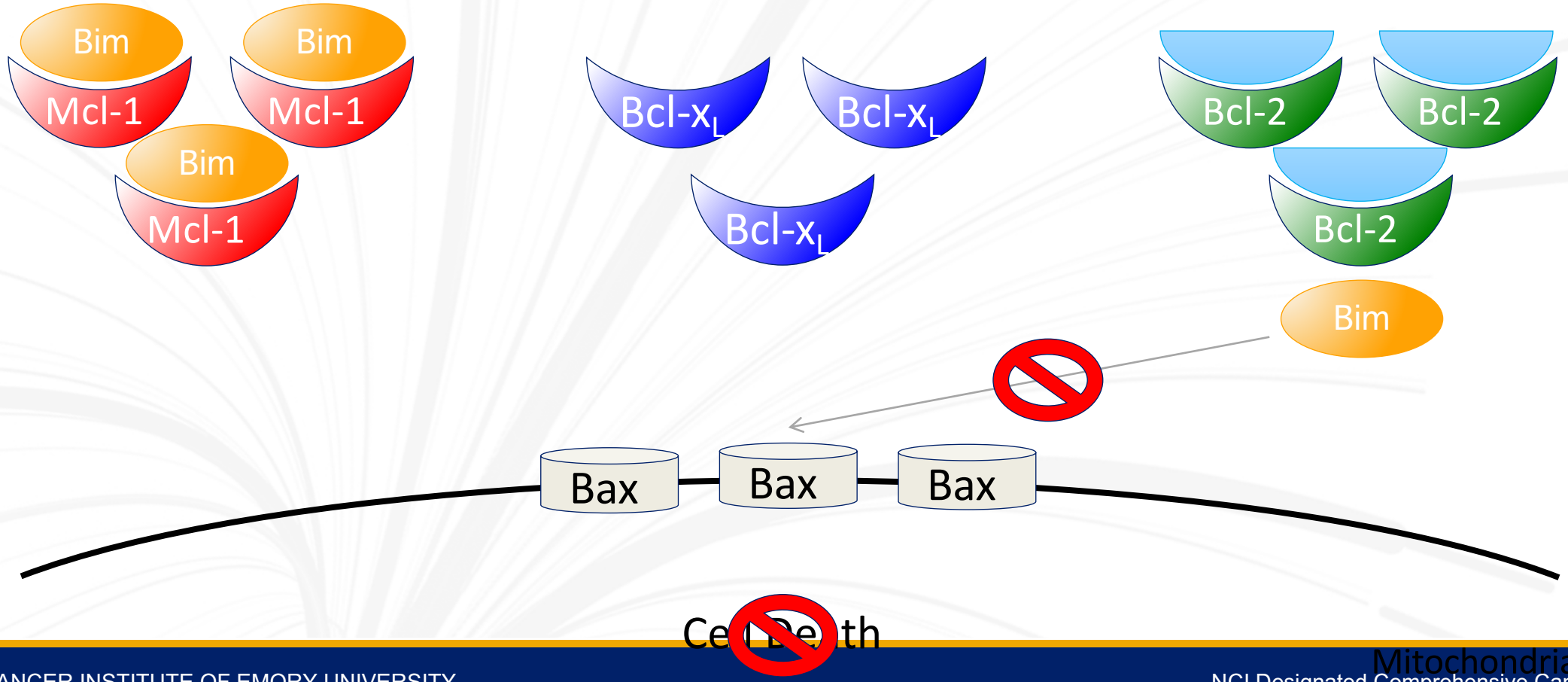




Bcl-2 Dependent Venetoclax sensitive



Mcl-1 Dependent Venetoclax Resistant



TRANSLOCATION (11;14) CORRELATES WITH ABT-199 SENSITIVITY

Samples	ABT-199	ABT-737	t(11;14)
MM80	0.04	ND	+
MM76-2	0.05	0.06	+
MM76	0.056	0.5	+
MM67	0.06	0.06	+
MM70	0.06	0.06	-
MM81	0.06	0.08	-
MM82	0.07	0.17	-
MM78	0.09	0.09	-
MM72	0.1	0.41	-
MM59	0.2	0.07	+
MM58	0.25	0.07	+
MM69	0.27	0.64	-
MM60	0.3	0.26	+
MM51	0.32	0.08	NA
MM73	0.36	0.1	-
MM75	0.36	0.3	-
MM56	0.45	0.2	+
MM74	1.4	0.7	-
MM54	1.4	1.1	-
MM68	1.4	2	-
MM55	1.7	0.1	-
MM58-2	1.98	ND	+
MM64	2.2	1.1	-
MM52	2.3	0.69	-
MM65	2.5	2.4	-
MM66	3.3	2.4	-
MM62	4.2	1.2	-
MM61	4.7	2.7	+
MM49	6.7	4.1	NA
MM70-2	7	0.4	-
MM79	10	5.6	-
MM77	12	ND	+
MM63	18.4	30.2	-

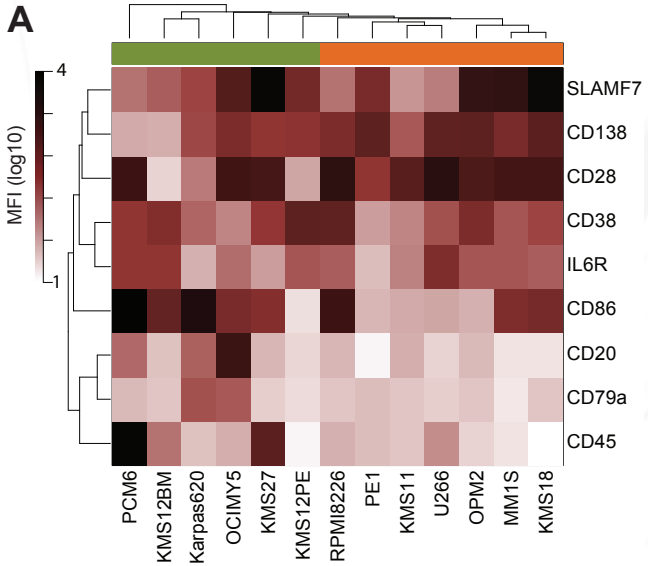
Not all t(11;14) are sensitive

Some non-t(11;14) are sensitive

There is no connection between Cyclin D1 and the Bcl-2 family

Vikas Gupta,
Shannon Matulis
Larry Boise

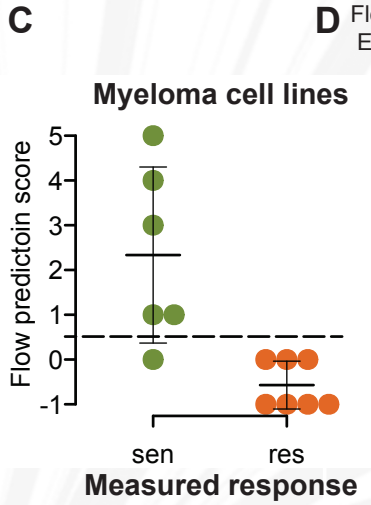
FLOW CYTOMETRY OF CELL SURFACE MARKERS PREDICTS VENETOCLAX SENSITIVITY IN MM PATIENT SAMPLES

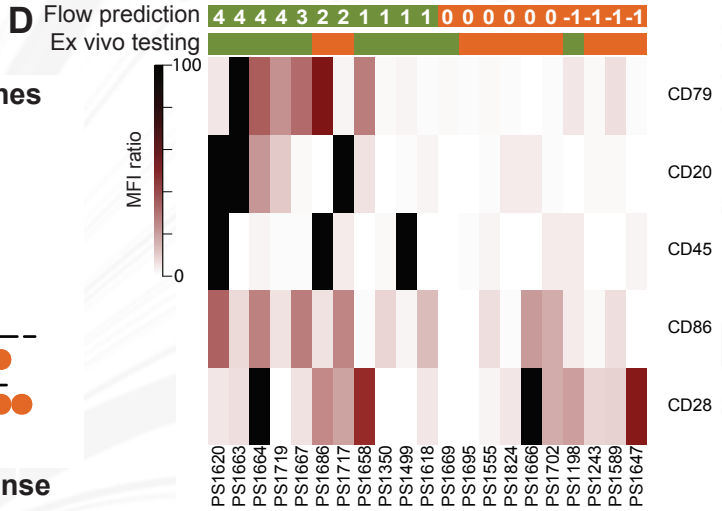


B

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

Sensitive	Resistant
≥1	≤0





82% Sensitivity
80% Specificity
P=0.0089 (Fisher's exact)

Gupta *et al., Blood*, 2021

CASE PRESENTATION

1. 38 y/o woman diagnosed in 04/2011, when she noted the presence of recurrent upper respiratory infections. Lab work showed she was profoundly anemic with a hemoglobin of 6 and a hematocrit of 18.6. Total protein was elevated at 12, and creatinine was 1.7. Calcium was 11. No evidence of lytic bone lesions. Bone marrow biopsy showed extensive involvement with plasmacytosis, 95% cellularity with about 79% plasma cells that were kappa light chain restricted. She was noted to have a serum free kappa light chain of about 2000 with a lambda of 18 for a ratio of 111, and her beta-2 at diagnosis was 6.1. Albumin was 2.2. FISH studies did show the presence of 11;14 translocation.
a. RVD x 5 cycles, best response PR
b. cyclophosphamide with stem cell collection and then autologous transplant in 11/2011. Best response VGPR
c. lenalidomide as maintenance therapy. Did well for about 20 months when she was noted to have progression of her protein.
d. In 09/2013, she was started again on RVD for 2 cycles with no significant response.
e. was then switched to pomalidomide with dexamethasone for about a month, then received a month of bendamustine. Progressed on treatment.

F. Referred for second opinion.

Bone Marrow with extensive involvement with myeloma. 90% plasma cells. Hg 8.6

Multiple Myeloma Panel, FISH

POSITIVE for gain of one copy of 1q CKS1B) in 43 of 50 cells

POSITIVE for t(11;14) in 47 of 50 cells

POSITIVE for gain of one copy of 13q14in 42 of 50 cells

f. At age 42 she enrolled on the phase I clinical trial with venetoclax.

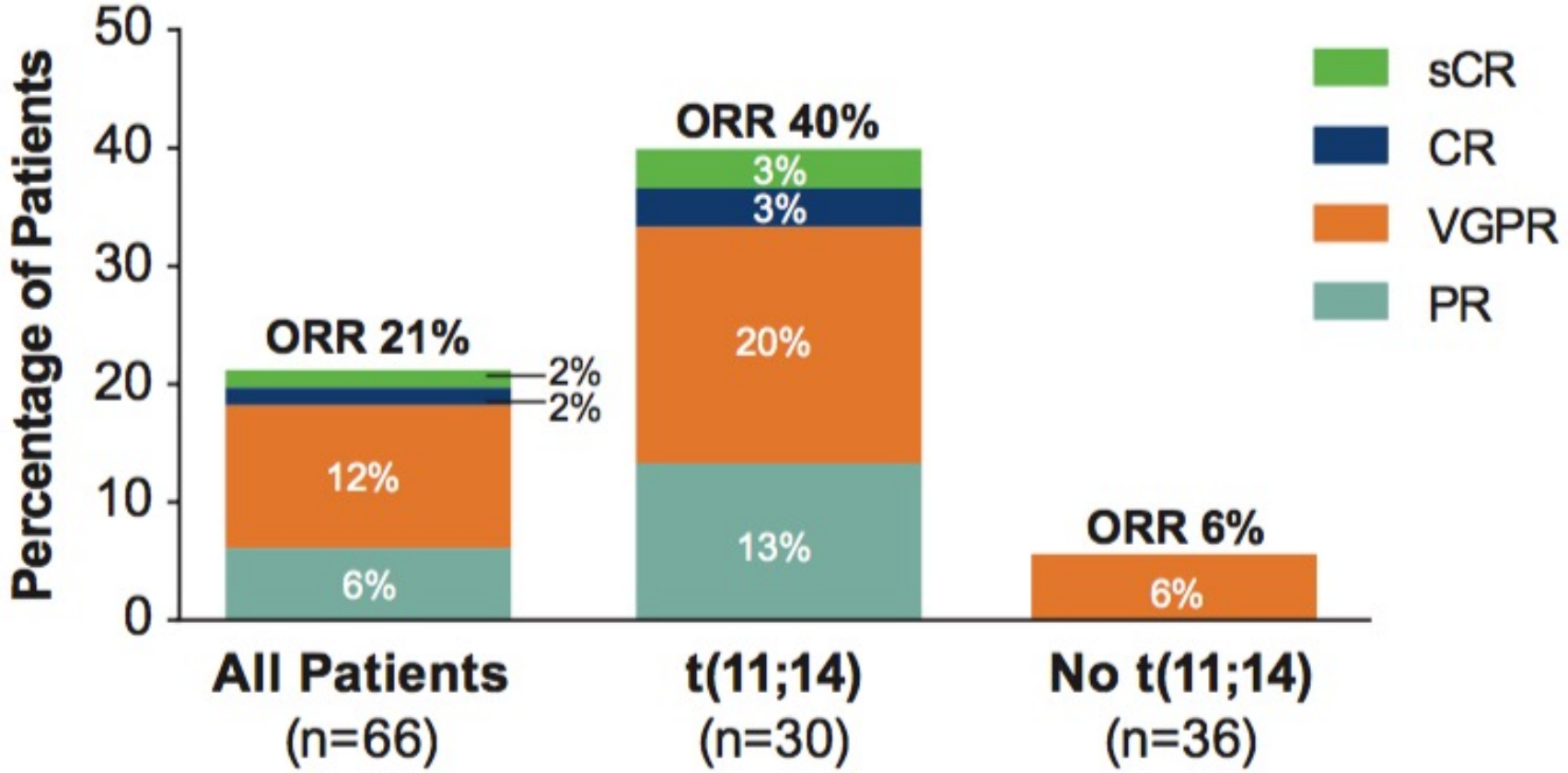
Phase 1 Venetoclax Monotherapy for Relapsed/Refractory Multiple Myeloma

8032

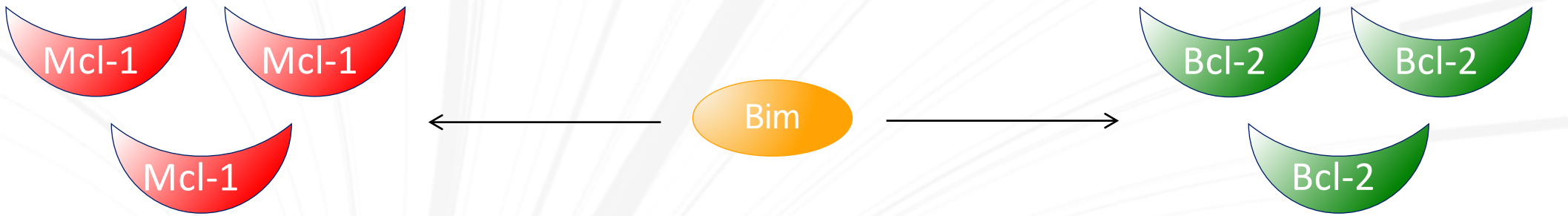
Shaji Kumar,[1] Ravi Vij,[2] Jonathan L Kaufman,[3] Joseph Mikhael,[4] Thierry Facon,[5] Brigitte Pegourie,[6] Lofti Benboubker,[7] Cristina Gasparetto,[8] Martine Amiot,[9] Philippe Moreau,[9] Susan Diehl,[10] Stefanie Alzate,[10] Jeremy Ross,[10] Martin Dunbar,[10] Ming Zhu,[10] Suresh Agarwal,[10] Joel Leverson,[10] Paulo Maciag,[10] Maria Verdugo,[10] Cyrille Touzeau[9]

[1]Mayo Clinic, Rochester, MN, USA; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [4]Mayo Clinic, Scottsdale, AZ, USA; [5]CHRU Lille, Hopital Huriez, France; [6]CHU Grenoble, France; [7]CHRU Tours, France; [8]Duke University, Hematologic Malignancies & Cellular Therapy, Durham, NC, USA; [9]CHU de Nantes, Hotel Dieu—HME, France; [10]AbbVie Inc., North Chicago, IL, USA

Figure 4. Objective Response Rates by t(11;14) Status



Is there a way to shift from Mcl-1 dependence to Bcl-2 dependence in myeloma?



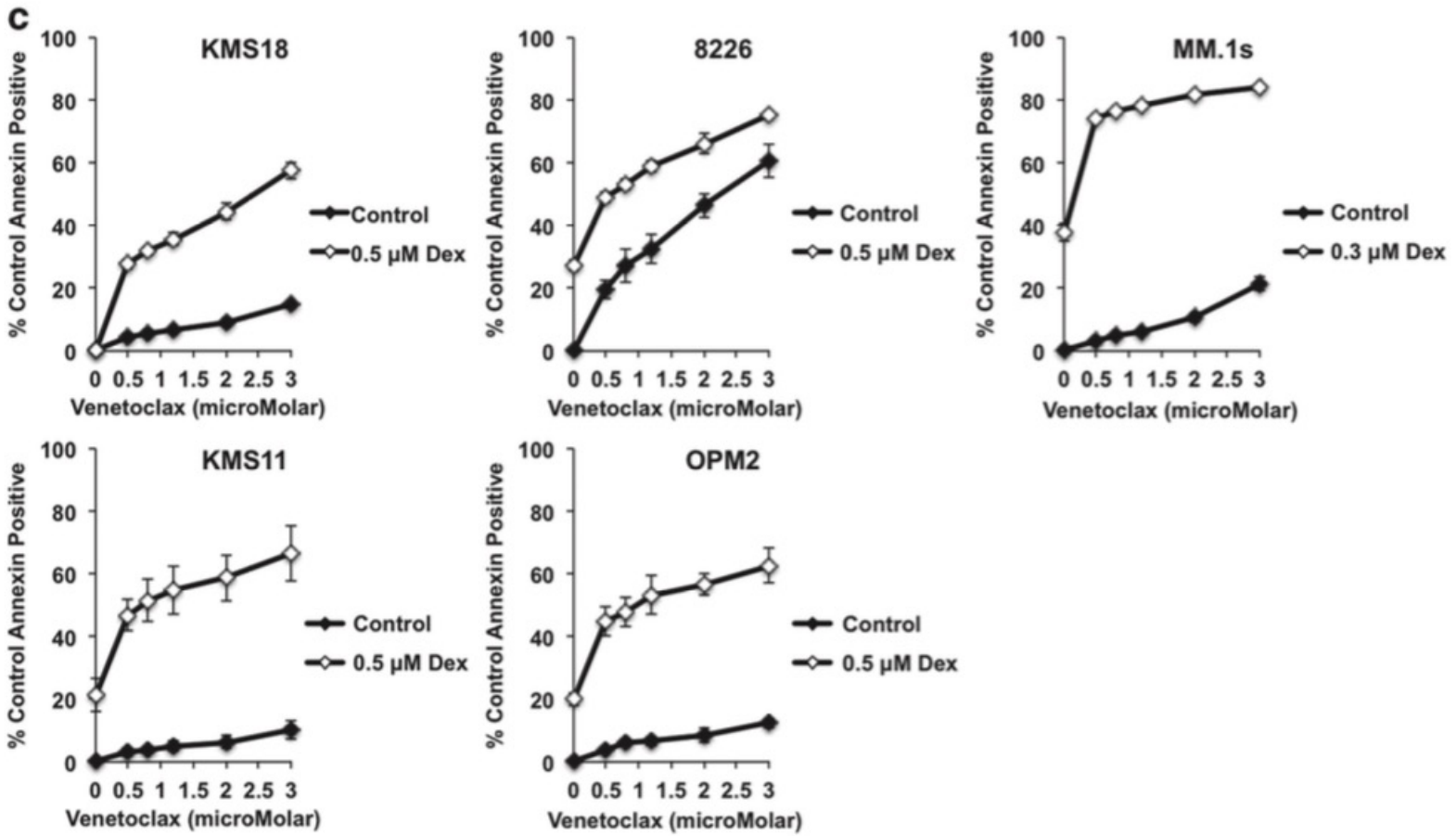
Venetoclax resistant

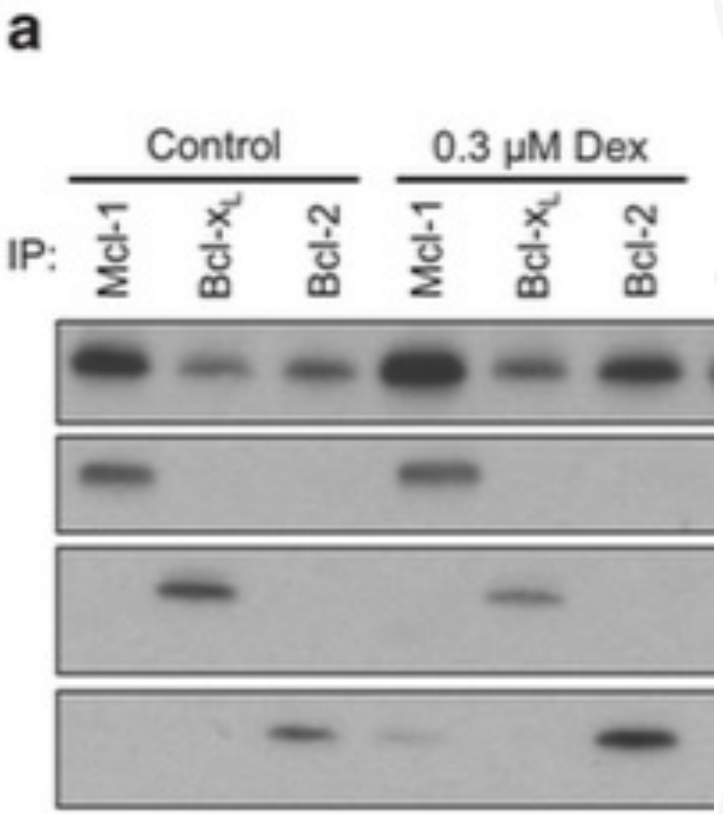
Venetoclax sensitive

ORIGINAL ARTICLE

Dexamethasone treatment promotes Bcl-2 dependence in multiple myeloma resulting in sensitivity to venetoclax

SM Matulis[1], VA Gupta[1,2], AK Nooka[1,2], HV Hollen[2], JL Kaufman[1,2], S Lonial[1,2] and LH Boise[1,2]

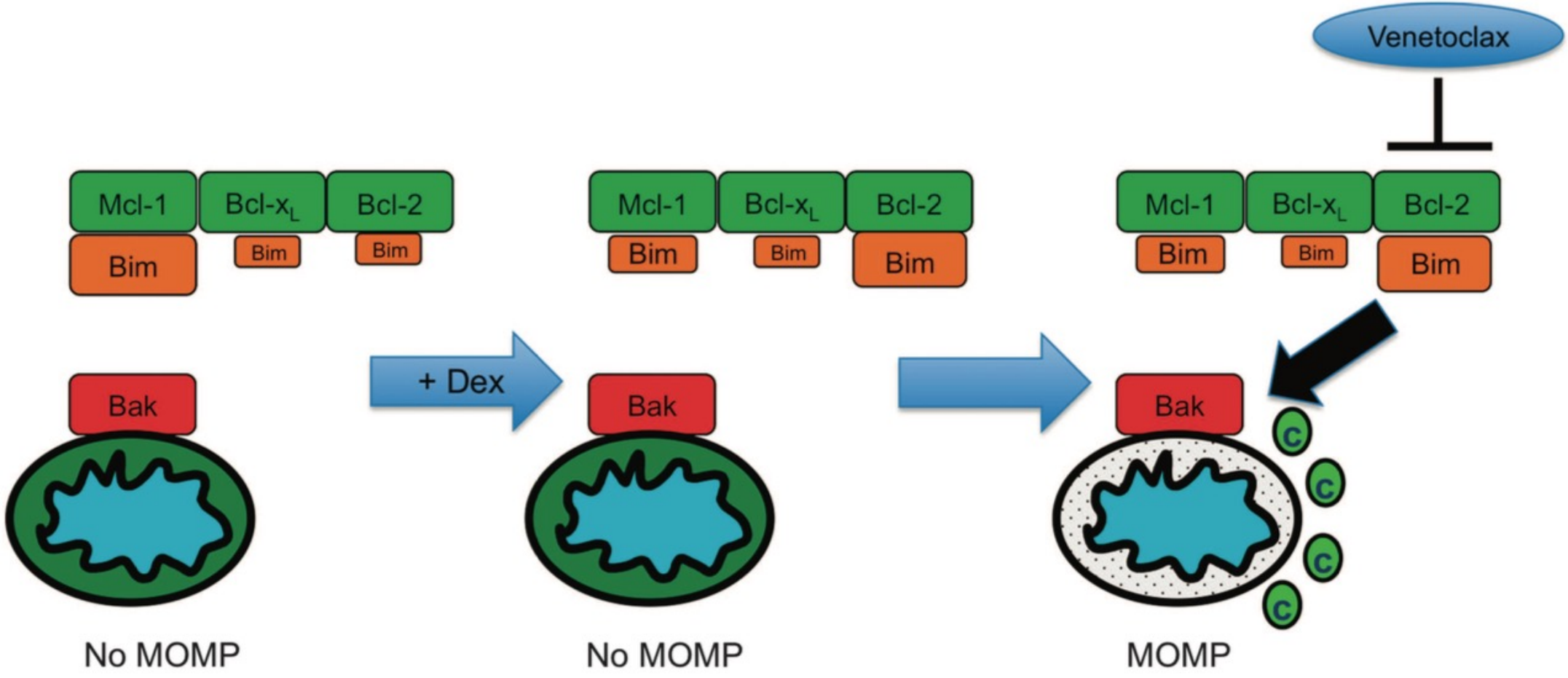




Leukemia (2016), 1–8

www.nature.com/leu

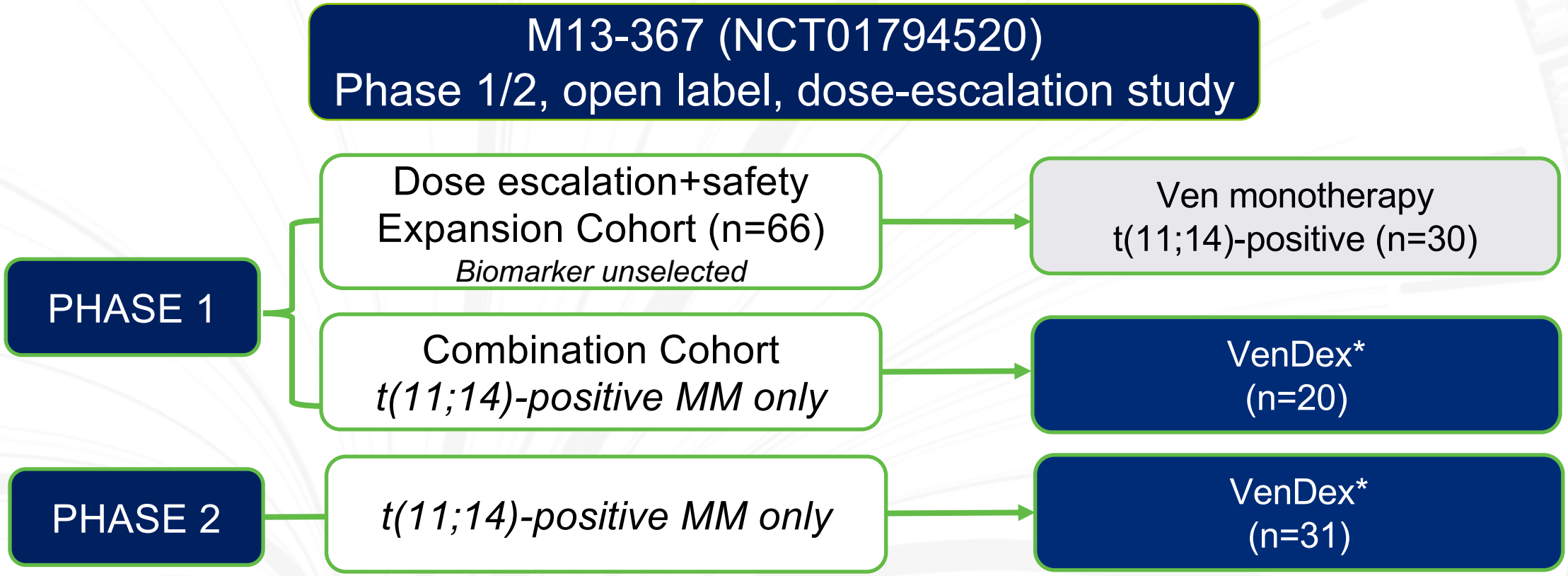
MODEL OF DEXAMETHASONE PRIMING



Leukemia (2016), 1–8

www.nature.com/leu

STUDY DESIGN AND OBJECTIVES

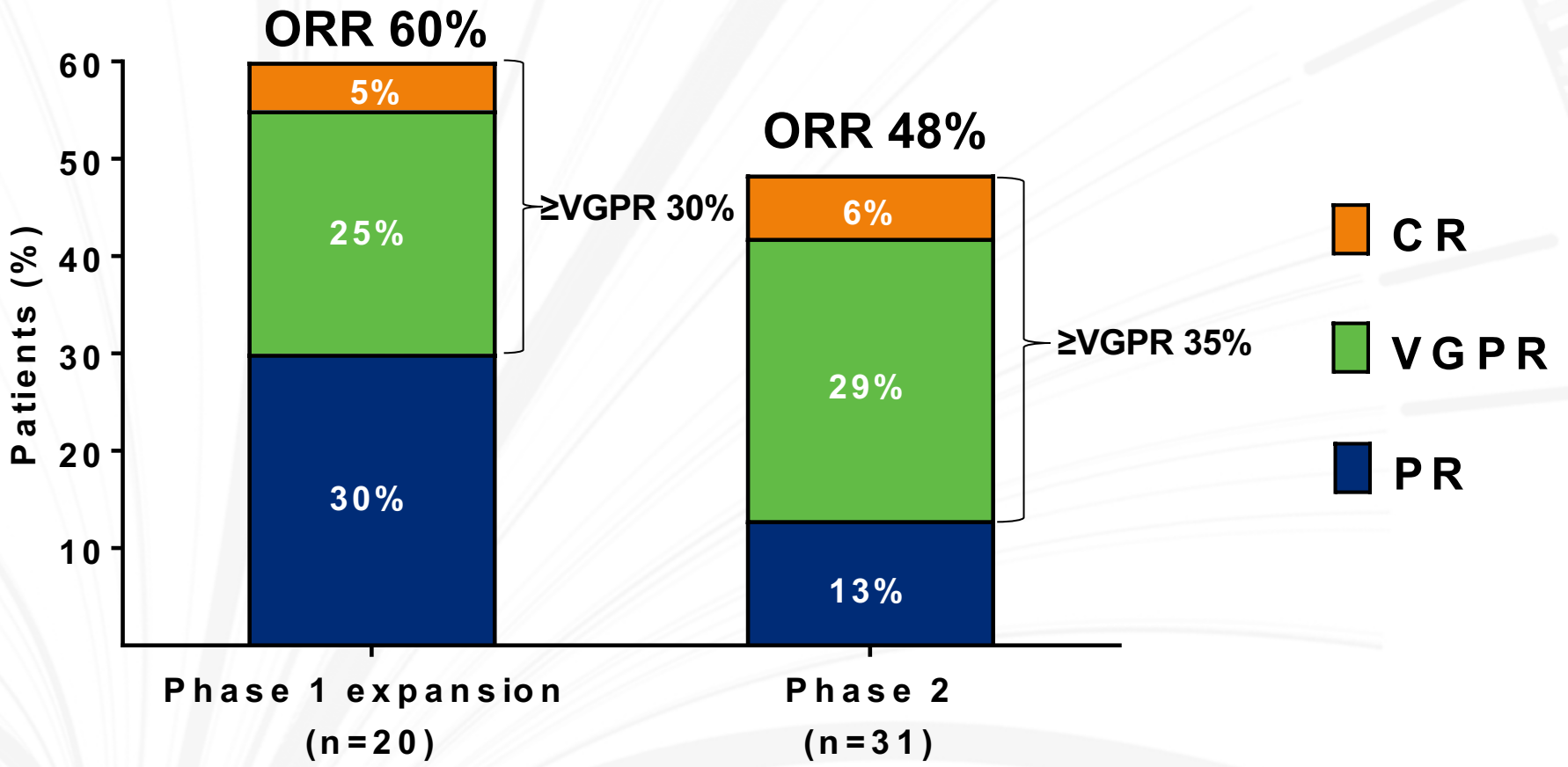


Study Objective

- Evaluate safety and efficacy of t(11;14) RRMM patients treated with VenDex

*Dosing: oral venetoclax 800 mg/day+oral dexamethasone 40 mg (20 mg for pts ≥75 years of age) on days 1, 8, and 15 of each 21-day cycle

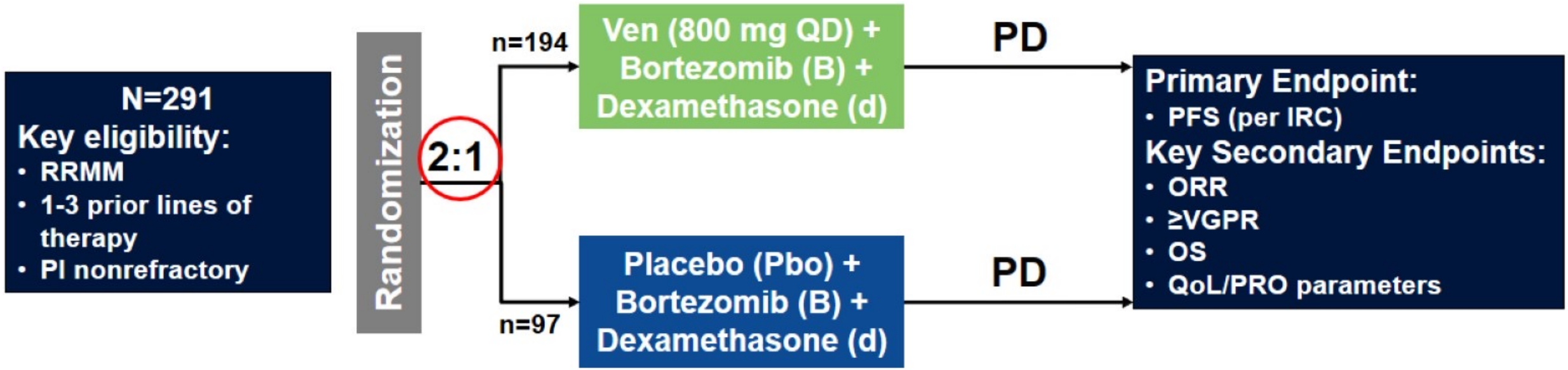
CLINICAL EFFICACY OF VENDEX



Daratumumab refractory, (%)	**20%**	**87%**
Lines of prior therapy, median (range)	**3 (1-8)**	**5 (2-12)**

CR: Complete remission; ORR: Objective response rate; VGPR: Very good partial response; PR: Partial response

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* gene expression

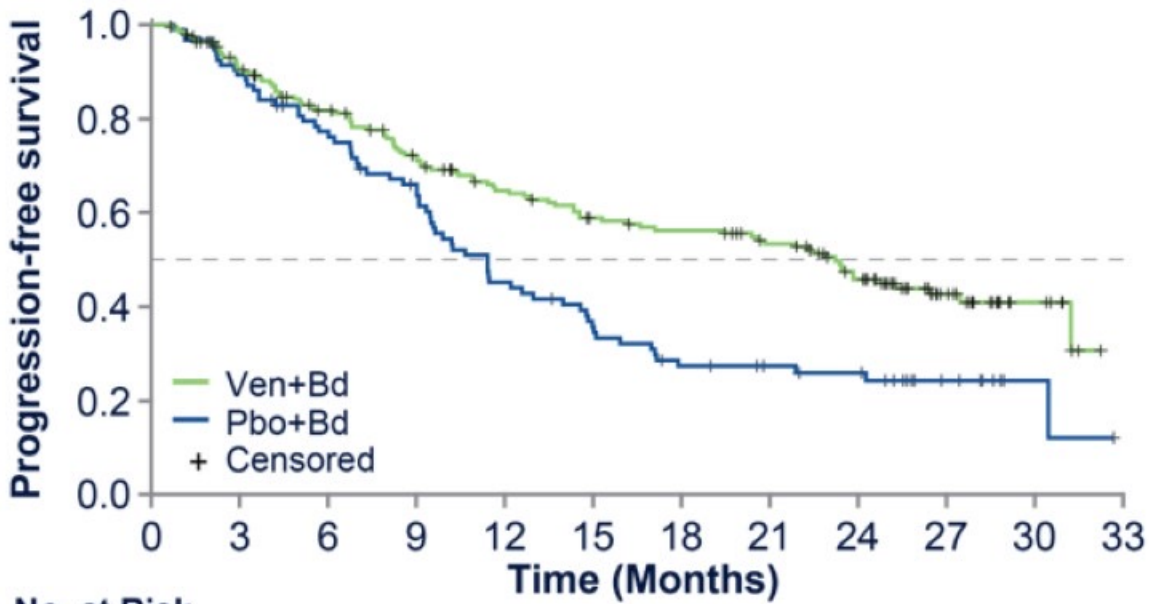
DOR, duration of response; GHS, global health status; IHC, immunohistochemistry; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PRO, patient reported outcome; QD, daily; QoL, quality of life; RRMM, relapsed/refractory multiple myeloma; TTP, time to progression; VGPR, very good partial response.

Adapted from the Harrison presentation at ASH on Dec 7, 2019

PFS and OS in All Patients (ITT)

Clinical Data Cutoff: 15 Jul 2019

Investigator-Assessed PFS

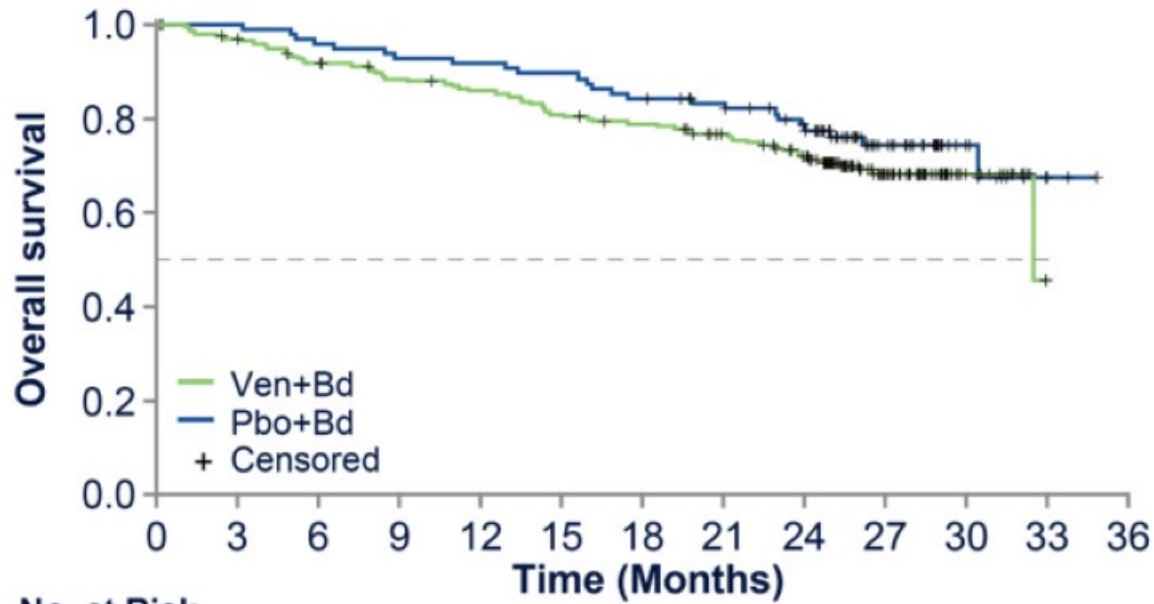


No. at Risk

194	163	140	118	101	89	84	75	58	27	9	0
97	83	69	57	39	30	22	19	17	8	2	0

PFS	Ven+Bd	Pbo+Bd
Median, months	23.2	11.4
HR (95% CI)	0.60 (0.44, 0.83)	
P value	0.001	

OS



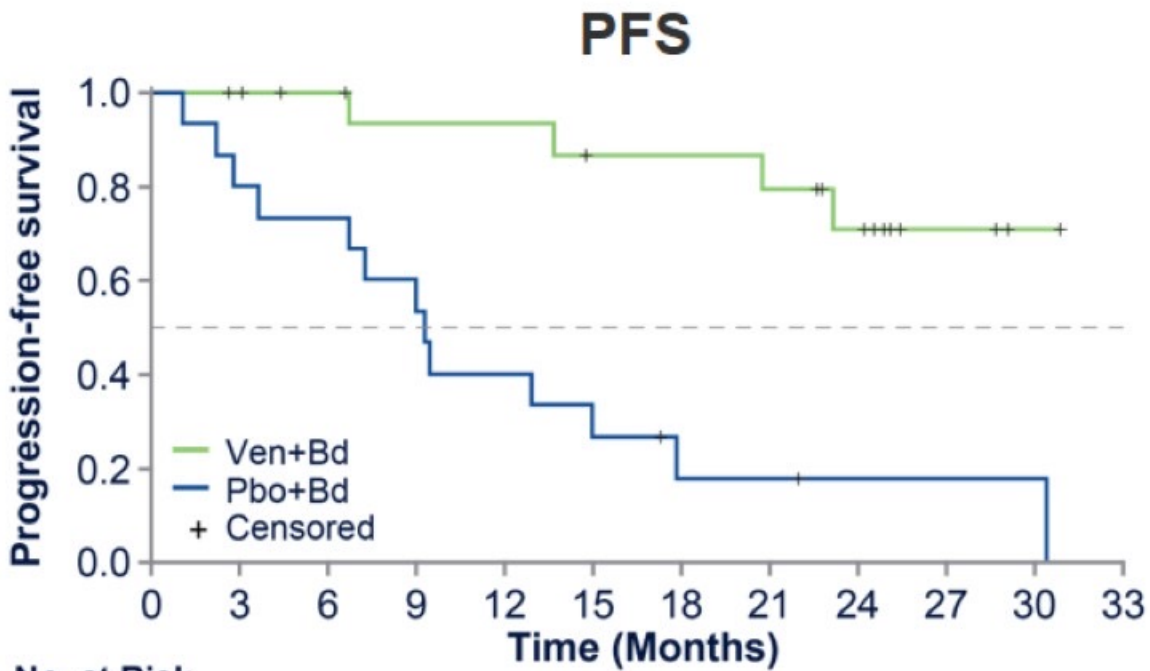
No. at Risk

194	186	174	165	159	150	144	133	118	62	18	0	
97	95	91	88	87	85	80	75	66	33	12	2	0

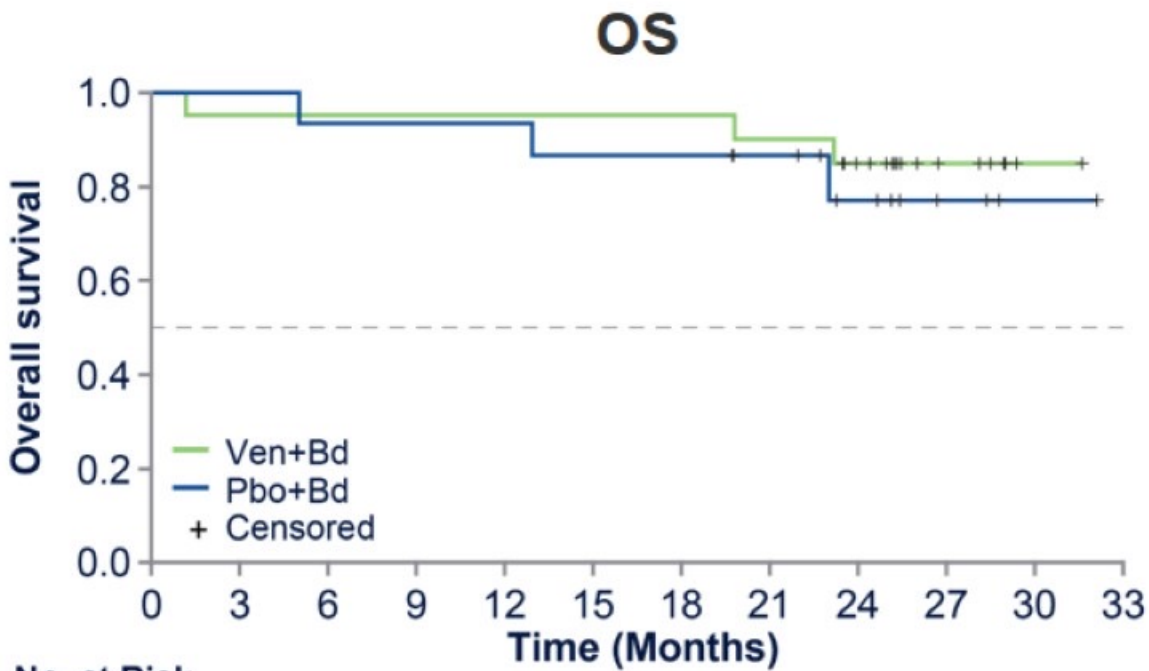
OS	Ven+Bd	Pbo+Bd
Median, months	32.5[a]	Not reached
HR (95% CI)	1.32 (0.82, 2.12)	
P value	0.256	

[a]Because of a large number of patients who were censored before reaching the median, the estimated median could change when longer follow-up data are available.

PFS and OS in Patients with t(11;14)



PFS	Ven+Bd	Pbo+Bd
Median, months	Not reached	9.3
HR (95% CI)	0.09 (0.02, 0.44)	
P value	0.003	



OS	Ven+Bd	Pbo+Bd
Median, months	Not reached	Not reached
HR (95% CI)	0.68 (0.13, 3.48)	
P value	0.647	

High *BCL2* gene expression was determined by qPCR.

Adapted from the Harrison presentation at ASH on Dec 7, 2019

SAFETY AND PRELIMINARY EFFICACY FROM THE EXPANSION COHORT OF A PHASE 1/2 STUDY OF VENETOCLAX PLUS DARATUMUMAB AND DEXAMETHASONE VS DARATUMUMAB PLUS BORTEZOMIB AND DEXAMETHASONE IN PATIENTS WITH T(11;14) RELAPSED/REFRACTORY MULTIPLE MYELOMA

Jonathan L. Kaufman[1], Hang Quach[2], Rachid Baz[3], Annette Juul Vangsted[4], Shir-Jing Ho[5], Simon J. Harrison[6], Torben Plesner[7], Philippe Moreau[8], Simon Gibbs[9], Eva Medvedova[10], Vasudha Sehgal[11], Kingston Kang[11], Jeremy A. Ross[11], Leanne L Fleming[11], Yan Luo[11], Nizar J. Bahlis[12]

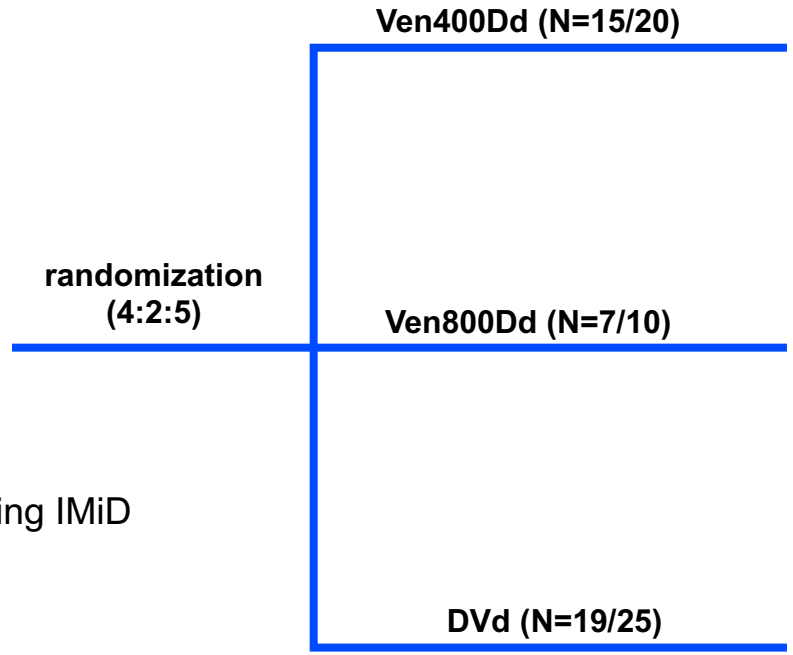
[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA, [2]St. Vincent's Hospital, University of Melbourne, Melbourne, VIC, Australia; [3]Department of Malignant Hematology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [4]Department of Hematology, University of Copenhagen, Copenhagen, Denmark; [5]St. George Hospital, Sydney, NSW, Australia; [6]Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Sir Peter MacCallum dept of Oncology, University of Melbourne, Melbourne, Victoria, Australia; [7]University of Southern Denmark & Vejle Hospital, Denmark; [8]Department of Hematology, University Hospital, Nantes, France; [9]Box Hill Hospital, Eastern Health Clinical School, Monash University, Melbourne, VIC, Australia; [10]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [11]AbbVie, Inc., North Chicago, IL, USA; [12]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, Alberta, Canada

American Society of Hematology 2021 Annual Meeting, December 11 – 14, 2021, Atlanta, Georgia

abbvie

Part 3 of NCT03314181 is a randomized, open-label expansion of VenDd in patients with t(11;14) RRMM

- t(11:14) RRMM
- non-refractory to PIs
- ≥ 1 prior line of therapy including IMiD



Data cutoff date : August 2, 2021

Primary Objective

- To compare and further evaluate the safety and preliminary efficacy of VenDd at 400mg or 800mg Ven dose levels with DVd

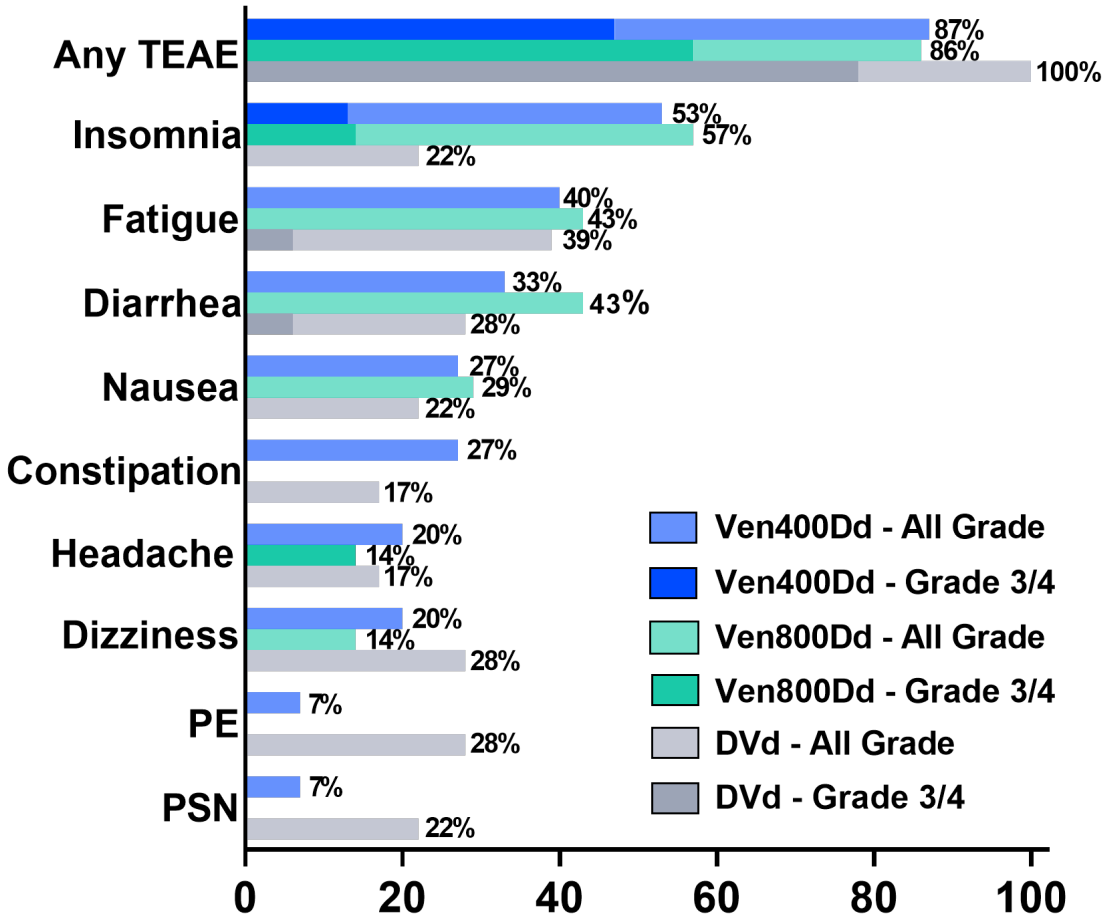
Treatment Regimen

VenDd			
Cycle	**Ven (400/800 mg) oral**	**D (1800mg) SC**	**d (40 mg) oral or IV**
1 – 2 (28 days)	Once daily	Days 1, 8,15, 22	Weekly
3 – 6 (28 days)	Once daily	Days 1 and 15	Weekly
7+ (28 days)	Once daily	Day 1	Weekly
DVd			
Cycle	**V (1.3 mg/m^2) SC or IV**	**D (1800 mg) SC**	**d (20 mg) oral or IV**
1 – 3 (28 days)	Days 1, 4, 8,11	Day 1, 8,15	Day 1, 2, 4, 5, 8, 9, 11, 12, and 15
4 – 8 (28 days)	Days 1, 4, 8,11	Day 1	Day 1, 2, 4, 5, 8, 9, 11, and 12
9+ (21 days)	-	Day 1	Day 1

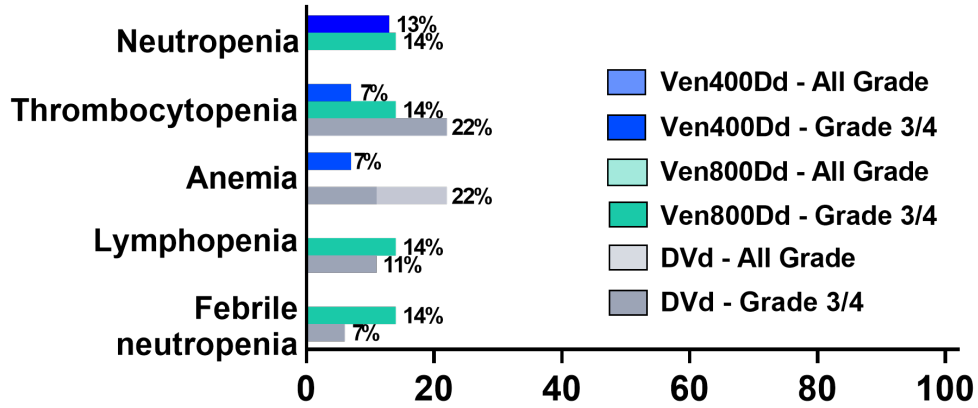
Ven, venetoclax; Ven400, venetoclax 400 mg; Ven800, venetoclax 800 mg; D, daratumumab; d, dexamethasone; Ab, antibody; V, bortezomib; RRMM, relapsed refractory multiple myeloma; PI, proteosome inhibitor; IMID, immunomodulatory agent; SC, subcutaneous; IV, intravenous

Patients treated with VenDd demonstrated a tolerable safety profile

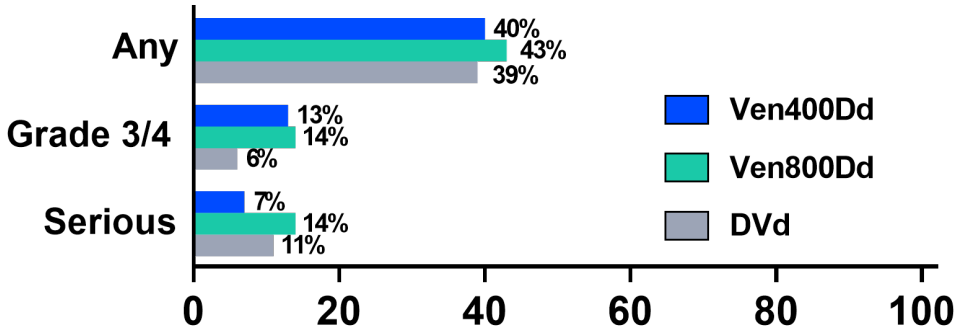
AEs in ≥20% of Patients



Most Common Hematologic AEs



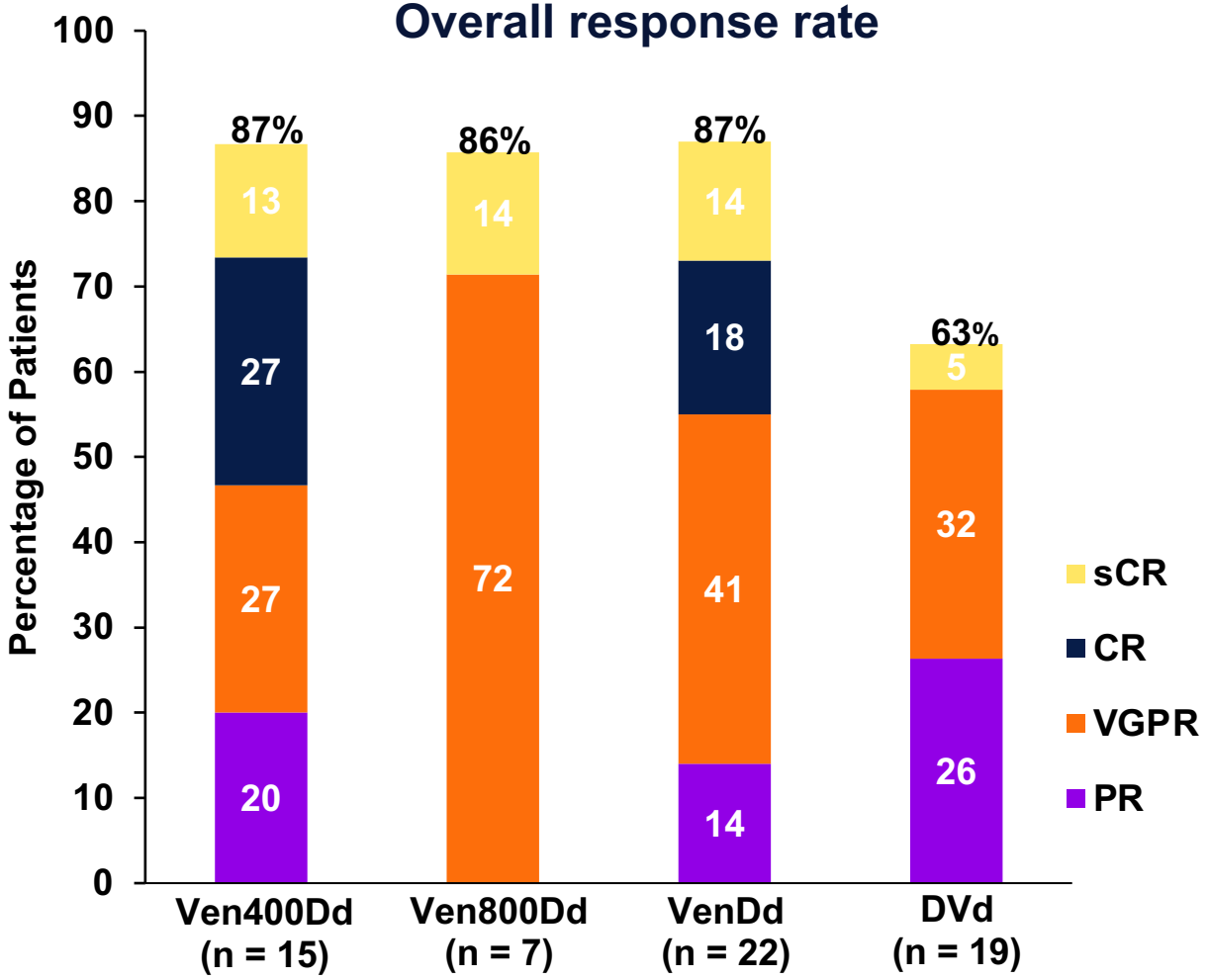
Infections



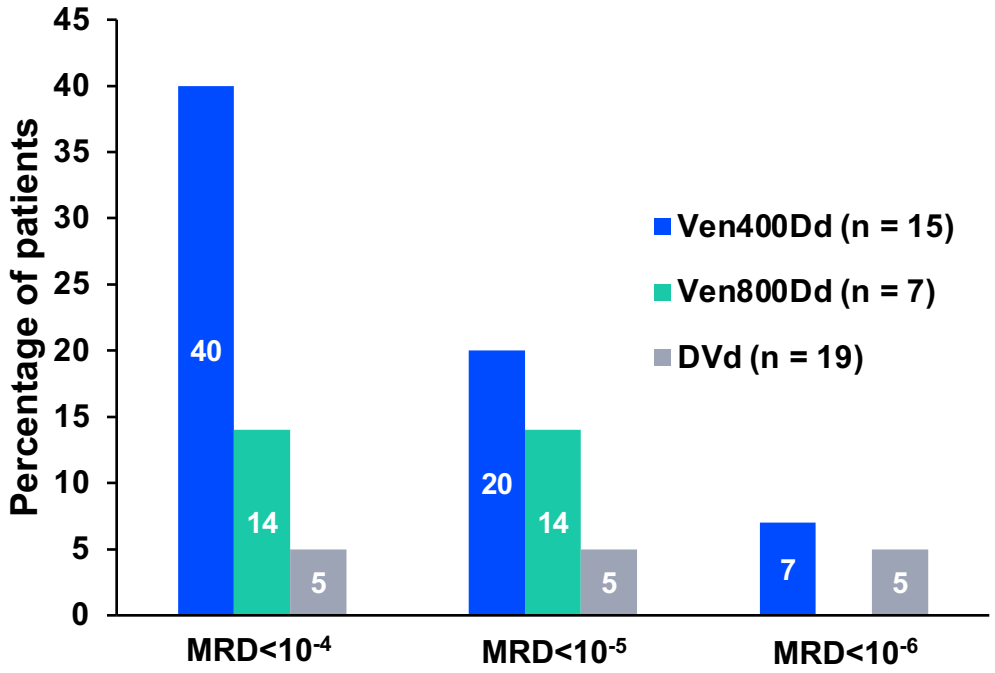
Ven, venetoclax; Ven400, venetoclax 400 mg; Ven800, venetoclax 800 mg; D, daratumumab; d, dexamethasone; V, bortezomib, AE, adverse event; SAEs, serious adverse events; TEAE, treatment emergent adverse event; PE, peripheral edema; PSN, peripheral sensory neuropathy

VenDd arms achieved deep responses including MRD negativity

Overall response rate

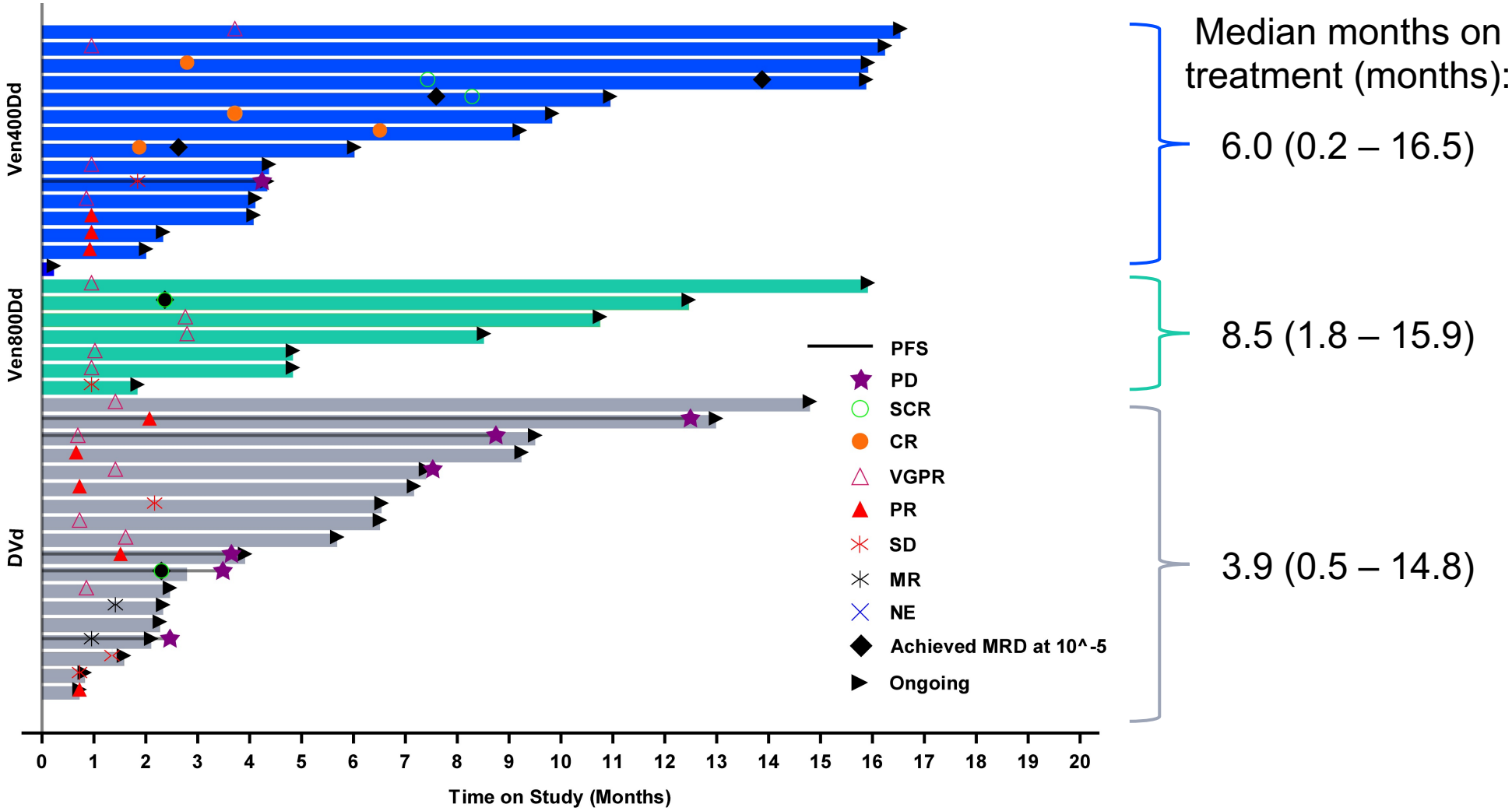


Minimal residual disease



sCR, stringent complete response, CR, complete response; ORR, overall response rate; VGPR, very good partial response; PR, partial response, MRD, minimal residual disease; Ven, venetoclax; Ven400, venetoclax 400 mg; Ven800, venetoclax 800 mg; D, daratumumab; d, dexamethasone; V, bortezomib

Preliminary responses on VenDd appear durable; follow-up is ongoing



Median months on treatment (months):

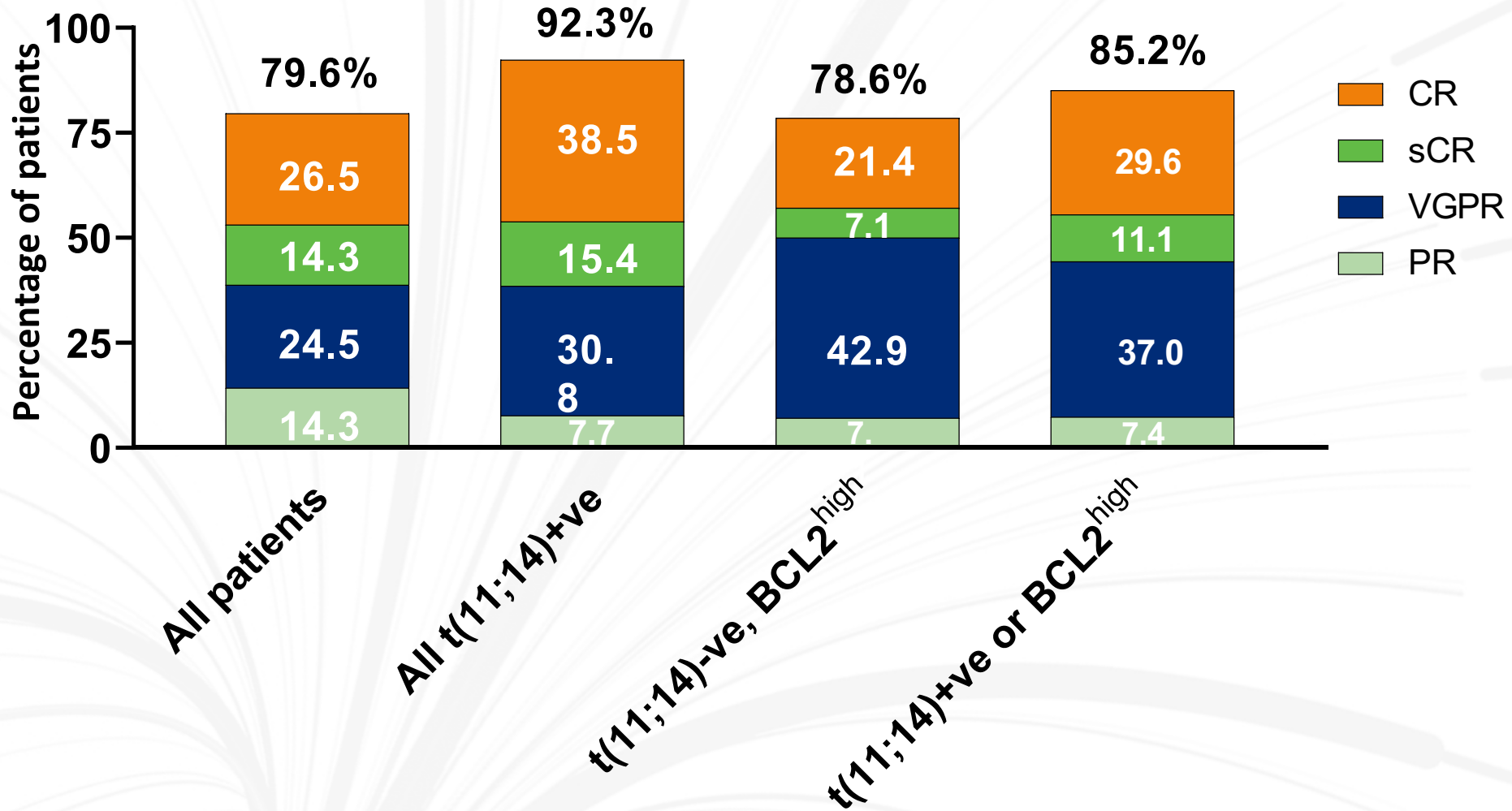
6.0 (0.2 – 16.5)

8.5 (1.8 – 15.9)

3.9 (0.5 – 14.8)

PFS, progression free disease; PD, progressive disease; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; MR, minimal response; NE, not evaluable; Ven, venetoclax; Ven400, venetoclax 400 mg; Ven800, venetoclax 800 mg; D, daratumumab; d, dexamethasone; V, bortezomib

VENETOCLAX WITH CARFILZOMIB



VENETOCLAX CONCLUSION

Venetoclax is currently active and under investigation in t(11;14) but not yet approved

Current clinical trials comparing:

- Venetoclax/dex to pom/dex
- Venetoclax/dara/dex to bortezomib/dara/dex
- Venetoclax/carfilzomib/dex to carfilzomib/dex

Second generation BCL2 inhibitors and other partners overcoming resistance are being evaluated

POLLING QUESTION

In patients with myeloma, the starting dose of venetoclax is:

1. 400 mg daily

2. Step up dosing starting at 25 mg daily for one week increasing to 400 mg daily

3. 1200 mg once per week

4. 200 mg daily