EMORY
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New Drugs In Hematology
HDAC inhibitors

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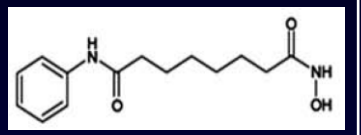
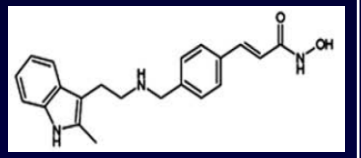
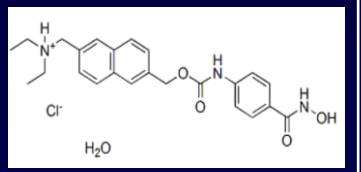
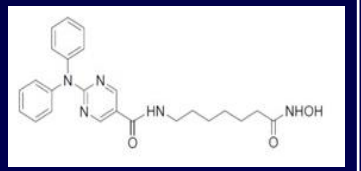
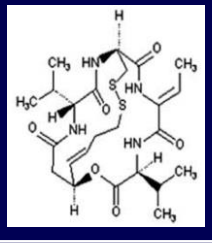
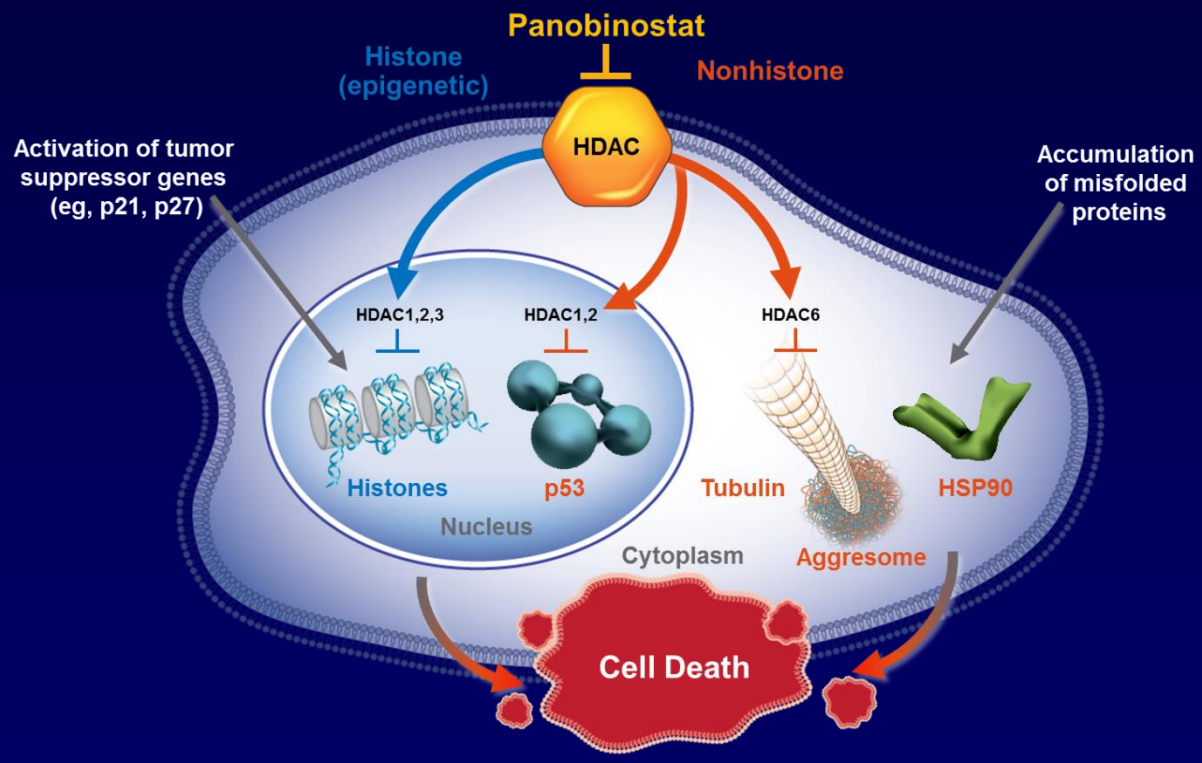
DAC inhibitors in MM

	Chemical Structure		Spectrum of DAC inhibition	Route and Dosing
Vorinostat (SAHA)	Hydroxamate		Pan-DAC (I & II)	po *Days 4-11*
Panobinostat (LBH589)	Hydroxamate		Pan-DAC (I & II)	po *M, W, F x 2 w / 21 days*
Givinostat (ITF2357)	Hydroxamate		Pan-DAC (I & II)	po *M-Th every week*
Ricolinostat (ACY1215)	Hidroxamate		HDAC-6 Selective	po *M-F for 2 weeks*
Romidepsin (FK228)	Cyclic Peptide		Class I DAC	iv *1, 8, 15 / 28 days*

Pan-DAC Inhibitors: Mechanism of Action

Pan-DACi, such as panobinostat, inhibit a broad range of deacetylase enzymes that target both histone and nonhistone proteins involved in oncogenesis[1]

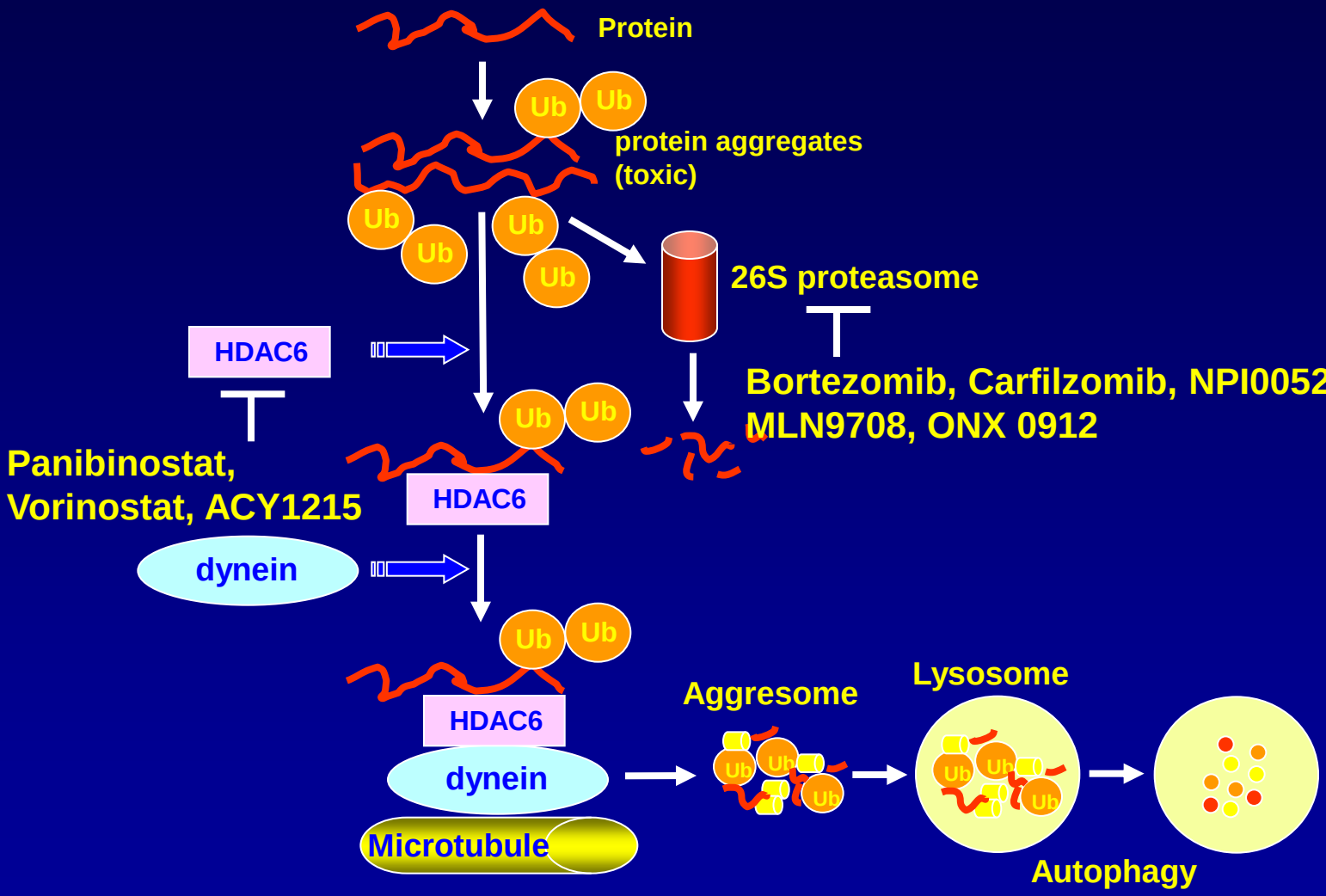


Pan-DACi inhibit growth and promote death of myeloma cells through inhibition of HDAC enzymes:

- **Histone proteins,** which are implicated in epigenetic dysregulation, resulting in activation of tumor suppressor genes[2-4]
- **Nonhistone proteins,** which promote toxic accumulation of misfolded proteins, leading to cell stress[2,5,6]

1. Farydak (panobinostat) [package insert]. East Hanover, NJ: Novartis; 2014; 2. Atadja P, et al. *Cancer Lett*. 2009;280:233-241; 3. Mannava S, et al. *Blood*. 2012;119:1450-1458; 4. Kalushkova A, et al. *PloS One*. 2010;5:e11483; 5. Catley L, et al. *Blood*. 2006;108:3441-3449; 6. Glozak MA and Seto E. *Oncogene*. 2007;26:5420-5432

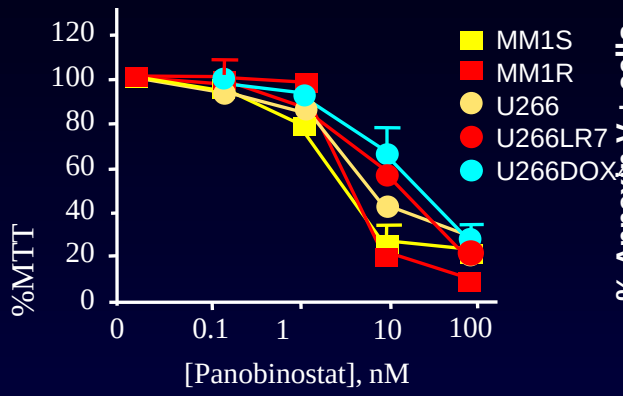
Development of Rationally-Based Combination Therapies (HDAC and Proteasome Inhibitors)



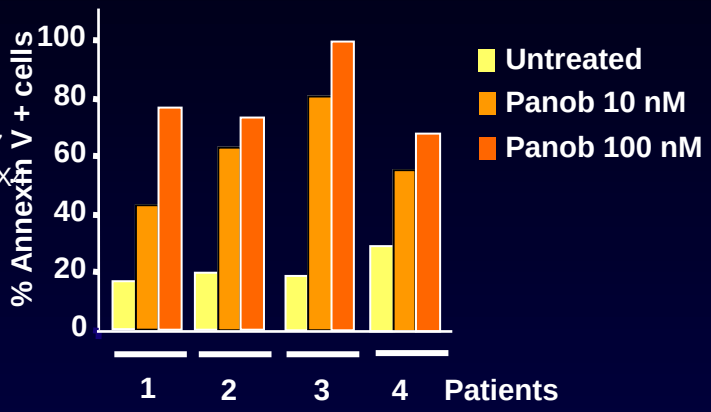
Hideshima et al. *Clin Cancer Res*. 2005;11:8530.Catley et al. *Blood*. 2006;108:3441-9.

Preclinical anti-MM activity of Panobinostat

Cell lines

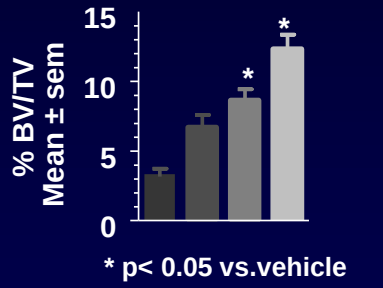


Patients' cells



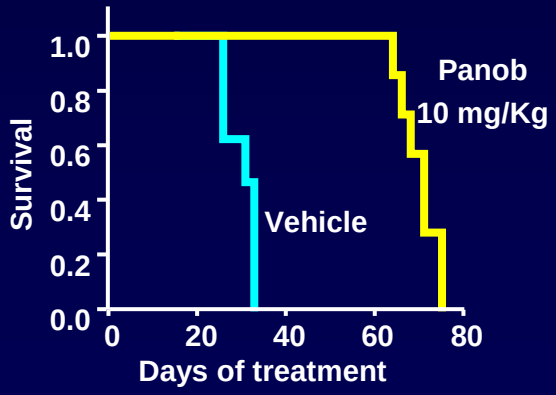
Bone Density

Trabecular Bone

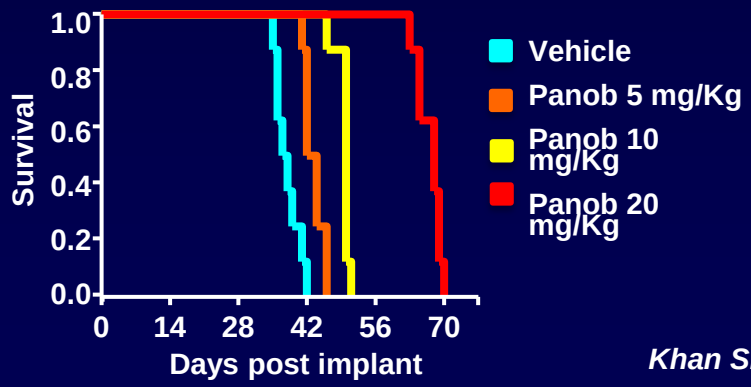


Survival *in vivo*

sc plasmacytoma



Disseminated MM

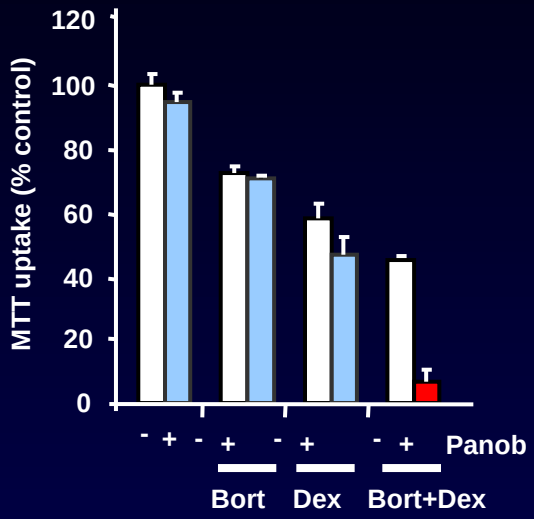


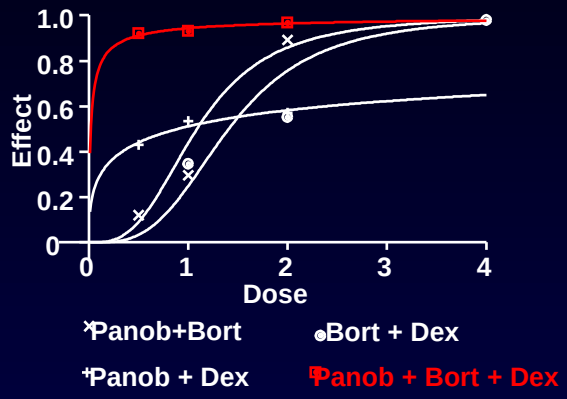
Maiso P. Cancer Res. 2006; Ocio EM, Haematologica 2010

Khan SB, Br J Haem. 2004	*Romidepsin*
Mitsiades CS, PNAS 2004	*Vorinostat*
Golay J, Leukemia 2007	*Givinostat*
Santo L, Blood 2012	*Rocilinostat*

Preclinical activity of HDACi + Bort + Dex in MM

Activity in vitro

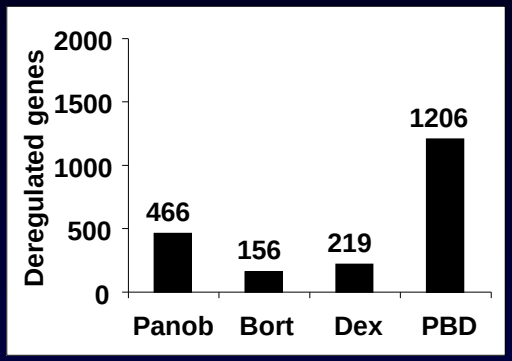




CI in the highly synergistic range (0.1-0.2)

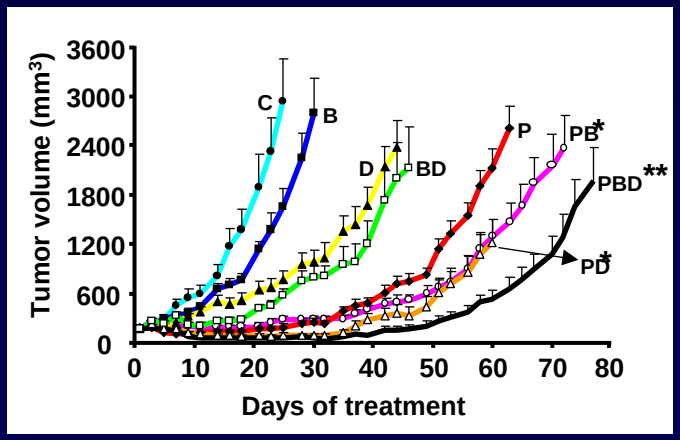
Changes in GEP

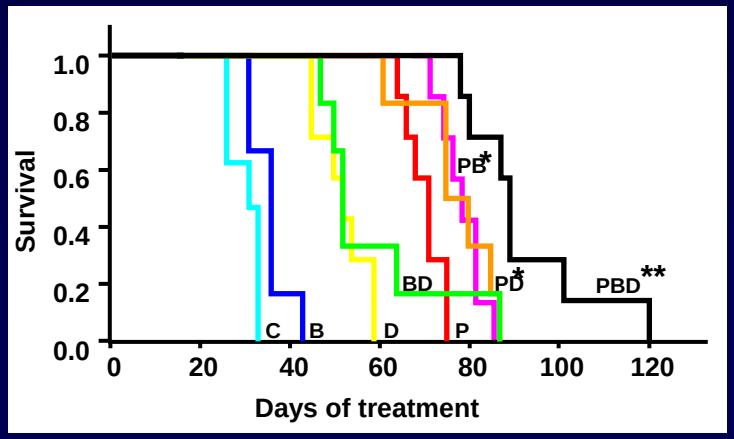
Apoptosis 15-25%



895 genes exclusive of PBD

Activity in vivo





* p<0.05 related to singles ** p<0.05 related to doubles

Ocio EM, Haematologica 2010

Activity of DACi as Monotherapy in MM

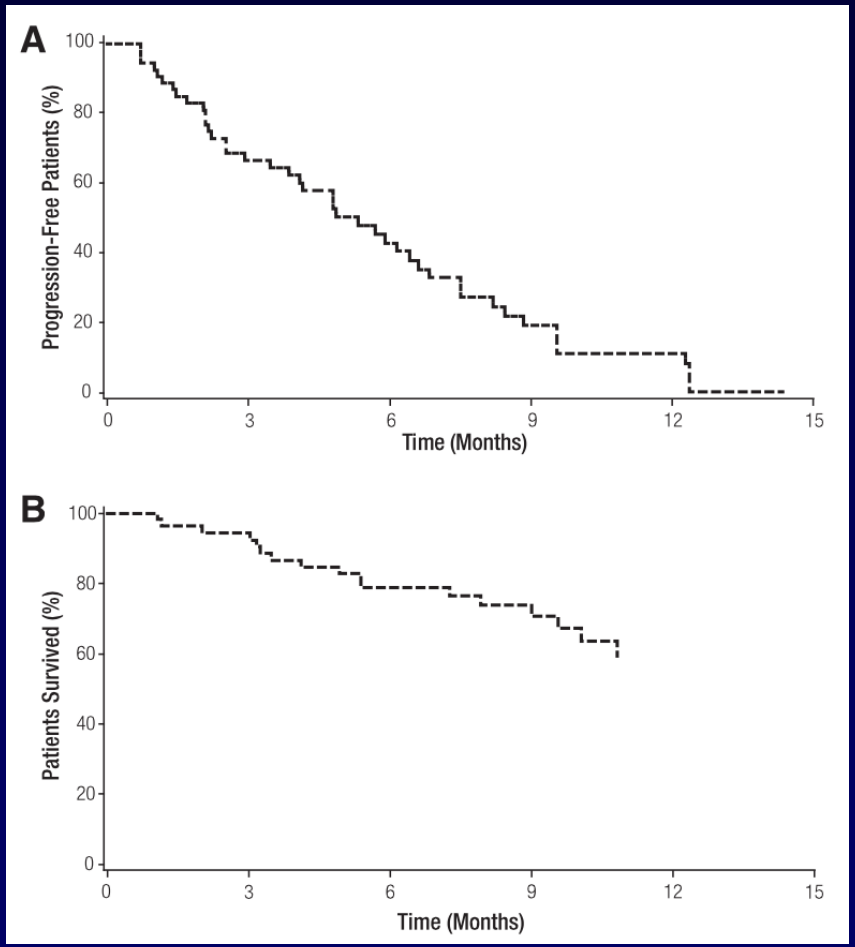
	n	≥ PR	Responses
Panobinostat[1]	38	3%	1 PR, 1 MR, 9 SD
Vorinostat[2]	10	0%	1 MR, 9 SD
Romidepsin[3]	12	0%	4 SD
ACY-1215[4]	15	0%	6 SD
ITF2357[5]	19	0%	5 SD

1. Wolf JL, et al. *Leuk Lymphoma*. 2012;53:1820-1823.
2. Richardson PG, et al. *Leuk Lymphoma*. 2008;49:502-507.
3. Niesvizky R, et al. *Cancer*. 2011;117:336-342.
4. Raje N, et al. *Blood*. 2012;120:Abstract 4061.
5. Galli M, et al. *Ann Hematol*. 2010;89:185-190.

Panorama 2 Response and Duration

Table 2. Best response (confirmed at 6 weeks) at the end of 8 cycles

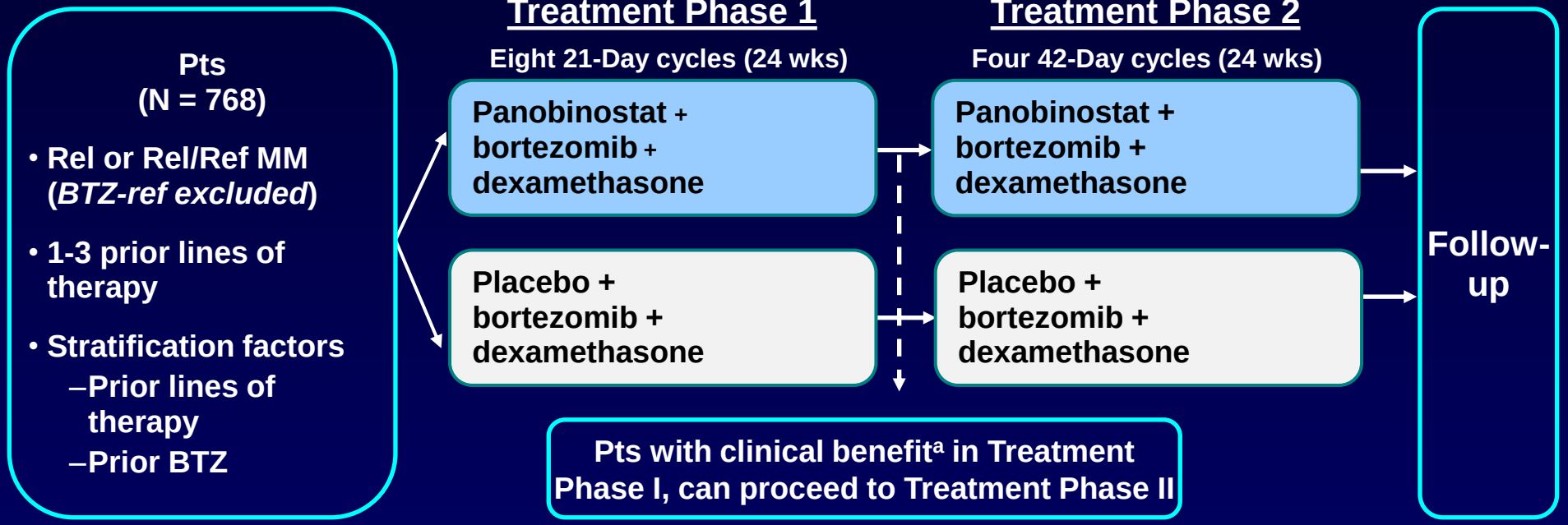
	N = 55 n (%)
Overall response (at least partial response)	19 (34.5)
Complete response	0
Near-complete response	1 (1.8)
Partial response	18 (32.7)
Clinical benefit rate (at least minimal response)	29 (52.7)
Minimal response	10 (18.2)
Stable disease	20 (36.4)
Progressive disease	3 (5.5)
Unknown*	3 (5.5)
Very good partial response†	3 (5.5)



Richardson et al, Blood 2013

PANORAMA 1 Study Design

Randomized, Double-Blind, Phase 3 Study in Relapsed or Relapsed and Refractory MM



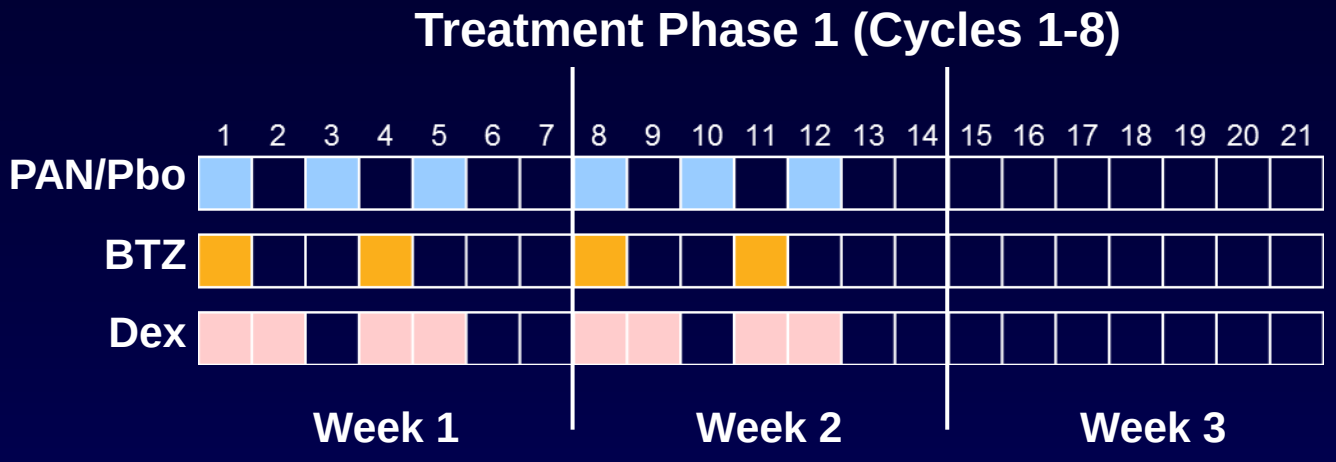
- **Primary endpoint: PFS (per modified EBMT criteria per investigator)[1,2]**
- **Key secondary endpoint: OS**
- **Other secondary endpoints: ORR, nCR/CR rate, DOR, TTR, TTP, QoL, and safety**

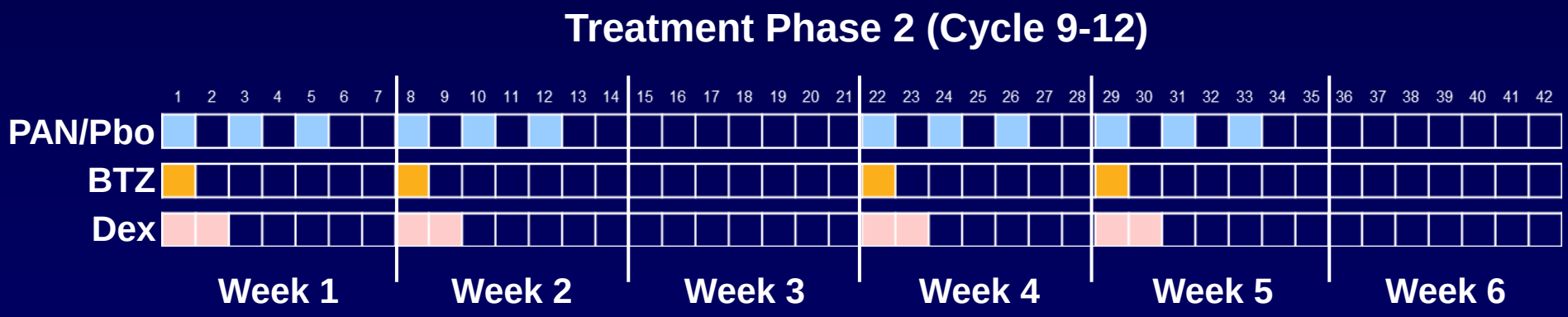
Study conducted at 215 centers across 34 countries[3]

[a] Achieving ≥ no change according to modified EBMT criteria (NC or better)

1. Blade J, et al. *Br J Haematol*. 1998;102:1115-1123
2. Richardson PG, et al. *N Engl J Med*. 2003; 348:2609-2617
3. San-Miguel JF, et al. *Lancet Oncol*. 2014;15:1195-1206

PANORAMA 1 Treatment Schedule

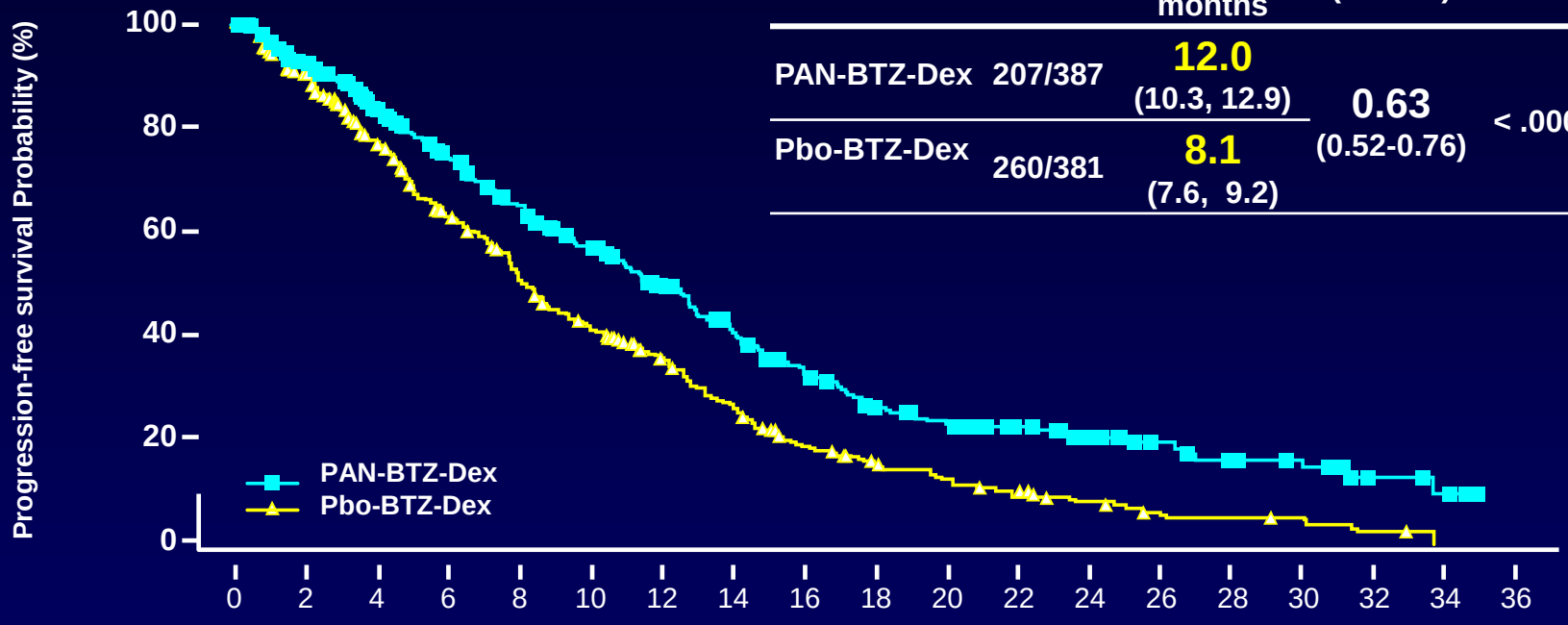




- PAN: Panobinostat 20 mg oral
- BTZ: Bortezomib 1.3 mg/m^2 IV
- Dex: Dexamethasone 20 mg oral

PANORAMA 1: Primary Endpoint Met (PFS)

	Events	Median PFS (95% CI) months	HR (95% CI)	*P* value
PAN-BTZ-Dex	207/387	12.0 (10.3, 12.9)	0.63 (0.52-0.76)	< .0001
Pbo-BTZ-Dex	260/381	8.1 (7.6, 9.2)		



Primary endpoint was met (P < .0001), with clinically relevant increase in median PFS of 3.9 months for PAN-BTZ-Dex arm

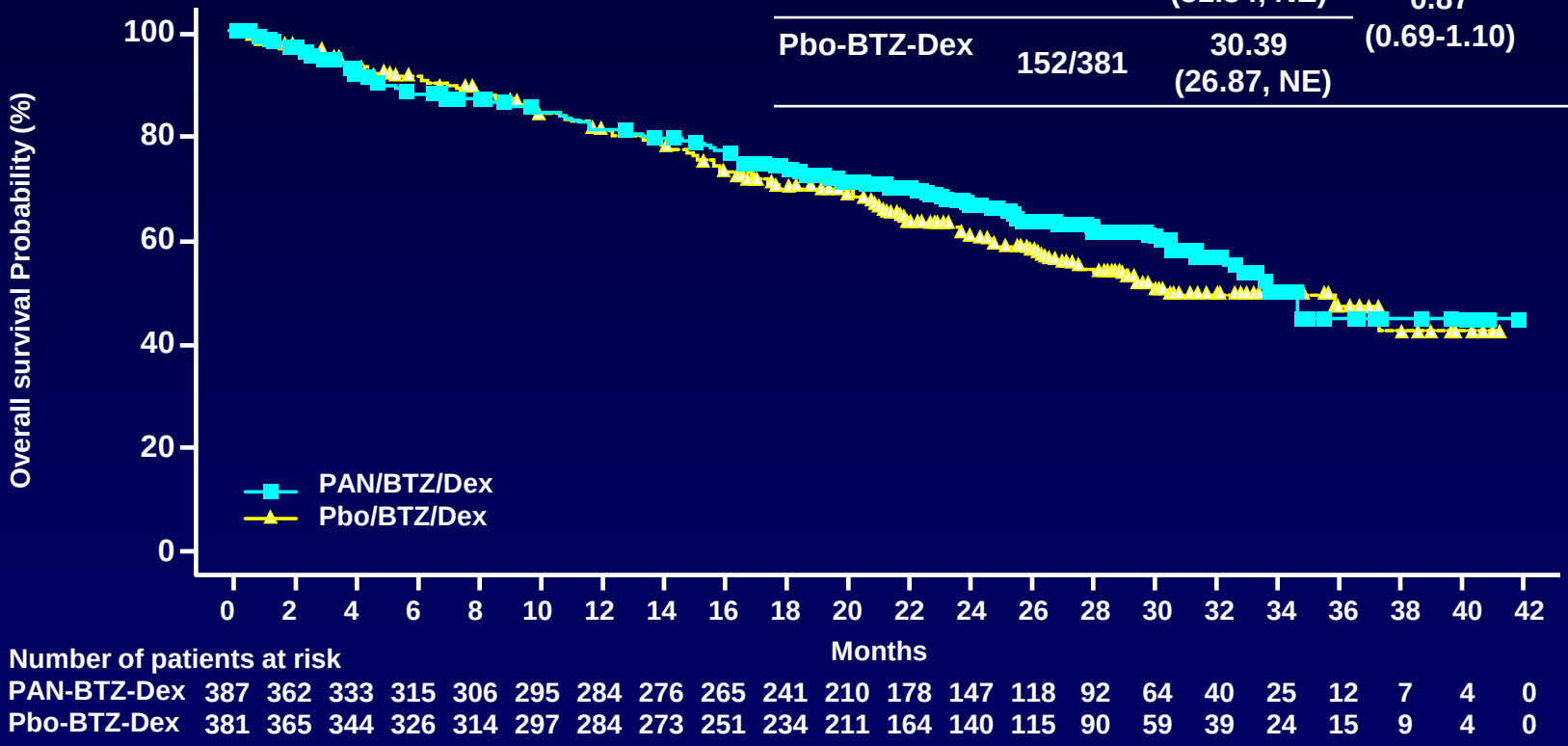
San-Miguel JF, et al. *Lancet Oncol*. 2014;15:1195-1206

Overall Survival (Interim Analysis)

PANORAMA 1

Key Secondary Endpoint

	Events	Median OS, months (95% CI)	HR (95% CI)	*P* value
PAN-BTZ-Dex	134/387	33.64 (31.34, NE)	0.87 (0.69-1.10)	NS
Pbo-BTZ-Dex	152/381	30.39 (26.87, NE)		

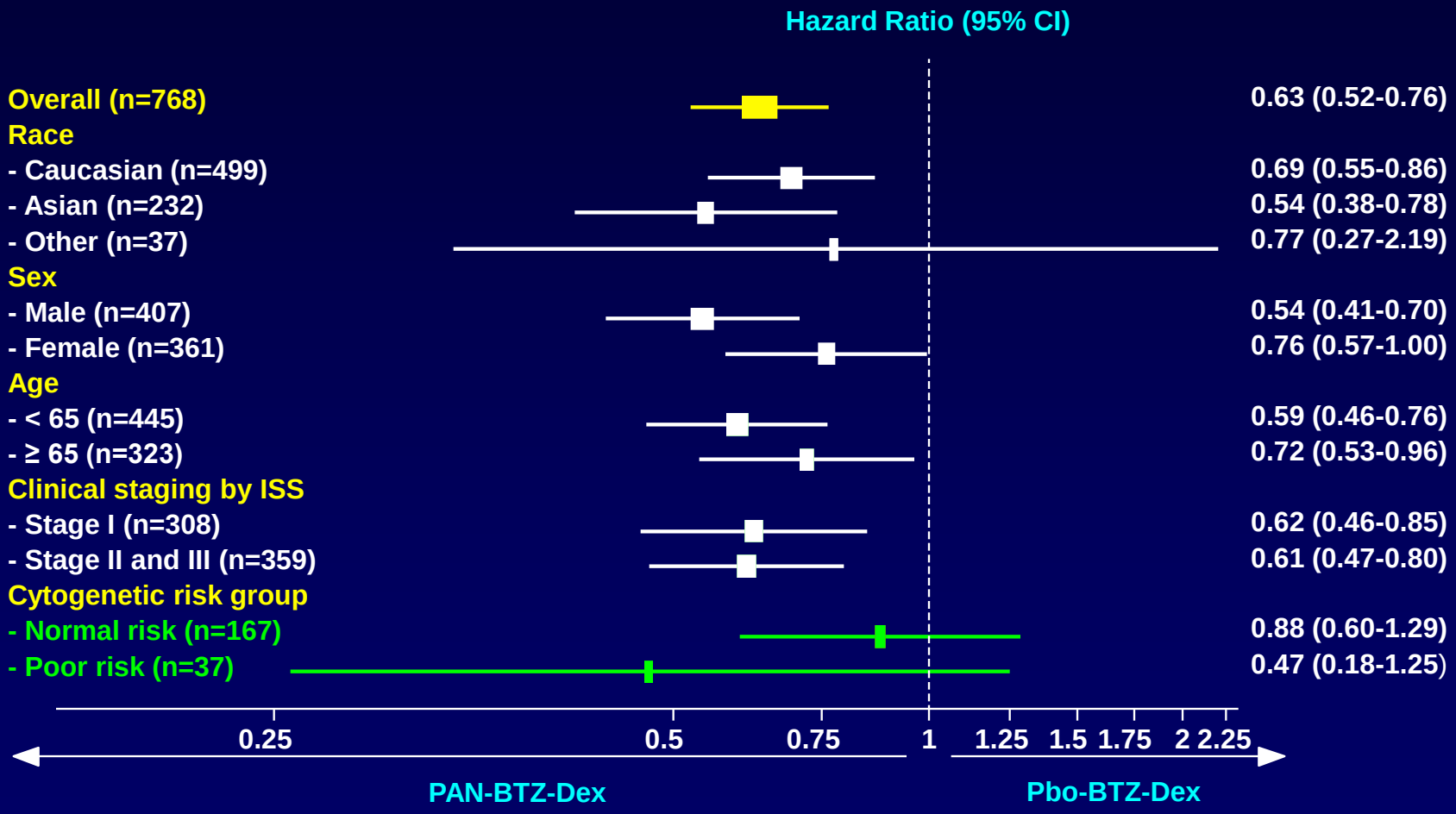


Number of patients at risk

PAN-BTZ-Dex	387	362	333	315	306	295	284	276	265	241	210	178	147	118	92	64	40	25	12	7	4	0
Pbo-BTZ-Dex	381	365	344	326	314	297	284	273	251	234	211	164	140	115	90	59	39	24	15	9	4	0

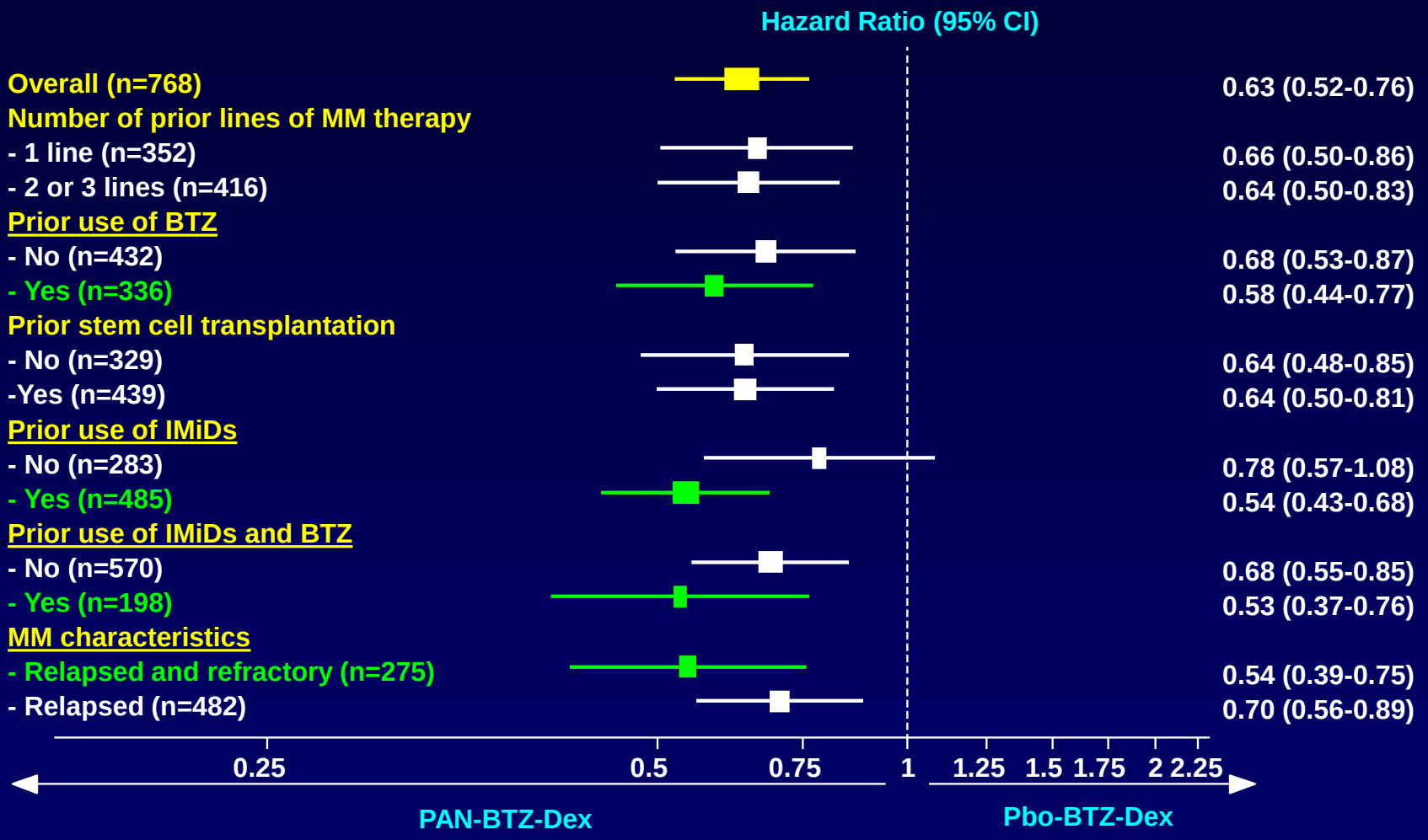
Subgroup Analysis of PFS

Benefit Maintained Regardless of Baseline Characteristics

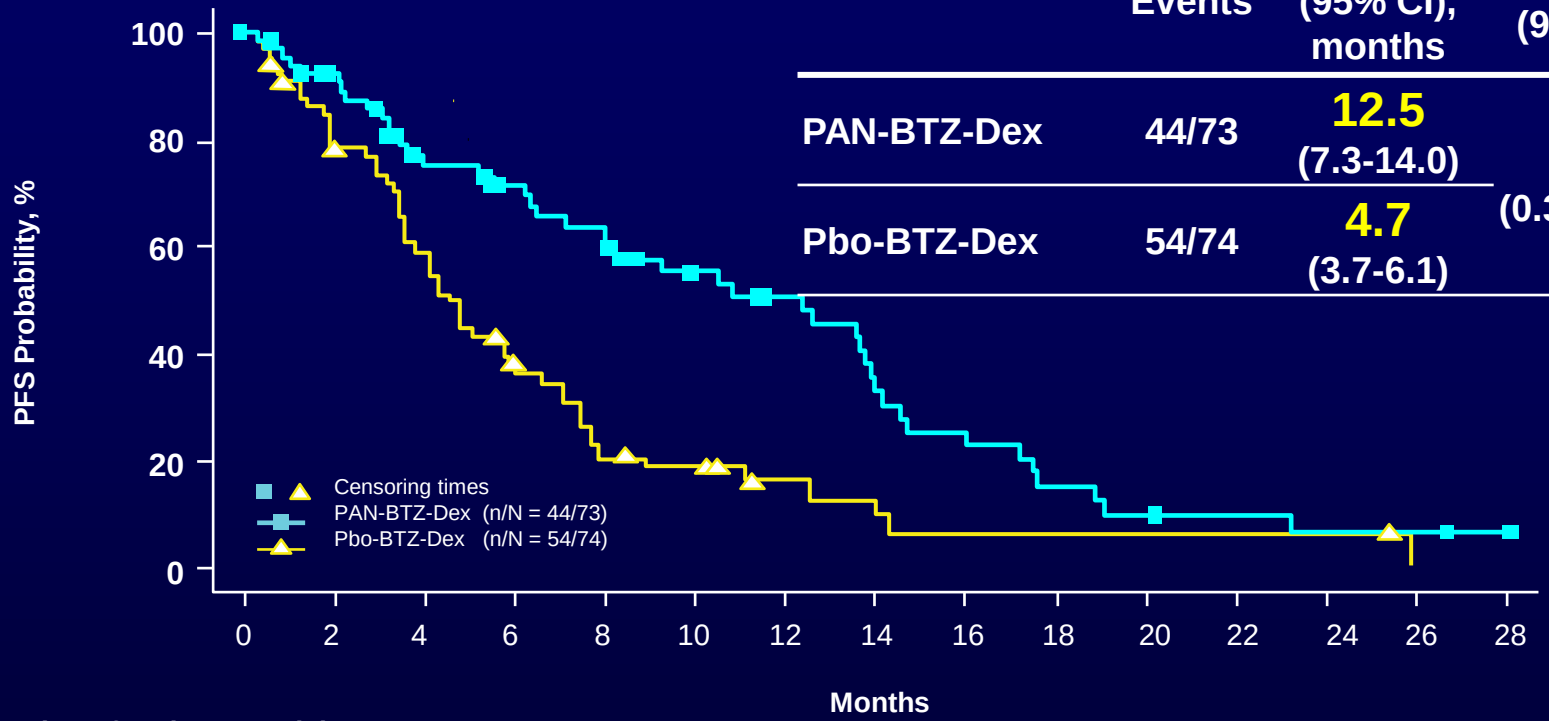


Subgroup Analysis of PFS

Benefit Maintained Regardless of Prior Treatment History



Subgroup Analysis by Prior Treatment:
PFS ≥ 2 Prior Regimens Including BTZ and an IMiD



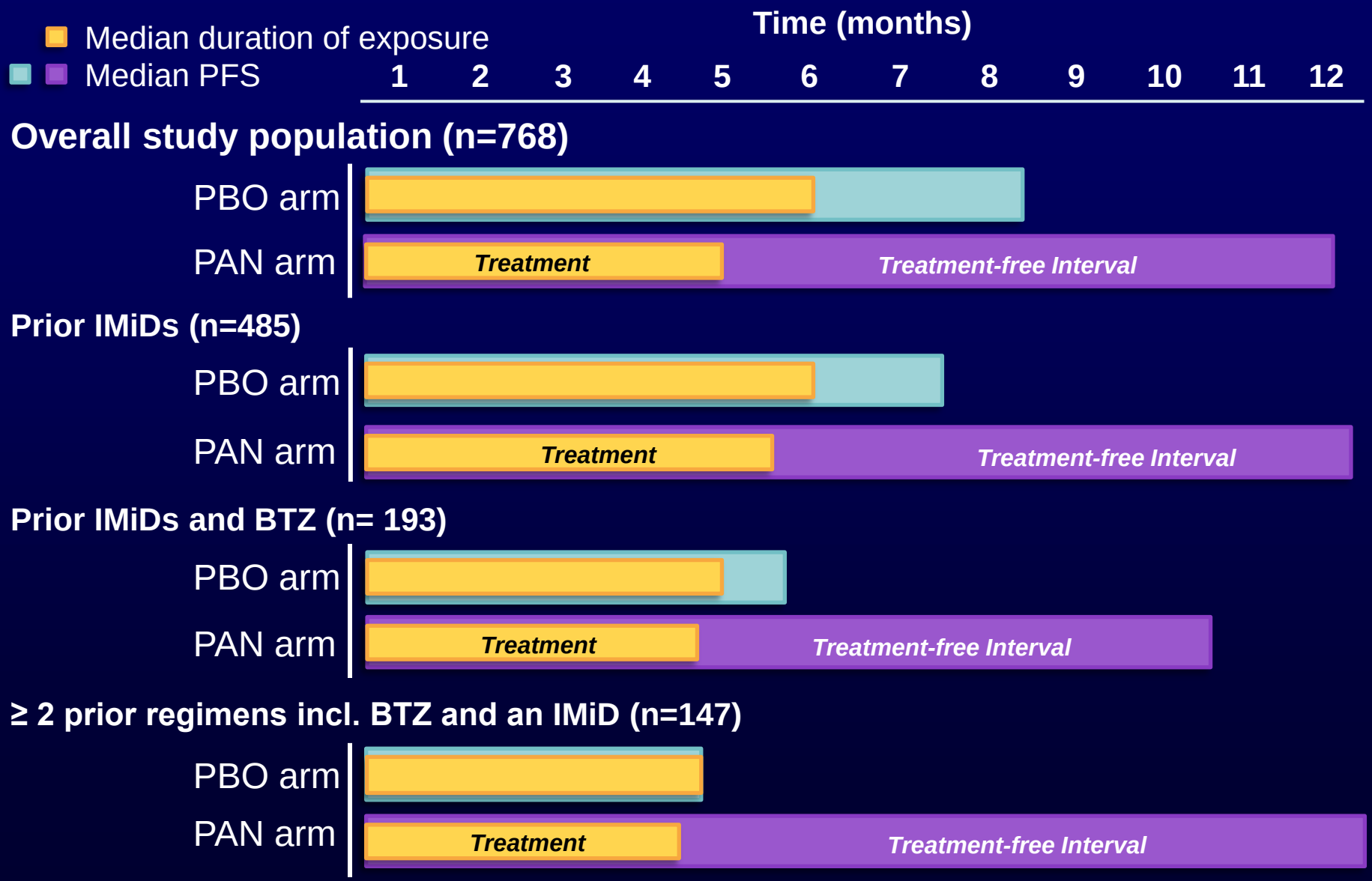
	Events	Median PFS (95% CI), months	HR (95% CI)
PAN-BTZ-Dex	44/73	12.5 (7.3-14.0)	0.47 (0.31-0.72)
Pbo-BTZ-Dex	54/74	4.7 (3.7-6.1)	

Number of Patients at Risk

PAN-BTZ-Dex	73	57	42	36	32	25	20	15	10	6	4	3	2	2	1
Pbo-BTZ-Dex	74	54	37	23	11	9	5	4	2	2	2	2	2	0	0

- Among the subgroup of patients with ≥ 2 prior regimens including BTZ and an IMiD the difference in median PFS benefit was 7.8 months

Subgroup Analysis by Prior Treatment:
Longer PFS Linked With Longer "Treatment-free Interval" (TFI)



Subgroup Analysis of Safety:
Common (≥ 30%) non-hematologic Adverse Events by Prior Treatment

	Prior IMiD				Prior BTZ + IMiD				≥ 2 Prior Regimens Incl. BTZ and an IMiD			
	PAN-BTZ-Dex (n = 241)		Pbo-BTZ-Dex (n = 239)		PAN-BTZ-Dex (n = 92)		Pbo-BTZ-Dex (n = 99)		PAN-BTZ-Dex (n = 72)		Pbo-BTZ-Dex (n = 73)	
AE, n (%)	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Diarrhea	167 (69.3)	63 (26.1)	97 (40.6)	19 (7.9)	67 (72.8)	28 (30.4)	46 (46.5)	13 (13.1)	55 (76.4)	24 (33.3)	34 (46.6)	11 (15.1)
Fatigue/asthenia	144 (59.8)	61 (25.3)	93 (38.9)	28 (11.7)	55 (59.8)	23 (25.0)	44 (44.4)	12 (12.1)	43 (59.7)	19 (26.4)	36 (49.3)	10 (13.7)
Peripheral neuropathy	149 (61.8)	41 (17.0)	160 (66.9)	34 (14.2)	51 (55.4)	14 (15.2)	52 (52.5)	9 (9.1)	42 (58.3)	12 (16.7)	39 (53.4)	5 (6.8)
Nausea	89 (36.9)	14 (5.8)	54 (22.6)	2 (0.8)	35 (38.0)	8 (8.7)	21 (21.2)	1 (1.0)	27 (37.5)	8 (11.1)	16 (21.9)	1 (1.4)
Upper respiratory tract infection	60 (24.9)	7 (2.9)	40 (16.7)	4 (1.7)	30 (32.6)	4 (4.3)	17 (17.2)	0 (0.0)	21 (29.2)	4 (5.6)	12 (16.4)	0 (0.0)
Constipation	59 (24.5)	3 (1.2)	73 (30.5)	3 (1.3)	25 (27.2)	2 (2.2)	32 (32.3)	2 (2.0)	19 (26.4)	2 (2.8)	20 (27.4)	2 (2.7)

Toxicity Across studies

Table 3. Drug-related adverse events (≥20% grade 3/4): panobinostat monotherapy vs combinatorial therapy.

Adverse event	Phase II (N = 38)		Phase Ib Dose Expansion (n = 15)		PANORAMA 2 (N = 55)		PANORAMA 1 (n = 381)	
	All grades, %	Grade 3/4,%	All grades, %	Grade 3/4,%	All grades, %	Grade 3/4, %	All grades, %	Grade 3/4, %
Hematologic								
Thrombocytopenia	40	26	73	67	66	64	98	67
Neutropenia	34	32	60	47	18	15	75	35
Anemia	34	18	33	7	47	15	62	20
Nonhematologic								
Diarrhea	42	3	87	20	71	20	68	25
Fatigue	47	5	73	20	69	20	61[a]	24[a]

Note: [a] In PANORAMA 1, fatigue/asthenia were combined.

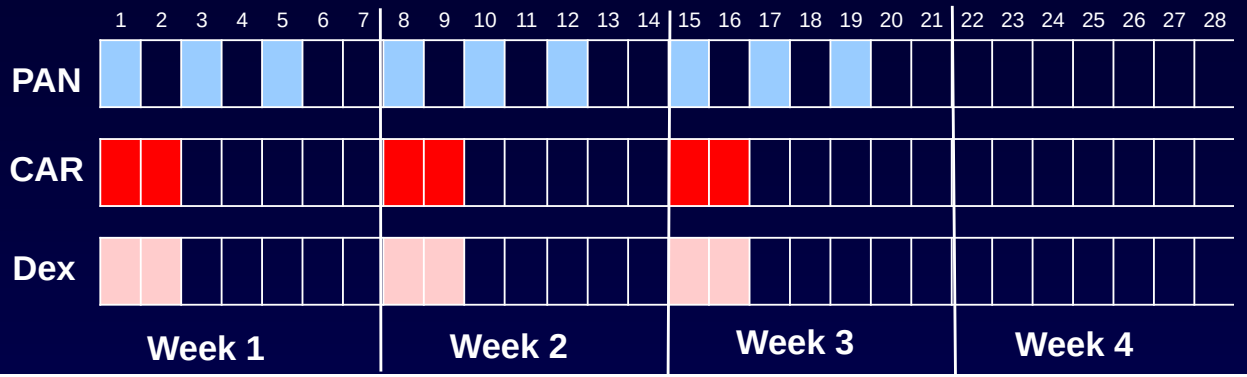
Richardson et al, *Expert Review of Pharmacology*, 2015

Are There Better Partners?

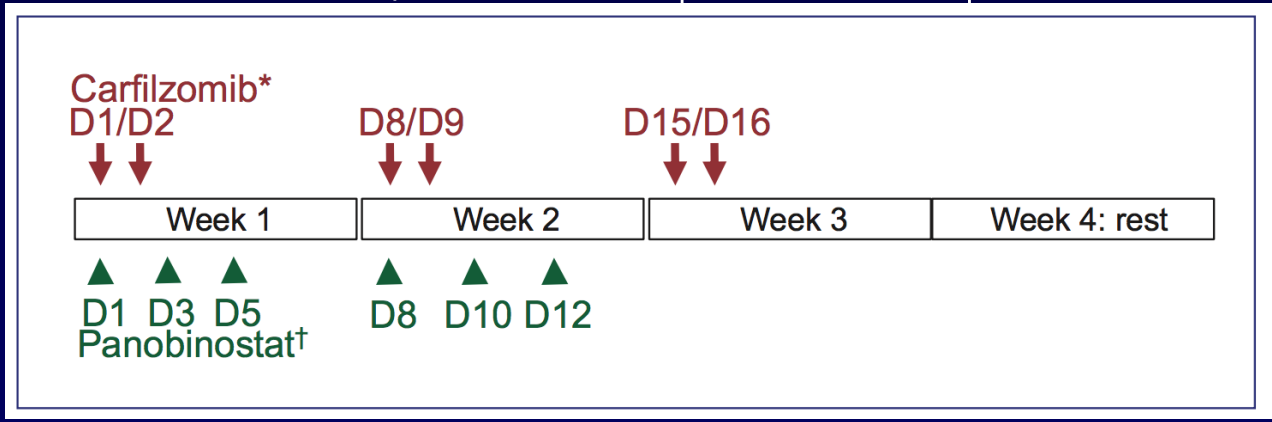
- Data with other PIs now available
- Carfilzomib appears to have a better pattern of potential synergy with less overlapping GI tox
- SQ Bz an unknown variable
- Ixazomib studies in progress
- IMID combinations not fully explored

Different Car/Pan Schedules

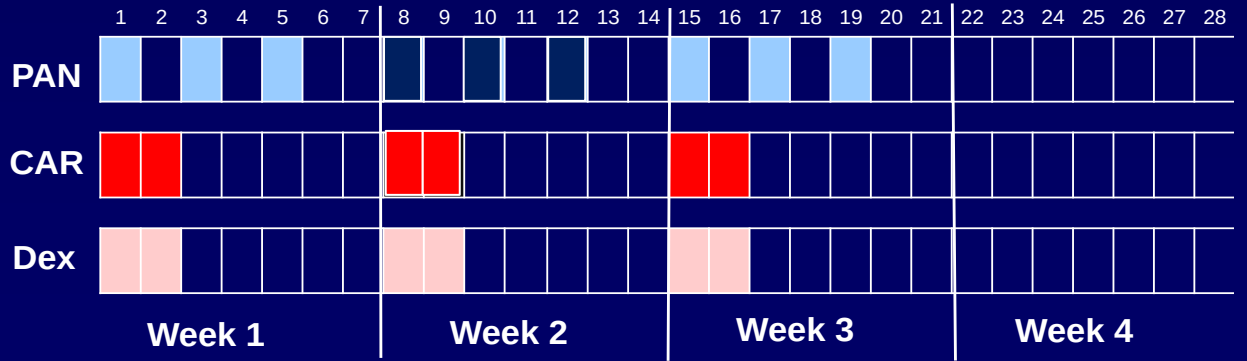
Kaufman Schedule



Shah Schedule



Berdeja Schedule



Kaufman Car/Pan Schedule

Best confirmed response	N = 26 (%)	BTZ Refractory N = 16 (%)
Overall response (CR + VGPR + PR)	12 (46)	7 (44)
Complete response	1 (4)	1 (6)
VGPR	5 (19)	1 (6)
Partial response	6 (23)	5 (31)
MR	3 (12)	1 (6)
SD	3 (12)	3 (19)
PD	6 (23)	4 (25)

- All responses occurred in the first 2 cycles
- Two patients maintained response for 18 months
- Median DOR is 7.5 months and 8 patients remain on treatment
- 1 patient was not evaluable for response

Kaufman et al, ASH 2014

Adverse Events

Occurring in ≥ 5% (grade 3/4) of patients (n = 26)

AE, regardless of relationship to study drug	Grade 3/4	
Number of Subjects with at Least One Event	20 (77%)	Pan/ Bor/Dex[1]
Anemia	10 (38%)	15%
Thrombocytopenia	10 (38%)	64%
Neutropenia	5 (19%)	15%
Fatigue	3 (12%)	20%
Decreased appetite	2 (8%)	
Diarrhea	2 (8%)	20%
Elevated creatinine	2 (8%)	
Hyperglycemia	2 (8%)	
Hypertension	2 (8%)	
Hyponatremia	2 (8%)	

1. Richardson et al; Panorama 2; Blood: 122 (14), 2013.

Berdeja Car/Pan Schedule

Table 3. Response to treatment.

Response assessment	All patients n=42	Dose level 4 n=32	Prior bortezomib n=37	Refractory to bortezomib n=15	Refractory to IMiD n=12	Dual refractory n=5	High risk* n=11	Standard risk** n=21
ORR, n. (%)	28 (67%)	23 (72%)	26 (70%)	10 (67%)	9 (75%)	4 (80%)	8 (73%)	15 (71%)
CBR, n. (%)	33 (79%)	28 (88%)	31 (84%)	13 (87%)	11 (92%)	5 (100%)	9 (82%)	16 (76%)
≥VGPR, n. (%)	14 (33%)	12 (38%)	13 (35%)	3 (20%)	5 (42%)	1 (20%)	5 (46%)	8 (38%)
PR, n. (%)	14 (33%)	11 (34%)	13 (35%)	7 (47%)	4 (33%)	3 (60%)	3 (27%)	7 (33%)
MR, n. (%)	5 (12%)	5 (16%)	5 (14%)	3 (20%)	2 (17%)	1 (20%)	1 (9%)	1 (5%)
SD, n. (%)	7 (17%)	2 (6%)	5 (14%)	2 (13%)	1 (8%)	0	1 (9%)	4 (19%)
P D, n. (%)	2 (5%)	2 (6%)	1 (3%)	0	0	0	1 (9%)	1 (5%)

**High risk is defined as fluorescence* in situ *hybridization showing (FISH) 1q amp, or 1p del, or t(4;14), or t(14;16), or 17p del, or cytogenetics 13 q del. **Excludes patients without FISH data.IMiD: immune modulating drug.*

Berdeja et al, Haematologica 2015

Adverse Events/Time to Event Curves

Table 4. Incidence of all grade 3/4 treatment-related toxicities*, and treatment related deaths (n=44).

	Grade 3	Grade 4	Total
Hematologic, n. (%)			
Thrombocytopenia	16 (36%)	1 (2%)	17 (38%)
Neutropenia	8 (18%)	1 (2%)	9 (21%)
Anemia	4 (9%)	0	4 (9%)
Leukopenia	3 (7%)	0	3 (7%)
Non-hematologic, n. (%)			
Fatigue	5 (11%)	0	5 (11%)
Hypertension	4 (9%)	0	4 (9%)
Diarrhea	3 (7%)	0	3 (7%)
Dyspnea	3 (7%)	0	3 (7%)
Nausea	2 (5%)	0	2 (5%)
Pneumonia	2 (5%)	0	2 (5%)
Vomiting	2 (5%)	0	2 (5%)
Atypical hemolytic-uremic syndrome	0	1 (2%)	1 (2%)
Abdominal pain	1 (2%)	0	1 (2%)
Alanine aminotransferase increased	1 (2%)	0	1 (2%)
Alkaline phosphatase increased	1 (2%)	0	1 (2%)
Aspartate aminotransferase increased	1 (2%)	0	1 (2%)
Asthenia	1 (2%)	0	1 (2%)
Chest pain	1 (2%)	0	1 (2%)
Confusion	1 (2%)	0	1 (2%)
Heart failure	1 (2%)	0	1 (2%)
Hypercalcemia	1 (2%)	0	1 (2%)
Hyponatremia	1 (2%)	0	1 (2%)
Proteinuria	1 (2%)	0	1 (2%)
Treatment-related death**	1 (2%)		

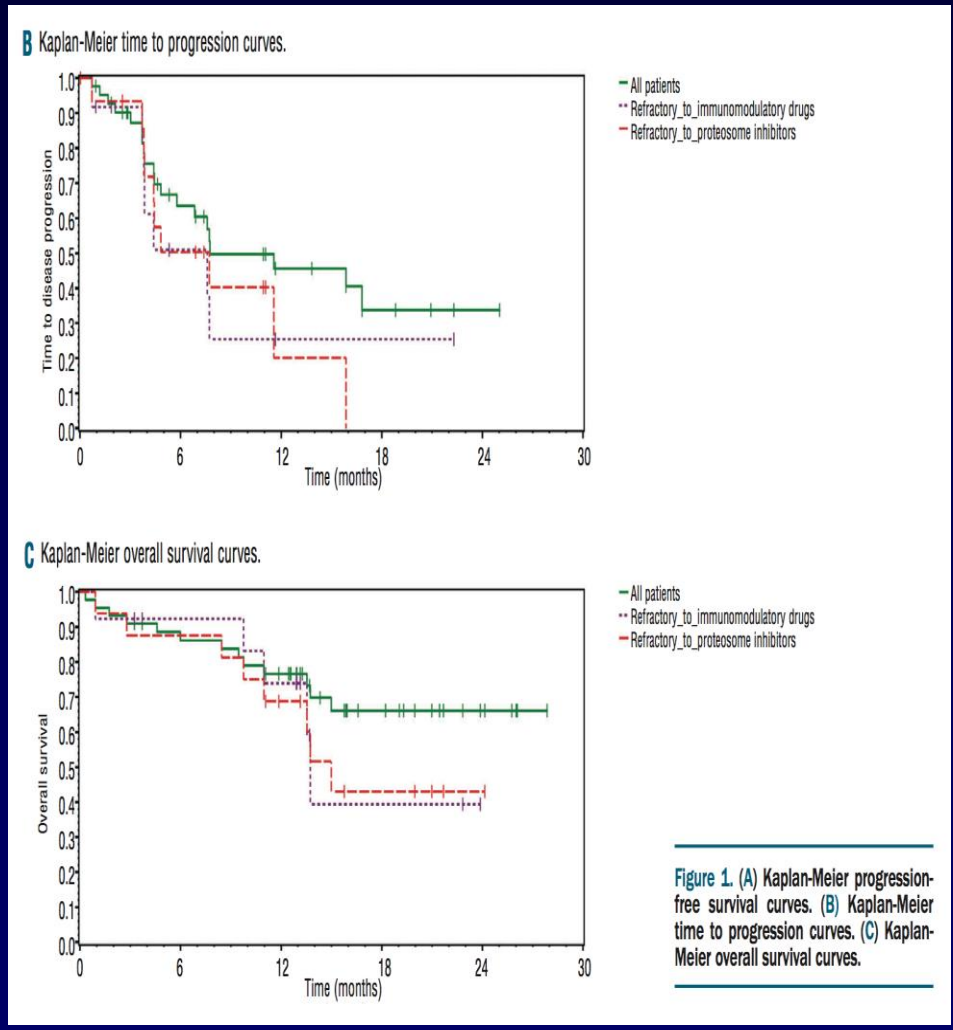


Figure 1. (A) Kaplan-Meier progression-free survival curves. (B) Kaplan-Meier time to progression curves. (C) Kaplan-Meier overall survival curves.

Berdeja et al, Haematologica 2015

Optimize treatment administration

(DACi and partners)

&

DACi as maintenance

Panobinostat + RVD in NDMM

VRD + Panob x 8 21 days cycles

Len 1-14; **Btz SQ** 1, 4, 8, 11; Dex 1, 2, 4, 5, 8, 9, 11, 12; Panob 1, 3, 5, 8, 10, 12

Maintenance with Len + Panob + Dex as tolerated

High Efficacy

	After 1-4 Cycles N=48
sCR/CR/nCR	22 (46%)
VGPR	10 (21%)
PR	13 (27%)
MR	1 (2%)
SD	2 (4%)

ORR 94%

Improved tolerability

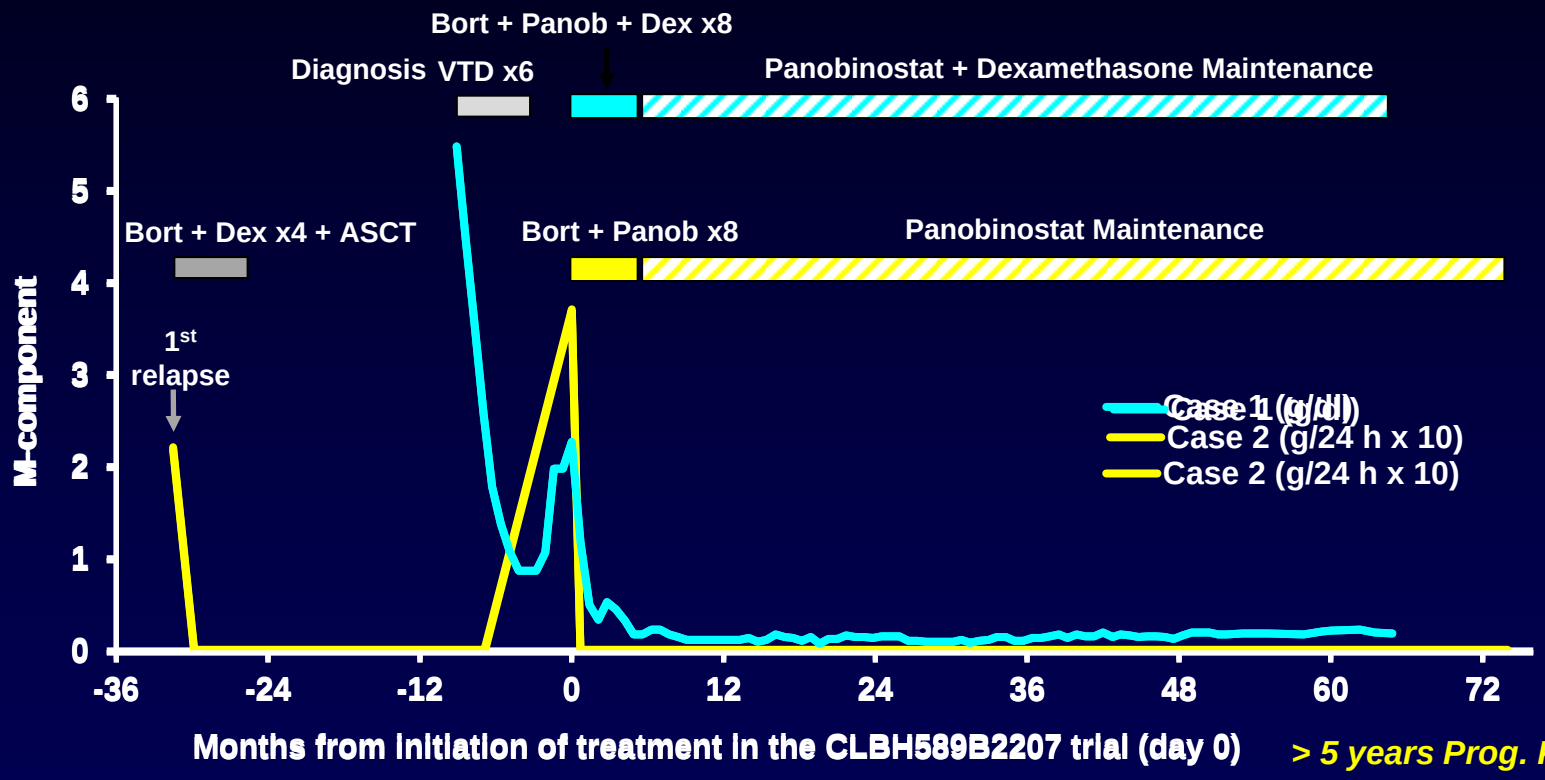
	G1	G2	G3	G4	G3/G4
Alanine Aminotransferase Increased	15	2	1	0	1/50 (2%)
Alkaline Phosphatase Increased	7	2	0	0	
Aspartate Aminotransferase Increased	12	4	1	0	1/50 (2%)
Blood Bilirubin Increased	8	3	0	0	
Nausea	15	15	3	0	3/50 (6%)
Vomiting (Emesis)	10	3	1	0	1/50 (2%)
Constipation	11	17	2	0	2/50 (4%)
Diarrhea	15	10	4	0	4/50 (8%)
Blurred Vision	20	7	0	0	
Dry Eye	17	0	0	0	
Dyspnea	19	7	2	0	2/50 (4%)
Edema Limbs	17	5	0	0	
Watering eyes	16	6	0	0	
Fatigue	13	21	6	0	6/50 (12%)

Shah J et al. ASH 2015

Long term disease control with Panobinostat

- **42 years old woman:** VBCMP/VBAD + ASCT + IFN/Prd; Bort-Dex + 2nd ASCT
- **56 years old man:** VTD x 6 → PR but PD before ASCT

Phase I/II B2207



Ocio et al. Haematologica 2015

Trials evaluating VTD or VRD + Panobinostat followed by Panobinostat maintenance ongoing.

More specific DACi (DAC-6 specific)

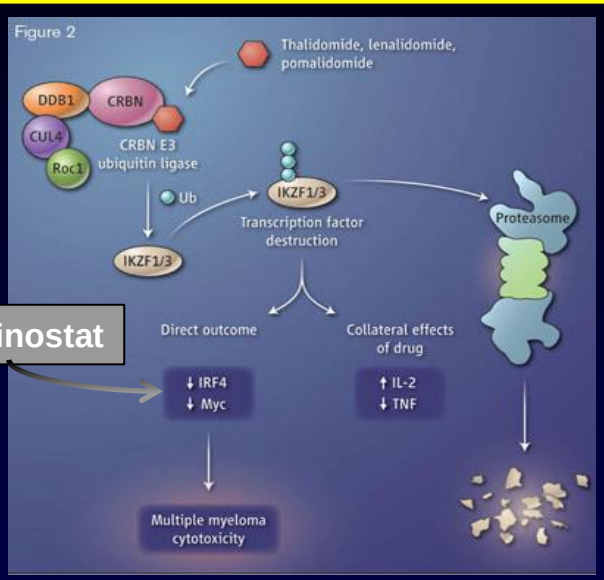
Trial ACY-100: Ricolinostat (ACY-1215) + Bortezomib + Dex

	All Patients	Bortezomib Refractory
Enrolled	43	27
Evaluable for response	29	14
Withdrew prior to C2D15	14	13
Responses		
CR	0	0
VGPR	3	1
PR	10	3
MR	2	2
SD	10	5
PD	4	3
ORR (≥PR) in evaluable pts	45%	29%
ORR (≥PR) in all pts	30%	14%
Clinical benefit (≥MR) in all pts	34%	21%

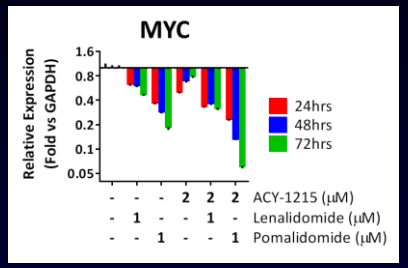
- 160 mg QD days 1-5, 8-12 po is well tolerated in combination with bortezomib and Dex
- Main toxicity grade 2 diarrhea with BID dosing, but no formal MTD identified

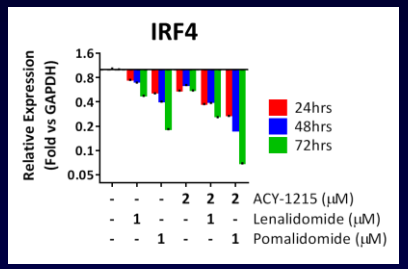
Vogl et al. ASH 2014

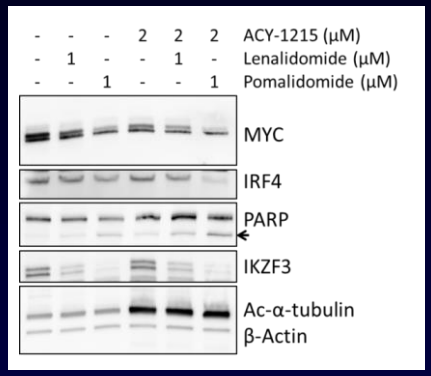
Ricolinostat (ACY-1215) + IMiDs + Dex. MoA

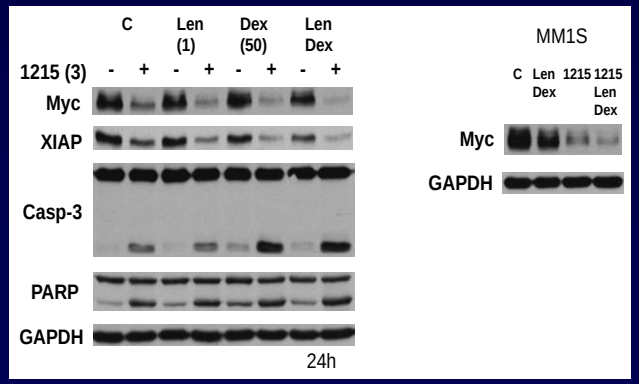


Adapted from Stewart KA, *Science*. 2014









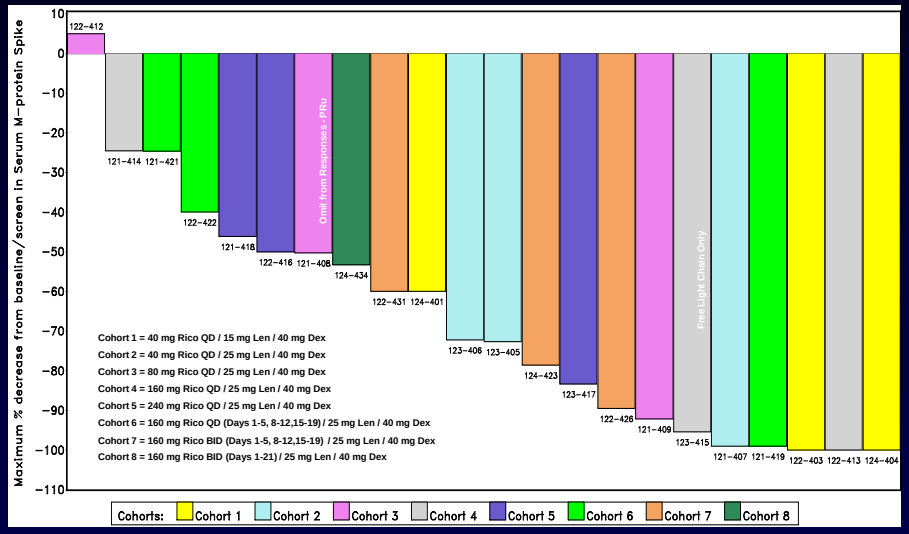
Hideshima et al, Blood Cancer Cell,2015

- **Synergy of Ricolinostat with IMiDs is mediated by a Myc and IRF-4 inhibition.**

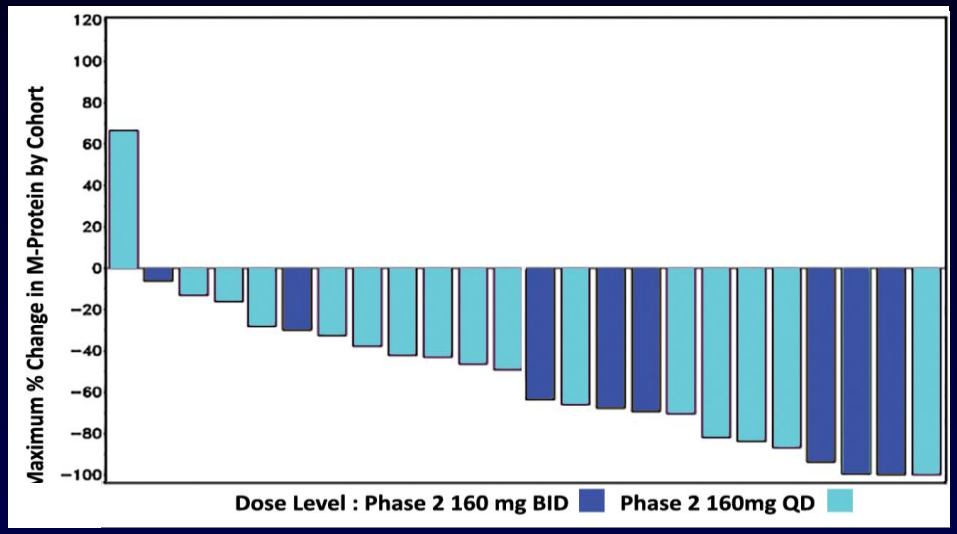
Kindly provided by N. Raje and adapted

Ricolinostat (ACY-1215) + IMiDs + Dex. Activity

+ Len-Dex (ACE-MM-101 trial)



+ Pom-Dex (ACE-MM-102 trial)



- Ricolinostat is well tolerated dosed 160 mg QD for 21 days of a 28 day cycle
- No MTD has been established
- Overall response rate is 64% and includes responses in IMWG defined refractory patients

- Phase 2 dose 160 mg QD for 21 days with pomalidomide 4 mg and dexamethasone
- Overall confirmed response rate (≥ PR) was 29% with 3 VGPR
- Clinical benefit rate (≥ MR) was 50%, and 68% including SD

Raje et al. EHA 2015

TKI's in MM

- Targets are less clear
- Some activity with MEK/BRAF
- Minimal activity with BTK
- FGFR3 data to date has been underwhelming
- Targeting with TKI may have greater impact in the context of MRD rather than overt disease

Conclusions

- Activity of HDAC based therapy is best suited for combinations
- Partner in combination will be important to mitigate toxicity
- Newer more selective agents are in the works
- Use of TKI based approaches are evolving in MM

Patients and Families

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