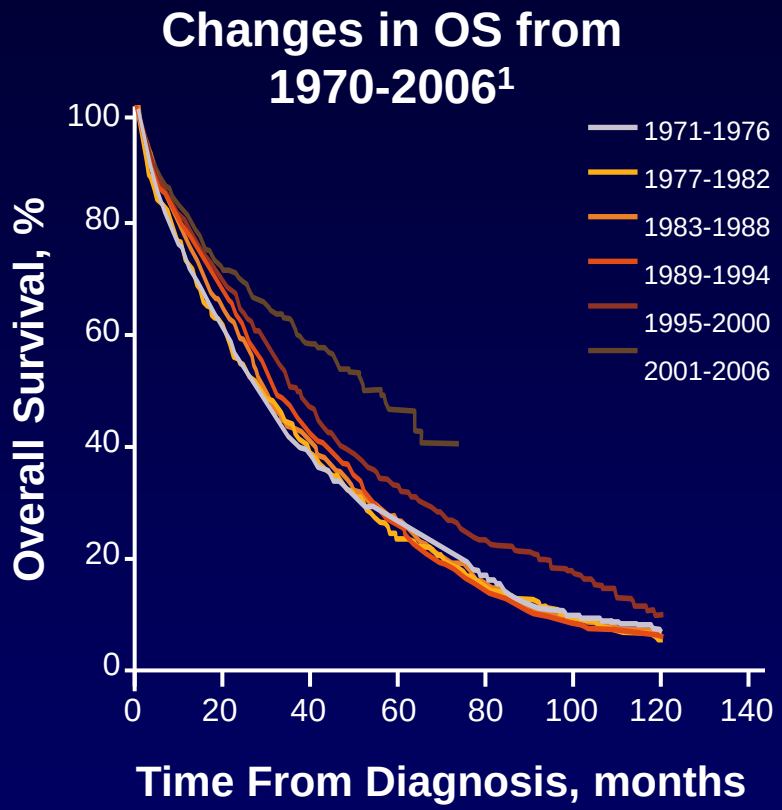
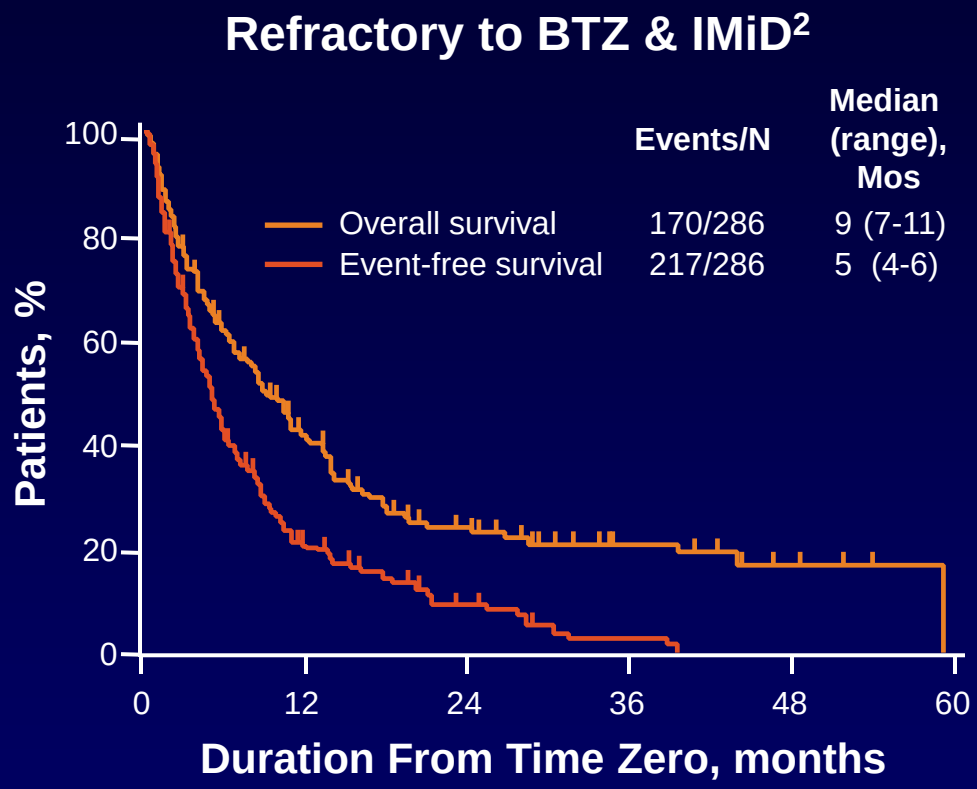
PANORAMA 1: Further Characterization of Safety and Efficacy Update on ASH 2014 Presentations

Abstract #4742

San-Miguel JF

PANORAMA 1: Outcome of Myeloma Patients





Despite the benefit observed with novel agents in the last years, … other drugs are still needed for relapsed/refractory patients

1. Kumar SK, et al. *Blood*. 2008;111:2516-2520 2. Kumar SK, et al. *Leukemia*. 2012;26:149-157.

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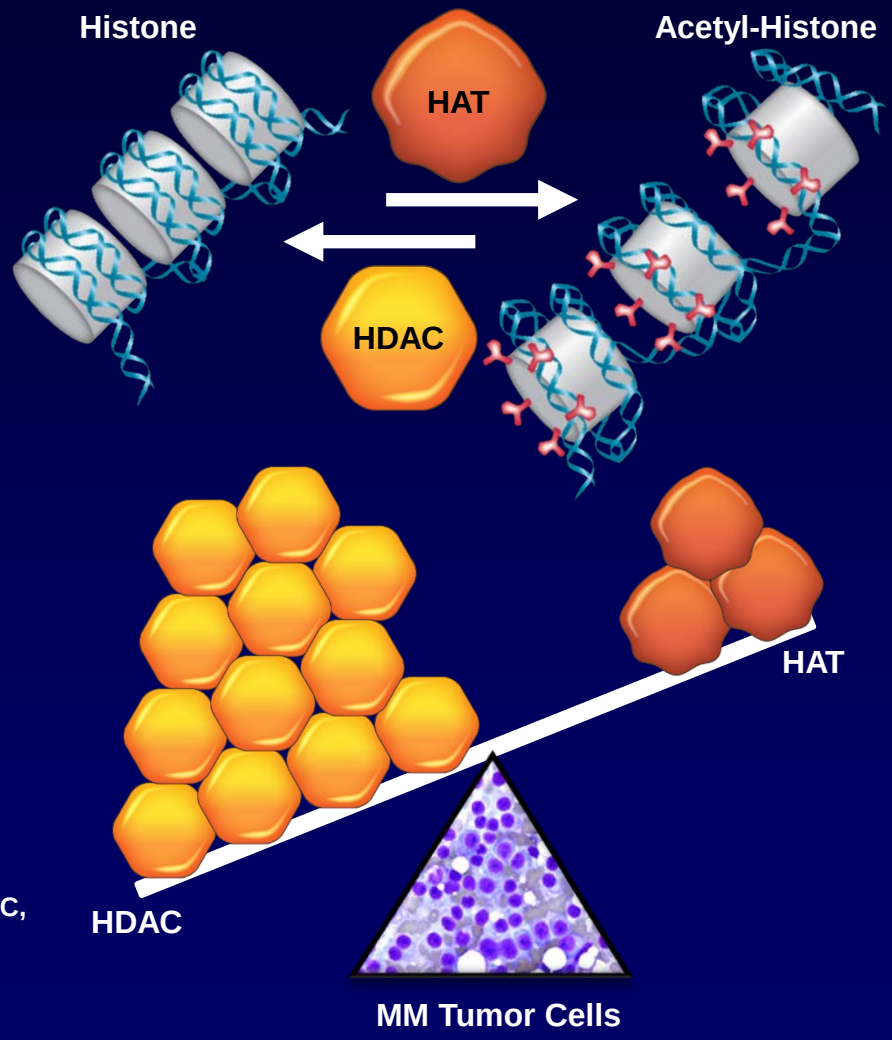
Histone Deacetylases (DACs): Role in Cancer

- DACs are a family of enzymes that regulate target protein activity through removal of acetyl groups[1]
- Dysregulated DAC activity is an epigenetic hallmark of cancer (including MM) resulting in aberrant gene expression and cellular signaling that promotes cell cycle progression, cell growth and survival, and resistance to apoptosis[3-5]
- Panobinostat (PAN) is a potent, oral pan-DACi that increases acetylation of proteins involved in multiple oncogenic pathways



1. Bolden JE, et al. *Nat Rev Drug Discov*. 2006;5:769-784. 2. Choudhary C, et al. *Science.* 2009;324:834-840. 3. West AC, et al. *J Clin Invest.* 2014;124:30-39. 4. Gryder BE, et al. *Future Med Chem.* 2012;4:505-524. 5. Stimson L, et al. *Ann Oncol.* 2009;20:1293-1302.

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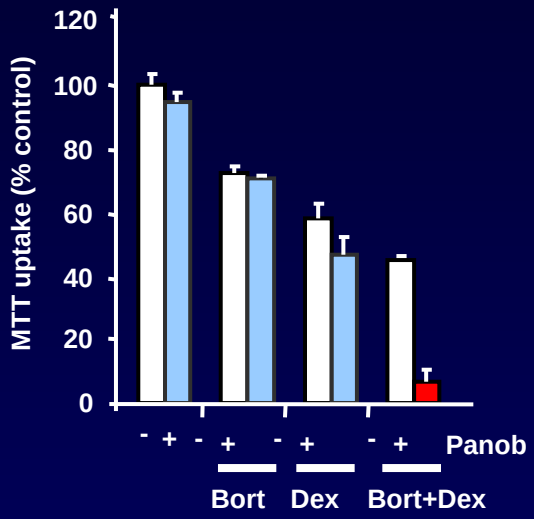
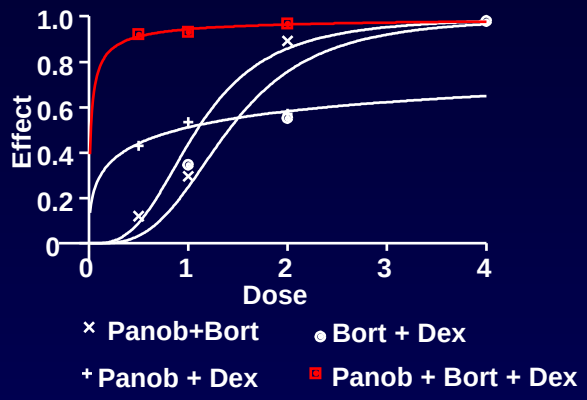
PANORAMA 1: Preclinical Activity of PAN-BTZ-Dex in MM

Activity *in vitro*

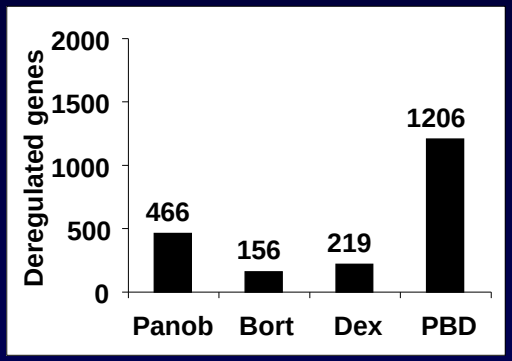




CI in the highly synergistic range (0.1-0.2)

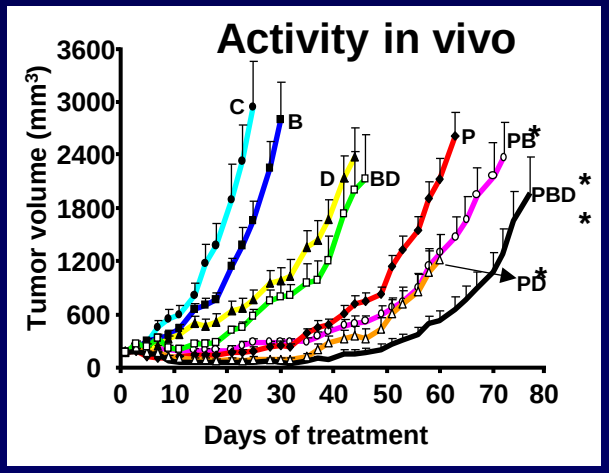
Changes in GEP

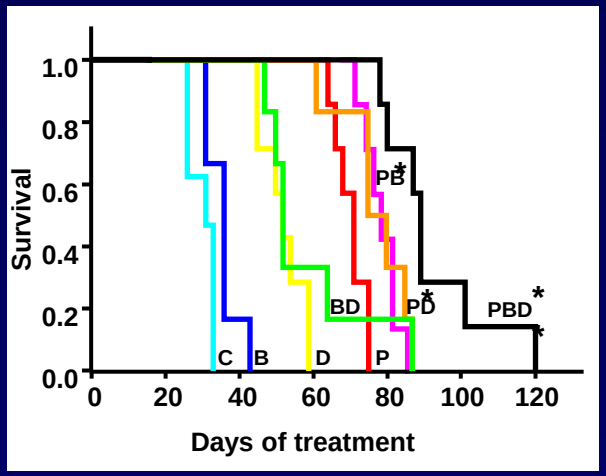
Apoptosis 15-25%



895 genes exclusive of PBD

Activity in vivo





Trabecular bone

Vehicle

Panobinostat

Mitsiades CS, et al. *Cancer Res*. 2008;68(13):5216-5225. Ocio EM, et al. *Haematologica*. 2010;95(5):794-803.

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PANORAMA 1: Panobinostat + Bortezomib + (Dex) in Relapsed MM: Phase I and II Experience

- **Phase Ib[1*]**
  - **62 patients …… 61% ≥MR (51% PR)**
    - **BTZ refractory …… 42% ≥MR (26% PR)**
    - **AE (Grade 3): thrombocytopenia 66%, neutropenia 43, fatigue 15% , PN 2% (expansion)**
- **Phase II (PANORAMA 2)[2†] (BTZ-Ref and ≥1 IMiD: Len 98%)**
  - **55 patients…… 52% ≥ MR (34% PR) PFS: 5.4 months**
  - **PAN-BTZ-Dex can recapture responses in BTZ-refractory MM**

1. San Miguel JF, et al. *J Clin Oncol.* 2013;31:3696-3703.
2. Richardson PG, et al. *Blood*. 2013;122:2331-2337.

*Three wk cycles × 8 (MTD: 20 mg PAN; 1.3 mg/m^2 BTZ) (2 wks on /1 wk off) (47 in escalation and 15 in expansion phase)

†Eight 3 w cycles PAN (20 mg) + BTZ (1.3 mg/m^2)+ Dex (20 mg)

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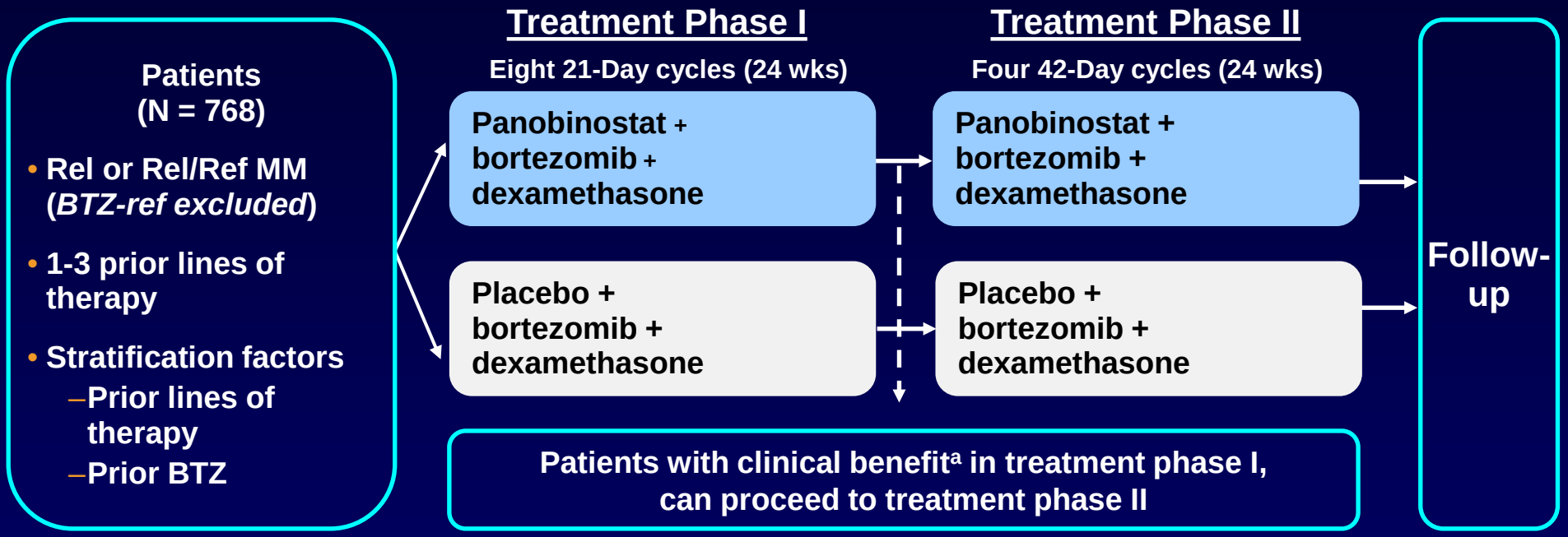
PANORAMA 1: Study Design
Randomized, Double-Blind, Phase III Study in Relapsed or Relapsed and Refractory MM



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

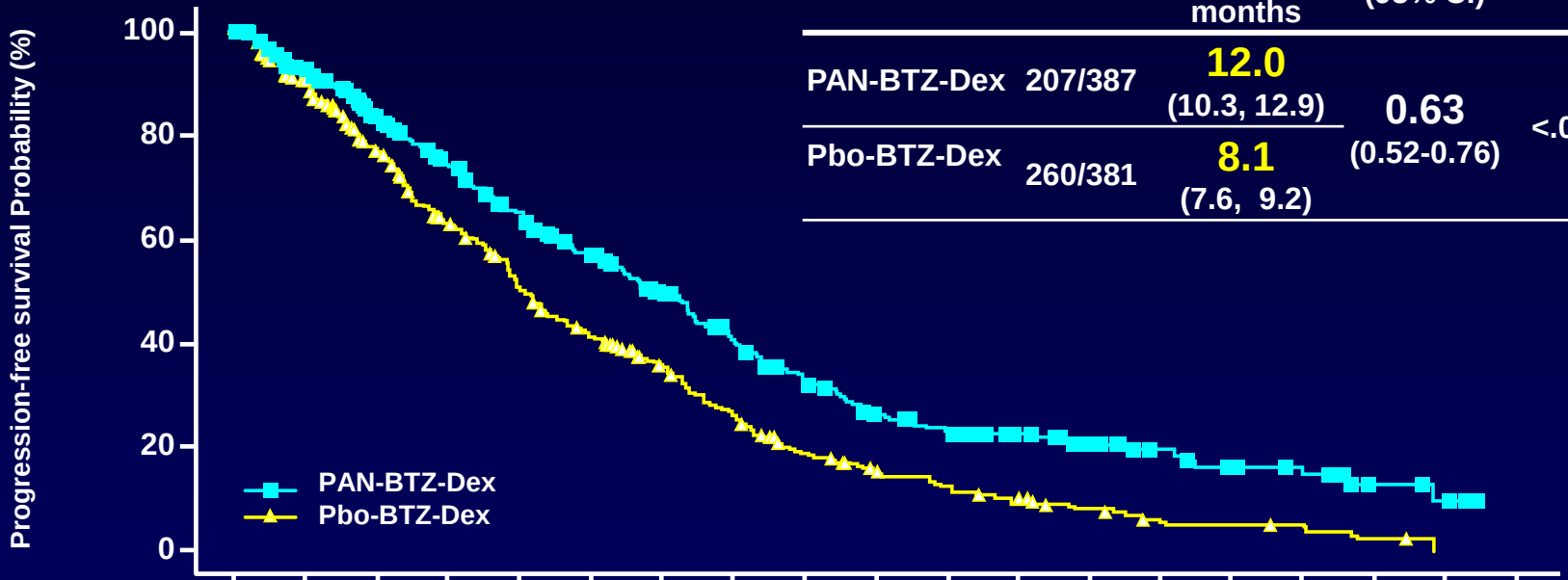
Study conducted at 215 centers across 34 countries

[a]Achieving ≥no change according to modified EBMT criteria (SD 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.
San-Miguel JF, et al. *Blood.* 2014;124: Abstract 4742.

PANORAMA 1: 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)		



Number of patients at risk

PAN-BTZ-Dex	387	288	241	202	171	143	113	89	69	52	44	35	26	18	13	10	5	3	0
Pbo-BTZ-Dex	381	296	235	185	143	114	89	64	42	32	24	18	12	5	5	3	2	0	0

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

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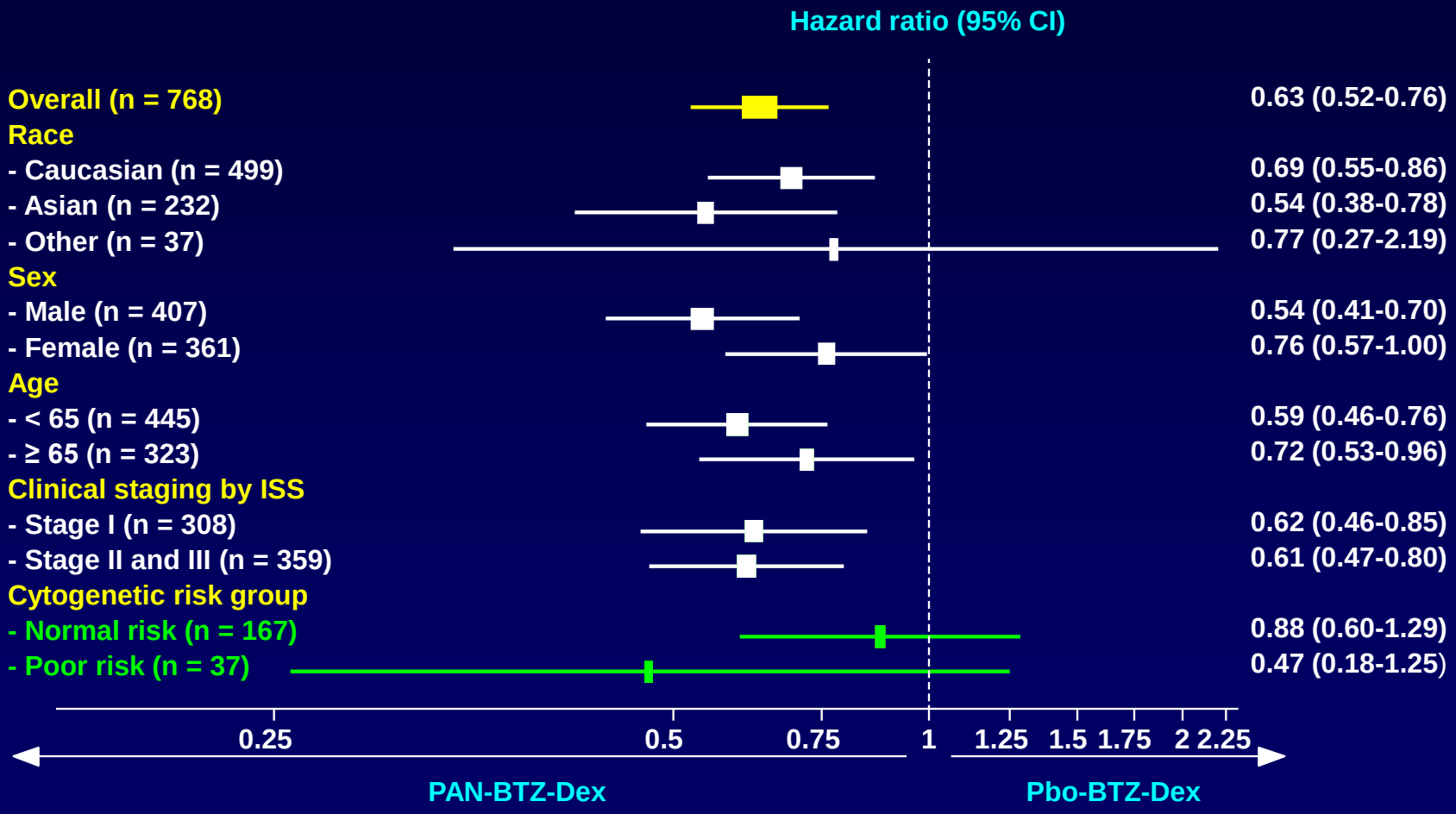
PANORAMA 1: Subgroup Analysis of PFS

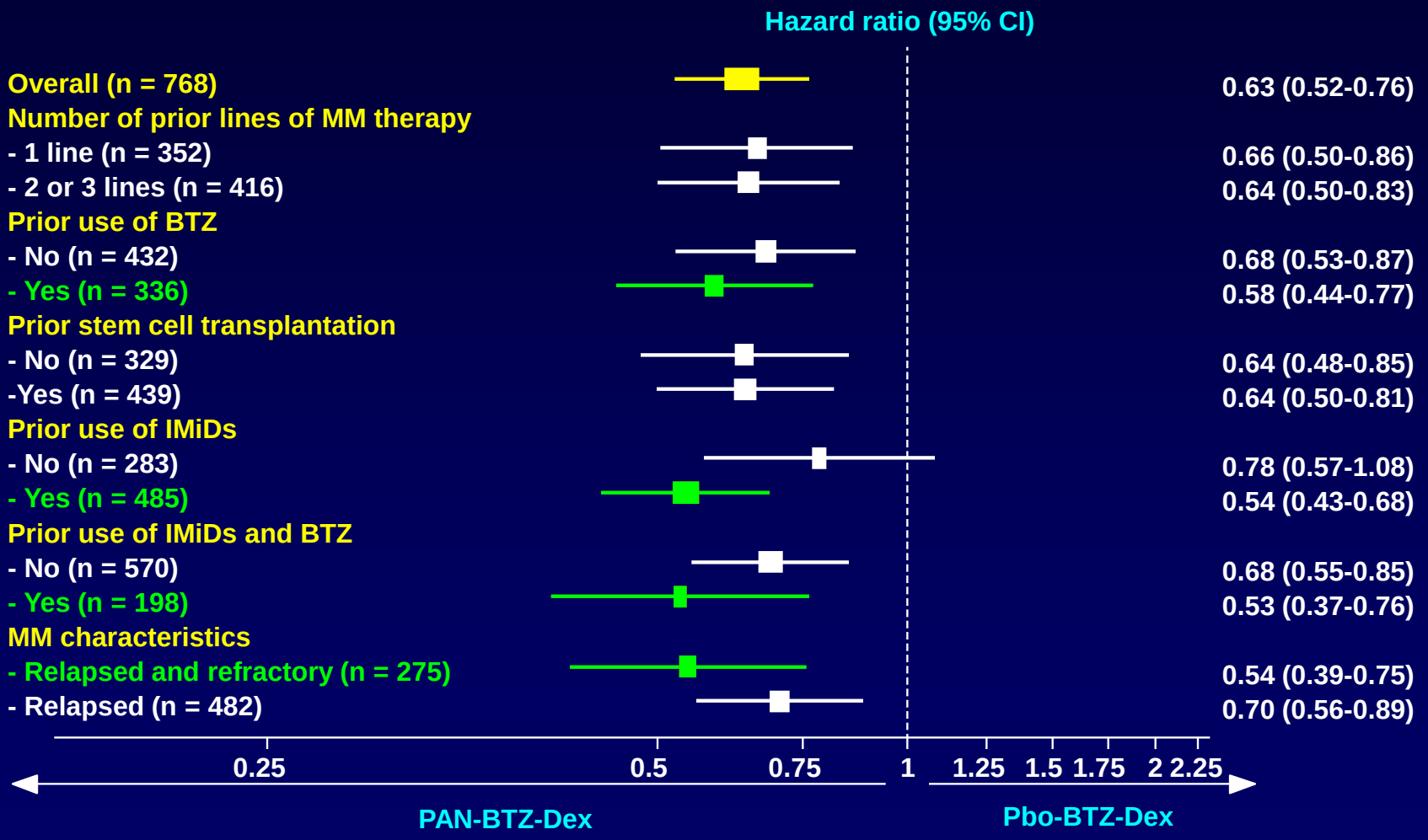
Benefit Maintained Regardless of Baseline Characteristics



San-Miguel JF, et al. *Blood.* 2014;124: Abstract 4742.

PANORAMA 1: Subgroup Analysis of PFS

Benefit Maintained Regardless of Prior Treatment History



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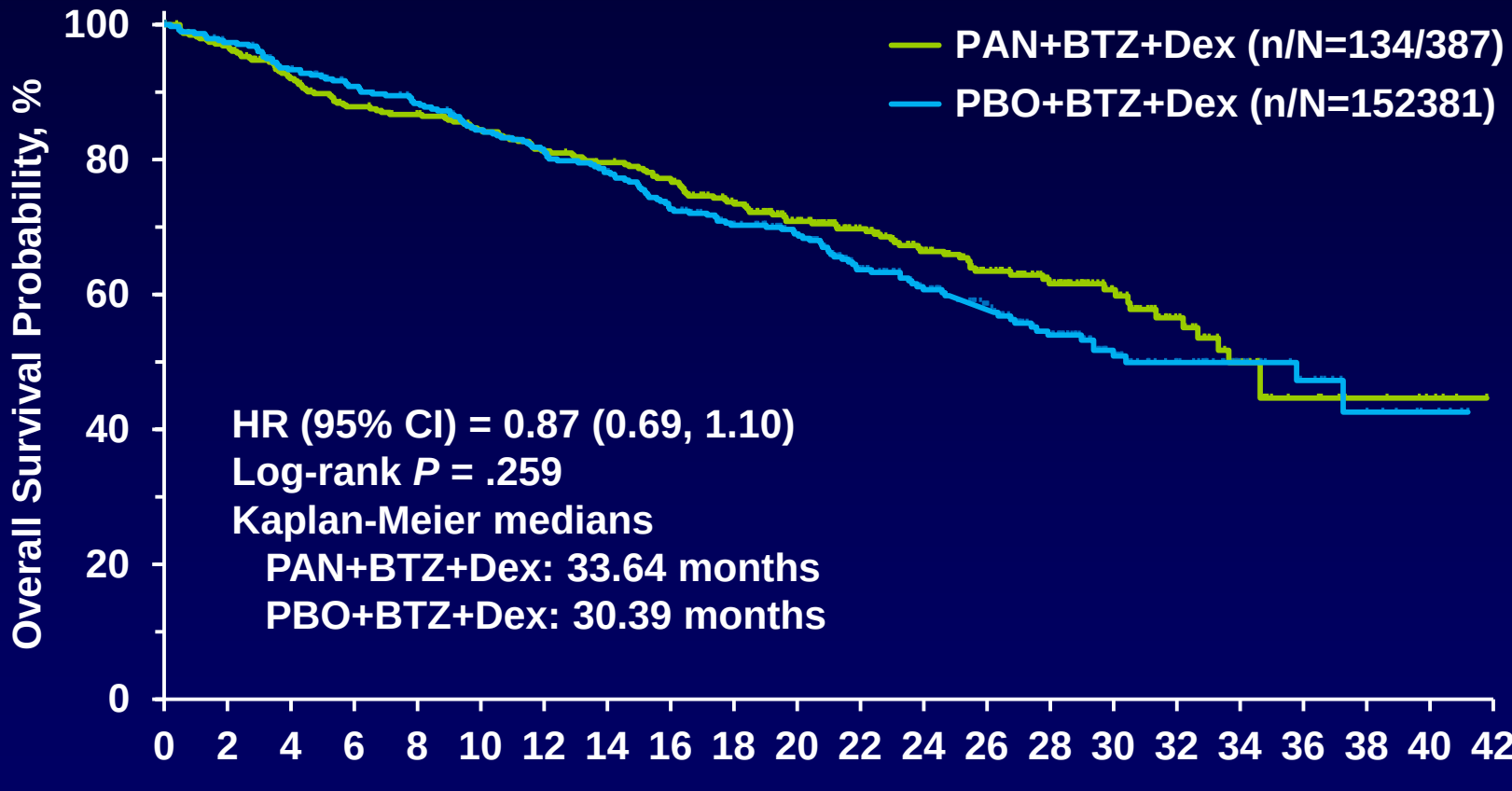
Overall Survival at Time of Final PFS Analysis

Study D2308



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

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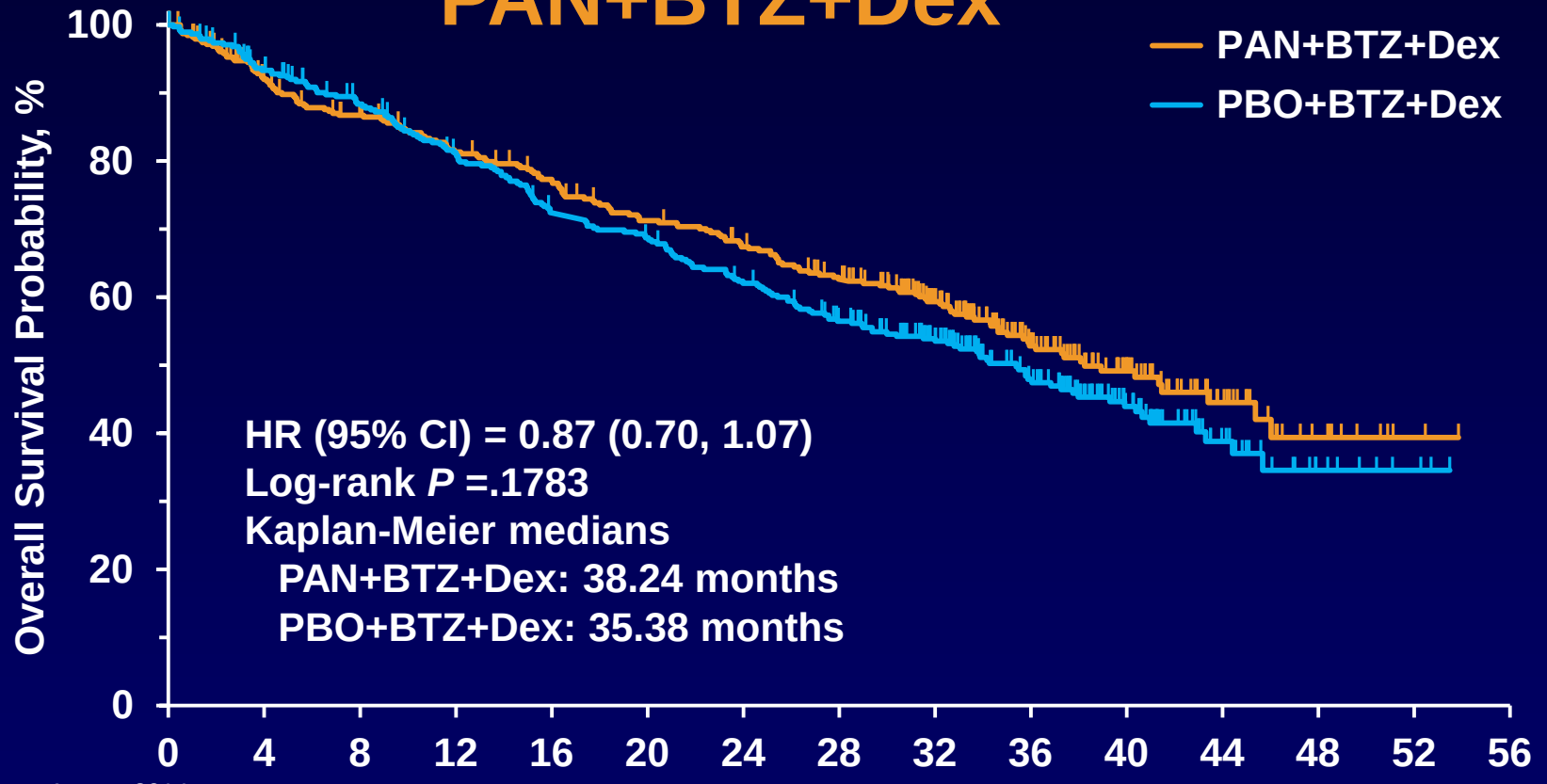
OS: Second Interim Analysis (86% of Events) PANORAMA 1: Longer Median OS With PAN+BTZ+Dex



Cut-off date: August 2014

Patients at risk

PAN+BTZ+Dex	387	363	308	286	267	244	228	206	163	101	59	26	10	2	0
PBO+BTZ+Dex	381	345	315	284	251	238	213	187	150	101	60	24	8	3	0

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PANORAMA 1: Dose Intensity

	PAN-BTZ-Dex n = 387			Pbo-BTZ-Dex n = 381		
	PAN	BTZ	Dex	Pbo	BTZ	Dex
Relative dose intensity, %						
Median	80.7	75.7	87.5	95.1	86.7	95.1
(range)	(41-104)	(31-106)	(35-106)	(45-250)	(31-105)	(27-106)

- **Relative dose intensity of PAN decreased to 78.2% at cycle 3 and remained stable through the remainder of the trial**
- **Dose reduction of PAN 20 mg → 15 mg → 10 mg per protocol**
- **Median duration of treatment**
  - **PAN-BTZ-Dex: 152 days (3-411)**
  - **Pbo-BTZ-Dex: 187 days (3-443)**

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Introduction: TP1/TP2 Analysis

- Panobinostat is a pan-deacetylase inhibitor that inhibits a broad range of deacetylase enzymes, which target key aberrations in MM cell biology, including protein metabolism and epigenetics[1]
- In the phase 3 PANORAMA 1 trial, PAN-BTZ-Dex demonstrated an ~ 4 month PFS benefit compared with Pbo-BTZ-Dex[2]
- A higher rate of grade 3/4 adverse events (AEs) and laboratory abnormalities were observed in patients receiving PAN vs Pbo: thrombocytopenia (67% vs 31%); lymphopenia (53% vs 40%); diarrhea (26% vs 8%); asthenia/fatigue (24% vs 12%); and peripheral neuropathy (18% vs 15%)

1. Atadja P. *Cancer Lett*. 2009;280:233-224. 2. San-Miguel JF, et al. *Lancet Oncol*. 2014;15:1195-1206.

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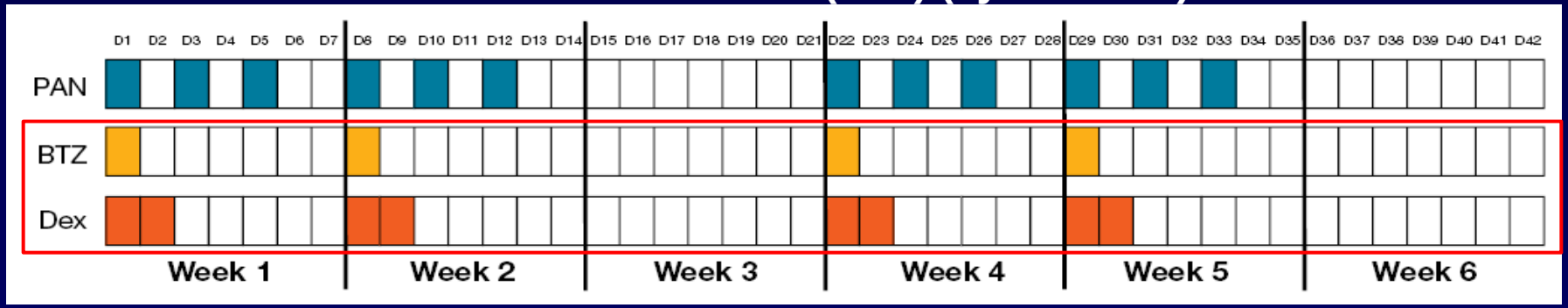
TP1/TP2 Analysis

PANORAMA 1: Treatment Schedule

Treatment Phase I (TP1) (cycles 1-8)

Treatment Phase II (TP2) (cycles 9-12)



- PAN: Panobinostat 20 mg orally
- BTZ: Bortezomib 1.3 mg/m^2 intravenously
- Dex: Dexamethasone 20 mg orally

- **Patients who demonstrated clinical benefit (≥ SD) in TP1 could proceed to TP2 in which BTZ was administered less frequently on a once-weekly schedule**

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Rationale and Methods

- Recent data have demonstrated that once-weekly BTZ is associated with improved tolerability in patients with MM[1]
  - Therefore a detailed analysis of the safety and efficacy profile of patients treated in TP2, where BTZ was administered once weekly, are of interest to further understand and characterize this combination
- Efficacy and safety outcomes were analyzed by treatment phase
  - TP1: Includes patients who completed 8 cycles of treatment and received at least 1 dose in cycle 9
  - TP2: Includes patients who completed 12 cycles of treatment per protocol

1.Bringhen S, et al. *Blood*. 2010;116:4745-4753.

San-Miguel JF, et al. *Blood.* 2014;124: Abstract 4742.

Reasons for Treatment Discontinuation

	All patients		During TP1 (cycles 1-8)	
Primary reason for end of treatment, n (%)	PAN+BTZ+Dex n = 387	Pbo+BTZ+Dex n = 381	PAN+BTZ+Dex n = 387	Pbo+BTZ+Dex n = 381
Adverse event(s)	130 (33.6)	66 (17.3)	112 (28.9)	63 (16.5)
Disease progression	82 (21.2)	153 (40.2)	41 (10.6)	78 (20.5)
Withdrew consent	34 (8.8)	18 (4.7)	31 (8.0)	17 (4.5)
Death	21 (5.4)	17 (4.5)	20 (5.2)	16 (4.2)
Other	18 (4.7)	25 (6.6)	14 (3.6)	15 (3.9)
Treatment duration completed	102 (26.4)	102 (26.8)	169 (43.7)	192 (50.4)

- In the PAN-BTZ-Dex arm (n = 387), the most common reasons for discontinuation in TP1 were: AEs (28.9%), disease progression (10.6%), withdrawal of consent (8.0%), and death (5.2%)

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Summary of Efficacy by Treatment Phase

All patients	PAN+BTZ+Dex N = 387	Pbo+BTZ+Dex N = 381
ORR, % (95% CI)	60.7 (55.7, 65.6)	54.6 (49.4, 59.7)
nCR/CR, % (95% CI)	27.6 (23.2, 32.4)	15.7 (12.2, 19.8)
Median PFS, mo (CI)	11.99 (10.32, 12.94)	8.08 (7.56, 9.23)[a]
Completed TP1 (n)	n = 169	n = 192
ORR, % (95% CI)	85.2 (78.9, 90.2)	80.2 (73.9, 85.6)
nCR/CR, % (95% CI)	46.2 (38.5, 54.0)	25.0 (19.0, 31.7)
Median PFS, mo (CI)	14.65 (12.94,16.85)	12.09 (10.61, 13.14)
Completed TP2 (n)	n = 102	n = 102
ORR, % (95% CI)	88.2 (80.4, 93.8)	91.2 (83.9, 95.9)
nCR/CR, % (95% CI)	52.9 (42.8, 62.9)	38.2 (28.8, 48.4)
Median PFS, mo (CI)	17.64 (15.9, 20.07)	15.64 (14.39, 18.00)

[a]*P*<.0001

- As expected, a longer duration of treatment was associated with an increased rate of higher quality responses (nCR/CR) and median PFS

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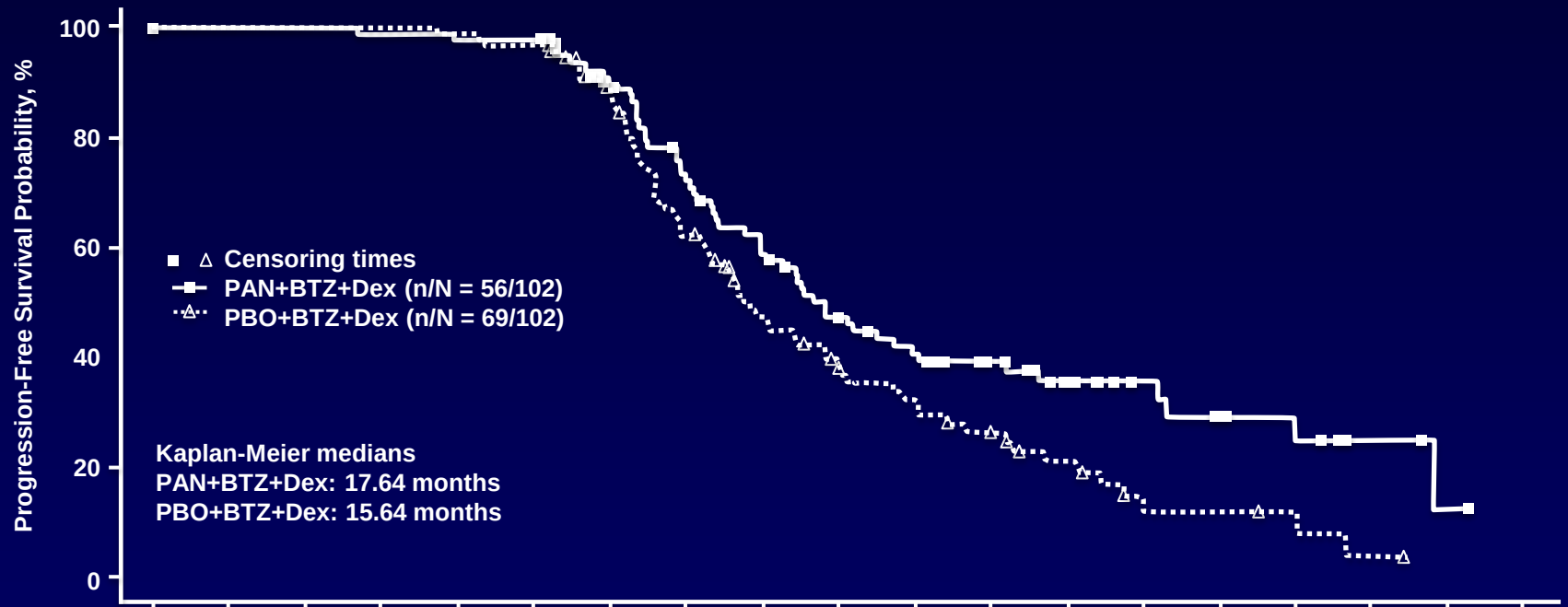
Summary of Efficacy by Treatment Phase for Patients Who Completed TP2



No. of patients still at risk

Time, months	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
PAN+BTZ+Dex	102	95	95	94	93	93	76	60	48	36	30	24	17	11	8	6	3	1	0
PBO+BTZ+Dex	102	96	96	96	95	93	78	54	37	28	22	16	11	4	4	2	1	0	0

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Summary of Adverse Events by Treatment Phase (Occurring in >30% of Patients in Either Arm)

	TP1				TP2			
	PAN+BTZ+Dex n = 381		Pbo+BTZ+Dex n = 377		PAN+BTZ+Dex n = 168[a]		Pbo+BTZ+Dex n = 193[a]	
Preferred term	All grades, %	Grades 3/4, %	All grade, %	Grades 3/4, %	All grades, %	Grades 3/4, %	All grades, %	Grades 3/4, %
Diarrhea	65.9	24.1	38.2	8.0	29.8	7.1	20.2	0.0
Thombocytopenia	64.3	56.7	40.1	24.4	18.5	6.0	5.2	1.0
Anemia	39.9	15.5	31.8	15.1	13.7	3.0	9.3	3.6
Fatigue	39.6	16.3	28.9	8.8	8.9	1.8	4.7	0.0
Nausea	35.2	5.5	19.4	0.5	5.4	0.0	4.7	0.0
Neuropathy peripheral	29.4	6.0	32.9	4.8	6.5	3.0	11.9	1.6
Constipation	26.0	1.0	31.8	1.1	3.6	0.0	5.7	0.0

[a]One patient randomly assigned to receive panobinostat was given placebo during cycles 1 and 2 because of a misallocation error; the patient was subsequently given panobinostat from cycle 3 until discontinuation of treatment, but was included in the placebo group for the safety analysis.

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Summary of AEs by Treatment Phase Among Patients Who Completed TP2 (Occurring in >30% of Patients in Either Arm)

	TP1				TP2[a]			
	PAN+BTZ+Dex n = 102		Pbo+BTZ+Dex n = 102		PAN+BTZ+Dex n = 102		Pbo+BTZ+Dex n = 102	
Preferred Term	**All grades, %**	**Grades 3/4, %**	**All grades, %**	**Grades 3/4, %**	**All grades, %**	**Grades 3/4, %**	**All grades, %**	**Grades 3/4, %**
Diarrhea	74.5	25.5	35.3	5.9	32.4	8.8	21.6	0.0
Thrombocytopenia	60.8	47.1	30.4	10.8	21.6	5.9	6.9	1.0
Fatigue	44.1	14.7	27.5	3.9	9.8	2.0	5.9	0.0
Peripheral edema	37.3	1.0	25.5	1.0	11.8	0.0	7.8	0.0
Neuropathy peripheral	36.3	7.8	34.3	2.0	3.9	2.9	13.7	1.0
Neutropenia	32.4	21.6	11.8	7.8	20.6	12.7	4.9	1.0
Anemia	32.4	7.8	22.5	6.9	10.8	0.0	5.9	1.0
Nausea	31.4	3.9	16.7	1.0	3.9	0.0	4.9	0.0
Constipation	28.4	1.0	31.4	2.0	3.9	0.0	5.9	0.0

[a]Newly occurring or worsening adverse events

- **Among patients in the PAN-BTZ-Dex arm who completed TP2, the incidence of newly occurring or worsening grade 3/4 AEs decreased in TP2**
  - **Thrombocytopenia (47.1% vs 5.9%); diarrhea (25.5% vs 8.8%); neutropenia (21.6% vs 12.7%)**

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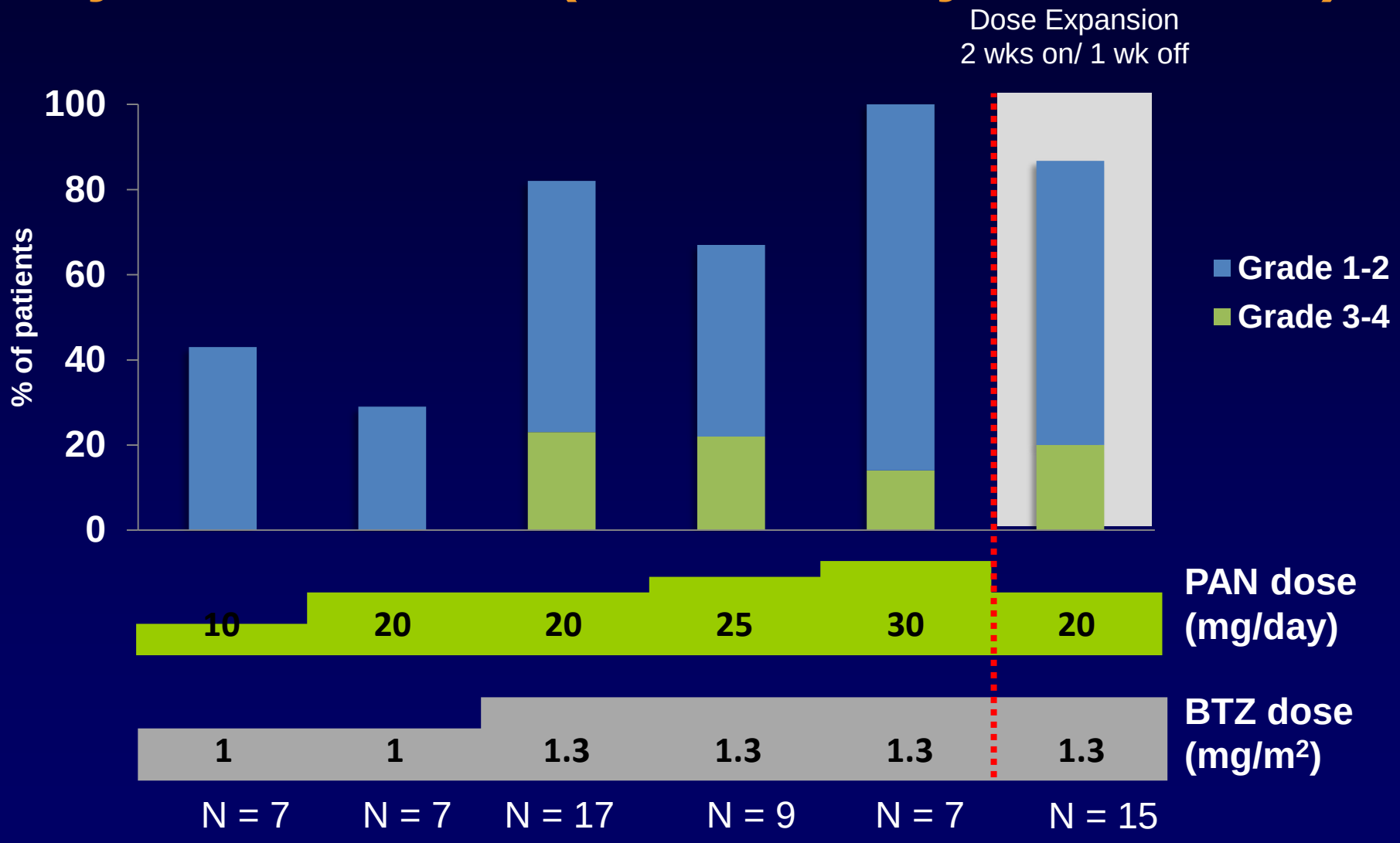
Phase I Experience: Incidence of Diarrhea by Dose Cohort (B2207 Study PAN + Dex)



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Clinical Impact of Diarrhea in the PANORAMA 1 Study

	PAN-BTZ-Dex n = 381	Pbo-BTZ-Dex n = 377
Any grade, %	68	42
Grade 3/4 AE, %	26	8
Grade 3 AE	24	8
Grade 4 AE	1	0.5
Serious AEs, %	11	2
Dose adjusted/temporarily interrupted, %	26	9
Study drug permanently discontinued, %	5	2
Concomitant medication taken/nondrug therapy given, %	49	26
Hospitalization, %	10	2
Grade 3/4 AE episodes per patient		
Median (range), n	1 (1-9)	1 (1-4)
1 episode, %[a]	65	65
2 episodes, %[a]	21	32
≥3 episodes, %[a]	14	3

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Antidiarrheal Concomitant Medications

	PAN-BTZ-Dex N = 381	Pbo-BTZ/Dex N = 377
Total %	54	32
Loperamide	44	24
Diosmectite	7	3
Diphenoxylate/atropine	3	1
Potassium chloride	2	0
Ciprofloxacin	2	1

- For management of diarrhea, loperamide was most frequently administered: PAN-BTZ-Dex arm, 44%; Pbo-BTZ-Dex arm, 24%

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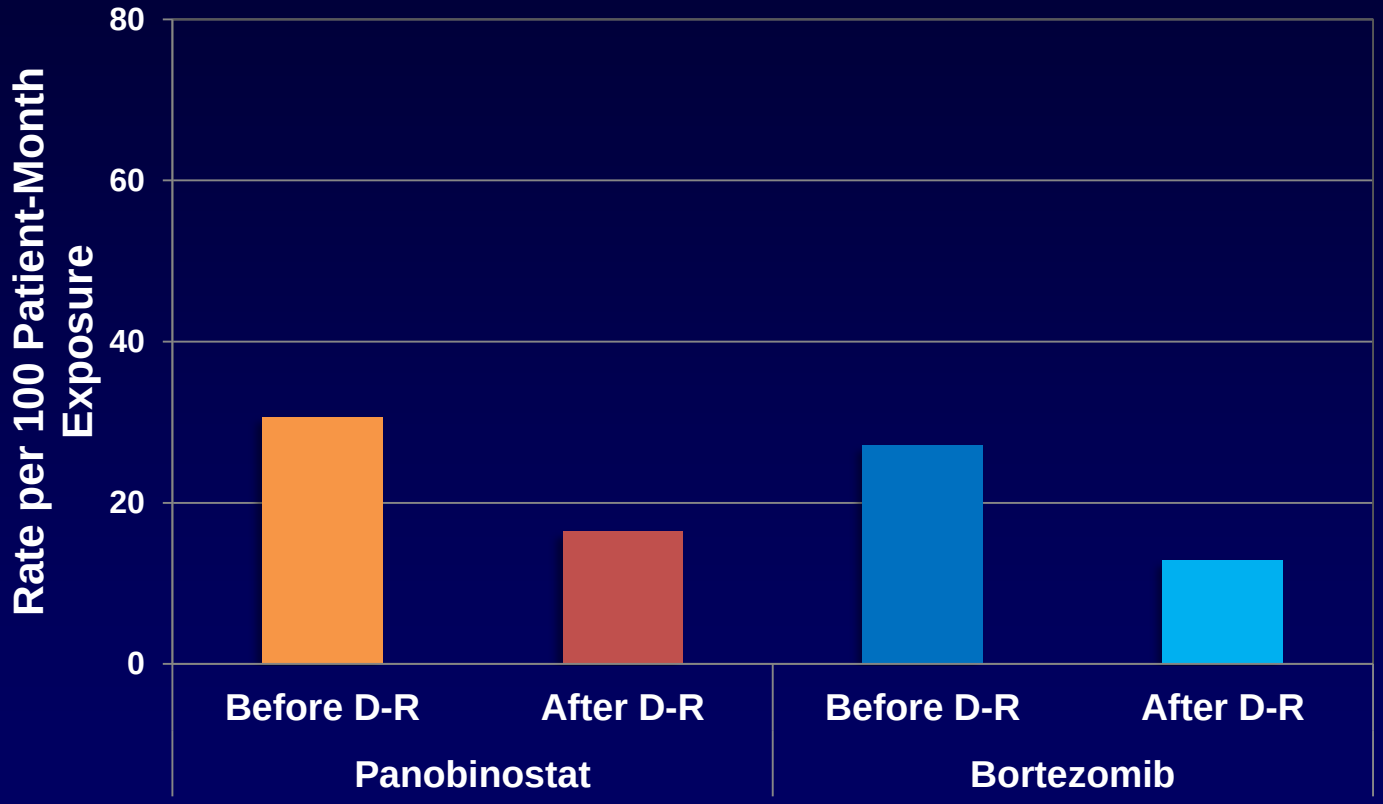
Rate of Diarrhea Before and After the First Dose Reduction for Patients Who Received PAN-BTZ-Dex in Treatment Phase I



- **Rate of diarrhea decreased after the first dose reduction of panobinostat and bortezomib**

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Conclusions: TP1/TP2 Analysis

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