

Phase II Study of the Pan-Deacetylase Inhibitor Panobinostat in Combination With Bortezomib and Dexamethasone in Relapsed and Bortezomib-Refractory Multiple Myeloma (PANORAMA 2)

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Multiple Myeloma

Disease status

- Multiple myeloma (MM) remains an incurable disease with a high unmet need for pts in the relapsed and refractory treatment setting¹
- Novel agents, including the first in class proteasome inhibitor bortezomib (BTZ) and immunomodulatory drugs (IMiDs) lenalidomide and thalidomide, are commonly used for MM treatment²⁻⁷
- Pts with MM refractory to both BTZ and IMiDs have very poor prognosis⁸
 - Median overall survival and event-free survival of 9 and 5 mos, respectively
 - Response rate for subsequent BTZ-containing regimen is 20%

1. Kumar SK, et al. *Blood*. 2008;111:2516-2520. 2. Kane RC, et al. *Oncologist*. 2003;8:508-513.
3. Richardson PG, et al. *N Engl J Med*. 2003;348:2609-2617. 4. Rajkumar SV, et al. *J Clin Oncol*. 2006;24:431-436.
5. Rajkumar SV, et al. *J Clin Oncol*. 2002;20:4319-4323. 6. Weber DM, et al. *N Engl J Med*. 2007;357:2133-2142.
7. Dimopoulos M, et al. *N Engl J Med*. 2007;357:2123-2132. 8. Kumar SK, et al. *Leukemia*. 2011; epub.

Panobinostat

Potent, oral pan-deacetylase inhibitor (pan-DACi)

- Panobinostat has low nanomolar activity against all class I, II, and IV histone deacetylase (HDAC) enzymes¹
- Panobinostat increases acetylation of proteins involved in multiple oncogenic pathways¹

IC₅₀ of Enzyme Inhibition [nM]

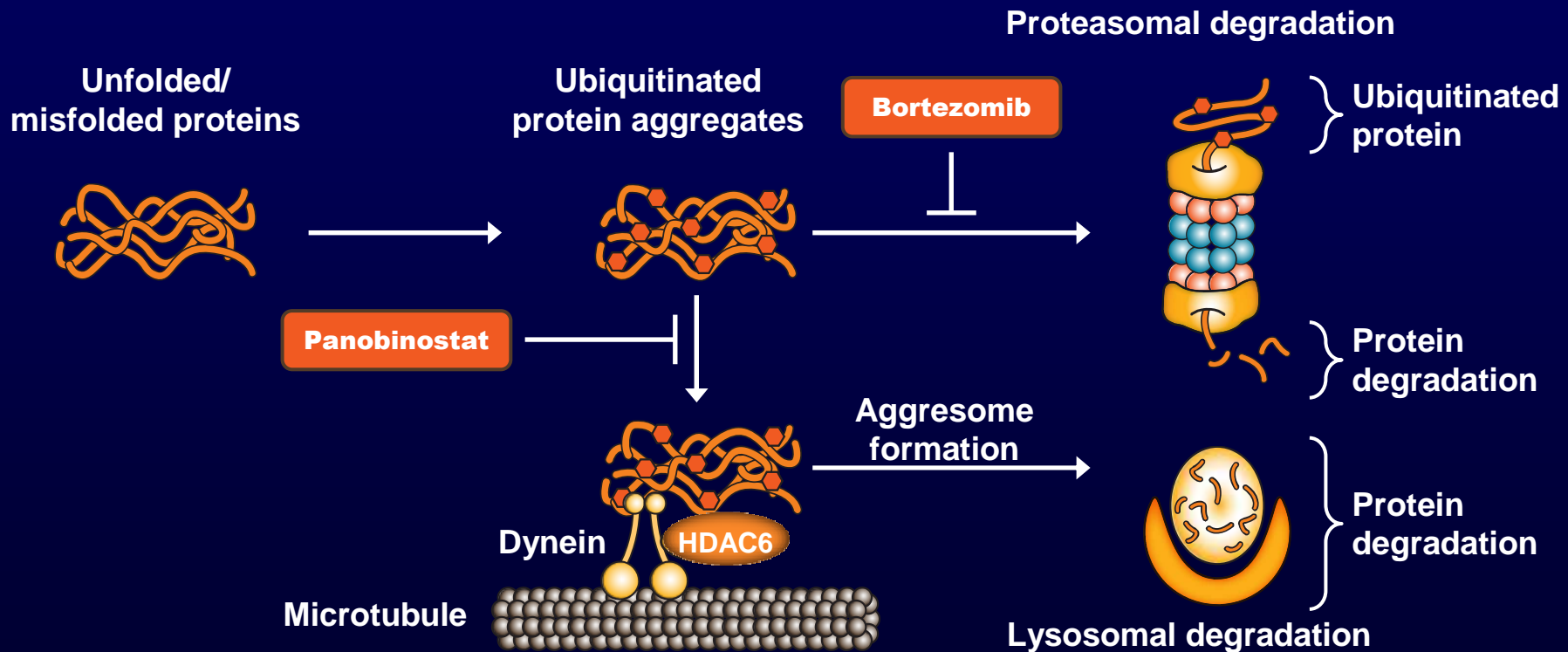
Drug	Class I			Class II						Class IV	
	HDAC1	HDAC2	HDAC3	HDAC8	HDAC4	HDAC5	HDAC6	HDAC7	HDAC9	HDAC10	HDAC11
Panobinostat ¹	2.5	13.2	2.1	277	203	7.8	10.5	531	5.7	2.3	2.7
Vorinostat ¹	75.5	362	57.4	1069	15056	163	27.1	12522	78.1	88.4	109
Romidepsin ²	7	28	103	34	96	80	33	279	2729	368	64

Implicated as potential tumor targets in MM

Panobinostat + Bortezomib

Synergistic anti-myeloma activity

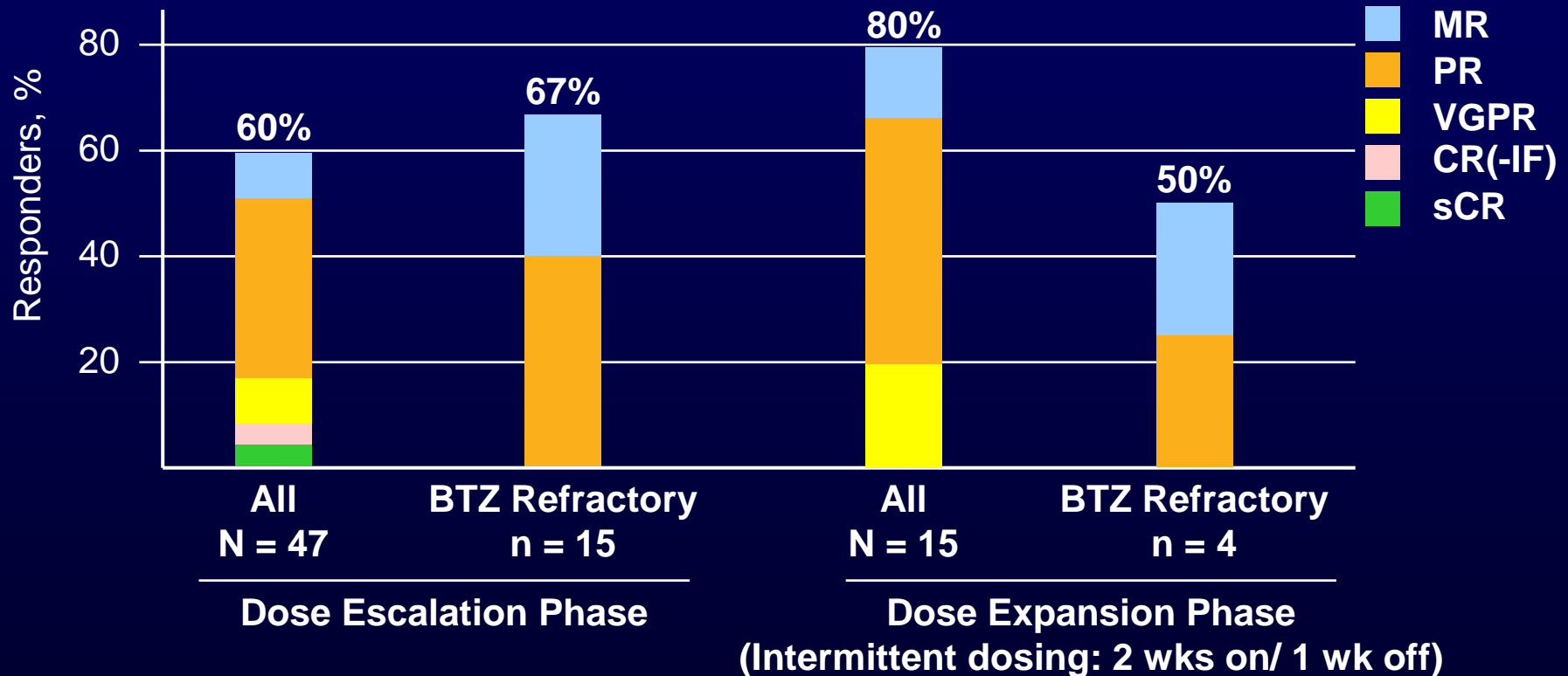
- Inhibition of the aggresome and proteasome pathways causes a buildup of intracellular misfolded cytotoxic proteins, leading to MM cell apoptosis¹⁻⁴



Panobinostat + Bortezomib

Activity in BTZ-refractory myeloma patients

- In a phase Ib trial, the combination of panobinostat and BTZ demonstrated efficacy in MM pts, including a subset of pts refractory to BTZ therapy¹



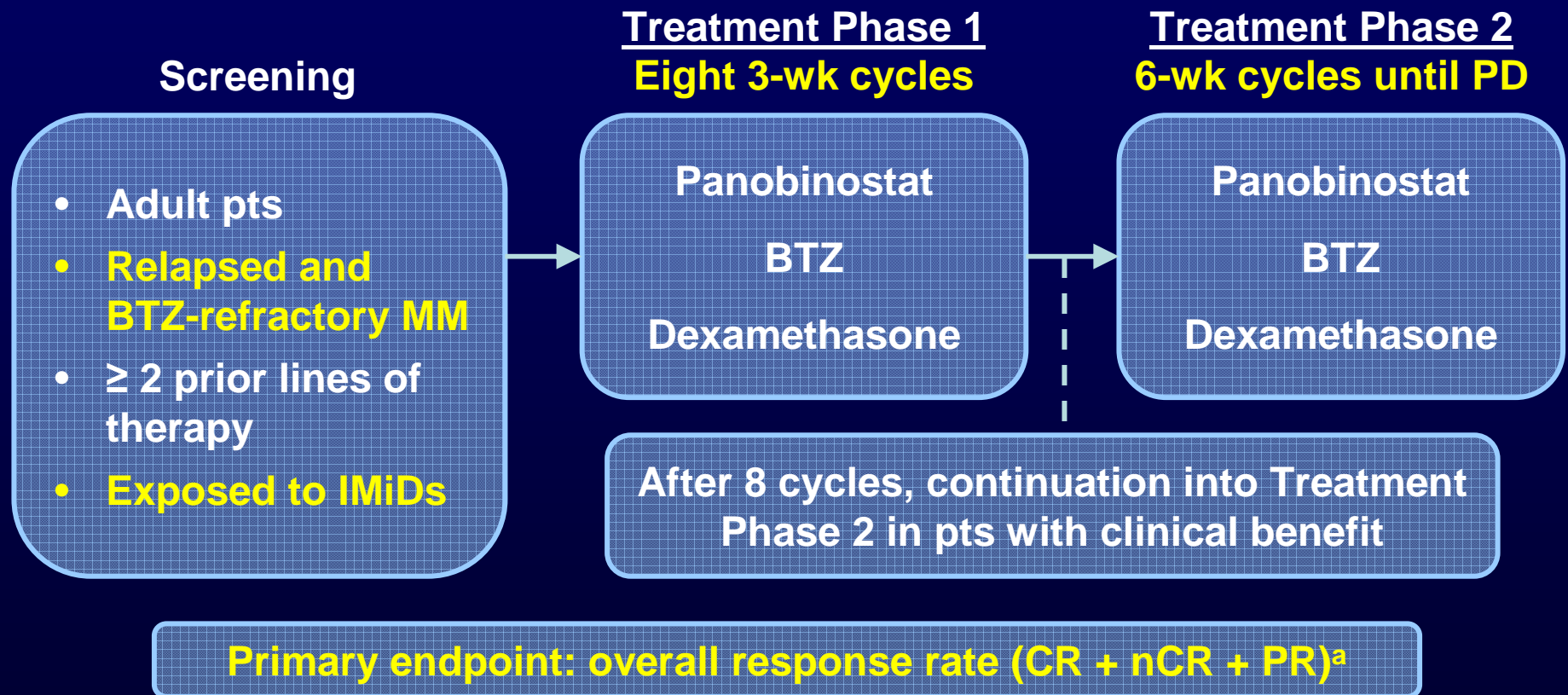
CR (-IF), immunofixation-negative complete response;
 MR, minimal response; PR, partial response; sCR, stringent CR; VGPR, very good PR.

1. San Miguel J, et al. *European Hematology Association*. 2011;Abstract 0314.

PANORAMA 2 Study Design

Phase II, Simon 2-stage study in BTZ-refractory MM

BTZ-refractory disease defined as relapse on or within 60 days of last BTZ-containing line of therapy¹



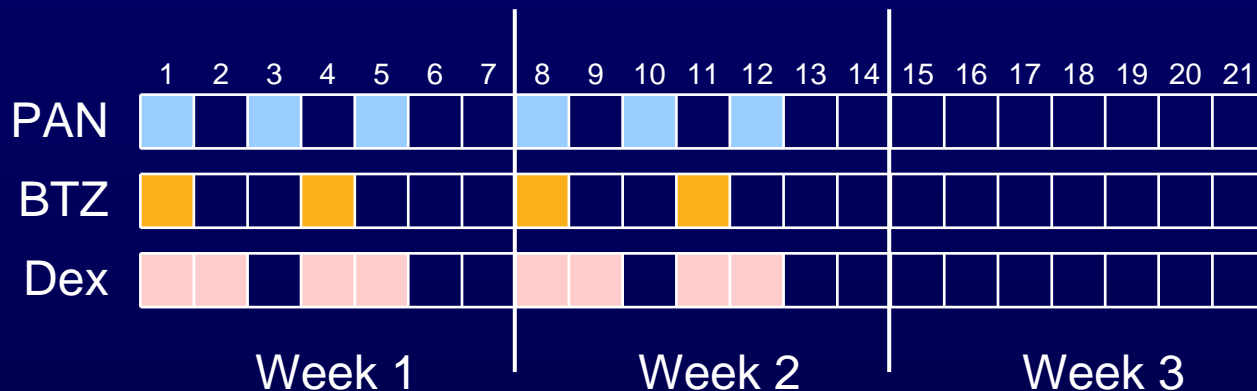
^a Response measured according to modified European Group for Blood and Marrow Transplantation 1998 criteria. CR, complete response; nCR, near CR; PD, disease progression; PR, partial response.

1. Anderson KC, et al. *Leukemia*. 2008;22:231-239.

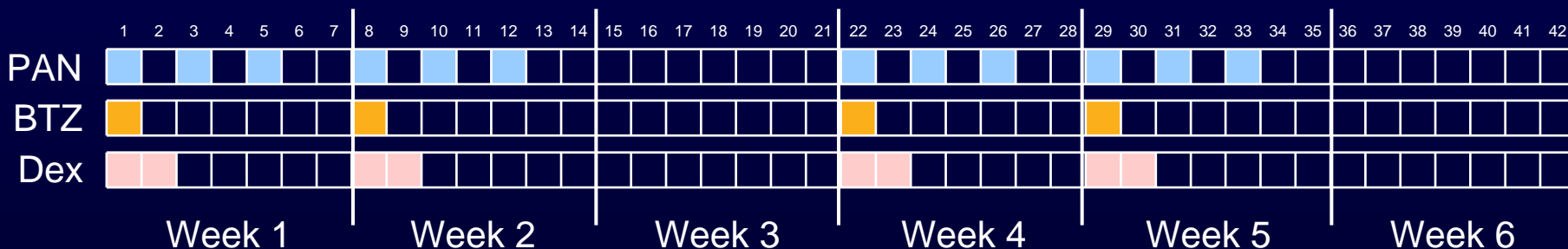
PANORAMA 2

Dosing schedule

Treatment Phase 1 (Cycles 1-8)



Treatment Phase 2 (Cycle 9+)



- PAN: Panobinostat 20 mg oral
- BTZ: Bortezomib 1.3 mg/m² IV
- Dex: Dexamethasone 20 mg oral

Study Design

Objectives and assessments

- **Primary efficacy endpoint**
 - Overall response rate (CR + nCR + PR)
- **Secondary endpoints include:**
 - MR, TTR, DOR (from first PR or better)
 - PFS, TTP, OS
 - AEs by CTCAE v4.0, and SAE, ECG, and peripheral neuropathy assessments (FACT/GOG-NTX v4.0)
- **Efficacy assessment by modified EBMT and Uniform Criteria¹⁻⁴**
 - Disease assessments performed every 3 wks
 - Response confirmed after 6 wks
 - Pts who discontinue treatment for reasons other than PD will have assessments every 6 wks until PD or death
- **ECG monitoring performed throughout the first 8 cycles**

CTCAE, Common Terminology Criteria for Adverse Events; EBMT, European Bone Marrow Transplant organization.

1. Bladé J, et al. *British J Haematol.* 1998;102:1115-1123. 2. Richardson PG, et al. *N Engl J Med.* 2003;348:2609-2617.
3. Durie BG, et al. *Leukemia.* 2006;20:1467-1473. 4. Rajkumar SV, et al. *Blood.* 2011;117:4691-4695.

Patient Characteristics

A heavily pretreated, BTZ-refractory patient population

	N = 55
Female/male, %	53/47
Median age, y (range)	61 (41-88)
ECOG performance status 0-1 / 2 / missing, %	93 / 5 / 2
Prior regimens, median (range)	4 (2-14)
Prior autologous stem cell transplant, n (%)	35 (64)
Prior BTZ regimens, median (range)	2 (1-6)

- **Pts received multiple prior regimens, including multiple prior BTZ combinations**

Preliminary Response Data

Activity in BTZ-refractory MM patients

Best confirmed response (confirmed at 6 wks)	N = 55
Overall response (CR + nCR + PR)	16 (29%)
Complete response	–
Near complete response	2 (4%)
Partial response	14 (25%)
Clinical benefit (CR + nCR + PR + MR)¹⁻³	27 (49%)
Minimal response	11 (20%)
VGPR	3 (6%)

- Responses were typically observed after 1 to 2 cycles
- Stable disease observed in 2 pts; progressive disease in 10 pts

1. Anderson KC, et al. *Leukemia*. 2008;22:231-239.

2. Richardson PG, et al. *Br J Haematol*. 2009;144:895-903. 3. Niesvizky R, et al. *Br J Haematol*. 2009;143:46-53.

Patient Disposition

Prolonged study participation

	N = 55
Patients ongoing	17 (31%)
Off treatment	38 (69%)
In follow-up	24 (44%)
Off study	14 (25%)
Death	11 (20%)
Withdrew consent	2 (4%)
Lost due to follow-up	1 (2%)

- Pts have been on study an average of 4.7 mos (range, < 1-12.5)
- 16 pts completed the first 8 cycles and entered treatment phase 2
 - 10 pts still on study in treatment phase 2
 - 2 pts completed \geq 12 cycles (48 wks)

Adverse Events

Occurring in $\geq 5\%$ (grade 3/4) of patients (n = 51)

AE, regardless of relationship to study drug	All	Grade 3/4
Thrombocytopenia	32 (63%)	27 (53%)
Fatigue	32 (63%)	8 (16%)
Diarrhea	29 (57%)	7 (14%)
Anemia	19 (37%)	8 (16%)
Nausea	30 (59%)	3 (6%)
Neutropenia	10 (20%)	6 (12%)
Hypotension	9 (18%)	3 (6%)
Pneumonia	8 (16%)	7 (14%)
Dehydration	8 (16%)	3 (6%)
Abdominal distension	8 (16%)	3 (6%)
Asthenia	7 (14%)	3 (6%)
Abdominal pain	6 (12%)	3 (6%)
Syncope	4 (8%)	4 (8%)

Safety

Generally well tolerated with manageable AEs

- **Thrombocytopenia, the most common grade 3/4 AE (53%), managed with dose reduction/interruption**
 - **Less thrombocytopenia observed in the 2 wks on/1 wk off schedule compared with the weekly schedule¹**
 - **No bleeding AEs in pts with thrombocytopenia**
- **Treatment-emergent peripheral neuropathy (24% overall), generally mild, with only one grade 3/4 event (2%)**
- **Fatigue and asthenia (63% and 14% overall), predominantly mild and managed with hydration, dose reduction, and supportive care**
- **No reports of QTc prolongation**

Case Study

58-year-old man with Durie-Salmon stage IIIa λ chain MM

- **History**
 - Right sternal plasmacytoma with multiple lytic bone lesions
 - 30% plasma cells in marrow; normal cytogenetics, counts, kidney function
- **Treatment**

Date	Treatment	Best Response
August 2005	Radiation to sternum; Thal/Dex	PR
March 2006	Consolidation (high-dose melphalan + ASCT)	VGPR
January 2009	Len/Dex started after progression	PD
May 2009	RVD (6 cycles)	SD (\rightarrow PD)
November 2009	CyBorD (8 cycles)	SD (\rightarrow PD)
March 2010	Thal/Dex (4 cycles)	PD
October 2010	Enrolled in PANORAMA 2	nCR in November 2010
December 2011	Ongoing on PANORAMA 2 (cycle 14)	

Conclusions & Future Directions

- **Panobinostat synergizes with BTZ in recapturing responses in heavily pretreated, BTZ-refractory MM pts**
 - All pts BTZ refractory: median of 4 prior regimens
 - Clinical benefit rate: 49% (2 nCR, 14 PR, 11 MR)
 - 16 pts completed 8 cycles, 2 pts completed ≥ 12 cycles
 - Treatment ongoing in 17 pts
- **Combination generally well tolerated**
 - Most common hematologic grade 3/4 AEs proved manageable with dose interruption/reduction
 - Intermittent panobinostat dosing reduced thrombocytopenia
- **This study and the phase III PANORAMA 1 trial will further define the role of panobinostat combined with BTZ + Dex in the care of MM pts**
- **Panobinostat is also being explored in combinations with other agents for MM treatment, including RVD, pomalidomide, carfilzomib, and thalidomide**

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