A Phase I/II Trial Evaluating the Safety and Efficacy of Panobinostat + RVD (Bortezomib + Lenalidomide + Dexamethasone) in Patients With Newly Diagnosed Multiple Myeloma

Abstract #33

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prIME oncology

Background

- **Panobintostat, is a potent pan-DAC inhibitor with novel, multiple mechanisms of action:**
  - **Epigenetic modification: via increased histone acetylation, cellular reprogramming, and subsequent expression of genes**
  - **Increased acetylation of non-histone proteins - such as hsp90 and p53**
- **Preclinical data demonstrating synergy support the combination of panobinostat with both proteasome inhibitors and IMiDs by affecting multiple protein metabolism pathways**
- **PANORAMA 1: Large Phase III randomized in RRMM (1-3 lines)**
  - **Bort/dex vs Bort/dex + Panobinostat**
  - **Clinically and statistically significant improvement in PFS by 3.9 months**
  - **Near doubling in CR from 15.7 to 27.6%**

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Background

- **Bortezomib/Lenalidomide/dex** in NDMM full dose therapy and high response rates and CR at 4 cycles < 10%
- **IFM 2008-01:** VRD x 3 induction therapy prior to ASCT: 23% CR/sCR after induction therapy
- **RVD** is a highly active combination and one of the standard of care options used in the front line setting, however as an induction therapy prior to ASCT, the CR rate at 3-4 cycles is still 10-20%.
- **R2V2:** RVD + Vorinostat in NDMM: ORR 100% and CR 33% after 4 cyles.
- **The hypothesis** is that the combination of Panobinostat with RVD in NDMM will be tolerable, and lead to improvement in depth of response

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Phase I Study Objectives

Primary Objectives:

- To determine the MTD of the combination of panobinostat with bortezomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma patients

Secondary Objectives:

- Evaluate the overall response rate after 4 cycles
- Evaluate time to progression
- Evaluate time to next therapy
- Evaluate the progression free survival
- Evaluate the tolerability and toxicity
- For patients who elect to proceed to stem cell harvesting and autologous stem cell transplant, evaluate the number of CD34+ cells (per kg) collected and the days of harvest required, as well as engraftment parameters if available as exploratory endpoints; response rates at 3, 6 and 9 months post ASCT

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Study Design

- Phase I: 3 + 3 Dose Escalation Study
- Dose expansion at maximum tolerated dose (MTD) n = 20
  - Continuous monitoring for DLT

	Lenalidomide	Bortezomib (subq)	Dexamethasone	Panobinostat
Cohort -1	15 mg	1.0 mg/m^2	20 mg	10 mg
Cohort 1: (initial dose level)	25	1.3 mg/m^2	20	10
Cohort 2:	25	1.3 mg/m^2	20	15
Cohort 3:	25	1.3 mg/m^2	20	20

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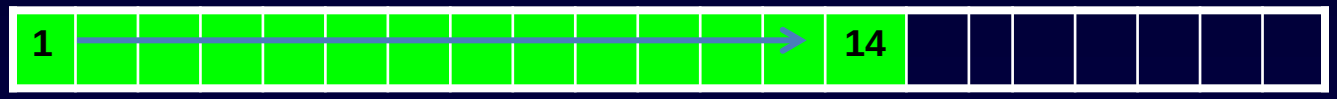
Treatment Schema

Cycle 1-8: 21 day cycle

Lenalidomide



Bortezomib subq

Dexamethasone

Panobinostat

Cycle 8 + : Maintenance Cycles

Lenalidomide, panobinostat as tolerated; dexamethasone 20 weekly

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- **Patients treated until ASCT/ progressive disease / unacceptable toxicity/ withdrawal on consent**
- **Concomitant medications:**
  - **Anti-viral therapy**
  - **Anticoagulation: Aspirin 81 mg; LMWH in ASA intolerant**

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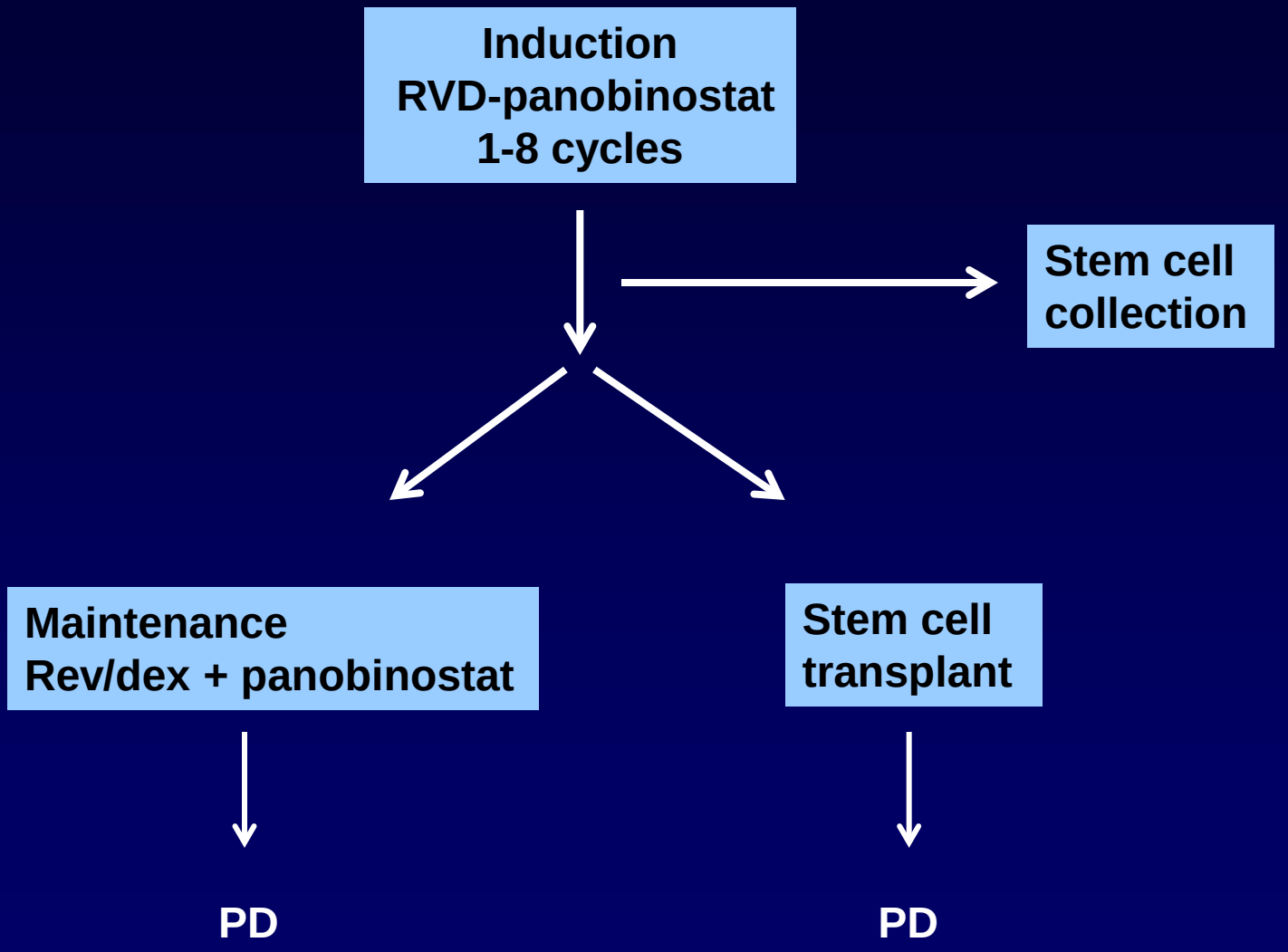
Treatment Flow



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Key Inclusion Criteria

- Patients must have confirmed diagnosis of multiple myeloma by the International Myeloma Foundation 2003 Diagnostic Criteria
- Patient must not have been previously treated with any prior systemic therapy for the treatment of multiple myeloma
  - Prior treatment of hypercalcemia or spinal cord compression with corticosteroids permitted
  - Bisphosphonates are permitted
- ECOG 0-2
- Patients must adequate hematologic, renal, liver, cardiac function:
  - ANC ≥1.0 x 10^9/L
  - Hemoglobin ≥8 g/dl(Transfusion permitted)
  - Platelets ≥70 x 10^9/L
  - AST and ALT ≤2.5 x ULN
  - Serum bilirubin <1.5 x ULN
  - Baseline MUGA or ECHO must demonstrate LVEF ≥50%
  - Renal insufficiency Creatinine <2.5 mg/dl

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Patient Demographics

	N = 31
Gender	Male: 24 (77%) Female: 7 (23%)
ECOG PS	0: 8 (26%) 1: 23 (74%)
Age, median (range)	61 yrs (48 to 79)
ISS Stage	I: 19 (61%) II: 8 (26%) III: 4 (13%)

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FISH / Cytogenetics

	N = 31
Hyperdiploid	14 (45%)
t(11;14)	4 (13%)
Del(13)	10 (32%)
CKS1B amplification	8 (26%)
FGFR	1 (3%)
Del(17p) / p53	1 (3%)

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DLT Criteria

Grade 3 or greater non-hematologic toxicity except the following:

- Nausea or vomiting that responds to symptomatic therapy
- Fatigue that responds to maximal management
- Hyperglycemia
- Isolated Grade 3 elevation of liver function tests (LFTs) without associated clinical symptoms, lasting for ≤ 7 days in duration.
- Isolated Grade 3 elevation of amylase without associated clinical symptoms
- Grade 3 hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hyphosphatemia which responds to medical intervention.

Hematologic toxicities defined as :

- Grade 4 thrombocytopenia OR platelet count <25,000/μL on more than one occasion despite platelet transfusion for more than 7 days
- Grade 4 neutropenia for more than 7 days and/or neutropenic fever (≥101 degrees F) confirmed on two occasions; Neupogen is allowed after DLT is recorded.
- Grade 3-4 thrombocytopenia associated with bleeding.

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Phase I: Dose Escalation

- 12 patients enrolled in dose escalation phase I

	Lenalidomide (mg)	Bortezomib (subq)	Dex (mg)	Panobinostat (mg)	DLT
Cohort -1	15	1.0 mg/m^2	20	10 mg	
Cohort 1:	25	1.3 mg/m^2	20	10	0/6
Cohort 2:	25	1.3 mg/m^2	20	15	2/6 DLT

- One patient Grade 4 PLT / G3 diarrhea / G4 Hypocalcemia
- Second patient: Grade 3 diarrhea without supportive care resolved immediately with supportive care last <12 hours
  - G3 diarrhea with/without supportive care was considered DLT
- MTD was cohort 1: And 19/20 additional pts enrolled in dose expansion

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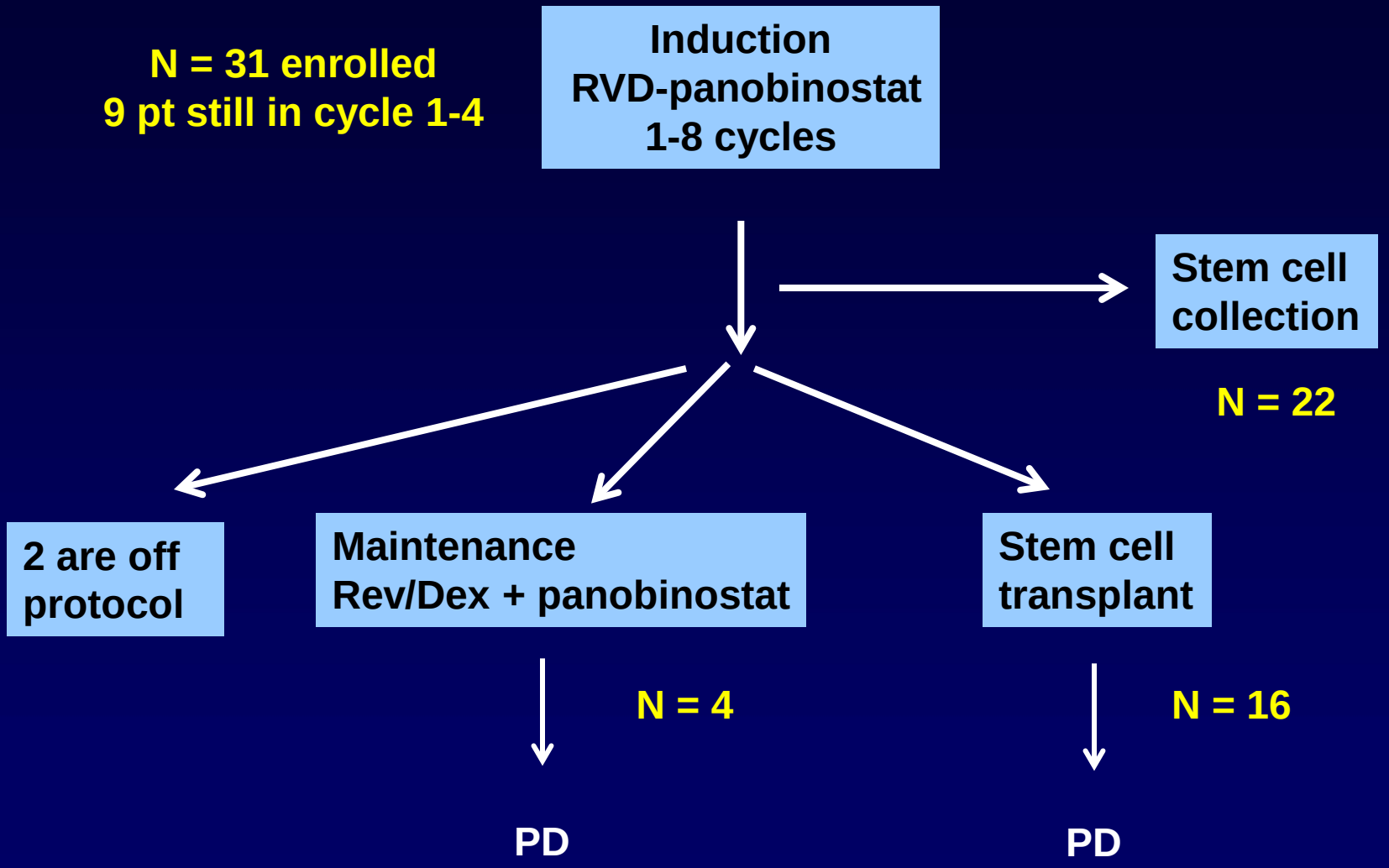
Treatment Flow: Patients on Study

N = 31 enrolled
9 pt still in cycle 1-4



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Hematologic Adverse Events (n = 31)

	G1	G2	G3	G4	G3/4
Anemia	17	10	4	0	4/31 (13%)
Neutropenia	5	7	3	1	4/31 (13%)
Thrombocytopenia	12	3	8	1	9/31 (29%)
Leukopenia	2	6	2	1	3/31(9%)

Limited hematologic toxicities

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Non-Hematologic Adverse Event n = 31 (> 30%)

	G1	G2	G3	G4
Alanine aminotransferase	11	0	2	0
Alkaline phosphatase	9	2	0	0
Aspartate aminotransferase	10	1	1	0
Constipation	10	10	2	0
Diarrhea	6	2	2	0
Dyspnea	10	5	1	0
Nausea	10	5	0	0
Edema limbs	9	4	0	0
Fatigue	10	12	1	0
Peripheral sensory neuropathy	15	3	1	0

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Additional Non-Hematologic Adverse Event n = 31

	G1	G2	G3	G4
Creatinine	3	2	0	0
Emesis	4	1	0	0
Thromboembolic event	1	1	2	0
Infections	1	9	7	1

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Serious Adverse Events

- 2 patients with G2 diarrhea; G3 diarrhea
- Fever/rash; Skin infection; Pneumonia n = 5;
- Elevated INR
- VTE
- A fib
- Acute Coronary syndrome (Cycle 2, CABG, CAD, HTN, Lipid on Aspirin) unrelated
- Seizure unrelated chronic history

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Clinical Activity: Response Rates (ITT) at 4 Cycles, N = 22; Patients Who Completed 4 cycles, 9 Are Ongoing in C1-4

	N = 22
nCr/Cr	11 (50%)
VGPR	6 (27%)
PR	4 (18%)
SD	1 (5%)

ORR (≥PR) = 95%

- All patients had adequate stem cell collection
- No unexpected post transplant toxicity

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Conclusions

- The maximum tolerated dose **without supportive care** was lenalidomide 25 mg, bortezomib 1.3 mg/m^2, dexamethasone, panobinostat 10 mg in newly diagnosed myeloma
- This is the first experience of panobinostat in combination lenalidomide/bortezomib/dex
- First experience with panobinostat and subcutaneous administration of bortezomib
- Combination was very well tolerated with limited g3/4 toxicity; g3/4 Diarrhea/Constipation (6%) with no unexpected toxicity

≥ORR at 4 cycles	95%
≥VGPR (median)	77%
CR/nCR	50%

- The combination of RVD + Panobinostat is highly active with high depth response and rapid disease control at **4 cycles** (historical expect VRD 4 cycle CR: 10%-23%
- No effect of panobinostat on stem cell collection/mobilization
- Enrollment in dose expansion expanded additional patients
- Subsequent randomized phase II planned

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