

Safety and Efficacy of Novel Combination Therapy with Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide in Newly Diagnosed Multiple Myeloma (VDCR): Initial Results from the Phase I/II Multi-Center EVOLUTION Study

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Disclosures for Dr Shaji Kumar

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Presentation includes discussion of the following off-label use of a drug or medical device:
Bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in a novel combination in newly diagnosed MM

Introduction

- ▶ Combinations of bortezomib (VELCADE[®], Vc), lenalidomide (REVLIMID[®], Rev), dexamethasone (Dex), and/or cyclophosphamide (Cy) have substantial activity in untreated multiple myeloma
- ▶ The combination of all 4 agents (VDCR) may result in even deeper responses in this patient population
- ▶ The randomized Phase I/II EVOLUTION trial is investigating VRD, VDC, and VDCR in patients with previously untreated MM

Objectives

- ▶ **Primary objectives:**

- **Phase I:** Determine the maximum tolerated dose (MTD) of cyclophosphamide in combination with VRD

- **Phase II:** Determine the combined rate of complete response (CR) plus very good partial response (VGPR) for the VRD, VDC, and VDCR combinations

Objectives

▶ Secondary objectives:

- Safety and tolerability of the combinations
- Overall response rate (CR+VGPR+PR), stringent CR rate (sCR), and CR/ near-CR (nCR) rate
- Time to response and duration of response (DOR)
- Time to disease progression (TTP), progression-free survival (PFS), and overall survival (OS)

▶ Exploratory objectives:

- Frequency of flow cytometric remission

Patients

▶ Inclusion criteria:

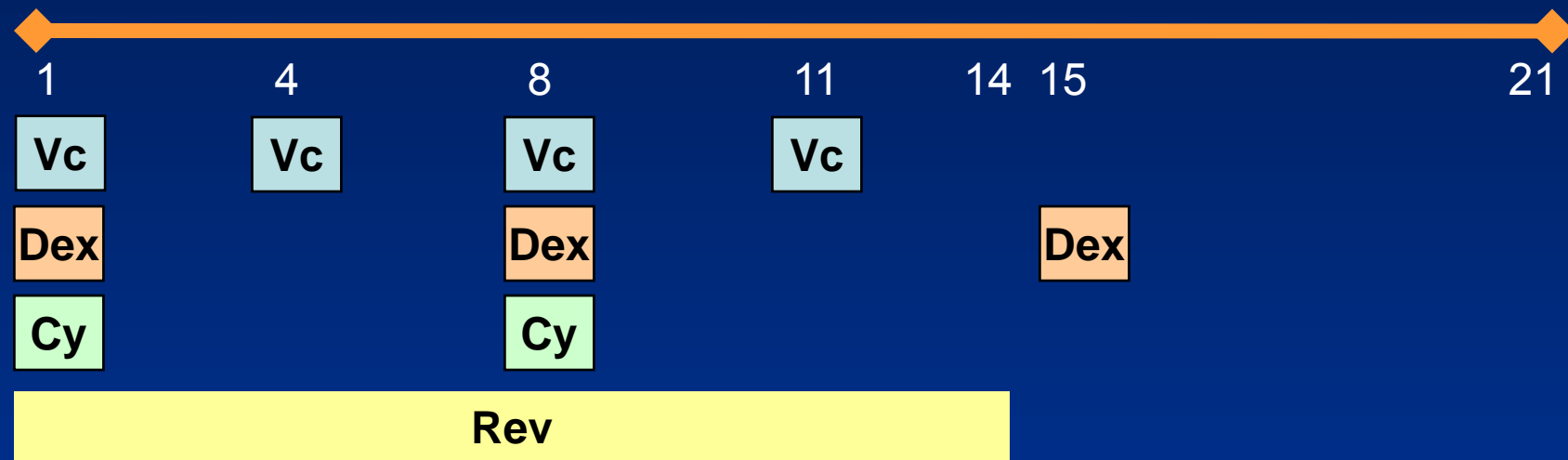
- Previously untreated MM with measurable disease
- Karnofsky Performance Status (KPS) $\geq 50\%$

▶ Exclusion criteria:

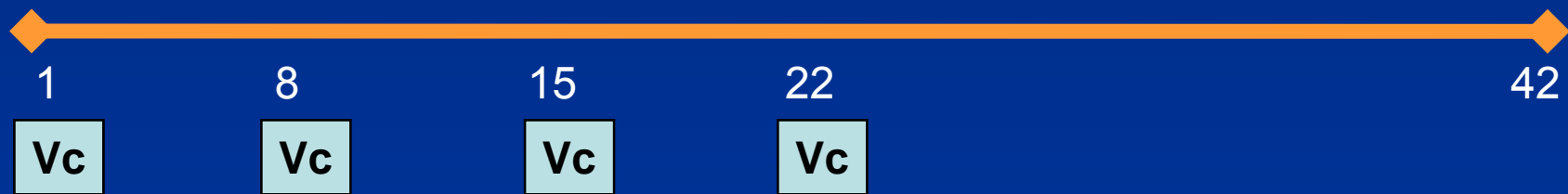
- Peripheral neuropathy Grade ≥ 2 (NCI CTCAE v3.0)
- Renal insufficiency (serum creatinine > 2.5 mg/dl)
- ANC $< 1,000$ cells/mm³
- Platelets $< 70,000$ cells/mm³
- AST/ALT > 2 x ULN
- Total bilirubin > 3 x ULN

Phase I: Study design

Dose escalation of Cy: up to eight 21-day cycles



Maintenance therapy: up to four 42-day cycles



- ▶ Prophylactic antibiotics, acyclovir, transfusion support, and anticoagulants as required
- ▶ Eligible patients could undergo ASCT after 4 cycles

Phase I: Dosing

- ▶ Dose escalation of Cy
 - Vc 1.3 mg/m² IV
 - Dex 40 mg PO
 - Rev 15 mg PO
 - Cy 100–500 mg/m² PO

Dose level	Cy dose
1	100 mg/m ²
2	200 mg/m ²
3	300 mg/m ²
4	400 mg/m ²
5	500 mg/m ²

Dose escalation

- ▶ 3+3 dose escalation design, 3–6 patients per dose level
- ▶ Dose escalation depending on dose-limiting toxicities (DLTs):
 - Platelet count $<25,000/\text{mm}^3$ lasting >7 days or any platelet count $<10,000/\text{mm}^3$
 - Grade 4 neutropenia lasting >7 days
 - Grade ≥ 3 non-hematologic toxicity related to Cy (except inadequately treated nausea, vomiting, and diarrhea), or any toxicity resulting in >2 week treatment delay
- ▶ MTD was defined as the highest dose of Cy in combination with VDR resulting in ≤ 1 DLT in 6 patients

Assessments

- ▶ Response assessed every other cycle using IMWG Uniform Response Criteria with the addition of nCR
 - Follow-up assessments of serum and urine protein electrophoresis with immunofixation, and serum free light chains
 - Bone marrow assessment required for CR
- ▶ A central laboratory was used for M-protein and free-light chain quantification, and immunofixation
- ▶ Toxicities graded by NCI CTCAE v3.0

Baseline characteristics

Characteristic	N=25
Median age (range), years	61 (49–79)
Male, n (%)	13 (52)
Myeloma type, n (%)	
IgG	15 (60)
IgA	5 (20)
λ light-chain	3 (12)
κ light-chain	2 (8)
ISS stage at diagnosis, n (%)	
I	12 (48)
II	12 (48)
III	1 (4)
KPS ≤80%, n (%)	11 (44)
Eligible for ASCT at baseline, n (%)	22 (88)

Treatment assignment

Dose level	Enrolled	Treated	Patients undergoing ASCT	Remain on treatment
1 (Cy 100 mg/m ²)	3	3	3	0
2 (Cy 200 mg/m ²)	4	4*	1	0
3 (Cy 300 mg/m ²)	4	4*	1	0
4 (Cy 400 mg/m ²)	8	7**	4	1
5 (Cy 500 mg/m ²)	7	7*	N/A†	5
Total	26	25	9	6

*One patient not evaluable for DLT per protocol

**One patient excluded (did not receive study treatment due to a heart problem), one other patient not evaluable for DLT per protocol

†Patients have not undergone sufficient cycles (4)

MTD and DLTs

- ▶ MTD not reached
 - One DLT at dose level 4 (Cy 400 mg/m²)
 - Grade 4 febrile neutropenia
 - One DLT at dose level 5 (Cy 500 mg/m²)
 - Grade 3 herpes zoster virus reactivation despite antiviral prophylaxis
- ▶ Recommended Phase II dose of Cy was 500 mg/m²

Most common non-hematologic treatment-emergent AEs

AE	N=25	
	All Grades, n (%)	Grade \geq 3, n (%)
Constipation	17 (68)	0
Fatigue	16 (64)	1 (4)
Nausea	13 (52)	1 (4)
Peripheral sensory neuropathy	11 (44)	1 (4)
Diarrhea	9 (36)	1 (4)
Dizziness (excluding vertigo)	9 (36)	0
Peripheral neuropathy NOS	8 (32)	3 (12)
Insomnia	8 (32)	0
Vomiting	8 (32)	1 (4)

- ▶ No deep-vein thrombosis/pulmonary embolism reported

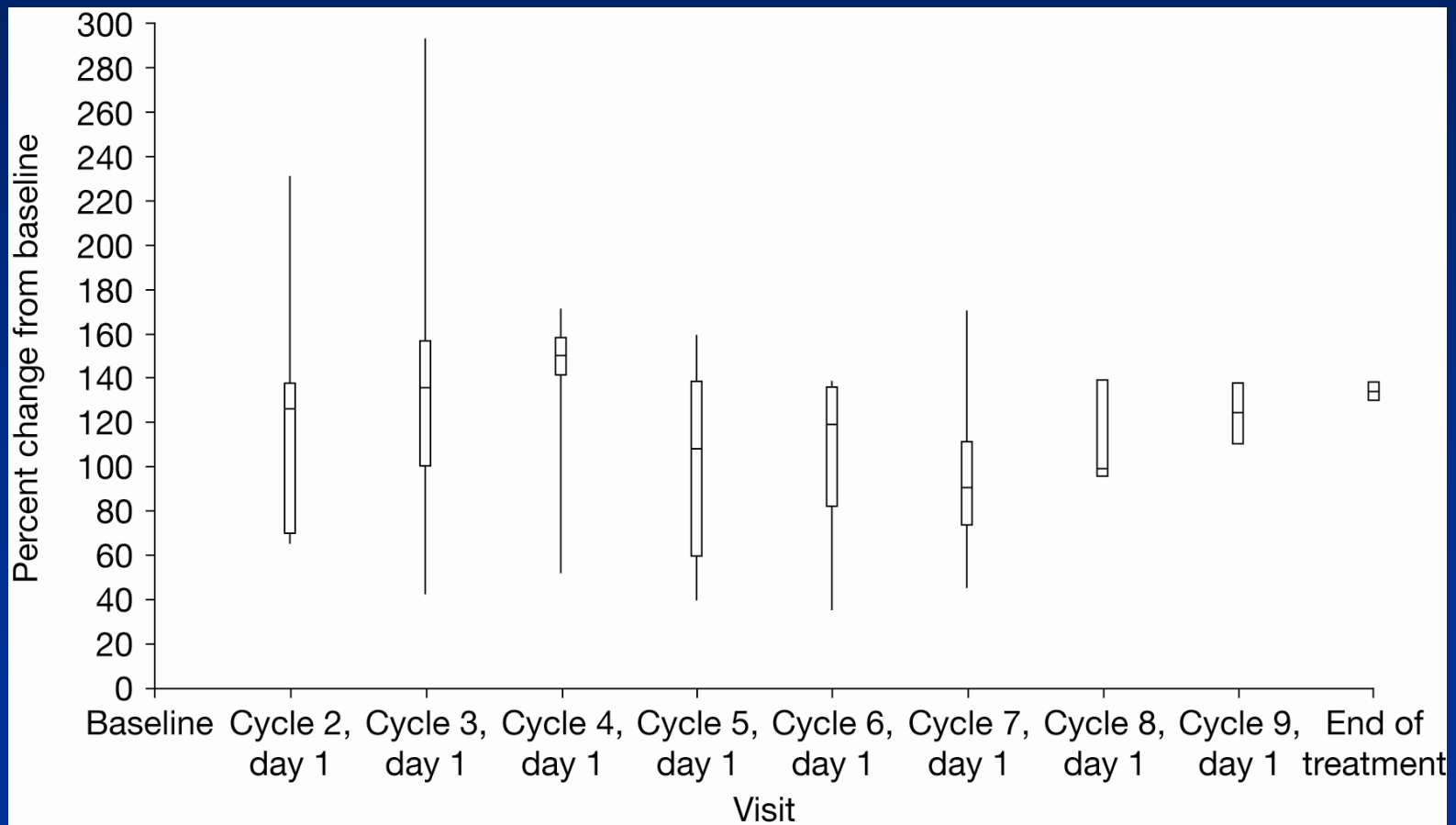
Treatment-emergent hematologic toxicities

	N=25		
Hematologic toxicity	Grade 0–2	Grade 3	Grade 4
Anemia, n (%)	22 (88)	2 (8)	1 (4)
Neutropenia, n (%)*	19 (76)	5 (20)	1 (4)
Thrombocytopenia, n (%)	22 (88)	0	3 (12)

- ▶ 10 patients (40%) had ≥ 1 SAE

No cumulative hematologic toxicity

Change in platelets for patients treated at dose level 5



Best unconfirmed response to treatment

- ▶ Response rates to date (25 Nov 08) in 25 evaluable patients:

Response	n (%)
sCR	5 (20)
≥ CR	9 (36)
≥ VGPR	17 (68)
≥ PR	25 (100)

ORR 100%

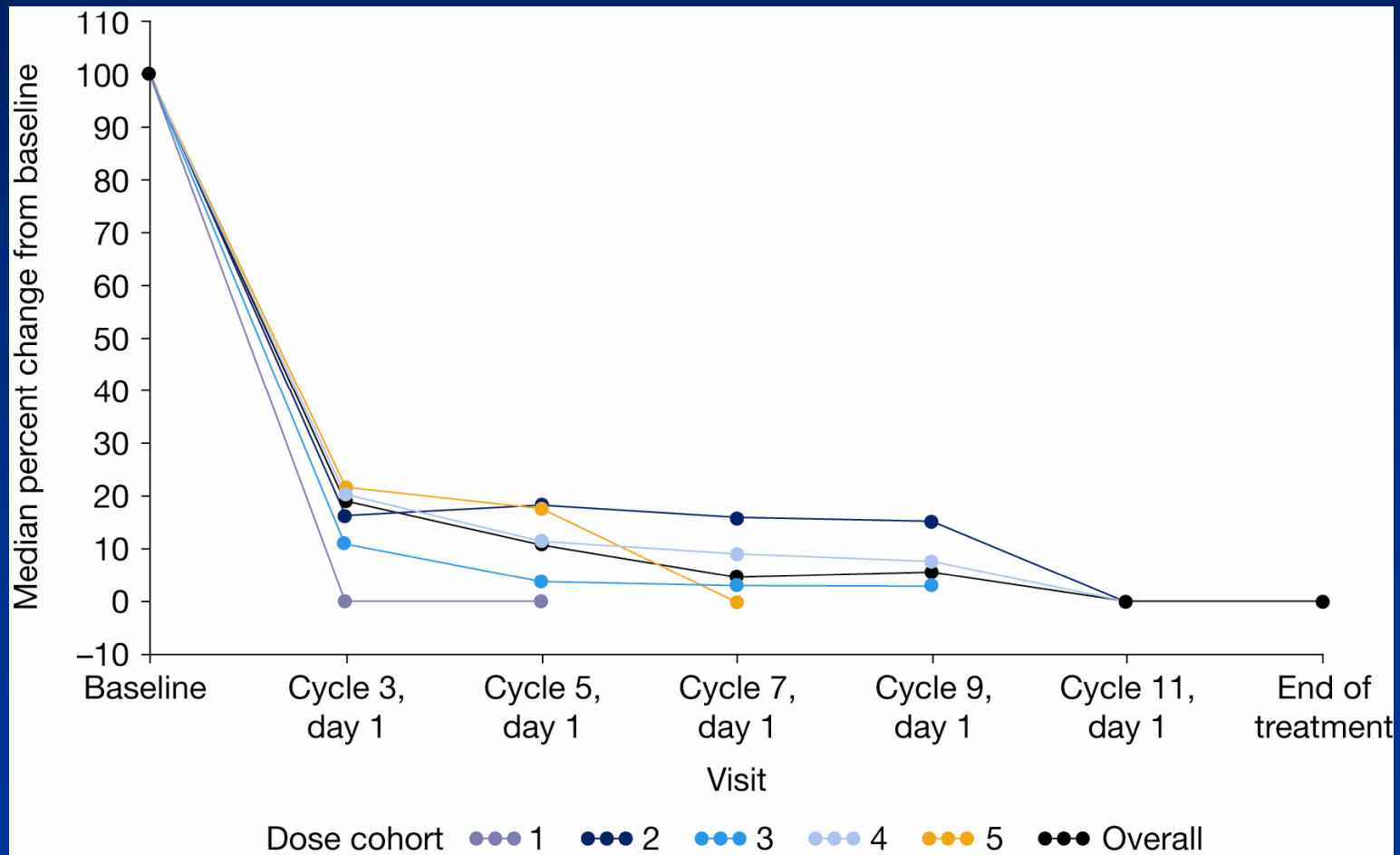
- ▶ Median treatment duration: 6 cycles (range 3–12)

Response by cohort

Best unconfirmed response, N=25

Dose level	Patients	CR (sCR)	VGPR (nCR)	PR
1 (Cy 100 mg/m ²)	3	2 (2)	1	-
2 (Cy 200 mg/m ²)	4	1 (1)	-	3
3 (Cy 300 mg/m ²)	4	2 (1)	2 (1)	-
4 (Cy 400 mg/m ²)	7	2	3	2
5 (Cy 500 mg/m ²)	7	2 (1)	2	3
Total patients	25	9 (5)	8 (1)	8

Change in serum M-protein by cycle



Phase I: Other endpoints

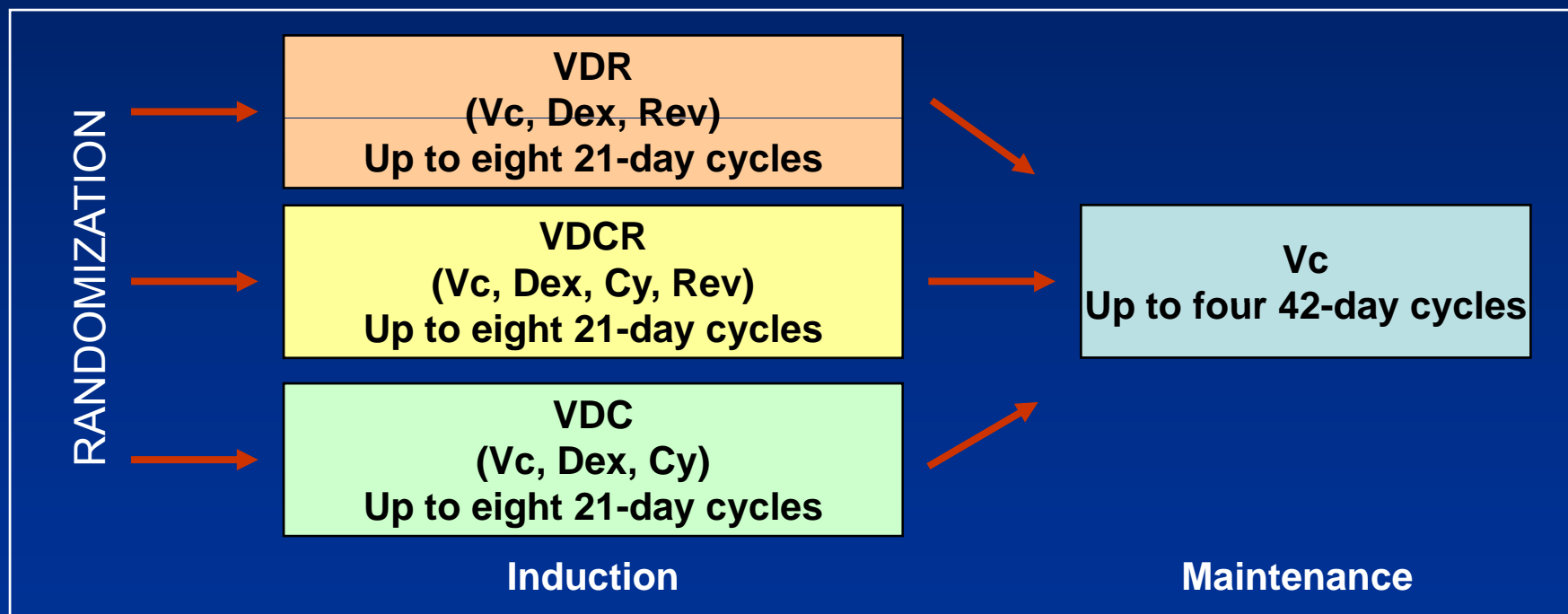
- ▶ Eligible patients could discontinue study therapy to undergo ASCT after 4 cycles
 - 11 patients have undergone stem cell mobilization
 - Median CD34+ yield: $5.9 \times 10^6/\text{kg}$
 - 2 patients required a second cycle of stem cell mobilization
 - 9 patients have discontinued treatment to undergo ASCT

Phase I: Conclusions

- ▶ Phase I: MTD was not reached
 - Recommended Phase II dose of cyclophosphamide is 500 mg/m², the highest dose level tested
- ▶ VDCR is highly active and well tolerated in patients with newly diagnosed MM
 - 100% ≥PR including 68% ≥VGPR, 36% CR/sCR and 20% sCR
 - Hematologic toxicities manageable
 - No reports of deep-vein thrombosis/pulmonary embolism

Phase II: Study design

- ▶ Enrollment to Phase II portion of the study (VDR, VDC, and VDCR arms) is ongoing



- ▶ Eligible patients could undergo ASCT after 4 cycles

Phase II: Dosing and enrollment

Induction	Vc 1.3 mg/m ² Days 1, 4, 8, 11	Dex 40 mg Days 1, 8, 15	Rev Days 1–14	Cy 500 mg/m ² Days 1, 8
VDR	x	x	x (25 mg)	
VDCR	x	x	x (15 mg)	x
VDC	x	x		x
Maintenance		Vc 1.3 mg/m ² Days 1, 8, 15, 22		

- ▶ Vc, Dex and Cy doses and schedules identical in all arms
- ▶ Target enrollment is 39 evaluable patients in each arm
- ▶ 46 patients enrolled in Phase II to date

Phase II: Baseline characteristics

Characteristic	VDR, N=14	VDCR, N=17	VDC, N=15
Median age (range), years	60.5 (47–71)	62 (49–81)	60 (40–75)
Male, n (%)	11 (79)	9 (53)	5 (33)
Myeloma type, n (%)			
IgG	6 (43)	8 (47)	8 (53)
IgA	3 (21)	4 (24)	2 (13)
λ light-chain	0	1 (6)	0
κ light-chain	3 (21)	2 (12)	1 (7)
Unknown	2 (14)	2 (12)	4 (27)
ISS stage at diagnosis, n (%)			
I	6 (43)	6 (35)	6 (40)
II	5 (36)	8 (47)	6 (40)
III	3 (21)	2 (12)	3 (20)
KPS ≤80%, n (%)	7 (50)	7 (41)	3 (20)
Eligible for ASCT at baseline, n (%)	14 (100)	14 (82)	13 (87)

Phase II: Preliminary efficacy and safety data

Stay tuned...