Novel Three- and Four-Drug Combinations of Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide, for Newly Diagnosed Multiple Myeloma: Results from the Multi-Center, Randomized, Phase 2 EVOLUTION Study

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Introduction

- Three-drug regimens adding bortezomib (VELCADE®, V) and dexamethasone (D), to either cyclophosphamide (C), or lenalidomide (Revlimid®, R) have shown significant activity in untreated multiple myeloma (MM)[1–3]
- Combining these agents in a novel 4-drug regimen, VDCR, may result in even greater activity, with improved depth and duration of response
- The randomized Phase 1/2 multi-center EVOLUTION trial designed to investigate VDCR, VDR, and VDC in patients with previously untreated MM

1. Richardson PG *et al*. Clin Lymphoma Myeloma 2009;9:S38 (abstract)
2. Reeder et al, Leukemia, 2008
3. Kumar S *et al*. Blood 2008;112:40a (abstract).

Phase I

- In the phase 1 dose-escalation portion,[1] the MTD of cyclophosphamide in combination with VDR was tested
  - Recommended phase 2 dose of C was 500 mg/m^2, the highest dose tested
- VDCR was highly active and generally well tolerated

1. Kumar S *et al*. Clin Lymphoma Myeloma 2009;9:S43–44 (abstract).

Phase 2 objectives

- Primary objective
  - Determine the combined rate of complete response (CR) plus very good partial response (VGPR) for VDCR, VDR, and VDC
- Secondary objectives include:
  - Safety and tolerability
  - Overall response rate (CR+VGPR+partial response [PR]), stringent CR (sCR) rate, and CR/near-CR (nCR) rate
  - Time to response and duration of response
  - Feasibility of minimal residual disease (MRD) analysis by flow cytometry

Phase 2 treatment schedule

Induction **x 8 3-wk cycles**	V 1.3 mg/m^2 days 1, 4, 8, 11	D 40 mg days 1, 8, 15	C 500 mg/m^2 days 1, 8	R days 1–14
VDCR	x	x	x	x (15 mg)
VDR	x	x		x (25 mg)
VDC	x	x	x	
VDC-mod	x	x	x (+ day 15)	
Maintenance **x 4 6-wk cycles**	V 1.3 mg/m^2 (days 1, 8, 15, 22)			

- Patients received prophylactic antibiotics, acyclovir, transfusion support, and anticoagulants as required

Patients

- Previously untreated MM with measurable disease and Karnofsky Performance Status (KPS) ≥50%
- Patients included regardless of eligibility for ASCT
  - Stem cell mobilization allowed any time after cycle 2 and ASCT any time after cycle 4
- Exclusion criteria included:
  - ANC <1 x 10^9 cells/L
  - Platelets <70 x 10^9 cells/L
  - Renal insufficiency (serum creatinine >2.5 mg/dl)
  - AST/ALT >2 x ULN
  - Total bilirubin >3 x ULN
  - Peripheral neuropathy Grade ≥2 (NCI CTCAE v3.0)

Assessments

- Response assessed every other cycle by IMWG Uniform Response Criteria[1] plus nCR[2]
  - Central laboratory used for serum and urine M-protein and free-light chain quantification, immunofixation, and MRD
- Responses determined using an automated computer algorithm to assure consistent, rigorous assessment of response across all patients
- Toxicities graded by NCI CTCAE v3.0
- Data cut-off: December 1, 2009
  - Median duration of follow-up: 7.3 months

1. Durie BG *et al*. Leukemia 2006;20:1467–73.
2. Richardson PG *et al*. N Engl J Med 2003;348:2609–17.

Baseline characteristics (N=138)

Characteristic	VDCR (N=48)	VDR (N=42)	VDC (N=33)	VDC-mod (N=15)
Median age, years (range)	61.5 (41–81)	60 (42–85)	62 (40–75)	63 (46–72)
Myeloma type*, %				
IgG / IgA	69 / 19	64 / 21	67 / 21	47 / 13
Light chain/ Other	12 / 0	14 / 0	9 / 3	33 / 7
ISS stage, %				
I	33	38	36	47
II	46	43	30	40
III	21	19	33	13
KPS ≤80%, %	31	38	30	47
Eligible for ASCT, %	96	98	94	80

*Myeloma type unknown in 6 patients in the VDCR arm; these patients not included in response-evaluable population

Cytogenetics / FISH

Abnormality, %	VDCR (N=48) %	VDR (N=42) %	VDC (N=32) %	VDC-mod (N=15) %
del 13 / -13q14 (metaphase cytogenetics)	5	5	4	7
t(4;14)	6	2	6	7
t(14;16)	0	0	0	0
-17p13	6	10	16	7
Total high risk	15	17	22	20

Response

Response, %	VDCR (N=41)	VDR (N=42)	VDC (N=32)	VDC-mod (N=15)
CR	**20**	**24**	**22**	**40**
sCR	2	10	3	0
VGPR	39	31	25	20
nCR	12	14	3	0
≥VGPR (sCR + CR + nCR + VGPR)	59	55	47	60
≥nCR (sCR+CR+nCR)	32	38	25	40
≥PR	**93**	**93**	**91**	**93**
Stable disease	7	5	6	7
Progressive disease	0	2	3	0

Patients categorized as VGPR include those who have no measurable M-protein but have not yet had bone marrow assessments to confirm CR/nCR status

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Stem cell mobilization and ASCT

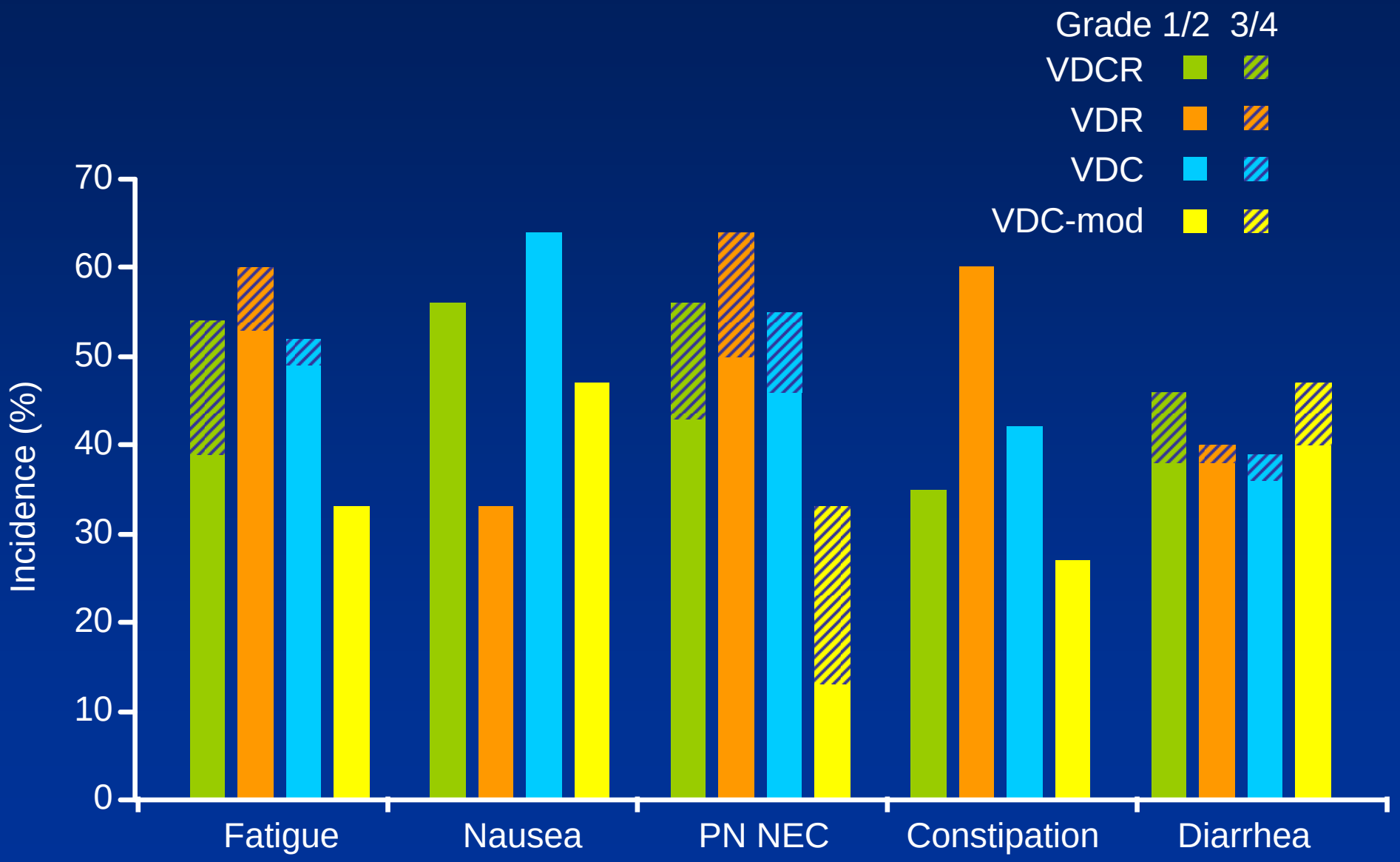
	VDCR	VDR	VDC	VDC-mod
Patients undergoing stem cell mobilization with data available, n	13	18	13	2
Median CD34+ cells yield, x 10^6/kg (range)	8.50 (0.3–11.7)	6.05 (0–26.0)	7.70 (3.1–17.6)	7.30 (4.5–10.1)
Number of patients with <2.5 x 10^6/kg CD34+ cells during first attempt, n (%)	2 (15%)	3 (17%)	0	0
Patients undergoing ASCT with data available, n	11	13	8	0

Safety profile (N=138)

AE, %	VDCR (N=48)	VDR (N=42)	VDC (N=33)	VDC-mod (N=15)
At least one AE	98	100	100	100
At least one grade ≥3 AE	75	76	76	73
At least one serious AE	40	40	21	47
AE resulting in discontinuation	17	17	12	7
On-study deaths	2*	0	0	0

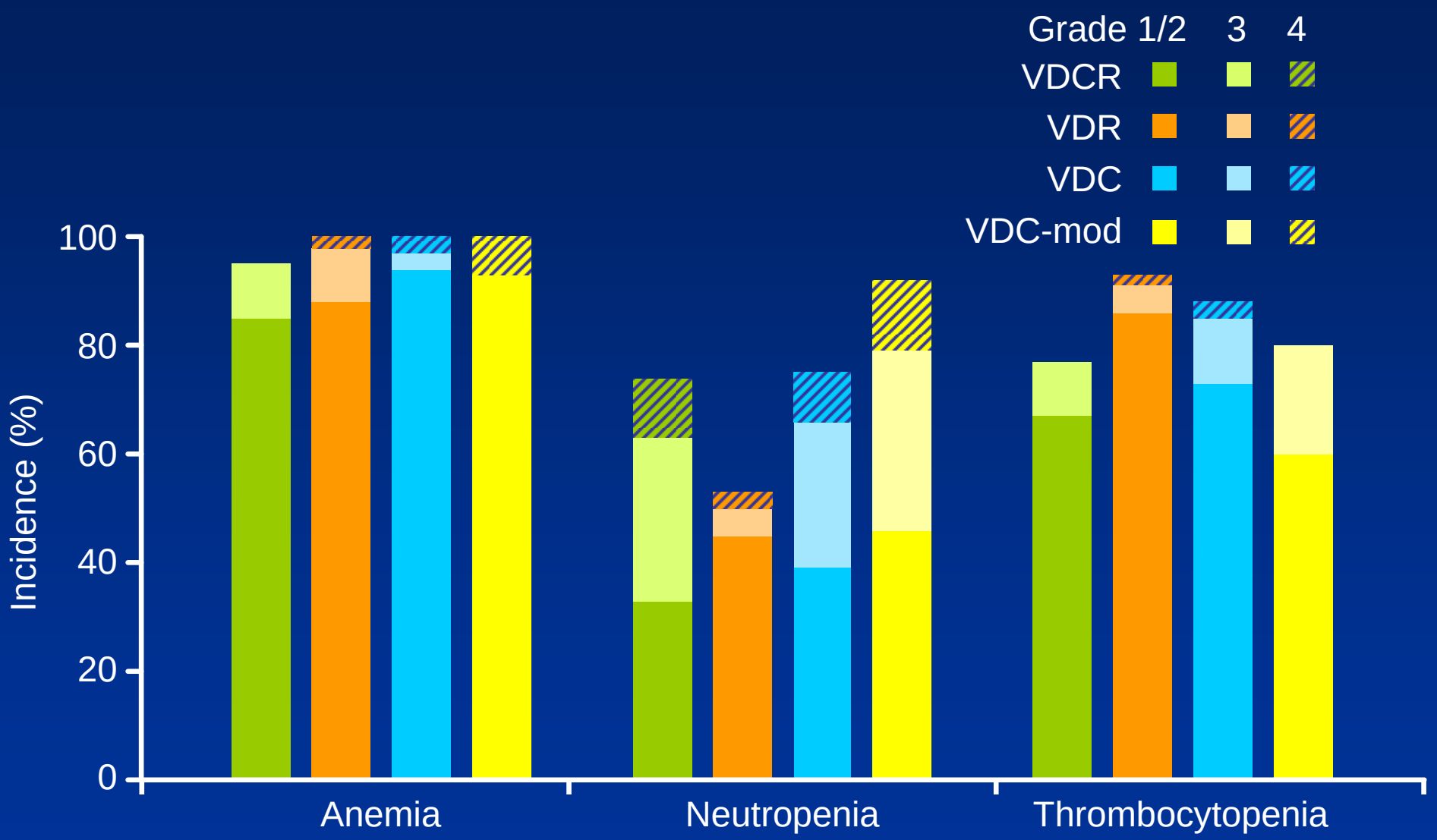
*n=1, due to renal failure considered treatment-related

Most common non-hematologic AEs



PN NEC, peripheral neuropathy not elsewhere classified: high-level term including peripheral sensory neuropathy, peripheral motor neuropathy, and peripheral neuropathy not otherwise specified

Hematologic toxicity



Neutropenia data missing for 2 patients in each of the VDCR and VDR arms

Febrile neutropenia reported in 3 (6%), 1 (2%), 2 (6%), and 0 patients in the VDCR, VDR, VDC, and VDC-mod arms, respectively (all grade 3/4 except 1 in VDCR arm)

MRD assay feasibility in a multicenter study

- Flow cytometry based assessment on marrow aspirates; aspirates collected at screening and at time of suspected CR
- Samples collected in fixative, shipped to central lab for analysis in <48 hr by flow cytometry

Patients enrolled on study	Enrolled pts that submitted screening samples	Percentage
159	154	97%

# post-screen marrows on study	# post-screen marrows submitted for MRD	Percentage
84	62	74%

Conclusions: Efficacy

- VDCR, VDR, and VDC (initial and modified) are highly active and generally well-tolerated regimens in previously untreated MM
  - Best response rates to date, including rates of CR+VGPR, did not appear higher in VDCR than VDR arm
  - A number of patients in each arm remain on treatment, and several pts require marrow assessments to evaluate nCR/CR; so response rates are likely to improve with time, particularly in the VDC-mod arm
- Early responses in the VDC-mod arm, especially CRs and VGPRs are encouraging
- Long term follow up required to assess the MRD status and durability of response

Conclusion: Safety

- Rates of the most common non-hematologic AEs appear generally similar between treatment arms
- Overall rates of most hematologic AEs also appear similar between arms
  - Grade 3/4 neutropenia appeared more frequent with C-containing regimens
- Overall rate of serious AEs appeared to be lower in the initial VDC arm

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