Novel Three- and Four-Drug Combination Regimens of Bortezomib, Dexamethasone, Cyclophosphamide, and Lenalidomide for Previously Untreated Multiple Myeloma: Results from the Multi-Center, Randomized, Phase 2 EVOLUTION Study

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Introduction

◆ Bortezomib (VELCADE[®], V) and dexamethasone (D) combined with cyclophosphamide (C), or lenalidomide (Revlimid[®], R) has significant efficacy in untreated multiple myeloma (MM)[1–3]

◆ Combining these agents in a novel 4-drug regimen, VDCR, may further improve the <u>depth</u> and <u>duration</u> of response

◆ The randomized, phase 1/2, multi-center EVOLUTION trial (NCT00507442) was designed to investigate VDCR, along with the two common, 3-drug regimens, VDR and VDC, in previously untreated MM

1.Richardson PG *et al*. Blood. 2010;116:679–86.
2.Reeder CB *et al*. Leukemia.2009;23:1337–1341.
3.Kumar S *et al*. Blood 2009;114: [Abs. 127].

Phase I

- In the phase 1 dose-escalation portion,[1] the MTD of cyclophosphamide in combination with VDR was evaluated

  - Recommended phase 2 dose of cyclophosphamide was 500 mg/m^2, the highest dose tested

- VDCR was highly active and generally well tolerated

1. Kumar S *et al, Leukemia*. 2010;24:1350–1356.

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 included:

– Safety and tolerability

– Rates of overall response (ORR: CR + VGPR + partial response [PR]), stringent CR (sCR), and CR / near-CR (nCR)

– 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	✓	✓	✓	✓ (15 mg)
VDR	✓	✓		✓ (25 mg)
VDC	✓	✓	✓	
VDC-mod	✓	✓	✓ (+ day 15)	
Maintenance x 4 6-wk cycles	V 1.3 mg/m^2 (days 1, 8, 15, 22)			

- ◆ Patients received standard supportive care including prophylactic acyclovir
- ◆ Stem cell mobilization was allowed any time after cycle 2 and ASCT any time after cycle 4

Patients

- ◆ Untreated MM with measurable disease and Karnofsky Performance Status $\geq$ 50%

- ◆ Patients included regardless of eligibility for ASCT

- ◆ 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 $\geq$ 2 (NCI CTCAE v3.0)[1]

ULN = upper limit of normal

1. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0. http://ctep.info.nih.gov/reporting/ctc.html

Assessments

- Response assessed every other cycle by IMWG Uniform Response Criteria[1] plus nCR[2]

    - Central laboratory used for disease measurements and MRD assessment

- Responses determined using an automated computer algorithm to assure consistent assessment

- Toxicities graded by NCI CTCAE v3.0[3]

- Data cut-off: November 11, 2010

1. Durie BG *et al.* Leukemia 2006;20:1467–73.
2. Blade J *et al.* Br J Haematol 1998;102:1115–23.
3. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0. http://ctep.info.nih.gov/reporting/ctc.html

Baseline characteristics (N = 140)

Characteristic	VDCR (n = 48)	VDR (n = 42)	VDC (n = 33)	VDC-mod (n = 17)
Median age, years (range)	61.5 (41–81)	60 (42–75)	62 (40–75)	63 (40–72)
Myeloma type, %				
IgG / IgA	69 / 17	64 / 21	67 / 21	47 / 12
Light chain / other	15 / 0	14 / 0	9 / 3	35 / 6
ISS stage, %				
I	33	38	33	47
II	46	43	33	35
III	21	19	33	18
Eligible for ASCT, %	96	98	94	82
High risk[‡]	15%	17%	23%	18%

[‡]High-risk defined as any del 13/–13q14 by conventional cytogenetics, any of t(4;14), t(14;16), or –17p13 by conventional metaphase or FISH and hypodiploidy by conventional metaphase cytogenetics analysis.

Patient follow up

	VDCR (n = 48)	VDR (n = 42)	VDC (n = 33)	VDC-mod (n = 17)
Median follow up, months	18.7	19.7	21.2	14.3
Median cycles (range)	5 (1–12)	6 (1–12)	6 (3–12)	6 (3–12)
Completed induction	16 (33)	17 (40)	15 (45)	7 (41)
Completed maintenance	12 (25)	8 (19)	10 (30)	5 (29)
Proceeded to SCT	14 (29)	18 (43)	8 (24)	7 (41)

Time to treatment discontinuation (uncensored)
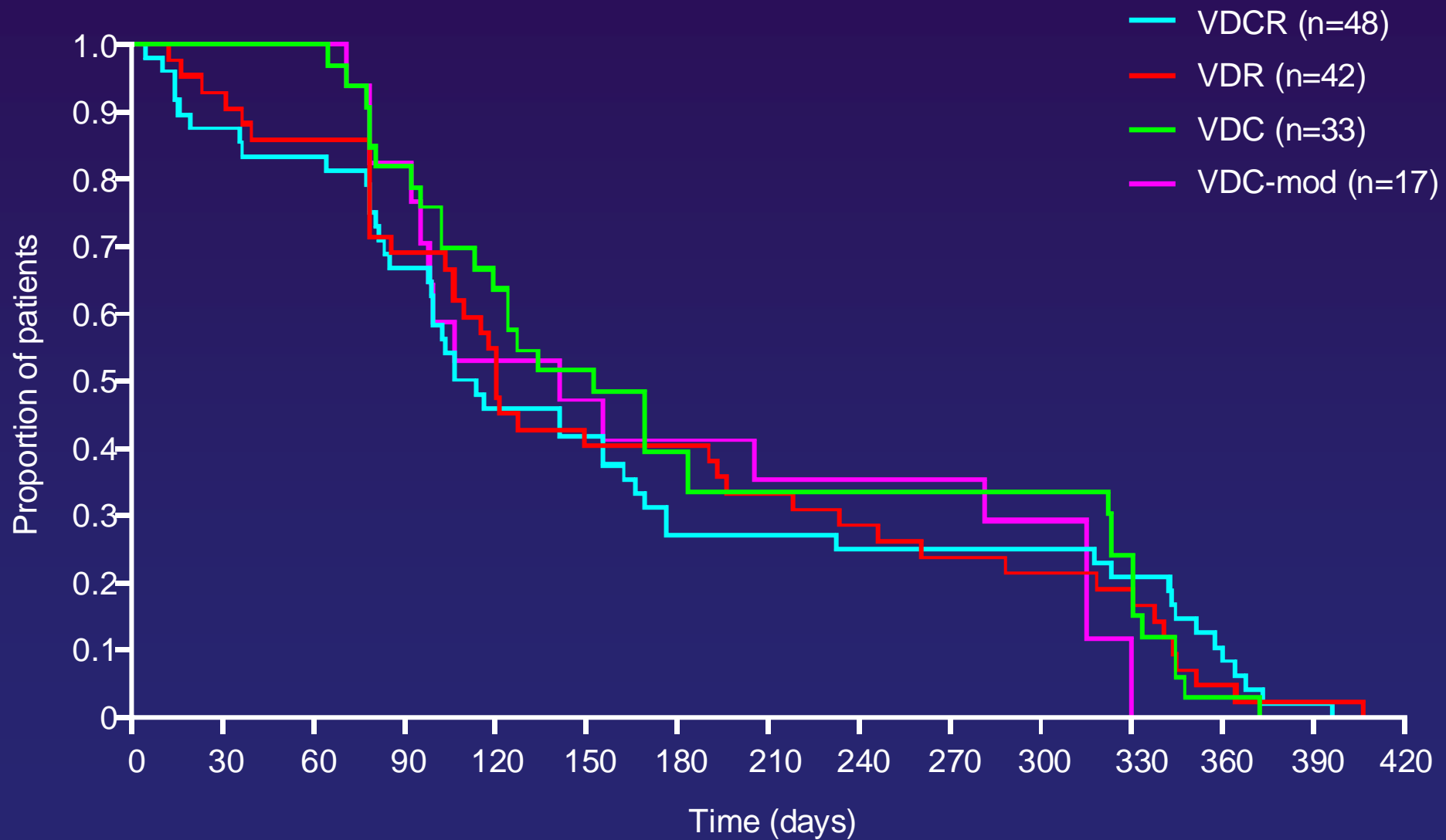
Best confirmed response at 4 cycles

| Response, n (%)	VDCR (n = 42)	VDR (n = 42)	VDC (n = 32)	VDC-mod (n = 17)
CR	2 (5)	3 (7)	1 (3)	2 (12)
sCR	1 (2)	1 (2)	0	2 (12)
VGPR	11 (26)	10 (24)	3 (9)	5 (29)
≥ VGPR	13 (31)	13 (31)	4 (13)	7 (41)
≥ nCR	4 (10)	3 (7)	1 (3)	3 (18)
ORR (≥ PR)	33 (79)	30 (71)	20 (63)	14 (82)
Progressive disease	0	0	0	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
Response determined according to automated computer algorithm

Best confirmed response across all cycles

Response, n (%)	VDCR (n = 42)	VDR (n = 42)	VDC (n = 32)	VDC-mod (n = 17)
CR	10 (24)	10 (24)	7 (22)	8 (47)
sCR	6 (14)	8 (19)	3 (9)	5 (29)
VGPR	14 (33)	11 (26)	6 (19)	1 (6)
≥ VGPR	24 (57)	21 (50)	13 (41)	9 (53)
≥ nCR	14 (33)	14 (40)	10 (31)	8 (47)
ORR (≥ PR)	36 (86)	35 (83)	24 (75)	17 (100)
Progressive disease	1 (2)	1 (2)	1 (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
Response determined according to automated computer algorithm

Safety profile (N = 140)

AE, n (%)	VDCR (n = 48)	VDR (n = 42)	VDC (n = 33)	VDC-mod (n = 17)
At least 1 grade ≥ 3 AE	40 (83)	32 (76)	26 (79)	15 (88)
AE resulting in discontinuation	10 (21)	8 (19)	4 (12)	1 (6)
On-study deaths	2 (4)	0	0	0

Most common non-hematologic AEs
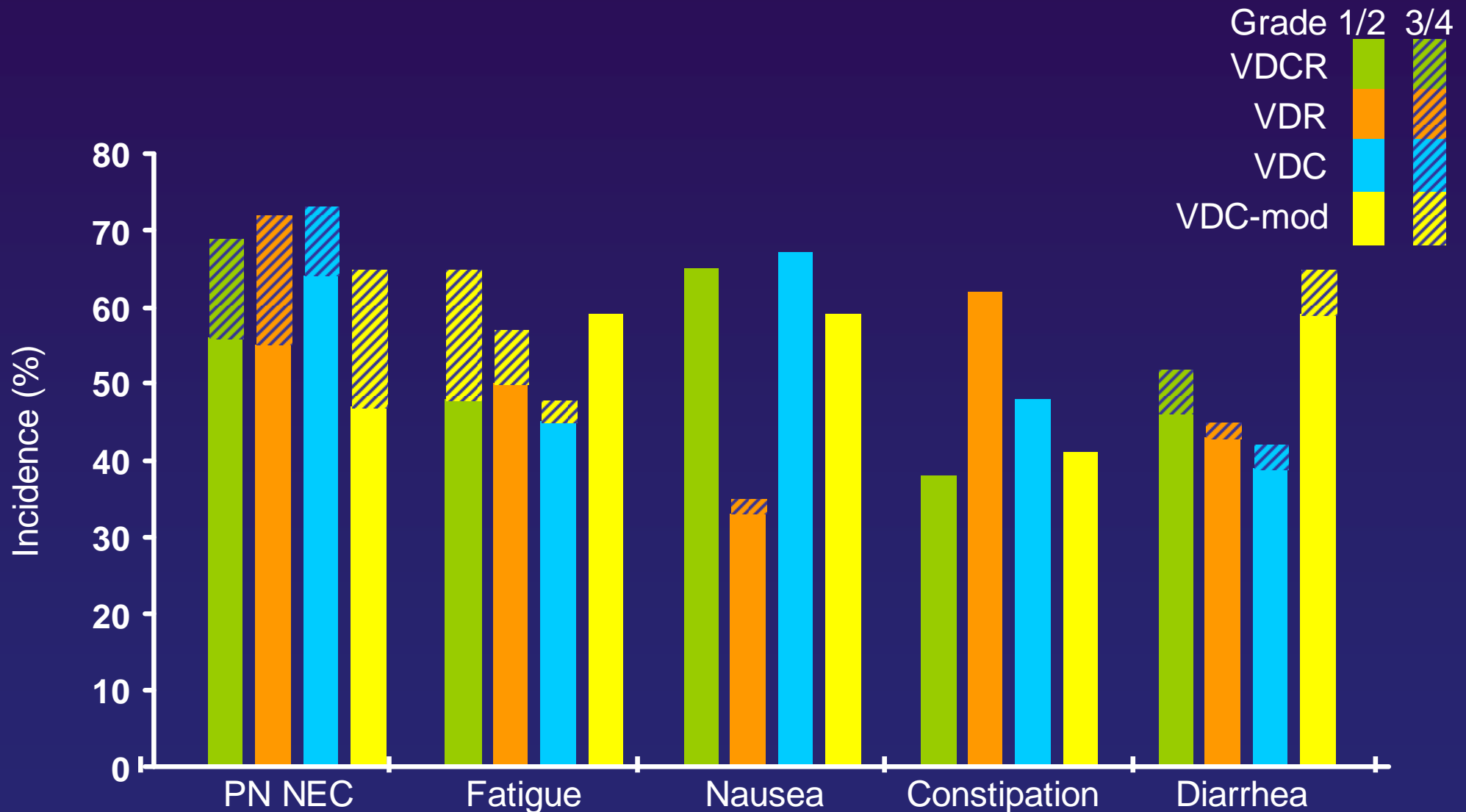
PN NEC, peripheral neuropathy not elsewhere classified: high-level term including peripheral sensory neuropathy, peripheral motor neuropathy, and peripheral neuropathy not otherwise specified

Hematologic toxicity
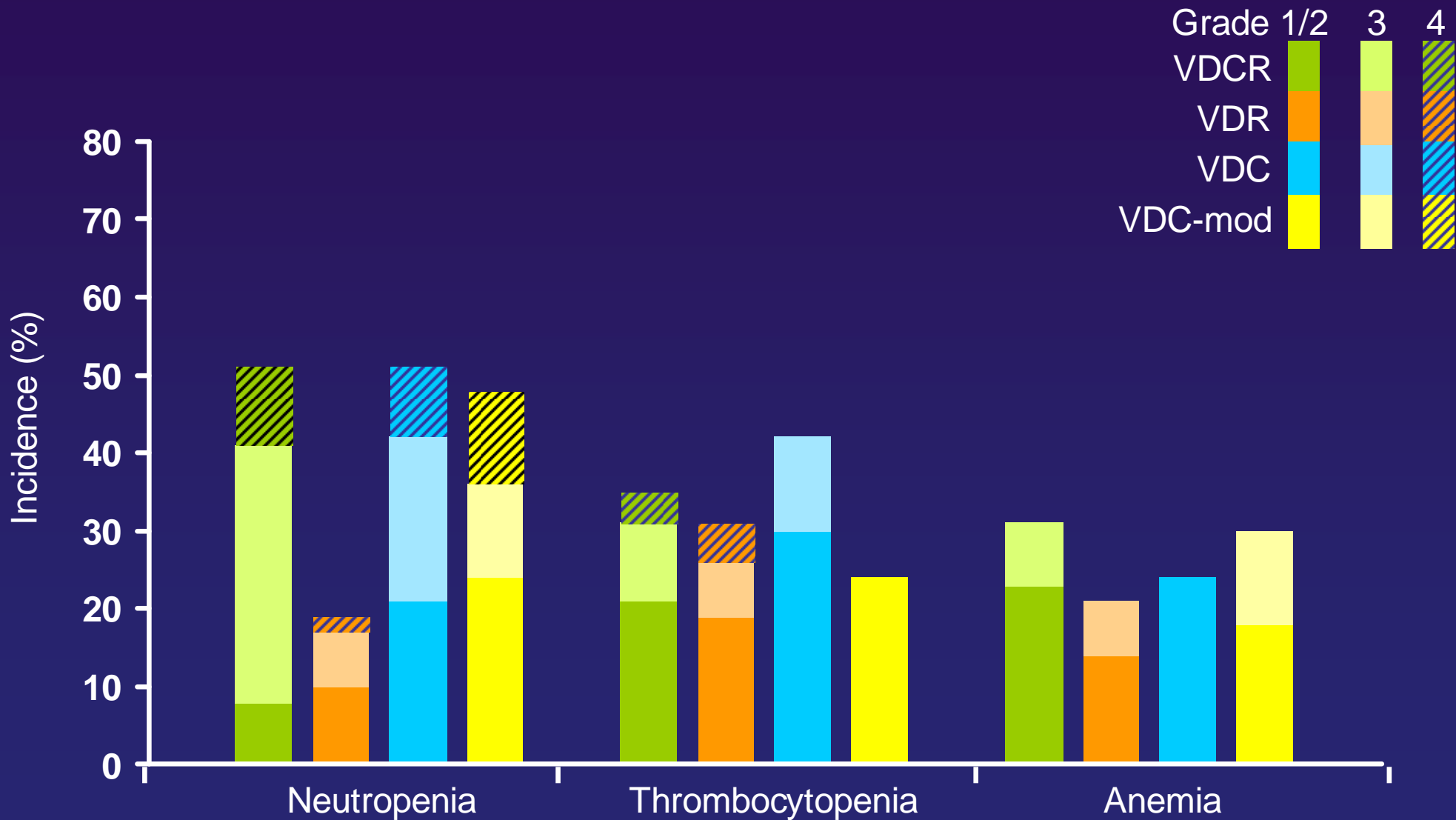
Febrile neutropenia reported in 8 (12%), 1 (2%), 2 (6%), and 1 (6%) patients in the VDCR, VDR, VDC, and VDC-mod arms, respectively (all grade 3/4 except 1 in VDCR arm and 1 in VCD-mod arm)

Stem cell mobilization and ASCT

	VDCR (n = 48)	VDR (n = 42)	VDC (n = 33)	VDC-mod (n = 17)
Patients undergoing stem cell mobilization with data available, n (%)	25 (52)	26 (62)	14 (42)	10 (59)
Median CD34+ cells yield, x 10^6/kg (range)	6.8 (0.3–21)	7.8 (2.2–25.9)	7.95 (3.1–17.6)	7.75 (2.1–20)
Patients with < 2.5 x 10^6/kg CD34+ cells during first attempt, n (%)	4 (8)	3 (7)	0	2 (12)
Patients undergoing ASCT with data available, n (%)	20 (42)	19 (45)	10 (30)	10 (59)

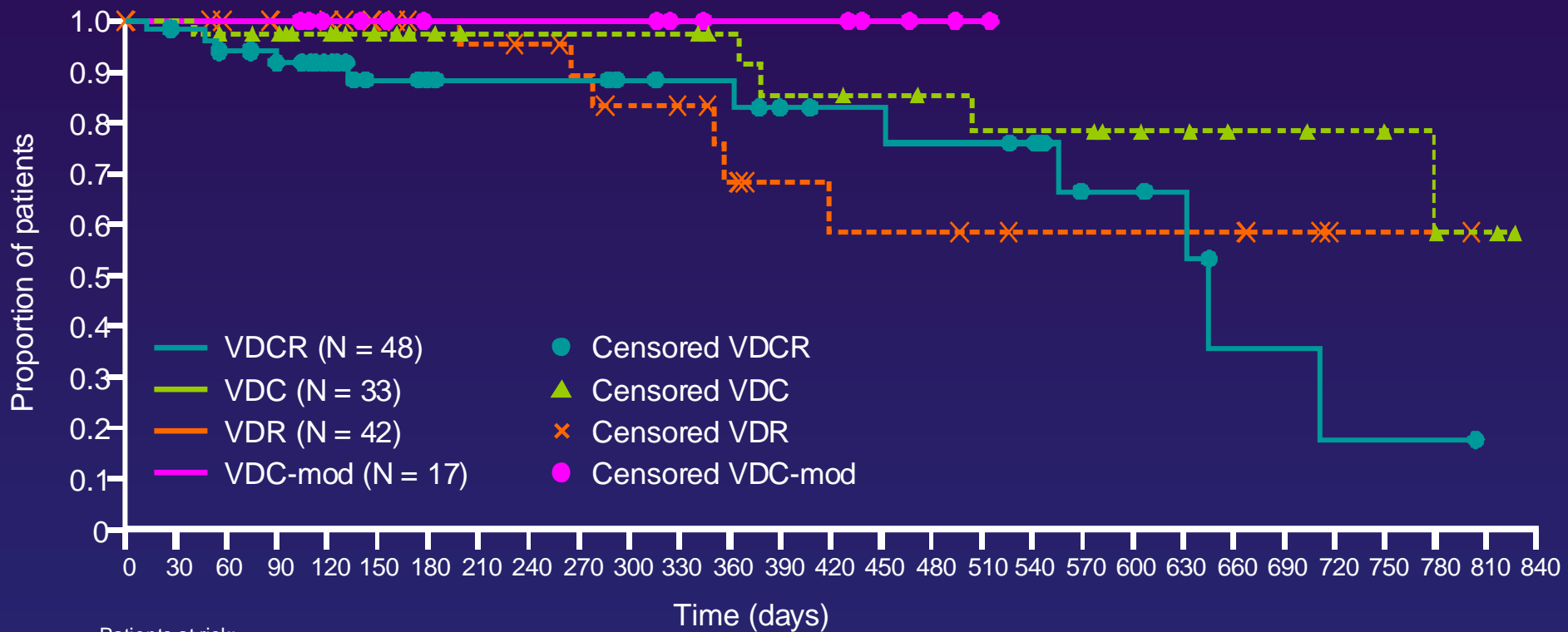# Progression free survival (uncensored for transplant)

	VDCR (n = 48)	**VDR** (n = 42)	**VDC** (n = 33)	**VDC-mod** (n = 17)
Median PFS, days (range)	710 (1*–802*)	NE (1*–800*)	NE (41–825*)	NE (178*–515*)
PFS at 1 year, %	85	83	93	100

*censored observation
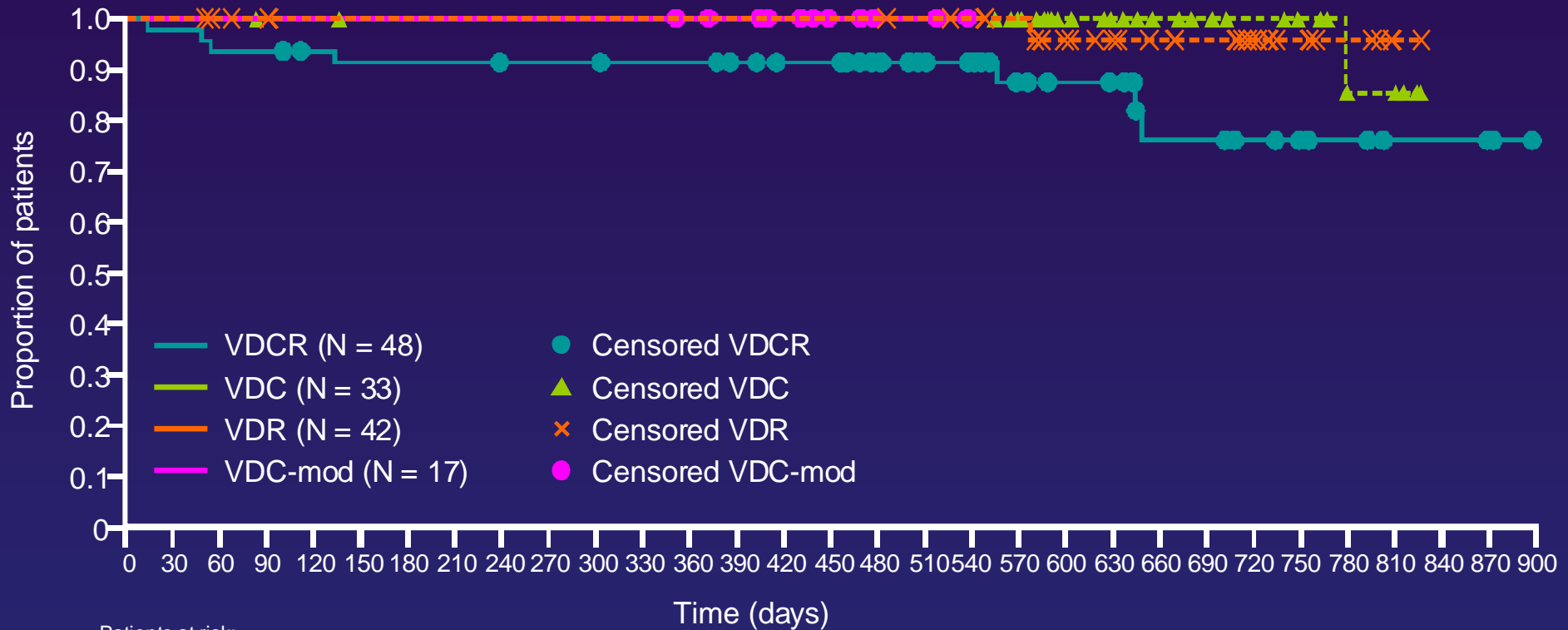
Progression free survival (censoring at transplant)

	VDCR (n = 48)	**VDR** (n = 42)	**VDC** (n = 33)	**VDC-mod** (n = 17)
Median PFS, days (range)	644 (1*–802*)	NE (1*–800*)	NE (41–825*)	NE (104*–515*)
PFS at 1 year, %	82	68	97	100

*censored observation

Overall survival

	VDCR (n = 48)	VDR (n = 42)	VDC (n = 33)	VDC-mod (n = 17)
Survival at 1 year, %	92	100	100	100
Survival at 2 years, %	76	96	100	NE

Outcomes in patients < 65 years

Best confirmed response, n (%)	VDCR (n = 27)	VDR (n = 27)	VDC (n = 20)	VDC-mod (n = 11)
CR	6 (22)	6 (22)	2 (10)	6 (55)
sCR	4 (15)	4 (15)	0	4 (36)
VGPR	9 (33)	10 (37)	3 (15)	1 (9)
≥ VGPR	15 (56)	16 (59)	5 (25)	7 (64)
≥ nCR	8 (30)	12 (44)	4 (20)	6 (55)
ORR (≥ PR)	22 (81)	24 (89)	14 (70)	11 (100)
Stable disease	2 (7)	1 (4)	4 (20)	0
Progressive disease	1 (4)	1 (4)	0	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
5 patients were not evaluable
Response determined according to automated computer algorithm

Detection of minimal residual disease

- ◆ Flow cytometry based assessment of marrow aspirates from screening and suspected CR

- ◆ Samples in fixative, shipped to central lab for analysis in < 48 hr

- ◆ CD38, CD45, CD138, CD19, CD56, kappa / lambda

Patients enrolled on study	Enrolled pts that submitted screening samples	Percentage
159	155	97%

# patients ≥ CR in expansion arms	# ≥ CR patients that submitted MRD sample	
35	28	80%

MRD negativity across arms

Response by algorithm (overall population), n (%)	VDCR (n = 42)	VDR (n = 42)	VDC (n = 32)	VDC-mod (n = 17)	TOTAL
CR	10 (24)	10 (24)	7 (22)	8 (47)	35
MRD sampling					
Patients ≥CR providing MRD sample, n (%)	10 of 10 (100)	7 of 10 (70)	4 of 7 (57)	7 of 8 (88)	28
Patients ≥CR MRD –ve, n (%)	5 of 10 (50)	6 of 7 (85)	0 of 4 (0)	2 of 7 (29)	13 of 28 (46)

Conclusions

◆ Of the four regimens studied, VDC (mod) and VDR appear highly active with reasonable toxicity profile representing excellent induction regimens

◆ VDCR and VDC (initial) while effective do not appear to have any striking advantages over VDR and VDC (mod) in efficacy or toxicity

◆ Phase III studies should compare VDR and VDC (mod), and assess the impact of the differences in VGPR, MRD-negative state and PFS seen here

Additional Conclusions

◆ Among those who provided samples, almost half of the patients with ≥CR were MRD negative

◆ Rates of the most common non-hematologic AEs appear generally similar between treatment arms

◆ Overall rates of most hematologic AEs also appear largely similar between arms

    – Grade 3/4 neutropenia appeared more frequent with C-containing regimens

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