Carfilzomib, Cyclophosphamide and Dexamethasone (KCd) Versus Bortezomib, Cyclophosphamide and Dexamethasone (VCd) For Treatment of First Relapse or Primary Refractory Multiple Myeloma (MM): First Final Analysis of the Phase 2 MUK *five* Study

Kwee L Yong, Samantha Hinsley, Holger Auner, Debbie Sherratt, Ruth M de Tute, Sarah Brown, Louise Flanagan, Catherine Williams, Jamie Cavenagh, Martin F Kaiser, Neil Rabin, Karthik Ramasamy, Mamta Garg, Stephen Hawkins, Ceri Bygrave, Gareth Morgan, Faith Davies and Roger G Owen

on behalf of the MUK five investigators and Myeloma UK Early Phase Clinical Trial Network

ctru University of Leeds
NHS National Institute for Health Research
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MyelomaUK
UNIVERSITY OF LEEDS
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MUK *five:* **Background**

- Three proteasome inhibitors are licensed for the treatment of multiple myeloma: bortezomib, carfilzomib and ixazomib

- Head-to-head comparisons of carfilzomib with bortezomib have used differing dosing schedules in different patient groups
  - **ENDEAVOR** in Relapsed disease: Carfilzomib 20/56mg/m2 + Dex ***vs*** Bortezomib + Dex (Doublet, extended therapy)
  - **CLARION** in ND NTE MM: Carfilzomib 20/36mg/m2 + Melphalan + Prednisolone (MP) ***vs*** Bortezomib + MP (Triplet, nine cycles)

- We designed MUK *five* to assess anti-myeloma activity of carfilzomib versus bortezomib in triplet regimen with Cyclo + Dex at second line only

MUK *five:* **Design**

Randomisation* 2:1 (n=300)

*Stratified by:
- Previous Bortezomib
- β2 microglobulin
- Previous ASCT
- Time from diagnosis

KCd (n=201) 6 cycles of 28 days (24 weeks)

Carfilzomib	IV	20mg/m²* 36 mg/m²	Days 1, 2, 8, 9, 15, 16
Cyclophosphamide	Oral	500mg	Days 1, 8, 15
Dexamethasone	Oral	40 mg	Days 1, 8, 15, 22

*cycle 1, days 1 and 2 only

VCd (n=99) 8 cycles of 21 days (24 weeks)

Velcade (bortezomib)	SC	1.3mg/m²	Days 1, 4, 8, 11
Cyclophosphamide	Oral	500mg	Days 1, 8, 15
Dexamethasone	Oral	40 mg	Days 1, 8, 15

Randomisation 1:1 (n=141)
Participants with ≥ stable disease

Carfilzomib maintenance (n=69)
for up to 18 months
6 cycles of 28 days:
36mg/m² days 1, 2, 15, 16
then 12 cycles of 28 days:
36mg/m² days 1, 2

No maintenance therapy (n=72)

Primary endpoint (KCd vs. VCd)

≥VGPR at 24 weeks

Non-inferiority (NI) comparison KCd vs. VCd

NI margin of 5% (i.e. allowing KCd to be up to 5% worse)

Designed assuming ≥VGPR = 35% VCd, 45% KCd

MUK *five:* **Inclusion/exclusion criteria**

Key inclusion criteria

- MM patients at first relapse, or refractory to 1 prior line of therapy
- ECOG 0-2
- Hb≥ 80g/L, neutrophils ≥1.0x10^9/L, platelets ≥75x10^9/L
- GFR ≥20ml/min
- LVEF ≥40%

Key exclusion criteria

- Significant co-morbidity or cardiovascular disease (NYHA Class III/IV heart failure, myocardial infarction within 6 months))
- Uncontrolled hypertension
- Previous carfilzomib therapy
- Previous refractory to bortezomib (<PR or progression within 6 months of last dose)
- Significant neuropathy (G≥3 or G2 with pain) within 14 days

MUK *five:* **Objectives**

Two Co-Primary Endpoints

- ≥VGPR rate at 24 weeks (non-inferiority activity of KCd)
- PFS (superiority of maintenance treatment with Carfilzomib post-KCd vs no maintenance post-KCd)

Secondary Endpoints

- Key: Rate of ≥G3 neuropathy or ≥G2 neuropathy with pain during the initial treatment period
- Safety, toxicity, overall response, overall survival, time to next treatment
- MRD at end of treatment and after 6 and 12 months of maintenance
- Correlation of treatment outcomes with genetic subgroups

MUK *five:* **Patient and disease characteristics**

Stratification factors

		KCd (n=201) n (%)	VCd (n=99) n (%)	Total (n=300) n (%)
Previous bortezomib		44 (21.9)	21 (21.2)	65 (21.7)
Previous ASCT		133 (66.2)	67 (67.7)	200 (66.7)
β2 microglobulin	<3.5 mg/L	120 (59.7)	57 (57.6)	177 (59.0)
	3.5 to ≤5.5 mg/L	53 (26.4)	27 (27.3)	80 (26.7)
	>5.5 mg/L	28 (13.9)	15 (15.2)	43 (14.3)

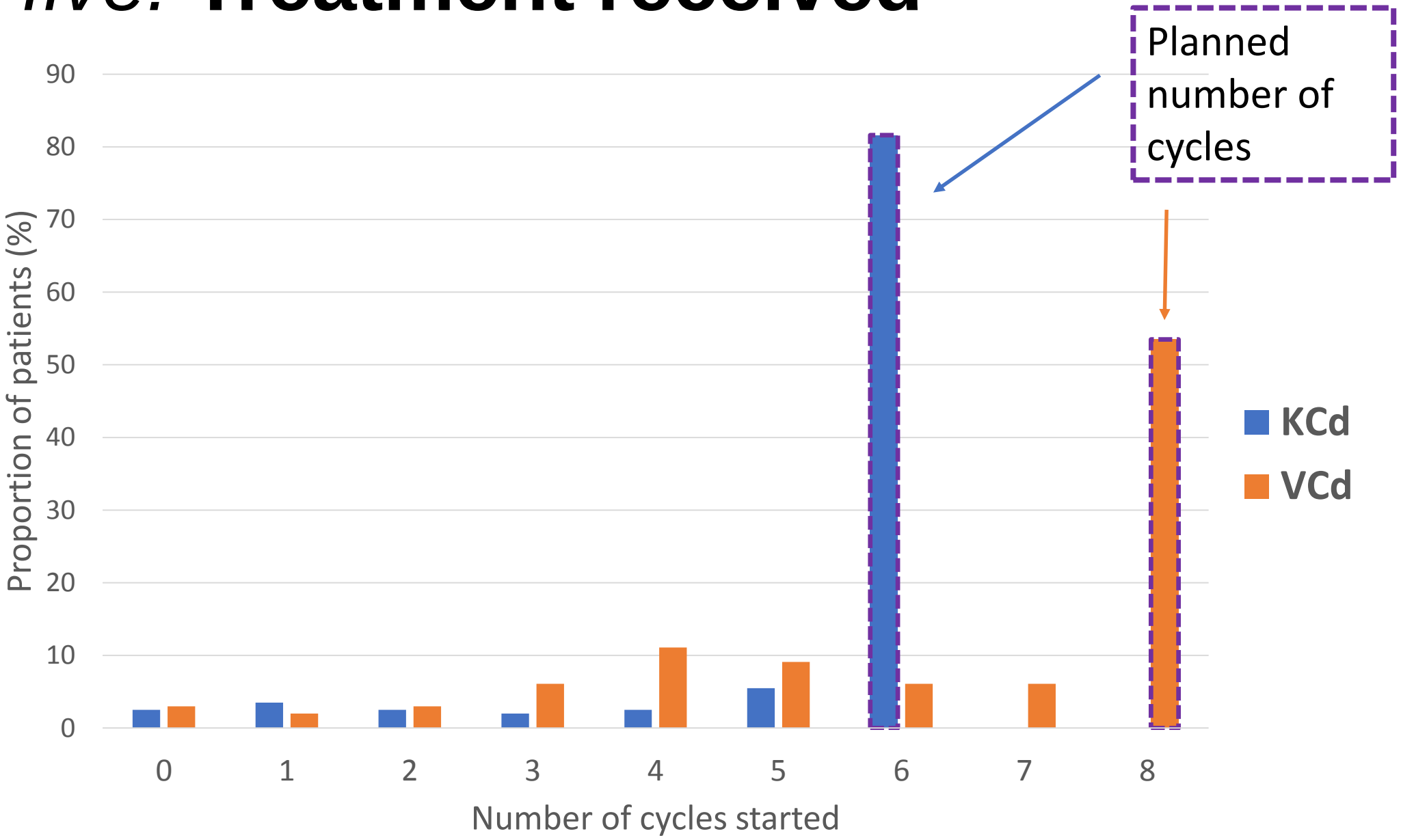
MUK *five:* **Patient and disease characteristics**

	KCd (n=200)*	VCd (n=99)	Total (n=299)
Age: Median (years)	67	69	68
≥75 years	37 (18.4%)	21 (21.2%)	58 (19.3%)
Male	115 (57.5%)	64 (64.6%)	179 (59.9%)
ECOG PS 0-1	187 (93.5%)	94 (94.9%)	281 (94.0%)
Median time since diagnosis (months)	32.5	36.1	33.7
Median time from last tmt (months)	20.1	20.5	20.2
ISS II / III	100 (50.0%)	45 (45.5%)	145 (48.5%)
Creatinine clearance <30mL/min	2 (1.0%)	2 (2.0%)	4 (1.3%)
Received previous autograft	133 (66.2%)	67 (67.7%)	200 (66.7%)
High risk disease**	44/87 (50.6%)	26/50 (52.0%)	70/137 (51.1%)

*No baseline data received for one participant found to be ineligible after randomisation

**At least one of del(17p), gain(1q), t(4;14), t(14;16), t(14;20). Available in 46% of patients.

MUK *five:* **Treatment received**

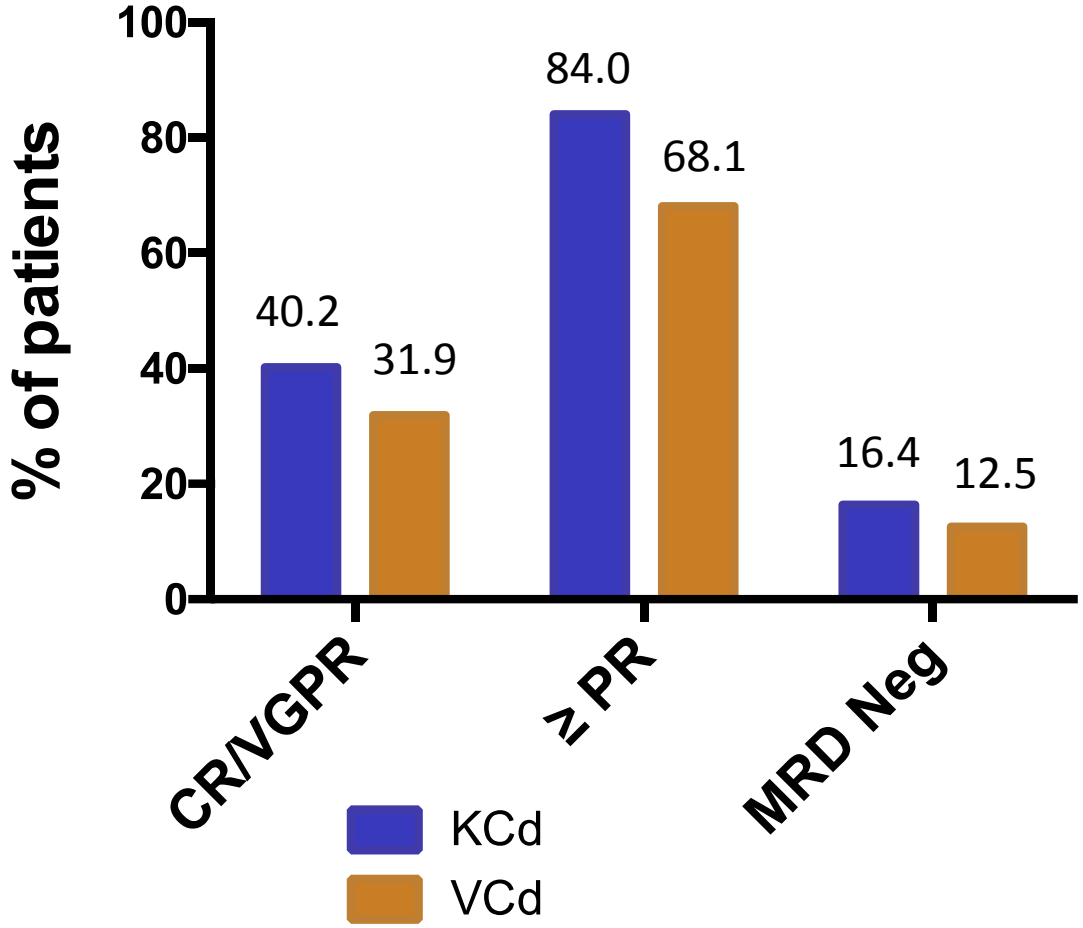


MUK *five:* **Treatment discontinuation reasons**

Reasons for not receiving planned number of cycles	KCd (n=201) (%)	VCd (n=99) (%)	Total (n=300) (%)
Clinician decision	6 (3.0)	11 (11.1)	17 (5.7)
Unacceptable toxicity	11 (5.5)	18 (18.2)	29 (9.7)
Disease progression	12 (6.0)	5 (5.1)	17 (5.7)
Withdrew consent	5 (2.5)	9 (9.1)	14 (4.7)
Patient died	4 (2.0)	1 (1.0)	5 (1.7)
Other	3 (1.5)	1 (1.0)	4 (1.3)
Total	41 (20.4)	45 (45.4)	86 (28.7)

MUK *five:* **Response at 24 weeks**

PRIMARY ENDPOINT MET

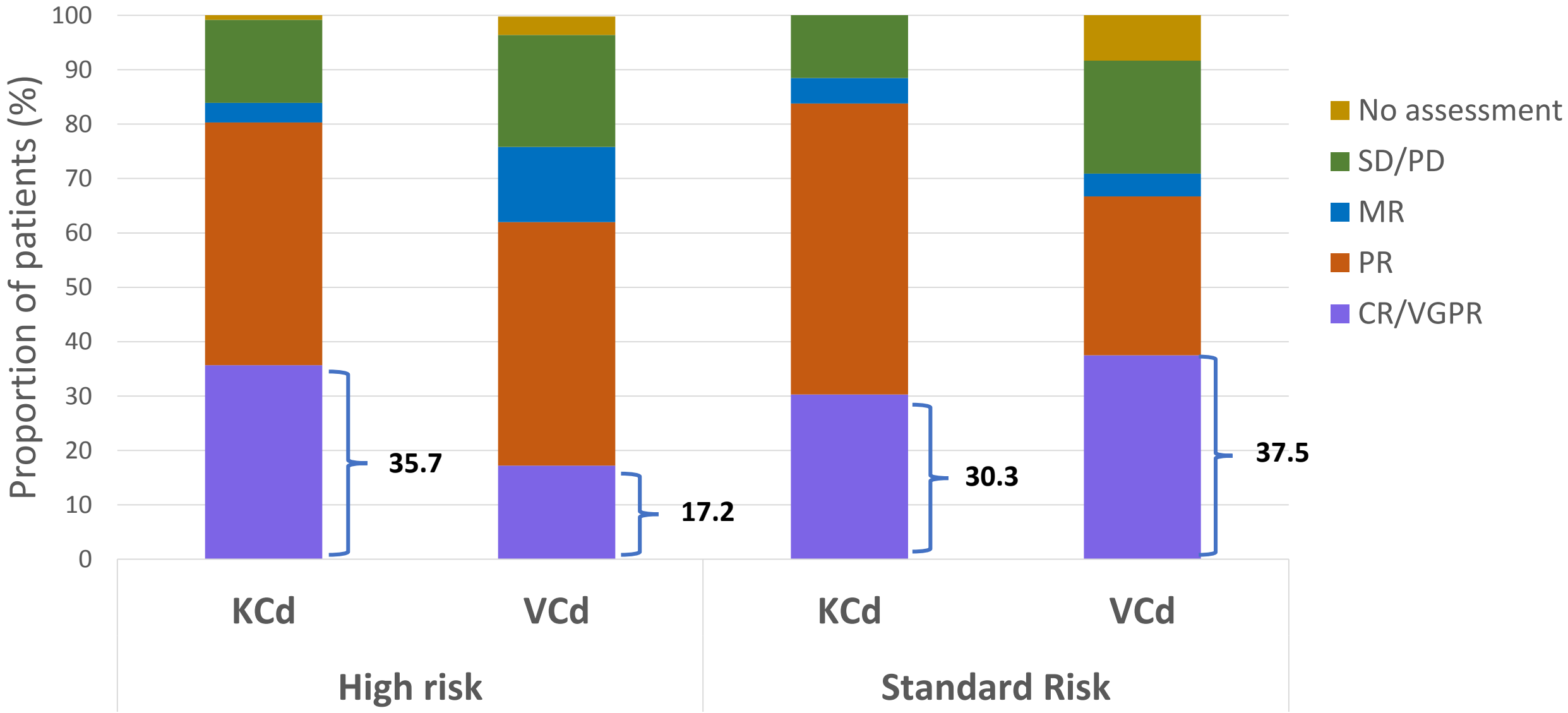


CR/VGPR Difference: 8.3, 90% CI: (-1.6, 18.2)
Odds Ratio (OR): 1.48, 90% CI: (0.95, 2.31)
NON-INFERIOR

Overall response rate
Odds Ratio: 2.72, 90% CI: (1.62, 4.55)
SUPERIOR (p=0.0014)

MRD Negativity
Odds Ratio: 1.40, 90% CI: (0.61, 3.24)
(Total N=134 KCd; 48 VCd)

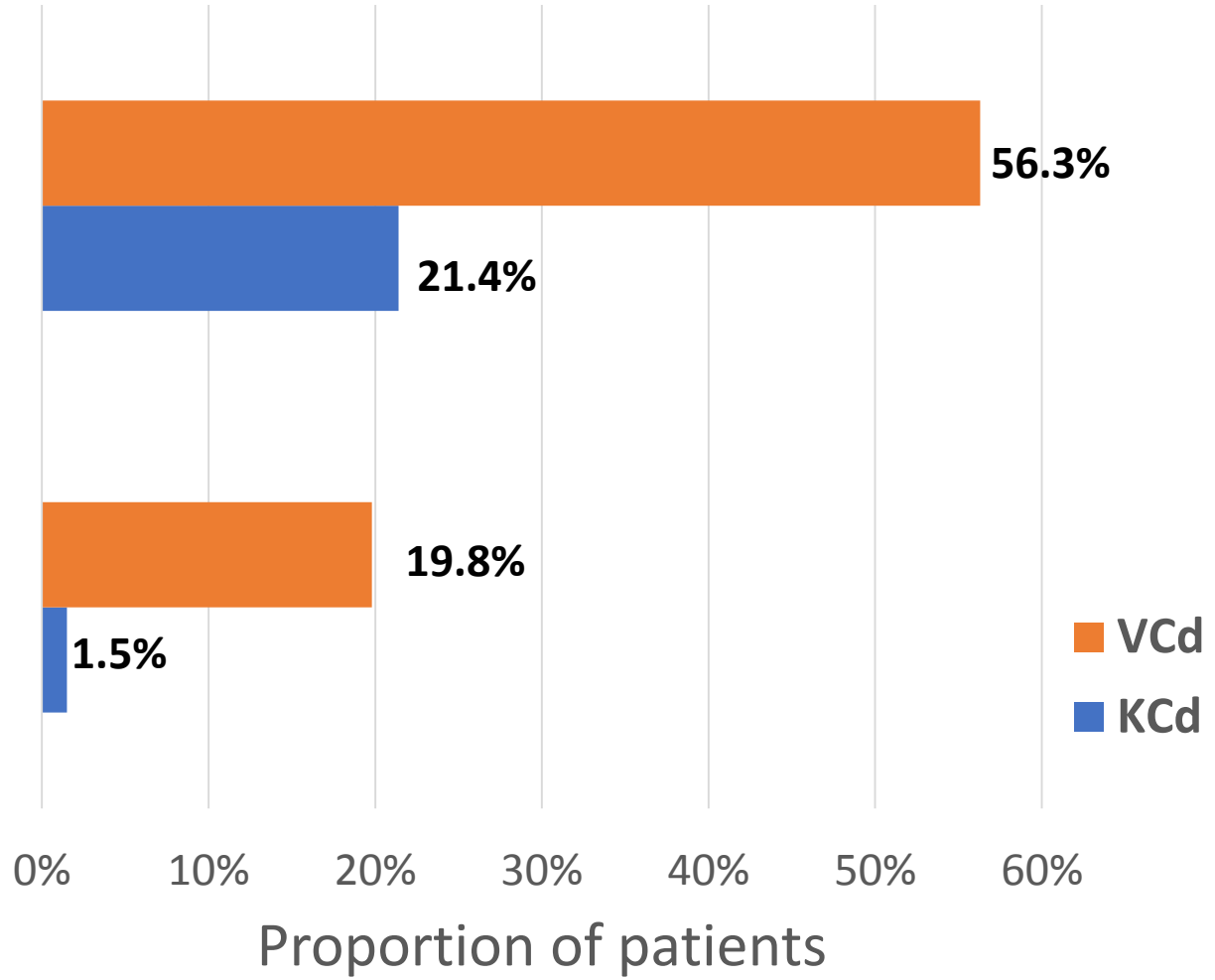
MUK *five:* Response at 24 weeks by genetic risk



MUK *five:* **Neuropathy**

Treatment emergent neuropathy

Key secondary endpoint:
≥G3 neuropathy or ≥G2 neuropathy with pain



Difference: -18.3%
95% CI: (-26.4, -10.1)
p<0.0001

MUK *five:* **Safety and toxicity: SAEs**

	KCd (n=196)	VCd (n=96)
Number of SAEs	142	74
Number of patients with an SAE	88 (44.9%)	45 (46.9%)
Proportion of SAEs categorized as:		
Neurological	0.7%	8.1%
Cardiac	4.2%	1.4%
Renal and urinary	3.5%	5.4%
Gastrointestinal	7.7%	5.4%
Infections	51.4%	47.3%

MUK *five:* **Safety and toxicity: ARs of interest**

	KCd (n=196)	VCd (n=96)
Proportion of patients with each AR type:		
Cardiac (all grades)	17 (8.7%)	8 (8.3%)
Cardiac (≥ Grade 3)	6 (3.7%)* ←	0 (0%)
Grade ≥3 neutropenia	11.3%	21.9% ←
Grade ≥3 thrombocytopenia	11.8%	36.5% ←
Grade ≥3 anaemia	16.8% ←	10.4%
Grade ≥3 infections	12.8%	16.7%
Grade ≥2 hypertension	4.1% ←	2.1%

*Dilated cardiomyopathy, acute coronary syndrome, arrhythmia, myocardial infarction, hypertension, other

MUK *five:* **Summary and Conclusions**

- MUK *five* is the third head-to-head study comparing carfilzomib and bortezomib, and the second study in the relapsed setting
- Carfilzomib meets the primary endpoint of non-inferiority in ≥VGPR rate
- Overall response rate (≥PR) was higher in patients receiving carfilzomib
  - This was the case for both high and standard risk patients
- 81.6% of patients completed KCd treatment compared to 53.5% for VCd
- Adverse events were consistent with known toxicity profile of each drug
  - More neurotoxicity with bortezomib but more cardiac AE's with carfilzomib
- Additional follow up is needed for evaluation of extended K treatment and PFS readout

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MUK five participants

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Martin F Kaiser

Leeds HMDS
Ruth M de Tute
Roger G Owen

Leeds CTRU
Samantha Hinsley
Debbie Sherratt
Sarah Brown
Louise Flanagan
Paul McGarry
Saqib Saghir
Sue Bourne
Emma Ingleson
Katie Robinson
Alan Wan
Wendy Burton
Diane Hartley
Matthew Newby
Lucy Bailey
Suja George
Rachel Naylor
Walter Gregory
Alex Szubert
Jenny Fell

Trial Steering Committee
Chris Twelves
Simon Rule
Tomasz Burzykowski
Michael Brown

Data Monitoring and Ethics Committee
Alan Anthoney
Graham Jackson
James Wason

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