Carfilzomib or bortezomib in combination with cyclophosphamide and dexamethasone followed by carfilzomib maintenance for patients with multiple myeloma after one prior therapy: results from a multicenter, phase II, randomized, controlled trial (MUK*five*)

Kwee L. Yong,[1]* Samantha Hinsley,[2]* Holger W. Auner,[3] Ceri Bygrave,[4] Martin F. Kaiser,[5] Karthik Ramasamy,[6] Ruth M. de Tute,[7] Debbie Sherratt,[2] Louise Flanagan,[2] Mamta Garg,[8] Stephen Hawkins,[9] Catherine Williams,[10] Jamie Cavenagh,[11] Neil K. Rabin,[12] James Croft,[5] Gareth Morgan,[13] Faith Davies,[13] Roger G. Owen[14] and Sarah R. Brown[2]

[1]Cancer Institute, University College London, London, UK; [2]Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK; [3]Department of Immunology and Inflammation and The Hugh and Josseline Langmuir Centre for Myeloma Research, Imperial College London, London, UK; [4]Cardiff and Vale University Health Board, Cardiff, UK; [5]The Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust, London, UK; [6]Department of Clinical Haematology, Oxford University Hospitals NHS Trust, Oxford, UK; [7]Department of Clinical Haematology, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [8]Department of Haematology, University Hospitals of Leicester NHS Trust, Leicester, UK; [9]The Clatterbridge Cancer Centre, Liverpool, UK; [10]Centre for Clinical Haematology, Nottingham University Hospitals, Nottingham, UK; [11]Department of Haematology, St Bartholomew's Hospital, London, UK; [12]Department of Haematology, University College Hospital, London, UK; [13]Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA and [14]Haematological Malignancy Diagnostic Service (HMDS), St James's University Hospital, Leeds, UK

**KLY and SH contributed equally as co-first authors.*

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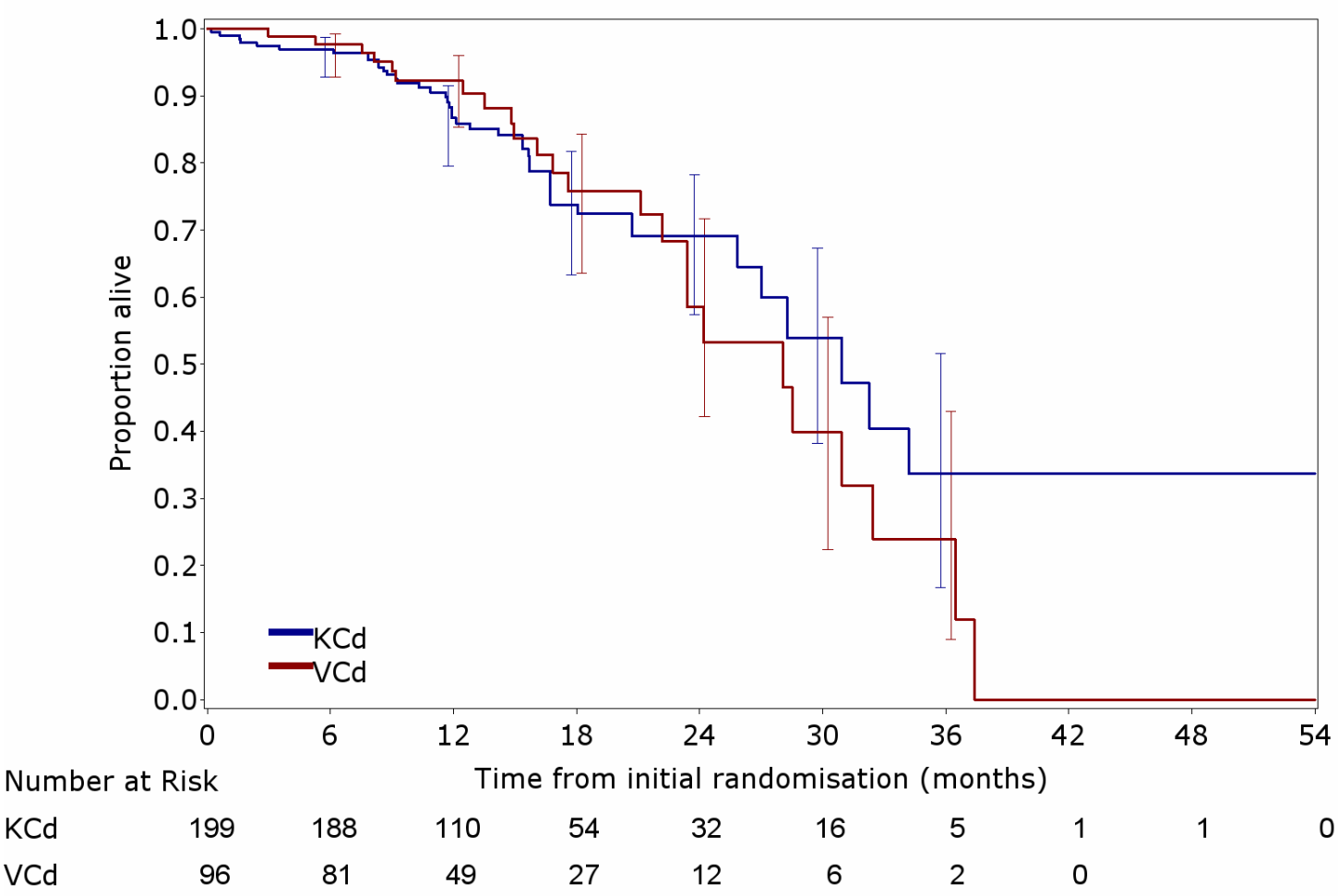
Correspondence: *KWEE L YONG* - kwee.yong@ucl.ac.uk

Supplementary Figures and Tables

Figure S1. Weighted overall survival from initial randomisation



Number at Risk										
KCd	199	188	110	54	32	16	5	1	1	0
VCd	96	81	49	27	12	6	2	0		

Figure S2. Dynamics of MRD status during maintenance vs observation

104 participants had evaluable samples at randomisation to maintenance; at 6 months 75 participants had an evaluable sample or had progressed. In the maintenance arm, 5/8 MRD negative patients remained MRD negative at 6 months, while only 1/10 MRD negative patients in the control arm remained MRD negative; 4 of 40 MRD positive patients who received maintenance became MRD negative at 6 months, while no MRD positive patients in the control arm became MRD negative.

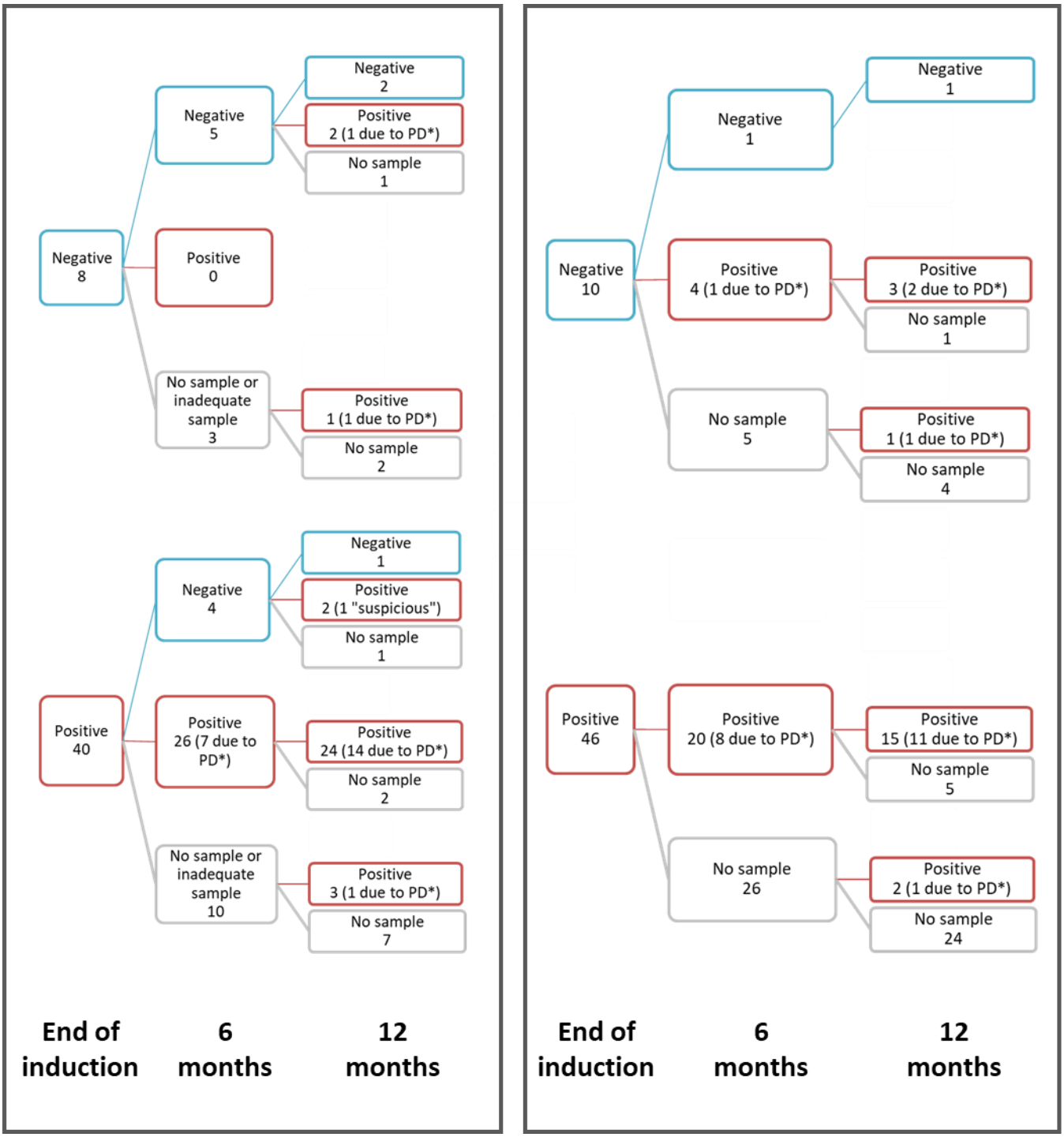
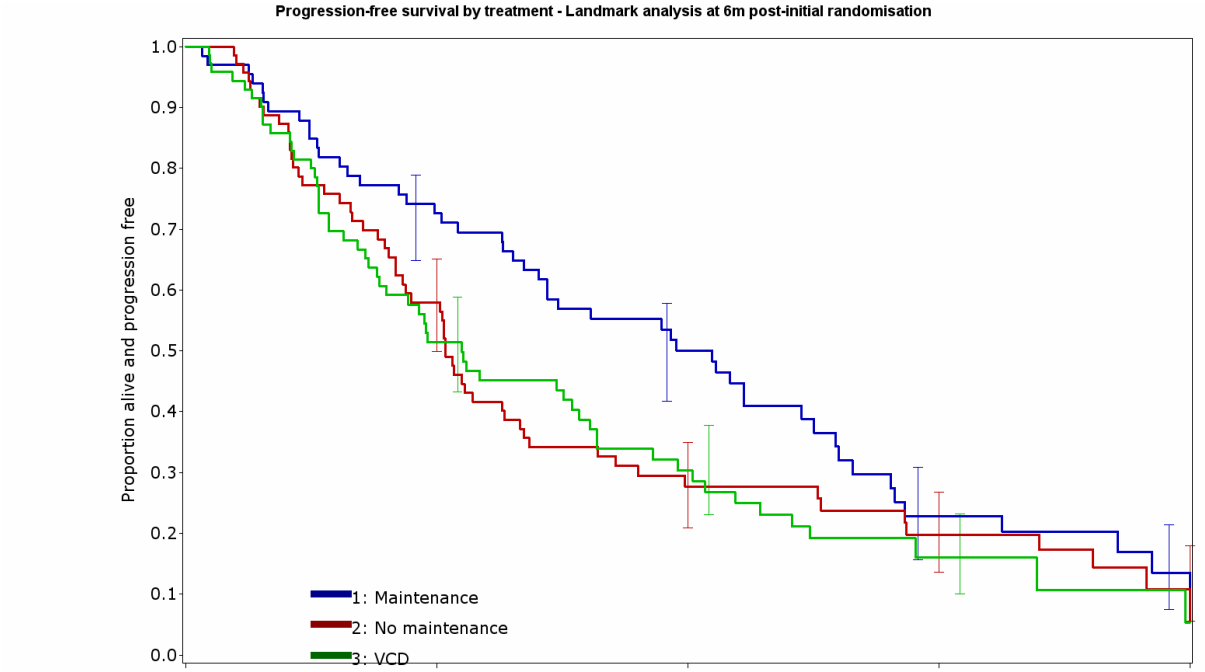


Figure S3. Landmark analysis of PFS at 6 months post first randomisation

A post-hoc landmark analysis was performed at 6 months post first randomisation, to assess PFS for those patients who had not progressed at this time, comparing VCD with KCD plus maintenance, and KCD with no maintenance.



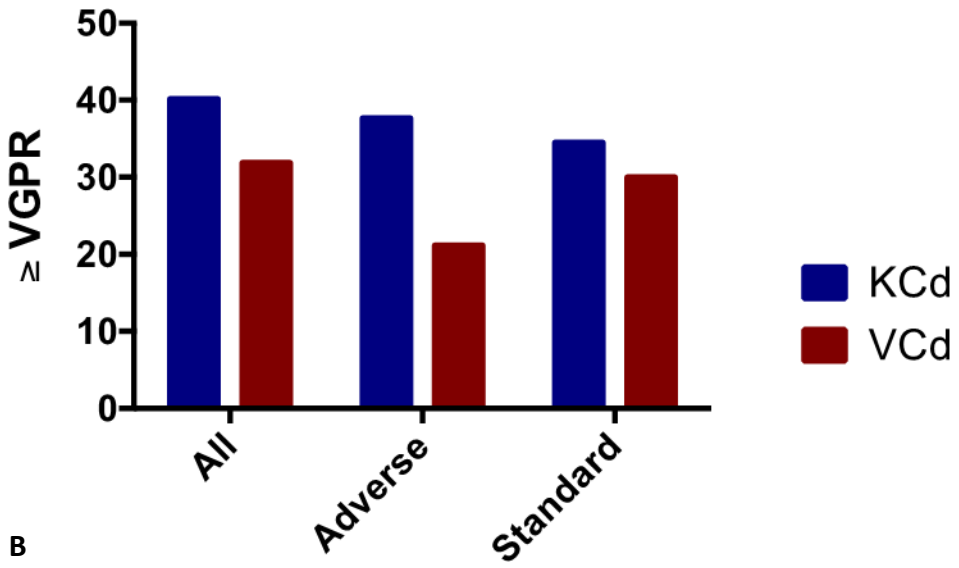
Number at Risk	0	6	12	18	24
1: Maintenance	66	47	29	10	4
2: No maintenance	71	39	16	10	2
3: VCD	72	33	17	5	1

Figure S4. At least VGPR rate at end of induction by genetic risk, and treatment arm

A. ≥VGPR rate (%) according to adverse or standard risk

B. ≥VGPR rate (%) according to particular high risk lesion, numbers in bars indicate number of patients in each subgroup. None of the 8 patients with del(17p) who received VCd achieved at least VGPR

A



B

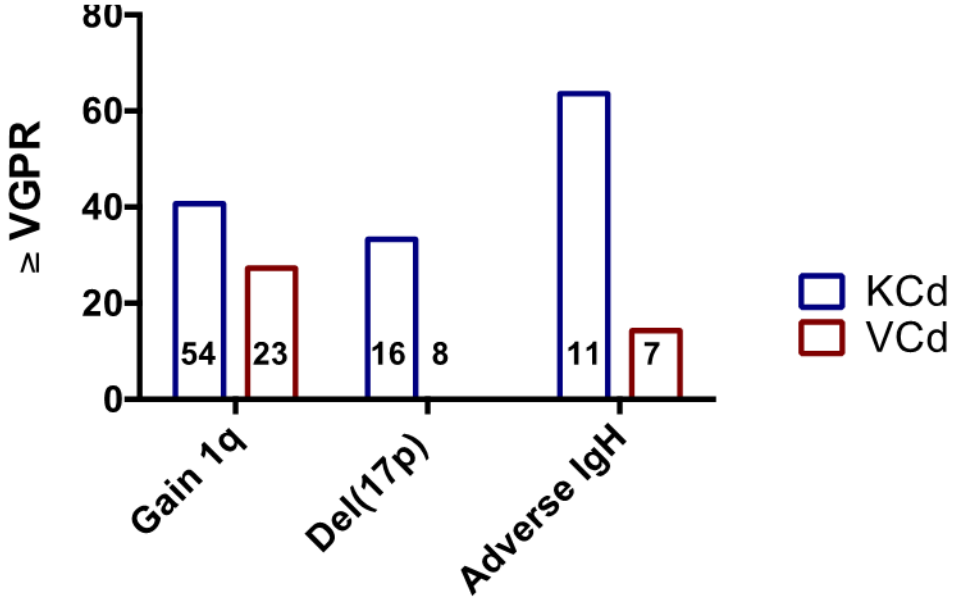
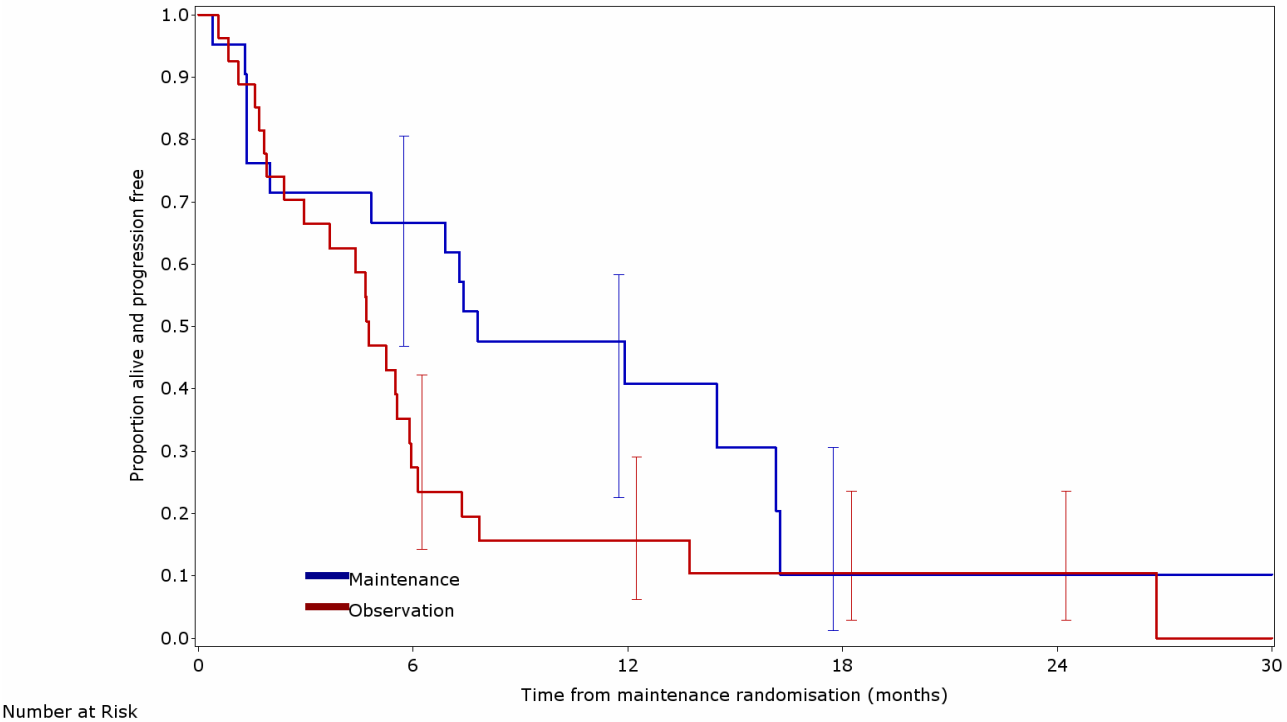


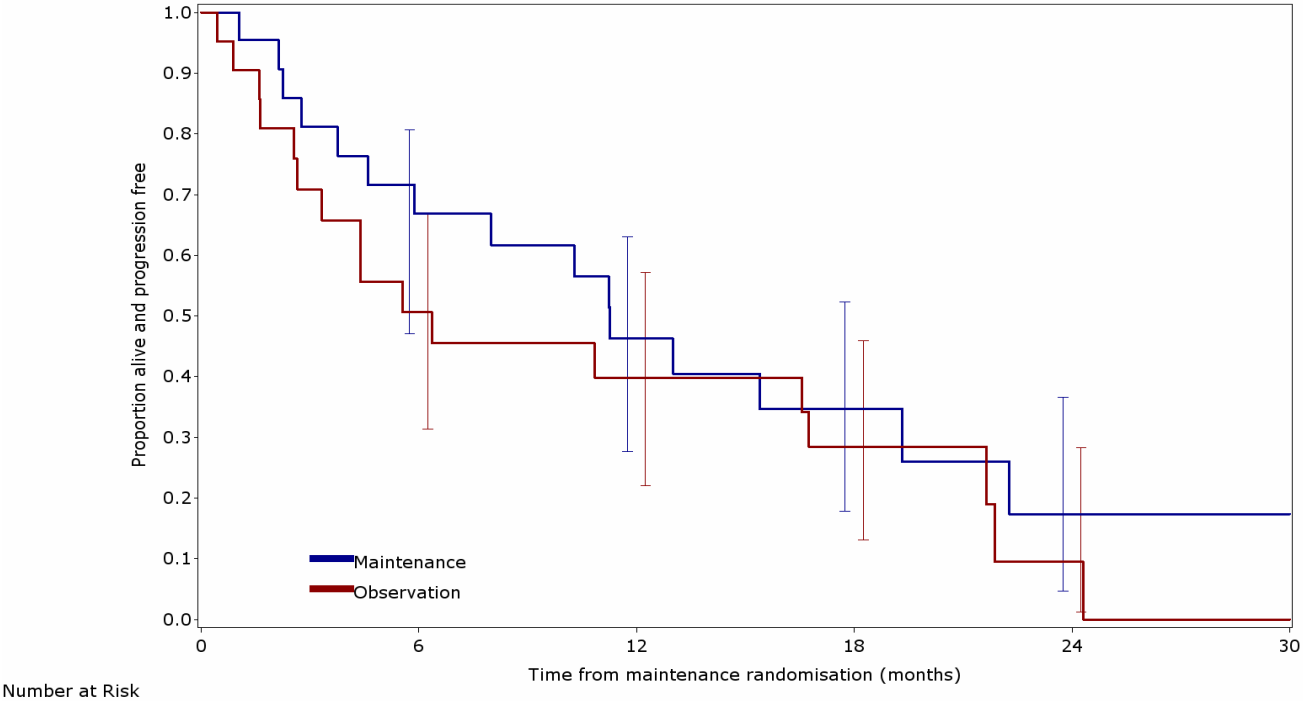
Figure S5. PFS from maintenance randomisation according to genetic risk

Adverse risk



Number at Risk						
Maintenance	21	14	5	1	0	
Observation	27	7	4	2	1	0

Standard risk



Number at Risk						
Maintenance	22	14	9	6	2	0
Observation	21	10	7	4	1	0

Table S1: Weighting of participants in the KCd vs. VCd comparison of PFS and OS using inverse probability of censoring weighted methodology

Participant group	Weight
VCd	1
KCd, not undergoing maintenance randomisation	1 [probability of receiving maintenance is 0 as can only receive maintenance if undergo the randomisation]
KCd, randomised to maintenance	0
KCd, randomised to no maintenance	2 [probability of receiving maintenance = 0·5 due to 1:1 randomisation]

Table S2: Response to treatment (induction treatment, best response within 12 months)

*10 and 13 participants were included with their maximum response, within 12 months and overall, respectively, taken at the time of maintenance randomisation in the main analysis and their maximum response within 12 months and overall, regardless of maintenance treatment, in the sensitivity analyses.

Time-point	Outcome		KCd	VCd	KCd vs. VCd comparison	
					Difference (%), 90% CI	OR, 90% CI, p-value
Within 12 months of initial randomisation	**Participants with available response**		201*	98		
	Maximum response (main analysis: conservative)	**sCR**	0%	1·1%	-1·1 (-11·4, 9·3)	N/A
		CR	3·1%	3·2%	-0·1 (-10·4, 10·2)	
		VGPR	49·5%	41·1%	8·4 (-1·9, 18·7)	
		PR	38·8%	33·7%	5·1 (-5·3, 15·4)	
		MR	3·1%	11·6%	-8·5 (-18·7, 1·8)	
		SD/NC	1·5%	8·4%	-6·9 (-17·1, 3·4)	
	Maximum response (sensitivity analysis: ignoring maintenance)	**sCR**	0%	1·1%	-1·1 (-11·4, 9·3)	N/A
		CR	5·6%	3·2%	2·5 (-7·9, 12·7)	
		VGPR	50·0%	41·1%	8·9 (-1·4, 19·2)	
		PR	35·7%	33·7%	2·0 (-8·3, 12·4)	
		MR	3·1%	11·6%	-8·5 (-18·7, 1·8)	
		SD/NC	1·5%	8·4%	-6·9 (-17·1, 3·4)	
	Overall response: ≥PR		91·3%	78·9%	12·4, (2·0, 22·6)	2·95, (1·61, 5·41), p=0·0034
Overall	**Participants with available response**		201*	98		
	Maximum response (main analysis: conservative)	**sCR**	0%	1·1%	-1·1 (-11·4, 9·3)	N/A
		CR	3·1%	3·2%	-0·1 (-10·4, 10·2)	
		VGPR	50·0%	41·1%	8·9 (-1·4, 19·2)	
		PR	38·3%	33·7%	4·6 (-5·8, 14·9)	
		MR	3·1%	11·6%	-8·5 (-18·7, 1·8)	
		SD/NC	1·5%	8·4%	-6·9 (-17·1, 3·4)	
	Maximum response (sensitivity analysis: ignoring maintenance)	**sCR**	0%	1·1%	-1·1 (-11·4, 9·3)	N/A
		CR	6·1%	3·2%	3·0 (-7·4, 13·2)	
		VGPR	50·5%	41·1%	9·5 (-0·9, 19·7)	
		PR	34·7%	33·7%	1·0 (-9·3, 11·4)	
		MR	3·6%	11·6%	-8·0 (-18·2, 2·3)	
		SD/NC	1·0%	8·4%	-7·4 (-17·6, 2·9)	

Table S3. Minimal residual disease at end of induction treatment

Sample received?	KCd (n=196)	VCd (n=96)	Total (n=292)
Yes	**134 (67.9%)**	**49 (51.0%)**	**182 (62.3%)**
MRD positive	93 (69.9%)	39 (79.6%)	132 (72.5%)
MRD negative	22 (16.5%)	6 (12.2%)	28 (15.4%)
Suspicious	6 (4.5%)	1 (2.0%)	7 (3.8%)
Inadequate sample	11 (8.3%)	3 (6.1%)	14 (7.7%)
Not evaluable	1 (0.8%)	0 (0.0%)	1 (0.5%)
No	**63 (32.1%)**	**47 (49.0%)**	**110 (37.7%)**

Table S4 Weighted Cox's proportional hazards modelling for progression-free survival, adjusted for minimisation factors (induction comparison)*

Variable	Hazard ratio (HR)	80% CI lower limit for HR	80% CI upper limit for HR	Chi-square test statistic	Degrees of freedom	p-value
Randomisation treatment: KCd vs. VCd	0.95	0.77	1.18	0.1020	1	0.7494
B2M: 3.3-5.5 vs <3.5	1.71	1.34	2.19	19.0949	2	<0.0001
B2M: >5.5 vs <3.5	2.27	1.67	3.08			
Previous bortezomib: Yes vs. No	1.35	1.01	1.79	2.7527	1	0.0971
Previous autograft: Yes vs. No	1.56	1.24	1.95	8.9275	1	0.0028
Relapse timing/primary refractory: 1st relapse ≥12 months vs <12 months	0.78	0.56	1.10	2.6068	2	0.2716
Relapse timing/primary refractory: primary refractory vs 1st relapse <12 months	0.49	0.18	1.32			

*CIs created using sandwich variance estimate to account for weighting

Table S5. Reasons for stopping induction treatment

Reason(s) for stopping treatment	KCd (n=201)	VCd (n=99)	Total (n=300)
Maximum number of cycles	157 (78.1%)	52 (52.5%)	209 (69.7%)
Maximum number of cycles, Disease progression	1 (0.5%)	1 (1.0%)	2 (0.7%)
Maximum number of cycles, Patient died	1 (0.5%)	0 (0.0%)	1 (0.3%)
Maximum number of cycles, Unacceptable toxicity	1 (0.5%)	0 (0.0%)	1 (0.3%)
Maximum number of cycles, Withdrew consent	0 (0.0%)	1 (1.0%)	1 (0.3%)
Unacceptable toxicity	11 (5.5%)	13 (13.1%)	24 (8.0%)
Unacceptable toxicity, Clinician decision	0 (0.0%)	4 (4.0%)	4 (1.3%)
Unacceptable toxicity, Disease progression	1 (0.5%)	1 (1.0%)	2 (0.7%)
Unacceptable toxicity, Patient died	1 (0.5%)	0 (0.0%)	1 (0.3%)
Unacceptable toxicity, Withdrew consent	0 (0.0%)	1 (1.0%)	1 (0.3%)
Disease progression	10 (5.0%)	4 (4.0%)	14 (4.7%)
Disease progression, Clinician decision	1 (0.5%)	0 (0.0%)	1 (0.3%)
Patient died	2 (1.0%)	1 (1.0%)	3 (1.0%)
Patient died, Clinician decision	1 (0.5%)	0 (0.0%)	1 (0.3%)
Clinician decision	6 (3.0%)	10 (10.1%)	16 (5.3%)
Clinician decision, Other	0 (0.0%)	1 (1.0%)	1 (0.3%)
Clinician decision, Withdrew consent	0 (0.0%)	1 (1.0%)	1 (0.3%)
Withdrew consent	5 (2.5%)	8 (8.1%)	13(4.3%)
Other	3 (1.5%)	1 (1.0%)	4 (1.3%)

Table S6. Drug modifications during induction

	Cycle 1 only		All cycles	
Modification to any drug?	**KCd (n=196)**	**VCd (n=96)**	**KCd (n=196)**	**VCd (n=96)**
Yes	**55 (28.1%)**	**22 (22.9%)**	**154 (78.6%)**	**82 (85.4%)**
Bortezomib	N/A	15 (68.2%)	N/A	79 (96.3%)
Carfilzomib	44 (80.0%)	N/A	136 (88.3%)	N/A
Cyclophosphamide	29 (52.7%)	8 (36.4%)	95 (61.7%)	48 (58.5%)
Dexamethasone	32 (58.2%)	12 (54.5%)	116 (75.3%)	54 (65.9%)
No	**141 (71.9%)**	**74 (77.1%)**	**42 (21.4%)**	**14 (14.6%)**

Table S7A: Neuropathy during induction: ≥grade 3 or ≥grade 2 with pain

Neuropathy Grade 3+ or Grade 2+ with pain?	KCd (n=196)	VCd (n=96)	Total (n=292)
Yes	**3 (1.5%)**	**19 (19.8%)**	**22 (7.5%)**
Grade 2 with pain	2 (66.7%)	18 (94.7%)	20 (90.9%)
Grade 3 (without pain)	1 (33.3%)	0 (0.0%)	1 (4.5%)
Grade 3 with pain	0 (0.0%)	1 (5.3%)	1 (4.5%)
No	**193 (98.5%)**	**77 (80.2%)**	**270 (92.5%)**

Table S7B. Neuropathy at baseline and worsening during induction treatment

	Present at baseline			Starting or worsening during treatment		
	KCd (n=196)	VCd (n=96)	Total (n=292)	KCd (n=196)	VCd (n=96)	Total (n=292)
Did the patient have neuropathy?						
Yes	36 (18.4%)	25 (26.0%)	61 (20.9%)	42 (21.4%)	54 (56.3%)	96 (32.9%)
No	160 (81.6%)	71 (74.0%)	231 (79.1%)	154 (78.6%)	42 (43.8%)	196 (67.1%)
Number of events per patient						
Mean (SD)	1.0 (0.17)	1.0 (0.00)	1.0 (0.13)	1.1 (0.42)	1.7 (1.50)	1.5 (1.19)
Median (Range)	1.0 (1.0, 2.0)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	1.0 (1.0, 3.0)	1.0 (1.0, 9.0)	1.0 (1.0, 9.0)
Total number of events	37 (100%)	25 (100%)	62 (100%)	48 (100%)	93 (100%)	141 (100%)
Reason for inclusion as starting or worsening during treatment (by # events)						
Increase in CTC grade and development of associated pain				1 (2.1%)	10 (10.8%)	11 (7.8%)
Development of associated pain				0 (0.0%)	2 (2.2%)	2 (1.4%)
Increase in CTC grade				4 (8.3%)	2 (2.2%)	6 (4.3%)
Started during induction				43 (89.6%)	79 (84.9%)	122 (86.5%)
Type of neuropathy						
Motor	1 (2.7%)	1 (4.0%)	2 (3.2%)	3 (6.3%)	6 (6.5%)	9 (6.4%)
Sensory	35 (94.6%)	24 (96.0%)	59 (95.2%)	44 (91.7%)	85 (91.4%)	129 (91.5%)
Autonomic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.2%)	2 (1.4%)
Missing	1 (2.7%)	0 (0.0%)	1 (1.6%)	1 (2.1%)	0 (0.0%)	1 (0.7%)
Associated pain						
Yes	3 (8.1%)	3 (12.0%)	6 (9.7%)	10 (20.8%)	34 (36.6%)	44 (31.2%)
No	34 (91.9%)	22 (88.0%)	56 (90.3%)	36 (75.0%)	59 (63.4%)	95 (67.4%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.2%)	0 (0.0%)	2 (1.4%)
CTCAE grade						
1	34 (91.9%)	25 (100.0%)	59 (95.2%)	40 (83.3%)	59 (63.4%)	99 (70.2%)
2	3 (8.1%)	0 (0.0%)	3 (4.8%)	7 (14.6%)	31 (33.3%)	38 (27.0%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.1%)	3 (3.2%)	4 (2.8%)

Table S8A. Serious adverse events occurring during induction

	KCd (n=196 participants)	VCd (n=96 participants)
Patients with SAEs	88 (44·9%)	45 (46·9%)
SAEs: # events	142	74
SAEs related to treatment	88 (including 3 SUSARs)	39 (0 SUSARs)
SAEs resulting in death	1 x multi-organ failure 1 x chest infection 1 x H1N1 infection	None
Categorisation of all SAEs		
Cardiac	6 (4·2%)	1 (1·4%)
Renal/urinary	5 (3·5%)	4 (5·4%)
Gastrointestinal	11 (7·7%)	4 (5·4%)
Infections/Infestations	73 (51·4%)	35 (47·3%)
Other categorisations	47 (33·0%)	30 (40·5%)
Maximum CTCAE grade for all SAEs		
1	10 (7.0)	3 (4.1)
2	25 (17.6)	16 (21.6)
3	88 (62.0)	49 (66.2)
4	16 (11.3)	6 (8.1)
5	3 (2.1)*	0 (0.0)
Outcome for all SAEs		
Recovered	114 (80.3)	63 (85.1)
Recovered with sequelae	14 (9.9)	7 (9.5)
Condition improving	1 (0.7)	2 (2.7)
Death	3 (2.1)	0 (0.0)
Ongoing at time of death	9 (6.3)	2 (2.7)
Missing	1 (0.7)	0 (0.0)

Table S8B: Adverse reactions experienced by at least 5% of participants (in either treatment arm during induction treatment) at grade 3 or above

Adverse reaction	KCd (n=196)	VCd (n=96)
Thrombocytopenia	23 (11·7%)	35 (36·5%)
Neutropenia	22 (11·2%)	21 (21·9%)
Anaemia	33 (16·8%)	10 (10·4%)
Lung infection	15 (7·7%)	8 (8·3%)
Hyponatremia	19 (9·7%)	4 (4·2%)
White blood cell decreased	15 (7·7%)	4 (4·2%)
Hypophosphatemia	15 (7·7%)	0 (0·0%)

Table S8C: Specific adverse reactions of interest (regardless of frequency): maximum grade experienced during induction treatment

	KCd (n=196)				VCd (n=96)			
	1	**2**	**3**	**4/5**	**1**	**2**	**3**	**4/5**
Lung infection	3 (1.5%)	15 (7.7%)	15 (7.7%)	0	2 (2.1%)	12 (12.5%)	8 (8.3%)	0
Upper respiratory infection	9 (4.6%)	33 (16.8%)	6 (3.1%)	0	3 (3.1%)	13 (13.5%)	3 (3.1%)	0
Cardiac events	7 (3·6%)	4 (2·0%)	6 (3·6%)	0	3 (3·1%)	5 (5·2%)	0	0
Hypertension	2 (1.0%)	1 (0.5%)	7 (3.6%)	0	0	2 (2.1%)	0	0
Dyspnea	36 (18.4%)	16 (8.2%)	4 (2.0%)	0	13 (13.5%)	2 (2.1%)	0	0
Bronchial infection	2 (1.0%)	7 (3.6%)	0	0	0	4 (4.2%)	1 (1.0%)	0

Table S9. Safety and treatment tolerability by age and renal function, induction comparison
CrCl = Creatinine clearance

	KCd	VCd
Patients receiving intended 24 weeks of treatment		
Age <70	95/118 (80.5%)	28/53 (52.8%)
Age ≥70	69/83 (83.1%)	25/46 (54.3%)
CrCl ≤60ml/min	47/67 (70.1%)	15 (60.0%)
CrCl >60ml/min	117/133 (88.0%)	38/74 (51.4%)
Median duration of treatment (for patients starting treatment)		
Age <70	24 weeks	24 weeks
Age ≥70	24 weeks	24 weeks
CrCl ≤60ml/min	24 weeks	24 weeks
CrCl >60ml/min	24 weeks	24 weeks
Number of patients in safety analyses		
Age <70	115	51
Age ≥70	81	45
CrCl ≤60ml/min	65	24
CrCl >60ml/min	131	72
Number of patients with an SAE		
Age <70	50 (43.5%)	24 (47.1%)
Age ≥70	38 (46.9%)	21 (46.7%)
CrCl ≤60ml/min	32 (49.2%)	11 (45.8%)
CrCl >60ml/min	56 (42.7%)	34 (47.2%)
Number of SAEs reported		
Age <70	84	40
Age ≥70	58	34
CrCl ≤60ml/min	55	19
CrCl >60ml/min	87	55

Table S10: Maintenance randomization: Cox Proportional Hazards modelling for PFS adjusting for minimization factors

	Hazard ratio (80% CI)	Chi-square test statistic	p-value
Randomisation treatment: Maintenance with carfilzomib vs. no maintenance	0.59 (0.46,0.77)	6.9091	0.0086
Response category at the end of therapy with KCD: VGPR, CR or sCR vs. PR, MR or SD	0.42 (0.32, 0.55)	17.5214	<.0001
Previous autograft: Yes vs. No	1.32 (1.00, 1.73)	1.7049	0.1916

Table S11: Adverse reactions in maintenance Carfilzomib arm (n=67)

	CTCAE grade – n (%)					
	0 (Not experienced)	**1**	**2**	**3**	**4**	**5**
Neutropenia	49 (73.1)	10 (14.9)	7 (10.4)	1 (1.5)	0	0
Thrombocytopenia	38 (56.7)	25 (37.3)	4 (6.0)		0	0
Anaemia	8 (11.9)	38 (56.7)	18 (26.9)	3 (4.5)	0	0
Nausea	44 (65.7)	16 (23.9)	6 (9.0)	1 (1.5)	0	0
Vomiting	53 (79.1)	9 (13.4)	3 (4.5)	2 (3.0)	0	0
Diarrhoea	53 (79.1)	11 (16.4)	2 (3.0)	1 (1.5)	0	0
Constipation	59 (88.1)	7 (10.4)	1 (1.5)	0	0	0
Hypotension	65 (97.0)	0	1 (1.5)	1 (1.5)	0	0
Infusion reactions	60 (89.6)	3 (4.5)	4 (6.0)	0	0	0
DVT	67 (100.0)	0	0	0	0	0
Pulmonary embolism	67 (100.0)	0	0	0	0	0
Chest pain cardiac	66 (98.5)	0	1 (1.5)	0	0	0
Acute kidney injury	61 (91.0)	3 (4.5)	2 (3.0)	1. (1.5)	0	0
Hypertension	63 (94.0)	1 (1.5)	1 (1.5)	2 (3.0)	0	0
Upper respiratory infection	45 (67.2)	3 (4.5)	18 (26.9)	1 (1.5)	0	0
Bronchial infection	64 (95.5)	0	3 (4.5)	0	0	0
Lung infection	61 (91.0)	1 (1.5)	2 (3.0)	3 (4.5)	0	0

Table S12. Treatment cycles of induction received by genetic risk group

	KCd	VCd
Patients receiving intended 24 weeks of treatment		
Adverse risk	54/69 (78.3%)	21/33 (63.6%)
Standard risk	51/55 (92.7%)	13/30 (43.3%)
Median duration of treatment (for patients starting treatment)		
Adverse risk	24 weeks	24 weeks
Standard risk	24 weeks	18 weeks