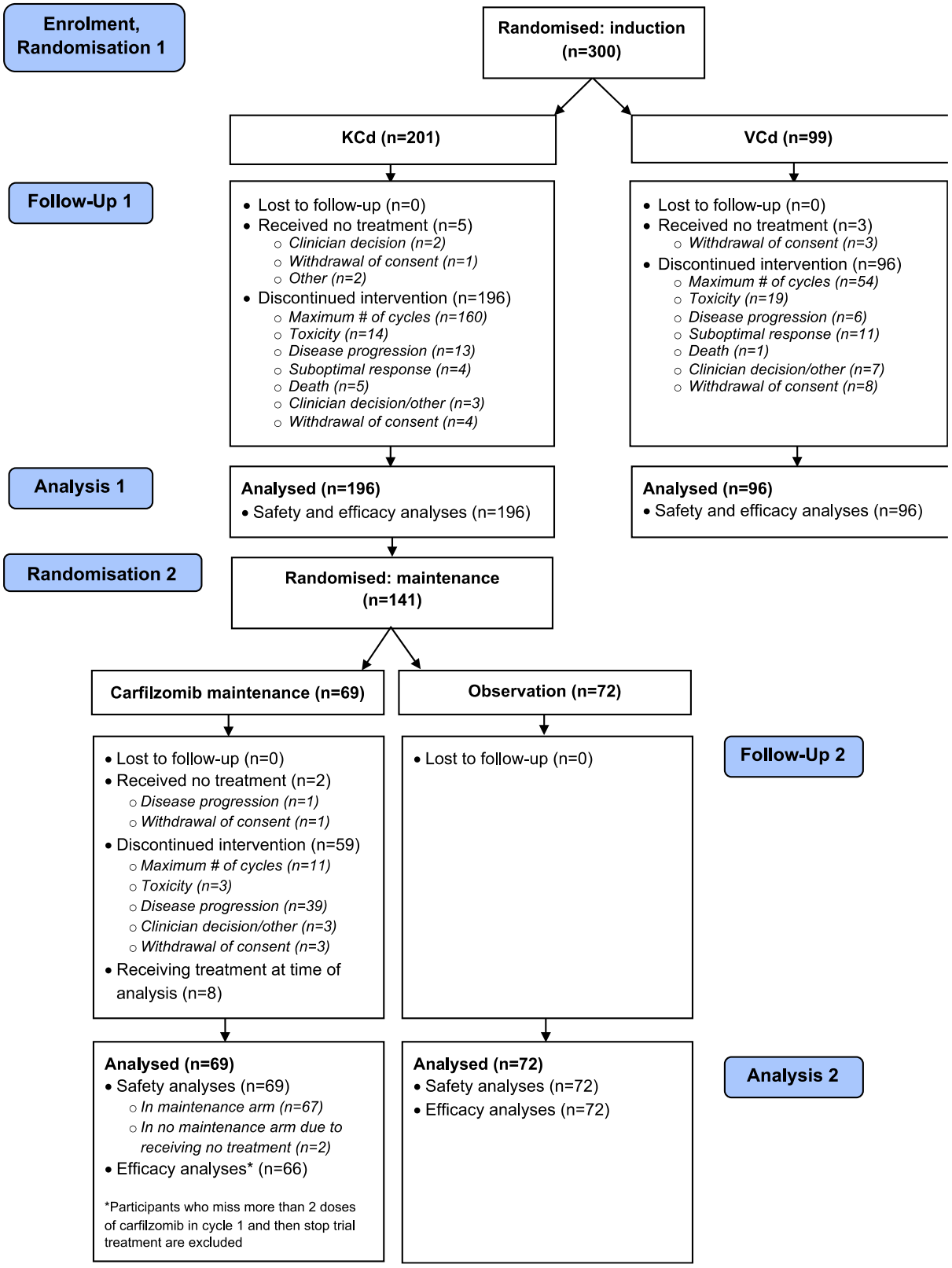
ISRCTN basic results report – MUK Five ISRCTN17354232

Participant flow



Baseline characteristics

Induction comparison

		KCd (n=201) N (%)	VCd (n=99) N (%)	Total (n=300) N (%)
Minimisation factors				
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)
Timing to first relapse or primary refractory	<12 months	23 (11·4)	7 (7·1)	30 (10·0)
	≥12 months	175 (87·1)	91 (91·9)	266 (88·7)
	Primary refractory	3 (1·5)	1 (1·0)	4 (1·3)
Previous bortezomib?	Yes	44 (21·9)	21 (21·2)	65 (21·7)
Previous ASCT?	Yes	133 (66·2)	67 (67·7)	200 (66·7)
Baseline characteristics*				
Age	Median (Range)	67·0 (41·0, 85·0)	69·0 (32·0, 82·0)	68·0 (32·0, 85·0)
	≥75 years	37 (18·4)	21 (21·2)	58 (19·3)
Sex	Male	115 (57·5)	64 (64·6)	179 (59·9)
	Female	85 (42·5)	35 (35·4)	120 (40·1)
ECOG performance status	0	114 (57·0)	54 (54·5)	168 (56·2)
	1	73 (36·5)	40 (40·4)	113 (37·8)
	2	11 (5·5)	4 (4·0)	15 (5·0)
	Missing	2 (1·0)	1 (1·0)	3 (1·0)
ISS stage	I	100 (50·0)	54 (54·5)	154 (51·5)
	II	71 (35·5)	30 (30·3)	101 (33·8)
	III	29 (14·5)	15 (15·2)	44 (14·7)
Lytic bone disease	None	79 (39·5)	44 (44·4)	123 (41·1)
	Mild	35 (17·5)	16 (16·2)	51 (17·1)
	Moderate	29 (14·5)	14 (14·1)	43 (14·4)
	Severe	54 (27·0)	24 (24·2)	78 (26·1)
	Missing	3 (1·5)	1 (1·0)	4 (1·3)
Heavy chain paraprotein type	IgG	128 (64·0)	63 (63·6)	191 (63·9)
	IgA	47 (23·5)	20 (20·2)	67 (22·4)
	IgM	0 (0·0)	1 (1·0)	1 (0·3)
	IgD	0 (0·0)	1 (1·0)	1 (0·3)
	Light chain only	25 (12·5)	14 (14·1)	39 (13·0)
Light chain type	Kappa	136 (68·0)	64 (64·6)	200 (66·9)
	Lambda	64 (32·0)	35 (35·4)	99 (33·1)
Received previous lenalidomide?	Yes	45 (22.5)	23 (23.2)	68 (22.7)
	No	155 (77.5)	76 (76.8)	231 (77.3)
Genetic risk (n=187)	High risk	69 (55·6)	33 (52·4)	102 (54·5)
	Standard risk	55 (44·4)	30 (47·6)	85 (45·5)
	Total with confirmed risk status	124	63	187

*One participant in the KCd arm is excluded from summaries of baseline characteristics due to being ineligible after randomisation

Maintenance comparison

		Maintenance (n=69) N (%)	No maintenance (n=72) N (%)	Total (n=141) N (%)
Baseline characteristics at initial randomisation				
Age at trial entry	Median (Range)	65 (35, 80)	69 (48, 83)	68 (35, 83)
	≥70 years	29 (42.0%)	34 (47.2%)	63 (44.7%)
Sex	Male	43 (62.3%)	42 (58.3%)	85 (60.3%)
	Female	26 (37.7%)	30 (41.7%)	56 (39.7%)
Timing of first relapse	Primary refractory	1 (1.4%)	1 (1.4%)	2 (1.4%)
	<12 months	10 (14.5%)	8 (11.1%)	18 (12.8%)
	≥12 months	58 (84.1%)	63 (87.5%)	121 (85.8%)
ISS stage	I	39 (56.5%)	42 (58.3%)	81 (57.4%)
	II	24 (34.8%)	24 (33.3%)	48 (34.0%)
	III	6 (8.7%)	6 (8.3%)	12 (8.5%)
Disease isotype	IgG	45 (65.2%)	50 (69.4%)	95 (67.4%)
	IgA	18 (26.1%)	14 (19.4%)	32 (22.7%)
	Light chain only	6 (8.7%)	8 (11.1%)	14 (9.9%)
Light chain type	Kappa	46 (66.7%)	51 (70.8%)	97 (68.8%)
	Lambda	23 (33.3%)	21 (29.2%)	44 (31.2%)
Received previous bortezomib?	Yes	19 (27.5%)	13 (18.1%)	32 (22.7%)
	No	50 (72.5%)	59 (81.9%)	109 (77.3%)
Genetic risk at trial entry (n=109)	High risk	22 (42.3%)	27 (47.4%)	49 (45.0%)
	Standard risk	23 (44.2%)	22 (38.6%)	45 (41.3%)
	Risk unconfirmed	7 (13.5%)	8 (14.0%)	15 (13.8%)
Minimisation factors at maintenance randomisation				
Response category at the end of therapy	VGPR, CR or sCR	40 (58.0%)	39 (54.2%)	79 (56.0%)
	PR, MR or SD/NC	29 (42.0%)	33 (45.8%)	62 (44.0%)
Previous ASCT?	Yes	46 (66.7%)	48 (66.7%)	94 (66.7%)
Participant characteristics at maintenance randomisation				
ECOG performance status	0	43 (62.3%)	38 (52.8%)	81 (57.4%)
	1	22 (31.9%)	32 (44.4%)	54 (38.3%)
	2	1 (1.4%)	1 (1.4%)	2 (1.4%)
	Missing	3 (4.3%)	1 (1.4%)	4 (2.8%)
MRD at end of initial treatment	Positive	39 (56.5%)	42 (58.3%)	81 (57.4%)
	Negative	8 (11.6%)	10 (13.9%)	18 (12.8%)
	Suspicious	2 (2.9%)	4 (5.6%)	6 (4.3%)
	No MRD sample	13 (18.8%)	11 (15.3%)	24 (17.0%)
	Not evaluable	0 (0.0%)	1 (1.4%)	1 (0.7%)
	Inadequate sample	7 (10.1%)	4 (5.6%)	11 (7.8%)
Response at time of randomisation	CR	2 (2.9%)	1 (1.4%)	3 (2.1%)
	VGPR	30 (43.5%)	29 (40.3%)	59 (41.8%)
	PR	33 (47.8%)	39 (54.2%)	72 (51.1%)
	MR	2 (2.9%)	2 (2.8%)	4 (2.8%)
	SD or NC	1 (1.4%)	0 (0.0%)	1 (0.7%)
	PD	1 (1.4%)	1 (1.4%)	2 (1.4%)

Outcome measures

Induction comparison

Primary outcome = Proportion of participants achieving at least VGPR measured at 24 weeks post initial randomisation (non-inferiority comparison)

	Proportion of patients (%)	90% CI
CCD	40.2	(34.4, 46.0)
CVD	31.9	(23.8, 39.9)
Difference	8.3	(-1.6, 18.2)

Logistic regression of >=VGPR adjusted for randomised treatment and minimisation factors

Factor	Level	Parameter estimate	SE	Odds Ratio	90% CI for OR
Randomised treatment	CCD vs CVD	-0.91	0.34	1.48	(0.95, 2.31)
β2M	3.5 to 5.5 vs <3.5	0.19	0.14	0.73	(0.45, 1.20)
	>5.5 vs <3.5	-0.30	0.20	1.32	(0.72, 2.40)
Prior bortezomib:	Yes vs No	0.29	0.24	0.82	(0.49, 1.36)
Prior ASCT:	Yes vs No	-0.10	0.16	0.81	(0.52, 1.27)
Relapse timing / refractory	≥12m vs <12m	-0.11	0.14	1.58	(0.84, 2.97)
	Primary refractory vs <12m	0.41	0.33	0.72	(0.16, 3.30)

Secondary outcome = progression-free survival from initial randomisation

Treatment arm	Median PFS	80% CI lower limit	80% CI upper limit
CCD	11.7	10.8	12.2
CVD	10.2	9.3	11.3

Weighted Cox proportional hazards modelling for progression-free survival (induction), adjusting for minimisation factors

Variable	Estimate	Standard Error	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: CCD vs. CVD	-0.05	0.17	0.95	0.77	1.18	0.1020	1	0.7494
B2M: 3.3-5.5 vs <3.5	0.54	0.19	1.71	1.34	2.19	19.0949	2	<0.0001
B2M: >5.5 vs <3.5	0.82	0.24	2.27	1.67	3.08			
Previous bortezomib: Yes vs. No	0.30	0.22	1.35	1.01	1.79	2.7527	1	0.0971
Previous autograft: Yes vs. No	0.44	0.18	1.56	1.24	1.95	8.9275	1	0.0028
Relapse timing/primary refractory: 1st relapse ≥12 months vs <12 months	-0.24	0.27	0.78	0.56	1.10	2.6068	2	0.2716
Relapse timing/primary refractory: primary refractory vs 1st relapse <12 months	-0.72	0.78	0.49	0.18	1.32			

Maintenance comparison

Primary outcome = progression-free survival from maintenance randomisation

Treatment arm	Median PFS	80% CI lower limit	80% CI upper limit
Maintenance with carfilzomib	11.9	8.0	13.1
No maintenance chemotherapy	5.6	4.8	6.4

Cox proportional hazards modelling for progression-free survival (maintenance), adjusting for minimisation factors at maintenance randomisation

Variable	Estimate	Standard Error	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: Maintenance with carfilzomib vs. no maintenance	-0.52	0.20	0.59	0.46	0.77	6.9091	1	0.0086
Response category at the end of therapy with CCD: VGPR, CR or sCR vs. PR, MR or SD	-0.87	0.21	0.42	0.32	0.55	17.5214	1	<.0001
Previous autograft: Yes vs. No	0.28	0.21	1.32	1.00	1.73	1.7049	1	0.1916

Adverse events

Induction comparison

Serious adverse events – summary statistics

	CCD	CVD	Total
Number of patients with one or more SAE	88	45	133
Number of SAEs reported	142	74	216
Number of SAEs per patient			
Mean (Standard Deviation)	1.6 (0.84)	1.6 (1.17)	1.6 (0.96)
Median (Interquartile Range)	1.0 (1, 2)	1.0 (1, 2)	1.0 (1, 2)
Range	(1, 4)	(1, 5)	(1, 5)

Serious adverse events – number of events by MedDRA code

MedDRA System Organ Class	CCD N (%)	CVD N (%)	Total N (%)
Blood and lymphatic system disorders	3 (2.1)	6 (8.1)	9 (4.2)
Cardiac disorders	6 (4.2)	1 (1.4)	7 (3.2)
Gastrointestinal disorders	11 (7.7)	4 (5.4)	15 (6.9)
Hepatobiliary disorders	3 (2.1)	0 (0.0)	3 (1.4)
Infections and infestations	73 (51.4)	35 (47.3)	108 (50.0)
Metabolism and nutrition disorders	4 (2.8)	2 (2.7)	6 (2.8)
Musculoskeletal and connective tissue disorders	9 (6.3)	9 (12.2)	18 (8.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7)	1 (1.4)	2 (0.9)
Nervous system disorders	1 (0.7)	6 (8.1)	7 (3.2)
Renal and urinary disorders	5 (3.5)	4 (5.4)	9 (4.2)
Respiratory, thoracic and mediastinal disorders	9 (6.3)	1 (1.4)	10 (4.6)
Skin and subcutaneous tissue disorders	2 (1.4)	0 (0.0)	2 (0.9)
Surgical and medical procedures	1 (0.7)	0 (0.0)	1 (0.5)
Vascular disorders	10 (7.0)	5 (6.8)	15 (6.9)
Endocrine disorders	4 (2.8)	0 (0.0)	4 (1.9)
Total	**142 (100.0)**	**74 (100.0)**	**216 (100.0)**

Proportion of patients with ≥ grade 3 neuropathy or ≥ grade 2 neuropathy with pain

Neuropathy Grade 3+ or Grade 2+ with pain?	CCD (n=196)	CVD (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%)**

Adverse events related to treatment – maximum CTCAE grade experienced (number of participants)

	All cycles		
	CCD (n=196)	**CVD (n=96)**	**Total (n=292)**
Neutropenia			
0	98 (50.0%)	31 (32.3%)	129 (44.2%)
1	44 (22.4%)	17 (17.7%)	61 (20.9%)
2	32 (16.3%)	27 (28.1%)	59 (20.2%)
3	16 (8.2%)	18 (18.8%)	34 (11.6%)
4	6 (3.1%)	3 (3.1%)	9 (3.1%)
Thrombocytope			
0	29 (14.8%)	7 (7.3%)	36 (12.3%)
1	109 (55.6%)	37 (38.5%)	146 (50.0%)
2	35 (17.9%)	17 (17.7%)	52 (17.8%)
3	17 (8.7%)	26 (27.1%)	43 (14.7%)
4	6 (3.1%)	9 (9.4%)	15 (5.1%)
Anaemia			
0	3 (1.5%)	7 (7.3%)	10 (3.4%)
1	50 (25.5%)	42 (43.8%)	92 (31.5%)
2	110 (56.1%)	37 (38.5%)	147 (50.3%)
3	31 (15.8%)	10 (10.4%)	41 (14.0%)
4	2 (1.0%)	0 (0.0%)	2 (0.7%)
Nausea			
0	125 (63.8%)	57 (59.4%)	182 (62.3%)
1	59 (30.1%)	31 (32.3%)	90 (30.8%)
2	10 (5.1%)	8 (8.3%)	18 (6.2%)
3	2 (1.0%)	0 (0.0%)	2 (0.7%)
Vomiting			
0	157 (80.1%)	79 (82.3%)	236 (80.8%)
1	29 (14.8%)	13 (13.5%)	42 (14.4%)

	All cycles		
	CCD (n=196)	CVD (n=96)	Total (n=292)
2	5 (2.6%)	4 (4.2%)	9 (3.1%)
3	5 (2.6%)	0 (0.0%)	5 (1.7%)
Diarrhoea			
0	142 (72.4%)	57 (59.4%)	199 (68.2%)
1	40 (20.4%)	26 (27.1%)	66 (22.6%)
2	12 (6.1%)	11 (11.5%)	23 (7.9%)
3	2 (1.0%)	2 (2.1%)	4 (1.4%)
Constipation			
0	150 (76.5%)	57 (59.4%)	207 (70.9%)
1	40 (20.4%)	32 (33.3%)	72 (24.7%)
2	6 (3.1%)	6 (6.3%)	12 (4.1%)
3	0 (0.0%)	1 (1.0%)	1 (0.3%)
Hypotension			
0	188 (95.9%)	83 (86.5%)	271 (92.8%)
1	6 (3.1%)	8 (8.3%)	14 (4.8%)
2	1 (0.5%)	3 (3.1%)	4 (1.4%)
3	1 (0.5%)	2 (2.1%)	3 (1.0%)
Infusion			
0	187 (95.4%)	89 (92.7%)	276 (94.5%)
1	5 (2.6%)	5 (5.2%)	10 (3.4%)
2	4 (2.0%)	2 (2.1%)	6 (2.1%)
DVT			
0	192 (98.0%)	96 (100.0%)	288 (98.6%)
1	2 (1.0%)	0 (0.0%)	2 (0.7%)
2	2 (1.0%)	0 (0.0%)	2 (0.7%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary			
0	192 (98.0%)	95 (99.0%)	287 (98.3%)
1	1 (0.5%)	0 (0.0%)	1 (0.3%)
2	1 (0.5%)	1 (1.0%)	2 (0.7%)
3	1 (0.5%)	0 (0.0%)	1 (0.3%)
4	1 (0.5%)	0 (0.0%)	1 (0.3%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acute coronary syndrome			
0	194 (99.0%)	96 (100.0%)	290 (99.3%)
3	2 (1.0%)	0 (0.0%)	2 (0.7%)

	All cycles		
	CCD (n=196)	**CVD (n=96)**	**Total (n=292)**
Chest pain - cardiac			
0	189 (96.4%)	94 (97.9%)	283 (96.9%)
1	5 (2.6%)	2 (2.1%)	7 (2.4%)
2	1 (0.5%)	0 (0.0%)	1 (0.3%)
3	1 (0.5%)	0 (0.0%)	1 (0.3%)
Acute kidney injury			
0	187 (95.4%)	95 (99.0%)	282 (96.6%)
1	8 (4.1%)	0 (0.0%)	8 (2.7%)
2	1 (0.5%)	1 (1.0%)	2 (0.7%)
Hypertension			
0	186 (94.9%)	94 (97.9%)	280 (95.9%)
1	2 (1.0%)	0 (0.0%)	2 (0.7%)
2	1 (0.5%)	2 (2.1%)	3 (1.0%)
3	7 (3.6%)	0 (0.0%)	7 (2.4%)
Upper respiratory infection			
0	148 (75.5%)	77 (80.2%)	225 (77.1%)
1	9 (4.6%)	3 (3.1%)	12 (4.1%)
2	33 (16.8%)	13 (13.5%)	46 (15.8%)
3	6 (3.1%)	3 (3.1%)	9 (3.1%)
Bronchial infection			
0	187 (95.4%)	91 (94.8%)	278 (95.2%)
1	2 (1.0%)	0 (0.0%)	2 (0.7%)
2	7 (3.6%)	4 (4.2%)	11 (3.8%)
3	0 (0.0%)	1 (1.0%)	1 (0.3%)
Lung infection			
0	163 (83.2%)	74 (77.1%)	237 (81.2%)
1	3 (1.5%)	2 (2.1%)	5 (1.7%)
2	15 (7.7%)	12 (12.5%)	27 (9.2%)

	All cycles		
	CCD (n=196)	**CVD (n=96)**	**Total (n=292)**
3	15 (7.7%)	8 (8.3%)	23 (7.9%)

Maintenance comparison

Serious adverse events – summary statistics

	Carfilzomib maintenance	No maintenance	Total
Number of patients with one or more SAE	24	6	30
Number of SAEs reported	34	6	40
Number of SAEs per patient			
Mean (Standard Deviation)	1.4 (0.78)	1.0 (0.00)	1.3 (0.71)
Median (Interquartile Range)	1.0 (1, 2)	1.0 (1, 1)	1.0 (1, 1)
Range	(1, 4)	(1, 1)	(1, 4)

Serious adverse events – number of events by MedDRA code

MedDRA System Organ Class	Carfilzomib maintenance N (%)	No maintenance N (%)	Total N (%)
Blood and lymphatic system disorders	2 (5.9)	0 (0.0)	2 (5.0)
Cardiac disorders	1 (2.9)	0 (0.0)	1 (2.5)
Gastrointestinal disorders	8 (23.5)	0 (0.0)	8 (20.0)
Hepatobiliary disorders	0 (0.0)	1 (16.7)	1 (2.5)
Infections and infestations	18 (52.9)	1 (16.7)	19 (47.5)
Injury, poisoning and procedural complications	1 (2.9)	1 (16.7)	2 (5.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (2.9)	3 (50.0)	4 (10.0)
Nervous system disorders	2 (5.9)	0 (0.0)	2 (5.0)
Renal and urinary disorders	1 (2.9)	0 (0.0)	1 (2.5)
Total	**34 (100.0)**	**6 (100.0)**	**40 (100.0)**

Adverse events related to treatment – maximum CTCAE grade experienced (number of participants)

	Maintenance with carfilzomib (n=67)
Neutropenia	
0 (not experienced)	49 (73.1%)
1	10 (14.9%)
2	7 (10.4%)
3	1 (1.5%)

	Maintenance with carfilzomib (n=67)
Thrombocytopenia	
0 (not experienced)	38 (56.7%)
1	25 (37.3%)
2	4 (6.0%)
Anaemia	
0 (not experienced)	8 (11.9%)
1	38 (56.7%)
2	18 (26.9%)
3	3 (4.5%)
Nausea	
0 (not experienced)	44 (65.7%)
1	16 (23.9%)
2	6 (9.0%)
3	1 (1.5%)
Vomiting	
0 (not experienced)	53 (79.1%)
1	9 (13.4%)
2	3 (4.5%)
3	2 (3.0%)
Diarrhoea	
0 (not experienced)	53 (79.1%)
1	11 (16.4%)
2	2 (3.0%)
3	1 (1.5%)
Constipation	
0 (not experienced)	59 (88.1%)
1	7 (10.4%)
2	1 (1.5%)
Hypotension	
0 (not experienced)	65 (97.0%)
2	1 (1.5%)
3	1 (1.5%)
Infusion reactions	
0 (not experienced)	60 (89.6%)
1	3 (4.5%)
2	4 (6.0%)
Chest pain cardiac	
0 (not experienced)	66 (98.5%)
2	1 (1.5%)

	Maintenance with carfilzomib (n=67)
Acute kidney injury	
0 (not experienced)	61 (91.0%)
1	3 (4.5%)
2	2 (3.0%)
3	1 (1.5%)
Hypertension	
0 (not experienced)	63 (94.0%)
1	1 (1.5%)
2	1 (1.5%)
3	2 (3.0%)
Upper respiratory infection	
0 (not experienced)	45 (67.2%)
1	3 (4.5%)
2	18 (26.9%)
3	1 (1.5%)
Bronchial infection	
0 (not experienced)	64 (95.5%)
2	3 (4.5%)
Lung infection	
0 (not experienced)	61 (91.0%)
1	1 (1.5%)
2	2 (3.0%)
3	3 (4.5%)