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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*)

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ABSTRACT

The proteasome inhibitors, carfilzomib and bortezomib, are widely used to treat myeloma but head-to-head comparisons have produced conflicting results. We compared the activity of these proteasome inhibitors in combination with cyclophosphamide and dexamethasone (KCd *vs.* VCd) in second-line treatment using fixed duration therapy and evaluated the efficacy of carfilzomib maintenance. MUK*five* was a phase II controlled, parallel group trial that randomized patients (2:1) to KCd (n=201) or VCd (n=99); responding patients on carfilzomib were randomized to maintenance carfilzomib (n=69) or no further treatment (n=72). Primary endpoints were: (i) very good partial response (non-inferiority, odds ratio [OR] 0.8) at 24 weeks, and (ii) progression-free survival. More participants achieved a very good partial response or better with carfilzomib than with bortezomib (40.2% *vs.* 31.9%, OR=1.48, 90% confidence interval [CI]: 0.95, 2.31; non-inferior), with a trend for particular benefit in patients with adverse-risk disease. KCd was associated with higher overall response (partial response or better, 84.0% *vs.* 68.1%, OR=2.72, 90% CI: 1.62, 4.55, *P*=0.001). Neuropathy (grade ≥3 or ≥2 with pain) was more common with bortezomib (19.8% *vs.* 1.5%, *P*<0.0001), while grade ≥3 cardiac events and hypertension were only reported in the KCd arm (3.6% each). The median progression-free survival in the KCd arm was 11.7 months *vs.* 10.2 months in the VCd arm (hazard ratio [HR]=0.95, 80% CI: 0.77, 1.18). Carfilzomib maintenance was associated with longer progression-free survival, median 11.9 months *vs.* 5.6 months for no maintenance (HR 0.59, 80% CI: 0.46-0.77, *P*=0.0086). When used as fixed duration therapy in first relapase, KCd is at least as effective as VCd, and carfilzomib is an effective maintenance agent. This trial was registered with International Standard Randomised Controlled Trial Number (ISRCTN) identifier: ISRCTN17354232.

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Introduction

Proteasome inhibitors form the backbone of many regimens used to treat multiple myeloma (MM).[1] Bortezomib is a boronic acid-based reversible proteasome inhibitor commonly combined with corticosteroids, alkylating agents, immunomodulatory drugs, or antibodies.[2] Peripheral neuropathy is a common cause for treatment discontinuation, although this problem may be mitigated by subcutaneous and once-weekly (instead of bi-weekly) administration.[3] Carfilzomib is an epoxyketone drug that binds irreversibly to the proteasome and is approved for the treatment of relapsed myeloma in combination with dexamethasone, or dexamethasone plus lenalidomide, or daratumumab.[4-6] While carfilzomib has limited neurotoxicity, it has been linked to clinically relevant cardiovascular complications, in particular hypertension, heart failure, and renal failure.[7] Both bortezomib and carfilzomib predominantly target the β5 subunit of the constitutive proteasome and the immunoproteasome; at higher concentrations they also co-inhibit either β1 and/or β2 subunits with different inhibition profiles that determine cytotoxicity and may thus be clinically relevant.[8]

Head-to-head comparison studies of carfilzomib with bortezomib have yielded mixed results. In patients with relapsed or refractory multiple myeloma (RRMM), carfilzomib was compared to bortezomib, both given with dexamethasone: it was found that carfilzomib improved both progression-free survival (PFS) and overall survival (OS).[4,9] In this study (ENDEAVOR), the carfilzomib dose was 56 mg/m^2 twice weekly, and patients received treatment until progression. In contrast, carfilzomib did not improve PFS, OS, or response rates compared to bortezomib when given in combination with melphalan and prednisolone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM).[10] The carfilzomib dose used in this trial (CLARION) was 36 mg/m^2 twice weekly, and treatment duration was fixed at nine cycles. Similarly, carfilzomib given at a dose of 36 mg/m^2 was not superior to bortezomib when given in combination with lenalidomide and dexamethasone for a fixed period (36 weeks) in standard-risk NDMM patients without intention for immediate autologous stem-cell transplantation (ASCT).[11] Thus, the optimal choice of proteasome inhibitor, combination, dose and duration of therapy, remains to be established. Superior results seen with carfilzomib in ENDEAVOR indicate a safety profile that lends itself to continuous treatment approaches, suggesting suitability for maintenance. Maintenance with carfilzomib following fixed-duration treatment with cyclophosphamide and dexamethasone in NDMM transplant-ineligible patients has been reported.[12] The role of carfilzomib maintenance treatment in patients with RRMM remains unexplored.

Triplet regimens have become standard of care for RRMM in patients who are sufficiently fit and these regimens often contain a proteasome inhibitor. The combination of either carfilzomib or bortezomib with dexamethasone and cyclophosphamide is effective[12-14] and economically less challenging than three-drug combinations that contain two novel agents. We designed the Myeloma UK five (MUK*five*) study, a phase II randomized, controlled, parallel group, multicenter trial for MM patients at first relapse or refractory to just one treatment line, with two main objectives. The first was to compare, in a uniform group of patients, the efficacy of carfilzomib (K) and bortezomib (V), given in combination with cyclophosphamide (C) and dexamethasone (d), i.e., KCd *versus* VCd, as fixed-duration therapy (24 weeks), in achieving at least very good partial responses (VGPR). The second objective was to evaluate the PFS benefit of maintenance with single-agent carfilzomib in patients responding to KCd.

Methods

The full trial protocol, including eligibility criteria and sample size, have already been published.[15] The trial received national research ethics approval from the NHS National Research Ethics Service London, (REC number: 12/LO/1078). Three hundred participants were randomized (2:1) to KCd or VCd, using minimization with a random element. KCd participants in at least stable disease after six cycles were randomized (1:1) to receive maintenance carfilzomib or observation. Figure 1 shows the minimization factors and treatment regimens.

The MUK*five* trial had two co-primary endpoints: (i) a comparison of the induction regimens' capacity to produce ≥VGPR at 24 weeks after initial randomization (non-inferiority [NI] comparison with NI margin -5% [difference in proportion]/0.8 [odds ratio; OR], one-sided 5% significance, i.e. 90% confidence interval [CI]) and (ii) comparison of maintenance: PFS with maintenance treatment (superiority comparison target hazard ratio [HR]=0.67, two-sided 20% significance, i.e. 80% CI)

Secondary endpoints included: neuropathy grade ≥3, or grade ≥2 with pain (induction comparison only); complete responses (CR) and overall response rate (ORR); time to maximum response; duration of response; minimal residual disease (MRD); OS; time to next treatment (TTNT); safety/toxicity; and treatment compliance.

Responses were defined according to International Myeloma Working Group (IMWG) guidelines.[16] Safety and toxicity data were graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Flow cytometry to detect MRD was performed as previously reported[17] with a limit of detection of 10^{-5}, assessing 500,000 cells using six-color antibody combinations. Samples classified as "suspicious" (the sample was likely to be positive but there was insufficient evidence) were designated as not MRD negative.[18] Central assessment of genetic risk was performed as previously described,[19] supplemented, where appropriate, by local reports that were centrally reviewed. Genetic high risk was defined as at least one of del(17p), gain(1q), or any adverse IgH translocation: t(4;14), t(14;16), or t(14;20).

Total sample sizes of 300 patients for the induction comparison (200 KCd:100 VCd) and 140 for the maintenance comparison were required.[15] All analyses were pre-planned, unless specified. The analysis population was defined as all participants who received at least one full cycle of allocated chemotherapy. The primary induction endpoint was analyzed using logistic regression, adjusting for minimization factors, with KCd declared non-inferior to VCd if the 90% confidence interval for the odds ratio was above 0.8. PFS, time to maximum response, duration of response, OS and TTNT were analyzed using Kaplan-Meier curves, a log-rank test and Cox proportional hazards models, adjusting for minimization factors. Carfilzomib maintenance was declared superior to no maintenance if the PFS hazard ratio was <0.67 and significant at a two-sided 20% level. TTNT was also analyzed using cumulative incidence

function curves and Fine and Gray modeling,[20] considering deaths as competing risks (exploratory).

For the induction comparison of PFS and OS, inverse probability of censoring weighted methods[21] were used to provide an unbiased comparison of KCd without maintenance, compared to VCd (*Online Supplementary Table S1*). The proportions of participants experiencing neuropathy grade ≥3 or grade ≥2 with pain, CR, ORR and MRD status were analyzed using logistic regression, adjusting for minimization factors. Safety, toxicity and treatment compliance were summarized descriptively. As per trial design, 90% confidence intervals were calculated for induction endpoints and 80% confidence intervals for PFS.[15] For all other maintenance endpoints, 95% confidence intervals were calculated. Induction comparisons were analyzed to evaluate non-inferiority; therefore, *P*-values for these results are only provided to aid interpretation where superiority is observed.

Results

Induction comparison (KCd *vs.* VCd)

Between February 2013 and September 2016, 300 participants from 35 UK centers were randomized between KCd (n=201) and VCd (n=99) (Figure 2). The final analysis took place in two parts with short-term endpoints up to 24 weeks after the initial randomization analyzed as of May 3, 2017 (median follow-up 11.6 months), and remaining endpoints analyzed as of January 3, 2018 (median follow-up from initial randomization 13.9 months: KCd 15 months, VCd 12.6 months). Overall, 196 KCd and 96 VCd participants were eligible for the safety and efficacy analyses. The baseline characteristics of the patients in the two treatment arms (Table 1) were similar, with around 20% having been exposed to bortezomib and/or lenalidomide.

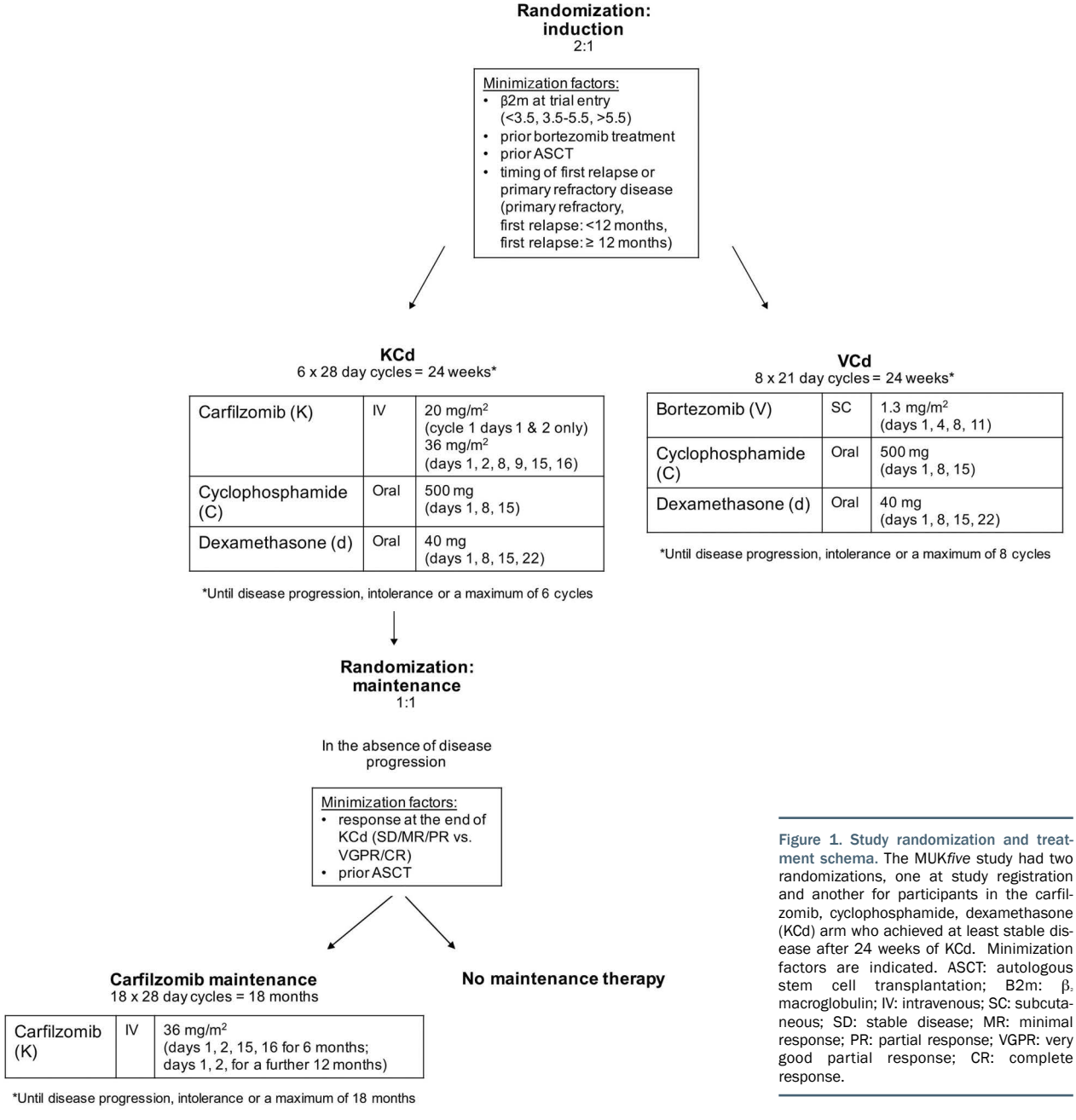


Figure 1. Study randomization and treatment schema. The MUK*five* study had two randomizations, one at study registration and another for participants in the carfilzomib, cyclophosphamide, dexamethasone (KCd) arm who achieved at least stable disease after 24 weeks of KCd. Minimization factors are indicated. ASCT: autologous stem cell transplantation; B2m: β_2 macroglobulin; IV: intravenous; SC: subcutaneous; SD: stable disease; MR: minimal response; PR: partial response; VGPR: very good partial response; CR: complete response.

Response to treatment

Response at 24 weeks was available for 285 participants. More participants receiving KCd achieved ≥VGPR compared to those receiving VCd (40.2% *vs*. 31.9%, for a difference of 8.3% [90% CI: -1.6, 18.2], non-inferior). In logistic regression modeling of ≥VGPR at 24 weeks, the odds ratio was 1.48 (90% CI: 0.95, 2.31), demonstrating non-inferiority (Table 2A). Analysis of patient- and disease-related factors showed broadly similar effects across subgroups (Figure 3A). The proportion of participants

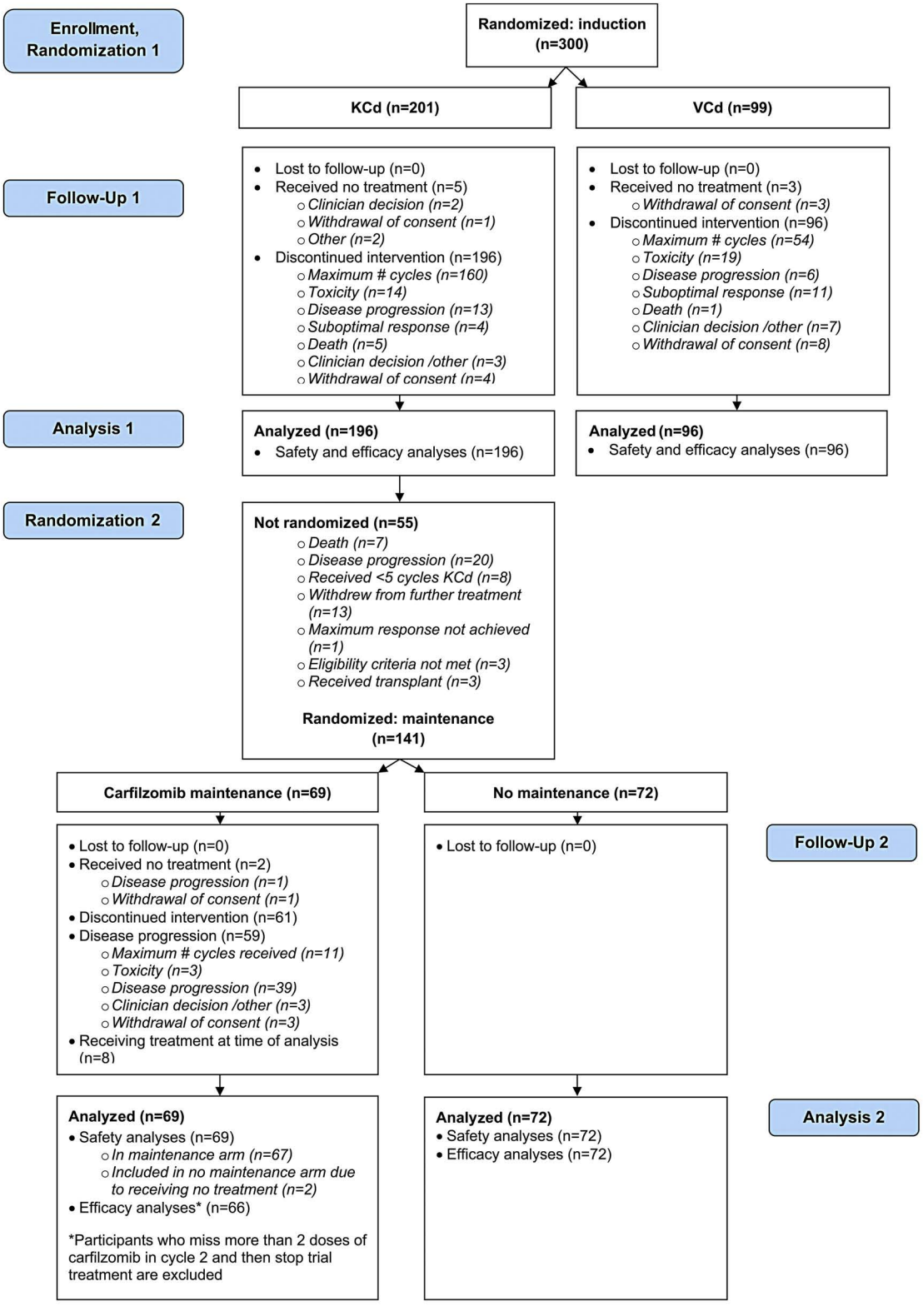


Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram. The patients' flow through the study, according to randomization points and treatment arms. KCd: carfilzomib, cyclophosphamide, dexamethasone; VCd: bortezomib, cyclophosphamide, dexamethasone.

achieving an objective response (i.e., ≥partial response) at 24 weeks was higher for KCd than for VCd (84.0% *vs*. 68.1%, respectively), with a difference of 15.9% (90% CI: 6.8, 25.0). In logistic regression modeling of overall response at 24 weeks, the odds ratio was 2.72 (90% CI: 1.62, 4.55; *P*=0.0014). Subgroup analysis (Figure 3B) indicated broadly similar treatment effects across all subgroups, except that patients not treated with ASCT and those relapsing within 12 months had particular benefit from carfilzomib (interaction *P*<0.05 for both).

Similar results were observed for ORR and VGPR within 12 months (*Online Supplementary Table S2*). Participants in the KCd arm had significantly longer time to maximum response (median 2.9 *vs*. 2.2 months for VCd: HR=0.74, 90% CI: 0.60, 0.92; *P*=0.0220). The median duration of response was 11.1 months for KCd *vs*. 10.1 months for VCd (HR=0.87 and 90% CI: 0.64, 1.17; *P*=0.441).

MRD was assessed at 24 weeks in 157 samples that were received and evaluable, 121 for the KCd arm, and 46 for the VCd arm. For KCd, 22 (18.2%) participants were MRD negative, compared to six (13.0%) for VCd (OR=1.48, 90% CI: 0.64, 3.40) (*Online Supplementary Table S3*).

Progression-free survival, overall survival and time to next treatment

All participants in the analysis population were included in the inverse probability of censoring weighted PFS analysis (n=169 events in participants not weighted 0) (*Online Supplementary Table S1*). The median PFS in the

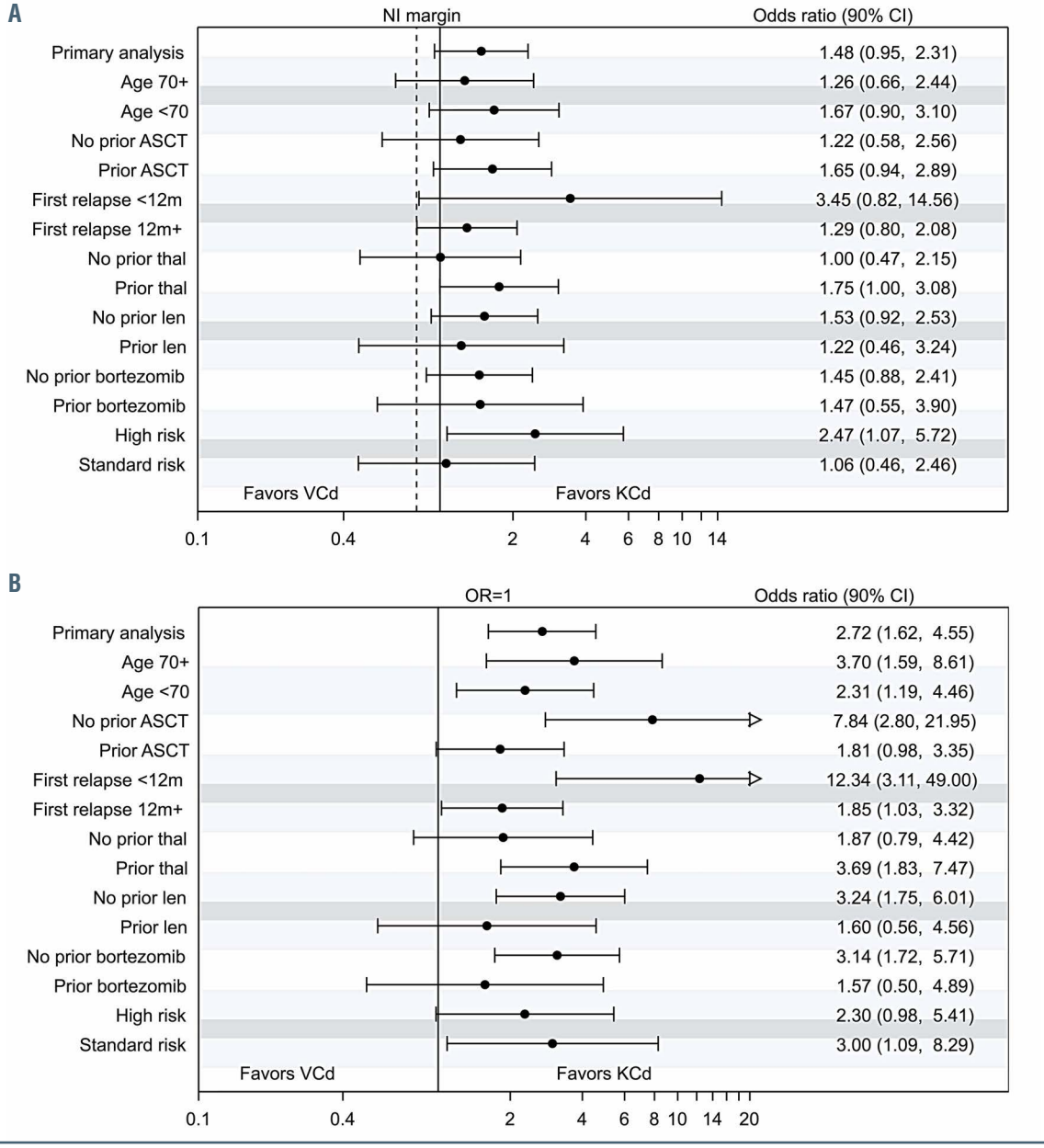


Figure 3. Forest plots of responses at 24 weeks after the initial randomization. The Forest plots show results of an analysis of (A) very good partial response and (B) overall response rate in pre-specified subgroups of the intention-to-treat population, at 24 weeks after the initial randomization. The odds ratio (OR) is provided from logistic regression modeling. NI: non-inferiority; CI: confidence interval; ASCT: autologous stem cell transplantation; 12m: 12 months; thal: thalidomide; len: lenalidomide; KCd: carfilzomib, cyclophosphamide, dexamethasone; VCd: bortezomib, cyclophosphamide, dexamethasone.

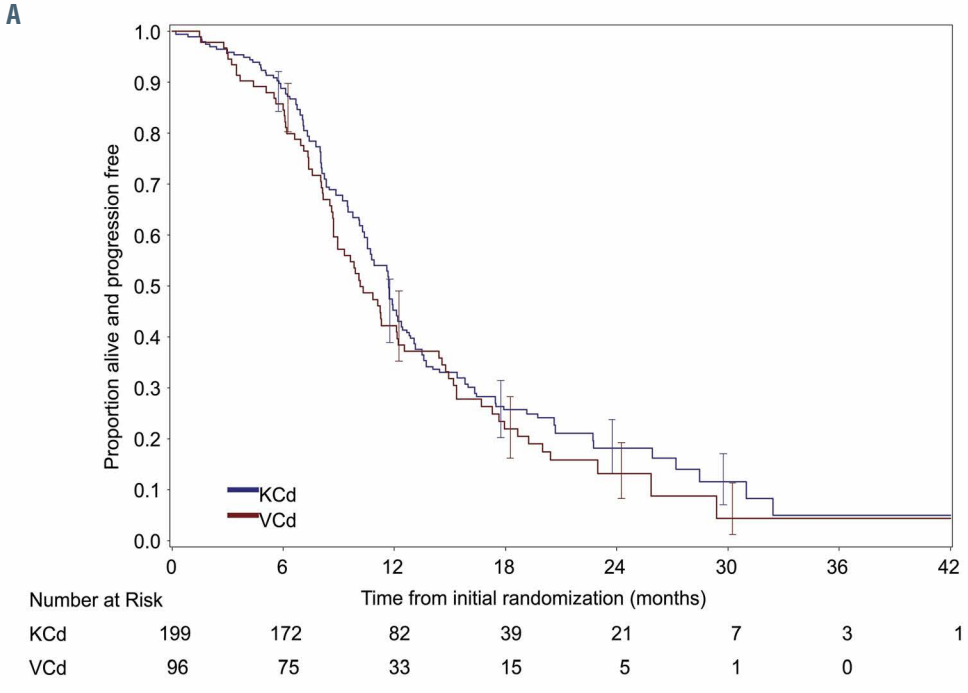
KCd arm was 11.7 months *versus* 10.2 months in the VCd arm (HR=0.95, 80% CI: 0.77, 1.18) (Figure 4A). Factors prognostic for longer PFS were no previous ASCT and lower β2-microglobulin level (*Online Supplementary Table S4*). PFS was not significantly different between treatment arms; however, subgroup analysis suggests that patients relapsing earlier and/or who had not received ASCT may benefit from KCd therapy (Figure 4B). For analysis of TTNT, 66 participants in the KCd arm were censored at maintenance randomization. The median TTNT in the KCd arm was 19.1 months, compared with 17.7 months in the VCd arm.

All participants in the analysis population were included in the OS analysis (n=59 events in participants not weighted 0). The median (inverse probability of censoring weighted) OS with KCd was 30.9 months *versus* 28.1 months with VCd (HR=1.10, 90% CI: 0.68, 1.80) (*Online Supplementary Figure S1*).

Safety and tolerability of induction treatment

The number of participants who received the planned 24 weeks of treatment was 164 of 201 (81.6%) in the KCd arm, compared to 53 of 99 (53.5%) in the VCd arm. Among the patients receiving KCd, 14 (7.0%) stopped treatment because of toxicity, compared to 19 (19.2%) of those receiving VCd (*Online Supplementary Table S5*). In the KCd arm, 11 (5.4%) subjects stopped treatment because of the patients' withdrawal or clinicians' decision, compared to 20 (20%) in the VCd arm (*Online Supplementary Table S5*). Dose modifications were reported for 78.6% of KCd participants, compared to 85.4% for VCd (*Online Supplementary Table S6*). Neuropathy (grade ≥3, or ≥2 with pain) was more common with VCd (19.8%) than with KCd (1.5%) for a proportional difference of -18.3 (90% CI: -25.1, -11.4; *P*<0.0001) *(Online Supplementary Table S7A, B*).

There were 142 serious adverse events in 88 (44.9%) participants in the KCd arm, compared with 74 events in



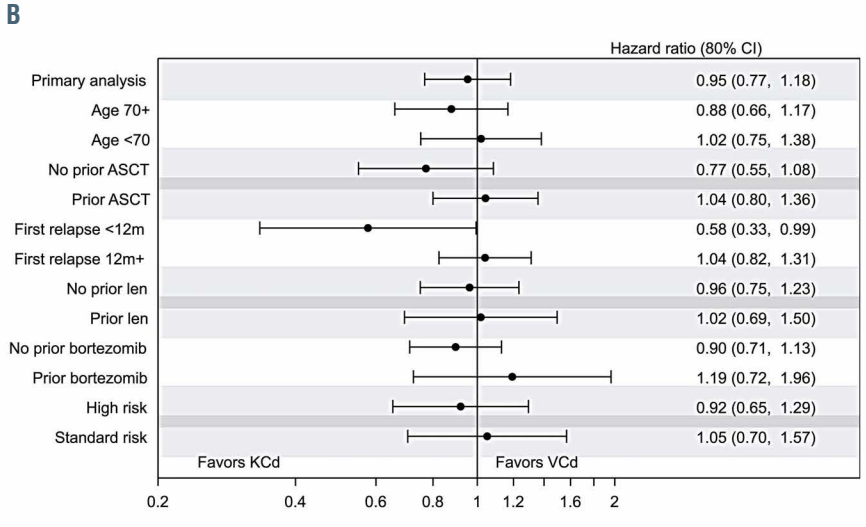
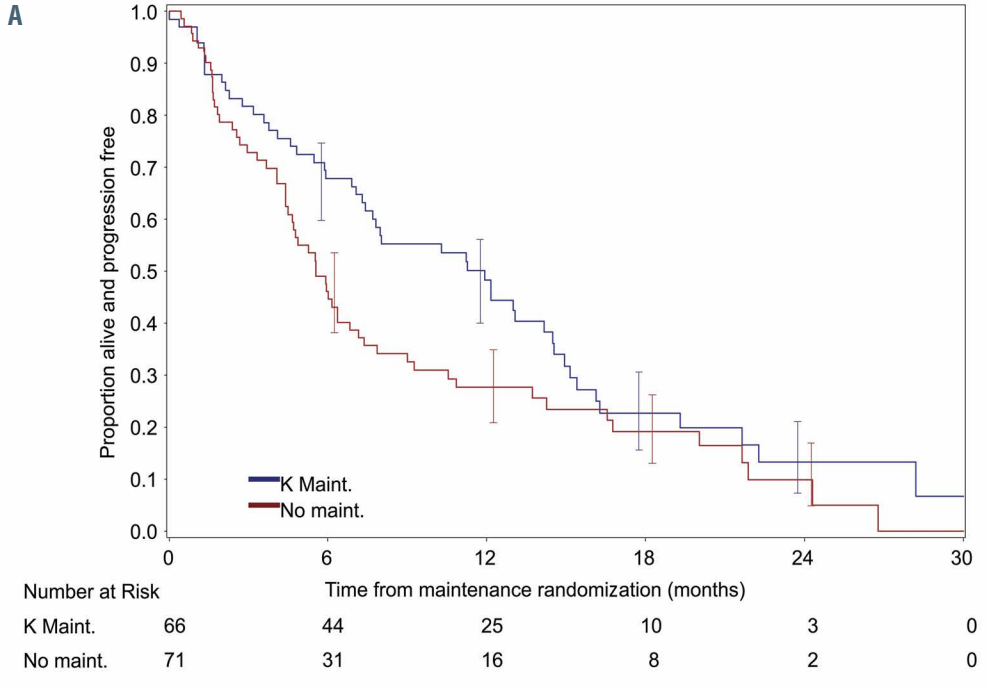


Figure 4. Progression-free survival according to induction randomization. (A) The inverse probability of censoring weighted methodology was used to provide estimates of the progression-free survival (PFS), which is shown with 80% confidence intervals. (B) Results are shown of an analysis of PFS in pre-specified subgroups of the intention-to-treat population. Forest plot hazard ratios were provided from Cox proportional hazards modeling, using the inverse probability of censoring weighted methodology. KCd: carfilzomib, cyclophosphamide, dexamethasone; VCd: bortezomib, cyclophosphamide, dexamethasone; ASCT: autologous stem cell transplantation; 12m: 12 months; len: lenalidomide; CI: confidence interval.

45 (46.9%) participants in the VCd arm (*Online Supplementary Table S8A*). Serious adverse events reported more frequently with KCd included cardiac, respiratory/thoracic, vascular and renal events while neurological and blood/lymphatic events were more frequent with VCd. The grade ≥3 adverse reactions that occurred are summarized in *Online Supplementary Table S8B, C*. More participants in the VCd arm experienced thrombocytopenia and neutropenia, but more in the KCd arm experienced anemia, hyponatremia and hypophosphatemia. Cardiac adverse reactions were similar in both arms, although grade 3 events were only reported in the KCd arm (n=6, 3.6%). Hypertension grade ≥3 was only reported among patients receiving KCd (3.6%). Infections accounted for around half of the serious adverse events, with rates being similar in the two arms. There were six deaths during the induction phase, of which five were in the KCd arm. Safety and treatment tolerability were not influenced by age (≥70 years) or renal impairment (glomerular filtration rate ≤60 mL/min) (*Online Supplementary Table S9*).

Maintenance comparison

A total of 141 participants were randomized between maintenance (n=69) and no maintenance (n=72) between August 2013 and March 2017. The data lock took place on January 3, 2018 (median follow-up from maintenance randomization 10.5 months: maintenance 12.7, observation 7.3). All participants were eligible for the safety analysis: two participants randomized to maintenance did not actually receive the maintenance therapy and were included in the no maintenance arm for the safety analysis (Figure 2). Sixty-six patients given maintenance and 72 not given maintenance were eligible for the efficacy analysis. The patients in the two arms were balanced for baseline characteristics at study entry, and disease response at the time of maintenance randomization (Table 3). The median number of cycles received in the maintenance arm was



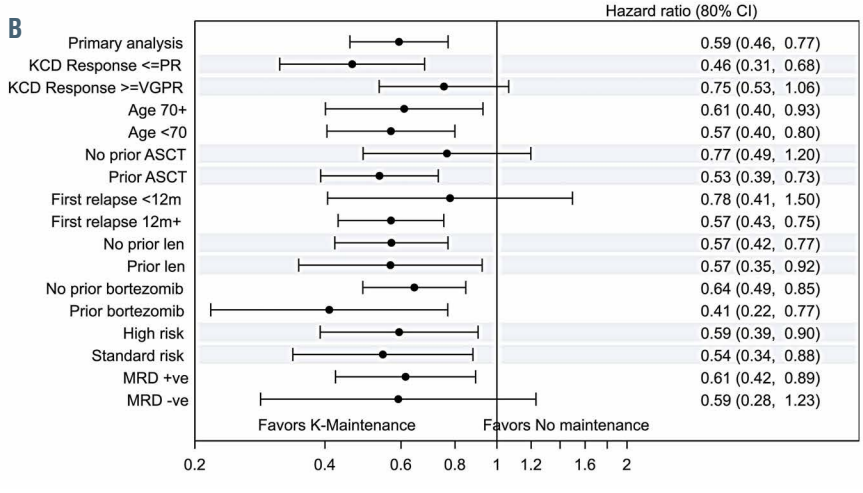


Figure 5. Progression-free survival according to maintenance randomization. (A) Kaplan-Meier estimate of progression-free survival (PFS), shown with 80% confidence intervals, and numbers at risk indicated. (B) Forest plot of PFS in pre-specified subgroups, with hazard ratios and 80% confidence intervals. K Maint: maintenance with carfilzomib; No maint: no maintenance therapy; CI: confidence interval; KCd: carfilzomib, cyclophosphamide, dexamethasone; VCd: bortezomib, cyclophosphamide, dexamethasone; ASCT, autologous stem cell transplantation; 12m: 12 months; len: lenalidomide;.KCD: carfilzomib, cyclophosphamide, dexamethasone; PR: partial response; VGPR: very good partial response; ASCT: autologous stem cell transplantation; 12m: 12 months; len: lenalidomide; MRD: minimal residual disease.

eight (range, 0-19). At the time of analysis, eight patients were still on treatment, 61 had stopped, of whom 11 patients received the maximum of 18 cycles, and 23 (37.7%) had received fewer than six cycles.

Progression-free survival

All participants in the analysis population were included in the PFS analysis, with the exception of one patient who progressed prior to maintenance treatment. A total of 107 events were observed (104 disease progression, 3 deaths). Patients in the carfilzomib maintenance arm had significantly longer PFS (median 11.9 months, 80% CI: 8.0, 13.1), than those who did not receive maintenance therapy (median 5.6 months, 80% CI: 4.8, 6.4; HR=0.59, 80% CI: 0.46, 0.77; *P*=0.0086) (Figure 5A). Disease response at the time of randomization (≥VGPR) was also significantly associated with longer PFS (HR=0.42, 80% CI: 0.32, 0.55; *P*<0.0001) (*Online Supplementary Table S10*). The benefit of maintenance was seen across all subgroups (Figure 5B) and also in patients over 70 years old, who accounted for more than 40% of the participants. Treatment effects were larger for patients whose response to initial therapy was partial response or less or those who had had a prior ASCT. It is also worth noting that treatment effects were similar between patients in standard- and high-risk genetic subgroups, and did not differ according to MRD status at the end of initial treatment. No significant interactions were observed between subgroups and maintenance treatment.

Overall survival, time to next treatment and response depth: maintenance randomization

At the time of analysis, 26/138 participants had died. The median OS from the time of maintenance randomization was 25.7 months (95% CI: 20.8, upper limit not estimated) for maintenance and 24.1 months (95% CI: 21.5, upper limit not estimated) for observation (HR=0.86, 95% CI: 0.39, 1.87; *P*=0.6965). The median time from maintenance randomization to next treatment in the maintenance arm was 21.4 months (95% CI: 20.3, upper limit not estimated) whereas it was 12.9 months (95% CI: 8.3-27.5) in the control group (Fine and Gray HR=0.59, 95% CI: 0.34-1.02; *P*=0.0566).

Table 1. Minimization factors for induction randomization, and baseline characteristics.

	KCd (N=201) n (%)	VCd (N=99) n (%)	Total (N=300) n (%)
Minimization 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)
≥70 years	83 (41.3)	46 (46.5)	129 (43.0)
Sex			
Male	115 (57.2)	64 (64.6)	179 (59.9)
Female	85 (42.3)	35 (35.4)	120 (40.1)
Missing	1 (0.5)	0 (0.0)	1 (0.3)
ECOG performance status			
0	114 (56.7)	54 (54.5)	168 (56.0)
1	73 (36.3)	40 (40.4)	113 (37.7)
2	11 (5.5)	4 (4.0)	15 (5.0)
Missing	3 (1.5)	1 (1.0)	4 (1.3)
ISS stage			
I	100 (49.8)	54 (54.5)	154 (51.3)
II	71 (35.3)	30 (30.3)	101 (33.7)
III	29 (14.4)	15 (15.2)	44 (14.7)
Missing	1 (0.5)	0 (0.0)	1 (0.3)
Lytic bone disease**			
None	79 (39.3)	44 (44.4)	123 (41.0)
Mild	35 (17.4)	16 (16.2)	51 (17.0)
Moderate	29 (14.4)	14 (14.1)	43 (14.3)
Severe	54 (26.8)	24 (24.2)	78 (26.0)
Missing	4 (2.0)	1 (1.0)	4 (1.7)
Heavy chain paraprotein type			
IgG	128 (63.7)	63 (63.6)	191 (63.7)
IgA	47 (23.4)	20 (20.2)	67 (22.3)
IgM	0 (0.0)	1 (1.0)	1 (0.3)
IgD	0 (0.0)	1 (1.0)	1 (0.3)
Light chain only	25 (12.4)	14 (14.1)	39 (13.0)
Missing	1 (0.5)	0 (0.0)	1 (0.3)
Light chain type			
Kappa	136 (67.7)	64 (64.6)	200 (66.7)
Lambda	64 (31.8)	35 (35.4)	99 (33.0)
Missing	1 (0.5)	0 (0.0)	1 (0.3)
Previous lenalidomide?			
Yes	45 (22.5)	23 (23.2)	68 (22.7)
Other previous treatments regimens			
TD/CTD	122 (60.7)	68 (68.7)	190 (63.3)
VD/VCD/PAD	33 (16.4)	18 (18.2)	51 (17.0)
MP/MPT/VMP	7 (3.5)	1 (1.0)	8 (2.7)
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
High-risk lesions (n=102)			
Del(17p) only	11 (15.9)	6 (18.2)	17 (16.7)
Gain(1q) only	43 (62.3)	19 (57.6)	62 (60.8)
Any adverse IGH translocation only	4 (5.8)	4 (12.1)	8 (7.9)
Gain(1q) and del(17p)	4 (5.8)	1 (3.0)	5 (4.9)
Gain(1q) and any adverse IGH translocation	6 (8.7)	2 (6.0)	8 (7.9)
Gain(1q), del(17p) and t(4;14)	1 (1.4)	1 (3.0)	2 (2.0)

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*One participant in the KCd arm was found to be ineligible after randomization, therefore no subsequent data were collected, including baseline characteristics. **Mild = one fracture (any site including vertebrae) or lytic lesion. Moderate = two or three fractures (any site including vertebrae) or lytic lesions. Severe = three or more fractures (any site including vertebrae) or lytic lesions. ***Genetic high risk was defined as at least one of del(17p), gain(1q), or any adverse IgH translocation: t(4;14), t(14;16), or t(14;20). KCd: carfilzomib, cyclophosphamide, dexamethasone; VCd: bortezomib, cyclophosphamide, dexamethasone; ASCT: autologous stem cell transplantation; ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System.

Maintenance improved disease response in 13 participants: one patient with stable disease had a minimal response, eight with partial responses developed ≥VGPR, and four with VGPR achieved complete responses. In the control arm, eight participants' response deepened: seven improved from having partial responses to VGPR and one with a VGPR achieved a complete response. Thus, in the maintenance arm, 10.6% patients achieved a complete response and 50.0% a VGPR as their maximum response overall, compared to 4.2% and 55.6% respectively, in the control arm. Maintenance also increased the rate of MRD negativity (*Online Supplementary Figure S2*). Maintenance was significantly associated with a higher MRD negative rate at 6 months (24.4% *vs*. 3.3%; OR=9.66, 95% CI: 1.17, 80.02; *P*=0.0071). The difference was not statistically significant at 12 months.

Safety and tolerability of carfilzomib maintenance

Of the 50 patients who stopped carfilzomib maintenance therapy early, 40 (80.0%) did so because of disease progression, three stopped due to toxicity (after 5, 6, and 17 cycles), and seven due to the patients' or clinicians' choice. Dose modifications were reported for 55 of 67 participants who received treatment (82.1%), with 11.3% of cycles being delayed. The median dose received was 36 mg/m^2 (target dose). Thirty-four serious adverse events were reported in 24 participants receiving maintenance: 19 serious adverse events, 15 serious adverse reactions (infection or infestation [n=11]; gastrointestinal, cardiac, renal and secondary primary malignancy [n=1 each), no suspected unexpected adverse reaction. In the group not receiving maintenance, six serious adverse events were reported in six participants. Most events (90%) resolved (1 serious adverse event was present and unchanged, 1 resulted in death, 2 were ongoing at the time of death). Adverse reactions are summarized in *Online Supplementary Table S11*. Among adverse reactions of interest, there was one cardiac adverse reaction (grade 2, chest pain), six cases of acute kidney injury (1 grade 3), four of hypertension (2 grade 3), 25 upper respiratory tract/bronchial infections (1 grade 3), and six lung infections (3 grade 3). Toxicity did not appear to increase over time.

Landmark analysis of VCd *versus* KCd-K *versus* KCd

A *post-hoc* landmark analysis was performed at 6 months after first randomization to assess PFS for those patients who had not progressed at this time, comparing VCd with KCd plus maintenance (with carfilzomib), and KCd with no maintenance. The median PFS for patients receiving VCd was 6.6 months (95% CI: 4.6, 9.7), similar to that for patients receiving KCd without maintenance (6.2 months, 95% CI: 5.2, 8.0) (*Online Supplementary Figure S3*). For patients receiving maintenance therapy the median PFS was 12.6 months (95% CI: 8.4, 15.0), reflecting that observed in the primary analysis. The PFS from initial randomization for patients receiving KCd followed by carfilzomib maintenance was also evaluated: among these patients, the median PFS was 18.1 months (95% CI: 14.0, 20.5).

Influence of genetic risk

Genetic risk status at trial entry was available for 187 (62.3%) participants; 55.6% and 52.4% of participants in the KCd and VCd arms, respectively, had adverse-risk genetics (Table 1). Among participants with adverse risk, 78.3% and 63.6% received the planned six cycles of KCd and eight cycles of VCd, respectively, compared to 92.7% and 43.3% of the standard-risk participants (*Online Supplementary Table S12*). The reason for this difference is unclear, but a greater proportion of standard-risk participants in the VCd arm discontinued therapy.

With respect to the initial treatment, more participants with adverse risk achieved ≥VGPR (over 24 weeks) on KCd compared with VCd (38.2% *vs*. 21.9%, OR=2.47, 90% CI: 1.07, 5.72), while standard-risk participants had a similar ≥VGPR rate in the two arms (KCd 34.5%, VCd 33.3%, *P*(interaction)=0.2425) (*Online Supplementary Figure*

Table 2A. Response to treatment at 24 weeks after the initial randomization.

Outcome	KCd	VCd	KCd vs. VCd comparison	
			Difference (%), 90% CI	OR, 90% CI, *P*-value
Participants with available response	194	91		
≥VGPR (primary endpoint)	40.2%	31.9%	8.3 (-1.6, 18.2)	1.48, (0.95, 2.31) NI comparison so *P*-value not relevant
Overall response: ≥PR	84.0%	68.1%	15.9 (6.8, 25.0)	2.72, (1.62, 4.55), *P*=0.0014
Complete response	1.5%	3.3%	-1.8 (-5.2, 1.7)	Logistic regression not performed

Table 2B. Response to treatment at 24 weeks after initial randomization, by genetic risk.

Outcome	High risk			Standard risk			*P*-value for interaction
	KCd	VCd	KCd *vs.* VCd: OR (90% CI)	KCd	VCd	KCd *vs.* VCd: OR (90% CI)	
Participants with available response	68	32		55	27		
≥VGPR	38.2%	21.9%	2.47 (1.07, 5.72)	34.5%	33.3%	1.06 (0.46, 2.46)	0.2425
Overall response: ≥PR	79.4%	68.8%	2.30 (0.98, 5.41)	87.3%	70.4%	3.00 (1.09, 8.29)	0.7403
Participants with available MRD data	52	17		41	15		
MRD negativity	17.3%	17.6%	1.13 (0.32, 3.95)	12.2%	13.3%	0.85 (0.18, 3.99)	0.8153

KCd: carfilzomib, cyclophosphamide, dexamethasone; VCd: bortezomib, cyclophosphamide, dexamethasone; OR: odds ratio; CI: confidence interval; VGPR: very good partial response; PR: partial response; NI: non-inferiority; MRD: minimal residual disease.

S4A, Table 2B). This difference between risk groups was not seen for the ORR, with there being more responses to KCd than to VCd in both adverse- and standard-risk participants, (79.4% *vs*. 68.8%, and 87.3% *vs*. 70.4%). Of participants with an adverse IgH translocation, only one of seven (14.3%) in the VCd arm achieved a VGPR, compared to seven of 11 (63.6%) in the KCd arm (*Online Supplementary Figure S4B*). There was no significant difference in MRD-negative rates (Table 2B) or PFS between the KCd and VCd arms in either adverse- or standard-risk patients.

With regard to the maintenance randomization, genetic risk status was available overall for 94 participants (67%) (Table 3), with 48.4% adverse-risk patients in the maintenance arm, and 55.1% in the observation arm. Of those completing treatment, the standard-risk patients received a median of nine cycles (range, 0-19), compared with five cycles (range, 1-18) for the adverse-risk patients. While 11 of 23 (47.8%) standard-risk patients received >12 months of maintenance, only three of 17 (17.6%) adverse-risk patients did so. In a Cox proportional hazards model for PFS, including genetic risk and MRD, in addition to minimization factors, genetic risk was independently prognostic, alongside treatment and disease response at the time of randomization (genetic risk: HR=1.91, 80% CI: 1.27, 2.59; *P*=0.0333). No difference in the impact of maintenance on PFS was observed between the risk groups: both benefited from maintenance treatment (Figure 5B, *Online Supplementary Figure S5*).

Table 3. Characteristics of patients in the maintenance randomization: at study entry and at randomization.

	Maintenance (N=69) n (%)	No maintenance (N=72) n (%)	Total (N=141) n (%)
Baseline characteristics at initial randomization			
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%)
High risk lesions (n=49)			
Del(17p) only	5 (22.7%)	3 (11.1%)	8 (16.3%)
Gain(1q) only	15 (68.2%)	15 (55.6%)	30 (61.2%)
t(4;14) only	1 (4.5%)	3 (11.1%)	4 (8.2%)
Gain(1q) and del(17p)	0	3 (11.1%)	3 (6.1%)
Gain(1q) and any adverse IGH translocation	1 (4.5%)	2 (7.4%)	3 (6.1%)
Gain(1q), del(17p) and t(4;14)	0	1 (3.7%)	1 (2.0%)
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 randomization			
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 randomization			
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%)

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ISS: International Staging System; CR: complete response; VGPR: very good partial response; sCR: stringent complete response; PR: partial response; MR: minimal response; SD: stable disease; NC: no change; PD: progressive disease; ASCT: autologous stem cell transplantation; ECOG: Eastern Cooperative Oncology Group; MRD: minimal residual disease.

Discussion

Despite three published head-to-head studies of carfilzomib *versus* bortezomib,[4,9-11] the relative benefits of one proteasome inhibitor over the other remain unresolved. Here we show that, when used as second-line therapy, carfilzomib is at least as efficacious as bortezomib, in terms of major disease response, when given for a fixed duration in combination with cyclophosphamide and dexamethasone. There were fewer discontinuations among patients treated with KCd than among those treated with VCd, indicating that KCd was tolerated better than VCd. Carfilzomib was also well tolerated and effective as a maintenance agent, providing a PFS benefit when compared with observation only. No new safety signals were seen, as toxicity profiles reflected previous experience with these proteasome inhibitors, carfilzomib being predominantly associated with anemia and cardiovascular complications while bortezomib was linked to a higher incidence of peripheral neuropathy, thrombocytopenia

and neutropenia. Notably, the carfilzomib dose of 36 mg/m^2 in the current study was associated with a relatively low incidence of cardiovascular adverse events (3.6%) and grade ≥3 hypertension (3.6%) when compared with the higher dose of 56 mg/m^2 in the ENDEAVOR trial (6.5% and 9.0%, respectively).[4,9] Relatively high rates of infectious serious adverse events in both arms indicate that antibiotic prophylaxis may be considered for relapsed patients treated with proteasome inhibitor triplets, at least for the first few cycles.

The broadly equivalent outcomes of carfilzomib and bortezomib when used in fixed duration protocols, as demonstrated in this study, are in line with the results of the CLARION and ENDURANCE studies, indicating that the PFS and OS benefits seen with carfilzomib in ENDEAVOR were related to the greater tolerability of this proteasome inhibitor, facilitating extended therapy. Another contributing factor to the differing results between our study and ENDEAVOR may be the smaller percentage of our cohort who were exposed to bortezomib and who were, thus, less likely to be resistant. Here we extend our observations to show that maintenance with single-agent carfilzomib is effective in prolonging PFS. Taken as a whole, our observations and the results of previous studies suggest that optimal clinical benefit from carfilzomib can be achieved using well-tolerated extended protocols. This notion is further supported by the more recent studies of carfilzomib in combination with the CD38 antibodies, daratumumab and isatuximab, in which outcomes of patients treated at first relapse may indeed be impressive.[6,22] With increasing use of carfilzomib leading to improved management of the drug's toxicity profile, and considering promising results with weekly dosing,[23] durable disease control may be achievable with this proteasome inhibitor, especially in the setting of relapsed disease.

Certain features of our cohort of patients may have influenced the comparative tolerability of KCd and VCd. Even with a fixed duration of treatment of 6 months, there were fewer discontinuations with KCd than with VCd, and a substantial proportion of patients in the VCd arm discontinued due to their own choice or a clinician's decision. While we do not have details of these decisions, it is noteworthy that over half of patients in this study had previously received a thalidomide regimen, hence several may have been especially sensitive to or intolerant of a salvage regimen containing yet another neurotoxic drug, thus accounting for the high rates of discontinuation in the VCd arm.

We demonstrate that carfilzomib maintenance is efficacious regardless of genetic risk, and in renally impaired and older patients. Our findings on the activity and tolerability of carfilzomib maintenance in the RRMM setting add to those from two phase I/II studies in newly diagnosed patients ≥65 years old, or ineligible for transplantation, who received single-agent carfilzomib maintenance (until progression) after nine cycles of KCd.[12,13] In those studies, responses deepened during the maintenance phase, and the 3-year OS rate of around 70% in the two trials indicates that extended treatment with carfilzomib can produce promising results when used early in the treatment pathway. In our study in RRMM patients, carfilzomib maintenance was well tolerated, and the incidence and severity of known toxicities were similar to those in previous studies. Maintenance was associated with a higher rate of MRD negativity at 6, but not at 12 months, perhaps linked to the reduction from four to two doses per cycle of carfilzomib. Thus, patients in MUK*five* trial who received KCd followed by carfilzomib maintenance had a combined median PFS of 18.1 months, which was slightly shorter than the median of 22.2 months for patients treated at second line in ENDEAVOR. In the A.R.R.O.W. study,[24] a dose of 70 mg/m^2 was administered weekly until progression to patients treated at third line, with the median treatment duration being 38 weeks (range, 0.1-84.1), suggesting that it may be possible to deliver a weekly maintenance schedule for an extended period.

Our results indicate potentially superior activity of KCd over VCd, in terms of ≥VGPR rate in patients with adverse genetic risk, and ORR in those relapsing early (<12 months) from first-line therapy. The superior major response rate for participants with adverse risk in the KCd arm cannot be explained by higher discontinuation rates in the VCd arm, as the major response rates were similar in the two arms for standard-risk patients among whom the difference in discontinuation rates was more pronounced (56.7% for VCd compared to 7.3% for KCd). We also observed that patients with del(17p) and adverse IgH translocations may have benefited especially from KCd in terms of VGPR (*Online Supplementary Figure S4B*). Despite a higher VGPR rate in adverse-risk patients in the carfilzomib arm, we did not observe a difference in MRD-negative response, nor a PFS benefit. This is likely because the short duration of triplet therapy (6 cycles), and limited carfilzomib maintenance may be insufficient for optimal disease response in these relapsed patients. We note with interest that the KCd regimen, when used in newly diagnosed patients ineligible for ASCT, followed by carfilzomib maintenance until progression, was recently reported to overcome the inferior prognosis of high-risk patients. However, these frontline studies used nine cycles of KCd followed by carfilzomib maintenance with four doses per cycle until progression, altogether a more intensive regimen than in the MUK*five* study.[25] There is, therefore, increasing evidence that carfilzomib has good activity in adverse-risk disease, although regimen intensity may be vital. In this context, it is interesting to consider the recent ENDURANCE study,[11] in which carfilzomib was compared with bortezomib in NDMM patients when given in combination with lenalidomide and dexamethasone. In this trial, high-risk patients, apart from those with t(4;14), were excluded.

One attraction of the KCd regimen is its relatively modest cost, hence its use in studies for RRMM and NDMM patients. In the Nordic CARFI phase II study, patients were treated at first relapse with four cycles of KCd followed by ASCT conditioned with high-dose melphalan plus two doses of carfilzomib.[26] KCd has been used to treat non-transplant-eligible, newly diagnosed patients, with the carfilzomib given bi-weekly or weekly,[12,27] for up to nine cycles of induction, followed by carfilzomib maintenance. The regimen was reported to have been tolerated well in the older patient group, as we also found.

In summary, the results from the MUK*five* study demonstrate the non-inferiority of carfilzomib over bortezomib in combination with cyclophosphamide and dexamethasone in the early relapse setting, and the efficacy of carfilzomib maintenance. Our data are also consistent with the high activity of carfilzomib in adverse-risk disease, both in terms of a higher VGPR rate, when compared with

that achieved in response to bortezomib, and in the efficacy of maintenance therapy. With an increasing number of patients who, at first relapse, are exposed or refractory to bortezomib and lenalidomide, KCd followed by carfilzomib maintenance represents an economically competitive and clinically feasible regimen, reserving other novel agent combinations such as those with CD38 and pomalidomide, or the new agents targeting B-cell maturation antigen and T-cell redirecting therapies, for a subsequent relapse or progression. Further studies are needed to explore the potential greater activity of carfilzomib in patients with adverse-risk disease, in whom the tolerability during prolonged use may make this the proteasome inhibitor of choice.

Disclosures

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Contributions

KLY, DS, LF, CW, JCa, RGO, GM, FD and SRB designed the study. KLY, KR, MG, NR, CW, JCa, NKR, RGO and MFK performed the research and collected data. DS and LF performed trial and data management. HWA, SHa and CB performed independent clinical review of endpoint data. SHi and SRB performed statistical analyses. RMdT and RGO performed analysis of minimal residual disease. MFK and JCr performed central assessment of genetic risk. KLY, HWA, CB, SHi and SRB wrote the manuscript. All authors provided input into, and had control over, the final version of the manuscript.

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Data-sharing statement

Any requests for trial data will be reviewed by the trial management group in the first instance. Only requests that have a methodologically sound proposal and whose proposed use of the data has been approved by the independent trial steering committee will be considered. Proposals should be directed to the corresponding author in the first instance; to gain access; data requestors will need to sign a data access agreement. The study protocol is publicly available.[15]

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