

Randomized phase II study of weekly carfilzomib 70 mg/m² and dexamethasone with or without cyclophosphamide in relapsed and/or refractory multiple myeloma patients

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Authors contributions

BP and VGC have contributed equally to this work. MVM and EMO: conceptualization of the study. MVM, BP and VGC: methodology, investigation, writing original draft, writing-review and editing, formal analysis and visualization. The rest of authors (AS, MJM, AO, EG, LR, JL, FE, JML, ECarillo, EClavero, RRT, BRB, APGR, VD, FdA, SG, JPO, MTH, AGM, JBargay, JBladé, JJL JFSM and EMO): investigation, writing-review and editing.

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Data sharing statement

The data that support the findings of this study are available from the corresponding author, [MVM] and the first [BP] and second authors [VGC] upon reasonable request.

Clinical trial information

The trial is registered at ClinicalTrials.gov, number NCT03336073.

Abstract

In this randomized phase 2 study (GEM-KyCyDex), the combination of weekly carfilzomib 70 mg/m², cyclophosphamide and dexamethasone was compared to carfilzomib and dexamethasone (Kd) in relapsed/refractory multiple myeloma (RRMM) after 1-3 prior lines (PLs). 197 patients were included and randomized 1:1 to receive KCd (97 patients) or Kd (100 patients) in 28-day cycles until progressive disease or unacceptable toxicity occurred. Patient median age was 70 years, and the median number of PLs was 1 (1-3). More than 90% of patients had previously been exposed to proteasome inhibitors, ≈70% to immunomodulators, and ≈50% were refractory to their last line (mainly lenalidomide) in both groups. After a median follow-up of 37 months, median progression-free survival (PFS) was 19.1 and 16.6 months in KCd and Kd, respectively (*P*=0.577). Of note, in the post hoc analysis of the lenalidomide-refractory population, the addition of cyclophosphamide to Kd resulted in a significant benefit in terms of PFS: 18.4 vs. 11.3 months (Hazard ratio 1.7 [1.1-2.7]; *P*=0.043). The overall response rate and the percentage of patients who achieved complete response was around 70% and 20% in both groups. The addition of cyclophosphamide to Kd did not result in any safety signal, except for severe infections (7% vs. 2%). In conclusion, the combination of cyclophosphamide with Kd 70 mg/m² weekly does not improve outcomes as compared with Kd alone in RRMM after 1-3 PLs, but a significant benefit in PFS was observed with the triplet in the lenalidomide-refractory population. The administration of weekly carfilzomib 70 mg/m² was safe and convenient, and, overall, the toxicity was manageable in both arms.

Introduction

The introduction of agents such as bortezomib and lenalidomide in the upfront treatment of multiple myeloma (MM) drastically improved the survival of MM patients¹. However, most patients end up relapsing. Novel rescue therapies are emerging for the treatment at the moment of the relapse, some of which have a different mechanism of action from bortezomib or lenalidomide, while others belong to the same class.

Carfilzomib is a tetrapeptide epoxyketone second-generation proteasome inhibitor that irreversibly inhibits the chymotrypsin-like (CT-L) activities of the constitutive proteasome and immunoproteasome². Several studies and clinical trials have been designed to improve the efficacy of carfilzomib by increasing its dose³, combining it with another agent^{4,5}, reducing infusion-related events and toxicity, as well as developing a most convenient schedule^{6,7}.

The results of the randomized, open-label, multicenter Phase 3 study (ENDEAVOR trial)⁵ have led to the combination of carfilzomib plus dexamethasone becoming one of the backbones of RRMM treatment. In this trial, patients with RRMM after 1 to 3 prior lines of therapy were randomized to receive carfilzomib at a dose of 56 mg/m² twice-weekly in a 30-min infusion or bortezomib at a dose of 1.3 mg/m² intravenously or subcutaneously, plus low dose dexamethasone in both arms. The carfilzomib group showed an improved ORR compared to bortezomib group (77% vs. 63%). Substantial numbers achieved at least very good partial response (VGPR) (54% vs. 29%) and even complete response (CR) (13% vs. 6%), with a good safety profile. Overall, these

responses in the carfilzomib group led to significantly better progression-free survival (PFS) (18.7 vs. 9.4 months) and overall survival (OS) (47.6 vs. 40.0 months)⁸.

However, the twice-weekly schedule of carfilzomib treatment is likely to be burdensome. For this reason, phase 1/2 and phase 3 studies, the CHAMPION-1 and A.R.R.O.W. trials, respectively, were developed to adapt the treatment to allow once-weekly administration^{6,7}. The A.R.R.O.W. trial, which compared carfilzomib 27 mg/m² given twice weekly with carfilzomib 70 mg/m² once weekly in RRMM after 2-3 prior lines, showed significant statistically differences in ORR (62.9% vs. 40.8%) and in PFS (11.2 vs. 7.6 months) that favored the once-weekly arm.

Cyclophosphamide (Cy) is a convenient alkylating agent with a well-known anti-tumoral activity which has been widely used in combination with bortezomib⁹⁻¹² in MM patients, improving the efficacy with a good safety profile. Based on this background, the Spanish Myeloma Group (GEM/PETHEMA) designed a randomized, open-label, multicenter Phase 2 study (GEM-KyCyDex) to evaluate the safety and efficacy of the combination of once-weekly carfilzomib 70 mg/m² and dexamethasone plus/minus cyclophosphamide in RRMM patients. Here we report, the results of this trial.

Methods

Study design and participants

Patients were recruited from 24 Spanish hospitals, and had to meet the following inclusion criteria: 1) age ≥ 18 years; 2) ECOG performance status ≤ 2 ; 3) RRMM after 1-3 lines of therapy; and 4) measurable disease according to the International Myeloma Working Group (IMWG) criteria¹³. Refractoriness to PI was an exclusion criterion. All participants provided written informed consent and the study protocol was approved by the institutional review boards or ethics committees of all participating institutions. The trial is registered at ClinicalTrials.gov, number NCT03336073.

Randomization

Patients were randomized (1:1) to receive either carfilzomib, Cy and dexamethasone (KCd group) or carfilzomib and dexamethasone (Kd group).

Procedures

Patients received a 30-min infusion carfilzomib at a dose of 20 mg/m² on day 1 of cycle 1, and of 70 mg/m² given thereafter on days 1, 8, and 15. Patients older than 75 years received 56 mg/m² during cycles 1 and 2, and 70 mg/m² thereafter if it was well-tolerated. Patients also received dexamethasone (20 mg orally or intravenously; 10 mg for those >75 years) on the day carfilzomib was administered and the day after, plus/minus Cy at a dose of 300 mg/m² intravenously on days 1, 8 and 15 during the first 12 cycles. After the 12th cycle, treatment was administered every other week. The treatment was administered in 28-day cycles until progression disease, the occurrence of unacceptable

toxicity, a physician's decision, or the revocation of a participant's informed consent. Dose reductions were allowed to manage the toxicity.

Adverse events were reported until 30 days after the final dose of the study treatment and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events 4.0.

Cytogenetic risk status was assessed using fluorescence *in situ* hybridization in a central laboratory¹⁴. Cytogenetic high-risk was defined based on IMWG criteria¹⁵.

Responses were assessed monthly according to 2014 IMWG criteria¹⁶. A bone marrow aspiration was performed in central laboratories to confirm suspected CR and to measure the minimal residual disease (MRD)¹⁷.

Outcomes

The primary endpoint was progression-free survival (PFS), defined as the time from randomization to disease progression or death from any cause. Secondary endpoints were overall response rate (ORR), defined as the attainment of a partial response (PR) or better; percentage of immunophenotypic CR; time to progression (TTP), defined as the time from randomization to disease progression; overall survival (OS), defined as the time from randomization until death from any cause; incidence and grade of adverse events (AEs); and discontinuation of treatment in both groups.

Statistical analysis

The necessary sample size was estimated using the one-sample survival method, based on the primary endpoint of the study. A median PFS of 23

months in the KCd arm would be considered effective based on the 18-month median PFS of Kd previously reported⁸. Two hundred and fifty-six patients were required to provide a power of 80% to demonstrate the efficacy of the experimental arm at a significance level (alpha) of 0.05.

The distributions of PFS, TTP and OS were estimated using the Kaplan–Meier method. The differences between survival in the two arms were defined using the log-rank test, and the corresponding hazard ratio (HR) and 95% confidence interval (CI) were estimated using by Cox regression. Chi-square tests identified statistically significant differences between qualitative variables and the associated odds ratio (OR) and 95% CI were estimated by logistic regression.

The analysis included all randomized patients who had received at least one dose of a study treatment.

Values of $P < 0.05$ were considered significant. Statistical analysis was performed with IBM SPSS Statistics, version 26.

Results

Between February 2018 and April 2020, 229 patients were considered for inclusion in the trial. The 197 of them who met the inclusion criteria were randomly allocated to the carfilzomib, cyclophosphamide and dexamethasone (KCd, N=97) or the carfilzomib and dexamethasone (Kd, N=100) groups (Figure 1). There were no significant statistically differences between the characteristics of the two groups (Table 1). The median number of prior lines (PL) of therapy was 1 (range, 1-3), 90% and 12% of patients had previously been exposed to PI and to Cy, respectively, 60% had received IMiDs, and approximately 50% were refractory to lenalidomide (43 (44.3%) and 46 (46.0%) patients in the KCd and Kd groups, respectively).

At the cut-off date (April 2022), the median follow-up was 37 months (4.7-50.2 months), by which time 173 events had been reported, 72 (74.2%) in the KCd arm and 78 (78.0%) in the Kd arm. Twenty-four patients were still under treatment. At least 12 cycles were administered in 51% of patients of the KCd group, and in 49.5% of the Kd group ($P=0.821$), with a median of 12 (range, 1-45) and 11 (range, 1-40) cycles ($P=0.833$), respectively.

Efficacy and survival

Median PFS was 19.1 months in the KCd group, and 16.6 months in the Kd group (HR 1.1 [95% CI, 0.8-1.5]; $P=0.577$) (Figure 2A). The entire post hoc subgroup analysis is shown in Table 2. It is worth mentioning that patients who received KCd and who were refractory to the last line of therapy (regardless of the treatment received) achieved better PFS than patients treated with Kd (19.1 vs. 11.7 months; HR 1.8 [95% CI, 1.1-2.8]; $P=0.014$). It is also of note that the

addition of Cy resulted in better PFS in the lenalidomide-refractory population compared with the Kd group, with a median PFS of 18.4 vs. 11.3 months (HR 1.7 [95% CI, 1.1-2.7], $P=0.043$) (Figure 2B). This improvement was focused on lenalidomide-refractory patients after 1 PL.

No differences were observed in the ORR, CR or MRD rates between the KCd and Kd groups (Table 3). However, 11.3% and 12.2% of patients achieved MRD negativity in the KCd and Kd groups, respectively, and PFS was significantly better in patients in the triplet arm who reached this response (not estimated, HR 8.9 [95% CI, 1.1-73.6]; $P=0.044$) (Figure S1). In addition, lenalidomide-refractory patients allocated to KCd were significantly more likely to reach stringent CR (22.0% vs. 6.5%; OR 4.0 [95% CI, 1.0-16.1]; $P=0.047$) and MRD negativity (22.0% vs. 2.1%; OR 54.0 [95% CI, 2.8-1040.0]; $P=0.008$) (Table 3).

With regard to TTP, 58 (59.7%) and 73 (73%) patients experienced progressive disease in the KCd and Kd groups, respectively. However, no differences were observed between patients treated with the alkylator-containing vs. alkylator-free regimen, with TTPs of 25.5 vs. 17.1 months (HR 1.3 [95% CI, 0.9-1.8]; $P=0.168$) (Figure 3A).

Turning, finally, to OS, 46 (47.4%) and 36 (36.0%) events occurred in the KCd and Kd arms, respectively. No statistically significant differences were noted. The median OS of the triplet regimen was 39.7 months, and it was not reached in the doublet scheme (HR 1.4 [95% CI, 0.9-2.2]; $P=0.111$) (Figure 3B). In addition, no difference in OS was observed in lenalidomide-refractory patients between KCd and Kd groups (37.0 vs. 38.0 months, HR 1.2 [95% CI, 0.7-2.2]; $P=0.574$). A post hoc analysis of PFS2, defined as the time from randomization

to disease progression after the next line of treatment or death from any cause, was performed. Overall, 49 (50.5%) and 65 (65.0%) patients in the KCd and Kd groups received next line of therapy ($P=0.255$). No differences were observed in the subsequent line of treatment received (Table S1), and majority of patients in both arms were rescued by daratumumab-based combinations (37 (69.4%) patients in the KCd arm and 44 (67.7%) patients in the Kd arm ($P=0.847$)). The probability of achieving PR or better was 73.3% and 77.4% in the KCd and Kd arms, respectively ($P=0.627$). However, the median PFS2 was shorter in the KCd arm compared to the Kd arm: 23.7 months vs. 36.3 months (HR 1.5 [95% CI, 0.9-2.3]; $P=0.073$) (Figure S2).

Safety profile

The most frequent adverse events (AEs) and the AEs of interest in the safety population are summarized in Tables 4 and 5, respectively. Adverse events grade (G) ≥ 3 were reported in 53.6% (44 of 97) and 43% (43 of 100) of patients in the KCd and Kd groups, respectively. After twelve cycles, the median dose intensity of carfilzomib in the KCd arm was 90% (interquartile range, 76.1-100.0) and 89.2% (interquartile range, 76.4-97.2) in the Kd arm. In general terms, the addition of cyclophosphamide to Kd did not result in any new safety signal, but there was a trend towards higher toxicity in the triplet group. With regard to hematological toxicity, no differences were observed between both groups, except for neutropenia (Table 4). The incidence of any grade of neutropenia was higher in the KCd group (24.7% vs. 16.0%), especially the grade AE G ≥ 3 (13.4% vs. 5.0%; OR 3.0 [95% CI, 1.1-8.6]; $P=0.049$). Considering solely the non-hematological AEs, asthenia was the only AE reported in KCd with a statistically significant difference compared with Kd

(32.9% vs. 20.0%; OR 2.0 [95% CI, 1.1-3.8]; $P=0.040$). Infections were the main type of non-hematological toxicity reported in the trial, occurring in roughly equal proportions in the two groups (Table 4). However, it is worth noting that G4 infections (sepsis) were more frequent in patients treated with KCd (7.2% vs. 2.0%; $P=0.080$). Although no differences in any grade or $G\geq 3$ of hypertension between groups, the addition of cyclophosphamide showed a numerical increase in cardiovascular events (including atrial fibrillation, cardiac failure, acute pulmonary edema, ischemic cardiac disease and pulmonary hypertension) (12.4% vs. 5.0%; $P=0.065$). In addition, it is important to mention that 9 grade 5 AEs were notified, five in the KCd (one due to sudden death, and the others due to various types of pneumonia (aspiration, nosocomial, Influenza A, and bilateral SARS-CoV2 pneumonia) and four in the Kd group (two due to acute respiratory distress syndrome, one to *Legionella pneumoniae* sepsis, and one to uremic hemolytic syndrome).

There were no differences in the percentages of patients who delayed their treatment between the KCd (44 patients, 44.5%) and Kd (41 patients, 41.0%) groups (Table S2). In the triplet regimen, the most common reason for delay were upper respiratory infections (12.4%), neutropenia (8.2%), diarrhea (6.2%) and asthenia (6.2%). However, upper respiratory tract infections (12.0%), other infections (7.0%) and pneumonia (5.0%) occurred in the doublet regimen. There were also no significant differences in patients who required dose reductions due to AEs, 23 (23.7%) patients with KCd, and 22 (22.0%) patients with Kd. The foremost causes of treatment dose reduction were asthenia (5.2%) in the KCd group and arterial hypertension (8.0%) in the Kd group. Carfilzomib was the

drug most often adjusted after the development of adverse events in both arms of the study.

During treatment, 173 patients discontinued, mainly because of progressive disease. Discontinuation due to progression was less frequent in the KCd (47.0%) than the Kd group (67.8%) (OR 2.4 [95% CI, 1.3-4.4]; $P=0.006$). Toxicity was the second most common cause of discontinuation and was higher in the KCd than the Kd group, with 16 vs. 7 patients (19.3% vs. 7.8%; OR 2.8 [95% CI, 1.1-7.3]; $P=0.031$). Within KCd group, 3 patients discontinued due to renal impairment, 3 due to cardiac failure, 2 due to bad tolerance, and 8 (1 patient each severe AE) due to neutropenia, atrial fibrillation, myocardial infarction, acute pulmonary edema, pulmonary hypertension, thrombotic microangiopathy, hemolytic anemia and hepatic toxicity. In contrast, 3 patients discontinued Kd due to bad tolerance, 2 due to cardiac failure, and 1 due to uremic hemolytic syndrome and 1 due to posterior reversible encephalopathy syndrome. No differences were observed in the occurrence of cardiotoxicity as a cause of discontinuation (8 patients in KCd and 3 in Kd). Sixty percent of patients who presented this unacceptable toxicity were over 70 years of age. However, the timing of the occurrence of toxicity differed between the arms. Patients treated with KCd developed AEs, resulting in earlier discontinuation than in those treated with Kd, after a median of 5 (1-26) vs. 17 cycles (10-20) cycles.

After 37 months of follow-up, 56% and 66% of patients in KCd and Kd, respectively, were still alive. During the clinical trial, and within 30 days of receiving the last dose of the study treatment, 10 patients died in the KCd group (3 from disease progression, 4 from an unrelated cause, and 3 due to

infections), and 7 in the Kd group (3 from disease progression, 3 due to infections and 1 due to uremic hemolytic syndrome).

Discussion

In this randomized phase 2 trial, a 70 mg/m² dose of carfilzomib once weekly with dexamethasone plus/minus Cy was effective in RRMM after 1-3 PL. The addition of Cy to Kd showed no significant statistical differences compared with patients treated with Kd in PFS, TTP, OS, ORR or the other response categories when all randomized patients were analyzed. However, Kd alone was suboptimal in patients who were refractory to lenalidomide with a median PFS of 11.3 months, whereas these patients treated with KCd achieved a median PFS of 18.4 months, similar to all randomized subjects. Moreover, the addition of Cy to Kd in this subgroup of patients resulted into a significantly higher percentage of stringent CR and MRD-negative rates.

The results of GEM-KyCyDex study are consistent with those of other clinical trials that tested the KCd combination. The Phase 2 MUK*five* trial¹⁸ showed greater efficacy of KCd over VCd (bortezomib, cyclophosphamide, dexamethasone) in RRMM after one PL. In this study, carfilzomib was administered twice weekly at a dose of 36 mg/m² and oral Cy was given weekly (on days 1, 8 and 15) at a fixed dose of 500 mg. In addition, after 6 cycles, patients were randomized 1:1 to receive carfilzomib maintenance on days 1 and 15, or nothing. This twice-weekly KCd yielded an ORR of 84.0%, which is slightly higher than that reported in our study. However, the population of the MUK*five* study was RRMM after 1 prior line, less exposed to PI and IMiDs (1 out of 5 patients to each drug), if we focus on those patients who received maintenance with Kd, PFS and OS were not different to those reported in our study (19 and 32 months, respectively). In the single arm, multicenter, Canadian phase 2 trial (MCRN-003/CCTGMYX.1)¹⁹, the target population was similar to

that of the patients enrolled in our trial: RRMM after 1-3 PL, almost 90% and 80% of patients exposed to PI and IMiDs, respectively; and similar drug schedule: weekly Kd 70 mg/m² and weekly oral dose of 300 mg/m² Cy (capped at 500 mg and discontinued after the 12th cycle). This combination resulted in a similar ORR (85%) but the 29% of patients achieving at least CR was higher than in our study. However, this did not translate into a more prolonged PFS or OS than that reported in our study, 17.2 and 27.4 months, respectively.

One finding to be highlighted is the potential benefit of the addition of Cy to Kd to overcome the dismal prognosis of the lenalidomide-refractory population. In our trial, Kd alone was suboptimal in this population with a PFS of 11.3 months. This discouraging result is consistent with most experimental treatments explored in phase 3 trials of RRMM after 1-3 PL²⁰⁻²³, except for the combination of antiCD38 monoclonal antibodies and Kd^{24,25}. Our results, with a median PFS of 18.4 months in the lenalidomide-refractory population, argue in favor of this combination. Therefore, KCd once weekly could be a cost-effective treatment in these populations, especially if the antiCD38 monoclonal antibody is not a valid option because of safety or other issues. Although majority of the patients in this study were naïve for antiCD38 monoclonal antibodies, this combination could represent an option in the future for patients already exposed to both lenalidomide and antiCD38 monoclonal antibodies.

The twice-weekly Kd combination had been investigated in several phase 3 trials. However, in the present study, weekly Kd was explored with the aim of conciliating efficacy and patient quality of life. Our Kd arm resulted in a median PFS of almost 17 months, slightly lower than that of the twice-weekly Kd of the ENDEAVOR trial (18.7 months)⁵. Notably, patients enrolled in the ENDEAVOR

study were less exposed to bortezomib (54%), and less exposed and refractory to lenalidomide (38% and 24% respectively). Also, Kd 56 mg/m² twice weekly was the control arm of the phase 3 CANDOR and IKEMA trials^{24,26}. Both studies enrolled patients with similar characteristics: RRMM after 1-3 PL (50% after ≥2 lines), 80-90% and 70-80% have been previously exposed to PIs and IMiDs, and 1 out of 3 patients were refractory to PIs or IMiDs. In the CANDOR trial, twice-weekly Kd showed consistent results to our weekly Kd in ORR (73.0%), at least CR (13.0%) and PFS (15.2 months). The results showed in the IKEMA trial were slightly better in response (ORR: 83.7% and CR rate: 28.5%) and PFS (19.2 months). Hence, weekly 70 mg/m² Kd presented comparable efficacy to twice-weekly 56 mg/m² Kd and this schedule could be a suitable and convenient option for Kd-eligible patients, as previously reported in the A.R.R.O.W study although it was only focused in patients after 2-3 prior lines⁷. In addition, since no differences were noted between both arms of our trial, some subset of patients might benefit from Kd alone, such as elderly patients who are not refractory to lenalidomide or patients with a poor bone marrow reserve.

The trend towards worse OS with KCd in our study was an unexpected result. No differences were observed in the death rates during the clinical trial, or within 30 days following the last dose of the study treatment. In the post hoc analysis of PFS2, fewer patients received rescue therapies in the KCd group compared with the Kd group. Although both groups were treated with similar salvage therapies, the PFS2 in patients assigned to the KCd group was shorter. There is no clear explanation for this exploratory finding, but cumulative toxicity with KCd might have had a role in this poorer outcome. In addition, a

speculative hypothesis could be that the addition of Cy may have caused further DNA damage in the tumor cell, with consequent genomic instability, resulting in a more aggressive and difficult-to-treat disease.

No new safety signals were reported in the GEM-KyCyDex trial. As expected, the triplet was more toxic than the doublet scheme. This fact resulted in a significant higher discontinuation rate in the KCd arm, especially in older patients (≥ 70 years) and during the early cycles. In this regard, we propose that the dose of carfilzomib in the KCd group could be raised to 56 mg/m^2 instead of 70 mg/m^2 considering the efficacy as well as the safety profile. In addition, it is unclear whether a medium-high dose of cyclophosphamide produces the same tumor activity as a daily low dose. Switching to daily oral low-dose cyclophosphamide could improve safety without substantially changing effectiveness. Both strategies are worth investigating to mitigate toxicity and individualize the dose, especially in the elderly population.

Our trial has some limitations such as being a phase 2 randomized trial, the completion of recruitment earlier than expected because of the SARS-Cov-2 pandemic, and the study population. Enrolled patients do not represent the current RRMM after 1-3 PL because most of them have been already exposed to PIs, IMiDs and antiCD38 monoclonal antibodies, whilst only 5% of patients in our study were exposed to anti-CD38 drug, and those refractory to PIs were not included. Therefore, the real-world candidates to receive weekly KCd or Kd are unrepresented in this trial.

In summary, this study has not met its primary endpoint, and in general terms, there were no differences between KCd and Kd. However, the GEM-KyCyDex trial has shown how weekly Kd plus/minus Cy is a feasible, effective, and well-

tolerated regimen for RRMM patients after 1-3 PL. Our data points to the addition of Cy to Kd could result in a significant clinical impact in the lenalidomide-refractory population. KCd could be used as cost-effective salvage therapy in places where access to anti-CD38 monoclonal antibodies is limited, or as a rescue tool until new immunotherapies are approved for treating patients with earlier relapses.

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Table legends

Table 1. Baseline characteristics of patients included in the trial.

Table 2. Progression-free survival: *post hoc* subgroup analysis.

Table 3. Responses achieved in the trial: all randomized and lenalidomide-refractory patients.

Table 4. Hematological and non-hematological adverse events.

Table 5. Adverse events of interest in safety population.

Table 1. Baseline characteristics of patients included in the trial.

	KCd (N=97)	Kd (N=100)
Age, median (range)	70 (40-88)	71 (46-88)
>75 years, N (%)	24 (24)	33 (33)
Male, N (%)	49 (50.5)	51 (51)
ECOG 0-1, N (%)	94 (97)	93 (93)
MM subtype, N (%)		
IgG	44 (45.6)	58 (58)
IgA	33 (34)	22 (22)
IgD	2 (2.1)	1 (1)
Bence-Jones	18 (18.5)	18 (18)
ISS, N (%)		
I	32 (33)	24 (24)
II	26 (25.8)	37 (37)
III	23 (23.7)	16 (16)
Missing	17 (17.5)	23 (23)
Elevated LDH, N (%)	13 (13.4)	12 (12)
CTG, N (%)		
SR	48 (49.5)	48 (48)
HRCA	24 (24.7)	28 (28)
Missing	26 (25.8)	24 (24)
HRCA if 1q is considered, N (%)	44 (45.4)	48 (48)
Extramedullary disease, N (%)	14 (14.4)	11 (11)
LVEF, median (range)	65 (51-80)	64 (55-86)
Median number of PL (range)	1 (1-3)	1 (1-3)
1 PL (%)	66 (67)	65 (65)
2 PL (%)	23 (23.7)	25 (25)
3 PL (%)	9 (9.3)	10 (10)
Prior PI therapy (%)	92 (94.8)	91 (91)
V/K/Ixa, %	92.8/0/5	90/0/2
Prior IMiD therapy, N (%)	72 (74.2)	66 (66)
Tal/Len/Pom, %	30.9/56.7/4.1	21/53/3
Refractory to lenalidomide, N (%)	43 (44)	46 (46)
Prior antiCD38 mAbs, N (%)	4 (4)	5 (5)
Refractory to antiCD38, N (%)	4 (4.2)	5 (5)
Prior cyclophosphamide, N (%)	12 (12.4)	12 (12)
Prior ASCT, N (%)	49 (50.5)	44 (44)
Refractory to the last line of therapy, N (%)	45 (46.4)	46 (46)

Abbreviations: MM: Multiple myeloma; ISS: international Staging System; LDH: lactate dehydrogenase; CTG: Cytogenetic; SR: standard-risk; HRCA: High-risk cytogenetic abnormalities; ECOG: Eastern Cooperative Oncology Group; LVEF: Left Ventricular Ejection Fraction; PL: Prior line; PI: Proteasome inhibitor; V: Bortezomib; Ixa: Ixazomib; Tal: Thalidomide; Len: lenalidomide; Pom: Pomalidomide; IMiD: immunomodulator; mAbs: monoclonal antibody; KCd: Carfilzomib, cyclophosphamide and dexamethasone; Kd: Carfilzomib and dexamethasone; ASCT: Autologous stem cell transplantation.

Table 2. Progression-free survival: *post hoc* subgroup analysis.

Subgroups	KCd (N=97)		Kd (N=100)		HR CI 95%, <i>P</i> value
	Events/Patients	Median PFS (months)	Events/Patients	Median PFS (months)	
All randomized patients	72/97	19.1	78/100	16.6	1.1 (0.8-1.5), 0.577
≤65 years	21/30	22.2	25/30	12.6	1.6 (0.9-2.8), 0.136
>65 years	48/63	17.5	52/68	17.1	1.0 (0.7-1.5), 0.982
≥75 years	17/24	20.0	23/33	20.7	1.1 (0.6-2.1), 0.768
Extramedullary disease	14/14	5.9	9/11	7.0	1.4 (0.6-3.2), 0.478
ISS I	17/32	35.7	18/24	25.2	1.3 (0.7-2.5), 0.437
ISS II-III	38/48	17.5	39/53	11.7	1.1 (0.7-1.7), 0.772
SR CTG	32/48	21.8	32/48	22.3	1.0 (0.6-1.7), 0.915
HRCA CTG	22/24	12.1	24/28	15.4	1.3 (0.7-2.3), 0.417
HRCA if 1q gain is considered	36/44	15.8	39/48	16.6	1.2 (0.7-1.8), 0.515
1 PL	49/65	19.8	49/65	17.1	1.1 (0.7-1.6), 0.784
2 PL	19/23	17.0	21/25	16.4	1.0 (0.5-1.9), 0.966
3 PL	4/9	NR	8/10	7.2	1.9 (0.6-6.6), 0.300
PI Naïve	2/5	NR	6/9	27.7	2.3 (0.5-11.5), 0.313
PI Exposed	70/92	18.0	72/91	16.4	1.1 (0.8-1.5), 0.652
IMiD Naïve	19/25	19.8	25/34	21.6	1.2 (0.6-2.1), 0.598
IMiD Exposed	53/72	18.4	53/66	14.1	1.2 (0.8-1.8), 0.272
Cy exposed	6/12	14.2	9/12	9.6	1.8 (0.6-5.1), 0.269
Refractory to last line of therapy	27/45	19.1	40/46	11.7	1.8 (1.1-2.8), 0.014
Lenalidomide-refractory after any PL	27/43	18.4	39/46	11.3	1.7 (1.1-2.7); 0.043
After 1 PL	12/21	18.4	18/20	11.7	1.9 (0.9-4.0); 0.079
After 2 PL	12/15	17.0	15/18	11.3	1.1 (0.5-2.5); 0.702
After 3 PL	3/7	NR	6/8	6.6	2.4 (0.6-9.8); 0.220

Abbreviations: KCd: Carfilzomib, cyclophosphamide and dexamethasone; Kd: Carfilzomib and dexamethasone; Cy: Cyclophosphamide; HR: Hazard ratio; CI: Confidence interval; PFS: Progression-free survival; ISS: International Staging System; SR: Standard-risk; HRCA: High-risk chromosomal abnormalities; PL: Prior lines; PI: proteasome inhibitor; IMiD: Immunomodulators.

Table 3. Responses achieved in the trial: all randomized and lenalidomide-refractory patients.

	All randomized patients			Lenalidomide-refractory patients		
	KCd (N=94)	Kd (N=98)	P value	KCd (N=41)	Kd (N=46)	P value
CR or better, N (%)	19 (20.2)	22 (22.4)	NS	11 (26.8)	7 (15.2)	NS
Stringent CR, N (%)	16 (17.2)	16 (16.5)		9 (22.0)	3 (6.5)	0.037
CR MRD neg, N (%)	11 (11.3)	12 (12.2)		9 (22.0)	1 (2.1)	0.005
CR MRD pos, N (%)	6 (6.3)	9 (9.2)		1 (2.4)	6 (13.0)	
MRD not evaluated, N (%)	2	1		1 (2.4)	0 (0)	
VGPR or better, N (%)	51 (54.3)	50 (51.1)	NS	24 (58.5)	20 (43.5)	NS
VGPR, N (%)	32 (34.0)	28 (28.6)		13 (31.7)	13 (28.3)	
PR, N (%)	17 (18.1)	19 (19.4)		4 (9.8)	7 (15.2)	
MR, N (%)	4 (4.3)	7 (7.1)		2 (4.9)	3 (6.5)	
SD, N (%)	20 (21.3)	16 (16.3)		10 (24.4)	12 (26.1)	
PD, N (%)	2 (2.1)	6 (6.1)		1 (2.4)	4 (8.7)	
ORR, N (%)	68 (72.3)	69 (70.4)	NS	28 (68.3)	27 (58.7)	NS

*Response no evaluated in 3 patients in the KCd group and in 2 patients in the Kd group.

Abbreviations: KCd: Carfilzomib, cyclophosphamide and dexamethasone; Kd: Carfilzomib and dexamethasone; CR: complete response; MRD: minimal residual disease; Neg: negative; Pos: positive; VGPR: Very good partial response; PR: partial response; MR: minimal response; SD: stable disease; PD: progression disease; ORR: Overall rate response; NS: Non-significant.

Table 4. Hematological and non-hematological adverse events.

	KCd (N=97)			Kd (N=100)		
	Grade 1-2	Grade 3-4	Grade 5	Grade 1-2	Grade 3-4	Grade 5
Hematological adverse events						
Anemia	20.6%	8.2%	0%	24%	11%	0%
Neutropenia	11.3%	13.4%	0%	11%	5%	0%
Thrombocytopenia	13.4%	2%	0%	13%	8%	0%
Non-hematological adverse events						
Upper respiratory tract infection	21.6%	6.2%	0%	28%	7%	0%
Urinary tract Infection	6.2%	3.1%	0%	1%	0%	0%
Gastrointestinal Infection	2%	3.1%	0%	0%	0%	0%
Other infections	9.3%	4.1%	0%	14%	4%	0%
Atrial fibrillation	0%	3.1%	0%	0%	1%	0%
Arterial hypertension	13.4%	4.1%	0%	8%	10%	0%
Dyspnoea	5.2%	1%	0%	4%	2%	0%
Rash	2%	0%	0%	1%	0%	0%
Nausea	11.3%	0%	0%	15%	0%	0%
Vomiting	3.1%	0%	0%	7%	0%	0%
Diarrhea	18.6%	1%	0%	11%	0%	0%
Constipation	2%	0%	0%	2%	1%	0%
Dyspepsia	3.1%	0%	0%	3%	0%	0%
Anorexy	1%	0%	0%	0%	0%	0%
Asthenia	28.8%	4.1%	0%	18%	2%	0%
Peripheral edema	6.2%	0%	0%	3%	0%	0%
Non-infectious fever	11.3%	0%	0%	11%	2%	0%

Abbreviations: KCd: carfilzomib, cyclophosphamide and dexamethasone; Kd: carfilzomib and dexamethasone.

Table 5. Adverse events of interest in safety population.

	KCd (N=97)			Kd (N=100)		
	Grade 1-2	Grade 3-4	Grade 5	Grade 1-2	Grade 3-4	Grade 5
Peripheral neuropathy	15.5%	0%	0%	8%	0%	0%
Acute renal failure	2%	4.1%	0%	3%	7%	0%
Hemolytic uremic syndrome	0%	0%	0%	0%	1%	1%
Cardiac failure	3.1%	2%	0%	2%	1%	0%
Pneumonia	0%	9.3%	3%	0%	9%	1%
Sepsis	0%	6.2%	1%	0%	1%	1%
Ischemic cardiac disease	0%	1%	0%	0%	0%	0%
Acute pulmonary edema	0%	2%	0%	0%	0%	0%
Pulmonary hypertension	0%	1%	0%	0%	1%	0%

Abbreviations: KCd: carfilzomib, cyclophosphamide and dexamethasone; Kd: carfilzomib and dexamethasone.

Figure legends

Figure 1. Trial profile. Abbreviations: KCd: carfilzomib, cyclophosphamide and dexamethasone; Kd: carfilzomib and dexamethasone.

Figure 2. Primary endpoint: progression-free survival. **(A)** Progression-free survival in the entire cohort. **(B)** Progression-free survival in the lenalidomide-refractory patients. Abbreviations: CI: confidence interval; HR: hazard ratio; KCd: carfilzomib, cyclophosphamide and dexamethasone; Kd: carfilzomib and dexamethasone.

Figure 3. Secondary endpoints in the entire cohort. **(A)** Time to progression. **(B)** Overall survival. Abbreviations: CI: confidence interval; HR: hazard ratio; KCd: carfilzomib, cyclophosphamide and dexamethasone; Kd: carfilzomib and dexamethasone.

**229 patients assessed
for eligibility**

Excluded (N=32)

23 met exclusion criteria
9 due to other reasons

**197 patients
randomly allocated**

**KCd arm
(N=97)**

**Kd arm
(N=100)**

83 discontinued treatment

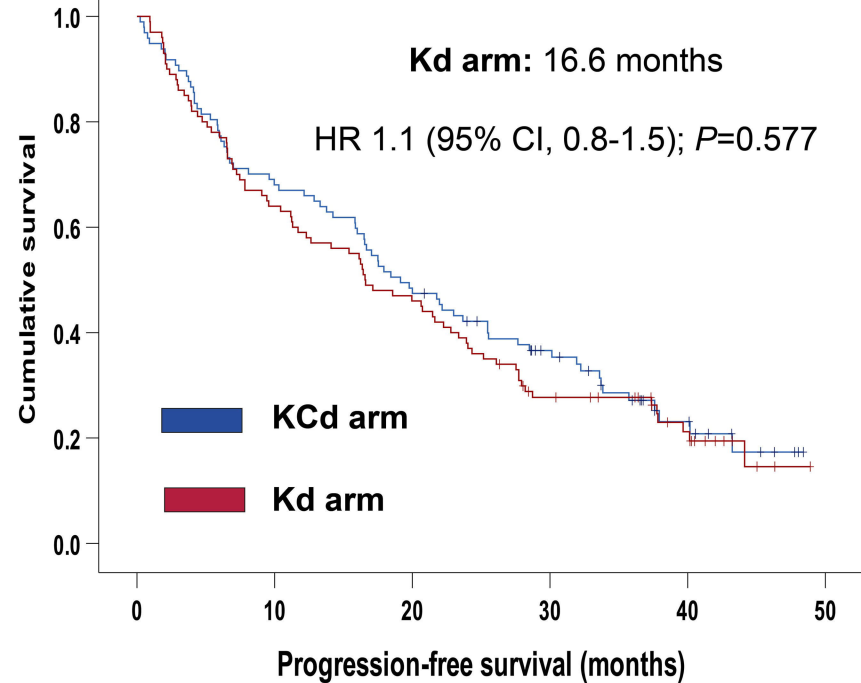
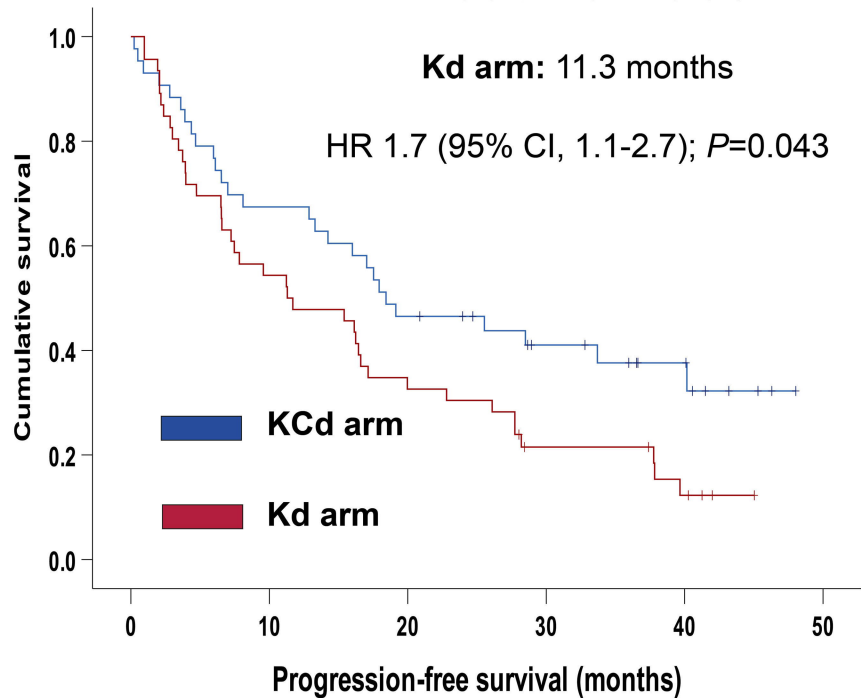
39 due to disease progression
16 due to toxicity
11 withdrew informed consent
8 for investigator decision
7 due to death
1 lost follow-up
1 due to other reasons

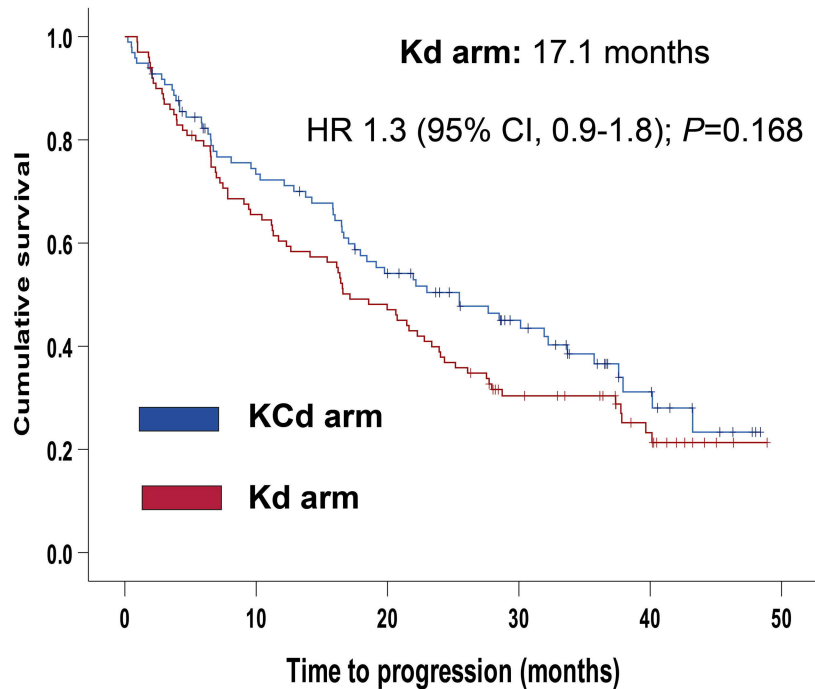
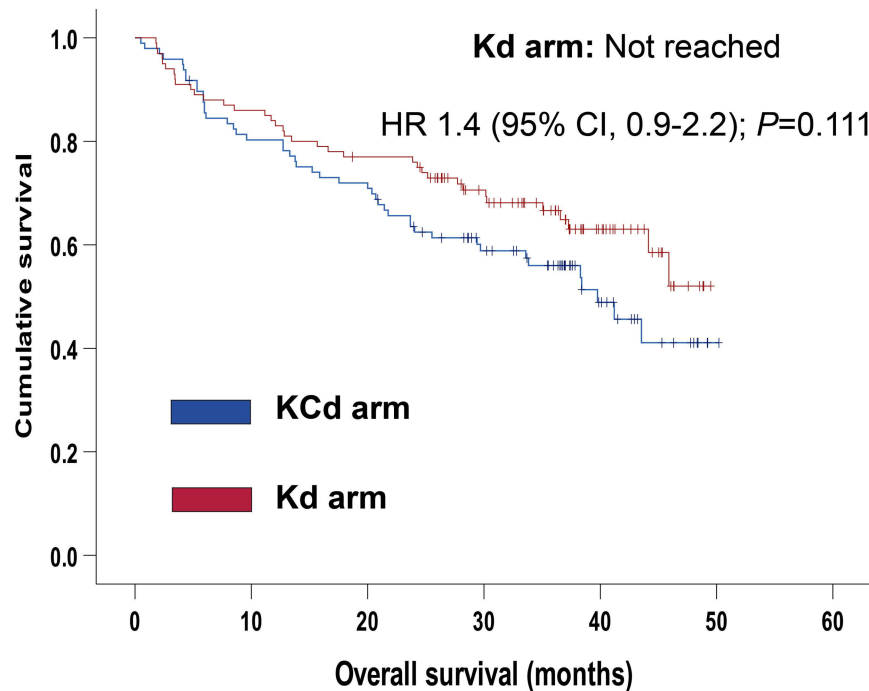
90 discontinued treatment

61 due to disease progression
7 due to toxicity
7 for investigator decision
6 withdrew informed consent
6 due to death
2 due to other reasons
1 lost follow-up

**97 analyzed
for efficacy
and safety**

**100 analyzed
for efficacy
and safety**

A**KCd arm: 19.1 months****Kd arm: 16.6 months**HR 1.1 (95% CI, 0.8-1.5); $P=0.577$ **B****KCd arm: 18.4 months****Kd arm: 11.3 months**HR 1.7 (95% CI, 1.1-2.7); $P=0.043$ 

A**KCd arm: 25.5 months****Kd arm: 17.1 months**HR 1.3 (95% CI, 0.9-1.8); $P=0.168$ **B****KCd arm: 39.7 months****Kd arm: Not reached**HR 1.4 (95% CI, 0.9-2.2); $P=0.111$ 

Supplementary data legends

Table S1. Subsequent antimyeloma therapies.

Table S2. Adverse events: main cause of dose delay and dose reduction.

Figure S1. Progression-free survival in patients who achieved MRD negative.

Figure S2. Progression-free survival 2.

Table S1. Subsequent antineoplastic therapies.

		KCd arm (N=49)	Kd arm (N=65)
Daratumumab-based combinations	Daratumumab alone	2	2
	D-Rd	23	31
	D-Vd	6	5
	D-Pd	3	4
	D-Id	0	1
	D-SVd	0	1
Pomalidomide-based combinations	PCd	2	5
	Pd	0	1
BCMA-targeted therapy	Belantamab mafodotin	1	1
	CAR T-cells	1	4
Alkylating agents	Polychemotherapy	1	1
	Melfufen	1	0
Other combinations	CELMoDs	0	1
	VRd	0	1
	Rd	7	7
	Kd	1	0
	RT	1	0

Abbreviations: C: cyclophosphamide; CAR: chimeric antigenic receptor; CELMoDs: cereblon E3 ligase modulators; D: daratumumab; d: dexamethasone; I: ibrutinib; K: carfilzomib; P: pomalidomide; R: lenalidomide; RT: radiotherapy; S: selinexor; V: bortezomib.

Table S2. Adverse events: main cause of dose delay and dose reduction.

	KCD (N=97)		KD (N=100)	
	Dose delay	Dose reduction	Dose delay	Dose reduction
Hematological adverse events				
Anemia	1%	0%	3%	0%
Neutropenia	8.2%	0%	1%	1%
Thrombocytopenia	1%	0%	4%	0%
Non-hematological adverse events				
Sepsis	2%	0%	0%	0%
Upper respiratory tract infection	12.4%	1%	12%	1%
Pneumonia	3.1%	0%	5%	0%
Other infections	5.2%	0%	7%	0%
Atrial fibrillation	0%	0%	1%	0%
Arterial hypertension	5.2%	1%	2%	9%
Cardiac failure	2%	2.1%	1%	3%
Dyspnoea	2%	2.1%	1%	1%
Pulmonary hypertension	0%	0%	0%	1%
Nausea	0%	1%	0%	0%
Diarrhea	6.2%	1%	2%	0%
Mucositis	2%	0%	0%	0%
Dyspepsia	0%	1%	0%	0%
Acute renal failure	1%	0%	3%	1%
Peripheral neuropathy	1%	0%	1%	0%
Anorexy	1%	0%	0%	0%
Asthenia	6.2%	5.2%	0%	2%
Non-infectious fever	1%	0%	0%	0%

KCd: Carfilzomib, cyclophosphamide and dexamethasone; Kd: Carfilzomib and dexamethasone

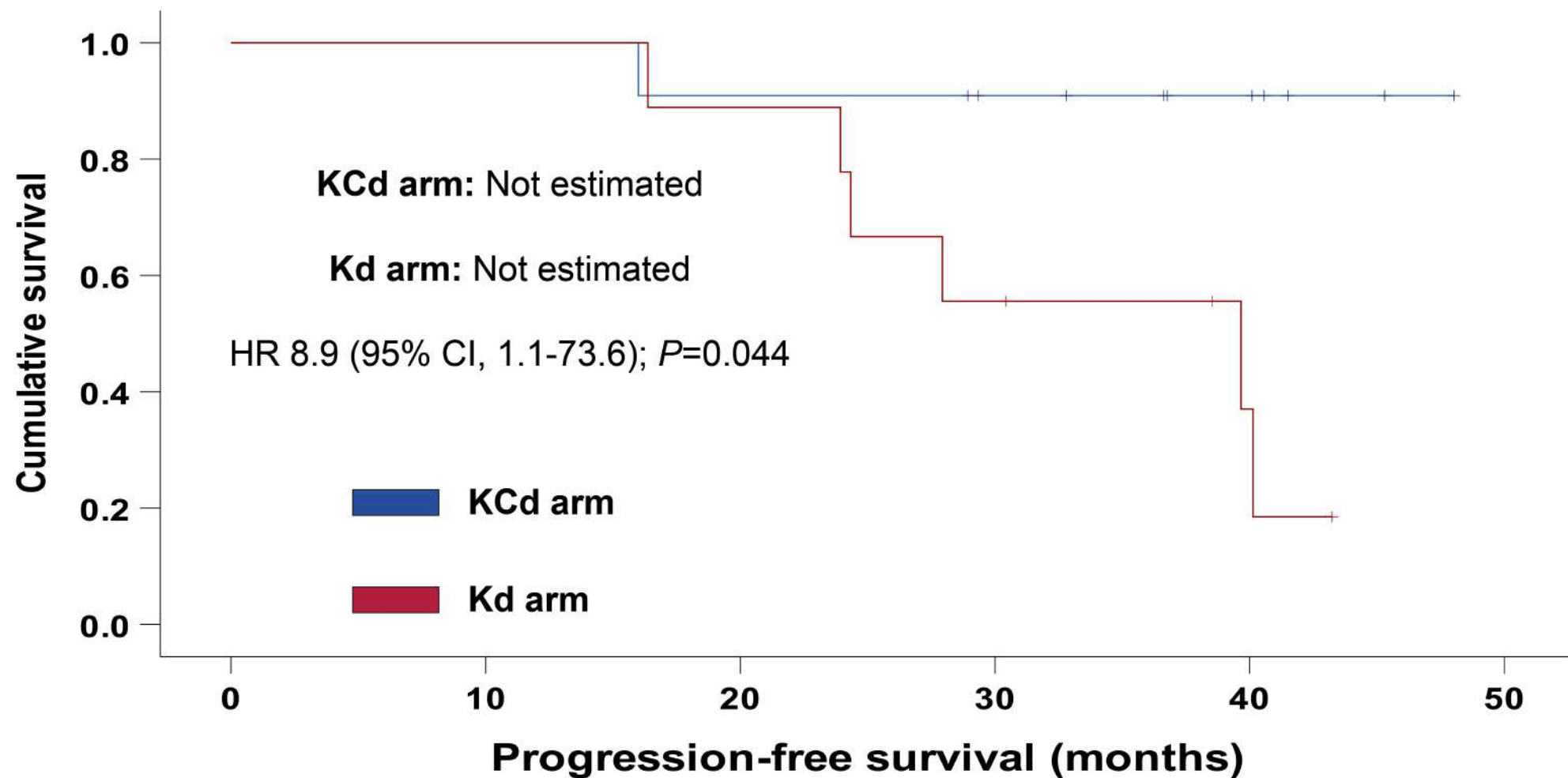


Figure S1. Progression-free survival in patients who achieved minimal residual disease negative.

Abbreviations: CI: confidence interval; HR: hazard ratio.

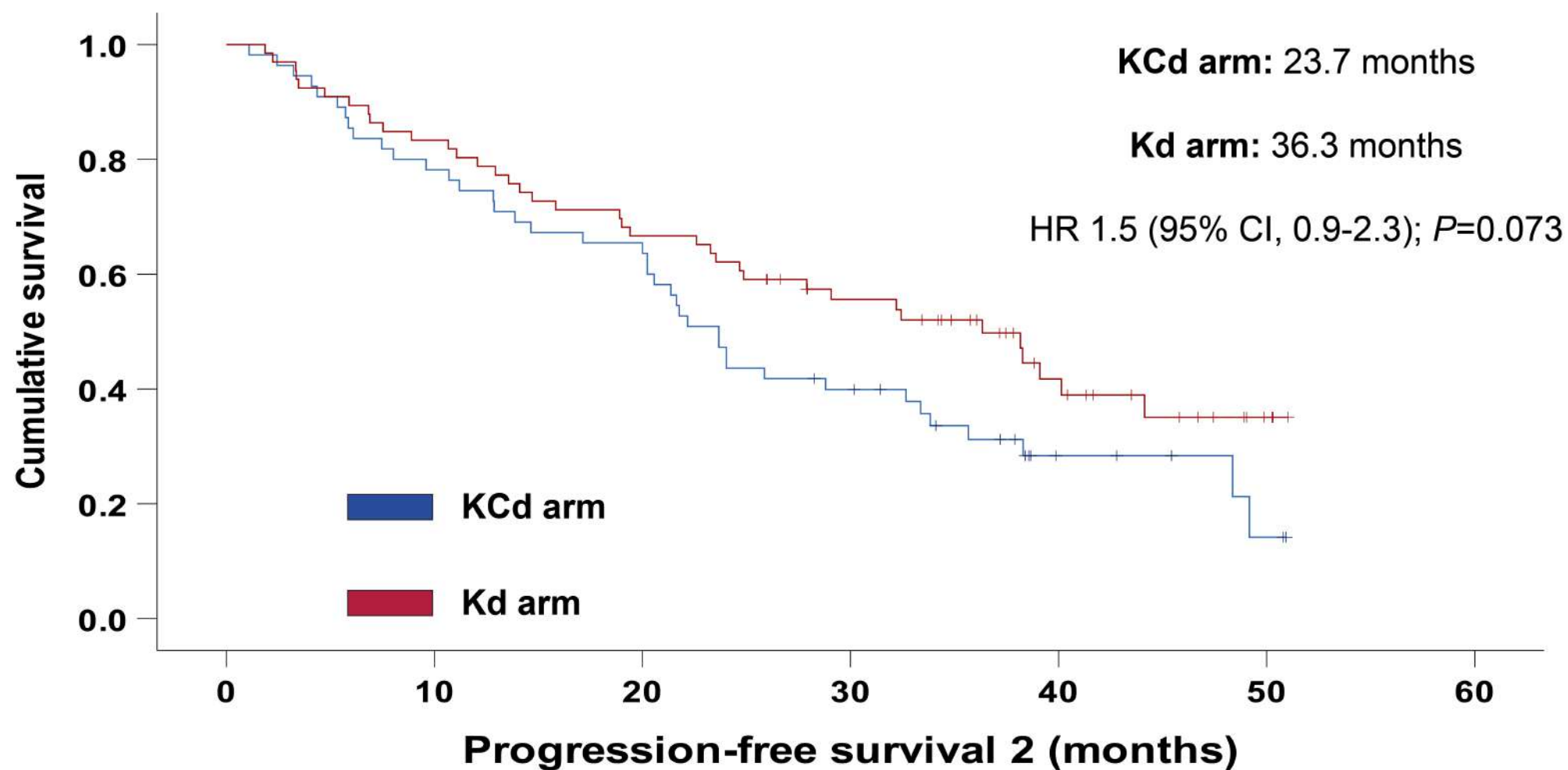


Figure S2. Progression-free survival 2.

Abbreviations: CI: confidence interval; HR: hazard ratio.