Upfront autologous haematopoietic stem-cell transplantation versus carfilzomib–cyclophosphamide–dexamethasone consolidation with carfilzomib maintenance in patients with newly diagnosed multiple myeloma in England and Wales (CARDAMON): a randomised, phase 2, non-inferiority trial

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Summary

Background Standard-of-care treatment for patients with newly diagnosed multiple myeloma is bortezomib-based induction followed by high-dose melphalan and autologous haematopoietic stem-cell transplantation (HSCT) and lenalidomide maintenance. We aimed to evaluate whether an immunomodulatory-free carfilzomib-based induction, consolidation, and maintenance protocol without autologous HSCT was non-inferior to the same induction regimen followed by autologous HSCT and maintenance.

Methods CARDAMON is a randomised, open-label, phase 2 trial in 19 hospitals in England and Wales, UK. Newly diagnosed, transplantation-eligible patients with multiple myeloma aged 18 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 received four 28-day cycles of carfilzomib (56 mg/m² intravenously on days 1, 2, 8, 9, 15, and 16), cyclophosphamide (500 mg orally on days 1, 8, and 15), and dexamethasone (40 mg orally on days 1, 8, 15, and 22; KCd), followed by peripheral blood stem cell mobilisation. Patients with at least a partial response were randomly assigned (1:1) to either high-dose melphalan and autologous HSCT or four cycles of KCd. All randomised patients received 18 cycles of carfilzomib maintenance (56 mg/m² intravenously on days 1, 8, and 15). The primary outcomes were the proportion of patients with at least a very good partial response after induction and difference in progression-free survival rate at 2 years from randomisation (non-inferiority margin 10%), both assessed by intention to treat. Safety was assessed in all patients who started treatment. The trial is registered with ClinicalTrials.gov (NCT02315716); recruitment is complete and all patients are in follow-up.

Findings Between June 16, 2015, and July 8, 2019, 281 patients were enrolled, with 218 proceeding to randomisation (109 assigned to the KCd consolidation group [99 of whom completed consolidation] and 109 to the HSCT group [104 of whom underwent transplantation]). A further seven patients withdrew before initiation of carfilzomib maintenance (two in the KCd consolidation group *vs* five in the HSCT group). Median age was 59 years (IQR 52 to 64); 166 (59%) of 281 patients were male and 115 (41%) were female. 152 (71%) of 214 patients with known ethnicity were White, 37 (17%) were Black, 18 (8%) were Asian, 5 (2%) identified as Mixed, and 2 (1%) identified as other. Median follow-up from randomisation was 40·2 months (IQR 32·7 to 51·8). After induction, 162 (57·7%; 95% CI 51·6 to 63·5) of 281 patients had at least a very good partial response. The 2-year progression-free survival was 75% (95% CI 65 to 82) in the HSCT group versus 68% (95% CI 58 to 76) in the KCd group (difference –7·2%, 70% CI –11·1 to –2·8), exceeding the non-inferiority margin. The most common grade 3–4 events during KCd induction and consolidation were lymphocytopenia (72 [26%] of 278 patients who started induction; 15 [14%] of 109 patients who started consolidation) and infection (50 [18%] of 278 for induction; 15 [14%] of 109 for consolidation), and during carfilzomib maintenance were hypertension (20 [21%] of 97 patients in the KCd consolidation group *vs* 23 [23%] of 99 patients in the HSCT group) and infection (16 [16%] of 97 patients *vs* 25 [25%] of 99). Treatment-related serious adverse events at any point during the trial were reported in 109 (39%) of 278 patients who started induction, with infections (80 [29%]) being the most common. Treatment-emergent deaths were reported in five (2%) of 278 patients during induction (three from infection, one from cardiac event, and one from renal failure) and one of 99 patients during maintenance after autologous HSCT (oesophageal carcinoma).

Interpretation KCd did not meet the criteria for non-inferiority compared with autologous HSCT, but the marginal difference in progression-free survival suggests that further studies are warranted to explore deferred autologous HSCT in some subgroups, such as individuals who are MRD negative after induction.

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Introduction

The role of upfront autologous haematopoietic stem-cell transplantation (HSCT) for newly diagnosed transplantation-eligible patients with multiple myeloma has been examined in phase 3 clinical trials published between 2017 and 2022. The IFM 2009 study,[1] EMN02/HO95,[2] and DETERMINATION trials[3] showed an improvement in progression-free survival for individuals receiving upfront autologous HSCT compared with ongoing treatment. All studies used a bortezomib-containing induction regimen, then lenalidomide maintenance after HSCT. These studies incorporated lenalidomide maintenance, which has the greatest benefit in standard-risk disease, but there is evidence that extended proteasome inhibitor treatment after HSCT might benefit patients with high risk (eg, patients with multiple myeloma with 17p deletion).[4]

Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 1980, and March 31, 2022, using the search terms "myeloma", "newly diagnosed", "transplantation", "carfilzomib", "cyclophosphamide", and "maintenance" in the title or abstract and added the search filter "clinical trials". We identified six full-text articles reporting data from clinical trials in newly diagnosed patients with multiple myeloma: one phase 2 trial evaluating carfilzomib, lenalidomide, and dexamethasone (KRd), carfilzomib–cyclophosphamide–dexamethasone (KCd) with transplantation, and KRd with transplantation; one phase 3 trial evaluating KRd with cyclophosphamide and transplantation; three phase 2 or phase 1b/2 trials evaluating KCd without transplantation; and one phase 1b/2 trial evaluating KCd with thalidomide and transplantation. Phase 3 trials published in the past 10 years have evaluated upfront autologous haematopoietic stem-cell transplantation (HSCT) in fit patients with newly diagnosed myeloma, but, except for the phase 2 study evaluating carfilzomib regimens, these trials have used bortezomib-based induction triplets. Until now, all studies have shown more advantages from autologous HSCT in terms of progression-free survival than novel agent combinations, including one study comparing KRd for four cycles with transplantation to KRd for 12 cycles without transplantation. Nevertheless, these trials have been powered to show superiority of autologous HSCT, whereas our study was designed to evaluate non-inferiority of no autologous HSCT. The phase 2 trial examining KRd without HSCT, KCd with HSCT, and KRd with HSCT showed the superiority of KRd with autologous HSCT over the other two groups. However, no randomised trial has evaluated a KCd-based first-line regimen with or without autologous HSCT in combination with carfilzomib maintenance.

Added value of this study

Our results provide a starting point for further research testing the delayed autologous HSCT pathway in selected groups of patients with newly diagnosed multiple myeloma. Our data show that KCd consolidation did not meet the criteria for non-inferiority when compared with autologous HSCT, thus corroborating previously reported studies using bortezomib-based or carfilzomib-based induction and lenalidomide maintenance. However, the non-inferiority margin of 10% was only slightly exceeded (–11·1%), and we provide preliminary evidence that patients with minimal residual disease (MRD) negativity after KCd induction could be candidates for deferred autologous HSCT and continued chemotherapy. This important observation required testing of MRD after induction and before autologous HSCT, which has not been previously reported. We also show that single-agent carfilzomib is tolerable as maintenance therapy, which is important because extended therapy with a proteasome inhibitor is likely to be required to maintain response in patients with high-risk multiple myeloma. Our data on an immunomodulatory-drug-free induction and maintenance protocol will be of value for patients who are unable to tolerate IMiDs and for health-care systems that cannot reimburse KRd.

Implications of all the available evidence

Our study shows that an immunomodulatory-drug-free treatment pathway using carfilzomib is deliverable, tolerable, and induces good response rates. Studies published in 2017 that used lenalidomide-containing regimens and lenalidomide maintenance have reported the superiority of upfront autologous HSCT, and our results are similar in terms of the relative difference in progression-free survival. Our work complements these studies by assessing the benefits of upfront autologous HSCT in a different way. Upfront autologous HSCT should remain the preferred treatment option for transplant-eligible, newly diagnosed multiple myeloma. However, deferred autologous HSCT in some patient subgroups should be investigated in large prospective trials. Alongside data from the FORTE study, our results with single-agent carfilzomib maintenance will inform its use for maintenance therapy in high-risk multiple myeloma, with appropriate mitigation and management of side-effects. The ATLAS study is currently investigating KRd maintenance after autologous HSCT, with de-escalation to lenalidomide for MRD-negative patients with standard risk, and will help further refine maintenance approaches. Further work to refine the approach based on MRD status after induction and to adapt to the depth of response will help clinicians to use an ever-increasing number of active agents to maximise benefit while avoiding unnecessary toxicity.

Extended therapy with bortezomib, however, is limited by neurotoxicity.[5] Although ixazomib is an oral proteasome inhibitor, results as a maintenance therapy have not shown a consistent benefit.[6,7]

Carfilzomib is commonly used to treat relapsed multiple myeloma. However, there are increasing data for its use as a first-line therapy,[8–10] resulting in high response rates and high rates of minimal residual disease (MRD) negativity. The FORTE study[8] has reported responses to carfilzomib triplets in transplantation-eligible patients with multiple myeloma, including MRD-negativity rates. Data are accumulating regarding the efficacy of carfilzomib in high-risk disease multiple myeloma,[11,12] in which extended use of proteasome inhibitor regimens might be advantageous. Alternatives to lenalidomide as a maintenance therapy are also being studied, most notably CD38 antibodies,[13] and carfilzomib, lenalidomide, and dexamethasone (KRd) in an MRD-risk-adapted way,[14] but the use of proteasome inhibitor-based maintenance remains to be established after autologous HSCT.

All randomised trials investigating the benefit of autologous HSCT as an upfront therapy have been designed to support the statistical superiority of transplantation over a non-transplantation consolidation approach. Despite a clear progression-free survival advantage of autologous HSCT in these studies,[1–4] an overall survival advantage has not yet emerged, which prompts the question of whether patients are harmed by not receiving upfront autologous HSCT. This is a pertinent question because, despite advances in supportive care, autologous HSCT remains associated with considerable morbidity, recovery time, and a small mortality rate. The lack of a substantiated long-term overall survival benefit of upfront autologous HSCT is also emphasised by increasingly effective first-line and salvage regimens, which allow the debate between upfront autologous HSCT and deferred HSCT to continue.

The CARDAMON trial was designed to investigate any detrimental effect of allocating patients to a non-transplantation group using a carfilzomib-based induction, consolidation, and maintenance approach. The primary aims were to establish the efficacy of the triple regimen of carfilzomib, cyclophosphamide, and dexamethasone (KCd) as induction in transplantation-eligible patients with newly diagnosed multiple myeloma and to evaluate the non-inferiority of KCd consolidation compared with upfront autologous HSCT in patients with at least a partial response to induction.

Methods

Study design and participants

CARDAMON is a randomised, open-label, phase 2 trial in 19 hospitals in England and Wales, UK (appendix p 17). The protocol was approved by the UK Medicines and Healthcare Products Regulatory Agency (London, UK) and the London–City and East Research Ethics Committee (London, UK; date of favourable ethical opinion Feb 23, 2015), and was managed by the Cancer Research UK and University College London Cancer Trials Centre (London, UK). The protocol can be found in the appendix (pp 18–161).

Eligible patients were aged 18 years or older; had symptomatic multiple myeloma eligible for high-dose therapy and HSCT; had an ECOG performance status of 0–2 (>2 was permitted if resulting from complications related to myeloma); had measurable disease according to standard criteria;[15] had a life expectancy of 3 months or more; and had adequate neutrophil count, platelet count, haemoglobin, and creatinine clearance. Exclusion criteria included previous systemic treatment for myeloma (except local palliative radiotherapy or corticosteroids for a maximum of 4 days) and substantial cardiac comorbidity (appendix pp 18–161). Sex was reported on case report forms by trial investigators during patient registration. The options for this data field were male and female. Data on gender were not collected. All patients provided written informed consent in accordance with the World Medical Association Declaration of Helsinki.

Randomisation and masking

Patient randomisation was done after completion of four cycles of KCd induction and peripheral blood stem cell (PBSC) harvesting for patients that had at least a partial response. Patients were randomly assigned (1:1) to either high-dose melphalan and autologous HSCT followed by carfilzomib maintenance or to KCd consolidation followed by carfilzomib maintenance. Randomisation was done centrally by a computer program set up by the data service at the Cancer Research UK and University College London Cancer Trials Centre with a minimisation approach stratified by hospital, depth of response to induction, International Staging System stage, and genetic risk. Patients were approached and assessed for eligibility for the trial by investigators at participating hospital sites (appendix p 17). Patient eligibility was confirmed by Cancer Research UK and University College London Cancer Trials Centre before study entry. Investigators are responsible for site-based responsibilities as delegated by Principal Investigators. Cancer Research UK and University College London Cancer Trials Centre are responsible for central trial activities as delegated by the Chief Investigator. Patients, people giving the interventions, those assessing outcomes, and those analysing the data were not masked to group assignment. Individuals who did not have at least a partial response to induction therapy were treated with salvage therapy outside of the trial.

Procedures

See Online for appendix

As induction therapy, patients received four 28-day cycles of carfilzomib (56 mg/m² administered intravenously on days 1, 2, 8, 9, 15, and 16 of every cycle; 20 mg/m² administered intravenously on days 1 and 2 of the first cycle), cyclophosphamide (500 mg administered orally

on days 1, 8, and 15 of all cycles) and dexamethasone (40 mg administered orally on days 1, 8, 15, and 22 of all cycles) before PBSC harvesting and randomisation.

For the consolidation phase, responders received high-dose melphalan according to local protocols and autologous HSCT (HSCT group), or four further cycles of KCd (KCd group), at the same dose, route, and schedule of administration as the induction protocol, including the step-up dosing in the first cycle of consolidation. This step-up dosing was introduced halfway through the trial to reduce adverse events.

All randomly assigned patients received carfilzomib maintenance (56 mg/m² on days 1, 8, and 15 of a 28-day cycle for up to 18 cycles, with 20 mg/m² on the first day of the first cycle). Each dose of carfilzomib was administered with dexamethasone 10 mg pre-medication (intravenously or orally). Treatment delays of up to 4 weeks were permitted. During the COVID-19 pandemic, after March 25, 2020, delays were permitted up to 14 weeks and when more than 12 months of maintenance had been completed, treatment could stop at the discretion of the investigator.[16] After cases of thrombotic micro-angiopathy were reported, the protocol was amended to include a step-up carfilzomib dose at the reduced amount of 20 mg/m² for any patient resuming treatment after a break of more than 4 weeks, before returning to the protocol dose of 56 mg/m² (or the last dose amount administered after any reduction).

Prespecified carfilzomib dose modifications were permitted for grade 4 thrombocytopenia (or grade 3 with active bleeding), grade 4 neutropenia, and grade 3–4 carfilzomib-related, non-haematological toxic effects (appendix pp 18–161). Unless explicitly withdrawing consent, patients who withdrew from trial treatment continued to be followed up for collection of outcome data.

Disease response assessments were recorded for each cycle of treatment according to modified *International Myeloma Working Group* (IMWG) criteria[17] and were centrally reviewed. Bone marrow examination to assess complete response was mandated after PBSC harvesting at the end of KCd consolidation, 100 days after autologous HSCT, 6 months after maintenance start, and at the end of maintenance. MRD was assessed in all patients centrally, regardless of serological response, by flow cytometry (threshold of 10^{-5}; one tumour cell in 100 000 bone marrow cells) after PBSC harvesting, after autologous HSCT or KCd consolidation, and at 6 months of maintenance. Adverse events, recorded from initiation of trial treatment until 30 days after final trial treatment administration, were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

Outcomes

This phase 2 study had two stages with no halt to recruitment between stages and separate primary endpoints for each stage. The primary outcome for the induction stage was the proportion of patients with at least a very good partial response after induction and the difference in 2-year progression-free survival (defined as the time between randomisation and first progression or death from any cause) after the randomisation phase.

The secondary outcomes were disease response and MRD rates at each timepoint, time until second progression or death, overall survival (measured from both registration and randomisation until death from any cause), toxicity, and quality of life. Follow-up for time until second progression or death and overall survival data are immature and the quality-of-life assessment is ongoing. These data will be reported elsewhere.

An important prespecified exploratory analysis assessed the relationship between fluorescence in-situ hybridisation (FISH) abnormalities and clinical outcomes. An adverse FISH result was defined as the presence of one or more of the cytogenetic abnormalities: t(4;14), t(14;16), and t(14;20) and del(17p) in 50% or more of bone marrow plasma cells. Post-hoc analyses examined progression-free survival in subgroups defined by MRD status at different timepoints.

Statistical analysis

The sample size for the induction stage was calculated with an A'Hern single-stage phase 2 design,[18] considering the first primary endpoint (ie, induction response). We aimed to rule out a major response (eg, at least very good partial response) rate of less than 30%, with an anticipated rate of more than 50% with KCd induction. Using a one-sided 5% α value and 90% power, we required a minimum of 22 (42%) of 53 patients to respond to treatment. For the phase after randomisation we aimed to show that, in combination with KCd induction and carfilzomib maintenance, KCd consolidation was non-inferior to autologous HSCT in terms of progression-free survival. Assuming a 2-year progression-free survival rate of 85% in the HSCT group,[19] we estimated that 210 randomly assigned patients (43 events of disease progression or death) would achieve 80% power with a one-sided 15% α value and non-inferiority margin for a difference in 2-year progression-free survival of 10%. Assuming at least a 75% partial response rate to induction, we aimed to recruit 280 patients. The 10% non-inferiority margin is justified by the fact that transplantation will remain a salvage option for most patients with disease progression in the KCd consolidation group, and by evidence that a 10% (or smaller) difference in progression-free survival is expected to translate to a much smaller, if any, difference in overall survival.[2] Data cutoff was April 7, 2022.

Efficacy outcomes were analysed by intention to treat. Progression-free survival and overall survival were estimated by the Kaplan-Meier method, measured from registration or from randomisation when comparing

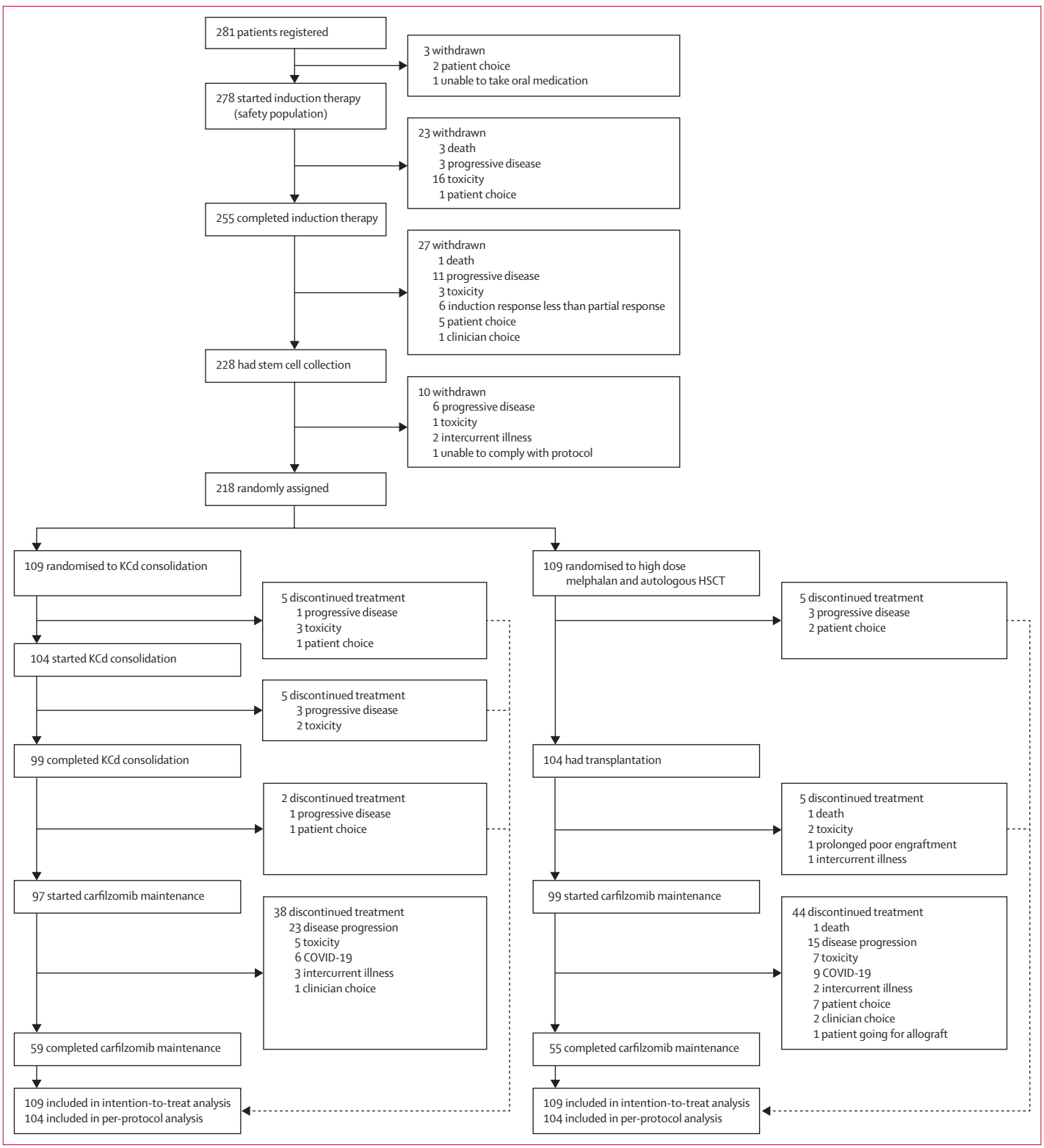

Figure 1: **Trial profile**
HSCT=haematopoietic stem-cell transplantation. KCd=carfilzomib–cyclophosphamide–dexamethasone.

	KCd induction (n=281)	Consolidation	
		KCd group (n=109)	HSCT group (n=109)
Age, years			
Median (IQR)	59 (52–64)	60 (52–65)	58 (53–64)
Range	33–74	33–73	34–74
Sex			
Female	115 (41%)	45 (41%)	47 (43%)
Male	166 (59%)	64 (59%)	62 (57%)
Race or ethnicity*			
Asian	18/214 (8%)	8/91 (9%)	7/88 (8%)
Black	37/214 (17%)	15/91 (16%)	15/88 (17%)
Mixed	5/214 (2%)	1/91 (1%)	4/88 (5%)
White	152/214 (71%)	67/91 (74%)	62/88 (70%)
Other	2/214 (1%)	0/91	0/88
Unknown†	67	18	21
ECOG performance status			
0	149 (53%)	65 (60%)	61 (56%)
1	105 (37%)	37 (34%)	41 (38%)
2	23 (8%)	7 (6%)	7 (6%)
3	3 (1%)	0	0
4	1 (<1%)	0	0
International Staging System stage			
I	129 (46%)	54 (50%)	53 (49%)
II	99 (35%)	34 (31%)	46 (42%)
III	53 (19%)	21 (19%)	10 (9%)
Genetic risk			
Standard risk	207/259 (80%)	79/101 (78%)	85/104 (82%)
Gain (1q) or del(1p)	70/259 (27%)	25/101 (25%)	29/104 (28%)
High risk	52/259 (20%)	22/101 (22%)	19/104 (18%)
t(4;14)	27/259 (10%)	11/101 (11%)	11/104 (11%)
t(14;16)	10/259 (4%)	7/101 (7%)	2/104 (2%)
t(14;20)	1/259 (<1%)	1/101 (1%)	0/104
del(17p) >50%	17/259 (7%)	4/101 (4%)	7/104 (7%)
Unknown†	22	8	5
Revised International Staging System stage			
I	72/245 (29%)	28/95 (29%)	32/96 (33%)
II	149/245 (61%)	57/95 (60%)	59/96 (61%)
III	24/245 (10%)	10/95 (11%)	5/96 (5%)
Unknown†	36	14	13

(Table 1 continues on next page)

randomised groups. Patients were censored at the date last seen if they did not have an event, or at the date of new, off-trial treatment if it happened before progression (for the progression-free survival endpoint only). When examining associations between MRD and progression-free survival, we used landmark analyses from the date of MRD assessment. p-values for comparisons between treatment groups were calculated with Cox regression analyses for survival outcomes and the χ^2 test for response rates. The difference in 2-year progression-free survival between the two treatment groups and 70% CI (corresponding to our choice of a one-sided 15% α value) was calculated by applying the hazard ratio (HR) to the 2-year rate in the KCd consolidation group to get the corresponding rate in the autologous HSCT group, then subtracting this from the 2-year rate in the KCd consolidation group. A separate, post hoc, per-protocol analysis was done, excluding patients who did not start randomised treatment. If the proportional hazards assumption was violated, the difference in restricted mean survival time (RMST)[20] was reported instead of the HR. The timepoint used for calculating the difference in RMST was taken as the largest observed time to event of either treatment group. A sensitivity analysis excluding patients whose maintenance was delayed or stopped because of the COVID-19 pandemic was performed on the primary progression-free survival outcome. Safety data were assessed in all patients who received at least one dose of any study drug. All analyses were performed with Stata version 16.1. This study is registered with ClinicalTrials.gov, number NCT02315716 and all patients are in follow-up.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication.

Results

Between June 16, 2015, and July 8, 2019, 281 patients were enrolled in this study. Data on the number of patients screened are not available. 278 participants started induction, 228 met eligibility criteria for stem cell mobilisation, and 218 proceeded to randomisation and were assigned to KCd consolidation (n=109) or high dose melphalan and autologous HSCT (n=109). Of the 60 patients who started induction therapy but were not randomised, 26 (43%) had early disease progression or had less than a partial response, 20 (33%) were withdrawn due to toxicity, six (10%) chose to withdraw, four (7%) died, and one (2%) withdrew due to clinician choice (figure 1). Median time from starting induction therapy to randomisation was 5·6 months (IQR 5·3–5·9). Median follow-up from registration was 45·5 months (37·1–56·9) and from randomisation was 40·2 months (32·7–51·8).

In the 281 patients registered for induction therapy, the median age was 59 years (IQR 52–64), 115 (41%) participants were female, and 37 (17%) of 214 patients with known ethnicity were Black. Baseline demographics and disease characteristics are in table 1.

255 (91%) of 281 patients completed all four cycles of induction, with a median carfilzomib dose of 52 mg/m² (IQR 48–53). 40 (15%) patients received at least one reduced dose of carfilzomib during induction, two of whom subsequently withdrew before completing induction. Of the 109 patients randomly assigned to receive KCd consolidation, 99 (91%) completed all four cycles with a median carfilzomib dose of 54·5 mg/m²

(IQR 47–56). 104 (95%) of 109 patients randomly assigned to autologous HSCT had transplantation. 18 (29%) of 63 patients who had disease progression after KCd consolidation were reported to have received a subsequent transplantation.

196 (90%) of 218 randomised patients began carfilzomib maintenance treatment (97 [89%] of 109 in the KCd group and 99 [91%] of 109 in the HSCT group), of whom 114 (58%; 59 [61%] of 97 in the KCd group and 55 [56%] of 99 in the HSCT group) completed all 18 cycles. Withdrawals due to adverse events or patient or clinician decision were more common in the HSCT group than in the KCd group (six [6%] of 97 patients in the KCd group *vs* 16 [16%] of 99 patients in the HSCT group, p=0·027). 15 patients (five in the KCd group and ten in the HSCT group) discontinued maintenance due to the COVID-19 pandemic, and 41 patients (23 in the KCd group and 18 in the HSCT group) had their treatment interrupted or delayed because of it.

The first primary endpoint was met, with 43 (81%) of the first 53 patients having at least a very good partial response after induction (revised to 37 [70%] of the first 53 patients after central review). The proportion of patients who had at least a very good partial response after induction therapy in the entire intention-to-treat population (n=281) was 57·7% (n=162; 95% CI 51·6–63·5), the overall response rate (ie, at least a partial response) was 85·8% (241 of 281 patients; 81·1–89·6), and 22·8% (64 of 281 patients; 18·0–28·1) of patients were MRD negative (table 2).

Randomised groups were balanced in terms of depth of response and MRD negativity rate after induction (table 1). Serological response rates increased after randomised treatment but were similar across both treatment groups (at least a very good partial response occurred in 85 [78%] of 109 patients in the KCd group *vs* 84 [77%] of 109 in the HSCT group, p=0·87; table 2). After randomised treatment, more patients in the HSCT group had MRD negativity than patients in the KCd group (33 [30%] of 109 *vs* 52 [48%] of 109, p=0·0083). This difference in MRD negativity was still apparent at the 6-month maintenance timepoint (34 [31%] of 109 *vs* 50 [46%] of 109], p=0·026; appendix p 6). Exclusion of patients who were negative for MRD with less than a very good partial response did not alter these conclusions (appendix p 6).

For the second primary endpoint, 150 events of disease progression or death have been reported, of which 117 (64 in the KCd group and 53 in the HSCT group) occurred after randomisation. Median progression-free survival for all 281 patients from registration was 38·1 months (95% CI 33·1 to 44·8; figure 2A). Median progression-free survival for all 218 patients from randomisation was 42·4 months (32·6–59·5) for the HSCT group and 33·8 months (28·3–40·6) for the KCd group (HR 1·35, 70% CI 1·11 to 1·64, p=0·11; figure 2B). The 2-year progression-free survival was 75% (95% CI 65–82) in the HSCT group and 68% (95% CI 58–76) in the KCd group, resulting in a calculated difference of –7·2% (70% CI –11·1 to –2·8). In the 208 patients who started randomised treatment in the per-protocol population, this difference was –8·5%, 70% CI –12·3 to –4·1 (2-year progression-free survival 77%, 95% CI 68–84 in the HSCT group *vs* 2-year progression-free survival 68%, 95% CI 58–76 KCD group; HR 1·44, 70% CI 1·18–1·75, p=0·058). The 2-year progression free survival

	KCd induction (n=281)	Consolidation	
		KCd group (n=109)	HSCT group (n=109)
(Continued from previous page)			
Myeloma type			
Secretory	277 (99%)	106 (97%)	108 (99%)
Single paraprotein expressed	225 (80%)	78 (72%)	93 (85%)
Biclonal	8 (3%)	4 (4%)	3 (3%)
Light chain only	44 (16%)	24 (22%)	12 (11%)
Non-secretory	4 (1%)	3 (3%)	1 (1%)
Response to induction			
At least very good partial response	162 (58%)	75 (69%)	75 (69%)
MRD negative	64 (23%)	30 (28%)	31 (28%)

Data are n (%), unless otherwise specified. Some patients had more than one genetic risk factor. HSCT=haematopoietic stem-cell transplantation. del=deletion. ECOG=Eastern Cooperative Oncology Group. KCd=carfilzomib–cyclophosphamide–dexamethasone. t=translocation. MRD=minimal residual disease. *Demographics case report form introduced Sept 21, 2018, to record patient ethnicity. †Excluded from denominator.

Table 1: **Baseline and disease characteristics of the intention-to-treat population**

	KCd induction (n=281)	Consolidation	
		KCd group (n=109)	HSCT group (n=109)
Stringent complete response	15 (5%)	18 (17%)	10 (9%)
Complete response	8 (3%)	9 (8%)	5 (5%)
Very good partial response	139 (49%)	58 (53%)	69 (63%)
Partial response	79 (28%)	12 (11%)	17 (16%)
Minor response	6 (2%)	0	0
Progressive disease	7 (2%)	1 (1%)	0
Withdrew before response assessment	27 (10%)	10 (9%)	6 (6%)
Death	4* (1%)	0	1 (1%)
Progressive disease	3 (1%)	4 (4%)	3 (3%)
Toxicity	16 (6%)	5 (5%)	0
Other reason	4 (1%)	1 (1%)	2 (2%)
Not evaluable	0	1 (1%)	2 (2%)
MRD negative by flow cytometry, sensitivity 10^{-5}	64 (23%)	33 (30%)	52 (48%)
At least partial response rate†	85·8% (81·1–89·6)	89·0% (81·6–94·2)	92·7% (86·0–96·8)
At least very good partial response rate‡	57·7% (51·6–63·5)	78·0% (69·0–85·4)	77·1% (68·0–84·6)
MRD negative by flow cytometry rate, sensitivity 10^{-5}§	22·8% (18·0–28·1)	30·3% (21·8–39·8)	47·7% (38·1–57·5)

Data are n (%) or % (95% CI). HSCT=haematopoietic stem-cell transplantation. KCd=carfilzomib–cyclophosphamide–dexamethasone. MRD=minimal residual disease. *One patient died shortly after completing four cycles of induction before being assessed for response. †Comparison between KCd consolidation and autologous HSCT, p=0·35. ‡Comparison between KCd consolidation and autologous HSCT, p=0·87. §Comparison between KCd consolidation and ASCT, p=0·0083.

Table 2: **Response rates after treatment in the intention-to-treat population**

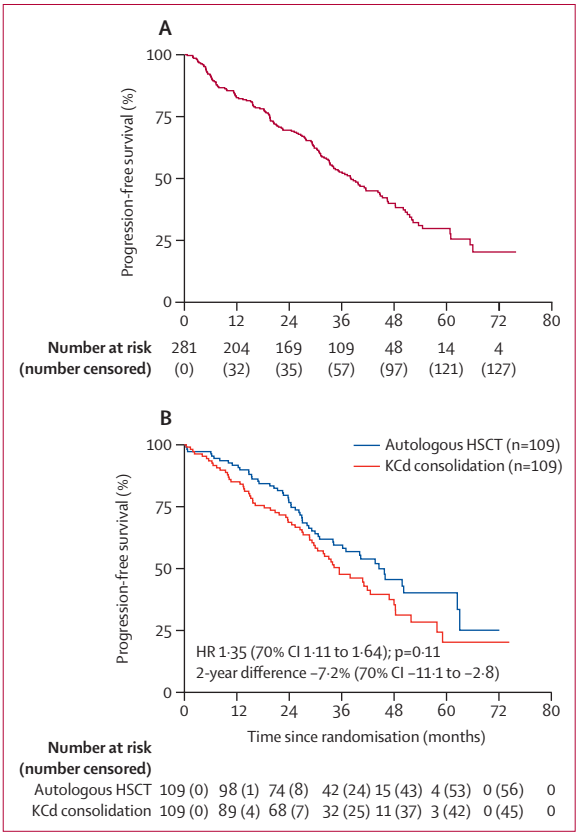

Figure 2: **Progression-free survival**
(A) In all registered patients (n=281). (B) In all randomly assigned patients (n=218), per treatment group. HSCT=haematopoietic stem-cell transplantation. HR=hazard ratio. KCd=carfilzomib–cyclophosphamide–dexamethasone.

rates in the per-protocol population were 77% (95% CI 64–84) in the HSCT group and 68% (95% CI 58–76) in the KCD group. This difference does not meet the criteria for non-inferiority of KCd consolidation as the lower confidence limit is outside the boundary of the margin, therefore the second primary endpoint was not met. Excluding patients whose maintenance treatment was delayed or stopped because of the COVID-19 pandemic did not alter this conclusion (71%, 95% CI 60–80 in the HSCT group *vs* 64%, 95% CI 52–74 KCD group; difference in 2-year progression-free survival −8·5%, 70% CI −13·3 to −3·1; n=162).

65 deaths have been reported during follow-up, with 36 (19 in the KCd group and 17 in the HSCT group) occurring after randomisation. Median overall survival for all patients from registration has not yet been reached, with a 2-year rate of 89·1% (95% CI 84·8 to 92·3). The 2-year overall survival from randomisation are 90·8% (83·5 to 94·9) for the KCd group and 94·4% (87·9 to 97·4) for the HSCT group, with a calculated difference of −1·1% (95% CI −4·9 to 5·9).

Treatment-related serious adverse events were reported in 109 (39%) of 278 patients who started induction, occurring in 73 (26%) of 278 patients during KCd induction, in 18 (8%) of 218 patients between randomisation and maintenance start (17 [16%] of 109 in the KCd consolidation group *vs* one [1%] of 109 in the HSCT group [transplantation-related events were not reported]), and in 38 (19%) of 196 patients during carfilzomib maintenance (16 [16%] of 97 *vs* 22 [22%] of 99). Some patients had serious adverse events in more than one phase. The most common treatment-related serious adverse events were infections, which occurred in 80 (29%) of 278 patients who started induction: 46 (17%) of 278 patients during KCd induction, 13 (6%) of 218 patients between randomisation and maintenance start (12 [11%] of 109 in the KCd consolidation group *vs* one [1%] of 109 in the HSCT group [transplantation-related events were not reported]), and 29 (15%) of 196 patients during maintenance (13 [13%] of 97 *vs* 16 [16%] of 99; appendix p 8).

All adverse events of grade 1–2 that occurred in at least 10% of patients, and all adverse events of grade 3 or worse, that occurred during the trial, except those related to transplantation (standard of care), have been summarised (table 3). The most common grade 3 or worse adverse events during induction treatment were lymphocytopenia (occurring in 72 [26%] of 278 patients), infections (53 [19%]), hypertension (33 [12%]), neutropenia (32 [12%]), and anaemia (29 [10%]). 11 (4%) of 278 patients had grade 3 or worse cardiac disorders during induction, with five (2%) of 278 patients having myocardial ischaemia (myocardial infarction or acute coronary syndrome). The proportion of patients with grade 3 or worse hypertension during KCd consolidation (12 [11%] of 109) was similar to that seen during induction, whereas the proportion of patients who had grade 3 or worse lymphocytopenia (15 [14%]), neutropenia (one [1%]), anaemia (two [2%]), or infection (15 [14%]) were reduced. During maintenance treatment, there was a higher incidence of grade 3 or worse events in patients who had HSCT (65 [66%] of 99) than in patients who received KCd consolidation (44 [45%] of 97; p=0·0042). This difference was because of a higher proportion of lung infections and cytopenia in the HSCT group than in the consolidation group. There were five treatment-emergent deaths during the induction phase. Four patients died while receiving induction treatment (three from infection and one from a cardiac event). The fifth patient withdrew due to sepsis before dying 4 months later of renal failure. One patient in the HSCT group died from an infection 114 days after transplantation and another patient from the HSCT group died during maintenance due to an oesophageal malignancy.

Of 259 patients with complete FISH data, 52 (20%) had high genetic risk. Response rates to KCd induction were similar irrespective of genetic risk (at least a very good partial response occurred in 31 [60%] of 52 patients with high risk *vs* 120 [58%] of 207 patients with standard risk). MRD negativity rates were also similar, occurring in 12 (23%) of 52 patients with high risk versus 48 (23%) of

	KCd induction (n=278)				Consolidation KCd group (n=109)			Carfilzomib maintenance after KCd consolidation (n=97)			Carfilzomib maintenance after autologous HSCT (n=99)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders	110 (40%)	32 (12%)	0	0	40 (37%)	3 (3%)	2 (2%)	19 (20%)	0	1 (1%)	41 (41%)	4 (4%)	0	0
Anaemia	111 (40%)	29 (10%)	0	0	41 (38%)	2 (2%)	0	19 (20%)	0	0	40 (40%)	2 (2%)	0	0
Febrile neutropenia	..	1 (<1%)	0	0	..	0	0	..	0	0	..	0	0	0
Thrombotic microangiopathy	..	2 (1%)	0	0	..	1 (1%)	2 (2%)	..	0	1 (1%)	..	2 (2%)	0	0
Cardiac disorders	35 (13%)	7 (3%)	0	4 (1%)	..	1 (1%)	0	..	0	0	..	2 (2%)	0	0
Acute coronary syndrome	..	2 (1%)	0	0	..	0	0	..	0	0	..	0	0	0
Cardiac arrest	..	0	1 (<1%)	2 (1%)	..	0	0	..	0	0	..	0	0	0
Myocardial infarction	..	2 (1%)	0	1 (<1%)	..	0	0	..	0	0	..	0	0	0
Left ventricular impairment	..	0	0	1 (<1%)	..	0	0	..	0	0	..	0	0	0
Eye disorders	29 (10%)	0	0	0	..	0	0	11 (11%)	4 (4%)	0	18 (18%)	2 (2%)	0	0
Gastrointestinal disorders	180 (65%)	12 (4%)	0	1 (<1%)	52 (48%)	7 (6%)	0	54 (56%)	6 (6%)	0	61 (62%)	5 (5%)	0	0
General disorders and administration site conditions	192 (69%)	12 (4%)	0	0	54 (50%)	4 (4%)	0	66 (68%)	4 (4%)	0	60 (61%)	6 (6%)	0	0
Fatigue	144 (52%)	6 (2%)	0	0	42 (39%)	2 (2%)	0	43 (44%)	1 (1%)	0	44 (44%)	2 (2%)	0	0
Fever	45 (16%)	5 (2%)	0	0	14 (13%)	0	0	13 (13%)	1 (1%)	0	17 (17%)	1 (1%)	0	0
Hepatobiliary disorders	..	0	0	0	..	0	0	..	0	0	..	2 (2%)	0	0
Immune system disorders	..	3 (1%)	0	0	..	0	0	..	0	0	..	0	0	0
Infections and infestations	62 (22%)	45 (16%)	5 (2%)	3 (1%)	26 (24%)	13 (12%)	2 (2%)	48 (49%)	16 (16%)	0	40 (40%)	23 (23%)	2 (2%)	0
Lung infection	..	26 (9%)	4 (1%)	1 (<1%)	..	6 (6%)	0	13 (13%)	5 (5%)	0	18 (18%)	11 (11%)	0	0
Other respiratory infection	37 (13%)	10 (4%)	1 (<1%)	1 (<1%)	15 (14%)	2 (2%)	1 (1%)	33 (34%)	3 (3%)	0	42 (42%)	4 (4%)	1 (1%)	0
Injury, poisoning, and procedural complications	..	3 (1%)	0	0	..	0	0	..	0	0	..	0	0	0
Investigations	69 (25%)	84 (30%)	27 (10%)	0	37 (34%)	12 (11%)	6 (6%)	36 (37%)	4 (4%)	2 (2%)	37 (37%)	17 (17%)	0	0
Lymphocyte count decreased	..	58 (21%)	14 (5%)	0	12 (11%)	10 (9%)	5 (5%)	18 (19%)	2 (2%)	2 (2%)	17 (17%)	6 (6%)	0	0
Neutrophil count decreased	43 (15%)	23 (8%)	9 (3%)	0	17 (16%)	1 (1%)	0	..	2 (2%)	0	18 (18%)	5 (5%)	0	0
Platelet count decreased	93 (33%)	8 (3%)	3 (1%)	0	40 (37%)	0	1 (1%)	17 (18%)	0	0	29 (29%)	4 (4%)	0	0
Metabolism and nutrition disorders	57 (21%)	26 (9%)	4 (1%)	0	15 (14%)	2 (2%)	0	24 (25%)	2 (2%)	1 (1%)	31 (31%)	2 (2%)	0	0
Musculoskeletal and connective tissue disorders	86 (31%)	11 (4%)	0	0	27 (25%)	1 (1%)	0	45 (46%)	3 (3%)	0	47 (47%)	3 (3%)	0	0
Neoplasms benign, malignant, and unspecified	..	0	0	0	..	0	0	..	0	0	..	1 (1%)	0	0
Malignant melanoma	..	0	0	0	..	0	0	..	0	0	..	1 (1%)	0	0
Oesophageal carcinoma	..	0	0	0	..	0	0	..	0	0	..	0	0	1 (1%)
Nervous system disorders	126 (45%)	10 (4%)	0	0	39 (36%)	2 (2%)	0	31 (32%)	3 (3%)	0	54 (55%)	0	0	0
Psychiatric disorders	72 (26%)	15 (5%)	0	0	28 (26%)	2 (2%)	0	31 (32%)	3 (3%)	0	32 (32%)	4 (4%)	0	0

(Table 3 continues on next page)

	KCd induction (n=278)				Consolidation KCd group (n=109)				Carfilzomib maintenance after KCd consolidation (n=97)				Carfilzomib maintenance after autologous HSCT (n=99)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4		Grade 1–2	Grade 3	Grade 4		Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)																
Renal and urinary disorders	..	7 (3%)	0	1 (<1%)	..	2 (2%)	1 (1%)		..	2 (2%)	0		12 (12%)	1 (1%)	0	0
Acute kidney injury	..	7 (3%)	1 (<1%)	0	..	2 (2%)	1 (1%)		..	1 (1%)	0		..	0	0	0
Respiratory, thoracic, and mediastinal disorders	121 (44%)	6 (2%)	3 (1%)	0	40 (37%)	1 (1%)	0		43 (44%)	1 (1%)	0		61 (62%)	1 (1%)	0	0
Dyspnoea	91 (33%)	4 (1%)	0	0	28 (26%)	0	0		19 (20%)	1 (1%)	0		30 (30%)	1 (1%)	0	0
Pulmonary oedema	..	0	2 (1%)	0	..	1 (1%)	0		..	0	0		..	0	0	0
Skin and subcutaneous tissue disorders	61 (22%)	3 (1%)	0	0	20 (18%)	0	0		14 (14%)	1 (1%)	0		18 (18%)	1 (1%)	0	0
Vascular disorders	84 (30%)	35 (13%)	2 (1%)	0	49 (45%)	12 (11%)	0		48 (49%)	21 (22%)	0		39 (39%)	25 (25%)	1 (1%)	0
Hypertension	65 (23%)	32 (12%)	1 (<1%)	0	42 (39%)	12 (11%)	0		46 (47%)	20 (21%)	0		39 (39%)	23 (23%)	0	0
Thromboembolic event	..	3 (1%)	0	0	..	0	0		..	1 (1%)	0		..	1 (1%)	1 (1%)	0
Any adverse events	88 (32%)	150 (54%)	33 (12%)	5 (2%)	53 (49%)	40 (37%)	9 (8%)		50 (52%)	40 (41%)	4 (4%)		32 (32%)	62 (63%)	2 (2%)	1 (1%)

Data are number of patients with at least one event (%). All adverse events of grade 1–2 that occurred in at least 10% of patients, and all adverse events of grade 3 or worse, are reported here. Adverse events are recorded from treatment start until 30 days after last trial treatment administration (or after this date if the event meets the criteria of serious adverse event and is thought to be related to trial treatment; appendix p 10). HSCT=haematopoietic stem-cell transplantation. KCd=carfilzomib–cyclophosphamide–dexamethasone.

Table 3: **Adverse events**

207 patients with standard risk (appendix p 2). Response rates after randomised treatment also appeared to be independent of genetic risk ($p_{interaction}$=0·21) and similar across treatment groups; however, the number of randomised patients with high risk was relatively small (22 in the KCd consolidation group and 19 in the HSCT group). At least a very good partial response occurred in 17 (77%) of 22 patients with high risk in the KCd consolidation group versus 17 (89%) of 19 in the HSCT group (p=0·30), and in 63 (80%) of 79 patients with standard risk in the KCd consolidation group versus 63 (74%) of 85 in the HSCT group (p=0·39). The association between randomised treatment and an MRD-negative response did not differ according to genetic risk ($p_{interaction}$=0·48): in patients with high risk, six (27%) of 22 in the KCd consolidation group had MRD negativity versus ten (53%) of 19 in the HSCT group (p=0·097), and in patients with standard risk, 25 (32%) of 79 in the KCd consolidation group had MRD negativity versus 38 (45%) of 85 in the HSCT group (p=0·086; appendix p 2).

Despite similar response rates, patients with high risk had inferior outcomes compared with patients with standard risk, with 2-year progression-free survival rates of 49·2% (95% CI 34·3–62·6) in the high-risk group versus 75·2% (68·4–80·8) in the standard-risk group (HR 2·21, 95% CI 1·49–3·27, p<0·0001; appendix p 4). This difference was independent of randomised treatment ($p_{interaction}$=0·56): progression-free survival was worse in patients with high risk than in patients with standard risk after KCd consolidation (HR 2·29 [1·26–4·16], p=0·0056) and after HSCT (HR 2·99 [1·54–5·78], p=0·0012; appendix p 4).

Among the 164 randomised patients with standard risk, the calculated difference in 2-year progression-free survival between KCd consolidation and HSCT was –7·4% (70% CI –10·9 to –3·0), similar to the result seen in the intention-to-treat population. In patients with high risk, those receiving HSCT had better outcomes initially than those receiving KCd consolidation. However, the progression-free survival curves came together at 26 months and therefore cannot be compared with Cox regression. RMST estimates suggest that patients with high risk receiving KCd consolidation had a non-significant –3·8 month (95% CI –13·3 to 5·7) difference in progression-free survival over 42·4 months compared with patients in the HSCT group (p=0·42; appendix pp 3–4).

In a post-hoc analysis, an MRD-negative response after induction was not associated with significantly improved progression-free survival (RMST difference in MRD positive patients *vs* MRD negative patients –5·2 months [95% CI –11·5 to 1·2] over 60·3 months, p=0·11; appendix p 5). However, patients who were MRD negative after randomised treatment, regardless of randomisation, had longer progression-free survival than patients who were MRD positive (HR 1·90, 95% CI 1·26–2·87, p=0·0024; appendix p 5).

There was no evidence of a benefit of HSCT in patients who were MRD negative after induction (RMST difference between KCd consolidation and HSCT was –0·6 months [95% CI –10·5 to 9·4] over 59·5 months, p=0·91). However, progression-free survival was better after HSCT than after KCd consolidation for patients who were MRD positive after induction (RMST difference between KCd consolidation and HSCT was –7·3 months [95% CI –14·5 to –0·2] over 60·1 months, p=0·045). Among patients who were MRD negative 100 days after HSCT or KCd consolidation, KCd consolidation was non-inferior to HSCT by the definition used for the primary endpoint, with a calculated difference in 2-year progression-free survival of –4·9% (70% CI –9·5 to 1·0). KCd consolidation was not non-inferior to HSCT among patients who were MRD positive after randomised treatment, with the difference exceeding the 10% margin (–12·2% [70% CI –20·2 to –3·1]; appendix pp 3,5).

Discussion

Studies published in the past 6 years[1–3,8] have all shown a superior progression-free survival for autologous HSCT compared with consolidation in newly diagnosed, transplantation-eligible patients with multiple myeloma. However, only one study has shown an improvement in overall survival,[21] and with increasingly effective induction regimens, any true long-term benefit to patients remains unclear. Rather than showing superiority, our study sought to assess if ongoing treatment with KCd was non-inferior to KCd induction followed by autologous HSCT in newly diagnosed, transplantation-eligible patients with multiple myeloma, with both groups receiving carfilzomib maintenance. Our results show that KCd consolidation did not meet the criteria for non-inferiority when compared with upfront transplantation. However, the non-inferiority margin was only exceeded by a small amount (confidence limit –11·1%, prespecified margin –10%), although this study was a phase 2 trial with 15% significance level. Therefore, there are likely to be subgroups of patients for whom deferred transplantation might be an option, which should be explored in future prospective trials.

Our progression-free survival outcomes are similar to those in the IFM 2009 study that also used restricted duration maintenance, albeit with lenalidomide. We observed a median progression-free survival from randomisation of 33·8 months in the KCd consolidation group versus 42·4 months in the HSCT group (HR 1·35), whereas the IFM 2009 trial reported a median progression-free survival from registration of 35·0 months for lenalidomide–bortezomib–dexamethasone (VRd) consolidation versus 47·3 months for HSCT (HR 1·43).[22] Studies with lenalidomide maintenance until progression[3] reported longer progression-free survival overall than trials with fixed-duration lenalidomide maintenance, although the relative difference between treatment groups is similar across trials (appendix p 16).

Supporting the efficacy of KCd in patients with high risk, the very good partial response rate and MRD-negative rate after KCd induction were similar between patients with standard risk and patients with high risk, and these measures of response were also similar after randomised treatment. Although very good partial response rates were similar between randomisation groups, MRD-negative rates were higher in the HSCT group for both patients with high risk and patients with standard risk than in the KCd consolidation group, with little difference between patients with high risk and patients with standard risk. Despite this finding, patients with high-risk genetics had inferior progression-free survival compared with patients with standard risk. Reasons for this finding could be the restricted duration of maintenance carfilzomib (18 months) and the absence of consolidation after autologous HSCT, which could be beneficial in high-risk multiple myeloma. In the FORTE study,[8] patients with high risk benefitted from the addition of carfilzomib to lenalidomide, thus, a proteasome inhibitor and immunomodulatory drug approach to maintenance is likely to be required for optimal outcomes in this group. The interim results of the ATLAS study showed a median progression-free survival of 59·0 months for KRd followed by lenalidomide maintenance after autologous HSCT, with more benefit for patients with high risk than with lenalidomide maintenance alone.[14]

The importance of MRD as a prognostic marker has led to speculations on its use in treatment decisions, with several current trials addressing this important question in the context of first-line treatments.[23] The IFM 2009 study showed that MRD was the strongest driver of progression-free survival,[24] regardless of randomisation group. However, as MRD testing was not done before autologous HSCT or consolidation, the IFM 2009 study could not address the relative benefit of HSCT in MRD-negative patients after induction. In our current study, there was no clear benefit of HSCT in patients who had an MRD-negative response after induction, whereas for individuals who are MRD positive, autologous HSCT could be beneficial. We also showed that there was no difference in progression-free survival between the autologous HSCT and consolidation groups for patients with an MRD-negative response after autologous HSCT or consolidation. Acknowledging that patient numbers were small and analyses were not prespecified, our results suggest that patients who are MRD positive after induction could benefit more from autologous HSCT than from consolidation chemotherapy. Conversely, individuals who are MRD negative should be investigated on a deferred autologous HSCT pathway in a larger prospective randomised trial. Ongoing trials, such as MIDAS (NCT04934475) and MASTER-2 (NCT05231629), could answer these questions.[25] An interim analysis from the ATLAS study also showed that MRD could be used to de-escalate the intensity of maintenance.[15]

Overall, this carfilzomib-based treatment pathway was feasible, although discontinuations because of adverse events were noted. This study used a higher dose of carfilzomib (56 mg/m²) than other carfilzomib triplets used in twice per week dosing. Discontinuations related to adverse events during KCd induction were more common in our CARDAMON study than in the FORTE study (7% *vs* 3%).[8] However, 5 (25%) of the 20 patients who withdrew from our study were older than 65 years and would have been excluded from FORTE. Overall, 78% of patients proceeded from induction to randomisation in CARDAMON, a rate that is similar to that in the KCd group (84%) in FORTE, especially given the age limit of 65 years. Although the discontinuation rates at randomisation from the DETERMINATION trial (5%; NCT01208662) are lower than in our study, this finding is partly because of design; randomisation occurred after one induction cycle whereas in CARDAMON randomisation occurred after four induction cycles. However, the adverse event profile of carfilzomib requires careful proactive management, particularly in individuals older than 65 years, in whom a low carfilzomib dose might be better tolerated than a high carfilzomib dose. Fewer discontinuations were observed after the implementation of further safety measures than before. For example, eight cases of thrombotic microangiopathy were noted,[26] with no further cases after proactive management of hypertension and introduction of step-up dosing at the start of maintenance. The main adverse event during carfilzomib maintenance was hypertension, suggesting that cumulative drug doses might have had an effect. More patients in the autologous HSCT group discontinued maintenance than in the KCd consolidation group, potentially because of the higher incidence of infections and cytopenias. Withdrawals from carfilzomib maintenance might also have been influenced by the COVID-19 pandemic, as guidance was issued to allow discontinuations in patients who had completed at least 12 months of maintenance. The quality-of-life data are currently under analysis and might provide further insights into the tolerability of this regimen.

KCd induction resulted in high response rates (more than the prespecified target) and high MRD-negativity rates without the use of an immunomodulatory drug, results that are similar to the KCd plus autologous HSCT group in FORTE (very good partial response rates of 57·7% in CARDAMON *vs* 53% in FORTE; 77·1% after autologous HSCT in CARDAMON *vs* 77% in FORTE).[8] The MRD-negativity rates at the start of maintenance are also similar (47·7% in CARDAMON *vs* 43% in FORTE). Although the KRd regimen was shown to be superior to KCd,[8] cyclophosphamide might be useful in countries where the combination with lenalidomide could be costly or for patients who are intolerant to lenalidomide. There were also fewer mobilisation failures with KCd than with KRd in the FORTE study, and we did not see any mobilisation failures in CARDAMON. Continuous proteasome-inhibitor-based treatment could be effective in patients who are unable to tolerate long-term immunomodulatory drugs or who have high-risk multiple myeloma in which lenalidomide-based treatments are less effective than for patients with standard-risk disease. Carfilzomib has been previously shown to be superior to bortezomib for patients with disease relapse,[27] making it a preferred option in this setting. However, this superiority has not been shown when used as a first-line treatment,[28,29] and further comparative studies are required. However, the requirement for clinic visits once or twice per week for carfilzomib maintenance, depending on the schedule, needs to be balanced against the convenience of oral lenalidomide or subcutaneous daratumumab administered once per month. The FORTE study has reported superior outcomes of combined maintenance with carfilzomib and lenalidomide, and ATLAS showed more of a progression-free survival benefit for KRd than for lenalidomide.

The addition of CD38 antibodies to standard-of-care triplets has been shown to improve responses and MRD negativity rates that were maintained after autologous HSCT.[30,31] Daratumumab plus bortezomib–thalidomide–dexamethasone has already become the standard of care in many countries and daratumumab plus bortezomib–lenalidomide–dexamethasone could also become a standard approach, with tolerability advantages of lenalidomide. The addition of a CD38 antibody to a carfilzomib-based triplet has encouraging preliminary data.[23,32] The benefits of upfront autologous HSCT should continue to be examined in individuals who have deep, sustained responses to induction therapy.

There are some limitations to our study. Due to the non-inferiority design of CARDAMON, we cannot comment on the superiority of autologous HSCT in the context of this study. Furthermore, to keep the trial at a feasible size, it was not powered to assess non-inferiority in subgroup analyses and there might be additional subpopulations (eg, based on individual cytogenetic factors) that deserve further evaluation. Transplantation-related events were not reported as autologous HSCT is standard of care and the toxicity profile is already well documented. However, by not doing so we are unable to make a direct comparison of toxicity between treatment groups during the randomised phase of treatment. The reported rate of patients who received a deferred transplant after disease progression might be an underestimation of the true value, as these data are collected on long-term follow-up forms. The COVID-19 pandemic led to patient withdrawals during maintenance (five withdrawals in the KCd consolidation group and ten in the autologous HSCT group), alongside treatment delays and interruptions, which could have resulted in worse clinical outcomes overall for the trial cohort than if COVID-19 had not affected treatment.

The CARDAMON trial provides preliminary evidence that MRD assessment after induction could be used to guide treatment choice. Future trials that stratify by a composite of genetic risk and depth of response will be able to accurately identify patients likely to benefit from autologous HSCT, leading to a personalised treatment approach.

In conclusion, the CARDAMON trial showed that carfilzomib-based induction, consolidation, and maintenance did not meet the criteria for non-inferiority when compared with upfront transplantation. Research should continue to explore the benefit of upfront autologous HSCT in specific patient populations (eg, patients with standard risk genetics *vs* high risk genetics and patients who are MRD negative or positive after induction therapy). Although autologous HSCT continues to be regarded as a first-line, standard-of-care treatment for multiple myeloma, its role will continue to be assessed, especially with highly efficacious quadruplet regimens and for patients who have MRD negativity early on. Current risk-stratified trials should also aim to identify patients who benefit from upfront autologous HSCT, and the optimal post-autologous HSCT therapy needed to maintain disease response.

Contributors

KY, WW, RP, JC, and RGO contributed to the conception and design of the trial. KY, MCa, KR, MS, JS, CAB, RB, MCh, SJC, MdMC, JC, RGO, and RP contributed to the data acquisition, including enrolling and treating patients. KY, WW, RMdT, MCa, EHP, GP, RJ, TD, SK, LC-H, RGO, and RP analysed the data. All authors had access to, verified, and interpreted the data; contributed to the development of the manuscript; and approved the final version for publication. All authors attest that the trial was done in accordance with the protocol and vouch for the accuracy and completeness of the data and analyses. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

KY receives honoraria from GlaxoSmithKline, Takeda, Janssen, Amgen, and Sanofi; and research funding from Janssen, Bristol Myers Squibb, and Autolus. KR receives honoraria from Karyopharm, Pfizer Oncology, Celgene, Takeda, Janssen, Amgen, Adaptive Biotech, Oncopeptides, GlaxoSmithKline, and Sanofi; is a member of an advisory committee for Karyopharm, Pfizer Oncology, Celgene, Takeda, Janssen, Amgen, Adaptive Biotech, Oncopeptides, GlaxoSmithKline, and Sanofi; receives fees for travel from Janssen, Amgen, Takeda, and Bristol Myers Squibb; receives fees for conference registration from Janssen, Amgen, Takeda, Bristol Myers Squibb (Celgene), Karyopharm, GlaxoSmithKline, Pfizer, Sanofi, and Abbvie; and receives research funding from Bristol Myers Squibb, Janssen, Takeda, Amgen, and GlaxoSmithKline. MS receives consultancy fees from Celgene, Sanofi, and EUSA Pharma. LC-H receives research funding from Bristol-Myers Squibb. RGO receives honoraria from Janssen, Beigene, and AstraZeneca, and is a member of an advisory committee for Janssen and Beigene. RP receives consultancy fees from GlaxoSmithKline, Abbvie, Takeda, Janssen, and Celgene; honoraria from GlaxoSmithKline, AbbVie, Bristol Myers Squibb, Janssen, Oncopeptides, Amgen, and Takeda; research funding from GlaxoSmithKline; fees for travel, fees for accommodation, and expenses from Takeda; and fees for travel from Janssen and Bristol Myers Squibb. The haematology team at the Cancer Research UK and University College London Cancer Trials Centre (LC-H, GP, RJ, TD, WW, and SK) has received funding (which in part pays staff salary) to sponsor and coordinate clinical trials from Amgen, Celgene, Merck Sharp and Dohme, Janssen, Pfizer, and Millennium Pharmaceuticals. All other authors declare no competing interests.

Data sharing

There was no data sharing plan set out at the beginning of this trial. Specific requests for non-identifiable data for valid academic reasons as judged by the trial management group will be granted, with appropriate data sharing agreement, and should be sent to the chief investigator (KY). The study protocol will be available in the appendix with publication.

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