




Carfilzomib and dexamethasone maintenance following salvage ASCT in multiple myeloma: A randomised phase 2 trial by the Nordic Myeloma Study Group

Henrik Gregersen¹ | Valdas Peceliunas² | Kari Remes³ | Fredrik Schjesvold^{4,5}  |
Niels Abildgaard^{6,7} | Hareth Nahi⁸ | Niels Frost Andersen⁹ | Annette Juul Vangsted¹⁰  |
Tobias Wirenfeldt Klausen¹¹ | Carsten Helleberg¹¹ | Kristina Carlson¹² |
Ulf Christian Frølund¹³ | Per Axelsson¹⁴ | Olga Stromberg⁸ | Cecilie Hveding Blimark¹⁵  |
Jacob Crafoord¹⁶ | Galina Tsykunova¹⁷ | Henrik Rode Eshoj^{18,19} | Anders Waage²⁰ |
Markus Hansson²¹ | Nina Gulbrandsen⁴

¹Department of Haematology, Aalborg University Hospital, Aalborg, Denmark

²Department of Haematology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania

³Department of Haematology, Turku University Hospital, Turku, Finland

⁴Oslo Myeloma Center, Oslo University Hospital, Oslo, Norway

⁵KG Jebsen Center for B cell malignancies, University of Oslo, Oslo, Norway

⁶Department of Haematology, Odense University Hospital, Odense, Denmark

⁷Department of Clinical Research, University of Southern Denmark, Odense, Denmark

⁸Department of Haematology, Karolinska University Hospital, Stockholm, Sweden

⁹Department of Haematology, Aarhus University Hospital, Aarhus, Denmark

¹⁰Department of Haematology, Rigshospitalet, Copenhagen, Denmark

¹¹Department of Haematology, Herlev Hospital, Herlev, Denmark

¹²Department of Haematology, Uppsala University Hospital, Uppsala, Sweden

¹³Department of Haematology, Zealand University Hospital, Roskilde, Denmark

¹⁴Department of Haematology, Helsingborg Hospital, Helsingborg, Sweden

¹⁵Department of Haematology, Sahlgrenska University Hospital, Göteborg, Sweden

¹⁶Department of Haematology, Örebro University Hospital, Örebro, Sweden

¹⁷Department of Haematology, Haukeland University Hospital, Bergen, Norway

¹⁸Quality of Life Research Center, Department of Haematology, Odense University Hospital, Odense, Denmark

¹⁹OPEN, Open Patient data Explorative Network, Odense University Hospital, Region of Southern Denmark, Denmark

²⁰Department of Haematology, St Olavs hospital and Institute of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

²¹Department of Haematology, Skåne University Hospital, Lund, Sweden

Novelty Statement: • This randomised phase II study assessed the role of carfilzomib in salvage ASCT.

- The use of carfilzomib-containing induction therapy before salvage ASCT was feasible with manageable toxicity, and subsequent carfilzomib-dexamethasone maintenance prolonged time to progression with 8 months compared with no maintenance.
- The study indicates that maintenance therapy might have a role after salvage ASCT.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *European Journal of Haematology* published by John Wiley & Sons Ltd.

Correspondence

Henrik Gregersen, M.D., Ph.D., Department of Haematology, Aalborg University Hospital, Mølleparkvej 4, DK-9000 Aalborg, Denmark.
Email: henrik.gregersen@rn.dk

Funding information

Amgen

Abstract

Objective: We investigated the efficacy and safety of carfilzomib-containing induction before salvage high-dose melphalan with autologous stem-cell transplantation (salvage ASCT) and maintenance with carfilzomib and dexamethasone after salvage ASCT in multiple myeloma.

Methods: This randomised, open-label, phase 2 trial included patients with first relapse of multiple myeloma after upfront ASCT who were re-induced with four cycles of carfilzomib, cyclophosphamide and dexamethasone. Two months after salvage, ASCT patients were randomised to either observation or maintenance therapy with iv carfilzomib 27 → 56 mg/sqm and p.o. dexamethasone 20 mg every second week. The study enrolled 200 patients of which 168 were randomised to either maintenance with carfilzomib and dexamethasone (n = 82) or observation (n = 86).

Results: Median time to progression (TTP) after randomisation was 25.1 months (22.5-NR) in the carfilzomib-dexamethasone maintenance group and 16.7 months (14.4–21.8) in the control group (HR 0.46, 95% CI 0.30–0.71; *P* = .0004). The most common adverse events during maintenance were thrombocytopenia, anaemia, hypertension, dyspnoea and bacterial infections.

Conclusion: In summary, maintenance therapy with carfilzomib and dexamethasone after salvage ASCT prolonged TTP with 8 months. The maintenance treatment was in general well-tolerated with manageable toxicity.

KEYWORDS

carfilzomib, induction chemotherapy, maintenance chemotherapy, multiple myeloma, salvage therapy

1 | INTRODUCTION

High-dose melphalan with autologous stem-cell transplantation (ASCT) has for three decades been standard of care in younger patients with newly diagnosed multiple myeloma, and recent studies do not indicate imminent replacement of ASCT with treatment regimens solely based on novel drugs.^{1,2} However, almost all patients will ultimately experience relapse after ASCT and salvage ASCT is an appealing option in selected patients due to the potential of second long-term disease control.³ Data on the effect of salvage ASCT are relatively sparse and mainly originate from small retrospective single-centre studies and case-matched studies, some of them performed before induction with the novel agents.^{4–9} Salvage ASCT has only been evaluated in two prospective randomised studies. The British Myeloma X trial showed prolonged progression-free survival (PFS) and overall survival (OS) after salvage ASCT compared with 12 weeks of conventional chemotherapy.¹⁰ The recently published German ReLApsE trial did not find any PFS or OS benefit between patients randomised to lenalidomide-dexamethasone induction followed by salvage ASCT with subsequent lenalidomide maintenance versus patients randomised to continuous lenalidomide-dexamethasone.¹¹ However, a landmark analysis from the time of salvage ASCT showed superior PFS and OS in patients who received

salvage ASCT. A meta-analysis from 2013 on upfront ASCT data supports the use of bortezomib-containing induction therapy and indicates that an improved response after induction therapy translates into improved response and prolonged progression-free survival after ASCT.¹² There is lack of data on the optimal induction regimen before salvage ASCT and a general need for studies that incorporate novel agents into the salvage ASCT setting.

Lenalidomide maintenance after upfront ASCT has become standard of care and prolongs time to progression (TTP) and OS.¹³ There are limited data on the role of maintenance therapy after salvage ASCT although extrapolation of first-line data suggests that this will also be beneficial in the relapse setting. Two small retrospective studies have indicated that maintenance with lenalidomide might prolong TTP after salvage ASCT.^{8,14} However, other retrospective studies have not indicated any effect of various types of maintenance therapy following salvage ASCT.^{4,6} In a small phase 1/2 study, 27 patients with relapsed/refractory multiple myeloma received carfilzomib maintenance after ASCT and the treatment was feasible.¹⁵ However, the study included patients with different lines of therapy and only approximately half of the patients had received previous ASCT. It emphasises the need for prospective studies on the use of maintenance therapy after salvage ASCT in the era of the novel drugs.



The next-generation proteasome inhibitor carfilzomib is commonly used in treatment of relapsed and/or refractory multiple myeloma, and the combination of carfilzomib and dexamethasone demonstrated in the ENDEAVOR trial superior progression-free survival and OS compared to combination of bortezomib and dexamethasone.¹⁶ Furthermore, carfilzomib has demonstrated clinical effect in patients with previous exposure to bortezomib and in patients refractory to bortezomib.¹⁷ Importantly, carfilzomib is not associated with the high risk of peripheral neuropathy seen with bortezomib treatment, but is on the other hand accompanied by an increased risk of cardiac and pulmonary adverse events, most often in the form of dyspnoea, hypertension, heart failure or ischaemic heart disease.¹⁸ Data are sparse on the use of carfilzomib-containing induction therapy before salvage ASCT and as maintenance therapy after salvage ASCT.

The Nordic Myeloma Study Group (NMSG) initiated the CARFI study, a randomised, open-label, phase II study to evaluate the efficacy and safety of induction therapy with carfilzomib-cyclophosphamide-dexamethasone (CAR-CY-DEX) before salvage ASCT and to prospectively evaluate the efficacy and safety of carfilzomib/dexamethasone maintenance after salvage ASCT.

2 | SUBJECTS AND METHODS

2.1 | Trial design

This randomised, open-label, phase II study was designed and conducted by the Nordic Myeloma Study Group (NMSG). It included multiple myeloma patients from 25 hospitals in Denmark, Finland, Lithuania, Norway and Sweden. The study was approved by North Denmark Region Committee on Health Research Ethics (N-20130064), Danish Health and Medicines Authority (No. 2013092582) and Danish Data Protection Agency (No. 2008-58-0028). The trial was approved in each country by ethics committees and drug agencies. EudraCT and ClinicalTrials.gov numbers are 2013-003789-15 and NCT02572492 respectively. Patients provided written informed consent, and the trial was conducted in accordance with the principles of the Declaration of Helsinki.

2.2 | Patients

The study included multiple myeloma patients with first relapse more than 1 year after upfront single or double ASCT with $\geq 2.0 \times 10^6$ frozen CD34+ stem cells/kg body weight stored. Progressive or relapsed disease was defined according to the International Myeloma Working Group criteria.¹⁹

The key exclusion criteria were any myeloma treatment after the first ASCT, including maintenance treatment (exceptions were radiotherapy, bisphosphonates, denosumab and short-term corticosteroids), previous treatment with carfilzomib, WHO performance

status ≥ 3 , significant neuropathy (grade 3–4, or grade 2 with pain) and any comorbidity that would preclude treatment with carfilzomib or ASCT.

2.3 | Trial treatment

Patients received four cycles of CAR-CY-DEX: IV carfilzomib (20 mg/sqm on days 1 and 2 of cycle 1; 36 mg/sqm given thereafter) on days 1, 2, 8, 9, 15 and 16, oral cyclophosphamide 300 mg/sqm on days 1, 8 and 15 and oral dexamethasone 20 mg on days 1, 2, 8, 9, 15 and 16 in each 28-days cycle. The conditioning regimen consisted of IV carfilzomib 27 mg/sqm on day -2 and -1 and IV melphalan 200 mg/sqm on day -2. Two months after ASCT patients were randomised (1:1) to either observation or maintenance therapy with IV carfilzomib 27 mg/sqm every second week and oral dexamethasone 20 mg every second week. The maintenance dose of carfilzomib was escalated to 56 mg/sqm after 4 weeks provided acceptable side effects. The randomisation was stratified according to relapse 1–2 year or >2 years after ASCT, ISS stage and standard-risk versus high-risk cytogenetics. High-risk cytogenetic abnormalities were defined as t(4;14), t(14;16), or del(17p). Maintenance treatment continued until progression, unacceptable adverse effects, withdrawal of consent or 1 September 2019 which was predetermined date for study termination corresponding to follow-up of the last included patient for 9 months after randomisation.

2.4 | End points and assessments

We defined two primary end points in the study, one was comparison of TTP after upfront ASCT and TTP after salvage ASCT with CAR-CY-DEX induction and the second was comparison of TTP between carfilzomib-dexamethasone maintenance and observation in patients treated with salvage ASCT. The response was assessed according to the International Myeloma Working Group criteria for response in multiple myeloma.¹⁹ Secondary end points were toxicity of CAR-CY-DEX as induction regimen and carfilzomib as part of the high-dose melphalan conditioning, response rates of induction therapy and ASCT, time to bone marrow regeneration (neutrophil and platelet recovery) after ASCT, toxicity of maintenance treatment with carfilzomib-dexamethasone, comparison of OS between carfilzomib-dexamethasone maintenance and observation in patients treated with a salvage ASCT, patient-reported health-related quality of life (HRQL) and neurotoxicity. HRQL was assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Module (QLQ-C30) and the Multiple Myeloma Module (QLQ-MY20) questionnaires whereas neurotoxicity was assessed with the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) subscale. Patients completed the questionnaires before randomisation and every other month subsequently.^{20–22} The main HRQL analysis was conducted on the EORTC QLQ-C30 subscale



Global Health Status/Quality of Life (GHS/QoL) from baseline and until 2 years from randomisation, including all visits in between. The remaining data on HRQL and neurotoxicity will be reported in a separate publication.

2.5 | Safety assessment

Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (NCI CTC) Version 4.0.

2.6 | Statistical analysis

Baseline characteristics were presented with frequencies and percentages for categorical variables and median and interquartile range (IQR) or mean and standard deviation (SD). Comparisons of categorical variables between groups were performed using chi-square tests or Fisher's exact test in the case of expected cell counts below 5 and low total number. Continuous and ordinal variables were compared using Mann-Whitney test. All time to event outcomes were analysed using the Kaplan-Meier method. The primary end points were analysed according to intention-to-treat in the way that all patients were included in analyses independently of compliance to treatment. In the maintenance part, patients were analysed according to initial randomisation. The primary end points were time to event outcomes and analysed using the Kaplan-Meier method. Median TTP and progression-free proportions at specific time points extracted from the Kaplan-Meier statistics were presented. For comparisons between TTP after ASCT at diagnosis and salvage ASCT, the Gehan-Wilcoxon test was used, and no hazard ratios were calculated as proportional hazard was not expected. For comparisons between the randomised treatment arms, the log-rank test was used. We further calculated hazard ratios (HR) using a Cox proportional hazard model. Cox regressions were used for subgroup analyses.

For the EORTC GHS/QoL subscale, an overall estimate of the mean treatment effect over time between treatment groups was calculated using a restricted maximum likelihood-based mixed model for repeated measures (MMRM). The model included fixed effects of treatment arm and visit and patients as random effects.

All tests were two-sided. *P*-values below 0.05 were considered statistically significant, and estimates were presented using 95% confidence intervals (CI). All calculations were performed using R software, version 3.6.1. (R Foundation for Statistical Computing, Vienna, Austria).

2.7 | Role of the funding source

Amgen, the funder of the study, had no role in study design, data collection, data analysis, data interpretation or writing of the manuscript. The corresponding author had full access to all the data in

the study and had final responsibility for the decision to submit for publication.

3 | RESULTS

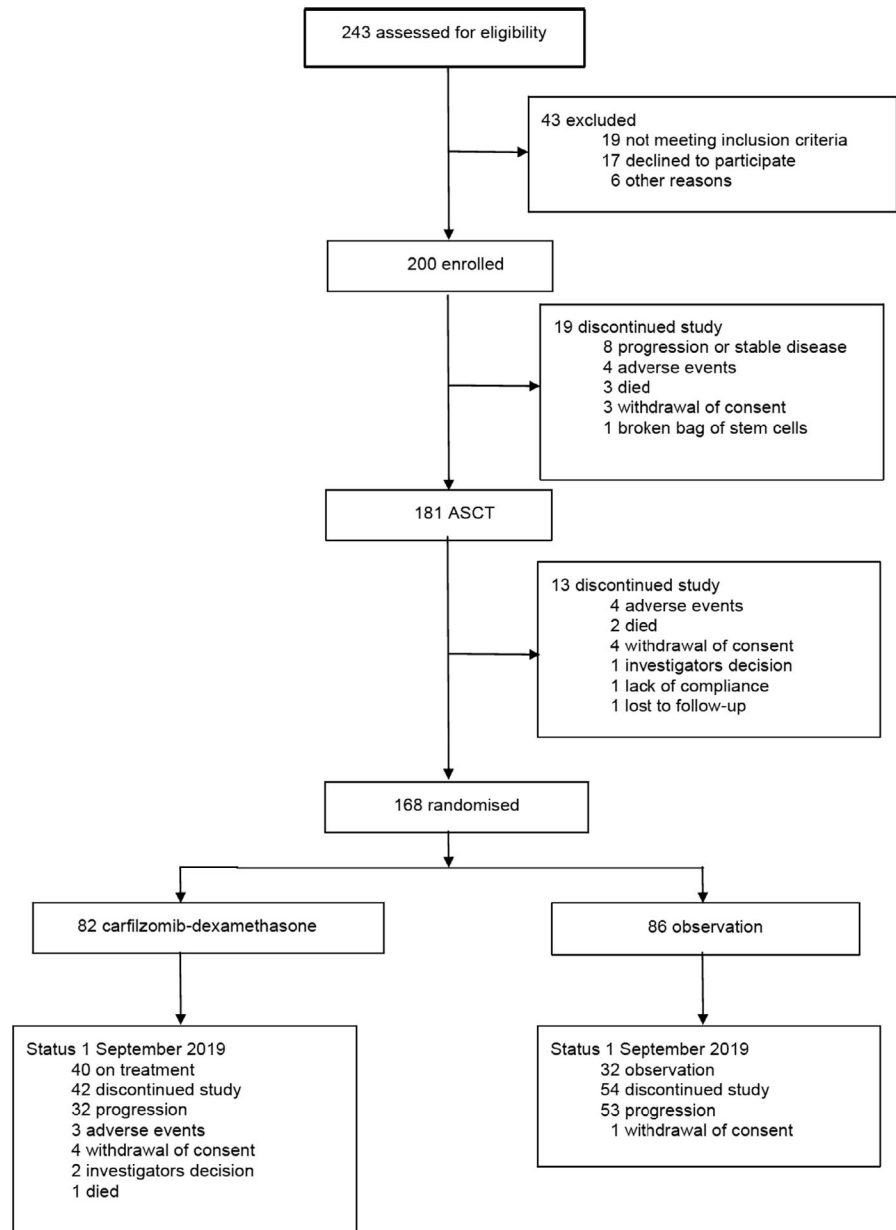
Between 26 January 2015 and 30 April 2018, 200 patients were enrolled, of which 82 were randomly assigned to the carfilzomib-dexamethason maintenance and 86 to observation after completion of salvage ASCT (Figure 1). Median age at study entry was 62 years (IQR 56–66 years), and the median time from upfront ASCT to study entry was 41.3 months (30.0–58.4 months). Demographic and clinical characteristics at time of randomisation were well-balanced between groups, except a slightly younger age in the carfilzomib-dexamethason group versus the control group (Table 1). The majority of patients (83.5%) had received previous treatment with bortezomib as part of induction therapy before upfront ASCT (Table 1). The median follow-up for this analysis was 24.0 months from inclusion until data cut-off which was 1 September 2019, the date of study termination.

There was no difference in quality of treatment response after upfront induction therapy at diagnosis and the four cycles of CAR-CY-DEX induction before salvage ASCT in the study (Table 2). Upfront ASCT and salvage ASCT lead to further improvement of response, but this was most pronounced after upfront ASCT where 32.5% achieved complete remission (CR) or stringent complete remission (sCR) versus 22.8% CR or sCR after salvage ASCT (*P* = .033) (Table 2). Previous bortezomib exposure did not affect quality of response after CAR-CY-DEX or after salvage ASCT. Median TTP from start of induction therapy was 33.2 months (30.4–37.7) for the upfront treatment and 26.7 months (24.2–30.7) for the salvage treatment (*P* < .0001). TTP after upfront treatment was an important predictor of TTP after salvage ASCT, for example median 20.7 months (17.8–25.9) in patients with remission shorter than 24 months and median 29.3 months (26.2–35.4) in patients with remission longer than 24 months (*P* = .025).

Toxicities related to induction treatment with CAR-CY-DEX mainly consisted of low-grade haematologic adverse events and infections, including five cases of septicaemia (Table S1). Cardiac adverse events were observed in 22 patients and in one case lead to withdrawal from the study. Three patients died in the induction period due to septicaemia (two cases) and progression of multiple myeloma (one case). A total of 19 patients left the study from start of CAR-CY-DEX induction until salvage ASCT (Figure 1).

A salvage ASCT was performed in 181 patients. Four patients (2.4%) received a lower dose of melphalan than 200 mg/sqm (range 140–193), and the median number of infused CD34+ stem cells was 4×10^6 /kg (3–5). The most frequent adverse events observed from salvage ASCT until randomisation were haematologic events and infections, including 10 cases of septicaemia. Two patients died during this period which in both cases were caused by fungus septicaemia and corresponds to a 100-day mortality of 1.1%. Four patients

FIGURE 1 Study profile



withdrew their consent to participate in the study during this period (Figure 1). A total of 93 and 57 serious adverse events (SAE) were filed in the induction phase and the time following salvage ASCT respectively.

Mean time to neutrophils above $1.0 \times 10^9/L$ after upfront ASCT and salvage ASCT was 16.9 days (standard deviation 9.4) and 13.4 days (3.5) respectively ($P < .0001$). Mean time to platelets above $100 \times 10^9/L$ was 21.9 days (11.0) and 21.1 days (8.9) respectively ($P = .91$). The use of granulocyte-colony stimulating factor (G-CSF) was not registered.

Median TTP after randomisation was 25.1 months (22.5-NR) in the carfilzomib-dexamethasone maintenance group and 16.7 months (14.4–21.8) in the control group (HR 0.46, 95% CI 0.30–0.71; $P = .0004$; Figure 2). The benefit in TTP for the carfilzomib-dexamethasone maintenance group was observed

across prespecified subgroups, except the small group of proteasome inhibitor-naïve patients (Figure 3). The group of patients randomised to maintenance had the same TTP from start of induction therapy in the upfront and salvage treatment, namely median 31.1 months (29.2–36.8) and 31.5 months (29.3-NR) respectively. Median OS until data cut-off (1 September 2019) was not reached in the maintenance group and was 44.5 months (39.8-NA) in the control group (HR 0.47 (95% CI; 0.18–1.19, $P = .10$)). Improvement of response was observed more often in the maintenance group (43 patients (52.4%)) than in the control group (30 patients (34.9%)) ($P = .003$). This improvement was mainly confined to patients with partial response at time of randomisation, namely in 14 of 16 (88%) patients in the maintenance group versus 6 of 16 (38%) patients in the control group ($P = .009$) (Table S2).


TABLE 1 Demographic, baseline disease and clinical characteristics

	Carfilzomib group (N = 82)	Observation group (N = 86)	All participants (N = 200)
Median age (years)	60 (53–64)	62 (58–67)	62 (56–66)
Sex			
Male	43 (52%)	53 (62%)	116 (58%)
Female	39 (48%)	33 (38%)	84 (42%)
Time from MM diagnosis (months)	40.4 (30.0–58.5)	42.0 (30.8–54.7)	41.3 (30.0–58.4)
Type of myeloma at initial diagnosis			
IgA	9 (11%)	18 (21%)	36 (18.0%)
IgG	54 (66%)	52 (61%)	121 (61%)
Light chain	18 (22%)	15 (17%)	40 (20%)
Other	1 (1%)	1 (1%)	3 (2%)
Previous induction regimen			
VAD	0	1 (1%)	1 (<1%)
CY-DEX	1 (1%)	1 (1%)	4 (2%)
CY-BOR-DEX	60 (73%)	63 (73%)	145 (73%)
CY-THAL-DEX	6 (7%)	5 (6%)	12 (6%)
BOR-DEX	10 (12%)	8 (9%)	22 (11%)
Other	5 (6%)	8 (9%)	16 (8%)
WHO performance status			
0	54 (66%)	56 (65%)	120 (60%)
1	25 (30%)	23 (27%)	63 (32%)
2	0	3 (3%)	8 (4%)
3 or 4	0	0	0
Missing	3 (4%)	4 (5%)	9 (5%)
International Staging System			
I	47 (57%)	50 (58%)	106 (53%)
II	26 (32%)	24 (28%)	65 (33%)
III	4 (5%)	8 (9%)	18 (9%)
Missing	5 (6%)	4 (5%)	11 (6%)
FISH			
Standard risk	63 (77%)	59 (69%)	142 (71%)
High risk	14 (17%)	15 (17%)	39 (20%)
Not done/missing	5 (6%)	12 (14%)	19 (10%)

Note: Data are median (IQR) and n (%). There were no significant between-group differences in the characteristics, with the exception of slightly older patients in the observation arm ($P = .008$).

Abbreviations: VAD, vincristine-doxorubicin-dexamethasone; CY-DEX, cyclophosphamide-dexamethasone; CY-BOR-DEX, cyclophosphamide-bortezomib-dexamethasone; CY-THAL-DEX, cyclophosphamide-thalidomide-dexamethasone; BOR-DEX, bortezomib-dexamethasone; High-risk cytogenetic, t(4;14), t(14;16) or del(17p).

3.1 | Safety

The most common haematological adverse events during carfilzomib-dexamethasone maintenance were thrombocytopenia (in 29% of the patients in the maintenance group vs. 21% of those in the control group) and anaemia (58% vs. 44%), whereas frequent non-haematological adverse events were hypertension (19% vs. 3%), dyspnoea (24% vs. 11%) and bacterial infections (41%

vs. 26%) (Table 3). The occurrence of other cardiac adverse events was low, namely atrial fibrillation in one patient in the maintenance group and in the control group respectively. Adverse events attributable to use of steroids were observed in some patients in the maintenance group, for example mood alterations, insomnia and avascular necrosis of the femoral head (Table 3). A total of 53 serious adverse events (SAEs) were reported in 25 (30.5%) patients in the maintenance group and 38 SAEs in 21 (24.4%) patients in the



TABLE 2 Response after induction and ASCT

Induction	After induction before upfront ASCT (N = 200)	After CAR-CY-DEX induction (N = 200)	After upfront ASCT (N = 200)	After salvage ASCT (N = 168)
sCR	2 (1%)	4 (2%)	13 (7%)	19 (11%)
CR	22 (11%)	14 (8%)	52 (26%)	19 (11%)
VGPR	69 (35%)	71 (38%)	95 (48%)	82 (49%)
PR	89 (45%)	80 (43%)	37 (19%)	45 (27%)
SD	11 (6%)	11 (6%)	2 (1%)	2 (1%)
PD	1 (<1%)	3 (2%)	0	0
Unable to asses	3 (2%)	3 (2%)	1 (1%)	0
Unknown	3	14	0	1

Note: Data are n (%).

Abbreviations: ASCT, high-dose melphalan with autologous stem-cell transplantation; CAR-CY-DEX, carfilzomib-cyclophosphamide-dexamethasone; sCR, stringent complete remission; CR, complete remission; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease.

Response to induction before upfront ASCT versus CAR-CY-DEX induction (not significant). Response after upfront ASCT versus response after salvage ASCT ($P = .04$).

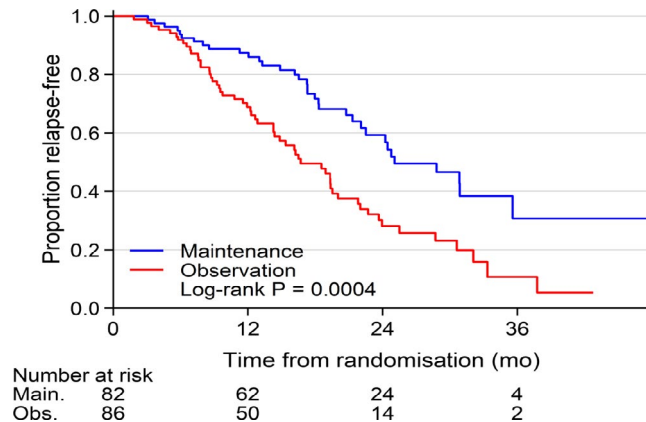


FIGURE 2 Kaplan–Meier analysis of TTP from randomisation in the carfilzomib-dexamethasone maintenance group and the control group

control group. One patient died during maintenance treatment, and none died in the control group. Median duration of carfilzomib maintenance was 16.9 months (range 0.7 - 41.3 months). Dose of carfilzomib was escalated to full dose (56 mg/sqm) in 73 patients (89%). Adverse events led to dose reduction or discontinuation of carfilzomib or dexamethasone in 25 (30.5%) patients and 20 (23.3%) patients respectively (Table S2). We observed no between-group difference in HRQL (EORTC QLQ-C30 GHS/QOL subscale) during the 2-year follow-up period (between-group mean difference 2.24 (95% CI -1.61 to 6.09; $P = .255$)).

4 | DISCUSSION

This trial shows that CAR-CY-DEX induction before salvage ASCT and CAR-DEX maintenance is a feasible and efficacious treatment option in patients with recurrent multiple myeloma after upfront

ASCT. The quality of response after CAR-CY-DEX induction therapy was similar to the quality of response obtained after the initial induction therapy despite that most patients had received previous bortezomib-containing induction regimens. Incorporation of a potent proteasome inhibitor into the induction treatment is therefore an appealing option. The quality of response further improved after salvage ASCT, although less pronounced than after upfront ASCT. We observed a shorter duration of response after salvage ASCT compared with upfront ASCT, which is a common observation in salvage ASCT studies.^{4-6,8,9} The TTP observed in the CARFI study was longer than reported in most other studies on salvage ASCT.⁴⁻⁹ However, comparison of studies is difficult due to heterogeneity of study populations, including the length of response to the first ASCT as an important predictor of length of response to salvage ASCT.³⁻⁵

High-dose melphalan in ASCT is the only setting in current myeloma treatment where a single drug is used and a pending question is whether the effect of this conditioning regimen might be enhanced by adding other agents in pursuit of synergistic effects. A case-matched study has indicated potential effect of bortezomib when combined with high-dose melphalan, and synergy between proteasome inhibitors and melphalan has been pursued in other settings.^{23,24} Carfilzomib was administered on day -2 and -1 in the CARFI study but the design of the trial did not permit a formal evaluation of the effect of adding carfilzomib to high-dose melphalan. Our data do not indicate any increase in adverse events or complications following salvage ASCT. Furthermore, the use of carfilzomib with high-dose melphalan did not affect bone marrow regeneration, and the faster neutrophil recovery after salvage ASCT may be attributed to more consistent use of G-CSF in recent years. Our confirmation of the feasibility of concomitant high-dose melphalan and carfilzomib extend the findings from the small phase 1/2 study by Costa et al, where carfilzomib was given on day -3 og -2 before ASCT, although the study included a mixture of patients treated with first-time ASCT after several previous treatments and salvage ASCT as defined in

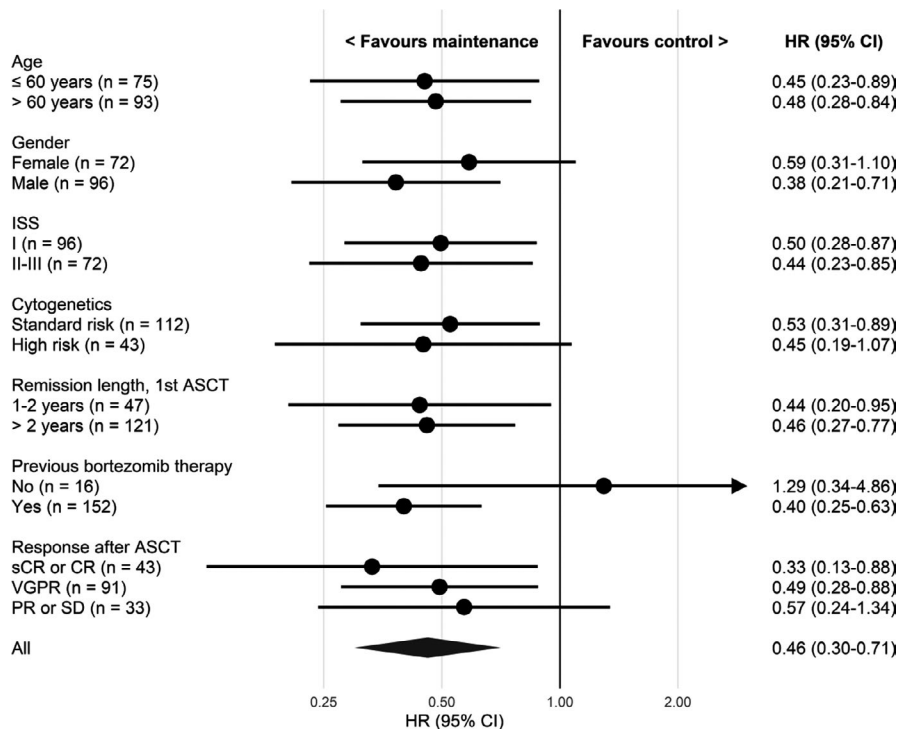


FIGURE 3 Subgroup analyses of TTP in the carfilzomib-dexamethasone maintenance group and the control group. Hazard ratios lower than 1 indicate lower risk of progression in the maintenance group compared with the control group. Subgroups were defined according to baseline characteristics. The I bars represent 95% confidence intervals. ISS denotes the International Staging System. High-risk cytogenetics was defined as t(4;14), t(14;16) or del(17p)

our study.¹⁵ The potential favourable impact of this dual treatment in salvage ASCT remains to be assessed in randomised trials.

The toxicity observed during CAR-CY-DEX induction and following the subsequent salvage ASCT were comparable with the level of adverse events reported in other studies and particular the risk of cardio-toxicity was in line with other studies.^{6,7,16,25,26} The all-cause day 100 mortality after salvage ASCT in our study was 1.1% which is in accordance with the day 100 mortality of 0 to 5% found in other salvage ASCT studies.^{5,8,25}

To the best of our knowledge, this study is the first published randomised prospective study on maintenance treatment following salvage ASCT. We found that the use of carfilzomib and dexamethasone prolonged TTP with approximately 8 months and our study provides a number of interesting data on the use of carfilzomib in this setting. The benefit in TTP for carfilzomib-dexamethasone maintenance compared with no maintenance was in general consistent across different subgroups, including cytogenetic status. This observation is consistent with the recently published MUKfive study where carfilzomib maintenance was associated with an approximate increase of 6 months in PFS compared with no maintenance in patients treated with CAR-CY-DEX at first relapse.²⁶ In contrast to our study the MUKfive study did not include consolidation with salvage ASCT or use of dexamethasone in the maintenance phase. Notably, the MUKfive study also found that carfilzomib maintenance was efficacious in several subgroups, including high-risk genetic abnormalities. Another interesting observation in our trial was the similar TTP after upfront treatment and salvage treatment in patients randomised to carfilzomib-dexamethasone maintenance which indicates that continued treatment with a proteasome inhibitor might overcome the known inferior response duration of salvage ASCT compared with upfront ASCT.^{4,5,8}

The number of adverse events in patients on carfilzomib-dexamethasone maintenance was higher than in the control group but was in general lower than reported in previous clinical trials on carfilzomib.^{16,17} In addition, the occurrence of cardio-pulmonary adverse events was low compared with other studies.^{16,18} It is probably due to the relatively low cumulative dose of carfilzomib in the maintenance phase compared with standard carfilzomib-containing regimes and selection of patients by completing the carfilzomib-containing induction phase and fulfilling the eligibility criteria for salvage ASCT. We observed some adverse events clearly related to the concomitant administration of dexamethasone, for example two cases of avascular necrosis of the femoral head, and it also plausible that dexamethasone has contributed to the two cases of septicæmia observed in the maintenance group. The use of steroid in combination with carfilzomib has probably also contributed to the effect observed in the maintenance group. It was inspired by a phase 2 study showing that addition of dexamethasone to single-agent carfilzomib improved response in patients, who did not achieve partial response with single-agent carfilzomib within the first few cycles.^{27,28} However, these adverse events raise the question whether the dose of dexamethasone could be lower or in fact be omitted.

We noticed dropout of a few patients before the randomisation between carfilzomib/dexamethasone maintenance and observation, and a minor fraction of patients withdrew their consent during the maintenance, which did not seem to relate to progression or side effects. It may reflect the inconvenience of parenteral administration of carfilzomib demanding visits to hospitals or outpatient clinics. This observation is consistent with the study by Costa et al where three of 27 patients withdrew their consent during maintenance therapy.¹⁵ Despite this lack of adherence to maintenance treatment in a few patients, it is noteworthy that we did not observe any difference in



TABLE 3 Most common adverse events in the carfilzomib-dexamethasone maintenance group and the control group

	Carfilzomib-dexamethasone maintenance group No = 82			Control group No = 86		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Haematologic events						
Anaemia	47 (57%)	1 (1%)	0	38 (44%)	0	0
Thrombocytopenia	24 (29%)	0	0	18 (21%)	1 (1%)	1 (1%)
Neutropenia	24 (29%)	2 (2%)	1 (1%)	23 (27%)	3 (3%)	1 (1%)
Cardiac and pulmonary						
Atrial fibrillation		1 (1%)	0	0	1 (1%)	0
Hypertension	12 (15%)	3 (4%)	0	2 (2%)	1 (1%)	0
Dyspnoea	17 (21%)	2 (2%)	1 (1%)	9 (10%)	1 (1%)	0
Gastrointestinal						
Nausea	16 (20%)	3 (4%)	0	3 (3%)	3 (3%)	1 (1%)
Diarrhoea	16 (20%)	1 (1%)	0	16 (19%)	0	0
Constipation	3 (4%)	0	0	4 (5%)	0	0
Bacterial infections						
Pneumonia	2 (2%)	10 (12%)	0	0	8 (9%)	0
Other respiratory tract infection	4 (5%)	5 (6%)	0	1 (1%)	5 (6%)	0
Septicaemia	0	0	2 (2%)	0	0	0
Urinary tract infection	1 (1%)	1 (1%)	0	0	3 (3%)	0
Gastrointestinal track infections	0	3 (4%)	0	0	0	0
Fever without focus	2 (2%)	5 (6%)	0	2 (2%)	7 (8%)	0
Misc infections	1 (1%)	1 (1%)	0	2 (2%)	1 (1%)	0
Viral infections						
Influenza	3 (4%)	3 (4%)	0	0	1 (1%)	0
RSV infection	2 (2%)	2 (2%)	0	0	2 (2%)	0
Herpes zoster	8 (10%)	0	0	14 (16%)	0	0
Misc. infections	0	1 (1%)	0	1 (1%)	0	0
Other adverse events						
Mood alteration	16 (20%)	1 (1%)	1 (1%)	5 (6%)	0	0
Fatigue	10 (12%)	0	0	6 (7%)	0	0
Insomnia	10 (12%)	0	0	0	0	0
Pain	17 (21%)	0	0	18 (21%)	0	0
Adenocarcinoma	0	1 (1%)	1 (1%)	0	0	0
Avascular necrosis of the femoral head	0	2 (2%)	0	0	0	0
Thrombosis	0	1 (1)	0	0	0	0

Note: Data are n (%). The table includes adverse events that occurred in at least 10% of patients or were of clinical interest. The adverse events were recorded from date of randomisation.

Abbreviation: RSV, respiratory syncytial virus.

Global Health Status/Quality of Life between the maintenance and control group, and we noticed that more patients in the maintenance group improved their response.

One limitation of our study is the lack of lenalidomide maintenance after upfront ASCT. This exclusion criterion was applied to standardise the study cohort since lenalidomide maintenance was not approved at the time of the study and infrequently used in the Nordic countries and Lithuania prior to and during the study.

Lenalidomide maintenance treatment was first approved by the European Medicines Agency (EMA) in January 2017 and later reimbursed in the Nordic countries, for example August 2019 in Denmark. It limits the generalisability of the results because maintenance after upfront ASCT is today considered standard of care. However, a large part of current patients with multiple myeloma have not received lenalidomide maintenance after their upfront ASCT and our results are applicable for this group. In addition, the missing lenalidomide



maintenance is not likely to affect the comparison of carfilzomib-dexamethasone maintenance and observation after salvage ASCT in this study. Another limitation is the use of TTP instead of PFS. This outcome was chosen for the sake of the primary end point comparing the upfront ASCT with the salvage ASCT because the immortality of the patients in the retrospective period renders PFS unsuitable. TTP was therefore chosen as general outcome measure including maintenance after salvage ASCT. We only observed one death during the maintenance phase and the difference between TTP and PFS was therefore negligible.

In conclusion, CAR-CY-DEX induction followed by salvage ASCT was feasible, tolerable and with a prospect of obtaining a long-term treatment response. Maintenance therapy with carfilzomib and dexamethasone after salvage ASCT prolonged TTP with 8 months, and the maintenance treatment was in general well-tolerated with manageable toxicity.

ACKNOWLEDGEMENTS

The study received financial support and free study drug from Amgen. The authors would like to thank Peter Gimsing for inspiration for the study, Sanne Kjær at the Clinical Trial Unit, Aalborg University Hospital for administrative assistance, www.FACIT.org for permission to use the FACT/GOG-NTX Scale, EORTC for permission to use the quality of life QLQ-C30 and MY20 questionnaires, Open Patient data Explorative Network (OPEN) for help with the QOL data and Berit Bjelkåsen, Enhet for anvendt klinisk forskning (AKF) at NTNU in Trondheim, Norway for data management. Finally, we thank the patients and staff members at the trial sites for participation in the trial.

CONFLICT OF INTEREST

The authors have nothing to disclose.

AUTHOR CONTRIBUTIONS



HG, KR, NA, NG, MH and AW contributed to the conception and design of the study. NG, MH, KR, VP and HG provided administrative support. VP, KR, FS, NA, HN, NFA, AJV, CH, KS, UCF, PA, OS, CHB, JC, GT, HRE, AW, MH, NG and HG were responsible for the provision of study data and patients. TWK, HG and HRE contributed to the data management and data analysis. FS, NA, AJV, CHB, HRE, TWK and AW contributed to interpretation of the results and drafting the manuscript. All authors provided critical revision for the content, reviewed and approved the final version of the manuscript. TWK, HRE and HG verified the underlying data.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not available online due to restrictions from the ethical approval.

ORCID

Fredrik Schjesvold  <https://orcid.org/0000-0003-1096-0569>

Annette Juul Vangsted  <https://orcid.org/0000-0002-2131-731X>
Cecilie Hveding Blimark  <https://orcid.org/0000-0003-3297-6019>

REFERENCES

- Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371(10):895-905.
- Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. *Lancet Haematol*. 2020;7(6):e456-e468.
- Hagen PA, Stiff P. The role of salvage second autologous hematopoietic cell transplantation in relapsed multiple myeloma. *Biol Blood Marrow Transplant*. 2019;25(3):e98-e107.
- Gonsalves WI, Gertz MA, Lacy MQ, et al. Second auto-SCT for treatment of relapsed multiple myeloma. *Bone Marrow Transplant*. 2013;48(4):568-573.
- Singh Abbi KK, Zheng J, Devlin SM, Giralt S, Landau H. Second autologous stem cell transplant: an effective therapy for relapsed multiple myeloma. *Biol Blood Marrow Transplant*. 2015;21(3):468-472.
- Jimenez-Zepeda VH, Mikhael J, Winter A, et al. Second autologous stem cell transplantation as salvage therapy for multiple myeloma: impact on progression-free and overall survival. *Biol Blood Marrow Transplant*. 2012;18(5):773-779.
- Gimsing P, Hjertner O, Abildgaard N, et al. Salvage bortezomib-dexamethasone and high-dose melphalan (HDM) and autologous stem cell support (ASCT) in myeloma patients at first relapse after HDM with ASCT. A phase-2 trial. *Bone Marrow Transplant*. 2015;50(10):1306-1311.
- Gossi U, Jeker B, Mansouri TB, et al. Prolonged survival after second autologous transplantation and lenalidomide maintenance for salvage treatment of myeloma patients at first relapse after prior autograft. *Hematol Oncol*. 2018;36(2):436-444.
- Muta T, Miyamoto T, Kamimura T, et al. Significance of salvage autologous stem cell transplantation for relapsed multiple myeloma: a Nationwide Retrospective Study in Japan. *Acta Haematol*. 2018;139(1):35-44.
- Cook G, Ashcroft AJ, Cairns DA, et al. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2016;3(7):e340-e351.
- Goldschmidt H, Baertsch MA, Schlenzka J, et al. Salvage autologous transplant and lenalidomide maintenance vs. lenalidomide/dexamethasone for relapsed multiple myeloma: the randomized GMMG phase III trial ReLApsE. *Leukemia*. 2020;35(4):1134-1144.
- Nooka AK, Kaufman JL, Behera M, et al. Bortezomib-containing induction regimens in transplant-eligible myeloma patients: a meta-analysis of phase 3 randomized clinical trials. *Cancer*. 2013;119(23):4119-4128.
- Jackson GH, Davies FE, Pawlyn C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2019;20(1):57-73.
- Lemieux E, Hulin C, Caillot D, et al. Autologous stem cell transplantation: an effective salvage therapy in multiple myeloma. *Biol Blood Marrow Transplant*. 2013;19(3):445-449.
- Costa LJ, Landau HJ, Chhabra S, et al. Phase 1/2 trial of carfilzomib plus high-dose melphalan preparative regimen for salvage autologous hematopoietic cell transplantation followed by maintenance



- carfilzomib in patients with relapsed/refractory multiple myeloma. *Biol Blood Marrow Transplant*. 2018;24(7):1379-1385.
16. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol*. 2016;17(1):27-38.
 17. Dimopoulos MA, Stewart AK, Masszi T, et al. Carfilzomib-lenalidomide-dexamethasone vs lenalidomide-dexamethasone in relapsed multiple myeloma by previous treatment. *Blood Cancer J*. 2017;7(4):e554.
 18. Fakhri B, Fiala MA, Shah N, Vij R, Wildes TM. Measuring cardiopulmonary complications of carfilzomib treatment and associated risk factors using the SEER-Medicare database. *Cancer*. 2020;126(4):808-813.
 19. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel. *Blood*. 2011;117(18):4691-4695.
 20. Cocks K, Cohen D, Wisloff F, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. *Eur J Cancer*. 2007;43(11):1670-1678.
 21. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
 22. Huang HQ, Brady MF, Cella D, Fleming G. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. *Int J Gynecol Cancer*. 2007;17(2):387-393.
 23. Facon T, Lee JH, Moreau P, et al. Carfilzomib or bortezomib with melphalan-prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma. *Blood*. 2019;133(18):1953-1963.
 24. Roussel M, Moreau P, Huynh A, et al. Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: a phase 2 study of the Intergroupe Francophone du Myelome (IFM). *Blood*. 2010;115(1):32-37.
 25. Fenk R, Liese V, Neubauer F, et al. Predictive factors for successful salvage high-dose therapy in patients with multiple myeloma relapsing after autologous blood stem cell transplantation. *Leuk Lymphoma*. 2011;52(8):1455-1462.
 26. Yong KL, Hinsley S, Auner HW, Bygrave C, Kaiser MF, Ramasamy K, De Tute RM, Sherratt D, Flanagan L, Garg M, Hawkins S, Williams C, Cavenagh J, Rabin NK, Croft J, Morgan G, Davies F, Owen RG, Brown SR. Carfilzomib or bortezomib in combination with cyclophosphamide and dexamethasone followed by carfilzomib maintenance for patients with multiple myeloma after one prior therapy: results from a multi-centre, phase II, randomized, controlled trial (MUKfive). *Haematologica*. 2021. <http://dx.doi.org/10.3324/haematol.2021.278399>
 27. Lendvai N, Hilden P, Devlin S, et al. A phase 2 single-center study of carfilzomib 56 mg/m² with or without low-dose dexamethasone in relapsed multiple myeloma. *Blood*. 2014;124(6):899-906.
 28. Sudalagunta P, Silva MC, Canevarolo RR, et al. A pharmacodynamic model of clinical synergy in multiple myeloma. *EBioMedicine*. 2020;54:102716.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Gregersen H, Peceliunas V, Remes K, et al. Carfilzomib and dexamethasone maintenance following salvage ASCT in multiple myeloma: A randomised phase 2 trial by the Nordic Myeloma Study Group. *Eur J Haematol*. 2021;00:1-11. <https://doi.org/10.1111/ejh.13709>