Research in context

Evidence before this study

The combination of the second-generation proteasome inhibitor carfilzomib with lenalidomide and dexamethasone (KRd) showed efficacy in patients with relapsed or refractory multiple myeloma and was considered an emerging option for first-line therapy. Based on the good efficacy and safety profile of the bortezomib plus cyclophosphamide plus dexamethasone combination upfront, carfilzomib in combination with cyclophosphamide and dexamethasone (KCd) was also considered as a potential alternative. On Aug 11, 2021, we searched PubMed using the search terms "myeloma", "newly diagnosed", "carfilzomib", "lenalidomide" or "cyclophosphamide", and "maintenance" in the "title/abstract" field, and we added the search filter "clinical trial". We identified eight full-text articles reporting data from clinical trials: three phase 1–2 trials evaluating KCd, and three phase 2 trials and one phase 3 trial evaluating KRd. So far, upfront autologous stem-cell transplantation (ASCT) has shown a consistent advantage in terms of progression-free survival over all tested combinations containing novel agents. Nevertheless, no trials have previously evaluated a carfilzomib-based first-line therapy with or without ASCT intensification in a randomised fashion. Proteasome inhibitors such as bortezomib and ixazomib have also been tested in the maintenance setting. To improve the efficacy of maintenance treatment with lenalidomide alone (the current standard of care), in our trial the proteasome inhibitor carfilzomib was added to lenalidomide as maintenance treatment, with a reduced intensity in the schedule of administration and for a fixed duration of 2 years.

Added value of this study

To our knowledge, FORTE is the first multicentre, open-label, randomised trial that enrolled transplant-eligible patients with newly diagnosed multiple myeloma and that compared different carfilzomib-based therapies in the context of upfront or delayed transplantation. Moreover, so far, no trial has compared the efficacy and toxicity profiles of carfilzomib plus lenalidomide versus lenalidomide alone as maintenance treatments. Our data confirmed that combination therapies comprising proteasome inhibitors and immunomodulatory agents improved responses over combination therapies of proteasome inhibitors plus chemotherapy. Furthermore, our exploratory analysis comparing KRd plus ASCT versus KRd for 12 cycles confirmed the important additive role of transplantation in improving progression-free survival even in the context of a very effective approach based on KRd. Carfilzomib plus lenalidomide as maintenance treatment improved progression-free survival and rate of conversion to minimal residual disease negativity compared with lenalidomide alone. Although, as expected, we observed a higher rate of non-haematological adverse events with a doublet versus a single agent (mainly vascular and cardiac events in the carfilzomib plus lenalidomide group), we did not observe an increase in treatment discontinuation due to toxicity with carfilzomib plus lenalidomide versus lenalidomide alone. The subgroup analyses showed a consistent benefit of KRd plus ASCT as induction–intensification–consolidation therapy and carfilzomib plus lenalidomide as maintenance therapy in all prognostic subgroups, with similar hazard ratios in the high-risk and standard-risk populations.

Implications of all the available evidence

Our results confirm that the KRd regimen plus high-dose chemotherapy and ASCT leads to deep and durable responses, without a high toxicity burden. A carfilzomib-based therapy is also particularly effective in high-risk patients, in whom there is currently an unmet clinical need. These data compare favourably with standards of care such as bortezomib plus lenalidomide plus dexamethasone plus ASCT and daratumumab plus bortezomib plus thalidomide plus dexamethasone in patients eligible for ASCT (including high-risk patients) and support the further evaluation of KRd plus ASCT alone or in combination with anti-CD38 monoclonal antibodies. Maintenance treatment with carfilzomib plus lenalidomide, even if associated with slightly higher toxicity, showed a high level of efficacy, which supports its potential role as a new standard of care, especially with strategies to minimise the risk of toxicity and improve compliance (eg, the administration of carfilzomib once every 2 weeks). Future steps, regarding both the induction–consolidation phases and the maintenance phase, could include a more tailored approach to treatment, which could be based on patient eligibility for specific therapies, risk-adapted therapy, and response-adapted therapy, in order to avoid unnecessary toxicity and maximise treatment efficacy.

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Methods

Study design and participants

UNITO-MM-01/FORTE was a randomised, open-label, phase 2 trial that enrolled patients from 42 Italian academic and community practice centres (appendix 2 pp 8–9). Transplant-eligible patients with newly diagnosed multiple myeloma aged 65 years or younger with symptomatic, measurable disease defined according to standard criteria[14] were eligible. Other inclusion criteria were a Karnofsky performance status of 60% or higher, life expectancy greater than 6 months, absolute neutrophil count of at least 1×10^9 cells per L, platelet count of at least 70×10^9 per L, left ventricular ejection fraction of 40% or greater, and creatinine clearance of 30 mL/min or greater. Exclusion criteria included other malignancies within the past 3 years; peripheral neuropathy worse than grade 2 or grade 2 with pain; unstable angina or myocardial infarction within 4 months before randomisation; New York Heart Association functional class III or IV heart failure; uncontrolled angina; history of severe coronary artery disease; severe uncontrolled ventricular arrhythmias; sick sinus syndrome or electrocardiographic evidence of acute ischaemia, or grade 3 conduction system abnormalities unless the patient had a pacemaker; and

See Online for appendix 2

any notable clinical condition that placed the patient at a substantial risk if they participated in the trial.

This trial, its protocol, and its amendments (appendix 2 pp 5, 7, 10, 29) were approved by the ethics committees or institutional review boards at each of the participating centres. The protocol is in appendix 2 (pp 28–171). All patients gave written, informed consent before participating in the trial, which was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Randomisation and masking

At enrolment, a computer system randomly assigned patients (1:1:1) to treatment into one of the three induction–intensification–consolidation groups. A block randomisation (block size 12), stratified according to International Staging System (ISS)[15] stage (I *vs* II/III) and age (<60 years *vs* 60–65 years), was generated at enrolment by a computer program and implemented into a web-based procedure by the investigator or designated research staff. Patients were eligible for maintenance treatment if they did not experience unacceptable toxicity or progression during the induction, intensification, and consolidation phases. Maintenance randomisation was balanced with a permuted block (block size 8) and was stratified according to induction–intensification–consolidation treatment in a 1:1 ratio.

Procedures

At enrolment, patients were randomly assigned (first randomisation) into one of the three induction–intensification–consolidation groups (appendix 2 p 16).

Patients in the KRd plus ASCT group received four 28-day induction cycles with KRd (carfilzomib 20 mg/m² intravenously administered on days 1–2 of cycle 1, followed by 36 mg/m² intravenously administered on days 8–9 and 15–16 of cycle 1, then 36 mg/m² intravenously administered for all subsequent doses on days 1–2, 8–9, and 15–16; lenalidomide 25 mg orally administered on days 1–21; dexamethasone 20 mg orally or intravenously administered on days 1–2, 8–9, 15–16, and 22–23); followed by stem-cell mobilisation and collection (cyclophosphamide at 2000 mg/m² intravenously administered on day 1 plus 10 µg/kg of granulocyte colony-stimulating factor [G-CSF] subcutaneously administered from day 5 until stem-cell collection was completed). Thereafter, patients received intensification with MEL200-ASCT and, between day 90 and 120, started consolidation with four KRd cycles (same dose and schedule used during the induction phase).

Patients in the KRd12 group received four 28-day induction cycles with KRd, followed by stem-cell mobilisation and collection as in the other groups, but they did not proceed with MEL200-ASCT; instead, they received eight KRd cycles (same dose and schedule used during the induction phase).

Patients in the KCd plus ASCT group received four 28-day induction cycles with KCd (carfilzomib 20 mg/m² intravenously administered on days 1–2 of cycle 1, followed by 36 mg/m² intravenously administered on days 8–9 and 15–16 of cycle 1, then 36 mg/m² intravenously administered for all subsequent doses on days 1–2, 8–9, and 15–16; cyclophosphamide 300 mg/m² orally administered on days 1, 8, and 15; dexamethasone 20 mg orally or intravenously administered on days 1–2, 8–9, 15–16, and 22–23); followed by stem-cell mobilisation and collection and MEL200-ASCT, as in the KRd plus ASCT group. Between day 90 and 120, patients started consolidation with four KCd cycles (same dose and schedule used during the induction phase).

After the end of consolidation, eligible patients were randomly assigned (second randomisation) to maintenance treatment with either lenalidomide (10 mg orally administered daily on days 1–21 every 28 days until progression or intolerance) plus carfilzomib (36 mg/m² intravenously administered once daily on days 1–2 and 15–16 every 28 days [ie, twice every 2 weeks]; the trial was subsequently amended on Feb 11, 2019, changing the carfilzomib dose and schedule to 70 mg/m² intravenously administered once daily on days 1 and 15 for up to 2 years [ie once every 2 weeks]) or lenalidomide alone until progression or intolerance.

Carfilzomib dose reductions, delays, or interruptions were permitted after occurrence of haematological adverse events (grade 4 thrombocytopenia with active bleeding and grade 4 lymphopenia lasting for >14 days) and grade 3–4 non-haematological adverse events related to carfilzomib (allergic reaction, tumor lysis syndrome, infection, herpes zoster, neuropathy, renal dysfunction with creatinine clearance <30 mL/min, and heart failure). Subsequent treatment with carfilzomib could be resumed reducing the dose by one dose level, according to the protocol (appendix 2 pp 9, 10). If toxicity continued or re-occurred after two dose reductions, carfilzomib administration was interrupted. Lenalidomide dose adjustments were based on clinical and laboratory findings (appendix 2 pp 10, 11). Patients enrolled with creatinine clearance less than 50 mL/min started with a reduced dose of lenalidomide according to the dose adjustment guideline for renal dysfunction (appendix 2 p 10). In case of grade 4 haematological and grade 3–4 non-haematological toxicities related to cyclophosphamide, the drug was temporarily discontinued for up to 4 weeks, until the adverse event was resolved. Dexamethasone dose modifications due to common dexamethasone-related toxicities are listed in appendix 2 (pp 11–12). Details of dose reductions and interruptions and other study procedures are included in appendix 2 (pp 3, 6–7, 9–12).

MRI, PET/CT, or x-ray skeletal survey were done within 8 weeks before the first dose of the study drug. The x-ray skeletal survey was done during the screening period and then once a year. MRI, (low-dose) CT, or PET/CT were

done at screening and, in case of bone lesions or bone-soft tissue plasmacytoma, were done after four cycles of the induction phase or after the mobilisation phase and at the end of the consolidation phase (before maintenance treatment), in order to evaluate response to treatment, and, thereafter, when clinically indicated.

Laboratory tests for haematology clinical chemistry were done before every infusion of carfilzomib during the first induction cycle and, from cycle 2, repeated only once weekly at the physician's discretion and based on the patient's condition. Disease assessments, comprising serum protein electrophoresis and 24 h urine protein electrophoresis were done every cycle at day 1. Serum free light chain (FLC) analysis was done at screening, to evaluate response for patients with oligosecretory or non-secretory multiple myeloma, and to confirm stringent complete response for patients with baseline serum FLC concentrations greater than 10 mg/dL.

The response rate was defined according to the International Uniform Response Criteria.[16] A centralised minimal residual disease evaluation was done before maintenance and, thereafter, every 6 months during maintenance by multiparameter flow cytometry (sensitivity 10^{-5})[17] in all patients achieving at least a very good partial response and by next-generation sequencing (NGS; sensitivity 10^{-5})[18] in a subset of patients achieving at least a complete response (pre-planned sub-study). More details of response definitions are provided in appendix 2 (p 4). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0)[19] and summarised by the worst National Cancer Institute Common Terminology Criteria for Adverse Events grade. Serious adverse events were monitored during the study and second primary malignancies were monitored as events of interest.

Outcomes

The primary study endpoints were the proportion of patients with at least a very good partial response with KRd versus KCd as induction therapy and progression-free survival from maintenance randomisation with carfilzomib plus lenalidomide versus lenalidomide alone. Key secondary endpoints were the proportion of patients with a stringent complete response and progression-free survival with KRd plus ASCT and KRd12 versus KCd plus ASCT. Other secondary endpoints included overall survival, overall response rate, minimal residual disease negativity, rate of 1-year sustained minimal residual disease negativity, safety, success of stem-cell harvest, time to progression, time to next treatment, duration of response, progression-free survival 2, comparison of maintenance treatment with carfilzomib once every 2 weeks plus lenalidomide versus maintenance treatment with carfilzomib twice every 2 weeks plus lenalidomide (safety, progression-free survival, progression-free survival 2, and overall survival), and exploratory comparative analyses between subgroups of patients, defined according to known prognostic factors (a detailed list of all secondary endpoints and exploratory analyses is provided in appendix 2 p 4).

Data on progression-free survival 2 are immature and are not reported here, because of the very low number of progression-free survival 2 events. Progression-free survival, progression-free survival 2, and overall survival for the comparison of the administrations of carfilzomib once every 2 weeks versus twice every 2 weeks in the maintenance phase are not reported here because of the low number of patients who received the once every 2 weeks administration. This was due to the late approval of protocol amendment 5 on Feb 11, 2019, which allowed the use of the once every 2 weeks schedule.

Statistical analysis

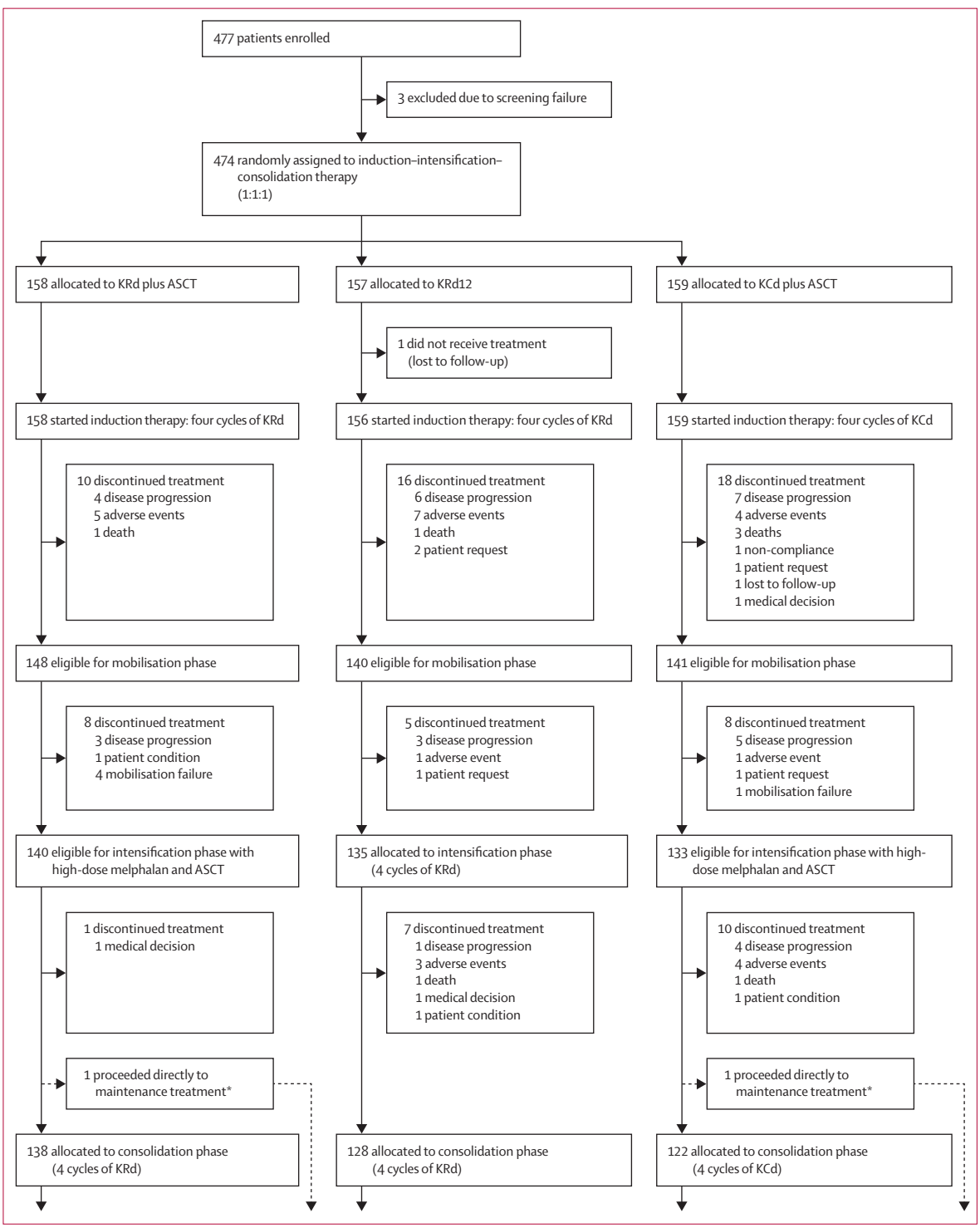
The calculation of the sample size for the first primary endpoint (the proportion of patients with at least a very good partial response after induction with KRd *vs* KCd) was based on the following assumptions, considering the intention-to-treat population: a two-sided alpha of 0·05 and power of 90%, 62% of patients having at least a very good partial response with KCd, and 80% having at least a very good partial response with KRd. The KRd plus ASCT and KRd12 groups were pooled (2:1) for analysis of patients with at least a very good partial response, since the treatment population was the same until that point. Using the two-group continuity-corrected χ^2 test, the required sample size for each group was 143, and 429 patients overall. After considering that around 10% of patients would be lost to follow-up, the total sample size was updated to 477 patients.

The calculation of the sample size for the second primary endpoint (progression-free survival from the second randomisation with carfilzomib plus lenalidomide *vs* lenalidomide alone) was based on the following assumption, considering the intention-to-treat population: a 4-year progression-free survival of 40% with lenalidomide alone and 60% with carfilzomib plus lenalidomide (HR 0·558) with a two-sided alpha of 0·05 and beta of 0·2. With an unstratified log-rank test, the sample size required was 196 patients and the number of events required was 92.

Efficacy analyses were based on the intention-to-treat principle. All patients eligible to receive treatment and randomly assigned were included in efficacy analyses. A hierarchical testing procedure was used for the first primary endpoint (H1: proportion of patients with at least a very good partial response with KRd *vs* KCd induction) and key secondary endpoints (H2: stringent complete response rate; H3: progression-free survival from the first randomisation in the three induction–intensification–consolidation groups) to achieve control of the overall familywise type I error rate at a two-sided significance level of 0·05. Details of the statistical analysis of key secondary endpoints are reported in appendix 2 (p 5).

A post-hoc analysis was done to compare the KRd plus ASCT and KRd12 groups and to analyse the different

minimal residual disease conversion rates (from positivity to negativity), from the pre-maintenance phase and during maintenance treatment, in the different maintenance groups. A post-hoc analysis was done to compare outcomes in patients who were negative for minimal residual disease versus patients positive for minimal residual disease in the different treatment groups during the pre-maintenance and maintenance phases and in patients who achieved a sustained minimal residual disease negativity.



(Figure 1 continues on next page)

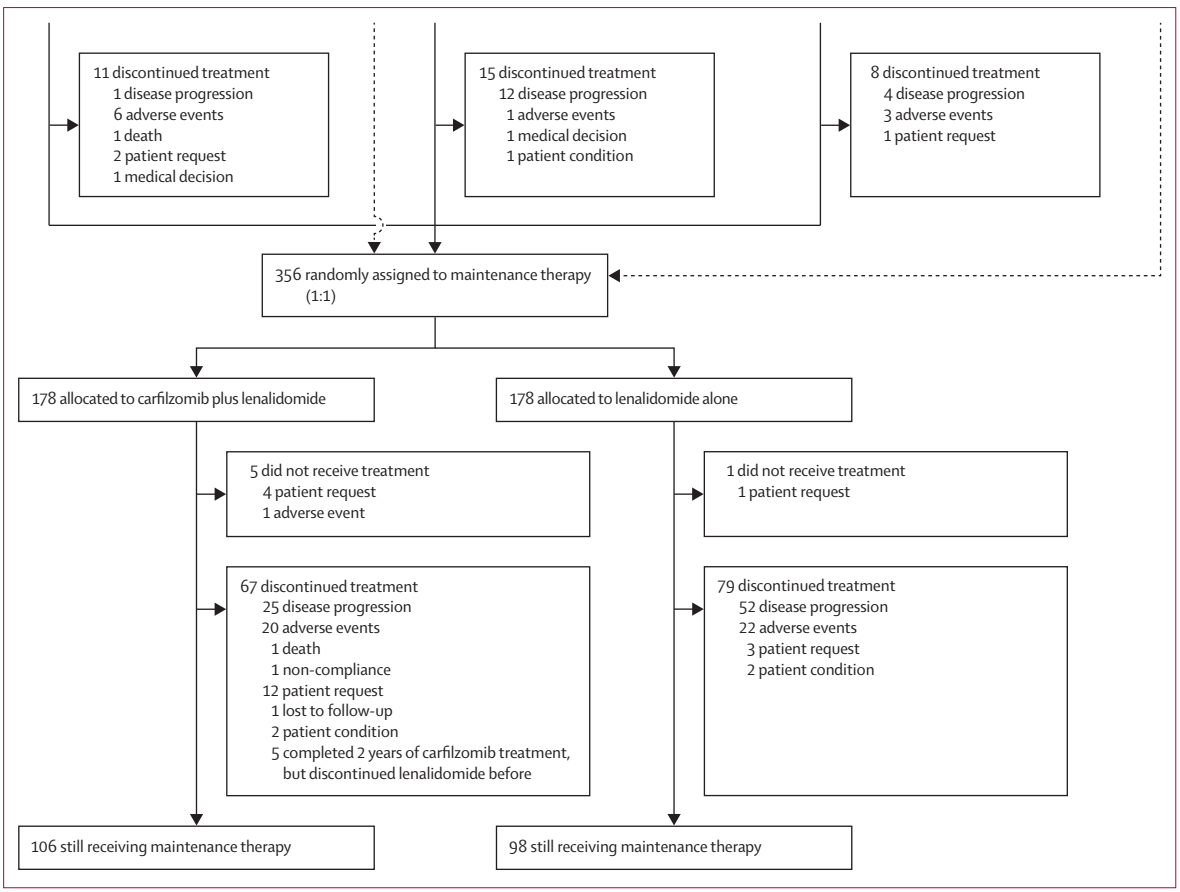


Figure 1: **Trial profile**
KRd=carfilzomib plus lenalidomide plus dexamethasone. ASCT=autologous stem-cell transplantation. KCd=carfilzomib plus cyclophosphamide plus dexamethasone. MEL200=melphalan at 200 mg/m². KRd plus ASCT=four KRd induction cycles, MEL200-ASCT, four KRd consolidation cycles. KRd12=12 KRd cycles. KCd plus ASCT=four KCd induction cycles, MEL200-ASCT, four KCd consolidation cycles. *After intensification, two patients proceeded directly to maintenance treatment: one patient from the KRd plus ASCT group due to grade 2 prolonged thrombocytopenia; and one patient from the KCd plus ASCT group due to grade 3 prolonged thrombocytopenia.

The rate of minimal residual disease negativity detected by multiparameter flow cytometry was analysed according to the intention-to-treat principle, and patients missing a minimal residual disease evaluation or not achieving a partial response or better were considered positive for minimal residual disease. The rate of minimal residual disease negativity detected by NGS was instead calculated in patients who had a complete response and were included in the substudy. For the analysis of the rate of 1-year sustained minimal residual disease negativity detected by multiparameter flow cytometry, patients were considered negative for sustained minimal residual disease if they were negative before maintenance treatment and maintained the negative status for minimal residual disease for at least 1 year. According to the intention-to-treat principle, patients who were positive before maintenance treatment or missed the follow-up evaluation of minimal residual disease or had a positive minimal residual disease evaluation at 1 year were considered to have non-sustained minimal residual disease. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs for the main comparisons. We did the Grambsch and Therneau test for the proportional hazards assumption.[20] All analyses were adjusted according to stratification factors. Details of the analysed outcomes are reported in appendix 2 (p 4).

Data from all patients who received any study drug were included in the safety analyses. Adverse events leading to death or to treatment discontinuation, grade 3–4 events, study-drug-related events, and serious adverse events were summarised separately. An independent data monitoring committee reviewed the safety data. Between-group differences in responses and adverse events were evaluated with the Mann–Whitney U-test and the χ^2 or Fisher's exact tests, as appropriate, for continuous and categorical variables, respectively. A pre-planned, interim safety analysis of the administrations of carfilzomib once every 2 weeks versus twice every 2 weeks was done after four cycles of treatment.

We reported two-sided p-values with the threshold as described above in the hierarchical procedures. Statistical

	Induction, intensification, and consolidation			Maintenance	
	KRd plus ASCT (n=158)	KRd12 (n=157)	KCd plus ASCT (n=159)	Carfilzomib plus lenalidomide (n=178)	Lenalidomide alone (n=178)
Age, years	57 (52–62)	57 (51–62)	57 (52–62)	56 (52–62)	57 (51–62)
≥60 years	62 (39%)	60 (38%)	62 (39%)	62 (35%)	66 (37%)
Sex					
Female	71 (45%)	69 (44%)	72 (45%)	76 (43%)	88 (49%)
Male	87 (55%)	88 (56%)	87 (55%)	102 (57%)	90 (51%)
ISS					
I	80 (51%)	80 (51%)	80 (50%)	96 (54%)	98 (55%)
II	55 (35%)	46 (29%)	51 (32%)	52 (29%)	61 (34%)
III	23(15%)	31 (20%)	28 (18%)	30 (17%)	19 (11%)
Chromosomal abnormalities*					
High risk					
[del(17p), t(4;14), t(14;16)]	46 (34%)	38 (29%)	49 (35%)	39 (27%)	44 (28%)
Data missing	22	27	17	33	23
[del(17p), t(4;14), t(14;16), amp(1q)]	80 (59%)	68 (52%)	86 (61%)	80 (56%)	82 (53%)
Data missing	23	27	19	36	23
LDH >ULN†	21 (14%)	18 (12%)	22 (15%)	17 (10%)	18 (10%)
Data missing	3	5	8	9	4
R-ISS					
I	49 (35%)	40 (30%)	38 (27%)	50 (34%)	58 (37%)
II	76 (54%)	80 (60%)	91 (65%)	82 (55%)	89 (57%)
III	16 (11%)	14 (10%)	12 (9%)	16 (11%)	9 (6%)
Not estimable	17	23	18	30	22

Data are n (%) or median (IQR). KRd=carfilzomib plus lenalidomide plus dexamethasone. ASCT=autologous stem-cell transplantation. KRd12=12 KRd cycles. KCd=carfilzomib plus cyclophosphamide plus dexamethasone. MEL200=melphalan at 200 mg/m². KRd plus ASCT=four KRd induction cycles, MEL200-ASCT, and four KRd consolidation cycles. KCd plus ASCT=four KCd induction cycles, MEL200-ASCT, and four KCd consolidation cycles. ISS=International Staging System. R-ISS=Revised ISS stage. del=deletion. t=translocation. amp=amplification. LDH=lactate dehydrogenase. ULN=upper limit of normal. *Percentage calculated on patients with available data. †LDH >ULN defined according to the ULN determined by laboratories in different participating centres. Percentages might not total 100 because of rounding.

Table 1: **Baseline demographics and disease characteristics**

analyses were done with R (version 4.0.2). The data cutoff date was Jan 7, 2021.

This trial is registered with ClinicalTrials.gov, NCT02203643. Study recruitment is complete, and all patients are in the follow-up or maintenance phases.

Role of the funding source

The UNITO-MM-01/FORTE trial was sponsored by the Università degli Studi di Torino (Turin, Italy), Department of Molecular Biotechnology and Health Sciences. Amgen and Celgene/Bristol Myers Squibb provided an unrestricted grant to conduct the trial, but had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the manuscript for publication.

Results

Between Feb 23, 2015, and April 5, 2017, 477 patients were enrolled. 474 patients were randomly assigned to one of the induction–intensification–consolidation groups (158 to KRd plus ASCT, 157 to KRd12, and 159 to KCd plus ASCT), and three were not included because of screening failure. A similar proportion of patients in the three groups entered the intensification and consolidation phases (figure 1). At the end of consolidation, 356 patients were eligible for maintenance treatment and randomly assigned to carfilzomib plus lenalidomide (n=178) or lenalidomide alone (n=178; figure 1). Baseline demographics and disease characteristics are shown in table 1. At the data cutoff (Jan 7, 2021), 198 (42%) of 474 patients had progressed or died, 106 (60%) of 178 patients were receiving therapy with carfilzomib plus lenalidomide (all of these patients completed 2 years of carfilzomib and were subsequently receiving lenalidomide alone), and 98 (55%) of 178 were receiving therapy with lenalidomide alone. The median duration of follow-up was 50·9 months (IQR 45·7–55·3) from the first randomisation and 37·3 months (32·9–41·9) from the second randomisation.

With regard to the primary endpoint related to the first randomisation, in the intention-to-treat population, 222 (70%) of 315 patients receiving KRd and 84 (53%) of 159 patients receiving KCd had at least a very good partial response after induction (odds ratio [OR] 2·14 [95% CI 1·44–3·19], p=0·0002; appendix 2 p 12). Response rates increased during intensification and consolidation, leading to significantly different proportions of patients with at least a very good partial response, at least a complete response, and a stringent complete response in the three groups (appendix 2 p 12; table 2). In particular, the stringent complete response rates in the intention-to-treat analysis (first key secondary endpoint) were 72 (46%) of 158 patients in the KRd plus ASCT group, 69 (44%) of 157 in the KRd12 group, and 51 (32%) of 159 in the KCd plus ASCT group (KRd plus ASCT *vs* KCd plus ASCT: OR 1·77 [95% CI 1·12–2·81], p=0·014; KRd12 *vs* KCd plus ASCT: 1·66 [1·05–2·63], p=0·030). The rate of pre-maintenance minimal residual disease negativity detected by multiparameter flow cytometry (sensitivity 10^{-5}) in the intention-to-treat population was significantly higher with KRd plus ASCT (98 [62%] of 158 patients) and KRd12 (88 [56%] of 157) than with KCd plus ASCT (69 [43%] of 159; KRd plus ASCT *vs* KCd plus ASCT: OR 2·14 [95% CI 1·36–3·35], p=0·0010; KRd12 *vs* KCd plus ASCT: 1·66 [1·07–2·60], p=0·025). The rate of 1-year sustained minimal residual disease negativity (multiparameter flow cytometry, 10^{-5} cutoff) in the intention-to-treat analysis was higher with KRd plus ASCT (74 [47%] of 158 patients) than with KRd12 (54 [35%] of 157) or with KCd plus ASCT (39 [25%] of 159; KRd plus ASCT *vs* KCd plus ASCT: OR 2·72 [95% CI 1·69–4·44], p<0·0001; KRd plus ASCT *vs* KRd12: 1·69 [1·07–2·66], p=0·024).

In the intention-to-treat population, the 4-year progression-free survival from the first randomisation was 69% with KRd plus ASCT (95% CI 62–77; median not reached [NR; 95% CI NR–NR]), 56% with KRd12 (48–64; median 55·3 months [95% CI 44–NR]), and 51% with KCd plus ASCT (44–60; median 53 months [95% CI

	Induction, intensification, and consolidation			Maintenance	
	KRd-ASCT (n=158)	KRd12 (n=157)	KCd plus ASCT (n=159)	Carfilzomib plus lenalidomide (n=178)	Lenalidomide (n=178)
Overall response	153 (97%)	148 (94%)	144 (91%)	178 (100%)	178 (100%)
Stringent complete response*	72 (46%)*	69 (44%)*	51 (32%)*	121 (68%)	115 (65%)
Complete response	13 (8%)	20 (13%)	15 (9%)	17 (10%)	18 (10%)
At least a complete response†	85 (54%)†	89 (57%)†	66 (42%)†	138 (78%)	133 (75%)
Very good partial response	55 (35%)	47 (30%)	55 (35%)	38 (21%)	38 (21%)
At least a very good partial response‡	140 (89%)‡	136 (87%)‡	121 (76%)‡	176 (99%)	171 (96%)
Partial response	13 (8%)	12 (8%)	23 (14%)	2 (1%)	7 (4%)
Stable disease	2 (1%)	1 (1%)	6 (4%)	..	..
Progressive disease	1 (1%)	..	5 (3%)	..	..
Not evaluable	2 (1%)	8 (5%)	4 (3%)	..	..
Minimal residual disease by multiparameter flow cytometry (sensitivity 10^{-5})§	98 (62%)§	88 (56%)§	69 (43%)§	145 (81%)	140 (79%)
Complete response: evaluable population	56	58	41	100	99
Minimal residual disease by next-generation sequencing (sensitivity 10^{-5})¶	45 (80%)	40 (69%)	30 (73%)	88 (88%)	82 (83%)

Data are n, n (%), or n (%; 95% CI). KRd=carfilzomib plus lenalidomide plus dexamethasone. ASCT=autologous stem-cell transplantation. KCd=carfilzomib plus cyclophosphamide plus dexamethasone. MEL200=melphalan at 200 mg/m². KRd-ASCT=four KRd induction cycles, MEL200-ASCT, four KRd consolidation cycles. KRd12=12 KRd cycles. KCd plus ASCT=four KCd induction cycles, MEL200-ASCT, four KCd consolidation cycles. *p=0·027 for the overall comparison. †p=0·016 for the overall comparison. ‡p=0·0070 for the overall comparison. §p=0·0032 for the overall comparison. ¶In patients evaluable for complete response.

Table 2: **Best response in the intention-to-treat population**

36–NR]; figure 2A). Patients in the KRd plus ASCT group had a significant reduction in the risk of progression or death, compared with patients treated with KCd plus ASCT (HR 0·54 [95% CI 0·38–0·78], p=0·0008); no significant differences were reported between the KRd12 and KCd plus ASCT groups (HR 0·88 [95% CI 0·64–1·22], p=0·45). Subgroup analyses of the KRd plus ASCT versus KCd plus ASCT groups are reported in appendix 2 (p 17). In a post-hoc analysis, we also observed a significant survival advantage of KRd plus ASCT versus KRd12 (HR 0·61 [95% CI 0·43–0·88], p=0·0084) that was consistent across most subgroups (appendix 2 p 18). In patients who were negative for minimal residual disease by multiparameter flow cytometry before maintenance treatment, the survival advantage with KRd plus ASCT (4-year progression-free survival 83% [95% CI 75–91]) versus KCd plus ASCT (63% [53–76]; HR 0·44 [95% CI 0·24–0·80], p=0·0077) and versus KRd12 (69% [60–79]; HR 0·51 [95% CI 0·28–0·92], p=0·026) was retained. By contrast, a similar 4-year progression-free survival was reported in the three groups in patients who achieved a 1-year sustained minimal residual disease negativity: 87% with KRd plus ASCT (95% CI 80–95), 92% with KRd12 (85–100), and 84% with KCd plus ASCT (74–97; appendix 2 p 19). 4-year overall survival was 86% with KRd plus ASCT (95% CI 81–92), 85% with KRd12 (80–91), and 76% with KCd plus ASCT (70–84), with no significant differences at the current follow-up (appendix 2 p 20).

To assess the improvement of the depth of response during maintenance treatment, we did a post-hoc analysis of minimal residual disease conversion from positivity to negativity with carfilzomib plus lenalidomide versus lenalidomide alone in patients who were positive for minimal residual disease before maintenance treatment and who had a second sample available within 2 years of maintenance. 29 (46%) of 63 patients converted to minimal residual disease negative status by multiparameter flow cytometry with carfilzomib plus lenalidomide versus 18 (30%) of 60 with lenalidomide alone (p=0·046, adjusted for first randomisation); 14 (56%) of 25 patients turned negative for minimal residual disease by NGS with carfilzomib plus lenalidomide versus seven (30%) of 23 with lenalidomide alone (p=0·046, adjusted for first randomisation).

With regard to the primary endpoint related to the maintenance comparison, 3-year progression-free survival from the second randomisation in the intention-to-treat population was 75% with carfilzomib plus lenalidomide (95% CI 68–82, median NR [95% CI NR–NR]) versus 65% with lenalidomide alone (58–72, median NR [NR–NR]; HR 0·64 [95% CI 0·44–0·94], p=0·023; figure 2B). A subgroup analysis of progression-free survival with carfilzomib plus lenalidomide versus lenalidomide alone is shown in appendix 2 (p 21). The significant advantage in terms of progression-free survival with carfilzomib plus lenalidomide versus lenalidomide alone was also maintained in patients negative for minimal residual disease: 3-year progression-free survival was 82% with carfilzomib plus lenalidomide (95% CI 75–89) versus 72% with lenalidomide alone (65–80; HR 0·59 [95% CI 0·36–0·95], p=0·030). 3-year overall survival was 94% with

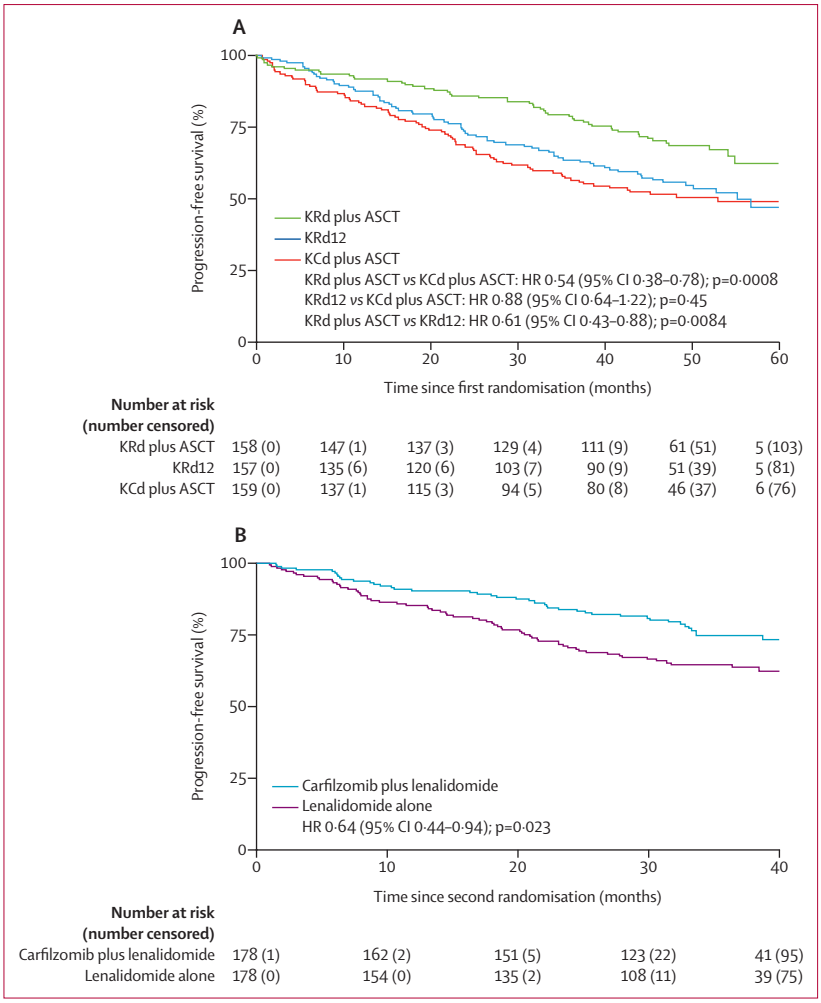


Figure 2: **Survival outcomes according to first and second randomisation**
(A) Kaplan-Meier estimates of progression-free survival from first randomisation. (B) Kaplan-Meier estimates of progression-free survival from second (maintenance) randomisation. HR=hazard ratio. KRd=carfilzomib plus lenalidomide plus dexamethasone. ASCT=autologous stem-cell transplantation. KCd=carfilzomib plus cyclophosphamide plus dexamethasone. MEL200=melphalan at 200 mg/m². KRd plus ASCT=four KRd induction cycles, MEL200-ASCT, and four KRd consolidation cycles. KRd12=12 KRd cycles. KCd plus ASCT=four KCd induction cycles, MEL200-ASCT, and four KCd consolidation cycles.

carfilzomib plus lenalidomide (95% CI 90–98) versus 90% with lenalidomide alone (85–95), with no significant differences at the current follow-up (appendix 2 p 22).

Time to progression, time to next treatment, and duration of response are reported in appendix 2 (pp 5, 23–27).

The most common grade 1–2, grade 3, and grade 4 adverse events related to the study drugs (carfilzomib, lenalidomide, dexamethasone, and cyclophosphamide) are summarised in table 3. Toxicities that occurred during standard-of-care treatment with mobilisation and MEL200-ASCT are not reported, except when they caused protocol discontinuation.

During induction and consolidation, the most common grade 3–4 adverse events were neutropenia (21 [13%] of 158 patients in the KRd plus ASCT group *vs* 15 [10%] of 156 in the KRd12 group *vs* 18 [11%] of 159 in the KCd plus ASCT group); dermatological toxicity (nine [6%] *vs* 12 [8%] *vs* one [1%]); and hepatic toxicity (13 [8%] *vs* 12 [8%] *vs* none). In the pre-maintenance phase, treatment-related serious adverse events were reported in 18 (11%) of 158 patients in the KRd plus ASCT group, 29 (19%) of 156 in the KRd12 group, and 17 (11%) of 159 in the KCd plus ASCT group. The most common treatment-related serious adverse events (appendix p 13) were pneumonia (seven [4%] of 158 patients in the KRd plus ASCT group, four [3%] of 156 in the KRd12 group, and five (3%) of 159 in the KCd plus ASCT group) and renal failure (two [1%] of 158, three [2%] of 156, and two [1%] of 159). Rates of treatment discontinuation due to an adverse event were similar in the three groups: 11 (7%) of 158 patients in the KRd plus ASCT group, 12 (8%) of 156 in the KRd12 group, and 12 (8%) of 159 in the KCd-ASCT group discontinued treatment due to an adverse event. The main causes of treatment discontinuation due to toxicity in each group according to each treatment phase (induction, mobilisation, intensification, and consolidation) and details of cardiac, pulmonary, and renal adverse events are summarised in appendix 2 (pp 5, 14, 15).

Four patients treated with KRd versus one patient treated with KCd discontinued treatment due to mobilisation failure after induction treatment. The median number of CD34+ stem cells collected was $6{\cdot}7\times10^6$ cells per kg (IQR $4{\cdot}7\times10^6$ to 9×10^6) with KRd versus $8{\cdot}9\times10^6$ cells per kg (7×10^6 to $11{\cdot}2\times10^6$) with KCd ($p<0{\cdot}0001$). Overall, 76 (26%) of 288 patients required plerixafor after induction with KRd versus eight (6%) of 141 with KCd ($p<0{\cdot}0001$). The median number of CD34+ transplanted cells was $3{\cdot}9\times10^6$ cells per kg (IQR $3{\cdot}0\times10^6$–$4{\cdot}6\times10^6$) in the KRd plus ASCT group and $4{\cdot}4\times10^6$ cells per kg ($3{\cdot}5\times10^6$–$5{\cdot}38\times10^6$) in the KCd plus ASCT group ($p=0{\cdot}0001$).

Five patients died during induction: one due to progressive disease (in the KCd plus ASCT group), and four due to adverse events (one heart failure in the KRd plus ASCT group; one cardiac arrest in the KRd12 group; and one pneumonia and one cardiac arrest in the KCd plus ASCT group). Two patients died during intensification due to an adverse event (one cardiac arrest in the KRd12 group and one heart failure in the KCd plus ASCT group). One patient died during consolidation due to cardiac arrest in the KRd plus ASCT group.

In the maintenance phase, the most common grade 3–4 adverse events were neutropenia (35 [20%] of 173 patients on carfilzomib plus lenalidomide *vs* 41 [23%] of 177 patients on lenalidomide alone), infections (eight [5%] *vs* 13 [7%]), and vascular events (12 [7%] *vs* one [1%]). During maintenance treatment, study-related serious adverse events were reported in 24 (14%) of 173 patients on carfilzomib plus lenalidomide versus 15 (8%) of 177 on lenalidomide alone. The most common treatment-related serious adverse events (appendix p 13) were pneumonia (six [3%] of 173 patients on carfilzomib

	KRd plus ASCT (n=158)			KRd12 (n=156)			KCd plus ASCT (n=159)			Carfilzomib plus lenalidomide (n=173)			Lenalidomide alone (n=177)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Overall	105 (66%)	56 (35%)	12 (8%)	107 (69%)	50 (32%)	13 (8%)	76 (48%)	33 (21%)	10 (6%)	109 (63%)	64 (37%)	20 (12%)	85 (48%)	56 (32%)	12 (7%)
Haematological*	38 (24%)	27 (17%)	8 (5%)	30 (19%)	19 (12%)	5 (3%)	27 (17%)	21(13%)	5 (3%)	17 (10%)	29 (17%)	15 (9%)	18 (10%)	35 (20%)	11 (6%)
Anaemia	26 (16%)	3 (2%)	..	15 (10%)	3 (2%)	..	20 (13%)	5 (3%)	..	4 (2%)	4 (2%)	1 (1%)	4 (2%)	1 (1%)	..
Neutropenia	6 (4%)	16 (10%)	5 (3%)	9 (6%)	13 (8%)	2 (1%)	3 (2%)	13 (8%)	5 (3%)	10 (6%)	26 (15%)	9 (5%)	7 (4%)	32 (18%)	9 (5%)
Thrombocytopenia	19 (12%)	12 (8%)	3 (2%)	13 (8%)	8 (5%)	3 (2%)	9 (6%)	5 (3%)	1 (1%)	6 (3%)	2 (1%)	5 (3%)	9 (5%)	2 (1%)	3 (2%)
Non-haematological†	98 (62%)	36 (23%)	4 (3%)	101 (65%)	41 (26%)	9 (6%)	67 (42%)	19 (12%)	5 (3%)	108 (62%)	42 (24%)	6 (3%)	78 (44%)	24 (14%)	1 (1%)
Cardiac	3 (2%)	2 (1%)	..	6 (4%)	1 (1%)	1 (1%)	5 (3%)	2 (1%)	..	3 (2%)	5 (3%)	..	1 (1%)	..	1 (1%)
Coronary heart disease	..	1 (1%)	..	..	..	1 (1%)	..	..	..	..	2 (1%)	..	..	..	1 (1%)
Heart failure	2 (1%)	..	..	..	..	..	2 (1%)	1 (1%)	..	..	3 (2%)	..	..	..	..
Tachyarrhythmia	1 (1%)	1 (1%)	..	4 (3%)	1 (1%)	..	3 (2%)	..	..	1 (1%)	3 (2%)	..	..	..	..
Dermatological	27 (17%)	9 (6%)	..	28 (18%)	11 (7%)	1 (1%)	5 (3%)	1 (1%)	..	14 (8%)	2 (1%)	..	12 (7%)	3 (2%)	..
Rash	23 (15%)	9 (6%)	..	21 (13%)	11 (7%)	1 (1%)	3 (2%)	1 (1%)	..	9 (5%)	2 (1%)	..	8 (5%)	3 (2%)	..
Gastroenterological	28 (18%)	3 (2%)	..	36 (23%)	2 (1%)	..	13 (8%)	1 (1%)	..	55 (32%)	9 (5%)	..	38 (21%)	4 (2%)	..
Diarrhoea	15 (9%)	3 (2%)	..	16 (10%)	1 (1%)	..	5 (3%)	1 (1%)	..	28 (16%)	7 (4%)	..	35 (20%)	2 (1%)	..
Nausea and vomiting	9 (6%)	1 (1%)	..	7 (4%)	1 (1%)	..	7 (4%)	..	..	37 (21%)	2 (1%)	..	1 (1%)	..	..
Hepatic	7 (4%)	11 (7%)	2 (1%)	13 (8%)	10 (6%)	2 (1%)	5 (3%)	..	..	3 (2%)	2 (1%)	..	4 (2%)	..	..
Cholestasis	2 (1%)	2 (1%)	..	1 (1%)	3 (2%)	..	..	..	..	1 (1%)	..	..	..	..	..
Hepatic failure	..	2 (1%)	..	1 (1%)	..	..	..	..	..	..	1 (1%)	..	..	..	..
Aminotransferases increased	5 (3%)	7 (4%)	2 (1%)	9 (6%)	6 (4%)	2 (1%)	4 (3%)	..	..	2 (1%)	1 (1%)	..	4 (2%)	..	..
Infection	24 (15%)	9 (6%)	..	25 (16%)	9 (6%)	1 (1%)	14 (9%)	6 (4%)	1 (1%)	28 (16%)	8 (5%)	..	30 (17%)	13 (7%)	..
Febrile neutropenia	..	..	..	..	1 (1%)	..	..	..	..	..	..	..	..	2 (1%)	..
Sepsis	1 (1%)	1 (1%)	..	..	..	1 (1%)	..	..	1 (1%)	..	..	..	..	..	..
Pneumonia	2 (1%)	5 (3%)	..	3 (2%)	5 (3%)	..	4 (3%)	6 (4%)	..	3 (2%)	5 (3%)	..	6 (3%)	4 (2%)	..
Lower respiratory tract	9 (6%)	1 (1%)	..	4 (3%)	1 (1%)	..	1 (1%)	..	..	10 (6%)	1 (1%)	..	10 (6%)	2 (1%)	..
Upper respiratory tract	8 (5%)	1 (1%)	..	9 (6%)	1 (1%)	..	8 (5%)	..	..	10 (6%)	1 (1%)	..	17 (10%)	..	..
Gastroenteritis	..	1 (1%)	..	..	..	..	..	..	..	1 (1%)	..	..	1 (1%)	..	..
Genitourinary tract	1 (1%)	..	..	7 (4%)	..	..	1 (1%)	..	..	3 (2%)	..	..	3 (2%)	1 (1%)	..
Neurological	19 (12%)	2 (1%)	..	27 (17%)	1 (1%)	..	11 (7%)	..	..	14 (8%)	2 (1%)	1 (1%)	11 (6%)	1 (1%)	..
Cerebrovascular disease	..	..	..	..	..	..	..	..	..	..	..	..	1 (1%)	1 (1%)	..
Renal‡	3 (2%)	..	2 (1%)	10 (6%)	2 (1%)	1 (1%)	4 (3%)	2 (1%)	..	3 (2%)	..	2 (1%)	3 (2%)	1 (1%)	..
Creatinine increase	2 (1%)	..	..	3 (2%)	..	..	3 (2%)	1 (1%)	..	..	..	..	1 (1%)	..	..
Renal failure	..	..	2 (1%)	..	2 (1%)	1 (1%)	1 (1%)	2 (1%)	..	1 (1%)	..	2 (1%)	1 (1%)	1 (1%)	..
Respiratory	13 (8%)	..	..	14 (9%)	..	..	10 (6%)	1 (1%)	1 (1%)	12 (7%)	2 (1%)	..	2 (1%)	..	..
Respiratory failure	..	..	..	..	..	..	..	..	1 (1%)	1 (1%)	..	..	..	..	..

(Table 3 continues on next page)

	KRd plus ASCT (n=158)			KRd12 (n=156)			KCd plus ASCT (n=159)			Carfilzomib plus lenalidomide (n=173)			Lenalidomide alone (n=177)		
	Grade 1–2	Grade 3	Grade4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)															
Vascular	27 (17%)	4 (3%)	..	21 (13%)	11 (7%)	3 (2%)	14 (9%)	5 (3%)	..	28 (16%)	8 (5%)	4 (2%)	3 (2%)	1 (1%)	..
Hypertension	4 (3%)	3 (2%)	..	8 (5%)	10 (6%)	..	10 (6%)	4 (3%)	..	18 (10%)	6 (3%)	..	..	..	..
Venous thromboembolism§	9 (6%)	..	..	5 (3%)	..	1 (1%)	..	1 (1%)	..	..	1 (1%)	..	..	1 (1%)	..
Other thrombosis	11 (7%)	..	..	10 (6%)	..	..	3 (2%)	1 (1%)	..	4 (2%)	..	..	1 (1%)	..	..
Thrombotic microangiopathy	..	..	..	..	..	2 (1%)	..	..	..	..	1 (1%)	4 (2%)	..	..	..
Other	45 (28%)	7 (4%)	..	48 (31%)	6 (4%)	..	28 (18%)	3 (2%)	..	63 (36%)	2 (1%)	..	21 (12%)	5 (3%)	..
Fatigue	17 (11%)	1 (1%)	..	16 (10%)	3 (2%)	..	5 (3%)	..	..	13 (8%)	1 (1%)	..	6 (3%)	5 (3%)	..
Fever of unknown origin	18 (11%)	2 (1%)	..	26 (17%)	2 (1%)	..	16 (10%)	2 (1%)	..	36 (21%)	1 (1%)	..	7 (4%)	..	..

Data are n (%). KRd=carfilzomib plus lenalidomide plus dexamethasone. ASCT=autologous stem-cell transplantation. KCd=carfilzomib plus cyclophosphamide plus dexamethasone. MEL200=melphalan at 200 mg/m². KRd plus ASCT=four KRd induction cycles, MEL200-ASCT, and four KRd consolidation cycles. KRd12=12 KRd cycles. KCd plus ASCT=four KCd induction cycles, MEL200-ASCT, and four KCd consolidation cycles. Only treatment-emergent adverse events related to study drugs are reported. All grade 1–2 adverse events occurring in at least 10% of patients are included. All grade 3–4 adverse events of the same event class (even when they did not occur in ≥10% of patients) are included. Adverse events that occurred during the intensification phase with ASCT and are considered as part of the standard-of-care treatment are not reported. Grade 5 adverse events during the pre-maintenance phase: two heart failures (one in the KRd plus ASCT group and one in the KCd plus ASCT group), four cardiac arrests (one in the KRd plus ASCT group, two in the KRd12 group, and one in the KCd plus ASCT group), and one pneumonia (in the KCd plus ASCT group). During maintenance treatment, one patient had grade 5 acute renal failure in the carfilzomib plus lenalidomide group. *At least one haematological adverse event. †At least one non-haematological adverse event. ‡Other renal adverse events include urinary retention, dysuria, haematuria, and stranguria. §Only one case of grade 4 pulmonary embolism in a patient treated in the KRd group during induction.

Table 3: **Treatment-emergent adverse events related to study drugs**

plus lenalidomide *vs* five [3%] of 177 on lenalidomide alone), thrombotic microangiopathy (five [3%] of 173 *vs* none), renal failure (two [1%] of 173 *vs* one [1%] of 177), and coronary artery disease (two [1%] of 173 *vs* none). Rates of treatment discontinuation due to adverse events were similar in the two maintenance groups: 20 [12%] of 173 patients on carfilzomib plus lenalidomide versus 22 [12%] of 177 on lenalidomide discontinued treatment due to an adverse event (appendix 2 pp 6, 7). During maintenance treatment, one patient died due to an adverse event (acute renal failure) in the carfilzomib plus lenalidomide group.

14 (3%) of 474 patients developed second primary malignancies. During mobilisation, one patient was diagnosed with melanoma (in the KRd plus ASCT group) and one with metastatic breast cancer (in the KCd plus ASCT group). During intensification, one patient was diagnosed with melanoma (in the KCd plus ASCT group). During consolidation, one patient developed non-melanoma skin cancer (in the KRd12 group). During maintenance treatment, second primary malignancies were detected in six patients in the carfilzomib plus lenalidomide group (one colon carcinoma, one non-melanoma skin cancer, one myelodysplastic syndrome, one thyroid cancer, one duodenal cancer, and one breast cancer) versus four patients in the lenalidomide group (three non-melanoma skin cancers and one endometrial cancer). A safety interim analysis of the administrations of carfilzomib once every 2 weeks versus twice every 2 weeks after four cycles of treatment, comparing the first 19 patients treated with 70 mg/m² and the last 19 patients randomly assigned to maintenance treatment with carfilzomib at 36 mg/m², is reported in appendix 2 (pp 7, 15).

Discussion

To the best of our knowledge, this was the first randomised trial to investigate carfilzomib-based treatment in transplant-eligible patients with newly diagnosed multiple myeloma. A significantly larger proportion of patients treated with KRd versus KCd in the induction phase had at least a very good partial response, thus confirming the superiority of a combination therapy regimen based on a proteasome inhibitor plus an immunomodulatory agent over a proteasome inhibitor plus chemotherapy, also with the more effective second-generation proteasome inhibitor carfilzomib. Non-haematological adverse events were more frequent with KRd, but the rate of discontinuation due to toxicity after induction was similar (4% with KRd *vs* 3% with KCd). Similarly, treatment in both groups allowed the collection of an adequate number of stem cells to proceed with MEL200-ASCT, even if the use of plerixafor was necessary in a higher proportion of patients on KRd than those on KCd. In line with the superiority of the combination of a proteasome inhibitor plus an immunomodulatory agent,[2] KRd plus ASCT was superior to KCd plus ASCT in terms of pre-maintenance