Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): And randomised, phase 3, open-label, multicentre study

UNIVERSITÀ DEGLI STUDI DI TORINO

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Prof Meletios A Dimopoulos, MDa, Prof Philippe Moreau, MDb, Prof Antonio Palumbo, MDc, Prof Douglas Joshua, MDd, Prof Ludek Pour, MDe, Prof Roman Hájek, MDf, Prof Thierry Facon, MDg, Prof Heinz Ludwig, MDh, Prof Albert Oriol, MDi, Prof Hartmut Goldschmidt, MDj, Prof Laura Rosiñol, MDk, Prof Jan Straub, MDl, Prof Aleksandr Suvorov, MDm, Prof Carla Araujo, MDn, Prof Elena Rimashevskaya, MDo, Prof Tomas Pika, MDp, Prof Gianluca Gaidano, MDq, Prof Katja Weisel, MDr, Prof Vesselina Goranova-Marinova, MDs, Prof Anthony Schwarer, MDt, Prof Leonard Minuk, MDu, Prof Tamás Masszi, MDv, Prof Ievgenii Karamanesht, MDw, Prof Massimo Offidani, MDx, Prof Vania Hungria, MDy, Prof Andrew Spencer, MDz, Robert Z Orlowski, MDaa, Heidi H Gillenwater, MDab, Nehal Mohamed, PhDab, Shibao Feng, PhDab, Prof Wee-Joo Chng, MDac, for the ENDEAVOR investigators

Summary

Background

Bortezomib with dexamethasone is a standard treatment option for relapsed or refractory multiple myeloma. Carfilzomib with dexamethasone has shown promising activity in patients in this disease setting. The aim of this study was to compare the combination of carfilzomib and dexamethasone with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma.

Methods

In this randomised, phase 3, open-label, multicentre study, patients with relapsed or refractory multiple myeloma who had one to three previous treatments were randomly assigned (1:1) using a blocked randomisation scheme (block size of four) to receive carfilzomib with dexamethasone (carfilzomib group) or bortezomib with dexamethasone (bortezomib group). Randomisation was stratified by previous proteasome inhibitor therapy, previous lines of treatment, International Staging System stage, and planned route of bortezomib administration if randomly assigned to bortezomib with dexamethasone. Patients received treatment until progression with carfilzomib (20 mg/m2 on days 1 and 2 of cycle 1; 56 mg/m2 thereafter; 30 min intravenous infusion) and dexamethasone (20 mg oral or intravenous infusion) or bortezomib (1·3 mg/m2; intravenous bolus or subcutaneous injection) and dexamethasone (20 mg oral or intravenous infusion). The primary endpoint was progression-free survival in the intention-to-treat population. All participants who received at least one dose of study drug were included in the safety analyses. The study is ongoing but not enrolling participants; results for the interim analysis of the primary endpoint are presented. The trial is registered at ClinicalTrials.gov, number NCT01568866.

Findings

Between June 20, 2012, and June 30, 2014, 929 patients were randomly assigned (464 to the carfilzomib group; 465 to the bortezomib group). Median follow-up was 11·9 months (IQR 9·3–16·1) in the carfilzomib group and 11·1 months (8·2–14·3) in the bortezomib group. Median progression-free survival was 18·7 months (95% CI 15·6–not estimable) in the carfilzomib group versus 9·4 months (8·4–10·4) in the bortezomib group at a preplanned interim analysis (hazard ratio [HR] 0·53 [95% CI 0·44–0·65]; p<0·0001). On-study death due to adverse events occurred in 18 (4%) of 464 patients in the carfilzomib group and in 16 (3%) of 465 patients in the bortezomib group. Serious adverse events were reported in 224 (48%) of 463

patients in the carfilzomib group and in 162 (36%) of 456 patients in the bortezomib group. The most frequent grade 3 or higher adverse events were anaemia (67 [14%] of 463 patients in the carfilzomib group vs 45 [10%] of 456 patients in the bortezomib group), hypertension (41 [9%] vs 12 [3%]), thrombocytopenia (39 [8%] vs 43 [9%]), and pneumonia (32 [7%] vs 36 [8%]).

Interpretation

For patients with relapsed or refractory multiple myeloma, carfilzomib with dexamethasone could be considered in cases in which bortezomib with dexamethasone is a potential treatment option.

Funding

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Introduction

Multiple myeloma is a common and often fatal haematological malignancy. New treatment options, such as the first-in-class proteasome inhibitor bortezomib, have prolonged survival in patients with this disease.1 and 2 Bortezomib was first approved in 2003 in the USA for the treatment of multiple myeloma and is given with dexamethasone as a standard treatment for relapsed or refractory disease worldwide.3 and 4 Importantly, bortezomib given twice weekly as an intravenous infusion is associated with high rates of peripheral neuropathy (all grades, 34–54%; grade 3 or higher, 8–16%).3, 4, 5 and 6 Furthermore, peripheral neuropathy is among the most common adverse events leading to treatment discontinuation (4–8% of patients) in phase 2 and 3 studies with bortezomib.3, 6 and 7

When compared with intravenous administration, subcutaneous administration of bortezomib showed non-inferior efficacy (overall response in 42% of patients in both groups) and lower frequency grade 2 or higher (24% vs 39%) and grade 3 or higher peripheral neuropathy (6% vs 16%). 5 Additionally, a once-weekly infusion of bortezomib in combination with melphalan and prednisone with or without thalidomide showed significantly reduced frequencies of grade 3–4 peripheral neuropathy compared with a twice-weekly schedule (8% vs 28%) without a reduction in efficacy. 8 However, there are no published data from randomised trials that have compared the once-weekly schedule of bortezomib alone with the standard twice-weekly schedule, and the once-weekly schedule is not included in the bortezomib label. Although once-weekly and subcutaneous administration of bortezomib is associated with improved tolerability and convenience of this drug compared with twice-weekly administration, new anti-myeloma regimens are needed that are more effective and better tolerated.

Carfilzomib is a selective proteasome inhibitor that is approved in the USA for use as a single agent in patients with relapsed and refractory multiple myeloma or in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma (one to three previous lines of therapy), at doses of 20 mg/m2 (starting dose) and 27 mg/m2 (target dose) infused over 10 min. Carfilzomib irreversibly binds to the proteasome, which results in more sustained proteasomal inhibition than that produced by bortezomib. In a phase 1b/2 study,9 carfilzomib given at higher doses (20 mg/m2 [starting dose] and 56 mg/m2 [target dose]) and for a longer infusion time (30 min) showed promising activity and tolerability in combination with dexamethasone in patients with relapsed or refractory multiple myeloma or both. We

initiated this randomised, open-label, multicentre, phase 3 study (ENDEAVOR) to compare carfilzomib and dexamethasone with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma.

Methods

Study design and participants

In this randomised, open-label, phase 3 study patients were recruited from 198 sites in North America, Europe, South America, and the Asia-Pacific region (appendix pp 3–6). Patients aged 18 years or older with relapsed or refractory multiple myeloma, measurable disease (ie, serum M-protein of at least 5 g/L or urine M-protein of at least 200 mg/24 h; or in patients without detectable serum or urine M-protein, serum free light chain of at least 100 mg/L [involved light chain] and an abnormal serum κ:λ ratio), Eastern Cooperative Oncology Group performance status of 0 to 2, one to three previous treatments, and at least a partial response to at least one previous treatment were eligible. Previous treatments could include carfilzomib or bortezomib if patients achieved at least a partial response before relapse or progression, were not discontinued due to toxic effects, and had at least a 6 month proteasome inhibitor treatment-free interval before enrolment (patients could have received maintenance therapy with drugs that are not in the proteasome inhibitor class during this 6 month interval). Eligible patients were required to have an absolute neutrophil count of at least 1000 cells per μL and a platelet count of at least 50 000 cells per μL (≥30 000 cells per μL if myeloma involvement in the bone marrow was >50%) within 21 days before randomisation; left ventricular ejection fraction of at least 40%; and creatinine clearance of at least 15 mL/min. Patients were excluded if they had grade 2 (with pain), grade 3, or grade 4 peripheral neuropathy within 14 days before randomisation, myocardial infarction within 4 months before randomisation, or New York Heart Association class III or IV heart failure. All patients provided written informed consent. The study protocol was approved by the institutional review boards or ethics committees of all participating institutions.

Randomisation and masking

Patients were randomly assigned (1:1) using an interactive voice and web response system to receive carfilzomib and dexamethasone (carfilzomib group) or bortezomib and dexamethasone (bortezomib group). Randomisation was stratified by previous proteasome inhibitor therapy (yes vs no), previous lines of treatment (one vs two or three), International Staging System stage (I vs II–III), and planned route of bortezomib administration (intravenous vs subcutaneous) if randomly assigned to the bortezomib group. Within each stratum, patients were randomly assigned using a block randomisation scheme (block size of four). Due to the different dosing schedules of the treatment regimens, the study was open label, and therefore the allocated treatment was not masked from study investigators or patients. Potential bias in the assessment of the primary endpoint was mitigated by using an independent review committee, masked to treatment allocation, for the determination of disease status. Furthermore, the funder remained masked to per-group treatment results during the study. The success of masking was not assessed.

Procedures

The carfilzomib group received carfilzomib (20 mg/m2 on days 1 and 2 of cycle 1; 56 mg/m2 given thereafter; 30 min intravenous infusion) on days 1, 2, 8, 9, 15, and 16 and dexamethasone (20 mg oral or intravenous infusion) on days 1, 2, 8, 9, 15, 16, 22, and 23 of a 28-day cycle. The rationale for using these doses rather than the approved doses of 20 mg/m2 and 27 mg/m2 was based on preliminary efficacy results from the 56 mg/m2 cohort of a phase 1b/2 study of carfilzomib in patients with relapsed or refractory multiple myeloma or both, in which a higher proportion of patients responded than that in a similar population from the pivotal phase 2 study of single-agent carfilzomib (27 mg/m2), but with a qualitatively comparable safety profile.9 and 10 Intravenous hydration (250–500 mL before and after dose administration) was given during cycle 1 and at the investigator's discretion thereafter. The bortezomib group received bortezomib (1·3 mg/m2; 3–5 s intravenous bolus or subcutaneous injection) on days 1, 4, 8, and 11, and dexamethasone (20 mg oral or intravenous infusion) on days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle. Intravenous hydration was not required in the bortezomib group. The route of administration of bortezomib was chosen by the investigators in accordance with local regulatory approval. Relative dose intensity was calculated as the ratio of the actual dose intensity to the planned dose intensity that was based on the above-standard dosing level and schedule throughout the treatment period. Cycles were repeated until disease progression, withdrawal of consent, or unacceptable toxic effects. All patients received antiviral and proton pump inhibitor therapies.

Dose reductions were permitted to manage toxic effects. Protocol-specific guidance for carfilzomib or bortezomib dose modifications was given for several adverse events (appendix pp 7–11). Conditions not requiring dose reductions included grade 3 nausea, vomiting, or diarrhoea (unless persisting more than 3 days despite adequate treatment with antiemetics or antidiarrhoeal agents), grade 3 fatigue (unless persisting for more than 14 days), any grade anaemia or lymphopenia, and alopecia.

Blood and urine samples to assess disease status were collected at baseline and every 4 weeks thereafter, and were analysed at a central laboratory using serum protein electrophoresis, urine protein electrophoresis, immunofixation, and measurement of serum-free light-chain concentrations and quantitative immunoglobulins. Disease response data were assessed in a masked manner by an independent review committee, and were used for the primary analyses of progression-free survival, overall response, and duration of response. Additional details regarding the independent review committee are given in the appendix (p 7). Response assessments were made using the International Myeloma Working Group—Uniform Response Criteria.11 and 12 After study treatment discontinuation, patients were followed for disease status every 4 weeks until progression (if not already progressed during treatment) and for survival every 3 months until study closure.

Adverse event and laboratory data were collected until 30 days after last dose of study treatment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Haematological laboratory assessments were done at a central laboratory at screening and on days 1, 8, and 15 (carfilzomib group) or days 1 and 8 (bortezomib group) of each treatment cycle. Full serum chemistries (appendix p 12) were measured at a central laboratory at screening and on day 1 of each treatment cycle. Abbreviated serum chemistries were done on days 8 and 15 (carfilzomib group) or day 8 (bortezomib group) of each cycle. Abbreviated serum chemistries (appendix p 12) were also done on days 2, 9, and 16 (carfilzomib group) or on days 4 and 11 (bortezomib group) of cycle 1. We assessed cytogenetic risk status using fluorescence in-situ hybridisation. Patients were defined as high risk if they had the genetic subtypes t(4;14) or t(14;16) in 10% or more of screened plasma cells, or deletion 17p in 20% or more of

screened plasma cells based on central review of bone marrow samples obtained at study entry; the group at standard risk were patients without these genetic subtypes; patients with unknown cytogenetics had samples that were sent to the central laboratory for testing, but these were not analysable or did not yield a definitive result; patients with missing cytogenetics did not have samples that were sent to the central laboratory for testing.

A subset of patients was enrolled in a preplanned substudy assessing right and left heart function. Patients were assessed with two-dimensional transthoracic echocardiogram at baseline, every 12 weeks, and at the end-of-treatment visit. Additional methods relating to the echocardiogram substudy are presented in the appendix (p 12).

Outcomes

The primary endpoint was progression-free survival based on the independent review committee's disease outcome assessments, defined as the time from randomisation until disease progression or death due to any cause, whichever occurred first. Secondary endpoints included overall survival (defined as the time from randomisation to death due to any cause), overall response (partial response or better), duration of response (calculated for patients who achieved a partial response or better; for such patients, duration of response was defined as the time from first evidence of a partial response or better to confirmation of disease progression or death from any cause), incidence of grade 2 or higher peripheral neuropathy events, and safety. A stringent complete response was defined by a negative immunofixation test for myeloma protein in urine and the disappearance of any soft-tissue plasmacytomas, with less than 5% of plasma cells in bone marrow, a normal serum free light chain ratio, and an absence of clonal cells in the bone marrow; definitions of complete response, very good partial response, partial response, minimal response, stable disease, and progressive disease are in the appendix (p 18).

Statistical analysis

Progression-free survival and overall survival were compared between treatment groups using a log-rank test and the corresponding hazard ratio (HR) was estimated using a Cox regression model. In total, 526 events (disease progression or death) were needed to provide 90% power to detect a 25% reduction in the risk of disease progression or death (HR 0·75) at a two-sided significance level of 0·05. Based on the assumptions of an exponential distribution of progression-free survival, median progression-free survival of 10·0 months in the bortezomib group and 13·3 months in the carfilzomib group, and a 3% dropout rate, a total of 888 patients enrolled over a 22 month period (including a 9 month enrolment ramp-up period and an 8 month follow-up period after planned closure of enrolment) was expected to result in the required 526 events.

An interim analysis was scheduled after about 395 events had occurred (75% of the required total). The objective of the planned interim analysis was to monitor differences between treatment groups for evidence of substantial benefit of carfilzomib and dexamethasone versus bortezomib and dexamethasone. An O'Brien-Fleming stopping boundary for efficacy was calculated with the use of a Lan-DeMets alpha-spending function so that the overall type I error was less than or equal to 0·05 (two-sided).13 and 14 The stopping boundary was to be based on the actual number of events (disease progression or death) recorded up to the data cutoff date. An independent data and safety monitoring committee, which

monitored overall study conduct and assessed safety and efficacy data, reviewed the study data, designated as arm A and arm B instead of the actual control and test treatment groups; unmasking of the study occurred at the interim analysis. The membership criteria and other details regarding this committee are presented in the appendix (p 7).

If the data monitoring committee determined that the observed p value at the interim analysis of progression-free survival was less than or equal to the stopping boundary (nominal significance level), then the study was to be regarded as having met its primary endpoint. If the primary endpoint showed a significant difference between treatment groups at the interim analysis, then the secondary endpoints of overall survival, overall response, and the incidence of grade 2 or higher neuropathy events were to be tested. The multiplicity in the secondary endpoint testing was adjusted by the group sequential Holm procedure to ensure a strong control of the overall studywise type 1 error at 0·05.15 For the interim overall survival analysis, a two-sided significance level of 0·0002 was used for the prespecified monitoring boundary for efficacy. Duration of response was summarised descriptively using the Kaplan-Meier method. Efficacy assessments were based on the intention-to-treat population (consisting of all randomly assigned patients). The safety analysis included patients who received at least one dose of study treatment.

The overall response was compared between groups using a Mantel-Haenszel test, and the associated odds ratio (OR) and 95% CI were estimated. A Pearson $\chi 2$ test was used to compare the incidence of grade 2 or higher peripheral neuropathy between treatment groups, and the OR and 95% CI were estimated. For the echocardiogram substudy, we used a mixed model for repeated measures under the assumption of missing-at-random to estimate longitudinal differences between the treatment groups in the reduction of left ventricular ejection fraction and right ventricular function.

For the distribution of time-to-event endpoints, the medians and 95% CIs were estimated using the Kaplan-Meier point estimates. For median follow-up data, the IQR was calculated. All reported p values are two-sided. SAS software version 9.3 was used for the statistical analyses. This study is registered with Clinicaltrials.gov, number NCT01568866.

Role of the funding source

The trial was designed by the senior authors (MAD, PM, AP, DJ, RH, TF, HL, HG, RO, HHG, NM, SF, WJC) and the funder. Data were collected and analysed by the funder. The funder collaborated with the authors in the interpretation of the data. An initial draft of the manuscript was prepared by the funder and a professional medical writer paid by the funder in collaboration with the authors. All authors contributed to subsequent drafts, had full access to the data, made the decision to submit the manuscript for publication, and agreed to be accountable for the accuracy and integrity of the data and analyses. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 20, 2012, and June 30, 2014, 929 patients from North America, Europe, South America, and the Asia-Pacific region were randomly assigned to treatment (464 to the carfilzomib group and 465 to the bortezomib group; figure 1). 360 (79%) patients in the bortezomib group received subcutaneous bortezomib throughout study treatment; all others received intravenous bortezomib at some point during treatment. Baseline characteristics were generally balanced between treatment groups (table 1; appendix p 15). 215 (46%) of 464 patients in the carfilzomib group and 244 (52%) of 465 in the bortezomib group had a history of peripheral neuropathy.

The cutoff date for the prespecified interim analysis was Nov 10, 2014. At data cutoff, 200 (43%) of 464 patients in the carfilzomib group and 105 (23%) of 465 in the bortezomib group were still receiving treatment. In the intention-to-treat population, 414 events (disease progression or death), based on outcomes assessed by the independent review committee, had occurred (171 events in the carfilzomib group; 243 events in the bortezomib group). Based on this number of events, the O'Brien-Fleming stopping boundary for efficacy (two-sided p value) was 0·023. Median follow-up for progression-free survival was 11·9 months (IQR 9·3–16·1) in the carfilzomib group and 11·1 months (8·2–14·3) in the bortezomib group.

Median progression-free survival was 18·7 months (95% CI 15·6 to not estimable) in the carfilzomib group versus 9·4 months (8·4–10·4) in the bortezomib group (HR 0·53 [95% CI 0·44–0·65]; p<0·0001; figure 2A). In pre-planned exploratory subgroup analyses, the effect of carfilzomib on progression-free survival in patients with or without previous bortezomib treatment (figure 2B and C), and in all other subgroups was similar to that in the overall population (figure 3; appendix pp 13, 16–17). Because of the small number of patients with previous carfilzomib exposure in this study, the effect of carfilzomib on progression-free survival in patients with or without previous carfilzomib exposure was not analysed.

The proportion of patients achieving an objective response was 77% (95% CI 73–81) in the carfilzomib group compared with 63% (58–67) in the bortezomib group (odds ratio [OR] 2·03 [95% CI 1·52–2·72]; p<0·0001). The best overall responses are shown in table 2. The median duration of response was 21·3 months (95% CI 21·3 to not estimable) for the carfilzomib group and 10·4 months (95% CI 9·3–13·8) for the bortezomib group. Median time to response was 1·1 months (IQR 1·0–2·0) in the carfilzomib group and 1·1 months (1·0–1·9) in the bortezomib group.

Overall survival data were immature at the interim analysis (with 163 [33%] of 496 total deaths required for final analysis) and did not cross the prespecified monitoring boundary (two-sided significance level of 0·0002). Median follow-up for overall survival was 12·5 months (IQR 9·6–16·6) in the carfilzomib group and 11·9 months (9·3–15·9) in the bortezomib group. As of data cutoff on Nov 10, 2014, there were 75 deaths in the carfilzomib group and 88 deaths in the bortezomib group (HR 0·79 [95% CI 0·58–1·08]; p=0·13; appendix p 14).

The median duration of treatment was 39·9 weeks (IQR 23·7–53·0) in the carfilzomib group and 26·8 weeks (15·0–42·0) in the bortezomib group. Median relative dose intensity of proteasome inhibitor treatment was 93% (IQR 84–98) in the carfilzomib group and 86% (71–96) in the bortezomib group.

The most common adverse events and adverse events of interest are shown in Table 3 and Table 4; all other adverse events are shown in the appendix (pp 22–28). The most common grade 3 or higher adverse events were anaemia (67 [14%] of 463 patients in the carfilzomib group vs 45 [10%] of 456 patients in the bortezomib group), hypertension (41 [9%] vs 12 [3%]), thrombocytopenia (39 [8%] vs 43 [9%]), and pneumonia (32 [7%] vs 36 [8%]).

The number of patients who had grade 2 or higher peripheral neuropathy (grouped term) was significantly higher in the bortezomib group than in the carfilzomib group (146 [32% (95% CI 27·7–36·3)] of 456 vs 28 [6% (3·9–8·2)] of 463 patients; OR 0·14 [95% CI 0·09–0·21] p<0·0001); this result was irrespective of peripheral neuropathy status at baseline (appendix pp 23–24). Although grade 3 or higher peripheral neuropathy (grouped term) was more common in patients who received bortezomib intravenously throughout treatment than in patients who received bortezomib subcutaneously throughout treatment (seven [9%] of 75 vs 27 [8%] of 360 patients; 21 patients switched between subcutaneous and intravenous bortezomib during treatment), grade 2 or higher peripheral neuropathy (grouped term) was more common with subcutaneous bortezomib treatment than with intravenous bortezomib treatment (120 [33%] of 360 patients vs 16 [21%] of 75 patients).

Serious adverse events were reported in 224 (48%) of 463 patients in the carfilzomib group and 162 (36%) of 456 patients in the bortezomib group (appendix p 25). In the intention-to-treat population, 263 (57%) of 464 patients in the carfilzomib group and 351 (75%) of 465 patients in the bortezomib group discontinued treatment (figure 1; appendix p 19). The most common adverse events leading to treatment discontinuation in the safety population are shown in the appendix (p 20). Peripheral neuropathy was the most common adverse event to result in treatment discontinuation in the study in the safety population, occurring in ten (2%) of 456 patients in the bortezomib group and in no patients in the carfilzomib group (appendix p 20). Dose reductions due to adverse events occurred in 106 (23%) of 463 patients in the carfilzomib group and in 218 (48%) of 456 patients in the bortezomib group (appendix p 21). 135 (62%) of 218 dose reductions in the bortezomib group were due to neuropathy-related adverse events compared with seven (7%) of 106 in the carfilzomib group. Bortezomib dose reductions due to peripheral neuropathy (grouped term) occurred in 29 (31%) of 95 patients who received intravenous bortezomib at first dose and 106 (29%) of 361 patients who received subcutaneous bortezomib at first dose (the numbers here are for patients who received subcutaneous bortezomib at first dose, but not necessarily throughout treatment).

During treatment, or within 30 days of receiving the last dose of study treatment, 22 (5%) of 464 patients in the carfilzomib group died (six due to infection, five to cardiac events, four to disease progression, two to sudden deaths, one to acute myeloid leukaemia, one to hepatic failure, one to respiratory failure, one to spinal cord compression, and one to tumour lysis syndrome) and 21 (5%) of 465 patients in the bortezomib group died (eight due to infection, six to cardiac events, four to disease progression, one to head injury, one to lung disorder, and one unknown).

In a preplanned substudy, serial echocardiograms from 151 patients (75 from the carfilzomib group and 76 from the bortezomib group) identified one patient (in the bortezomib group) with significant left ventricular ejection fraction reduction within the first 24 weeks of study treatment. Three additional patients (two from the carfilzomib group and one from the bortezomib group) had a significant reduction in left ventricular ejection fraction at any time during the study. All patients but one (in the carfilzomib group) had resolution to normal left ventricular ejection fraction on follow-up. Mixed models for repeated measures analysis of left ventricular ejection fraction reduction and right ventricular function found that neither treatment effect nor the treatment-by-time interaction were significantly different between the treatment groups (p values ranged from 0·07 to 0·91).

Discussion

In this randomised, phase 3 study, patients treated with carfilzomib and dexamethasone had longer progression-free survival than those treated with bortezomib and dexamethasone. Progression-free survival in all subgroups, including bortezomib-naive patients and patients with high-risk or standard-risk cytogenetics, was longer in the carfilzomib group than in the bortezomib group. However, neither proteasome inhibitor appeared to significantly overcome the adverse prognostic effect of high-risk cytogenetics; in both treatment groups, patients with high-risk cytogenetics had shorter progression-free survival than the overall population. Progression-free survival was also longer for patients in the carfilzomib group than for those in the bortezomib group irrespective of previous transplant status; the difference between the treatment groups was smaller in patients with a previous transplant versus those without, possibly because the former is a more challenging population to treat due to transplant-related toxic effects. Overall survival data were immature at the time of the interim analysis. Patients will continue to be followed for mortality until the final overall survival analysis is done; the end of the study will be defined as when the final overall survival analysis takes place, or in one of the planned interim analyses.

The proportion of patients achieving an objective response in the carfilzomib group was higher than that of the bortezomib group, and the carfilzomib group had a longer median duration of response. The finding that the proportion of patients with a complete response or better and very good partial response or better was higher in the carfilzomib group than in the bortezomib group is encouraging because studies have shown an association between depth of response and improved survival in patients with multiple myeloma.16

In the bortezomib group, the median progression-free survival was consistent with historical data from phase 2 and 3 clinical trials17, 18 and 19 assessing bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (median progression-free survival, 3·8–11·9 months). Although bortezomib plus dexamethasone is considered a standard of care, bortezomib-related peripheral neuropathy was among the most common adverse events that led to treatment discontinuation in phase 2 and 3 studies of bortezomib.3, 6 and 7 In the present study, peripheral neuropathy was the most common adverse event to result in treatment discontinuation in either treatment group.

The duration of treatment was longer in the carfilzomib group than in the bortezomib group, which might have contributed to a higher frequency of grade 3 or higher adverse events and serious adverse events; however, treatment discontinuations and treatment-related deaths due to adverse events were comparable between groups. A number of known adverse drug reactions were reported more frequently in the carfilzomib group than in the bortezomib group, including any-grade dyspnoea, hypertension, pyrexia, and cough (preferred terms), any-grade cardiac failure, and acute renal failure (grouped terms). A higher frequency of grade 3 or higher hypertension (preferred term), dyspnoea (preferred term), cardiac failure (grouped term), acute renal failure (grouped term), and pulmonary hypertension (grouped term) were also noted in the carfilzomib group compared with the bortezomib group. Hypertension, in particular, is a known and manageable side-effect with carfilzomib. Grade 3 or higher ischaemic heart disease (grouped term) was similar between the groups.

The proportion of patients in the carfilzomib group with grade 2 or higher neuropathy was lower than that in the bortezomib group. In the bortezomib group, grade 2 or higher peripheral neuropathy was more frequent in patients who received subcutaneous administration of bortezomib compared with those who received intravenous administration. This finding might be because patients with a history of peripheral neuropathy were more likely to have received subcutaneous administration of bortezomib than intravenous administration.

Importantly, a preplanned substudy using serial echocardiograms showed no evidence of cumulative cardiac injury or increased risk of left or right ventricular dysfunction in patients treated with carfilzomib compared with bortezomib, suggesting limited use for serial screening with echocardiography as a risk mitigation tool for unselected patients receiving carfilzomib. The factors associated with the higher risk for certain cardiac and pulmonary adverse events in the overall study population is unclear and probably multifactorial (eg, pre-existing comorbidities, disease characteristics, possible volume overload as a result of pre-carfilzomib and post-carfilzomib hydration, and, for hypertension, carfilzomib dose). Although cross-trial comparisons should be viewed with caution, the frequency of any-grade cardiac failure (grouped term) reported in the carfilzomib group of this study with carfilzomib doses of 20 mg/m2 and 56 mg/m2 were consistent with frequencies reported in the ASPIRE20 study with carfilzomib doses of 20 mg/m2 and 27 mg/m2 when given in combination with lenalidomide and dexamethasone (8·2% vs 6·4%), and in the phase 2 studies 21 of single-agent carfilzomib at doses of 20 mg/m2 and 27 mg/m2 in patients with relapsed or refractory multiple myeloma or both (7·2%).

To our knowledge, the ENDEAVOR trial is the first phase 3 head-to-head comparison between two proteasome inhibitors and the largest phase 3 randomised trial to date in patients with relapsed or refractory myeloma. Although limited by an open-label design, our study provides important information about the relative efficacy and safety of these two proteasome inhibitors. In this study, the longer progression-free survival in patients treated with carfilzomib and dexamethasone compared with bortezomib and dexamethasone is probably the result of several factors. By contrast with bortezomib, carfilzomib is an irreversible proteasome inhibitor that produces sustained proteasomal inhibition. Preclinically, carfilzomib is more potent than bortezomib in proteasome inhibitor-naive multiple myeloma cell lines and can overcome bortezomib resistance in multiple myeloma cell lines and patient samples.22 In preclinical models, carfilzomib had less off-target activity against serine proteases compared with bortezomib.23 This selectivity might have been responsible for the lower frequency of grade 2 or higher peripheral neuropathy in the carfilzomib group compared with the bortezomib group in this study. The acceptable safety and tolerability profile of carfilzomib given as a 30 min infusion, particularly with respect to peripheral neuropathy, might allow patients to receive carfilzomib at a higher dose than the approved label dose (20 mg/m2 and 56 mg/m2vs 20 mg/m2 and 27 mg/m2), with a longer treatment duration and fewer dose reductions compared with bortezomib at a dose of 1·3 mg/m2, as reported in this study. The ongoing randomised phase 2 S1304 study (NCT01903811), which is comparing carfilzomib 20 mg/m2 and 27 mg/m2 plus dexamethasone versus carfilzomib 20 mg/m2 and 56 mg/m2 plus dexamethasone in patients with relapsed or refractory multiple myeloma, will provide important information about the relative efficacy and safety of these doses.

Taken together, the results from the ENDEAVOR study suggest an important role for carfilzomib-based regimens for patients with relapsed or refractory multiple myeloma. In this patient population, one might consider using carfilzomib and dexamethasone in cases where bortezomib and dexamethasone would also be a potential treatment option.

Research in context

Evidence before this study

Bortezomib and dexamethasone is a standard treatment option worldwide for patients with multiple myeloma. We searched PubMed for clinical studies in multiple myeloma that have assessed carfilzomib with dexamethasone in patients with relapsed or refractory multiple myeloma. Specific search terms included "carfilzomib", "dexamethasone", "relapsed", "refractory", "second-line", "third-line", "salvage", and "multiple myeloma". We included all English language studies published until June 14, 2015.

We identified two studies that assessed the combination of carfilzomib and dexamethasone in patients with advanced multiple myeloma. In a phase 1b/2 study, carfilzomib showed promising activity and tolerability in combination with dexamethasone in patients with relapsed or refractory multiple myeloma or both. In a phase 2 study, treatment with carfilzomib with or without dexamethasone resulted in a high overall response and durable disease control in heavily pretreated patients with relapsed or refractory multiple myeloma, but was also associated with hypertension and heart failure. These studies suggested that carfilzomib with dexamethasone is a promising treatment option for patients with relapsed or refractory multiple myeloma.

Added value of this study

To our knowledge, ENDEAVOR is the first phase 3 head-to-head comparison between two proteasome inhibitors and is the largest phase 3 randomised trial to date in patients with relapsed or refractory multiple myeloma. In this study, patients treated with carfilzomib and dexamethasone had longer progression-free survival compared with those treated with bortezomib and dexamethasone. Overall, the results from ENDEAVOR suggest an important role for carfilzomib-based regimens for the treatment of patients with relapsed or refractory multiple myeloma.

Implications of all the available evidence

Compared with bortezomib and dexamethasone, carfilzomib with dexamethasone was associated with a significant and clinically meaningful improvement in progression-free survival. Furthermore, carfilzomib with dexamethasone had an acceptable adverse event profile. These results delineate the favourable benefit–risk profile of this regimen. Carfilzomib and dexamethasone should be considered as a treatment option for patients with multiple myeloma for whom bortezomib and dexamethasone could also be considered.

Contributors

MAD, PM, AP, DJ, LP, RH, TF, HL, AO, HG, LR, JS, ASu, CA, ER, TP, GG, KW, VG-M, ASc, LM, TM, IK, MO, VH, ASp, RZO, and W-JC collected data and participated in the analysis and interpretation of data. HHG, NM, and SF contributed to the study design, data analysis, and interpretation of data. All authors participated in drafting and revising the manuscript and approved the final version before submission.

Declaration of interests

MAD reports non-financial support from Onyx Pharmaceuticals, during the conduct of the study, and non-financial support from Celgene Corporation and Ortho-Biotech, outside the submitted work. PM reports receipt of personal fees from Onyx Pharmaceuticals and Amgen during the conduct of the study. AP has served as a consultant and received honoraria from Amgen, Bristol-Myers Squibb, Genmab A/S, Janssen-Cilag, Millennium Pharmaceuticals, Onyx Pharmaceuticals, and Celgene Corporation; and received honoraria from Sanofi Aventis. RH reports financial support from Celgene Corporation, Janssen Pharmaceuticals, and Merck. HL reports receipt of personal fees and non-financial support from Celgene Corporation and Janssen-Cilag. AO has served as a consultant and board member for Celgene Corporation and Janssen Pharmaceuticals. HG has served as a consultant and received honoraria from Janssen Pharmaceuticals, Celgene Corporation, Novartis, Onyx Pharmaceuticals, and Millennium Pharmaceuticals; received honoraria from Chugai; served as a consultant for Bristol-Myers Squibb; received research funding from Janssen Pharmaceuticals, Celgene Corporation, Novartis, Chugai, and Bristol-Myers Squibb. LR reports receipt of personal fees for data monitoring support from Onyx Pharmaceuticals during the conduct of this study; and has received honoraria from Janssen Pharmaceuticals and Celgene Corporation. LM reports receipt of a grant from Onyx Pharmaceuticals during the conduct of this study; receipt of research funding from Bristol-Myers Squibb, Amgen, Janssen Pharmaceuticals, and Celgene Corporation; receipt of honoraria from Celgene Corporation and Janssen Pharmaceuticals. MO has received honoraria from Amgen and Janssen Pharmaceuticals. RZO has received research funding from Array BioPharma, Bristol-Myers Squibb, Celgene, Janssen Pharmaceuticals, Millennium, Onyx, Spectrum Pharmaceuticals, FORMA Therapeutics, Genentech, and Novartis; and has served as a consultant or in an advisory role for Array BioPharma, Bristol-Myers Squibb, Celgene, Janssen Pharmaceuticals, Millennium, Onyx, Spectrum Pharmaceuticals, FORMA Therapeutics, Genentech, and Novartis. HHG, NM, and SF are employees and stockholders of Onyx Pharmaceuticals, an Amgen subsidiary. ASc reports personal fees from Celgene during the conduct of this study. VH, ER, DJ, LP, TF, JS, ASu, ASp, CA, TP, GG, KW, VG-M, TM, IK, and W-JC declare no competing interests.

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Figure 1 Trial profile

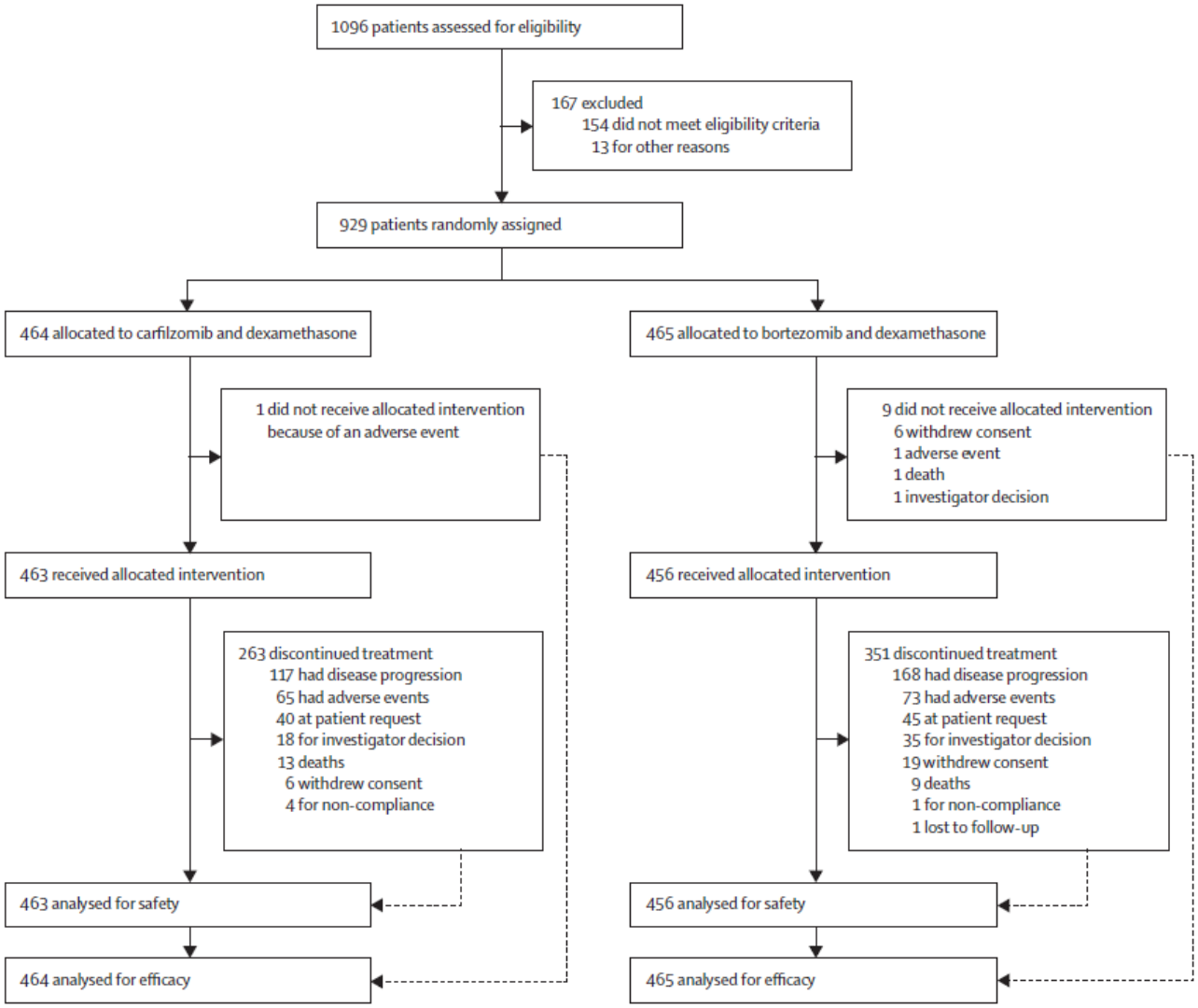
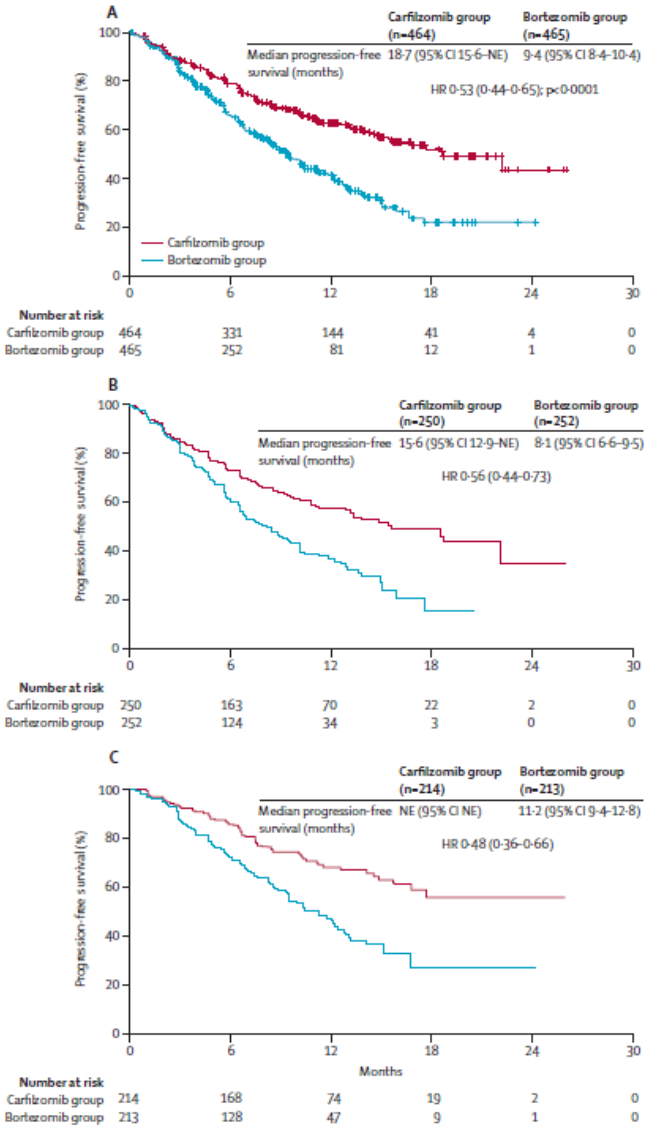


Figure 2 Progression free survival by independent review committee.



Kaplan-Meier curves and median progression-free survival (A) in the intention-to-treat population, (B) in patients with previous bortezomib treatment, and (C) in patients without previous bortezomib treatment. NE=not estimable.

Figure 3 Progression free survival in subgroups

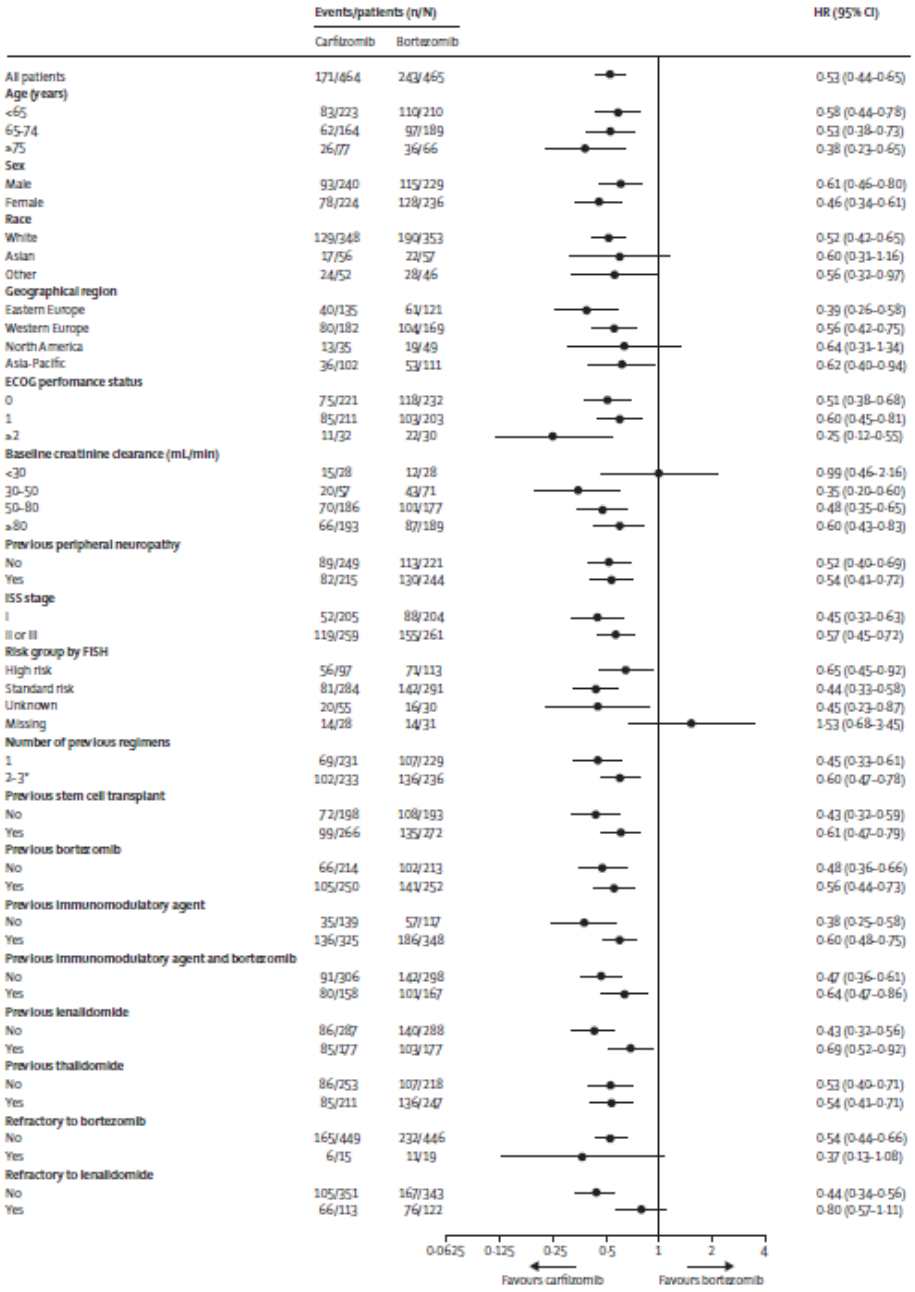


Table 1 Baseline characteristics of the intention to treat population

	Carfilzomib group (n=464)	Bortezomib group (n=465)
Age (years)		
Median (range)	65 (35–89)	65 (30–88)
<65	223 (48%)	210 (45%)
65–74	164 (35%)	189 (41%)
≥75	77 (17%)	66 (14%)
Sex		
Male	240 (52%)	229 (49%)
Female	224 (48%)	236 (51%)
ECOG performance status		
0	221 (48%)	232 (50%)
1	211 (45%)	203 (44%)
2	32 (7%)	30 (6%)
ISS stage		
I	205 (44%)	204 (44%)
II–III	259 (56%)	261 (56%)
Cytogenetics		
High risk	97 (21%)	113 (24%)
Standard risk	284 (61%)	291 (63%)
Unknown	55 (12%)	30 (6%)
Missing	28 (6%)	31 (7%)
Race		
White	348 (75%)	353 (76%)
Black	8 (2%)	9 (2%)
Asian	58 (13%)	57 (12%)
Not reported	50 (11%)	45 (10%)
Multiple	0	1 (<1%)
Geographical region		
Eastern Europe	135 (29%)	121 (26%)
Western Europe	182 (39%)	169 (36%)
North America	35 (8%)	49 (11%)
South America	10 (2%)	15 (3%)
Asia-Pacific	102 (22%)	111 (24%)
Creatinine clearance (mL/min)		
Mean (SD)	76·7 (31·8)	75·1 (32·4)
<30	28 (6%)	28 (6%)
30 to <50	57 (12%)	71 (15%)
50 to <80	186 (40%)	177 (38%)
≥80	193 (42%)	189 (41%)
Serum β_2 microglobulin (mg/L)		
Mean (SD)	4·6 (3·0)	4·8 (3·9)
<3·5	220 (47%)	216 (46%)
≥3·5	244 (53%)	249 (54%)
Previous regimens*		
Median (IQR)	2 (1–2)	2 (1–2)
One	232 (50%)	232 (50%)
Two	157 (34%)	145 (31%)
Three	75 (16%)	87 (19%)
History of peripheral neuropathy		
No	249 (54%)	221 (48%)
Yes	215 (46%)	244 (52%)
Ongoing peripheral neuropathy at screening		
Grade 1	133 (29%)	159 (34%)
Grade 2	10 (2%)	10 (2%)
Previous proteasome inhibitor treatment†		
Bortezomib	250 (54%)	252 (54%)
Carfilzomib	2 (<1%)	1 (<1%)
None	212 (46%)	212 (46%)
Previous immunomodulatory agent treatment		
Lenalidomide	177 (38%)	177 (38%)
Thalidomide	211 (45%)	247 (53%)

Data are n (%) unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. *One patient in the bortezomib group received four previous regimens (a protocol deviation). †Defined as patients who achieved at least a partial response and had at least 6 months since last proteasome inhibitor treatment; all patients who had received previous carfilzomib and all except one patient (a protocol deviation in the carfilzomib group) who had received previous bortezomib met the above entry criteria for previous proteasome inhibitor therapy.

Table 2 Treatment responses in the intention to treat population

	Carfilzomib group (n=464)	Bortezomib group (n=465)
Complete response or better†	58 (13%)	29 (6%)
Stringent complete response	8 (2%)	9 (2%)
Complete response	50 (11%)	20 (4%)
Very good partial response or better‡	252 (54%)	133 (29%)
Very good partial response	194 (42%)	104 (22%)
Partial response	104 (22%)	157 (34%)
Minimal response	24 (5%)	53 (11%)
Stable disease	40 (9%)	53 (11%)
Progressive disease	25 (5%)	31 (7%)

Data are n (%) or median (IQR). * Treatment responses were assessed by an independent review committee.
†p=0·0010. ‡p<0·0001.

Table 3 Adverse events in the safety population

	Carfilzomib group (n=463)				Bortezomib group (n=456)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Common haematological adverse events (preferred terms)								
Anaemia	115 (25%)	66 (14%)	1 (<1%)	0	78 (17%)	44 (10%)	1 (<1%)	0
Thrombocytopenia	56 (12%)	21 (5%)	18 (4%)	0	35 (8%)	20 (4%)	23 (5%)	0
Common non-haematological adverse events (preferred terms)								
Diarrhoea	127 (27%)	16 (3%)	0	0	141 (31%)	33 (7%)	1 (<1%)	0
Fatigue	111 (24%)	25 (5%)	0	0	98 (21%)	32 (7%)	0	0
Dyspnoea	107 (23%)	25 (5%)	0	0	50 (11%)	10 (2%)	0	0
Pyrexia	119 (26%)	9 (2%)	2 (<1%)	0	59 (13%)	3 (<1%)	0	0
Insomnia	110 (24%)	7 (2%)	0	0	108 (24%)	11 (2%)	0	0
Cough	115 (25%)	0	0	0	63 (14%)	1 (<1%)	0	0
Hypertension	74 (16%)	41 (9%)	0	0	28 (6%)	12 (3%)	0	0
Peripheral oedema	97 (21%)	4 (<1%)	0	0	75 (16%)	3 (<1%)	0	0
Asthenia	78 (17%)	16 (3%)	0	0	61 (13%)	13 (3%)	1 (<1%)	0
Upper respiratory tract infection	85 (18%)	9 (2%)	0	0	64 (14%)	3 (<1%)	0	0
Nausea	84 (18%)	6 (1%)	0	0	79 (17%)	3 (<1%)	0	0
Back pain	78 (17%)	7 (2%)	1 (<1%)	0	59 (13%)	12 (3%)	0	0
Muscle spasms	85 (18%)	1 (<1%)	0	0	24 (5%)	3 (<1%)	0	0
Headache	75 (16%)	4 (<1%)	0	0	43 (9%)	3 (<1%)	0	0
Bronchitis	66 (14%)	10 (2%)	0	0	37 (8%)	4 (<1%)	0	0
Constipation	66 (14%)	2 (<1%)	0	0	114 (25%)	9 (2%)	0	0
Nasopharyngitis	66 (14%)	0	0	0	50 (11%)	1 (<1%)	0	0
Vomiting	59 (13%)	6 (1%)	0	0	34 (7%)	6 (1%)	0	0
Pain in extremity	45 (10%)	2 (<1%)	0	0	46 (10%)	3 (<1%)	0	0
Peripheral neuropathy	37 (8%)	6 (1%)	0	0	97 (21%)	23 (5%)	1 (<1%)	0
Decreased appetite	36 (8%)	4 (<1%)	0	0	52 (11%)	5 (1%)	0	0
Dizziness	36 (8%)	1 (<1%)	0	0	64 (14%)	3 (<1%)	0	0
Paraesthesia	35 (8%)	1 (<1%)	0	0	72 (16%)	2 (<1%)	0	0
Peripheral sensory neuropathy	26 (6%)	1 (<1%)	0	0	61 (13%)	6 (1%)	0	0
Neuralgia	6 (1%)	3 (<1%)	0	0	63 (14%)	7 (2%)	0	0

Data are n (%). Adverse events (preferred terms) of grades 1–2 occurring in at least 10% of patients in either treatment group are listed. All grade 3 or higher adverse events not shown here are reported in the appendix. On-study deaths due to adverse events occurred in 18 (4%) of 464 patients in the carfilzomib group and in 16 (3%) of 465 patients in the bortezomib group.

Table 4 Adverse events of interest in the safety population

	Carfilzomib group (n=463)				Bortezomib group (n=456)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Peripheral neuropathy*	77 (17%)	10 (2%)	0	0	198 (43%)	36 (8%)	1 (<1%)	0
Acute renal failure†	19 (4%)	15 (3%)	3 (<1%)	1 (<1%)	10 (2%)	11 (2%)	1 (<1%)	0
Cardiac failure‡	16 (3%)	17 (4%)	3 (<1%)	2 (<1%)	5 (1%)	5 (1%)	1 (<1%)	2 (<1%)
Pneumonia	9 (2%)	30 (6%)	1 (<1%)	1 (<1%)	12 (3%)	33 (7%)	1 (<1%)	2 (<1%)
Ischaemic heart disease§	4 (<1%)	5 (1%)	3 (<1%)	0	2 (<1%)	3 (<1%)	1 (<1%)	3 (<1%)
Pulmonary hypertension‖	3 (<1%)	3 (<1%)	0	0	0	1 (<1%)	0	0

Data are n (%). *Peripheral neuropathy included (in descending order of frequency): peripheral neuropathy, peripheral sensory neuropathy, neuralgia, decreased vibratory sense, polyneuropathy, sensory loss, amyotrophy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, sensory disturbance, and toxic neuropathy. †Acute renal failure included (in descending order of frequency): acute renal failure, renal failure, renal impairment, acute prerenal failure, anuria, oliguria, and prerenal failure. ‡Cardiac failure included (in descending order of frequency): cardiac failure, ejection fraction decreased, pulmonary oedema, acute cardiac failure, congestive cardiac failure, acute pulmonary oedema, acute left ventricular failure, chronic cardiac failure, cardiopulmonary failure, hepatojugular reflex, right ventricular failure, and left ventricular failure. §Ischaemic heart disease included (in descending order of frequency): angina pectoris, acute coronary syndrome, myocardial infarction, increased troponin T, coronary artery disease, increased troponin I, acute myocardial infarction, myocardial ischaemia, and cardiomyopathy stress. ‖Pulmonary hypertension included (in decreasing order of frequency): pulmonary hypertension, right ventricular failure, and pulmonary arterial hypertension.