Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study

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Summary

Background Lenalidomide and bortezomib frontline exposure has raised a growing need for novel treatments for patients with relapsed or refractory multiple myeloma. Carfilzomib in combination with daratumumab has shown substantial efficacy with tolerable safety in relapsed or refractory multiple myeloma in a phase 1 study. In this study, we aimed to compare the efficacy and safety of carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma.

Methods In this randomised, multicentre, open-label, phase 3 study, 466 patients recruited from 102 sites across North America, Europe, Australia, and Asia with relapsed or refractory multiple myeloma were randomly assigned 2:1 to carfilzomib, dexamethasone, and daratumumab (KdD) or carfilzomib and dexamethasone (Kd). All patients received twice per week carfilzomib at 56 mg/m² (20 mg/m²; days 1 and 2 during cycle 1). Daratumumab (8 mg/kg) was administered intravenously on days 1 and 2 of cycle 1 and at 16 mg/kg weekly for the remaining doses of the first two cycles, then every 2 weeks for four cycles (cycles 3–6), and every 4 weeks thereafter. Patients received 40 mg dexamethasone weekly (20 mg for patients ≥75 years old starting on the second week). The primary endpoint was progression-free survival assessed by intention to treat. Adverse events were assessed in the safety population. This trial (NCT03158688) is registered with ClinicalTrials.gov, and is active but not recruiting.

Findings Between June 13, 2017, and June 25, 2018, 466 patients of 569 assessed for eligibility were enrolled. After median follow-up of approximately 17 months, median progression-free survival was not reached in the KdD group versus 15·8 months in the Kd group (hazard ratio 0·63; 95% CI 0·46–0·85; p=0·0027). Median treatment duration was longer in the KdD versus the Kd group (70·1 *vs* 40·3 weeks). Grade 3 or higher adverse events were reported in 253 (82%) patients in the KdD group and 113 (74%) patients in the Kd group. The frequency of adverse events leading to treatment discontinuation was similar in both groups (KdD, 69 [22%]; Kd, 38 [25%]).

Interpretation KdD significantly prolonged progression-free survival versus Kd in patients with relapsed or refractory multiple myeloma and was associated with a favourable benefit–risk profile.

Funding Amgen.

Introduction

The availability of novel agents has increased survival for patients with multiple myeloma.[1–3] Despite therapeutic advances, relapse is inevitable, and myeloma remains largely incurable.[4,5] Prolonged lenalidomide-based treatment has become standard frontline therapy.[6–9] With exposure of many newly diagnosed patients with multiple myeloma to bortezomib or lenalidomide, resistance to these agents develops.[10,11] Moreover, lenalidomide intolerance might ensue with long-term lenalidomide maintenance therapy.[11] There is a need to define active and tolerable therapeutic options for relapsed or refractory multiple myeloma.

Carfilzomib is a selective proteasome inhibitor that irreversibly binds the proteasome, eliciting antimyeloma activity through unfolded protein stress response and other mechanisms.[12] Carfilzomib is approved for single-agent use, or as part of doublet or triplet combination regimens for relapsed or refractory multiple myeloma.[3,13–18]

The anti-CD38 monoclonal antibody daratumumab exerts antimyeloma effects through immune-mediated, direct on-tumour and immunoregulatory actions.[19] Daratumumab has been combined with standards of care, including proteasome inhibitors, for treatment of relapsed or refractory multiple myeloma,[20–22] and is approved for treatment of newly diagnosed patients with relapsed or refractory multiple myeloma.[23]

The clinical benefit of combining daratumumab with proteasome inhibition was confirmed in the phase 3 CASTOR study[22] in which patients received up to eight

Research in context

Evidence before this study

The increased use of lenalidomide and bortezomib has improved survival for newly diagnosed patients with multiple myeloma. Despite therapeutic advances, many patients either progress on or discontinue these agents owing to toxicity. There is a growing need for active and tolerable therapeutic options for managing relapsed or refractory multiple myeloma. We searched PubMed for clinical trial studies published between Sept 1, 2011, and Sept 1, 2019, using the search terms "multiple myeloma", "carfilzomib", "daratumumab", "relapsed", "refractory", "bortezomib", and "lenalidomide". In the phase 3 CASTOR study, the anti-CD38 monoclonal antibody daratumumab in combination with the first-in-class proteasome inhibitor bortezomib plus dexamethasone improved clinical outcomes compared with bortezomib and dexamethasone alone in patients with relapsed or refractory multiple myeloma. The randomised phase 3 ENDEAVOR study showed superiority of the second-generation irreversible proteasome inhibitor carfilzomib over bortezomib. The clinical benefit of combining carfilzomib with daratumumab was initially communicated in the publication of the non-randomised phase 1b study MMY1001, which showed tolerability and activity of the carfilzomib–dexamethasone–daratumumab triplet combination in patients with multiple myeloma who were nearly entirely pre-exposed to lenalidomide and 60% lenalidomide refractory. At a time when many patients are progressing on lenalidomide treatment, encouraging results from the MMY1001 study show that the carfilzomib–dexamethasone–daratumumab combination is a relevant and efficacious lenalidomide-free regimen and set a precedent for the randomised, multicentre phase 3 CANDOR study.

Added value of this study

CANDOR is the first randomised phase 3 study that compared the efficacy and safety of carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. In this study, patients treated with carfilzomib, dexamethasone, and daratumumab had significantly longer progression-free survival and achieved deeper responses, with a nearly 10-times higher minimal residual disease negative–complete response rate compared with patients treated with carfilzomib and dexamethasone alone. The observed benefit for the carfilzomib–dexamethasone–daratumumab combination was generally consistent across prespecified subgroups of clinical relevance, including patients exposed to lenalidomide or who are lenalidomide refractory.

Implications of all the available evidence

Overall, our results show a favourable benefit–risk profile for carfilzomib, dexamethasone, and daratumumab compared with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma with one to three previous lines of treatment. The triplet combination of carfilzomib, dexamethasone, and daratumumab should be considered as an efficacious and tolerable novel treatment option for relapsed or refractory multiple myeloma, including for patients exposed to lenalidomide or who are lenalidomide refractory.

cycles of bortezomib and dexamethasone and showed improved outcomes with daratumumab–bortezomib–dexamethasone versus bortezomib-dexamethasone. Carfilzomib (56 mg/m² twice per week) has shown superior efficacy over bortezomib in the randomised phase 3 ENDEAVOR trial.[17] Compelling efficacy and safety of combining daratumumab with carfilzomib (70 mg/m² once-weekly)–dexamethasone was initially shown in the non-randomised phase 1b MMY1001 study in relapsed or refractory multiple myeloma.[24] Here we present the primary analysis of the randomised, open-label, multicentre phase 3 CANDOR study evaluating carfilzomib-dexamethasone-daratumumab (KdD) versus carfilzomib-dexamethasone (Kd) alone in patients with relapsed or refractory multiple myeloma.

Methods

Study design and participants

CANDOR was a phase 3, randomised, open-label, multicentre trial comparing KdD versus Kd in patients with relapsed or refractory multiple myeloma. Between June 13, 2017, and June 25, 2018, 466 patients were recruited from 102 sites across North America, Europe, Australia, and Asia (for more detail, see appendix p 3). Key eligibility criteria included patients with relapsed or refractory multiple myeloma with measurable disease who had received 1–3 previous treatment lines with partial response or better to at least 1 previous therapy line; left ventricular ejection fraction 40% and above; absolute neutrophil count (ANC) ≥1×10⁹ per L within 21 days before random assignment; platelet count 75×10⁹ per L and above (≥50×10⁹ per L if myeloma involvement in the bone marrow was ≥50%) within 21 days before random assignment; and calculated or measured creatinine clearance of ≥20 mL/min within 21 days before random assignment. Key exclusion criteria related to significant baseline pulmonary and cardiac disease, including uncontrolled hypertension (defined as an average systolic blood pressure >159 mm Hg or diastolic >99 mm Hg, despite optimal treatment). Analysis of left ventricular ejection fraction changes over time was done. Long-term corticosteroid treatment equivalent to a dexamethasone dose of 4·0 mg/day or prednisone at a dose of more than 20 mg/day was not permitted while receiving study treatment. Corticosteroids administered short term (up to 2 weeks) were permitted, provided the cumulative dose was less than a 40 mg per week dexamethasone equivalent. The study protocol, which

See Online for appendix

includes a full listing of eligibility criteria, is available in the appendix.

According to International Myeloma Working Group (IMWG) criteria, patients were defined as lenalidomide refractory when their disease was non-responsive while on a lenalidomide-containing primary or salvage therapy, or their disease had progressed within 60 days of the last date of cessation of lenalidomide treatment. A line of therapy was defined as one or more cycles of a planned treatment programme. This might have consisted of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy started when a planned course of therapy was modified to include other treatment agents owing to lack of adequate response, disease progression (even if the degree of progression did not yet meet IMWG-Uniform Response Criteria [IMWG-URC] for progressive disease), relapse, or toxicity. A new line of therapy also began when a planned period of observation off therapy was interrupted by a need for additional treatment for the disease.

All patients provided written informed consent. The study protocol was approved by institutional review boards or independent ethics committees of all participating institutions.

Randomisation and masking

Patients were randomised 2:1 to receive carfilzomib with dexamethasone and daratumumab (KdD group) or carfilzomib and dexamethasone alone (Kd) in 28-day cycles until disease progression. Randomisation was done by means of an interactive voice or web response system. Patients were stratified by International Staging System at screening (stage 1 or 2 *vs* stage 3), previous proteasome inhibitor exposure (yes *vs* no), number of previous lines of therapy (1 *vs* ≥2), and previous CD38 antibody therapy (yes *vs* no). In each stratum defined by the stratification factors, patients were randomly assigned to treatment based on a blocked randomisation scheme (block size of six).

Procedures

All patients received carfilzomib as a 30-min intravenous infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m² on days 1 and 2 during cycle 1 and 56 mg/m² thereafter). Daratumumab (8 mg per kg) was administered as an intravenous infusion on days 1 and 2 of cycle 1 and at 16 mg per kg once weekly for the remaining doses of the first 2 cycles, then every 2 weeks for 4 cycles (cycles 3 to 6), and every 4 weeks thereafter. Dexamethasone was administered orally or by intravenous infusion at 40 mg weekly or 20 mg weekly for patients older than 75 years of age. A split dose of dexamethasone at 20 mg each day was administered when taken on successive days.

Disease assessments were made per IMWG-URC; appendix p 10),[25] by means of central laboratory test results obtained every 28 (SD 7) days until confirmed disease progression. After disease progression or treatment discontinuation, patients had two follow-up visits, and then were followed-up for survival every 3 months. Minimal residual disease negative–complete response was defined according to the 2016 IMWG-URC[25] and assessed in the bone marrow by next-generation sequencing at a threshold of 1 tumour cell per 10^{-5} white cells at a fixed landmark of 12 months (SD 4 weeks).

Adverse events were collected up to 30 days following last study treatment dose. Events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). All treatment-related and serious adverse events were followed-up until stabilisation or reversibility.

Outcomes

The primary endpoint was progression-free survival. Secondary endpoints included overall response rate, minimal residual disease negative–complete response rate at 12 months, overall survival, time to response, and safety. Definitions for these outcomes are provided in the appendix (p 12).

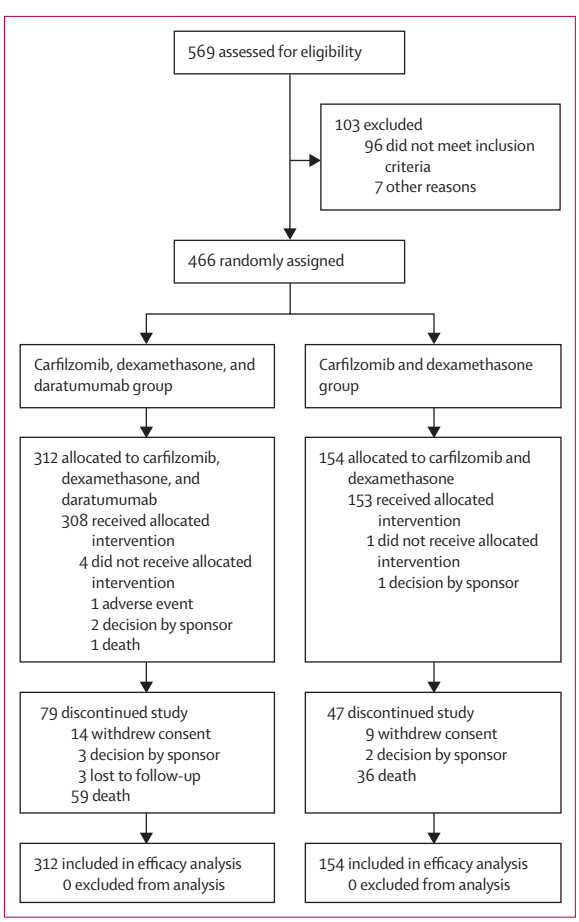

Figure 1: **Trial profile**

Statistical analysis

Efficacy evaluations were based on the intention-to-treat population. Safety analyses included all patients with at least one study treatment dose. For primary and key secondary endpoints, response and disease progression were established by a masked Independent Review Committee. Additionally, they were established locally by investigators in an unmasked manner and centrally by the sponsor by means of a validated computer algorithm, which served as sensitivity analysis of progression-free survival. Sample size was established such that a total of 188 disease progression or death events provided at least 90% power to show superiority at an alternate hazard ratio (HR) of 0·6 (KdD group *vs* Kd group), by means of a log-rank test at a two-sided overall significance level of 0·05.

Hierarchical sequential testing adjusted for multiplicity: if progression-free survival was met, key secondary endpoints were sequentially tested in the order of overall response rate, minimal residual disease negative–complete response rate, and overall survival. Comparisons of progression-free survival and overall survival between groups was done by means of a stratified log-rank test. HRs were estimated by means of a stratified Cox proportional hazards model. Kaplan-Meier methodology was used to summarise distributions. The adequacy of the proportional hazard assumption for Cox regression models was assessed by means of the plot of the logarithm of the estimated hazard functions based on the Kaplan-Meier method against the logarithm of time-to-event endpoints (appendix p 6), as well as the plot of the scaled Schoenfeld residuals by time (appendix p 7). Based on the visual interpretation, no major violation on proportional hazard assumption was observed.

Overall response rate and minimal residual disease negative–complete response rate were compared between groups by means of Cochran-Mantel-Haenszel χ^2 methods. Odds ratios (ORs) and corresponding 95% CIs were estimated by means of Mantel-Haenszel methods. These analyses were stratified by means of randomisation strata.

In addition, the primary endpoint was analysed by patient characteristics and demographics. To evaluate the subgroup effects, the adjusted HR with the corresponding 95% CI were presented by means of the stratified Cox proportional hazard model with the stratification factors (as assessed at randomisation) including: International Staging System stage (stage 1 or 2 *vs* stage 3) at screening; previous proteasome inhibitor exposure (yes *vs* no); number of previous lines of therapy (1 *vs* ≥2). The treatment effect was also evaluated by means of Gail and Simon quantitative interaction tests (1985) based on the same stratified Cox proportional hazard model. Post-hoc power for a nominal two-sided 5% significance level test are calculated to aid the assessment.

Descriptive statistics identified the extent of missing data. Incomplete adverse event start dates, concomitant medications start or stop dates, and death date were imputed. The handling of incomplete and partial dates for adverse events and concomitant medications are described in the appendix (p 4). For patients who died on study, the death date was recorded on the end of study case report form page at the end of the study date. If only the day of

	Carfilzomib, dexamethasone, and daratumumab group (n=312)	Carfilzomib and dexamethasone group (n=154)
Age		
Median, years	64·0 (57–70)	64·5 (59–71)
Distribution		
18–64	163 (52%)	77 (50%)
65–74	121 (39%)	55 (36%)
≥75	28 (9%)	22 (14%)
Sex		
Female	135 (43%)	63 (41%)
Male	177 (57%)	91 (59%)
Geographical region		
Europe	207 (66%)	103 (67%)
Asia Pacific	84 (27%)	39 (25%)
North America	21 (7%)	12 (8%)
Eastern Cooperative Oncology Group performance status		
0 or 1	295 (95%)	147 (95%)
2	15 (5%)	7 (5%)
Missing	2 (<1%)	0
International Staging System disease stage at baseline		
I	147 (47%)	79 (51%)
II	103 (33%)	48 (31%)
III	61 (20%)	27 (18%)
Unknown	1 (<1%)	0
Cytogenetic risk group established by fluorescence in-situ hybridisation (%)*		
High risk	48 (15%)	26 (17%)
Standard risk	104 (33%)	52 (34%)
Unknown	160 (51%)	76 (49%)
Creatinine clearance		
Mean, mL/min	85·8 (32·5)	81·9 (32·7)
Distribution		
≥15 to <30 mL/min	5 (2%)	3 (2%)
≥30 to <50 mL/min	33 (11%)	24 (16%)
≥50 to <80 mL/min	97 (31%)	50 (32%)
≥80 mL/min	176 (56%)	77 (50%)
Missing	1 (<1)	0
Beta-2 microglobulin		
<3·5 mg/L	158 (51%)	83 (54%)
≥3·5 and <5·5 mg/L	92 (29%)	44 (29%)
≥5·5 mg/L	61 (20%)	27 (18%)
Unknown	1 (<1%)	0
Time since initial diagnosis to randomisation, months	37·5 (24·7–62·1)	34·6 (21·0–55·2)
Previous lines of therapy		
Median	2·0 (1–2)	2·0 (1–2)
Distribution		
One line of therapy	144 (46%)	70 (45%)
≥Two lines of therapy	168 (54%)	84 (55%)

(Table 1 continues on next page)

	Carfilzomib, dexamethasone, and daratumumab group (n=312)	Carfilzomib and dexamethasone group (n=154)
(Continued from previous page)		
Previous therapies		
Transplant	195 (63%)	75 (49%)
CD38 antibody therapy†	1 (<1%)	0
Proteasome inhibitor	290 (93%)	139 (90%)
Immunomodulatory drug	206 (66%)	110 (71%)
Bortezomib	287 (92%)	134 (87%)
Refractory to any previous bortezomib-including regimen‡	88 (28%)	47 (31%)
Lenalidomide	123 (39%)	74 (48%)
Refractory to any previous lenalidomide-including regimen‡	99 (32%)	55 (36%)

Data are median (IQR), n (%), or mean (SD). *Fluorescence in-situ hybridisation analysis was conducted by the central laboratory. The high-risk group consisted of patients with the genetic subtypes t(4;14), t(14;16), or deletion 17p. The standard-risk group consisted of patients without t(4; 14), t(14; 16), and deletion 17p. The unknown risk group consisted of patients with fluorescence in-situ hybridisation results that failed or were cancelled. †Based on the Interactive Voice and Web Response System at the time of randomisation. ‡Patients were considered refractory to a drug received in previous regimens if any of the following criteria were met: best response to any regimen containing the drug was stable disease or progressive disease; reason the drug was stopped was progression in any regimen; date of relapse or progression was after start date and within 60 days after stop date of the drug in any regimen.

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

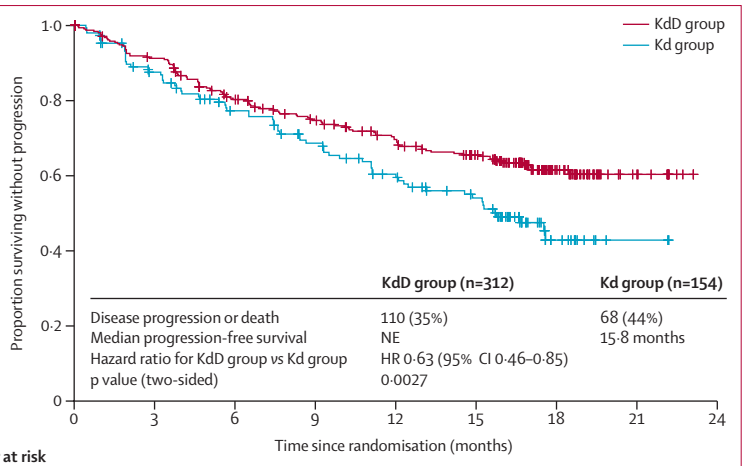

Figure 2: **Progression-free survival**

KdD=carfilzomib, dexamethasone, and daratumumab. Kd=carfilzomib and dexamethasone. NE=not estimable. HR=Hazard ratio.

death date was missing, death date was imputed by means of the following rules: day 1 of the month was used to impute if year and month indicate that death happened later than last known alive date; one day after last known alive date was used to impute if death happened in the same month and year as last known alive date. The imputed death date was used in calculation of duration of response, progression-free survival, and overall survival. SAS 9.4 statistical software was used. This trial (NCT03158688) is registered with ClinicalTrials.gov.

Role of the funding source

The funder of the study had a role in the study design, data collection, data analysis, data interpretation, and writing of the report, and the decision to submit the paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 13, 2017, and June 25, 2018, 466 patients of 569 assessed for eligibility were enrolled and randomly assigned to either KdD (n=312) or Kd (n=154; figure 1). Four of the 312 patients in the KdD group did not receive allocated treatment (adverse event [n=1], sponsor's decision [n=2], death [n=1]). One of the 154 patients in the Kd group did not receive treatment (sponsor's decision [n=1]). The groups differed only in the higher proportion of patients with a previous stem-cell transplant in the KdD group compared with the Kd group (195 [63%] of 312 *vs* 75 [49%] of 154) and a higher proportion of patients of 75 years of age and above in the Kd group (KdD, 28 [9%]); Kd, 22 [14%]; table 1).

Of 466 randomly assigned patients, 197 (42%) received previous lenalidomide-containing regimens; 421 (90%) received previous bortezomib-containing regimens. 154 (33%) were lenalidomide refractory; 135 (29%) were bortezomib refractory.

At the data cutoff date of July 14, 2019, 233 patients in the KdD group (75%) and 107 in the Kd group (69%) continued in the study. 178 (38%) of 466 patients had progression-free survival events (110 [35%] of 312 events in the KdD group; 68 [44%] of 154 events in the Kd group) at data cutoff. Of the randomly assigned patients, 286 patients (179 [57%] of 312 in the KdD group; 107 [69%] of 154 in the Kd group) discontinued carfilzomib owing to adverse events (KdD, n=52 [17%]; Kd, n=28 [18%]), disease progression (KdD, n=80 [26%]; Kd, n=60 [39%]), and other factors (KdD, n=47 [15%]; Kd, n=19 [12%]). 151 (48%) of 312 patients discontinued daratumumab in the KdD group owing to adverse events (n=18 [6%]), disease progression (n=88 [28%]), and other factors (n=45 [14%]). 269 patients (n=161 [52%] of 312 in the KdD group; n=108 [70%] of 154 in the Kd group) discontinued dexamethasone owing to adverse events (KdD, n=23 [7%]; Kd, n=31 [20%]), disease progression (KdD, n=85 [27%]; Kd, n=58 [38%]), and other factors (KdD group, n=53 [17%]; Kd group, n=19 [12%]). The primary endpoint of progression-free survival was met. Median follow-up time for progression-free survival was 16·9 months (95% CI 16·7–17·5; IQR 15·9–18·6) in the KdD group and 16·3 months (15·9–16·7; IQR 12·1–17·6) in the Kd group. The HR for progression or death in the KdD group versus the Kd group was 0·63 (95% CI 0·46–0·85; two-sided p=0·0027; figure 2). Median progression-free survival was not reached in the KdD group (95% CI not

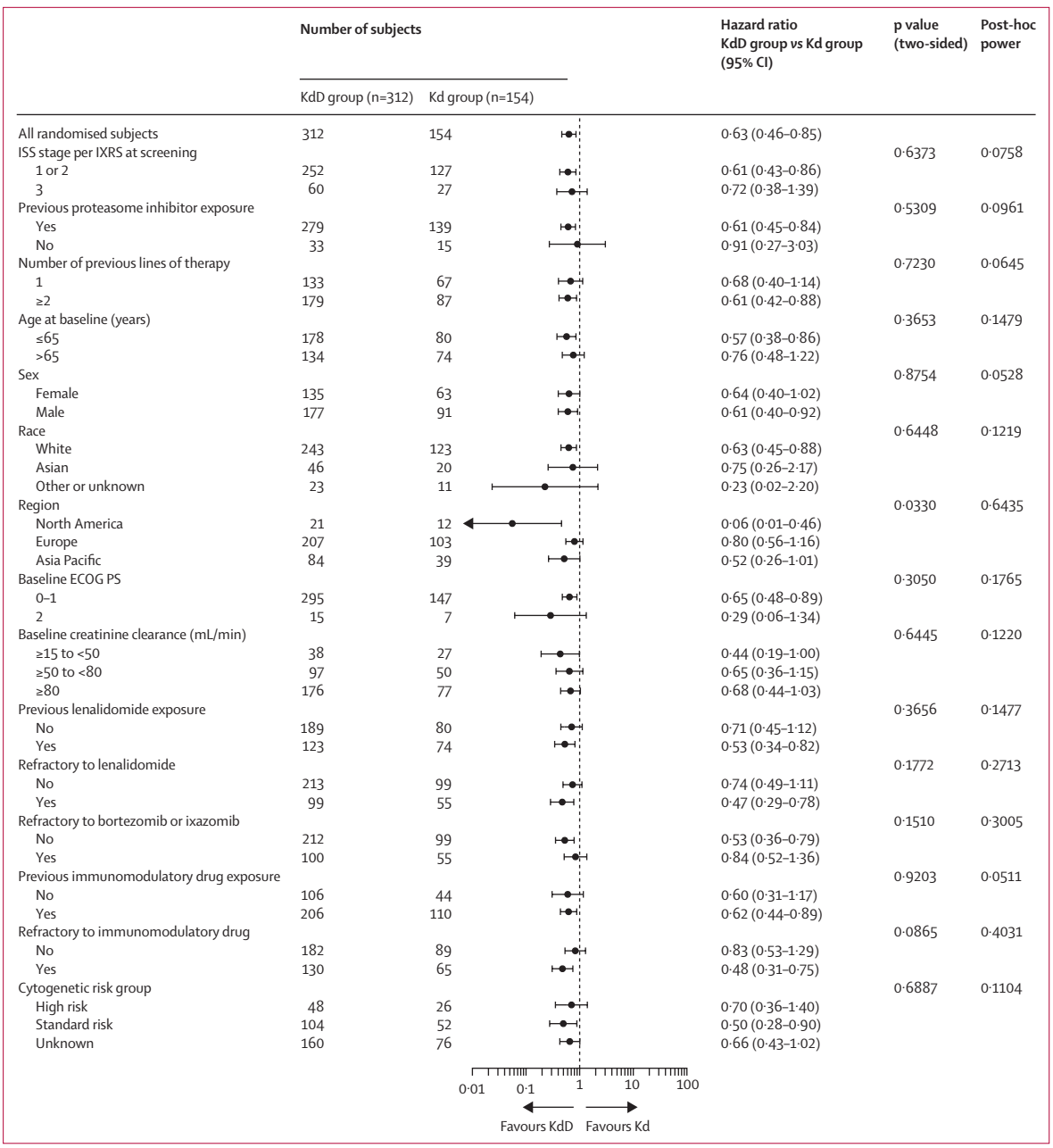

Figure 3: **Hazard ratios and 95% CIs for progression-free survival in subgroups (stratified)**
Hazard ratios were calculated based on stratified Cox proportional hazards model. p values and post-hoc power were calculated by means of Gail and Simon quantitative and qualitative interaction tests and a post-hoc power test based on stratified Cox proportional hazards model. KdD=carfilzomib, dexamethasone, and daratumumab. Kd=carfilzomib and dexamethasone. ISS=International Staging System. IXRS=interactive voice–web response system. ECOG PS=Eastern Cooperative Oncology Group performance status.

estimable) versus 15·8 months (95% CI 12·1 to not estimable) in the Kd group (figure 2). The Kaplan-Meier 18-month progression-free survival rates were 62% (95% CI 55·4–67·1) in the KdD group and 43% (95% CI 32·4–52·8) in the Kd group. Median time to progression was not reached (95% CI, not estimable) in the KdD group and was 17·5 months (95% CI, 13·2–not estimable) in the Kd group.

Progression-free survival benefit was generally consistent across prespecified subgroups of clinical relevance (figure 3). Median progression-free survival was not reached (95% CI 18·5–not estimable) in the KdD group versus 12·1 months (95% CI 8·4–15·3) in the Kd group for patients who had previous exposure to lenalidomide (HR, 0·529; 95% CI 0·342–0·818). Similarly, median progression-free survival was not reached (95% CI 18·5 to

	Carfilzomib, dexamethasone, and daratumumab group (n=312)	Carfilzomib and dexamethasone group (n=154)	Odds ratio (95% CI)	p value (two-sided)
Best response†				
Complete response	89 (29%)	16 (10%)	..	..
Minimum residual disease-negative complete response‡	43 (14%)	5 (3%)	..	..
Very good partial response or better	216 (69%)	75 (49%)	..	..
Stable or progressive disease	23 (7%)	22 (14%)	..	..
Minimum residual disease-negative rate, 12 months§	55 (18%; 13·6–22·3)	6 (4%; 1·4–8·3)	5·8 (2·4–14·0)	<0·0001
Minimum residual disease-negative complete response rate, 12 months¶	39 (13%; 9·0–16·7)	2 (1%; 0·2–4·6)	11·3 (2·7–47·5)	<0·0001
Overall response rate‖	263 (84%; 79·8–88·1)	115 (75%; 67·0–81·3)	1·9 (1·2–3·1)	0·0080
Time to overall response, months**				
Mean	1·4 (1·4)	1·5 (1·1)	..	..
Median	1·0 (0·99–1·09)	1·0 (0·99–1·94)	..	..
Time to complete response, months**				
Mean	8·7 (3·1)	7·5 (3·4)	..	..
Median (IQR)	8·4 (6·2–11·9)	7·0 (5·5–9·8)	..	..
Duration of overall response, months††				
Median	Not estimable	16·6	..	..
95% CI	Not estimable–not estimable	13·9–not estimable	..	..

Data are n (%), n (%; 95% CI), mean (SD), or median (IQR). *Best overall responses and duration of response were assessed by an independent review committee. †Best responses were established per International Myeloma Working Group Uniform Response Criteria. These criteria are listed in the protocol in the appendix (p 7). ‡Minimum residual disease-negative complete response was defined by achievement of a complete response and minimum residual disease-negativity by next-generation sequencing at any time during the study. §Minimum residual disease-negative rate at 12 months was defined as achievement of minimum residual disease-negative status as assessed by next-generation sequencing at the 12-month landmark (from 8 months to 13 months window). ¶Minimum residual disease-negative complete response at 12 months was defined by achievement of a complete response and minimum residual disease-negativity by next-generation sequencing at the 12-month landmark. ‖Overall response rate was defined as the proportion of patients with a partial response or better. **Time to overall response was defined as the time from randomisation to the earliest of stringent complete response, complete response, very good partial response, or partial response. ††Duration of overall response was calculated for patients who achieved a partial response or better.

Table 2: **Treatment responses in the intention-to-treat population***

not estimable) in the KdD group versus 11·1 months (95% CI 7·4–14·9) in the Kd group for patients who were lenalidomide refractory at any previous line of treatment (HR 0·474; 95% CI 0·288–0·781; figure 3). Median progression-free survival was not reached in either treatment group (95% CI for KdD, not estimable; 95% CI for Kd, 15·8 to not estimable) for patients who had no previous exposure to lenalidomide (HR 0·708; 95% CI 0·448–1·120). Median progression-free survival was also not reached in either treatment group (95% CI for KdD, not estimable; 95% CI for Kd, 15·7 to not estimable) for patients who were not refractory to lenalidomide (HR 0·738; 95% CI 0·492–1·108).

Overall response was achieved by 263 (84%; 95% CI 79·8–88·1) of 312 patients in the KdD group and 115 (75%; 67·0–81·3) of 154 patients in the Kd group (OR 1·925; p=0·0080), with 216 (69%) in the KdD group and 75 (49%) patients in the Kd group, achieving very good partial response or better, and 89 (29%) in the KdD group and 16 (10%) patients in the Kd group, achieving complete response (table 2). Median time to first response was 1 month in both treatment groups; median time to complete response was 8·4 months for the KdD group and 7·0 months for the Kd group. Minimal residual disease-negativity at 12 months was achieved by 55 (18%; 95% CI 13·6–22·3) of 312 patients in the KdD group and 6 (4%; 1·4–8·3) of 154 patients in the Kd group (OR, 5·8; 95% CI 2·4–14·0; p<0·0001). The number of randomly assigned patients achieving a complete response per IMWG response criteria and minimal residual disease-negative status at any time during the study was 43 (14%) in the KdD group and 5 (3%) in the Kd group. Minimal residual disease negative–complete response at 12 months was achieved by 39 patients (13%; 95% CI 9·0–16·7) in the KdD group versus two patients (1%; 95% CI 0·2–4·6) in the Kd group (OR 11·3; 95% CI 2·7–47·5; p<0·0001; table 2).

At a median follow-up time of 17·2 months (KdD group; IQR, 16·3–18·7) and 17·1 months (Kd group; IQR, 16·2–18·7), median overall survival was not reached in either treatment group (HR for death, 0·75; 95% CI 0·49–1·13, p=0·17; appendix p 7). A total of 95 deaths had occurred by the data cutoff date, with 59 (19%) reported in the KdD group and 36 (23%) deaths reported in the Kd groups. The Kaplan-Meier 18-month overall survival rates were 80% (95% CI 74·6–84·2) in the KdD group and 74% (95% CI 65·9–81·1) in the Kd group.

	Carfilzomib, dexamethasone, and daratumumab group (n=308)					Carfilzomib and dexamethasone group (n=153)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological adverse events										
Thrombocytopenia	115 (37%)	40 (13%)	49 (16%)	26 (8%)	0	45 (29%)	20 (13%)	19 (12%)	6 (4%)	0
Anaemia	101 (33%)	50 (16%)	48 (16%)	3 (1%)	0	48 (31%)	26 (17%)	21 (14%)	1 (1%)	0
Neutropenia	43 (14%)	17 (6%)	24 (8%)	2 (1%)	0	15 (10%)	6 (4%)	7 (5%)	2 (1%)	0
Lymphopenia	27 (9%)	6 (2%)	9 (3%)	12 (4%)	0	12 (8%)	1 (1%)	9 (6%)	2 (1%)	0
Non-haematological adverse events										
Hypertension	94 (31%)	40 (13%)	54 (18%)	0	0	42 (27%)	22 (14%)	20 (13%)	0	0
Upper respiratory tract infection	90 (29%)	82 (27%)	7 (2%)	1 (<1%)	0	35 (23%)	33 (22%)	2 (1%)	0	0
Diarrhoea	97 (31%)	85 (28%)	12 (4%)	0	0	22 (14%)	21 (14%)	1 (1%)	0	0
Fatigue	75 (24%)	51 (17%)	23 (7%)	1 (<1%)	0	28 (18%)	21 (14%)	7 (5%)	0	0
Dyspnoea	61 (20%)	49 (16%)	12 (4%)	0	0	34 (22%)	30 (20%)	4 (3%)	0	0
Pneumonia	55 (18%)	14 (5%)	32 (10%)	5 (2%)	4 (1%)	19 (12%)	6 (4%)	12 (8%)	1 (1%)	0
Adverse events of interest										
Respiratory tract infections (HLGT)	225 (73%)	136 (44%)	77 (25%)	7 (2%)	5 (2%)	84 (55%)	60 (39%)	22 (14%)	1 (1%)	1 (1%)
Viral infection (JMQ)	63 (20%)	44 (14%)	19 (6%)	0	0	22 (14%)	19 (12%)	2 (1%)	0	1 (1%)
Peripheral neuropathy (SMQN)	53 (17%)	50 (16%)	3 (1%)	0	0	13 (8%)	13 (8%)	0	0	0
Daratumumab-related infusion reaction (AMQN)†	56 (18%)	49 (16%)	7 (2%)	0	0	0	0	0	0	0
Cardiac failure (SMQN)	23 (7%)	11 (4%)	9 (3%)	1 (<1%)	2 (1%)	16 (10%)	3 (2%)	10 (7%)	3 (2%)	0
Acute renal failure (SMQN)	18 (6%)	9 (3%)	5 (2%)	4 (1%)	0	12 (8%)	2 (1%)	6 (4%)	4 (3%)	0
Ischaemic heart disease (SMQN)	13 (4%)	4 (1%)	7 (2%)	2 (1%)	0	5 (3%)	1 (1%)	4 (3%)	0	0

Data are n (%). Haematological and non-haematological all-grade adverse events (preferred terms) occurring in ≥20% of patients and grade ≥3 adverse events (preferred terms) occurring in >5% of patients in either treatment group are shown; no percentage cutoff was applied to adverse events of interest. AMQN=Amgen MedDRA query—narrow. HLGT=high level group terms. JMQ=Janssen MedDRA query. MedDRA=Medical Dictionary of Regulatory Activities. SMQN=Standardised MedDRA query—narrow. *The safety population included all patients who received at least 1 dose of trial treatment. †Event on same date or next date of any daratumumab dosing.

Table 3: **Adverse events in the safety population***

308 patients in the KdD group and 153 in the Kd group received at least one dose of study treatment. Median treatment duration was 70·1 weeks (IQR 28·1–77·1) in the KdD group and 40·3 weeks (IQR 15·3–71·4) in the Kd group.

All-grade treatment-emergent adverse events occurred in 306 (99%) of 308 patients in the KdD group and 147 (96%) of 153 patients in the Kd group. Grade 3 or higher (253 [82%] in the KdD group and 113 [74%] in the Kd group) and serious adverse events (173 [56%] and 70 [46%]) are reported in the appendix (pp 11, 17). Common haematological and non-hematological treatment-emergent all-grade adverse events and adverse events of interest in the safety population are presented in table 3. Common all-grade adverse events (≥20% preferred term in either group) were thrombocytopenia, anaemia, diarrhoea, hypertension, upper respiratory tract infection, fatigue, and dyspnoea; of these, thrombocytopenia (115 [37%] in the KdD group and 45 [29%] Kd group), diarrhoea (97 [31%] and 22 [14%]), upper respiratory tract infection (90 [29%] and 35 [23%]), and fatigue (75 [24%] and 28 [18%]) occurred with a ≥5% higher incidence in the KdD group than the Kd group.

Frequent grade 3 or higher adverse events (≥5% preferred term in either group) were thrombocytopenia, hypertension, anaemia, pneumonia, neutropenia, fatigue, and lymphopenia (table 3). Grade 3 or higher adverse events (preferred term) with at least a 2% higher incidence in the KdD than Kd group were thrombocytopenia, hypertension, neutropenia, anaemia, fatigue, pneumonia, influenza, sepsis, and diarrhoea (table 3; appendix p 11). Grade 3 or higher adverse events of interest (grouped term) included acute renal failure (9 [3%] in the KdD group and 10 [7%] in the Kd group), cardiac failure (12 [4%] and 13 [8%]), ischaemic heart disease (9 [3%] and 4 [3%]), respiratory tract infections (89 [29%] and 24 [16%]), peripheral neuropathy (3 [1%] and 0), daratumumab-related infusion reactions (7 [2%] and 0), and viral infections (19 [6%] and 3 [2%]; table 3).

Adverse events leading to treatment discontinuation occurred in 69 (22%) of 308 KdD-treated patients and 38 (25%) of 153 Kd-treated patients (appendix p 22). Overall, 98 patients (21%) of 461 treated patients discontinued carfilzomib owing to adverse events. Adverse events leading to carfilzomib discontinuation occurred in 65 (21%) of 308 patients in the KdD group and 33 (22%) of 153 patients in the Kd group (appendix p 25). Adverse events leading to daratumumab discontinuation occurred in 28 (9%) of 308 patients in the KdD group (appendix p 27). Cardiac failure (KdD, 6 [2%] and Kd, 3 [2%]) was the most common adverse event leading to

	KdD group (n=308)	Kd group (n=153)	Risk ratio
Grade 3 or higher	195·8 (173·1–221·5)	172·5 (143·4–207·4)	1·1 (0·9–1·4)
Serious	75·9 (65·4–88·1)	73·4 (58·0–92·7)	1·0 (0·8–1·4)
Fatal	9·1 (6·4–13·0)	6·2 (3·1–12·4)	1·5 (0·7–3·2)

Data are exposure-adjusted risk estimates per 100 patient-years (95% CI) or risk ratio (95% CI). KdD=carfilzomib, dexamethasone, and daratumumab. Kd=carfilzomib and dexamethasone. *The safety population included all patients who received at least one dose of trial treatment.

Table 4: **Exposure-adjusted treatment-emergent adverse events in the safety population***

carfilzomib discontinuation and pneumonia (4 [1%] and 0) was the most common adverse event leading to daratumumab discontinuation. Adverse events resulted in dose reductions in 119 (39%) patients in the KdD group and 53 (35%) patients in the Kd group (appendix p 28). Adverse events leading to carfilzomib dose reduction were reported in 77 (25%) patients in the KdD group and 30 (20%) patients in the Kd group (appendix p 31). Dose modification for adverse events consisted of dose delays and not dose reductions for daratumumab. Daratumumab dose delays occurred in 88 (29%) patients in the KdD group.

Treatment-emergent fatal adverse events occurred in 30 (10%) patients in the KdD group and eight (5%) patients in the Kd group (appendix p 33). Five deaths were reported as treatment-related, all in the KdD group (pneumonia; sepsis with development of *Clostridium difficile* enterocolitis; septic shock in the setting of pneumocystis pneumonia; acinetobacter infection; and cardiorespiratory arrest [n=1 each]). Among patients ≥65 years of age, treatment-emergent fatal adverse events occurred in 20 (14%) of 146 patients in the KdD group and two (3%) of 76 patients in the Kd group (appendix p 34). Among patients defined by the investigator as intermediate fit, treatment-emergent fatal adverse events occurred in ten (19%) of 53 patients in the KdD group and one (3%) of 35 patients in the Kd group (the number of frail patients was low; appendix p 35). For the 11 patients with intermediate fit status who had a fatal adverse event, no hypertension or cardiac adverse events were reported in either treatment group before the fatal event. Of the 22 patients of 65 years of age and above who had a fatal event, two patients reported cardiac failure and two patients reported hypertension events in the KdD group.

Rates of exposure-adjusted grade 3 or higher, serious, and fatal adverse events were calculated to adjust for differences in treatment duration between treatment groups. The exposure-adjusted risk estimates (per 100 patient-years) were 195·8 in the KdD group and 172·5 in the Kd group (risk ratio, 1·1) for grade 3 or higher adverse events, 75·9 and 73·4 (risk ratio, 1·0) for serious adverse events, and 9·1 and 6·2 (risk ratio, 1·5) for fatal adverse events (table 4; appendix p 36).

Discussion

The clinical benefit of combining a CD38-targeting antibody with proteasome inhibition was first confirmed in the phase 3 CASTOR study.[22] The CASTOR study showed a 61% decreased risk in progression or death when daratumumab was combined with bortezomib and dexamethasone versus bortezomib and dexamethasone alone. Notably, in CASTOR, bortezomib was administered for a fixed duration of eight cycles in both groups, whereas daratumumab was given until disease progression in the experimental group only. The CANDOR study shows that a second-generation proteasome inhibitor can be combined with daratumumab and administered until disease progression. Moreover, Kd has shown superior efficacy over bortezomib and dexamethasone.[17]

The results from this large phase 3 study show that KdD significantly prolonged progression-free survival and reduced the risk of progression or death by 37% compared with Kd among patients with relapsed or refractory multiple myeloma. Consistent with outcomes in the overall population, the risk of progression or death was reduced with KdD versus Kd across prespecified subgroups. In addition, most patients (90%) in the CANDOR study were previously treated with bortezomib-containing regimens, reflecting the multiple myeloma treatment landscape. KdD showed a clinical benefit over Kd by reducing the risk of progression or death by 36% for patients with previous proteasome inhibitor exposure, including bortezomib. The risk of progression or death was also reduced with KdD among CANDOR patients with high-risk or standard-risk cytogenetic status. Although the HR for progression-free survival is intriguing for patients from North America (HR=0·056), the Gail and Simon qualitative test did not show any significance (appendix p 37). Hence, this finding should be interpreted with caution, as it might largely be associated with the small sample size.

Deep responses, including minimal residual disease negativity, have been associated with longer progression-free survival and overall survival in newly diagnosed and relapsed or refractory multiple myeloma.[2,26,27,28] In this study, patients were assessed for minimal residual disease negative–complete response per IMWG uniform response criteria. KdD-treated patients had a significantly higher overall response rate and achieved deeper responses, with a nearly 10-times higher rate of achieving minimal residual disease negative–complete response at 12 months compared with Kd-treated patients. Best minimal residual disease negative–complete response rates were also higher for KdD compared with Kd (14% *vs* 3%).

The prolonged progression-free survival and deep responses achieved with KdD in the CANDOR study are consistent with findings from the phase 1b MMY1001 study[24] of daratumumab with once-weekly carfilzomib at 70 mg/m² and dexamethasone in patients nearly entirely pre-exposed to lenalidomide and 60% lenalidomide

refractory, and reinforce the efficacy of KdD for treatment of relapsed or refractory multiple myeloma. In the MMY1001 study, median progression-free survival was not reached for KdD in the overall population and was 25·7 months for patients who are lenalidomide refractory. Overall response rate was 84%; complete response rate was 33%.

At a median follow-up of nearly 17 months, overall survival was not yet mature; however, fewer deaths occurred in the KdD group (19%) versus the Kd group (23%) and a trend towards an overall survival benefit for KdD versus Kd was observed (appendix p 7). Overall survival will be reassessed in a subsequent preplanned analysis.

While KdD was associated with higher rates of any-grade, grade 3 or higher, and fatal adverse events compared with Kd, treatment duration was almost two times longer in the KdD group than the Kd group. The incidence of adverse events leading to treatment discontinuation was similar in both treatment groups (22% *vs* 25%). Exposure adjustment attenuated the observed difference in adverse event rates between the KdD and Kd groups. The risk estimates for grade 3 or higher and serious adverse events were similar in the treatment groups after exposure adjustment.

Grade 3 or higher respiratory tract infections (grouped term) were adverse events of interest that occurred more frequently with KdD (KdD, 29%; Kd, 16%]) and are consistent with higher incidences of respiratory infections observed in the daratumumab group of the CASTOR study.[22] Aggressive monitoring and timely management of infections would be appropriate for patients deemed at high risk for complications.

Grade 3 or higher cardiac failure (grouped term: KdD, 4%; Kd, 8%) and acute renal failure (grouped term: 3% and 7%) rates were lower in the KdD group compared with the Kd group. The rate of cardiac failure events leading to carfilzomib treatment discontinuation was similar in the KdD and Kd group (2% and 2%) whereas the rate of renal events leading to carfilzomib treatment discontinuation was lower in the KdD group (1% and 4%).

Additional analyses of patient baseline risk factors are under way. Importantly, no new cardiovascular safety risks were identified with the addition of daratumumab to carfilzomib-dexamethasone.

Most treatment-related fatal adverse events were the result of infections. On evaluation of baseline patient characteristics, we found a higher frequency of treatment-emergent fatal adverse events in the KdD than Kd group (KdD, 14%; Kd, 3%) in the older patient population (age ≥65 years) relative to younger patients <65 years (KdD, 6%; Kd, 8%; appendix p 35). Furthermore, a higher proportion of patients in the KdD group who were classified by the investigator as intermediately fit had fatal adverse events compared with the Kd group (19% *vs* 3%; appendix p 36). Neutropenia was not associated with the higher rates of infection-related fatal adverse events in the KdD group. Although the TEAMM study[29] showed that infection prophylaxis with levofloxacin during the first 12 weeks of newly diagnosed multiple myeloma therapy significantly reduces febrile episodes compared with placebo within the first 3 months of multiple myeloma treatment, its survival benefit could not be shown by 12 months. Infection-related fatal adverse events in CANDOR occurred generally after 90 days from the start of study treatment. Given that prolonged antibiotic prophylaxis after 12 weeks still requires investigation, close monitoring and management of infections should be considered when administering KdD, particularly in older or less healthy patients.

With increased use of frontline lenalidomide therapy, there is a rising need for new, tolerable and efficacious lenalidomide-free regimens for patients who have been exposed to, or have relapsed after stopping, lenalidomide treatment. The results for KdD were generally consistent across prespecified subgroups, including lenalidomide-exposed and lenalidomide-refractory patients. The observation of a median progression-free survival not reached after 17 months of follow-up for KdD compares favourably with the median progression-free survival range of 7·8 months to 11·2 months reported for other lenalidomide-free regimens in lenalidomide-exposed or lenalidomide-refractory populations.[10,26,30,31]

One of the limitations of the CANDOR study was the open-label study design, which could have resulted in a higher proportion of patients dropping out early from treatment in the control group. However, considering the similar rates of patients requesting to end treatment before disease progression (KdD, 15 [4·8%]; Kd, 10 [6·5%]), the open-label design did not seem to have an effect. Response and disease progression were established by a masked independent review committee to reduce bias. Other limitations were the small number of enrolled patients of 75 years of age and above, which prevented significant conclusions being drawn regarding the benefit–risk in this age group, and the proportion of patients with unknown cytogenetic risk in the study. Considering the consistent progression-free survival outcomes in patients with unknown and defined cytogenetic risk, we believe that patients were optimally differentiated, and the outcomes were not influenced by the frequency of unknown cytogenetic risk status. Lastly, the relatively short follow-up time of 17 months might have contributed to the low number of death events at the time of the primary analysis. Despite the promising higher 18-month overall survival rate for KdD versus Kd, definite conclusions on overall survival can only be drawn after further accrual of overall survival data with longer follow-up time.

In summary, KdD resulted in a significant progression-free survival benefit compared with Kd. In addition, patients treated with KdD achieved improved overall and deeper responses, with a nearly 10-times higher minimal residual disease negative–complete response

rate at 12 months. The treatment effect on progression-free survival was generally consistent across prespecified clinically important subgroups, including lenalidomide-exposed and lenalidomide-refractory subgroups. The observed adverse events associated with KdD were consistent with the known safety profiles of each agent, suggesting that combining daratumumab with carfilzomib does not result in additional toxicity. Overall, the immunomodulatory drug-free KdD regimen showed a favourable benefit–risk profile and represents an efficacious new standard of care for patients with relapsed or refractory multiple myeloma, including patients for whom lenalidomide is no longer a treatment option.

Contributors

All authors participated in the conception and design of the study, analysis and interpretation of data, the writing of the manuscript, and the decision to submit for publication. Patient data were collected by MD, HQ, M-VM, XL, DS, and SZU.

Declaration of interests

MD reports consulting fees, lecture fees, and honoraria from Janssen, Amgen, Celgene, and Takeda; research funding from Janssen, Amgen, Takeda, and Genesis Pharma; and consulting fees from Bristol-Myers Squibb. HQ reports grants from Celgene and Amgen; honoraria from Takeda and Janssen; and free drug for investigator-initiated study from Sanofi. M-VM reports consulting fees from Janssen, Celgene, Amgen, Takeda, AbbVie, GlaxoSmithKline, Pharmamar, Adaptive, and Mundipharma EDO. OL reports grants from the US National Institutes of Health, the Food and Drug Administration, the Multiple Myeloma Research Foundation, International Myeloma Foundation, the Leukemia and Lymphoma Society, the Perelman Family Foundation, Rising Tides Foundation, Janssen, Takeda, Glenmark, Seattle Genetics, and Karyopharm; personal fees from Adaptive Biotech, Binding Site, Bristol-Myers Squibb, Cellectis, Juno, and Pfizer; and other from Takeda, Merck, and Janssen. XL reports honoraria from Janssen, Celgene, Amgen, Takeda, Merck, GlaxoSmithKline, Sanofi, Carsgen, AbbVie, Incyte, and Novartis. DS reports honoraria and speakers' bureau fees from Amgen, Celgene, Takeda, Novartis, Bristol-Myers Squibb, and Janssen, and honoraria from Karyopharm. KW reports honoraria, consultancy fees, and research funding from Amgen, Celgene, Janssen, and Sanofi; honoraria and consultancy fees from Bristol-Myers Squibb, Adaptive Biotech, and Takeda; honoraria from GlaxoSmithKline; and consultancy fees from Juno. HY, ZK, and AZ-K report employment and equity ownership in Amgen. SZU reports grants and personal fees from Amgen, Celgene, Sanofi, Seattle Genetics, Janssen, Takeda, and SkylineDX; personal fees from AbbVie and MundiPharma; and grants from Bristol-Myers Squibb and Pharmacyclics.

Data sharing

Qualified researchers can request data from Amgen clinical studies. Complete details are available on the website.

For **complete details** see https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/

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