REGULAR ARTICLE

blood advances

Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study

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Key Points

- The final analysis of CANDOR confirmed a PFS benefit and showed a trend in OS favoring KdD vs Kd.
- Results reinforce KdD as a standard of care for RRMM, especially in clinically relevant patient subgroups.

CANDOR (NCT03158688) is a phase 3, randomized, open-label trial comparing carfilzomib, daratumumab, and dexamethasone (KdD) vs carfilzomib and dexamethasone (Kd) in adults with relapsed/refectory multiple myeloma (RRMM) with 1 to 3 prior therapies. The CANDOR study met its primary end point of progression-free survival (PFS) in the primary analysis. Here, we report the final analysis of the study, including secondary end points and subgroup analyses thereof. The median follow-up was 50 months. Patients treated with KdD had higher minimal residual disease–negative (MRD^-) achievement rates (28% vs 9%; odds ratio [OR], 4.22; 95% confidence interval [95% CI], 2.28-7.83) and MRD^- complete response rates (22% vs 8%; OR, 3.55; 95% CI, 1.83-6.88) than those treated with Kd. Median PFS was 28.4 months for KdD vs 15.2 months for Kd (hazard ratio [HR], 0.64; 95% CI, 0.49-0.83). Median overall survival (OS) for KdD was 50.8 months vs 43.6 months for Kd (HR, 0.78 [0.60-1.03]; P = .042). Trends toward improved OS occurred in predefined subgroups, including patients refractory to lenalidomide (KdD, not reached vs Kd, 38.2 months; HR, 0.69 [0.43-1.11]) and refractory to proteasome inhibitor (KdD, 43.2 months vs Kd, 30.0 months; HR, 0.70 [0.45-1.09]), and there was significant improvement in patients with high-risk cytogenetics (KdD, 34.3 months vs Kd: 17.1 months; HR, 0.52 [0.29-0.94]). No new safety signals were identified. In summary, the final analysis of CANDOR confirmed the PFS benefit and showed a trend in OS benefit with KdD vs Kd. These findings reinforce KdD as a standard of care for RRMM, especially in clinically relevant patient subgroups. This trial was registered at www.clinicaltrials.gov as #NCT03158688.

Introduction

Multiple myeloma (MM) remains largely incurable, despite improvements in survival outcomes in the last decade because of the availability of novel therapeutics, including immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies.[1] Selective treatment pressures lead to clonal expansion and heterogeneity, followed by subsequent resistance to therapy and relapse.[2,3] The IMiD

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The full-text version of this article contains a data supplement.

lenalidomide is frequently used during front-line induction and maintenance therapy for MM.[4] Because lenalidomide is typically administered until disease progression, patients who relapse are often refractory to lenalidomide, creating a need for lenalidomide-sparing treatment options for relapsed/refractory (RR) MM.[5]

Carfilzomib, a second-generation PI, is approved as a treatment for RRMM, and carfilzomib-containing regimens are widely included in treatment guidelines for patients with previously treated myeloma.[4,6-9] The phase 3 CANDOR trial (NCT03158688) compared carfilzomib, daratumumab, and dexamethasone (KdD) vs carfilzomib and dexamethasone (Kd) in adult patients with RRMM who had received from 1 to 3 prior therapies. In the primary analysis (data cutoff on 14 July 2019), the study met its primary end point of progression-free survival (PFS) and 2 key secondary efficacy end points (overall response rate and minimal residual disease–negative [MRD^-] complete response [CR] at 12 months).[10] At a subsequent interim analysis (data cutoff on 15 June 2020) with a median follow-up of 27 months, KdD continued to demonstrate improved median PFS vs Kd (28.6 vs 15.2 months; hazard ratio [HR], 0.59; 95% confidence interval [95% CI], 0.45-0.78).[11] The improvement in PFS was consistent across clinically relevant subgroups, including patients refractory to lenalidomide.[11] Here, we report the final analysis of the study, including updated efficacy and safety results in clinically important patient subgroups from the final analysis of the CANDOR trial.

Methods

Study design and participants

CANDOR, a phase 3, randomized, open-label trial comparing KdD with Kd in patients with RRMM recruited 466 patients from 102 international sites. A detailed description of the CANDOR study design has been previously published.[10,11]

In brief, inclusion criteria for patients included being aged ≥18 years with RRMM, having an Eastern Cooperative Oncology Group performance status from 0 to 2, having undergone between 1 and 3 prior lines of therapy, and having experienced a partial or better response to at least 1 previous therapy. Patients were excluded if they had received antimyeloma immunotherapy or chemotherapy within 21 days or high-dose steroids within 14 days before randomization. An interactive voice or web response system was used to randomize patients in a ratio of 2:1 to receive 28-day cycles of KdD or Kd. Randomization was stratified based on the international staging system at screening (I or II vs III), previous PI exposure (yes vs no), number of previous lines of therapy (1 vs 2-3), and previous anti-CD38 monoclonal antibody therapy (yes vs no).

Patients received study treatment for a maximum of ~5 years, up to 30 days before the final analysis data cutoff date (15 April 2022) or until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or death (whichever occurs first). Data on survival status were obtained every 12 weeks (±2 weeks) after safety follow-up visit until the patient had withdrawn consent, was lost to follow-up, died, or reached the final analysis data cutoff, whichever occurred earliest. The CANDOR final analysis was prespecified to occur after 230 survival events or 58 months after the first patient was enrolled, whichever came first.

Carfilzomib was administered as intravenous infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m^2 on days 1 and 2 of cycle 1 and 56 mg/m^2 thereafter). Patients received dexamethasone as oral or IV infusion weekly at 40 mg (20 mg for patients aged >75 years). A split dose of 20 mg dexamethasone each day was administered when taken on successive days. Patients in the KdD arm received daratumumab as an IV infusion of 8 mg/kg on days 1 and 2 of cycle 1, 16 mg/kg once weekly for the remaining doses of the first 2 cycles, then every 2 weeks for 4 cycles (cycles 3-6), and every 4 weeks thereafter.

All patients provided written informed consent, and the study protocol was approved by institutional review boards or independent ethics committees at all participating institutions. X.S. and C.L. analyzed the data, and all authors had access to the primary clinical trial data. CANDOR is registered at www.clinicaltrials.gov as #NCT03158688.

Assessments

MRD was assessed in bone marrow aspirates via next-generation sequencing at a threshold of 1 tumor cell per 10^{-5} white blood cells, using the Adaptive clonoSEQ assay (version 2.0; Adaptive Biotechnologies, Seattle, WA). MRD^- CR rate was defined as patients who were MRD^- who achieved CR as assessed by an independent review committee per International Myeloma Working Group (IMWG) uniform response criteria.[12] Efficacy results are reported in the intent-to-treat population.

PFS was defined as the time from randomization until confirmed disease progression or death due to any cause, whichever occurred first. Disease progression was centrally assessed every 28 ± 7 days based on the IMWG uniform response criteria using a validated Onyx Response Computer Algorithm in a blinded manner by the sponsor.

Cutoffs for cytogenetic abnormalities are as follows: for t(4:14), 13 out of 100 CD138 cells present with 1R1G1F fluorescence in situ hybridization (FISH) signal or 3 out of 100 CD128 cells present with 1R1G2F FISH signal was considered positive; for t(14:16), 15 out of 100 CD138 cells present with 1R1G1F FISH signal or 3 out of 100 CD128 cells present with 1R1G2F FISH signal was considered positive; for del17p, 9 out of 100 CD138 cells present with 1R2G FISH signal or 5 out of 100 CD138 cells present with 1R1G FISH signal was considered positive.

The final analysis for overall survival (OS) occurred 58 months after the first patient was enrolled. OS was defined as the time from randomization to the date of death from any cause.

Adverse events (AEs) were collected up to 30 days after the last dose of any study treatment or at end of study, whichever occurred first. AEs were graded per the National Cancer Institute Common Terminology Criteria for AEs (version 4.03).[13] All patients with treatment-related and serious AEs were followed up until the AEs were stabilized or resolved.

Statistical analysis

There were 3 prior preplanned interim OS analyses in the CANDOR study. For OS, the Lan-DeMets alpha spending function was used to construct the O'Brien-Fleming type stopping boundaries such that the overall type 1 error was ≤0.025 for the log-rank test. OS was tested via stratified log-rank test and reached significance if the 1-sided *P*-value met the statistical significance level of .021 (1-sided) per the O'Brien-Fleming boundary for the final

analysis. OS was summarized using the Kaplan-Meier method, with a stratified Cox proportional hazards model used to estimate HR and corresponding 95% CI. PFS was summarized descriptively using the Kaplan-Meier method with HRs estimated using a stratified Cox proportional hazards model.

A sensitivity analysis for OS was performed using the inverse probability of censoring weights method, which provides an unbiased estimate of treatment effect if all baseline and time-dependent prognostic factors are measured and available (no unmeasured confounders assumption).[14] A predictive model was built for the probability of each patient remaining nonswitching until a certain timepoint and then weighed at each time point per the inverse probability of nonswitching during each prespecified time interval. In the adjusted analysis, higher weights were assigned to nonswitching patients with characteristics similar to the switching patients. After weights were calculated, a weighted Cox stratified model was used to estimate the adjusted HR for treatment effect.

The post hoc analysis of derived time to subsequent progression or death (dPFS2) was defined as the time from randomization to dPFS2, whichever occurred first. Because the date of subsequent disease progression was not collected in the CANDOR study, dPFS2 was assessed using an algorithm that found time from randomization to start of next treatment. If a patient had disease progression on CANDOR therapy, the start date of next line of therapy was used; if a patient stopped receiving KdD or Kd for reason other than progressive disease, the start date of the third line of therapy was used. Death in follow-up was also considered a surrogate for progressive disease when calculating dPFS2. Comparison of dPFS2 among treatment arms was conducted using stratified log-rank test.

Time to next treatment was defined as the time from randomization to the start of subsequent MM therapy. If a patient did not move on to a next treatment, then they were censored.

Safety analyses used the safety population, which included all patients receiving a dose of study treatment. Exposure-adjusted analyses of treatment-emergent AEs (TEAEs) and fatal TEAEs were performed post hoc to clarify differences in treatment duration.

Results

Between 13 June 2017 and 25 June 2018, a total of 466 patients were randomized with the ratio of 2:1 for KdD (n = 312) to Kd (n = 154), as described previously.[10,11] Patients were allowed to continue treatment until disease progression but not longer than up to 30 days before the final analysis data cutoff (15 April 2022), by the time all patients had completed protocol-specified procedures. The most common reason for carfilzomib or daratumumab discontinuation was disease progression (Figure 1). The median follow-up time was 50.6 months (range, 0-57) in the KdD arm and 50.1 months (range, 0-58) in the Kd arm.

Patient baseline characteristics were generally balanced among treatment arms (Table 1). Most patients had received prior bortezomib (KdD, 92% [n = 287/312]; Kd, 87% [n = 134/154]), whereas many received prior lenalidomide (KdD, 39% [n = 123/312]; Kd, 48% [n = 74/154]) and more than one-third were refractory to lenalidomide (KdD, 32% [n = 99/312]; Kd, 36% [n = 55/154]).

Since the primary analysis, additional MRD samples have become available; a summary of MRD sample availability is shown in supplemental Table 1. The MRD^- rates at the 12-month landmark and at any time during the study were more than threefold higher in the KdD arm than in the Kd arm (Table 2). MRD^- CR rates were consistently higher in the KdD group, with MRD^- CR rates at 12 months being 13% (n = 40/312) vs 2% (n = 3/154) in the key secondary end point landmark analysis and MRD^- CR rates at any time being 22% (n = 68/312) vs 8% (n = 12/154).

The most recent data cutoff with centrally assessed PFS available for all patients was 14 June 2021 (median follow-up, ~39 months in the KdD arm). Median PFS was 28.4 months (95% CI, 22.7-36.2) in the KdD arm vs 15.2 months (95% CI, 11.1-19.9) in the Kd arm (HR, 0.64 [0.49-0.83]; supplemental Figure 1).

After a median follow-up of >50 months, the median OS was 50.8 months (95% CI, 44.7 to not estimable [NE]) in the KdD arm vs 43.6 (95% CI, 35.3 to NE) months in the Kd arm, with an HR of 0.78 (95% CI, 0.60-1.03; Figure 2). Although there is a 7.2-month numerical difference in OS in favor of KdD, the 1-sided *P*-value of .0417 did not meet the prespecified statistical significance level of .021 (1-sided). These results were generally consistent across 4 prespecified OS sensitivity analyses (supplemental Table 2). Prespecified subgroup analyses showed an OS improvement trend with KdD vs Kd in most subgroups, including patients with lenalidomide-exposed, lenalidomide-refractory, PI-exposed, or PI-refractory disease. The greatest OS benefit of KdD was seen in patients with high-risk cytogenetics (HR, 0.52 [0.29-0.94]) and in patients with international staging system stage III at screening (HR, 0.58 [0.35-0.99]; Figure 3).

In the KdD arm, 153 of 312 (49%) patients received subsequent antimyeloma therapy vs 105/ of 154 (68%) in the Kd arm (supplemental Table 3). In both groups, the most common categories of subsequent therapies were IMiDs and corticosteroids. Patients in the Kd arm were 4-times more likely to receive the anti-CD38 monoclonal antibody therapies daratumumab or isatuximab in the next line of therapy (KdD, 7% [n = 23/312]; Kd, 28% [n = 43/154]). Subsequent therapies were otherwise mostly similar between arms. The median time to next treatment was 37.4 months (95% CI 30.1-47.8) for the KdD arm and 17.8 months (95% CI 13.5-23.1) for the Kd arm. In a post hoc analysis, the median dPFS2 was 44.6 months for KdD and 35.5 months for Kd (HR, 0.800; 95% CI, 0.614-1.044).

The median study treatment duration was 79 weeks (0.3-236) and 40 weeks (0.3-236) in the KdD and Kd arms, respectively. In the KdD group, the median treatment duration of carfilzomib was 61 weeks (0.3-236), and the median treatment duration of daratumumab was 79 weeks (0.1-236). In the Kd arm, the median treatment duration of carfilzomib was 40 weeks (0.3-235). The median relative dose intensity of carfilzomib was 88% in the KdD arm and 91% in the Kd arm; for daratumumab, the median relative dose intensity was 95% (supplemental Table 4).

Safety outcomes were mostly similar across treatment arms and consistent with the results observed in previous analyses.[10,11] TEAEs of any grade occurred in 306 of 308 (99%) patients in the KdD arm and in 149 of 153 (97%) in the Kd arm (Table 3). Grade ≥3 TEAEs occurred in 273 of 308 (87%) and 120 of 153 (78%) patients, respectively, with the most common being

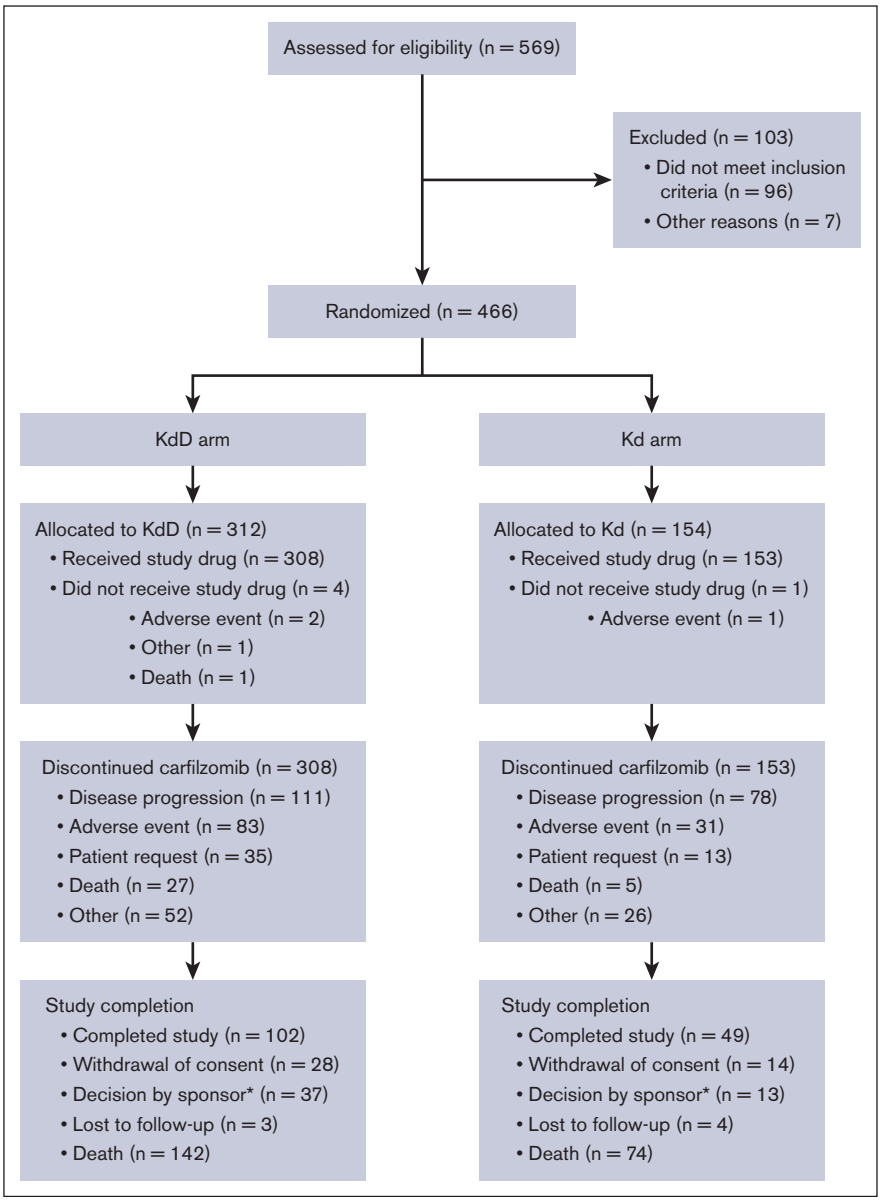

Figure 1. Patient flowchart. *Category includes patients who discontinued study treatment at study closure per the protocol.

thrombocytopenia, hypertension, pneumonia, and anemia in both groups. Serious TEAEs occurred in 211 of 308 (68%) and 80 of 153 (52%) patients.

Fatal TEAEs occurred in 35 of 308 (11%) and 9 of 153 (6%) patients in the KdD and Kd arms, respectively (excluding patients with a fatal TEAE of plasma cell myeloma; supplemental Table 5). The most common causes of fatal TEAEs were infections (KdD, 7% [n = 21/308]; Kd, 3% [n = 5/153]) and cardiac disorders (KdD, 2% [n = 6/308]; Kd, 0%). The exposure-adjusted rates of fatal TEAEs were 6.5 and 5.6 per 100 patient-years for the KdD and Kd arms, respectively (supplemental Table 4). Fatal treatment-related AEs occurred in 5 of 308 (2%) patients in the KdD arm (1 each of acinetobacter infection, cardiorespiratory arrest, pneumonia, sepsis, and septic shock) and no patients in the Kd arm. No new treatment-related fatal AEs occurred after the primary analysis.[10]

TEAEs of interest are shown in Table 3. Grade ≥3 infections and infestations occurred in 142 of 308 (46%) patients in the KdD arm and in 49 of 153 (32%) of those in the Kd arm and led to carfilzomib discontinuation in 69 of 308 (22%) and 30 of 153 (20%) patients, respectively. Fatal infection rates were 7% (n = 21/308) and 3% (n = 5/153); when adjusted for exposure, rates of fatal infection were 3.5 and 2.55 per 100 patient-years, respectively. TEAEs related to COVID-19 (combined Medical Dictionary for Regulatory Activities [version 25.0] terms of COVID-19, COVID-19 pneumonia, asymptomatic pneumonia, and severe acute respiratory syndrome coronavirus 2) occurred in 33 of 308 (11%) patients in the KdD arm and in 6 of 153 (4%) of those in the Kd arm; deaths

Table 1. Baseline patient characteristics

Characteristic	KdD (n = 312)	Kd (n = 154)
Median (range) age, years	64.0 (57-70)	64.5 (59-71)
≤64, n (%)	163 (52)	77 (50)
65–74, n (%)	121 (39)	55 (38)
≥75, n (%)	28 (9)	22 (14)
Baseline ECOG PS, n (%)		
0-1	295 (95)	147 (95)
2	15 (5)	7 (5)
ISS stage at screening, n (%)		
I	147 (47)	79 (51)
II	103 (33)	48 (31)
III	61 (20)	27 (18)
Unknown	1 (0)	0
Cytogenetic risk group based on FISH,* n (%)		
High	48 (15)	26 (17)
Standard	108 (35)	56 (36)
Unknown	156 (50)	72 (47)
Number of prior therapies, n (%)		
1	144 (46)	70 (45)
2-3	168 (54)	84 (55)
Prior therapies, n (%)		
Bortezomib	287 (92)	134 (87)
Lenalidomide	123 (39)	74 (48)
Pomalidomide	14 (4)	10 (6)
Refractory† to bortezomib and lenalidomide, n (%)	37 (12)	18 (12)
Refractory to prior bortezomib, n (%)	88 (28)	47 (31)
As last line of prior therapy	47 (15)	31 (20)
Refractory to prior lenalidomide, n (%)	99 (32)	55 (36)
As last line of prior therapy	74 (24)	38 (25)
After 1 prior line of therapy	19 (6)	6 (4)
After 2–3 prior lines of therapy	80 (26)	49 (32)
Refractory to pomalidomide, n (%)	10 (3)	9 (6)

ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, international staging system.

*FISH 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 FISH results that failed or were canceled.

†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 for which the drug was stopped was progression in any regimen; and date of relapse or progression was after start date and within 60 days after stop date of the drug in any regimen.

related to COVID-19 occurred in 6 of 308 (2%) and 1 of 153 (1%) patients, respectively.

In the KdD arm, 105 of 308 (34%) patients discontinued any study treatment because of TEAEs vs 41 of 153 (27%) patients in the Kd arm (supplemental Table 4). Incidence of carfilzomib and daratumumab discontinuation because of TEAEs decreased over time, with most discontinuations because of TEAEs occurring in the first 18 months (supplemental Figure 2A,B).

Discussion

After a median follow-up of >4 years, the final analysis of the CANDOR trial reinforces the favorable risk-benefit profile of the KdD triplet in patients with RRMM. In the primary analysis, the trial met its primary end point, with a significant improvement in PFS reported for KdD vs Kd (median PFS, not reached for KdD vs 15.8 months for Kd; HR, 0.63; 95% CI, 0.46-0.85) as well as select secondary end points, including overall response rate and MRD^- CR at 12 months.[10] The PFS benefit of KdD compared with Kd was maintained in the preplanned interim analysis at 27-months median follow-up (KdD, 28.6 months; Kd, 15.2 months; HR, 0.59; 95% CI, 0.45-0.78).[11] These results are consistent with the recently reported interim analysis of the phase 3 IKEMA study of isatuximab plus Kd (Isa-Kd), an analogous triplet combination, vs Kd for RRMM (median PFS: Isa-Kd, 35.7 months; Kd, 19.2 months; HR, 0.58; 95.4% CI, 0.42-0.79).[15] In this final analysis, MRD, PFS, and OS results show the favorable efficacy of KdD, consistent with the previously reported results. Patients treated with KdD had deep responses, with MRD^- CR rates at 12 months 6 times higher and MRD^- CR rates at any time 3 times higher than for patients in the Kd arm. Although the prespecified level of statistical significance was not met for OS, there was an absolute difference of 7.2 months in median OS between the 2 arms, and the OS curves remained separated for the study duration, with an HR of 0.78 (95% CI, 0.60-1.03). Meanwhile, lower OS HRs (indicating greater benefit of KdD vs Kd) were observed in patients with high-risk cytogenetics (HR, 0.52; 95% CI, 0.29-0.94) and those refractory to lenalidomide (HR, 0.69; 95% CI, 0.43-1.11) or bortezomib (HR, 0.70; 95% CI, 0.45-1.09) in the prespecified subgroup analyses, which may address unmet treatment needs in these patient populations.

Subsequent antimyeloma therapies might have confounded the OS results in the overall study population because more patients receiving Kd had subsequent antimyeloma therapy than did patients receiving KdD (68% vs 49%). Access to subsequent daratumumab across international sites depended on local regulatory approval. Consequently, because CANDOR was not a crossover trial, patients received subsequent antimyeloma therapy at the discretion of treating physicians after progression.[16] Although CANDOR did not have a crossover design, 28% of patients in the Kd arm and 7% in the KdD arm received subsequent anti-CD38 monoclonal antibody–containing therapy after disease progression. A prespecified sensitivity analysis using an inverse probability of censoring weights model that censored patient data in the Kd arm at time of subsequent anti-CD38 monoclonal antibody therapy initiation further supports this hypothesis; the HR for the median OS was lower (0.74) than that in the CANDOR study, and the 95% CI did not cross 1.0 (0.55-0.99) in the sensitivity analysis.

In previously published RRMM studies, such as ASPIRE, ENDEAVOR, CASTOR, and POLLUX,[17-20] a statistically significant improvement in OS was observed in an era when subsequent lines of therapies did not include highly effective novel agents. However, the confounding effect of potent therapies after progression and the prolonged follow-up required have hindered the utility of using OS as an end point in recent years.[21] Improved myeloma therapies over the last decade have resulted in median survival approaching 10 years,[22] resulting in a steady approval of new therapies that will be available before the end point is met.[23]

Table 2. MRD negativity (10^{-5}) rates

	KdD % (95% CI) n = 312	Kd % (95% CI) n = 154	ORs KdD/Kd (95% CI)
MRD^- rate at 12 mo	n = 57 18.3 (14.1-23.0)	n = 8 5.2 (2.3-10.0)	4.403 (2.007-9.656)
MRD^- CR rate at 12 mo	n = 40 12.8 (9.3-17.0)	n = 3 1.9 (0.4-5.6)	7.819 (2.364-25.858)
MRD^- rate at any time	n = 87 27.9 (23.0-33.2)	n = 14 9.1 (5.1-14.8)	4.222 (2.277-7.829)
MRD^- CR rate at any time	n = 68 21.8 (17.3-26.8)	n = 12 7.8 (4.1-13.2)	3.551 (1.833-6.877)

OR, odds ratio.

Given the increasing challenges of using OS as an end point in myeloma clinical trials, there is an effort underway to develop surrogate end points that can be used at earlier timepoints. There is also a need for a precise and sensitive measure of myeloma disease state because many, but not all, patients who achieve CR eventually relapse. In the CANDOR study, the MRD^- rate was 28% and the MRD^- CR rate was 22% in patients treated with KdD. MRD negativity and MRD^- CR have shown to be predictive of long-term clinical outcomes. A meta-analysis ahowed a strong prognostic value of MRD negativity in patients with very good response or better response and patients with MRD^- having improved PFS (HR, 0.33; 95% CI, 0.29-0.37; $P < .001$) and OS (HR, 0.45; 95% CI, 0.39-0.51; $P < .001$), including in the RRMM setting.[24] On the basis of the correlation between MRD^- status and improved outcomes in RRMM, the IMWG has incorporated MRD assessment into their MM uniform response criteria,[12] and the US Food and Drug Administration has published guidance on the use of MRD negativity as a secondary or exploratory end point in clinical trials.[25] In the CASTOR and POLLUX phase 3 trials of daratumumab-containing triplets in RRMM, patients achieving MRD^- response had improved PFS.[26] The IKEMA study had similar rates of MRD^- (30% Isa-Kd, 13% Kd) and MRD^- CR (20% Isa-Kd, 11% Kd) as CANDOR (MRD^-: 28% KdD, 9% Kd; MRD^- CR: 22% KdD, 8% Kd).[27] Patients treated with Isa-Kd in IKEMA who were MRD^- also had longer PFS than patients who remained MRD^+.

Because many patients with RRMM are lenalidomide refractory, there is a strong need for lenalidomide-sparing treatments, such as KdD. The KdD triplet maintains strong efficacy in patients who are refractory to lenalidomide, with improved PFS (HR, 0.59)[11] and OS (HR, 0.69) compared with Kd. Similar trends in OS benefit were observed in subgroups with prior PI, lenalidomide exposure, or high-risk cytogenetics.

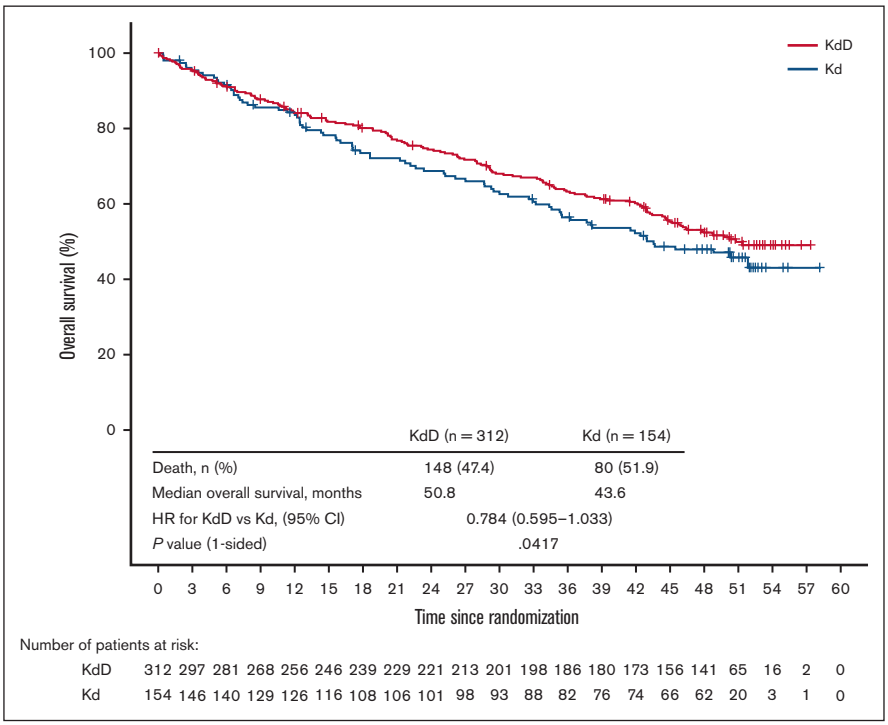

Figure 2. Kaplan-Meier estimates of OS.

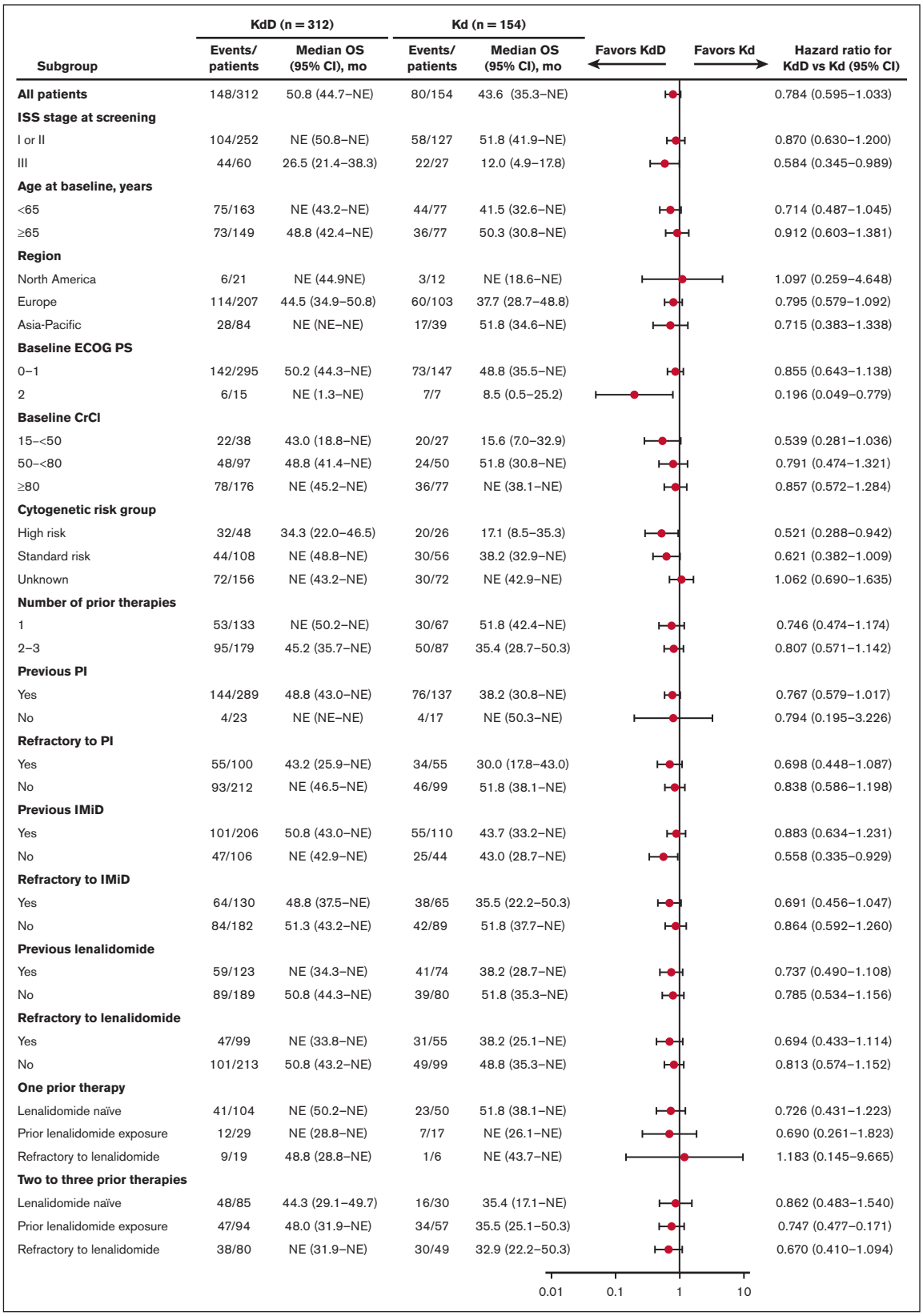

Figure 3. Prespecified subgroup analyses of OS. CrCl, creatinine clearance.

Table 3. TEAEs in the safety population

TEAEs, n (%)	KdD n = 308		Kd n = 153	
	Any grade*	Grade ≥3†	Any grade*	Grade ≥3†
All TEAEs	306 (99.4)	273 (88.6)	149 (97.4)	120 (78.4)
Hematologic TEAEs				
Thrombocytopenia	119 (38.6)	76 (24.7)	46 (30.1)	25 (16.3)
Anemia	114 (37.0)	54 (17.5)	52 (34.0)	25 (16.3)
Neutropenia	49 (15.9)	31 (10.1)	15 (9.8)	10 (6.5)
Lymphopenia	29 (9.4)	22 (7.1)	13 (8.5)	11 (7.2)
Nonhematologic TEAEs				
Diarrhea	118 (38.3)	18 (5.8)	28 (18.3)	1 (0.7)
Hypertension	115 (37.3)	72 (23.4)	49 (32.0)	27 (17.6)
Upper respiratory tract infection	105 (34.1)	12 (3.9)	37 (24.2)	2 (1.3)
Fatigue	81 (26.3)	25 (8.1)	29 (19.0)	7 (4.6)
Pneumonia	79 (25.6)	57 (18.5)	24 (15.7)	14 (9.2)
Dyspnea	70 (22.7)	16 (5.2)	35 (22.9)	4 (2.6)
Pyrexia	66 (21.4)	6 (1.9)	27 (17.6)	2 (1.3)
Insomnia	64 (20.8)	16 (5.2)	19 (12.4)	3 (2.0)
Back pain	63 (20.5)	7 (2.3)	21 (13.7)	2 (1.3)
Nausea	62 (20.1)	0	22 (14.4)	1 (0.7)
Hyperglycemia	31 (10.1)	16 (5.2)	13 (8.5)	5 (3.3)
Cataract	34 (11.0)	15 (4.9)	13 (8.5)	8 (5.2)
Events of interest				
Respiratory tract infection	243 (78.9)	117 (38.0)	90 (58.8)	27 (17.6)
Infusion reaction (on same day as any carfilzomib)	142 (46.1)	47 (15.3)	50 (32.7)	12 (7.8)
Peripheral neuropathy	66 (21.4)	6 (1.9)	15 (9.8)	1 (0.7)
Cardiac failure	29 (9.4)	12 (3.9)	17 (11.1)	13 (8.5)
Acute renal failure	25 (8.1)	11 (3.6)	14 (9.2)	10 (6.5)
Ischemic heart disease	19 (6.2)	16 (5.2)	8 (5.2)	5 (3.3)

*Any grade TEAEs occurring in ≥20% of the patients.
†Grade ≥3 TEAEs occurring in ≥5% of the patients.

With extended follow-up, the safety profile of KdD in this final analysis remains consistent with previously reported results.[10,11] No new or unexpected safety signals were identified. Although a greater percentage of patients in the KdD arm had grade ≥3 TEAEs or fatal TEAEs, when adjusted for treatment exposure, the rates were similar between the KdD arm and Kd arms. Older adult patients had a higher frequency of fatal TEAEs in the KdD vs the Kd arm; among patients aged <65 years, rates of fatal TEAEs were similar between arms. No new treatment-related fatal AEs occurred after the primary analysis.[10] Given that rates of TEAE were higher in patients aged >65 years, closer monitoring for signs of infection and consideration of a possible role for prophylaxis may be warranted in older adult patients, consistent with current MM supportive care guidelines.[11,28,29]

Although discontinuation of any study treatment or carfilzomib treatment because of TEAEs occurred slightly more frequently in patients treated with KdD vs Kd, discontinuation of carfilzomib or daratumumab because of TEAEs decreased over time in both groups, suggesting no cumulative toxicity. Infections continued to be 1 of the most common AEs in patients in both the KdD and Kd arms, including respiratory tract infections and pneumonia. In keeping with the known safety profile of anti-CD38 monoclonal antibodies,[30,31] there were higher rates of neutropenia and infections in the KdD arm; however, differences in rates of fatal infection were attenuated when adjusted for exposure. Rates of upper respiratory tract infection and pneumonia were similar in the IKEMA study (upper respiratory tract infection [Isa-Kd, 36%; Kd, 24%] and pneumonia [Isa-Kd, 29%; Kd, 23%]).[32] Close monitoring and timely management of infections are appropriate for patients at high risk for complications.

Limitations of the CANDOR study include the small number of enrolled patients aged ≥75 years, which makes it difficult to fully evaluate the benefit-risk of treatment in this age group, as well as inherent limitations associated with an open-label trial design. Another limitation of this study is that there was a relatively high proportion of patients with unknown cytogenetics, which may have reduced the ability to accurately report outcomes in subgroups defined by cytogenetic risk. In addition, there were insufficient data to support analyses of outcomes in subgroups with 1 vs 2 vs 3 of the high-risk chromosomal abnormalities. Efficacy outcomes after

subsequent anti-CD38 monoclonal antibody rescue therapy were not collected, and thus do not address the question of how to optimally sequence myeloma therapies. Finally, PFS2 was not a prespecified end point in CANDOR, therefore dPFS2 is reported as an indirect measure of efficacy.

In summary, after a median follow-up of ~50 months, the CANDOR study shows a clear PFS benefit and a trend in OS favoring KdD vs Kd, reinforcing KdD as a standard of care in RRMM, especially in patients previously exposed/refractory to lenalidomide and in those with high-risk cytogenetics.

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Authorship

Contribution: S.Z.U., H.Q., M.-V.M., O.L., X.L., D.S., K.W., and M.D. collected the data; S.Z.U., H.Q., M.-V.M., O.L., X.L., D.S., K.W., X.S., C.L., and M.D. were involved in study conceptualization and design, data analysis and interpretation, and manuscript writing; and all authors gave the final approval of the manuscript and are accountable for all aspects of the work.

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