Carfilzomib, Dexamethasone, and Daratumumab (KdD) Versus Kd in Relapsed or Refractory Multiple Myeloma: Subgroup Analysis of the Phase 3 CANDOR study by Number of Prior Lines of Therapy and Prior Therapies

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INTRODUCTION

- As lenalidomide- and bortezomib-based therapies are increasingly used for frontline multiple myeloma (MM) treatment, resistance to these agents can be present at relapse[1–3]
- There is a need to develop lenalidomide- and bortezomib-sparing options for patients with relapsed and/or refractory MM with previous exposure to lenalidomide and/or bortezomib; furthermore, given that the rate and duration of response diminish after each successive regimen,[4–6] effective treatments are needed at early relapse
- Carfilzomib is an irreversible proteasome inhibitor that is approved in combination with dexamethasone alone (Kd) or with lenalidomide and dexamethasone (KRd) for the treatment of patients with relapsed or refractory MM[7]
  - Whereas bortezomib has been associated with peripheral neuropathy (PN), carfilzomib is an alternative proteasome inhibitor with lower PN rates and a tolerable safety profile[8]
- Daratumumab, an anti-CD38 monoclonal antibody, is approved for the treatment of patients with newly diagnosed and relapsed or refractory MM[9] and has been successfully combined with proteasome inhibitors for MM treatment
- The phase 3 CANDOR trial demonstrated that progression-free survival (PFS) was significantly longer with carfilzomib, dexamethasone, and daratumumab (KdD) versus Kd (median PFS, not reached versus 15.8 months; hazard ratio [HR] 0.63; 95% confidence interval [CI], 0.46–0.85; two-sided P=0.0027) in patients with relapsed or refractory MM[10]

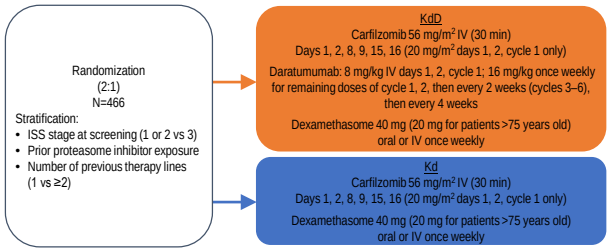
OBJECTIVE

- In this subgroup analysis of CANDOR, we evaluated efficacy and safety by the **number of prior lines of therapy (1 versus ≥2), and efficacy by previous exposure to** bortezomib or lenalidomide and refractory status to bortezomib or lenalidomide

METHODS

- CANDOR (NCT03158688) was a phase 3, open-label, randomized trial that enrolled adult patients with relapsed or refractory MM treated with 1–3 prior lines of therapy[10] (Figure 1)
- In this secondary analysis, the following subgroups were studied: number of prior lines of therapy (1 vs ≥2); prior lenalidomide exposure (yes vs no), prior lenalidomide refractory status (yes vs no), prior bortezomib exposure (yes vs no), and prior bortezomib refractory status (yes vs no)
  - Five patients in the prior bortezomib subgroups were exposed to ixazomib
- PFS was compared between treatment arms using a stratified log-rank test; overall response rate (ORR) and minimal residual disease (MRD)-negative complete response (CR) were compared between treatment arms using Cochran-Mantel-Haenszel chi-square methods

Figure 1. Study design for CANDOR



Primary endpoint: PFS
Secondary endpoint: ORR, MRD-negative CR at 12 months (threshold, 10^{-5}), safety

CR, complete response; ISS, International Staging System; IV, intravenous; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone, and daratumumab; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival.

RESULTS

Patients

- Baseline characteristics were generally balanced between KdD and Kd treatment groups, regardless of previous treatment history (Table 1)

Table 1. Baseline characteristics by (A) number of prior lines of therapy, (B) prior lenalidomide exposure and refractory status, and (C) prior bortezomib exposure and refractory status

(A)

	1 prior line		≥2 prior lines	
	KdD group (n=133)	Kd group (n=67)	KdD group (n=179)	Kd group (n=87)
Median age, years (range)	63.0 (29-83)	66.0 (35–81)	65.0 (33–84)	63.0 (35–83)
Race, n (%)				
White	99 (74.4)	56 (83.6)	144 (80.4)	67 (77.0)
Asian	23 (17.3)	8 (11.9)	23 (12.8)	12 (13.8)
Black/African American	3 (2.3)	0	4 (2.2)	2 (2.3)
Other	8 (6.0)	3 (4.5)	8 (4.5)	6 (6.9)
ISS stage at baseline, n (%)				
I	64 (48.1)	35 (52.2)	83 (46.4)	44 (50.6)
II	45 (33.8)	21 (31.3)	58 (32.4)	27 (31.0)
III	23 (17.3)	11 (16.4)	38 (21.2)	16 (18.4)
Unknown	1 (0.8)	0	0	0
Cytogenetic risk group per FISH,*n (%)				
High risk	24 (18.0)	11 (16.4)	24 (13.4)	15 (17.2)
Standard risk	45 (33.8)	23 (34.3)	59 (33.0)	29 (33.3)
Unknown risk	64 (48.1)	33 (49.3)	96 (53.6)	43 (49.4)
Mean CrCL, mL/min (SD)	87.60 (36.08)	82.06 (30.05)	84.53 (29.61)	81.80 (34.75)
Previous therapies, n (%)				
Bortezomib or ixazomib	117 (88.0)	55 (82.1)	172 (96.1)	82 (94.3)
Refractory to bortezomib or ixazomib in any previous regimen	21 (15.8)	14 (20.9)	79 (44.1)	41 (47.1)
Lenalidomide	29 (21.8)	17 (25.4)	94 (52.5)	57 (65.5)
Refractory to lenalidomide in any previous regimen	19 (14.3)	6 (9.0)	80 (44.7)	49 (56.3)
Transplant	86 (64.7)	33 (49.3)	109 (60.9)	42 (48.3)

(B)

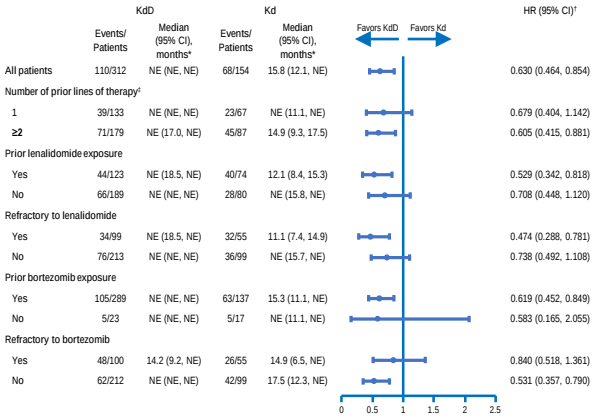
	Lenalidomide-exposed		Lenalidomide-naive		Lenalidomide-refractory		Lenalidomide non-refractory	
	KdD group (n=123)	Kd group (n=74)	KdD group (n=189)	Kd group (n=80)	KdD group (n=99)	Kd group (n=55)	KdD group (n=213)	Kd group (n=99)
Median age, years (range)	65.0 (37– 83)	65.0 (35–82)	63.0 (29–84)	64.5 (35–83)	65.0 (37–83)	64.0 (35–82)	64.0 (29–84)	65.0 (35–83)
Race, n (%)								
White	90 (73.2)	57 (77.0)	153 (81.0)	66 (82.5)	74 (74.7)	44 (80.0)	169 (79.3)	79 (79.8)
Asian	20 (16.3)	10 (13.5)	26 (13.8)	10 (12.5)	16 (16.2)	7 (12.7)	30 (14.1)	13 (13.1)
Black/African American	5 (4.1)	1 (1.4)	2 (1.1)	1 (1.3)	3 (3.0)	0	4 (1.9)	2 (2.0)
Other	8 (6.5)	6 (8.1)	8 (4.2)	3 (3.8)	6 (6.1)	4 (7.3)	10 (4.7)	5 (5.1)
ISS stage at baseline, n (%)								
I	62 (50.4)	37 (50.0)	85 (45.0)	42 (52.5)	53 (53.5)	27 (49.1)	94 (44.1)	52 (52.5)
II	36 (29.3)	23 (31.1)	67 (35.4)	25 (31.3)	29 (29.3)	18 (32.7)	74 (34.7)	30 (30.3)
III	24 (19.5)	14 (18.9)	37 (19.6)	13 (16.3)	17 (17.2)	10 (18.2)	44 (20.7)	17 (17.2)
Unknown	1 (0.8)	0	0	0	0	0	1 (0.5)	0
Cytogenetic risk group per FISH,*n (%)								
High risk	16 (13.0)	11 (14.9)	32 (16.9)	15 (18.8)	13 (13.1)	8 (14.5)	35 (16.4)	18 (18.2)
Standard risk	36 (29.3)	26 (35.1)	68 (36.0)	26 (32.5)	29 (29.3)	23 (41.8)	75 (35.2)	29 (29.3)
Unknown risk	71 (57.7)	37 (50.0)	89 (47.1)	39 (48.8)	57 (57.6)	24 (43.6)	103 (48.4)	52 (52.5)
Mean CrCL, mL/min (SD)	86.96 (33.59)	81.06 (36.21)	85.09 (31.63)	82.71 (29.28)	89.55 (35.16)	80.75 (35.43)	84.10 (31.11)	82.56 (31.22)
Median prior lines of therapy, n (range)	2.0 (1–3)	2.0 (1–4)	1.0 (1–3)	1.0 (1–3)	2.0 (1–3)	2.0 (1–3)	1.0 (1–3)	1.0 (1–4)
Previous therapies, n (%)								
Bortezomib or ixazomib	118 (95.9)	65 (87.8)	171 (90.5)	72 (90.0)	96 (97.0)	50 (90.9)	193 (90.6)	87 (87.9)
Refractory to bortezomib or ixazomib in any previous regimen	46 (37.4)	29 (39.2)	54 (28.6)	26 (32.5)	43 (43.4)	22 (40.0)	57 (26.8)	33 (33.3)
Lenalidomide	123 (100)	74 (100)	0	0	99 (100)	55 (100)	0	0
Refractory to lenalidomide in any previous regimen	99 (80.5)	55 (74.3)	0	0	99 (100)	55 (100)	0	0
Transplant	76 (61.8)	35 (47.3)	119 (63.0)	40 (50.0)	58 (58.6)	23 (41.8)	137 (64.3)	52 (52.5)
	KdD group (n=289)	Kd group (n=137)	KdD group (n=23)	Kd group (n=17)	KdD group (n=100)	Kd group (n=55)	KdD group (n=212)	Kd group (n=99)
Median age, years (range)	64.0 (29–84)	64.0 (35–82)	69.0 (42–76)	70.0 (51–83)	64.0 (33–84)	64.0 (36–77)	64.0 (29–83)	65.0 (35–83)
Race, n (%)								
White	227 (78.5)	110 (80.3)	16 (69.6)	13 (76.5)	80 (80.0)	42 (76.4)	163 (76.9)	81 (81.8)
Asian	40 (13.8)	16 (11.7)	6 (26.1)	4 (23.5)	14 (14.0)	11 (20.0)	32 (15.1)	9 (9.1)
Black/African American	7 (2.4)	2 (1.5)	0	0	1 (1.0)	1 (1.8)	6 (2.8)	1 (1.0)
Other	15 (5.2)	9 (6.6)	1 (4.3)	0	5 (5.0)	1 (1.8)	11 (5.2)	8 (8.1)
ISS stage at baseline, n (%)								
I	129 (44.6)	70 (51.1)	18 (78.3)	9 (52.9)	43 (43.0)	27 (49.1)	104 (49.1)	52 (52.5)
II	98 (33.9)	40 (29.2)	5 (21.7)	8 (47.1)	29 (29.0)	15 (27.3)	74 (34.9)	33 (33.3)
III	61 (21.1)	27 (19.7)	0	0	28 (28.0)	13 (23.6)	33 (15.6)	14 (14.1)
Unknown	1 (0.3)	0	0	0	0	0	1 (0.5)	0
Cytogenetic risk group per FISH,*n (%)								
High risk	46 (15.9)	24 (17.5)	2 (8.7)	2 (11.8)	14 (14.0)	11 (20.0)	34 (16.0)	15 (15.2)
Standard risk	92 (31.8)	44 (32.1)	12 (52.2)	8 (47.1)	33 (33.0)	19 (34.5)	71 (33.5)	33 (33.3)
Unknown risk	151 (52.2)	69 (50.4)	9 (39.1)	7 (41.2)	53 (53.0)	25 (45.5)	107 (50.5)	51 (51.5)
Mean CrCL, mL/min (SD)	85.45 (32.25)	82.11 (31.70)	90.63 (35.83)	80.33 (40.88)	85.22 (29.22)	78.08 (31.14)	86.12 (34.00)	84.04 (33.48)
Median prior lines of therapy, n (range)	2.0 (1–3)	2.0 (1–4)	1.0 (1–3)	1.0 (1–3)	2.0 (1–3)	2.0 (1–4)	1.0 (1–3)	1.0 (1–3)
Previous therapies, n (%)								
Bortezomib or ixazomib	289 (100.0)	137 (100.0)	0	0	100 (100.0)	55 (100.0)	189 (89.2)	82 (82.8)
Refractory to bortezomib or ixazomib in any previous regimen	100 (34.6)	55 (40.1)	0	0	100 (100.0)	55 (100.0)	0	0
Lenalidomide	118 (40.8)	65 (47.4)	5 (21.7)	9 (52.9)	46 (46.0)	29 (52.7)	77 (36.3)	45 (45.5)
Refractory to lenalidomide in any previous regimen	96 (33.2)	50 (36.5)	3 (13.0)	5 (29.4)	43 (43.0)	22 (40.0)	56 (26.4)	33 (33.3)
Transplant	178 (61.6)	67 (48.9)	17 (73.9)	8 (47.1)	51 (51.0)	17 (30.9)	144 (67.9)	58 (58.6)

CrCL, creatinine clearance; FISH, fluorescence in situ hybridization; ISS, International Staging System; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone, and daratumumab; SD, standard deviation.

Efficacy

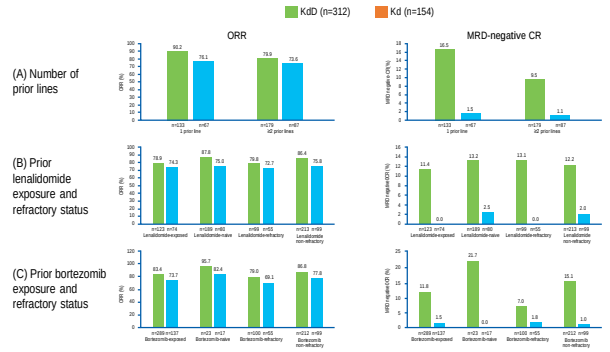
- PFS results by number of prior lines of therapy, prior lenalidomide exposure and refractory status, and prior bortezomib exposure and refractory status are summarized in Figure 2
- The ORR and MRD-negative CR rates by number of prior lines of therapy, prior lenalidomide exposure and refractory status, and prior bortezomib exposure and refractory status are summarized in Figure 3

Figure 2. PFS in prior treatment subgroups



CI, confidence interval; HR, hazard ratio; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone, and daratumumab; NE, not estimable; PFS, progression-free survival.
*Medians were estimated using the Kaplan-Meier method; corresponding 95% CIs were estimated. †HRs and corresponding 95% CIs were estimated using a stratified Cox proportional hazards model. ‡Based on the Interactive Voice and Web Response System at the time of randomization.

Figure 3. ORR and MRD-negative CR rates by (A) number of prior lines of therapy, (B) prior lenalidomide exposure and refractory status, and (C) prior bortezomib exposure and refractory status*,†



CR, complete response; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone, and daratumumab; MRD, minimal residual disease; ORR, overall response rate.
*Based on the intention-to-treat population. †Disease assessments were made per International Myeloma Working Group Uniform Response Criteria.[11] MRD-negative CR was assessed in the bone marrow using next generation sequencing at a threshold of 1 tumor cell per 10^{-5} white cells at 12 months (±4 weeks).

Safety by prior lines of therapy

- Adverse events (AEs) by number of prior lines are summarized in Table 2

Table 2. AEs of interest by prior lines of therapy*

	1 prior line		≥2 prior lines	
	KdD group (n=131)	Kd group (n=66)	KdD group (n=177)	Kd group (n=87)
Any AE	129 (98.5)	63 (95.5)	177 (100.0)	84 (96.6)
Grade ≥3 AE	108 (82.4)	49 (74.2)	145 (81.9)	64 (73.6)
Serious AE	74 (56.5)	31 (47.0)	99 (55.9)	39 (44.8)
Fatal AE	9 (6.9)	4 (6.1)	21 (11.9)	4 (4.6)
AEs of special interest				
Respiratory tract infection (HLGT)	98 (74.8)	39 (59.1)	127 (71.8)	45 (51.7)
Viral infection (JMQ)	25 (19.1)	5 (7.6)	38 (21.5)	17 (19.5)
Peripheral neuropathy (SMQN)	19 (14.5)	5 (7.6)	34 (19.2)	8 (9.2)
Daratumumab-related infusion reaction (AMQN)†	26 (19.8)	0	30 (16.9)	0
Cardiac failure (SMQN)	8 (6.1)	9 (13.6)	15 (8.5)	7 (8.0)
Acute renal failure (SMQN)	4 (3.1)	4 (6.1)	14 (7.9)	8 (9.2)
Ischemic heart disease (SMQN)	6 (4.6)	3 (4.5)	7 (4.0)	2 (2.3)

AE, adverse event; AMQN, Amgen MedDRA Query–Narrow; HLGT, High-level group terms; JMQ, Janssen MedDRA Query; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone, and daratumumab; SMQN, Standardized MedDRA Query–Narrow.
All values are n (%).
*Safety population included all patients with ≥1 study treatment dose. †Event on same date or next date of any daratumumab dosing.

CONCLUSIONS

- In this subgroup analysis of CANDOR, the benefit-risk profile of KdD vs Kd was generally consistent across subgroups, regardless of number of prior lines of therapy or prior treatment with lenalidomide or bortezomib
  - MRD-negative CR rates were higher for the KdD group, regardless of previous drug exposure or refractory status
  - The PFS HR (KdD vs Kd) was comparable between 1 and ≥2 prior lines subgroups
  - Among patients categorized by previous lenalidomide treatment, the PFS HR was comparable between the lenalidomide-exposed and lenalidomide-refractory subgroups, but the observed PFS difference was lower in the lenalidomide-naive subgroup
  - The PFS HR was comparable across the bortezomib-exposed, bortezomib-naive, and bortezomib non-refractory subgroups, but the observed PFS difference was lower in the bortezomib-refractory subgroup
  - Similar to the primary CANDOR analysis, there were no new cardiovascular safety risks with the addition of daratumumab to carfilzomib-dexamethasone
- These results indicate that KdD is an important treatment option for patients with relapsed and/or refractory MM, including for those with one or multiple relapses, and for those with previous exposure to lenalidomide or bortezomib
- Earlier treatment with the KdD combination is expected to yield better depth of response and MRD negativity rates

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