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POSTER ABSTRACTS

653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

Carfilzomib, Daratumumab, and Dexamethasone (KdD) Vs Carfilzomib and Dexamethasone (Kd) for Relapsed/Refractory Multiple Myeloma (RRMM) in the Phase 3 Candor Study: Subgroup Analysis According to Renal Functioning

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Renal impairment frequently occurs in patients (pts) with multiple myeloma (MM) and is associated with poor survival outcomes. In the phase 3 CANDOR trial, carfilzomib, dexamethasone, and daratumumab (KdD) met its primary endpoint of prolonged progression-free survival (PFS) vs carfilzomib and dexamethasone (Kd) (28.4 vs 15.2 mo; hazard ratio [HR]: 0.64; 95% CI: 0.49-0.83) after 50 months (mo) follow-up (Usmani *Blood Adv* 2023). The study aim was to perform a prespecified subgroup analysis of efficacy and safety by baseline renal function in pts with relapsed/refractory MM (RRMM) receiving KdD vs Kd in the CANDOR trial.

Adult pts with RRMM were randomized 2:1 to KdD or Kd in the open-label, phase 3 CANDOR trial (NCT03158688) (Dimopoulos *Lancet* 2020). RRMM pts with measurable disease who had received 1-3 prior lines of therapy, with partial response or better to ≥1 line of therapy were eligible. Dialysis was an exclusion criterion. All pts received carfilzomib (K) as a 30-min intravenous (IV) infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m ^{2} on days 1 and 2 during cycle 1 and 56 mg/m ^{2} thereafter). Daratumumab (8 mg/kg) was administered IV on days 1 and 2 of cycle 1 and at 16 mg/kg once weekly for the remaining doses of the first 2 cycles, then every 2 weeks (wks) for 4 cycles (cycles 3 to 6), and every 4 wks thereafter. All pts received 40 mg dexamethasone oral or IV weekly (20 mg for pts >75 years). Pts were grouped according to baseline renal function (creatinine clearance [CrCl] ≥15-<60 mL/min, ≥60-<90 mL/min, and ≥90 mL/min (Dimopoulous *J Clin Onc* 2016). The Cockcroft-Gault formula was used to calculate baseline and on study renal function. PFS and overall response rates (ORRs) were protocol-derived/investigator-assessed. Median PFS was estimated using the Kaplan-Meier method, with HRs and corresponding 95% CIs estimated using a stratified Cox proportional hazards model. Response rates were summarized descriptively, with odds ratios (ORs) and corresponding 95% CIs estimated by Mantel-Haenszel methods using stratified randomization. Renal response was defined as pt CrCl improvement to ≥60 mL/min in any 2 consecutive study visits in pts with baseline CrCl of <50 mL/min.

A total of 466 pts were randomized; renal subgroups were CrCl ≥15-<60 mL/min (renal impairment), n=67 and n=36; ≥60-<90 mL/min, n=112 and n=57; and ≥90 mL/min, n=132 and n=61 for KdD and Kd, respectively. One pt in the KdD arm with missing baseline CrCl was excluded. Baseline characteristics were generally balanced between treatment arms and renal subgroups (**Table 1**). After a median follow-up of ~50 mo (data cutoff: April 15, 2022), pts treated with KdD vs Kd had improved median PFS across all renal subgroups; median PFS was 24.9 mo vs 8.4 mo (HR, 0.61; 95% CI, 0.35-1.06), 31.6 mo vs 19.9 mo (0.63; 0.41-0.96), and 27.4 mo vs 15.3 mo (0.64; 0.43-0.95) for pts with CrCl ≥15-<60 mL/min, ≥60-<90 mL/min, and ≥90 mL/min, respectively (**Table 2**). Median overall survival (OS) for KdD vs Kd was 44.6 mo vs 25.2 mo (HR, 0.58; 95% CI, 0.32-1.03), 48.0 mo vs 43.7 mo (0.91; 0.58-1.43), and NE vs NE (0.74; 0.46-1.20), respectively. ORRs were 87% vs 50% (OR, 8.02; 95% CI, 2.84-22.65);

85% vs 82% (1.26; 0.49-3.27); and 86% vs 80% (1.59; 0.69-3.68), respectively. Complete response rates were 36% vs 8% (7.43; 1.85-29.74); 44% vs 21% (3.17; 1.47-6.87); and 38% vs 21% (2.20; 1.08-4.49), respectively. Among 38 KdD pts and 27 Kd pts with baseline CrCl <50 mL/min, the renal response rate was 21% vs 11% (OR, 2.65; 95% CI, 0.63-11.11), respectively.
In pts with renal impairment, most common grade ≥3 TEAEs were thrombocytopenia (38% [25/66] vs 23% [8/35]), hypertension (24% [16/66] vs 20% [7/35]), anemia (24% [16/66] vs 29% [10/35]), and pneumonia (23% [15/66] vs 9% [3/35]) in the KdD arm vs Kd arm. Most common grade ≥3 TEAEs of interest in pts with renal impairment were respiratory tract infections (32% vs 14%), hypertension (26% vs 20%), and infusion reaction on the same date of any carfilzomib dosing (14% vs 11%), respectively. Grade ≥3 acute renal failure occurred in 6% vs 11%, 4% vs 7%, and 2% vs 3% of pts with baseline CrCl ≥15-<60 mL/min, ≥60-<90 mL/min, and ≥90 mL/min, respectively. Overall, the safety profile in each subgroups was consistent with the established carfilzomib safety profile (Usmani *Blood Adv* 2023).
KdD showed consistent clinical benefit vs Kd in median PFS, ORR and OS irrespective of the baseline renal function. Safety findings were consistent with the overall study population.

Disclosures Landgren: *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Adaptive:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Theradex:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees; *Merck:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Membership on independent data monitoring committees. **Siegel:** *BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Karyopharm:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Celularity Scientific:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Oriol:** *GSK:* Consultancy, Honoraria, Speakers Bureau; *Amgen:* Consultancy, Other: Consulting fees; *BMS/Celgene:* Consultancy, Honoraria, Speakers Bureau. **Najdi:** *Amgen Inc.:* Current Employment, Current holder of *stock options* in a privately-held company. **Li:** *Amgen Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Mezzi:** *Amgen Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Shu:** *Parexel:* Current Employment. **Quach:** *Karyopharm:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: receipt of study materials, Research Funding; *Sanofi:* Consultancy, Other: receipt of study materials; *BMS:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Leadership or fiduciary role; *GSK:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: receipt of study materials; Leadership or fiduciary role, Research Funding.

Table 1. Baseline Characteristics

	≥15–<60 mL/min		≥60–<90 mL/min		≥90 mL/min	
	KdD n=67	Kd n=36	KdD n=112	Kd n=57	KdD n=132	Kd n=61
ISS stage at baseline*, n (%)						
I	2 (3)	3 (8)	14 (13)	7 (12)	21 (16)	15 (25)
II	19 (28)	13 (36)	29 (26)	16 (28)	34 (26)	11 (18)
III	13 (19)	7 (19)	7 (6)	7 (12)	5 (4)	0
Unknown	33 (49)	13 (36)	62 (55)	27 (47)	72 (55)	35 (57)
High risk cytogenetics†, n (%)	15 (22)	9 (25)	16 (14)	11 (19)	17 (13)	6 (10)
Number of prior transplants, n (%)						
1	23 (34)	8 (22)	57 (51)	26 (46)	81 (61)	32 (52)
2	7 (10)	1 (3)	9 (8)	4 (7)	16 (12)	4 (7)
>2	0	0	0	0	1 (1)	0
Number of prior therapies, n (%)						
1	30 (45)	14 (39)	52 (46)	30 (53)	61 (46)	26 (43)
2–3	37 (55)	22 (61)	60 (54)	27 (47)	71 (54)	34 (56)
>3	0	0	0	0	0	1 (2)
Prior therapies						
Bortezomib	62 (93)	31 (86)	101 (90)	47 (82)	123 (93)	56 (92)
Lenalidomide	24 (36)	21 (58)	52 (46)	24 (42)	47 (36)	29 (48)
PI	63 (94)	33 (92)	103 (92)	49 (86)	123 (93)	57 (93)
IMiD	33 (49)	26 (72)	82 (73)	39 (68)	90 (68)	45 (74)

Excluded patient whose baseline renal impairment with missing value (KdD, n=1; Kd, n=0).
*Revised ISS stage: R-Stage 1: ISS stage 1 and standard risk group by FISH and normal LDH; R-Stage 2: neither R-ISS stage 1 nor 3; and R-Stage 3: ISS stage 3 and (either high-risk group by FISH or high LDH).
†The high-risk group consisted of the genetic subtypes t(4; 14), t(14; 16), or deletion17p.
FISH, fluorescence in situ hybridization; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone, and daratumumab; LDH, lactate dehydrogenase; IMiD, immunomodulatory drugs; ISS, International Staging System; PI, proteasome inhibitor.

Table 2. Efficacy and Safety Outcomes in KdD vs Kd Cohort

	≥15–<60 mL/min		≥60–<90 mL/min		≥90 mL/min	
	KdD n=67	Kd n=36	KdD n=112	Kd n=57	KdD n=132	Kd n=61
Median PFS (95% CI), mo	24.9 (13.0–41.8)	8.4 (3.3–32.8)	31.6 (20.3–43.2)	19.9 (11.1–33.2)	27.4 (18.7–35.1)	15.3 (10.8–20.3)
HR (KdD/Kd) (95% CI)	0.61 (0.35–1.06)		0.63 (0.41–0.96)		0.64 (0.43–0.95)	
Median OS, (95% CI), mo	44.6 (24.2, NE)	25.2 (12.4, NE)	48.0 (39.4, NE)	43.7 (35.4, NE)	NE (44.9, NE)	NE (34.6, NE)
HR (KdD/Kd) (95% CI)	0.58 (0.32, 1.03)		0.91 (0.58, 1.43)		0.74 (0.46, 1.20)	
ORR*, n (%)	58 (87)	18 (50)	95 (85)	47 (82)	113 (86)	49 (80)
OR (KdD/Kd) (95% CI)	8.02 (2.84–22.65)		1.26 (0.49–3.27)		1.59 (0.69–3.68)	
CR rate†, n (%)	24 (36)	3 (8)	49 (44)	12 (21)	50 (38)	13 (21)
OR (KdD/Kd) (95% CI)	7.43 (1.85–29.74)		3.17 (1.47–6.87)		2.20 (1.08–4.49)	
Treatment duration, wks, median (range)	67 (0–227)	21 (0–222)	90 (1–236)	56 (1–222)	76 (0–236)	47 (1.3–236)
Most common TEAEs‡	n=66	n=35	n=110	n=57	n=131	n=61
Grade ≥3, n (%)	59 (89)	32 (91)	96 (87)	45 (79)	117 (89)	43 (70)
Thrombocytopenia	25 (38)	8 (23)	23 (21)	10 (18)	28 (21)	7 (11)
Hypertension	16 (24)	7 (20)	24 (22)	13 (23)	32 (24)	7 (11)
Anemia	16 (24)	10 (29)	20 (18)	7 (12)	18 (14)	8 (13)
Pneumonia	15 (23)	3 (9)	20 (18)	6 (11)	22 (17)	5 (8)
TEAEs of interest, n (%)						
Respiratory tract infections	21 (32)	5 (14)	46 (42)	11 (19)	49 (37)	11 (18)
Hypertension	17 (26)	7 (20)	25 (23)	14 (25)	32 (24)	7 (11)
Infusion reaction (on same date of any carfilzomib dosing)	9 (14)	4 (11)	16 (15)	5 (9)	22 (17)	3 (5)
Cardiac failure	3 (5)	4 (11)	5 (5)	6 (11)	4 (3)	3 (5)
Viral infection	3 (5)	0	10 (9)	0	9 (7)	3 (5)
Acute renal failure	4 (6)	4 (11)	4 (4)	4 (7)	3 (2)	2 (3)
Dyspnea	6 (9)	1 (3)	4 (4)	2 (4)	6 (5)	1 (2)

Excluded patient whose baseline renal impairment with missing value (KdD, n=1; Kd, n=0).
*ORR is defined as the proportion of intent-to-treat patients who achieve stringent CR, CR, very good partial response, or partial response per the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) as their best response.
†CR rate is defined as the proportion of intent-to-treat patients who achieve stringent CR or CR per International Myeloma Working Group Uniform Response Criteria as their best response.
‡Grade ≥3 TEAEs include those reported in ≥15% of patients. TEAEs of interest include those reported in ≥5% of patients.
CR, complete response; HR, hazard ratio; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone, and daratumumab; mo, months; NE, not estimable; OR, odds ratio; ORR, overall response rate; OS, overall survival; TEAE, adverse event; wks, weeks.

Figure 1

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