LBA-6 Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (RRMM): Primary Analysis Results from the Randomized, Open-Label, Phase 3 Study Candor (NCT03158688)

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Introduction:

The use of lenalidomide (LEN) and bortezomib (BTZ) in newly diagnosed multiple myeloma (MM) patients (pts), along with continuous or maintenance therapy paradigm have improved survival outcomes. However, many pts progress while on these agents or discontinue them due to toxicity. There is a need for novel, efficacious, and tolerable regimens that can treat MM pts who are exposed or refractory to LEN or BTZ. The proteasome inhibitor carfilzomib and the anti-CD38 monoclonal antibody daratumumab have both been approved as single agents or as components of combination regimens for the treatment of RRMM. The combination of carfilzomib, dexamethasone, and daratumumab has been shown to be efficacious and safe in RRMM in the phase 1 study MMY1001 (Chari, *Blood* 2019). We present results from the primary analysis of CANDOR, a multicenter, phase 3, randomized study comparing carfilzomib, dexamethasone, and daratumumab (KdD) vs carfilzomib and dexamethasone (Kd) in RRMM pts.

Methods:

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. Pts were randomized 2:1 to KdD or Kd. 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/m² on days 1 and 2 during cycle 1 and 56 mg/m² 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 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). The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall response rate (ORR), minimal residual disease (MRD) negative-complete response at 12 months (threshold, 10⁻⁵ cells), overall survival (OS), time to response, and safety.

Results:

466 pts (KdD: 312; Kd: 154) from 102 sites worldwide were randomized. Baseline characteristics were balanced between the two arms. Median age was 64 years. Of the randomized pts, 42.3% and 90.3% received previous LEN- and BTZ-containing regimens, respectively. 33% of pts were LEN-refractory. The primary endpoint of PFS was met after a median follow-up of 16.9 mo and 16.3 mo for the KdD and Kd arms, respectively. Median PFS was not reached for the KdD arm vs 15.8 mo for the Kd arm (HR, 0.63; 95% CI, 0.46-0.85; P=0.0014; Figure). PFS HRs favored KdD vs Kd across prespecified subgroups. Importantly, median PFS (KdD vs Kd) was not reached vs 12.1 mo in the LEN-exposed group (HR, 0.52; 95% CI, 0.34-0.80), and was not reached vs 11.1 mo in the LEN-refractory group (HR, 0.45; 95% CI, 0.28-0.74). Median time to first response was 1 mo in the KdD and Kd arms. ORR was 84.3% vs 74.7% (P=0.0040), and the rate of complete response or better was 28.5% vs 10.4%. MRD-negative complete response rate at 12 mo was 12.5% for KdD vs 1.3% for Kd (P<0.0001). Median OS was not reached in either arm at a median follow-up time of 17 mo (HR, 0.75; 95% CI, 0.49-1.13; P=0.08). Median treatment duration was longer in the KdD than Kd arm (70.1 vs 40.3 wks). The incidence of grade ≥3 AEs was 82.1% and 73.9% in the KdD and Kd arms, respectively. Serious AEs occurred in 56.2% (KdD) and 45.8% (Kd). The rate of treatment discontinuation due to AEs was similar in both arms (KdD, 22.4%; Kd, 24.8%). The frequency of grade ≥3 cardiac failure was 3.9% (KdD) and 8.5% (Kd); rate of cardiac failure event leading to K discontinuation was similar in the arms (3.9% and 4.6%). 5 deaths were reported as treatment-related, all in the KdD arm (pneumonia, sepsis, septic shock, acinetobacter infection, and cardio-respiratory arrest [n=1 each]). Additional efficacy endpoints, including key subgroup analyses will be presented.

Conclusion:

KdD resulted in a significant PFS benefit over Kd, with a 37% reduction in the risk of progression or death. Pts treated with KdD achieved deeper responses, with a nearly 10-times higher MRD negative-complete response rate vs Kd-treated pts. The PFS benefit of KdD was maintained across prespecified clinically important subgroups, particularly among LEN-exposed and LEN-refractory pts. AEs were generally manageable and the incidence of AEs leading to treatment discontinuation was similar in the arms. Overall, KdD was associated with a favorable benefit-risk

profile and represents an efficacious new regimen for RRMM, including for LEN-exposed and/or LEN-refractory pts.

	KdD group (n=312)	Control group (Kd) (n=154)
Disease progression or death – no. (%)	110 (35.3)	68 (44.2)
Median progression-free survival – mo	NE	15.8
Hazard ratio for KdD group vs. control group (95% CI)	0.63 (0.46–0.85)	
P-value (1-sided)	0.0014	

No. at Risk

KdD group	312	279	236	211	189	165	57	14	0
Control group	154	122	100	85	70	55	13	2	0