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Carfilzomib, dexamethasone and daratumumab in relapsed or refractory multiple myeloma: results of the phase III study CANDOR by prior lines of therapy

Running title: Prior lines and therapy analysis of CANDOR

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Bortezomib- and lenalidomide-based therapies have become standard frontline treatment for multiple myeloma (MM)[1] resulting in many patients being refractory to bortezomib or lenalidomide at first relapse.[2,3] This may negatively impact the efficacy of later lines of therapy (LOT)[4] and makes optimal sequencing of MM therapies challenging.

Carfilzomib is a second-generation proteasome inhibitor approved in combination with dexamethasone (Kd), and also with lenalidomide (KRd), and daratumumab (KdD) for patients with relapsed/refractory MM (RRMM).[5,6] Clinically meaningful improvements in progression-free survival (PFS) and overall survival have been observed with KRd vs. Rd (ASPIRE) and Kd vs. Vd (ENDEAVOR), regardless of the type or number of prior LOT, indicating the superiority of carfilzomib-based regimens relative to previous standards of care in patients with RRMM previously exposed to lenalidomide or bortezomib.[7–11] Improved clinical outcomes have also been observed in several MM trials combining daratumumab, an anti-CD38 monoclonal antibody, with standards of care, including proteasome inhibitors.[12,13] In the phase III, randomised, open-label CANDOR trial, KdD improved PFS vs. Kd (median PFS not reached vs. 15.8 months; hazard ratio [HR] 0.63; 95% confidence interval [CI] 0.46–0.85; two-sided *P*=0.0027) in patients with RRMM (42% of whom were lenalidomide-exposed).[12]

Given the challenges of effectively treating patients with RRMM and the common use of frontline bortezomib and lenalidomide, we performed a pre-planned subgroup analysis of CANDOR to evaluate efficacy and safety by number of prior LOT (1 vs. ≥2), as well as a post hoc analysis of patients with previous exposure or refractory status to bortezomib/ixazomib or

lenalidomide. The study design and patient eligibility criteria for the CANDOR trial (NCT03158688) have been previously described[12] and are summarized in the Supplement.

A total of 466 patients were randomised 2:1 to either KdD (*n*=312) or Kd (*n*=154) between 13 June 2017 and 25 June 2018 (data cut-off: 14 July 2019).[12] Across both arms, 43% had one prior LOT, 57% had ≥2 prior LOT, 42% were lenalidomide-exposed, 33% were lenalidomide-refractory, 91% were bortezomib/ixazomib-exposed, and 33% were bortezomib/ixazomib-refractory. Baseline characteristics were generally balanced between arms across subgroups **(Table S1)**.

Results from the subgroup analyses were generally consistent with the overall PFS HR of the study. Among patients with one prior LOT, the PFS HR (95% CI) for KdD vs. Kd was 0.68 (0.40–1.14) compared to 0.61 (0.42–0.88) for ≥2 prior LOT **(Fig 1)**. For patients with one prior LOT, the PFS HR was 0.90 (0.48–1.70) for lenalidomide-naive patients, 0.30 (0.10–0.86) for lenalidomide-exposed patients, and 0.11 (0.02–0.52) for lenalidomide-refractory patients. ORR was 90.2% vs. 76.1% (odds ratio [OR] 2.90; 1.30–6.46) among patients with one prior LOT compared to 79.9% vs. 73.6% (OR 1.43; 0.78–2.60) for ≥2 prior LOT **(Fig 2A)**. For patients with one prior LOT, minimal residual disease (MRD)-negative complete response (CR) rate was 16.5% vs. 1.5% (OR 13.08; 1.72–99.31) compared to 9.5% vs. 1.1% (OR 9.03; 1.18–68.97) for ≥2 prior LOT **(Fig 2A)**.

The PFS HR (95% CI) was 0.71 (0.45–1.12) for lenalidomide-naive patients, 0.53 (0.34–0.82) for lenalidomide-exposed patients, and 0.47 (0.29–0.78) for lenalidomide-refractory patients **(Fig 1)**. The ORR was 87.8% vs. 75.0% (OR 2.41; 95% CI 1.23–4.69) for lenalidomide-naive patients, 78.9% vs. 74.3% (OR 1.29; 0.65–2.54) for lenalidomide-exposed patients, and 79.8% vs. 72.7% (OR 1.48; 0.69–3.20) for lenalidomide-refractory patients **(Fig 2B)**. The MRD-negative CR rate was 13.2% vs. 2.5% (OR 5.95; 1.37–25.74) for lenalidomide-naive patients, 11.4% vs. 0% (OR non-estimable [NE]; NE–NE) for lenalidomide-exposed patients, and 13.1% vs. 0% (OR NE; NE–NE) for lenalidomide-refractory patients **(Fig 2B)**.

The PFS HR (95% CI) was 0.58 (0.17–2.06) for bortezomib/ixazomib-naive patients, 0.62 (0.45–0.85) for bortezomib/ixazomib-exposed patients, and 0.84 (0.52–1.36) for bortezomib/ixazomib-refractory patients **(Fig 1)**. The ORR was 95.7% vs. 82.4% (OR 4.71; 95% CI 0.45–49.94) for bortezomib/ixazomib-naive patients, 83.4% vs. 73.7% (OR 1.79; 1.10–2.92) for bortezomib/ixazomib-exposed patients, and 79.0% vs. 69.1% (OR 1.68; 0.80–3.55) for bortezomib/ixazomib-refractory patients **(Fig 2C)**. The MRD-negative CR rate was 21.7% vs. 0% (OR NE; NE–NE) for bortezomib/ixazomib-naive patients, 11.8% vs. 1.5% (OR 9.00; 2.13–38.03) for bortezomib/ixazomib-exposed patients, and 7.0% vs. 1.8% (OR 4.07; 0.49–33.93) for bortezomib/ixazomib-refractory patients **(Fig 2C)**.

Best overall responses by LOT and prior bortezomib/ixazomib or lenalidomide exposure/refractory status are shown in **Tables S2-4**.

Rates of any grade adverse events (AEs), grade ≥3 AEs, AEs leading to carfilzomib or daratumumab discontinuation, and deaths due to AEs were generally consistent across subgroups for KdD and Kd (summarized in **Table S5**).

The primary analysis of CANDOR demonstrated a clinically meaningful improvement in PFS, ORR, and MRD-negative CR with KdD vs. Kd in patients with RRMM with 1–3 prior LOT.[12] In this subgroup analysis of CANDOR, efficacy and safety results were generally consistent with the benefit of KdD over Kd observed for the overall analyses in the intention-to-treat population. At a median follow-up of ~17 months, PFS HRs for KdD vs. Kd ranged from 0.47–0.84 across subgroups, comparable to the statistically significant PFS HR of 0.63 observed in the CANDOR primary analysis. MRD-negative CR rates were higher for the KdD group than the Kd group, regardless of previous drug exposure/refractory status.

Significant challenges exist when treating RRMM, given that efficacy diminishes with each subsequent treatment.[14] Effective treatments are needed at first relapse to achieve deep and durable responses before further resistance develops. Our analysis showed a consistent benefit with PFS HRs favouring KdD vs. Kd regardless of prior treatment, consistent with other studies

showing the value of adding agents with distinct mechanisms of action to established doublets to overcome treatment resistance and enhance clinical efficacy in RRMM. [15]

Due to widespread use of frontline lenalidomide therapy for MM, there is also a need for effective and tolerable lenalidomide-free regimens for later lines. Our subgroup analysis of CANDOR showed evidence that PFS HRs favoured KdD vs. Kd, with median PFS not reached in both lenalidomide-exposed and lenalidomide-refractory patients treated with KdD after a median follow-up of ~17 months. These findings align with results from the overall population in the primary CANDOR analysis, which also reported that median PFS was not reached with KdD,[12] and compare favourably with the median PFS reported for other lenalidomide-free regimens in lenalidomide-exposed or -refractory populations.[2]

In the safety analysis, rates of grade ≥3 AEs and serious AEs were consistent for KdD and Kd across subgroups. As in the primary CANDOR population, there were no new cardiovascular safety risks with the addition of daratumumab to carfilzomib-dexamethasone in this analysis by prior treatment.

Although subgroups were prespecified, the CANDOR study was not statistically powered for subgroup analyses and results should be interpreted with caution.

In conclusion, prior therapy subgroup analyses results were generally consistent with the favourable benefit-risk profile of KdD in the CANDOR primary analysis. These results uphold KdD as an important treatment option for patients with RRMM, including for those with previous exposure or resistance to bortezomib/ixazomib or lenalidomide.

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Author contributions

All authors (HQ, AN, OS, CPV, KK, TF, AS, SZU, SG, KS, SD, KW, MO, AZK, MVM) 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 HQ, AN, OS, CPV, KK, TF, AS, SZU, SG, KS, SD, KW, and MVM.

Conflicts of interest

HQ reports grants from Celgene and Amgen; consultancy and/or membership on an advisory committee from Takeda, GlaxoSmithKline, Karyopharm, Celgene and Janssen; and free drug for investigator-initiated study from Sanofi. **AN** reports consultancy and/or membership on an advisory committee for Spectrum Pharmaceuticals, Bristol-Myers Squibb, Adaptive Biotechnologies, Amgen, Celgene, Takeda, GlaxoSmithKline and Janssen. **OS** has no conflicts to report. **CPV** has received honoraria from Johnson & Johnson, Celgene, Amgen and Takeda. **KK** reports research funding from Celgene and has received honoraria from Takeda, Celgene, Amgen and Janssen. **TF** served as a consultant or advisor for Janssen, Celgene, Amgen, Takeda, Karyopharm and Oncopeptides, and served on the speakers' bureau for Janssen, Celgene and Takeda. **AS** has received honoraria and research funding from Celgene. **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 BMS and Pharmacyclics. **SG** has no conflicts to report. **KS** reports research funding from Ono; honoraria and research funding from BMS; and honoraria from Takeda, Janssen and Celgene. **SD** has no conflicts to report. **KW** reports honoraria, consultancy fees and research funding from Amgen, Celgene, Janssen and Sanofi; honoraria and consultancy fees from BMS, Adaptive Biotech and Takeda; honoraria from GSK; and consultancy fees from Juno. **MO** and **AZ-K** report employment and equity ownership in Amgen. **M-VM** reports consulting fees from Janssen, Celgene, Amgen, Takeda, AbbVie, GSK, Pharmamar, Adaptive and EDOMundipharma.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Methods

Table S1. Baseline characteristics by subgroup.

Table S2. Best overall response by number of prior lines of therapy.

Table S3. Best overall response by prior lenalidomide exposure.

Table S4. Best overall response by prior bortezomib/ixazomib exposure.

Table S5. Safety summary by subgroup.

References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Chronic Myeloid Leukemia Version 3.2020. Fort Washington, PA: National Comprehensive Cancer Network; 2020.
2. Moreau P, Zamagni E, Mateos MV. Treatment of patients with multiple myeloma progressing on frontline-therapy with lenalidomide. *Blood Cancer J.* 2019;**9:**38.
3. Migkou M, Gavriatopoulou M, Terpos E, Dimopoulos MA. Optimizing therapy in bortezomib-exposed patients with multiple myeloma. *Expert Rev Hematol.* 2018;**11:**463–9.
4. Harousseau JL, Attal M. How I treat first relapse of myeloma. *Blood.* 2017;**130:**963–73.
5. KYPROLIS® (carfilzomib) [package insert]. Thousand Oaks, CA: Amgen, Inc.; 2020.
6. KYPROLIS® (carfilzomib) EPAR – Product Information. European Medicines Agency; 2020.
7. Siegel DS, Dimopoulos MA, Ludwig H, Facon T, Goldschmidt H, Jakubowiak A, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol.* 2018;**36:**728–34.
8. Dimopoulos MA, Goldschmidt H, Niesvizky R, Joshua D, Chng W-J, Oriol A, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2017;**18:**1327–37.
9. Dimopoulos MA, Stewart AK, Masszi T, Spicka I, Oriol A, Hajek R, et al. Carfilzomib-lenalidomide-dexamethasone vs lenalidomide-dexamethasone in relapsed multiple myeloma by previous treatment. *Blood Cancer J.* 2017;**7:**e554.
10. Moreau P, Joshua D, Chng W-J, Palumbo A, Goldschmidt H, Hajek R, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study. *Leukemia.* 2017;**31:**115–22.

11. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med.* 2015;**372:**142–52.

12. Dimopoulos M, Quach H, Mateos M-V, Landgren O, Leleu X, Siegel D, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): primary analysis results from a randomized, multicenter, open-label, phase 3 study. *Lancet.* 2020;**18:**396:186–97.

13. Palumbo A, Chanan-Khan A, Weisel K, Nooka AJ, Masszi T, Beksac M, et al; CASTOR Investigators. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med.* 2016;**375:**754–66.

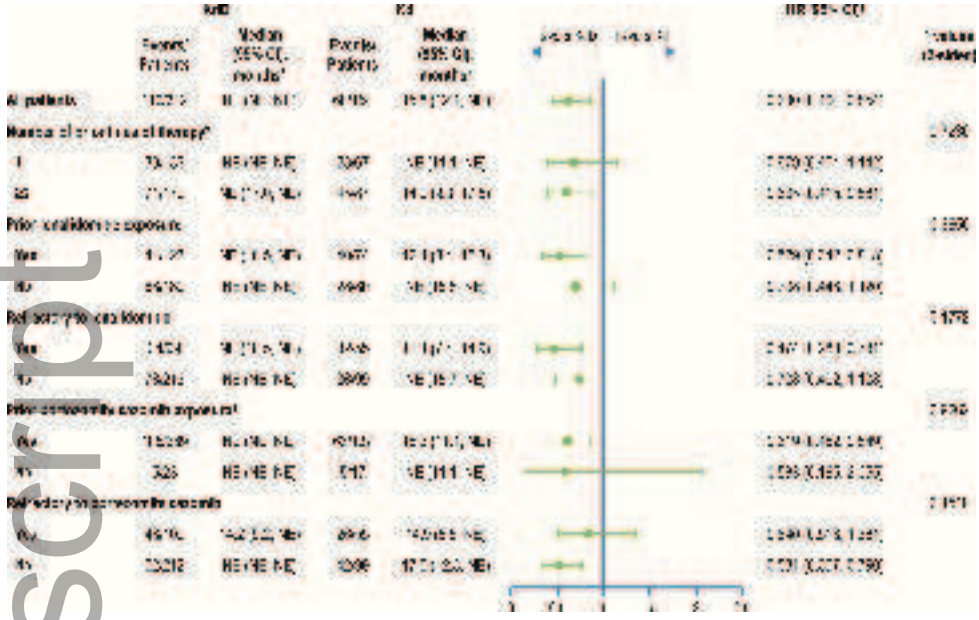
14. Kumar SK, Therneau TM, Gertz MA, Lacy MQ, Dispenzieri A, Rajkumar SV, et al. Clinical course of patients with relapsed multiple myeloma. *Mayo Clin Proc.* 2004;**79:**867–74.

15. Boudreault JS, Touzeau C, Moreau P. Triplet combinations in relapsed/refractory myeloma: update on recent phase 3 trials. *Expert Rev Hematol.* 2017;10:207–215.

Figure legends

Fig 1. 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. ‡Two-sided p values were calculated using Gail and Simon interaction tests. §Based on the Interactive Voice and Web Response System at the time of randomisation. ǁFive patients in the prior bortezomib/ixazomib subgroups were exposed to ixazomib (KdD, n=2; Kd, n=3).

Fig 2. ORR and MRD-negative CR rates by (A) number of prior lines of therapy, (B) prior lenalidomide exposure and (C) prior bortezomib/ixazomib exposure. CR, complete response; Kd, carfilzomib and dexamethasone; KdD, carfilzomib, dexamethasone and daratumumab; MRD, minimal residual disease; NE, non-estimable; ORR, overall response rate. All p values are 1-sided and derived from Fisher's exact test. *Defined as achievement of CR (including stringent complete response) per IMWG-URC by IRC and MRD-negative status as assessed by NGS (10^{-5} sensitivity) at 12 months. †Five patients in the prior bortezomib/ixazomib subgroups were exposed to ixazomib (KdD, n=2; Kd, n=3).



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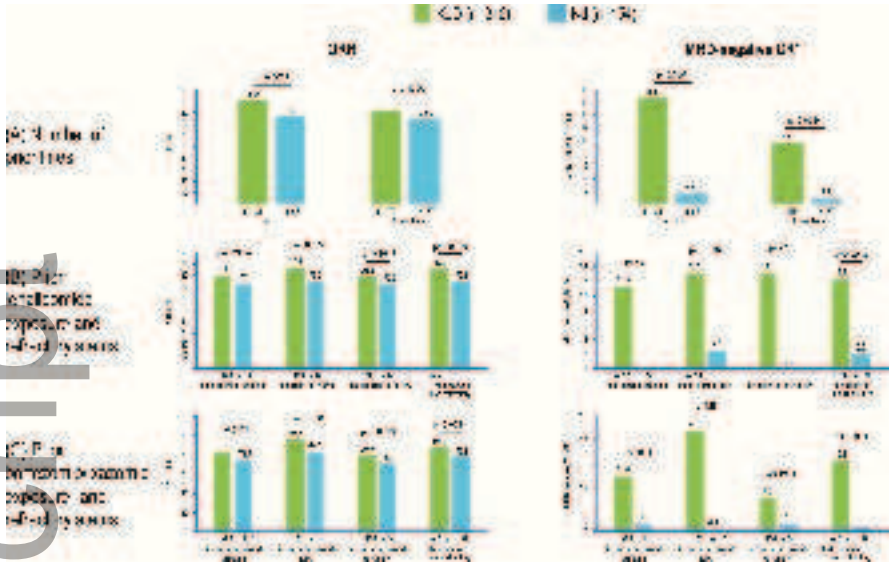

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