Carfilzomib in combination with dexamethasone and daratumumab (KdD) versus carfilzomib in combination with lenalidomide and dexamethasone (KRd) in relapsed and/or refractory multiple myeloma: an indirect treatment comparison

CO157

Jessie Wang, PhD[1]; Sachin Patel, MSc[2]; Hongbo Yang, PhD[3]; Xinglei Chai, PhD[3]; Shimin Bi, MS[3]; Mandy Du, PhD[3]

[1] Amgen Inc., Thousand Oaks, CA, USA; [2]Amgen Ltd, Uxbridge, UK; [3]Analysis Group Inc., Boston, MA, USA.

INTRODUCTION

- Carfilzomib in combination with dexamethasone and daratumomab (KdD) has been approved since 2020 in the US and Europe for the treatment of relapsed and/or refractory multiple myeloma (R/RMM) based on the CANDOR trial.[1,2] In this clinical trial, KdD was associated with a significantly longer progression-free survival (PFS) than carfilzomib in combination with dexamethasone (Kd).[3]
- Since 2015, carfilzomib in combination with lenalidomide (len) and dexamethasone (KRd) has been approved in the R/RMM population in the US and Europe based on the ASPIRE trial,[1,2] where carfilzomib was given for 18 cycles, resulting in KRd significantly improving PFS compared with lenalidomide and dexamethasone (Rd).[4]
- KdD and KRd were effective in both trials,[3,4] but their outcomes haven't been compared directly in a head-to-head trial.
- Comparing KdD and KRd among the len-exposed subgroup is of interest given the increased use of lenalidomide in the frontline MM setting.[5,6]
- An indirect treatment comparison (ITC) between KdD and KRd was deemed to be a feasible option using data from CANDOR and ASPIRE trials, respectively, in both the overall study population and in the len-exposed subgroup.

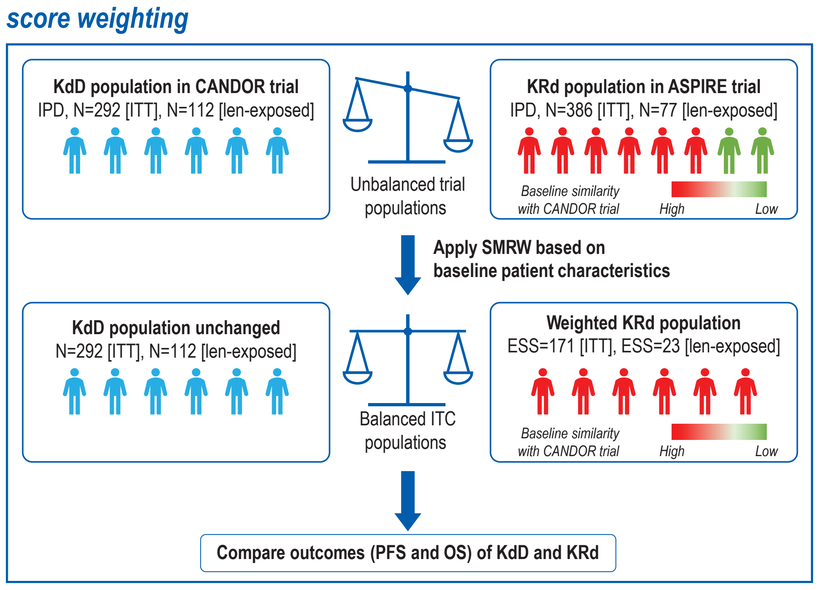
OBJECTIVES

- **We performed an ITC study comparing the PFS and overall survival (OS) between KdD and KRd using a patient-level ITC approach based on propensity score (PS) weighting among adult patients with R/RMM overall and in the len-exposed subgroup.**

METHODS

- Individual patient-level data from CANDOR (datacut: June 6, 2022; KdD; N = 292 [Intention to treat, ITT]; n = 112 [len-exposed]) and ASPIRE (datacut: January 31, 2018; KRd; N = 386 [ITT]; n = 77 [len-exposed]) trials were used for the analysis. The median follow-up time was 50.6 months for the KdD group, and 67.1 months in the unweighted sample for the KRd group.
- Patient-level ITC using propensity score weighting was used to compare KdD with KRd.[7,8] Patient characteristics were adjusted and balanced using PS weights calculated based on the standardized mortality ratio weighting (SMRW) approach to minimize bias due to confounding effects (**Figure 1**). Specifically, age, Eastern Cooperative Oncology Group (ECOG) status, international staging system (ISS) stage, creatinine clearance, β_2-microglobulin, time from diagnosis, time from last relapse, number of prior treatments, prior SCT use, prior lenalidomide exposure (in ITT populations only), prior bortezomib exposure, and refractory to last prior treatment were considered for adjustment. The list was informed based on literature and clinical expert advice.[9] Weight was set to 1 for the KdD arm and the reference KRd arm was weighted by the odds of treatment probability (PS/[1−PS]).

FIGURE 1. Methodology of the patient-level ITC based on propensity score weighting



ESS, effective sample size; ITT, intention to treat; IPD, individual patient data; ITC, indirect treatment comparison; KdD, carfilzomib in combination with dexamethasone and daratumumab; KRd, carfilzomib in combination with lenalidomide and dexamethasone; len, lenalidomide; OS, overall survival; PFS, progression-free survival; SMRW, standardized mortality ratio weighting.

- Standardized mean difference (SMD) was used to assess the balance in patient characteristics between CANDOR and ASPIRE after weighting, where a value less than 0.1 was considered as negligible imbalance.[10]
- For both trials, the PFS was defined as time from randomization until disease progression or death from any cause, whichever occurred first; OS was defined as time from randomization until death from any cause.
- PFS and OS of KdD vs KRd comparisons were performed in both the ITT populations as well as the len-exposed subgroup. Kaplan-Meier (KM) estimates, PFS and OS rates at 24 months, and hazard ratios (HRs) were calculated with 95% confidence intervals (CIs). After weighting, weighted Cox regression model was conducted to estimate HRs, and bootstrapping approach was used to estimate the standard error (SE) and 95% confidence interval (CI) of the HRs.
- Proportional hazard (PH) assumption was assessed to evaluate if HR for KdD and KRd groups was constant over time. If violated, time-varying weighted hazard models were assessed before and after 18 cycles (28-day cycle) in the ITT populations. Cycle 18 was chosen as the cutoff point as carfilzomib was discontinued after cycle 18 in the KRd arm. This time-varying model was not applied in the len-exposed subgroup due to small sample size.

REFERENCES

1. Kyprolis FDA label (updated 2022). https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/202714s034lbl.pdf
2. Kyprolis EMA SmPC. https://www.ema.europa.eu/en/documents/product-information/kyprolis-epar-product-information_en.pdf
3. Usmani SZ, et al (2023). *Blood Adv* 7(14):3739-3748.
4. Siegel DS, et al. (2018). *J Clin Oncol* 36(8):728-734.
5. Holstein SA, et al. (2018). *Ther Adv Hematol* 9(7):175-190.
6. Nijhof IS, et al. (2018). *Drugs* 78(1):19-37.
7. Desai RJ, and Franklin JM (2019). *BMJ.* 367: 15657
8. IQWiG (2020). https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2019/a19-43-wissenschaftliche-ausarbeitung-von-konzepten-zur-generierung-versorgungsnaher-daten-und-deren-auswertung-zum-zwecke-der-nutzenbewertung-von-arzneimitteln-nach-35a-sgb-v-rapid-report.11901.html (last visited: 11.09.2020).
9. Majer IM, et al (2019). *Pharmacoeconomics* 37(5):727-737.
10. Austin, P. C. (2015). *Stat Med* 34(28), 3661-3679.

DISCLOSURES AND ACKNOWLEDGEMENTS

JW and SP are employees of Amgen and stockholders.

HY, XC, SB, and MD are employees of Analysis Group, Inc which received consulting funds from Amgen.

This study was funded by Amgen Inc.

RESULTS
Indirect Comparisons of the ITT Populations

Imbalances Between KdD and KRd Had Been Greatly Reduced by Weighting (Table 1)

- Before weighting, prior lenalidomide exposure, prior bortezomib exposure, and refractory to last prior treatment had large standardized mean differences (SMDs; range: 0.414 to 0.707), indicating large differences existed between KdD and KRd treatment groups.
- After weighting of KRd ITT population, very satisfactory balance, i.e., SMD less than or on the margin of 0.1, was achieved for all of the important baseline prognostic variables included in the PS modelling.

TABLE 1. Baseline variables for KdD and KRd before and after weighting in the ITT populations

Baseline variable	ITT populations				
		Before weighting		After weighting	
	KdD N=292	KRd N=386	SMD	KRd N=286.4*	SMD
Age - n (%)					
<65 years	159 (54.5)	205 (53.1)	0.027	153.7 (53.7)	0.016
≥65 years	133 (45.5)	181 (46.9)		132.8 (46.3)	
ECOG - n (%)					
0	125 (42.8)	162 (42.0)	0.017	137.5 (48.0)	0.104
1-2	167 (57.2)	224 (58.0)		149.0 (52.0)	
ISS stage - n (%)					
I	138 (47.3)	184 (47.7)	0.008	140.2 (49.0)	0.034
II-III	154 (52.7)	202 (52.3)		146.2 (51.0)	
Creatinine clearance - n (%)					
<80 mL/min	127 (43.5)	194 (50.3)	0.136	123.1 (43.0)	0.011
≥80 mL/min	165 (56.5)	192 (49.7)		163.4 (57.0)	
Number of prior treatments - n (%)					
<3	230 (78.8)	296 (76.7)	0.050	233.8 (81.6)	0.072
≥ 3	62 (21.2)	90 (23.3)		52.6 (18.4)	
Prior SCT use - n (%)					
No	112 (38.4)	172 (44.6)	0.126	102.5 (35.8)	0.053
Yes	180 (61.6)	214 (55.4)		184.0 (64.2)	
Prior lenalidomide exposure - n (%)					
No	180 (61.6)	309 (80.1)	0.414	185.1 (64.6)	0.062
Yes	112 (38.4)	77 (19.9)		101.4 (35.4)	
Prior bortezomib exposure - n (%)					
No	21 (7.2)	132 (34.2)	0.707	22.0 (7.7)	0.019
Yes	271 (92.8)	254 (65.8)		264.4 (92.3)	
Refractory to last prior treatment - n (%)					
No	138 (47.3)	278 (72.0)	0.522	147.4 (51.5)	0.084
Yes	154 (52.7)	108 (28.0)		139.0 (48.5)	
β_2-microglobulin (mg/L) - mean (SD)	4.19 (2.80)	4.07 (2.09)	0.047	4.13 (2.29)	0.02
Time from diagnosis (months) - mean (SD)	47.72 (34.64)	45.07 (35.33)	0.076	50.16 (42.52)	0.063
Time from last relapse (months) - mean (SD)	4.71 (10.53)	4.50 (7.20)	0.024	5.20 (8.02)	0.052

ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; ISS, International staging system; KdD, carfilzomib in combination with dexamethasone and daratumumab; KRd, carfilzomib in combination with lenalidomide and dexamethasone; SCT, stem cell transplant; SD, standard deviation; SMD, standardized mean difference.

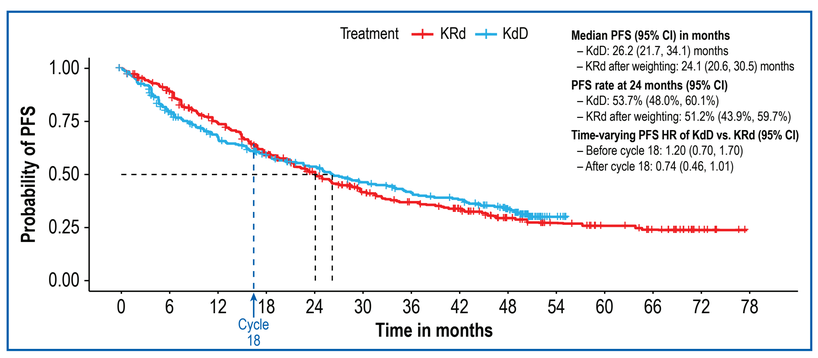
Note:

*For ITT populations, sample size after weighting (i.e., sum of weights) was 286.4 for KRd arm and effective sample size was 171.

Outcomes (PFS and OS) of KdD vs KRd were Comparable (Figure 2, Figure 3)

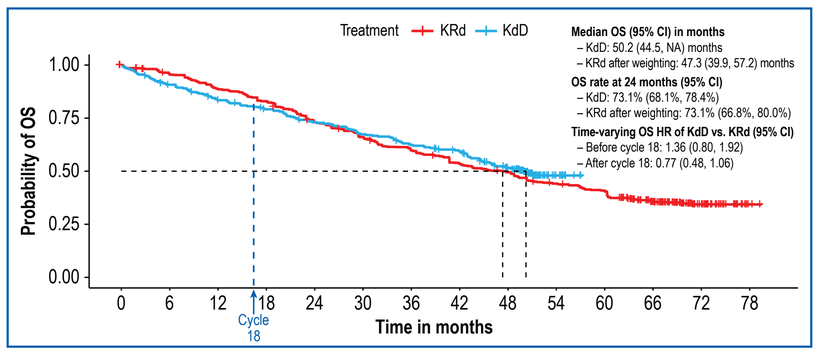
- The median PFS was 26.2 months for KdD and 24.1 months for KRd after weighting.
- At 24 months, the PFS rate was 53.7% for KdD and 51.2% for KRd after weighting, and the HR estimate of KdD vs KRd after weighting and bootstrap was 0.98 (95% CI: 0.72, 1.24), indicating similar efficacy between the two treatments.
- Time-varying hazard model was assessed due to violation of the proportional hazard assumption. The weighted time-varying PFS HRs of KdD vs KRd were 1.20 (95% CI: 0.70, 1.70) before cycle 18 (i.e., 72 weeks) and 0.74 (95% CI: 0.46, 1.01) after cycle 18, respectively, but the comparisons were not statistically significant.

FIGURE 2. PFS of KdD and KRd after weighting for ITT populations



- The median OS was 50.2 months for KdD and 47.3 months for KRd after weighting.
- At 24 months, the OS rate was 73.1% for KdD and 73.1% for KRd after weighting, and the HR estimate of KdD vs KRd after weighting and bootstrap was 0.94 (95% CI: 0.68, 1.19), indicating similar efficacy between the two treatments.
- Time-varying hazard model was assessed due to the intertwined KM curves. The weighted time-varying OS HRs of KdD vs KRd were 1.36 (95% CI: 0.80, 1.92) and 0.77 (95% CI: 0.48, 1.06) before and after cycle 18, respectively. The results trended towards improvement in OS of KRd before cycle 18, and improvement in OS of KdD after cycle 18.

FIGURE 3. OS of KdD and KRd after weighting for ITT populations



RESULTS
Indirect Comparisons of the Len-exposed Subgroups

Imbalances Between KdD and KRd Had Been Reduced by Weighting (Table 2)

- Among the len-exposed subgroups, multiple baseline characteristics, such as time from last relapse, prior bortezomib exposure, and refractory to last prior treatment, differ between these two treatments before weighting. After weighting of KRd len-exposed subgroup, differences were reduced with SMDs being less than or on the margin of 0.1 between the two treatments for most baseline characteristics.
- However, differences still exist in ISS stage, creatinine clearance, time from diagnosis, number of prior regimens, prior SCT use, and prior bortezomib exposure after weighting.

TABLE 2. Baseline variables for KdD and KRd before and after weighting in the len-exposed subgroups

Baseline variable	Len-exposed subgroups				
		Before weighting		After weighting	
	KdD N=112	KRd N=77	SMD	KRd N=97.4*	SMD
Age - n (%)					
<65 years	58 (51.8)	34 (44.2)	0.153	50.3 (51.7)	0.002
≥65 years	54 (48.2)	43 (55.8)		47.1 (48.3)	
ECOG - n (%)					
0	52 (46.4)	37 (48.1)	0.033	49.1 (50.4)	0.080
1-2	60 (53.6)	40 (51.9)		48.3 (49.6)	
ISS stage - n (%)					
I	58 (51.8)	39 (50.6)	0.023	55.5 (57.0)	0.106
II-III	54 (48.2)	38 (49.4)		41.8 (43.0)	
Creatinine clearance - n (%)					
<80 mL/min	49 (43.8)	36 (46.8)	0.060	33.8 (34.7)	0.186
≥80 mL/min	63 (56.2)	41 (53.2)		63.6 (65.3)	
Number of prior treatments - n (%)					
<3	69 (61.6)	50 (64.9)	0.069	72.4 (74.4)	0.276
≥ 3	43 (38.4)	27 (35.1)		25.0 (25.6)	
Prior SCT use - n (%)					
No	44 (39.3)	30 (39.0)	0.007	27.7 (28.4)	0.231
Yes	68 (60.7)	47 (61.0)		69.7 (71.6)	
Prior bortezomib exposure - n (%)					
No	5 (4.5)	19 (24.7)	0.598	7.8 (8.0)	0.147
Yes	107 (95.5)	58 (75.3)		89.6 (92.0)	
Refractory to last prior treatment - n (%)					
No	25 (22.3)	56 (72.7)	1.169	24.3 (25.0)	0.063
Yes	87 (77.7)	21 (27.3)		73.1 (75.0)	
β_2-microglobulin (mg/L) - mean (SD)	3.98 (2.68)	3.82 (1.92)	0.069	4.01 (2.40)	0.011
Time from diagnosis (months) - mean (SD)	48.79 (31.31)	43.37 (28.81)	0.180	42.87 (34.83)	0.179
Time from last relapse (months) - mean (SD)	2.56 (2.83)	4.00 (5.19)	0.344	2.44 (3.52)	0.036

ECOG, Eastern Cooperative Oncology Group; ISS, International staging system; KdD, carfilzomib in combination with dexamethasone and daratumumab; KRd, carfilzomib in combination with lenalidomide and dexamethasone; len, lenalidomide; SCT, stem cell transplant; SD, standard deviation; SMD, standardized mean difference.

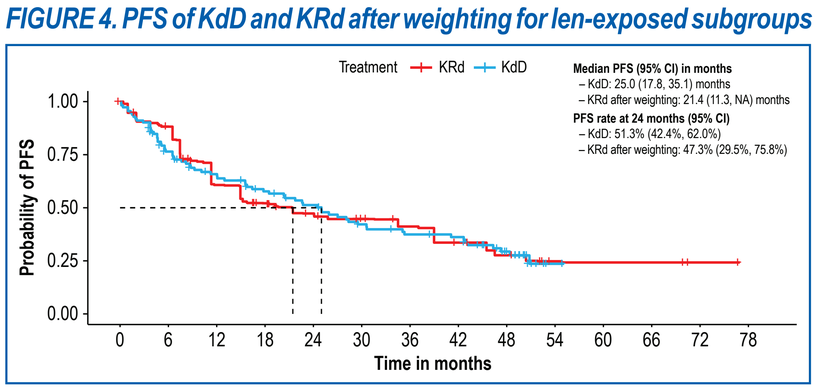
Note:

*For the len-exposed subgroup, sample size after weighting was 97.4 for KRd arm and effective sample size was 23.

Outcomes (PFS and OS) of KdD vs KRd Subgroups of Len-exposed Patients were Similar (Figure 4, Figure 5)

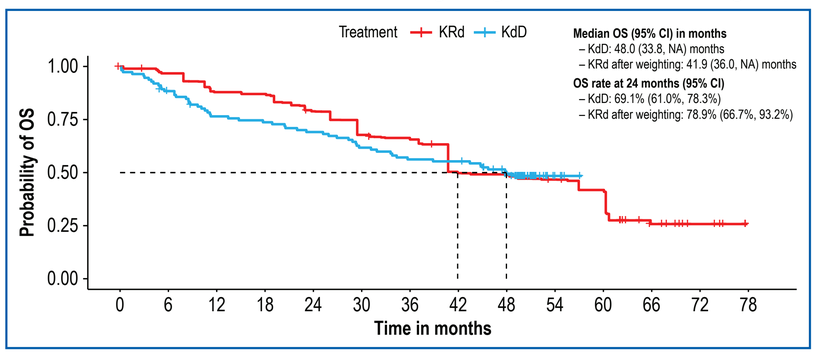
- The median PFS was 25.0 months for KdD and 21.4 months for KRd after weighting.
- At 24 months, the PFS rate was 51.3% for KdD and 47.3% for KRd after weighting, and the HR estimate of KdD vs KRd after weighting and bootstrap was 1.01 (95% CI: 0.38, 1.64), indicating similar efficacy between the two treatments.

FIGURE 4. PFS of KdD and KRd after weighting for len-exposed subgroups



- The median OS was 48.0 months for KdD and 41.9 months for KRd after weighting.
- At 24 months, the OS rate was 69.1% for KdD and 78.9% for KRd after weighting, and the HR estimate of KdD vs KRd after weighting and bootstrap was 1.11 (95% CI: 0.47, 1.75), indicating similar efficacy between the two treatments.

FIGURE 5. OS of KdD and KRd after weighting for len-exposed subgroups



CONCLUSIONS

- In a mixed population with the majority being len-naïve, KdD and KRd are equally effective.
- There is a trend towards a more favorable long-term OS benefit in KdD vs KRd after cycle 18, and in the ITT populations mainly composed of len-naïve patients.
- The results of len-exposed subgroup after weighting should be interpreted with caution due to small effective sample size of the KRd arm.