IMW 2019 | A.R.R.O.W.: Subgroup analysis by frailty score

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On Saturday 14th September, 2019, Professor (Prof.) Maria-Victoria Mateos, University Hospital Salamanca, Salamanca, ES, presented a subgroup analysis from the phase III A.R.R.O.W study at the XVII International Myeloma Workshop (IMW) in Boston, US. The results of this analysis are provided here by the Multiple Myeloma (MM) Hub.[1]

Background

The A.R.R.O.W. study evaluated the safety and efficacy of once-weekly *versus* twice-weekly carfilzomib (K), in combination with dexamethasone (d, Kd), in patients with relapsed/refractory MM (RRMM). Patients with RRMM who had received two to three prior lines of treatment, including exposure to a proteasome inhibitor (not K or oprozomib), and an immunomodulatory drug were enrolled.[1] Patients (n= 478) were randomized (1:1) to receive K once-weekly (n= 240) as a 30-minute intravenous (IV) infusion (70mg/m^2, Kd70) or twice weekly (n= 238) as a 10-minute IV infusion (27mg/m^2, Kd27).[1,2] The results from a pre-planned interim analysis of the A.R.R.O.W study were presented at the American Society of Clinical Oncology (ASCO) meeting in 2018 and can be viewed here.[2]

A subgroup analysis of patients < 65 years *vs* ≥ 65, showed hazard ratios (HRs) favored Kd70 (HR: 0.6, 95% CI, 0.42–0.86) over Kd27 (HR: 0.84, 95% CI, 0.61–1.15) for progression-free survival (PFS) in both patient groups.[3] Aside from age, frailty is an important factor to consider when determining the appropriate treatment of patients with MM. Prof. Mateos and colleagues, therefore, conducted a subgroup analysis which aimed to evaluate efficacy and safety, post-hoc, by frailty status in the A.R.R.O.W. study.[1]

Frailty subgroup analysis[1]

Prof. Mateos and colleagues used a modified frailty index to explore patient outcomes in the A.R.R.O.W. study. The frailty algorithm considered age, medical history (derived Charlson comorbidity index [CCI]), and Eastern Cooperative Oncology Group (ECOG) score. Patients were evaluated and assigned frailty scores (**Table 1**), which were balanced between arms.

Table 1. Frailty scores in the Kd70 and Kd27 groups

	Kd70 (n= 240)	**Kd27 (n= 238)**
Age group, years, n (%)		
< 75	194 (81)	206 (87)
75–80	35 (15)	29 (12)
≥ 80	11 (5)	3 (1)
Modified CCI score, n (%)		
≤ 1	124 (52)	138 (58)

CCI, Charlson comorbidity index; d, dexamethasone; ECOG, Eastern Cooperative Oncology Group ECOG; K, carfilzomib

> 1	105 (44)	92 (39)
Missing	11 (5)	8 (3)
ECOG performance status, n (%)		
0	118 (49)	118 (50)
1	121 (50)	120 (50)
≥ 2	1 (0.4)	0
Frailty score, n (%)		
0 (fit)	60 (25)	66 (28)
1 (intermediate)	89 (37)	103 (43)
≥ 2 (frail)	80 (33)	61 (26)
Missing	11 (5)	8 (3)

CCI, Charlson comorbidity index; d, dexamethasone; ECOG, Eastern Cooperative Oncology Group ECOG; K, carfilzomib

- PFS analysis:
  - In the total cohort, PFS was improved with Kd70 compared to Kd27[2]
    - Median PFS (Kd70 *vs* Kd27): 11.2 *vs* 7.6 months (HR: 0.69, 95% CI, 0.54–0.83)[2]
  - This benefit was maintained across the subgroups according to frailty status (**Table 2**)[1]
    - The HR for progression was 0.76 in the frail group, which is similar to the total cohort[1]
- ORR was similar in the Kd70 group, irrespective of frailty status (fit *vs* intermediate *vs* frail: 67% *vs* 64% *vs* 56%), which was in line with the total cohort ORR in the Kd70 arm of 63%[1]

Table 2. PFS by frailty score and K-dosing regimen[1]

	Fit		**Intermediate**		**Frail**	
	Kd70	**Kd27**	**Kd70**	**Kd27**	**Kd70**	**Kd27**
n	60	66	89	103	80	61
Median PFS (months)	15.7	5.7	11.7	7.7	10.3	6.6
HR (95% CI)	0.53 (0.33–0.86)		0.81 (0.55–1.19)		0.76 (0.49–1.16)	
HR, hazard ratio; PFS, progression free survival						

Table 3. Best overall response by frailty score[1]

	Fit		Intermediate		Frail	
N (%)	**Kd70**	**Kd27**	**Kd70**	**Kd27**	**Kd70**	**Kd27**
n	60	66	89	103	80	61
sCR	1 (2)	0	2 (2)	0	0	0
CR	5 (8)	2 (3)	5 (6)	2 (2)	3 (4)	0
VGPR	18 (30)	4 (6)	23 (26)	14 (14)	20 (25)	9 (15)
PR	16 (27)	13 (20)	27 (30)	33 (32)	22 (28)	16 (26)
Overall response rate, % (95% CI)	67 53–78	29 18–41	64 53–74	48 38–58	56 45–67	41 29–54
CR, complete response; d, dexamehasone; K, carfilzomib; PR, partial response; sCR, stringent complete response; VGPR, Very good partial response						

- Safety analysis:[1]

- Kd70 was well-tolerated with similar incidences of hematological and non-hematological AEs as in Kd27 arm (**Table 4**)
- AEs of interest were low in incidence across all subgroups and K-dosing regimens

Table 4. Safety by frailty status in the safety population[1]

	Fit		**Intermediate**		**Frail**	
N (%)	**Kd70**	**Kd27**	**Kd70**	**Kd27**	**Kd70**	**Kd27**
n	60	66	88	101	79	60
Grade ≥ III TEAE	33 (55)	41 (62)	60 (68)	58 (57)	61 (81)	42 (70)
Grade ≥ III TEAEs of interest						
Peripheral neuropathy	0	1 (2)	0	0	0	0
Acute renal failure	0	3 (5)	6 (7)	6 (6)	3 (4)	4 (7)
Cardiac failure	1 (2)	1 (2)	3 (3)	3 (3)	3 (4)	5 (8)

d, dexamethasone; K, carfilzomibTEAE, treatment-related adverse events

Ischemic heart disease	1 (2)	0	0	1 (1)	0	1 (2)
Pulmonary hypertension	0	0	0	0	0	1 (2)
TEAE leading to discontinuation of K	2 (3)	5 (8)	11 (13)	11 (11)	16 (20)	11 (18)
d, dexamethasone; K, carfilzomibTEAE, treatment-related adverse events						

Conclusion

Prof. Mateos concluded that both fit and frail patients experience a clinical benefit with Kd70 (once-weekly dosing of K) compared to Kd27 (twice-weekly). Additionally, no new safety signals were detected by subgroup analysis indicating a similar profile in fit and frail patients as per the general population. It was also noted that grade III or higher TEAEs of interest were uncommon across all subgroups.

This analysis supports the use of once-weekly carfilzomib for both fit and frail patients with RRMM.

References:

1. Mateos M-V. *et al.,* Safety and efficacy of once-weekly carfilzomib (K) dosing in frail patients (pts): a subgroup analysis from the phase 3 A.R.R.O.W. study. Abstract #OAB-046. XVII International Myeloma Workshop (IMW), Boston, US. 2019 Sep 14.

2. Mateos M-V. *et al*., Once-weekly vs twice-weekly carfilzomib (K) dosing plus dexamethasone (d) in patients with relapsed and refractory multiple myeloma (RRMM): Results of the randomized phase 3 study A.R.R.O.W. Abstract #8002. American Society of Clinical Oncology (ASCO) Annual Meeting, 2018 June 1–5; Chicago, IL, US.

3. Moreau P. *et al*., Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis

results of a randomised, phase 3 study. Lancet Onc. 2018 Jun 01. DOI: 10.1016/S1470-2045(18)30354-1

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