ARROW2 manuscript Supplemental Data Page 1 of 8

A.R.R.O.W.2: Once- vs twice-weekly carfilzomib, lenalidomide, and dexamethasone in relapsed/refractory multiple myeloma

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Supplemental Data

Supplemental Table 1. Grade ≥ 3 TEAEs in ≥ 5% of patients

	Twice-weekly KRd27 (N = 231) n (%)	Once-weekly KRd56 (N = 223) n (%)
Number of patients who reported grade ≥ 3 TEAEs	144 (62.3)	141 (63.2)
Neutropenia	57 (24.7)	54 (24.2)
Thrombocytopenia	24 (10.4)	27 (12.1)
Anemia	20 (8.7)	26 (11.7)
Hypertension	23 (10.0)	21 (9.4)
Pneumonia	7 (3.0)	12 (5.4)

d, dexamethasone; K, carfilzomib; R, lenalidomide; TEAE, treatment-emergent adverse event.

Supplemental Table 2. Treatment-emergent SAEs in ≥ 2% of patients

	Twice-weekly KRd27 (N = 231) n (%)	Once-weekly KRd56 (N = 223) n (%)
Number of patients who reported treatment-emergent		
SAEs	75 (32.5)	84 (37.7)
Pneumonia	9 (3.9)	12 (5.4)
COVID-19 pneumonia	11 (4.8)	8 (3.6)
COVID-19	3 (1.3)	6 (2.7)

COVID-19, coronavirus disease 2019; d, dexamethasone; K, carfilzomib; R, lenalidomide; SAE, serious adverse event.

Supplemental Table 3. TEAEs of interest of any grade in ≥ 5% of patients

	Twice-weekly KRd27 (N = 231)*	Once-weekly KRd56 (N = 223)†
TEAEs of interest, n (%)		
Neutropenia	74 (32.0)	65 (29.1)
Hypertension	56 (24.2)	48 (21.5)
Upper respiratory tract infection	33 (14.3)	32 (14.3)
Pneumonia	18 (7.8)	16 (7.2)

d, dexamethasone; K, carfilzomib; R, lenalidomide; TEAE, treatment-emergent adverse event.

^{*}One patient experienced grade 2 left ventricular failure.

[†]Two patients experienced ejection fraction decreased, and one patient experienced grade 1 left ventricular hypertrophy.

Supplemental Table 4. Fatal TEAEs

	Twice-weekly KRd27 (N = 231) n (%)	Once-weekly KRd56 (N = 223) n (%)
Fatal TEAEs	10 (4.3)	12 (5.4)
COVID-19 pneumonia	1 (0.4)	4 (1.8)
Death	0 (0.0)	3 (1.3)
COVID-19	1 (0.4)	1 (0.4)
Plasma cell myeloma	1 (0.4)	1 (0.4)
Cardiac arrest	0 (0.0)	1 (0.4)
Hyperglycemia	0 (0.0)	1 (0.4)
Septic shock	0 (0.0)	1 (0.4)
Pneumonia	3 (1.3)	0 (0.0)
Heart failure	1 (0.4)	0 (0.0)
Hepatorenal syndrome	1 (0.4)	0 (0.0)
Multiple organ dysfunction syndrome	1 (0.4)	0 (0.0)
Pulmonary embolism	1 (0.4)	0 (0.0)

COVID-19, coronavirus disease 2019; d, dexamethasone; K, carfilzomib; R, lenalidomide; TEAE, treatment-emergent adverse event.

Supplemental Table 5. Screened patients excluded from randomization

Eligibility criteria	Number of patients excluded*
ANC $< 1 \times 10^9$ /L within 21 d prior to randomization. Screening ANC should be independent of growth factor support for ≥ 1 wk.	23
Calculated or measured creatinine clearance $< 1.0 \text{mL/s}$ (calculation must be based on the Cockcroft-Gault formula) within 21 d prior to randomization.	15
Hemoglobin < 80 g/L within 21 d prior to randomization. Use of erythropoietic stimulating factors and RBC transfusions per institutional guidelines is allowed; however, most recent RBC transfusion must not have been performed within 7 d prior to obtaining screening hemoglobin level.	20
Hepatic dysfunction within 21 d prior to randomization: bilirubin \geq 1.5x ULN; AST or ALT \geq 2.5x ULN.	15
Platelet count $< 50 \times 10^9/L$ ($\le 30 \times 10^9/L$ if myeloma involvement in the bone marrow is $> 50\%$) within 28 d prior to randomization. Patients should not have received platelet transfusions for ≥ 1 wk prior to obtaining the screening platelet count.	18
Uncontrolled hypertension, defined as blood pressure \geq 160 mmHg systolic or \geq 100 mmHg diastolic, in accordance with the European Society of Hypertension/European Society of Cardiology 2018 guidelines.	8
Plasma cell leukemia (> $2.0 \times 10^9/L$ circulating plasma cells by standard differential).	1
Left ventricular ejection fraction < 40%, assessed by transthoracic ECHO.	1
Calculated or measured creatinine clearance < 30 mL/min (calculation must be based on the Cockcroft-Gault formula) within 28 d prior to randomization.	1

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ECHO, echocardiogram; RBC, red blood cell; ULN, upper limit of normal.

^{*}There was a total of 150 screen failures; however, some patients were excluded based on > 1 eligibility criterion.

Supplemental Figure 1. Subgroup analysis of ORR.

	(N = 226)		Risk ratio for ORR
Number of responde	ers/Number of patient	ts	(95% CI)*
188/228	195/226	H	0.954 (0.882–1.032)
r derived)			
172/209	178/209	H	0.965 (0.888–1.049)
16/19	17/17	├	0.793 (0.609–1.032)
		.[
		<u> </u>	0.955 (0.880–1.037)
13/14	8/8	H	0.946 (0.849–1.055)
15/21	1.4/1.7		0.022 (0.565, 1.105)
		— <u> </u>	0.822 (0.565–1.195)
1/3/20/	181/209	I ^o l	0.965 (0.890–1.046)
06/116	90/107	<u>, </u>	0.993 (0.883–1.117)
		Ţ	0.993 (0.883–1.117)
72/112	100/117	٦	0.510 (0.815–1.015)
06/116	20/107	4	0.993 (0.883–1.117)
		I	0.950 (0.848–1.063)
			0.744 (0.500–1.107)
14/20	10/17	' '	0.744 (0.500 1.107)
178/214	185/215	i i	0.966 (0.891–1.046)
		⊢	0.869 (0.604–1.249)
		. .	
9/13	4/4	⊢ •-	0.760 (0.557-1.038)
179/215	191/222	le le	0.966 (0.891–1.047)
			,
137/157	137/154	W	0.987 (0.909–1.072)
51/71	58/72	H	0.883 (0.731–1.067)
137/157	137/154	H	0.987 (0.909–1.072)
37/49	35/43	H	0.938 (0.755–1.167)
14/22	23/29	 -	0.718 (0.443–1.165)
	35/40	₩	0.981 (0.818–1.177)
		₩	0.979 (0.872–1.100)
58/72	71/80	ŀ	0.925 (0.807–1.061)
10 -		. .	
		H	0.949 (0.792–1.137)
125/143	134/147	M	0.959 (0.885–1.039)
25/20	27/40		0.056 (0.679, 1.240)
			0.956 (0.678–1.349)
103/189	108/180	7	0.953 (0.885–1.026)
171/210	181/211	4	0.954 (0.877–1.037)
		\mathbb{L}	1.047 (0.879–1.246)
17/10	14/13	171	1.047 (0.07) 1.240)
12/19	13/16	⊢	0.735 (0.463–1.167)
		. 4	0.969 (0.895–1.049)
		Ϊ	(
129/153	128/148	H	0.974 (0.887–1.070)
59/75	67/78	H	0.905 (0.782–1.049)
	0.1	1	
	←		10
	172/209 16/19 175/214 13/14 15/21 173/207 96/116 92/112 96/116 78/92 14/20 178/214 10/14 9/13 179/215 137/157 51/71 137/157 37/49 14/22 37/44 93/112 58/72 63/85 125/143 25/39 163/189 171/210 17/18 12/19 176/209 129/153	172/209 178/209 16/19 17/17 175/214 187/218 13/14 8/8 15/21 14/17 173/207 181/209 96/116 89/107 92/112 106/119 96/116 89/107 78/92 90/102 14/20 16/17 178/214 185/215 10/14 10/11 9/13 4/4 179/215 191/222 137/157 137/154 51/71 58/72 137/157 35/43 14/22 23/29 37/44 35/40 93/112 89/106 58/72 71/80 63/85 61/79 125/143 134/147 25/39 27/40 163/189 168/186 171/210 181/211 17/18 14/15 12/19 13/16 176/209 182/210 129/153 128/148 59/75 67/78	172/209 178/209 16/19 17/17 175/214 187/218 13/14 8/8 15/21 14/17 173/207 181/209 96/116 89/107 92/112 106/119 96/116 89/107 14/20 16/17 178/214 185/215 10/14 10/11

BIW, twice-weekly; CI, confidence interval; FISH, fluorescence in-situ hybridization; ISS, International Staging System; KRd, carfilzomib-lenalidomide-dexamethasone; KRd27, carfilzomib (27 mg/m²)-

ARROW2 manuscript Supplemental Data

Page **8** of **8**

lenalidomide-dexamethasone; KRd56, carfilzomib (56 mg/m²)-lenalidomide-dexamethasone; ORR, overall response rate; PI, proteasome inhibitor; QW, once-weekly.

*The risk ratios and 95% CIs were calculated using the Cochran-Mantel-Haenszel method, controlling for randomization stratification factors. Stratification factors included the original ISS stage at study entry (stage 1 or 2 vs stage 3), prior lenalidomide treatment (yes vs no), prior PI treatment (yes vs no), and prior anti-CD38 exposure (yes vs no).

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