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

Meletios A. Dimopoulos, Daniel Coriu, Sosana Delimpasi, Ivan Spicka, Terry Upchurch, Belle Fang, Rakhshandra Talpur, Edward Faber, Meral Beksac, and Xavier Leleu

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.

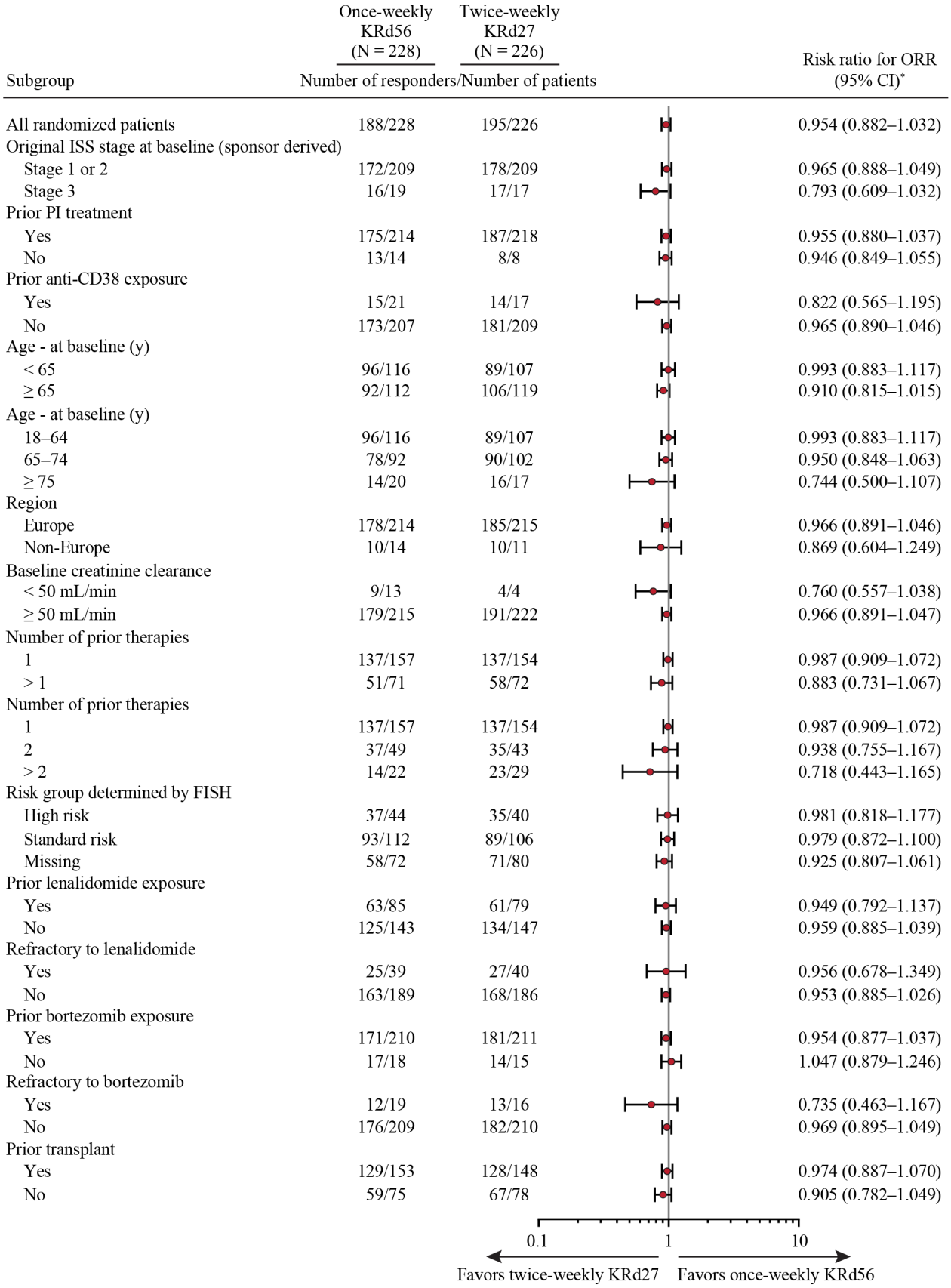
Supplemental Table 5. Screened patients excluded from randomization

Eligibility criteria	Number of patients excluded*
ANC < 1×10^9/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 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 ≥ 1.5x ULN; AST or ALT ≥ 2.5x ULN.	15
Platelet count < 50×10^9/L (≤ 30×10^9/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 ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic, in accordance with the European Society of Hypertension/European Society of Cardiology 2018 guidelines.	8
Plasma cell leukemia (> 2.0×10^9/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.



BIW, twice-weekly; CI, confidence interval; FISH, fluorescence in-situ hybridization; ISS, International Staging System; KRd, carfilzomib-lenalidomide-dexamethasone; KRd27, carfilzomib (27 mg/m^2)-

lenalidomide-dexamethasone; KRd56, carfilzomib (56 mg/m^2)-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).

References

1. Richardson PG, Xie W, Jagannath S, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. *Blood*. 2014;123(10):1461-1469.
2. Moreau P, Masszi T, Grzasko N, et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016;374(17):1621-1634.
3. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016;375(14):1319-1331.
4. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016;375(8):754-766.
5. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2019;394(10214):2096-2107.
6. Voorhees PM, Suman VJ, Tuchman SA, et al. A phase I/II study of ixazomib, pomalidomide, and dexamethasone for lenalidomide and proteasome inhibitor refractory multiple myeloma (Alliance A061202). *Am J Hematol*. 2021;96(12):1595-1603.
7. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(6):781-794.
8. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372(2):142-152.
9. Dimopoulos M, Quach H, Mateos M-V, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2020;396(10245):186-197.