Superior outcomes and high-risk features with carfilzomib, lenalidomide, and dexamethasone combination therapy for patients with relapsed and refractory multiple myeloma: results of the multicenter KMMWP2201 study

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Supplements

Supplementary methods

Supplementary Table and Figure legends

Supplementary Table 1. Post-KRd treatment

*Pomalidomide/dexamethasone, pomalidomide/cyclophosphamide/dexamethasone, and carfilzomib/pomalidomide/dexamethasone

Cyclophosphamide/dexamethasone, melphalan/dexamethasone, bendamustine, dexamethasone/cyclophosphamide/etoposide/cisplatin

‡Daratumumab, daratumumab/bortezomib/dexamethasone, and daratumumab/pomalidomide/dexamethasone

§Velyx, bortezomib, and bortezomib/dexamethasone

¶Belantamab, belantamab/bortezomib/lenalidomide/dexamethasone, belanatamab/dostarimab, and belantamab/bortezomib/dexamethasone

‖Teclistamab/daratumumab/dexamethasone

**Elranatamab, elranatamab/daratumumab

Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone

Supplementary Table 2. Univariate and multivariate analyses of the patient characteristics affecting progression-free and overall survival

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Group Performance Status; HR, hazard ratio.

Supplementary Table 3. Univariate and multivariate analyses of previous treatments and responses affecting progression-free and overall survival

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number; SCT, stem cell transplantation.

Supplementary Table 4. Cause of treatment cessation owing to adverse events

Abbreviations: AE, adverse event; n, number; SAE, severe adverse event.

Supplementary Table 5. Toxicity profile after KRd therapy

*Newly developed or aggravated peripheral neuropathy after administering carfilzomib, lenalidomide, and dexamethasone combination therapy.

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Supplementary Figure 1. Characteristics of the trial-ineligible patients.
Abbreviations: ANC, Absolute neutrophil count; CCr, creatinine clearance; ECOG PS, Eastern cooperative group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; LOT, lines of therapy; PLT, platelet; PN, peripheral neuropathy.

Supplementary Figure 2. Overall response rated according to patient, treatment, and disease related factors.
Abbreviations: ISS, International Staging System; M protein, monoclonal protein; R-ISS, Revised International Staging System; SCT, stem cell transplantation.

Supplementary Figure 3. Survival according to clinical trial eligibility
(A) Progression-free survival
(B) Overall survival.
[1]The Kaplan–Meier curve does not reach the probability of 0.5.

Supplementary Figure 4. Differences of baseline creatinine clearance according to acute kidney injury after KRd therapy.
Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone

Supplementary methods

This study included patients with RRMM whose disease was refractory, relapsed and refractory, or progressive after at least one line of therapy[1]. KRd was administered according to the ASPIRE study protocol[1]: carfilzomib was infused intravenously starting with 20 mg/m^2 on days 1 and 2 of cycle 1. This was increased to 27 mg/m^2 on days 1, 2, 8, 9, 15, and 16 until cycle 12, and on days 1, 2, 15, and 16 during cycles 13–18, after which carfilzomib was stopped. Lenalidomide was administered orally at a dose of 25 mg on days 1–21. Its dosage was adjusted according to renal impairment. Dexamethasone was administered at a dosage and schedule that was determined by the treating physician. Additionally, 62 patients were evaluated for minimal residual disease (MRD) by using the EuroFlow standard operative procedure. Responses were designated according to the IMWG response criteria as follows: MRD-negative complete response (CR), stringent complete response (sCR), CR, very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), and progressive disease (PD)[2]. Refractoriness to bortezomib or thalidomide was defined as a disease that did not achieve MR, progressed during treatment, or progressed within 60 days after the administration of bortezomib or thalidomide. Clinical trial-ineligibility was not meeting the eligibility criteria specified in ASPIRE trial: Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3, ongoing heart disease, chronic or active hepatitis B virus (HBV), hepatitis C virus (HCV) infection, absolute neutrophil count (ANC) < 1,000/μL, hemoglobin < 8 g/dL, platelet count < 50,000/μL, calculated creatinine clearance (CCr) < 50 mL/min, plasma cell leukemia, ongoing > grade 2 peripheral neuropathy, underlying cancer, > 3 prior lines of therapy, primary refractoriness to previous therapy, bortezomib-refractoriness, and lenalidomide-refractoriness. Symptomatic diseases were excluded from the trial-ineligibility criteria because recent clinical trials did not preclude the biochemical progression of the disease. AEs observed during KRd treatment were assessed using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03.

1. Anderson KC, Kyle RA, Rajkumar SV, et al. Clinically relevant end points and new drug approvals for myeloma. *Leukemia* 2008;22(2):231-9.

2. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.

Supplementary Tables

Supplementary Table 1. Post-KRd treatment

	n (%)
Consolidative transplantation	25 (6.9)
Autologous SCT	21 (5.8)
Allogeneic SCT	4 (1.1)
Salvage chemotherapy	197 (54.1)
Pomalidomide-based combination therapy*	137 (37.6)
Alkylator-based†	18 (4.9)
Daratumumab-based combination therapy‡	14 (3.8)
Thalidomide/cyclophosphamide/dexamethasone	10 (2.7)
Bortezomib-based combination therapy§	8 (2.2)
Belantamab-combination therapy¶	5 (1.4)
Teclistamab-combination therapy‖	4 (1.1)
Ixazomib/lenalidomide/dexamethasone	3 (0.8)
Elranatamab-combination therapy**	2 (0.5)
Venetoclax/dexamethasone	1 (0.3)

*Pomalidomide/dexamethasone, pomalidomide/cyclophosphamide/dexamethasone, and carfilzomib/pomalidomide/dexamethasone

†Cyclophosphamide/dexamethasone, melphalan/dexamethasone, bendamustine, dexamethasone/cyclophosphamide/etoposide/cisplatin

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**Elranatamab, elranatamab/daratumumab

Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone

Supplementary Table 2. Univariate and multivariate analysis of patient characteristics affecting progression-free and overall survival

				Progression free survival						Overall survival			
				Univariate analysis		Multivariate analysis				Univariate analysis		Multivariate analysis	
		n	Event	HR (95% CI)	P value	HR (95% CI)	P value	n	Event	HR (95% CI)	P value	HR (95% CI)	P value
Patient characteristics													
Age	< 65	215	156					215	71				
	≥ 65	149	109	1.043 (0.816-1.333)	0.7343			149	68	1.496 (1.072-2.087)	0.0178	1.480 (1.050-2.086)	0.0253
ECOG PS	0-2	338	243					338	125				
	≥ 3	21	17	1.494 (0.913-2.445)	0.1102			21	11	1.725 (0.930-3.199)	0.0835		
Platelet	≥ 50,000/μL	330	235					330	116				
	< 50,000/μL	23	22	5.443 (3.442-8.610)	<0.0001	5.443 (3.442-8.610)	<0.0001	23	20	7.251 (4.410-11.920)	<0.0001	7.442 (4.517-12.261)	<0.0001
ANC	≥ 1,000/μL	336	242					336	128				

	< 1,000/μL	16	14	1.882 (1.095-3.233)	0.0221			16	8	1.624 (0.795-3.320)	0.1834		
Hemoglobin	≥ 8 g/dL	345	251					345	131				
	< 8 g/dL	8	6	1.398 (0.621-3.146)	0.4180			8	5	2.211 (0.904-5.407)	0.082		
Underlying liver disease	No	349	252					349	136				
	Yes	15	13	1.470 (0.841-2.570)	0.176			15	3	0.586 (0.187-1.841)	0.3601		
Underlying heart disease	No	345	250					345	130				
	Yes	19	15	1.276 (0.757-2.151)	0.3598			19	9	1.648 (0.838-3.240)	0.1479		
Underlying cancer	No	354	257					354	132				
	Yes	10	8	1.081 (0.535-2.185)	0.8286			10	7	1.804 (0.843-3.860)	0.1283		
Creatinine clearance	≥ 50 mL/min	262	184					262	89				
	< 50 mL/min	84	67	1.230 (0.928-	0.1497			84	42	1.571 (1.087-	0.0162		

				1.630)						2.272)			

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Group Performance Status; HR, hazard ratio.

Supplementary Table 3. Univariate and multivariate analysis of previous treatment and response affecting progression-free and overall survival

		Progression free survival						Overall survival					
				Univariate analysis		Multivariate analysis				Univariate analysis		Multivariate analysis	
		n	Event	HR (95% CI)	P value	HR (95% CI)	P value	n	Event	HR (95% CI)	P value	HR (95% CI)	P value
Previous therapy													
Autologous SCT	No	163	123					163	78				
	Yes	201	142	0.769 (0.604-0.979)	0.0331			201	61	0.518 (0.370-0.725)	0.0001		
Prior bortezomib	No	38	20					38	8				
	Yes	326	245	2.514 (1.573-4.018)	0.0001			326	131	2.696 (1.310-5.549)	0.0071		
Prior thalidomide	No	125	88					125	57				
	Yes	239	177	1.088 (0.842-1.406)	0.5176			239	82	0.694 (0.495-0.974)	0.0346		
Bortezomib refractory	No	205	151					205	78				
	Yes	120	94	1.294 (1.000-	0.0501			120	53	1.382 (0.974-	0.0699		

				1.676)						1.961)			
Bortezomib response duration	< 12mo	128	105					128	62				
	≥ 12mo	156	108	0.619 (0.473-0.810)	0.0005	0.619 (0.473-0.810)	0.0005	156	49	0.499 (0.342-0.726)	0.0003	0.499 (0.342-0.726)	0.0003
Thalidomide refractory	No	147	106					147	46				
	Yes	92	71	1.365 (1.010-1.845)	0.0432			92	36	1.511 (0.975-2.344)	0.0650		
Thalidomide response	< 12mo	87	71					87	36				
	≥ 12mo	119	81	0.534 (0.387-0.736)	0.0001			119	30	0.438 (0.268-0.716)	0.0010		

Abbreviations: CI, confidence interval; HR, hazard ratio; n, number; SCT, stem cell transplantation.

Supplementary Table 4. Cause of treatment cessation due to adverse events

Non-fatal AEs	n
Secondary malignancy (colon cancer, esophageal cancer, pancreatic cancer, and myelodysplastic syndrome)	4
Fatigue	4
Bone pain	2
Acute pulmonary thromboembolism	2
Congestive heart failure	2
Ischemic heart disease	1
Cerebrovascular disease	1
Septic shock	1
Pneumonia	2
COVID-19 infection	1
Foot gangrene due to cholesterol embolism	1
Cellulitis	1
Rhabomyolysis	1
Pancytopenia	1
Liver function abnormality	1
Fatal AEs	
Pneumonia	2
Ventricullar fibrillation associated with congestive heart failure	1
Lung cancer	1
Leukemia	2

Abbreviations: AE, adverse event; n, number; SAE, severe adverse event.

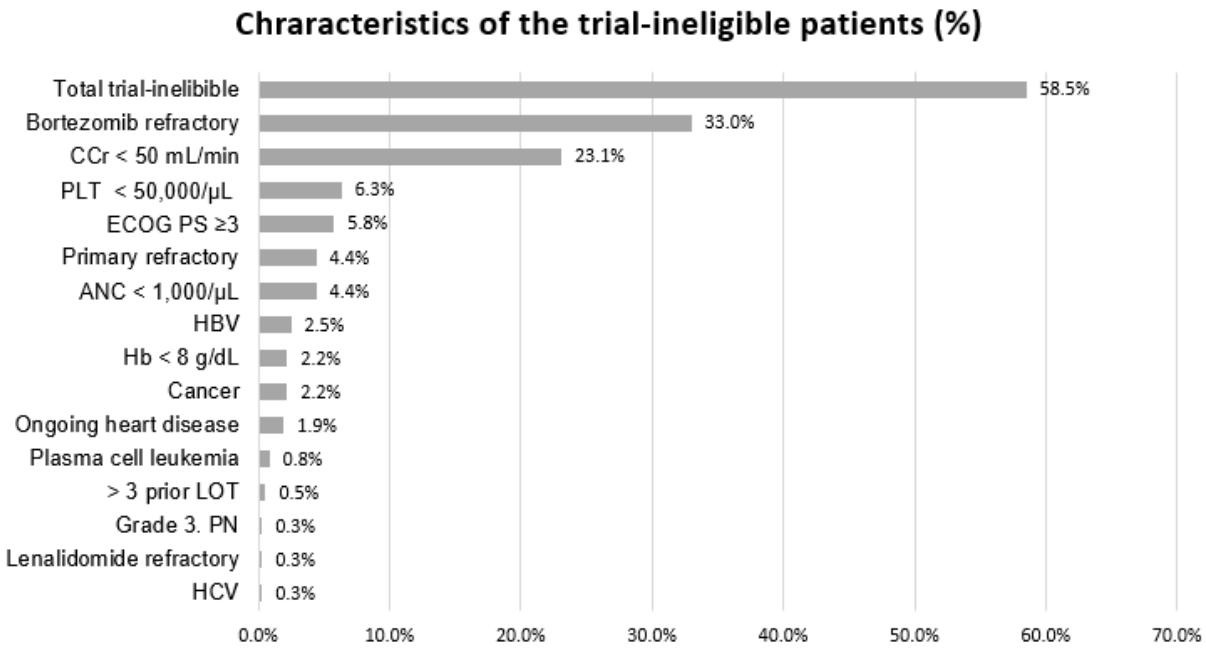
Supplementary Table 5. Toxicity profile after KRd therapy

	All grades	Grade ≥ 3 AEs	All grades	Grade ≥ 3 AEs
Hematologic adverse events, n (%)				
Anemia	138 (38)	60 (16)	167 (43)	70 (18)
Thrombocytopenia	155 (43)	73 (20)	114 (29)	65 (17)
Neutropenia	171 (47)	123 (34)	148 (38)	116 (30)
Neutropenic fever	17 (5)	11 (3)		
Non-hematologic adverse events, n (%)				
Fatigue	119 (33)	34 (9)	129 (33)	30 (8)
Hypokalemia	10 (3)	2 (1)	108 (28)	37 (9)
Cough	32 (9)	2 (1)	113 (29)	1 (0.3)
Pyrexia	24 (7)	5 (1)	112 (29)	7 (2)
Upper respiratory tract infection	63 (17)	3 (1)	112 (29)	7 (2)
Muscle spasm	32 (9)	4 (1)	104 (27)	4 (1)
Back pain	68 (19)	17 (5)		
Liver function test abnormalities	50 (14)	16 (4)		
Diarrhea	44 (12)	8 (2)		
Peripheral neuropathy*	31 (9)	9 (2)	67 (17)	10 (3)
Abdominal discomfort	36 (10)	2 (1)		
Dyspepsia	34 (9)	2 (1)		
Nausea	31 (9)	0		
Vomiting	17 (5)	2 (1)		
Constipation	50 (14)	1 (0.3)		
Rash	53 (15)	12 (3)		
Itching	42 (12)	12 (3)		
Headache	28 (8)	1 (0.3)		
Peripheral edema	29 (8)	4 (1)		
Insomnia	38 (10)	0		
Encephalopathy	2 (1)	2 (1)		
Interstitial lung disease	3 (1)	1 (0.3)		
Infection	77 (21)	42 (12)		

*Newly developed or aggravated peripheral neuropathy after administering carfilzomib, lenalidomide, and dexamethasone combination therapy.

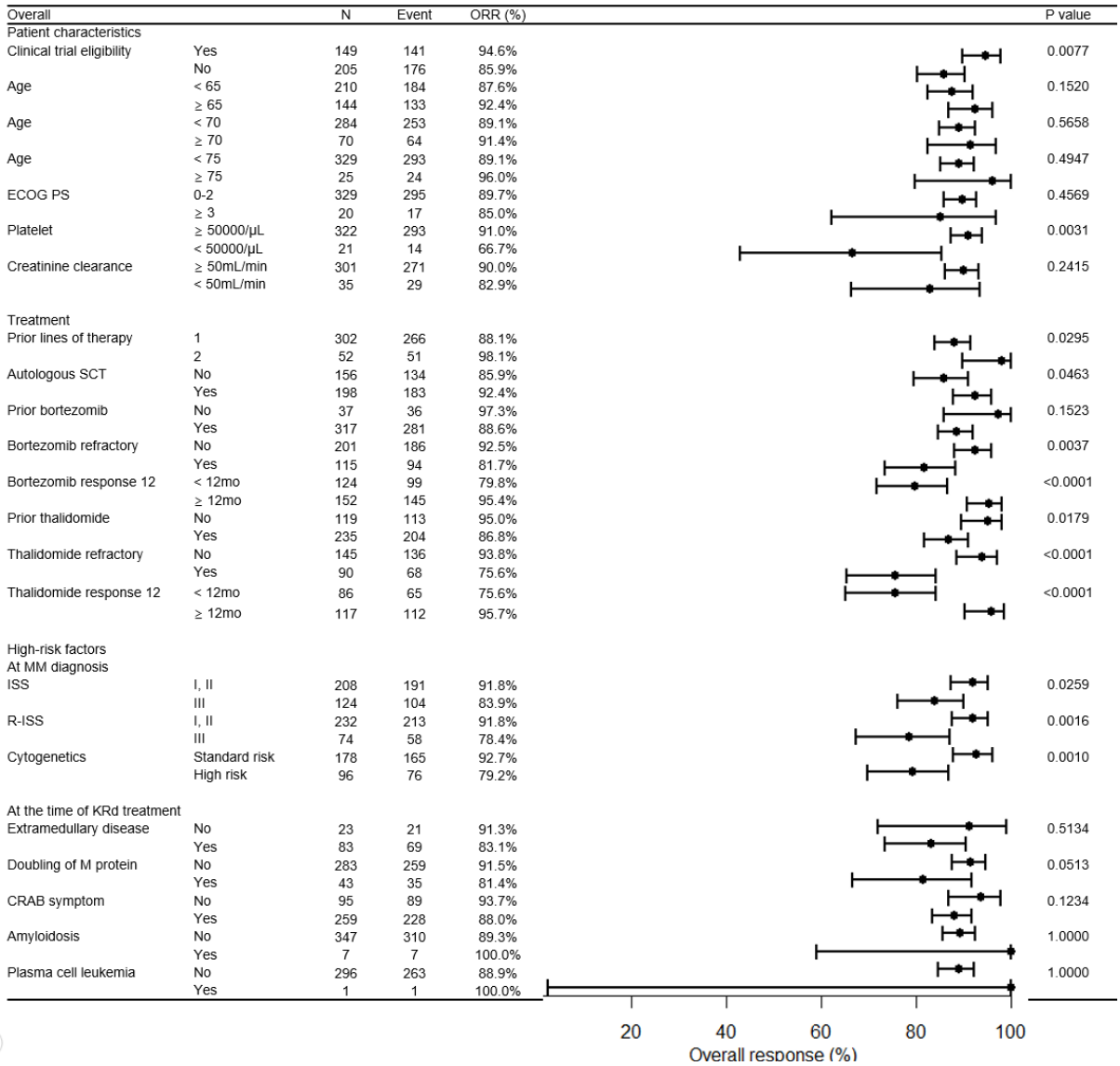
Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone

Supplementary Figure 1. Characteristics of the trial-ineligible patients.



Abbreviations: ANC, Absolute neutrophil count; CCr, creatinine clearance; ECOG PS, Eastern cooperative group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; LOT, lines of therapy; PLT, platelet; PN, peripheral neuropathy.

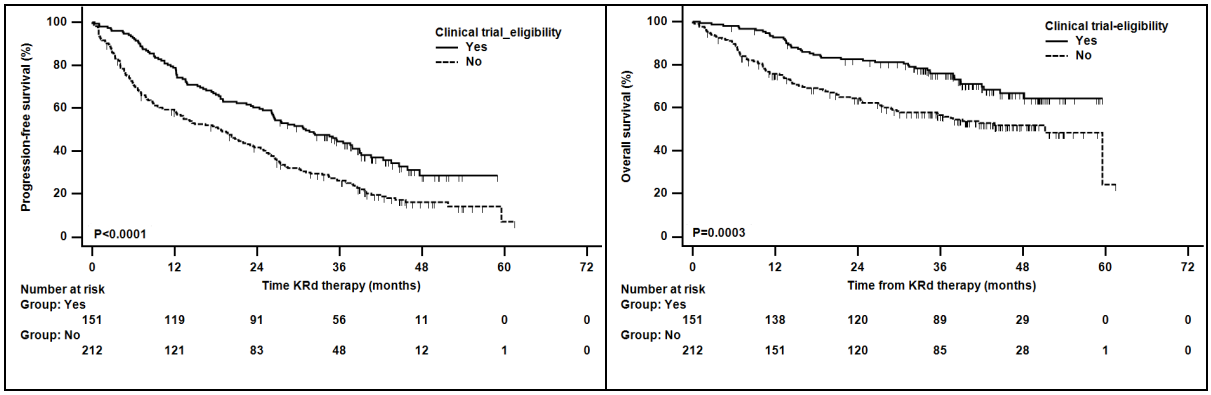
Supplementary Figure 2. Overall response rated according to patient, treatment, and disease related factors.



Abbreviations: ISS, International Staging System; M protein, monoclonal protein; R-ISS, Revised International Staging System; SCT, stem cell transplantation.

Supplementary Figure 3. Survival according to clinical trial eligibility

(A) Progression-free survival (B) Overall survival.



Progression-free survival

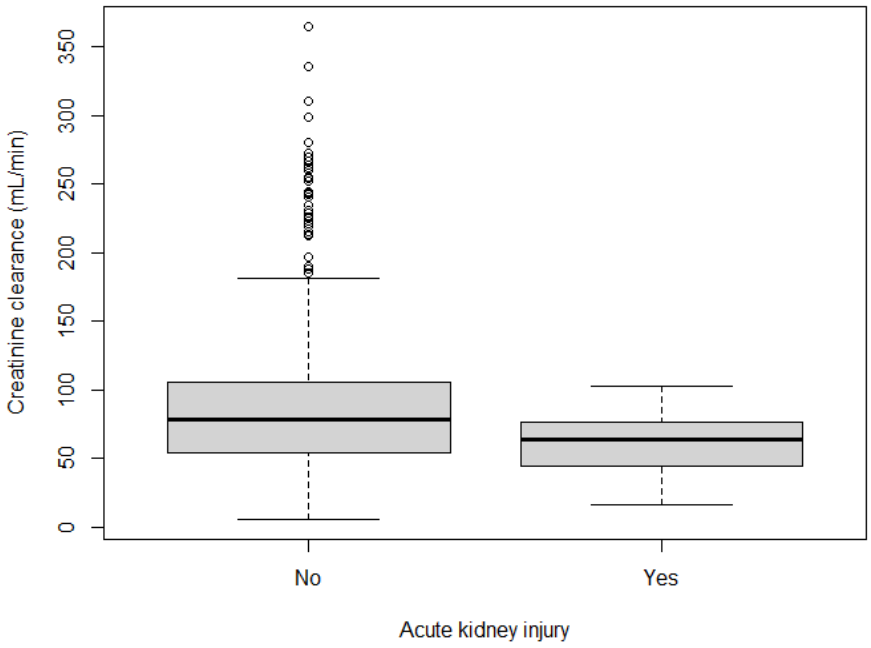
	overall	Clinical trial-eligibility	
		yes	no
median	23.4 months (95% CI, 19.0-26.4 months)	31.1 months (95% CI, 26.1-37.8 months)	18.7 months (95% CI, 12.4-22.6 months)
3-year	33.9% (95% CI, 29.3%-39.2%)	44.4% (95% CI, 37.1%-53.2%)	26.2% (95% CI, 20.7%-33.0%)

Overall survival

	overall	Clinical trial-eligibility	
		yes	no
Median	59.5 months (95% CI, 51.2-59.5 months)	-[1]	51.2 months (95% CI, 35.5-59.5 months)
3-year	64.7% (95% CI, 59.8%-70.0%)	75.9% (95% CI, 69.2%-83.2%)	56.5% (95% CI, 49.9%-63.9%)

[1] The Kaplan-Meier curve does not reach at probability of 0.5.

Supplementary Figure 4. Differences of baseline creatinine clearance according to acute kidney injury after KRd therapy.



Abbreviations: KRd, Carfilzomib, lenalidomide, and dexamethasone