Table S1. Baseline characteristics of all patients (N=384)

Characteristics	No. (%)
Age, median (range) years	
≥65 years	194 (50.5)
Sex	
Male	215 (56.0)
Female	169 (44.0)
ISS stage	
I	82 (21.4)
II	121 (31.5)
III	161 (41.9)
Unknown	20 (5.2)
R-ISS stage	
I	28 (7.3)
II	207 (53.9)
III	87 (22.7)
Unknown	62 (16.1)
Cytogenetics abnormalities	
Standard risk	200 (52.1)
High risk*	94 (24.5)
Unknown	90 (23.4)
Bortezomib exposure	
Yes	330 (84.6)
Upfront ASCT	
Yes	143 (37.2)
Early relapse	
<2 years	224 (58.3)
Second-line therapy	
Carfilzomib based	310 (80.7)
Ixazomib based	74 (19.3)
Best response to second-line therapy	
CR	123 (32.0)
VGRP	96 (25.0)
PR	104 (27.1)
SD	27 (7.0)
PD	13 (3.4)
Not evaluated	21 (5.5)

*High-risk cytogenetics: presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16) by iFISH

Table S2. Univariate and multivariate Cox regression analysis for PFS in rapid and slow responders (n=223)

(A) At diagnosis

	PFS			
	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (≥65 years vs. <65 years)	0.876 (0.583–1.316)	0.523		
ISS stage (III vs. I)	1.219 (0.934–1.590)	0.145		
R-ISS stage (III vs. I)	1.274 (0.862–1.883)	0.225		
Cytogenetics abnormalities (High vs. Standard)	1.651 (1.000–2.728)	0.050	1.451 (0.874–2.407)	0.150
Bortezomib exposure (Yes vs. No)	1.128 (0.639–1.991)	0.6786		
Upfront ASCT (Yes vs. No)	1.115 (0.739–1.680)	0.604		
Early relapse (<2 years vs. ≥2 years)	1.048 (0.699–1.573)	0.824		
Response kinetics (Slow responders vs. Rapid responders)	0.612 (0.495–0.757)	<0.001	0.646 (0.507–0.824)	**<0.001**

Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ISS, International Staging System; R-ISS, Revised-International Staging System; ASCT, autologous stem-cell transplantation.

(B) At second-line therapy

	PFS			
	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Second-line treatment (Ixazomib vs. Cafilzomib)	1.505 (0.931–2.433)	0.095	0.713 (0.292–1.736)	0.456
Albumin (≥3.5 mg/dL vs. <3.5 mg/dL)	0.427 (0.275–0.663)	< 0.001	0.472 (0.220–1.013)	0.0539
LDH (High vs. Low)	0.880 (0.527–1.469)	0.624		
Beta-2 microglobulin (≥3.5 mg/dL vs. <3.5 mg/dL)	1.801 (0.966–3.356)	0.064	1.798 (0.805–4.020)	0.153
Creatinine (>2 mg/dL vs. ≤2.0 mg/dL)	0.936 (0.432–2.025)	0.866		
Calcium (>11.0 mg/dL vs. <11.0 mg/dL)	0.000 (0–inf)	0.996		

Plasmacytoma (Yes vs. No)	3.473 (2.031–5.940)	<0.001	2.393 (1.058–5.414)	**0.036**
Light chain difference (≥300 vs. <300)	1.253 (0.823–1.908)	0.293		
Hb. (≥10.0 g/dL vs. <10.0 g/dL)	0.396 (0.527–0.609)	<0.001	0.463 (0.202–1.063)	0.069
Platelets (≥100,000 /μL vs. <100,000/μL)	0.522 (0.324–0.840)	0.007	1.235 (0.512–2.981)	0.638
ALC/WBC ratio (≥20% vs <20%)	1.264 (0.634–2.520)	0.506		
Best response to second-line therapy (PR vs. CR)	1.668 (1.300–2.139)	<0.001	1.595 (1.055–2.412)	**0.027**
Response kinetics (Slow responders vs. Rapid responders)	0.612 (0.495–0.757)	<0.001	0.454 (0.304–0.678)	**<0.001**

Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; Hb., hemoglobin; ALC/WBC, absolute lymphocyte count/white blood cell count; CR, complete response; PR, partial response.

Table S2. Univariate and multivariate Cox regression analysis for OS in rapid and slow responders (n=223)

(A) At diagnosis

	OS			
	Univariate		Multivariate	
	HR (95% CI)		HR (95% CI)	
Age (≥65 years vs. <65 years)	1.347 (0.889–2.042)	0.160		
ISS stage (III vs. I)	1.434 (1.080–1.904)	0.013	1.212 (0.859–1.711)	0.274
R-ISS stage (III vs. I)	1.460 (0.980–2.176)	0.063		
Cytogenetics abnormalities (High vs. Standard)	1.627 (0.973–2.722)	0.064	1.199 (0.679–2.116)	0.532
Bortezomib exposure (Yes vs. No)	0.965 (0.554–1.680)	0.8995		
Upfront ASCT (Yes vs. No)	0.909 (0.593–1.395)	0.662		
Early relapse (<2 years vs. ≥2 years)	1.503 (0.981–2.302)	0.061	1.920 (1.107–3.329)	**0.020**
Response kinetics (Slow responders vs. Rapid responders)	0.696 (0.563–0.861)	<0.001	0.756 (0.578–0.988)	**0.040**

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; ISS, International Staging System; R-ISS, Revised-International Staging System; ASCT, autologous stem-cell transplantation.

(B) At second-line therapy

	OS			
	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Second-line treatment (Ixazomib vs. Cafilzomib)	0.748 (0.415–1.350)	0.335		
Albumin (≥3.5 mg/dL vs. <3.5 mg/dL)	0.525 (0.338–0.816)	0.001	0.4802 (0.204–1.130)	0.093
LDH (High vs. Low)	1.953 (1.222–3.118)	0.005	1.116 (0.494–2.524)	0.791
Beta-2 microglobulin (≥3.5 mg/dL vs. <3.5 mg/dL)	2.134 (1.161–3.921)	0.014	1.261 (0.551–2.885)	0.583
Creatinine (>2 mg/dL vs. ≤2.0 mg/dL)	1.436 (0.746–2.775)	0.281		
Calcium (>11.0 mg/dL vs. <11.0 mg/dL)	3.726 (0.9054–15.330)	0.068		

Plasmacytoma (Yes vs. No)	1.773 (1.007–3.121)	0.047	1.846 (0.771–4.419)	0.169
Light chain difference (≥300 vs. <300)	1.203 (0.793–1.824)	0.385		
Hb. (≥10.0 g/dL vs. <10.0 g/dL)	0.431 (0.282–0.659)	<0.001	0.828 (0.356 –1.928)	0.662
Platelets (≥100,000 /μL vs. <100,000/μL)	0.395 (0.253–0.615)	<0.001	0.728 (0.309–1.717)	0.469
ALC/WBC ratio (≥20% vs <20%)	0.434 (0.263–0.716)	0.001	0.403 (0.138–1.178)	0.097
Best response to second-line therapy (PR vs. CR)	1.427 (1.118–1.821)	0.004	1.816 (1.159–2.843)	**0.009**
Response kinetics (Slow responders vs. Rapid responders)	0.696 (0.563–0.861)	<0.001	0.628 (0.420–0.941)	**0.024**

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; Hb., hemoglobin; ALC/WBC, absolute lymphocyte count/white blood cell count; CR, complete response; PR, partial response.

Figure S1. CONSORT diagram

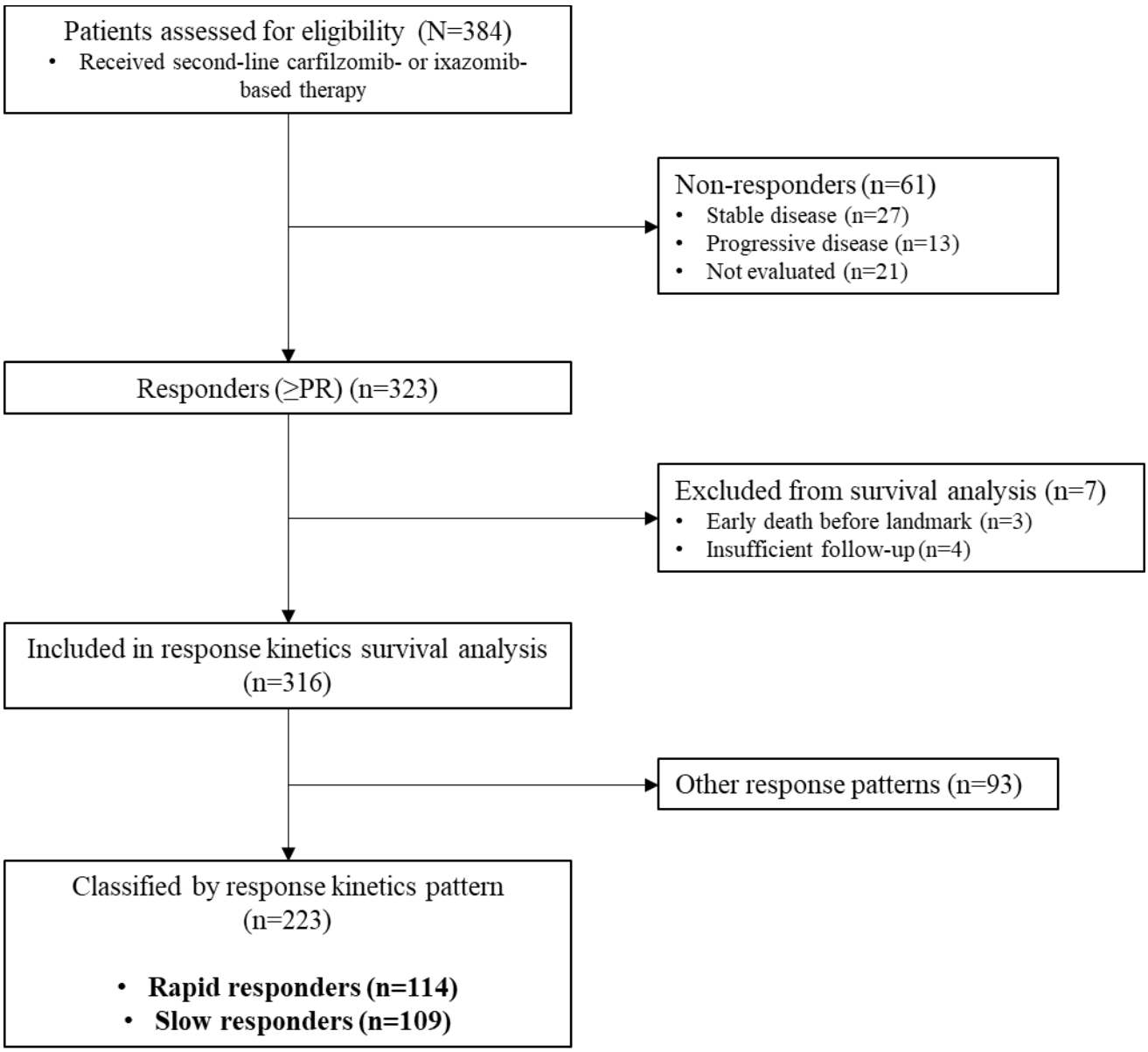
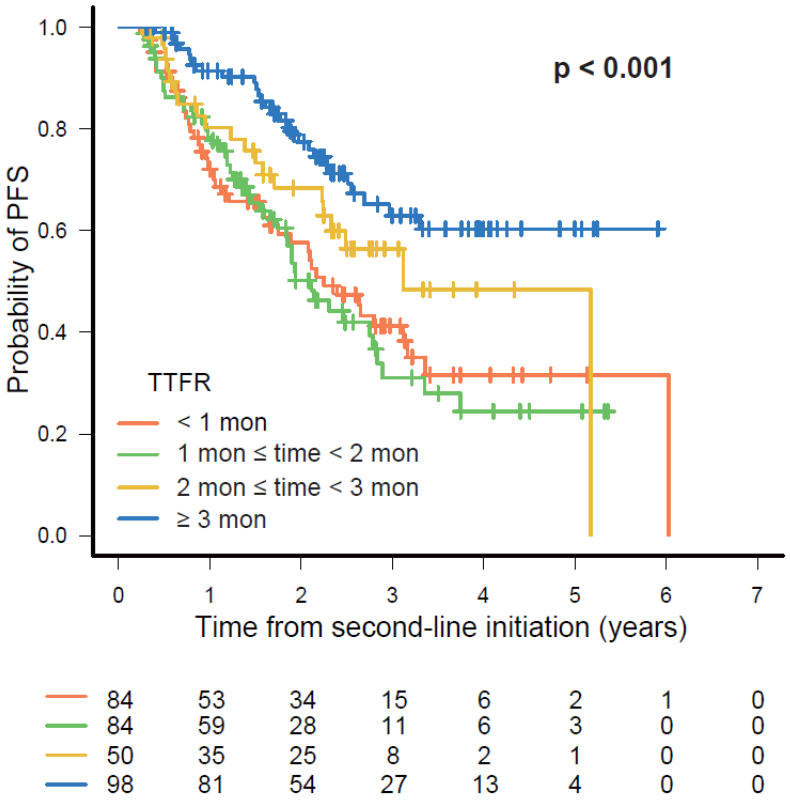


Figure S2. Survival outcomes according to the time to first response after second-line therapy with landmark analysis (n=316)



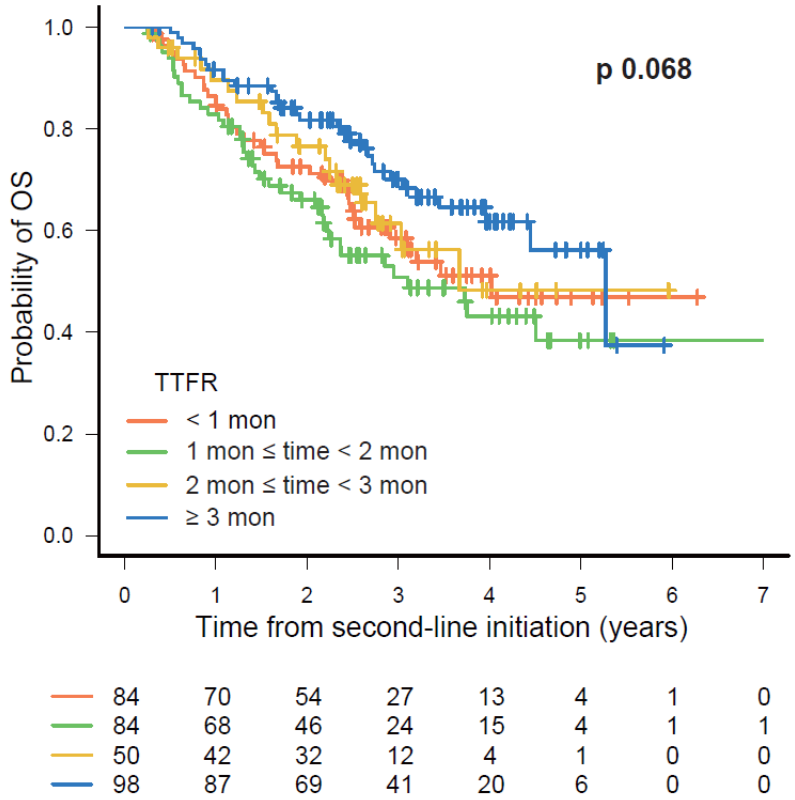


Figure S3. Survival outcomes according to the time to best response after second-line therapy with landmark analysis (n=316)