Supplementary Appendix

~~**The natural history of systemic AL Amyloidosis following upfront treatment with Bortezomib: An analysis of longitudinal data in a real-world setting.**~~

Haematologic responses and survival do not significantly decrease with subsequent lines of therapy in systemic AL amyloidosis: Results from an analysis of real-world longitudinal data

Table of contents

Table SA 1	Page 3
Table SA 2	Page 4
Table SA 3	Page 5
Table SA 4	Page 5
Figure Legends	Page 7
Figure SA1	Page 10
Figure SA2	Page 10
Figure SA3	Page 11
Figure SA4	Page 11
Figure SA5	Page 12
Figure SA6	Page 12
Figure SA7	Page 13
Figure SA8	Page 13

Figure SA9 Page 14

Figure SA10 Page 14

Figure SA11 Page15

Figure SA12 Page 15

Figure SA13 Page 16

Figure SA14 Page 16

Table SA 1: Case mix of AL amyloidosis- 2009-2019

Year	No. enrolled in ALchemy	No. treated with Bortezomib (%)	Boretzomib cohort		
			Cardiac (%)	Renal (%)	Liver (%)
2009	49	0 (0)			
2010	111	8 (7)	3 (38)	7 (88)	3 (38)
2011	178	41 (23)	38 (93)	30 (73)	6 (15)
2012	195	90 (46)	62 (69)	52 (58)	8 (9)
2013	180	102 (57)	76 (75)	73 (72)	17 (17)
2014	233	172 (74)	96 (56)	126 (73)	30 (17)
2015	217	184 (85)	113 (61)	124 (67)	24 (13)
2016	234	186 (79)	117 (63)	135 (73)	28 (15)
2017	230	187 (81)	119 (64)	133 (71)	14 (7)
2018	246	203 (83)	129 (64)	141 (69)	13 (6)
2019	138	103 (75)	56 (54)	57 (56)	11 (11)
Total	2011	1276 (63.5)	809 (63)	878 (69)	154 (12)

Table SA 2: Baseline characteristics at start of 2nd, 3rd and 4th lines of treatment

Characteristic, Median (Range)	**2nd line**	**3rd line**	**4th line**
dFLC, mg/l	91.5 (1.6-6064)	96.5 (1.3-2500)	136.4 (33.2-4076)
NT-ProBNP, ng/l	1463.5 (42-117874)	1260 (69-70000)	906.5 (96-70000)
Creatinine, µmol/l	107 (33-1051)	105 (33-1211)	119 (71-900)
Urine protein,gm/24 hours	2.05 (0-22.2)	0.8 (0.1-16.6)	0.5 (0.1-10.4)
ALP, u/l	86.5 (28-1203)	85 (28-486)	79.5 (32-516)

NT-proBNP, N-terminal pro B-type natriuretic peptide; dFLC, difference between involved and uninvolved light chains; ALP, Alkaline phosphatase

Table SA3: Treatment agents

Principle agent	**2nd line N=376**	**3rd line N=117**	**4th line N=32**	**5th line N=8**	**6th line N=2(%)**
Bortezomib	24 (6.4)	2 (1.7)	1 (3.1)		
Lenalidomide	175 (46.5)	50 (42.6)	8 (25)	1 (12.5)	
Melphalan	35 (9.3)	2 (1.7)	1 (3.1)	1 (12.5)	
Daratumumab	50 (13.3)	26 (22.2)	14 (43.8)	2 (25)	1 (50)
Autologous HSCT	34 (9)	10 (8.5)	2 (6.3)	2 (25)	
Panabinostat		4 (3.4)			1 (50)
Pomalidomide	6 (1.6)	11 (9.4)	5 (15.6)	2 (25)	
Carfilzomib	4 (1.1)	2 (1.7)			
Bendamustine	25 (6.6)	5 (4.3)			
Rituximab	3 (0.8)				
Thalidomide	12 (3.2)	1 (0.9)	1 (3.1)		
Cyclophosphamide	5 (1.3)				
Ixazomib	2 (0.6)	1 (0.9)			
Venetoclax	1 (0.3)				
Ibrutinib		1 (0.9)			
Platinum		1 (0.9)			
Allogeneic HSCT		1 (0.9)			

Table SA4: Reason for treatment

	2nd line (n=376)	**3rd line (n=117)**	**4th line (n=32)**
Haematologic or organ progression	243 (64.6%)	60 (51.2%)	21 (65.6%)
Inadequate response	113 (30.1)	47 (40.2)	10 (31.3)
Toxicity	14 (3.7)	3 (2.6)	0
Maintenance	3 (0.8)	7 (6)	1 (3.1)

Physician Choice	3 (0.8)	0	0

Figure legends

Figure SA1: Kaplan-Meier curve comparing OS in patients (ITT cohort) with FLC ratio < 100 at diagnosis based on lines of treatments (> 1 line vs only 1 line). Patients with > 1 line of treatment had a significantly better survival than those without any subsequent therapy after 1st line- median OS 74 months (95% CI 58.40-89.59 months) vs. 49 months (95% CI 36.91-61.09 months) ($p < 0.005$).

Figure SA2: Kaplan-Meier curve comparing OS in patients (ITT cohort) with FLC ratio ≥ 100 at diagnosis based on lines of treatments (> 1 line vs only 1 line). Patients with > 1 line of treatment had a significantly better survival than those without any subsequent therapy after 1st line- median OS not reached vs. 8 months (95% CI 36.91-61.09 months) ($p < 0.005$).

Figure SA3: Kaplan-Meier curve comparing OS in patients (12-month landmark cohort) with FLC ratio < 100 at diagnosis based on lines of treatments (> 1 line vs only 1 line). There was no significant difference in survival between patients with > 1 line of treatment and those without any subsequent therapy after 1st line- median OS 80 months (95% CI 66.95-93.04 months) vs. 89 months ($p = 0.070$).

Figure SA4: Kaplan-Meier curve comparing OS in patients (12-month landmark cohort) with FLC ratio > 100 at diagnosis based on lines of treatments (> 1 line vs only 1 line). There was no significant difference in survival between patients with > 1 line of treatment and those without any subsequent therapy after 1st line- median OS not reached in both groups ($p = 0.638$).

Figure SA5: Kaplan-Meier curve comparing OS in Mayo stage I patients (ITT cohort) based on lines of treatments (> 1 line vs only 1 line). There was no significant difference in survival between patients with > 1 line of treatment and those without any subsequent therapy after 1st line- median OS 87 months vs not reached ($p = 0.089$).

Figure SA6: Kaplan-Meier curve comparing OS in Mayo stage II patients (ITT cohort) based on lines of treatments (> 1 line vs only 1 line). Patients with > 1 line of treatment had a significantly better survival compared to patients without subsequent therapy after 1st line- median OS not reached vs 80 months (95% CI 66.14-93.86 months) (p = 0.043).

Figure SA7: Kaplan-Meier curve comparing OS in Mayo stage III patients (ITT cohort) based on lines of treatments (> 1 line vs only 1 line). Patients with > 1 line of treatment had a significantly better survival compared to patients without subsequent therapy after 1st line- median OS 58 months (95% CI 48.19-67.80 months) vs 26 months (95% CI 19.03-32.96 months) (p < 0.005).

Figure SA8: Kaplan-Meier curve comparing OS in Mayo stage IIIb patients (ITT cohort) based on lines of treatments (> 1 line vs only 1 line). Patients with > 1 line of treatment had a significantly better survival compared to patients without subsequent therapy after 1st line- median OS not reached vs 4 months (95% CI 2.85-5.14 months) (p < 0.005).

Figure SA9: Kaplan-Meier curve comparing OS in Mayo stage I patients (12-month landmark cohort) based on lines of treatments (> 1 line vs only 1 line). Patients with > 1 line of treatment had a significantly poorer survival compared to patients without subsequent therapy after 1st line- median OS 87 months vs not reached (p = 0.001).

Figure SA10: Kaplan-Meier curve comparing OS in Mayo stage II patients (12-month landmark cohort) based on lines of treatments (> 1 line vs only 1 line). There was no significant difference in survival between the two groups- median OS 109 months (95% CI 61.48-156.52 months) vs not reached (p = 0.158).

Figure SA11: Kaplan-Meier curve comparing OS in Mayo stage III patients (12-month landmark cohort) based on lines of treatments (> 1 line vs only 1 line). There was no significant difference in survival between the two groups- median OS 61 months vs 60 months (95% CI 50.16-69.84 months) (p = 0.534).

Figure SA12: Kaplan-Meier curve comparing OS in Mayo stage IIIb patients (12-month landmark cohort) based on lines of treatments (> 1 line vs only 1 line). There was no significant difference in survival between the two groups- median OS not reached vs 71 months (95% CI 45.26-96.73 months) (p = 0.795).

Figure SA13: Kaplan-Meier curve showing the impact of haematologic response after 3rd line on OS after 3rd line treatment. Patients with CR or VGPR had a significantly better survival than those with a PR or NR- median OS not reached / non reached vs. 31 months (95% CI 15.52-46.47 months) / 19 months (95% CI 16.85-21.14 months) (p < 0.005). There was no difference in survival between CR and VGPR (p = 0.596).

Figure SA14: Kaplan-Meier curve showing the impact of haematologic response after 3rd line on TNT after 3rd line treatment. Patients with CR or VGPR after 3rd line had a significantly longer TNT than those with PR/NR- median TNT 32 months (24.46-39.53) / 44 months vs. 36 months / 13 months (95% CI 5.11-20.88 months) (p=0.008). There was no difference in TNT between CR and VGPR (p = 0.436).

Figure SA1

Overall Survival in patients with FLC ratio < 100: > 1 line vs only 1 line (ITT cohort)

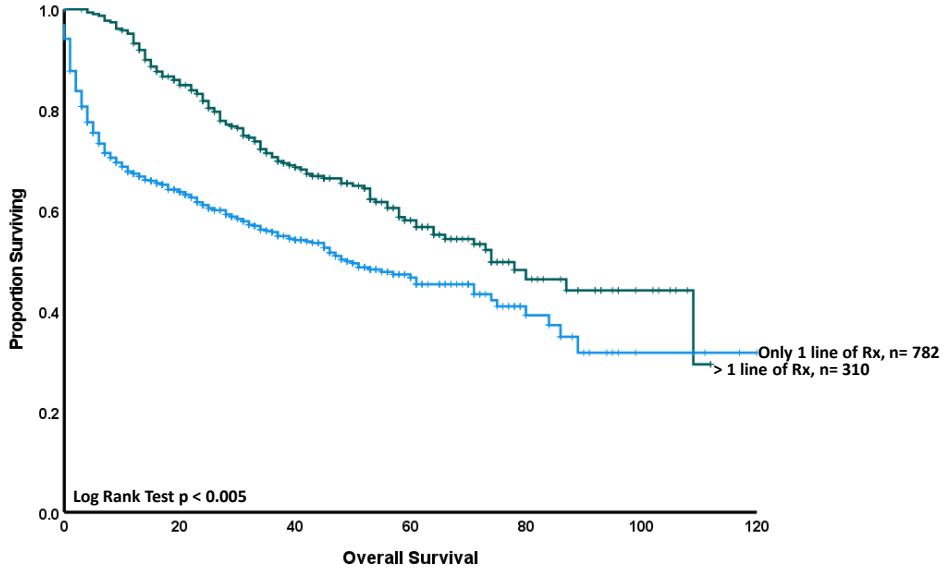


Figure SA2

Overall Survival in patients with FLC ratio > 100: > 1 line vs only 1 line (ITT cohort)

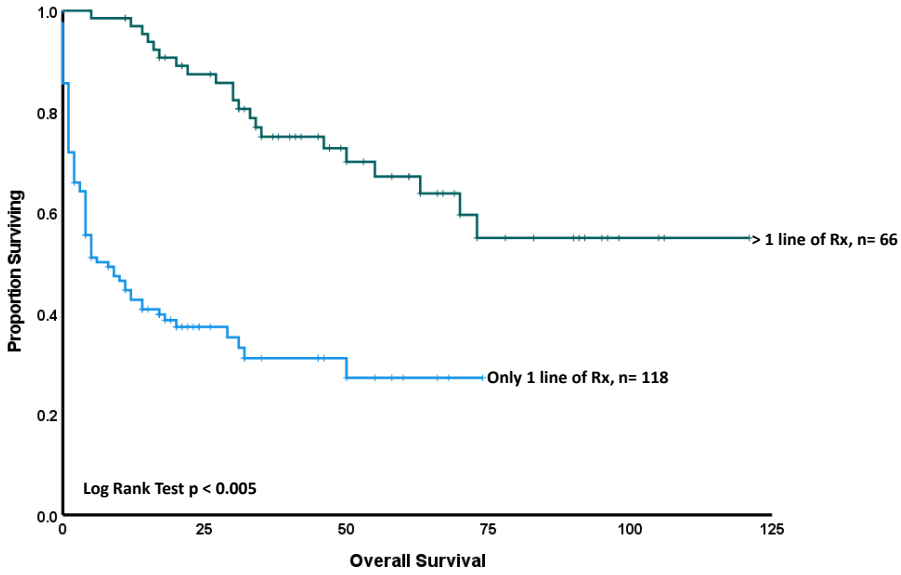


Figure SA3

Overall Survival in patients with FLC ratio < 100: > 1 line vs only 1 line (12-month cohort)

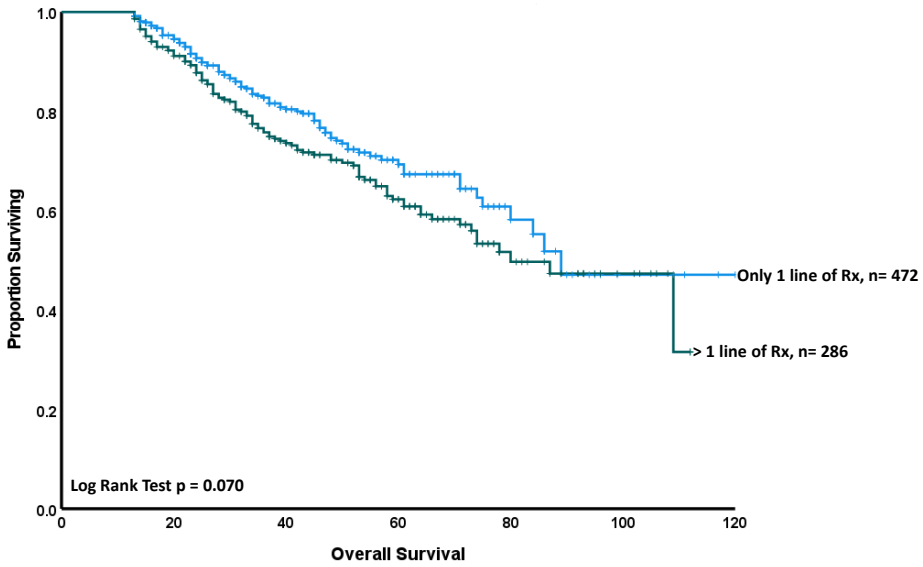


Figure SA4

Overall Survival in patients with FLC ratio > 100: > 1 line vs only 1 line (12 -months landmark cohort)

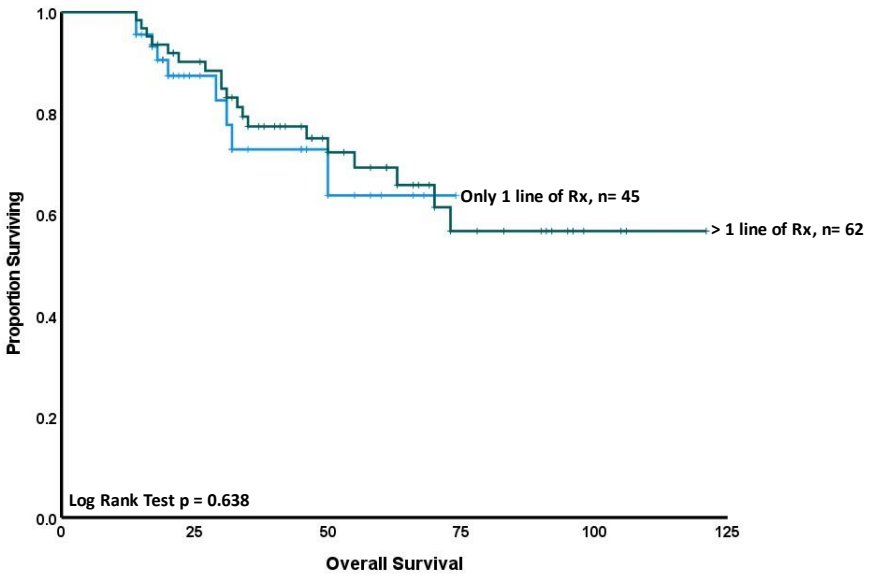


Figure SA5

ITT cohort, Mayo stage I: > 1 line vs only 1 line

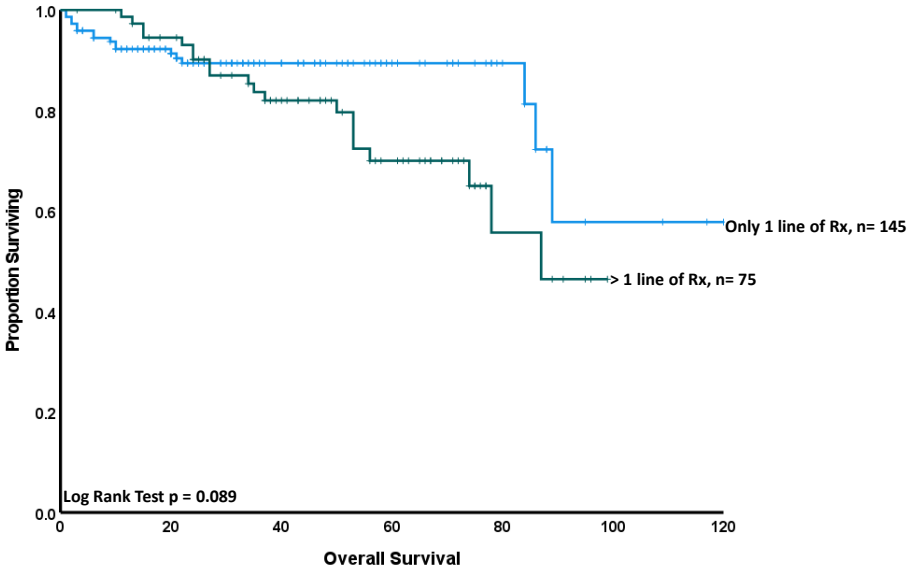


Figure SA6

ITT cohort, Mayo stage II: > 1 line vs only 1 line

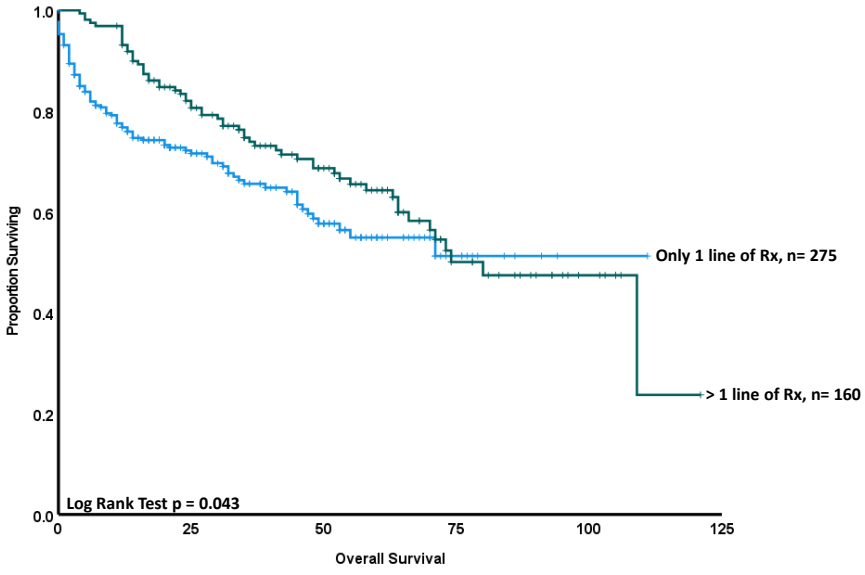


Figure SA7

ITT cohort, Mayo stage III: > 1 line vs only 1 line

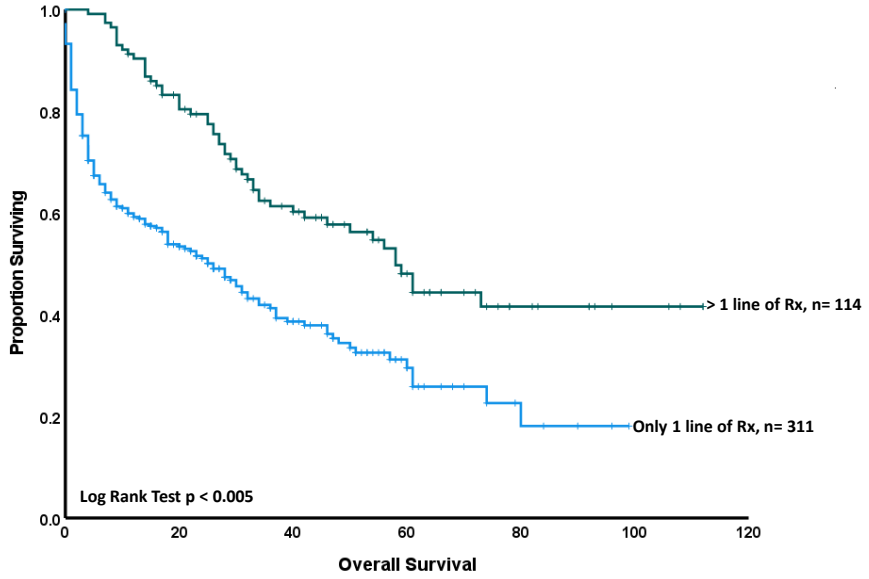


Figure SA8

ITT cohort, Mayo stage IIIb: > 1 line vs only 1 line

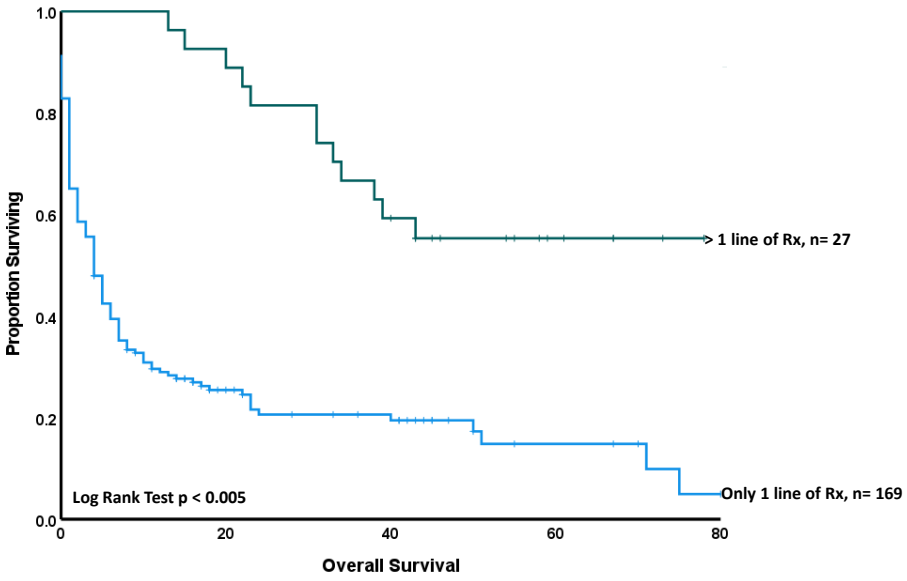


Figure SA9

12-month landmark cohort, Mayo stage I: > 1 line vs only 1 line

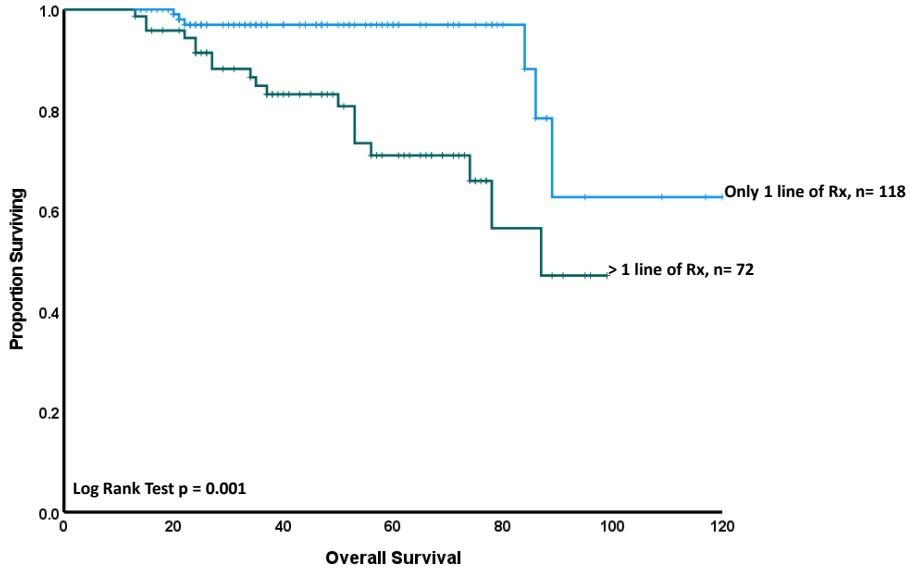


Figure SA10

12-month landmark cohort, Mayo stage II: > 1 line vs only 1 line

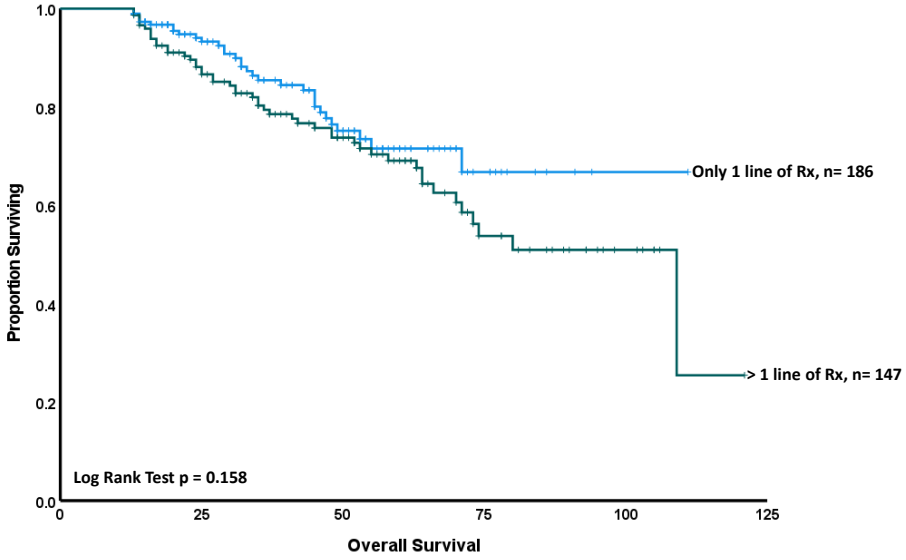


Figure SA11

12-month landmark cohort, Mayo stage III: > 1 line vs only 1 line

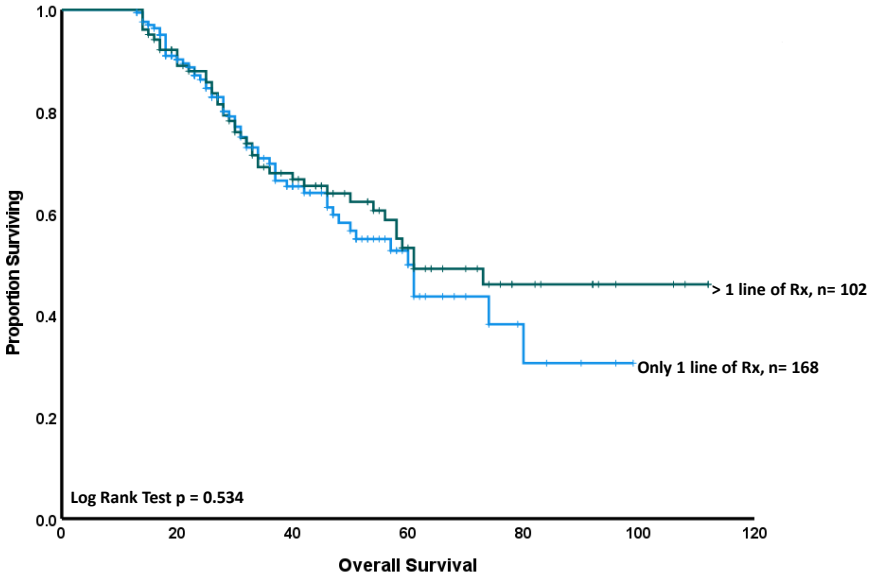


Figure SA12

12-month landmark cohort, Mayo stage IIIb: > 1 line vs only 1 line

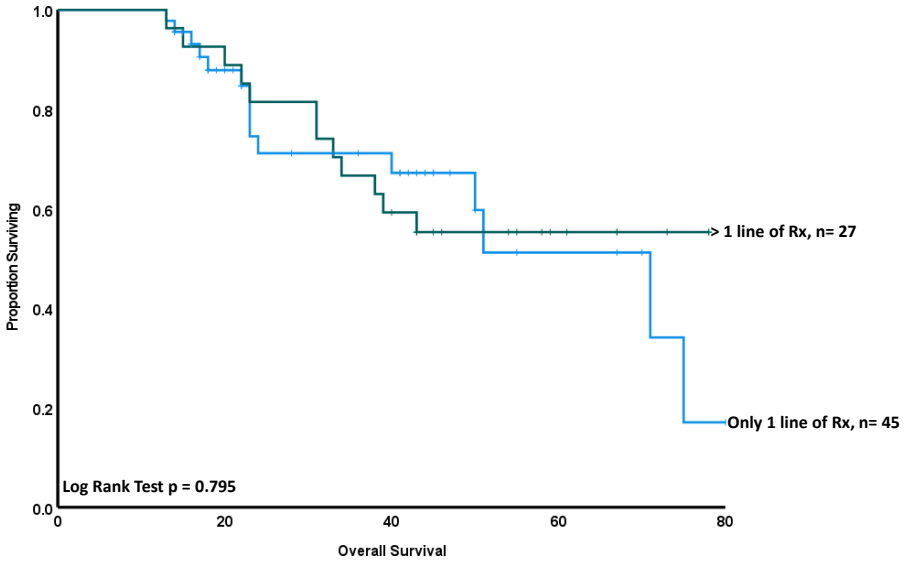


Figure SA13

Impact of haematologic response (after 3rd line) on OS from 3rd line

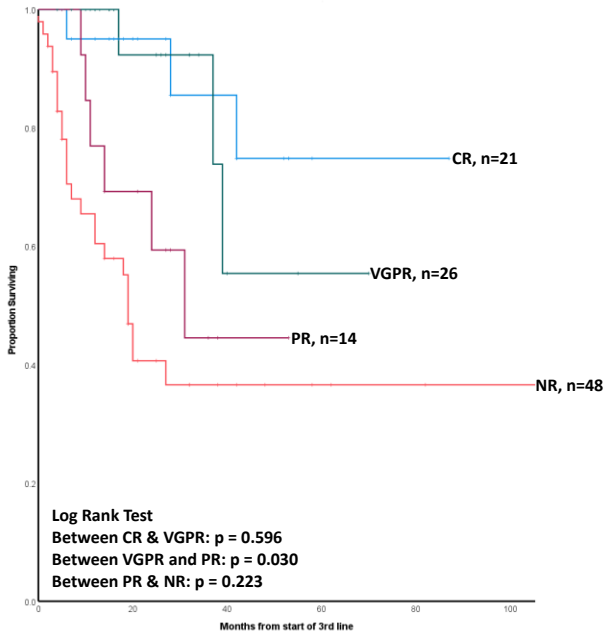
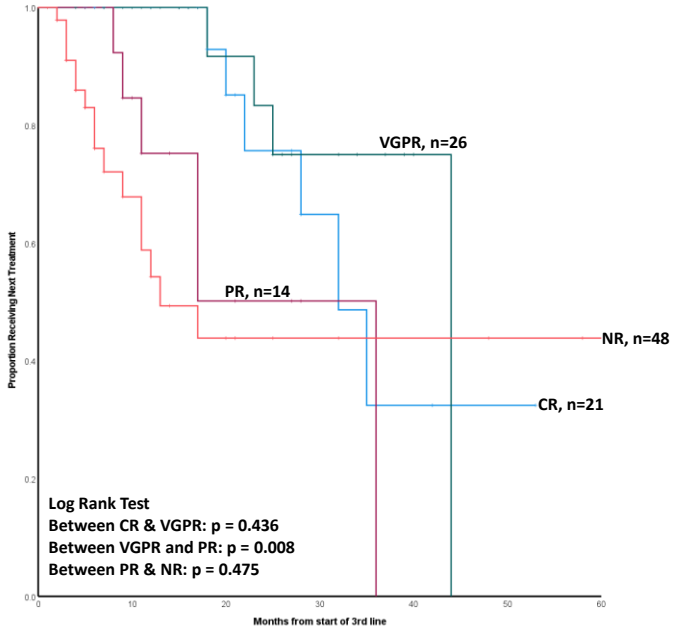


Figure SA14

Impact of haematologic response (after 3rd line) on TNT from 3rd line