Clonal plasma cell features in light chain amyloidosis are associated with depth and timing of cardiac response independent of hematologic response

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Supplement to clonal plasma cell features in light-chain amyloidosis are associated with depth and timing of cardiac response independent of hematologic response.

Methods:

Exclusion criteria included previous treatment for a related hematologic disease. Acceptable time periods for milestone data not conforming to the exact milestone date were: 6 months +/- 1 month, 12 months +/- 2 months, 24 months +/- 3 months. HRCAs included: del(17p), t(4;14), t(14;16), and t(14;20). FISH probes for gain/amplification of chromosome 1q were not uniformly performed between 2010 and 2014, as such 1q status was unknown in 56 (19%) of patients, and therefore was not included in the main analyses.

Due to the heterogeneity of treatments used over the study period, they were categorized as follows: chemotherapy refers to melphalan-based, steroid monotherapy or bendamustine-based regimens, proteasome inhibitor (PI)-based refers to any PI containing regimen which did not contain an immunomodulatory agent (IMID), venetoclax or an anti-CD38 monoclonal antibody, IMID-based refers to any IMID containing regimen which did not contain an anti-CD38 monoclonal antibody, daratumumab-based refers to any anti-CD38 containing regimen, and venetoclax-based refers to any venetoclax containing regimen. Autologous stem cell transplant (ASCT) was applied in several ways over the study period, some patients proceeded to ASCT without any induction therapy while others received induction. Front-line ASCT was defined as ASCT received as part of first-line treatment, with or without prior induction. Only front-line ASCT was included as a covariate in predictors of CarR and survival.

Continuous and quantitative discrete variables were described as a median and interquartile range (IQR); categorical variables were described as a number and percentage. A two-sided P-value <0.05 was considered statistically significant. Group comparisons were performed using the Pearson χ2-squared test and Kruskal-Wallis test for nominal and continuous variables respectively. As cardiac response is a time-dependent covariate, the Simon-Makuch method was used to graph the influence of cardiac response on overall survival. This method is a non-parametric graphical representation of survival for time-dependent covariates.

Supplemental Figure 1. Cumulative incidence of deep cardiac response (≥CarVGPR) with death as a competing event according to attainment of a deep hematological response (≥HemVGPR) within 3- and 6-months of commencing treatment.
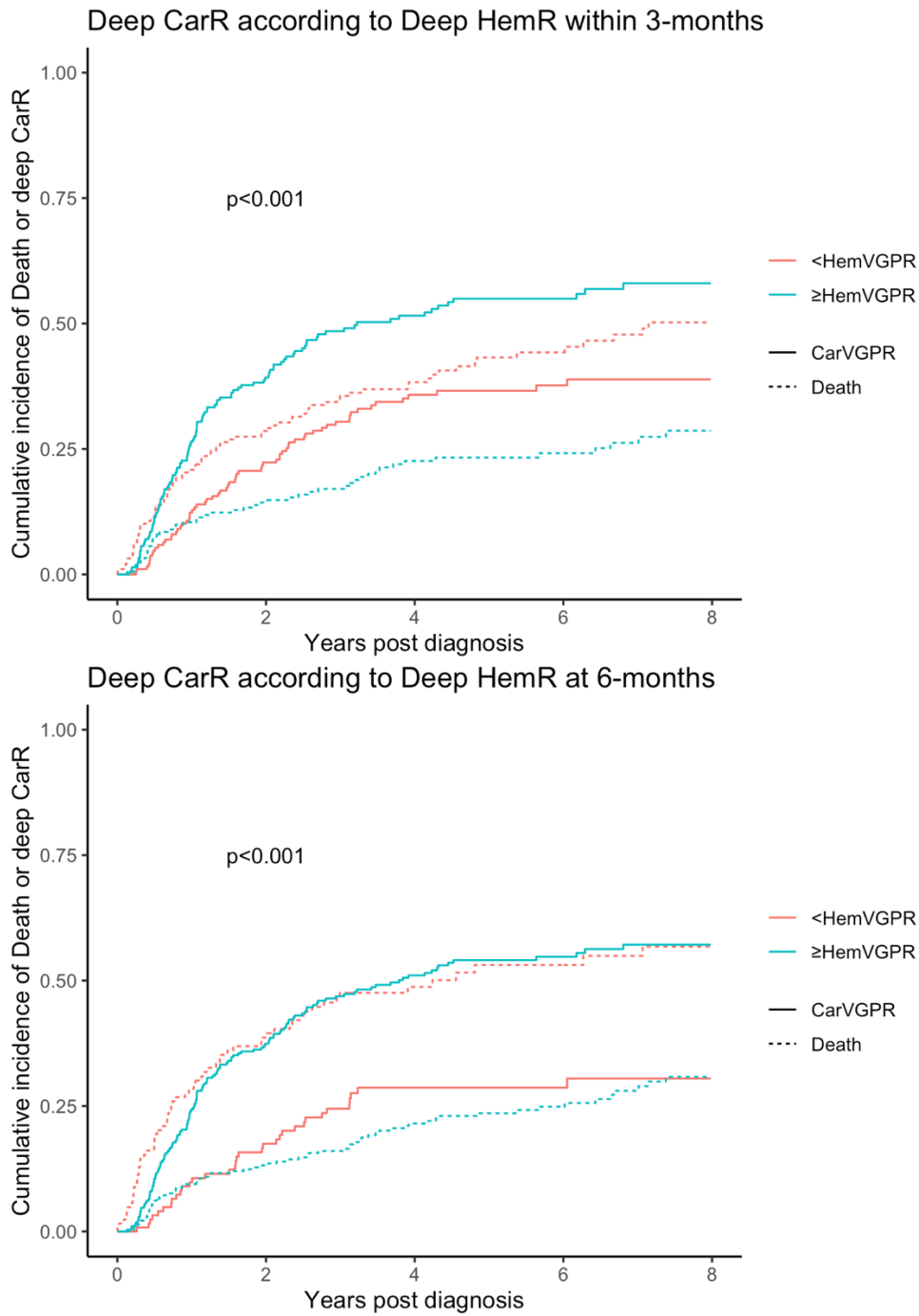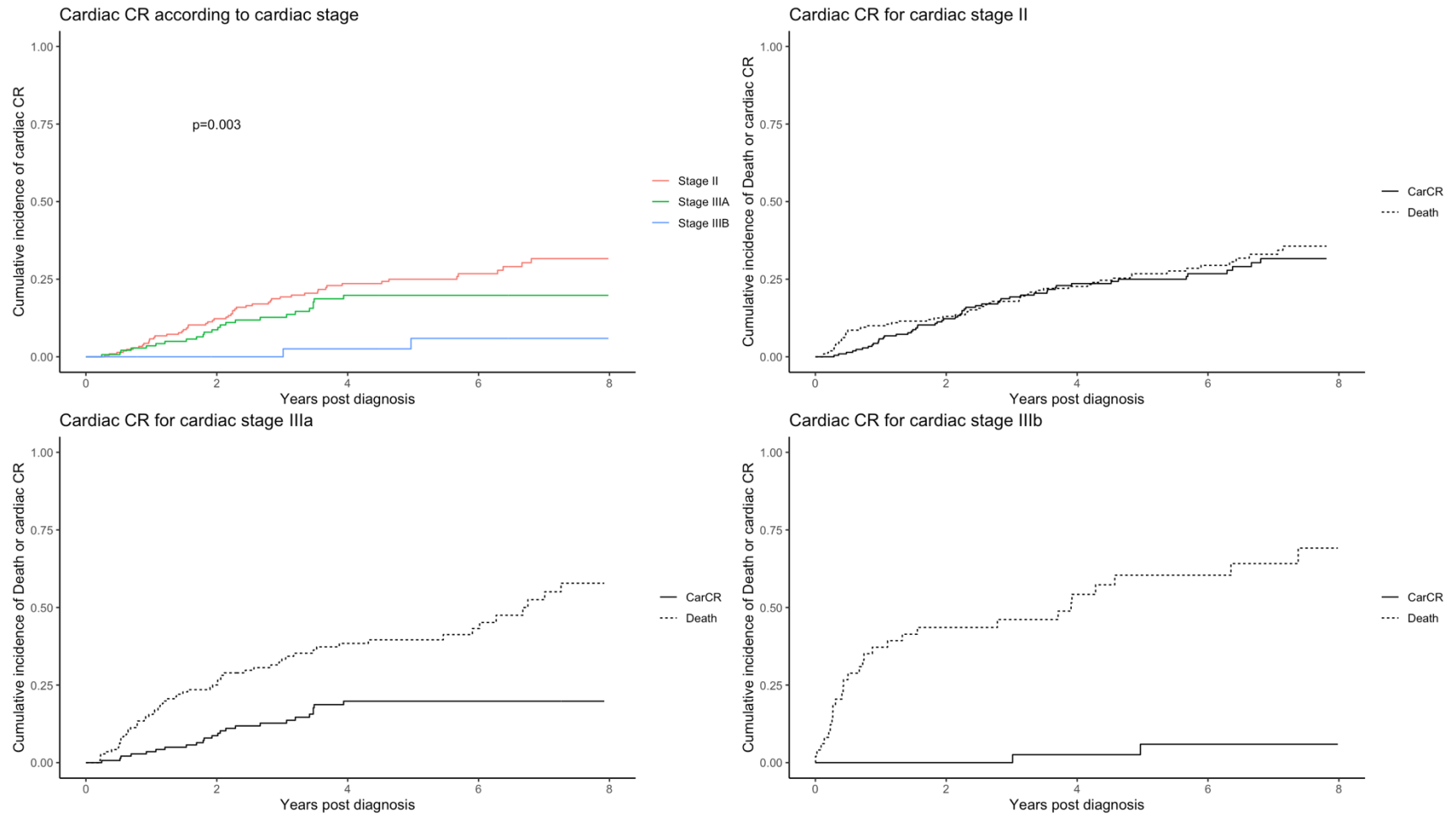
Supplemental Figure 2. **Cumulative incidence of deep cardiac response (≥CarVGPR) with death as a competing event according to cardiac stage.**
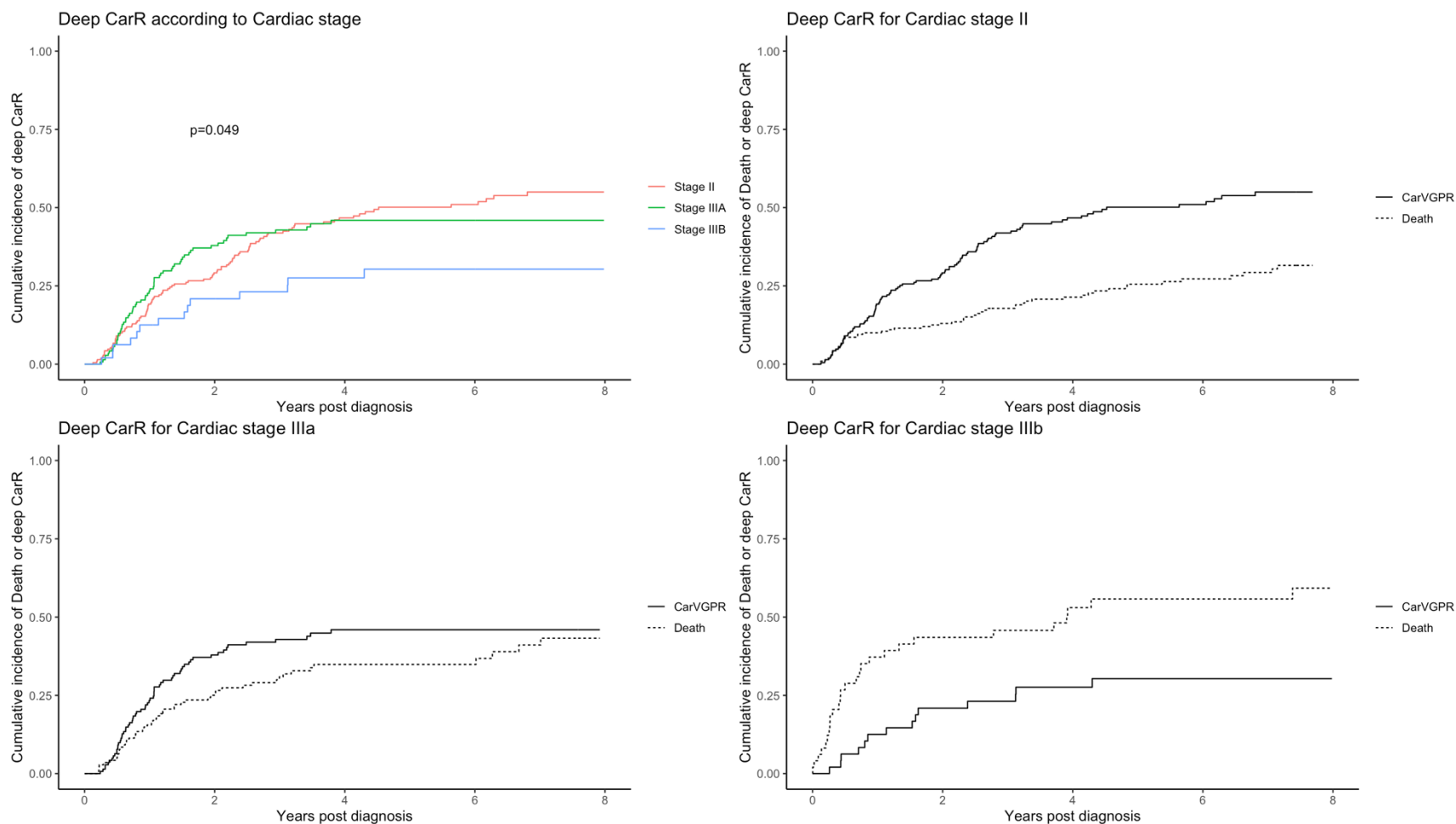
Supplementary Figure 3. Cumulative incidence of complete cardiac response with death as a competing event according to cardiac stage.

Supplementary Table 1. First and second line treatments received.

	TREATMENT	NUMBER (%)
1st Line treatment	VCd	234 (58%)
	Dara-VCd	42 (10%)
	ASCT no induction	37 (9%)
	MDex	23 (6%)
	ICd	19 (5%)
	Vd	15 (4%)
	VRd	7 (2%)
	BRit	5 (1%)
	Dara-Vd	5 (1%)
	Dara only	4 (1%)
	MPred	1 (0.2%)
	Rd	1 (0.2%)
	VMPred	1 (0.2%)
	RCd	1 (0.2%)
	BRit-V	1 (0.2%)
	Dara-Rd	1 (0.2%)
	Dara-Pd	1 (0.2%)
	Rit-VCd	1 (0.2%)
	Dara-Cd	1 (0.2%)
	Rit-Cd	1 (0.2%)
Categories of 1st line treatment	PI-based	270 (67%)
	Dara-based	54 (13%)
	ASCT no induction	37 (9%)
	Chemotherapy	30 (7%)
	IMID-based	10 (2%)
2nd Line treatment	No 2nd line treatment	214 (53%)
	Dara only	48 (12%)
	VCd	28 (7%)
	Vd	18 (4%)
	Dara-Vd	18 (4%)
	Rd	13 (3%)
	MDex	7 (2%)
	Dara-Pd	7 (2%)
	Ven	5 (1%)
	Id	5 (1%)

	TREATMENT	NUMBER (%)
	Dara-VCd	5 (1%)
	Dara-Rd	4 (1%)
	VRD	3 (1%)
	R alone	3 (1%)
	V alone	3 (1%)
	Ird	3 (1%)
	Rit-VCd	2 (0.4%)
	ASCT no salvage	2 (0.4%)
	VMPred	2 (0.4%)
	Kd	2 (0.4%)
	Dara-Kd	2 (0.4%)
	Pd	2 (0.4%)
	Dexamethasone alone	1 (0.2%)
	KPd	1 (0.2%)
	Elo-Pd	1 (0.2%)
	Dara-Cd	1 (0.2%)
	Rit-Cd	1 (0.2%)
Categories of 2ND line treatment	No 2nd line treatment	214 (53%)
	Dara-based	85 (21%)
	PI-based	60 (15%)
	IMID-based	27 (7%)
	Chemotherapy	8 (2%)
	Ven-based	5 (1%)
	ASCT no salvage	2 (0.4%)

V= bortezomib, K = carfilzomib, d = dexamethasone, Dara = daratumumab, C = cyclophosphamide, M = melphalan, R = lenalidomide, P = pomalidomide, Pred = prednisone, I = ixazomib, B = bendamustine, Rit = rituximab, ASCT = autologous stem cell transplant, Ven = venetoclax, Isa = isatuximab, Elo = elotuzumab

Supplement Table 2. Best cardiac response by landmark time points and best cardiac response achieved overall.

Cardiac response	N = 401[1]	N = 401[1]	N = 401[1]	N = 401[1]
	6-months	12-months	24-months	Best response
Death	34 (8%)	58 (14%)	84 (21%)	-
NR	235 (59%)	157 (39%)	101 (25%)	148 (37%)
PR	85 (21%)	90 (22%)	82 (20%)	74 (18%)
VGPR	40 (10%)	74 (18%)	89 (22%)	97 (24%)
CR	7 (2%)	22 (5.5%)	45 (11%)	82 (20%)

NR, no response; PR, partial response; VGPR, very good partial response; CR, complete response.

Supplement Table 3. Univariate logistic regression of variables associated with any CaR (≥CarPR) at 6-months and deep CaR (≥CarVGPR) at 12, 24-months or best response on univariate logistic regression.

Characteristic	6-month any CarR (≥CarPR)				12-month deep CarR (≥CarVGPR)				24-month deep CarR (≥CarVGPR)				Deep CarR at best response (≥CarVGPR)			
	N	OR[1]	95% CI[1]	p-value	N	OR[1]	95% CI[1]	p-value	N	OR[1]	95% CI[1]	p-value	N	OR[1]	95% CI[1]	p-value
Age≥ 60-years	401	0.89	0.58, 1.39	0.6	401	0.61	0.38, 0.99	**0.044**	401	0.65	0.42, 1.01	0.055	401	0.56	0.37, 0.86	**0.007**
≥6 months from 1st medical encounter to Dx	395	0.66	0.43, 1.01	0.057	395	0.64	0.40, 1.03	0.064	395	0.68	0.45, 1.05	0.083	395	0.67	0.44, 1.01	0.057
Previous LPD	399	0.95	0.49, 1.76	0.9	399	0.76	0.35, 1.54	0.5	399	0.74	0.37, 1.40	0.4	399	0.66	0.35, 1.20	0.2
Lambda isotype	401	0.60	0.38, 0.95	**0.029**	401	0.64	0.39, 1.06	0.080	401	0.62	0.39, 0.98	**0.040**	401	0.58	0.37, 0.90	**0.015**
Bone-marrow PC≥20%	401	2.27	1.41, 3.64	**<0.001**	401	2.85	1.72, 4.70	**<0.001**	401	2.07	1.29, 3.32	**0.003**	401	1.91	1.20, 3.05	**0.007**
dFLC≥60mg/dL	401	1.80	1.13, 2.85	**0.012**	401	1.70	1.02, 2.78	**0.037**	401	1.65	1.04, 2.61	**0.033**	401	1.69	1.08, 2.66	**0.021**
HRCAs [Del17p, t(4;14), t(14;16), t(14;20)]	291	1.91	0.91, 4.02	0.086	291	3.76	1.77, 8.06	**<0.001**	291	3.84	1.80, 8.60	**<0.001**	291	3.10	1.43, 7.31	**0.006**
t(11;14)	291	0.60	0.37, 0.97	**0.038**	291	0.52	0.30, 0.88	**0.017**	291	0.50	0.31, 0.81	**0.006**	291	0.53	0.33, 0.85	**0.008**
Cardiac stage - Mayo 2004 with Modification	401				401				401				401			
Stage II		—	—			—	—			—	—			—	—	
Stage IIIA		1.05	0.67, 1.65	0.8		1.24	0.76, 2.02	0.4		1.29	0.83, 2.01	0.3		0.84	0.55, 1.29	0.4
Stage IIIB		0.72	0.35, 1.42	0.4		0.64	0.26, 1.40	0.3		0.52	0.24, 1.07	0.092		0.42	0.21, 0.82	**0.013**
≥HemVGPR within 6 months	401	2.85	1.73, 4.85	**<0.001**	401	3.65	2.01, 7.14	**<0.001**	401	3.38	2.03, 5.85	**<0.001**	401	2.91	1.85, 4.65	**<0.001**
Dara-based induction	401	1.62	0.89, 2.90	0.11	401	1.72	0.91, 3.17	0.085	401	1.32	0.72, 2.37	0.4	401	1.40	0.79, 2.49	0.3
Front-line ASCT	401	1.80	1.15, 2.82	**0.010**	401	1.96	1.21, 3.16	**0.006**	401	2.63	1.69, 4.12	**<0.001**	401	2.85	1.84, 4.47	**<0.001**

[1]OR = Odds Ratio, CI = Confidence Interval, Dx = diagnosis, LPD = lymphoproliferative disease, PC = plasma cell, dFLC = difference between involved and uninvolved free light chain, HRCA = high risk cytogenetic abnormality, HemVGPR = hematological very good partial response, ASCT = autologous stem cell transplant, Dara = daratumumab.

Supplement Table 4. Multivariable logistic regression model of covariates associated with any CarR (≥CarPR) at 6-months and deep CarR (≥CarVGPR) at 12, 24-months or best response, including dFLC≥60mg/dL in place of bone marrow plasma cell percentage.

Characteristic	6-month any CarR (≥CarPR)			12-month deep CarR (≥CarVGPR)			24-month deep CarR (≥CarVGPR)			Deep CarR at best response (≥CarVGPR)		
	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value
dFLC≥60 (mg/dL)	2.01	1.13, 3.61	**0.017**	1.92	1.01, 3.66	**0.047**	1.84	1.01, 3.39	**0.047**	1.42	0.80, 2.54	0.2
Lambda isotype	0.57	0.32, 1.02	0.059	0.52	0.27, 0.99	**0.046**	0.51	0.28, 0.93	**0.030**	0.48	0.26, 0.86	**0.014**
HRCAs [Del17p, t(4;14), t(14;16), t(14;20)]	1.63	0.75, 3.52	0.2	3.49	1.58, 7.82	**0.002**	3.97	1.76, 9.42	**<0.001**	2.80	1.23, 6.85	**0.013**
≥HemVGPR within 6 months	3.18	1.74, 6.07	**<0.001**	3.26	1.61, 7.11	**<0.001**	3.52	1.87, 6.91	**<0.001**	2.31	1.32, 4.13	**0.003**
≥6 months from 1st medical encounter to Dx	0.67	0.40, 1.13	0.13	0.54	0.31, 0.96	**0.037**		Not included		0.71	0.42, 1.19	0.2
Age ≥60 yrs		Not included		0.55	0.31, 1.00	**0.050**		Not included			Not included	
Front-line ASCT		Not included			Not included		2.39	1.32, 4.38	**0.004**	2.42	1.40, 4.26	**0.002**
Cardiac stage - Mayo 2004 with Modification		Not included			Not included				**0.014**		Not included	
Stage II							Ref	—				
Stage IIIA							2.37	1.31, 4.35				
Stage IIIB							1.20	0.45, 3.09				

[1]OR = Odds Ratio, CI = Confidence Interval

Supplement Table 5. Multivariable logistic regression model of covariates associated with any CarR (≥CarPR) at 6-months and deep CarR (≥CarVGPR) at 12, 24-months or best response, including gain/amplification of chromosome 1q as a HRCA (n=235).

Characteristic	6-month any CarR (≥CarPR)			12-month deep CarR (≥CarVGPR)			24-month deep CarR (≥CarVGPR)			Deep CarR at best response (≥CarVGPR)		
	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value
Bone-marrow PC≥20%	2.45	1.30, 4.64	**0.005**	3.08	1.58, 6.08	**<0.001**	1.58	0.82, 3.03	0.2	1.71	0.92, 3.22	0.091
Lambda isotype	0.50	0.26, 0.97	**0.039**	0.42	0.21, 0.84	**0.014**	0.51	0.26, 0.99	**0.046**	0.51	0.26, 0.98	**0.043**
HRCAs [1q+, del17p, t(4;14), t(14;16), t(14;20)]	2.41	1.31, 4.49	**0.005**	1.83	0.95, 3.51	0.071	2.66	1.43, 5.01	**0.002**	1.93	1.05, 3.59	**0.035**
≥HemVGPR within 6 months	2.97	1.51, 6.14	**0.001**	3.47	1.62, 8.09	**0.001**	3.40	1.68, 7.30	**<0.001**	2.02	1.08, 3.86	**0.028**
≥6 months from 1st medical encounter to Dx	0.62	0.34, 1.12	0.11	0.53	0.28, 1.01	0.052				0.62	0.35, 1.11	0.11
Age ≥60 yrs				0.59	0.31, 1.14	0.11						
Front-line ASCT							2.54	1.27, 5.15	**0.008**	2.87	1.50, 5.66	**0.001**
Cardiac stage - Mayo 2004 with Modification									0.13			
Stage II							—	—				
Stage IIIA							1.96	0.99, 3.94				
Stage IIIB							1.03	0.34, 2.94				

[1] OR = Odds Ratio, CI = Confidence Interval

Supplementary Table 6. Multivariable proportional subdistribution hazards (Fine-Gray) model of factors associated with obtaining a deep CaR (≥CarVGPR), treating death as a competing risk, analysis includes gain/amplification of chromosome 1q as a HRCA (n=235).

Characteristic	HR[1]	95% CI[1]	p-value
Age ≥ 60 yrs	0.80	0.54, 1.18	0.3
Bone-marrow PC≥20%	1.37	0.89, 2.11	0.2
Lambda isotype	0.60	0.41, 0.90	**0.012**
HRCAs [1q+, del17p, t(4;14), t(14;16), t(14;20)]	1.85	1.20, 2.86	**0.005**
≥HemVGPR within 6 months	1.98	1.24, 3.16	**0.004**
Cardiac stage - Mayo 2004 with Modification			0.4
Stage II	—	—	
Stage IIIA	1.30	0.82, 2.09	
Stage IIIB	0.73	0.31, 1.72	
Front-line ASCT	1.76	1.13, 2.72	**0.011**

[1] HR = Hazard Ratio, CI = Confidence Interval

Supplementary Table 7. Multivariable cox proportional hazards model of covariates associated with overall survival.

Characteristic	HR[1]	95% CI[1]	p-value
Age ≥ 60 yrs	1.33	0.93, 1.90	0.11
Bone-marrow PC≥20%	0.86	0.58, 1.28	0.5
Lambda isotype	1.75	1.17, 2.62	**0.004**
≥HemVGPR within 6 months	0.44	0.31, 0.61	**<0.001**
Cardiac stage - Mayo 2004 with Modification			**0.003**
Stage II	—	—	
Stage IIIA	1.48	1.03, 2.12	
Stage IIIB	2.21	1.40, 3.49	
Front-line ASCT	0.55	0.37, 0.82	**0.002**

[1]HR = Hazard Ratio, CI = Confidence Interval

Supplementary Table 8. Hematological response at 6-, 12- and best response ever obtained according to 1st line ASCT.

Characteristic	No 1st line ASCT N = 283[1]	Received 1st line ASCT N = 118[1]	p-value[2]
6-month HemR			0.7
No-response	20 (8%)	8 (7%)	
PR	51 (21%)	25 (23%)	
dFLC-PR	5 (2%)	0 (0%)	
VGPR	102 (41%)	46 (41%)	
CR	69 (28%)	32 (29%)	
12-month HemR			0.8
No-response	10 (5%)	2 (2%)	
PR	27 (12%)	12 (11%)	
dFLC-PR	4 (2%)	1 (1%)	
VGPR	90 (40%)	43 (39%)	
CR	93 (42%)	51 (47%)	
Best HemR*			**0.006**
No-response	15 (5%)	1 (1%)	
PR	34 (12%)	5 (4%)	
dFLC-PR	3 (1%)	1 (1%)	
VGPR	90 (32%)	36 (31%)	
CR	141 (50%)	74 (63%)	

[1]n (%).[2] Fisher's exact test * Not assessed in 1 patient. PR, partial response; VGPR, very good partial response; dFLC-PR, difference of free light-chains partial response; CR, complete response; ASCT, autologous stem cell transplant.