Supplementary material

Supplementary Table S1. Whole cohort characteristics

	CRP available n=222	**No CRP available* n=48**
Clinical data		
Age (years), *mean [range]*	64.5 [28.4-88.2]	60.9 [36.8-82.2]
Male*, n (%)*	147/222 (66)	26/48 (54)
Lymphadenopathies, *n (%)*	52/219 (24)	13/46 (28)
Splenomegaly, *n (%)*	25/218 (11)	5/46 (11)
Hyperviscosity, *n (%)*	16/219 (7)	2/46 (4)
Past history of dysimmune conditions**	17/202 (8)	9/43 (21)
Biological data		
CRP (mg/L), *mean [range]*	16.7 [0-263.0]	NR
Kappa isotype, *n (%)*	174/221 (79)	34/46 (74)
M spike (g/L), *mean [range]*	17.0 [0.1-71.0]	20.6 [2.4-78.6]
Anemia (<11.5 g/dL), *n (%)*	106/167 (63)	22/34 (65)
Thrombopenia (<100 G/L), *n (%)*	24/166 (14)	5/30 (17)
Medullary infiltration (%), *mean [range]*	38.8 [2.0-97.0]	41.3 [10.0-90.0]
Albumin (g/L), *mean [range*]	38.4 [15.0-50.5]	38.0 [24.9-45.6]
β2 microglobulin (mg/L), *mean [range]*	3.3 [1.2-33.0]	2.6 [0.1-6.3]
Cytogenetics/molecular biology		
6q deletion, *n (%)*	49/178 (28)	11/40 (28)
TP53 abnormalities, *n (%)*	20/190 (11)	6/41 (15)
Complex karyotype, *n (%)*	27/159 (17)	4/31 (13)
Trisomy 12, *n (%)*	12/177 (7)	5/40 (13)
Trisomy 4, *n (%)*	20/178 (11)	7/40 (18)
MYD88 mutation, *n (%)*	148/164 (90)	30/32 (94)
CXCR4 mutation, *n (%)*	37/157 (24)	10/31 (32)
CD79A or B mutation, *n (%)*	9/135 (7)	1/27 (4)
MLL2 mutation, n(%)	12/109 (11)	3/22 (14)
ARID1A mutation, *n(%)*	13/135 (10)	1/27 (4)
Follow-up		
Need for treatment, *n (%)*	167/222 (75)	38/48 (79)
ORR***, *n(%)*	99/160 (62)	21/35 (60)
VGPR+CR, *n(%)*	32/160 (20)	1/35 (3)
DLBCL transformation, *n (%)*	11/222 (5)	3/48 (6)
CRP after 1st line treatment (mg/L), *mean [range]*	3.6 [0.0-69.0]	NR

**If patients had only one dosage of CRP (n=12), they were excluded and considered as part of the "no CRP available" group (n=48). Nine patients had unconfirmed high levels of CRP, in most of the cases because of a transient and documented infectious event. These patients were considered as non-inflammatory patients.*

*** Among: thyroiditis (Hashimoto/Basedow; n=10), pseudopolyarthritis rhizomelic (n=4), Raynaud syndrome without cryoglobulinemia (n=2), autoimmune hepatitis/cholangitis (n=2), type 1 mellitus diabetes (n=1), lupus*

erythematosus (n=1), celiac disease (n=1), myasthenia gravis (n=1), psoariasis (n=1), Gougerot-Sjogren syndrome (n=1), familial Mediterranean fever (n=1) and polymyositis (n=1).
**** ORR = CR + VGPR + PR*
Abbreviations: CRP, C-reactive protein ; ORR, Overall Response Rate ; CR, Complete Response ; VGPR, Very Good Partial Response ; PR, Partial Response ; DLBCL = Diffuse Large B Cell Lymphoma ; NR, Not Relevant

Supplementary Table S2. Association between patients' characteristics and CRP as a continuous variable.

	CRP value (mg/L), n=222	
Clinical data	HR [CI95%] or r	p
Age at diagnosis	0.03	-
Male	1.02[1.00-1.03]	**0.04**
Lymphadenopathies	1.02[1.01-1.03]	**$<10^{-2}$**
Splenomegaly	1.00 [0.98-1.01]	0.9
Biological data		
M spike (g/L)	0.03	-
Anaemia (< 11.5 g/dL)	1.04 [1.02-1.07]	$<10^{-3}$
Thrombocytopenia (< 100 G/L)	0.99 [0.97-1.01]	0.41
Medullar infiltration (%)	0.03	-
Albumin (g/L)	-0.55	**-**
β2 microglobulin (mg/L)	0.23	**-**
Cytogenetic/molecular biology		
6q deletion	**1.02 [1.00-1.03]**	**0.01**
TP53 abnormalities	1.00 [0.99-1.01]	0.57
MYD88 mutation	1.00 [0.99-1.03]	0.8
CXCR4 mutation	0.99 [0.97-1.00]	0.27
Follow-up		
Need for treatment initiation	1.02 [1.00-1.04]	0.07
ORR*	1.01 [1.00-1.02]	0.19
CRP after 1st line treatment (mg/L)	0.46	-

Logistic regressions were performed to determine the association between CRP value and binary variables, reported with HR [CI95%] and p-value. Pearson's correlation coefficient (r) was used to study the association between CRP value and quantitative variables.

Supplementary Table S3. Uni- and multivariate analyses of variables associated with TFT, PFS and OS in the entire cohort.

	Treatment-free survival (n=65)						Progression-free survival (n=167)				Overall survival (n=222)					
	Univariate			Multivariate			Univariate			Multivariate	Univariate			Multivariate		
	HR	*CI95%*	*p*	*HR*	*CI95%*	*p*	*HR*	*CI95%*	*p*		*HR*	*CI95%*	*p*	*HR*	*CI95%*	*p*
CRP (continuous)	1	0.99-1.01	0.94	-	-	-	1.01	1.00-1.03	0.06	-	1.01	0.99-1.02	0.3	-	-	-
CRP (≥ 5 mg/L)	1.27	0.75-2.12	0.37	-	-	-	1.93	0.80-4-66	0.14	-	2.01	0.96-4.23	0.06	-	-	-
Anaemia	**0.53**	**0.33-0.88**	**0.01**	0.48	0.22-1.08	0.08	1.17	0.53-2.54	0.7	-	**2.72**	**1.20-6.17**	**0.02**	2.09	0.84-5.22	0.12
Thrombocytopenia	**0.38**	**0.17-0.87**	**0.02**	0.37	0.09-1.41	0.14	0.43	0.12-1.56	0.2	-	1.3	0.57-2.97	0.5	-	-	-
Hypoalbuminemia	**0.93**	**0.86-0.99**	**0.03**	**0.91**	**0.84-0.98**	**0.02**	1	0.86-1.15	0.97	-	0.96	0.90-1.04	0.3	-	-	-
IPSSWM	1.01	0.75-1.35	0.97	-	-	-	1.08	0.70-1.67	0.74	-	**2.18**	**1.35-3.54**	**$<10^{-2}$**	*NA*	*NA*	*NA*
Del6q	1.03	0.60-1.75	0.92	-	-	-	2	0.97-4.10	0.06	-	**2.36**	**1.24-4.49**	**$<10^{-2}$**	1.58	0.74-3.34	0.23
Tri4	1.36	0.62-3.00	0.45	-	-	-	1.91	0.73-5.01	0.19	-	**2.4**	**1.09-5.30**	**0.03**	1.75	0.75-4.07	0.19
TP53abn	1.41	0.67-2.97	0.37	-	-	-	1.95	0.67-5.69	0.22	-	**3.09**	**1.49-6.39**	**$<10^{-2}$**	**2.49**	**1.06-5.86**	**0.04**

Uni- and multivariate analyses were performed using the Cox proportional hazard regression model. For multivariate analyses, we considered only variables that were significant (P ≤ 0.05) in univariate analyses.

Abbreviations: CI, confidence interval; HR, hazard ratio; IPSSWM, international prognostic scoring system for Waldenström macroglobulinemia