SUPPLEMENTARY APPENDIX

MYD88 mutations identify a molecular subgroup of diffuse large B-cell lymphoma with an unfavorable prognosis

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MYD88 mutations identify a molecular subgroup of Diffuse Large B-Cell Lymphoma with an unfavourable prognosis

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Running heads:

MYD88 mutational status improves classification and prognostication in DLBCL

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Supplementary information

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Supplemental Methods - Antibodies for staining, EBV and FISH

Immunohistochemical staining - antibodies:
The following immunohistochemical stains were performed with the DAKO Autostainer Link 48, Agilent (LUMC) or the Labvision Autostainer 480S from Thermo Fisher Scientific (AUMC), according to the manufacturer's recommendations, with the antibodies as listed in table 1.

Table 1. Antibodies:

	AUMC	LUMC
CD20	Clone L26, DAKO, Glostrup, Denmark	Clone L26, DAKO, Glostrup, Denmark
CD10	Clone 56C6, Thermo Fisher Scientific, Rockford, IL, USA	Clone 56C6, DAKO
MUM1	Clone MUM1p, DAKO, Glostrup, Denmark	Clone MUM1p, DAKO,
BCL2	Clone 124, DAKO, Glostrup, Denmark	Clone 124, DAKO Glostrup, Denmark
BCL6	Clone PG-B6p, DAKO, Glostrup, Denmark	Clone PG-B6p, Invitrogen

Epstein-Barr virus early RNA *in situ hybridization* (EBER-ISH)

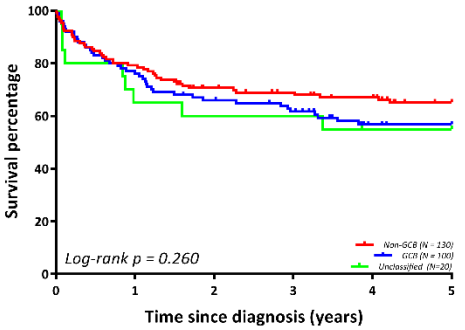
In situ hybridization for Epstein-Barr virus early RNA (EBER-ISH) was performed with EBER probes from Ventana (LUMC) or Biogenex (AUMC), according to the manufacturer's recommendations.

Fluorescence in situ hybridization (FISH) for *MYC*, *BCL2* and *BCL6*

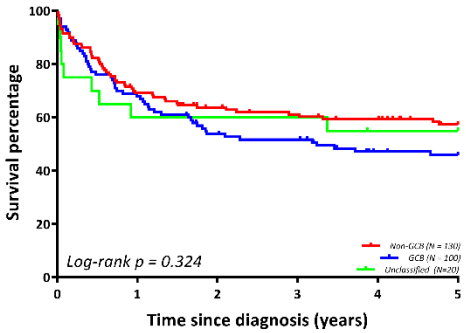
Fluorescence in situ hybridization was performed with break apart rearrangement probes for *MYC*, *BCL2* and *BCL6* from Abbott (LUMC) or DAKO (AUMC), with the DAKO Histology FISH Accessory Kit, Agilent, according to the manufacturer's recommendations.

Supplemental figure 1 - Survival outcomes of COO and other aberrations

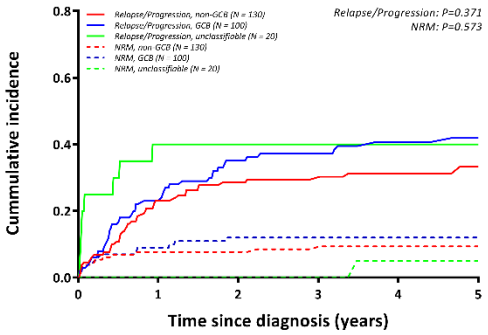
Supplemental 1A. Cell-of-Origin (OS)



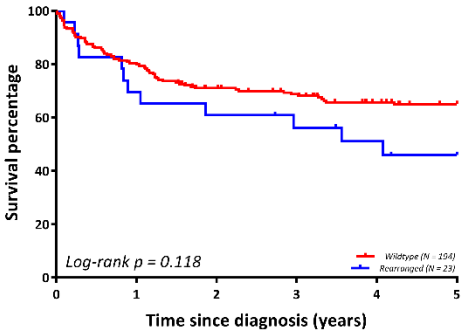
Supplemental 1B. Cell-of-Origin (PFS)



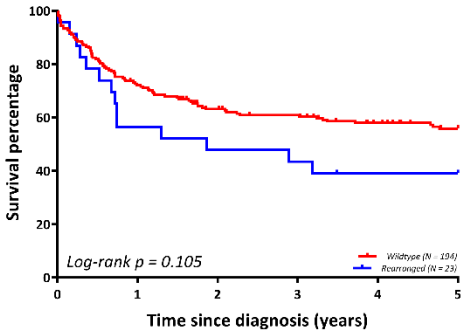
Supplemental 1C. Cell-of-Origin (CRS)



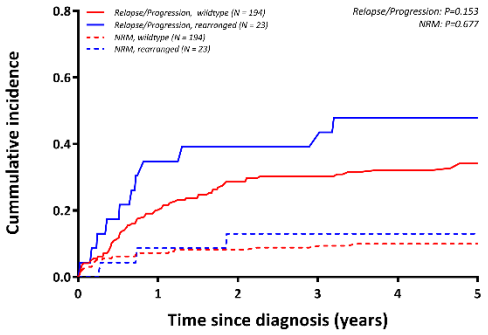
Supplemental 1D. MYC status (OS)



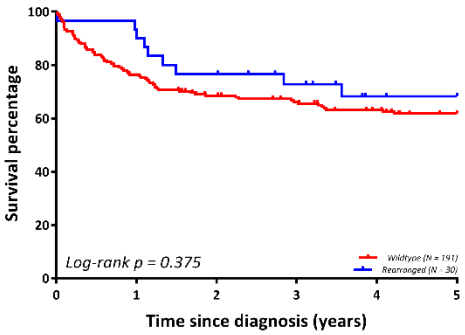
Supplemental 1E. MYC status (PFS)



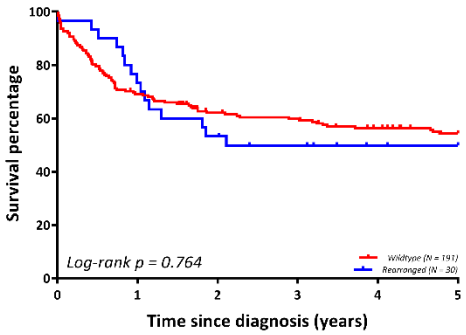
Supplemental 1F. MYC status (CRS)



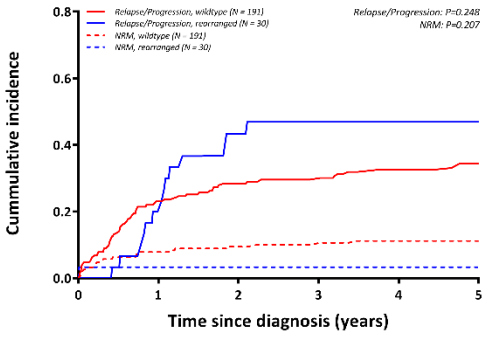
Supplemental 1G. BCL2 status (OS)



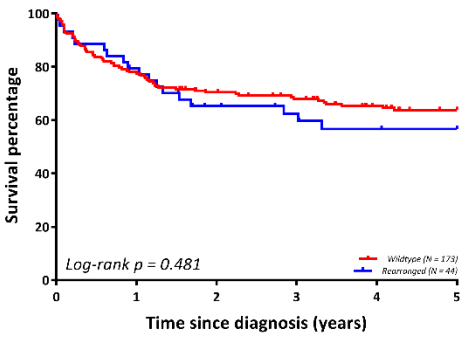
Supplemental 1H. BCL2 status (PFS)



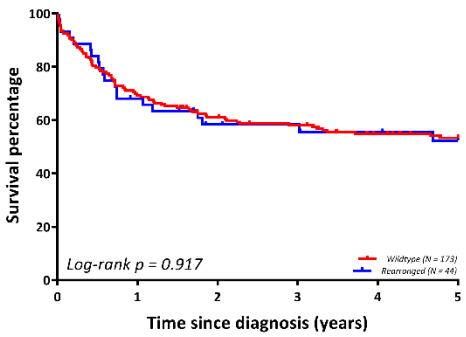
Supplemental 1I. BCL2 status (CRS)



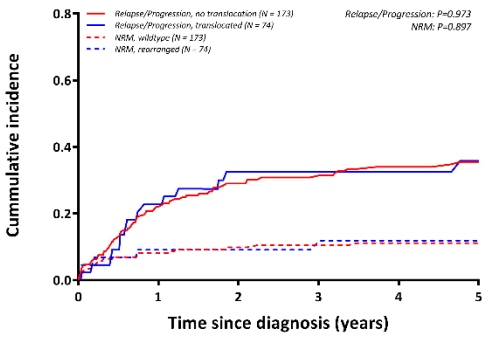
Supplemental 1J. BCL6 status (OS)



Supplemental 1K. BCL6 status (PFS)

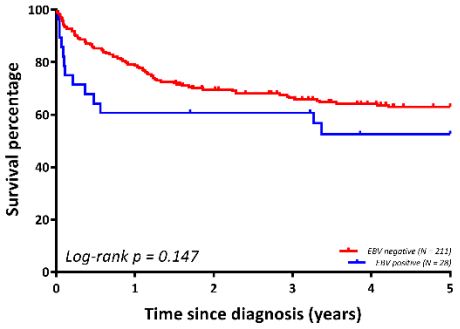


Supplemental 1L. BCL6 status (CRS)

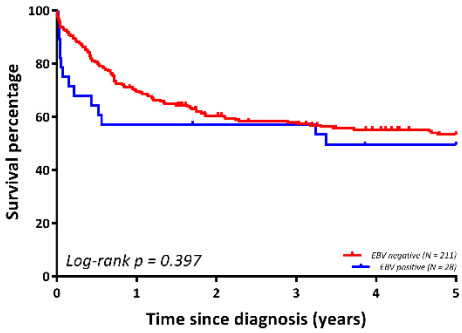


Supplemental figure 1 - (*continued*)

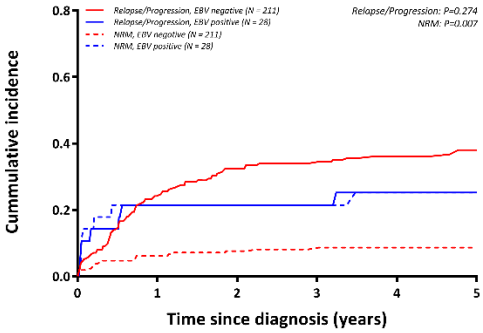
Supplemental 1M. EBV status (OS)



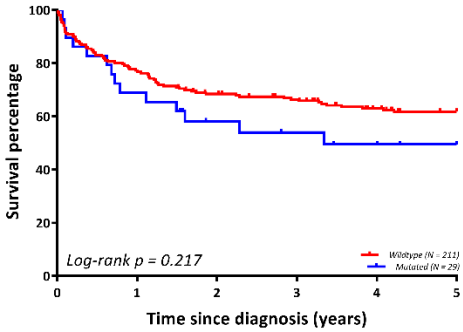
Supplemental 1N. EBV status (OS)



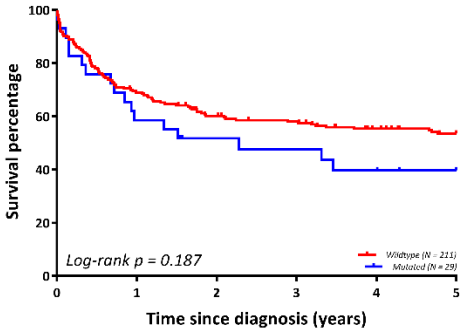
Supplemental 1O. EBV status (CRS)



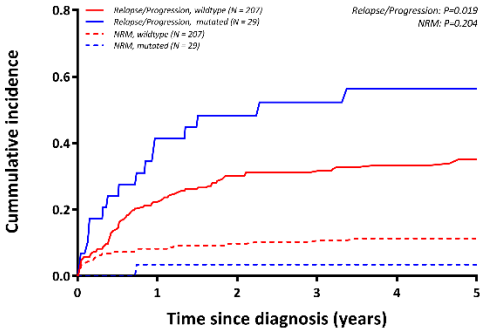
Supplemental 1P. CD79B status (OS)



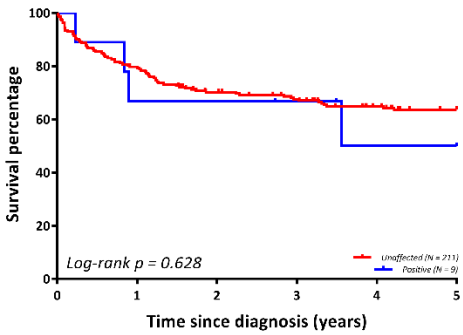
Supplemental 1Q. CD79B status (PFS)



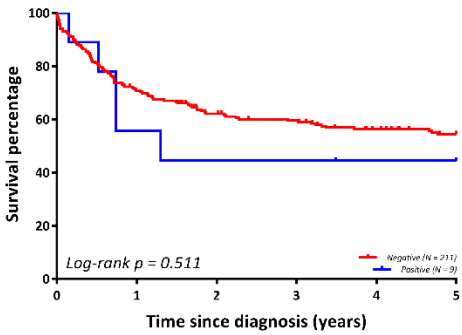
Supplemental 1R. *CD79B* status (CRS)



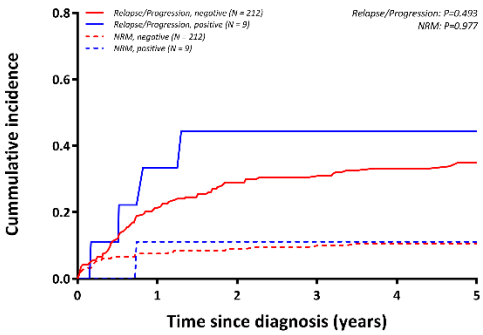
Supplemental 1S. High-grade B-cell lymphoma's (OS)



Supplemental 1T. High-grade B-cell lymphoma's (PFS)



Supplemental 1U. High-grade B-cell lymphoma's (CRS)



Supplemental table 1 - Prognostic impact of molecular aberrations, anatomical lymphoma location and IPI risk factors on overall survival: univariable and multivariable analysis

	Overall survival							
	Univariable		Multivariable Model 1 (IPI)		Multivariable Model 4 (IPI + anatomical localizations + aberrations WHO 2016)		Multivariable Model 5 (IPI + anatomical localizations + aberrations WHO 2016 + MYD88 + CD79B)	
	HR	95%-CI	HR	95%-CI	HR	95%-CI	HR	95%-CI
IPI: >2 Extranodal Yes (vs No)	1.37	0.91-2.07	1.41	0.90-2.22	1.59	0.92-2.74	1.64	0.96-2.80
IPI: Stage III/IV (vs I/II)	**2.33**	1.41-3.85	1.67	0.98-2.84	1.66	0.94-2.94	**1.87**	1.05-3.33
IPI: ECOG Performance Score >2 (vs ≤1)	**8.15**	5.23-12.7	**7.53**	4.67-12.15	**7.69**	4.65-12.72	**7.74**	4.64-12.92
IPI: Age ≥60 (vs <60)	**1.54**	1.00-2.37	1.35	0.85-2.13	1.25	0.78-2.00	1.24	0.77-2.00
IPI: LDH >Upper limit (vs Normal)	**1.53**	1.01-2.31	1.14	0.74-1.77	1.34	0.84-2.15	1.43	0.89-2.29
Anatomical localization Nodal Extranodal (+/- nodal) Immune-privileged	 1.42 **2.37**	 0.83-2.41 1.38-4.08			 1.39 **2.47**	 0.74-2.62 1.30-4.71	 1.55 **2.24**	 0.81-2.93 1.08-4.62
MYC Rearranged (vs Wildtype)	1.62	0.88-3.00			**2.00**	1.03-3.91	1.92	0.95-3.85
BCL2 Rearranged (vs Wildtype)	0.74	0.37-1.47			0.62	0.29-1.34	0.67	0.31-1.47
BCL6 Rearranged (vs Wildtype)	1.21	0.71-2.04			0.96	0.54-1.71	0.92	0.50-1.70
EBV Status Positive (vs Negative)	1.54	0.86-2.78			1.65	0.84-3.23	1.72	0.86-3.45
CD79B Mutated (vs Wildtype)	1.43	0.81-2.53					0.68	0.34-1.35
MYD88 Mutated (vs Wildtype)	**1.64**	1.08-2.48					1.45	0.78-2.71
Cross-validated C-index			***0.67***		***0.71***		***0.71***	

For the multivariable model, unknown was regarded as a separate category for these variables for which some data were missing (not reported)