

Lymphome double hit

Questions

- De quoi parle t'on?
- Quelles caractéristiques cliniques?
- Quel pronostic?
- Quel traitement?

Questions

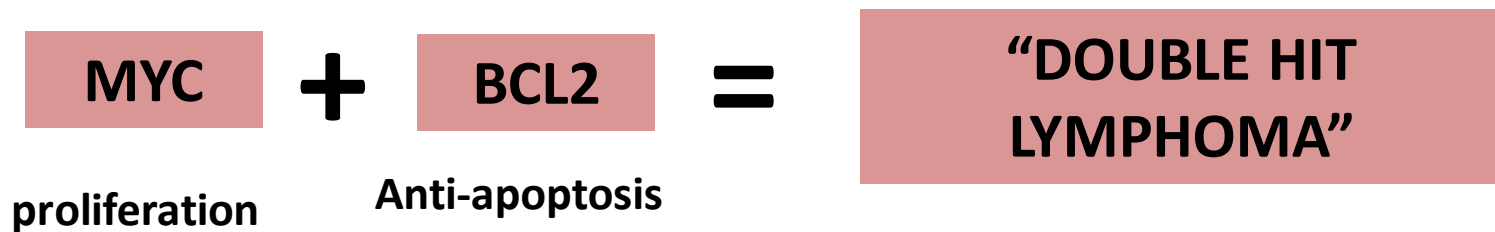
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- Recurrent oncogene **rearrangements**, one being MYC
- MYC and BCL2 rearrangements most common
- BCL6, CCND1 and BCL3 may also occur
- Can also have “triple hit”



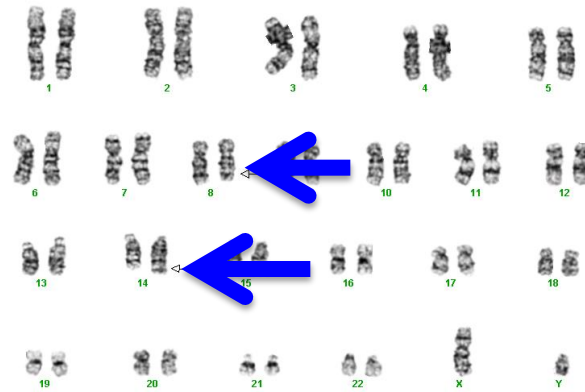
Frequency of MYC and BCL2-rearrangements in DLBCL

Ref.	N	MYC rearr.	MYC <i>and</i> BCL2 rearr.	Comments
Barrans	245	35 (14%)	19 (7.7%)	MYC as sole abnl was rare (2%)
BCCA	135	12 (9%)	3 (2%)	
Japan	394	24 (6%)	19 (4.8%)	Only looked at pts with cytogenetic abnl

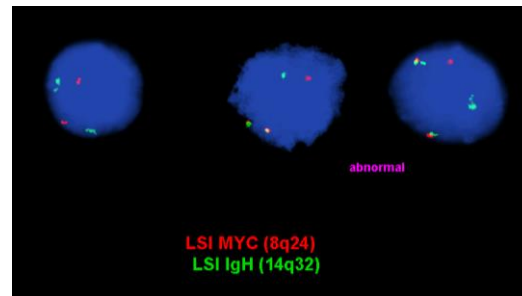


How to detect MYC aberrations

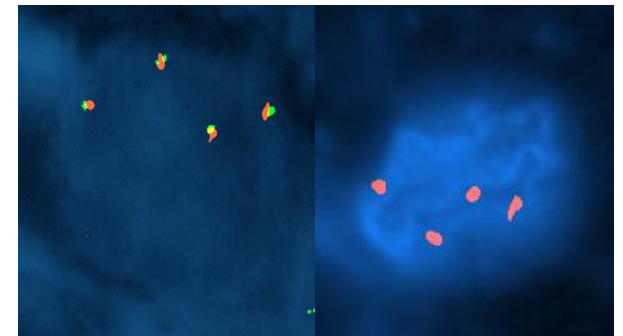
**Routine
karyotyping**



FISH break-apart

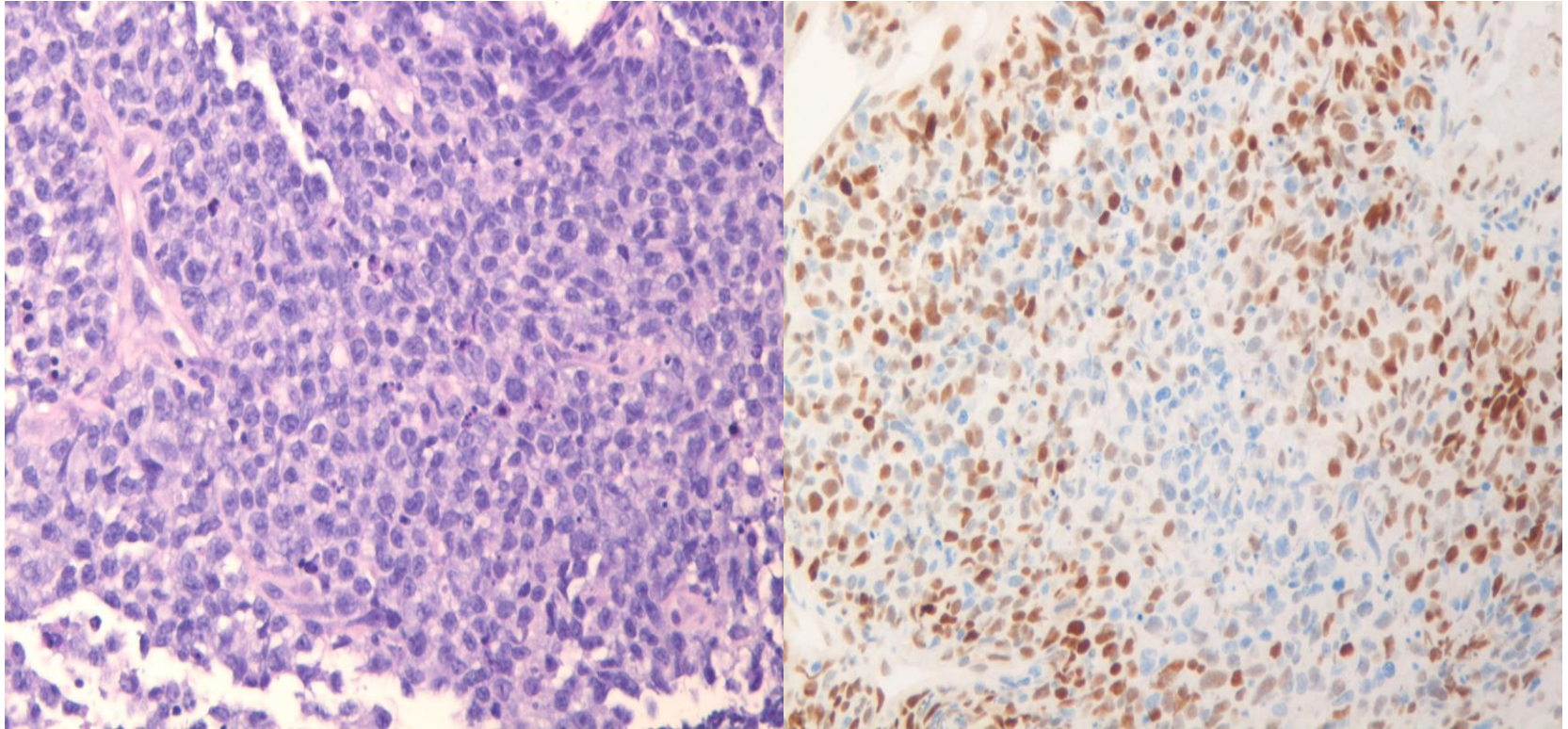


Rearrangement

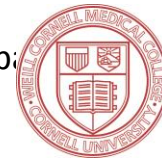


**Increased copy
number**

NEW: Immunohistochemistry for MYC



Images courtesy of Dr. Girish Venkataraman, The University of Chicago Hematopathologist



Weill Cornell Medical College

Relative frequency of MYC via IHC

Ref.	N	Subtype	MYC rearr	MYC IHC	BCL2 rearr	BCL2 IHC	BCL2 <i>and</i> MYC IHC
Horn 2013	442	DLBCL (RICOVER)	8.8%	32% (>40%)	13.5%	80% (>0%)	
Johnson 2012	167	DLBCL (training)	11%	29% (>40%)	18%	44%	18% overall (vs. 5% with DHL)
Johnson 2012	140	DLBCL (validation)	13%	37% (>40%)	30%	62%	
Hu 2013	466	DLBCL (training)	NR	64% (>40%)	NR	50% (>70%)	34% (vs. 3% with DHL)



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Clinicopathologic features lymphoma expressing MYC and Bcl2

	Overall			DP	Non-DP	P value
	N (%)	OS, P	PFS, P	N (%)	N (%)	
Patients	466 (100)			157 (100)	309 (100)	
Gender						
Male	272 (58)	.7477	.4730	90 (57)	182 (59)	.7445
Female	194 (42)			67 (43)	127 (41)	
Age						
≤60	194 (42)	.0004	.0016	49 (31)	145 (47)	.0011
>60	272 (58)			108 (69)	164 (53)	
B symptoms*						
Absence	276 (68)	.0015	.0014	88 (62)	188 (72)	.0541
Presence	127 (32)			53 (38)	74 (28)	
ECOG performance status*						
<2	350 (88)	<.0001	<.0001	111 (83)	239 (90)	.0453
≥2	50 (12)			23 (17)	27 (10)	
Stage*						
I-II	219 (49)	<.0001	<.0001	50 (33)	169 (57)	<.0001
III-IV	228 (51)			100 (67)	128 (43)	
Extranodal sites*						
<2	346 (78)	<.0001	<.0001	106 (72)	240 (82)	.0160
≥2	96 (22)			42 (28)	54 (18)	
Lactate dehydrogenase*						
Normal	168 (40)	.0003	<.0001	51 (36)	117 (42)	.2908
Elevated	252 (60)			89 (64)	163 (58)	
IPI risk group*						
0-2	263 (64)	<.0001	<.0001	70 (51)	193 (70)	.0001
3-5	148 (36)			67 (49)	81 (30)	
Tumor size, cm*						
<7.5	253 (77)	.0100	.0172	81 (73)	172 (79)	.2587
≥7.5	77 (23)			30 (27)	47 (21)	
Treatment response						
CR	354 (76)	<.0001	<.0001	103 (66)	251 (84)	<.0001
Others	112 (24)			54 (34)	48 (16)	
COO classification						
GCB	241 (52)	.0080	.0075	53 (34)	188 (61)	<.0001
ABC	225 (48)			104 (66)	121 (39)	
Ki-67*						
<70	158 (34)	.2998	.3434	41 (26)	117 (38)	.0086
≥70	304 (66)			116 (74)	188 (62)	
TP53 mutations						
Absence	357 (77)			117 (75)	240 (78)	.4480
Presence	109 (23)	.0005	.0004	40 (25)	69 (22)	

Age, PS, B sx,
stage

IPI

CR, COO,
Ki67

Clinical Characteristics of Double hit Lymphoma

- Higher IPI
- Worse PS
- Higher LDH
- Increased advanced stage disease
- Increased extranodal sites
- Increased CNS disease



Immunophenotype of Double hit Lymphoma

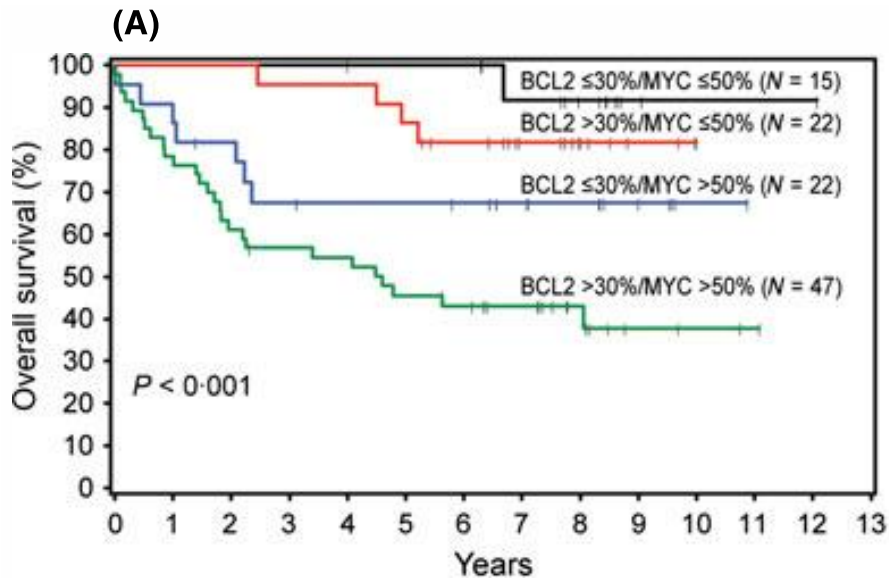
- DLBCL and BCL, U histology
- CD10+, GCB phenotype
- BCL2 + in 95% of cases
- High proliferative index
 - median 90% Ki67+



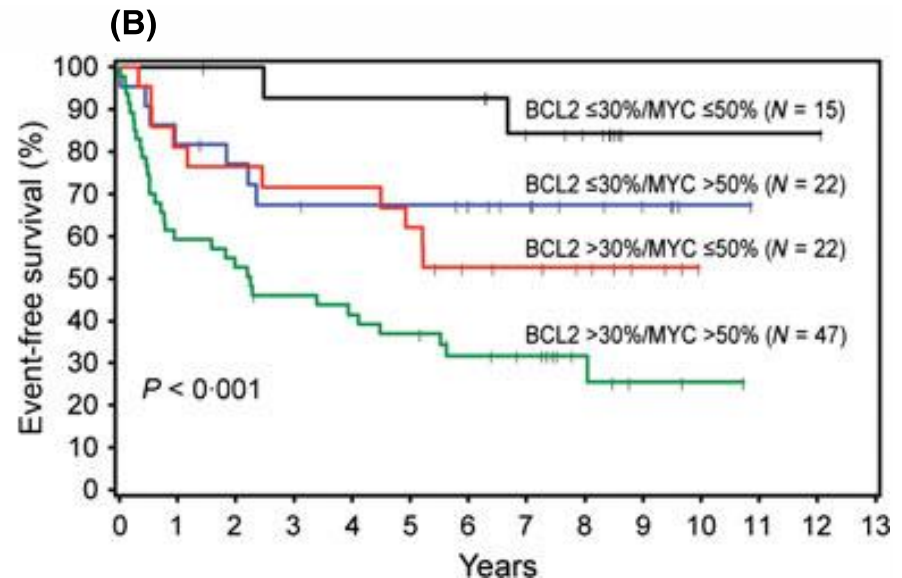
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IHC expression of BCL2 and MYC is associated with poor prognosis



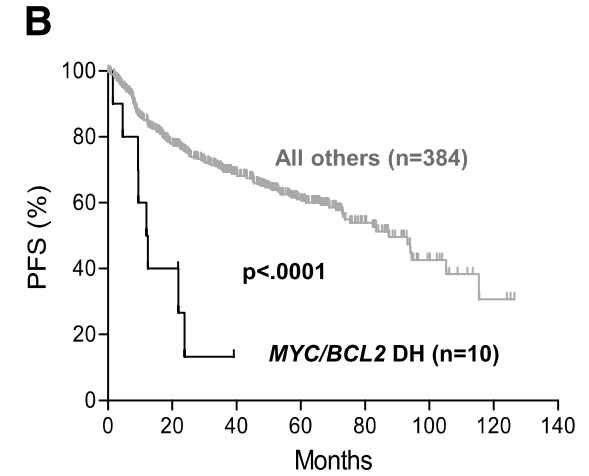
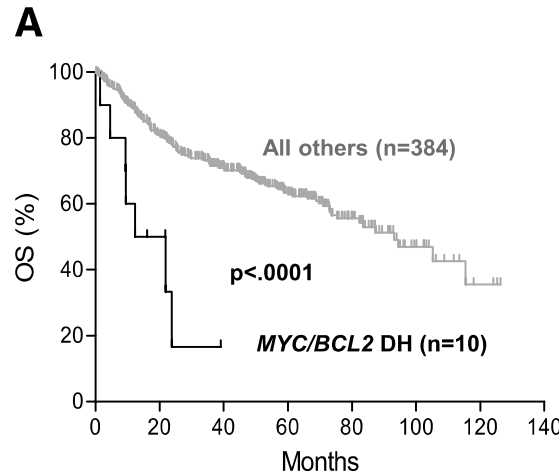
Overall survival



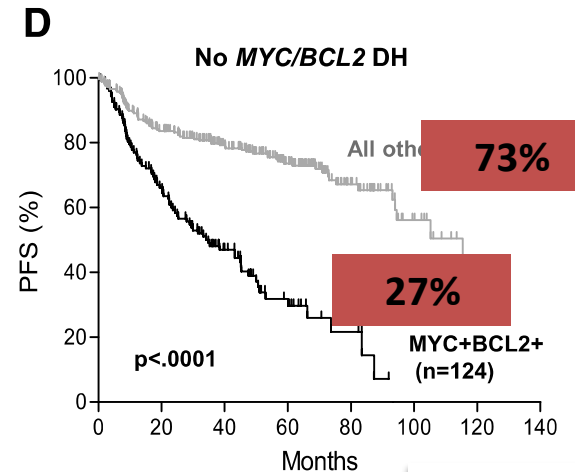
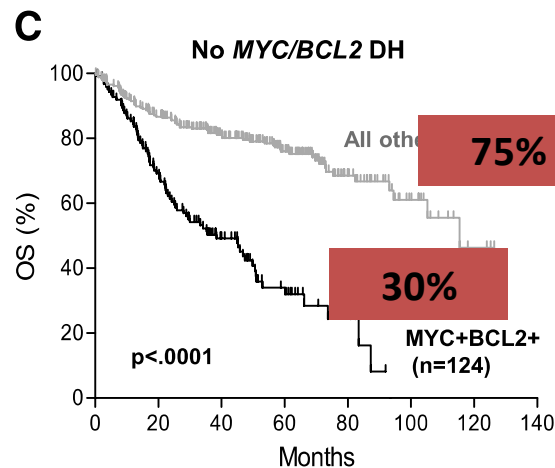
EFS

Prognosis of classic double hit lymphoma vs. MYC/BCL2 expressing lymphomas

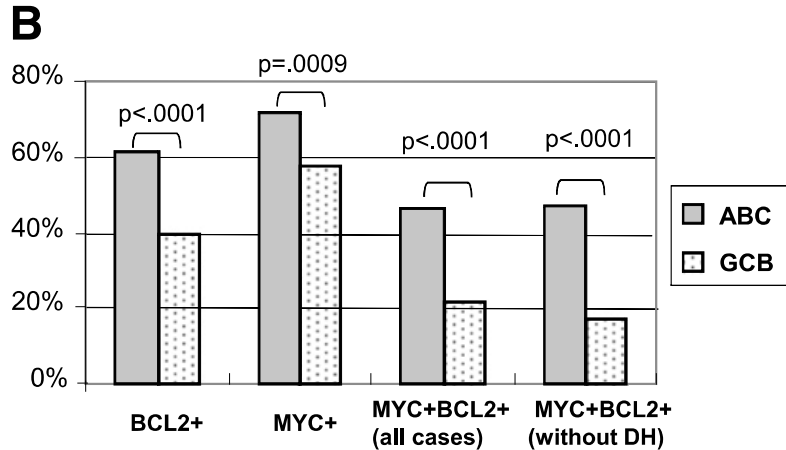
OS and PFS for classic DHL (MYC/BCL2 rearranged)



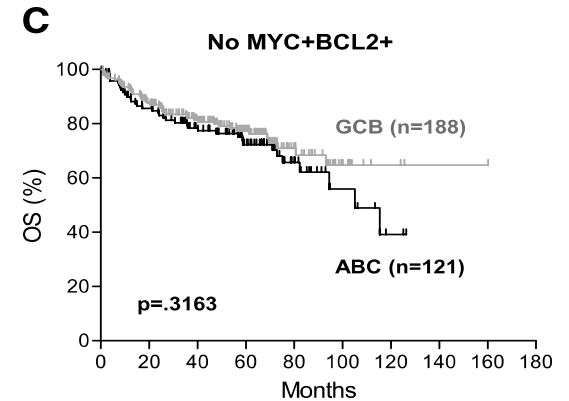
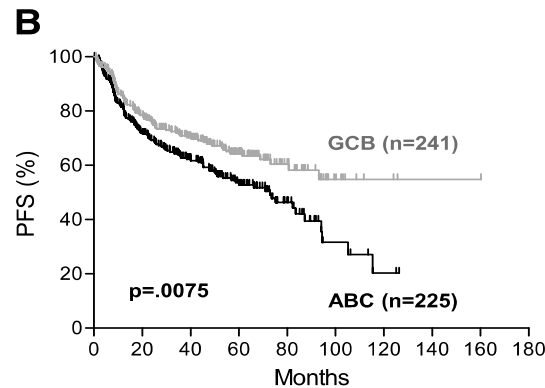
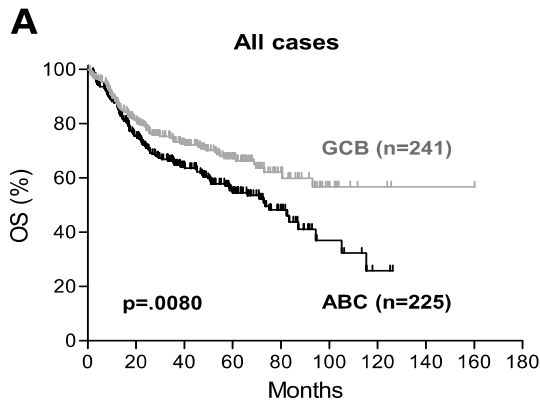
OS and PFS for MYC/BCL2 expression



Prognostic relevance of COO and MYC/Bcl2 protein expression



Co-expression of BCL2 and MYC is 2-fold higher in ABC DLBCL



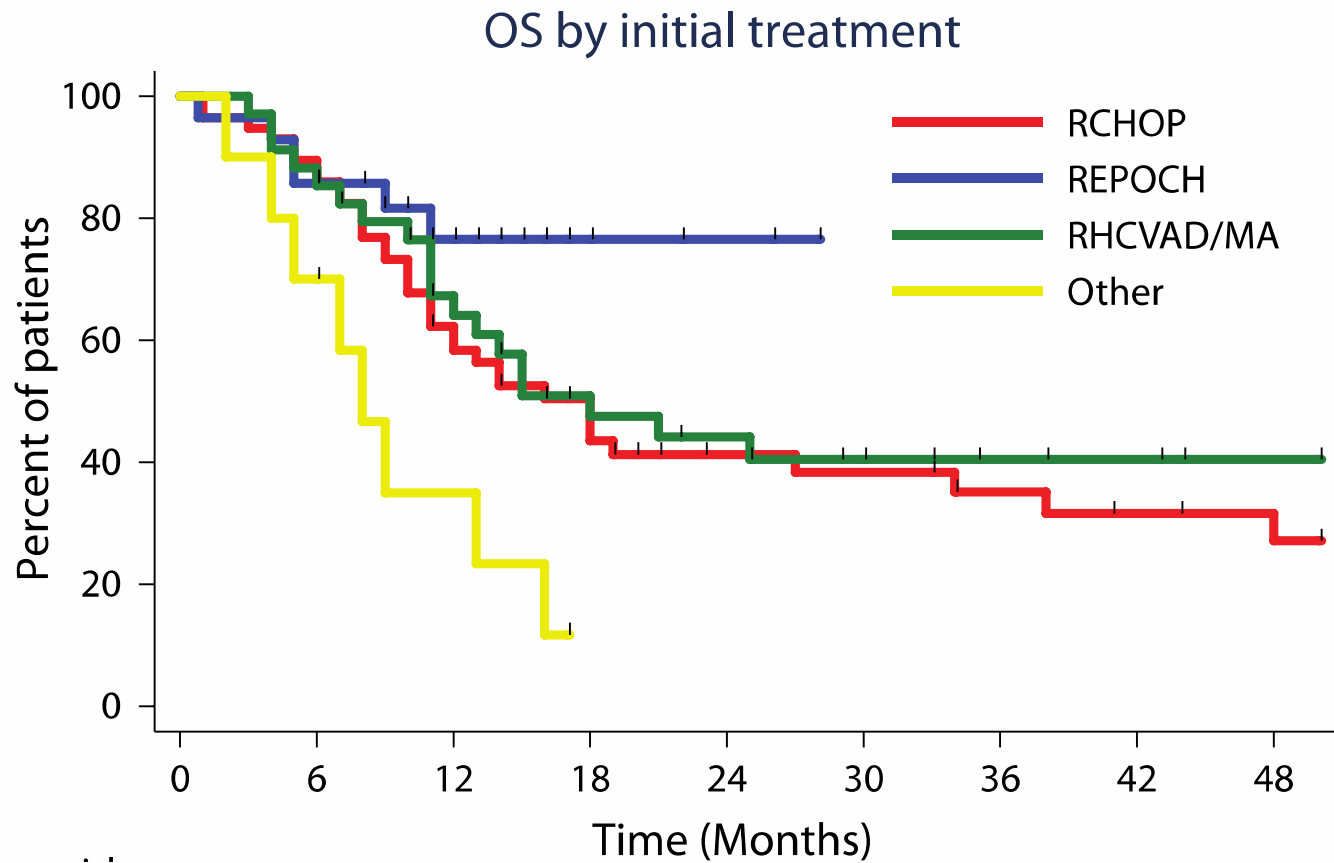
Co-expression of BCL2 and MYC drives the negative outcomes in ABC DLBCL

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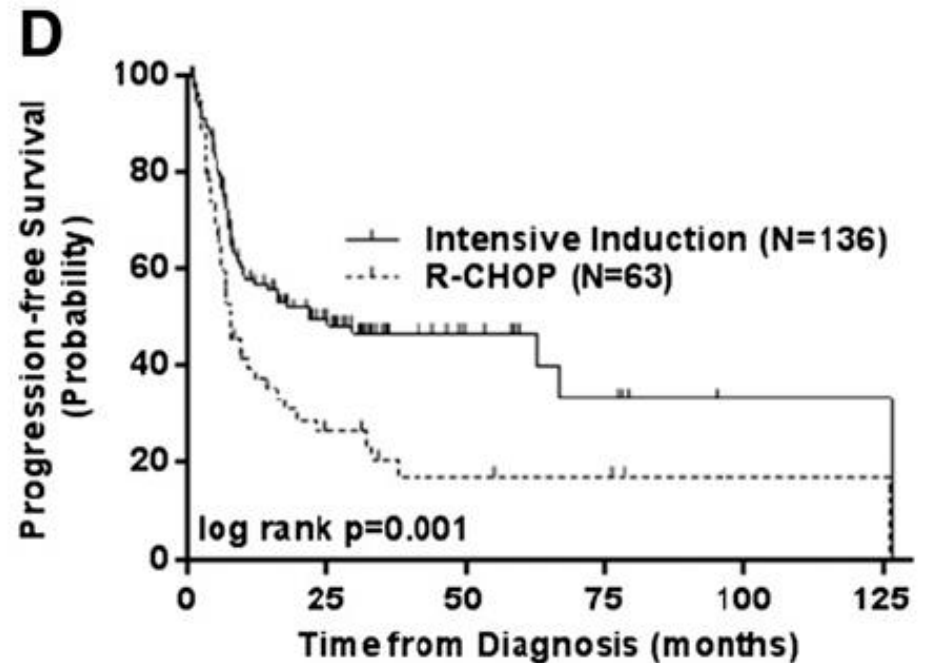
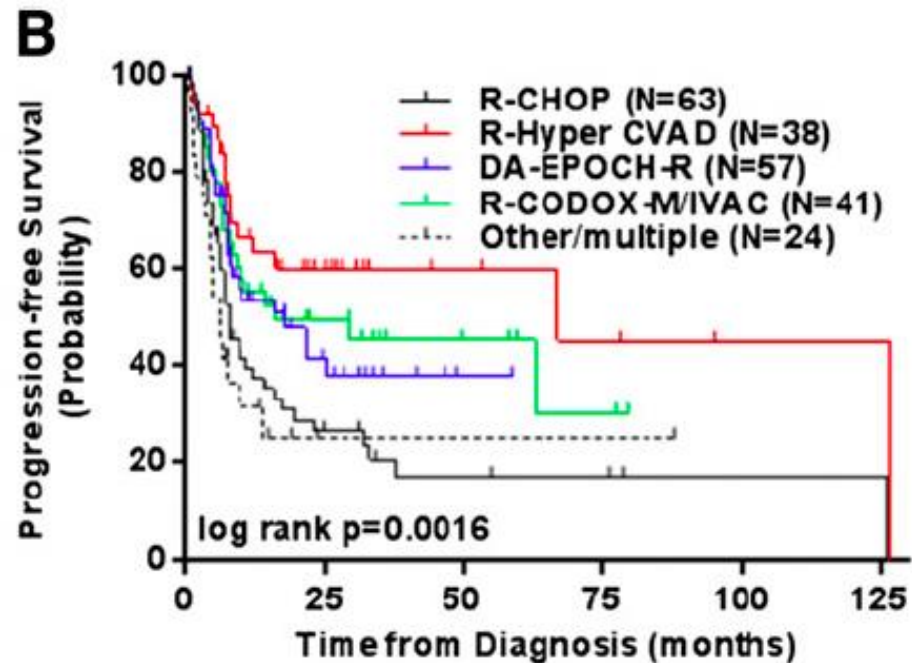
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Are more intensive regimens better?

MDACC experience

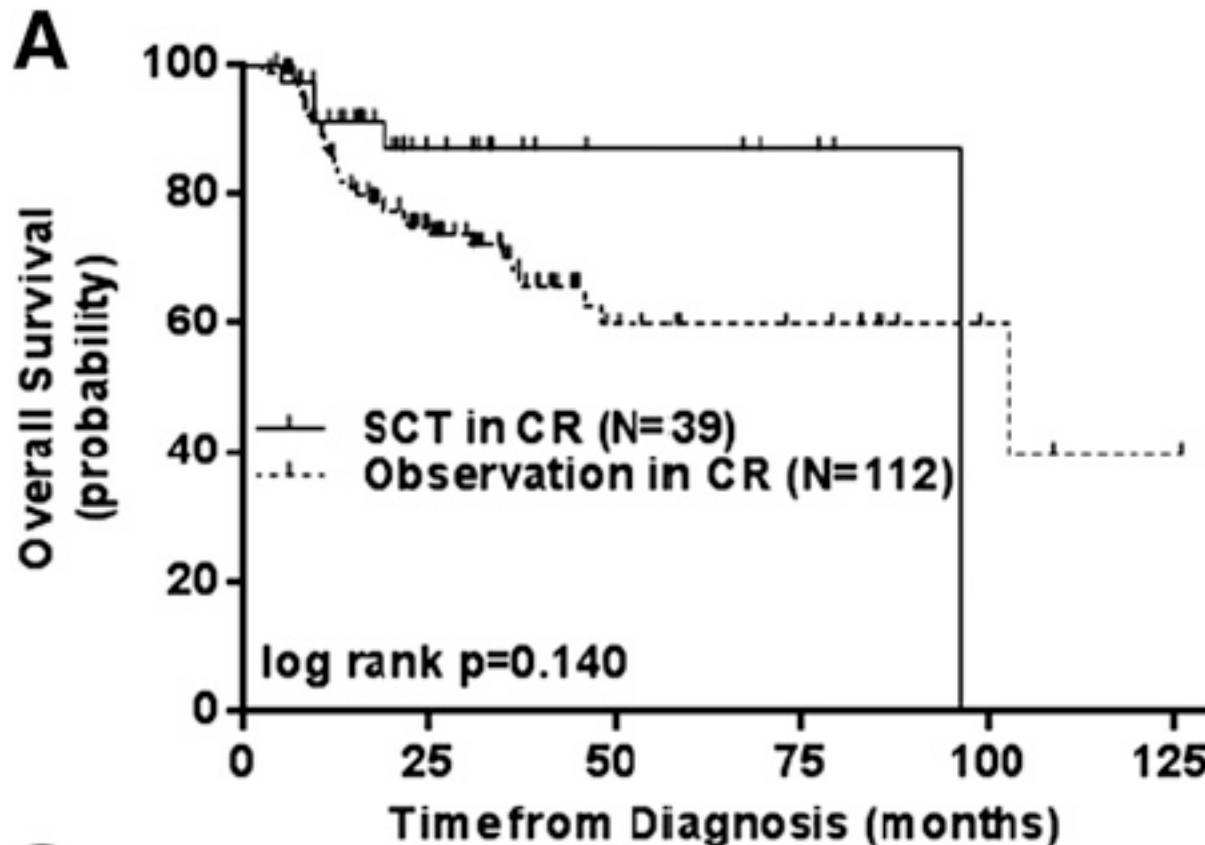


Are more intensive regimens better?



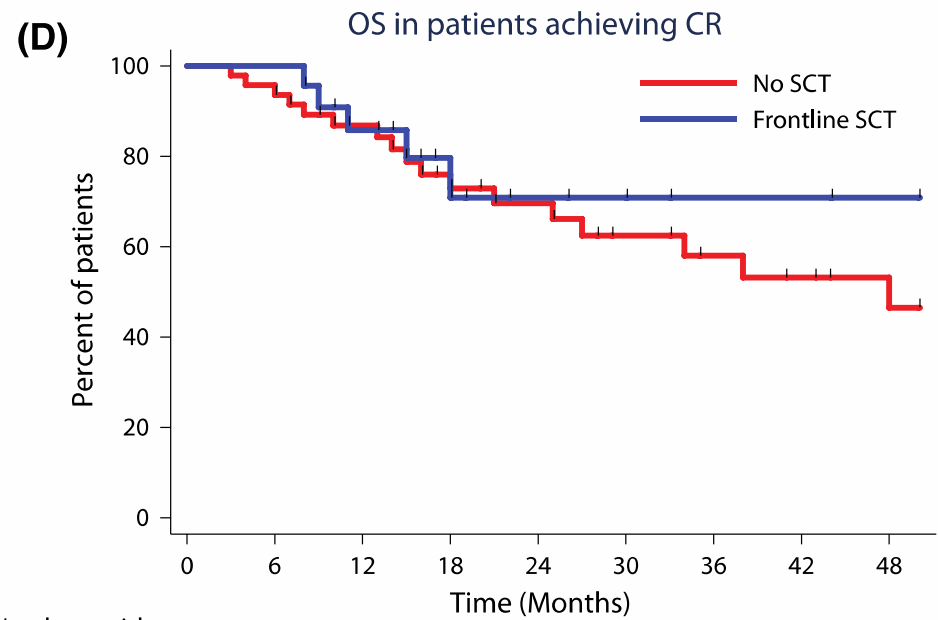
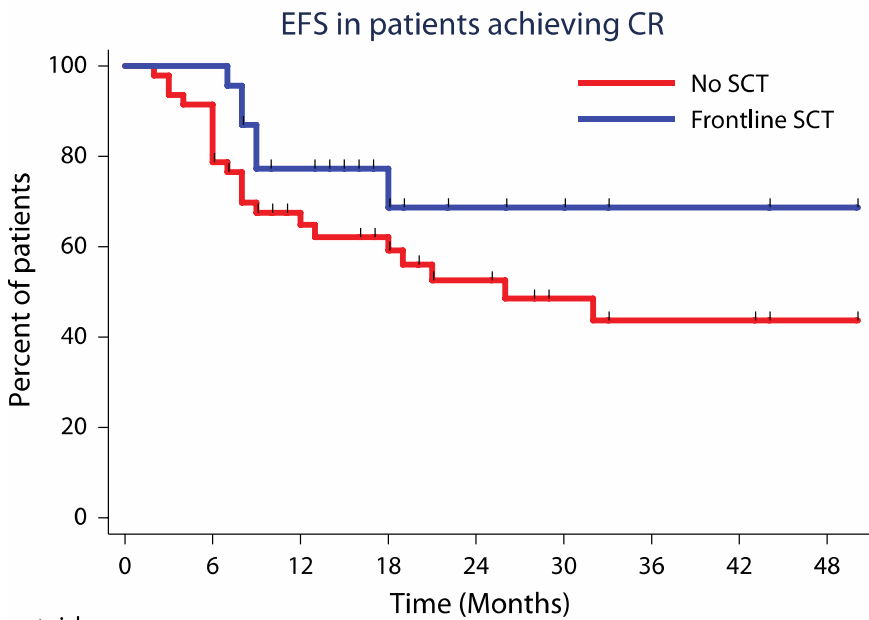
Petrich et al, Blood 124 (15), 2014

What is the role of SCT in patients who achieve a CR?



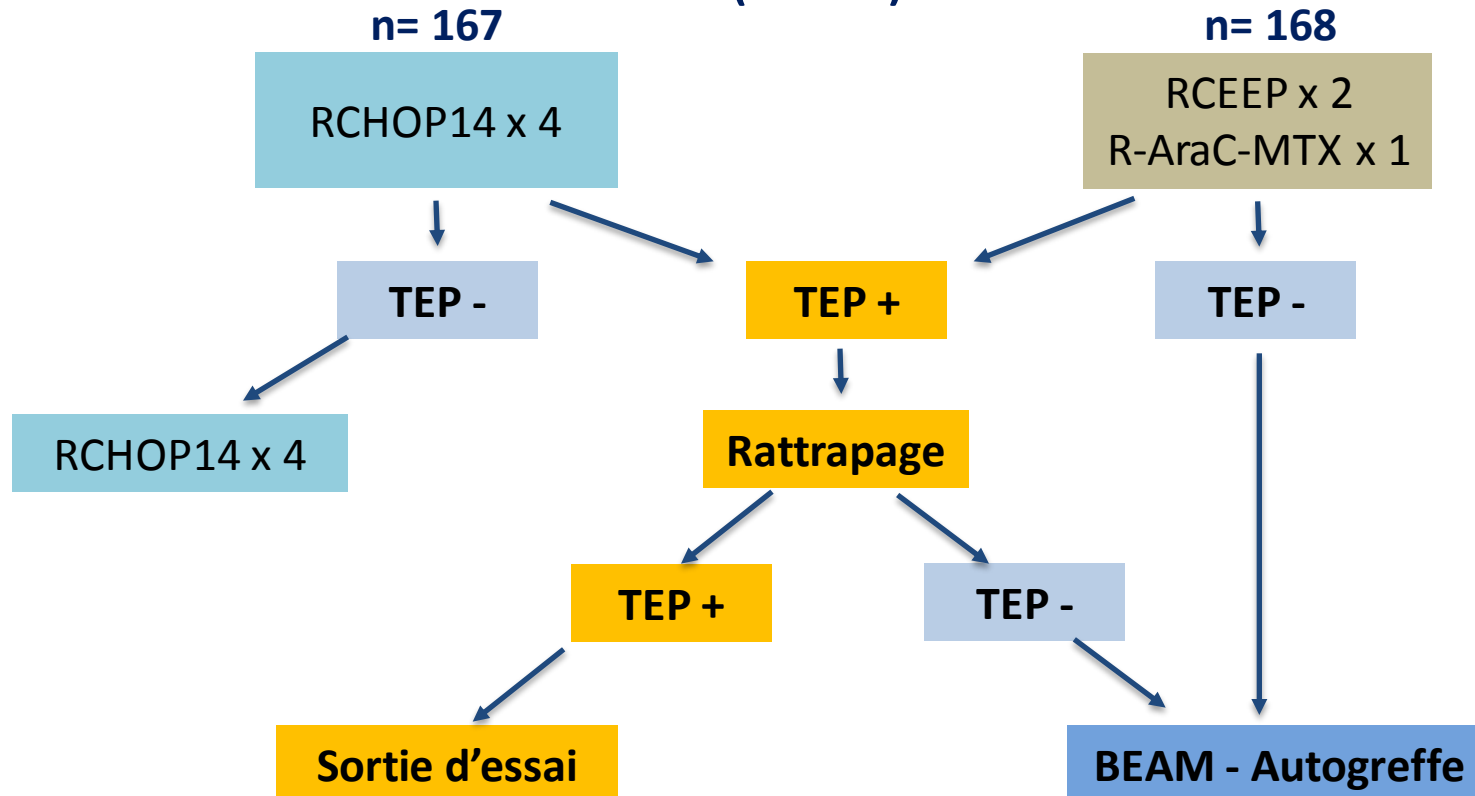
Petrich et al, Blood 124 (15), 2014

MDACC: SCT in patients achieving CR



Essai GOELAMS-075

Patients atteints de LBDGC, de stade avancé III-IV ou I-II >7cm,
âgés de 18 à 60 ans, non antérieurement traités,
inclus et randomisés dans l'essai GOELAMS-075 entre 2005 et 2010
(n= 335)





Expression des oncoprotéines BCL2 et MYC

Expression des protéines BCL2 et MYC:

BCL2 : évaluable pour 90% (n=268) de la cohorte d'étude

MYC : évaluable pour 63% (n=185) de la cohorte d'étude

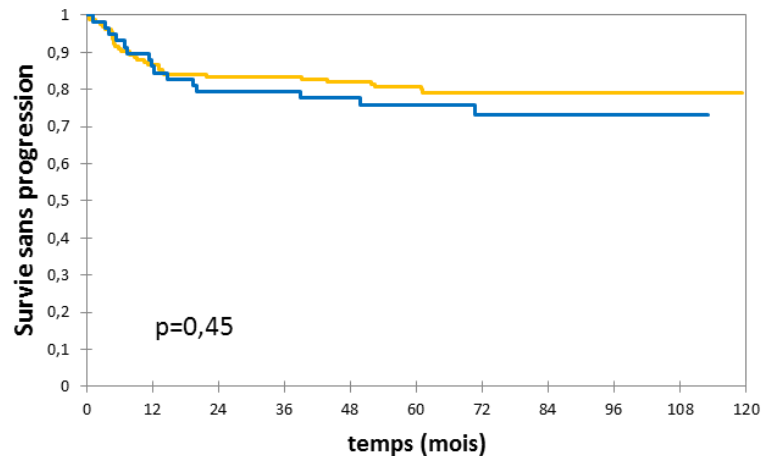
Caractéristiques	LBDGC confirmés (n=296)		Bras RCHOP (n=147)		Bras intensif (n=149)		Test du Chi ² p-value
	No.	%	No.	%	No.	%	
Expression protéine BCL2 (IHC)							
≥ 50%	175/268	65	86/131	66	89/137	65	0,99
≥ 70%	147/268	55	72/131	55	75/137	55	0,93
Expression protéine MYC (IHC)							
≥ 40%	86/185	46	43/93	46	43/92	47	0,94
Coexpression protéines MYC-BCL2 (≥ 50%) (IHC)	59/184	32	31/93	33	28/91	31	0,83
Coexpression protéines MYC-BCL2 (≥ 70%) (IHC)	52/184	28	26/93	28	26/91	29	0,94



PFS BCL2 et MYC

Survie sans progression – coexpression BCL2-MYC :

Survie sans progression selon la coexpression de MYC et BCL2 (seuil 50%)



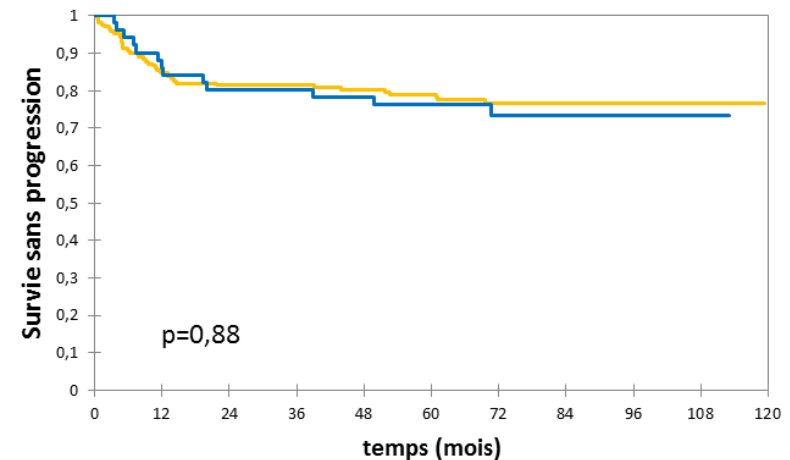
— MYC < 40% ou BCL2 < 50% — MYC ≥ 40% et BCL2 ≥ 50%

PFS à 5 ans :

MYC < 40% ou BCL2 < 50% = 79% ± 3%

MYC ≥ 40% et BCL2 ≥ 50% = 73% ± 6%

Survie sans progression selon la coexpression de MYC et BCL2 (seuil 70%)



— MYC < 40% ou BCL2 < 70% — MYC ≥ 40% et BCL2 ≥ 70%

PFS à 5 ans :

MYC < 40% ou BCL2 < 70% = 74% ± 4%

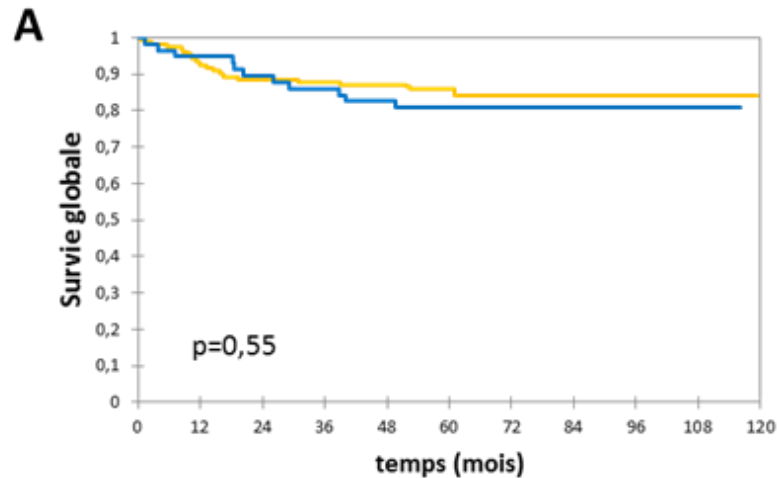
MYC ≥ 40% et BCL2 ≥ 70% = 73% ± 6%



OS BCL2 et MYC

Survie globale – coexpression BCL2-MYC :

Survie globale selon la coexpression de MYC et BCL2 (seuil 50%)



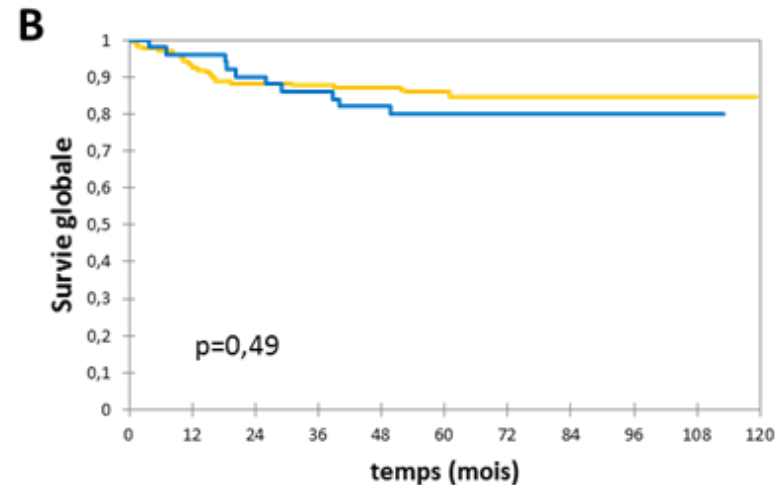
— MYC < 40% ou BCL2 < 50% — MYC \geq 40% et BCL2 \geq 50%

OS à 5 ans :

MYC < 40% ou BCL2 < 50% = 84% \pm 3%

MYC \geq 40% et BCL2 \geq 50% = 81% \pm 5%

Survie globale selon la coexpression de MYC et BCL2 (seuil 70%)



— MYC < 40% or BCL2 < 70% — MYC \geq 40% and BCL2 \geq 70%

OS à 5 ans :

MYC < 40% ou BCL2 < 70% = 84% \pm 3%

MYC \geq 40% et BCL2 \geq 70% = 80% \pm 6%