Lymphome folliculaire : épidémiologie et facteurs pronostiques

Dr Emmanuel BACHY

Centre Hospitalier Lyon Sud – Inserm U1052

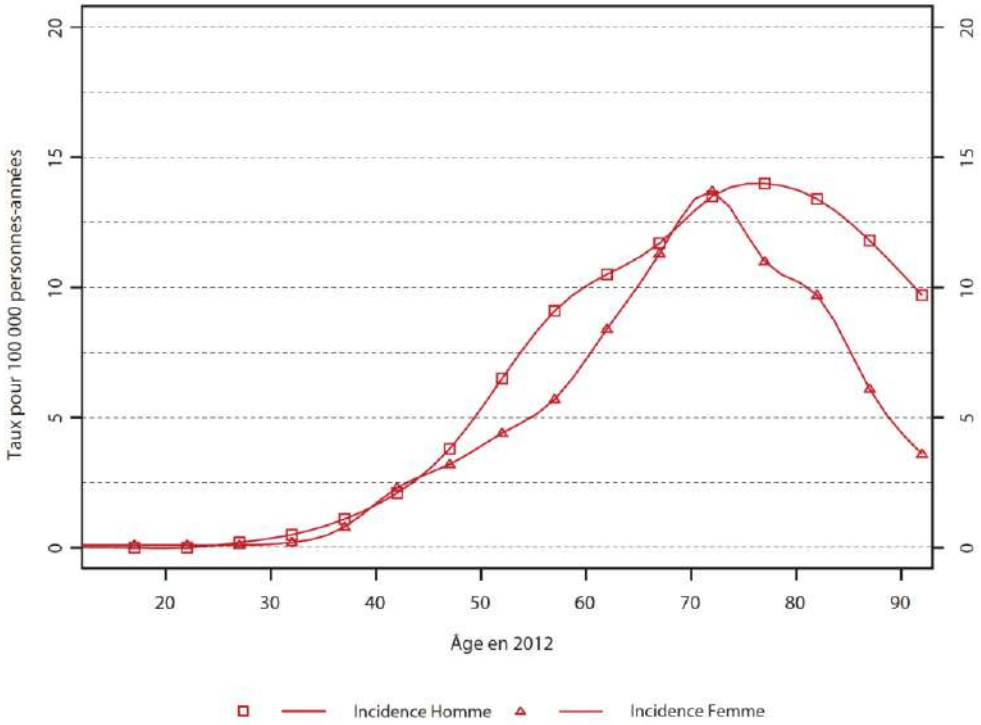
Cours DES Paris 17 Nov 2017

Epidémiologie du lymphome folliculaire

Estimation nationale incidence/mortalité à partir du réseau FRANCIM

- Incidence environ 2,5/100000 et 2,1/100000 personne/année (homme/femme)
- Sex ratio homme/femme : 1.2
- 2530 nouveaux cas en France en 2012
- 2ème lymphome en terme de fréquence derrière les LBDGC
- Médiane d'âge de survenue 64 ans chez l'homme / 66 ans chez la femme
- Survie nette en France sur la période 2000-2004: 80% à 5 ans
- Actuellement probablement médiane de survie globale > 15 ans

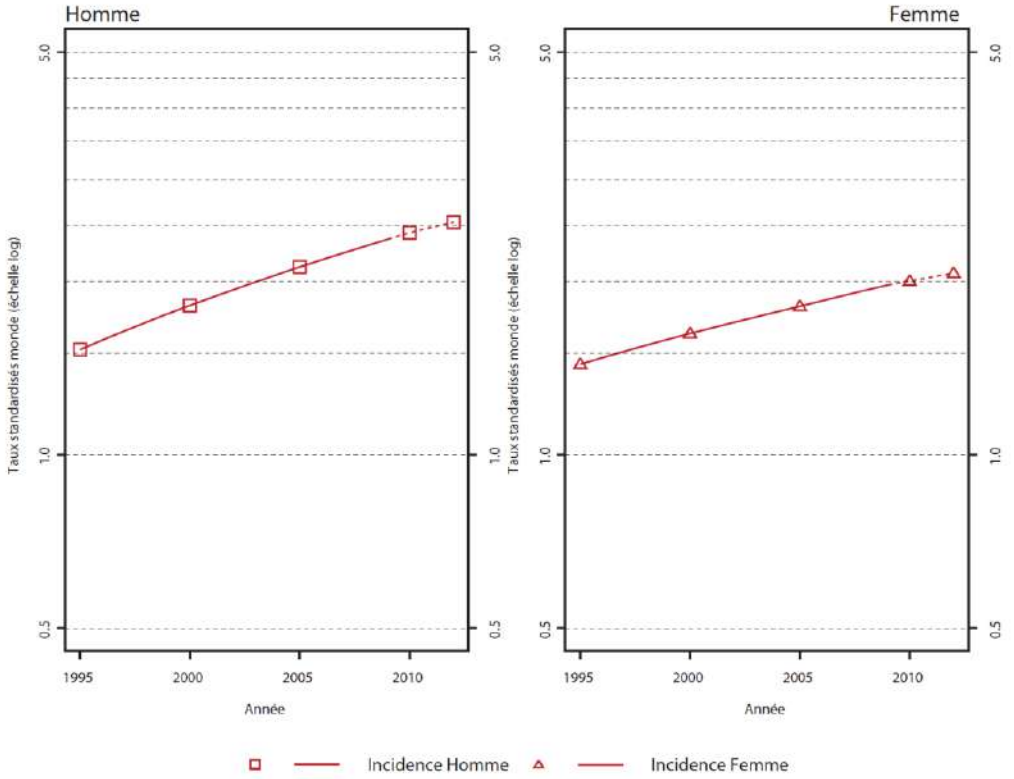
Estimation nationale incidence/mortalité à partir du réseau FRANCIM



I Tableau 3 I Taux pour 100 000 personnes-années par tranche d'âge et par sexe en France en 2012 - Lymphome folliculaire

Âge		[00 ;14]	[15 ;19]	[20 ;24]	[25 ;29]	[30 ;34]	[35 ;39]	[40 ;44]	[45 ;49]	[50 ;54]	[55 ;59]	[60 ;64]	[65 ;69]	[70 ;74]	[75 ;79]	[80 ;84]	[85 ;89]	[90 ;94]	[95 ;++]
Incidence	Homme	0,0	0,0	0,0	0,2	0,5	1,1	2,1	3,8	6,5	9,1	10,5	11,7	13,5	14,0	13,4	11,8	9,7	8,1
	Femme	0,1	0,1	0,1	0,1	0,2	0,8	2,3	3,2	4,4	5,7	8,4	11,3	13,7	11,0	9,7	6,1	3,6	3,6

Estimation nationale incidence/mortalité à partir du réseau FRANCIM



I Tableau 5 I Taux d'incidence en France selon l'année (standardisés monde pour 100 000 personnes-années) - Lymphome folliculaire

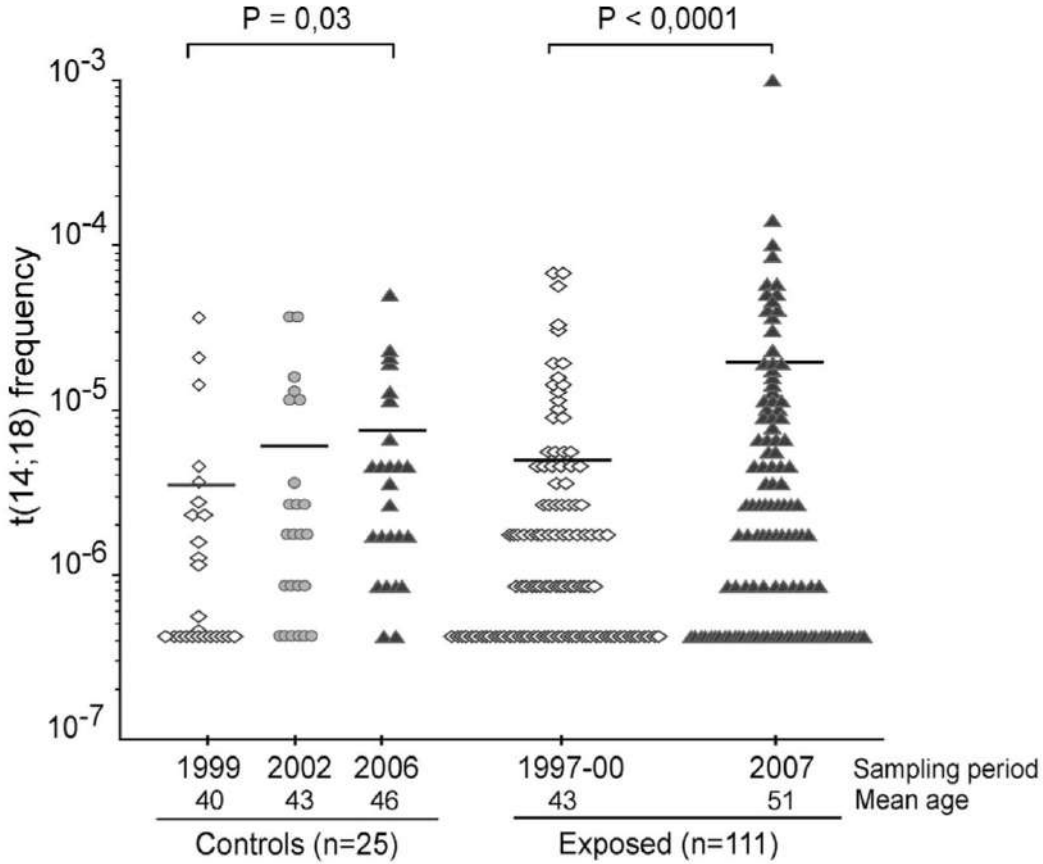
	Sexe	Année					Taux annuel moyen d'évolution (%)	
		1995	2000	2005	2010	2012	De 1995 à 2012	De 2005 à 2012
Incidence	Homme	1,5	1,8	2,1	2,4	2,5	3,0	2,6
	Femme	1,4	1,6	1,8	2,0	2,1	2,2	1,9

Facteurs de risque cliniques et environnementaux

Peu de facteurs de risques décrits
Beaucoup d'études contradictoires

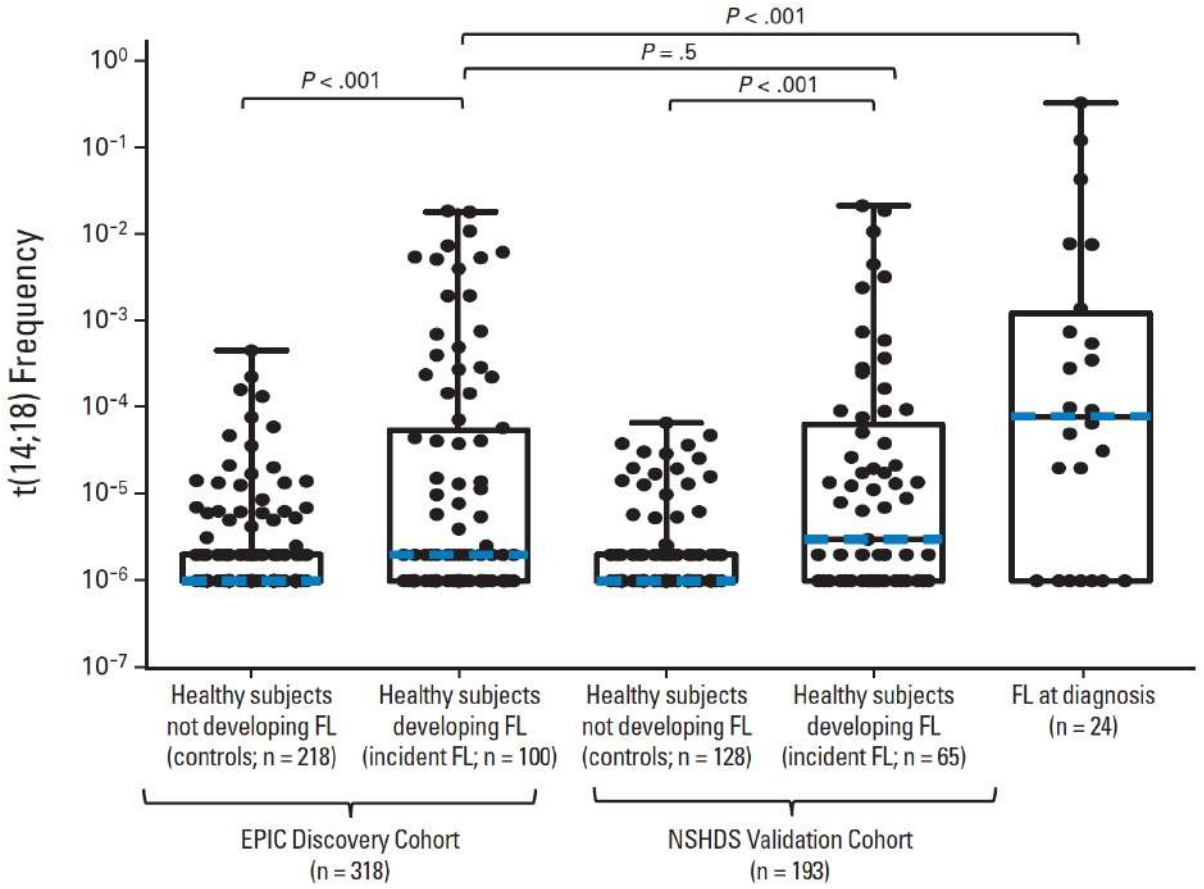
	Increased risk	Protective effect	No effect
Tabac	Talamini et al. Int J Cancer 2005 Morton et al. BJC 2003	Troy et al. Am J Epidemiology 2010	
Alcool	Résultats contradictoires / pas d'étude spécifique du FL / facteur de risque si consommation passée / protecteur si actif ?		
IMC	Skibola et al. Cancer Epidemiol Biomarkers Prev 2004		Cerhan et al. AJH 2002 Cheng et al. JNCI 2005

Facteurs de risque environnementaux



Roulland et al. JEM 2009

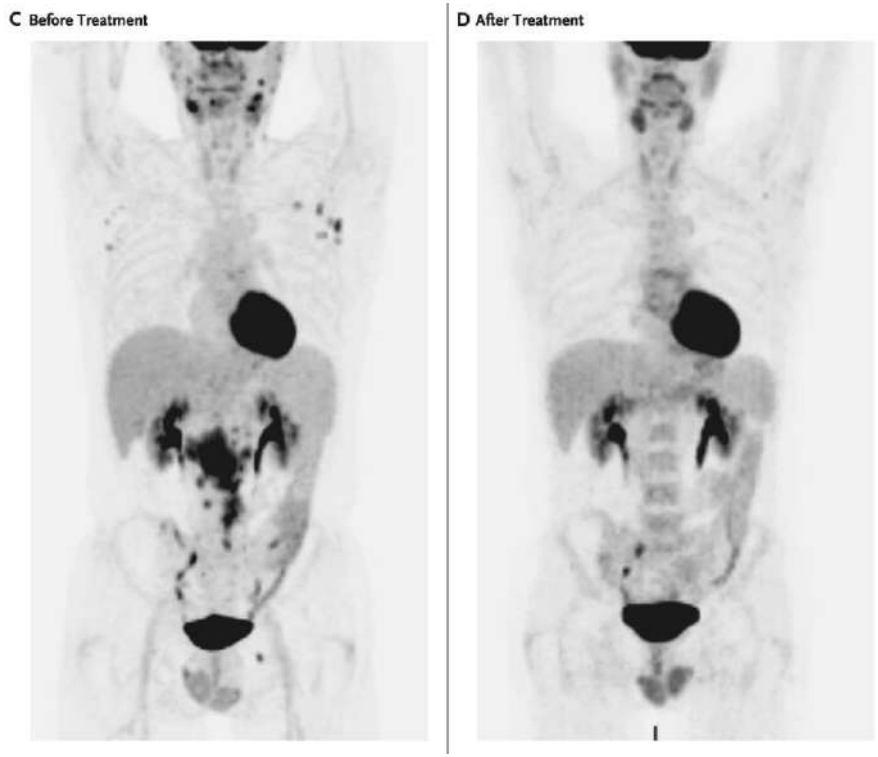
Facteurs de risque environnementaux



Roulland et al., JCO 2014

Virus et lymphome folliculaire: l'hypothèse VHC ?

1. Le virus du VHC n'est pas associé à une sur-incidence de LF[1]
2. Mais la fréquence de clones t(14;18) est augmentée dans le sang de patients VHC+ notamment cryo+[2]
3. Un case-report de régression complète du LF après éradication du VHC par sofosbuvir+ribavirine[3]

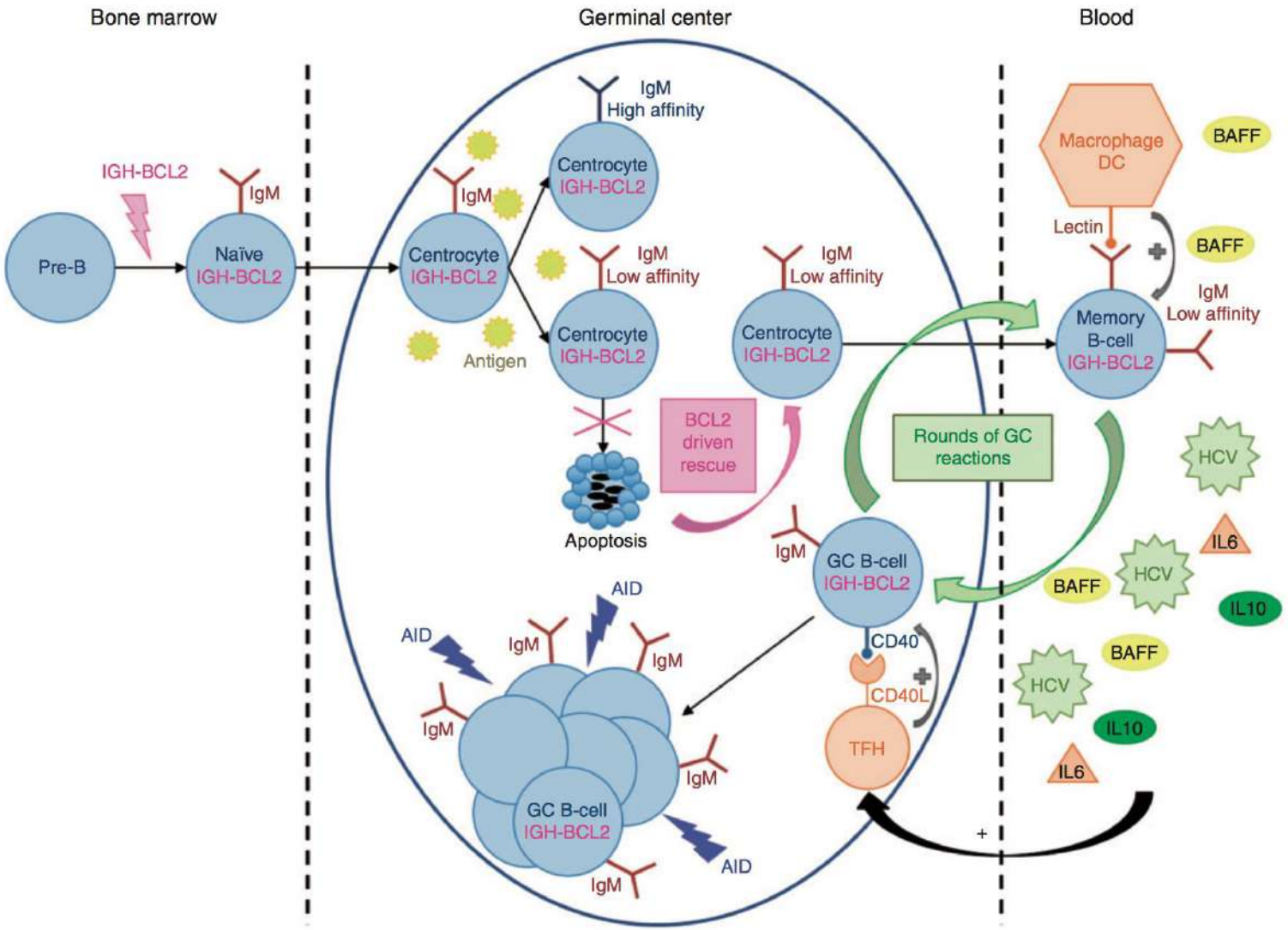


[1]Iqbal et al., Int J Cancer 2016

[2]Kitay Cohen et al., Blood 2000 & Zuckermann et al., BJH 2001

[3]Maciocia et al., NEJM, 2016

Virus et lymphome folliculaire: l'hypothèse VHC ?



Couronné L et al., Ann Oncol, 2017

Facteurs de risque génétiques

SNP	Chromosome	Region	OR	p	Etude
rs10484561	6q21.32	**HLAII**	1.95 (95% CI: 1.72-2.22)	1.12×10^{-29}	Conde et al. Nat Genetics 2010
rs2647012	6q21.32	**HLAII**	0.64	2×10^{-21}	Smedby et al. PLoS Genetics 2011
rs17203612	6q21.32	**HLAII**	1.44	4.59×10^{-16}	Skibola et al., Am J Hum Genet 2014
rs3130437	6q21	**HLAI**	1.23	8.23×10^{-9}	
rs4938573	11q23.3	**CXCR5**	-	5.79×10^{-20}	
rs4937362	11q24.3	**ETS1**	-	6.76×10^{-11}	
rs6444305	3q28	**LPP**	-	1.1×10^{-10}	
rs17749561	18q21.33	**BCL2**	-	8.28×10^{-10}	
rs13254990	8q24.21	**PVT1**	-	1.06×10^{-8}	

Facteurs pronostiques

Les variables pré-thérapeutiques

Point méthodologique: ne pas confondre variable et score pronostiques

A nombre de patients suffisants quasiment toutes les variables usuelles sont pronostiques

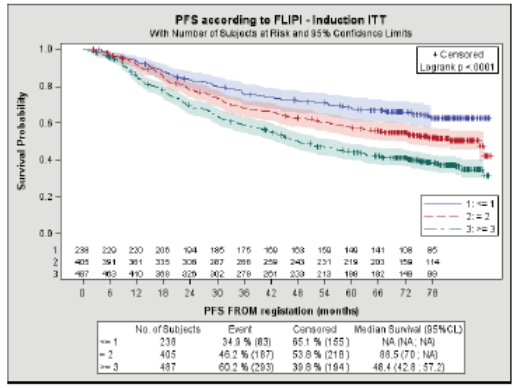
Table 2. Characteristics of the patients and results of the univariate analysis of prognostic factors

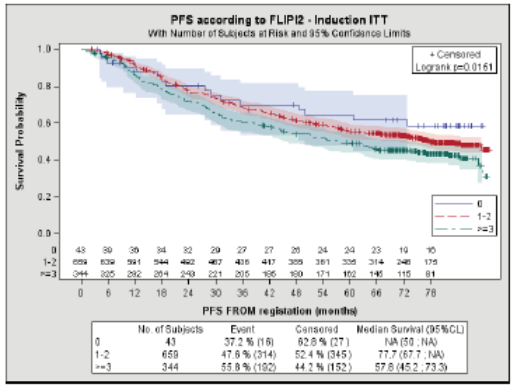
Parameter	n	%	5-year survival, % (SE)	10-year survival, % (SE)	Log rank, P
Sex	4167				.0025
Female		49	72.5 (1.0)	51.0 (1.4)	
Male		51	68.7 (1.0)	46.2 (1.4)	
Age	4167				$< 10^{-4}$
Younger than 60 y		63	78.1 (0.8)	58.4 (1.2)	
60 y or older		37	57.7 (1.3)	32.3 (1.6)	
Cell type	3511				.1065
Small cell		50	71.8 (1.1)	48.6 (1.5)	
Mixed		41	71.1 (1.2)	50.4 (1.7)	
Large cell		9	66.1 (2.7)	40.0 (3.9)	
Ann Arbor stage	4162				$< 10^{-4}$
I-II		22	83.2 (1.2)	64.3 (2.0)	
III-IV		78	67.0 (0.8)	44.1 (1.1)	
B symptoms	3965				$< 10^{-4}$
Absence		81	73.8 (0.8)	50.7 (1.2)	
Presence		19	55.8 (1.8)	36.8 (2.3)	
Performance status (ECOG)	3602				$< 10^{-4}$
0-1		88	72.4 (0.8)	50.0 (1.2)	
More than 1		12	58.6 (2.4)	37.8 (3.0)	
Number of nodal sites	3322				$< 10^{-4}$
0-4		65	77.0 (0.9)	54.6 (1.4)	
5 or more		35	63.7 (1.4)	42.1 (1.9)	
Number of extra nodal sites other than bone marrow	3741				$< 10^{-4}$
0		62	76.1 (0.9)	55.4 (1.3)	
1 or more		38	63.7 (1.3)	40.8 (1.7)	
Bone marrow involvement	4016				$< 10^{-4}$
Absence		52	75.6 (0.9)	56.2 (1.3)	
Presence		48	65.7 (1.1)	40.4 (1.6)	
Spleen involvement	3816				$< 10^{-4}$
Absence		78	74.8 (0.8)	53.0 (1.2)	
Presence		22	57.6 (1.7)	36.5 (2.1)	
Serum β_2 microglobulin	716				$< 10^{-4}$
Less than or equal to ULN		59	86.0 (1.7)	65.1 (3.9)	
Greater than ULN		41	65.0 (2.8)	42.5 (3.8)	
ESR	2256				$< 10^{-4}$
Less than or equal to 40 mm/h		89	73.3 (1.0)	52.0 (1.4)	
Greater than 40 mm/h		11	43.6 (3.2)	28.5 (3.6)	
Serum LDH	2565				$< 10^{-4}$
Less than or equal to ULN		79	76.6 (0.9)	53.9 (1.6)	
Greater than ULN		21	57.6 (2.1)	41.4 (2.7)	
Thrombocyte count	3655				$< 10^{-4}$
Greater than or equal to 150×10^9/L		88	72.2 (0.8)	50.5 (1.2)	
Less than 150×10^9/L		12	59.9 (2.3)	36.1 (3.1)	
Hemoglobin level	3813				$< 10^{-4}$
Greater than or equal to 120 g/L		82	74.9 (0.8)	51.7 (1.2)	
Less than 120 g/L		18	50.7 (1.9)	35.0 (2.3)	
PB lymphocyte count	3122				$< 10^{-4}$
Greater than or equal to 1×10^9/L*		80	73.3 (0.9)	51.5 (1.3)	
Less than 1×10^9/L		20	62.5 (2.0)	39.2 (2.6)	
Serum albumin level	2116				$< 10^{-4}$
Greater than or equal to 35 g/L		90	72.3 (1.0)	50.3 (1.4)	
Less than 35 g/L		10	48.3 (3.5)	25.8 (4.0)	

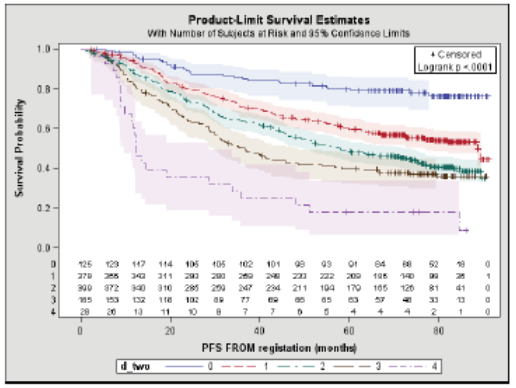
$<10^{-4}$

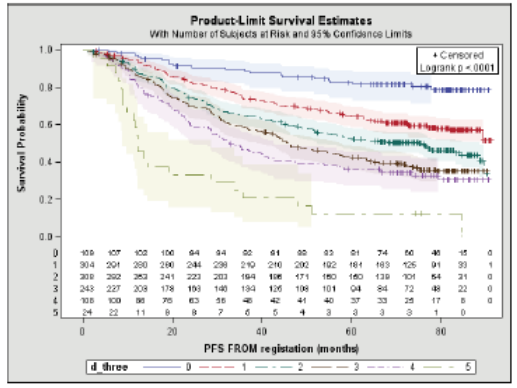
Solal-Celigny et al. Blood 2004

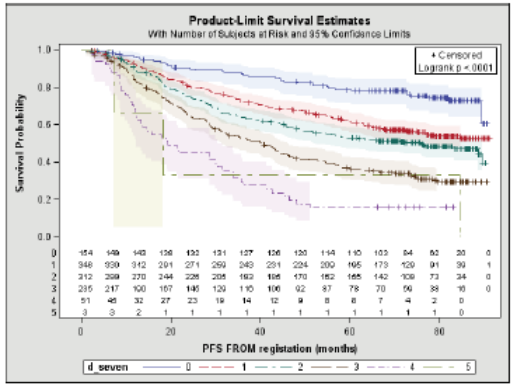
Point méthodologique: attention la construction des scores est complexe!

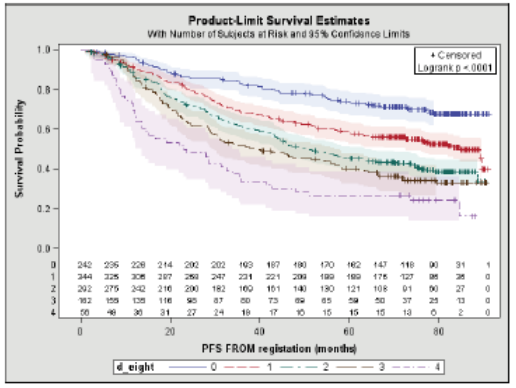


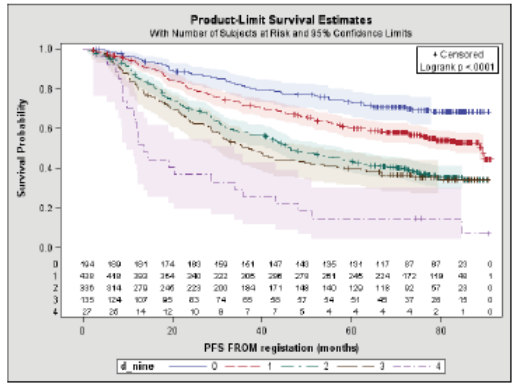


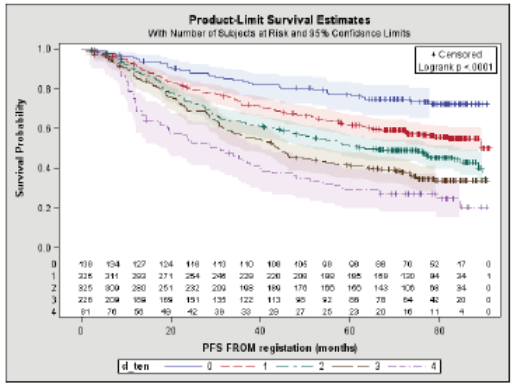


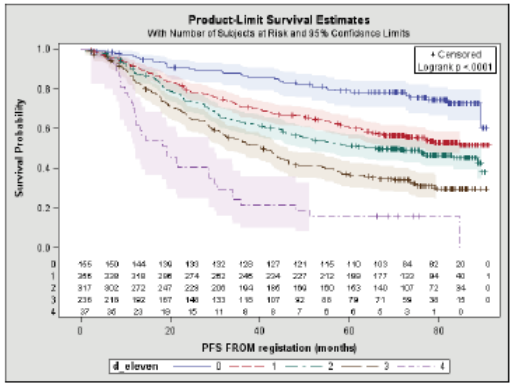




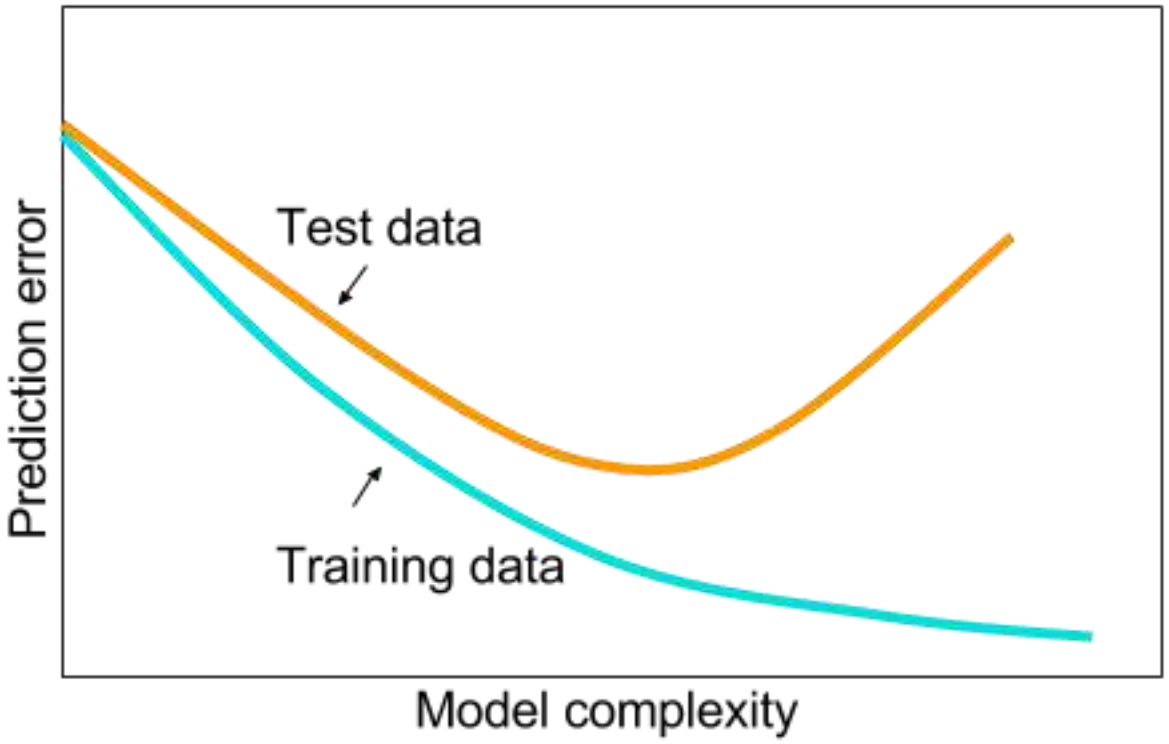




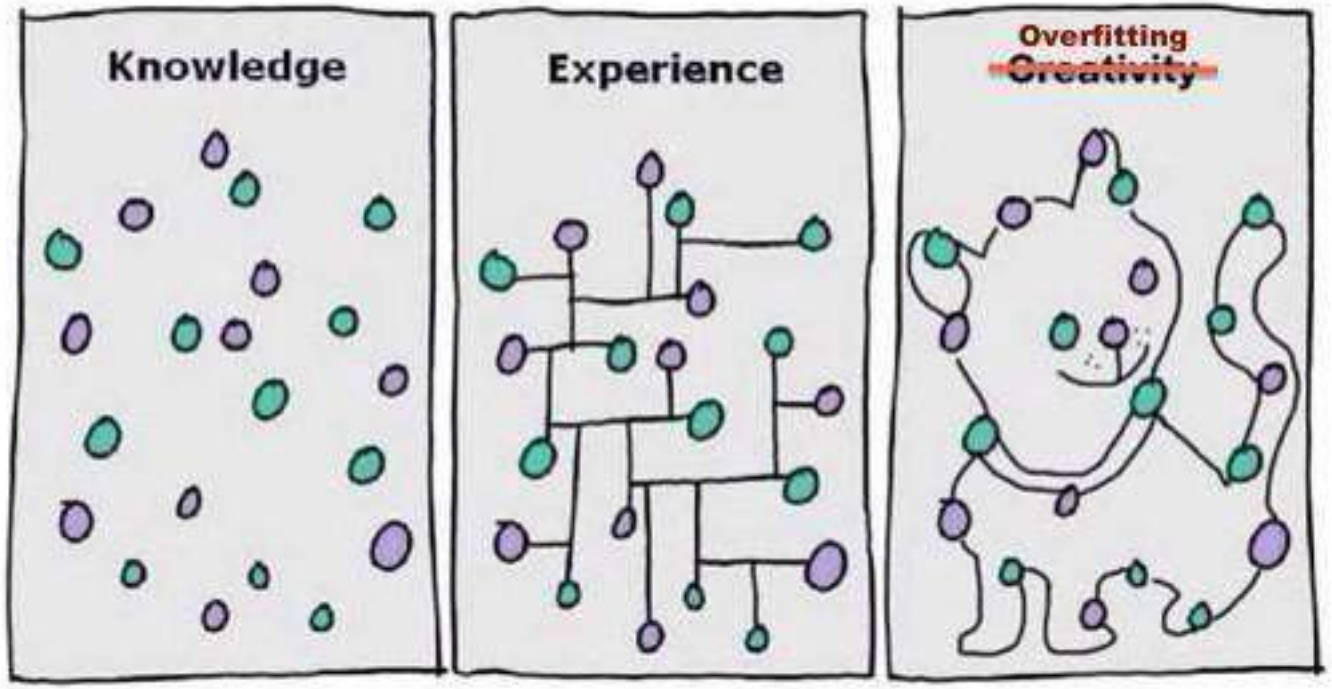




Point méthodologique: sans « validation set » un score ne veut rien dire

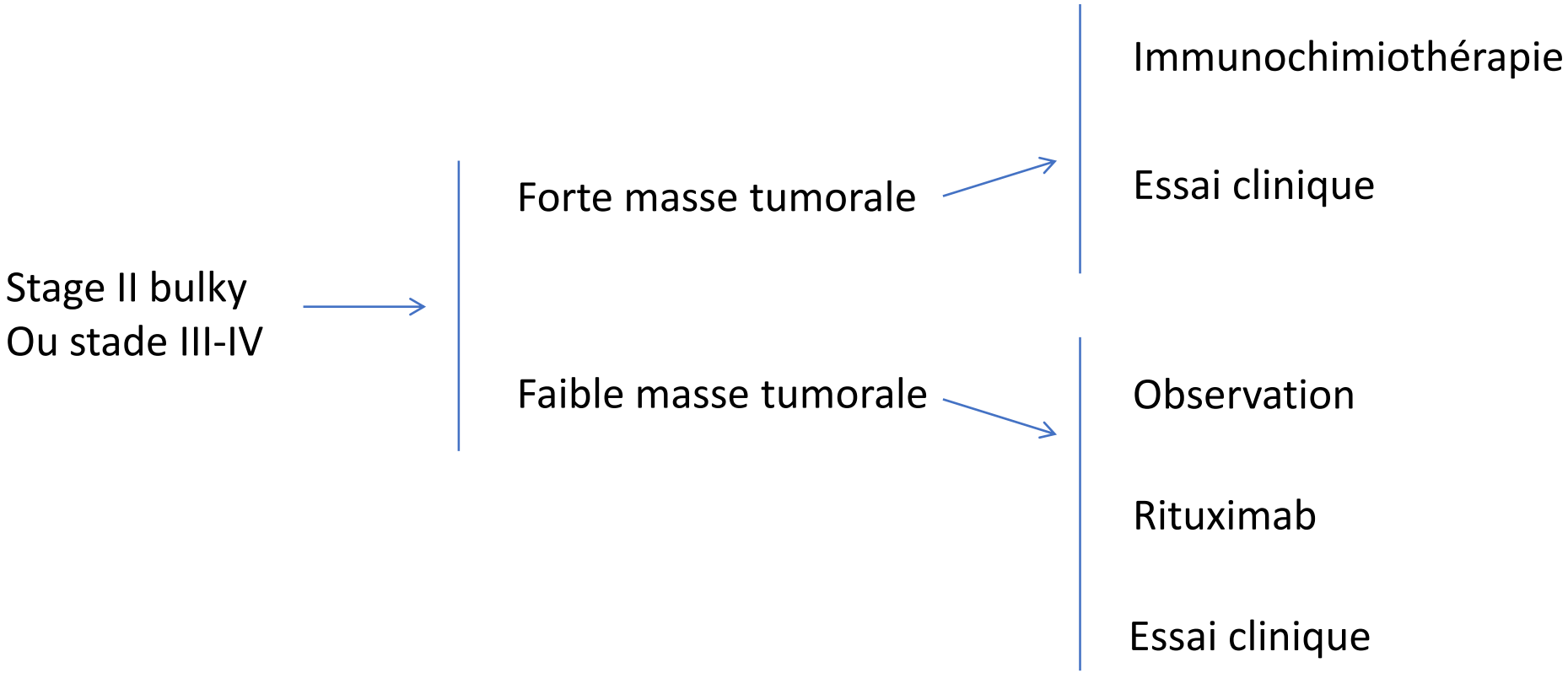


Point méthodologique: attention la construction des scores est complexe!



Impact de la masse tumorale sur le pronostic

Recommandations NCCN/ESMO



Impact de la masse tumorale sur le pronostic

Critères GELF/GELA de forte masse tumorale

- Symptômes B / PS > 1

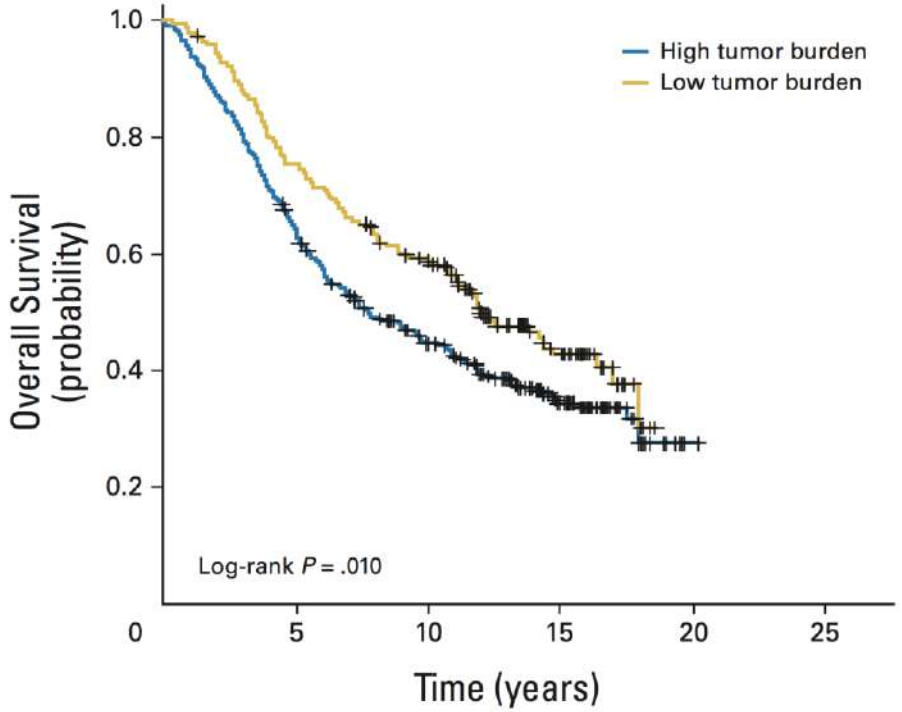
- Masse > 7cm / ≥ 3 ganglions > 3 cm
- Splénomégalie massive

- Compression
- Epanchement
- Cellules circulantes (> 5 G/L)

- Cytopénies
- ß2-microglobuline > 3 mg/L
- LDH > normale

Impact de la masse tumorale sur le pronostic

Essai GELF86

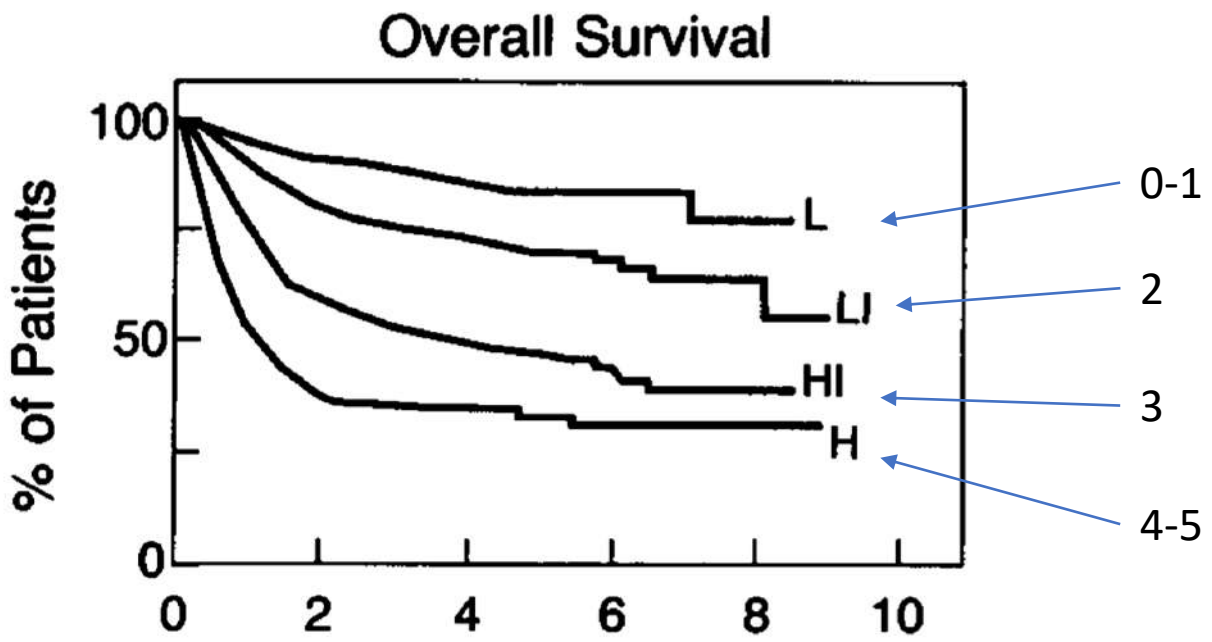


Bachy et al., JCO 2010

Les scores clinico-biologiques : l'IPI

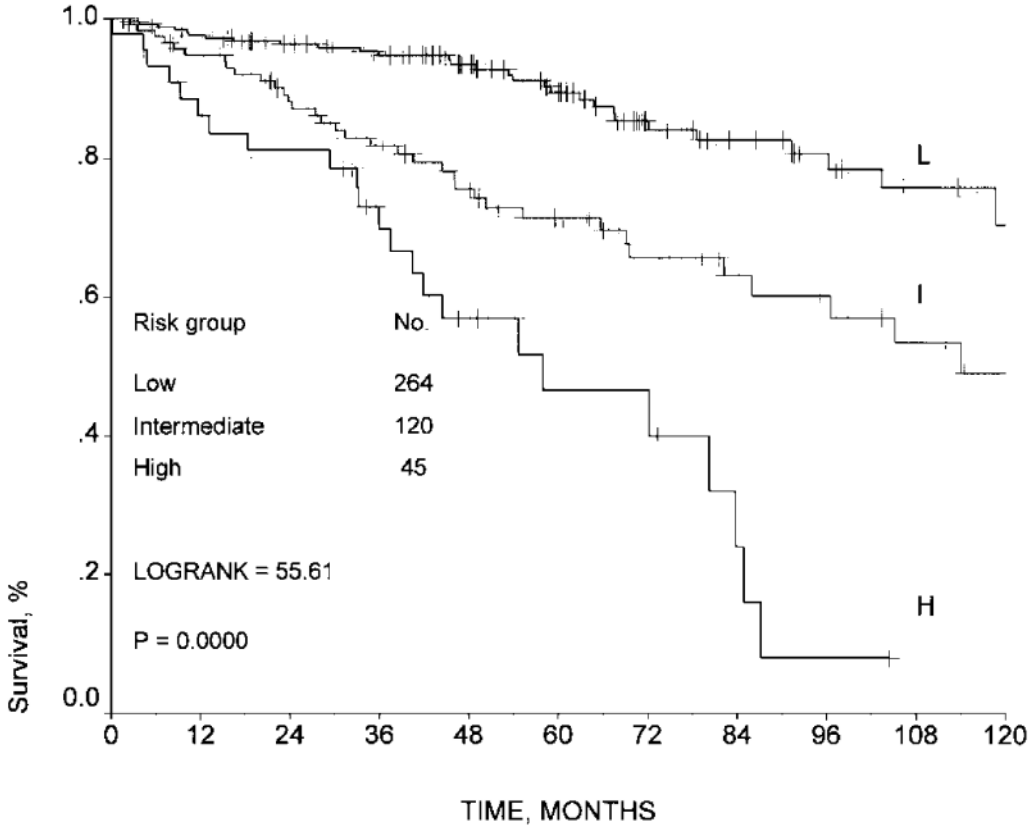
Variables
Stade (I-II v III-IV)
Age (≤60 ans v > 60 ans)
Aires extra-ganglionnaires (≤1 v >1)
LDH (≤limite supérieure v >limite supérieure)
PS (≤1 ou >1)

Dans les LBDGC



The International NHL prognostic factor project, NEJM 1993

Les scores clinico-biologiques : l'IPI

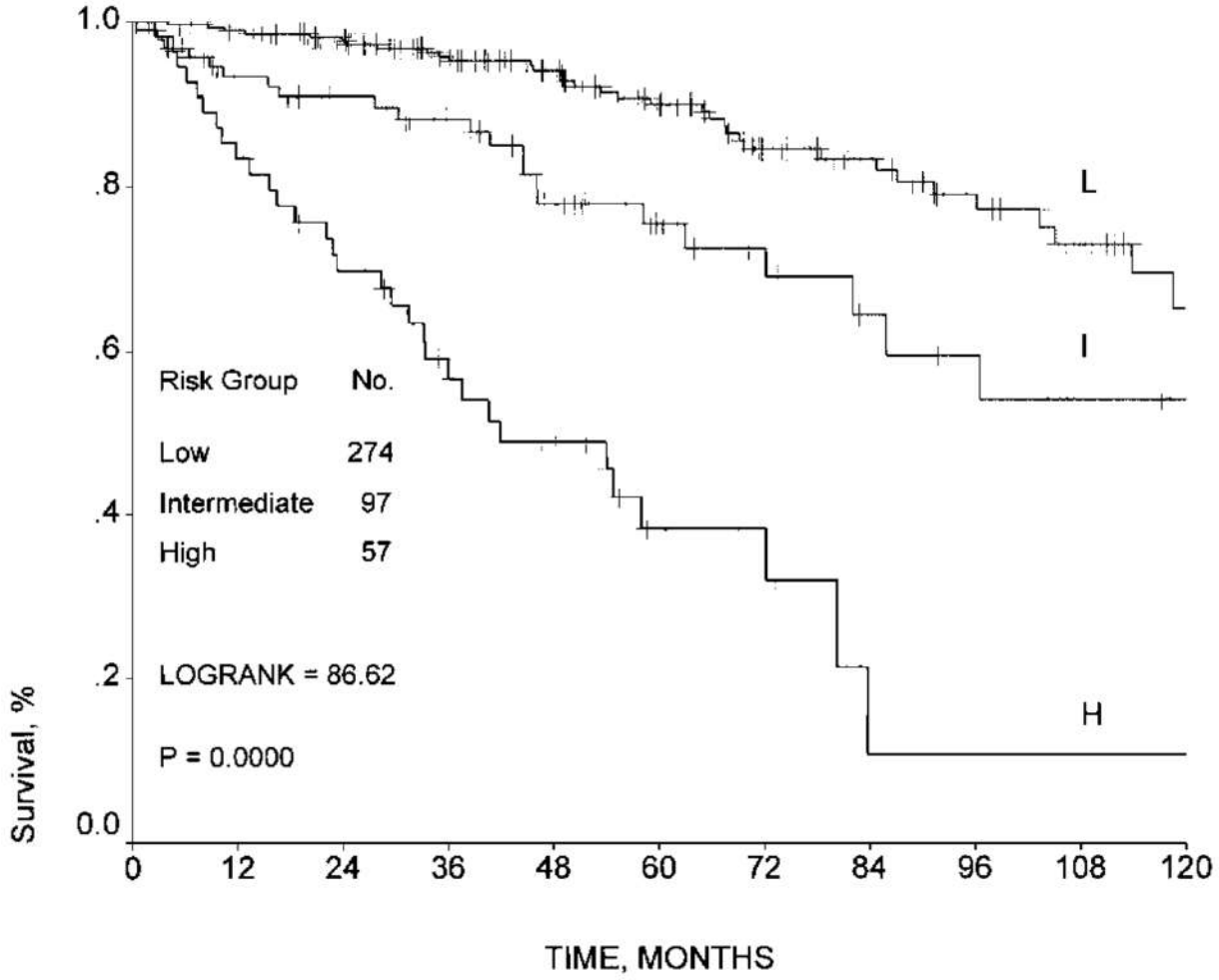


Federico et al., Blood, 2000

Les scores clinico-biologiques : le score de l'intergroupe italien du lymphome

Table 3. Factors with independent prognostic value of survival in the training sample

Factor	Relative Risk of Death	95% CI	*P* Value
Age (no more than 60 vs greater than 60)	2.6	1.6-4.1	<.0001
Sex (F vs M)	1.8	1.2-2.8	.0079
Extranodal sites (0-1 vs at least 2)	2.1	1.0-4.2	.0445
Serum LDH (normal vs elevated)	2.0	1.2-3.5	.0074
B symptoms (absent vs present)	2.2	1.2-4.1	.0128
ESR (less than 30 vs at least 30)	2.4	1.5-4.1	.0006



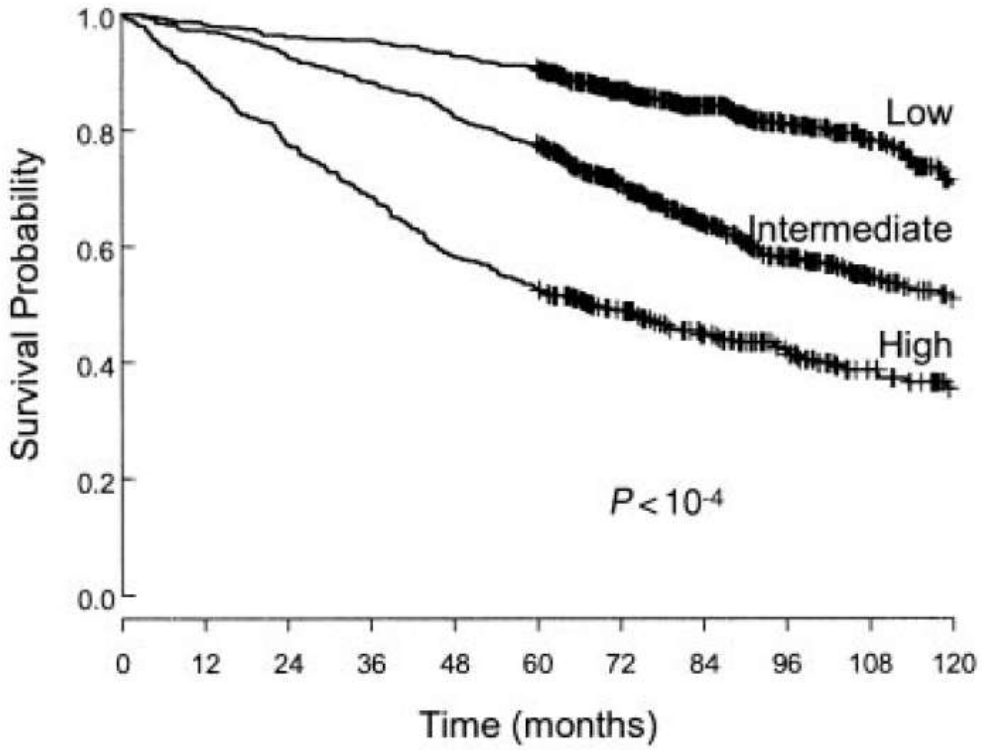
Federico et al., Blood, 2000

Les scores clinico-biologiques : le FLIPI

Variables	FLIPI	% de patients au diagnostic	Survie globale à 5 ans	Survie globale à 10 ans
Stade (I-II v III-IV)	bas=0-1	bas=36%	bas=91%	bas=71%
Age (≤60 ans v > 60 ans)	intermédiaire=2	intermédiaire=37%	intermédiaire=78%	intermédiaire=51%
Aires ganglionnaires (≤4 v >4)	élevé=3-4-5	élevé=27%	élevé=52%	élevé=35%
LDH (≤limite supérieure v >limite supérieure)				
Hémoglobine (≥12g/dL v <12g/dL)				

Solal-Celigny et al. Blood 2004

Les scores clinico-biologiques : le FLIPI



No. of Events											
Low	-	12	25	29	46	60	83	95	106	113	125
Intermediate	-	19	49	79	118	150	192	225	247	255	261
High	-	54	109	152	202	229	245	260	268	274	278
No. at Risk											
Low	641	629	616	612	595	581	450	337	241	157	93
Intermediate	670	651	621	591	552	519	385	263	178	108	68
High	484	430	375	332	282	255	193	139	98	56	33

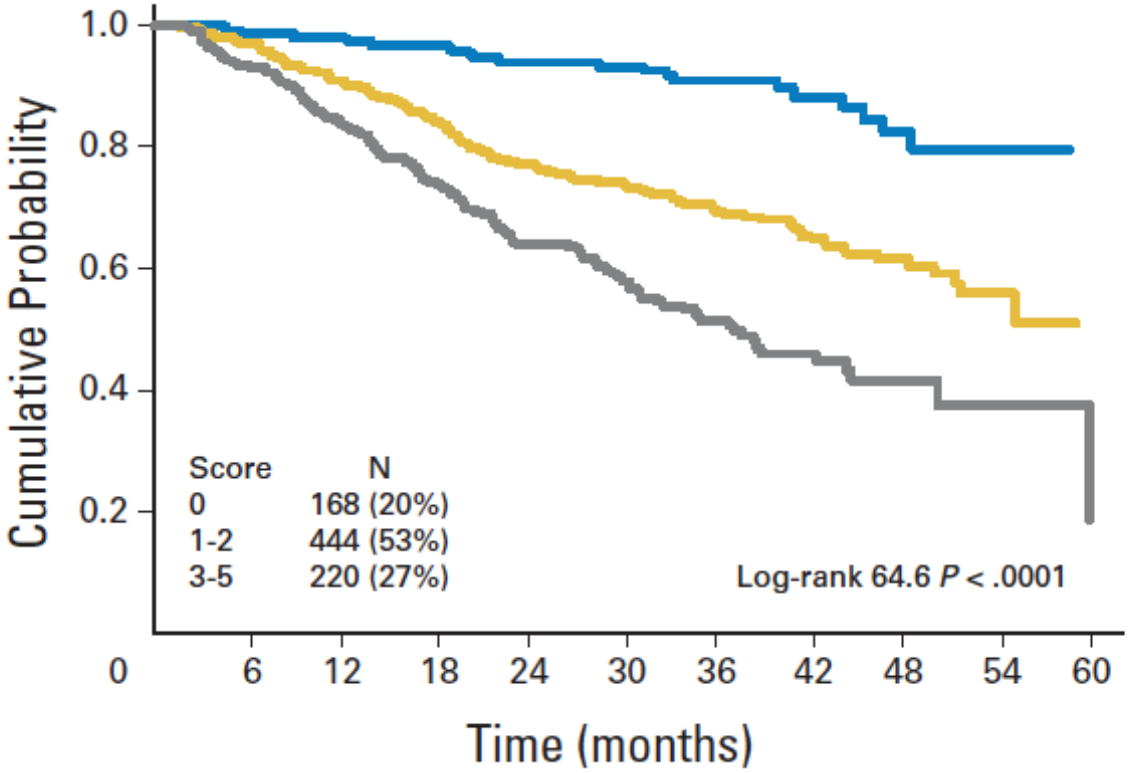
Solal-Celigny et al. Blood 2004

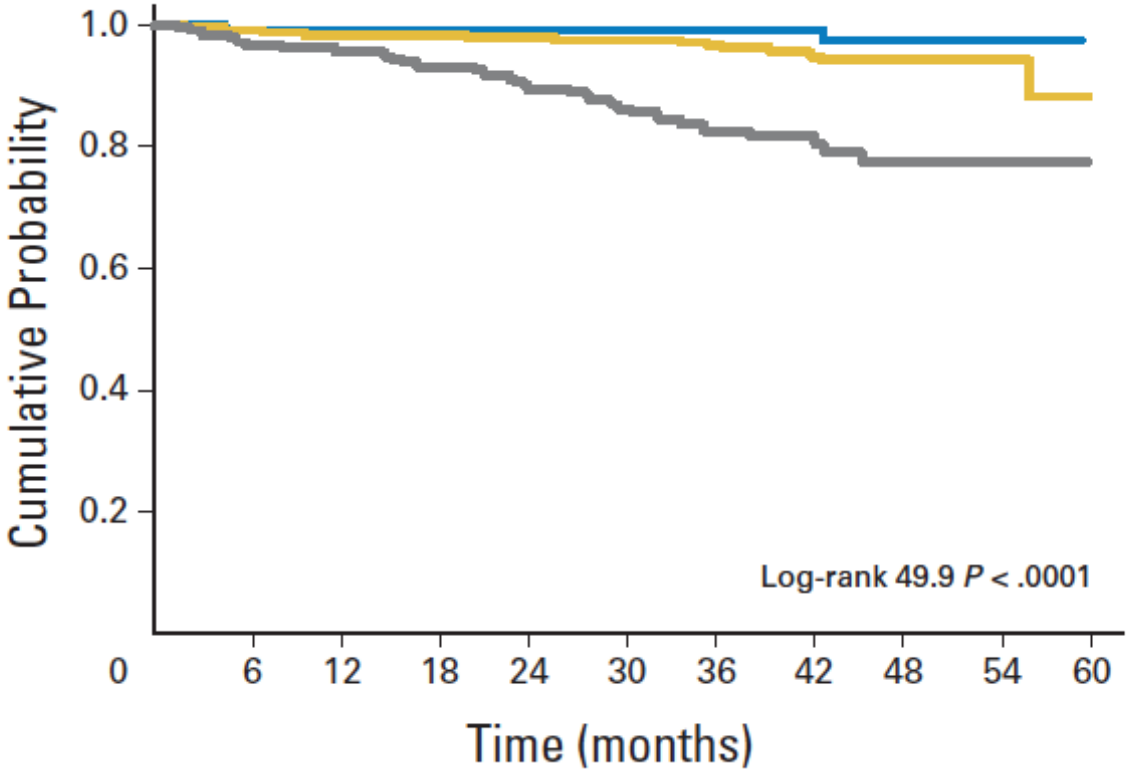
Les scores clinico-biologiques : le FLIPI2

Variables	FLIPI2	% de patients au diagnostic	Survie sans progression à 3 ans	Survie sans progression à 5 ans
ß2-microglobuline (≤limite supérieure v >limite supérieure)	bas=0	bas=20%	bas=91%	bas=79%
Age (≤60 ans v > 60 ans)	intermédiaire=1-2	intermédiaire=53%	intermédiaire=69%	intermédiaire=51%
Diamètre maximal de l'adénomathie la plus volumineuse (≤6cm v > 6cm)	élevé=3-4-5	élevé=27%	élevé=51%	élevé=19%
Envahissement médullaire (non v oui)				
Hémoglobine (≥12g/dL v <12g/dL)				

Federico et al., JCO 2009

Les scores clinico-biologiques : le FLIPI2

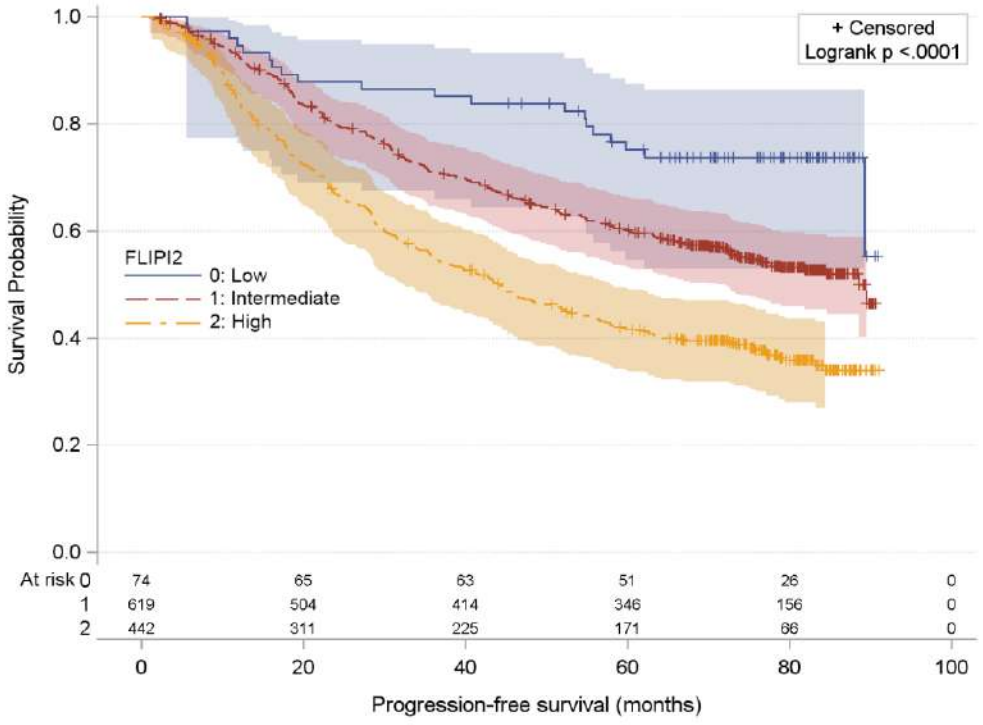


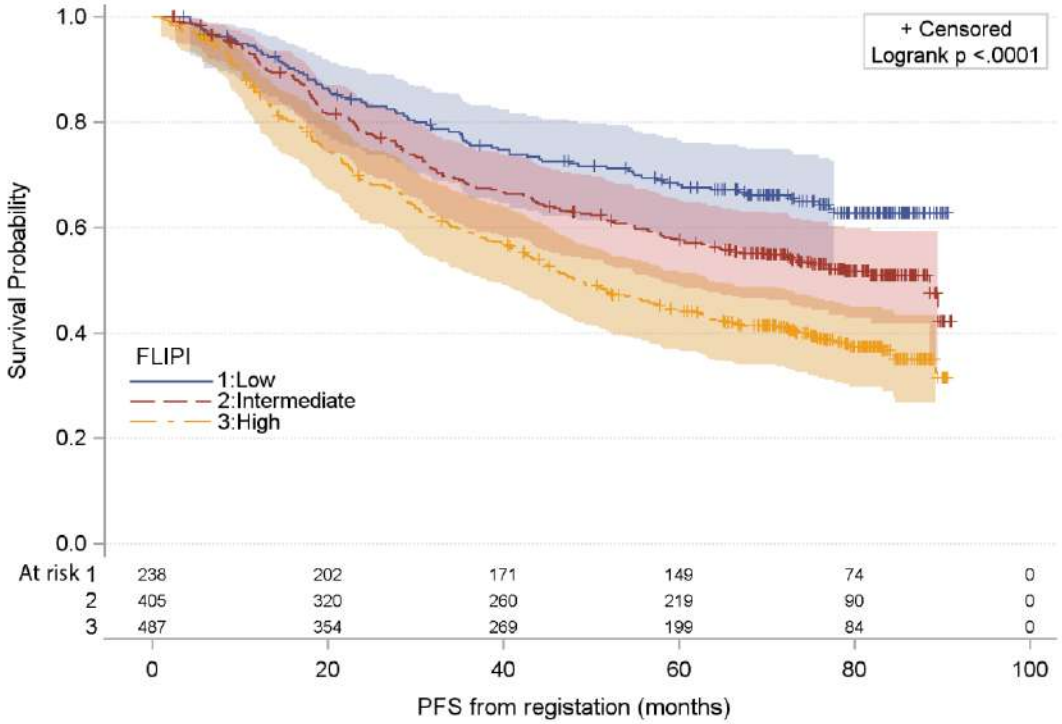


Federico et al., JCO 2009

Les scores clinico-biologiques : le FLIPI2

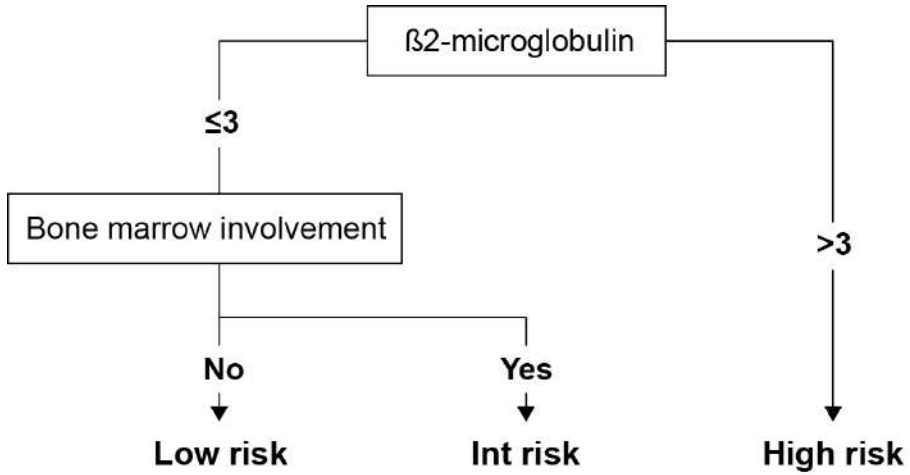
Cohorte PRIMA

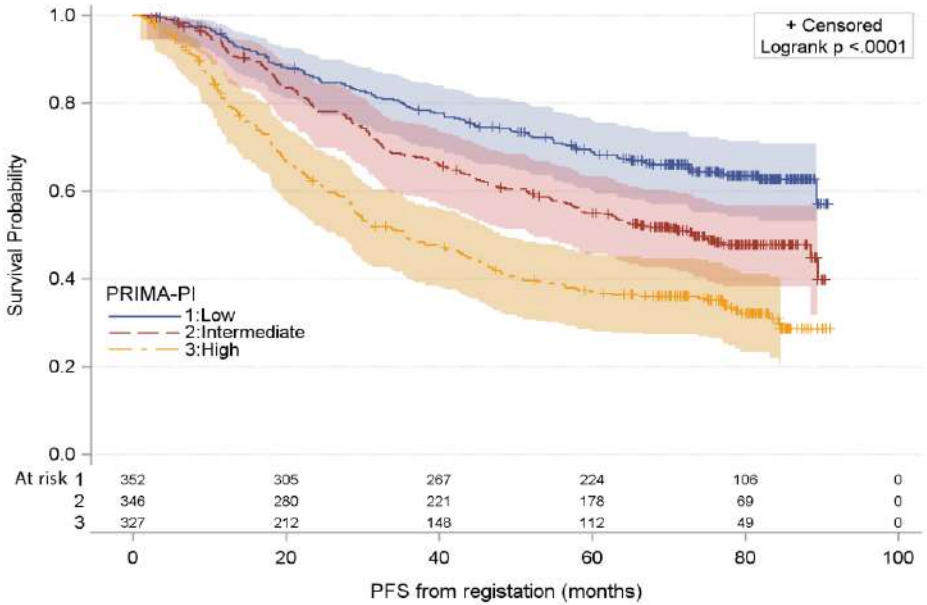


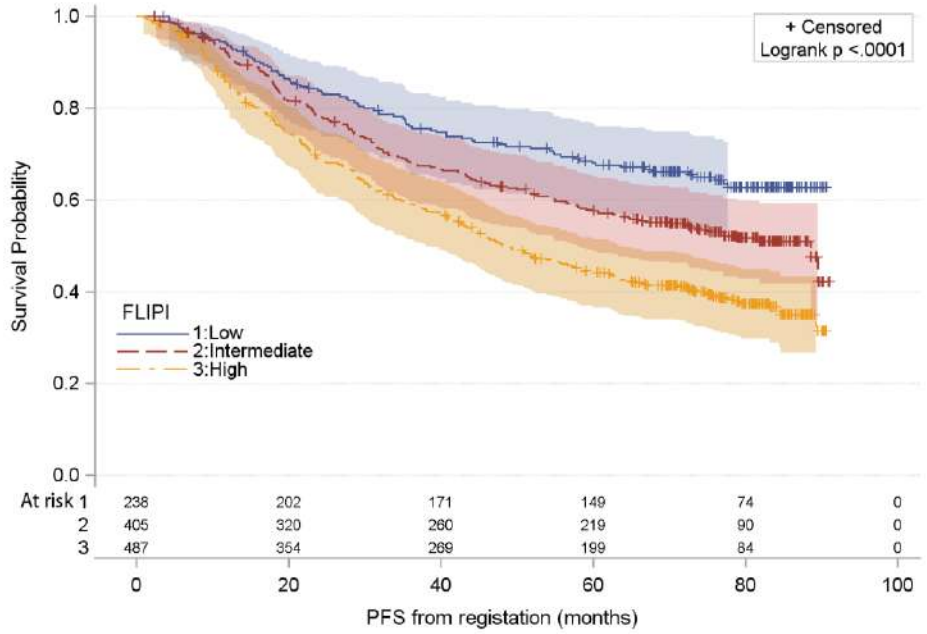


Bachy et al. ASH 2017 Abstract 413

Les scores clinico-biologiques : le PRIMA-PI (forte masse uniquement)

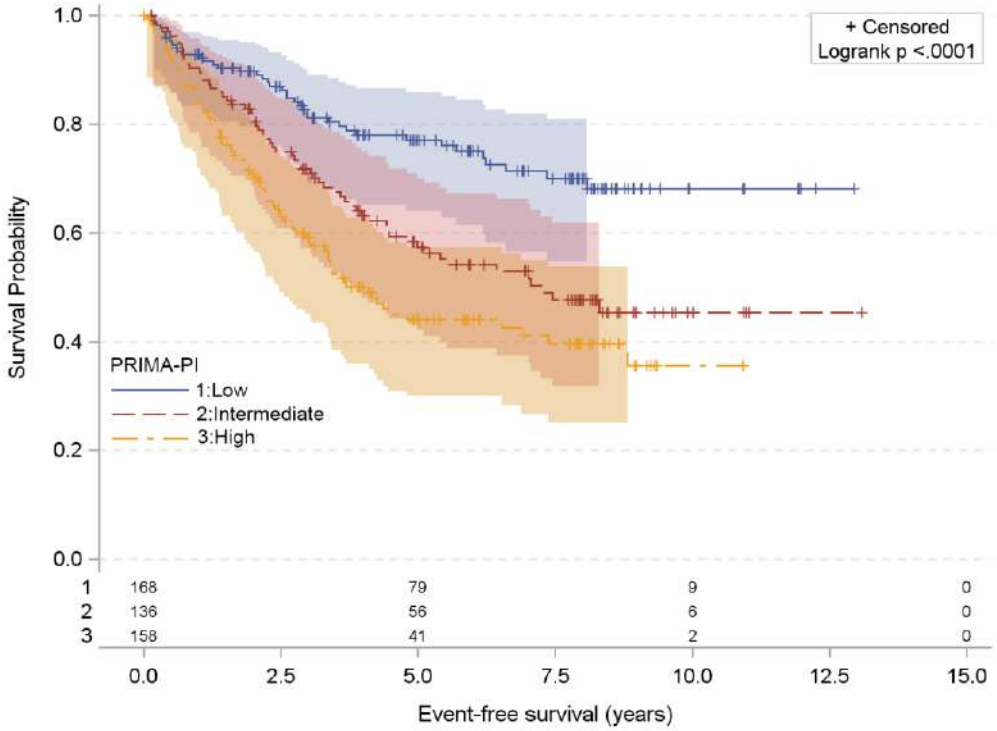


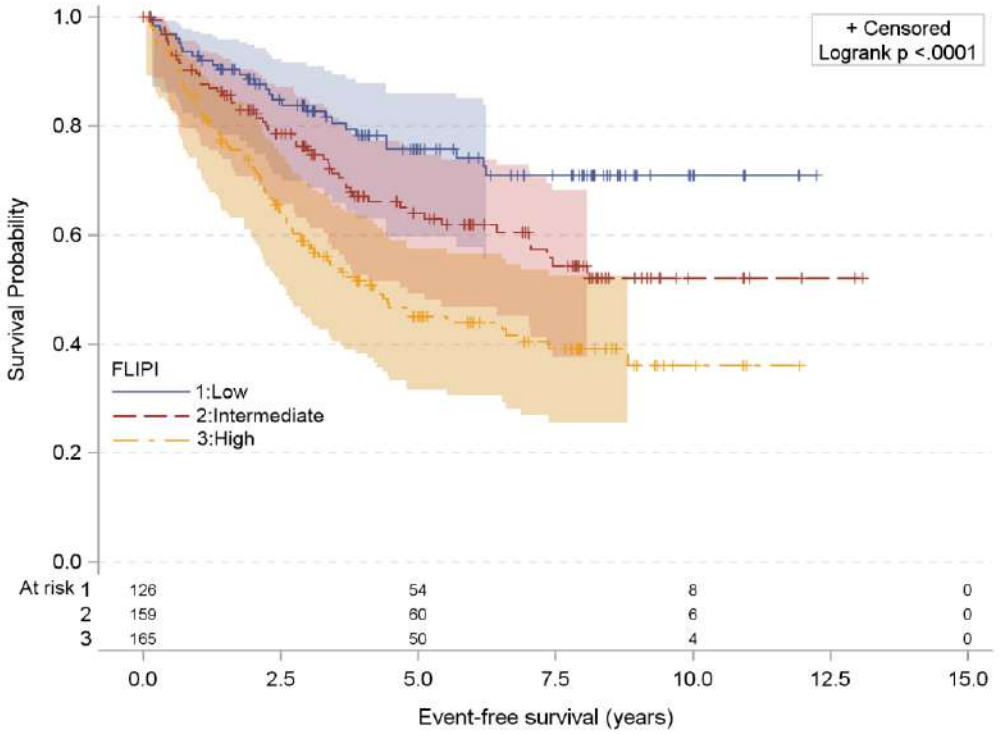




Bachy et al. ASH 2017 Abstract 413

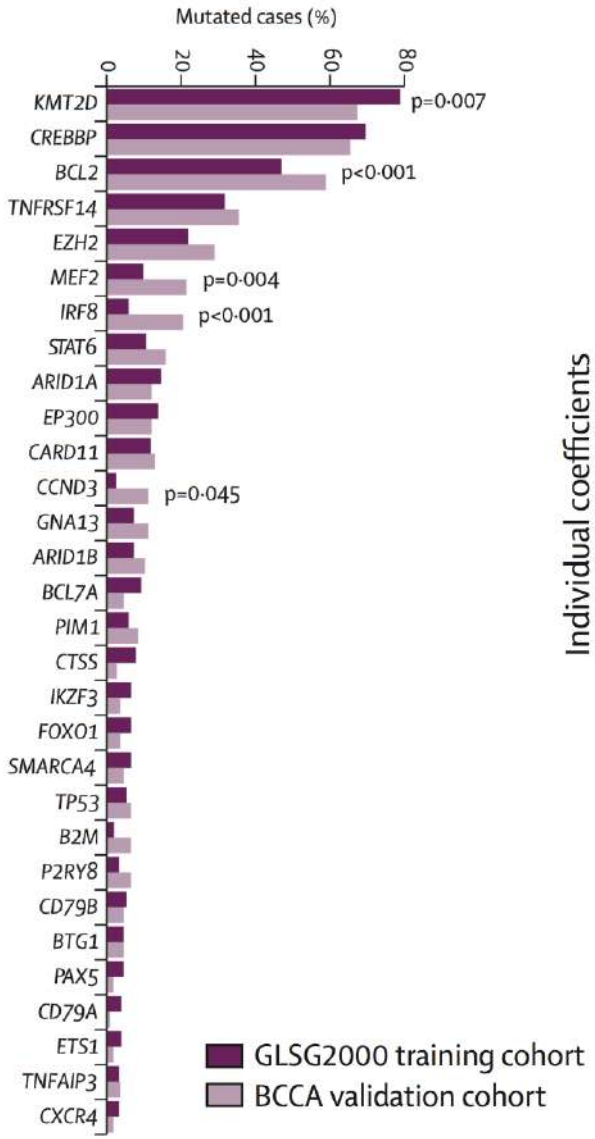
Les scores clinico-biologiques : FL2000 + MER validation

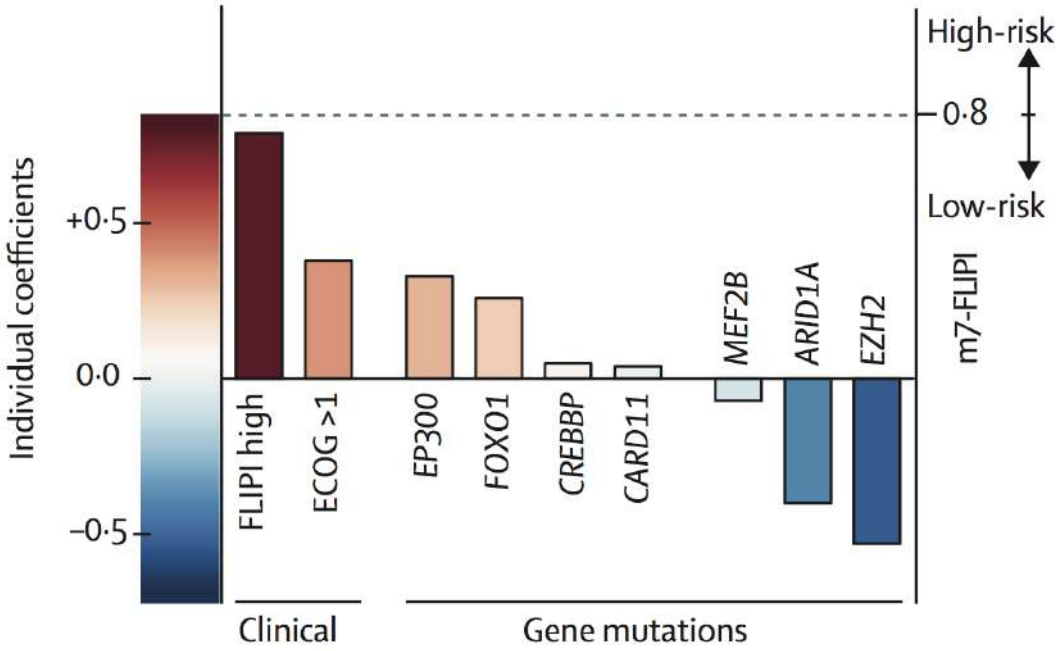




Bachy et al. ASH 2017 Abstract 413

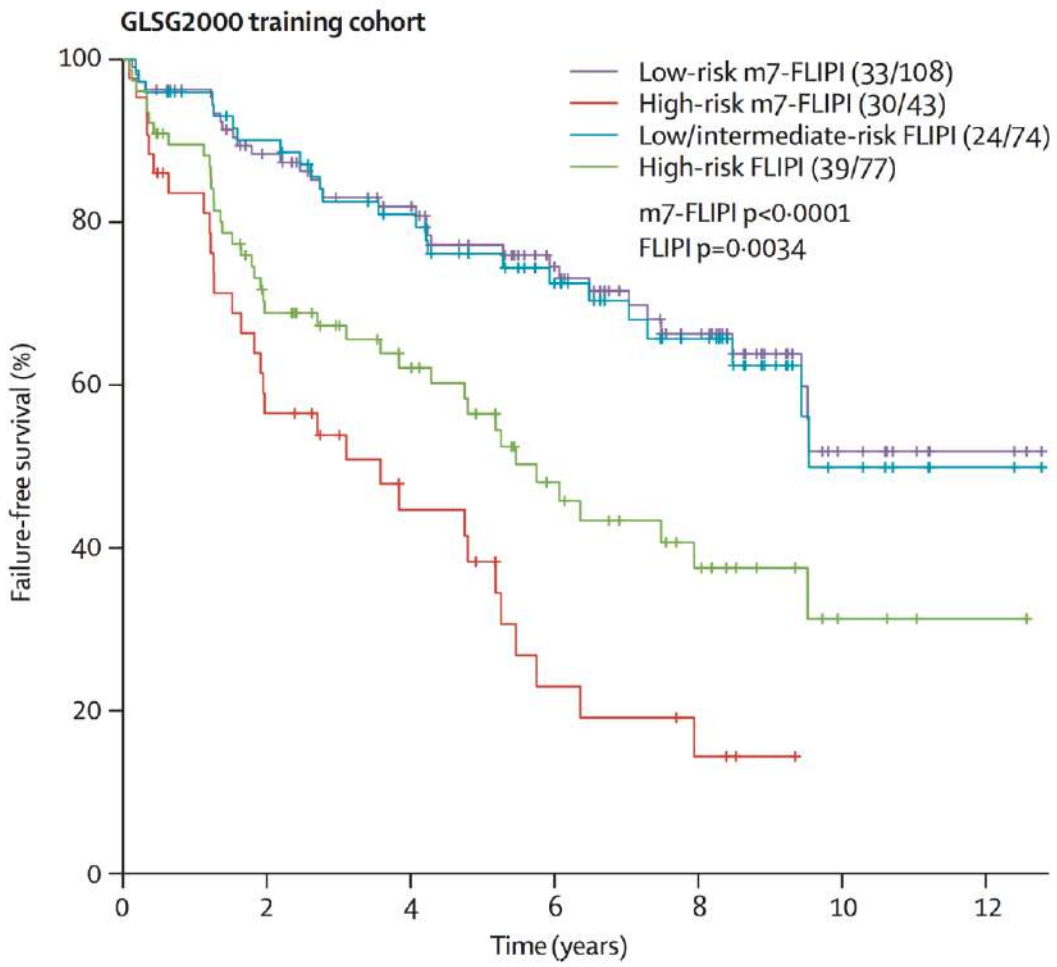
Les scores bio-moléculaires : le m7-FLIPI

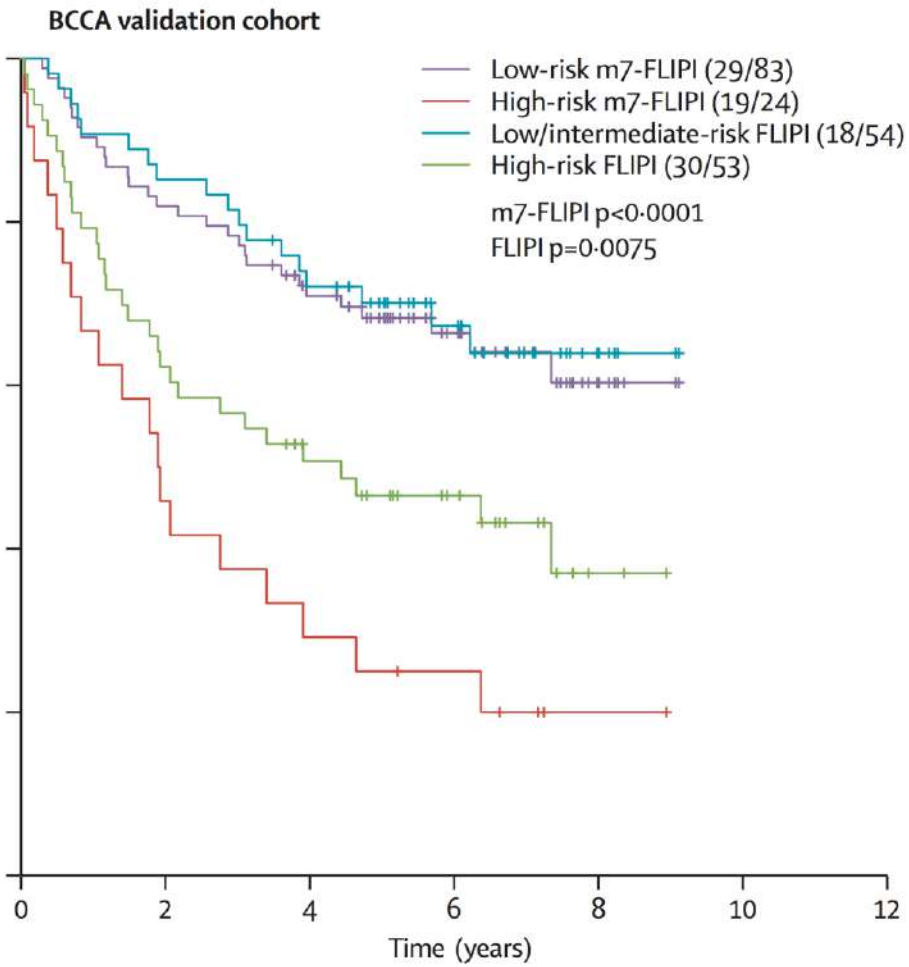




Pastore et al. Lancet Oncol. 2015

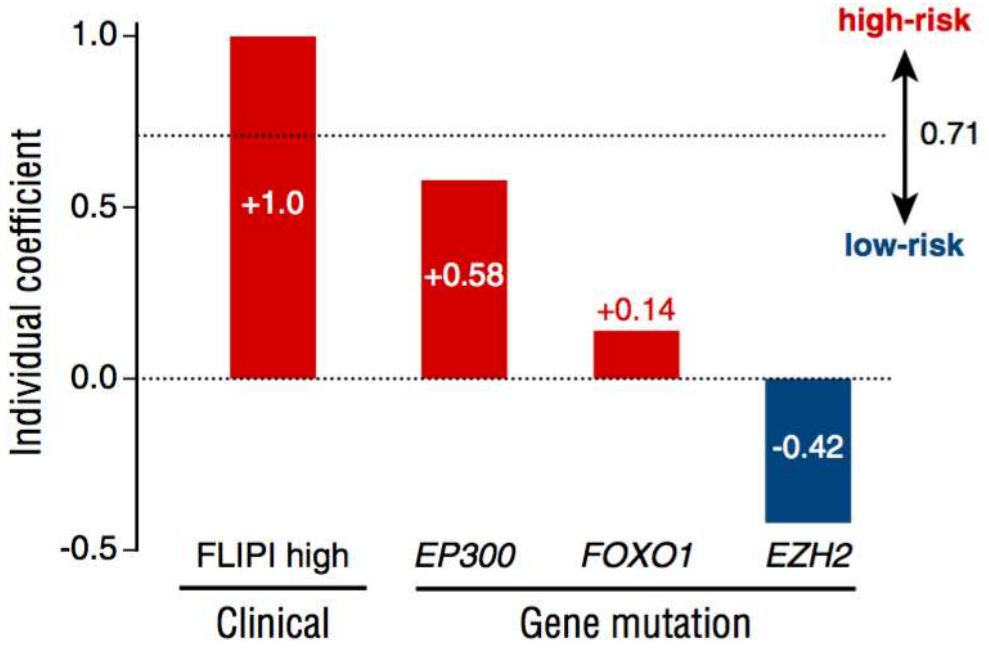
Les scores bio-moléculaires : le m7-FLIPI





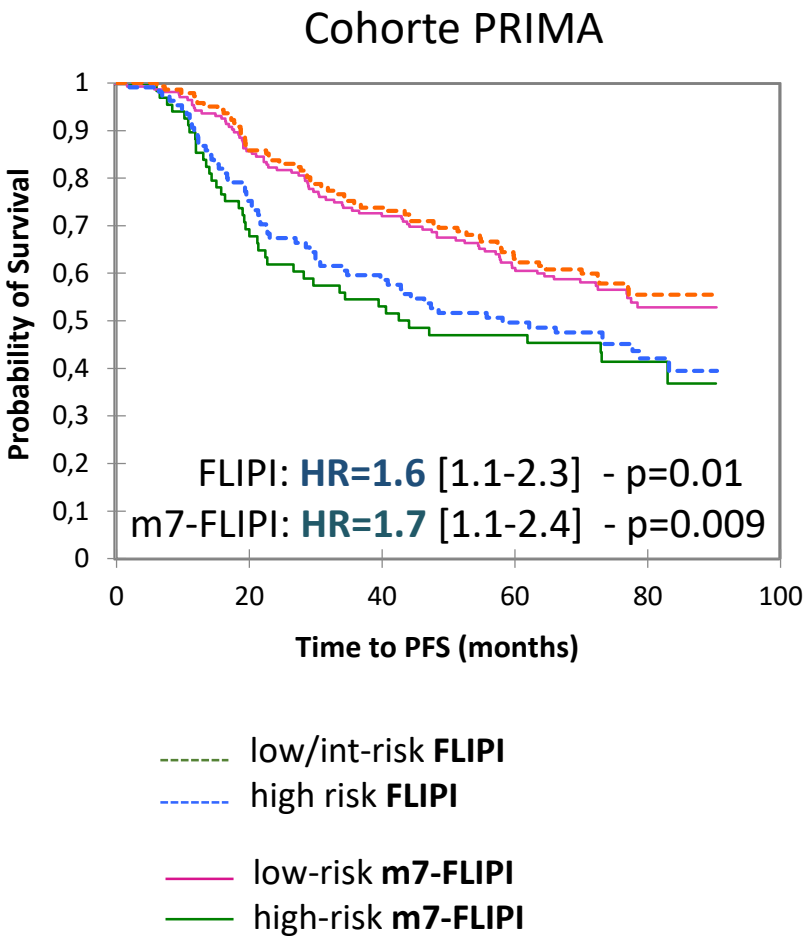
Pastore et al. Lancet Oncol. 2015

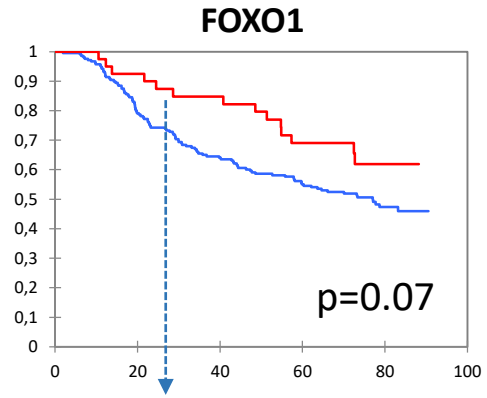
Les scores bio-moléculaires : le POD-PI



Jurinovic et al., Blood 2016

Les scores bio-moléculaires : le m7-FLIPI

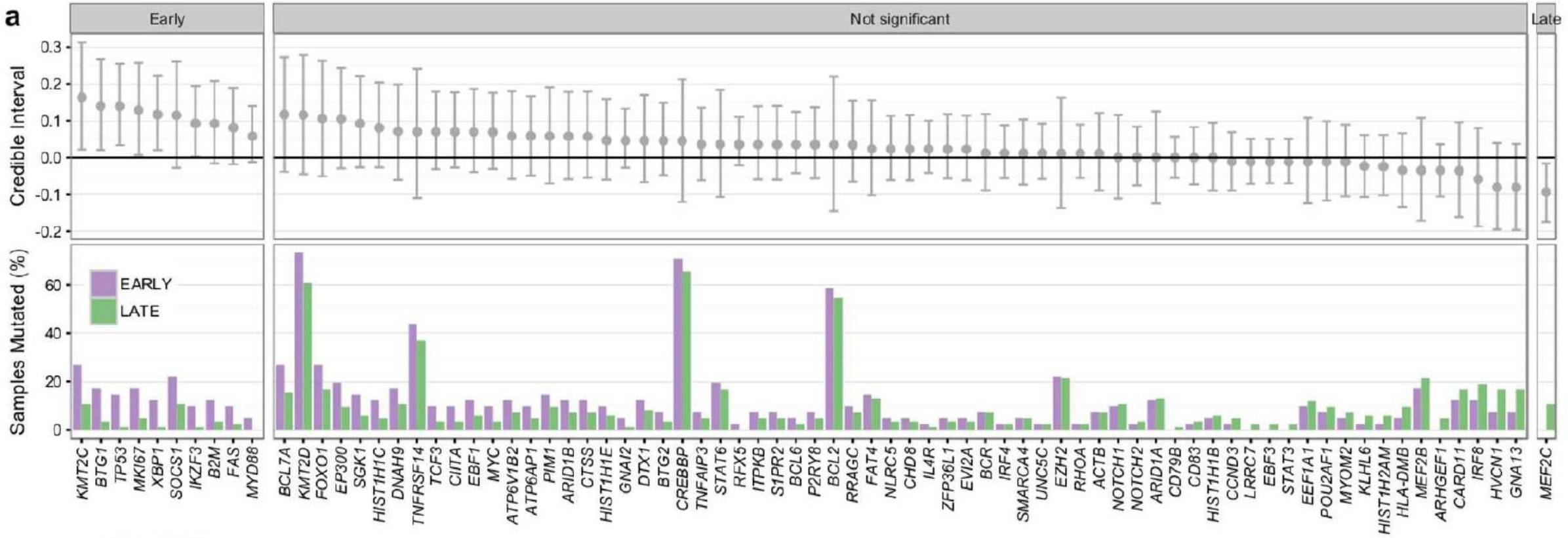




POD24 : 10% vs 25% (p=0.04)

Huet et al, ICML 2017

Les scores bio-moléculaires : Vancouver study



Kridel et al., PlosMed 2016

Un score basé sur l'expression de 23 gènes

23-Gene Predictor

Genes
VPREB1
CXCR4
FOXO1
E2F5
PRDM15
FCRL2
AFF3
TAGAP
ORAI2
SEMA4B
KIAA0040
USP44
EML6
TCF4
DCAF12
RASSF6
GADD45A
ABCB1
METRNL
VCL
ALDH2
RGS10
SHISA8

Model development:

- 23 genes selected

- Coefficients for each gene

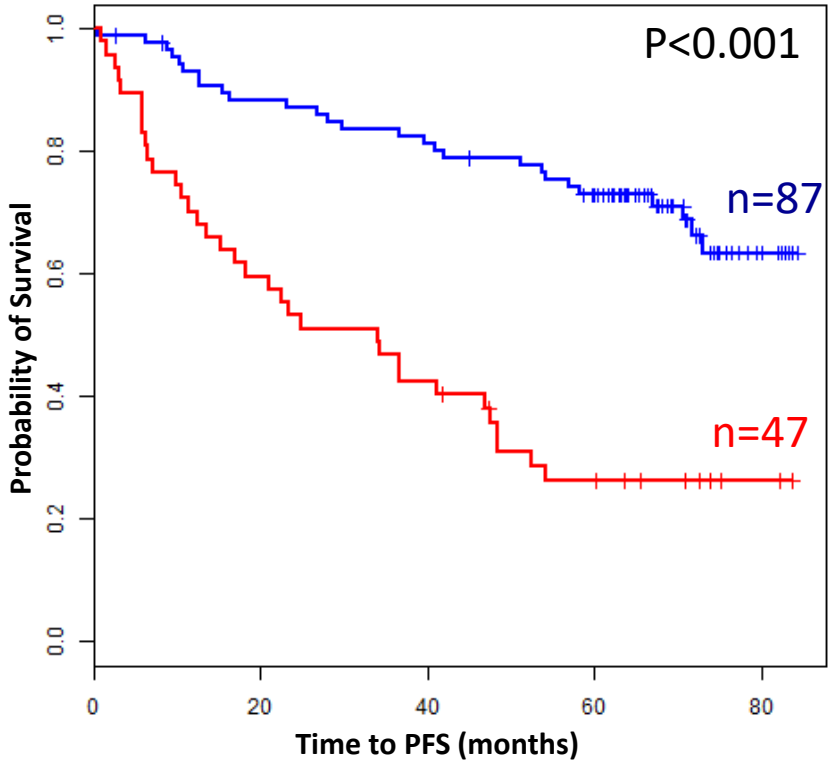
- Optimal cut-off

Gene expression ↗
associated with shorter time to progression

Gene expression ↗
associated with longer time to progression

Huet et al, ICML 2017

Un score basé sur l'expression de 23 gènes



- **Univariate analysis for PFS:**
  Score C-index: 0.709
  (FLIPI C-index: 0.578)

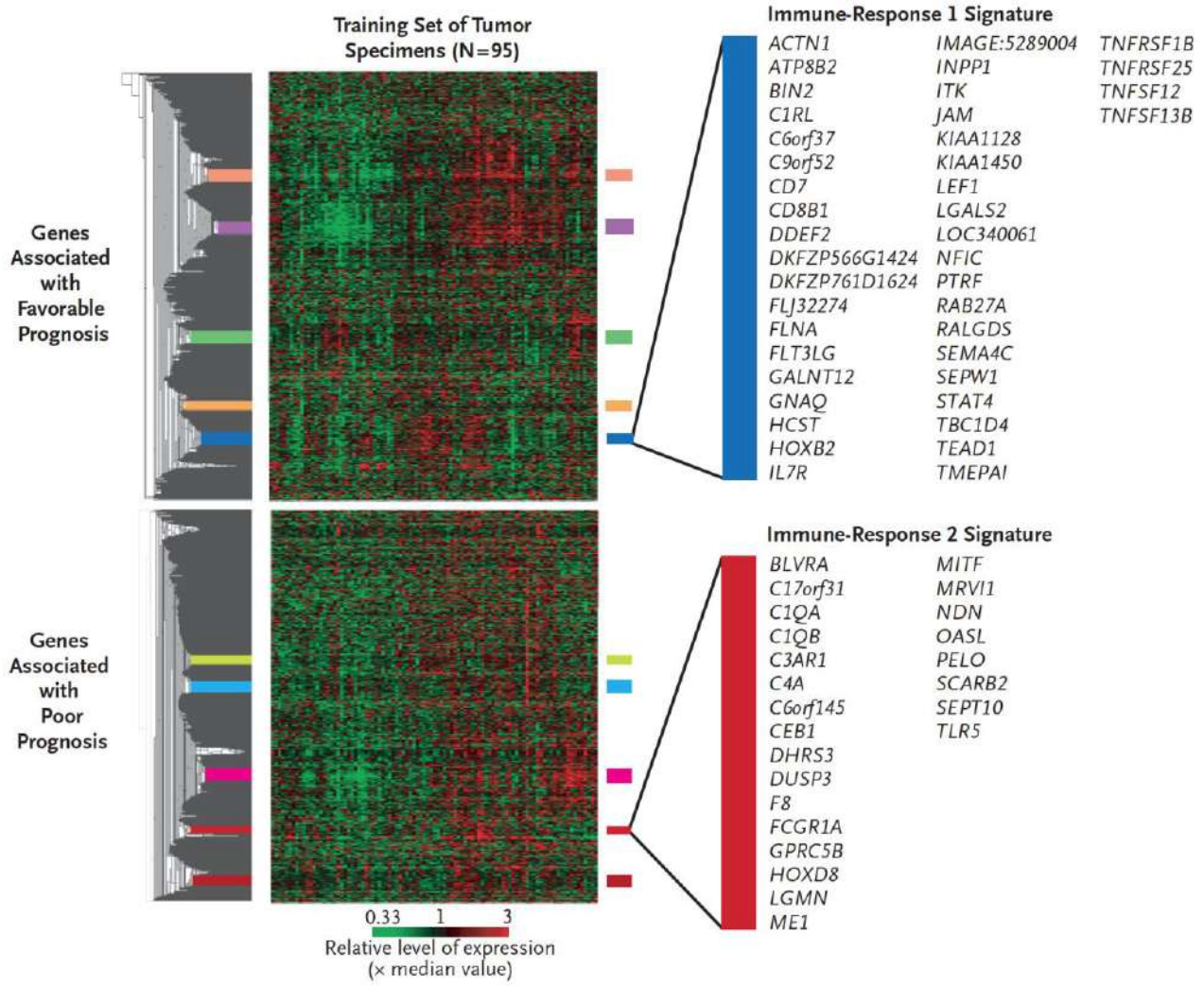
- **Multivariate analysis including FLIPI and maintenance:**

covariate	p value (EFS)
FLIPI	0.066
Maintenance	0.013
23-gene Score	**<0.001**

HR: 3.68 (95%CI: 2.19-6.17)

Huet et al, ICML 2017

Microenvironnement dans le LF et pronostic



Dave et al., NEJM 2004

Microenvironnement dans le LF et pronostic

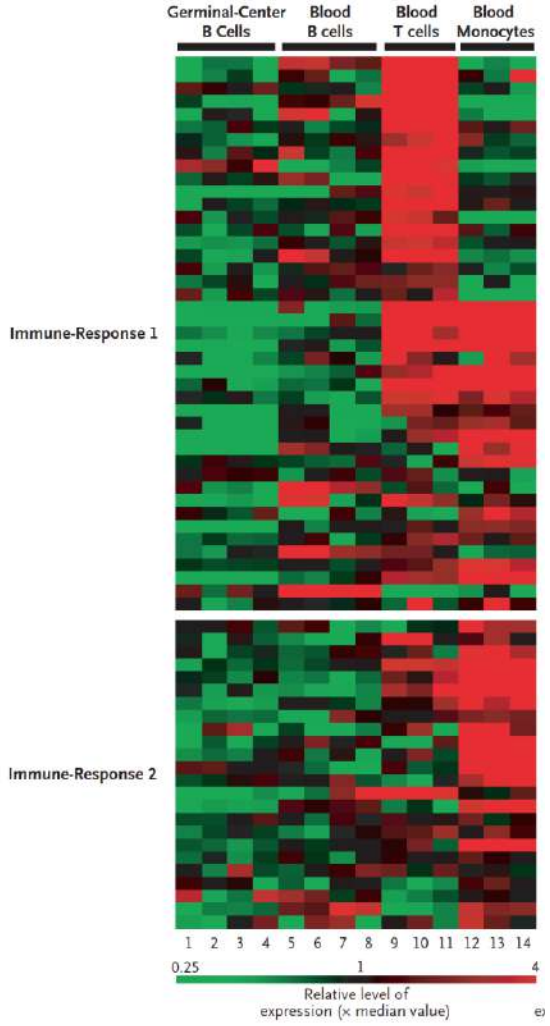


Table 2. Predictive Power of Gene-Expression Signatures in Follicular Lymphoma.*

Gene-Expression Signature	P Value for Contribution to Model in Test Set	Relative Risk of Death (95% CI)*	Effect of Increased Gene Expression on Survival
Immune-response 1	<0.001	0.15 (0.05–0.46)	Favorable
Immune-response 2	<0.001	9.35 (3.02–28.90)	Unfavorable

Dave et al., NEJM 2004

Microenvironnement dans le LF et pronostic

Table 1. Comparison of published data and results from this study on clinico-pathological correlations for T-cell populations, macrophages and follicular dendritic cells.

	Lee[9]	Glas[5]	Carreras[11]	Farinha[8]	Alvaro[10]	Klapper[12]	Taskinen[13]		Wahlin[14]	EORTC 20921	
							R-CHOP	CHOP	[g]	FLUDA	CVP
Interfollicular component	nd	-	nd	-	nd	-	nd		nd	-	-
CD3 dense infiltrate	nd	-	-	-	-	-	-	-	nd	Poor	-
CD3 pattern interfollicular	nd	-	-	nd	-	-	-	-	nd	Good	-
CD4 dense infiltrate	Good	-	-	-	Good	nd	nd		-	Good	Good
CD4 sparse infiltrate	Poor	-	-	-	Poor	nd	nd		-	Poor	Poor
CD4 pattern interfollicular	-	Good	-	nd	Good	nd	nd		nd	Good	Good
CD8 dense infiltrate	-	-	nd	-	Good	nd	nd		good	Good	Good
CD8 sparse infiltrate	-	-	nd	-	Poor	nd	nd		poor	Poor	Poor
CD8 pattern interfollicular	-	-	nd	nd	Good	nd	nd		nd	Poor	Good
FoxP3 dense infiltrate	Good	-	Good	Poor[a]	Good	nd	nd		nd	Poor	Good
FoxP3 sparse infiltrate	Poor	-	Poor	Good[a]	Poor	nd	nd		nd	Good	Poor
FoxP3 pattern interfollicular	Good[b]	Good	Good	nd	Good	nd	nd		nd	Good	Good
FoxP3 pattern intrafollicular	nd	-	Good	nd	nd	nd	nd		nd	-	-
CD68 dense infiltrate	-	-	nd	Poor	Good	-	Good[c]	Poor[c]	nd	Poor	Good
CD68 sparse infiltrate	-	-	nd	Good	Poor	-	Poor[c]	Good[c]	nd	Good	Poor
CD68 pattern interfollicular	-	nd	nd	nd	nd	nd	na	na	nd	Good	-
MIB1	nd	-	nd	-	nd	-	nd		nd	-	-
CD21/CD23	nd	Poor	nd	-	nd	-	nd		nd	Poor	Good
TIA1	-	-	nd	-	-	nd	nd		nd	nd	
CD57	nd	-	nd	-	Good	nd	nd		nd	nd	

Type of analysis	e-o-s	e-o-s	Continuous	Continuous	Continuous	Continuous	Continuous		Continuous	Continuous	
Number of patients	59	66	97	99	211	158	96	45	139	31	30
End point	OS	transformation	OS	OS, PFS	OS, PFS	OS, PFS	OS,PFS		OS, DSS	PFS	
Treatment	Various indolent regimens	Various indolent regimens, mostly CVP	Various, 58% CHOP, 14% fludarabine	BP-VACOP+RT	Various, 44% CHOP, 15% CVP	MCP/CHOP randomized	R-CHOP	CHOP	Highly various	Fludarabine	CVP
Median age (years)	61/46	52/44	55	44	+/- 56	n.a.	n.a.	n.a.	59.8	56	56
(FL)IPI range (%)	n.a.	51/20/27 versus 91/9/0	37/27/36	59/40/1	61/60/36	22/67/65	61/30/7	51/31/18	32/32/35	26/42/32	27/47/27

exemple

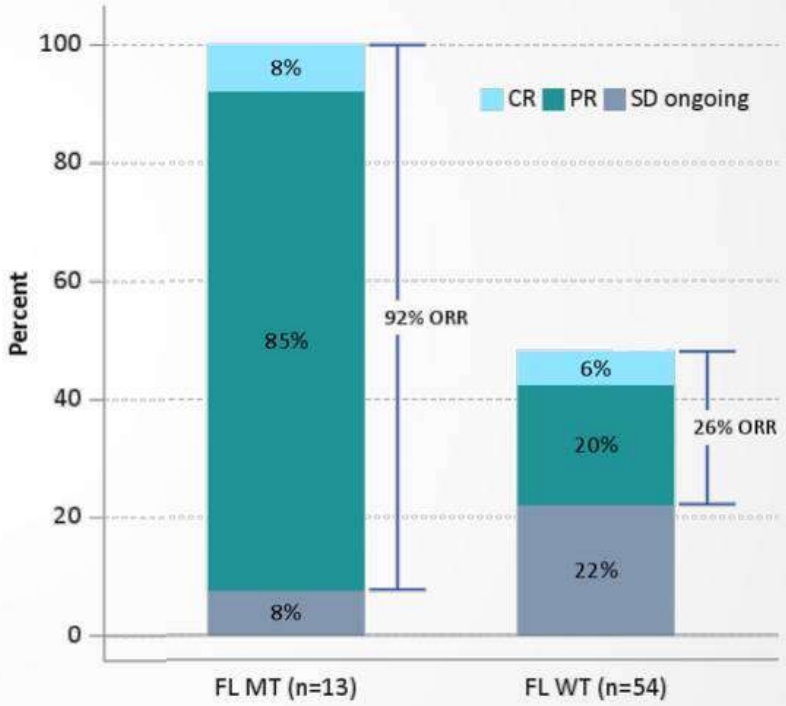
De Jong et al., Haematologica 2009

L’avenir: les variables dites « théranostiques »

POSITIVE INTERIM PHASE 2 EFFICACY RESULTS IN FOLLICULAR LYMPHOMA

Best Response	FL EZH2 MT (n=13)	FL EZH2 WT (n=54)
Objective Response Rate (CR + PR)	**12 (92%)**	**14 (26%)**
Complete Response (CR)	1 (8%)	3 (6%)
Partial Response (PR)	11 (85%)	11 (20%)
Stable Disease (SD)	1 (8%)	23 (43%)
SD study drug ongoing	1 (8%)	12 (22%)
Progressive Disease	0	13 (24%)
No Data, Unknown (UNK)	0	4 (7%)
Time to first Response (weeks) median (range)	11.9 (6.9 – 35.9)	15.2 (8.1 - 32.1)

Ongoing patients with Best Response of 'No Data, Unknown' are not included in the efficacy table. Patients who discontinued due to clinical or radiological progression without a valid response assessment are included in PD.



Epizyme

Data as of 06/01/17

*Percentages may not total to 100% due to rounding

7

Morschhauser et al., ICML 2017

Les variables post-thérapeutiques

Rôle de la PCR BCL2/IGH sur sang (et moelle)

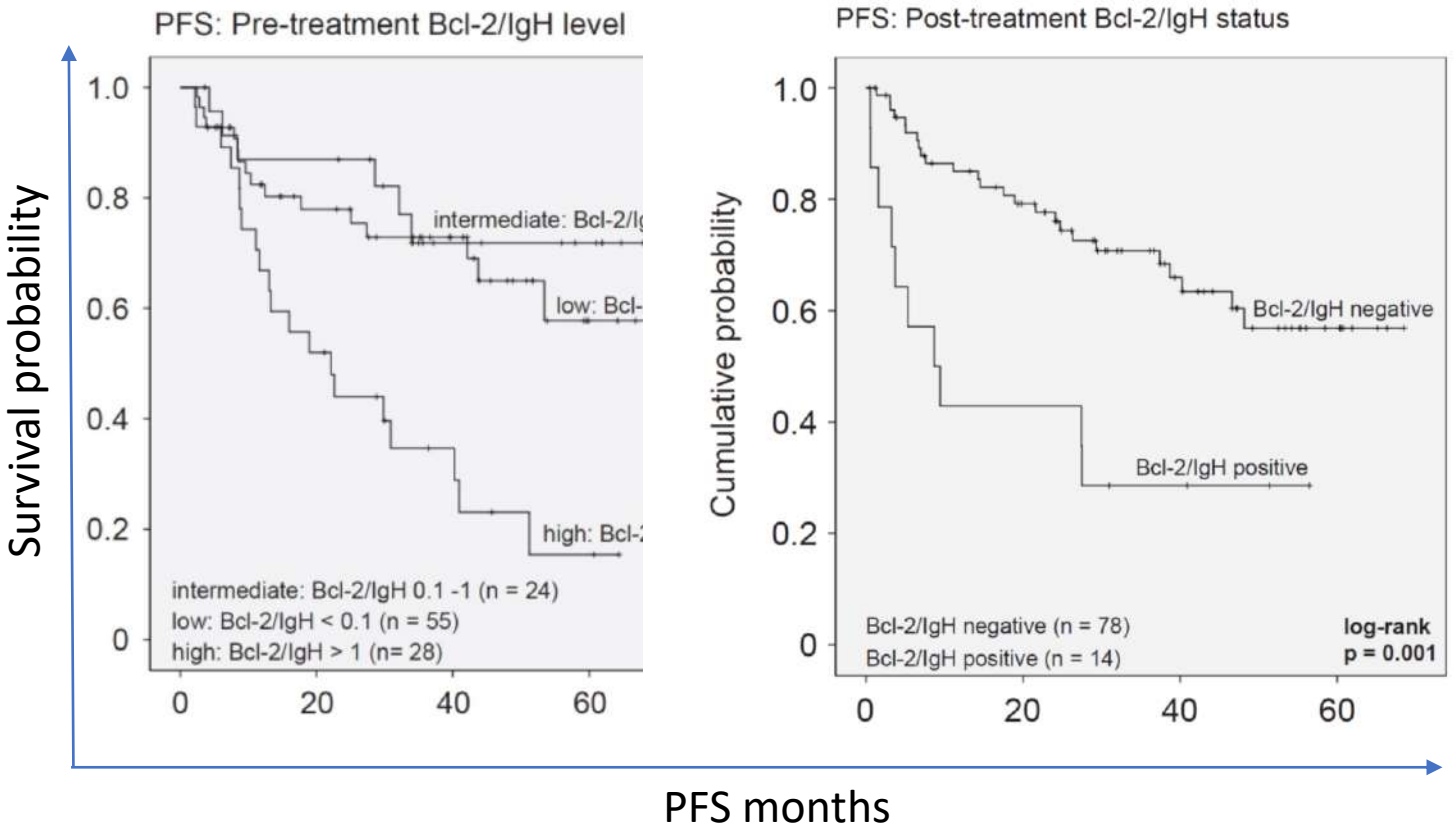


Table 3: Prognostic factor analysis for PFS post-treatment

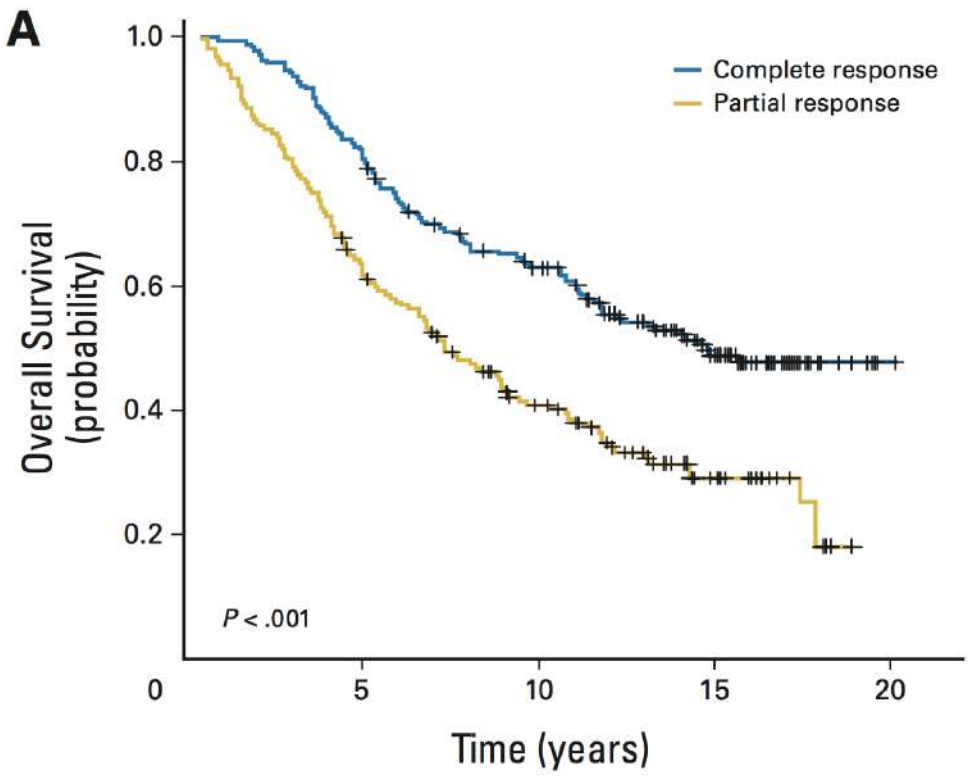
	Univariate (log rank)	Multivariate (Cox Regression)	
	p value	Hazard Ratio (95% CL)	p value
Pre-treatment Bcl-2/IgH level >1 <1	0.000	4.023 (1.990-8.135)	< 0.001
Post-treatment Bcl-2/IgH status positive negative	0.001	2.694 (1.243-5.842)	0.012
Ann Arbor Stage IV ≤ III	0.066	1.209 (0.467-3.130)	0.696
FLIPI (score) & risk groups (≥ 2) intermediate- & high-risk (0-1) low-risk	0.182	n.a.	
Treatment response CR No CR	0.437	n.a.	
Treatment regimen Bendamustine-R R-CHOP	0.629	n.a.	

1/3 des patients n'ont pas transcrit de fusion détectable dans le sang

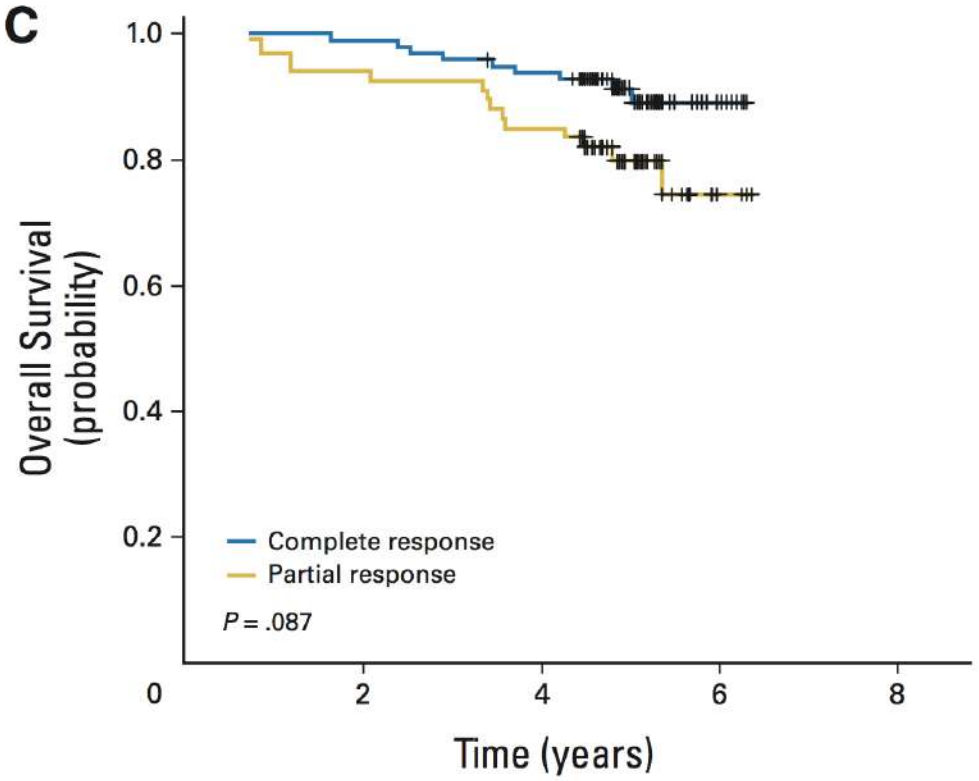
Zohren et al., Blood 2015

Impact de la réponse au traitement : évaluation conventionnelle

GELF86



FL2000



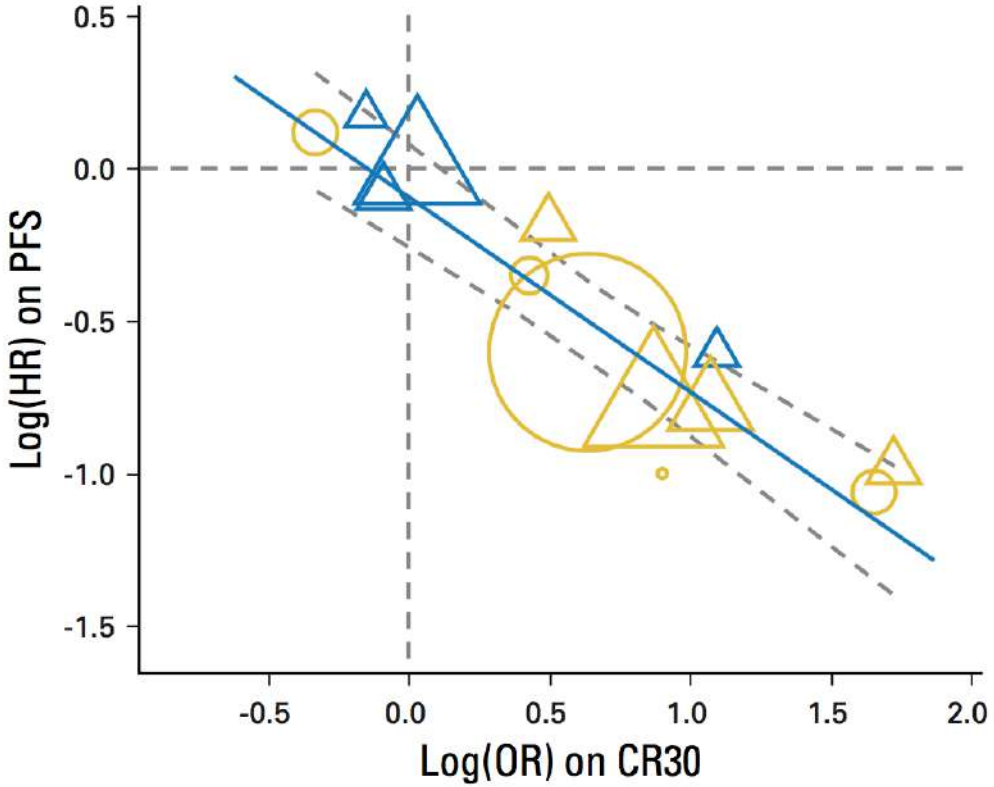
Bachy et al., JCO 2010

Impact de la réponse au traitement : évaluation conventionnelle

Parameter	Overall Survival*		
	HR	95% CI	*P*
CR (*v* PR)	0.53	0.38 to 0.73	**< .001**
FLIPI			
High (*v* low)	1.64	1.04 to 2.58	**.032**
Intermediate (*v* low)	1.43	0.94 to 2.19	.098
IFN	0.83	0.61 to 1.12	.229
High tumor burden	1.27	0.86 to 1.87	.231
BM involvement	0.99	0.69 to 1.42	.953
Male sex	1.21	0.89 to 1.66	.224
Lymphocyte count < 1G/L	1.67	1.18 to 2.37	**.004**
Platelet count < 150 G/L	1.24	0.83 to 1.84	.291
ESR > 40 mm	2.53	1.52 to 4.20	**< .001**
Albumin level < 35 g/L	0.72	0.41 to 1.28	.274
B symptoms	0.97	0.65 to 1.45	.897

Bachy et al., JCO 2010

La réponse complète à 30 mois comme surrogate marker (CR30) : étude FLASH



Shi et al., JCO 2016

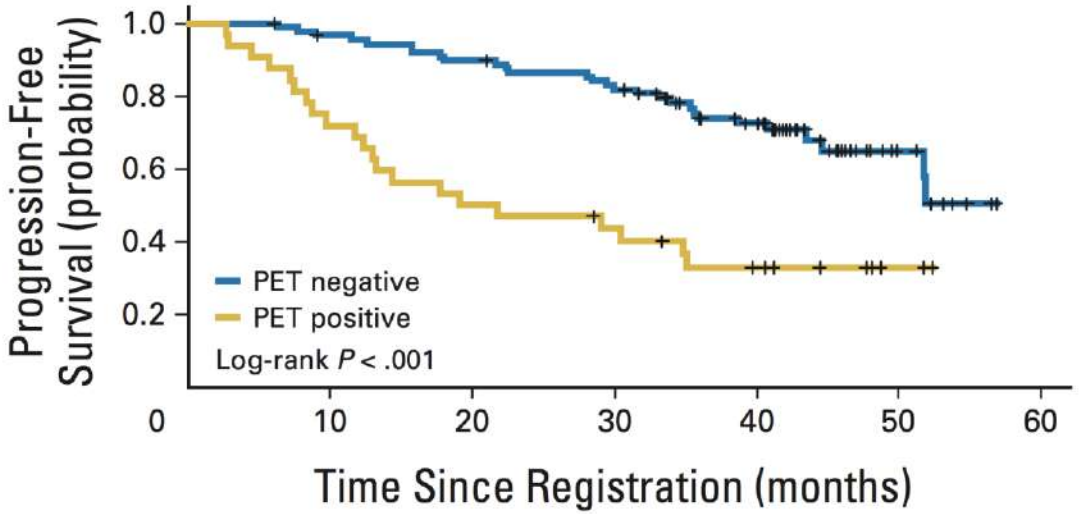
Impact de la réponse au traitement : évaluation métabolique

Table 2. Response Evaluation in Accordance With 1999 IWC and 2007 Revised Response Criteria

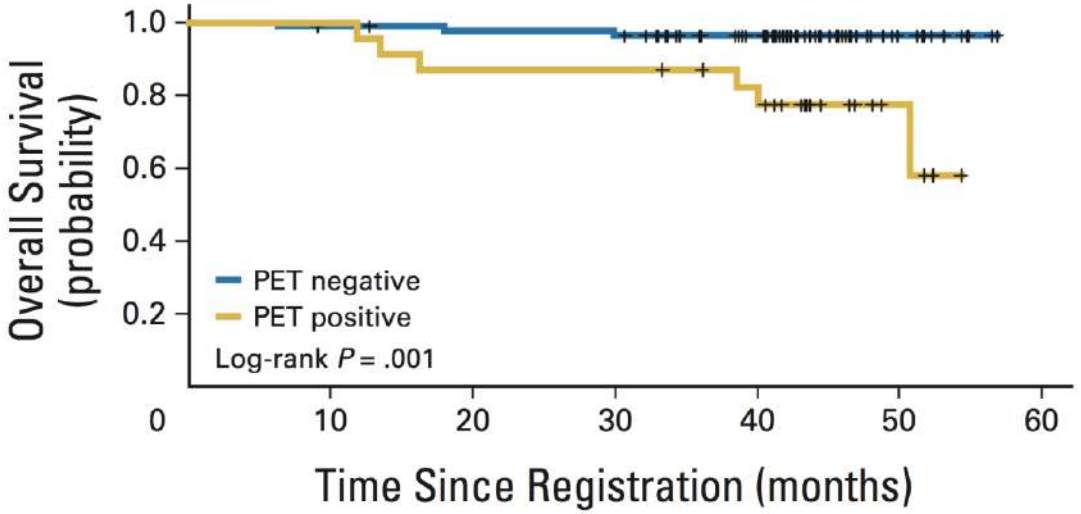
1999 IWC Response to Induction Regimen	Revised Response Criteria (IWC plus PET)				
	CR	PR	SD	PD	Total
CR	45	4	0	0	49
CRu	27	12	0	0	39
PR	16	10	0	0	26
SD	1*	0	2	0	3
PD	1†	0	0	4	5
Total	90	26	2	4	122

Trotman et al., JCO 2011

Impact de la réponse au traitement : évaluation métabolique



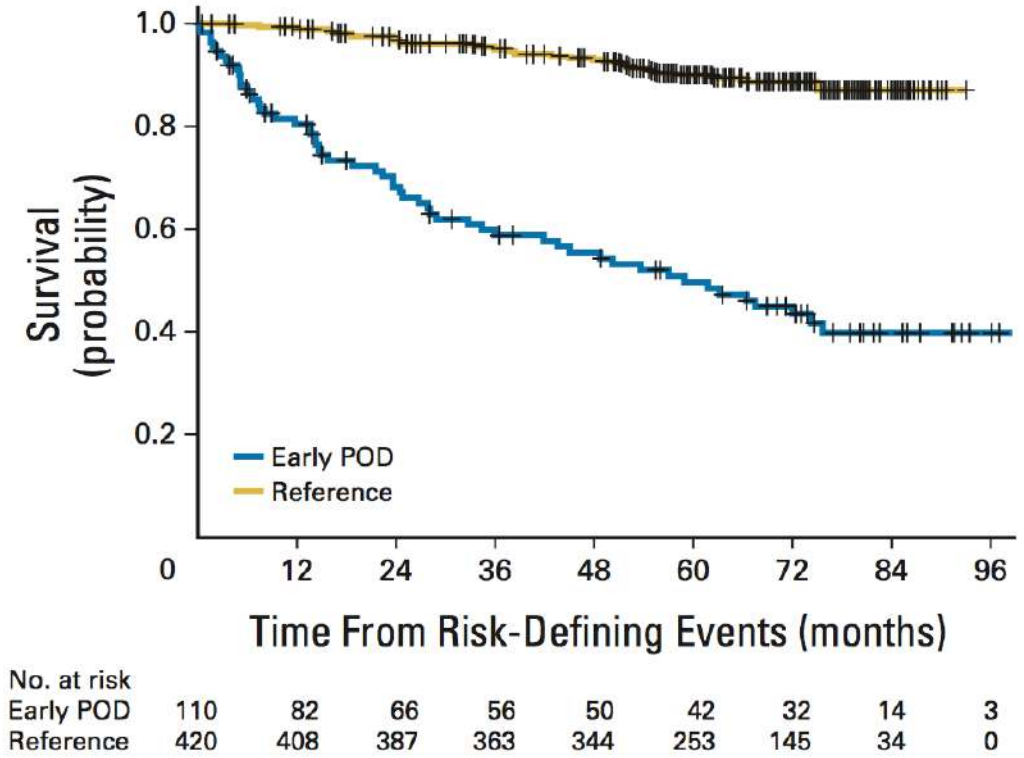
	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	28 (31%)	62 (69%)	NA (51.75 to NA)
PET positive	32	21 (66%)	11 (34%)	20.45 (12.29 to 35.09)



	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	3 (3%)	87 (97%)	NA (NA to NA)
PET positive	32	7 (22%)	25 (78%)	NA (50.69 to NA)

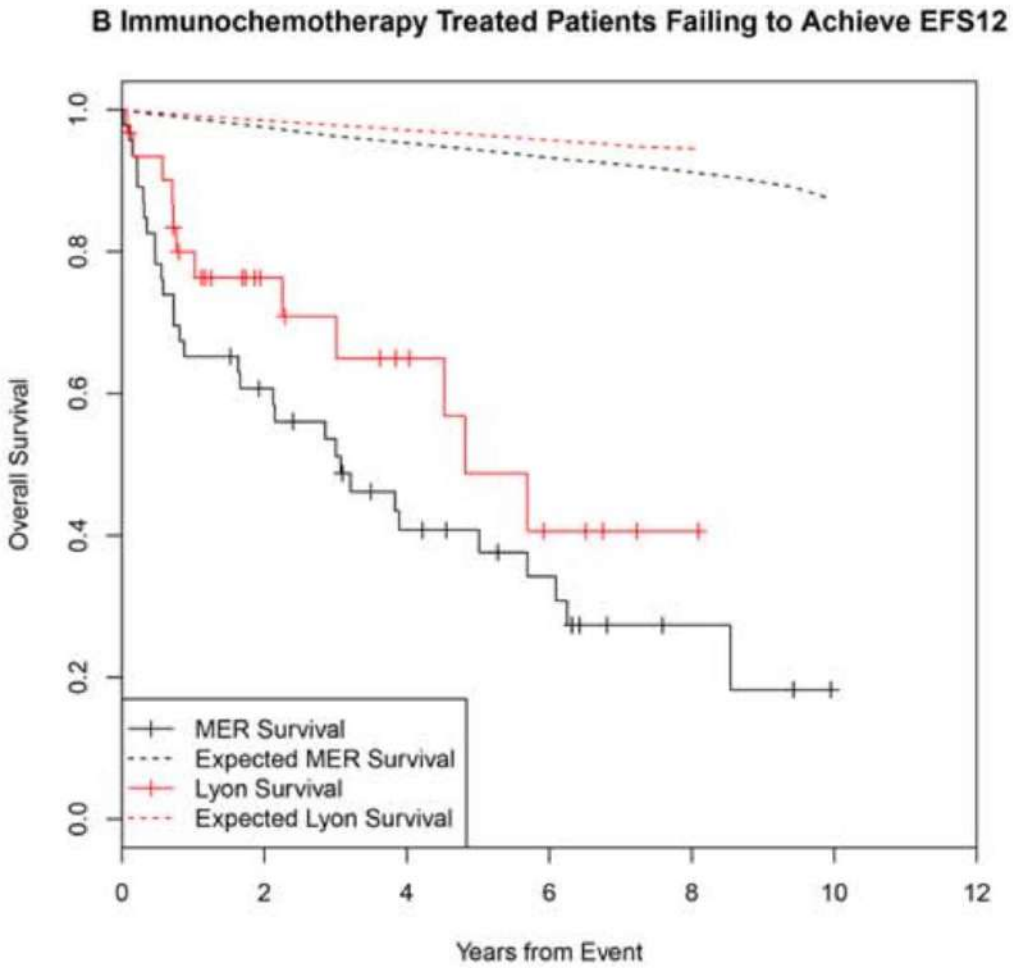
Trotman et al., JCO 2011

Impact du délai à la rechute sur la survie globale



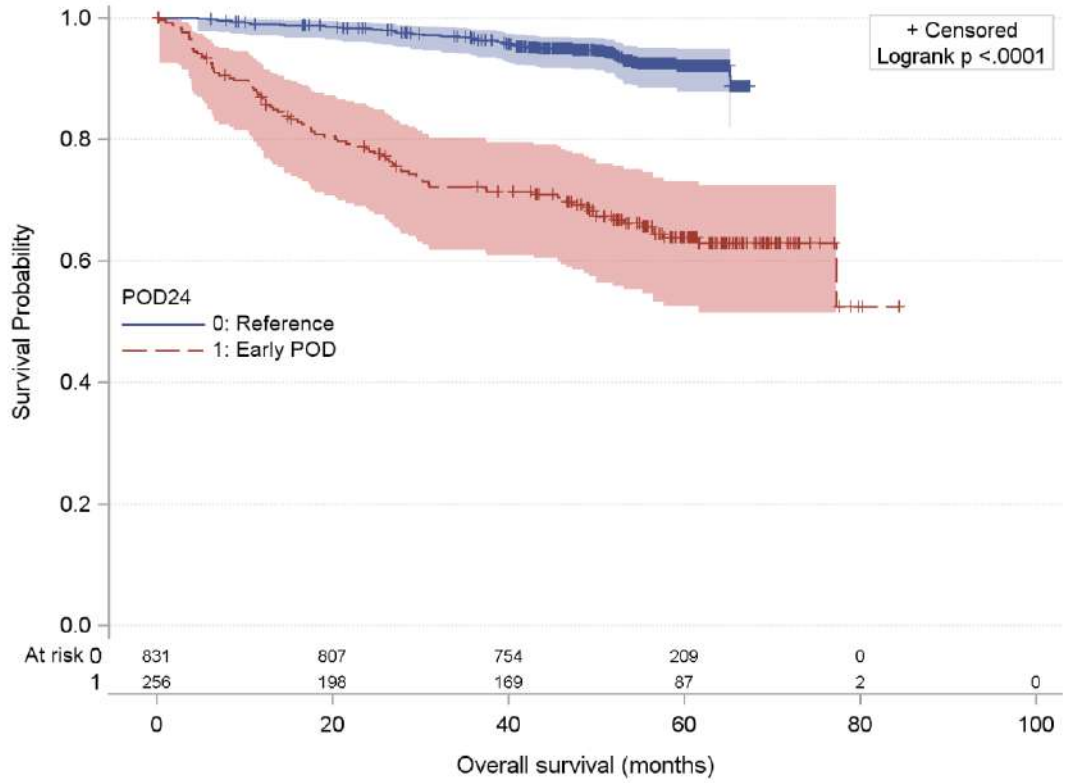
Casulo et al., JCO 2015

Impact du délai à la rechute sur la survie globale



Maurer et al., AJH 2016

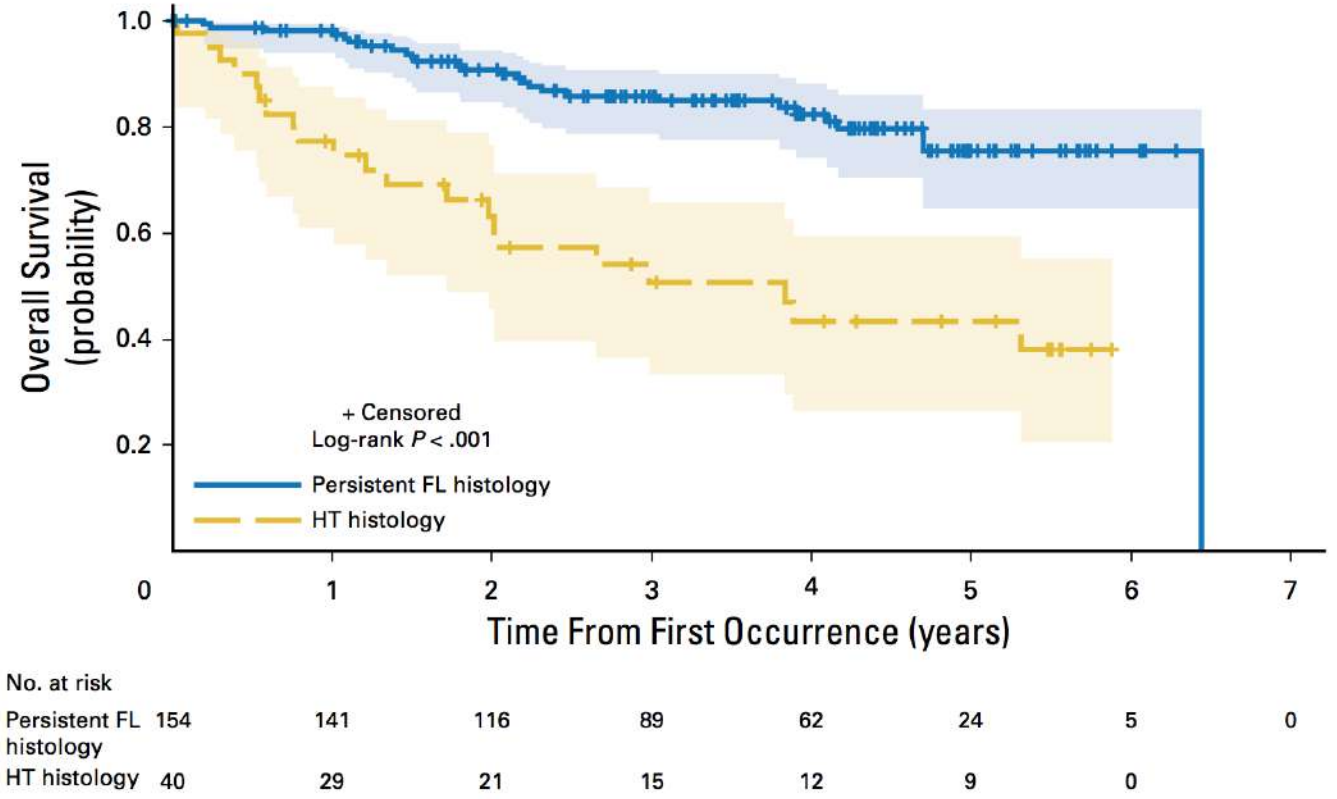
Confirmé dans la cohorte PRIMA



Bachy et al. ASH 2017 Abstract 413

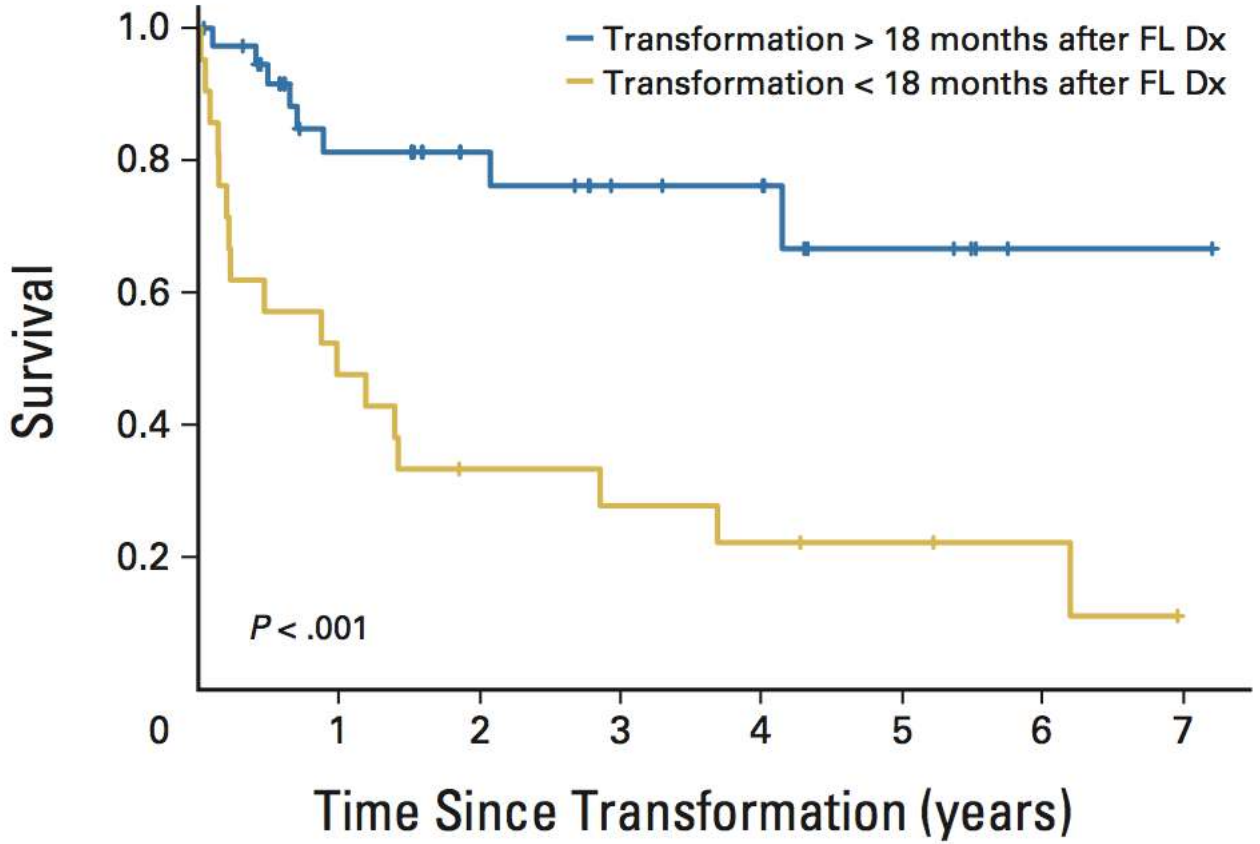
La transformation comme événement pronostique

Impact de la transformation sur la survie globale



Sarkozy et al, JCO 2016

Impact du délai à la transformation sur la survie globale



Link et al., JCO 2013

Quels facteurs prédictifs de transformation ?

Study	Pts number	Incidence	Median survival after transformation	PS 2-4	Stage III-IV	Hb low	LDH high	FLIPI	Effect of Tt
Bastion, JCO, 1997	220	31% at 10 y	0.6	-	-		-		
Giné, Ann Oncol 2006	276	15% at 10 y	1.2				+	+	No effect
Montoto, JCO 2007	325	28% at 10 y	1.2		+			+	Observation ↑ risk
Al-Tourah, JCO 2008	600	30% at 10 y	1.7	-	+	-	-	-	Observation: no effect Alkylator + purine ↑ risk
Conconi, BJH 2012	281	15% at 10 y	2.7	-	-	-	-	-	R-chemo ↑ risk R-mono ↓ risk Chemo or obs : no effect
Link, JCO 2013	631	10.7% at 5 y	4.2	-	-	+	+	+	Observation ↑ risk R-mono ↓ risk
Kridel, Blood 2015	126		3.9	-	-	-	+	-	
Wagner-Johnston, Blood 2015	2652	14.3% at 6.8 y	5.0	+	-	-	+		Observation ↑ risk R-CHOP v R-CVP : no effect
Sarkozy, JCO 2016	1018		3.8	+	-	+	+	+	R-maintenance : no effect R-CHOP v R-CVP v R-FCM : no effect

Kridel et al. Blood 2017

Conclusion

- Un lymphome fréquent, en augmentation, sans facteur de risque clairement identifié
- De multiples scores pronostiques pré-thérapeutiques: le FLIPI apparaît comme très robuste
- Un essor des scores bio-moléculaires mais le poids des variables moléculaires reste modéré et peu reproductible
- Les variables théranostiques sont clairement prometteuses
- Etant donnée la durée d'évolution de la maladie, les variables post-thérapeutiques ont tout leur intérêt dans le LF