



Centre  
International  
de Recherche  
en Infectiologie

# Facteurs pronostiques et critères de traitement

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## **Les questions :**

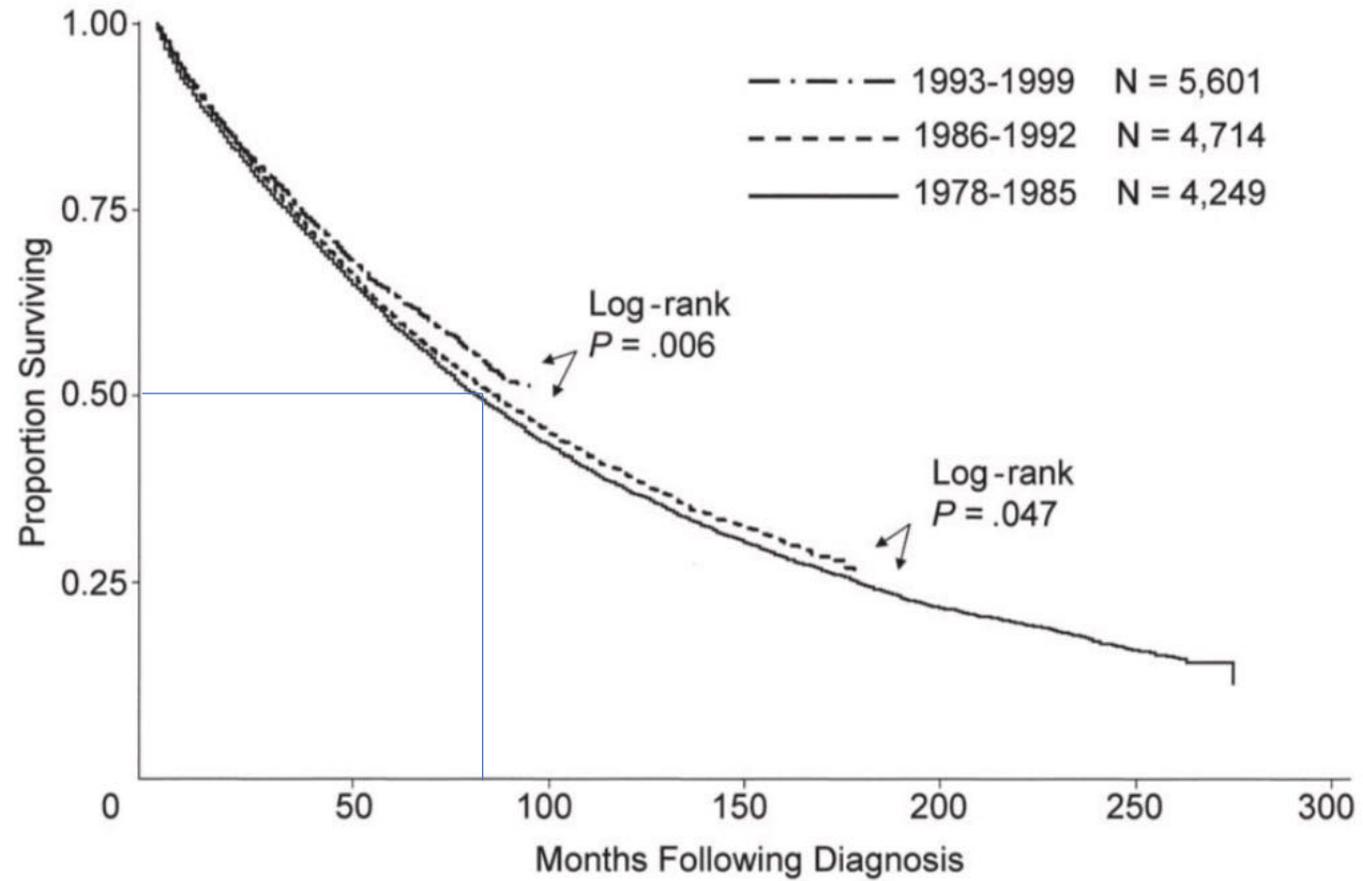
- 1. A quoi sert un facteur pronostique ou un score pronostique ?**
- 2. En quoi le lymphome folliculaire se prête-t-il particulièrement à la détermination de scores pronostiques ?**
- 3. Quelles sont les limites des scores pronostiques ?**
- 4. Quel est l'apport des scores pronostiques ?**

# Plan

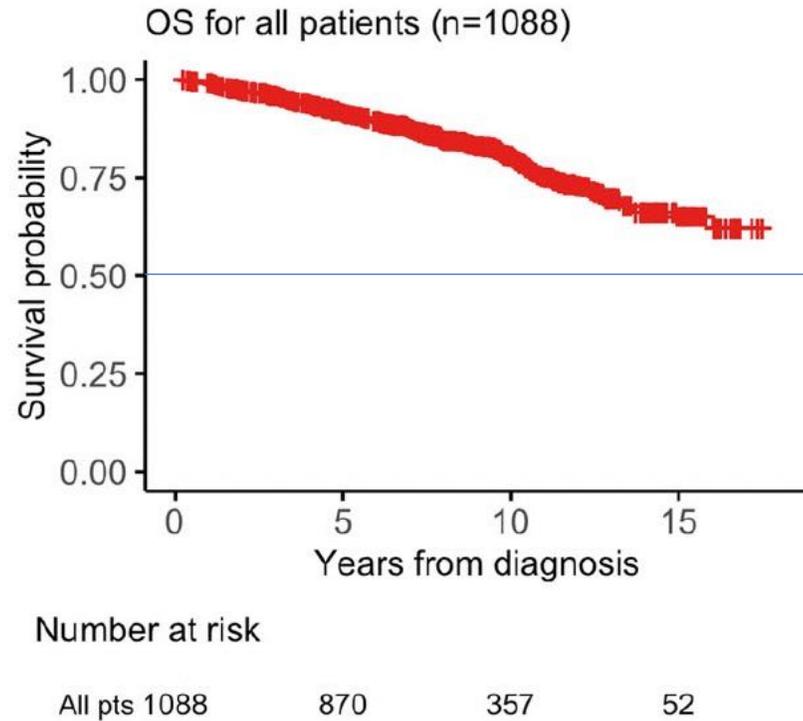
- **Les facteurs pronostiques dans le LF : une nécessité ?**
- **Considérations méthodologiques**
- **Les scores clinico-biologiques**
- **Les scores biomoléculaires**
- **Le microenvironnement**
- **Les facteurs post-thérapeutiques**
- **La transformation histologique**
- **Pronostic versus prédiction**

# **Les facteurs pronostiques dans le LF : une nécessité ?**

# Espérance de vie dans le LF

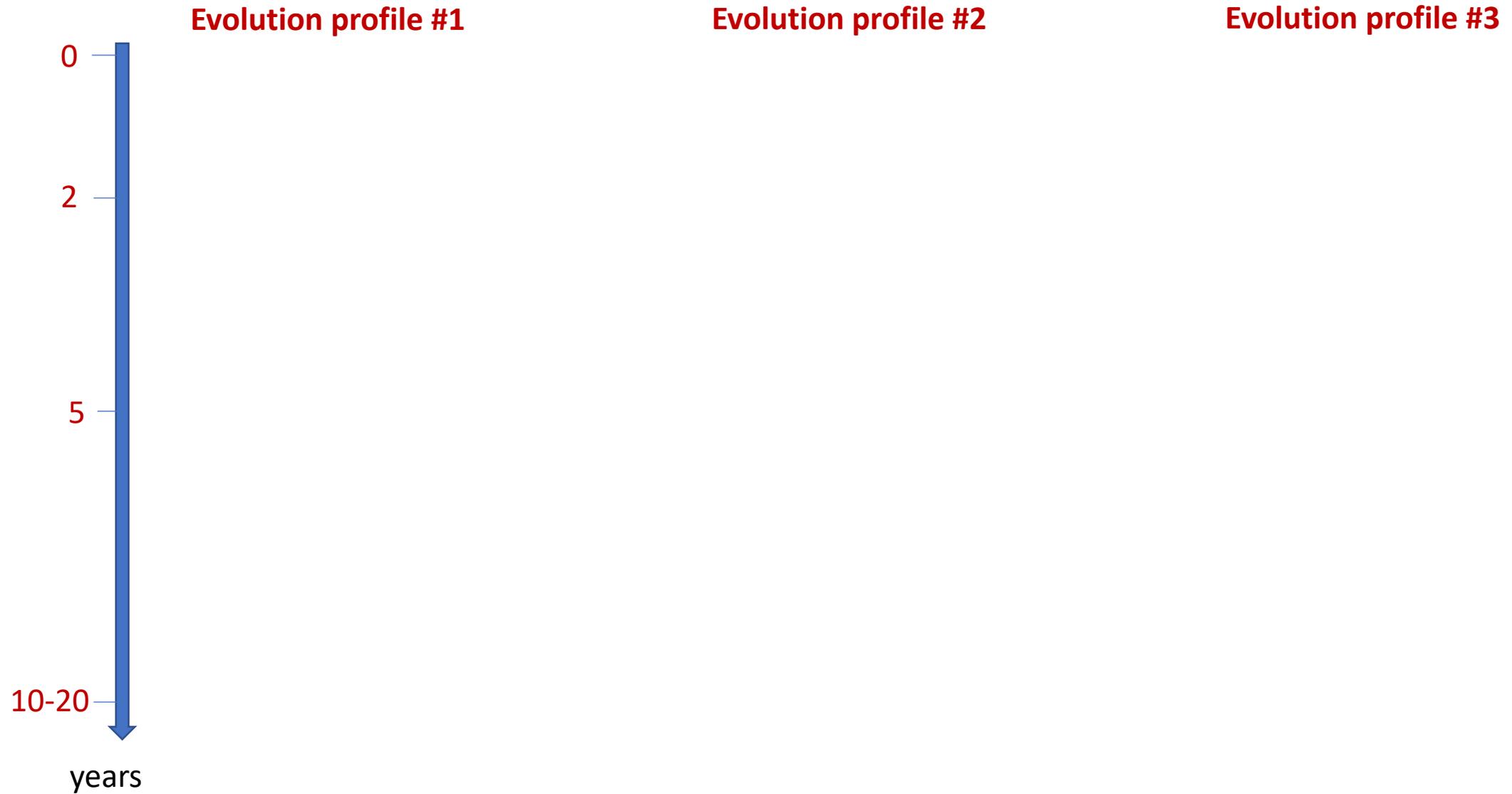


# Espérance de vie dans le LF

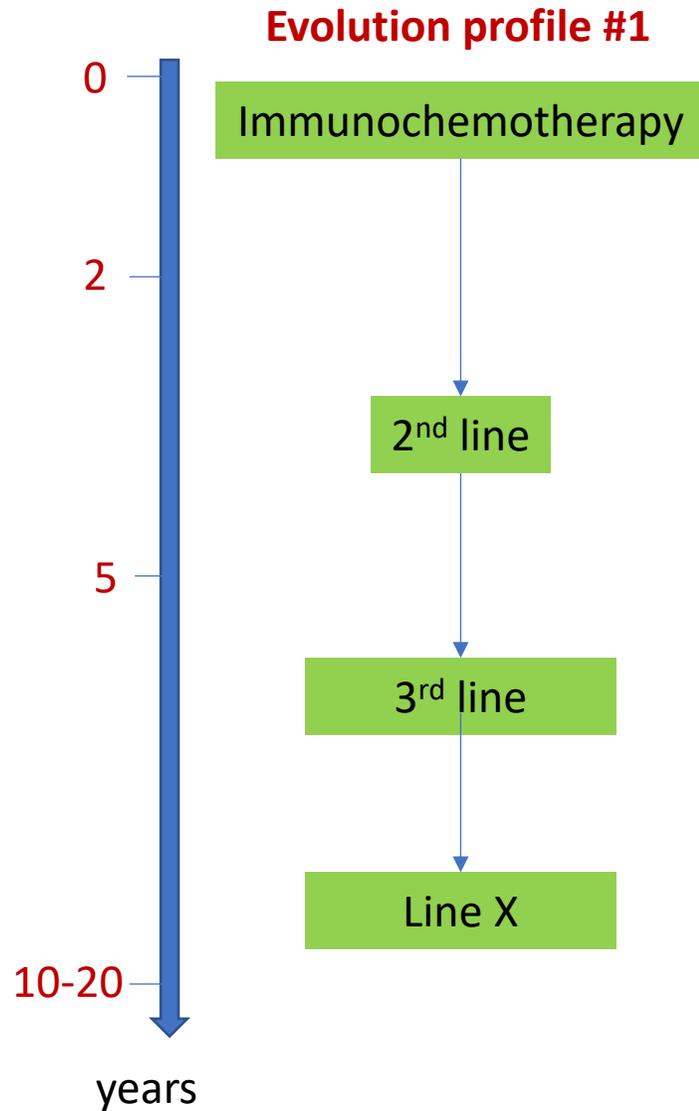


Median overall survival expected to be longer than 20 years for all newly diagnosed FL

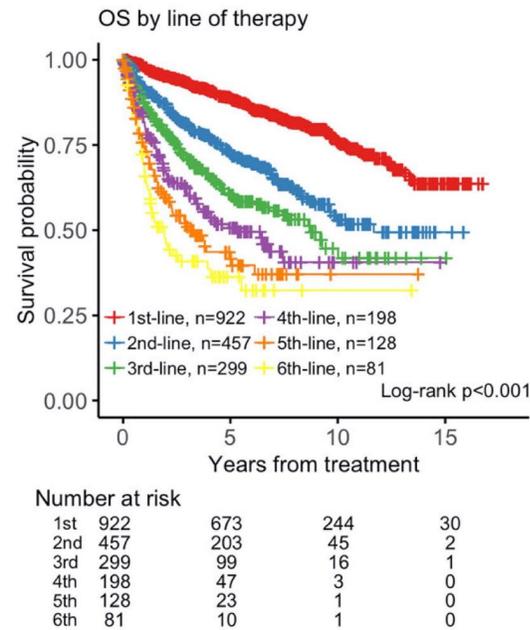
# Histoire naturelle du lymphome folliculaire



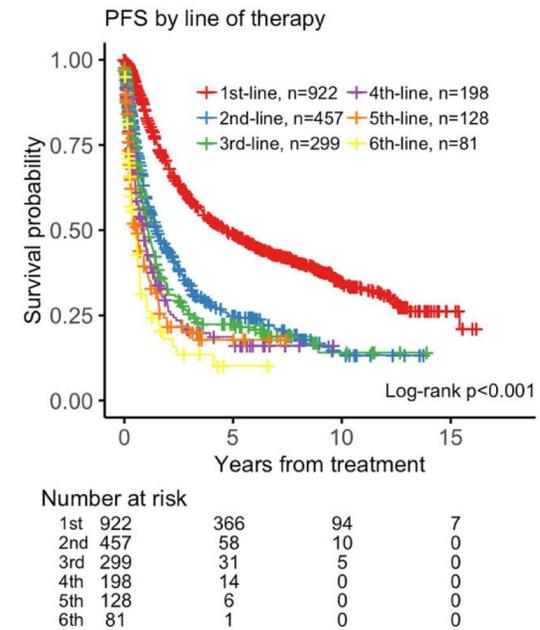
# Histoire naturelle du lymphoma folliculaire



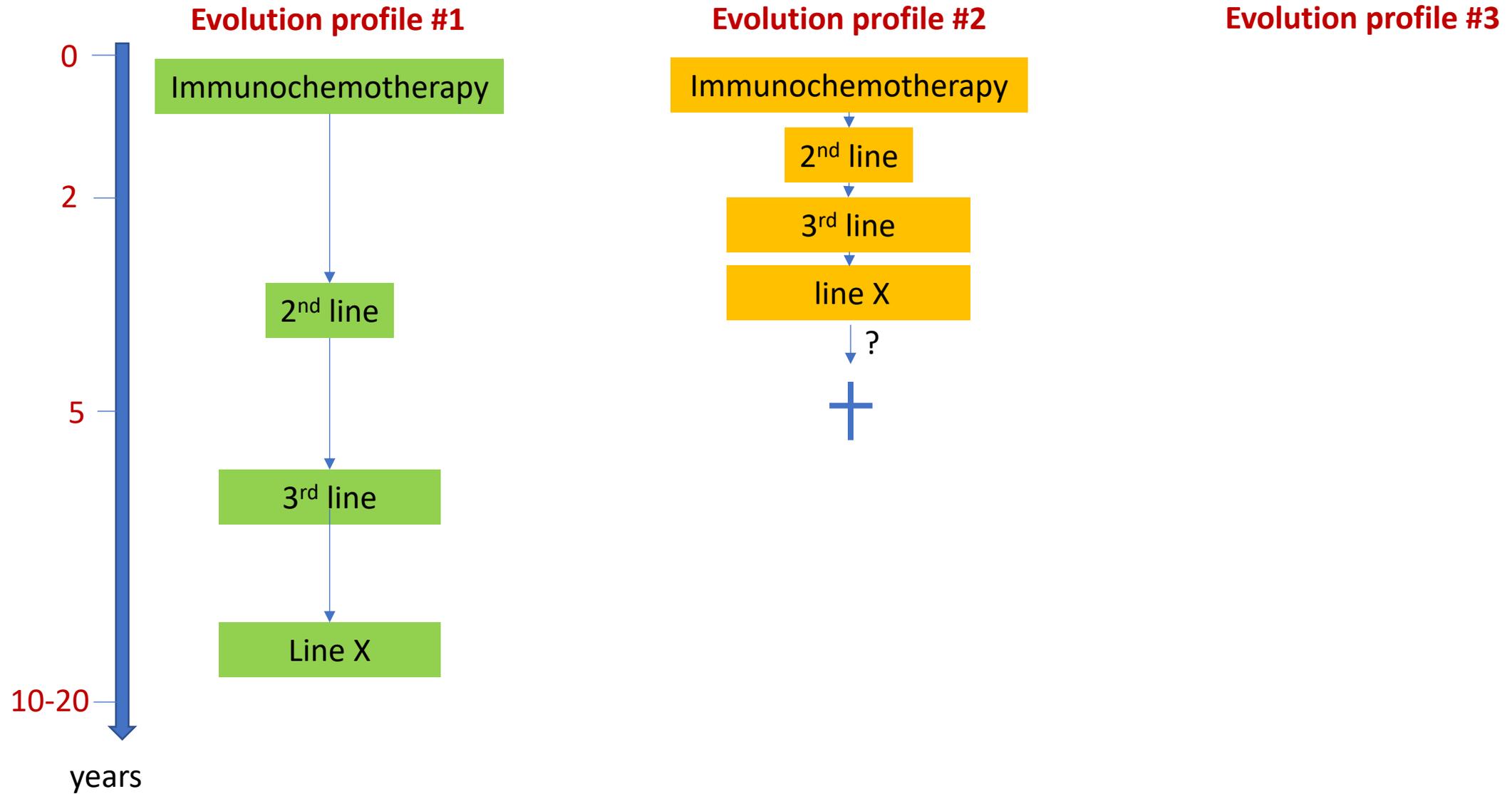
**Evolution profile #2**



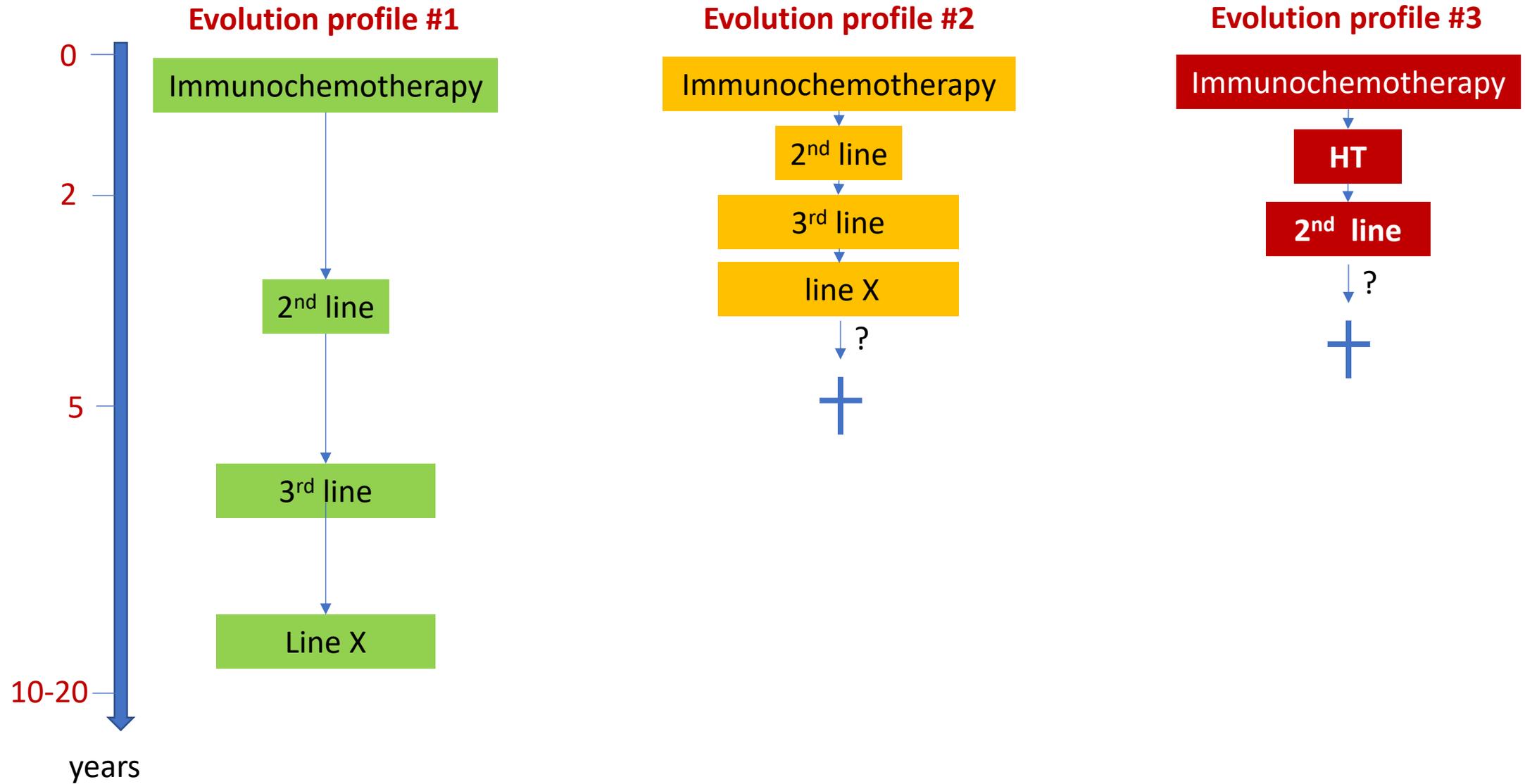
**Evolution profile #3**



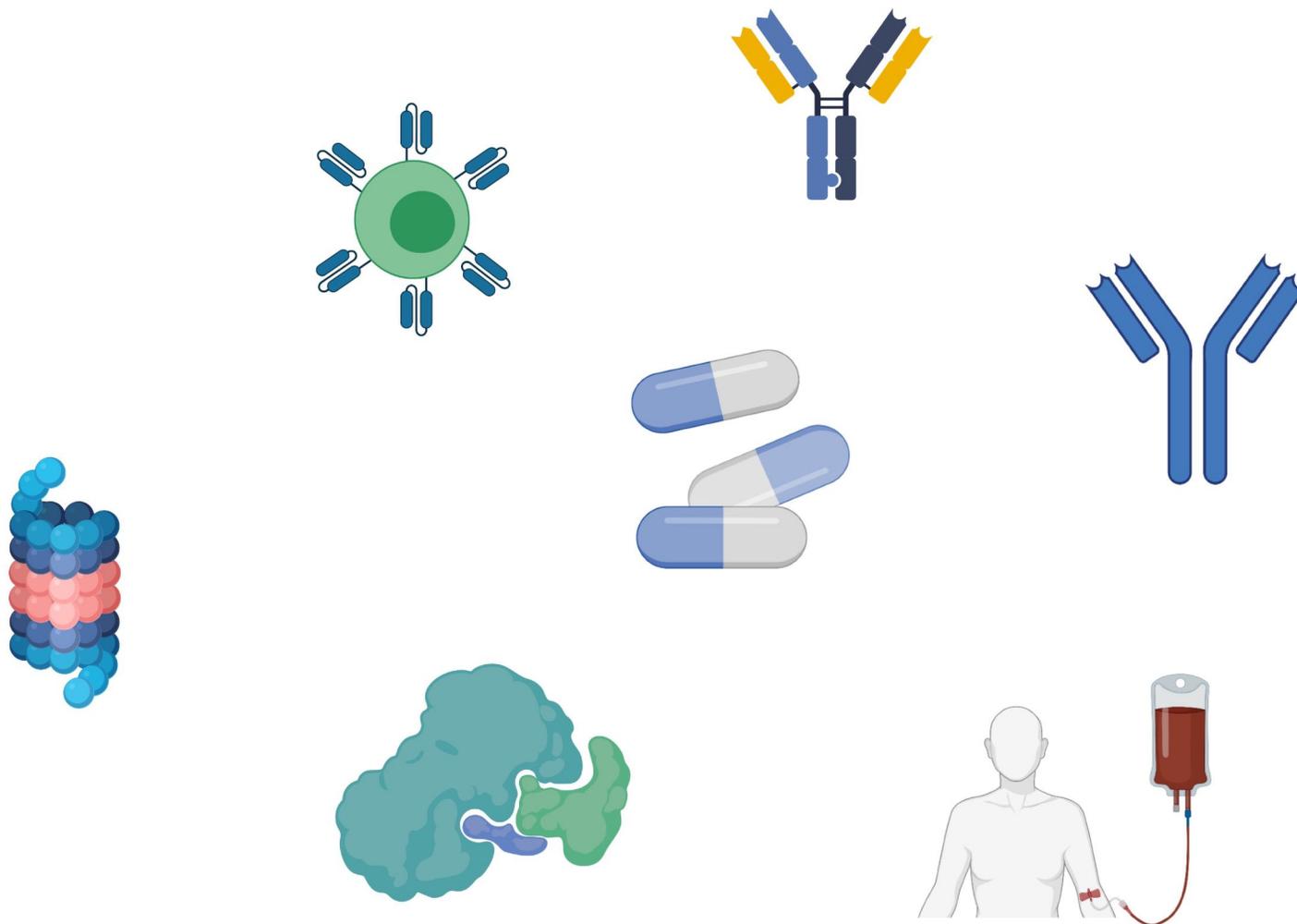
# Histoire naturelle du lymphoma folliculaire



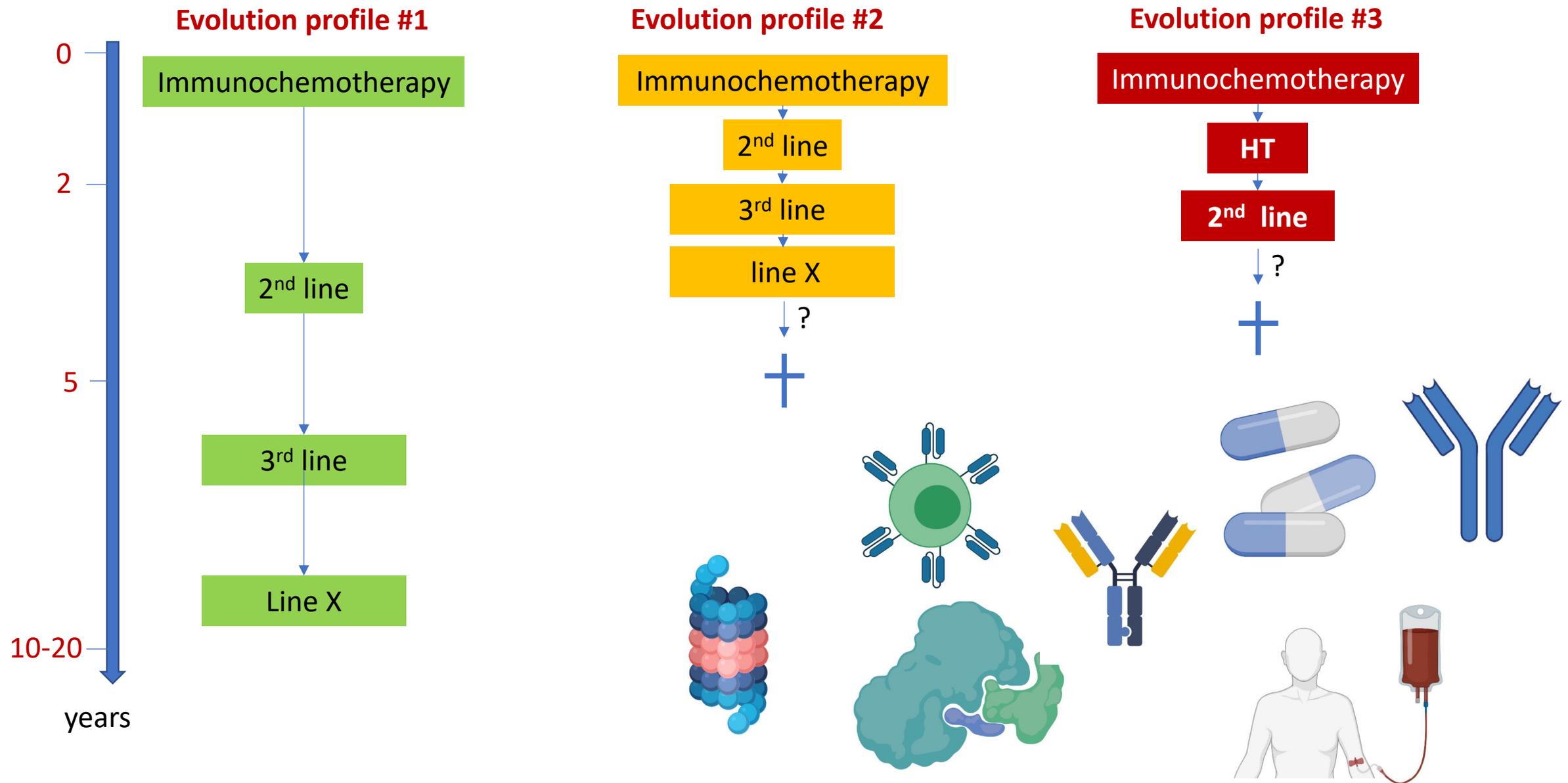
# Histoire naturelle du lymphoma folliculaire



# Options thérapeutiques disponibles



# Comment choisir ?



# Considérations méthodologiques

# Toujours les mêmes facteurs ?

TABLEAU 1 Classification schématique des facteurs fréquemment associés à un mauvais pronostic dans les différents types de lymphome *	
→ Terrain	<ul style="list-style-type: none"><li>• Sexe masculin</li><li>• Âge avancé</li></ul>
→ Lymphome	<ul style="list-style-type: none"><li>• Stade Ann Arbor III ou IV</li><li>• Envahissement médullaire</li><li>• Atteinte extraganglionnaire</li><li>• Volumineuse masse tumorale (Bulky syndrome)</li><li>• LDH supérieures à la normale</li><li>• <math>\beta</math>2-microglobuline augmentée</li></ul>
→ Répercussions sur le patient	<ul style="list-style-type: none"><li>• Indice d'activité OMS <math>\geq</math> 2</li><li>• Symptômes B</li><li>• Taux d'hémoglobine abaissé</li><li>• Albumine inférieure à la normale</li></ul>

\* Les valeurs seuils pour l'âge, le nombre de sites extraganglionnaires envahis, ou encore la taille de la masse tumorale sont propres à chaque score pronostique. LDH : lactico-déshydrogénases ; OMS : Organisation mondiale de la santé. **Symptômes B** : sueurs nocturnes obligeant le patient à se changer, température  $> 38$  °C pendant plus de 8 jours, ou perte de poids de plus de 10 % au cours des 6 derniers mois.

# Ne pas confondre variable et score pronostiques

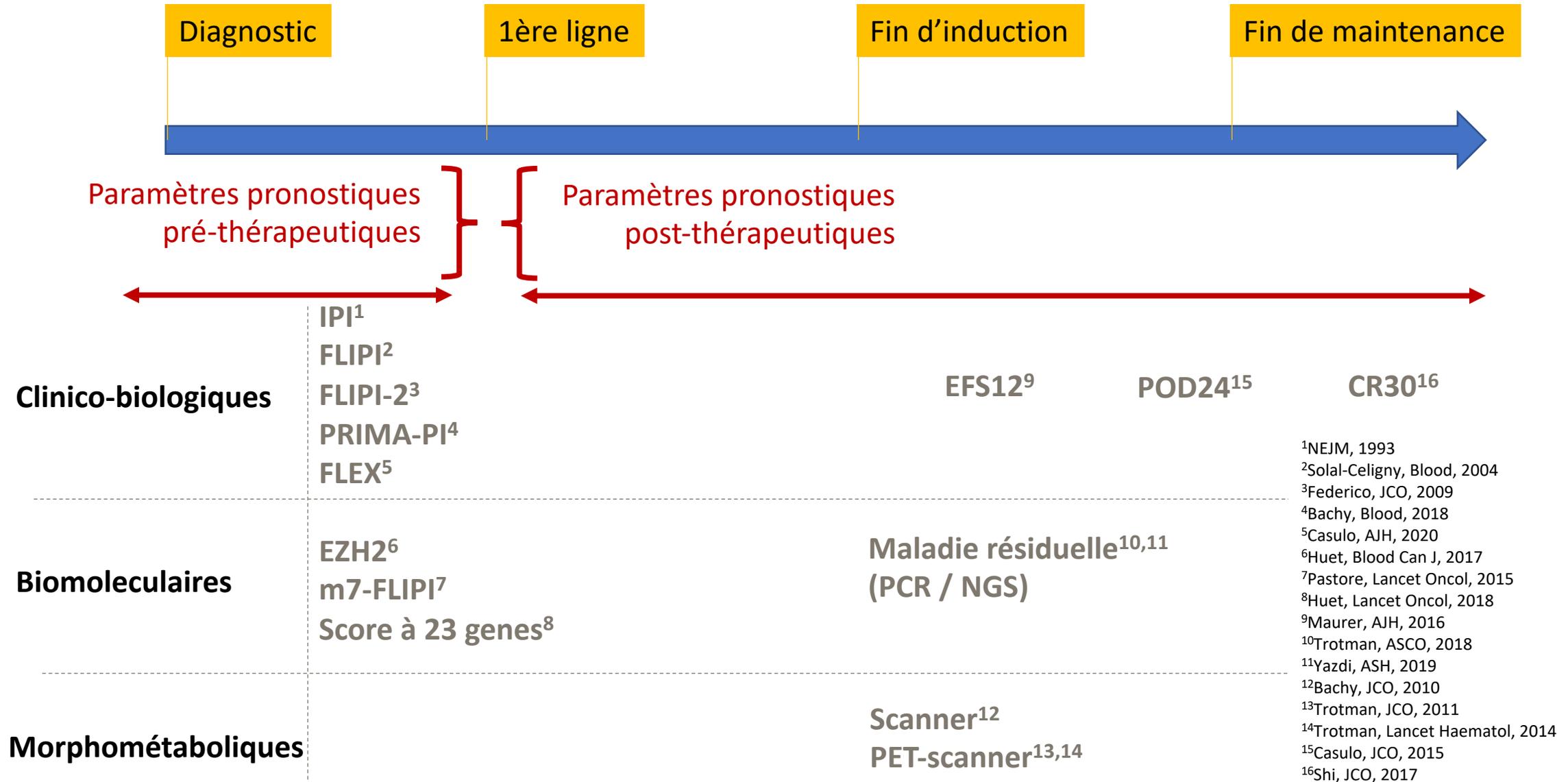
A nombre de patients  
suffisants quasiment toutes  
les variables usuelles sont  
pronostiques

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

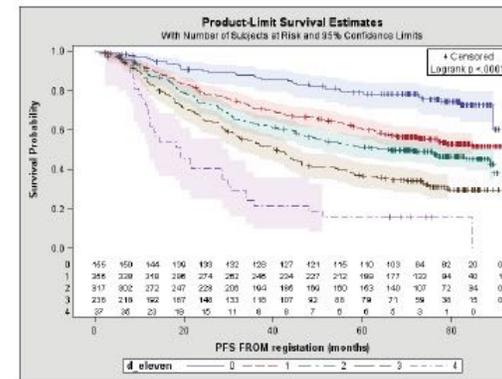
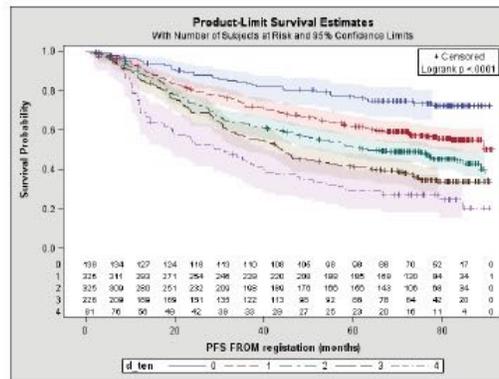
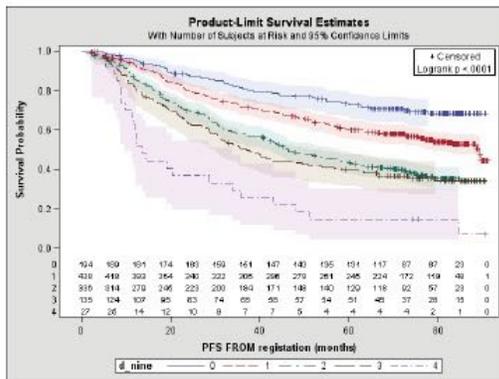
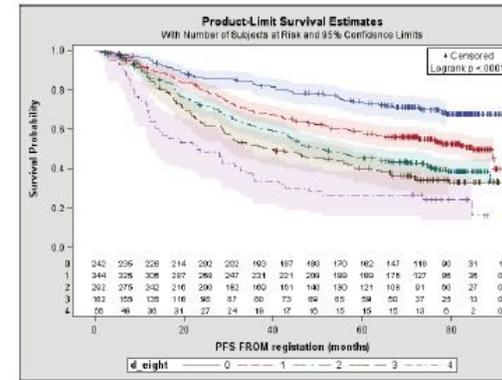
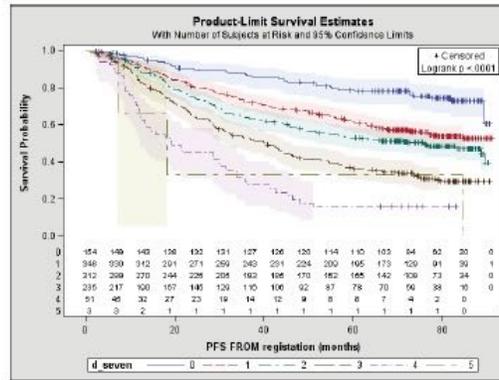
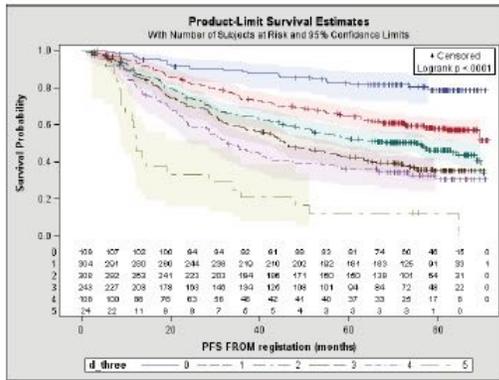
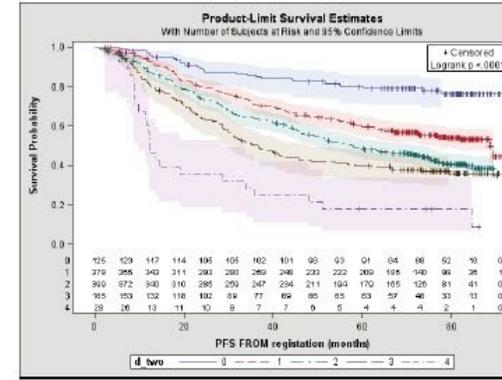
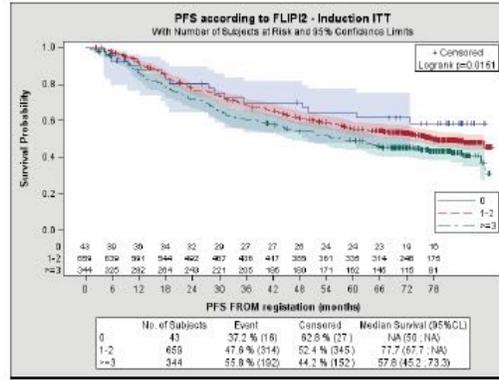
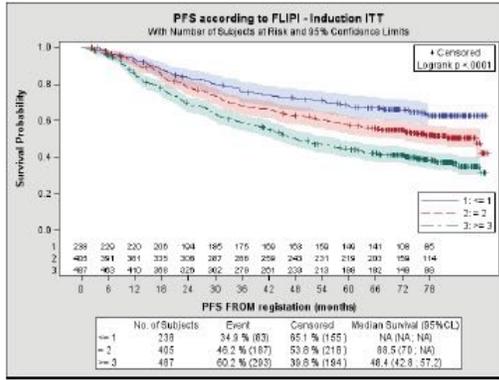
Parameter	n	%	5-year survival, % (SE)	10-year survival, % (SE)	Log rank, P
<b>Sex</b>	4167				.0025
Female	49		72.5 (1.0)	51.0 (1.4)	
Male	51		68.7 (1.0)	46.2 (1.4)	
<b>Age</b>	4167				< 10 <sup>-4</sup>
Younger than 60 y	63		78.1 (0.8)	58.4 (1.2)	
60 y or older	37		57.7 (1.3)	32.3 (1.6)	
<b>Cell type</b>	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)	
<b>Ann Arbor stage</b>	4162				< 10 <sup>-4</sup>
I-II	22		83.2 (1.2)	64.3 (2.0)	
III-IV	78		67.0 (0.8)	44.1 (1.1)	
<b>B symptoms</b>	3965				< 10 <sup>-4</sup>
Absence	81		73.8 (0.8)	50.7 (1.2)	
Presence	19		55.8 (1.8)	36.8 (2.3)	
<b>Performance status (ECOG)</b>	3602				< 10 <sup>-4</sup>
0-1	88		72.4 (0.8)	50.0 (1.2)	
More than 1	12		58.6 (2.4)	37.8 (3.0)	
<b>Number of nodal sites</b>	3322				< 10 <sup>-4</sup>
0-4	65		77.0 (0.9)	54.6 (1.4)	
5 or more	35		63.7 (1.4)	42.1 (1.9)	
<b>Number of extra nodal sites other than bone marrow</b>	3741				< 10 <sup>-4</sup>
0	62		76.1 (0.9)	55.4 (1.3)	
1 or more	38		63.7 (1.3)	40.8 (1.7)	
<b>Bone marrow involvement</b>	4016				< 10 <sup>-4</sup>
Absence	52		75.6 (0.9)	56.2 (1.3)	
Presence	48		65.7 (1.1)	40.4 (1.6)	
<b>Spleen involvement</b>	3816				< 10 <sup>-4</sup>
Absence	78		74.8 (0.8)	53.0 (1.2)	
Presence	22		57.6 (1.7)	36.5 (2.1)	
<b>Serum <math>\beta_2</math> microglobulin</b>	716				< 10 <sup>-4</sup>
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)	
<b>ESR</b>	2256				< 10 <sup>-4</sup>
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)	
<b>Serum LDH</b>	2565				< 10 <sup>-4</sup>
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)	
<b>Thrombocyte count</b>	3655				< 10 <sup>-4</sup>
Greater than or equal to $150 \times 10^9/L$	88		72.2 (0.8)	50.5 (1.2)	
Less than $150 \times 10^9/L$	12		59.9 (2.3)	36.1 (3.1)	
<b>Hemoglobin level</b>	3813				< 10 <sup>-4</sup>
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)	
<b>PB lymphocyte count</b>	3122				< 10 <sup>-4</sup>
Greater than or equal to $1 \times 10^9/L^*$	80		73.3 (0.9)	51.5 (1.3)	
Less than $1 \times 10^9/L$	20		62.5 (2.0)	39.2 (2.6)	
<b>Serum albumin level</b>	2116				< 10 <sup>-4</sup>
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<sup>-4</sup>

# UNE MULTITUDE DE SCORE DANS LE LF

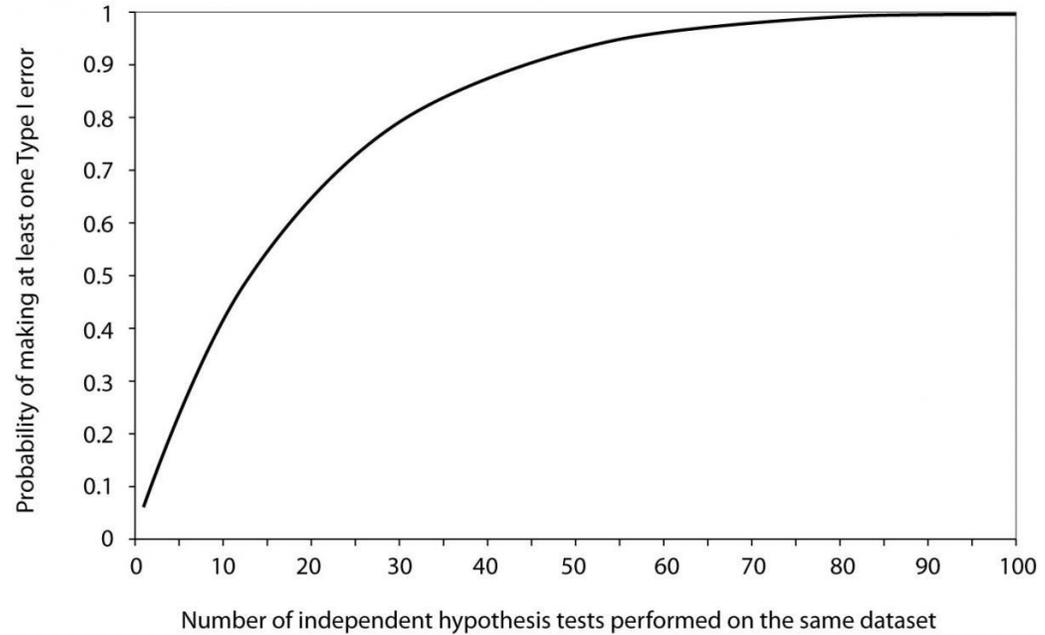


# La construction des scores est complexe!



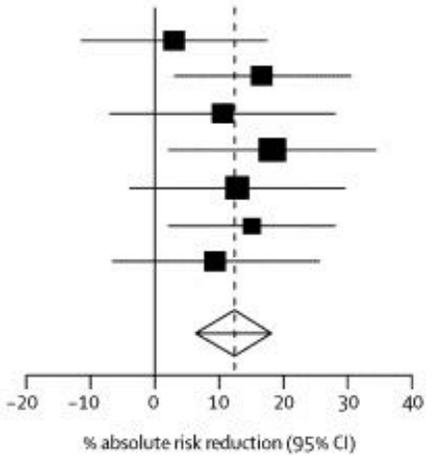
# Facteur pronostic et erreur de type I : autre source de non reproductibilité

With a type I error set up at 0.05

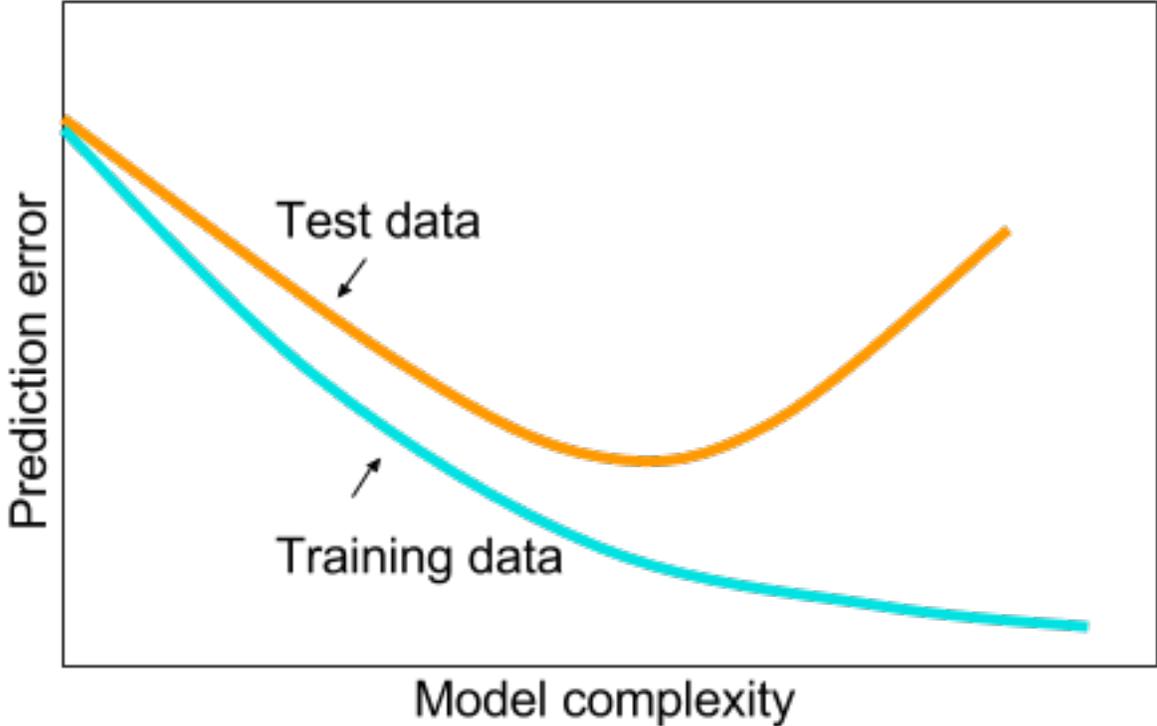


Day of birth	Events/patients		ARR (%)	95% CI	p value
	Surgical	Medical			
Sunday	7/56	6/41	3.1	-11.3 to 17.5	0.34
Monday	4/66	10/44	16.7	3.0 to 30.3	0.008
Tuesday	8/76	6/28	10.5	-6.9 to 27.9	0.12
Wednesday	8/67	13/47	18.3	2.3 to 34.2	0.01
Thursday	9/75	9/36	12.8	-3.8 to 29.4	0.07
Friday	1/56	6/37	15.1	2.3 to 27.9	0.01
Saturday	6/51	8/41	9.5	-6.6 to 25.6	0.12
<b>Total</b>	<b>43/447</b>	<b>58/274</b>	<b>12.3</b>	<b>6.5 to 18.1</b>	<b>&lt;0.001</b>

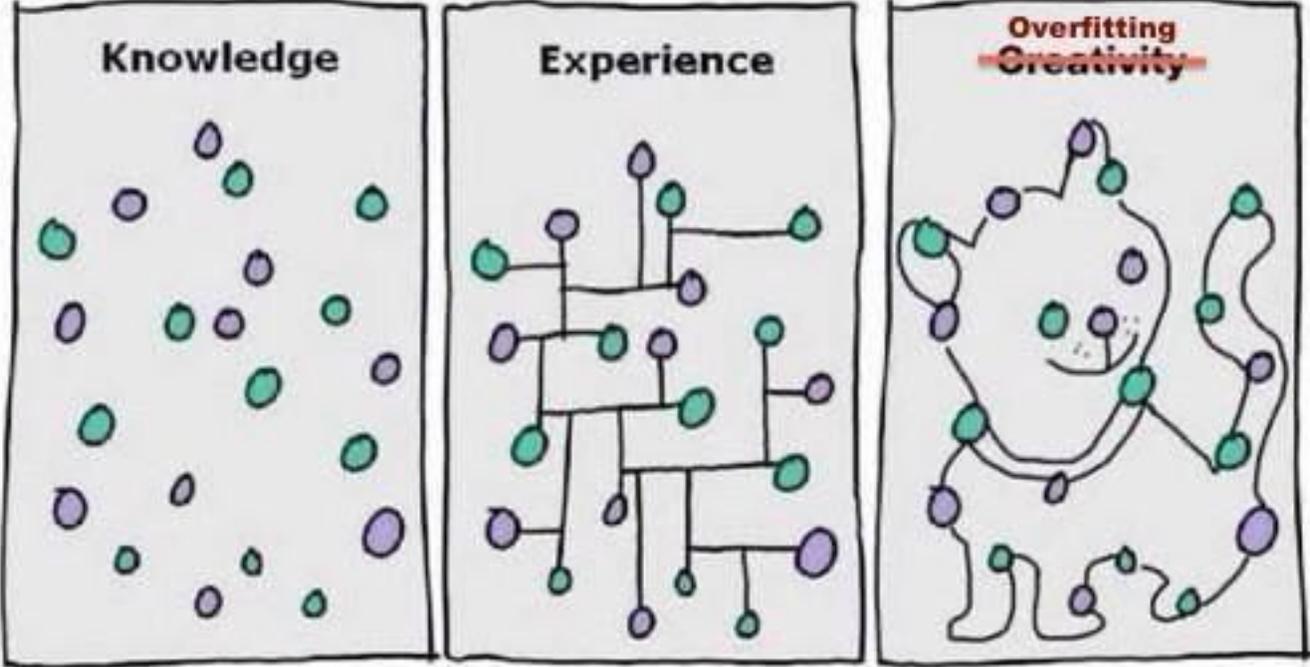
Heterogeneity: p=0.83



# Sans « validation set » un score ne veut rien dire



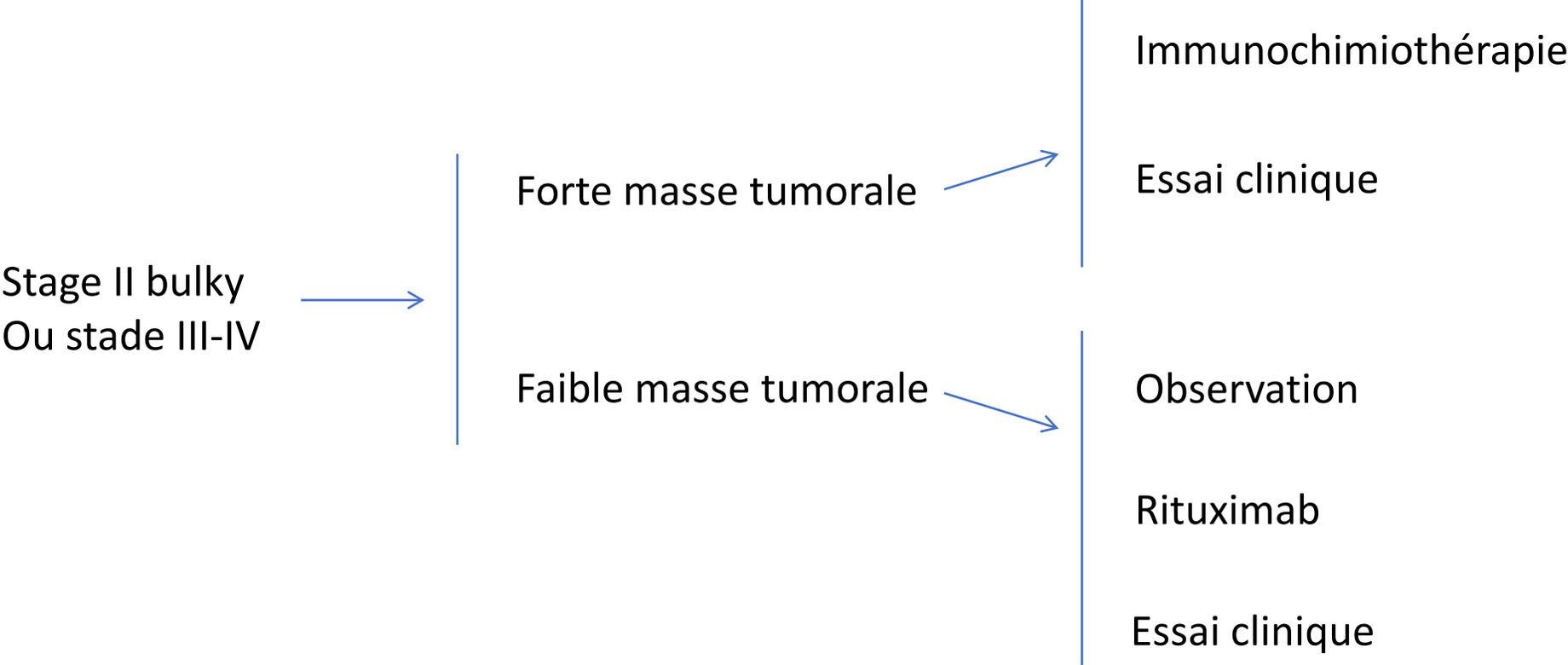
# La construction des scores est complexe!



# **Les scores clinico-biologiques**

# Impact de la masse tumorale sur le pronostic : critères de traitement

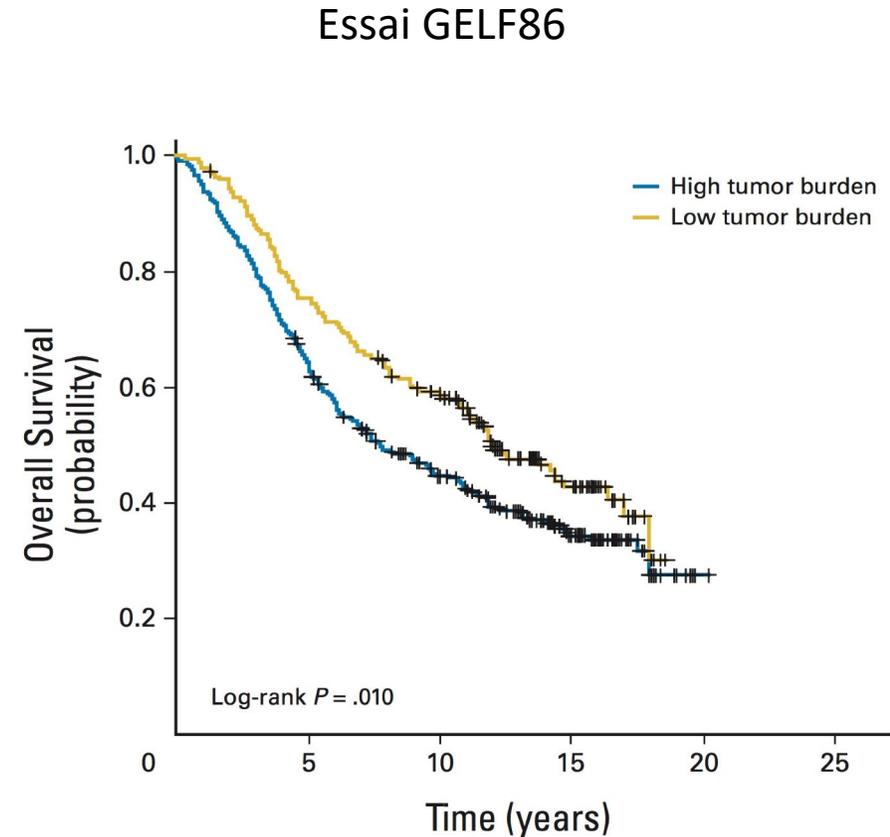
## Recommandations NCCN/ESMO



# Impact de la masse tumorale sur le pronostic

## Critères GELF/GELA de forte masse tumorale

- Symptômes B / PS > 1
- Masse > 7cm /  $\geq 3$  ganglions > 3 cm
- Splénomégalie massive
- Compression
- Epanchement
- Cellules circulantes (> 5 G/L)
- Cytopénies
- $\beta 2$ -microglobuline > 3 mg/L
- LDH > normale

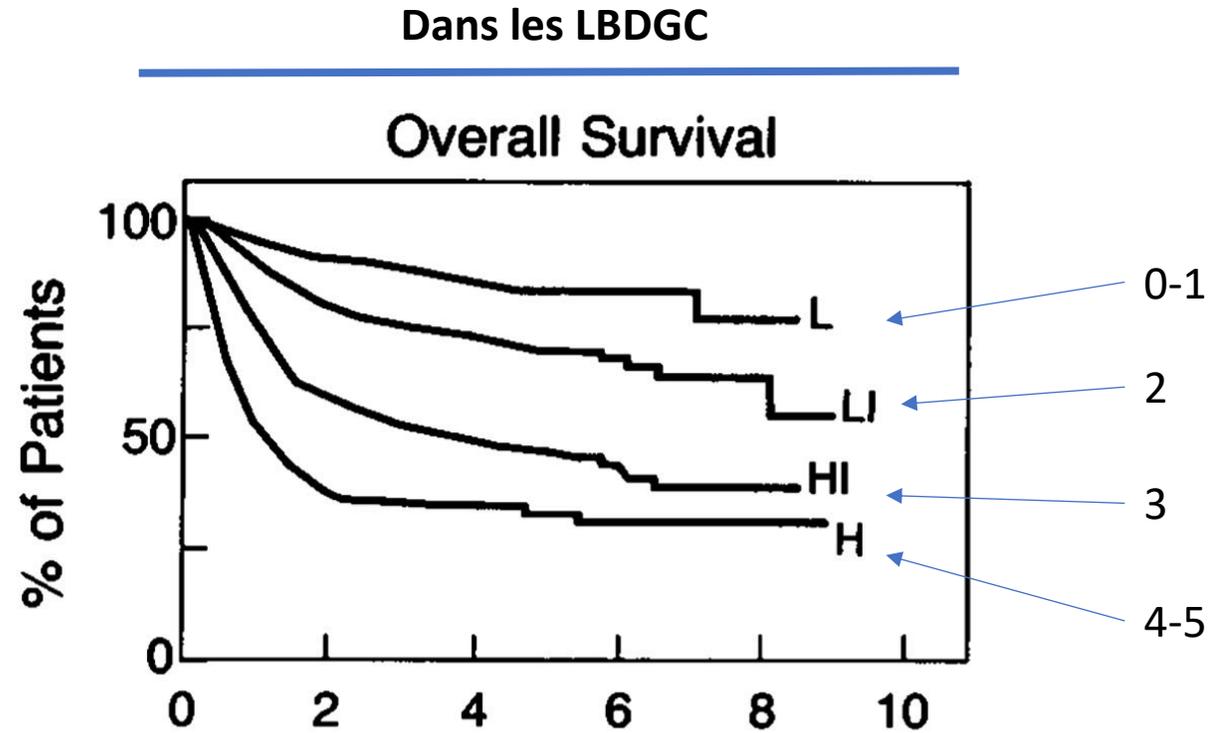


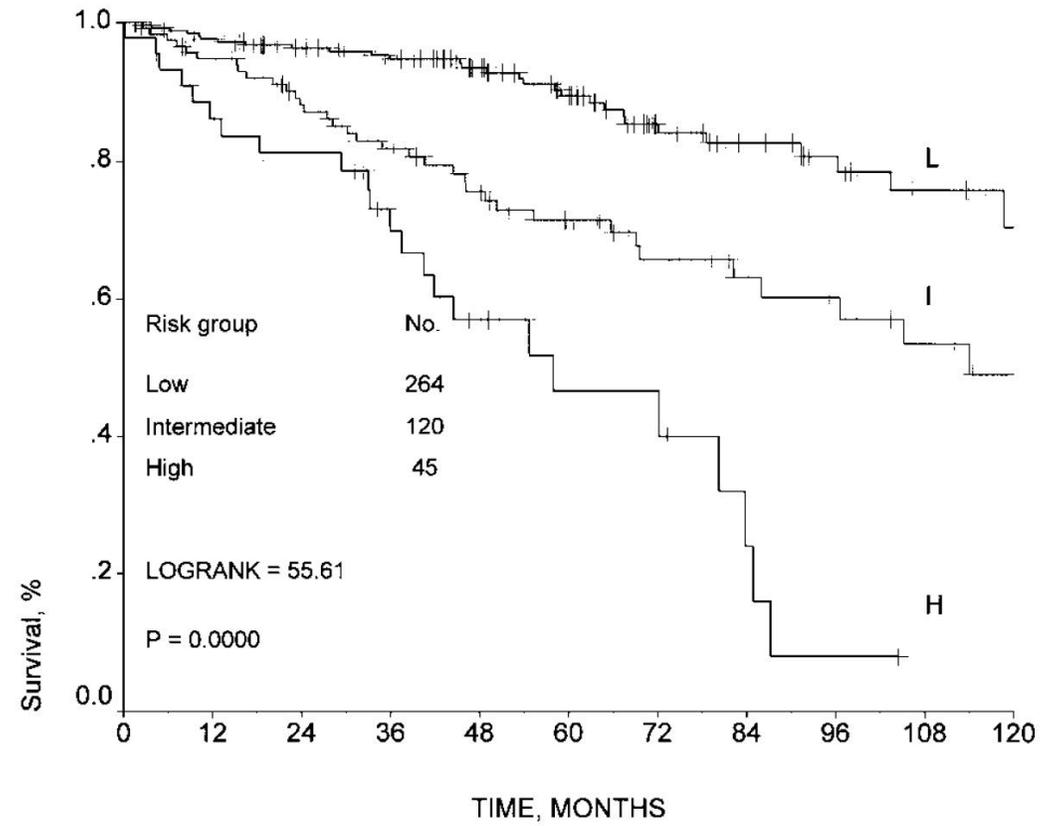
# Les différents scores pronostiques dans le LF

IPI	FLIPI	FLIPI2	PRIMA-PI	FLEX
Age > 60	Age > 60	Age > 60	$\beta$ 2m > 3 mg/L	Sexe masculin
LDH > normale	LDH > normale	$\beta$ 2m > normale	Envahissement médullaire	Somme des produits des diamètres > 75 <sup>ème</sup> percentile
Stade III-IV	Stade III-IV	Diamètre du ganglion le plus volumineux > 6cm		Grade 3A
ECOG PS $\geq$ 2	Hb < 12 g/dL	Hb < 12 g/dL		$\geq$ 2 aires extra-ganglionnaires
$\geq$ 2 aires extra-ganglionnaires	> 4 aires ganglionnaires	Envahissement médullaire		ECOG PS > 1
				Hb < 12 g/dL
				$\beta$ 2m > normale
				Compte de NK < 100/ $\mu$ L
				LDH > normale

# Les scores clinico-biologiques : l'IPI

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

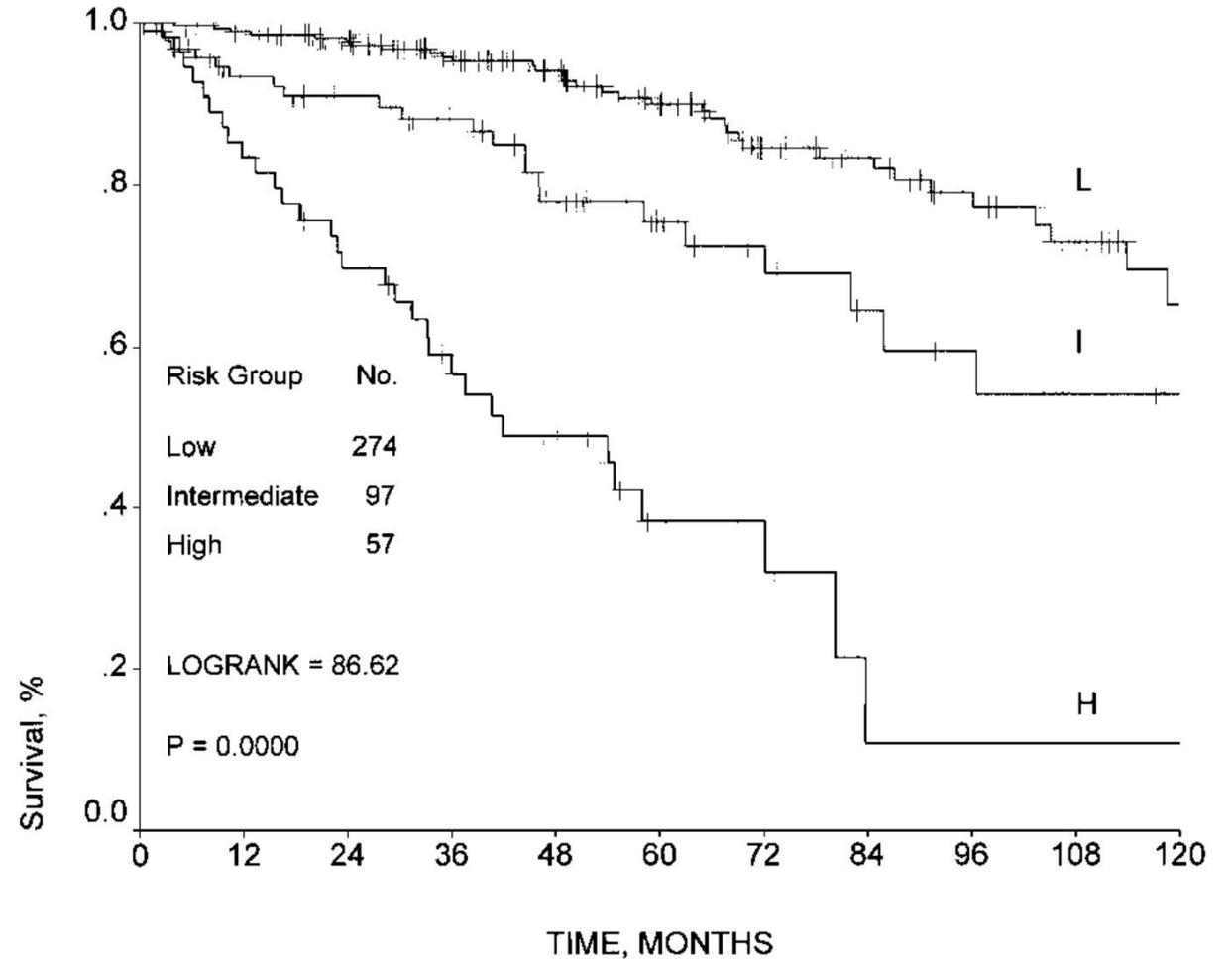




# Le score de l'intergroupe italien du lymphome

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

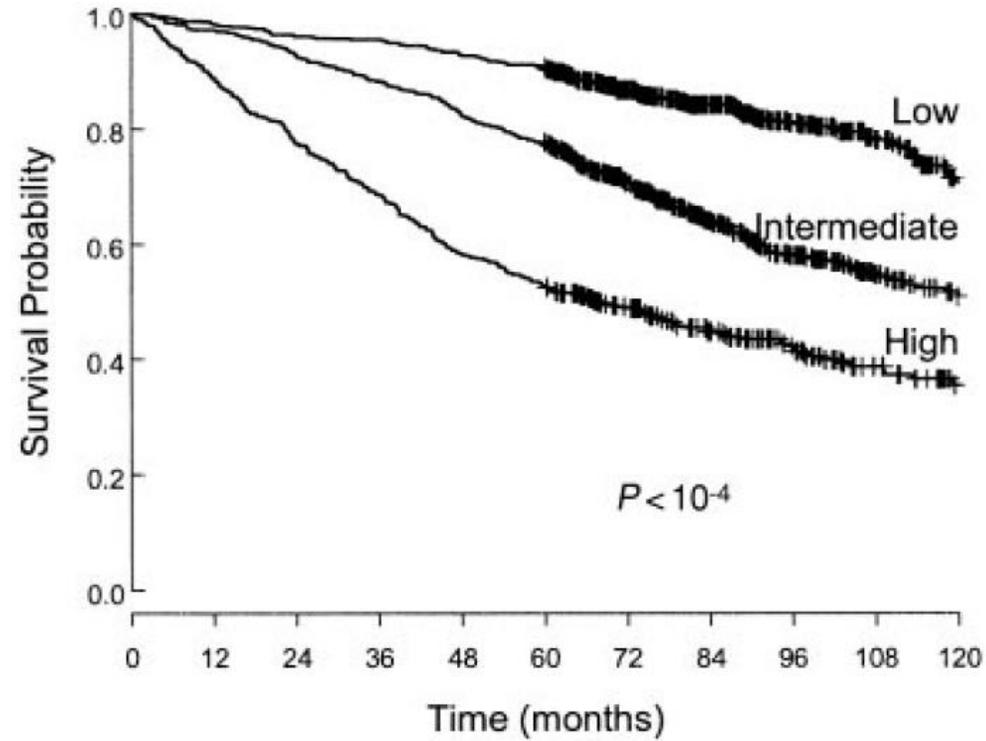
Factor	Relative Risk of Death	95% CI	P Value
Age (no more than 60 vs greater than 60)	2.6	1.6-4.1	<.0001
Sex (F vs M)	1.8	1.2-2.8	.0079
Extranodal sites (0-1 vs at least 2)	2.1	1.0-4.2	.0445
Serum LDH (normal vs elevated)	2.0	1.2-3.5	.0074
B symptoms (absent vs present)	2.2	1.2-4.1	.0128
ESR (less than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



# Le FLIPI

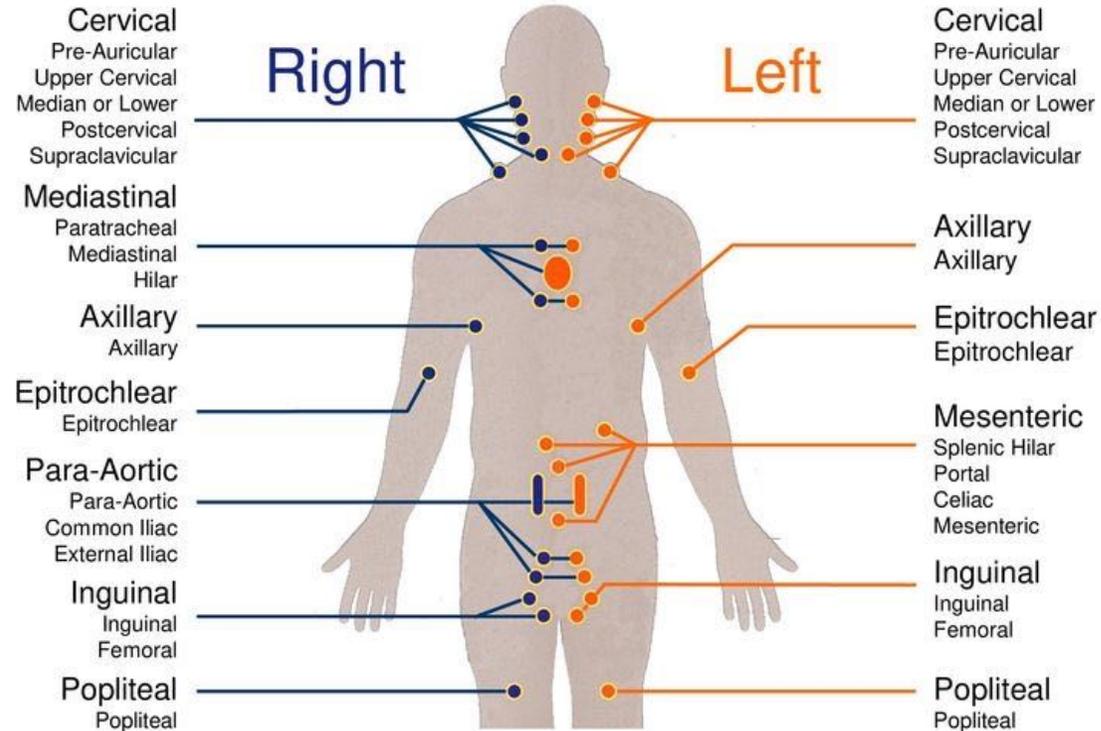
Variables	FLIPI	% de patients au diagnostic	Survie globale à 5 ans	Survie globale à 10 ans
Stade (I-II v III-IV)	bas=0-1	36%	91%	71%
Age ( $\leq 60$ ans v $> 60$ ans)	intermédiaire=2	37%	78%	51%
Aires ganglionnaires ( $\leq 4$ v $> 4$ )	élevé=3-4-5	27%	52%	35%
LDH ( $\leq$ limite supérieure v $>$ limite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

# Le FLIPI



No. of Events		0	12	24	36	48	60	72	84	96	108	120
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		0	12	24	36	48	60	72	84	96	108	120
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

## FLIPI—Lymph Node Groups

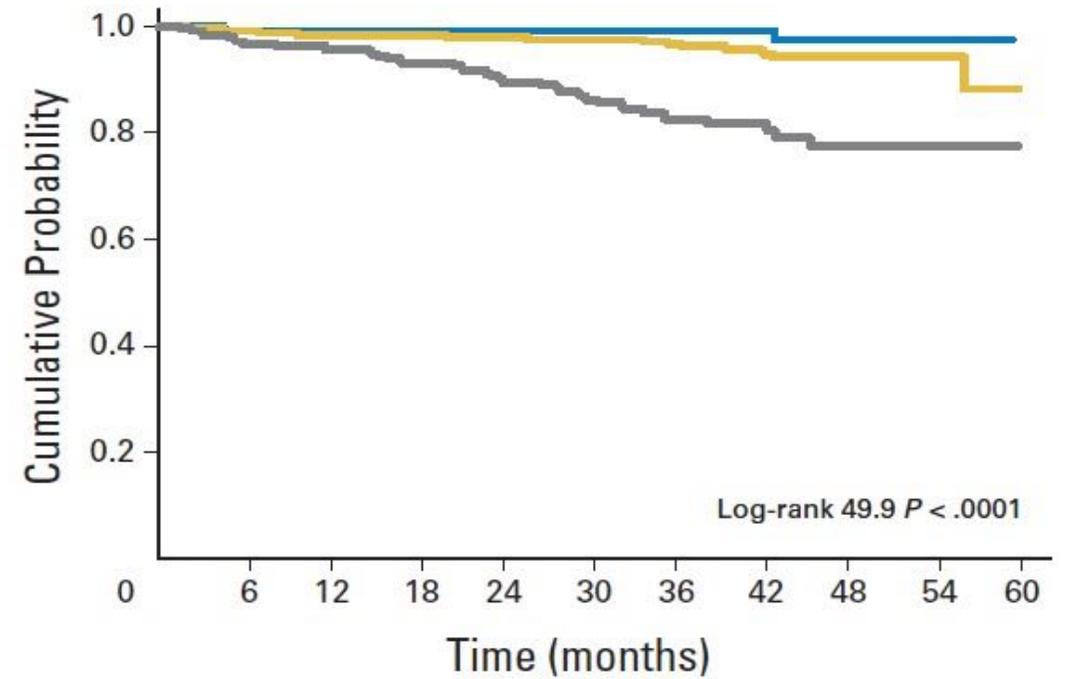
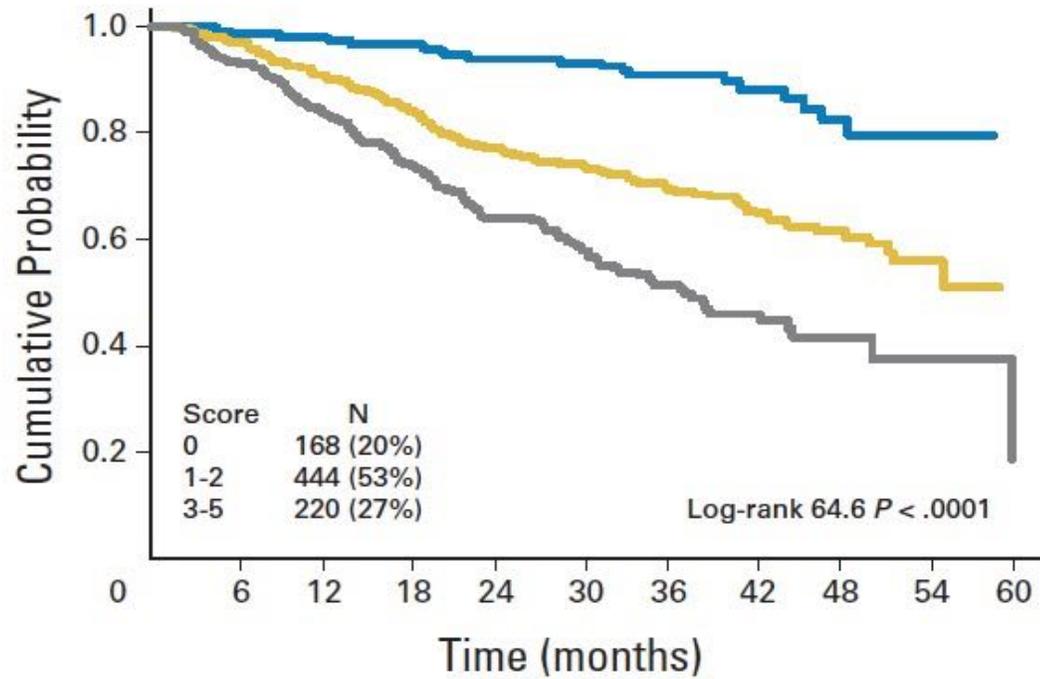


Each of the right or left cervical, axillary, epitrochlear, inguinal, or popliteal nodal areas are considered separate areas.

# Le FLIPI2

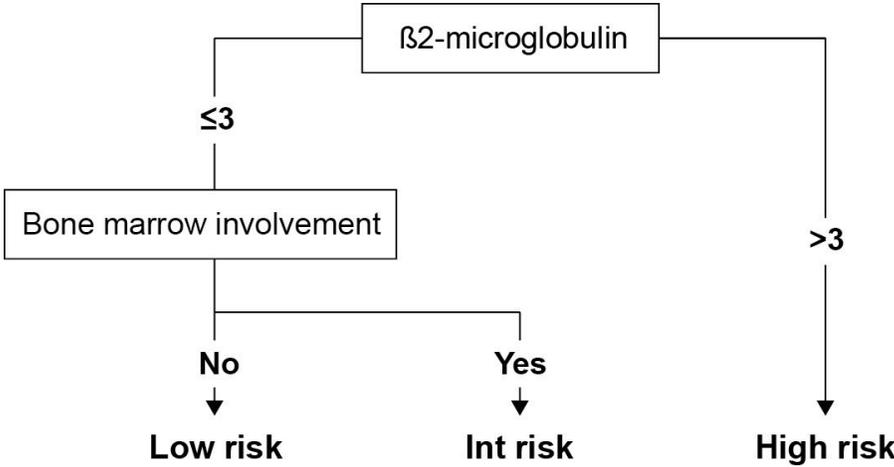
Variables	FLIPI2	% de patients au diagnostic	Survie sans progression à 3 ans	Survie sans progression à 5 ans
$\beta$ 2-microglobuline ( $\leq$ limite supérieure v $>$ limite supérieure)	bas=0	20%	91%	79%
Age ( $\leq$ 60 ans v $>$ 60 ans)	intermédiaire =1-2	53%	69%	51%
Diamètre maximal de l'adénopathie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

# Le FLIPI2

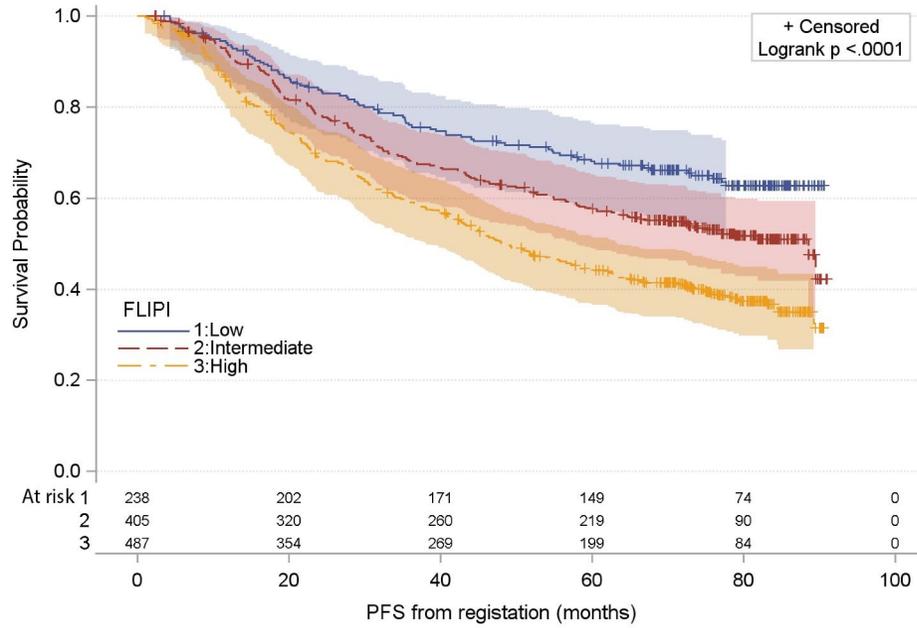
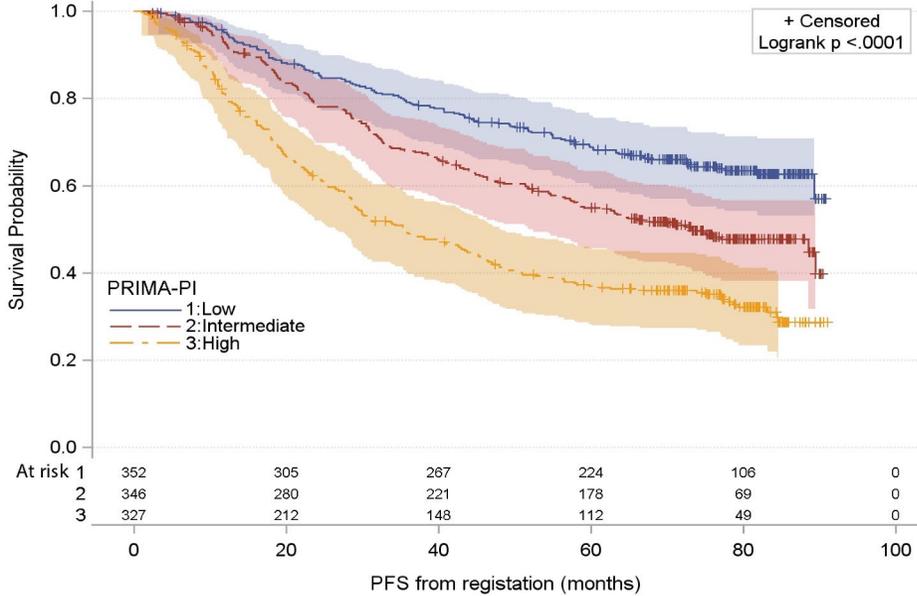


A fait le pari d'une prédiction sur l'ensemble des patients (localisé/disséminé/faible/forte masse): peu utilisé

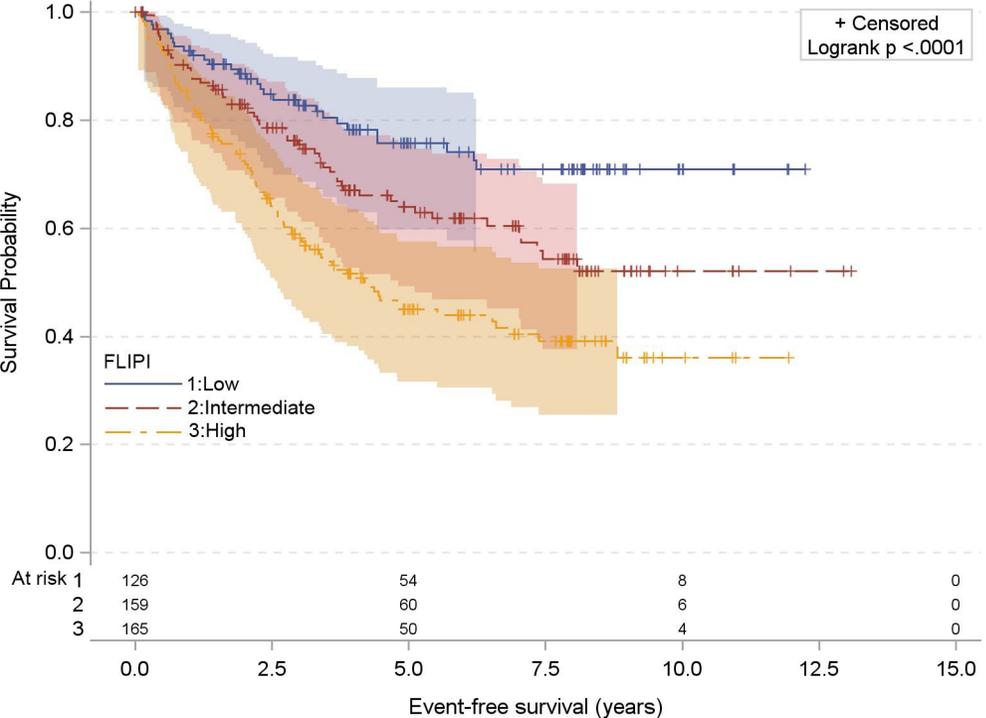
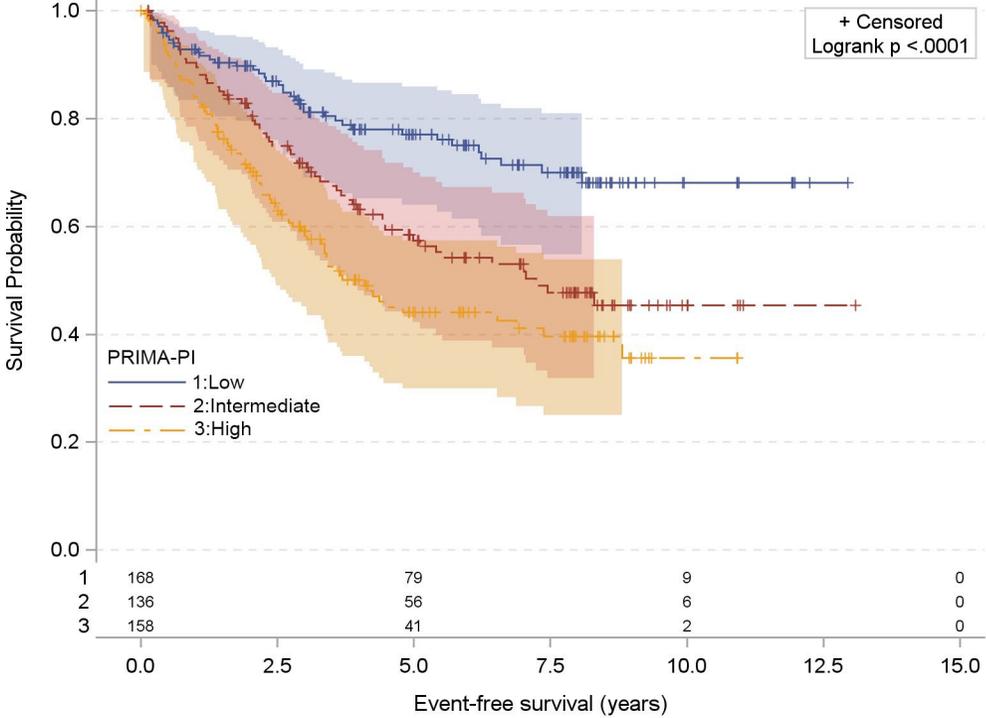
# Le PRIMA-PI (forte masse uniquement)



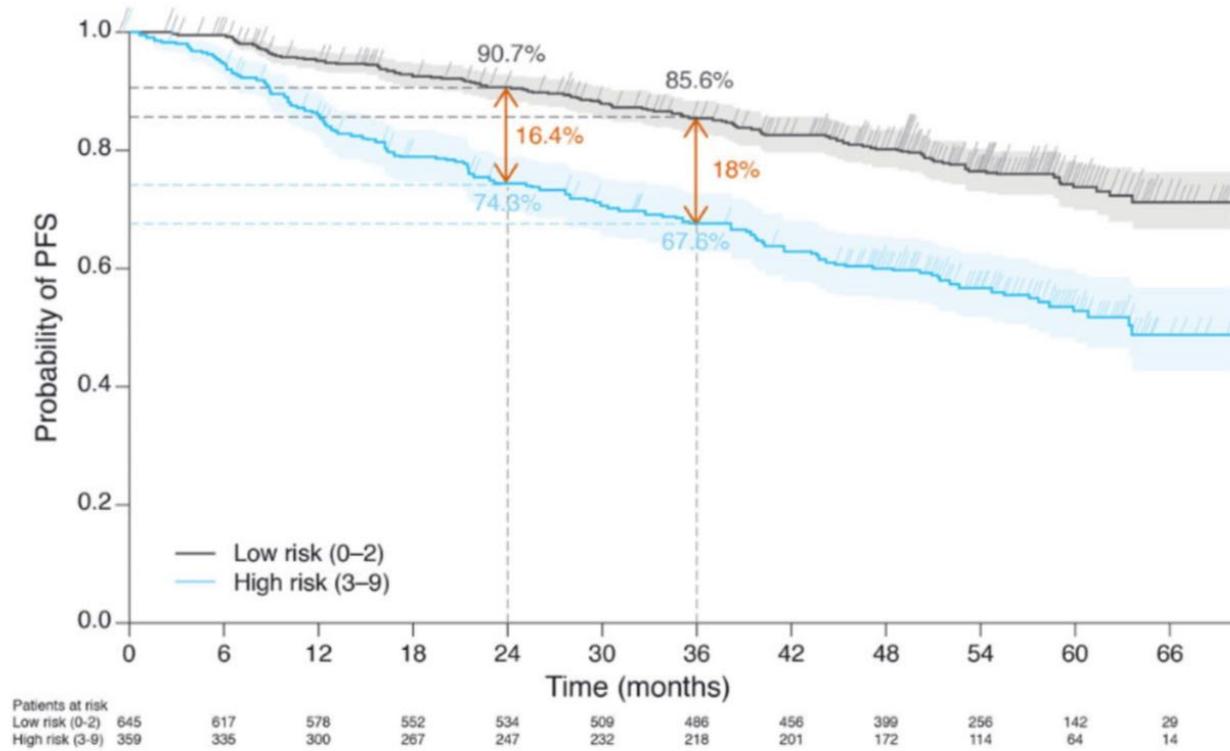
Bachy et al. Blood, 2018



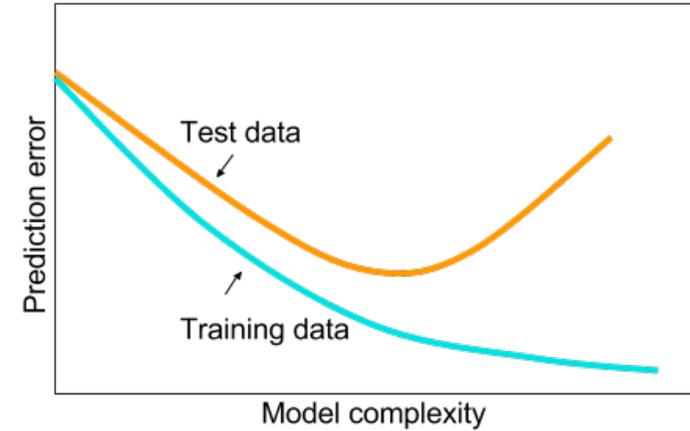
# Le PRIMA-PI (forte masse uniquement)



# Le FLEX



- FLEX**
- Sexe masculin
  - Somme des produits des diamètres > 75<sup>ème</sup> percentile
  - Grade 3A
  - ≥ 2 aires extra-ganglionnaires
  - ECOG PS > 1
  - Hb < 12 g/dL
  - β2m > normale
  - Compte de NK < 100/μL
  - LDH > normale



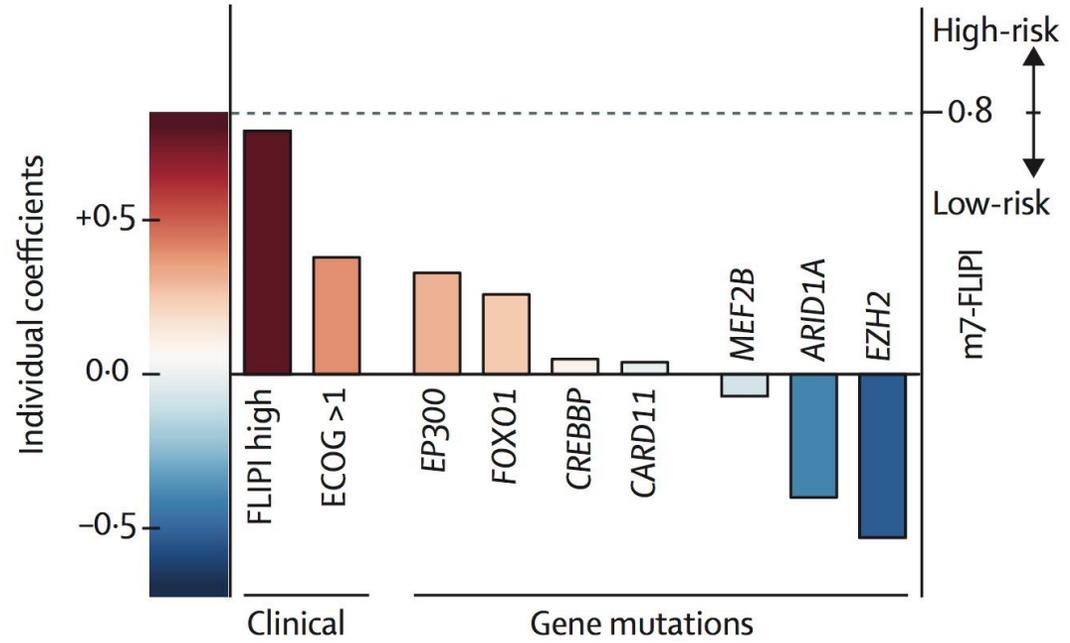
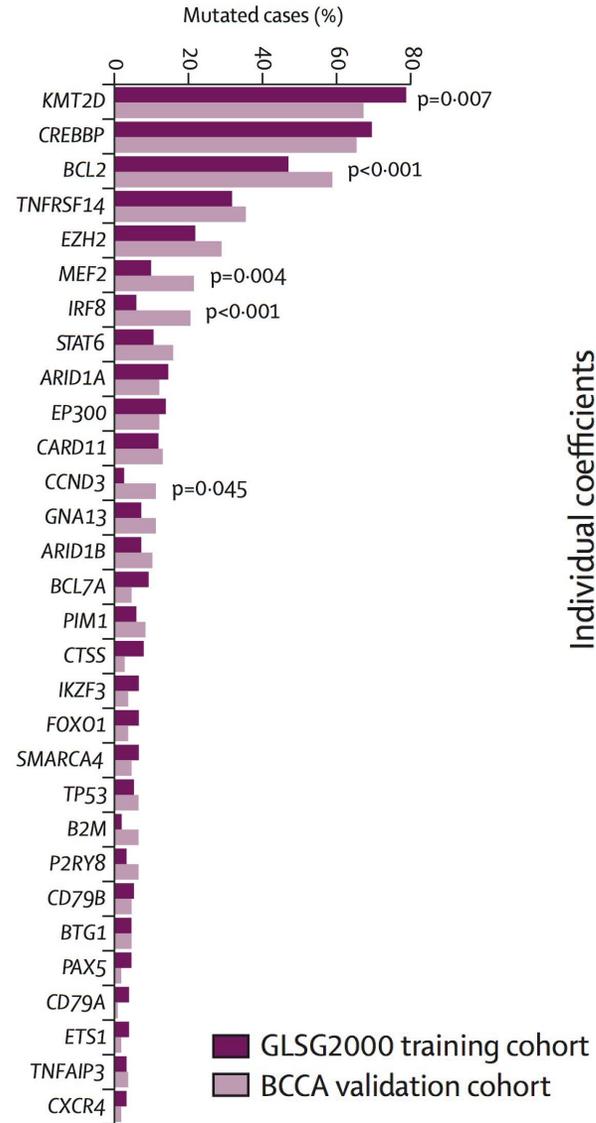
# Les différents scores pronostiques dans le LF

IPI	FLIPI	FLIPI2	PRIMA-PI	FLEX	
Age > 60	Age > 60	Age > 60	$\beta$ 2m	Male sex	
LDH > UNL	LDH > UNL	$\beta$ 2m > ULN	<b>Bone marrow infiltration</b>	<b>SPD &gt; 75<sup>th</sup></b>	
Stage III-IV	Stage III-IV	Node > 6cm		<b>Grade 3A</b>	
<b>ECOG PS <math>\geq</math> 2</b>	Hb < 12 g/dL	Hb < 12 g/dL		>2 extra-nodal areas	
<b><math>\geq</math> 2 extra-nodal areas</b>	<b>&gt; 4 nodal areas</b>	<b>BM involvement</b>		ECOG PS > 1	
				Hb < 12 g/dL	
				$\beta$ 2m > UNL	
				<b>NK count &lt; 100/<math>\mu</math>L</b>	
				LDH > UNL	
<b>Pros</b>	easy	Reproducibility / OS	FLIPI2 low : good	easy	Accuracy
<b>Cons</b>	Accuracy lower	Nodal areas	Imbalanced / BM	BM	complicated

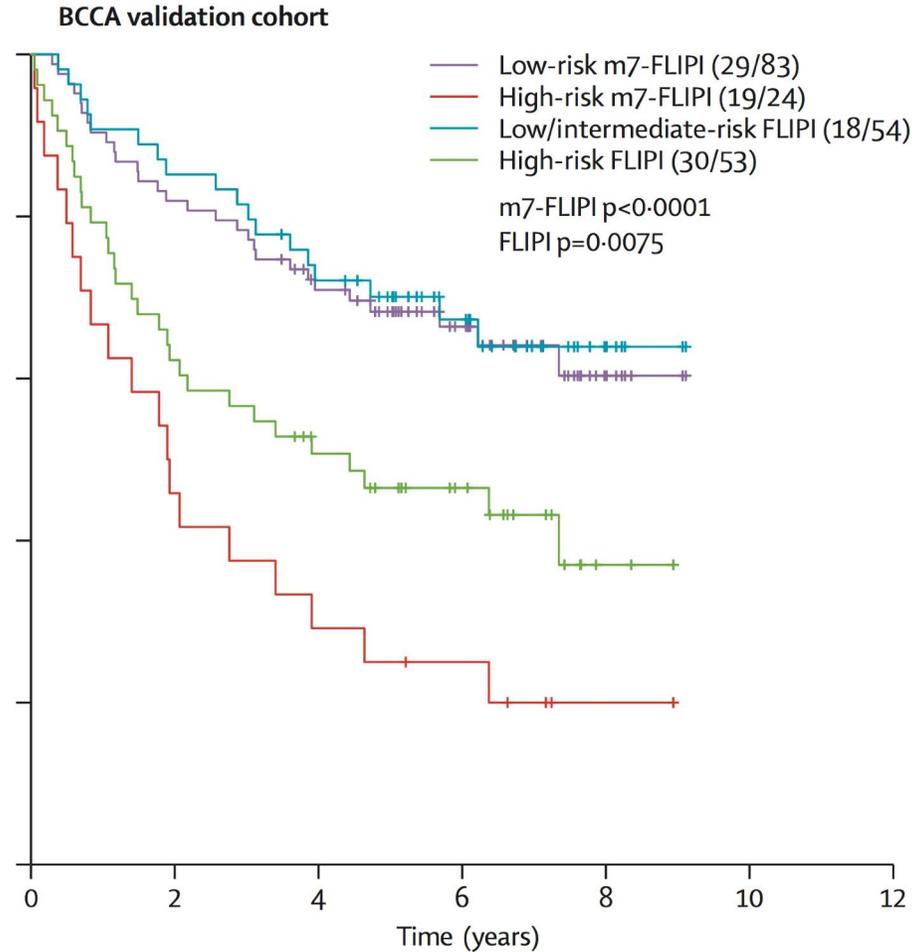
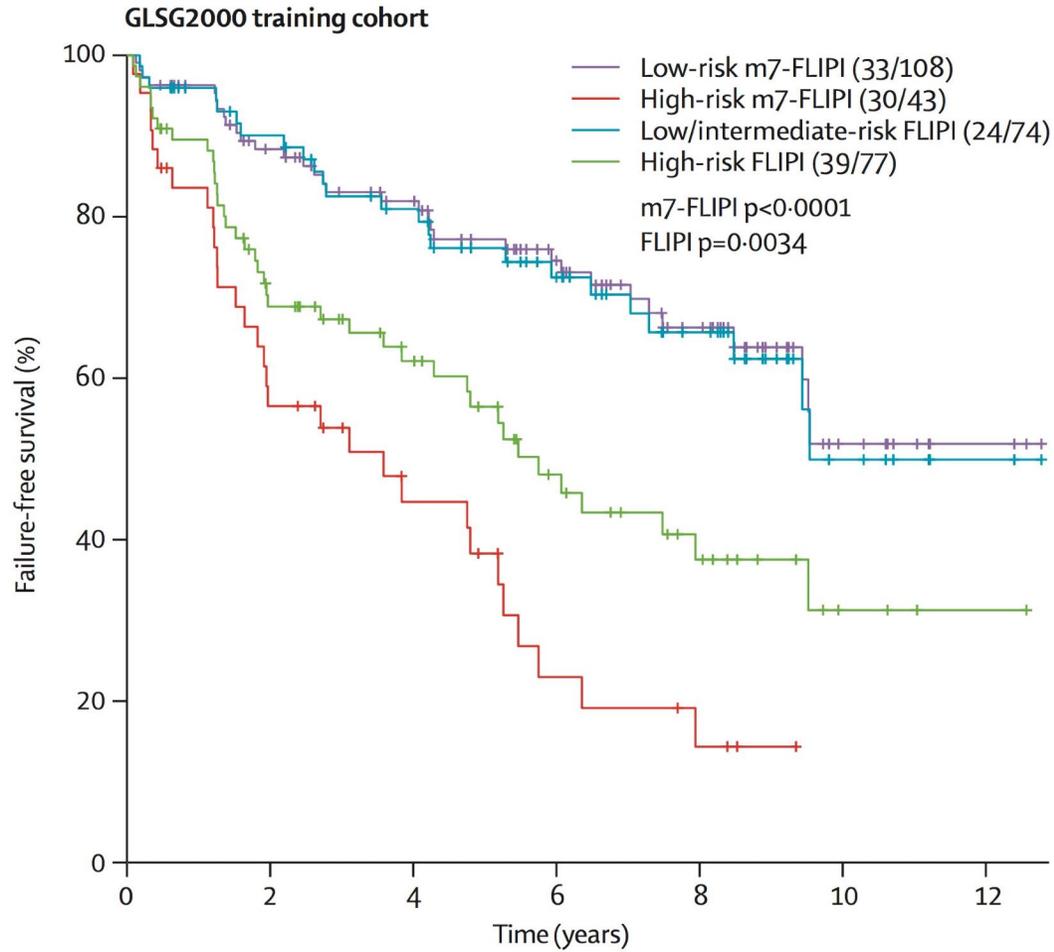
LDH : lactate dehydrogenase, UNL : upper normal limit, PS : performance status, Hb : hemoglobin,  $\beta$ 2m :  $\beta$ 2-microglobulin, NK : natural killer, SPD : sum of the product of the diameters

# Les scores bio-moléculaires

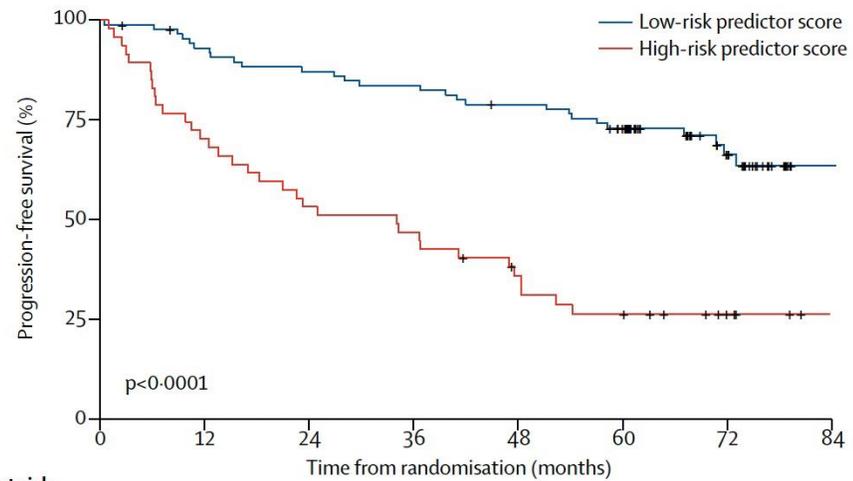
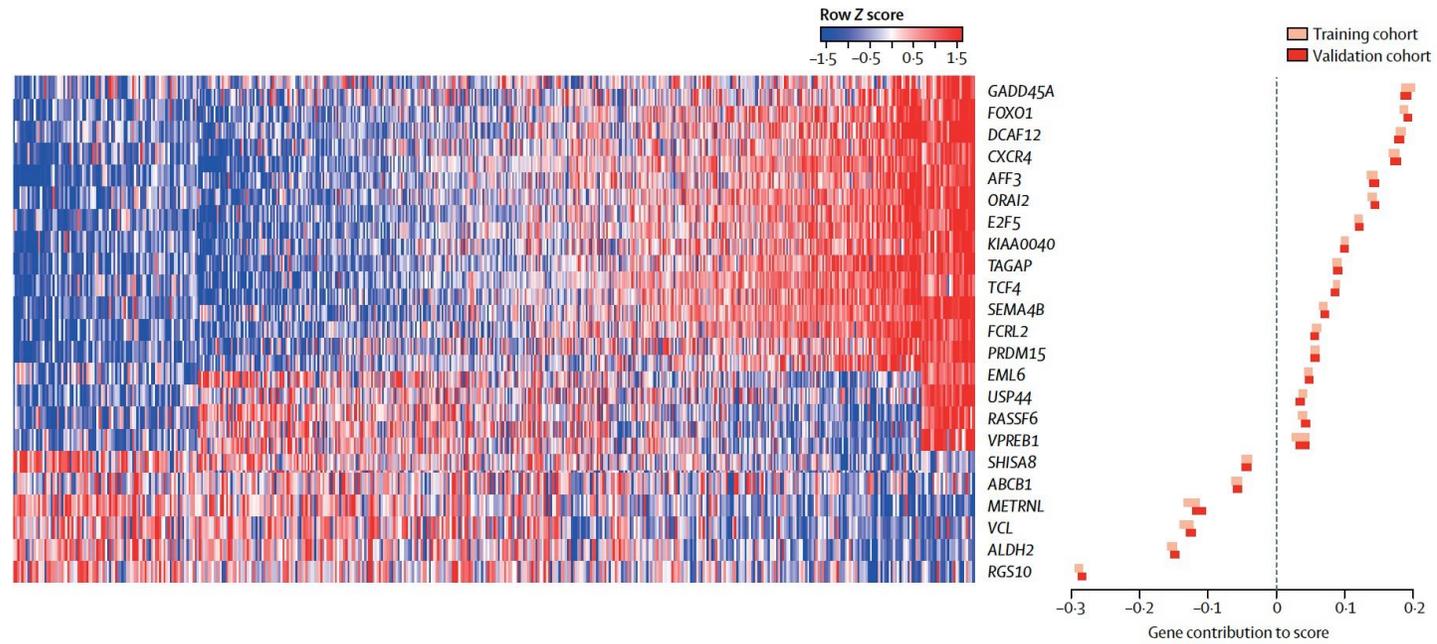
# Le m7-FLIPI



# Le m7-FLIPI



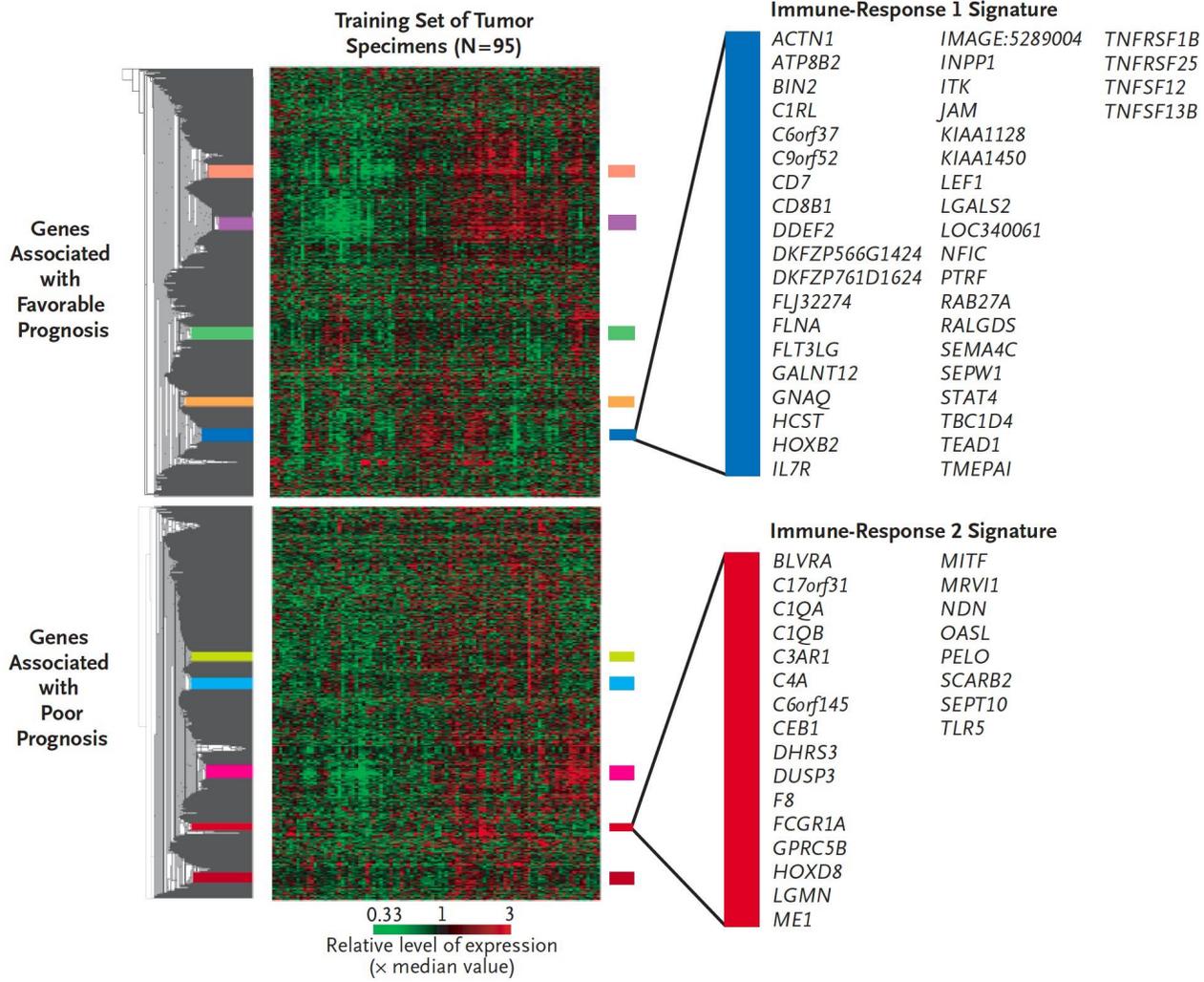
# 23-gene score



	Number at risk (number censored)							
	0	12	24	36	48	60	72	84
Low-risk predictor score	87 (0)	79 (2)	74 (2)	71 (2)	66 (3)	59 (5)	27 (34)	2 (58)
High-risk predictor score	47 (0)	33 (0)	33 (0)	22 (0)	15 (2)	11 (2)	7 (6)	0 (13)

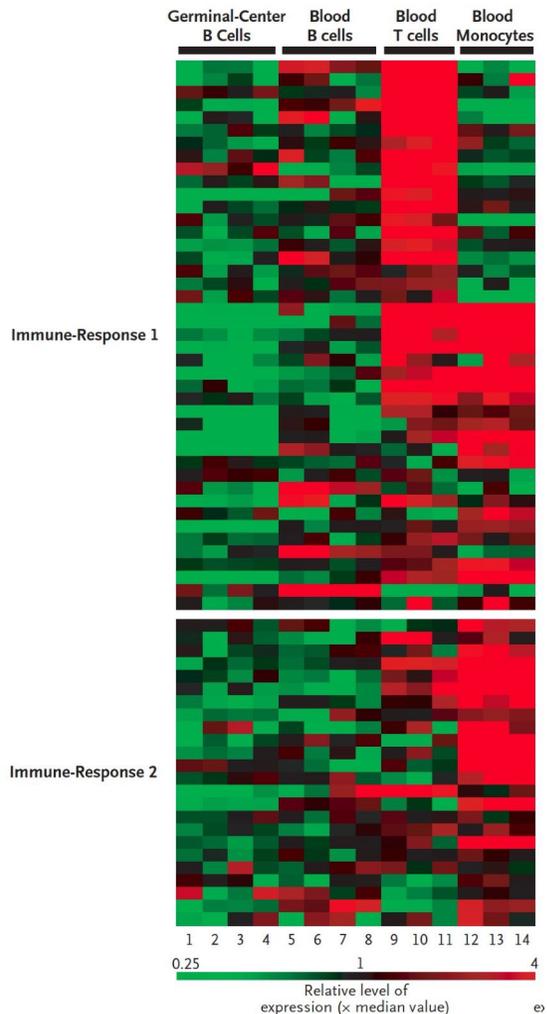
# **Le microenvironnement**

# Microenvironnement



Dave et al., NEJM 2004

# Microenvironnement



**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

**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 <sup>9</sup>	Glas <sup>5</sup>	Carreras <sup>11</sup>	Farinha <sup>8</sup>	Alvaro <sup>10</sup>	Klapper <sup>12</sup>	Taskinen <sup>13</sup>		Wahlin <sup>14</sup>	EORTC 20921	
							R-CHOP	CHOP		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 <sup>a</sup>	Good	nd	nd		nd	Poor	Good
FoxP3 sparse infiltrate	Poor	-	Poor	Good <sup>a</sup>	Poor	nd	nd		nd	Good	Poor
FoxP3 pattern interfollicular	Good <sup>b</sup>	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 <sup>c</sup>	Poor <sup>c</sup>	nd	Poor	Good
CD68 sparse infiltrate	-	-	nd	Good	Poor	-	Poor <sup>c</sup>	Good <sup>c</sup>	nd	Good	Poor
CD68 pattern interfollicular	-	nd	nd	nd	nd	nd	nd	nd	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	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)PI 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

# **Les variables post-thérapeutiques**

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

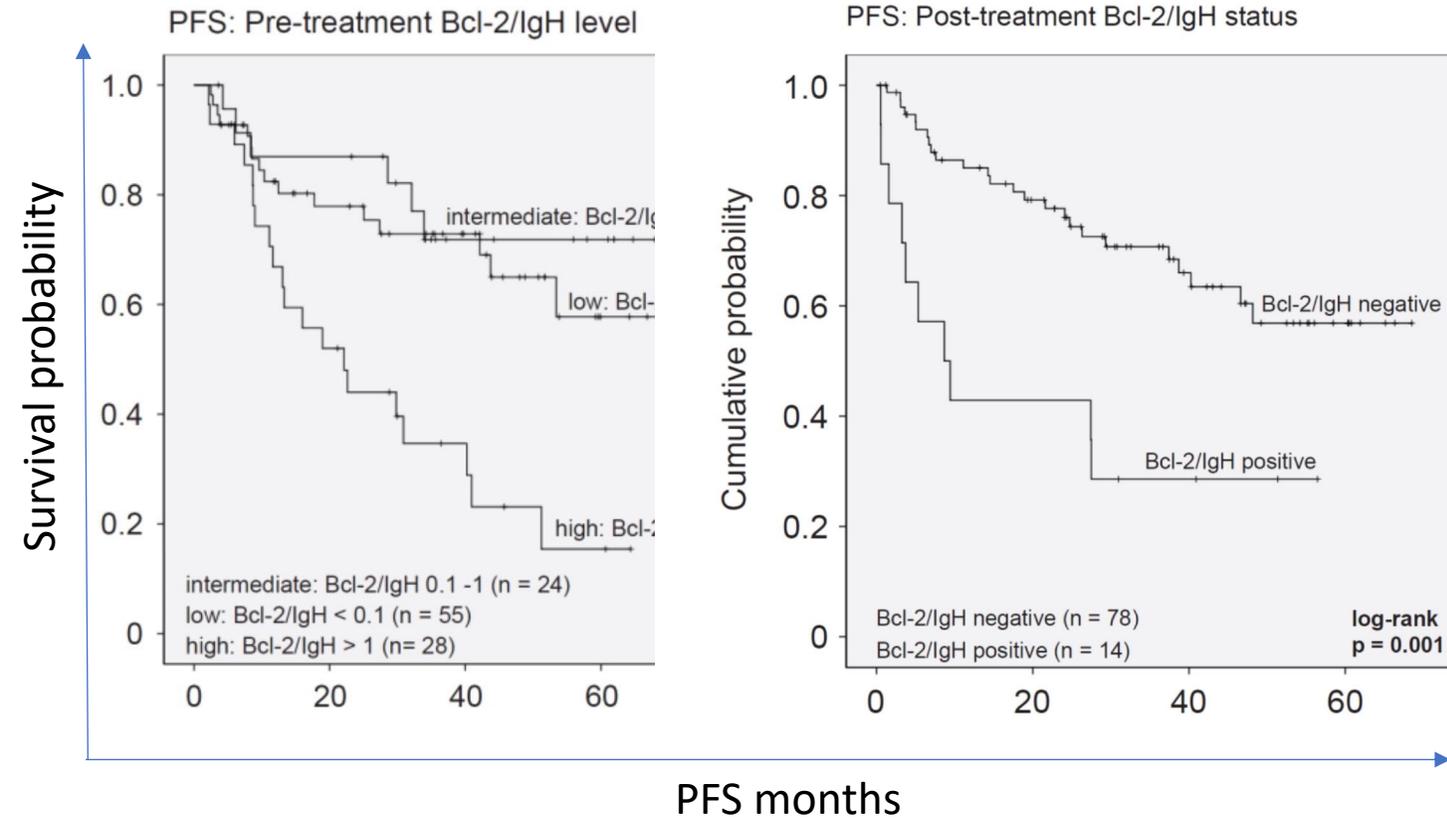


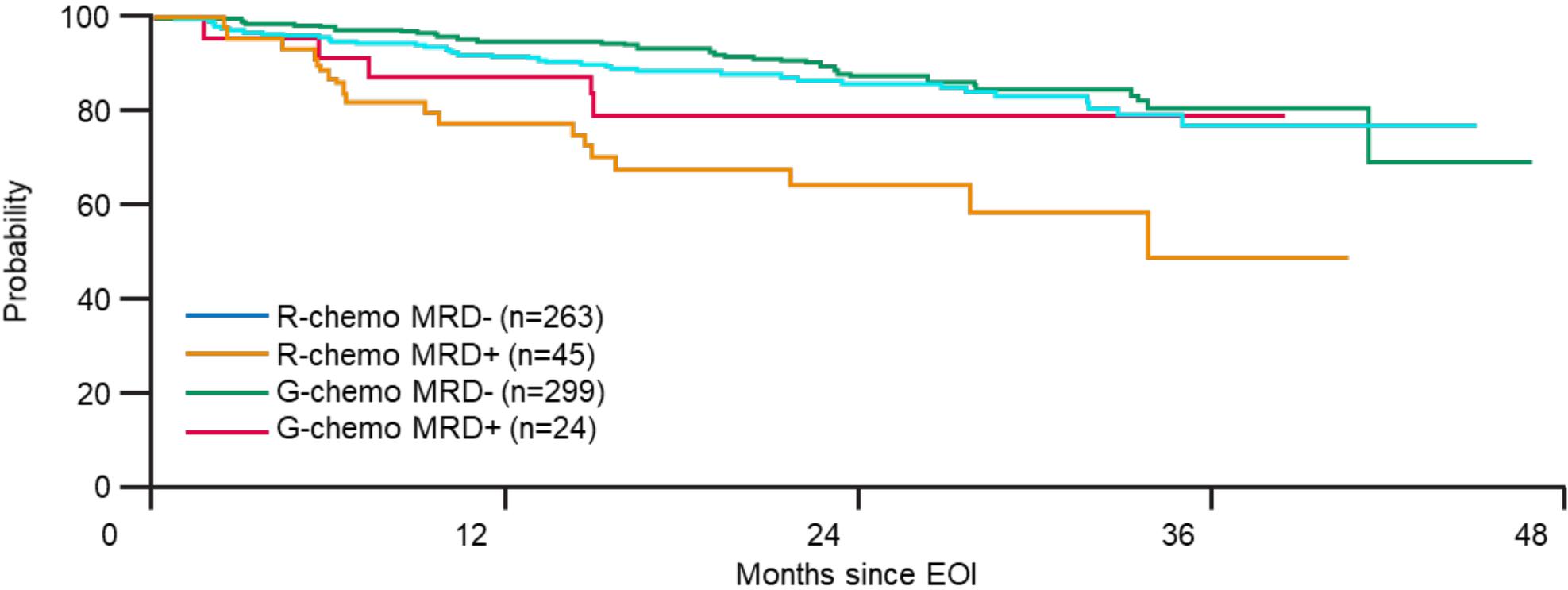
Table 3: Prognostic factor analysis for PFS post-treatment

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

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

Zohren et al., Blood 2015

# Rôle de la PCR BCL2/IGH

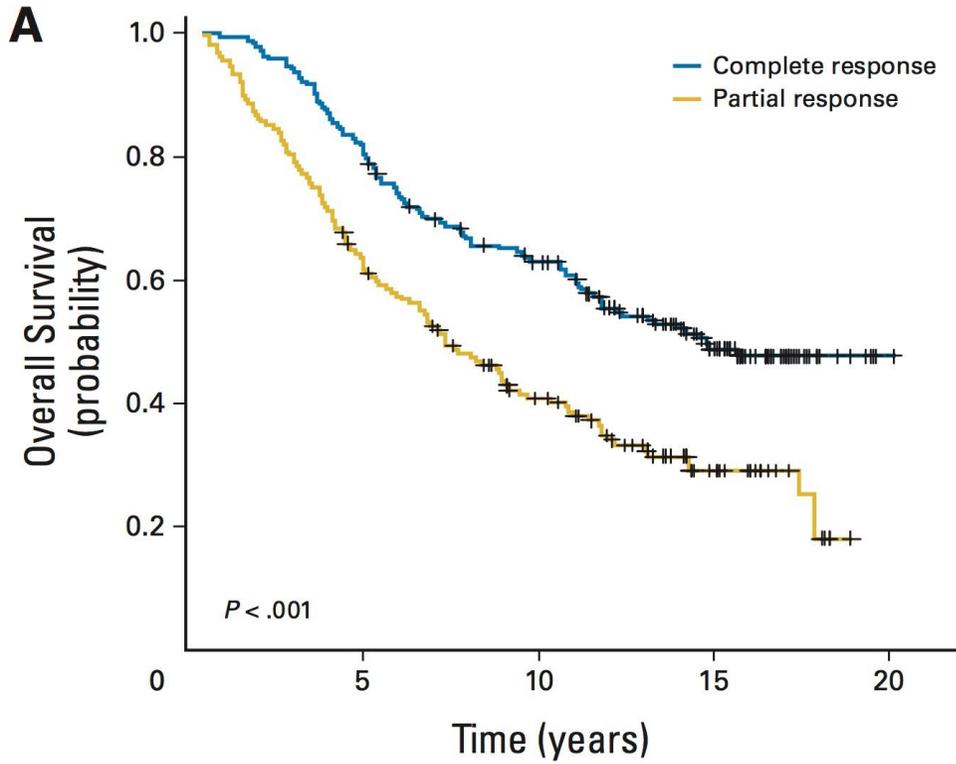


No. of patients at risk		0	12	24	36	48			
R-chemo MRD-	263	244	230	185	134	77	31	4	0
R-chemo MRD+	45	38	33	27	12	10	4	0	0
G-chemo MRD-	299	291	273	223	153	93	41	5	0
G-chemo MRD+	24	22	21	16	6	3	1	0	0

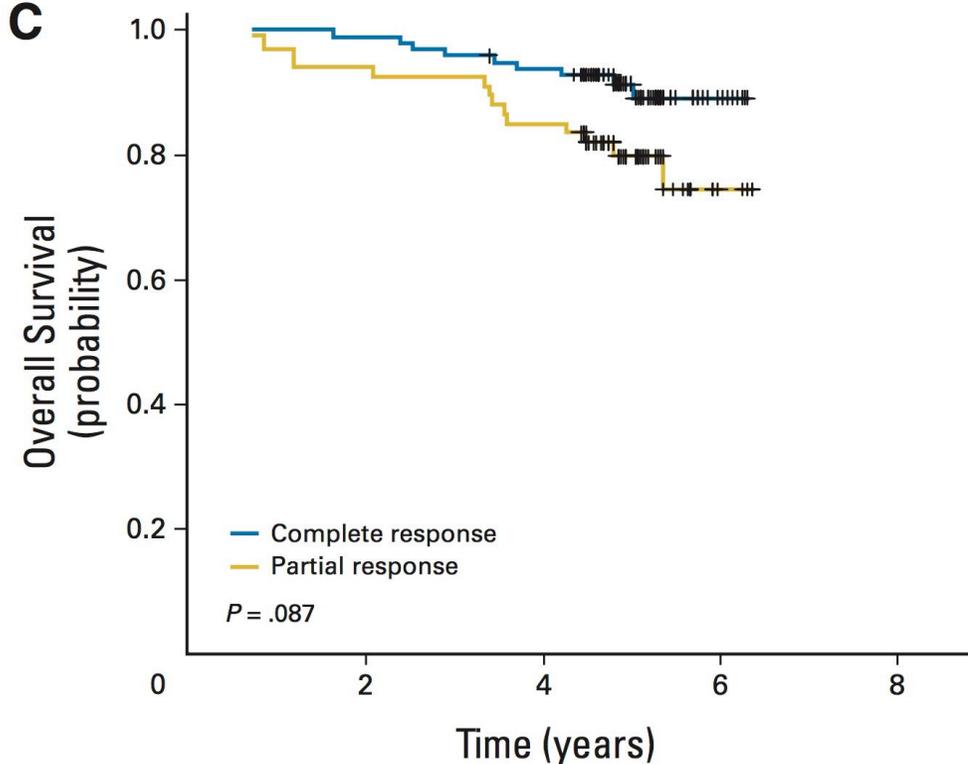
Pott C et al. oral presentation at ASH 2016: Abstract #613

# Evaluation conventionnelle

### GELF86



### FL2000



# Evaluation conventionnelle

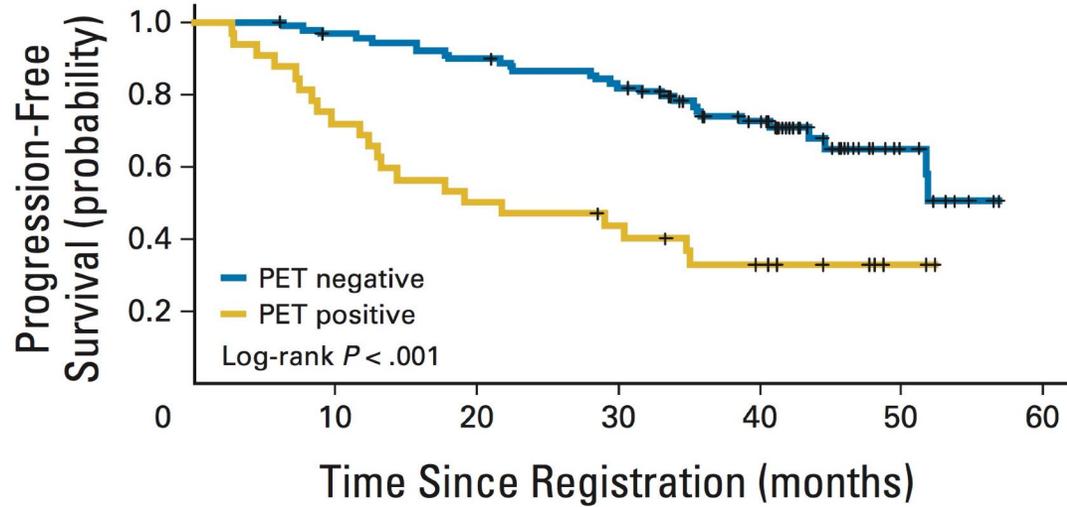
Parameter	Overall Survival*		
	HR	95% CI	<i>P</i>
CR (v PR)	0.53	0.38 to 0.73	<b>&lt; .001</b>
FLIPI			
High (v low)	1.64	1.04 to 2.58	<b>.032</b>
Intermediate (v low)	1.43	0.94 to 2.19	.098
IFN	0.83	0.61 to 1.12	.229
High tumor burden	1.27	0.86 to 1.87	.231
BM involvement	0.99	0.69 to 1.42	.953
Male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

# Evaluation métabolique

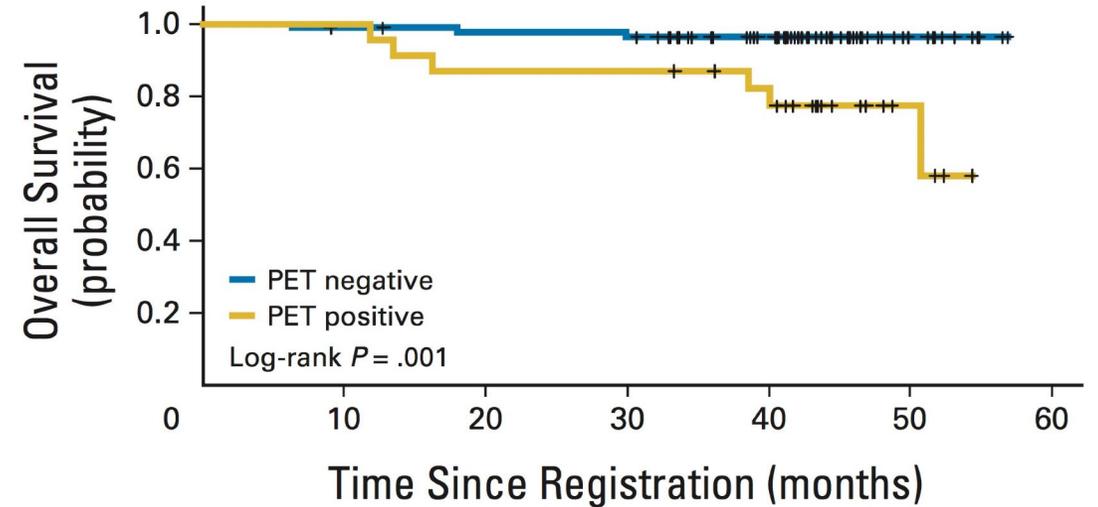
**Table 2.** Response Evaluation in Accordance With 1999 IWC and 2007 Revised Response Criteria

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

# Evaluation métabolique

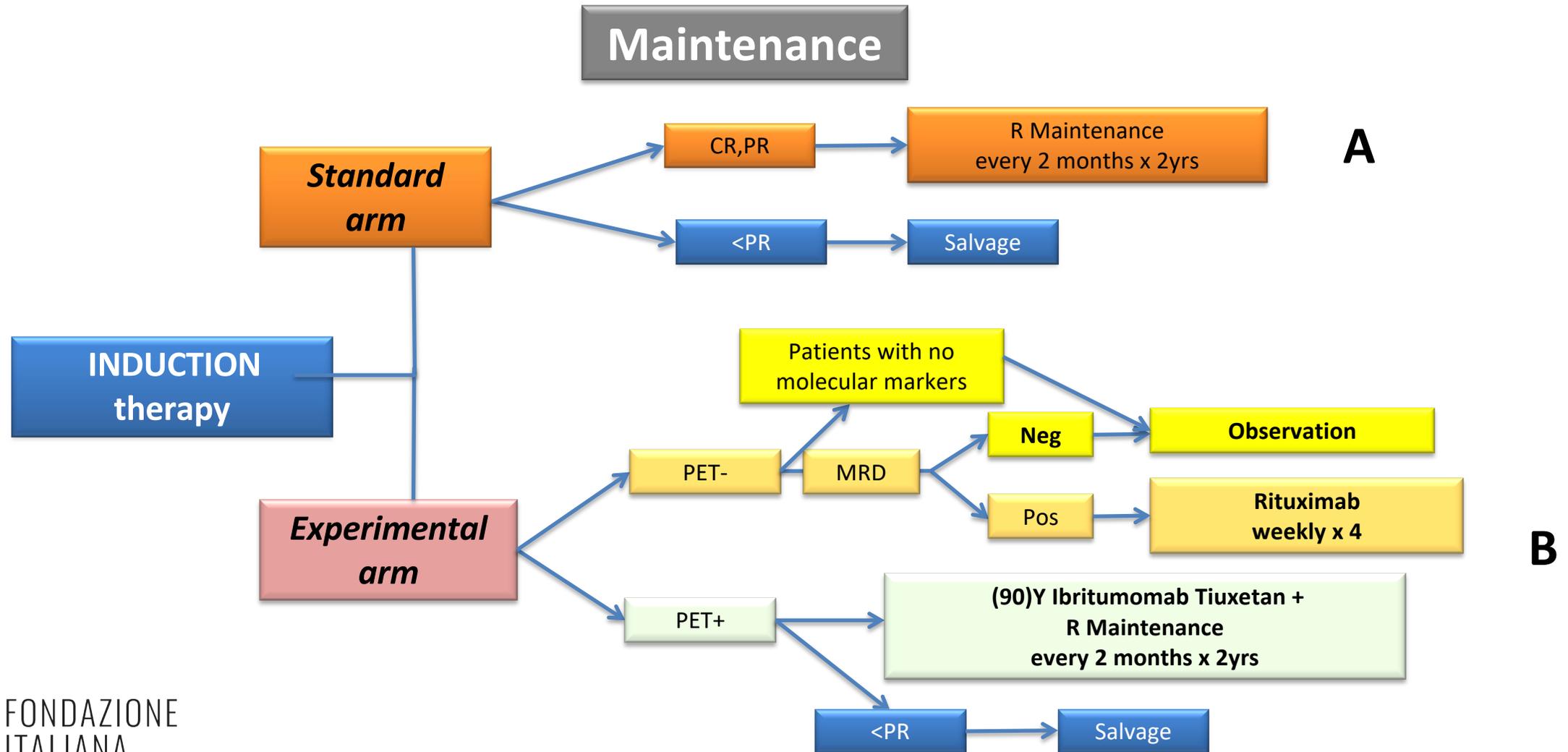


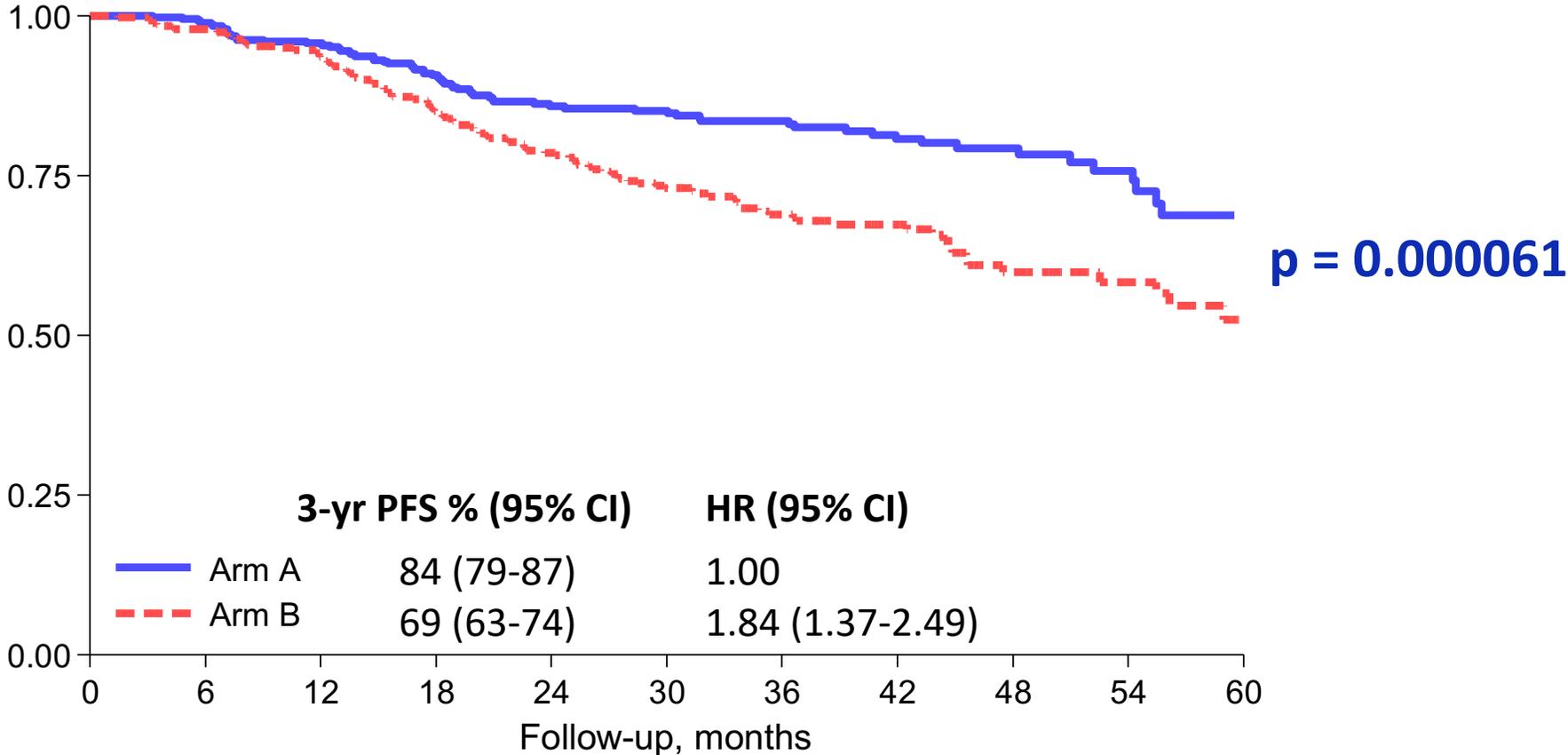
	No. of Patients	Events	Censored	Median Survival (95% CI)
PET negative	90	28 (31%)	62 (69%)	NA (51.75 to NA)
PET positive	32	21 (66%)	11 (34%)	20.45 (12.29 to 35.09)



	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)

# FOLL12 trial design response adapted maintenance therapy

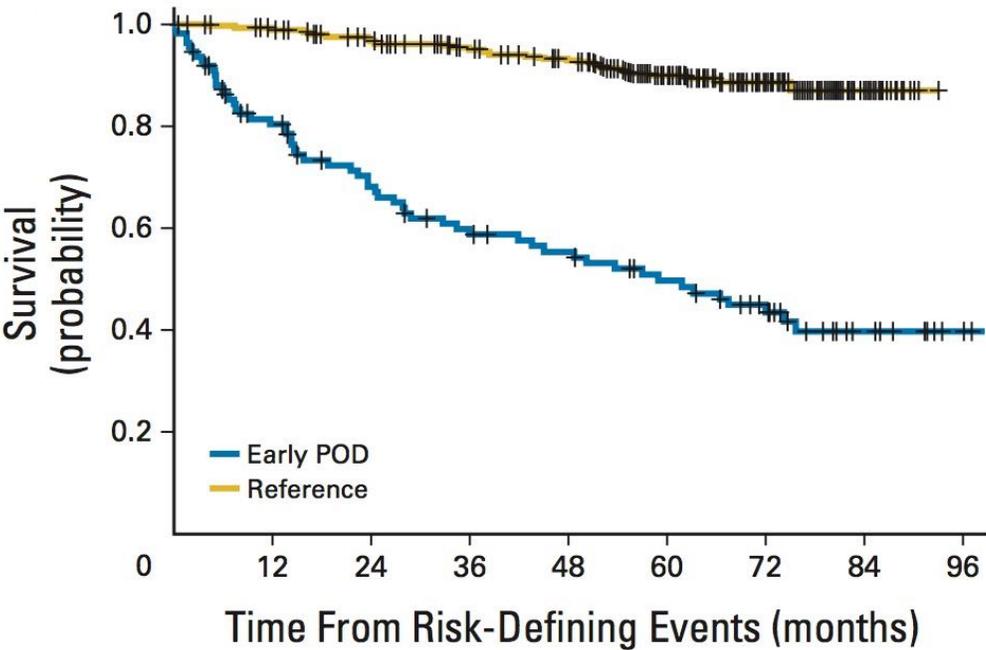




At risk

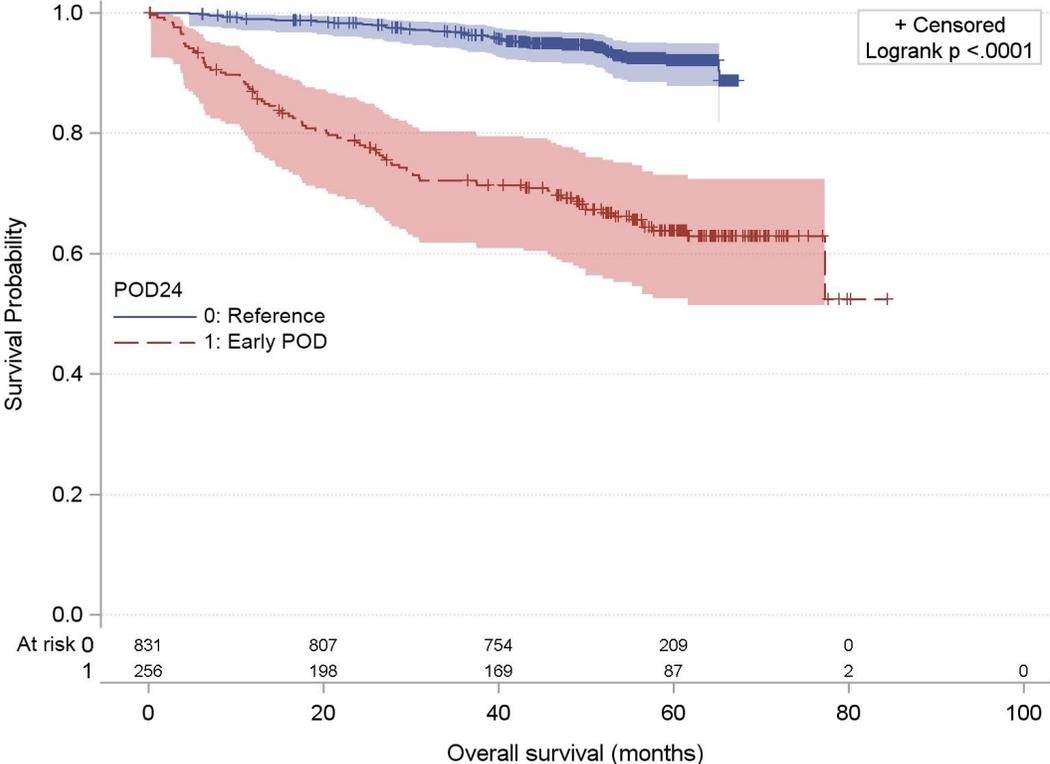
A	387	374	338	294	245	217	177	125	82	51	20
B	390	369	327	270	225	185	137	94	54	36	20

# Impact du délai à la rechute sur la survie globale



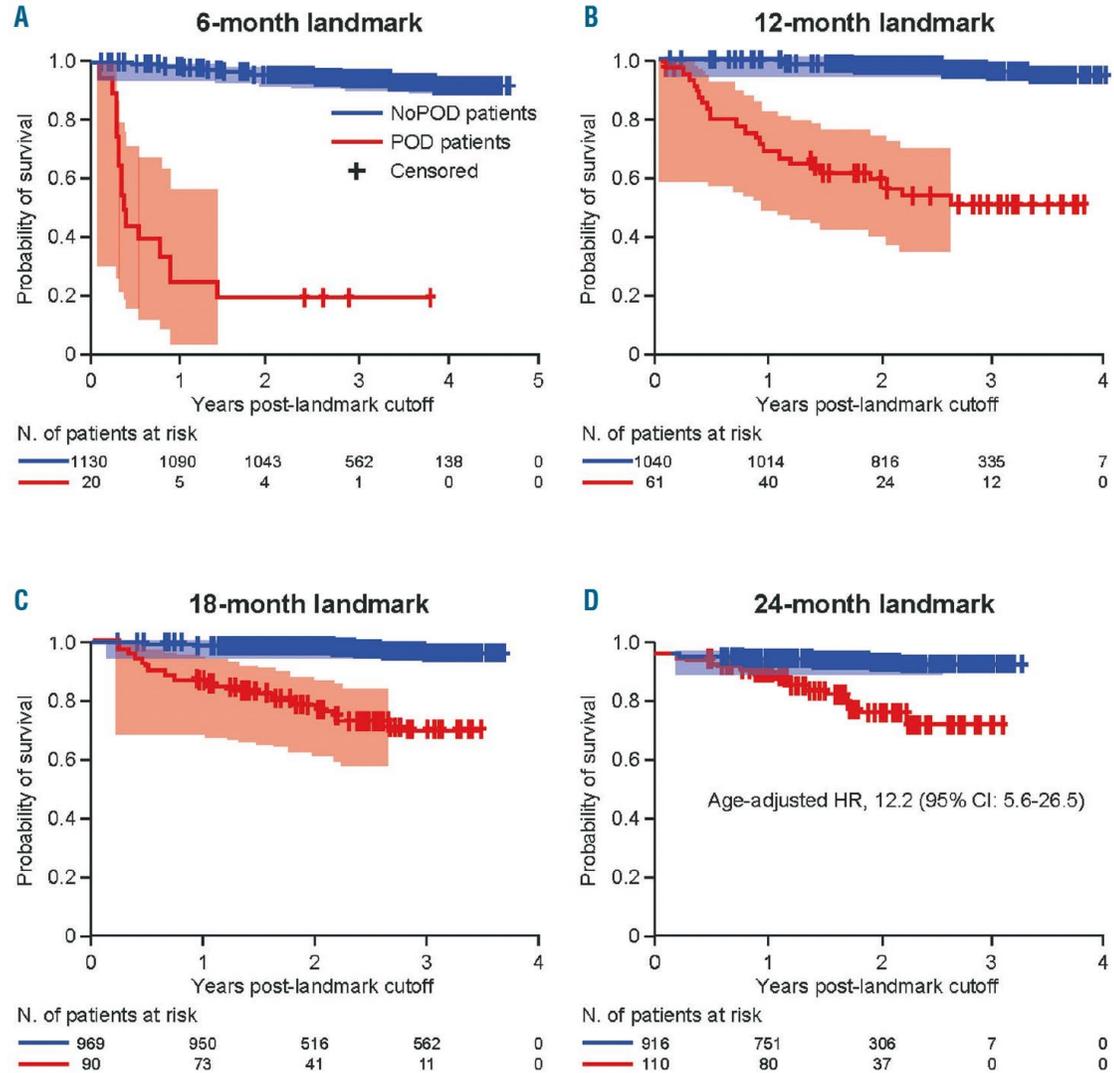
No. at risk	0	12	24	36	48	60	72	84	96
Early POD	110	82	66	56	50	42	32	14	3
Reference	420	408	387	363	344	253	145	34	0

Casulo et al., JCO 2015



Bachy et al. Blood, 2018

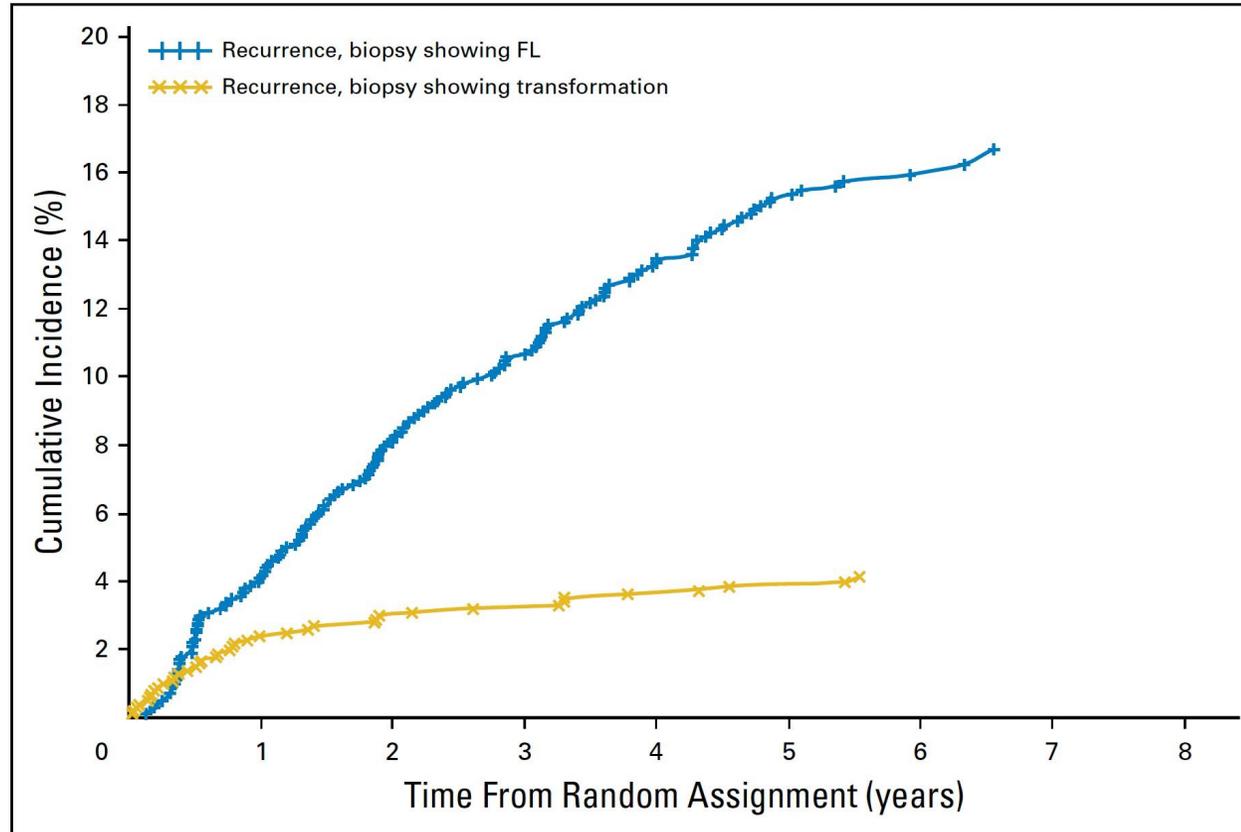
# Impact du délai à la rechute sur la survie globale



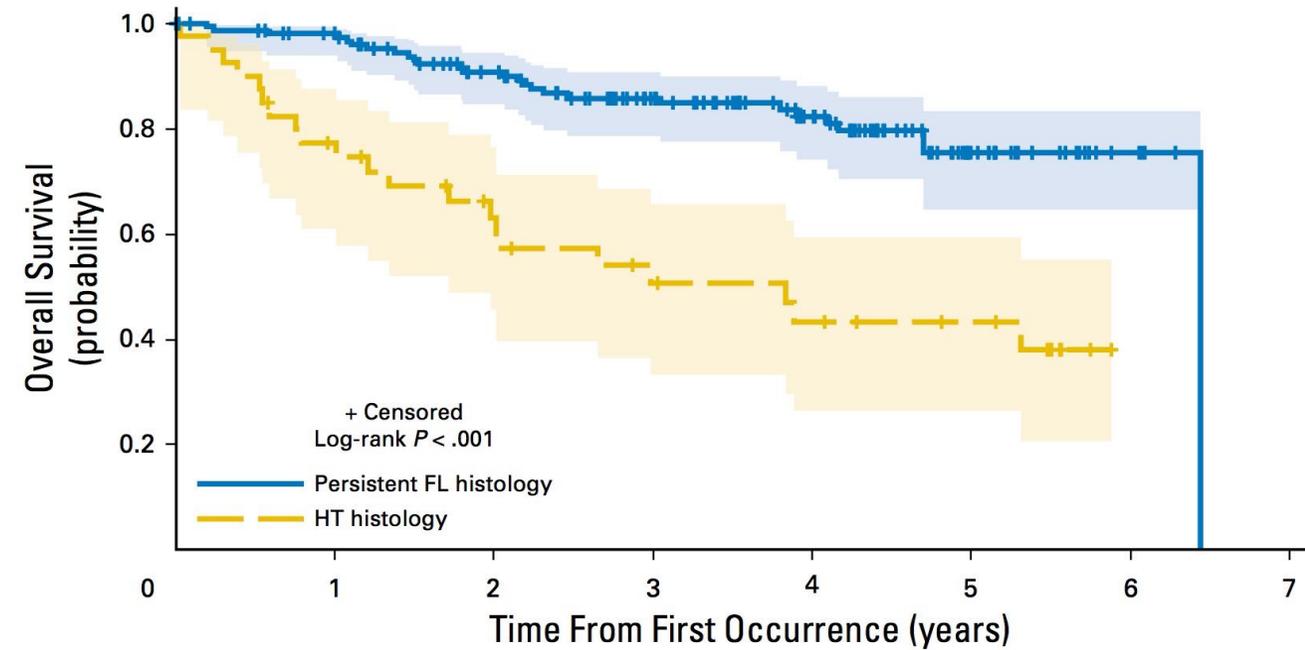
Progression précoce (cut-off)	% de la cohorte initiale	Survie globale à 2 ans	IC à 95%
6 mois	~2%	20%	2-37%
12 mois	~5%	58%	45-71%
18 mois	~8%	76%	67-86%
24 mois	~10%	82%	74-91%

# **La transformation comme événement pronostique**

# Incidence

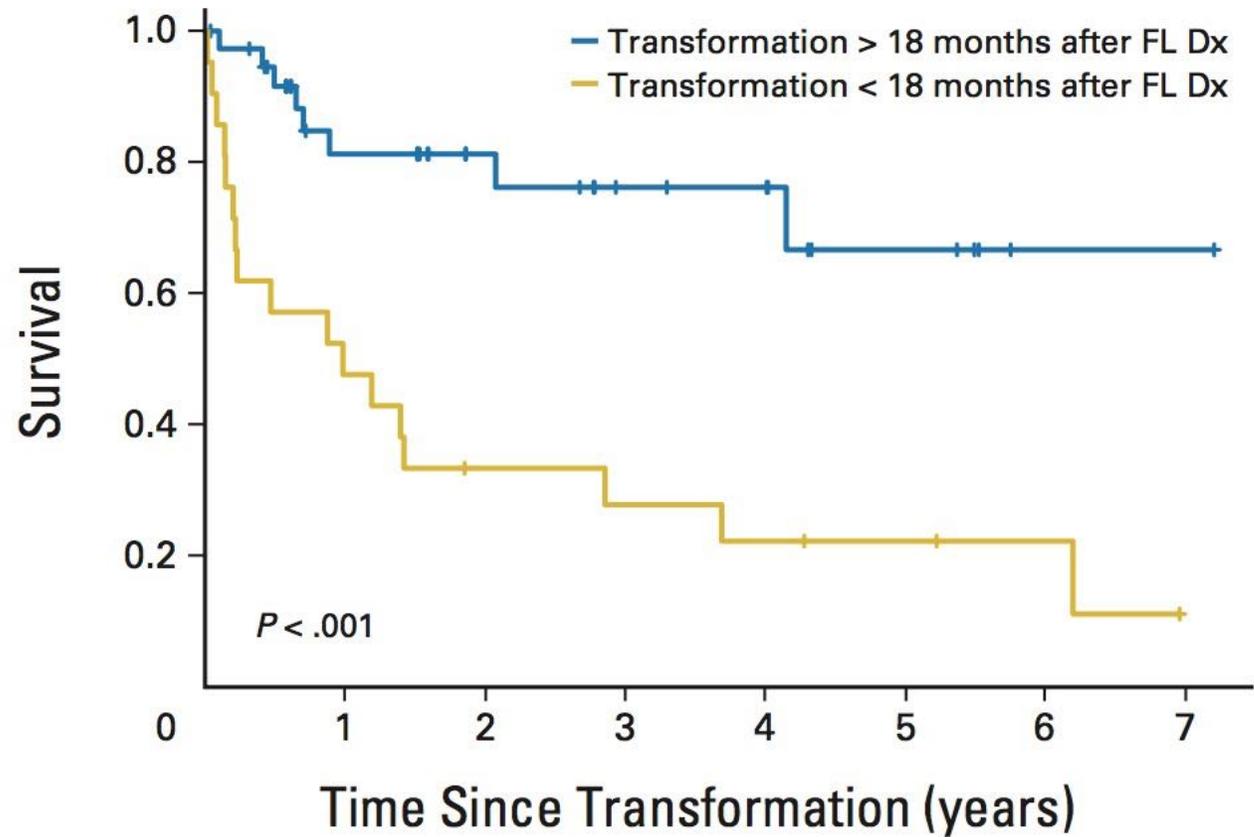


# Impact de la transformation sur la survie globale



No. at risk	0	1	2	3	4	5	6	7
Persistent FL histology	154	141	116	89	62	24	5	0
HT histology	40	29	21	15	12	9	0	

# Impact du délai à la transformation sur la survie globale

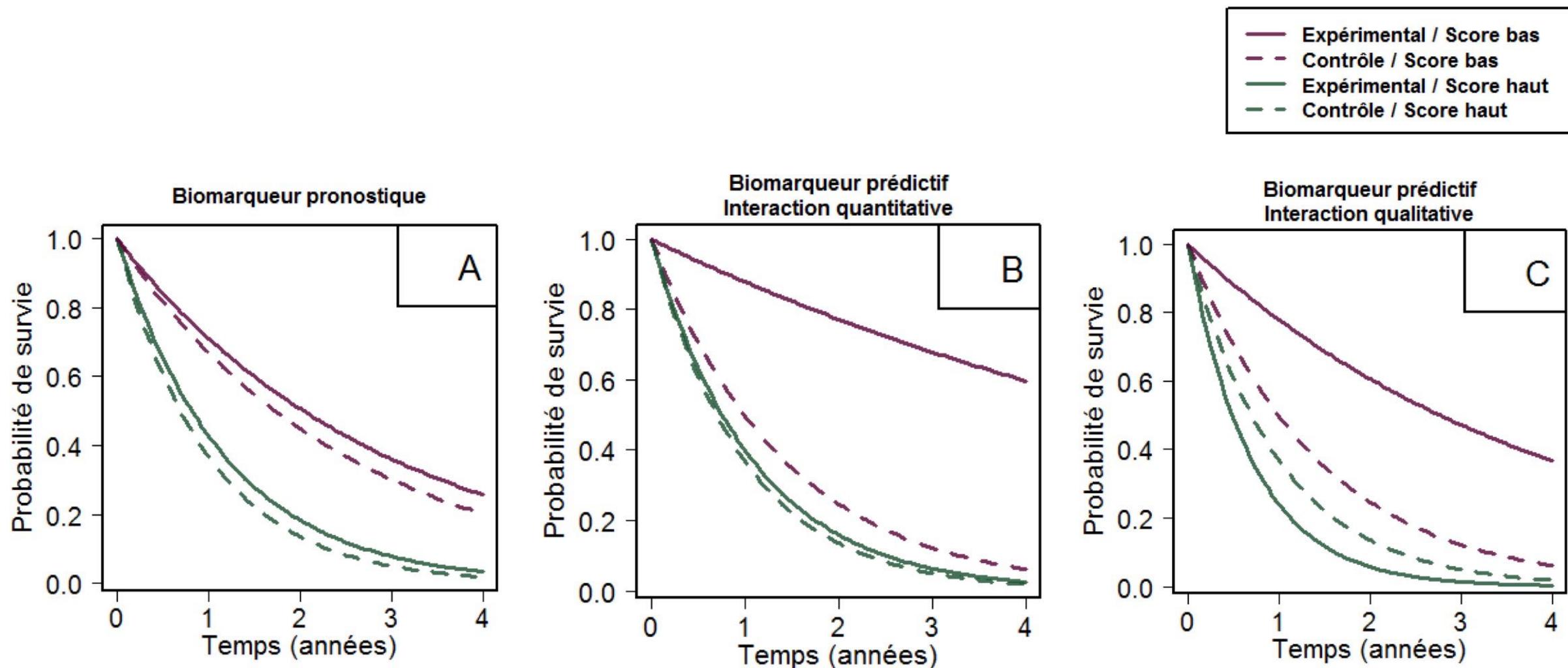


# Quels facteurs prédictifs de transformation ?

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

# **Pronostic versus prédiction**

# Difference score prognostic / score prédictif

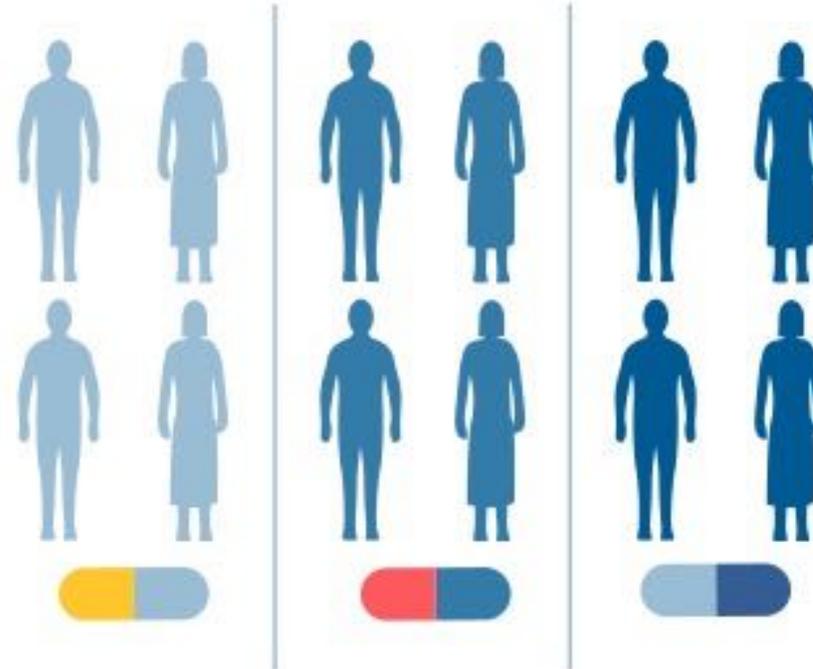


# Les facteurs dits “théranostiques”

Traditional Therapies



Precision Medicine

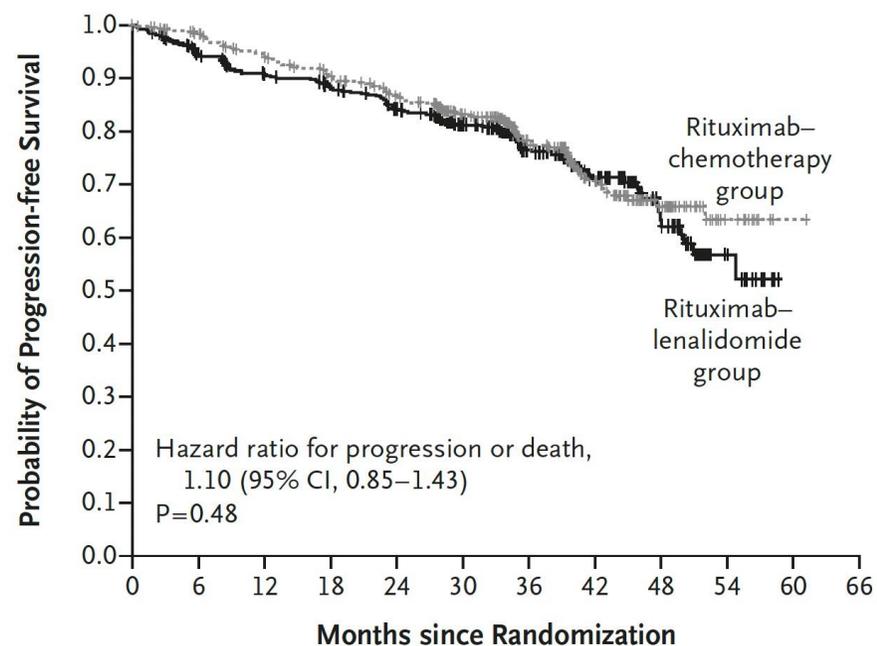


# Le GRAAL ?



# Quelques exemples : RELEVANCE

**A Progression-free Survival**



**No. at Risk**

Rituximab–lenalidomide group	513	435	409	393	364	282	174	107	49	13	0	
Rituximab–chemotherapy group	517	474	446	417	387	287	175	109	51	14	1	0

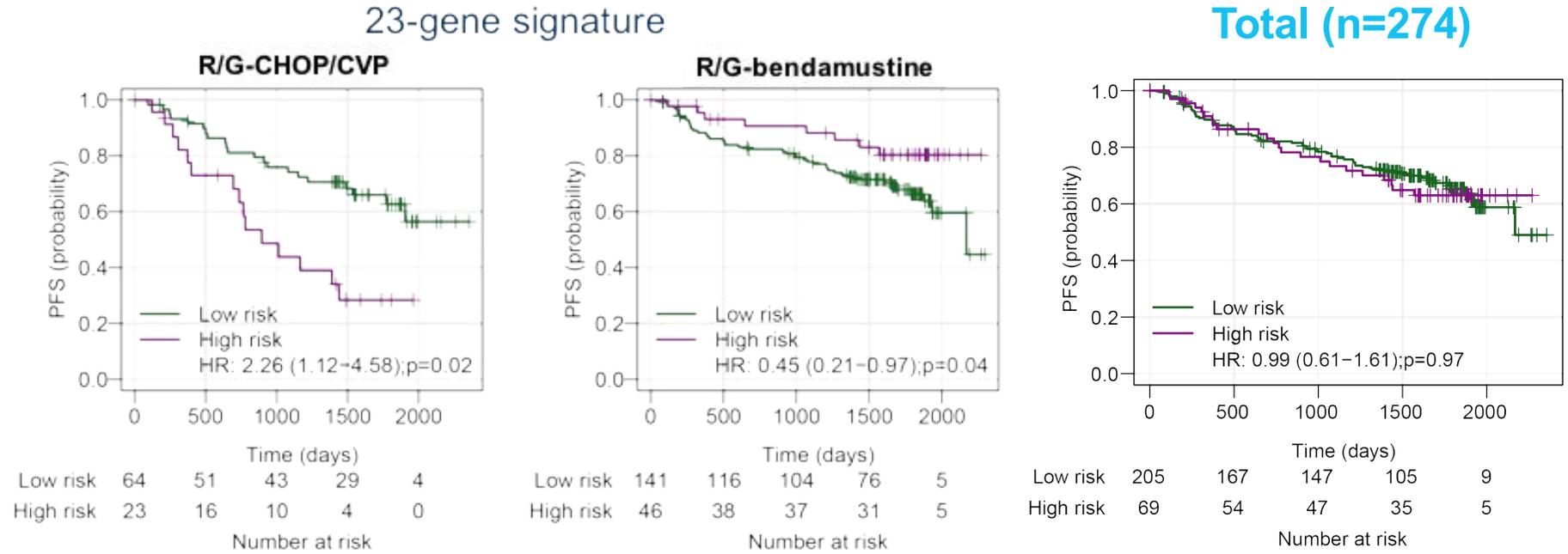
Morschhauser et al. NEJM 2018

	p (logrank)	NRI (95% CI)
<b>Total population</b>		
<b>FLIPI</b>	0.029	ref
<b>FLIPI2</b>	0.094	-0.06 (-0.266 ; 0.064)
<b>PRIMA-PI</b>	0.004	0.16 (-0.008 ; 0.318)
<b>R-chemotherapy</b>		
<b>FLIPI</b>	0.007	ref
<b>FLIPI2</b>	0.084	-0.20 (-0.207 ; 0.275)
<b>PRIMA-PI</b>	0.004	0.03 (-0.208 ; 0.275)
<b>R-lenalidomide</b>		
<b>FLIPI</b>	0.818	ref
<b>FLIPI2</b>	0.254	-0.03 (-0.037 ; 0.435)
<b>PRIMA-PI</b>	0.267	0.20 (-0.260,0.196)

Julia et al., ASH 2019

# 23-gene score

## GALLIUM study



Bolen CR, et al. ICML 2019

Blood CR Blood 2021

# Microenvironnement

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

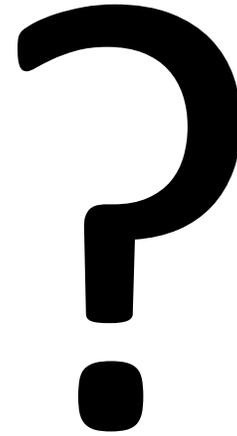
	Lee <sup>3</sup>	Glas <sup>6</sup>	Carreras <sup>11</sup>	Farinha <sup>8</sup>	Alvaro <sup>10</sup>	Klapper <sup>12</sup>	Taskinen <sup>13</sup>		Wahlin <sup>14</sup>	EORTC 20921	
							R-CHOP	CHOP		FLUDA	CVP
Interfollicular component	nd	-	nd	-	nd	-	nd		nd	-	-
CD3 dense infiltrate	nd	-	-	-	-	-	-	-	nd	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 <sup>a</sup>	Good	nd	nd		nd	Poor	Good
FoxP3 sparse infiltrate	Poor	-	Poor	Good <sup>a</sup>	Poor	nd	nd		nd	Good	Poor
FoxP3 pattern interfollicular	Good <sup>b</sup>	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 <sup>c</sup>	Poor <sup>c</sup>	nd	Poor	Good
CD68 sparse infiltrate	-	-	nd	Good	Poor	-	Poor <sup>c</sup>	Good <sup>c</sup>	nd	Good	Poor
CD68 pattern interfollicular	-	nd	nd	nd	nd	nd	nd	nd	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

exemple



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

Valeur heuristique avant tout

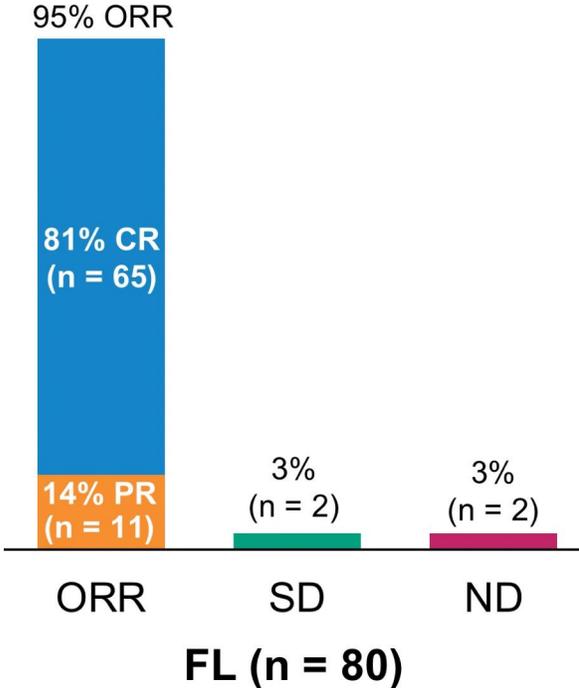
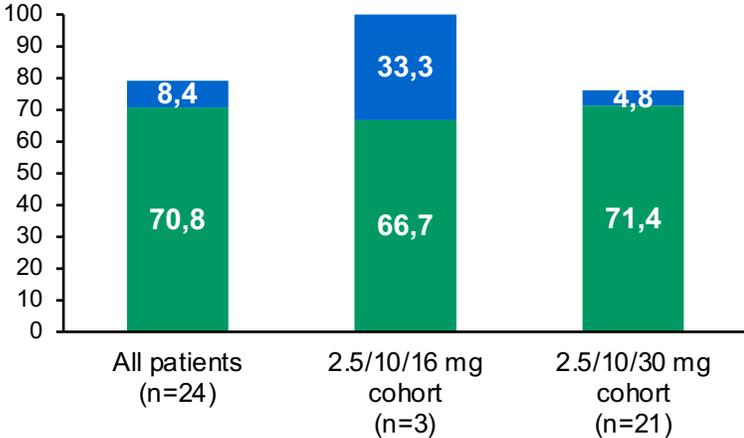


# 1<sup>er</sup> objectif des scores : « comparer » des essais cliniques

Glofitamab

Axicabtagene

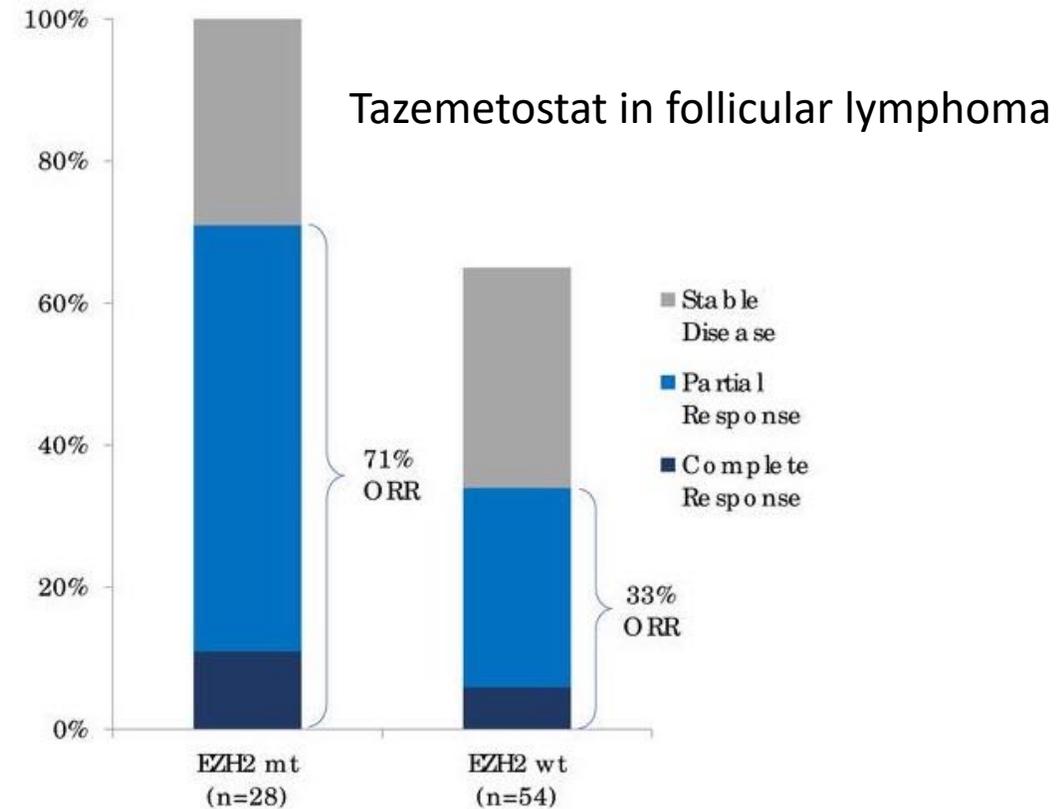
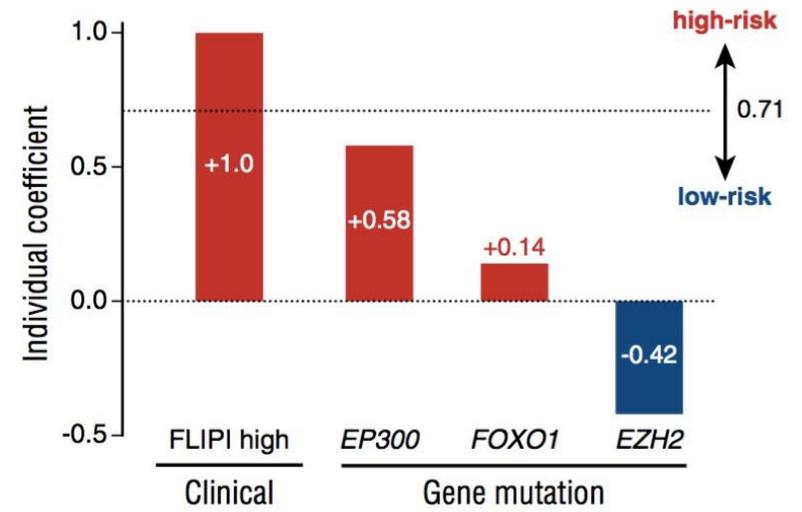
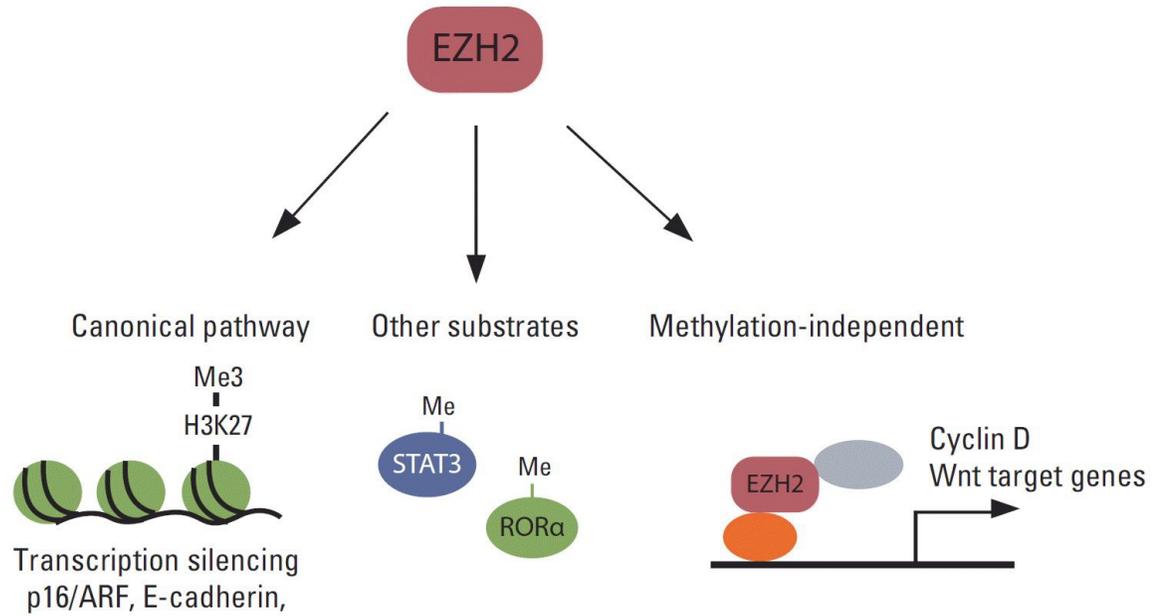
Indolent NHL



Carlo-Stella et al, Lugano 2021

Jacobson et al, EHA 2020

# 1<sup>er</sup> paramètre thérapeutique dans le LF ?



# Les questions :

## 1. A quoi sert un facteur pronostique ou un score pronostique ?

- N'est pas un paramètre décisionnel dans le lymphome folliculaire
- Est peu utile dans la pratique courante pour le LF
- Sert essentiellement à la comparaison des essais cliniques
- Est pourvoyeur d'une compréhension de la pathologie

## 2. En quoi le lymphome folliculaire se prête-t-il particulièrement à la détermination de scores pronostiques ?

- L'évolution de la maladie est très longue (intérêt des variables post-traitement)
- Cette évolution est extrêmement disparate

## 3. Quelles sont les limites des scores pronostiques ?

- A nb de patients suffisant tous les facteurs pronostiques usuels sont significatifs
- Un score doit être parcimonieux, robuste, reproductible

## 4. Quel est l'apport des scores pronostiques ?

- EZH2 montre l'utilité de ces allers-retours entre pronostic et thérapeutique