Journée SFPO

Les lymphomes
Avancées cliniques

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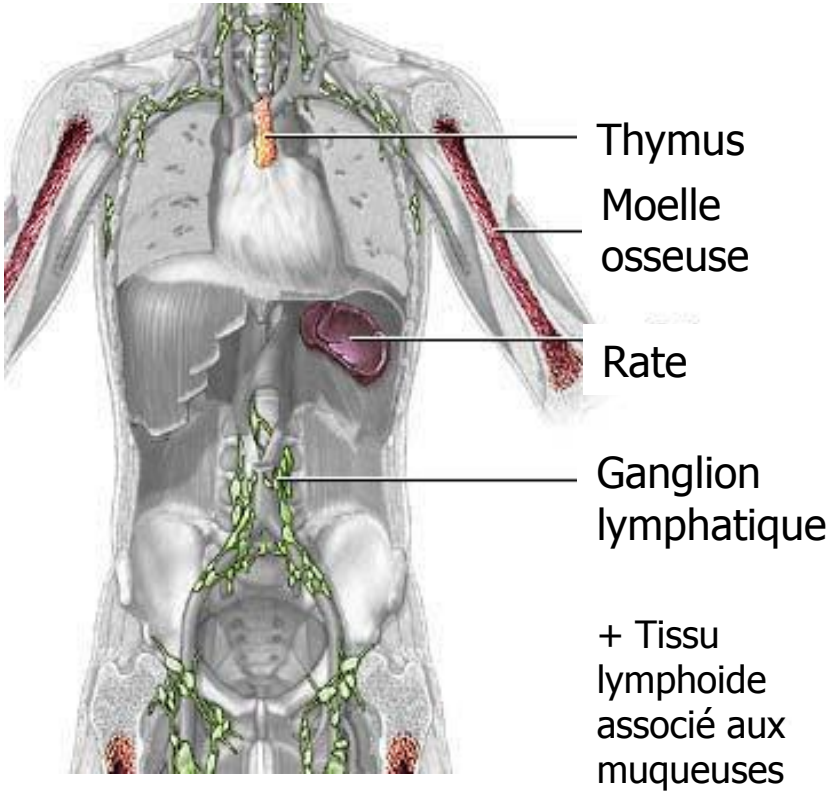
Hôpital Saint-Louis

11 octobre 2012

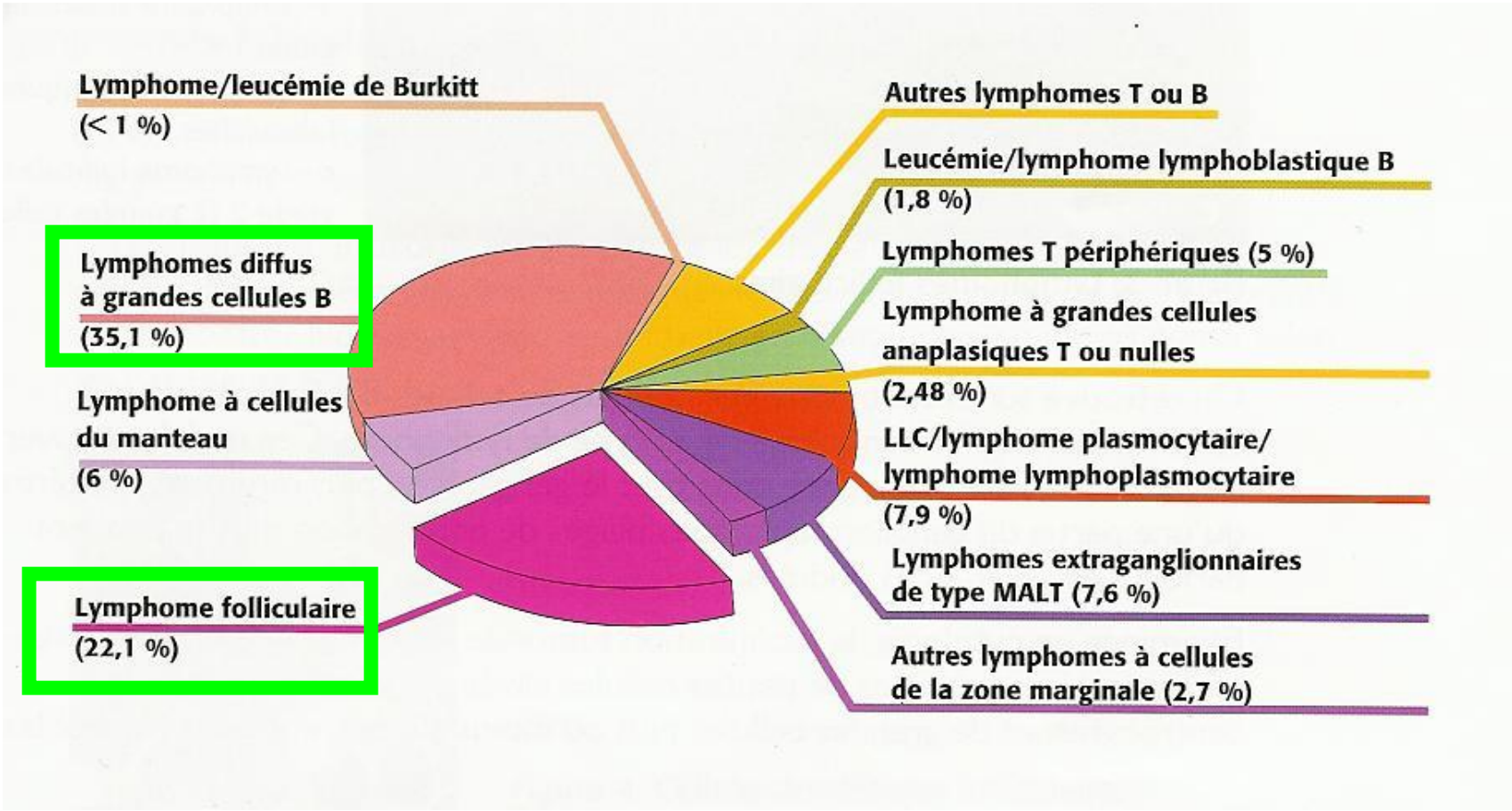
LES LYMPHOMES

Lymphomes non Hodgkinien (LNH) / Lymphomes de Hodgkin (LH)

Prolifération maligne monoclonale de cellules lymphoïdes (ganglions ++ ou organes avec tissu lymphoïde)



De nombreuses entités de lymphomes



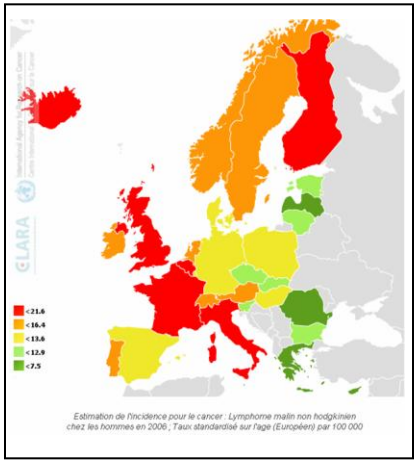
Epidémiologie

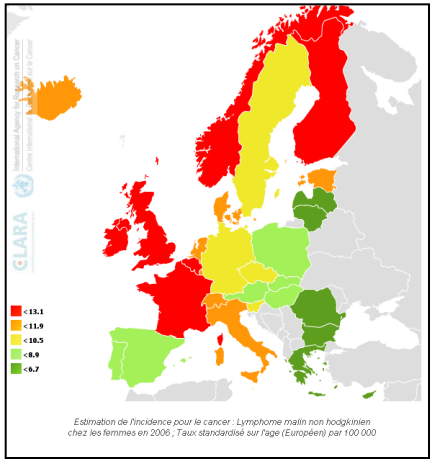
- **Incidence** *(données françaises 2005 – Réseau Francim)* :

  # **12 000 nouveaux cas annuels** (10/100 000 PA)

  – **10 224 cas LNH (6ème cancer le plus fréquent) + 1 544 cas LH**

♂





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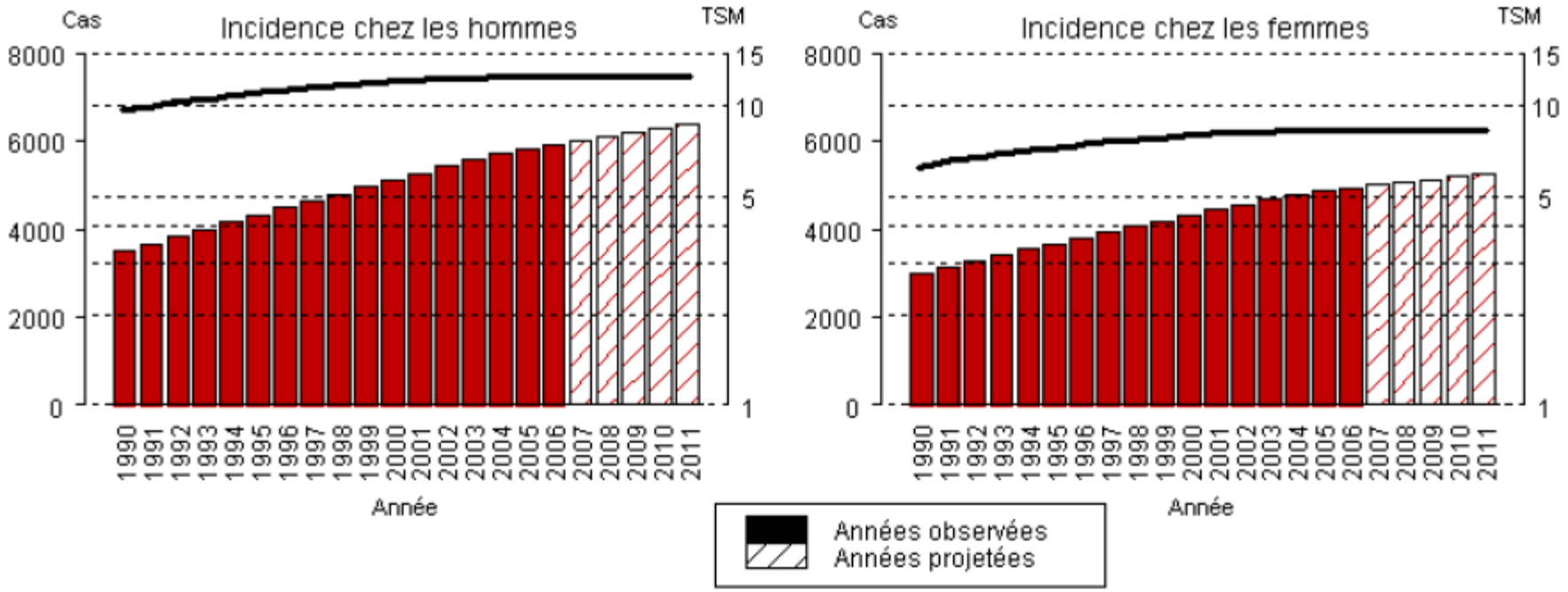
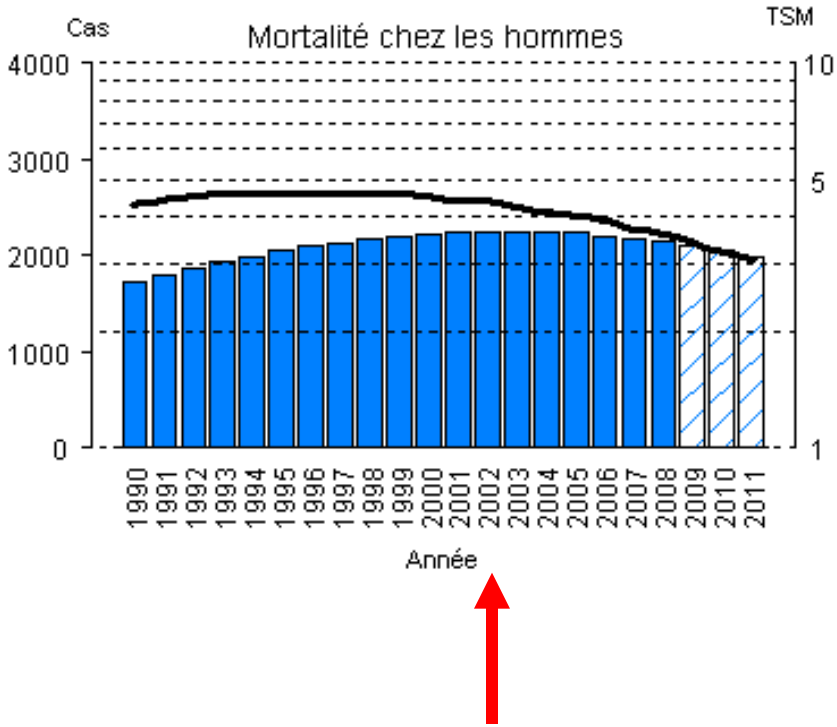
INCIDENCE

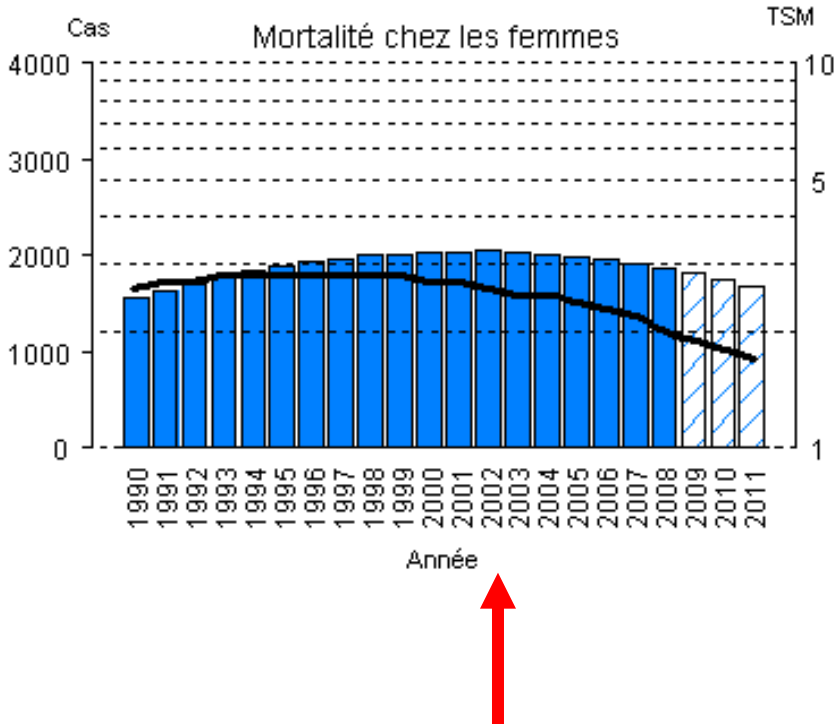


Réseau Français des Registres de Cancer

FRANCIM

MORTALITE





Réseau Français des Registres de Cancer
FRANCIM

2 avancées majeures

- **Connaissance biologique : séquençage du génome humain (Fev 2001)**

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- **RITUXIMAB (FDA 1997)**

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Gela

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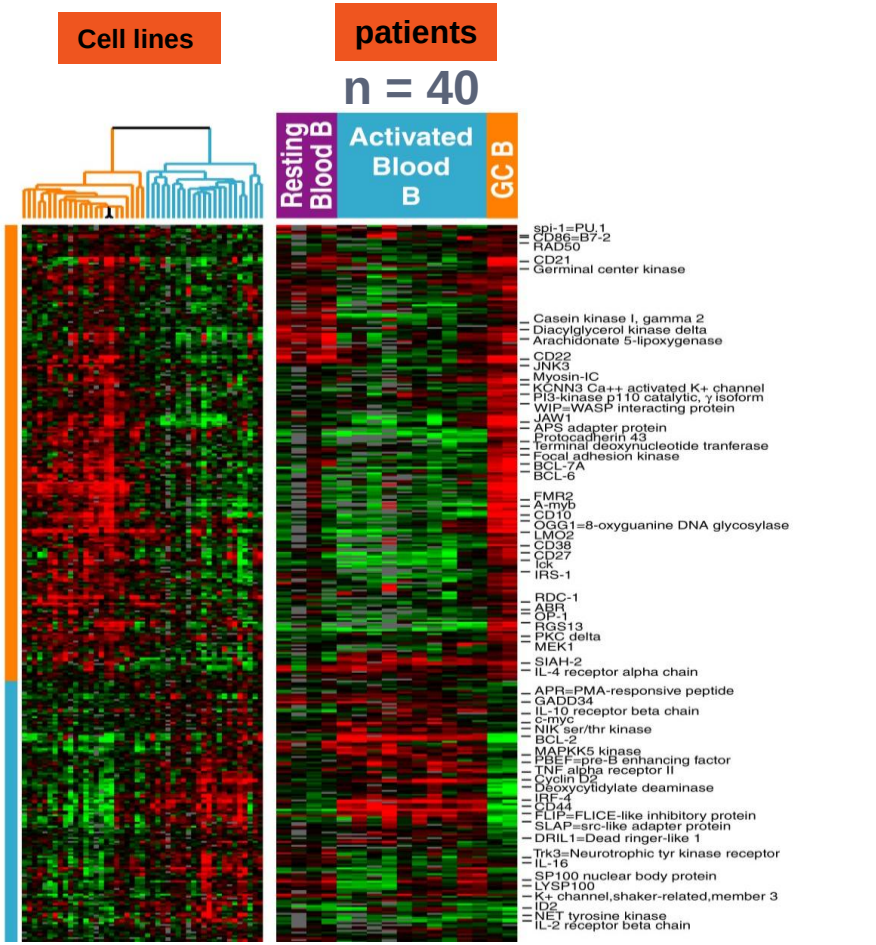
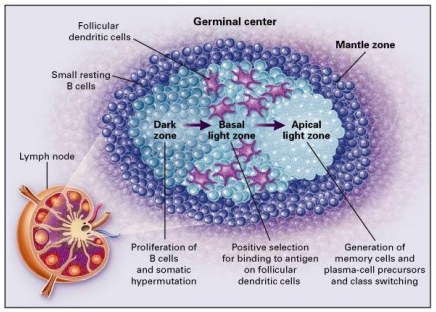
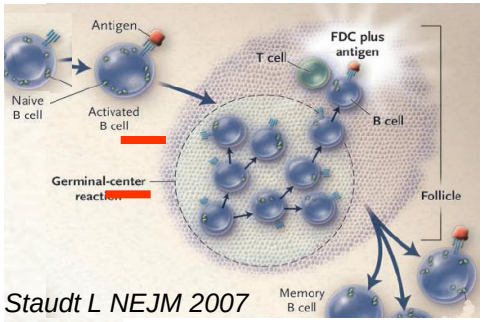
Gela

"Cell of Origin" model for DLBCL







Staudt L NEJM 2007

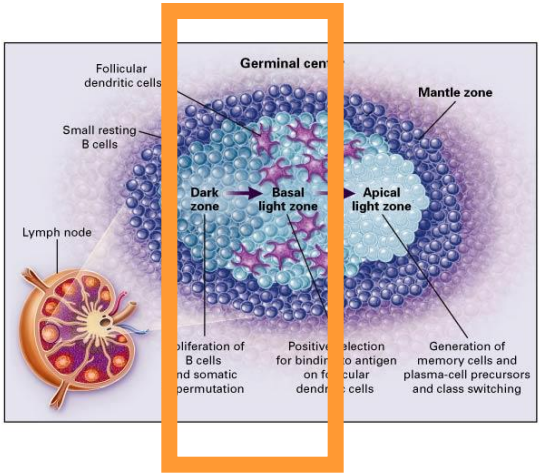
Molecular Profil

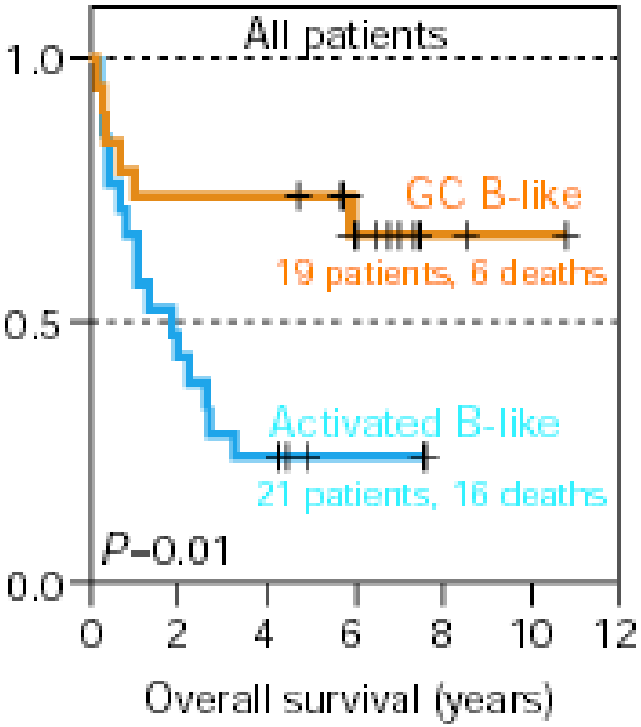
Germinal center B-cell

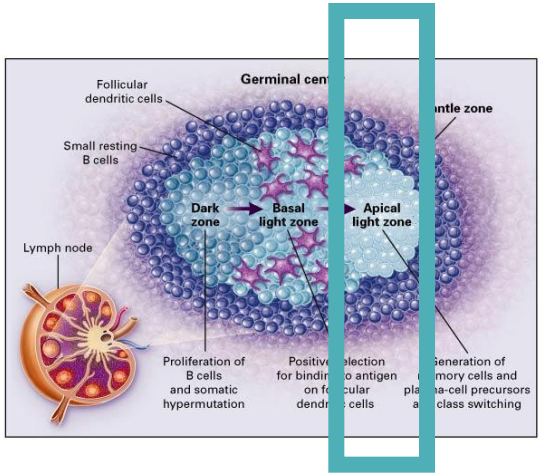
Non-germinal center B-cell = activated B-cell

Alizadeh et al. *Nature* 2000; 403:503

Power of GCB/ABC Classification





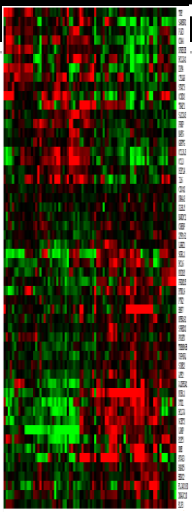


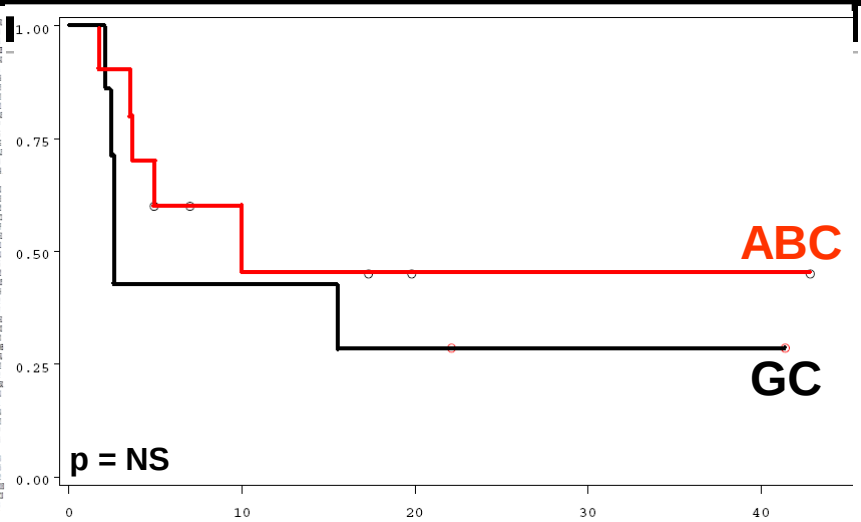
Alizadeh et al. *Nature* 2000; 403:503

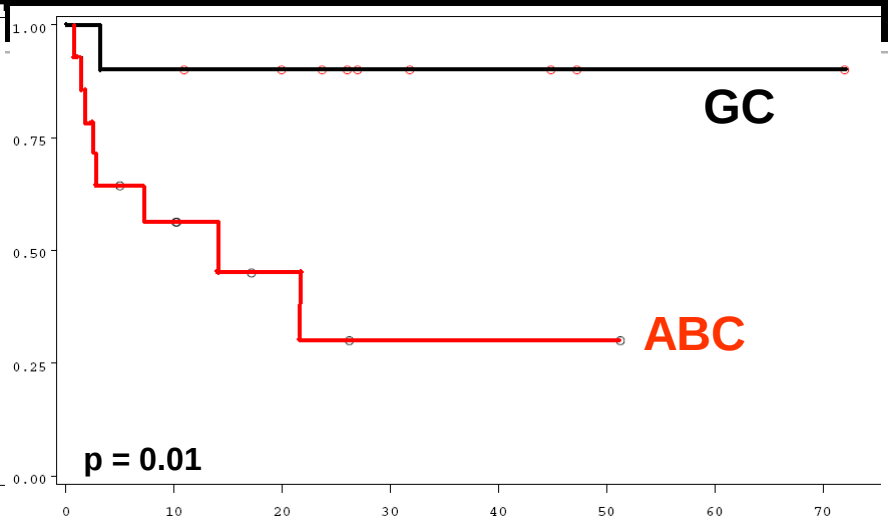
R-ICE

R-DHAP

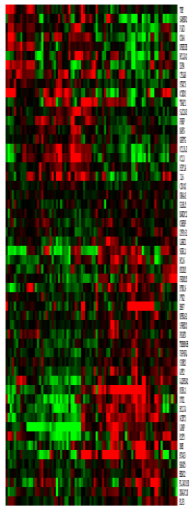
Progression Free Survival

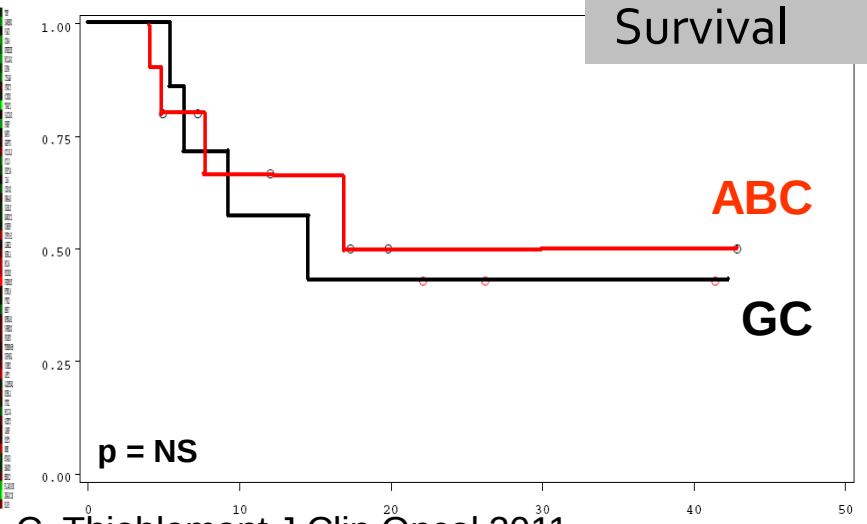


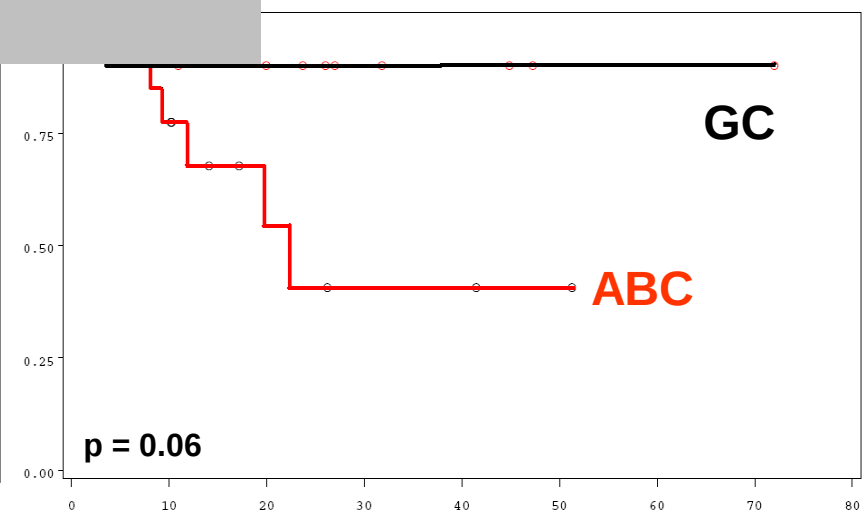




Overall Survival







C. Thieblemont J Clin Oncol 2011

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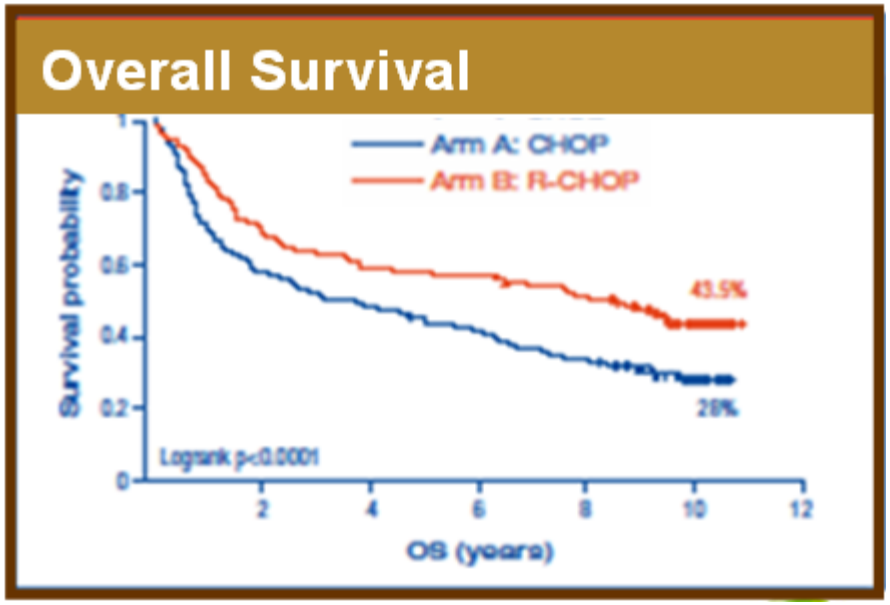
Gela

L’apport des AC monoclonaux

Lymphomes diffus à grandes cellules B

RITUXIMAB

AC anti-CD20



Coiffier B et al. 2011

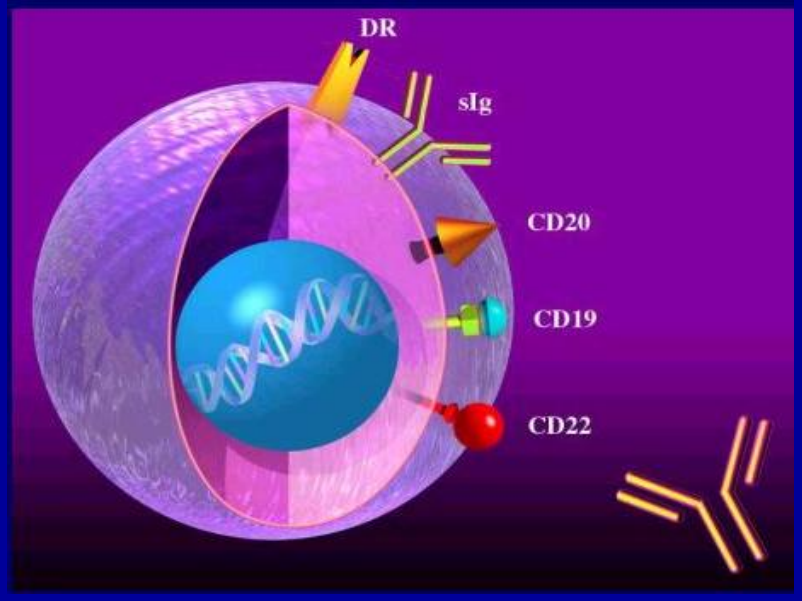
Gela

Le traitement des lymphomes : une combinaison de molécules

Traitement ciblé

Anticorps monoclonal

Exemple : rituximab = anti-CD20



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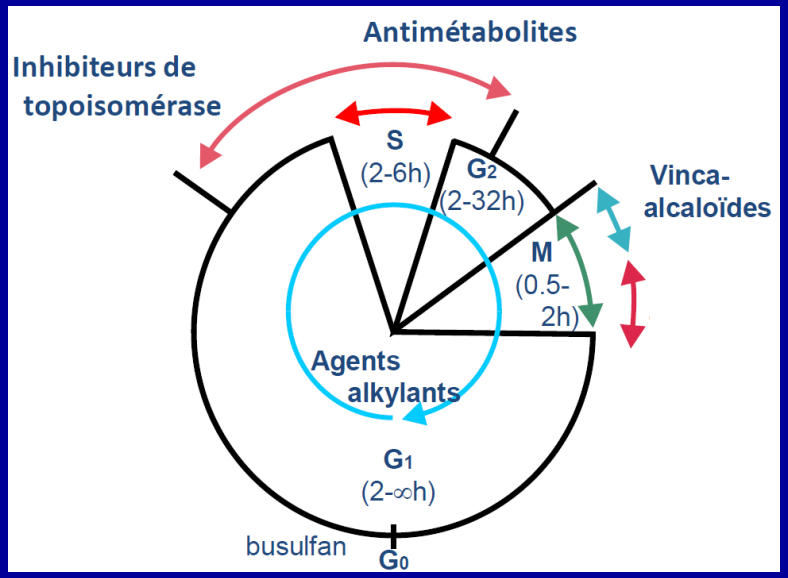
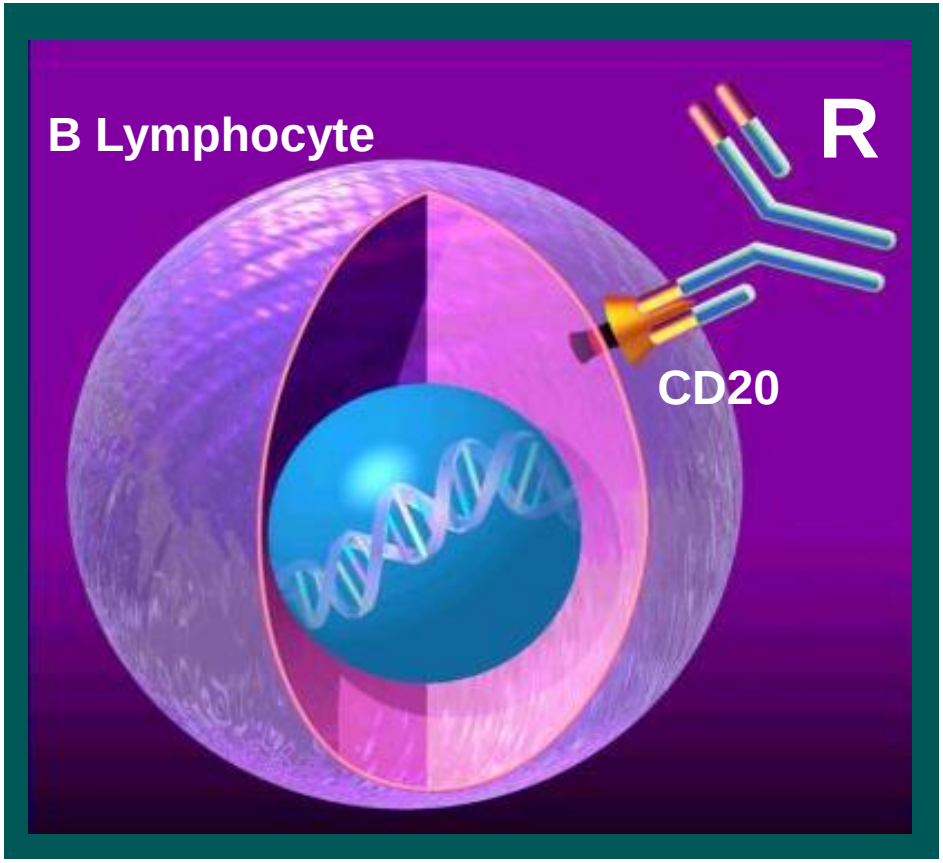
Chimiothérapie

Agents cytotoxiques -> Cycle Cellulaire



Rituximab

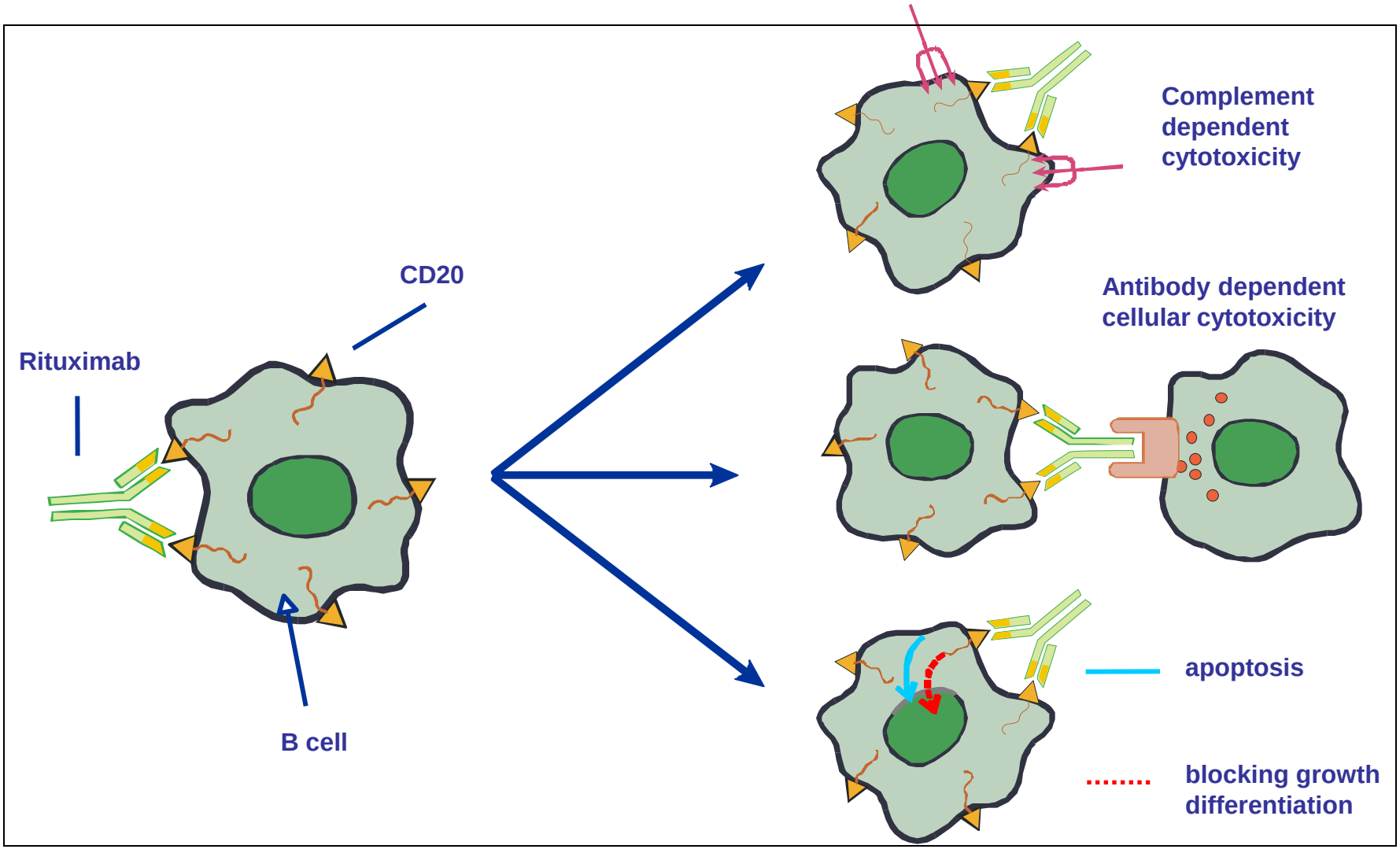


- **Cible: CD20 – B lymphocyte**
- **B-cell lymphoma**
- **Chronic lymphocytic lymphoma**
- **First approved by FDA -november 97**
- **The only one to have demonstrated efficacy in phase III trial**

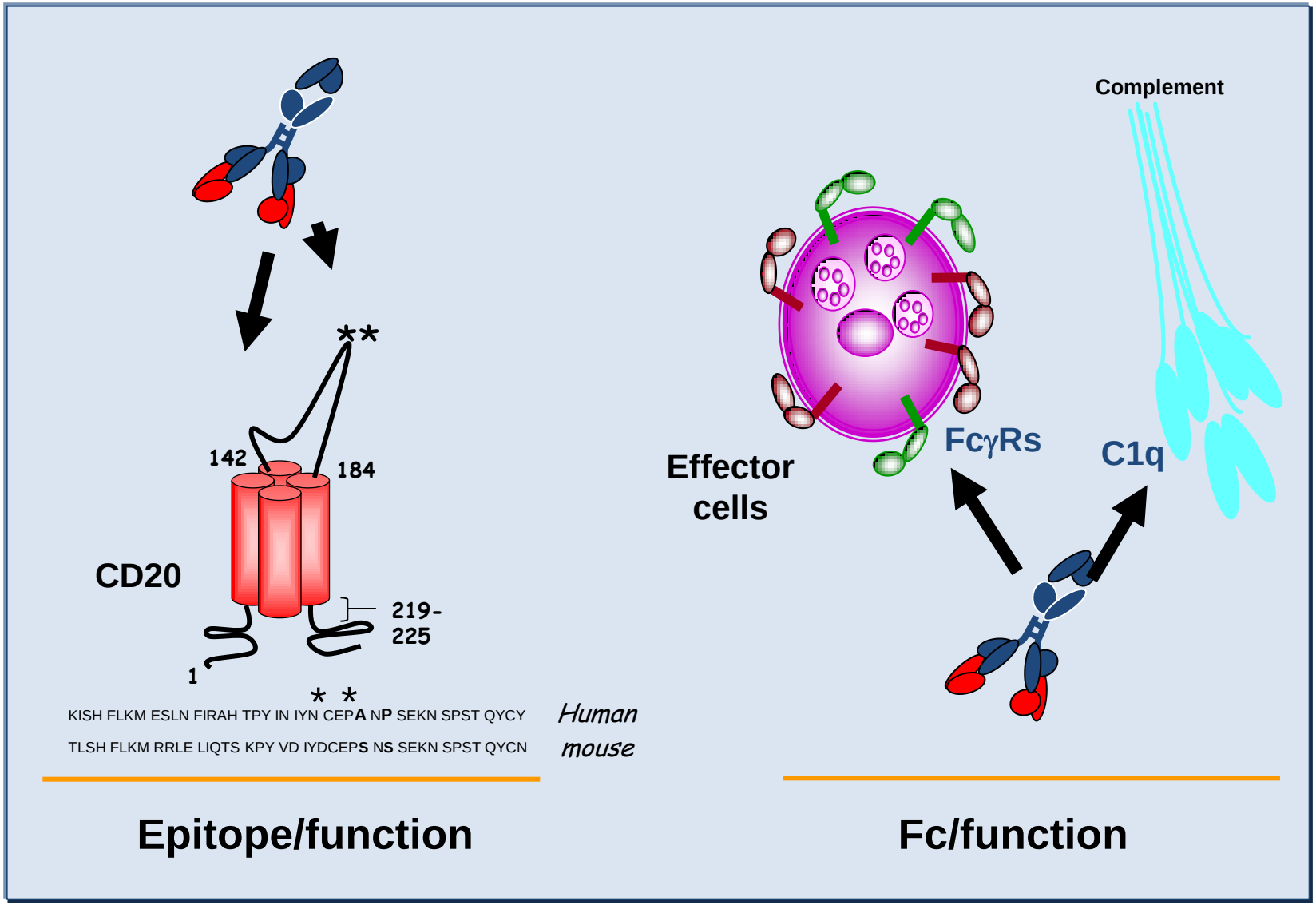
CD20 : a transmembrane calcium channel

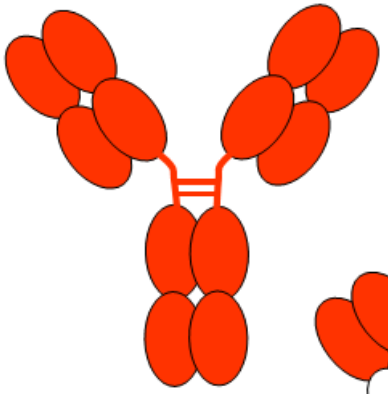
Role in B-cell activation, proliferation , differenciation

Mécanisme d'action des anticorps monoclonaux : Rituximab

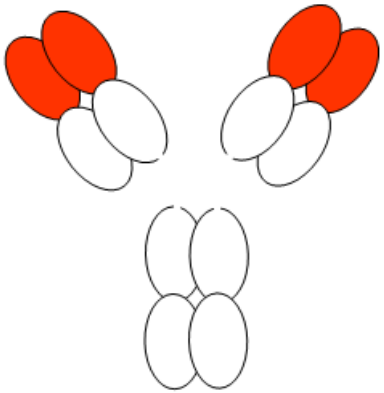


Ways to new antibodies
The anti-CD20 AB

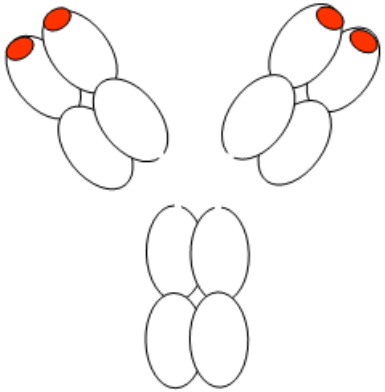




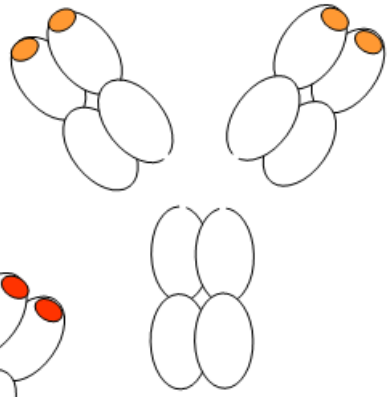
Murin AB
1975
…momab



Chimeric AB
1984
…ximab



Humanized AB
1988-1991
…zumab



Human AB
1994-1999
…mumab

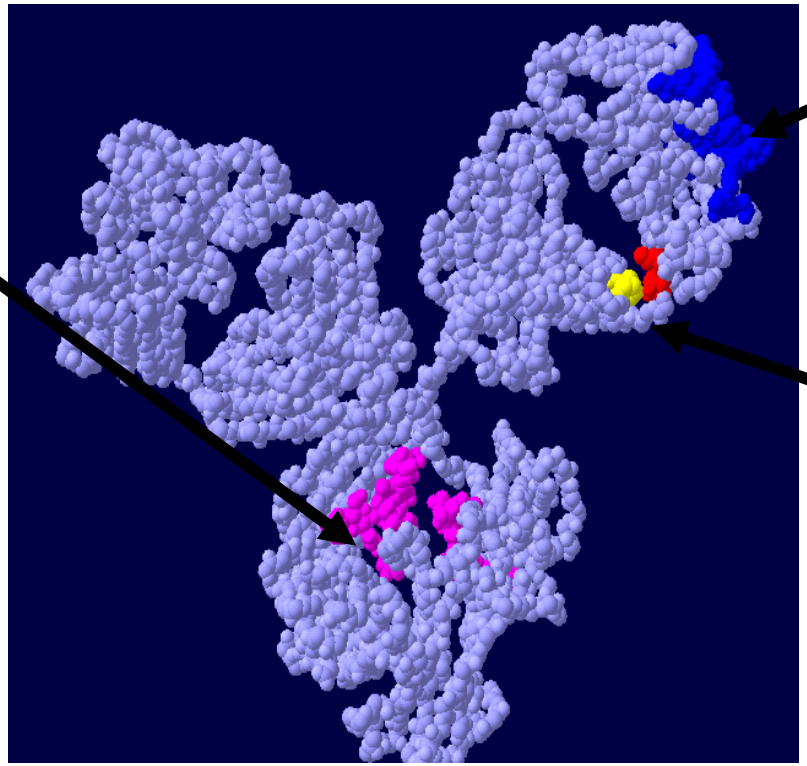
CD20- antibodies

	Rituximab	Veltuzumab	Ofatumumab	AME-133	GA101
Ab type	Chimeric	Humanised	Human	Humanised and Fc-engineered	Humanised and glyco-engineered
Development status	Launched	Phase II	Phase II/III	Phase I	Phase I/II/III
Epitope	Type I	Type I	Type I	Type I	Type II

First monoclonal AB approved by FDA in november 1997

The only AB that has proved an efficacy in phase III trial

GA-101: A glycoengineered anti-CD20 antibody



Type II epitope

CDC: 0

Low fucose content

↑ ADCC

Elbow hinge substitution

↑ Apoptose

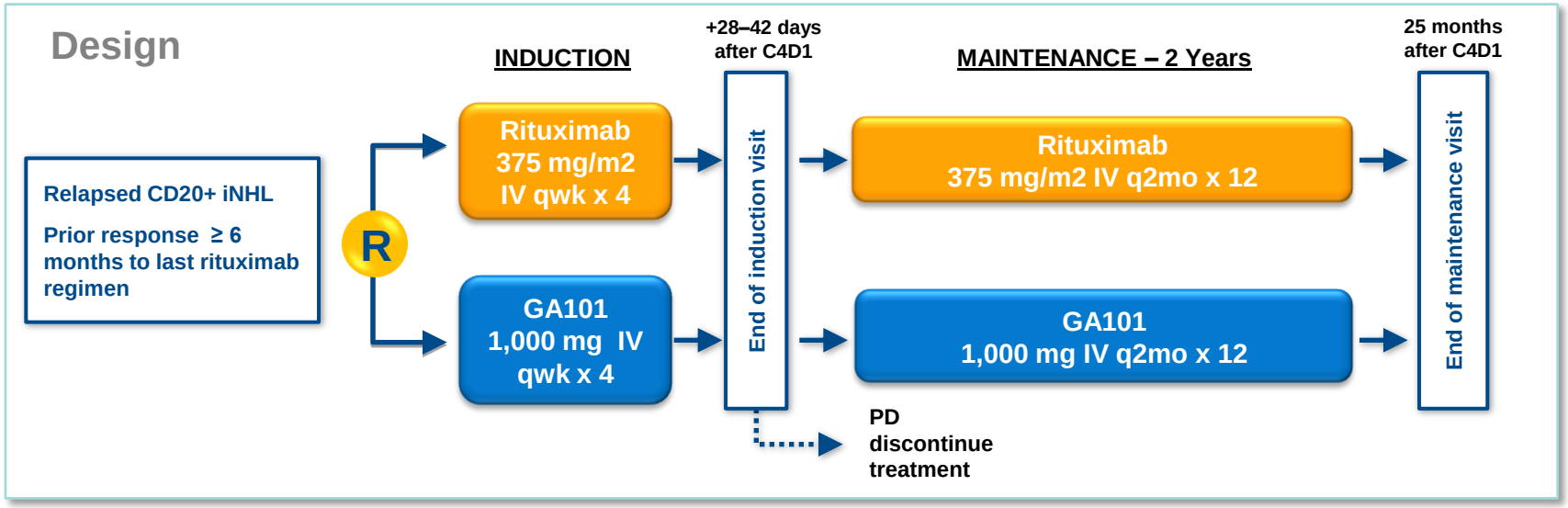
(Non-caspase dependent cell death)

Clone B-Ly1

Umaña P, *et al. Ann Oncol* 2008; 19:Abstract 098.
Umaña P, *et al. Blood* 2006; 108:Abstract 229.

1ère étude randomisée
GA101 (Obinutuzumab vs Rituximab
Etude GAUSS (BO21003)

- 175 LNH indolents en rechute et non réfractaires au Rituximab
  - → 149 LNH folliculaires (LF)
  - → 26 LNH non folliculaires



- Objectif primaire : réponse dans les LNH folliculaires évaluée en fin de ttt d'induction

L. Sehn *et al.*, ASH 2011; Abs. 269

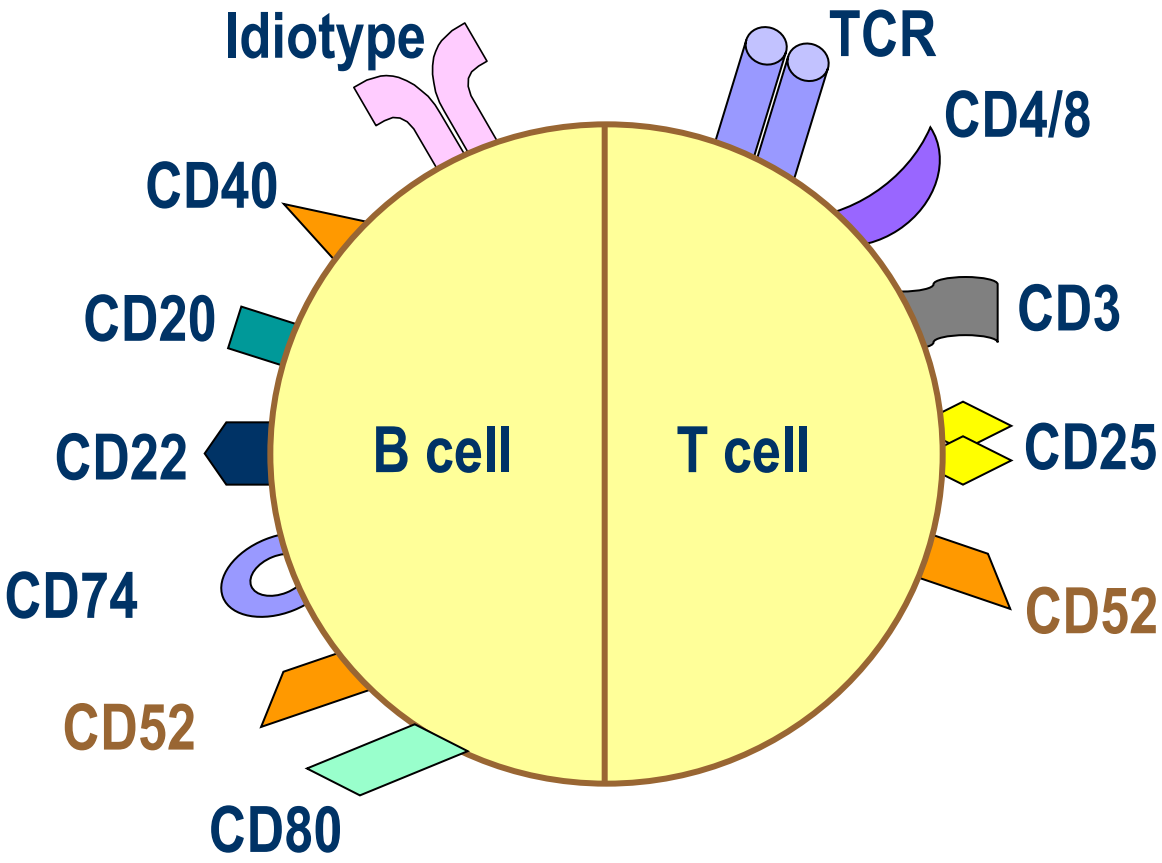
1ère étude randomisée
GA101 (Obinutuzumab vs Rituximab
Etude GAUSS (BO21003)

- 99% des patients avaient reçu du Rituximab

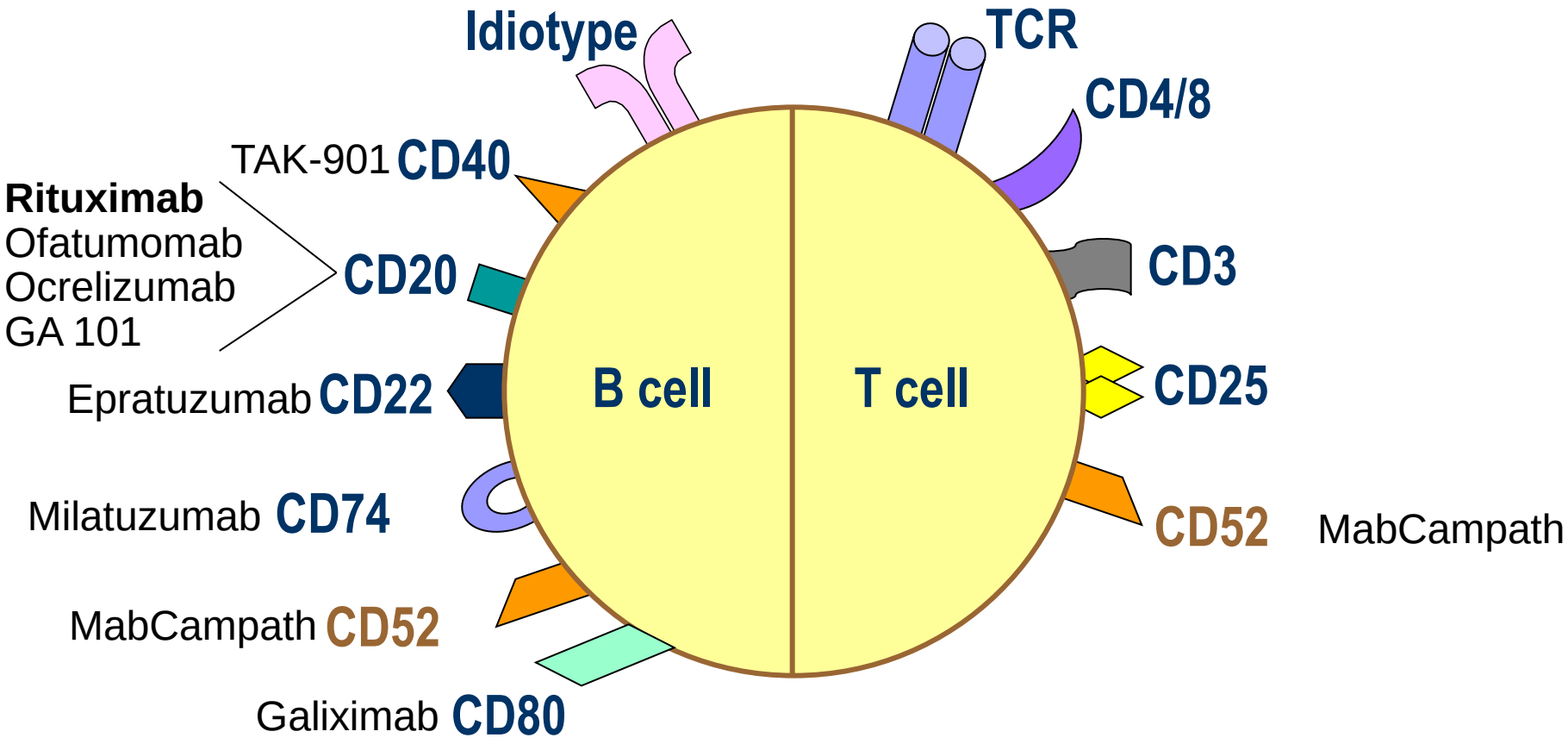
	GA101	RITUXIMAB	p
Réponses LNH folliculaires - Réponse globale (RG) - Rémissions complètes/Rcu	N=74 33 (44.6%) 9 (12.2%)	N=75 25 (33.3%) 4 (5.3%)	 p=0.01 p=0.04
Réponses (tous les types histo) : - Réponse globale	N=88 37/88 (42%)	N=87 21/87 (24.1%)	

L. Sehn *et al.*, ASH 2011; Abs. 269

Anticorps monoclonaux



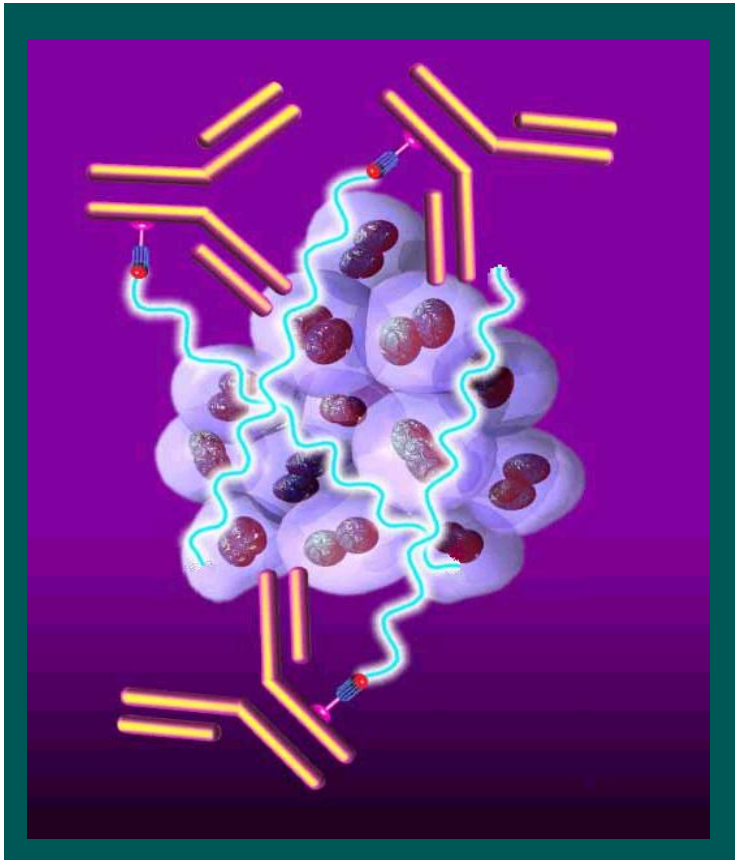
Anticorps monoclonaux



Monoclonal antibodies

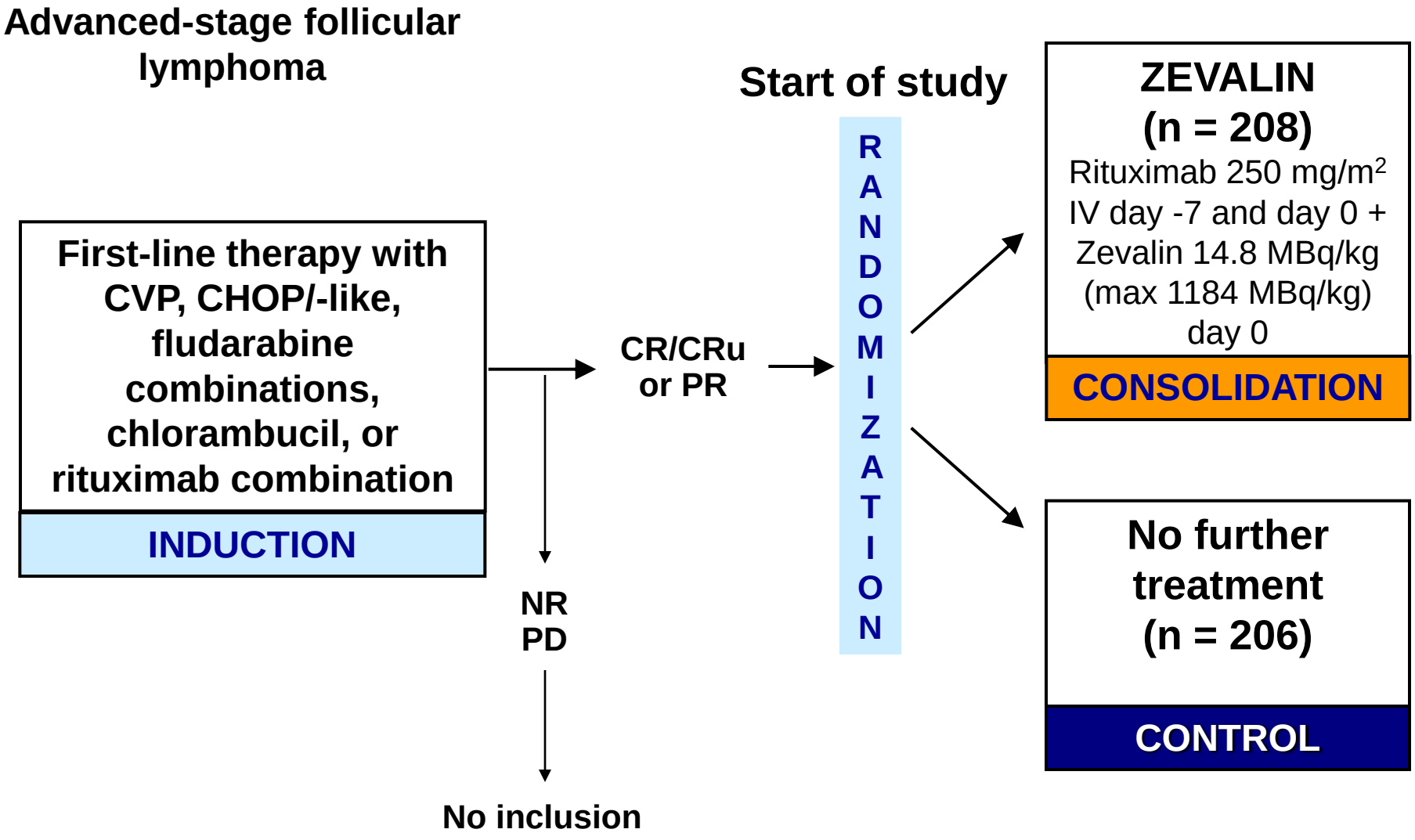
- **Naked MAb**
  - Rituximab — anti-CD20
  - Alemtuzumab — anti-CD52
  - Epratuzumab — anti-CD22
  - Galiximab — anti-CD80
  - Humanized anti-CD20s (ocraluzumab, ofatumomab, veltuzumab)
  - Modified anti-CD20s (GA 101, R603)
  - Bevacizumab — anti-VEGF
  - Zanolimumab — anti-CD4
  - siplizumab — anti-CD2
- **MAb + radionucleide**
  - ^{90}Y ibritumomab tiuxetan — anti-CD20
  - ^{131}I tositumomab — anti-CD20
- **MAb + toxin**
  - *CMC-544 (calicheamicin)* — anti-CD22
  - SAR3419 (DM4, maytansinoid) — anti-CD19
  - SGN35 — anti-CD30

Radioimmunotherapy



- **Bexxar I^{131} tositumomab**
- **Zevalin Y^{90} ibritumomab**

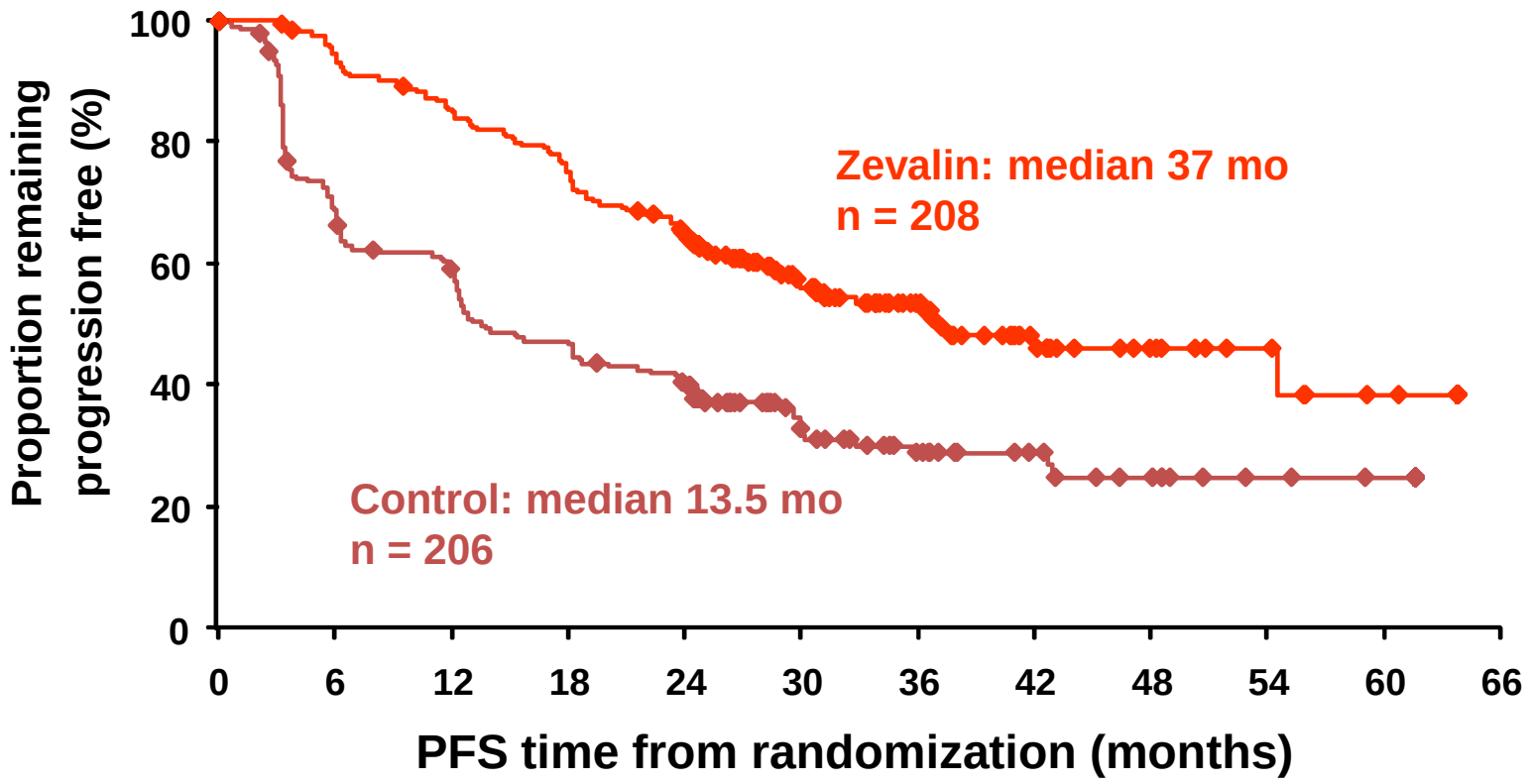
FIT Study Schema



F Morschhauser et al. JCO 2008

FIT Primary End Point: Median PFS in All Patients*

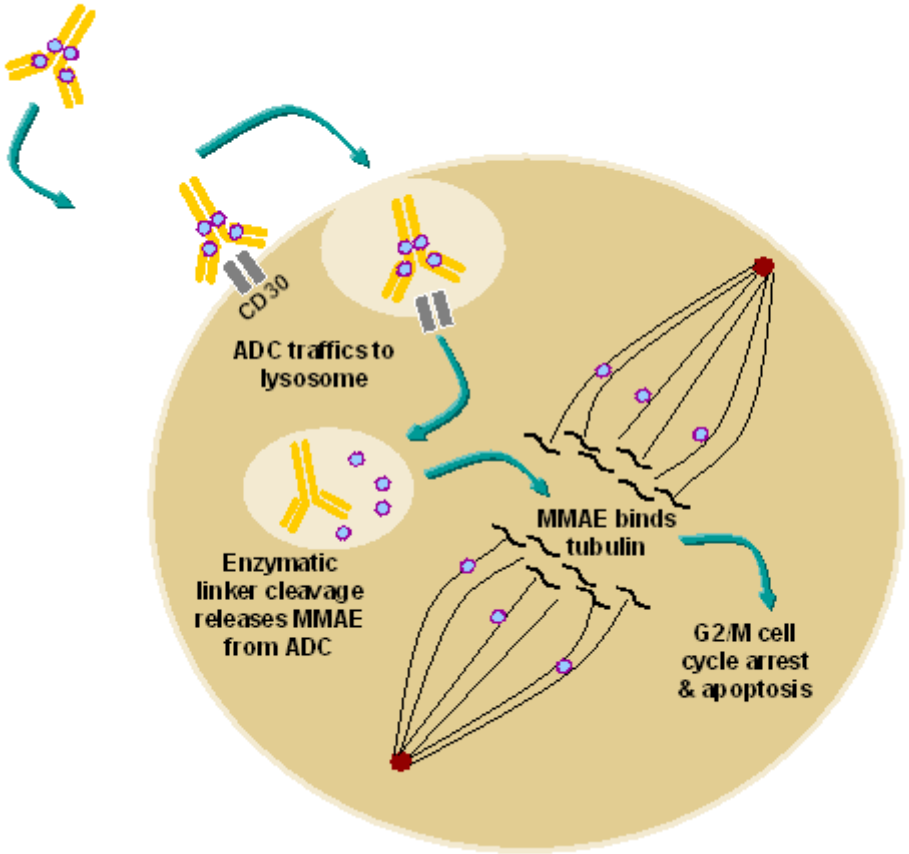
*Median observation period was 3.5 years.



A Hagenbeek Blood 2007;110:643a

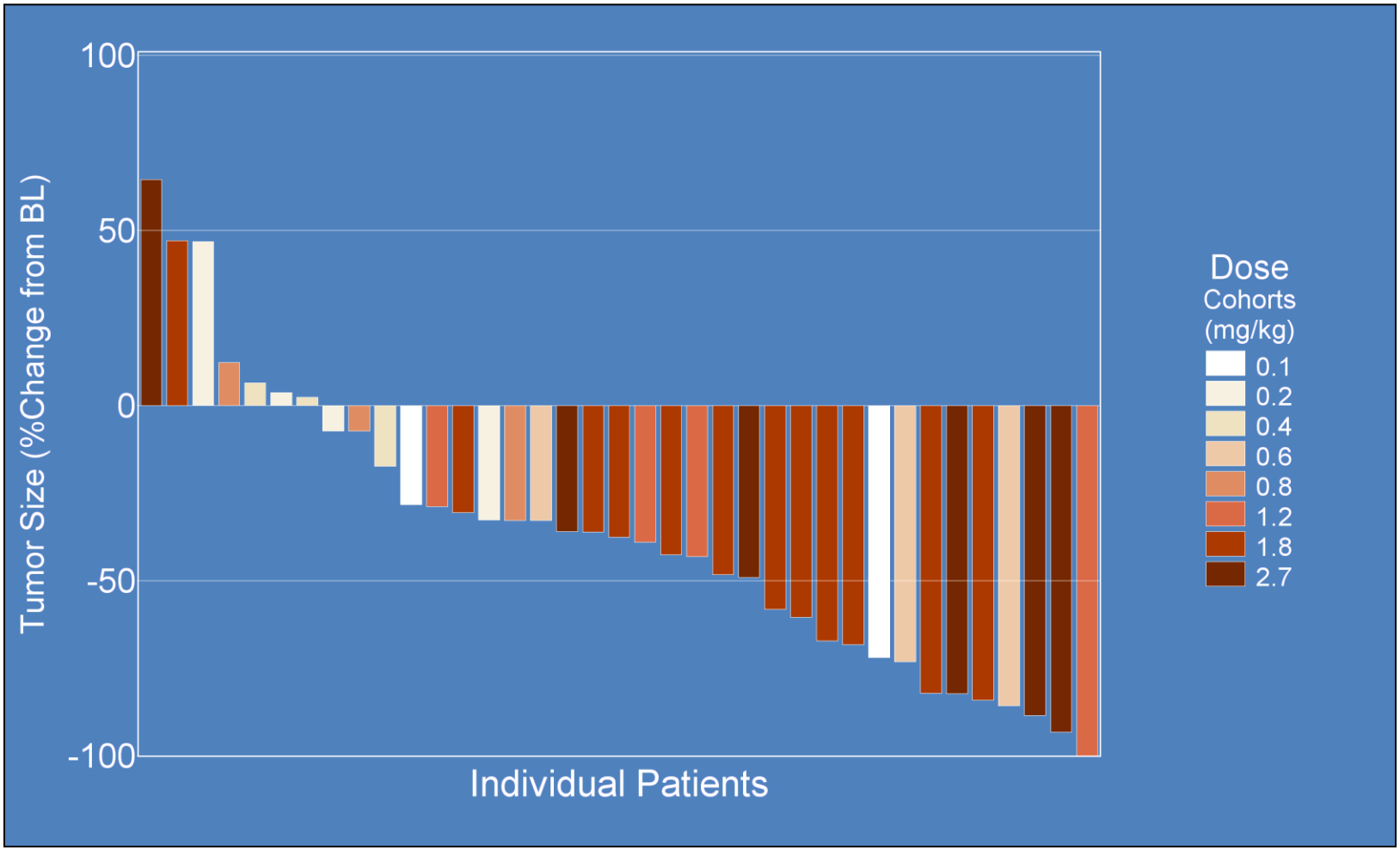
SGN-35 Mechanism of Action

SGN35 = **Anti-CD30 + Auristatin** (MMAE), anti-tubulin agent



CD30-positive hematologic lymphoma : Hodgkin lymphoma and Anaplastic T–cell lymphoma

Phase-I Study
Relapsed cHL and ALCL
Best responses (N=39)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas

Anas Younes, M.D., Nancy L. Bartlett, M.D., John P. Leonard, M.D., Dana A. Kennedy, Pharm.D., Carmel M. Lynch, Ph.D., Eric L. Sievers, M.D., and Andres Forero-Torres, M.D.

RESULTS

The maximum tolerated dose was 1.8 mg per kilogram, administered every 3 weeks. Objective responses, including 11 complete remissions, were observed in 17 patients. Of 12 patients who received the 1.8-mg-per-kilogram dose, 6 (50%) had an objective response. The median duration of response was at least 9.7 months. Tumor regression was observed in 36 of 42 patients who could be evaluated (86%). The most common adverse events were fatigue, pyrexia, diarrhea, nausea, neutropenia, and peripheral neuropathy.

N Engl J Med 2010;363:1812-21.

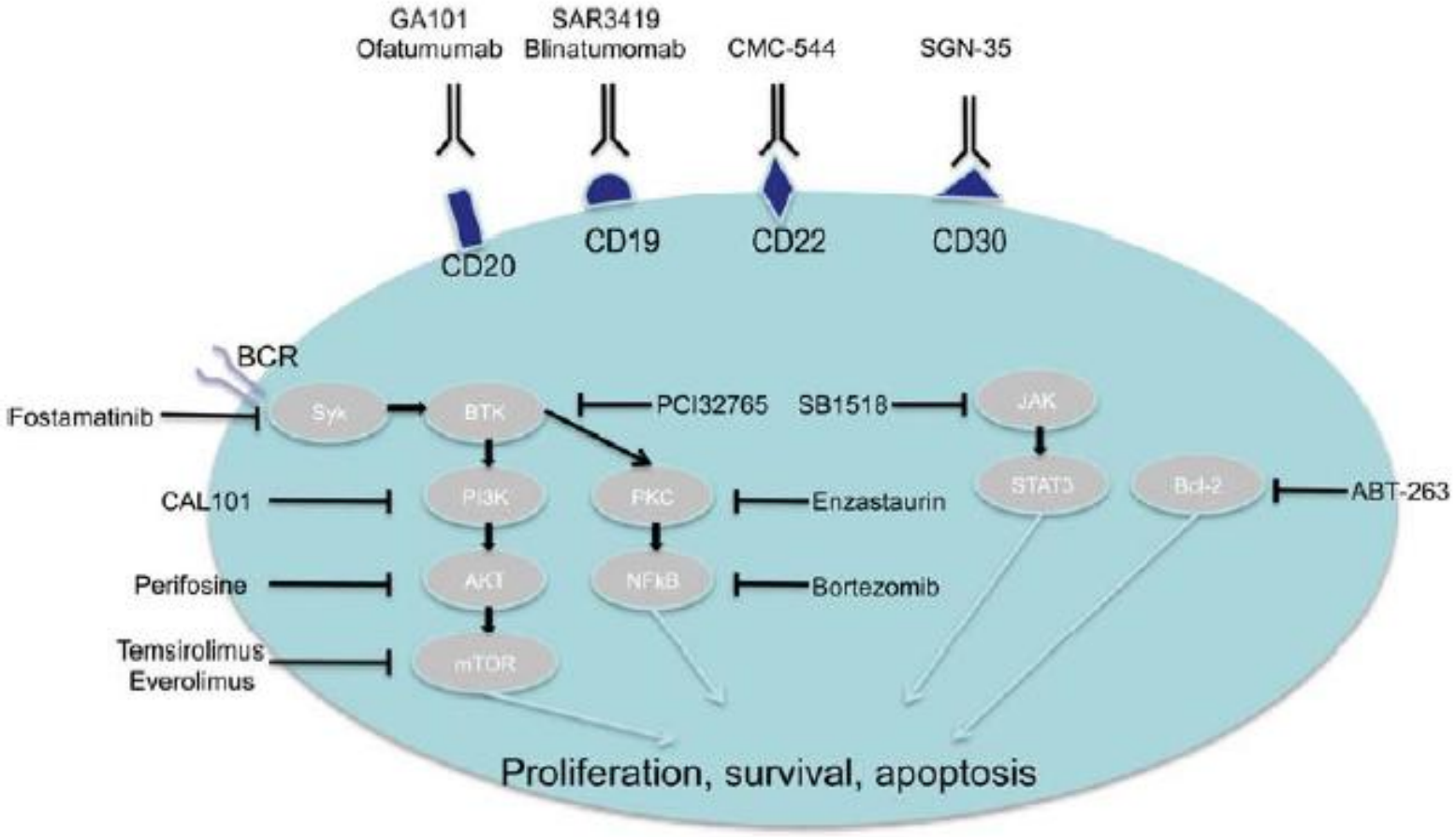
Nouvelles drogues dans les lymphomes

- **Monoclonal antibodies**

- **Targeted therapies**
  - mTOR inhibitors: Temsirolimus, RAD001
  - IMIDs: lenalidomide, pomalidomide
  - Proteasome inhibitors: bortezomib, carfilzomib
  - HDAC inhibitors: romidepsine, panobinostat …
  - Fostamatinib
  - BH3 inhibitors: ABT-263
  - PI3kinase inhibitor

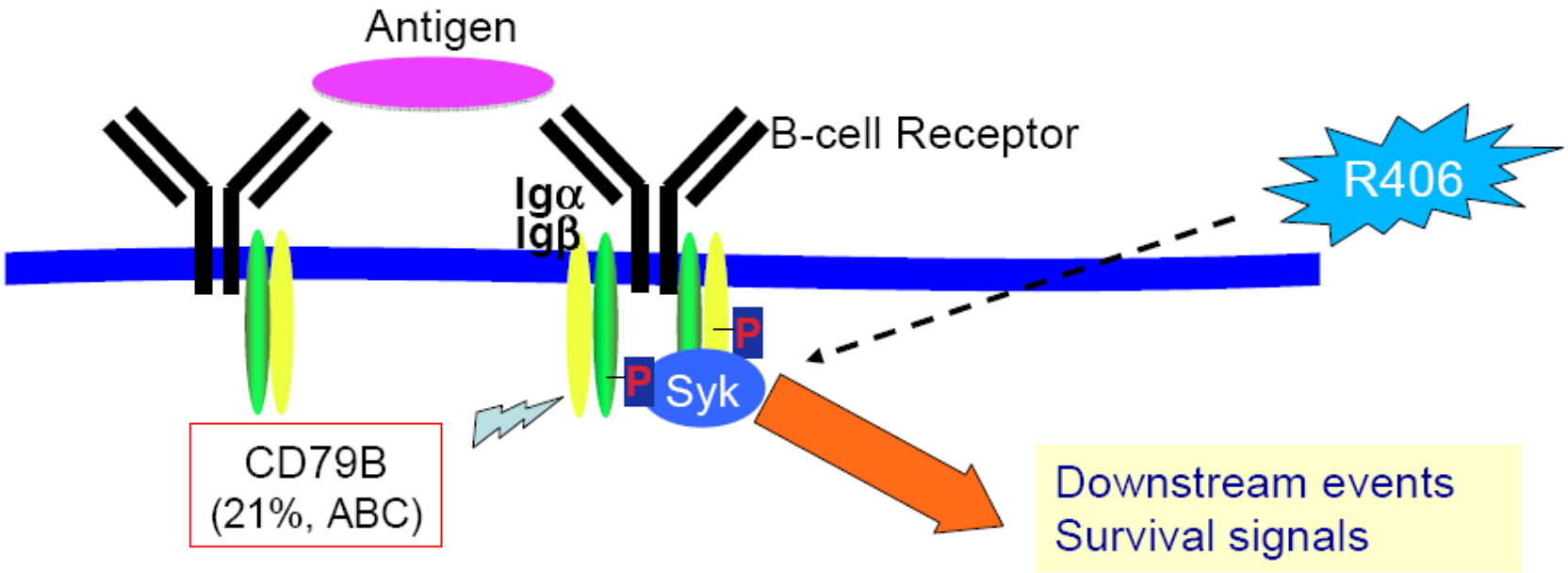
- **Chemotherapy**
  - Pralatrexate
  - Forodesin
  - Pixantrone
  - Bendamustin

Cibles thérapeutiques



Un modèle de développement autour du Récepteur B

- "BCR" BLBCL can be identified by gene expression profile
- "chronic active" BCR signaling is required for cell survival in ABC DLBCL
- Tonic BCR signaling requires Syk expression & phosphorylation



Tonic BCR signaling can be targeted with a SYK inhibitor (R406)

Clinical trials of SYK/BCR, BTK,… inhibitions are promising

"BCR" DLBCL are good candidate for BCL6 inhibitor *(Cerchietti. Blood 2009)*

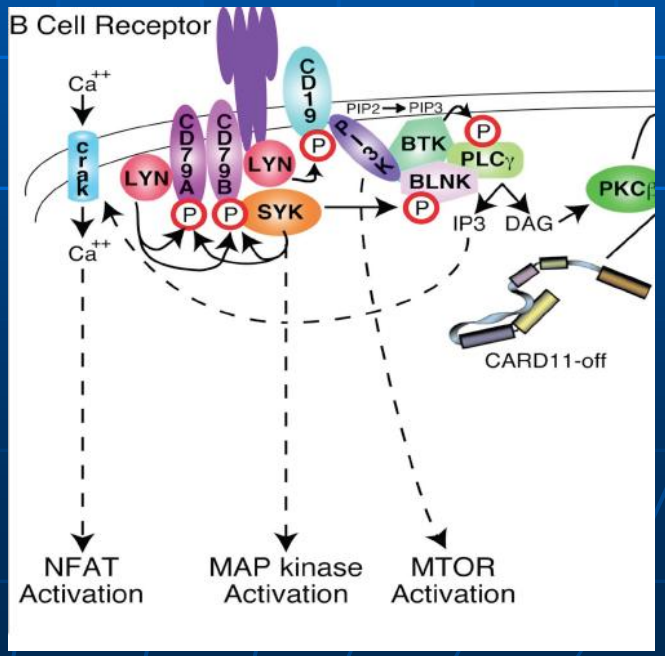
(Chen et al. Blood, 2008; Davis RE et al. Nature 2010)

Inhibiteurs de BTK

- La tyrosine kinase de Bruton joue un rôle central dans les voies de signalisation du BCR
- Le PCI-32765

est un inhibiteur oral

de la BTK



Les résultats spectaculaires à l'ASH 2011

- dans une série de LLC en rechute ou réfractaire (n=61)

avec des taux de réponse globale à 70% à 10.2 mois de suivi

(Abstract 938 – S. O'Brien et al.)

- **dans une série de lymphome DLBCL type ABC**

avec des taux de RC à 25% (Abstract 2716 – L. Staudt et al.),

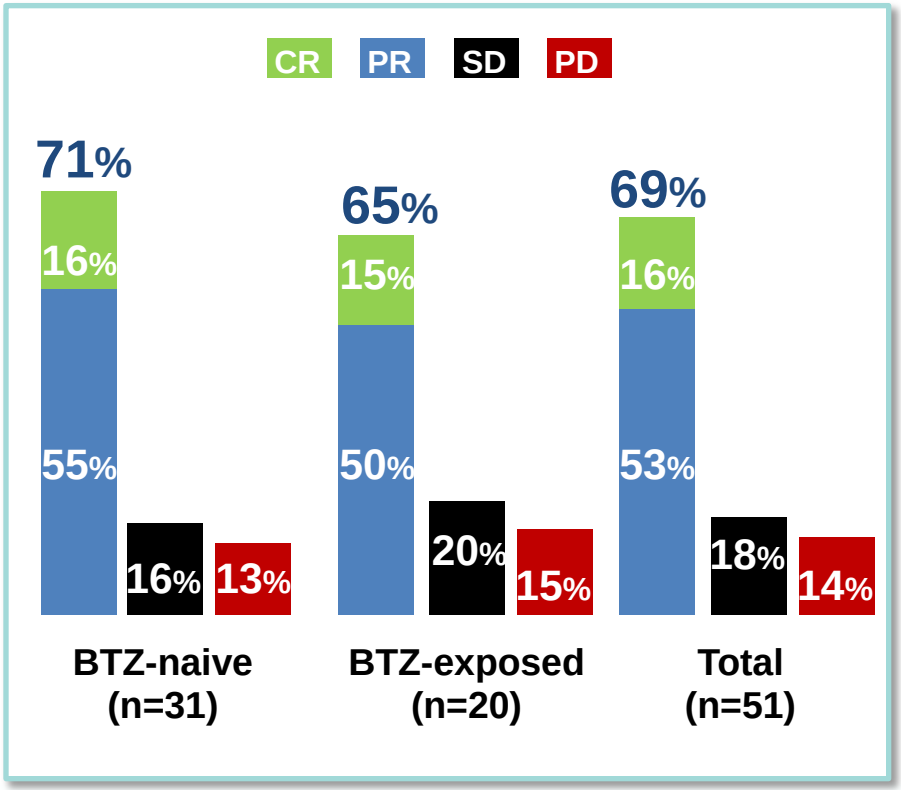
- dans une série de lymphome de manteau (n=51)

avec des taux de réponse globale à 77%,

(Abstract 442 - L. Wang et al.).

Résulats de l'analyse préliminaire -MCL

Best response

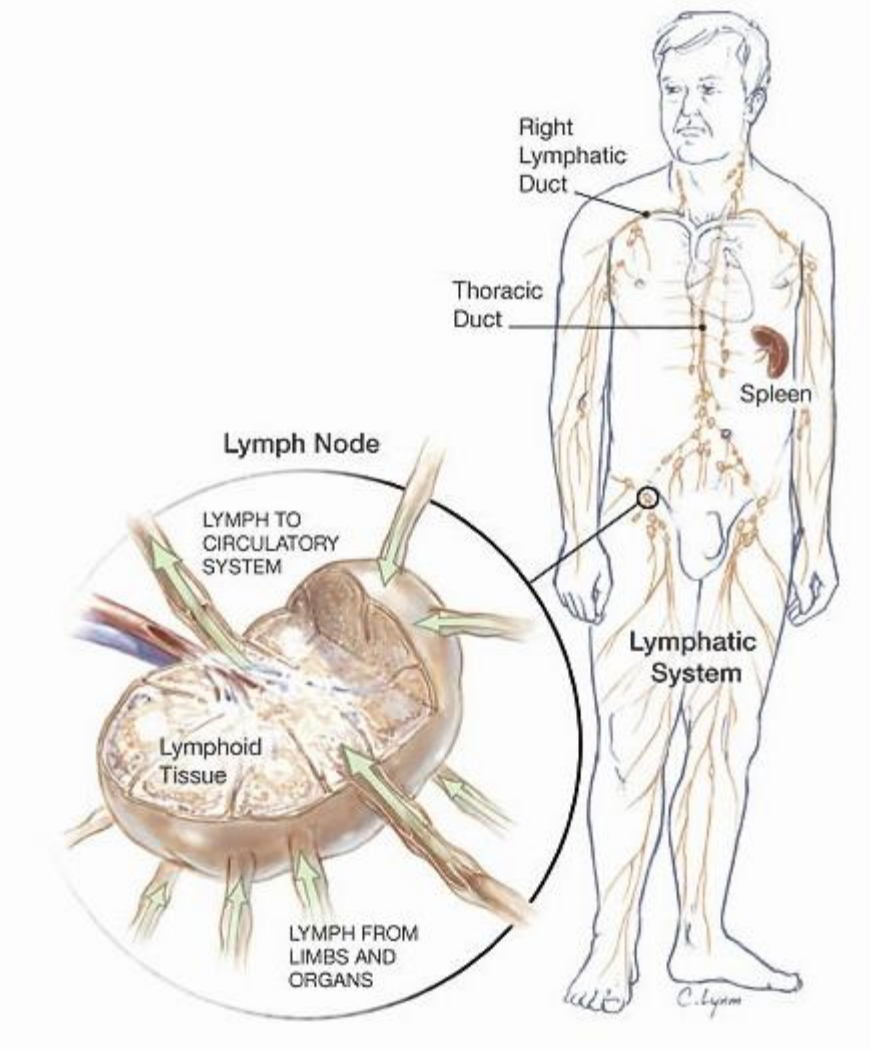


	n/N	ORR %
All Patients	35/51	69
Bulky Disease	4/7	57
Refractory :		
Yes	14/21	67
No	21/30	70
Prior cancer treatment		
< 3 regimens	23/30	77
≥ 3 regimens	12/21	57
Prior high intensity therapy		
Yes	22/31	71
No	13/20	65
MIPI Score :		
Low Risk	6/8	75
Intermediate Risk	13/20	65
High Risk	15/20	75

BTZ = bortezomib

Profil de tolérance satisfaisant, aucun arrêt de traitement pour effet indésirable

Grade ¾ Hematology toxicity[1]	Total (n=61)	
	Grade 3	Grade 4
Neutropenia	2%	3%
Febrile neutropenia	3%	0%
Anemia	3%	0%
Thrombocitopenia	3%	0%
Pancytopenia	0%	2%



Cancer =

- Tumoral cells

- Environment

Immune Environment

New immunomodulartory AB

Targetting innate and adaptative immune response

- **Monoclonal Abs activate stimulatory receptors or block inhibitory receptors expressed on the surface of immune cells and thereby enhance their function**

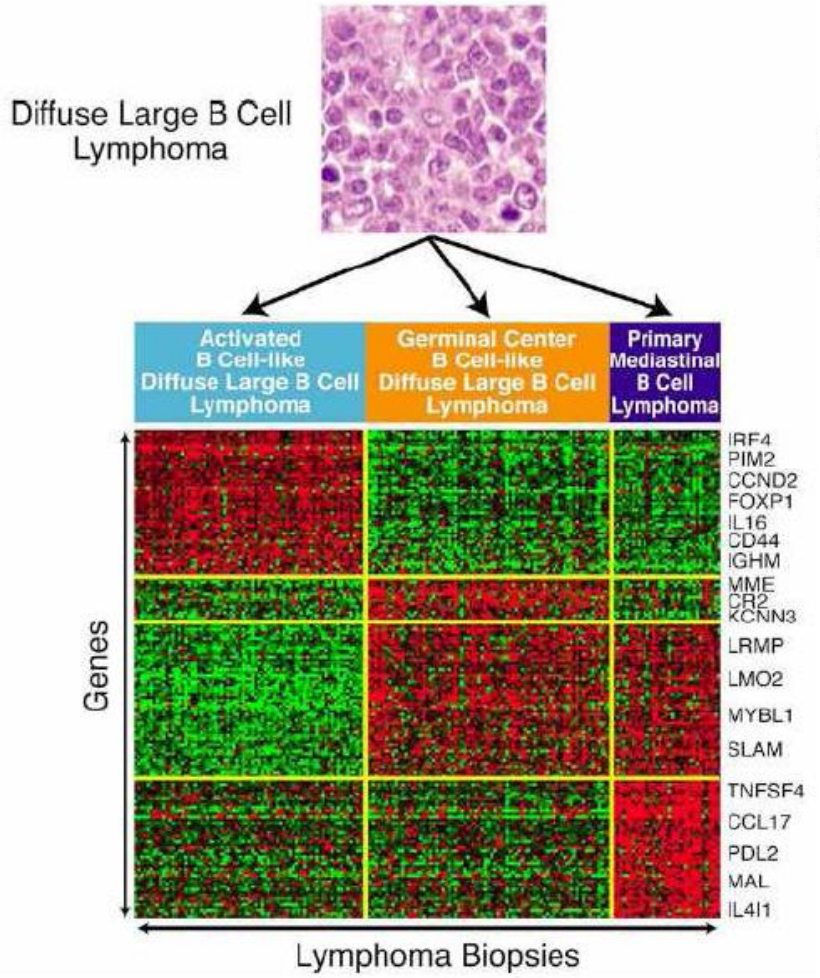
Cell	Receptors	Mechanisms of action
T cells	CD137 OX40 CTLA-4 PD-1	adaptive immune response
Dendritic cells	CD40	antigen presentation
NK cells	KIR	innate immune

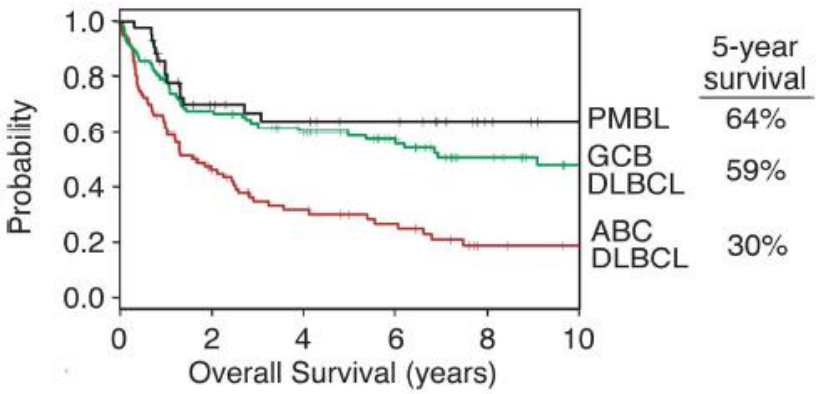
Immunomodularoty ABs lymphoma Clinical trials

Ab target	Generic Ab name *(trade name ; sponsoring company)*	Reference	No	Diseases	Tumor response
CTLA-4	Ipilimumab *(MDX-010 ; Bristol-Myers Squibb)*	O'Mahony et al, 2007 [115]	11	Advanced malignancies progressing after cancer vaccine, including 4 NHL (2 FL, 2 MCL)	2 tumor regressions in NHL patients including 1 mixed response (MCL) and 1 PR (FL)
		Bashey et al, 2009 [116]	29	Cancer patients relapsing after allogeneic hematopoietic stem transplantation including 27 hematological malignancies (14 HD, 6 MM, 2 AML, 2 CML, 2 CLL and 1 MCL)	2 CR (HD), 1 PR (MCL)
		Ansell et al, 2009 [117]	18	Refractory or recurrent B-cell NHL patients (14 FL, 3 DLBCL, 1 MCL)	1 CR (DLBCL), 1 PR (FL)
PD-1	CT-011 *(Curetech)*	Berger et al, 2008 [23]	17	Advanced hematological malignancies (4 NHL, 1 HD, 3 CLL, 1 MM, 7 AML, 1MDS)	1 CR (FL), 1 minimal response (AML)
CD40	Dacetuzumab *(SGN-40 ; Seattle Genetics)*	Advani et al, 2009 [32]	50	Refractory or recurrent NHL patients (21 DLBCL, 12 FL, 10 MCL, 3 MZL, 1 SLL)	One third of patients experienced tumor regression including 6 OR (12%): 1 CR (DLBCL) and 5 PR (3 DLBCL, 1 MZL, 1 MCL)
		Furman et al, 2010 [33]	12	Recurrent CLL	5 SD
		Hussein et al, 2010 [34]	44	Recurrent or refractory MM	9 SD (20%)
	HCD122 *(Novartis/XOMA)*	Byrd et al, 2006 [36]	14	Relapsed and refractory CLL	Transient decrease of peripheral CLL cells during Ab infusion in the majority of patients (not maintained week-to-week)
		Bensinger et al, 2006 [37]	9	Relapsed and refractory MM	1 PR
CD3/CD19	Blinatumomab *(MT103 ; Micromet)*	Goebeler et al, 2010 [46]	14	Relapsed indolent NHL (FL, MCL)	9 PR and 4 CR out of 13 evaluable patients (100% ORR) treated at the dose of 60µg/m^2/d
		Topp et al, 2009 [47]	19	B-precursor ALL patients in complete hematological remission with persistent or reappeared MRD after consolidation of front-line therapy	13/16 patients (81%) converted into a molecular CR

R. Houot et al. in submission, 2010

Des arguments pour un traitement ciblé

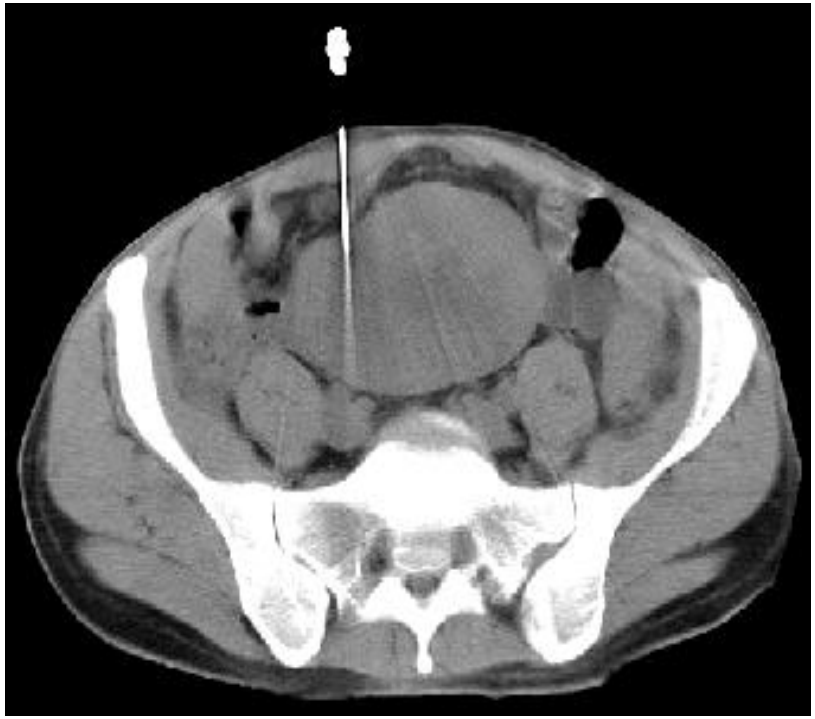




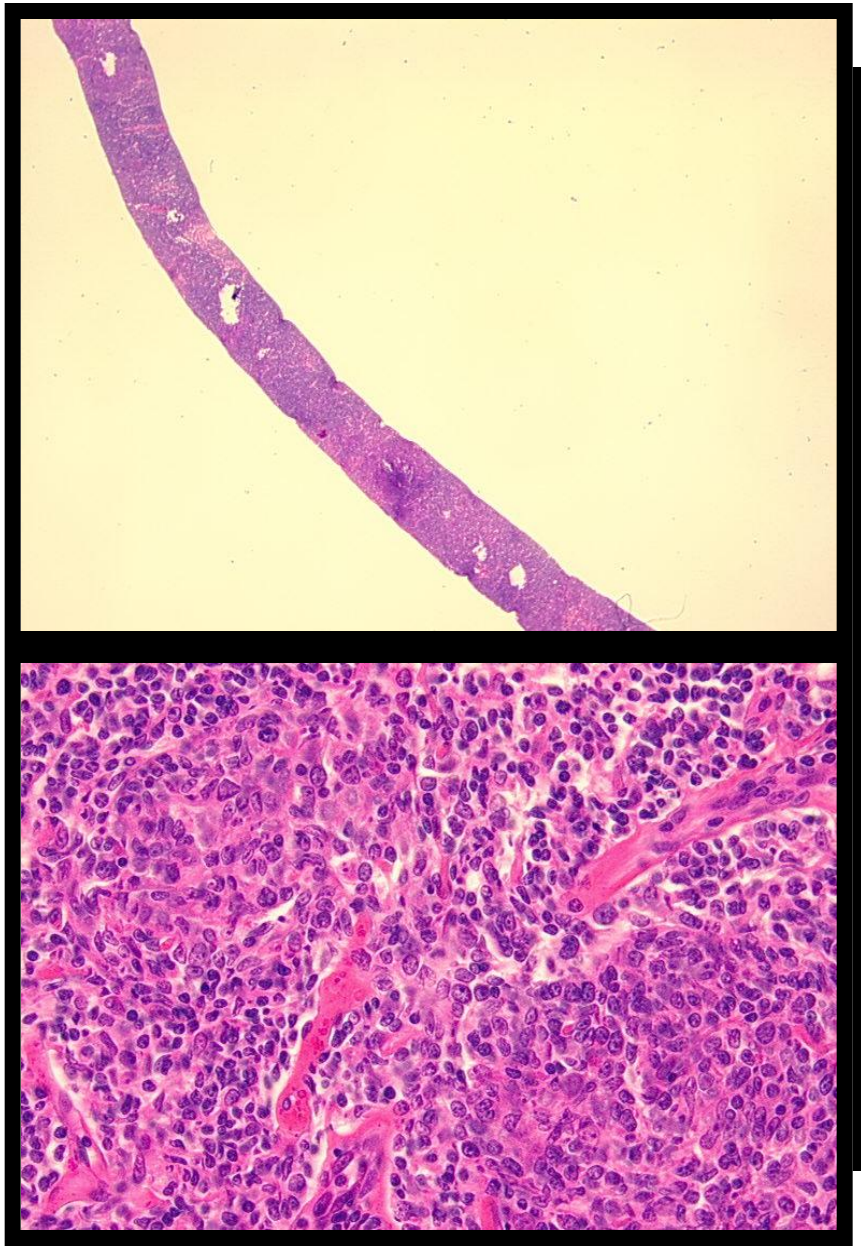
- **Cell of origin**
- **Clinical relevance independently of the IPI**
- **Distinct genetic features & oncogenic pathways**

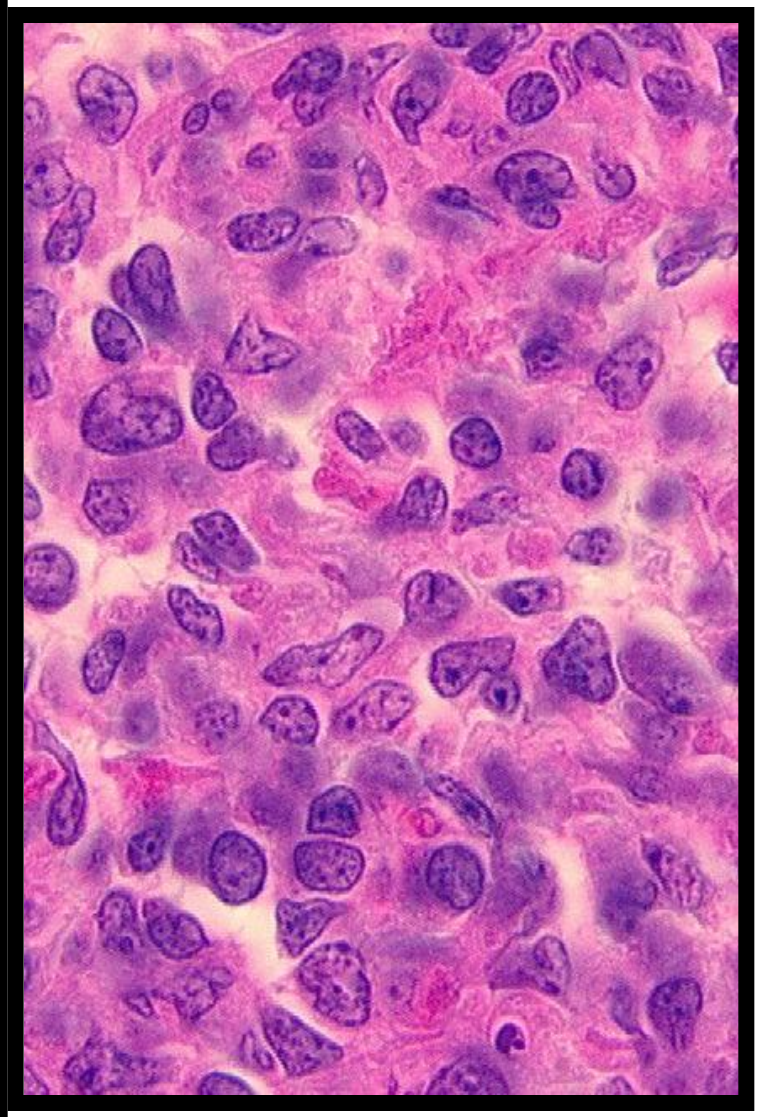
Rosenwald et al. NEJM 2002
Rosenwald et al. J Exp Med 2003

L’analyse de la tumeur
Etape essentielle du traitement



E. De Kerviler, H. Saint-Louis, Paris



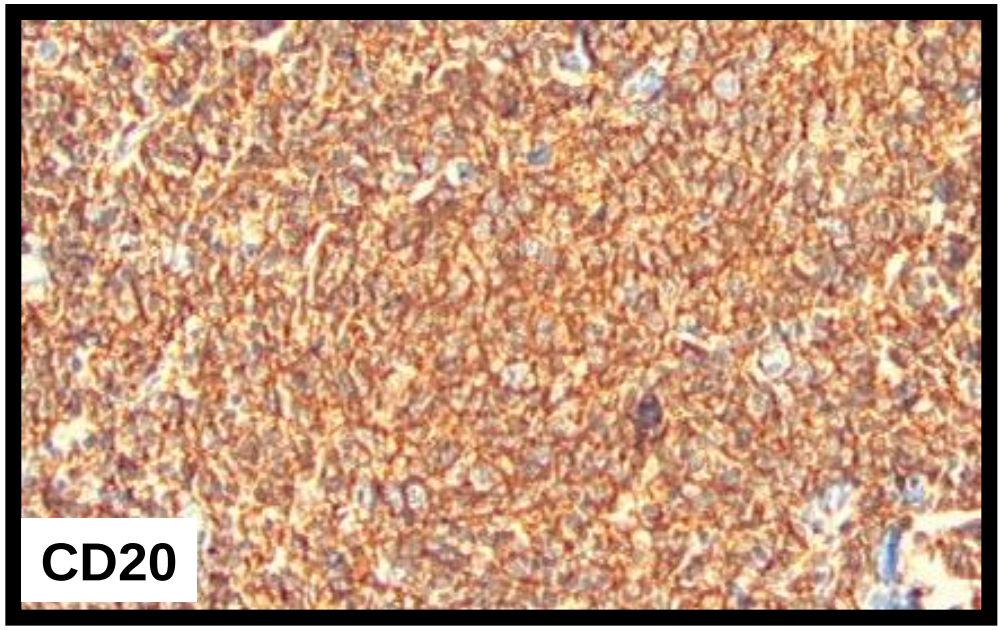


J .Brière, H. Saint-Louis, Paris

IMMUNOPHENOTYPE

Expression du CD20

Anticorps anti CD20



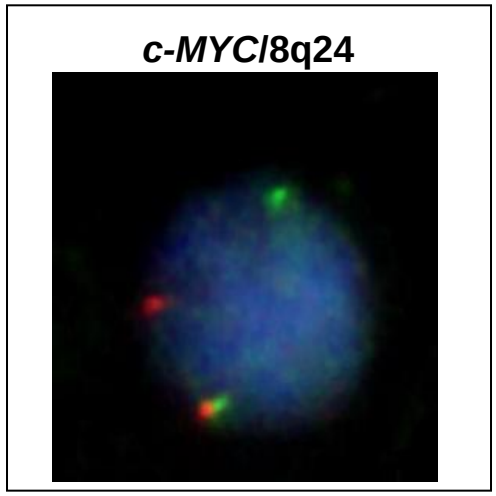
J. Brière – BioCORAL study

LES ANOMALIES CHROMOSOMIQUES

Caryotype

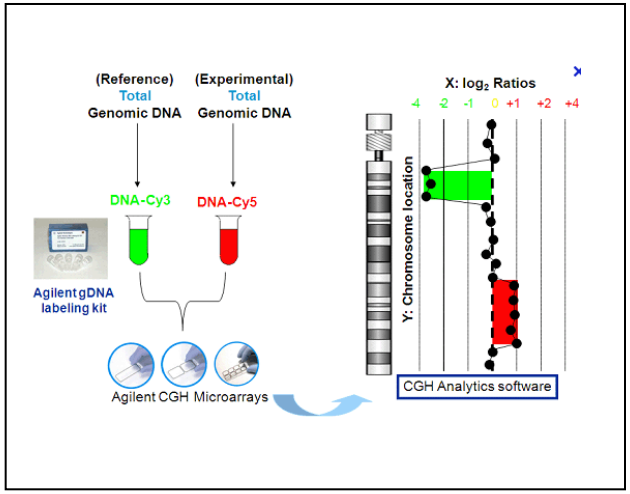
FISH

= hybridation fluorescent in situ



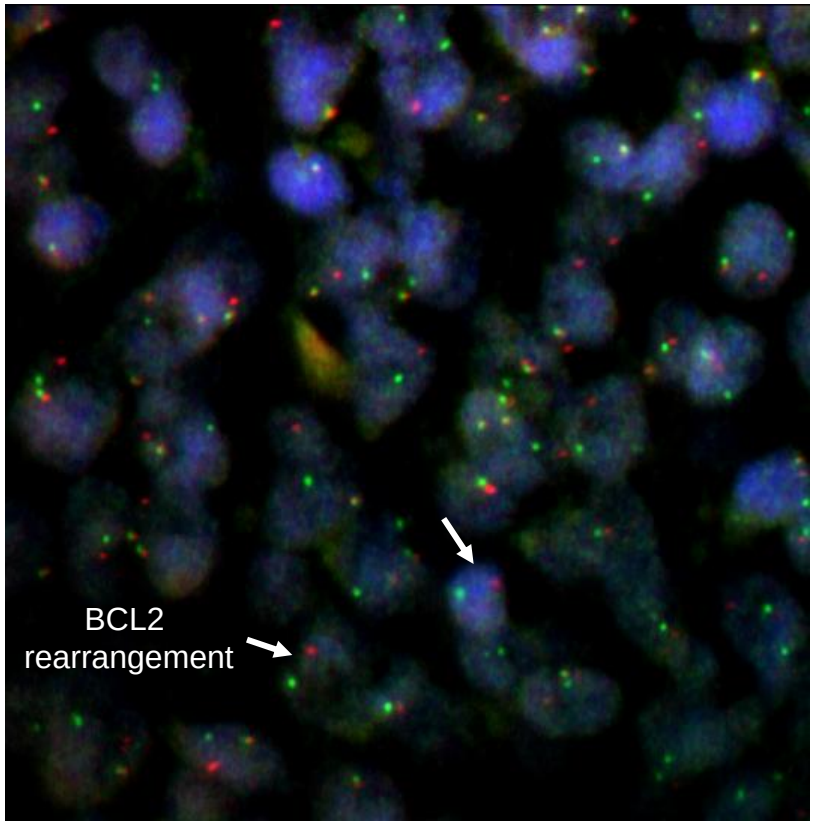
CGH array

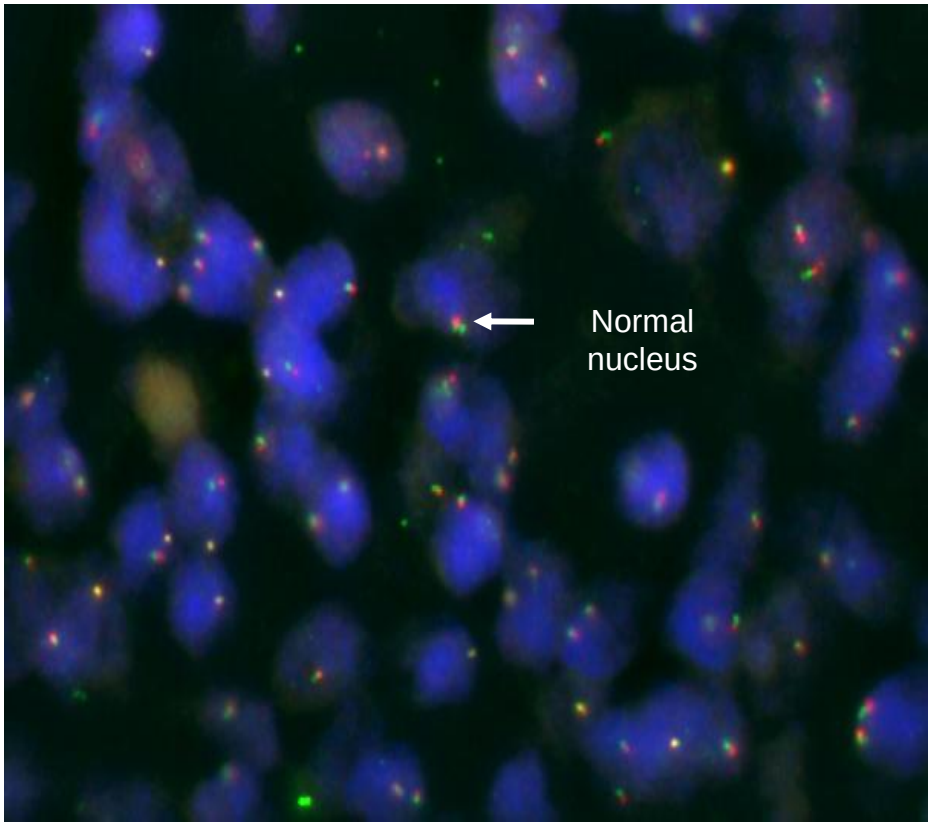
= Puce d'hybridation génomique comparative



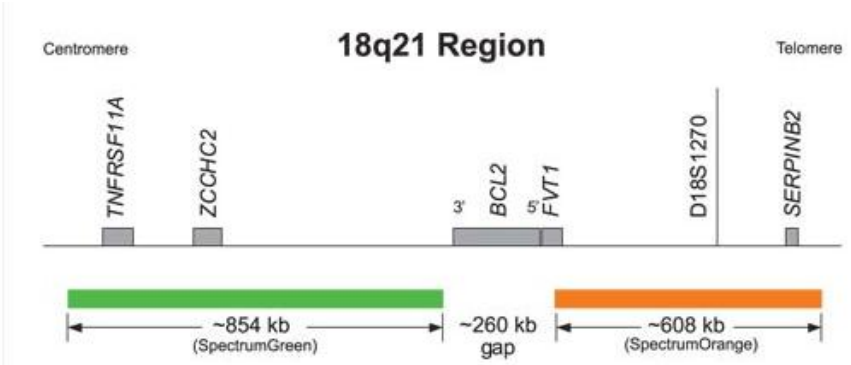
Gain *ou* perte *ou* translocation

Gain *ou* perte





BCL2, dual color, break apart FISH probe (Vysis Abbott)

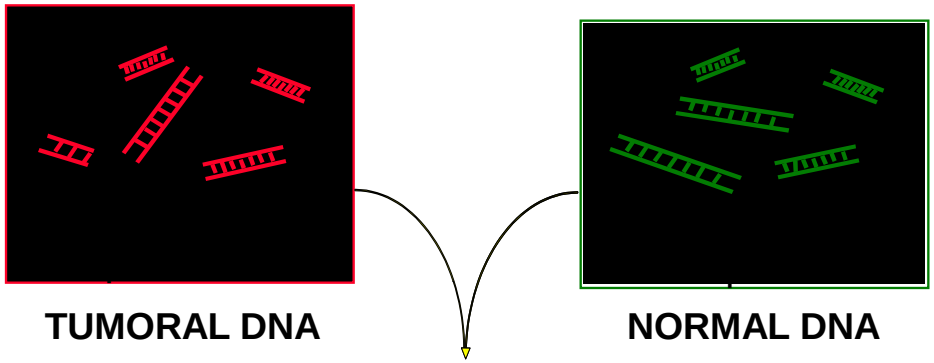


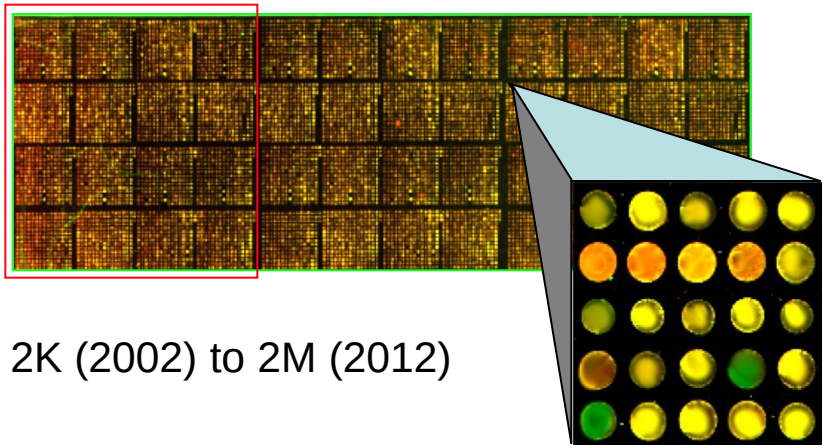
BCL2 Probe Map

W. Cuccini & J. Soulier – BioCORAL study

CGH-array

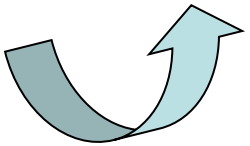
Hybridation comparative sur puces à ADN





Densité: 2K (2002) to 2M (2012)

Ratios indiqué sur une carte du génome « caryotype virtuel »

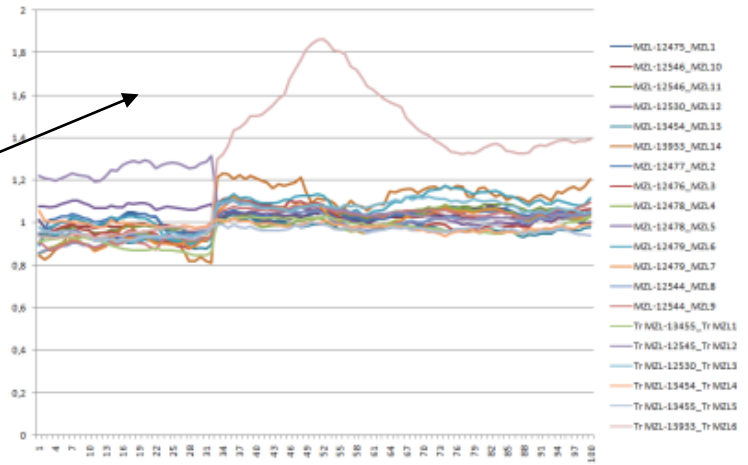


Pas besoin de culture et de mitoses
Détecte les gains et les pertes de matériel chromosomique mais pas les translocations équilibrées

LES ANOMALIES GENETIQUES

ADN de la tumeur

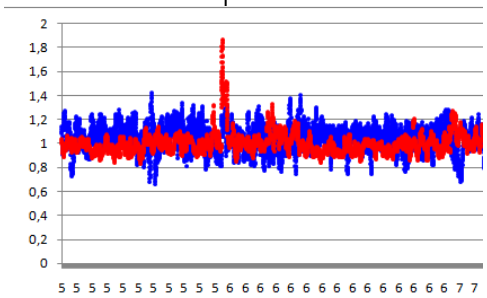
IRF4
DUSP22
EXOC2



All cases
SMZL and HP-MZL

SMZL

HP-SMZL

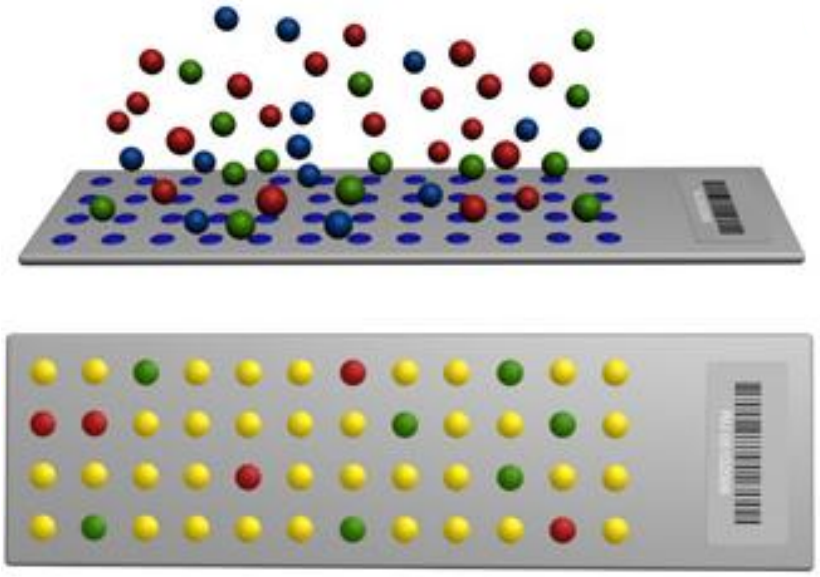


Matched cases

LE PORTRAIT MOLECULAIRE

Analyse de l'EXPRESSION des gènes

ARN de la tumeur

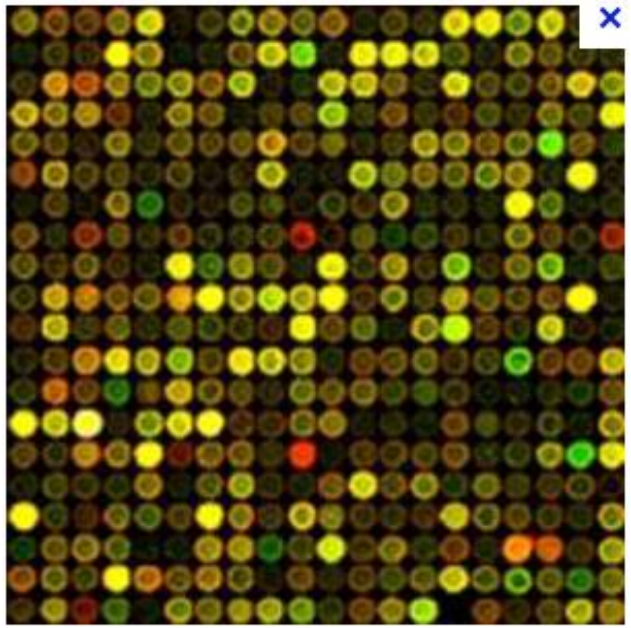


LE PORTRAIT MOLECULAIRE

Analyse de l'EXPRESSION des gènes

Rouge : surexpression

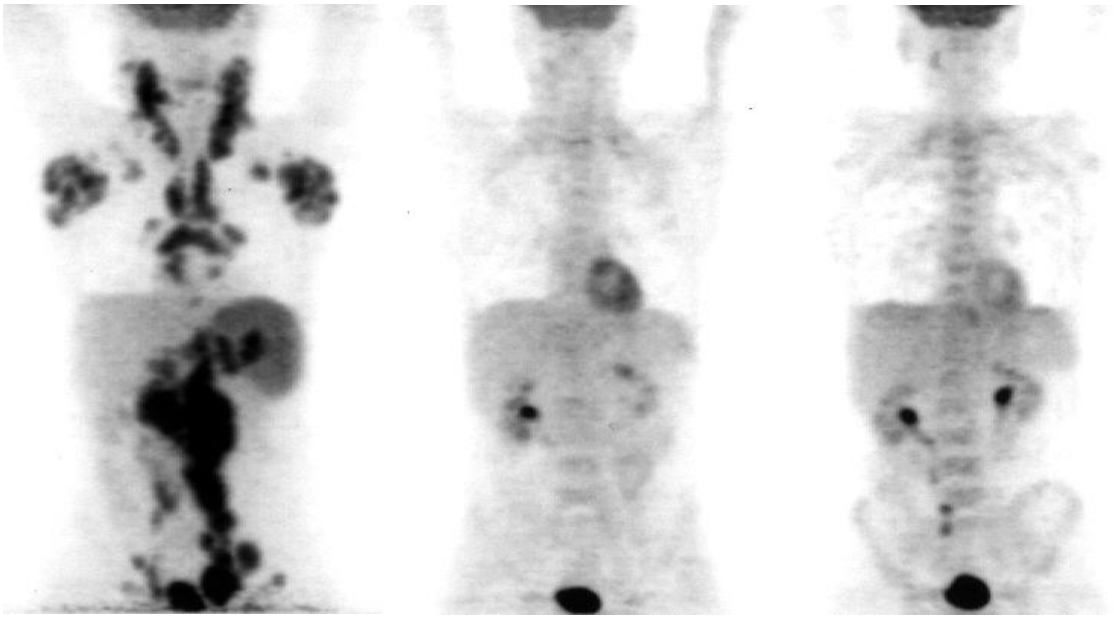
Vert : sous-expression



Le petscan

Réponse thérapeutique précoce

= **Chimiosensibilité**



AVANT TT **à 2 cycles** **à 4 cycles**

FDG-PET2 (-)

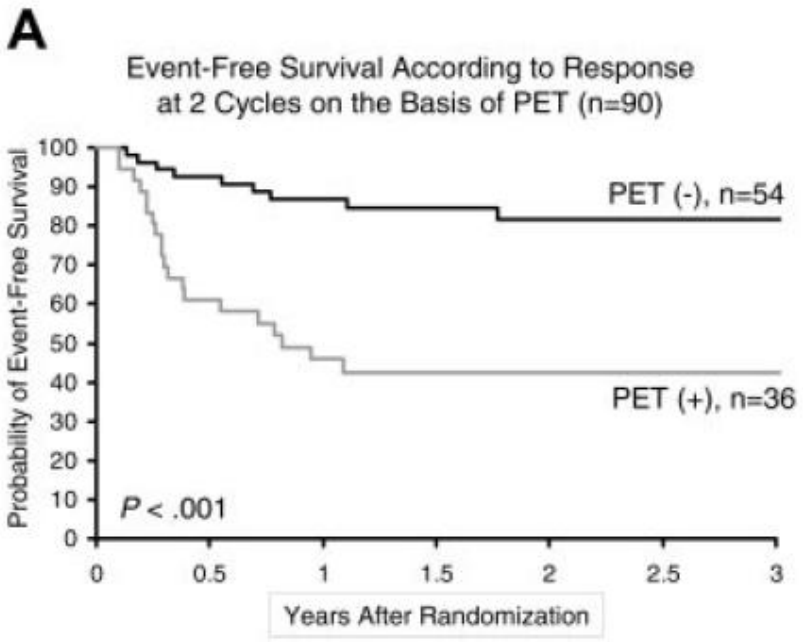
Haioun C et al. Blood 2005

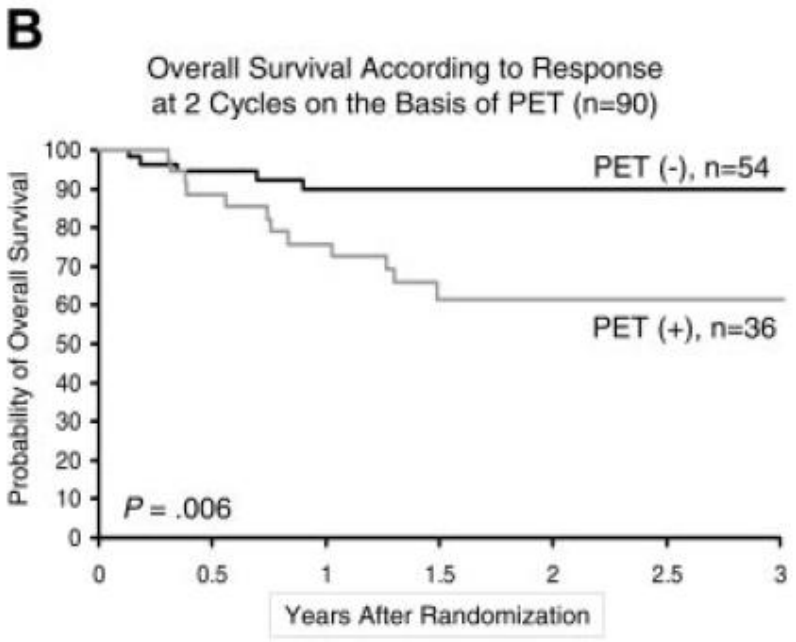
Le petscan

Dans les lymphomes non Hodgkiniens

Traitement:

Induction : R-ACVB x 4 et consolidation par intensification + autogreffe de CSP





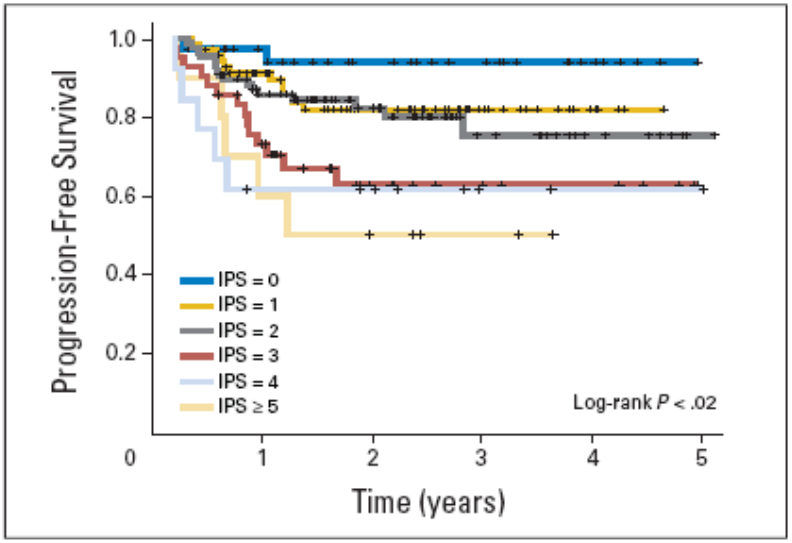
Haioun C et al. Blood 2005

Le petscan

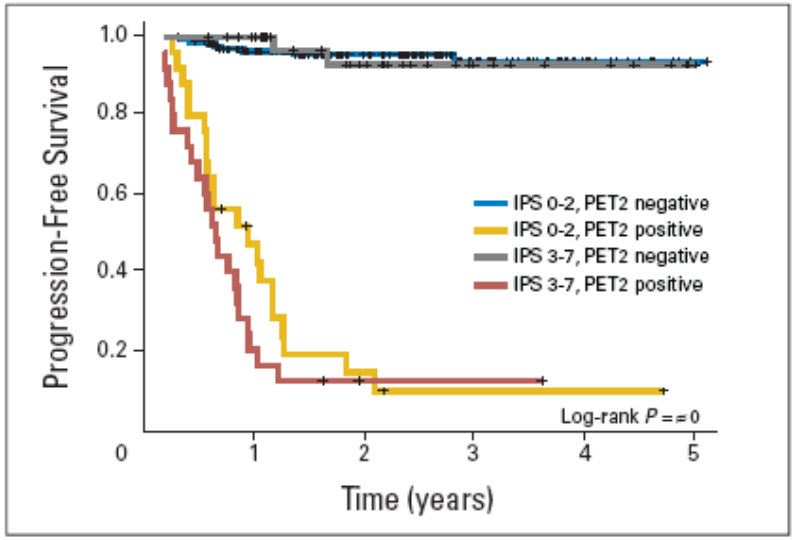
Dans les lymphomes Hodgkiniens

n = 163 patients

EFS en fonction de l'IPS



EFS en fonction PET à 2 cures et selon IPS



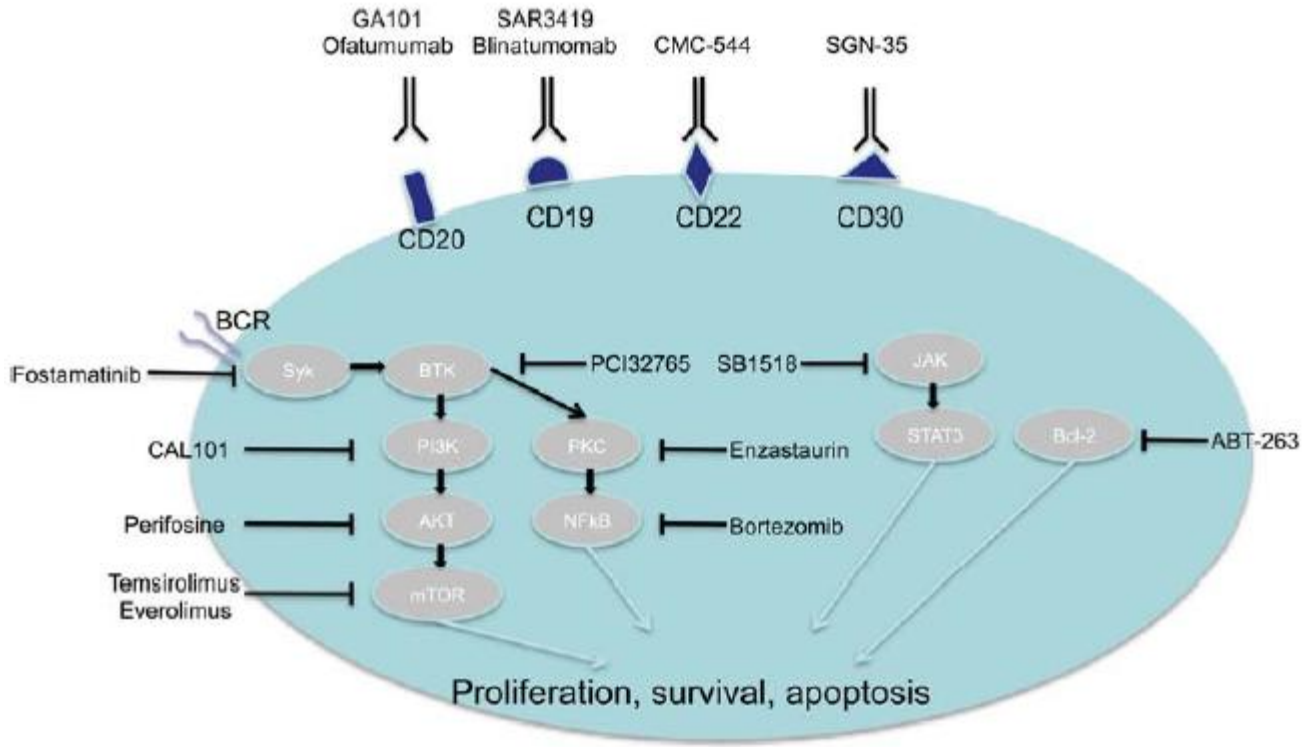
IPS

FACTOR
Serum albumin, <4 g/dl
Hemoglobin, <10.5 g/dl
Male sex
Stage IV disease
Age, ≥45 yr
White-cell count, ≥15,000/mm³
Lymphocyte count, <600/mm³ or <8% of white-cell count

Gallamini et al. JCO 2007

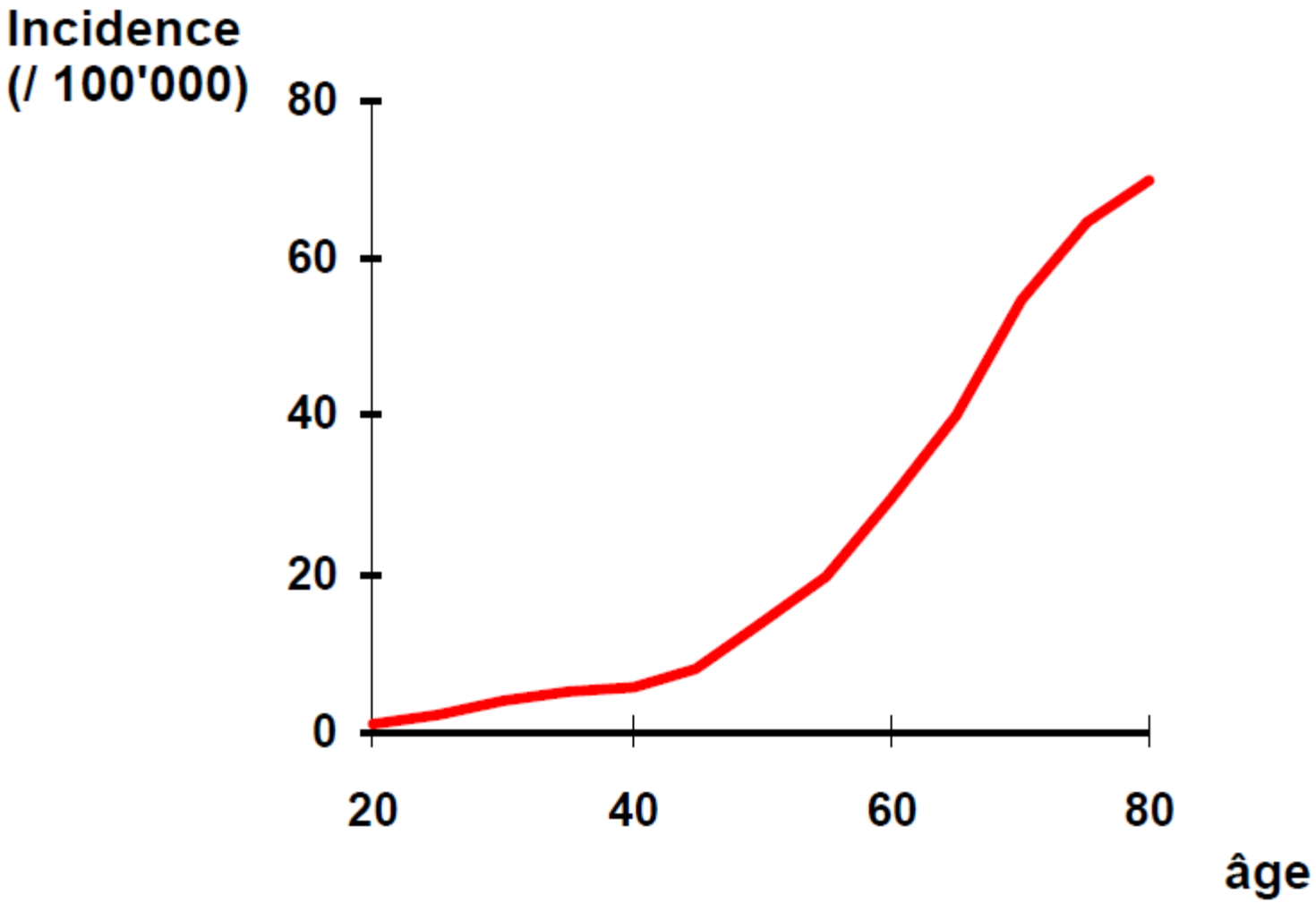
Conclusions

- **Depuis 10 ans**
  - **Progrès majeurs**
  - **Anticorps monoclonaux**
  - **Thérapies ciblées**
  - **Modalités d'administration différentes des traitements : entretien avec un impact sur la survie**
- **Partenariat avec les industriels**
- **Implication des pharmaciens dans les essais thérapeutiques**



Stathis A et al. Ann Oncol 2012; 23 (Suppl 10): x92–x97

Incidence et âge



Epidémiologie

- **Il n'y a pas de FR important connu**
- **Rôles de l'environnement**
  - Pesticides, industrie chimique et pétrolières?
- **Rôle marginal mais bien identifié de certaines infections**
  - Helicobacter pylori et LNH MALT
  - HCV et immunocytome
  - HTLV1 et Lymphome/leucémie T
  - EBV et LNH Burkitt (en association avec le paludisme)
  - EBV et lymphomes de haut grade post-transplantation
  - HHV-8 et LNH primaire des épanchements
- Immunodéficiences acquises ou héréditaires
- Maladies autoimmunes

Zevalin Consolidation Improved Response Quality in 77% of Patients: Conversion From PR to CR/CRu

First-line regimen	Control n / N (%)*	Zevalin n / N (%)*	*P* value
All patients	**17 / 97 (17.5)**	**78 / 101 (77.2)**	**< 0.001**
Chlorambucil	1 / 13 (7.7)	11 / 13 (84.6)	< 0.001
CVP / COP	3 / 29 (10.3)	16 / 22 (72.7)	< 0.001
CHOP	8 / 32 (25.0)	31 / 41 (75.6)	< 0.001
CHOP-like	0 / 8 (0)	10 / 13 (76.9)	< 0.005
Fludarabine comb.	0 / 3 (0)	5 / 5 (100.0)	< 0.05
Rituximab comb.	5 / 12 (41.7)	5 / 7 (71.4)	= 0.34

***Proportion of patients with PR after first-line therapy who converted to CR/CRu post-randomization.**

A Hagenbeek Blood 2007;110:643a