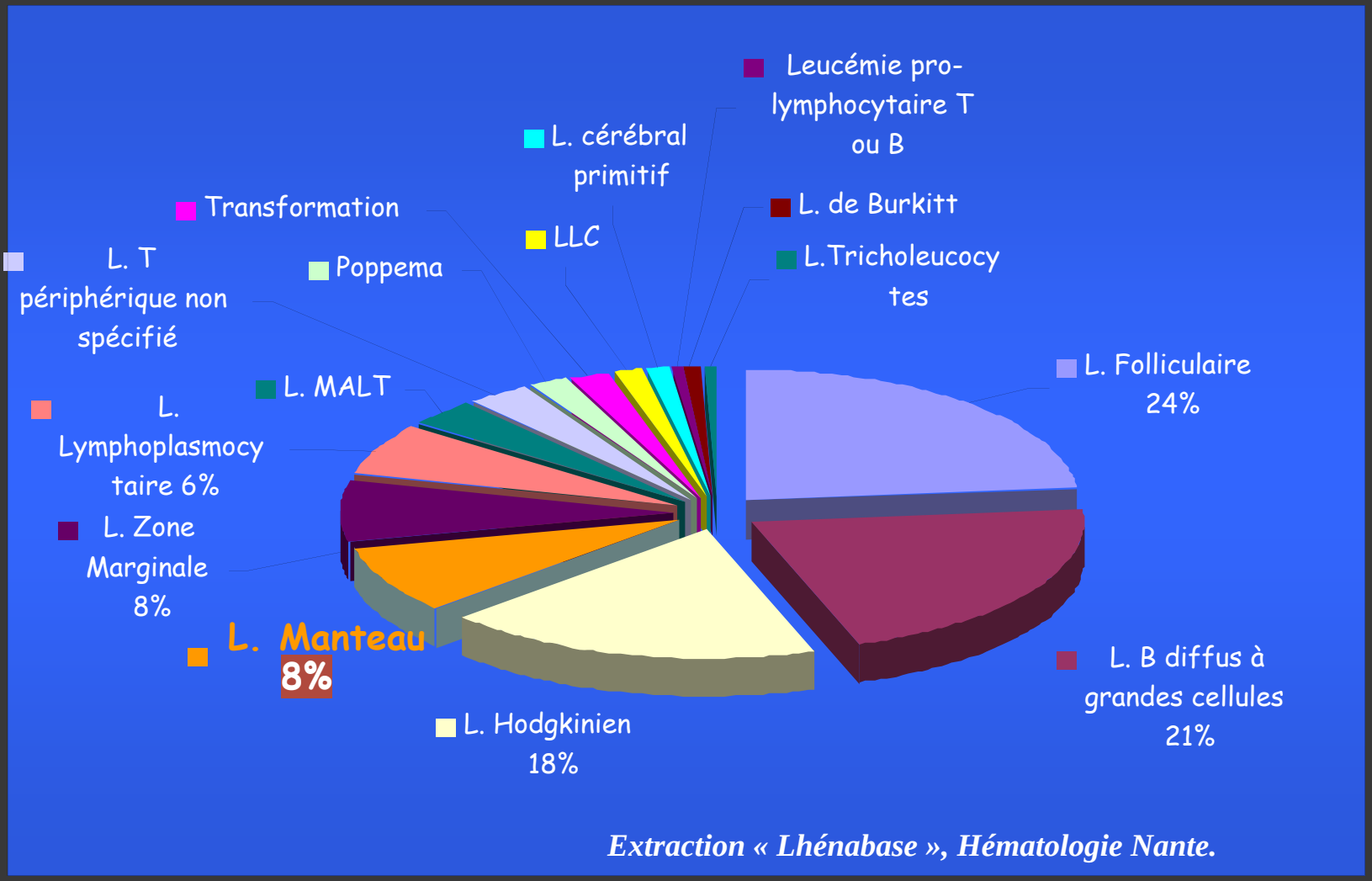
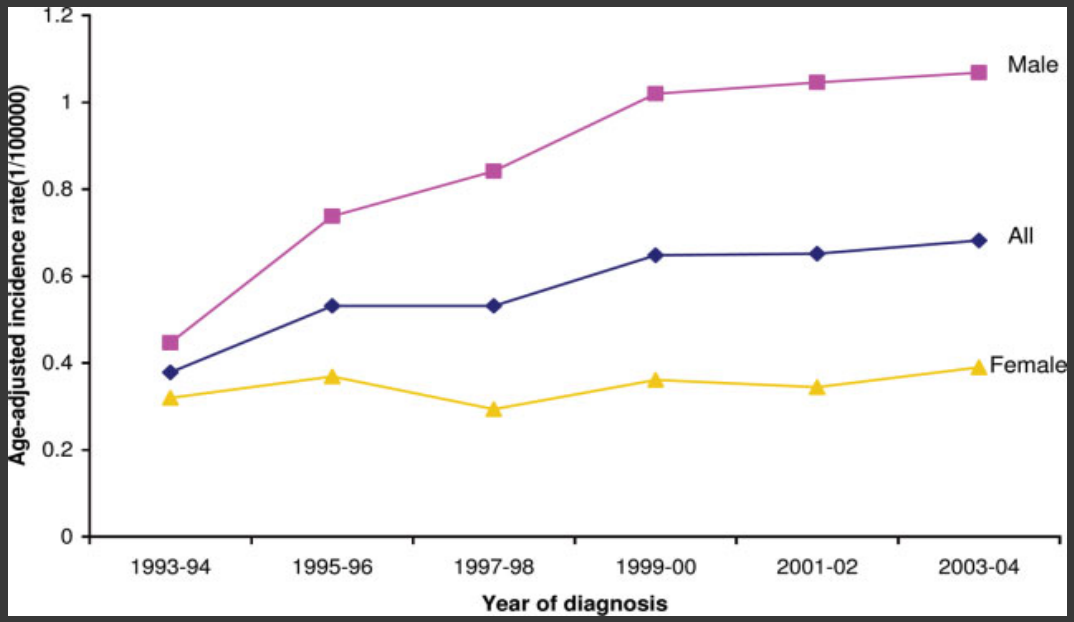
Lymphome à cellules du manteau: chimiothérapies, perspectives thérapeutiques

Dr Le Gouill Steven, MCU-PH, Service d'hématologie clinique, Nantes.

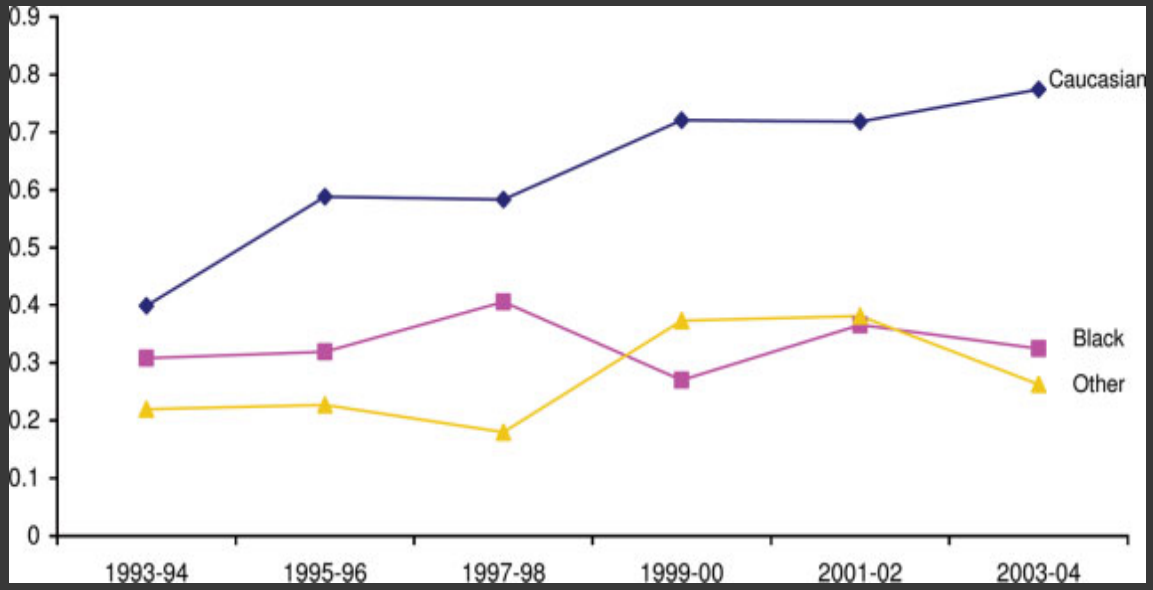


de .07 à 3 cas pour 100 000 hbts/an



Zhou Y et al. Cancer

Argatoff LH, Connors JM, Klasa RJ, Horsman DE, Gascoyne RD. Mantle cell lymphoma: a clinicopathologic study of 80 cases. Blood 1997;89(6):2067-78.
Hiddemann W, Unterhalt M, Herrmann R, Wöltjen HH, Kreuser ED, Trümper L et al. Mantle-cell lymphomas have more widespread disease and a slower response to chemotherapy compared with follicle-center lymphomas: results of a prospective comparative analysis of the German Low-Grade Lymphoma Study Group. J Clin Oncol 1998;16(5):1922-30.
Barista I, Romaguera JE, Cabanillas F. Mantle-cell lymphoma. Lancet Oncol 2001;2(3):141-8.
Zhou Y, Wang H, Fang W, Romaguer JE, Zhang Y, Delasalle KB et al. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. Cancer 2008;113(4):791-8.



Age, y	Age-adjusted Incidence Rate per 100,000	Relative Risk (95% CI)
<50	0.07 (0.06-0.08)	1.00
50-59	0.83 (0.76-0.92)	11.72 (10.00-13.76)
60-69	1.96 (1.81-2.12)	27.55 (23.77-32.01)
70-79	2.97 (2.76-3.19)	41.70 (36.08-48.34)
80	2.78 (2.51-3.07)	39.10 (33.29-45.99)

Zhou Y et al. Cancer

ASPECTS THERAPEUTIQUES

Quelle Chimiothérapie ?

Anthracyclines-based chemotherapy without rituximab in MCL

Auteurs	Ref	Chimiothérapie	n	stade	RC (en %)	R. globale (%)
Meusers	Hematol Oncol, 1989	CHOP (vs COP)	26	avancés	58%	89%
Dreyling	Blood 2005	CHOP(interféron)	122	diagn	35%	75%
Gressin	Ann Oncol (suppl) 1997	VAD-chl			43%	
Khouri	JCO 1998	hyper C-VAD/ MTX	45	diag/rech	38%	93.5%
Zinzani	JCO 2000	Fluda-Ida (vs fluda)	18	diag	33%	61%

Place de l’aracytine en première ligne

High dose Ara-C in MCL

Khouri et al., 1999 : Hyper-CVAD

(n= 45)

CR/OR 38%/93%

Puis autogreffe

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*Lefrere et al., 2002 :*CHOP-DHAP

(n=28)	CR	OR
4x CHOP	7%	57%
4x DHAP	84%	92%

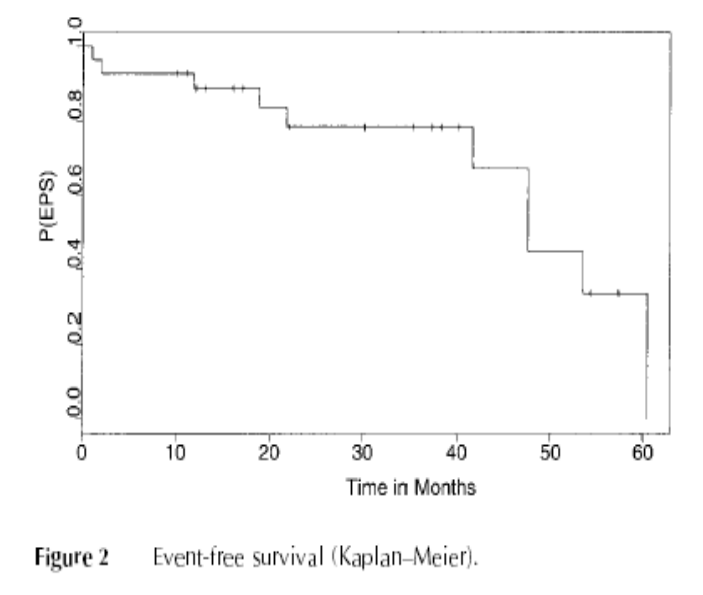


Figure 2 Event-free survival (Kaplan–Meier).

Lefrère Leukemia 2002

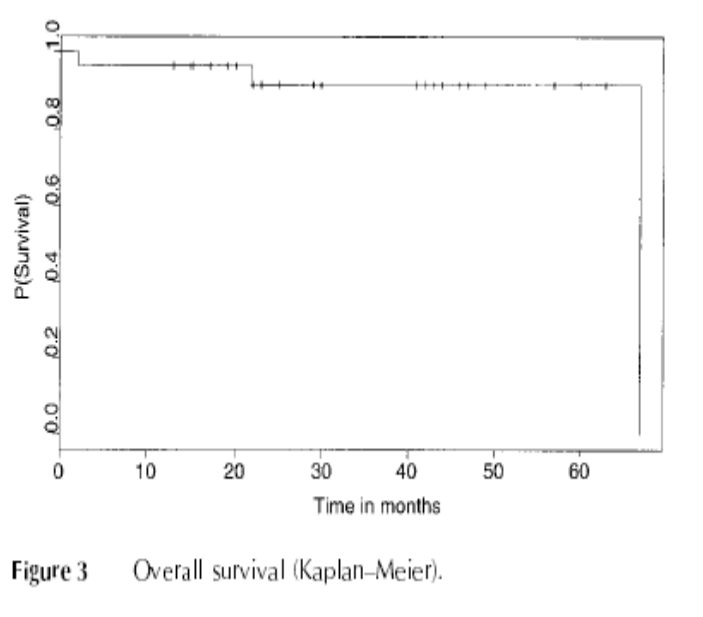


Figure 3 Overall survival (Kaplan–Meier).

De Guibert et al. (haematologica; 2006):

N=24

4 x R-DHAP: 92% CR/Cru

Geisler et al (Blood 2008)

	RC/RCu
Maxi CHOP	27%
R+maxi CHOP/HDARA-C	54.4%

French Protocol GELA

2 CHOP

↓

1 CHOP + anti-CD20

↓

3 DHAP + anti-CD20

↓

CSP collection

↓

TAM 6 + ABMT

Delarue et al., 2003

	After three courses (R)-CHOP	After three courses of R-DHAP
Evaluable Patients	42	39
CR	6/42 (14%)	20/39 (51%)
PR	31/42 (74%)	11/39 (28%)
Stable Disease	3/42 (7%)	1/39 (3%)
Patient exclusion	2/42 (5%)	7/39 (18%)
Progressive disease	0/42	2/39

Place du Rituximab ?

Chimiothérapie avec rituximab

auteur	Ref	ttt		n	RC/Cru
Romaguera	JCO oct 2005	R-hyper CVAD/MTX arac	diag	97	87%
Howard	JCO 2002	CHOP-R	diag	40	48%
Wilson	Blood (Abst 358) 2003	EPOCH-R		26	92%
Lenz	JCO 2005	CHOP (21) x 6	diag	60	7%
	vs	CHOP-R (21) x6		62	34%
Forstpointner	Blood 2004 (FL et MCL)	FCM vs	rech	24	CR: 0%
		FCM-R		24	29%
De Guibert	Haematologica 2006	R-DHAP	Diag	24	92%
Geisler	**Blood**	**R+CHOP/HD AraC**	**Diag**	**160**	**54.4%**

Immunochemotherapy With Rituximab and Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Significantly Improves Response and Time to Treatment Failure, But Not Long-Term Outcome in Patients With Previously Untreated Mantle Cell Lymphoma: Results of a Prospective Randomized Trial of the German Low Grade Lymphoma Study Group (GLSG)

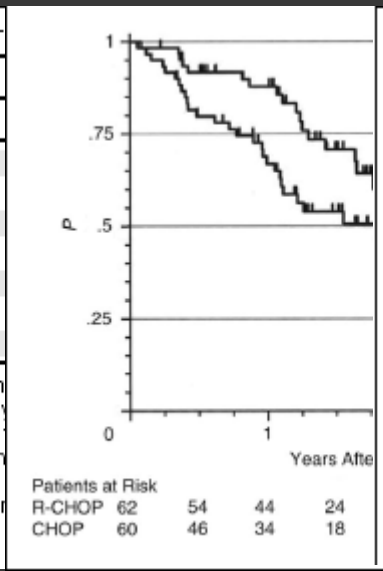
Georg Lenz, Martin Dreyling, Eva Hoster, Bernhard Wörmann, Ulrich Dührsen, Bernd Metzner, Hartmut Eimermacher, Andreas Neubauer, Hannes Wandt, Hjalmar Steinhauer, Sonja Martin, Else Heidemann, Ali Aldaoud, Reza Parwaresch, Joerg Hasford, Michael Unterhalt, and Wolfgang Hiddemann

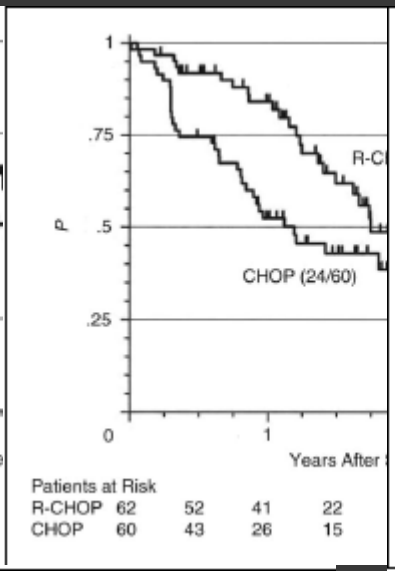
A B S T R A C T

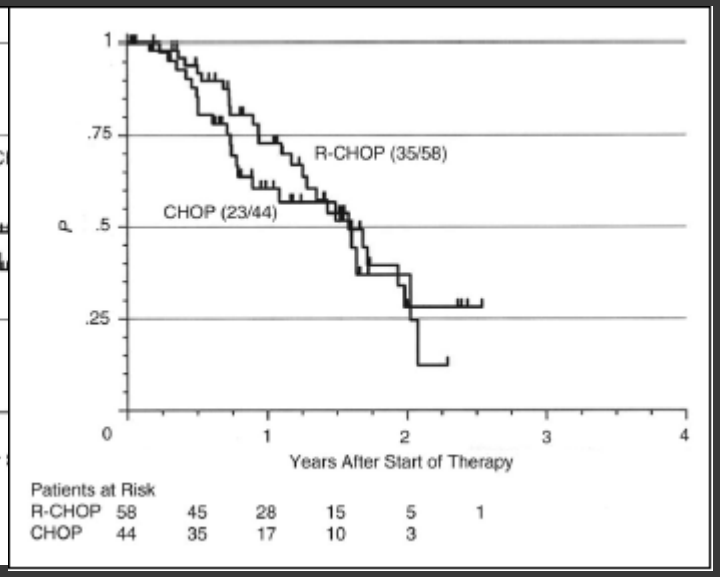
Table 2. Response to Induction T

	CHOP
	No.
Total No.	59*
CR or PR	44
CR	4
PR	40
MR/SD	11
PD	4
Ex	0

NOTE. Rituximab plus cyclophosph prednisone (R-CHOP) was significantly remission (CR) rate (P = .00024) and
Abbreviations: PR, partial remission disease; PD, progressive disease; Ex,
*Only 59 patients assessable, as in o after therapy.



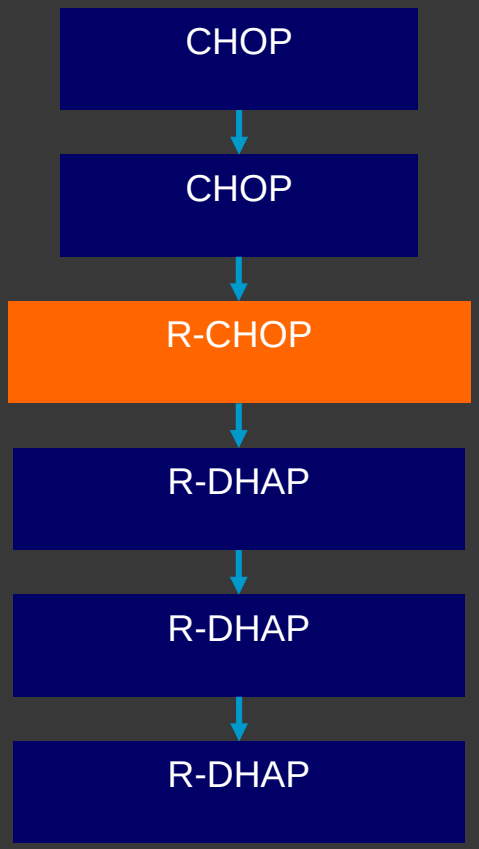




Taux de réponse **Délai traitement de rechute** **TTF** **OS**

Lymphome du manteau : RCHOP et RDHAP suivi d'une autogreffe
Analyse finale de l'étude de phase II du GELA

- 60 patients de moins de 66 ans
- Lymphome du Manteau
- non traités
- Stade III ou IV



Autogreffe de cellules souches périphériques
(TAM 6 ou BEAM)

ASH 2008 - D'après R. Delarue et al., Abstract 581 actualisé

Chimiothérapie d'induction

Autogreffe ?

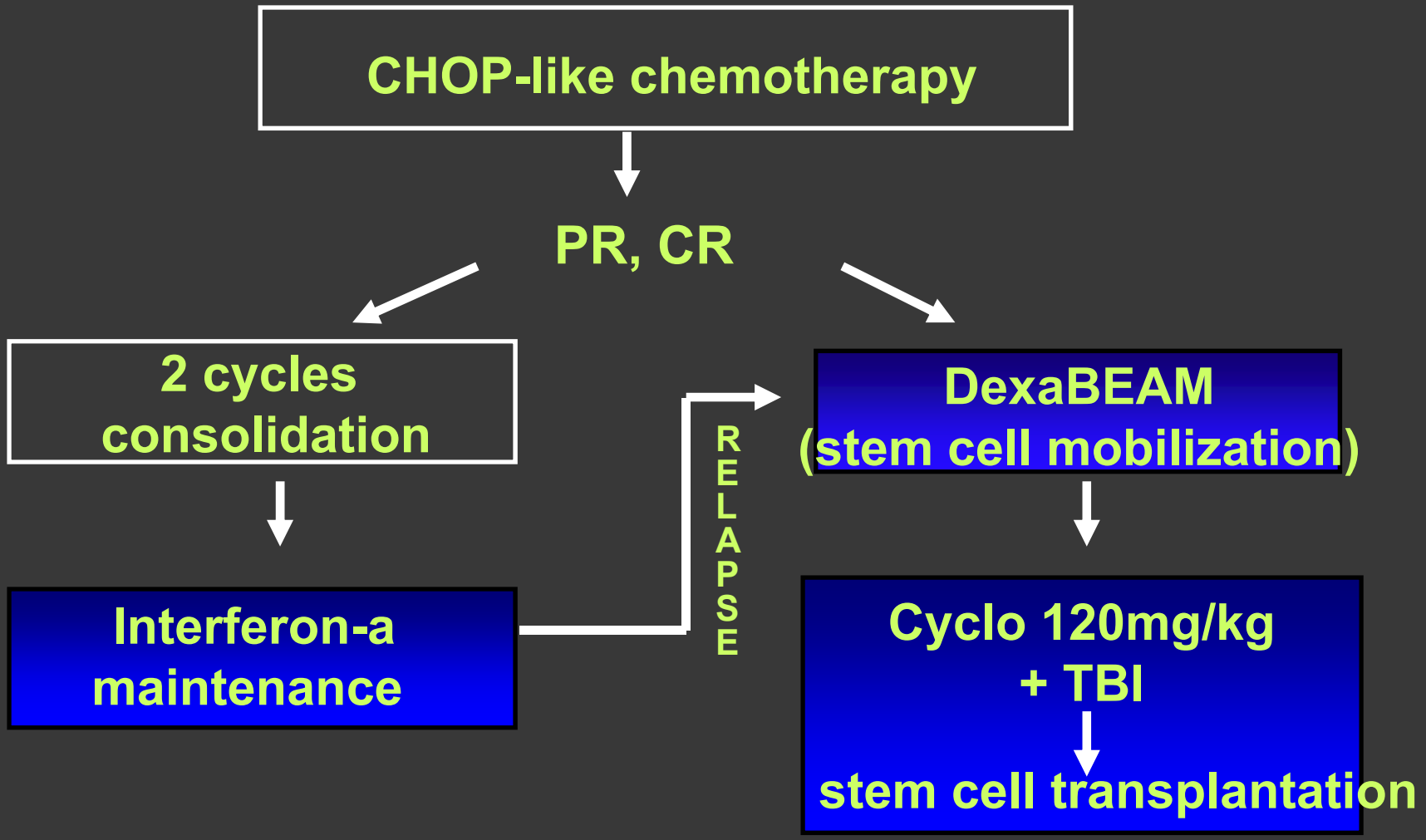
R-CHOP

R-CHOP/Aracytine

R-Aracytine

R-Hyper C-VAD

European MCL Network: ASCT vs. IFN

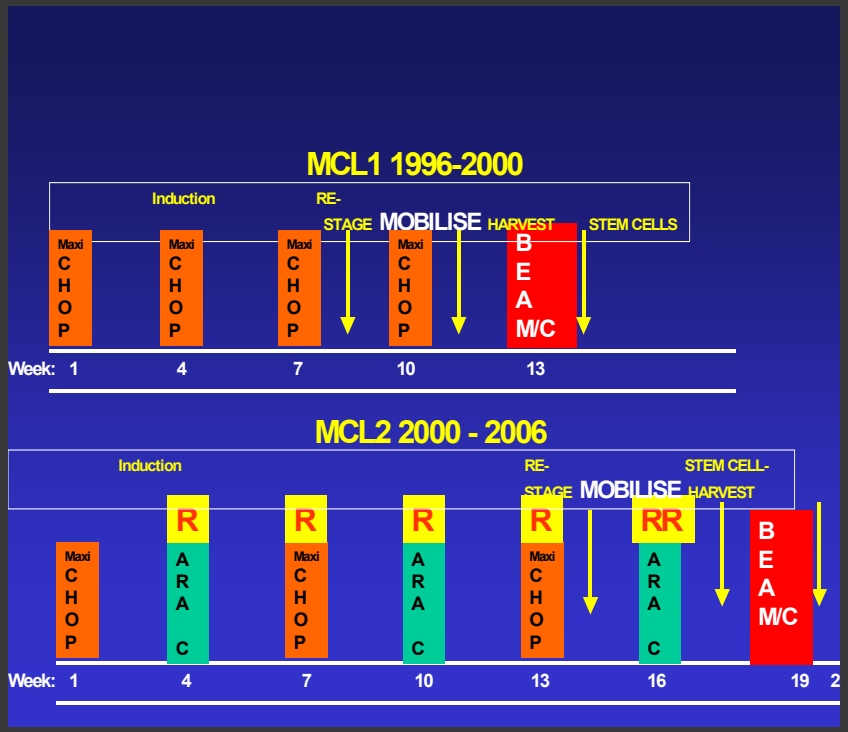


European MCL Network: ASCT vs. IFN
Best response after consolidation (PP)

	CR	PR
ASCT	**49 (78%)**	**13 (21%)**
IFN	**24 (35%)**	**44 (64%)**

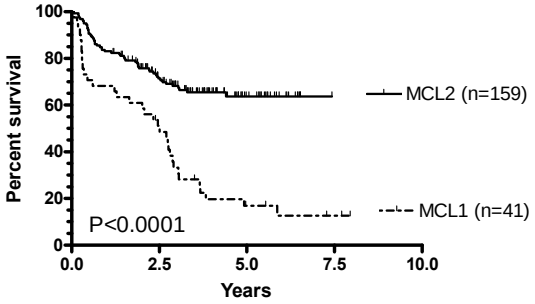
ASCT-related deaths: 6 of 75 (8%)

Dreyling et al. ASH 2008

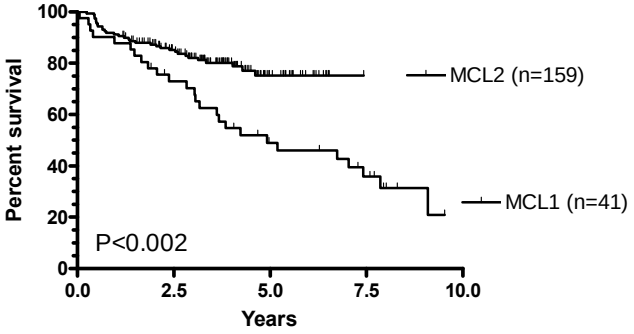


Nordic MCL1 and MCL2 protocols:

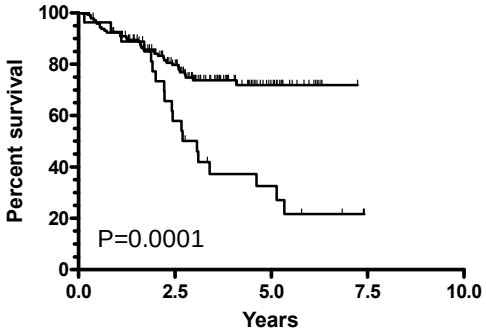
A: Event-free Survival proportions



B: Survival



C: Response duration



Autogreffe

auteur	Ref	Ttt avant greffe		N	RC/Cru post auto	ORR	Median FU	PFS	OS
Dreyling	Blood 2005	CHOP+/-R like	Diag	62	81%	98%	39m	54% - 3y	83% - 3y
Khouri	Cancer 2003	Hyper C-VAD/MTX arac	Diag	33	100%	100%	49m	43% - 5y	77% - 5y
Gianni	Blood 2003	R HD chimio/2 auto (Melph)	Diag	28	100%	100%	35m	79% - 4.5y	89% - 4.5y
Thieblemont	Cancer 2005	R-chimio ou chimio puis R	Diag (n=29)	34	77%	100%	31m	71% - 3y	87% - 3y
Vigouroux	Haematologica	CHOP like+/- DHAP	Diag	30	87%	97%	55m	40% - 5y	62% - 5y
Geisler	Blood 2008	R-HD-CHOP/HD-ARA	diag	160	89.7%	96%	47m	66% - 6y	70% - 6y

Chimiothérapie d'induction	Autogreffe
R-CHOP	**TBI/endox ?**
R-CHOP/Aracytine	**TAM ?**
R-Aracytine	**BEAM ?**
R-Hyper C-VAD	

BMT, Milpied et al., 1998

N=18

FU= 36 mois

DFS à 4ans: 48%

OS à 4 ans: 80%

TBI> no TBI en DFS et OS

Chimiothérapie d'induction + rituximab	autogreffe	Entretien ?

R-VAD-C

R-CHOP 14

R-CHOP14 /R-DHAP

R-DHAP

TBI/Endoxan

TAM

BEAM

Z-BEAM

Lefrère Leukemia 2002

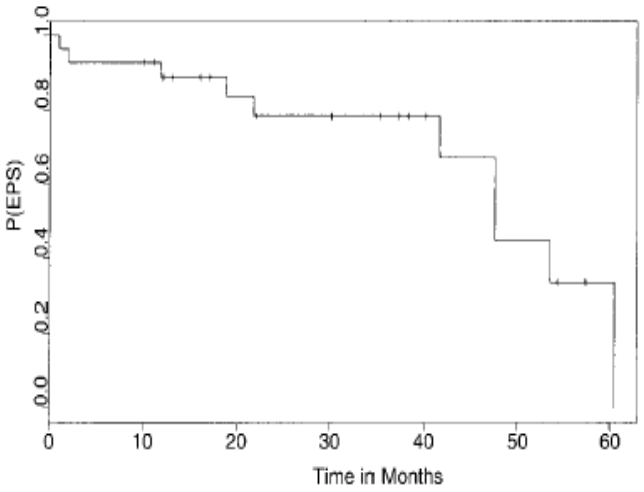


Figure 2 Event-free survival (Kaplan–Meier).

Lefrère Haematologica 2004

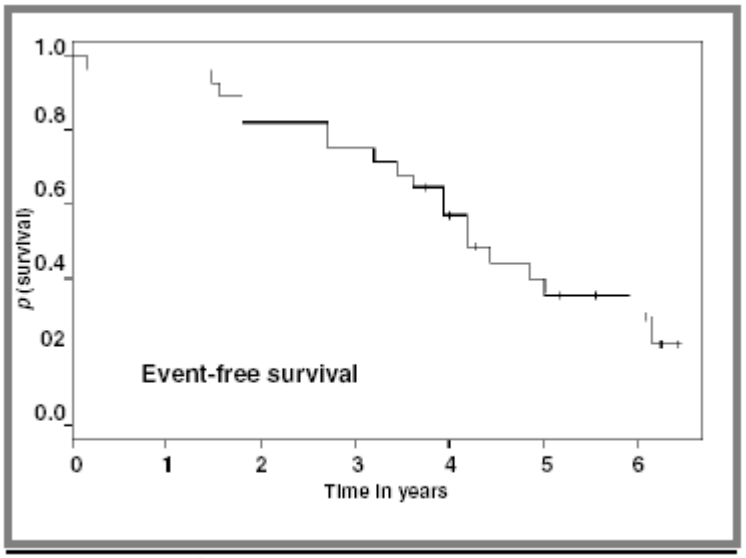


Figure 2. Event-free survival (Kaplan-Meier).

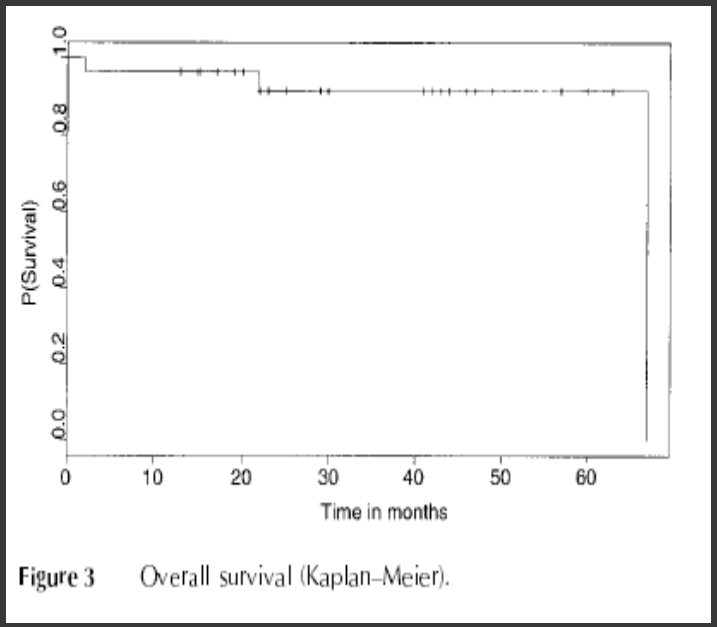


Figure 3 Overall survival (Kaplan–Meier).

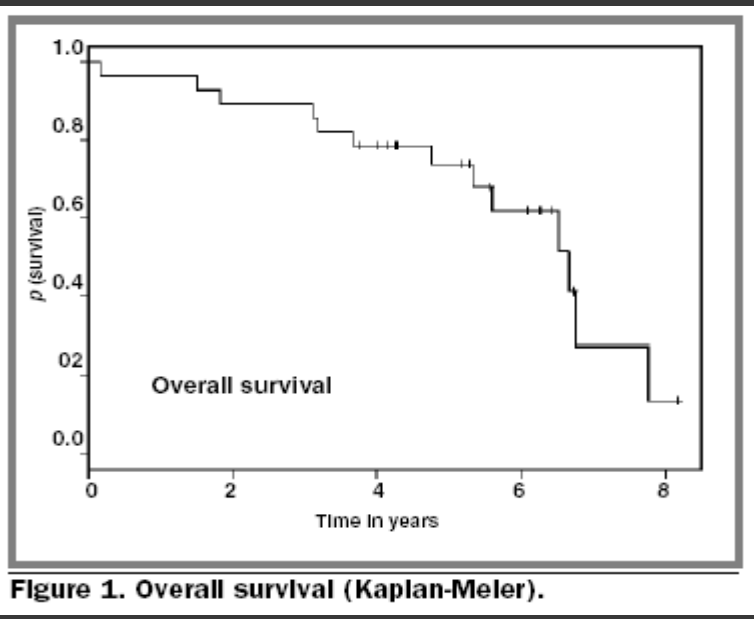
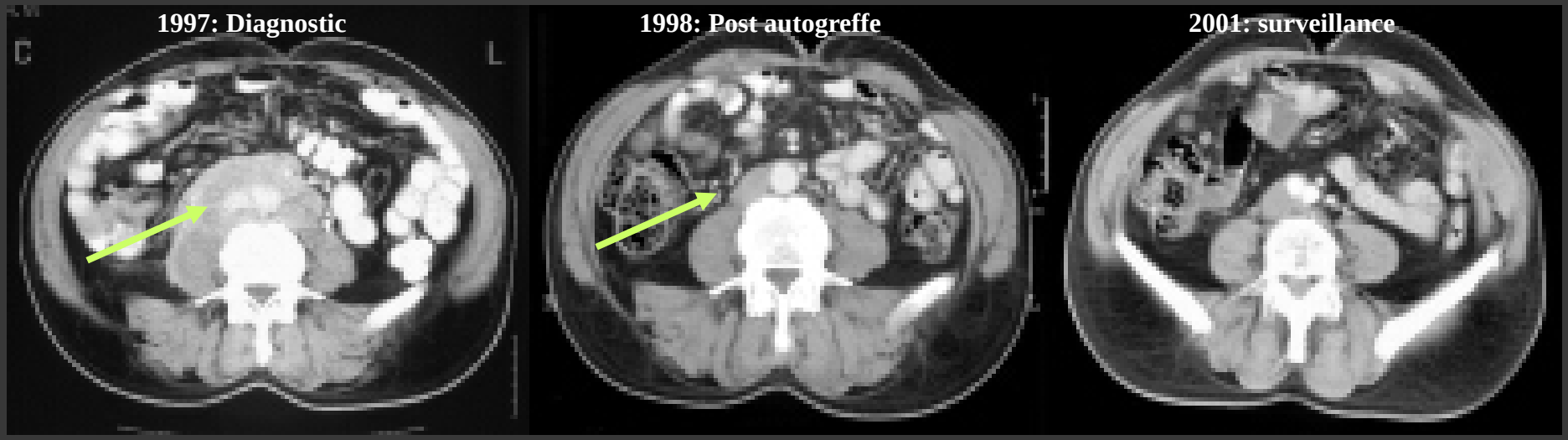
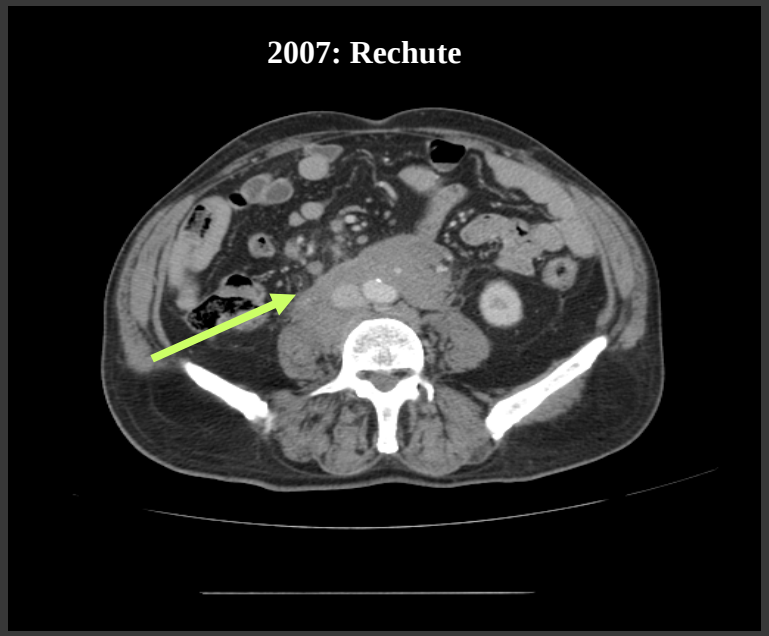


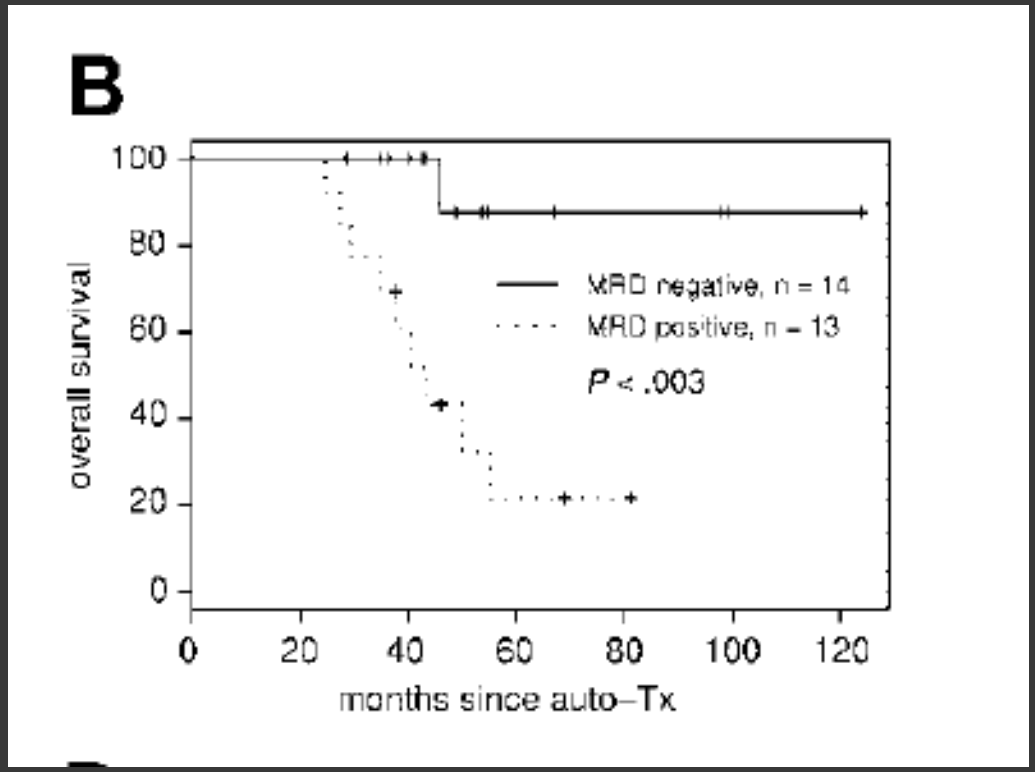
Figure 1. Overall survival (Kaplan-Meier).


1997: Diagnostic
1998: Post autogreffe
2001: surveillance


2007: Rechute

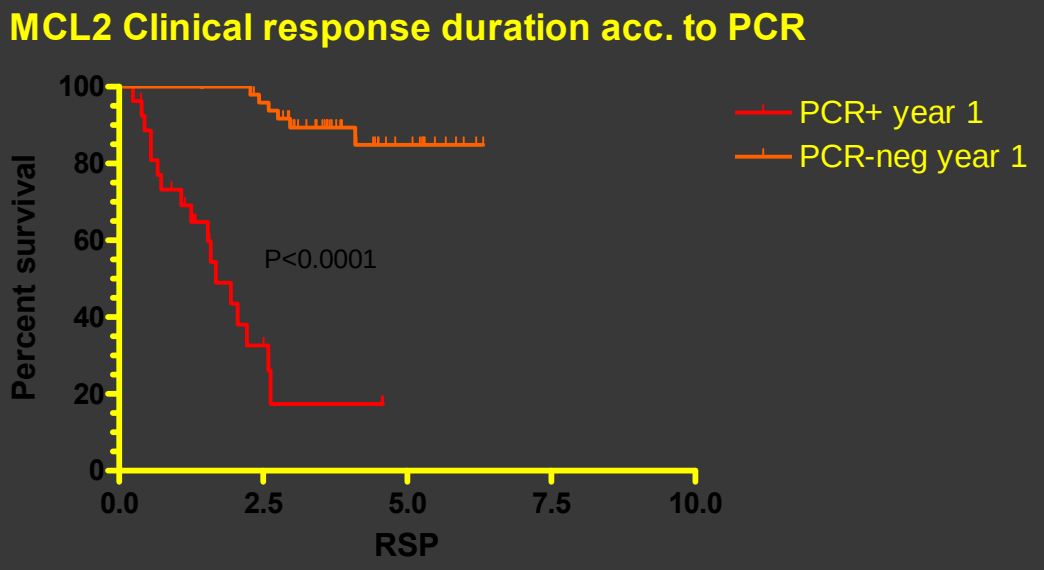
Quantitative assessment of molecular remission after high-dose therapy with autologous stem cell transplantation predicts long-term remission in mantle cell lymphoma

Christiane Pott, Carsten Schrader, Stefan Gesk, Lana Harder, Markus Tiemann, Thorsten Raff, Monika Brüggemann, Matthias Ritgen, Benedikt Hahn, Michael Unterhalt, Martin Dreyling, Wolfgang Hiddemann, Rainer Siebert, Peter Dreger, and Michael Kneba



Nordic MCL protocols: Results

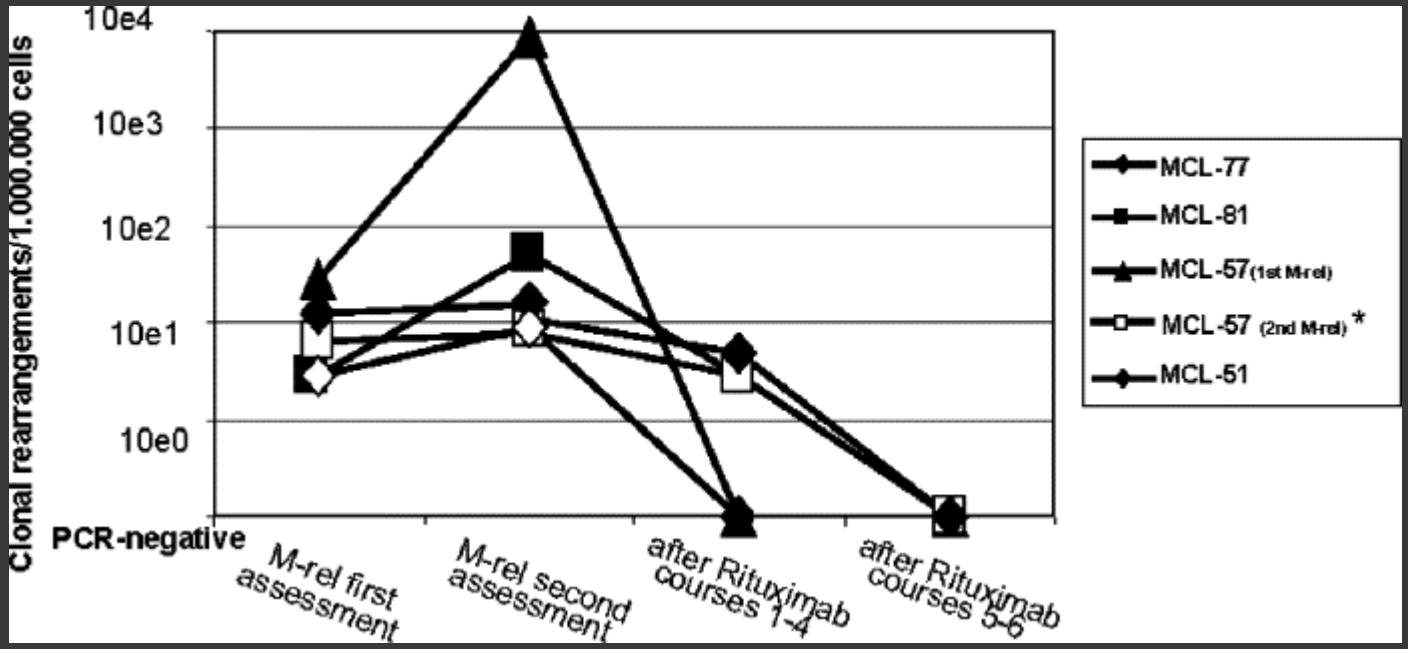
Clinical response duration According to PCR



Chimiothérapie d'induction + rituximab	autogreffe	Entretien ?
R-VAD-C	TBI/Endoxan	Rituximab ?
R-CHOP 14	TAM	
R-CHOP14 /R-DHAP	BEAM	
R-DHAP	Z-BEAM	

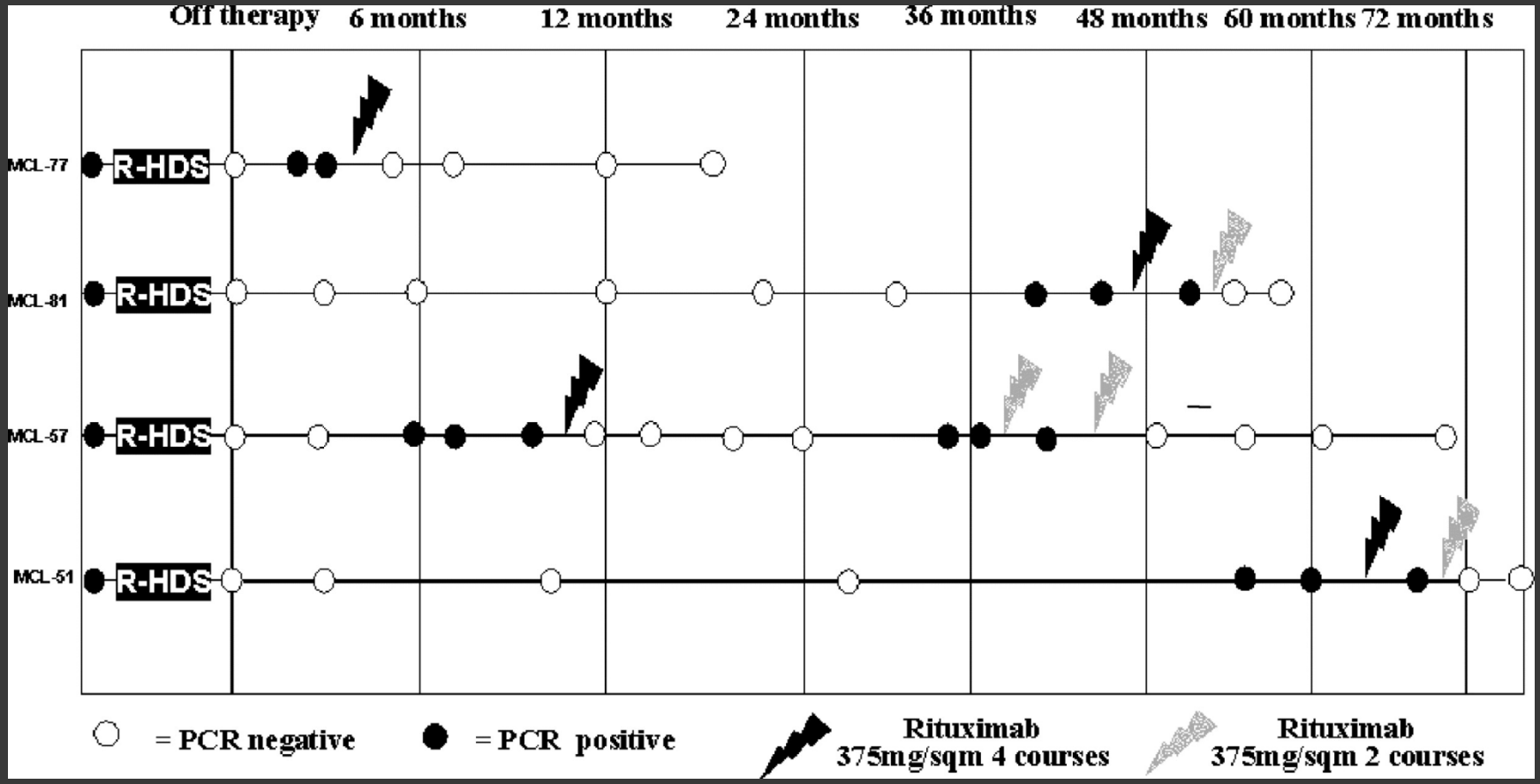
Rituximab Induces Effective Clearance of Minimal Residual Disease in Molecular Relapses of Mantle Cell Lymphoma

Marco Ladetto,[1] Michele Magni,[2] Gloria Pagliano,[1] Federica De Marco,[1] Daniela Drandi,[1] Irene Ricca,[1] Monica Astolfi,[1] Paola Matteucci,[1] Anna Guidetti,[1] Barbara Mantoan,[1] Chiara Lobetti Bodoni,[1] Manuela Zanni,[1] Mario Boccadoro,[1] Alessandro M. Gianni,[2,3] Corrado Tarella[1]



« Rituximab Induces Effective Clearance of Minimal Residual Disease in Molecular Relapses of Mantle Cell Lymphoma » Marco Ladettoet al.

Biology of Blood and Marrow Transplantation, dec 2006

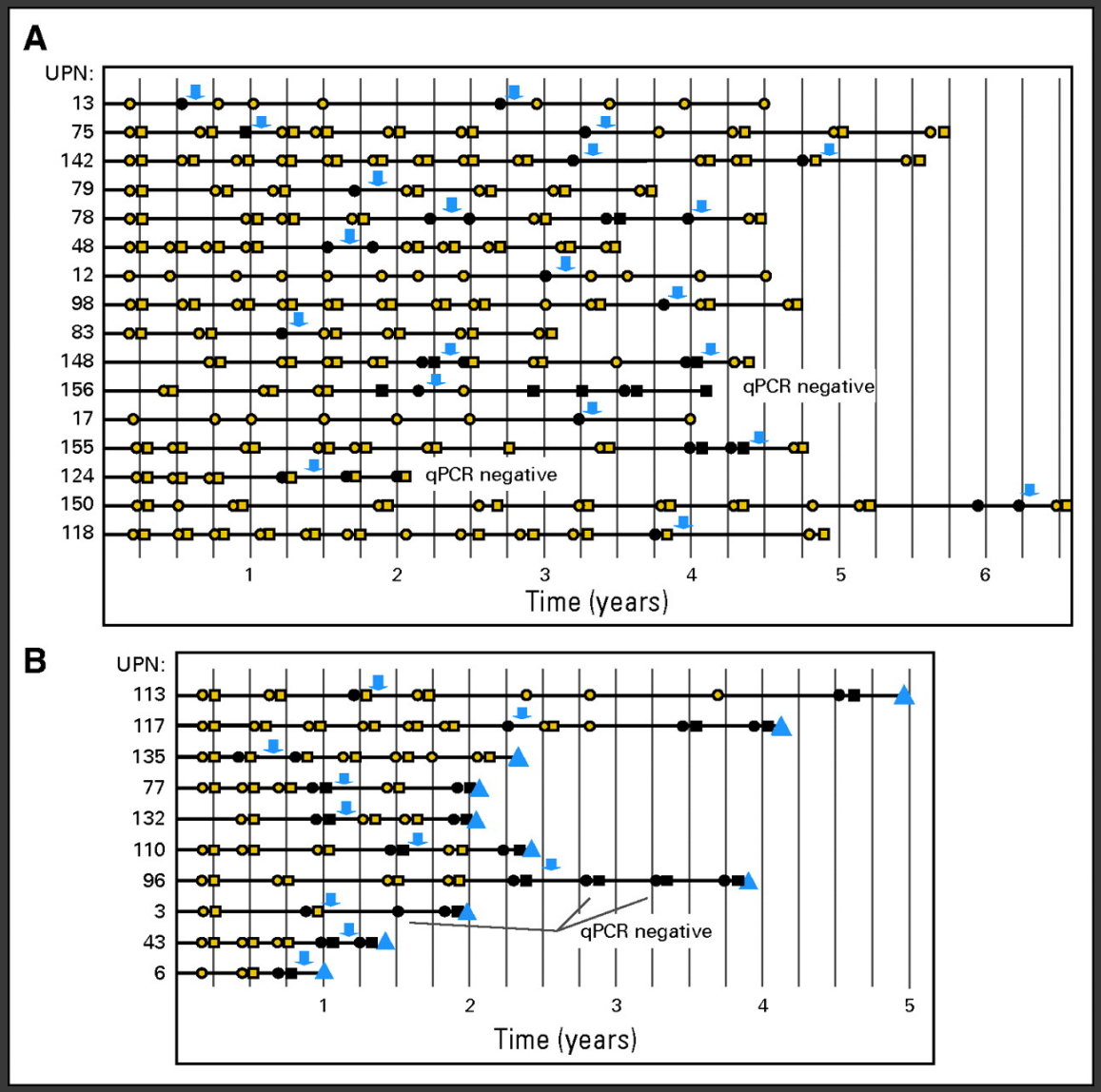


« Rituximab Induces Effective Clearance of Minimal Residual Disease in Molecular Relapses of Mantle Cell Lymphoma » Marco Ladettoet al.

Biology of Blood and Marrow Transplantation, dec 2006

sang MO Neg Pos Ritu Rechute cliniqu

Patients en RC clinique

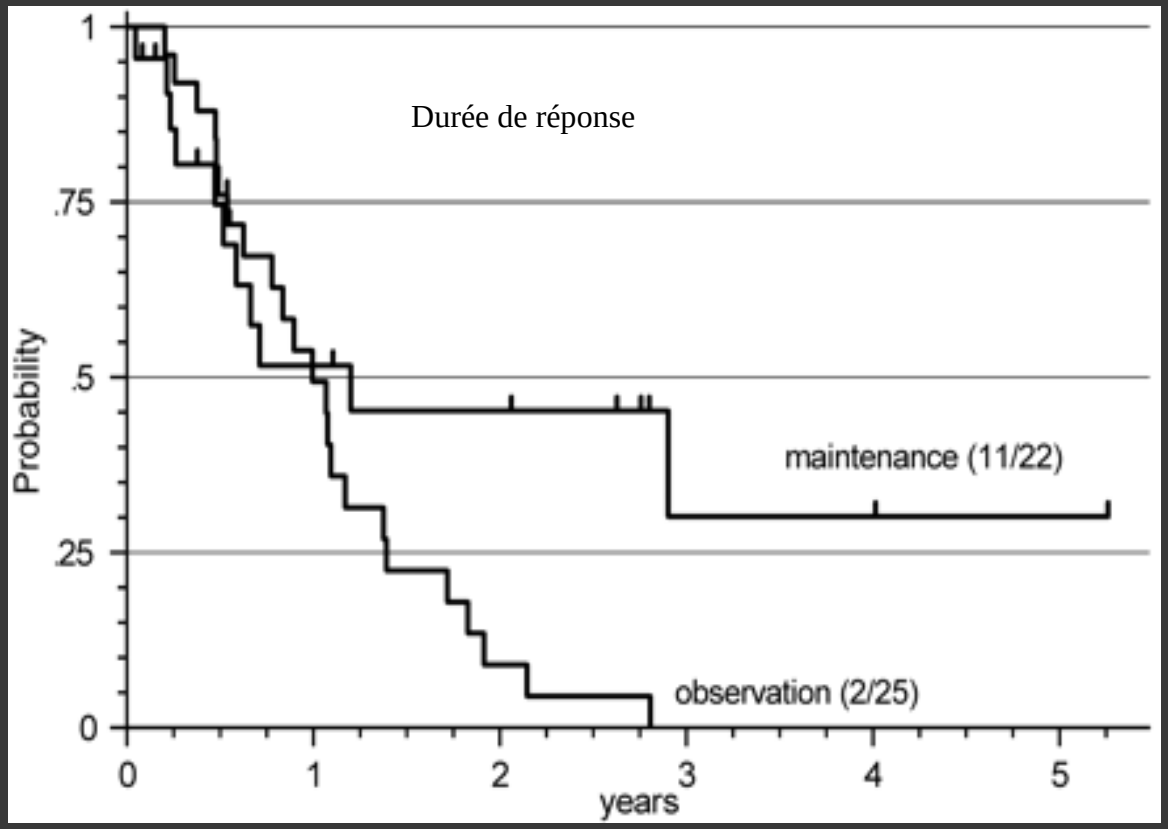


Nested-PCR

Patients avec rechute clinique après

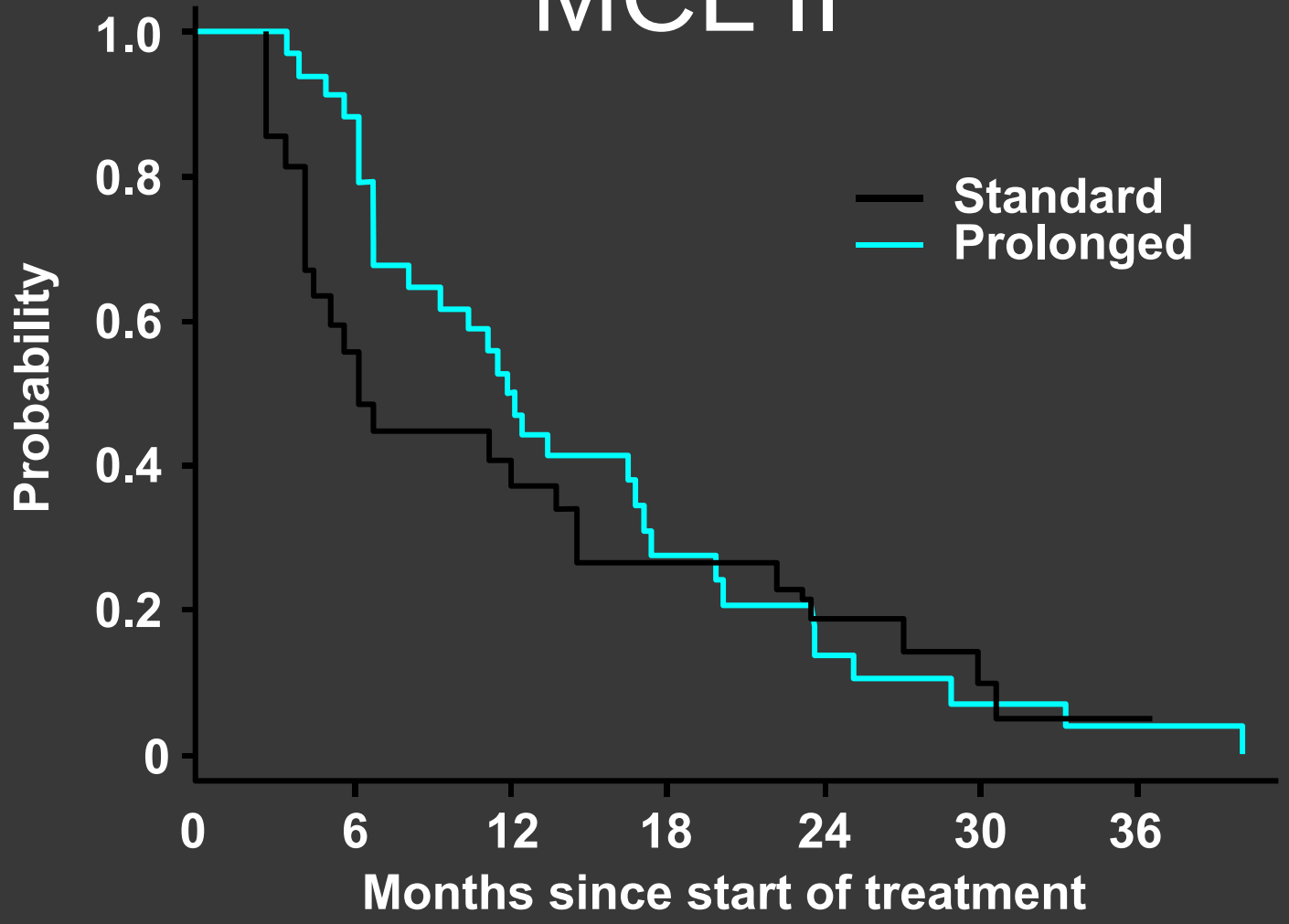
Andersen, N. S. et al. J Clin Oncol; 27:4365-4370 2009

Rituximab et entretien



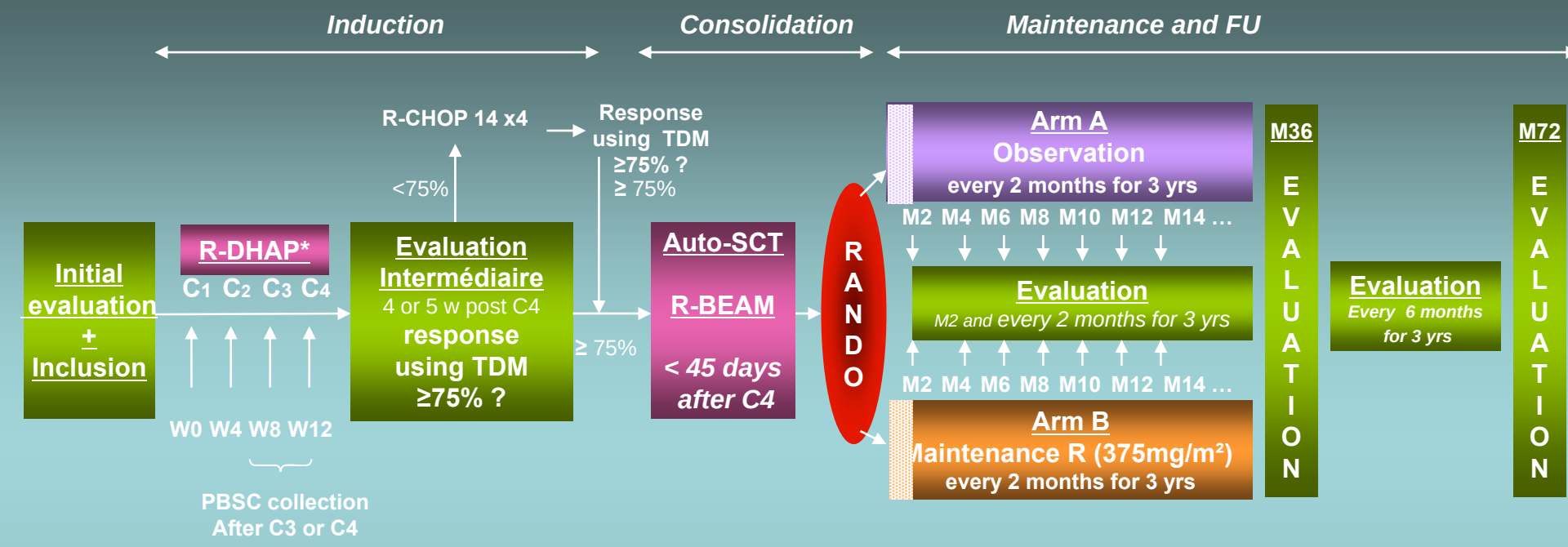
Forstpointner et al Blood 2006

Rituximab maintenance in MCL II



Ghielmini M, *et al. J Clin Oncol* 2005; **23:**705–711.

Etude LyMA



	Before R-DHAP	Before ASCT	M2		M36		M72
TDM	●	●	●	● : every 6 months	●	● : every year	●
PET	▲	▲	▲	▲ : M12			
Biological studies (MRD)							
Blood	◆	◆	◆	◆ : M6,12,18, 24, 30	◆	◆ : M42, M48	
BM	⧗	⧗	⧗	⧗ : M12, 24	⧗	⧗ : M48	

R-DHAP or R-DHA-Carboplatin or R-DHA-Oxaliplatinum*

Chimiothérapie d'induction + rituximab	autogreffe	Entretien ?

R-VAD-C

R-CHOP 14

R-CHOP14 /R-DHAP

R-DHAP

Autre:
Revlimid
Velcade
Bendamustine

TBI/Endoxan

TAM

BEAM

Z-BEAM

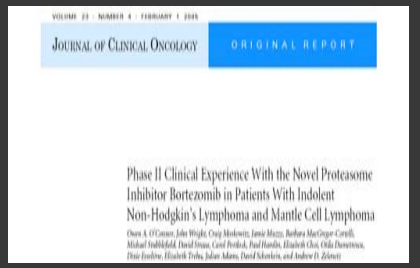
Rituximab ?

…

Traitement rechute moléculaire ?

Phase II clinical experience with the novel proteasome inhibitor Bortezomib in patients with indolent Non-Hodgkin's Lymphoma and Mantle Cell lymphoma

O'Connor *et al* JCO février 2005 (vol 23, (4) 676-684)



Phase II study of proteasome inhibitor Bortezomib in relapsed or refractory B-Cell Non-Hodgkin's Lymphoma

A Goy *et al* JCO février 2005 (vol 23, (4) 667-675)

Multicenter phase II study of bortezomib in patients with relapsed or refractory MCL

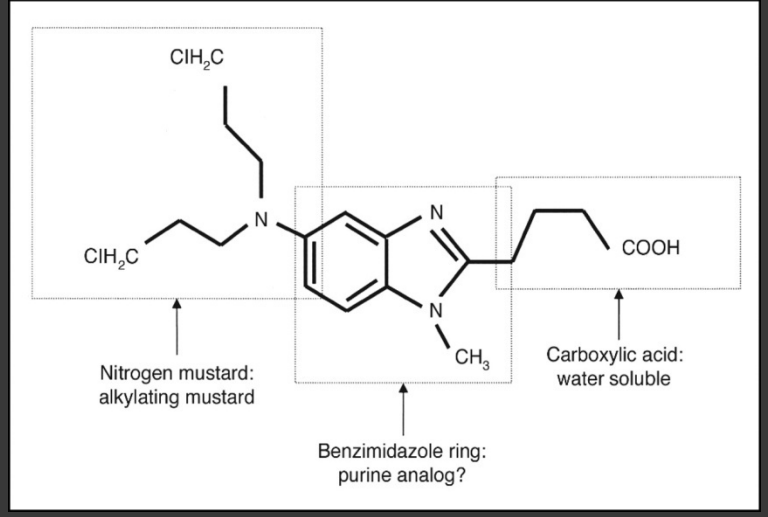
Fisher R et al. JCO octobre 2006

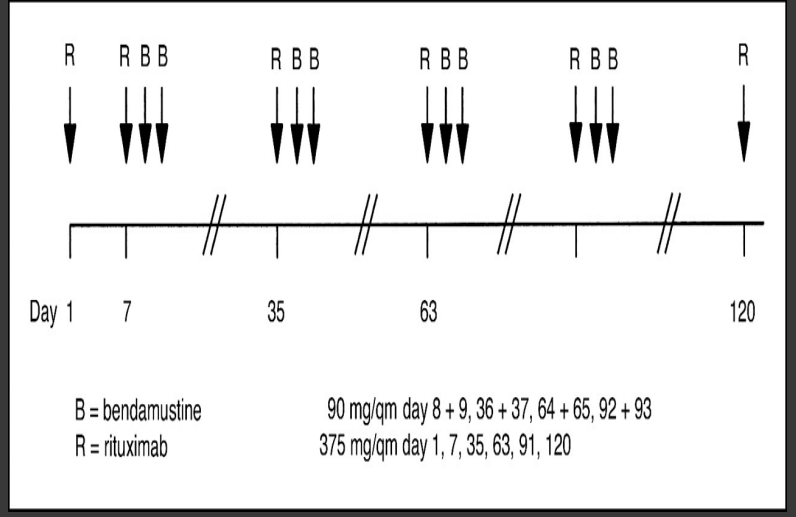
- 155 patients en rechute de MCL (de 1 à 3 lignes de ttt avant)
- Taux de réponse: 33%
- Taux de RC/Rcu: 8%
- TTP 6.2 mois
- Durée médiane de réponse: 9.2 mois

Velcade-Hyper-CVAD-rituximab

Velcade- Hig-dose aracytine-rituximab (Leuk. and Lymphoma)

Ri-PAD





RECHUTE:

Rummel, M. J. et al. J Clin Oncol; 23:3383-3389 2005

MCL =16 patients
RC = 8
PR=4
PFS médiane = 18 mois

Robinson, K. S. et al. J Clin Oncol; 26:4473-4479 2008
MCL =12 patients
RC = 5

Première ligne:

Rummel ASH 2007 abstact 385
R-CHOP vs R-B : taux de RC identique: 40% RC

REVLIMID

MCL =15 pts

CR/Cru =2

PR =6

Wiernick JCO 2008

Habbermann BJH 2009

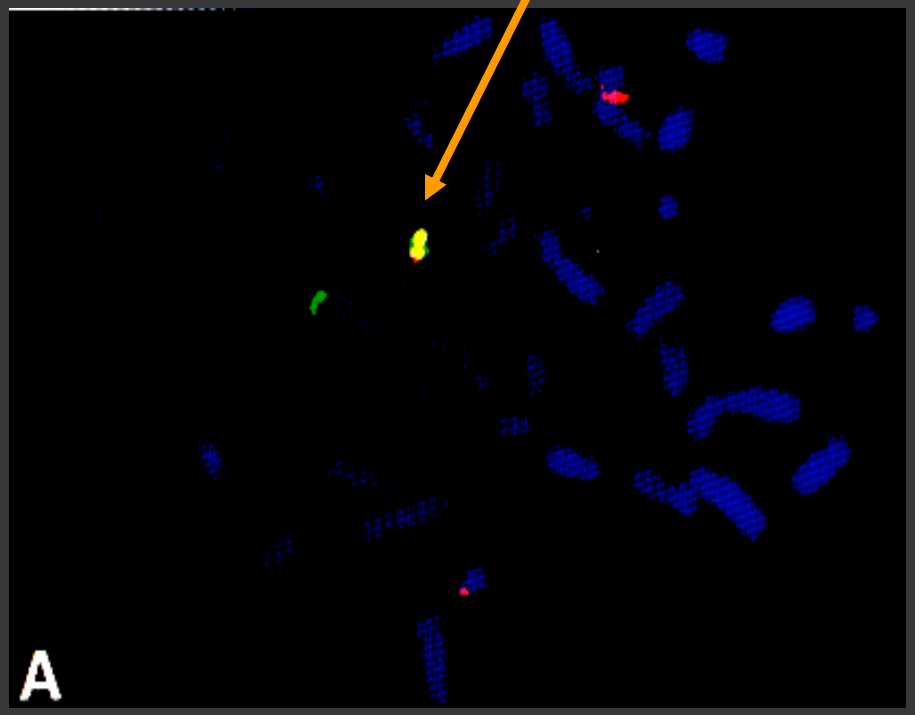
ORR 53%

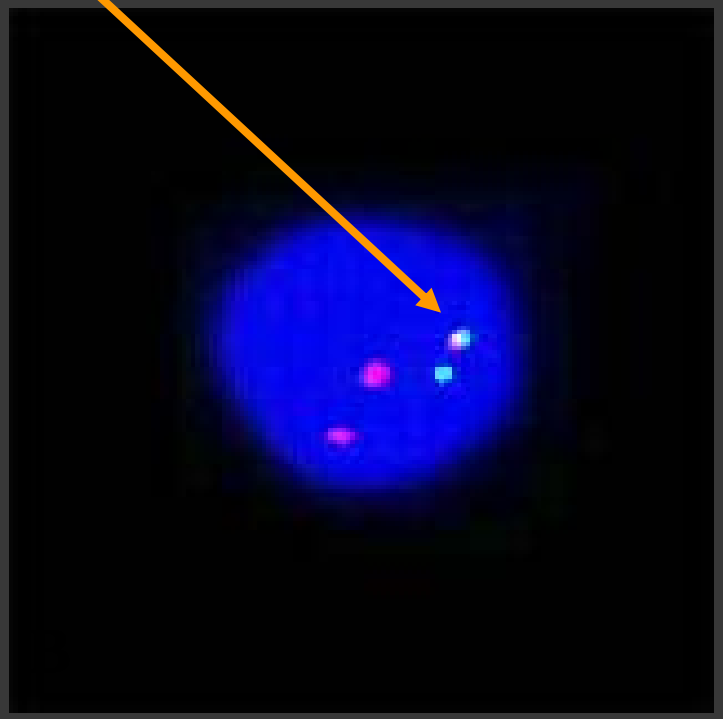
Durée médiane de réponse = 13.7

PFS = 5.6m

Nouvelles alternatives thérapeutiques ?

Fusion BCL1-IgH





FISH sur métaphase

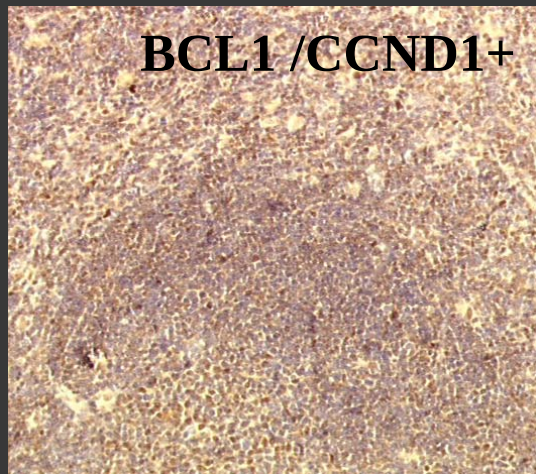
FISH interphasique

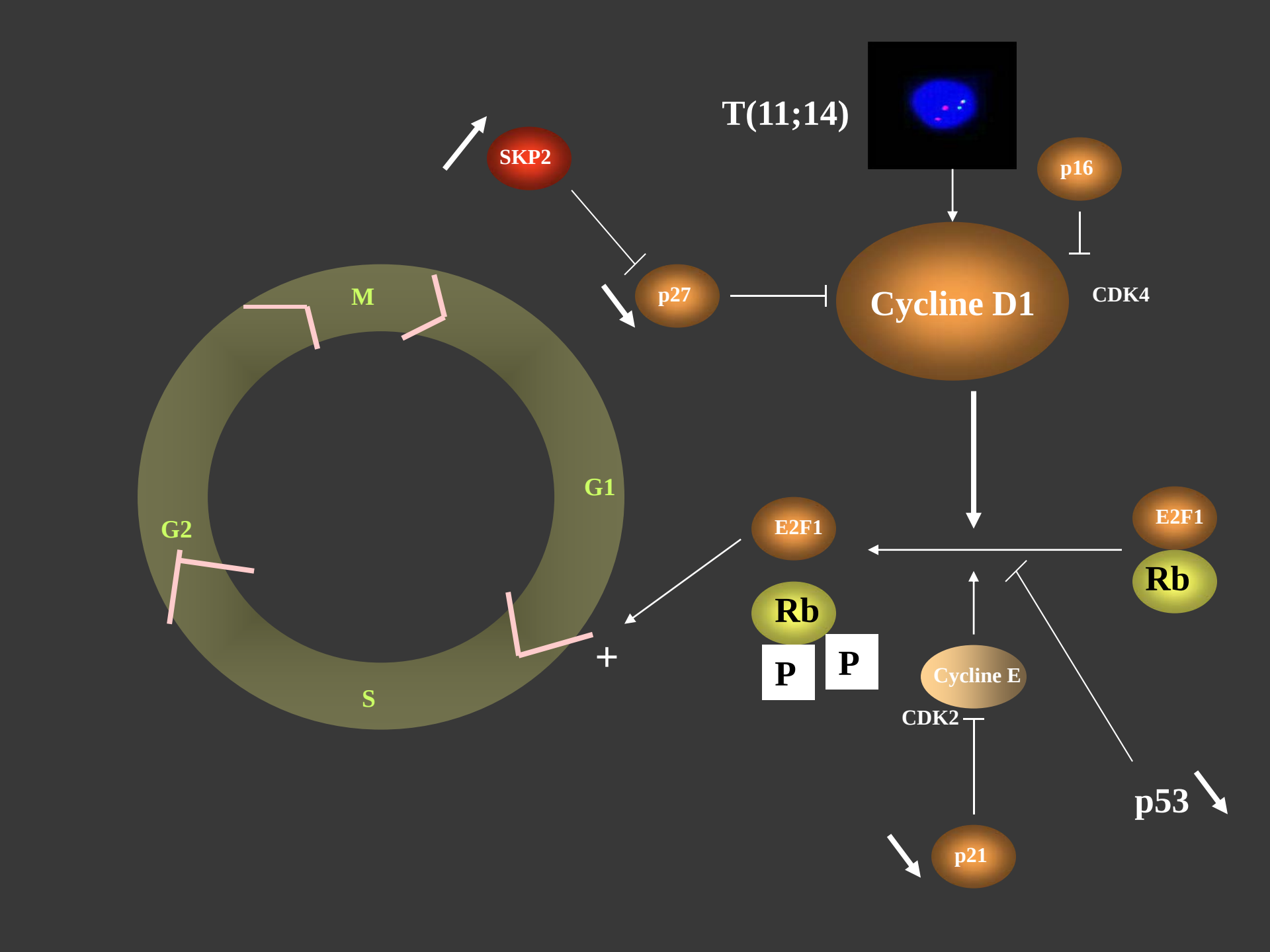
détection de la t(11;14) en FISH

sondes CCND1 (rouge) et IgH (verte)

Immuno-histochimie sur coupe

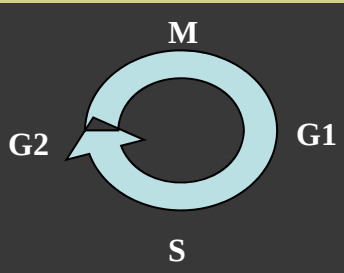
hyper-expression de la cycline D1 (CCND1)

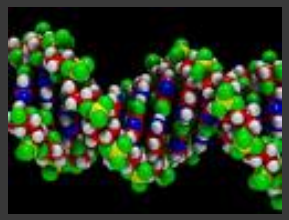


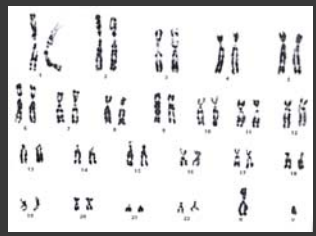

T(11;14)
SKP2
p16
p27
Cycline D1
CDK4
M
G1
G2
S
E2F1
E2F1
Rb
Rb
P
P
+
Cycline E
CDK2
p53
p21

t(11;14)(q13;q32) + Evènement(s) oncogénique(s)

Cycle cellulaire + Voie de réparation de l' ADN + Apoptose + Anomalie caryotype







Lymphome à cellules du manteau

Cycle cellulaire

t(11;14): Cycline D1

Cycline D2 ou D3

Voie p53 (ARF-MDM2-p53)

Voie RB (INK4a-CDK4-RB1)

p27: cycline D1, cycline E-CDK2, CDK4,

p21: Cycline E, CDK4

CDK4 et ses inhibiteurs INK4 (p15, p16)

mTOR

Voie de réparation de l' ADN

Mutation *ATM*

CHK2 et CHK1 voie p53

Anomalie caryotype*

NOMBRE tétraploïdie

GAINS:

3q25	
4p12-13	
7p21-22	
8q21	*MYC*
9q22	*SYK*
10p11-12	*BMI1*
12q13	*CDK4*
18q11-q23	*BCL2*

PERTES:

1p13-p31	
2q13	*BIM*
6q23-q278p21	
9p21-22	*CDKN2A*
10p14-15	
11q22-23	*ATM*
13q11-q13	
13q14-q34	
17p13	*p53*
22q12	

Apoptose

Protéines:

BCL-2

BIM

FLIP

Voies régulatrices:

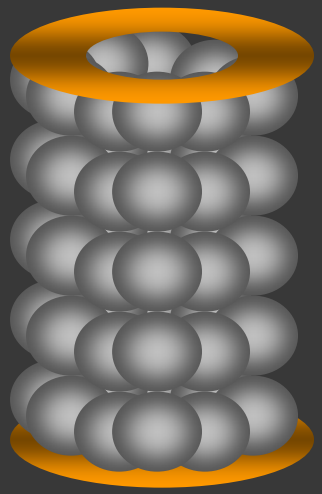
NFkB

Akt (PTEN)

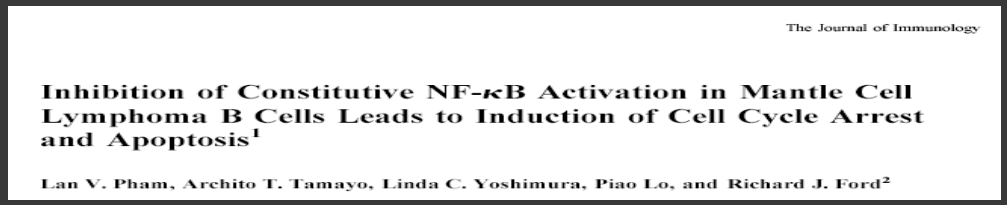
STAT-3 via Cycline D1

* d'après Jares et al. Nature Reviews cancer oct 2007

Inhibiteur du protéasome



- Inhibition de dégradation
- inhibition NfkB
- Limite progression cycle cellulaire (p21 p27)
- Potentialise autres molécules



The Journal of Immunology

Inhibition of Constitutive NF-κB Activation in Mantle Cell Lymphoma B Cells Leads to Induction of Cell Cycle Arrest and Apoptosis[1]

Lan V. Pham, Archito T. Tamayo, Linda C. Yoshimura, Piao Lo, and Richard J. Ford[2]

Cycle cellulaire

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Cycline D2 ou D3

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22q12	

Apoptose

Protéines:

BCL-2

BIM

FLIP

Voies régulatrices:

NFkB

Akt (PTEN)

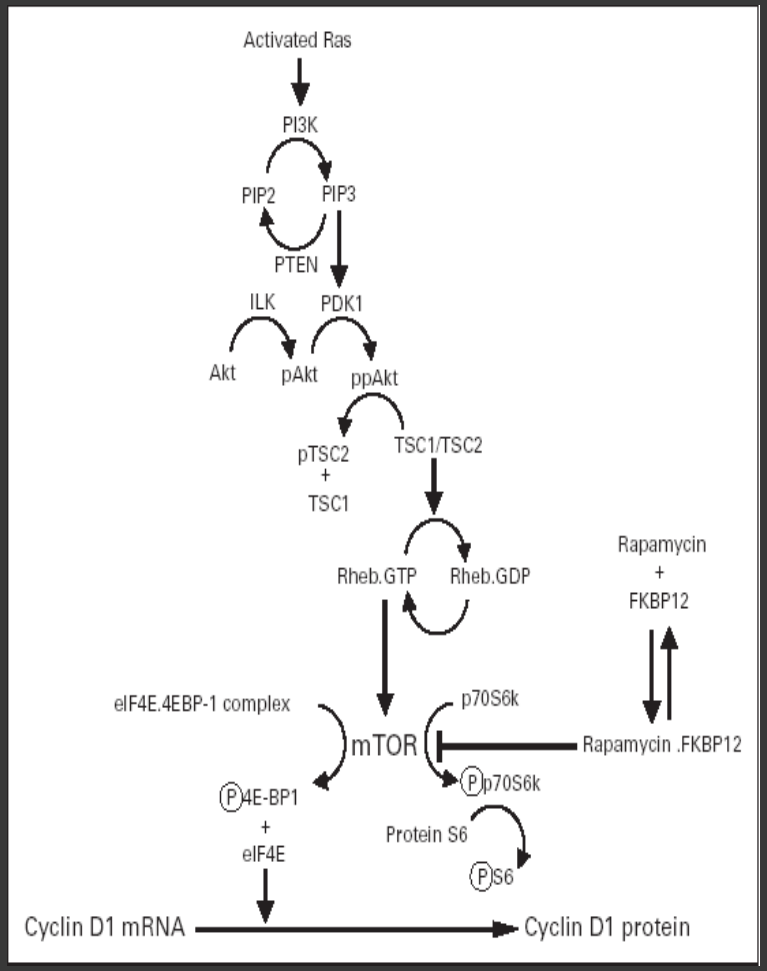
STAT-3 via Cycline D1

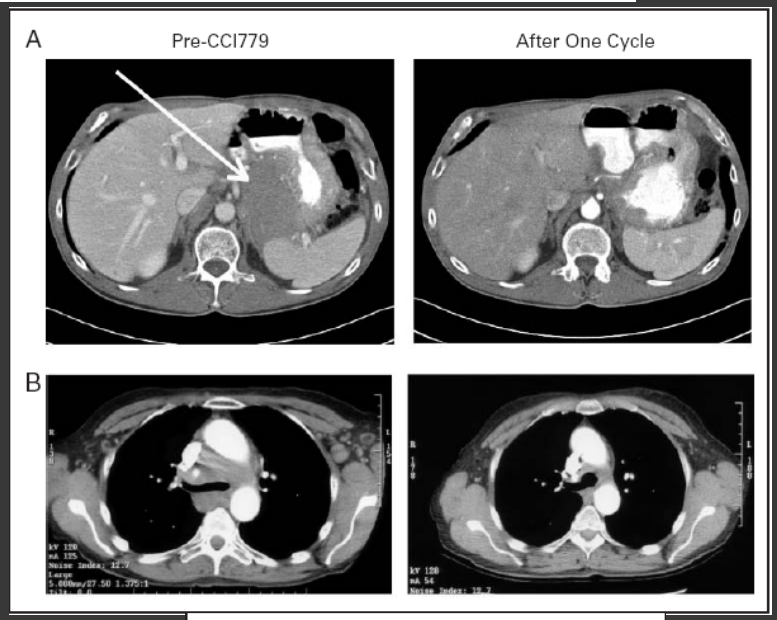
* d'après Jares et al. Nature Reviews cancer oct 2007

Phase II Trial of Single-Agent Temsirolimus (CCI-779) for Relapsed Mantle Cell Lymphoma

Thomas E. Witzig, Susan M. Geyer, Irene Ghobrial, David J. Inwards, Rafael Fonseca, Paul Kurtin, Stephen M. Ansell, Ronnie Luyun, Patrick J. Flynn, Roscoe F. Morton, Shaker R. Dakhil, Howard Gross, and Scott H. Kaufmann

A B S T R A C T





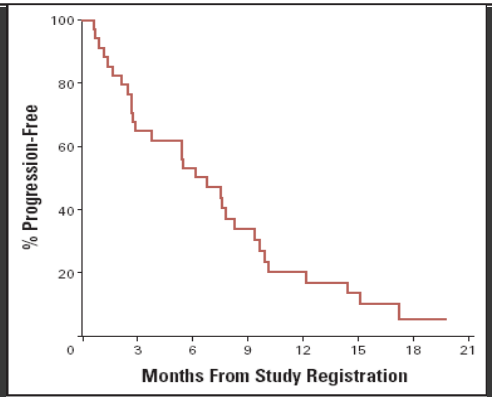
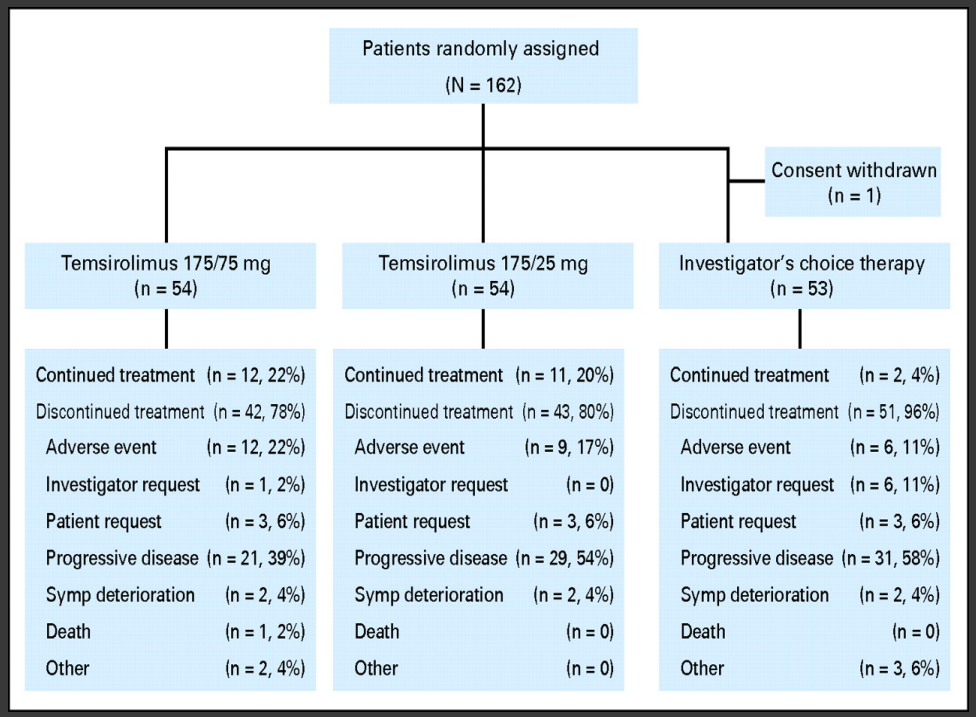
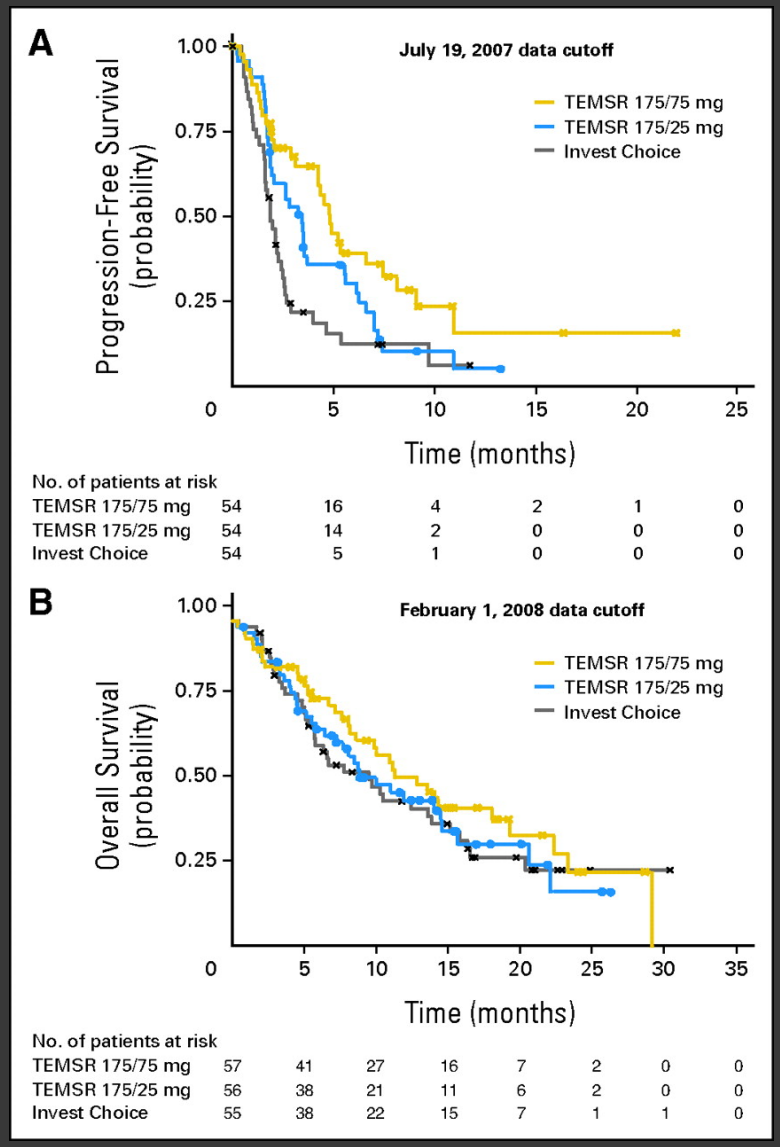


Fig 3. Time to progression after temsirolimus in all 34 patients.





Hess, G. et al. J Clin Oncol; 27:3822-3829 2009

Qui est posé sur la benchside et qui ira (peut-être) jusqu’au bedside ?

Immunothérapie/ Radio-immunothérapie

Inhibiteur des voies de transduction

HDAC

Peptides agissant sur les voie la régulation de l’apoptose

Inhibiteurs du cycle cellulaire

Autres molécules:

CD20:

forme humanisée:

Ofatumumab (Coiffier et al. Blood 2007: LLC)

Ocrelizumab (Morshhaueser et al ASH 2007)

Forte affinitée au FCgR: Augmenter l'ADCC

AME-133 (hA20)

rhuMAB v114

GA-101

CD52: **Campath (Alemtuzumab)**

CD23 (?): **Lumiliximab (préclinique: Blood 2007): apoptose, chimérique (homme/macaque); LLC**

CD22: **Epratuzumab (seul ou en association avec anti-CD20; RIT): ADCC/tyrosine phosphorylation**

CMC-544: anti-CD22 + calichamicine (exotoxine psuedomonas)

CD80: **Galiximab (JCO 2005; LF 11% de réponse): ADCC**

CD40: **SGN-40**

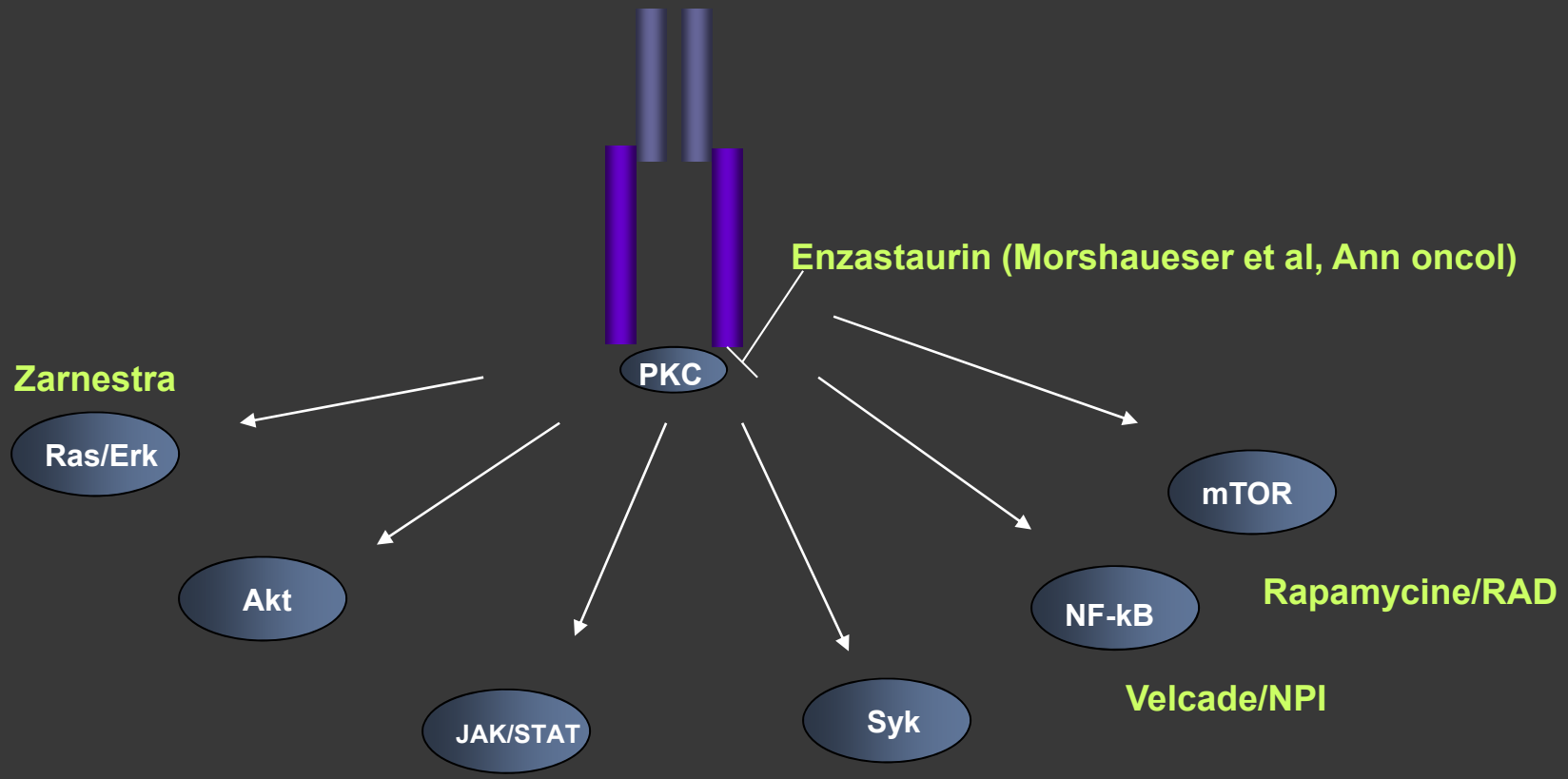
HCD 122

CD30/CD25/CD2 ….

VEGF: Avastin

Antagonsite de TRAIL DR4 et DR5

Inhibiteur des voies de transduction

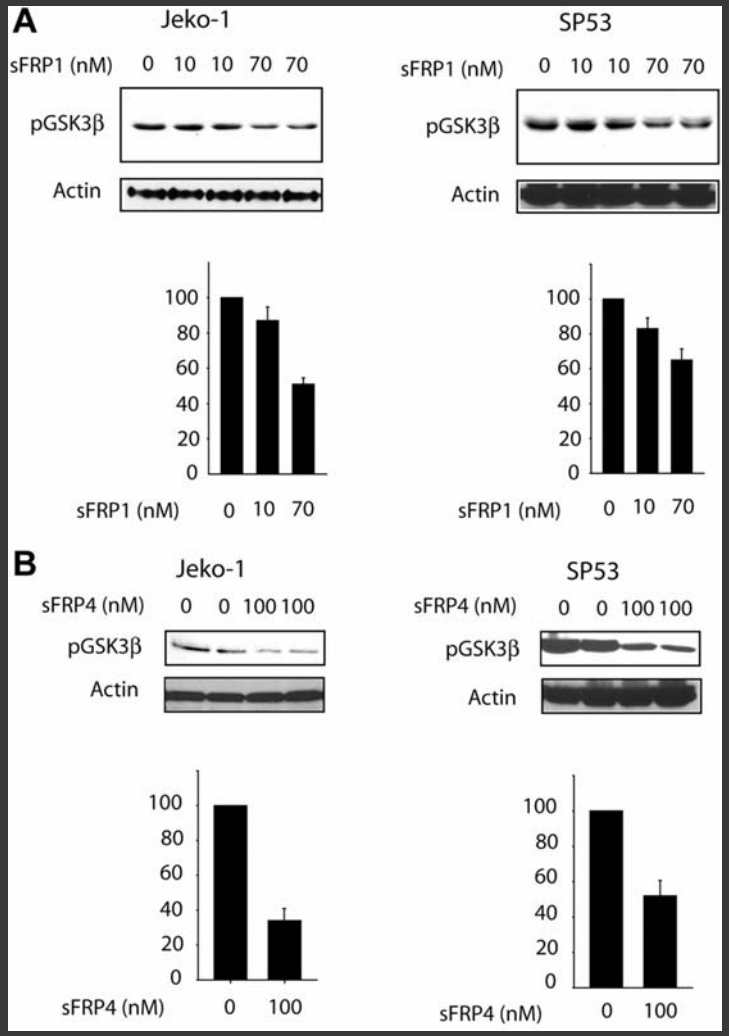


blood

Prepublished online Sep 11, 2008;
doi:10.1182/blood-2008-02-139212

Constitutive activation of the Wnt canonical pathway in mantle cell lymphoma

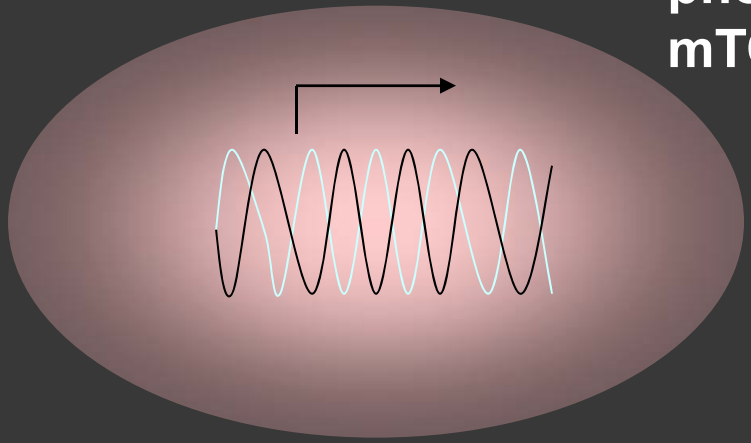
Pascal Gelebart, Mona Anand, Hanan Armanious, Anthea C. Peters, Jennifer Dien Bard, Hesham M. Amin and Raymond Lai



HDAC

Vorinostat

Depsipeptide



Baisse niveau cycline D1

Inhibition de phosphorylation Akt, mTOR

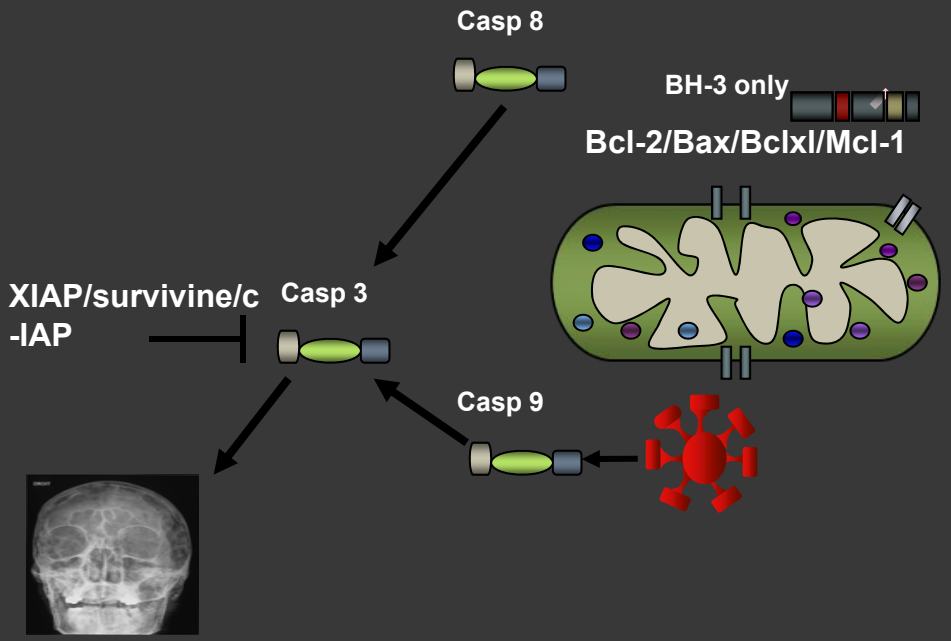
Peptides agissant sur les voie la régulation de l'apoptose

Anti-Bcl2

GX 15-070

YM-155

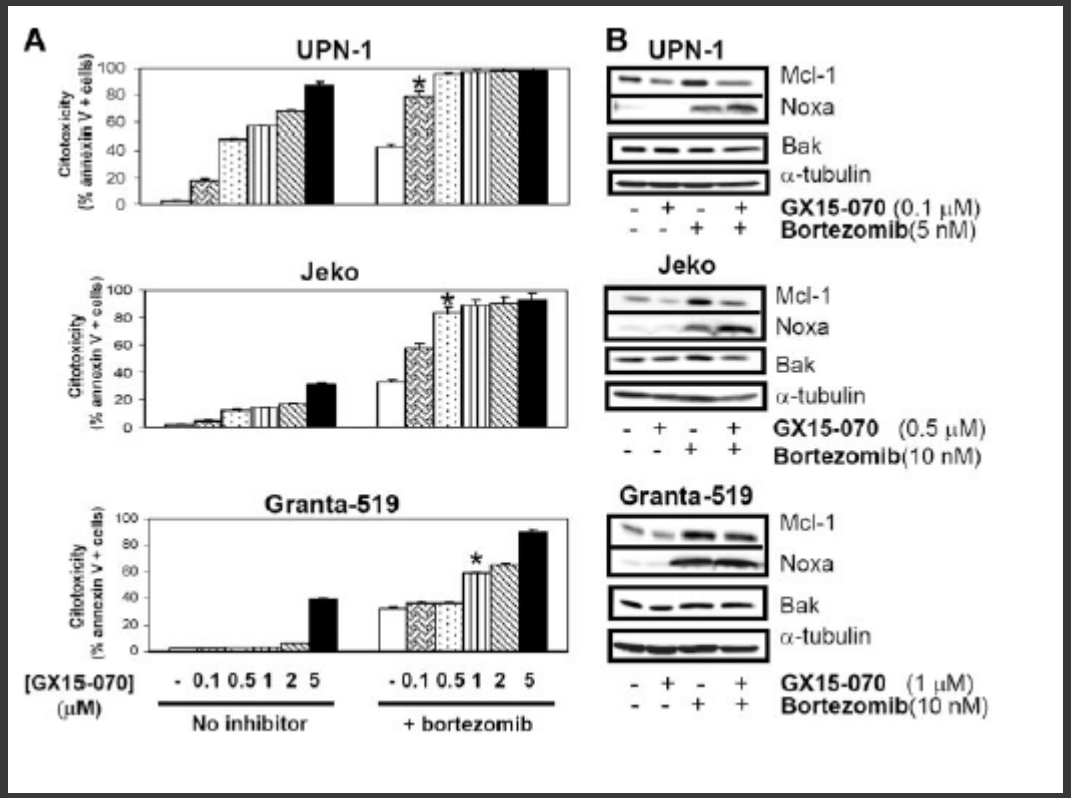
ABT-737



The BH3-mimetic GX15-070 synergizes with bortezomib in mantle cell lymphoma by enhancing Noxa-mediated activation of Bak

Patricia Pérez-Galán,[1] Gaël Roué,[1] Neus Villamor,[1] Elias Campo,[1] and Dolors Colomer[1]

[1]Hematopathology Unit, Department of Pathology, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Spain



American Journal of Pathology, Vol. 164, No. 2, February 2004

Nuclear Survivin Expression in Mantle Cell Lymphoma Is Associated with Cell Proliferation and Survival

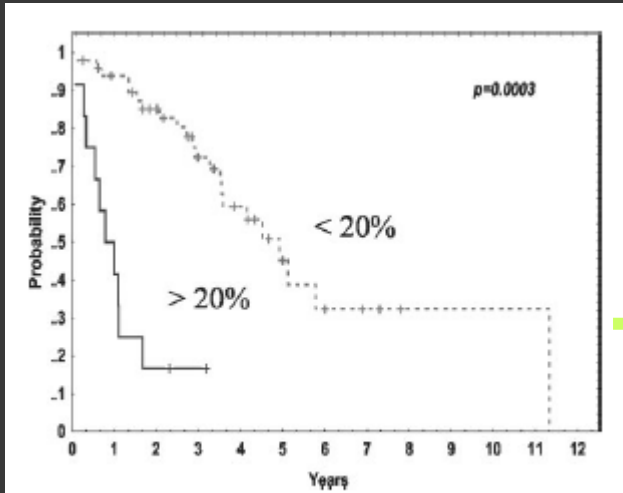


Figure 7. Overall survival of 62 MCL patients according to survivin protein expression analyzed by immunohistochemistry.

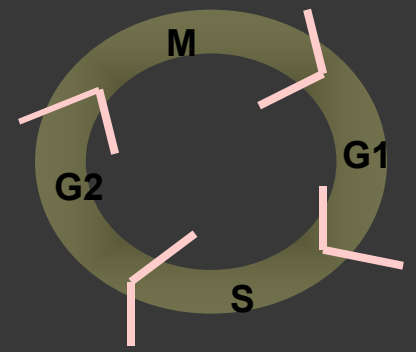
YM-155 ?

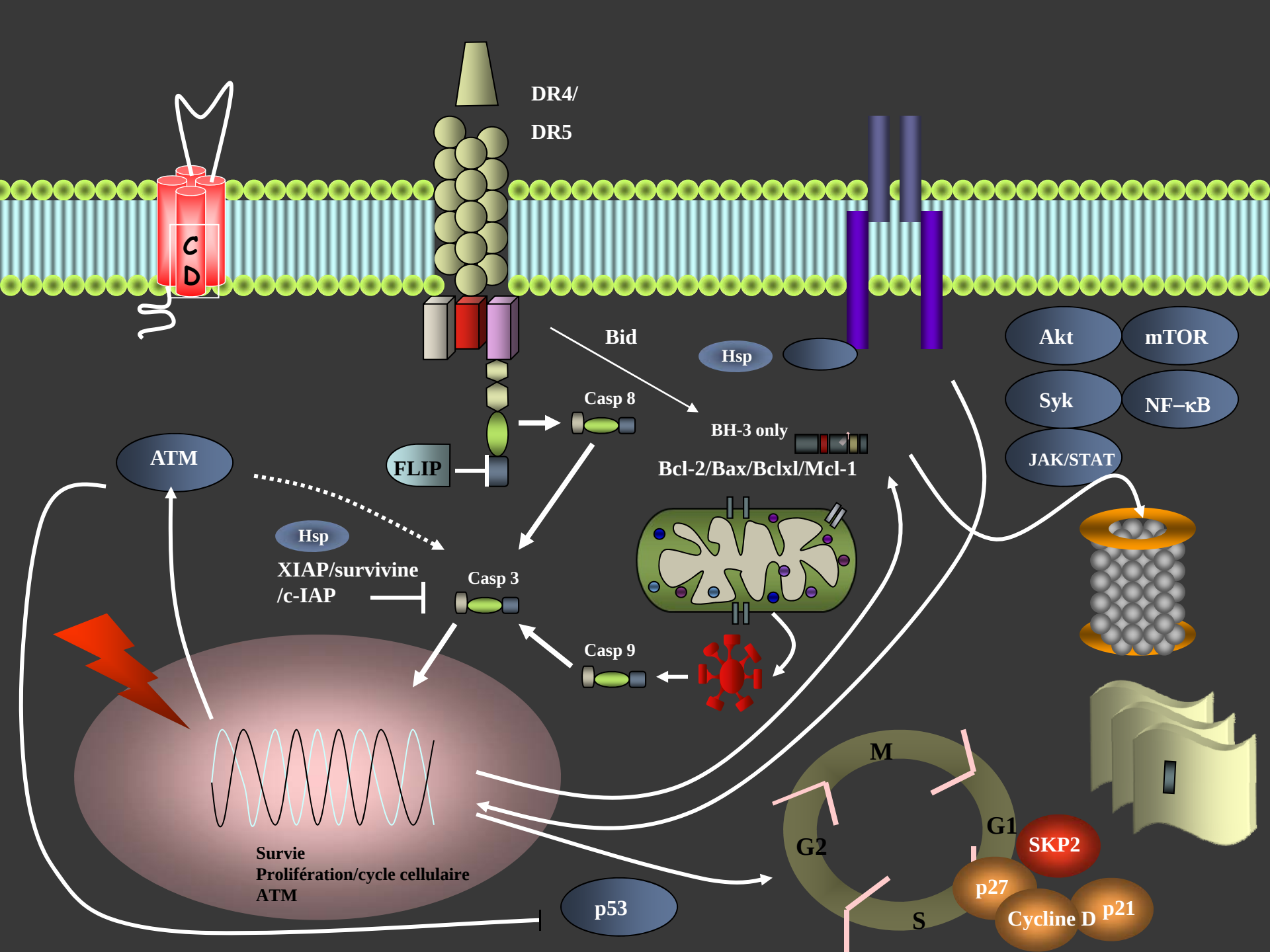
Inhibiteurs du cycle cellulaire

Flavopiridol: cdk inhibiteur

Inhibition sélective cdk:

roscovitine




DR4/
DR5
C
D
Bid
Hsp
Akt
mTOR
Syk
NF−κB
JAK/STAT
Casp 8
FLIP
BH-3 only
Bcl-2/Bax/Bclxl/Mcl-1
ATM
Hsp
XIAP/survivine
/c-IAP
Casp 3
Casp 9
Survie
Prolifération/cycle cellulaire
ATM
p53
M
G1
G2
S
SKP2
p27
Cycline D
p21

INSERM UMR 892, IRCNA

Service d'hématologie clinique
CHU de Nantes