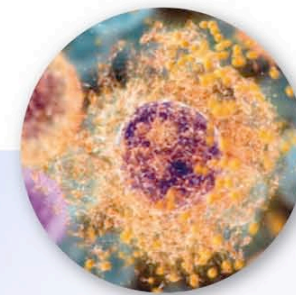
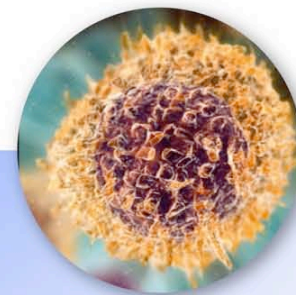
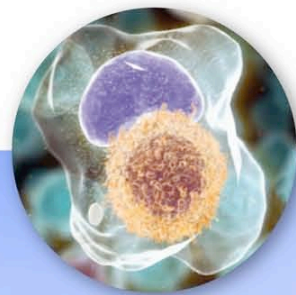




Les Ateliers Lymphomes et LLC

22 – 24 octobre 2009

Le Moulin de la Forge – Le Vaumain (60)



Sous le patronage de



En collaboration avec



En partenariat avec



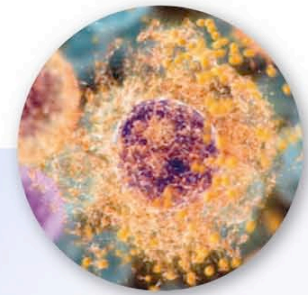
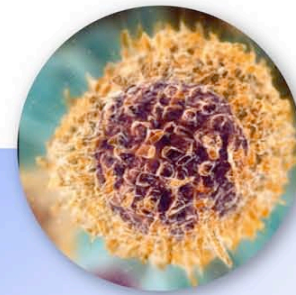
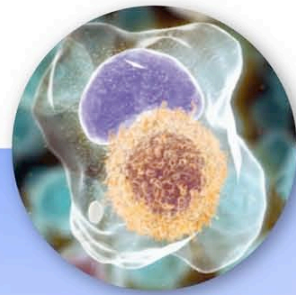
Avec le soutien institutionnel de





3^{ème} session : Lymphome du manteau

Modérée par Catherine THIEBLEMONT



Sous le patronage de

sfh

En collaboration avec

Gela
GROUPE D'ETUDE DES LYMPHOMES DE LA CÔTE

GOELC/MW
GROUPE D'ETUDE FRANÇAIS DES LYMPHOMES DE LA CÔTE / MANTOUILLON

GOELAMS
GROUPE D'ETUDE DE LYMPHOMES AGILES ET DES MANTOUILLON

En partenariat avec

AH

Avec le soutien institutionnel de

Roche



Programme de la session

3^{ème} session : Lymphome du manteau – Modérée par C. Thieblemont

Anatomopathologie	N. Brousse
Facteurs pronostiques cliniques et biologiques	F. Morschhauser
Thérapeutiques de 1^{ère} ligne	S. Le Guill
Cas clinique interactif	Présenté par C. Thieblemont





**Lymphome à cellules du manteau :
traitements de première ligne du manteau**

Steven LE GOUILL


INSERM UMR 892, IRCNA

Service Hématologie Clinique, CHU de Nantes



Inserm

Institut national
de la santé et de la recherche médicale



Lymphome à cellules du manteau : traitements de première ligne du manteau





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%	
Khoury	JCO 1998	hyper C-VAD/ MTX	45	diag/rech	38%	93.5%
Zinzani	JCO 2000	Fluda-Ida (vs fluda)	18	diag	33%	61%

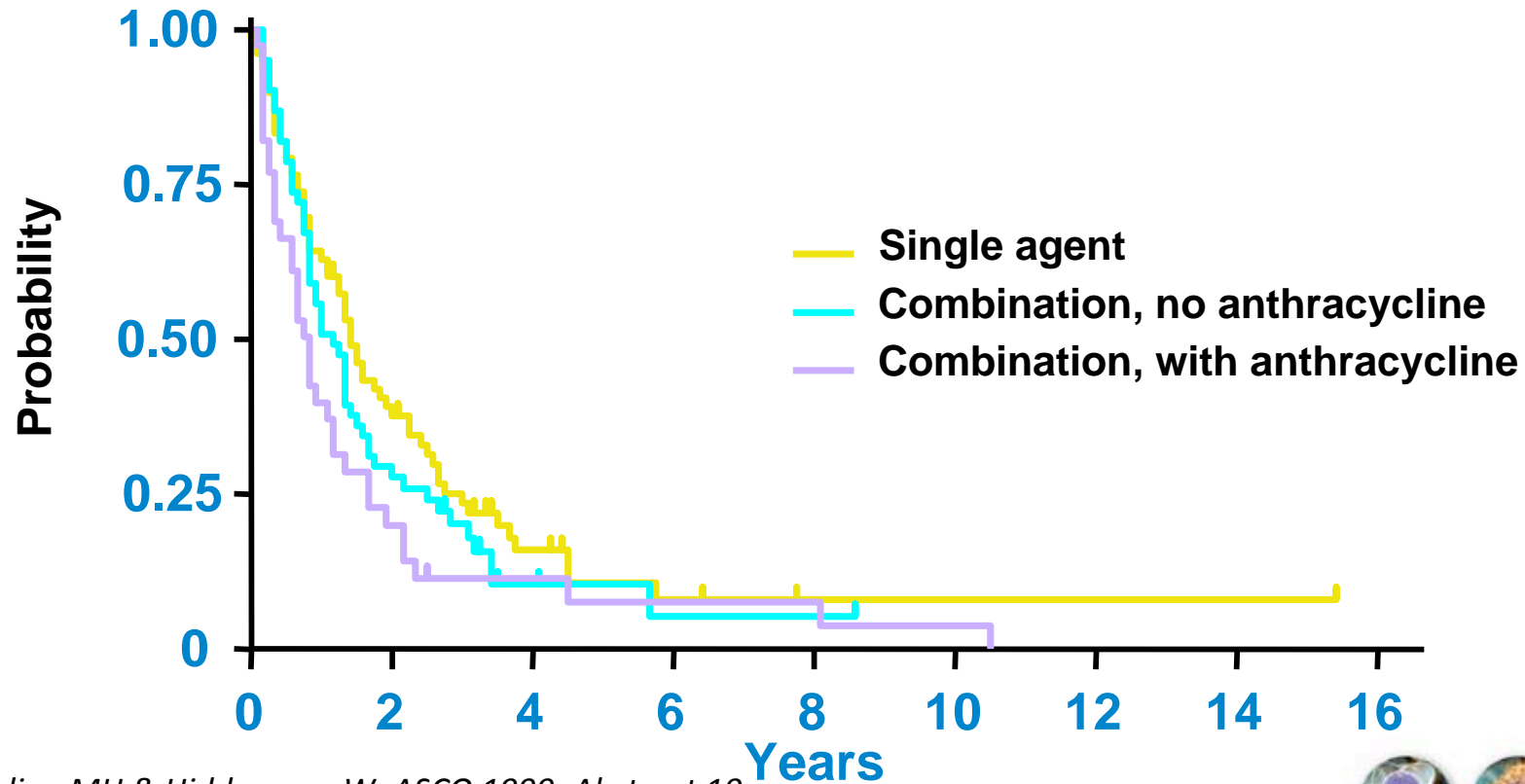


Efficacy of conventional chemotherapy

Multicentre evaluation of MCL

Annecy Criteria fulfilled

Event-free interval after chemotherapy in stages III + IV

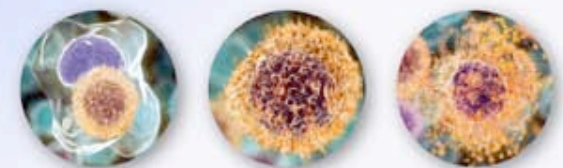


Dreyling MH & Hiddemann W, ASCO 1999; Abstract 10.





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

DAY		1	2	3	4	5	11	12	13	14
Course 1	CTX 300 mg/m ²	↓	↓	↓	↓					
	DOXO 25 mg/m ²					↓	↓			
	VCR 2 mg					↓		↓		
	DEXA 40 mg	↓	↓	↓	↓		↓	↓	↓	↓
Course 2	MTX 200 mg/m ²	↓								
	MTX 800 mg/m ²	→→→→								
	ARA-C 3,000 mg/m ²		↓	↓	↓	↓				

Lefrere et al., 2002 :CHOP-DHAP (n=28)

	CR	OR
4x CHOP	7%	57%
4x DHAP	84%	92%



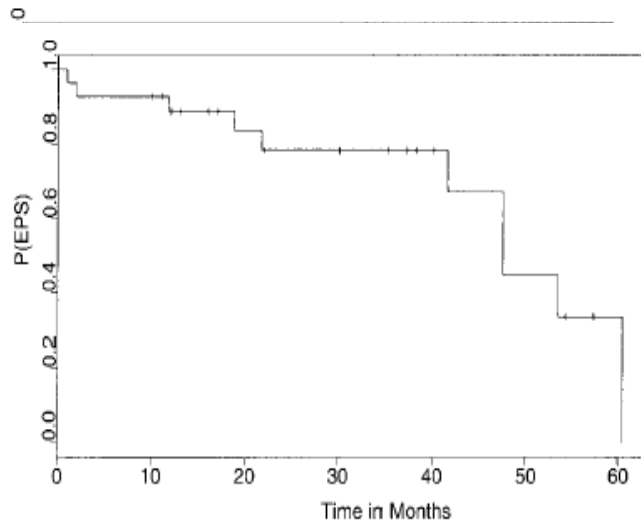


Figure 2 Event-free survival (Kaplan-Meier).

Lefrère Leukemia 2002
Lefrère Leukemia 2002

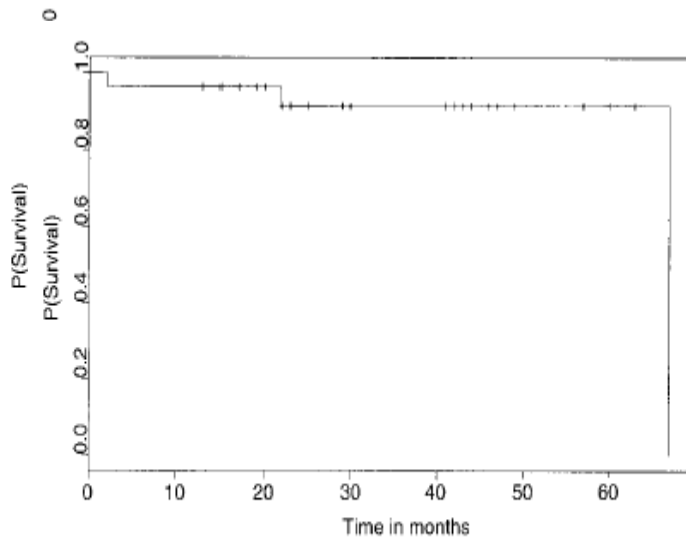


Figure 3 Overall survival (Kaplan-Meier).

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



	After three courses (R)-CHOP	After three courses of R-DHAP
Evaluatable 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 ?



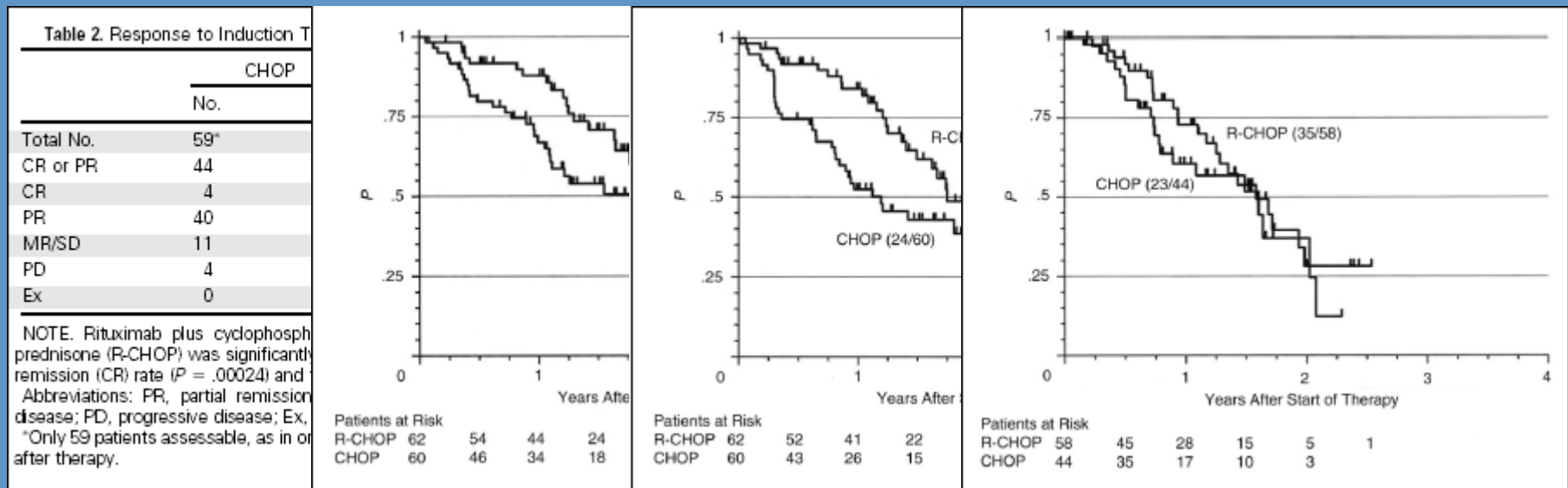
Chimiothérapie avec rituximab

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 Wärmann, Ulrich Dührsen, Bernd Metzner, Hartmut Eimermacher, Andreas Neubauer, Hannes Wanzel, Hjalmar Steinbauer, Sonja Martin, Else Heidemann, Ali Aldaoud, Reza Parwaresch, Joerg Hasford, Michael Unterhalt, and Wolfgang Hiddemann

A B S T R A C T



Taux de réponse

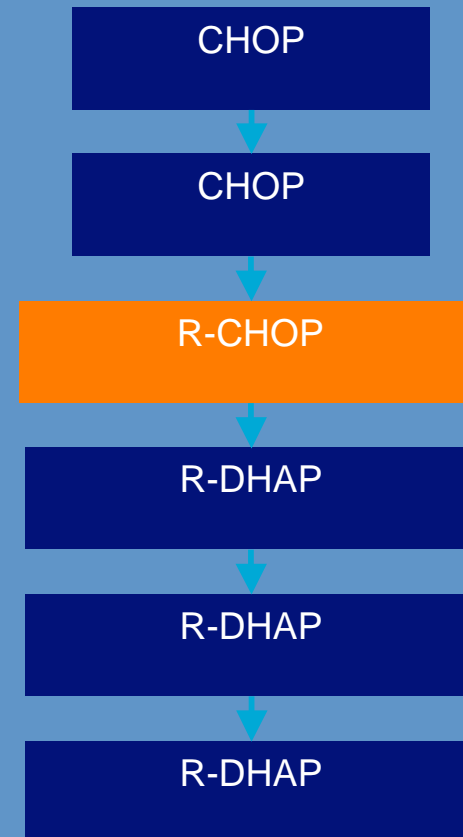
Délai traitement de rechute

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)**

Chimiothérapie
d'induction

Autogreffe ?

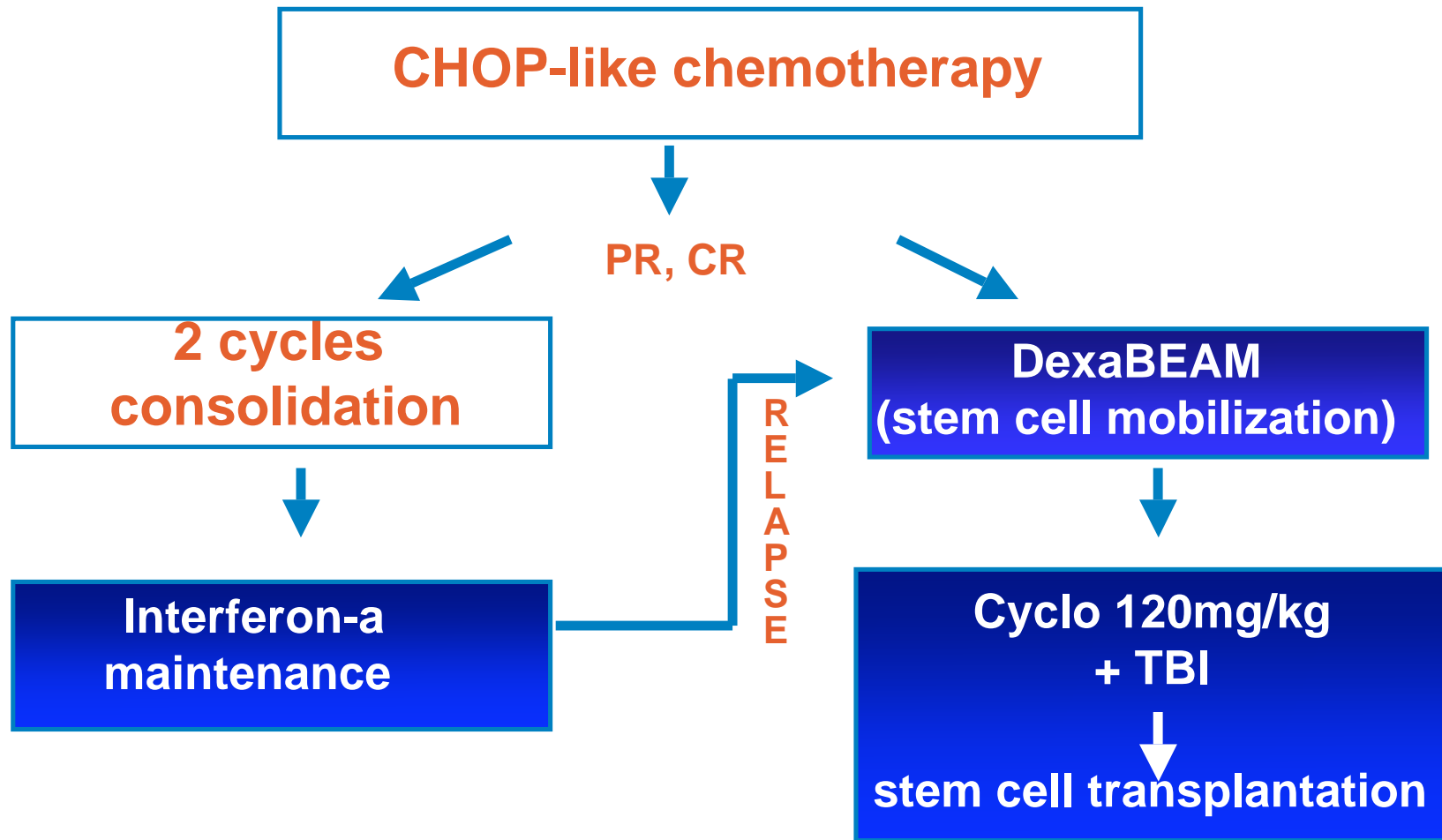
R-CHOP

R-CHOP/Aracytine

R-Aracytine

R-Hyper C-VAD

European MCL Network: ASCT vs. IFN





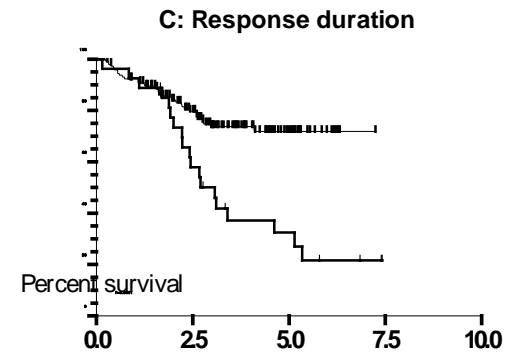
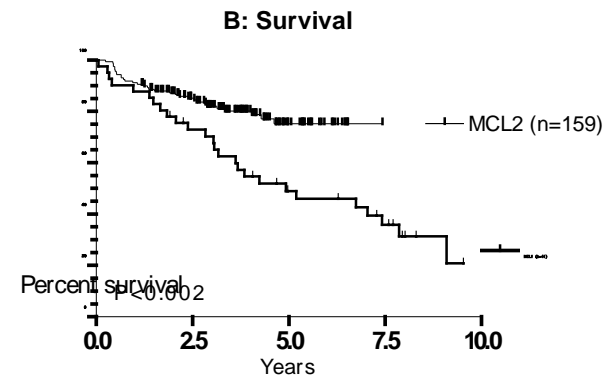
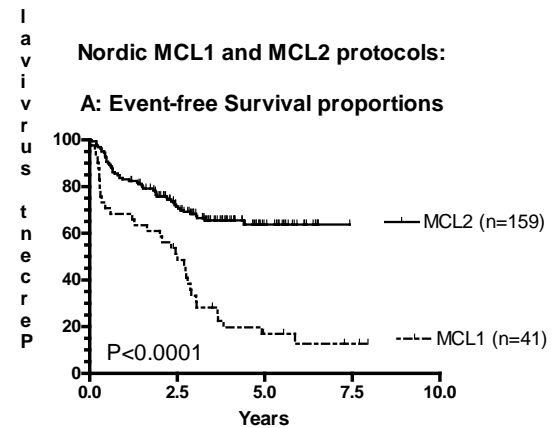
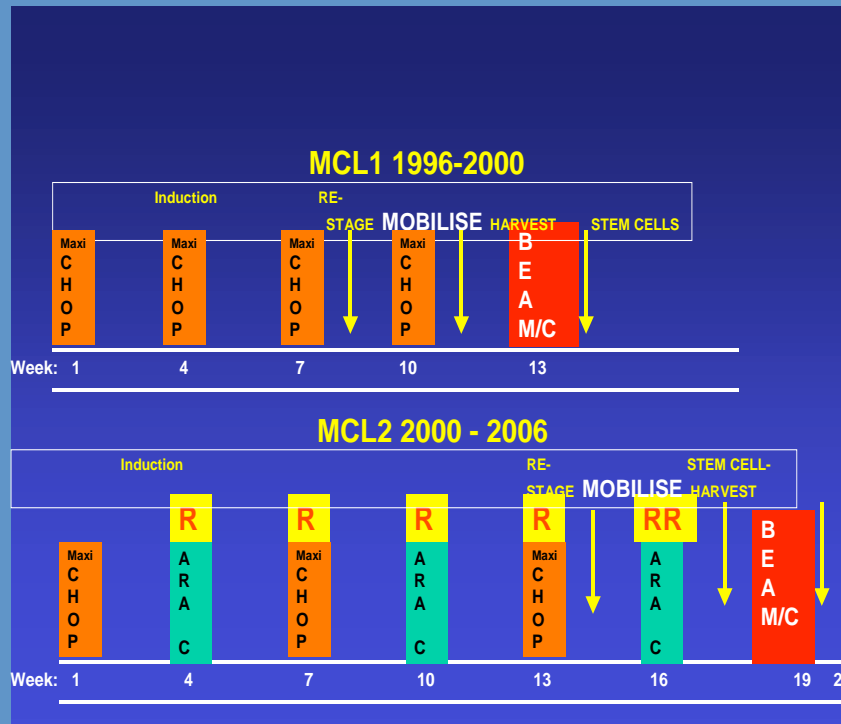
European MCL Network: ASCT vs. IFN

Best response after consolidation (PP)

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

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





Autogreffe

auteur	Ref	Ttt avant greffe		N	RC/Cr u 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

R-CHOP/Aracytine

R-Aracytine

R-Hyper C-VAD

TBI/endox ?

TAM ?

BEAM ?



BMT, Milpied et al., 1998



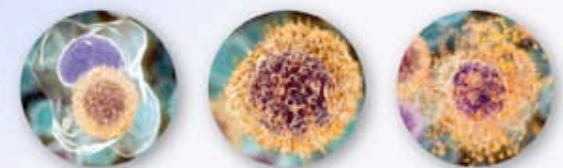
N=18

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

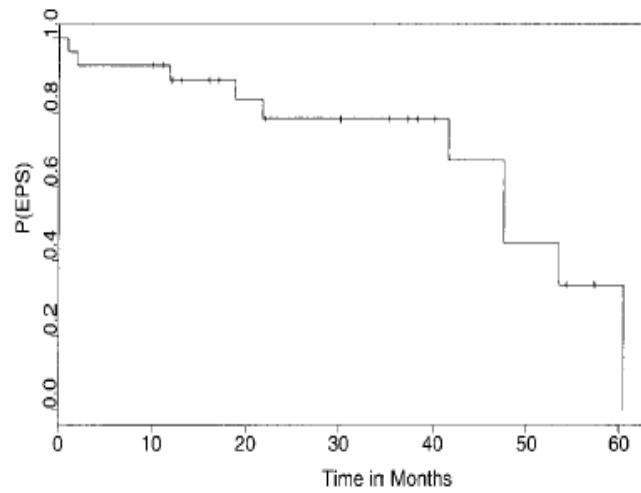


Figure 2 Event-free survival (Kaplan-Meier).

Lefrère Haematologica 2004

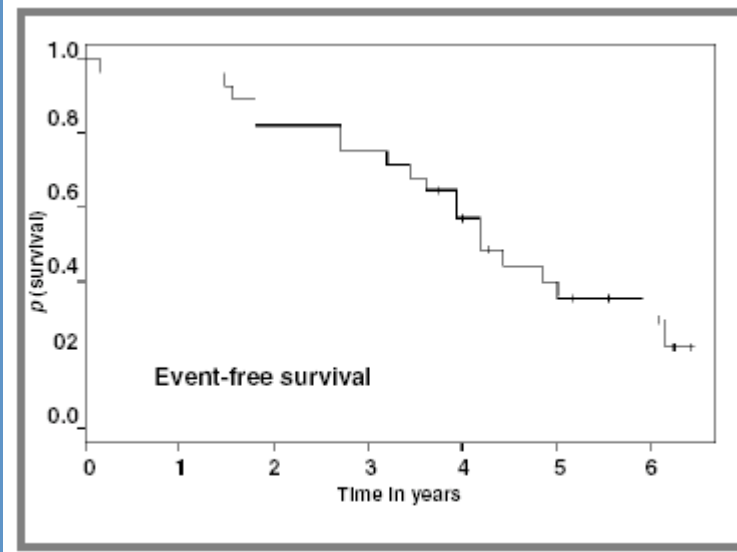


Figure 2. Event-free survival (Kaplan-Meier).

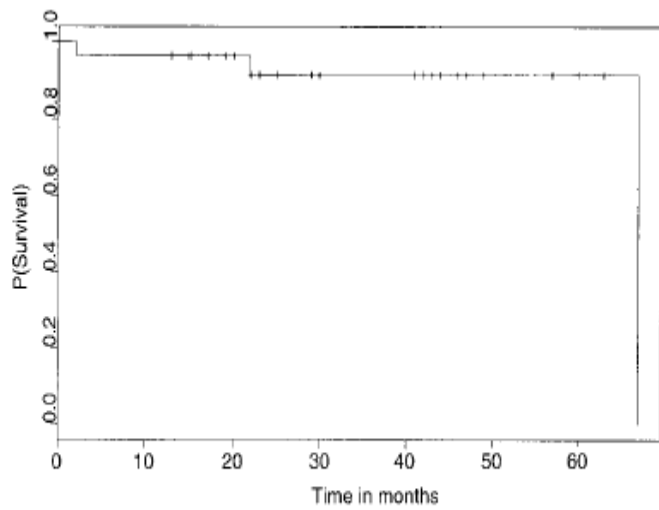


Figure 3 Overall survival (Kaplan-Meier).

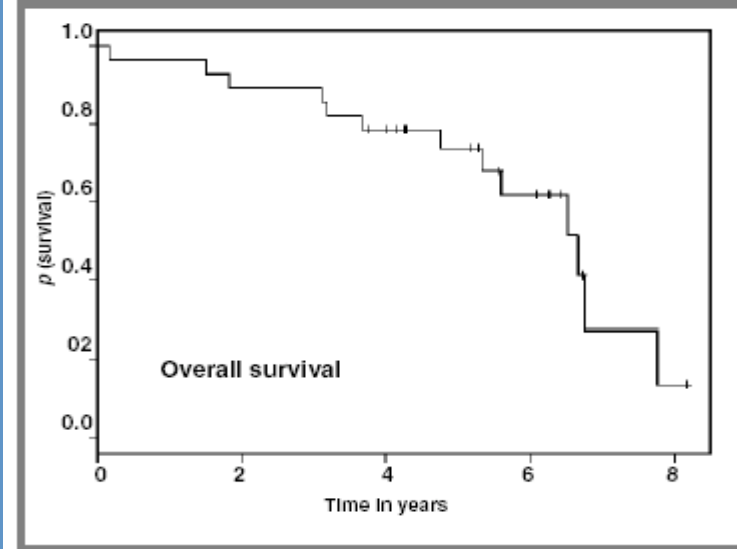
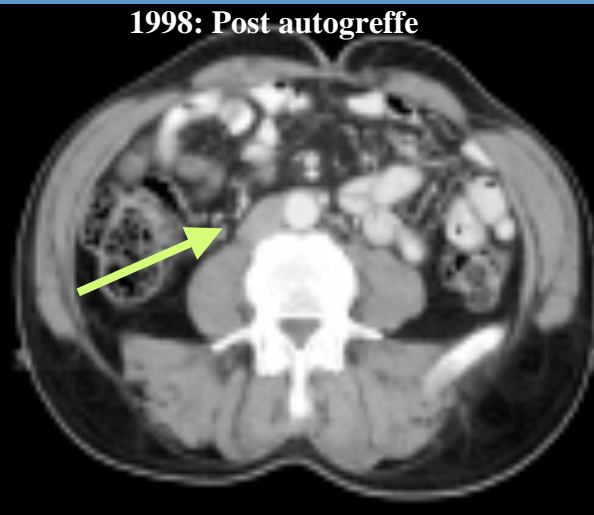
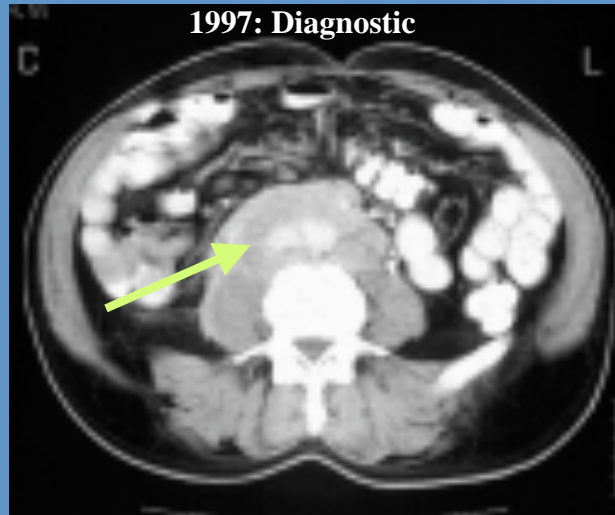


Figure 1. Overall survival (Kaplan-Meier).





Chimiothérapie
d'induction +
rituximab

autogreffe

Entretien ?

- R-VAD-C
- R-CHOP 14
- R-CHOP14 /R-DHAP
- R-DHAP

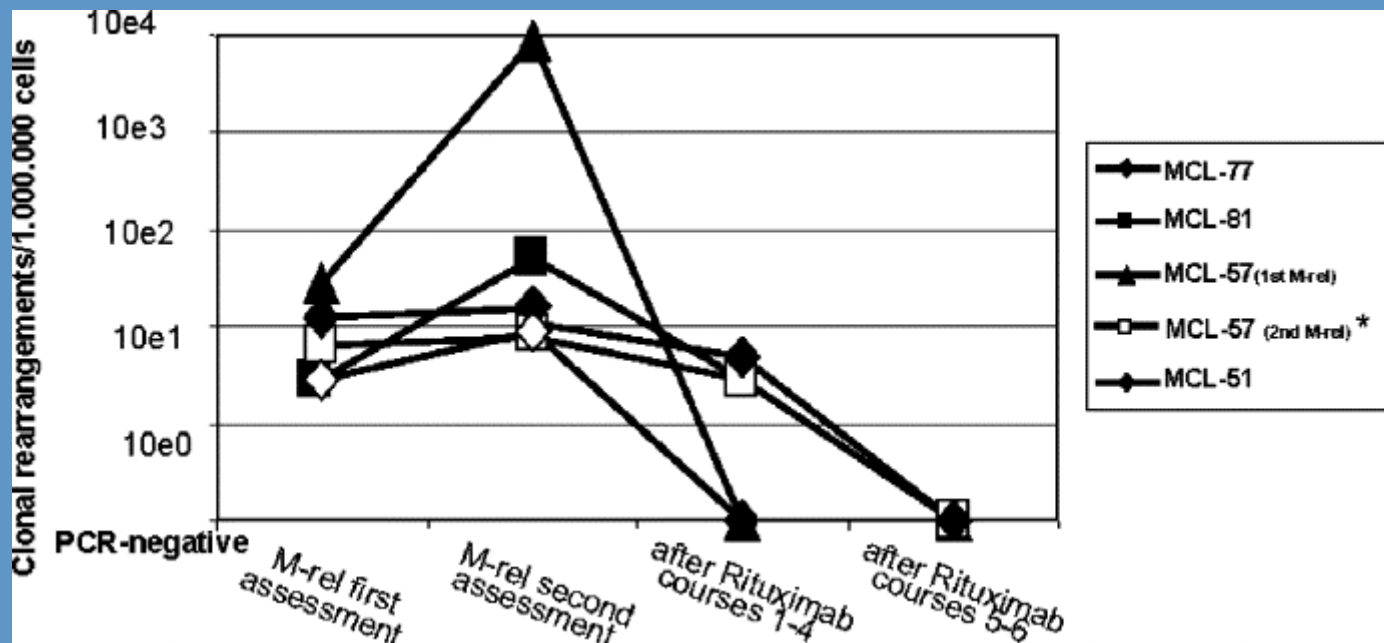
- TBI/Endoxan
- TAM
- BEAM
- Z-BEAM

Rituximab ?



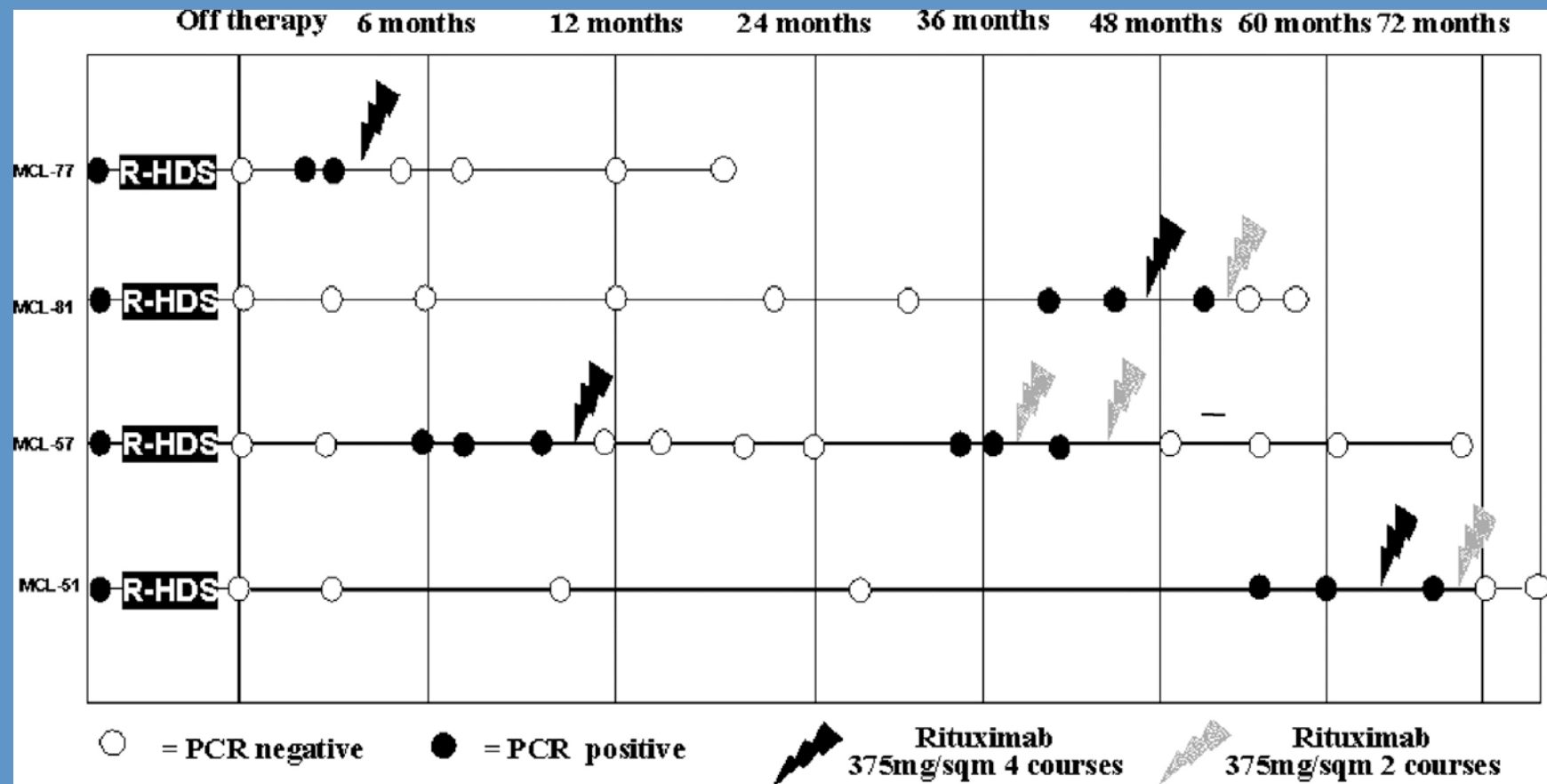
Rituximab Induces Effective Clearance of Minimal Residual Disease in Molecular Relapses of Mantle Cell Lymphoma

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 Boccardo,¹ Alessandro M. Gianni,^{2,3} Corrado Tarella¹



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

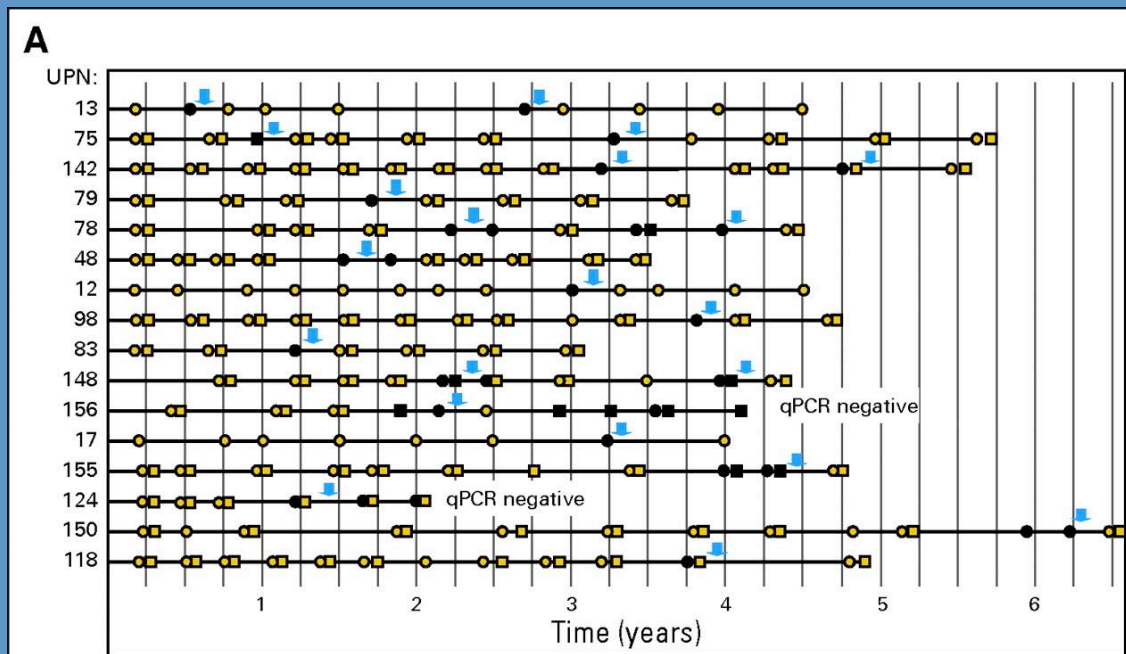
Biology of Blood and Marrow Transplantation, dec 2006



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

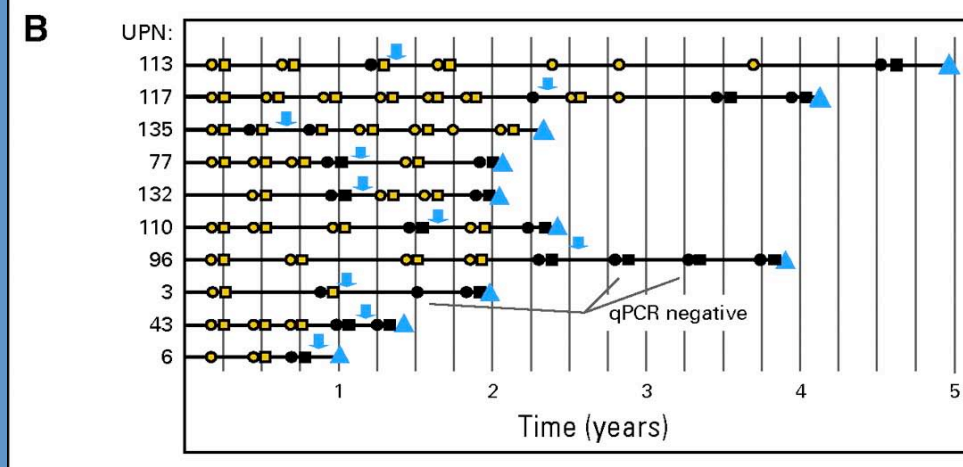
□ sang ○ MO — Neg — Pos ↓ Ritu ▲ Rechute clinique

Patients en RC clinique

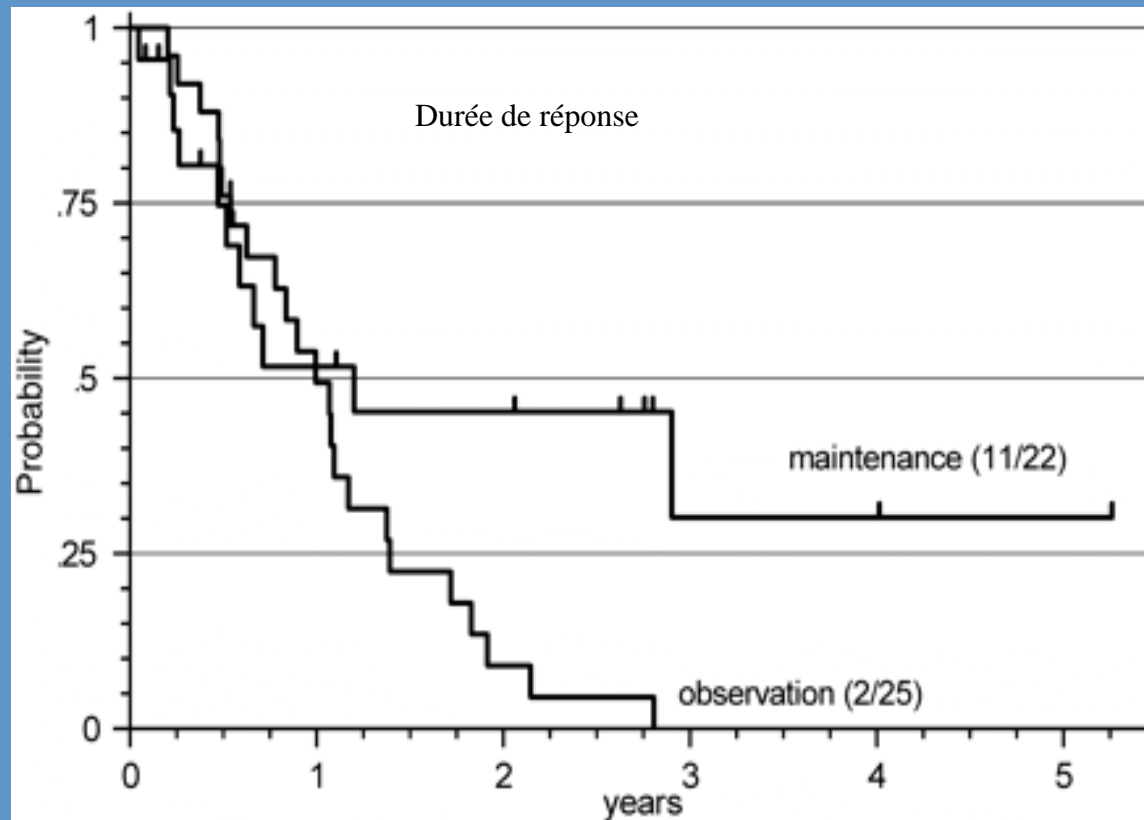


Nested-PCR

Patients avec rechute clinique après

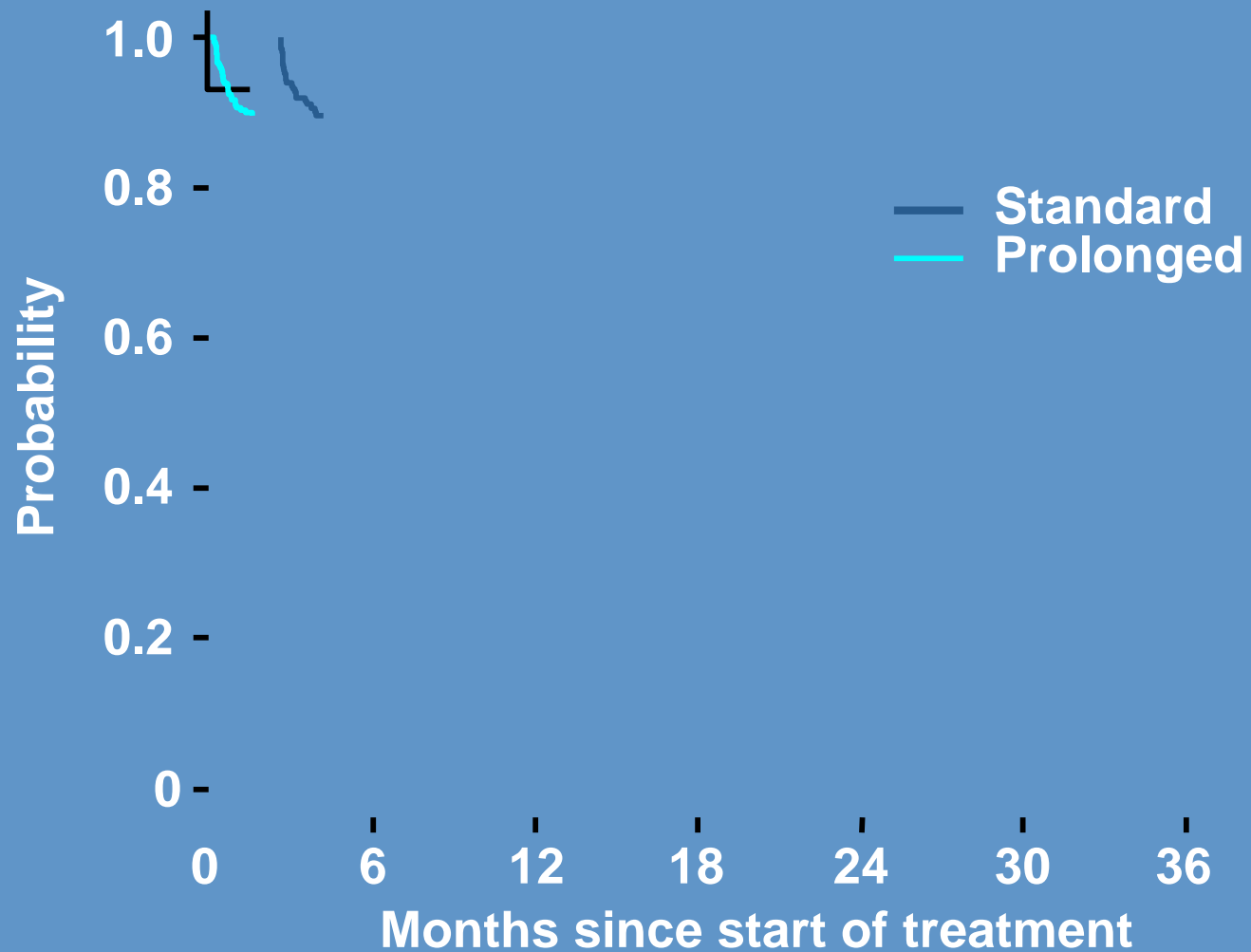


Rituximab et entretien

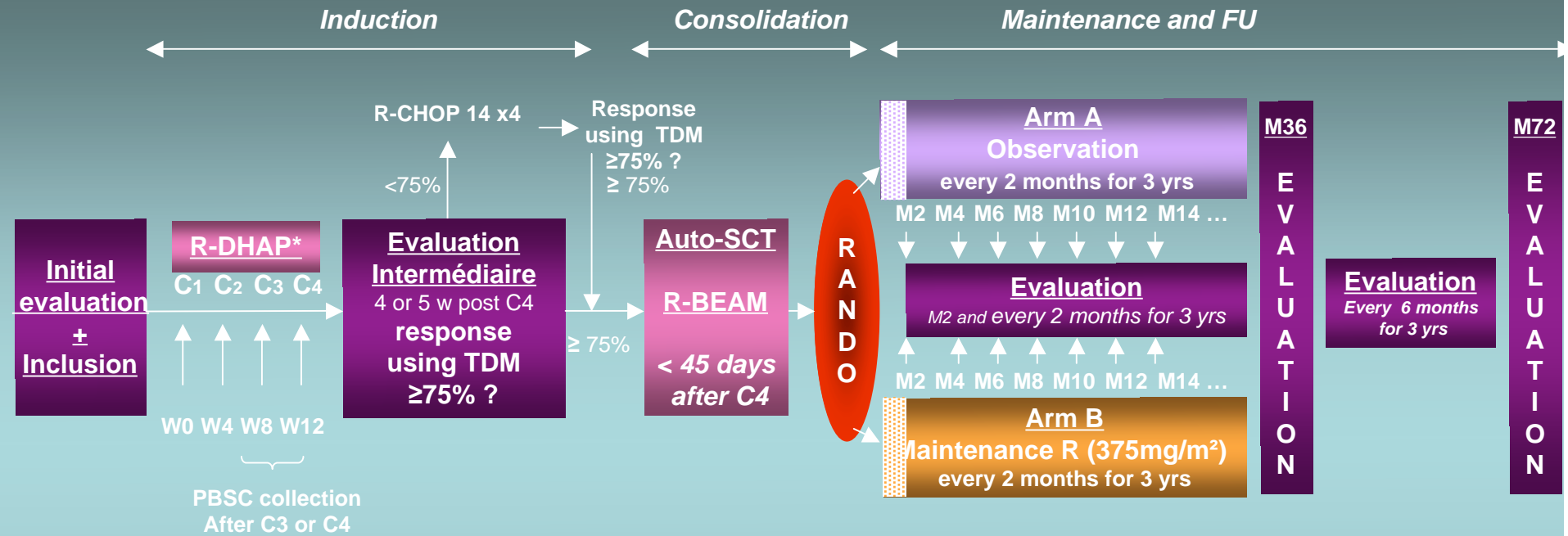


Forstpointner et al Blood 2006

Rituximab maintenance in MCL II



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 ?





Nouvelles alternatives thérapeutiques ?





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)

VOLUME 23 • NUMBER 4 • FEBRUARY 7 2005
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Clinical Experience With the Novel Proteasome Inhibitor Bortezomib in Patients With Indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma
Chen S, O'Connor, John Wright, Craig Melnicki, Anne Mazy, Barbara MacGregor-Corliss, Michael Ishidat, David Jones, Carol Perlick, Paul Hamble, Elizabeth Choi, Chris Chomson, Peter Lindner, Elizabeth Tebb, Julian Mann, David Sklar, and Andrew D. Zeleny

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

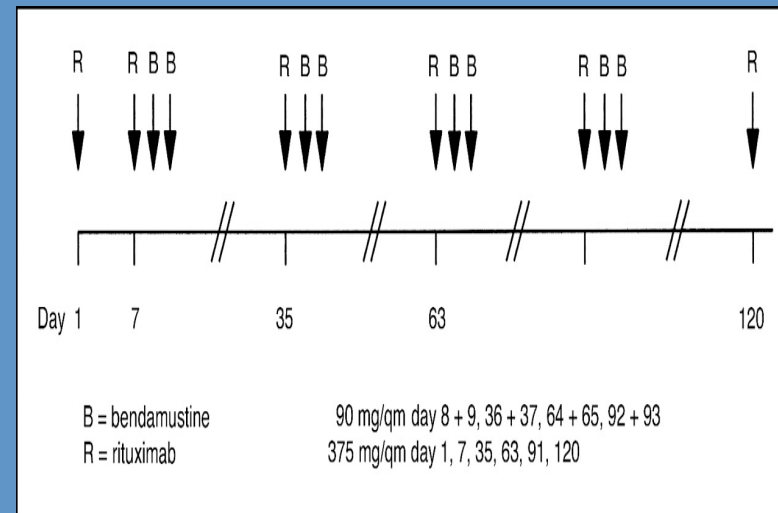
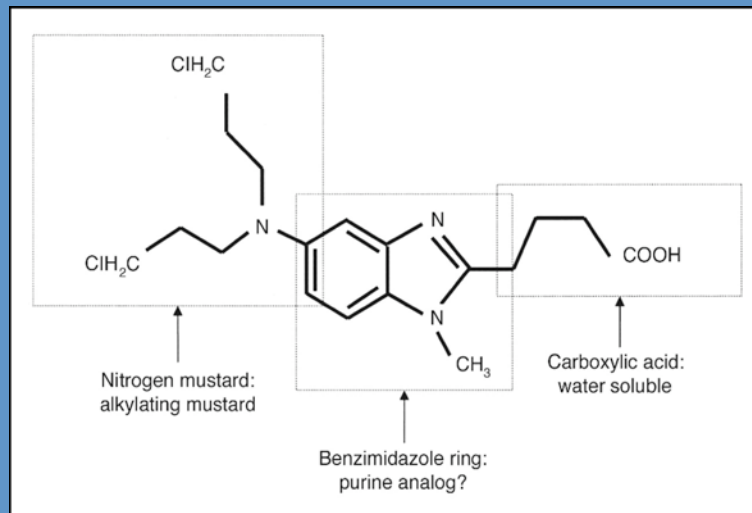
A Goy et al JCO février 2005 (vol 23, (4) 667-675)

VOLUME 23 • NUMBER 4 • FEBRUARY 7 2005
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Study of Proteasome Inhibitor Bortezomib in Relapsed or Refractory B-Cell Non-Hodgkin's Lymphoma
Ahn G, Ann Tannir, Peter McLaughlin, Barbara Pro, Jang E, Romaguera, Frederick Higginson, Lee Jang, Kim H, Dang, Ashly Somanigala, Michael Wang, Kristina Wright, Barry Swartz, Paulie Collins, Andrew S. Serlin, Anne Hays, Elizabeth Tebb, David Sklar, Fernando Caballero, and John H. Rodigan





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 abstract 385

R-CHOP vs R-B : taux de RC identique: 40% RC



Phase II Study of Yttrium-90–Ibritumomab Tiuxetan in Patients With Relapsed or Refractory Mantle Cell Lymphoma

Michael Wang, Yasuhiro Oki, Barbara Pro, Jorge Enrique Romaguera, Maria Alma Rodriguez,
Felipe Samaniego, Peter McLaughlin, Frederick Hagemeister, Sattva Neelapu, Amanda Copeland,
Barry I. Samuels, Evelyn M. Loyer, Yuan Ji, and Anas Younes

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

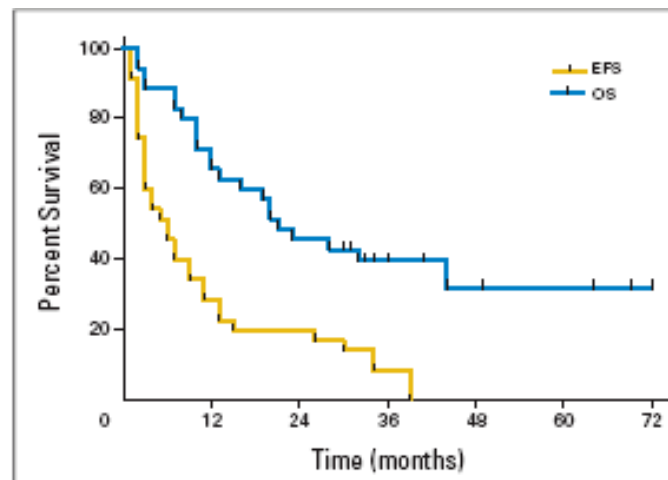


Fig 2. Event-free survival (EFS) and overall survival (OS) durations based on intent-to-treat analysis of all 35 registered patients.



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

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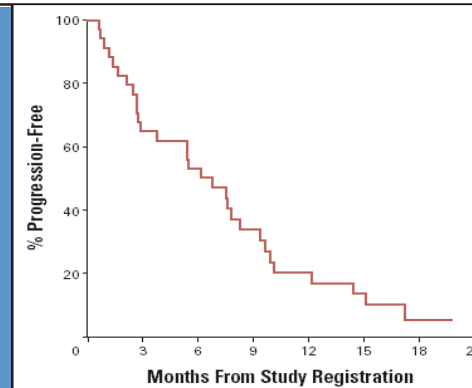
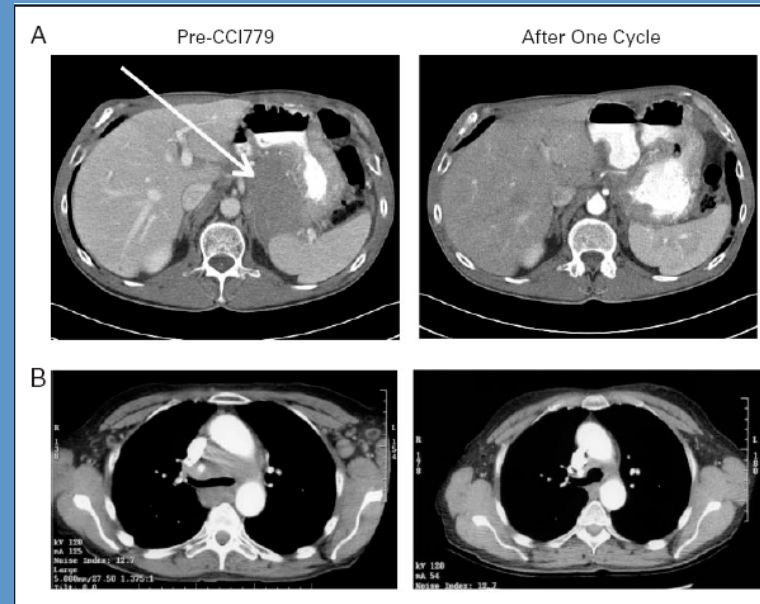
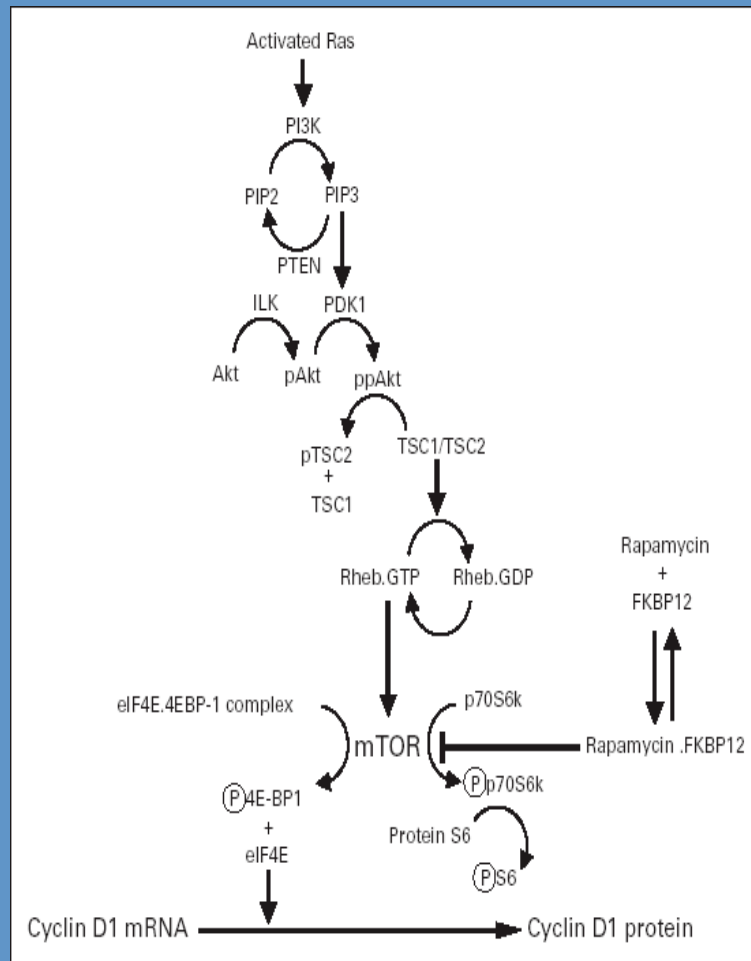
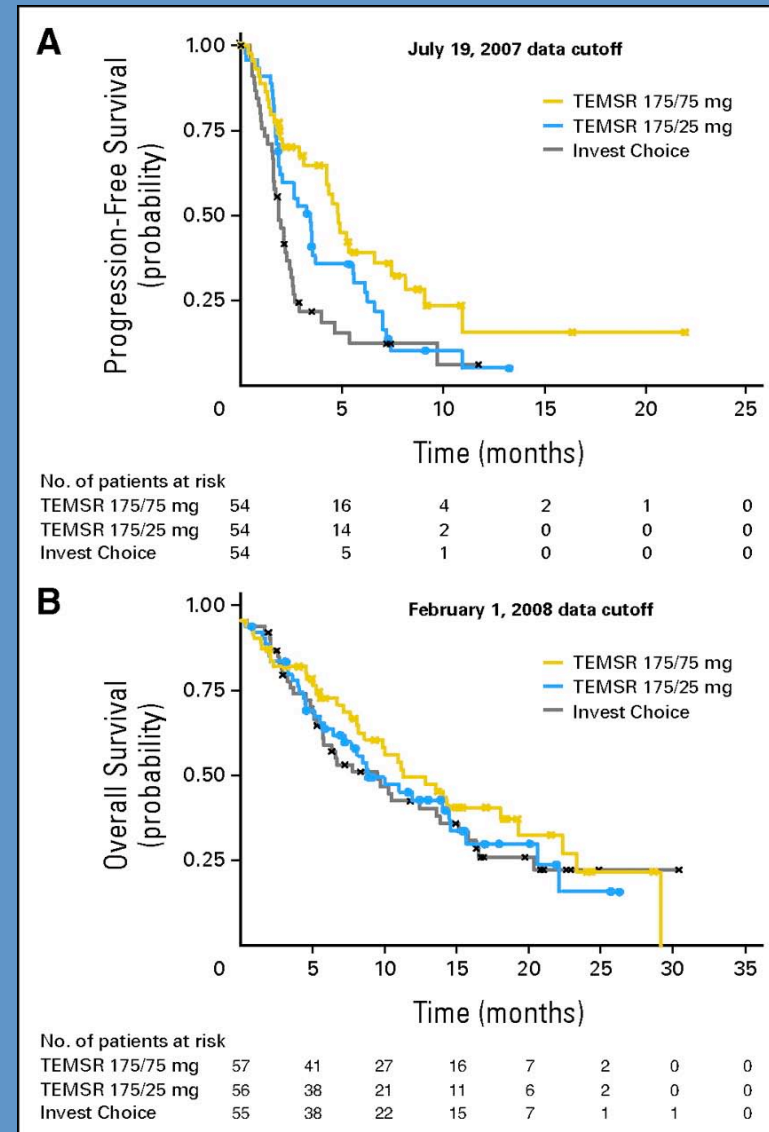
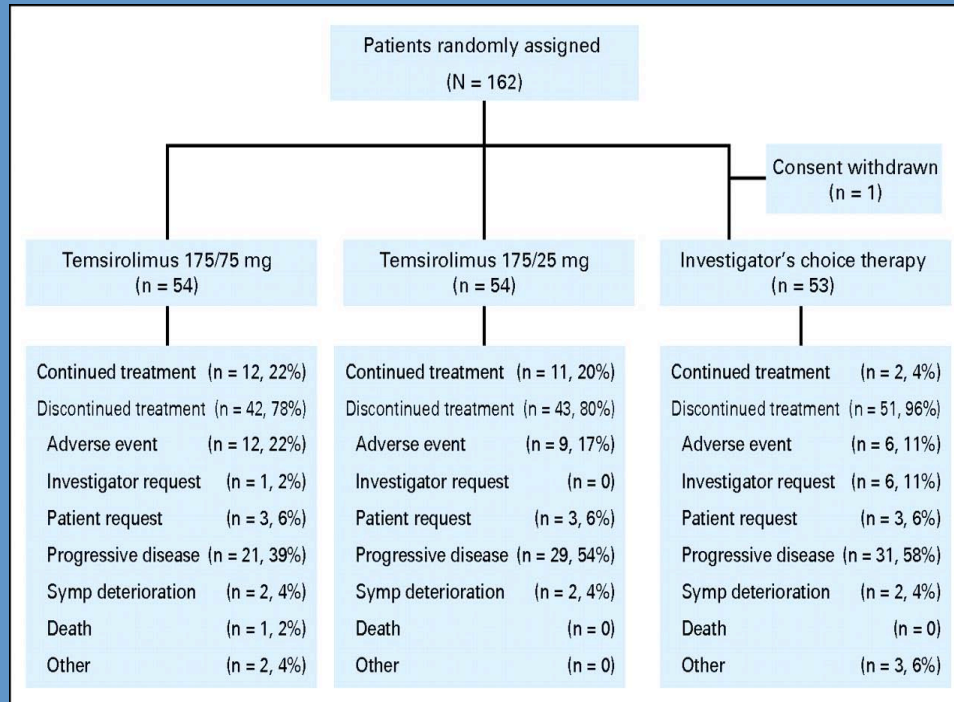


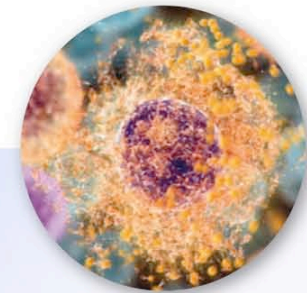
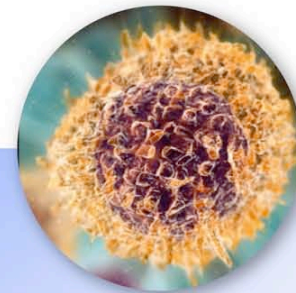
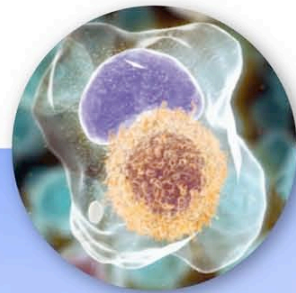
Fig 3. Time to progression after temsirolimus in all 34 patients.



Les Ateliers Lymphomes et LLC

22 – 24 octobre 2009

Le Moulin de la Forge – Le Vaumain (60)



Sous le patronage de



En collaboration avec



En partenariat avec



Avec le soutien institutionnel de

