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UNIVERSITÉ DE NANTES

L'HEMA SOINS ET RECHERCHES EN HÉMATOLOGIE
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Inserm
Institut national de la santé et de la recherche médicale

CRCINA

Lysa

Anomalies moléculaires d'intérêt clinique dans le lymphome à cellules du manteau

GBMHM le 8 octobre 2019

Yannick Le Bris

Service d'hématologie biologique CHU de Nantes

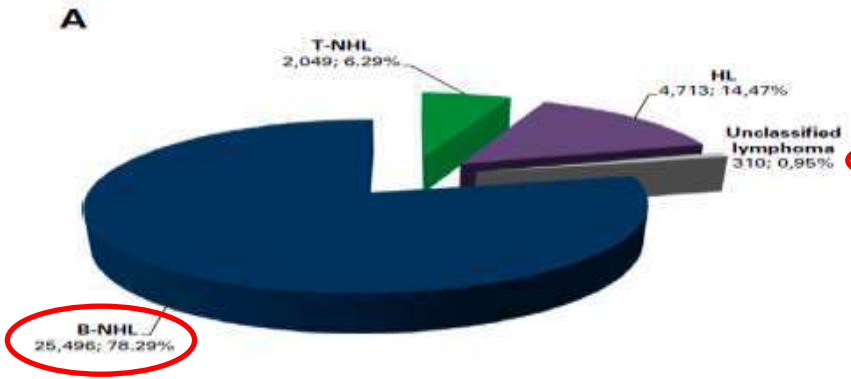
Lymphomes à cellules du manteau

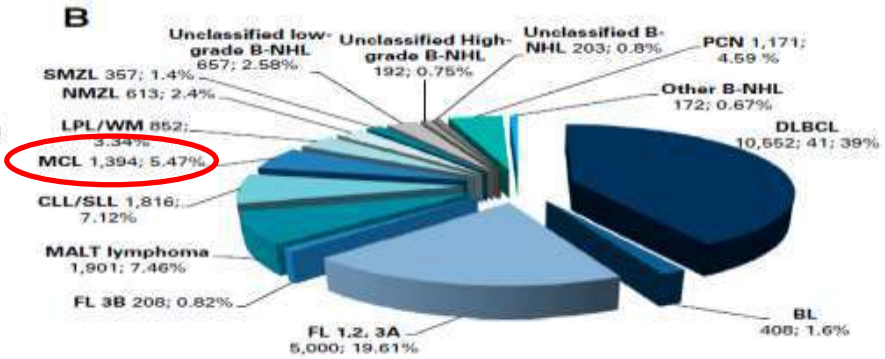
5 à 10 % des LNH
Prévalence : 3/100 000 hab/an
Médiane d'âge : 60-65 ans
Prédominance masculine (sex ratio = 4/1)

VOLUME 35 · NUMBER 18 · JUNE 20, 2017
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

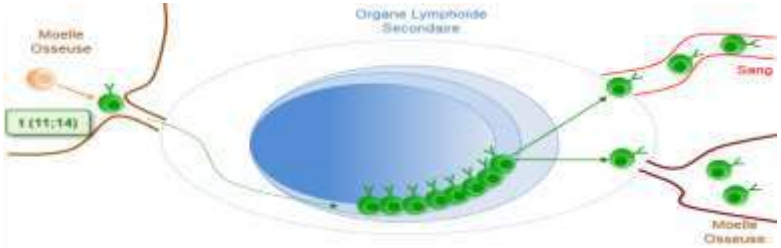
Impact of Expert Pathologic Review of Lymphoma Diagnosis: Study of Patients From the French Lymphopath Network

From January 2010 to December 2013, 42,145 samples

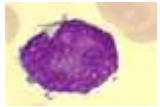




LCM : un diagnostic intégré



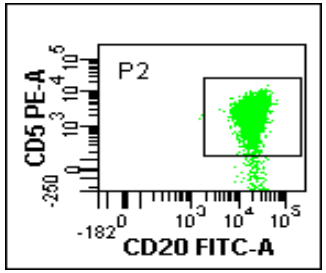
Petits lymphocytes matures



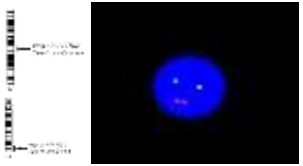
BOM

Variant blastoïde

Cycline D1



CD19+ CD20+
CD5+ CD10- CD23- CD200-



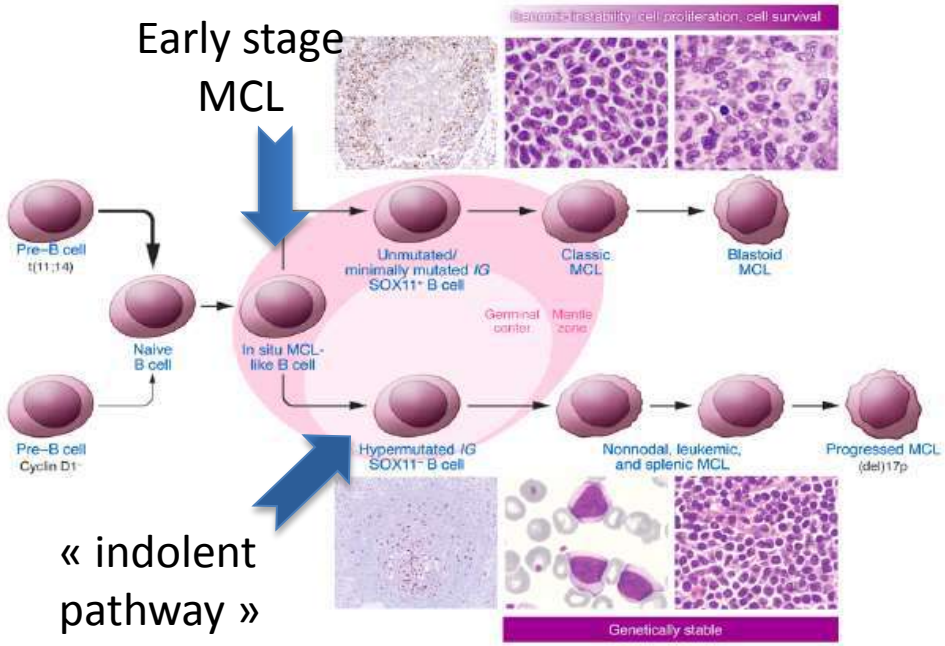
t(11;14)(q13;q32)
CCND1-IGH

FISH ou PCR

Molecular pathogenesis of mantle cell lymphoma

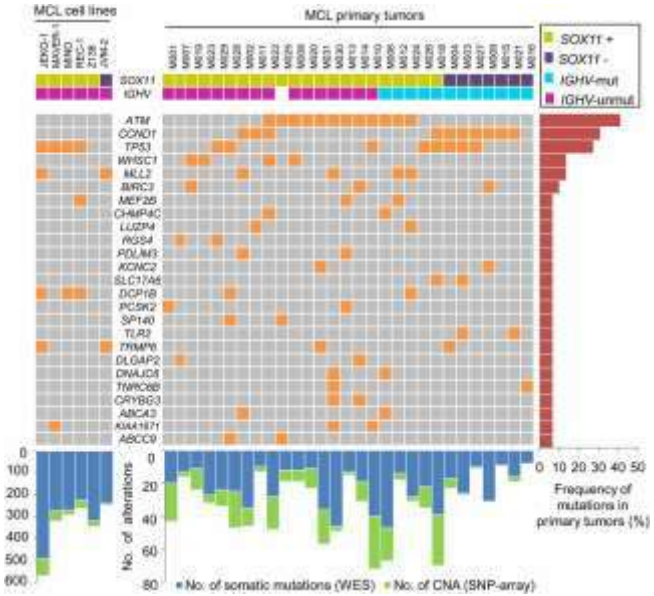
Pedro Jares, Dolors Colomer, and Elias Campo

Hematopathology Section, Department of Pathology, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain.



MCL biology: a complex genomic landscape

WES in 29 cases and 6 MCL cell lines: 25 significantly recurrent mutated genes (Bea et al)



LCM = 3,700 mutations somatiques/patient (1.2 per Mb)
LLC = 1,426 mutations somatiques/patient (0.5 per Mb)

Burns Leukemia 2018

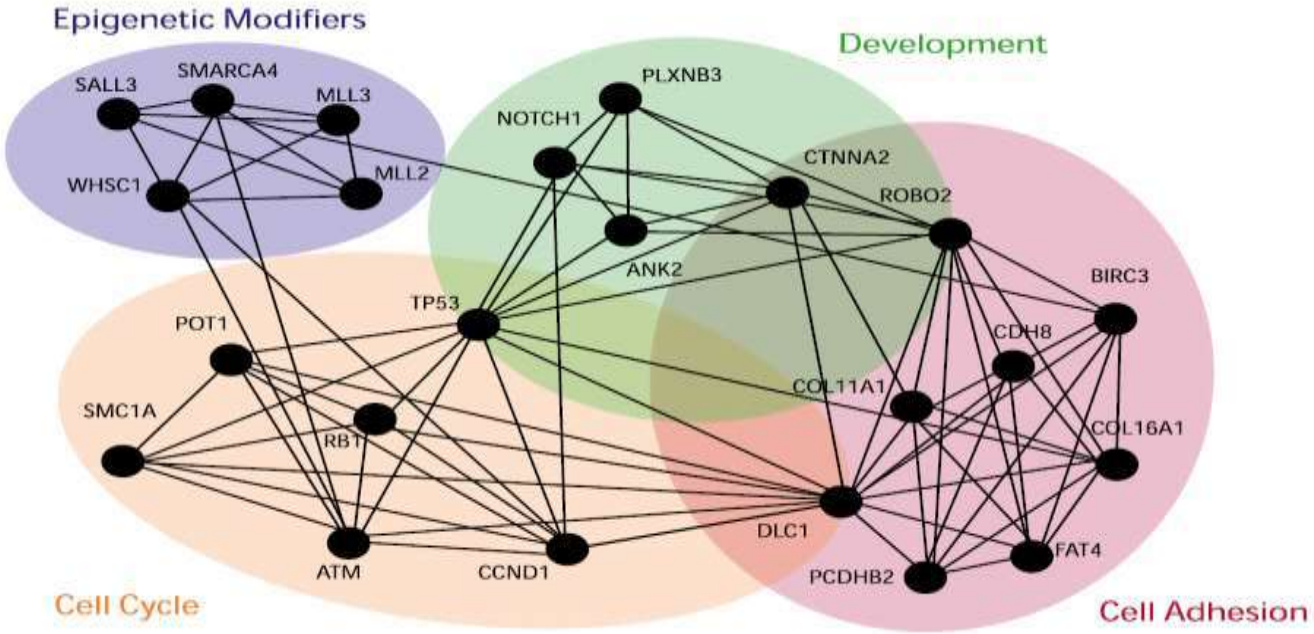
Gene	Cell lines	MCL cases, %	SOX11+ MCL, %	*IGHV*-U MCL, %
ATM		41 (12/29)	55 (12/22)*	50 (8/16)
CCND1		35 (10/29)	18 (4/22)*	19 (3/16)*
MLL2	2/9	14 (4/29)	18 (4/22)	13 (2/16)
WHSC1		10 (13/130)	15 (12/82)*	14 (11/80)
BIRC3		6 (11/173)	7 (7/95)	9 (9/97)
NOTCH2		5 (9/172)	6 (6/93)	6 (6/95)
NOTCH1	2/9	5 (8/172)	5 (5/95)	7 (7/95)
MEF2B	1/9	3 (6/187)	5 (5/100)	4 (4/102)
TLR2		1 (2/171)	0/94	0/96

Data are from WES and Sanger sequencing. *IGHV*-U, *IGHV*-unmutated gene.

Sílvia Beà et al. PNAS 2013;110:18250-18255

PNAS

Dérégulations génomiques et épigénomiques complexes impliquant de nombreuses voies de signalisation

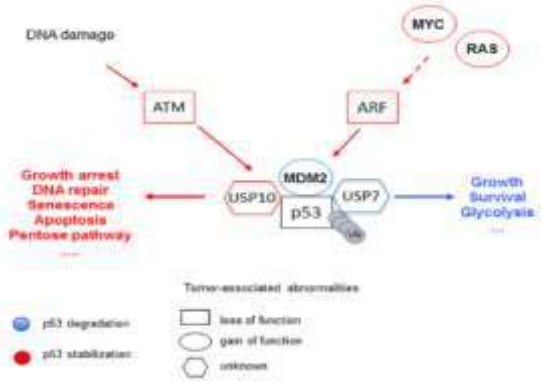


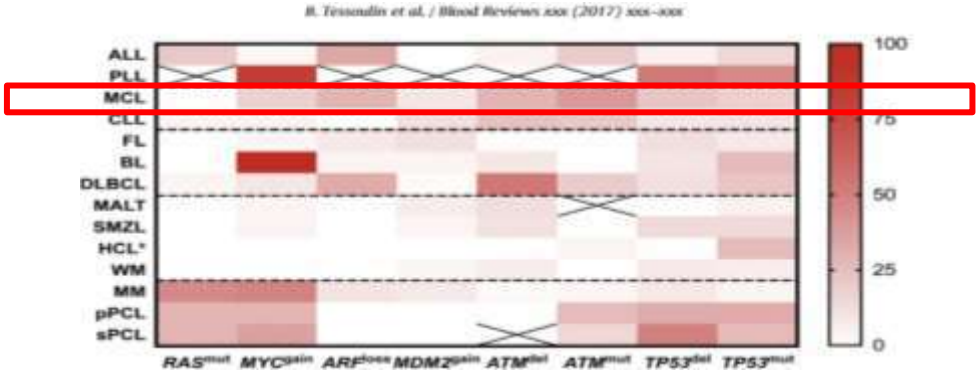
LYMPHOID NEOPLASIA

The genomic landscape of mantle cell lymphoma is related to the epigenetically determined chromatin state of normal B cells

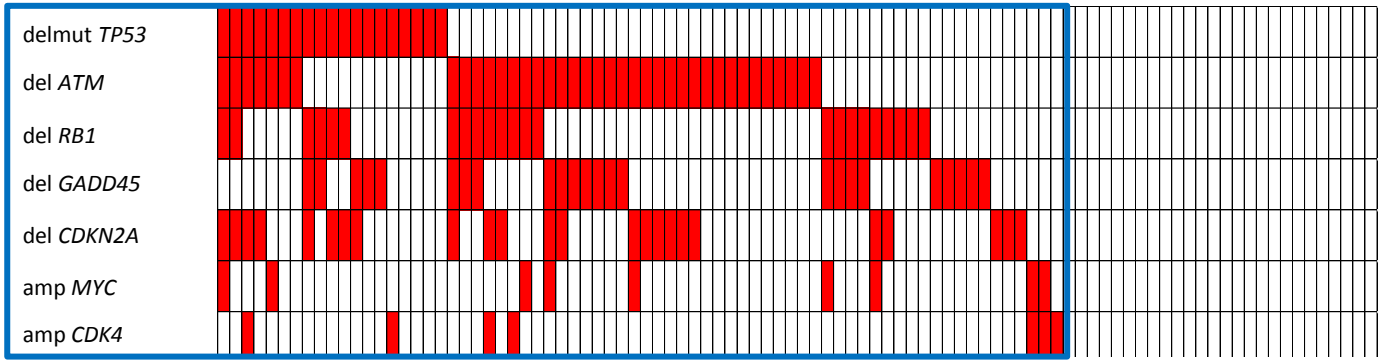
Jenny Zhang,[1,2] Dereje Jima,[1] Andrea B. Moffitt,[1] Qingquan Liu,[1] Magdalena Czader,[3] Eric D. Hsi,[4] Yuri Fedoriw,[5] Cherie H. Dunphy,[6] Kristy L. Richards,[5] Javed I. Gill,[6] Zhen Sun,[1] Cassandra Love,[1] Paula Scotland,[1] Eric Lock,[7] Shawn Levy,[8] David S. Hsu,[1,2] David Dunson,[7] and Sandeep S. Dave[1,2,9]

Voie p53 centrale dans le LCM



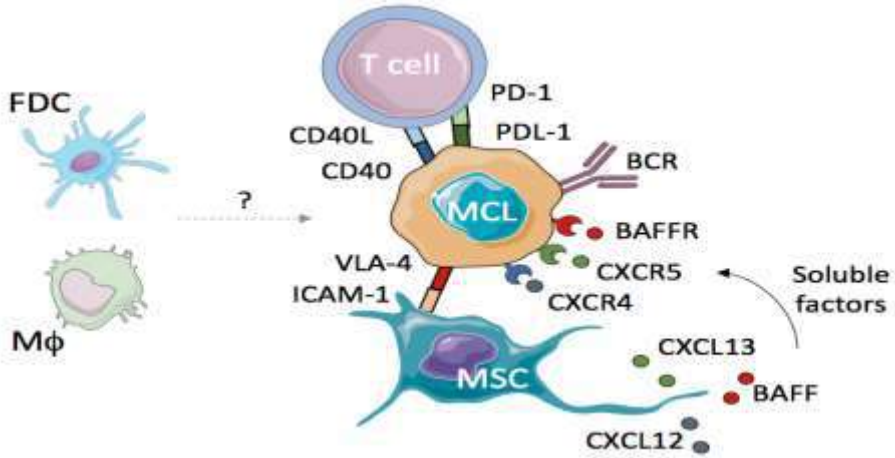


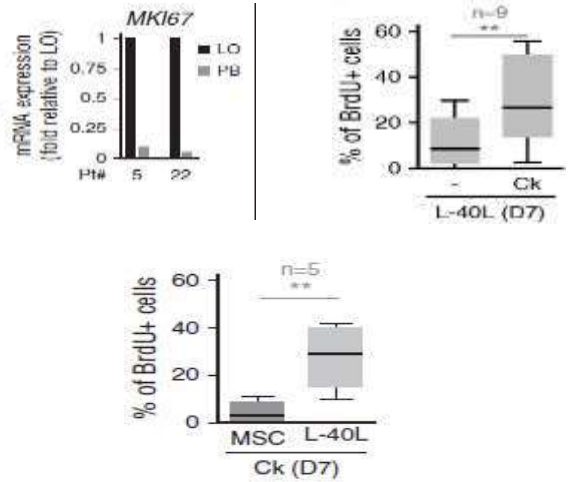
Voie p53 impliquée chez >60% des patients dans le LyMa (n=96 gg diagnostic ; SNP-array Oncoscan®)



Poster ASH 2016 #92536 – Le Bris Y

La cellule du lymphome à cellule du manteau interagit et dépend de son environnement



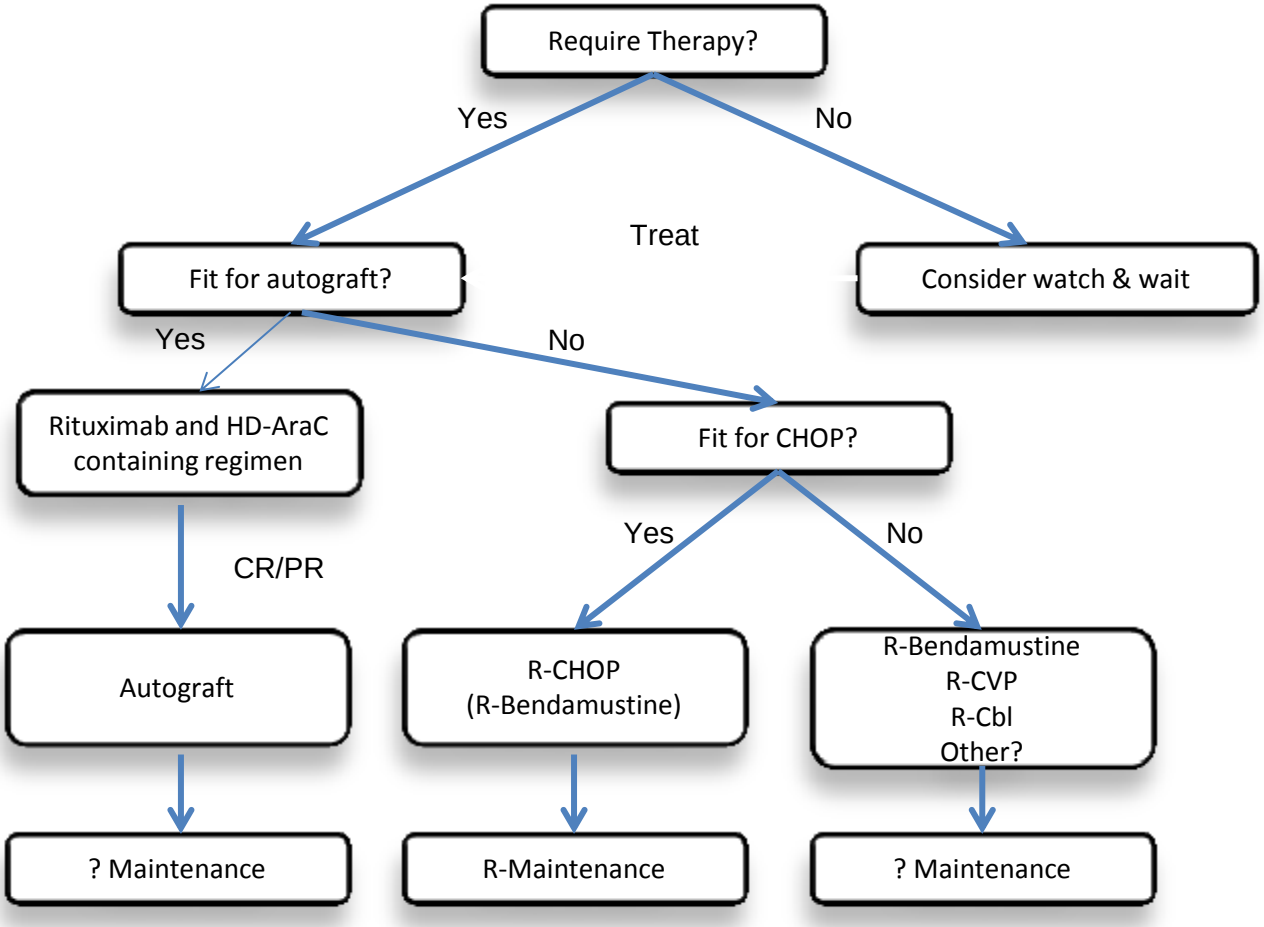


Papin et al. *Leukemia Lymphoma* 2018

Chiron et al *Blood* 2016

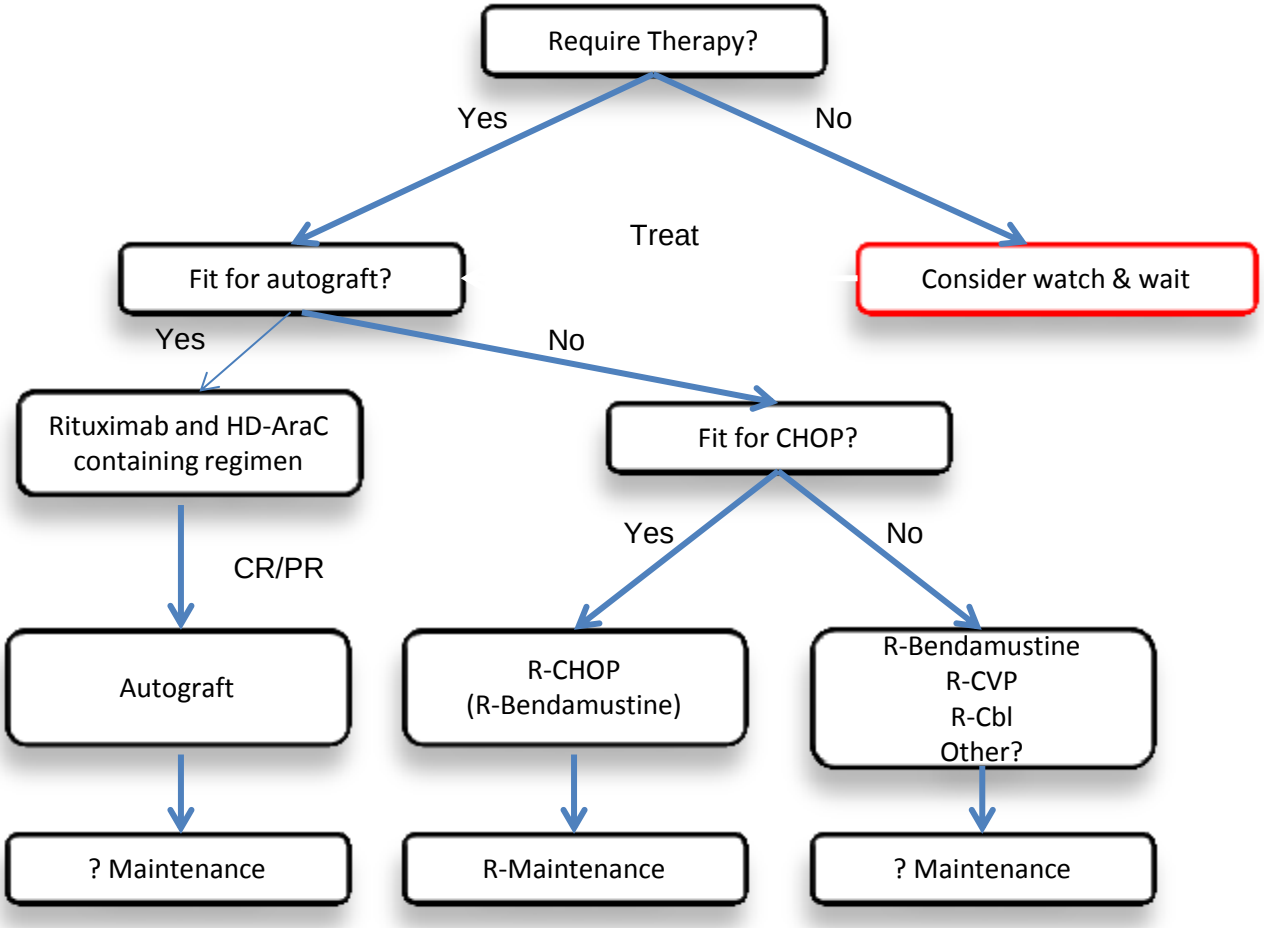
QUELLES SONT LES STRATÉGIES THÉRAPEUTIQUES DANS LE LCM ET QUELS SONT LES BIOMARQUEURS DISPONIBLES?

Management des patients avec LCM au <u>diagnostic</u>



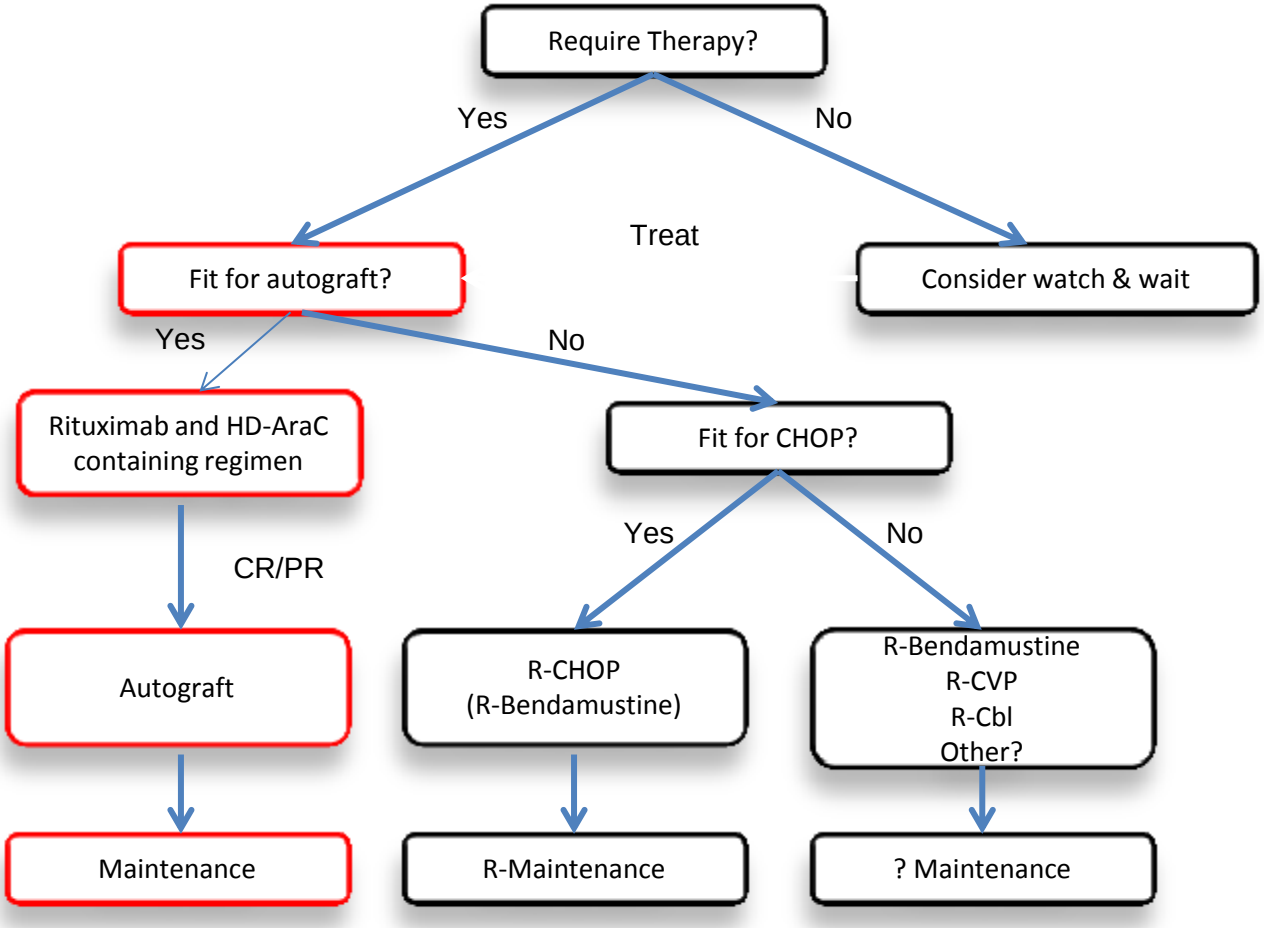
Campo & Rule Blood 2014

Management des patients avec LCM indolent (<5% des LCM)



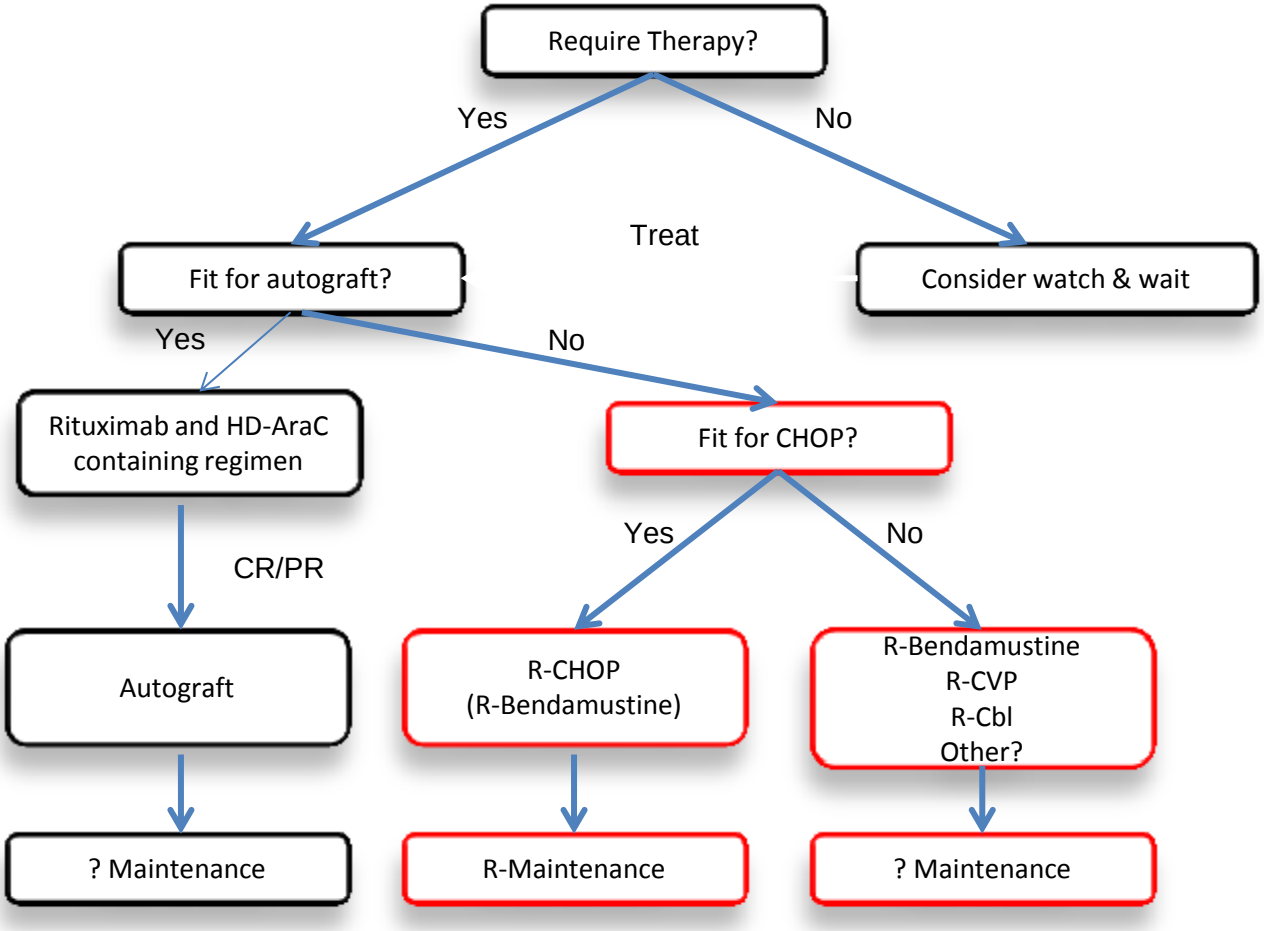
Campo & Rule Blood 2014

Management des patients jeunes avec LCM



Campo & Rule Blood 2014

Management des patients âgés avec LCM



Campo & Rule Blood 2014

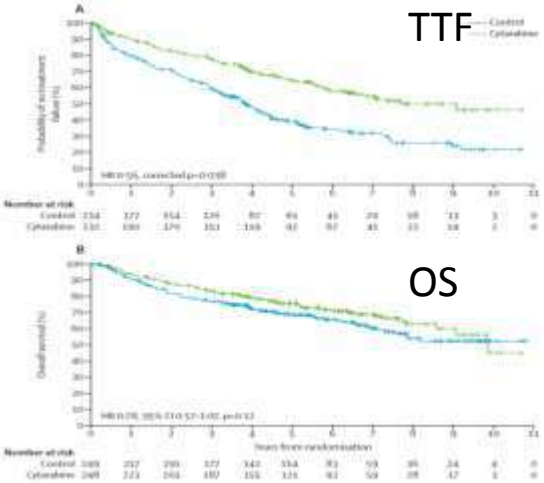
Traitement de 1ère ligne

Sujets jeunes

EU-MCL Younger / LYMA trial

- Cytarabine haute dose puis autogreffe

- Entretien par Rituximab (anti-CD20)



Hermine et al. Lancet 2016

Maladie très hétérogène

Groupe de haut risque

10% de réfractaires ou de rechute <1 ans après la fin du traitement

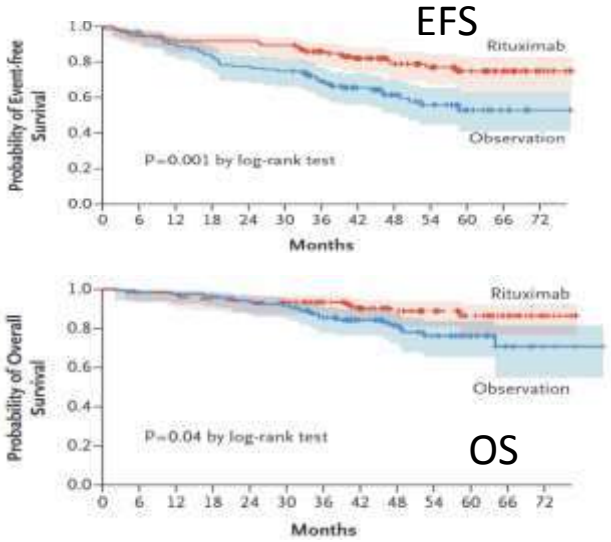
(5-years OS=34%)

Risque Intermédiaire

Rechutes = 10-15%/an;

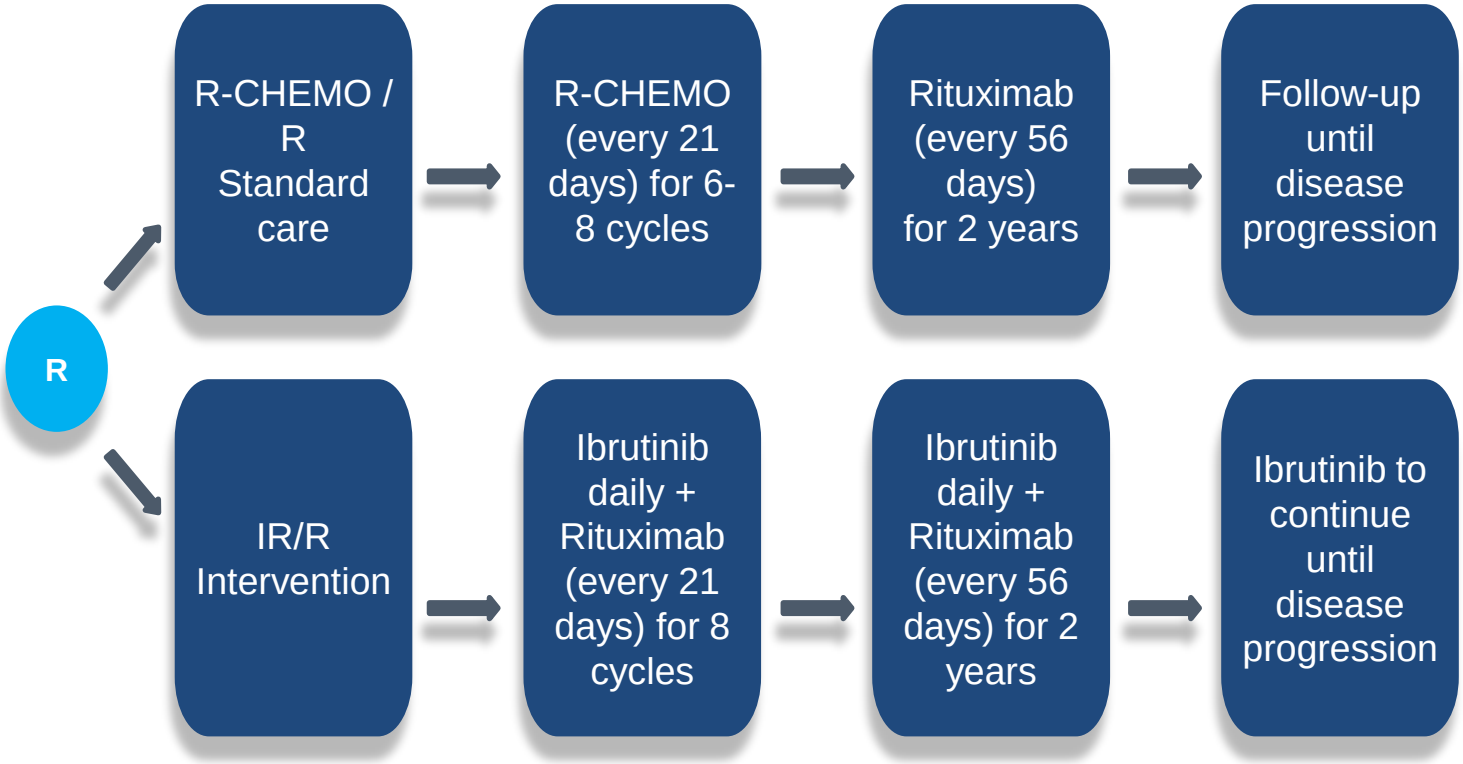
Faible risque

Rémission Complète > 5 ans



Le Gouill et al. NEJM 2017

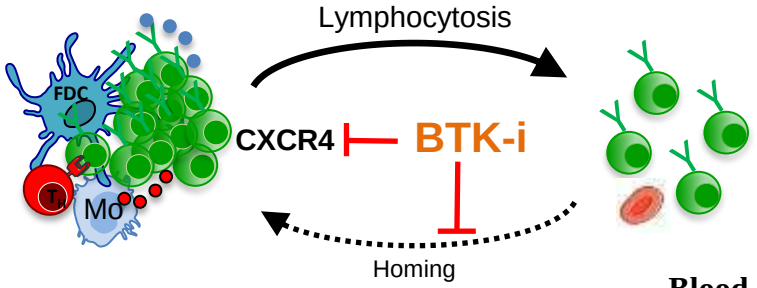
ENRICH –Randomised open label phase III trial of rituximab & ibrutinib vs rituximab & chemotherapy in elderly MCL



CI S Rule

OASIS TRIAL

Egress from lymph nodes using a BTKi (neutralization of BCR and CXCR4 axis)



Lymph Nodes
BCLXL high
Venetoclax Resistance

Obinutuzumab

Blood
BCLXL low
Venetoclax Sensitivity

Obinutuzumab

Rapid loss of BCLXL expression in PB

Chiron et al Oncotarget 2015

Clinical Trial

Oasis Trial

NTC#02558816

PI : Pr. S Le Gouill

2016

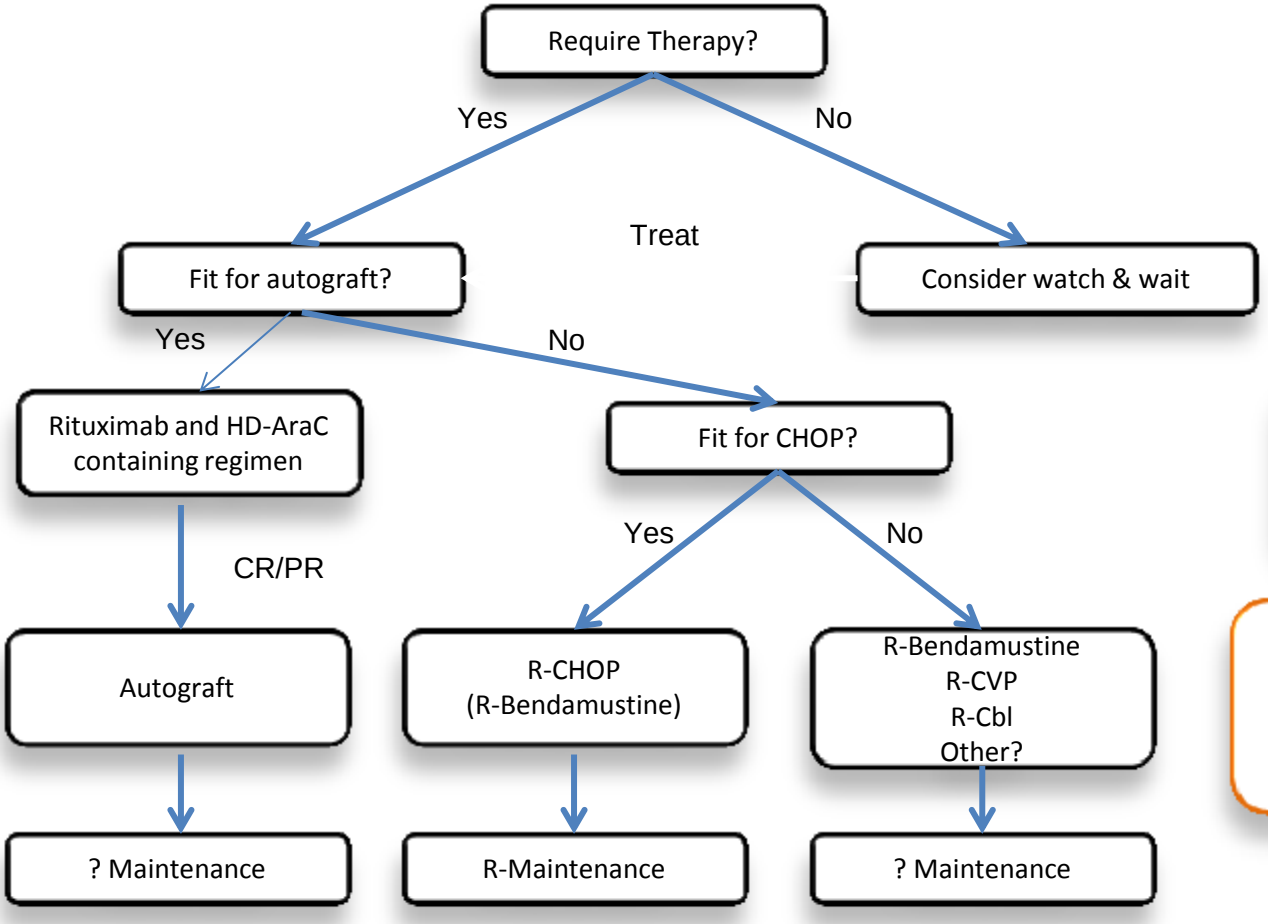
CHU de Nantes

Plymouth Hospitals NHS

BTK-i (Ibrutinib) // anti-CD20 (GA101) // Venetoclax

Le Gouill et al. ASCO 2016 abstract TPS7583
Chiron D et al. ASH 2016 oral session

Management des patients avec LCM au diagnostic dans un futur très proche



Ongoing frontline trials with chemo-free approach

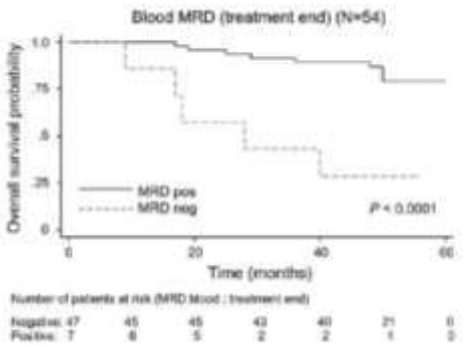
ENRICH = Ibrutinib + R
ACE-LY-308= Acalabrutinib +/- R
AIM = Venetoclax + Ibrutinib
OASIS = Ibrutinib + Venetoclax + GA101

Campo & Rule Blood 2014

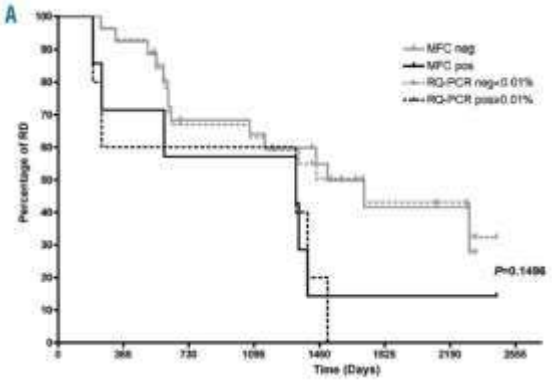
Marqueurs prédictifs de la réponse au diagnostic

- Score MIPI et bio-MIPI
- Pourcentage de cellules KI67 positive
- Expression SOX11 (indolent vs non-indolent MCL)
- Morphologie blastoïde
- Profile de mutation IGVH (LCM indolent vs non-indolent)
- MRD

Un poids pronostique majeur de la MRD dans le LCM



Gressin Haematologica 2018



Cheminant et al. Haematologica 2016

UN CHOIX GUIDÉ PAR LA GÉNOMIQUE EST-IL POSSIBLE?

Uniparental disomies, homozygous deletions, amplifications, and target genes in mantle cell lymphoma revealed by integrative high-resolution whole-genome profiling

Silvia Beà,[1] Itziar Salaverria,[1] Lluís Armengol,[2] Magda Pinyol,[1] Verónica Fernández,[1] Elena M. Hartmann,[3] Pedro Jares,[1] Virginia Amador,[1] Luís Hernández,[1] Alba Navarro,[1] German Ott,[3,4] Andreas Rosenwald,[3] Xavier Estivill,[2] and Elias Campo[1]

NEOPLASIA

Increased Number of Chromosomal Imbalances and High-Level DNA Amplifications in Mantle Cell Lymphoma Are Associated With Blastoid Variants

By Silvia Beà, Maria Ribas, Jesús M. Hernández, Francesc Bosch, Magda Pinyol, Luis Hernández, Juan Luis García, Teresa Flores, Marcos González, Armando Lopez-Guillermo, Miguel A. Piris, Antonio Cardesa, Emilio Montserrat, Rosa Miró, and Elias Campo

Landscape of somatic mutations and clonal evolution in mantle cell lymphoma

Silvia Beà[a,1], Rafael Valdés-Mas[b], Alba Navarro[a], Itziar Salaverria[a], David Martin-Garcia[a], Pedro Jares[a], Eva Giné[a], Magda Pinyol[a], Cristina Royo[a], Ferran Nadeu[a], Laura Conde[a], Montserrat Juan[a], Guillem Clot[a], Pedro Vizán[a], Luciano Di Croce[c], Diana A. Puente[b], Mónica López-Guerra[a], Alexandra Moros[a], Gael Roué[a], Marta Aymerich[a], Neus Villamor[a], Lluís Colomer[a], Antonio Martínez[a], Alexandra Valera[a], José I. Martin-Subero[d], Virginia Amador[a], Luis Hernández[a], Maria Rozman[a], Anna Enjuanes[a], Pilar Forcada[a], Ana Muntanola[a], Elena M. Hartmann[e], Maria J. Calasanz[f], Andreas Rosenwald[g], German Ott[h], Jesús M. Hernández-Rivas[b], Wolfram Klapper[i], Reiner Siebert[j], Adrian Wiestner[k], Wyndham H. Wilson[l], Dolors Colomer[a], Armando López-Guillermo[a], Carlos López-Otín[b,1], Xose S. Puente[b,1,2], and Elias Campo[a,1,2]

LYMPHOID NEOPLASIA

The genomic landscape of mantle cell lymphoma is related to the epigenetically determined chromatin state of normal B cells

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British Journal of Haematology, 2002, 116, 291–298

Identification of novel regions of amplification and deletion within mantle cell lymphoma DNA by comparative genomic hybridization

Jennifer E. Allen,[1] Rachael E. Hogg,[1] John R. Gosney,[1] Sarah Bowskill,[1] Gil A. Wilson,[2] Helen E. Allott,[1] Margaret Rabbitts,[1] Paul C. Lorigan,[3] Elizabeth A. Vandenberghe,[2] Barry W. Hancock[3] and David W. Hammond[1] [1]Institute for Cancer Studies, Division of Genomic Medicine, University Medical School, [2]Molecular Haematology Unit and [3]Department of Pathology, Royal Hallamshire Hospital, and [4]Section of Clinical Oncology, Division of Genomic Medicine, University Medical School, Sheffield, UK

TP53 Mutation and Complex Karyotype Portends a Dismal Prognosis in Patients With Mantle Cell Lymphoma

Aleš Obr,[1] Vít Procházka,[1] Andrea Jirkuvová,[2] Helena Urbánková,[1] Eva Kriegova,[3] Petra Schneiderová,[3] Michaela Vatolíková,[1] Tomáš Papajík[1]

Human Molecular Genetics, 2004, Vol. 13, No. 17 1827–1837
doi:10.1093/hmg/ddh195
Advance Access published on June 30, 2004

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 6, No. 39

High incidence of MYC and BCL2 abnormalities in mantle cell lymphoma, although only MYC abnormality predicts poor survival

bjh research paper

Detection of gene copy number aberrations in mantle cell lymphoma by a single quantitative multiplex PCR assay: clinicopathological relevance and prognosis value

Fabien Guille, Jean Michel Picquenot, Jean-Luc Cornillet, Philippe Jourdain, Alain Cochet, Hyacinthe Foulley, Philippe Lenormand, Fabienne Lamy, Frédéric Commes, Catherine Berthou, Eric Le Gouill, Aurélie Cabelguenne, Christian Berard and Herve Dilly.

HEMEL, CHROMOSOMES & CANCER 49:429–441 (2010)

Comprehensive whole genome array CGH profiling of mantle cell lymphoma model genomes

Ronald J. de Leeuw[1,*], Jonathan J. Davies[1], Andreas Rosenwald[4,5], Gwyn Bebb[2], Randy D. Gascoyne[3], Martin J.S. Dyer[6], Louis M. Staudt[5], Jose A. Martinez-Climent[7] and Wan L. Lam[1]

Whole transcriptome sequencing reveals recurrent *NOTCH1* mutations in mantle cell lymphoma

Robert Kridel,[1,2] Barbara Meissner,[1] Sanja Rogic,[1] Merrill Boyle,[1] Adele Telenius,[1] Bruce Woolcock,[1] Jay Gunawardana, Christopher Jenkins,[1] Chris Cochrane,[1] Susana Ben-Neriah,[1] King Tan,[1] Ryan D. Morin,[4] Stephen Opat,[3] Laurie H. Sehn, Joseph M. Connors,[1] Marco A. Marra,[4] *Andrew P. Weng,[3] *Christian Steidl,[1,2] and *Randy D. Gascoyne[1,2]

Genomic aberrations in mantle cell lymphoma detected by interphase fluorescence *in situ* hybridization. Incidence and clinicopathological correlations

Sandrine Sander,[1,2] Lars Bullinger,[1] Elke Leupolt,[1] Axel Benner,[1] Dirk Kienle,[1] Tiemo Katzenberger,[1] Jörg Kalla,[1] German Ott,[1] Hans Konrad Müller-Hermelink[1], Thomas F.E. Barth,[1] Peter Möller,[1] Peter Lichter,[1] Hartmut Döhner,[1] and Stephan Stilgenbauer[1]

Incidence and Prognostic Impact of Secondary Cytogenetic Aberrations in a Series of 145 Patients with Mantle Cell Lymphoma

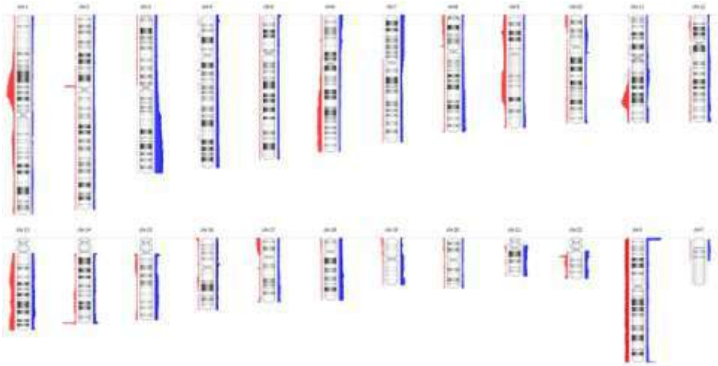
Blanca Espinet,[1,2] Itziar Salaverria,[1,3] Silvia Beà,[1] Neus Ruiz-Xivillo,[1] Olga Balagué,[1] Maria Sebio, Dolors Costa,[1] Joaquín Carreras,[1] Ana Eugenia Rodríguez-Vicente,[1] Juan Luis García,[1] Jesús María Hernández-Rivas,[1] María José Calasanz,[1] Rainer Siebert,[2] Ana Ferrer,[1] Antonio Salar,[1] Ana Cuevas,[1] Matutidad Piris,[1] José Antonio García-Marco,[1] Alicia Domingo,[1] Eva González-Barca,[1] Vicente Garaugaza,[1] Isabel Marzoa,[1] Armando López-Guillermo,[1] Francesca Millá,[1] José Luis Mate,[1] Elisa Luño,[1] Carmen Sanz,[1] Rosa Collado,[1] Isabel Olivar,[1] Soledad Mercadal,[1] Antonio Pelaez,[1] Teresa González,[1] Francesc Bosch,[1] Benito Salinas,[1] María Teresa Arribas,[1] Llorenç Font,[1] Lourdes Escoda,[1] Lourdes Florensa, Sergi Serrano,[1] Elias Campo,[1] and Francesc Solé[1]

Poster ASH 2016 #92536 – Le Bris Y ….. Le Gouill S.

High-Resolution Whole-Genome Copy Number Profiling Identifies High-Risk and Low-Risk Patients with Mantle Cell Lymphoma, a Result of the Lyma-Genomic Project Conducted on Behalf the Lysa Group.

- *96* MCL patients traités dans l'essai de **phase 3 du LyMa**
  - 9 patients de haut risque en rechute/réfractaire <1 an du diagnostic
  - 87 patients en RC après 1 an du diagnostic don't 64 faible risque en RC prolongée (30 mois après le diagnostic)
- ADN extrait de ganglions FFPE prélevés au diagnostic
- Whole-genome copy number profiling (OncoScan® Affymetrix FFPE Assay)

Regions	(%)	Gènes d'intérêt
Del 1p21.2	44	*S1PR1*
Del 11q22.3	40	*ATM*
Dup 3q26-27	34	*BCL6, PIK3CA, ETV5*
Dup 3q21	26	*GATA2*
Del 9p21	26	*CDKN2A, CDKN2B*
Del 1p32-12	26	*BCL10, CD58, GADD45A, NOTCH2, S1PR1, VCAM1*
Del 11q14-23	26	*BIRC2, BIRC3, ATM*
Del 13q14	24	*RB1*
Del 9q22-31	21	*TGFBR1/Rc-TGFb*
Del 13q33-34	21	*TNFSF13B/Baff, SOX1, TFDP1*
Del 6q25	17	*ARID1B*
Del 17p13	17	*TP53, TNFSF12*
Dup 11q13	11	*CCND1, FADD, FGF4*
Dup 13q31	10	*MIR17HG*
Dup 7p22	9	*CARD11, MAD1L1*



Poster ASH 2016 #92536 – Le Bris Y ….. Le Gouill S.

High-Resolution Whole-Genome Copy Number Profiling Identifies High-Risk and Low-Risk Patients with Mantle Cell Lymphoma, a Result of the Lyma-Genomic Project Conducted on Behalf the Lysa Group.

- *96* MCL patients traités dans l'essai de **phase 3 du LyMa**
  - 9 patients de haut risque en rechute/réfractaire <1 an du diagnostic
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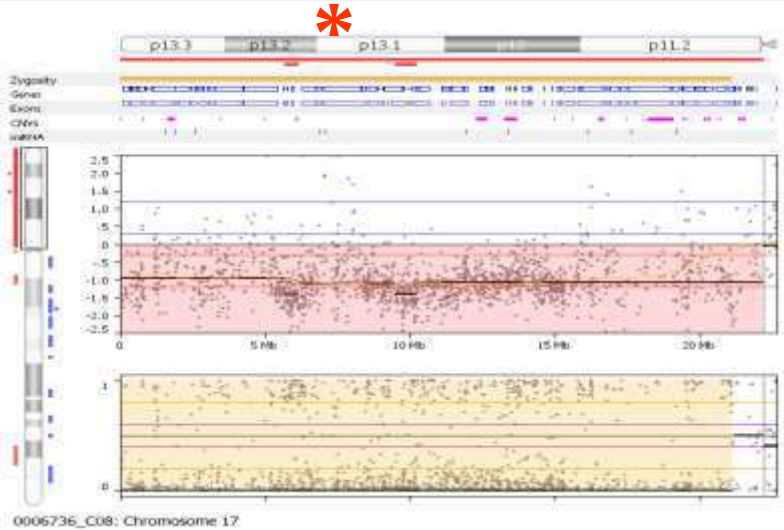
- ADN extrait de ganglions FFPE prélevés au diagnostic
- Whole-genome copy number profiling (OncoScan® Affymetrix FFPE Assay)

Délétion 17p (17%)

de *TP53*



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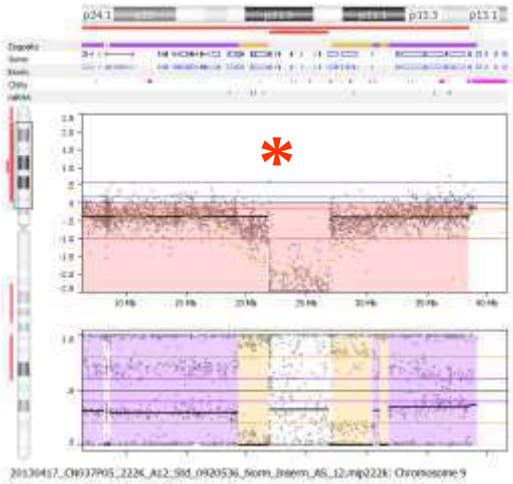
Délétions (25%)

bi-alléliques

de *CDKN2A/2B*



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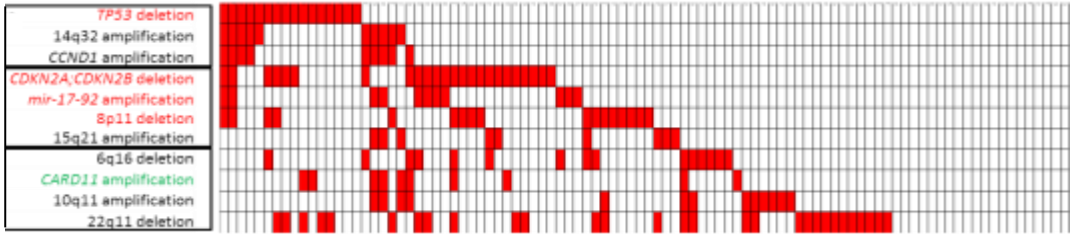
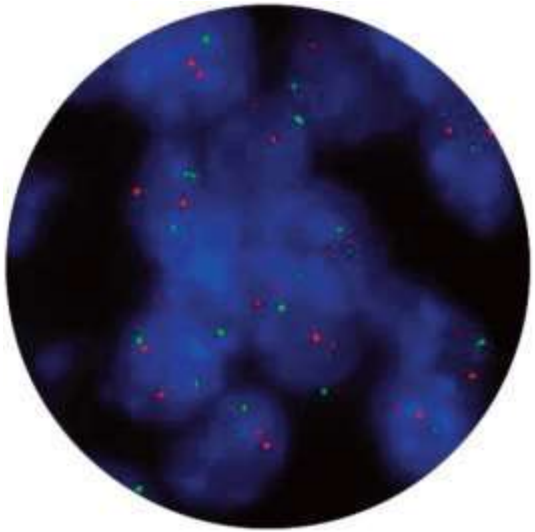
- Whole-genome copy number profiling (OncoScan® Affymetrix FFPE Assay)

- **Détection d'anomalies récurrentes (>5 patients) chez > 98% des patients**

CNAs
Avec un impact prognosis
(interim analysis)



- Les CNAs associées au patients de haut risque incluent les délétions de *TP53* et de *CDKN2A/B*
- Autres anomalies de mauvais pronostiques: gain du locus *mir-17-92* (12%)
- Autres anomalies de bon pronostiques amplification: gains 7p (10%)



LES DÉLÉTIONS DE *TP53* DANS LE LCM

Incidence des délétions de *TP53* et de *CDKN2A*

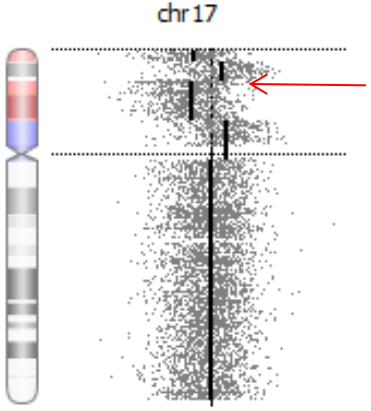
	Beà Blood 1999	Allen JE Br J Haematol 2002	Rosenwald A Cancer Cell 2003	Kohlhammer H Blood 2004	Schraders Blood 2005	Tagawa H Oncogène 2005	Rubio-Moscardo Blood 2005	Salaverria JC0 2007	Beà Blood 2009	Salaverria Genes Chromosomes Cancer. 2008	Kawamata N Exp Hematol 2009	Halldórsdóttir AM Gen Chr Cancer 2011	Beà PNAS 2013	Delfau Larue Blood 2015	Shuhua Yi Oncotarget 2015	Flordal Leuk Res. 2007	Katzenberger Br J Haematol 2008	Sander Haematologica 2008	Jardin Br J Haematol. 2009
n	45	39	85	53	14	29	68	77	28	22	28	30	201	135	50	37	223	103	42
Methods	CGH	CGH	RQPCR	CGH/FISH	CGH	CGH	aCGH/FISH	CGH	WES	FISH/CGH/RQPCR	SNP	SNP	WGS/WES/SNP	QMPSF/MLPA	FISH	CGH	FISH/Conv Cytog	FISH	QMPSF
9p21	16%	17%	21%	36%		41%	18%	19%	18%	9p: 15%	21%		17%	25%		29%	31%	35%	31%
17p13	16%	23%	11%	21%		45%	22%	12%		17p: 15%	21%	32%	21%	22%	34%		26%	26%	10%

Sur 1300 cas de LCM :

Délétion *CDKN2A* = 23%

Délétion *TP53* = 21%

Caractéristiques des délétions 17p impliquant *TP53* dans le LCM



Taille du gène *TP53* ~18kb

Analyse Oncoscan ® – SNP array
(sensibilité de détection des CNV = 50kb)

Les délétions de *TP53* impliquent des pertes de taille très variables

Médiane = 18 Mb (n=16)
Min = 470 kb focalisée sur le gène *TP53*
Max = 28 Mb implique tout le bras 17p

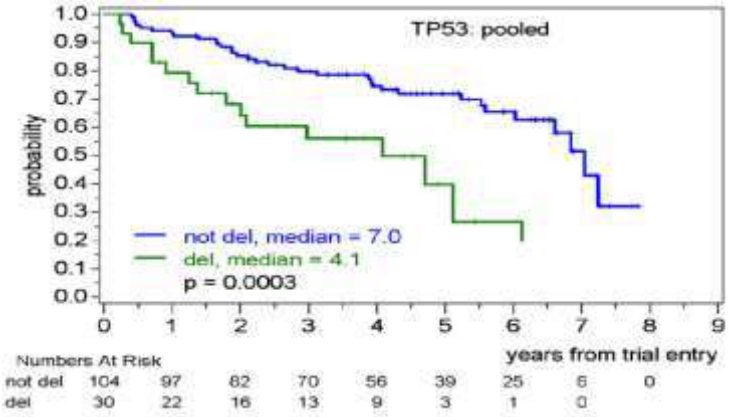
Anomalies parfois complexe

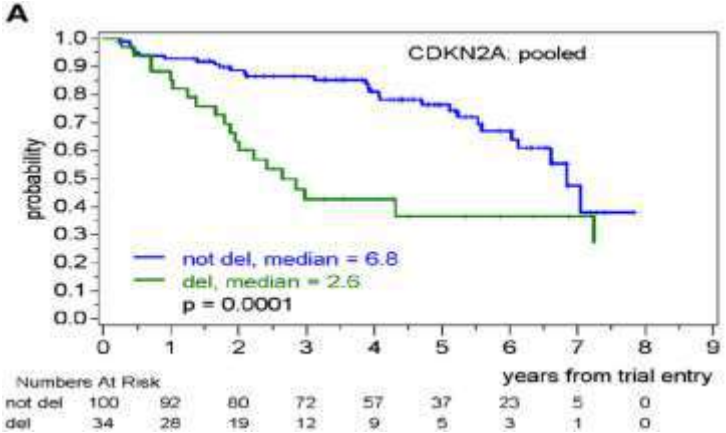
Majorité de pertes *TP53* sont mono-alléliques à la différences des délétion de *CDKN2A* (50% mono et 50% bialléliques)

High-dose cytarabine does not overcome the adverse prognostic value of *CDKN2A* and *TP53* deletions in mantle cell lymphoma

Marie-Hélène Delfau-Larue,[1,2,3] Wolfram Klapper,[4] Françoise Berger,[5] Fabrice Jardin,[6] Josette Briere,[7] Gilles Salles,[8] Olivier Casasnovas,[9] Pierre Feugier,[10] Corinne Haioun,[3,11] Vincent Ribrag,[12] Catherine Thieblemont,[13] Michael Unterhalt,[14] Martin Dreyling,[14] Elizabeth Macintyre,[15] Christiane Pott,[16] Olivier Hermine,[17] and Eva Hoster,[14,18] on behalf of the European Mantle Cell Lymphoma Network

2015





Del *TP53* (17p) (22%)

Mono-allélique 22%

Bi-allélique 0%

<u>Associées aux f. blastoïdes 50% vs 13%</u>

<u>Indépendantes du Ki-67</u>

Del *CDKN2A* (p16) (25%)

Mono-allélique 14%

Bi-allélique 11%

<u>Associées à un Ki-67 >30%</u>

N=134

Quantitative multiplex PCR of short fluorescent fragments (QMPSF) et Multiplex ligation-dependent probe amplification (MLPA)

Mais l'impact des délétions seules de *TP53* et de *CDKN2A* sur la PFS n'est pas confirmé en analyse multivariée…

- **LyMa**

Le Bris et al ASH 2018

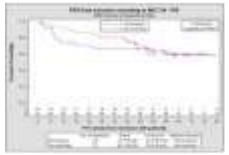
Ganglions au diagnostic

analysés sur Oncoscan®

PFS OS

TP53 del

CDKN2A del



- **Nordic MCL2 and MCL3 trials**

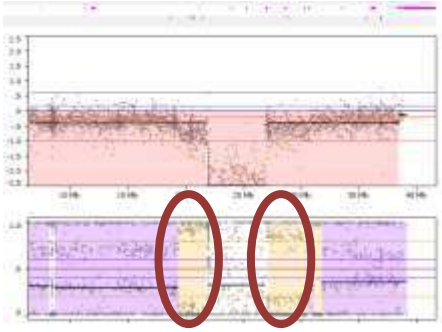
Eskelund Blood 2017

Table 2 : Multivariate Cox regression analyses (n=147)

	OS			PFS			CR		
Variables	*HR*	*95% CI*	*p*	*HR*	*95% CI*	*p*	*HR*	*95% CI*	*p*
mut *TP53*	6.2	(2.6-14.9)	<0.0001	6.8	(3.4-13.8)	<0.0001	6.0	(3.3-14.5)	<0.0001
mut *NOTCH1*	2.7	(0.9-8.6)	0.09	2.3	(0.9-6.3)	0.10	2.2	(0.7-6.5)	0.17
del *TP53*	1.4	(0.7-2.8)	0.37	1.5	(0.9-2.7)	0.15	1.7	(0.9-3.0)	0.10
del *CDKN2A*	1.3	(0.6-2.7)	0.55	1.3	(0.7-2.4)	0.40	1.3	(0.7-2.5)	0.43
Blastoid	1.3	(0.6-2.5)	0.53	0.8	(0.4-1.6)	0.62	0.9	(0.4-1.7)	0.65
MIPI-c high-risk*	1.8	(0.9-3.9)	0.11	2.2	(1.2-4.0)	0.01	2.6	(1.4-4.9)	0.003
mut *WHSC1***	0.8	(0.3-1.9)	0.58	-	-	-	-	-	-

**MIPI-c index included as a bimodal variable of MIPI-c high-risk or not.*

***WHSC1 mutations only included for OS, since they did not show significant prognostic impact for PFS and CIR in univariate analyses.*



LES PERTES D'HÉTÉROZYGOTIES SANS ANOMALIE DU NOMBRE DE COPIE OU DISOMIE UNIPARENTALE ACQUISE DU LOCUS 17P13 (*TP53*) DANS LE LCM

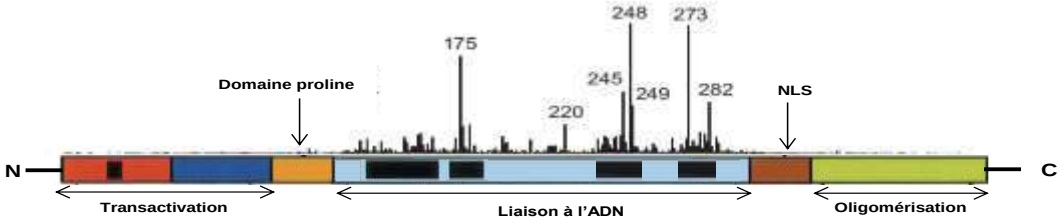
Les pertes d'hétérozygoties de *TP53* sont rares et peuvent être associées à des mutations du gène

- LyMa – SNP-array

1/96 (taille=4,9Mb) chez un patient ayant rechuté précocement à 17 mois du diagnostic

- Beà 2009 – SNP array

2/28 dont 1 avec mutation *TP53*



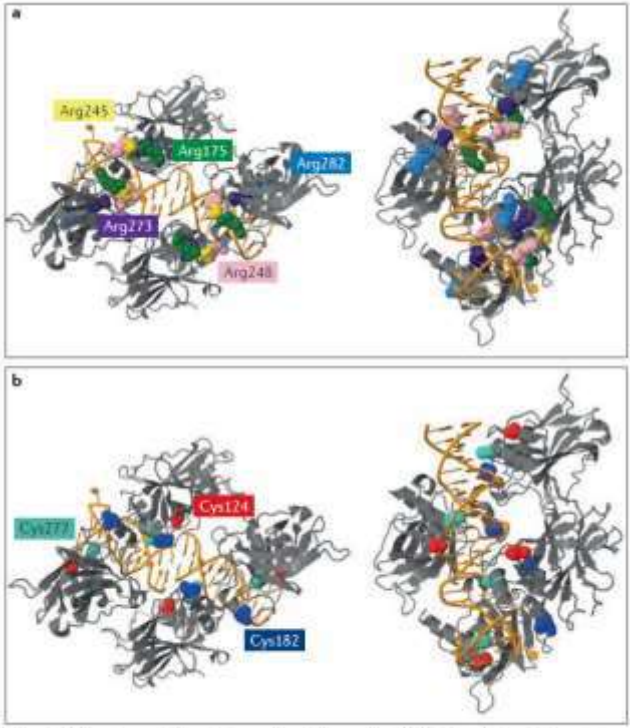


Figure 2 | **Structure of the p53 core domain bound to DNA.** The p53 core domain is shown as a tetramer bound to DNA from two different rotation angles. **a** | Residues

Bykov et al, 2018, Nat Rev Cancer

LES MUTATIONS DE *TP53* DANS LE LCM

Incidence et profil des LCM avec mutations de *TP53*

	Bea et al. N=29	Greiner et al. N=92	Zhang et al. N=56	Rahal et al. N=165	Kridel et al. N=20	Meissner et al. N=102	Rossi et al. N=151	Eskelund et al. N=183	LyMa NCK N=39
	PB, LN	LN	LN		LN	LN	BM	BM	PB, BM
ATM	**41,4%**	**40%**	**41,9%**	**49,5%**		**50%**	**42%**	**27%**	**46%**
CCND1	34,5%		16%	19%	19%	18,6%	14%	9%	
TP53	**31%**	**26%**	**19,6%**	**14%**	**25%**	**13,7%**	**7%**	**11%**	**36%**
MLL2	13,8%		19,6%	12%			12%		
MLL3			16%	16%					
TRAF2				7%			1%		
NOTCH1	**4,6%**		**14,2%**	**14%**		**13,7%**	**6%**	**4%**	**15%**
WHSC1	10%		7%				13%	6%	
BIRC3	**6,4%**		**8,9%**	**8%**			**5%**	**4%**	**10%**
NOTCH2	**5,2%**							**3%**	**10%**
UBR5			7,1%	18%		17,6%			

Sur 837 cas de LCM : Fréquence des mutations de TP53 = 15%

Diapositive transmise par Sophie Kaltenbach

Impact des mutations dans le LCM

- Nordic MCL2 and MCL3 trials
  Eskelund Blood 2017

ddPCR – deletion
8 gene panel – ion ampliseq

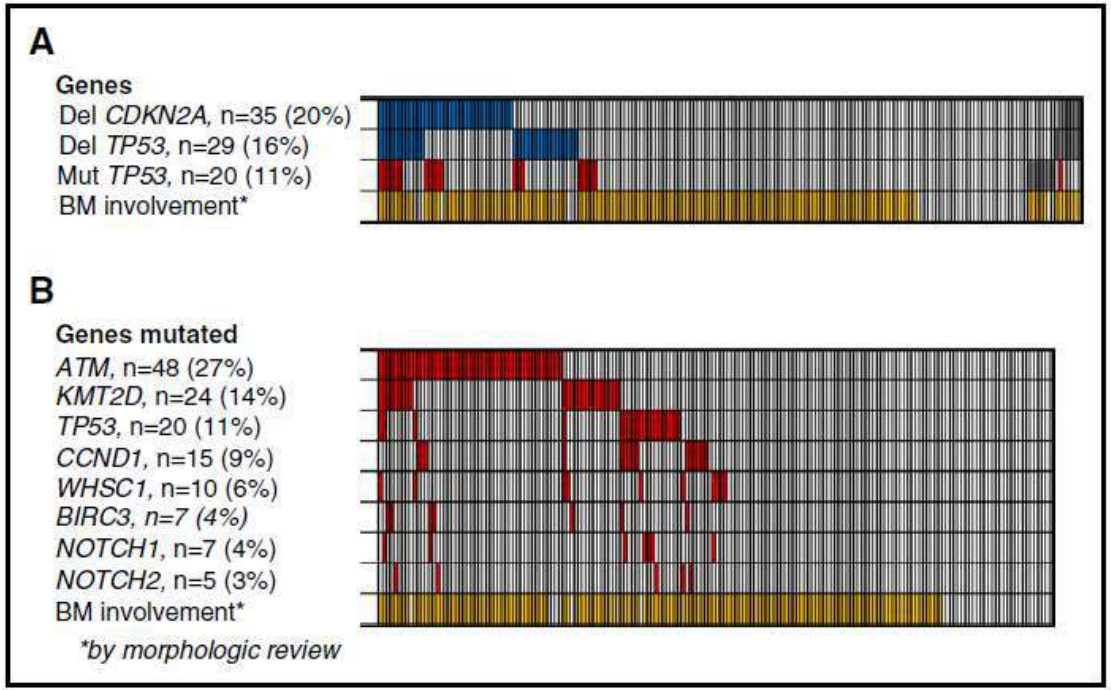


Figure 1. Deletions and point mutations in MCL2 and MCL3 patients. (A) Deletions of *CDKN2A* and *TP53* (blue) and mutations of *TP53* for comparison (red), according to BM involvement of MCL by morphologic review (yellow). Gray boxes indicate samples not tested. (B) Mutation frequency of 8 selected genes. *BM involvement by morphologic assessment.

Impact des mutations dans le LCM

- Eskelund Blood 2017

ddPCR – deletion
8 gene panel – ion ampliseq

	OS			PFS		
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mut *WHSC1***	0.8	(0.3-1.9)	0.58	-	-	-

Les patients avec mutations de *TP53* ont un profil de haut risque

Eskelund Blood 2017

Table 3: Characterization of TP53 mutated MCLs

		TP53 unmutated (N=156)		TP53 mutated (N=20)		
	(N)	N	%	N	%	*p*
Baseline characteristics						
MIPI high risk	*(176)*	24	***15***	14	***70***	*<0.0001*
MIPI-c high risk	*(152)*	12	***9***	11	***58***	*<0.0001*
Blastoid morph.	*(176)*	19	***12***	12	***60***	*<0.0001*
KI67>30%	*(152)*	50	***38***	15	***79***	*0.001*
Treatment response						
CR pre-ASCT*	*(176)*	111	***71***	5	***25***	*0.0002*
CR post-ASCT*	*(176)*	141	***90***	9	***45***	*<0.0001*
No ASCT	*(176)*	8	***5***	5	***25***	*0.001*
MRD assesment						
MRD pos., pre-ASCT	*(99)*	32	***36***	7	***70***	*0.037*
MRD pos., post-ASCT	*(135)*	10	***8***	6	***50***	*<0.0001*

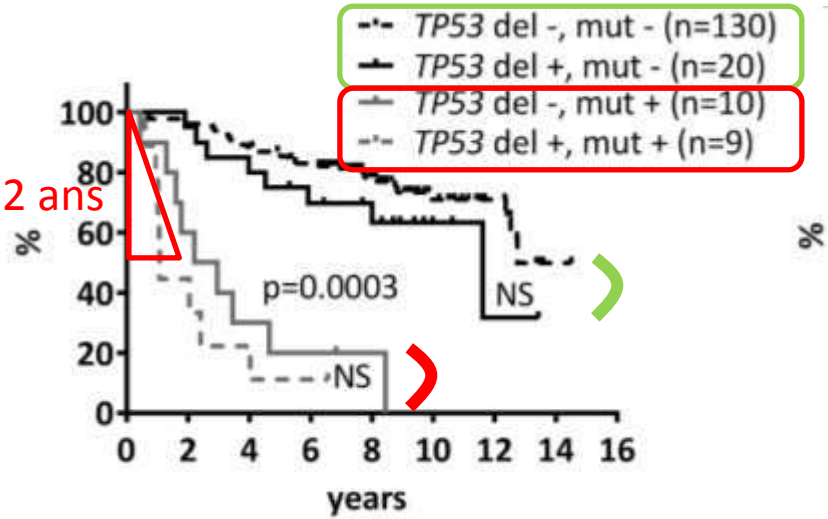
** CR or CRu.*

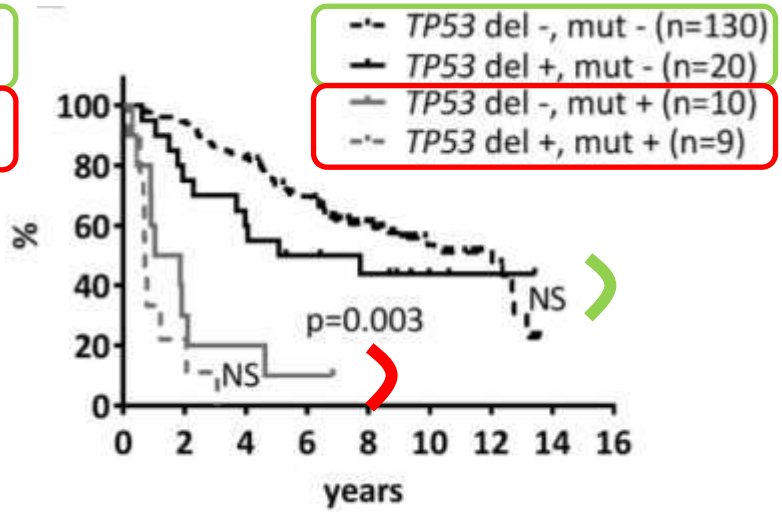
TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy

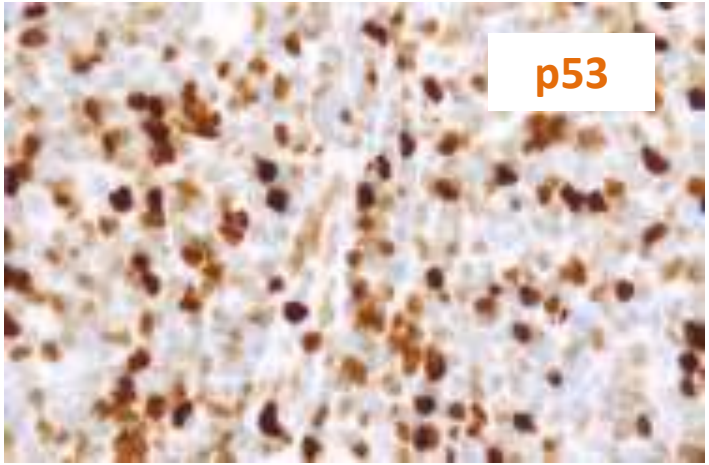
Christian W. Eskelund,[1,2] Christina Dahl,[3] Jakob W. Hansen,[1,2] Maj Westman,[4] Arne Kolstad,[5] Lone B. Pedersen,[1] Carmen P. Montano-Almendras,[1,2] Simon Husby,[1,2] Catja Freiburghaus,[6] Sara Ek,[6] Anja Pedersen,[1,2] Carsten Niemann,[1] Riikka Räty,[7] Peter Brown,[1] Christian H. Geisler,[1] Mette K. Andersen,[4] Per Guldberg,[3] Mats Jerkeman,[8] and Kirsten Grønbæk[1,2]

Blood 2017

-50% en 2 ans







EXPRESSION DE P53 DANS LE LCM

Expression p53 et p16 en immunohistochimie

ASH 2017 Canioni et al.

Etude LyMa N=166

Surexpression p16 et p53 impactent négativement OS et PFS

En analyse uni et multivariée

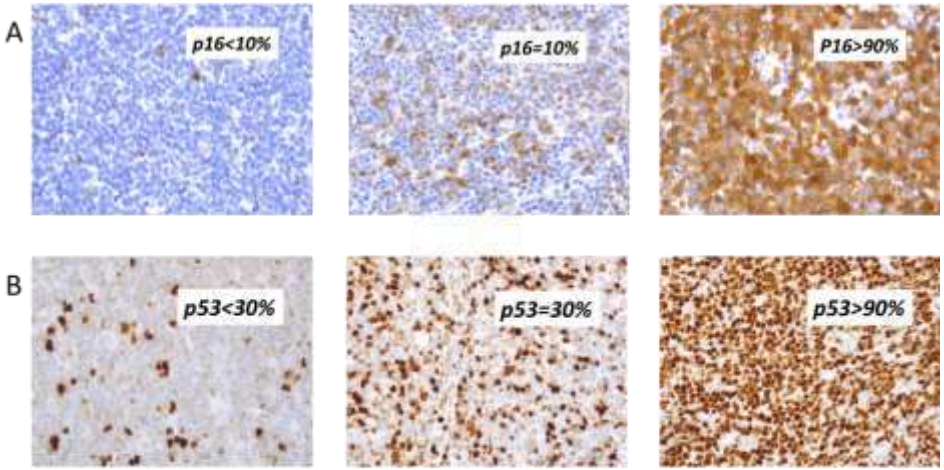


Figure 2: Immunomarquages de p16INK4A (A) et p53 (B).
Surexpression (>10%) de p16INK4A chez 11% des patients
Surexpression (>30%) de la protéine p53 chez 55% des patients

Expression of TP53 is associated with the outcome of MCL independent of MIPI and Ki-67 in trials of the European MCL Network

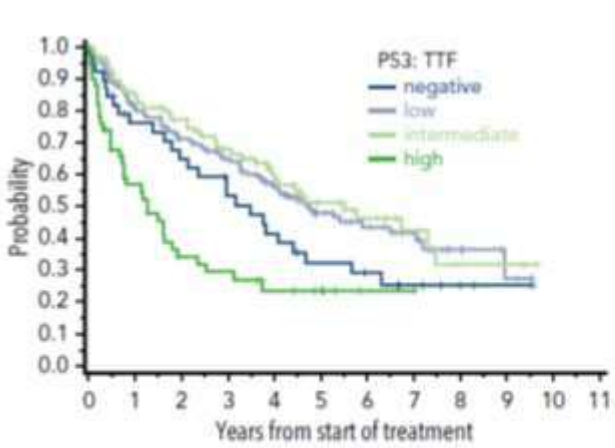
Siebie M. Aukema,[1,*] Eva Hoster,[2,3,*] Andreas Rosenwald,[4,5] Danielle Canoni,[6] Marie-Hélène Delfau-Larue,[7,8] Grzegorz Rymkiewicz,[9] Christoph Thorns,[11] Sylvia Hartmann,[12] Hanneke Kluin-Nelemans,[13] Olivier Hermine,[14,15] Martin Dreyling,[2,*] and Wolfram Klapper[2,*]

KEY POINTS

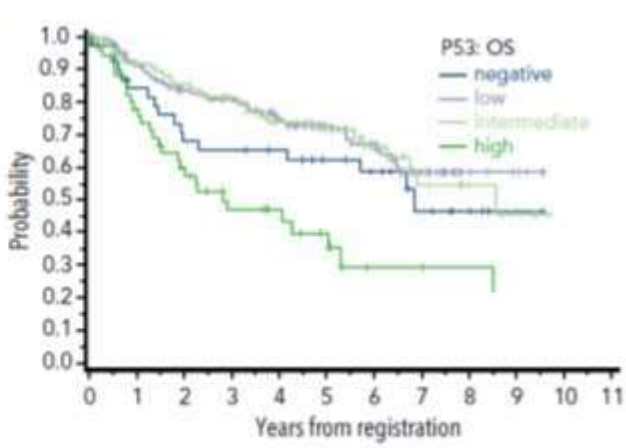
- **TP53 expression (>50% positive cells) has shorter TTF and poor OS independent of both MIPI score and Ki67 index.**

Blood 2018

N=365



Numbers At Risk											
negative	40	27	23	18	14	10	8	5	3	1	0
low	151	112	93	80	61	35	27	17	7	3	0
intermediate	87	70	60	47	35	24	17	9	4	3	0
high	50	25	14	12	7	5	1		0		



Numbers At Risk											
negative	42	31	25	24	22	18	15	7	4	1	0
low	157	129	110	98	79	55	42	24	10	5	0
intermediate	95	76	66	53	40	31	23	12	6	3	0
high	54	35	24	17	13	9	2		1	0	

Y A-T-IL D'<u>AUTRES</u> ANOMALIES GÉNOMIQUES D'INTÉRÊT EN 1ÈRE LIGNE DE TRAITEMENT DU LYMPHOME À CELLULES DU MANTEAU PAR IMMUNOCHIMIOTHÉRAPIE?

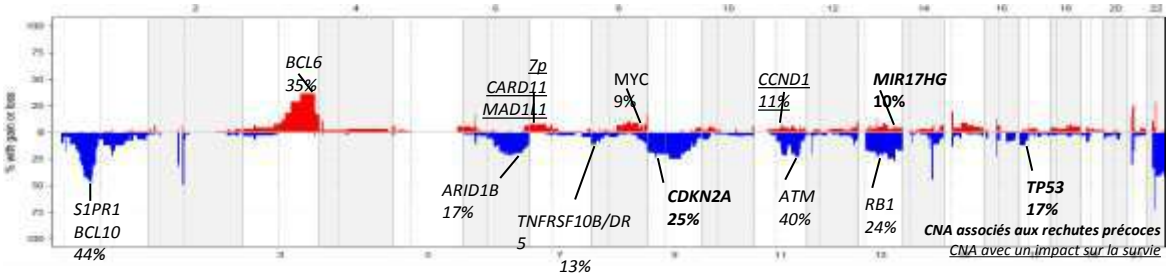
ASH 2018

Poor Prognosis Associated with Gains of *CCND1* in Mantle Cell Lymphoma Treated by First Line Immuno-Chemotherapy - A Study by the LYSA Group. Poster #4099

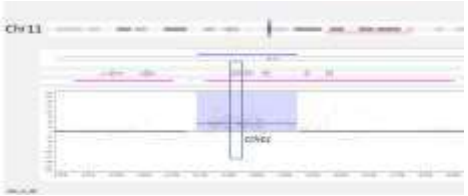
Yannick Le Bris, PharmD1,2*, Olivier Theisen, MD2*, Anne Moreau, MD3*, Florence Magrangeas, PhD1,4*, Danielle Canioni, MD5*, Barbara Burroni, MD6*, Catherine Thieblemont, MD, PhD7, Lucie Oberic, MD8*, Krimo Bouabdallah, MD9*, Emmanuel Gyan, MD-PhD10, David Chiron, PhD1*, Catherine Pellat-Deceunynck, PhD1*, Benoit Tessoulin, MD1,11*, Catherine Godon, MD2*, Marie-Hélène Delfau, MD, PhD13*, Mary Callanan, PhD14*, Stéphane Minvielle, PhD4,5*, Marie C Béné, PharmSciD, PhD1,2*, Olivier Hermine, MD, PhD14* and Steven Le Gouill, MD, PhD1,11*

Les gains de *CCND1* sont observés chez 10% des patients. Ils sont associés à la del17p (*TP53*) et à un mauvais pronostic

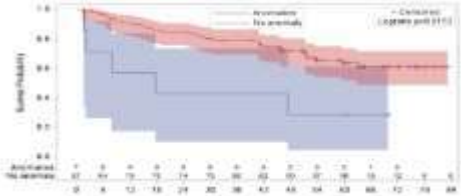
Cohorte LyMa n=100 ganglion au diagnostic – Oncoscan®



Duplications larges (N=7) ou focalisées de *CCND1* (N=3)



PFS – LyMa Cohort

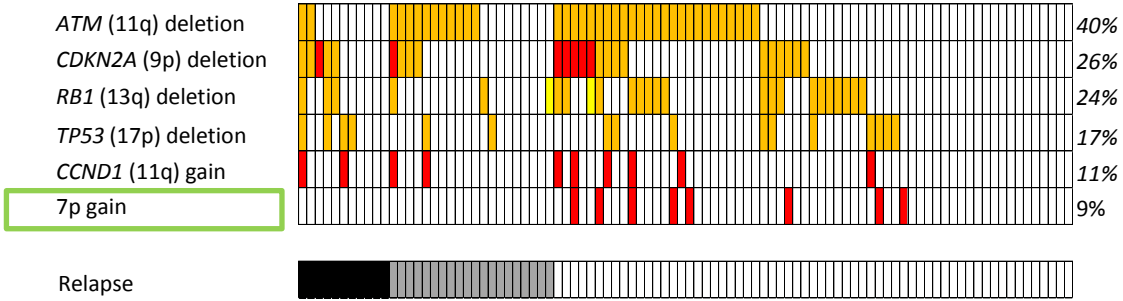


EHA 2017

CARD11 duplication at diagnosis identifies very low-risk mantle cell lymphoma patients:results of the lyma-genomic project conducted on behalf of the lysa group. Poster #2355

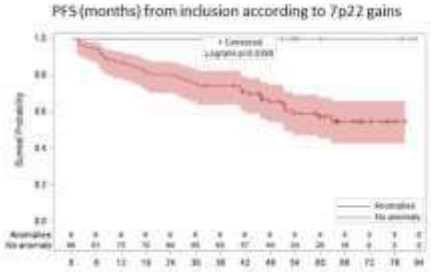
Yannick Le Bris*1 2, Florence Magrangeas2, Olivier Hermine3, Marie-Hélène Delfau-Larue4, Mary Callanan5, Elizabeth Macintyre6, David Chiron2, Danielle Canioni7, Anne Moreau8, Marie C Béné1, Loic Campion2, Stéphane Minvielle2, Steven Le Gouill2,9

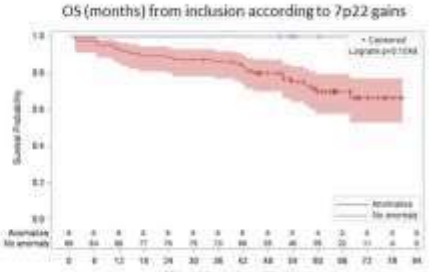
Les gains 7p22 (5Mb) sont observés chez 9% des patients. Ils sont associés à un bon pronostic



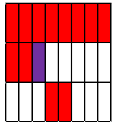
Deux gènes d'intérêt potentiel : ***CARD11*** et ***MAD1L1***

Plus fréquente chez les patients en rémission durable e**n dépit d'autres anomalies de haut risque** (del *TP53* et *CDKN2A*)





7p gain
CDKN2A deletion
TP53 deletion

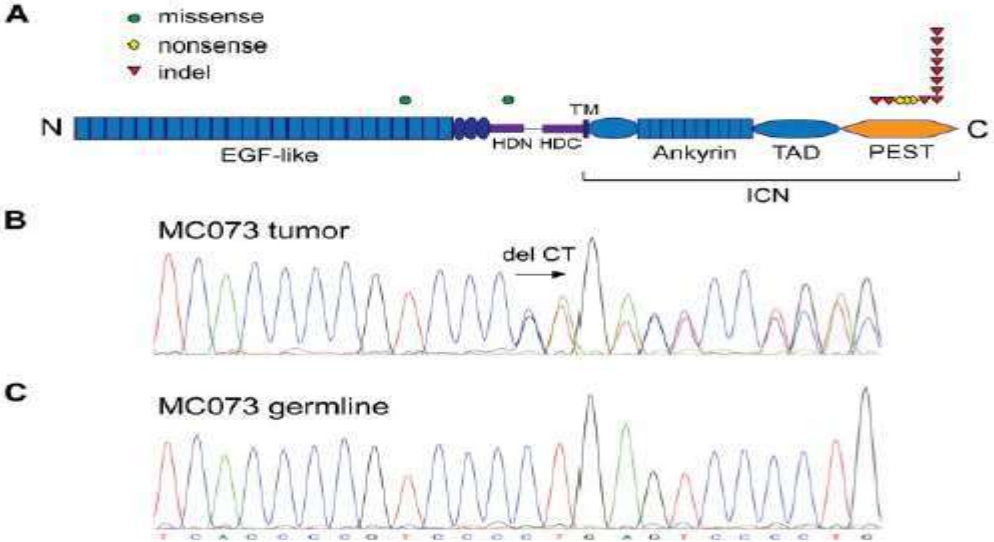


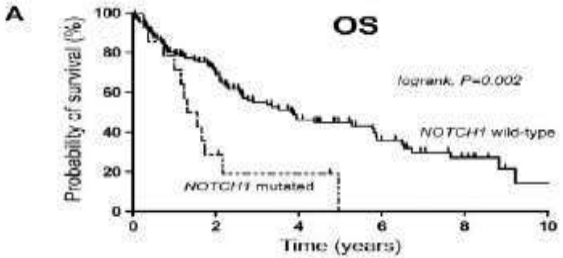
Pas de rechute à 5 ans

Whole transcriptome sequencing reveals recurrent *NOTCH1* mutations in mantle cell lymphoma

Robert Kridel,[1,2] Barbara Meissner,[1] Sanja Rogic,[1] Merrill Boyle,[1] Adele Telenius,[1] Bruce Woolcock,[1] Jay Gunawardana,[1,2] Christopher Jenkins,[3] Chris Cochrane,[3] Susana Ben-Neriah,[1] King Tan,[1] Ryan D. Morin,[4] Stephen Opat,[1] Laurie H. Sehn,[1] Joseph M. Connors,[1] Marco A. Marra,[4] *Andrew P. Weng,[3] *Christian Steidl,[1,2] and *Randy D. Gascoyne[1,2]

[1]Centre for Lymphoid Cancer, British Columbia Cancer Agency, Vancouver, BC; [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC; [3]Terry Fox Laboratory, British Columbia Cancer Agency, Vancouver, BC; and [4]Canada's Michael Smith Genome Sciences Centre, British Columbia Cancer Agency, Vancouver, BC





Impact des mutations de *NOTCH1* dans les cohortes avec un traitement contrôlé

Eskelund Blood 2017

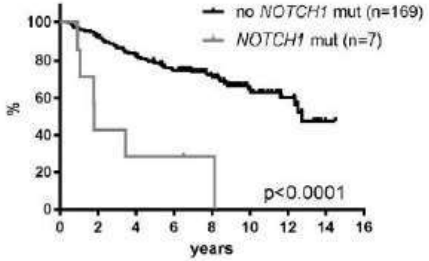


Table 2: Multivariate Cox regression analyses (n=147)

	OS			PFS			CIR		
Variables	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
mut *TP53*	6.2	(2.6-14.9)	<0.0001	6.8	(3.4-13.8)	<0.0001	6.9	(3.3-14.5)	<0.0001
mut *NOTCH1*	2.7	(0.9-8.6)	0.09	2.3	(0.9-6.3)	0.10	2.2	(0.7-6.5)	0.17
del *TP53*	1.4	(0.7-2.8)	0.37	1.5	(0.9-2.7)	0.15	1.7	(0.9-3.0)	0.10
del *CDKN2A*	1.3	(0.6-2.7)	0.55	1.3	(0.7-2.4)	0.40	1.3	(0.7-2.5)	0.43
Blastoid	1.3	(0.6-2.5)	0.53	0.8	(0.4-1.6)	0.62	0.9	(0.4-1.7)	0.65
MIPI-c high-risk*	1.8	(0.9-3.9)	0.11	2.2	(1.2-4.0)	0.01	2.6	(1.4-4.9)	0.003
mut *WHSC1***	0.8	(0.3-1.9)	0.58	-	-	-	-	-	-

**MIPI-c index included as a bimodal variable of MIPI-c high-risk or not.*

***WHSC1 mutations only included for OS, since they did not show significant prognostic impact for PFS and CIR in univariate analyses.*

Ferrero Haematologica 2019

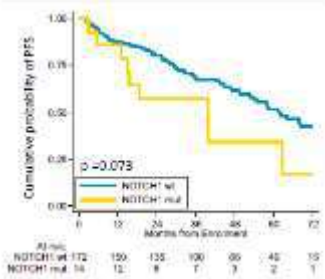


Table 2. Univariate and multivariate Cox-regression analysis in terms of PFS an OS

	Progression free survival						Overall survival					
	Univariate			Multivariate (MIPI-c and blastoid variant adjusted)			Univariate			Multivariate (MIPI-c and blastoid variant adjusted)		
Genes	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
ATM mut	1.29	0.64-1.97	0.245	1.19	0.77-1.83	0.432	1.52	0.62-2.51	0.527	1.05	0.52-2.12	0.887
WHSC1 mut	1.53	0.90-2.60	0.119	1.51	0.87-2.61	0.140	0.85	0.30-2.41	0.755	0.741	0.25-2.15	0.583
CCND1 mut	0.83	0.41-1.66	0.595	0.94	0.46-1.92	0.860	0.75	0.23-2.48	0.643	1.01	0.29-3.53	0.980
KMT2D mut	2.59	1.50-4.48	0.001	2.74	1.55-4.84	0.001	3.20	1.48-6.92	0.003	2.48	1.12-5.46	0.024
TP53 mut	[illegible]	[illegible]	0.001	2.55	1.36-4.78	0.001	5.28	2.64-13.45	<0.0001	1.28	1.06-1.96	0.031
NOTCH1 mut	1.86	0.93-3.72	0.078	1.57	0.76-3.24	0.226	1.34	0.41-4.40	0.629	0.61	0.17-2.12	0.609
WHSC1 mut	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TP53 del	3.51	2.09-5.88	<0.0001	3.13	1.73-5.68	<0.001	4.46	2.14-9.29	<0.0001	2.63	1.06-6.58	0.036
TP53 dis	3.39	2.10-5.45	<0.0001	3.17	1.87-5.38	<0.0001	4.26	2.09-8.67	<0.0001	2.63	1.10-6.37	0.030

Del, deleted; dis, disrupted; PFS, Progression Free Survival; OS, overall survival; HR, Hazard Ratio; CI, Confidence Interval

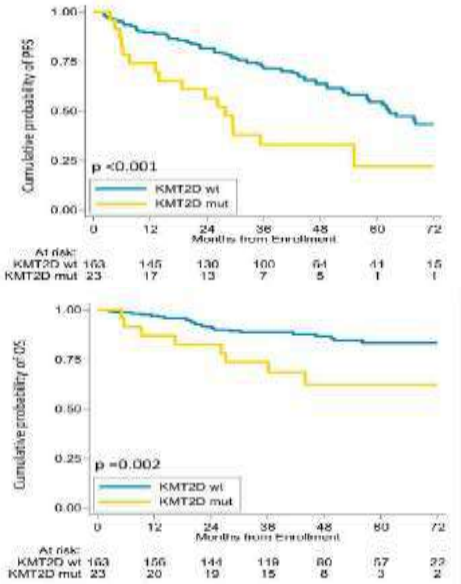
haematologica
Journal of The Ferrata Storti Foundation

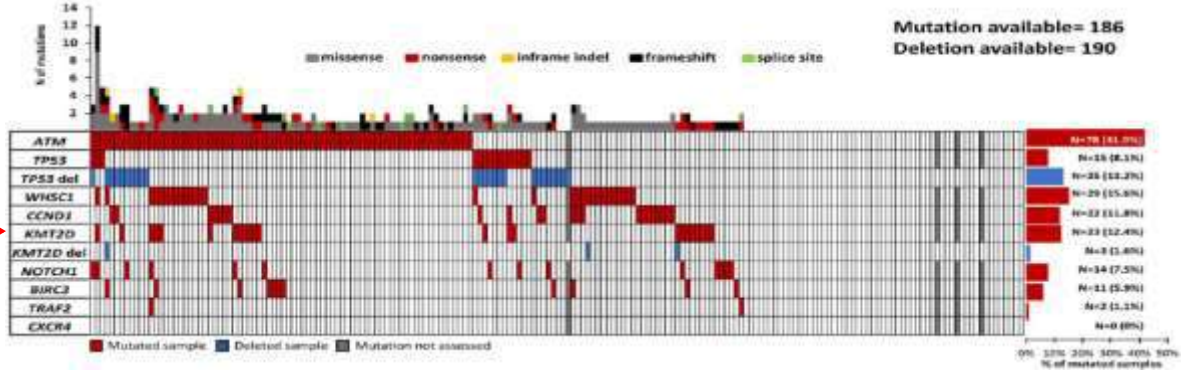
KMT2D mutations and *TP53* disruptions are poor prognostic biomarkers in mantle cell lymphoma receiving high-dose therapy: a FIL study

by Simone Ferrero, Davide Rossi, Andrea Rinaldi, Alessio Bruscaggin, Valeria Spina, Christian W. Eskelund, Andrea Evangelista, Riccardo Moia, Ivo Kwee, Christina Dahl, Alice Di Rocco, Vittorio Stefoni, Fary Diop, Chiara Favini, Paola Ghione, Abdurraouf Mokhtar Mahmoud, Mattia Schipani, Arne Kolstad, Daniela Barbero, Domenico Novero, Marco Paulli, Alberto Zamò, Mats Jerkeman, Maria Gomez da Silva, Armando Santoro, Annalia Molinari, Andres Ferreri, Kirsten Grønbæk, Andrea Piccin, Sergio Cortelazzo, Francesco Bertoni, Marco Ladetto, and Gianluca Gaidano

Haematologica 2019 [Epub ahead of print]

Mutations *KMT2D* 12%

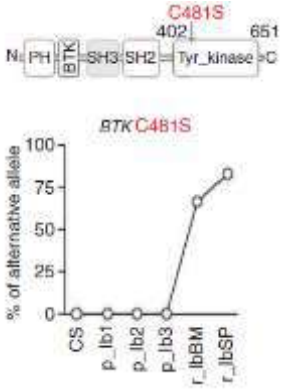


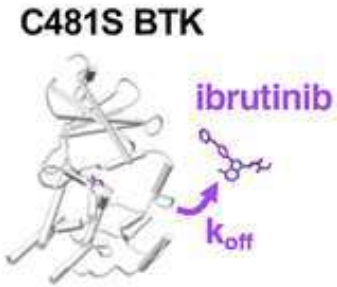


DE NOUVEAUX MARQUEURS DE RÉSISTANCE AUX APPROCHES « CHEMO-FREE » ?

Résistance à l’ibrutinib : des mécanismes multiples

La mutation du BTK **C481S** est responsable de 20% de résistance à l’ibrutinib



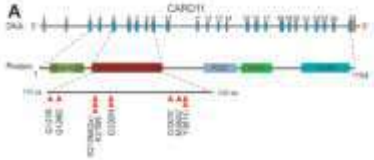


Chiron D, Cancer Discov. 2014
Martin P, Blood. 2016
Jain P, Br J Haematol. 2018
Zhao X Nat Commun 2017

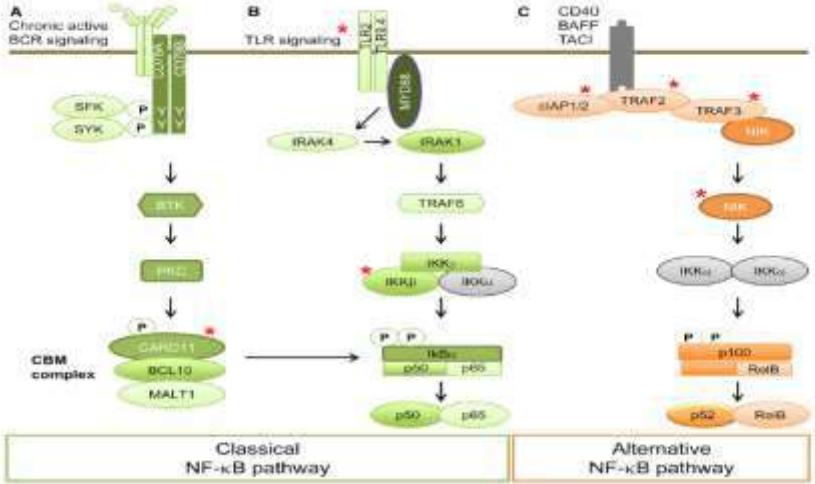
Rôle de la voie NFKB dans la résistance à l'ibrutinib

Genetic heterogeneity in primary and relapsed mantle cell lymphomas: Impact of recurrent *CARD11* mutations

Chenglin Wu[1], Noel FCC de Miranda[1,*], Longyun Chen[1,2,*], Agata M. Wasik[3,*], Larry Mansouri[4], Wojciech Jurczak[5], Krystyna Galazka[6], Monika Dlugosz-Danecka[5], Maciej Machaczka[7], Huilai Zhang[8], Roujun Peng[9], Ryan D. Morin[10], Richard Rosenquist[4], Birgitta Sander[1], Qiang Pan-Hammarström[1]

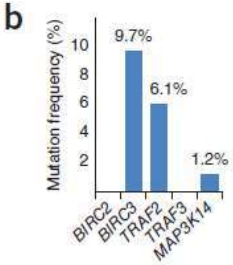


Mutation *CARD11* (5%)
N=173



Pharmacological and genomic profiling identifies NF-κB–targeted treatment strategies for mantle cell lymphoma

Rami Bahal[1,2], Mareike Frick[2,7], Rodrigo Romero[1], Joshua M Korn[1], Robert Kridel[3], Fong Chun Chan[3], Barbara Meissner[3], Hyo-eun Bhang[1], Dave Ruddy[1], Audrey Kauffmann[4], Ali Farsidjani[1], Adnan Derti[1], Daniel Rakiec[1], Tara Naylor[1], Estelle Pfister[4], Steve Kovats[1], Sunkyu Kim[3], Kerstin Dietze[2], Bernd Dörken[5], Christian Steidl[3], Alexandar Tzankov[5], Michael Hummel[6], John Monahan[1], Michael P Morrissey[1], Christine Fritsch[4], William R Sellers[3], Vesselina G Cooke[1], Randy D Gascoyne[3], Georg Lenz[2,7] & Frank Stegmeier[3,7]



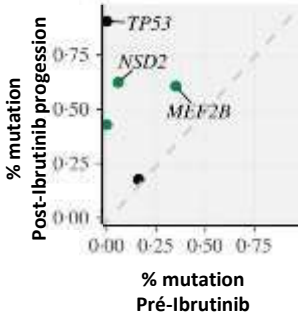
N=165

Impact des mutations de *TP53* dans la résistance à l'ibrutinib

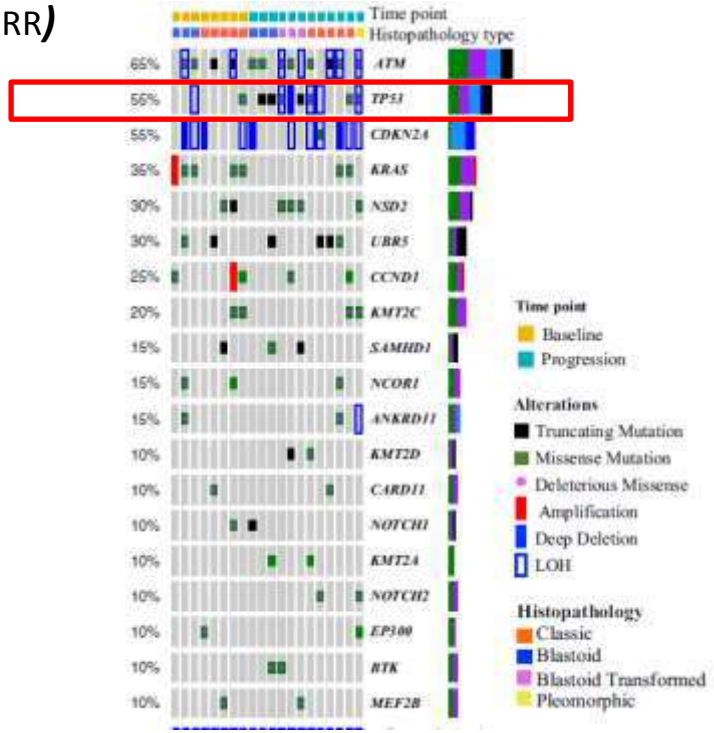
Fréquence des mutations *TP53* (n=80, 4FL, 75RR)

Pré-ibru = 12%

Progression post-Ibru = 67%



Pas de mutation PLCG2



Jain BJH 2018

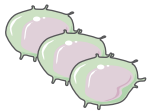
Leukemia

Article | Published: 02 April 2019

Lymphoma

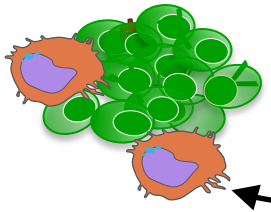
CSF1R and BTK inhibitions as novel strategies to disrupt the dialog between mantle cell lymphoma and macrophages

Antonin Papin, Benoit Tessoulin, Céline Bellanger, Anne Moreau, Yannick Le Bris, Hervé Maisonneuve, Philippe Moreau, Cyrille Touzeau, Martine Amiot, Catherine Pellat-Deceunynck, Steven Le Gouill & David Chiron

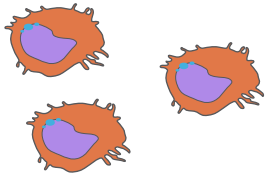


Sang

Mono CD163^{+}



Niche tumorale



Ibrutinib

CSF1, IL10

Survie
Prolifération

Contact
Facteurs solubles

Polarisation M2

- Les macrophages générés par co-culture permettent la survie et la prolifération des cellules de LCM
- Les cellules de LCM polarisent les monocytes en macrophages M2 *in vitro* (CSF1, IL10).
- L'Ibrutinib altère le dialogue entre les monocytes macrophages et les cellules de LCM.

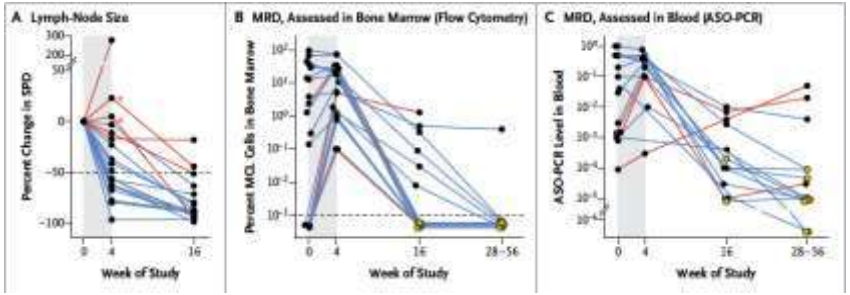
ORIGINAL ARTICLE

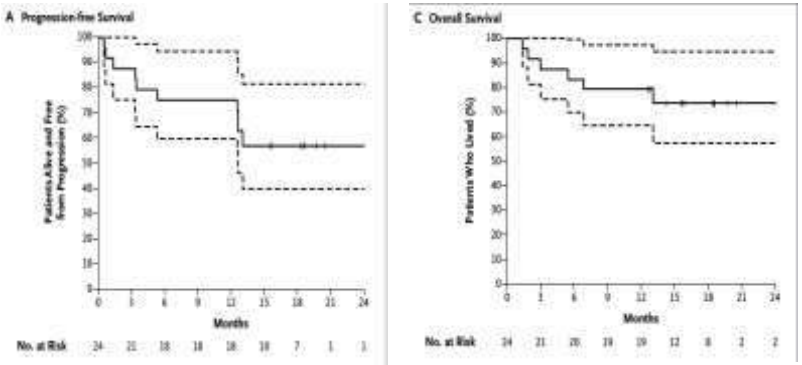
Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma

Constantine S. Tam, M.B., B.S., M.D., Mary Ann Anderson, M.B., B.S., Ph.D., Christiane Pott, M.D., Ph.D., Rishu Agarwal, M.B., B.S., Sasanka Handunnetti, M.B., B.S., Rodney J. Hicks, M.B., B.S., Kate Burbury, M.B., B.S., Gillian Turner, B.N., M.I.P.H., Juliana Di Iulio, Ph.D., Mathias Bressel, M.Sc., David Westerman, M.B., B.S., Stephen Lade, M.B., B.S., Martin Dreyling, M.D., Sarah-Jane Dawson, M.B., B.S., Ph.D., Mark A. Dawson, M.B., B.S., Ph.D., John F. Seymour, M.B., B.S., Ph.D., and Andrew W. Roberts, M.B., B.S., Ph.D.

Blastic or pleomorphic mantle-cell lymphoma — no./total no. (%	1/21 (5)
Ki-67 ≥30% — no./total no. (%)	9/21 (43)
TP53 status — no. (%)	
Mutated with deletion	4 (17)
Mutated without deletion	7 (29)
Deletion without mutation	1 (4)
NF-κB pathway mutations in *CARD11*, *BIRC3*, or *TRAF2* — no. (	6 (25)

(1 patient). Patients were 47 to 81 years of age, and the number of previous treatments ranged from none to six. Half the patients had aberrations of TP53, and 75% had a high-risk prognostic score. The complete response rate according to computed tomography at week 16 was 42%, which was higher than the historical result of 9% at this time point with ibrutinib monotherapy ($P<0.001$). The rate of complete response as assessed by positron-emission tomography was 62% at week 16 and 71% overall. MRD clearance was confirmed by flow cytometry in 67% of the patients and by ASO-PCR in 38%.





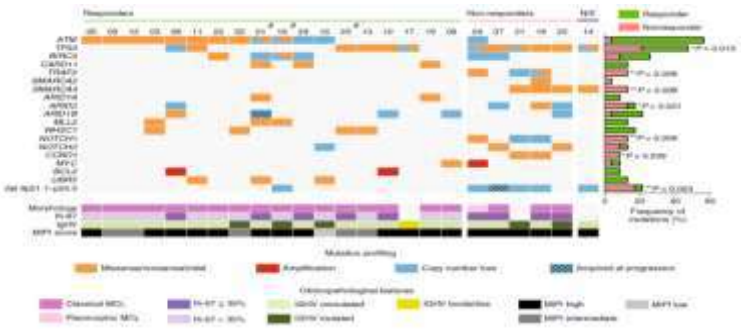
nature medicine

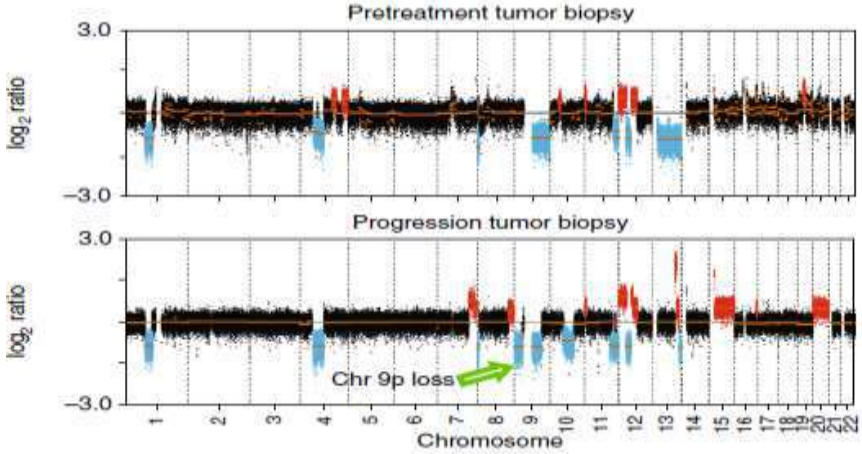
ARTICLES

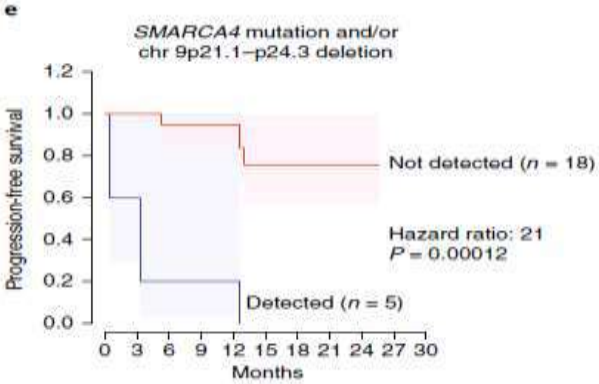
https://doi.org/10.1038/s41591-018-0243-z

Dynamic molecular monitoring reveals that SWI–SNF mutations mediate resistance to ibrutinib plus venetoclax in mantle cell lymphoma

Rishu Agarwal[1,2,12], Yih-Chih Chan[1,2,12], Constantine S. Tam[3,4,5], Tane Hunter[1,2], Dane Vassiliadis[1,2], Charis E. Teh[6,7], Rachel Thijssen[6,7], Paul Yeh[1,2,3], Stephen Q. Wong[1], Sarah Ftouni[1], Enid Y. N. Lam[1,2], Mary Ann Anderson[3,6,7], Christiane Pott[8], Omer Gilan[1,2], Charles C. Bell[1,2], Kathy Knezevic[1], Piers Blombery[1,3], Kathleen Rayeroux[9], Adrian Zordan[9], Jason Li[1,2], David C. S. Huang[6,7], Meaghan Wall[5,9,10], John F. Seymour[2,3], Daniel H. D. Gray[6,7], Andrew W. Roberts[3,6,7,11], Mark A. Dawson[1,2,3,11*] and Sarah-Jane Dawson[1,2,11*]







Vers un traitement de 1ère ligne sans chimiothérapie (thérapies ciblées ?) pour de nombreux patients ?

- JEUNES patients pour éviter les effets secondaires de l'autogreffe et/ou des chimiothérapies intensives
- Patients âgés/fragiles pour qui les chimiothérapies sont trop toxiques

Vers un traitement de 1ère ligne sans chimiothérapie (thérapies ciblées ?) pour de nombreux patients ?

⇒ Quels patients sont de mauvais pronostiques qui ne répondent pas à la chimiothérapie standard

bio-MIPI / *TP53* / …

⇒ Quels patients sont de bon pronostiques = pourraient également profiter d'une chimiothérapie non intensive en premier lieu

faible score MIPI, Ki-67% <30%

⇒ Screener tous les patients?

QUELLES RECOMMANDATIONS EN PRATIQUE?

TP53 dans le LCM

- Recommandations « ERIC – like »

Leukemia (2018) 32:1070–1080
https://doi.org/10.1038/s41375-017-0007-7

REVIEW ARTICLE

Chronic lymphocytic leukemia

mantle cell lymphoma

ERIC recommendations for *TP53* mutation analysis in ~~chronic lymphocytic leukemia~~—update on methodological approaches and results interpretation

- Expérience du GBMHM
  - Panel NGS/ CNV en NGS

HemaSphere

The need for a consensus next-generation-sequencing panel for mature lymphoid malignancies

- Expérience du LYSA
  - Seuil clinique / score intégratif

HemaSphere
OPEN ACCESS JOURNAL OF THE EUROPEAN HEMATOLOGY ASSOCIATION

The need for a consensus next-generation-sequencing panel for mature lymphoid malignancies

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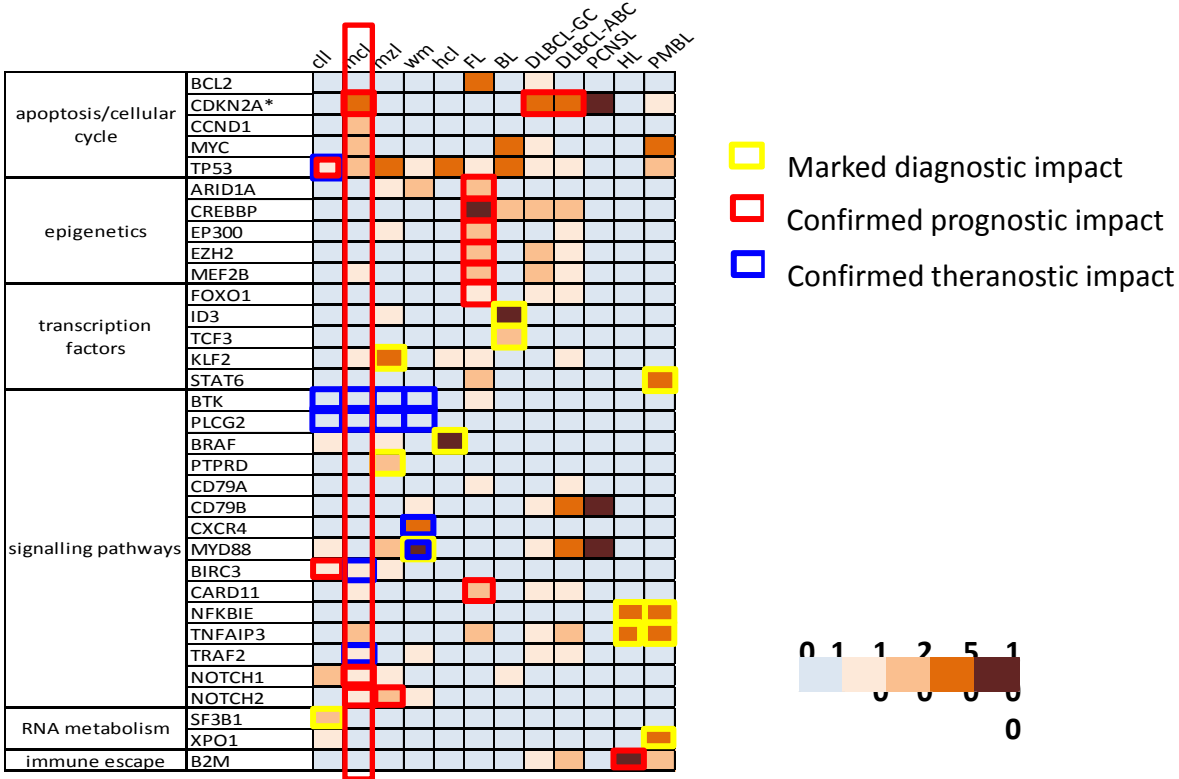
Revue de la littérature par des duo clinicien/biologiste “experts” des gènes **<u>mutés</u>** avec un intérêt clinique:

33 genes identifiés pour les lymphomes B:

- Gènes d’intérêt diagnostique
- Gènes d’intérêt pronostique
- Gènes d’intérêt theranostique



Atelier LYSA : *TP53* dans le LCM

2 juillet 2019 à Paris

Necker E Macintyre , S Kaltenach**,** M Cheminant, O Hermine, D Daniele Canioni, **Cochin** = B Burron, **Dijon** = M Callanan et son équipe, **Nantes =** Y Le Bris B Tessoulin C Pellat, **Créteil** exc. MH Delfau

Focus sur les données - état des lieux et projets LYSA :

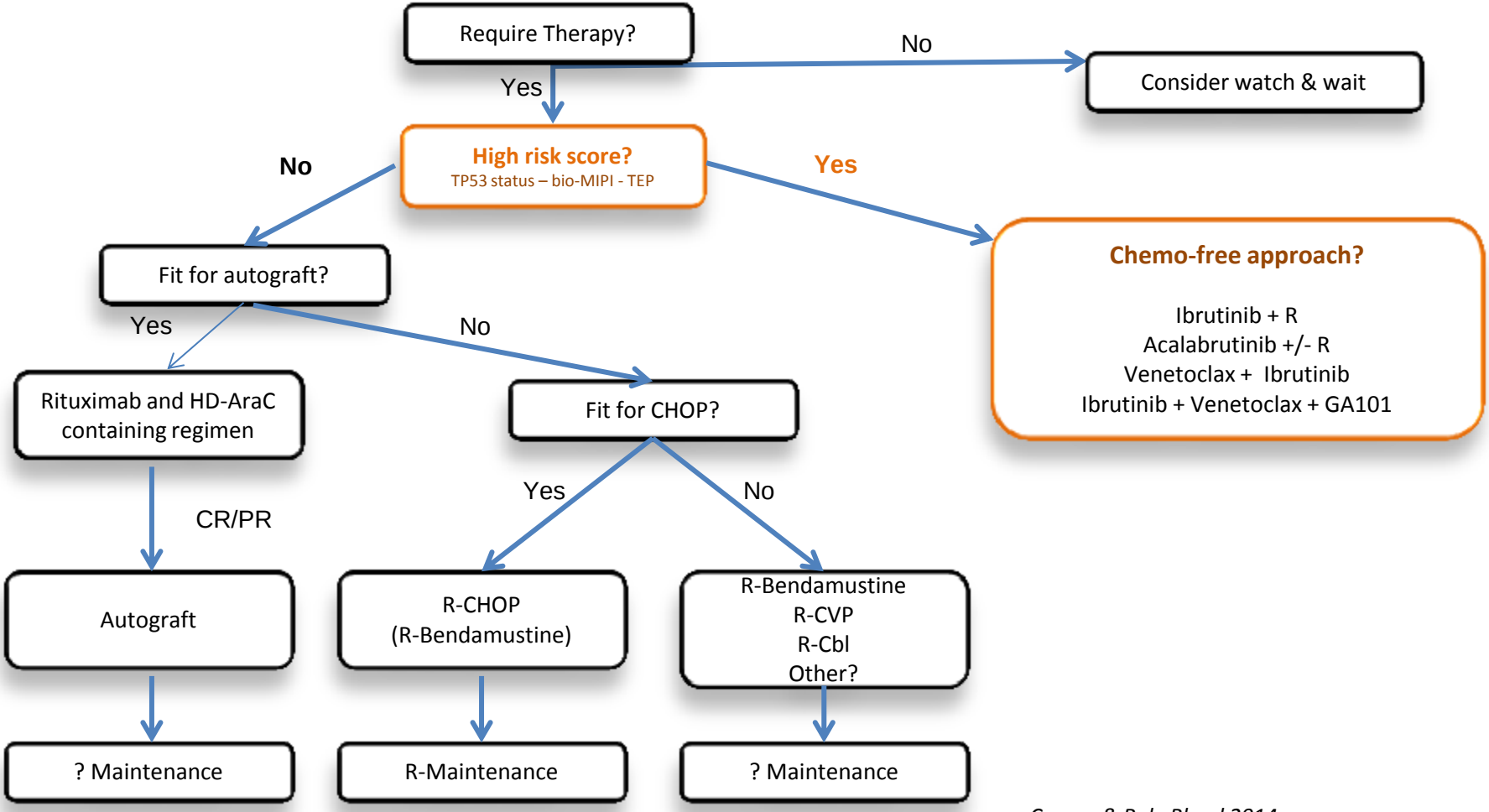
SNP-array
Profil d'expression IHC
Stratégies NGS TP53 MCL
Mutations coopératrices de TP53 dans les MCL – (sang)
Exomes des LCM réfractaires
Approches fonctionnelles TP53 et voie BCL2
Approches cliniques

Perspectives

Intégration des données du LyMa : CNV, mutations, MRD, statut IGHV, TEP

= > Score prédictif d'impact pronostique et théranostique

Management des patients avec LCM au diagnostic dans un futur très proche?



Campo & Rule Blood 2014

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