

Macroglobulinémie de Waldenström

Actualités cliniques et biologiques

Macroglobulinémie de Waldenström (MW)

- Généralités
- Des questions biologiques
 - lymphomagénèse ? hiérarchie clonale ? cellule d'origine ?
 - anomalies (cyto)génétiques : impact pronostique ? prédictif ?
- Des questions cliniques
 - immunochemiothérapie versus thérapies ciblées ?
 - formes cliniques particulières / gammopathies de signification clinique ?

Macroglobulinémie de Waldenström (MW)

Acta Medica Scandinavica. Vol. CXVII, fasc. III—IV, 1944.

(From Med. Clin. Akad. Hospital, Upsala (Sweden). Chief: Prof. G. Bergmark).

Incipient myelomatosis or «essential» hyperglobulinemia with fibrinogenopenia — a new syndrome?

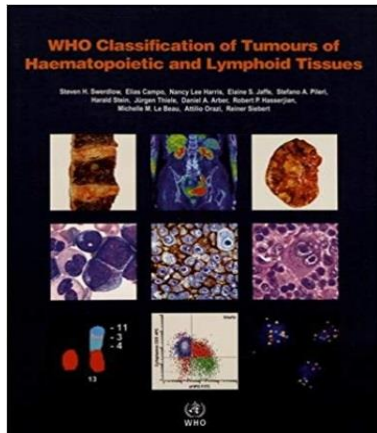
By

JAN WALDENSTRÖM.

Submitted for publication September 2, 1943.



MW - Définition



Swerdlow S.H.
Cook J.R.
Sohani A.R.
Pileri S.A.
Harris N.L.
Jaffe E.S.
Stein H.

Lymphoplasmacytic lymphoma

Definition

Lymphoplasmacytic lymphoma (LPL) is a neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, usually involving bone marrow and sometimes lymph nodes and spleen, which

Although LPL is often associated with a paraprotein, usually of IgM type, this is not required for the diagnosis. Waldenström macroglobulinaemia (WM) is found in a substantial subset of patients with LPL, but is not synonymous with it; it is defined as LPL with bone marrow involvement and an IgM monoclonal gammopathy of any concentration

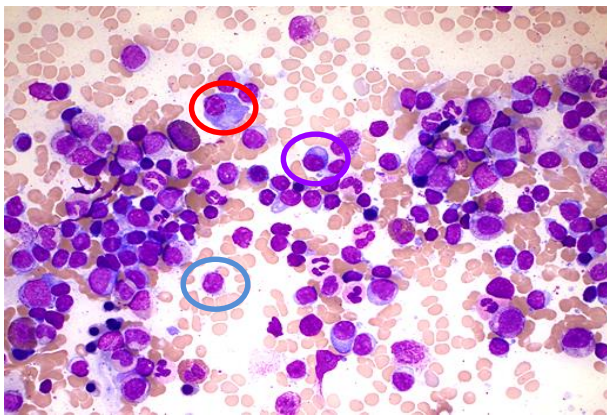


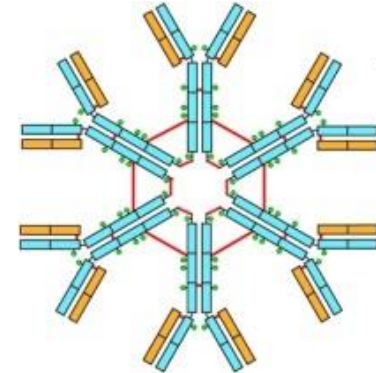
Table 2. Highlights of changes in 2016 WHO classification of lymphoid, histiocytic, and dendritic neoplasms

Entity/category	Change
Lymphoplasmacytic lymphoma (LPL)	<ul style="list-style-type: none">• <i>MYD88</i> L265P mutation in vast majority of cases impacting diagnostic criteria even though finding is not specific for LPL.• IgM MGUS is more closely related to LPL and other B-cell lymphomas than to myeloma.

MW- Diagnostic différentiel

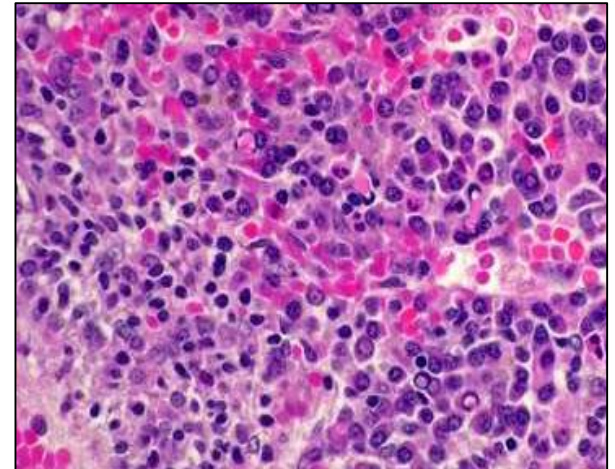
- **Lymphoprolifération + IgM :**

- MW
- **LZM**
- LLC
- MM (très rare)



- **Lymphome lymphoplasmocytaire :**

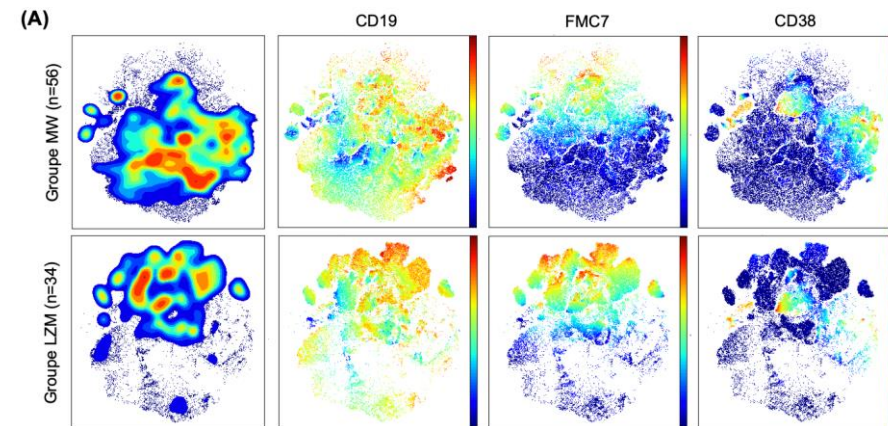
- + IgM = MW
- + IgG ou A ou non sécréteur (< 5%)



MW- Diagnostic différentiel

- **Phénotypage :**
 - lymphocytes B matures avec différenciation plasmocytaire incomplète
 - pan B, 5-, 10-, 23-
- **CD22 faible, CD25+, CD103-, CD13+**
- **CD5 : 5 à 20% des cas**

	LLC	LCM	LF	LZM	MW
CD19	+	+	+ faible	+	+
Ig de surface	+ faible ou -	++	++	+++	+
CD5	+	+	-	-/+	-/+
CD23	+	-	-/+	-	-
FMC7	+ faible ou -	+	+	++	+/-
CD22	+ faible ou -	+	+	+	+ faible
CD79b	+ faible ou -	++	+	++	+
CD43	+ forte	+ faible/-	-	-	-
CD20	+ faible	+	+	++	+
CD10	-	-/+	+/-	-	-
CD103	-	-	-	-/+	-
CD11c	+ faible/-	-	-/+	-/+	-
CD25	+/-	-	-/+	-/+	+
CD38	-/+	+/-	+	-/+	-/+
CD27	+/-	-/+	+	+/-	+
CD180	-	-	NA	+	NA
CD13	-	-	-	-/+	+

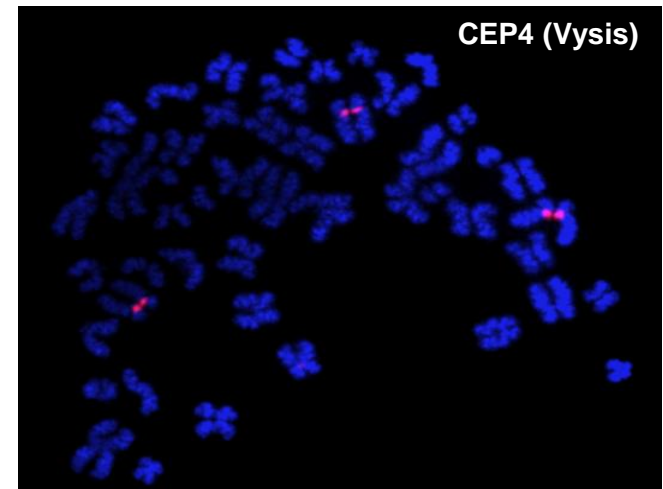
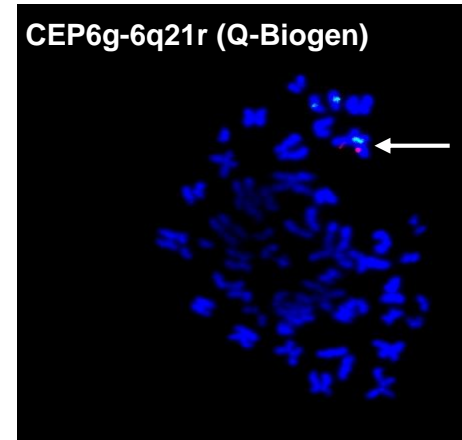
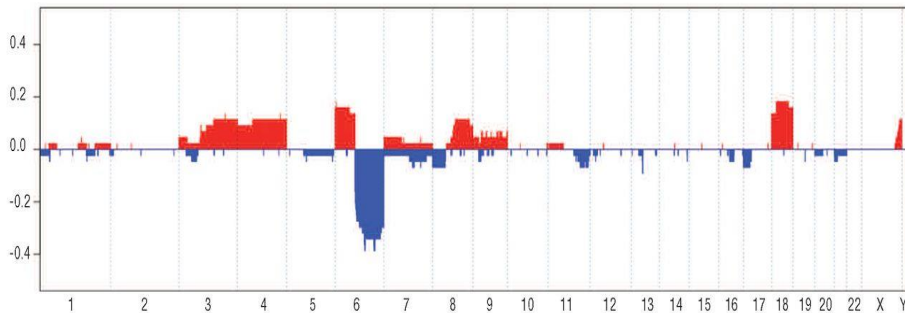


	0 point	1 point
Intensité du CD19	Normale ou forte	Faible
Intensité du FMC7	Normale ou forte	Négative ou faible
Intensité du CD22	Normale ou forte	Faible
Si CD22 faible, intensité du CD79b	Faible ou normale	Forte
Intensité du CD27	Normal	Négative ou faible
CD13 (%)	< 2%	≥ 2%

MW- Diagnostic différentiel

Cytogénétique ?

+4	Not yet known	12-20
+6p	Not yet known	17
-6q21	<i>PRDM1</i>	38-50
-6q23	<i>TNFAIP3</i>	38-50
-13q14.3	<i>MIRN15A</i> and <i>MIRN16-1</i>	10
-14q32	<i>TRAF3</i>	6
-17p13.1	<i>TP53</i>	7-10
+18	<i>MALT1, BCL2</i>	17



MW- Diagnostic différentiel

Cytogénétique ?

		MW	LZM	LLC
Anomalies chromosomiques	Délétion 6q	++++	++	+
	Délétion 13q	++	+	++++
	Trisomie 4	++	-	-
	Trisomie 12	+	++	++
	Délétion 17p (<i>TP53</i>)	+++	++	+
	Caryotype complexe	++	+++	++
	Trisomie 18	+	++	+
	Délétion 7q	-	+++	-
	Délétion 11q (<i>ATM</i>)	+	-	++

MW- *Diagnostic différentiel*

Cytogénétique ? Del 6q/tri4 vs. del7q ?

Biologie moléculaire ?

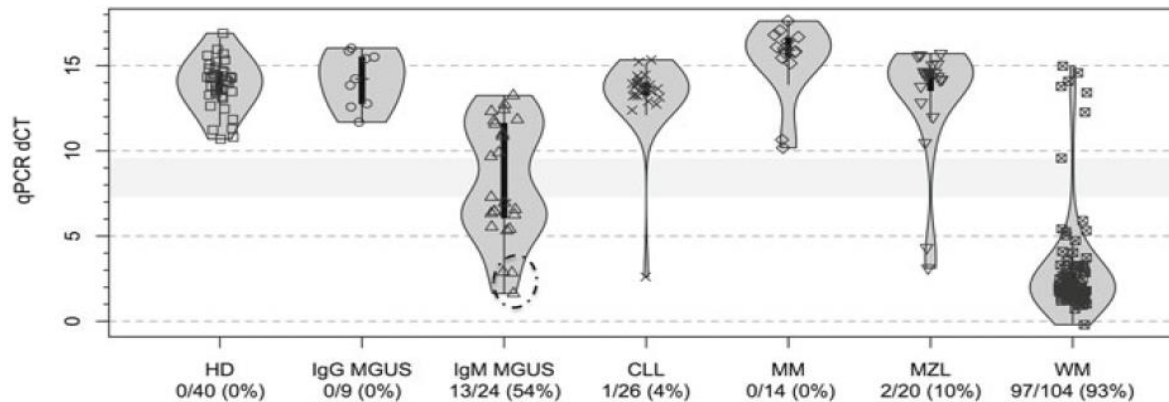
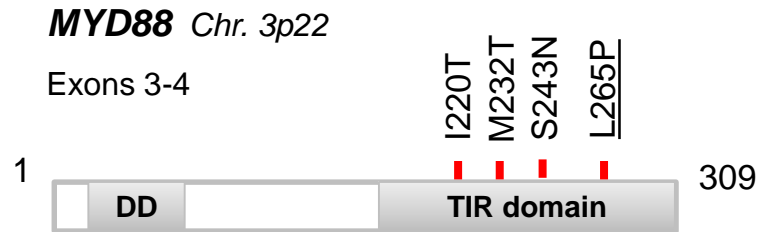
MW – Mutations MYD88

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

- **MYD88 L265P** (>90%), hétéro- ou homozygote
- Substitution nucléotidique unique (T pour C)
- **L265P** dans > 98% des cas
- Autres : domaine TIR (1-2%)
- Evénement le plus souvent **clonal** (précoce)

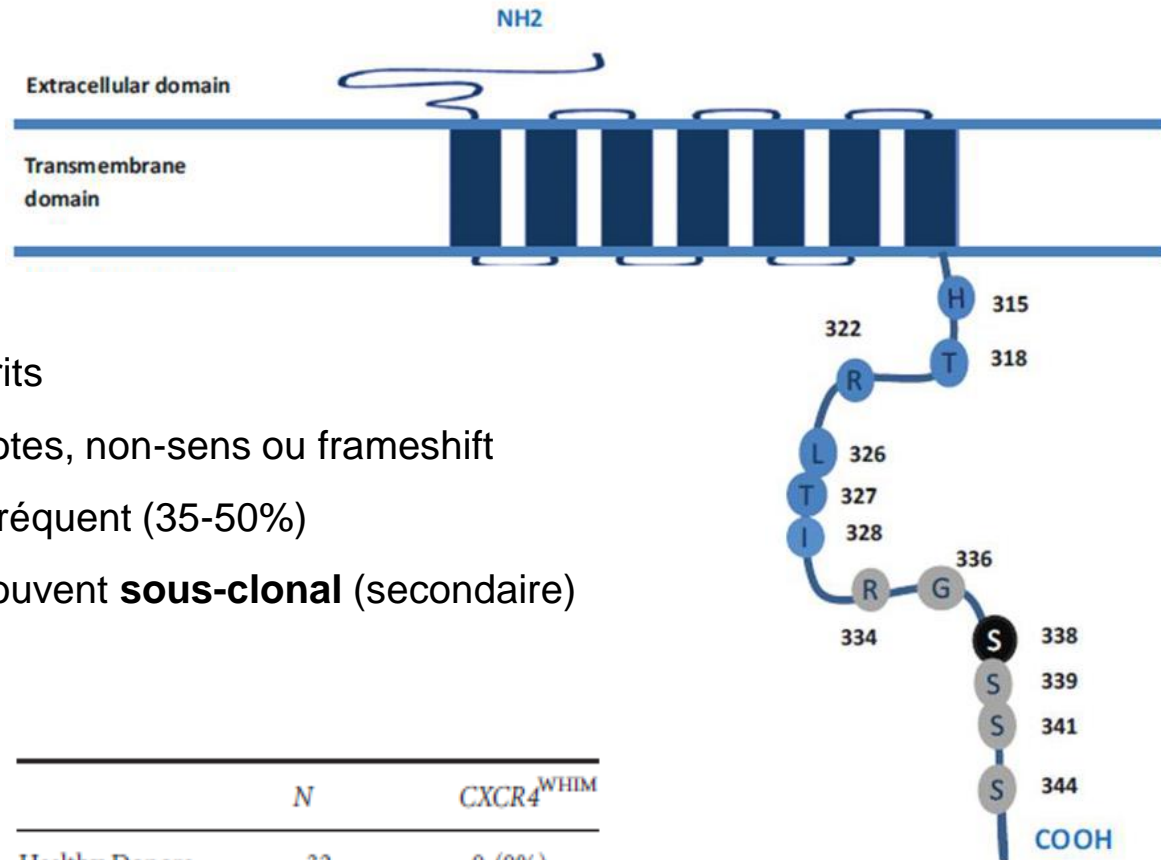


GMSI IgM (80%), LBDGC-ABC (30%), LZM (5-10%), LLC (2-5%)

MW – Mutations CXCR4

CXCR4 Chr. 2q22.1

Exon 2



- + de 50 variants décrits
- Mutations hétérozygotes, non-sens ou frameshift
- **S338X** (WHIM) le + fréquent (35-50%)
- Événement le plus souvent **sous-clonal** (secondaire)

PCR allèle
spécifique
S338

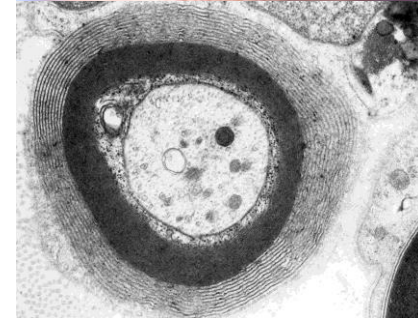
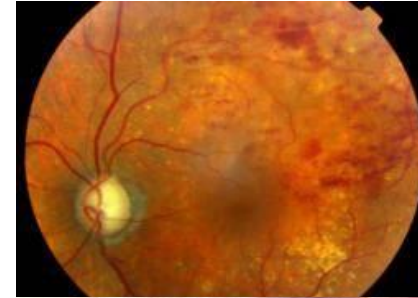
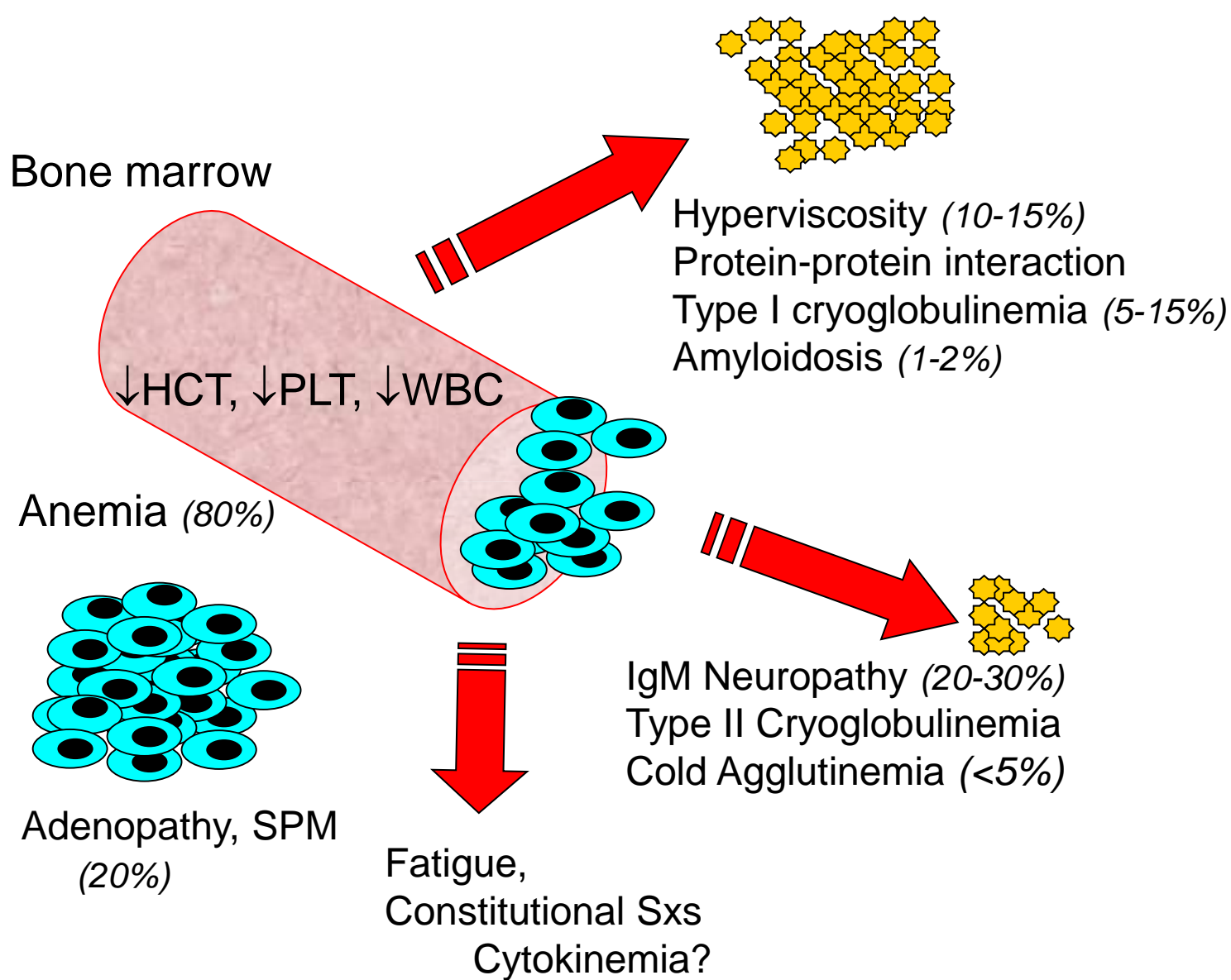
	N	CXCR4 ^{WHIM}
Healthy Donors	32	0 (0%)
IgM MGUS	12	2 (17%)
Non-IgM MGUS	7	0 (0%)
Untreated WM	102	44 (43%)
Treated WM	62	21 (34%)
MZL	20	1 (5%)
CLL	32	0 (0%)
MM	14	0 (0%)

MW - Clinique

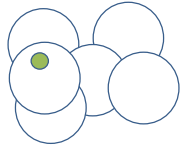
- **Rare**, 1-2% des hémopathies lymphoïdes
- Sujet **âgé** (âge médian, 72 ans)
- Précédée d'une **gammopathie monoclonale (GMSI) IgM** (40%)
- Symptômes liés au **syndrome tumoral** et/ou sécrétion **IgM** monoclonale
= protéiforme +++

Cause	Symptômes
Signes généraux	Fièvre, sueurs nocturnes Amaigrissement, altération de l'état général
Infiltration tumorale	Cytopénies (anémie +++) Adénopathies, organomégalie Infiltrations extra-ganglionnaires rares (rénale, hépatique, neuro...)
IgM sérique : propriétés physicochimiques	Syndrome d'hyperviscosité Troubles de l'hémostase (Willebrand acquis) Cryoglobuline de type I Dépôts : amylose AL ou dépôts de l'IgM complète
IgM sérique : spécificités antigéniques	Neuropathies périphériques (anti-MAG en premier lieu) Cryoglobuline de type II Agglutinines froides

MW - Clinique



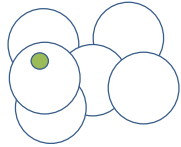
MW- Maladie multi-étapes



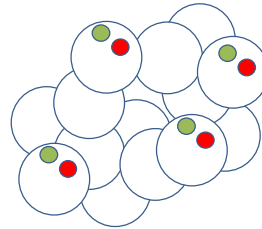
MGUS IgM

	IgM monoclonale bénigne asymptomatique
IgM sérique	+
Infiltration médullaire en morphologie	-
Symptômes liés à l'infiltration tumorale	-
Symptômes liés à l'IgM	-

MW- *Maladie multi-étapes*



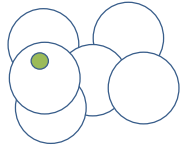
MGUS IgM



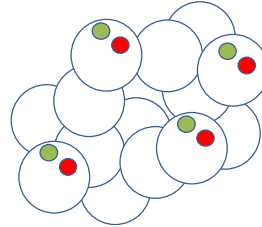
MW indolent

	IgM monoclonale bénigne asymptomatique	MW asymptomatique
IgM sérique	+	+
Infiltration médullaire en morphologie	-	+
Symptômes liés à l'infiltration tumorale	-	-
Symptômes liés à l'IgM	-	-

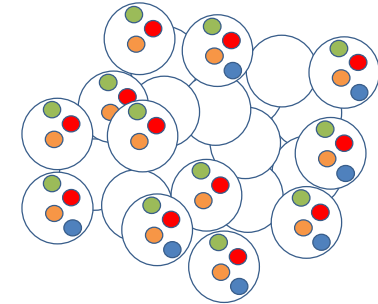
MW- Maladie multi-étapes



MGUS IgM



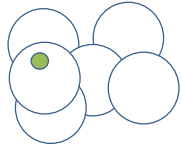
MW indolent



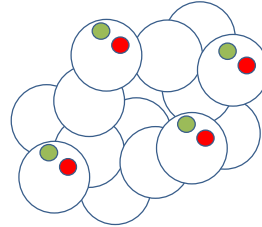
MW symptomatique

	IgM monoclonale bénigne asymptomatique	MW asymptomatique	MW symptomatique
IgM sérique	+	+	+
Infiltration médullaire en morphologie	-	+	+
Symptômes liés à l'infiltration tumorale	-	-	+
Symptômes liés à l'IgM	-	-	+

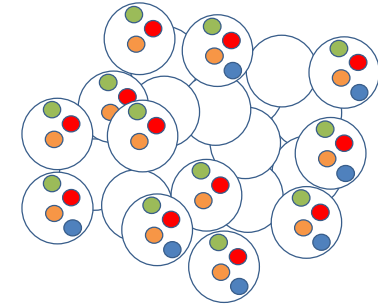
MW- Maladie multi-étapes



MGUS IgM



MW indolent



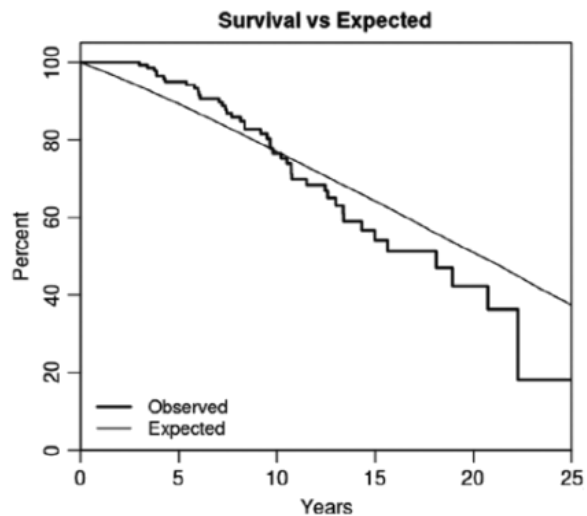
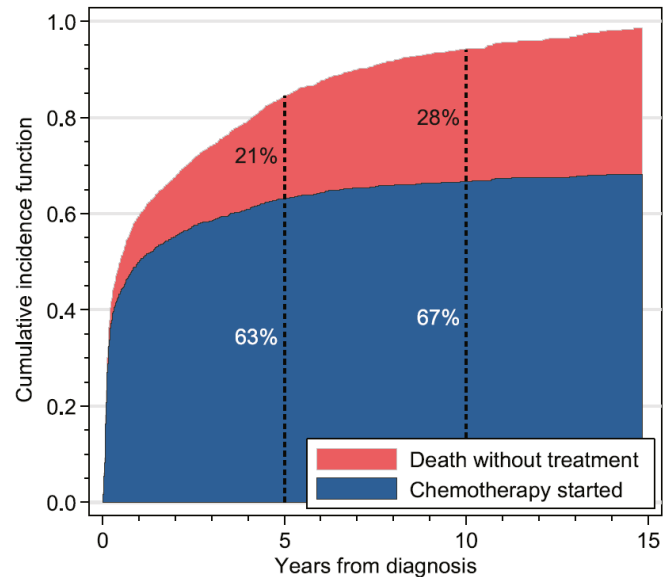
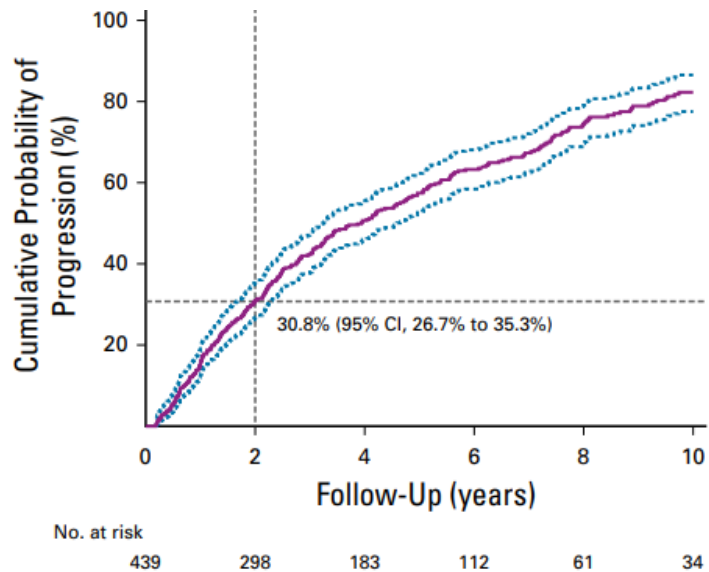
MW symptomatique

	IgM monoclonale bénigne asymptomatique	MW asymptomatique	MW symptomatique	IgM monoclonale bénigne symptomatique
IgM sérique	+	+	+	+
Infiltration médullaire en morphologie	-	+	+	-
Symptômes liés à l'infiltration tumorale	-	-	+	-
Symptômes liés à l'IgM	-	-	+	+

Anti-MAG
Cryoglobulinémie

...

MW- Incurable ?



MW- Critères de traitement

- **Signes généraux** (sueurs, AEG)
- **Cytopénies** : hémoglobine < 100 g/L ou plaquettes < 100 G/L
- **Masse tumorale** symptomatique ou volumineuse
- **Activité** délétère de l'IgM (hyperviscosité, cryoglobuline, anti-MAG sévère, amylose AL ...)

MW- *Principes thérapeutiques en 2022*

Seules les **MW symptomatiques** sont à traiter (survie médiane = 10 ans)

L'**immunochimiothérapie** reste le traitement de choix en 1^{ère} ligne

Association anti-CD20 + alkylants (RDC, R-Bendamustine)

Les **thérapies ciblées** font leur apparition

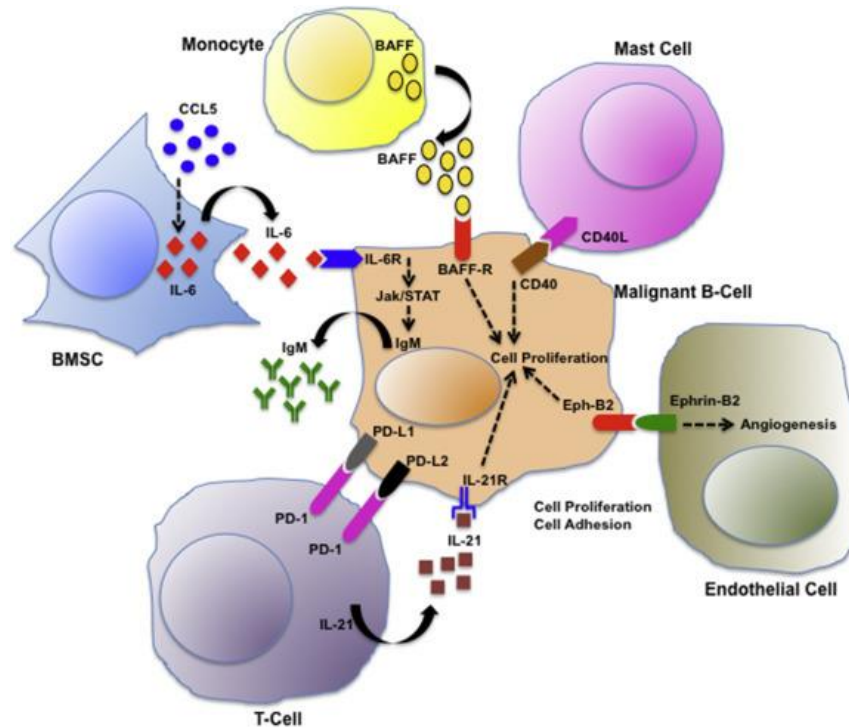
WM - Intrinsic and extrinsic abnormalities analyses

Cytogenetics

WES
Targeted NGS

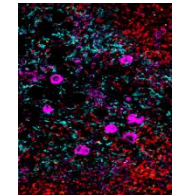
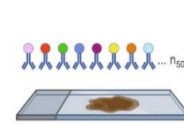
IGHV repertoire

DNA methylation



**Tumoral
microenvironment**

Mass cytometry (Hyperion)
Single-cell RNAseq

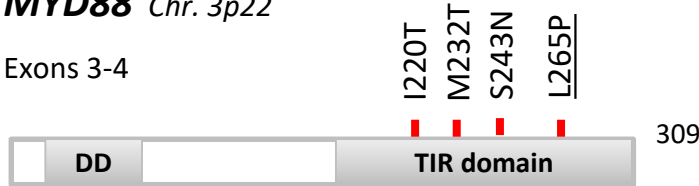


Génomique (MW) – Mutations MYD88 et CXCR4

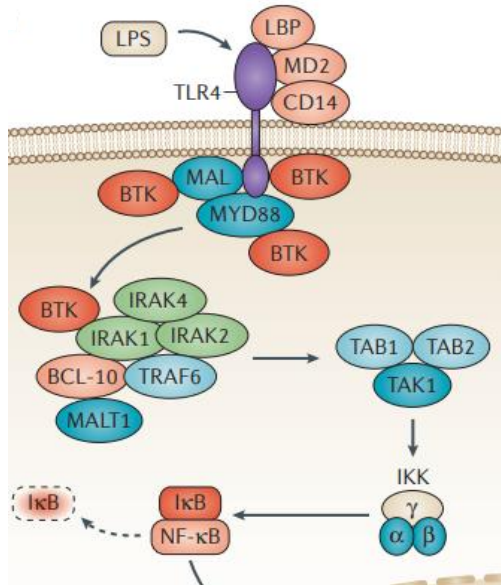
MYD88 Chr. 3p22

Exons 3-4

1



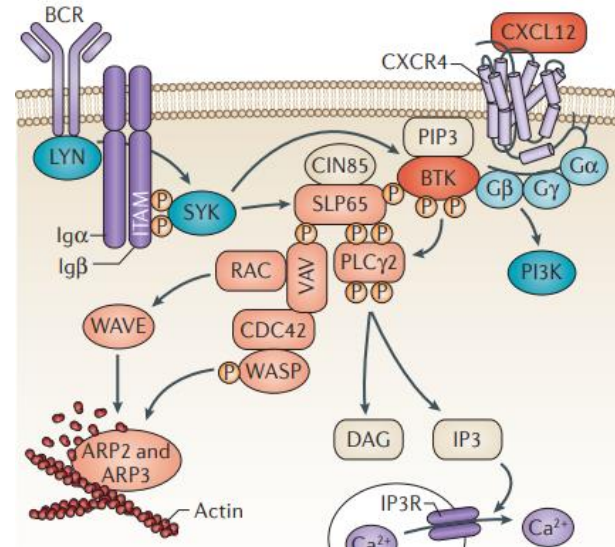
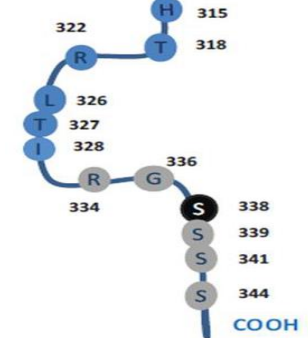
> 95 %



CXCR4 Chr. 2q22.1

Exon 2

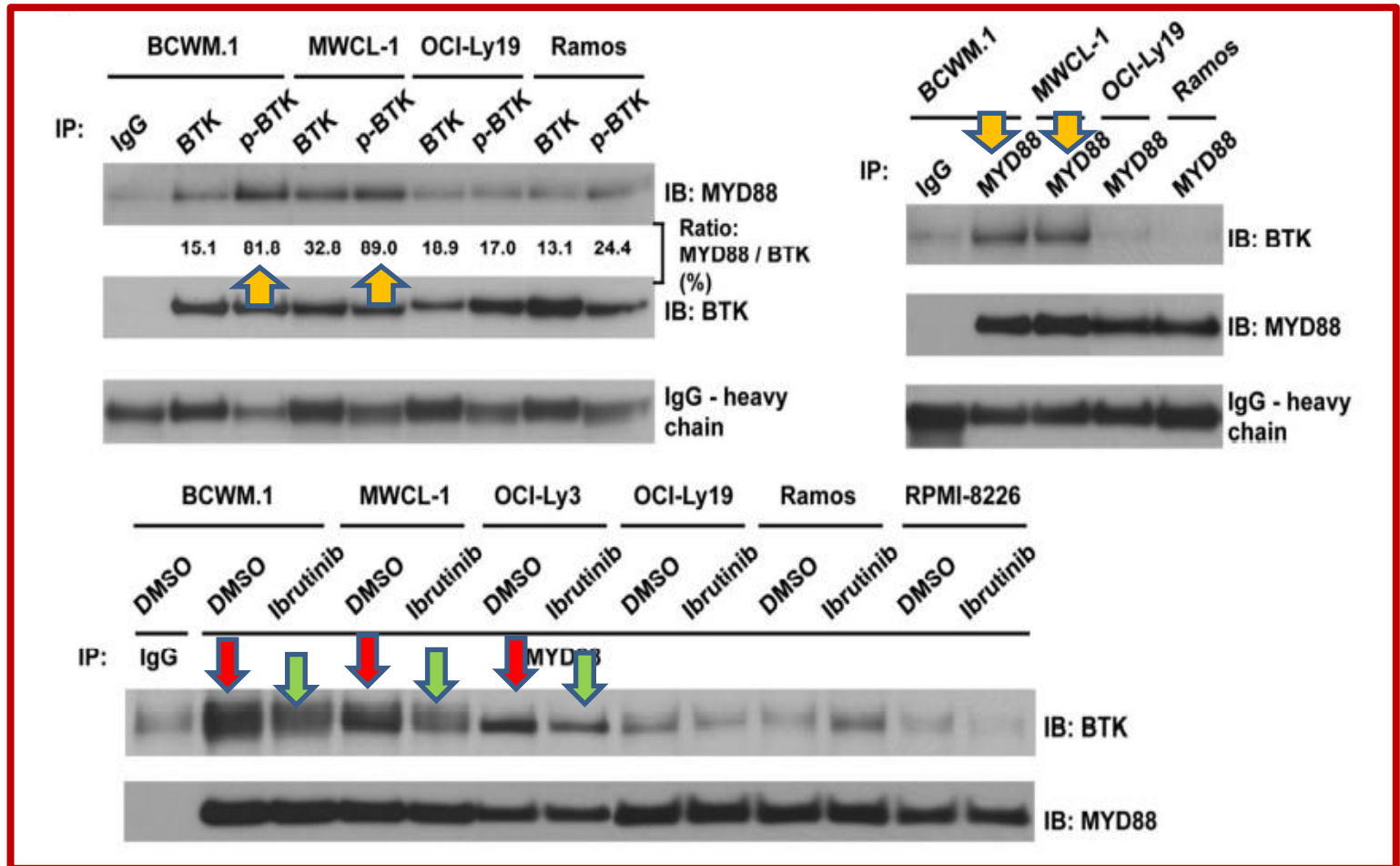
30-40 %



- Treon NEJM 2012
- Hunter Blood 2014
- Poulain Clin Cancer Res 2016
- Burger Nat Rev Cancer 2018

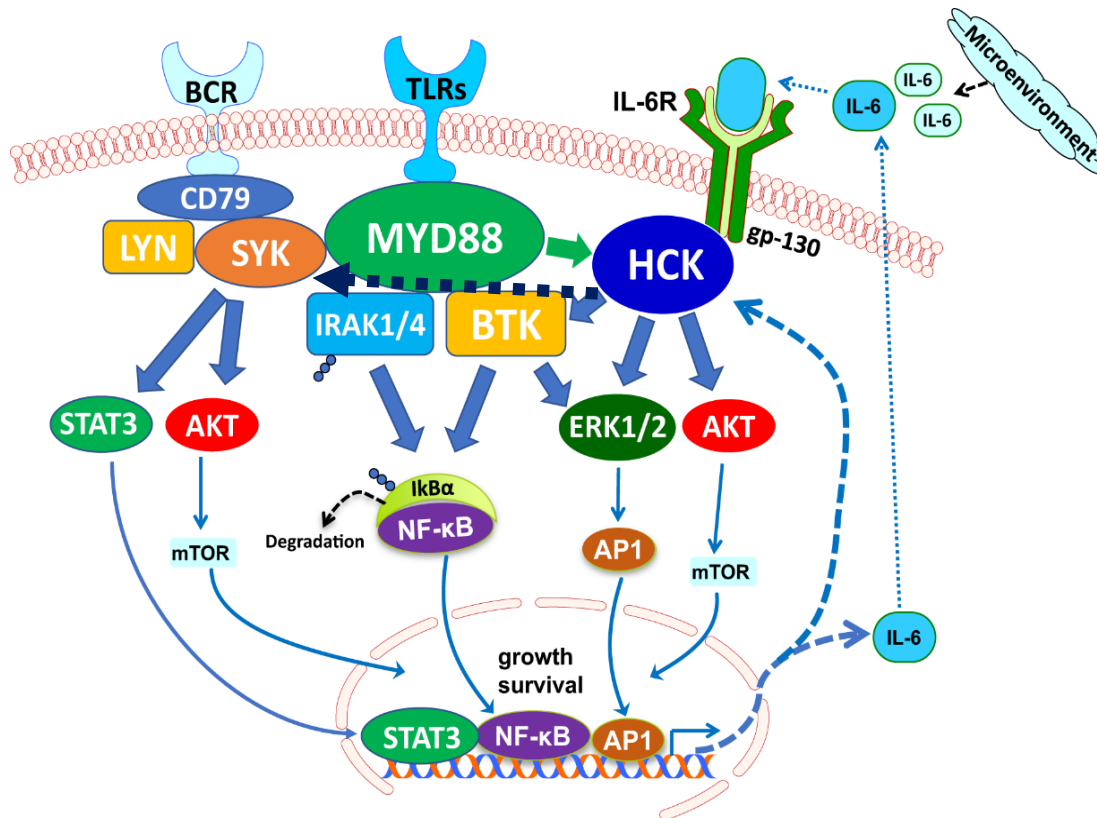
MYD88/BTK (MW) – MYD88 L265P active BTK

A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenström macroglobulinemia

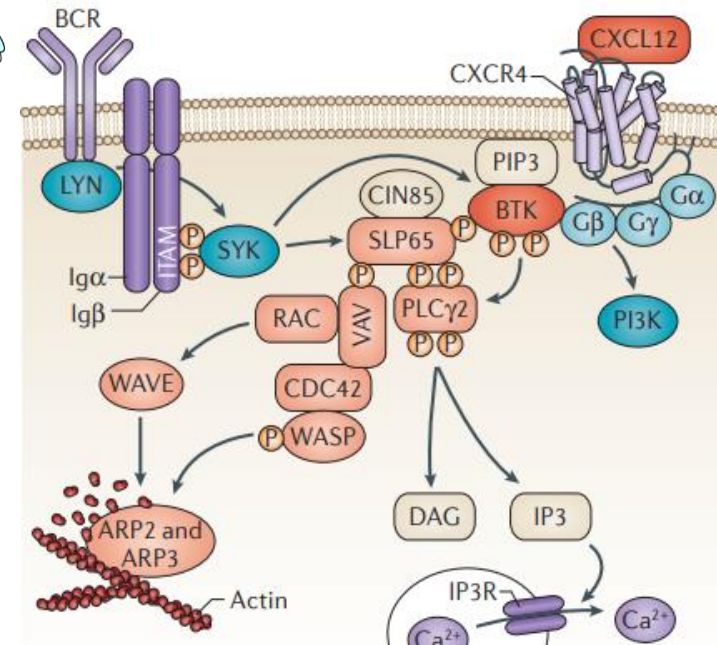


Pathogénèse MW – Voies/signaux

95-97% mutations *MYD88*



30-40% mutations *CXCR4*

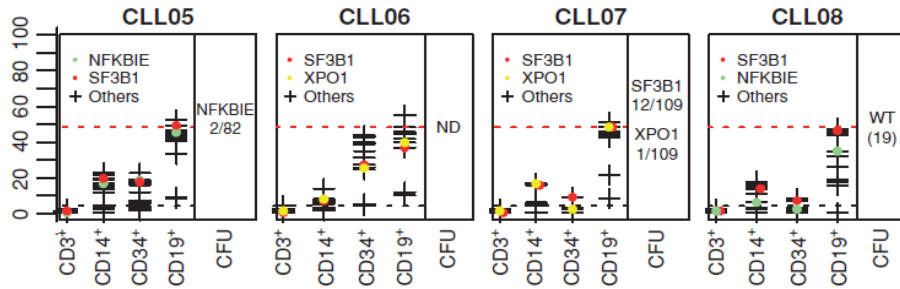


Treon NEJM 2012
 Hunter Blood 2014
 Poulain Clin Cancer Res 2016
 Burger Nat Rev Cancer 2018
 Yang Blood 2013 et 2016
 Munshi and Yang BCJ 2020

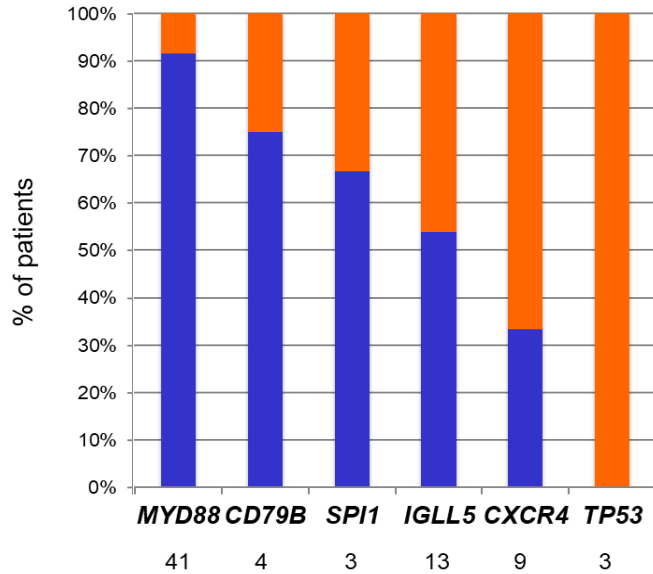


Rôle central de l'inhibition de BTK
Intérêt cibler autres TK ? HCK/PI3K/SYK ?
HCK = effet « off-target » iBTK

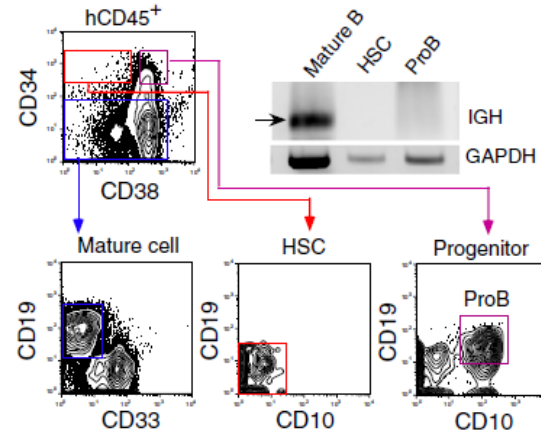
MW- Hiérarchie clonale ?



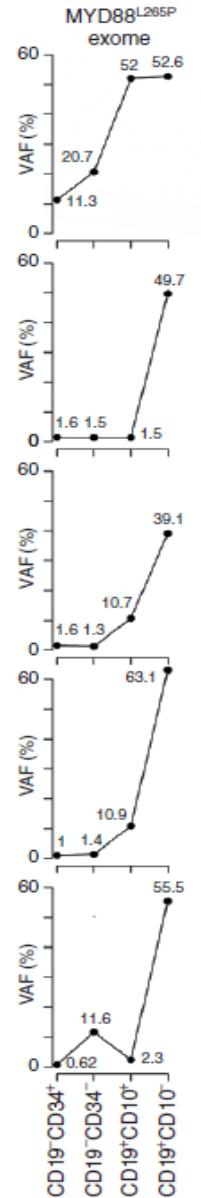
■ Clonal (VAF > 40%)
 ■ Subclonal (VAF < 40%)



CLL-HSC transplant



Gene	WES	PCR	Cell Type
CD34-positive HPCs	0/10	1/9	CD34-positive HPCs
B cell precursors	1/9	6/8	B cell precursors
Mature B lymphocytes	4/6	6/6	Mature B lymphocytes
Tumor B cells	10/10	9/9	Tumor B cells
Plasma cells	9/9	9/9	Plasma cells



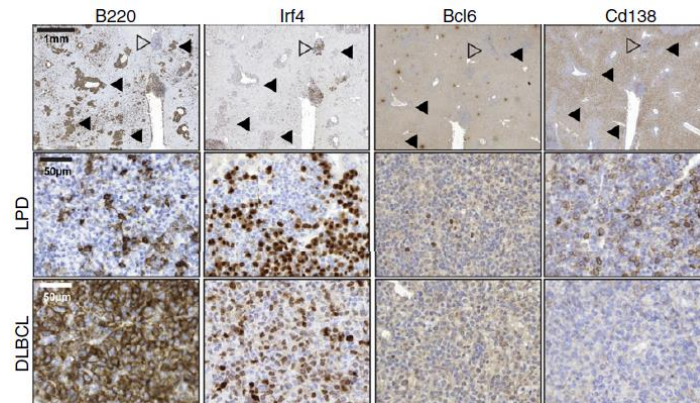
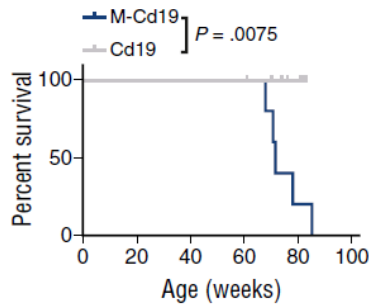
Modèles murins MW – MYD88

Modèles murins KI MYD88 L265P conditionnels

- . CD19 Cre (Knittel, Cologne)
- . AID Cre (Carrasco, Dana-Farber)

Développement lymphoproliférations B

- . Tardives (> 1 an), **oligoclonales**
- . Phénotype ? Lympho-plasmocytes ?
- . Rarement LBGC BCL6-, IRF4+ (ABC)

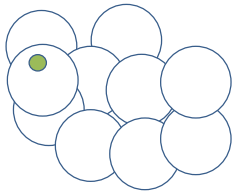


MYD88 L265P seul insuffisant pour transformation tumorale

MW : nécessité d'événements supplémentaires ? CXCR4 ? del6q ?

Scénario ?

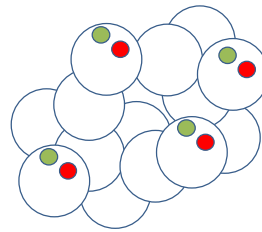
MYD88
Autres ?



LyB

Pré-CG ?
Progéniteurs ?
(proB, HSC)

MYD88
+/- CXCR4, ARID1A
+/- del6q, tri4/12



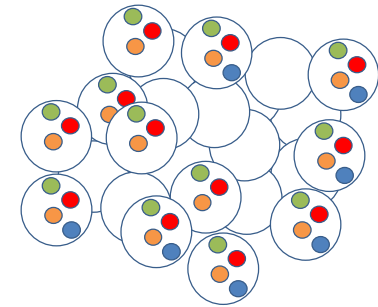
LyB mature

(CD22 low/25+/27+/IgM+)

MW indolent

Activation, survie ++
Blocage différenciation
(TLR/BCR, recombinaison VDJ,
absence switch)

MYD88
CXCR4, ARID1A
CD79B, MLL2,
del6q, tri4

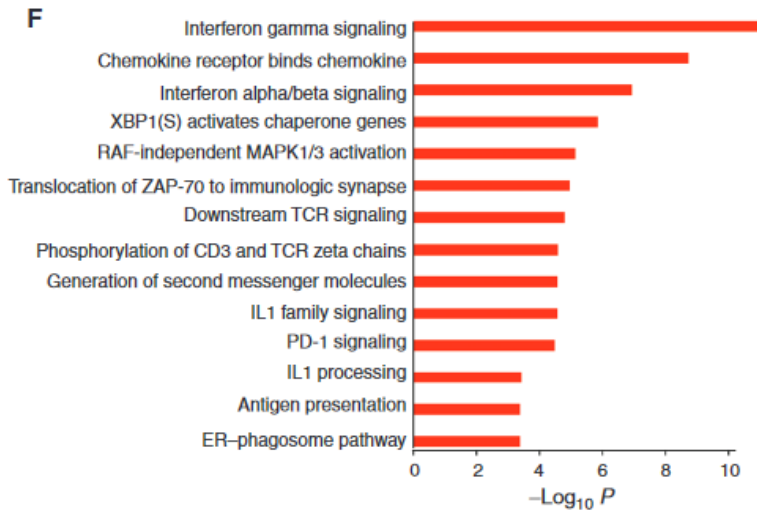
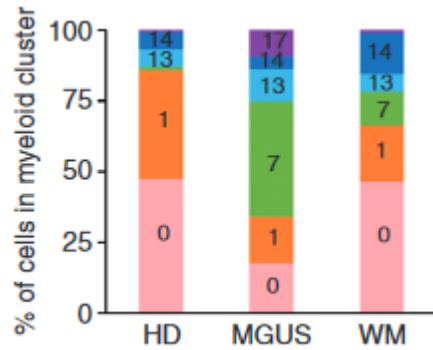
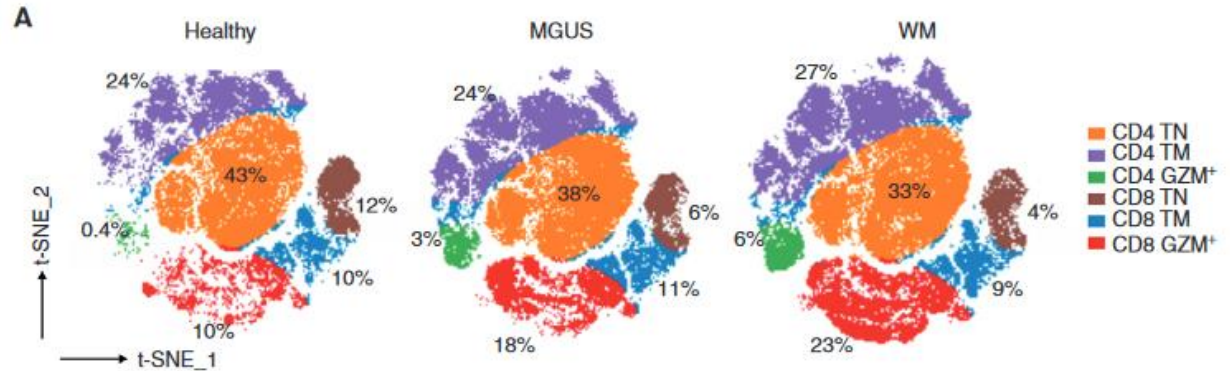
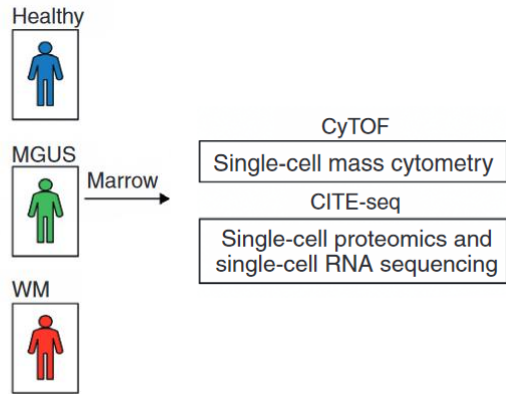


MW symptomatique

Prolifération ++

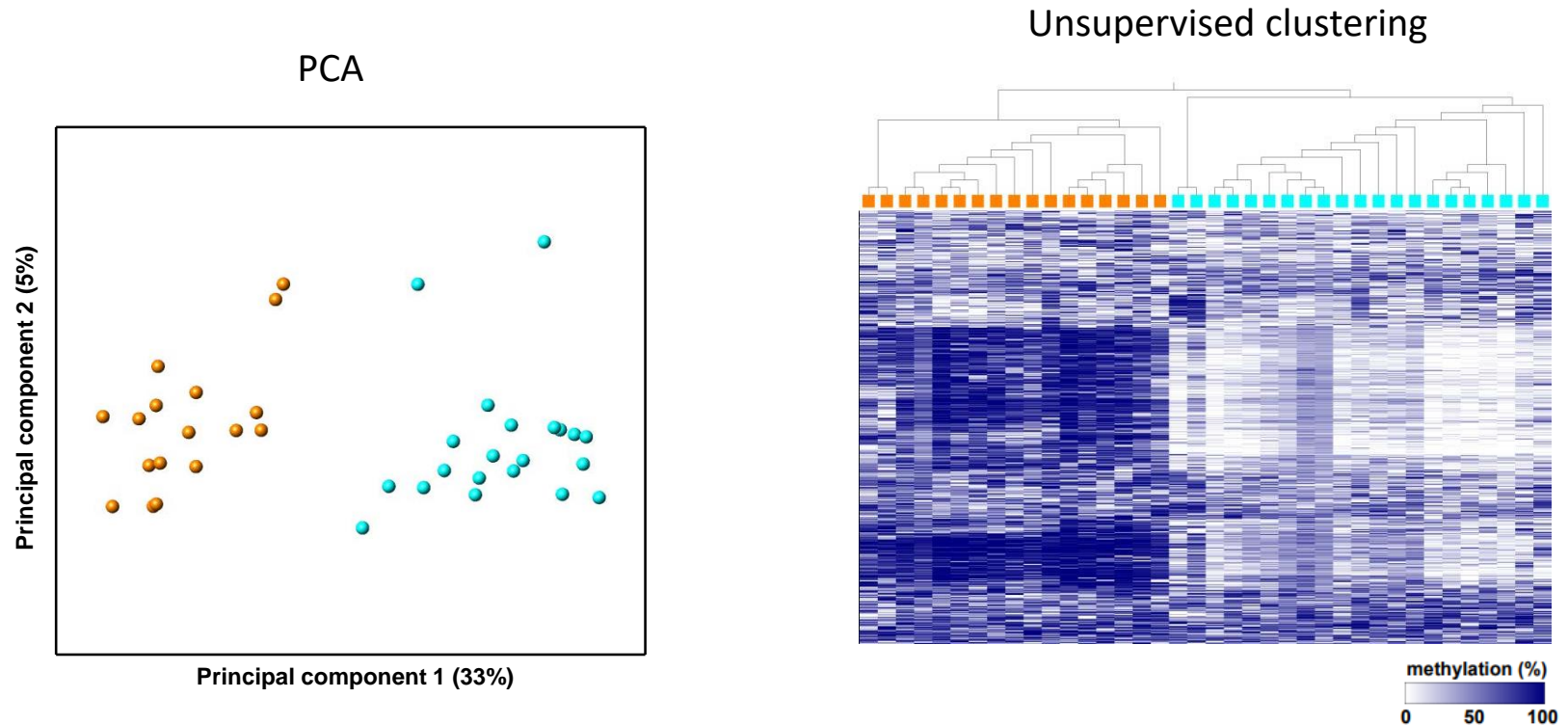
Epigénétique ?
Microenvironnement ?

MW- Microenvironnement ?



WM – Epigenetics ?

Global DNA methylation analysis



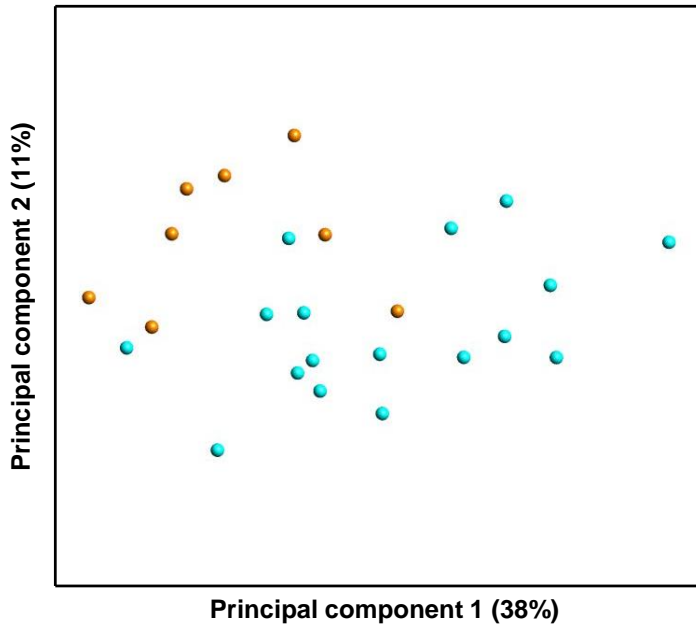
35 WM patients (14+21)
All *MYD88* mutated (VAF > 30%)

ILLUMINA EPIC/850K ARRAYS
Principal component analysis (PCA) of the top 1% most-variable CpGs

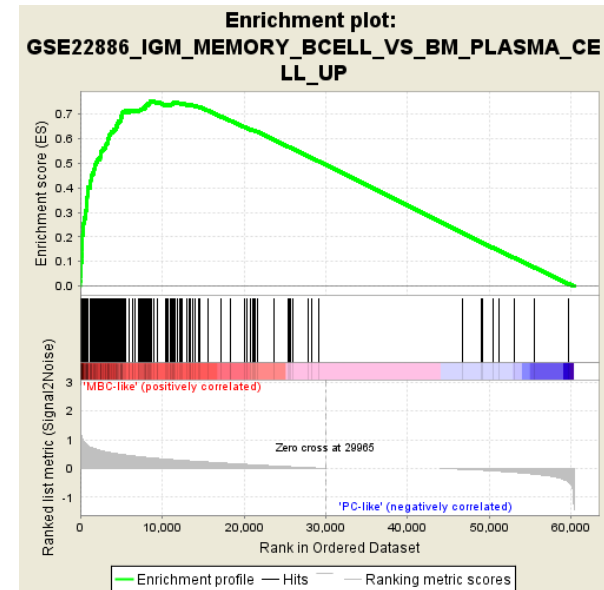
RNA sequencing analysis

24 WM patients (11+14)
All *MYD88* mutated (VAF > 30%)

PCA



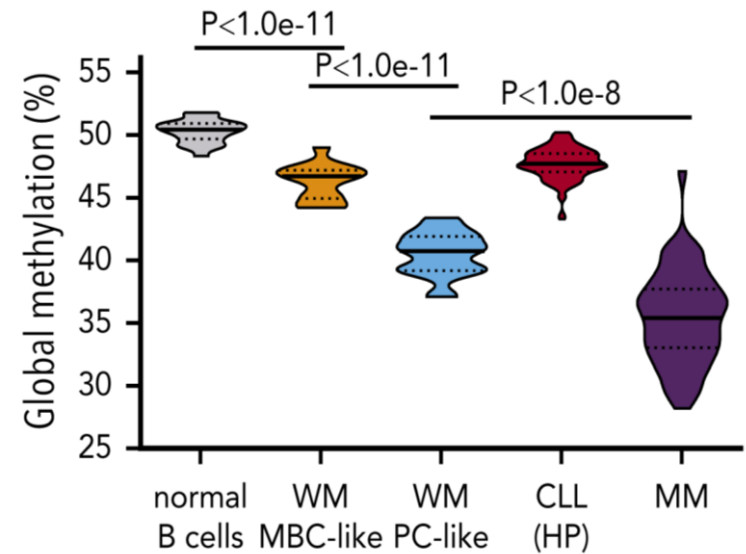
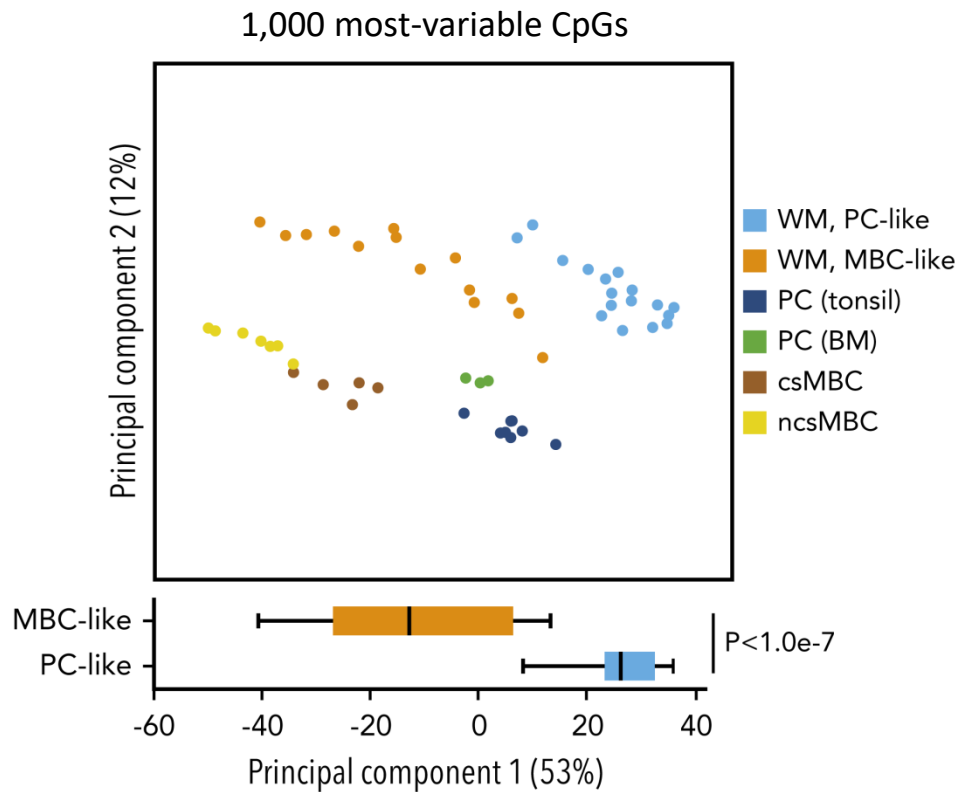
GSEA



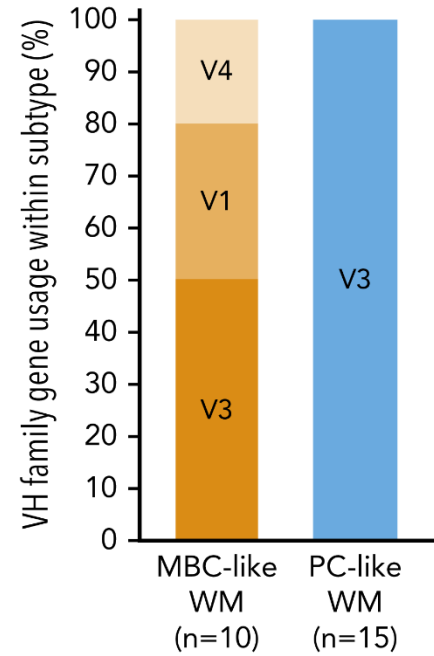
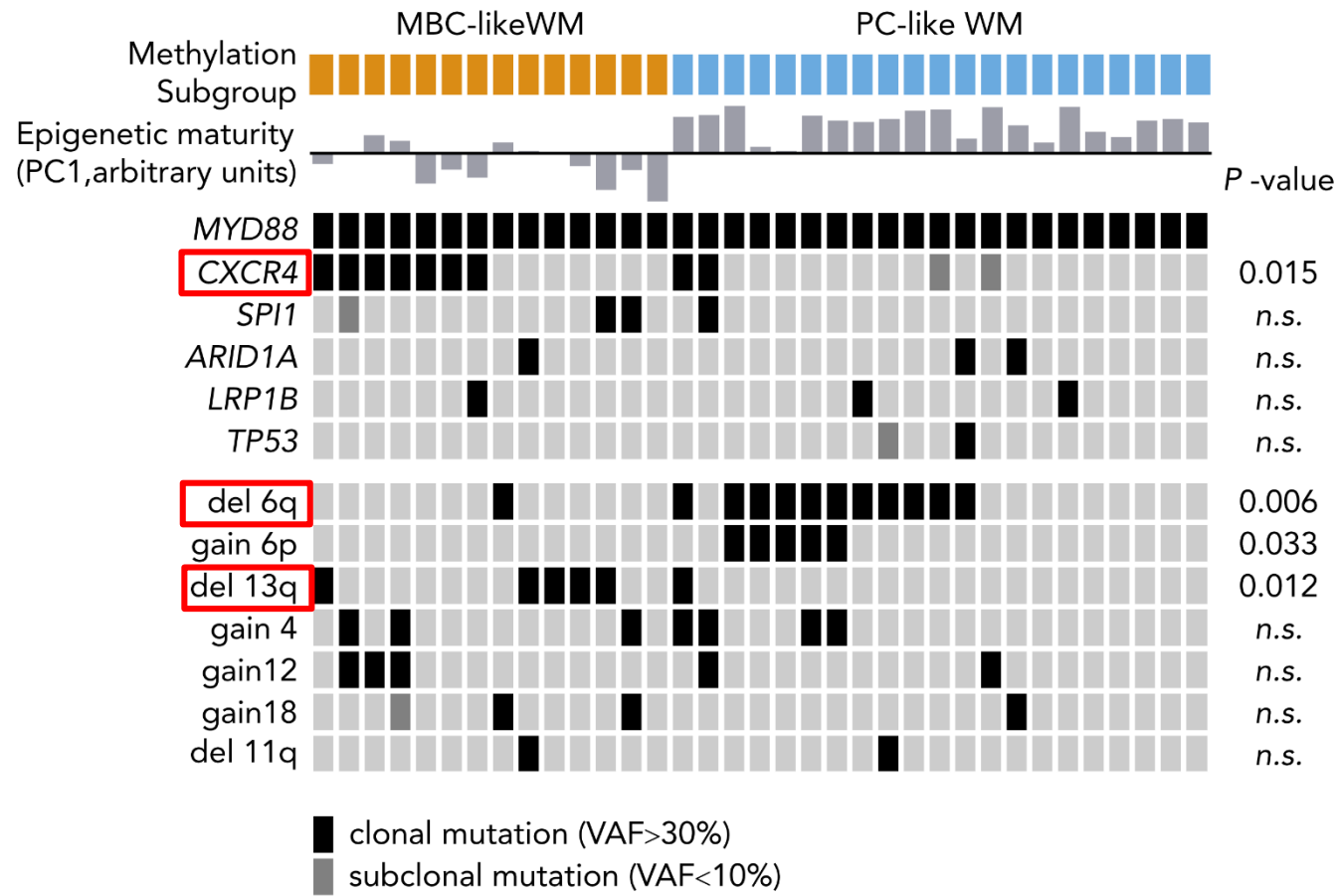
top hit = gene set comparing **IgM memory B cells to plasma cells**
7 of the top 10 most enriched gene sets

2 groups, B-cell maturation
Memory B-cell (MBC)-like, Plasma-Cell (PC)-like

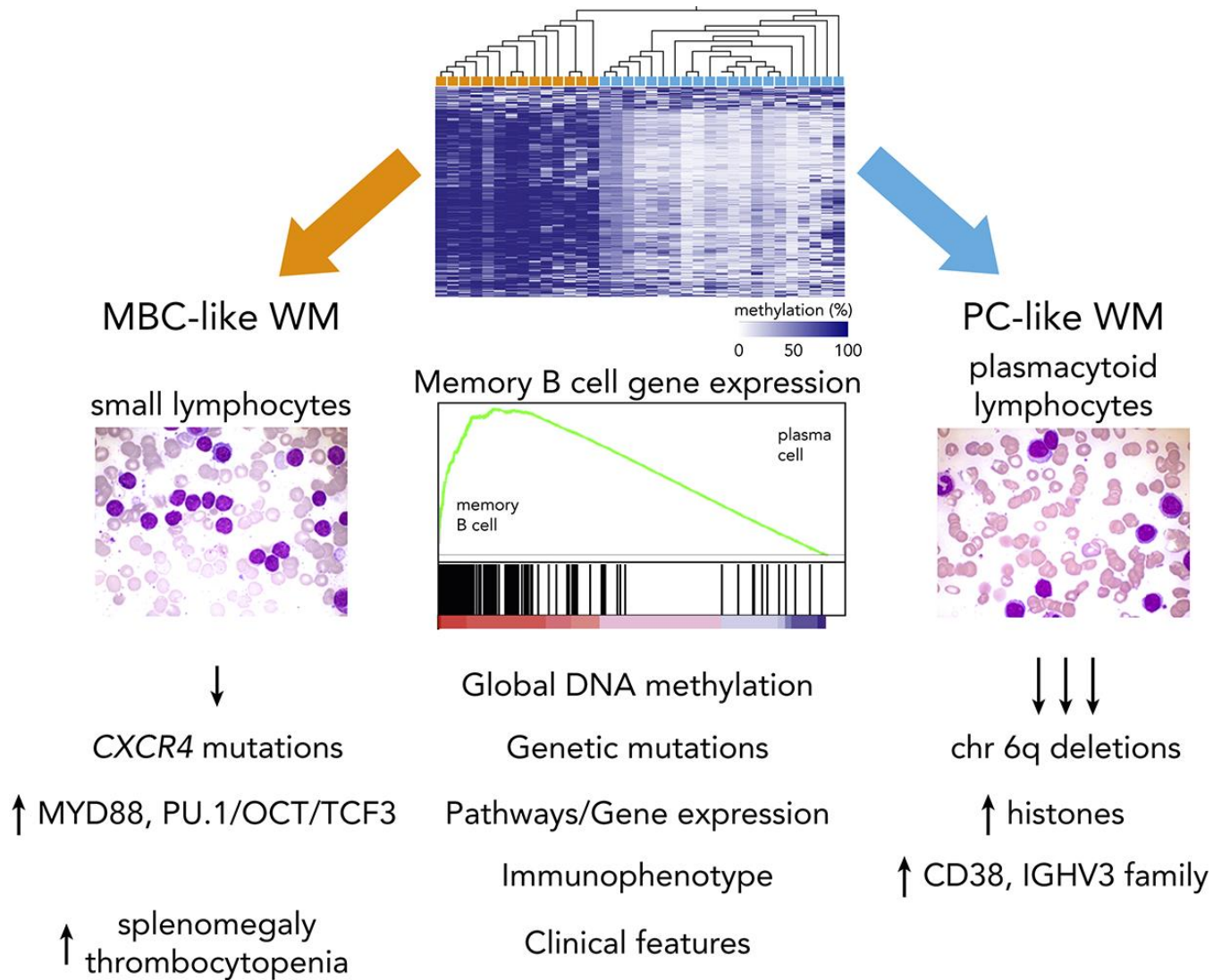
DNA methylation patterns - WM vs. normal B cells



Distinct biological features - *MBC-* and *PC-like* subtypes



WM - DNA methylation analysis



Macroglobulinémie de Waldenström (MW)

- *Généralités*
- *Des questions biologiques*
 - *lymphomagénèse ? hiérarchie clonale ? cellule d'origine ?*
 - anomalies (cyto)génétiques : impact pronostique ? prédictif ?
- **Des questions cliniques**
 - immunochimiothérapie versus thérapies ciblées ?
 - formes cliniques particulières / gammopathies de signification clinique ?

MW- Thérapeutique en 2022

Rituximab
monothérapie

**Bortezomib +
rituximab +
dexaméthasone**
(BDR)

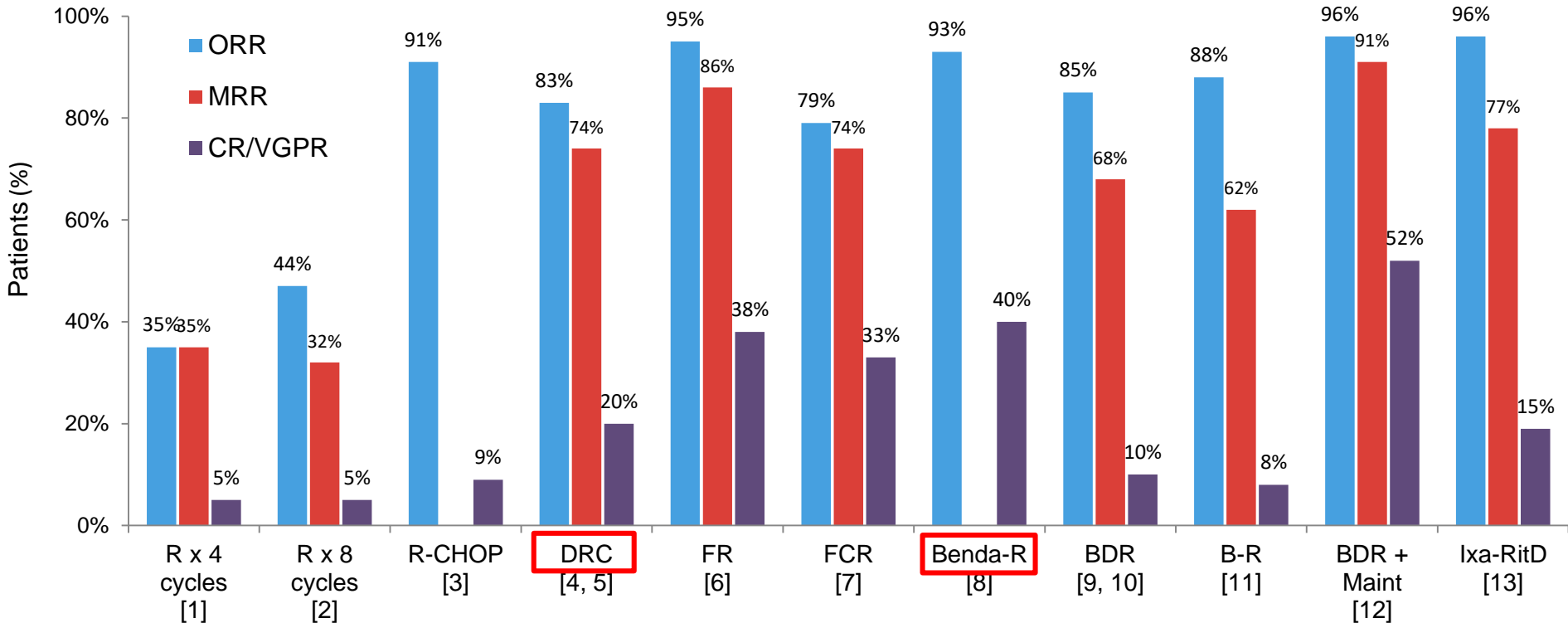
Immunochimiothérapie (ICT)

- . Cyclophosphamide (DRC)
- . Bendamustine (BR)
- . Fludarabine (FR, FCR)

iBTK

- . Ibrutinib +/- R
- . Zanubrutinib

MW- Immunochimiothérapie (ICT)



B, bortezomib;

Benda, bendamustine;

C, cyclophosphamide;

D, dexamethasone;

F, fludarabine;

R, rituximab;

1. Dimopoulos Clin Lymphoma. 2002

2. Dimopoulos J Clin Oncol 2002

3. Buske Leukemia. 2009

4. Dimopoulos J Clin Oncol 2007

5. Kastritis Blood 2015

6. Treon Blood 2009

7. Tedeschi A Cancer 2012

8. Rummel Lancet 2013

9. Dimopoulos Blood 2013

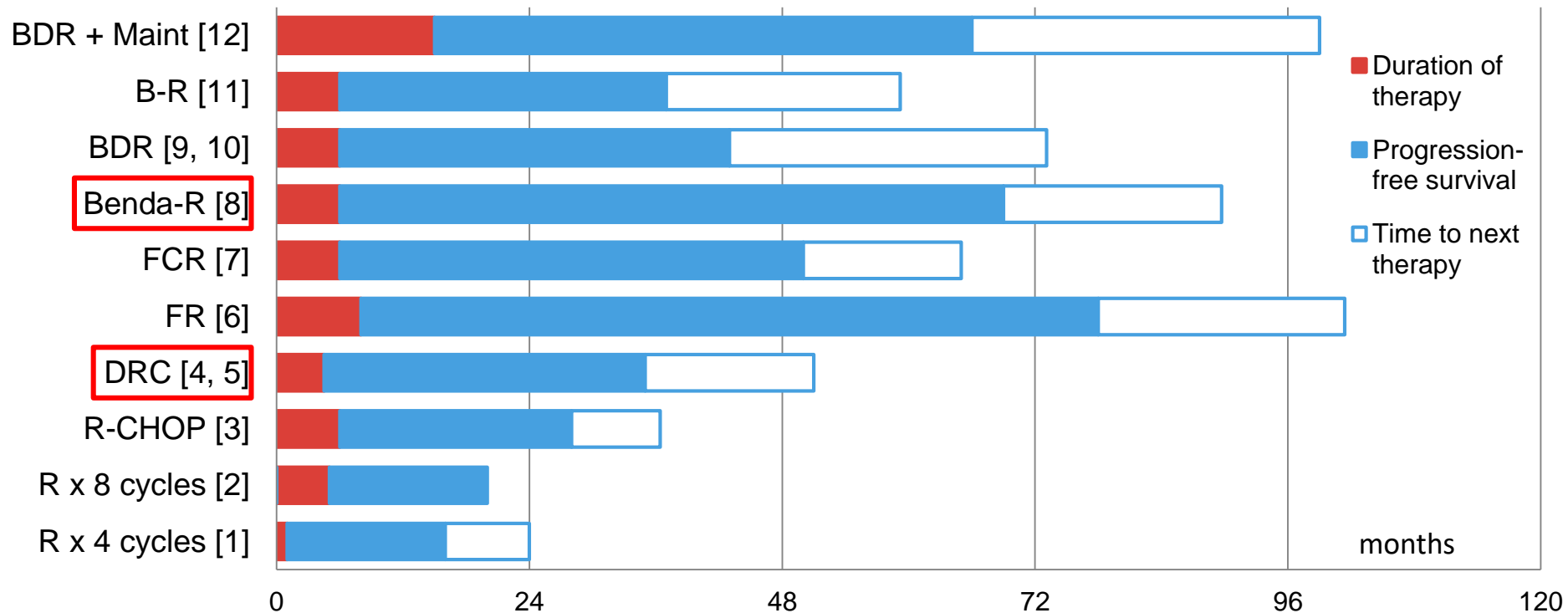
10. Gavriatopoulou Blood 2017

11. Ghobrial Am J Hematol 2010

12. Treon Blood 2015 Abstract #1833

MW- Immunochimiothérapie (ICT)

Duration of therapy, PFS and time to next therapy



B, bortezomib;

Benda, bendamustine;

C, cyclophosphamide;

D, dexamethasone;

F, fludarabine;

R, rituximab;

1. Dimopoulos Clin Lymphoma. 2002

2. Dimopoulos J Clin Oncol 2002

3. Buske Leukemia. 2009

4. Dimopoulos J Clin Oncol 2007

5. Kastritis Blood 2015

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11. Ghobrial Am J Hematol 2010

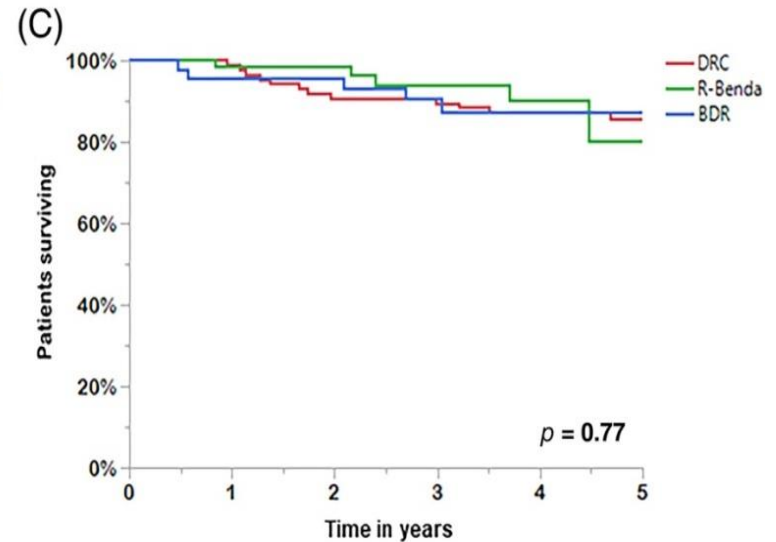
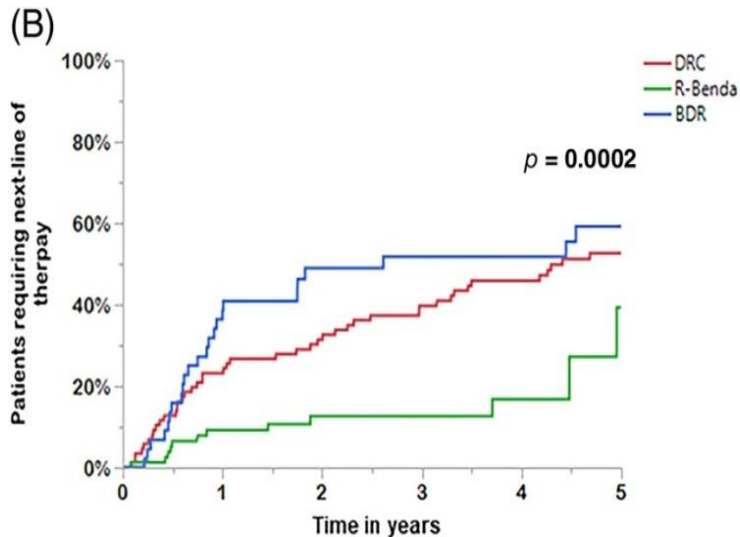
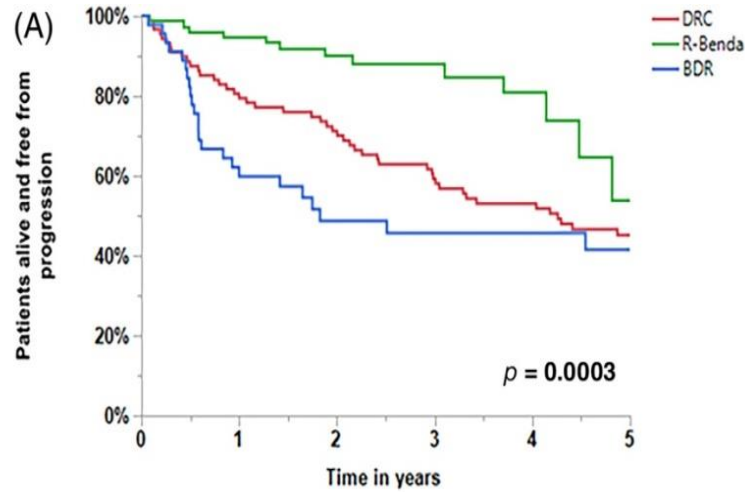
12. Treon Blood. 2015 Abstract #1833

MW- Immunochimiothérapie (ICT)

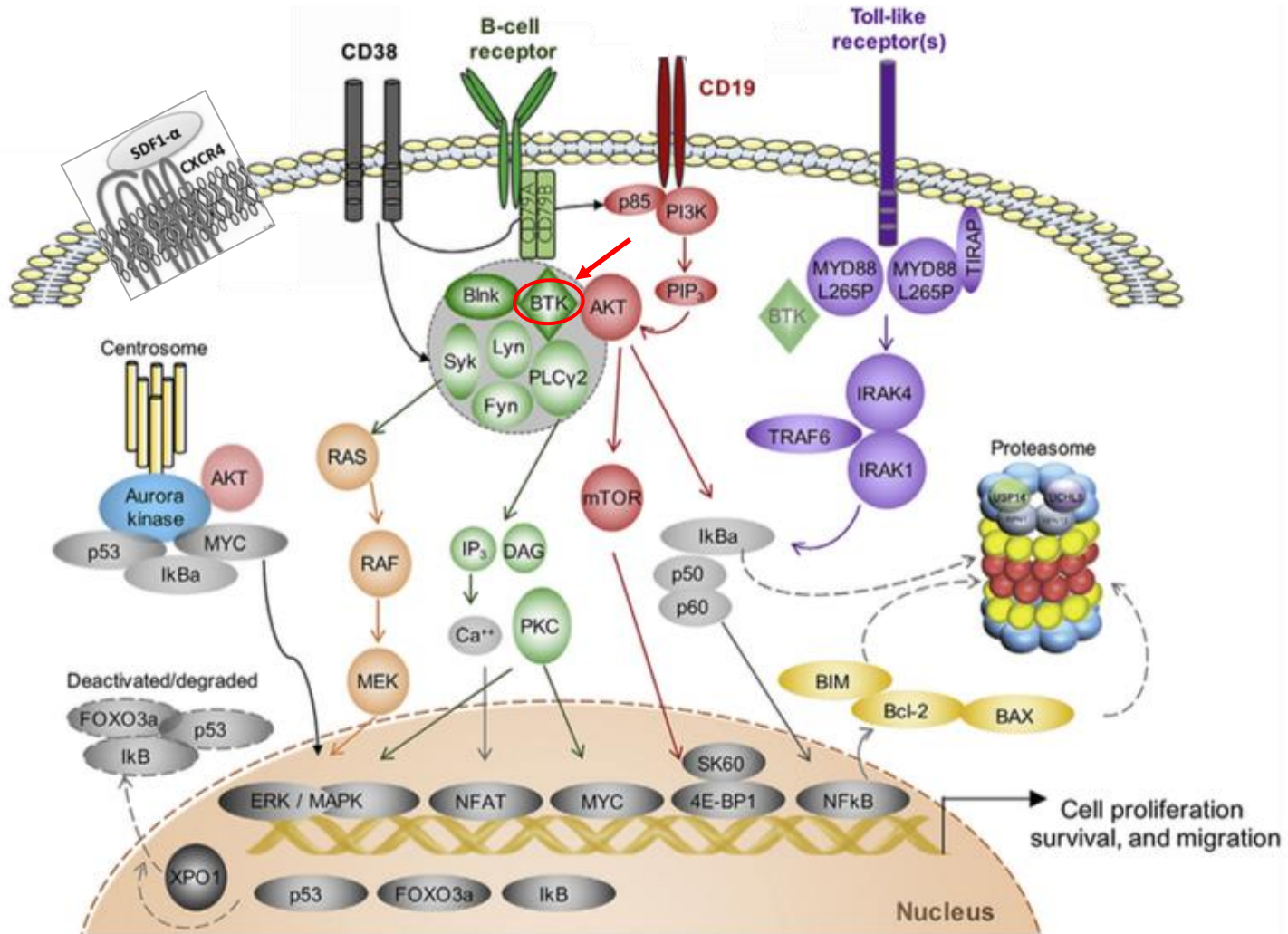
DRC (n = 92)

R-Benda (n = 83)

BDR (n = 45)

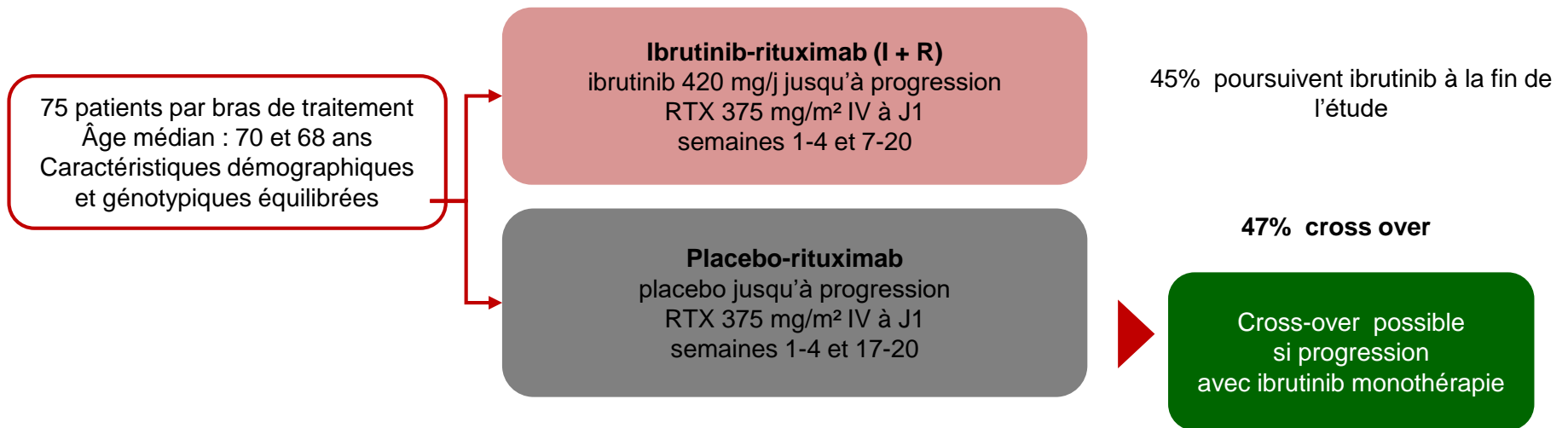


MW- De la biologie à la thérapeutique



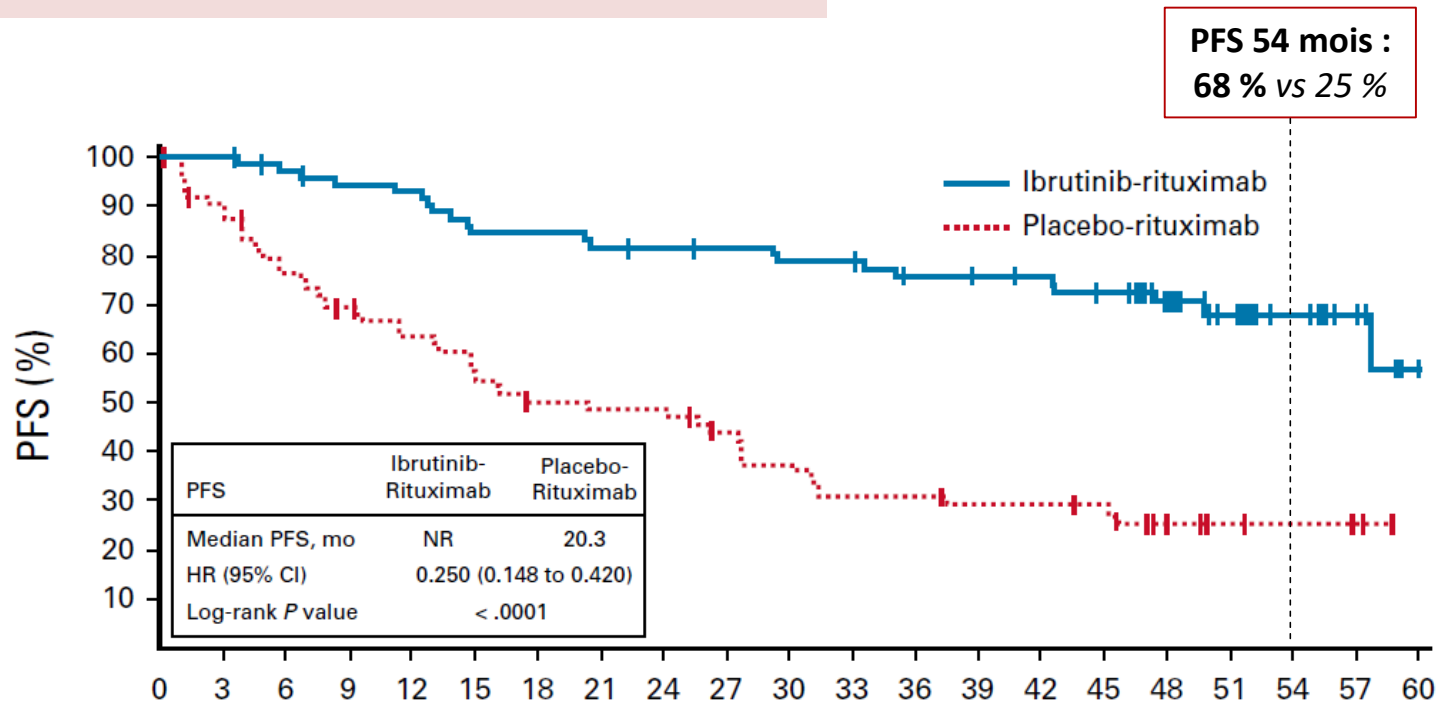
iBTK (MW) - Ibrutinib

- **INNOVATE** : essai de phase 3 randomisée
ibrutinib + rituximab vs rituximab + placebo
1^{ère} ligne (**1L**) et en rechute/réfractaire (**R/R**)



iBTK (MW) - Ibrutinib

- **INNOVATE** : essai phase 3 randomisé
Analyse finale à 5 ans



Supériorité du bras I+R quels que soient

- . caractéristiques du patient
- . traitement 1^{ère} ligne versus rechute
- . génotype (MYD88/CXCR4)

Inhibiteurs de BTK

- 1^{ère} génération

ibrutinib

- 2^{ème} génération

acalabrutinib

zanubrutinib

tirabrutinib

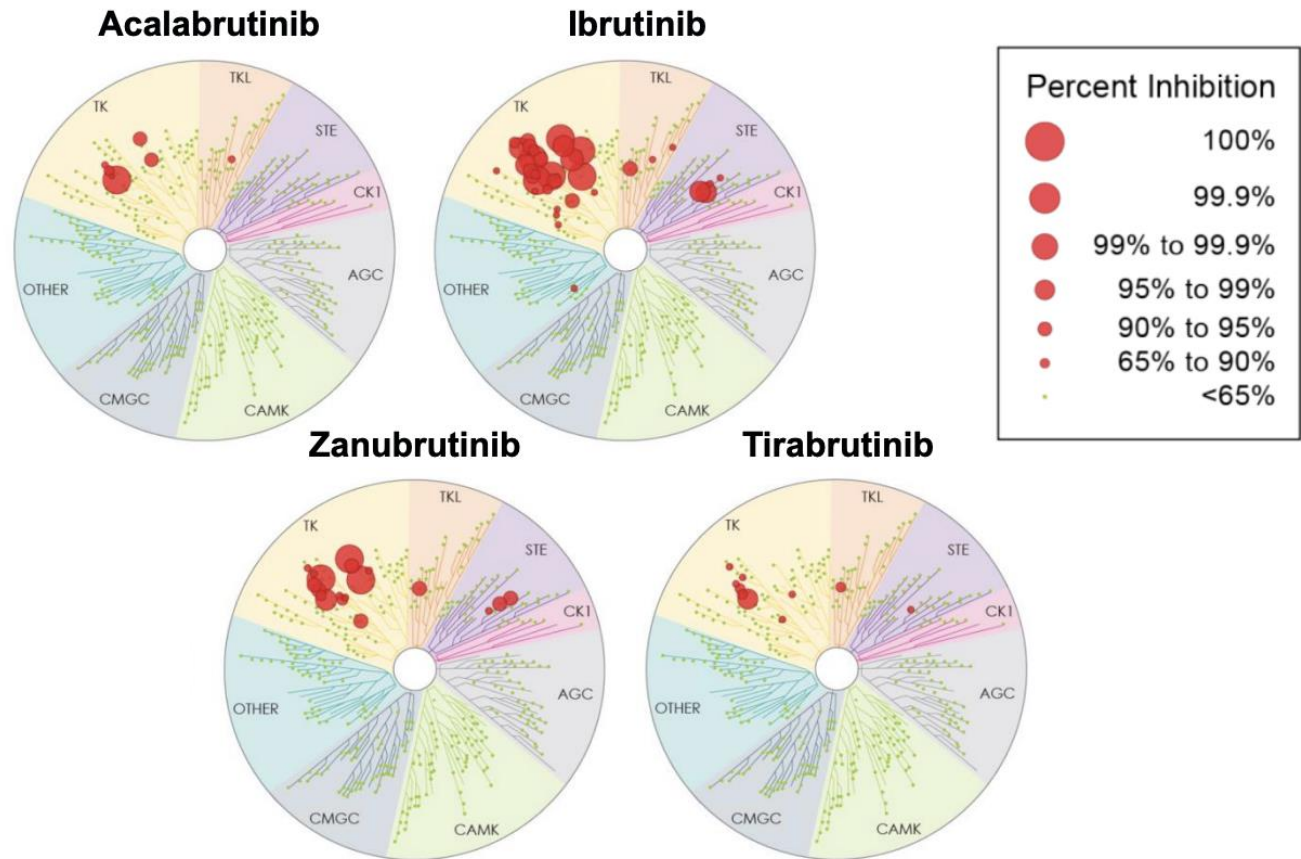
spebrutinib

- Non-covalent /non-C481 iBTK

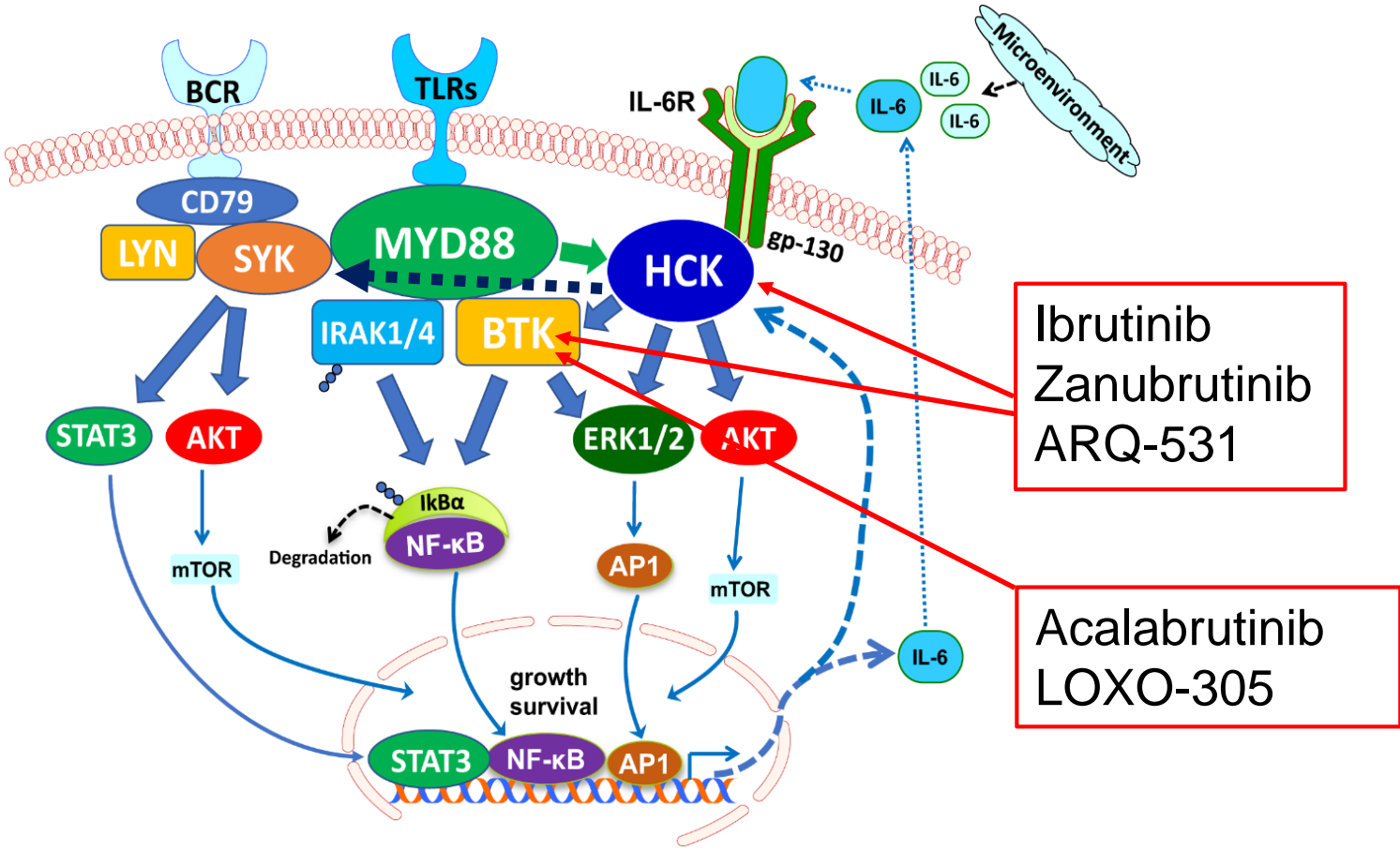
pirtobrutinib

nemtabrutinib

vecabrutinib



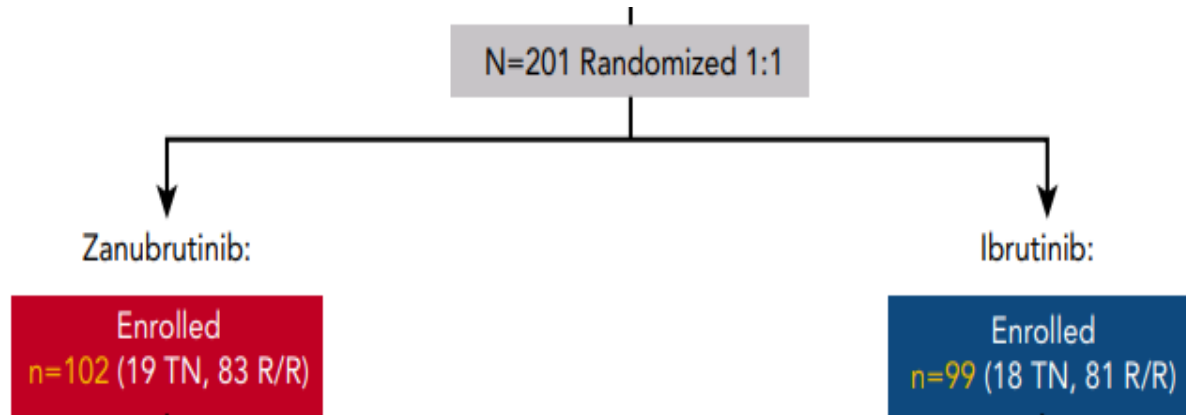
MW- BTK et autres TK



Yang Blood 2013, Blood 2016
 Munshi and Yang BCJ 2020
 Trotman Blood 2020
 Kapoor Blood 2020

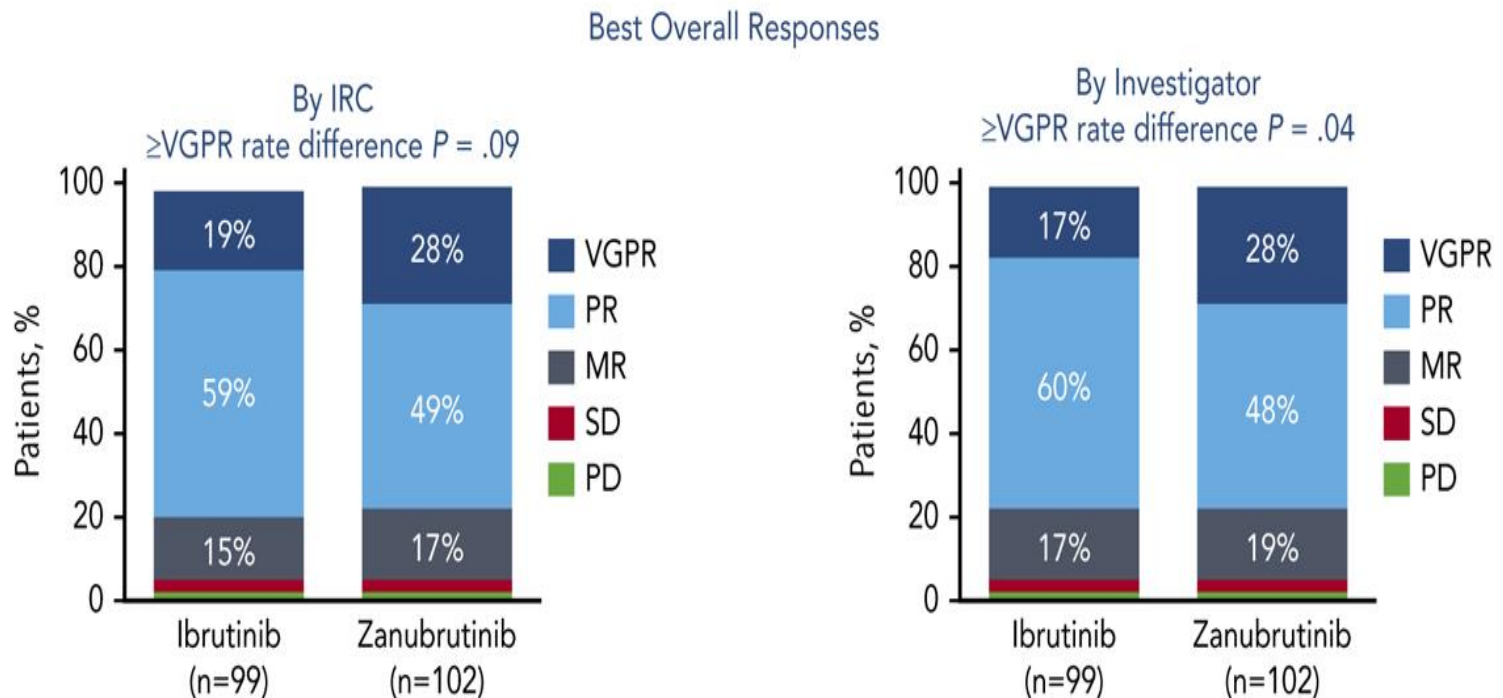
iBTK (MW) - *Zanubrutinib*

ASPEN : essai phase 3 randomisé
Zanubrutinib 160 mg 2x/j vs. ibrutinib 420 mg/j
Jusqu'à progression ou intolérance



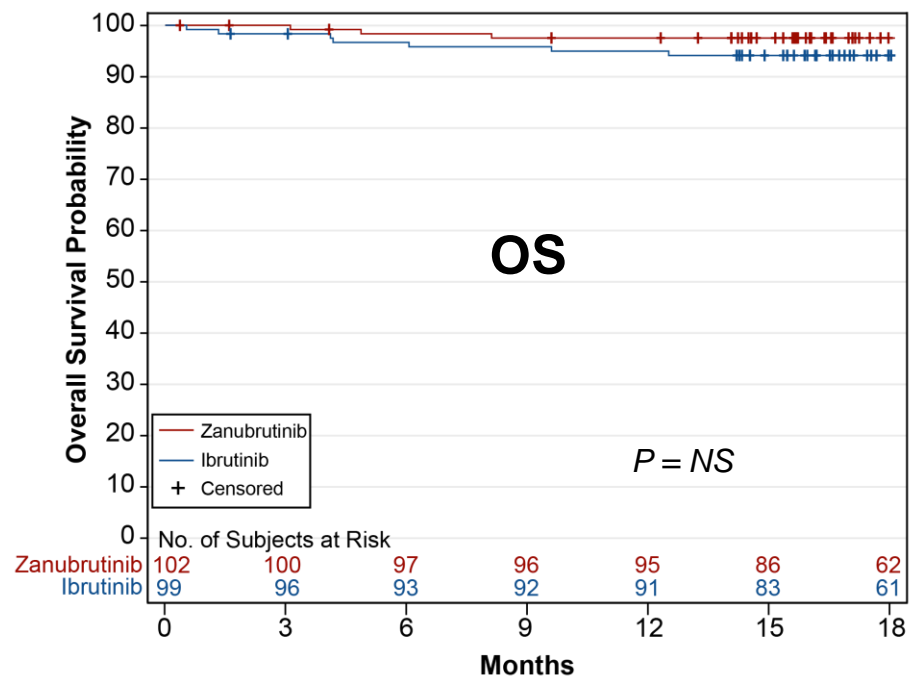
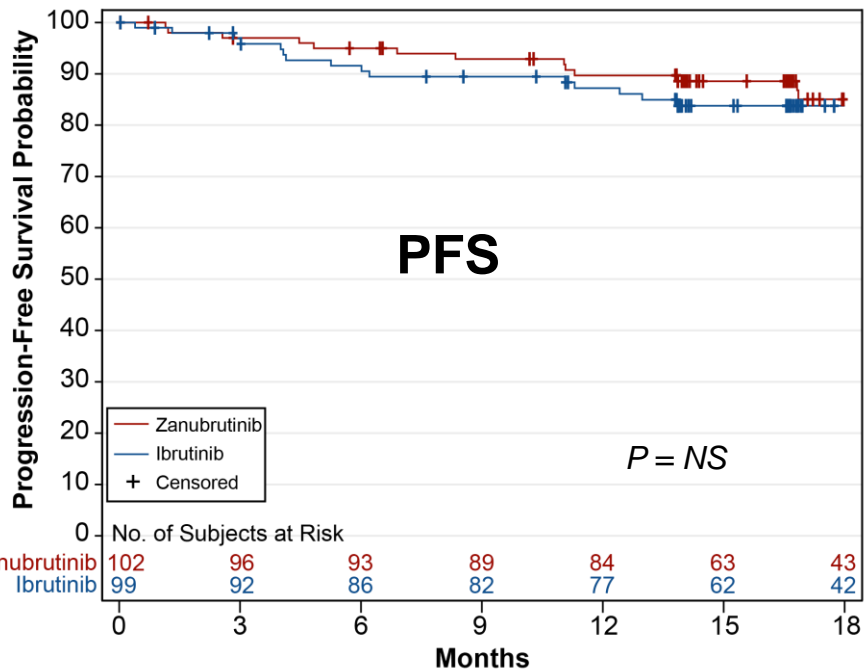
iBTK (MW) - Zanubrutinib

- **ASPEN** : essai phase 3 randomisé
Zanubrutinib vs. ibrutinib



iBTK (MW) - Zanubrutinib

- **ASPEN** : essai phase 3 randomisé Zanubrutinib vs. ibrutinib



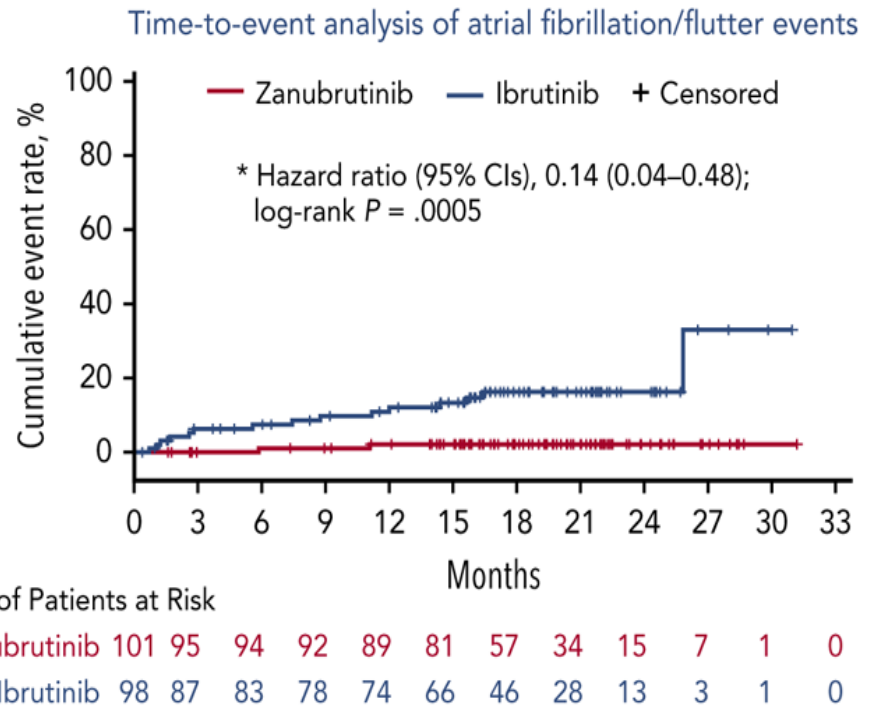
iBTK (MW) - Zanubrutinib

- **ASPEN** : essai phase 3 randomisé Zanubrutinib vs. ibrutinib

AE Categories, n (%) (Pooled Terms)	All Grades	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	15 (15.3)	2 (2.0)
Diarrhea (PT)	31 (31.6)	21 (20.8)
Hemorrhage	58 (59.2)	49 (48.5)
Major hemorrhage	9 (9.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)
Neutropenia*	13 (13.3)	30 (29.7)
Infection	66 (67.3)	67 (66.3)

*Descriptive 2-sided $P < .05$

Data cutoff
31Aug2019



- **Bras zanubrutinib**
- . réduction nette du risque d'AC/FA
 - . neutropénie plus fréquente mais risque d'infection identique

iBTK (MW) – Synthèse 1^{ère} ligne

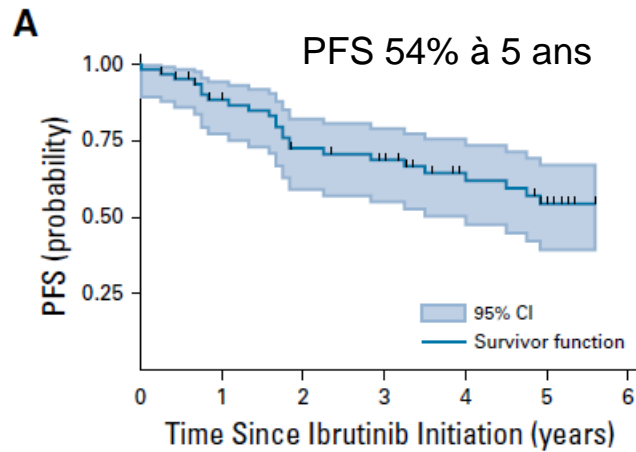
iBTK	Ibrutinib		Zanubrutinib vs. ibrutinib		Zanubrutinib	Acalabrutinib
Articles prospectifs	<i>Treon JCO 2018</i>	<i>Dimopoulos NEJM 2018</i>	<i>Tam Blood 2020</i>		<i>Trotman Blood 2020</i>	<i>Owen Lancet Haematol 2019</i>
Nombre de patients	30	34	18	19	24	14
Survie sans progression (temps, %, IC)	18 mois 92 % (73-98)	24 mois 84 % (non fourni)	18 mois 94 % (63-99)	18 mois 78 % (52-91)	24 mois 91 % (70-98)	24 mois 90 % (47-98)
Age	67	?	72	74	65	73

iBTK chez patients MW en 1L

Survie sans progression : 78-90% M24

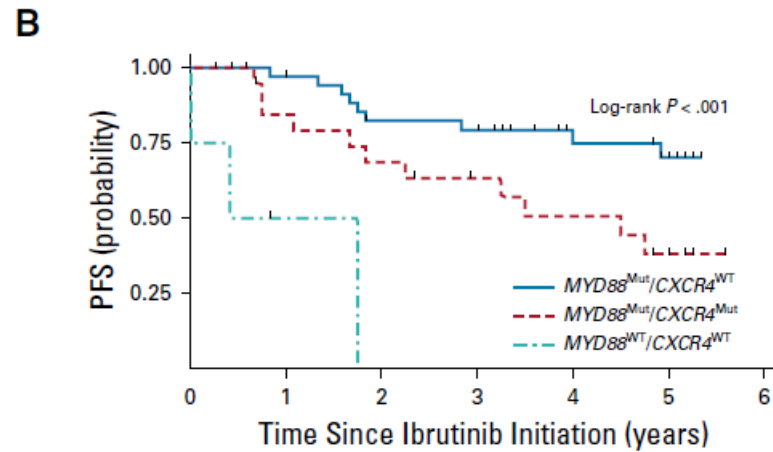
(70% M48 Innovate)

iBTK (MW) en rechute – Ibrutinib



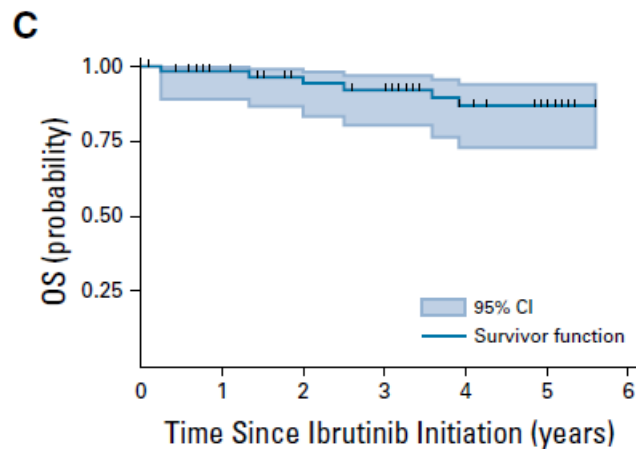
No. at risk:

63	51	39	35	26	19	0
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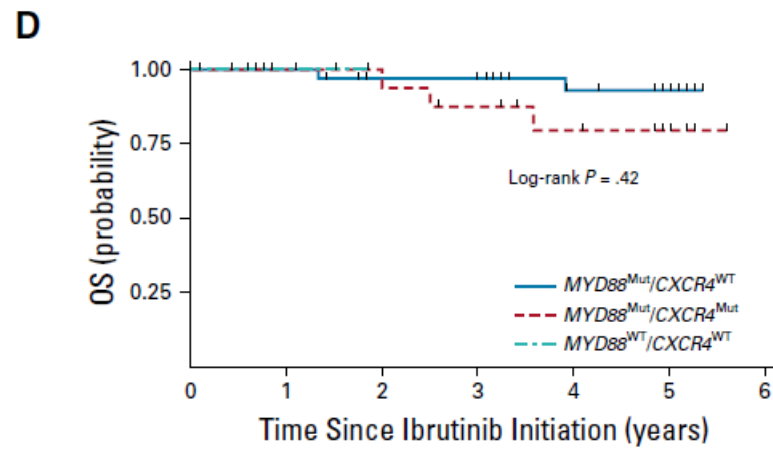
No. at risk:

$MYD88^{Mut}/CXCR4^{WT}$	36	34	26	25	18	14	0
$MYD88^{Mut}/CXCR4^{Mut}$	22	16	13	10	8	5	0
$MYD88^{WT}/CXCR4^{Mut}$	4	1	0	0	0	0	0



No. at risk:

63	55	45	42	32	25	0
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No. at risk:

$MYD88^{Mut}/CXCR4^{WT}$	36	35	29	29	22	18	0
$MYD88^{Mut}/CXCR4^{Mut}$	22	18	16	13	10	7	0
$MYD88^{WT}/CXCR4^{Mut}$	4	2	0	0	0	0	0

iBTK (MW) – Synthèse en rechute

iBTK	Ibrutinib	R-ibrutinib	Ibrutinib	Zanubrutinib vs. ibrutinib		Acalabrutinib	Zanubrutinib
Articles prospectifs	<i>Treon JCO 2022</i>	<i>Dimopoulos NEJM 2018</i>	<i>Dimopoulos Lancet 2017</i>	<i>Tam Blood 2020</i>		<i>Owen Lancet Haematol 2019</i>	<i>Trotman Blood 2020</i>
Nombre de patients	63	41	31 réfractaire au Rituximab	81	83	92	53
Survie sans progression (temps, %, IC)	60 mois 54 % (45-70)	24 mois 80 % (non fourni)	18 mois 87 % (66-94)	18 mois 82 % (71-89)	18 mois 86 % (74-93)	24 mois 82 % (72-88)	18 mois 76 % (61-86)
Age	63	?	?	69	69	69	68

iBTK chez patients MW en R/R

PFS : 70-85% M24, 50-60% M60

iBTK (MW) - AMM

Ibrutinib (France)

- patients adultes atteints de MW ayant reçu au moins un traitement antérieur
- ou en 1L chez les patients pour lesquels une chimio-immunothérapie n'est pas appropriée

Zanubrutinib (Europe)

- patients adultes atteints de MW ayant reçu au moins un traitement antérieur
- ou en 1L chez les patients pour lesquels une chimio-immunothérapie n'est pas appropriée.

iBTK vs. ICT – 1^{ère} ligne

- Aucun résultat d'études randomisées
- Une étude randomisée en cours : RAINBOW (NCT04061512)
rituximab + ibrutinib (5 ans) vs. DRC
- Données de la littérature en 1L ou R/R :

Immunochimiothérapie (ICT)
(DRC/BR)

Survie sans progression
1L : 55-90% M36
R/R : 50-60% M36

iBTK

Survie sans progression
1L : 78-90% M24
R/R : 70-85% M24

iBTK vs. ICT – 1^{ère} ligne

7566

Poster Session

Bendamustine rituximab (BR) versus ibrutinib (Ibr) as primary therapy for Waldenström macroglobulinemia (WM): An international collaborative study.

N=347
Europe, USA
2011-2021

Jithma P. Abeykoon, Shaji Kumar, Jorge J. Castillo, Shirley D'Sa, Efstathios Kastritis, Eric Durot, Encarl Uppal, Pierre Morel, Jonas Paludo, Reema Tawfiq, Shayna Sarosiek, M Olabisi Ogunbiyi, Pascale Cornillet-Lefebvre, Robert A. Kyle, Alain Delmer, Morie A. Gertz, Meletios A. Dimopoulos, Steven P. Treon, Stephen M. Ansell, Prashant Kapoor

	BR	Ibr	p
Follow up, median, 95%CI, y	4.5 (3.7-4.9)	4.5 (4-4.7)	0.7
Age, median, range, y	68 (40-86)	68 (39-86)	0.9
IPSS%			0.63
Low	11	17	
Intermediate	33	33	
High	56	48	
Cycles, median (range)	6 (1-6)	42 (0.3-98)	
	>4 cycles, 77%		
Overall response rate %	94	94	0.91
Major response rate %	92	83	0.05
Complete response %	20	2	<0.001
≥VGPR %	50	33	0.009

1:1 age-matched analysis

246 pts : Ibr (n=123), BR (n=123)

4-y PFS : similar [72% (95% CI 63-82) for BR v 78% (95% CI 70- 87) for Ibr, p=0.14]

4-y OS : 95% (95% CI 91-99) with BR v 86% (95% CI 80-93) with Ibr (p=0.3)

iBTK vs. ICT

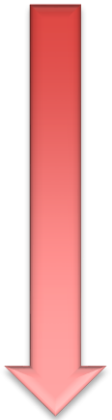
Chemo-immunotherapy

iBTK



- **Fixed duration of therapy**
- Treatment free interval
- Extended experience
- Low cost
- Toxicity (+/-)

- Oral therapy
- Efficacy
- Toxicity (+/-)
- Rapid activity
- Penetrates CNS



- Toxicity: short / long term (+/-)
- Low CR rate
- Slower response with some combos
- Parenteral therapy (IV / SQ)

- **Continuous therapy**
- No CRs (or low)
- Toxicities (AF, HTA)
- High cost
- Long term experience (?)
- Affected by genotype (?)
- (Opportunistic) infections

Critères de choix de traitement

- **Patient characteristics**

- Age

- Comorbidities

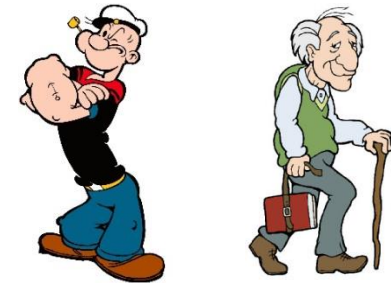
- > 65y:

- 25% > 2 comorbidities

- 21% hypertension,

- 13% cardiovascular disease

- Performance status more than age



- **Disease characteristics**

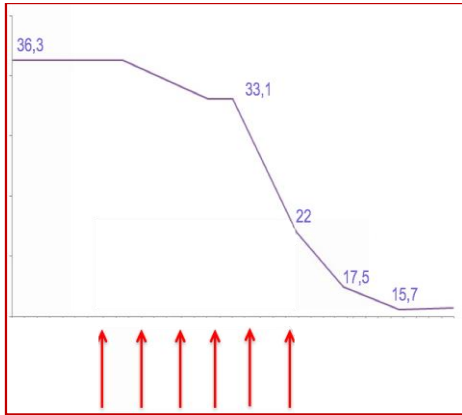
- Cytopenia, need for rapid control of the disease, bulky disease, neuropathy

- **Genomic profile?**

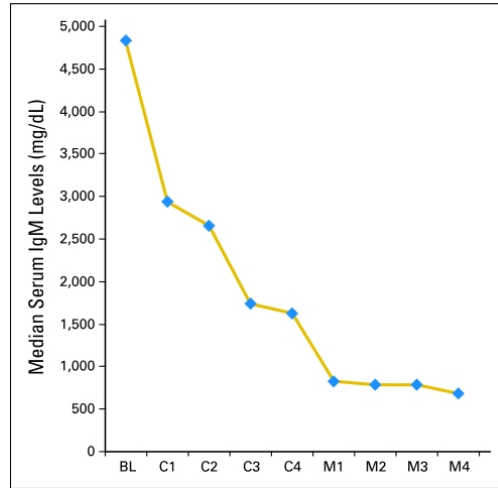
- Mutations in *MYD88*, *CXCR4*, *TP53* ?

- Drug availability and coverage based on respective national and/or institutional guidelines

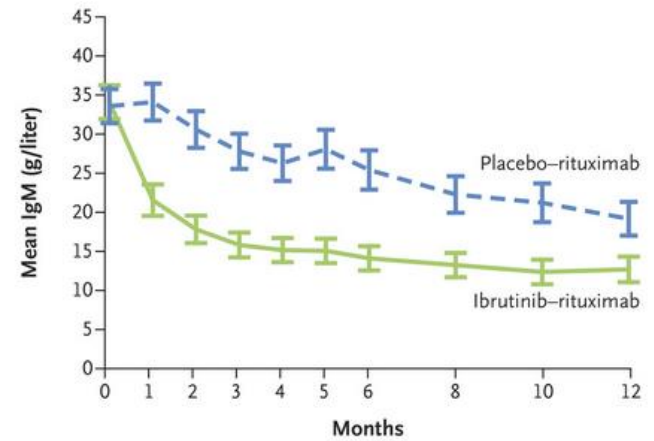
Cinétique de réponse



RDC

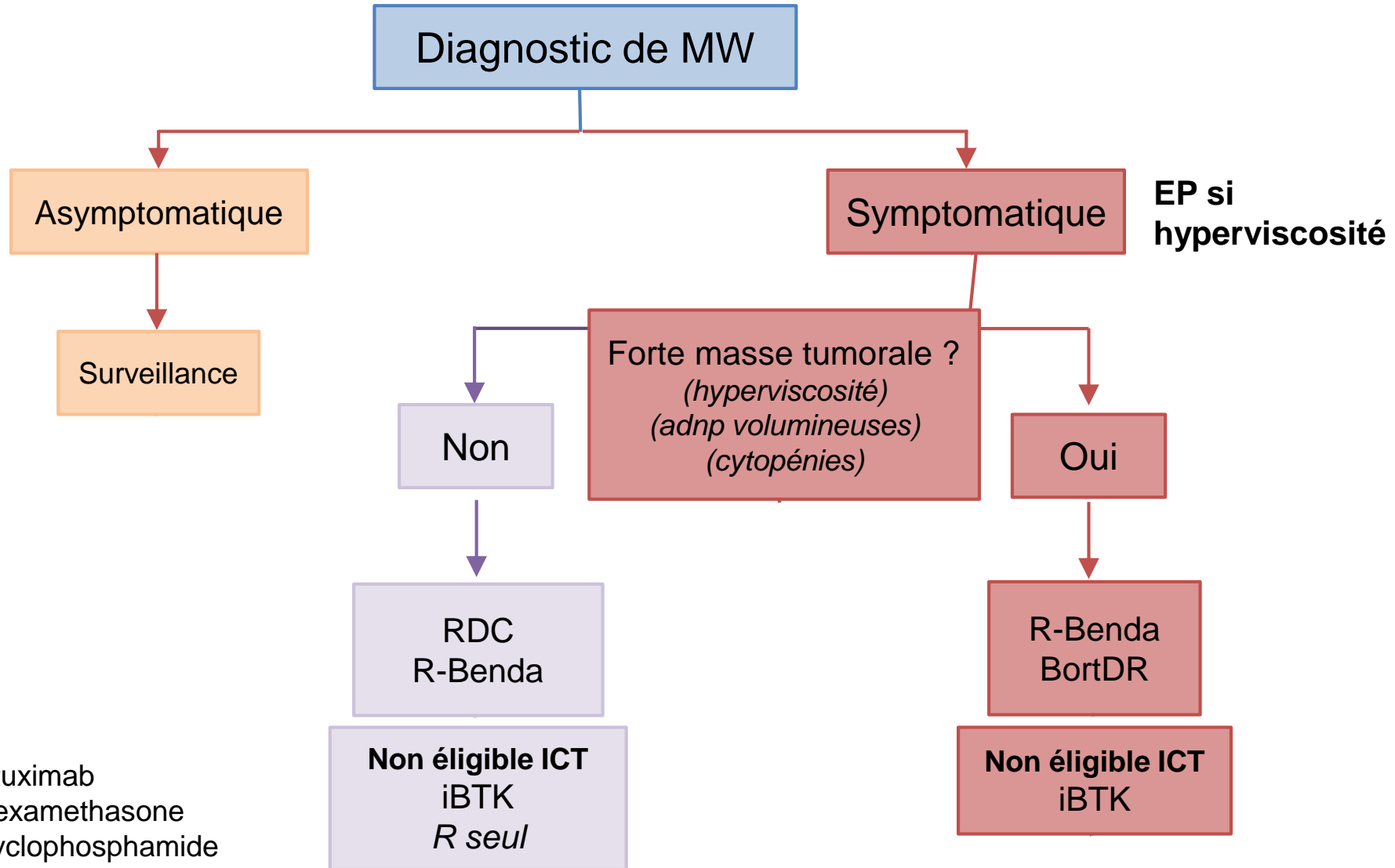


Bortezomib



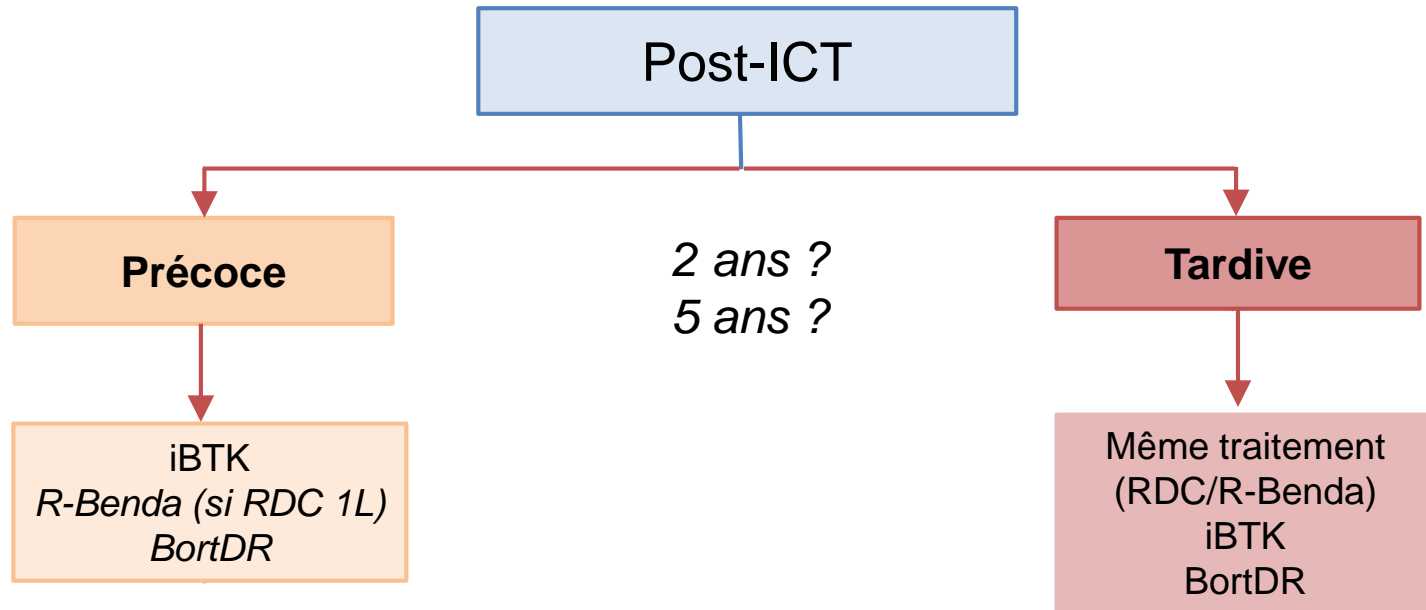
Ibrutinib

2022 - 1^{ère} ligne



R = rituximab
D = dexaméthasone
C = cyclophosphamide
Benda = bendamustine
Bort = bortezomib

2022 – 1^{ère} Rechute



Rechutes multiples ou réfractaire chez un sujet jeune :

Autogreffe
Allogreffe

R = rituximab
D = dexamethasone
C = cyclophosphamide
Benda = bendamustine
Bort = bortezomib

Facteurs prédictifs ?

Clinique

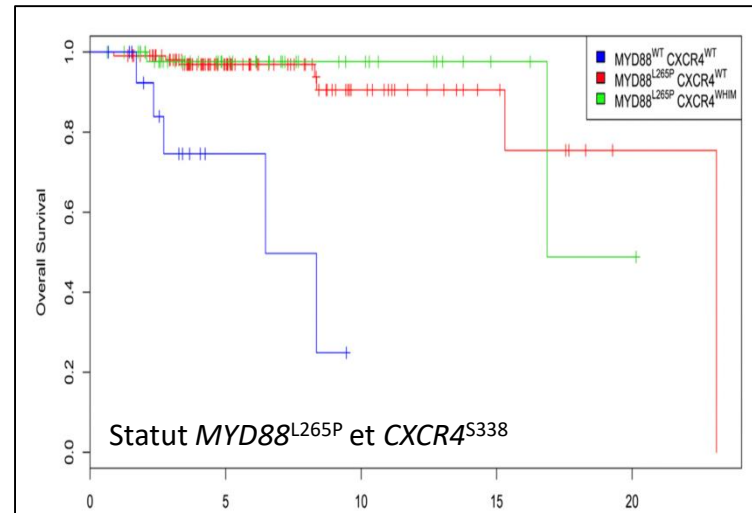
Génomique ?

Limites :

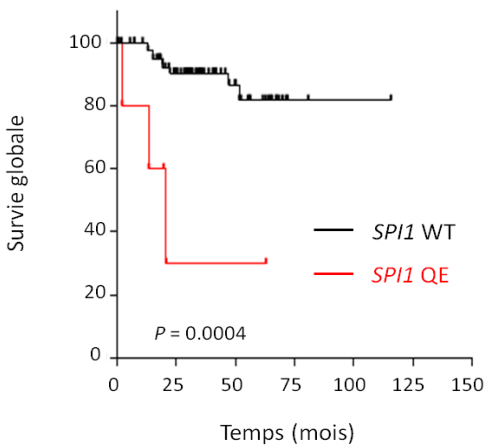
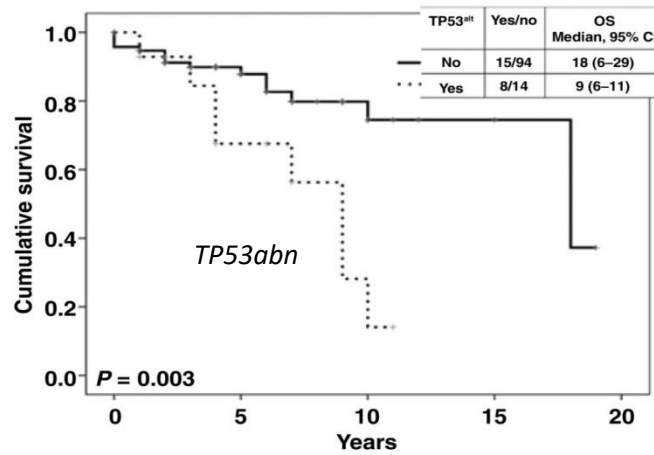
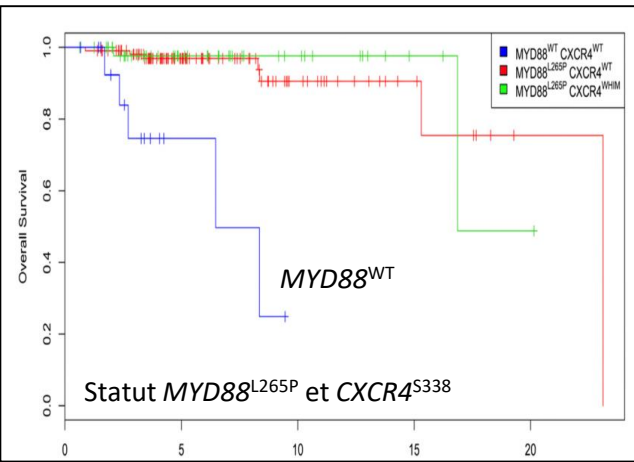
technique

effectifs (sous-groupes)

hétérogénéité (rétrospective)



Hétérogénéité clinique - (Cyto)génétique pronostique ?



	Overall survival (OS)					
	Univariate (n=239)			Multivariate (n=136)		
	HR	IC 95%	P	HR	IC 95%	P
IPSSWM	3.70	1.47-9.10	0.002	3.06	1.26-5.96	0.03
Del6q	2.02	1.07-3.83	0.027	-	-	NS
Tri4	2.38	1.08-5.22	0.026	-	-	NS
High-CK	3.44	1.30-9.10	0.01	-	-	NS
TP53abn	2.95	1.43-6.07	0.002	2.41	1.19-4.83	0.04
SPI1 mutations	4.10	1.01-12.4	0.037	-	-	NS

Facteurs prédictifs – Statut *MYD88* / *CXCR4* ?

MYD88 WT

« WT » vs. L265P

- . immunophénotype comparable
- . moins hypermutation *IGHV* (69 vs. 96%, $p=.02$)
- . moins *VH3-23* (8 vs. 24%, $p=.04$)

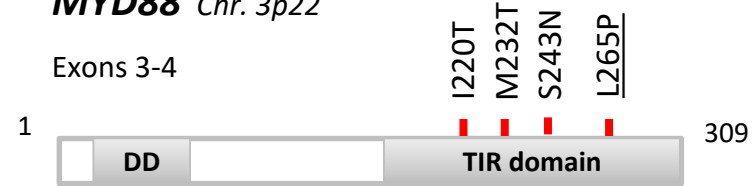
WES (n=18 patients *MYD88*^{WT}) :

- . Voie NF-KB : *TBL1XR1*, *PTPN13*, *MALT1*, *BCL10*...
- . Voie BCR : *CD79B*
- . Epigénétique : *KMT2D*, *KMT2C*, *EZH2*...
- . Réparation ADN : *TP53*, *ATM*, *TRRAP*

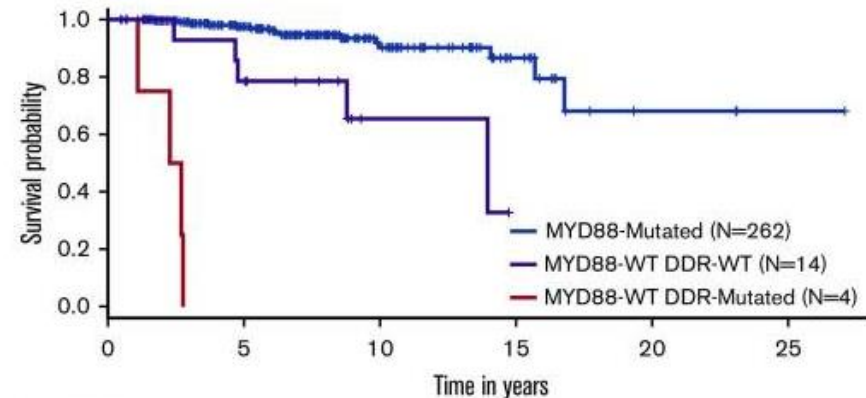
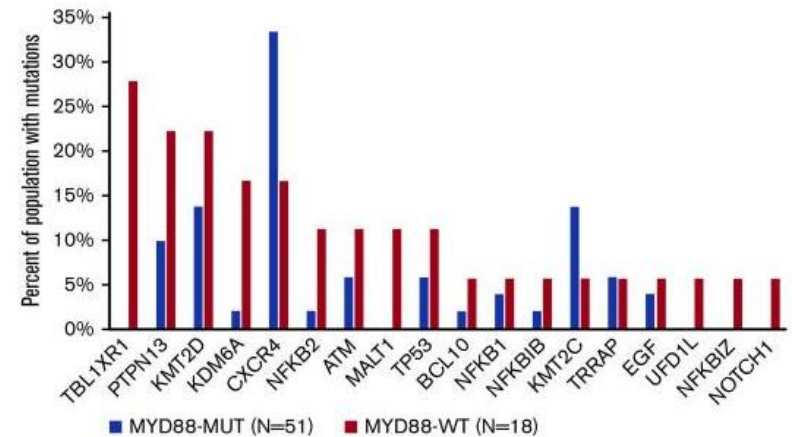
Intérêt des iBTK 2.0 ?

MYD88 Chr. 3p22

Exons 3-4

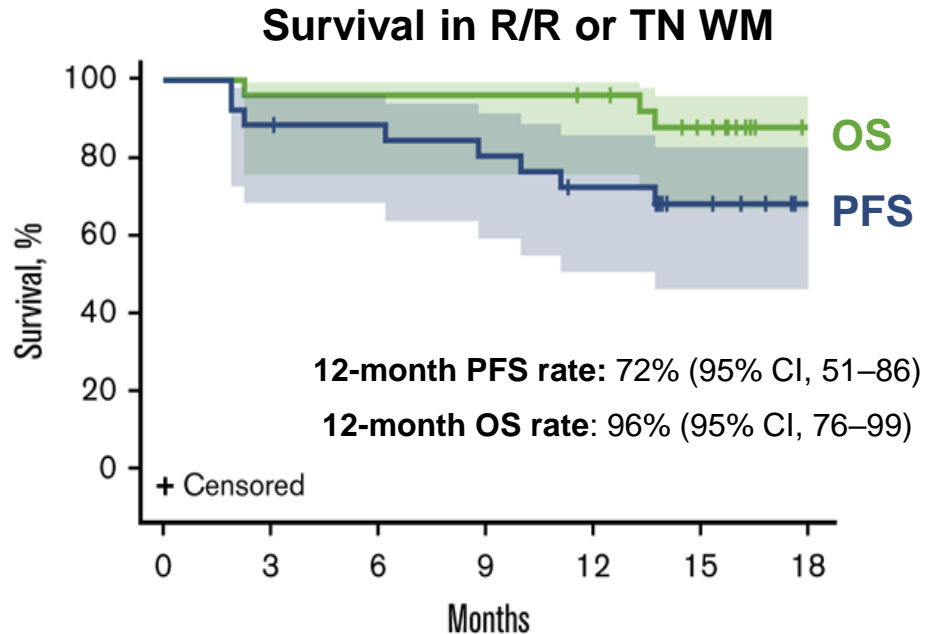
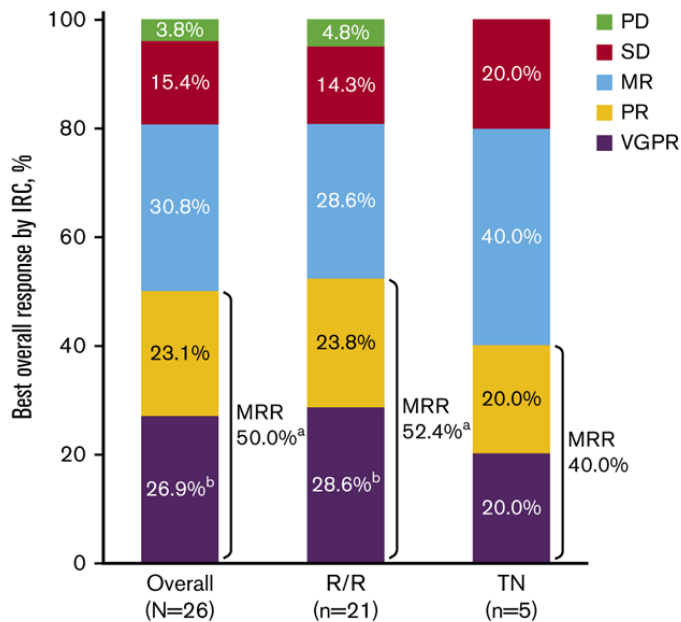


> 95 %



iBTK (MW) - Zanubrutinib

- **ASPEN** : *MYD88* WT
Zanubrutinib

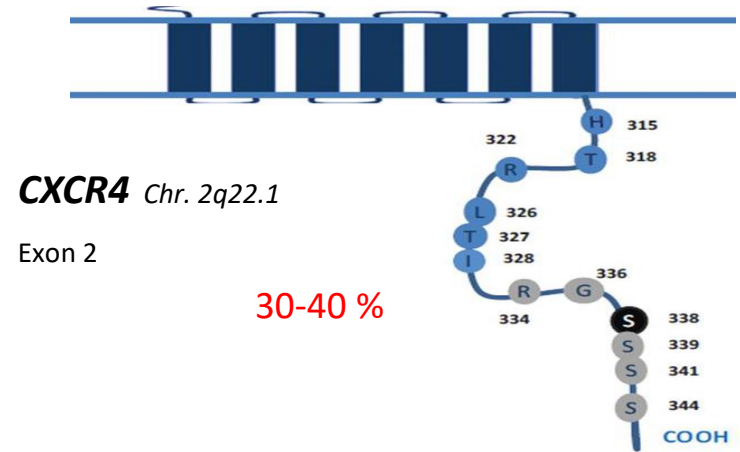


No. of pts at risk

PFS	26	23	22	20	17	12	7
OS	26	25	25	25	24	19	10

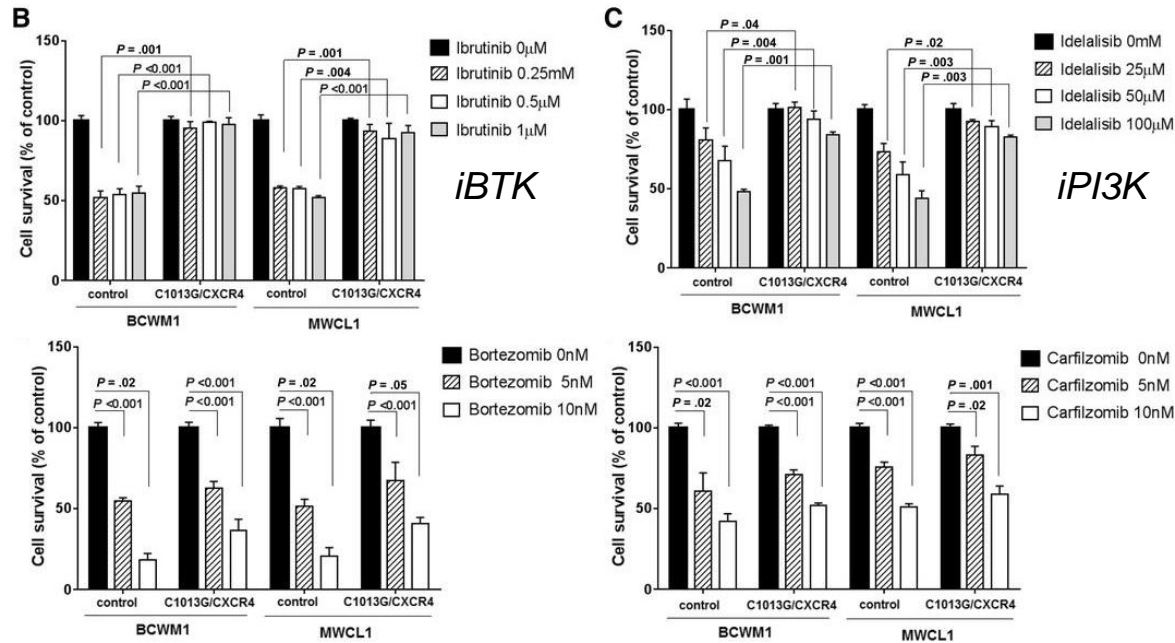
Facteurs prédictifs – Statut MYD88 / CXCR4 ?

CXCR4 muté

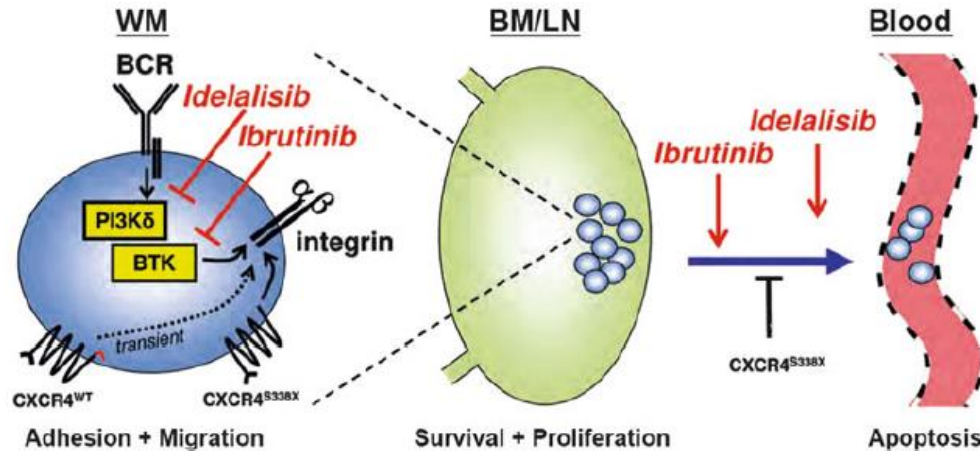


MW- CXCR4 et résistance aux drogues ?

IBCR



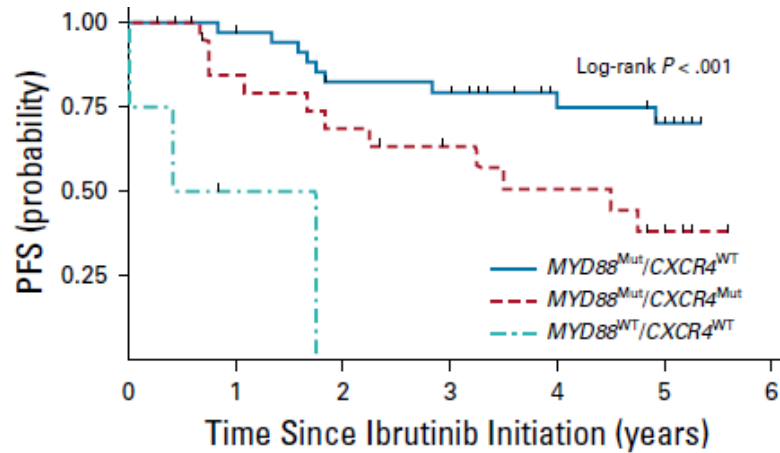
IPs



Intérêt des inhibiteurs du protéasome ? CXCR4 ? ERK ?

MW- CXCR4 et résistance aux drogues ?

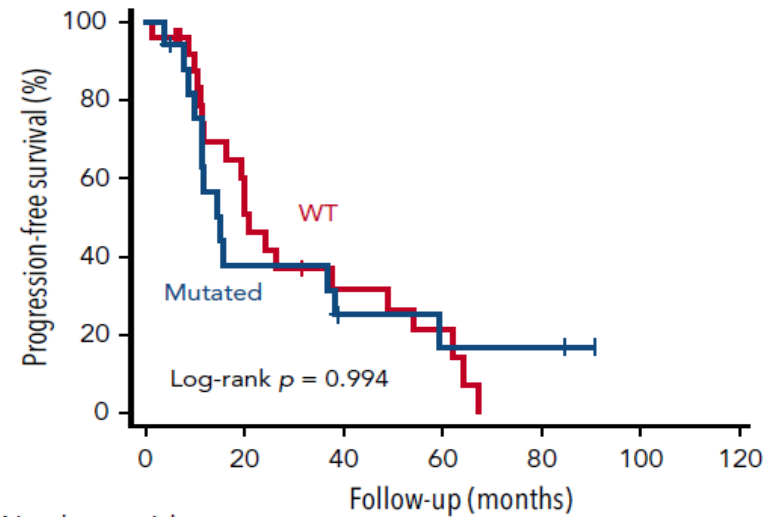
iBTK (ibrutinib)



No. at risk:

	0	1	2	3	4	5	6
$MYD88^{Mut}/CXCR4^{WT}$	36	34	26	25	18	14	0
$MYD88^{Mut}/CXCR4^{Mut}$	22	16	13	10	8	5	0
$MYD88^{WT}/CXCR4^{WT}$	4	1	0	0	0	0	0

Bortezomib

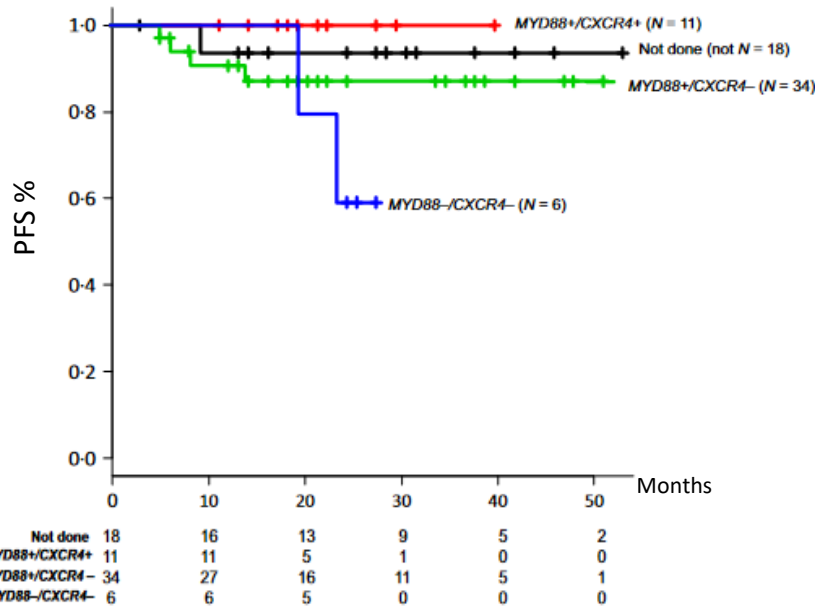


Number at risk

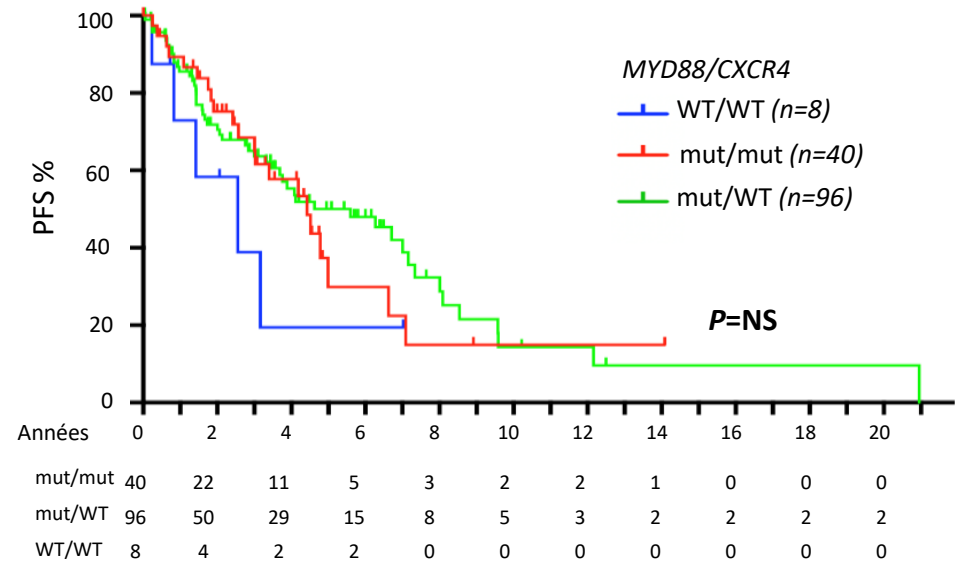
	0	20	40	60	80	100	120
WT	26	12	6	3	0	0	0
Mutated	17	6	3	2	2	0	0

MW- CXCR4 et résistance aux drogues ?

ICT (R-Benda)



ICT (RDC ou R-Benda)

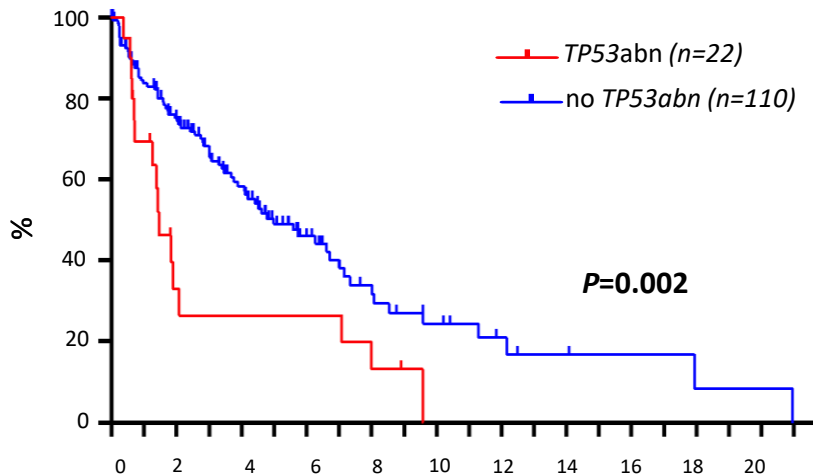


Intérêt ICT ou bortezomib vs. iBTK pour MW CXCR4^{mut} ?

MW- Impact anomalies TP53 ?

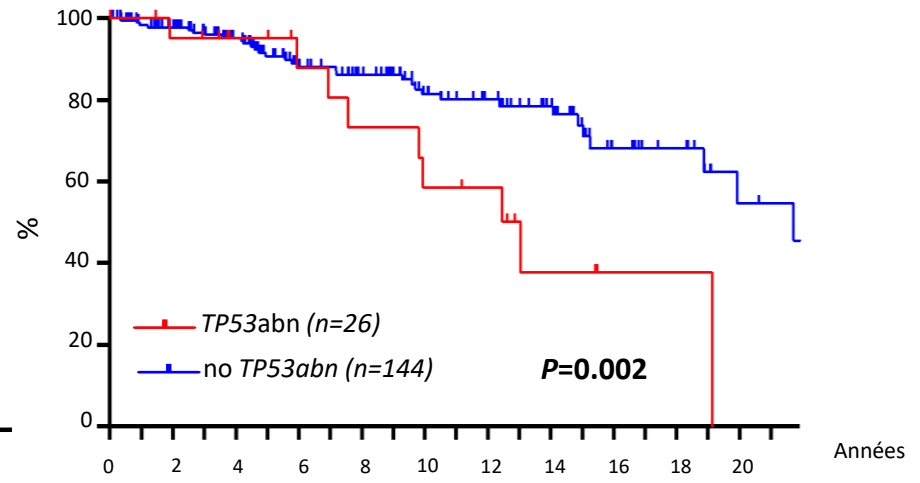
ICT (RDC ou R-Benda)

Survie sans progression (SSP)



TP53abn	22	7	5	5	3	0	0	0	0	0
No TP53abn	110	82	47	25	14	8	5	3	3	2

Survie globale (SG)

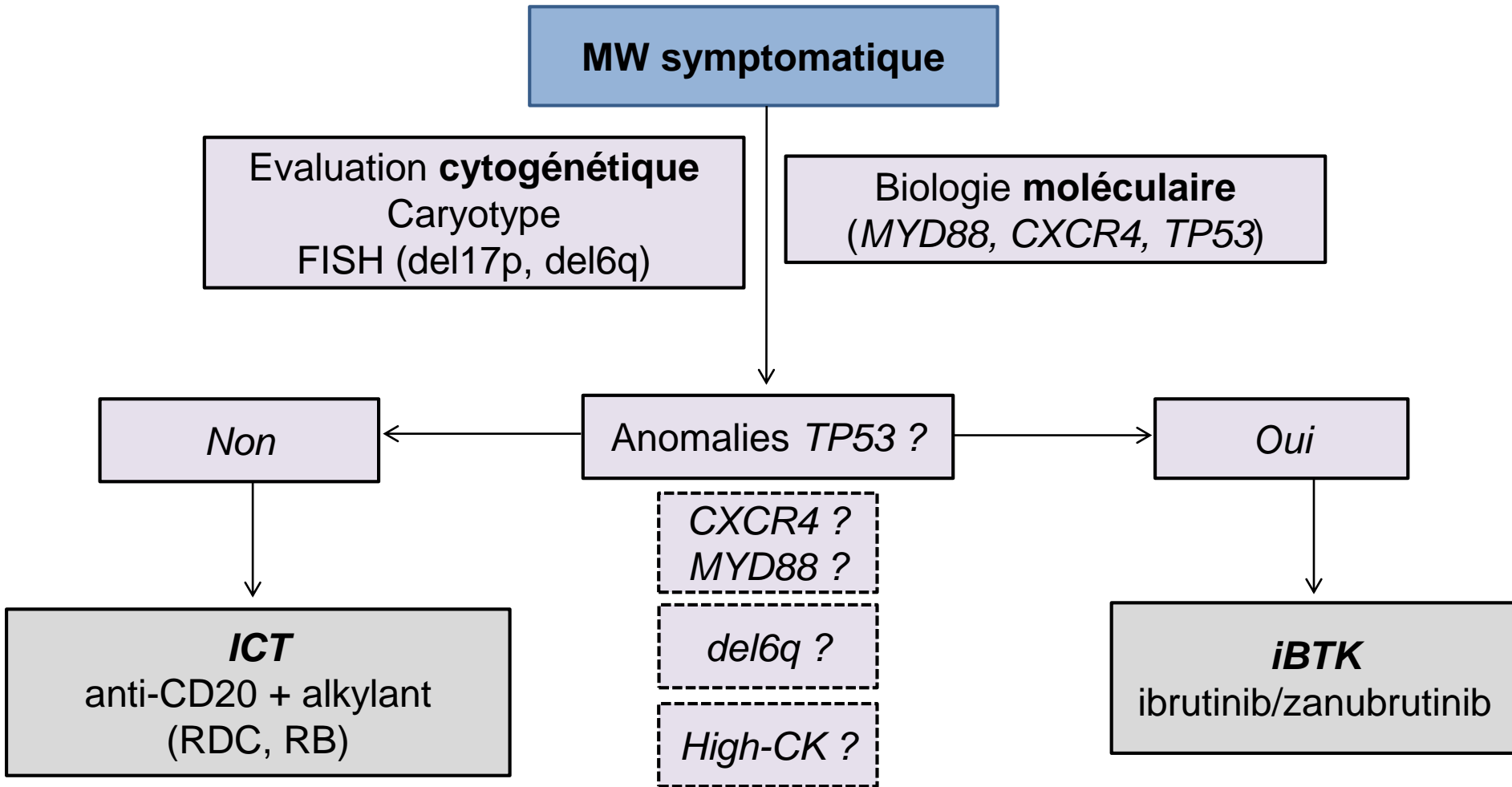


TP53abn	26	23	18	13	11	9	7	4	2	2	0
No TP53abn	144	120	106	83	72	54	37	25	19	12	8

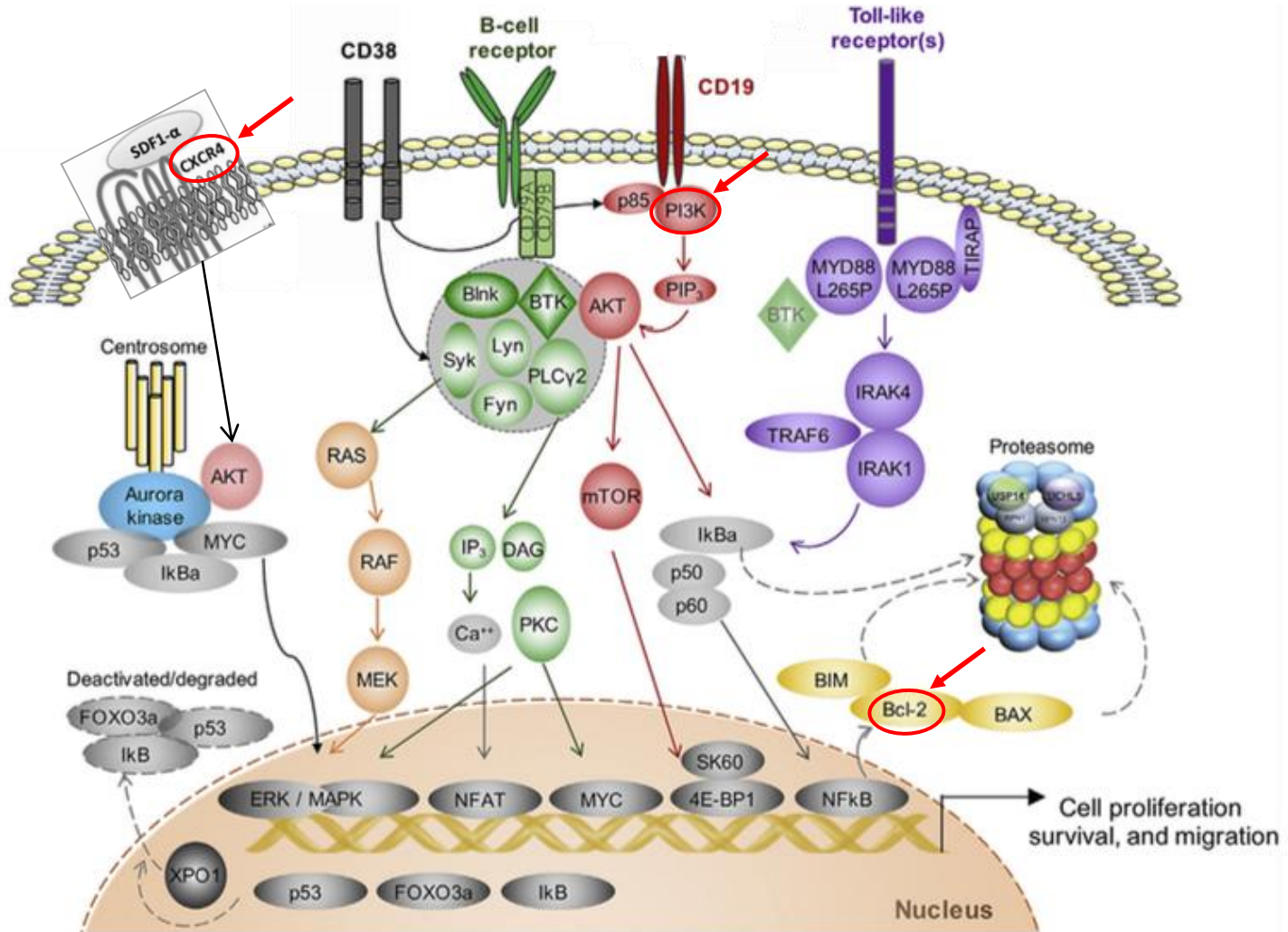
Anomalies TP53 associées à une SSP et SG plus courtes

Intérêt iBTK pour WM avec anomalies TP53 ?

MW- Perspectives ?



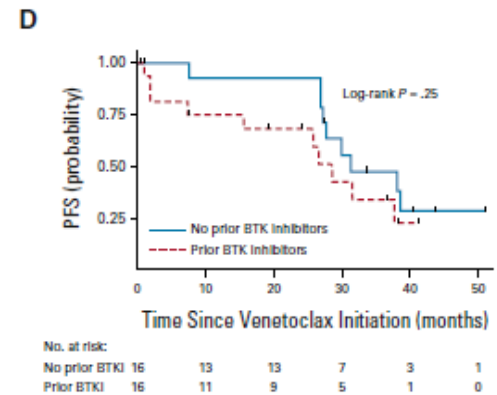
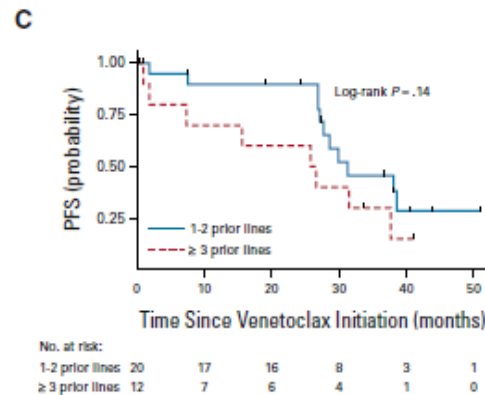
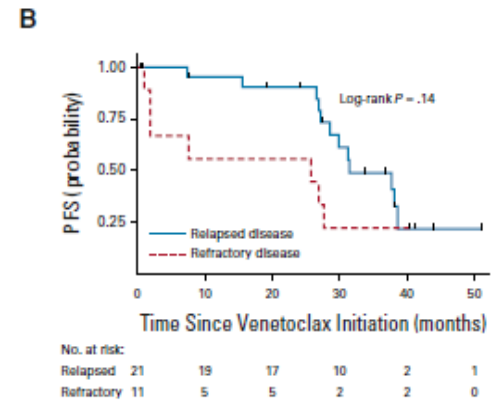
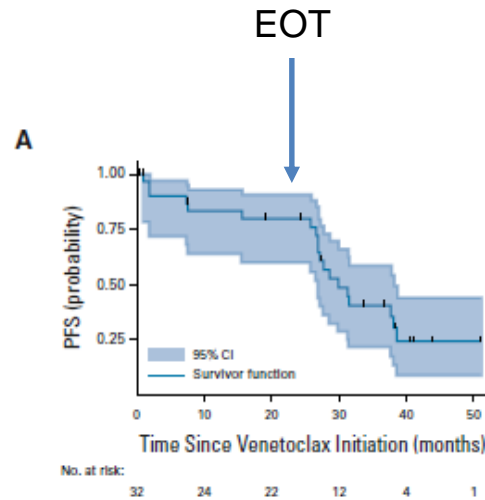
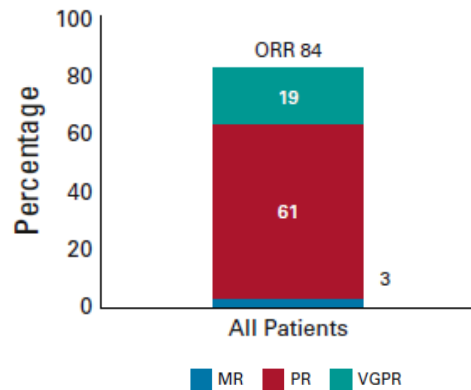
MW- Pistes thérapeutiques ?



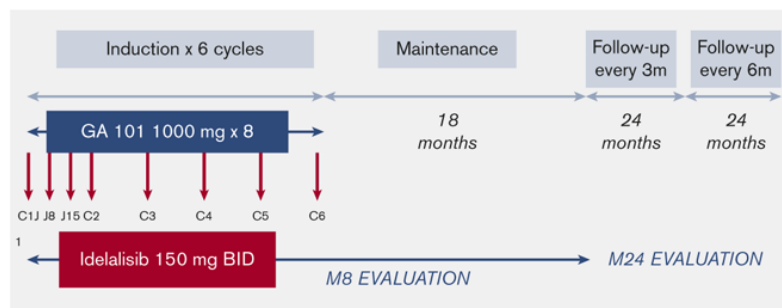
MW - Venetoclax

MW en rechute/réfractaire
n=32

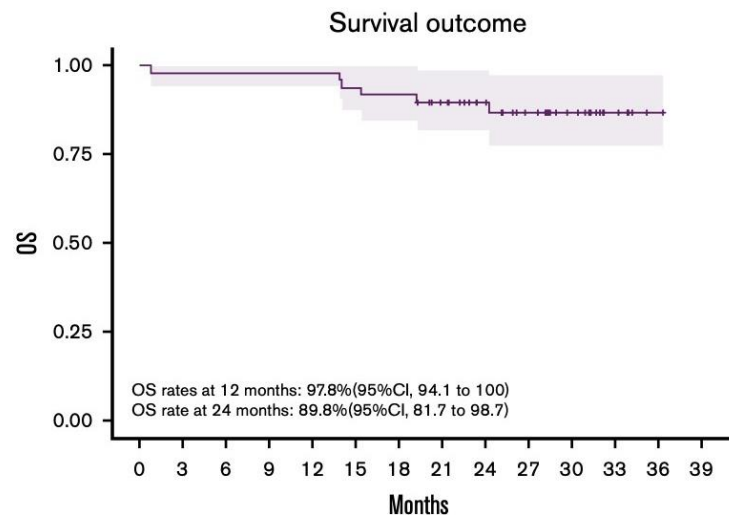
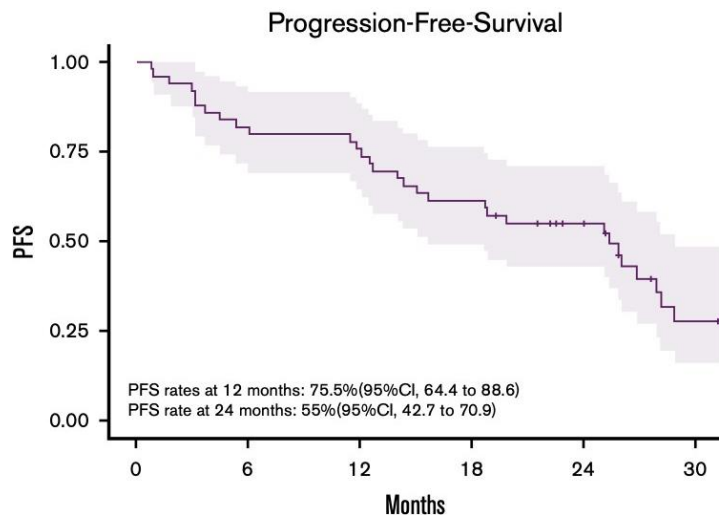
Prior therapies	
Median No. of prior therapies (range)	2 (1-10)
≥ 3 prior therapies, No. (%)	12 (38)
Previous anti-CD20 monoclonal antibodies, No. (%)	28 (88)
Previous proteasome inhibitors, No. (%)	21 (66)
Previous BTKi, No. (%)	16 (50)
Previous chemotherapy, No. (%)	15 (47)
Refractory to most recent therapy, No. (%)	11 (34)



MW - *iPI3K*



Etude FILO phase 2 ouverte sur 49 patients R/R



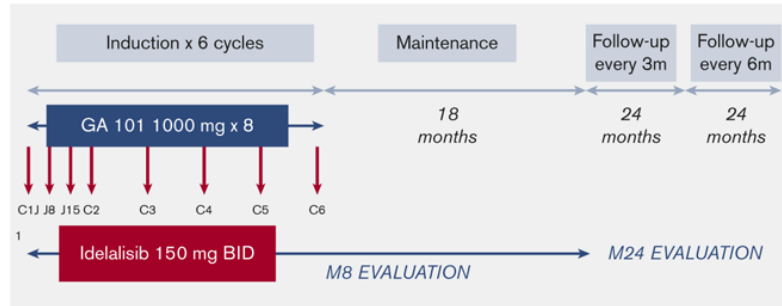
Suivi médian : 26 mois

Tolérance :

- Arrêt définitif pour EI : 26 (53%) après 3 cycles (médiane)
- Réduction de dose : 21 (43%)

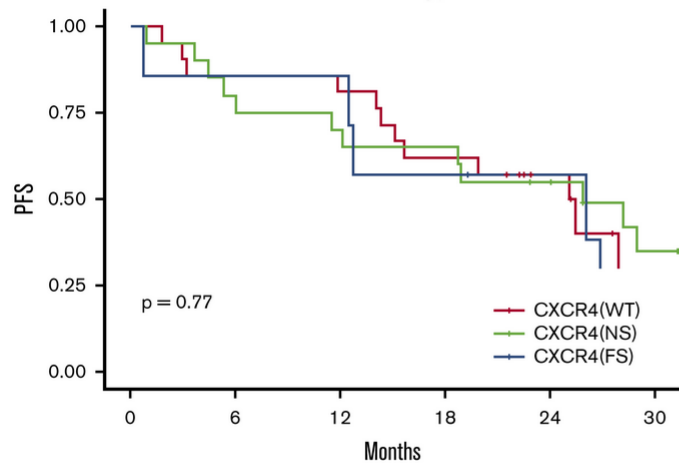
	PFS	OS
Médiane	25.4	NE
12 mois	75.5%	97.8%
24 mois	55%	89.8%

MW - iPI3K



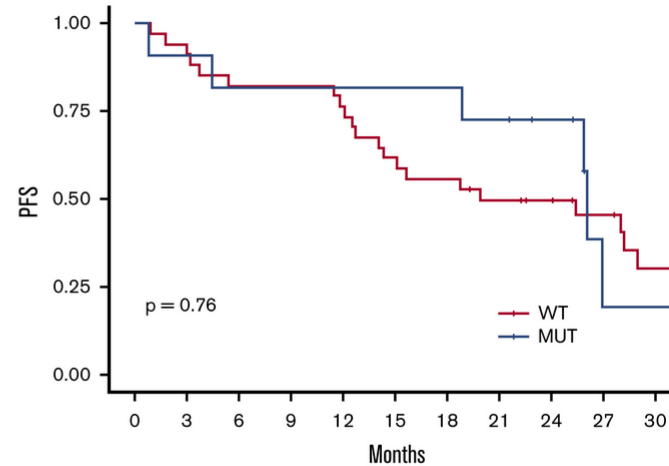
Etude FILO phase 2 ouverte sur 49 patients R/R

Progression-free survival according to CXCR4 mutational status and type of CXCR4 mutations



	No. at risk	0	6	12	18	24	30
CXCR4(WT)	21	18	17	13	8	2	
CXCR4(NS)	20	16	14	13	10	5	
CXCR4(FS)	7	6	6	4	3	0	

Progression-free survival according to TP53 mutational status

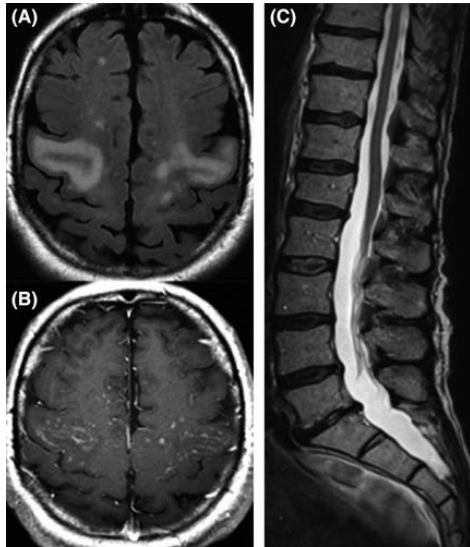


	No. at risk	0	3	6	9	12	15	18	21	24	27	30
WT	34	31	28	28	26	21	19	16	14	11	6	
MUT	11	10	9	9	9	9	9	8	6	1	1	

Macroglobulinémie de Waldenström (MW)

- *Généralités*
- *Des questions biologiques*
 - *lymphomagénèse ? hiérarchie clonale ? cellule d'origine ?*
 - *anomalies (cyto)génétiques : impact pronostique ? prédictif ?*
- **Des questions cliniques**
 - *immunochimiothérapie versus thérapies ciblées ?*
 - **formes cliniques particulières / gammopathies de signification clinique ?**

Syndrome Bing-Neel



● Non-Hodgkin Lymphoma

ARTICLE

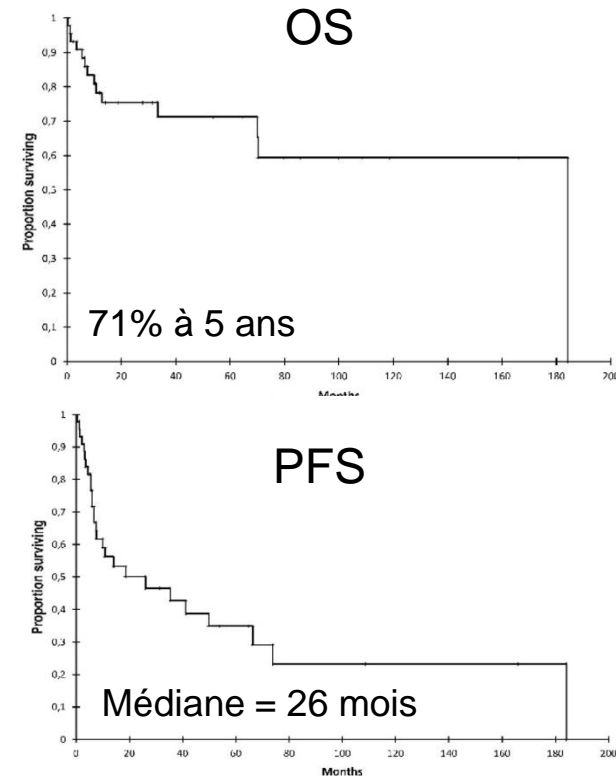


Bing-Neel syndrome, a rare complication of Waldenström macroglobulinemia: analysis of 44 cases and review of the literature. A study on behalf of the French Innovative Leukemia Organization (FILO).

Laurence Simon,¹ Aikaterini Fitsiori,² Richard Lemal,³ Jehan Dupuis,⁴ Benjamin Carpentier,⁵ Laurys Boudin,⁶ Anne Corby,⁷ Thérèse Aurran-Schleinitz,⁸ Lauris Gastaud,⁹ Alexis Talbot,¹⁰ Stéphane Leprêtre,¹¹ Béatrice Mahe,¹² Camille Payet,¹³ Carole Soussain,¹⁴ Charlotte Bonnet,¹⁵ Laure Vincent,¹⁶ Séverine Lissandre,¹⁷ Raoul Herbrecht,¹ Stéphane Kremer,² Véronique Leblond,¹⁸ and Luc-Matthieu Fornecker¹

First-line regimens	Responses
Methotrexate HD	
Alone (+/- R)	1 CR (with radiotherapy), 3 PR, 2 PD
+ cytarabine HD	2 PR, 1 PD
+ cytarabine HD + CVP	1 PR
+ CHOP (+/-R)	2 CR, 3 PR (including 1 ASCT)
+ vincristine-procarbazine	1 PD
+ BVP	1 PD
+ CAP	1 PD
Cytarabine HD	
+ DHAP/C + R	2 CR (including 2 ASCT), 1 PR
+ ifosfamide + R	1 CR (including 1 ASCT), 1 PR
Fludarabine (+/-R)	2 CR, 1 PD
+ cyclophosphamide (+/-R)	2 PR, 1 PD
Intrathecal chemotherapy alone	1 PR, 1 PD
+ R	1 CR
+ ASCT	1 PR
Rituximab alone	1 PR
CD (+/-R)	2 PD
Bendamustine +R	1 PR (with radiotherapy)
CHOP (+/-R)	2 CR (including 1 ASCT)

ORR 1L 70%



Syndrome Bing-Neel

Drugs crossing the Blood Brain Barrier

- Fludarabine
- Bendamustine
- High dose MTX (> 1g/m²) +/- AraC
- iBTK (ibrutinib, zanubrutinib)
- Autologous SCT (BEAM, Thiotepa-based)
 - OS rate after BNS diagnosis was 84% at 5 years and 63% at 10 years.
 - PFS rate after BNS diagnosis was 65% at 10 years.

Conclusion

- Pathogénèse MW = multi-étapes
- Rôle des anomalies intrinsèques et extrinsèques à la cellule tumorale
- Meilleure compréhension : développement pistes thérapeutiques

- Clinique très variable (de MGCS à lymphoma-like)
- Seules les MGCS / **MW symptomatiques** sont à traiter
- **ICT** reste le traitement de choix en 1L (RDC, R-Bendamustine)
- **iBTK** : place de choix en rechute, à définir en 1L

- **Thérapie guidée par les anomalies moléculaires / cytogénétiques ?**

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