Maladie de Waldenström

Véronique Leblond

18 èmes Rencontres de Recherche Clinique du FILO

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FRENCH INNOVATIVE
LEUKEMIA ORGANIZATION

Disclosures

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- **MSD**
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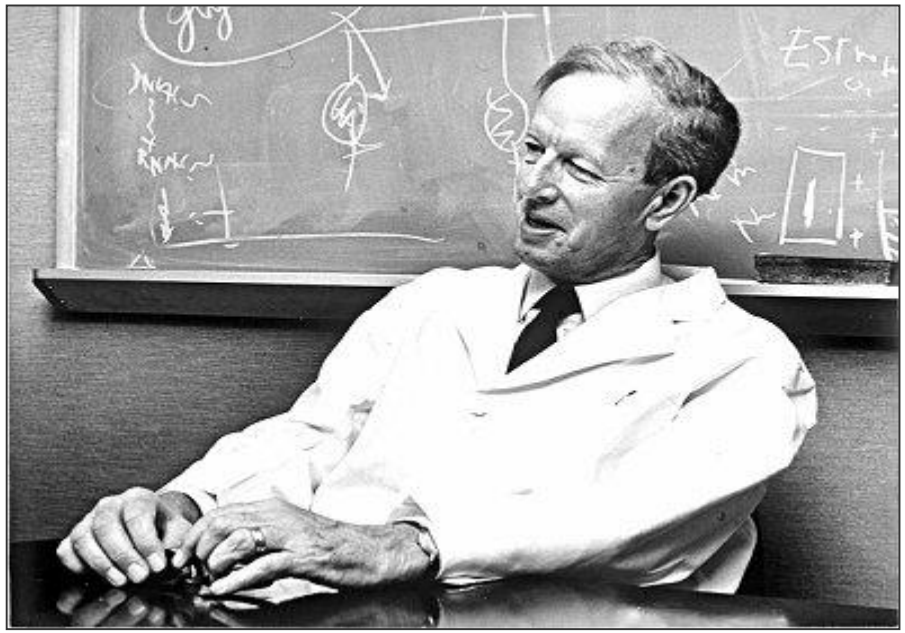
- **Beigene**
- **Lilly**

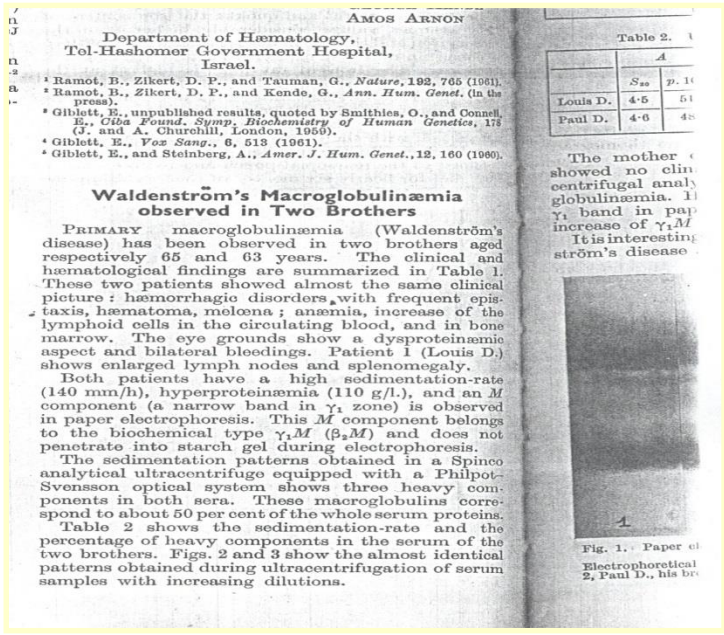
Maladie de Waldenström (MW)



Waldenström's macroglobulinemia

- Rare chronic B lymphoproliferative disorder: 3.4 per million person-years at risk in males, 1.7 in females
- Incidence rises over 75 yrs: 36.3 in males, 16.4 in females
- 2% of malignant blood diseases
- Median age: 72 yrs
- May be a genetic predisposition: family clusters are seen

Waldenström's macroglobulinemia
Genetic predisposition: familial clusters



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[2] Ramot, B., Zikert, D. P., and Kende, G., *Ann. Hum. Genet.* (in the press).
[3] Giblett, E., unpublished results, quoted by Smithies, O., and Connell, E., *Ciba Found. Symp. Biochemistry of Human Genetics*, 175 (J. and A. Churchill, London, 1959).
[4] Giblett, E., *Vox Sang.*, 6, 513 (1961).
[5] Giblett, E., and Steinberg, A., *Amer. J. Hum. Genet.*, 12, 160 (1960).

Waldenström's Macroglobulinæmia observed in Two Brothers

PRIMARY macroglobulinæmia (Waldenström's disease) has been observed in two brothers aged respectively 65 and 63 years. The clinical and hæmatological findings are summarized in Table 1. These two patients showed almost the same clinical picture: hæmorrhagic disorders, with frequent epistaxis, hæmatoma, melœna; anæmia, increase of the lymphoid cells in the circulating blood, and in bone marrow. The eye grounds show a dysproteinæmic aspect and bilateral bleedings. Patient 1 (Louis D.) shows enlarged lymph nodes and splenomegaly.

Both patients have a high sedimentation-rate (140 mm/h), hyperproteinæmia (110 g/l.), and an *M* component (a narrow band in γ_1 zone) is observed in paper electrophoresis. This *M* component belongs to the biochemical type $\gamma_1 M$ ($\beta_2 M$) and does not penetrate into starch gel during electrophoresis.

The sedimentation patterns obtained in a Spinco analytical ultracentrifuge equipped with a Philpot-Svensson optical system shows three heavy components in both sera. These macroglobulins correspond to about 50 per cent of the whole serum proteins.

Table 2 shows the sedimentation-rate and the percentage of heavy components in the serum of the two brothers. Figs. 2 and 3 show the almost identical patterns obtained during ultracentrifugation of serum samples with increasing dilutions.

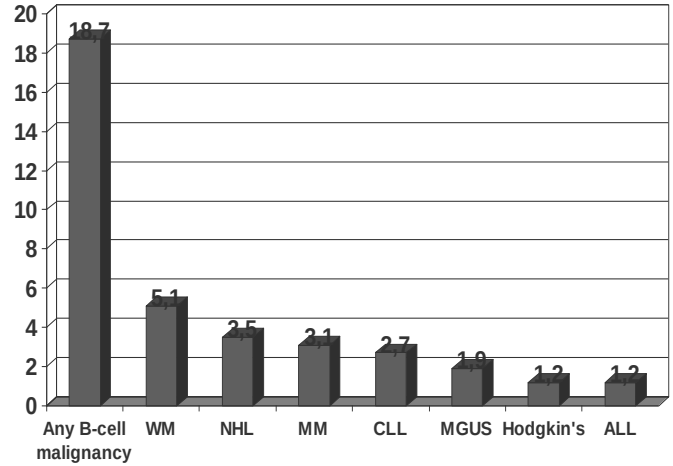
Table 2.

	A	
	S_{20}	p.
Louis D.	4·5	5
Paul D.	4·6	4

The mother showed no clin centrifugal analy globulinæmia. 1 γ_1 band in pap increase of $\gamma_1 M$ It is interestin strom's disease

Fig. 1. Paper el

Electrophoretical 2, Paul D., his br



N=492

Treon et al, *Ann Oncol* 2005

N=2144 LPL/WM

Pitié-Salpêtrière: 492 families

CLL	NHL	HL	WM	MM	HCL
208 (114)	161(49)	87(26)	99(41)	63(12)	8(3)

41 families with only WM cases

First - degree relatives
WM X 20
NHL X 3
CLL X 3.4
MGUS X 5

Krinstinsson S et al, Blood 2008

Critères diagnostiques

DOI: 10.1002/ajh.25292

WILEY AJH

ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

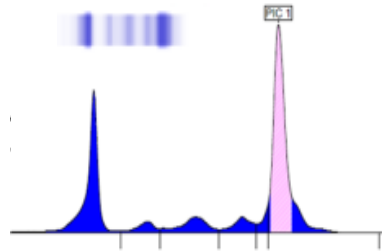
Waldenström macroglobulinemia: 2019 update on diagnosis, risk stratification, and management

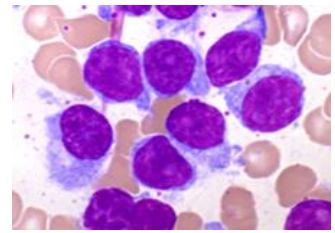
Morie A. Gertz

TABLE 1 Definitions of IgM-related phenomenon in Macroglobulinemia

	IgM monoclonal component	Symptoms of tumor mass/infiltration (Adenopathy anemia)	Marrow infiltration >10%	IgM-mediated symptoms
MGUS	+	–	–	–
Smoldering macroglobulinemia	+	–	+	–
IgM-related disorder (eg, cold agglutinin hemolytic anemia, type II cryoglobulin, neuropathy, amyloidosis)	+	–	±	+
Macroglobulinemia	+	+	+	±

Abbreviations: IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; +, positive; –, negative; ±, equivocal.



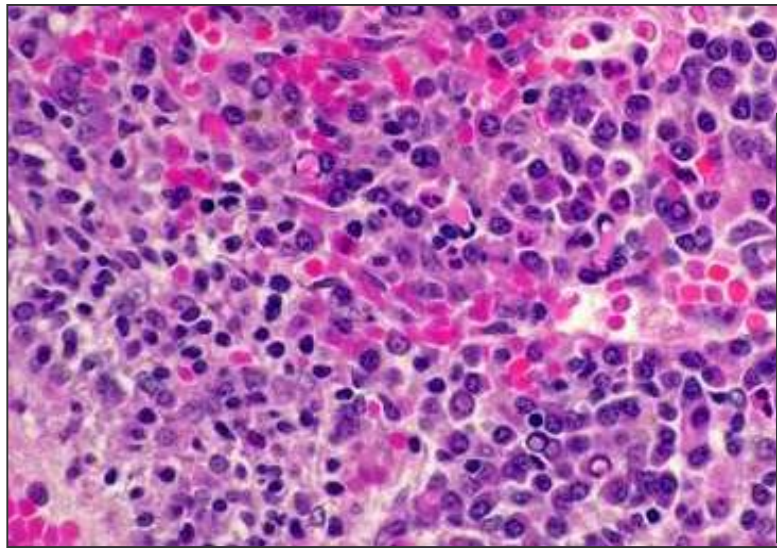


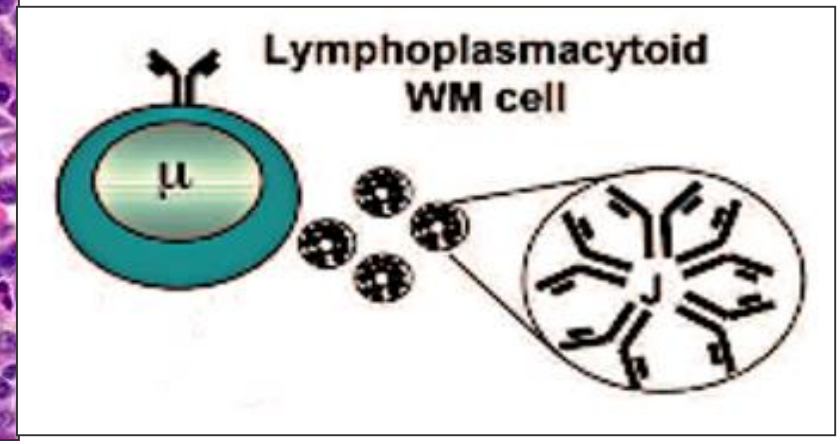
MW - Définition

- **Lymphome B indolent,** syndrome **lymphoprolifératif B** chronique
- **Lymphome lympho-plasmocytaire**
- Définie par (critères OMS 2018) :

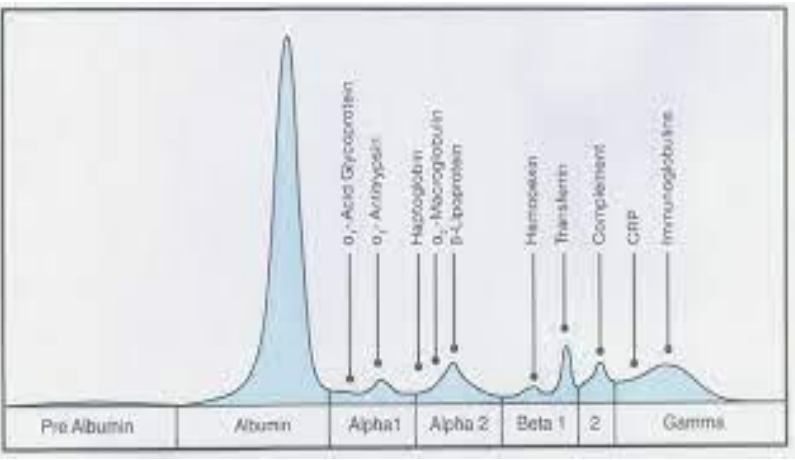
  1- Infiltration de la moelle osseuse (≥ 10% lymphocytes B, lympho-plasmocytes, plasmocytes) (+/- ganglions, rate)

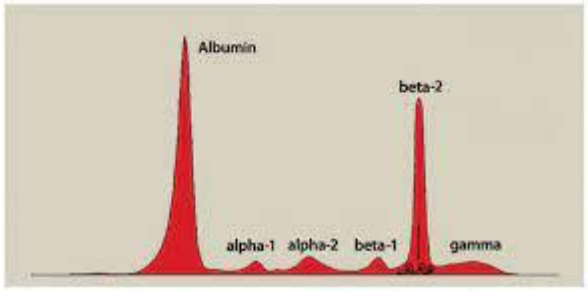
  2- Sécrétion anticorps/IgM monoclonale, quelque soit son taux (

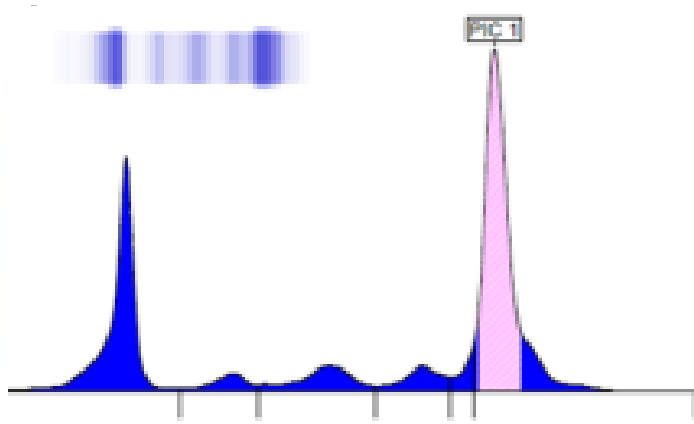




Quantification de l'immunoglobuline monoclonale







Selon les protéines, les valeurs de référence doivent se situer entre :

- Albumine : 55 et 65 % soit 36 et 50 g / L ;
- Alpha1 - globulines : 1 et 4 % soit 1 et 5 g / L ;
- Alpha 2 - globulines : 6 et 10 % soit 4 et 8 g/ L ;
- Beta - globulines : 8 et 14 % soit 5 et 12 g / L ;
- Gamma globulines 6 à 12g/litre

IgG 7-16g/l
IgA 0,7-4 g/l
IgM:0,4-2,3g/l

La quantification de l'immunoglobuline monoclonale est directement réalisée sur l'électrophorèse des protéines par la mesure de l'aire sous la courbe. Remarque : le dosage des immunoglobulines (anciennement appelé « dosage pondéral des immunogloblulines ») ne doit pas être utilisé pour quantifier une immunoglobuline monoclonale. Il permet seulement de doser des immunoglobulines polyclonales résiduelles

Quantification du pic 25 g sur l électrophorèse et 40 g /l sur le dosage pondéral

Essential evaluation of patients with Waldenström Macroglobulinemia.

Castillo J, Br J Haematol 2016

For everybody

- **History & physical examination Include funduscopic examination**
- **Laboratory studies:**
- **Complete blood count**
- **Complete metabolic panel**
- **Serum immunoglobulin levels (IgA, IgG, IgM)**
- **Serum and urine electrophoresis with immunofixation**
- **Serum beta-2-microglobulin level**

If clinically indicated

- **Cryoglobulins**
- **Cold agglutinin titer**
- **Von Willebrand screening**
- **24-hour urine protein quantification**
- **Lumbar puncture**
- **Anti Nerve antibodies**
- **Free light chains**
- **NT proBNP/ Troponin**

Essential evaluation of patients with Waldenström Macroglobulinemia.

Castillo J, Br J Hematol 2016

Bone marrow aspiration and biopsy

- **Immunohistochemistry**
- **Flow cytometry**
- **Include testing for MYD88 L265P gene mutation**
- **Cytogenetic profile ?**

Computed tomography scans of the chest, abdomen and pelvis with IV contrast In patients being considered for therapy

Both WM and MZL express pan-B cell markers (CD19, CD20, CD22), but expression weaker in WM. sIgM expression higher in WM; marked predominance of K vs L in WM

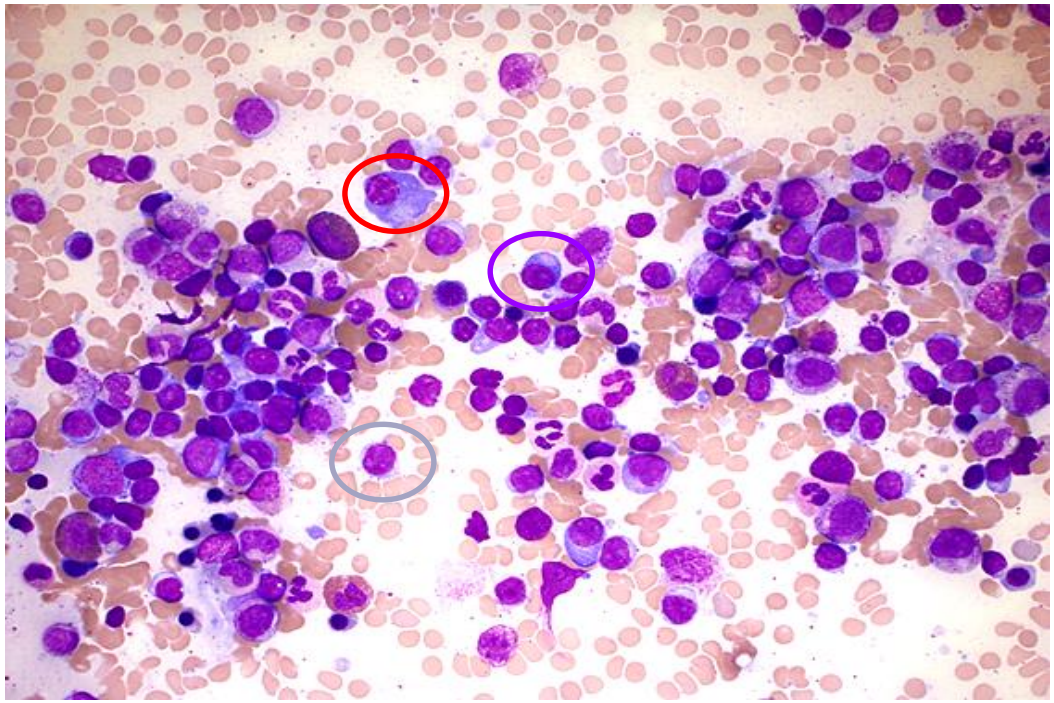
CD5, CD23, CD103, and CD10 typically negative in WM

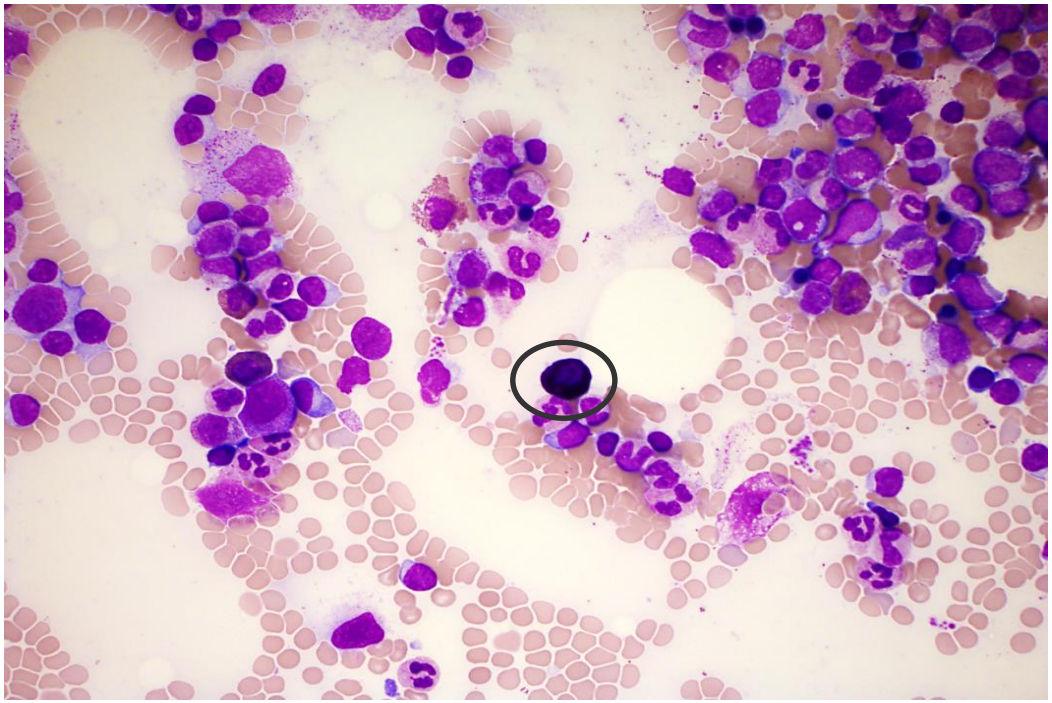
CD11c is + in 33% of WM *vs* 70% of MZL. CD25 expressed in most WM cases, whereas only in ~50% MZL CD305 upregulated in MZL, usually negative in WM.

Myélogramme

Infiltration lymphocytaire, lymphoplasmocytaire (en proportion variable) et plasmocytaire (minoritaires)

Plasmocytes Lymphoplasmocytes

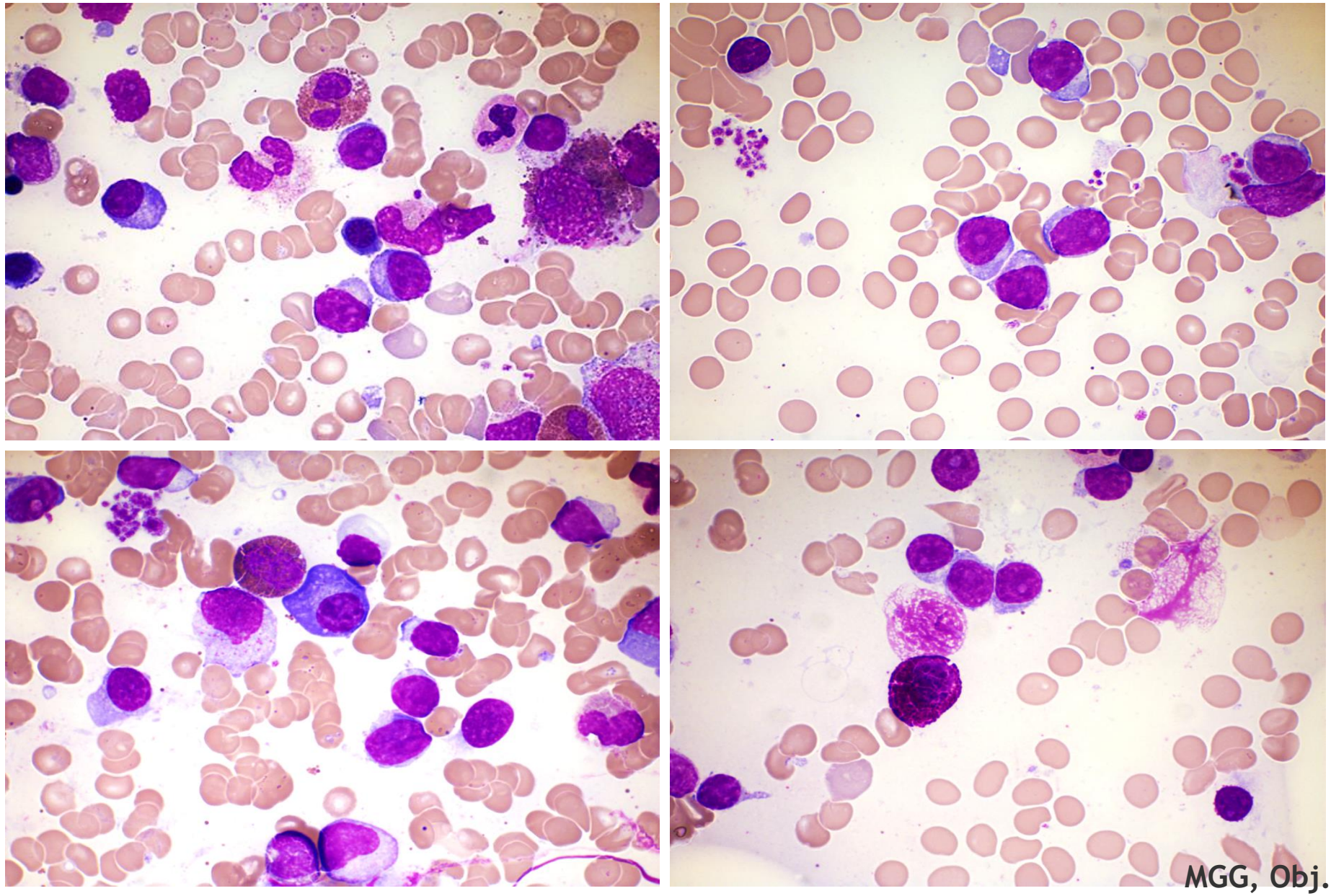




Lymphocytes

Mastocytes

MGG, Obj. 50

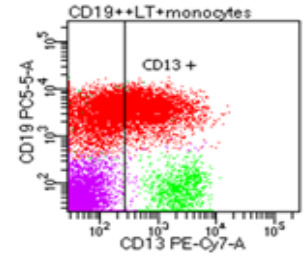


MGG, Obj. 100

Immunophénotypage

« La » cellule de MW : composant lymphoplasmocytaire + plasmocytaire

- Clone lymphocytaire/lymphoplasmocytaire B
  Expression constante des marqueurs pan-B : CD19, CD20, CD22 avec l'expression de l'IgM de surface
  et une restriction isotypique (Kappa ou Lambda)
  Particularité : prédominance ++ des cas monotypiques Kappa / autres SLPB
  → ratio cas κ/cas λ : 5/1
  Score de Matutes <3
  CD22+ faible (81% des cas) - distinction des lymphocytes B matures
  CD25+ CD79b+ CD81+ CD24+
  Expression hétérogène : CD27 (51%), CD38 (50%), CD200 (62%), FMC7 (70%)
  CD5- CD11c- CD23- CD10-
  CD103- CD305-



Owen RG et al. Hematological oncology. 2000
San Miguel JF et al. Semin Oncol. 2003
Paiva B et al. Leukemia. 2014

- Origine de la cellule de Waldenström : lymphocyte B activé CD25+ CD22+faible

→ Phénotype $CD22^{faible}CD25^{+}$: "hallmark" de MW
même si pas entièrement spécifique (LZM et LLC)

Paiva B et al. Blood. 2015

- Composant plasmocytaire monoclonal CD38+CD138+, sans les aberrations antigéniques myélomateuses
  et de même restriction isotypique, CD19+, CD45+, CD56-, souvent CD20+

Chromosomal aberrations and their prognostic value in a series of 174 untreated patients with Waldenström's macroglobulinemia

Table 1. Summary of cytogenetic findings in 174 WM patients.

Successful karyotyping	141/172 (82%)°
Abnormal karyotype	66/141 (47%)
Abnormalities (K)[§] (n=141)	
Median	0
Mean	1.1
Range	0-11
Abnormalities (K)* (n=66)	
Median	1.5
Mean	2.4
Range	1-11
Complex karyotype*	20/66 (30%)
Translocation*	23/66 (35%)
Sex chromosome loss*	20/66 (30%)
6q deletion (K+F)	43/141 (30%)
(K)*	18/66 (27%)
(F)	40/139 (29%)
Trisomy 18 (K+F)	17/117 (15%)
(K)*	8/66 (12%)
(F)	15/117 (13%)
Trisomy 4 (K+F)	11/139 (8%)
(K)*	6/66 (9%)
(F)	10/139 (7%)
Trisomy 12 (K+F)	6/140 (4%)¤¤
(K)*	5/66 (8%)
(F)	5/140 (4%)
13q14 deletion (F)[§]	19/145 (13%)
17p13 (*TP53*) deletion (F)[§]	11/140 (8%)
11q22 (*ATM*) deletion (F)[§]	10/139 (7%)
14q32 (*IGH*) translocation (F)[§]	3/129 (2%)¤
Abnormalities (F) (n=113)	
Median	1
Mean	0.8
Range	0 - 5
Abnormalities (K+F) (n=97)[§§]	
Median	1
Mean	1.4
Range	0-11

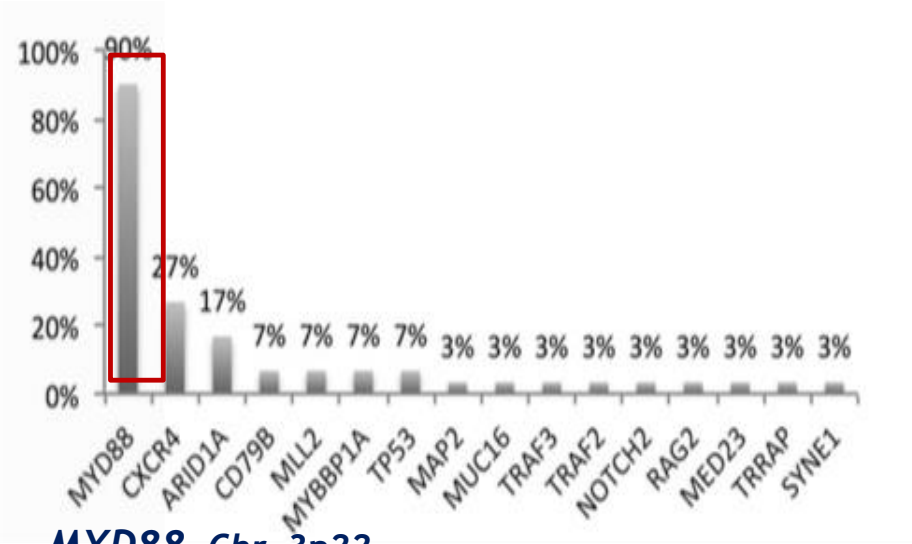
*WM: Waldenström's macroglobulinemia: °Karyotyping was performed in 172 of 174 patients. *In patients with an abnormal karyotype. K: Observed by karyotyping. K +F: observed by karyotyping and/or FISH. F: observed by FISH. [§]Successful karyotype. [§§]Number of patients with successful karyotyping and analysis with all eight FISH probes to detect: 6q, 13q14, 17p13 (TP53), and 11q22 (ATM) deletions, trisomy 18, 4 and 12, and 14q32 (IGH) translocations. ¤One t(14;18)(q32;q21) (involving BCL2) and two unknown partners; there were two normal karyotypes and one failure. [§]Karyotype analyses did not detect additional cases. ¤¤One patient had 4/40 mitoses with trisomy 12 by karyotyping. Trisomy 12 was not observed using FISH.*

Mutational profile in WM – *MYD88*: a diagnostic tool

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

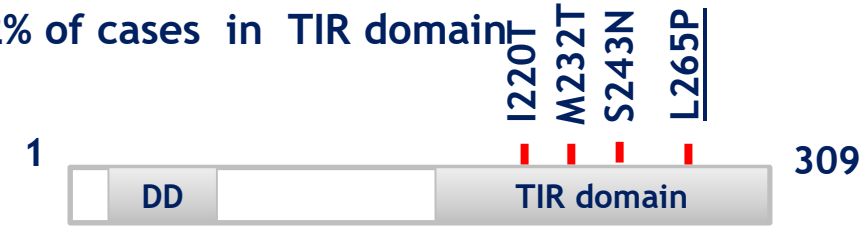
MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia



MYD88 *Chr. 3p22*

Exons 3-4

- L265P in 98% of cases
- In 1-2% of cases in TIR domain



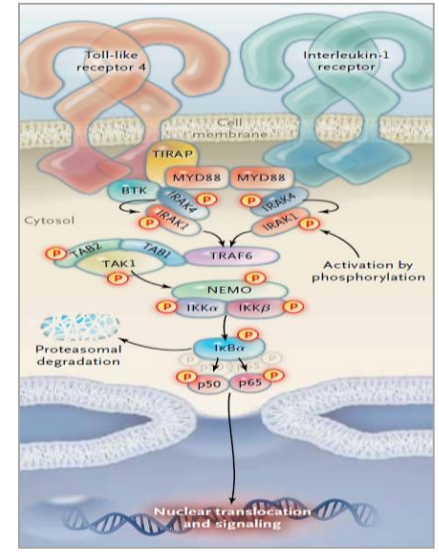
MYD88 L265P **: 90 – 94 %**

Early clonal event

MYD88 **L265P :**

> 90 % WM

- **50 – 80 % MGUS IgM**
- **25 % DLBCL ABC**
- **10 % MZL**

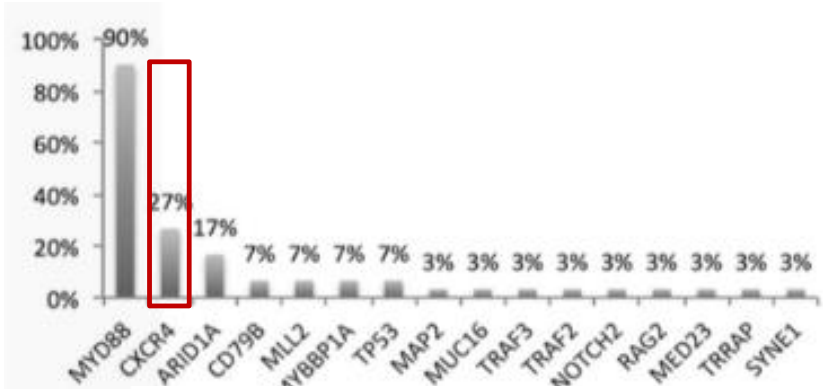


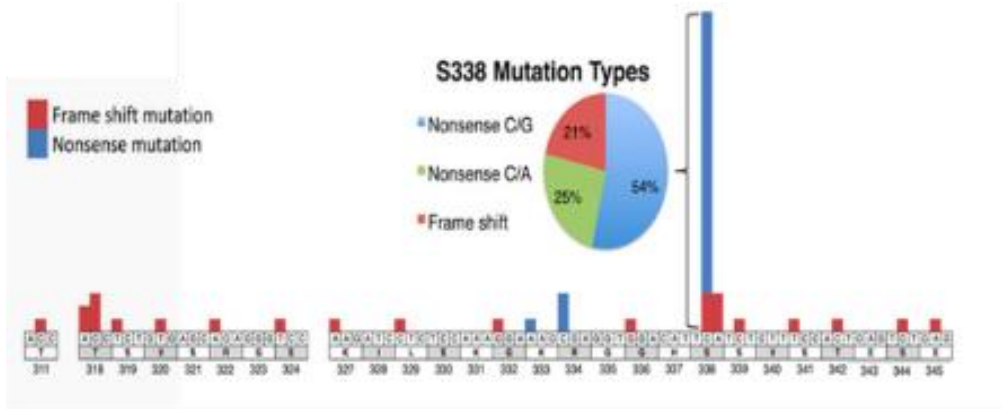
WT *vs* L265P

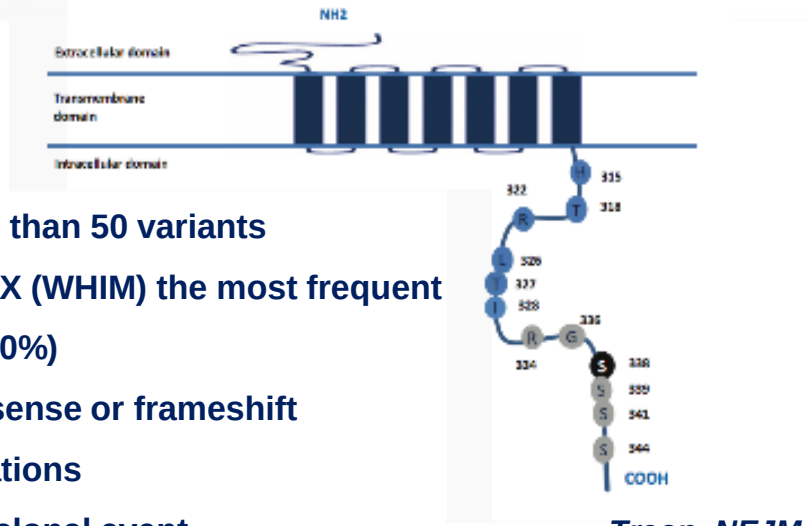
- **F > M (43 *vs* 24 %, p= 0.001)**
- **lymphocytosis > 5 G/L (24 *vs* 5 %, p=0.006)**
- **Bone marrow infiltration (23 *vs* 33 %, p=0.005)**
- **LDH (371 *vs* 265 UI/L, p=0.002)**

Treon, NEJM 2012 ; Jimenez, Leukemia 2013 ; Gachard, Leukemia 2013 ; Xu, Blood 2013 ; Hunter, Blood 2014 ; Poulain, Blood 2014 ; Treon, Blood 2014 ; Cao, Ann Hematol 2017 ; Correa, BJH 2017

CXCR4 mutations are associated with a more agressive phenotype







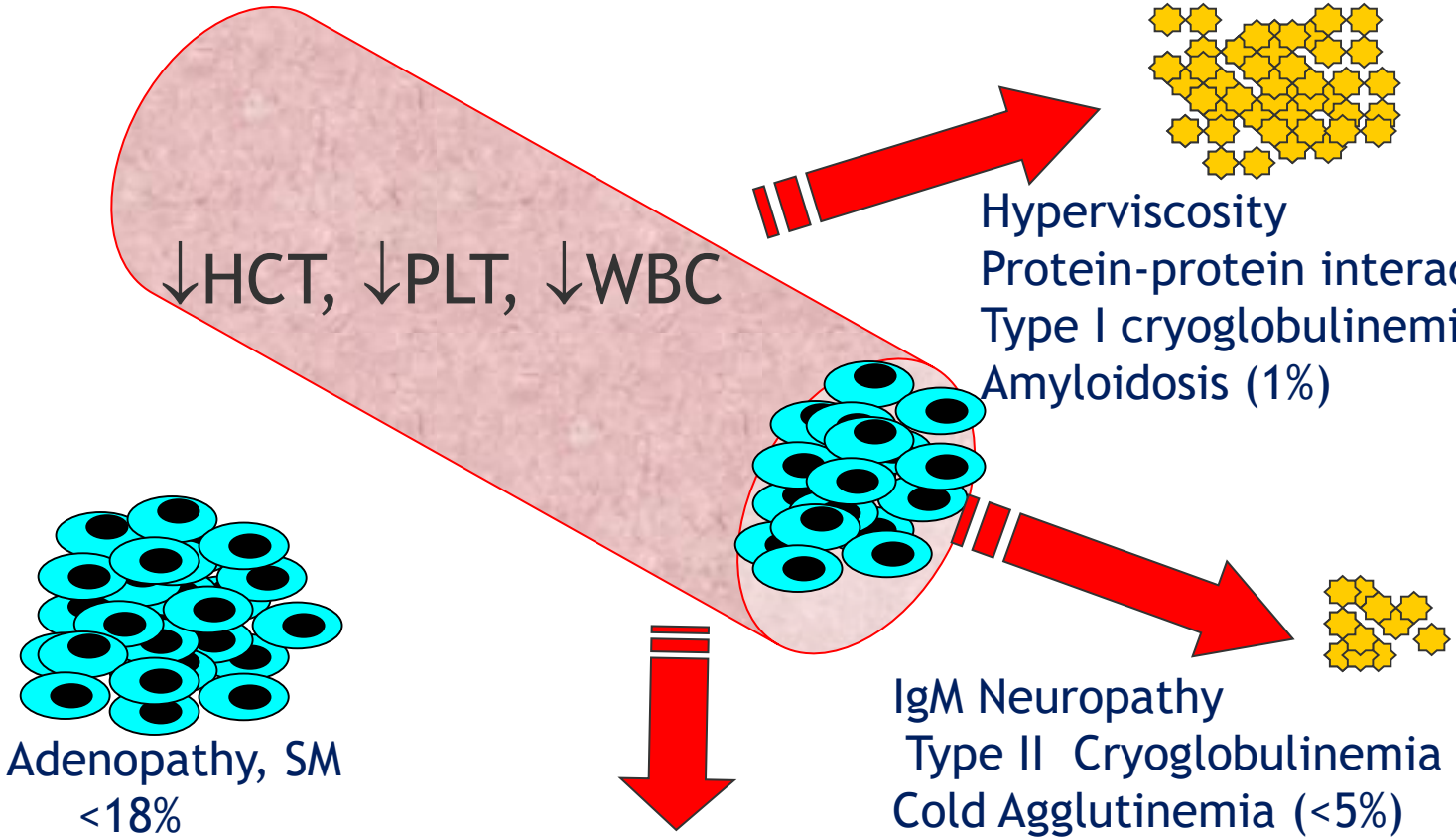
- More than 50 variants
- S338X (WHIM) the most frequent (35-50%)
- Nonsense or frameshift mutations
- Sub clonal event

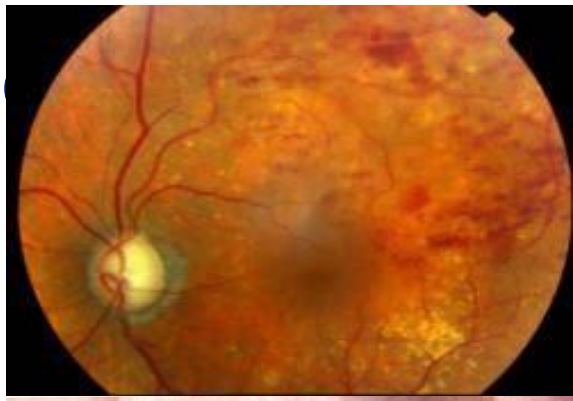
CXCR4 mutations : 25 - 30 %

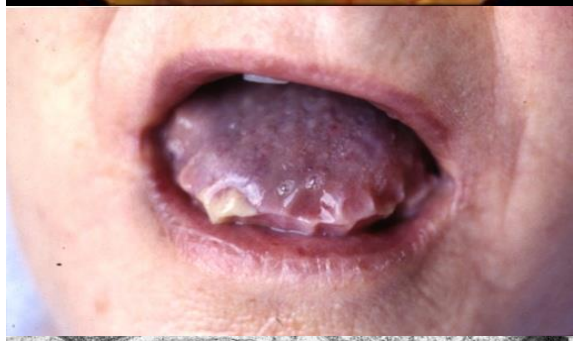
- bone marrow infiltration
- cytopenia
- tumor mass (LN / SM)
- genomic complexicity
- IgM
- more agressive presentation

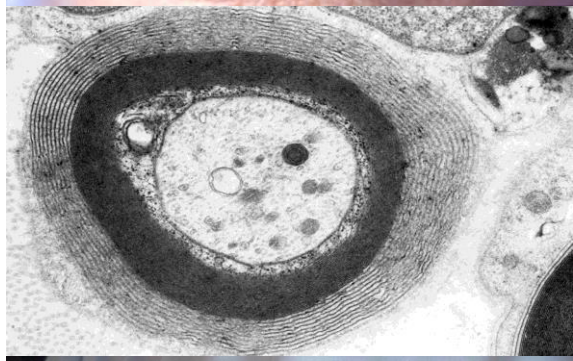
Treon, NEJM 2012 ; Hunter, Blood 2014 ; Treon, Blood 2014 ; Poulain S, Clin Canc Res. 2017

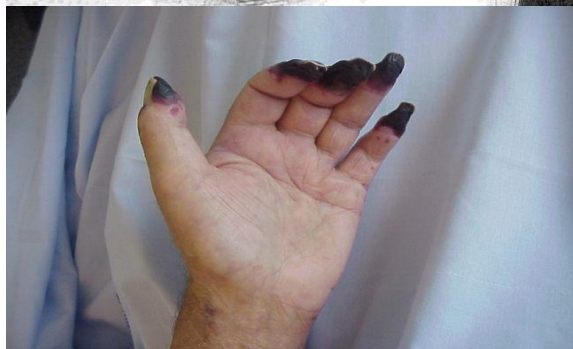
Clinicopathological manifestations Waldenström's macroglobulinemia







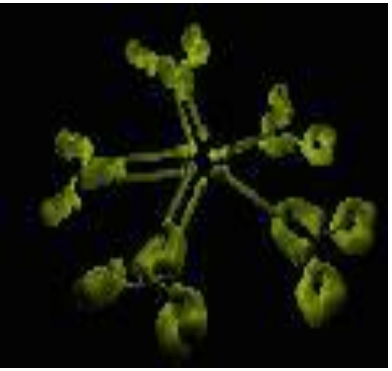




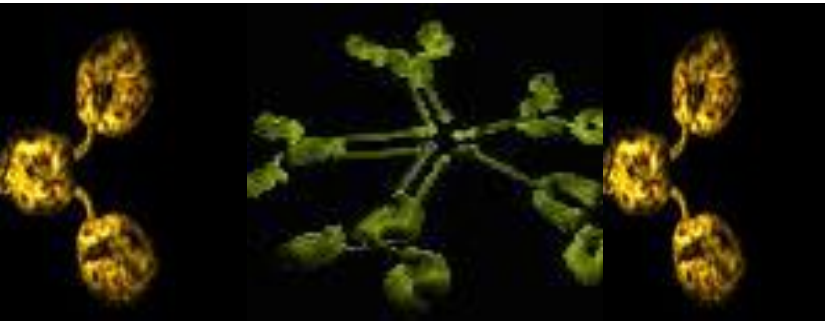
Cryoglobulins: Immunoglobulins that precipate or gel at temperature below 37°C and re-dissolve at 37°C

Type I: physicochemical properties of IgM

(20%)



Type II: Mixed cryoglobulimemia
Immune complexes IgM-IgG:monoclonal IgM anti-IgG (80%)



Clinical Manifestations

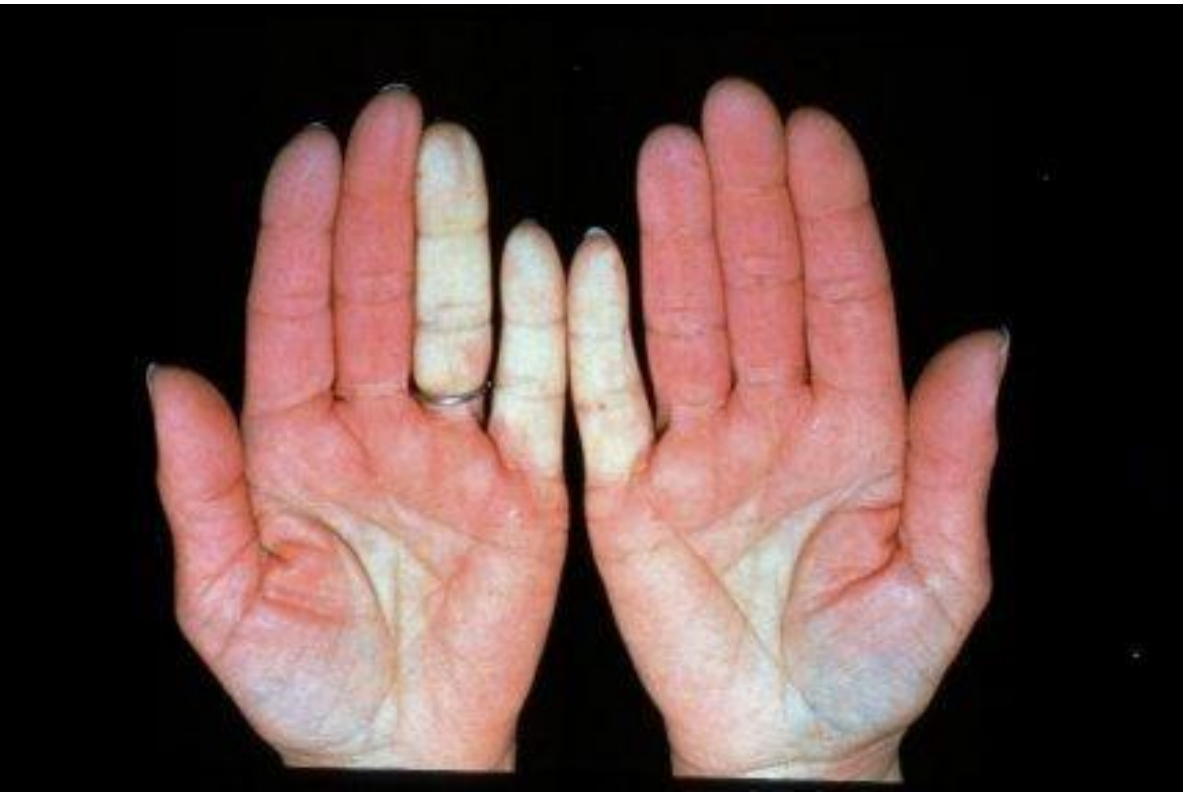
- Fatigue
- Skin (purpura, ulcers, necrosis , acrocyanosis etc..)
- Joint arthralgia
- Neuropathy
- Kidney manifestations

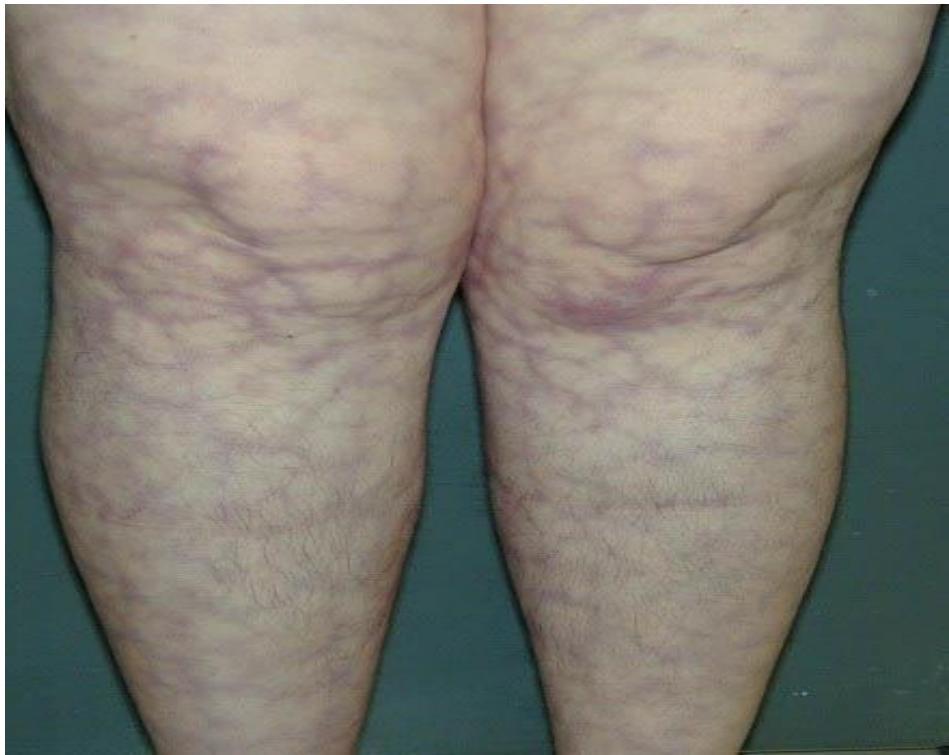
Skin manifestations

Type I : Cold sensitivity

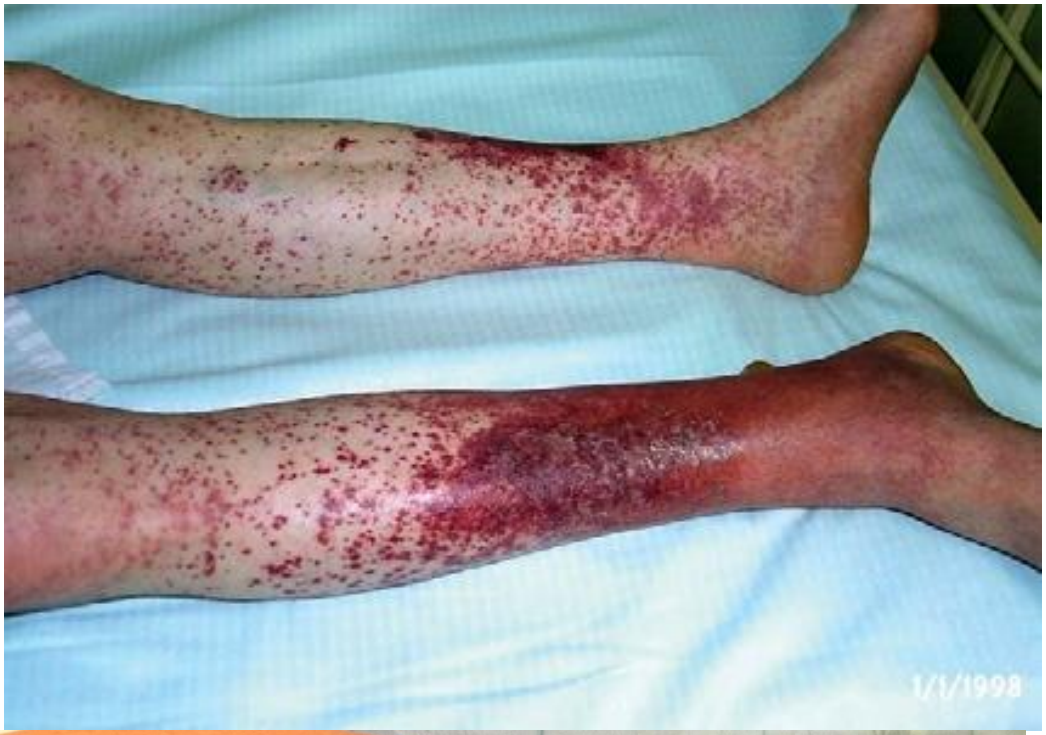
Raynaud phenomenon acrocyanosis

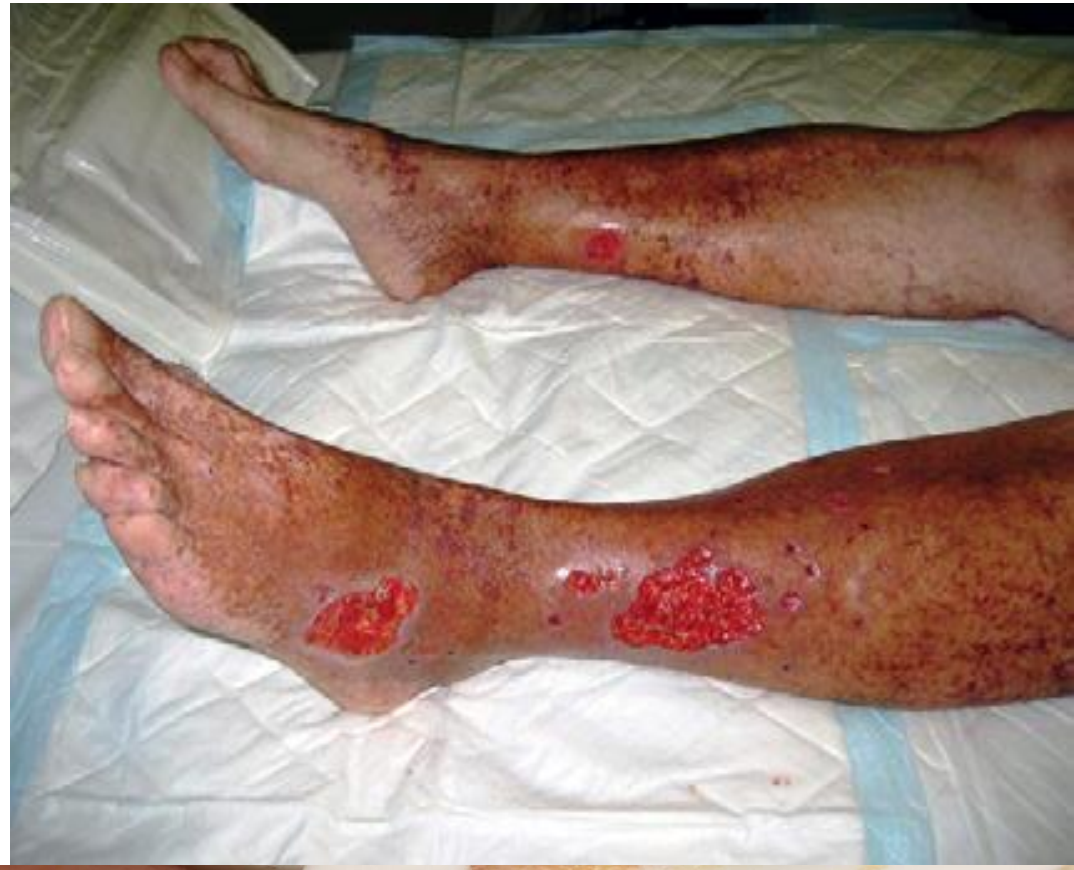
livedo

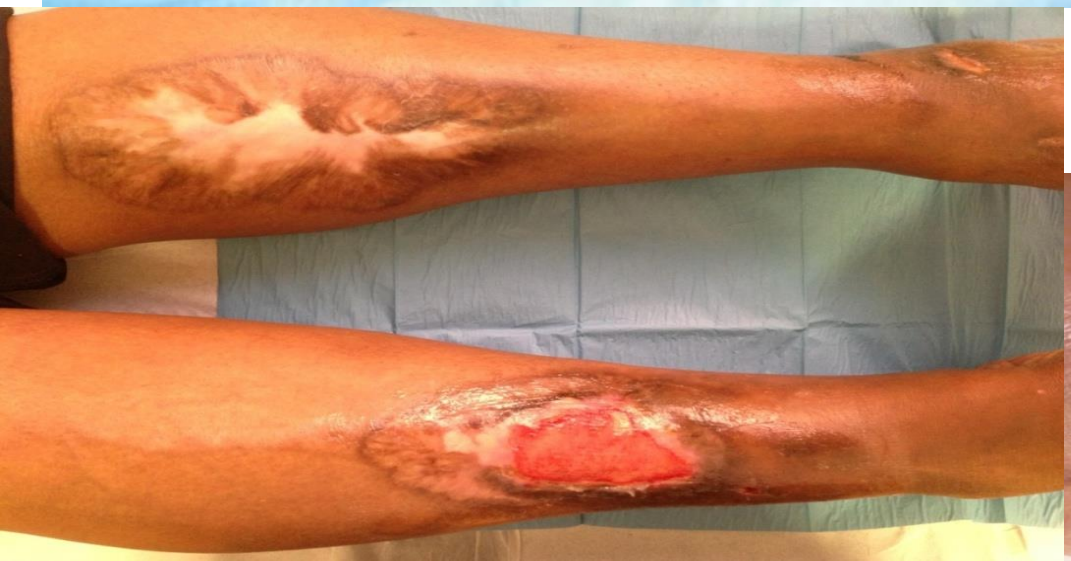


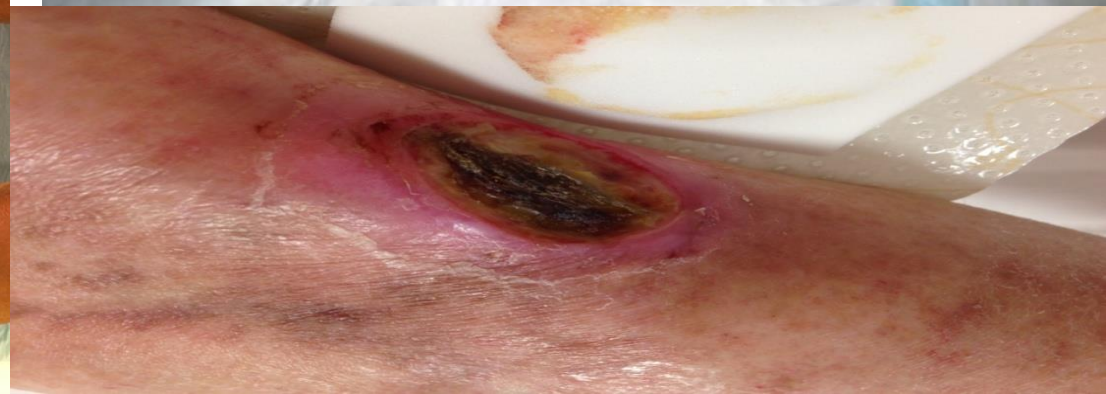


Skin manifestations: purpura, ulcers

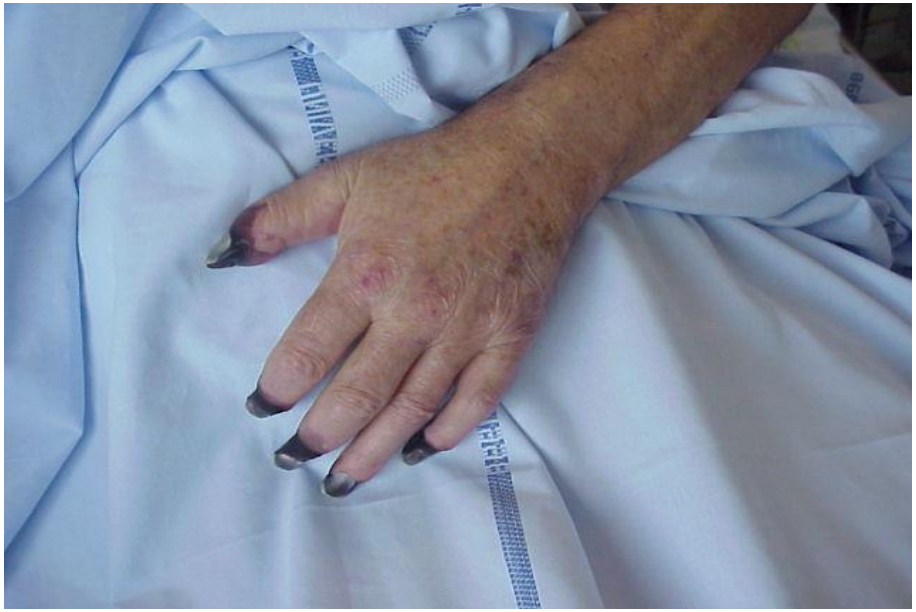


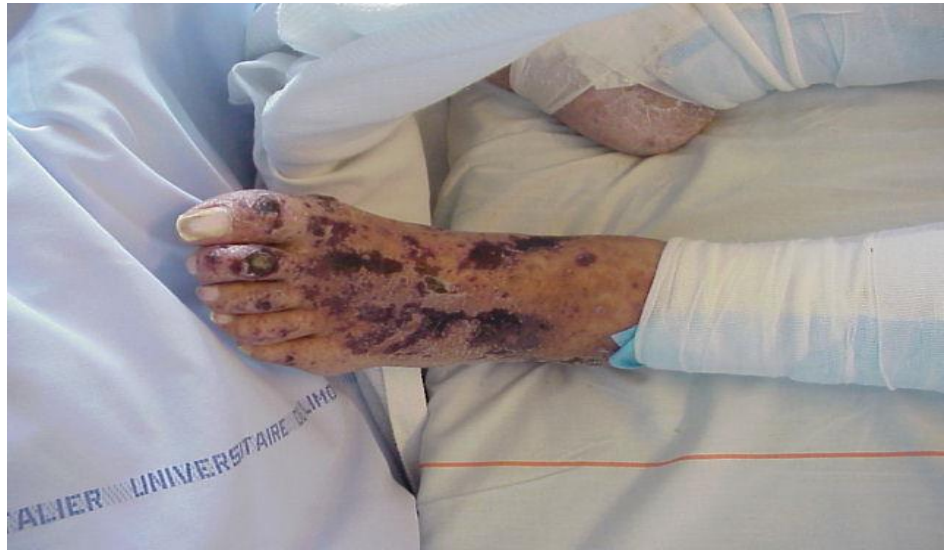


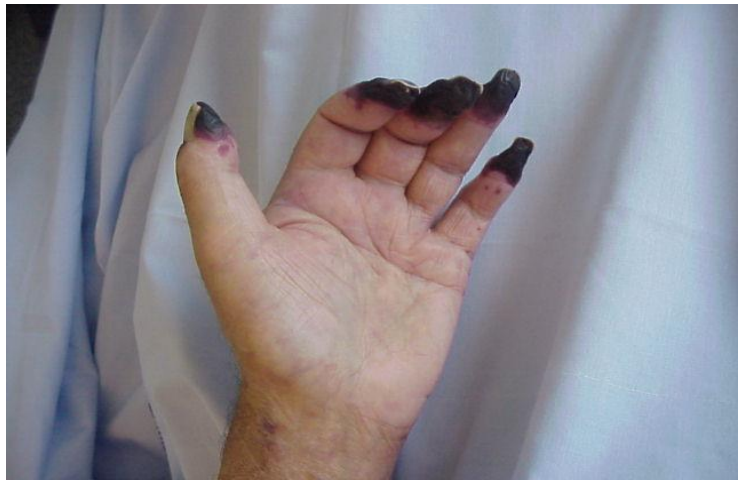


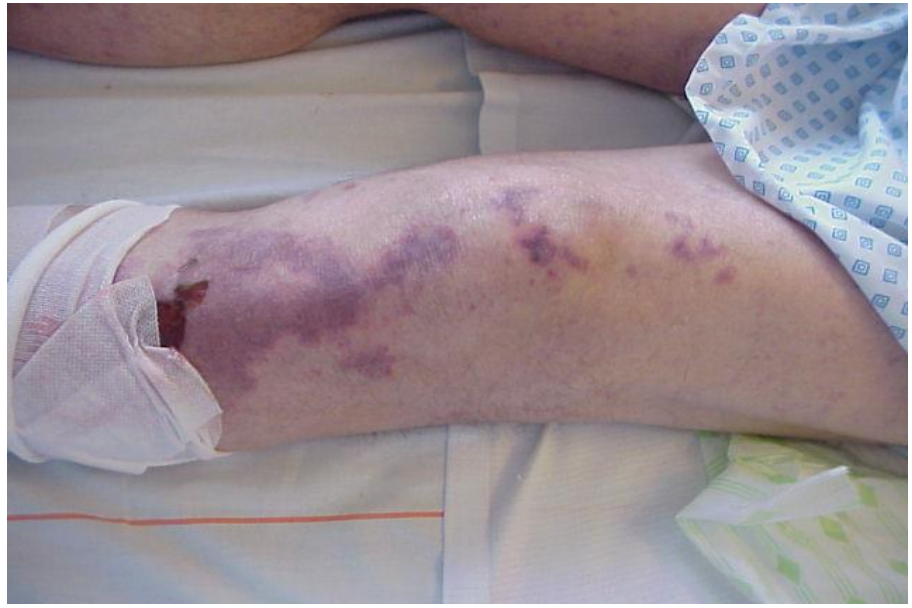


Skin manifestations: purpura, necrosis



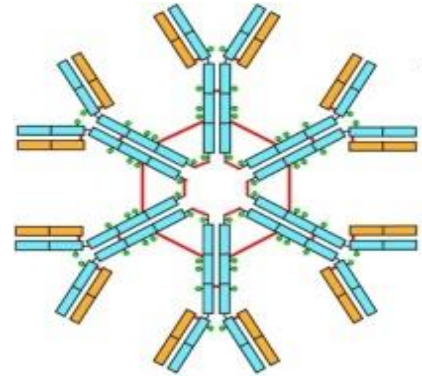






MW- Diagnostic différentiel

- **Pic IgM :**
  - **Maladie de Waldenström**
  - **Lymphome de la zone marginale**
  - **Leucémie lymphoïde chronique**



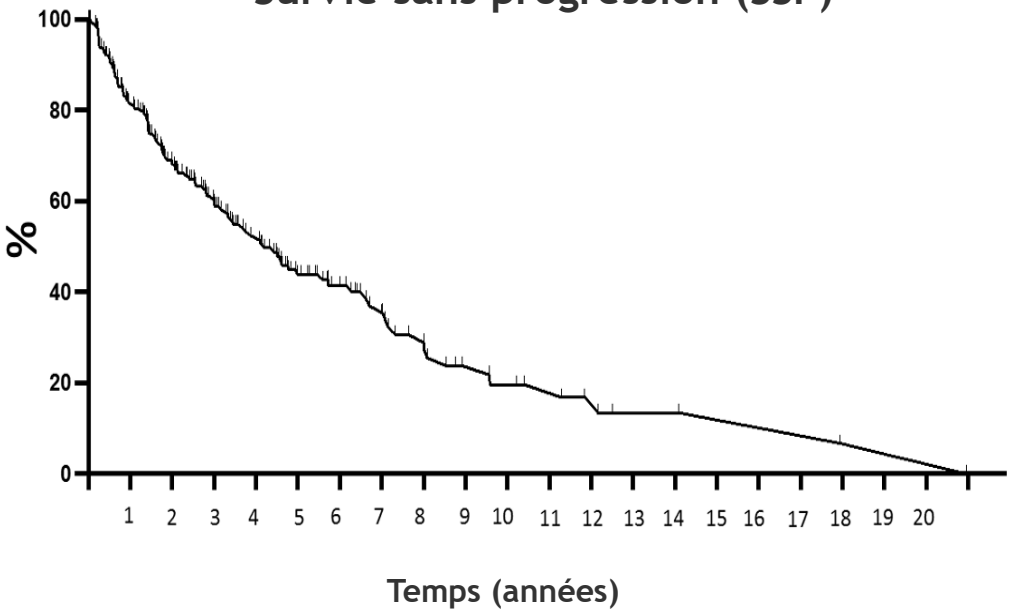
immunophénotypage lymphocytaire

recherche mutation *MYD88* **+++**

Pronostic – *Cohorte globale*

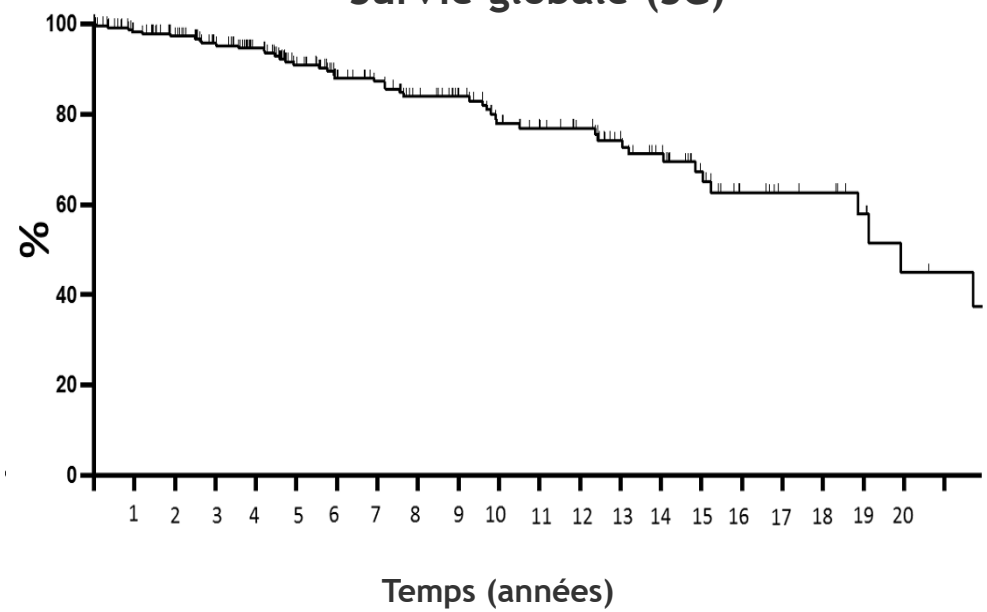
Médiane de suivi : 6 ans

Survie sans progression (SSP)



SSP médiane : 4,25 ans

Survie globale (SG)

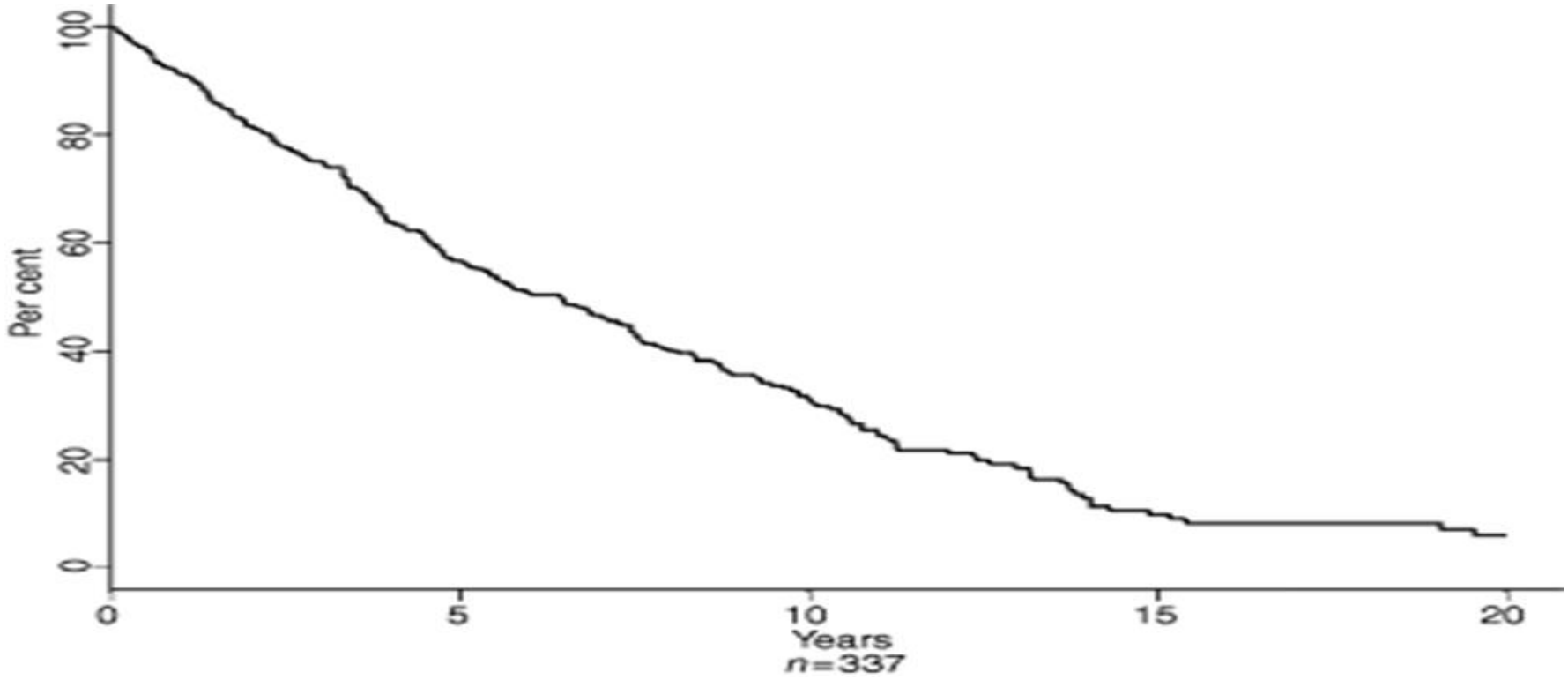


SG à 5 ans : 91%
SG à 10 ans : 75%

Krzisch Am J Hematol 2021

OVERALL SURVIVAL OF TREATED WM PATIENTS

- Median overall survival 6 - 8 years
- median overall survival (WM related - mortality) : 11.2 years



Dimopoulos *et al. Blood*. 2014

- **Eléments cliniques et biologiques impactant la décision thérapeutique**

Quelques notions sur l'évolutivité spontanée :

- **Temps médian pour initiation d'un traitement chez un patient initialement asymptomatique > 7 ans**

- **Probabilité cumulée de progression vers une maladie symptomatique:**
  - **6 % à 1 an**
  - **39 % à 3 ans**
  - **59 % à 5 ans**
  - **68 % à 10 ans**

On ne traite que les patients symptomatiques

Clinical and laboratory considerations for initiation of therapy in WM (2nd Workshop, Athens 2002)

Smoldering or asymptomatic WM

- No curative treatment

- 30% to 50% of cases are asymptomatic at diagnosis and do not require therapy

- Early treatment in other asymptomatic low-grade lymphoproliferative disorders does not prolong survival

Consensus panel recommendations for initiation of therapy in WM.

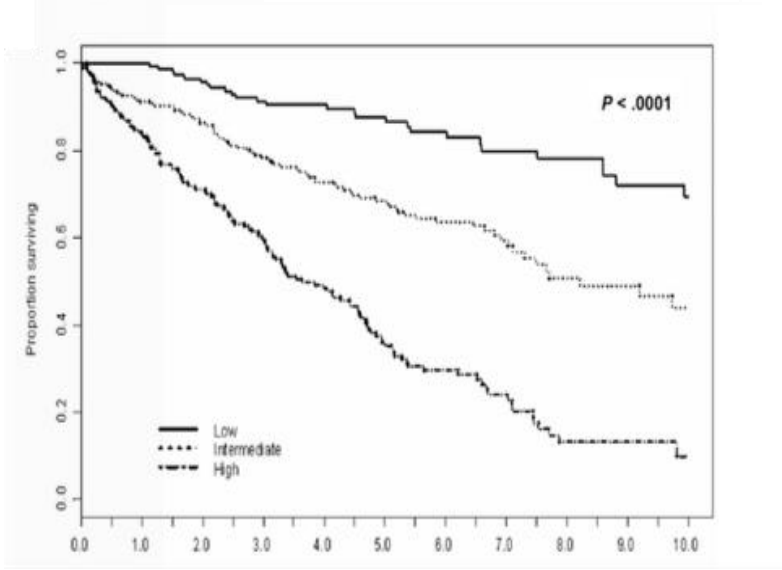
- A high IgM level is not by itself an indication to initiate therapy.
- Hct <30 or Hb <10; Platelet count <100,000.
- Alleviate symptoms attributable to WM.
- Symptomatic Hyperviscosity .
- Moderate-Severe Neuropathies.
- Symptomatic cryoglobulinemia, cold agglutinin disease.
- Monoclonal protein should be monitored by electrophoresis: nephelometry is unreliable

Semin Oncol 30: 116, 2003

Eléments pronostiques

Age > 65 y
Hemoglobin ≤ 11.5 g/dL
Platelet count ≤ 100 × 10^9/L
β2-microglobulin > 3 mg/L
Monoclonal IgM concentration > 7.0 g/dL

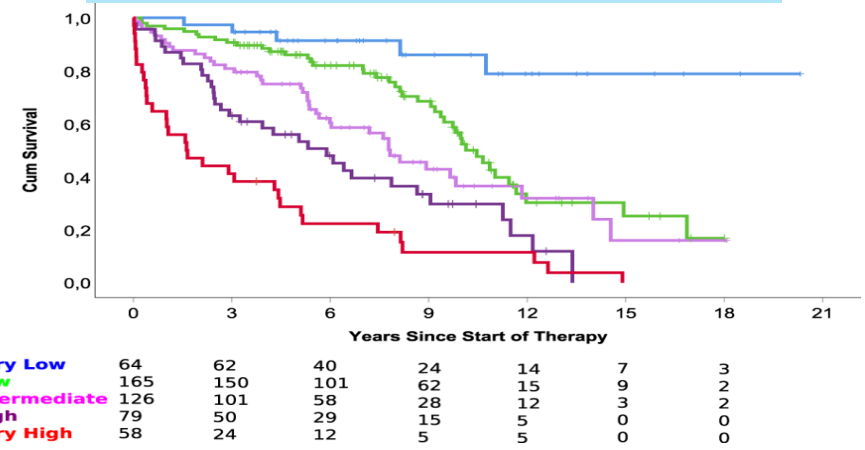
Low	0 or 1 (except age)
Intermediate	age or 2
High	≥ 3



Score ISSWM
Morel Blood 2009

A revised international prognostic score system for Waldenström's macroglobulinemia
Efstathios Kastritis Pierre Morel Leukemia (2019)

	Points
Age < 65	0
Age 66–75	1
Age > 75	2
B2microglobulin > 4 mg/L	1
LDH > 250 IU/L	1
Serum albumin < 3.5 gr/dl	1



Stage	Score	% of patients	3-year WM related mortality	5-year OS	10-year OS
Very low	0	13%	0%	95%	84%
Low	1	33.5%	10%	86%	59%
Intermediate	2	25.5%	14%	78%	37%
High	3	16%	38%	47%	19%
Very high	4–5	12%	48%	36%	9%

New IWWM 11 Response Assessment Criteria for Waldenström Macroglobulinemia

Category	Serum IgM Level Change	Extramedullary Disease[a]	Signs /Symptoms of Active Disease	Other Criteria
Complete response	Undetectable by immunofixation/Mass-Fix and absence of M protein on SPEP. Re-confirmation is not required.	Complete resolution¥[c]	None	Normal bone marrow aspirate and biopsy No evidence of LPL
Very Good Partial Response	≥ 90% reduction from baseline, or within normal range.	Assessment for EMD not required	No new	
Partial Response	≥ 50% to < 90% from baseline[b]	Assessment for EMD not required	No new	
Minor Response	≥ 25% but < 50% from baseline[b]	Assessment for EMD not required	No new	
Stable Disease	< 25% reduction to < 25% increase from baseline[b]		No new	
Progressive Disease	≥ 25%* increase from lowest nadir (requires reconfirmation by 2 sequential measurement)	Progressive, bulky adenopathy/organomegaly[c] as suggested by any new lesion (>1.5 cm in any axis) or increase by >50% in any axis to >1.5 cm in size of previously involved EMD from the nadir measurements. Any new lesion consistent with HT	Yes	Cytopenias, hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis
Non evaluable	Suspected IgM flare or IgM rebound, absence of data or suspected error in data reporting			

LPL lymphoplasmacytic lymphoma; EMD extramedullary disease; HT histologic transformation

[a]Extramedullary disease, e.g, lymphadenopathy and/or splenomegaly, if present at baseline [b]Sequential changes in IgM levels may be determined by nephelometry

[c]By computerized tomography For CR attainment, normalization of EMD, if present at baseline, will be considered complete resolution or mere decrease in size of lymph nodes (≤1.5 cm) or spleen (≤15 cm), or complete resolution of any other non-lymph node or non-splenic extramedullary mass(es) related to WM disease.

Treon S. et al.

Treatment options

- Plasmapheresis
- Alkylator-based therapy
- Purine analogs
- Monoclonal antibodies
- New compounds
- High-dose therapy and transplantation

Factors in selection of first-line treatment in WM

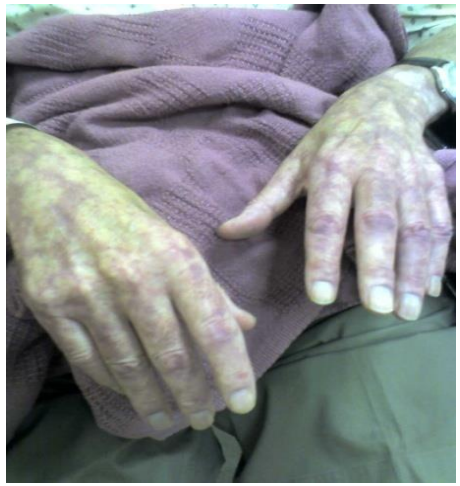
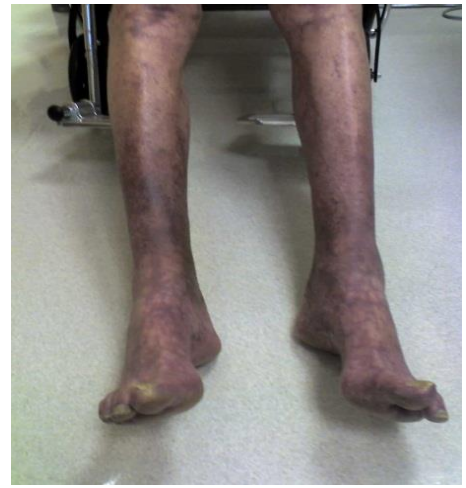
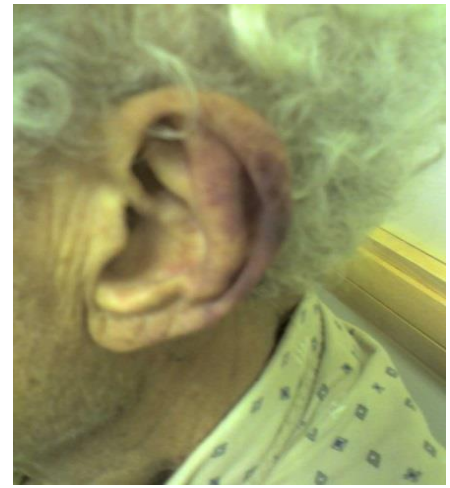
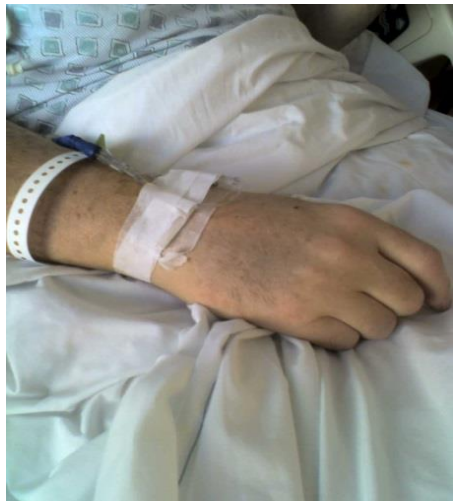
- Patient characteristics
  - Age
  - Comorbidities
    - >65y: 25% >2 comorbidities, 21% hypertension,
      13% cardiovascular disease
    - Performance status more than age
- Disease characteristics
  - Cytopenia, need for rapid control of the disease, bulky disease, neuropathy
- Genomic profile?
  - Mutations in *MYD88*, *CXCR4*, *TP53*
- Drug availability and coverage based on respective national and/or institutional guidelines

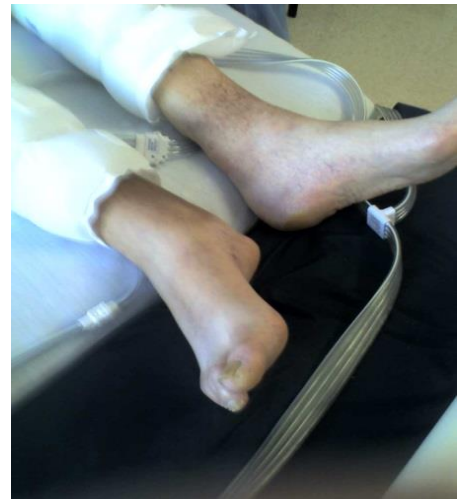
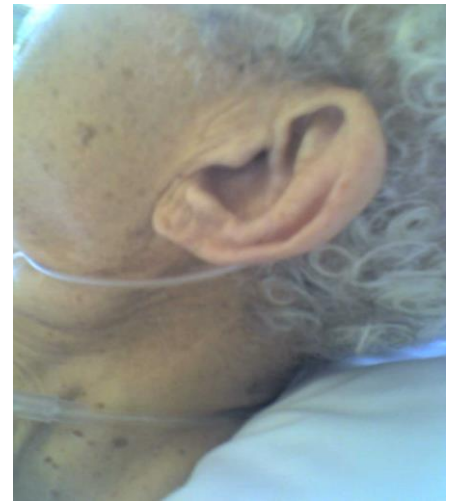
Mean number of comorbidities in older patients with cancer

Age (years)	Patients (%)[1]	Comorbidities (mean no.)[2]
≤ 54	11	n/a
55–64	19	2.9
65–74	27	3.6
75+	43	4.2

CXCR4, C-X-C chemokine receptor type 4; MYD88, myeloid differentiation primary response 88; TP53, tumor protein P53; WM, Waldenström's macroglobulinemia.
1. Ries LAG *et al.* SEER Cancer Statistics Review, 1975–2005. 2. Yancik R. *Cancer* 1997; 80: 1273–1283.

Type I Cryoglobulinemia in a patient with WM

Treon S. *2013*

Report of consensus panel 1 from the 11th International Workshop on Waldenstrom's Macroglobulinemia on management of symptomatic, treatment-naïve patients. **Buske C**, Castillo JJ, Abeykoon JP, Advani R, Arulogun SO, Branagan AR, Cao X, D'Sa S, Hou J, Kapoor P, Kastritis E, Kersten MJ, LeBlond V, Leiba M, Matous JV, Paludo J, Qiu L, Tam CS, Tedeschi A, Thomas SK, Tohidi-Esfahani I, Varettoni M, Vos JM, Garcia-Sanz R, San-Miguel J, Dimopoulos MA, Treon SP, Trotman J.Semin Hematol. 2023 Mar;60(2):73-79. doi: 10.1053/j.seminhematol.2023.03.005. Epub 2023 Mar 29

Report of consensus panel 2 from the 11th international workshop on Waldenström's macroglobulinemia on the management of relapsed or refractory WM patients. D'Sa S, Matous JV, Advani R, Buske C, Castillo JJ, Gatt M, Kapoor P, Kersten MJ, Leblond V, Leiba M, Palomba ML, Paludo J, Qiu L, Sarosiek S, Shadman M, Talaulikar D, Tam CS, Tedeschi A, Thomas SK, Tohidi-Esfahani I, Trotman J, Varettoni M, Vos J, Garcia-Sanz R, San-Miguel J, Dimopoulos MA, Treon SP, Kastritis E.Semin Hematol. 2023 Mar;60(2):80-89. doi: 10.1053/j.seminhematol.2023.03.003. Epub 2023 Mar 27


THE LANCET
Haematology
Volume 7, Issue 11, November 2020, Pages e827-e837

Review

Consensus treatment recommendations from the tenth International Workshop for Waldenström Macroglobulinaemia

Jorge J Castillo MD [a], Prof Ranjana H Advani MD [b], Andrew R Branagan MD [c], Prof Christian Buske MD [d], Prof Meletios A Dimopoulos MD [e], Shirley D'Sa MD [f], Prof Marie José Kersten MD [g], Prof Veronique Leblond MD [h], Prof Monique C Minnema MD [i], Roger G Owen FRCPath [j], M Lia Palomba MD [k], Dipti Talaulikar FRACP [l], Alessandra Tedeschi MD [m], Prof Judith Trotman MBChB [n], Marzia Varettoni MD [o], Josephine M Vos MD [g], Prof Steven P Treon MD [a], Efstathios Kastritis MD [e]

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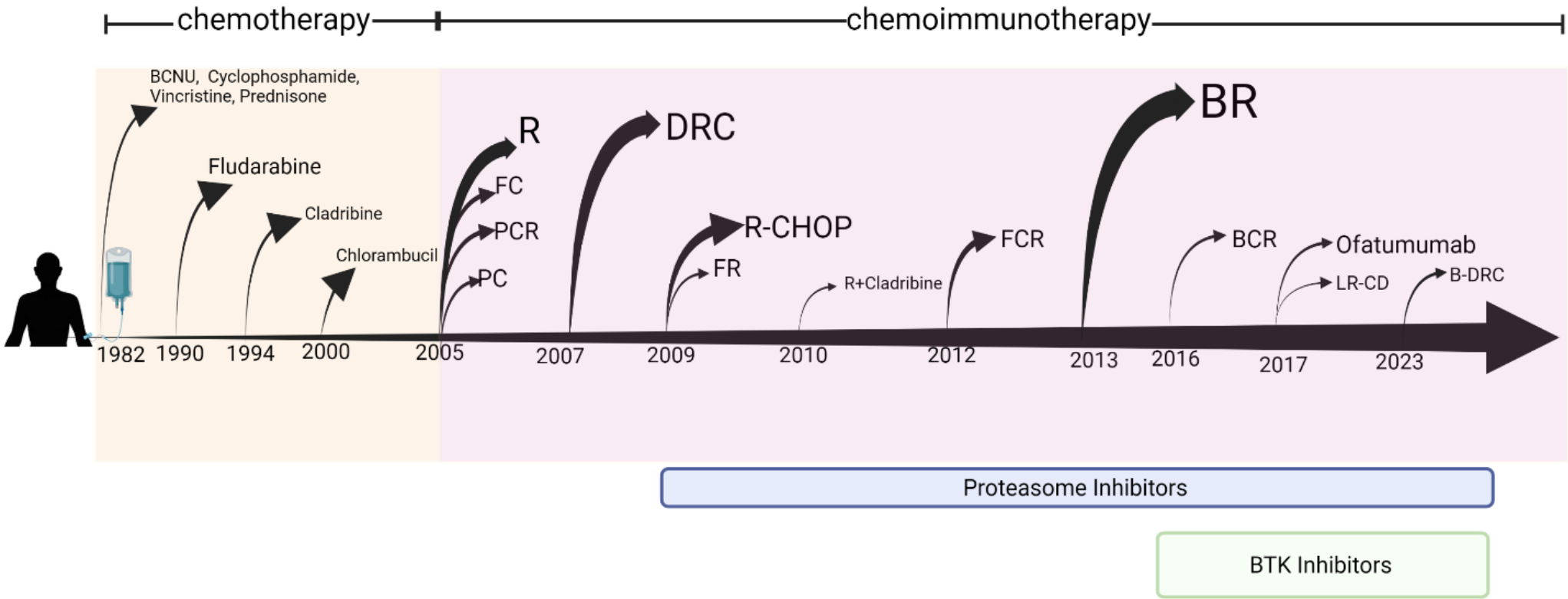
Treatment recommendations for patients with Waldenström's Macroglobulinemia (WM) and related disorders: consensus from the Eight International Workshop on WM

Véronique Leblond[1], Efstathios Kastritis[2], Ranjana Advani[3], Stephen.M Ansell[4], Christian Buske[5], Jorge J. Castillo[6], Ramón García-Sanz[7], MorieGertz[8], Eva Kimby[9], Charalampia Kyriakou[10], Giampaolo Merlini[11], Monique C Minnema[12], Pierre Morel[13], Enrica Morra[14], Mathias Rummel[15], Ashutosh Wechalekar[16], Steven P. Treon[6] and Meletios Dimopoulos[2 b] *Blood. 2016 Sep 8;128(10):1321-8*

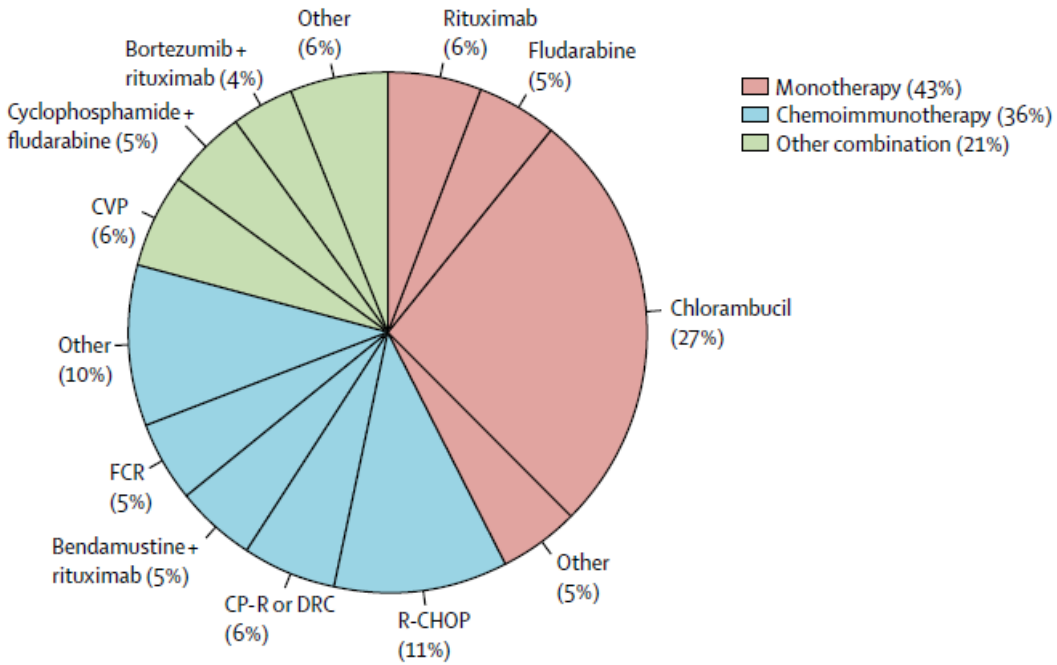


The font sizes and the arrow width depict the impact of the respective regimens in the frontline setting. The time points on the horizontal axis represent the year of the publication of the initial clinical trial(s) with the specific regimens. The horizontal bars at the bottom show the time interval during which other classes of frequently used agents were developed and continue to be used in WM.

Kapoor P. et al. 2023

IMMUNOCHEMOTHERAPY IS A FREQUENT OPTION IN EUROPE AND IS STILL AN OPTION IN WM THERAPY GUIDELINES

Front-line treatment choices in European patients with WM[1]



- CI regimens are recommended as first-line treatment options by both the ESMO and Mayo guidelines[2,3,]
- Recent IWWM-11 preferred options are [4,5]:
  - Bendamustine plus rituximab
  - Cyclophosphamide, dexamethasone, and rituximab
  - (Bortezomib, dexamethasone, and rituximab)
  - Ibrutinib (with or without rituximab)

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CI, chemoimmunotherapy; CP-R, cyclophosphamide, prednisone, and rituximab; CVP, cyclophosphamide, vincristine, and prednisone; DRC, dexamethasone, rituximab, and cyclophosphamide; FCR, fludarabine, cyclophosphamide, and rituximab; IWWM-10, 10th International Workshop on Waldenström's macroglobulinemia; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; WM, Waldenström's macroglobulinemia.

1. Buske CB *et al. Lancet Haematol.* 2018 Jul;5(7):e299-e309. 2. Kastritis E *et al., Ann Oncol* 2018; 29:41–50. 3. Kapoor P *et al., JAMA Oncol.* 2017; 3(9): 1257–1265. 4. Castillo JJ *et al., Lancet Haematol*2020 11: e827–e837 5. Buske C *et al, Sem Hematol 2023;* 60:73-79.

SELECTED DATA FROM PROSPECTIVE STUDIES IN TREATMENT-NAIVE PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA (Buske C *et al* 2023, IWWM -11)

Study	Regimen	N	PR or better	VGPR or better	PFS
Dimopoulos, 2007 Kastritis, 2015	Dexamethasone Rituximab Cyclophosphamide	72	74%	7%	35 months (median)
Rummel, 2019	Bendamustine Rituximab	257	88%	4%	65 months (median)
Treon, 2009 Treon, 2015	Bortezomib Dexamethasone Rituximab	23	83%	35%	66 months (median)
Dimopoulos, 2013 Gavriatopoulou, 2017	Bortezomib weekly Dexamethasone Rituximab	59	68%	10%	42 months (median)
Treon, 2014 Meid, 2017	Carfilzomib Dexamethasone Rituximab	28	68%	36%	46 months (median)
Castillo, 2018 Castillo, 2020	Ixazomib Dexamethasone Rituximab	26	77%	19%	40 months (median)
Buske, 2023	Bortezomib Cyclophosphamide Dexamethasone Rituximab	102	81%	17%	81% at 24 months
	Cyclophosphamide Dexamethasone	100	70%	10%	73% at 24 months

Efficacy of Covalent BTK Inhibitors for WM

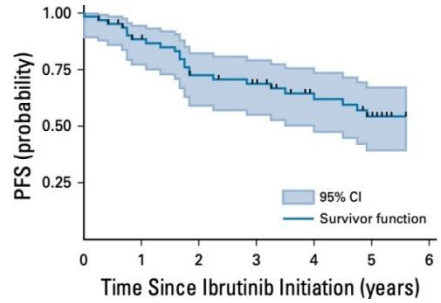
Study	N TN/Total	Population	ORR (%)	MRR (%)	PR (%)	VGPR+ (%)	PFS (%)
Ibrutinib	63	RR	91	79	49	30	5y 54
Ibrutinib	30	TN	100	87	57	30	4y 76
iNNOVATE Ibrutinib+ Rituximab Placebo + Rituximab	150 34/41 34/41	TN/RR	91/93 53/37	76/76 41/22	50/42 32/20	27/34 9/2	4y 70/71 32/20
Acalabrutinib	106 14 92	TN RR	93 95	78 84	71 57	7 23	5.5y 84 (TN) 52 (RR)
Zanubrutinib AU-003	77	TN+RR	100	83	37	44	2yr 81
Zanubrutinib AU-003	24	TN	100	87	54	33	2yr 91
ASPEN Cohort 1(MYD88^{mut}) Zanubrutinib Ibrutinib	102 99	TN/RR	95 94	81 67/80	45 55	28 36 19 22	1y 3.5y 90 78 87 70
Zanubrutinib	19	TN	94	73	53	26	1.5y 78
Ibrutinib	18	TN	89	67	50	17	1.5y 94
ASPEN Cohort 2 Zanubrutinib (MYD88^{WT})	26	TN/RR	81	65	35	31	1.5 3.5y 68 NA
Tirabrutinib	27	TN/RR	96	89	78	11	NR
Ibrutinib-venetoclax	45	TN	100	93	53	40	1y 92%

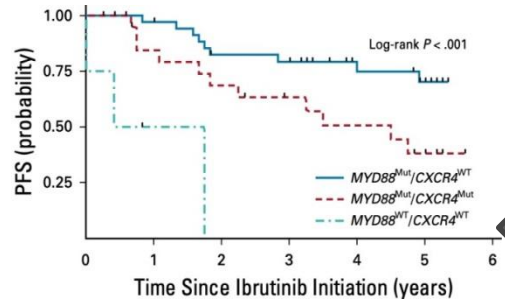
Treon SP et al. *J Clin Oncol*. 2021;39(6):565-575. Castillo JJ et al. *Leukemia*. 2022;36(2):532-539. Buske C et al. *J Clin Oncol*. 2022;40(1):52-62. Trotman J et al. *Clin Cancer Res*. 2021;27(21):5793-5800. Owen et al. *HemaSphere*. 2022. Trotman J et al. *Blood* 2020;136 (18): 2027-2037. Tam et al. *J Clin Oncol*. 2022. Sekaguchi et al. *Cancer Sci*. 2020. Zhou et al. ASH 2021. Mato AR et al. *Lancet*. 2021;397(10277):892-901. Palumba L et al. ASH 2022. Abstract 229. Castillo JJ et al. ASH 2022. Abstract 231.

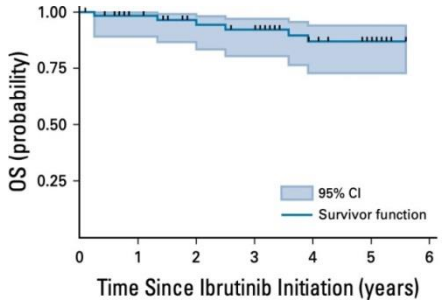
BTKi de première génération
Ibrutinib

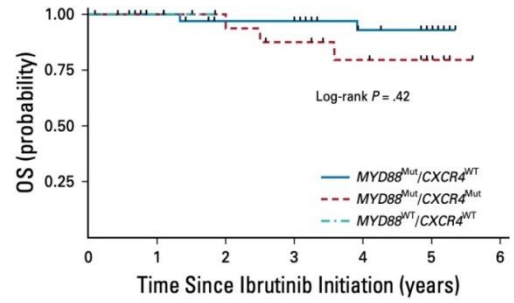
Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia

Mise à jour à 5 ans de suivi de l'étude princeps : Suivi médian 59 mois









ORR	90.5%
MR	80%
Taux de PFS	54%
Taux de SG	87%

Effet du génotype sur la PFS +++

EI ≥ grade 3*	Fréquence
Neutropénie	15,9%
Thrombopénie	11,1%
Pneumonie	3.2%

Fibrillation auriculaire : 12.7%

**** possiblement liés au traitement***

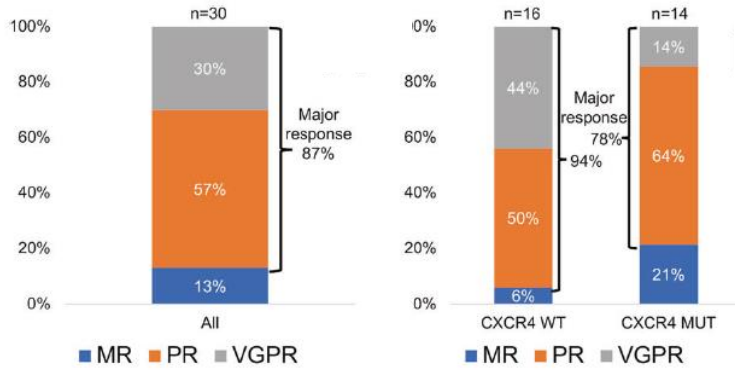
Treon and al Journal of Clinical Oncology 2021 39:6, 565-575

Long-Term Follow-Up of Ibrutinib Monotherapy in treatment- naive patients with Waldenström macroglobulinemia

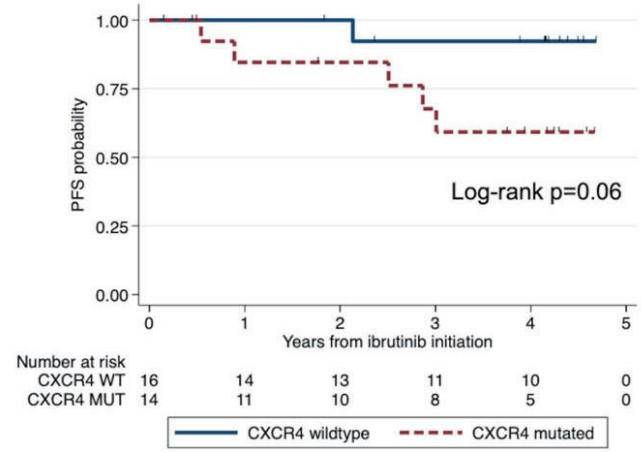
Mise à jour : Essai monocentrique ; 30 patients tous MYD88^{L265P} dont 14 CXCR4^{whim} : Suivi médian 50 mois

Impact négatif des mutations CXCR4 sur ORR et PFS

Taux de réponse à 4 ans : MR, PR, VGPR



PFS à 4 ans : 92% vs 59%



- **EI cardiovasculaires (tous grades) : fibrillation auriculaire ≥ grade 2 (20%), HTA (16,6%)**

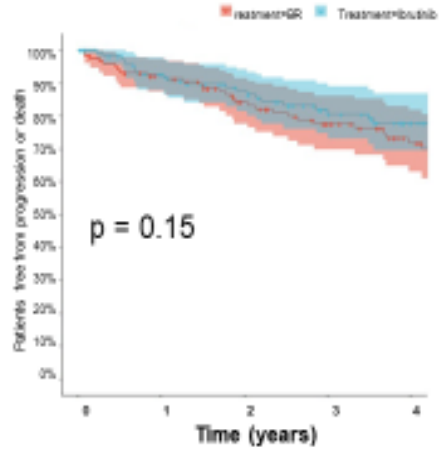
Castillo and al. Leukemia (2021)

Bendamustine Rituximab versus Ibrutinib as Primary Therapy for Waldenström Macroglobulinemia: An International Collaborative Study

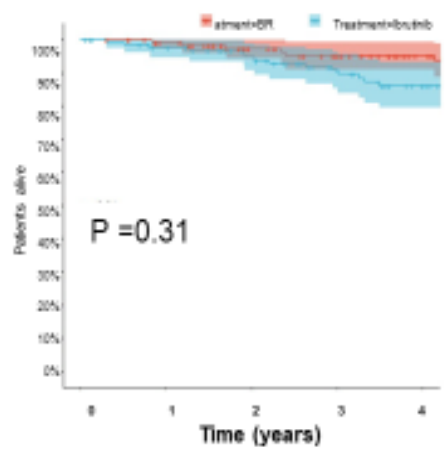
Jithma P. Abeykoon[1], Shaji Kumar[1], Jorge J. Castillo[2], Shirley D'sa[3], Efstathios Kastritis[4], Eric Durot[5], Encarl Uppal[3], Morel Pierre[6], Jonas Paludo[1], Reema Tawfiq[1], Shayna R Sarosiek[7], Olabisi Ogunbiyi[8], Pascale Cornillet-Lefebvre[9], Robert A. Kyle[1], Alain Delmer[10], Morie A. Gertz[1], Meletios A Dimopoulos[11], Steve P. Treon[2], Stephen M. Ansell[1], and Prashant Kapoor[1]

Variable	BR	Ibrutinib	p-value
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, %			
Low	11	17	0.63
Intermediate	33	33	
High	56	48	
Cycles, median (range)	6 (1-6) >4 cycles, 77%	42 (0.3-98)	
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**
4-year PFS, % (95%CI)	72 (63-82)	78 (70-87)	0.15
4-year OS, % (95%CI)	95 (91-99)	86 (80-93)	0.31

Progression-free survival



Overall survival



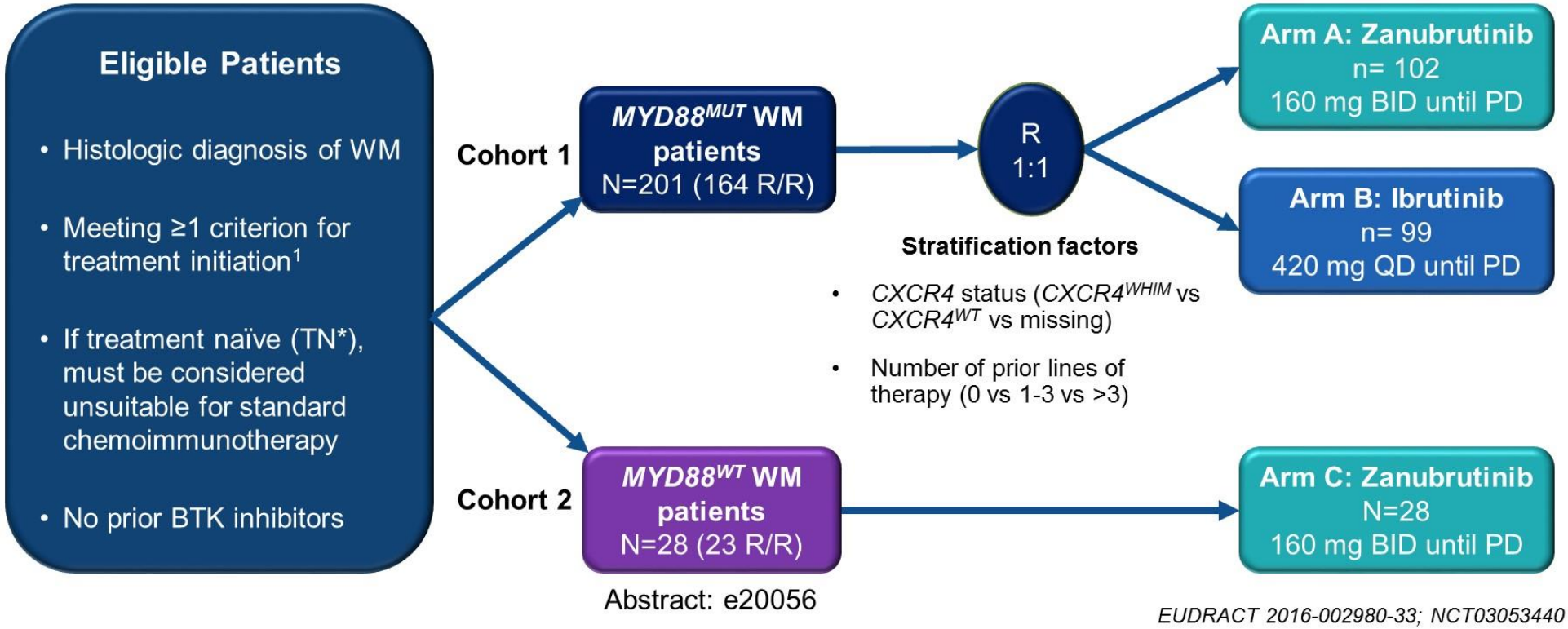
- Analysis of age-matched patients who received either BR or Ibrutinib (N=246)
- MYD88 WT patients excluded
- Median Follow-Up: 4.2 years

Abeykoon et al. Abstract 7566, ASCO 2022

Ibrutinib et MW: synthèse

- **Ibrutinib en monothérapie est clairement efficace dans MW et challenge les immunochimiothérapies quelle que soit la ligne de traitement**
- **Survie globale excellente**
- **Influence +++ du génotype: $MYD88^{L265P}CXCR4^{wt}$ > $MYD88^{L265P}CXCR4^{whim}$ >> $MYD88^{wt}CXCR4^{wt}$ sur tous les critères de réponse (taux/profondeur/durée)**
- **Ibrutinib *en monothérapie* médiocre si $MYD88^{wt}$**
- **$CXCR4^{whim}$ associé à réponses plus lentes/moins profondes et PFS plus courte**
- **Ajout de rituximab à l'ibrutinib améliore (peut-être) les réponses des génotypes moins favorables (INNOVATE)**

ASPEN Study Design: Zanubrutinib vs Ibrutinib in *MYD88*^{MUT} WM



BID, twice daily; BTK, Bruton tyrosine kinase; CXCR4, C-X-C Motif Chemokine Receptor 4; MYD88^{MUT}, myeloid differentiation primary response gene 88 mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström Macroglobulinemia; WT, wild-type.

*Up to 20% of the overall population.

1. Dimopoulos MA, et al. *Blood*. 2014;124:1404-1411.

ASPEN Réponses

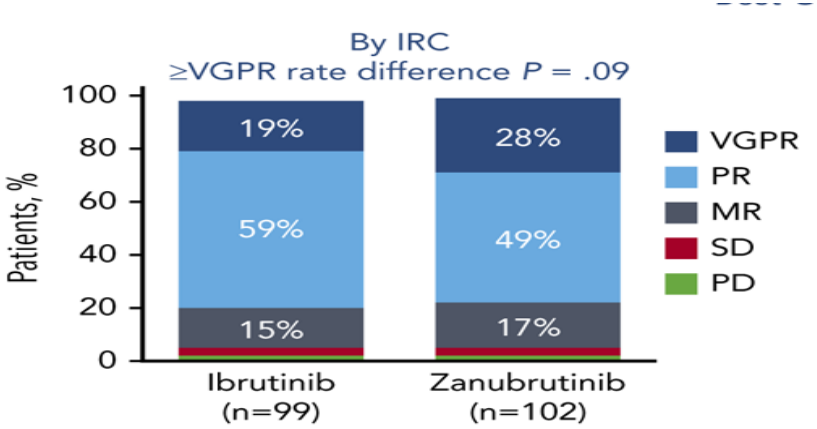
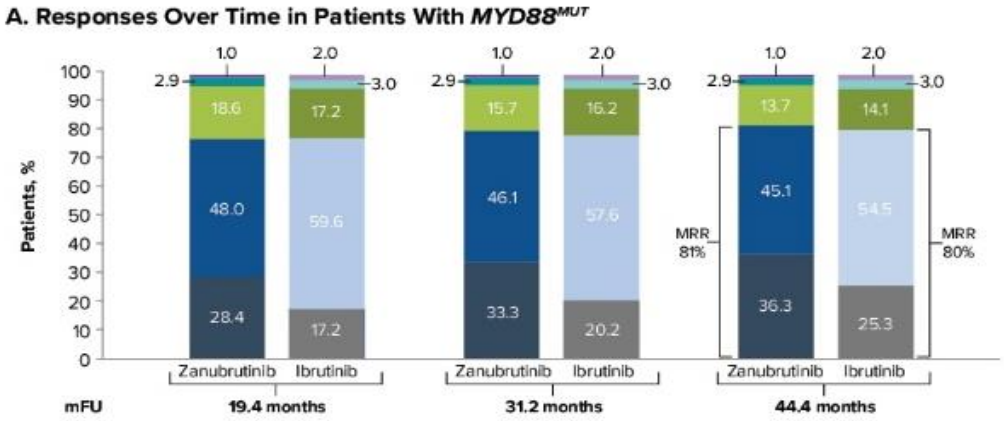
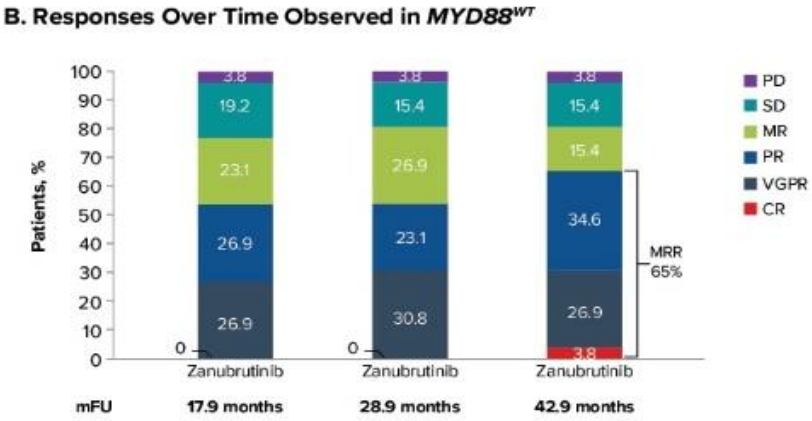


Table 2: Response Assessment by *CXCR4* Status[a]

	CXCR4^{MUT}		*CXCR4*^{WT}	
	Ibrutinib (n=20)	Zanubrutinib (n=33)	Ibrutinib (n=72)	Zanubrutinib (n=65)
VGPR or better	2 (10.0)	**7 (21.2)**	22 (30.6)	**29 (44.6)**
Major response	13 (65.0)	**26 (78.8)**	61 (84.7)	54 (83.1)
Overall response	19 (95.0)	30 (90.9)	68 (94.4)	63 (96.9)
Time to major response, median (months)	6.6	3.4	2.8	2.8
Time to VGPR, median (months)	31.3	11.1	11.3	6.5

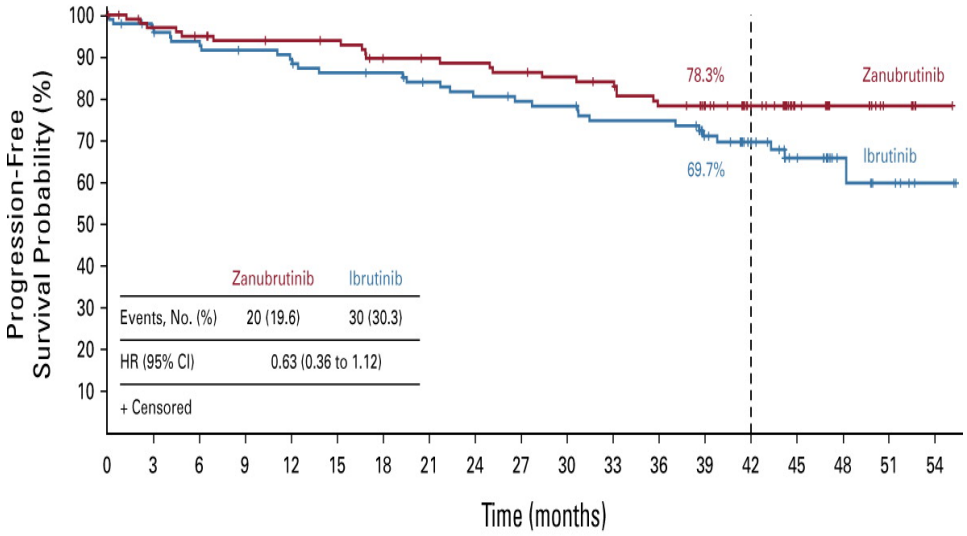
Bold text indicates >10% difference between arms. Data cutoff: October 31, 2021.
[a]*CXCR4* mutation determined by NGS. Ninety-two ibrutinib patients and 98 zanubrutinib patients had NGS results available.

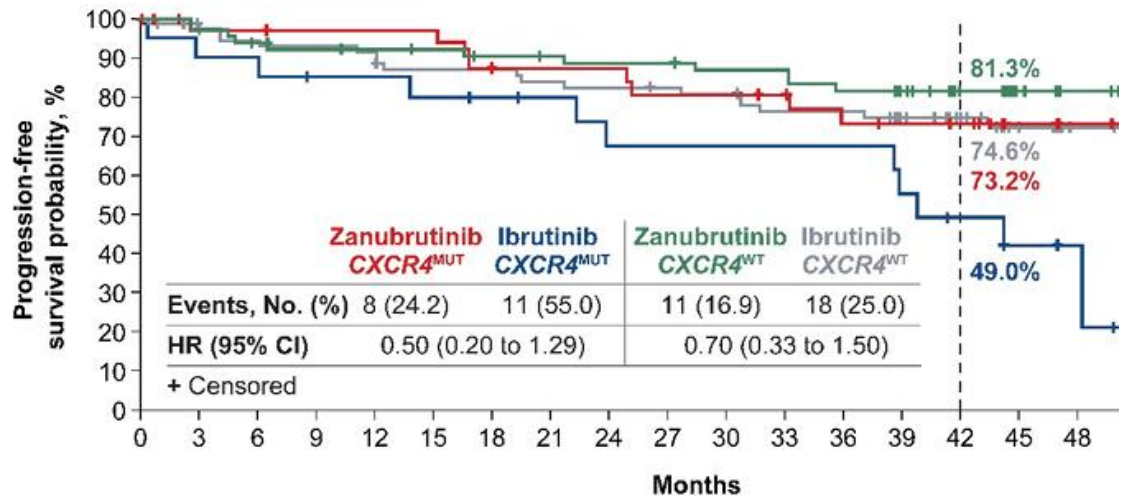


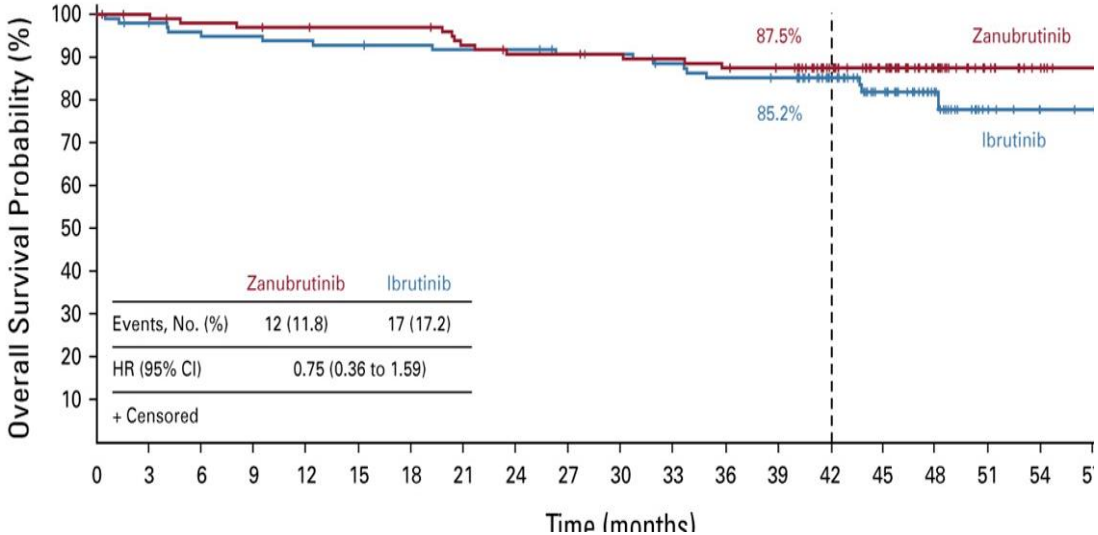


Data cutoff: October 31, 2021.

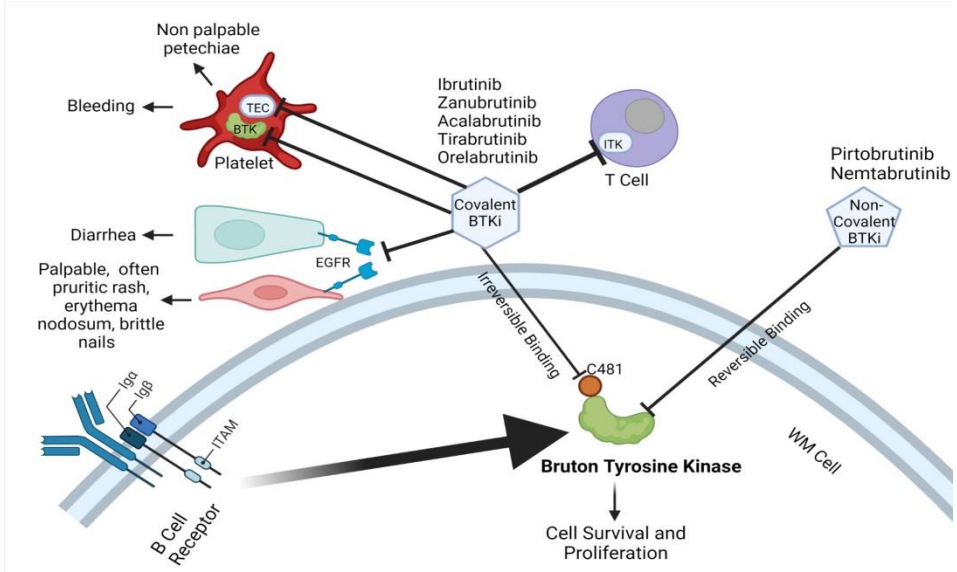
ASPEN Réponses







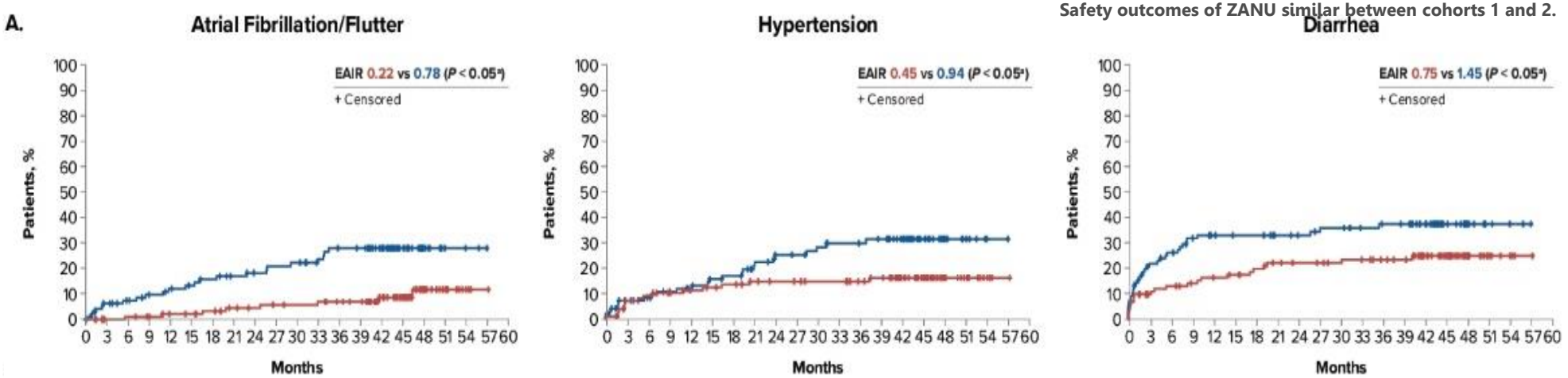
Covalent BTK Inhibitors Toxicity Profile



Chohan K. and Kapoor P 2023

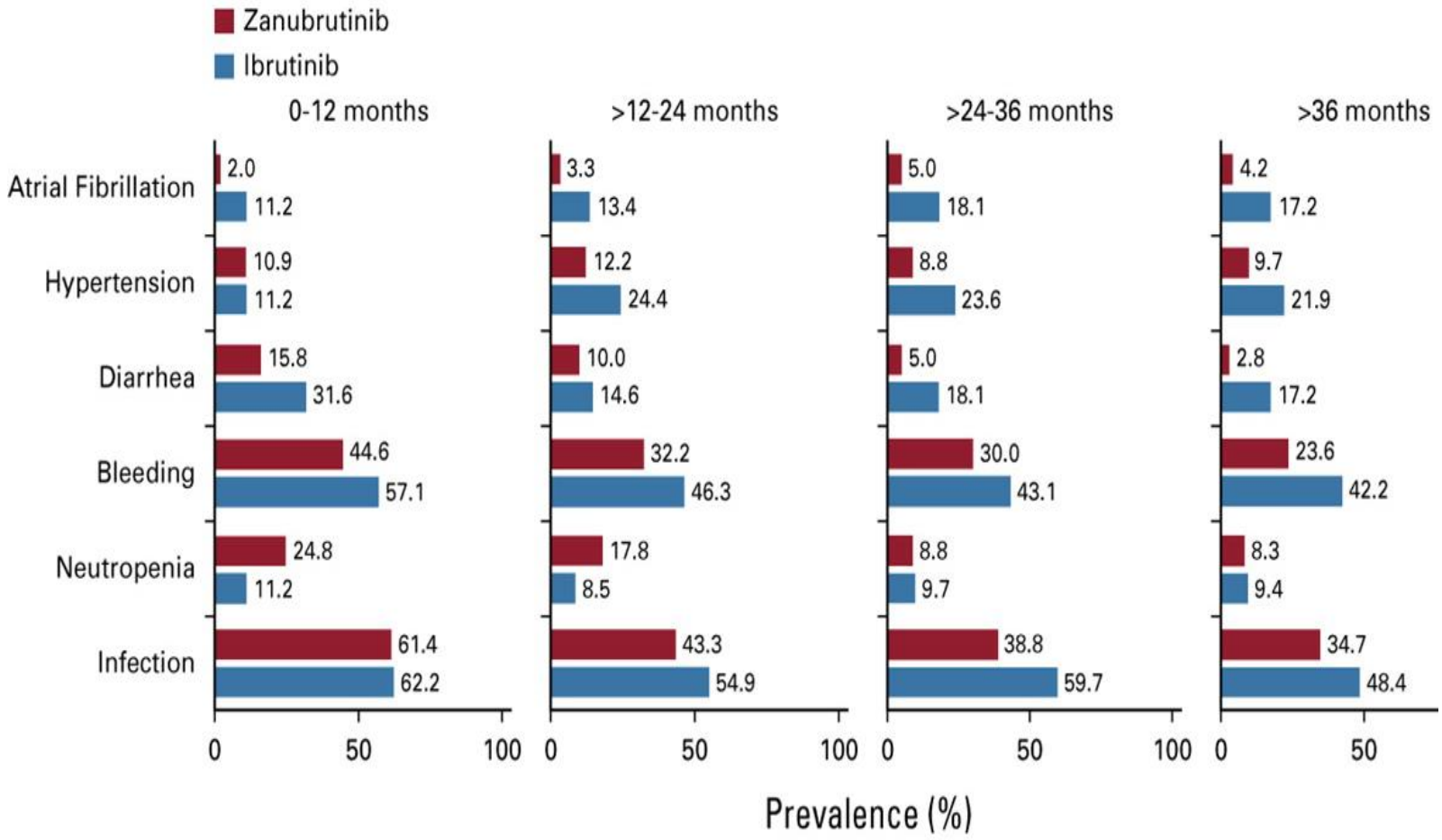
AEs,[a] n (%)	All grades		Grade ≥3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Infection	78 (79.6)	80 (79.2)	**27 (27.6)**	22 (21.8)
Bleeding	61 (62.2)	56 (55.4)	10 (10.2)	9 (8.9)
Diarrhea	**34 (34.7)**	23 (22.8)	2 (2.0)	3 (3.0)
Hypertension*	**25 (25.5)**	15 (14.9)	**20 (20.4)***	10 (9.9)
Atrial fibrillation/flutter*	**23 (23.5)***	8 (7.9)	**8 (8.2)***	2 (2.0)
Anemia	22 (22.4)	18 (17.8)	6 (6.1)	**12 (11.9)**
Neutropenia*[b]	20 (20.4)	**35 (34.7)***	10 (10.2)	**24 (23.8)***
Thrombocytopenia	17 (17.3)	17 (16.8)	6 (6.1)	11 (10.9)
Second primary malignancy/ nonskin cancers	17 (17.3)/ 6 (6.1)	17 (16.8)/ 6 (5.9)	3 (3.1)/ 3 (3.1)	6 (5.9)/ 4 (4.0)

Rate of neutropenia was higher and rate of grade ≥3 infection was lower with ZANU vs
Safety outcomes of ZANU similar between cohorts 1 and 2.



Expc ncidence rates of atrial fib/flutter and H ZANU vs IBR (0.2 vs 0.8 and 0.5 vs 1.( )0 person-months, respectively; $p < 0.05$).

Covalent BTK Inhibitors Toxicity Profile



Phase 1/2 BRUIN Study with Pirtobrutinib

Phase 1 Escalation + Expansion (25 to 300 mg QD)
Phase 2 (200 mg QD)
N=773

Safety Population

- **CLL/SLL** n=317
- **MCL** n=166
- **WM** n=80
- **Other**[a] n=210

Efficacy Population

WM n=80

- **Prior cBTKi** n=63
- **cBTKi Naïve** n=17

Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

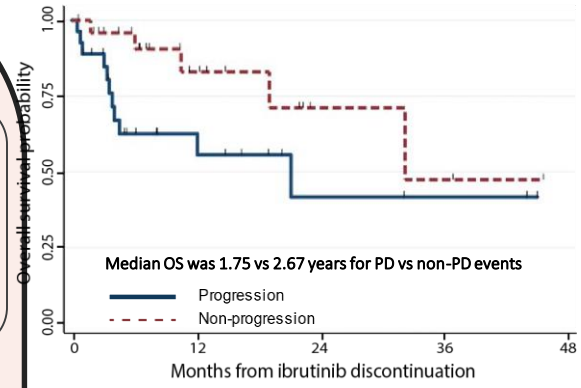
Eligibility

- Age ≥18
- ECOG 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and recommended Phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DoR (IWWM6/Modified IWWM6) as assessed by Investigator

- Inhibits both WT and C481-mutant BTK with equal low nM potency



Overall Survival according to cause of ibrutinib discontinuation

cBTKi, covalent Bruton tyrosine kinase inhibitor. Data cutoff date of 29 July 2022. [a]Other includes DLBCL, Richter transformation, FL, MZL, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

WM Patient Characteristics

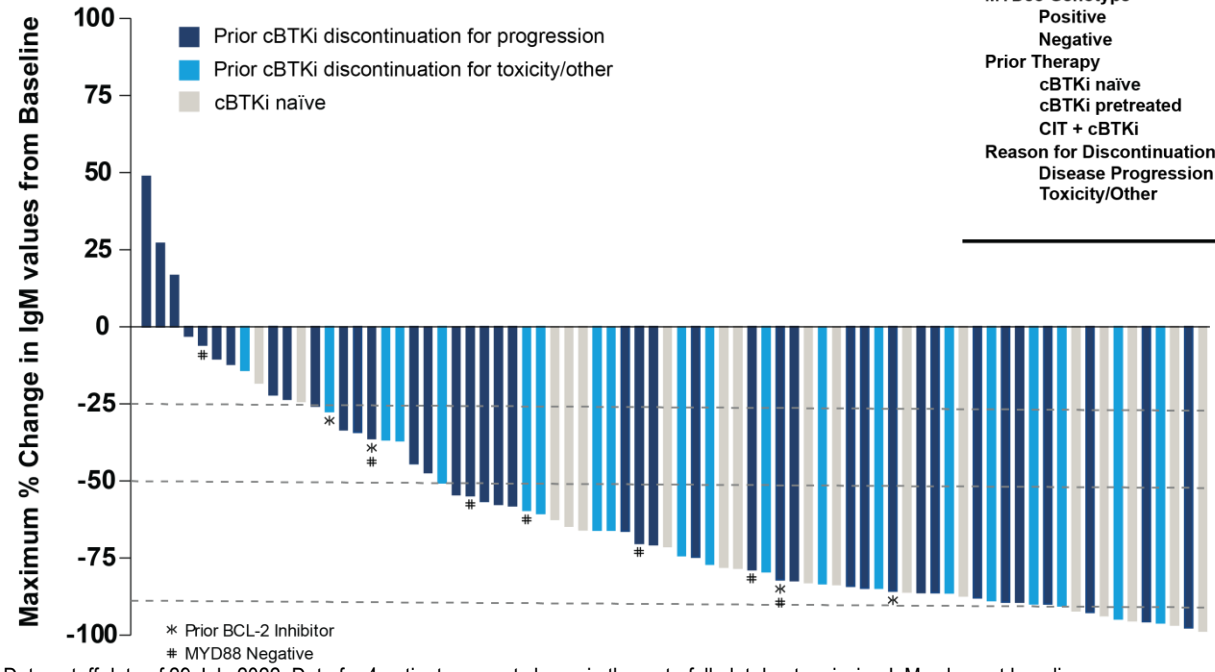
Characteristics	Prior cBTKi n=63	cBTKi Naïve n=17
Median age (range), years	69 (42-84)	68 (47-83)
Male, n (%)	42 (67)	10 (59)
ECOG PS, n (%)		
0	34 (54)	9 (53)
1	28 (44)	8 (47)
2	1 (2)	0 (0)
Median number prior lines of systemic therapy (range)	3 (1-11)	2 (1-4)
Prior therapy, n (%)		
cBTK inhibitor	63 (100)	0 (0)
Chemotherapy	52 (83)	17 (100)
Anti-CD20 antibody	58 (92)	16 (94)
CIT + BTK inhibitor	50 (79)	0 (0)
PI3K inhibitor	3 (5)	0 (0)
Immunomodulator	6 (10)	2 (12)
BCL2 inhibitor	4 (6)	0 (0)
Autologous stem cell transplant	4 (6)	0 (0)
Other systemic therapy	31 (49)	6 (35)
Reason discontinued any prior BTK inhibitor[a,b], n (%)		
Progressive disease	41 (65)	-
Toxicity/Other	21 (33)	-

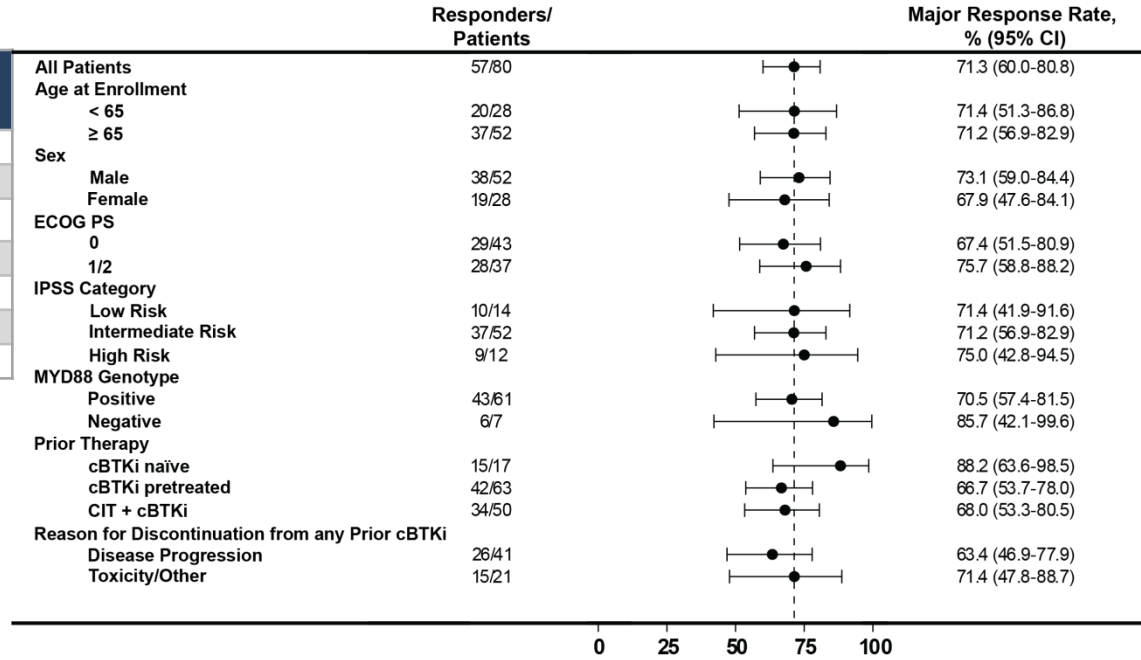
	Prior cBTKi n=63	cBTKi Naïve n=17
WM IPSS score, n (%)		
Low	13 (21)	1 (6)
Intermediate	38 (60)	14 (82)
High	10 (16)	2 (12)
Missing	2 (3)	0 (0)
IgM, median (min, max)	2.46 (0.1, 8.0)	2.59 (0.6, 6.1)
≤7 g/dL, n (%)	61 (97)	17 (100)
>7 g/dL, n (%)	2 (3)	0 (0)
β-2 Microglobulin, median, (min, max)	4.00 (1.6, 95.3)	3.36 (2.4, 11.8)
≤3 mg/L, n (%)	20 (32)	3 (18)
>3 mg/L, n (%)	41 (65)	14 (82)
Missing, n (%)	2 (3)	0 (0)
Peripheral blood cytopenias, n (%)		
Hemoglobin ≤11.5 g/dL	42 (68)	12 (71)
Platelet count ≤100 × 10^9/L	11 (18)	3 (18)
MYD88 genotype[c], n (%)		
Negative	7 (11)	0 (0)
Positive	52 (83)	9 (53)
Missing	4 (6)	8 (47)
CXCR4 genotype[c], n (%)		
Negative	11 (18)	0 (0)
Positive	9 (14)	0 (0)
Missing	43 (68)	17 (100)
Extramedullary disease, n (%)		
Lymphadenopathy	37 (59)	10 (59)
Splenomegaly	18 (29)	3 (18)

cBTKi, covalent Bruton tyrosine kinase inhibitor; CIT, chemoimmunotherapy; IPSS, International Prognostic Scoring System. Data cutoff date of 29 July 2022. Total % may be different than the sum of the individual components due to rounding. [a]In the event more than one reason was noted for discontinuation, disease progression took priority. [b]One patient had unknown reason for prior BTKi discontinuation. [c]Molecular characteristics were determined locally and are presented based on data availability.

Pirtobrutinib Efficacy in WM Patients

Response Evaluable WM Patients	Prior cBTKi n=63	cBTKi Naïve n=17
Major Response Rate[a], % (95% CI)	66.7 (53.7-78.0)	88.2 (63.6-98.5)
CR + VGPR Rate, % (95% CI)	23.8 (14.0-36.2)	29.4 (10.3-56.0)
Best Response		
VGPR, n (%)	15 (23.8)	5 (29.4)
PR, n (%)	27 (42.9)	10 (58.8)
MR, n (%)	9 (14.3)	0 (0)
SD, n (%)	9 (14.3)	2 (11.8)

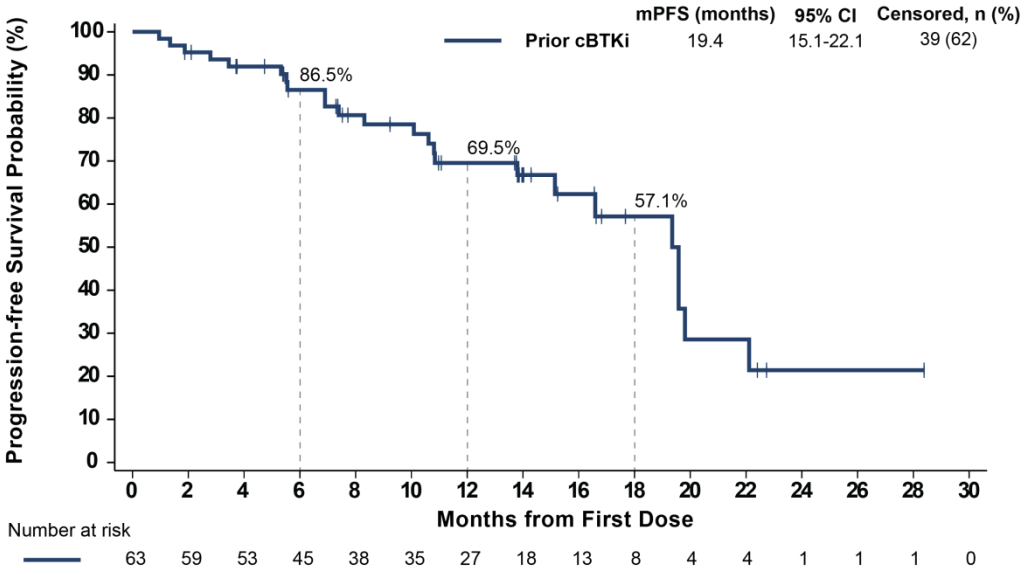




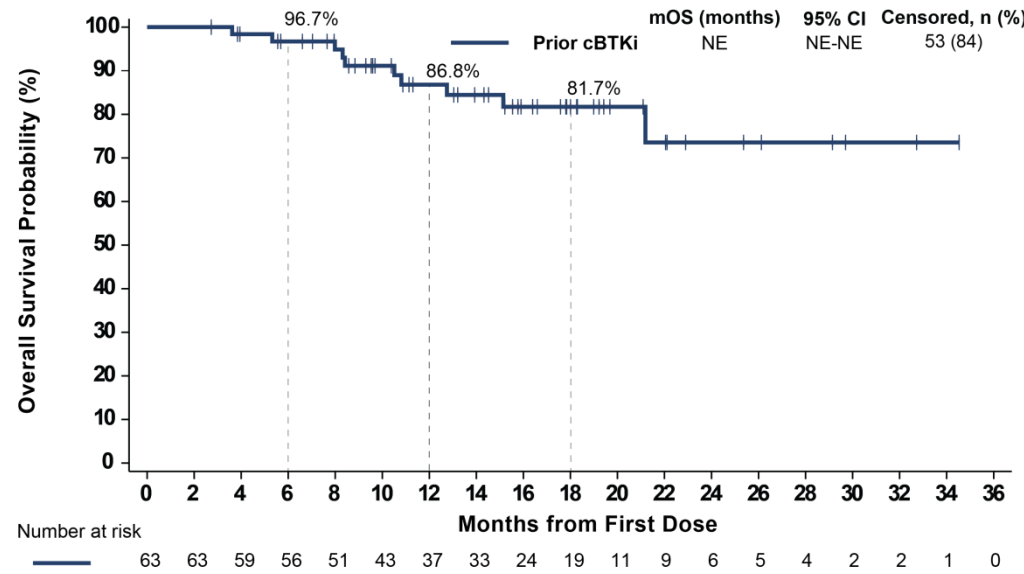
Data cutoff date of 29 July 2022. Data for 4 patients are not shown in the waterfall plot due to missing IgM values at baseline or response assessment. Response as assessed by investigator based on Modified IWWM6 (Owen's) criteria. Under modified IWWM6 criteria, a PR is upgraded to VGPR if corresponding IgM is in normal range or has at least 90% reduction from baseline. [a]Major response includes subjects with a best response of CR, VGPR, or PR. Total % may be different than the sum of the individual components due to rounding.

Progression-Free Survival and Overall Survival in Prior cBTKi Patients

Progression-Free Survival



Overall Survival



- The median follow-up for PFS and OS in patients who received prior cBTKi was 14 and 16 months, respectively
- 55.6% (35/63) of patients who received prior cBTKi remain on pirtobrutinib

Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.

Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

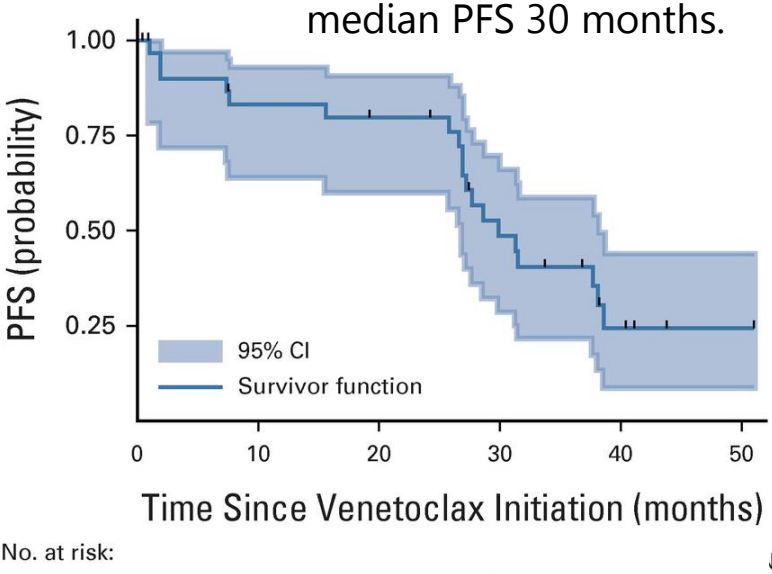
Median time on treatment for the overall safety population was 9.6 months
Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
Overall and WM safety profiles are generally consistent[h]

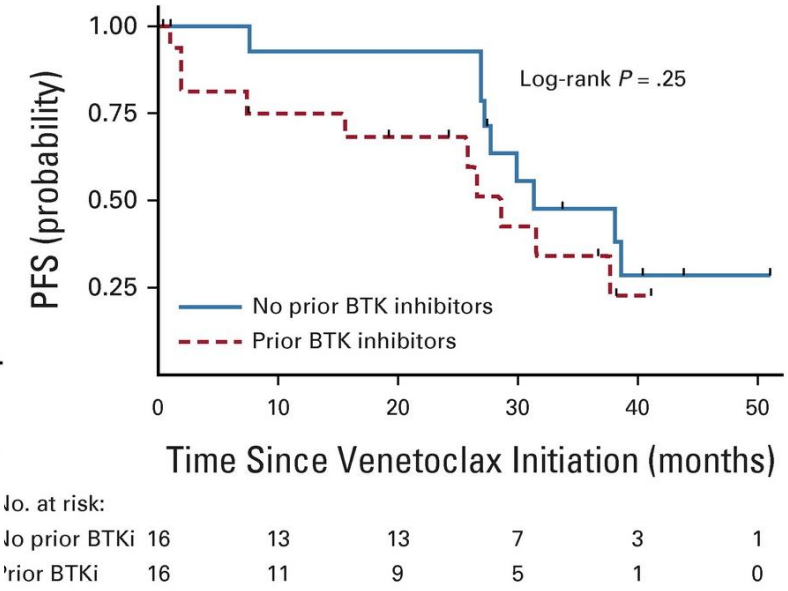
Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]WM safety population data can be found via QR code. Constipation is more commonly seen as a TEAE in the WM population than in all patients.

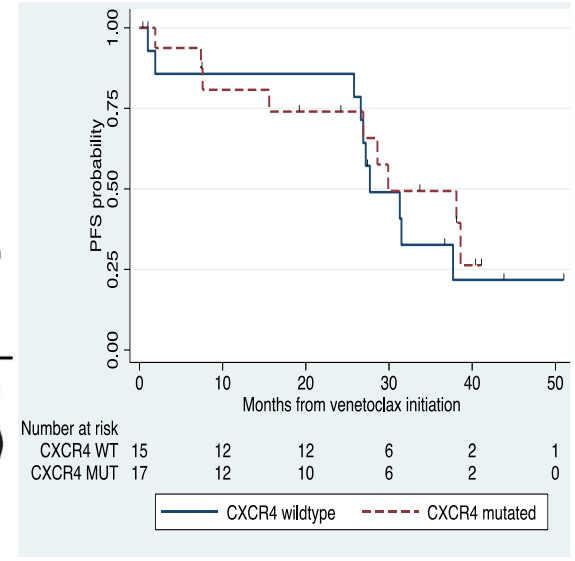
VENETOCLAX

Study	N	Patient Population	ORR (%)	MRR (%)	PR (%)	VGPR (%)	PFS (%)
Phase 1 Venetoclax	4	RR	100	100	100	0	NA
Phase 2 Venetoclax	32	RR	84	81	61	19	2-yr 80

median PFS 30 months.







CXCR4 mutations did not affect response or PFS

Davids, M. S. *et al. J Clin Oncol* **35**, 826-833, 2017
Castillo J. et al. JCO (January 01, 2022)

BGB-11417 (Bcl-2 Inhibitor) Monotherapy or Combination with Zanubrutinib in CLL/SLL Patients: Preliminary Phase 1 Data

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Introduction

- Bcl-2 inhibition is an established mechanism for treating B-cell malignancies such as CLL/SLL[1-2]
- BGB-11417 has shown more potent and selective Bcl-2 inhibition and better activity against BCL2 mutations than venetoclax *in vitro*[2]
- The combination of Bcl-2 and BTK inhibitors has potent activity in CLL and MCL[3-6]
- Ibrutinib with venetoclax in patients with CLL/SLL is effective, however, toxicities can limit use.[7] There remains a need to develop more tolerable BTKi + Bcl-2i combination
- Zanubrutinib has demonstrated superior efficacy and safety, especially cardiovascular, in head-to-head studies with ibrutinib[8,9]
- Here, we present the preliminary data from a phase 1 study with BGB-11417 as monotherapy or combination with zanubrutinib in patients with CLL/SLL

Bcl-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; SLL, small lymphocytic lymphoma.

1. Kapoor et al. *Cell Death Dis* 2020;11(11):941; 2. Hu et al. AACR 2020. Abstract 3077; 3. Soumerai, et al. *Lancet Haematol*. 2021;8(12):e879-e890; 4. Hillmen et al. *J Clin Oncol* 2019;37(30):2722-2729; 5. Jain et al. *N Engl J Med* 2019;380(22):2095-2103; 6. Wierda *J Clin Oncol* 39:3853-3865. 2021; 7. Kater et al. *NEJM Evidence*. 2022;1(7); 8. Brown, et al. Clinical Lymphoma Myeloma and Leukemia. 2022/10/01/ 2022;22:S266.

9. Tam, et al. ASCO 2022. Abstract 7521.

BGB-11417 Is More Potent and Selective Than Venetoclax

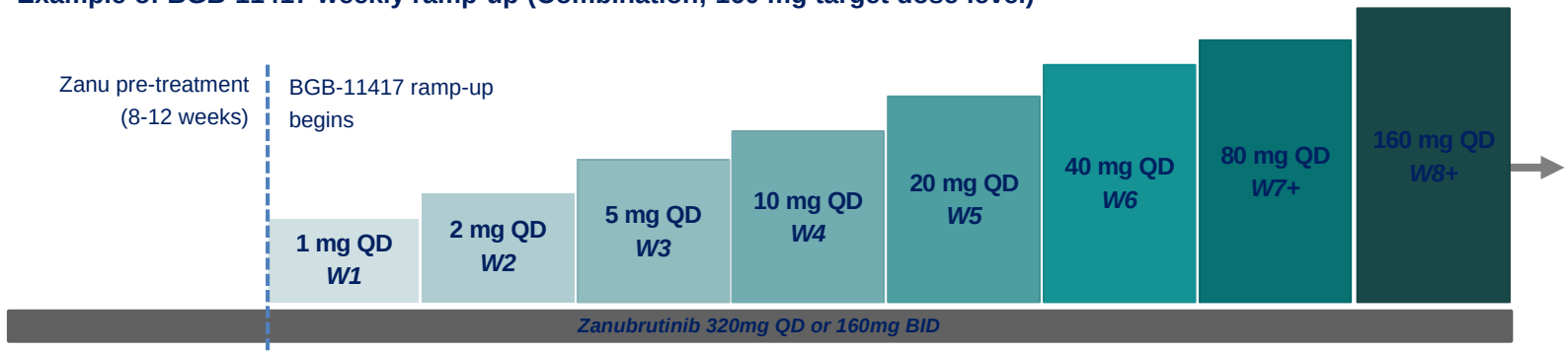
		Bcl-2 IC_{50} nM	Bcl-2 G101V IC_{50} nM
Highly potent[1,a]	BGB-11417	0.014 ± 0.0021	0.59 ± 0.08
	Venetoclax	0.20 ± 0.015	34 ± 3.8
	Ratio (BGB-11417:venetoclax)	**1:14**	**1:57**

		Bcl-2	BCLxL	BCL-w	MCL1	BCLA1
Highly selective[1,b]	BGB-11417	1	1/2000	1/129,000	<1/714,000	<1/714,000
	Venetoclax	1	1/325	1/13,700	<1/50,000	<1/50,000
	Ratio (BGB-11417:venetoclax)	-	**1:6**	**1:9**	-	-

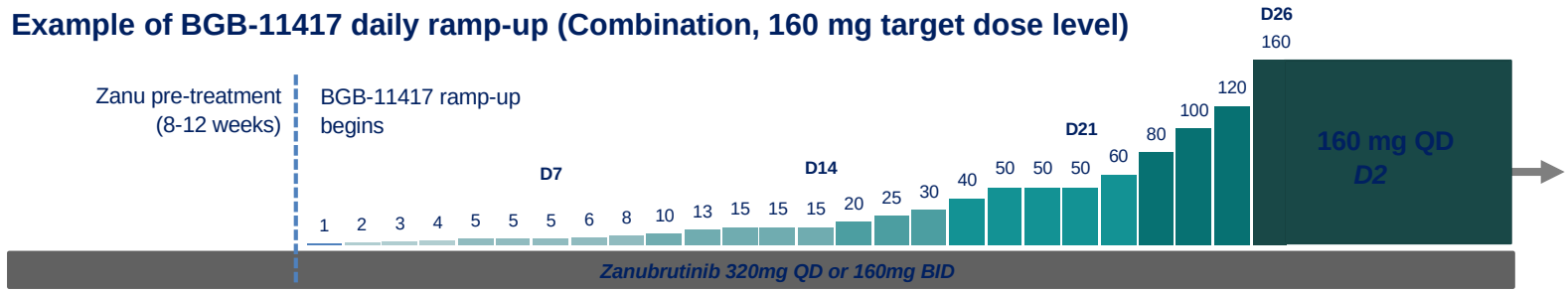
[a]Biochemical assays based on the time-resolved fluorescence resonance energy transfer methodology. [b]Relative selectivity compared to BCL2.
Bcl-2, B-cell lymphoma 2; BCLA1, B-cell lymphoma-A1; BCL-w, B-cell lymphoma-w; BCLxL, B-cell lymphoma-extra large; MCL1, myeloid cell leukemia-1.
1. Hu et al. AACR 2020. Abstract 3077

Dose Ramp-up Schedules

Example of BGB-11417 weekly ramp-up (Combination, 160 mg target dose level)



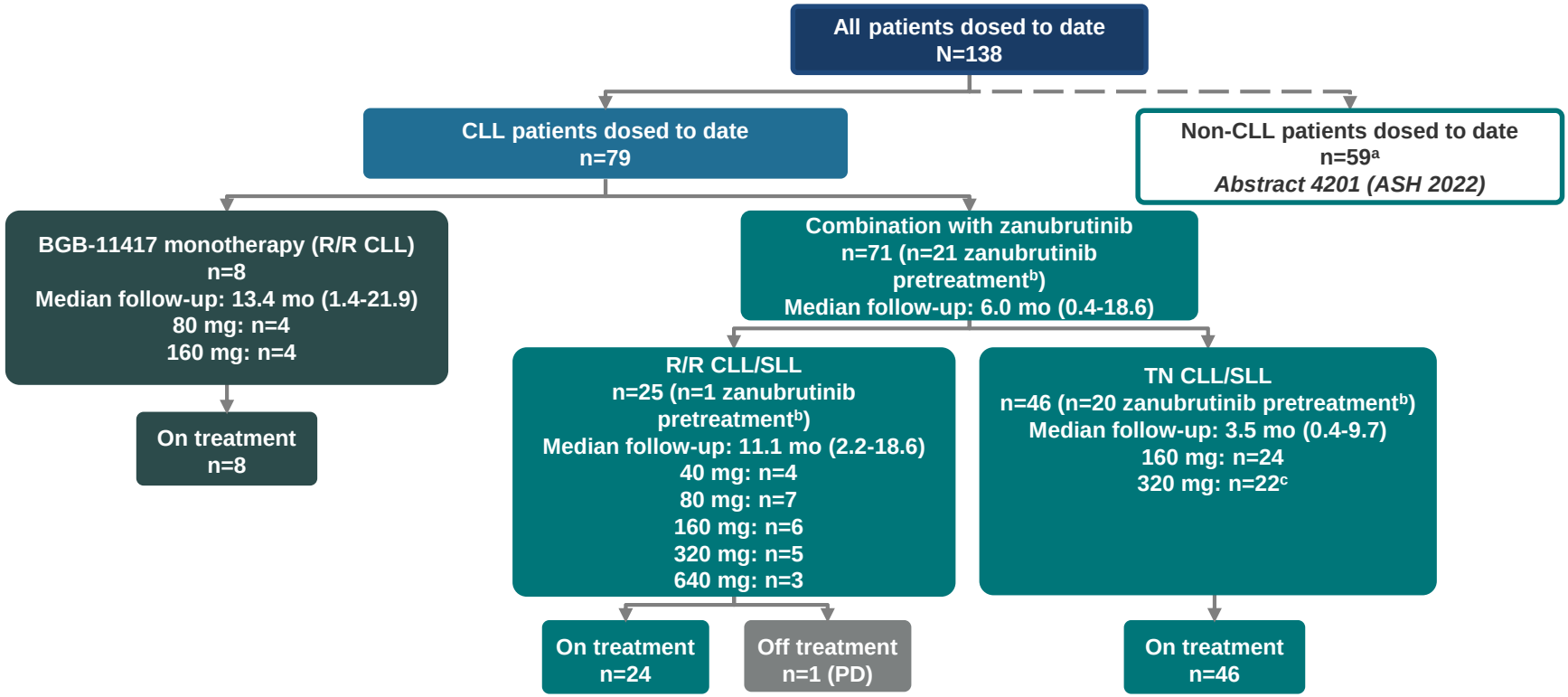
Example of BGB-11417 daily ramp-up (Combination, 160 mg target dose level)



- TLS prophylaxis included hydration, started 24-48 hours prior to first dose
- Allopurinol started 2-3 days prior to first dose and rasburicase as indicated
- Hospitalization for observation was initially required for each new ramp-up dose level for first 3 dose levels but the requirement has been removed per SMC

D, day; QD, every day; SMC, safety monitoring committee; TLS, tumor lysis syndrome; W, week; Zanu, zanubrutinib.

Patient Disposition



Data cutoff date: 01 Sep 2022.

[a]Poster is available after session. [b]Patients who are still in the zanubrutinib pretreatment phase and have not yet received BGB-11417. [c]All patients were assigned to a weekly ramp-up schedule except for n=4 TN patients (320mg dose level).

CLL, chronic lymphocytic leukemia; mo, months; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive.

Summary of Adverse Events and DLTs

- Only 1 DLT of febrile neutropenia noted among patients with CLL with BGB-11417 monotherapy at 80 mg; no DLTs were observed to date with the combination therapy at any dose level
- Toxicity does not seem dose dependent
- These AEs are consistent with BGB-11417 NHL data,[1] which tested through 640 mg with no MTD reached

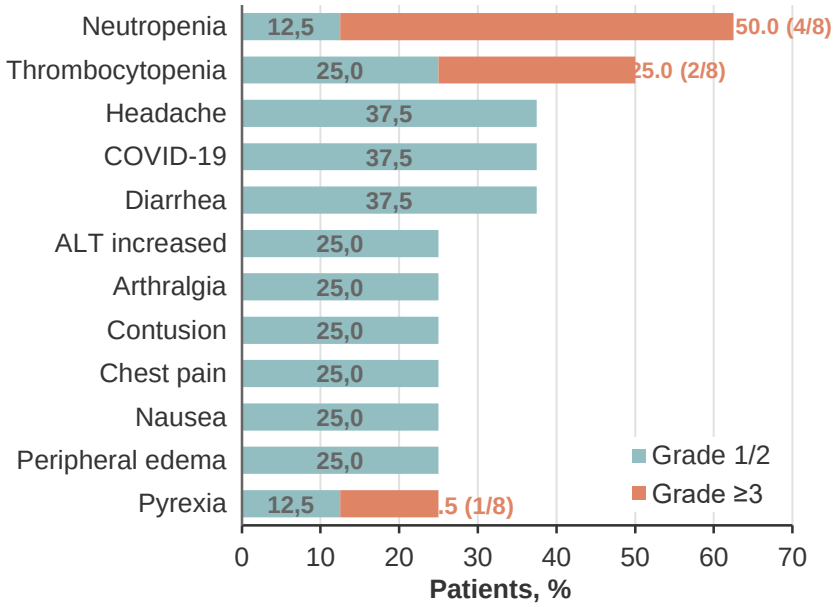
TEAE, n, %	BGB-11417 monotherapy (n=8)	BGB-11417 + zanubrutinib (N=71)	All patients with CLL (N=79)
Any AEs	8 (100)	61 (86)	69 (87)
Grade ≥3	5 (63)	20 (28)	25 (32)
Serious AEs	2 (25)	7 (10)	9 (11)
Leading to death	0	0	0
Treated with BGB-11417	**8**	**50**	**58**
Leading to hold of BGB-11417	5 (62.5)	14 (28)	19 (33)
Leading to dose reduction of BGB-11417	0	1 (2)	1 (2)
Leading to discontinuation of BGB-11417	0	0	0

AE, adverse event; CLL, chronic lymphocytic leukemia; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; TEAE, treatment-emergent adverse event.

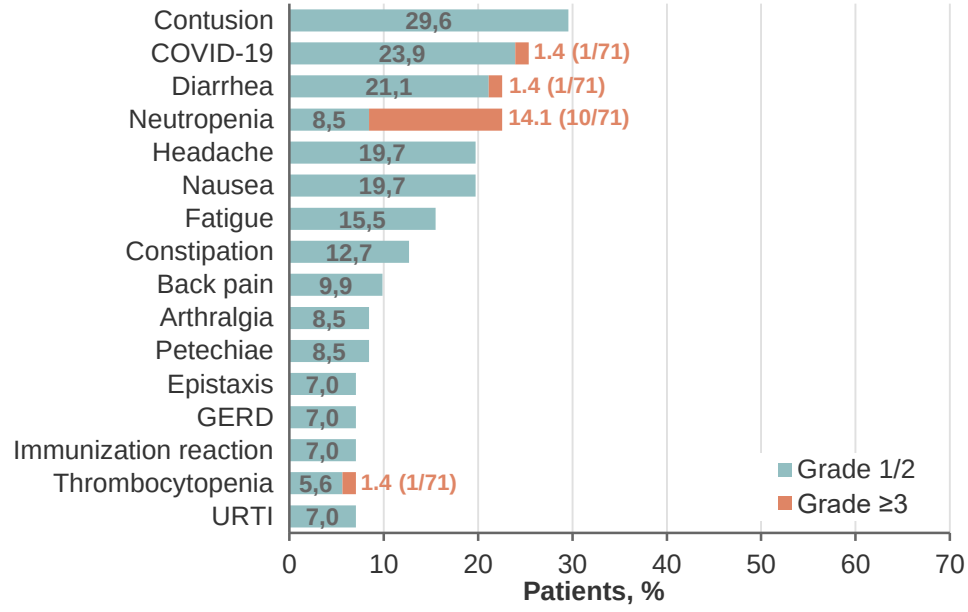
1. Soumerai, et al. ASH 2022. Abstract 4201.

Most Frequent Adverse Events

BGB-11417 Monotherapy, n=8
(Events in ≥2 Patients)



BGB-11417 + Zanubrutinib, n=71[a,b]
(Events in ≥5 Patients)



[a]Includes 21 patients who are still in zanubrutinib pretreatment phase and have not yet received BGB-11417. [b]Includes 46 patients who are TN.
ALT, alanine transaminase; GERD, gastroesophageal reflux disease; TN, treatment-naive; URTI, upper respiratory tract infection.

Selected TEAEs

- **TLS:**
  - No clinical TLS and only one lab TLS observed
    - Lab TLS patient had high tumor burden receiving monotherapy[a]
    - The pre-dose urate was elevated the phosphate rose post-dose
  - No TLS was observed with daily ramp-up (TN combination at 320mg; n=3)
- **GI toxicity:** diarrhea was mostly grade 1
  - Monotherapy grade ≥2: 12.5%; combination grade ≥2: 5.6% and grade 3: n=1
- **Neutropenia:**
  - G-CSF use[b]: monotherapy 4/8 (50%) patients; combination 10/71 (14.1%) patients
  - Only 3/78 (3.8%) patients used more than one course of G-CSF to treat neutropenia

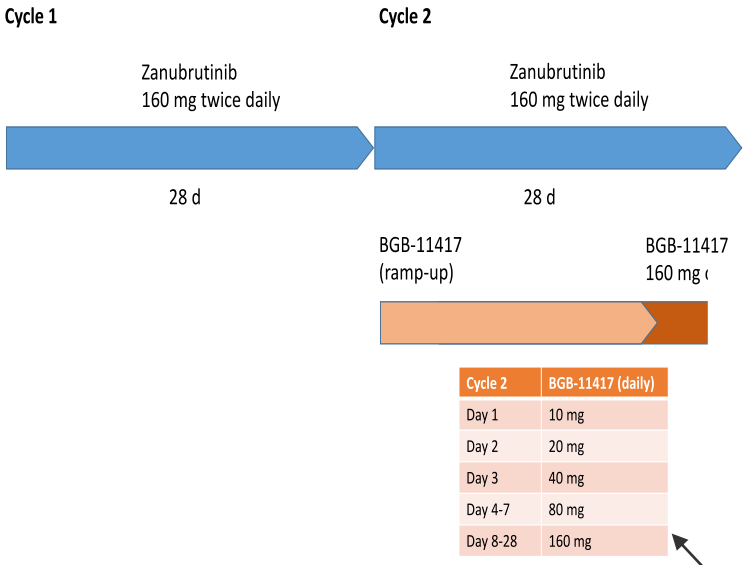
[a]High tumor burden is any node ≥10 cm or a node ≥5 and <10 cm with an ALC ≥25x10^9/L. If a patient is not classified as "high" they are classified as "low." [b]Includes all patients reporting G-CSF use during treatment, regardless of whether used for neutropenia or otherwise.
G-CSF, granulocyte colony stimulating factor; GI, gastrointestinal; TLS, tumor lysis syndrome; TN, treatment-naive.

Conclusions

- BGB-11417, alone or in combination with zanubrutinib, was well tolerated
  - Dose escalation continues to 640 mg with only one DLT; MTD was not achieved
  - Grade ≥3 neutropenia and grade ≥2 diarrhea were uncommon and manageable
  - Only one laboratory TLS was seen; TLS was mitigated by the prophylactic measures and ramp-up schedule
- Promising efficacy is seen in monotherapy and in combination with zanubrutinib in R/R and in TN CLL/SLL
- Based on ALC reduction, BGB-11417 may be about 5 times as potent as venetoclax by dose
- MRD data are preliminary but appear promising
- A venetoclax-treated CLL/SLL cohort is recruiting

FILOMW4-WaZaBi	**Co: *K Laribi/D Ghez/O Tournilhac*** ***Biologie: S Poulain***	**CDP: à définir** **PM: *V. Rouillé***
Synopsis	Open label phase 2 study evaluating the efficacy and tolerance of a **Za**nubrutinib and **B**GB-11417 combination in patients previously treated **Wa**ldenström macroglobulinemia	
Recrutement	102 patients	35 centres
Primary objective	Efficacy measured by the proportion of patients reaching a VGPR or CR, evaluated by investigator, according to the modified response criteria of the Sixth IWWM (Owen, BJH 2013) and NCCN Guidelines, Waldenström's Macroglobulinemia (2015: v2)	
Secondary objectives	Overall Response rate (MR+PR+VGPR+CR) Major Response Rate (PR+VGPR+CR) Efficacy measured by the time to response (TR) Efficacy measured by the time to best response (TBR) Efficacy measured by progression-free survival (PFS). Efficacy measured by duration of response (DOR) defined as the time from first determination of response (CR, VGPR or PR) until first documentation of progression or death, whichever comes first.	
Inclusion criterias	Patients must have received ≥ 1 prior line of treatment, excluding treatment with another BTKi or bcl-2 antagonist. Ecog ≤ 3 Adequate renal function defined as creatinine clearance ≥ 30 ml/min/1.73m2 as determined by the Cockroft-Gault equation	
Etat d'avancement	Engagement scientifique et questionnaire de faisabilité en cours d'envoi aux centres	

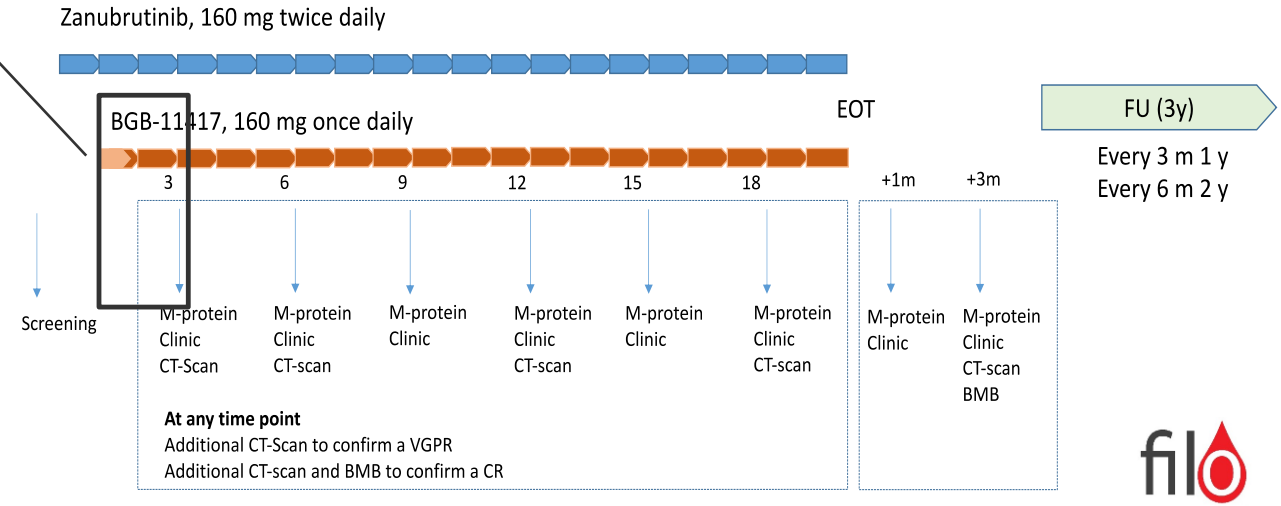
First cycles (C1 and C2)



Cycle 2	BGB-11417 (daily)
Day 1	10 mg
Day 2	20 mg
Day 3	40 mg
Day 4-7	80 mg
Day 8-28	160 mg

Full treatment : cycles 1 to 20

Treatment duration 560 days (18,4 months)



Primary endpoint : best response (VGPR+CR)

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CONCLUSIONS

- Asymptomatic patients do not need treatment
- A multidisciplinary approach involving subspecialists (neurologists, nephrologists, dermatologists) is necessary for best management
- Treatment should be graduated according to the severity of the clinical manifestation
- In some conditions (anti-MAG neuropathy) symptomatic care may be sufficient
- In life-threatening conditions rapidly acting regimens should be promptly instituted

CONCLUSIONS

More data are needed to tailor treatment to the genotype landscape

- Definition of the mutational profile in WM patients is useful and can be used as a diagnostic and prognostic tool

- The statement regarding the lack of effectiveness of ibrutinib in *MYD88* ^{WT} patients is based on a very small group of patients from the pivotal study

- There is a reasonable amount of data now emerging to at least cast some doubt on this lack of activity of BTK inhibitors in *MYD 88* ^{WT} patients. Activity was noted in INNOVATE, acalabrutinib and zanubrutinib studies

- In *CXCR4* ^{mut} patients the quality and the time to best response could be affect by the use of ibrutinib but more data are needed with second generation of BTK inhibitors

CONCLUSIONS

- Immunochemotherapy is the first treatment option in a majority of patients
- Chemo-free treatment are available in relapsing patients (ibrutinib, zanubritinib)
- Combination of new compounds with monoclonal antibodies or combination of new compounds targeting different pathways must be tested into clinical trials for preventing drug resistance and for stopping the drugs

THANK YOU FOR YOUR ATTENTION

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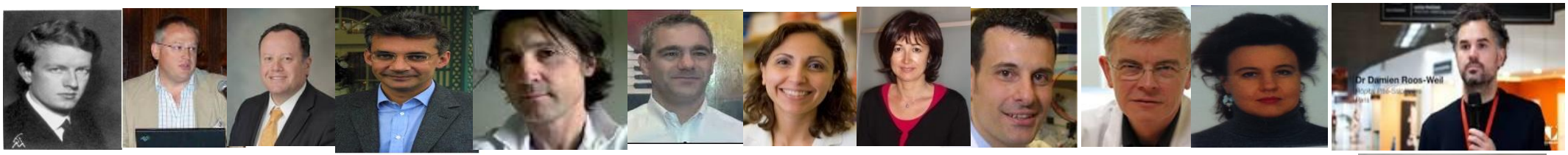

INTERNATIONAL WORKSHOP ON WALDENSTRÖM'S MACROGLOBULINEMIA
Madrid
IWWM-11
2022

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European Consortium for Waldenström's Macroglobulinemia

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Never give up!

Merci pour votre attention