

WALDENSTRÖM MACROGLOBULINEMIA/ LYMPHOPLASMACYTIC LYMPHOMA

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Waldenström Macroglobulinemia

- Described by Jan Waldenström in 1944
- Low grade B-cell lymphoma, 1% of NHL
- Approximately 1000-1500 new cases per year in USA
 - 3.8/million-persons/year
- Median age at diagnosis is 69 years
- More common in Caucasians
- Familial predisposition in up to 26% cases

(From Med. Clin. Akad. Hospital, Uppsala [Sweden]. Chief: Prof. G. Bergström).

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

by

JAN WALDENSTRÖM.

Submitted for publication September 2, 1943.

The real nature of myelomatosis.

The title of this paper may at first seem somewhat surprising. The myeloma has of old had a reputation as a well defined clinical entity. With the aid of the typical changes on the X-ray film and guided by the examination of the cells from a sternal puncture the diagnosis should therefore be easy and there ought not to be found any serious diagnostic troubles. In the following I am going to give a description of two cases, who have several symptoms suggesting myelomatosis but also show decided differences. They are very much alike even as regards details in the chemistry of the blood proteins and it seems probable according to my opinion, that they suffer from the same malady. A third case very much resembles these two patients but also shows other signs, that do not fit in so well with the picture.

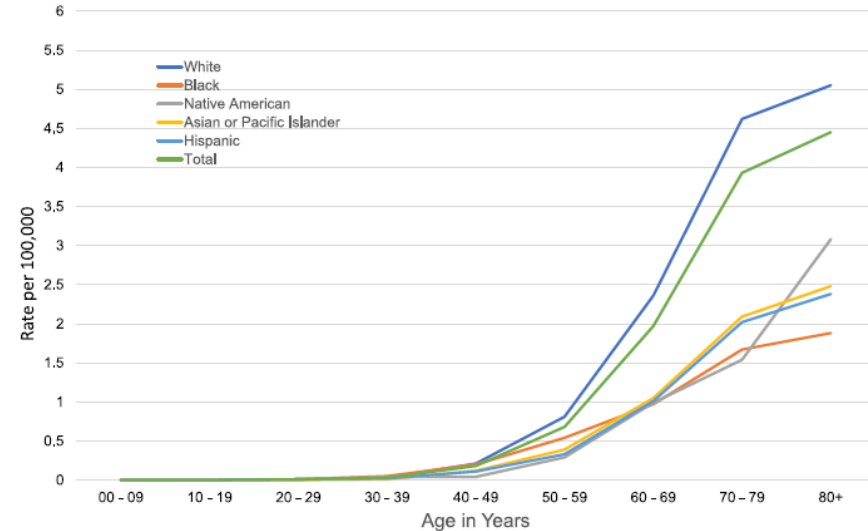
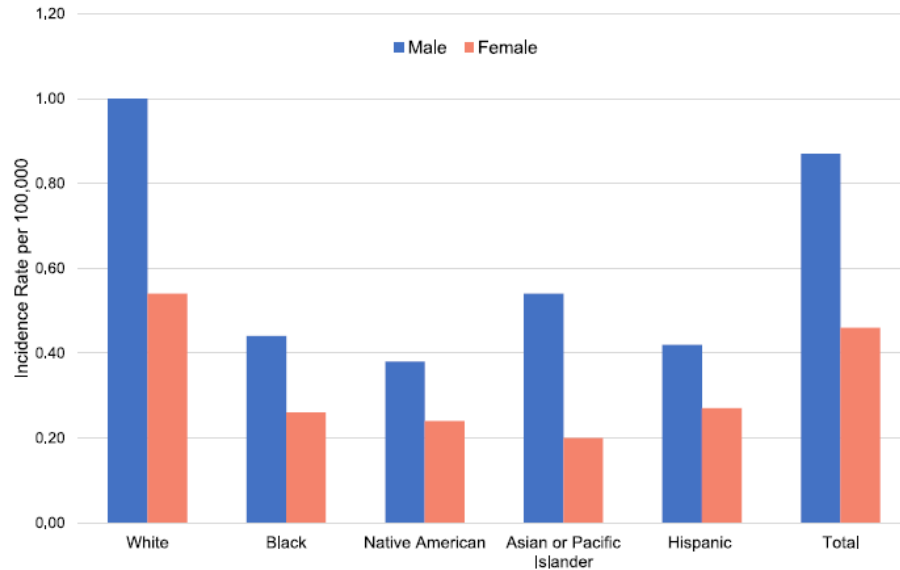
It might be possible to regard these patients as myeloma without myeloma I, i. e. the hypothesis may be propounded, that we have to do with a premyelomatous stage of the malady with only increase in serum globulins but not yet with the secondary deposition of myeloma tissue, plasma cells, in the bone marrow (Waldenström 1942). I have recently pointed out, that many facts in the

Jan Gösta Waldenström

(17.4.1906 – 1.12.1996)



Incidence rate of WM and LPL, USA 2000-2019 SEER Program



Race, Ethnicity, Sex, Age

WHO Criteria

- Lymphoplasmacytic lymphoma (LPL)
 - Neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells
 - Usually involving bone marrow and sometimes lymph nodes and spleen
 - Does not fulfill criteria of any other small B-cell lymphoid neoplasm that may also have plasmacytic differentiation
 - Swerdlow SH, et al. WHO 2017
- Waldenström Macroglobulinemia (WM)
 - Lymphoplasmacytic lymphoma with bone marrow involvement
 - IgM monoclonal gammopathy of any concentration
 - Owen RG, et al. Clinicopathological definition of Waldenstrom's Macroglobulinemia: Consensus Panel Recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol 2003;30:110-115

Waldenström Macroglobulinemia International Workshop Criteria

- Proposed criteria for the diagnosis of WM
 - IgM monoclonal gammopathy of any concentration
 - Bone marrow infiltration by small lymphocytes, plasmacytoid cells and plasma cells
 - Diffuse, interstitial, or nodular pattern of bone marrow infiltration
 - CD19+, CD20+, sIgM+; CD5, CD10, CD23 can be expressed in some cases of WM and does not exclude diagnosis
 - Owen RG. Developing diagnostic criteria in Waldenström's macroglobulinemia. Semin Oncol 2003;30:196-200.

Manifestations of WM



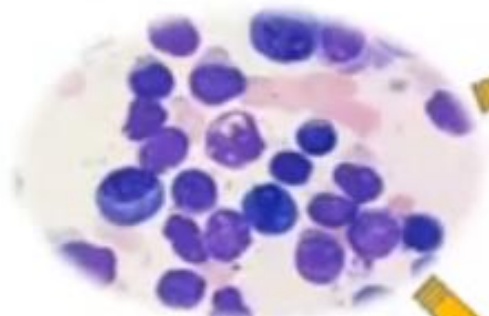
Bing Neel Syndrome,
rare CNS
infiltration with
lymphoma



Lymphadenopathy
≤20% at diagnosis;
50-60% at relapse.

Bone Marrow

↓HB>>> ↓PLT> ↓WBC



Hyperviscosity Syndrome:
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP



Cold Agglutininemia (5%)
Cryoglobulinemia (10%)
IgM Neuropathy (20%)
Amyloidosis (5-10%)



↑Hepcidin (protein regulator of iron)
↓Fe-> Anemia

Constitutional symptoms: fevers, night
sweats, weight loss, fatigue, itch

Diagnosis of WM

History and physical examination

Include familial history for WM and other B cell lymphoproliferative disorders

Screen for symptoms among others related to hyperviscosity, neuropathy, cold-agglutinins, amyloidosis, coagulation disorders and adapt further diagnostics accordingly

In the case of high IgM and suspicion of hyperviscosity perform fundoscopic examination

Laboratory analyses

Complete blood count

- Complete metabolic panel
- Serum Ig levels (IgA, IgG, IgM)
- Serum and urine electrophoresis with immunofixation
- Serum B2M level
- Coagulation status
- Viral serology (HBV, HCV and HIV)

If clinically indicated:

- Cryoglobulins
- Cold agglutinin titre
- Screening for acquired von Willebrand disease
- 24-h urine protein quantification
- Serum FLCs
- NTproBNP, cardiac troponins
- EMG, anti-MAG, anti-GM1 (consultation with neurologist)

Bone marrow biopsy

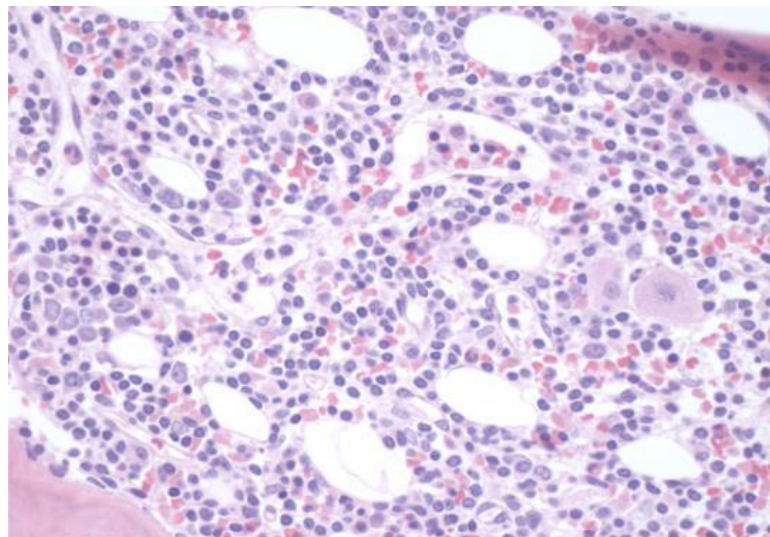
Testing for MYD88 and CXCR4.

Bone marrow aspirate with flow cytometry optional

Imaging

Sonography

CT chest, abdomen, pelvis (PET/CT not established)



IgM related syndromes (1)

- **Hyperviscosity syndrome** – 15%
 - Blurred vision, headache, dizziness, hearing impairment, confusion, stroke, bleeding
 - Often viscosity is >4.0 cp, IgM >3000 mg/dl
 - Symptomatic hyperviscosity syndrome may require urgent plasmapheresis
- **Peripheral neuropathy** -25%
 - Typically symmetrical, distal, sensory; progressive over years
 - 50% associated with demyelinating auto-antibody (MAG, GM1, sulfatide)
 - Some cases with axonal damage
 - Post patients have relatively low IgM level

IgM related syndromes (2)

- **Cold-agglutinin hemolytic anemia** – 5%
 - IgM autoantibody causing clumping of RBCs causing lysis of RBCs
- **Cryoglobulinemia** – 10%
 - IgM precipitate in cold temperature
 - Raynaud phenomenon, skin rash, finger tip cyanosis and necrosis
- **Amyloidosis** – 5%
 - Deposition of fibril material to various organs (heart, kidney, bowel, skin) detected by Congo red staining in BM or fat pad aspiration
- **IgM deposition syndromes**
 - Malabsorption (GI), cough and dyspnea (lungs), skin rash and thickening



Raynaud phenomenon

Papilledema with sausage-shaped (distended and tortuous) retinal veins and hemorrhage

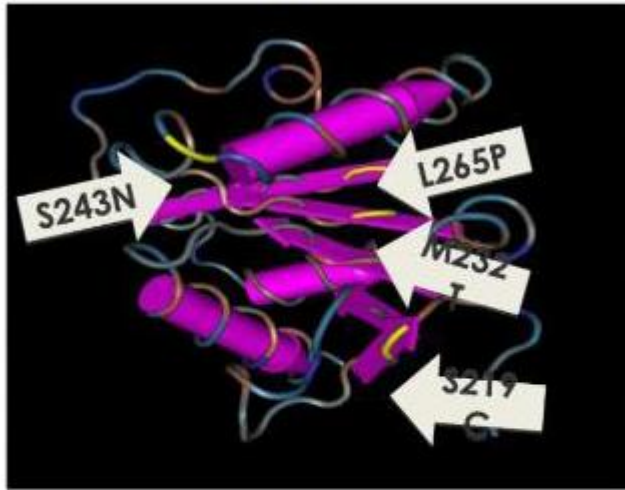
Bing Neel Syndrome

- Rare manifestation of WM due to CNS infiltration by malignant lymphoplasmacytic cells
- Symptoms
 - Headache
 - Cognitive decline
 - Cranial nerve deficits
 - Paresis
 - Psychiatric symptoms
- Diagnostic workup
 - CSF analysis with multi-parameter flow cytometry for B-cell clonality testing
 - Molecular diagnostic testing for mutated MYD88
 - MRI of brain and spinal cord prior to lumbar puncture to exclude mass effect and/or obstructive hydrocephalus and avoidance of non-specific meningeal enhancement

Genomic Mutations in WM

- Activating MYD88 as well as nonsense and frameshift WHIM-like CXCR4 somatic mutation are common in WM
 - MYD88 L265P mutation was found in 90-95% of WM patients
 - CXCR4 mutations (CXCR4^{WHIM/NS} and CXCR4^{WHIM/FS}) were found in 30% of WM patients
- CXCR4 NS mutations are present in aggressive cases including hyperviscosity syndrome, and MYD88 status is a determinant of survival

WM



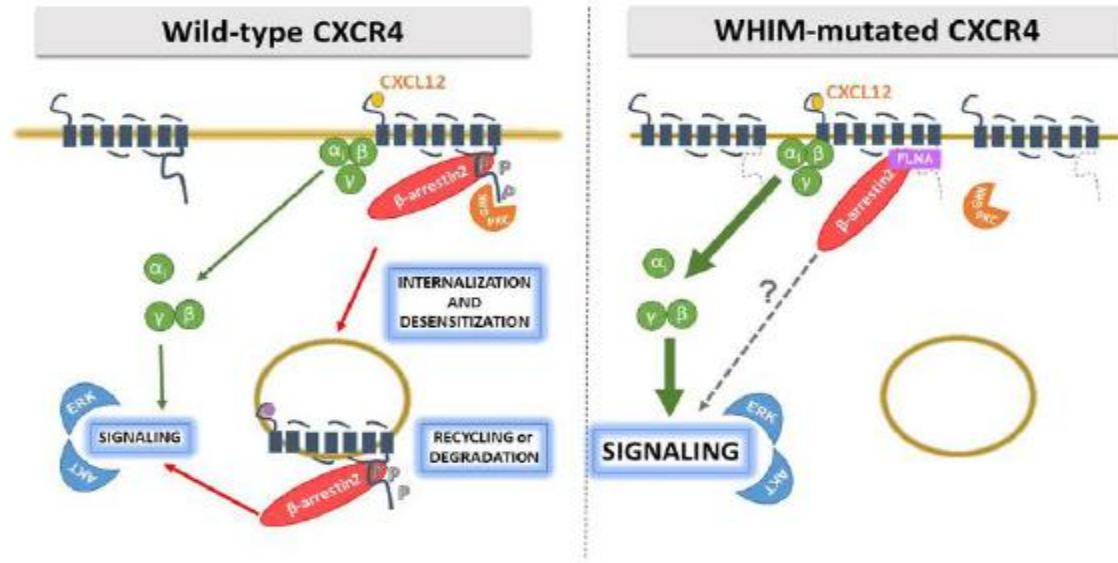
93-95% MYD88 L265P
2% Non-L265P MYD88

MYD88 Mutations

- 80-100% of WM patients
- 10-80% of IgM MGUS, higher risk of progression to WM
- Help distinguish WM from others (IgM MM, MZL, CLL)
- MYD88 L265P pts more likely to have higher IgM than MYD88 WT
- MYD88 L265P induces BTK in WM cells
- MYD88 WT occurs in <10% of patients and should not be used to exclude diagnosis of WM if other criteria are met

CXCR4 WHIM (Warts, Hypogammaglobulinemia, Infection, and Myelokathexis)

- 30-40% of WM patients
- >30 nonsense, frameshift mutations
- High serum IgM levels/hyperviscosity
- Promote ibrutinib resistance through enhanced AKT/ERK signaling



Hunter ZR et al. Blood. 2014 Mar 13;123(11):1637-46

Treon S et al. Blood. 2014 May 1;123(18):2791-6

Cao Y et al Leukemia. 2015 Jan;29(1):169-76

Clinical Presentation

S338X

Clinical Characteristics	MYD88 ^{L265P} CXCR4 ^{WT}	MYD88 ^{L265P} CXCR4 ^{WHIM/FS}	MYD88 ^{L265P} CXCR4 ^{WHIM/NS}	MYD88 ^{WT} CXCR4 ^{WT}
IgM	↑↑	↑↑	↑↑↑↑	↑
BM infiltration	↑↑↑	↑↑	↑↑↑↑	↑
Sensitivity to BTK inhibitors	↑↑↑	↑↑	↑	↓
Incidence, %	~60	27-40	27-40	< 10

Patients with MYD88 and Nonsense CXCR4 mutations (S338X) show high IGM levels, symptomatic hyperviscosity, and shorter time to initial treatment.

Progression of Waldenström Macroglobulinemia

- It is preceded by a precursor condition called an IgM MGUS
- WM can be either **symptomatic** or **asymptomatic** at initial diagnosis
 - IgM MGUS
 - **Asymptomatic/ minimally symptomatic** Waldenström Macroglobulinemia
 - **Symptomatic** Waldenström Macroglobulinemia

IgM MGUS

- Found in 1 in 600 persons over age 50
 - 3x more common than WM
- More common in the elderly
- Patients with IgM MGUS require lifelong monitoring
- Risk factors
 - Abnormal kappa/lambda ratio
 - M-spike >1.5 g/dl
- Risk for progression at 20 years
 - 2 risk factors: 55%
 - 1 risk factor: 41%
 - 0 risk factor: 19%

Asymptomatic/ minimally symptomatic WM

awmrisk.com

- Patients can fulfill diagnostic criteria for WM without symptoms related to disease
- Some patients with asymptomatic WM may not require therapy for prolonged periods of time
 - 6% at 1 year
 - 39% at 3 years
 - 59% at 5 years
 - 65% at 10 years

Treon SP, et al. Semin Hematol 2023;60(2):97-106.

AWM Patient Risk Calculator ⓘ
Asymptomatic Waldenström Macroglobulinemia
Developed by Dana-Farber Cancer Institute

Please complete all the fields below

Note: This page does not collect or store patient data.

Bone Marrow Infiltration %
50 %
Field allows 0-100%

IgM Protein Level
6000 mg/dL
Field allows 0-8000 mg/dL (reference: 37-286 mg/dL)

Beta2-Microglobulin Level
3 mg/L
Field allows 0-10 mg/L (reference: 0.7-1.8 mg/L)

Albumin Level
3 g/dL
Field allows 0-10 g/dL (reference: 3.5-5.5 g/dL)

If you are a patient diagnosed with AWM, we encourage you to enter your lab data here and share these results with your oncologist or healthcare provider. The tool may help you discuss your risks and treatment strategies.

Patient Results

Patient's Risk Score **8.3681**

Patient's Risk Group

Low	< 0.5019
Medium	0.5019 - 1.8512
High	> 1.8512

Median Time to Progression ⓘ
as determined by risk group **1.8 years**

0 2 4 6 8
Years

Calculate Risk Score

Re-Enter Fields

Revised IPSS Waldenström Macroglobulinemia Scoring System

Criteria for the Diagnosis of Waldenström Macroglobulinemia (only at the time of initial treatment prognostication)

Table 1

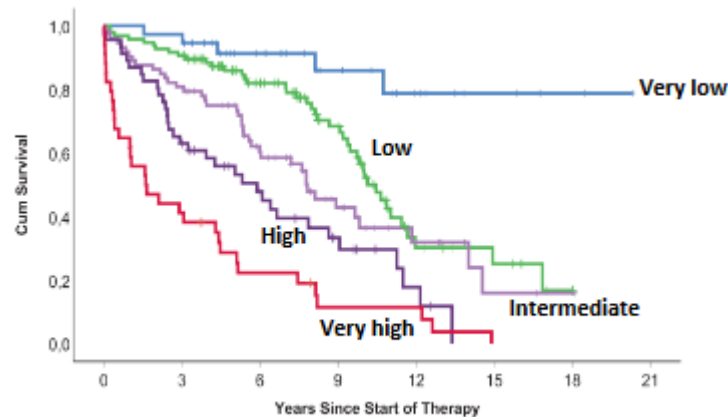
	Points
Age <65	0
Age 66–75	1
Age >75	2
B2 microglobulin >4 mg/L	1
LDH >250 IU/L	1
Serum albumin <3.5 g/dL	1

Table 2

Score*	Stage
0	Very Low
1	Low
2	Intermediate
3	High
4–5	Very High

*Sum of total points in Table 1

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



Indication to start treatment in WM

Clinical indications for initiation of therapy
Recurrent fever, night sweats, weight loss, fatigue
Hyperviscosity
Lymphadenopathy: either symptomatic or bulky (≥ 5 cm in maximum diameter)
Symptomatic hepatomegaly and/or splenomegaly
Symptomatic organomegaly and/or organ or tissue infiltration
Peripheral neuropathy because of WM
Laboratory indications for initiation of therapy
Symptomatic cryoglobulinemia
Symptomatic cold agglutinin anemia
Autoimmune hemolytic anemia and/or thrombocytopenia
Nephropathy that is related to WM
Amyloidosis that is related to WM
Hemoglobin ≤ 10 g/dL
Platelet count $< 100 \times 10^9/L$

Watch and Wait

- Monitoring with clinic visits and lab tests
 - CBC with differential count
 - IgM level
 - Symptoms (hyperviscosity syndrome, tumor mass or infiltration, effects of IgM)
 - Chemistry panel
- Imaging if needed



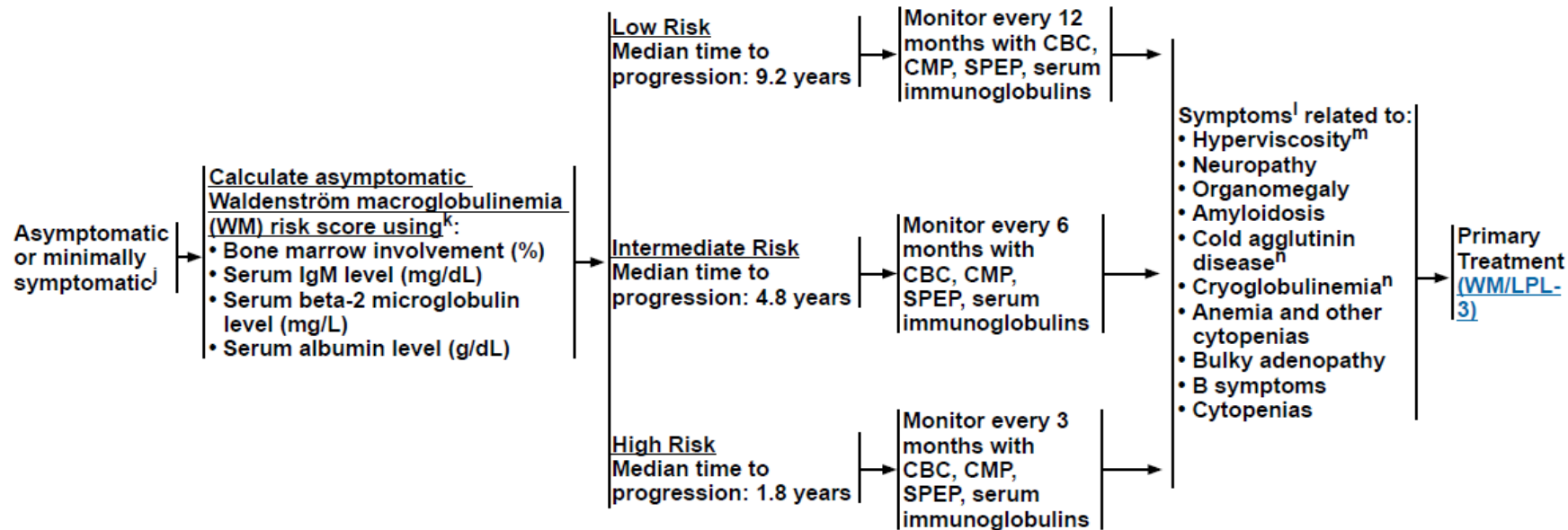
NCCN Guidelines Version 3.2025

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

ASYMPTOMATIC OR MINIMALLY SYMPTOMATIC WM

FOLLOW-UP

INDICATIONS FOR TREATMENT





NCCN Guidelines Version 3.2025 Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

PRIMARY TREATMENT°

MANAGEMENT AFTER PRIMARY TREATMENT

RELAPSE

Plasmapheresis for symptomatic hyperviscosity^p and Primary therapy, see [WM/LPL-B](#) or Clinical trial

If transformation, see [NCCN Guidelines for B-Cell Lymphomas](#). Histologic Transformation of Indolent Lymphoma to Diffuse Large B-cell Lymphoma (DLBCL)

If treated with fixed-duration chemoimmunotherapy regimens

Observe^{s,t} until progressive disease^{r,u}

If treated with BTK inhibitor regimens

Continue treatment until symptomatic disease progression (beyond biochemical progression) or unacceptable toxicity

If persistent symptoms^q

No response/
Progressive disease^r

Consider previously used regimens, if well tolerated and had a prolonged response^v see [WM/LPL-B](#)

Choose alternative therapy, see [WM/LPL-B^v](#)

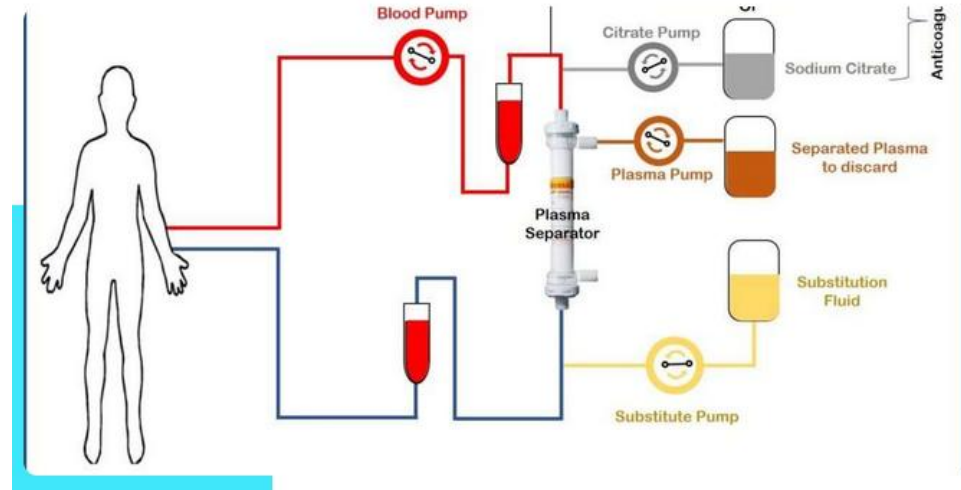
If transformation, see [NCCN Guidelines for B-Cell Lymphomas](#). Histologic Transformation of Indolent Lymphoma to DLBCL

Treatment of WM

- Plasmapheresis
 - For rapid reduction of IgM protein level
 - Does not treat the underlying lymphoma
- Cyto reduction therapy
 - To reduce the lymphoma disease burden
 - To reduce IgM production
- Maintenance therapy

Plasma exchange temporizes hyperviscosity

- Plasma exchange (plasmapheresis, PLEX)
- Removes excess IgM
 - To relieve hyperviscosity syndrome
 - To bring IgM to <4000 mg/dl prior to planned treatment (eg. Rituximab)
- Single PLEX is often sufficient



<https://www.arthritiscenters.net/resource/plasma-exchange-plasmapheresis/>

NCCN Guidelines Version 3.2025

Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

IWWM-11 RESPONSE CRITERIA FOR ASSESSMENT OF DISEASE RESPONSE IN WM/LPL¹

Response ^a	Serum Monoclonal IgM	Serum IgM Level	Bone Marrow Aspirate and Trephine Biopsy	Extramedullary disease
Complete Response (CR)	Absence of monoclonal IgM protein by SPEP and IFX.	Within normal range	Normal morphology; no evidence of LPL involvement.	Absence of extramedullary disease if present at baseline. See criteria for determination of resolution of extramedullary disease. ^e
Very good partial response (VGPR)		≥90% reduction in serum IgM levels or within normal range		
Partial response (PR)		≥50% to <90% reduction in serum IgM levels		
Minor response (MR)		≥25% to <50% reduction in serum IgM levels		
Stable disease (SD)		<25% reduction to <25% increase in serum IgM levels		
Progressive disease (PD)		≥25% increase in serum IgM levels with a minimum increase of 500 mg/dL from nadir. Reconfirmation is required by 2 sequential (back-to-back) measurements if the serum IgM is being used to support PD. Demonstration of PD by imaging does not require re-confirmation. ^{b,c}		Any new lesion (>1.5 cm in any axis) or unequivocal evidence of an increase by > 50% in any axis to >1.5 cm in size of previously involved extramedullary disease sites from their nadir measurements. Any new lesion consistent with transformed disease.
Nonevaluable (NE)		Suspected IgM flare or IgM rebound, absence of data or suspected error in data reporting ^d		



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Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

PRIMARY THERAPY FOR WM/LPL^{a,b}

(Order of regimens is alphabetical and does not indicate preference)

Preferred Regimens

- Bendamustine/rituximab
- Ibrutinib^c ± rituximab (category 1)
- Zanubrutinib^c (category 1)

Other Recommended Regimens

- | | |
|---------------------------------------|--|
| • Bendamustine | • Rituximab |
| • Bortezomib/dexamethasone/rituximab | • Rituximab/cyclophosphamide/dexamethasone ±
bortezomib |
| • Carfilzomib/rituximab/dexamethasone | • Rituximab/cyclophosphamide/prednisone |
| • Ixazomib/rituximab/dexamethasone | |



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Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

THERAPY FOR PREVIOUSLY TREATED WM/LPL ^{a,b} (Order of regimens is alphabetical and does not indicate preference)	
Preferred Regimens • Bendamustine/rituximab • Ibrutinib^c ± rituximab (category 1) • Rituximab/cyclophosphamide/dexamethasone • Zanubrutinib^c (category 1)	
Other Recommended Regimens • Acalabrutinib^c • Bortezomib/dexamethasone/rituximab • Ixazomib/rituximab/dexamethasone	• Rituximab/cyclophosphamide/prednisone • Venetoclax
Useful in Certain Circumstances • Bendamustine • Cladribine ± rituximab^d • Everolimus • Fludarabine ± rituximab^d	• Fludarabine/cyclophosphamide/rituximab^d • Pirtobrutinib • Rituximab • RCHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone)
Hematopoietic Cell Transplant • In selected patients HCT may be appropriate with either: ▶ Allogeneic HCT (ablative or nonablative)^e ▶ Autologous HCT	



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Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

MANAGEMENT OF BING NEEL SYNDROME

WORKUP

Neurological deficits concerning Bing Neel syndrome:

- Headaches
- Seizures
- Cranial nerve palsies
- Weakness in limbs
- Atypical neuropathy

Essential

- Brain and entire spine MRI with gadolinium enhancement
- Lumbar puncture for cerebrospinal fluid (CSF) analysis (cytology, multiparameter flow cytometry, PCR for *IgH* gene rearrangement, PCR for *MYD88* L265P)

Useful in Certain Circumstances

- Biopsy of affected tissue
- Concurrent bone marrow aspiration and biopsy for *IgH* gene rearrangement and *MYD88* L265P testing

Definitive Diagnosis

- Presence of clonal B cells in CSF or tissue biopsy with similar profile than systemic disease with or without leptomeningeal enhancement or masses in MRI

Probable Diagnosis

- Abnormal MRI findings without evidence of clonal B cells in CSF or tissue biopsy

Asymptomatic → Observation

Symptomatic^{a,b} →

Preferred Regimens

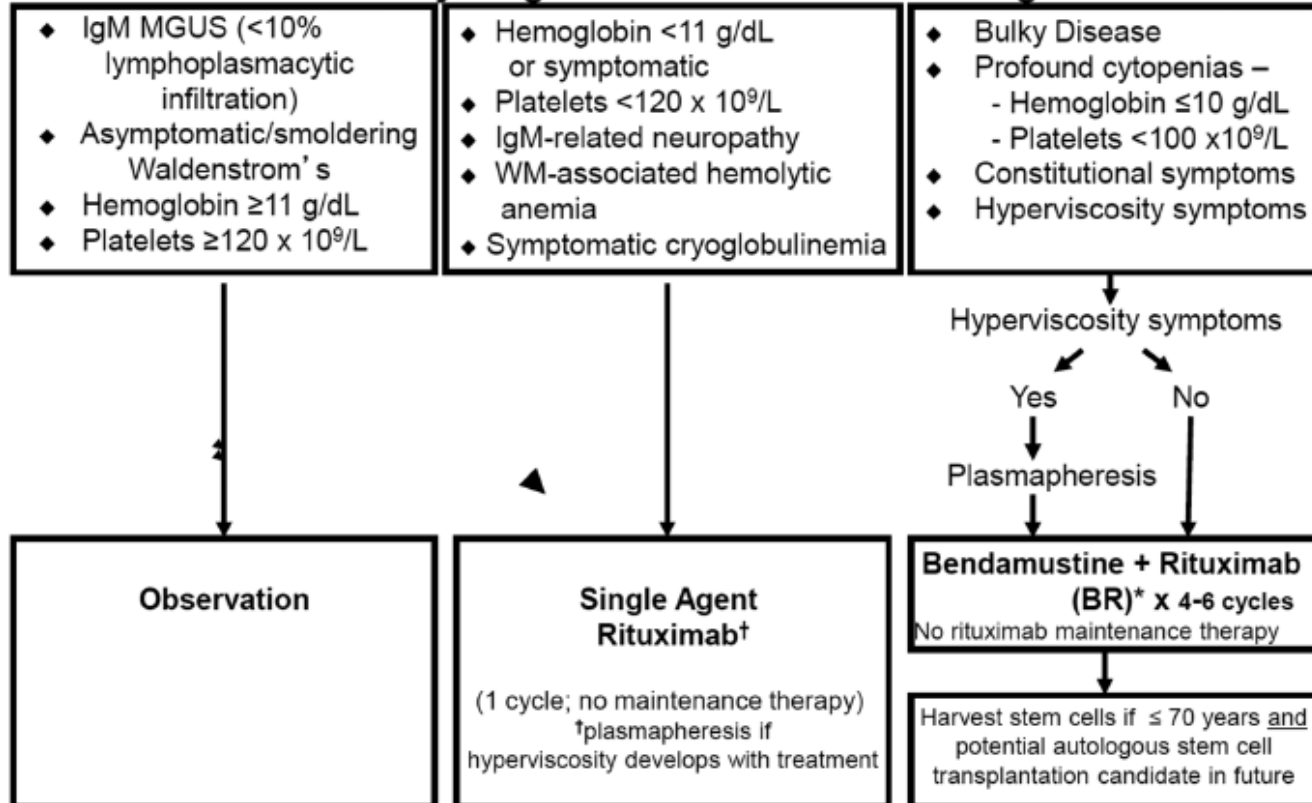
- Ibrutinib
- Zanubrutinib
- Other Recommended Regimens
- Bendamustine
- Cytarabine
- Fludarabine
- Methotrexate

Useful in Certain Circumstances

- Intrathecal methotrexate
- Radiotherapy

Mayo Clinic Consensus for Newly Dx WM

Consensus for Newly Diagnosed Waldenström Macroglobulinemia



Rituximab-based Treatments

- Rituximab alone
 - Previously untreated patients (4/8 weekly): ORR 35%/ 60%
 - Relapsed disease (4/8 weekly): ORR 25%/ 45%
 - DOR 16-29 months
- Rituximab-Chemotherapy combinations (ORR >80-90%)
 - R-Bendamustine
 - R-Cyclophosphamide-steroids
 - R-Purine analogue
 - R-Bortezomib-steroids

Rituximab-induced IgM flare

- Monotherapy (60%)
- Fludarabine/Rituximab (40%)
- Cyclophosphamide/Prednisone/Rituximab (20-30%)
- Thalidomide/Rituximab (50%)
- Lenalidomide/Rituximab (75%)
- Bortezomib/Dexamethasone/Rituximab (9%)

Plasmapheresis should be considered for patients with IgM >5 g/dl or serum viscosity >3.5 cp prior to rituximab treatment

iNNOVATE Study: R-Ibrutinib vs Rituximab alone in WM

Key eligibility criteria

- Confirmed WM^a (N=150)
- Measurable disease (serum IgM >0.5 g/dL)
- RTX sensitive
 - Not refractory to last prior RTX-based therapy
 - Had not received RTX <12 months before first study dose

1:1 Randomization

- Stratification
- IPSSWM (low vs intermediate vs high)
 - Number of prior regimens (0 vs 1-2 vs ≥3)
 - ECOG PS (0-1 vs 2)

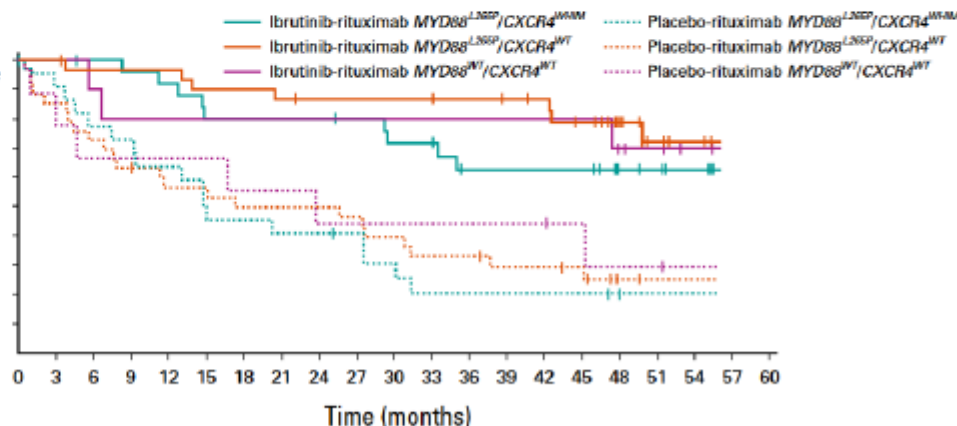
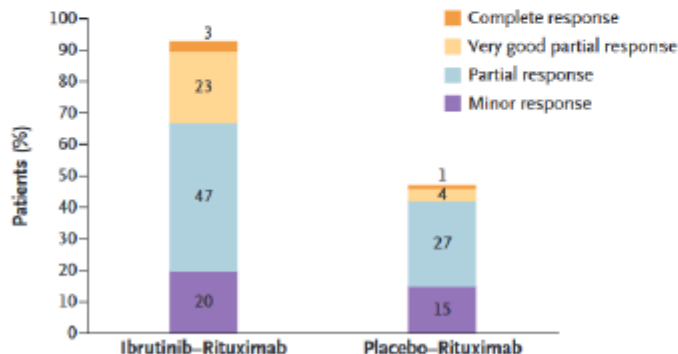
Arm A Ibrutinib-RTX

Oral ibrutinib 420 mg once daily until PD
RTX 375 mg/m² IV on day 1 of weeks 1-4 and 17-20

Arm B Placebo-RTX

Placebo until PD
RTX 375 mg/m² IV on day 1 of weeks 1-4 and 17-20

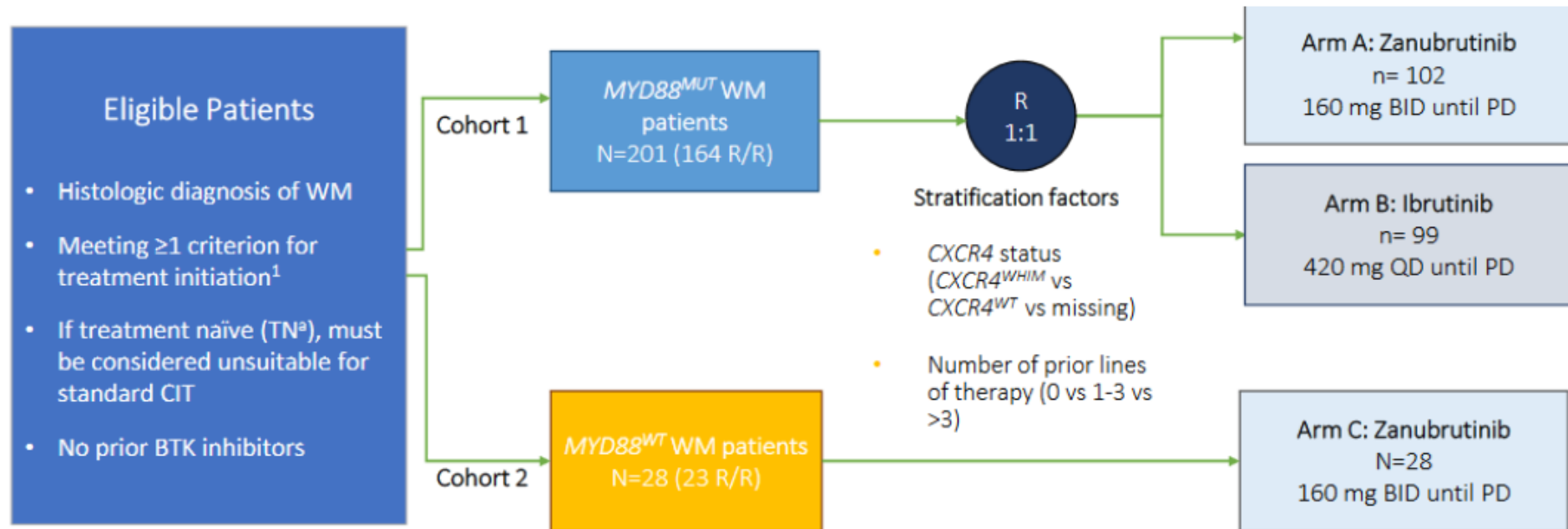
Crossover to single-agent ibrutinib allowed after PD^b



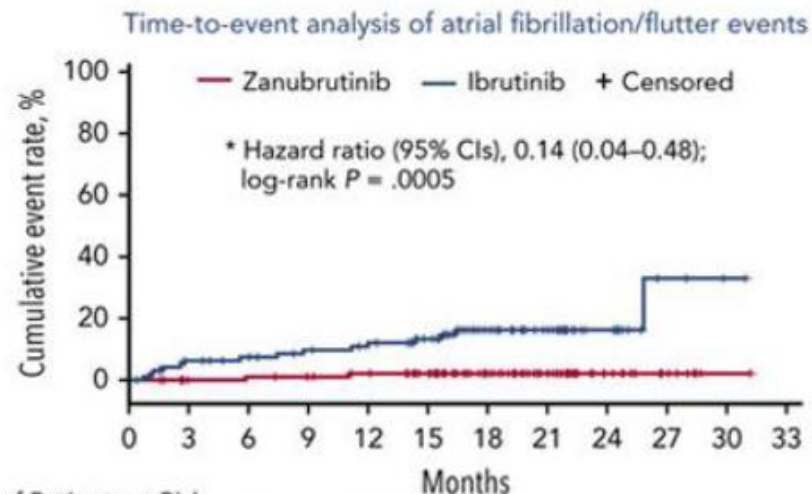
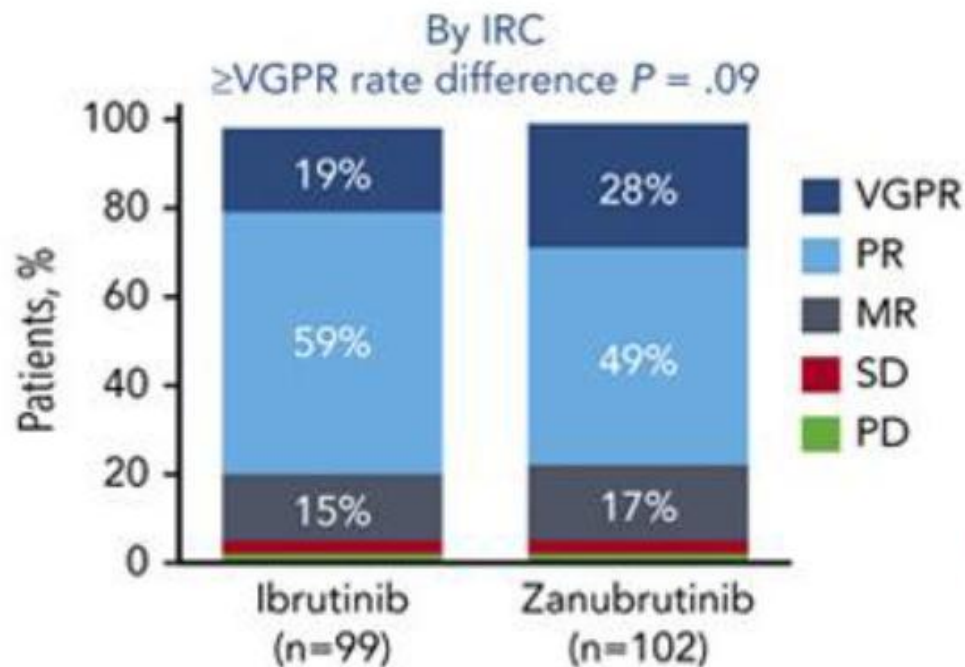
Ibrutinib-rituximab showed superiority outcomes in patients with WM regardless of *MYD88* or *CXCR4* mutation status

M.A. Dimopoulos. N Engl J Med 2018;378:2399-410.
Christian B. J Clin Oncol .2021;40:52-62.

ASPEN: Zanubrutinib vs Ibrutinib in WM



ASPEN: Zanubrutinib vs Ibrutinib in WM with MYD88^{L265P}



No. of Patients at Risk

Zanubrutinib	101	95	94	92	89	81	57	34	15	7	1	0
Ibrutinib	98	87	83	78	74	66	46	28	13	3	1	0

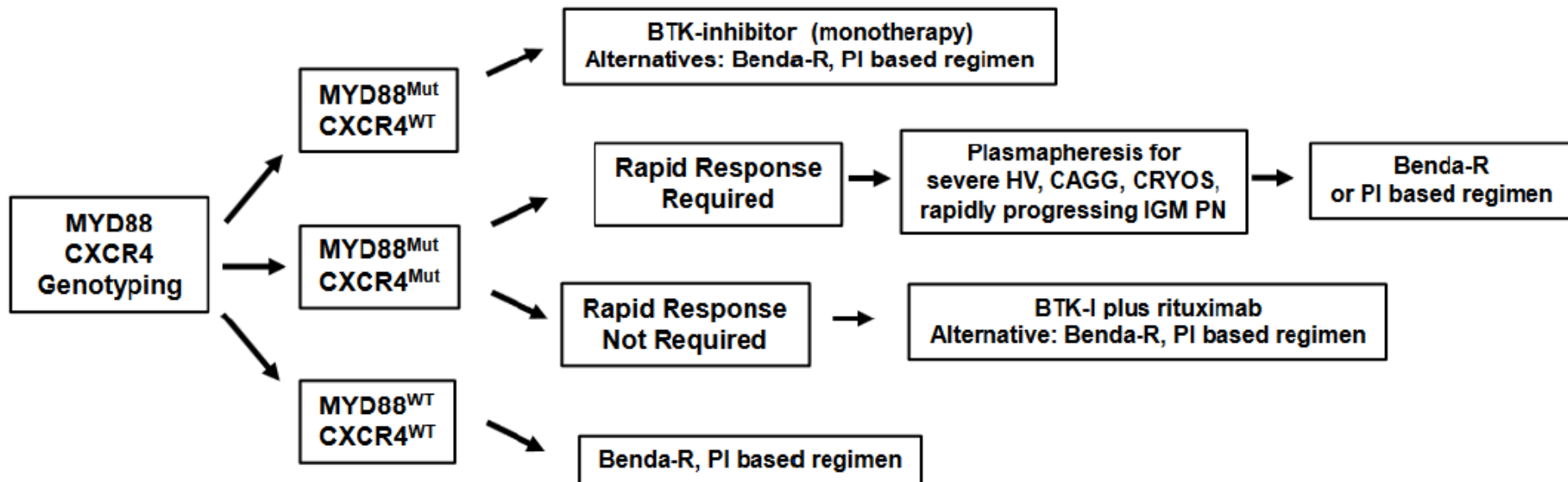
AE Categories, n (%) (Pooled Terms)	All Grades	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	15 (15.3)	2 (2.0)

Zanubrutinib and ibrutinib are highly effective in the treatment of WM, but zanubrutinib treatment was associated with a trend toward better response quality and less toxicity, particularly cardiovascular toxicity.

ASPEN: Zanubrutinib vs Ibrutinib in WM with MYD88^{L265P}

Mutation status	Zanubrutinib (N=101)		Ibrutinib (N=98)	
	MRR	VGPR	MRR	VGPR
Cohort 1				
ALL MYD88 ^{MUT}	77%	28%	78%	19%
MYD88 ^{MUT} CXCR4 ^{WT}	82%	34%	82%	24%
MYD88 ^{MUT} CXCR4 ^{WHIM}	70%	18%	65%	10%

Genomic Based Treatment Approach to Symptomatic Treatment Naïve WM



- Rituximab should be held for serum IgM > 4000 mg/dl
- Benda-R for bulky adenopathy or extramedullary disease
- PI-based regimen for symptomatic amyloidosis, and possible ASCT as consolidation
- Rituximab alone, or with ibrutinib if MYD88mut or bendamustine for IgM PN depending on severity and pace of progression

Future Directions of WM Therapy

- Novel 3rd generation BTK inhibitors (pirtobrutinib, ARQ-531)
- Bcl-2 inhibitor (venetoclax, BGB-11417)
- CAR-T Cell therapy
- Targeted therapy to MYD88 or CXCR4
- Novel anti-CD20 monoclonal Ab (obinutuzumab, ublituximab)
- Anti-CD38 monoclonal Ab (daratumumab)
- Anti-CXCR4 monoclonal Ab (ulocuplumab)
- Novel immunomodulatory agent (pomalidomide)

Conclusions

- WM is diagnosed with a clonal IgM population and BM infiltration by a lymphoplasmacytic lymphoma
- WM is preceded by IgM MGUS
- Treatment only with symptomatic patients
- Symptoms requiring treatments are related to hyperviscosity, tumor mass/infiltration, or direct effects from IgM
- Current treatments include rituximab, alkylating agents and/or BTK inhibitor
- Future treatments are various and promising