Management of Waldenström & Splenic marginal zone lymphoma

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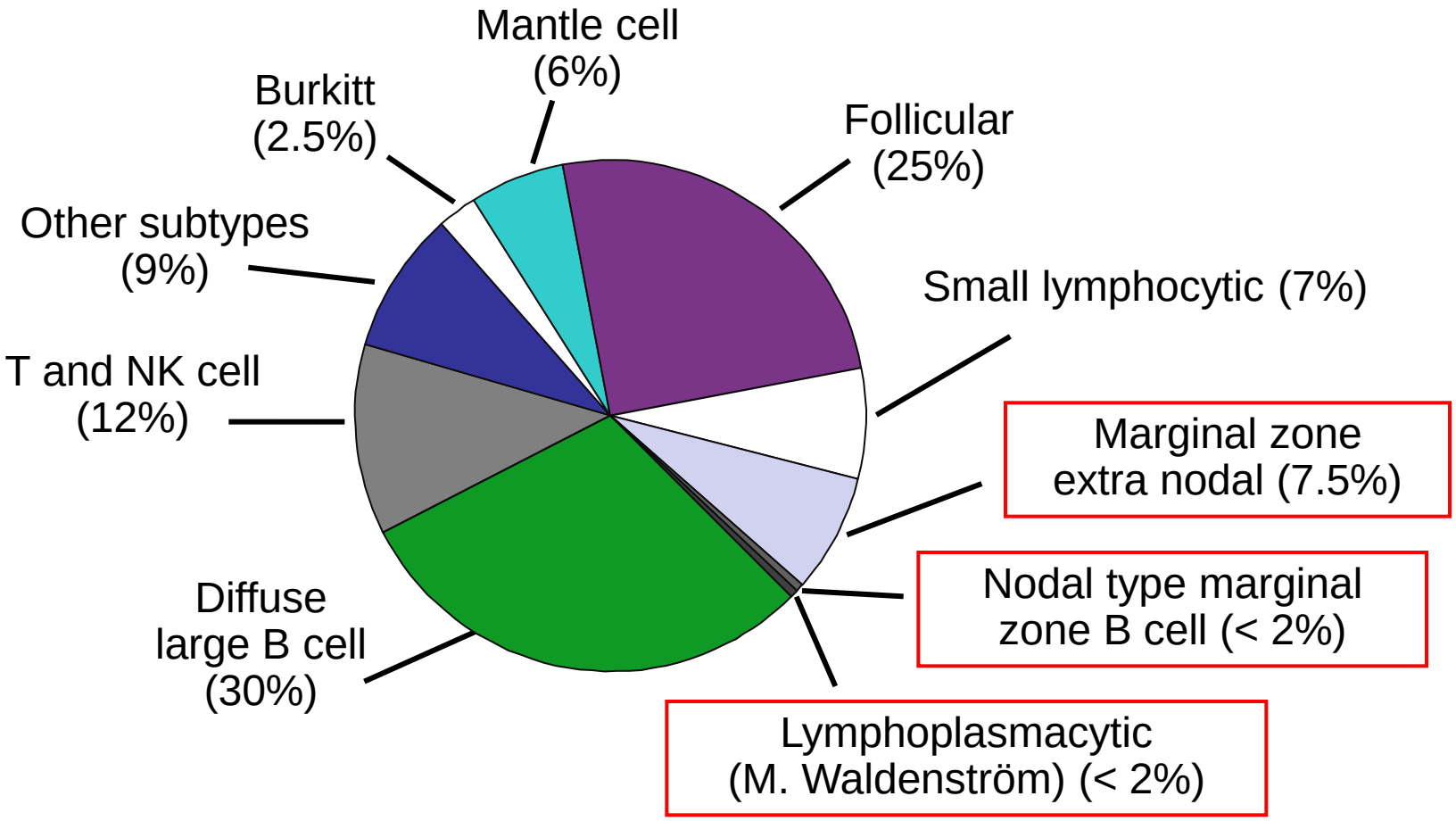
Disclosures

- I have provided consultation, attended advisory boards and/or provided lectures for:
- Celgene, Mundipharma, Roche Pharma, and Janssen

Non-Hodgkin`s Lymphoma Entities (%)



Adapted from Lichtman. Williams Hematology, 7th edition. 2006;1408.

Non-MALT marginal zone lymphomas (MZL)

Splenic marginal zone lymphoma (SMZL)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016 - SMZL

ESSENTIAL:
- **Physical exam with performance status**
- **CBC, differential, platelets**
- **Comprehensive metabolic panel**
- **LDH**
- **Hepatitis B testing[d] if rituximab contemplated**
- **Hepatitis C testing**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET-CT scan**
- **Bone marrow biopsy ± aspirate**
- **SPEP and/or quantitative immunoglobulin levels**
- **Pregnancy testing in women of child-bearing age (if chemotherapy planned)**

USEFUL IN SELECTED CASES:
- **Additional imaging as appropriate**
- **Discussion of fertility issues and sperm banking**
- **Immunofixation of blood (for elevated immunoglobulins or positive SPEP)**
- **Cryoglobulins**
- **Direct Coombs testing**

→ **See Management (SPLN-2)**

[b]Typical immunophenotype: CD10-, CD5-, CD20+, CD23-/+, CD43-/+ and cyclin D1-, BCL2- follicles, annexin A1, CD103- (distinction from hairy cell leukemia) with expression of both IgM and IgD.

[c]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[d]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

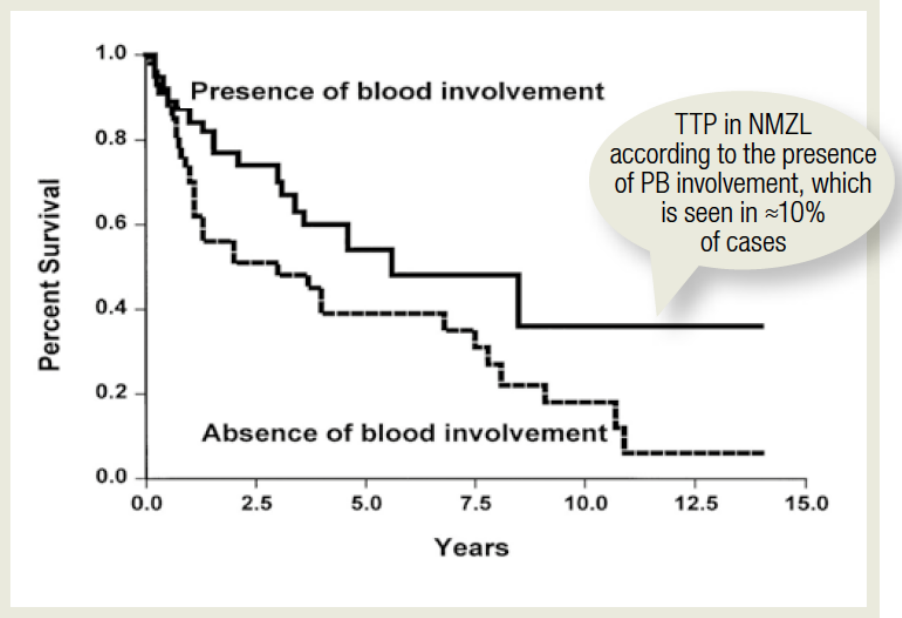
Clinical presentation and prognosis of Nodal-MZL and SMZL

Spenomegaly in most patients with SMZL

NMZL presents with localised or generalised enlarged lymph nodes (LN), with occasional bone marrow (BM) (~20%-40%) and peripheral blood (PB) involvement. Association with hepatitis C virus (HCV) is common in some geographical areas.

NMZL has an indolent course and many patients are asymptomatic, so treatment is required only when symptoms develop.

Time to progression (TTP) for NMZL is shorter that in SMZL, but the median overall survival (OS) is similar for both types (~9 years). Treatment is similar to that of SMZL.



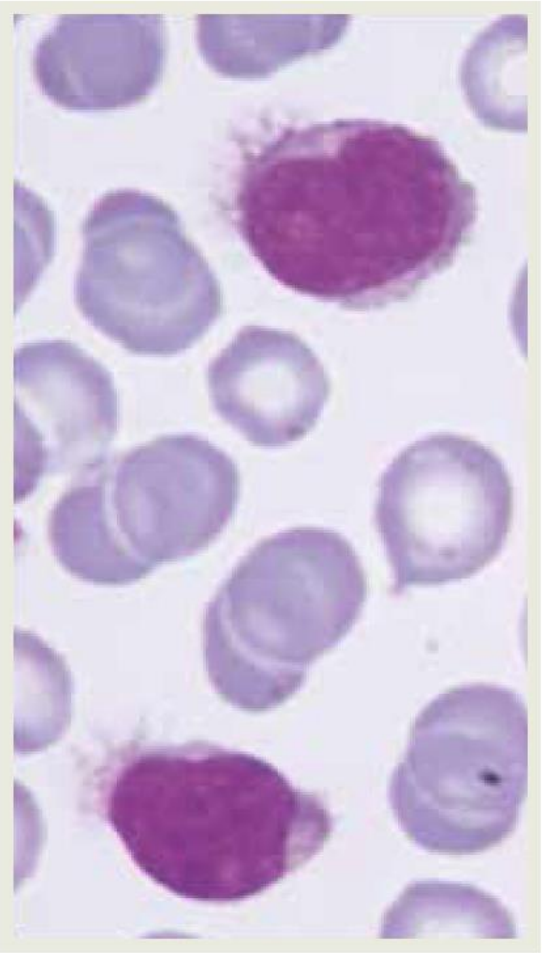
Lymphomas, Essentials for Clinicians. Editors: Ghielmini M & Montoto S. p97, 2015

SMZL
Morphology and Immunophenotype

SMZL is characterised by PB, BM, and splenic infiltration by small lymphocytes CD20+, CD79a+, CD5-, CD10-, CD23-, CD43-, cyclinD1-, AnexinA1-, CD103- (CLL [chronic lymphocytic leukaemia] score ≤2). Aberrant antigen expression (CD5+ and others) may occasionally occur.

Villous lymphocytes can be found in the PB, but they are not specific to SMZL and can be found (with subtle morphological features) in other lymphoproliferative disorders.

The most frequent cytogenetic abnormality is trisomy 3, but the most characteristic, that is unique to SMZL, is allelic loss of 7q31-32.



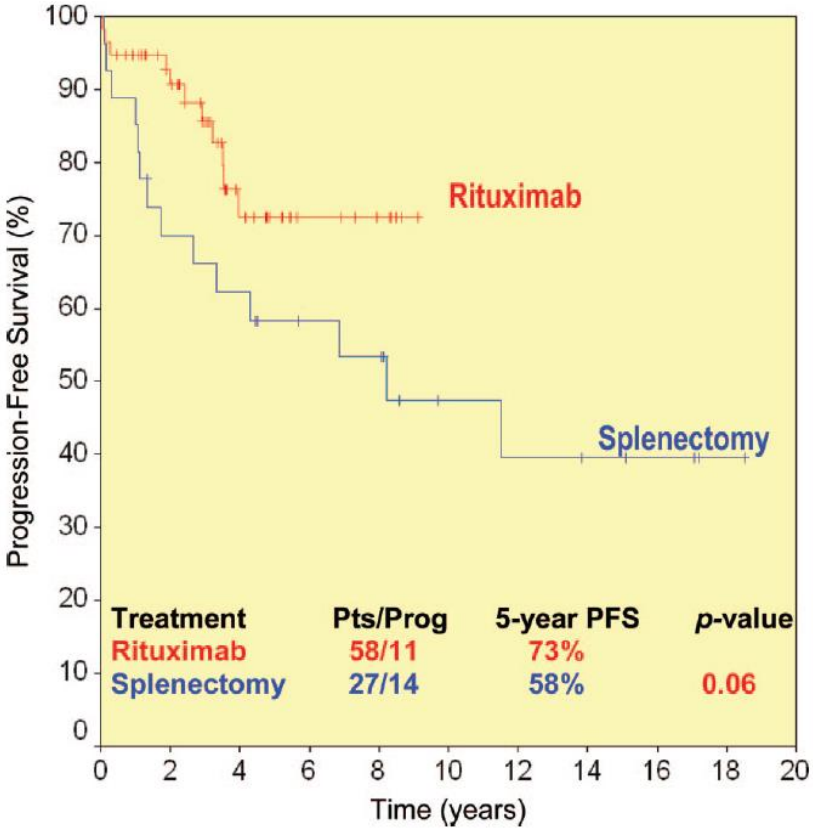
Lymphomas, Essentials for Clinicians. Editors: Ghielmini M & Montoto S. pp 98, 2015
Iannitto E , Tripodo C Blood 2011;117:2585-2595

Treatment of SMZL
Splenectomy vs. Rituximab

There is no standard treatment for SMZL. When present, treatment of HCV or malaria should precede other treatments. Splenectomy has been the classical historical treatment, resulting in clinical but not molecular responses and is no longer the best initial treatment.

Rituximab may achieve rapid clinical and molecular responses and may substitute splenectomy as the first step of treatment; whether the addition of chemotherapy can improve its effect or just increase toxicity is not yet known.

Risk stratification may eventually permit risk-adapted treatments to improve efficacy and decrease toxicity.



Lymphomas, Essentials for Clinicians. Editors: Ghielmini M & Montoto S. p98, 2015

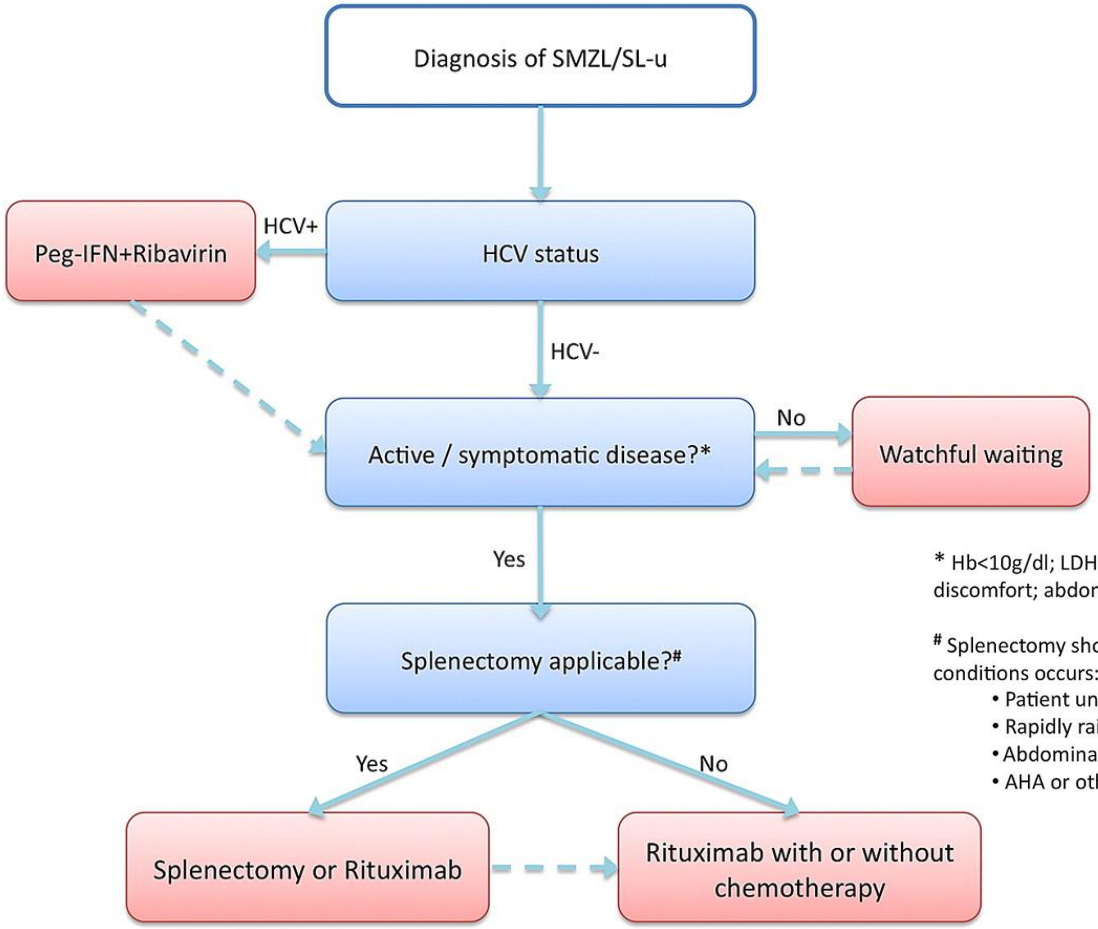
Response to treatment and survival of SMZL patients

Response/survival	Rituximab ($n = 58$)		Splenectomy ($n = 27$)	
	n	%	*n*	%
Overall response rate	55	95	23	85
Complete response	26	45	2[a]	7
Unconfirmed complete response	15	26		0
Partial response	14	24		0
Clinical and hematologic response			21	78
Relapse	8/55	15	9	39
5-year progression-free survival		73		58
5-year overall survival		92		77

[a]Two patients received rituximab consolidation after splenectomy.

Kalpadakis C et al., Oncologist 18: 190-197, 2013

Management of patients with SMZL/SL



* Hb<10g/dl; LDH>N; PLT≤ $80x10^9$/L; rapidly raising lymphocyte count; abdominal discomfort; abdominal lymph nodes and/or extranodal involvement.

Splenectomy should be considered not applicable if at least one of the following conditions occurs:

- Patient unwilling to undergo to / unfit for surgery
- Rapidly raising lymphocyte count
- Abdominal lymph nodes and/or extranodal involvement
- AHA or other autoimmune disorders

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Iannitto E , Tripodo C Blood 2011;117:2585-2595

Morbus Waldenström (WM)

Waldenström's Macroglobulinemia (WM) Background

- clonal, IgM-producing lymphoplasmacytic cells
- Association with Hepatitis C infection
- Only rarely lymphadenopathy or splenomegaly
- Diagnosis: monoclonal IgM paraprotein and BM-infiltration
- Hyperviscosity, cryoglobulinemia, polyneuropathy, skin infiltration and hematopoietic insufficiency (anemia)

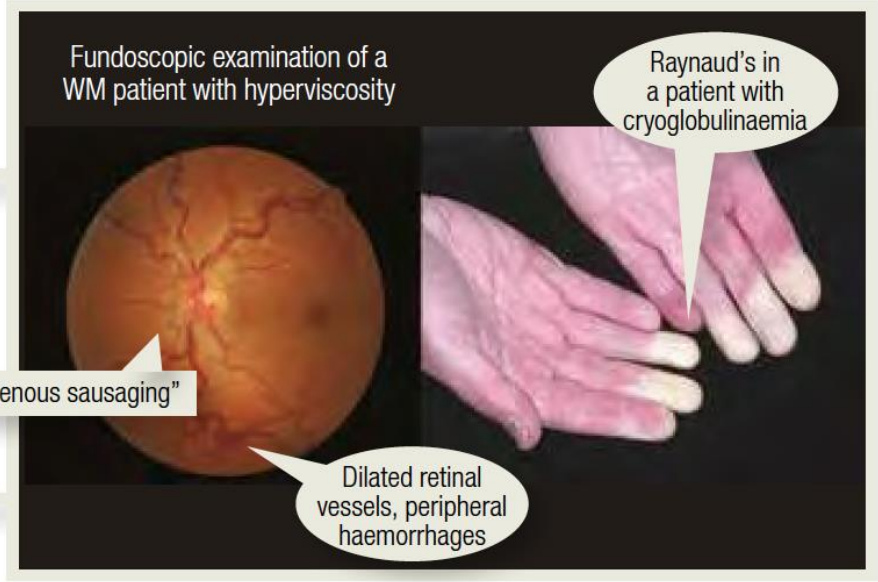
Treon S P Blood 2009;114:2375-2385

Hyperviscosity syndrome in WM

↑ IgM causes the hyper-viscosity syndrome, treated with plasmapheresis. This leads to resolution of the symptoms but the ↓ of IgM is transient.

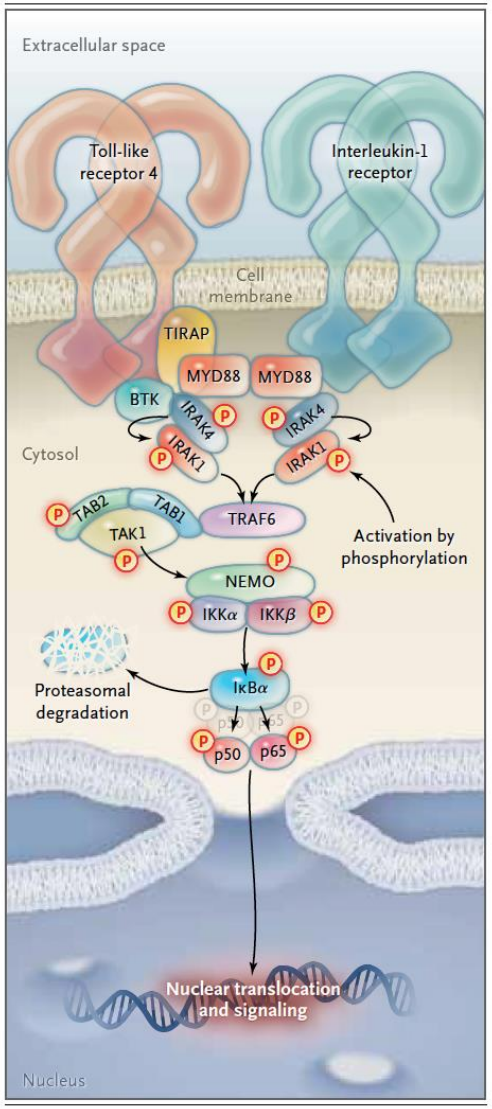
The IgM can have an auto-Ab activity, i.e. IgM against myelin-associated glycoprotein (MAG), causing a distal, symmetric, chronic demyelinating peripheral neuropathy.

Other clinical manifestations caused by the IgM are renal failure, cryoglobulinaemia, and Raynaud's syndrome.



Lymphomas, Essentials for Clinicians. Editors: Ghielmini M & Montoto S. p101, 2015

MYD88 mutations occur in > 90% of patients with WM

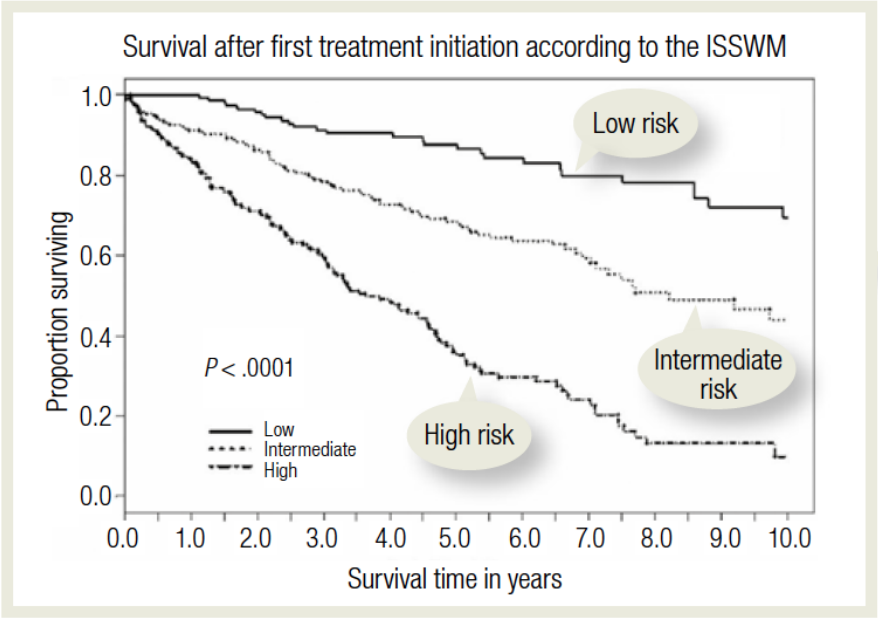


MYD88 (L265P) somatic mutation causes constitutive stimulation of NFκB through BTK. Ibrutinib, a selective BTK inhibitor, has shown major activity in relapsed / refractory WM.

Treon SC et al. NEJM August 2012

Lymphomas, Essentials for Clinicians. Editors: Ghielmini M & Montoto S. p101, 2015

International Prognostic Scoring System for Waldenstrom`s Macroglobulinemia (WM)



Indications for treatment include constitutional symptoms, IgM-related complications, bulky LN or splenomegaly, cytopaenias, or evidence of transformation.

The International Prognostic Scoring System for WM (ISSWM) (age, anaemia, thrombocytopaenia, ↑ β2-microglobulin, and ↑ monoclonal IgM) discriminates 3 risk groups.

Patients with an IgM-related disorder usually require treatment to ↓ the circulating IgM and to suppress the malignant clone producing the IgM.

Morel P, Duhamel A, Gobbi P et al. Blood 2009; 113: 4163–4170.

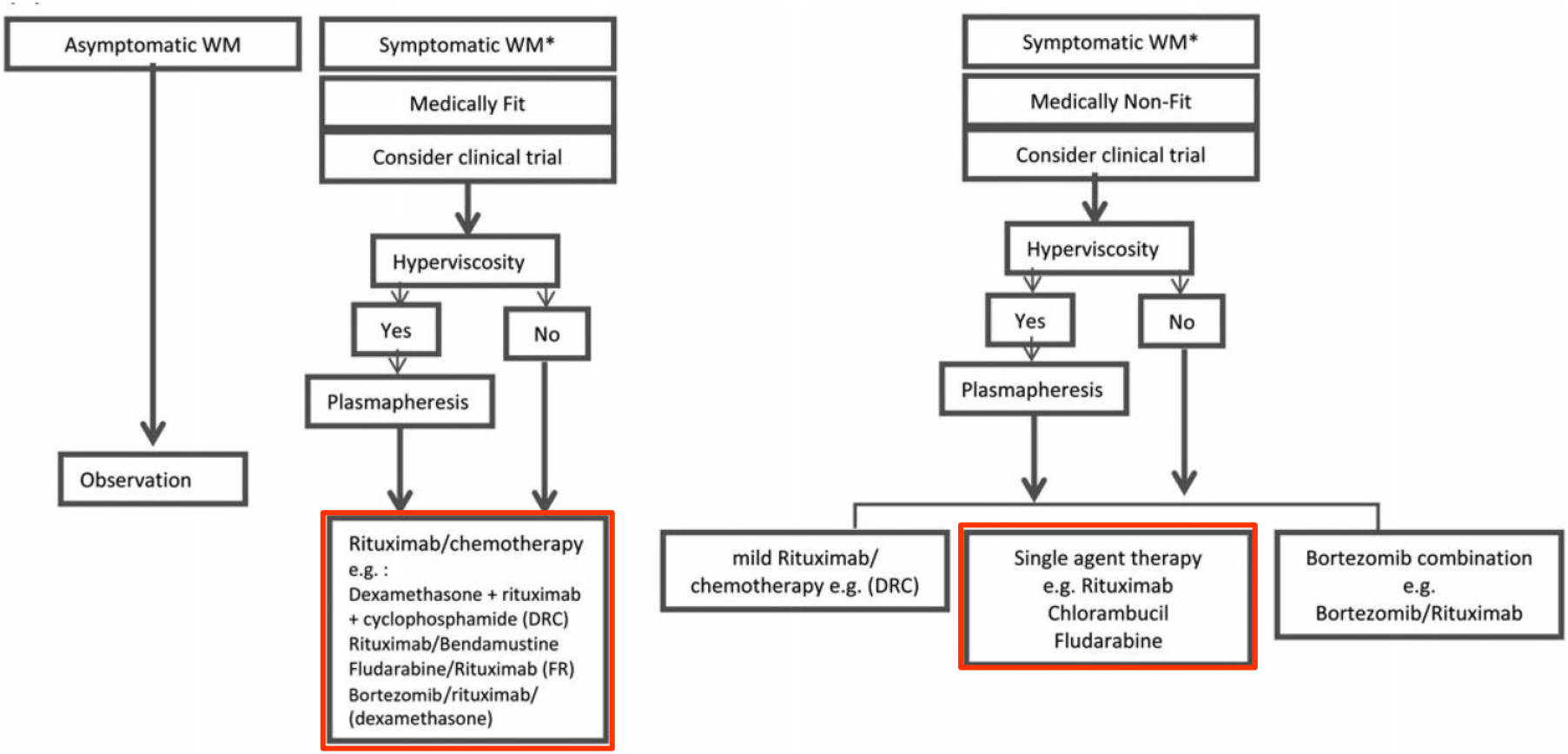
Lymphomas, Essentials for Clinicians. Editors: Ghielmini M & Montoto S. p101, 2015

Treatment options for WM

- **Chemoimmunotherapy**
  - **Bortezomib, Dexa and Rituximab (BDR)**
    - ORR: 96%, 22% CR
  - **Bendamustine-Rituximab**
  - **Cyclophosphamide, Dexa, Rituximab**
- **Cave: Rituximab mono → IgM flare in 40%-50%, control of IgM levels strongly advised**
- **Herpes zoster prophylaxis**
- **Role of Rituximab-Maintenance open→ NHL 7-2008 Protocol (StiL) (ongoing)**

Treon S P Blood 2009;114:2375-2385, Rummel MJ et al., ASCO 2012, Lancet 2013

ESMO Guideline in WM, first-line



Buske C et al. Ann Oncol, Suppl 6, 155-159, 2013.

NHL 1-2003 Studie: PFS - Subentities

FL

MCL

MZL

WM

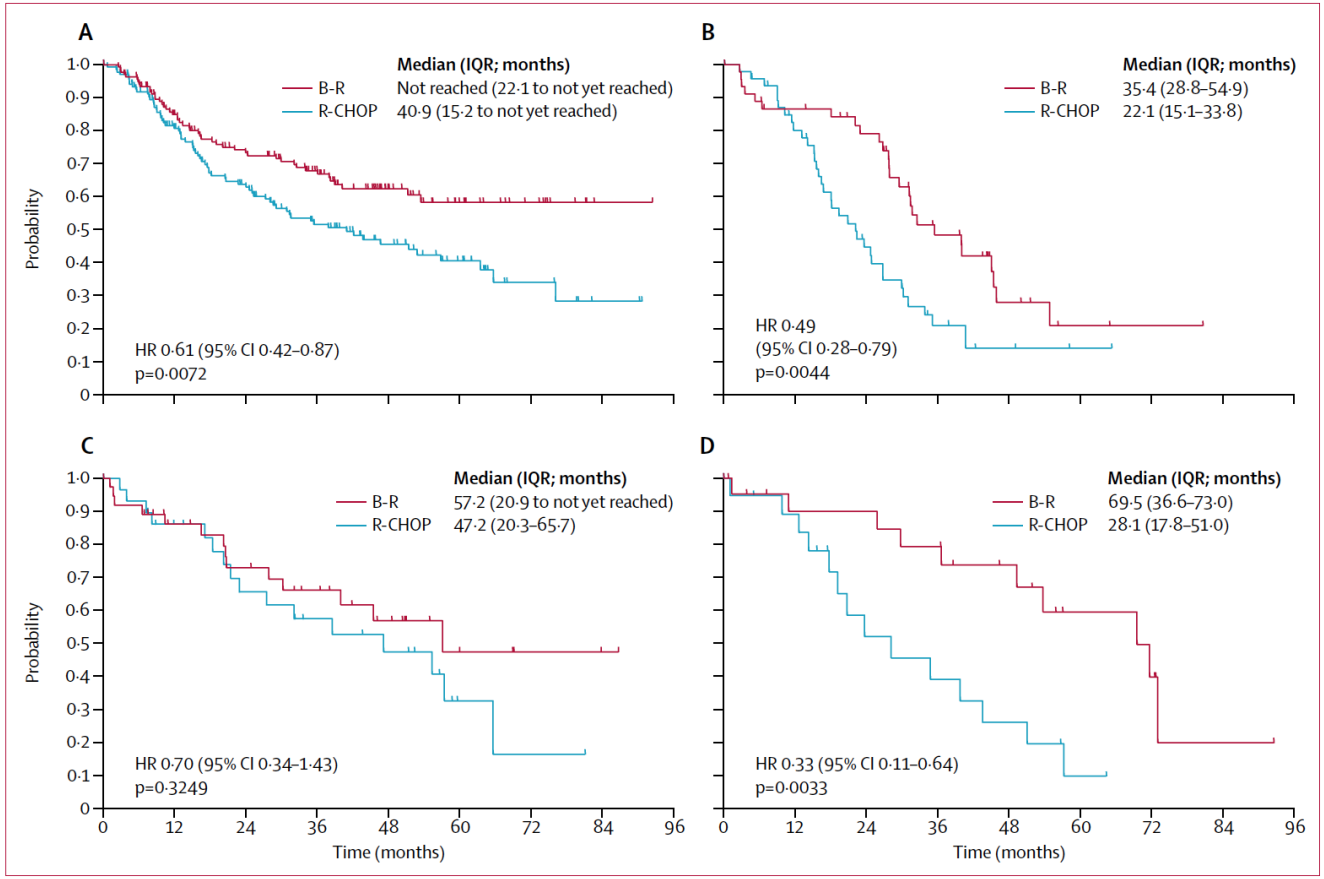
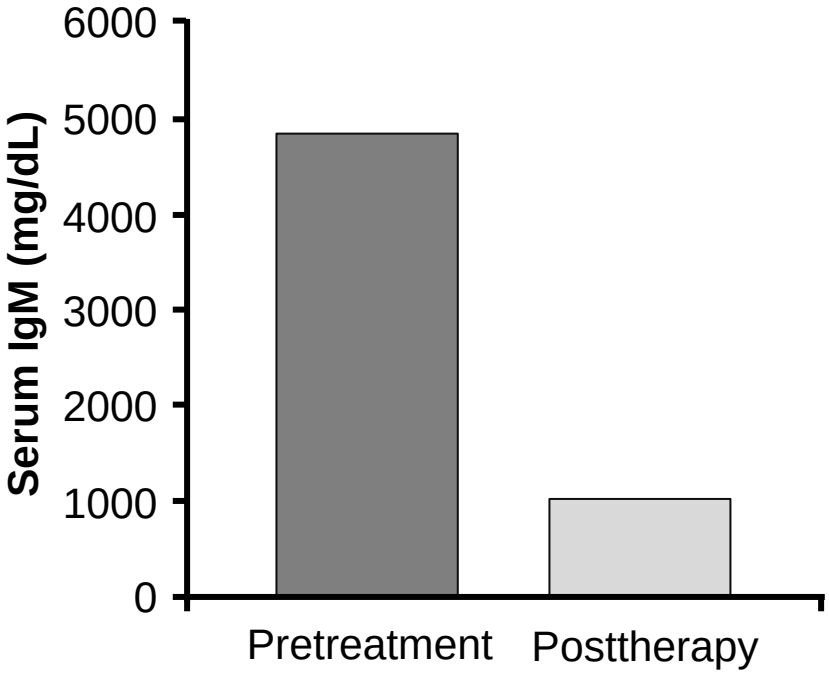


Figure 3: **Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D)**
B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

Rummel MJ ... Brugger W, Lancet 2013

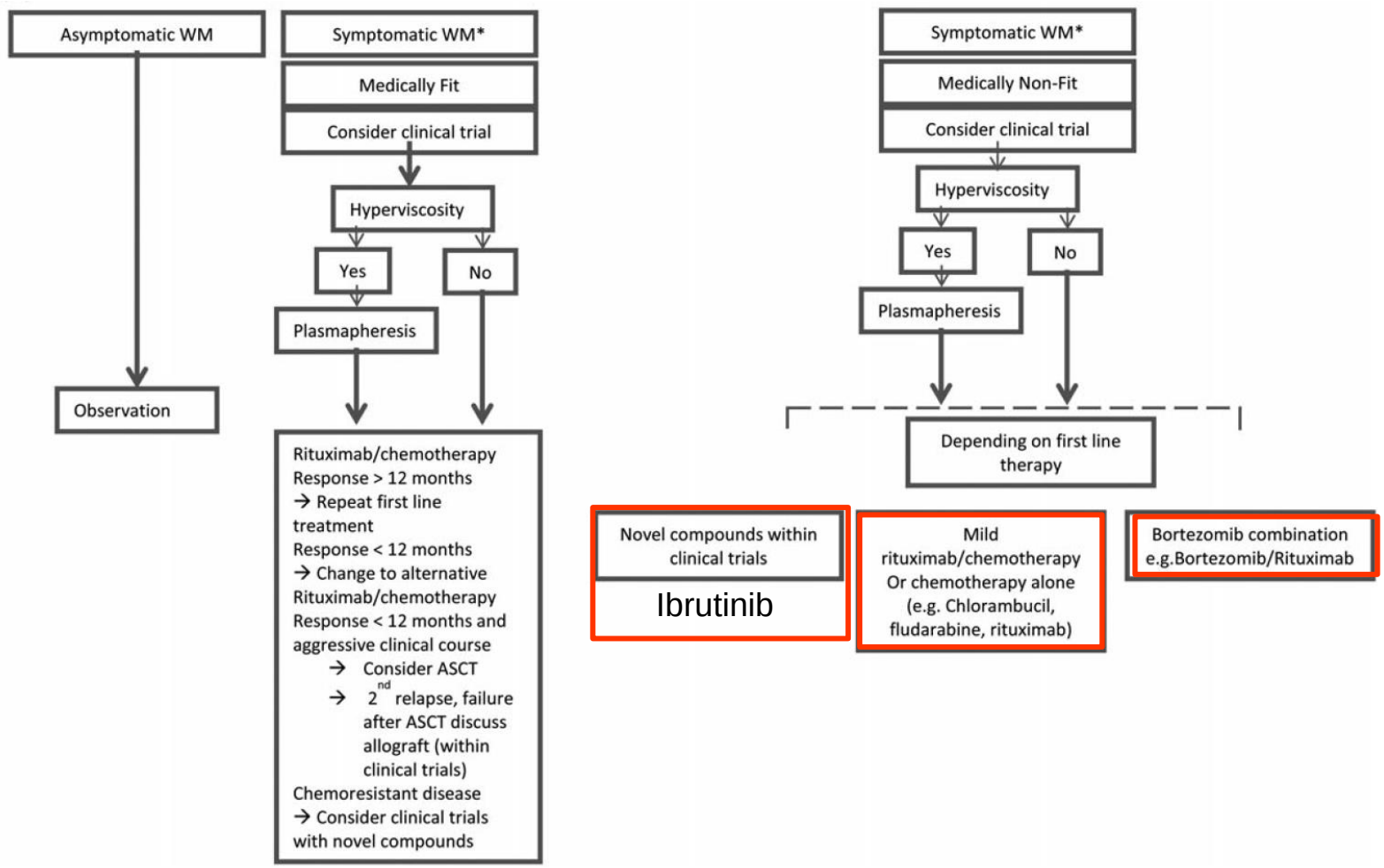
Bortezomib/Dexa/Rituximab as Primary Therapy for WM

- **Bortezomib/Dex/Rituximab used as first-line and maintenance therapy (N = 23)**
  - **Dosing: bort 1.3 mg/m^2, dex 40 mg, rituximab 375 mg/m^2**
  - **CR/nCR: 5 (22%)**
  - **PR: 14 (61%)**
  - **Grade ≥ 2 adverse events: neuroparasthesias (69%), leukopenia (13%)**
  - **19 patients remain progression free at median follow-up of 19.4 mos**



Treon SP, et al. ASCO 2008. Abstract 8519.

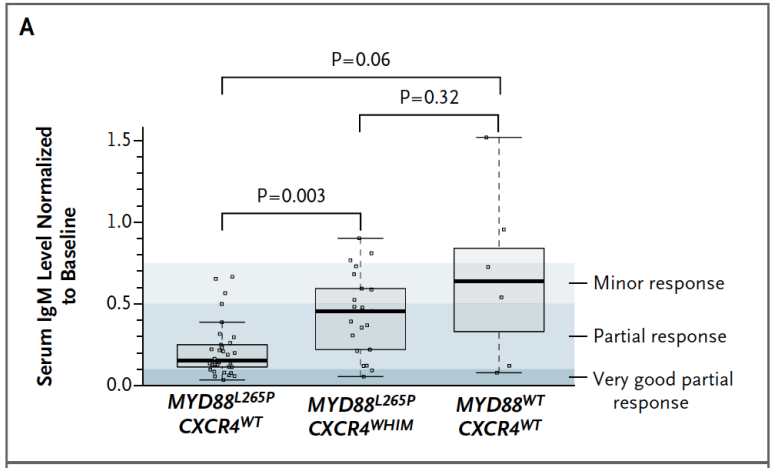
ESMO Guideline – WM, second-line

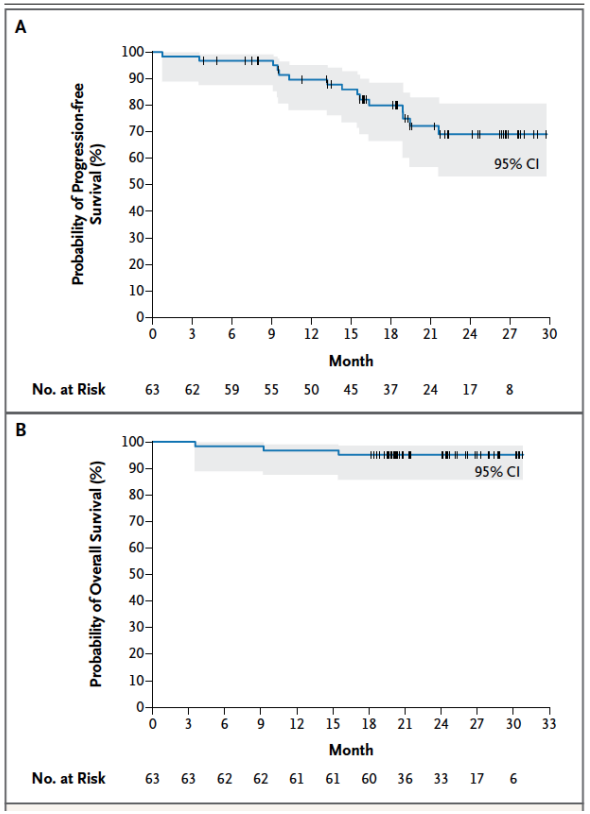


Buske C et al. Ann Oncol, Suppl 6, 155-159, 2013.

Ibrutinib as second-/third line treatment

MYD88^{L265P} and *CXCR4*^{WHIM} mutations are highly prevalent in Waldenström's macroglobulinemia. MYD88^{L265P} triggers tumor-cell growth through Bruton's tyrosine kinase, a target of ibrutinib. *CXCR4*^{WHIM} mutations confer in vitro resistance to ibrutinib.





Treon SP et al. NEJM April 2015

Thank you

SCHWARZWALD-BAAR
KLINIKUM

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LEHRKRANKENHAUS DER
UNIVERSITÄT FREIBURG