# NCCN Guidelines for LPL/Waldenstrom's Macroglobulinemia, IgM MGUS and IgM Related Disorders.

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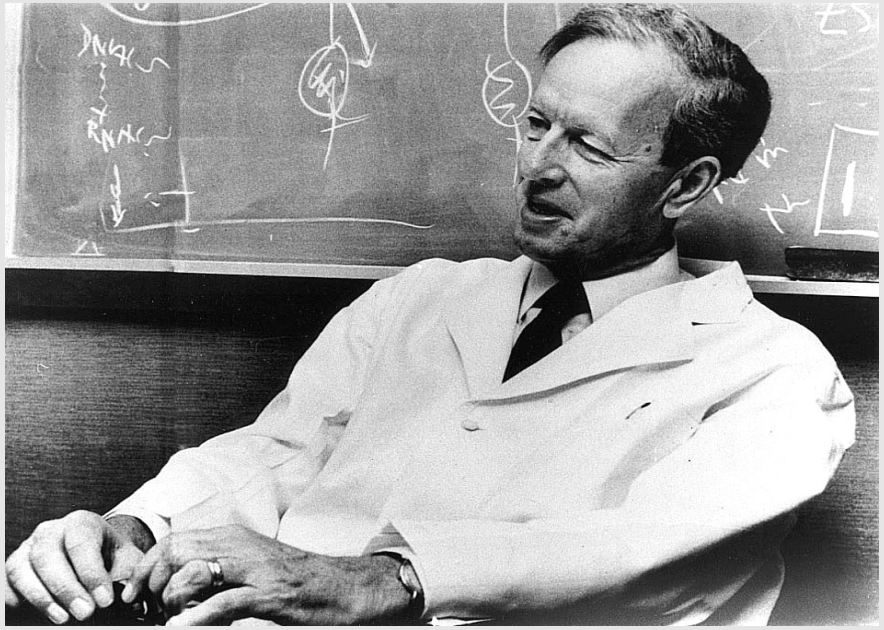
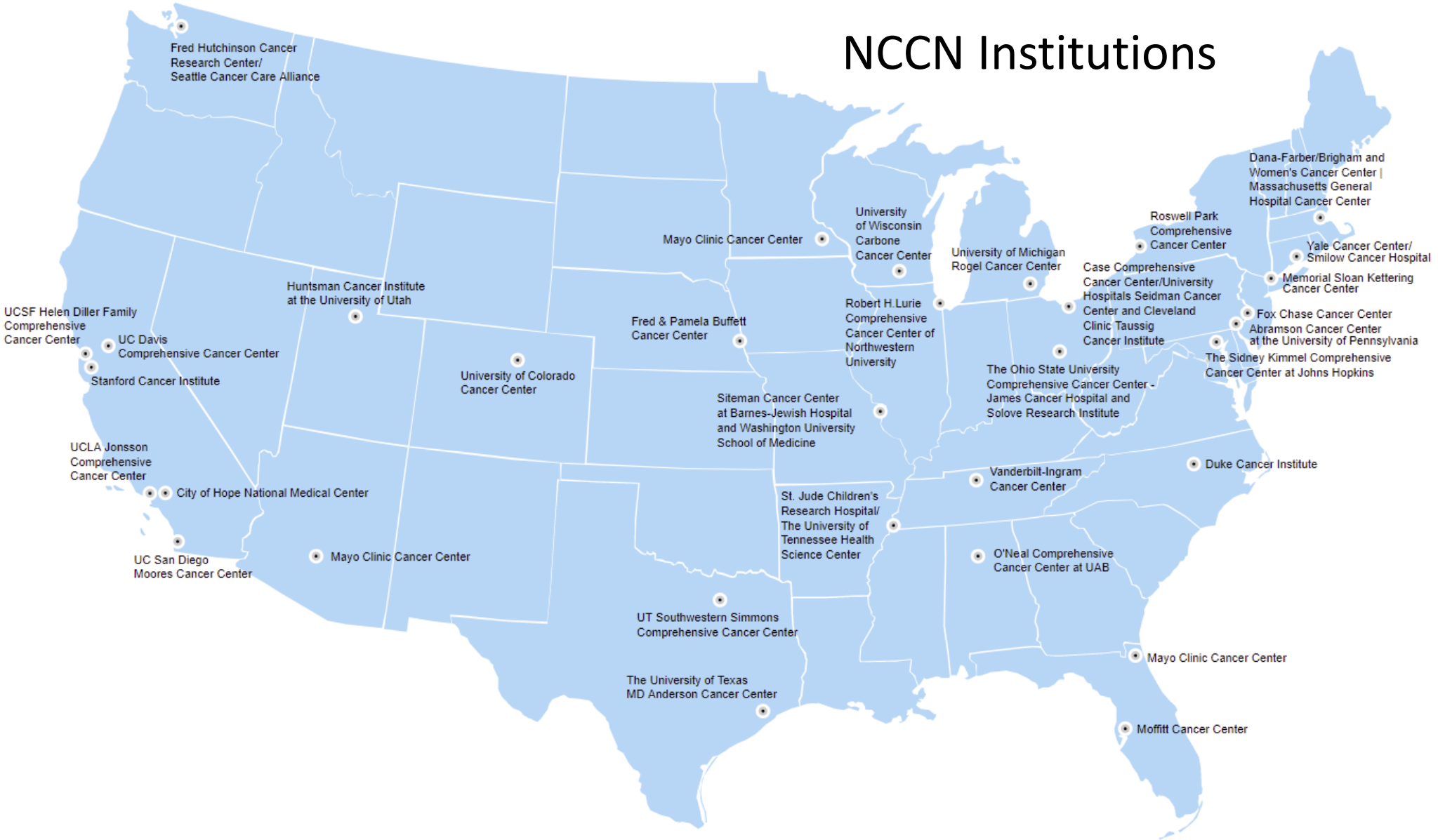
**Dana Farber Cancer Institute**



This presentation was made at the annual IWMF virtual meeting and is intended for educational purposes only and is based on best available information in the opinion of the presenter at the time of the presentation. The information presented is not for specific patient advise. Patients should consult their physician for specific information relative to their ongoing management and treatment.

# NCCN Institutions



## WHO CRITERIA FOR LYMPHOPLASMACYTIC LYMPHOMA AND WALDENSTRÖM MACROGLOBULINEMIA

- **Lymphoplasmacytic lymphoma:**
  - **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**

Reproduced with permission from Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon 2017.

- **Waldenström macroglobulinemia:**
  - **Lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy of any concentration**

Adapted with permission. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological Definition of Waldenstrom's Macroglobulinemia: Consensus Panel Recommendations from the Second International Workshop on Waldenstom's Macroglobulinemia. Semin Oncol. 2003;30:110-115.

## WALDENSTRÖM MACROGLOBULINEMIA INTERNATIONAL WORKSHOP CRITERIA

**Proposed Criteria for the Diagnosis of Waldenström Macroglobulinemia**

- **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 Waldenström macroglobulinemia and does not exclude diagnosis.**

Reprinted with permission from Elsevier. Owen RG. Developing diagnostic criteria in Waldenström's macroglobulinemia. Semin Oncol 2003;30:196-200.

## 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

Adapted with permission from: Kastritis E, Morel P, Duhamel A, et al. A revised international prognostic score system for Waldenström's macroglobulinemia. Leukemia 2019;33:2654-2661.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2022
# Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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## DIAGNOSIS

**Essential[b,c]**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor (Rebiopsy if consult material is nondiagnostic)
- Adequate tissue biopsy for immunophenotyping to establish diagnosis
  - Typical immunophenotype: CD19+, CD20+, sIgM+; CD5, CD10, CD23 may be positive in 10%–20% of cases and does not exclude diagnosis

## WORKUP[a]

**Essential**
- History and physical exam
- CBC, differential, platelet count
- Liver function tests (LFTs) as clinically indicated
- Peripheral blood smear
- Serum BUN/creatinine, electrolytes, albumin, calcium, serum uric acid, serum LDH, and beta-2 microglobulin
- Creatinine clearance (calculated or measured directly)
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- Unilateral bone marrow aspirate and biopsy, including immunohistochemistry (IHC) and/or multi-parameter flow cytometry
- Chest/abdominal/pelvic CT with contrast when possible
- MYD88,[d] L265P AS-PCR testing of bone marrow

**Useful in Certain Circumstances**
- Serum viscosity
- *CXCR4* gene mutation testing for patients being considered for ibrutinib[e]
- Testing for hepatitis B (if rituximab planned), hepatitis C,[f] and HIV
- Cryocrit[f,g]
- Consider coagulation and/or von Willebrand disease testing if symptoms present (excess bruising or bleeding) or if clinically indicated
- Cold agglutinins
- Neurology consult[h]
- Anti-MAG antibodies/anti-GM1[h]
- Nerve conduction study (NCS)/electromyogram (EMG)[h]
- Fat pad sampling and/or congo red staining of bone marrow for amyloid[h]
- Retinal exam (if IgM ≥3.0 g/dL or if hyperviscosity is suspected)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE)
- Amyloid tissue subtyping with mass spectrometry, if indicated
- Brain/spine MRI, if CNS symptoms

## INDICATIONS FOR TREATMENT

**Symptoms[i] related to:**
- Hyperviscosity
- Neuropathy
- Organomegaly
- Amyloidosis
- Cold agglutinin disease
- Cryoglobulinemia
- Anemia and other cytopenias associated with disease
- Bulky adenopathy
- B symptoms

→ See Primary Treatment (WM/LPL-2)

SUPPORT • EDUCATION • RESEARCH
IWMF
International Waldenstrom's Macroglobulinemia Foundation

The NEW ENGLAND JOURNAL of MEDICINE

Peter Bing MD

ORIGINAL ARTICLE

# MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

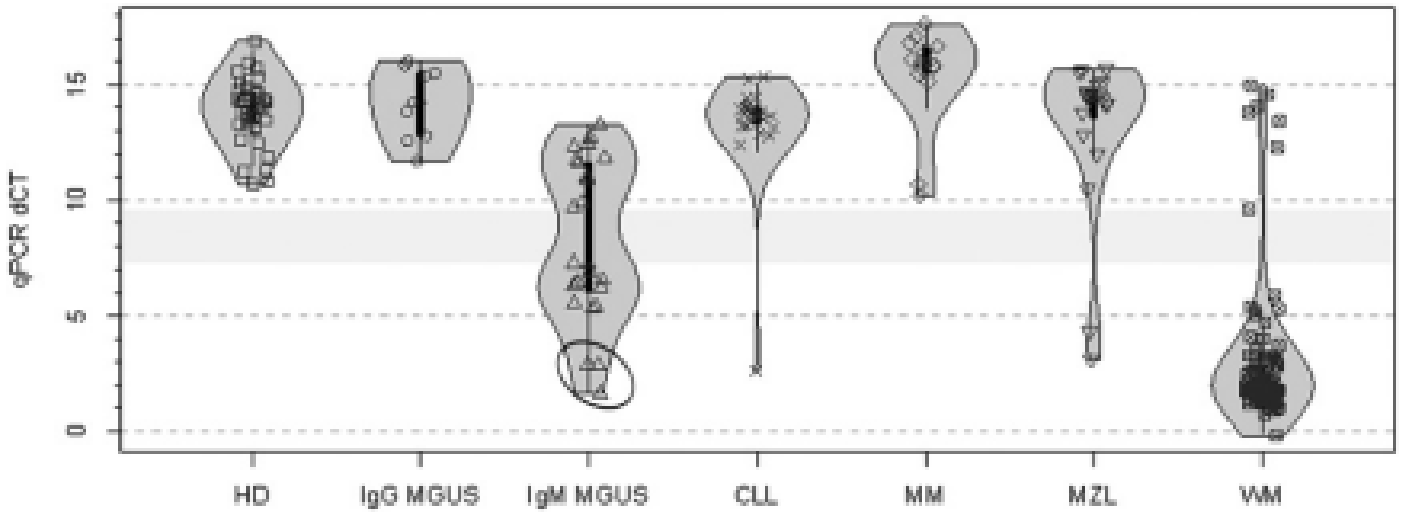
**91% of WM patients positive by Whole Genome Sequencing**

**Treon et al, New Engl J Med 2012**

# MYD88 L265P in WM/IGM MGUS

| | METHOD | TISSUE | WM | IGM MGUS |
|---|---|---|---|---|
| Treon | WGS/Sanger | BM CD19$^{+}$ | 91% | 10% |
| Xu | AS-PCR | BM CD19$^{+}$ | 93% | 54% |
| Gachard | PCR | BM | 70% | |
| Varettoni | AS-PCR | BM | 100% | 47% |
| Landgren | Sanger | BM | | 54% |
| Jiminez | AS-PCR | BM | 86% | 87% |
| Poulain | PCR | BM CD19$^{+}$ | 80% | |
| Argentou | PCR-RFLP | BM | 92% | 1/1 MGUS |
| Willenbacher | Sanger | BM | 86% | |
| Mori | AS-PCR/BSiE1 | BM | 80% | |
| Ondrejka | AS-PCR | BM | 100% | |
| Ansell | WES/AS-PCR | BM | 97% | |
| Patkar | AS-PCR | BM | 85% | |

# MYD88 Mutation Testing in B-cell LPDs




Negative Zone

Cutoff

Positive Zone

**Figure 4. Real-time AS-PCR results for MYD88 L265P in samples from patients with WM, IgM MGUS, and other B-cell lymphoproliferative disorders.** Violin plot representing AS-PCR differences in cycle threshold ($\Delta C_T$). The span of grey area for each cohort represents the kernel density estimation of the sample distribution, and highlights the bimodal nature of the data. Box plots with interquartile ranges are shown in black with an overlay of the individual data points. Samples evaluated were from healthy donors (HD, n = 40); along with patients with IgG (n = 9) and IgM (n = 24) MGUS; CLL (n = 26); MM including 3 patients with IgM myeloma (n = 14); MZL (n = 20), and WM (n = 104). The light grey bar represents the distance between the highest positive (7.3), and lowest negative (9.6) sample $\Delta C_T$ values. Circled area depicts results for 3 IgM MGUS patients who progressed to WM.

Xu et al, Blood 2013

# Progression of disease in IgM MGUS is related

- Absence of MYD88 and CXCR4 mutations in IGG and IGA MGUS.
- Mutated MYD88 and CXCR4 detected in 50 to 90% and 20% of IGM MGUS patients, respectively by AS-PCR.
- Presence of mutated MYD88 is an independent risk factor for progression.

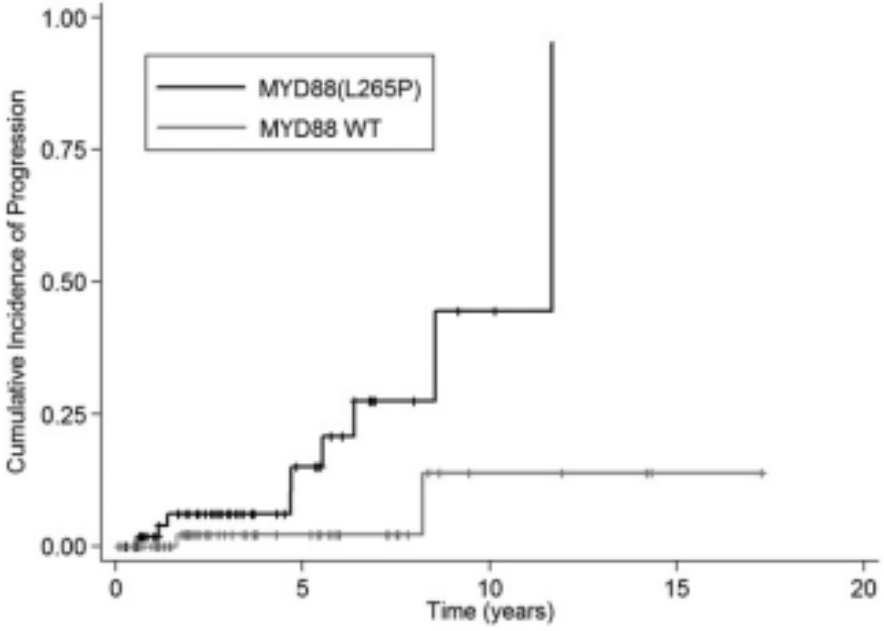



**Figure 1. Cumulative probability of progression to WM or to other LPDs in patients with IgM-MGUS according to their *MYD88* mutational status.**

***Varettoni study: IGM MGUS patients subjected to AS-PCR. 71/138 Positive for MYD88 L265P. 11 progressed during follow-up (median 34 mos). 9/11 (82%) to WM, 8 of whom were MYD88 mutated; 2 to MZL (18%), 1 of whom was MYD88 mutated.***

Varettoni et al, BLOOD 2013; Jimenez et al, Leukemia 2013; Xu et al, Blood 2013

# MYD88 status for classification of B-cell LPDS.

MYD88 status used to re-evaluate pathological diagnosis in 138 patients with B-cell LPDs. Mutation status was integrated with histologic and clinical data. Reclassification using molecular status is shown for five patients.

**TABLE 2.** Summary of Features of Reclassified Cases

| Case No | Initial Diagnosis | Light-chain Restriction by Plasma Cells | Revised Diagnosis | Diagnostic Sample | Splenomegaly | Bone Marrow Involvement | Serum IgM Paraprotein (g/L) |
|---|---|---|---|---|---|---|---|
| 1 | NMZL | λ | LPL | LN | Absent | Present | 24.0 |
| 2 | BCL-NOS vs LPL | κ | LPL | BM | Absent | Present | 11.0 |
| 3 | BCL-NOS | κ | LPL | BM | Absent | Present | 10.3 |
| 4 | SMZL | κ | LPL | SPLEEN | Present | Present | 7.3 |
| 5 | SMZL | λ | LPL | SPLEEN | Present | Present | 5.1 |

BM indicates bone marrow; LN, lymph node.

Martinez-Lopez et al, Am J Surg Pathol 2015.

# Differential Diagnosis of suspected non-MYD88 mutated LPL/WM

| Diagnosis | N= | Age (yrs) | Gender (% male) | BM (%) | sIgM (mg/dL) | Hb (g/dL) | Adenopathy (%) | Splenomegaly (%) |
|---|---|---|---|---|---|---|---|---|
| **WM** | 46 | 58.5 | 48 | 35 | 2,980 | 11.0 | 35 | 28 |
| **IgM MM** | 7 | 59 | 71 | 60 | 8,375 | 9.0 | 14 | 14 |
| **MZL** | 6 | 64.5 | 0 | 10 | 1,642 | 11.3 | 67 | 33 |
| **IgM PC MGUS** | 3 | 62 | 33 | 5 | 1,846 | 13.9 | 0 | 0 |
| **CLL** | 1 | 83 | 0 | 5 | 1,822 | 13.2 | 0 | 0 |
| **DLBCL** | 1 | 76 | 0 | 5 | 355 | 9.5 | 0 | 100 |

t(11;14); Cyclin D1 over-expression

N=64

Treon et al, BJH 2017

# MYD88 Testing for LPL/WM Extramedullary Pathology

## Bing Neel Syndrome

Table I. Clinical, imaging and biological features of patients with BNS at entry into the study.

| | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Age (years) | 36 | 59 | 68 |
| Symptoms | Visual loss, drop attacks Absence of tumoural syndrome | Progressive leg palsy and blurry vision Absence of tumoural syndrome | Confusion, cognitive decline, dysphagia, Facial hemiparesis, hearing loss, difficulty walking, Absence of tumoural syndrome |
| Magnetic resonance imaging | Dura-mater, leptomeningeal and occipital involvement | Abnormal medullary and optic nerve signal | Predominantly occipital involvement |
| M-spike on SPE (g/l) | 3·6 | 10·5 | 4 |
| Blood lymphocytes counts ($\times 10^9$/l) (CD19% by flow cytometry) | 2·6 (Not available) | 3·6 (65) | 1·4 (<1) |
| Protein concentration (g/l)* | 2·83 | 0·66 | 5 |
| Protein concentration index/M spike | 0·78 | 0·06 | 1·25 |
| Cellularity of CSF (/µl) | 54 | 9 | 15 |
| % of tumoural cells in CSF | 51 | 80 | 75 |
| Cytomorphology | Lymphoplasmacytic infiltration | Lymphoplasmacytic infiltration | Lymphoplasmacytic infiltration |
| Flow cytometry data on CSF | CD5-, CD10-, CD19 + , CD20 + , CD22 + , FMC7-, CD23-, CD38 + , IgM+, Kappa restriction | CD5-, CD10-, CD19 + , CD20 + , Kappa restriction | CD5 + , CD10-, CD19 + , CD20 + , Kappa restriction |
| Bone marrow involvement (%) | 10 | 50 | 20 |
| *MYD88* L265P mutation | | | |
| Blood | Absent | Present | Absent |
| Bone marrow | Present | Present | Present |
| CSF | Present | Present | Present |
| Brain biopsy | Present | Not available | Not available |

SPE serum protein electrophoresis; CSF: cerebrospinal fluid.
*normal range: 0·1-0·6 g/l.

Poulain et al, BJH 2014

## Malignant Pleural Effusions

Table I. Clinical presentation and diagnostic test results of patients with malignant pleural effusions.

| | | | | | | | Pleural fluid | | | *MYD88* mutation | | CXCR4 mutation | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Age (years) | Gender | Symptoms | Imaging | Presentation | Serum IgM (g/l) | Cytology | Flow cytometry | *IGH* rearrangement | Bone marrow | Pleural fluid | Bone marrow | Pleural fluid |
| 1 | 72 | Female | SOB, cough | Bilateral moderate to large PE | Progressive event off-therapy | 19·6 | No malignant cells | CD5⁻, CD10⁻, CD23⁻, CD19⁺, CD20⁺, polytypic LC | Polyclonal pattern | Present | Present | Present (S338X) | Not available |
| 2 | 54 | Female | SOB | Unilateral PE on right side | Progressive event while on ibrutinib | 5·5 | No malignant cells | CD5⁻, CD10⁻, CD23⁻, CD19⁺, CD20⁺, polytypic LC | Clonal pattern | Present | Present | Absent | Absent |
| 3 | 73 | Male | SOB, fatigue | Unilateral PE on left side | Progressive event while on ibrutinib | 45·8 | No malignant cells | CD5⁻, CD10⁻, CD23⁻, CD19⁺, CD20⁺, polytypic LC | Clonal pattern | Present | Present | Absent | Not available |
| 4 | 68 | Male | SOB, fatigue | Bilateral PE, left > right | Progressive event off-therapy | 22·1 | No malignant cells | CD5⁻, CD10⁻, CD23⁻, CD19⁺, CD20⁺, polytypic LC | Clonal pattern | Present | Present | Absent | Not available |
| 5 | 70 | Male | SOB, weight loss | Unilateral PE on left side | Progressive event off-therapy | 24·7 | No malignant cells | CD5⁻, CD10⁻, CD23⁻, CD19⁺, CD20⁺, polytypic LC | Clonal pattern | Present | Present | Absent | Absent |
| 6 | 51 | Male | SOB, fatigue | Unilateral PE on left side | Progressive event off-therapy | 44·2 | No malignant cells | CD5⁻, CD10⁻, CD23⁺, CD19⁺, CD20⁺, polytypic LC | Clonal pattern | Present | Present | Absent | Not available |
| 7 | 75 | Male | SOB | Unilateral PE on left side | Progressive event off-therapy | 25·5 | Malignant cells identified | CD5⁻, CD10⁻, CD23⁻, CD19⁺, CD20⁺, monotypic λ LC | Clonal pattern | Present | Present | Absent | Absent |
| 8 | 69 | Male | Cough on deep inspiration | Unilateral PE on left side | Progressive event off-therapy | 22·2 | No malignant cells | CD5⁻, CD10⁻, CD23⁺, CD19⁺, CD20⁺, polytypic LC | Not performed | Present | Present | Absent | Not available |
| 9 | 69 | Male | SOB, fatigue | Bilateral PE | Progressive event while on ibrutinib | 6·1 | Malignant cells identified | CD5⁻, CD10⁺, CD23⁻, CD19⁻, CD20⁺, monotypic λ LC | Not performed | Present* | Present* | Absent | Not available |

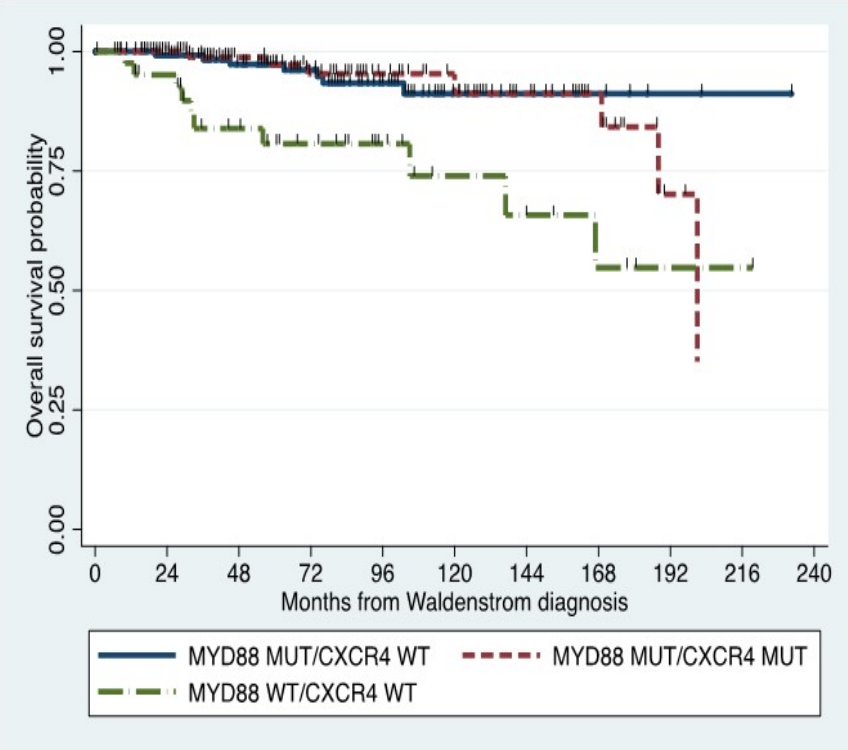
SOB, shortness of breath; PE, pleural effusion; LC, light chain.
*Patient 9 had *MYD88* S243N detected; all other patients had *MYD88* L265P identified.

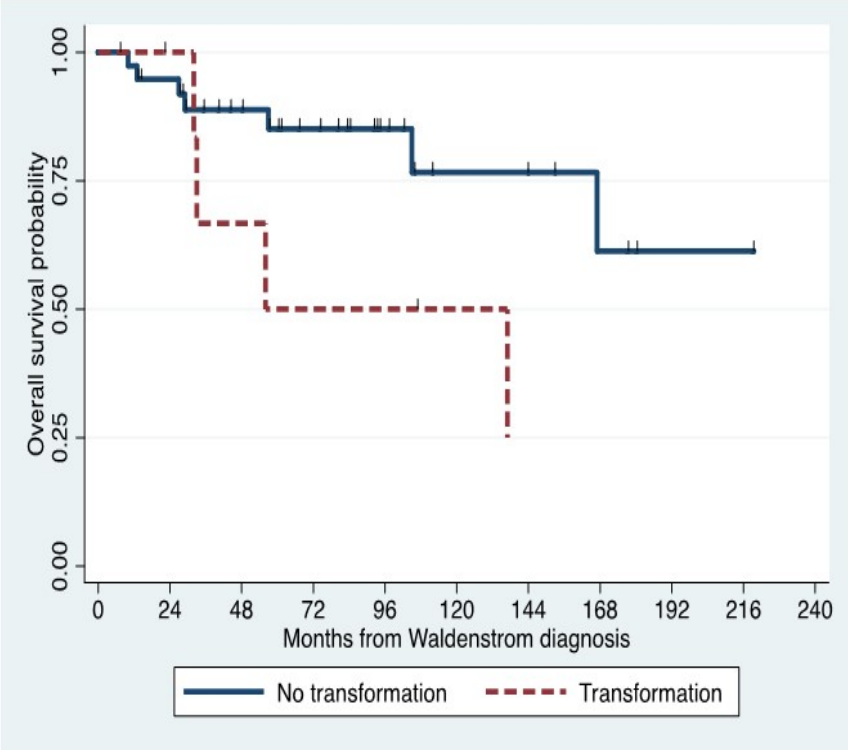
Gustine et al, BJH 2016



Other studies: Himecke-Jiwa et al, Hematol Oncol 2018; Pan ST, et al, Pathol. Intl. 2019;

# High risk of transformation and poorer survival accompany MYD88$^{Wild\text{-}Type}$ LPL/WM



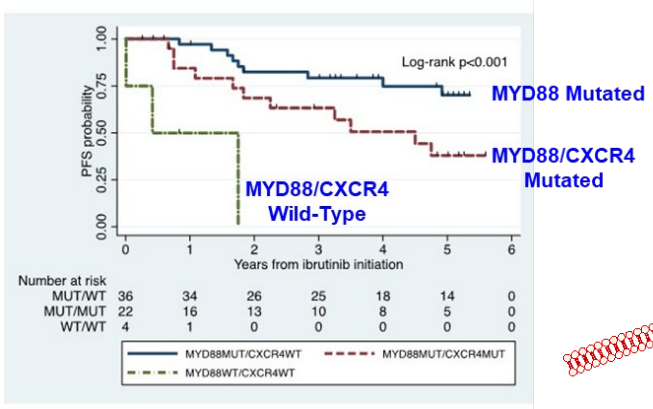

Transformation risk for MYD88 WT
(Odds ratio 23·3; 95% CI 4·2-233·8; p<0·001).

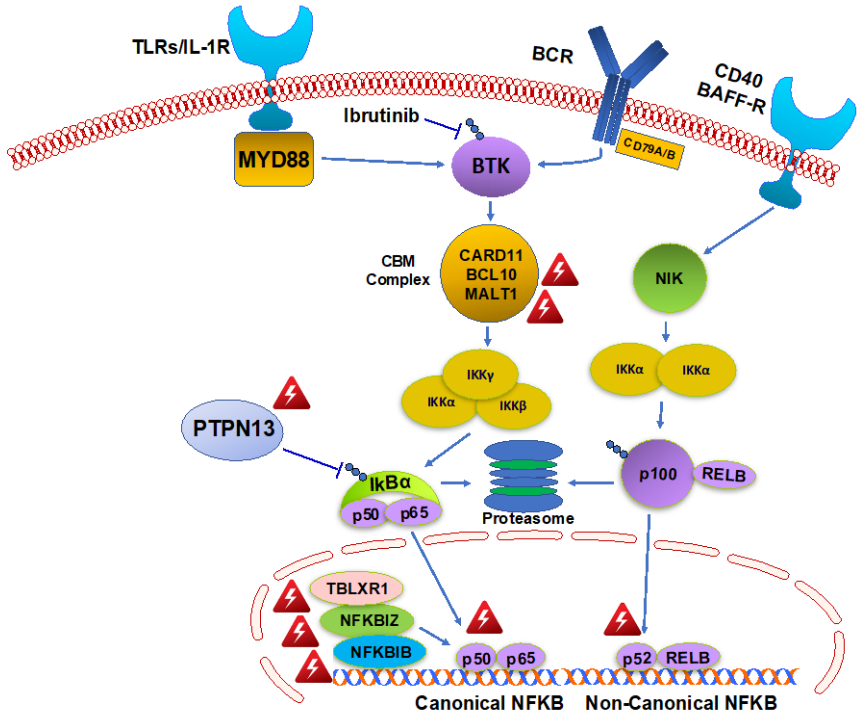
Treon et al, Br. J. Hematol. 2018; Zanwar et al, Am J Hematol 2020; Mian et al, Blood 2019 (134: Abst 5248); Wang et al, Neoplasia 2021.

# Response to BTK-Inhibitors is lower in non-MYD88 mutated (MYD88 wild-type) WM.

## Ibrutinib

| | All Patients | MYD88$^{MUT}$ CXCR4$^{WT}$ | MYD88$^{MUT}$ CXCR4$^{MUT}$ | MYD88$^{WT}$ CXCR4$^{WT}$ | P-value |
|---|---|---|---|---|---|
| N= | 63 | 36 | 22 | 4 | N/A |
| Overall Response Rate-no. (%) | 90.5% | 100% | 86.4% | 50% | <0.01 |
| Major Response Rate-no. (%) | **79.4%** | **97.2%** | **68.2%** | **0%** | **<0.0001** |
| Categorical responses | | | | | |
| Minor responses-no. (%) | 11.1% | 2.8% | 18.2% | 50% | <0.01 |
| Partial responses-no. (%) | 49.2% | 50% | 59.1% | 0% | 0.03 |
| Very good partial responses-no. (%) | **30.2%** | **47.2%** | **9.1%** | **0%** | **<0.01** |
| Median time to response (months) | | | | | |
| Minor response (≥Minor response) | 0.9 | 0.9 | 0.9 | 0.9 | 0.38 |
| Major response (≥Partial response) | **1.8** | **1.8** | **4.7** | **N/A** | **0.02** |



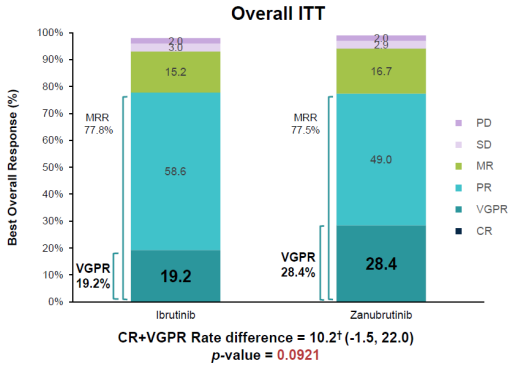




## Zanubrutinib

### MYD88 Mutated

**ASPEN: Efficacy – Response by IRC (Data cutoff: 31 August 2019)**

- Superiority in CR+VGPR rate compared to ibrutinib in relapsed/refractory population (primary study hypothesis) was not significant*

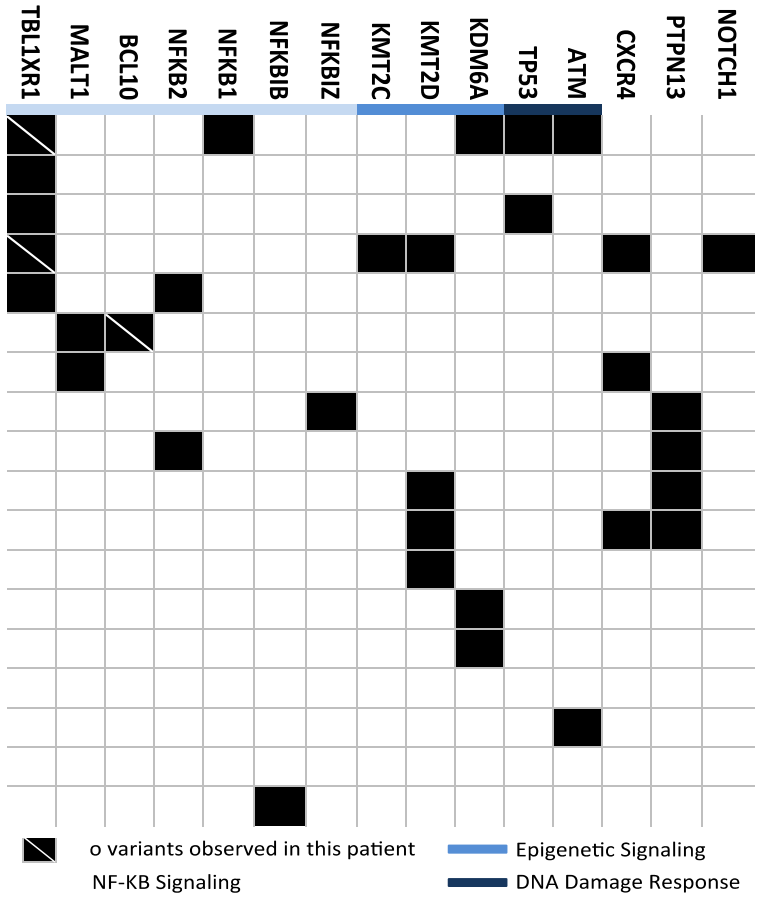


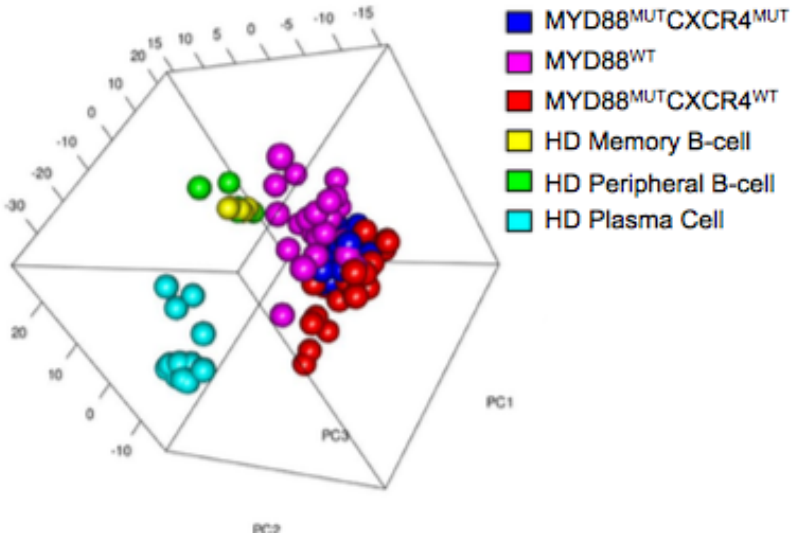

### MYD88 Wild-Type

| N=28 | N= | % |
|---|---|---|
| ORR | 23 | 81% |
| Major (PR or better) | 13 | 50% |
| VGPR | 7 | 27% |

Treon et al, NEJM 2015; JCO 2021; Tam et al, Blood 2020; Dimopoulos et al Blood Adv 2020; Hunter et al, Blood Adv 2018.

# Driver Mutations in WM patients without MYD88 mutations but gene expression overlaps with those who have the MYD88 mutation




Principal component analysis of top 500 high variance genes.

Hunter et al, Blood Adv. 2018

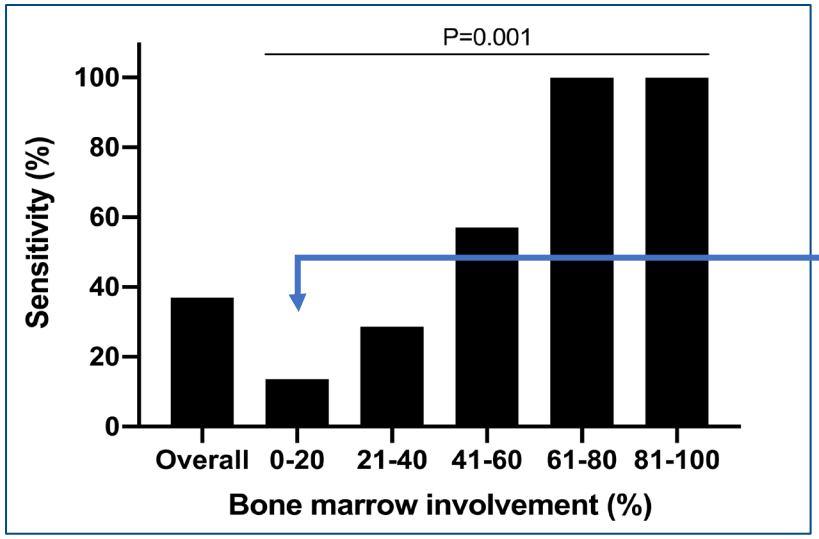
# Challenges of MYD88 detection in WM: Comparison of AS-PCR vs. Next Generation Sequencing

A. Kofides

J. Gustine

| | MYD88 L265P | |
|---|---|---|
| | AS-PCR | NGS |
| True Positive – no. | 391 | 259 |
| True Negative – no. | 23 | 23 |
| False Positive – no. | 0 | 0 |
| False Negative – no. | 0 | 132 |
| Concordance (κ) – % | Ref. | 68 (0.19) |
| Sensitivity (95% CI) – % | Ref. | 66 (61-71) |
| Specificity (95% CI) – % | Ref. | 100 (83-100) |
| PPV (95% CI) – % | Ref. | 100 (98-100) |
| NPV (95% CI) – % | Ref. | 15 (10-22) |

1 in 3 WM patients truly positive for MYD88 can be missed by NGS.




WM patients with lower BM disease(<20%) involvement are more likely to be misclassified by NGS.

Kofides et al, Hemasphere 2021

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# NCCN Guidelines Version 1.2022
# Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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## DIAGNOSIS

**Essential[b,c]**
- Hematopathology review of all slides with at least one paraffin block representative of the tumor (Rebiopsy if consult material is nondiagnostic)
- Adequate tissue biopsy for immunophenotyping to establish diagnosis
  - Typical immunophenotype: CD19+, CD20+, sIgM+; CD5, CD10, CD23 may be positive in 10%–20% of cases and does not exclude diagnosis

## WORKUP[a]

**Essential**
- History and physical exam
- CBC, differential, platelet count
- Liver function tests (LFTs) as clinically indicated
- Peripheral blood smear
- Serum BUN/creatinine, electrolytes, albumin, calcium, serum uric acid, serum LDH, and beta-2 microglobulin
- Creatinine clearance (calculated or measured directly)
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- Unilateral bone marrow aspirate and biopsy, including immunohistochemistry (IHC) and/or multi-parameter flow cytometry
- Chest/abdominal/pelvic CT with contrast when possible
- MYD88,[d] L265P AS-PCR testing of bone marrow

**Useful in Certain Circumstances**
- Serum viscosity
- *CXCR4* gene mutation testing for patients being considered for ibrutinib[e]
- Testing for hepatitis B (if rituximab planned), hepatitis C,[f] and HIV
- Cryocrit[f,g]
- Consider coagulation and/or von Willebrand disease testing if symptoms present (excess bruising or bleeding) or if clinically indicated
- Cold agglutinins
- Neurology consult[h]
- Anti-MAG antibodies/anti-GM1[h]
- Nerve conduction study (NCS)/electromyogram (EMG)[h]
- Fat pad sampling and/or congo red staining of bone marrow for amyloid[h]
- Retinal exam (if IgM ≥3.0 g/dL or if hyperviscosity is suspected)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE)
- Amyloid tissue subtyping with mass spectrometry, if indicated
- Brain/spine MRI, if CNS symptoms

## INDICATIONS FOR TREATMENT

**Symptoms[i] related to:**
- Hyperviscosity
- Neuropathy
- Organomegaly
- Amyloidosis
- Cold agglutinin disease
- Cryoglobulinemia
- Anemia and other cytopenias associated with disease
- Bulky adenopathy
- B symptoms

→ See Primary Treatment (WM/LPL-2)

# Discovery of CXCR4 mutations in WM -2013-



Plenary Paper

LYMPHOID NEOPLASIA

## The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis

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**Key Points**

- Highly recurring mutations are present in WM, including MYD88 L265P, warts, hypogammaglobulinemia, infection, and myelokathexis-syndrome–like mutations in CXCR4, and ARID1A.
- Small, previously undetected CNAs affecting B-cell regulatory genes are highly prevalent in WM.

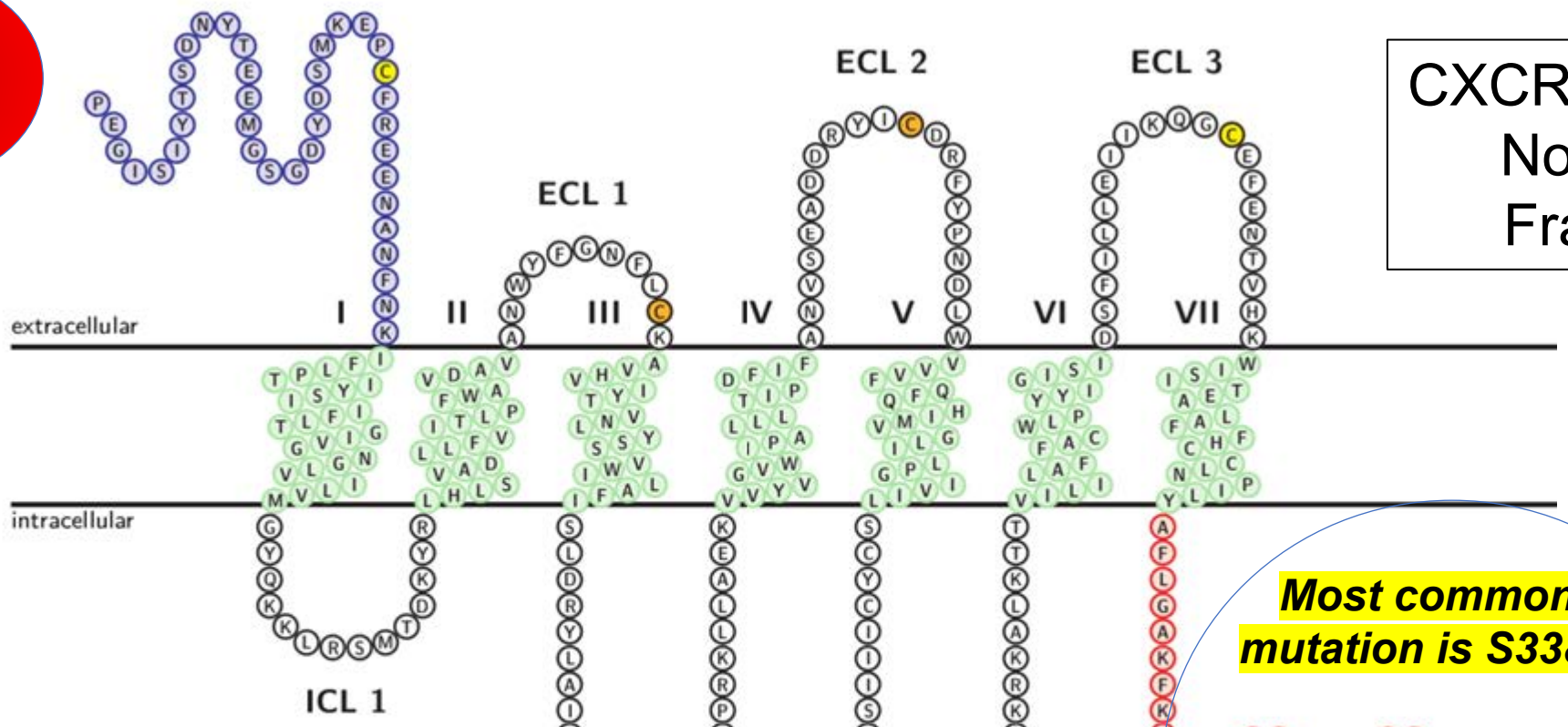
The genetic basis for Waldenström macroglobulinemia (WM) remains to be clarified. Although 6q losses are commonly present, recurring gene losses in this region remain to be defined. We therefore performed whole genome sequencing (WGS) in 30 WM patients, which included germline/tumor sequencing for 10 patients. Validated somatic mutations occurring in >10% of patients included *MYD88*, *CXCR4*, and *ARID1A* that were present in 90%, 27%, and 17% of patients, respectively, and included the activating mutation L265P in MYD88 and warts, hypogammaglobulinemia, infection, and myelokathexis-syndrome–like mutations in CXCR4 that previously have only been described in the germline. WGS also delineated copy number alterations (CNAs) and structural variants in the 10 paired patients. The CXCR4 and CNA findings were validated in independent expansion cohorts of 147 and 30 WM patients, respectively. Validated gene losses due to CNAs involved *PRDM2* (93%), *BTG1* (87%), *HIVEP2* (77%), *MKLN1* (77%), *PLEKHG1* (70%), *LYN* (60%), *ARID1B* (50%), and *FOXP1* (37%). Losses in *PLEKHG1*, *HIVEP2*, *ARID1B*, and *BCLAF1* constituted the most common deletions within chromosome 6. Although no recurrent translocations were observed, in 2 patients deletions in 6q corresponded with translocation events. These studies evidence highly recurring somatic events, and provide a genomic basis for understanding the pathogenesis of WM. (*Blood*. 2014;123(11):1637-1646)

Hunter et al, Blood 2013

30-40% of WM patients carry CXCR4 mutations

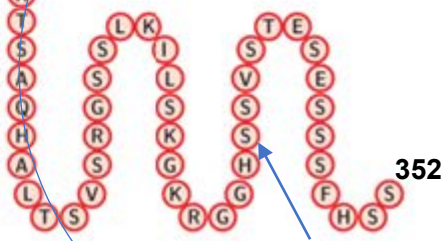
# CXCR4 receptor C-terminal domain (WHIM-like) mutations are common in WM

CXCL12




CXCR4 mutations
Non-sense
Frameshift

***Most common mutation is S338X***




**S338X**

>40 different types of CXCR4 mutations reported so far

Adapted from Kahler et al, AIMS Biophysics, 2016;
Hunter et al, Blood 2014; Poulain et al, Clin Cancer Res. 2016.

# MYD88 and CXCR4 Mutations

## 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 |

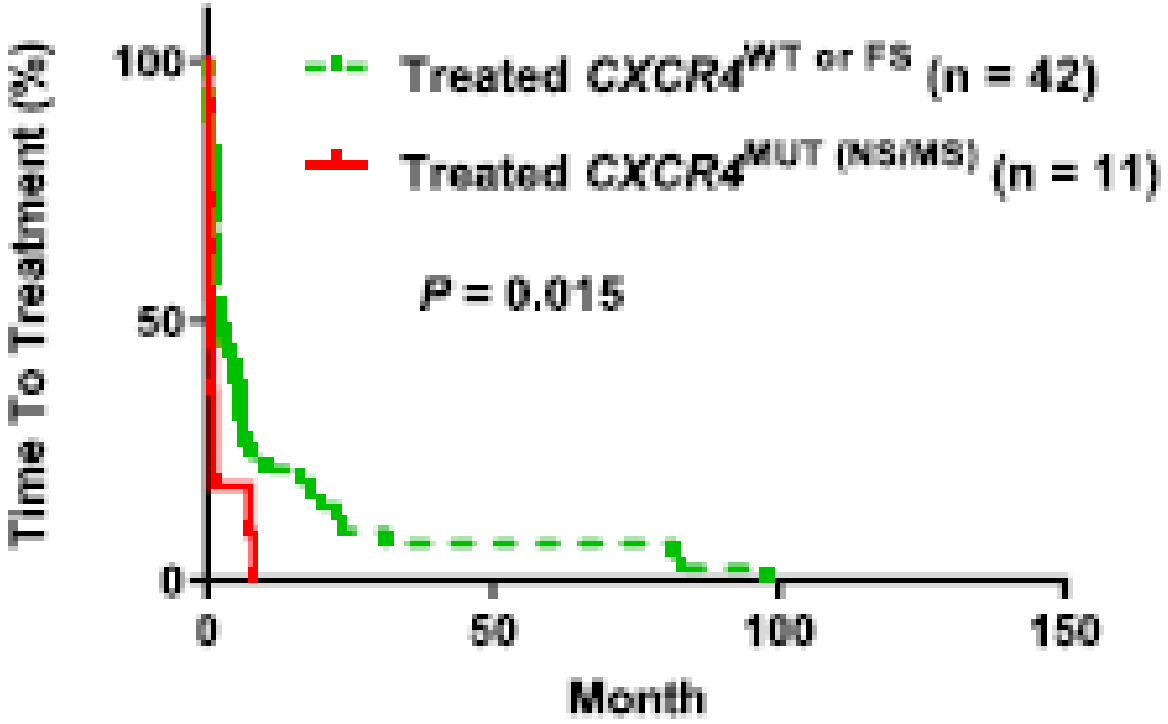
**Patients with MYD88 and Nonsense CXCR4 mutations (S338X) show high IGM levels, symptomatic hyperviscosity, and shorter time to initial treatment.**

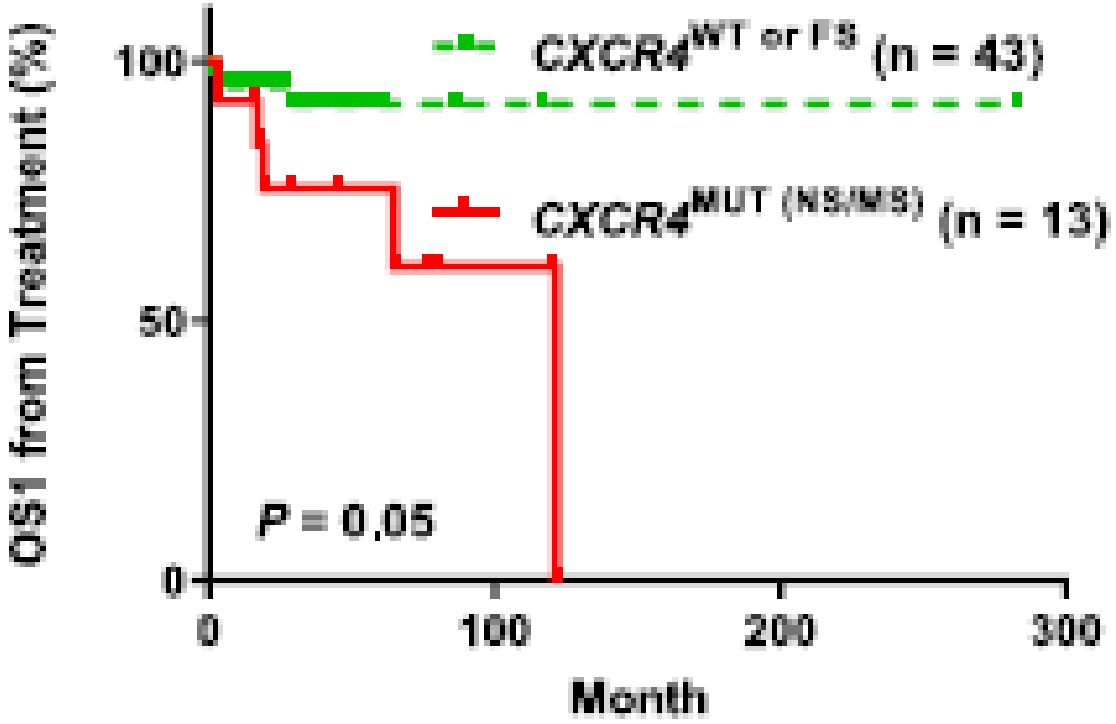
*BTK; Bruton's tyrosine kinase*

Treon et al, Blood 2014; Schmidt et al, BJH 2015; Abeykoon J, et al. *Cancer Manage and Res*. 2017;9:73-83; Wang et al, Neoplasia 2021.

# Time to Treatment and OS based on CXCR4 mutation status in WM/LPL patients

**MD Anderson Study**

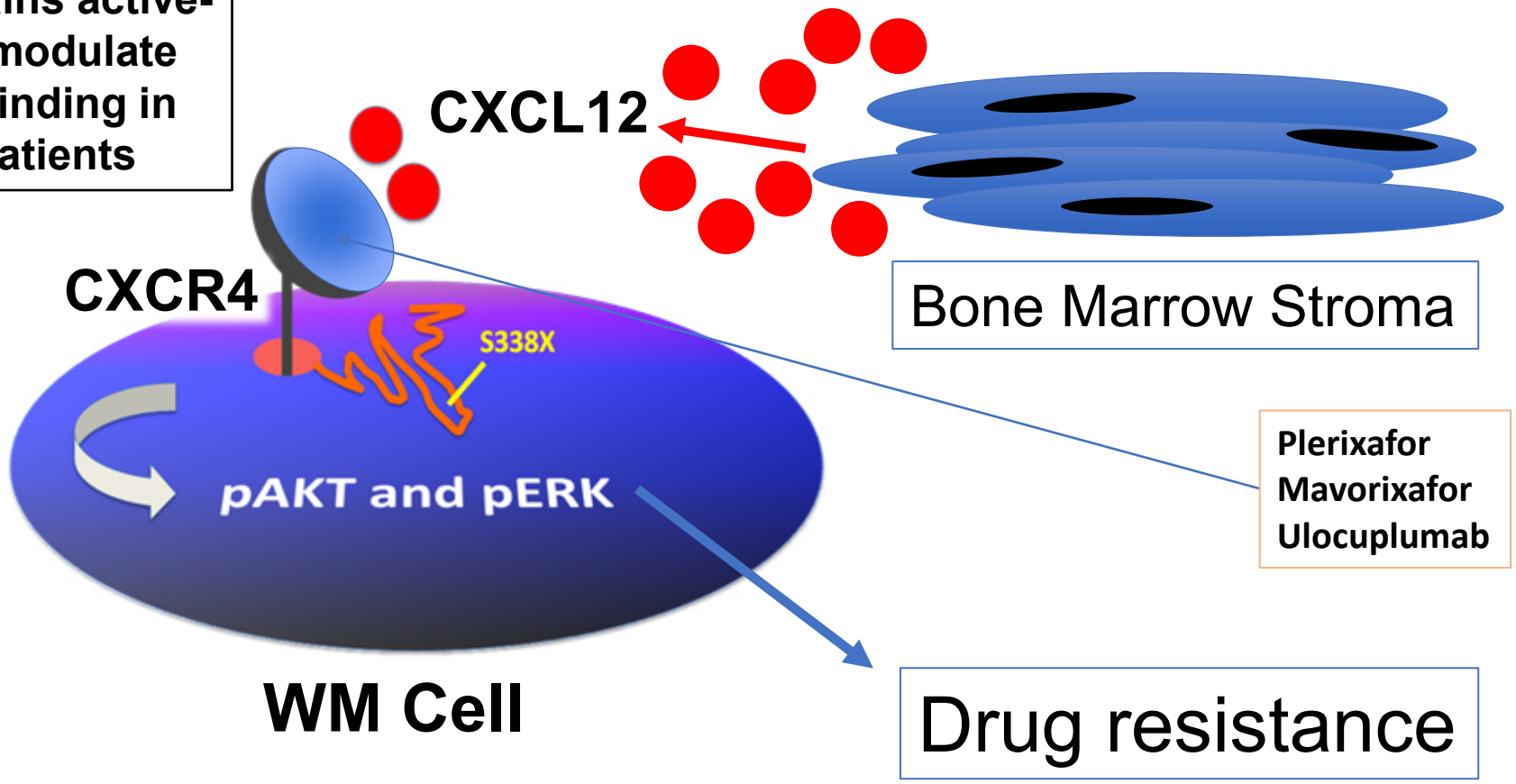



Wang et al, Neoplasia 2021

# Mutated CXCR4 permits ongoing pro-survival signaling by CXCL12

**CXCR4 receptor remains active- and does not downmodulate following CXCL12 binding in CXCR4 mutated patients**




30-40% of WM patients have mutations in CXCR4

Cao et al, Br J Haematol. 2015 Mar;168(5):701-7; Roccarro et al, Blood. 2014 Jun 26;123(26):4120-31

# Ibrutinib Activity in Previously Treated WM: Update of the Pivotal Trial (median f/u 59 mos)

| | All Patients | $MYD88^{MUT}$ $CXCR4^{WT}$ | $MYD88^{MUT}$ $CXCR4^{MUT}$ | $MYD88^{WT}$ $CXCR4^{WT}$ | P-value |
|---|---|---|---|---|---|
| N= | 63 | 36 | 22 | 4 | N/A |
| Overall Response Rate-no. (%) | 90.5% | 100% | 86.4% | 50% | <0.01 |
| Major Response Rate-no. (%) | **79.4%** | **97.2%** | **68.2%** | **0%** | **<0.0001** |
| Categorical responses | | | | | |
| Minor responses-no. (%) | 11.1% | 2.8% | 18.2% | 50% | <0.01 |
| Partial responses-no. (%) | 49.2% | 50% | 59.1% | 0% | 0.03 |
| Very good partial responses-no. (%) | **30.2%** | **47.2%** | **9.1%** | **0%** | **<0.01** |
| Median time to response (months) | | | | | |
| Minor response (≥Minor response) | 0.9 | 0.9 | 0.9 | 0.9 | 0.38 |
| Major response (≥Partial response) | **1.8** | **1.8** | **4.7** | **N/A** | **0.02** |

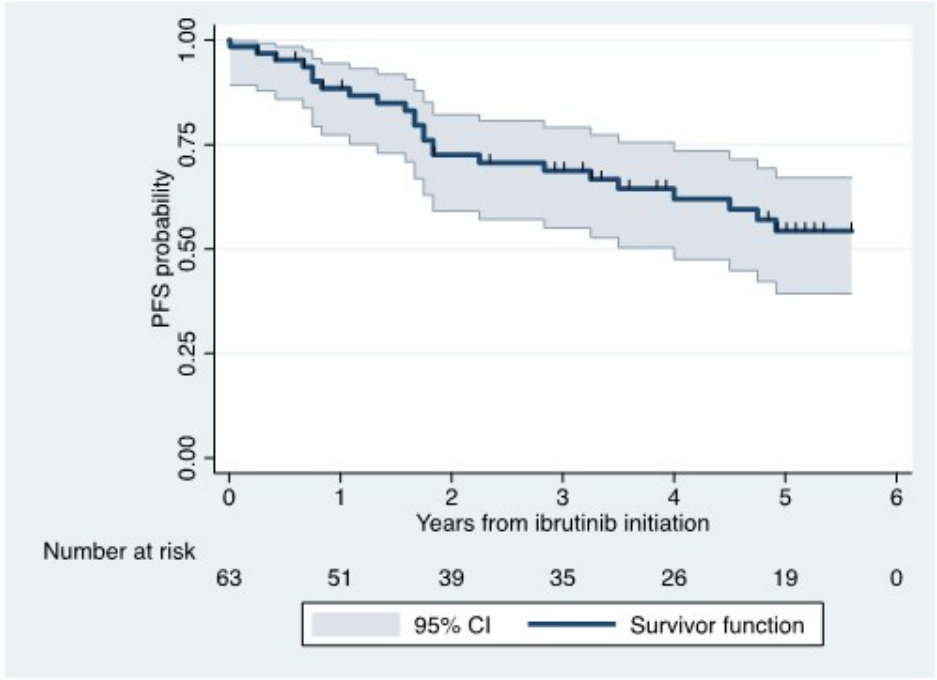
***One patient had MYD88 mutation, but no CXCR4 determination and had SD.**

**Treon et al, NEJM 2015; Updated JCO 2021**

# Ibrutinib in Previously Treated WM: Updated PFS

## All patients

A.

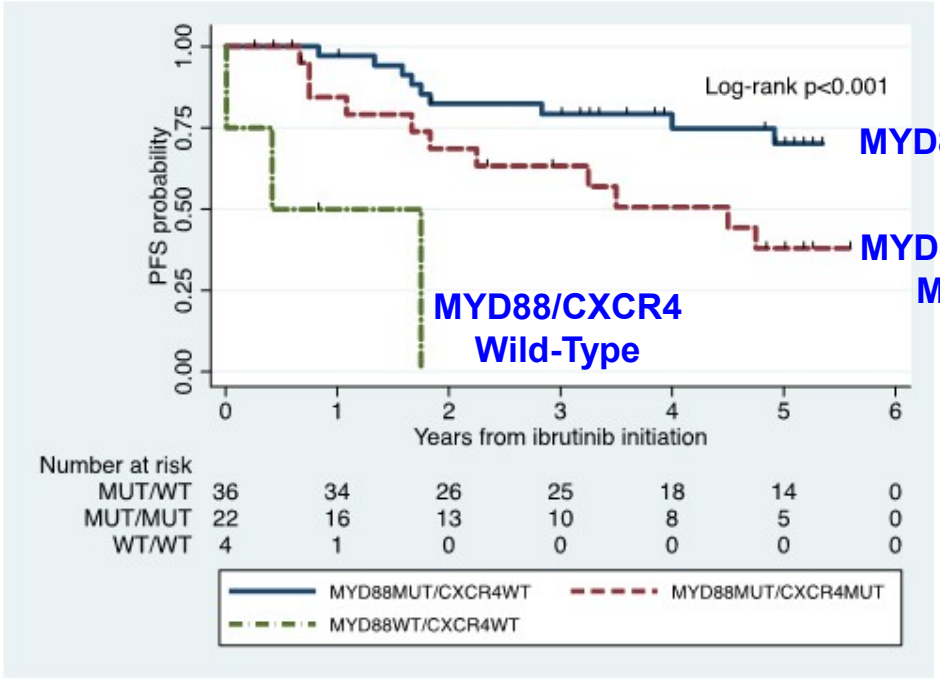



**5 year PFS: 54%**

**5 year OS: 87%**

## MYD88 and CXCR4 Mutation Status

B.

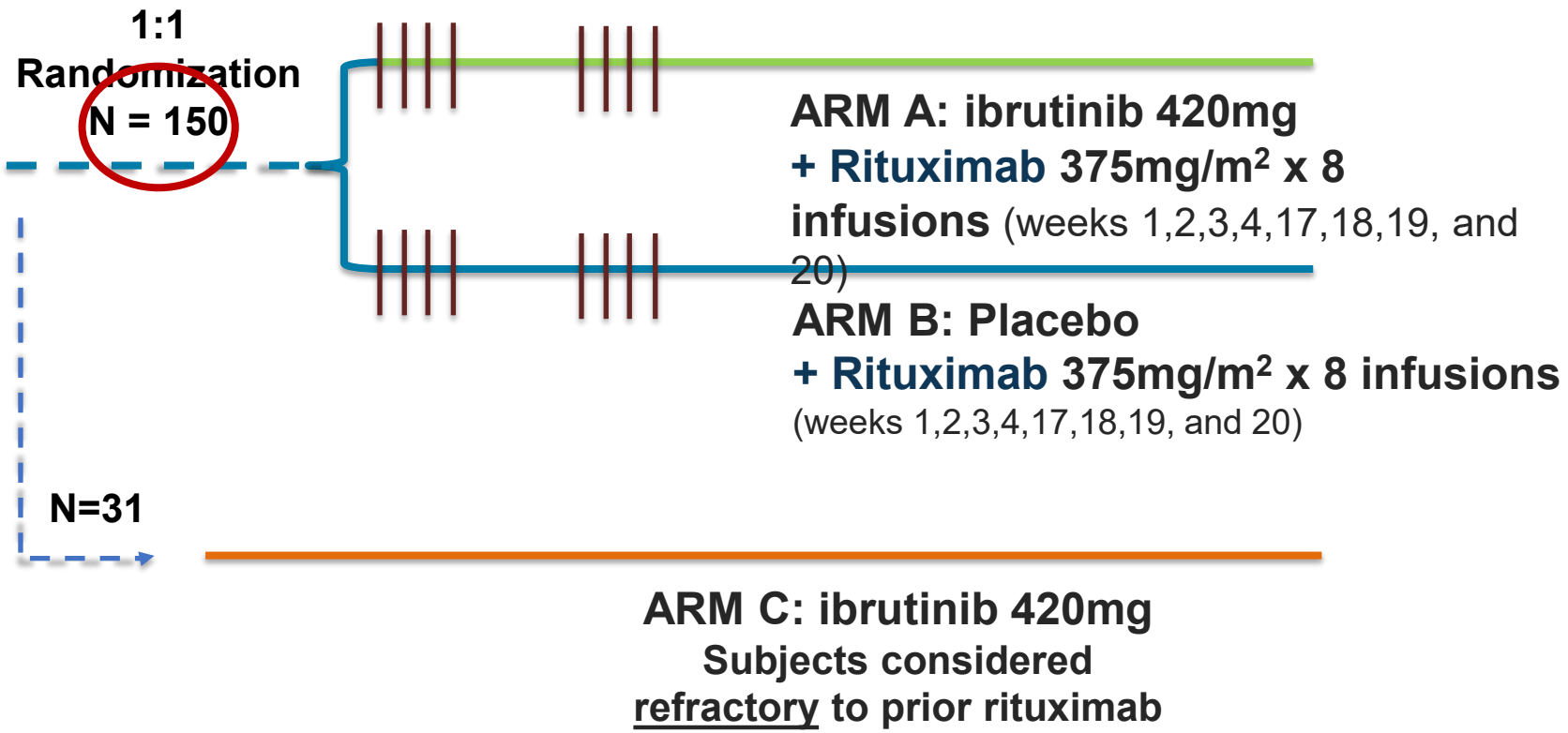



Treon et al, NEJM 2015; Updated JCO 2021

# iNNOVATE Study in WM

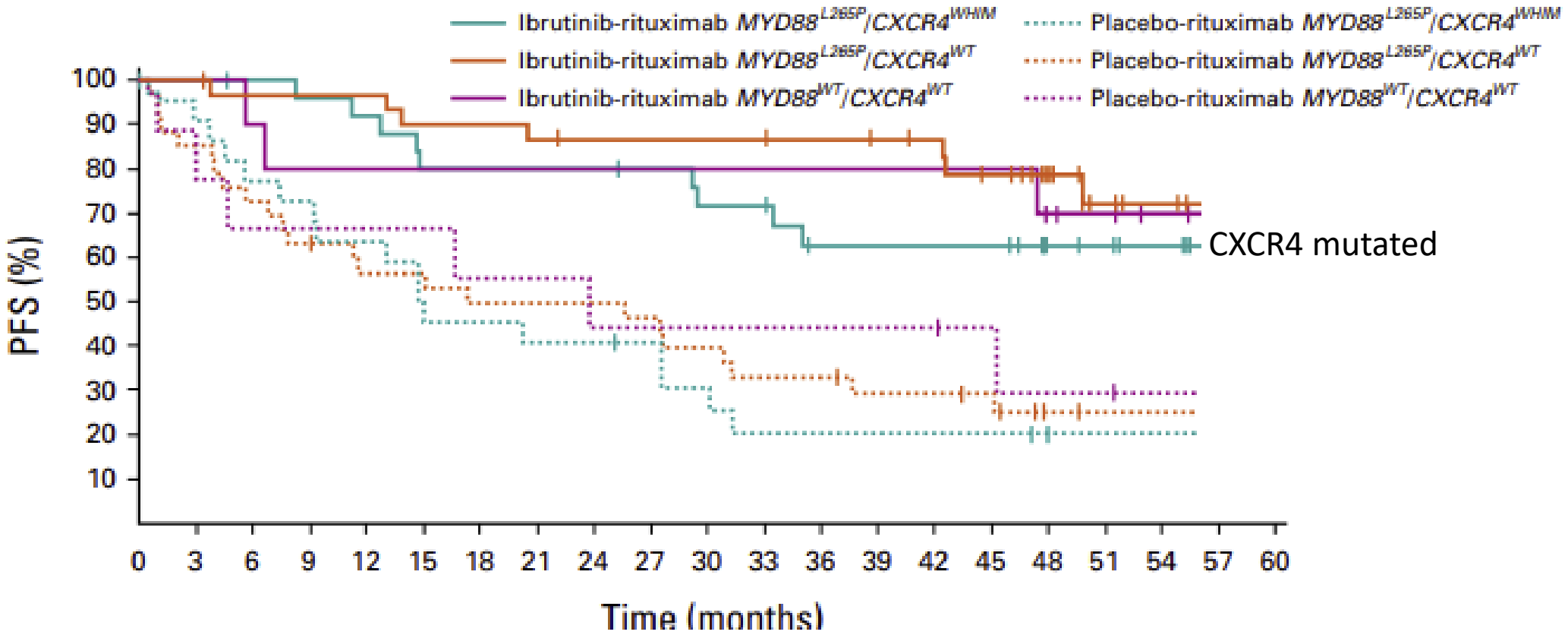
## Treatment Naïve + Previously Treated

## 45 centers in 9 countries


**ABC patients genotyped for MYD88 and CXCR4**

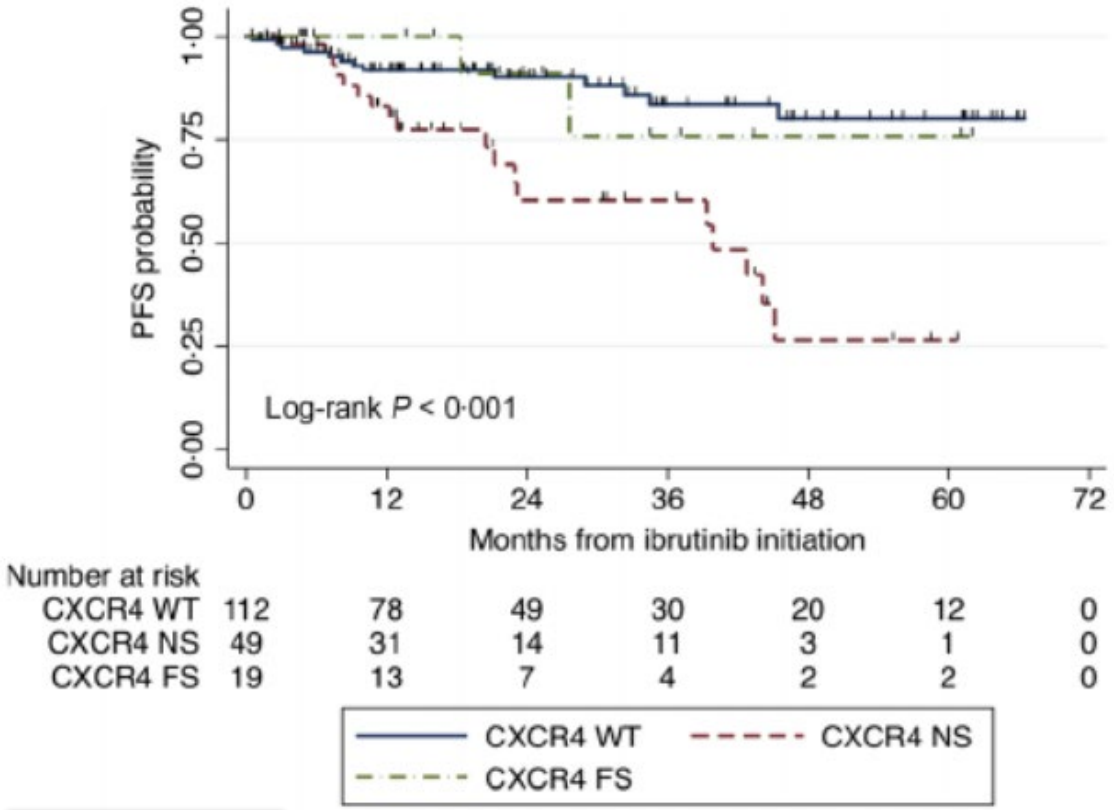
# Progression-Free Survival Benefit: Impact of MYD88/CXCR4 Genotype



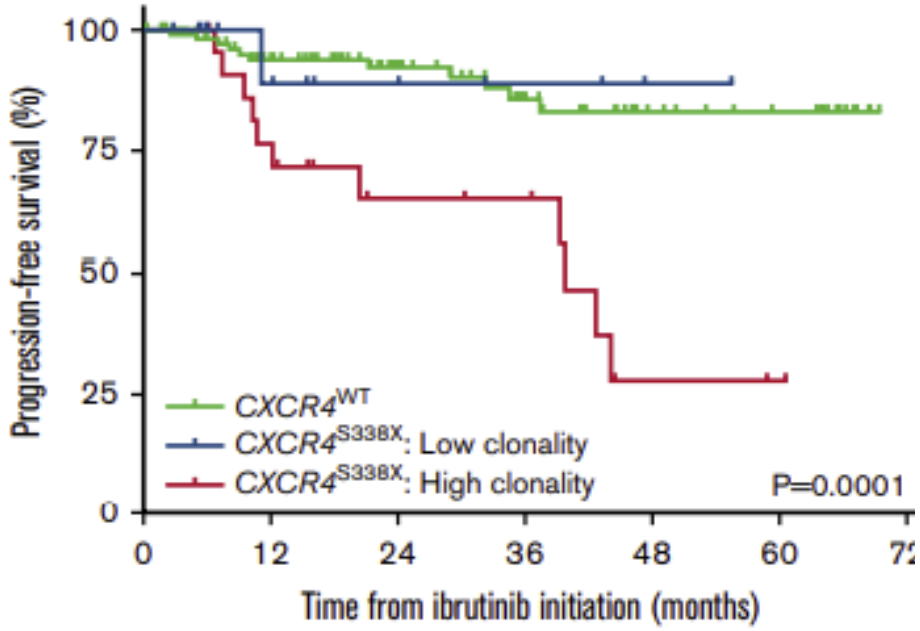

Buske et al., J Clin Oncol 2021

# CXCR4 Nonsense variants with high clonality impact ibrutinib PFS outcomes

**NS vs. FS CXCR4 Mutations**




**High vs. Low NS Clonality CXCR4 Mutations**




High clonality ≥25%

Castillo et al, BJH 2019; Gustine et al, Blood Adv 2019

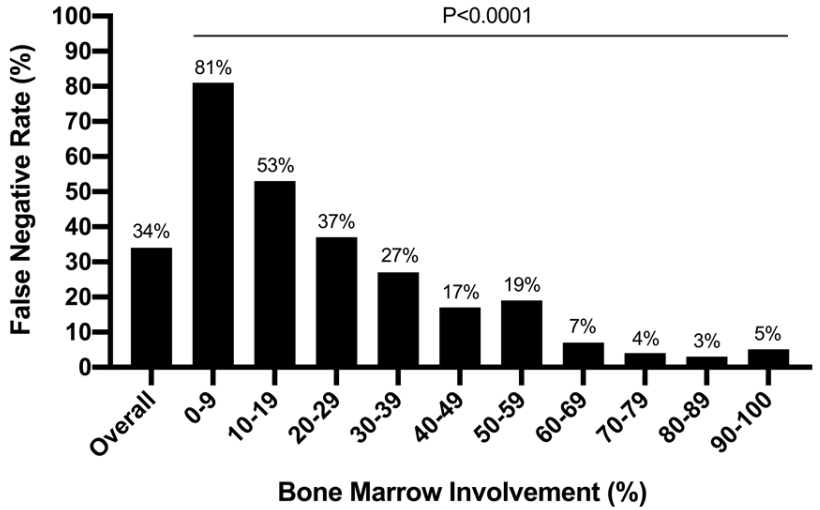
# Zanubrutinib: Response by Genotype (ASPEN)

| 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% |

1. Tam et al. *Blood* 2020;136(18):2038–2050. 2. Dimopoulos et al. *Blood Adv* 2020;4(23):6009–6018.

# Challenges of CXCR4 detection in WM: Comparison of NGS against AS-PCR/Sanger

J. Gustine

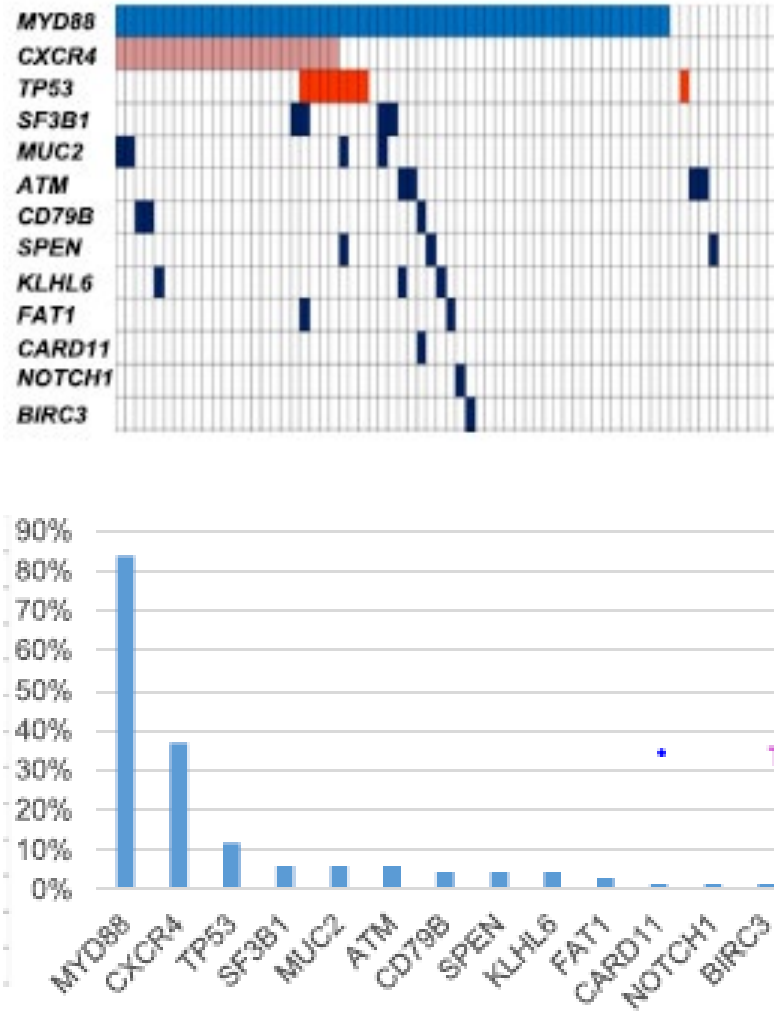



Sensitivity for mutated CXCR4 detection was 37% by NGS and unselected BM. Low BM involvement and clonality impacted detection.

Gustine et al, BJH 2021

# MD Anderson Sequencing Approach for MYD88 and CXCR4 mutations in WM

Routine clinical workup performed by the CLIA- certified molecular diagnostic laboratory in UT MD Anderson Cancer Center. *MYD88* L265P was determined by AS-PCR and *CXCR4* mutation status (codons 291-353) by targeted NGS. For targeted NGS, genomic DNA extracted from the bone marrow aspirate was used for preparing **sequencing libraries with molecular barcodes** using the Agilent HaloPlex Target Enrichment System (Agilent Technologies), followed by **bidirectional paired-end sequencing using the Miseq sequencer** (Illumina Inc.). Illumina Experiment Manager, MiSeq Control Software, Real Time Analysis, Sequence Analysis Viewer, MiSeq Reporter, and Agilent SureCall were utilized for experimental setup and NGS data analysis. Although the NGS assay is capable of achieving sensitivity of 1%, the effective lower limit of detection of the assays used for clinical workup was determined to be 5% to 10% taking into consideration the depth of coverage and the ability to confirm low-level mutations using independent conventional platforms.




Wang et al, Neoplasia 2021

# Cell-free DNA analysis for *MYD88*$^{L265P}$ and *CXCR4*$^{S338X}$ mutations in Waldenström macroglobulinemia.

| Variable | MYD88$^{L265P}$ | | CXCR4$^{S338X}$ | |
|---|---|---|---|---|
| | BM | cfDNA | BM | cfDNA |
| True positive – no. | 25 | 20 | 6 | 4 |
| True negative – no. | 3 | 3 | 17 | 17 |
| False positive – no. | 0 | 0 | 0 | 0 |
| False negative – no. | 0 | 5 | 0 | 2 |
| Concordance (Cohen κ) – %. | Ref. | 82 (0.46) | Ref. | 91 (0.75) |
| Sensitivity (95% CI) – % | Ref. | 80 (59-92) | Ref. | 67 (24-94) |
| Specificity (95% CI) – % | Ref. | 100 (31-100) | Ref. | 100 (77-100) |
| PPV (95% CI) – % | Ref. | 100 (80-100) | Ref. | 100 (40-100) |
| NPV (95% CI) – % | Ref. | 38 (10-74) | Ref. | 89 (65-98) |

**Adjusted test performance findings for cfDNA using both BM19+ and BMMC fractions as reference tissue.**

Demos et al, AJH 2021

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2022
# Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

| NCCN Categories of Evidence and Consensus | |
|---|---|
| **Category 1** | Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| **Category 2A** | Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| **Category 2B** | Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. |
| **Category 3** | Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |

All recommendations are category 2A unless otherwise indicated.

| NCCN Categories of Preference | |
|---|---|
| **Preferred intervention** | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. |
| **Other recommended intervention** | Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes. |
| **Useful in certain circumstances** | Other interventions that may be used for selected patient populations (defined with recommendation). |

All recommendations are considered appropriate.

- Category 1 studies are generally supported by large randomized trials
- Category 2 studies are generally supported by prospective Phase II trials. Larger multicenter studies, with confirmed findings generally rate 2A.
- Category 3 studies may include small patient series, or retrospective data analysis.

| PRIMARY THERAPY FOR WM/LPL[a] (Order of regimens is alphabetical and does not indicate preference) | |
|---|---|
| **Preferred Regimens** | |
| • Bendamustine/rituximab | • Rituximab/cyclophosphamide/dexamethasone |
| • Bortezomib/dexamethasone/rituximab[b] | • Zanubrutinib (category 1) |
| • Ibrutinib ± rituximab (category 1) | |
| **Other Recommended Regimens** | |
| • Bendamustine | • Fludarabine ± rituximab[c] |
| • Bortezomib ± rituximab[b] | • Fludarabine/cyclophosphamide/rituximab[c] |
| • Bortezomib/dexamethasone | • Ixazomib/rituximab/dexamethasone |
| • Carfilzomib/rituximab/dexamethasone | • Rituximab |
| • Cladribine ± rituximab[c] | • Rituximab/cyclophosphamide/prednisone |

[a] See General Considerations for Systemic Therapy for WM/LPL (WM/LPL-B 1 of 4).
[b] Consider for patients presenting with symptomatic hyperviscosity, or in whom rapid IgM reduction is required.
[c] May be associated with disease transformation and/or development of MDS/AML in patients with Waldenström macroglobulinemia.

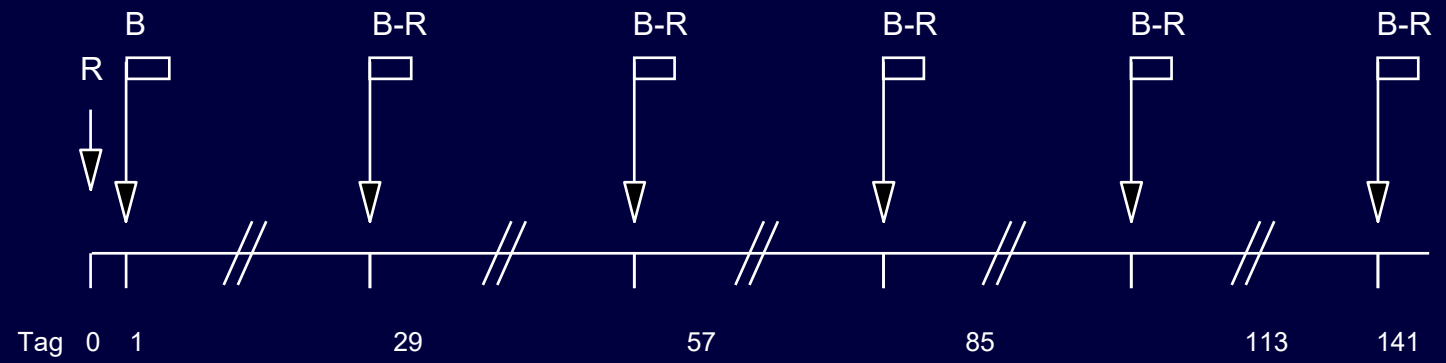
**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

Continued
References

# STIL GROUP STUDY: Bendamustine-Rituximab vs. CHOP-R

N=549

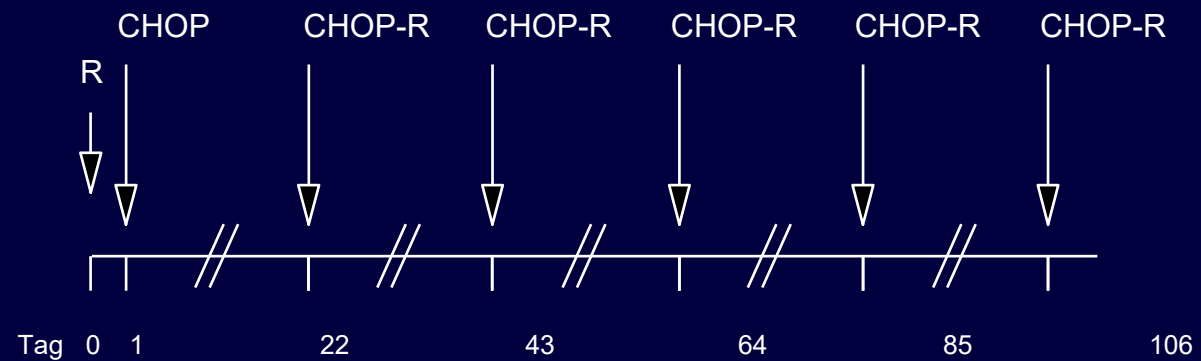
## Bendamustine plus Rituximab (B-R)




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| B = Bendamustine | 90 mg/m² | day | 1+2 | 29+30 | 57+58 | 85+86 | 113+114 | 141+142 |
| R = Rituximab | 375 mg/m² | day | 0 | 29 | 57 | 85 | 113 | 141 |

Randomization

## CHOP plus Rituximab (CHOP-R)




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CHOP | | day | 1 | 22 | 43 | 64 | 85 | 106 |
| Rituximab | 375 mg/m² | day | 0 | 22 | 43 | 64 | 85 | 106 |

M. Rummel

Rummel M. et al, ASH 2008

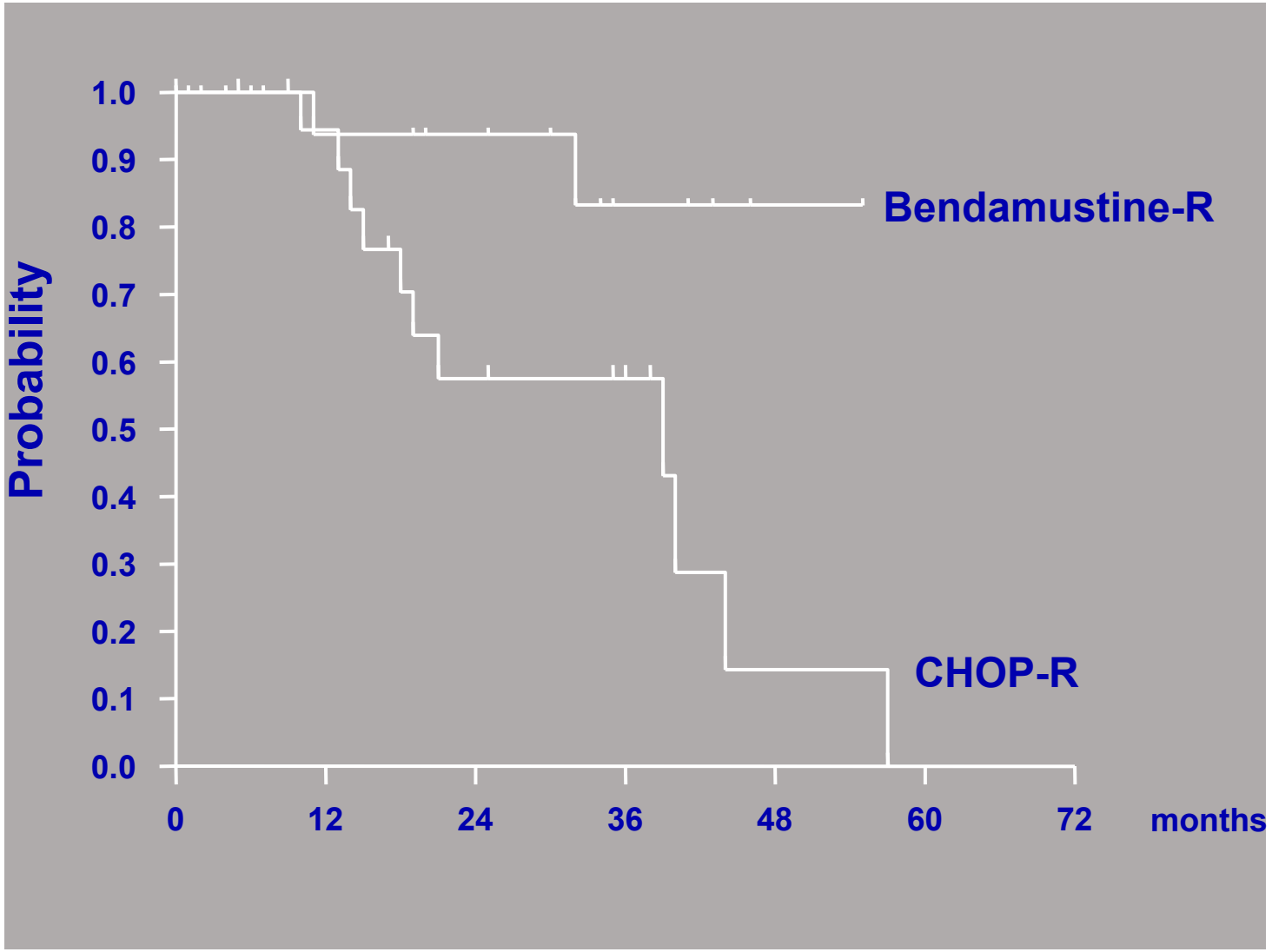
# Waldenström patients characteristics: B-R vs CHOP-R

N=40

| 20th Aug 2008<br>40 evaluable pts. | Bendamustine-R<br>(n=23) | CHOP-R<br>(n=17) |
|---|---|---|
| Age (median) | 65 yrs | 64 yrs |
| Stage IV | 100 % | 100 % |
| Beta-2 Microglobulin | 3,2 | 3,4 |
| IgM (median, mg/dl) | 2.790 | 1.690 |
| Range IgM (mg/dl) | 11.220 - 1.100 | 8.510 - 900 |
| Hb (median, g/dl) | 10,2 | 9,9 |
| Toxicity treatment associated | | |
| Neuropathy (patients) | 1 | 3 |

Rummel M, et al. Third International Pt Physic Summit on WM. May 1-3, 2009; Boston, MA.

# PFS: Benda-R vs CHOP-R in frontline WM

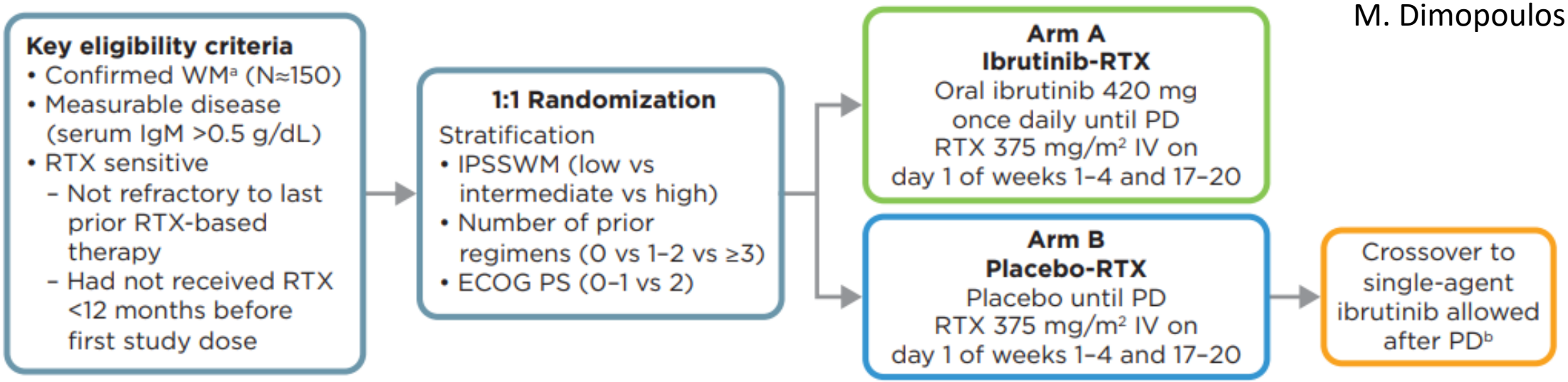



Presented on the Vth International Workshop on Waldenstrom´s Macroglobulinemia, Stockholm, Oct 15-19, 2008

# iNNOVATE Study Design

C. Buske

M. Dimopoulos




*ECOG PS, Eastern Cooperative Oncology Group performance status; IPSSWM, International Prognostic Scoring System for Waldenström's Macroglobulinemia; IRC, independent review committee; IV, intravenous; PD, progressive disease.*

*[a]Previously untreated patients were allowed to enroll following a protocol amendment (November 2015); therefore, their enrollment started later than patients who had relapsed.*
*[b]Patients in the placebo-RTX arm could receive next-line single-agent ibrutinib in crossover following IRC-confirmed PD.*

- iNNOVATE (PCYC-1127) was a double-blind, randomized, placebo-controlled, multicenter, international phase 3 study c assess the efficacy and safety of ibrutinib-RTX versus placebo-RTX in patients with WM (**Figure 1**).
- The primary endpoint was PFS by IRC. Secondary endpoints included response rate by IRC, time to next treatment, hemoglobin (Hgb) improvement, overall survival (OS), and safety.
- After study closure, patients without PD could continue ibrutinib in an extension program.

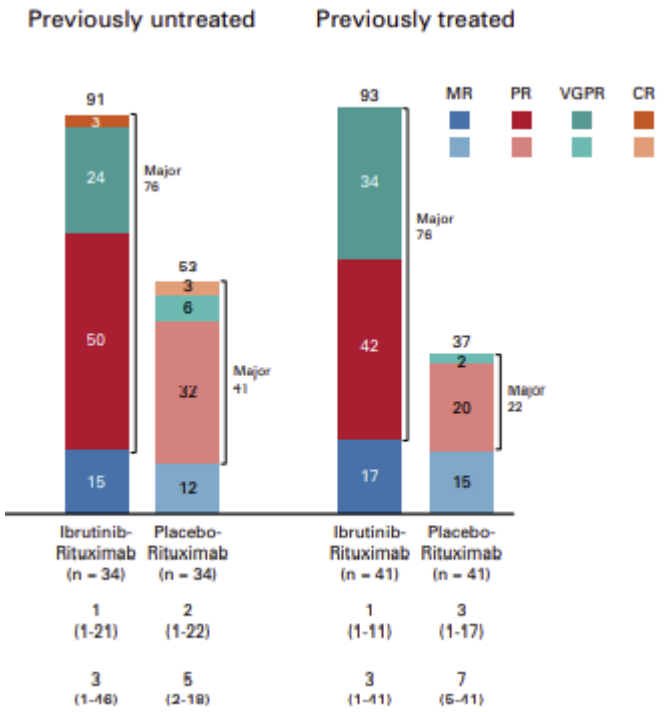
# iNNOVATE: Baseline Characteristics

| Characteristic | Ibrutinib + R (n=75) | Placebo + R (n=75) |
|---|---|---|
| Age, median (range), y | 70 (36-89) | 68 (39-85) |
| Male sex, n (%) | 45 (60) | 54 (72) |
| IPSSWM, n (%) | | |
| Low | 15 (20) | 17 (23) |
| Intermediate | 33 (44) | 28 (37) |
| High | 27 (36) | 30 (40) |
| Medium serum IgM, g/L (range) | 33 (6-78) | 32 (6-83) |
| Number of prior systemic therapies, n (%) | | |
| 0 | 34 (45) | 34 (45) |
| 1-2 | 34 (45) | 36 (48) |
| ≥3 | 7 (9) | 5 (7) |
| Genotype, n (%) | | |
| *MYD88*$^{L265P}$/*CXCR4*$^{WT}$ | 32 (43) | 35 (47) |
| *MYD88*$^{L265P}$/*CXCR4*$^{WT}$ | 26 (35) | 23 (31) |
| *MYD88*$^{L265P}$/*CXCR4*$^{WT}$ | 11 (15) | 9 (12) |
| Unkown | 6 (8) | 8 (11) |
| Bone marrow infiltration: mean % cellularity (range) | 73 (25-100) | 75 (2-100) |

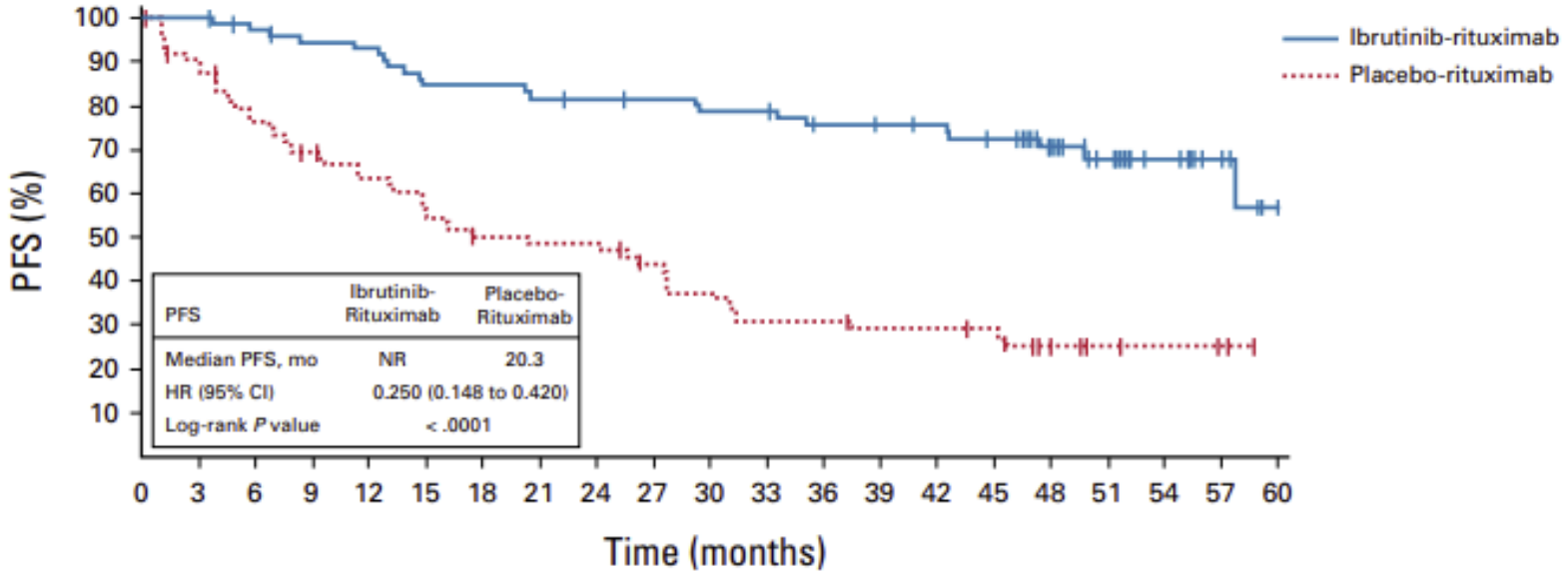
Buske C, et al. JCO 2021

# iNNOVATE Final Analysis

Response Rates




Progression-Free Survival



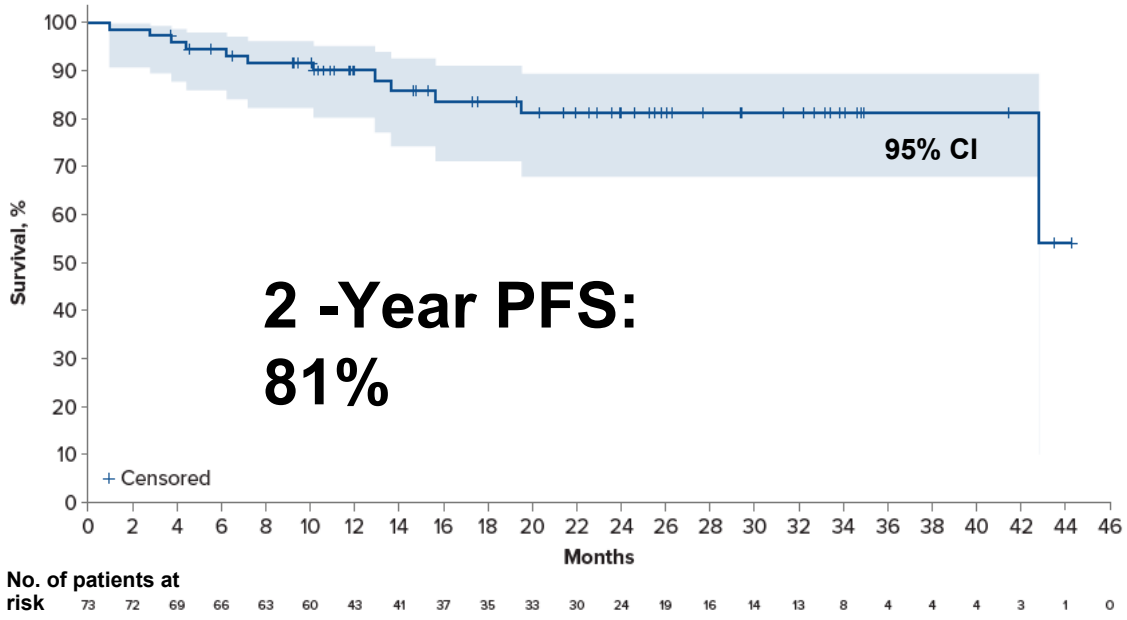

Buske C, et al. JCO 2021

# Zanubrutinib in WM:

## Phase 2 data in TN and previously treated pts.

| Best Response in WM | zanubrutinib | | |
|---|---|---|---|
| | Overall | TN | RR |
| Evaluable for efficacy, n | 73 | 24 | 49 |
| Median Follow-up | 23.9 mo | 12.3 mo | 24.8 mo |
| Response Criteria | Mod. 6th IWWM (IgM decreases only, and not extramedullary disease) | | |
| Median Prior Lines of Therapy | | 0 | 2 (1-8) |
| ORR | 92% | 96% | 90% |
| MRR | 82% | 87% | 78% |
| CR/VGPR[1] | 42% | 29% | 49% |
| PR | 40% | 58% | 31% |

**Progression Free Survival (PFS)**




**Zanubrutinib 320 mg qd to 160 mg BID**

Trotman et al, EHA 2019; Blood 2020; 10.1182/blood.2020006449. Online ahead of print.

# ASPEN: A Phase 3 Study of Zanubrutinib vs. Ibrutinib in WM

**Eligible Patients**

- Histologic diagnosis of WM
- Meeting ≥1 criterion for treatment initiation[1]
- If treatment naïve (TN[a]), must be considered unsuitable for standard CIT
- No prior BTK inhibitors

Cohort 1

*MYD88*$^{MUT}$ WM patients
N=201 (164 R/R)

R
1:1

Stratification factors

- *CXCR4* status (*CXCR4*$^{WHIM}$ vs *CXCR4*$^{WT}$ vs missing)
- Number of prior lines of therapy (0 vs 1-3 vs >3)

**Arm A: Zanubrutinib**
n= 102
160 mg BID until PD

**Arm B: Ibrutinib**
n= 99
420 mg QD until PD

Cohort 2

*MYD88*$^{WT}$ WM patients
N=28 (23 R/R)

**Arm C: Zanubrutinib**
N=28
160 mg BID until PD

BID, twice daily; BTK, Bruton tyrosine kinase; CIT, chemoimmunotherapy; 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.

[a]Up to 20% of the overall population.

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

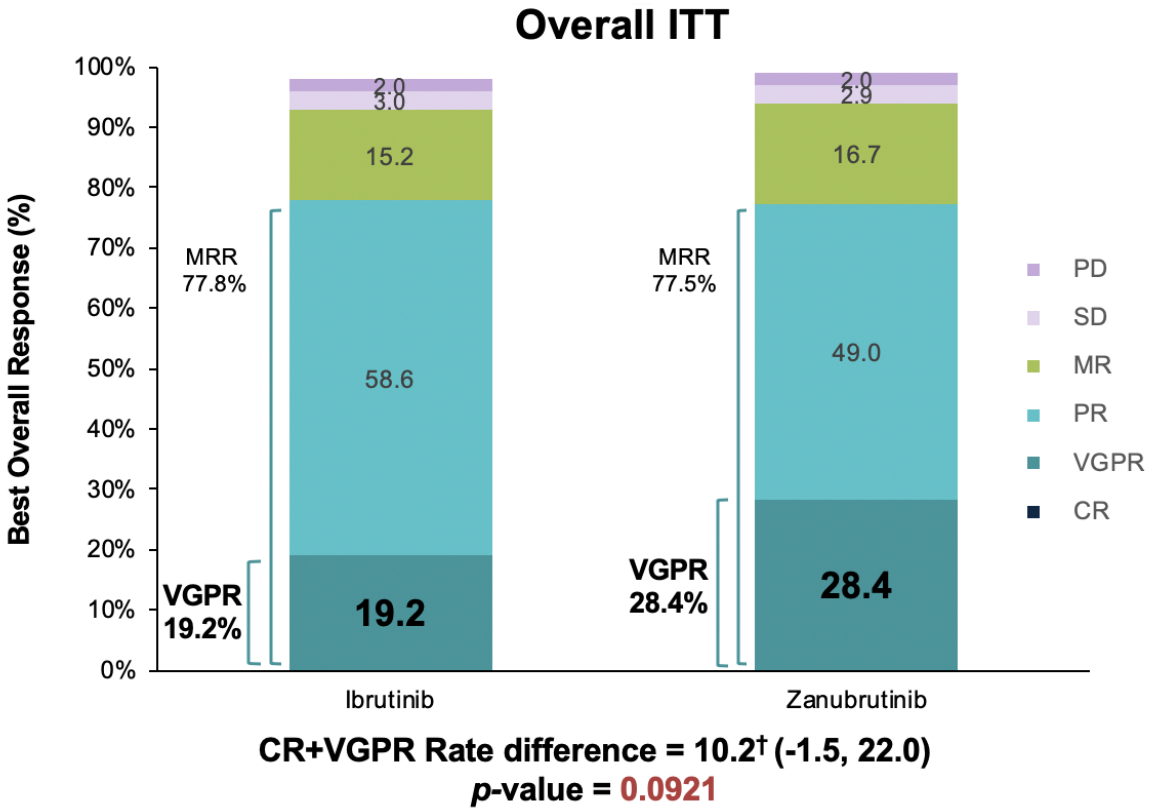
# ASPEN Cohort 1: Demographics and Disease Characteristics

| Characteristics, n (%) | Ibrutinib (n = 99) | Zanubrutinib (n =102) |
|---|---|---|
| Age, years median (range) | 70.0 (38, 90) | 70.0 (45, 87) |
| > 75 years | 22 (22) | 34 (33) |
| Gender, n (%) | | |
| Male | 65 (66) | 69 (68) |
| Prior lines of therapy, n (%) | | |
| 0 | 18 (18) | 19 (19) |
| 1-3 | 74 (75) | 76 (75) |
| >3 | 7 (7) | 7 (7) |
| Genotype by central lab, n (%)* | | |
| $MYD88^{L265P}/CXCR4^{WT}$ | 90 (91) | 91 (89) |
| $MYD88^{L265P}/CXCR4^{WHIM}$ | 8 (8) | 11 (11) |
| IPSS WM[1] | | |
| Low | 13 (13) | 17 (17) |
| Intermediate | 42 (42) | 38 (37) |
| High | 44 (44) | 47 (46) |
| Hemoglobin ≤ 110 g/L | 53 (54) | 67 (66) |

*"Wildtype-blocking PCR" for MYD88 and Sanger sequencing for CXCR4 using bone marrow aspirates. One patient had local NGS testing results of MYD88 L265P/ CXCR4 Unknown.

Tam CS, et al. *Blood*. 2020. Online ahead of print.

# ASPEN Cohort 1: Efficacy, Response by IRC




- Data cutoff: August 31, 2019
- Superiority in CR+VGPR rate compared to ibrutinib in relapsed/refractory population (primary study hypothesis) was not significant* (p-value 0.1160)

CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MRR, major response rate; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.
Overall concordance between Independent review and investigators = 94%
*All other *P* values are for descriptive purposes only. †Adjusted for stratification factors and age group.
1. Tam CS et al. *J Clin Oncol*. 2020;38(15 Suppl):8007.

# ASPEN: AE Categories of Interest (BTKi Class AEs)

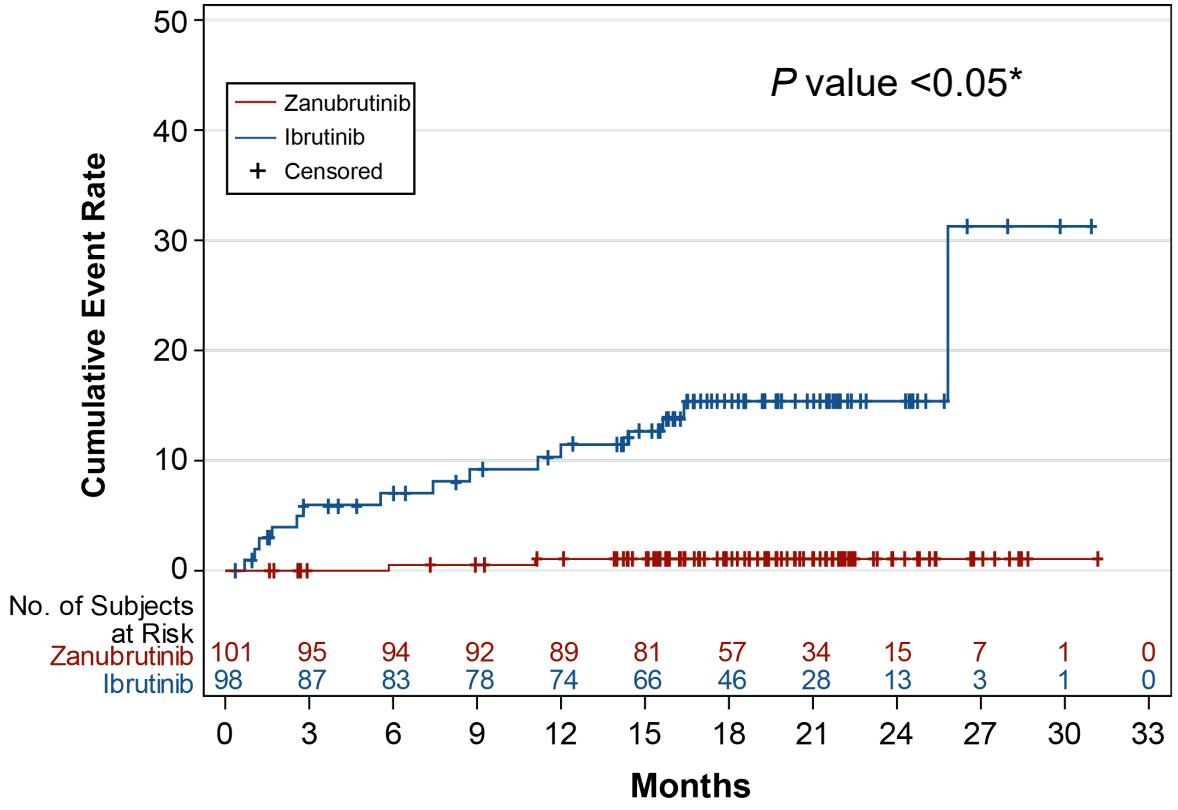
| AE *Categories*, n (%) (pooled terms) | All Grades | | Grade ≥ 3 | |
|---|---|---|---|---|
| | Ibrutinib (n = 98) | Zanubrutinib (n = 101) | Ibrutinib (n = 98) | Zanubrutinib (n = 101) |
| Atrial fibrillation/ flutter† | **15 (15.3)** | 2 (2.0) | 4 (4.1) | 0 (0.0) |
| Diarrhea (PT) | **31 (31.6)** | 21 (20.8) | 1 (1.0) | 3 (3.0) |
| Hemorrhage | **58 (59.2)** | 49 (48.5) | 8 (8.2) | 6 (5.9) |
| Major hemorrhage[a] | 9 (9.2) | 6 (5.9) | 8 (8.2) | 6 (5.9) |
| Hypertension | 17 (17.3) | 11 (10.9) | **12 (12.2)** | 6 (5.9) |
| Neutropenia[b]† | 13 (13.3) | **30 (29.7)** | 8 (8.2) | **20 (19.8)** |
| Infection | 66 (67.3) | 67 (66.3) | 19 (19.4) | 18 (17.8) |
| Second Malignancy | 11 (11.2) | 12 (11.9) | 1 (1.0) | 2 (2.0) |

Higher AE rate in bold blue with ≥ 10% difference in any grade or ≥ 5% difference in grade 3 or above.
No tumor lysis syndrome was reported. Opportunistic infection ibrutinib (n=2), zanubrutinib (n=1).
AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.
[a]Defined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.
[b]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.
† Descriptive two-sided *P*-value < 0.05.

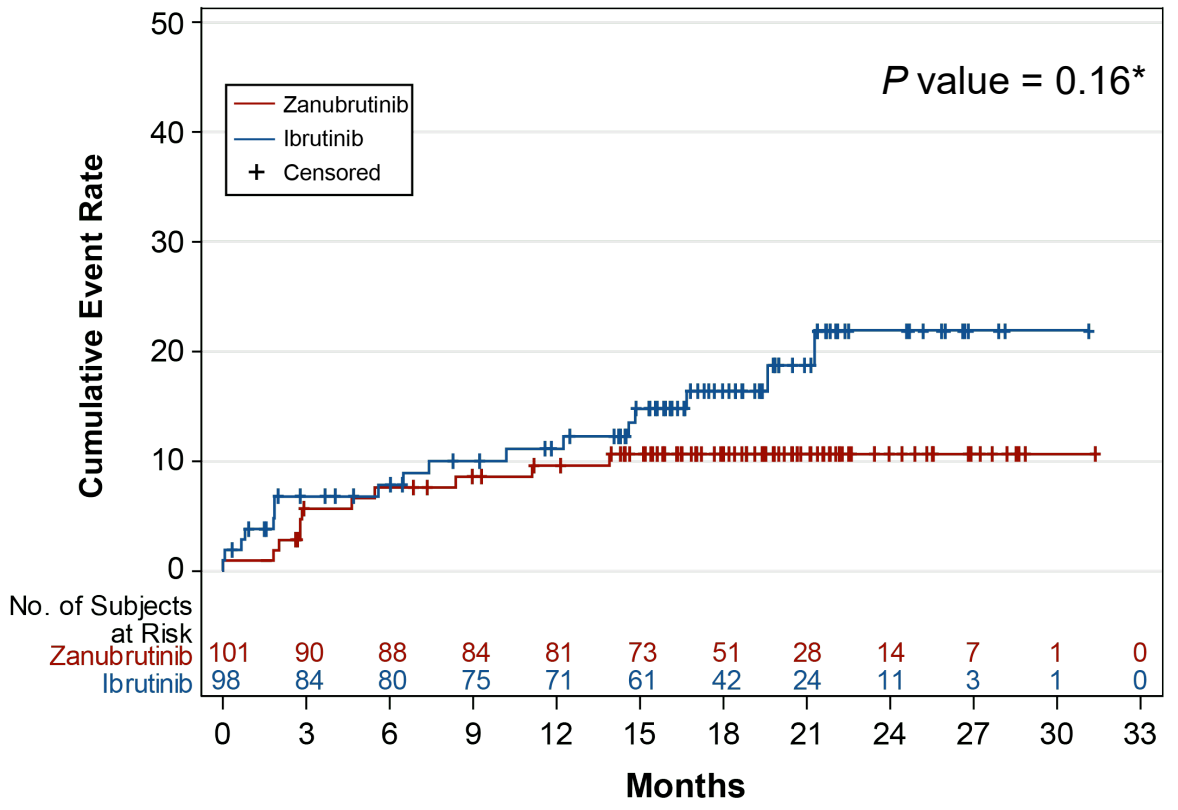
Tam et al, Blood 2020

# ASPEN Cohort 1: Time to AE, Risk Analysis Over Duration of Treatment

Kaplan-Meier Curve: Time to **Atrial Fibrillation/Flutter**




Kaplan-Meier Curve: Time to **Hypertension**




AE, adverse event.
*Descriptive purpose only.
Tam CS et al. *J Clin Oncol.* 2020;38(15 Suppl):8007.

# ASPEN Cohort 2: Patient and Disease Characteristics

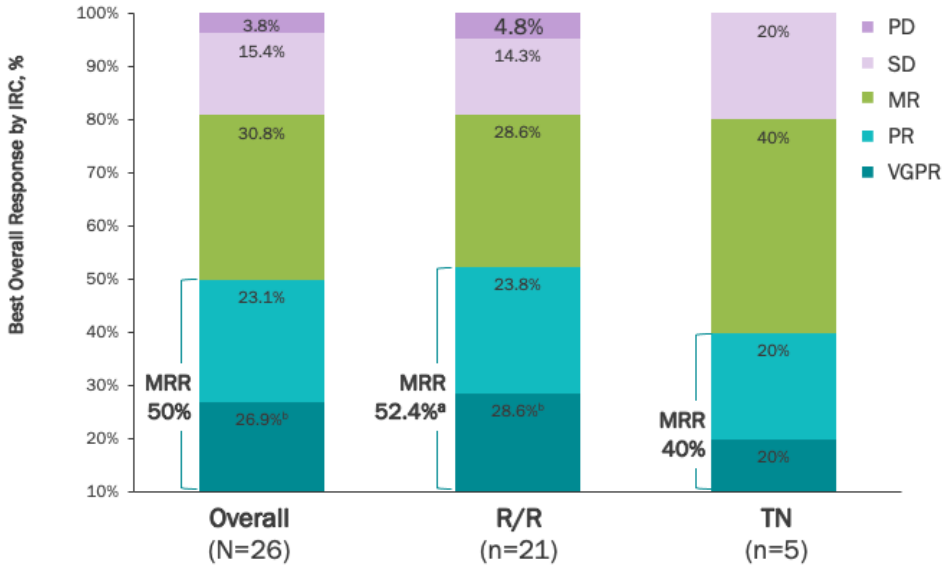
| Characteristic | Total (N=28) |
|---|---|
| Age, median (range), y | 70.1 (39-87) |
| >65 years, n (%) | 19 (67.9) |
| >75 years, n (%) | 12 (42.9) |
| Male sex, n (%) | 14 (50) |
| IPSSWM, n (%) | |
| Low | 5 (17.9) |
| Intermediate | 11 (39.3) |
| High | 12 (42.9) |
| Prior treatment status | |
| Treatment-naïve, n (%) | 5 (17.9) |
| R/R, n (%) | 23 (82.1) |
| No. of prior therapies for R/R pts, median (range) | 1 (1-5) |
| Extramedullary disease present at baseline by IRC, n (%) | 21 (75.0) |
| Median bone marrow involvement (n=26, central identified assay) | 23% |
| Median bone marrow involvement (n=24, 2 pts with $MYD88^{L265P}$ by NGS) | 15% |
| Bone marrow involvement >25%, (n=24) | 11 |

IPSSWM, International Prognostic Scoring System Waldenström Macroglobulinemia; pt, patient; R/R, relapsed/refractory; IRC, independent review committee.

Dimopoulos MA, et al. EHA 2020. EP1180.

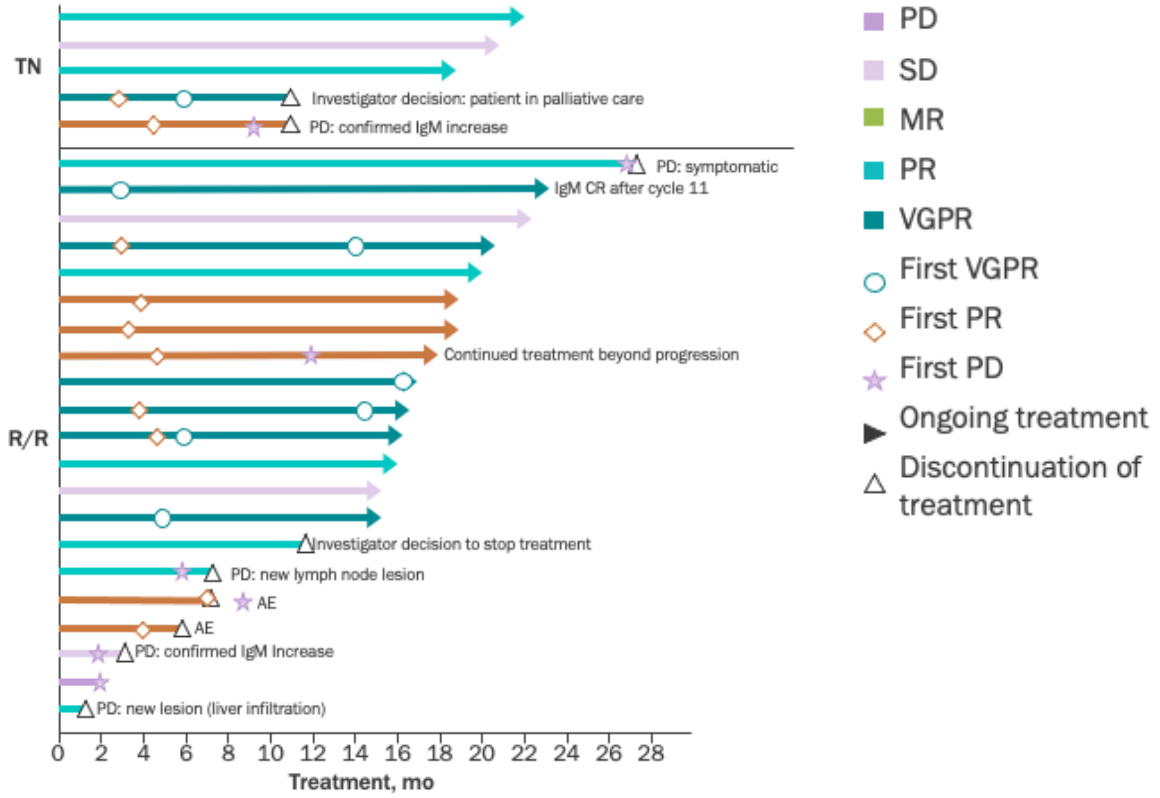
# ASPEN Cohort 2: Response

## Response by IRC




- Major response rate of 50.0% including 26.9% with VGPR
- Median time to first major response (partial response or better, requiring reduction in extramedullary disease if present at baseline), was 2.9 months (range, 1.9-16.1)
- Of the 11 patients with median BM involvement >25%: 3 VGPR, 5 PR, 2 MR, 1 SD, MRR=72.7%

## Response Over Time on Treatment




- Color of bars represents the best response for each patient

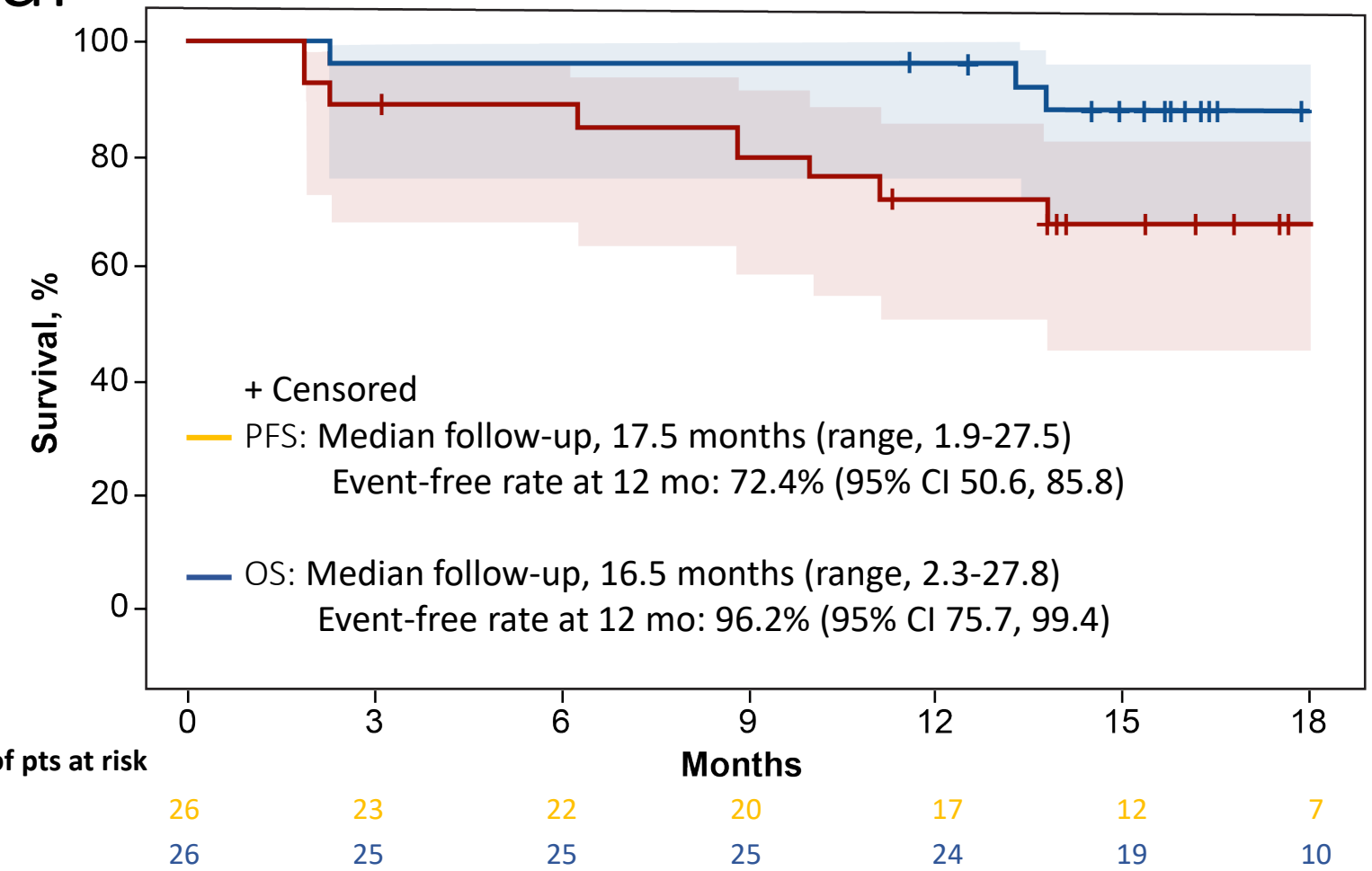
Data cutoff: August 31, 2019

AE, adverse event; CR, complete response; IgM, immunoglobulin M, IRC, independent review committee; MR, minor response; MRR, major response rate (≥PR); PD, progressive disease; PR, partial response; pt, patient; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve; VGPR, very good PR.

[a]Including pts confirmed by next-generation sequencing of no other activating *MYD88* mutations. [b]One pt achieved IgM complete response (normalized IgM and negative immunofixation since cycle 11, with bulky extramedullary disease improving).

Dimopoulos MA, et al. EHA 2020. EP1180.

# ASPEN Cohort 2: Progression-Free and Overall Survival




| No. of pts at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| PFS | 26 | 23 | 22 | 20 | 17 | 12 | 7 |
| OS | 26 | 25 | 25 | 25 | 24 | 19 | 10 |

Shaded areas show the 95% CI.
OS, overall survival; PFS, progression-free survival; pt, patient.
Dimopoulos MA, et al. EHA 2020. EP1180.

| THERAPY FOR PREVIOUSLY TREATED WM/LPL[a] (Order of regimens is alphabetical and does not indicate preference) | |
|---|---|
| **Preferred Regimens** | |
| • Bendamustine/rituximab<br>• Bortezomib/dexamethasone/rituximab[b]<br>• Ibrutinib ± rituximab (category 1) | • Rituximab/cyclophosphamide/dexamethasone<br>• Zanubrutinib (category 1) |
| **Other Recommended Regimens** | |
| • Acalabrutinib<br>• Bendamustine<br>• Bortezomib ± rituximab[b]<br>• Bortezomib/dexamethasone<br>• Cladribine ± rituximab[c] | • Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab<br>• Fludarabine ± rituximab[c]<br>• Fludarabine/cyclophosphamide/rituximab[c]<br>• Rituximab<br>• Rituximab/cyclophosphamide/prednisone |
| **Useful In Certain Circumstances** | |
| • Everolimus<br>• Ofatumumab (for rituximab-intolerant individuals)[d] | |
| **Hematopoietic Cell Transplant** | |
| • In selected cases hematopoietic cell transplantation may be appropriate with either:<br>▸ Allogeneic hematopoietic cell transplant (ablative or nonablative)[e]<br>▸ Autologous hematopoietic cell transplant | |

[a] See General Considerations for Systemic Therapy for WM/LPL (WM/LPL-B 1 of 4).
[b] Consider for patients presenting with symptomatic hyperviscosity, or in whom rapid IgM reduction is required.
[c] May be associated with disease transformation and/or development of MDS/AML in patients with Waldenström macroglobulinemia.
[d] Ofatumumab may be used for rituximab-intolerant individuals as a single agent or in combination therapy anywhere that rituximab is given. While ofatumumab is no longer commercially available, it may be obtained for clinical use.
[e] Should ideally be undertaken in the context of a clinical trial.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

References

# Acalabrutinib Phase 2 WM Study: Baseline Characteristics

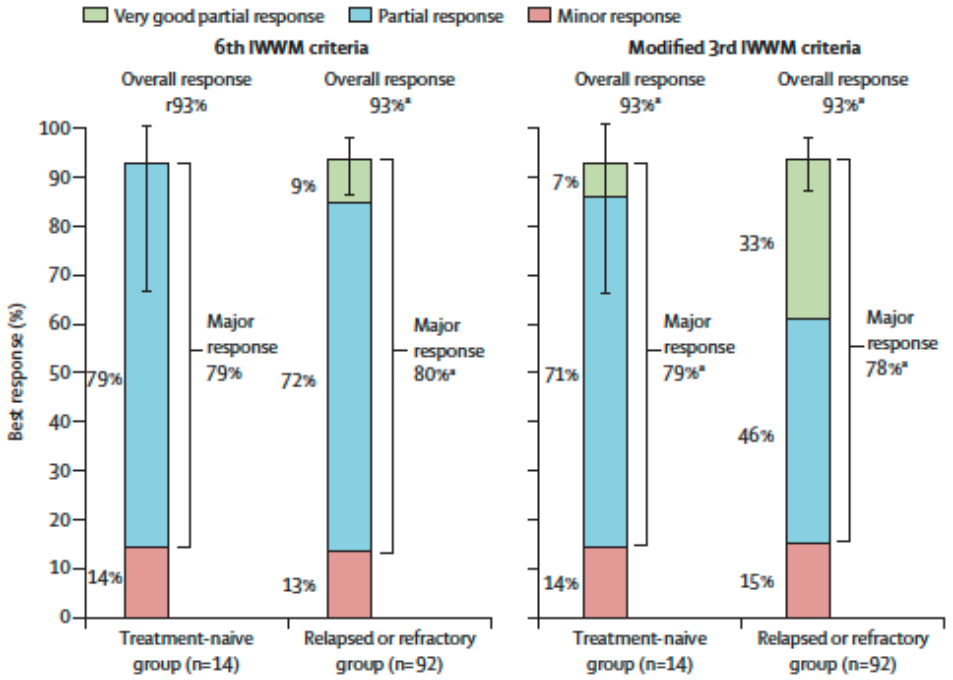
| Characteristic | Treatment Naïve (n=14) | Relapsed/Refractory (n=92) |
|---|---|---|
| Age, median (range), y | 73 (48-86) | 69 (39-90) |
| Male sex, n (%) | 10 (71%) | 63 (68%) |
| ECOG PS, n (%)<br>≤1<br>0<br>1<br>2 | <br>12 (86%)<br>3 (21%)<br>9 (64%)<br>2 (14%) | <br>88 (96%)<br>52 (57%)<br>36 (39%)<br>4 (4%) |
| Median time since initial WM diagnosis (range), y | 0.4 (0.04-5.8) | 6.1 (0.2-25.4) |
| Extramedullary disease[a], n (%) | 9 (64) | 59 (64) |
| Median time to last treatment, months (range | NA | 16.2 (0.03-89.6) |
| Median number of previous therapies (range) | NA | 2 (1-7) |
| ≥3 previous therapies | NA | 41 (45%) |

[a]Defined as lymphadenopathy (>1.5 cm) and splenomegaly (an enlarged spleen of any size).

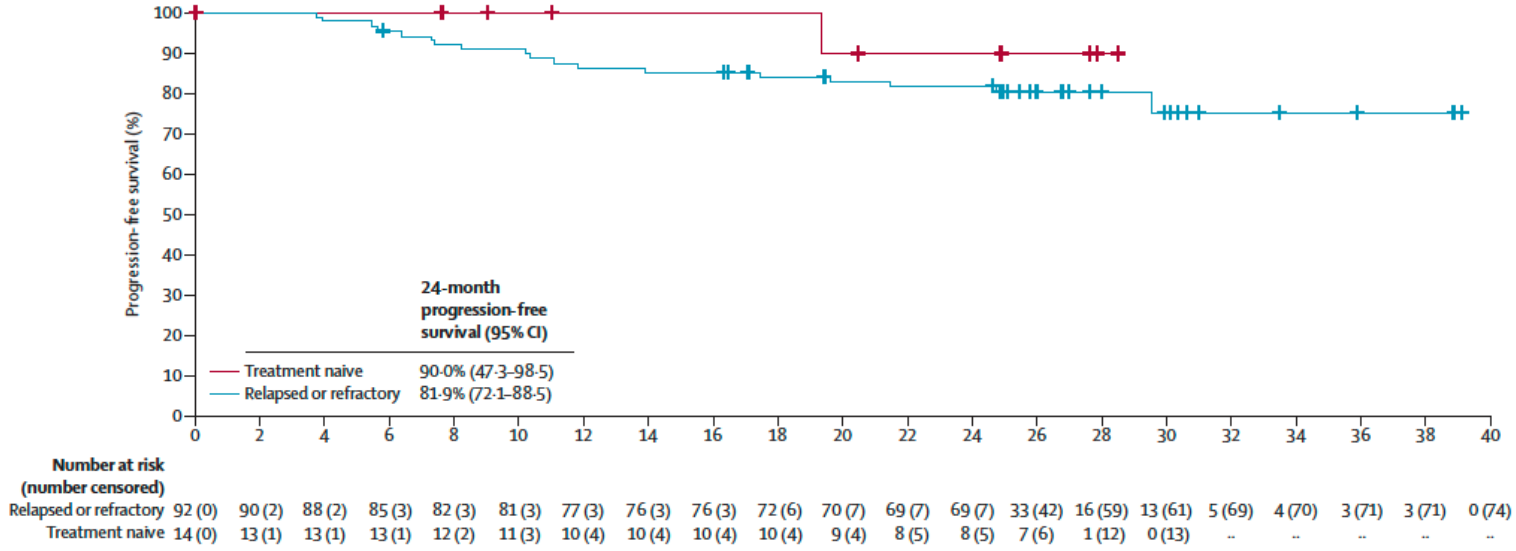
Owen RG, et al. *Lancet Haematol* 2020;7:e112–21.

# Acalabrutinib Phase 2 WM Study: Efficacy

## Overall Response




## Progression-Free Survival




- Median duration of follow-up was 27.4 months
- Median duration of response has not been reached
  - 24-month duration of response for treatment-naïve patients (90%) and relapsed/refractory patients (82%)
- Overall survival was 92% in treatment-naive patients and 89% in relapsed/refractory patients

Owen RG, et al. *Lancet Haematol* 2020;7:e112–21.

# Acalabrutinib Phase 2 WM Study: Safety and Tolerability

| Most Frequent AEs, n (%) | Grade 1-2 | Grade 3 | Grade 4 |
|---|---|---|---|
| Headache | 41 (39) | 0 | 0 |
| Diarrhea | 33 (31) | 2 (2) | 0 |
| Contusion | 31 (29) | 0 | 0 |
| Dizziness | 27 (25) | 0 | 0 |
| URTI | 23 (22) | 0 | 0 |
| Fatigue | 22 (21) | 2 (2) | 0 |
| Nausea | 22 (21) | 2 (2) | 0 |
| Constipation | 22 (21) | 0 | 0 |
| Arthralgia | 20 (19) | 1 (1) | 0 |
| Back pain | 18 (17) | 1 (1) | 0 |
| Cough | 18 (17) | 0 | 0 |
| Pyrexia | 17 (16) | 1 (1) | 0 |
| Vomiting | 17 (16) | 1 (1) | 0 |
| Rash | 16 (15) | 0 | 0 |

- Atrial fibrillation occurred in 5% (5/106) of patients
  - All events were grade 1-2 except for one (1%) grade 3 event
- Hypertension occurred in 5% (5/106) of patients
- 28% (30/106) of patients discontinued acalabrutinib during the study period
  - AEs led to discontinuation in 7% (7/106) of patients

Owen RG, et al. *Lancet Haematol* 2020;7:e112–21.

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2022
# Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

NCCN Guidelines Index
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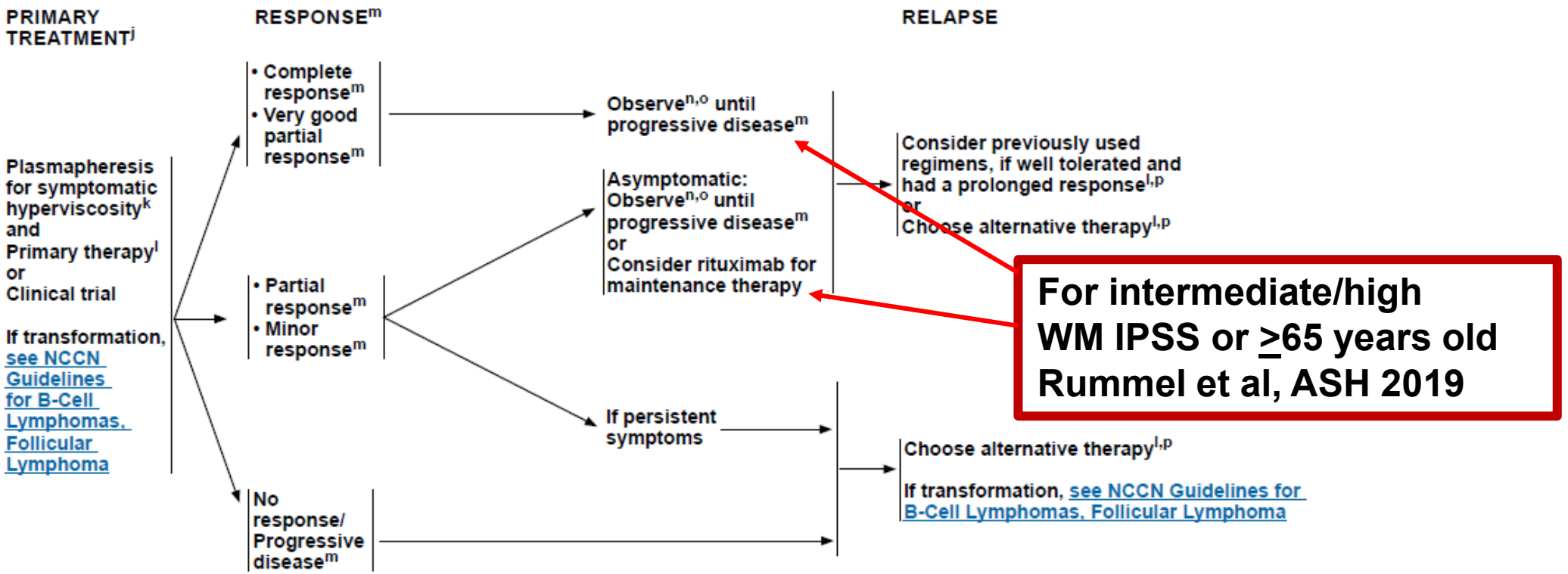
Discussion




**For intermediate/high WM IPSS or ≥65 years old**
**Rummel et al, ASH 2019**

[j] Intent of therapy should be based on palliation of symptoms, not necessarily levels of IgM unless the patient is exhibiting evidence of symptomatic hyperviscosity.

[k] Plasmapheresis should be performed for patients with symptomatic hyperviscosity, and before treatment with rituximab-containing regimen in patients with IgM ≥4000 mg/dL. IgM should be monitored closely in these patients thereafter and plasmapheresis should be considered again if symptomatic hyperviscosity recurs or if IgM is ≥4000 mg/dL while on rituximab-containing therapy. RBC transfusion, if indicated, should be done after plasmapheresis to prevent added hyperviscosity load.

[l] See Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Therapy (WM/LPL-B).

[m] See Response Criteria for WM/LPL (WM/LPL-C).

[n] See NCCN Guidelines for Survivorship.

[o] CBC, complete metabolic panel, and IgM every 3 months for 2 years, then every 4–6 months for additional 3 years, then every 6–12 months. Progression based on IgM levels alone, without symptoms, should not be reason to retreat.

[p] Caution should be used when re-treating with myelosuppressive regimens due to cumulative toxicities.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

# B-R + Watch & Wait vs. B-R + 2 years Rituximab

M. Rummel

## StiL NHL 7-2008 - MAINTAIN

WM → B-R → ≥ PR → R

n = 296

SD, PD → off study

n = 218

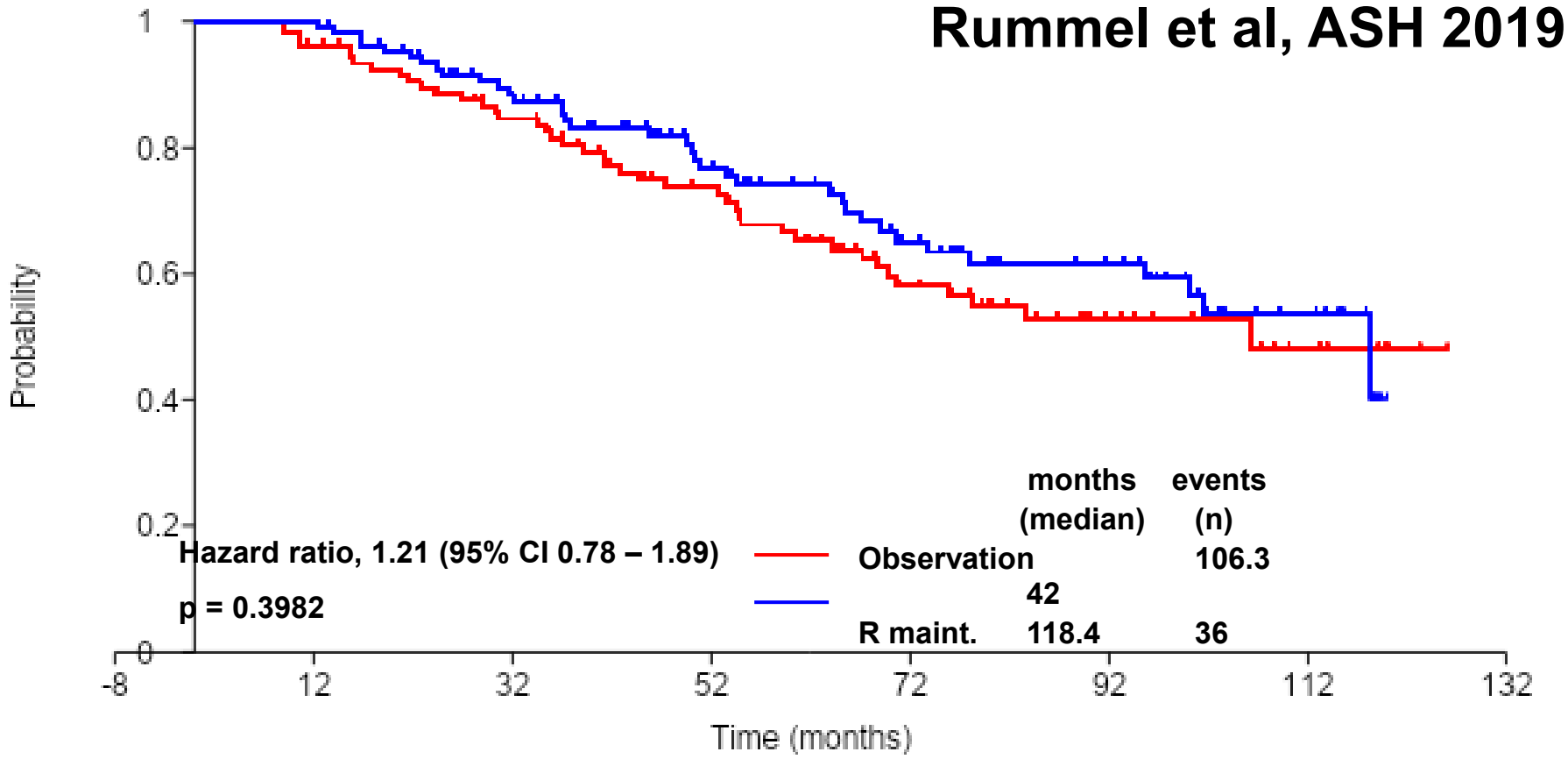
**Bendamustine-Rituximab**
**+ Watch & Wait**
**(n = 109)**

**Bendamustine-Rituximab**
**+ 2 years Rituximab**
**q 2 months**
**(n = 109)**

StiL
Studiengruppe indolente Lymphome

**Rummel et al, ASH 2019**

# Progression free survival (80 months median follow-up)

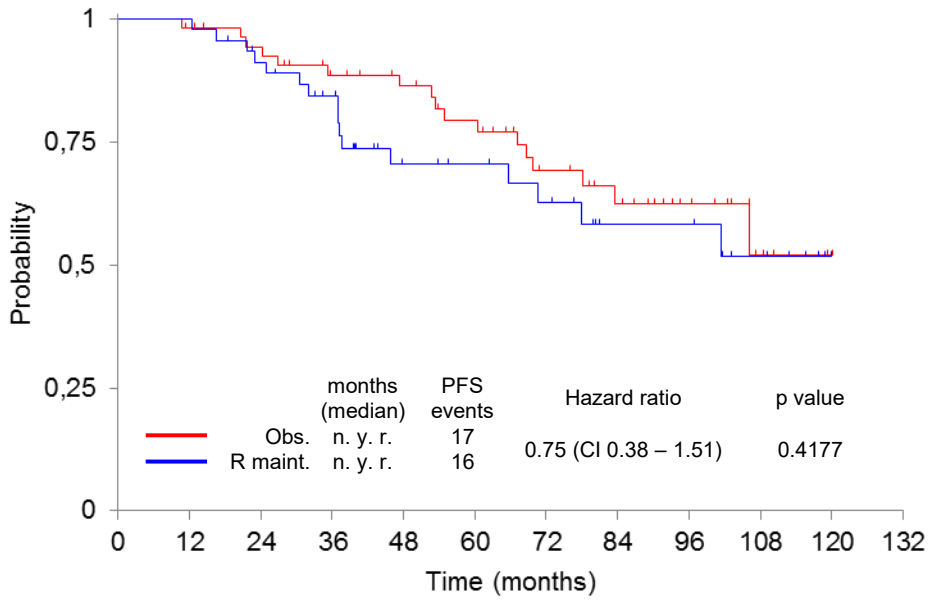



| Pts at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Observ. | 109 | 102 | 92 | 79 | 62 | 54 | 39 | 27 | 18 |
| | 9 | 3 | | | | | | | |
| R maint. | 109 | 109 | 96 | 83 | 65 | 52 | 41 | 30 | 25 |
| | 11 | 1 | | | | | | | |

# PFS: Patient age

Rummel et al, ASH 2019

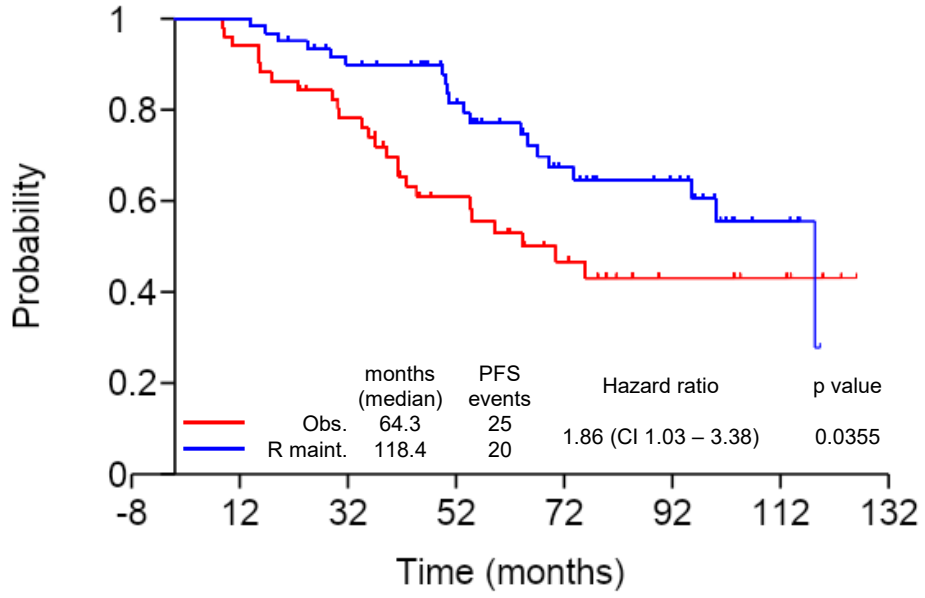
## Patients younger than 65 years




**Hazard ratio 0.75 (95% CI 0.38 – 1.51)**

**p = 0.4177**

## Patients older than 65 years




**Hazard ratio 1.86 (95% CI 1.03 – 3.38)**

**p = 0.0355**

# IWWM-2 Workshop Classification of WM, IGM MGUS, and IgM Related Disorders.

| | IgM Monoclonal Protein [1] | Histological Infiltration by LPL[2] | Symptomatic[3] |
|---|---|---|---|
| IgM MGUS | + | - | - |
| IgM Related Disorders | + | - | + |
| Asymptomatic WM | + | + | – |
| Symptomatic WM | + | + | + |

1. IgM monoclonal gammopathy of any concentration
2. Bone infiltration by small lymphocytes, plasmacytoid cells and plasma cells. Any level of detectable infiltrate by histological examination. Flow or molecular disease detection does not fulfill WM diagnostic criteria.
3. Symptomatic Status defined by IWWM-2 consensus criteria and indicative of need for treatment. Kyle et al, Semin Oncol. 2003.

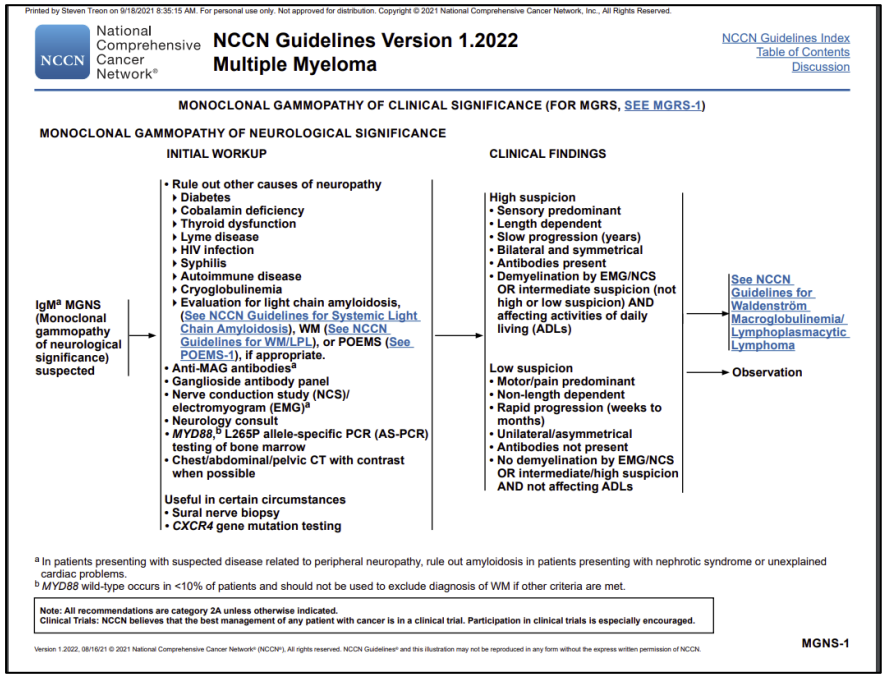
Owen et al, Semin Oncol 2003

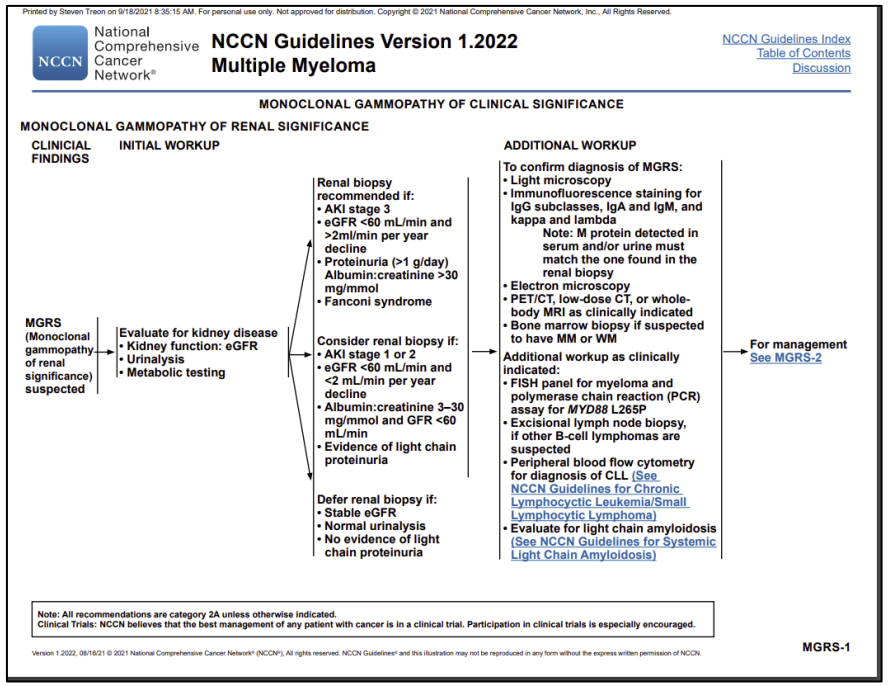
# Morbidities mediated by monoclonal IgM and associated light chains in WM.

| Property of IgM monoclonal protein | Diagnostic condition | Clinical manifestations |
|---|---|---|
| Pentameric structure | Hyperviscosity | Headaches, blurred vision, epistaxis, retinal hemorrhages, leg cramps, impaired mentation, intracranial hemorrhage |
| Precipitation on cooling | Cryoglobulinemia (type I) | Raynaud phenomenon, acrocyanosis, ulcers, purpura, cold urticaria |
| Autoantibody activity to myelin-associated glycoprotein (MAG), ganglioside M1 (GM1), sulfatide moieties on peripheral nerve sheaths | Peripheral neuropathies | Sensorimotor neuropathies, painful neuropathies, ataxic gait, bilateral foot drop |
| Autoantibody activity to IgG | Cryoglobulinemia (type II) | Purpura, arthralgias, renal failure, sensorimotor neuropathies |
| Autoantibody activity to red blood cell antigens | Cold agglutinins | Hemolytic anemia, Raynaud phenomenon, acrocyanosis, livedo reticularis |
| Tissue deposition as amorphous aggregates | Organ dysfunction | Skin: bullous skin disease, papules, Schnitzler syndrome; GI: diarrhea, malabsorption, bleeding; kidney: proteinuria, renal failure (light chain component) |
| Tissue deposition as amyloid fibrils (light chain component most commonly) | Organ dysfunction | Fatigue, weight loss, edema, hepatomegaly, macroglossia, organ dysfunction of involved organs: heart, kidney, liver, and peripheral sensory and autonomic nerves |

Treon et al, Blood 2009

# IGM MGCS treated under WM/LPL NCCN guidelines



# Mayo Stratification of WM and Risk-Adapted Therapy Guidelines

## Consensus for Newly Diagnosed WM

- IgM MGUS (< 10% lymphoplasmacytic infiltration)
- Asymptomatic/ smoldering WM
- Hemoglobin ≥ 11 g/dL
- Platelets ≥ 120 x $10^3$/µL

→ **Observation**

- Hemoglobin < 11 g/dL or symptomatic
- Platelets < 120 x $10^3$/µL
- IgM-related neuropathy
- WM-associated hemolytic anemia
- Symptomatic cryoglobulinemia

→ **Single-agent rituximab[a] (1 cycle; no maintenance tx) Plasmapheresis if hyperviscosity develops w/tx**

- Bulky disease
- Profound cytopenias
  - Hemoglobin ≤ 10 g/dL
  - Platelets < 100 x $10^3$/µL
- Constitutional symptoms
- Hyperviscosity symptoms

→ **Hyperviscosity symptoms**

**YES** → **Plasmapheresis**

**NO**

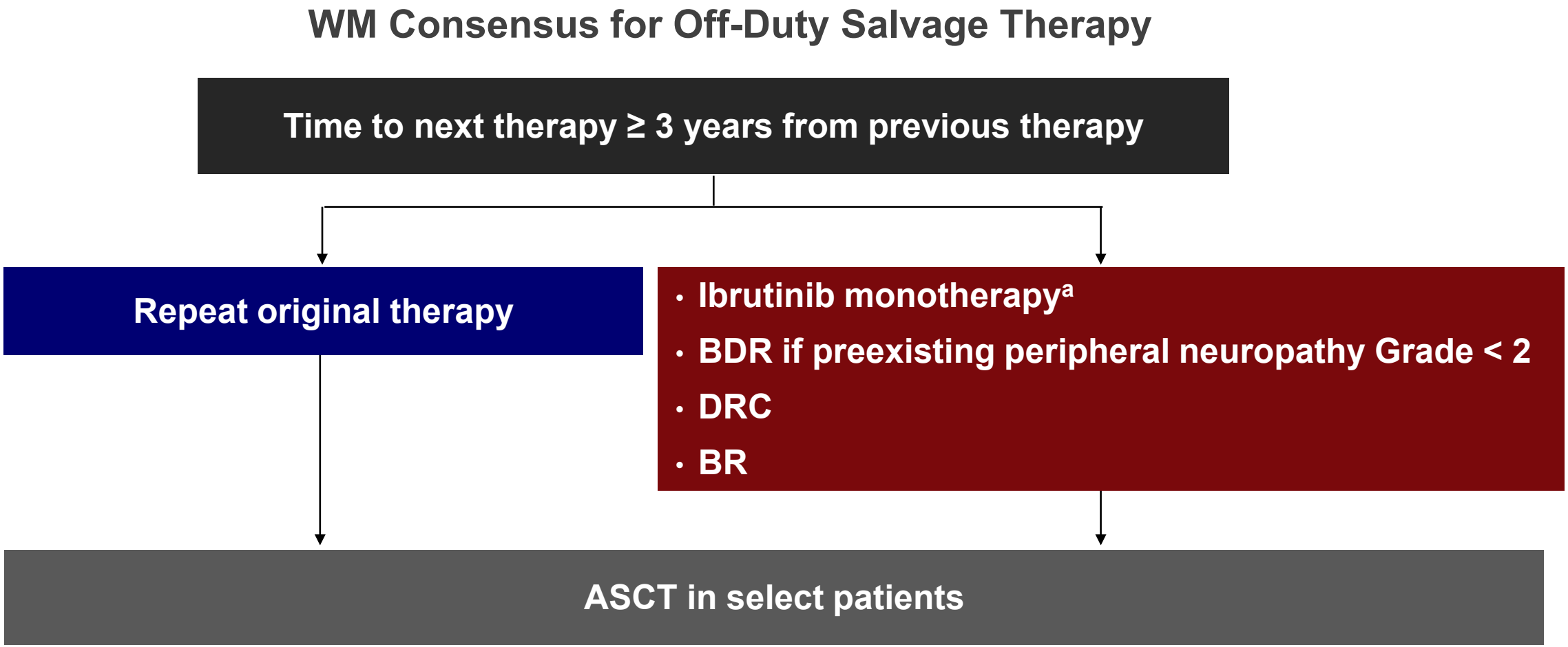
→ **BR[a] x 4-6 cycles No rituximab maintenance tx**

→ **Harvest stem cells if ≤ 70 years and potential ASCT candidate in future**

*[a]Six cycles of DRC is an alternative if the disease burden is low.*

Kapoor, et al. *JAMA Oncol*. 2017;3:1257-1265.

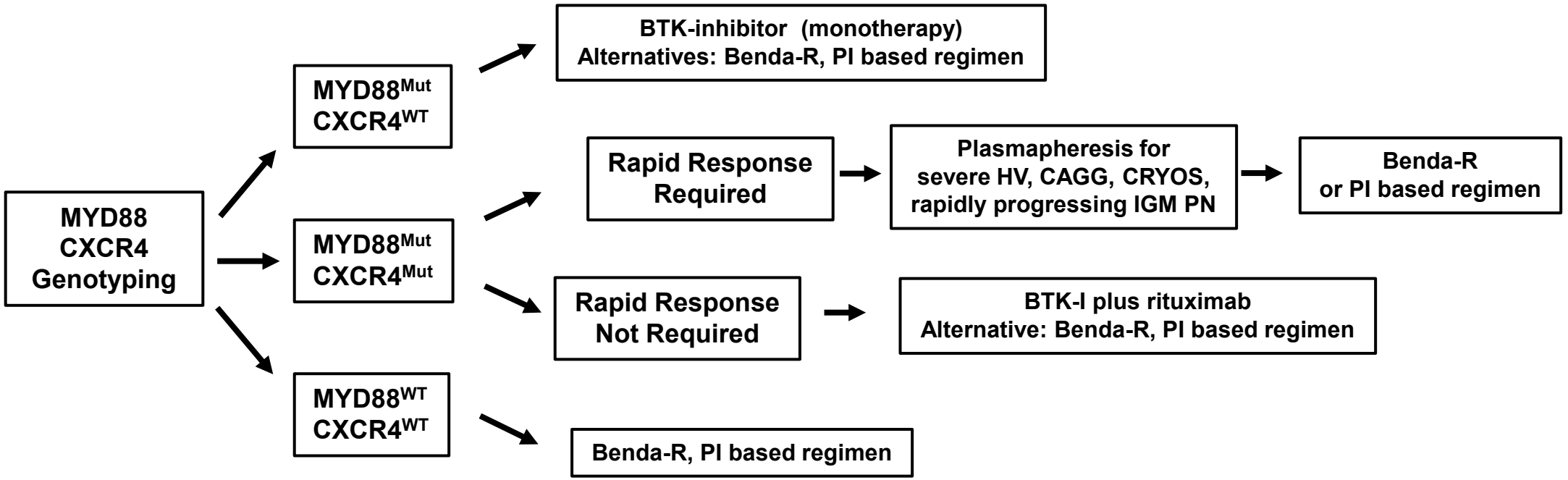
# Mayo Stratification of WM and Risk-Adapted Therapy Guidelines




[a]*If not previously used.*

Kapoor, et al. *JAMA Oncol*. 2017;3:1257-1265.

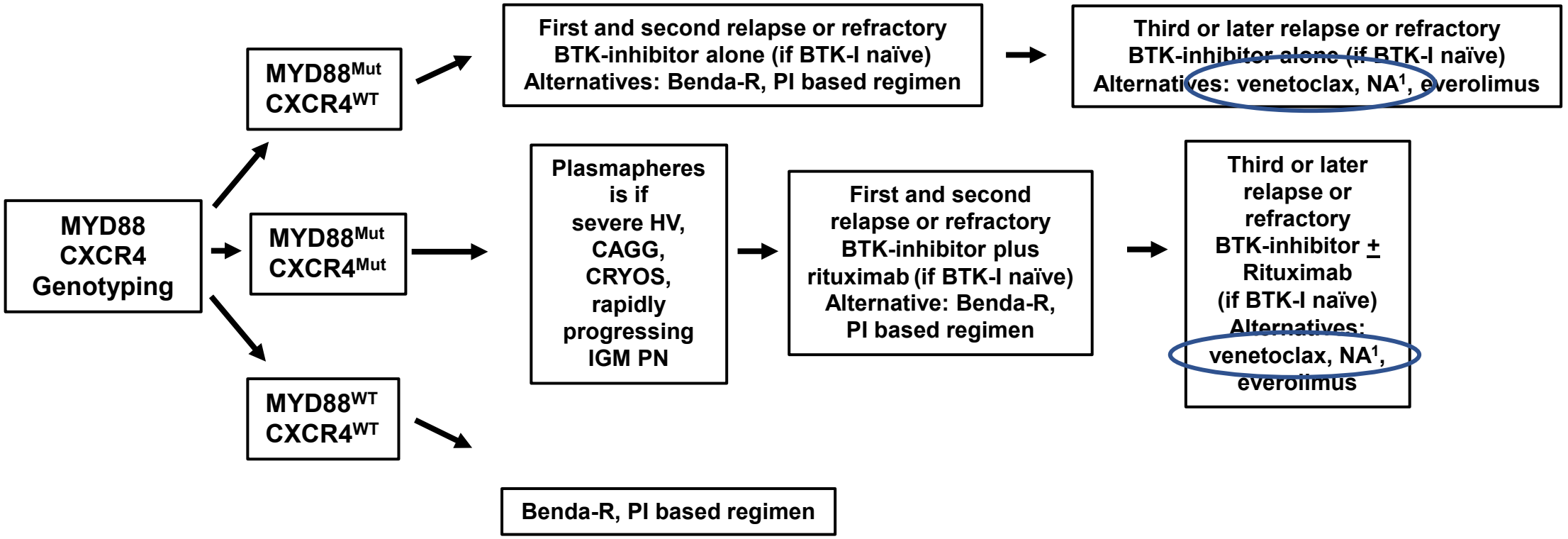
# Genomic Based Treatment Approach to Symptomatic Treatment Naïve WM




- Rituximab should be held for serum IgM ≥4,000 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 MYD88$^{Mut}$ or bendamustine for IgM PN depending on severity and pace of progression.
- Maintenance rituximab may be considered in patients responding to rituximab based regimens.

Treon et al, JCO 2020; 38:1198-1208

# Genomic Based Treatment Approach to Symptomatic Relapsed or Refractory WM




- Nucleoside analogues (NA) should be avoided in younger patients, and candidates for ASCT.[1]
- ASCT may be considered in patients with multiple relapses, and chemosensitive disease.

Treon et al, JCO 2020; 38:1198-1208

# 11th International Workshop for Waldenstrom's Macroglobulinemia

## Madrid, October 6-8, 2022


www.waldenstromsworkshop.org