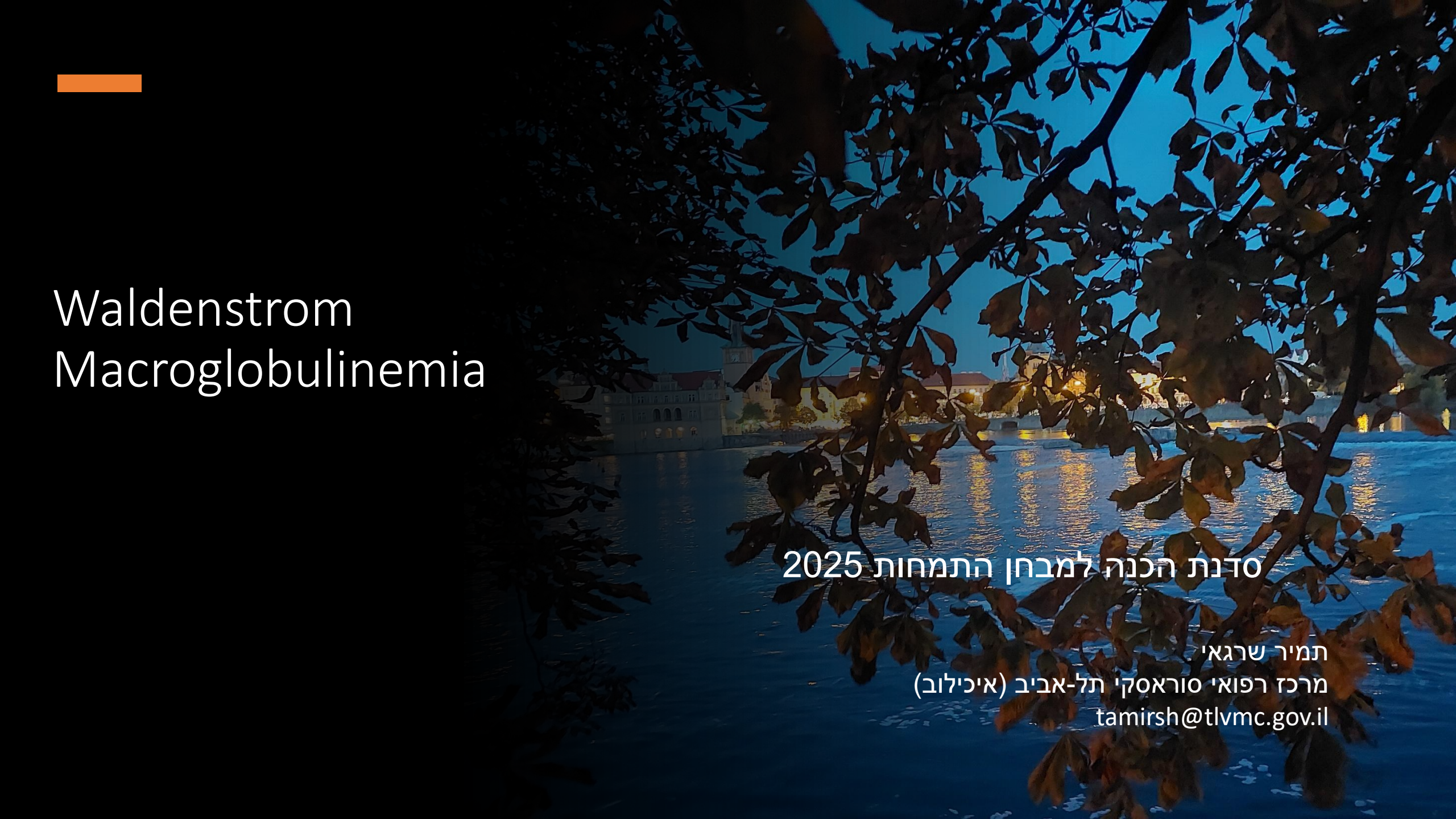
Waldenstrom Macroglobulinemia



סדנת הכנה למבחן התמחות 2025

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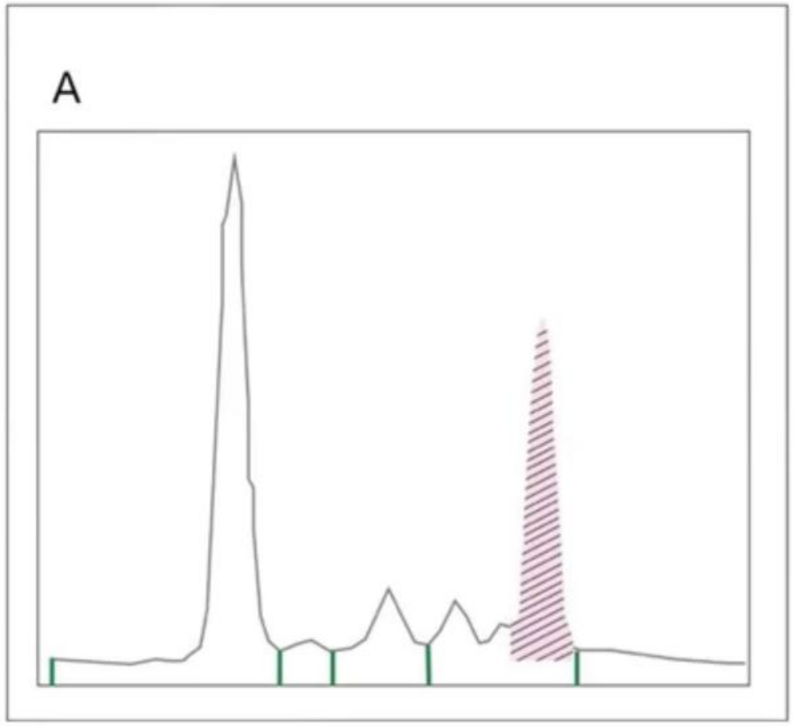
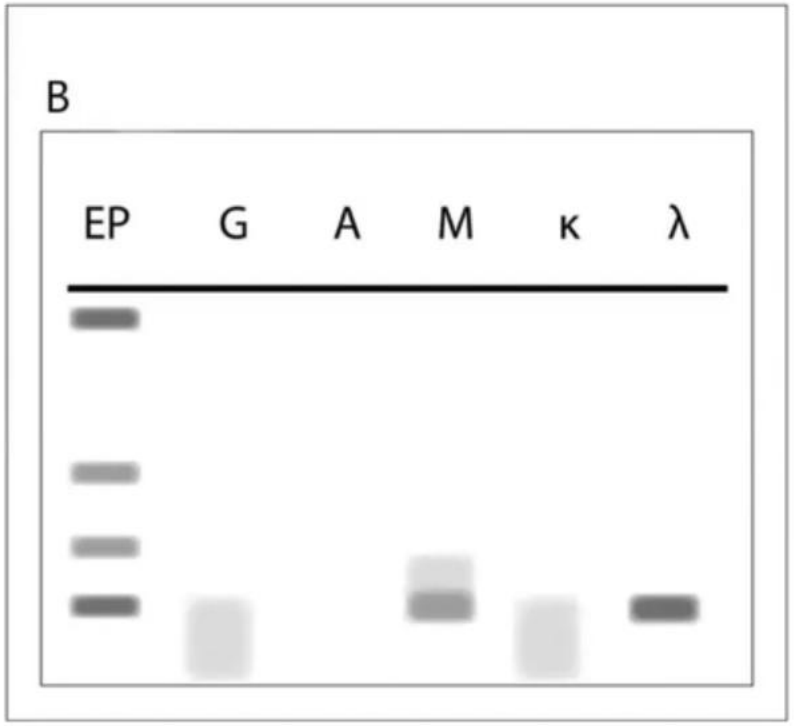
מקרה:

- בת 80, ברקע יתר לח"ד. עצמאית וצלולה. מצב תפקודי טוב
- הותחל בירור אנמיה עקב ירידת המוגלובין ל 9.5 , ANC 1600 טסיות 55
- משק ברזל תקין (ברזל 54 טרנספרין 138).
- היפרגלובולינמיה 45 IGA 66 IGG 805 IGM 2957 מ"ג לד"ל
- באימונופיקסציה: IgM kappa . ב SPEP: מקטע בגודל 1.7 גרם לד"ל
- קאפא 97 למבדא 19 יחס 1:5
- סירבה לבדיקת מח עצם
- אלבומין 3.63, קראטינין 0.9
- בנס גונס: עקבות קלים של free kappa
- ביצעה CT כלל גופי לפני מספר חודשים: טחול במימדים תקינים בצפיפות רגילה עם מספר נגעים היפודנסיים בקוטר של עד 1 ס"מ. ללא נגעים ליטיים

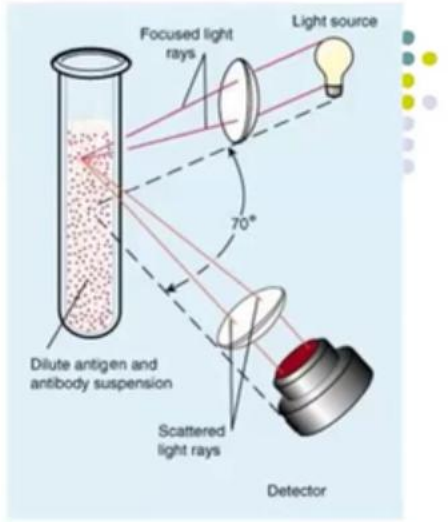
Protein electrophoresis

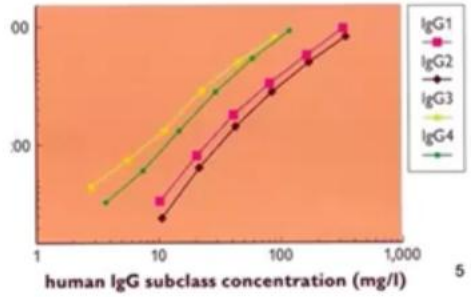


Immunofixation



Nephelometry





IgM monoclone: DD

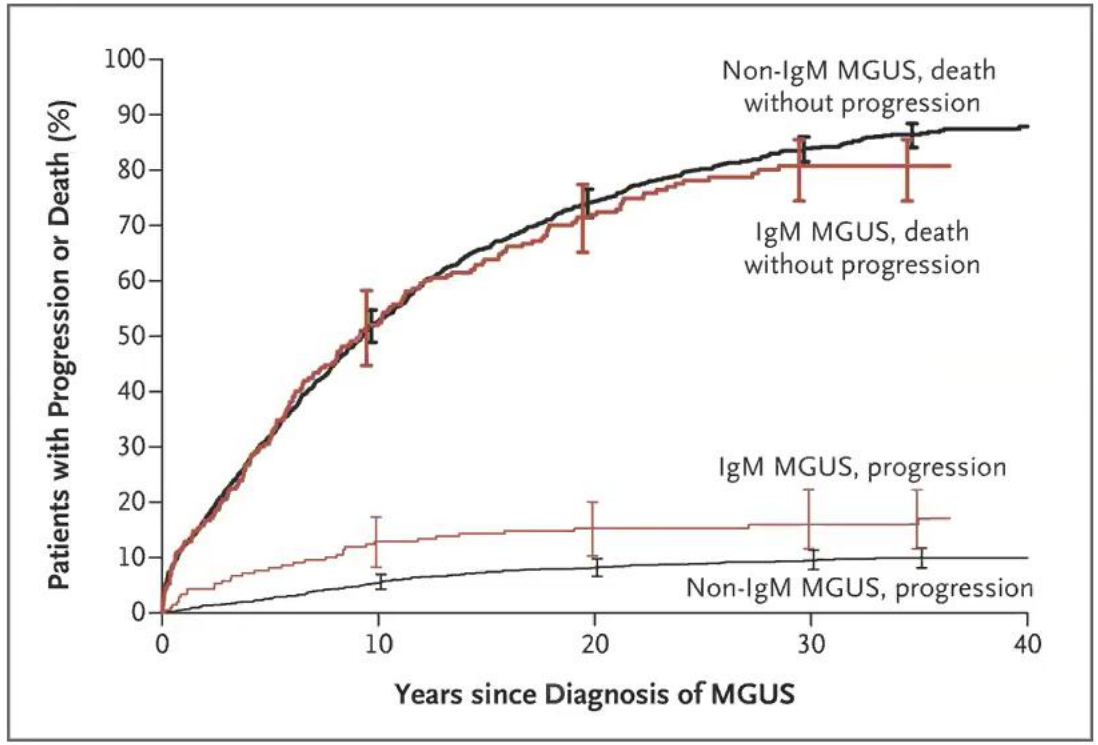
- IgM MGUS
- B-cell lymphoma
- Lymphoplasmacytic lymphoma
- Amyloidosis
- IgM myeloma
- Reactive

TABLE 1 Definitions of IgM-related phenomenon in macroglobulinemia

	IgM Monoclonal Component	Symptoms of Tumor Mass/Infiltration (Adenopathy Anemia)	Marrow Infiltration >10%	IgM-Mediated Symptoms
MGUS	+	–	–	–
Smoldering macroglobulinemia	+	–	+	–
IgM-related disorder (eg, cold agglutinin hemolytic anemia, type II cryoglobulin, neuropathy, amyloidosis)	+	–	±	+
Macroglobulinemia	+	+	+	±

IgM MGUS - progression

- 210 pts followed for 1893 person years
- 34 pts (15%) progressed
  - NHL 17
  - WM 11
  - CLL 3
  - AL amyloidosis 3
  - MM 0
- Risk factors: IgM>1.5gr/dl, abnormal FLC ration, immunoparesis



2%/y in first 10y; 1%/y beyond that

Kyle, NEJM 2018

Waldenström macroglobulinemia: Epidemiology

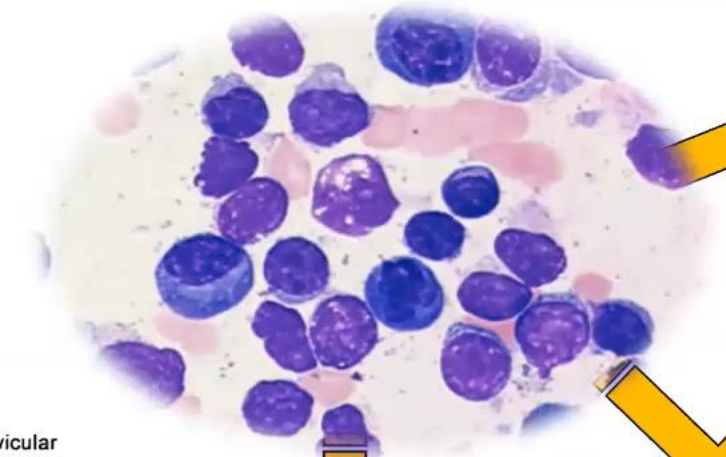
- Median age 71
- Incidence: 4.1/1,000,000 in whites. Less in blacks.
- M/F 3:1
- Family history: 4.3% (poorer outcome)

Manifestations of WM Disease

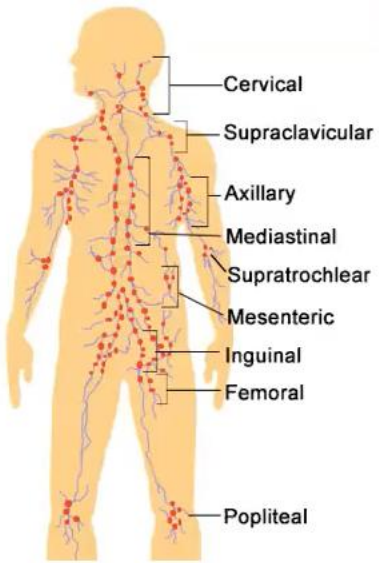
Bing Neel Syndrome

Bone Marrow

↓Hb>>> ↓PLT> ↓WBC



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



≤20% at diagnosis;
50-60% at relapse.

Hepcidin
↓Fe Anemia

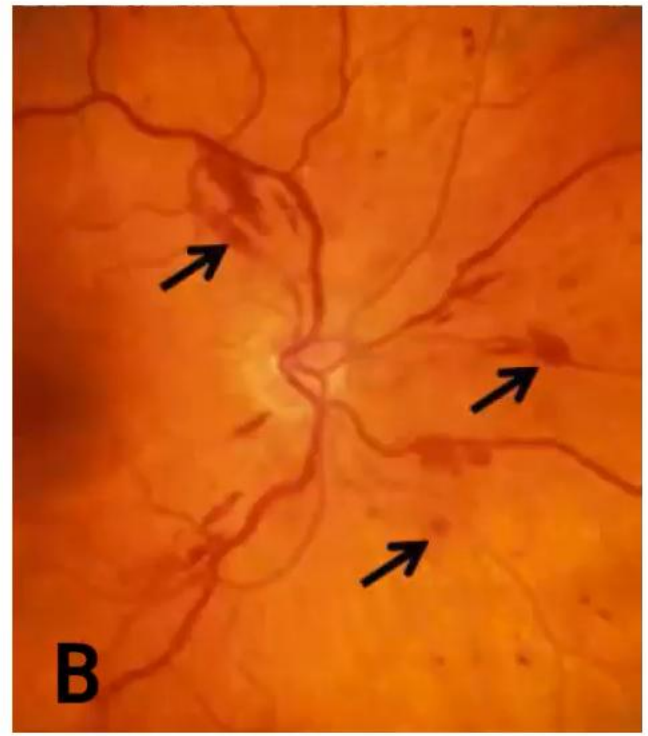
Cold Agglutinemia (5%)
Cryoglobulinemia (10%)
IgM Neuropathy (22%)
Amyloidosis (10-15%)

Treon S., Hematol Oncol. 2013; 31:76-80.

Fatigue, lack of energy	Anaemia
Constitutional symptoms	Disease progression
Recurrent sinus and bronchial infections	Hypogammaglobulinaemia
Headaches, blurry vision or visual loss, confusion, epistaxis	**Hyperviscosity**
Easy bruising, bleeding diathesis	Thrombocytopenia; acquired VWD; acquired coagulation factor deficiency
Progressive symmetrical numbness, tingling, burning, pain feet and hands	IgM-related neuropathy; amyloidosis
Raynaud-like symptoms, acrocyanosis, ulcerations on extremities	Cryoglobulinaemia; cold agglutinaemia
Diarrhoea, gastrointestinal cramping	Malabsorption
Foamy urine, bipedal oedema	Kidney dysfunction
Urticaria, papules, dermatitis	Schnitzler syndrome, IgM or tumor cell infiltration, amyloid deposition

Hyperviscosity syndrome

- Up to 30%
- Headache
- Blurring, loss of vision → Nystagmus, diplopia
- Neurological complinates
- Tinnitus, sudden deafness
- Dizziness, vertigo, ataxia
- Bleeding
- Confusion, disturbance in consciousness
- CVA



Plasmapheresis

- Indication – requirement of immediate IgM reduction
- HVS, symptomatic CG, severe CAD
- Consider blood warmers
- 2-3 plasmapheresis sessions
- Transient effect ~2-4 weeks
- Start definitive therapy
- DO NOT START RITUXIMAB – IgM flare

IgM flare

- Use of rituximab is associated with the risk of “flare”
- The initiation of rituximab treatment results in a transient rise in the level of IgM, which can produce an increase of serum viscosity
- Less frequently when rituximab is combined with cytotoxic chemotherapy
- In some trials, rituximab is delayed until the second cycle to allow cytotoxic therapy to reduce IgM levels and reduce the risk of hyperviscosity associated with the introduction of rituximab

WM- initial workup

- Serum protein electrophoresis
- Serum immunofixation
- Quantitative test for immunoglobulins
- 24-hour urine collection for protein electrophoresis
- Immunoglobulin free light chain assay (long-term value not established)
- Serum β2 microglobulin evaluation for prognosis
- Bone marrow biopsy
- Cytogenetic studies with optional fluorescence in situ hybridization
- MYD88 mutational analysis required, CXCR4 mutational analysis if MYD88 is mutated

WM- initial workup (cont'd)

- Computed tomography of abdomen and pelvis to detect organomegaly and lymphadenopathy (PETCT only if lymphoma suspected)
- Serum viscosity required when signs and symptoms of hyperviscosity syndrome are present or when IgM >4000 mg/dL
- Ophthalmologic evaluation for hyperviscosity
- On the basis of clinical presentation, analysis involves Coombs test (cold autoantibody) and cryoglobulin or tissue stains for amyloid deposits
- Hepatitis B and C screening is necessary if rituximab therapy is planned

	MYD88^{MUT} CXCR4^{WT} (50-60%)	MYD88^{MUT} CXCR4^{MUT} (30-40%)	MYD88^{WT} CXCR4^{WT} (5-10%)
Bone marrow involvement	++	+++	+
Lymphadenopathy	+	+	+++
Serum IgM levels	++	+++	++
Hyperviscosity	++	+++	++
Acquired VWD	+	+++	+
Risk of DLBCL	+	+	+++

Treon et al. Br J Haematol 2018; Castillo et al. Exp Rev Hematol 2019

MYD88

- The MYD88 mutation L265P is associated with WM and IgM MGUS
- MYD88 L265P is seen also in splenic marginal zone lymphoma (4%), IgM amyloidosis (71%) mucosa-associated lymphatic tissue lymphoma (7%), and PCNSL
- Conflicting data regarding prognostic value

Indications to start treatment:

- Symptomatic anemia (typically hemoglobin <10 g/dL) or thrombocytopenia due to bone marrow infiltration
- Constitutional symptoms attributable to WM
- Symptomatic hyperviscosity syndrome (e.g., visual changes, mucosal bleeding, confusion, headache)
- Significant lymphadenopathy or organomegaly causing symptoms or organ dysfunction
- WM-related peripheral neuropathy
- Amyloidosis, cryoglobulinemia, or cold agglutinin disease with clinical manifestations
- Bing-Neel syndrome (CNS involvement)
- Other evidence of end-organ damage directly attributable to WM
- Critically high IgM (>60 g/L)

Bing-Neel Syndrome

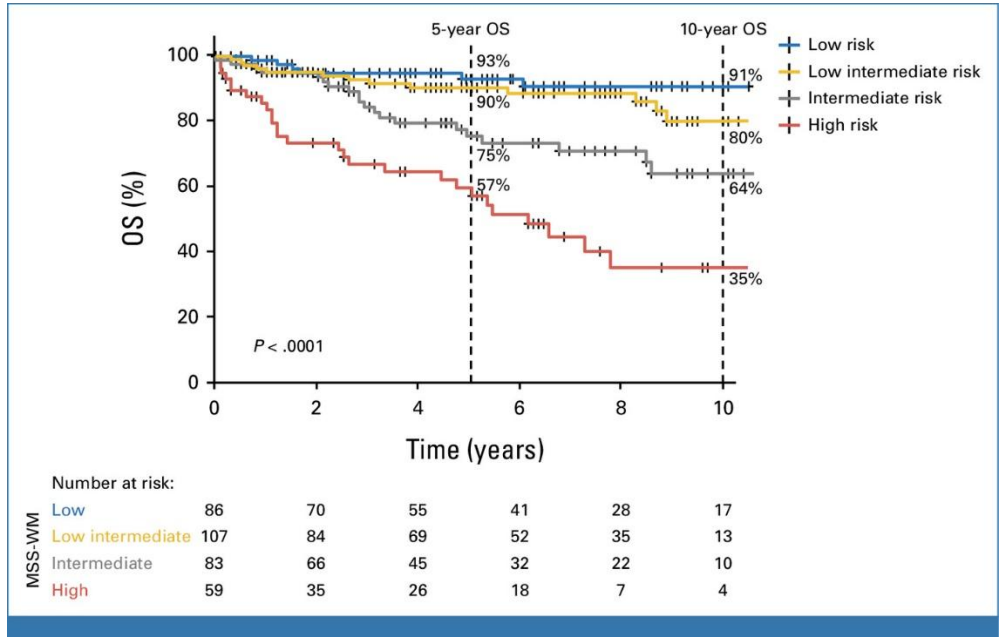
- Bing–Neel syndrome (BNS) is a rare manifestation WM, which is caused by infiltration of LPL)cells in the CNS
- Every WM patient with atypical or unexplained neurologic symptoms should be evaluated for BNS
- Key in the diagnostic workup is an MRI of the brain and spine and CSF examination or (if possible) cerebral biopsy to confirm the presence of LPL cells in the CNS
- Flow cytometry and molecular diagnostics aid in diagnosis by demonstrating a monoclonal B-cell population and the MYD88-mutation, respectively
- The aim of the treatment is clinical improvement; BTK inhibitor ibrutinib (or Zanubrutinib) is preferred as first-line therapy thanks to its high efficacy and limited toxicity

TABLE 2 International Prognostic Scoring System for Waldenström macroglobulinemia

Factor Associated With Prognosis		Value
Age, y		>65
Hemoglobin, g/dL		≤11.5
Platelet count, No./mcL		≤100 000
β_2-Microglobulin, mg/L		>3
Monoclonal IgM, g/dL		>7
Risk Stratum and Survival		
Risk Category	**Score**[a]	**Median Survival, mo**
Low	0 or 1 (except age)	142.5
Intermediate	2 or age > 65 y	98.6
High	>2	43.5

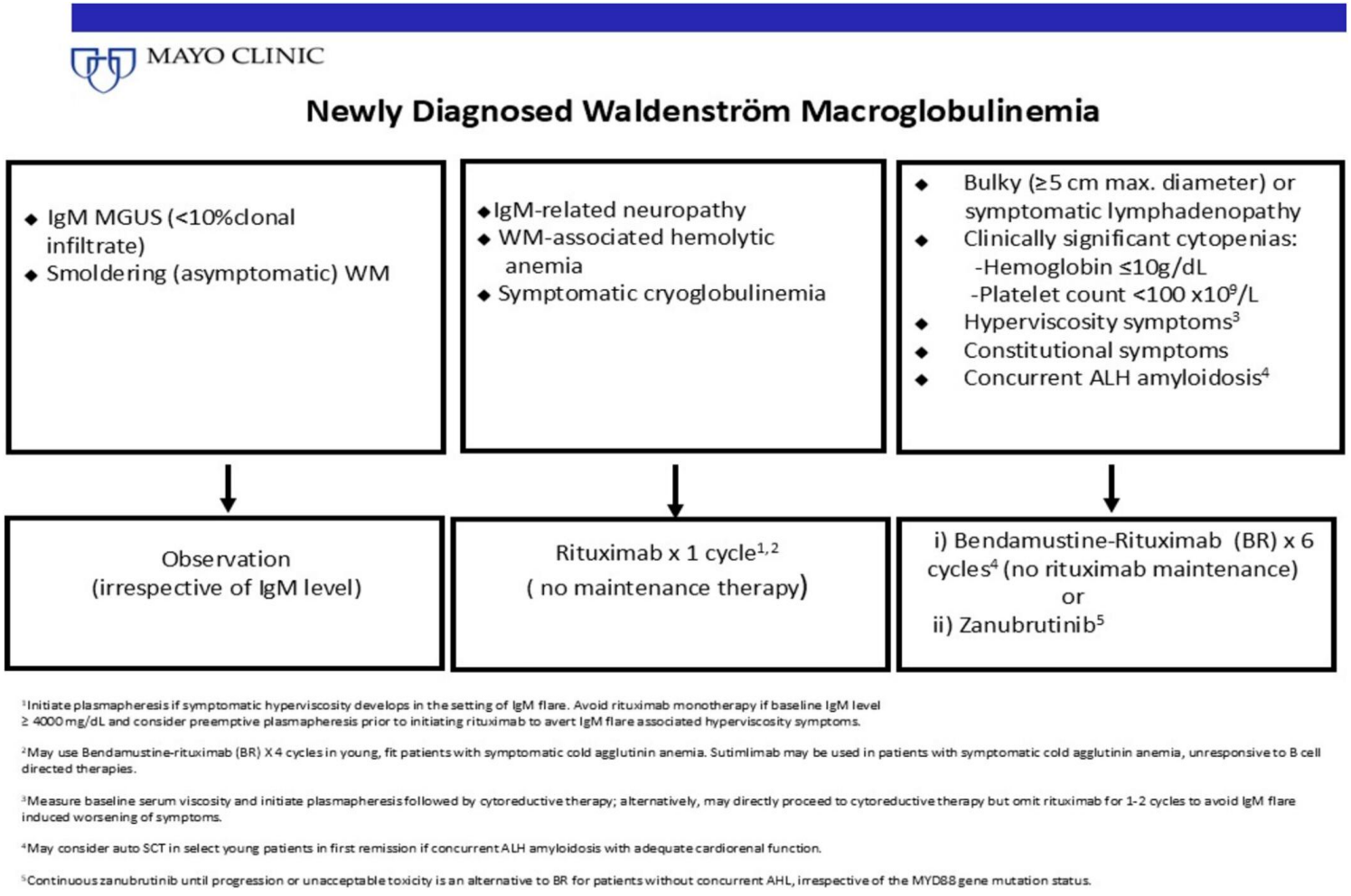
MSS-WM

Parameter	Points assigned
Albumin < 35 g/L	1
Age 66–75 years	1
Age > 75	2
LDH>ULN	1
Point score	**OS @ 5 years, %**
0 - low risk	93
1 - low-intermediate	82
2- intermediate	69
≥ 3 high risk	55



Zanwar et al. J *Clin Oncol* **42**, 2527-2536(2024)

Waldenström Macroglobulinemia: 2025 Update on Diagnosis, Risk Stratification, and Management



[1]Initiate plasmapheresis if symptomatic hyperviscosity develops in the setting of IgM flare. Avoid rituximab monotherapy if baseline IgM level ≥ 4000 mg/dL and consider preemptive plasmapheresis prior to initiating rituximab to avert IgM flare associated hyperviscosity symptoms.

[2]May use Bendamustine-rituximab (BR) X 4 cycles in young, fit patients with symptomatic cold agglutinin anemia. Sutimlimab may be used in patients with symptomatic cold agglutinin anemia, unresponsive to B cell directed therapies.

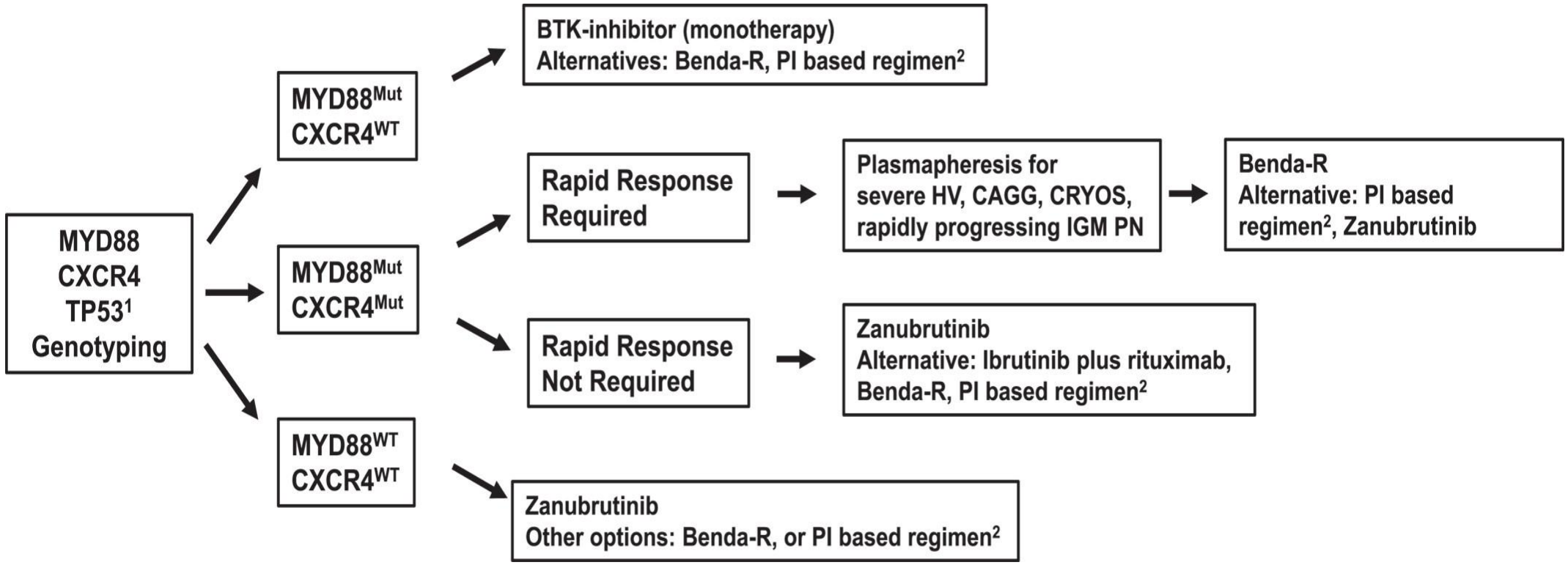
[3]Measure baseline serum viscosity and initiate plasmapheresis followed by cytoreductive therapy; alternatively, may directly proceed to cytoreductive therapy but omit rituximab for 1-2 cycles to avoid IgM flare induced worsening of symptoms.

[4]May consider auto SCT in select young patients in first remission if concurrent ALH amyloidosis with adequate cardiorenal function.

[5]Continuous zanubrutinib until progression or unacceptable toxicity is an alternative to BR for patients without concurrent AHL, irrespective of the MYD88 gene mutation status.

American J Hematol, Volume: 100, Issue: 6, Pages: 1061-1073, First published: 17 March 2025, DOI: (10.1002/ajh.27666)

Diagnosis and Management of Waldenstrom's Macroglobulinemia



Hematological Oncology, Volume: 43, Issue: S2, First published: 15 June 2025, DOI: (10.1002/hon.70071)

Choice of 1st line:

R-chemo (BR/DRC)

- Fixed duration
- Faster reduction of IGM with BR

- Deeper responses
- No rebound
- Lower risk of bleeding and Afib
- Concern regarding secondary malignancy

BTKi

- Treatment until PD/ toxicity
- Slow reduction with Ibrutinib (faster with Zanubrutinib)
- Mostly PR
- Rebound
- Lower risk of infections
- Lower risk (?) of SPM

IWWM-11 response criteria (also referred to as simplified IWWM-6 response criteria) for assessment of disease response in Waldenstrom's macroglobulinemia.

		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.*
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.†,‡		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§		

Regimen	ORR	CR	Median PFS (mo)
Rituximab x 4	25-30%	0-5%	13
Rituximab x 8	40-45%	0-5%	16-22
Rituximab/thalidomide	70%	5%	30
Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, CDR	70-80%	5-15%	30-36
Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R	70-90%	5-15%	36-62
Rituximab/Proteasome Inhibitor i.e. BDR, VR, CaRD	70-90%	5-15%	42-66
Rituximab/bendamustine	90%	5-15%	69

Reviewed in Dimopoulos et al, Blood 2014; 124(9):1404-11; Treon et al, Blood 2015 126:721-732; Rummel et al, ASH 2019

	Drugs	Treatment naive, relapsed or refractory	Overall response rate	Major response rate	Very good partial response rate or better	Progression-free survival (95% CI)*
Laszlo et al[17]	Cladribine and rituximab	16, 13 (n=29)	26 (90%)	23 (79%)	7 (24%)	Median: not reached at 43 months (NR)
Treon et al[18]	Fludarabine and rituximab	27, 16 (n=43)	41 (95%)	37 (86%)	16 (37%)	Median: 51 months (NR)
Buske et al[19]	CHOP	25, 0 (n=25)	15 (60%)	NR	NR	Median: 22 months (NR)
Buske et al[19]	R-CHOP	23, 0 (n=23)	21 (91%)	NR	NR	Median: 63 months (NR)
Dimopoulos et al[20]	Cyclophosphamide, dexamethasone, and rituximab	72, 0 (n=72)	60 (83%)	53 (74%)	5 (7%)	Median: 35 months (NR)
Rummel et al[21]	Bendamustine and rituximab	19, 0 (n=19)	NR	NR	NR	Median: 70 months (IQR 37–73)
Rummel et al[21]	R-CHOP	22, 0 (n=22)	NR	NR	NR	Median: 28 months (IQR 18–51)
Rummel et al[22]	Bendamustine and rituximab	257, 0 (n=257)	236 (92%)	226 (88%)	10 (4%)	Median: 65 months (NR)

Adverse events have been reported for nucleoside analogues (cytopenias, infections, myeloid neoplasms), CHOP (neuropathy, alopecia, stomatitis), and bendamustine (rash, constipation). CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone. R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. NR=not reported. *95%CI unless otherwise specified.

Table 2: Selected chemotherapy and rituximab combination regimens in patients with Waldenström macroglobulinemia

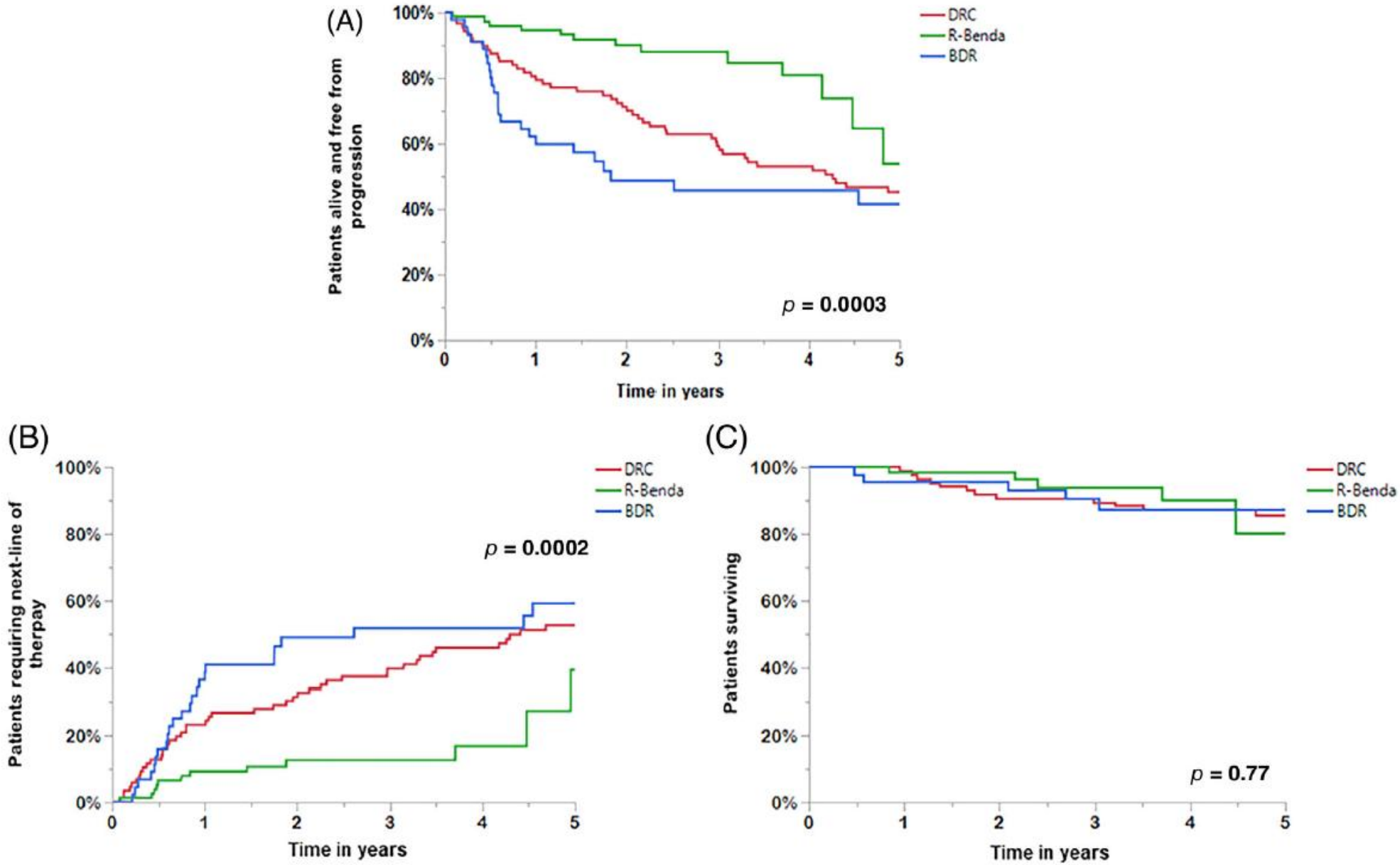
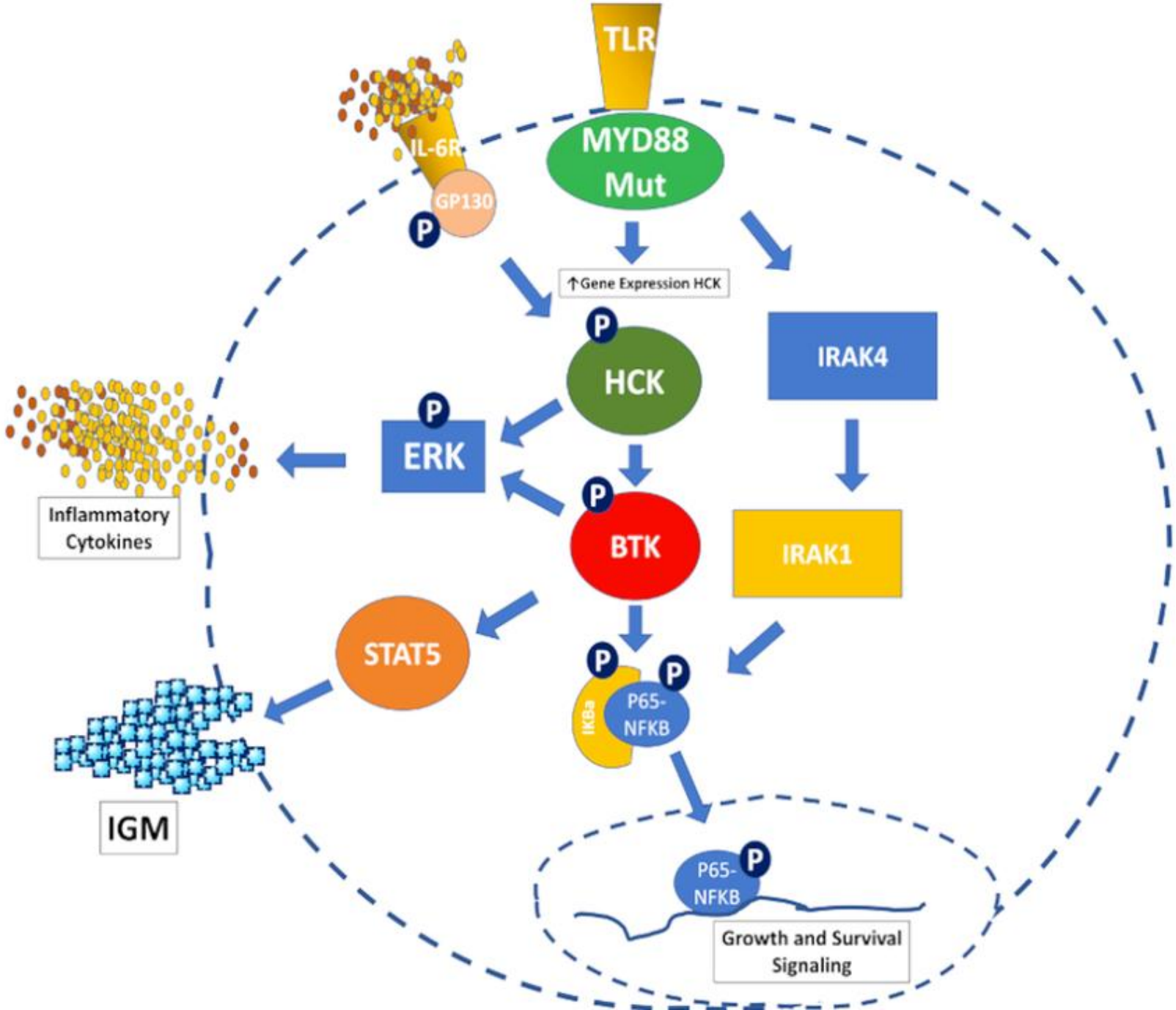

(A)
Patients alive and free from progression
100%
80%
60%
40%
20%
0%
0
1
2
3
4
5
Time in years
DRC
R-Benda
BDR
p = 0.0003
(B)
Patients requiring next-line of therpay
p = 0.0002
(C)
Patients surviving
p = 0.77

TABLE 2 Clinically relevant endpoints based on treatment regimen

Parameters	R-Benda	DRC	BDR	*p* value
Overall response rate, (%)	98	78	84	0.003
Major response rate, (%)	96	53	68	<0.001
Event free survival, range; years (95%CI)	NR (4.4-NR)	4.3 (2.4–5.8)	1.6 (0.6–5.6)	<0.001
Progression free survival, range; years (95%CI)	5.2 (4.5-NR)	4.3 (3.0–5.9)	1.8 (0.8–6.8)	0.001
Time-to-next therapy, range; years (95%CI)	NR (4.5-NR)	4.4 (3.0–5.9)	2.6 (0.9–6.9)	0.001
Time to best response, range; months (95%CI)	4.5 (3.8–5.1)	5.9 (4.8–7.6)	6.7 (5.1–9.0)	0.005
Duration of response, range; years (95%CI)	NR (4.5-NR)	3.9 (1.8–6.3)	3.6 (1.0-NR)	0.001
Four-year overall survival, (%)	90	87	87	0.8


TLR
MYD88
Mut
IL-6R
GP130
P
↑Gene Expression HCK
HCK
IRAK4
ERK
Inflammatory
Cytokines
BTK
IRAK1
STAT5
IGM
IκBa
P65-
NFKB
P65-
NFKB
Growth and Survival
Signaling

BTKi

	Drugs	Treatment naive, relapsed or refractory	Overall response rate	Major response rate	Very good partial response rate or better	Progression-free survival (95% CI)
Treon et al[37]	Ibrutinib	0, 63 (n=63)	57 (90%)	50 (79%)	19 (30%)	5-year: 54% (95% CI 39–67%)
Dimopoulos et al[29]	Ibrutinib	0, 31 (n=31)	28 (90%)	22 (71%)	4 (13%)	18-month: 86% (66–94)
Treon et al[38]	Ibrutinib	30, 0 (n=30)	30 (100%)	25 (83%)	6 (20%)	18-month: 92% (73–98)
Dimopoulos et al[39]	Ibrutinib, rituximab	34, 41 (n=75)	70 (93%)	55 (73%)	20 (27%)	30-month: 82% (NR)
Owen et al[40]	Acalabrutinib	14, 92 (n=106)	99 (93%)	83 (78%)	8 (8%; IWWM-6) and 31 (29%; IWWM-3)	24-month: 90% (47–99, TN); 82% (72–89, RR)

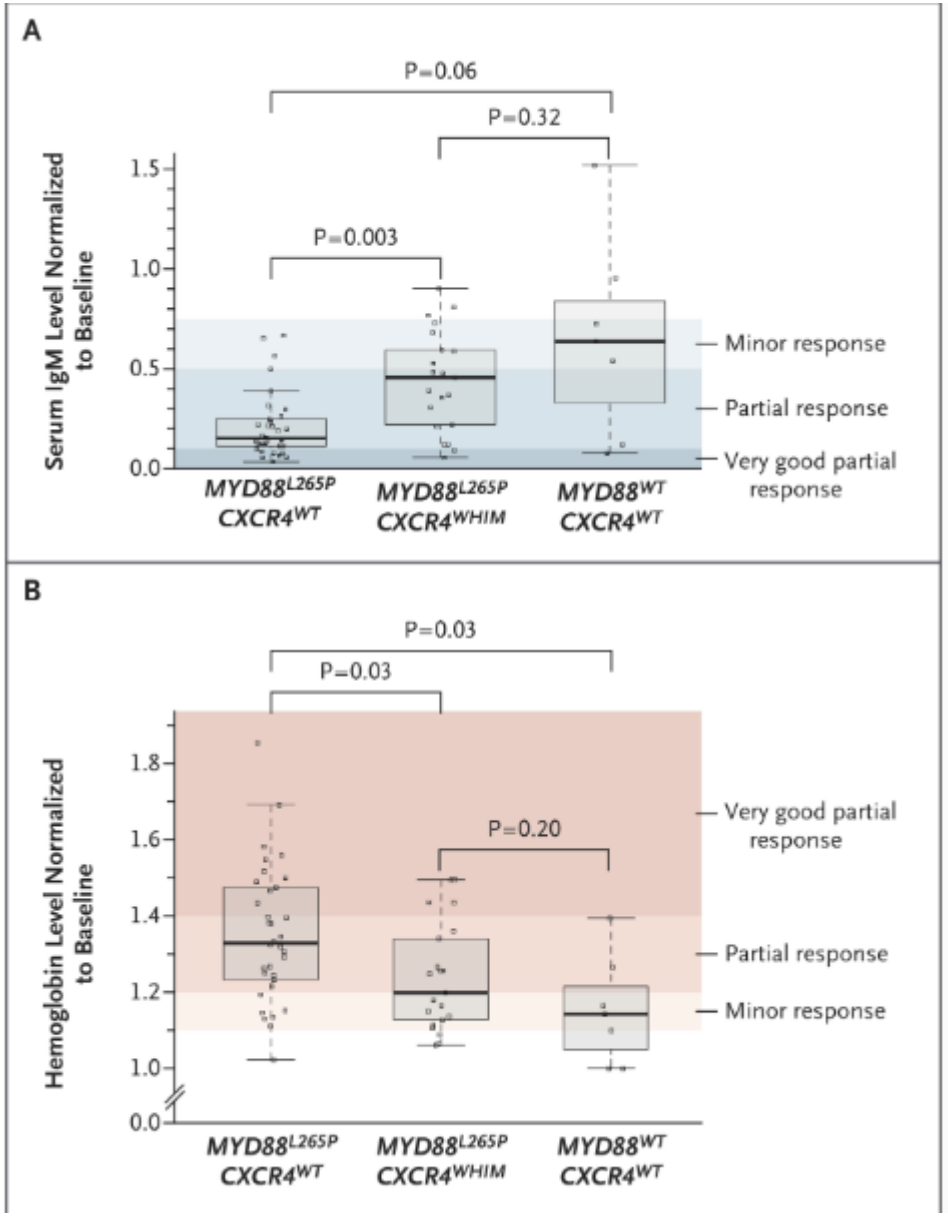
All studies reported adverse events of cytopenia, bleeding, arrythmias, and hypertension. IWWM=International Workshop for Waldenström Macroglobulinaemia. NR=not reported. RR=relapsed or refractory. TN= treatment naive.

Table 4: Selected BTK inhibitor-based regimens in patients with Waldenström macroglobulinaemia

Ibrutinib for previously treated WM

- ORR 90%, major response 73%
- MYD88 mut:

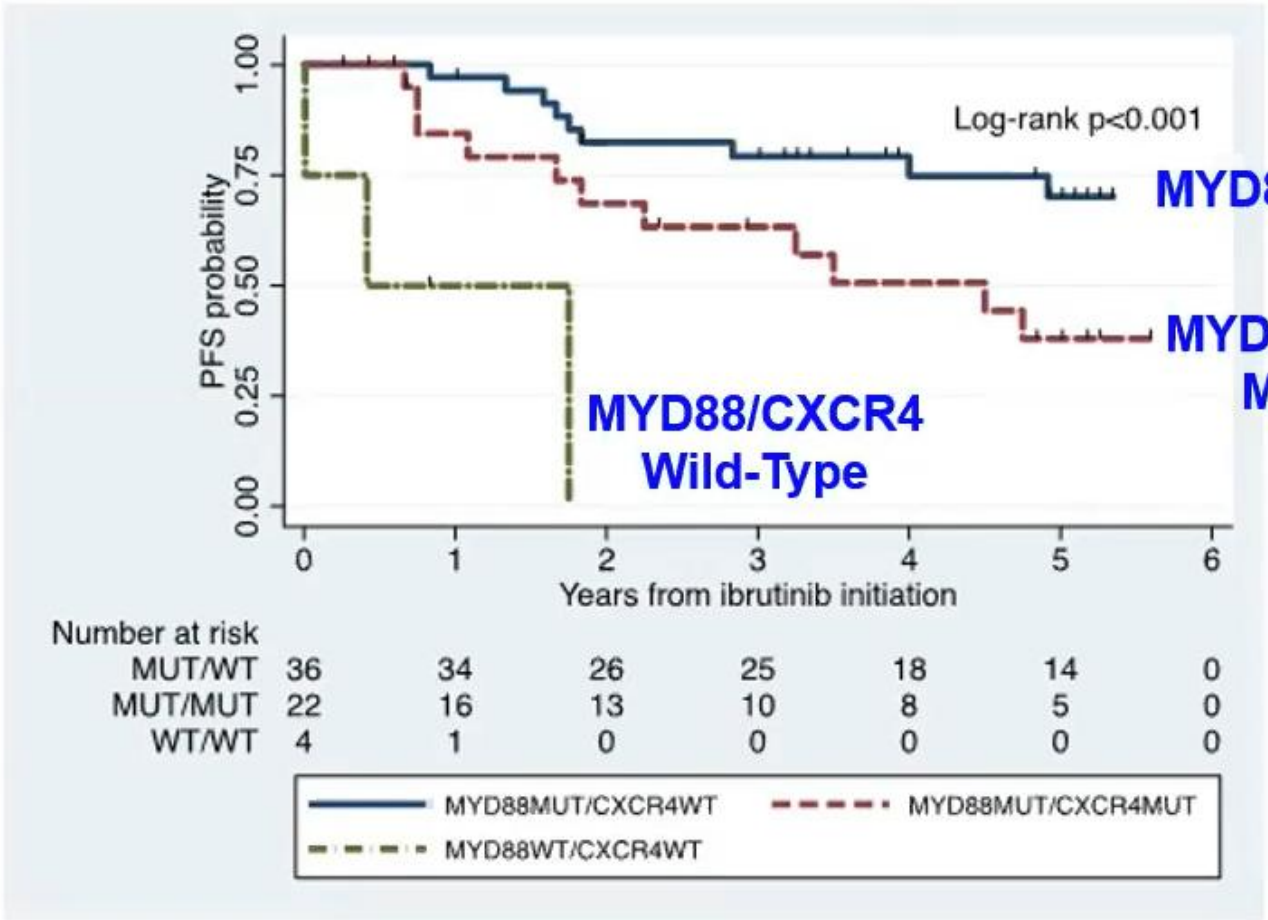
	CXCR ^{WT}	CXCR ^{WHIM}
ORR	100%	86%
Major response	91%	62%



Treon, NEJM 2015

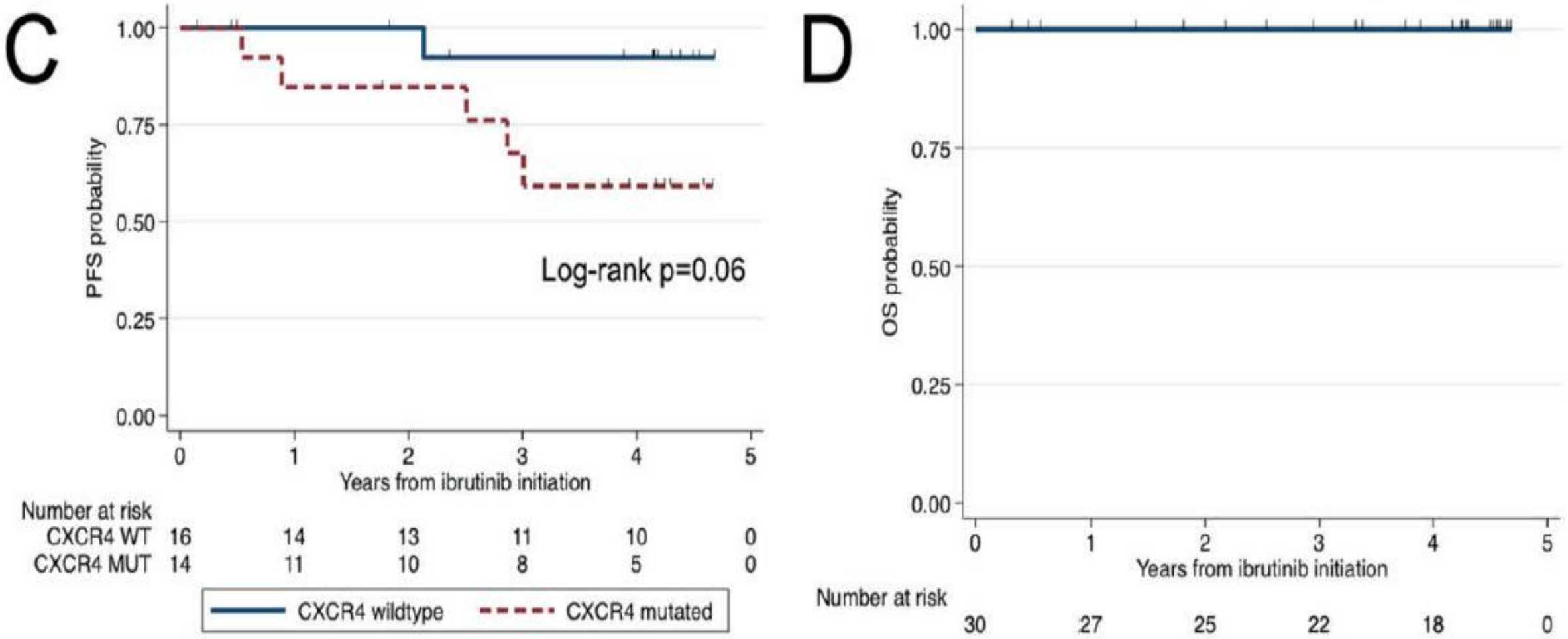
MYD88 and CXCR4 Mutation Status

B.



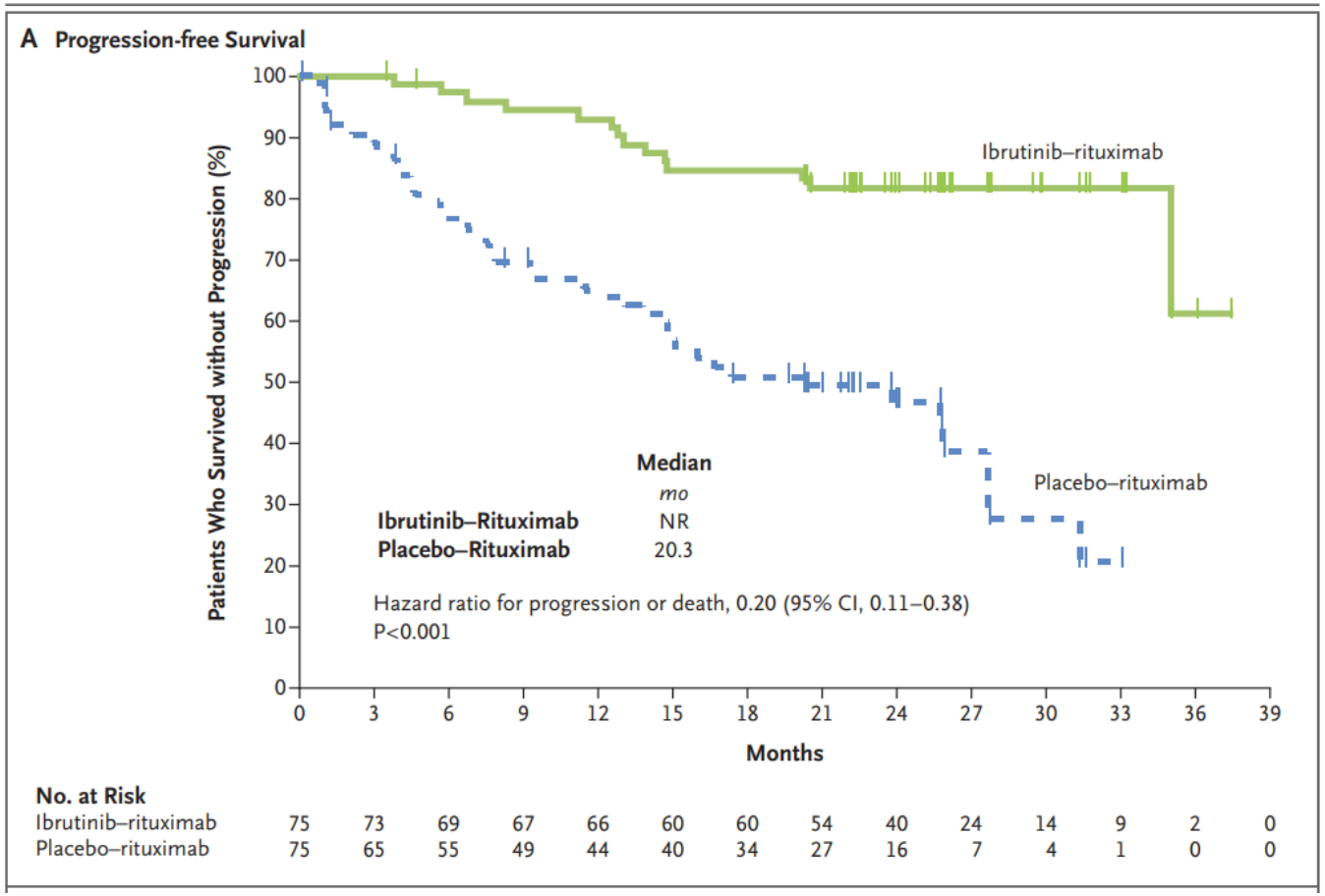
Updated from Treon et al, NEJM 2015

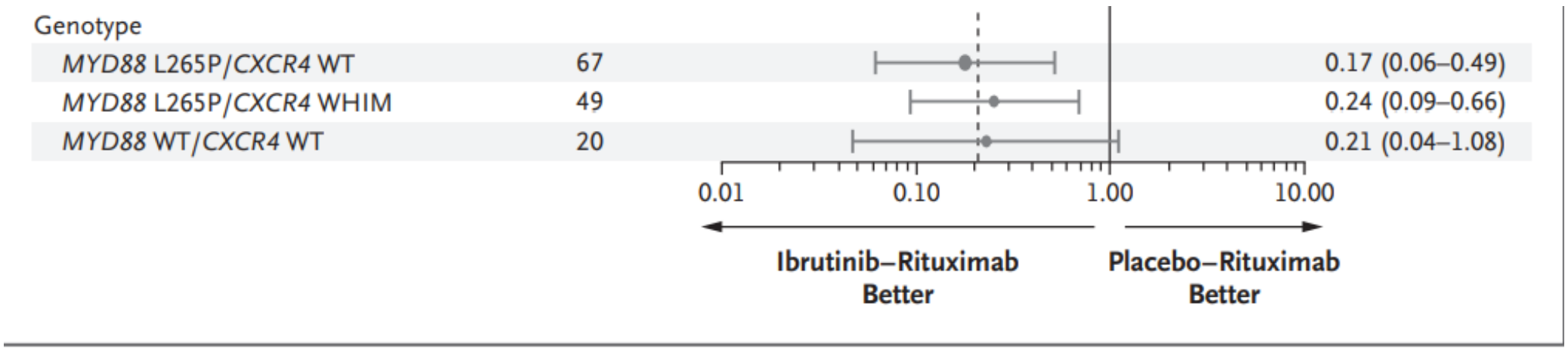
50 month f/u (Castillo, leukemia 2022)



iNNOVATE (Dimopoulus, NEJM 2018)

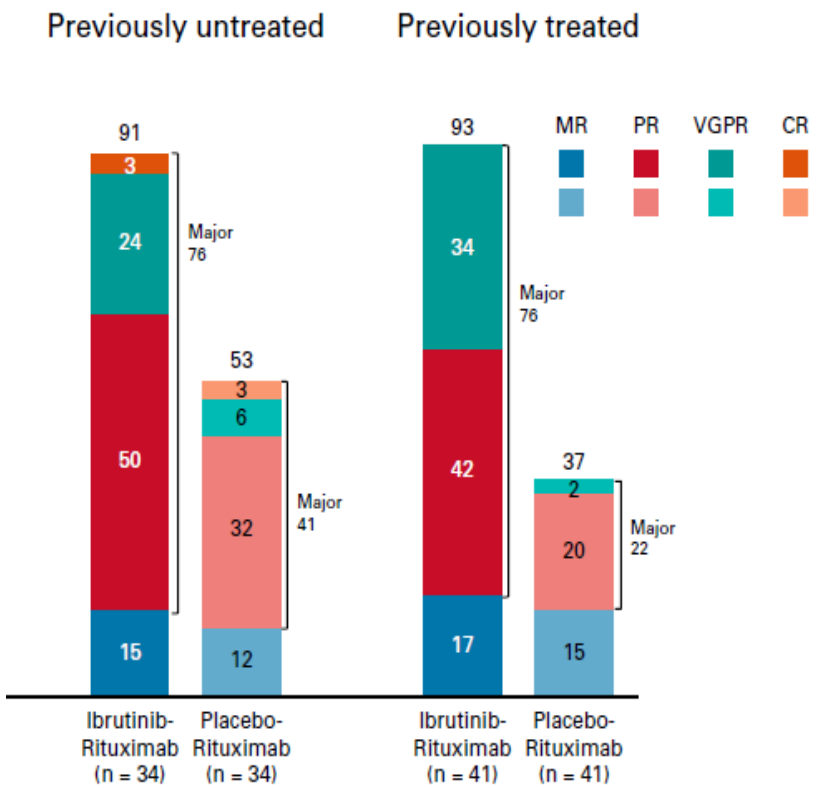
The NEW ENGLAND JOURNAL of MEDICINE

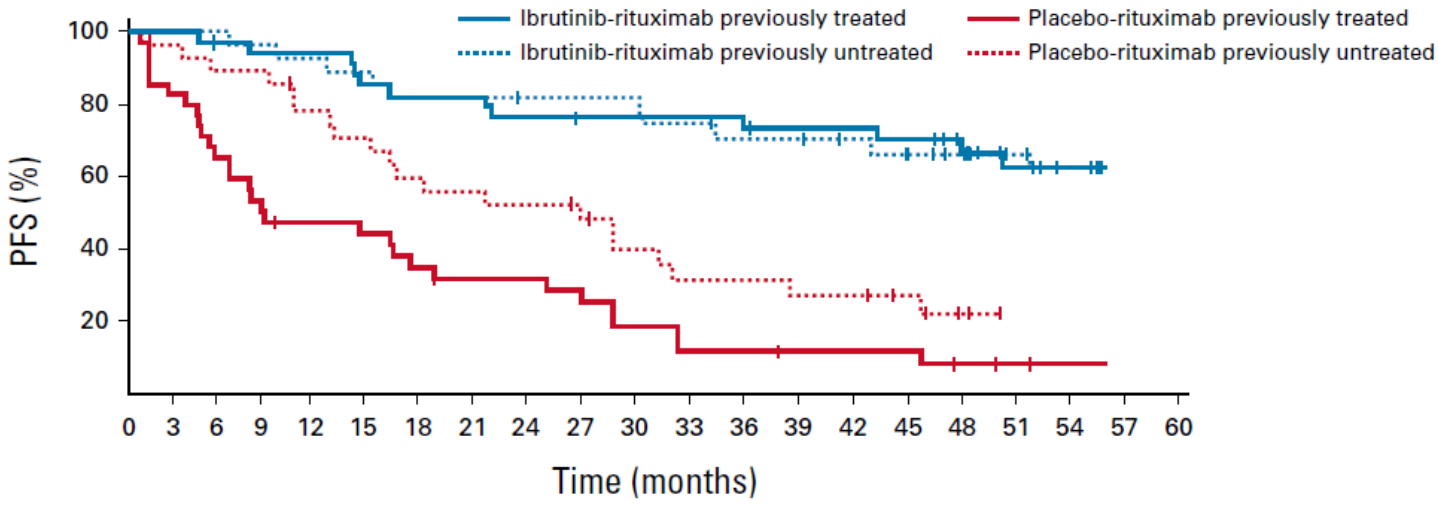



Genotype
MYD88 L265P/CXCR4 WT
67
0.17 (0.06–0.49)
MYD88 L265P/CXCR4 WHIM
49
0.24 (0.09–0.66)
MYD88 WT/CXCR4 WT
20
0.21 (0.04–1.08)
0.01
0.10
1.00
10.00
Ibrutinib–Rituximab Better
Placebo–Rituximab Better

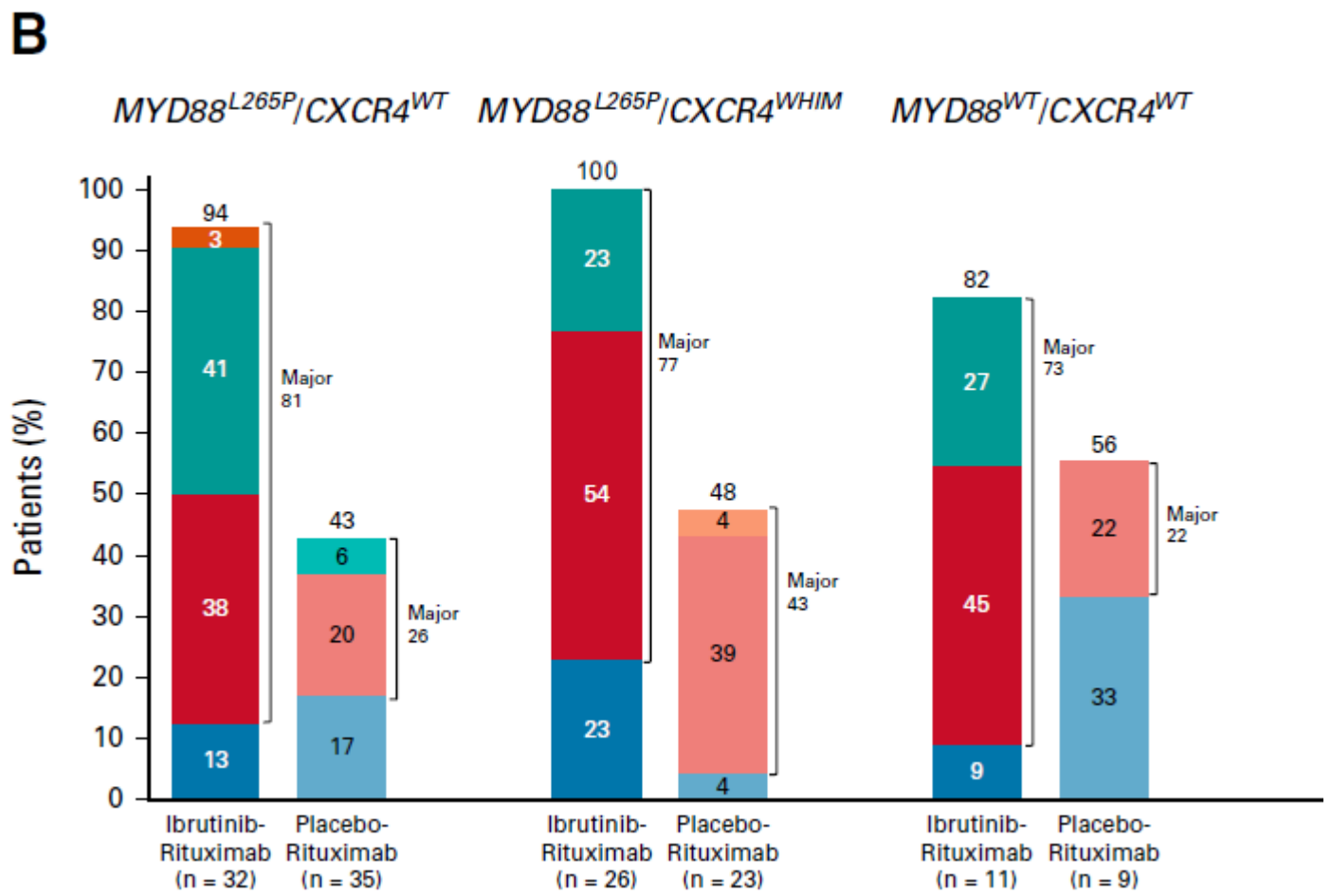
Most common adverse events of any grade — no. of patients (%)*		
Infusion-related reaction	32 (43)	44 (59)
Diarrhea	21 (28)	11 (15)
Arthralgia	18 (24)	8 (11)
Nausea	16 (21)	9 (12)
Anemia	14 (19)	22 (29)
Asthenia	12 (16)	19 (25)
Fatigue	10 (13)	20 (27)
Headache	10 (13)	17 (23)
IgM flare	6 (8)	35 (47)
Adverse event of grade ≥3 — no. of patients (%)†	45 (60)	46 (61)
Hypertension	10 (13)	3 (4)
Atrial fibrillation	9 (12)	1 (1)
Anemia	8 (11)	13 (17)
Neutropenia	7 (9)	2 (3)
Pneumonia	7 (9)	2 (3)

iNNOVATE- final analysis (Buske; JCO 2022)

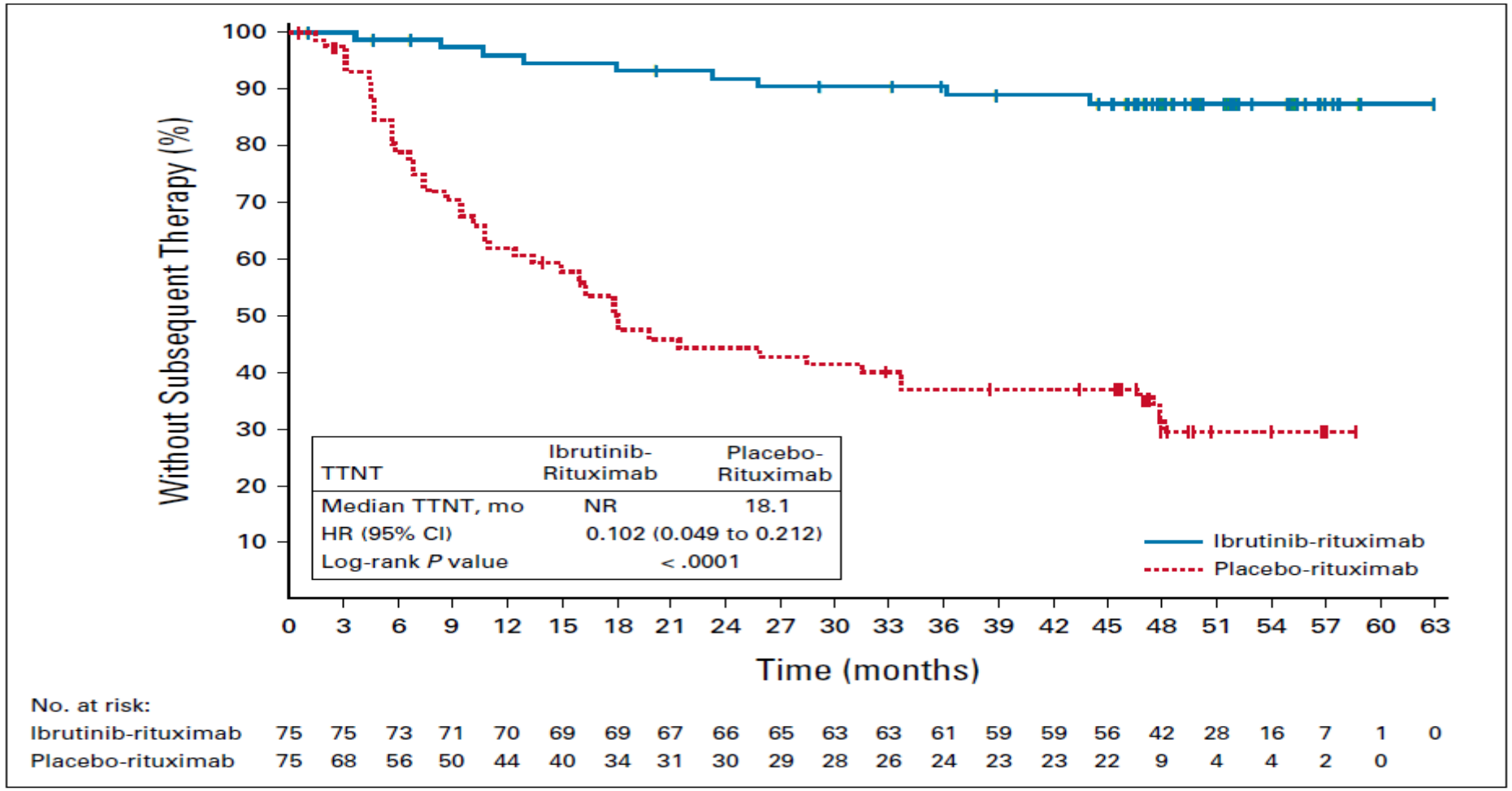




iNNOVATE- final analysis (Buske; JCO 2022)



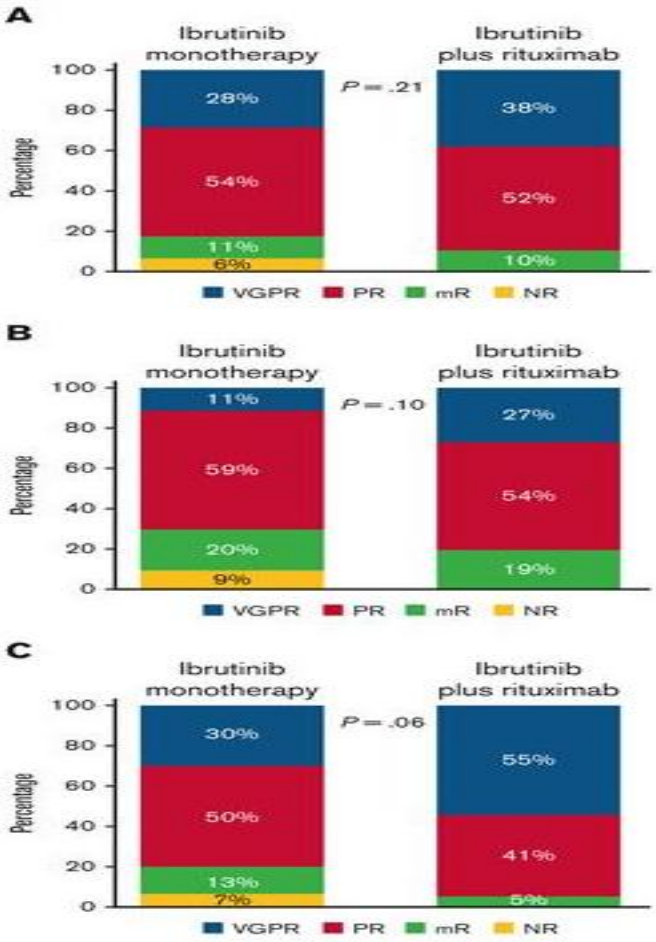
iNNOVATE- final analysis (Buske; JCO 2022)

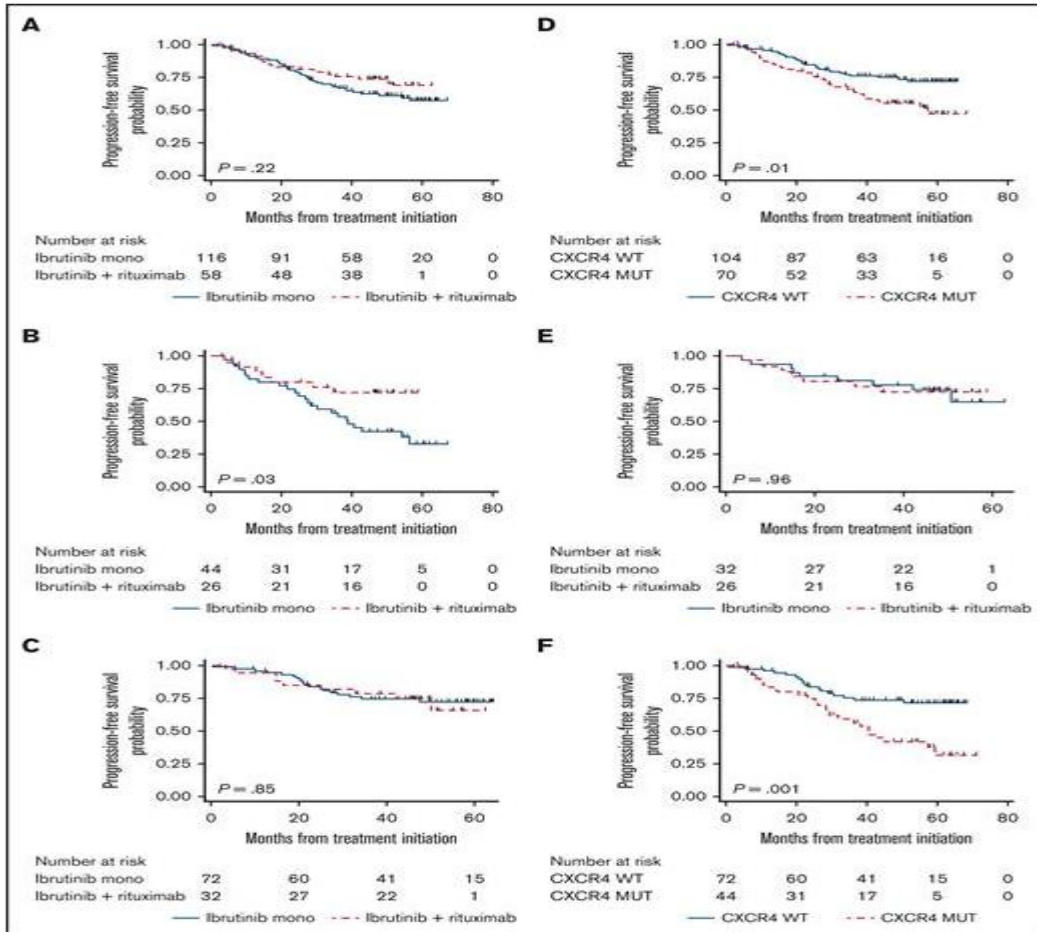


iNNOVATE- final analysis (Buske; JCO 2022)

	Ibrutinib-Rituximab, No. (%)					
	Prevalence by Year					
AE	Year 0-1 (n = 75)	Year 1-2 (n = 69)	Year 2-3 (n = 58)	Year 3-4 (n = 54)	Year 4-5 (n = 40)	Overall (n = 75)
AE leading to ibrutinib dose reduction	7 (9)	10 (15)	7 (12)	6 (11)	2 (5)	17 (23)
AE leading to ibrutinib discontinuation	1 (1)	2 (3)	2 (3)	2 (4)	1 (1)	8 (11)
Death as a result of TEAE	0	0	0	0	1 (3)[a]	1 (3)[a]
Major hemorrhage	2 (3)	0	3 (5)	0	0	5 (7)
Any grade atrial fibrillation	8 (11)	6 (9)	3 (5)	3 (6)	3 (8)	14 (19)

I mono or I+R?





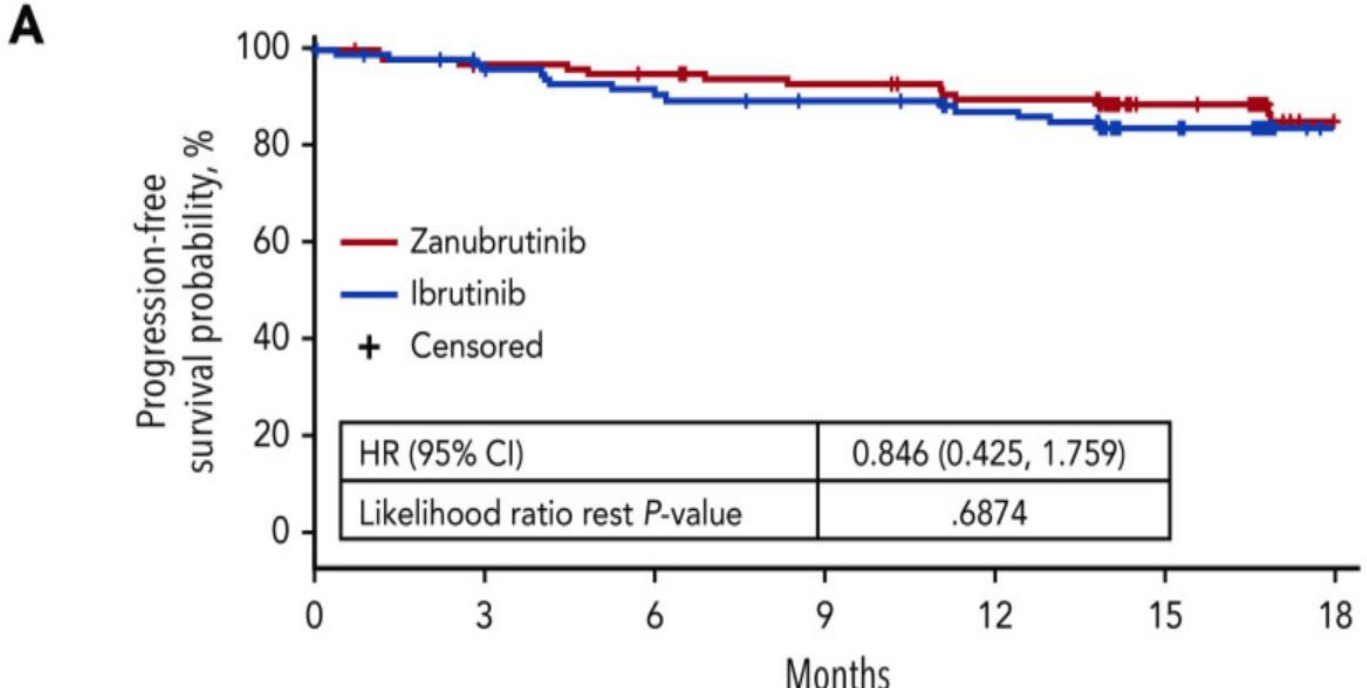
Guijosa et al. DOI: 10.1182/**bloodadvances**.2025016536

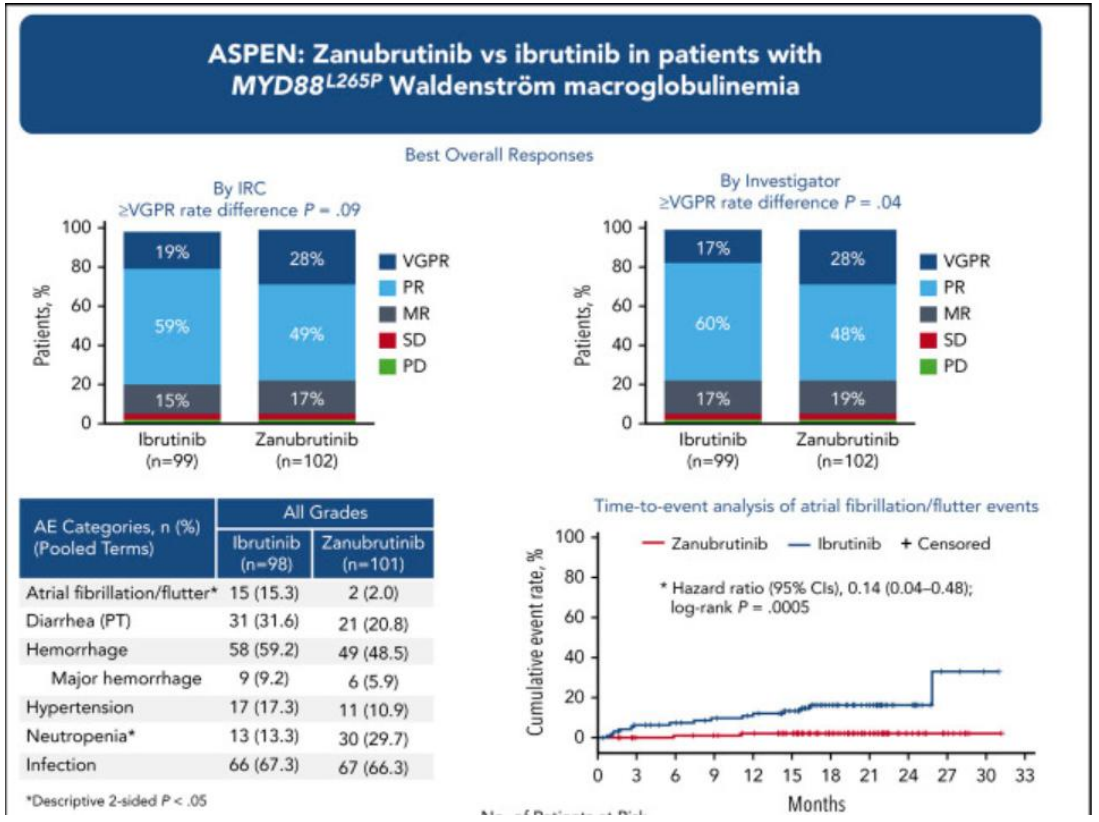
Ibrutinib

- Outside of a clinical trial setting (“real world”) 80 patients were reported receiving ibrutinib therapy, achieving an overall response rate of 91% with an 18 month progression-free survival of 82%; 21% of patients discontinued therapy due to treatment related toxicity. Atrial fibrillation was seen in 11%. The IgM rebound was seen in 36% of patients following ibrutinib discontinuation

Newer BTKi

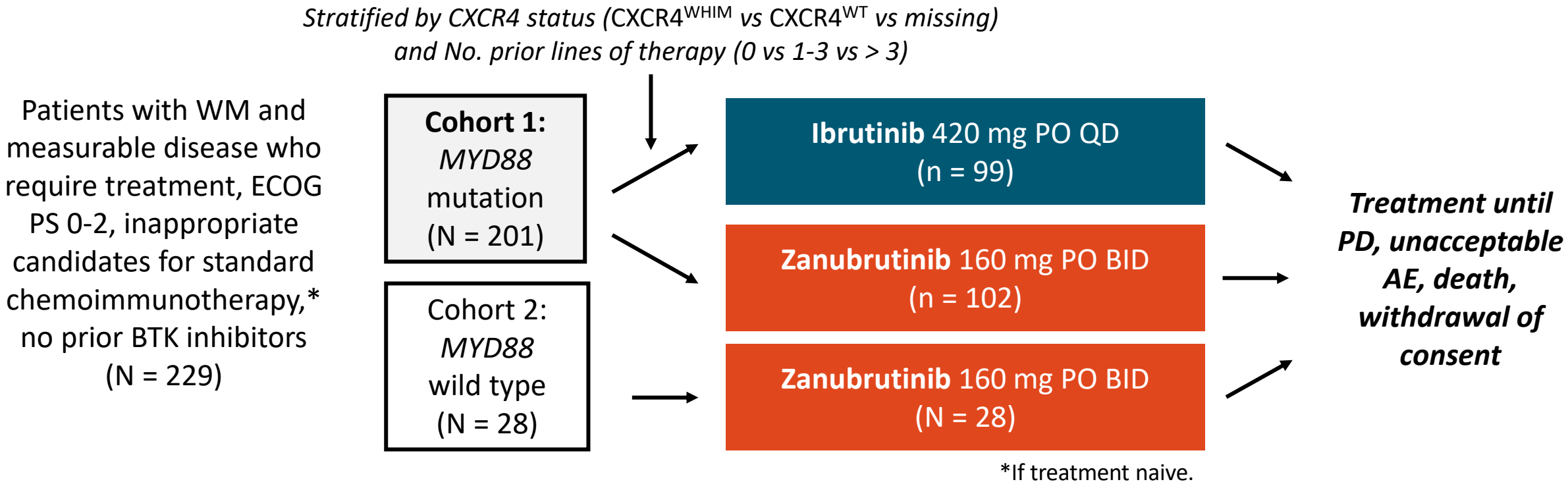
- Acalabrutinib: phase 2 only. 93% ORR. Fewer side effects
- Zanubrutinib: ASPEN trial, phase 3 (Zanubrutinib vs. Ibrutinib): similar efficacy, less side effects





ASPEN: Study Design

- Randomized, open-label, multicenter phase III study; current report presented cohort 1 data



- Primary endpoint: rate of CR or VGPR in Cohort 1
- Secondary endpoints: response, DoR, PFS, safety, QoL

Tam. ASCO 2020. Abstr 8007. NCT03053440.

Slide credit: clinicaloptions.com

ASPEN: Baseline Characteristics

Characteristics (ITT Population)	Zanubrutinib (n = 102)	Ibrutinib (n = 99)
Median age, yrs	70	70
▪ > 65 yrs, %	59.8	70.7
▪ > 75 yrs, %	33.3	22.2
Male, %	67.6	65.7
Prior treatments, %		
▪ 0	18.6	18.2
▪ 1-3	74.5	74.7
▪ > 3	6.9	7.1

Characteristics, % (ITT Population)	Zanubrutinib (n = 102)	Ibrutinib (n = 99)
Genotype		
▪ *MYD88*^{L265P}/ *CXCR4*^{WT}	89.2	90.9
▪ *MYD88*^{L265P}/ *CXCR4*^{WHIM}	10.8	8.1
Hemoglobin ≤ 110 g/L	65.7	53.5
IPSS WM		
▪ Low	16.7	13.1
▪ Intermediate	37.3	42.4
▪ High	46.1	44.4

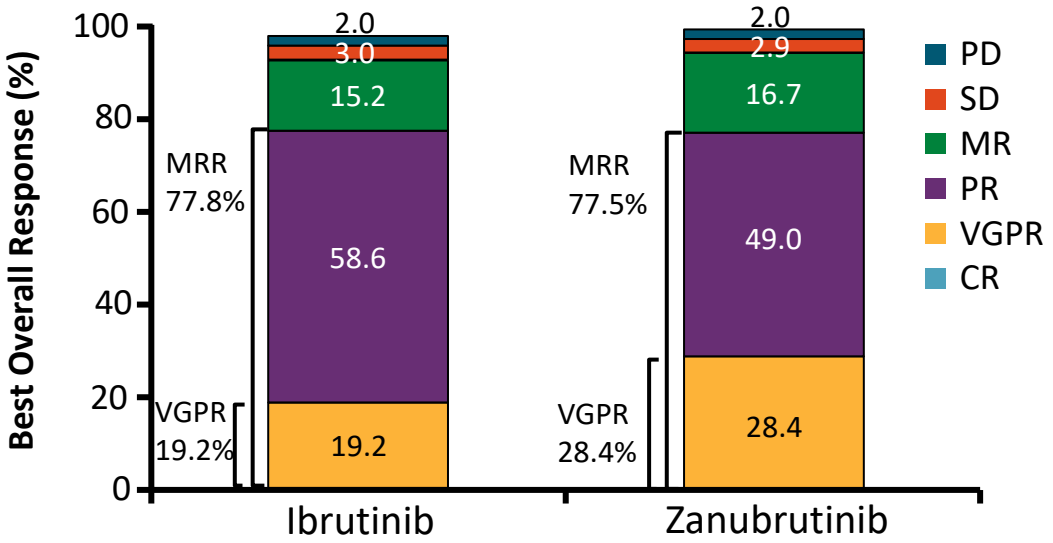
Tam. ASCO 2020. Abstr 8007.

Slide credit: clinicaloptions.com

ASPEN: Response in ITT Population

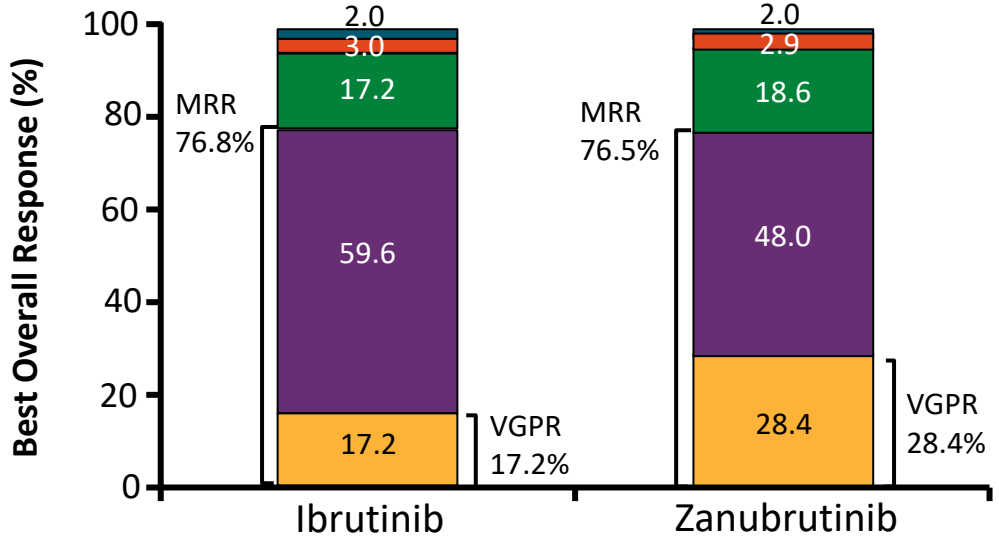
- Data cutoff: August 31, 2019

Response by Independent Review Committee*



CR + VGPR rate difference: 10.2 (-1.5 to 22.0; *P* = .0921)

Response by Investigator Review



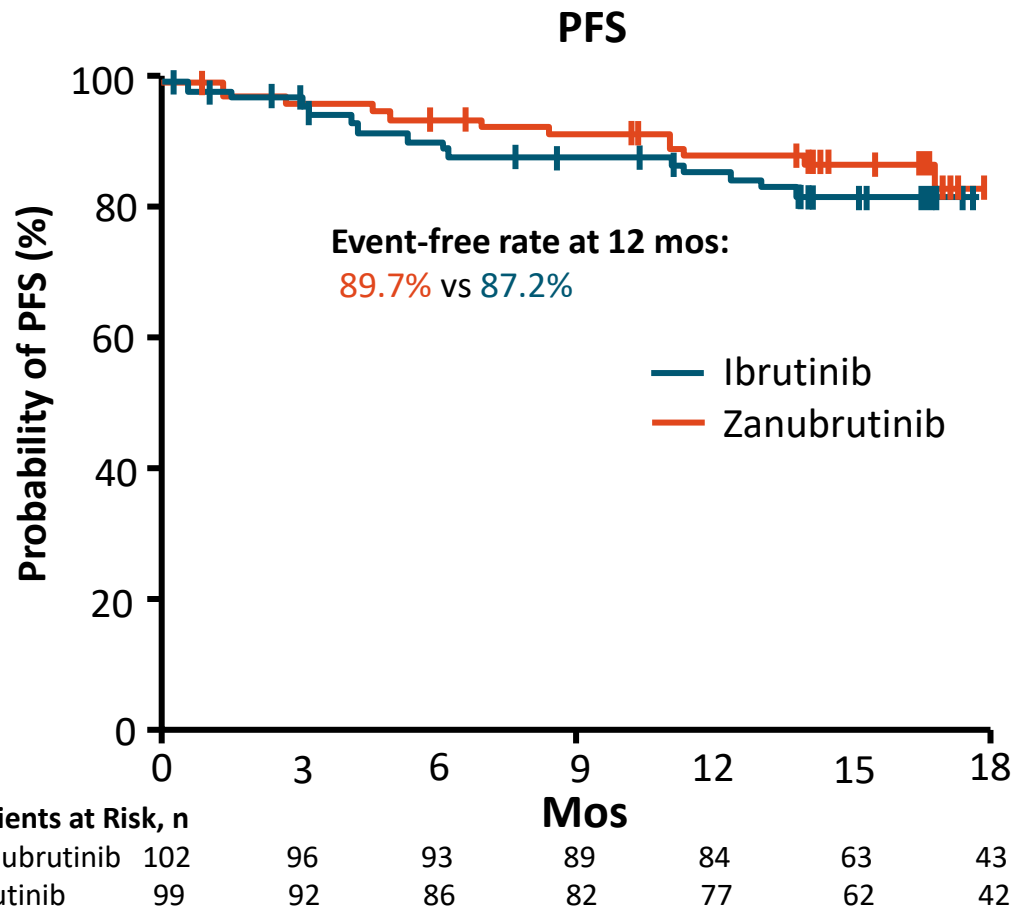
CR + VGPR rate difference: 12.1 (0.5-23.7; *P* = .0437)

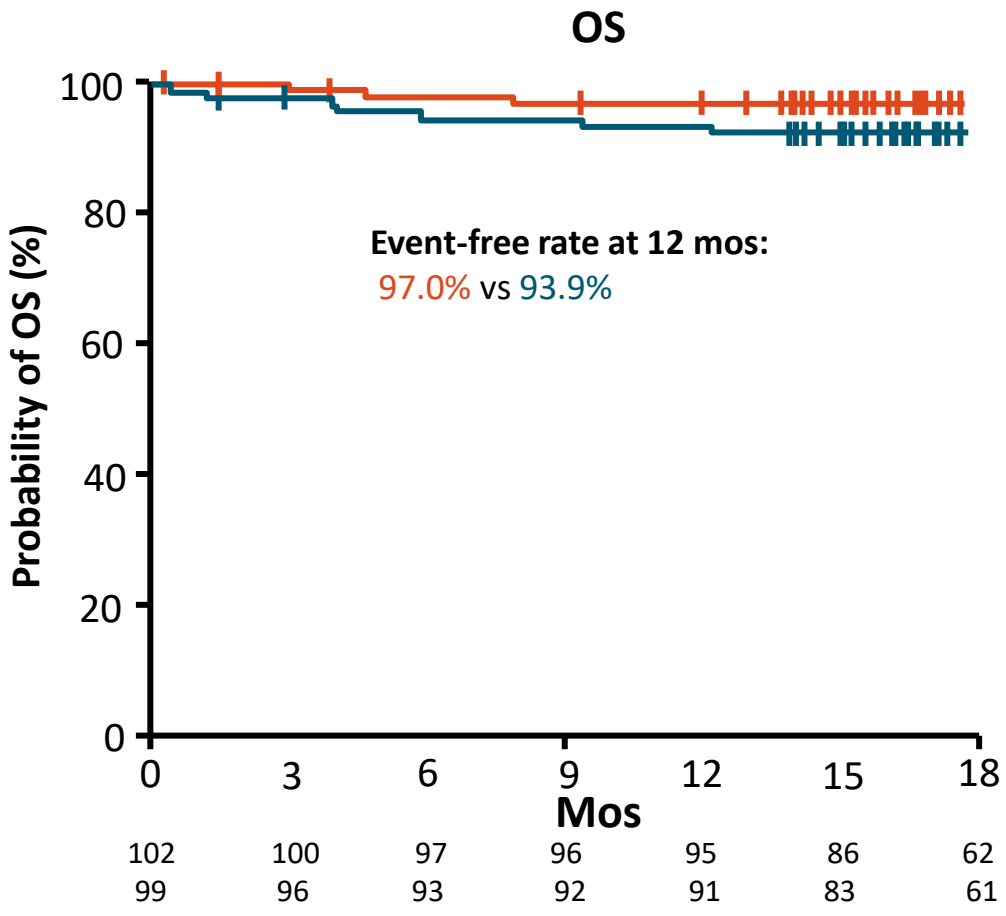
*Primary endpoint.

- CR + VGPR rate difference by investigator assessment after January 2020 data cutoff: 13.2 (1.4-25.1; *P* = .0302)
- In general, similar response rates (by IRC) with either BTK inhibitor across subgroups, including CXCR4 status, baseline hemoglobin, extramedullary disease

ASPEN: IgM Reduction and Survival

- Greater IgM reduction (AUC over time) with zanubrutinib vs ibrutinib (*P* = .037)





Tam. ASCO 2020. Abstr 8007.

Slide credit: clinicaloptions.com

ASPEN: Most Common Adverse Events

Most Common AEs, %*	All Grades		Grade ≥ 3	
	Zanubrutinib (n = 101)	Ibrutinib (n = 98)	Zanubrutinib (n = 101)	Ibrutinib (n = 98)
Diarrhea	21	32	3	1
Upper respiratory infection	24	29	0	1
Contusion	13	24	0	0
Muscle spasm†	10	24	0	1
Peripheral edema†	9	19	0	0
Hypertension	11	16	6	11
Atrial fibrillation†	2	14	0	3
Neutropenia†	25	12	16	8
Pneumonia†	2	12	1	7
Anemia	12	10	5	5
Thrombocytopenia	10	9	3	5

*Most common AEs, AEs occurring in ≥ 10% of patients, or AEs with ≥ 5% rate differences between groups. † Descriptive 2-sided $P < .05$.

Tam. ASCO 2020. Abstr 8007.

Slide credit: clinicaloptions.com

ASPEN: BTKi Class Adverse Events of Interest

AE Categories, %	All Grades		Grade ≥ 3	
	Zanubrutinib (n = 101)	Ibrutinib (n = 98)	Zanubrutinib (n = 101)	Ibrutinib (n = 98)
Atrial fibrillation/flutter*	3.0	18.4	0.0	7.1
Diarrhea (PT)	21.8	32.7	3.0	2.0
Hemorrhage	50.5	60.2	5.9	9.2
▪ Major hemorrhage‡	5.9	10.2	5.9	9.2
Hypertension	12.9	20.4	7.9	15.3
Neutropenia*†	31.7	15.3	22.8	8.2
Infection	69.3	71.4	18.8	23.5
Second malignancy	12.9	12.2	3.0	1.0

*Descriptive 2-sided $P < .05$.

Data cutoff: January 31, 2020.

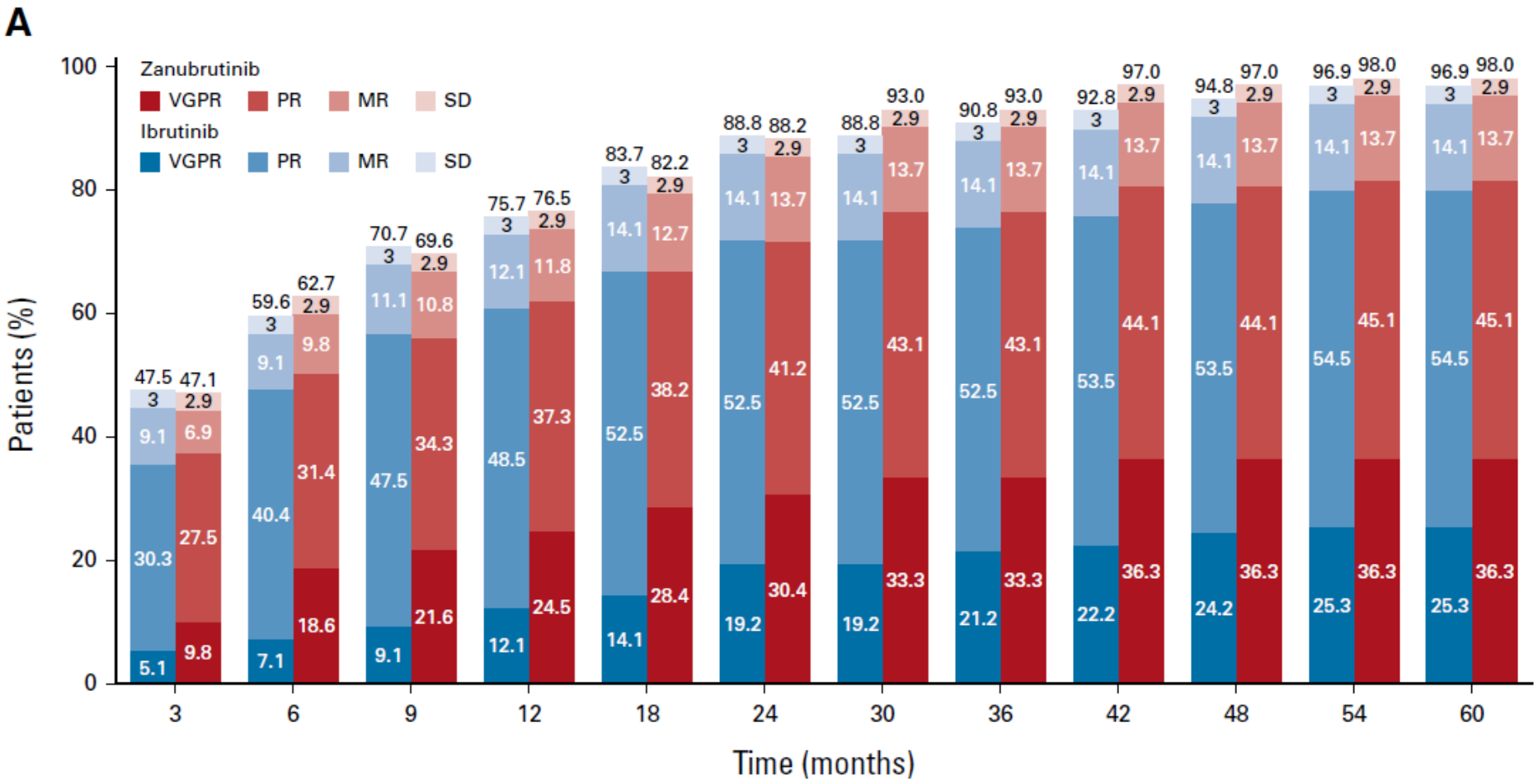
†PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.

‡Major hemorrhage defined as grade ≥ 3 hemorrhage or any grade CNS hemorrhage.

Tam. ASCO 2020. Abstr 8007.

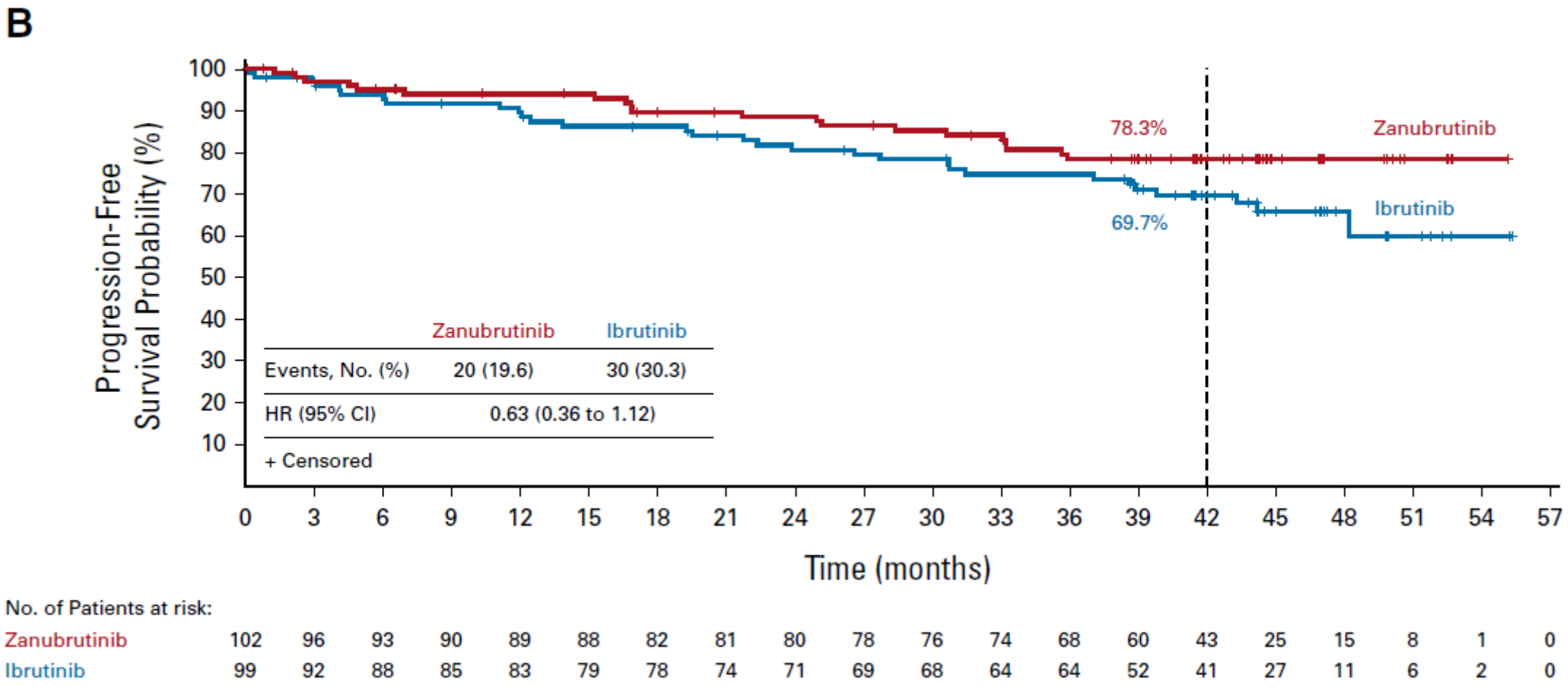
ASPEN- final analysis (Dimopoulus; JCO 2023)

- Median f/u 44 months



ASPEN- final analysis (Dimopoulus; JCO 2023)

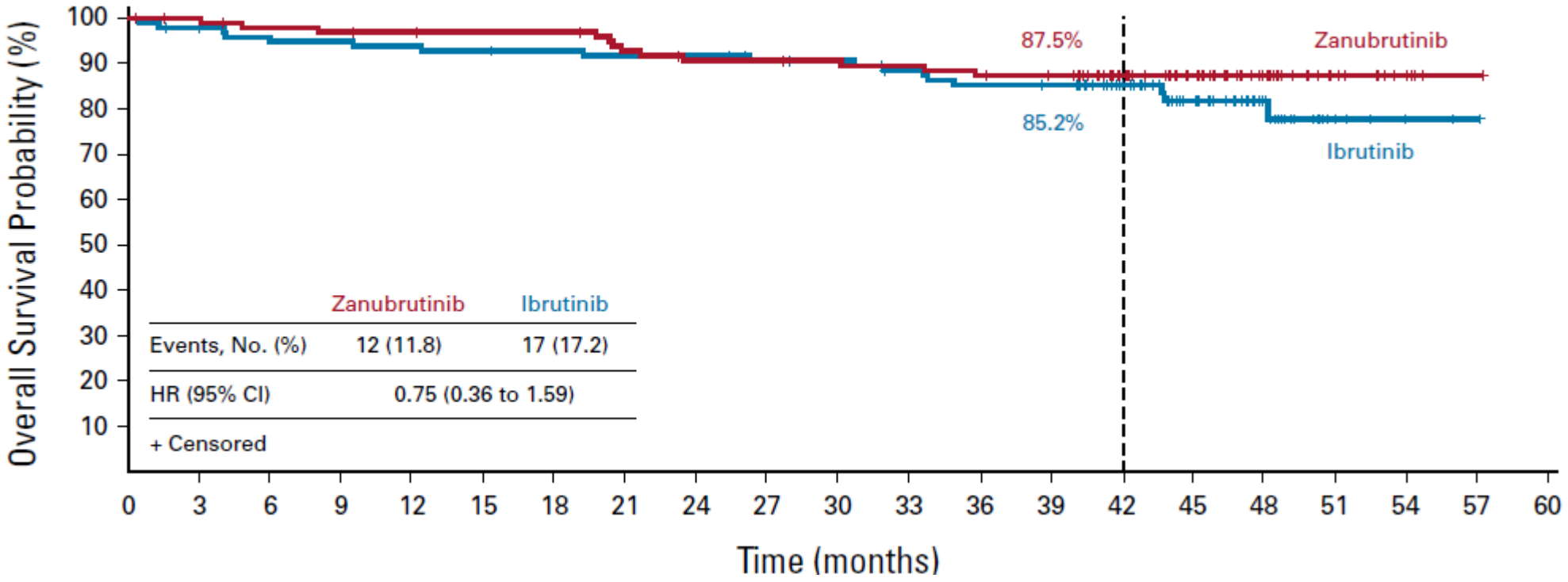
- Median f/u 44 months



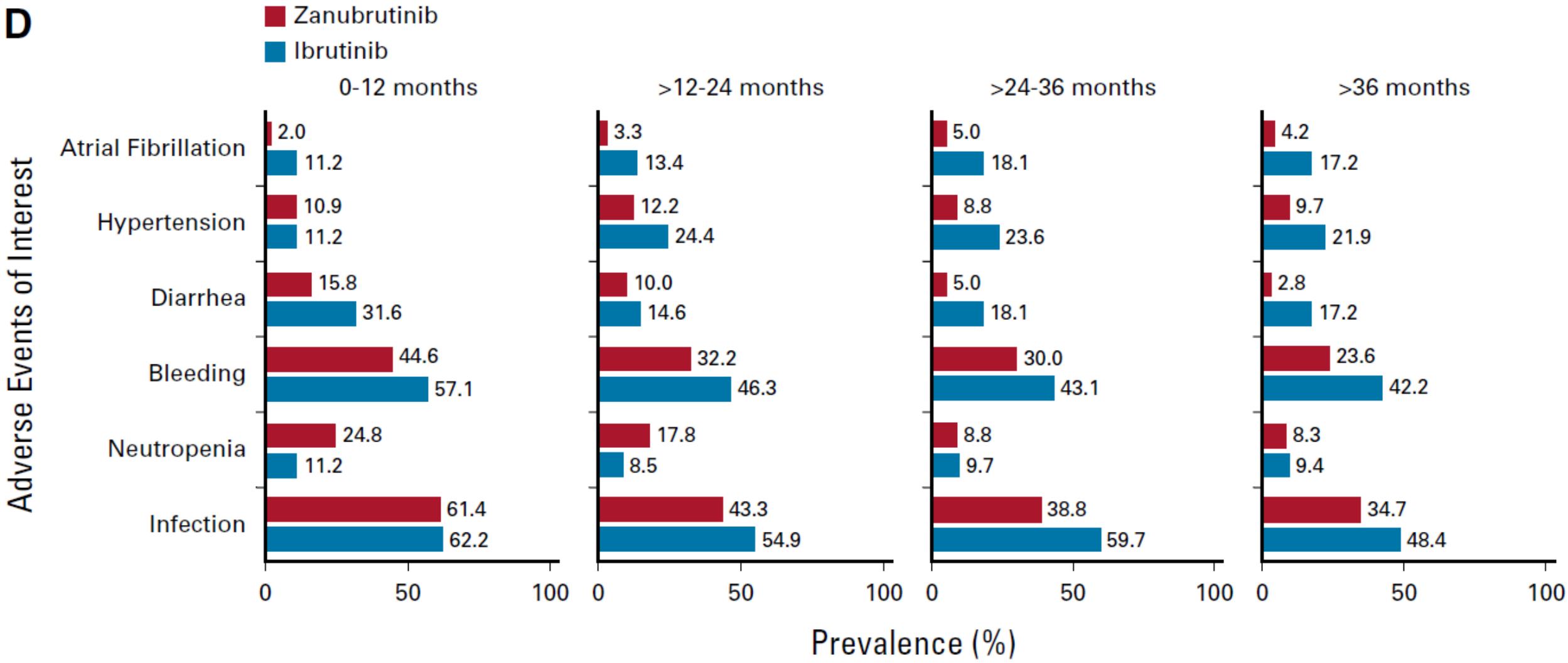
ASPEN- final analysis (Dimopoulus; JCO 2023)

- Median f/u 44 months

C



ASPEN- final analysis (Dimopoulus; JCO 2023)



Bortezomib

BLOOD, 7 NOVEMBER 2013 • VOLUME 122, NUMBER 19

Table 2. Overall response to BDR

	N (%)
CR	2 (3)
VGPR	4 (7)
PR	34 (58)
MR	10 (17)
SD	3 (5)
PD	6 (10)

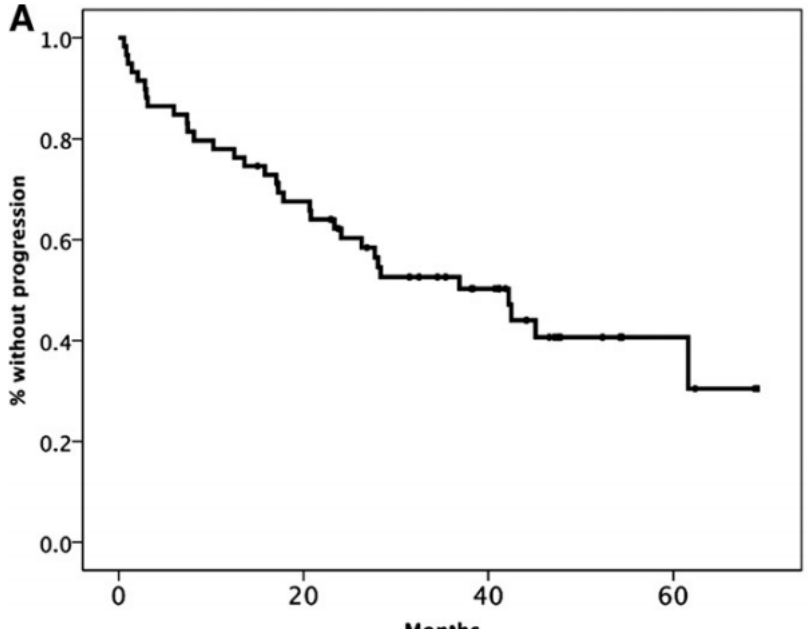
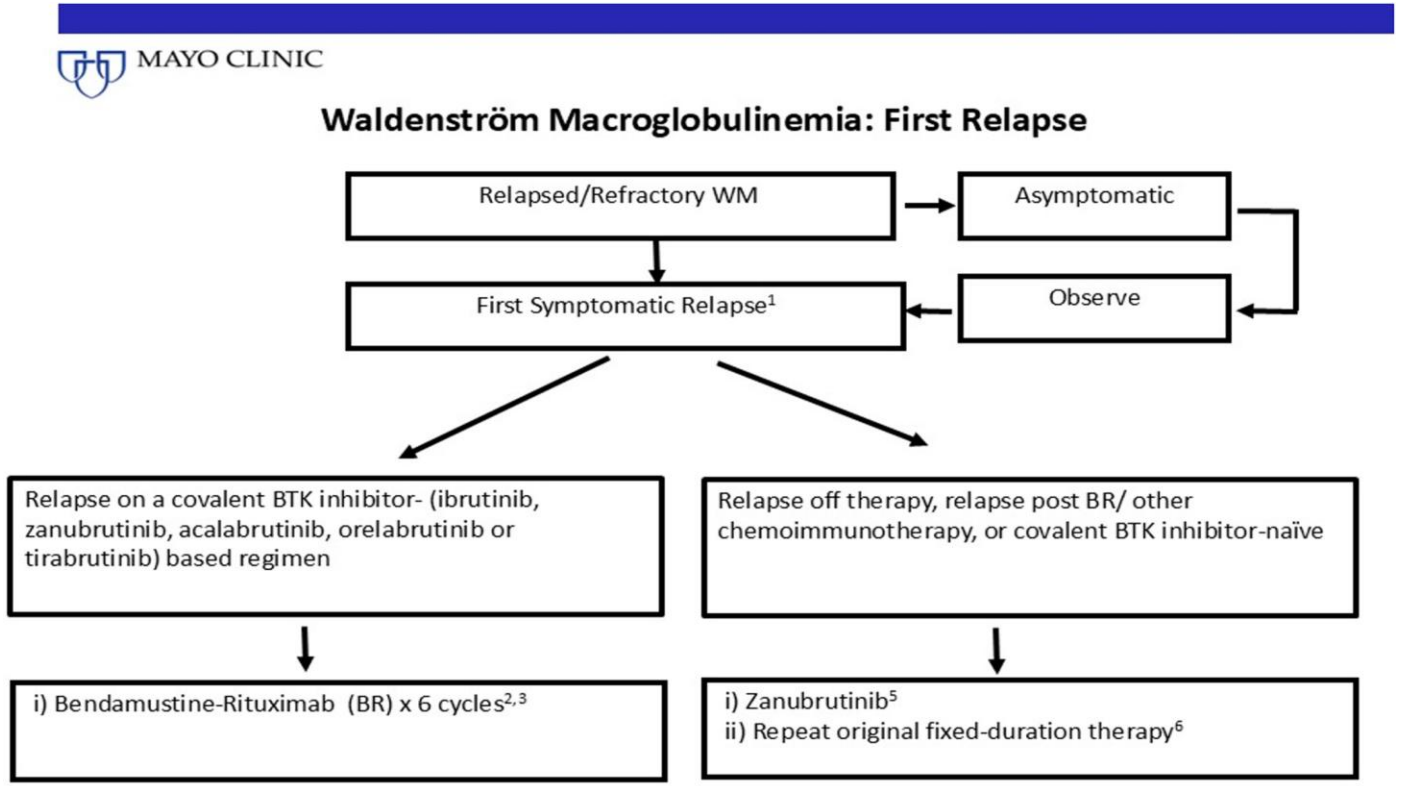


Table 3. Toxicity associated with BDR

	Any grade, N (%)	Grade ≥3, N (%)
Neutropenia	10 (17)	(15)
Thrombocytopenia	10 (17)	(5)
Anemia	6 (10)	0
Peripheral neuropathy (sensory)	27 (46)	4 (7)
Neuropathic pain	(20)	1 (2)
Fever NOS	9 (15)	3 (5)
Respiratory symptoms NOS	9 (15)	6 (10)
Pneumonitis	3 (5)	3 (5)
Infections NOS	13 (22)	4 (7)

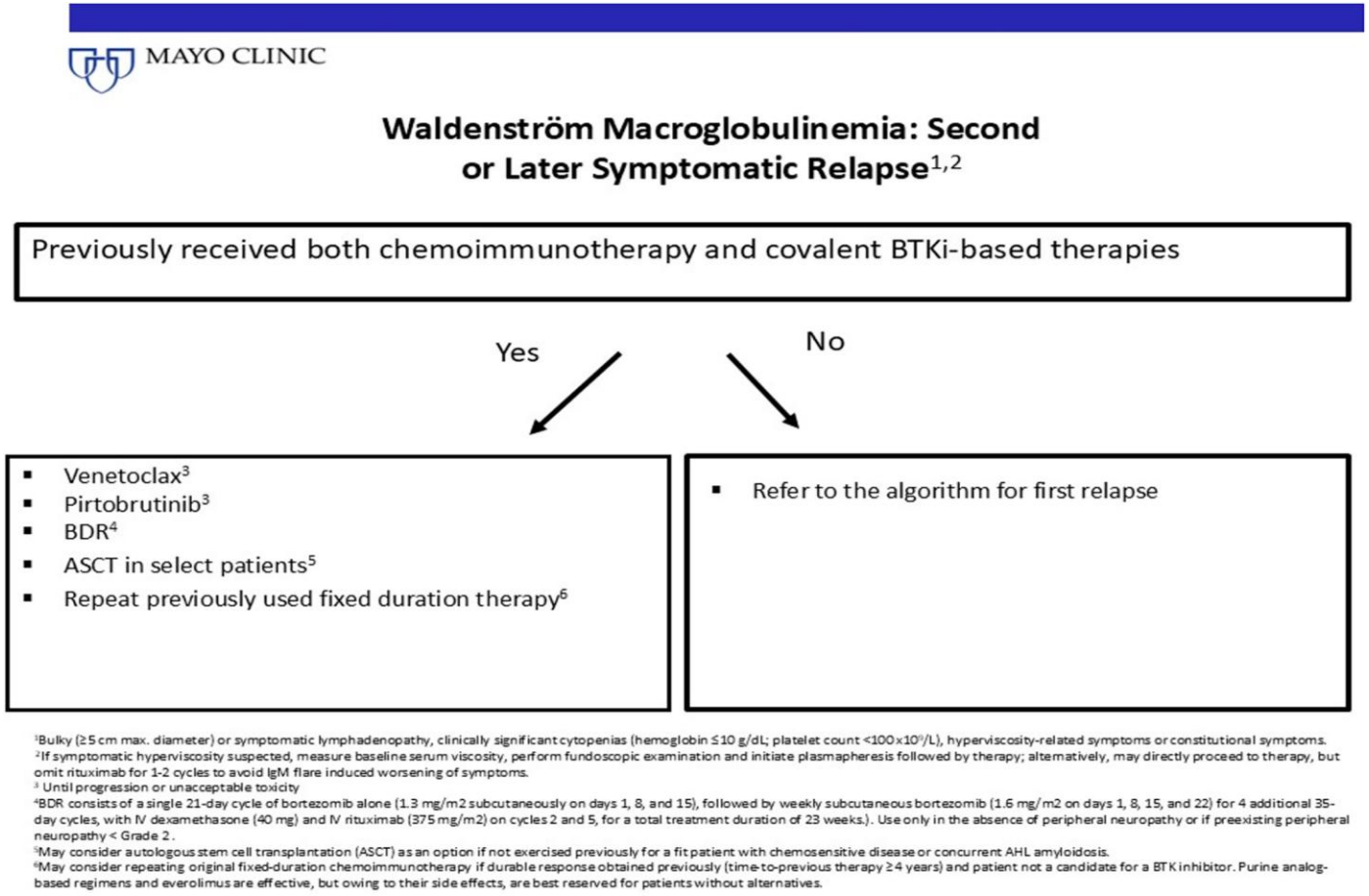
Waldenström Macroglobulinemia: 2025 Update on Diagnosis, Risk Stratification, and Management- 1st relapse



[1]Bulky (≥5 cm max. diameter) or symptomatic lymphadenopathy, clinically significant cytopenias (hemoglobin ≤10 g/dL; platelet count <100x10⁹/L), hyperviscosity-related symptoms or constitutional symptoms.
[2]If symptomatic hyperviscosity suspected, measure baseline serum viscosity, perform fundoscopic examination and initiate plasmapheresis followed by cytoreductive therapy; alternatively, may directly proceed to cytoreductive therapy, but omit rituximab for 1-2 cycles to avoid IgM flare induced worsening of symptoms.
[3]If chemoimmunotherapy not used previously. In the frail patient population, DRC (Dexamethasone, Rituximab, Cyclophosphamide) regimen may be used as an alternative to BR.
[5] If a BTK inhibitor not used previously; ibrutinib alone (only if the patient has MYD88^{mut}), ibrutinib-rituximab or acalabrutinib may be used if zanubrutinib unavailable.
[6]May consider repeating original fixed-duration chemoimmunotherapy if durable response obtained previously (time-to- previous therapy ≥4 years) and patient not a candidate for a BTK inhibitor.

American J Hematol, Volume: 100, Issue: 6, Pages: 1061-1073, First published: 17 March 2025, DOI: (10.1002/ajh.27666)

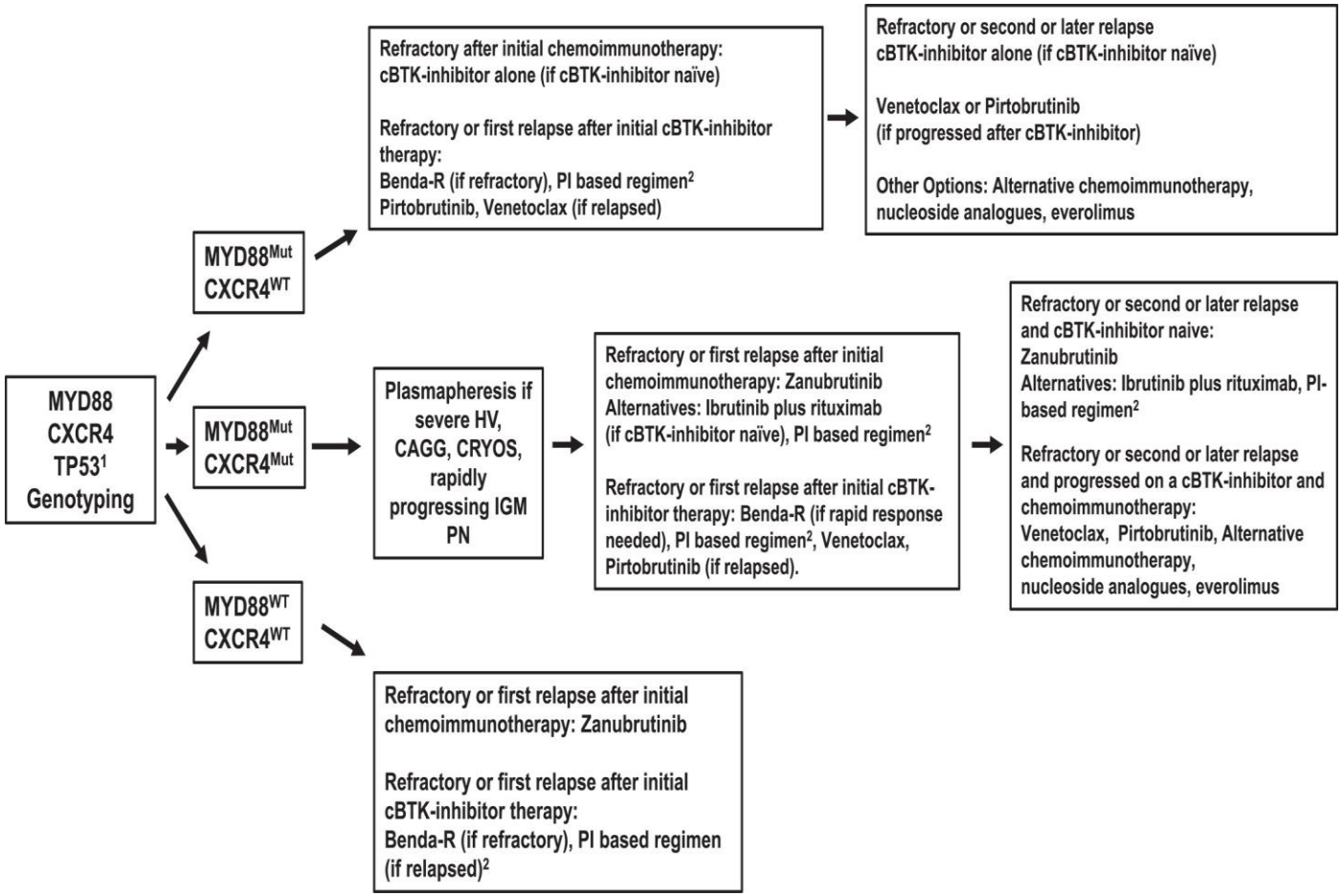
Waldenström Macroglobulinemia: 2025 Update on Diagnosis, Risk Stratification, and Management- 2nd or later relapse



[1]Bulky (≥5 cm max. diameter) or symptomatic lymphadenopathy, clinically significant cytopenias (hemoglobin ≤10 g/dL; platelet count <100x10^9/L), hyperviscosity-related symptoms or constitutional symptoms.
[2]If symptomatic hyperviscosity suspected, measure baseline serum viscosity, perform fundoscopic examination and initiate plasmapheresis followed by therapy; alternatively, may directly proceed to therapy, but omit rituximab for 1-2 cycles to avoid IgM flare induced worsening of symptoms.
[3] Until progression or unacceptable toxicity
[4]BDR consists of a single 21-day cycle of bortezomib alone (1.3 mg/m2 subcutaneously on days 1, 8, and 15), followed by weekly subcutaneous bortezomib (1.6 mg/m2 on days 1, 8, 15, and 22) for 4 additional 35-day cycles, with IV dexamethasone (40 mg) and IV rituximab (375 mg/m2) on cycles 2 and 5, for a total treatment duration of 23 weeks.). Use only in the absence of peripheral neuropathy or if preexisting peripheral neuropathy < Grade 2.
[5]May consider autologous stem cell transplantation (ASCT) as an option if not exercised previously for a fit patient with chemosensitive disease or concurrent AHL amyloidosis.
[6]May consider repeating original fixed-duration chemoimmunotherapy if durable response obtained previously (time-to-previous therapy ≥4 years) and patient not a candidate for a BTK inhibitor. Purine analog-based regimens and everolimus are effective, but owing to their side effects, are best reserved for patients without alternatives.

American J Hematol, Volume: 100, Issue: 6, Pages: 1061-1073, First published: 17 March 2025, DOI: (10.1002/ajh.27666)

Management of R/R Waldenstrom's Macroglobulinemia



Hematological Oncology, Volume: 43, Issue: S2, First published: 15 June 2025, DOI: (10.1002/hon.70071)

Non-covalent BTKi

- Virtually all patients eventually discontinue cBTKi, either d/t side effects or acquired resistance (most common: c481)
- The non-covalent BTKi pirtobrutinib shows promising efficacy and safety in patients with B-cell malignancies, including those previously exposed to cBTK (BRUIN study)
- The WM cohort in the BRUIN study includes 80 patients (63 BTKi exposed) with a median f/u of 22 months (and counting)
  - ORR 88% (BTKi naïve); 78% (BTKi exposed)
  - Major response 88% (BTKi naïve); 67% (BTKi exposed)
- Median PFS 22 months

Venetoclax

- Phase II trial: Venetoclax (800 mg QD for 2 years) used in relapsed/refractory WM.
- Overall response rate (ORR): 84%
- Major responses (PR/VGPR): 81%, with VGPR in 19% of patients
- Median progression-free survival: 30 months
- Effective regardless of CXCR4 mutation status

Castillo et al. DOI: 10.1182/bloodadvances.2025016890

בחזרה למטופלת הנשכחת

- החלה טיפול בפרוטוקול DRC
- השיגה PR
- מאז בהפוגה (מעל 4 שנים)

WM- take home massages

- An indolent disease
- Look for IGM-related complications, and CNS involvement
- Do no harm!
- 1st line: Choice between fixed duration chemo-immunotherapy to continuous BTKi

תודה על ההקשבה

ובהצלחה במבחן !