HIGHLIGHTS IN EMATOLOGIA

TREVISO
7-8 NOVEMBRE 2025

Update sulla Macroglobulinemia di Waldenström

Francesco Piazza, MD
Dipartimento di Medicina – Università degli Studi di Padova
UOC di Ematologia – Azienda Ospedale Università Padova

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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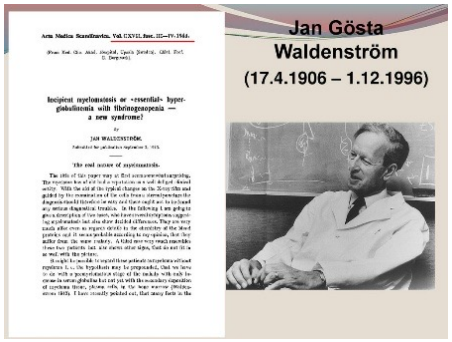
Roche			+			+	+
Kite Gilead	+		+			+	+
Takeda							
Janssen			+			+	+
Bejgene							+
Incyte			+			+	+



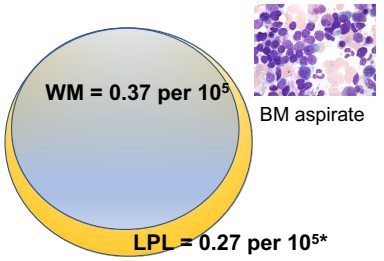
Clinicopathological Definition of Waldenstrom's Macroglobulinemia: Consensus Panel Recommendations From the Second International Workshop on Waldenstrom's Macroglobulinemia

Roger G. Owen, Steven P. Treon, Ayad Al-Katib, Rafael Fonseca, Philip R. Greipp, Mary L. McMaster, Enrica Morra, Gerassimos A. Pangalis, Jesus F. San Miguel, Andrew R. Branagan, and Meletios A. Dimopoulos

«WM is an **uncommon** B-cell lymphoproliferative disorder characterized primarily by **bone marrow infiltration** with a predominately intertrabecular pattern along with demonstration of an **IgM monoclonal gammopathy**.»

«The concentration of IgM varies widely in WM and **it is not possible to define a concentration** that reliably distinguishes WM from MGUS and other lymphoproliferative disorders.»

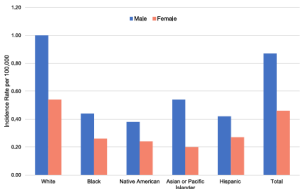
IgM MC + lymphoplasmacytic cells in the BM = WM



BM aspirate

*SEER data

Pathology series show WM 95% of cases of LPL



Male/female = 1.5:1 across ethnic groups

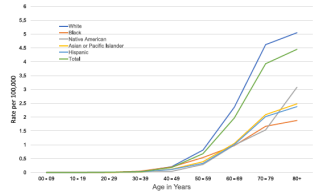


Fig. 2b. Incidence rates of WM and LPL by Race and Ethnicity and Age at Diagnosis in the USA, 2000-2019 SEER Program. White, Black, Native American and Asian or Pacific Islander groups include non-Hispanic ethnicity only. Hispanic group contains all races with Hispanic ethnicity. The Native American group contains both American Indians and Alaskan Natives. Asian or Pacific Islander subgroups were too small to permit subset analysis. Data computed as described in Figure 1.

Median age: 71 years

Alaggio R. et al., Leukemia 2022,
Campo E. et al., Blood 2022,
Treon SP et al., IWWM-11 2023

WHO HEM5 2022

LPL if clonal lymphoplasmacytic aggregates represents ≥ 10% of BM cellularity.

Two subtypes of lymphoplasmacytic lymphoma (LPL)

1) **IgM-LPL/ Waldenström Macroglobulinaemia (WM) type**.
2) **Non-WM type LPL** represents around 5% of LPL and includes:

(a) cases with IgG or IgA monoclonal proteins
(b) non-secretory LPL
(c) IgM LPL without bone marrow involvement

ICC 2022

LPL if abnormal lymphoplasmacytic aggregates in the bone marrow and evidence of clonal B cells and plasma cells, **even when the aggregates represent <10% of BM cellularity of the trephine biopsy**

IgM MGUS = IgM paraprotein with <10% bone marrow plasma cells and **lacking lymphoplasmacytic B-cell aggregates sufficient for a diagnosis of LPL**

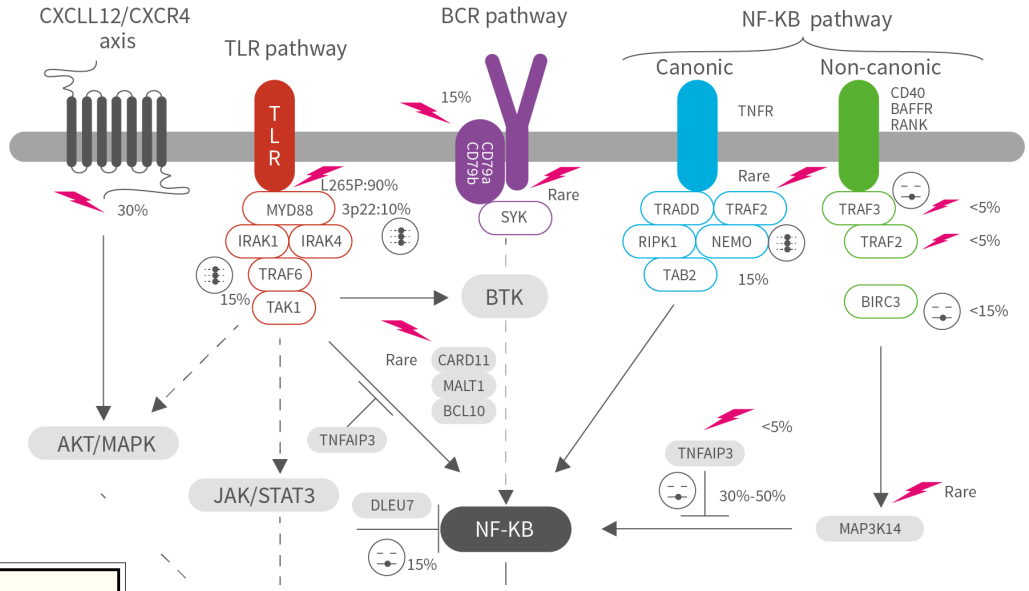
Two subtypes of IgM MGUS are now further distinguished:

- **IgM MGUS, plasma cell type** (no clonal lymphocytes, no MYD88 mut; IGH::CCND1 or other myeloma associated IGH rearrangements may be present).
- **IgM MGUS, not otherwise specified**

WM: Pathobiology

Cytogenetic abnormalities:
- **Del 6q** in 25-50% negatively affects time to transformation and survival
- **t(9;14)(p13.2;q32.33)** in up to 50% but it needs validation
- **Trisomy 4** in 20%
- **del17p** 7-15% associated with poor prognosis

Gene mutations:
- **Somatic Hypermutations partial usage of IGHV**
- **ARID1A** in 17% possible association with more advanced disease
- **CD79B** 8-15% possible association with transformation
- **TP53** <10% it needs further studies
- **TERT** worse outcome
- Less frequent mutations like **KMTD2 e MYBBP1A**
- **MYD88** in **up to 95%** of patients
- **CXCR4** in **up to 40%** of patients



The NEW ENGLAND JOURNAL of MEDICINE

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.

LYMPHOID NEOPLASIA

A multiomic analysis of Waldenström macroglobulinemia defines distinct disease subtypes

Dylan C. Gagler,[1,*] Hussein Ghamlouch,[1-3,*] Di Zhang,[1] Patrick Blaney,[1] Avital Tenenbaum,[1] James Langton,[1] Marine Armand,[4-6] Alexandre Eeckhoutte,[4] Amina Joudat,[4] Michaël Degaud,[4] Michela Esposito,[4] Gaurav Varma,[1] Yubao Wang,[1] Sanghoon Lee,[1] Sanxiong Liu,[1] Oscar Lahoud,[1] David Kaminetzky,[1] Marc Braunstein,[1] Louis Williams,[7] Florence Nguyen-Khac,[5,6] Brian Walker,[8] Damien Roos-Weil,[5,6,9] Faith E. Davies,[1] Olivier A. Bernard,[4] and Gareth J. Morgan[1]

Memory B cell like (MBC-like)

- Expanded population of MBCs blocked in their capacity to differentiate beyond the MBC stage.

1
- Peculiar IHC: CD24^{+}, CD74^{+}
- Most of CXCR4, HIST1H1E, MAP3K14 mutations; overall higher mutational burden
- Del(13q) more prevalent
- Diminished NF-kB signaling
- Upregulation of BCR signaling

2
- Greater circulating IgM levels
- Greater splenic enlargement
- Less adenopathy
- Elevated LDH

Plasma cell like (PC like)

Partial differentiation toward a PC

- Peculiar IHC: CD38^{+}, CD138^{+}, CD27^{+}, FCRL5^{+}
- SP140^{mut} esclusive of this subtype; overall lower mutational burden
- Del(6q) more prevalent
- Enhanced NF-kB signaling

- Higher platelet count
- Lymph node enlargement

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Mututation
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Mutation

Gagler DC et al. Blood 2025

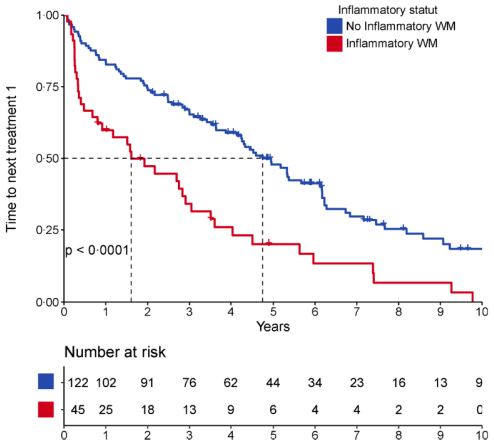
Inflammatory WM (IWM)

- Retrospective analysis of WM patients seen in a single tertiary referral centre from January 2007 to May 2021
- Excluded aetiologies for the inflammatory syndrome using a pertinent blood workup, including C-reactive protein (CRP), and imaging
- Results: **67 (28%) IWM**, 166 (68%) non-IWM, and 9 (4%) WM with inflammatory syndrome of unknown origin.

TABLE 1 Clinical and biological characteristics at treatment initiation of inflammatory and non-inflammatory Waldenström's macroglobulinaemia (WM)

Characteristics	Inflammatory $n = 64$	Non-inflammatory $n = 134$	p
Year of diagnosis, median (range)	2008 (1985–2018)	2010 (1983–2019)	0.25
Age, median (range)	69 (45–94)	72 (37–90)	0.32
Male, *n* (%)	43 (67)	88 (66)	0.83
Adenopathy/hepatosplenomegaly, *n* (%)	21 (33)	40 (30)	0.67
Clinical hyperviscosity, *n* (%)	3 (5)	22 (16)	**0.02**
Monoclonal IgM, g/l, median (range)	24.9 (4.8–77.3)	23.0 (1.1–61.5)	0.28
Haemoglobin, g/l, median (range)	90 (69–139)	99 (51–148)	**<0.01**
Platelet count, $\times 10^9$/l, median (range)	245 (18–513)	196 (11–884)	**<0.01**
C-reactive protein, mg/l, median (IQR)	43 (26–67)	6 (3–10)	**<0.0001**
Serum albumin, g/l, median (range)	30.8 (20.0–42.9)	35.9 (22.2–47.6)	**<0.0001**
Fibrinogen, g/l, median (range)	5.0 (2.5–7.7)	3.7 (1.4–6.4)	**<0.0001**
LDH, U/l (ULN < 225 iu/l), median (range)	147 (87–277)	162 (76–977)	0.06

Abbreviations: IQR, interquartile range; LDH, lactate dehydrogenase; UPN, upper limit of normal.
Bold value for $p < 0.05$ (that means statistically significant).



Overall survivals (OS) were similar (median OS: 17 vs 20 years; p = 0.11) but **time to next treatment (TNT) was significantly shorter for IWM** (TNT1: 1.6 vs 4.8 years, p < 0.0001). IWM mostly shared the same presentation and outcome as WM without inflammatory syndrome.

Elessa D BJH 2022

Inflammation in Waldenström macroglobulinemia is associated with 6q deletion and need for treatment initiation

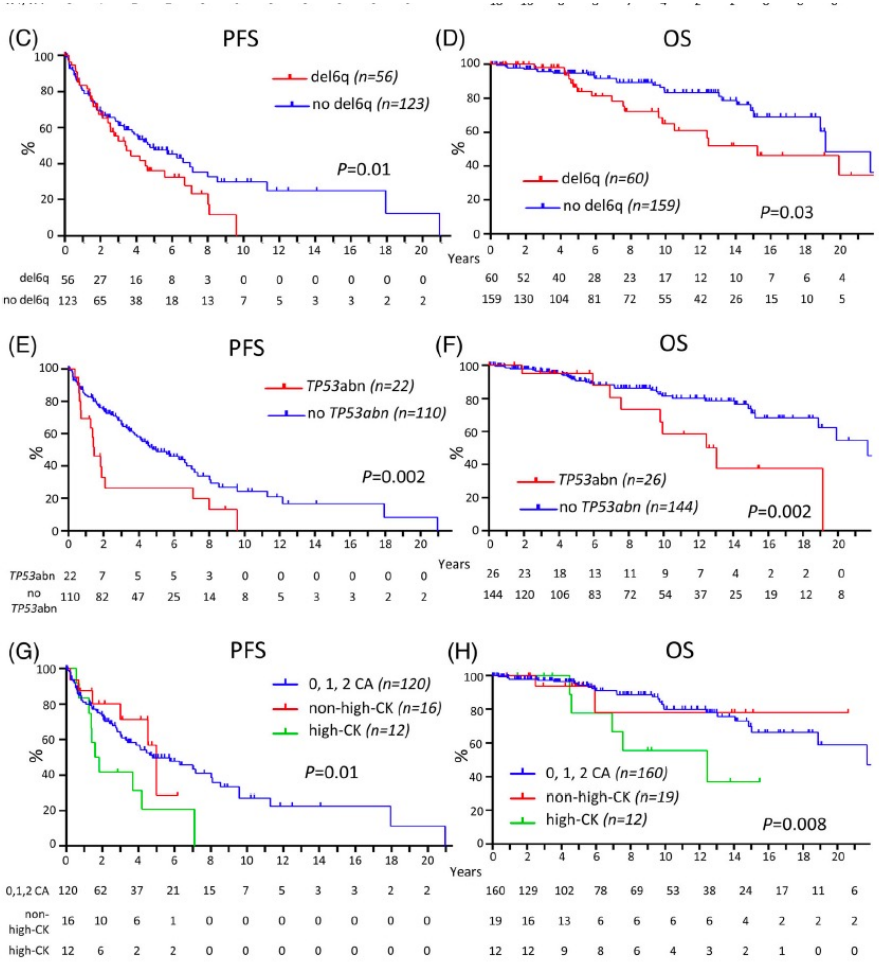
Table 1. Patients characteristics associated with inflammatory status

	Univariate			Multivariate	
	Non-Inflammatory WM (n=103)	**Inflammatory WM** (n=119)	*P*	OR[95CI]	*P*
Clinical data					
Age at diagnosis (years), *mean [range]*	64.3 [28.4-86.6]	64.6 [35.1-88.2]	1.00		
Male, *n (%)*	61/103 (59)	86/119 (72)	0.77		
Lymphadenopathies, *n (%)*	14/101 (14)	38/118 (32)	**0.04**	2.2[0.7-8.0]	0.21
Splenomegaly, *n (%)*	8/100 (8)	17/118 (14)	1.00		
Hyperviscosity syndrome, *n (%)*	6/101 (6)	10/118 (9)	1.00		
Past history of dysimmune conditions, *n (%)*	11/92 (12)	6/110 (5)	1.00		
Biological data					
M spike (g/L), *mean [range]*	16.0 [0.1-71.0]	17.8 [1.0-58.0]	1.00		
Anaemia (< 11.5 g/dL), *n (%)*	31/66 (47)	75/101 (74)	**$<10^{-2}$**	1.6[0.6-4.4]	0.32
Thrombocytopenia (< 100 G/L), *n (%)*	9/66 (14)	15/100 (15)	1.00		
Medullar infiltration (%), *mean [range]*	43 [10-97]	33 [10-95]	0.16		
CRP (mg/L), *mean [range]*	0.4 [0-4.4]	30.9 [5.0-263.0]	NR		
Albumin (g/L), *mean [range]*	40.4 [31.0-50.5]	36.3 [15.0-45.6]	**$<10^{-5}$**	**0.8[0.7-0.9]**	**$<10^{-2}$**
β2 microglobulin (mg/L), *mean [range]*	2.5 [1.2-12.0]	3.9 [1.5-33]	0.07		
IPSSWM: low; intermediate; high, *n (%)*	18/56 (32); 16/56 (29); 22/56 (39)	14/85 (16); 23/85 (27); 48/85 (56)	1.00		
Cytogenetic/molecular biology					
6q deletion, *n (%)*	8/74 (11)	41/104 (39)	**$<10^{-3}$**	**4.4[1.4-16.0]**	**0.02**
TP53 abnormalities, *n (%)*	6/79 (8)	14/111 (13)	1.00		
Complex karyotype, n (%)	9/68 (13)	18/91 (20)	1.00		
MYD88 mutation, *n (%)*	65/71 (92)	83/93 (89)	1.00		
CXCR4 mutation, *n (%)*	18/66 (27)	19/91 (21)	1.00		
Follow-up					
Need for treatment initiation, *n (%)*	66/103 (64)	101/119 (85)	**$<10^{-2}$**	**NA**	
ORR*, *n (%)*; VGPR+CR, *n (%)*	38/64 (59); 12/64 (19)	61/96 (64); 20/96 (21)	1.00		
CRP after 1L treatment (mg/L), *mean [range]*	1.0 [0-16]	5.5 [0-69]	0.08		

**ORR=CR+VGPR+PR. Abbreviations: OR, Odds Ratio ; CI, Confidence Interval; ORR, Overall Response Rate; VGPR, Very Good Partial Response; CR, Complete Response; 1L, fist-line; P, p-value; PR, Partial Reponse; DLBCL, Diffuse Large B Cell Lymphoma ; IPSSWM, International Prognostic Scoring System of WM. Subgroup comparisons were performed using Chi-square of Fisher's exact test for categorical variables, and Student's t test for continuous variables. Multiple hypothesis correction was performed with Holm's method for univariate analysis. A multivariate logistic regression was performed for multivariate analysis.*

- Eighty-three percent of del6q patients had CRP values ≥ 5 mg/L compared to 49% non-del6q WM patients.
- In multivariate analysis, only del6q (p=0.02) and albumin (p<10-2) were found to be significantly associated with inflammatory status, whereas lymphadenopathies and anaemia were not (Table 1).

Updated Data on Impact of Cytogenetic Abnormalities



Del6q

TP53 abnormalities

Complex Karyotype

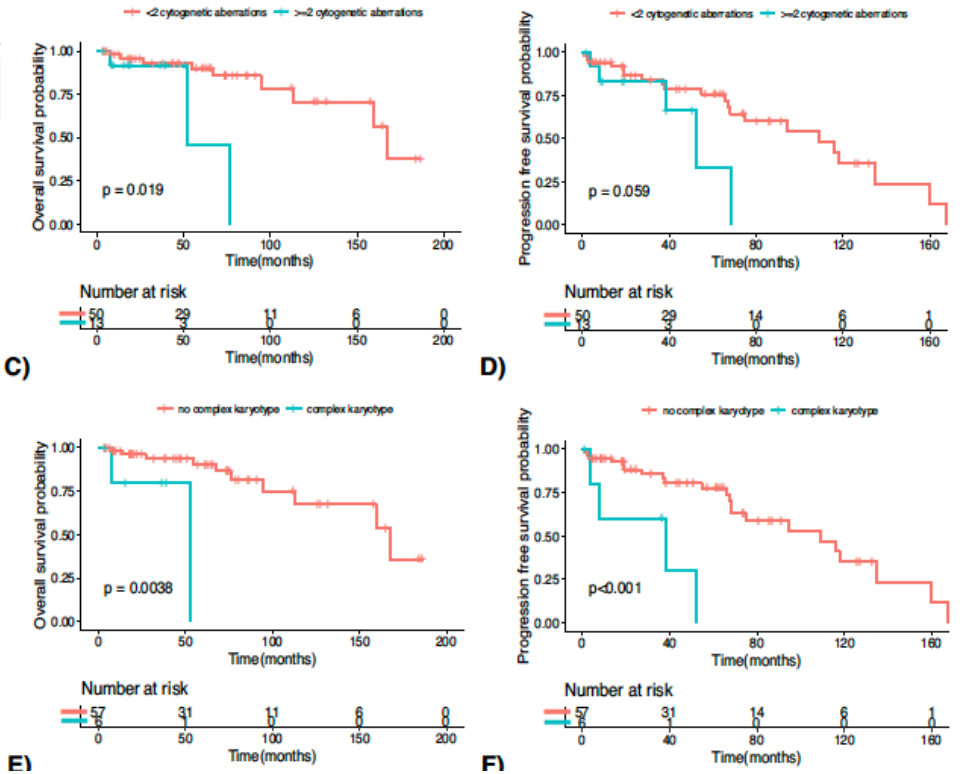
Krzisch D et al AJH 2021

Annals of Hematology
https://doi.org/10.1007/s00277-024-05770-4

RESEARCH

Impact of the presence and number of chromosomal abnormalities on the clinical outcome in Waldenström Macroglobulinemia: a monocentric experience

Nicolò Danesin[1] · Laura Bonaldi[2] · Annalisa Martines[2] · Silvia Nalio[2] · Roberta Bertorelle[2] · Sofia Compagno[2] · Raffaella Marcato[2] · Sabrina Manni[1,3] · Federico Scarmozzino[4] · Marco Pizzi[4] · Angelo Paolo Dei Tos[4] · Alessandro Cellini[1] · Greta Scapinello[1] · Andrea Visentin[1] · Livio Trentin[1] · Francesco Piazza[1,3]



Coorte 2000-2023
N=207
Cariotipo in 85
Analisi in 64

Table 4 Overall and progression free survival outcomes according to the karyotype

Subgroups	Median OS (months)	HR (CI 95%)	P value	Median PFS (months)	HR (CI 95%)	P value
Normal karyotype	76.1	4.35 (1.27–14.86)	0.01	65.8	2.90 (1.24–6.83)	0.01
Abnormal karyotype	167.7			117.8		
≥ 2 cytogenetic aberrations	52.3	5.28 (1.15–24.31)	0.02	52.3	2.69 (0.92–7.81)	0.06
< 2 cytogenetic aberrations	167.7			108.9		
Complex karyotype	52.3	9.14 (1.56–26.11)	0.004	38.6	6.05 (1.85–19.79)	< 0.001
No complex karyotype	167.7			108.9		

HR = Hazard Ratio; *CI* 95% = 95% confidence interval; *OS* = Overall Survival; *PFS* = Progression Free Survival

Danesin N et al. Ann Hematol 2024.

WM treatment

Chemo-Immunotherapy in Frontline WM: CR is rare!

Regimen	Overall response rate	Complete response	Median Progression Free Survival (months)
Rituximab x 4	25-30%	0-5%	13
Rituximab x 8	40-45%	0-5%	16-22
Rituximab/IMIDs	70%	5%	30
Rituximab/Cyclophosphamide/Dex	70-80%	5-15%	30-36
Rituximab/Nuceloside Analogues	70-90%	5-15%	36-62
Rituximab/Proteasome Inhibitors	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, Lancet Oncol 2016; 17:57-66.

Chemo-Immunotherapy in Frontline WM: be careful!

Agent	WM Toxicities
Rituximab	• **IgM flare (40-60%)->** Hyperviscosity crisis, Aggravation of IgM related PN, CAGG, Cryos. • Hypogammaglobulinemia-> infections, IVIG • Intolerance (10-15%)
Fludarabine	• Hypogammaglobulinemia-> infections, IVIG • **Transformation, AML/MDS (15%)**
Bendamustine	• Prolonged neutropenia, thrombocytopenia (especially after fludarabine) • **AML/MDS (5-8%)**
Bortezomib	• **Grade 2+3 Peripheral neuropathy (60-70%);** High discontinuation (20-60%)

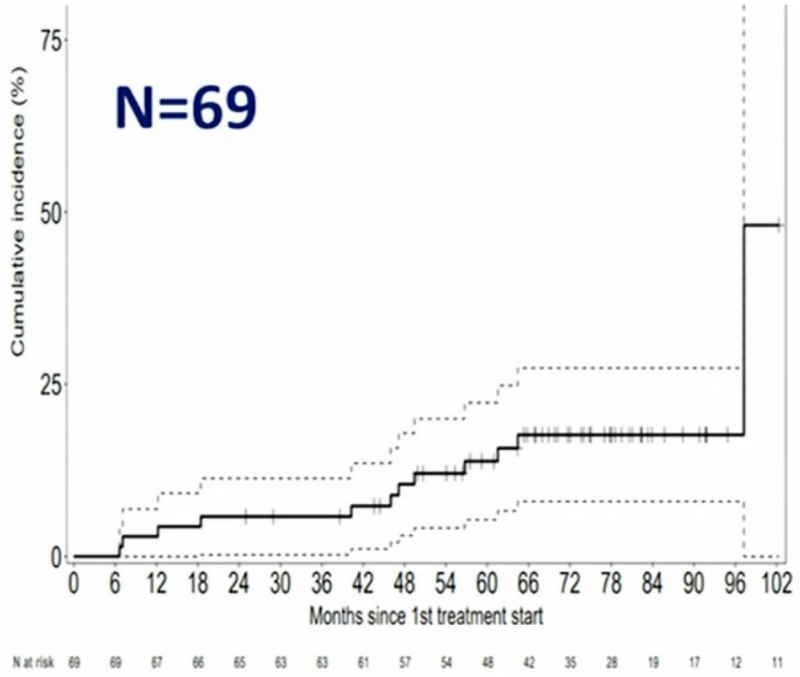
Treon et al, Blood 2015 126:721-732; Treon et al, JCO 2020; 38:1198-1208.

Response	N	%

Type of Cytopenia	N	%	Duration (median)
Neutropenia	26	38%	9m (3-24)
Anemia	17	25%	6m (3-36)
Thrombocytopenia	11	16%	9m (3-36)

- **Long–lasting cytopenia 35 pts (51%)**

- **Second malignancies: 12 patients (17.66%)**
  - 9 solid tumors (2 pancreas , 2 gastric, 1 colic, 1 oesophagus 1 lung, 1 skin, 1 breast)
  - 3 MDS with 2 AML



Cumulative incidence of second malignancies of 17.66% [7.99-27.64] at 66 months.

Leblond et al, IWWM-12, 2024

1L therapy: BTKi for patients not suitable for CIT

Study	Cohort	Agent (s)	N=	Time to Major Resp.	ORR/Major RR	≥VGPR	PFS
Pivotal Study	R/R	Ibrutinib	63	2 mo.	91% / 79%	30%	54% @ 60 mo.
Phase 2	TN	Ibrutinib	30	1.9 mo.	100% / 87%	30%	76% @ 48 mo.
INNOVATE Arms A, B	TN, R/R	Ibrutinib Rituximab	150	3 mo.	92% / 76%	31%	68% @ 54 mo.
Phase 2	TN, R/R	Zanubrutinib	77	2.8 mo.	96% / 82%	45%	76% @ 36 mo.
ASPEN-1 ($MYD88^{Mut}$)	TN, R/R	Ibrutinib	99	2.9 mo.	94% / 80%	25%	85% @ 42 mo.
	TN, R/R	Zanubrutinib	102	2.8 mo.	95% / 81%	36%	88% @ 42 mo.
ASPEN-2 ($MYD88^{WT}$)	TN, R/R	Zanubrutinib	28	3 mo.	78% / 63%	27%	84% @ 42 mo.
Phase 2	TN, R/R	Acalabrutinib	106	N/A	94% / 81%	39%	84% TN / 52% R/R (@ 66 mo.)
Phase 2	TN, R/R	Tirabrutinib	27	1.9 TN 2.1 R/R	96% / 93%	33%	93% @ 24 mo.

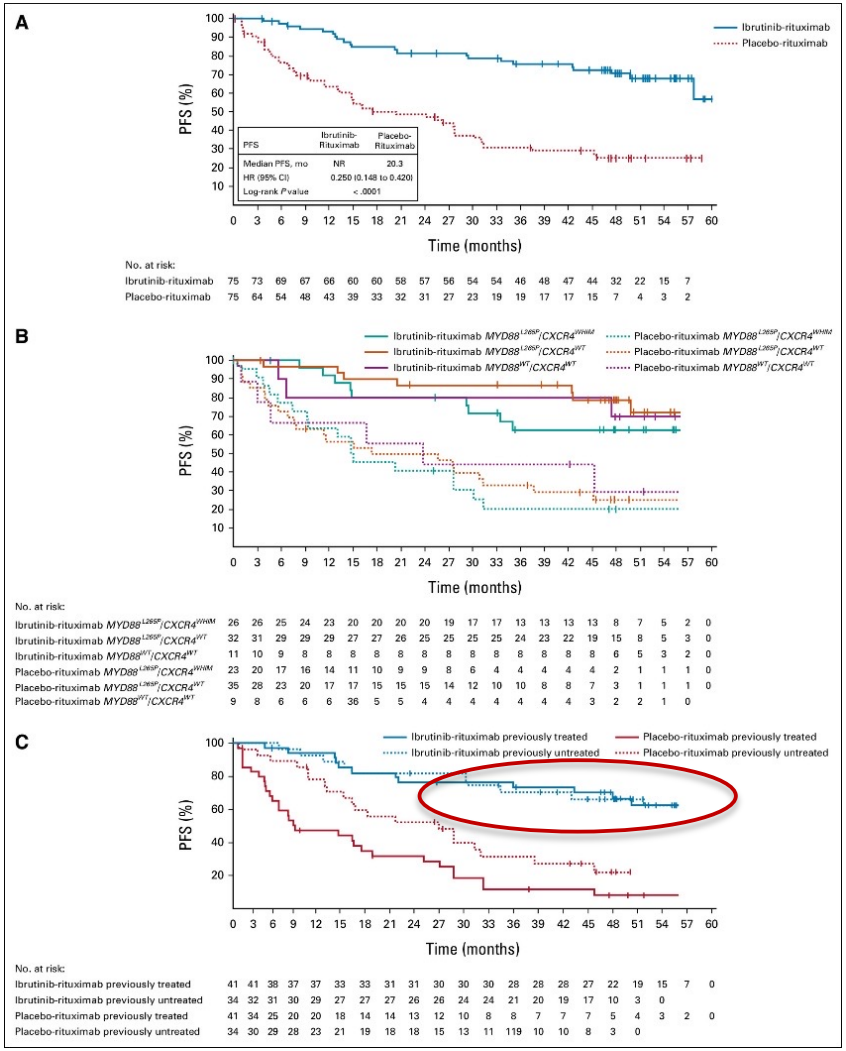
Median ORR 93%; MajorRR 81%; >=VGPR 30%; PFS 76% @4yrs

BTKi impact of the CXCR4 mutation

Study	Patient Population	Agent (s)	Time to Major Response ($CXCR^{Mut\ vs.\ WT}$)	Major Response Rate ($CXCR^{Mut\ vs.\ WT}$)	≥VGPR ($CXCR^{Mut\ vs.\ WT}$)	PFS ($CXCR^{Mut\ vs.\ WT}$)
$CXCR4^{Mut}$ vs $CXCR4^{WT}$						
Median Time to Major Response: (4.2 vs. 1.9 mos)						
Median Major RR: 71% vs. 87%						
Median ≥VGPR: 14% vs. 41%						
PFS: 59% vs. 75% @4 years						
						(@ 42 mo.)
ASPEN Cohort 1	TN, R/R	Ibrutinib	6.6 vs. 2.8 mos.	65% vs. 82%	10% vs. 24%	49% vs. 75% (@ 42 mo.)
	TN, R/R	Zanubrutinib	3.4 vs. 2.8 mos.	70% vs. 82%	18% vs. 34%	73% vs. 81% (@ 42 mo.)

- median PFS was not reached with **Ibrutinib-Rituximab vs Rituximab** alone, **HR. 0.25, p < 0.0001** so meeting the primary endpoint.
- The **benefit** was **regardless MYD88/CXCR4** mutational status, prior tx and key patient characteristics.

Same efficacy in untreated or previously treated



Buske C et al JCO 2022

1L therapy:
New proposals:

- Acala BR (studio BRAWN)
- Zanu BR (studio cinese)
- Bor-Ibr-R + maintenance Ibr + R (studio ECWM – Prof. C. Buske)
- Carlfilzomib + Ibrutinib versus Ibrutinib
- Ibrutinib + venetoclax

L'IDEA E' DI RENDERE LA RISPOSTA PIU' PROFONDA E DURATURA

1L therapy:
New proposals:

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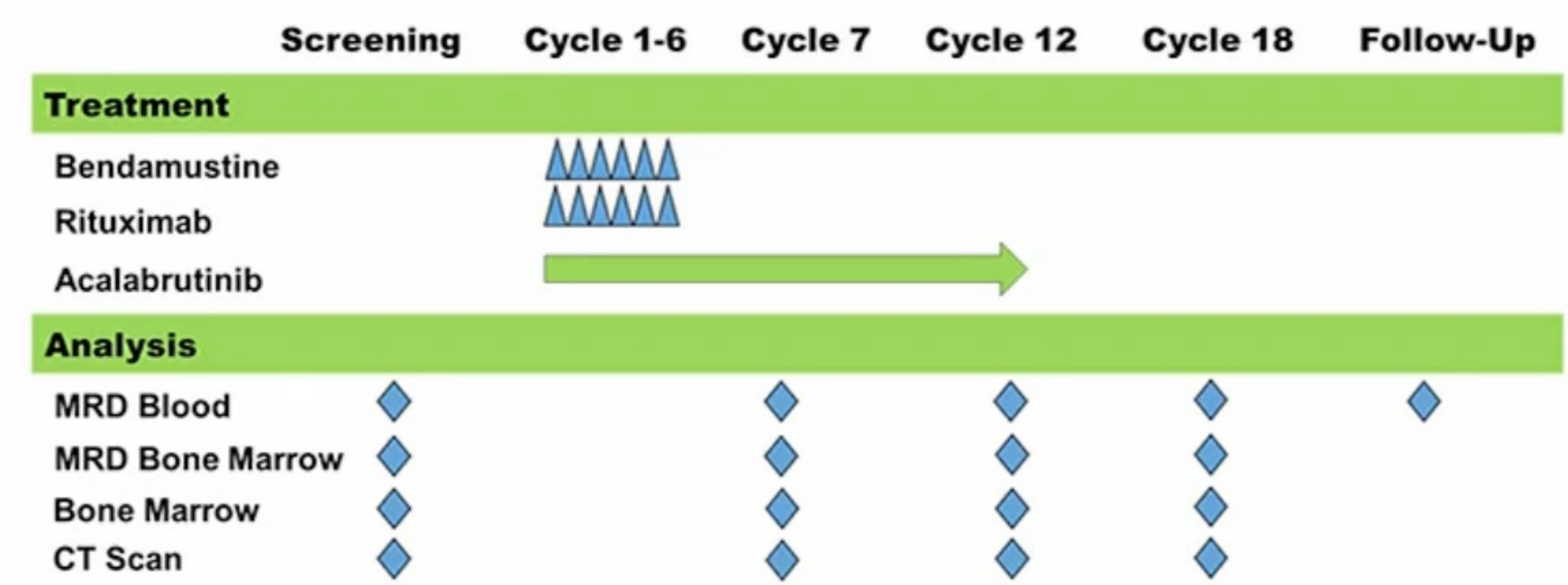
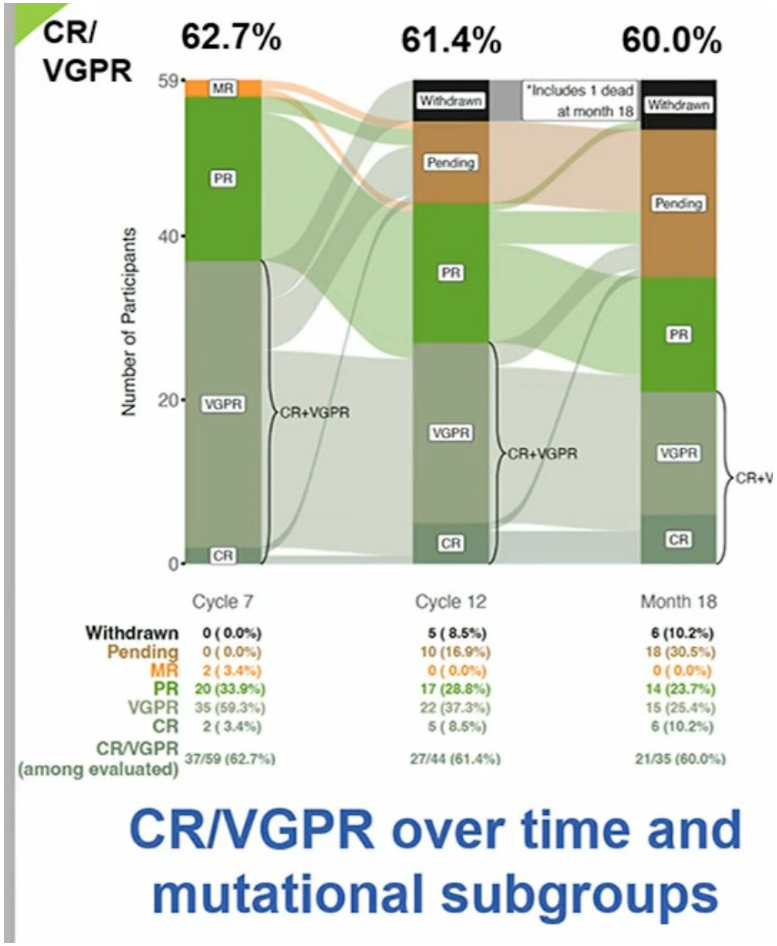
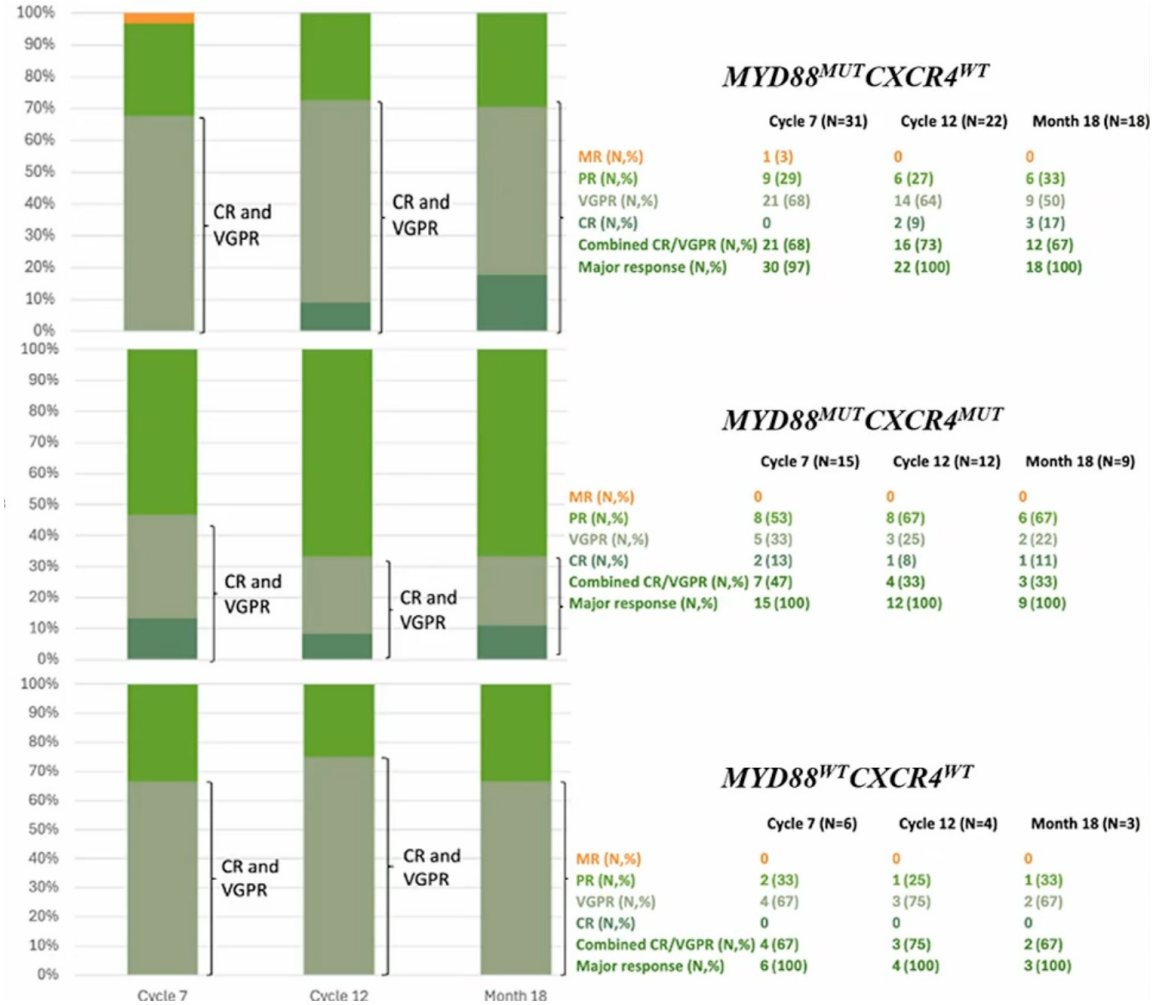


Berenstein N, ICML 2025





$MYD88^{MUT}CXCR4^{WT}$

	Cycle 7 (N=31)	Cycle 12 (N=22)	Month 18 (N=18)
MR (N,%)	1 (3)	0	0
PR (N,%)	9 (29)	6 (27)	6 (33)
VGPR (N,%)	21 (68)	14 (64)	9 (50)
CR (N,%)	0	2 (9)	3 (17)
Combined CR/VGPR (N,%)	21 (68)	16 (73)	12 (67)
Major response (N,%)	30 (97)	22 (100)	18 (100)

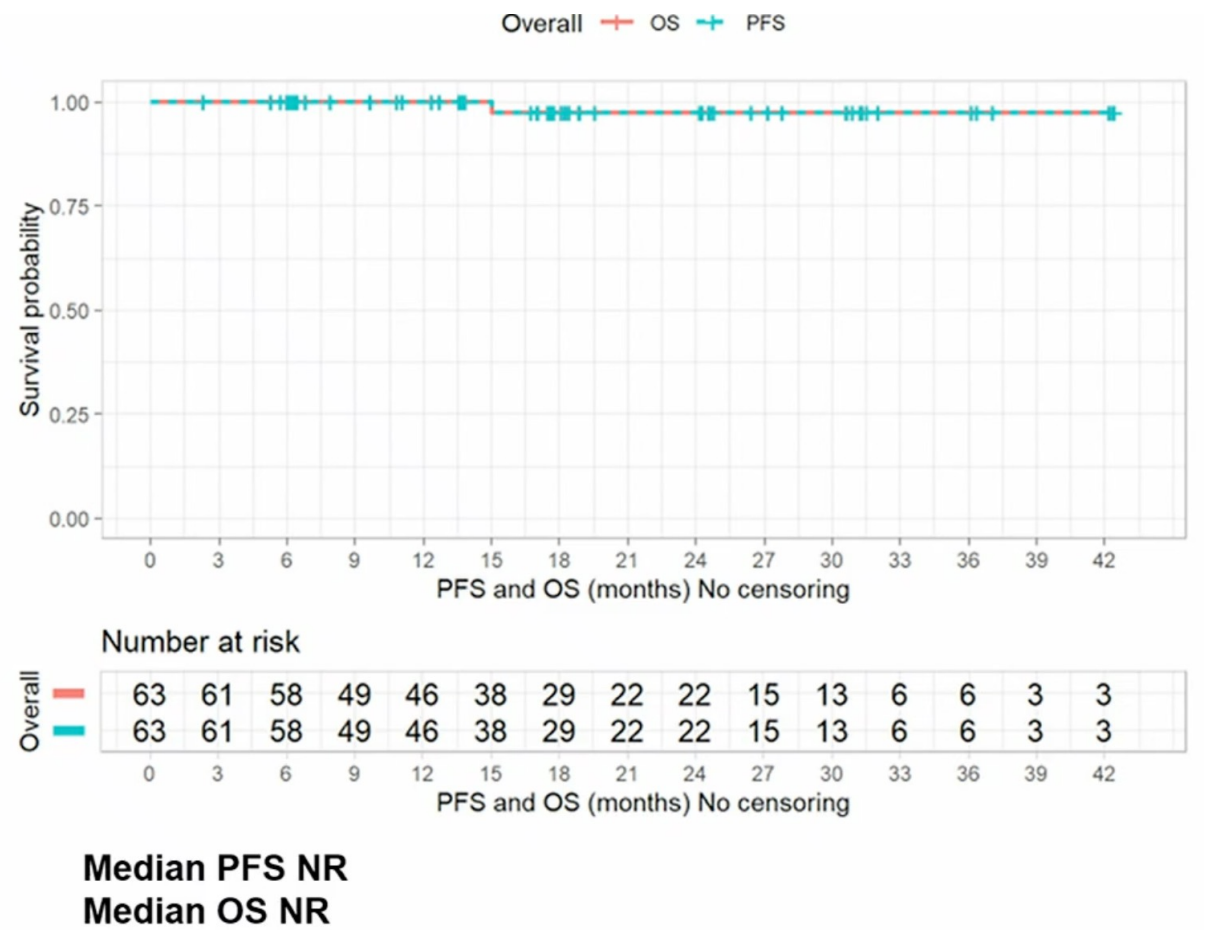
$MYD88^{MUT}CXCR4^{MUT}$

	Cycle 7 (N=15)	Cycle 12 (N=12)	Month 18 (N=9)
MR (N,%)	0	0	0
PR (N,%)	8 (53)	8 (67)	6 (67)
VGPR (N,%)	5 (33)	3 (25)	2 (22)
CR (N,%)	2 (13)	1 (8)	1 (11)
Combined CR/VGPR (N,%)	7 (47)	4 (33)	3 (33)
Major response (N,%)	15 (100)	12 (100)	9 (100)

$MYD88^{WT}CXCR4^{WT}$

	Cycle 7 (N=6)	Cycle 12 (N=4)	Month 18 (N=3)
MR (N,%)	0	0	0
PR (N,%)	2 (33)	1 (25)	1 (33)
VGPR (N,%)	4 (67)	3 (75)	2 (67)
CR (N,%)	0	0	0
Combined CR/VGPR (N,%)	4 (67)	3 (75)	2 (67)
Major response (N,%)	6 (100)	4 (100)	3 (100)

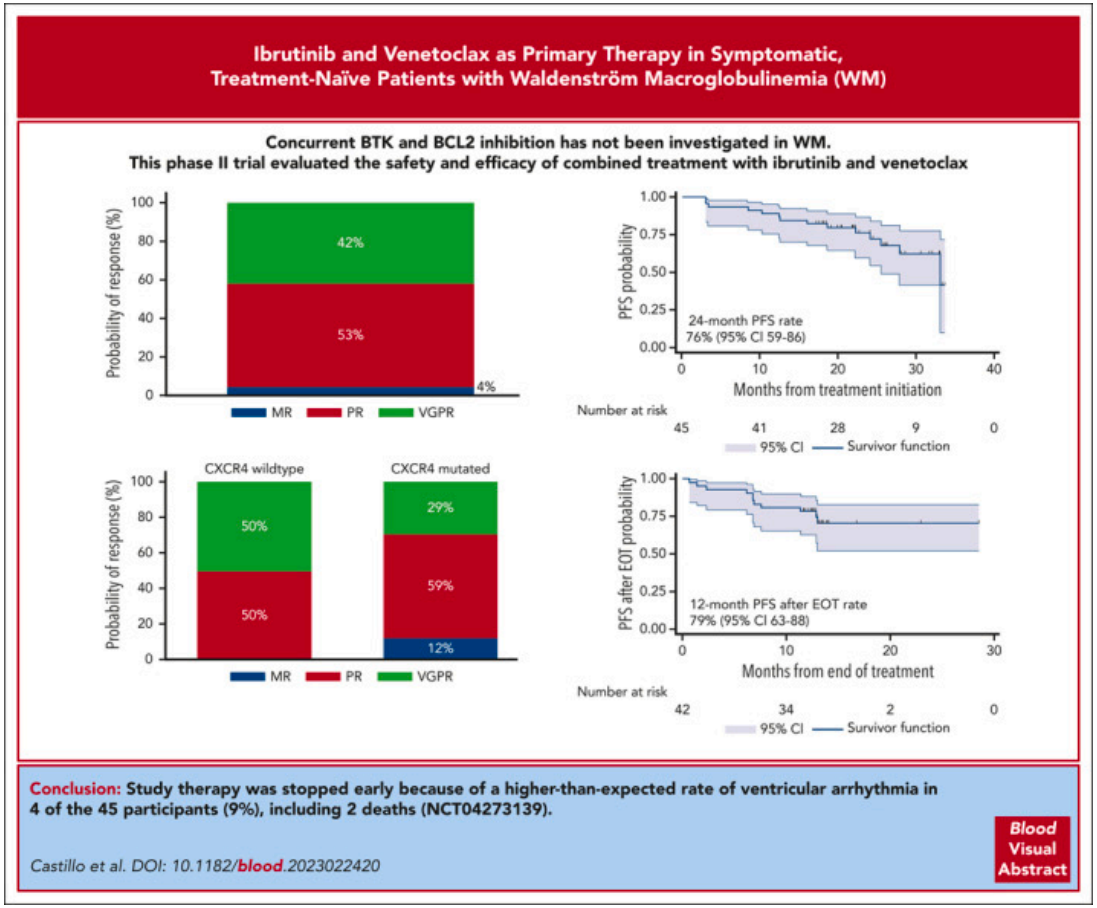
Berenstein N, ICML 2025



Highest VGPR and CR rates Reported for WM

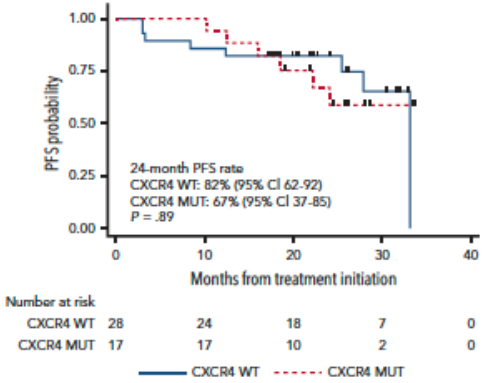
1L therapy:
New proposals:

- Acala BR (studio BRAWN)
- Zanu BR (studio cinese)
- Bor-Ibr-R + maintenance Ibr + R (studio Buske)
- Carlfilzomib + Ibrutinib versus Ibrutinib
- Ibrutinib + venetoclax



- Venetoclax 100mg>200mg>400mg
- ORR 100%(53% PR; 42% VGPR; 4% MR)
- No CR observed
- Grade 5 Ventricular Fib 9%

CXCR4 mutations were associated with a numerically, but not statistically significantly, lower VGPR rate (29% vs 50%) CXCR4 mutations did not impact PFS



Castillo J et al. Blood 2024

1L therapy: does quality of response really matter?

Depth of Response From Fixed-Duration Treatment Is Associated With Superior Survival in Waldenstrom Macroglobulinemia

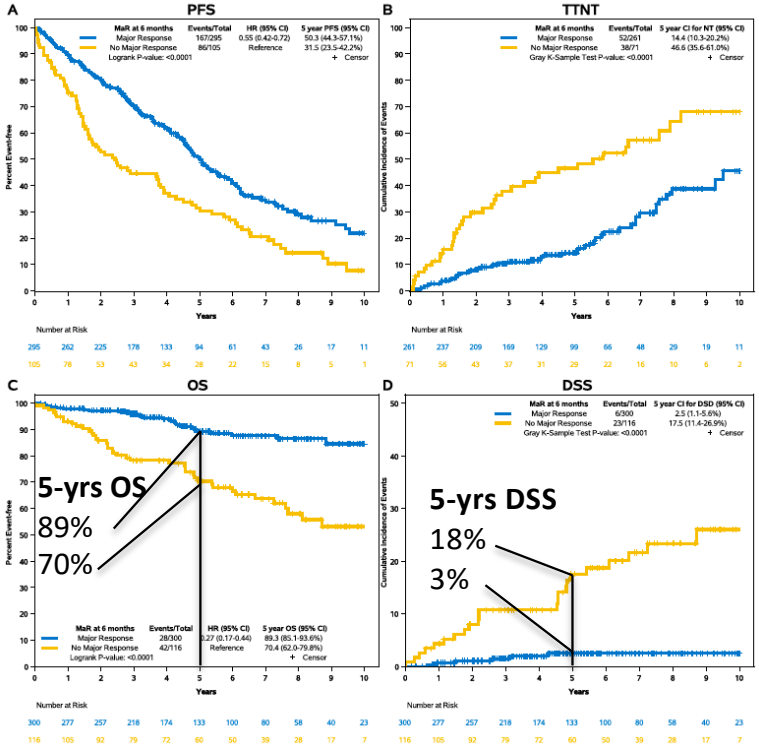
Jonas Paludo[1] | Jithma P. Abeykoon[1] | Nirosha D. Perera[2] | Shayna Sarosiek[3] | Joshua Gustine[4] | Andres Ramirez-Gamero[5] | Marzia Varettoni[6] | Alessandra Tedeschi[7] | Chiara Cavalloni[6] | Anna Maria Frustaci[7] | Levi D. Pederson[8] | Saurabh S. Zanwar[1] | Prashant Kapoor[1] | Thomas M. Habermann[1] | Thomas E. Witzig[1] | Robert A. Kyle[1] | Morie A. Gertz[1] | Susan M. Geyer[8] | Steven P. Treon[3] | Jorge J. Castillo[3] | Stephen M. Ansell[1]

- N = 440 consecutive patiens
- Fixed duration 1L therapy

Treatment regimen	
DRC	224 (51.5%)
BR	133 (30.6%)
BDR	78 (17.9%)
Missing	5

Equal Exposure to Rituximab Maintenance

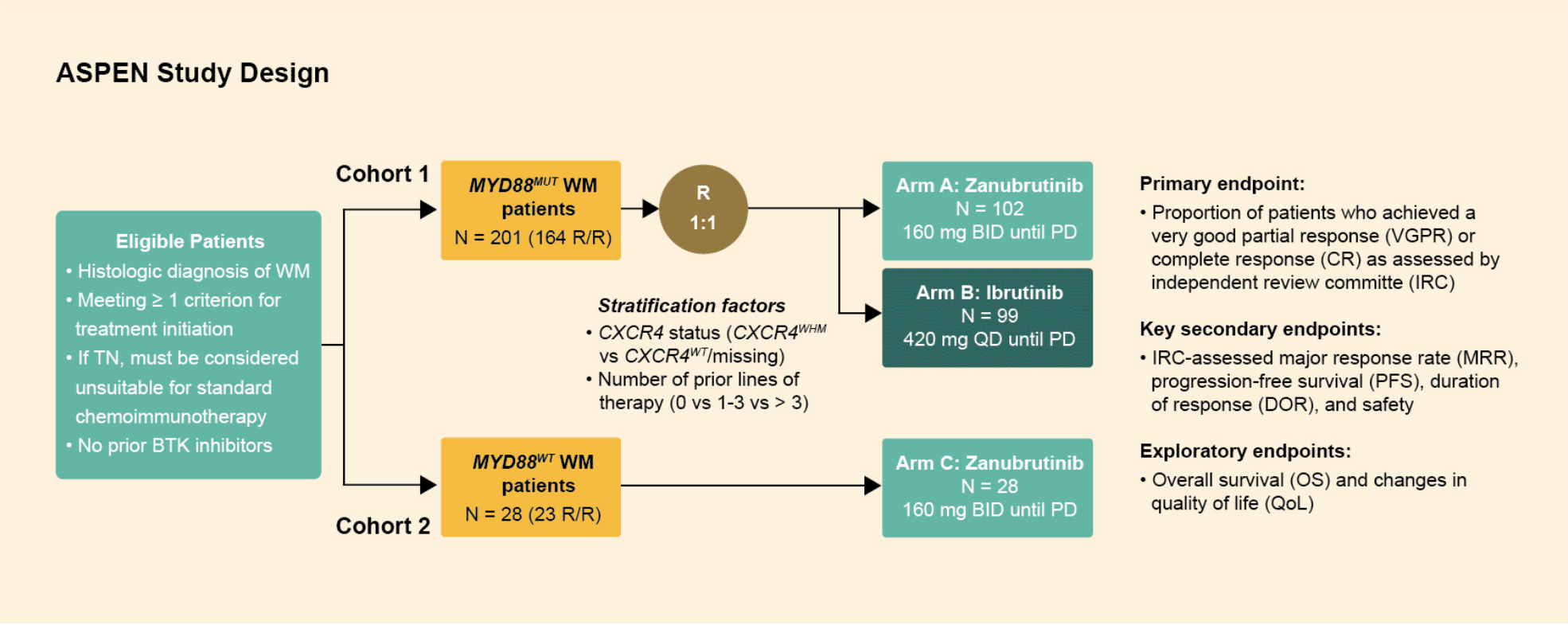
Paludo J et al Am J Hematol 2025



- Lower Disease-Specific deaths
- Major Response (MaR) = PR + VGPR + CR
- PFS and TTNT better in MaR than for < MaR
- VGPR + CR better than PR in TTNT = PFS and OS

Relapsed/Refractory
BTKi studio ASPEN

ASPEN trial

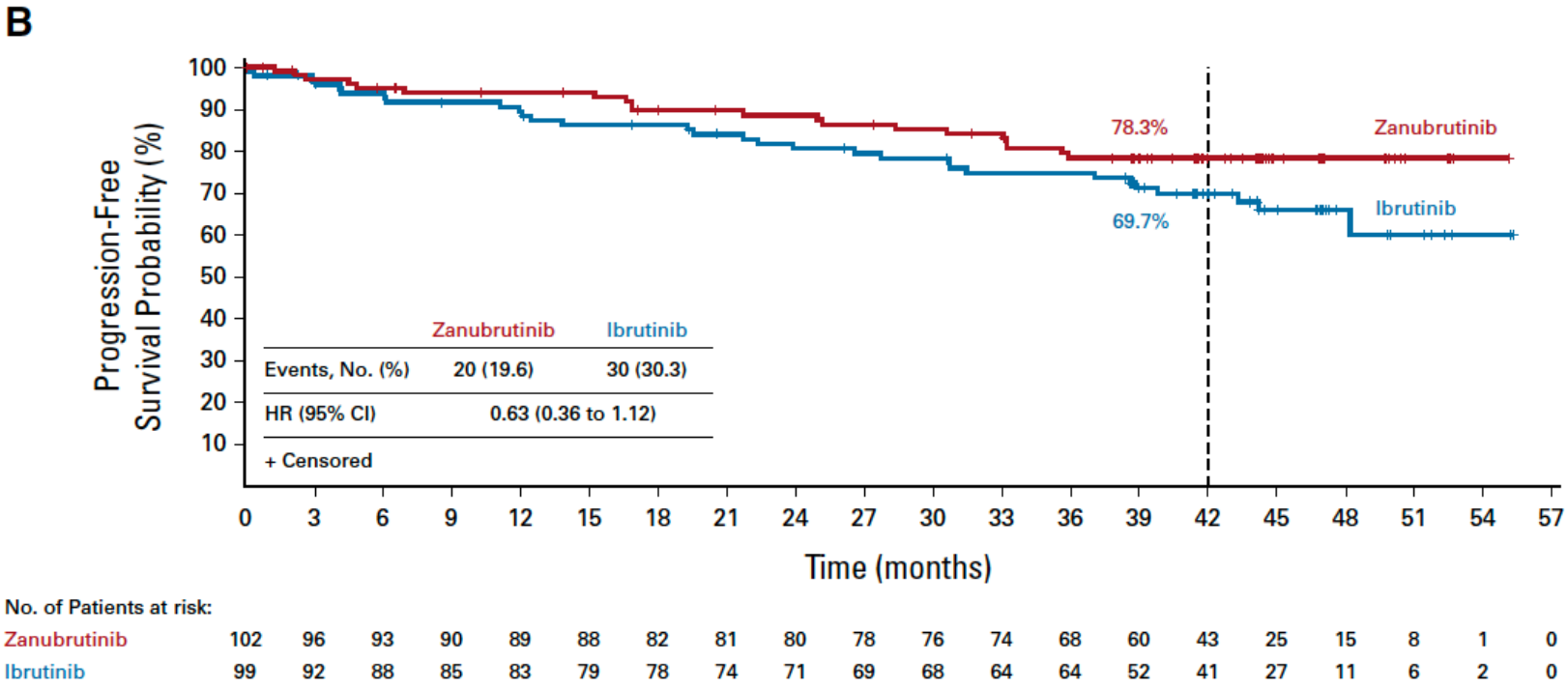


More patients randomly assigned to zanubrutinib than ibrutinib were older than 75 years (33.3% v 22.2%, respectively; P = .084) and had CXC motif chemokine receptor 4 mutation (CXCR4MUT) disease (32.4% v 20.2%, respectively; P = .073).

Tam C et al. Blood 2020; Dimopuolos M et al. JCO 2023

ASPEN trial

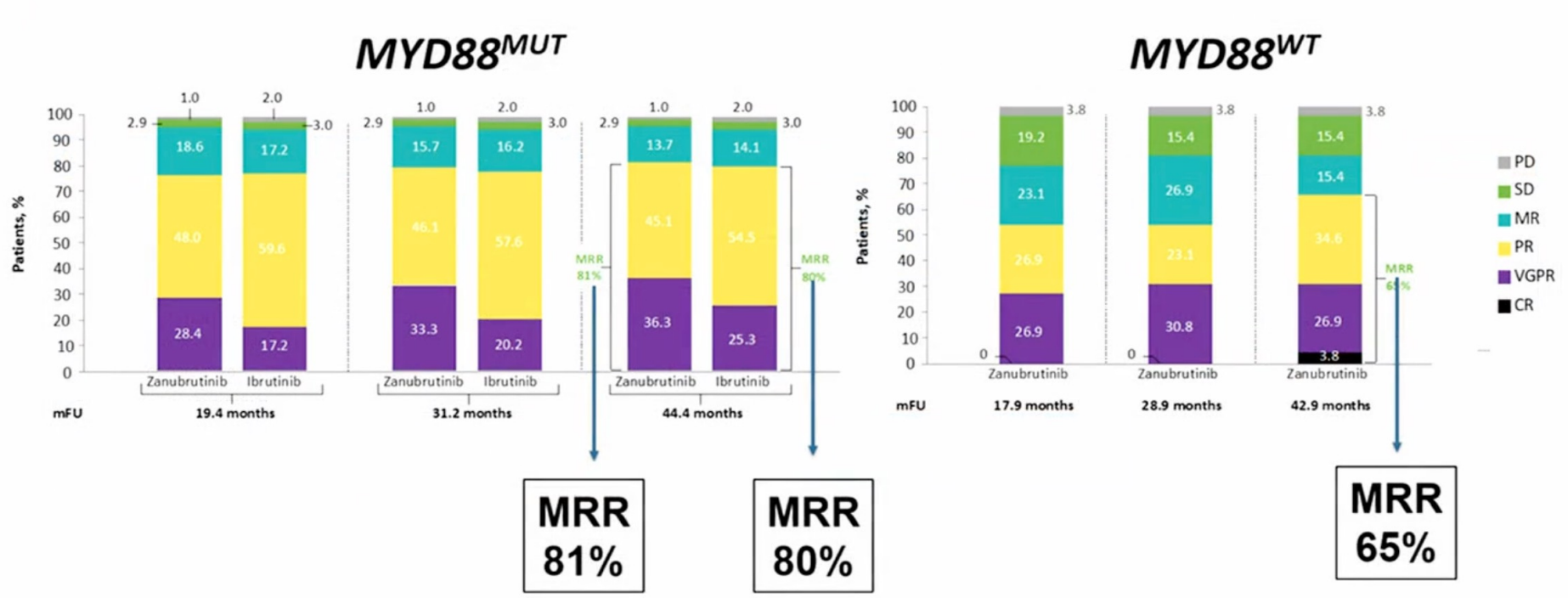
Median FU 44.4 mesi



Tam C et al. Blood 2020; Dimopuolos M et al. JCO 2023

ASPEN trial: Long Term

For patients from **cohort 2 (n=26, confirmed *MYD88*-wild type),** the ORR was 84.6% and the VGPR+ rate was 30.8% versus 80.8% and 30.8%, respectively, at ASPEN final analysis (Dimopoulos et al. *JCO*. 2023). Median duration of response was 55.7 mo (95% CI, 31.3, 68.4) for cohort 1 and 41.1 mo (95% CI, 15.7, NE) for cohort 2.

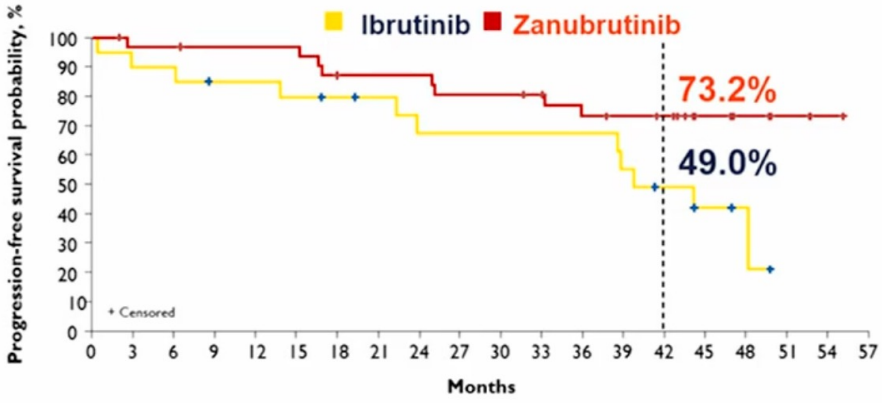


IWWM Prague 2024; ASH 2024; Blood 144; 3031-3033

ASPEN – Long-term follow-up (Cohort 1)

CXCR4 mutated

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



	Zanubrutinib	Ibrutinib
Events, n (%)	8 (24.2)	11 (55.0)
HR (95% CI)	0.50 (0.20, 1.29)	

Dimopoulos et al, IWWM-12, 2024

Adverse Events of Interest (Cohort 1)

ASPEN – Long-term follow-up

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

Dimopoulos et al, IWWM-12, 2024

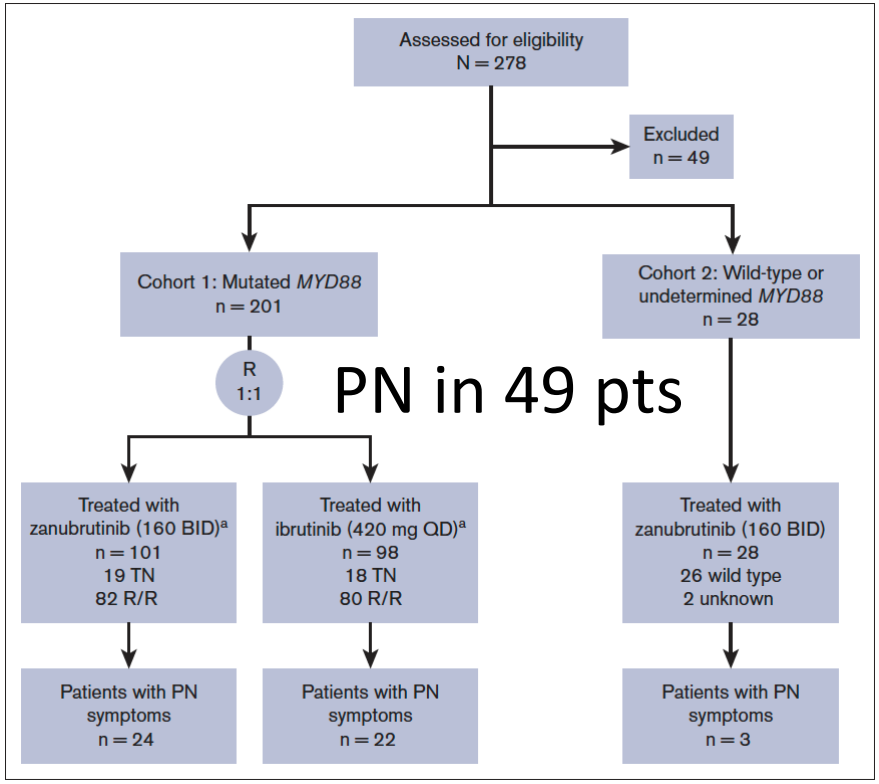
- Zanubrutinib exhibited **fewer side effects** associated with off-target binding, **especially cardiovascular** toxicities
- **Neutropenia** occurred early and was neither treatment-limiting **nor associated with a higher infection rate**
- Zanubrutinib was associated with **longer treatment duration** and lower risk of dose reduction or discontinuation because of Aes
- Patients previously intolerant to ibrutinib or acalabrutinib **did not experience a recurrence of treatment-related AEs with zanubrutinib**.

Terapia di manifestazioni più rare: neuropatia da anti-MAG

Table 1. Demographics and disease characteristics of patients with PN symptoms at study entry

	Cohort 1		Cohort 2	
	Zanubrutinib (n = 24)	Ibrutinib (n = 22)	Zanubrutinib (n = 3)	Total (n = 49)
Age, median (range), y	69.5 (50-87)	68 (57-83)	70 (57-85)	69 (50-87)
Male sex, n (%)	15 (62.5)	14 (63.6)	3 (100)	32 (65.3)
Prior lines of therapy, n (%)				
0	6 (25.0)	4 (18.2)	1 (33.3)	11 (22.4)
1-3	15 (62.5)	16 (72.7)	2 (66.7)	33 (67.3)
>3	3 (12.5)	2 (9.1)	0	5 (10.2)
Genotype by NGS, n (%)				
CXCR4^{WT}	18 (75.0)	15 (68.2)	3 (100)	36 (73.5)
CXCR4^{MUT}	6 (25.0)	5 (22.7)	0	11 (22.4)
CXCR4^{FS}	4 (16.7)	3 (13.6)	0	7 (14.3)
CXCR4^{NS}	2 (8.3)	2 (9.1)	0	4 (8.2)
Unknown	0	2 (9.1)	0	2 (4.1)
Baseline IgM (central laboratory), median (range), g/L	32.4 (6.7-68.9)	21 (6.8-54.9)	24 (13.8-42.5)	26 (6.72-68.9)
Baseline anti-MAG Ab, median (range), TU	70 (1 to >70 000)	138 (9 to >70 000)	70 (44-1545)	85 (1 to >70 000)
Anti-MAG Ab elevation (>999 TU) at baseline, n (%)	2 (8.3)	7 (31.8)	1 (33.3)	10 (20.4)

Ab, antibody; FS, frameshift; MUT, mutated; NGS, next-generation sequencing; NS, nonsense; WT, wild type.

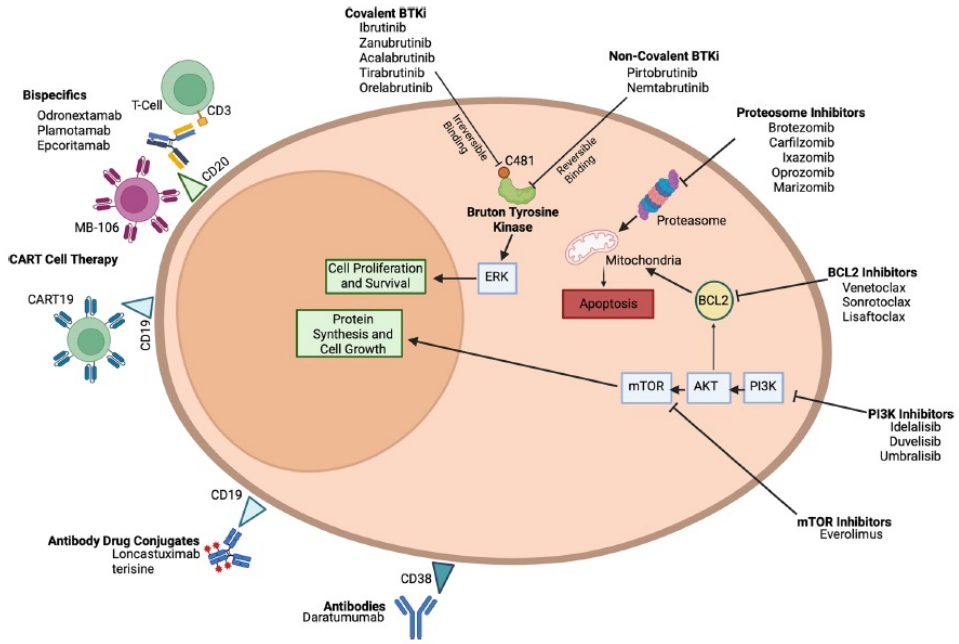


- 65% males
- 78% relapsed
- 74% CXCR4 WT

- 71.4% Resolution of symptoms: 78% 84% 66%

Heyman BM et al Blood Adv 2025

Relapsed WM: novel therapeutic targets



Current Hematologic Malignancy Reports (2024) 19:163–174
Danesin N et al. Front Hematol 2025

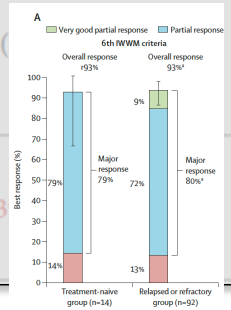
TABLE 1 Ongoing and concluded trials with novel treatment approaches in WM.

Drugs	Phase	Population features and sample size	Response rates	Toxicities (≥ grade 3)
Pembrolizumab and Rituximab (34)	II	N = 17 Median prior lines: 3 71% cBTKi refractory	Median FU: 27m 24w ORR: 47% 2y PFS: 19.4% 2y OS: 67%	Globally: 77% (Infections 29%)
Ixazomib, Rituximab and Dexamethasone (35)	I/II	N = 59 Median prior lines: 2 2% cBTKI exposed	Median FU: 24m 2y ORR: 85% 2y PFS: 56% 2y OS: 88%	Neuropathy: 7% Infections: 5%
Idelalisib and Obinutuzumab (36)	II	N = 49 30/49 one previous line 3/49 cBTKi exposed	Median FU: 26m 6m ORR: 71% 2y PFS: 55% 2y OS: 90%	Hematological: 21% Non-hematological: 28% (mostly diarrhea and hepatic cytolysis)
Zanubrutinib vs Ibrutinib (30)	III	Cohort 1: *MYD88*^{MUT} N = 201 Cohort 2: *MYD88*^{WT} N = 28 Median previous lines: 1-3	Median FU: 44m Cohort 1: VGPR+CR rates (36.8% vs 25.7%) Cohort 2: VGPR+CR 30%	(Ibrutinib vs Zanubrutinib) Infections (9% vs 1%) Hypertension (11% vs 6%) Atrial fibrillation (4% vs 2%) Neutropenia (8% vs 20%)
Acalabrutinib (37)	II	n = 106 Treatment naïve: 14 Relapsed/Refractory: 92 Median prior lines: 2	Median FU: 27m TN vs R/R 27m ORR: 93% 2y PFS: 90% vs 82%	Infections: 25% Neutropenia: 16% Atrial fibrillation: 5% Hypertension: 3% Bleeding: 3%
Orelabrutinib (38)	II	n= 47 Median prior lines: 1 (30/47) Not exposed to BTKi, PI3Ki, Syk-i, and BCL2i	Median FU: 16m 1y ORR: 90.3% 1y MRR: 81.5% Median PFS/OS not reached	Hematological: 17% Non hematological: 8.6% (mostly cataracts and pneumonia)
Tirabrutinib (39)	II	n = 27 18 TN; 9 R/R No previous BTKi.	Median FU: 8m MRR: 88.9% ORR: 96.3%	29.6% (mostly neutropenia and leucopenia)
Pirtobrutinib + Venetoclax (40)	II	n = 16 Median prior line: 1 Previous cBTKi exposure 9/16	Median FU: 6m (3-12) ORR 100% (VGPR 56%, PR 31%, MR 13%).	No arrhythmic events No other data available
Venetoclax (41)	II	n = 32 Median prior lines: 2 Previous BTKi 16/32	Median FU: 33m ORR 84% MRR 81%	Hematological: 45%, mostly neutropenia
Iopofosine 131 (42)	II	n = 65 Median prior lines: At least 2 including BTKi	Median FU: 8.8mo ORR 80% MRR 56%	Neutropenia 69% Thrombocytopenia 80% Infections 12%

BTKi, Bruton tyrosine kinase inhibitors; BCL2i, BCL2 inhibitors; ORR, overall response rate; MRR, major response rate; FU, follow up; VGPR, very good partial response; PR, partial response; MR, minor response.

Relapsed WM: novel covalent BTKi

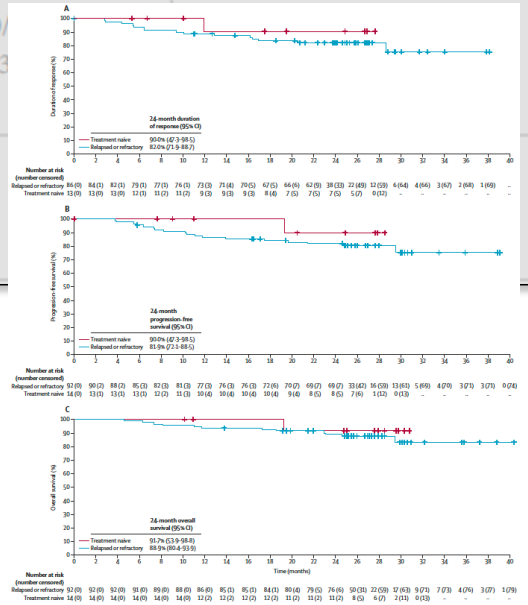
Acalabrutinib (37)	II	n = 106 Treatment naïve: 14 Relapsed/Refractory: 92 Median prior lines: 2	Median FU: 27m TN vs R/R 27m ORR: 93% 2y PFS: 90% vs 82%	Infections: 25% Neutropenia: 16% Atrial fibrillation: 5% Hypertension: 3% Bleeding: 3%
Orelabrutinib (	II	n= 47 Median prior (30/ Not exposed to BTKi, PI3 and BCL2i	Median FU: 16m	Hematological: 17% Non hematological: 8.6% (mostly cataracts and pneumonia)
Tirabrutinib (3	II	n = 27 18 TN; 9 R/R No previous B		29.6% (mostly neutropenia and leucopenia)



DOR

PFS

OS



Safety

Grade 3–4 adverse events occurring in more than 5% of patients were ~~neutropenia (17 [16%] of 106 patients)~~ and pneumonia (7 [7%]).

Grade 3–4 atrial fibrillation occurred in one (1%) patient and grade 3–4 bleeding occurred in three (3%) patients.

Lancet Haematol 2020;7: e112–21

Lancet Haematol 2020;7: e112–21

Relapsed WM: novel covalent BTKi

Orelabrutinib (38)	II	n= 47 Median prior lines: 1 (30/47) Not exposed to BTKi, PI3Ki, Syk-i, and BCL2i	Median FU: 16m 1y ORR: 90.3% 1y MRR: 81.5% Median PFS/OS not reached	Hematological: 17% Non hematological: 8.6% (mostly cataracts and pneumonia)

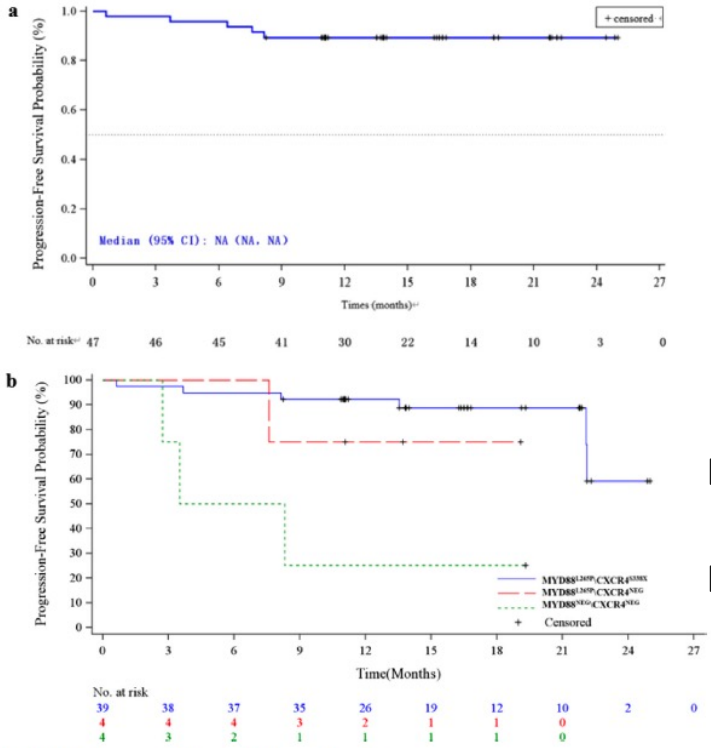


Figure 4. PFS Kaplan-Meier curve (ITT) (a) and PFS by genotype (b).
NA: not available.

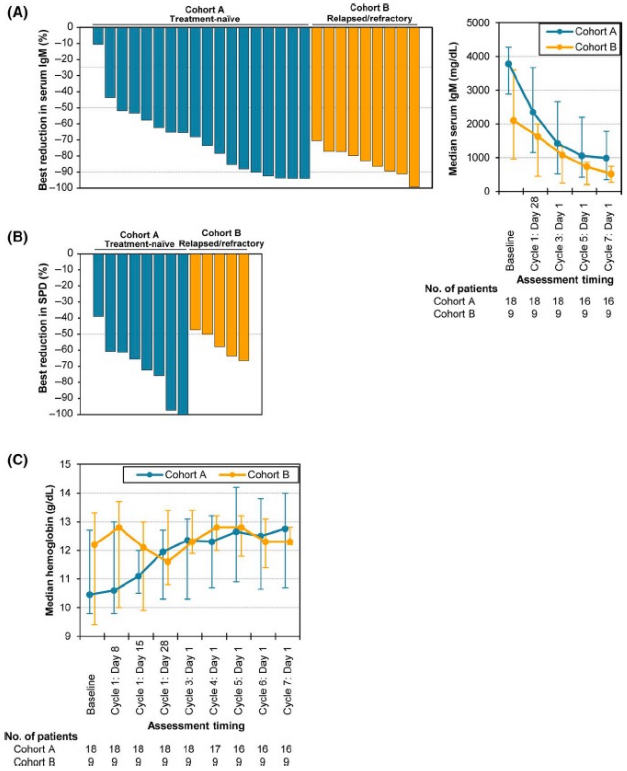
Doppi mutati = MYD88 singoli mutati

Doppi WT

Cao XX The Lancet 2022

Relapsed WM: novel covalent BTKi

Tirabrutinib (39)	II	n = 27 18 TN; 9 R/R No previous BTKi.	Median FU: 8m MRR: 88.9% ORR: 96.3%	29.6% (mostly neutropenia and leucopenia)



Sekiguch N Cancer Sci 2020

R/R WM: Advanced lines (>2 prior lines including cBTKi)

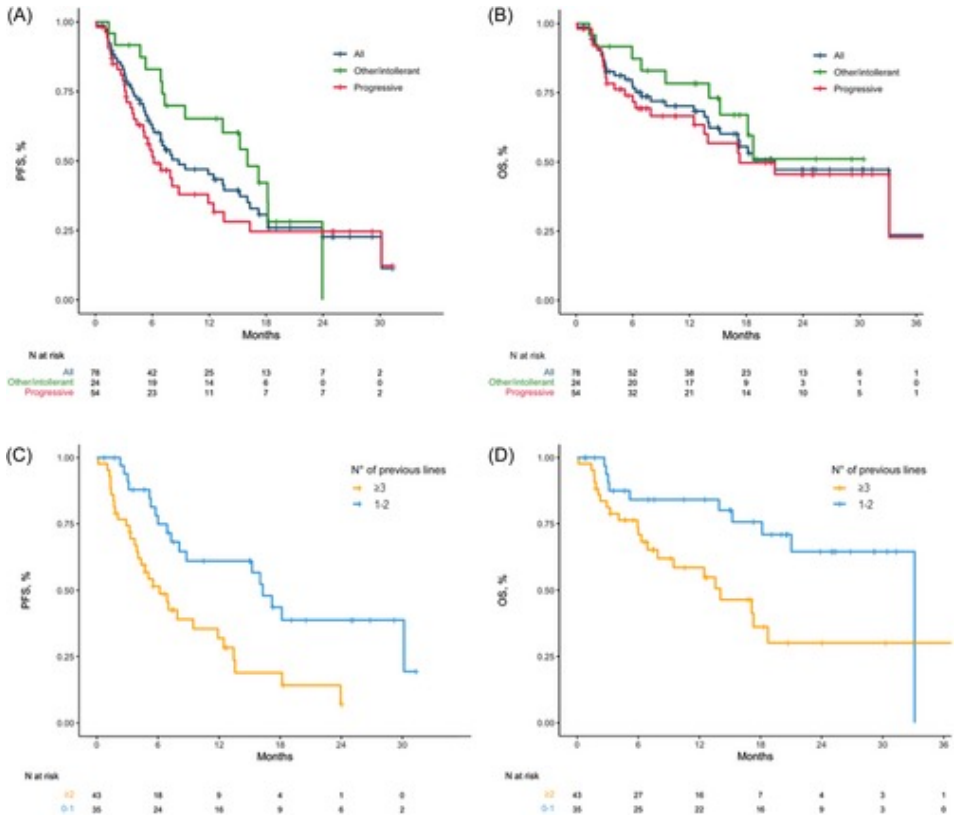
HemaSphere eha

LETTER | Open Access

Salvage treatment after covalent BTKi failure: An unmet need in clinical practice in Waldenstrom macroglobulinemia

Correction(s) for this article

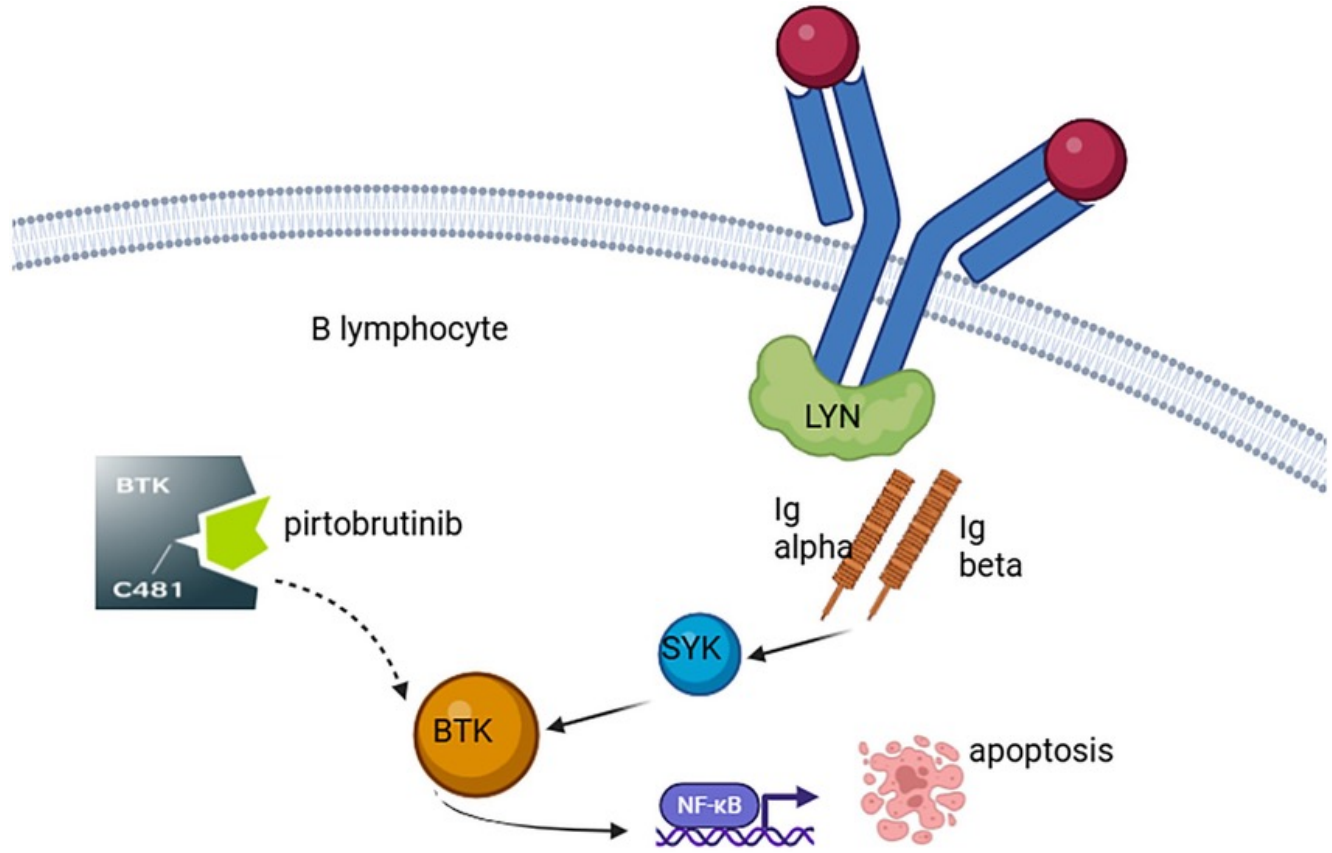
Anna Maria Frustaci, Arianna Zappaterra, Andrea Galitzia, Andrea Visentin, Michele Merli, Rita Rizzi, Isacco Ferrarini, Simone Ferrero, Vanessa Innao, Claudia Baratè, Pierluigi Zinzani, Benedetta Puccini, Francesco Autore, Monica Tani, Angela Ferrari, Gioacchino Catania, Maura Nicolosi, Raffaella Pasquale, Marina Motta, Roberta Murru, Silvia Gambara, Francesca Rezzonico, Marzia Varettoni, Emanuele Cencini, Enrico Lista, Nicolò Danesin, Bianca Maria Granelli, Marina Deodato, Francesco Piazza, Alessandra Tedeschi ... See fewer authors



AM Frustaci et Al, Hemasphere 2025

Non covalent BTKi

NC BTKi inhibits BTK through a **reversible binding that is independent of the cysteine residue**, even in the presence of mutations at the C481 site.



Relapsed WM: non covalent BTKI **PIRTOBRUTINIB**

BRUIN study phasel/II basket trial (LNH, n = 725)
78 R/R WM
78% ≥1 prior BTKi (≥2: 13/61, 21%),
64% CIT+BTKi

Efficacy

Total population (n=72) MRR 68%, *PR 44%, VGPR 24%, no CR*

cBTKi naïve: ***MRR: 69%,*** *PR:47%, VGPR: 22%*

cBTKi pretreated: ***MRR:64%,*** *PR: 40%, VGPR: 24%*

CIT + cBTKi pretreated: ***MRR:64%,*** *PR: 43%, VGPR: 21%,*

Safety

Safety cohort of all pirtobrutinib-treated patients with B-cell malignancies (n=725)

Most frequent TEAEs: fatigue (26%), diarrhea (22%), contusion (19%)

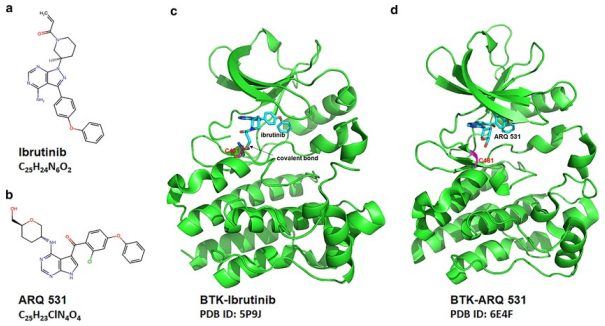
Most frequent Grade≥3 TEAE: neutropenia (20%).

Low rates of Grade≥3 TEAEs hypertension (3%), hemorrhage (2%), atrial fibrillation/flutter (1%) were observed. Overall, 15 (2%) patients discontinued due to treatment-related AE.

Scarfò L et al. EHA 2023

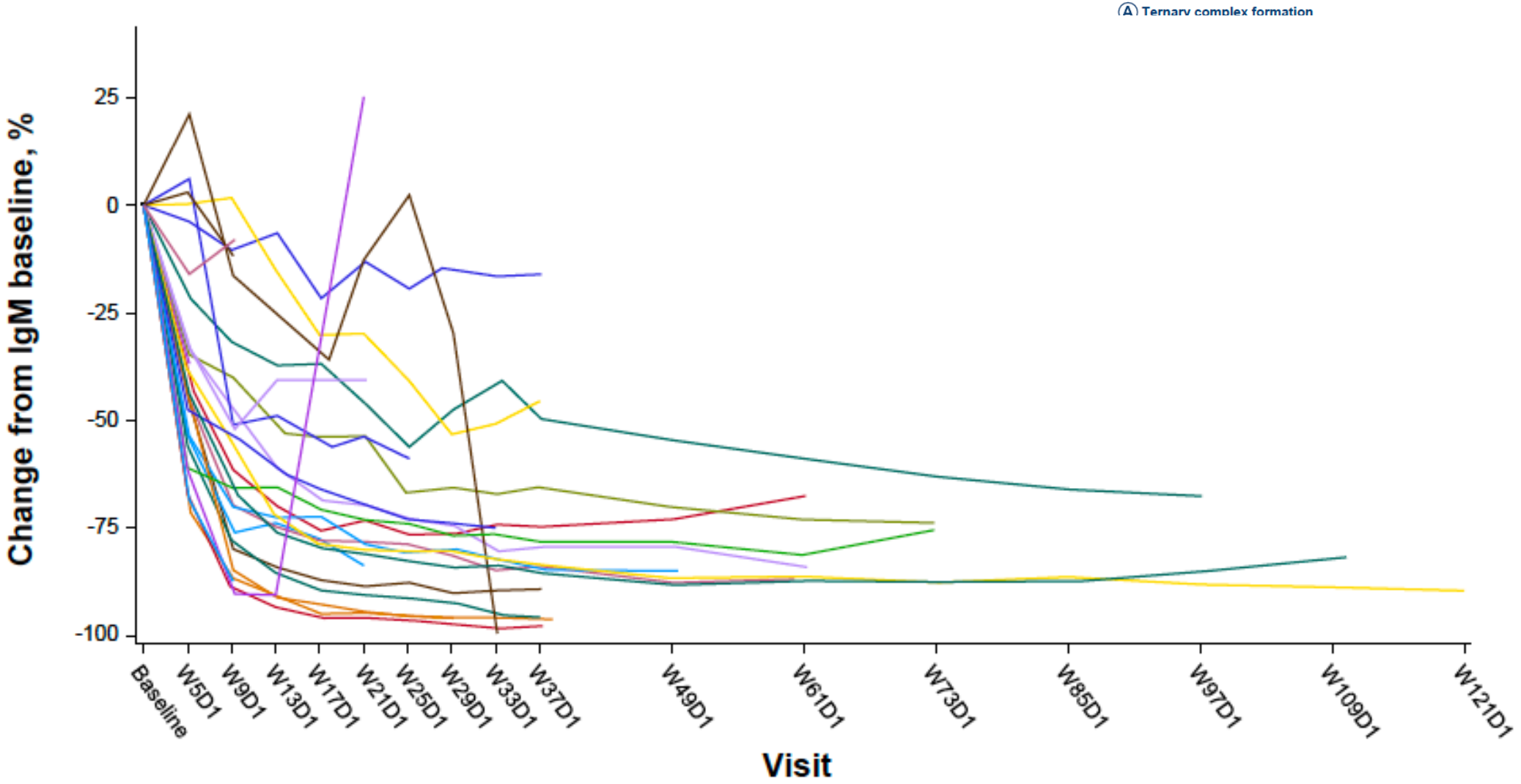
Relapsed WM: non covalent BTKi **NEMTABRUTINIB**

Nemtabrutinib (46) NCT04728893	II	WM, R/R to chemoimmunotherapy and covalent BTKi	ORR



A Phase 2 Study to Evaluate the Efficacy and Safety of MK-1026 in Participants With Hematologic Malignancies

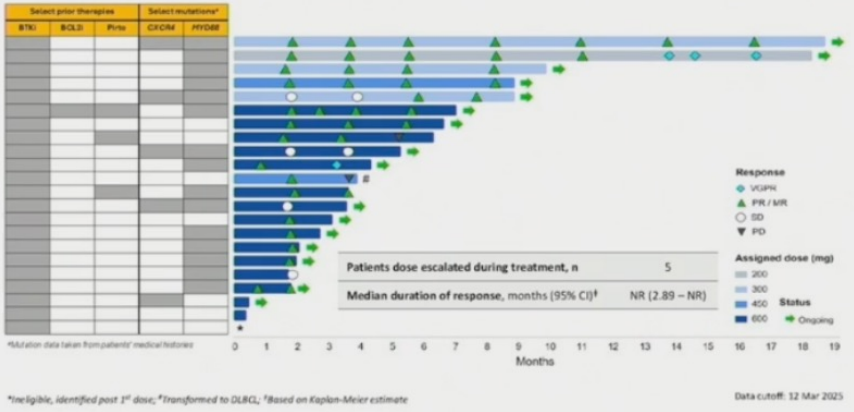
- Dose Escalation and Confirmation (Part 1)
- Cohort Expansion (Part 2).
- Determination of the recommended phase 2 dose (RP2D) in Part 1
- Part 2 using 8 disease-specific expansion cohorts (Cohorts A to H).


Ternary complex formation
Change from IgM baseline, %
25
0
-25
-50
-75
-100
Baseline
W5D1
W9D1
W13D1
W17D1
W21D1
W25D1
W29D1
W33D1
W37D1
W49D1
W61D1
W73D1
W85D1
W97D1
W109D1
W121D1
Visit

F.

Phase 1: NX-5948 in Relapsed/Refractory WM

WM response-evaluable patients	Primary response analysis[b] ≥1 response assessment(s) at 8 weeks (n=19)
Objective response rate (ORR),[a] %	84.2
Best response, n (%)	
CR	0 (0.0)
VGPR	2 (10.5)
PR	11 (57.9)
MR	3 (15.8)
SD	3 (15.8)
PD	0 (0.0)
Median follow-up, months[c] (range)[d]	3.7 (1.9–18.9)



N=22
Median Prior Therapies: 3 (2-5)
Previous BTK-i: 22 (4 NC-BTK-i)
Previous Chemo-Immunotherapy: 21
$MYD88^{Mut}$: 16 (68%)
$CXCR4^{Mut}$: 5 (23%)

El-Sharkawi D, et al. EHA, Poster Presentation 2025

Relapsed WM: BCL2i **VENETOCLAX**

Long-term follow-up of venetoclax monotherapy in previously treated patients with Waldenström macroglobulinemia

Jorge J. Castillo,[1,2] Alberto Guijosa,[1] John N. Allan,[3] Tanya Siddiqi,[4] Ranjana H. Advani,[5] Catherine A. Flynn,[1] Kirsten Meid,[1] Nina Budano,[1] Julia Nguyen,[1] Andres Ramirez-Gamero,[6] Nicholas Tsakmaklis,[1] Zachary R. Hunter,[1] Christopher J. Patterson,[1] Steven P. Treon,[1,2] and Shayna Sarosiek[1,2]

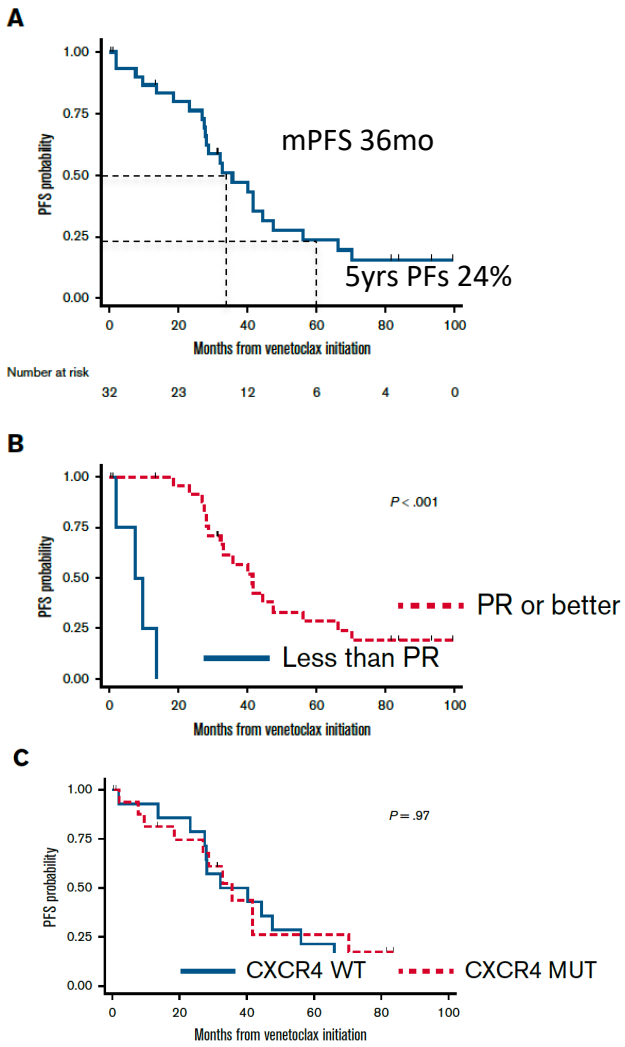
Table 1. Selected baseline characteristics

Characteristic	Participants (N = 32)
Age at WM diagnosis, median (range), y	58 (38-72)
Age at venetoclax initiation, median (range), y	66 (39-80)
Male sex, n (%)	18 (56)
Serum IgM level, median (range), mg/dL	3512 (642-7970)
Hemoglobin level, median (range), g/dL	10.6 (6.4-13.5)
Platelet count, median (range), $\times 10^3/\mu L$	216 (60-445)
Serum β2-microglobulin level, median (range), mg/L	3.6 (1.9-9.8)
Low IPSSWM score, n (%)	12 (38)
Intermediate IPSSWM score, n (%)	8 (25)
High IPSSWM score, n (%)	12 (38)
Bone marrow involvement, median (range), %	35 (4-90)
Adenopathy ≥1.5 cm, n (%)	9 (28)
Splenomegaly ≥15 cm, n (%)	8 (25)
MYD88 L265P mutation, n (%)	32 (100)
CXCR4 mutation, n (%)	17 (53)
No. of previous therapies, median (range)	2 (1-10)
Previous anti-CD20 therapy, n (%)	28 (88)
Previous BTK inhibitor, n (%)	16 (50)

IgM, immunoglobulin M; IPSSWM, International Prognostic Scoring for WM.

N=32
50% after BTKi
ORR 84%
>PR 81%
VGPR 19%
mPFS 36mo
5yrs PFs 24%
5yrs OS 95%

Most common AE =>G2: neutropenia in 53%



Castillo JJ Blood Adv 2025

Promising Single-Agent Antitumor Activity Across Dose Levels

Baseline Patient Characteristics (cont.)

HEMATOLOGIC MALIGNANCIES—LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

Check for upd

TPS7090

ASCO 2024

Poster Session

BGB-11417-203: An ongoing, phase 2 study of sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, in patients with Waldenström macroglobulinemia.

Hui-Peng Lee, Stephen Opat, John Hrom, David S. Kliman, Paula Marlton, Peng Liu, Chenmu Du, Amber Lussier, Jun Zhang, Haiyi Guo, Steven P. Treon; Flinders Medical Centre, Bedford Park, SA, Australia; Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; Hattiesburg Clinic, Hattiesburg, MS; Genesis Care North Shore, St Leonards, NSW, Australia; Princess Alexandra Hospital and University of Queensland, Brisbane, QLD, Australia; Affiliated Zhongshan Hospital of Fudan University, Shanghai, China; BeiGene (Beijing) Co, Ltd, Beijing, China; BeiGene USA, Inc, San Mateo, CA; BeiGene (Beijing) Co, Ltd, Shanghai, China; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Prior BTK inhibitor, n (%)	4 (67)	4 (50)	3 (60)	1 (100)	**12 (60)**
BTK inhibitor as last therapy, n (%)	–	–	–	–	9 (45)
Prior BTK inhibitor duration, median (range), months	60.7 (55.3-85.4)	48.4 (19.4-54.5)	13.1 (1.1-25.1)	68.5 (68.5-68.5)	53.7 (1.1-85.4)

BTKi, BTK inhibitor; MR, minor response; NE, not evaluable; VGPR, very good partial response.

BTKi

Time since first dose, months

Development of BCL2i and c/ncBTKi in WM:

1) Frontline setting

- combination of **venetoclax plus rituximab vs ibrutinib plus rituximab**

2) Relapsed

- combination of **venetoclax plus pirtobrutinib**.
- combo **sonrotoclax plus zanubrutinib**

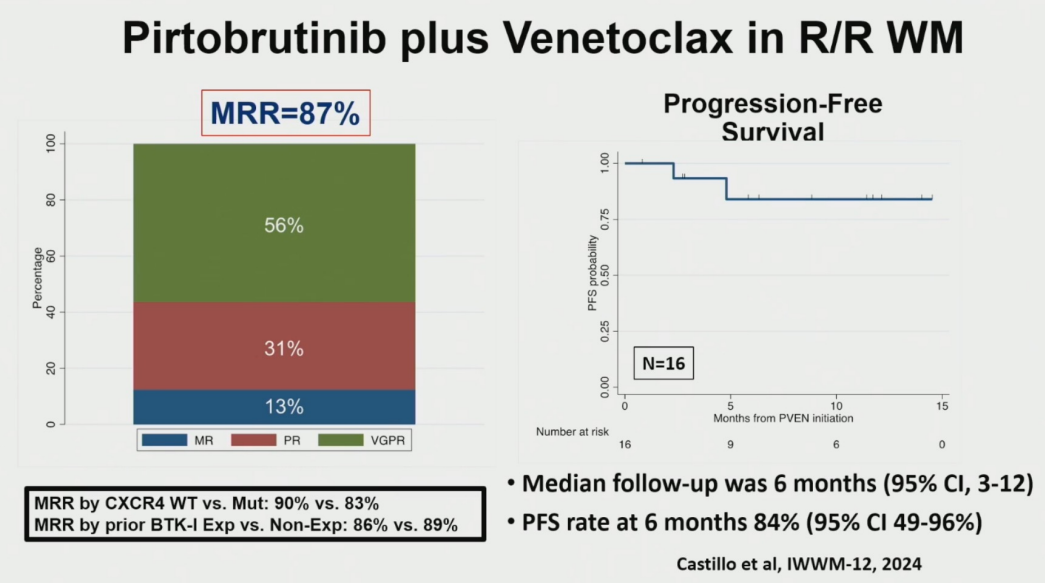
- https://www.clinicaltrials.gov/study/NCT04840602?term=AREA%5BBasicSearch%5D(gp2013)&rank=10
- https://www.clinicaltrials.gov/study/NCT05734495?term=PIRTOBRUTINIB&rank=1
- ClinicalTrials.gov identifier: NCT04840602
- https://www.clinicaltrials.gov/study/NCT05952037

Relapsed WM: non covalent BTKI **PIRTOBRUTINIB PLUS BCL2 INHIBITORS**

A Phase II Study of Pirtobrutinib and Venetoclax in Previously Treated Patients with Waldenström Macroglobulinemia: An Interim Analysis

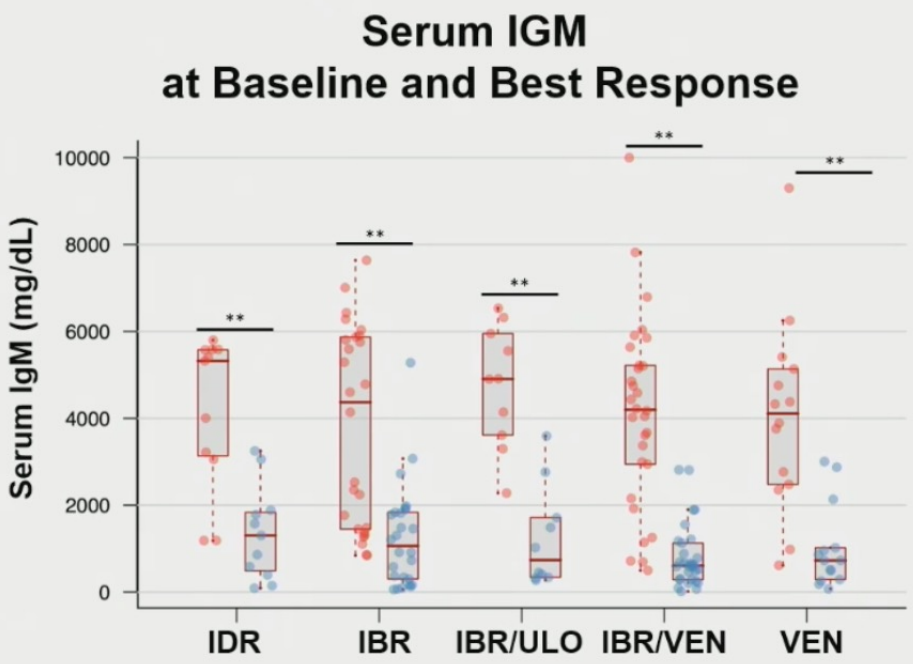
Jorge J. Castillo, MD[1], Shayna R Sarosiek[1], Andrew R. Branagan, MD[2], Gottfried von Keudell, MDPhD[3], Catherine A. Flynn, NP[1], Nina S Budano[1], Alexandra N. Eurell[1], Kirsten Meid, MPH[1], Andres Ramirez-Gamero, MD[1], Maria Luisa Guerrera, MD[1], Amanda Kofides, BA[1], Shirong Liu, MDPhD[1], Xia Liu, MD[1], Kris Richardson, PhD[1], Nickolas Tsakmaklis[1], Christopher J Patterson, MPH, MBA[1], Zachary R Hunter, PhD[1], Steven P. Treon, MDPhDFRCP[4]

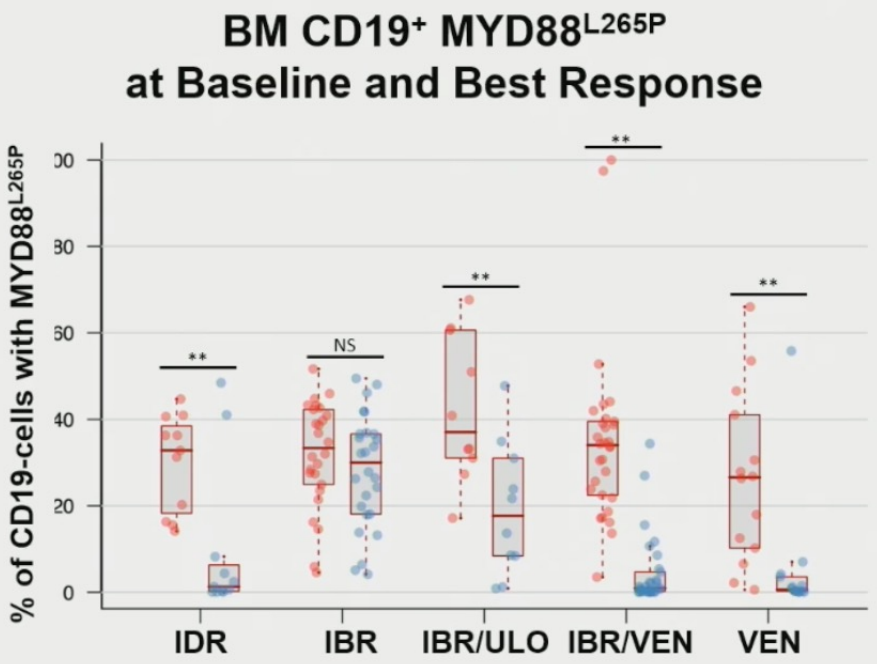
n = 16 Median prior line: 1 Previous cBTKi exposure 9/16	Median FU: 6m (3-12) ORR 100% (VGPR 56%, PR 31%, MR 13%).	No arrhythmic events No other data available



ASH annual meeting 2024

Serum IGM vs. changes in MYD88^{L265P} burden in prospective clinical trials in WM patients





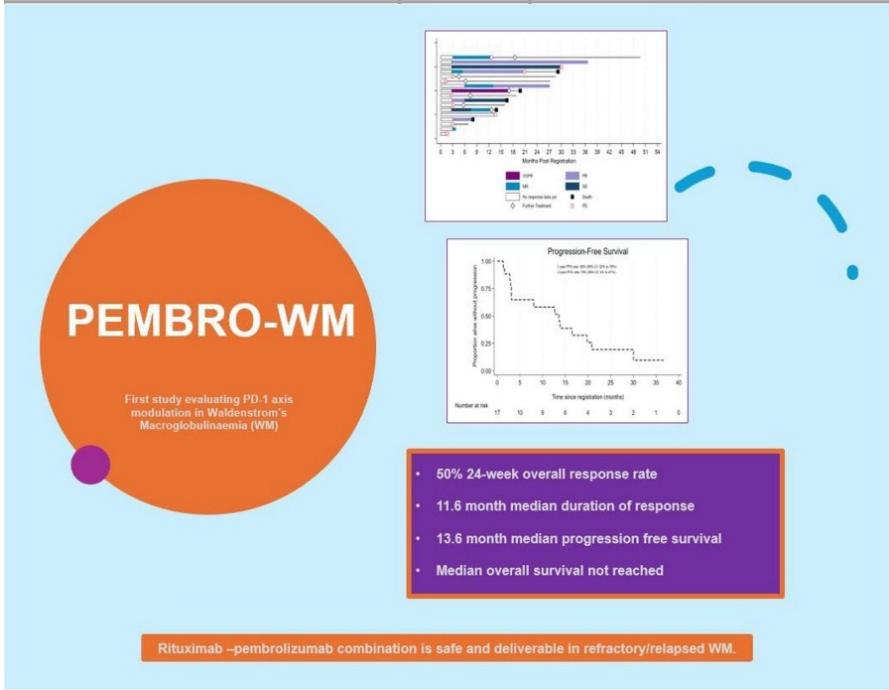
NS: not significant; *p<0.05; **p<0.005

Tsakmaklis et al, ASH 2024, Manuscript submitted.

Immunotherapy?

Relapsed WM: immunotherapy

Drugs	Phase	Population features and sample size	Response rates	Toxicities (≥ grade 3)
Pembrolizumab and Rituximab (34)	II	N = 17 Median prior lines: 3 71% cBTKi refractory	Median FU: 27m 24w ORR: 47% 2y PFS: 19.4% 2y OS: 67%	Globally: 77% (Infections 29%)



«PembroWM is the first study to evaluate the feasibility of PD-1 axis modulation in WM and has shown that in combination with Rituximab the combination is safe and deliverable»

Kothari J et al. Br J Haematol. (2024) 205:2273–81.

Regimen	Phase	Inclusion Criteria	Primary endpoint
Epcoritamab (51) NCT06510491	II	R/R WM	ORR
Brexucabtagene Autoleucel (52) NCT05537766	II	R/R WM	CR, VGPR, ORR
MB-106 (53) NCT05360238	I	3 NHL (1 WM) 5.5 median prior lines	ORR

Third generation CD20 CAR-T (MB-106)

51. Epcoritamab in previously treated WM. Available online at: https://clinicaltrials. gov/study/NCT06510491 (Accessed June 29, 2025).
52. Study of brexucabtagene autoleucel in adults with rare B-cell Malignancies (ZUMA-25). Available online at: https://clinicaltrials.gov/study/NCT05537766 (Accessed June 29, 2025).
53. Shadman M, Caimi PF, O'Brien SM, Reagan PM, Dezube B, Navaratnarajah P, et al. Efficacy and safety of a third generation CD20 CAR-T (MB-106) for treatment of relapsed/refractory indolent B-cell non-Hodgkin lymphoma: phase-1 results from a multicenter trial. ASH Annu meeting. (2023) 142 (supplement 1):2102. doi: 10.1182/blood-2023-175007

Update on WM: take home messages

- **Classifications**: WHO HEM5 and ICC 2022 **divergent**
- At least **two distinct types** of MYD88^{L265P}-mutated WM
- **Long-term toxicity** of CIT
- **Longer f.u. of efficacy/safety** of cBTKi Ibrutinib and Zanubrutinib
- **Novel 1L** approaches:
  - Acala BR (studio BRAWN)
  - Zanu BR (studio cinese)
  - Bor-Ibr-R + maintenance Ibr + R (studio Buske)
  - Carlfilzomib + Ibrutinib versus Ibrutinib
  - Ibrutinib + venetoclax
- **Relapsed** WM:
  - Novel cBTKI
  - ncBTKI
  - PROTACS BTKi degraders
  - BCL2i
  - COMBOS
- **Immunotherapy** is under initial development
  - Axicel; MB-106 (CAR-T)
  - Epcoritamab (HOVON study)

Acknowledgements

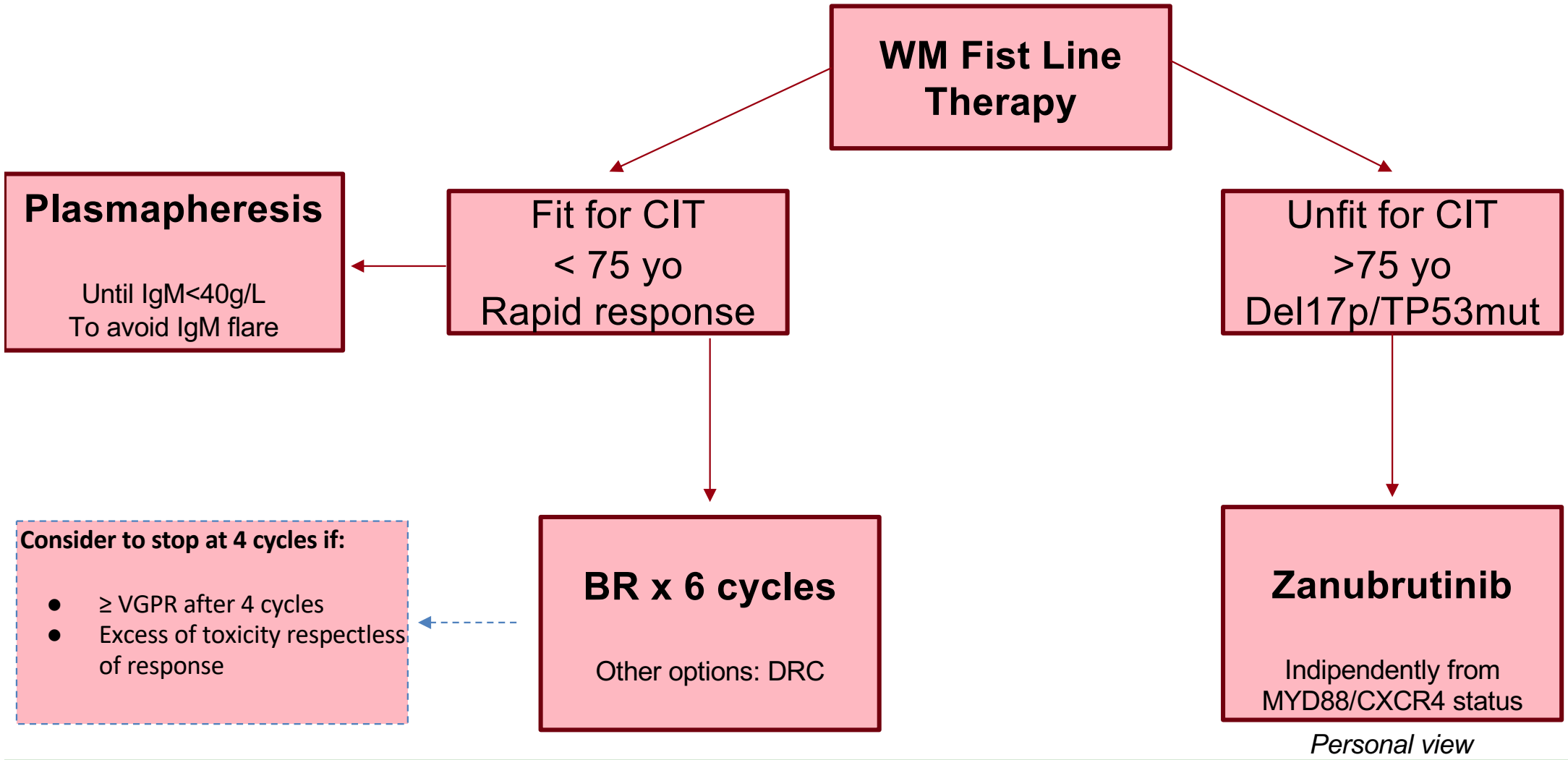
University of Padua - Department of Medicine
Padua University Hospital - Hematology
Chief: Prof. Livio Trentin

Lymphoma Physicians
Dott.ssa Greta Scapinello
Dott. Nicolò Danesin (Resident)
Dott. Marco Carraro (Resident)
Dott. Giovanni Leone

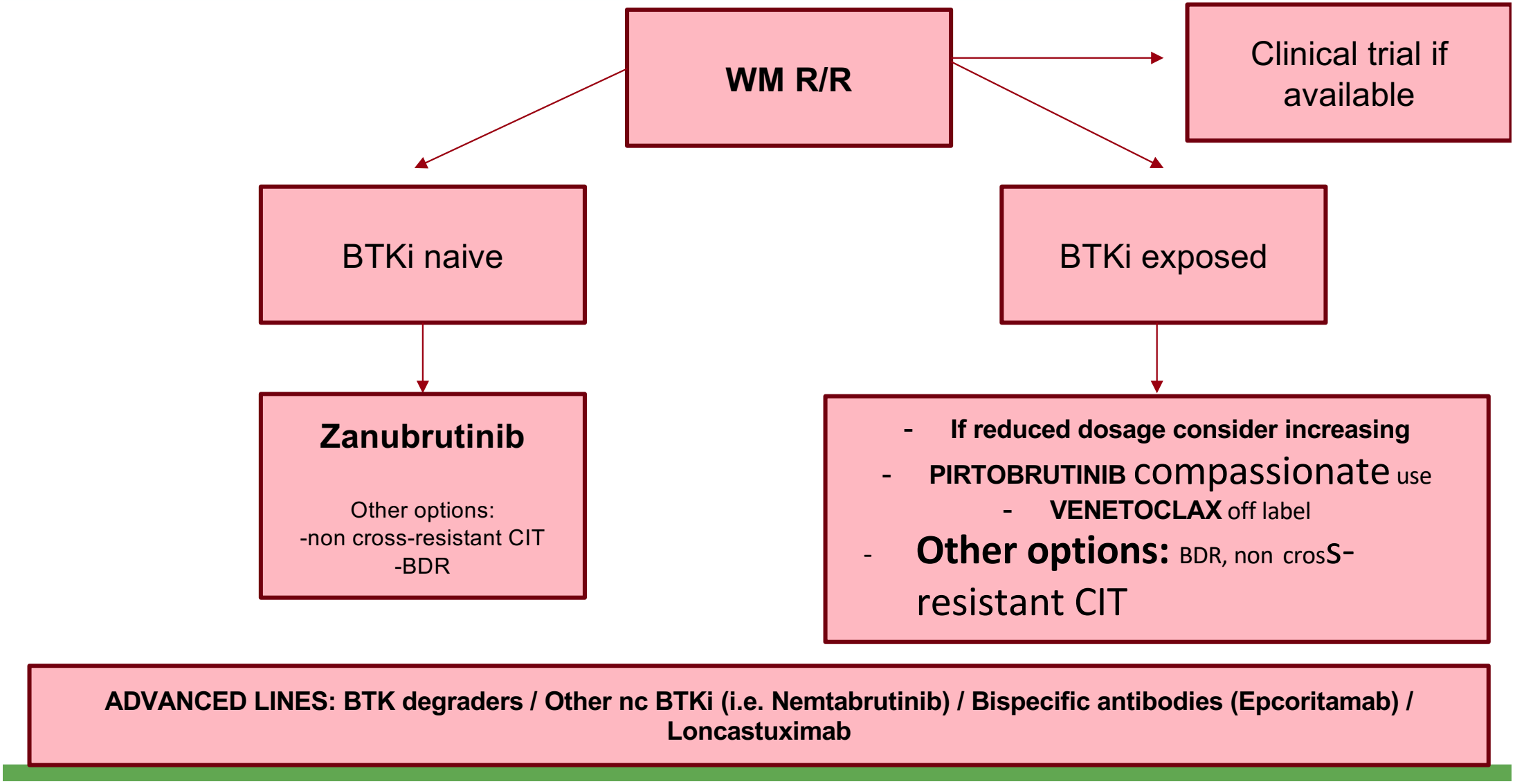
CLL team
Dott. Andrea Visentin
Dott. Francesco Angotzi
Dorr. Alessandro Cellini

for their support in patients' management and data analysis

You all for your attention!



Personal view


WM R/R
Clinical trial if available
BTKi naive
BTKi exposed
Zanubrutinib
Other options:
-non cross-resistant CIT
-BDR
- If reduced dosage consider increasing
- PIRTOBRUTINIB compassionate use
- VENETOCLAX off label
- Other options: BDR, non crosS-resistant CIT
ADVANCED LINES: BTK degraders / Other nc BTKi (i.e. Nemtabrutinib) / Bispecific antibodies (Epcoritamab) / Loncastuximab