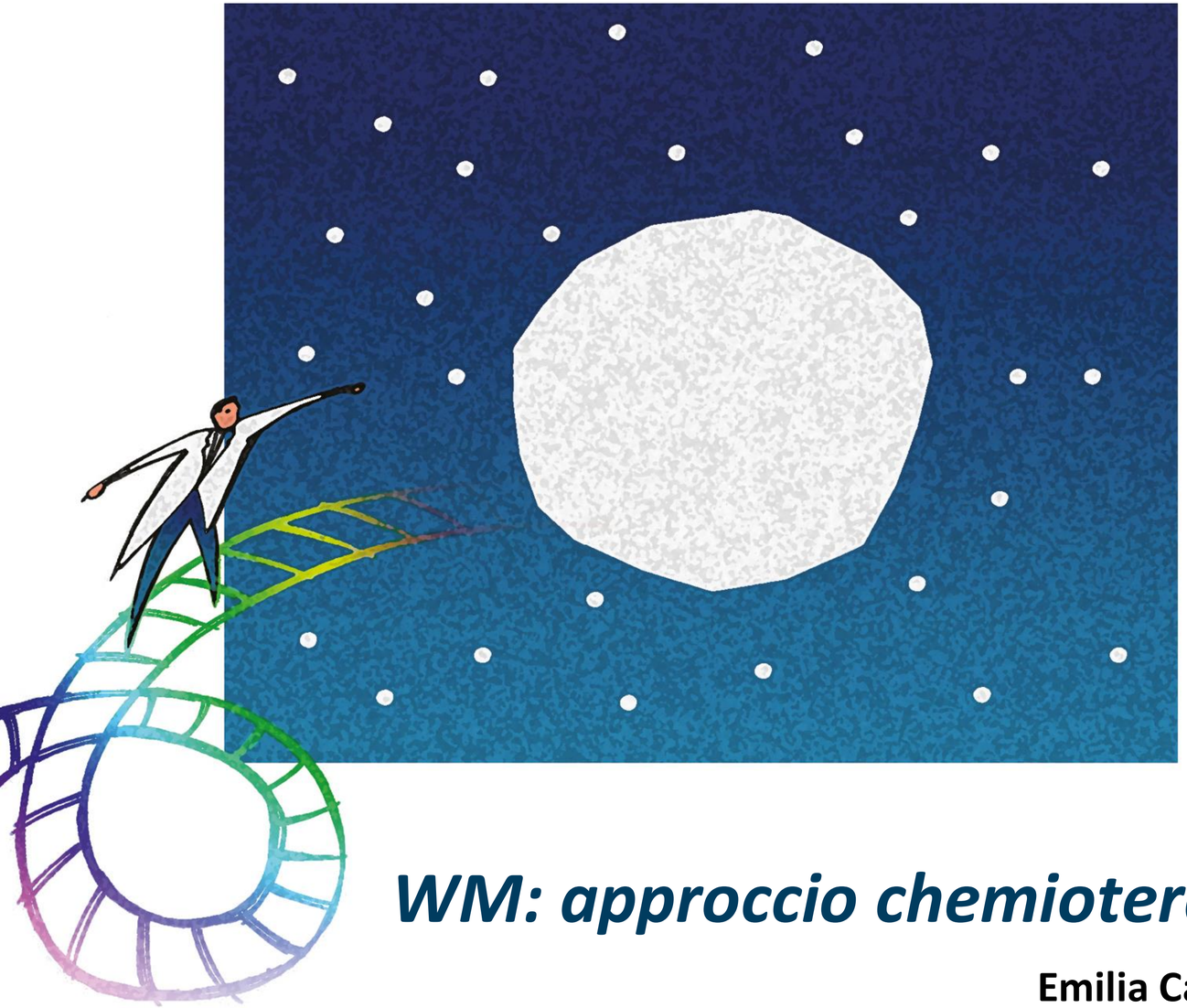


The young side of
LYMPHOMA

gli under 40 a confronto

Verona, Centro Congressi Camera di Commercio
26-27 settembre 2025

WM: approccio chemioterapico versus terapia chemo-free

Emilia Cappello

Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia

Disclosures of Emilia Cappello

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

None

Clinical case (1) - TN

October '24: (M.L.) 60-year old female presented to ER due to blurry vision, nosebleed and asthenia

Investigations

- **Lab tests.** Hb 3.9 g/dl, GB 3000/mmc (ANC 1000/mmc, ALC 600/mmc), PLT 29000/mmc, SPE with **IgM kappa** (4 g/dl), **sIgM 7000 mg/dl**, beta2microglobulin 4 mg/L;
- **FO**: retinal hemorrhages;
- **CT TB scan:** axillary and inguinal adenopathy (max 1.5 cm). No splenomegaly. No extramedullary and/or bulky disease;
- **Bone marrow biopsy:** 50% lymphoplasmacytic cell involvement, 5% PCs, mastocytes;
- **Molecular characteristics:** *MYD88^{L265P}, CXCR4^{S388X}, TP53^{WT}*. FISH: del17p: absent;
- **Comorbidities:** hypertension.

→ Waldenström Macroglobulinemia/LPL with monoclonal serum IgM kappa, treatment naïve, symptomatic for hyperviscosity, cytopenias, IgM levels > 60 g/L. *MYD88^{L265P}, CXCR4^{S388X}, TP53^{WT}*. FISH del17p: absent. IPSSWM: high

2 PEX with bleeding resolution…What's next?

Clinical indications for initiation of therapy
- Recurrent fever, night sweats, weight loss, fatigue
- Hyperviscosity
- Lymphadenopathy: either symptomatic or bulky (≥ 5 cm in maximum diameter)
- Symptomatic hepatomegaly and/or splenomegaly
- Symptomatic organomegaly and/or organ or tissue infiltration
- Peripheral neuropathy due to WM

Laboratory indications for initiation of therapy
- Symptomatic cryoglobulinaemia
- Symptomatic cold agglutinin anaemia
- Autoimmune haemolytic anaemia and/or thrombocytopaenia
- Nephropathy-related to WM
- Amyloidosis-related to WM
- Hb ≤ 10 g/dL
- Platelets < 100×10^9/L
- IgM levels > 60 g/L

Kyle RA. Semin Oncol 2003; 30: 116–120. [IWWM-2}

A. DRC (Dexamethasone-Rituximab-Cyclophosphamide)

B. Zanubrutinib

C. Rituximab-Bendamustine

D. Ibrutinib

Join at
slido.com
#3546 320

NCCN Guidelines for Waldenström Macroglobulinemia (TN)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1. 2026
Waldenström Macroglobulinemia/
Lymphoplasmacytic Lymphoma

Version 1.2026 – 24 June 2025

PRIMARY THERAPY FOR WM/LPL[a,b] (The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.)	
Preferred	
• Zanubrutinib[c,d] (category 1) • Bendamustine/Rituximab	
Other Recommended	
• Ibrutinib[c,d] (category 1) • Ibrutinib[c,d] + Rituximab (category 1) • Bendamustine • Bortezomib/Dexamethasone/Rituximab • Carfilzomib/Rituximab/Dexamethasone • Ixazomib/Rituximab/Dexamethasone	• Rituximab • Rituximab/Cyclophosphamide/Dexamethasone • Rituximab/Cyclophosphamide/Dexamethasone + Bortezomib • Rituximab/Cyclophosphamide/Prednisone

[a] General Considerations for Systemic Therapy for WM/LPL (WM/LPL-B 1 of 4).
[b] Obinutuzumab may be considered in patients who are unable to tolerate Rituximab (Wróbel T, et al. Hemasphere 2023;7:e4339598. doi: 10.1097/01.HS9.0000971308.43395.98).
[c] Rapid increases in IgM levels (IgM rebound) have been observed following discontinuation of BTK inhibitors. Consider continuing therapy with the BTK inhibitor until starting the next line of therapy or monitor for IgM rebound after discontinuation of BTK inhibitors.
[d] Should not be used in first-line for patients with LPL-associated amyloidosis.

Treatment choice in active WM requiring therapy

Patient characteristics

- Biological age
- Comorbidities
- Fitness
- Potential toxicity therapy-related

Prognostic factors

- IPSSWM score
- rIPSSWM score

Local guidelines

- Accessibility
- Reimbursment arrangements

Treatment choice in active WM

Disease factors

- Hyperviscosity syndrome
- Bulky and/or EMD disease
- WM-related AL amyloidosis
- Bing-Neel syndrome
- Symptomatic cryoglobulinemia
- Cold agglutinine disease
- IgM-related neurophaty
- Nephropathy related to WM

Molecular/biological features

- ***MYD88*** mutational status
- ***CXCR4*** mutational status
- ***TP53*** disruptions

Molecular hallmarks in WM

MYD88^{L265P} in WM pts (95-97%)[1]

MYD88^{WT} pts have a ***higher risk for disease transformation***, and/or show ***shorter OS***

1. Treon S et al, JCO 2020 2. Treon SP et al, Br J Haematol 2018

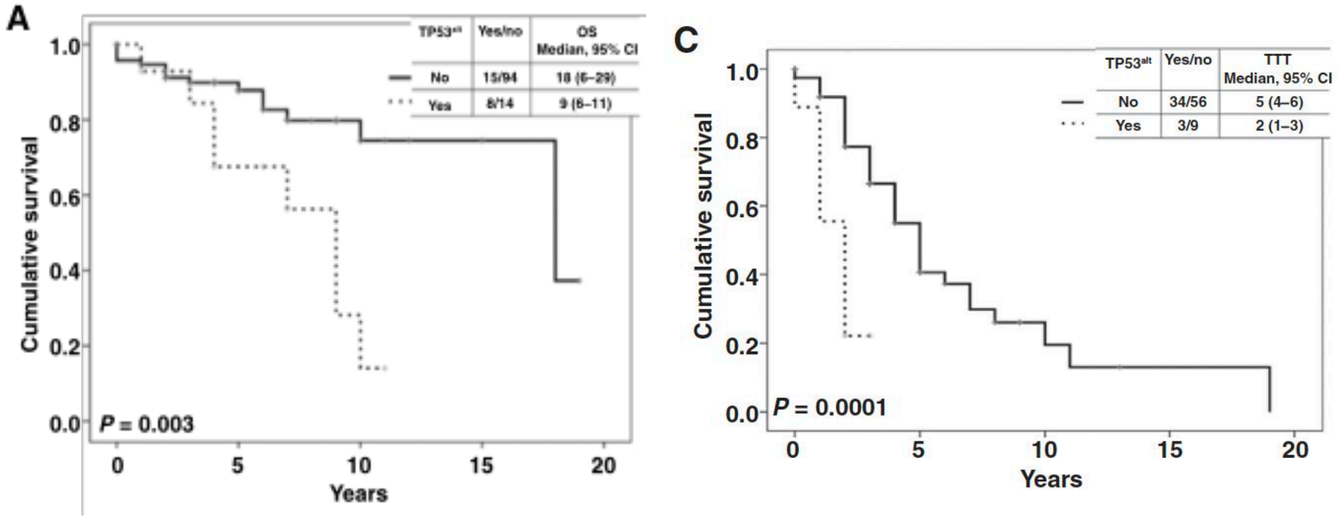
CXCR4^{MUT} in WM pts (30-40%)[3]

- **CXCR4**$^{Mut/NS}$**:** higher BM disease burden[4]; higher sIgM levels[4]; higher incidence of symptomatic hyperviscosity[4]; less adenophaty[4]; shorter TTFT[5];
- **CXCR4**$^{Mut/NS}$ adversely affect treatment outcomes with BTKis[6]

3. Castillo J et al, Exp Rev Hematol 2019 4. Treon SP et al, Blood 2014; 123: 2791-96
5. Varettoni et al, Haematologica 2017. 6 Dimopoulos et al JCO 2023

TP53 disruptions (*TP53*^{MUT} and del17p) in WM pts

5-10% of TN WM pts and **25%-30% of RR WM** pts who had been previously treated[7]



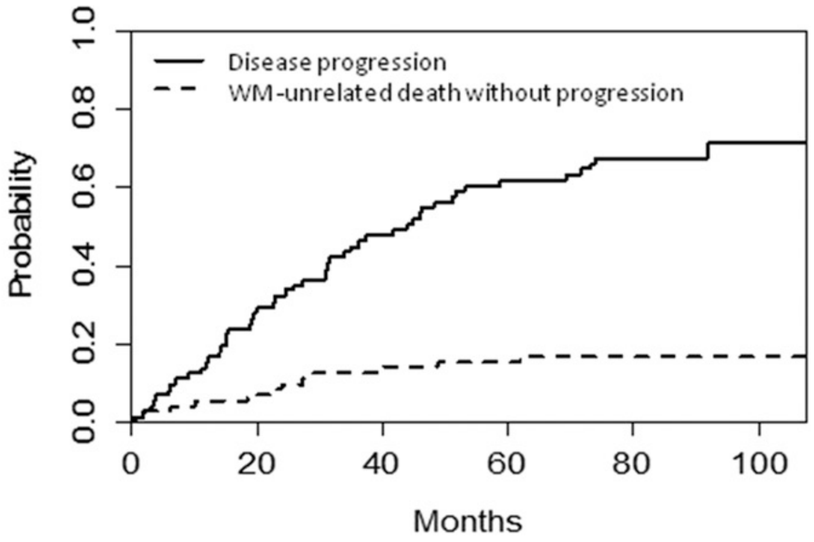
TP53^{MUT} patients had higher number of genomic abnormalities than *TP53*^{WT} patients (6.8 vs. 2.6, P <0.002), with shorter time to first treatment and shorter PFS and OS[8]

7. Treon et al Blood 2025 8. Poulain S et al, Clin Cancer Res 2017 9. Garcia-Sanz R et al. Semin Hematol. 2023

Chemo-immunotherapy options – *DRC, R-Bendamustine*

DRC as primary treatment of WM[1-2]

Study population: n=72 TN WM pts; M: 67%; median age at dx: 69 yo (range 45-88). Median FUP 8 yrs



Outcome
median-PFS: 35 mo (95%CI: 22-48)
median-OS: 95 mo (95%CI: 87-103)

Efficacy
ORR: 83% (CR 7%, PR 67%, MR 9%)
Median TTNT: 51 mo

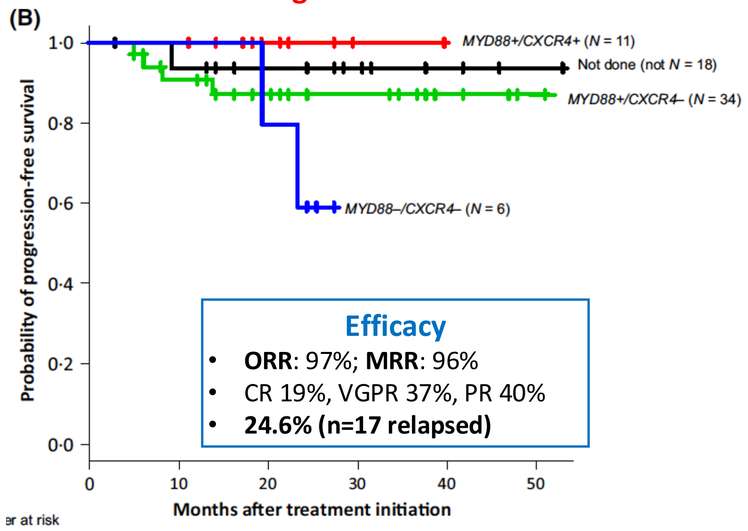
Long term toxicities
- 35 patients (49%) have died: 20 (57%) were WM-related, and in 15 (43%) death was unrelated to WM **(related to solid tumors in 8)**
- **1 pts developed MDS (and 2 pts developed DLBCL**

1. Dimopoulos et al, JCO 2007 2. Kastritis E. et al, Blood 2015

BR in newly-diagnosed WM patients. A study on behalf of FILO[4-5]

Study population: n=69 TN WM pts; M: 67%; median age at dx: 69 yo (range 45-88)

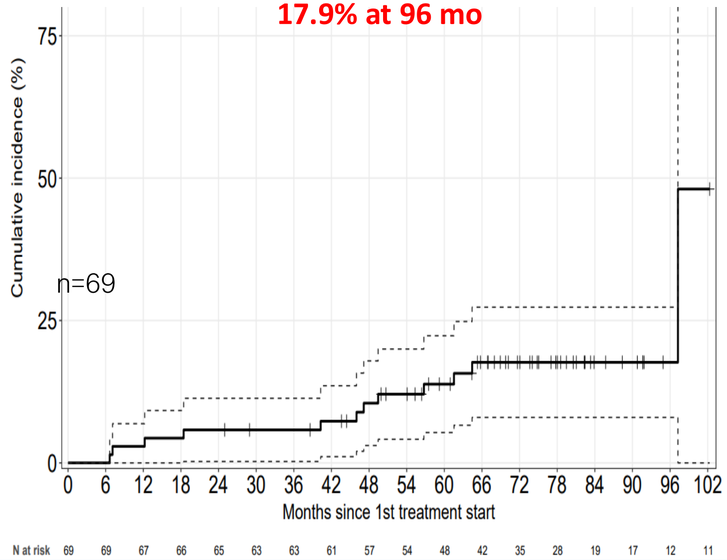
PFS according to *MYD88* and *CXCR4* status



Efficacy
- **ORR**: 97%; **MRR**: 96%
- CR 19%, VGPR 37%, PR 40%
- **24.6% (n=17 relapsed)**

Laribi et al, Br J Haematol 2018

Cumulative incidence of second malignancies: 17.9% at 96 mo



Outcomes (mFUP 97 mo)[3]
- **mOS:** NR
- **mPFS:** 82.2 mo (95%CI: 69.7-93.1)
- **mOS *MYD88*^{WT} pts**: 27.37 mo vs NR (*MYD88*^{L265P})
- **mOS NR whatever the *CXCR4* status**

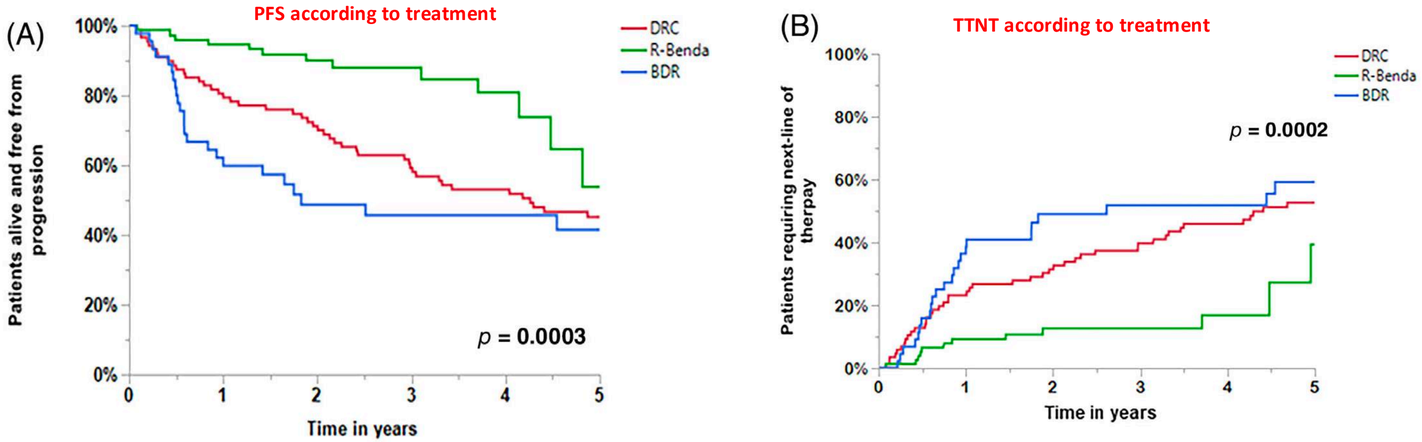
Long term toxicities[3]
- **Second malignancies: 12 pts** (9 solid tumors, **2 myelodysplastic syndromes, 1 AML**);
- **Long lasting cytopenias: 51% of pts** (G1-2), median duration of 9 mo

3. Leblond et al, IWWM-12, 2024 4. Laribi et al, Br J Haematol 2018 5. Laribi et al, Br J Haematol 2024

Comparison of Rituximab-based, fixed duration, therapies for TN WM pts

Comparative analysis of BR vs DRC vs BDR in 220 TN WM pts

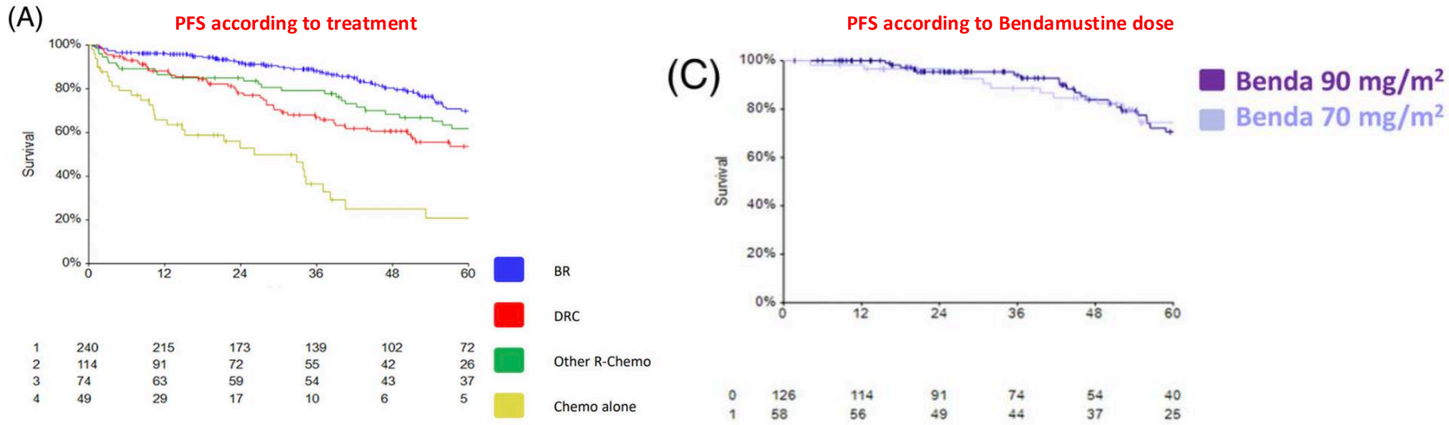
Study population: n= 220 (BR n=83, DRC n= 92, BDR n=45) at Mayo Clinic Nov 2000-Oct 2019



Abeykoon et al, Am J Hematol 2021

First line treatment of WM in Italy: multicenter real life study on 547 pts

Study population: n= 547 (BR n=245, DRC n= 116, other Chemo n=86, Chemo-alone n=52) – 14 FIL Centres Jan 2008-Dec 2022



Autore et al, Am J Hematol 2025

Chemo-free options, cBTK-i in WM

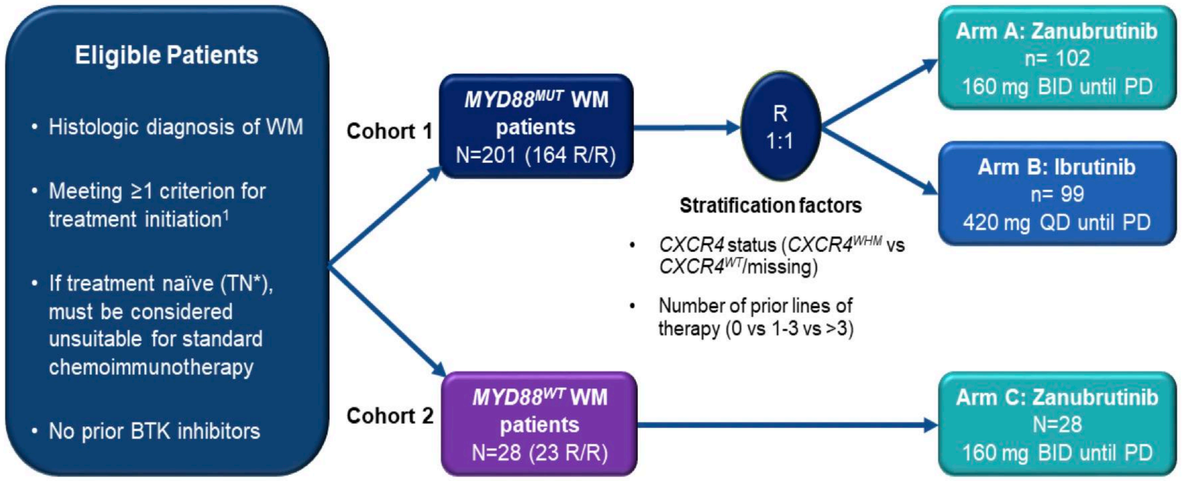
Study	Regimen	N	Cohort	ORR/MRR (%)	Results	Reference
Pivotal study	Ibrutinib	66	RR	91/79 m to major response: 1.8 mo	5-year PFS: 54% 5-year OS: 87%	Treon et al. JCO 2021
iNNOVATE (Arm C)	Ibrutinib	31	RR	87/74 m to major response: 2 mo	5-year PFS: 40%	Dimopoulos et al, Lancet Oncol 2017
Phase 2	Ibrutinib	30	TN	100/87 m to major response: 1.9 mo	4-year PFS: 76%	Castillo et al. Leukemia 2022
INNOVATE (Arms A, B)	Rituximab + Ibrutinib/Placebo	150	TN/RR	92/76 (IR) m to major response: 3 mo	54-mo PFS: 68%	Buske et al. J Clin Onc 2022
Phase 2	Zanubrutinib	77	TN/RR	96/82 m to major response: 2.8 mo	36-mo PFS: 76%	Trotman et al. Blood 2020
ASPEN (Cohort 1)	Ibrutinib	99	TN/RR	94/80 m to major response: 2.9 mo	42-mo PFS: 85%	Dimopoulos et al, J Clin Onc 2023
ASPEN (Cohort 1)	Zanubrutinib	102	TN/RR	95/81 m to major response: 2.8 mo	42-mo PFS: 88%	Dimopoulos et al, J Clin Onc 2023
ASPEN (Cohort 2)	Zanubrutinib	28	TN/RR	78/63 m to major response: 3 mo	42-mo PFS: 84%	Dimopoulos et al, J Clin Onc 2023
Phase 2	Acalabrutinib	106	TN/RR	94/81 m to major response: NA	66-mo PFS: 84% (TN) 66-mo PFS: 52% (RR)	Owen et al. Lancet Haematol 2020
Phase 2	Tirabrutinib	27	TN/RR	96/93 m to major response: 1.2 mo TN, 2.1 mo RR mo	24-mo PFS: 93%	Sekiguchi et al. Cancer Sci 2022
Phase 2	Orelabrutinib	47	RR	90.3/81.5 m to major response: NA	m-PFS: NR	Cao et al. EClinicalMedicine 2022

Chemo-free options: c-BTKi

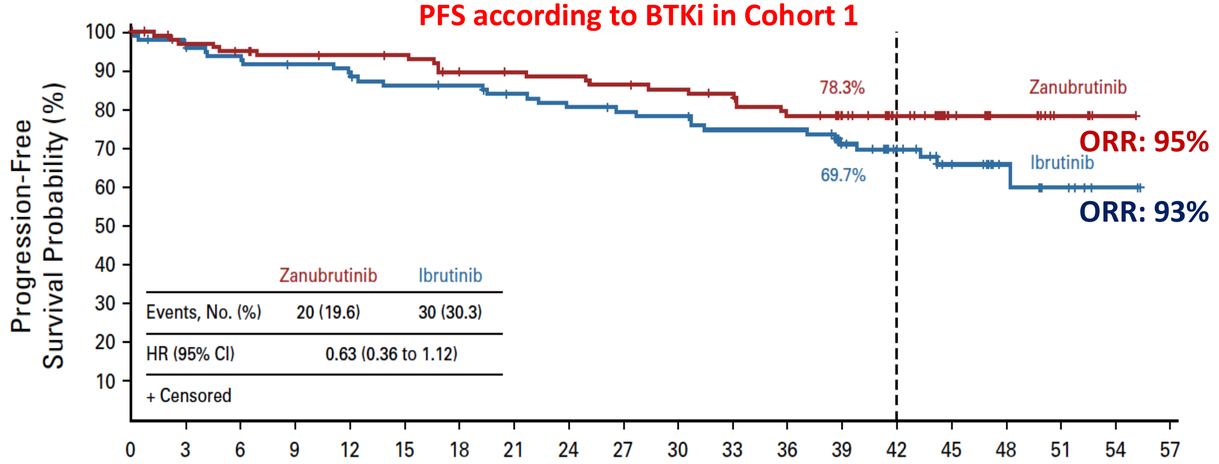
ASPEN study

Randomized, open-label, multicenter phase III study

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



PFS according to BTKi in Cohort 1



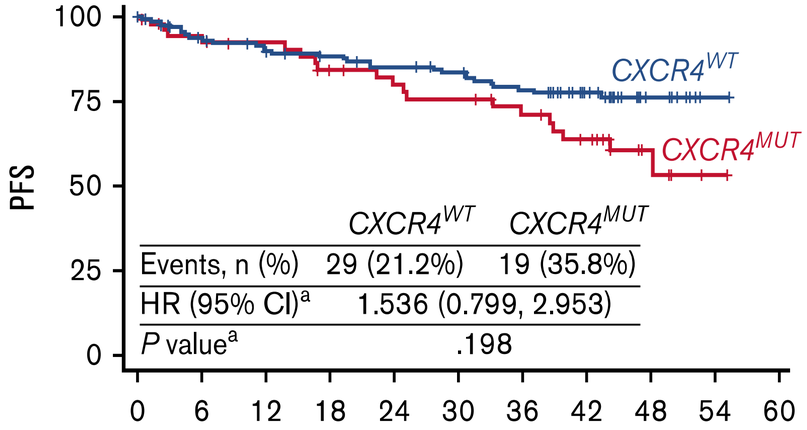
- ✓ **No superiority in CR+VGPR rate with Zanu vs Ibrutinib (*p=0.09)***
- ✓ **VGPR rates increased over time and were *numerically* higher with Zanu**
- ✓ **Median time to VGPR(+CR) rate was faster for patients on Zanu (16.6 mo vs 6.7 mo)**
- ✓ **No differences in PFS and OS according to BTKi**
- ✓ **CV safety profile (Z>I)**

AEIs (Grouped Terms),[a] No. (%)	Any grade		Grade ≥3	
	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[b]	**25 (25.5)**	15 (14.9)	**20 (20.4)[b]**	10 (9.9)
Atrial fibrillation/flutter[b]	**23 (23.5)[b]**	8 (7.9)	**8 (8.2)[b]**	2 (2.0)
Anemia	22 (22.4)	18 (17.8)	6 (6.1)	**12 (11.9)**
Neutropenia[b]	20 (20.4)	**35 (34.7)[b]**	10 (10.2)	**24 (23.8)[b]**
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, JCO 2023

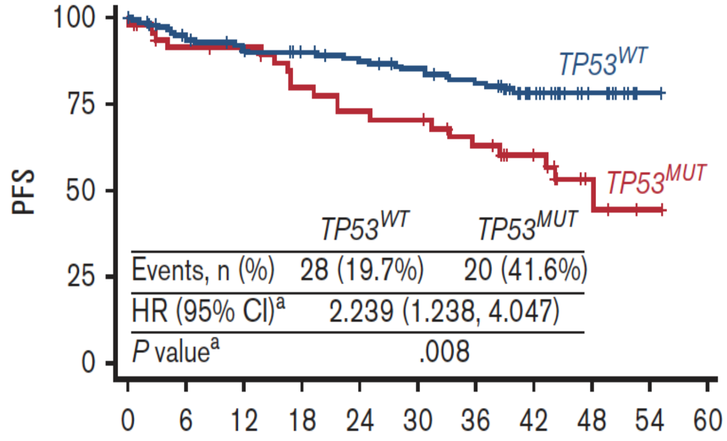
Chemo-free options: c-BTKi

ASPEN study – Response to Zanubrutinib and Ibrutinib according to CXCR4 and TP53 mutations



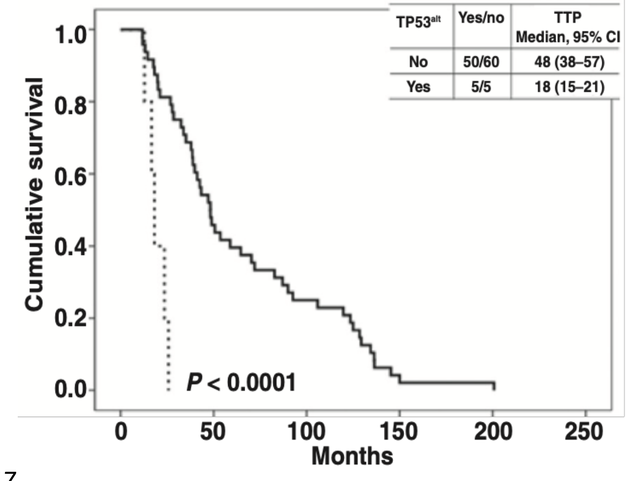
***CXCR4^{MUT}* pts (both NS and FS) have poorer prognosis after treatment with BTKi, with lower time to and VGPR+CR rates (p=0.02)**

Tam C et al, Blood Adv 2024



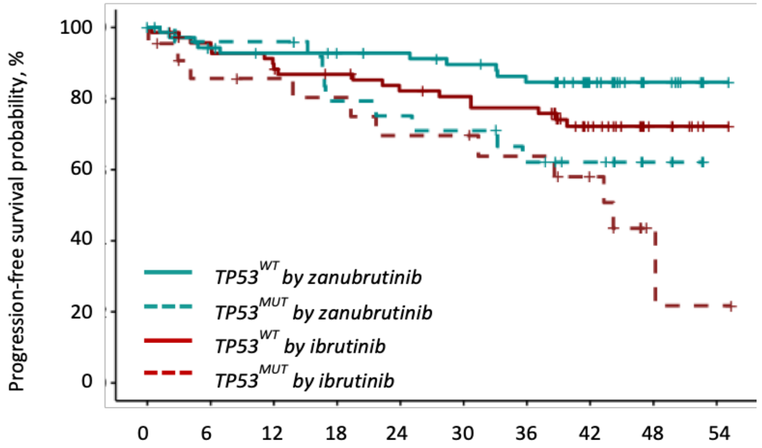
***TP53^{MUT}* pts have poorer prognosis after treatment with BTKi (vs *TP53^{WT} pts*)**

Median time to progression according to TP53^{Alt} status



Poulain S et al, Clin Cancer Res 2017

PFS according TP53^{Alt} status and BTKi



Tam C et al, Blood Adv 2024

Chemo-immunotherapy options

BR vs Ibrutinib

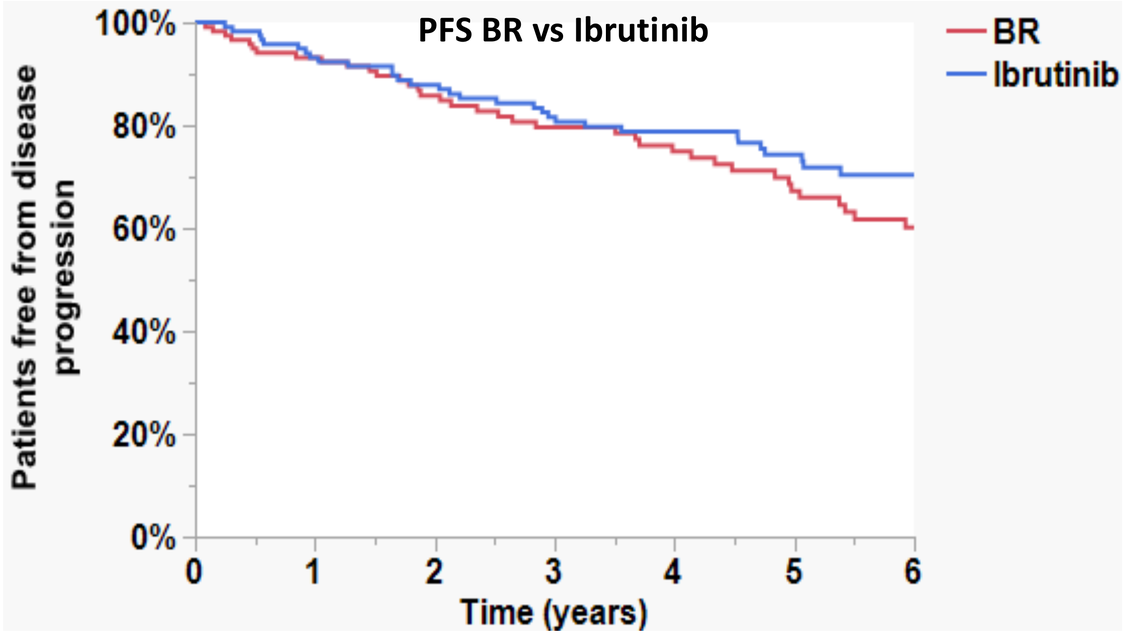
Bendamustine-Rituximab vs ibrutinib as primary therapy for WM: an international collaborative study

Study population: 246 pts who received Ibr (n=123) or BR (n=123) in US and Europe (2011-2021), TN, *MYD88^{L265P}* WM pts

Median FUP: 4.2 yrs

	BR	Ibr	p
Follow up, median, 95%CI, y	4.5 (3.7-4.9)	4.5 (4-4.7)	0.7
Age, median, range, y	68 (40-86)	68 (39-86)	0.9
IPSS%			0.63
Low	11	17	
Intermediate	33	33	
High	56	48	
Cycles, median (range)	6 (1-6) >4 cycles, 77%	42 (0.3-98)	
Overall response rate %	94	94	0.91
Major response rate %	92	83	0.05
Complete response %	20	2	<0.001
≥VGPR %	50	33	0.009

	BR (n=123)	I (n=123)	p-value
5-yrs PFS (%)	67%	74%	0.12
5-yrs OS (%)	86%	85%	0.79
Median TTNT (yrs)	NR	7 yrs	NA
TD due to AE (%)	8%	19.5%	0.003



BR and ibrutinib regimens in TN WM pts, THM:

✓ Deeper responses with BR

✓ Comparable outcomes

✓ Fewer patients discontinue BR due to adverse events

Abeykoon et al, IWWM-12, 2024

Chemoimmunotherapy vs chemo-free approach

Should BTKi be preferred to CIT frontline?

	Chemoimmunotherapy	BTKi inhibitors
Patient characteristics	Age, comorbidities, fitness, hematopoietic reserve	Age, comorbidities, fitness, hematopoietic reserve
Efficacy	High efficacy in TN patients consistently demonstrated in several studies	High efficacy in R/R and TN patients (N.B: clinical trials include only a limited number of TN patients), **but** rare CR
Toxicity	Acceptable short-term toxicity, **but** long-term toxicity typical of chemo (second tumors)	Favorable safety profile, **with some exceptions** Better with second generation BTKi
Administration	IV administration	Oral, easy administration
Duration of therapy	Fixed duration therapy Prolonged treatment-free interval	Treatment until progression No treatment-free interval
Cost	Low, especially after introduction of biosimilars	High (but we should not consider only direct costs —> pharmacoeconomy)
Biological features (MYD88, CXCR4, TP53)	No *MYD88* and *CXCR4* impact *TP53*^{Alt} related chemoresistance	*MYD88*^{WT}, *CXCR4*^{MUT}, *TP53*^{Alt} impact Role of *TP53* alterations needs to be further investigated

Ask patients!

Cancer Medicine. 2023;12:3376–3386

Patient preferences regarding treatment options for Waldenström's macroglobulinemia: A discrete choice experiment

Karima Amaador[1,2] | Pythia T. Nieuwkerk[3] | Monique C. Minnema[4] Marie José Kersten[1,2] | Josephine M. I. Vos[1,2]

the panel prefers to use zanubrutinib, if available, over other therapies in patients with mutated *TP53*^{MUT}.

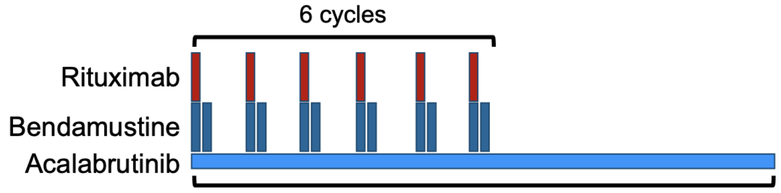
Kapoor et al. Semin Hemat 2025 (CP3)

New therapeutic approaches for WM therapy – TN pts

cBTKi + CIT combinations

BRAWM study (NCT04624906)

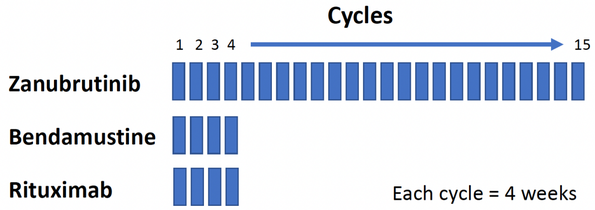
Multicenter, open-label, single-arm phase II trial of **BR+Acalabrutinib** in TN WM



Berenstein et al, IWWM-12, 2024

ZEBRA trial [WM-NET3] (NCT06561347)

Multicenter, phase II study of combination **zanubrutinib+BR (ZBR)** in TN WM



Xiong et al, IWWM-12, 2024

cBTKi-R or BCL2i-R vs CIT

RAINBOW (NCT04061512)

Randomized phase II/III study **RI vs DRC** in TN WM pts (R:1/1)

Experimental Arm
Ibrutinib
Rituximab

Comparator Arm
Cyclophosphamide
Dexamethasone
Rituximab

Primary outcomes
Response at 24 weeks
PFS at 2 years

Secondary Outcomes
Safety and tolerability
Overall response rate
Time to next treatment
Duration of response
Overall survival (OS)
Quality of Life

viWA-1 trial (NCT05099471)

Randomized phase II trial that compared **VR and DRC** in TN WM pts

Experimental Arm
Venetoclax
Rituximab

Comparator Arm
Cyclophosphamide
Dexamethasone
Rituximab

Primary outcome
CR/VGPR at 12 months after randomization

Secondary Outcomes
Safety and tolerability
Overall response rate
Duration of response
Progression-free survival
Overall survival
Quality of Life

cBTKi + Pi combinations

ECWM-2 trial (NCT03620903)

Multicenter, phase II trial, efficacy and toxicity of Bor-Ibr/Rix (B-IR) in TN WM pts

Buske et al. Blood 2024 (Suppl)

CZAR-1 trial (NCT04263480)

Multicenter, phase 2, open label, randomized Carfilzomib+Ibr vs Ibr in TN/RR WM pts

ZID combination (NCT04463953)

Phase II clinical trial to evaluate the efficacy and safety of zanubrutinib, ixazomib, and dexamethasone (ZID) in TN WM pts

Wenjie et al. Blood 2024 (Suppl)

cBKTi/BCL2i combinations

Venetoclax+Ibrutinib

Phase II study of I+V WM TN pts. Median FUP: 36 months
N=45 (all patients MYD88 L265P–mut, and 17 CXCR4-mut)
ORR: 100% , MRR: 95%, 36 mo-PFS: 51% 93%

Study stopped due to a higher-than-expected occurrence of ventricular arrhythmia in 4 (9%), including 2 G5 events

Castillo et al. Blood 2024

BGB-11417-203 (NCT05952037) – Cohort 4

Multicenter, phase 2, open label combination therapy with Sonrotoclax (BGB-11417) plus zanubrutinib for up to 20 cycles

Lee et al. Blood 2024 (Suppl)

Clinical case (2) - RR

February '25: (F.G.): 75-yrs old female WM pts in treatment with Zanubrutinib pts in visit with asthenia and systemic symptoms

- **2017:** diagnosed with asymptomatic WM (*MYD88^{L265P}, CXCR4^{WT}, TP53: NA*)
- **2019:** active disease (cytopenias, systemic symptoms); CT: mild splenomegaly (14 cm), no bulky or EMD disease. Same molecular features → **R-Bendamustine** (administered 4 cycles only due to persistent G4 neutropenia): **VGPR;**
- **2022:** first relapse (Hb 8.1 g/dl, weight loss, fatigue; sIgM progressive increase). **BM**: LPL; molecular features: *MYD88^{L265P}, CXCR4^{WT},* ***TP53^{Y220C}****. No significant comorbidities* → **Zanubrutinib 80 mg 2 cpr BID >> Until now**

Investigations (2025)

- **Lab tests.** Hb 8.5 g/dl, GB 3500/mmc (ANC 1500/mmc, ALC 600/mmc), PLT 229000/mmc, SPE with IgM-k (1.2 g/dl), sIgM 1200 mg/dl;
- **CT scan:** diffuse adenopathies (max 4.5 cm para-aortic). Splenomegaly (15 cm in dpb);
- **Bone marrow biopsy:** LPL; **molecular characteristics:** *MYD88^{L265P}, CXCR4^{WT}, TP53^{Y220C}*. FISH del17p: absent;
- ***BTK^{C481S}*** **mutation**: present

Next step?

A. Second course of CIT (BR or DRC)

B. Venetoclax

C. PI based scheme

D. Pirtobrutinib

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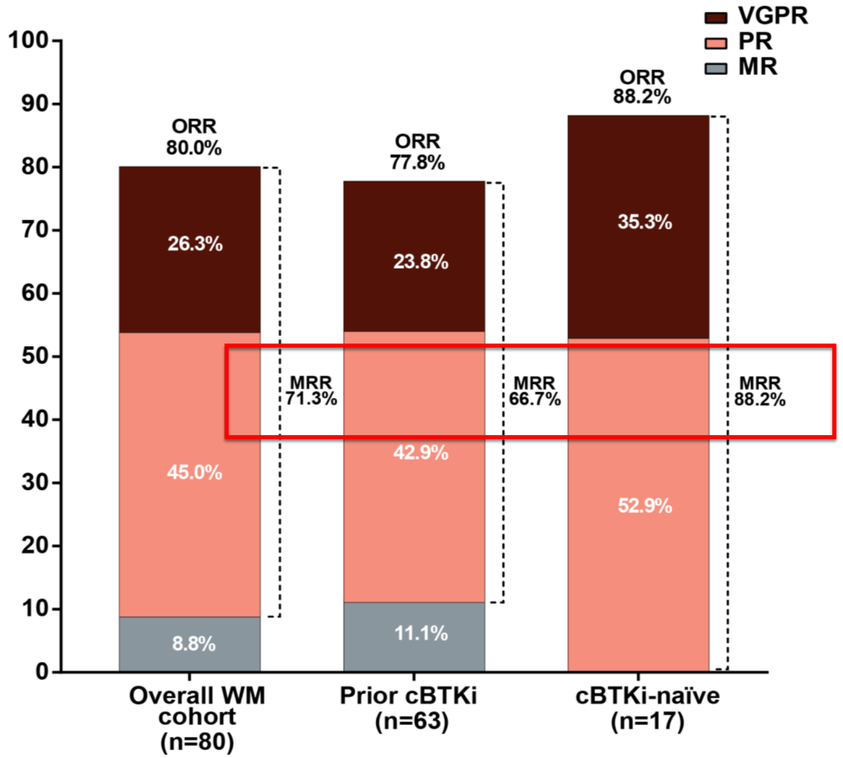
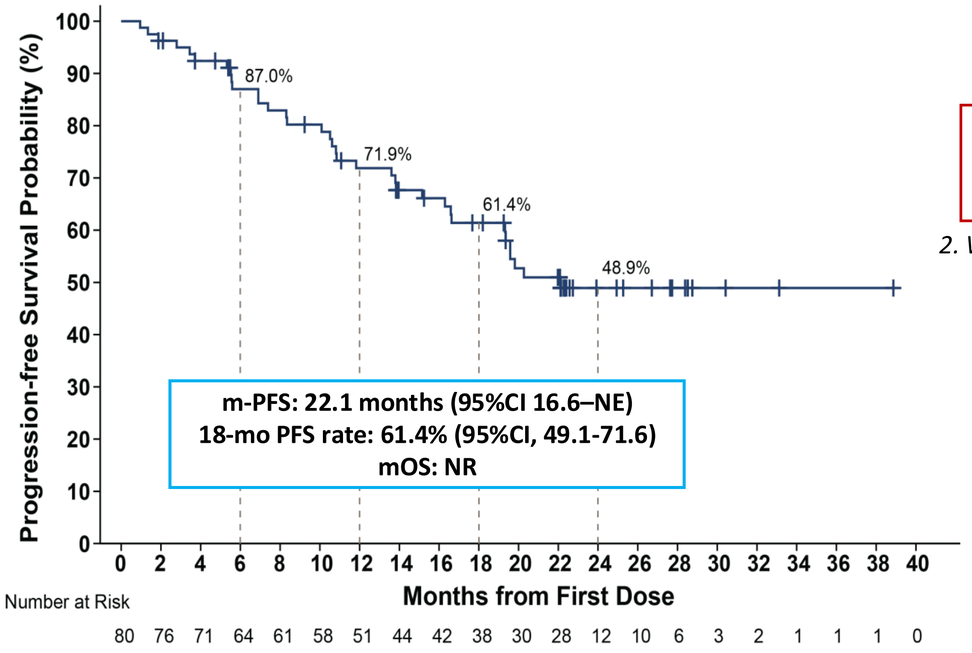
Chemo-free options: nc-BTKi

Pirtobrutinib

Pirtobrutinib in RR WM: Updated Results from the Phase 1/2 BRUIN Study

Study population: 80 WM RR pts, median age 69 yrs (range: 42–84)
Median number of prior lines of systemic therapy received was 3 (range, 1–11). 63 (79%) patients had received prior cBTKi treatment and 17 (21%) were cBTKi-naïve
Key endpoints: ORR, PFS, OS, safety





…and Nemtabrutinib[2,3,]

2. Woyach et al. Cancer Discov 2024
3. Perini et al. JCO 2023

ORR: 80% (95%CI: 69.6-88.1)
ORR in prior cBTKi: 77.8% (95%CI: 65.6-87.3)
ORR in BTKi naive: 88.2% (95%CI: 6.36-98.5)
G≥3 TEAE: hypertension (3.8%), hemorrhage/hematoma (3.8%), and atrial fibrillation/flutter (1.3%)

Palomba et al, IWWM-12, 2024

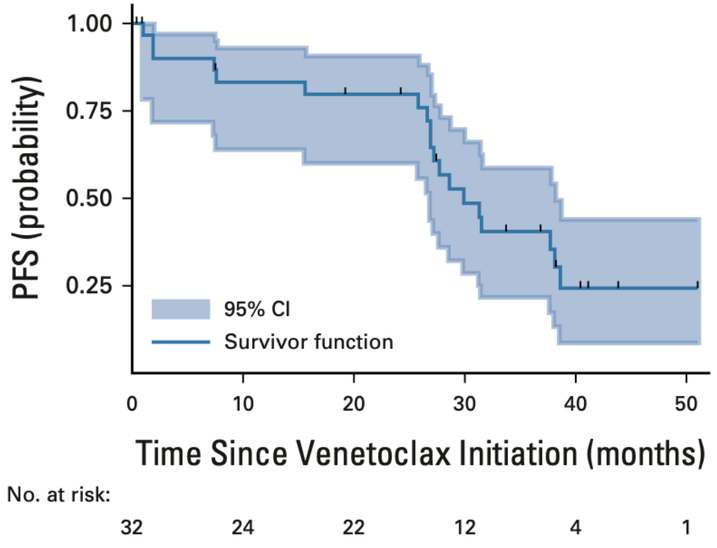
Chemo-free options: BCL2i

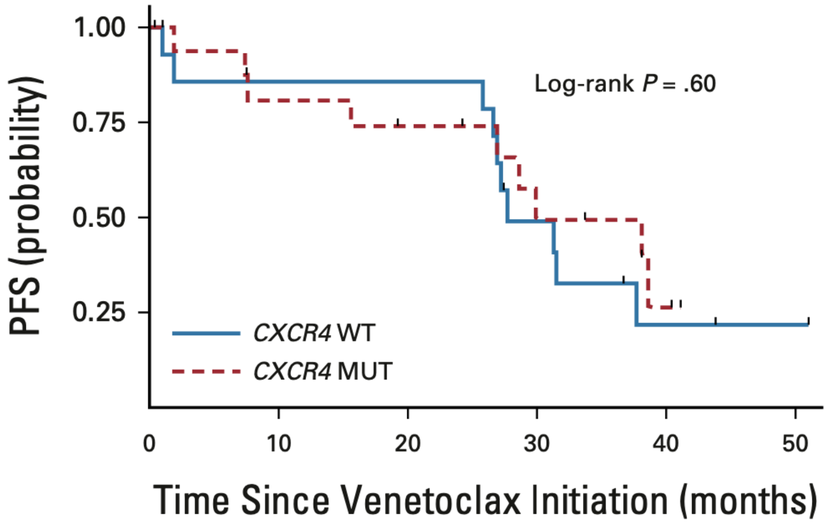
Venetoclax

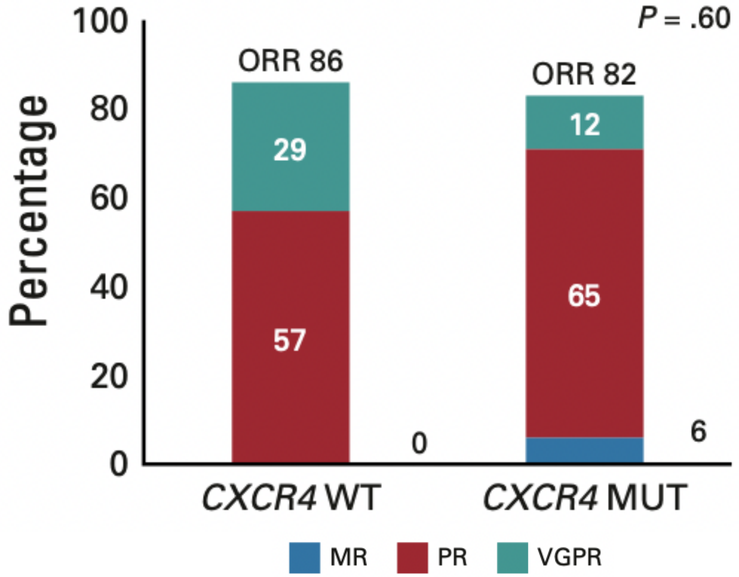
Venetoclax in RR WM pts

Phase II study of Ven in WM RR pts. Median FUP: 33 months
N=32 (**all** patients *MYD88(L265P)* mut, and 17 *CXCR4*^{MUT}). 16 prior cBTKi

Ven: dose escalated from 200 to 800 mg daily up to 2 yrs







m-PFS: 30 mo
ORR, MR and VGPR: 84%, 81% and 19% respectively
CXCR4-mut did not affect treatment response and PFS
Longer time to response in pts with prior BTKi (4.5 vs 1.4 months)
AE: G3 neutropenia 45% (1 febrile), 1 clinical TLS

Castillo et al. JCO 2021

New therapeutic approaches for WM therapy – RR pts

Bispecific Antibodies

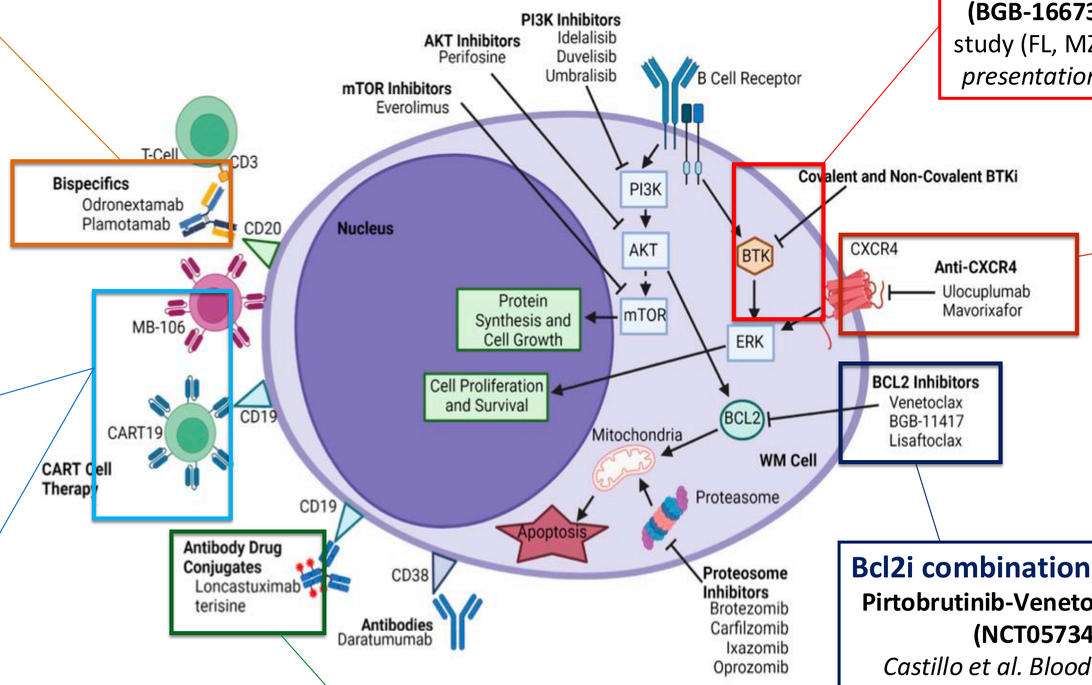
Epcoritamab (NCT06510491) – WM-NET2
Single-arm, multicenter, phase 2 study to evaluate the efficacy and safety of epcoritamab in patients with relapsed or refractory (R/R) WM/LPL
(Von Keudell et al. Blood 2024 ASH meeting)

CAR-T cells

MB-106 (third gen CD20-directed CAR-T therapy)
Phase 1/2 clinical trial with MB-106 at Fred Hutchinson Cancer Center *(Till B et al, Hemasphere. 2024; Shadman et al. 2023 ASH meeting)*

CAR-T cells

ZUMA-25 (NCT05537766)
Efficacy of Brexu-cel in rare B-cell malignancies including WM



BTK-degrader

Phase I/II study CADANCE-101 (BGB-16673-101). Ongoing first-in-human study (FL, MZL, WM). *Data presented as oral presentation at latest EHA by A.M. Frustaci*

Anti-CXCR4 agents

Ulocuplumab (mAb anti-CXCR4)
Mavorixafor (X4P-001)

Ab drug conjugates

Loncastuximab terisine (NCT05190705)– WM-NET1
Single-arm, multicenter, phase 2 study to evaluate the efficacy and safety of Lonca in patients with (R/R) WM/LPL
(Castillo et al. Blood 2024 ASH meeting)

Bcl2i combinations/Novel Bcl2i

Pirtobrutinib-Venetoclax in RR WM (NCT05734495)
Castillo et al. Blood 2024 (Suppl)

BGB-11417-203 (NCT05952037) – Cohort 1-2-3
Multicenter, phase 2, open label therapy with Sonrotoclax (BGB-11417) in RR WM pts
Lee et al. Blood 2024 (Suppl)

Iopofosine^{131} (CLR-131)

CLOVER-WaM study (NCT02952508)
Iopofosine 131 in RR WM pts (at least 2 LOT)
(Ailawadh et al. Blood 2024, ASH meeting)

PROTACs

KIN-8194 (dual HCK/BTK PROTAC)
(Yang G et al, Blood 2021)
DFCI-002-06 (dual HCK/BTK PROTAC)
(Liu S et al. Blood 2024 ASH meeting)

Checkpoint inhibitors (Cpi)

Phase II clinical trial evaluating a combination of **Pembrolizumab and Rituximab** RR WM pts
(Kothari J et al, BHJ 2024)

Adapted from Chohan KL and Kapoor P, Current Hematologic Malignancy Reports 2024

Chemoimmunotherapy vs chemo-free approach - Conclusions

- WM is a rare lymphoma usually characterized by an indolent course with deep responses and prolonged survival with chemoimmunotherapy;
- BTK inhibitors have changed treatment paradigm in R/R WM patients, and are now challenging CIT also as primary treatment;
- In the relapsed/refractory setting, the therapeutic panorama is increasingly chemo-free;
- At the moment, trials prospectively comparing BTKis with chemoimmunotherapy head-to-head are lacking;
- Currently, both chemoimmunotherapy and chemo-free approaches (cBTKi) represent valid options; treatment decisions should be individualized based on patient clinical characteristics and disease biology.

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