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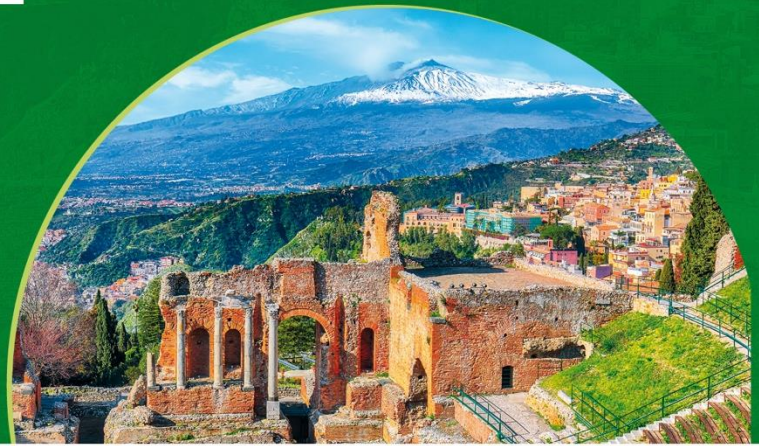

FONDAZIONE ITALIANA LINFOMI

“La terapia della macroglobulinemia di Waldenström e delle sue complicanze nel paziente anziano”

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Disclosures of Emanuele Cencini

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La Macroglobulinemia di Waldenstrom nel paziente anziano

DEFINIZIONE EPIDEMIOLOGIA

- Patologia rara caratterizzata da elementi clonali linfoplasmacellulari midollari e componente monoclonale IgM secernente catene leggere k
- Incidenza aumenta con l'età. Età mediana di incidenza 73 anni

FISIOPATOLOGIA CLINICA

- Presenza della mutazione L265P del gene MYD88 (>90%) e/o mutazioni di CXCR4 (30%)
- Astenia, sintomi sistemici, splenomegalia, sintomi da iperviscosità
- Complicanze della malattia (crioglobulinemia, neuropatia, nefropatia, amiloidosi) che si aggiungono alle comorbidità del paziente

DIAGNOSI

- Presenza di CM sierica di tipo IgM di qualsiasi entità.
- Alla BOM infiltrato linfoide e linfoplasmacellulare clonale con prevalente clonalità IgM k, frequente aumento dei mastociti

Quali pazienti devono essere trattati?

Asintomatici/Basso tumor burden

Osservazione

Le linee guida ESMO consigliano di attendere un livello di IgM >6000 mg/dL

Sintomatici/Elevato tumor burden e/o complicanze correlate alla malattia

Inizio trattamento

Table 1. Indications for treatment initiation

Clinical Criteria	Laboratory Criteria
Systemic symptoms (recurrent fever, night sweats, weight loss, fatigue)	Symptomatic cryglobulinemia
Hyperviscosity	Cold agglutinin anemia
Symptomatic or bulky (>/=5 cm in maximum diameter) lympadenopathy	Immune hemolytic anemia and/or thrombocytopenia
Symptomatic hepatomegaly and/or splenomegaly	Nephropathy related to WM
Symptomatic organomegaly and/or organ or tissue infiltration	Amyloidosis related to WM
Peripheral neuropathy due to WM	Hemoglobin </=10 g/dL
	Platelet count <100 x 10^9/L

Kyle RA, et al. Semin Oncol 2003; 30: 116–120; Kastritis E, et al. Ann Oncol 2018; 29 (Suppl_4): iv41–iv50; Gertz et al., AJH 2022

Drivers per la scelta del trattamento nel paziente anziano

Caratteristiche del paziente

- Età? (Nessuno studio ha un limite di età)
- PS
- Comorbidità
- sGA, fitness status?

Caratteristiche cliniche della malattia

- Necessità di un rapido controllo
- Citopenia
- Malattia Bulky
- Complicanze (Croglobulinemia/cold agglutinine, interessamento renale, neuropatia, Sindrome di Bing-Neel)

Obiettivo del trattamento

- alleviare i sintomi
- ridurre il rischio di danno d'organo
- ottenere una remissione duratura
- Durata del trattamento (fissa vs fino a progressione)
- Pesare efficacia e tossicità dei singoli schemi

Genetic profile?

- MYD88MUT/CXCR4WT, MYD88MUT/CXCR4MUT, MYD88WT/CXCR4WT)

-TP53

MAYO CLINIC

Newly Diagnosed Waldenström Macroglobulinemia

♦ IgM MGUS (<10% clonal infiltrate) ♦ Smoldering (asymptomatic) WM	♦ IgM-related neuropathy ♦ WM-associated hemolytic anemia ♦ Symptomatic cryoglobulinemia	♦ Bulky (≥5 cm max. diameter) or symptomatic lymphadenopathy ♦ Clinically significant cytopenias: -Hemoglobin ≤10g/dL -Platelet count <100 x10^9/L ♦ Hyperviscosity symptoms[3] ♦ Constitutional symptoms ♦ Concurrent ALH amyloidosis[4]
Observation (irrespective of IgM level)	Rituximab x 1 cycle[1,2] (no maintenance therapy)	i) Bendamustine-Rituximab (BR) x 6 cycles[4] (no rituximab maintenance) or ii) Zanubrutinib[5]

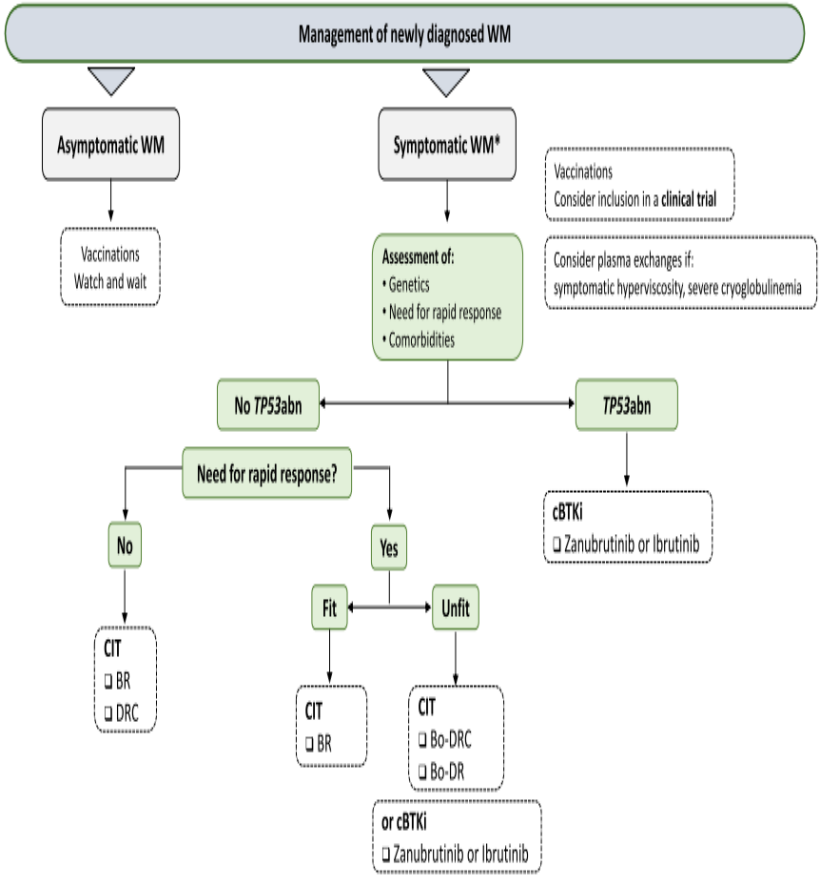
[1]Initiate plasmapheresis if symptomatic hyperviscosity develops in the setting of IgM flare. Avoid rituximab monotherapy if baseline IgM level ≥ 4000 mg/dL and consider preemptive plasmapheresis prior to initiating rituximab to avert IgM flare associated hyperviscosity symptoms.

[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.



Roos-Weil et al., EJC 2026; Gertz, AJH 2025

Schemi di chemioimmunoterapia

Pro:Durata fissa, risposta rapida, profonda e prolungata nel tempo (soprattutto BR) , tossicità limitata (soprattutto DRC)

Contro: immunosoppressione prolungata, infezioni, rischio di MDS/seconde neoplasie

Regimen	Patients	Untreated patients (%)	ORR%	CR%	Median PFS (months)	Reference
DRC	72	100	83	7	35	Dimopoulos JCO 2007 Kastritis, Blood 2015
R-Bendamustine	69	100	97	19	67% at 5 years	Laribi et al, Br J Haematol 2019; Br J Haematol 2024
R-Fludarabine	43	63	96	4	51	Treon, Blood 2009
FCR	43	65	79	12	50	Tedeschi, Cancer 2012
R-Cladribine	29	70	90	24	Not reached	Laszlo, JCO 2010

Schemi di terapia contenenti inibitori del proteasoma

Pro: chemo-free, durata fissa, risposta prolungata, efficacia indipendente dal profilo genetico

Contro: neuropatia, numerosi accessi in ambulatorio

Regimen	Pts	ORR%	CR%	Median PFS (months)	Grade 3-4 toxicity	Reference
BDR x 8 – WTCTG trial (Bortezomib bi-weekly)	23 TN	96	NR	66	Neuropathy 30% (61% discontinued due to PN)	Treon, JCO 2009; Treon Blood 2015
BDR x 5 - EMN trial (Bortezomib weekly)	65 TN	85	3	42	Neuropathy 7% (8% discontinued due to PN)	Dimopoulos, Blood 2013 Gavriatopoulou, Blood 2017
R+Carfilzomib+Dexamethasone (CaRD)	33 TN	87	3	64% at 15 months	Cardiomiopathy 3% Neuropathy 0%	Treon, Blood 2014
R+Ixazomib+Dexamethasone	26 TN	96	0	40	No grade 3-4 toxicity related to therapy	Castillo Clin Canc Res 2018 Castillo, Blood Adv 2020

First-line treatment of Waldenström's macroglobulinemia in Italy: A multicenter real-life study on 547 patients to evaluate the long-term efficacy and tolerability of different chemoimmunotherapy strategies

	Overall (n=499)	BR (n=245)	DRC (n=116)	Other R-chemo (n=86)	Chemo alone (n=52)
Gender M/F	64/36	65/35	59/41	67/33	62/38
Median age (range)	69.5 (30-90)	68 (38-88)	72 (30-90)	67 (36-84)	78 (55-90)
Age >65	317/496 (63.9%)	144/244 (59.0%)	82/116 (70.7%)	48/86 (55.8%)	43/50 (86.0%)
Age >75	159/496 (32.1%)	63/244 (25.8%)	48/116 (41.4%)	20/86 (23.2%)	28/50 (56.0%)
Plts <100000/mmc	60/492 (12.2%)	33/244 (13.5%)	18/114 (15.8%)	3/82 (3.7%)	6/52 (11.5%)
Hb < 10 g/dL	234/495 (47.3%)	123/245 (50.2%)	51/115 (44.3%)	34/83 (40.9%)	26/52 (50.0%)
IgM >6000 mg/dL	74/484 (15.3%)	47/241 (19.5%)	14/113 (12.4%)	7/81 (8.6%)	6/49 (12.2%)
Beta2microglobulin	336/437 (76.9%)	191/225 (84.9%)	64/100 (64.0%)	53/70 (75.7%)	28/42 (66.7%)
IPSSWM low risk	111/461 (24.1%)	49/225 (21.8%)	27/111 (24.3%)	24/76 (31.6%)	11/49 (22.4%)
IPSSWM intermediate risk	194/461 (42.1%)	93/225 (41.3%)	58/111 (52.2%)	26/76 (34.2%)	17/49 (34.7%)
IPSSWM high risk	156/461 (33.8%)	83/225 (36.9%)	26/111 (23.5%)	26/76 (34.2%)	21/49 (42.9%)

		Benda 90 (n=129)	Benda 70 (n=59)	p
Age	Median	64	70	0.005
Age	Up to 64	73 (56.6)	17 (28.8)	
	65-74	36 (27.9)	23 (39.0)	
	Over 75	20 (15.5)	19 (32.2)	0.001

	Overall (n=499)	BR (n=245)	DRC (n=116)	Other R-chemo (n=86)	Chemo alone (n=52)	p
N° cycles reduction	88/486 (18.1%)	40/244 (16.4%)	24/113 (21.2%)	11/82 (13.4%)	13/47 (27.6%)	0.148
Dose reduction	50/486 (10.3%)	35/244 (14.3%)	7/116 (6.0%)	4/81 (4.9%)	4/45 (8.9%)	0.026

Autore F., et al. AJH 2024

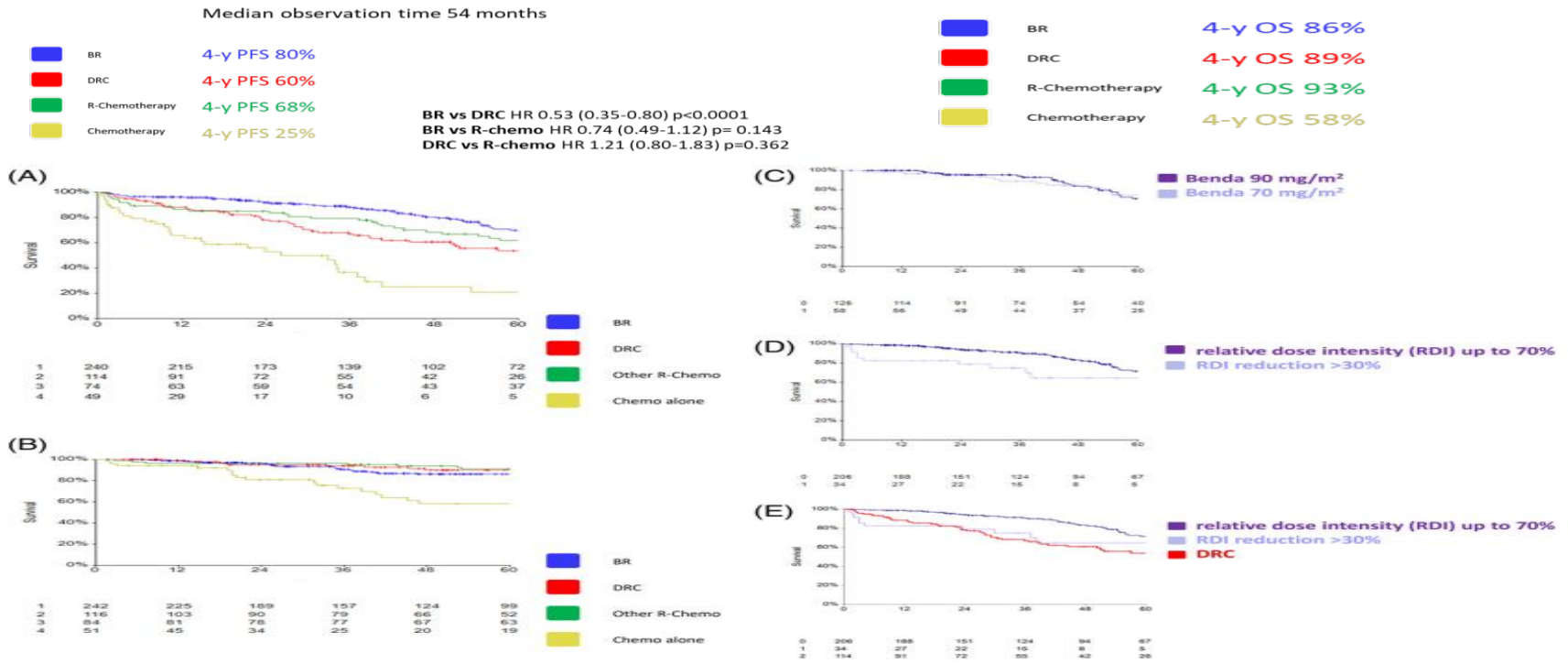
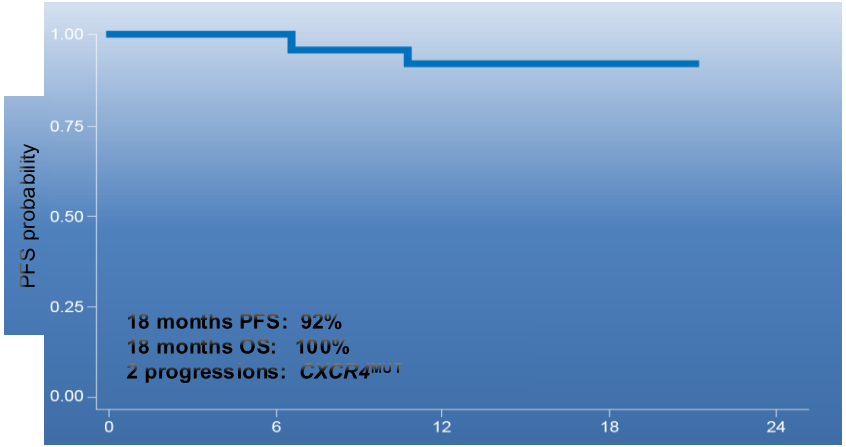


FIGURE 1 (A) Progression free survival (PFS) of the four Waldenström macroglobulinemia (WM) subgroups of treatment; (B) OS of the four WM subgroups of treatment; (C) PFS comparison between WM patients treated with BR at a bendamustine dose of 90 mg/m2 (0) and WM patients treated with BR at a bendamustine dose of 70 mg/m2 (1); (D) PFS comparison between WM patients treated with BR at a bendamustine dose with a relative dose intensity (RDI) up to 70% (0) and WM patients treated with BR at a bendamustine dose with an RDI reduction >30% (1); (E) PFS comparison between WM patients treated with BR at a bendamustine dose with an RDI up to 70% (0), WM patients treated with BR at a bendamustine dose with an RDI reduction >30% (1) and WM patients treated with DRC (2).

Autore F., et al. AJH 2024

Ibrutinib Monotherapy in Symptomatic, Treatment-Naïve Patients With Waldenström Macroglobulinemia

	All patients N=30	*MyD88*^{MUT} *CXCR4*^{WT} N=16	*MyD88*^{MUT} *CXCR4*^{MUT} N=14	p value
ORR N (%)	30 (100)	16 (100)	14 (100)	1.00
Major response rate N (%)	25 (83)	15 (94)	10 (71%)	0.16
Categorical response N (%)				
Minor	5 (17)	1 (6)	4 (29)	0.16
Partial	19 (63)	10 (63)	9 (64)	1.00
VGPR	6 (20)	5 (31)	1 (7)	0.18
Median time to response				
Minor response	1.0 m	0.9	1.7	0.07
Major response	1.9 m	1.8	7.3	0.01



La risposta dipende dal profilo genetico (MYD88 WT e CXCR4 MUT minore risposta)
Pochi studi di prima linea, NON approvato in Italia
Incidenza FA 10-15% nei vari studi

Treon SP, et al. J Clin Oncol 2018; 36: 2755–2761

Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study

Key eligibility criteria
- Confirmed WM[a] (N≈150)
- Measurable disease (serum IgM >0.5 g/dL)
- RTX sensitive
  - Not refractory to last prior RTX-based therapy
  - Had not received RTX <12 months before first study dose

1:1 Randomization

Stratification
- IPSSWM (low vs intermediate vs high)
- Number of prior regimens (0 vs 1–2 vs ≥3)
- ECOG PS (0–1 vs 2)

Arm A
Ibrutinib-RTX
Oral ibrutinib 420 mg once daily until PD
RTX 375 mg/m² IV on day 1 of weeks 1–4 and 17–20

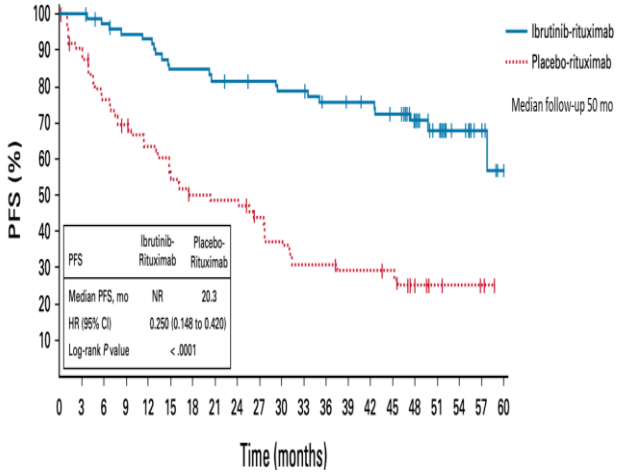
Arm B
Placebo-RTX
Placebo until PD
RTX 375 mg/m² IV on day 1 of weeks 1–4 and 17–20

Crossover to single-agent ibrutinib allowed after PD[b]

- **Endpoints:** PFS and response rates by IRC, OS, Hgb improvement, TTNT, safety
- At study closure, patients without PD could continue ibrutinib in an extension program

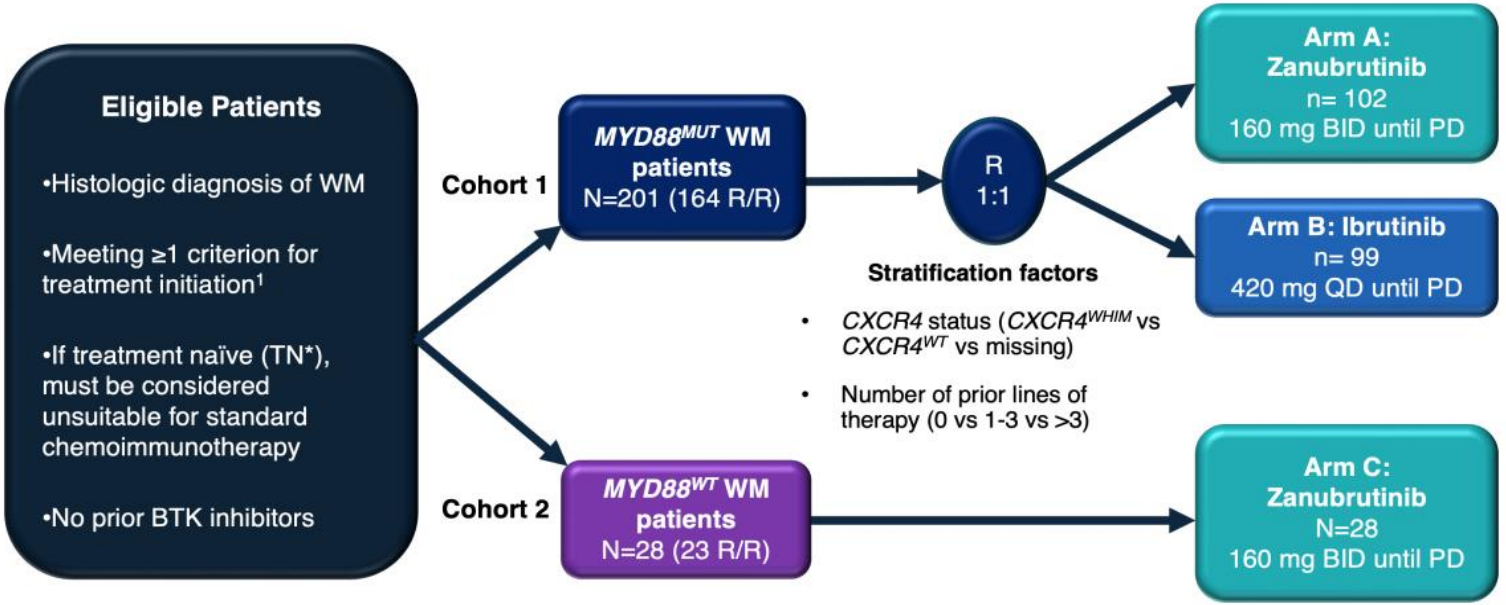
TABLE 1. Demographics and Clinical Characteristics of Patients at Baseline

Characteristic	Ibrutinib-Rituximab (n = 75)	Placebo-Rituximab (n = 75)
Median age, years (range)	70 (36-89)	68 (39-85)
Male, No. (%)	45 (60)	54 (72)
IPSSWM, No. (%)		
Low	15 (20)	17 (23)
Intermediate	33 (44)	28 (37)
High	27 (36)	30 (40)
Median Hgb, g/dL (range)	10.5 (6.9-15.5)	10.0 (6.6-16.1)
Baseline Hgb ≤ 11.0 g/dL, No. (%)	44 (59)	50 (67)
Median serum IgM, g/L (range)	33 (6-78)	32 (6-83)
No. of prior systemic therapies, No. (%)		
0	34 (45)	34 (45)
1-2	34 (45)	36 (48)
≥ 3	7 (9)	5 (7)
Genotype, No. (%)		
MYD88^{L265P}/*CXCR4*^{WT}	32 (43)	35 (47)
MYD88^{L265P}/*CXCR4*^{WHIM}	26 (35)	23 (31)
MYD88^{WT}/*CXCR4*^{WT}	11 (15)	9 (12)



Buske C., et al. JCO 2022

Zanubrutinib Versus Ibrutinib in Symptomatic Waldenström Macroglobulinemia: Final Analysis From the Randomized Phase III ASPEN Study



EUDRACT 2016-002980-33; NCT03053440

Primary endpoint:
CR or VGPR, per modified IWWM-6, by **independent review**

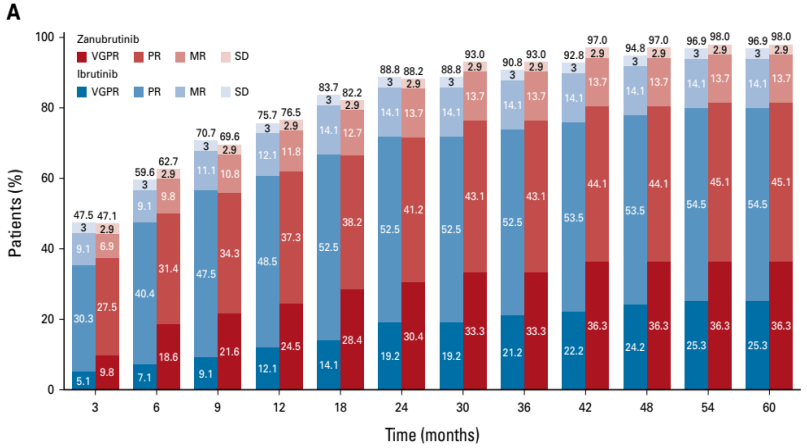
Secondary Endpoints:
1) MRR (≥PR)
2) PFS
3) Duration of response
4) Safety

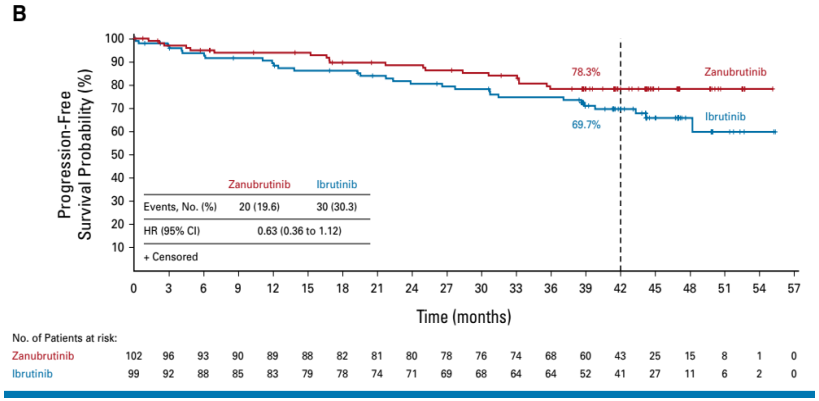
median follow-up cohort 1: 44.4 mo and cohort 2: 42.9 mo

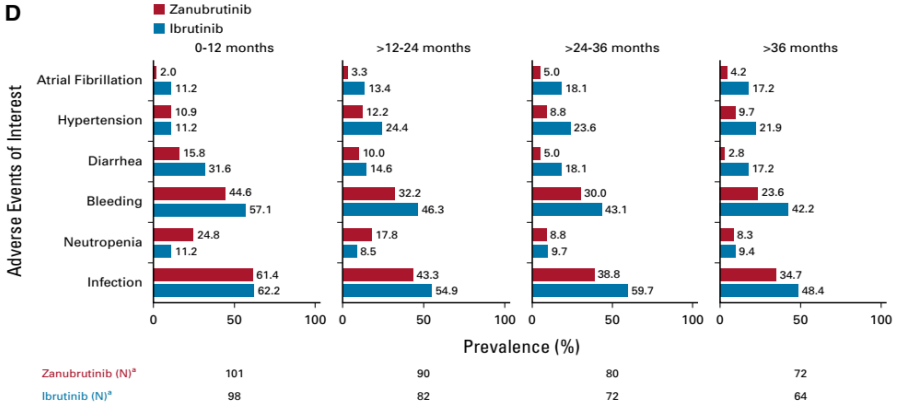
Dimopoulos MA. *J Clin Oncol*, 2023; Dimopoulos et al, IWWM-12, 2024

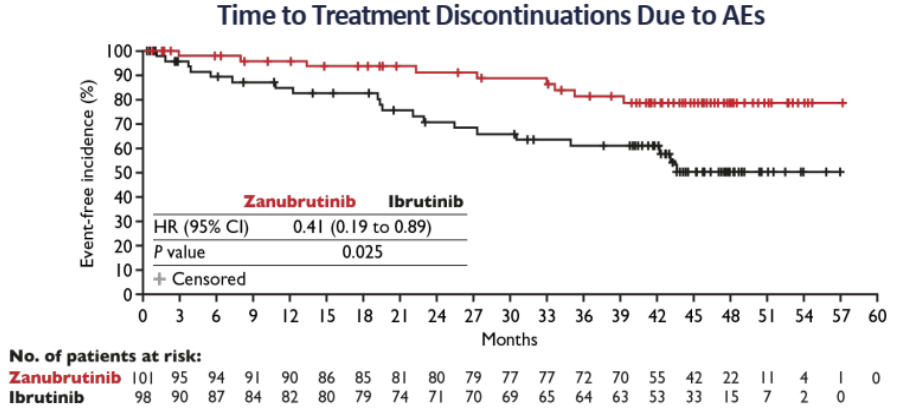
Characteristics	Cohort 1		Cohort 2
	Ibrutinib (n=99)	Zanubrutinib (n=102)	Zanubrutinib (N=28)
Age, years median (range) >65 years, n (%) >75 years, n (%)	70 (38-90) 70 (**70.7**) 22 (22.2)	70 (45-87) 61 (59.8) 34 (**33.3**)	72 (39-87) 19 (67.9) 12 (**42.9**)
Sex, n (%) Male	65 (65.7)	69 (67.6)	14 (50.0)
Prior lines of therapy, n (%) 0 1-3 >3	18 (18.2) 74 (74.7) 7 (7.1)	19 (18.6) 76 (74.5) 7 (6.9)	5 (17.9) 20 (71.4) 3 (10.7)
Genotype by NGS, n (%) *CXCR4*^{WT} *CXCR4*^{MUT} Unknown	72 (72.7) 20 (20.2) 7 (7.1)	65 (63.7) 33 (**32.4**) 4 (3.9)	27 (96.4) 1 (3.6) 0
IPSS WM, n (%) Low Intermediate High	13 (13.1) 42 (42.4) 44 (44.4)	17 (16.7) 38 (37.3) 47 (46.1)	5 (17.9) 11 (39.3) 12 (42.9)
Hemoglobin ≤110 g/L, n (%)	53 (53.5)	67 (**65.7**)	15 (53.6)
Baseline IgM (g/L, central lab), median (range)	34.2 (2.4-108.0)	31.8 (5.8-86.9)	28.5 (5.6-73.4)
Bone marrow involvement (%), median (range)	60 (0-90)	60 (0-90)	22.5 (0-50)
Extramedullary disease by investigator, n (%)	66 (66.7)	63 (61.8)	16 (57.1)

- **Più** pazienti con età **> 75 anni** randomizzati a **Zanubrutinib** rispetto a Ibrutinib (33% vs 22%)
- **Più** pazienti **anemici** randomizzati a **Zanubrutinib** rispetto a Ibrutinib (66% vs 54%)
- Più pazienti con mutazione CXCR4^{WHIM} in NGS trattati con Zanubrutinib (analisi post-hoc)
- Nella coorte 2 maggior percentuale di pazienti > 75 anni rispetto alla coorte 1



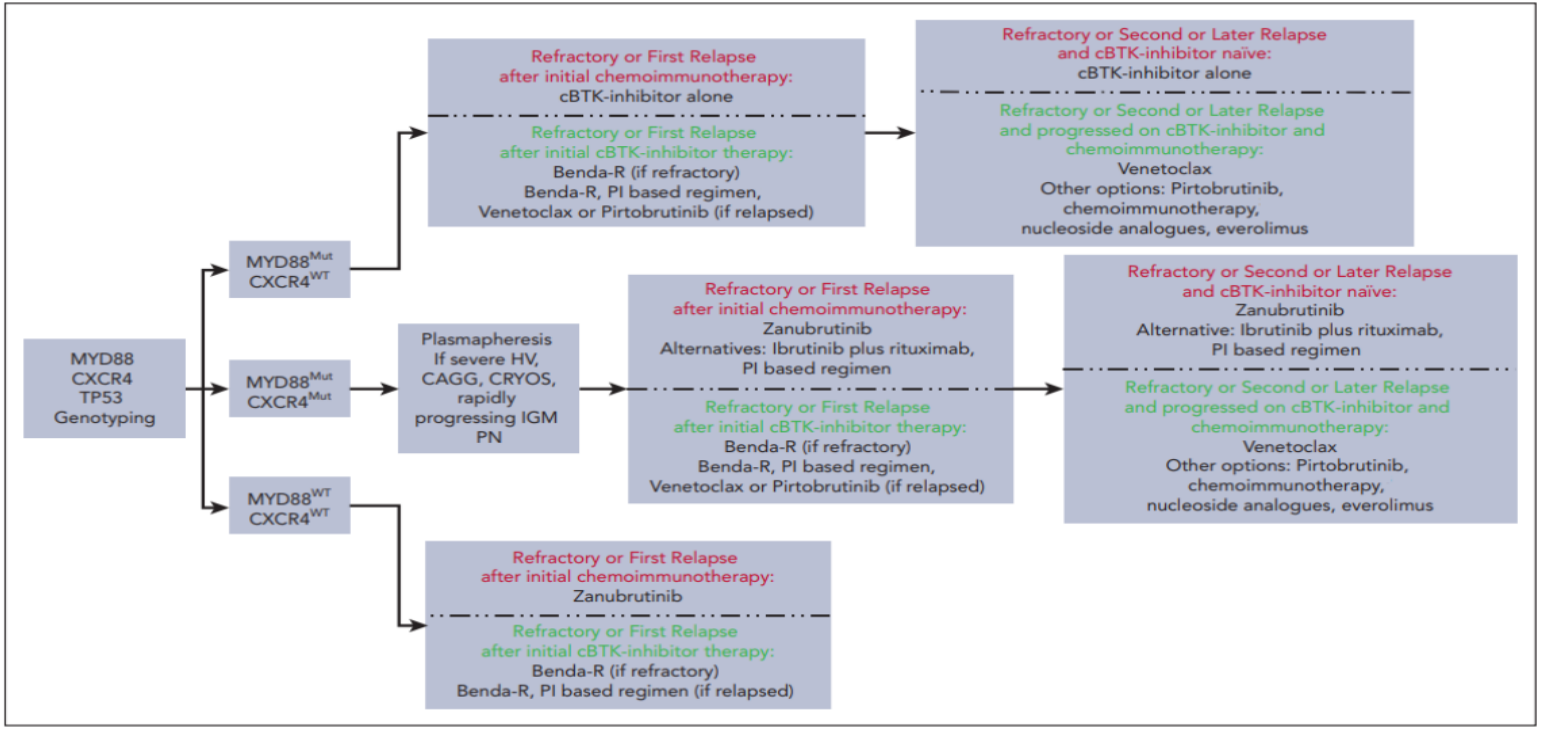






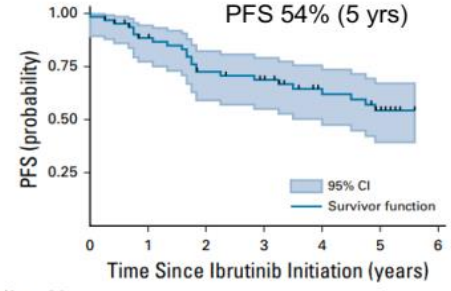
Dimopoulos, et al. JCO 2023

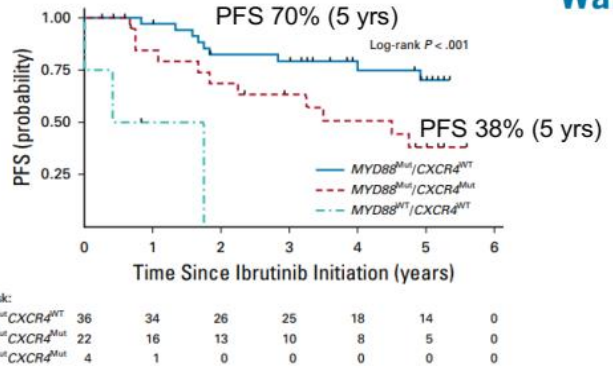
Algoritmo terapeutico per i pazienti ricaduti/refrattari in base alla terapia ricevuta in precedenza

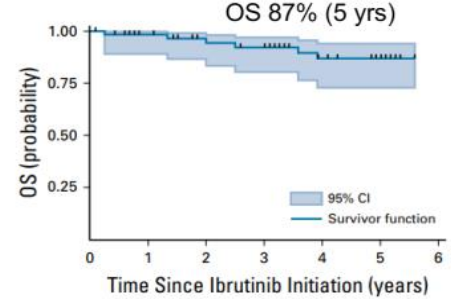


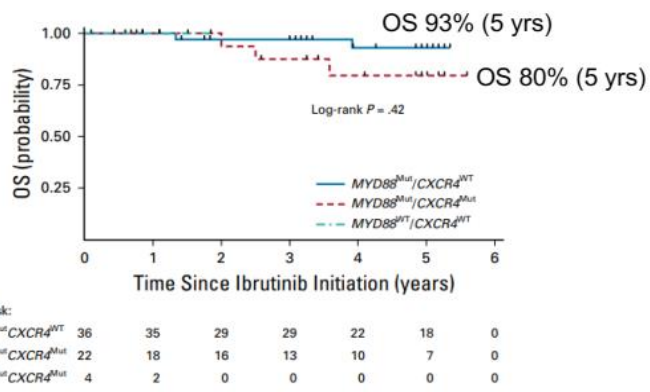
Buske C. *Semin Hematol*, 2023; 60: 73-79 — Treon SP. *Blood*, 2024; 143: 1702-1712

Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia









CXCR4 and MYD88 mutational status have an impact on PFS in pts treated with Ibrutinib

Median follow-up: 59 mo

Treon SP. *J Clin Oncol*, 2021; 39: 565-575

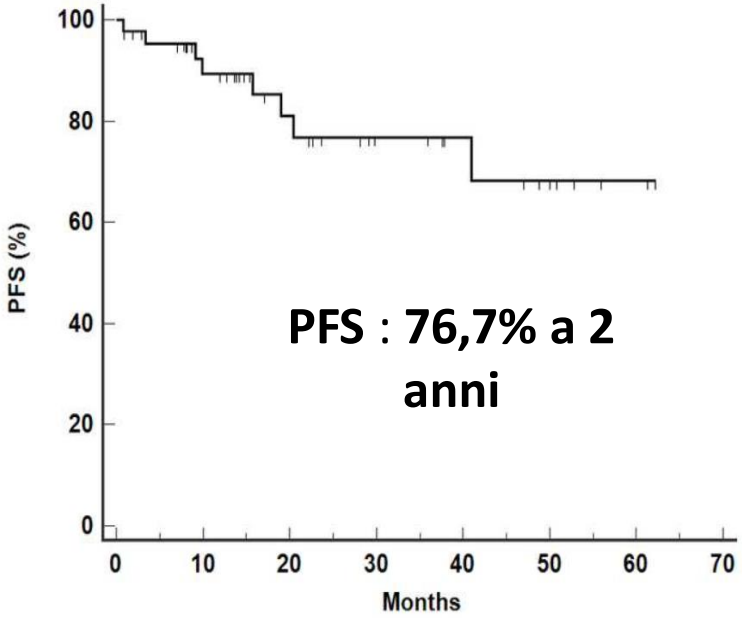
IBRU_WM studio retrospettivo multicentrico condotto in ambito «RTL»

Characteristic	Number of patients (%)
Age: median [range]	65 [32-86]
Male	38/49 (77.6%)
Female	11/49 (22.4%)
Hemoglobin, g/dl: median [range]	10.4 [32-86]
Platelet count, $10^3/mm^3$: median [range]	204 [24-501]
IgM, mg/dl: median [range]	3,094 [409-9000]
IgG, mg/dl: median [range]	450 [120-1880]
IgA, mg/dl: median [range]	34 [12-383]
LDH >upper limit of normal	7/49 (14.3%)
Beta 2 microglobulin >upper limit of normal	45/49 (91.8%)
Enlarged lymph nodes	14/49 (28.6%)
Splenomegaly	18/49 (36.7%)
Peripheral neuropathy	3/49 (6.1%)
IPSSWM score	
Low	14/49 (28.6%)
Intermediate	18/49 (36.7%)
High	17/49 (34.7%)
MYD88^{L265P} mutation	15/22 (68.2%)
Number of prior therapies: median [range]	2 [1-5]
One prior therapy	23/49 (46.9%)
Rituximab-containing regimens	45/49 (91.8%)
Refractory to previous therapeutic line	13/49 (26.5%)

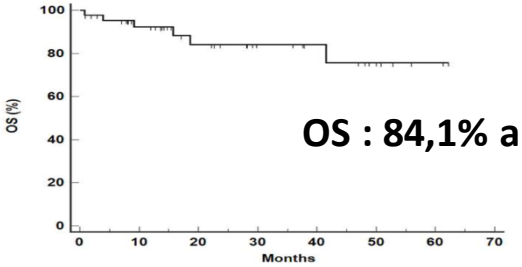
	Number of patients (%)
Dose reduction	13/49 (26.5%)
Atrial fibrillation	5/49 (10.2%)
Medical decision	2/49 (4.1%)
Infections	2/49 (4.1%)
Bleeding	2/49 (4.1%)
Neutropenia	1/49 (2%)
Mild renal toxicity	1/49 (2%)
Permanent discontinuation after dose reduction	3/49 (6.1%)
Permanent atrial fibrillation	2/49 (4.1%)
Progressive disease	1/49 (2%)
Neutropenia	2/49 (4.1%)
Grade 3-4	1/49 (2%)
Atrial fibrillation	6/49 (12.2%)
Grade 3-4	2/49 (4.1%)
Bleeding	6/49 (12.2%)
Grade 3-4	1/49 (2%)
Arthralgya/myalgia grade 1-2	5/49 (10.2%)
Infections	4/49 (8.2%)
Grade 3-4	1/49 (2%)
Diarrhea grade 2	1/49 (2%)
Renal toxicity grade 1	1/49 (2%)
Second malignancies	2/49 (4.1%)
Transient IgM flare	2/49 (4.1%)
Transient increase of lymphocyte count	6/49 (12.2%)

Cencini E., et al. Ann Hematol 2023

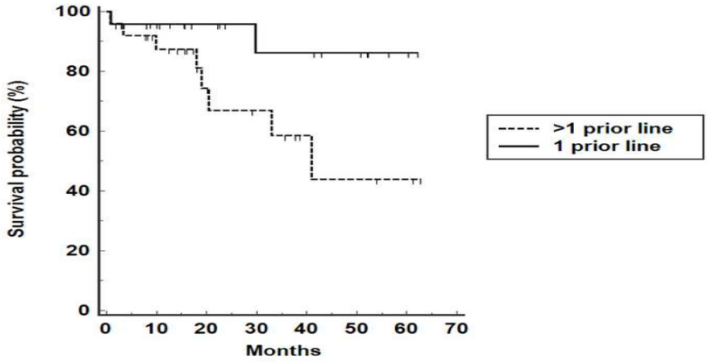
Analisi di sopravvivenza



PFS : 76,7% a 2 anni



OS : 84,1% a 2 anni



Ibrutinib or non-BTK inhibitor therapy in relapsed Waldenström Macroglobulinaemia? A real-life multicentre Italian study

Table 1. Patient characteristics of the Ibrutinib arm and non-BTKi arm.

	Ibrutinib (85 pts)	Non-BTKi treatments (BR + RCD + Bortezomib-based) (70 pts)	p-value
Age at treatment, median (Q1-Q3), years	75 (64-81)	72 (64-79)	0.213
Gender			0.566
M	56 (65.9)	43 (61.4)	
F	29 (34.1)	27 (38.6)	
Hb, median (Q1-Q3), g/dL	10.10 (9.40-11.53)	10.50 (9.35-11.85)	0.601
Plts, median (Q1-Q3), x10^9/L	210.5 (152.5-305.8)	214.0 (156.0-261.0)	0.45
Prot tot, median (Q1-Q3), g/dL	8.0 (7.2-8.9)	8.1 (7.2-9.7)	0.378
IgM, median (Q1-Q3), mg/L	2030 (525-3863)	2835 (1868-4251)	0.024
IPSSWM			0.719
1	18 (23.4)	18 (28.1)	
2	37 (48.0)	31 (48.4)	
3	22 (28.6)	15 (23.4)	
NA	8	9	
MYD88mut			0.695
Negative	6 (10.5)	5 (13.2)	
Positive	51 (89.5)	33 (86.8)	
NA	28	32	
CXCR4mut			0.116
Negative	20 (87.0)	7 (63.6)	
Positive	3 (13.0)	4 (36.4)	
NA	62	73	
CrCl, median (Q1-Q3), mL/min	67.50 (52.25-80.00)	68.00 (57.50-90.00)	0.321
CIRS>6			0.683
No	60 (73.2)	47 (70.1)	
Yes	22 (26.8)	20 (29.9)	
NA	3	3	

Figure 1

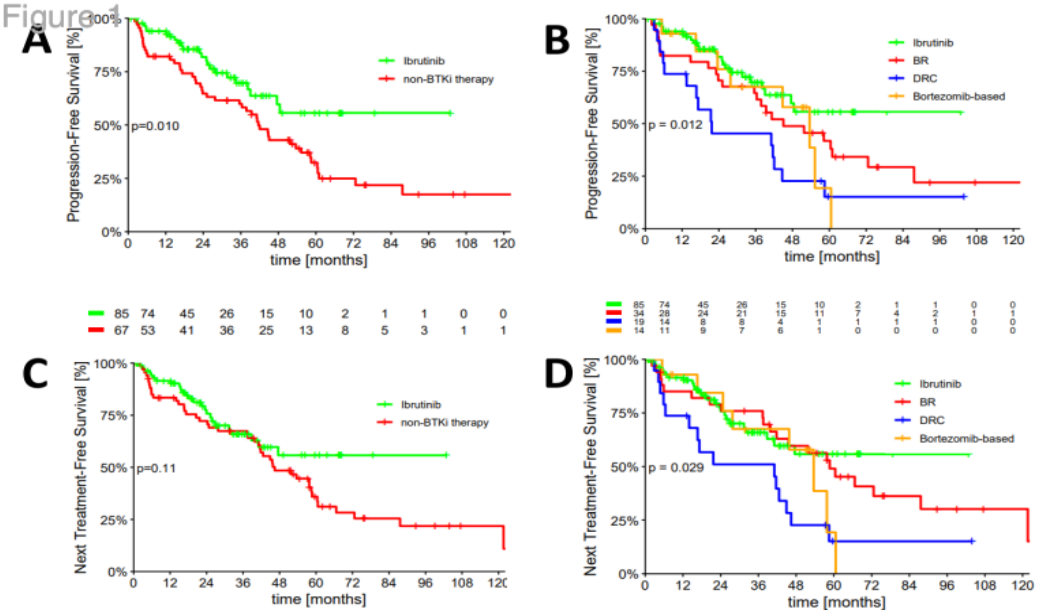


Figure 1A: PFS of ibrutinib in comparison to the non-BTKi therapy. 1B: PFS of ibrutinib in comparison to the 3 curves of the different non-BTKi therapy. 1C: TTNT of ibrutinib in comparison to the non-BTKi therapy. 1D: TTNT of ibrutinib in comparison to the 3 curves of the different non-BTKi therapy.

Autore F., et al., Blood Adv. 2026

Zanubrutinib nella real-life

Efficacia sovrapponibile ad ASPEN, tossicità limitata, in attesa dei risultati definitivi studio FIL BRUCE

	US	ISRAEL	ITALY
N° of patients, n	50	13	99
Age, median (IQR)	72 (47-93)	71 (50–85)	77 (70-85)
R/R, n (%)	33 (66)	12 (92)	63 (64)
TN, n (%)	17 (34)	1 (8)	36 (36)
ORR, %	85	83	89.7
VPGR, %	28	8	23 (75 MRR)
Median FU, mo	12.9	19.6	15

Frustaci A et al, ASH2024, Castillo EJ et al, Hematol 2023; Itchaki, Acta Hematologica 2025

Trattamento delle complicanze

- Neuropatia anti-MAG
- Sindrome di Bing-Neel
- Interessamento renale

Efficacy of rituximab in anti-myelin-associated glycoprotein demyelinating polyneuropathy: Clinical, hematological and neurophysiological correlations during 2 years of follow-up

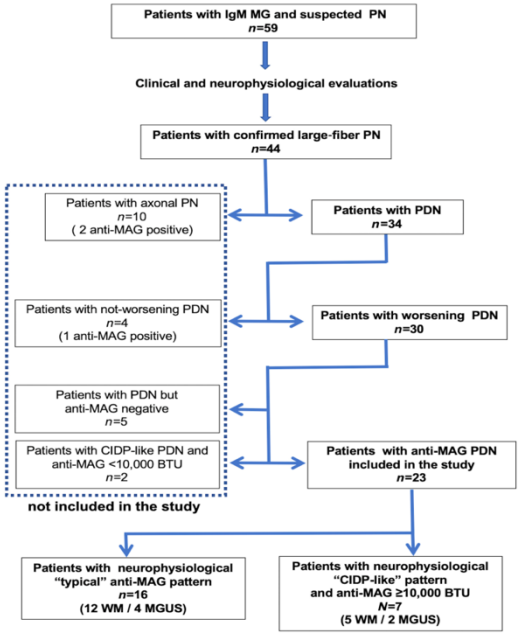


TABLE 2 Results for the analysis of clinical scores and haematological variables during 2-year follow-up of 23 patients affected by demyelinating polyneuropathy with anti-myelin-associated glycoprotein antibody immunoglobulin M monoclonal gammopathy treated with rituximab

Variable	Baseline (T0)	1-year (T1)	2-years (T2)	*p* value Overall	*p* value Comparisons
mISS					
Mean ± SD	10.9 ± 4.2	10.0 ± 4.4	9.5 ± 5.0	<0.001	T0 vs. T1: 0.030
Median (IQR)	10.0 (7.5–13.5)	10.0 (7.0–13)	8 (6–12.5)		T1 vs. T2: 0.16
					T0 vs. T2: 0.006
INCAT-ds score					
Mean ± SD	2.4 ± 1.3	1.9 ± 1.3	1.9 ± 1.4	<0.001	T0 vs. T1: 0.013
Median (IQR)	2.0 (2.0–3.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)		T1 vs. T2: 0.59
					T0 vs. T2: 0.006
INCAT-ds score, upper limbs					
Mean ± SD	1.0 ± 0.9	0.7 ± 0.8	0.7 ± 0.8	0.003	T0 vs. T1:0.036
Median (IQR)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.0 (0.0–1.0)		T1 vs. T2: 0.71
					T0 vs. T2: 0.024
INCAT-ds score, lower limbs					
Mean ± SD	1.4 ± 0.7	1.3 ± 0.8	1.2 ± 0.8	0.030	T0 vs. T1: 0.090
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–1.5)	1.0 (1.0–1.5)		T1 vs. T2: 0.56
					T0 vs. T2: 0.10
MRC sum score					
Mean ± SD	58.0 ± 2.2	58.4 ± 2.0	58.5 ± 2.0	0.010	
Median (IQR)	58.0 (58.0–60.0)	59.0 (58.0–60.0)	59.0 (58.0–60.0)		
PGIC scale					
Mean ± SD		3.4 ± 1.2	3.2 ± 1.3	0.325	
Median (IQR)		4.0 (2.0–4.0)	4.0 (2.0–4.0)		
IgM level, g/l					
Mean ± SD	6.6 ± 3.9	4.3 ± 2.8	4.4 ± 3.5	<0.001	T0 vs. T1: <0.001
Median (IQR)	6.2 (3.3–10.4)	3.6 (2.0–6.1)	3.3 (1.9–5.1)		T1 vs. T2: 0.236
					T0 vs. T2: <0.001

Abbreviations: IQR, first to third interquartile range; IgM, immunoglobulin M; INCAT-ds, Inflammatory Neuropathy Cause and Treatment Disability Scale; mISS, modified Inflammatory Neuropathy Cause and Treatment Sensory Score; MRC, Medical Research Council; PGIC, seven-point-Patients Global Impression of Change.

Rituximab 375mg/m^2
4 infusioni settimanali

Conclusions: This study suggests that RTX is effective in patients with clinically active demyelinating anti-MAG neuropathy over 2 years of follow-up, and that some neurophysiological variables might be useful for monitoring this efficacy.

The Bruton tyrosine kinase inhibitor ibrutinib improves anti-MAG antibody polyneuropathy

Francesca Castellani, MD,* Andrea Visentin, MD, PhD,* Marta Campagnolo, MD, Alessandro Salvalaggio, MD, Mario Cacciavillani, MD, PhD, Cinzia Candiotto, PhD, Roberta Bertorelle, MD, Livio Trentin, MD, and Chiara Briani, MD

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Neurol Neuroimmunol Neuroinflamm 2020;7:e720. doi:10.1212/NXI.0000000000000720

Methods

All 3 patients underwent bone marrow biopsy showing WM, with MYD88^{L265P} mutated and CXCR4^{S338X} wild type, and were started on ibrutinib 420 mg/die. Patients were assessed at baseline, at 3-6-9 months, and at 12 months in 2 patients with a longer follow-up, using Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score, INCAT sensory sum score, and Medical Research Council sum score. The modified International Cooperative Ataxia Rating Scale was performed in 2 patients, whereas it was not used in the patient with Parkinson disease as a major comorbidity. Responders were considered the patients improving by at least one point in 2 clinical scales.

Results

All the patients reported an early and subjective benefit, consistent with the objective improvement, especially of the sensory symptoms as shown by clinical scales. Treatment was well tolerated.

Efficacia spesso parziale, perchè ibrutinib è efficace nell'eliminare le cellule di WM, meno efficace nell'eliminare elementi linfoplasmocitari che producono Ab anti-MAG?
Tali elementi potrebbero avere un vantaggio di sopravvivenza?
Associazione rituximab+BTK inibitore (piccola coorte iNNOVATE, studio MAGNAZ ongoing)

Review

Bing–Neel Syndrome in Waldenström Macroglobulinemia: Updates on Clinical Management and BTK Inhibitor Efficacy

Masuho Saburi [1] and Naohiro Sekiguchi [2,*]

Diagnosis of BNS (biopsy- or CSF-proven, symptomatic)

First-Line Therapy

- Covalent BTK inhibitors (ibrutinib, zanubrutinib, and tirabrutinib) preferred irrespective of age or fitness
  * If BTK inhibitors are unavailable as first-line therapy, conventional chemotherapy such as BR or HD-MTX should be considered.

- Intolerance of or a suboptimal response to first-line BTKi
→ switch to an alternative covalent BTKi
- Mass-forming disease or rapid cytoreduction required (fit patients)
→ HD-MTX ± Ara-C ± rituximab induction, followed by transition to BTKi
- Leptomeningeal-predominant disease / older or unfit patients
→ BTKi monotherapy, with optional intrathecal therapy for symptom relief (not as monotherapy)

Adjunctive options

- Radiotherapy → for focal lesions requiring urgent control
- Intrathecal chemotherapy → for meningeal disease, as bridge therapy (not recommended as the sole treatment)
- Supportive care → infection prophylaxis, the management of hyperviscosity, rehabilitation

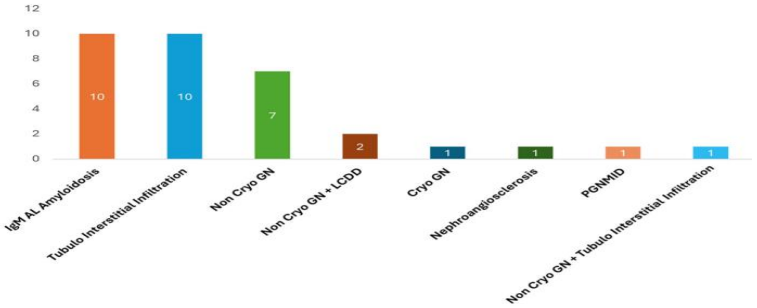
Relapsed / Refractory Disease

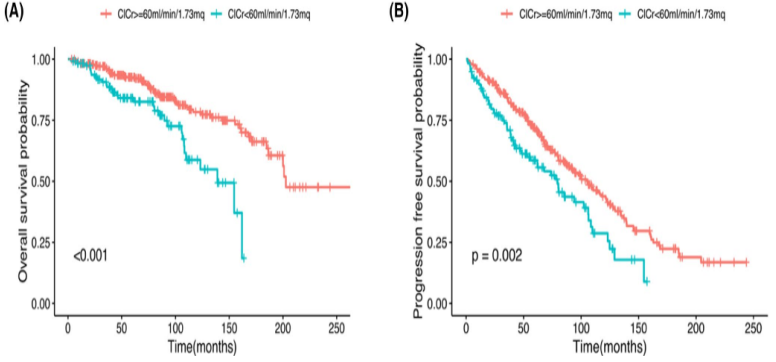
- After covalent BTKi failure
→ A non-covalent BTK inhibitor (pirtobrutinib) or HD-MTX–based chemotherapy
- For BTKi-naïve patients
→ initiate covalent BTKi (preferred over intensive chemotherapy unless urgent debulking is needed)

Renal dysfunction in symptomatic Waldenström macroglobulinaemia: A nationwide Italian multicentre study

TABLE 2 First-line treatment regimens, treatment modifications, toxicity and efficacy in sWM patients according to renal function status.

	Renal dysfunction ($n=119$)	Normal renal function ($N=283$)	p-value
CIT, n (%)	74/119 (62)	191/283 (68)	n.s.
BR	48/119 (40)	126/283 (45)	n.s.
RCD	26/119 (22)	63/282 (22)	n.s.
R-Chlorambucil	—	2/282 (1)	n.s.
Bortezomib-based regimens[a], n (%)	5/119 (4)	5/283(2)	n.s.
Other[b], n (%)	40/119 (34)	87/279 (32)	n.s.
Treatment modification, n (%)	33/119 (28)	59/283 (21)	n.s.
Dose reduction, n (%)	20/119 (17)	31/272 (11)	n.s.
Cycle reduction, n (%)	21/119 (18)	41/280 (15)	n.s.
Haem toxicity G3, n (%)	11/119 (9)	14/283 (5)	n.s.
No haem toxicity G3, n (%)	9/119 (8)	16/283 (6)	n.s.
MRR, n (%)	90/119 (75)	207/270 (77)	n.s.
ORR, n (%)	101/116 (84)	234/270 (87)	n.s.
CR	15/119 (12)	44/270 (16)	n.s.
VGPR	10/119 (9)	45/270 (17)	**0.03**
PR	65/119 (54)	118/270 (44)	n.s.
MR	11/119 (9)	27/270 (10)	n.s.
SD	10/119 (9)	20/270 (7)	n.s.
PD	8/119 (6)	16/270 (6)	n.s.
Death events, n (%)	32/119 (27)	53/279 (19)	**0.08**

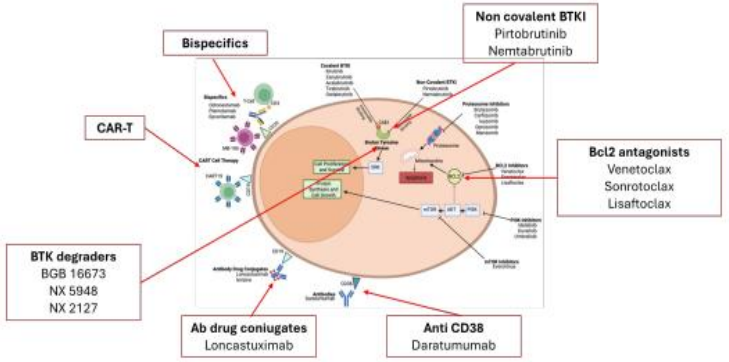




Danesin N. et al., BJH 2026

Take home messages

- La chemioterapia continua a giocare un ruolo rilevante nella terapia del MW, sia prima linea che R/R, anche nel paziente anziano
- Gli inibitori del proteasoma, da soli o in associazione a rituximab, rappresentano un'opzione nel pz R/R o non idoneo a chemioterapia
- I BTK inibitori trovano il loro setting di utilizzo preferenziale in seconda linea (ibru o zanu) o in prima linea nel pz non idoneo a chemioterapia (solo zanubrutinib)
- Zanubrutinib più efficace di ibrutinib soprattutto nei pz con profilo biologico sfavorevole e meglio tollerato (unica eccezione la neutropenia)
- I pz che hanno fallito terapia con iBTK unmet need
- Prospettive future:
  - venetoclax
  - pirtobrutinib
  - BTK degrader, nuovi inibitori BCL-2
  - sGA, studio della fitness




THANK YOU
FOR YOUR ATTENTION