



Gruppo di studio Linfomi Rete Oncologica Piemonte Valle D'Aosta

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Malattia di Waldenstrom Indicazioni diagnostiche e di trattamento

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LYMPHOPLASMOCYTIC LYMPHOMA/ WALDENSTROM'S MACROGLOBULINEMIA

- Bone marrow infiltration by LPL (>10%)

- Intertrabecular pattern of bone marrow infiltration
- Specific immunophenotype: sIgM+, CD19+, CD20+, CD22+, CD79+, FMC7+, CD52+, CD5±, CD10-, CD23-, CD25+, CD27+, CD103-, CD138-

- IgM monoclonal gammopathy (any level)



Waldenström macroglobulinemia (WM)

LPL and WM are closely related entities, they are not synonymous

Classification

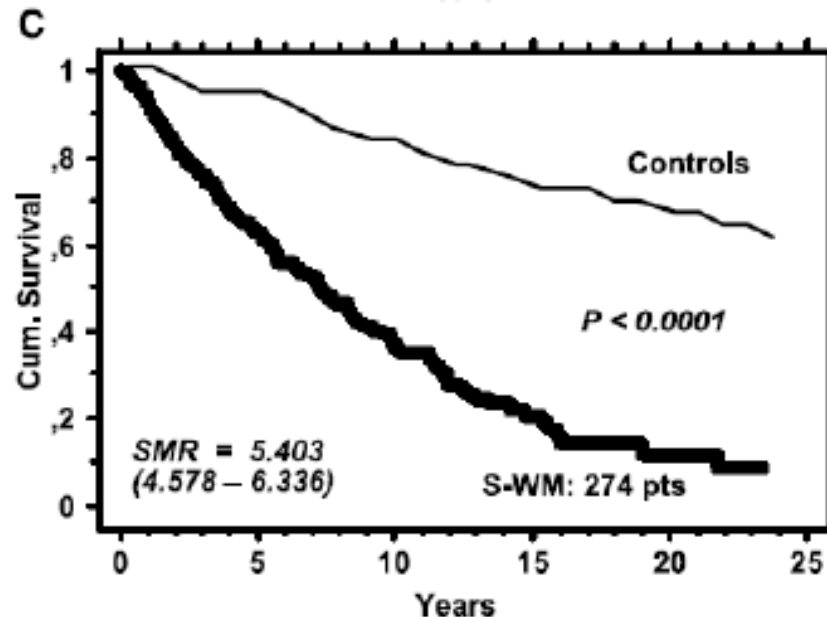
	<i>CM IgM</i>	<i>Bone Marrow Infiltration</i>	<i>Symptoms attributable to IgM*</i>	<i>Symtoms attributable to tumor infiltration **</i>
M-GUS	+	-	-	-
IgM-related disorders	+	-	+	-
MW asymptomatic	+	+	-	-
MW symtomatic	+	+	+	+

*Neuropathy, anemia da crioagglutinine, autoimmune thrombocytoepnia, cryoglobulinemia, amyloidosis

**Systemic Symptoms, cytopenia, lymphadenopathy, hepatosplenomegaly

Overall survival compared with the corresponding survival of the general population

274 patients with S-WM



	Standardized Mortality Ratio	Obs./Exp. Deaths	Median Follow-Up (Mo)
207 IgM-MGUS	0.4 (0.2-0.8)	9/21	61 (4-242)
217 A-WM	1.4 (0.9-2.0)	9/22	62 (2-228)
247 S-WM	5.4 (4.6-6.3)	152/28	67 (2-218)

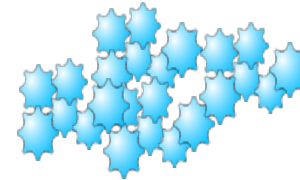
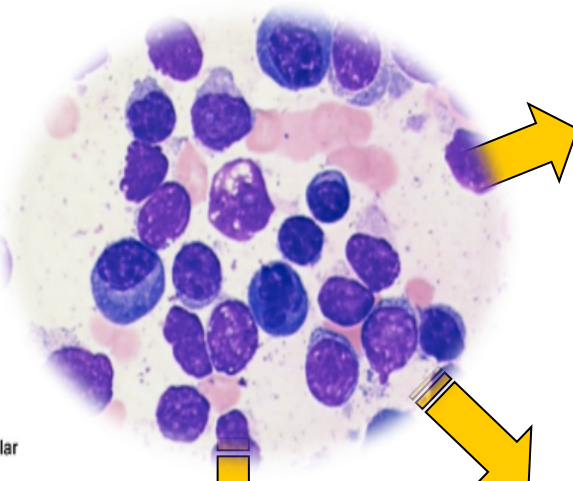
Manifestations of WM disease



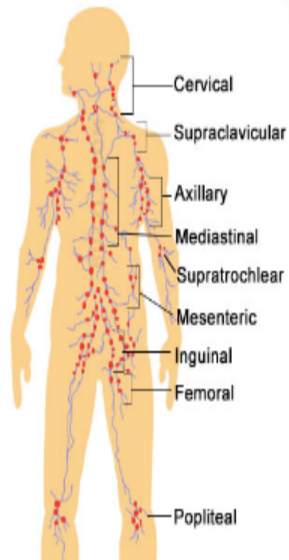
Bing Neel Syndrome

Bone Marrow

↓Hb>>> ↓PLT> ↓WBC



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



Hepcidin
↓Fe Anemia



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

≤20% at diagnosis;
50-60% at relapse.

Waldenstrom's Macroglobulinemia

Clinicopathological Manifestations

Ab activities

- ✓ *Cold agglutinin hemolytic anemia* < 10%
- ✓ *ITP*
- ✓ *Acquired VWD*
- ✓ *Schnitzler syndrome*

Protein-protein interaction

- ✓ Interactions with: fibrinogen factors V, VII, and VIII

Physicochemical effects of the IgM

- ✓ Cryoglobulins observed in 7%-20% → symptomatic in $\leq 5\%$
- ✓ Amyloidosis

Tissue deposition

- ✓ Amyloidosis

Hyperviscosity Syndrome (HVS)

→ observed in 15% of patients at diagnosis

- IgM level > 3g/dL – higher risk
- HVS unlikely unless > 4
- Viscosity levels vary between pts but correlate well with signs/sxs in the same patient
- Signs:
 - skin & mucosal bleeding,
 - blurred vision,
 - headache, dizziness, vertigo, ataxia, encephalopathy or altered consciousness
- Funduscopic exam diagnostic: venous engorgement (“sausaging”)
- Rx: plasmapheresis (followed by specific treatment)

Hyperviscosity Related Retinal Changes in WM



- Retinal vein dilatation seen IgM >3,000 mg/dL
- Retrograde flow and hemorrhages >6,000 mg/dL

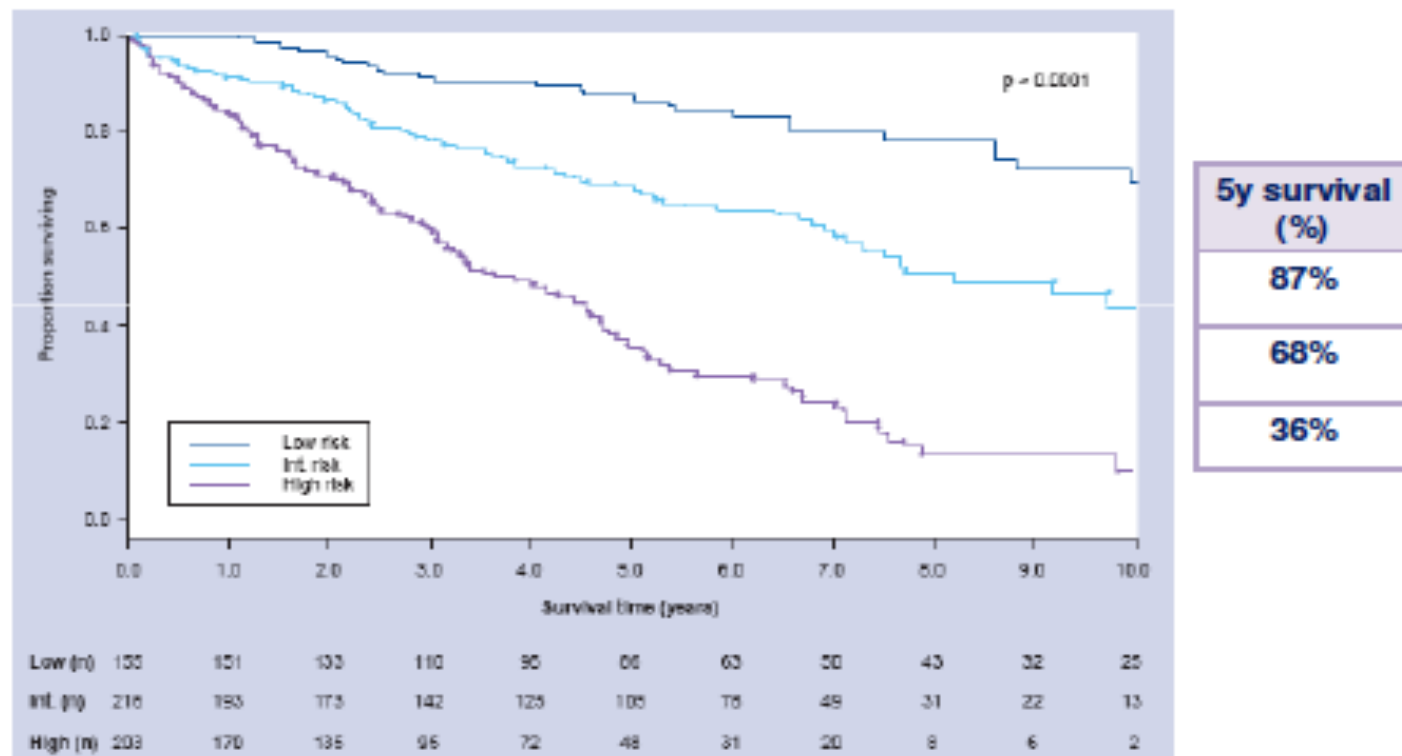
International Prognostic Scoring System for Waldenstrom's Macroglobulinemia

- Age > 65 years
- Hemoglobin ≤ 11.5 g/dL
- Platelets $\leq 100 \times 10^9/L$
- β_2 -microglobulin > 3000 mcg/L
- Monoclonal IgM > 7 g/dL

1 point to each positive factor

Risk category	Score	N.pts (%)	Median survival (mo)	5y survival (%)
Low	0-1 except age	155 (27%)	142.5	87%
Intermediate	Age >65 y or 2	216 (38%)	98.6	68%
High	>2	203 (35%)	43.5	36%

Overall survival according to the IPSS after first treatment initiation



Morel et al, Blood 2009

Categorical response definition in WM Update from the VIth International Workshop

Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation. Normal serum IgM level. Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline. Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable $\geq 90\%$ reduction in serum IgM level from baseline.* Complete resolution of extramedullary disease. No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable $\geq 50\%$ but $<90\%$ reduction in serum IgM level from baseline.* Reduction in extramedullary disease. No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable $\geq 25\%$ but $<50\%$ reduction in serum IgM level from baseline.* No new signs or symptoms of active disease
Stable disease (SD)	Monoclonal IgM protein is detectable $\leq 25\%$ reduction but $<25\%$ increase in serum IgM level from baseline.* No progression in extramedullary disease No new signs or symptoms of active disease
Progressive disease (PD)	$\geq 25\%$ increase in serum IgM level* from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

Owen RG et al, BJH 2012

Immuno-chemotherapy for WM: selected trials

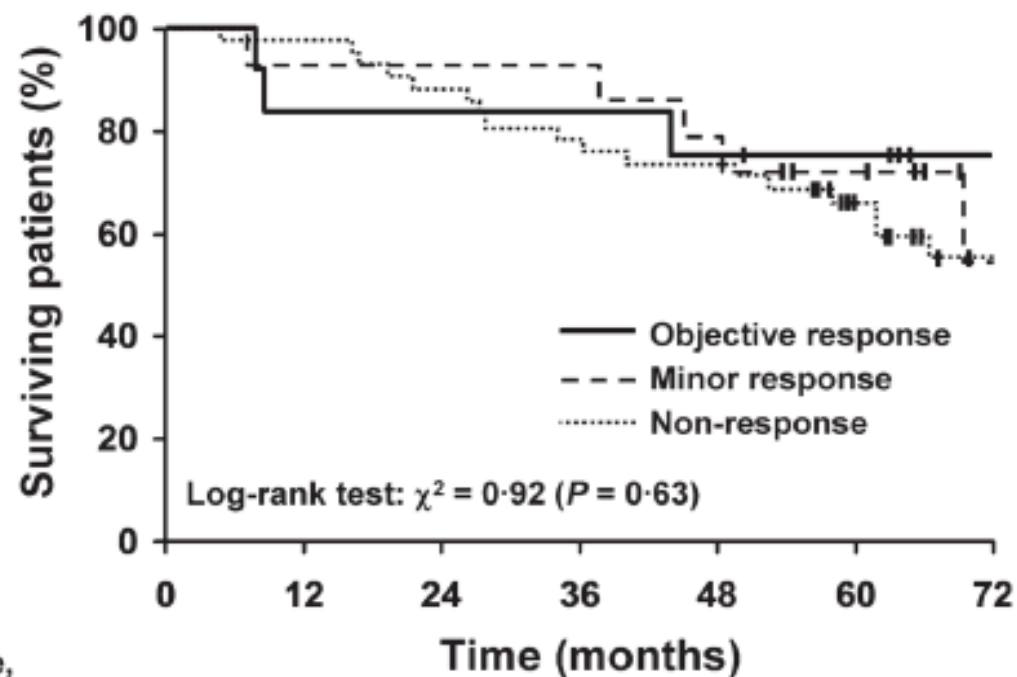
<i>Combination</i>	<i>n</i>	<i>naïve</i>	<i>ORR</i>	<i>Major</i>	<i>CR</i>	<i>TTP</i>	<i>Ref</i>
R + Cy + Dex (DRC)	72	100%	83%	74%	7%	35 mo	<i>Dimopoulos 2012</i>
R + Fludarabine	43	63%	95%	86%	4%	35 mo	<i>Treon SP 2008</i>
R + Flu + Cy (FCR)	43	65%	79%	74%	11%	50 mo	<i>Tedeschi A 2012</i>
R + Bendamustine	71	100%	80%	75%	7%	NR	<i>Tedeschi A 2015</i>
R + Bendamustine	22	100%	95%	ND	ND	69 mo	<i>Rummel MJ 2012</i>
R + Thalidomide	25	80%	72%	64%	4%	35 mo	<i>Treon SP 2008</i>
R + Bortezomib	26	100%	88%	65%	4%	NR	<i>Ghobrial IM 2010</i>
R + Bor + Dex (BDR)	23	100%	96%	83%	13%	NR	<i>Treon SP 2009</i>

Rituximab Monotherapy

Rituximab 375 mg/m² weeks 1-4, 12-16

- N=27 (15 treatment naïve) *Dimopoulos MA, JCO 2002*
 - PR 44%
 - Median time to response 3.3 mo
 - Lower OR if IgM > 4 gm/dl
 - TTP: 16 mo
- N=29 (12 treatment naïve) *Treon SP, Ann Oncol 2005*
 - PR 48%
 - Median time to response 7 mo
 - Lower OR if IgM > 6,000 mg/dl

Clinical value of minor responses after 4 doses of rituximab in Waldenström macroglobulinaemia: a follow-up of the Eastern Cooperative Oncology Group E3A98 trial *Br J Haematol.* 2009 December ;



OR 32%, RM 32%

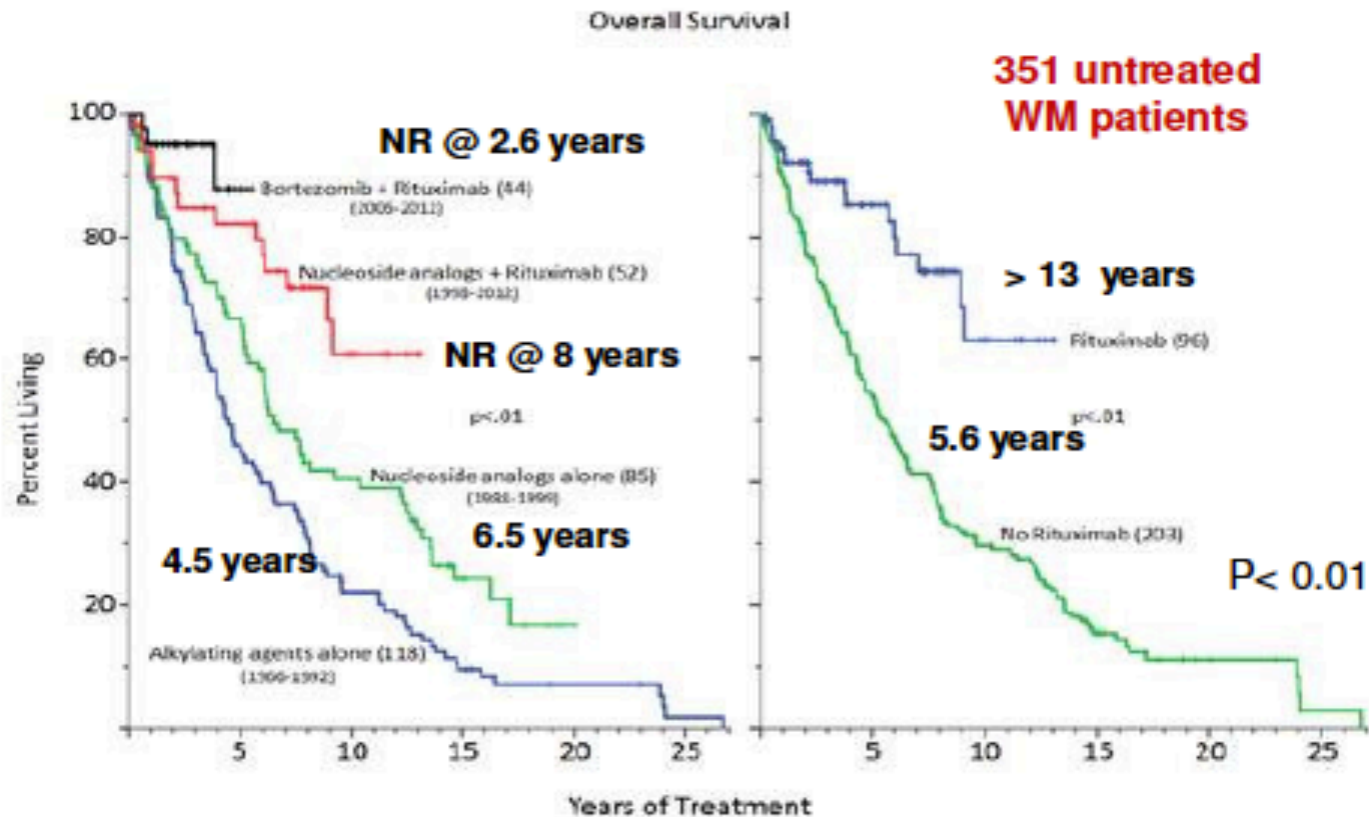
OS 5y 85%

Response, No. of patients	Time (months)						
Objective	12	10	10	10	9	8	5
Minor	14	13	13	13	11	8	3
Non-response	41	40	36	32	30	20	11

Fig 1.

Overall survival of all patients, stratified by degree of response. Survival was calculated (landmark analysis) starting 4 months after trial enrolment.

The addition of Rituximab to primary therapy for WM (MDACC)



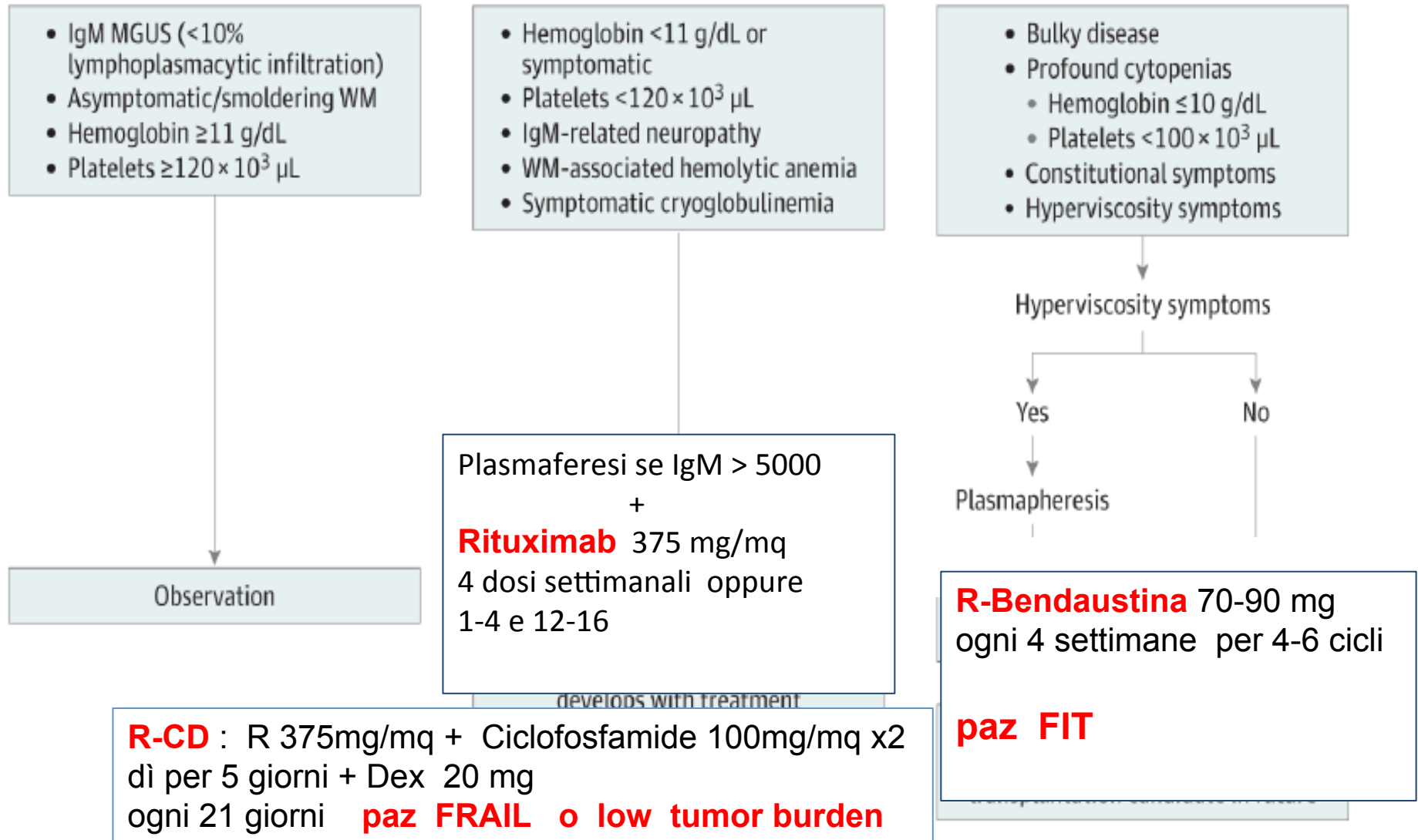
Thomas SK et al, ASH 2012 # 2734

Rituximab Flare

- Transient increase in serum IgM following Rituximab
- In up to 60% patients after Rituximab monotherapy
- Declines after 4 months
- May aggravate hyperviscosity, neuropathy, cryoglobulin levels
- May occur also when R is combined with other drugs
- Less frequent with R + Bortezomib and dexamethasone
- Use plasmapheresis prophylactically when IgM levels ≥ 5000 mg/dL to minimize risk of symptomatic hyperviscosity
- Release of IL-6 by Monocytes may account for the Rituximab IgM flare

TRATTAMENTO DI PRIMA LINEA

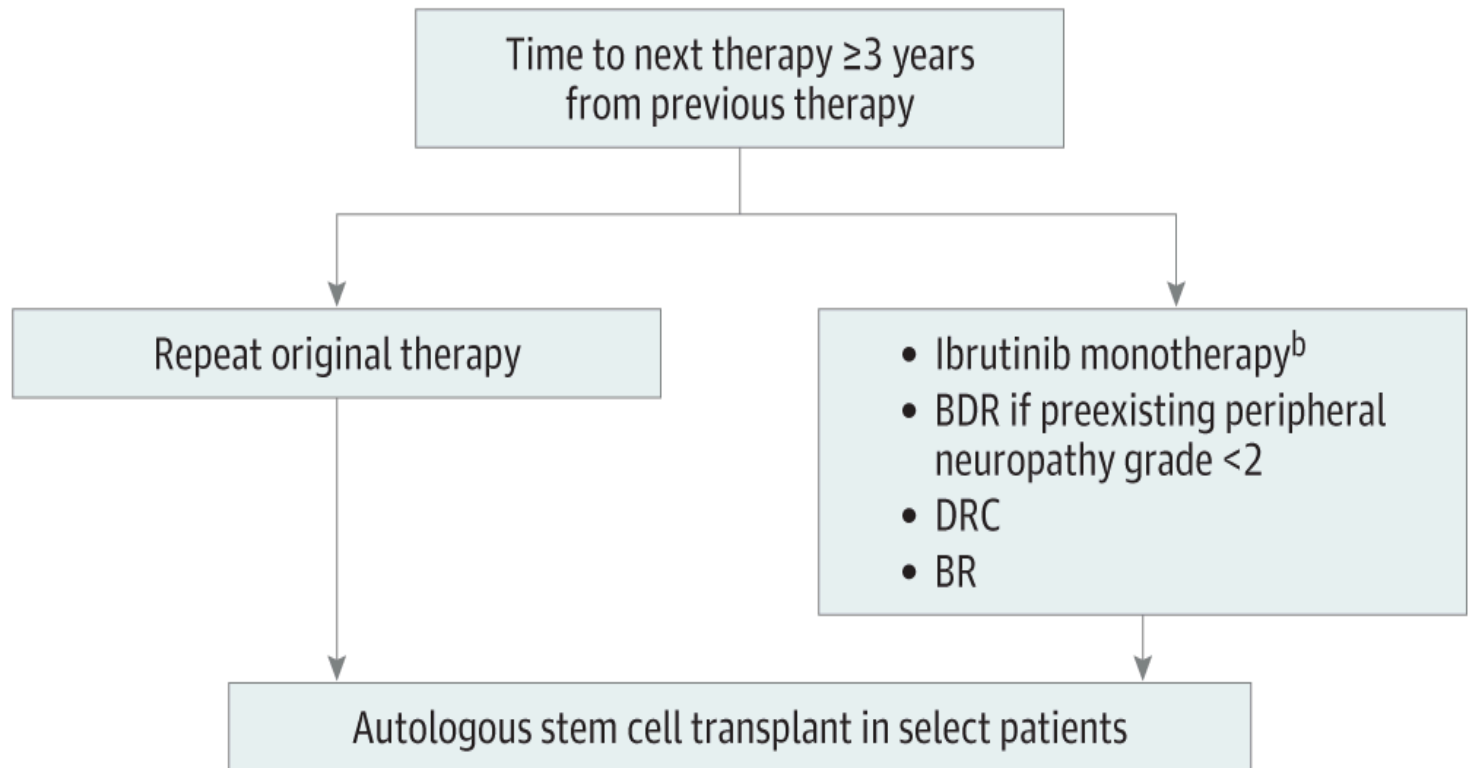
Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines



TRATTAMENTO DI II LINEA

Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines

B WM consensus for off-study salvage therapy



To summarize: Proteasome inhibitors

- Bortezomib-based regimens induce rapid IgM response
- Appropriate approach for patients with symptomatic hyperviscosity (R-Bortezomib + Dexamethazone) ± plasmapheresis
- Bortezomib and Rituximab are synergistic in WM
- Weekly bortezomib is associated with less neuropathy
- Prophylaxis against Hesperes Zoster needed

BORTEZOMIB – INDICAZIONI SCHEDA TECNICA

Utilizzo in monoterapia o in associazione a steroide e/o rituximab per i pazienti affetti da macroglobulinemia di Waldenstrom in seconda o successiva linea di trattamento (648).

IBRUTINIB - INDICAZIONI SCHEDA TECNICA

Nella Macroglobulinemia di Waldenstrom:

in monoterapia nei pazienti che hanno ricevuto almeno una linea di trattamento o in prima linea di terapia nei casi in cui è controindicato un trattamento chemio-immunoterapico (non rimborsabilità del farmaco nella prima linea)

PDTA regionali 2017

MALATTIA DI WALDENSTROM

I LINEA

Nei pazienti asintomatici solo osservazione (WW)

- Se sintomi da iperviscosità e CM IgM > 5000: Plasmaferesi pre-terapia per rischio FLARE
- Se sintomi da componente IgM (neuropatia da anti MAG o AEA): solo Rituximab
- Pazienti con basso tumor burden: RCD
- Pazienti sintomatici con malattia bulky: R-Benda,

II LINEA

- Recidiva < 2 anni: Ibrutinib, R-Benda, R-Bortezomib-Desametasone, BR (Bortezomib-Rituximab), Cladribina +/- Rituximab
- Recidiva >2 anni: Ripetere terapia di I linea o Ibrutinib
- Giovani: valutare indicazione al trapianto autologo/allogeneico e impiego di nuovi farmaci in protocollo

Long-term follow-up of previously treated patients who received ibrutinib for symptomatic WM: Update of pivotal clinical trial

Characteristic	Patients (N=63)
Age, years	63 (44-86)
Male sex	48 (76%)
IPSSWM score	
Low	14 (22%)
Intermediate	27 (43%)
High	22 (35%)
Serum IgM level, mg/dl	3,520 (724-8,390)
Hemoglobin level, g/dl	10.5 (8.2-13.8)
Serum β 2-microglobulin, mg/l	3.9 (1.3-14.2)
Adenopathy \geq 1.5 cm	37 (59%)
Splenomegaly \geq 15 cm	7 (11%)
Bone marrow involvement, %	60 (3-95)
Prior Therapies	2 (1-9)
Refractory to Last Therapy	25 (40%)
MYD88 Mutation (n=63)	58 (92%)
CXCR4 Mutation (n=62)	21 (34%)

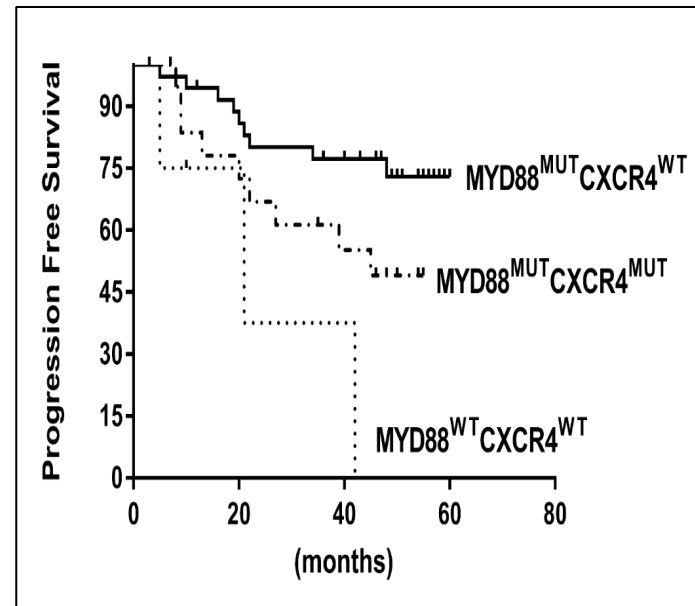
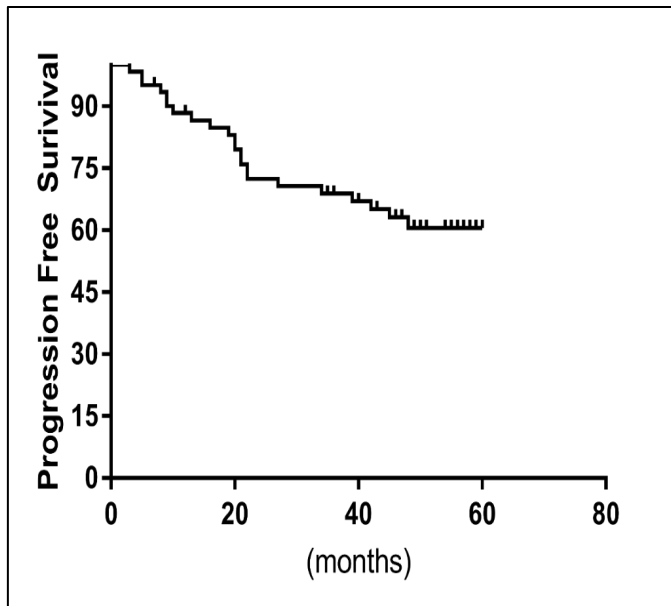
Long-term follow-up of previously treated patients who received ibrutinib for symptomatic WM: Update of pivotal clinical trial

The impact of MYD88 and CXCR4 mutation status on responses and time to at least minor (overall) and PR or better (major) responses

	All patients (n=63)	MYD88 ^{MUT} CXCR4 ^{WT} (n=36)	MYD88 ^{MUT} CXCR4 ^{MUT} (n=21)	MYD88 ^{WT} CXCR4 ^{WT} (n=5)	P-Value
Overall Responses (%)	90.4	100	85.7	60	0.0038
Major Responses (%)	77.7	97.2	66.6	0	<0.001
VGPR (%)	27	41.6	9.5	0	0.0114
Median Time to Minor Response or better (months)	1.0 (range 1.0-22.5)	1.0 (range 1.0-15)	1.0 (range 1.0-22.5)	1.0 (range 1.0-18)	0.1
Median Time to Major Response (months)	2.0 (range 1.0-49)	2.0 (range 1.0-49)	6.0 (range 1.0-40)	N/a	0.05

Median time on ibrutinib 46 months (0.5 – 60)

Long-term follow-up of previously treated patients who received ibrutinib for symptomatic WM: PFS



- The long-term follow-up of this pivotal study confirm that ibrutinib is highly active in symptomatic patients with relapsed and refractory WM, and produces durable responses.

Treon et al., ASH 2017 (abstract 2766, poster presentation)

Ibrutinib is highly active as first line therapy in symptomatic WM

Baseline clinical characteristics

Characteristic	Patients (N=30)
Age, years	67 (43-83)
Male sex	23 (77%)
IPSSWM score	
Low	5 (17%)
Intermediate	11 (37%)
High	14 (47%)
Serum IgM level, mg/dl	4369 (844-10,321)
Hemoglobin level, g/dl	10.3 (7.5-14.5)
Serum β 2-microglobulin, mg/l	3.8 (2.0-7.6)
Adenopathy \geq 1.5 cm	10 (30%)
Splenomegaly \geq 15 cm	5 (17%)
Bone marrow involvement, %	65 (5-95)
<i>MYD88</i> mutation	30 (100%)
<i>CXCR4</i> mutation	14 (47%)

- Ibrutinib at a daily dose of 420 mg was administered orally until disease progression or unacceptable toxicity.
- Dose reduction was permitted

Treon et al., ASH 2017 (abstract 2767, poster presentation)

Ibrutinib is highly active as first line therapy in symptomatic WM

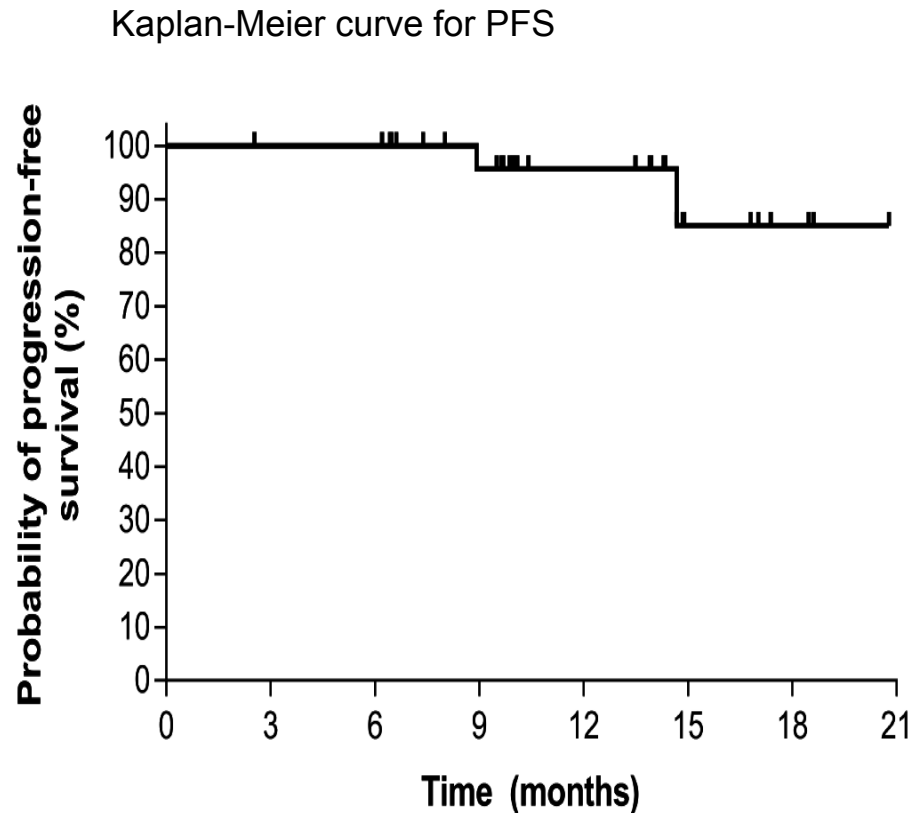
Response rates and kinetics to ibrutinib therapy

	All Patients (n=30)	<i>MYD88</i> ^{MUT} <i>CXCR4</i> ^{WT} (n=16)	<i>MYD88</i> ^{MUT} <i>CXCR4</i> ^{MUT} (n=14)	P-value
Overall responses (%)	97	100	93	0.47
Major responses (%)	80	88	71	0.38
Very good partial responses (%)	17	25	7	0.34
Median time to response (months)				
Minor response (≥MR)	1.0	1.0	2.0	0.10
Major response (≥PR)	2.0	2.0	8.0	0.05

Median time on ibrutinib 8.1 months
(2 – 16.4)

Treon et al., ASH 2017
(abstract 2767, poster presentation)

Ibrutinib is highly active as first line therapy in symptomatic WM



Treon et al., ASH 2017 (abstract 2767, poster presentation)