FONDAZIONE ITALIANA LINFOMI

I "LINFOMI INDOLENTI"

Milano, Best Western Hotel Madison
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Immunochemioterapia

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Disclosures of Francesco Autore

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					X		
Astrazeneca					X		
Be-one					X		
Johnson & Johnson					X		

First line treatment: guidelines

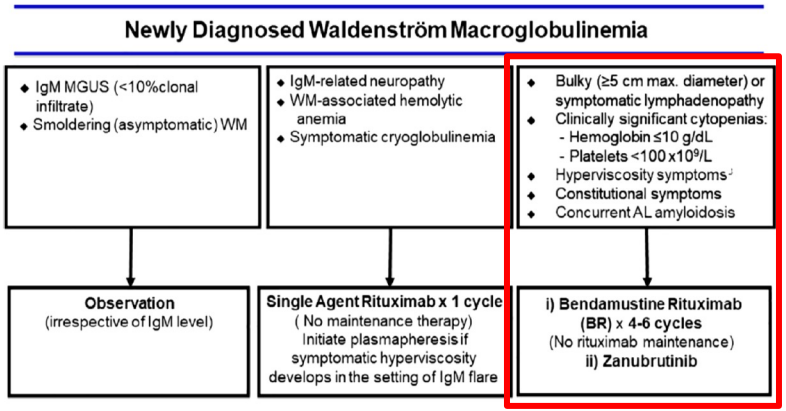
Received: 15 November 2022 | Accepted: 26 November 2022
DOI: 10.1002/ajh.26796

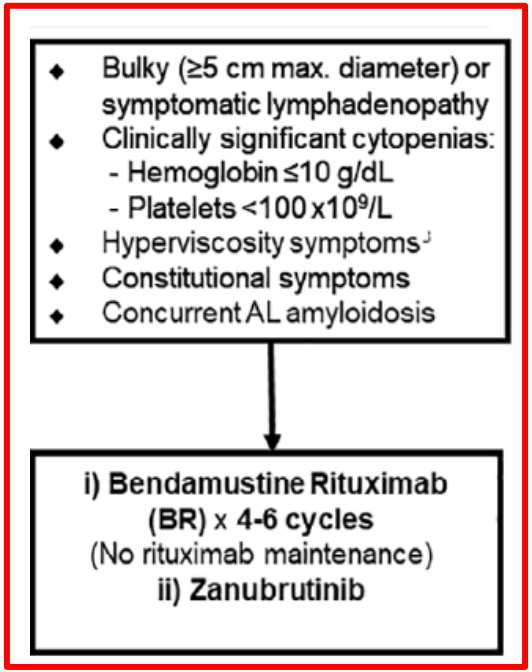
ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

Waldenström macroglobulinemia: 2023 update on diagnosis, risk stratification, and management

Morie A. Gertz

FIGURE 1 Mayo Clinic Consensus for Newly Diagnosed Waldenström Macroglobulinemia (WM). Hb indicates hemoglobin; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; RCD, rituximab, cyclophosphamide, and dexamethasone. (https://www.msmart.org/wm-treatment-guidelines) [Color figure can be viewed at wileyonlinelibrary.com]





Gertz MA. AJH, 2022

First line treatment

Seminars in Hematology 60 (2023) 73–79

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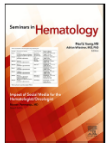


Report of consensus panel 1 from the 11th International Workshop on Waldenstrom's Macroglobulinemia on management of symptomatic, treatment-naïve patients

For first-line treatment, **chemoimmunotherapy regimens** continue to play a **central role in managing WM**, as *they are effective, of fixed duration, generally well-tolerated.*

Buske C, et al. Seminars in Hematology, 2023

Chemo-immuno treatments

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

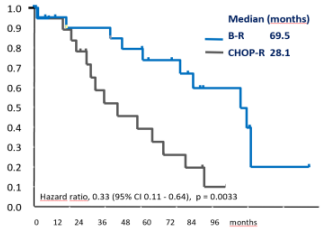
- High efficacy in TN patients
- Acceptable short and long-term toxicity
- Fixed duration therapy (4-6 months)
- Prolonged progression-free and treatment free-survival
- Cost saving

- Myelo-immune suppression
- Infections
- Secondary MDS

BR and DRC

Rituximab	375 mg/m² IV	Day 1, C1-6
Bendamustine	90 mg/m² IV	Day 1, C1-6
Bendamustine	90 mg/m² IV	Day 2, C1-6

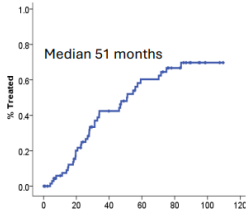
Benda R



PROS:
- ✓ Rapidly effective/Prolonged PFS
- ✓ No impact from CXCR4 mut

CONS:
- Myelotoxicity/late infectious toxicities: dose reduction to 70 mg/sqm or 4 courses
- Secondary MDS/LAM (?): ~0-3%

DRC



PROS:
- ✓ Minimal myelo/immuno-suppression
  89% pts completed 6 courses
- ✓ TTN 51 m

CONS:
- CR: 7%
- Median time to 50% IgM reduction: 4.1 m

Dexamethasone	20 mg IV or Oral	Day 1, C1-C6
Rituximab	375 mg/m² IV	Day 1, C1-C6
Cyclophosphamide	100 mg/m² Oral	Day 1 to 5, C1-C6

Bendamustine - Rituximab

Received: 7 November 2022 | Revised: 1 February 2023 | Accepted: 20 February 2023
DOI: 10.1002/ajh.26895

RESEARCH ARTICLE

AJH WILEY

Bendamustine plus rituximab for the treatment of Waldenström Macroglobulinemia: Patient outcomes and impact of bendamustine dosing

Background	Impact of bendamustine dose on response and survival outcomes is not well established.
Aim	To clarify the impact of depth of response and bendamustine dose on survival.
Population	250 WM patients treated with BR in the frontline or relapsed settings were included in this multicentre, retrospective cohort analysis
Results	Total bendamustine dose was predictive of PFS: - in the frontline setting, PFS was superior in the group receiving ≥1000mg/m^2 compared with those receiving 800-999mg/m^2 (p=0.04); - in the relapsed cohort, those who received doses of <600mg/m^2 had poorer PFS outcomes compared with those who received ≥600mg/m^2 (p=0.02).
Conclusion	Attaining CR/VGPR following BR results in superior survival, total bendamustine dose significantly impacts response and survival outcomes, in both frontline and relapsed settings.

Arulogun SO, et al. Am J Hematol. 2023

Bendamustine - Rituximab

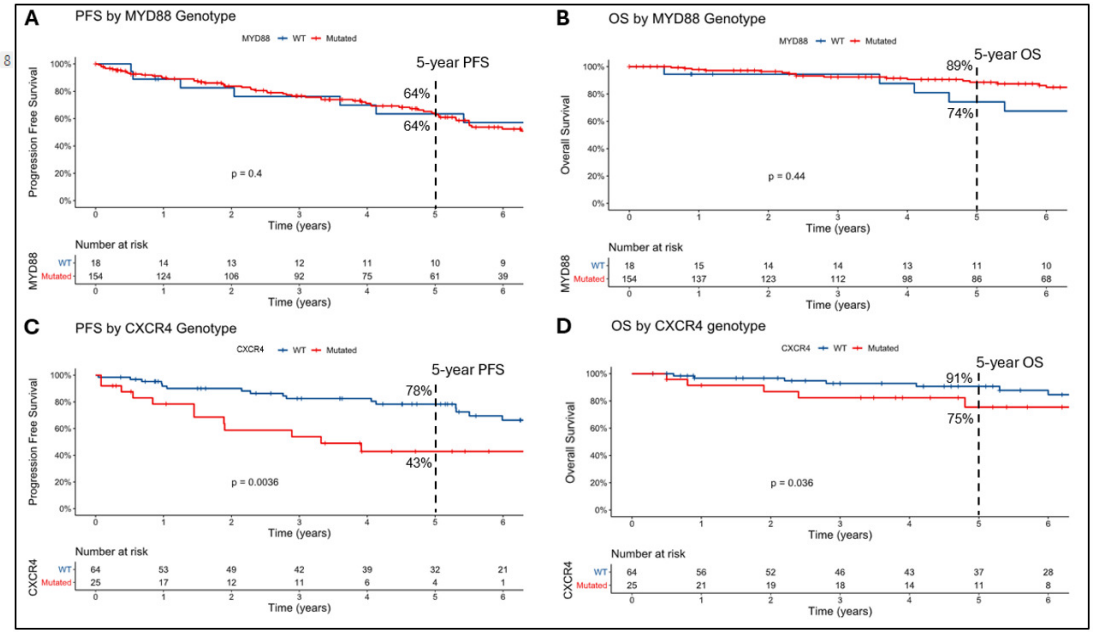
Blood Adv. 2026 Jan 7:bloodadvances.2025017751. doi: 10.1182/bloodadvances.2025017751.
Online ahead of print.

POD24 is a Novel Determinant of Prognosis in Patients with Waldenström Macroglobulinemia

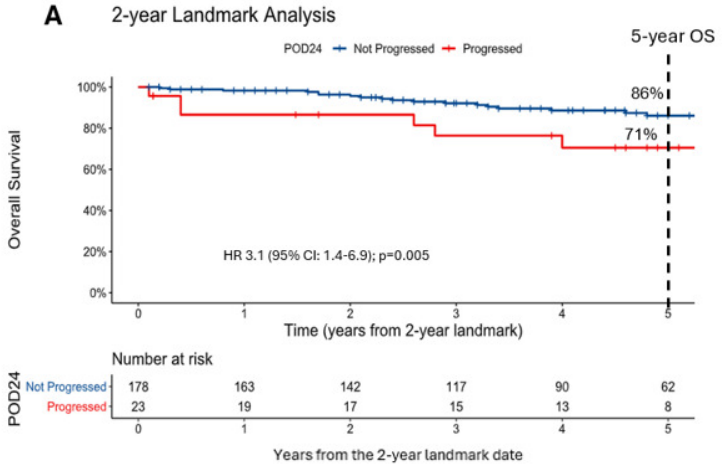
Saurabh Zanwar [1], Jithma P Abeykoon [2], Shirley D'Sa [3], Damien Roos-Weil [4], Dirk R Larson [2], Colin L Colby [1], Eric Durot [5], Efstathios Kastritis [6], Encarl Uppal [3], Oliver Tomkins [7], Pierre Morel [8], Patrizia Mondello [2], Lydia Montes [9], Jonas Paludo [2], Sikander Ailawadhi [10], Shayna Sarosiek [11], Olabisi Ogunbiyi [12], Pascalle Cornillet-Lefebvre [13], S Vincent Rajkumar [2], Anne Quinquenel [14], Angela Dispenzieri [2], Rafael Fonseca [15], Morie A Gertz [2], Shaji K Kumar [2], Meletios Athanasios Dimopoulos [6], Stephen M Ansell [2], Steven P Treon [11], Jorge J Castillo [16], Prashant Kapoor [17]

253 patients receiving frontline BR

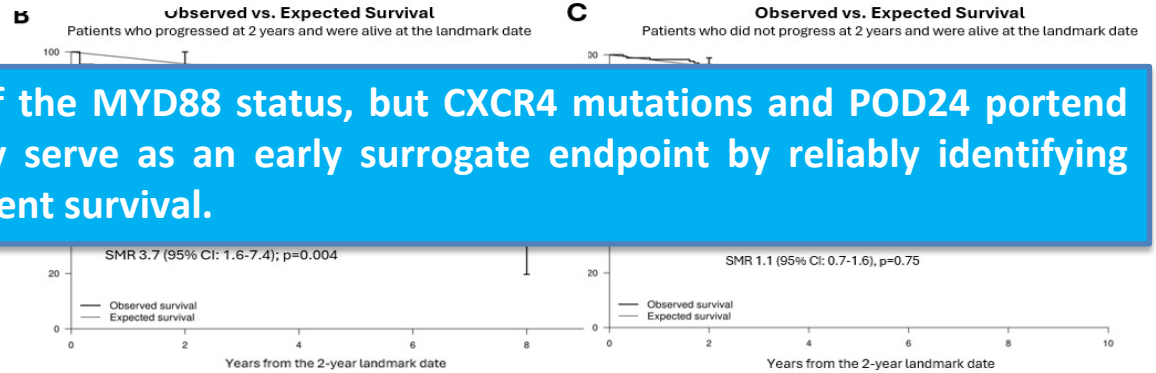
5-year PFS and OS were 65% and 87%, respectively.



Bendamustine - Rituximab



POD24 occurred in 11.5% of patients.
POD24 group demonstrated inferior subsequent OS (5-year OS: 71% versus 86%; HR 3.1, p=0.005) and higher mortality (SMR 3.7).
In non-POD24 group mortality was comparable to the matched general population (SMR 1.1).



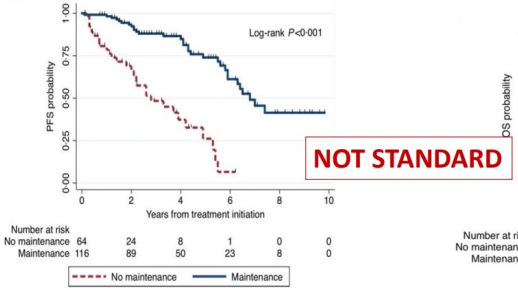
BR is effective, irrespective of the MYD88 status, but CXCR4 mutations and POD24 portend worse outcomes. POD24 may serve as an early surrogate endpoint by reliably identifying patients with inferior subsequent survival.

Rituximab maintenance

Maintenance associated with:

Major response rate higher: 97% vs. 68% *P< 0001*

Higher rates of deep response 45% vs. 29% P=003



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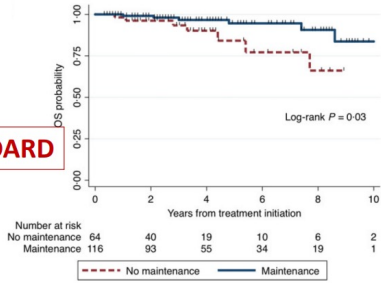


Regimen	HR (95% CI)	P
Observation	1.00 (Ref)	
Maintenance	0.54 (0.45-0.66)	<0.001

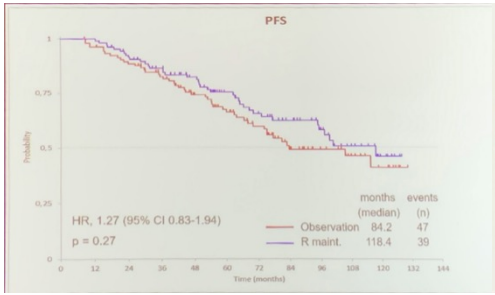
Regimen	HR (95% CI)	P
Observation	1.00 (Ref)	
Maintenance	0.72 (0.55-0.93)	0.01

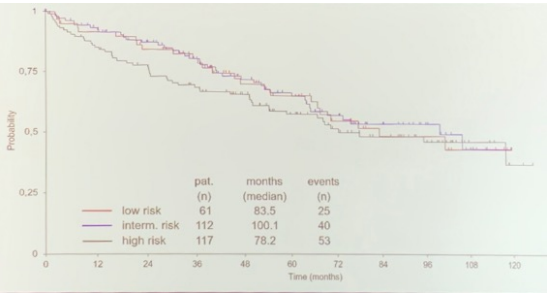
Castillo et al, 2018

Two years Rituximab maintenance versus observation after first line treatment with Bendamustine plus Rituximab in patients with Waldenströms Macroglobulinemia (WM): results from the StiL NHL7-2008 MAINTAIN trial

Results of a prospective, randomized, multicentre phase 3 study
(Study of the StiL NHL7-2008 MAINTAIN trial)

Mathias Rummel, Christian Lerchenmueller, Manfred Hensel, Martin Goerner, Christian Buske, Holger Schulz, Burkhard Schmidt, Georgi Kojuharoff, Elisabeth Lange, Wolfgang Willenbacher, Jan Dürig, Erik Engel, Frank Kauff, Juergen Barth, Alexander Burchardt, Axel Hinke, Jasmin Müller and Richard Greil on behalf of the
StiL Study group indolent Lymphomas, Germany and Austria





Proteasome-inhibitor based therapy

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

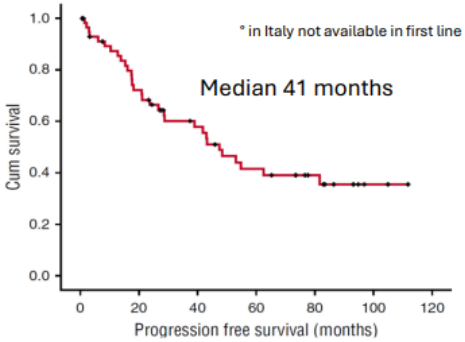
- High efficacy in TN patients
- Chemo-free regimen
- Fixed duration therapy
- Prolonged progression-free and treatment free-survival
- Response not impacted by CXCR4 mutation status

- Neurotoxicity

BDR

Bortezomib	1.3 mg/m² SC	Day 1,4,8,11; C1-C6
Dexamethasone	20-40 mg IV or Oral	Day 1,4,8,11; C1-C6
Rituximab	375 mg/m² IV	Day 1, C1-C6

Bortezomib°R



PROS:

- ✓ Rapid IgM decrease
- ✓ Lower myelo/immuno-suppression

CONS:

- High rate of Neuropathies

B-DRC

ECWM-1

Study Design: Phase II, randomized, multicenter, international trial

Patients: treatment naive WM patients

Treatment: DRC versus Bortezomib-DRC

Status of the Study: completed published (Buske et. al. JCO 2023), final analysis pending

Sponsor: University Hospital of Ulm, PI Christian Buske

abstract

PURPOSE Rituximab/chemotherapy is a cornerstone of treatment for Waldenström's macroglobulinemia (WM). In addition, bortezomib has shown significant activity in WM. This study evaluated the efficacy and safety of dexamethasone, rituximab, and cyclophosphamide (DRC) as first-line treatment in WM.

METHODS In this European study, treatment-naïve patients were randomly assigned to DRC or bortezomib-DRC B-DRC for six cycles. The primary end point was progression-free survival. Secondary end points included response rates, overall survival, and safety.

RESULTS Two hundred four patients were registered. After a median follow-up of 27.5 months, the estimated 24-month progression-free survival was 80.6% (95% CI, 69.5 to 88.0) for B-DRC and 72.8% (95% CI, 61.3 to 81.3) for DRC ($P = .32$). At the end of treatment, B-DRC and DRC induced major responses in 80.6% versus 69.9% and a complete response/very good partial response in 17.2% versus 9.6% of patients, respectively. The median time to first response was shorter for B-DRC with 3.0 (95% CI, 2.8 to 3.2) versus 5.5 (95% CI, 2.9 to 5.8) months for DRC. This resulted in higher major response rates (57.0% *v* 32.5%; $P < .01$) after three cycles of B-DRC compared with DRC. At best response, the complete response/very good partial response increased to 32.6% for B-DRC. Both treatments were well tolerated: grade ≥ 3 adverse events occurred in 49.2% of all patients (B-DRC, 49.5%; DRC, 49.0%). Peripheral sensory neuropathy grade 3 occurred in two patients treated with B-DRC and in none with DRC.

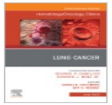
CONCLUSION This large randomized study illustrates that B-DRC is highly effective and well tolerated in WM. The data demonstrate that fixed duration immunochemotherapy remains an important pillar in the clinical management of WM.

J Clin Oncol 41:2607-2616. © 2023 by American Society of Clinical Oncology

- ✓ DRC is a highly active and very safe first-line treatment option for patients with WM.
- ✓ **Bortezomib,** SC at a dose of 1.6 mg/m2 once weekly, added to DRC, also when de-escalated by applying 4-week intervals, **shortened median time to first response and increased CR/VGPR**.
- ✓ This high activity of B-DRC did **not** translate into an **improved PFS or OS** compared with the DRC regimen.
- ✓ Neuropathy is a concern for bortezomib, and patients with pre-existing ≥ grade 2 neuropathy were excluded from the study.

Treatments: comparison

ELSEVIER
Hematology/Oncology Clinics of North America
Available online 26 May 2023
In Press, Corrected Proof What's this?



Frontline Management of Waldenström Macroglobulinemia with Chemoimmunotherapy

Background	Despite the introduction of effective novel agents, chemoimmunotherapy, with its widespread use, retains relevance and is one of the 2 strategies to treat WM, the alternative being the BTKi-based approach. Considerable evidence over the past decades supports the integration of the monoclonal anti-CD20 antibody to the CIT backbone in WM, a CD20+ malignancy.
First conclusion	A phase 3 randomized controlled trial reported substantially higher efficacy and a more favorable safety profile of the **BR compared with R-CHOP** among patients with WM.
Second conclusion	Subsequent studies reaffirmed high efficacy and tolerability of BR. High-quality evidence supporting the **use of BR over DRC**, another commonly used regimen, is lacking, as is its comparison with the continuous BTKi-based approach. However, DRC appeared less potent than BR in cross-trial comparisons and retrospective series involving treatment-naïve patients with WM.
Third conclusion	A recent retrospective, international study demonstrated comparable outcomes with **fixed-duration BR and continuous ibrutinib monotherapy** among previously untreated, age-matched patients exhibiting MYD88 L265P mutation. However, unlike ibrutinib, BR appears effective irrespective of the MYD88 mutation status.

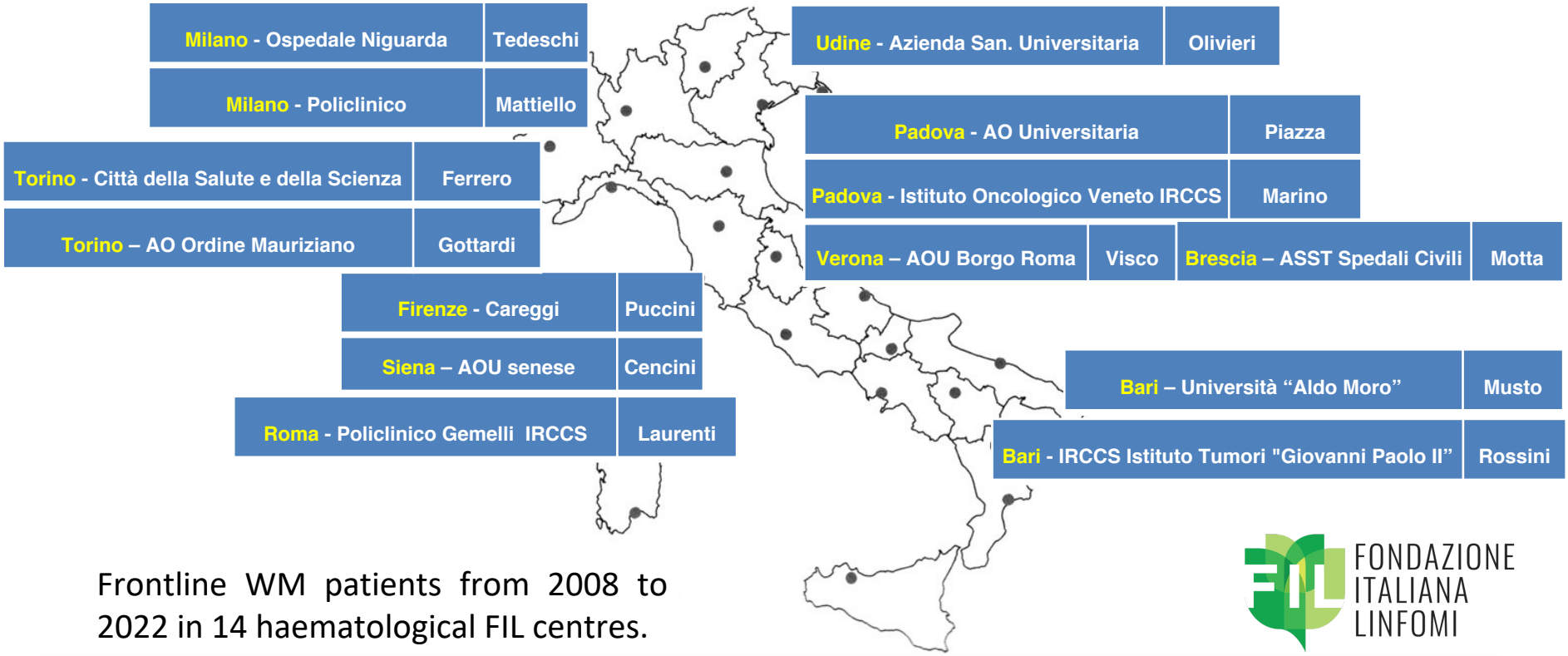
Kapoor P, et al. Hematol Oncol Clin North Am. 2023

Treatments: comparison

Background	No trials have assessed the comparative effectiveness of limited-duration BR chemoimmunotherapy and continuous orally administered ibrutinib
Aim	To compare BR and single-agent ibrutinib in patients with treatment naïve WM.
Population	BR (n=208) and ibrutinib (n=139) from a multi-institutional, international, collaborative study median age 66 (range 40-86) years and 69 (range 39-97) p=0.005
Results	Median follow-up: 4.2 years (95% CI: 3.8-4.5) - 4-year PFS: 73% in each group p=0.6 - 4-year OS: 94% (95% CI 91-98) in the BR vs 82% (95% CI: 75-90) in the ibrutinib-treated group p=0.01
Sub-analysis	Only age emerged as a predictor for OS (HR 7.2, p=0.0001) in bivariate analysis. A 1:1 age-matched analysis of 246 patients who received BR (n=123) or ibrutinib (n=123) was performed. IPSS-WM was comparable between the 2 groups. A higher proportion of patients on BR attained VGPR in comparison to the patients who received ibrutinib. 4-year PFS was similar: 72% (95% CI 63-82) for BR and 78% (95% CI 70-87) for ibrutinib, p=0.15 4-year OS was 95% (95% CI 91-99) with BR and 86% (95% CI 80-93) with ibrutinib, p=0.3 Premature discontinuation, during active treatment, due to AEs or lack of response was noted in 13% and 33% of patients on BR and Ibrutinib, respectively.

Abeykoon J. et al. IWWM 2022

First line treatment: Italian experience



Frontline WM patients from 2008 to 2022 in 14 haematological FIL centres.

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First line treatment: Italian experience

We enrolled 547 patients:

BR scheme (bendamustine-rituximab)	**245**
DRC scheme (dexamethasone-rituximab-cyclophosphamide)	**116**
Chemotherapy plus anti-CD20 (R-CHOP, R-Chl, R-CVP, FCR…)	**86**
Chemotherapeutic schemes (chlorambucil, cyclophosphamide)	**52**
Rituximab monotherapy	**48**

First line treatment: Italian experience

Results: efficacy

	Overall (n=499)	BR (n=245)	DRC (n=116)	R-chemo (n=86)	Chemo (n=52)
CR	18.6%	23.2%	10.3%	25.0%	4.0%
VGPR	14.7%	21.2%	8.6%	11.9%	2.0%
PR/MR	48.7%	48.9%	60.3%	38.1%	38.0%
SD	13.5%	5.3%	16.4%	19.1%	38.0%
PD	4.5%	1.4%	4.4%	5.9%	18.0%
ORR	82.0%	93.3%	79.2%	75.0%	44.0%

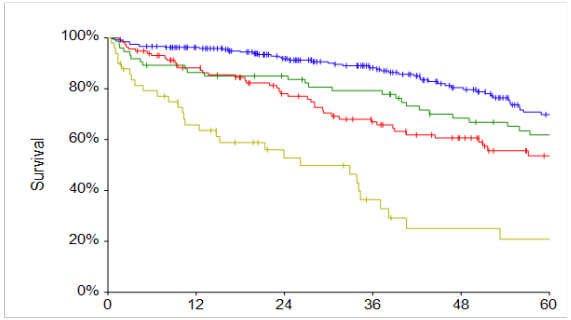
ORR

DRC vs BR: OR 3.71 (1.88-7.31), p<0.001

R-chemo vs BR: OR 4.75 (2.34-9.64), p<0.001

R-chemo vs DRC: OR 1.27 (0.65-2.49), p=0.471

First line treatment: Italian experience

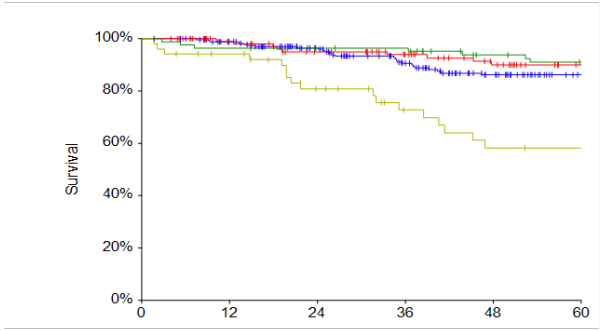


Median observation time 54 months

BR	4-y PFS 80%
DRC	4-y PFS 60%
R-Chemotherapy	4-y PFS 68%
Chemotherapy	4-y PFS 25%

BR vs DRC HR 0.53 (0.35-0.80) p<0.0001
BR vs R-chemo HR 0.74 (0.49-1.12) p= 0.143
DRC vs R-chemo HR 1.21 (0.80-1.83) p=0.362

When analysing the curves of PFS we noted a **PFS at 4-y 80% for BR** and **60% for DRC** (p<0.0001).



BR	4-y OS 86%
DRC	4-y OS 89%
R-Chemotherapy	4-y OS 93%
Chemotherapy	4-y OS 58%

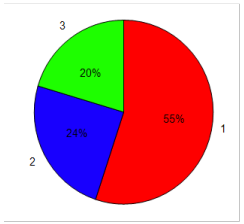
Curves of OS did not differ between the two schemes (**OS at 4-y 86% for BR** and **89% for DRC**).

First line treatment: Italian experience

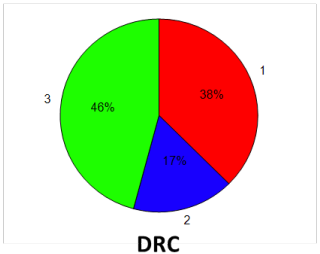
Results: tolerability

	Overall (n=499)	BR (n=245)	DRC (n=116)	R-chemo (n=86)	Chemo (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

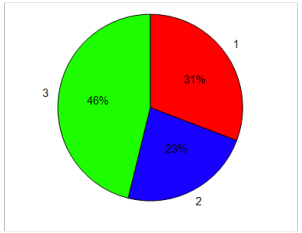
Interruptions of the treatments due to
- Hematological toxicity (1)
- Extrahematological toxicity (2)
- Other (3)



BR



DRC



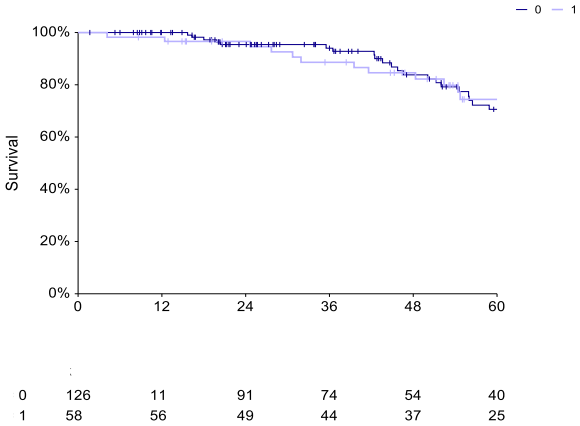
R-Chemotherapy

First line treatment: Italian experience

Results: tolerability

0: Benda 90 mg/m² (129 pts)

1: Benda 70 mg/m² (59 pts)



4-y PFS 90/m² 84%

4-y PFS 70/m² 85%

p=0.903

		Benda 90 (n=129)	Benda 70 (n=59)	p
Age	Median	64	70	0.005
Age	< 65	73 (56.6)	17 (28.8)	
	65-74	36 (27.9)	23 (39.0)	0.001
	≥ 75	20 (15.5)	19 (32.2)	
Gender	Males	90 (69.8)	36 (61)	0.236
	Females	39 (30.2)	23 (39)	
PLTs	> 100 G/mL	114 (88.4)	51 (87.9)	0.931
	≤ 100 G/mL	15 (11.6)	7 (12.1)	
Hb	> 10 g/dL	64 (49.6)	30 (50.8)	0.875
	≤ 10 g/dL	65 (50.4)	29 (49.2)	
Albumine	≥ 3,5 g/dL	91 (74.6)	38 (66.7)	0.271
	< 3,5 g/L	31 (25.4)	19 (33.3)	
IgM	< 6000	102 (79.7)	48 (82.8)	0.623
	≥ 6000	26 (20.3)	10 (17.2)	
MYD88	Unmut	18 (19.8)	4 (12.9)	0.389
	Mut	73 (80.2)	27 (83.1)	
ECOG	0-1	118 (93.7)	54 (91.5)	0.598
	2-4	8 (6.3)	5 (8.5)	
CIRS	≤ 6	113 (89.7)	55 (93.2)	0.437
	> 6	13 (10.3)	4 (6.8)	
IPSSWM	Low	31 (25.6)	12 (23.1)	0.924
	Int	48 (39.6)	22 (42.3)	
	high	42 (34.7)	18 (34.6)	

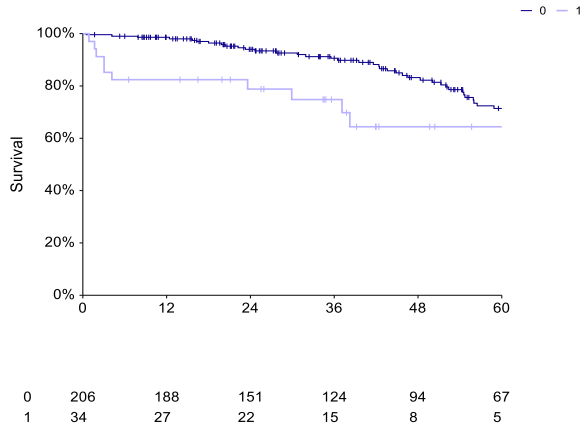
First line treatment: Italian experience

Results: tolerability

➢We used the percentage of **relative dose intensity (RDI)**, calculating for each patient the rate of RDI administered from the starting dose of 70-90 mg/m^2.

0: relative dose intensity (RDI) up to 70% (206 pts)

1: RDI reduction >30% (34 pts)



4-y PFS RDI ≥70% 83%

4-y PFS redRDI >30% 64%

p=0.035

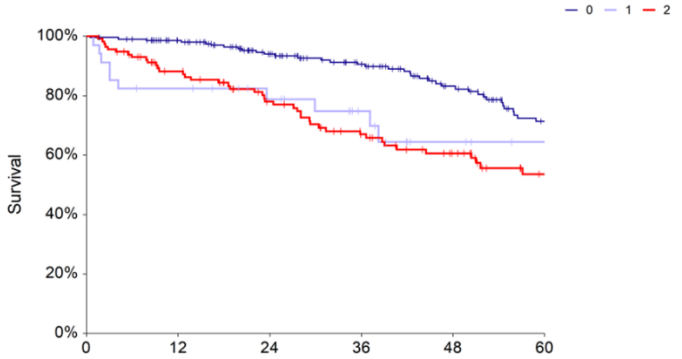
First line treatment: Italian experience

Results: tolerability

➢What is if we consider DRC too?

BR-treated patients with a RDI reduction >30% showed the same outcome as DRC-treated patients in terms of PFS

0: relative dose intensity (RDI) up to 70% (206 pts)
1: RDI reduction >30% (34 pts)
2: DRC (116 pts)



4-y PFS RDI >70% 83%
4-y PFS redRDI >30% 64%
4-y PFS DRC 60%

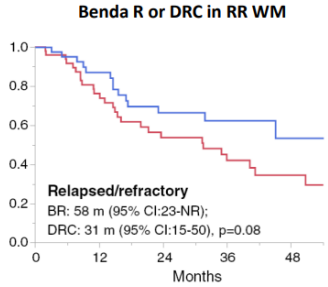
p=ns

Relapsed/Refractory WM

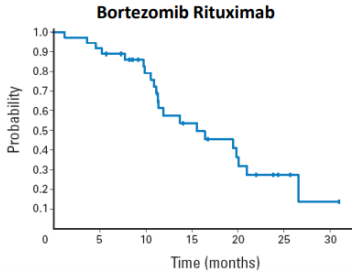
For symptomatic relapsed or refractory patients (R/R), the most important factors for determining other lines are

- patient characteristics (biological age, comorbidities and fitness)
- nature of the relapse
- duration of response to the previous therapies
- previous toxicities/ hematopoietic reserve
- cBTK exposure
- patient preferences

Repeat or alternate immuno-CHT
DRC or Benda R



Bortezomib-Rituximab



Second line treatment

Ibrutinib or chemo-immunotherapy as second line treatment in Waldenstrom Macroglobulinaemia? A real-life multicentre study.

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INTRODUCTION

In the setting of relapsed patients affected by Waldenström Macroglobulinaemia (WM) chemo-immunotherapy (CIT) has been substantially substituted by BTKis. Previous trials have investigated efficacy and safety of BTKis in second line without a direct comparison to CIT.

AIM

The aim of our retrospective study was to assess responses and outcomes with the treatment of BTKi or CIT in second line.

TABLE 1	Ibrutinib (85 pts)	Chemotherapy (BR + RCD + Bortezomib-based) (70 pts)	p-value
Age at treatment (Q1-Q3)	75 (64-81)	72 (64-79)	0.213
Gender			
M	56 (65.9)	43 (61.4)	0.566
F	29 (34.1)	27 (38.6)	
Hb, median (Q1-Q3)	10.10 (9.40-11.53)	10.50 (9.35-11.85)	0.601
Plts, median (Q1-Q3)	210.5 (152.5-305.8)	214.0 (156.0-301.0)	0.45
Prot tot, median (Q1-Q3)	8.0 (7.2-8.9)	8.1 (7.2-8.7)	0.378
IgM, median (Q1-Q3)	2030 (525-3863)	2835 (1868-4251)	0.024
IPSSWM			
1	18 (23.4)	18 (28.1)	0.719
2	37 (48.0)	31 (48.4)	
3	22 (28.6)	15 (23.4)	
NA	8	9	
MYD88mut			
0	6 (10.5)	5 (13.2)	0.695
1	51 (89.5)	33 (86.8)	
NA	28	32	
CXCR4mut			
0	20 (87.0)	7 (63.6)	0.116
1	3 (13.0)	4 (36.4)	
NA	62	73	
CrCl, mediana (Q1-Q3)	67.50 (52.25-80.00)	68.00 (57.50-90.00)	0.321
CrCl<70			
0	37 (45.1)	33 (48.5)	0.677
1	45 (54.9)	35 (51.5)	
NA	3	2	
CrCl<50			
0	64 (78.0)	61 (89.7)	0.057
1	18 (22.0)	7 (10.3)	
NA	3	6	
CIRS>6			
0	60 (73.2)	47 (70.1)	0.683
1	22 (26.8)	20 (29.9)	
NA	3	3	
Cardiac_comorbidity			
0	79 (92.9)	64 (91.4)	0.726
1	6 (7.1)	6 (8.6)	
Respiratory_comorbidity			
0	83 (97.7)	69 (98.6)	0.678
1	2 (2.3)	1 (1.4)	

RESULTS

We enrolled 155 WM patients relapsed in the period 2008-2022 from 15 FIL centres: 85 patients were treated with ibrutinib and 70 patients with CIT; of whom 34 patients with BR (bendamustine-rituximab), 21 DRC (dexamethasone-rituximab-cyclophosphamide), 15 bortezomib-based.

The two cohorts of ibrutinib and CIT showed similar basal clinical characteristics, prognostic factors, comorbidities and also times of retreatment between first and second line (35 vs 32 months, p=0.89).

Overall response rate (ORR) was achieved in 84.7% of patients after ibrutinib and in 72.9% after CIT (p=0.070), ibrutinib patients showed a better progression free survival (PFS) than CIT patients (4-y PFS of 67.0% vs 49.4%, p=0.009), but we did not find statistical differences in terms of time to next treatment (TTNT) and overall survival (OS); in particular 4-y TTNT was 66.6% for ibrutinib and 57.1% for CIT (p=0.18), 4-y OS was 78% for both (p=0.63). ORR for both the groups was independent from presence of treatment modifications and toxicities.

Considering the 3 different groups within the CIT cohort, they showed the same characteristics including the median age at treatment (BR: 70 yy, DRC: 75 yy, bortezomib-based: 69 yy; p=0.19). Non-significant difference among the 3 groups was seen in terms of ORR and PFS nor of TTNT and OS, even if we registered a better PFS for BR with a median PFS of 58.2 months, followed by bortezomib-based (PFS 53.6 mo) and DRC (PFS 44.6 mo).

When comparing ibrutinib to each of the 3 CIT groups, different ORR were observed in each group with Ibrutinib reporting the highest rate (84.7%). PFS of ibrutinib was superior to PFS of DRC, bortezomib-based (p=0.023, p=0.021, respectively) and it showed a trend versus PFS of BR (p=0.065). Analysis showed a significant difference (p=0.047) in terms of better PFS of ibrutinib in comparison to the other 3 curves. For TTNT and OS none difference was reported based on ibrutinib and type of CIT, except for the comparison of ibrutinib vs DRC in terms of OS and TTNT (p=0.040 for both comparison).

TABLE 2	BR (34 pts)	RCD (21 pts)	Bortezomib-based (15 pts)	p-value
Age at treatment (Q1-Q3)	70 (63-75)	75 (66-81)	69 (63-81)	0.199
Gender				
M	23 (67.7)	11 (52.4)	9 (60)	0.524
F	11 (32.3)	10 (47.6)	6 (40)	
Hb, median (Q1-Q3)	10.5 (9.5-11.8)	10.5 (9.3-11.5)	10.5 (9.6-11.9)	0.944
Plts, median (Q1-Q3)	208.0 (146.0-248.0)	211.0 (154.5-263.5)	243.0 (183.0-273.5)	0.569
Prot tot, median (Q1-Q3)	8.5 (7.7-10.2)	7.2 (6.8-8.1)	8.5 (7.9-9.3)	0.048
IgM, median (Q1-Q3)	2800 (1868-4640)	2105 (1800-3085)	3830 (2780-6251)	0.17
IPSSWM				
1	8 (25.0)	5 (29.5)	5 (33.3)	0.913
2	15 (46.9)	9 (52.9)	7 (46.7)	
3	9 (28.1)	3 (17.6)	3 (20.0)	
NA	2	4	0	
MYD88mut				
0	2 (10.0)	2 (22.2)	1 (11.1)	0.652
1	18 (90.0)	7 (77.8)	8 (88.9)	
NA	14	12	6	
CXCR4mut				
0	2	2	3	NA
1	2	0	2	
NA	30	19	10	
CrCl, mediana (Q1-Q3)	72 (60-91.8)	68.5 (59.8-90.5)	61.5 (56-71.5)	0.395
CrCl<70				
0	18 (52.9)	10 (50.0)	5 (35.7)	0.548
1	16 (47.1)	10 (50.0)	9 (64.3)	
NA	0	1	1	
CrCl<50				
0	31 (91.2)	19 (95.0)	11 (78.6)	0.277
1	3 (8.8)	1 (5.0)	3 (21.4)	
NA	0	1	1	
CIRS>6				
0	22 (68.7)	13 (61.9)	12 (85.7)	0.312
1	10 (31.3)	8 (38.1)	2 (14.3)	
NA	2	0	1	
Cardiac_comorbidity				
0	31 (91.2)	20 (95.2)	13 (86.7)	0.662
1	3 (8.8)	1 (4.8)	2 (13.3)	
Respiratory_comorbidity				
0	33 (97.1)	21	15	0.584
1	1 (2.9)	0	0	

No differences were noted in the two subgroups of ibrutinib patients who were treated with BR or DRC as first line therapy in terms of PFS, TTNT, OS, ORR and withdrawal or dose reduction due to toxicity.
Multivariate analysis found choice of the treatment (ibrutinib vs CIT), beta2microglobulin and female gender as significant variables that favourably impact on PFS, choice of the treatment, age and female gender on TTNT, age and female gender on OS.

Figure 1: PFS of ibrutinib in comparison to the CIT.

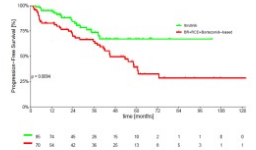
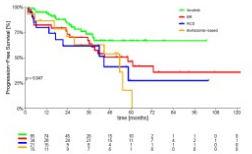


Figure 2: PFS of ibrutinib in comparison to the 3 curves of the different CIT.



CONCLUSIONS

This large retrospective real-life study showed advantages of ibrutinib versus CIT in terms of ORR and PFS, except for BR, but not in terms of TTNT and OS, except for DRC.

COI

Nothing to disclose.

CONTACT INFORMATION

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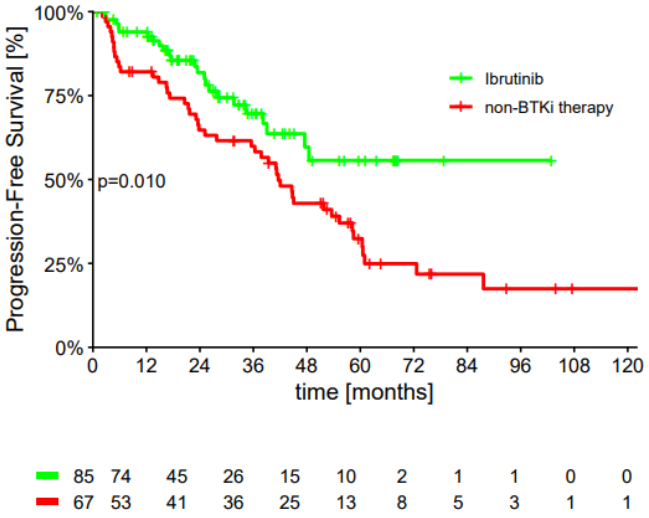
Second line treatment

	Ibrutinib (85 pts)	Non-BTKi treatments (34 BR + 21 DRC + 15 Bortezomib-based) (70 pts)	p-value
Age, median (Q1-Q3)	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)	
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	

	Ibrutinib (85 pts)	Non-BTKi treatments (34 BR + 21 DRC + 15 Bortezomib-based) (70 pts)
Median follow-up, months	34	75
Median interval time of retreatment, months	34	30
Treatment modifications	34.1%	31.4%
Dose reduction	17.6%	11.4%
Cycle reduction	10.6% (temporary) 22.4% (permanent)	25.7%
ORR	84.7%	74.6%

Second line treatment

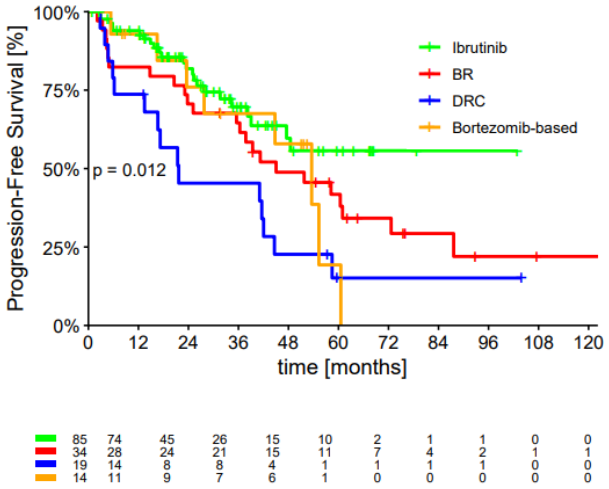


4-year PFS ibrutinib: **59.7%**
4-year PFS non-BTK therapy: **42.9%** (p=0.010).

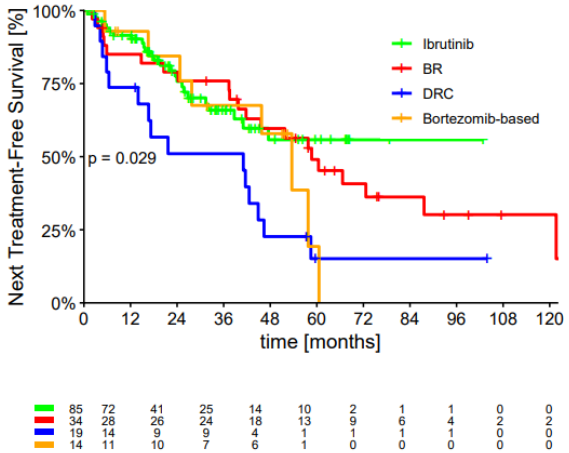
Median PFS ibrutinib: **not reached**
Median PFS non-BTK therapy: **41.6 months** (95% CI: 34.3-48.9)

Second line treatment

Among non-BTKi therapy subgroups, median ages were similar (BR: 70, DRC: 75, bortezomib-based: 68; p=0.37).



BR showed a median PFS of 45.0 months, bortezomib-based 53.6 months and DRC 21.7 months.
Ibrutinib showed **superior outcomes** compared to all non-BTKi therapy regimens combined **both in term of PFS (p=0.012) and TTNT (p=0.029).**
When comparing ibrutinib to each of the 3 non-BTKi therapy groups, different ORR were observed in each group with ibrutinib reporting a rate of **84.7%** (vs 76.5% for BR, 63.2% for DRC and 85.7% for bortezomib).



4-year PFS of ibrutinib (59.7%) was significantly superior to 4-year PFS of DRC (**22.7%**; p<0.001) but not to that of BR (48.8%; p=0.11) and of bortezomib-based (57.9%; p=0.21).
For TTNT and OS, differences were generally non-significant, except for ibrutinib vs DRC (OS p=0.039, TTNT p=0.004).

Infections

- Infections are a major source of morbidity and mortality in patients with Waldenström Macroglobulinemia.
- Data on infection incidence are generally extrapolated from clinical trials, and real-world evidence remains limited.

FCR

Three of our patients developed grade 3 or 4 infectious complications during treatment or within 6 months after. In the Italian prospective study, six patients developed major infections during treatment or within the first 6 months of follow-up: three patients developed late-onset infectious pneumonia and three patients died from pneumonia [8]. Likewise, in the Italian retrospective study, six major infectious complications occurred, and three patients died of infections [12]. These results suggest that RFC not only suppresses

Prospective study: 3 minor and 6 major out of 43 pts (**20.9%**)
Retrospective study: 6 out of 40 pts (**15%**)
Present study: 3 major out of 82 pts (**3.7%**)

Tedeschi, *Cancer* 2012; Tedeschi, *CLML* 2013;
Souchet, *AJH* 2016

R-CHOP vs R-CVP

across all response categories [8]. A prospective trial of 250 patients with indolent lymphoma (WM n = 13) randomized to RCHOP vs. RCVP found similar PFS, OS, and response rates, but significantly higher adverse events, cytopenia, and infection in the RCHOP group, demonstrating the relative low toxicity of the RCVP regimen [9]. With long-term follow-up of a real-world

Infection in 14 (**10,7%**) and 3 (**2,5%**) patients; p = 0011;

Walewski, *BJH* 2019

Infections

BR

11 relapses (58%) in the R-CHOP group. Bendamustine and rituximab treatment was better tolerated, with no alopecia, less hematotoxicity, lower frequency of infection, lower incidence of neuropathy, and reduced stomatitis.[51] Twenty-four previously treated patients

95 in BR vs 121 in CHOP-R, p=0.0403

Rummel, *Blood* 2019

Toxicity, %	BR		DRC	
	All	Grade ≥ 3	All	Grade ≥ 3
Neutropenia	39	11	39	20
Thrombocytopenia	26	2	20	7
Nausea/vomiting	9	2	7	0
Fever/chills	5	0	3	0
Headache	2	0	4	0
Hypotension	2	0	3	1
Infections	19	5	15	3

DRC

potentially harmful in this older patient population. Furthermore, the infectious complications after DRC were not as pronounced as those observed after the administration of combinations that include rituximab and nucleoside analogs.[18,19]

DRC 20 episodes in 72 pts (**27.9%**)

Dimopoulos, *JCO* 2007

60 received BR (43 with relapsed/refractory WM)
100 received DRC (50 had relapsed/refractory WM)

Paludo, *Ann Hematol* 2018

Infections in first line

A total of **489** patients were included, with the following rates per regimen:

	n	%
BR	**165**	33.7%
DRC	**152**	31.1%
other CIT	**62**	12.7%
Chemo	**41**	8.4%
BTKi	**17**	3.5%
Rituximab/steroid	**52**	10.6%

A total of **111** infections in **489** patients were recorded, with the following rates per regimen:

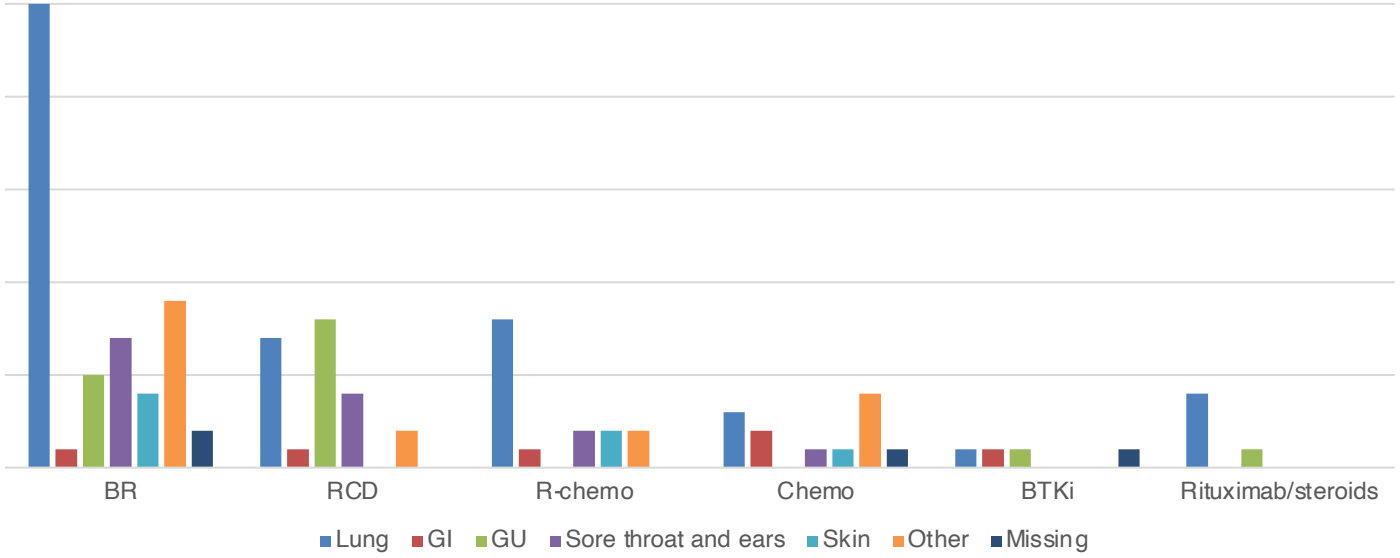
	Infections (Incidence)
BR	53 (32.1%)
DRC	22 (14.5%)
other CIT	15 (24.2%)
Chemo	12 (29.3%)
BTKi	4 (23.5%)
Rituximab/steroid	5 (9.6%)

BR: Bendamustine-Rituximam; DRC: Dexamethasone-Rituximab-Cyclophosphamide; CIT: chemoimmunotherapy; BTKi: Bruton Tyrosine Kinase inhibitor

Infections in first line

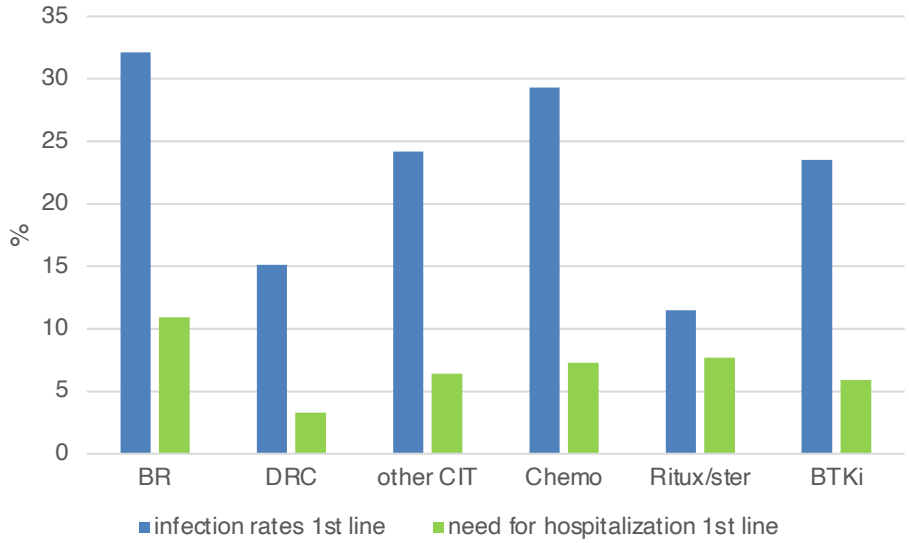
A total of **111** infections in **489** patients.

	BR	RCD	R-chemo	Chemo	BTKi	Rituximab/steroids
Infections	**53**	**22**	**15**	**12**	**4**	**5**
Incidence	**32.1%**	**14.5%**	**24.2%**	**29.3%**	**23.5%**	**9.6%**



GI: gastro-intestinal infections; GU: genito-urinary infections.

Infections in first line



BR had a hospitalization rate of 10.9%, DRC demonstrated the lowest hospitalization rate among CIT schemes.

BTKis showed one of the lower rate (5.9%).

Infections in second line

In the second-line setting, **203** patients received subsequent therapies, with the following rates per regimen:

	N	%
BR	26	12.7%
DRC	16	7.8%
Bortezomib based	19	9.3%
Chemo	22	10.8%
BTKi	102	50.0%
Rituximab	19	9.3%

A total of **63** infections in **203** patients were recorded, with the following rates per regimen:

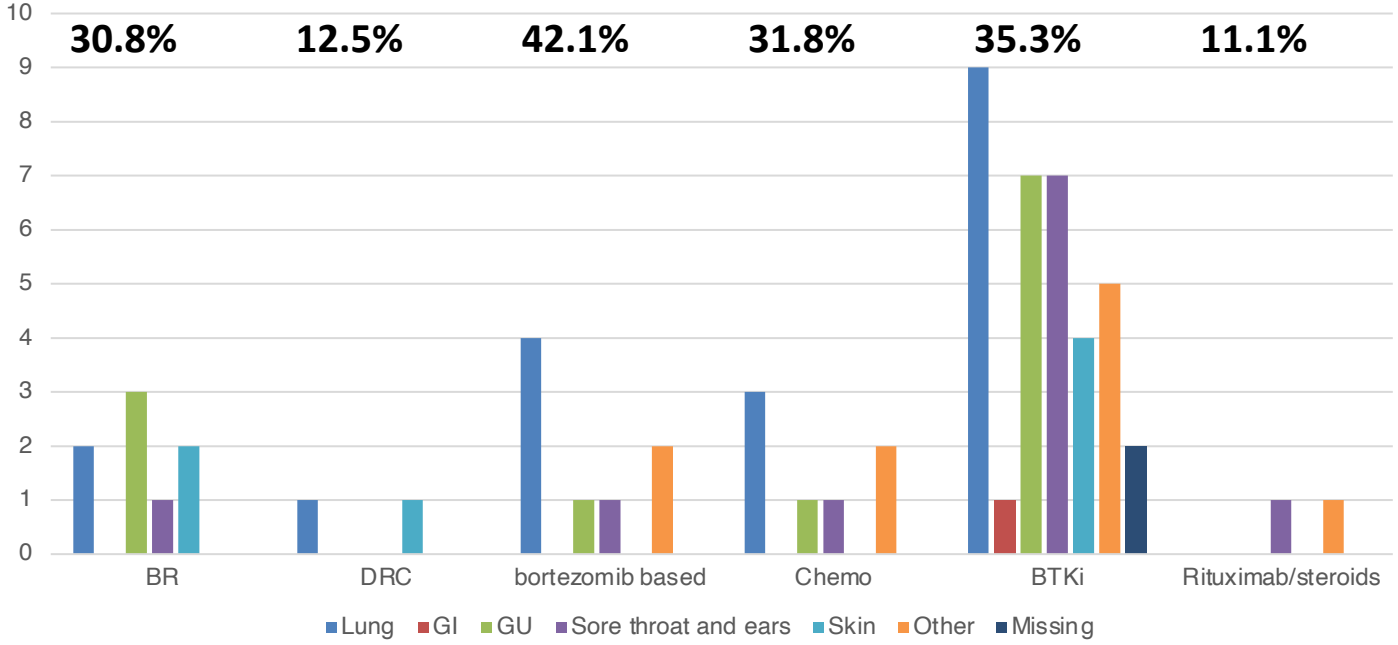
	Infections (Incidence)
BR	8 (30.8)
DRC	2 (12.5)
Bortezomib based	8 (42.1)
Chemo	7 (31.8)
BTKi	36 (35.3)
Rituximab	2 (11.1)

BR: Bendamustine-Rituximam; DRC: Dexamethasone-Rituximab-Cyclophosphamide; BTKi: Bruton Tyrosine Kinase inhibitor.

Infections in second line

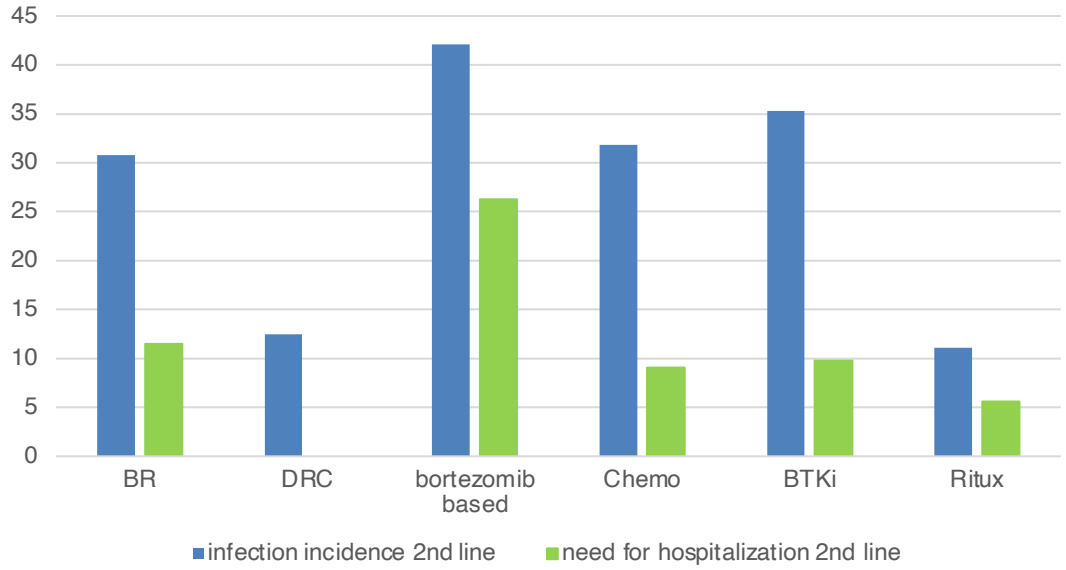
A total of **63** infections in **203** patients.

	BR	DRC	bortezomib based	Chemo	BTKi	Rituximab/steroids
Infections	**8**	**2**	**8**	**7**	**36**	**2**
Incidence	**30.8%**	**12.5%**	**42.1%**	**31.8%**	**35.3%**	**11.1%**



GI: gastro-intestinal infections; GU: genito-urinary infections.

Infections in second line



BTKis in second line had a hospitalization rate of 9.8%, BR and bortezomib based treatments showed higher rates. None hospitalization was registered in DRC.

Infections in second line

BR → BTKi

24 patients

10 (41.7%) infections

8 (33.3%) requiring therapy

5 (20.8%) need for hospitalization

DRC → BTKi

53 patients

14 (26.4%) infections

14 (26.4%) requiring therapy

2 (3.8%) need for hospitalization

Significant difference for severe infection (p=0.02)

Late toxicity

Leukemia. 2026 Jan;40(1):241-244. doi: 10.1038/s41375-025-02833-x. Epub 2025 Dec 9.

Late toxicity and long-term efficacy of first-line bendamustine and rituximab combination in patients with Waldenström macroglobulinemia

Véronique Leblond [1], Jean-Richard Eveillard [2], Driss Chaoui [3], Doriane Cavalieri [4], Caroline Dartigeas [5], Lise Willems [6], Ronan Le Calloch [7], Fathia Merabet [8], Xavier Roussel [9], Benoît Bareau [10], Sabine Tricot [11], Jehan Dupuis [12], Stéphanie Poulain [13], Kamel Laribi [14], Damien Roos-Weil [15]

The FILO group conducted a retrospective study on 69 WM patients treated by first-line BR.

Second Primary Malignancies (SPMs) were observed in 12 patients: nine developed solid tumors (pancreas, n = 2; stomach, n = 2; colorectal, n = 1; esophagus, n = 1; lung, n = 1; skin, n = 1; breast, n = 1) and three MDS, which progressed to AML in two patients.

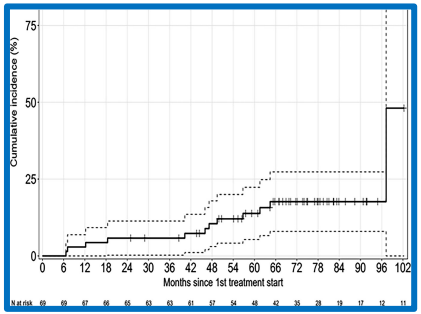
Late toxicity

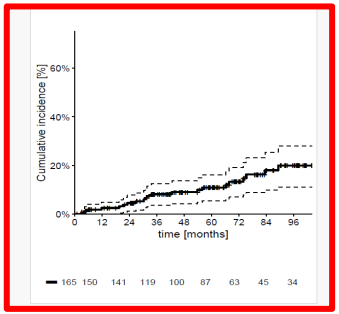
	Leblond et al.	Autore et al.
N pts	69	165
Median observation time (months)	97	72
Median OS (mo) Median PSS (mo) Median EFS (mo)	Not reached 82.2 81.5	Not reached 82.6 75.2
Relapses	17 (24.6%)	48 (29.1%)
Second lines cBTK CIT others	15 (21.7%) 9 6 -	42 (25.4%) 24 6 12
PFS with BTK PFS without BTK	Not reached 10.3	Not reached 57.7
SPM Solid Hematological	12 (17.4%) 9 3	21 (12.7%) 14 7

Late toxicity

	Leblond et al.	Autore et al.
SPM cumulative incidence at:		
-12 months	2.9%	2.5%
-24 months	5.8%	4.5%
-48 months	10.5%	9.0%
-96 months	17.6%	20.0%

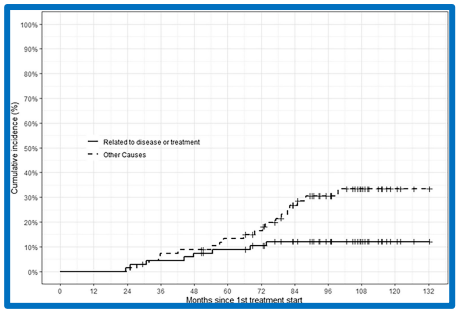
Curves of cumulative incidence of SPM

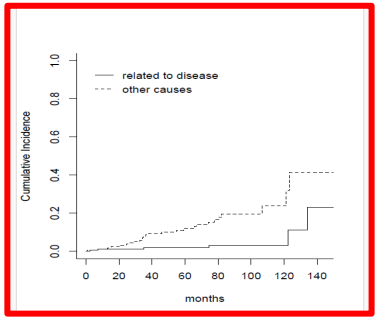




	Leblond et al.	Autore et al.
Deaths	29	32
due to		
-PD	8	6
-SPM	9	8
-non disease rel	8	14
-th-related AML	2	0
-unknown	2	4

Curves of cumulative incidence of not disease-related deaths vs disease- or treatment-related deaths





Late toxicity

The 67th ASH Annual Meeting Abstracts

ORAL

623. MANTLE CELL, FOLLICULAR, WALDENSTROM'S, AND OTHER INDOLENT B CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Double-hit alterations of TP53 identify ultra high-risk disease in previously treated, MYD88 mutated waldenstrom macroglobulinemia.

Nickolas Tsakmaklis [1], Alberto Guijosa [2], Andres Ramirez [1], Amanda Kofides [3], Abigail Peachey [1], Xia Liu [1], Hao Sun [1], Maria Luisa Guerrera [1], Christopher Patterson [1], Andrew Branagan [4], Shayna Sarosiek [1], Jorge Castillo [1], Zachary Hunter [1], Steven Treon [1]

[1] Dana-Farber Cancer Institute, Bing Center for Waldenstrom's Macroglobulinemia, Boston, United States
[2] Dana-Farber Cancer Institute, Department of Biological Chemistry and Molecular Pharmacology, Boston, United States
[3] Dana-Farber Cancer Institute, Department of Cancer Biology, Boston, United States
[4] Massachusetts General Hospital, Medical Oncology, Boston, United States

Aim: to **clarify prior treatment exposures and risk of acquiring TP53ALT**, as well as delineate types of TP53ALT that could contribute to high-risk disease in previously treated WM patients.

- ❑ OS was significantly worse for TP53ALT versus TP53WT WM patients (9-year OS: 45% vs. 74%; p=0.019).
- ❑ The 9-year OS for double versus single hits was 19% vs. 88%; p=0.098.
- ❑ Patients with single-hit TP53ALT showed no significant difference versus TP53 wild-type patients (9-year OS: 88% vs. 75%).

Late toxicity

164 patients: a median of 1.5 (range 1-9) prior therapies, and 50% had previous CT exposure.

TP53ALT in 19/164 patients (11.6%)
TP53 double hits in 10/19 (52.6%)

- TP53ALT were more common in CT-vs. non-CT- exposed patients (15.9% vs. 7.3%; p=0.088).
- Double-hit TP53ALT were more common in patients who received both AA and NA (18.8%) versus either an AA or NA (6.1%) or no CT (3.6%); p=0.069 for three-way comparison.

- Multivariate analysis showed an **association between prior CT exposure and acquisition of TP53ALT** (OR 2.8, p=0.10).

- A multivariate Cox regression confirmed sex (HR: 2.01, p=0.043), age (HR: 1.08, p<0.001), and **double-hit TP53ALT (HR: 3.6, p=0.002) significantly impacted OS**, whereas single-hit TP53 ALT was not significant (p=0.73).

Take home messages

- The **chemoimmunotherapy regimens such as BR and DRC** continue to play a central role in managing WM, as they are effective, of fixed duration, generally well-tolerated.
- Role of **proteasome-inhibitor** based therapies in Italy.
- Role of CIT In relapsed/refractory WM vs BTKi

- advantages of **ibrutinib** versus non-BTKi therapy in terms of PFS and TTNT, but not in terms of OS, except for DRC).

Tolerability/Safety in terms of infections and late toxicities as Second Primary Malignancies.

Risks of upfront CT use → Double-hit TP53ALT was a major predictor of poor survival thereby identifying an ultra-high risk disease population.

Future perspectives from Europe

ECWM-2

Study Design: Phase II, single arm, multicenter, international

Patients: treatment naive WM patients

Treatment: Bortezomib-Rituximab-Ibrutinib

Status of the Study: patient recruitment closed (last patient in November 2021, n= 53)

Sponsor: University Hospital of Ulm, PI Christian Buske

VIWA-1

Study Design: International phase II trial, explorative, multicenter, open label, and randomized

Patients: treatment naive WM patients

Treatment: Venetoclax, Rituximab

Status of the Study: patient recruitment started

Sponsor: University Hospital of Ulm, PI Christian Buske

CZAR-1

Study Design: Phase II, randomized, multicenter, international trial

Patients: treatment naive and relapsed WM patients

Treatment: Carfilzomib/Ibrutinib versus Ibrutinib

Status of the Study: recruiting (first patient in Feb 2021, n= 99)

Sponsor: University Hospital of Ulm, PI Christian Buske

Future perspectives from US

Recruiting

Zanubrutinib, Bendamustine, Rituximab Prev. Untreated WM (ZEBRA)

ClinicalTrials.gov ID NCT06561347

Sponsor Massachusetts General Hospital

Information provided by Andrew R. Branagan, M.D., Ph.D., Massachusetts General Hospital (Responsible Party)

Last Update Posted 2025-11-24

Participant Group/Arm

Experimental: Zanubrutinib + Bendamustine + Rituximab

Zanubrutinib will be taken orally once daily on days 1-28 of cycles 1-15.

Bendamustine will be given by intravenous infusion over about 10 to 60 minutes on days 1 and 2 of cycles 1 to 4.

Rituximab will be given by intravenous infusion over about 30 minutes on day 1 of cycles 1 to 4.

Drug diaries will be provided to participants to document information about the study treatment being taken.

The purpose of this study is to determine the very good partial response (VGPR) or better rate in participants with WM.

This is multi-center phase 2 of zanubrutinib, bendamustine, and rituximab (ZBR) in previously untreated Waldenström macroglobulinemia (WM).

Recruiting

A Study of Pirtobrutinib, Venetoclax, and Rituximab in People With Waldenström's Macroglobulinemia (WM)/Lymphoplasmacytic Lymphoma (LPL)

ClinicalTrials.gov ID NCT07231952

Sponsor Memorial Sloan Kettering Cancer Center

Information provided by Memorial Sloan Kettering Cancer Center (Responsible Party)

Last Update Posted 2025-11-17

Intervention/Treatment

Drug: Pirtobrutinib

- PO QD

Drug: Venetoclax

- PO QD

Drug: Rituximab

- IV or SC

A Phase II Study of Time-limited Combination of Pirtobrutinib, Venetoclax, and Rituximab in Treatment Naïve Patients With Waldenström's Macroglobulinemia (WM) / Lymphoplasmacytic Lymphoma (LPL) (PRoVen)

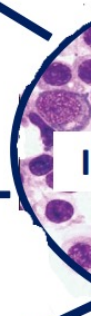
Thank you for your attention!

Treatment: indications

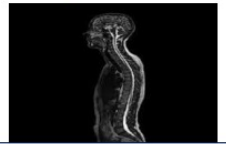
B symptoms
(Recurrent fever, night sweats, weight loss, fatigue)

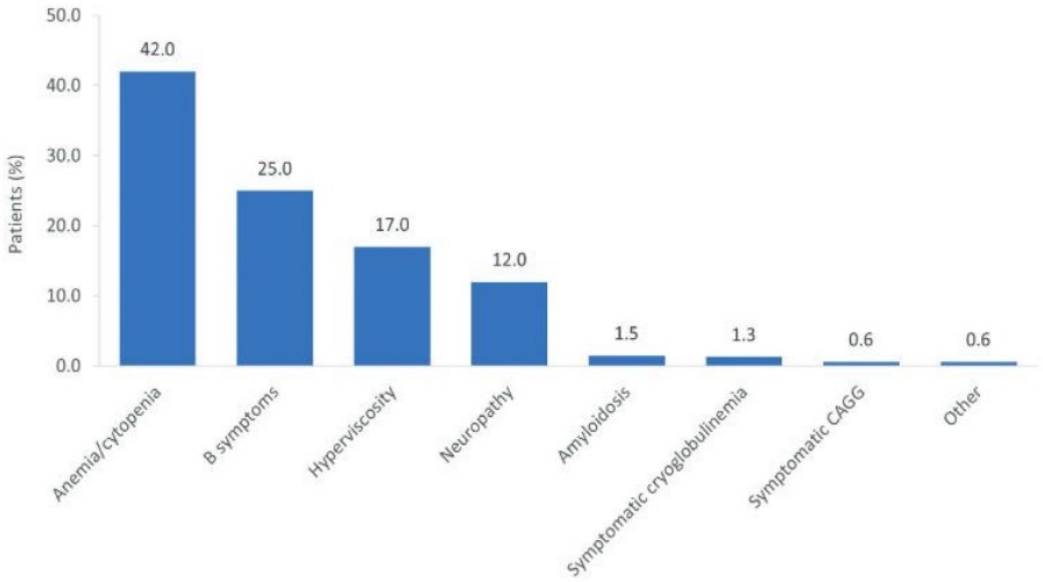
-Hemoglobin <10 g/dL (60-75%)
-Platelet count< 100 000 mcL

Symptomatic:
Lympadenopathy/bulky
Hepatomegaly
Splenomegaly
Organ or tissue infiltration
(≤20% in first Line)



Bing Neel Syndrome





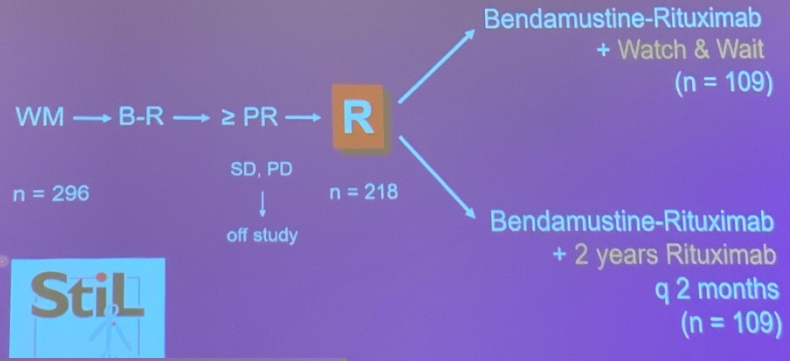
Two years Rituximab maintenance versus observation after first line treatment with Bendamustine plus Rituximab in patients with Waldenströms Macroglobulinemia (WM): results from the StiL NHL7-2008 MAINTAIN trial

Results of a prospective, randomized, multicentre phase 3 study
(Study of the StiL NHL7-2008 MAINTAIN trial)

Mathias Rummel, Christian Lerchenmueller, Manfred Hensel, Martin Goerner, Christian Buske, Holger Schulz, Burkhard Schmidt, Georgi Kojuharoff, Elisabeth Lange, Wolfgang Willenbacher, Jan Dürig, Erik Engel, Frank Kauff, Juergen Barth, Alexander Burchardt, Axel Hinke, Jasmin Müller and Richard Greil on behalf of the
StiL Study group indolent Lymphomas, Germany and Austria

B-R + Watch & Wait vs. B-R + 2 years Rituximab

StiL NHL 7-2008 - MAINTAIN



StiL NHL 7-2008 in WM: Objective and endpoints

- Objective:
  - Demonstrate PFS improvement of 2 years R-maintenance over observation after induction with B-R
- Primary endpoint:
  - Progression free survival (PFS)
- Secondary endpoints include:
  - Overall survival (OS), Time to next treatment (TTNT)
  - Response rates
  - Adverse events, short- and long-term toxicity, second primary malignancies

Rummel M., IWMW

Agent	WM Toxicities
Rituximab	• IgM flare (40-60%)-> Hyperiscosity crisis, Aggravation of IgM related PN, CAGG, Cryos. • Hypogammaglobulinemia-> infections, IVIG • Intolerance (10-15%)
Nucleoside Analogues	• Hypogammaglobulinemia-> infections, IVIG • Transformation, AML/MDS (15%)
IMIDS	• Peripheral Neuropathy (60% >grade 2 with Thalidomide) • Aggravated IgM flare (Revlimid and Pomalidomide) • Severe anemia (Revlimid)
Bortezomib	• Grade 2+3 Peripheral neuropathy (60-70%); High discontinuation (20-60%) using twice weekly schedule

Late toxicity

164 patients: a median of 1.5 (range 1-9) prior therapies, and 50% had previous CT exposure.

TP53ALT were identied in 19/164 patients (11.6%). Of these, TP53 double hits were observed in 10/19 (52.6%).

comprising cases with TP53 mutations plus del17p (n=6), UPD17 (n=3), and compound heterozygosity (n=1).

Single events were found in 9/19 (47.4%) of TP53ALT patients comprising single TP53Mut (n=5) or del17p (n=4).

TP53ALT were more common in CT-vs. non-CT- exposed patients (15.9% vs. 7.3%; p=0.088).

Double-hit TP53ALT were more common in patients who received both AA and NA (18.8%) versus either an AA or NA (6.1%) or no CT (3.6%); p=0.069 for three-way comparison.

Multivariate analysis adjusting for age, CXCR4 mutation status, progression status at study biopsy, and number of prior lines of therapy showed an association between prior CT exposure and acquisition of TP53ALT (OR 2.8, p=0.10).

A multivariate Cox regression conrmed sex (HR: 2.01, p=0.043), age (HR: 1.08, p<0.001), and double-hit TP53ALT (HR: 3.6, p=0.002) signicantly impacted OS, whereas single-hit TP53 ALT was not signicant (p=0.73).

Conclusions: Prior CT exposure is associated with increased acquisition of TP53ALT (including TP53Mut and del17p), as well as other somatic variants and copy number alterations when compared to CT-unexposed patients. Double-hit TP53ALT was a major predictor of poor survival thereby identifying an ultra-high risk disease population. Our studies further inform risks of upfront CT use and provide support for the routine assessment of TP53 and del17p in WM patients, and the investigation of novel treatment approaches for patients with ultra-high risk TP53ALT

Infections in first line

When evaluating hospitalization…

	Infections (%)	Infections requiring hospitalization (%)
BR	53 (32.1)	18 (10.9)
DRC	22 (14.5)	5 (3.3)
Other CIT	15 (24.2)	4 (6.4)
Chemo	12 (29.3)	3 (7.3)
BTKi	4 (23.5)	1 (5.9)
Rituximab/steroids	5 (9.6)	3 (5.8)

Infections in second line

When evaluating hospitalization…

	Infections (%)	Infections requiring hospitalization (%)
BR	8 (30.8)	3 (11.5)
DRC	2 (12.5)	0
Bortezomib based	8 (42.1)	5 (26.3)
Chemo	7 (31.8)	2 (9.1)
BTKi	36 (35.3)	10 (9.8)
Rituximab	2 (11.1)	1 (5.6)

Infections in second line

	BR	DRC	Bortezomib based	Chemo	BTKi	Rituximab	None	Total
BR	2	4	6	3	24	4	123	165 (33.7)
DRC	6	3	9	3	53	5	73	152 (31.1)
Other CIT	13	5	2	6	12	2	22	62 (12.7)
Chemo	5	0	1	10	7	1	17	41 (8.4)
BTKi	0	0	0	0	1	0	16	17 (3.5)
Rit/steroid	0	4	1	0	5	8	34	52 (10.6)
Total	26 (5.3)	16 (3.3)	19 (3.9)	22 (4.5)	102 (20.9)	19 (3.9)	285 (58.3)	489

Infections: conclusions

- ❖ This large retrospective real-world study highlights the importance of data collection.
- Merits: large study (489 patients), cohorts represented in all the centres, long follow-up
- Limits: retrospective study, indirect comparison, some cohorts are historical.
- ❖ Favourable infectious safety profile of BTKis in the treatment of WM
- ❖ Among CIT regimens, DRC also emerged as a well-tolerated alternative with a lower risk of infectious complications.

These findings underscore the importance of incorporating infection risk into treatment decisions and support the broader use of BTKis in appropriate clinical contexts.

First line treatment: Italian experience

This is one of the largest retrospective real-life studies on WM frontline patients treated with chemo-immunotherapy:

BR emerged as the best option of treatment in WM patients:

- BR scheme showed the **higher ORR** (93.3% vs 79.2% in DRC)
- BR curves confirmed a **better PFS** (80% at 4-y for BR and 60% for DRC; p<0.0001), but the same OS, than DRC patients
- A significant dose reduction of 14.3% for BR vs 6.0% for DRC was found (p=0.026) with an higher proportion of hematological toxicities in BR patients

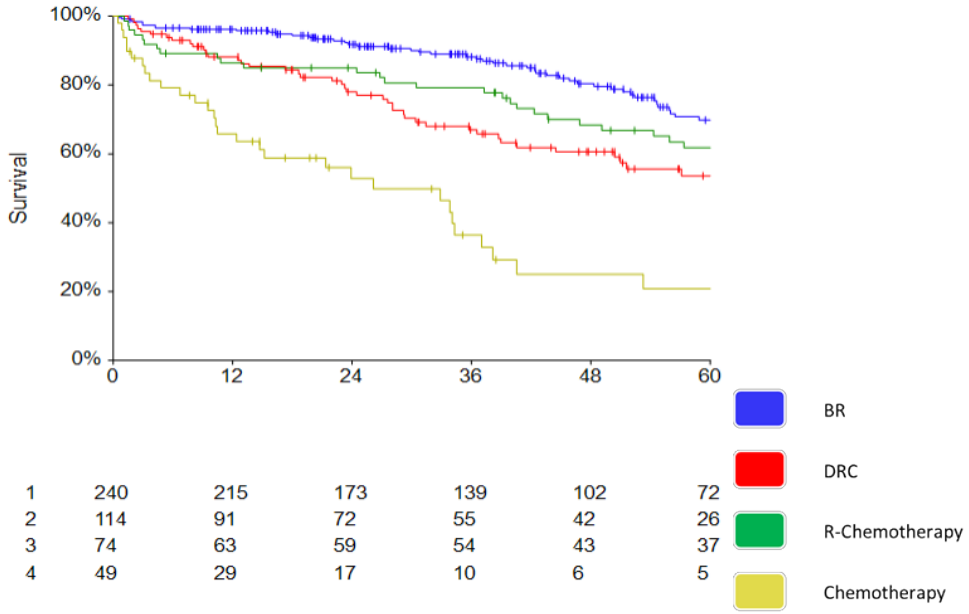
Bendamustine dose in BR: a relative dose intensity reduction higher than 30% is significant to select a group of patients with worse PFS comparable to that of DRC.

- **Age over 75 years** and **CrCl lower than 70 mmol/L** were the main risk factors for this significant dose reduction.

→ Patients with these characteristics are likely to benefit less from BR regimen and should be considered for alternative treatments.

First line treatment: Italian experience

Results: PFS



Median observation time 54 months

1: 4-y PFS 80%
2: 4-y PFS 60%
3: 4-y PFS 68%
4: 4-y PFS 25%

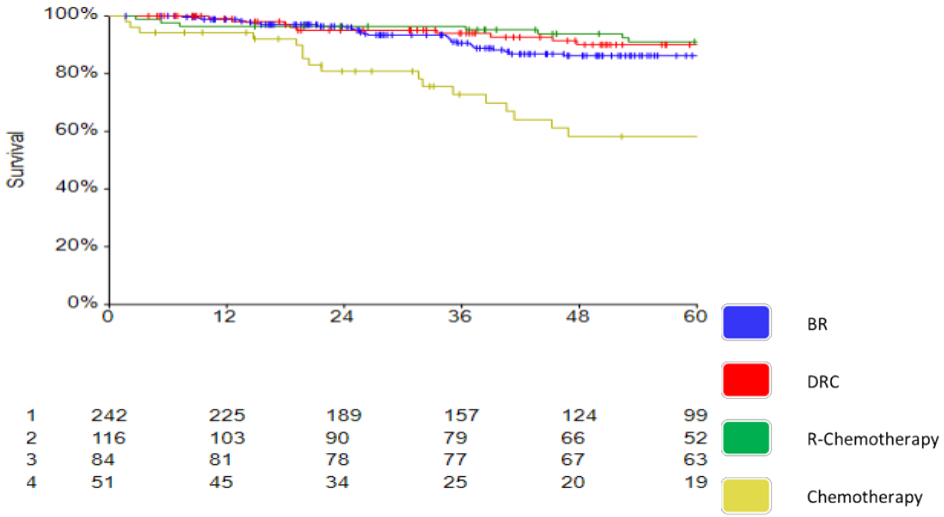
Diff 2-4 HR 0.48 (0.29-0.79) p=0.0007
Diff 3-4 HR 0.41 (0.24-0.69) p<0.0001
Diff 1-4 HR 0.28 (0.15-0.50) p<0.0001

Diff 1-2 HR 0.53 (0.35-0.80) p<0.0001
Diff 2-3 HR 1.21 (0.80-1.83) p=0.362
Diff 1-3 HR 0.74 (0.49-1.12) p= 0.143

When analysing the curves of PFS we noted a **PFS at 4-y 80% for BR** and **60% for DRC** (p<0.0001).

First line treatment: Italian experience

Results: OS



Median observation time 54 months

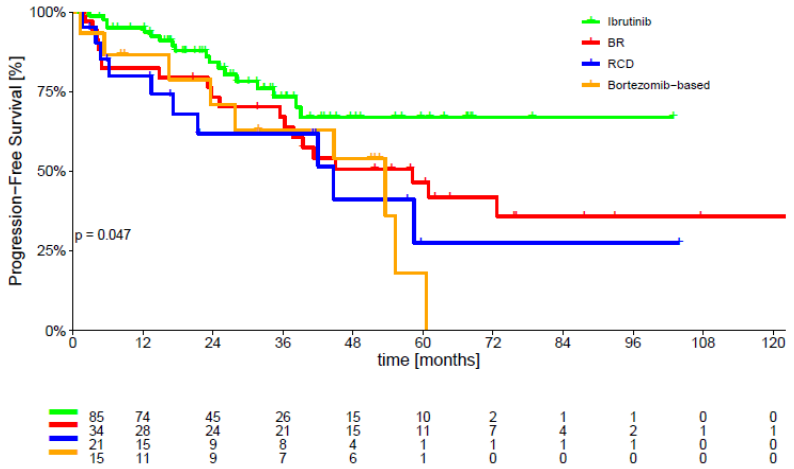
1: 4-y OS 86%
2: 4-y OS 89%
3: 4-y OS 93%
4: 4-y OS 58%

Diff 1-4 HR 0.40 (0.22-0.73) p<0.0001
Diff 2-4 HR 0.41 (0.22-0.76) p=0.002
Diff 3-4 HR 0.24 (0.12-0.48) p<0.0001

Curves of OS did not differ between the two schemes (**OS at 4-y 86% for BR** and **89% for DRC**).

Second line treatment

	Ibrutinib (n=85)	BR (n=34)	DRC (n=21)	Bortezomib-based (n=15)	Total
SEX					
M	56 (65.9)	23 (67.7)	11 (52.4)	9 (60.0)	99 (63.9)
F	29 (34.1)	11 (32.3)	10 (47.6)	6 (40.0)	56 (36.1)
AGE AT TREATMENT Median (Q1-Q3), years	75 (64-81)	70 (63-75)	75 (66-81)	69 (63-81)	73 (64-80)
BETA2M					
Normal	15 (17.6)	8 (23.5)	5 (23.8)	5 (33.3)	33 (21.3)
High	48 (56.5)	15 (44.1)	6 (28.6)	4 (26.7)	73 (47.1)
missing	22 (25.9)	11 (32.4)	10 (47.6)	6 (40.0)	49 (31.6)
Median (Q1-Q3), mg/L	3.9 (2.9-5.0)	3.6 (2.3-5.1)	3.0 (2.8-4.3)	3.0 (2.8-4.3)	3.6 (2.8-5.0)
LDH					
Normal	66 (77.6)	30 (88.2)	10 (47.6)	13 (86.7)	119 (76.8)
High	17 (20.0)	2 (5.9)	6 (28.6)	2 (13.3)	27 (17.4)
missing	2 (2.4)	2 (5.9)	5 (23.8)	0	9 (5.8)
Median (Q1-Q3), UI/L	135 (208-246)	170 (147-220)	223 (173-333)	162 (128-210)	178 (137-242)
IPSSWM					
Low	18 (21.2)	8 (23.5)	5 (23.8)	5 (33.3)	36 (23.2)
Intermediate	37 (43.5)	15 (44.1)	9 (42.9)	7 (46.7)	68 (43.9)
High	22 (25.9)	9 (26.5)	3 (14.3)	3 (20.0)	37 (23.9)
missing	8 (9.4)	2 (5.9)	4 (19.0)	0	14 (9.0)
Rev IPSSWM					
0	0 (0.0)	0	0	1 (6.7)	1 (0.6)
1	7 (8.2)	7 (20.6)	2 (9.5)	3 (20.0)	19 (12.3)
2	26 (30.6)	9 (26.5)	6 (28.6)	3 (20.0)	44 (28.4)
3	29 (34.2)	13 (38.2)	4 (19.1)	4 (26.7)	50 (32.3)
4	10 (11.8)	2 (5.9)	2 (9.5)	3 (20.0)	17 (11.0)
5	3 (3.5)	1 (2.9)	1 (4.8)	0	5 (3.2)
missing	10 (11.8)	2 (5.9)	6 (28.6)	1 (6.7)	19 (12.3)
CrCl					
<70 mL/min	45 (52.9)	16 (47.1)	10 (47.6)	9 (60.0)	80 (51.6)
<50 mL/min	18 (21.2)	3 (8.8)	1 (4.8)	3 (20.0)	25 (16.1)
Missing	3 (3.5)	0	1 (4.8)	1 (6.7)	5 (3.2)
Median (Q1-Q3), mL/min	67 (52-80)	72 (60-92)	68 (60-90)	61 (56-71)	67 (55-82)
CIRS					
>6	22 (25.9)	10 (29.4)	8 (38.1)	2 (13.3)	42 (27.1)
Missing	3 (3.5)	2 (5.9)	0	1 (6.7)	6 (3.9)
Median (Q1-Q3)	4 (3-7)	4 (2-7)	4 (2-8)	3 (1-5)	4 (2-7)
CARDIAC COMORBIDITY					
No	79 (92.9)	31 (91.2)	20 (95.2)	13 (86.7)	143 (92.3)
Yes	6 (7.1)	3 (8.8)	1 (4.8)	2 (13.3)	12 (7.7)
RESPIRATORY COMORBIDITY					
No	83 (97.7)	33 (97.1)	21 (100.0)	15 (100.0)	152 (98.1)
Yes	2 (2.3)	1 (2.9)	0	0	3 (1.9)
SPLEEN					
No	71 (83.5)	29 (85.3)	16 (76.2)	13 (86.7)	129 (83.2)
Yes	14 (14.5)	5 (14.7)	5 (23.8)	2 (13.3)	26 (16.8)
LYMPHNODE > 5cm	67 (78.8)	24 (70.6)	15 (71.4)	14 (93.3)	120 (77.4)
No	18 (21.2)	10 (29.4)	6 (28.6)	1 (6.7)	35 (22.6)
Yes					



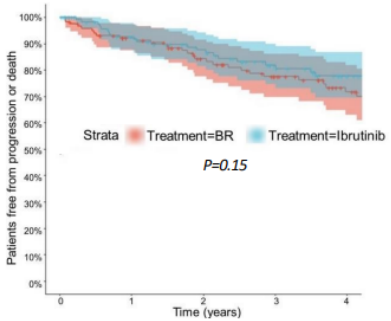
Bendamustine rituximab (BR) versus ibrutinib (Ibr) as primary therapy for Waldenström macroglobulinemia (WM): an international collaborative study

Multi-institutional, international study in Europe and the USA
Median follow-up: 4.2 years

1:1 age-matched analysis of 246 pts *MYD88*^{mut}
Ibrutinib (n=123) BR (n=123)
Significant higher responses with BR
Discontinuation due to AE: 13%BR and 33%ibrutinib

347 TN pts:
- **208 BR**
- **139 ibrutinib**

Progression-free survival



4-year OS: BR 95%(95%CI 91–99)
versus
Ibrutinib 86%(95%CI 80-93)
} *p=0.3*

In a bivariate analysis adjusting for age and the treatment type only age emerged as a predictor for OS (HR 7.2, p=0.0001)

For patients with *MYD88* L265P mutation, selection between the two approaches should be dictated by:
- Potential toxicities
- Patient comorbidities
- Patient/clinician preference (parenteral fixed duration vs. continuous oral)
- Access to therapies

AE, adverse event; BR, bendamustine–rituximab; CI, confidence interval; HR, hazard ratio; MUT, mutant; OS, overall survival; PFS, progression-free survival; pts, patients; TN, treatment-naive; WM, Waldenström's macroglobulinemia.
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