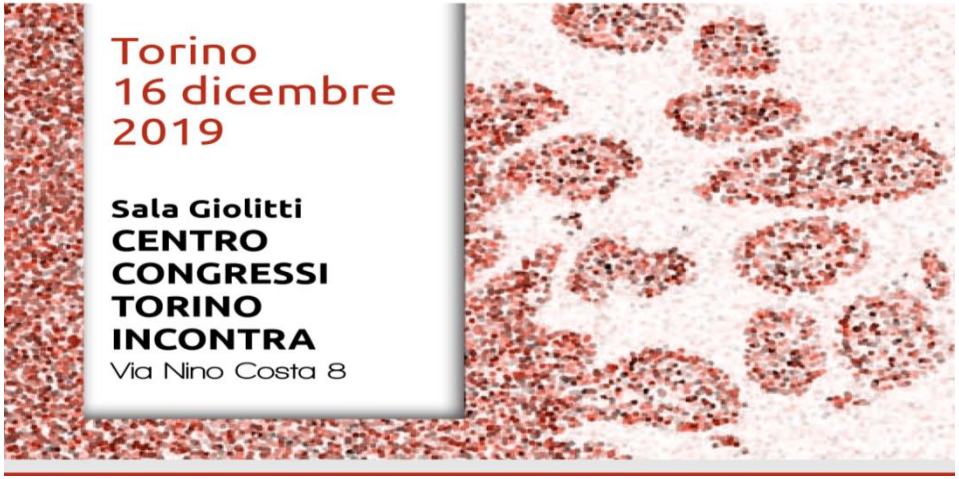
INCONTRO DI AGGIORNAMENTO SUI
DISORDINI LINFOPROLIFERATIVI
E SUI PROTOCOLLI DELLA
FONDAZIONE ITALIANA LINFOMI



Malattia di Waldenstrom
Diagnosi e nuove terapie

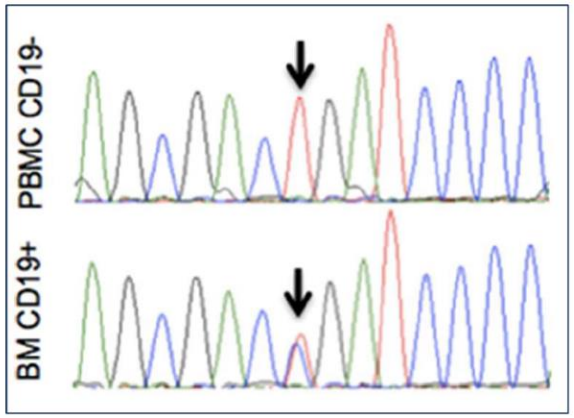
Alessandra Tedeschi

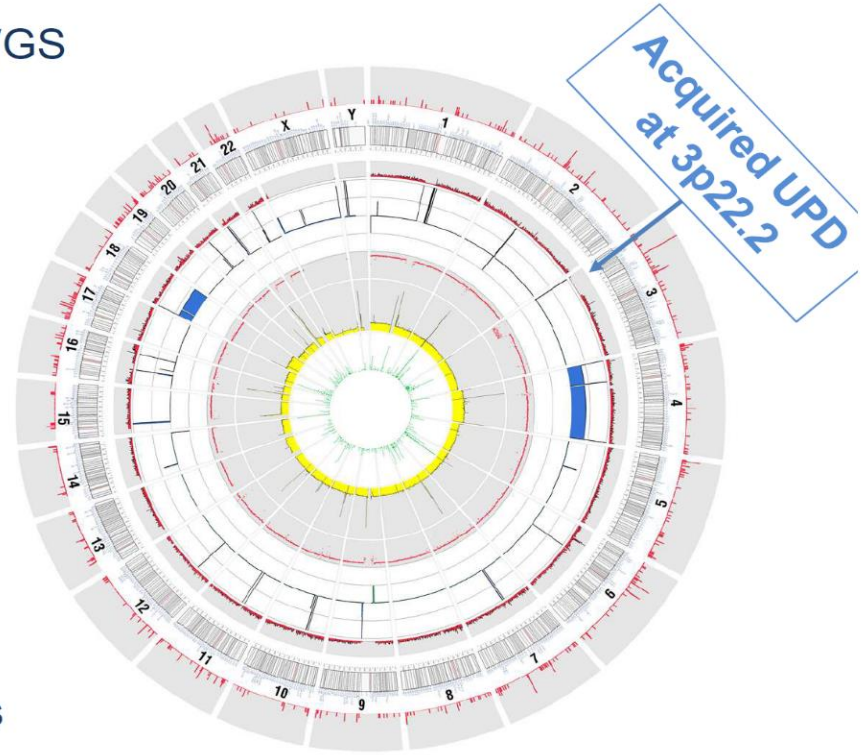
ASST Grande Ospedale Metropolitano Niguarda

Sistema Socio Sanitario
Ospedale Niguarda Cancer Center
Regione Lombardia

MYD88 L265P Somatic Mutation in WM

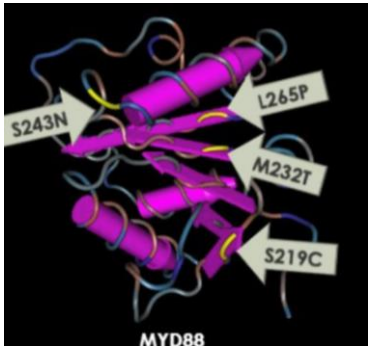
C > G at position 38186241
at 3p22.2 in 91% of WM Patients by WGS





- MYD88^{L265P} confirmed by AS-PCR in 93-97% WM pts;
- Usually heterozygous;
- 10% WM patients homozygous due to acquired UPD.
- MYD88 homozygosity increases with time.

Treon et al, NEJM 367:826, 2012



1% of Pts with MYD88 mutations L265P ^{WT}

Yang et al, 2013

MYD88 L265P in WM/IGM MGUS

	METHOD	TISSUE	WM	IGM MGUS
Treon	WGS/Sanger	BM CD19^{+}	91%	10%
Xu	AS-PCR	BM CD19^{+}	93%	54%
Gachard	PCR	BM	70%	
Varettoni	AS-PCR	BM CD19+	100%	47%
Landgren	Sanger	BM		54%
Jiminez	AS-PCR	BM	86%	87%
Poulain	PCR	BM CD19^{+}	80%	
Argentou	PCR-RFLP	BM	92%	1/1 MGUS
Willenbacher	Sanger	BM	86%	
Mori	AS-PCR/BSiE1	BM	80%	
Ondrejka	AS-PCR	BM	100%	
Ansell	WES/AS-PCR	BM CD19+	97%	
Patkar	AS-PCR	BM	85%	

>50 CONFIRMATIONAL STUDIES PUBLISHED

Discovery of CXCR4 mutations in WM -2013-

Plenary Paper

LYMPHOID NEOPLASIA

The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis

Zachary R. Hunter,[1,2] Lian Xu,[1] Guang Yang,[1] Yangsheng Zhou,[1] Xia Liu,[1] Yang Cao,[1] Robert J. Manning,[1] Christina Tripsas,[1] Christopher J. Patterson,[1] Patricia Sheehy,[1] and Steven P. Treon[1,3]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [2]Department of Pathology and Laboratory Medicine, Boston University School of Graduate Medical Sciences, Boston, MA; and [3]Harvard Medical School, Boston, MA

Key Points

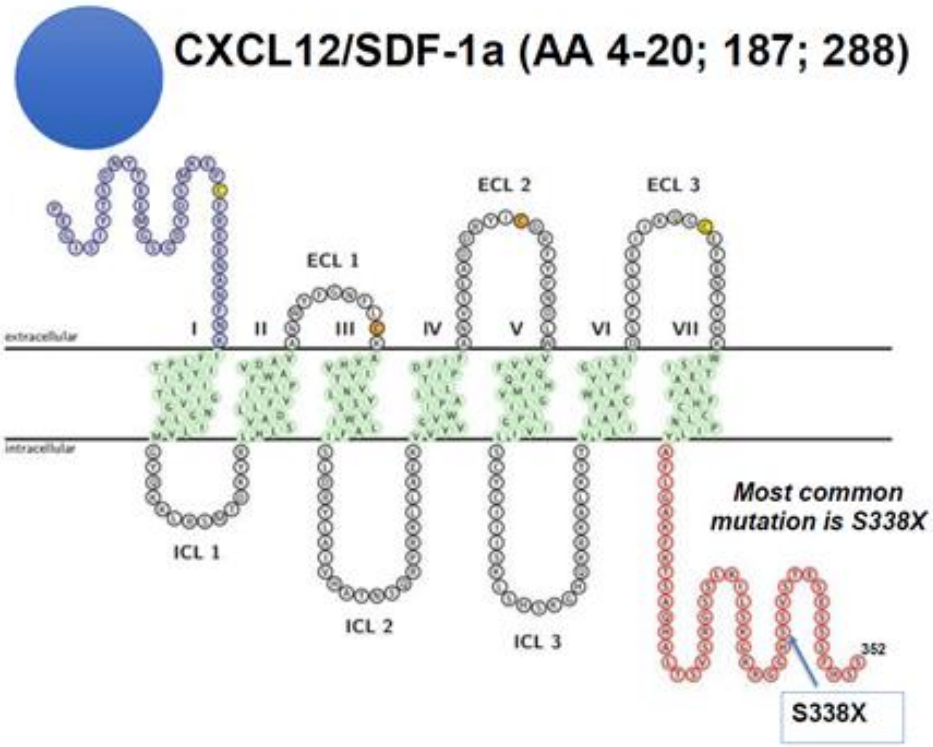
- Highly recurring mutations are present in WM, including MYD88 L265P, warts, hypogammaglobulinemia, infection, and myelokathexis-syndrome–like mutations in CXCR4, and ARID1A.
- Small, previously undetected CNAs affecting B-cell regulatory genes are highly prevalent in WM.

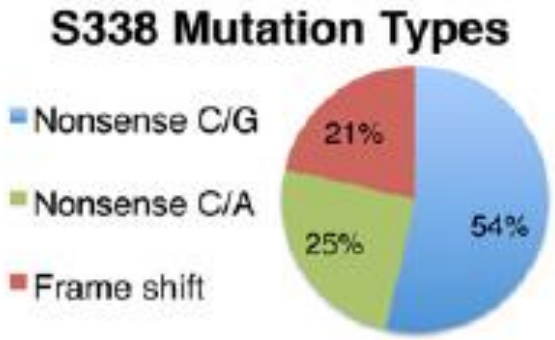
The genetic basis for Waldenström macroglobulinemia (WM) remains to be clarified. Although 6q losses are commonly present, recurring gene losses in this region remain to be defined. We therefore performed whole genome sequencing (WGS) in 30 WM patients, which included germline/tumor sequencing for 10 patients. Validated somatic mutations occurring in >10% of patients included *MYD88*, *CXCR4*, and *ARID1A* that were present in 90%, 27%, and 17% of patients, respectively, and included the activating mutation L265P in MYD88 and warts, hypogammaglobulinemia, infection, and myelokathexis-syndrome–like mutations in CXCR4 that previously have only been described in the germline. WGS also delineated copy number alterations (CNAs) and structural variants in the 10 paired patients. The CXCR4 and CNA findings were validated in independent expansion cohorts of 147 and 30 WM patients, respectively. Validated gene losses due to CNAs involved *PRDM2* (93%), *BTG1* (87%), *HIVEP2* (77%), *MKLN1* (77%), *PLEKHG1* (70%), *LYN* (60%), *ARID1B* (50%), and *FOXP1* (37%). Losses in *PLEKHG1*, *HIVEP2*, *ARID1B*, and *BCLAF1* constituted the most common deletions within chromosome 6. Although no recurrent translocations were observed, in 2 patients deletions in 6q corresponded with translocation events. These studies evidence highly recurring somatic events, and provide a genomic basis for understanding the pathogenesis of WM. (*Blood*. 2014;123(11):1637-1646)

30-40% of WM patients

WHIM-like CXCR4 mutations in WM

- 25-40% of WM pts
- Occur in the C-terminal domain
- Nonsense and frameshift mutations
- Frequent in MYD88 L265P,
- rare (~9%) in MYD88 WT
- Usually subclonal
- Multiple CXCR4 mutations can be present within an individual patient

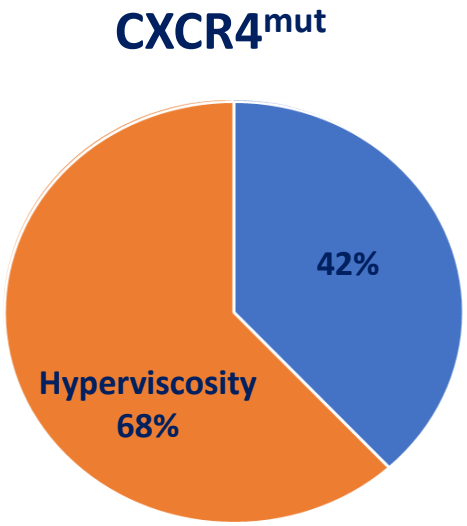




Hunter et al. Blood 2013
Roccaro et al. Blood 2014
Poulain et al. Blood 2016
Xu et al. BJH 2016
Varettoni et al. Haematologica 2016

CXCR4 mutations clinical impact

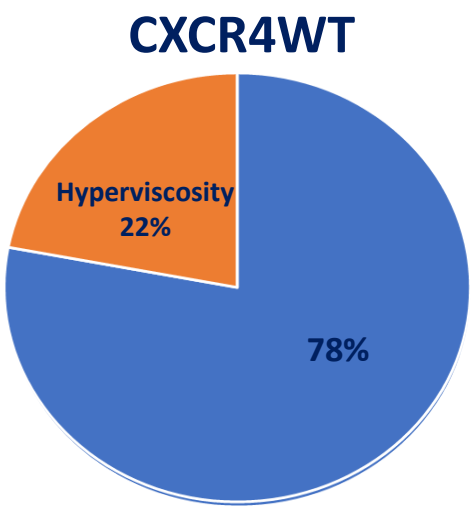
MYD88	WT	L265P	
CXCR4	WT	WHIM	WHIM-NS
$MYD88^{WT}CXCR4^{WT}$ ~10% pts Poor prognosis/OS Low serum IgM LowBM involv.	$MYD88^{L265P}CXCR4^{WT}$ ~60% pts	$MYD88^{L265P}CXCR4^{WHIM-FS}$ ~30% pts Low adenopathy No influence on ibrutinib response	$MYD88^{L265P}CXCR4^{WHIM-NS}$ ~50% pts of $CXCR4^{WHIM}$ High BM High IgM Hyperviscosity More symptomatic



CXCR4 MUT vs CXCR4 WT
OR 4.9, 96% CI 2.1-11.4; p <0.001

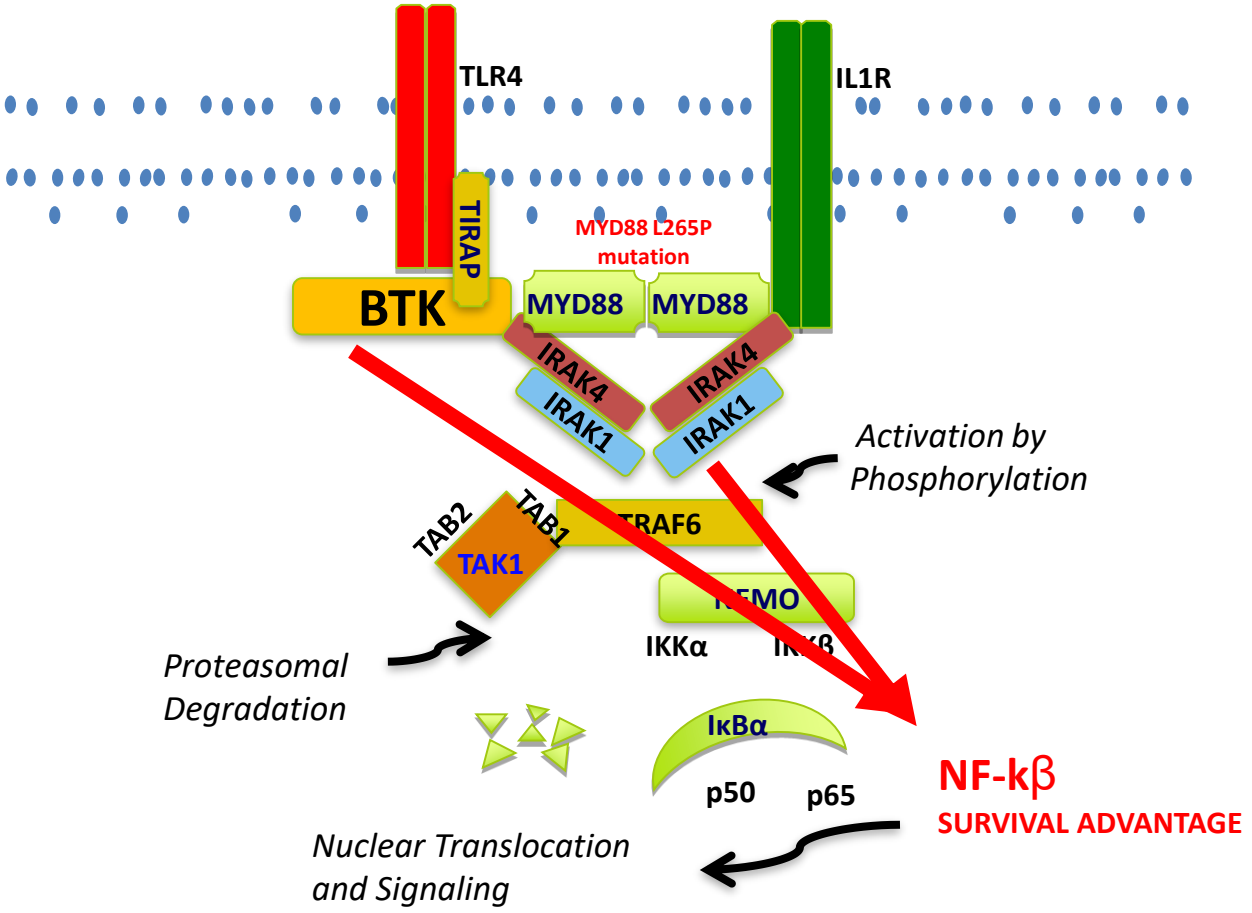
CXCR4 NS vs CXCR4 WT
OR 9.4, 96% CI 2.9-22.5; p <0.001

CXCR4 FS vs CXCR4 WT
OR 0.8, 96% CI 0.2-3.9; p =0.77

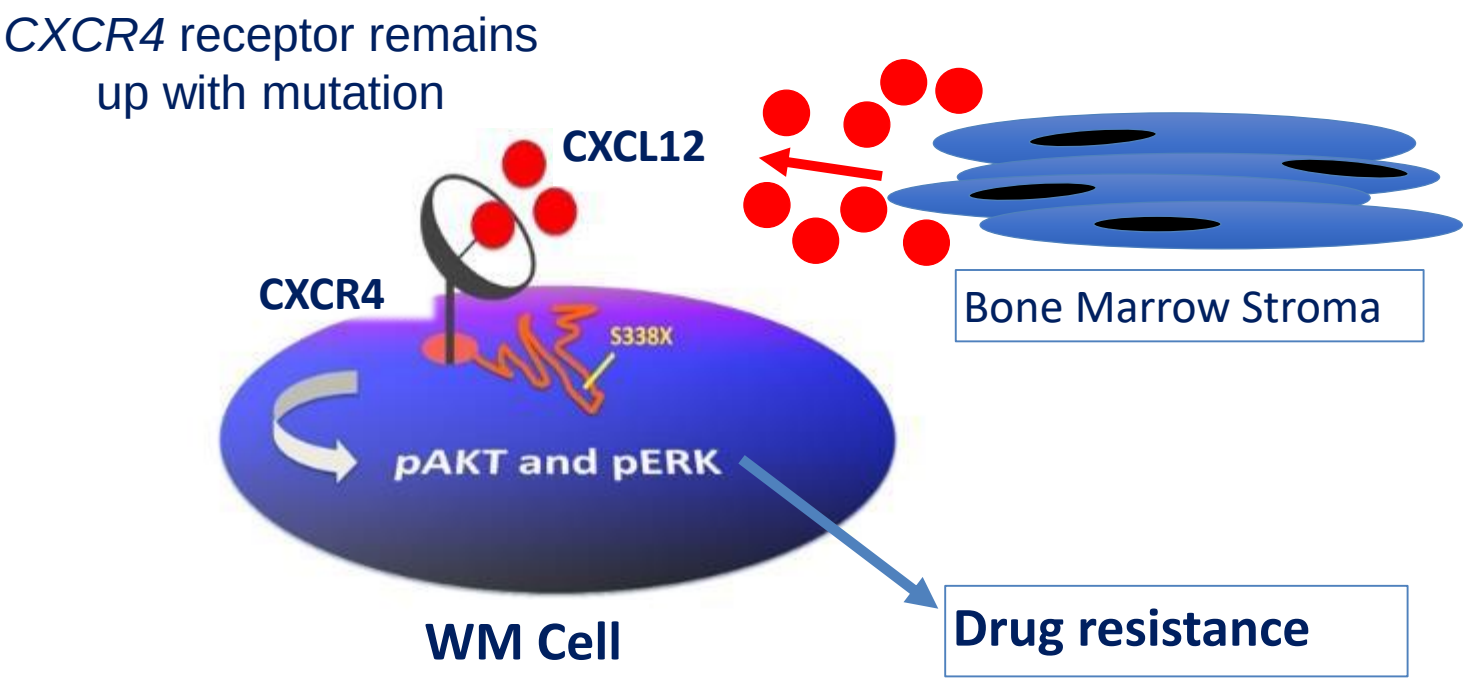


Treon SP et al 2013, Gustine et al 2017

TOLL RECEPTOR/ IL1R SIGNALING PATHWAY

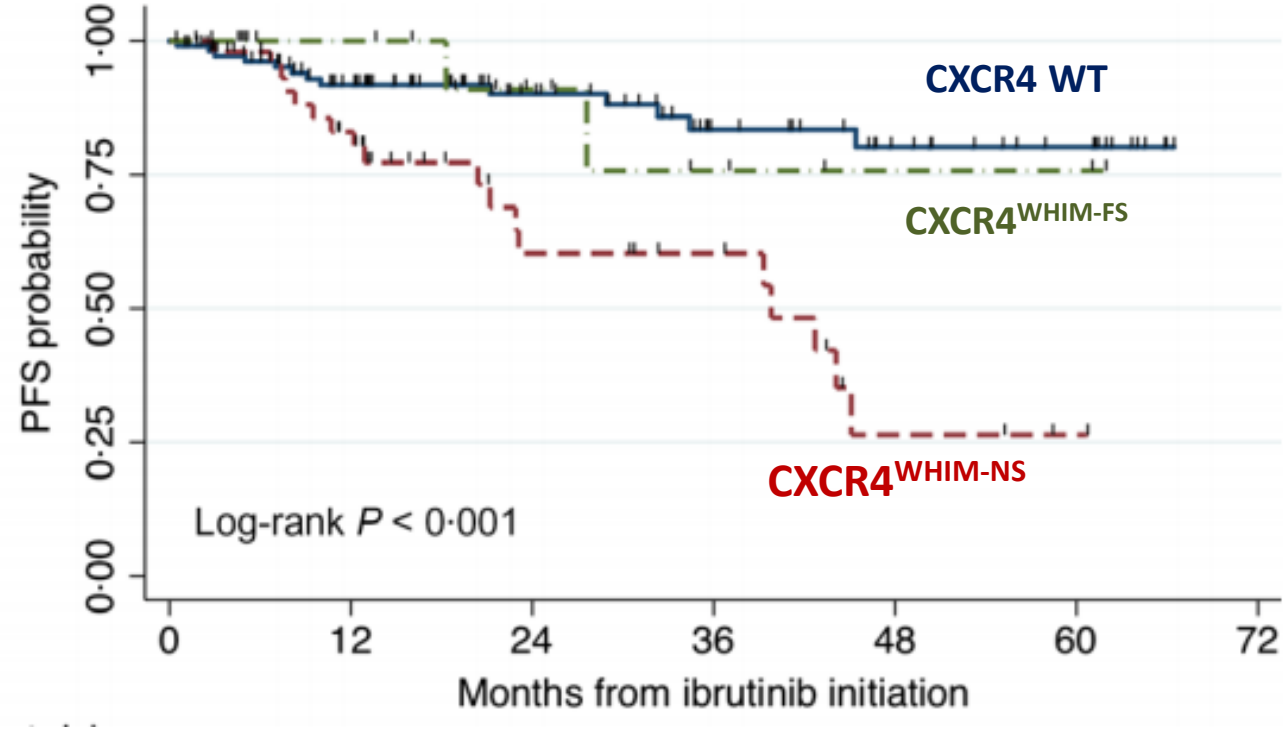


CXCR4 mutations permits ongoing pro-survival signaling by CXCL12, the ligand for CXCR4 Receptor



Cao et al, Br J Haematol. 2015 Mar;168(5):701-7; Roccarro et al, Blood. 2014 Jun 26;123(26):4120-31

CXCR4 mutations: clinical impact



- ❑ 138 pts treated with ibrutinib
- ❑ 68/138 pts CXCR4WHIM
  - 49 CXCR4NS
  - 19 CXCR4FS

Median FU 25 mo

No difference in Major response rate and PFS in $CXCR4^{WHIM-FS}$ vs CXCR4 WT

Castillo et al BJH 2019

Clinicopathological definition of WM

- **infiltration of lymphoplasmacytic cells in the bone marrow**

(lymphoplasmacytic lymphoma using REAL/WHO criteria)

- **presence of a monoclonal IgM protein, irrespective of serum level**

Bone marrow morphology:

- *intertrabecular pattern*
- *with or without nodules*
- *with or without paratrabecular and diffuse infiltrates*

- **Dutcher bodies: acid–Schiff+ intranuclear pseudoinclusions**
- **Mast cells: support the growth of the LPL**
- **Immunoglobulin deposition, amyloid, or crystal-storing histiocytosis**

- **Specific immunophenotype:**

  - *sIgM+, CD19+, CD20+, CD22+, CD79+, FMC7+, CD52+,*
  - *CD5±, CD10-, CD23-*
  - *CD25+, CD27+, CD103-, CD138-*
  - *plasmocytoid: cIgM, CD19+ CD45+ abnormal exprssion of CD138+ PAX5*

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

IWWM2, ATHENS 2002; Owen et al, Semin Oncol 2003

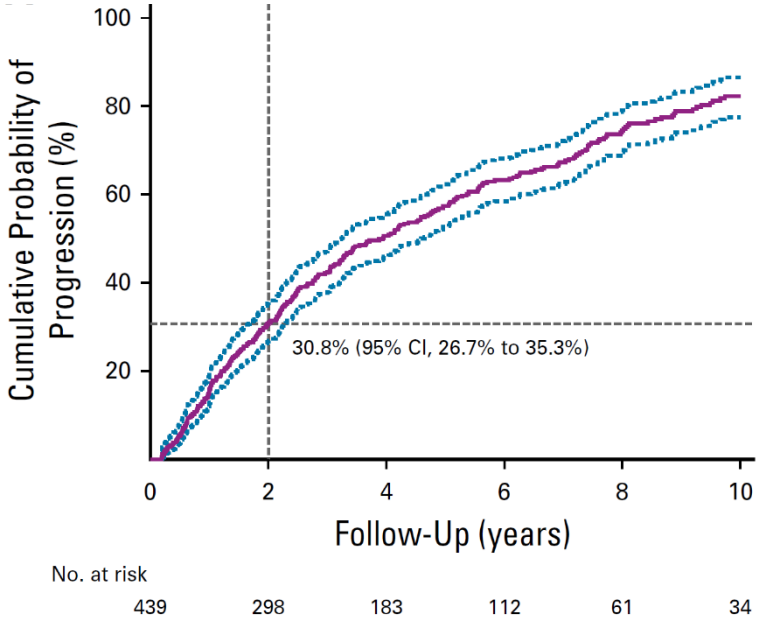
Management of WM patients

Asymptomatic

OBSERVATION

- **No OS benefit to treat asymptomatic pts**
- **Resistance development**
- **Not all pts will progress to symptomatic disease**

Cumulative probability of progression among asymptomatic patients



Kyle et al, 2012; Butoros et al, 2019

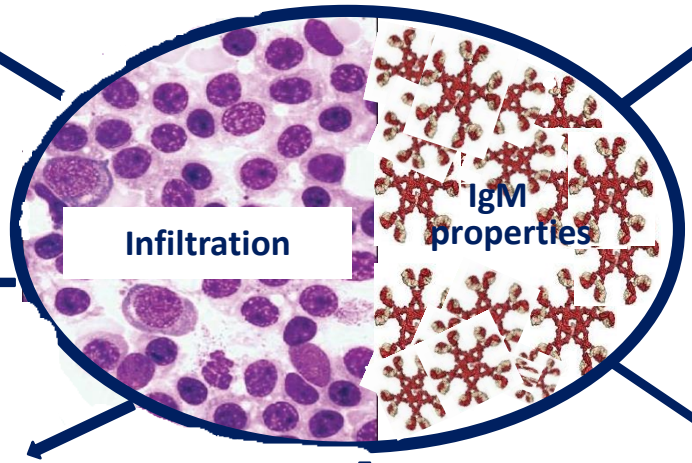
Indications for therapy initiation

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

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

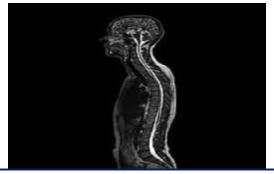
Hyperviscosity Syndrome (10-15%)
or IgM > 6000 mg/dL

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



Symptomatic cryoglobulinemia (10%)
Cold agglutinin anemia (5%)
Immune hemolytic anemia
Immune thrombocytopenia
Nephropathy related to WM
Amyloidosis related to WM (10-15%)

Bing Neel Syndrome



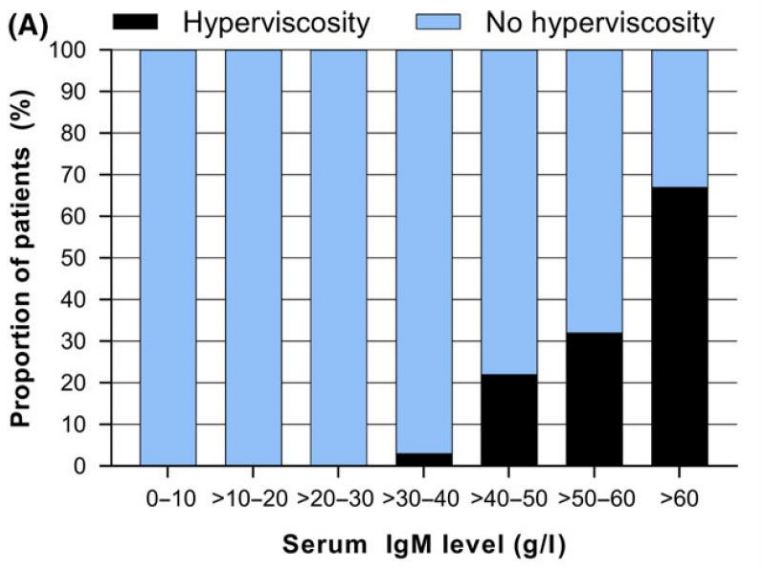
Peripheral neuropathy (20-25%)

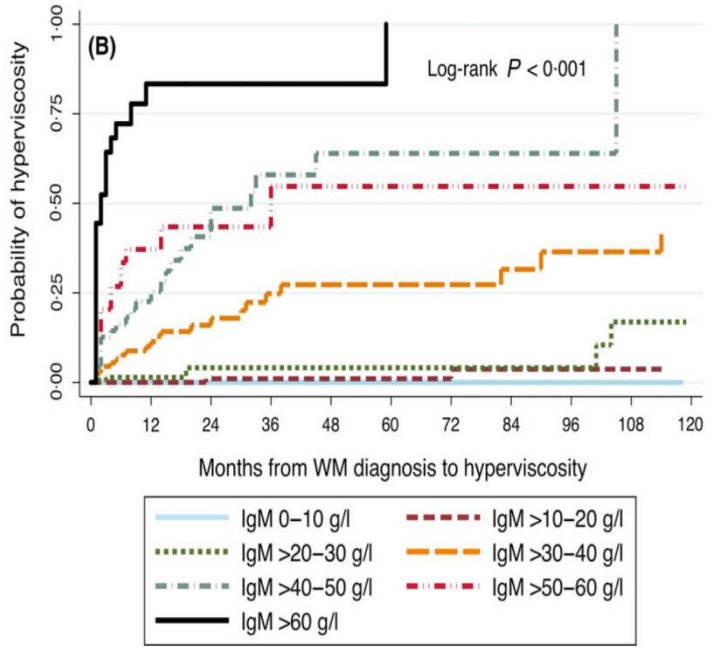
ESMO GUIDELINES Kastritis et al, 2018

bjh

Serum IgM level as predictor of symptomatic hyperviscosity in patients with Waldenström macroglobulinaemia

113 pts developed hyperviscosity/825 pts (14%)

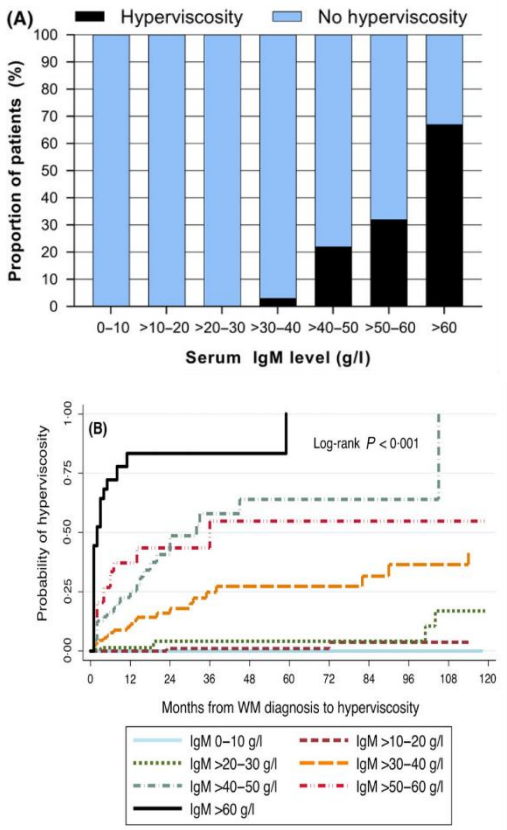




Reasonable treatment start when IgM level > 6000 mg/dL

Gustine JN et al, 2017

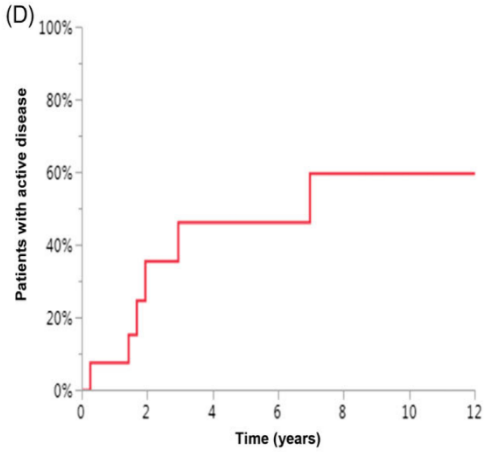
Serum IgM level as predictor of symptomatic hyperviscosity in patients with Waldenström macroglobulinaemia



Predictors of symptomatic hyperviscosity in Waldenström macroglobulinemia

130/997 pts developed hyperviscosity (13%)

Only 2.5% treatment in 3 mo
Median time to first line: 6.9 y
(no difference with pts < 6000 mg/dL)



Only independent predictive factor:
serum viscosity at diagnosis in asymptomatic pts>1.8 cp

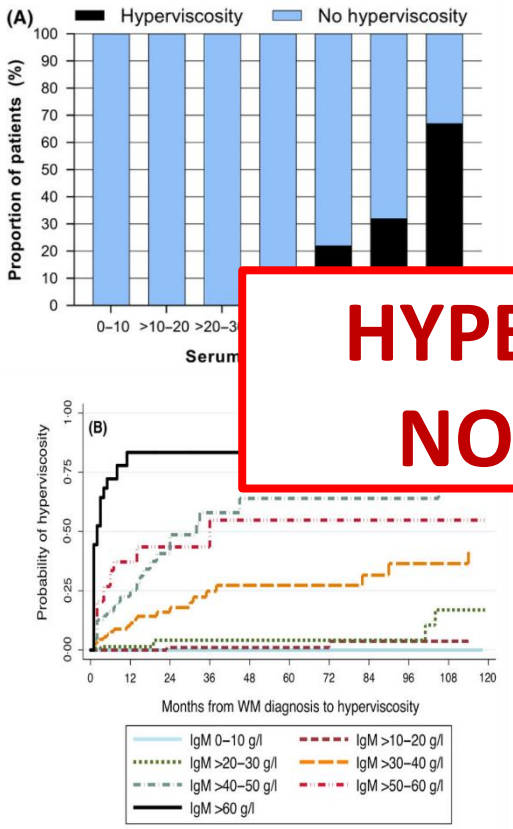
Gustine JN et al, 2017

Abeykoon JP et al, 2018

bjh

AJH

Serum IgM level as predictor of symptomatic hyperviscosity in patients with Waldenström macroglobulinaemia



Gustine JN et al, 2017

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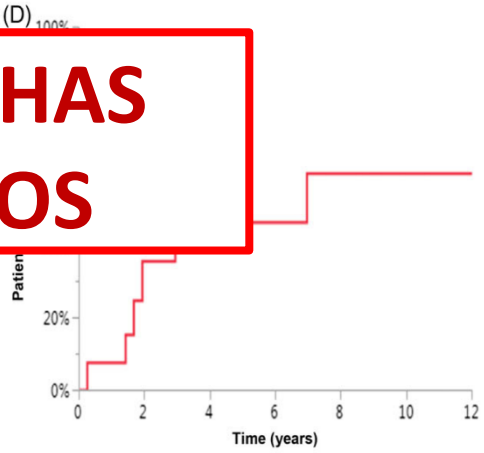
HYPERVISCOSITY HAS NO IMPACT ON OS



Only independent predictive factor:
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Abeykoon JP et al, 2018

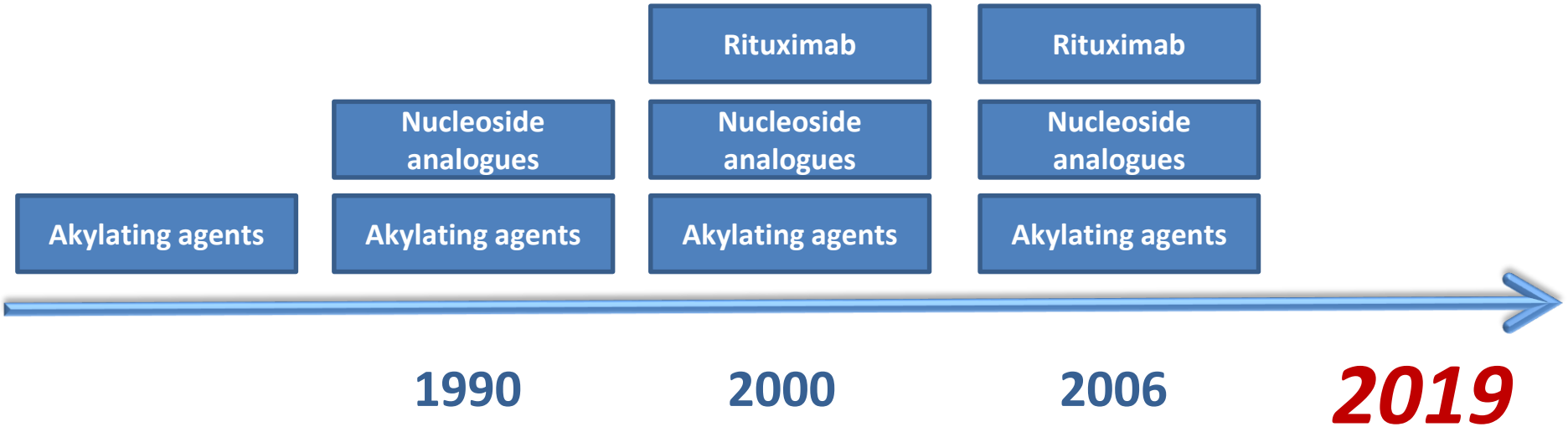
Treatment standard? A Challenge…..

Why a challenge?

- **Few randomized trials**
- **Phase 2 studies with low number of patients**
- **Lack of prolonged outcomes**
- **Treatment landscapes and data on treatment choices and their outcome in patients outside clinical trials are lacking**

Treatment options in WM

Proteasome Inhibitors:
(Bortezomib ,carfilzomib , ixazomib , oprozomib)
IMiDs
Bendamustine
Ibrutinib
Acalabrutinib
mTOR inhibitors
Venetoclax etc



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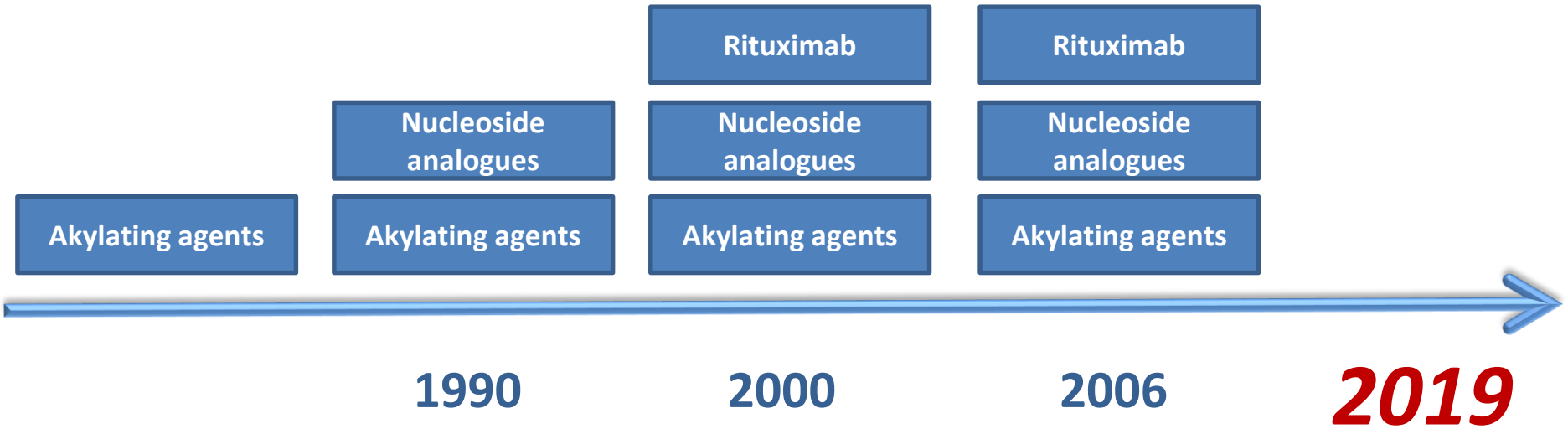
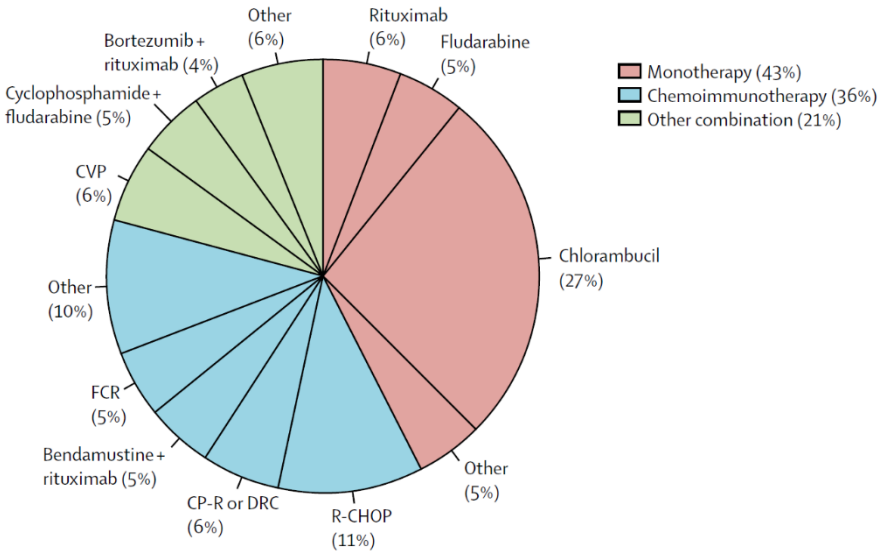


FIRST LINE: RITUXIMAB COMBINATION TREATMENT

Treatment and Outcome Patterns in Patients With Relapsed Waldenström Macroglobulinemia From a Large Observational Pan-European Data Platform 2000-2014



Front-line use by treatment centre type and age

	Overall (n=454)	Academic institution (n=306)	Community institution (n=148)	Age <65 years (n=223)	Age ≥65 years (n=231)
Monotherapy	193 (43%)	114 (37%)	79 (53%)	79 (35%)	114 (49%)
Chemoimmunotherapy	164 (36%)	135 (44%)	29 (20%)	90 (40%)	74 (32%)
Other combination	95 (21%)	55 (18%)	40 (27%)	52 (23%)	43 (19%)

Buske et al, 2018

Treatment choice

➢ **Patient**

- Age
- PS
- Comorbidities

➢ **Disease Presentation**

- Need for rapid disease control
- Cytopenia
- Neuropathy
- Bulky disease/extramedullary disease
- Cryoglobulinemmia/Cold agglutinine

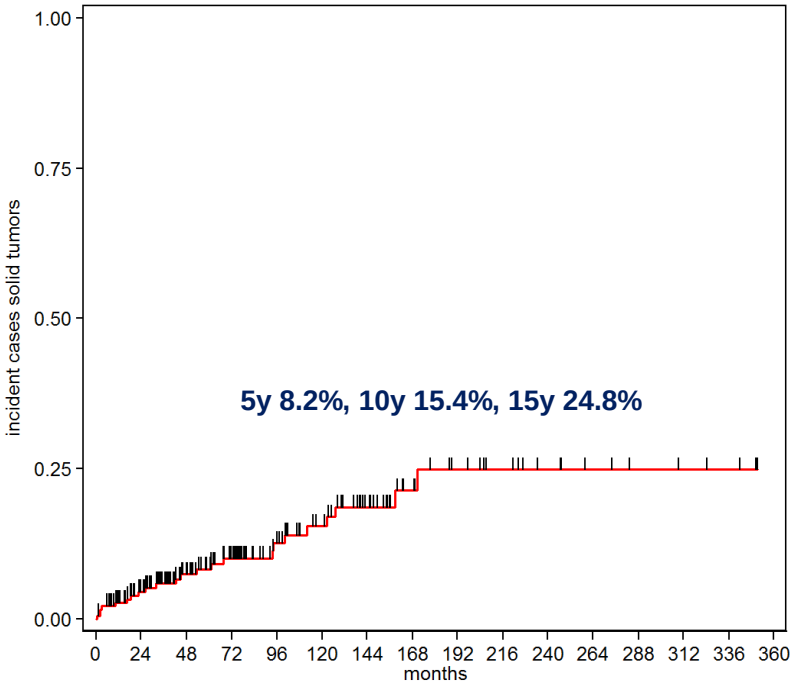
➢ **Therapy**

Treatment Goals:
- Time to IgM decrease
-Quality of response
-PFS, OS

Treatment Concerns
- Toxicity
(myelo/immuno-suppression, etc)
-Secondary Malignancies
(MDS/AML-DLBCL-solid tumors)

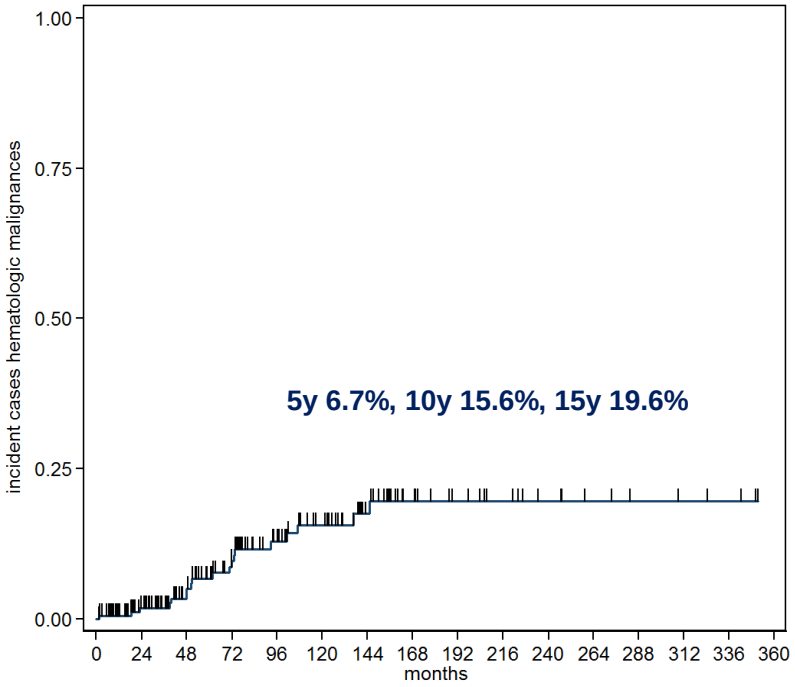
Cumulative incidence of SM after treatment

Solid Tumors



SN: 0.0013 pt/m (CI 95% 0.0009-0.0021)

Haematological Malignancies



Hematological: 0.0011 pt/m (CI 95% 0.0007-0.0013)

Tedeschi et al, IWWM 2018

Treatment choice

➢ **Patient**

- Age
- PS
- Comorbidities

➢ **Disease Presentation**

- Need for rapid disease control
- Cytopenia
- Neuropathy
- Bulky disease/extramedullary disease
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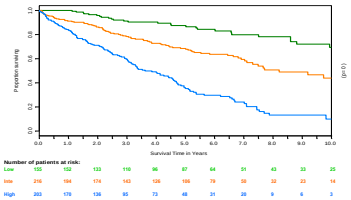
➢ ~~IPSSWM~~

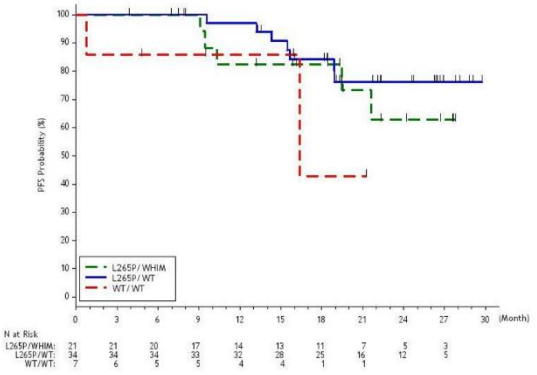


➢ **MYD88 & CXCR4 status ?**

PFS according to MYD88 & CXCR4 mutation status

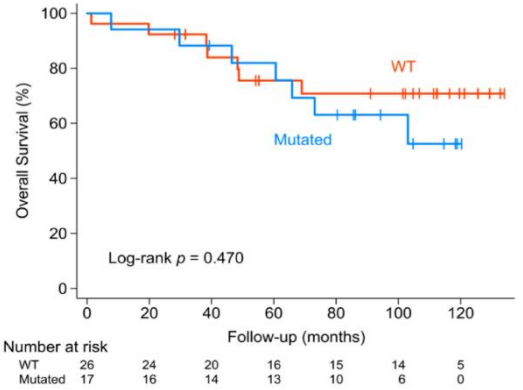
Ibrutinib Monotherapy R/R

	$MYD88^{L265P}$ $CXCR4^{WT}$	$MYD88^{L265P}$ $CXCR4^{WHIM}$	$MYD88^{WT}$ $CXCR4^{WT}$	p-value
N	34	21	7	
Overall RR	100%	80.9%	57.1%	<0.01
Major RR	88.2%	57.1%	28.6%	<0.01

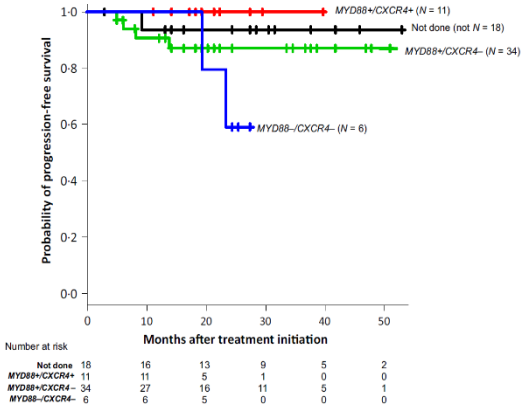


Treon et al, 2015

Bortezomib Rituximab First Line according to CXCR4 ^{mut}

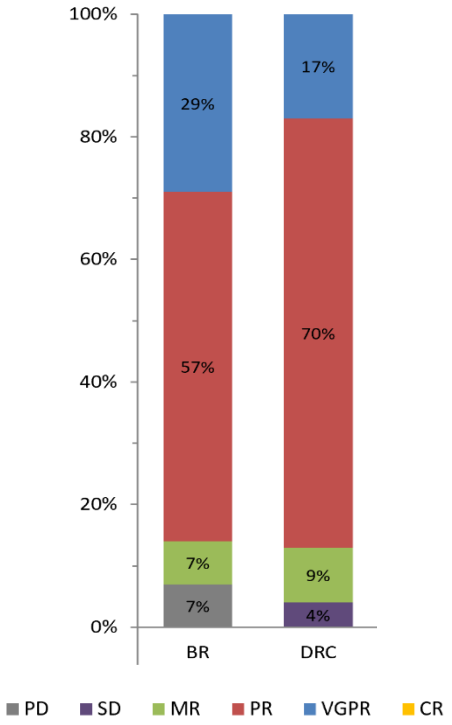


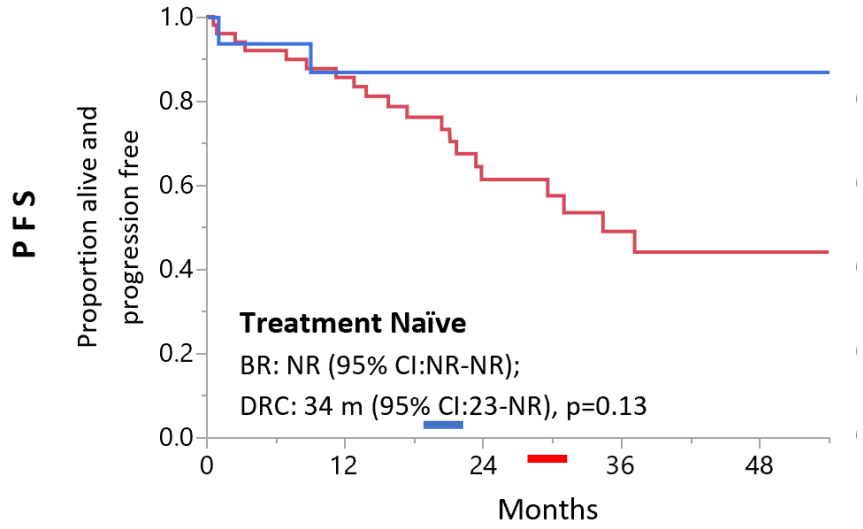
Bendamustine Rituximab First Line

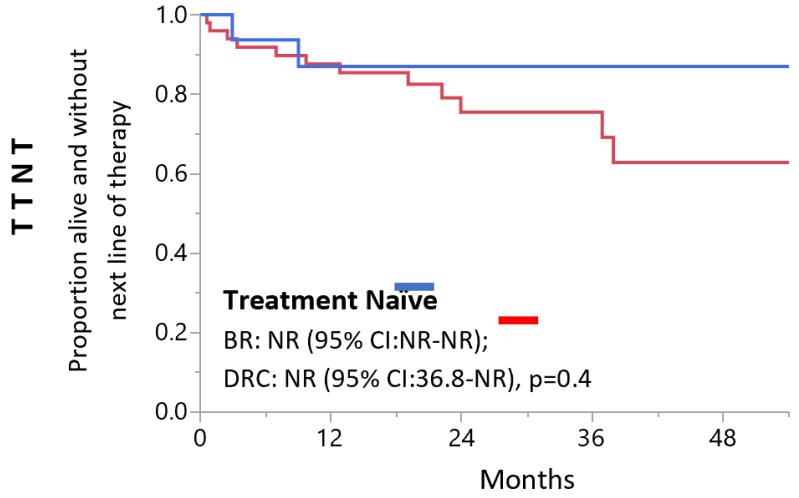


Tricot et al, 2018
Sklavenitis et al, 2018

Benda-Rituximab versus DRC in treatment naive WM (retrospective study)







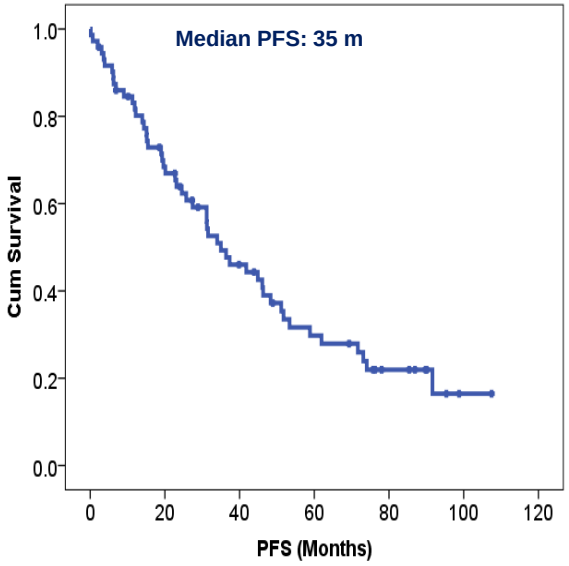
DRC or BR efficacy uneffected by MYD88 mutational status

Paludo et al, 2018

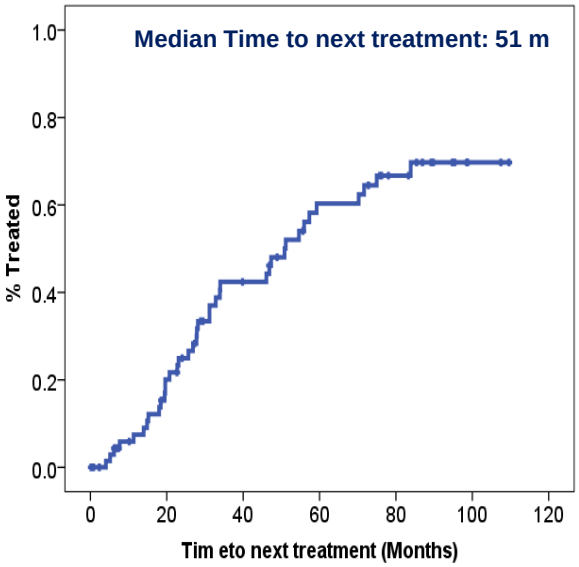
Dexamethasone, Rituximab and Cyclophosphamide primary therapy

(minimum follow up ≥7 years)

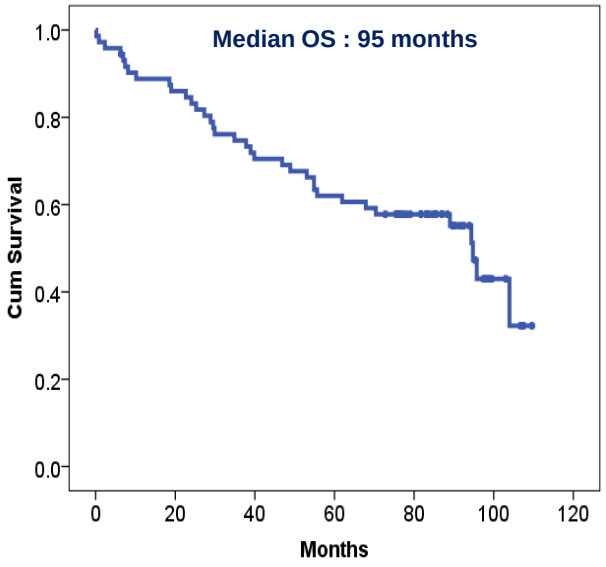
PFS



Time to next treatment



Overall survival



PROS:

- **Minimal myelo and immunosuppressive properties**
  89% of pts completed the expected 6 courses

CONS:

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

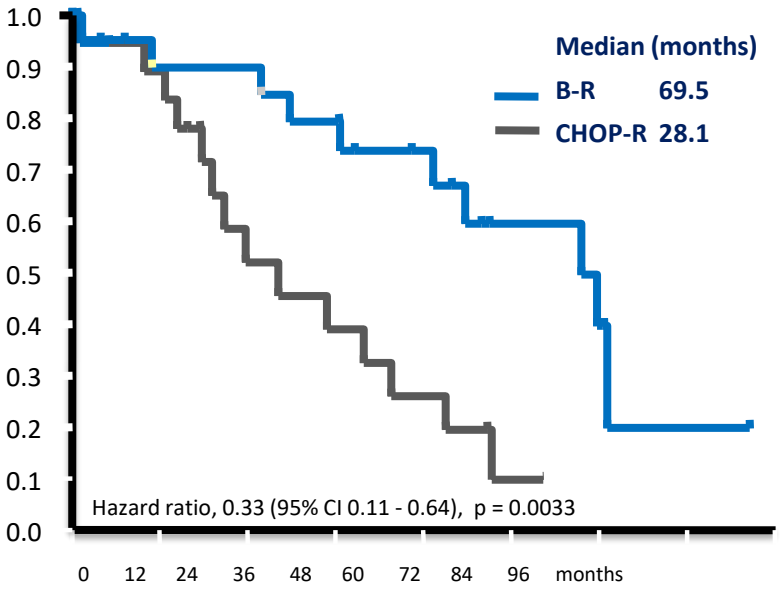
Kastritis et al, 2015

Bendamustine-Rituximab versus R-CHOP

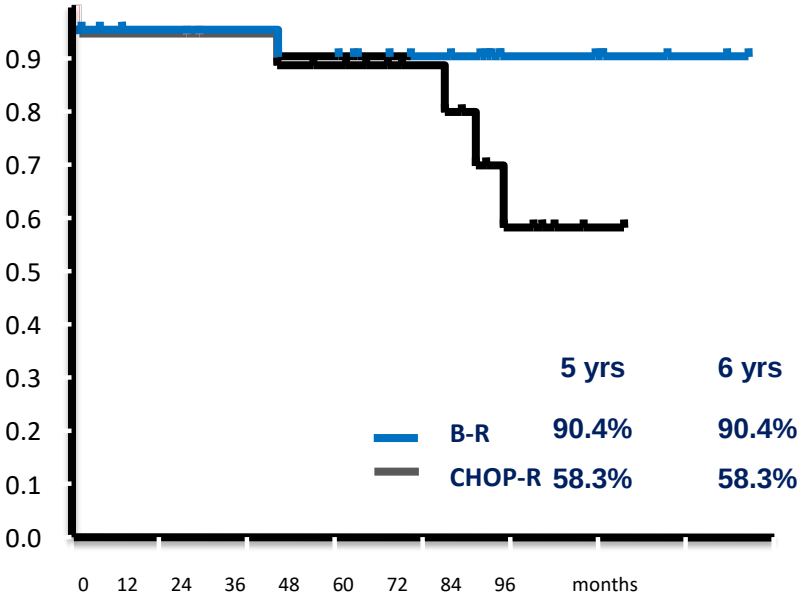
(subanalysis of the StiL NHL1 study in WM patients)

N=41 evaluable	Benda-R (N=22)	CHOP-R (N=19)
Response rate	21 (95%)	18 (95%)

Progression Free Survival

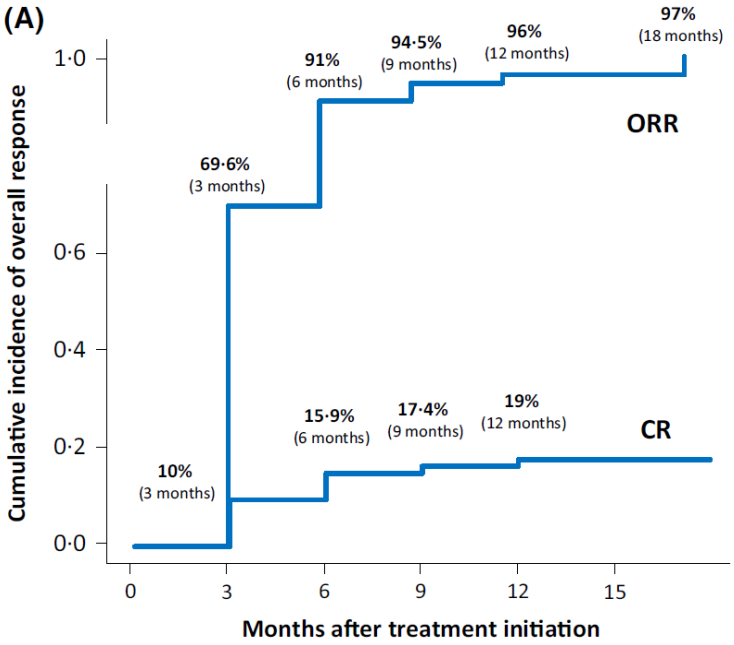


Overall Survival



Rummel et al, 2013

Bendamustine-Rituximab First Line retrospective French study



56%: pts completed the 6 cycles of BR at 90 mg/sqm

44%: had dose reduction to 70 mg/sqm and/or less than 6 or delayed cycles

No difference in PFS (2 y 87% vs 88%)

PROS:

- **Prolonged PFS**
- **Rapidly effective (bulky disease)**
- **No impact from CXCR4 mut**

CONS:

- **Myelotoxicity/late infectious toxicities:**
  -dose reduction to 70 mg/sqm in elderly patients
  -consider 4 courses
- **Secondary MDS/LAM (?): ~0-3%**

Tricot et al, 2018

First Line

DRC

- Elderly
- Severe Cytopenia
- WM with symptoms IgM related

- No bulky disese
- No hyperviscosity

BendaR

- Younger
- Bulky disease
- Hypervisocosity/High IgM level

- Cytopenias
- Reduced dose/N° cycles

Bortezomib and Rituximab based therapy

3 Phase II studies: with or without dexamethasone

- **BR** B: 1.6 mg/sqm iv d 1,8,15 every 28d for 6 cycles plus R: course 1,4
- **BDR** B: 1.3 mg/sqm iv and DEX 40 mg days 1, 4, 8, 11 plus R: d 21 for 4 cycles
  Maintenance: 4 cycles every 12 w
- **BDR** B iv 1.3 mg/sqm d: 1, 4, 8, 11 1st cycle
  B iv 1.6 mg/sqm with DEX 40 mg d: 1, 8, 15, 22 cycles 2 -5; R weekly cycles 2,5

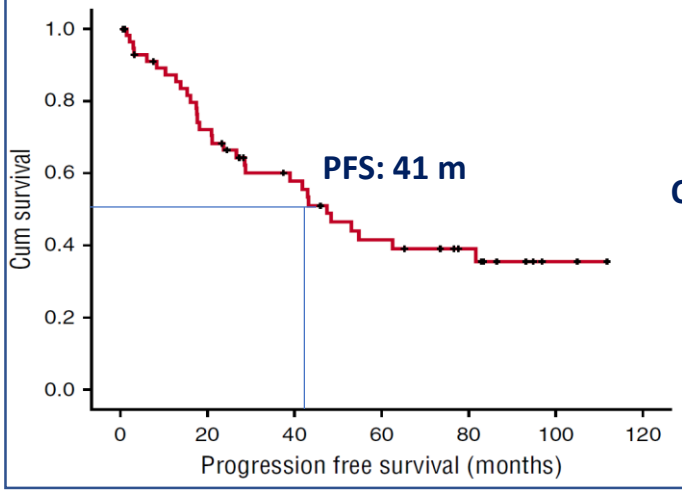
Responses

ORR: 88-96%
MRR: 65-83%
CR: 2-13%

BDR with maintenance

Median TTP: 52 m

BDR without maintenance



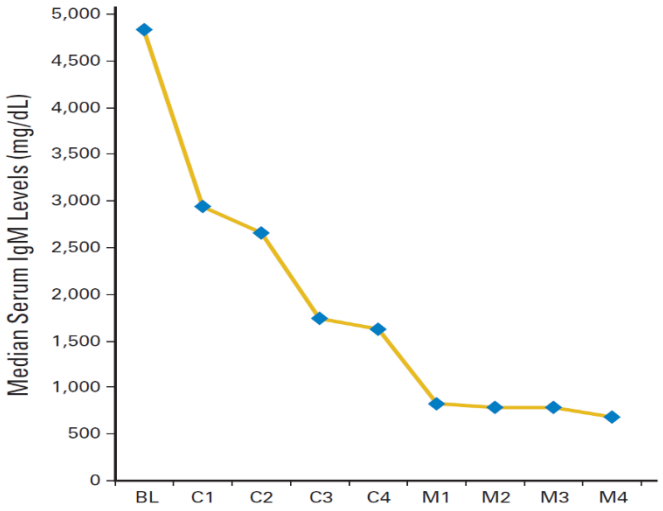
OS at 7years

66%

Treon et al, 2009-2015; Ghobrial et al 2010; Dimopoulos et al, 2013; Gavratopoulou et al 2017

Bortezomib and Rituximab based therapy

Median decrease IgM level



PROS:

- **Rapid IgM decrease**
- **Low Myelotoxicity rate**
- **Low risk of SM**
- **No impact CXCR4 mut status**

CONS

- **Peripheral neuropathy: 46%-69%**
  - **Grade 1: 22%-39%**
  - **Grade 2: 15%-30%**
  - **Grade 3: 7%**

Lower rate neuropathy with weekly schedule and sc administration

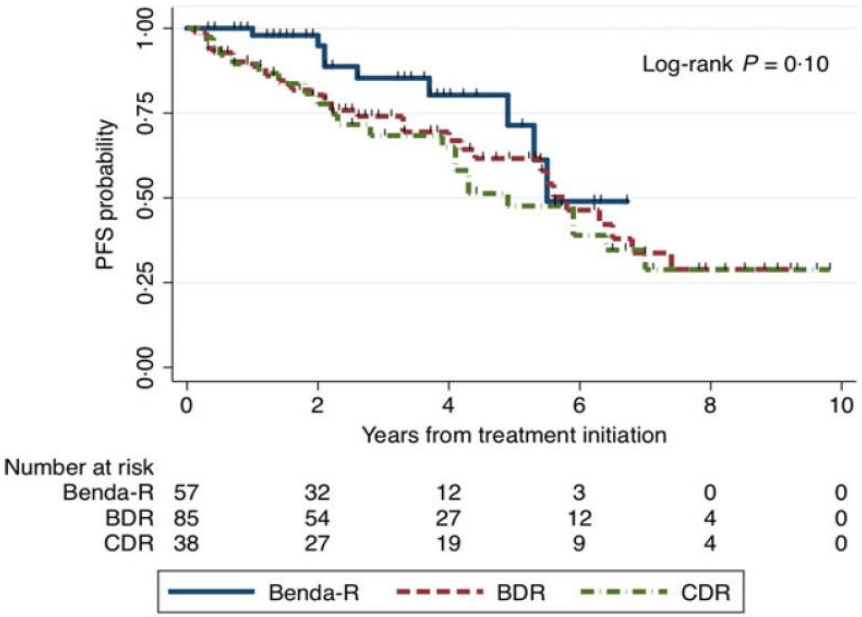
Steroids addition: Herpes Zooster prophilaxis

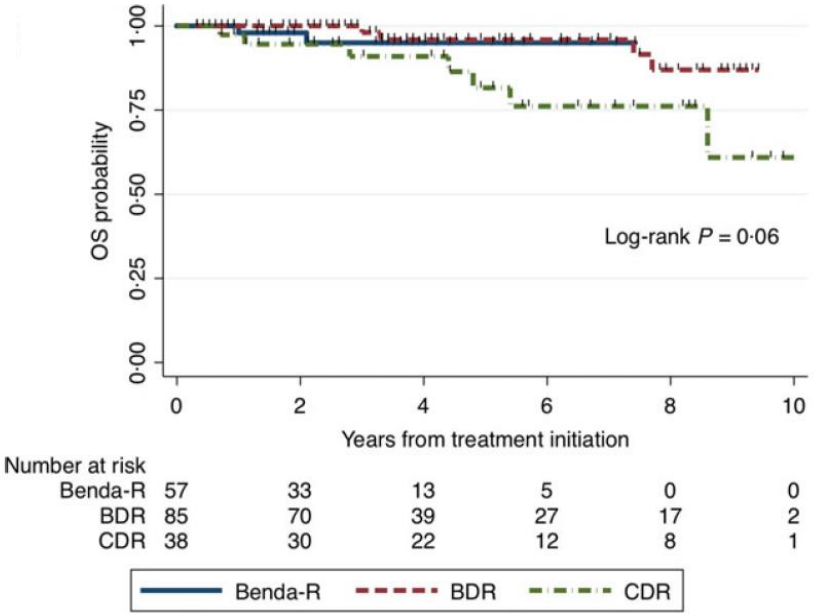
Treon et al, 2009, Ghobrial et al 2010, Dimopoulos et al, 2013

Response and survival for primary therapy and maintenance Rituximab

Benda-R	57 pts (31%)
BDR	87 pts (48%)
CDR	38 pts (21%)

No difference in response rates





Regimen	HR (95% CI)	P
CDR	1.00 (Ref)	
Benda-R	0.18 (0.007-0.43)	<0.001
BDR	0.55 (0.30-0.99)	0.046

Regimen	HR (95% CI)	P
CDR	1.00 (Ref)	
Benda-R	0.24 (0.05-1.27)	0.09
BDR	0.14 (0.03-0.61)	0.009

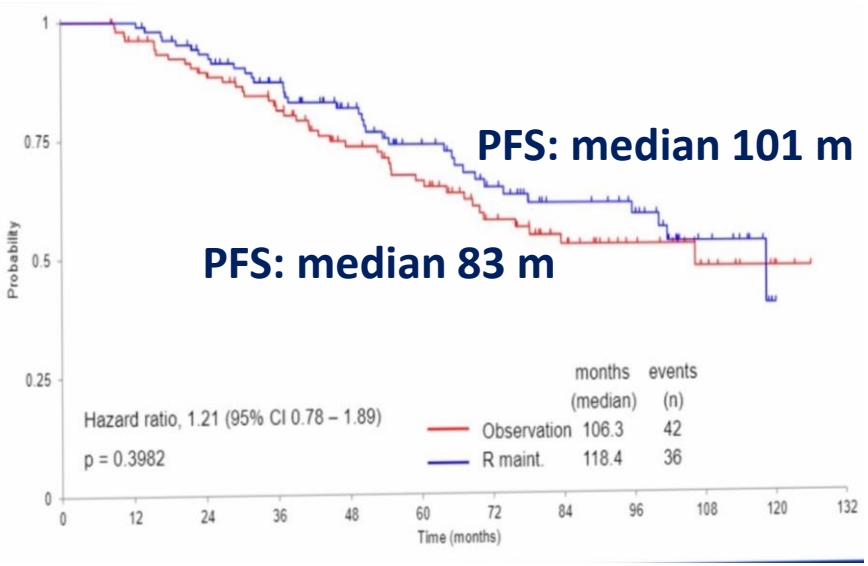
Castillo et al, 2018

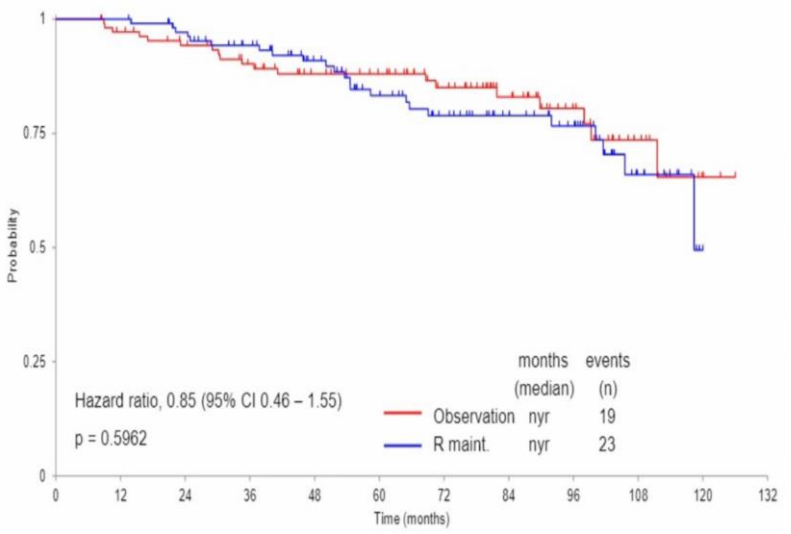
Two Years Rituximab Maintenance Vs. Observation after First Line Treatment with Bendamustine Plus Rituximab (B-R) in Patients with WM Results of a Prospective, Randomized, Multicenter Phase 3 Study (the StiL NHL7-2008 MAINTAIN trial)

218 pts BR responding patients randomized

RITUXIMAB MAINTENANCE 109

OBSERVATION 109





Rummel et al 2019

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

	All pts N=30	MYD88^{MUT} CXCR4^{WT} n=16	MYD88^{MUT} CXCR4^{MUT} n=14	P
ORR N (%)	30 (100)	16 (100)	14 (100)	1.00
Major Response Rate N (%)	25 (83)	15 (94)	10 (71%)	.16
Categorical Response N (%)				
Minor	5 (17)	1 (6)	4 (29)	.16
Partial	19 (63)	10 (63)	9 (64)	1.00
VGPR	6 (20)	5 (31)	1 (7)	.18
Median Time to Response				
Minor Response	1.0 m	0.9	1.7	.07
Major Response	1.9 m	1.8	7.3	.01

Treon et al , 2018

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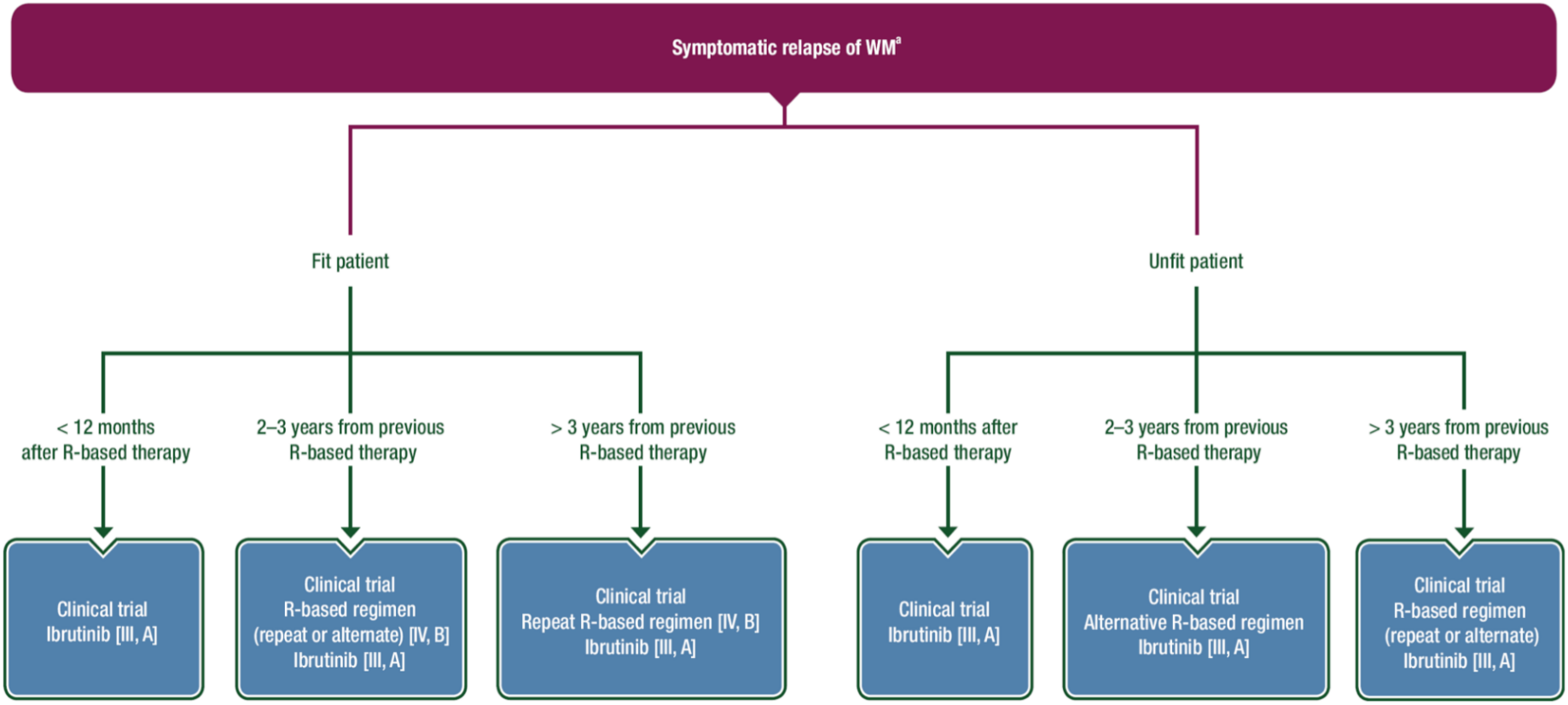
Partial	19 (63)	10 (63)	9 (64)	1.00
VGPR	6 (20)	5 (31)	1 (7)	.18
Median Time to Response				
Minor Response	1.0 m	0.9	1.7	.07
Major Response	1.9 m	1.8	7.3	.01

18 months PFS: 92%
18 monts OS: 100%
2 progressions: CXCR4^{MUT}

Treon et al , 2018

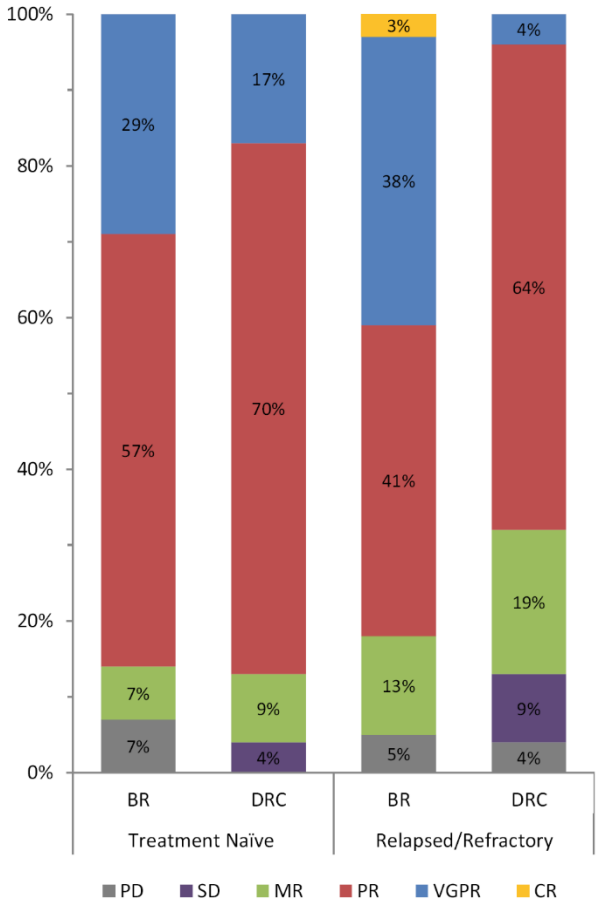
Therapeutic Algorithm – ESMO Guidelines 2018

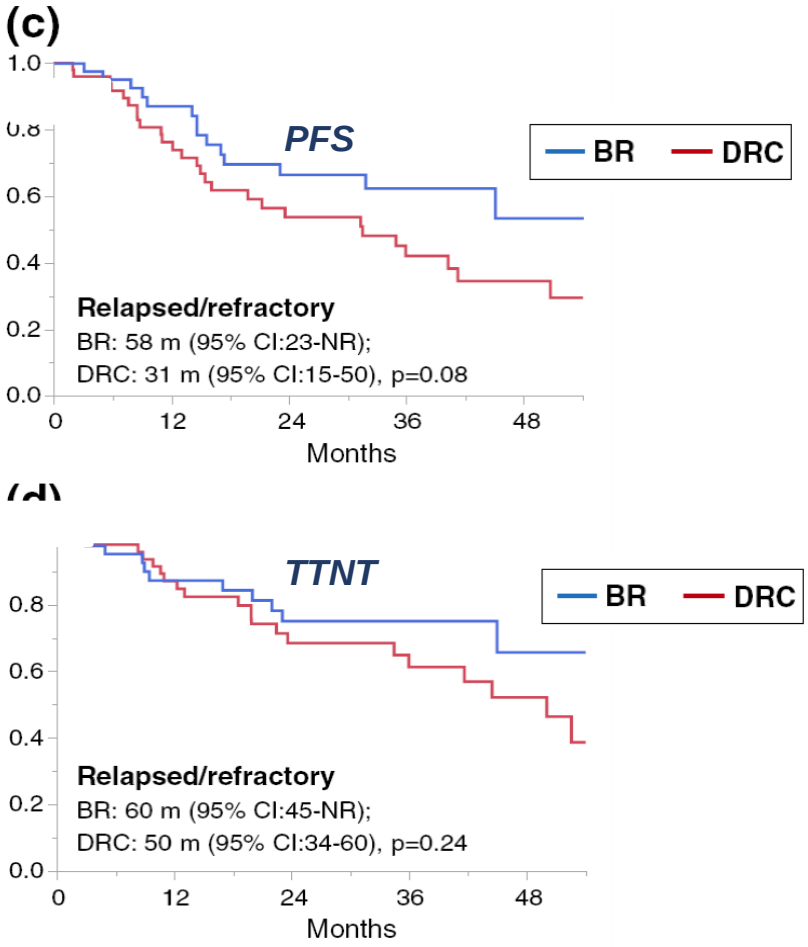


Kastritis E, ESMO Guidelines 2018

DRC and BR in relapsed WM
Retrospective monocentric analysis

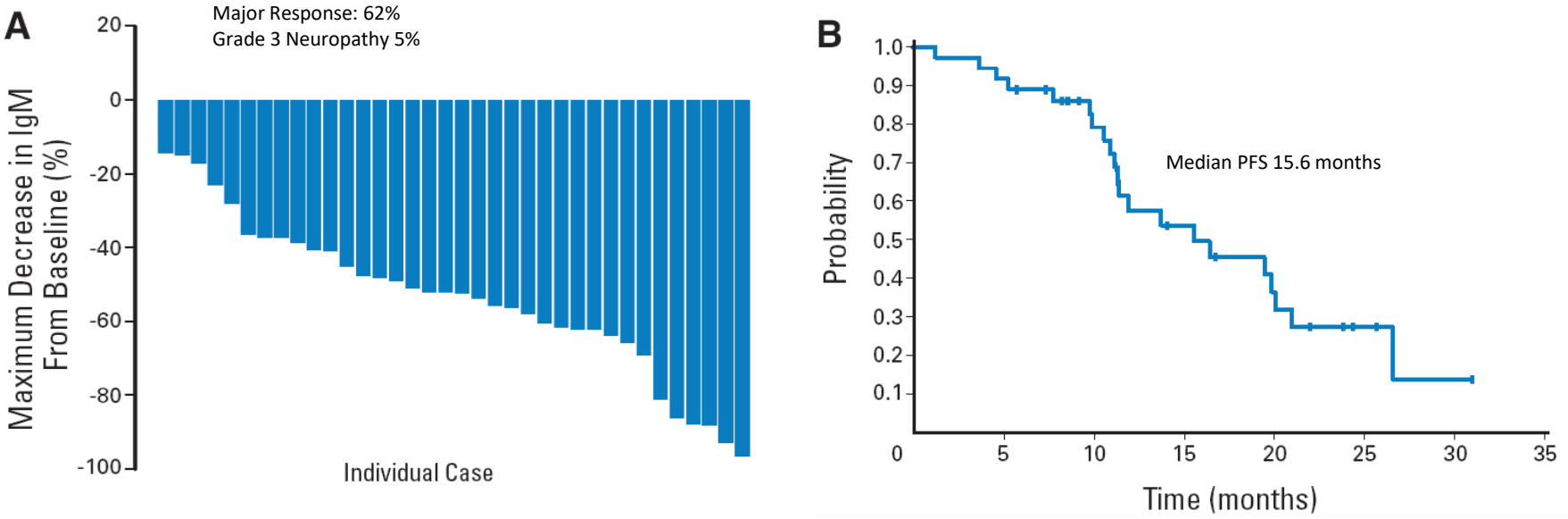
Responses





Paludo et al. Ann Hem 2018

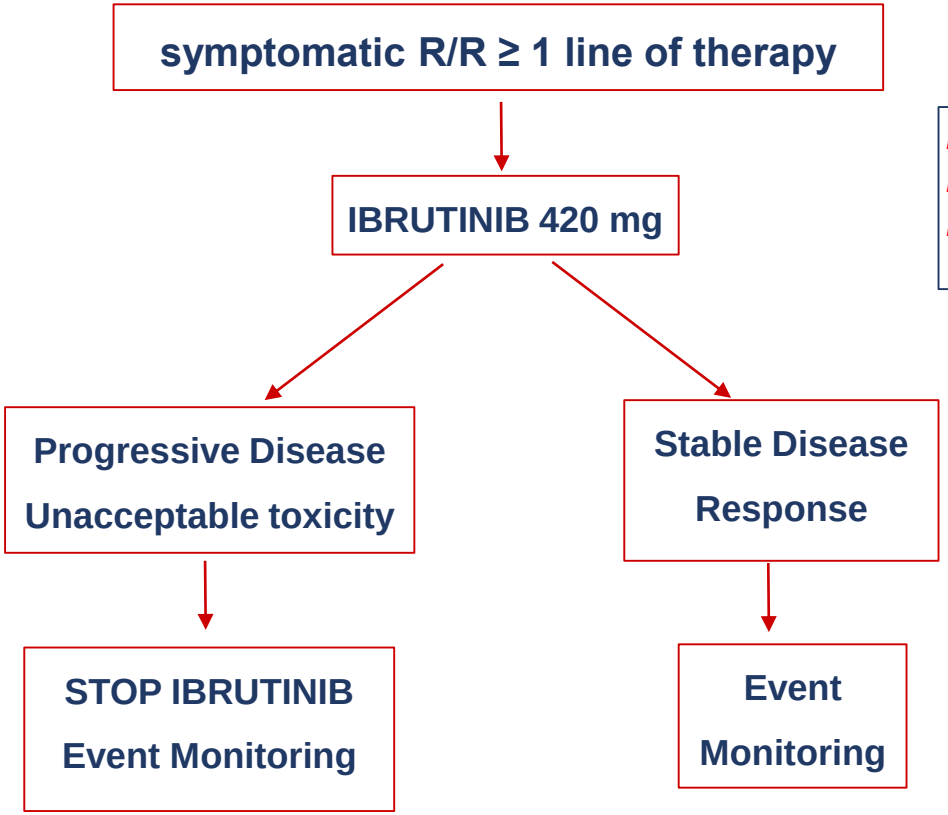
Weekly R-Bortezomib in relapsed WM



Ghobrial et al. JCO 2010

ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia



N 63
Prior therapies: 2
Refractory : 40%

Treon et al NEJM 2015

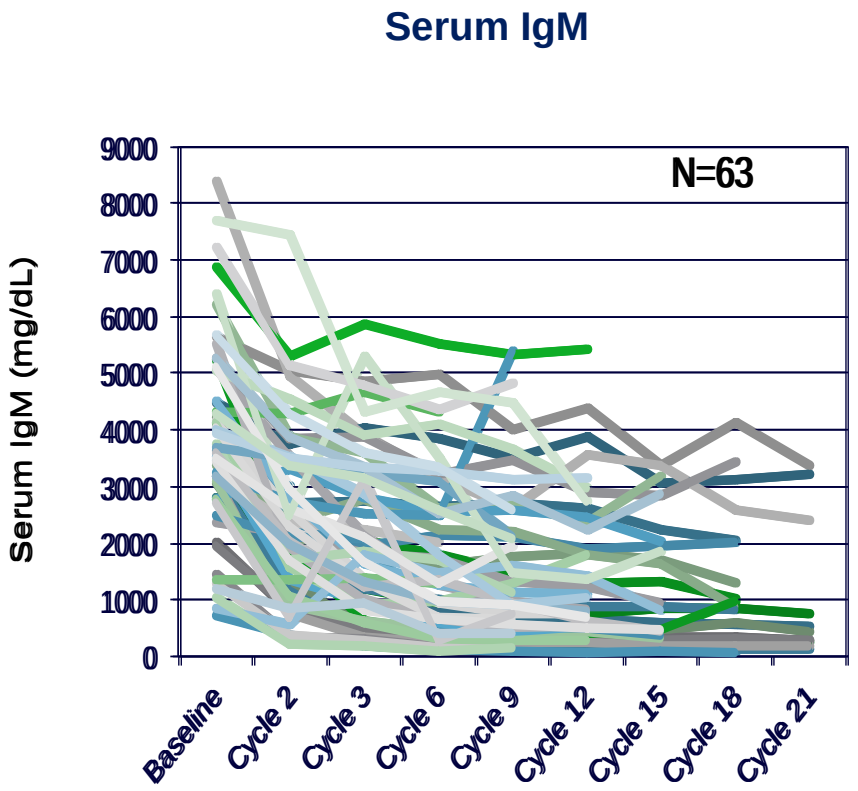
Ibrutinib in previously treated WM: updated results

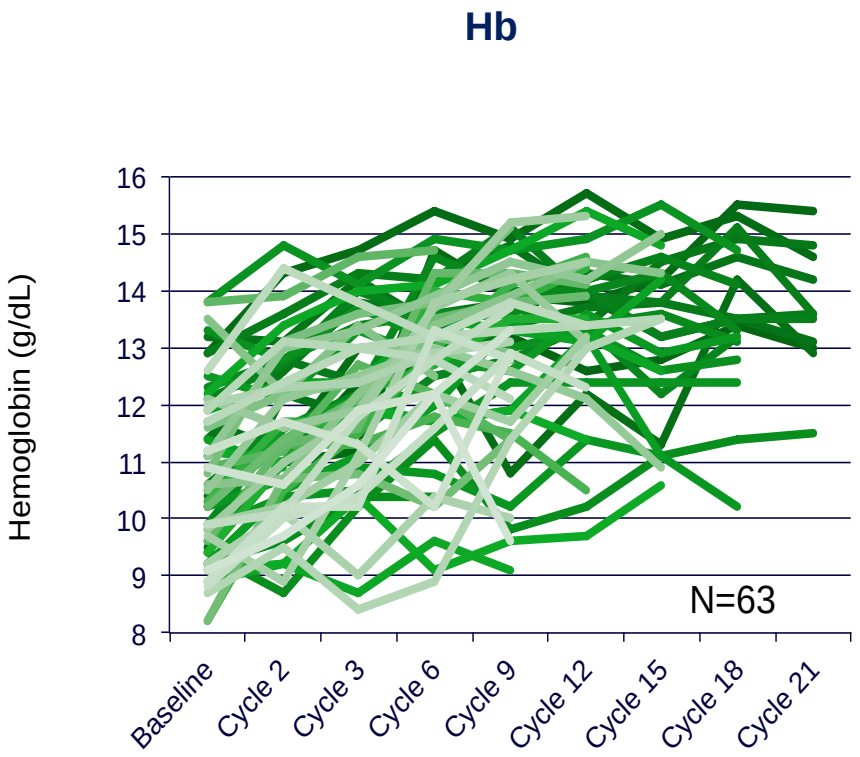
The **median time on ibrutinib was 46 months**

- **Improvements in categorical responses**
  - Median serum **IgM level** declined from 3,520 to 821 mg/dL ($p<0.0001$)
  - **Bone marrow involvement** declined from 60% to 20% ($p<0.0001$)
  - **Hemoglobin level** rise from 10.5 to 14.2 g/dL ($p<0.0001$)

Treon et al., ICML 2019

Serum IgM and Hb Levels Following Ibrutinib





Updated:

Best IgM Response:
3,520 to 821 mg/dL; p<0.001

Best Hemoglobin Response:
10.5 to 14.2; p<0.001

Updated Clinical Responses to Ibrutinib

ORR: 91% (No change) Major RR (≥ PR): 73→78%

	(N=)	(%)
VGPR	10→18	16%→29%
PR	36→31	57%→49%
MR	11→8	17%→13%

Median time to ≥ MR: 4 weeks

Median time to ≥ PR or better: 8 weeks

Data cutoff: December, 2017

Median time on treatment: 47 months

Treon et al., ICML 2019

Responses to ibrutinib are impacted by MYD88 and CXCR4 mutations

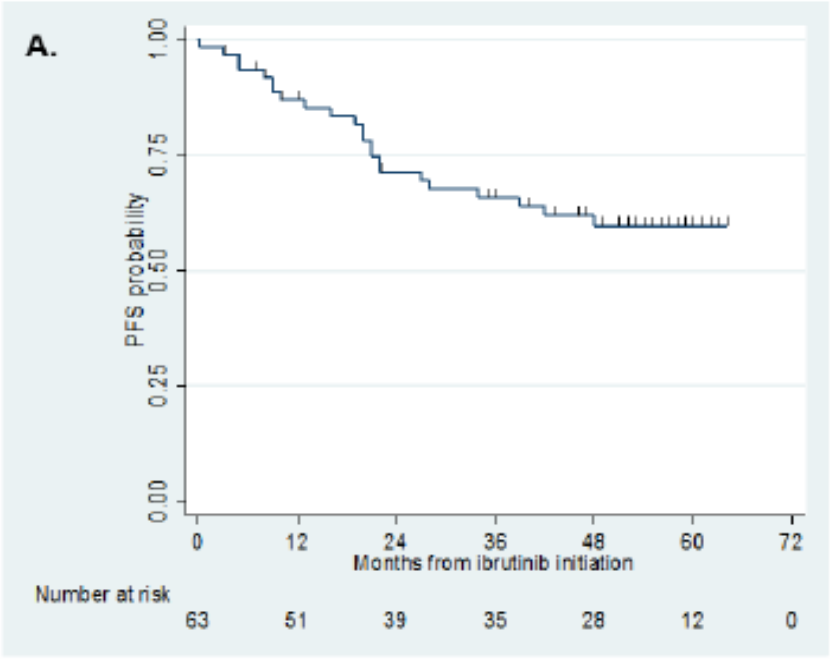
	ALL	MYD88mut CXCR4 wt	MYD88mut CXCR4 whim	MYD88 WT CXCR4 wt	P-value
N=	63	36	21	5*	
ORR	91%	100%	85.7%	60%	0.005
Major(>PR)	78%	97%	67%	0%	<0.001
VGPR	29%	44%	10%	0%	0.007
Time to Minor Response (mo)	1.0	1.0	1.0	1.0	0.10
Time to Major response (mo)	2.0	2.0	6.0	N/A	0.05

* 2 patients at initial reporting with major responses were discovered subsequently to have MYD88 mutate disease (S243N, L265P). One patient at initial reporting as unknown CXCR4 status was subsequently found to CXCR4 mutated disease upon genotyping of CD19-selected WM cells.

Treon et al., ICML 2019

Ibrutinib in previously treated WM, updated PFS

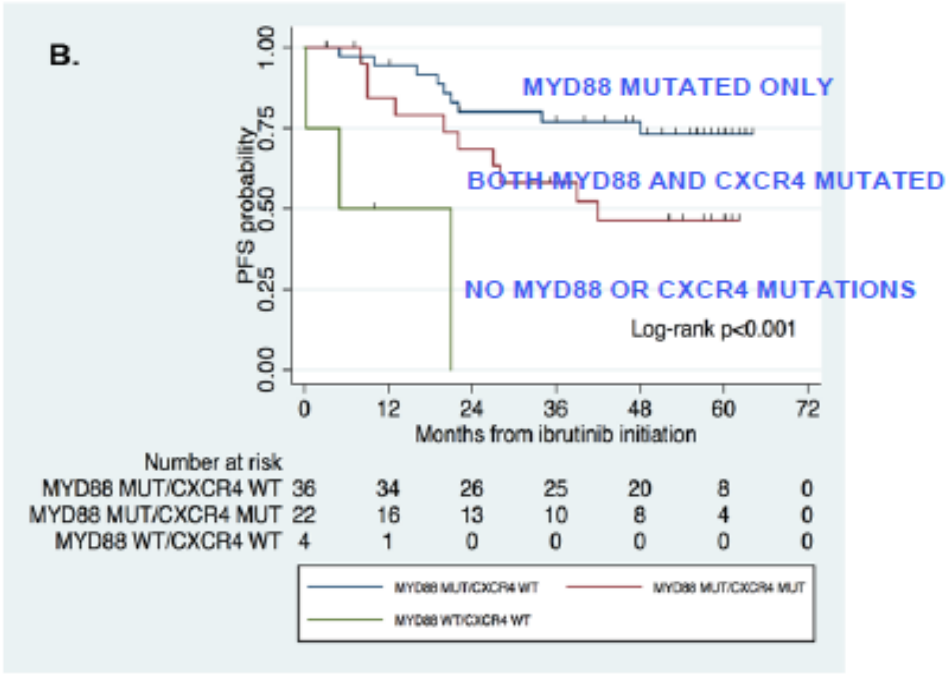
All patients



5-year PFS rate: 54%

5-year OS rate: 87%

MYD88 and CXCR4 Status

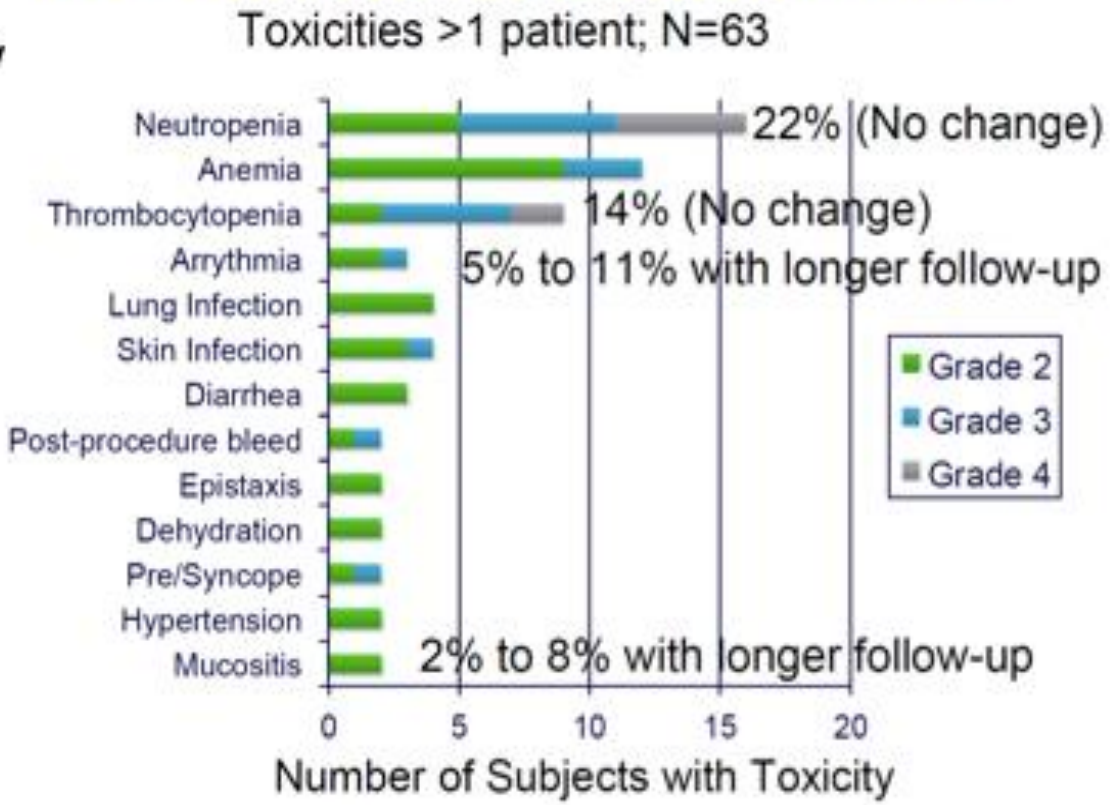


MYD^{Mut} $CXCR4^{WT}$	MYD^{Mut} $CXCR4^{mut}$	MYD^{WT} $CXCR4^{WT}$
m PFS: NR	m PFS: 42 m	m PFS: 5 m
5-year PFS rate: 71%	5-year PFS rate: 34%	-

Treon et al., ICML 2019

Ibrutinib Related Adverse Events in previously treated WM patients

Original Study



Update on Adverse Events (Grade ≥2) in ≥5% of patients: Neutropenia (22%); Thrombocytopenia (14%), Pneumonia (9%); GERD (8%); Hypertension (8%); anemia (6%); and skin infection (5%). Seven patients (11%) had atrial arrhythmia [Grade 1 (n=1); Grade 2 (n=5); Grade 3 (n=1)], and 6 continued ibrutinib following medical management.

Treon et al., 2019

The NEW ENGLAND JOURNAL of MEDICINE N ENGL J MED 378;25 NEJM.ORG JUNE 21, 2018

Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia

M.A. Dimopoulos, A. Tedeschi, J. Trotman, R. García-Sanz, D. Macdonald, V. Leblond, B. Mahe, C. Herbaux, C. Tam, L. Orsucci, M.L. Palomba, J.V. Matous, C. Shustik, E. Kastritis, S.P. Treon, J. Li, Z. Salman, T. Graef, and C. Buske, for the iNNOVATE Study Group and the European Consortium for Waldenström's Macroglobulinemia*

Key eligibility criteria

- Confirmed WM* (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 status (0–1 vs 2)

Arm A
ibrutinib-RTX
Oral ibrutinib 420 mg once daily until PD
RTX 375 mg/m^2 IV on day 1 of weeks 1–4 and 17–20

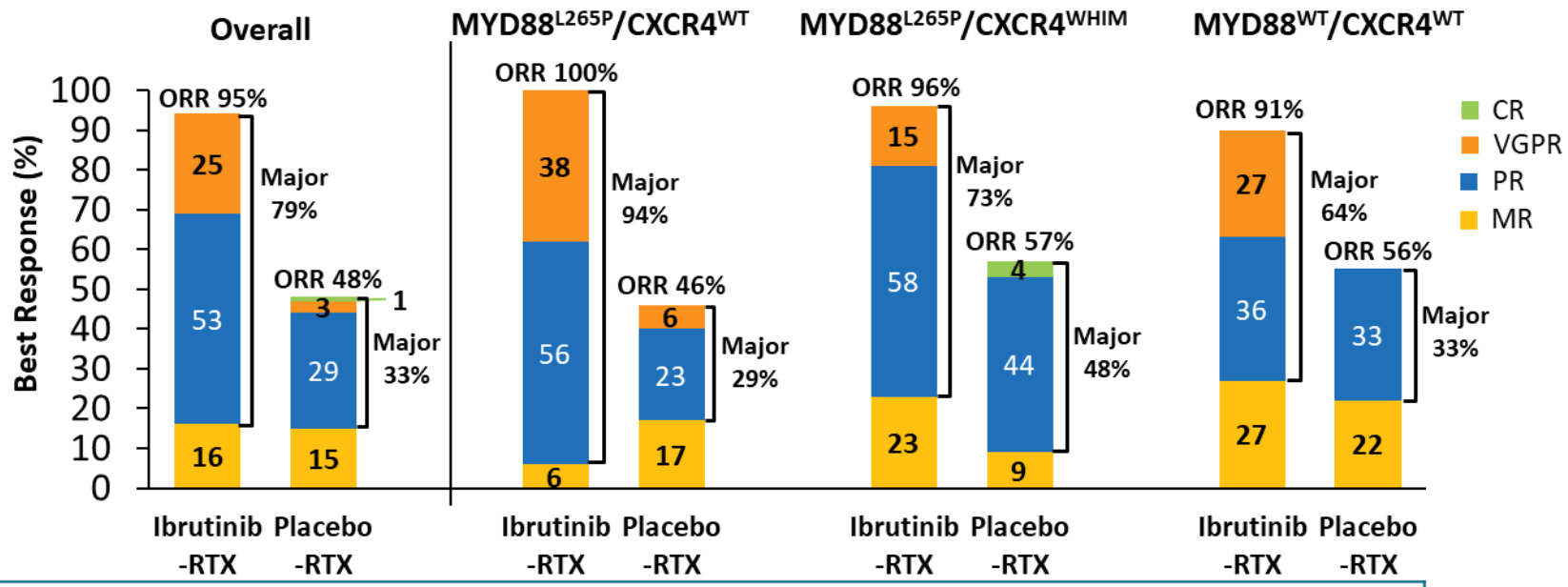
n pts	*prior therapies, n(%)*	
75 pts	0	34 (45%)
	1-2	34 (45%)
	3	7 (9%)

Arm B
placebo-RTX
3 matching placebo capsules until PD
RTX 375 mg/m^2 IV on day 1 of weeks 1–4 and 17–20

n pts	*prior therapies, n(%)*	
75 pts	0	34 (45%)
	1-2	36 (48%)
	5	7 (9%)

- Primary Endpoint: PFS by IRC
- Secondary Endpoints: Response rate, TTnT, sustained hematologic improvement, PROs, OS, safety

Randomized Study: Higher Response Rates With Ibrutinib-RTX Independent of MYD88/CXCR4 Genotype



	Overall		MYD88L265P/CXCR4WT		MYD88L265P/CXCR4WHIM		MYD88WT/CXCR4WT	
	Ibrutinib -RTX	Placebo -RTX	Ibrutinib -RTX	Placebo -RTX	Ibrutinib -RTX	Placebo -RTX	Ibrutinib -RTX	Placebo -RTX
Median time to ≥PR, months (range)	2 (1–28)	6 (2–26)	2 (1–28)	5 (2–17)	3 (1–19)	11 (4–18)	6 (1–17)	6 (5–26)
Median time to ≥MR, months (range)	1 (1–18)	3 (1–24)	1 (1–18)	3 (1–24)	1 (1–11)	3 (1–8)	2 (1-17)	3 (2–17)

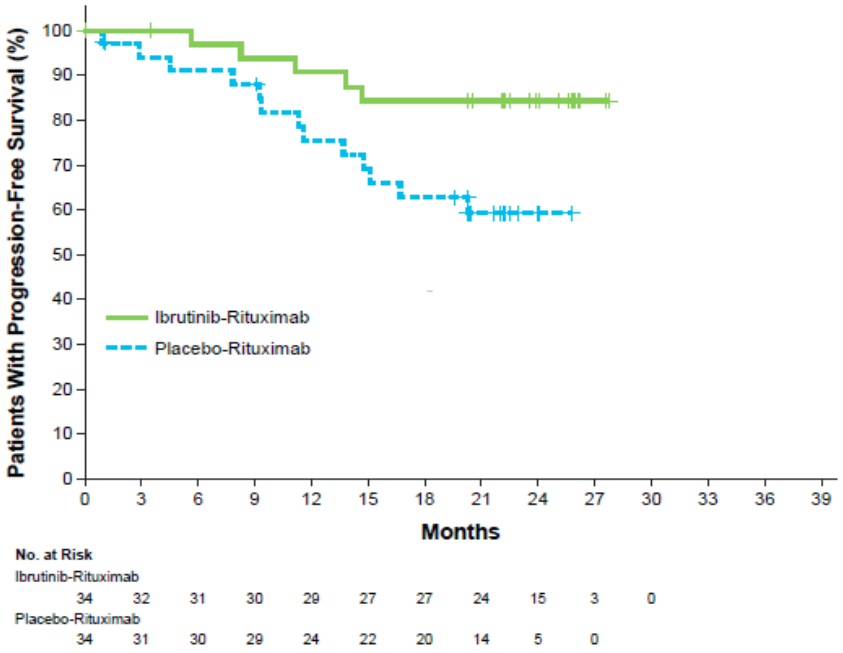
CR, complete response; MR, minor response; PR, partial response; VGPR, very good partial response.
[a]Following modified 6th IWWM Response Criteria (NCCN 2014); required two consecutive assessments.

Buske et al, ASH 2018

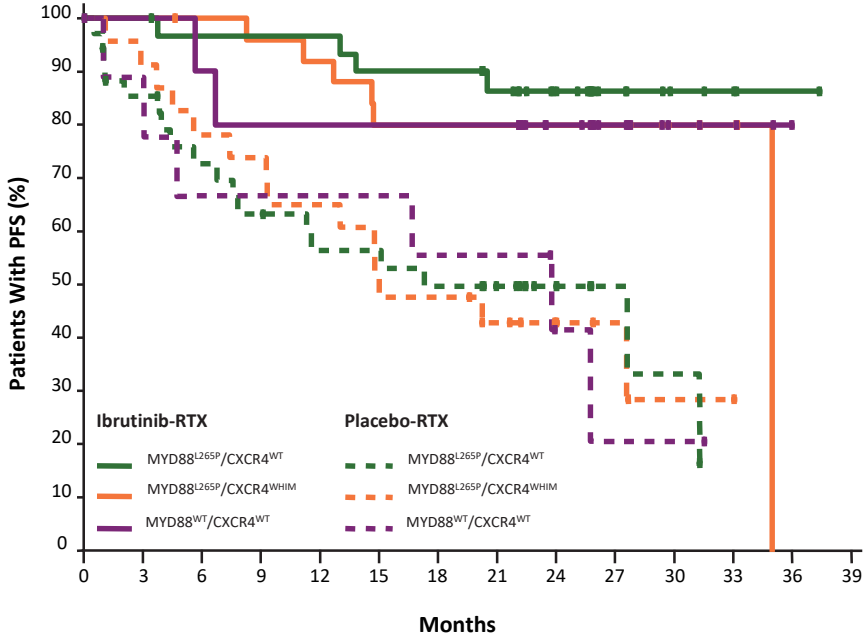
The NEW ENGLAND JOURNAL of MEDICINE

Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia

Progression-Free Survival Untreated Pts



Progression-Free Survival untreated and R/R



Dimopoulous et al. NEJM 2018

Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial

Lancet Oncol 2017; 18: 241–50

Refractory to last rituximab-containing regimen, defined as

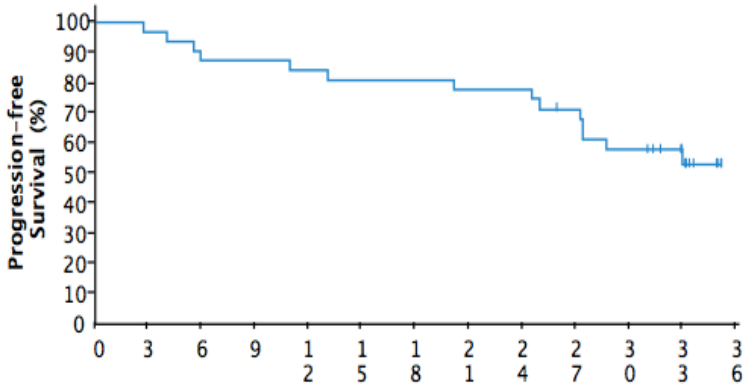
- Relapse after <12 months of treatment

or

- Failure to achieve at least a minor response

Arm C
Open-label substudy
N=31

Ibrutinib 420 mg once daily until PD



	Median PFS, months (95% CI)	30-month PFS rate
Ibrutinib (n=31)	Not reached (27.4 -NE)	57.5%

Dimopoulous et al 2017, Trotman 2018

Ibrutinib discontinuation and withdrawl symptoms

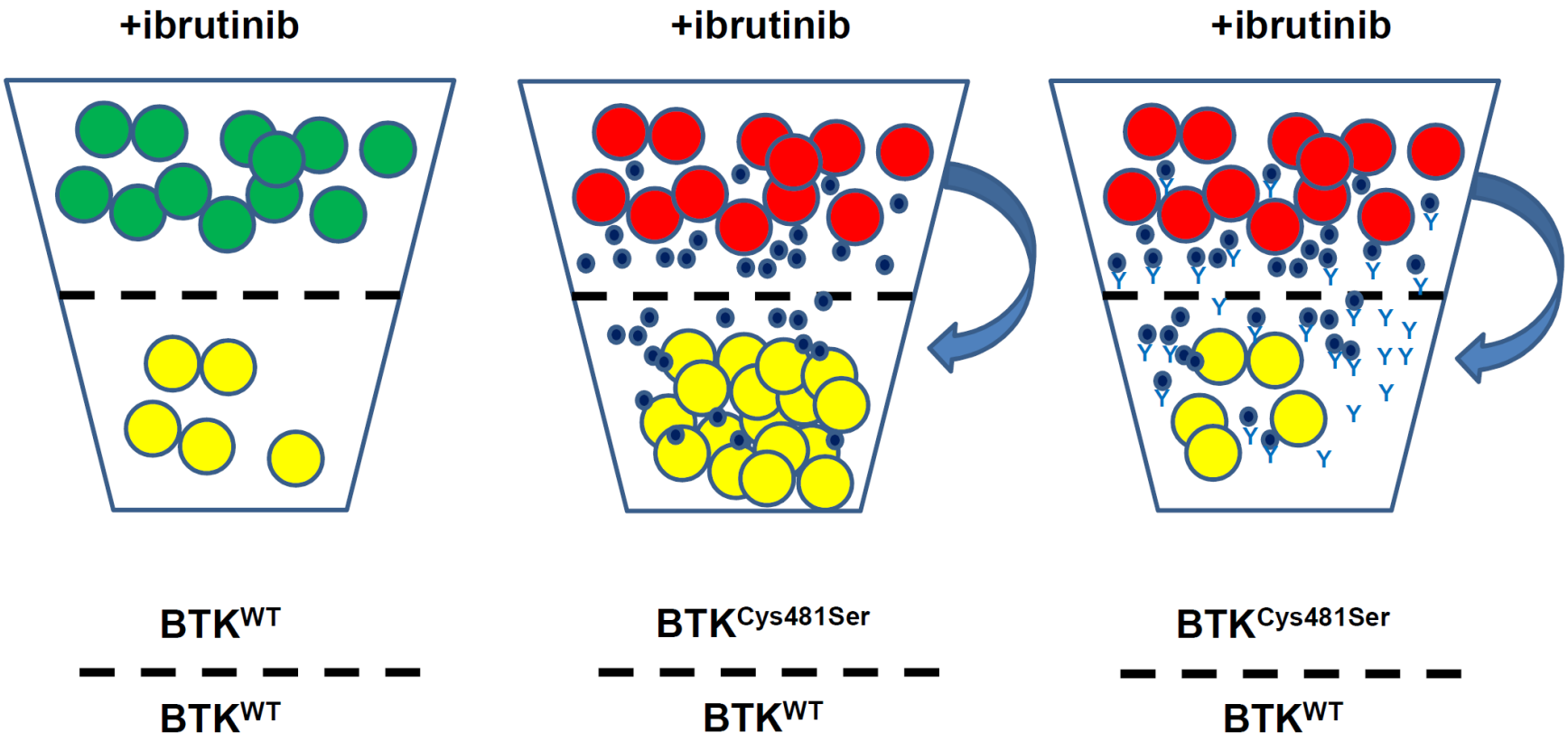
- **Temporary interruption of ibrutinib therapy is associated with transient increases in serum IgM level which appear to persist longer for patients with the *MYD88*^{MUT} *CXCR4*^{WHIM} tumor genotype**
  - *-Median increase in serum IgM level 50% (range, 4-555%)*
  - *-59% increases met criteria for PD*
- **18% of patients develop withdrawl symptoms (not always associated to PD)**

Adverse event	Grade 1	Grade 2	All Grades
Fever	12 (55%)	7 (32%)	19 (86%)
Body aches	8 (36%)	3 (14%)	11 (50%)
Night sweats	3 (14%)	3 (14%)	6 (28%)
Arthralgias	4 (18%)	1 (5%)	5 (23%)
Chills	3 (14%)	1 (5%)	4 (18%)
Headache	2 (9%)	2 (9%)	4 (18%)
Fatigue	2 (9%)	0 (0%)	2 (9%)

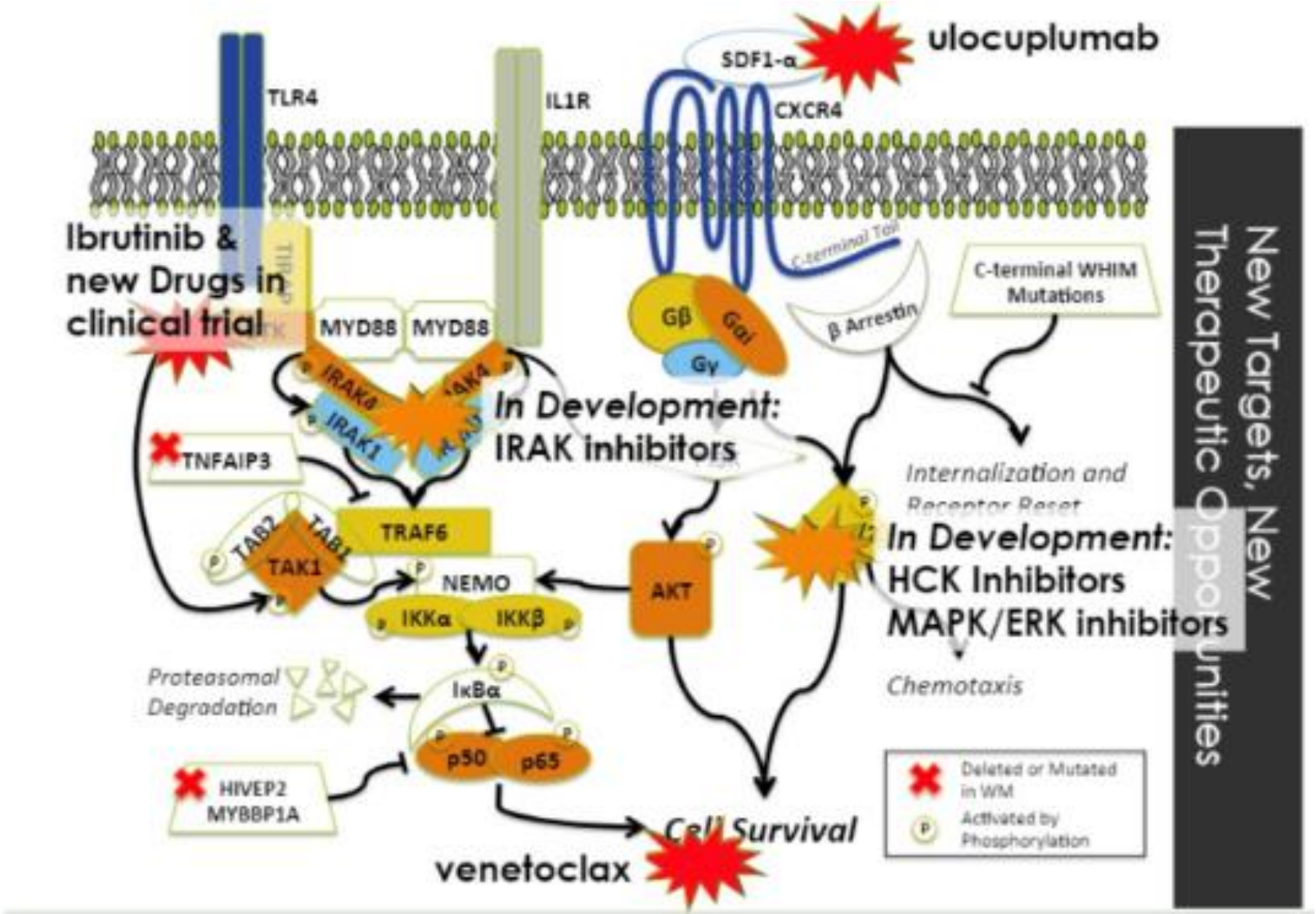
- **In one third of cases, withdrawal symptoms are associated with progressive disease characterized by increasing serum IgM levels, and in two thirds, symptoms occur in the absence of disease progression with no change in serum IgM or hemoglobin levels.**
- **Following the reinitiation of ibrutinib:**
  median time to a response of SD or better was 125 days for pts who met PD criteria
  significantly longer for pts with *MYD88*^{MUT}*CXCR4*^{WHIM} vs *MYD88*^{MUT}*CXCR4*^{WT} (207 vs. 101) ; p<0.0001)

Castillo et al 2018, Gustine et al 2018

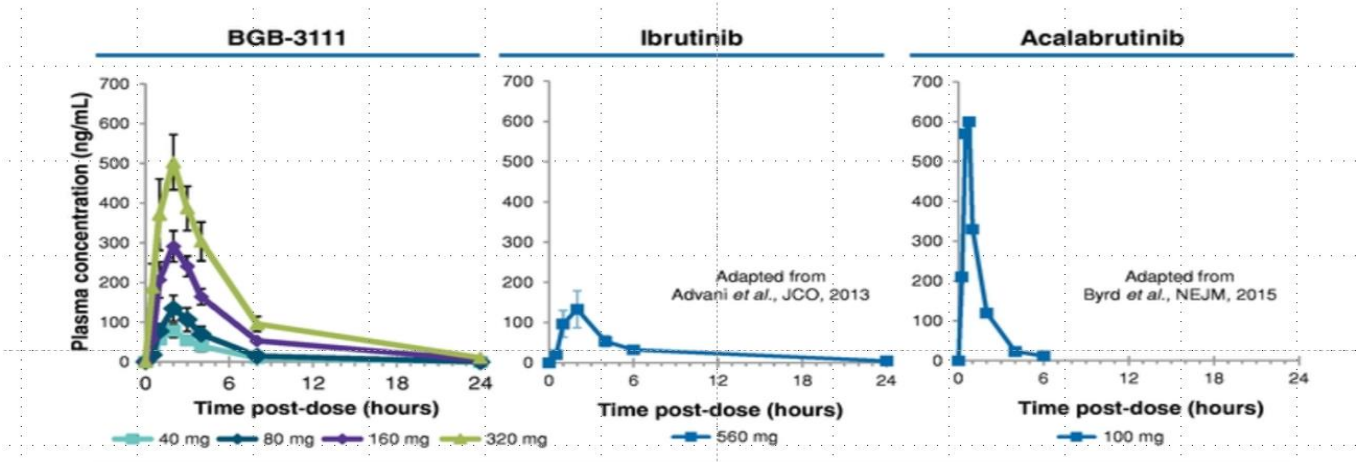
$BTK^{Cys481Ser}$ mutated clones release cytokines that protect BTK^{WT} clones from ibrutinib triggered cytotoxicity



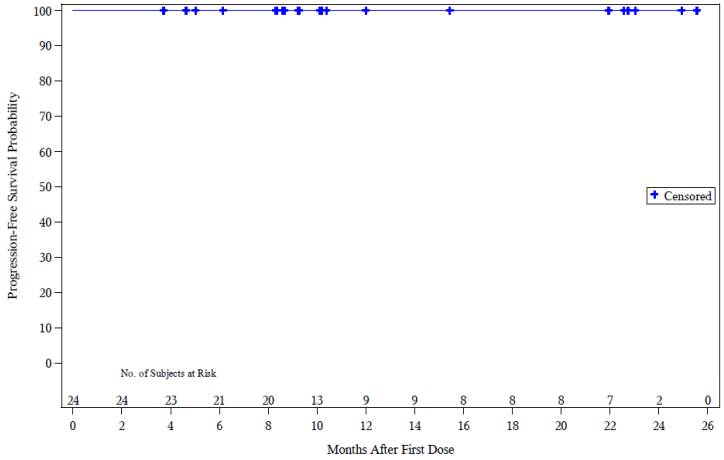
Chen et al, Blood 2018


ulocuplumab
SDF1-α
TLR4
IL1R
CXCR4
Ibrutinib &
new Drugs in
clinical trial
C-terminal Tail
C-terminal WHIM
Mutations
β Arrestin
Gβ
Gαi
Gγ
MYD88
MYD88
IRAK4
IRAK1
In Development:
IRAK inhibitors
TNFAIP3
Internalization and
Receptor Reset
TRAF6
TAB2
TAB1
TAK1
NEMO
AKT
In Development:
HCK Inhibitors
MAPK/ERK inhibitors
IKKα
IKKβ
Proteasomal
Degradation
IκBα
Chemotaxis
p50
p65
HIVEP2
MYBBP1A
Cell Survival
venetoclax
Deleted or Mutated
in WM
Activated by
Phosphorylation
New Targets, New
Therapeutic Opportunities

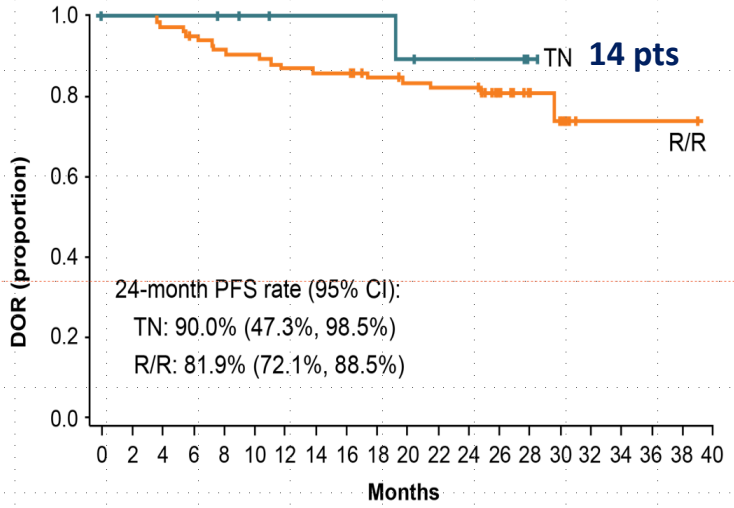
BTK inhibitors



Zanubrutinib AU-003
PFS



Acalabrutinib ACE-WM-001
PFS[a]



Trotman et al, 2019; Owen et al, 20

New proteasome inhibitors

First Line

CARFILZOMIB

Induction (q 21 days x 6 cycles):
iv CFZ, DEXA, Rituximab

Maintenance: (every 8 w for 8 cycles)
iv CFZ, DEXA, Rituximab

ORR	**87.1%**
MR	**67.7%**
CR/VGPR	**36 %**

Median PFS: 51 m

Treon et al, 2014

IXAZOMIB

Induction: (q 21 days x 6 cycles):
Oral Ixazomib, DEXA, Rituximab

Maintenance: (every 8 w for 8 cycles)
ixazomib, DEXA, Rituximab

ORR	**96%**
MR	**77%**
VGPR	**15%**

18 m PFS: 90%

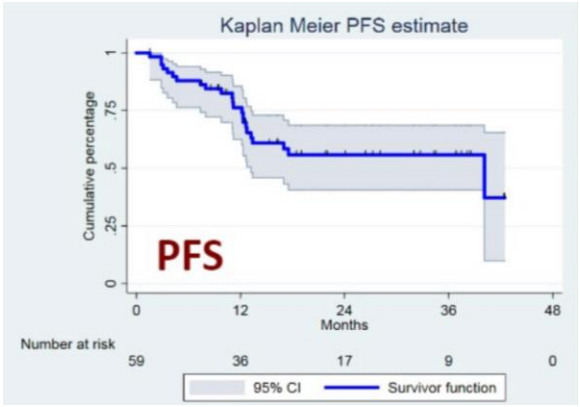
Castillo et al, 2018

R/R

IXAZOMIB

Induction: (q 21 days x 6 cycles):
Oral Ixazomib, DEXA, Rituximab sc
Maintenance: (every 3 m for 2 years)
Rituximab sc

24m PFS 56%



New proteasome inhibitors

First Line

CARFILZOMIB

Induction (q 21 days x 6 cycles):
iv CFZ, DEXA, Rituximab

Maintenance: (ev
iv CFZ, DEXA, Rit

ORR
MR
CR/VGPR

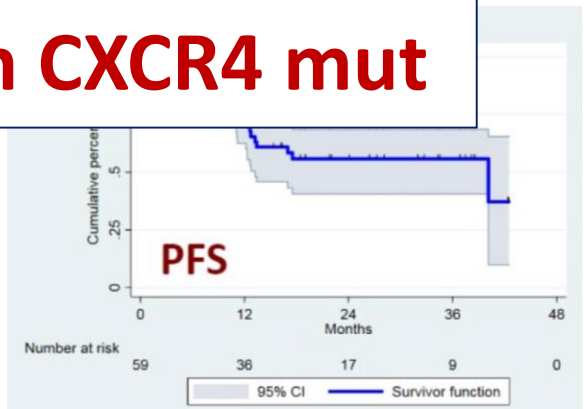
Median

PRO:

- **Low Neuropathy Rate: ~20%**
  - **Grade 2:0**
  - **Grade 3:3,2%**
- **NO impact from CXCR4 mut**

Maintenance: (every 3 m for 2 years)
Rituximab sc

24m PFS 56%



IXAZOMIB

Induction: (q 21 days x 6 cycles):
Oral Ixazomib, DEXA, Rituximab

Maintenance: (every 8 w for 8 cycles)

96%
77%
15%

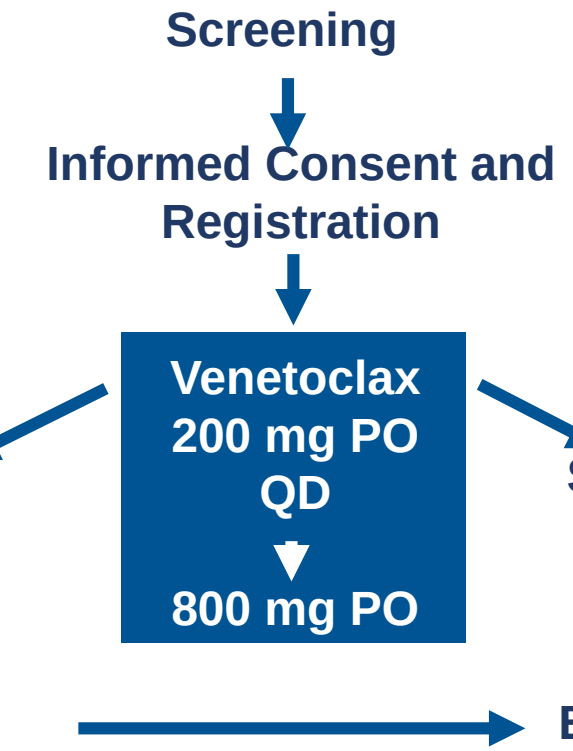
0%

Castillo et al, 2018

Phase II Study of Venetoclax in Previously Treated WM

Selected inclusion criteria:

- Clinicopathological diagnosis of WM
- Serum IgM >2 x ULN
- Previously treated
- Age ≥18 years
- Good performance
- Normal organ and marrow function



Selected exclusion criteria:

- Serious medical condition
- Concurrent anti-cancer agent
- Known CNS lymphoma
- Active HIV, HBV, HCV infection
- Lactating or pregnant women

www.clinicaltrials.gov: NCT02677324

Phase II Study of Venetoclax in Previously Treated WM

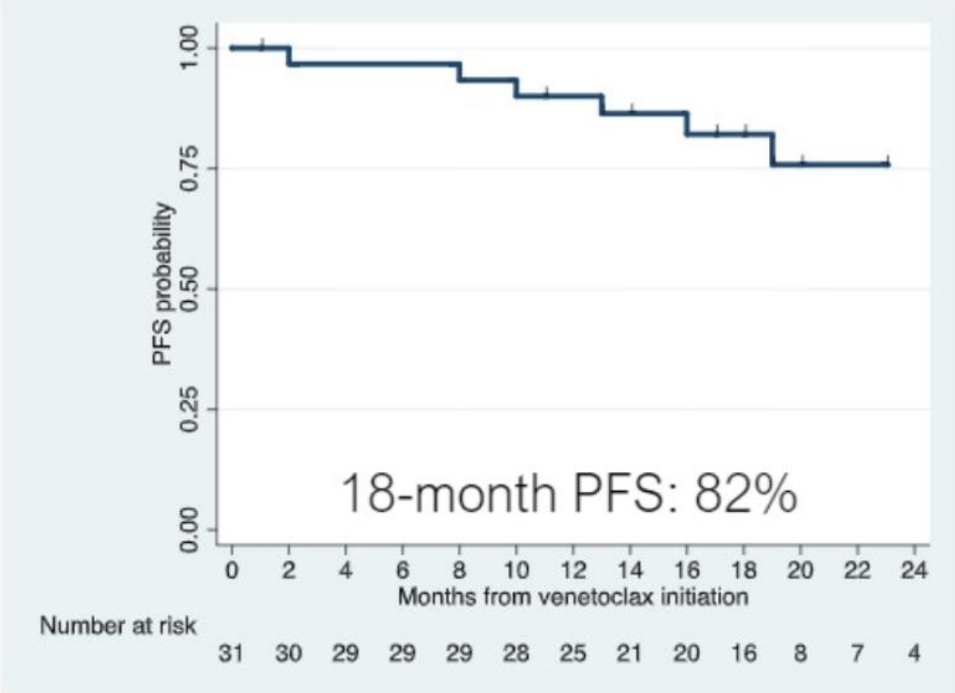
Response	N° Pts (n=30)	No prior ibrutinib (n=15)	Prior ibrutinib (n=15)
Overall	26 (87%)	14 (93%)	12 (80%)
Major	22 (74%)	13 (87%)	9 (60%)
Very good	5 (17%)	4 (27%)	1 (7%)
Partial	17 (57%)	9 (60%)	8 (53%)
Minor	4 (13%)	1 (7%)	3 (20%)
Stable	4 (13%)	1 (7%)	3 (20%)

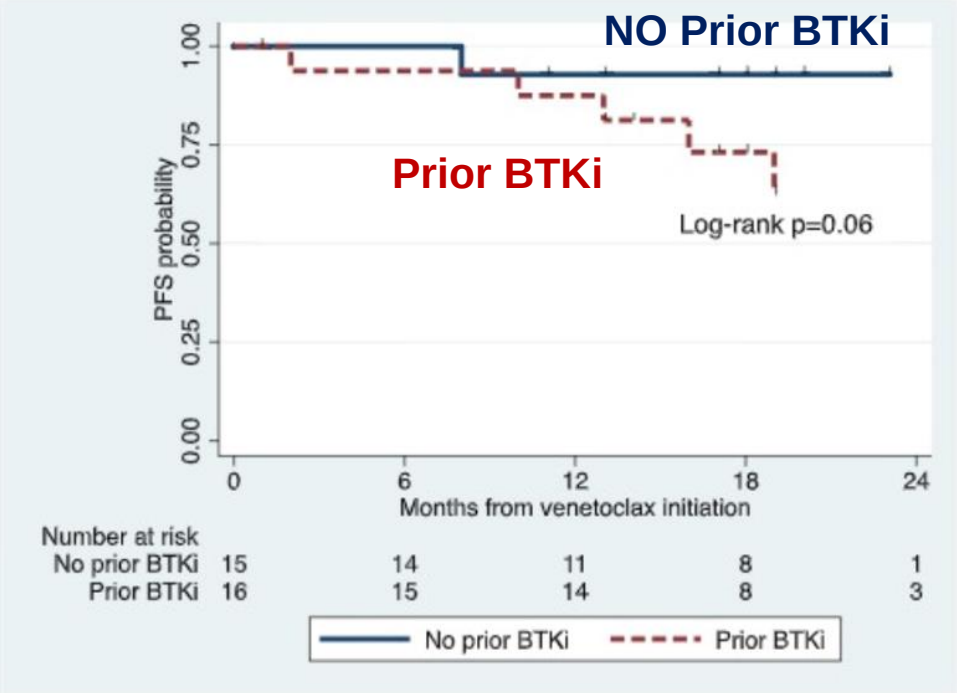
Response	CXCR4 mut	CXCR4wt
Major	13 (63%)	9 (86%)
Very Good	1 (7%)	4 (29%)

1 patient had progressive disease at 9 months (MYD88, CXCR4, TP53)

Castillo et al., 2019

Phase II Study of Venetoclax in Previously Treated WM





Castillo et al., 2019

Sistema Socio Sanitario

Ospedale Niguarda
Cancer Center

Regione
Lombardia