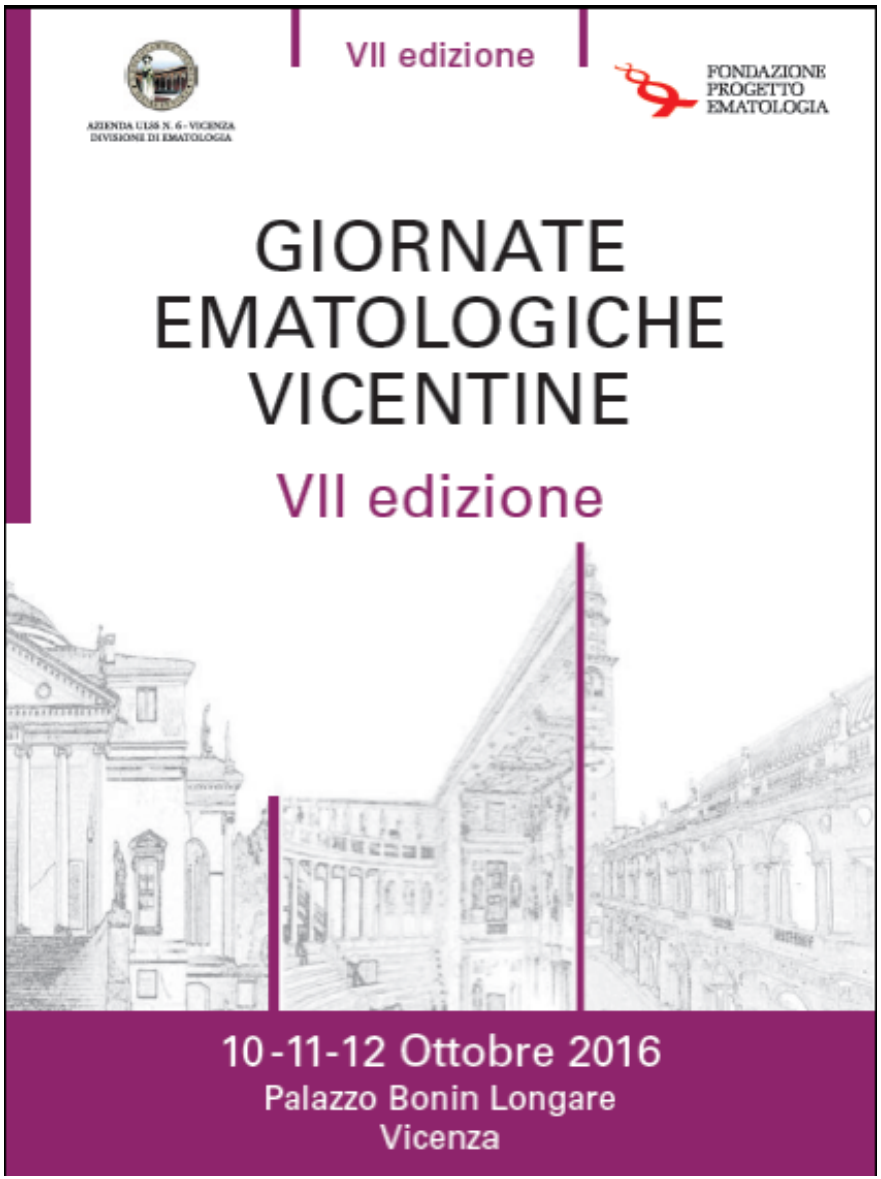

La malattia di Waldenström

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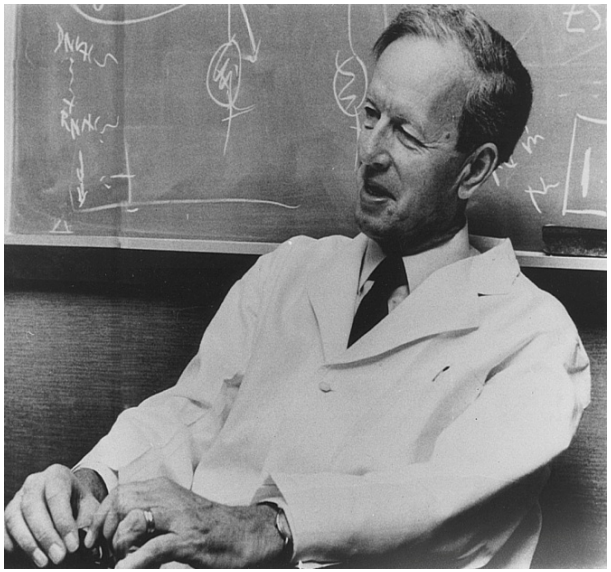
Pavia

Disclosures

Advisory board Janssen

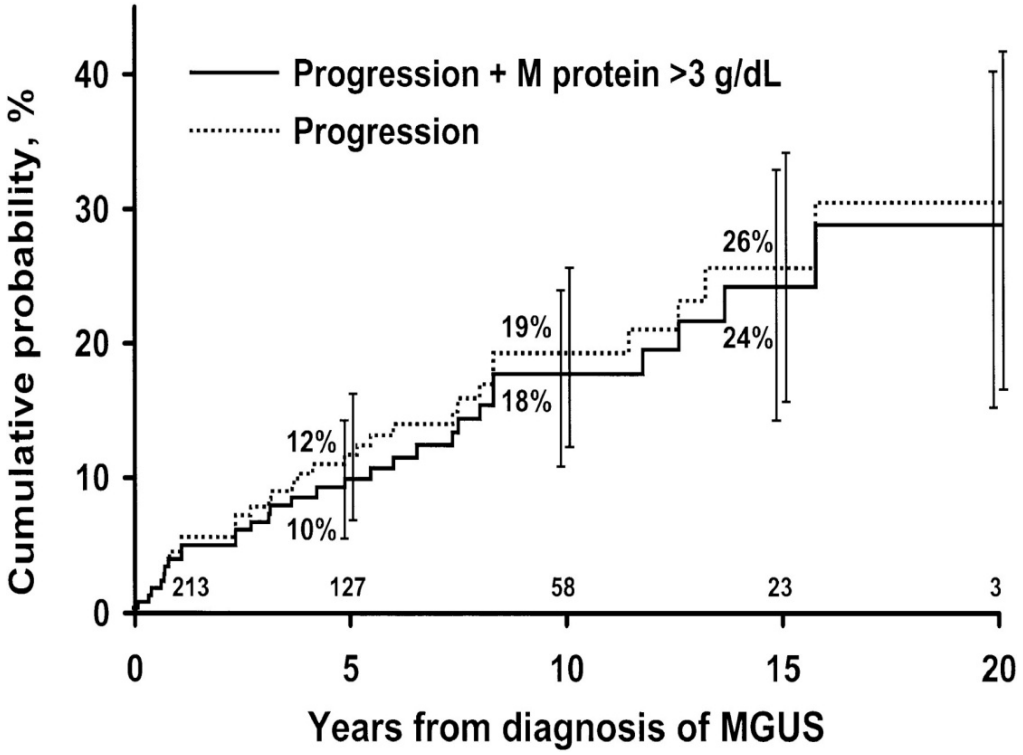
1944: first description of WM



- Rare disease (~ 1500 cases/year in USA)
- Median age at diagnosis: 65-70 years
- More common in males than females (60/40%)

- Familial predisposition in about 20% of cases

- Main risk factor for WM is history of IgM-MGUS (rate of progression to WM or other LPD: 1.5-2% per year)

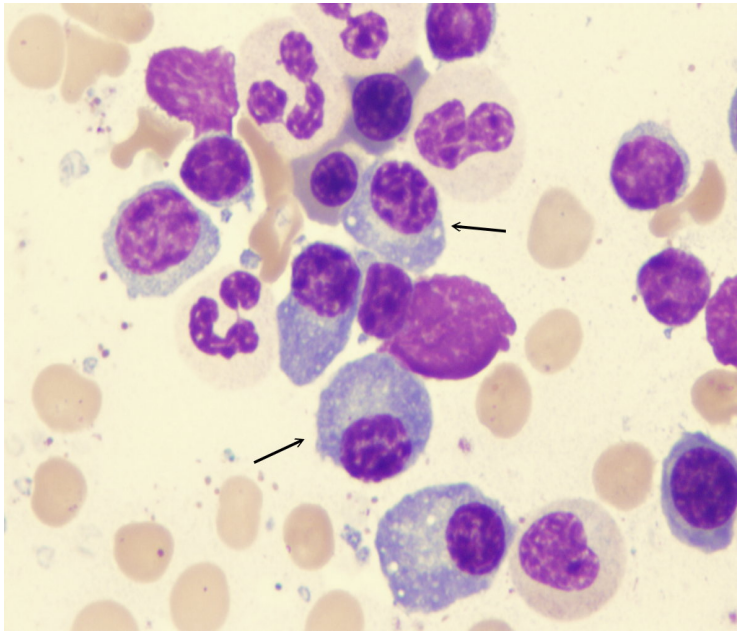


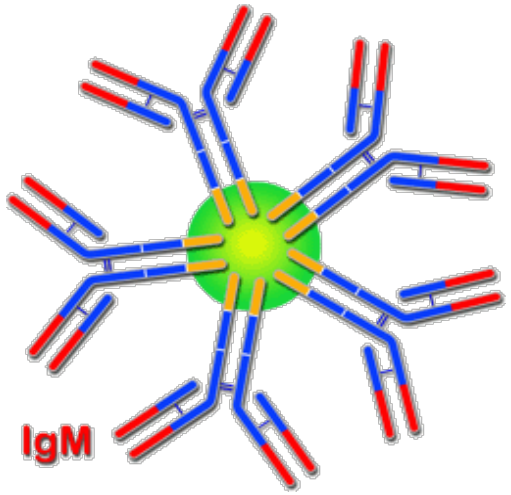
Kyle et al, Blood 2003

Diagnostic criteria of WM
IWWM, Athens 2002

Histologic diagnosis of **lymphoplasmacytic lymphoma** on bone marrow biopsy

- usually intertrabecular pattern of infiltration
- immunophenotype - sIgM+, CD19+, CD20+, CD79a+ and PAX5+, CD5−, CD10−, CD23-





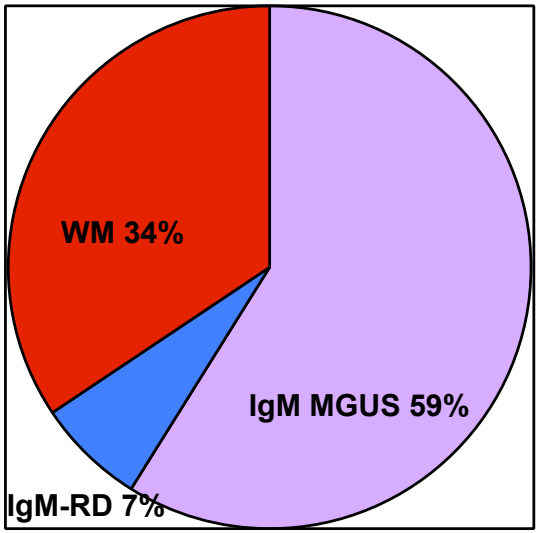
Serum **IgM monoclonal protein** of any size

Owen et al, Semin Oncol 2003; 30: 110-115; Treon S, Blood 2009; 114: 2375-2385

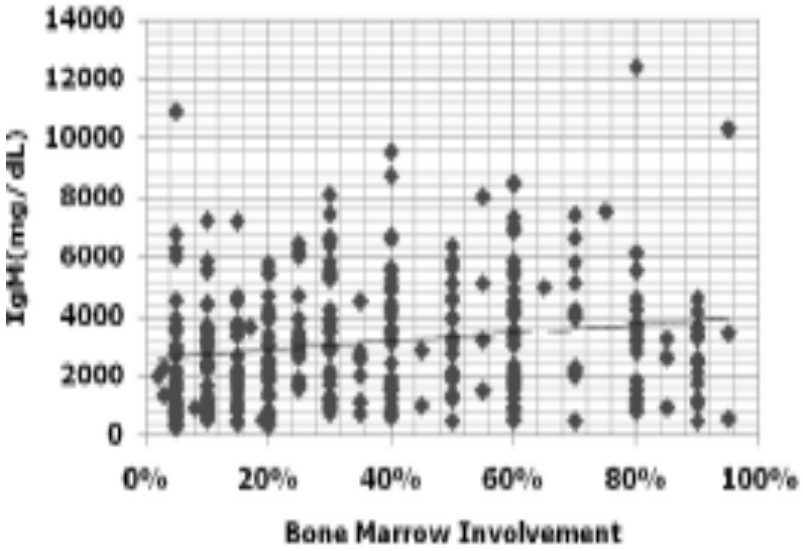
Classification of IgM monoclonal gammopathies

	IgM MC	BM infiltration	Symptoms attributable to MC	Symptoms attributable to neoplastic infiltration
Symptomatic WM	+	+	+	+
Asymptomatic WM	+	+	-	-
IgM-MGUS	+	-	-	-
IgM-related disorders	+	-	+	-

Pavia 2002-2012



No clear cut-off value in the serum IgM monoclonal protein between IgM-MGUS and WM



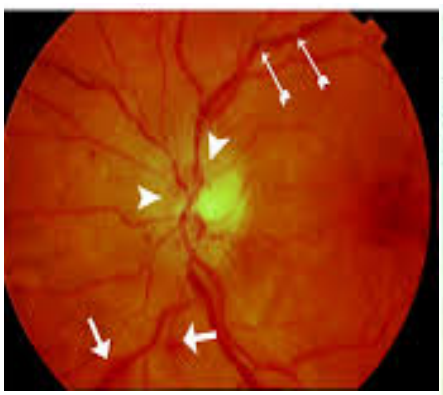
Owen et al, Semin Oncol 2003; Kyle et al, Blood 2003

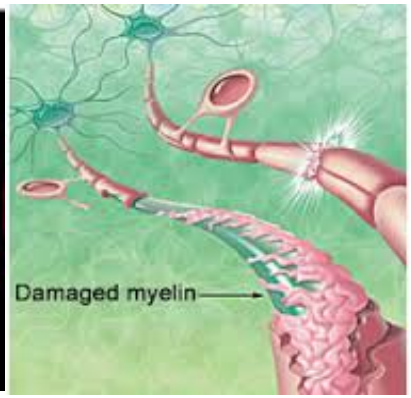
Clinical presentation of WM

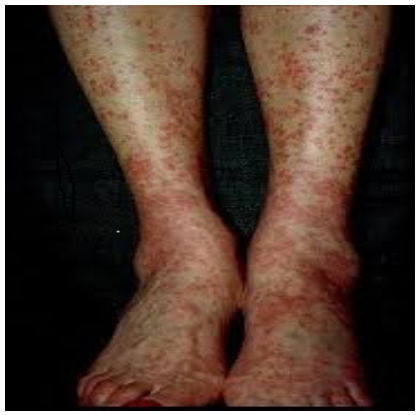
- **Constitutional symptoms**
  - fatigue
  - fever
  - weight loss
  - night sweats

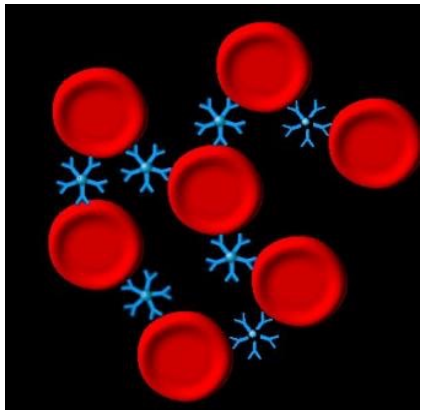
- **Symptoms due to neoplastic infiltration**
  - peripheral cytopenias
  - adenopathies
  - hepatosplenomegaly
  - Bing-Neel syndrome

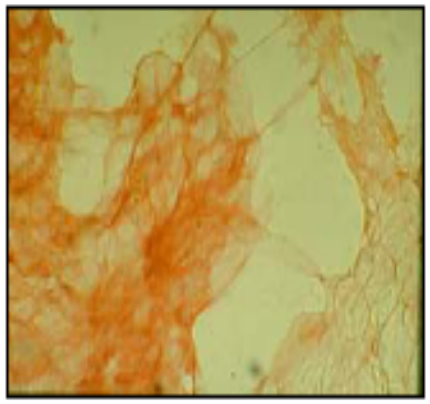
- **Symptoms due to MC**
  - hyperviscosity syndrome
  - peripheral neuropathy
  - cryoglobulinemia
  - cold agglutinin disease
  - amyloidosis











International Scoring System (ISS) for WM

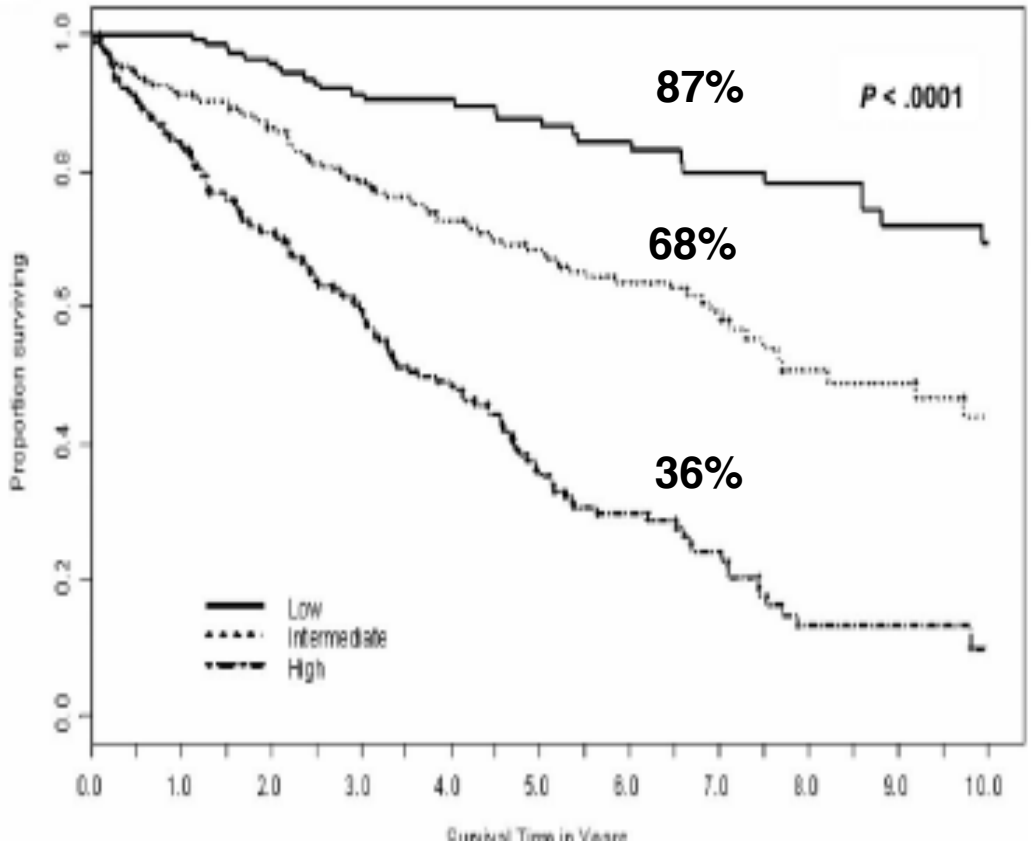
Risk factors

Age > 65 years

- Hb < 11.5 g/dL
- Platelets ≤ $100x10^9$/L
- β_2-microglobulin >3000 mcg/L
- Serum monoclonal component >7 g/dL

Risk	Score	N.Pts (%)
Low	0-1 except age	155 (27%)
Intermediate	Age>65 years or 2 factors	216 (38%)
High	> 2 factors	203 (35%)

5-year OS according to ISS-WM



Morel et al, Blood 2009; 113: 4163-4170

Genomic landscape of WM

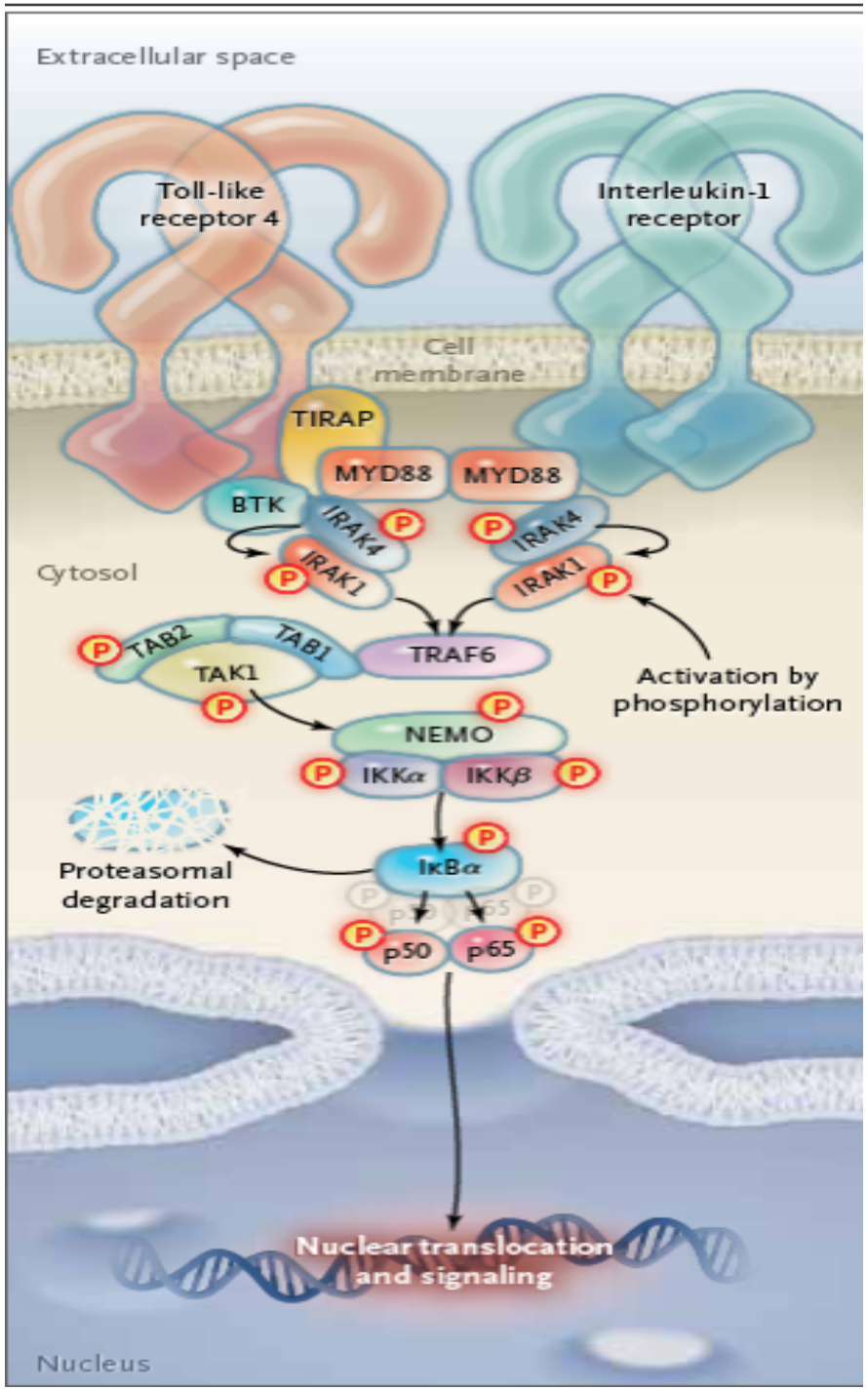
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

- Induces NFKB signaling via IRAK and BTK pathways
- Overexpression of MYD88 L265P promotes survival of WM cells
- Inhibition of MYD88 signaling leads to WM LPC apoptosis



Treon SP et al, NEJM 2012

MYD88 (L265P) mutation in patients with WM or IgM-MGUS

Reference	Method	Tissue	WM		IgM-MGUS	
			n. pts	MYD88 (L265P)	n. pts	MYD88 (L265P)
Treon et al, 2012	WGS/Sanger	BM CD19+	30/24	**91%**	21	**10%**
Landgren et al, 2012	Sanger	BM	-	-	9	**56%**
Xu et al, 2013	AS-PCR	BM CD19+	104	**93%**	24	**54%**
Varettoni et al, 2013	AS-PCR	BM	58	**100%**	77	**47%**
Jiménez et al, 2013	AS-PCR	BM	117	**86%**	31	**87%**
Gachard et al, 2013	PCR	BM	31	**67%**	-	-
Poulain et al, 2013	PCR	BM CD19+	67	**79%**	2	**50%**

blood

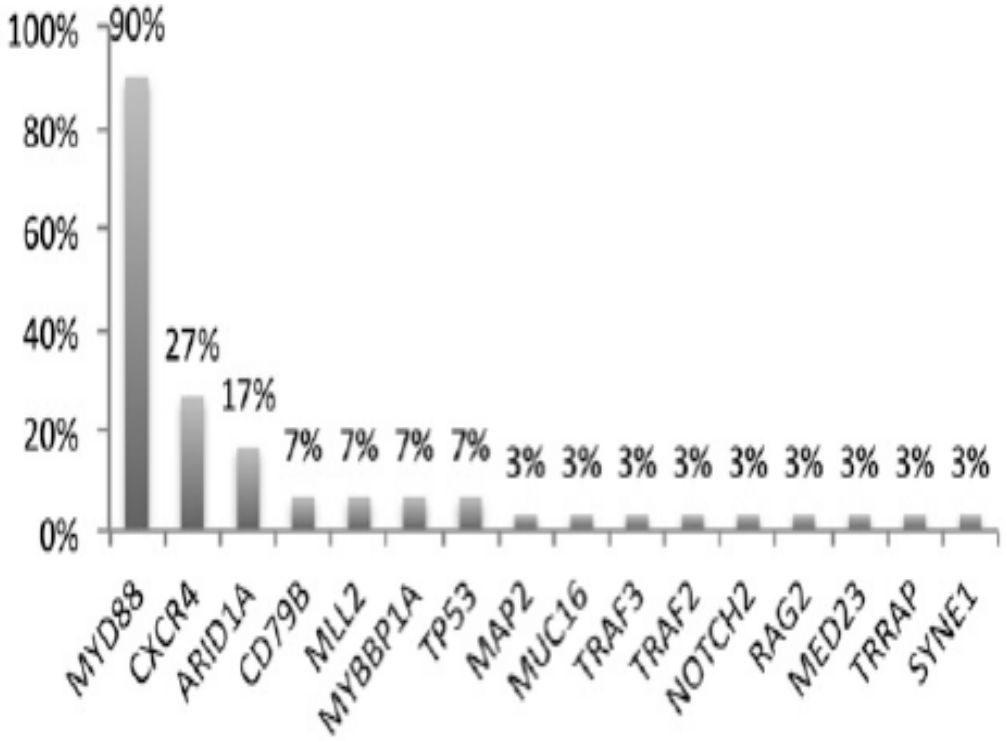
2013 121: 4434-4436
doi:10.1182/blood-2013-04-494849

A new era for Waldenstrom macroglobulinemia: MYD88 L265P

Steven P. Treon and Zachary R. Hunter

- Diagnostic tool (WM vs other B cell LPD)
- Prognostic marker in IgM-MGUS
- Response assessment after therapy
- Novel therapeutic target

Genomic landscape of WM



CXCR4 and its ligand SDF-1 (CXCL12) play a key role in hematopoietic progenitor cell homing to BM and lymphoid cell trafficking

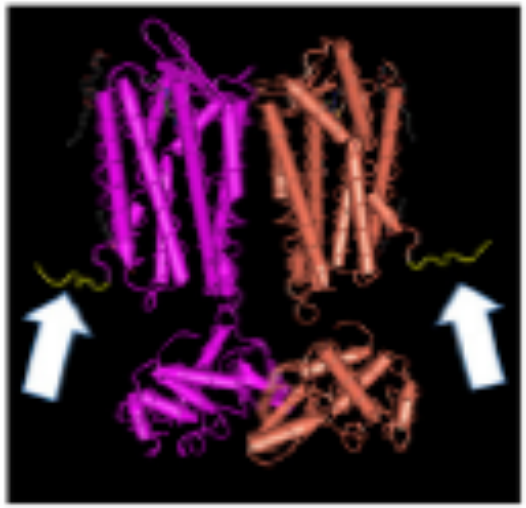
CXCR4 is expressed by tumor cells in several hematopoietic and solid cancers and promotes neoplastic dissemination

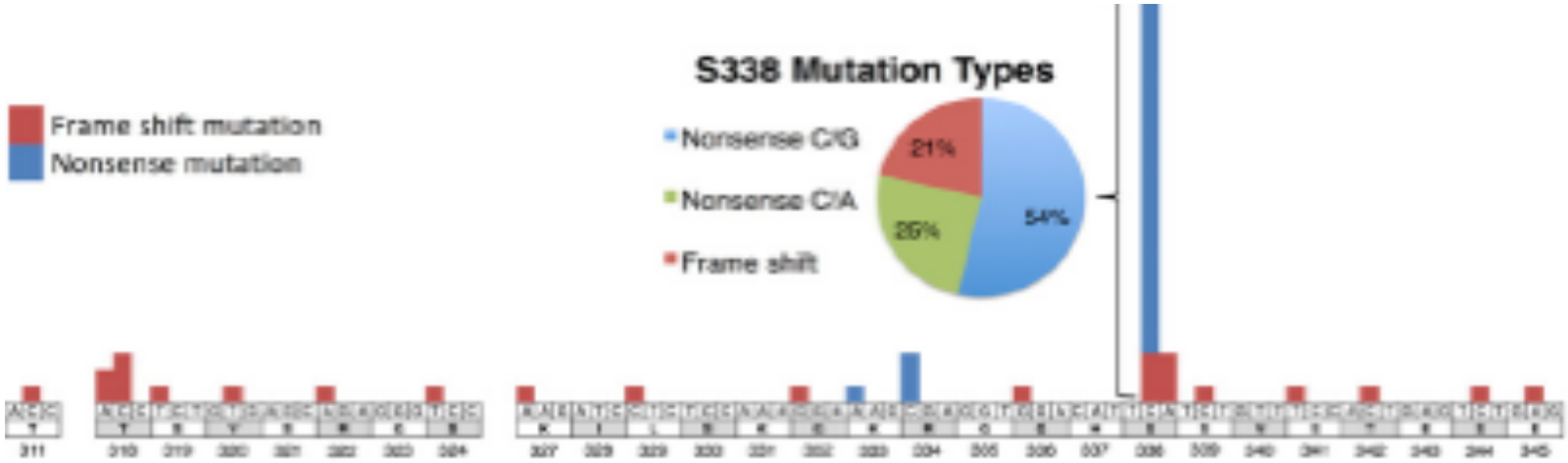
WM is the first cancer with reported somatic mutations of CXCR4

Hunter et al, Blood 2014; 123: 1637-1745
Burger JA and Kipps TJ, Blood 2006; 107: 1761-1767

CXCR4 WHIM-like mutations in WM

- Over 30 nonsense (NS) or frameshift (FS) C-tail mutations, impaired internalization and prolonged CXCR4 pathway activation
- The most common is S338X (~ 50% of CXCR4 mutations)
- Similar to germline mutations typical of WHIM syndrome





Hunter et al, Blood 2014; 123: 1637-1745

CXCR4 mutations in WM and IgM-MGUS

Reference	Method	WM		IgM-MGUS	
		n. pts	% of CXCR4 mutated pts	n. pts	% of CXCR4 mutated pts
Treon et al, 2014	WGS/Sanger	177	29%	-	-
Roccaro et al, 2014*	AS-PCR for S338X (C1013G)	131	28%	40	20%
Schmidt et al, 2015*	Sanger	47	36%	-	-
Xu et al, 2016*	Sanger/AS-PCR for S338X (C1013G and C1013A)	102 untreated 62 treated	43% 34%	12	17%
Poulain et al, 2016	Sanger/NGS	98	25%	-	-

* These studies included also MZL patients with a prevalence of CXCR4 mutations of 5-7%
No CXCR4 mutations were found in CLL, MM, IgA and IgG MGUS, HCL and healthy subjects

Treon SP et al, Blood 2014; Roccaro A et al, Blood 2014; Schmidt J et al, Br J Haematol 2015; Xu L et al, Br J Haematol 2016; Poulain S et al, CCR 2016

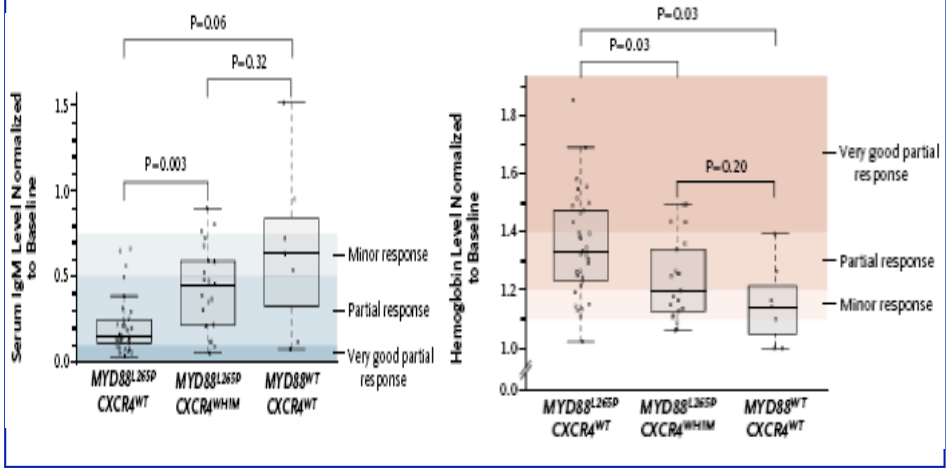
Clinical significance of CXCR4 mutations in WM

Disease presentation

- higher IgM levels[1,*2]
- higher incidence of hyperviscosity[1*]
- higher BM infiltration[1*]
- lower PLT,[2,3] Hb,[3] WBC[3] count
- less adenopathy[1,3]

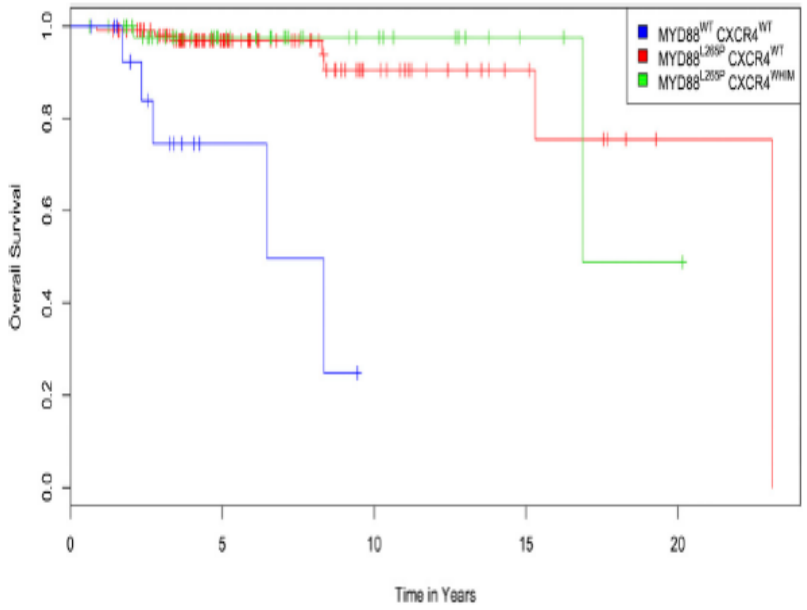
*CXCR4/NS

Clinical resistance to Ibrutinib[4]



Outcome

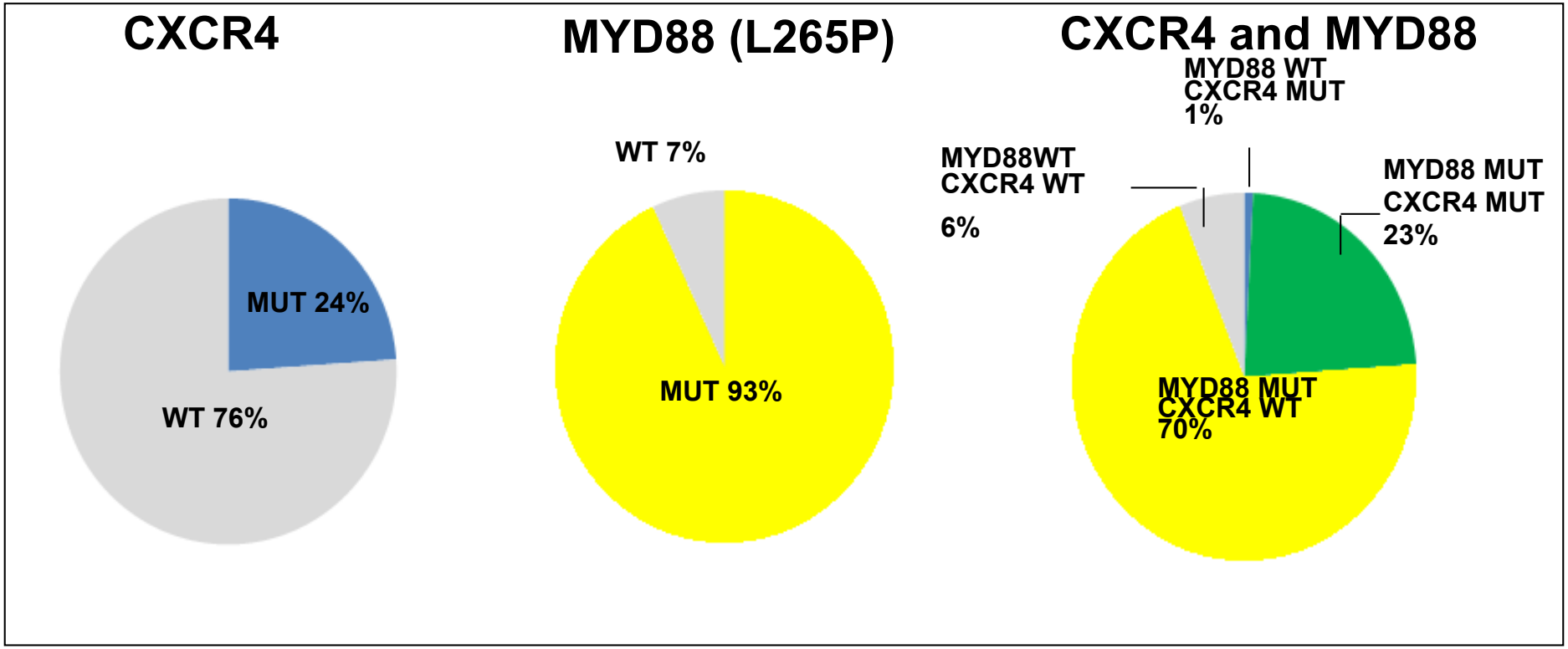
- No impact on OS[1,2]



1 Treon SP et al, Blood 2014; 123: 2791-96
2 Poulain S et al, Clin Cancer Res 2016; 22: 1480-88
3 Schmidt J et al, Br J Haematol 2015; 169: 795-803
4 Treon SP et al, NEJM 2015; 372: 1430-40

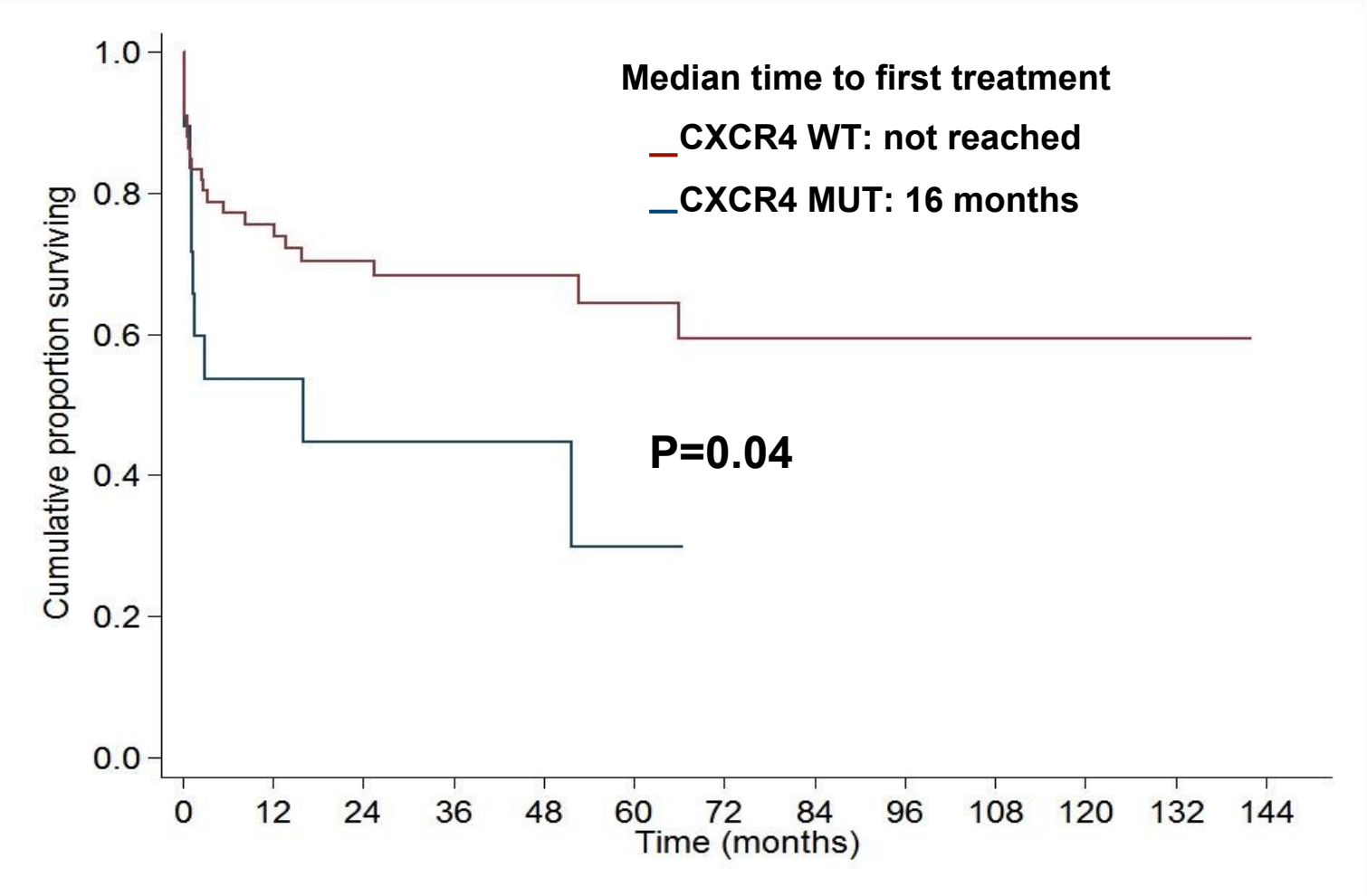
Prevalence of CXCR4 and MYD88 mutations in WM patients

n=113



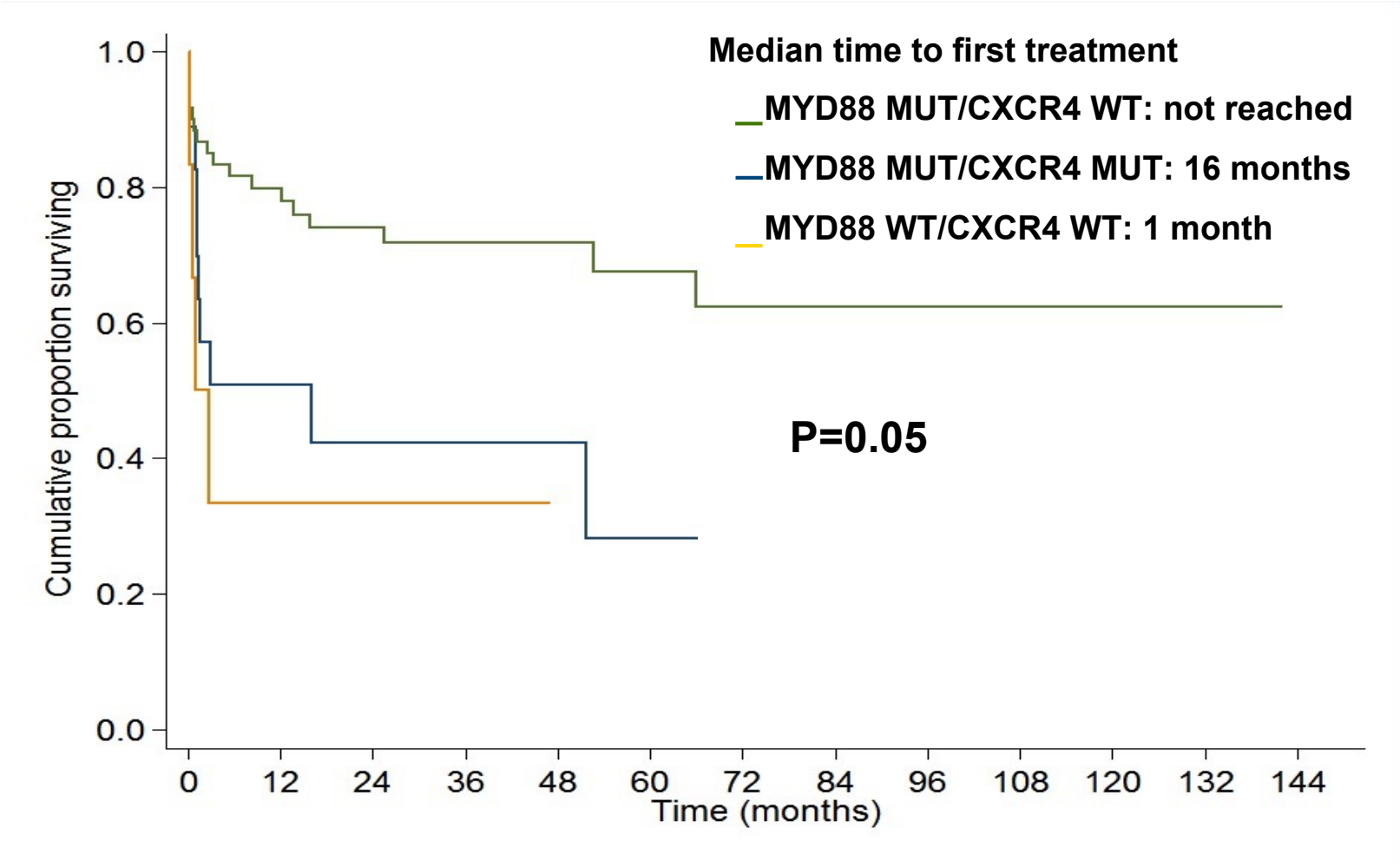
CXCR4 mutations associated with lower Hb levels (P=0.05), higher BM infiltration (P=0.04) and higher MYD88 allele burden (P=0.005) reflecting more advanced disease

Time to first treatment according to CXCR4 mutational status



Varettoni M et al, 9th IWWM, Amsterdam 5-9th October 2016

Time to first treatment according to MYD88 and CXCR4 mutational status



Varettoni M et al, 9th IWWM, Amsterdam 5-9th October 2016

Treatment of WM

Treatment recommendations from the Eighth International Workshop on Waldenström's Macroglobulinemia

Véronique Leblond,[1] Efstathios Kastritis,[2] Ranjana Advani,[3] Stephen M. Ansell,[4] Christian Buske,[5] Jorge J. Castillo,[6] Ramón García-Sanz,[7] Morie Gertz,[8] Eva Kimby,[9] Charalampia Kyriakou,[10] Giampaolo Merlini,[11] Monique C. Minnema,[12] Pierre Morel,[13] Enrica Morra,[14] Mathias Rummel,[15] Ashutosh Wechalekar,[16] Christopher J. Patterson,[6] Steven P. Treon,[6] and Meletios A. Dimopoulos[2]

- Not all patients with a diagnosis of WM need immediate therapy
- Criteria for the initiation of therapy include
  - IgM-related complications
  - Symptoms related to direct BM involvement by tumor cells such as cytopenias, constitutional symptoms, and bulky extramedullary disease

Leblond V et al, Blood 2016, 128: 1321-1328

Immuno-chemotherapy for WM: selected trials

Combination	Pts	Untreated	ORR	Major R	CR	TTP	Reference
R+Cy+Dex (DRC)	72	100%	83%	74%	7%	35 mo	*Dimopoulos, JCO 2007*
R-CHOP	23	100%	91%	80%	9%	62 mo	*Buske, Leukemia 2009*
R-Fludarabine	43	63%	95%	86%	4%	51 mo	*Treon, Blood 2009*
R-FluCy (FCR)	43	65%	79%	74%	11%	50 mo	*Tedeschi, Cancer 2012*
R-Cladribine	29	70%	89%	75%	20%	Not reached	*Lazlo, JCO 2010*
R+Bendamustine	32	100%	96%	-	43%	2y-PFS 97%	*Luminari, Leuk Lymph 2015*

- not reported

Alkylators-based therapy

Primary treatment of WM with Dexamethasone, Rituximab and Cyclophosphamide (DRC)

Phase II study, 72 patients

DRC schedule

Drug	Dose	d1	d2	d3	d4	d5
Dexamethasone iv	20 mg	♦				
Rituximab iv	375 mg/m^2	♦				
Cyclophosphamide po	200 mg/m^2	♦	♦	♦	♦	♦

Every 21 days for 6 cycles

Response to treatment

CR: 7%
PR: 67%
MR 9%

ORR: 83%

MRR: 74%

Median time to response: 4.1 m

Toxicity

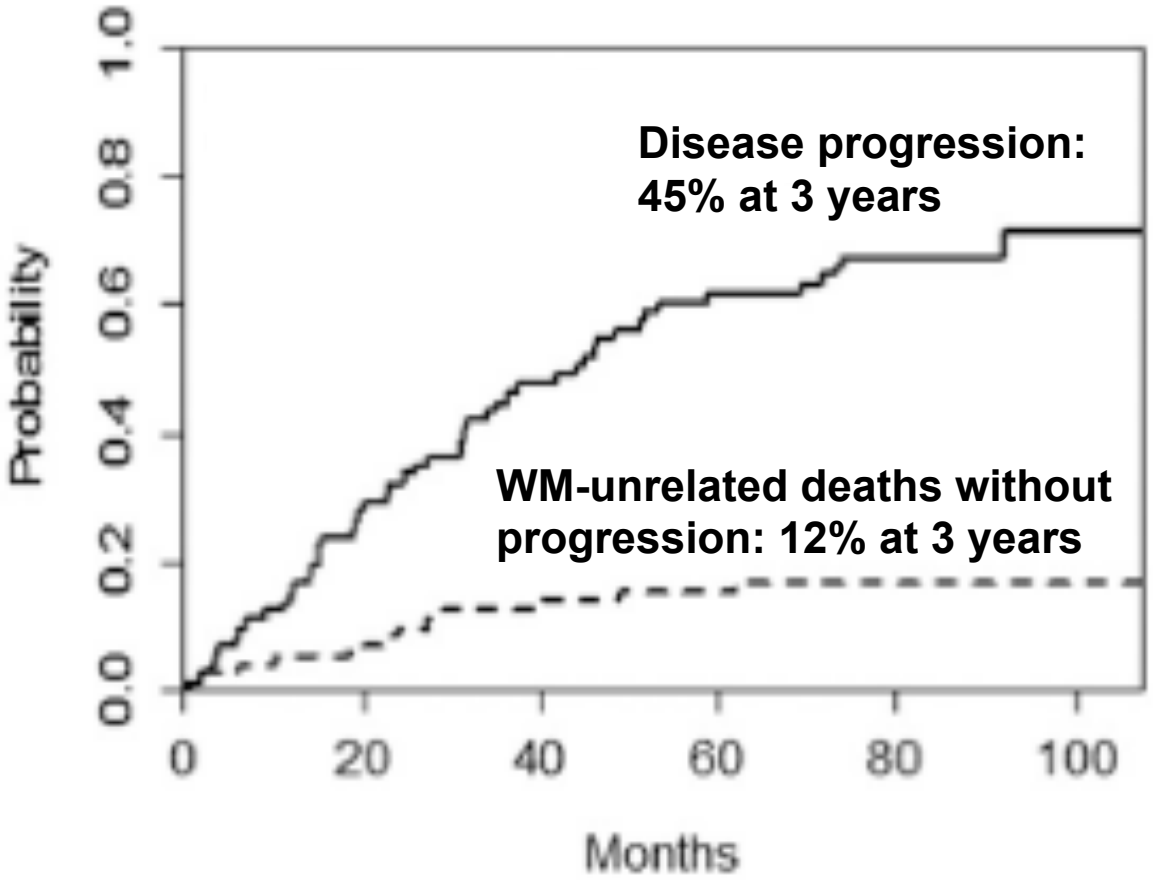
89% of pts completed the expected 6 courses

Toxicity, % of pts	*Grade*				
	0	*1*	*2*	*3*	*4*
Neutropenia	66	15	10	7	2
Thrombocytopenia	93	7	0	0	0
Nausea vomiting	62	25	13	0	0
Chills/Fever	84	12	4	0	0
Headache	81	15	2	2	0
Hypotension	94	2	0	4	0

Dimopoulos et al, JCO 2007: 25 (22): 3344-3349

DRC: final results

Median Follow-up 8 years (range: 7-10)



Kastritis E., et al Blood 2015; 126 (11)

Purine analogs

Fludarabine, Cyclophosphamide and Rituximab (FCR) in WM

Patients' characteristics

N. of patients: 43

Disease status:

First-line treatment: 28 (65%)

Relapsed: 12 (28%)

Refractory: 3 (7%)

Schedule of treatment

Drugs	*mg/m²*	*1*	*2*	*3*
Rituximab	375	X		
Fludarabine	25	X	X	X
Cyclophosphamide	250	X	X	X

Every 28 days for 6 cycles

Response to treatment

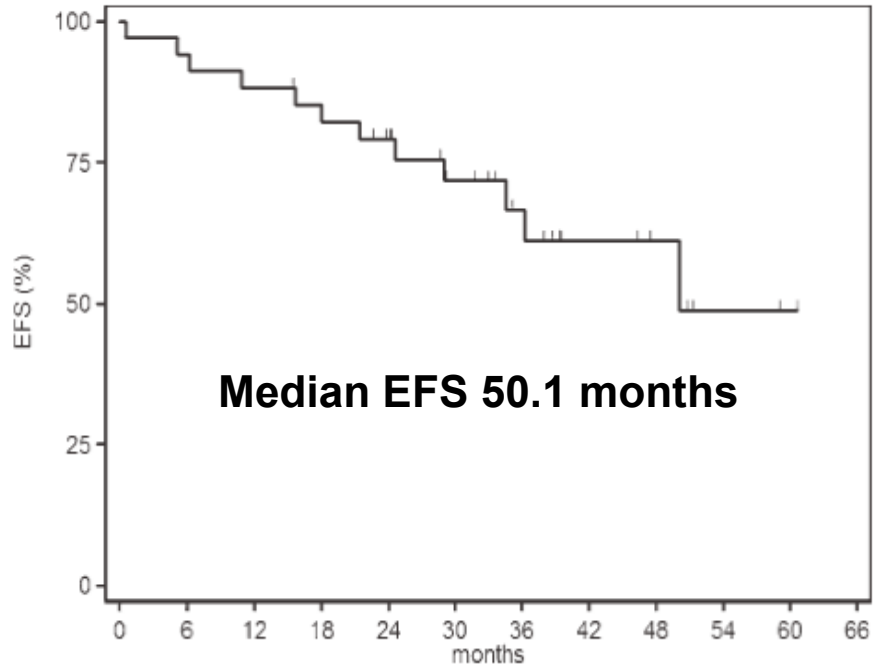
Response	End of treatment (% of pts)	During follow-up (% of pts)
ORR	**79%**	**79%**
Major RR	**75%**	**77%**
CR	**12%**	**19%**
VGPR	**21%**	**14%**
PR	**42%**	**44%**
MR	**4%**	**2%**
SD	**9%**	**9%**
PD	**12%**	**12%**

Tedeschi A et al, Cancer 2012; 118(2):434-43

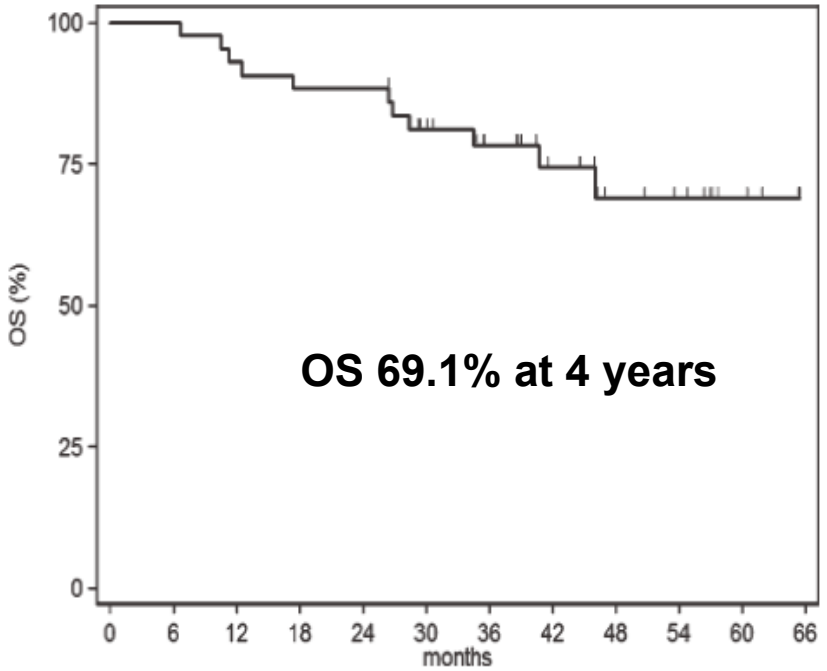
FCR in WM: DFS and OS

Median FU: 37.2 months (range 6 - 60)

Event-Free Survival



Overall Survival



Tedeschi et al, Cancer 2012; 118(2):434-43

FCR in WM: toxicity

	Grade 1-2 (% of pts)	Grade 3-4 (% of pts)
Hematologic toxicity		
Neutropenia	12	88
Anemia	30	2
Thrombocytopenia	3	5
Extrahematologic toxicity*		
Infusional reaction to Rituximab	49	5
Nausea-vomiting	21	0
Infections	7	12

* Occurring in ≥ 10% of pts

- 35% received <6 courses; the main reason for discontinuation was neutropenia
- 44% of pts had long lasting neutropenia (median duration 7 months) after the last course of treatment

Tedeschi et al, Cancer 2012; 118(2):434-43

Nucleoside Analogs-based therapy: balancing risk and benefits

- NA are associated with high rates of good quality and durable responses

  ORR 80-90%; CR ~ 10%; CR+VGPR ~ 30%; PFS > 50 months

- May cause prolonged neutropenia, immune suppression, opportunistic infections
- Potential stem cell damage: NA-based treatments should be avoided in younger patients and potential ASCT candidates
- Increased risk of DLBCL and MDS/AML has been reported

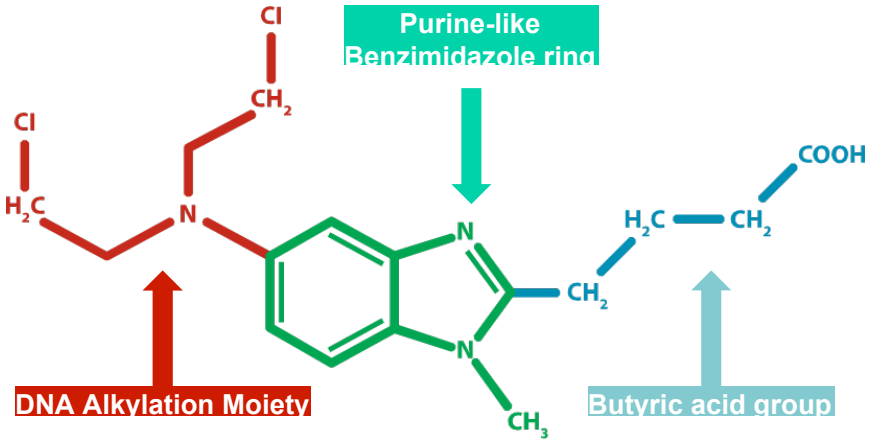
Treatment recommendations from 8th IWWM

"…because of the risk of long-lasting cytopenias and secondary malignancies with these combinations, first-line treatment is not recommended"

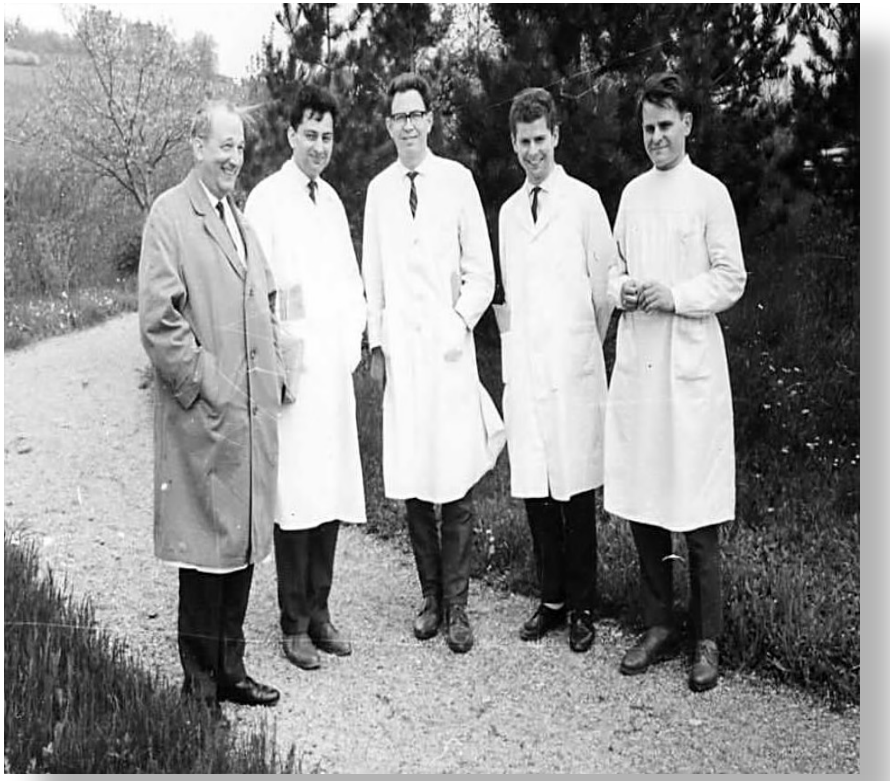
Weber et al, Semin Oncol 2003; Treon et al, Blood 2008; Leleu et al, JCO 2009; Tedeschi et al, Cancer 2012

Bendamustine

Bendamustine structure



- **Developed in the 60s in former East Germany**
- **A molecule with:**
  - -Bifunctional alkylator group (2-chloroethylamine group)
  - -Purine-like, benzimidazole ring with possible anti-metabolite properties



Ozegowski & coworkers, 1962

R-Bendamustine vs R-CHOP as first line treatment in indolent and mantle cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

	R-B	R-CHOP	P value
ORR	93%	91%	NS
CR	40%	30%	0.02
PFS	69.5 m	31.2 m	<0.0001

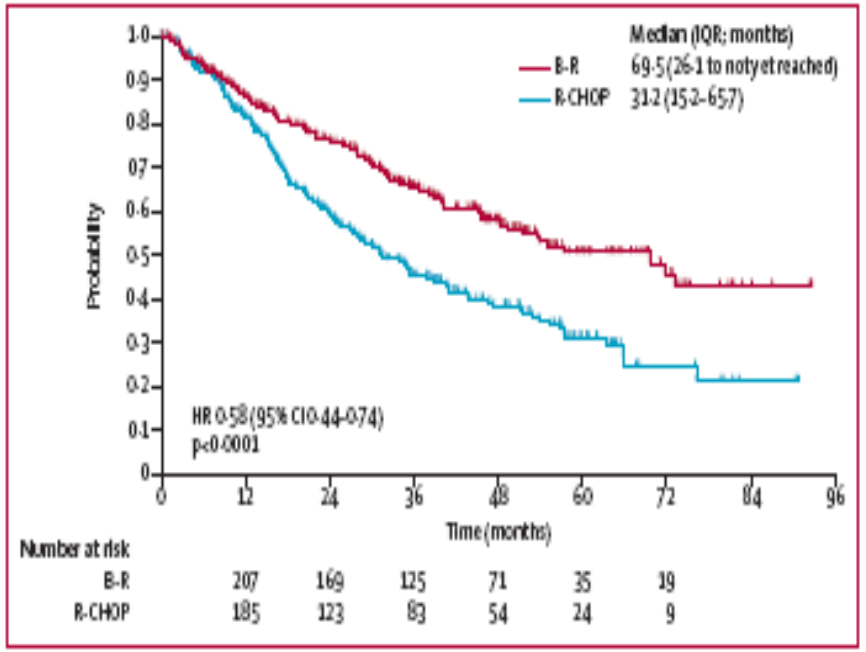


Figure 2: Progression-free survival
B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

ASH meeting 2014: poster #4407

-Updated results after median FU of 87 months

-Longer TTNT with R-B in iNHL and elderly MCL

-Trend for OS advantage in pts with iNHL treated with R-B

Rummel et al, Lancet 2013; 381: 1203-1210

R-Bendamustine vs R-CHOP as first line treatment in indolent and mantle cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

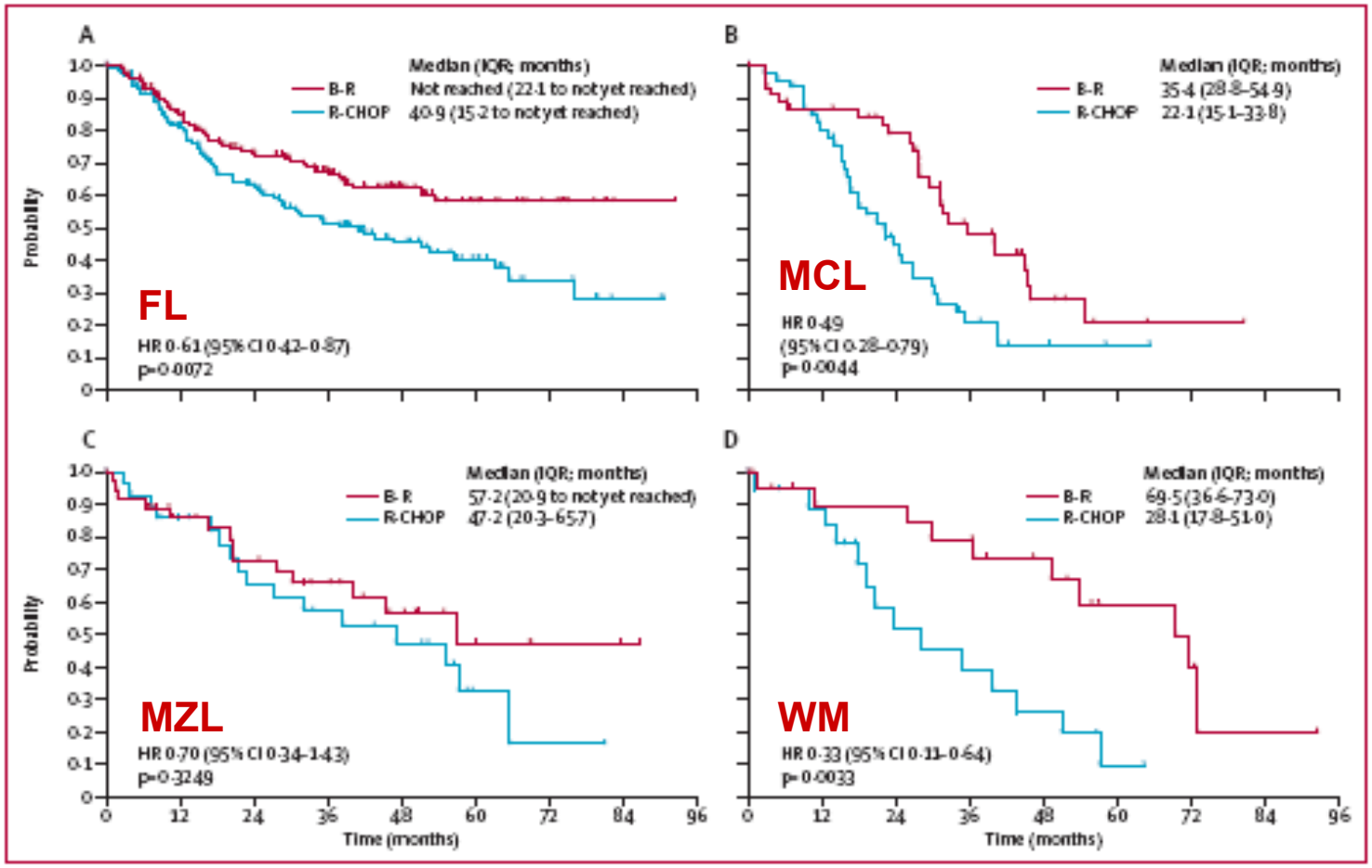


Figure 3: Progression-free survival in histological subtypes of follicular lymphoma (A), mantle-cell lymphoma (B), marginal-zone lymphoma (C), and Waldenstrom's macroglobulinaemia (D)
B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.

Rummel et al, Lancet 2013; 381: 1203-1210

R-Bendamustine vs R-CHOP as first line treatment in indolent and mantle cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

Hematologic toxicity

Grade 3-4 AEs	B-R	R-CHOP	P value
Neutropenia	29%	69%	<0.0001
Leucocytopenia	37%	72%	<0.0001
Lymphocytopenia	74%	43%	NS
Trombocytopenia	5%	6%	NS
Anemia	3%	5%	NS

Non-hematologic toxicity

Grade 3-4 AEs	B-R	R-CHOP	P value
Alopecia	0%	100%	<0.0001
Paresthesia	7%	29%	<0.0001
Stomatitis	6%	19%	<0.0001
Skin (erythema)	16%	9%	0.024
Allergic reactions (skin)	15%	6%	0.0006
Infectious episodes	37%	50%	0.0025
Sepsis	<1%	3%	0.019

Rummel et al, Lancet 2013; 381: 1203-1210

New treatment options in WM

- Proteasome inhibitors - Bortezomib, Carfilzomib, Ixazomib
- BTK inhibitors –Ibrutinib, CC-292, BGB-3111, ONO-4059
- PI3K delta inhibitors - Idelalisib
- Imids – Thalidomide, Lenalidomide
- mTOR inhibitors - Everolimus
- New anti-CD20 antibodies - Ofatumumab, Obinotuzumab
- Anti-bcl2 agents – ABT-199
- TLR antagonists - IMO-8400
- Anti-CXCR4 antibodies - Ulocuplumab

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*** 648/96 in R/R WM** **** Approved by FDA and EMA**

Proteasome inhibitors

Primary therapy of WM with Bortezomib, Dexamethasone, and Rituximab

Study	Treatment	Number of cycles	ORR	CR+PR	Grade 3-4 peripheral neuropathy
WMCTG trial (n=25)	Bor 1,3 mg/m^2 d 1,4,8,11 Dexa 40 mg d 1,4,8,11 Rituximab 375 mg/m^2 d 11	4+4	96%	83%	30% (61% discontinued treatment due to PN)
EMN trial (n=59)	Bor 1,3 mg/m^2 d 1,4,8,11 cycle 1 Bor 1,6 mg/m^2 d 1,8,15,22 cycle 2-5 Rituximab 375 mg/m^2 d 1,8,15,22 cycle 2 and 5 Dexa 40 mg d 1,8,15,22 cycle 2 and 5	6	85%	68%	7%

Treon et al, JCO 2009; Dimopoulos et al, Blood 2013

Primary therapy of WM with Bortezomib, Dexamethasone, and Rituximab

WMCTG trial

Table 2. Adverse Events Possibly, Probably, or Definitely Associated With Protocol Therapy

Toxicity Type	Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%
Anemia	18	78	1	4	0	0
Anorexia	2	9	0	0	0	0
Arrythmia	2	9	1	4	0	0
Cough	3	13	0	0	0	0
Diarrhea	2	9	0	0	0	0
Dehydration	3	13	0	0	0	0
Dyspnea	3	13	0	0	0	0
Edema	1	4	0	0	0	0
Fatigue	4	17	0	0	0	0
Herpes zoster	5	22	0	0	0	0
Hyperglycemia	6	26	0	0	0	0
Hypotension	0	0	1	4	0	0
Insomnia	3	13	0	0	0	0
Infection without neutropenia	10	43	0	0	0	0
Infection with neutropenia	0	0	1	4	0	0
Memory impairment	1	4	0	0	0	0
Myopathy	0	0	1	4	0	0
Neutropenia	6	26	6	26	1	4
Pneumonia	2	9	1	4	0	0
Peripheral neuropathy	9	39	7	30	0	0
Rash	1	4	0	0	0	0
Thrombocytopenia	8	35	2	9	0	0

EMN trial

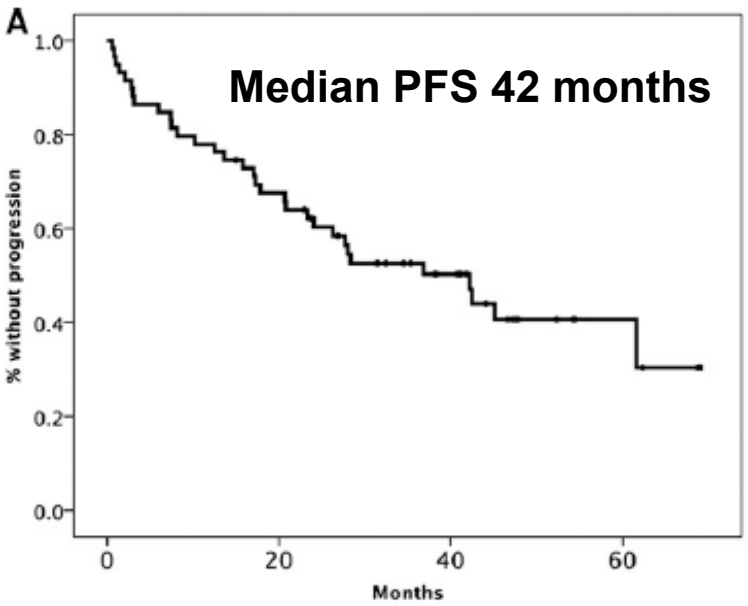
	Any grade, N (%)	Grade ≥3, N (%)
Neutropenia	10 (17)	(15)
Thrombocytopenia	10 (17)	(5)
Anemia	6 (10)	0
Peripheral neuropathy (sensory)	27 (46)	4 (7)
Neuropathic pain	(20)	1 (2)
Fever NOS	9 (15)	3 (5)
Respiratory symptoms NOS	9 (15)	6 (10)
Pneumonitis	3 (5)	3 (5)
Infections NOS	13 (22)	4 (7)
Diarrhea	14 (24)	2 (3)
Constipation	11 (19)	2 (3)
Fatigue	27 (46)	5 (9)
Nausea/vomiting	6 (10)	0
Hypotension	3 (5)	1 (2)
Weight loss	8 (14)	0
Renal (increased creatinine)	1 (2)	1 (2)
Cardiovascular NOS	1 (2)	1 (2)

Treon SP, et al, JCO 2009; 27 (23): 3830-3835; Dimopoulos et al, Blood 2014; 122: 3276-3282

Bortezomib, dexamethasone and rituximab (BDR): long-term results of a phase 2 study of the EMN

Median follow-up: 42 months

PFS



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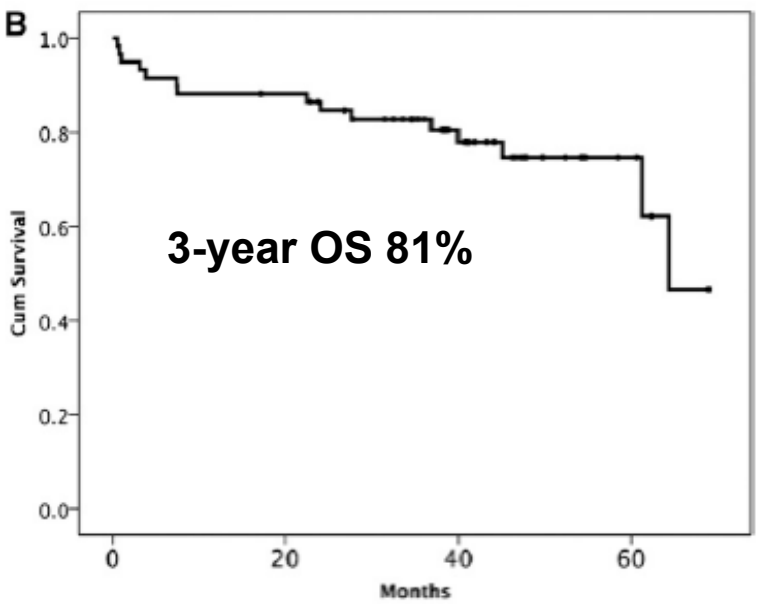


Dimopoulos et al, Blood 2013; 122: 3276-3282

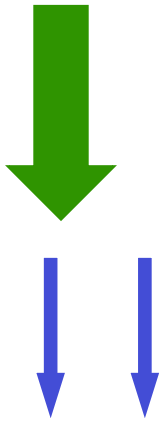
Phase II study with Bortezomib, Rituximab and Bendamustine (BRB) in patients with WM in first relapse

ID study: FIL BRB

EudraCT Number: 2013-005129-22

Rituximab 375 mg/m^2 i.v.

Bendamustine 90 mg/m^2 i.v.



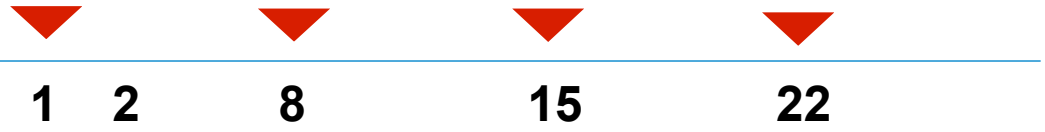
Primary objective

PFS (expected increase of 18-month PFS from 50%, reported with standard therapy, to 65%)

Sample size: 61 patients

Duration of the study: 4 years (2 years for recruitment and follow-up of 2 years after the enrollment of the last patient)

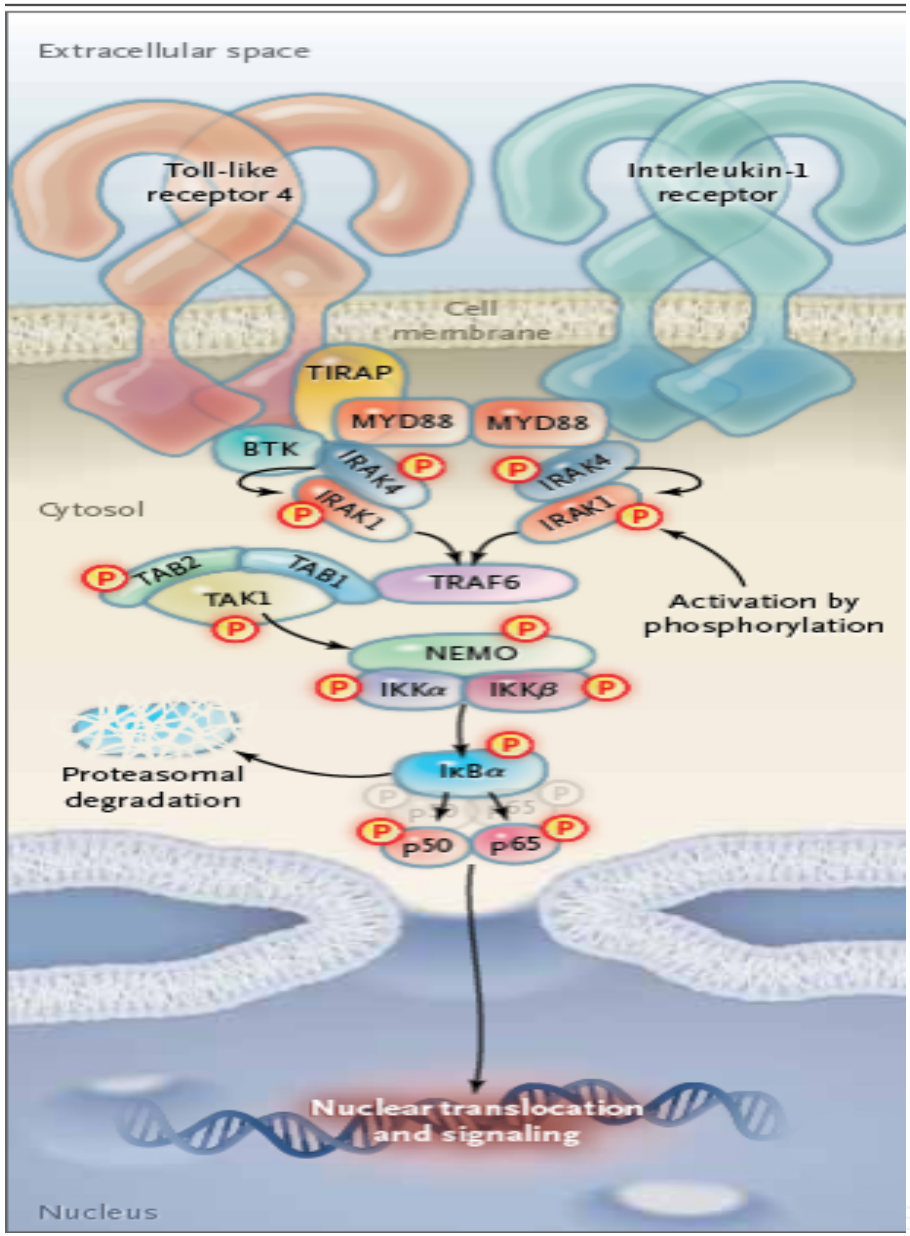
Bortezomib 1.3 mg/m^2 s.c.



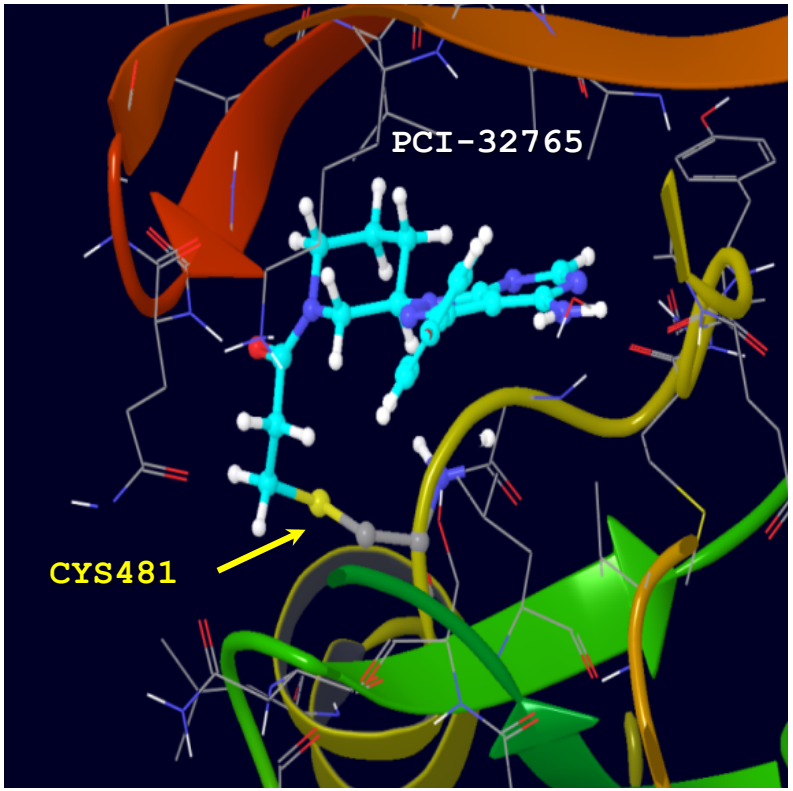
6 cycles (28 days)

Bruton's Tyrosine Kinase (BTK) inhibitors

BTK Inhibition with Ibrutinib



Ibrutinib forms a covalent bond with Cys481 of BTK



Ibrutinib in previously treated WM

Prospective multicenter phase II study

- Ibrutinib 420 mg p.o. until progression or unacceptable toxicity
- 63 R/R WM patients, median number of prior therapies: 2 (range: 1-9)
- 40% of patients were refractory to the most recent regimen

Median duration of therapy: 19.1 months (0.5-29)

Response:

VGPR: 10

PR: 36

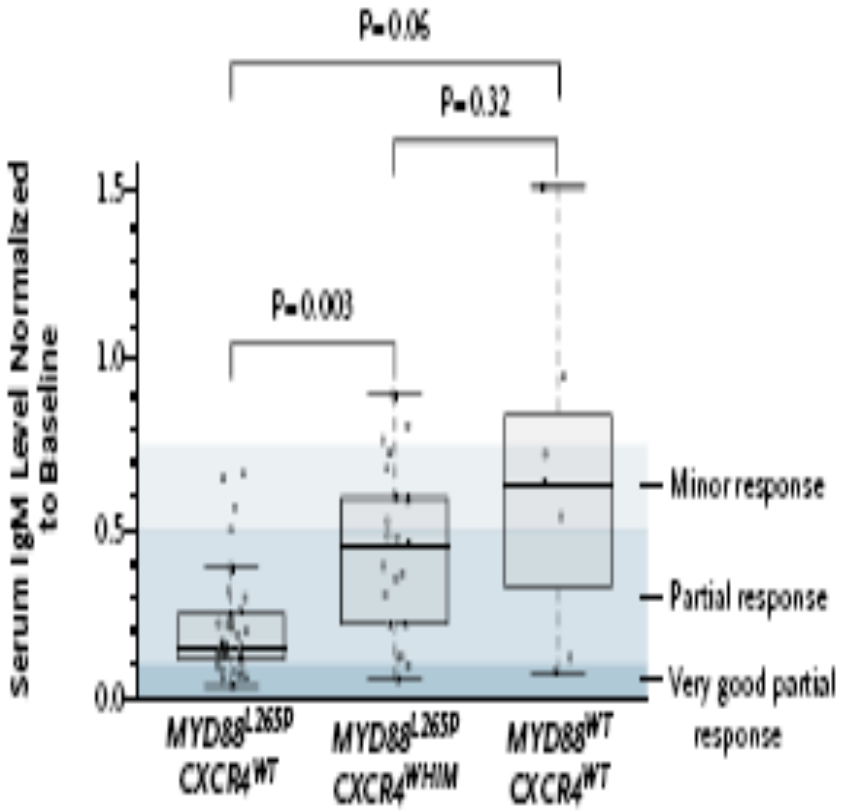
MR: 11

ORR: 90%

Major RR: 73%

Median time to first response: 4 weeks

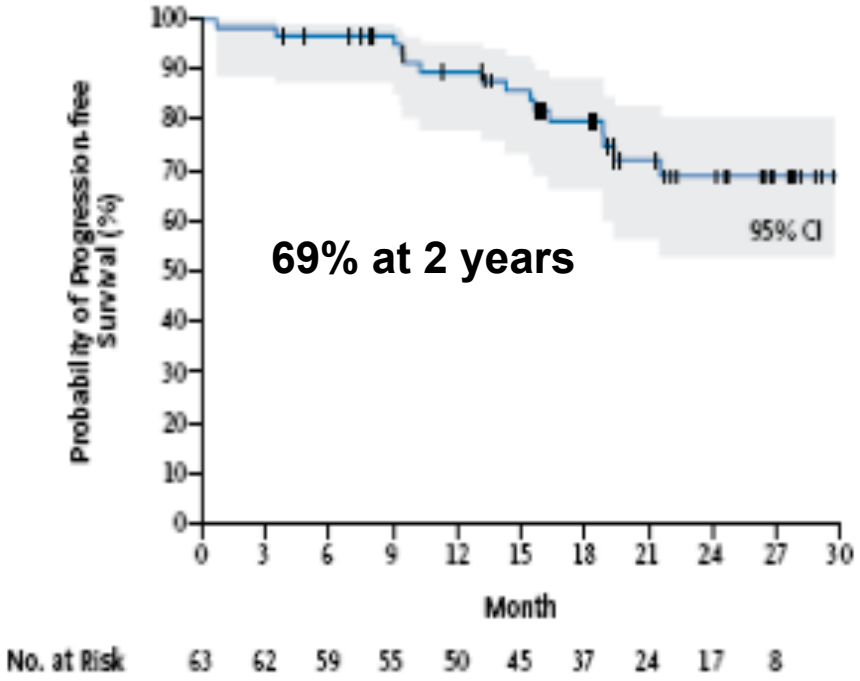
Effect of MYD88 and CXCR4 mutation status on response



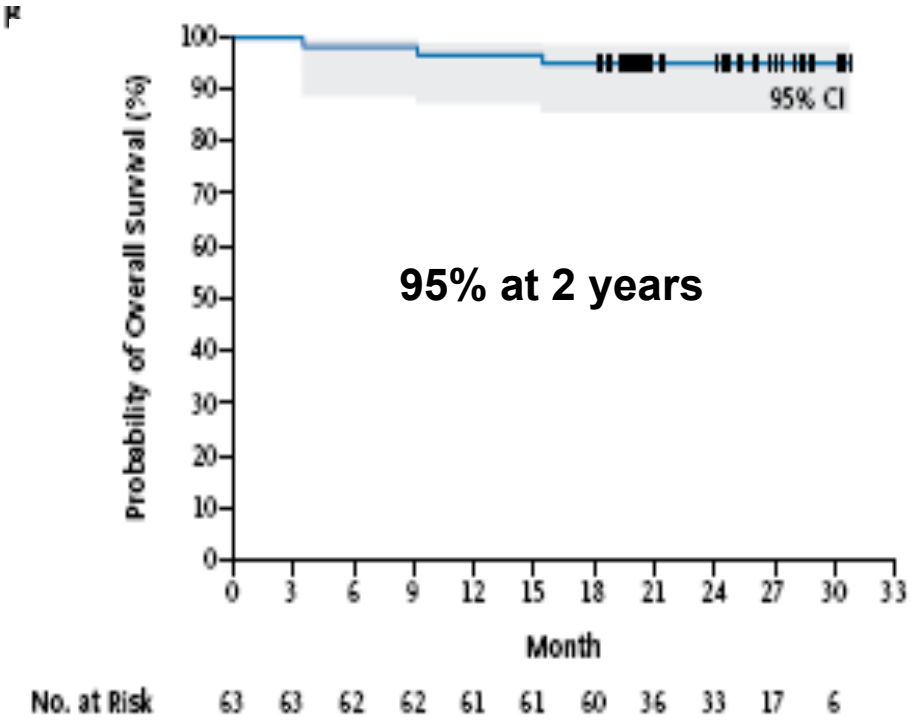
Treon et al, NEJM 2015; 372(15): 1430-1440

PFS and OS with Ibrutinib in WM

PFS



OS



Treon et al, NEJM 2015; 372(15): 1430-1440

Grade 3-4 adverse events associated with Ibrutinib

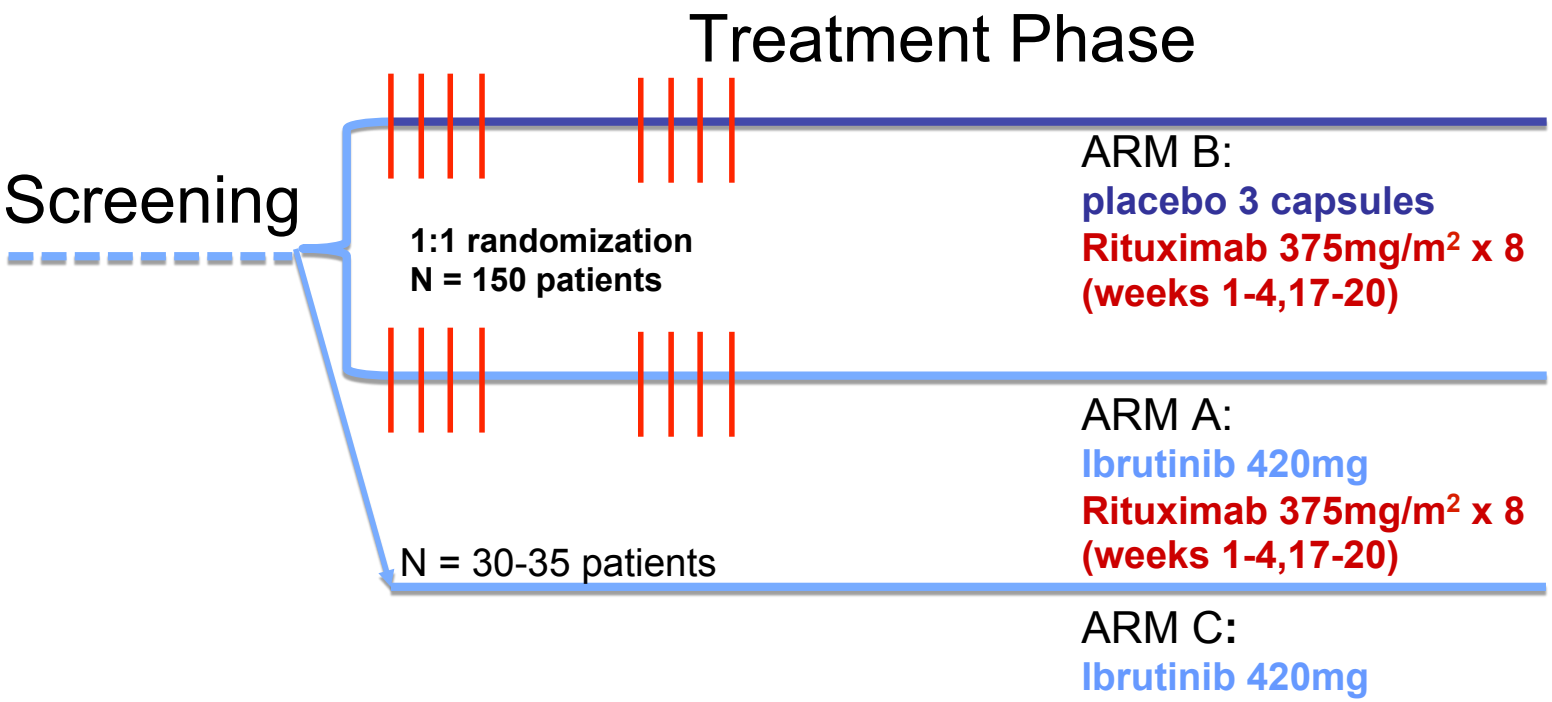
Event or abnormality	Grade 3 (% of pts)	Grade 4 (% of pts)
Neutropenia	10%	5%
Thrombocytopenia	10%	3%
Anemia	2%	-
Febrile Neutropenia	-	2%
Gastrointestinal disorders	-	-
Atrial fibrillation	-	2%
Infections	10%	-
Post-procedural hemorragic complications	2%	-
Syncope	2%	-

Gastrointestinal disorders in 16% pts, all grade 2 AEs

Treon et al, NEJM 2015; 372(15): 1430-1440

iNNOVATE Study

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with WM

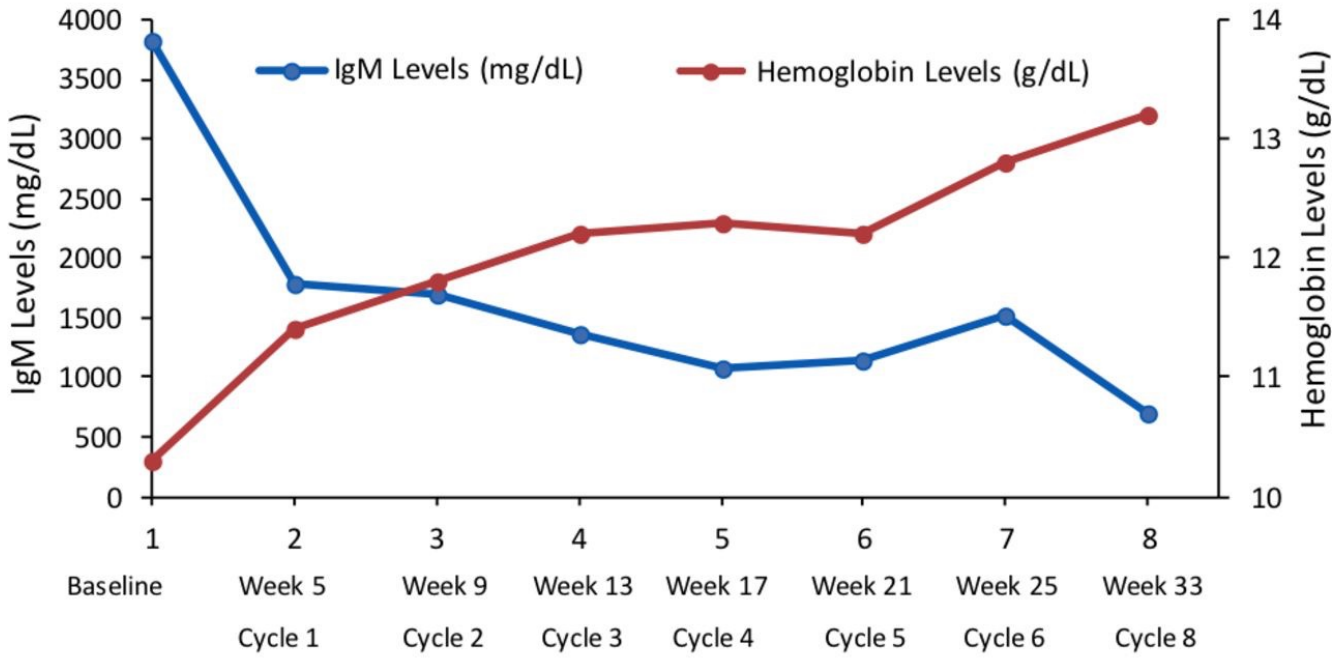


ARM C: To allow treatment of subjects considered refractory to prior Rituximab (relapse within 12 months or failure to achieve minimal response)

Ibrutinib in Rituximab-Refractory Patients with WM: Initial Results from an International, Multicenter, Open-Label Phase 3 Substudy

- 31 patients, all Rituximab refractory, median n. of prior therapies: 4 (1-8)
- Median FU 7.7 months
- ORR 84% (MRR 65%)

Figure. Median hemoglobin and IgM levels during early follow-up



Dimopoulos MA et al, ASH 2015

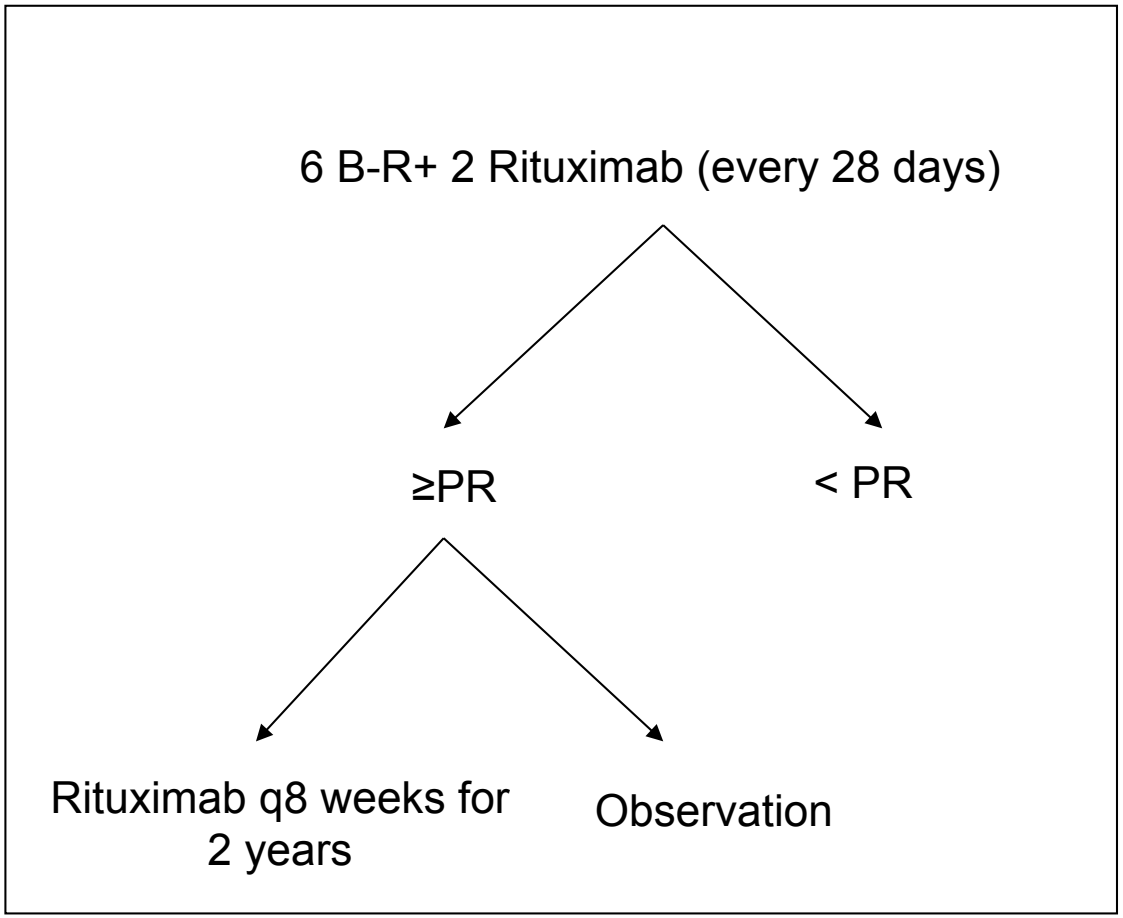
Role of maintenance in WM

Bendamustine-Rituximab Induction Followed by Observation or Rituximab Maintenance: Prospective, Randomized, Multicenter Study (StiL NHL 7-2008-MAINTAIN)

- Patients:
  - SLL
  - MZL
  - WM
  - MCL
- Primary endpoint: PFS

162 pts with WM enrolled
116 pts evaluable for response
90 randomized

ORR 86%
No results on maintenance



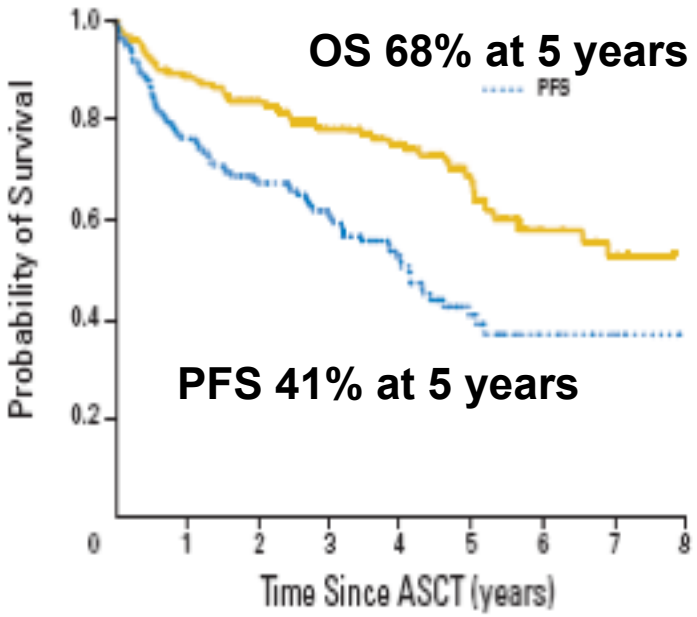
Rummel et al, 8° IWWM, London 13-17 August 2014

Role of transplant in WM

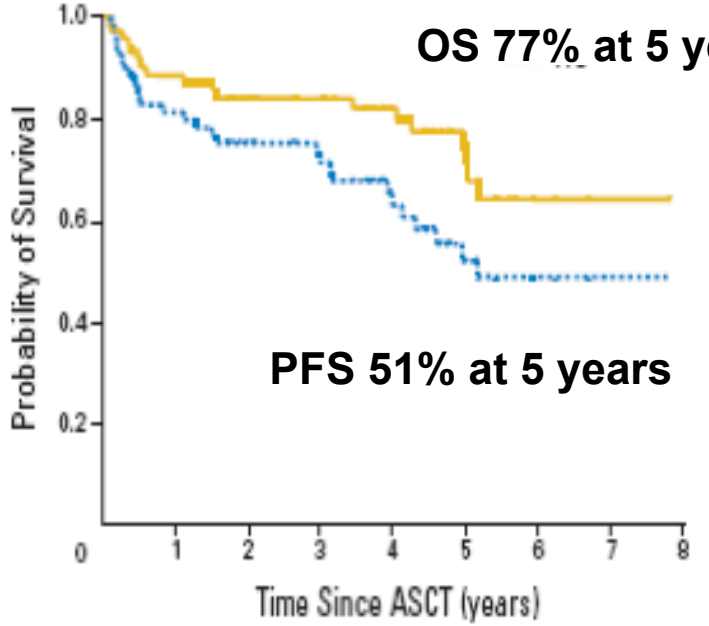
Autologous transplantion in WM

EBMT 1991-2005

All patients (N=158)



Patients in first PR/VGPR (N=69)



Adverse prognostic factors for PFS: 3 or more prior lines of therapy (P=.001)
refractory disease at ASCT (P <.001)

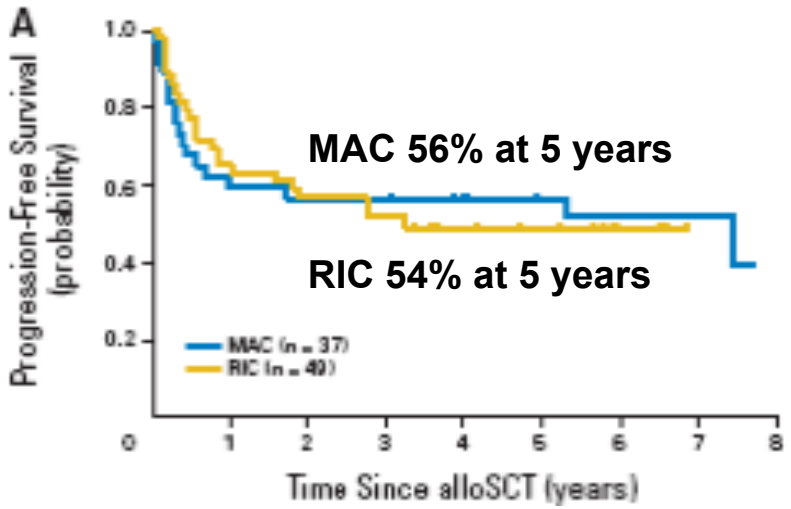
Consider as salvage therapy in younger patients with chemosensitive disease

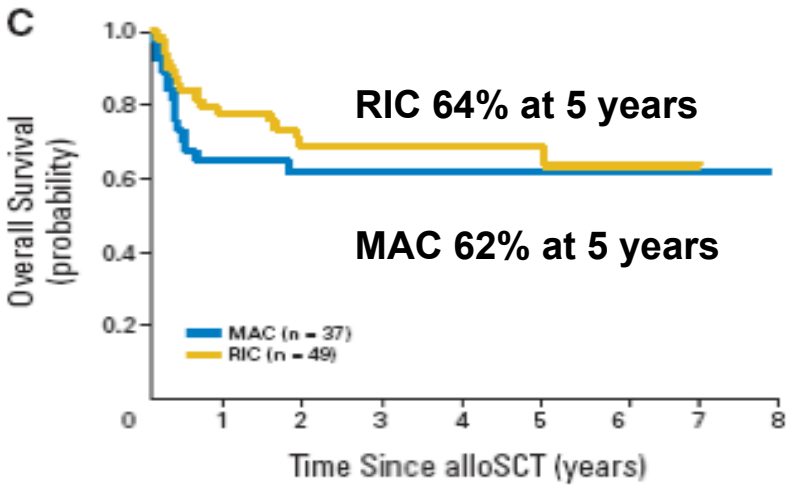
Kiriakou et al, JCO 2010; 28(13): 2227-2232

Allogeneic transplantion in WM

EBMT 1998-2005

- N=86
- Median age 49 years (23-64)
- Conditioning
  - Myeloablative (MA) n=37
  - RIC n=49
- 47 pts received ≥ 3 lines
- 8 pts failed prior ASCT
- 69% had chemosensitive disease
- Non-relapse mortality
  - MAC 33%
  - RIC 23%





Not recommended outside clinical trials

Kyriakou et al, JCO 2010; 28(33): 4926-4934

Conclusions and future directions

- Immunochemotherapy is currently the standard frontline treatment for WM, but the paucity of randomized trials does not allow the identification of the best regimen
- Type of immuno-chemotherapy depends on characteristics of patient (e.g. age, comorbidities, PS, candidacy to high dose therapy) and disease (e.g. cytopenias, neuropathy, hyperviscosity, bulky disease)
- Maintenance currently not indicated in the clinical practice
- ASCT may be considered in younger patients with chemosensitive relapse
- Novel drugs as single agents are associated with high ORR, but low CRR
- Combination of novel agents with chemotherapy and/or monoclonal antibodies will probably increase the quality and duration of response
- Integration of clinical characteristics with novel biomarkers may improve patient stratification and lead to the development of tailored treatment options

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