Onkopedia Webinar, 17. November 2023

Morbus Waldenström

Christian Buske, M.D.

Comprehensive Cancer Center Ulm
Tumorzentrum Alb-Allgäu-Bodensee

UNIVERSITÄTS KLINIKUM ulm

Offenlegungen

Research Support/P.I.	Roche, Janssen, Bayer, MSD, Amgen, Celltrion
Honoraria	Roche, Pfizer, Janssen, Hexal, Celltrion, AbbVie, Novartis, Bayer, Morphosys, Regeneron, Beigene

Agenda

1. **Wie alles begann…, und wo stehen wir heute**
2. **Der Morbus Waldentström – eine komplexe Erkrankung**
   - Definition der Erkrankung
   - molekulare Alterationen: Diagnostik und klinische Implikatonen
   - Definitionen Ansprechen
3. **Behandlung**
   - Immunchemotherapie
   - Stellenwert Erhaltungstherapie
   - Ibrutinib
   - Zanubrutinib
4. **Zukünftige Entwicklungen**
5. **Fallbeispiel**

Eine Frage vorab…

Wieviele Waldenström Patienten sehen Sie im *halben Jahr*?

1. keinen
2. 1-2
3. < 5
4. > 10

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As it started……

Acta Medica Scandinavica. Vol. CXVII, fasc. III—IV, 1944.

(From Med. Clin. Akad. Hospital, Upsala (Sweden). Chief: Prof. G. Bergmark).

Incipient myelomatosis or «essential« hyperglobulinemia with fibrinogenopenia — a new syndrome?

By

JAN WALDENSTRÖM.

Submitted for publication September 2, 1943.

The real nature of myelomatosis.

As it started……

The real nature of myelomatosis.

The title of this paper may at first seem somewhat surprising. The myeloma has of old had a reputation as a well defined clinical entity. With the aid of the typical changes on the X-ray film and guided by the examination of the cells from a sternal puncture the diagnosis should therefore be easy and there ought not to be found any serious diagnostical troubles. In the following I am going to give a description of two cases, who have several symptoms suggesting myelomatosis but also show decided differences. They are very much alike even as regards details in the chemistry of the blood proteins and it seems probable according to my opinion, that they suffer from the same malady. A third case very much resembles

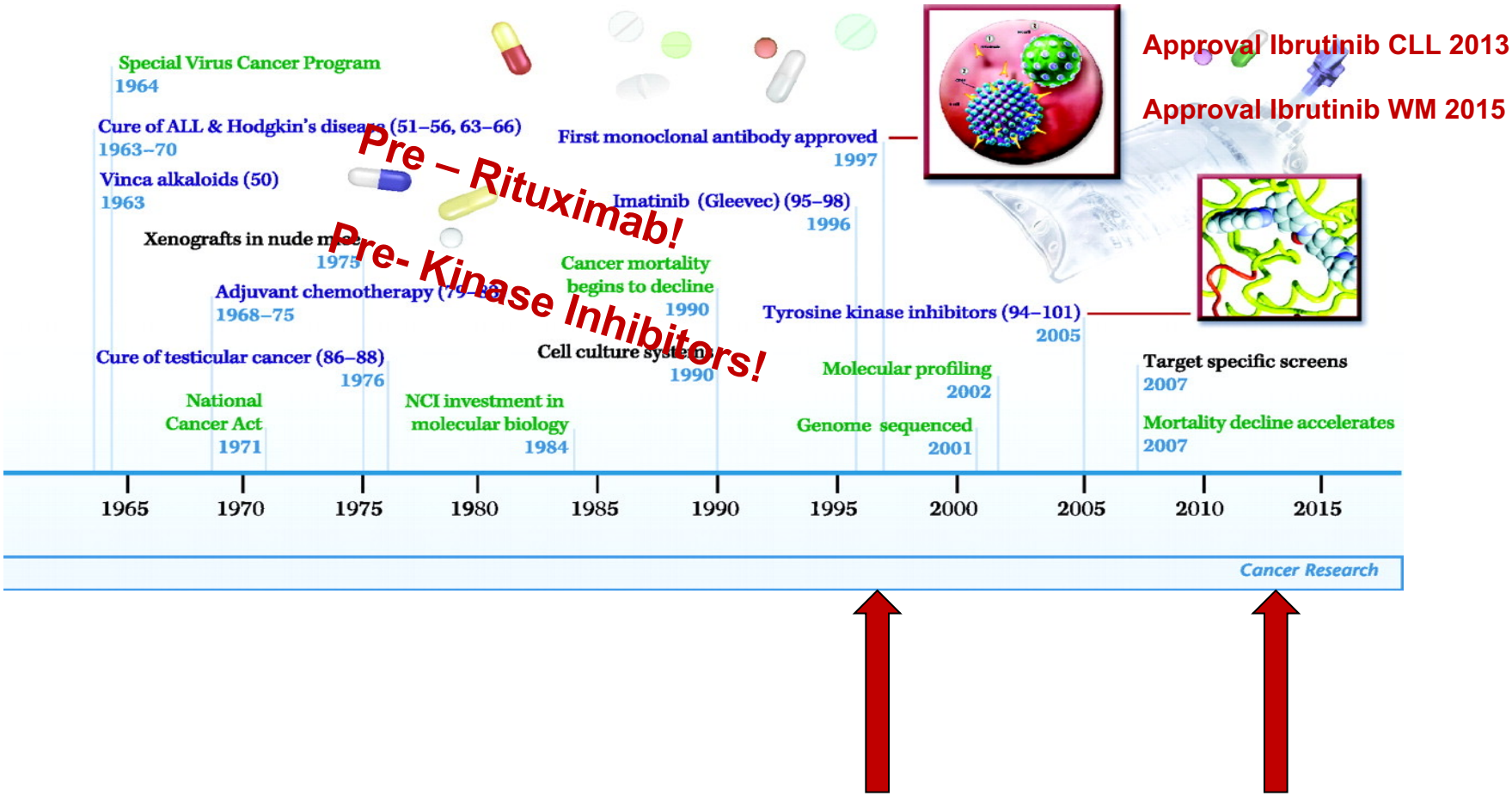
Discussion.

What may be regarded as the explanation of all these curious data? Why are these persons carriers of hitherto not described globulin fractions with giant molecules? If these are compared with other known proteins with a very high molecular weight we find, that their size most closely resembles some of the human antibodies e. g. against pneumonia (the specific pneumococcal anti-

May it be allowed to put forward another hypothesis as a possible explanation. We know from the experiments with plant viruses of different kinds, that the inoculation of an organism with a special virus may change a great part of the protein in the host plant into virus protein. This is e. g. a well established fact as regards tobacco mosaic virus. If a patient is »infected» with some virus protein it may be possible, that his own serum protein is transformed to virus protein instead. The hypothesis may possibly be

Pillars of lymphoma treatment

Key advances in the history of cancer chemotherapy



DeVita V T , and Chu E Cancer Res 2008;68:8643-8653

Where are we now……?

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The real nature of myelomatosis.

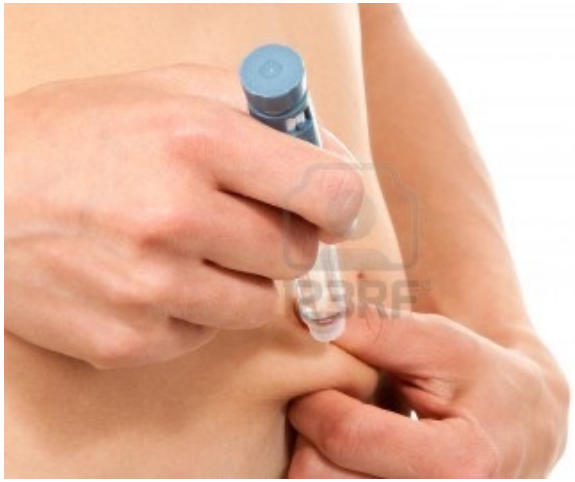
Pillars of lymphoma treatment

*) oft „Kinaseinhibitoren“

Trends: away from chemotherapy

Trends: away from ‘i.v.’ – therapy’

s.c. !



Oral Therapy!

The New World……..

Targeted therapies

Agenda

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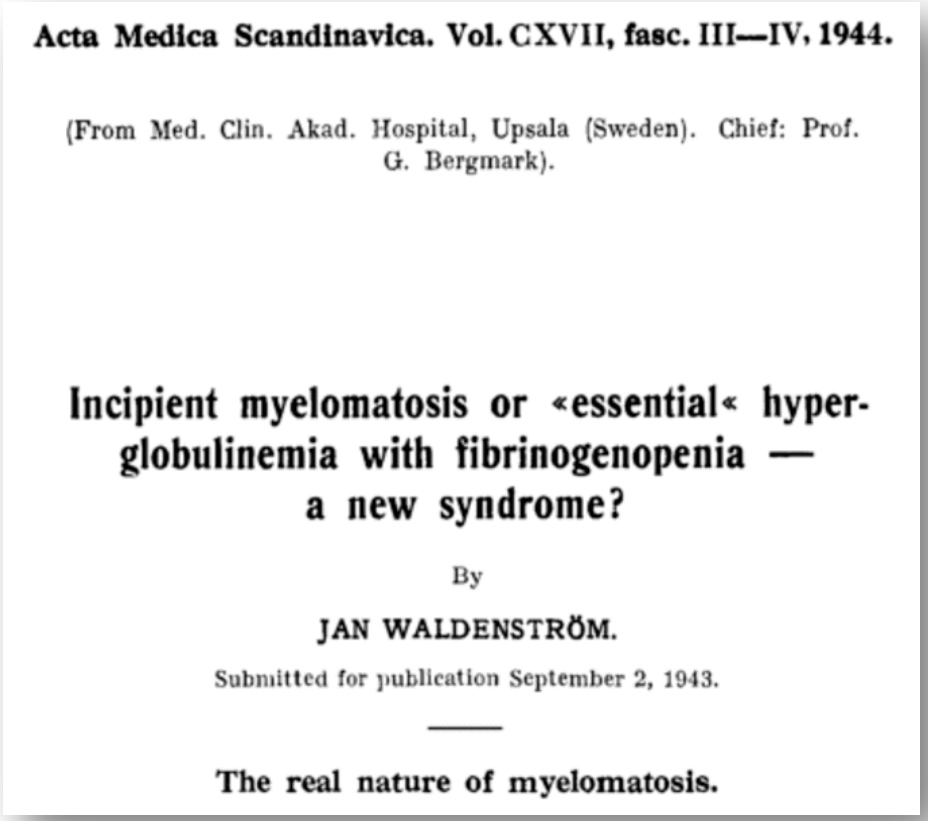
5. **Fallbeispiel**

One step back…….



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Submitted for publication September 2, 1943.

The real nature of myelomatosis.

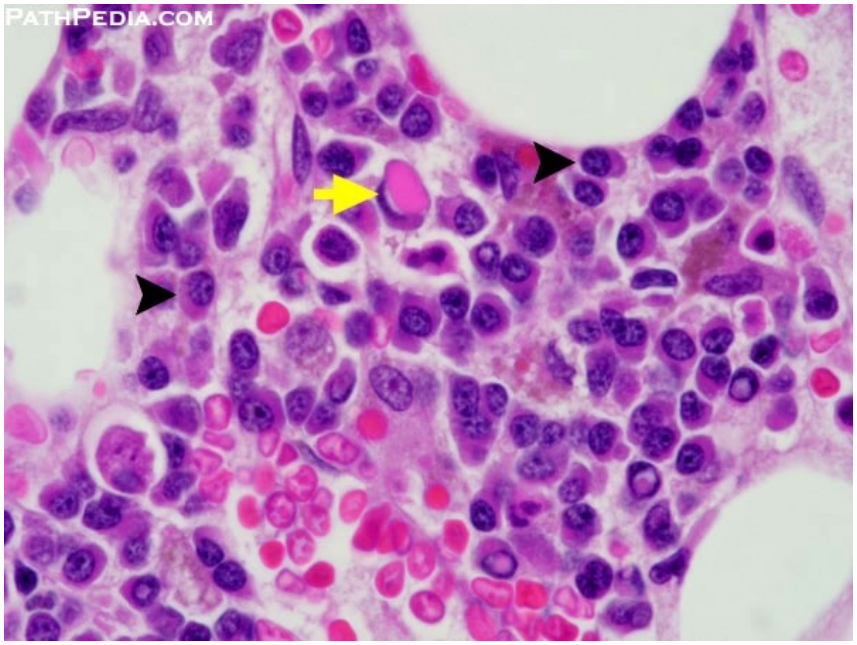
What do we know today?

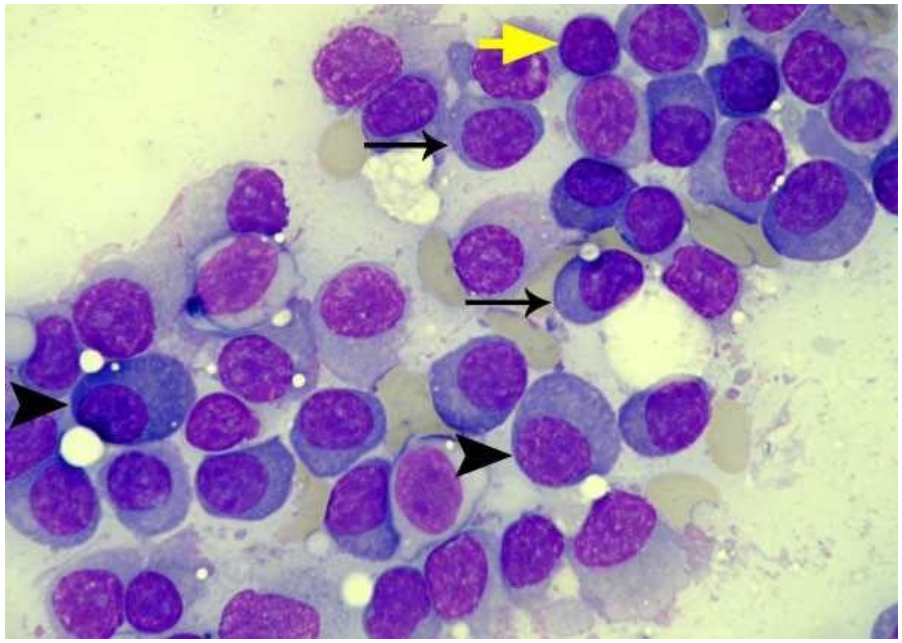
Waldenström's macroglobulinemia
Consensus Panel Recommendation – Diagnosis

"The clinicopathological definition of WM should be confined to those patients with
-- lymphoplasmacytic lymphoma and
-- bone marrow infiltration
-- IgM monoclonal gammopathy.

A diagnosis of WM can be made irrespective of the IgM concentration"

WM consists of two cellular populations!

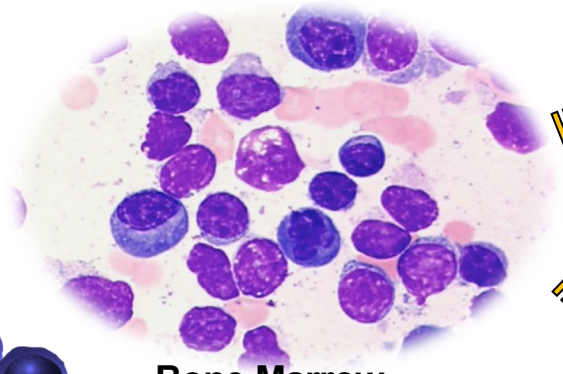




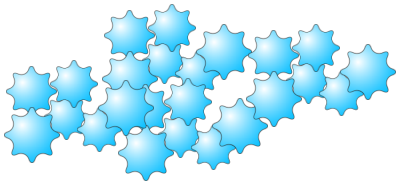
CD20^{+} lymphoid population <u>and</u> CD20^{-} CD38^{+} plasmacytic population!

A clinically heterogenous disease!

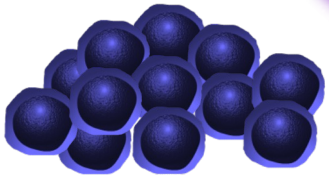
↓Hb>>> ↓PLT> ↓WBC



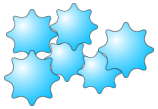
Bone Marrow



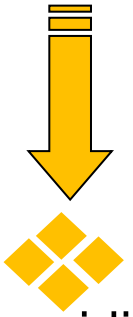
Hyperviscosity Syndrome:
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP



Adenopathy,
splenomegaly
≤20% at diagnosis;
50-60% at relapse.



IgM Neuropathy (22%)
Cryoglobulinemia (10%)
Cold Agglutinemia (5%)



Hepcidin
↓Fe Anemia

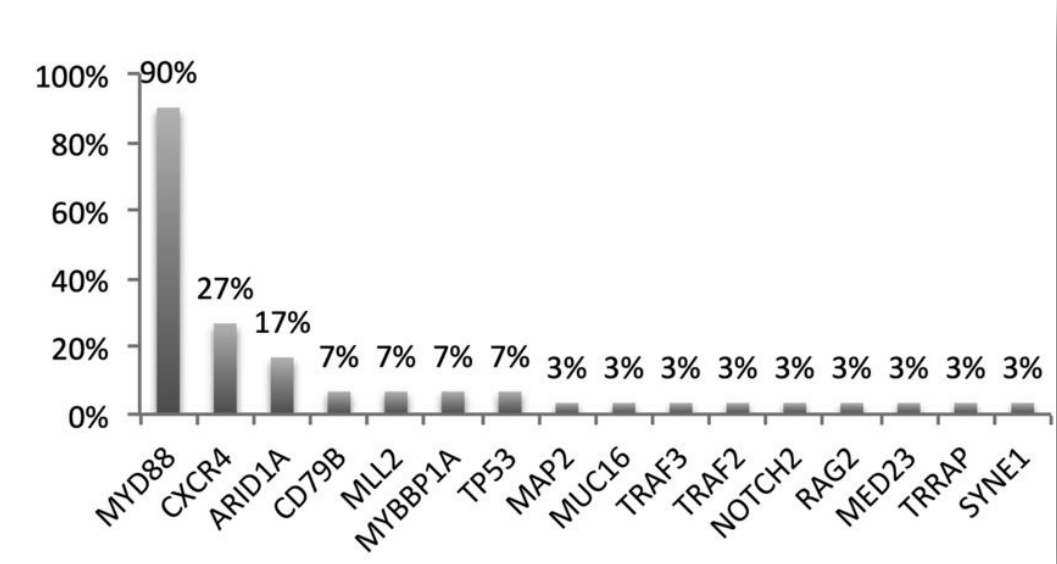
Treon S., Hematol Oncol. 2013; 31:76-80.

A molecularly heterogenous disease!

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]



Hunter et al., Blood. 2014 Mar 13;123(11):1637-46

MYD88 Mutation

Treon et al

- Whole Genome Seq. of 30 WM patients, validated by Sanger Seq.
- Sanger Seq. identified MYD88 $_{L265P}$ in 90% of patients (27/30 WM samples)
- 22/26 patients were heterozygous for MYD88 $_{L265P}$
- 9/9 patients with familial WM carried mutant MYD88 $_{L265P}$
- 2/21 patients with IgM-MGUS had MYD88 $_{L265P}$ expression

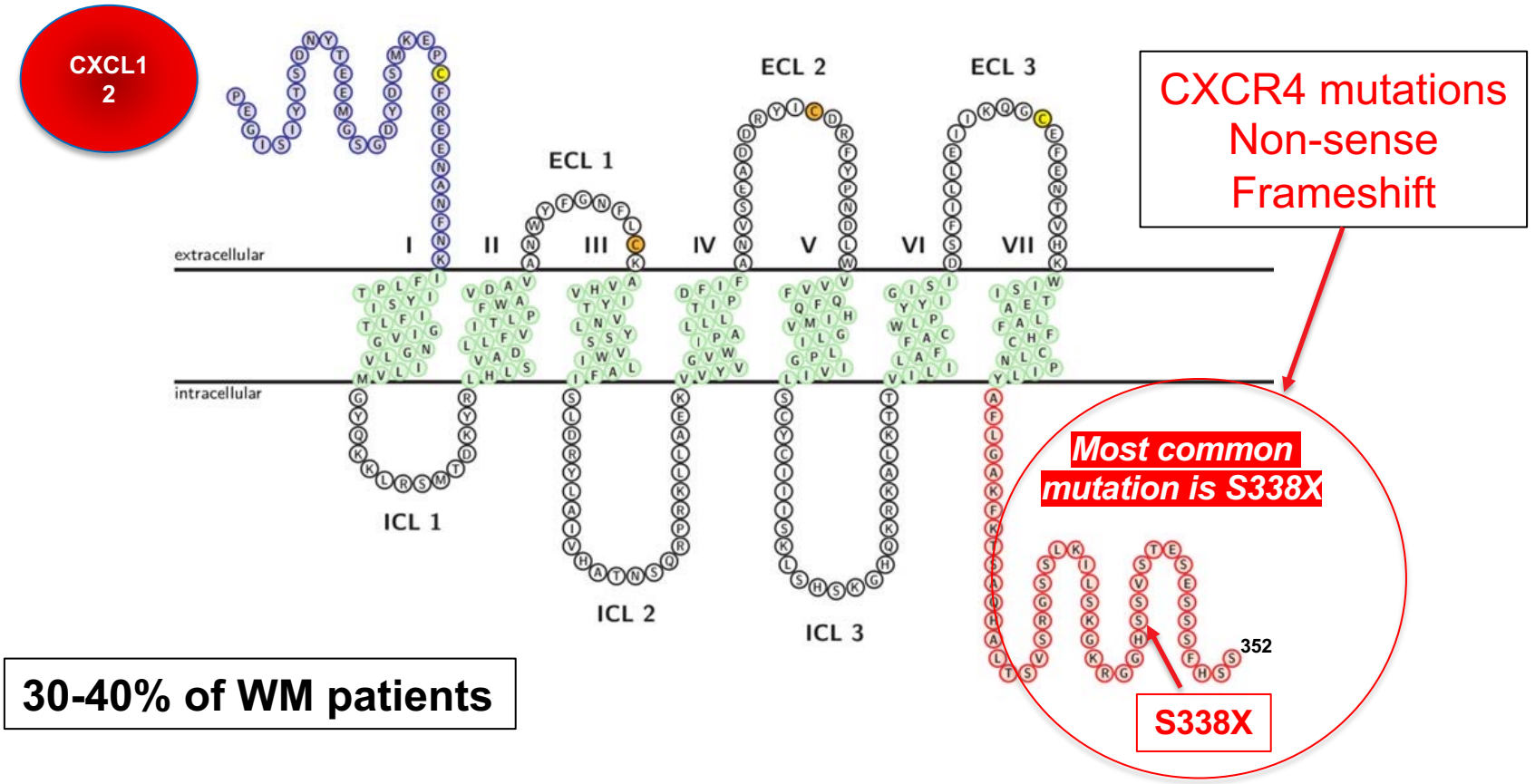
3-D structure of MY88 TIR domain

→ 95-97 % of all patients positive!

Base pair mismatch Leuc → Pro at position 265 in MYD88 coding region

Treon et al NEJM 2012; 367(9):826-33; Ngo et al Nature 2011; 470(7332):115-9

CXCR4 receptor C-terminal domain (WHIM-like) mutations are common in WM



30-40% of WM patients

Adapted from Kahler et al, AIMS Biophysics, 2016; 3(2): 211-231
Hunter et al, Blood 2014; 123 (11): 1637–1646; Poulain et al, Clin Cancer Res. 2016; 22(6):1480-8

Waldenström's Macroglobulinemia: WM is a heterogenous disease!

Molecular Markers

Any Implications?

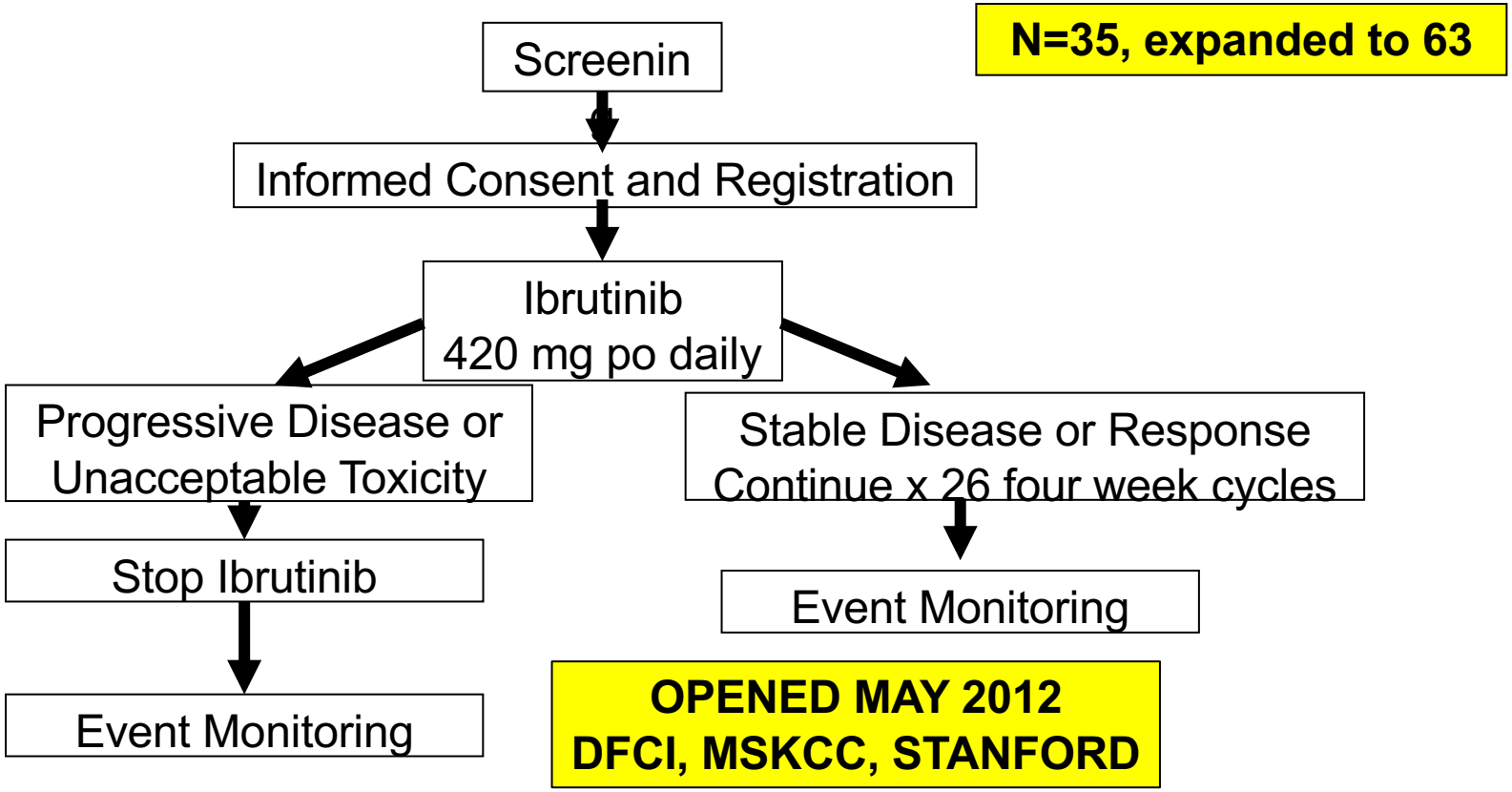
Waldenström's Macroglobulinemia: WM is a heterogenous disease!

Molecular Markers

Three groups

MYD88/ CXCR4	OR	VGPR/PR
+/WT		
+/+		
WT/WT		

Schema for Multicenter Phase II Study of Ibrutinib in Relapsed/Refractory WM



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

Clinical responses to ibrutinib: Median of 9 (range 1-18) Cycles

	(N= 63)	(%)
VGPR	10	15.9
PR	36	57
MR	11	17.5

Response criteria adapted from 3rd International Workshop on WM (Treon et al, BJH 2011)

ORR: 90.5% Major RR (≥ PR): 73%

Treon et al, NEJM 2015; 372(15):1430-40

Waldenström's Macroglobulinemia

What about Ibrutinib?

What can we achieve (and what not) with Ibrutinib?

Challenges!

Waldenström's Macroglobulinemia: WM is a heterogenous disease!

Molecular Markers

Three groups

MYD88/ CXCR4	OR	VGPR/PR
+/WT		
+/+		
WT/WT		

Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations

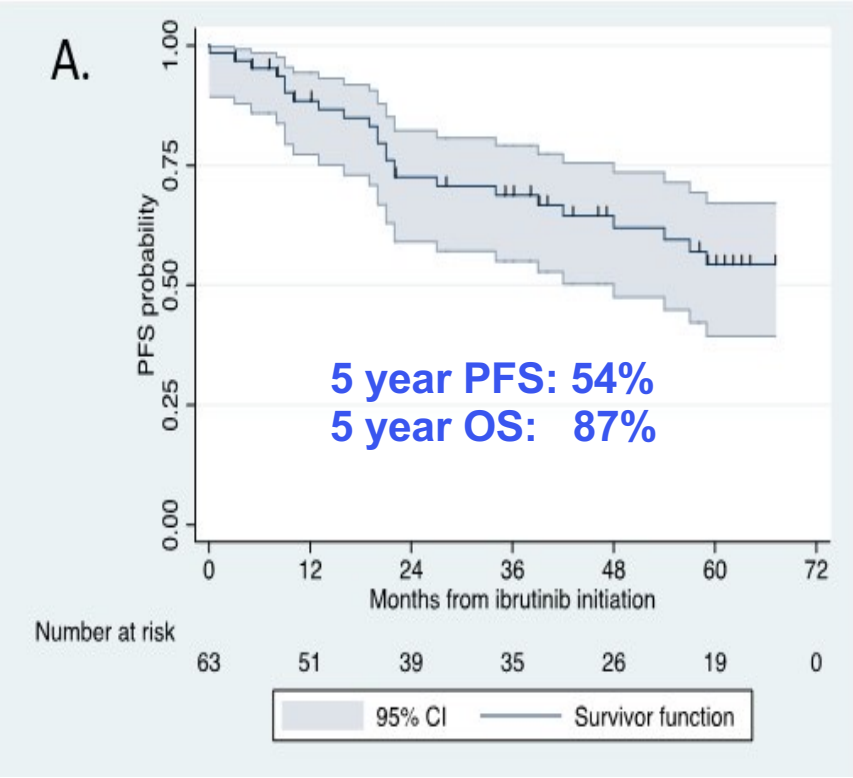
	$MYD88^{MUT}$ $CXCR4^{WT}$	$MYD88^{MUT}$ $CXCR4^{WHIM}$	$MYD88^{WT}$ $CXCR4^{WT}$	p-value
N=	36	21	5	
Overall RR	100%	85.7%	60%	<0.01
Major RR	91.7%	61.9%	0%	<0.01

2 patients subsequently found to have other MYD88 mutations not picked up by AS-PCR

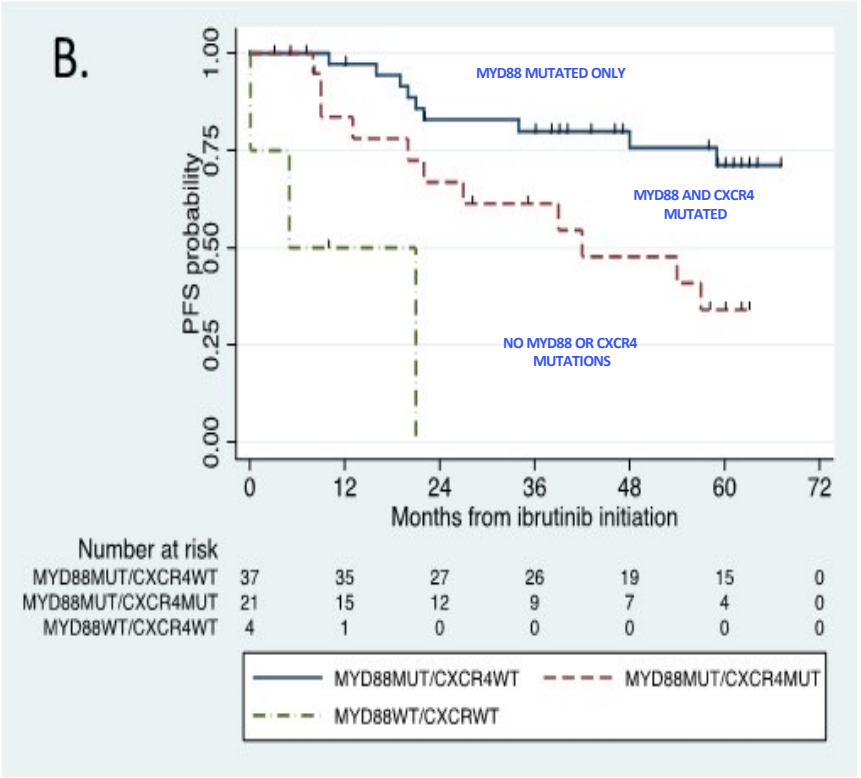
Treon et al, N Engl J Med. 2015; 372(15):1430-40; NEJM 2015; Letter, August 6, 2015.

Ibrutinib in previously treated WM: Updated PFS

All patients



MYD88 and CXCR4 Status



Treon et al, ICML 2019; abstract 135 (oral presentation)

DANA-FARBER CANCER INSTITUTE

Long-Term Follow-up of Previously Treated Patients Who Received Ibrutinib for Symptomatic Waldenström's Macroglobulinemia: Update of Pivotal Clinical Trial

Steven P. Treon, Kirsten Meid, Joshua Gustine, Kurt S. Bantilan, Toni Dubeau, Patricia Severns, Guang Yang, Lian Xu, Christopher Patterson, Irene M. Ghobrial, Jacob Laubach, Zachary R. Hunter, Jorge J. Castillo, Maria L. Palomba, and Ranjana H. Advani. Dana-Farber Cancer Institute, Boston, MA; Stanford Medical Center, Palo Alto, CA; Memorial Sloan Kettering, New York, NY.

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

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

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

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

Median time on ibrutinib 46 months (0.5 – 60)

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

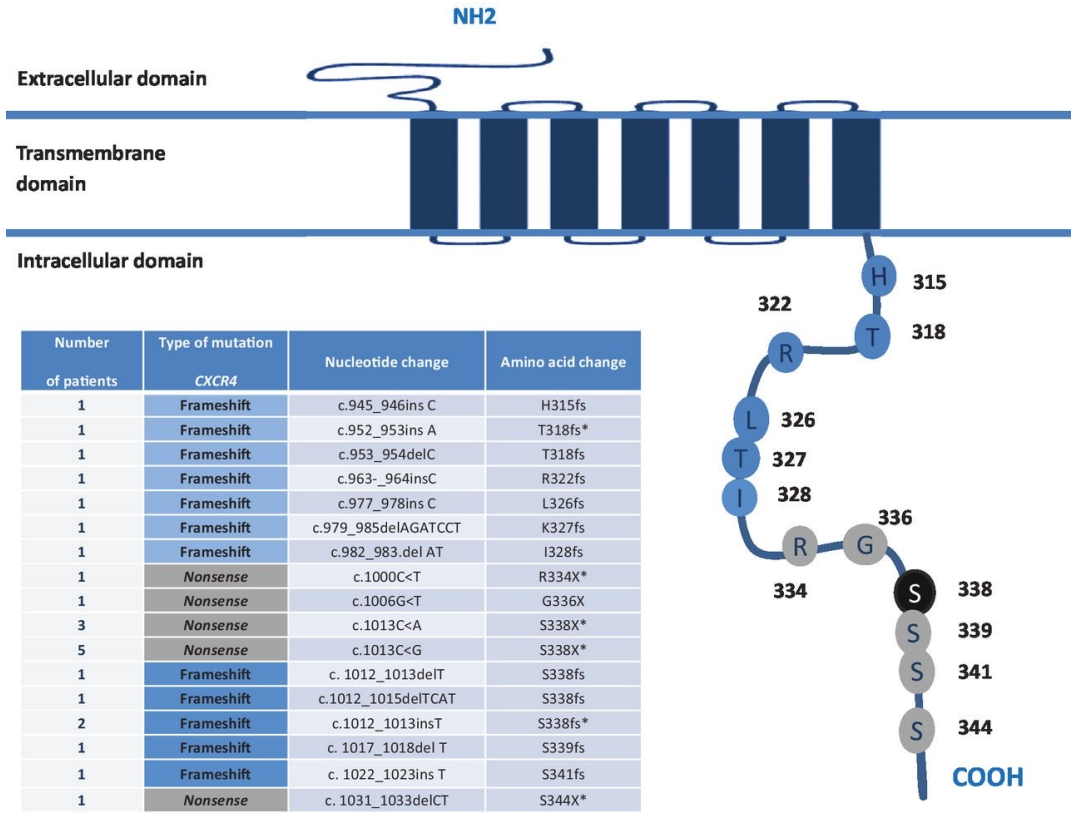
Waldenström's Macroglobulinemia: WM is a heterogenous disease!

Molecular Markers

MYD88 and CXCR4 mutational testing in all patients?

The *CXCR4* mutational landscape is complex

Over 40 different mutations described

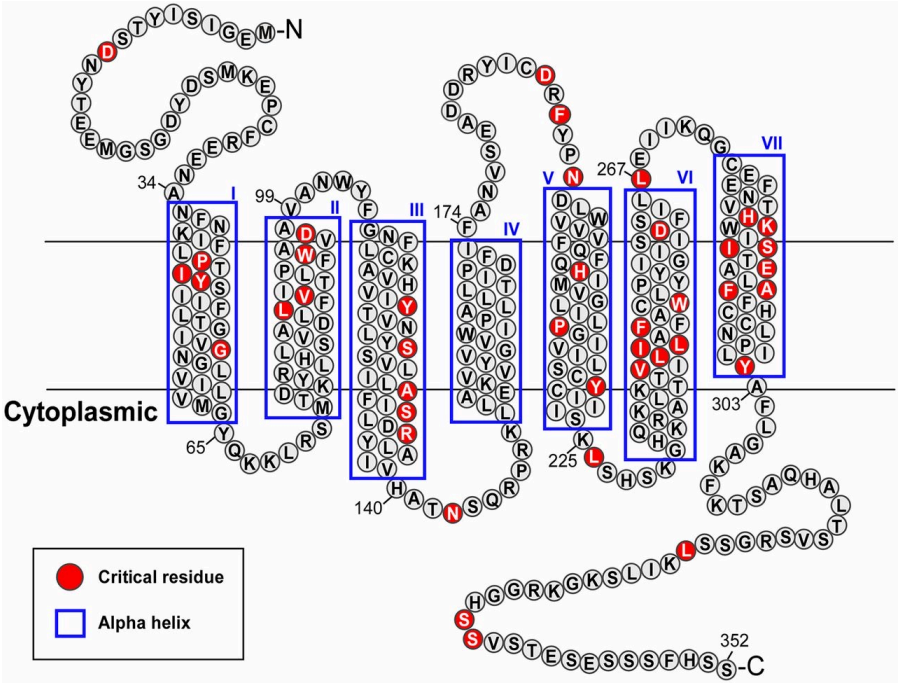


Number of patients	Type of mutation *CXCR4*	Nucleotide change	Amino acid change
1	Frameshift	c.945_946ins C	H315fs
1	Frameshift	c.952_953ins A	T318fs*
1	Frameshift	c.953_954delC	T318fs
1	Frameshift	c.963-_964insC	R322fs
1	Frameshift	c.977_978ins C	L326fs
1	Frameshift	c.979_985delAGATCCT	K327fs
1	Frameshift	c.982_983.del AT	I328fs
1	*Nonsense*	c.1000C<T	R334X*
1	*Nonsense*	c.1006G<T	G336X
3	*Nonsense*	c.1013C<A	S338X*
5	*Nonsense*	c.1013C<G	S338X*
1	Frameshift	c. 1012_1013delT	S338fs
1	Frameshift	c.1012_1015delTCAT	S338fs
2	Frameshift	c.1012_1013insT	S338fs*
1	Frameshift	c. 1017_1018del T	S339fs
1	Frameshift	c. 1022_1023ins T	S341fs
1	*Nonsense*	c. 1031_1033delCT	S344X*

CXCR4, C-X-C chemokine receptor type 4 gene; WM, Waldenström's macroglobulinemia.
Poulain S *et al. Clin Cancer Res* 2016; 22 (6): 1480–1488.

CXCR4 mutations are difficult to interpret

- The biological implications of many *CXCR4* mutations are unknown
- Frameshift versus Nonsense – different clinical impact?



CXCR4, C-X-C chemokine receptor type 4 gene.
Wescott MP *et al. Proc Natl Acad Sci U S A* 2016; 113 (35): 9928–9933.

Mutational testing can be technically challenging

- The optimal initial assay for *MYD88* is AS-PCR on bone marrow aspirates
  - Sanger sequencing or targeted NGS can be used to evaluate for non-L265P *MYD88* mutations
- Selection of CD19+ cells can improve detection rates but is not routinely performed
- Mutated *CXCR4* is subclonal, with highly variable clonality averaging approximately 35%
  - False negative results can occur
  - Ultra-deep NGS or Sanger sequencing may be required

AS-PCR, allele-specific polymerase chain reaction; CXCR4, C-X-C chemokine receptor type 4 gene; MYD88, myeloid differentiation primary response 88 gene; NGS, next-generation sequencing.
Treon SP *et al. J Clin Oncol* 2020; 38 (11): 1198–1208.

Standardization of testing and analysis must come first

- Standard protocols are needed to support clinicians and institutions testing for *MYD88* and *CXCR4* mutations, to avoid mistakes and promote continuity

CXCR4, C-X-C chemokine receptor type 4 gene; MYD88, myeloid differentiation primary response 88 gene

Contents lists available at ScienceDirect

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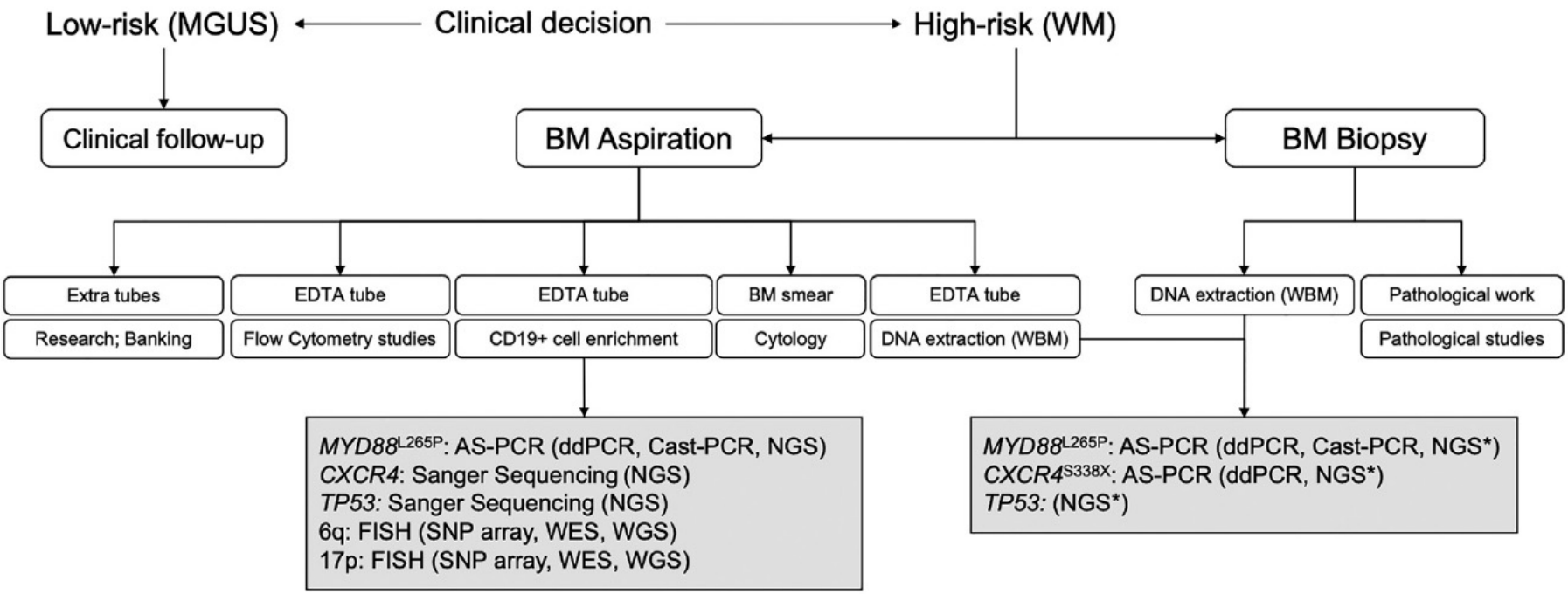
journal homepage: www.elsevier.com/locate/seminhematol

Report of Consensus Panel 3 from the 11th International workshop on Waldenström's Macroglobulinemia: Recommendations for molecular diagnosis in Waldenström's Macroglobulinemia

Ramón Garcia-Sanz[a,*], Marzia Varettoni[b], Cristina Jiménez[a], Simone Ferrero[c], Stephanie Poulain[d], Jesus F. San-Miguel[e], Maria L. Guerrera[f], Daniela Drandi[c], Tina Bagratuni[g], Mary McMaster[h], Aldo M. Roccaro[i], Damien Roos-Weil[j], Merav Leiba[k], Yong Li[l], Luigi Qiu[m], Jian Hou[n], C. Fernandez De Larrea[o], Jorge J. Castillo[f], M. Dimopoulos[g], R.G. Owen[p,q], S.P. Treon[f], Z.R. Hunter[f]



2022

Waldenström's Macroglobulinemia: WM is a heterogenous disease!

Molecular Markers

MYD88 and CXCR4 mutational testing in all patients?

MYD88 yes
CXCR4 if possible yes

Groves et al Cancer 1998(82); Stone et al Haematologica 2011(95); Koshiol et al Arch Intern Med 2008(168); Owens et al Semin Oncol 2003(30)

Table I. Categorical response definitions.

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

*Sequential changes in IgM levels may be determined either by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry.

Waldenström's macroglobulinemia - an Update

What about response?

Different parameters important: IgM, BM, LN, Spleen etc

Owen et al., 2012 BJH

Report of consensus Panel 4 from the 11th International Workshop on Waldenstrom's macroglobulinemia on diagnostic and response criteria

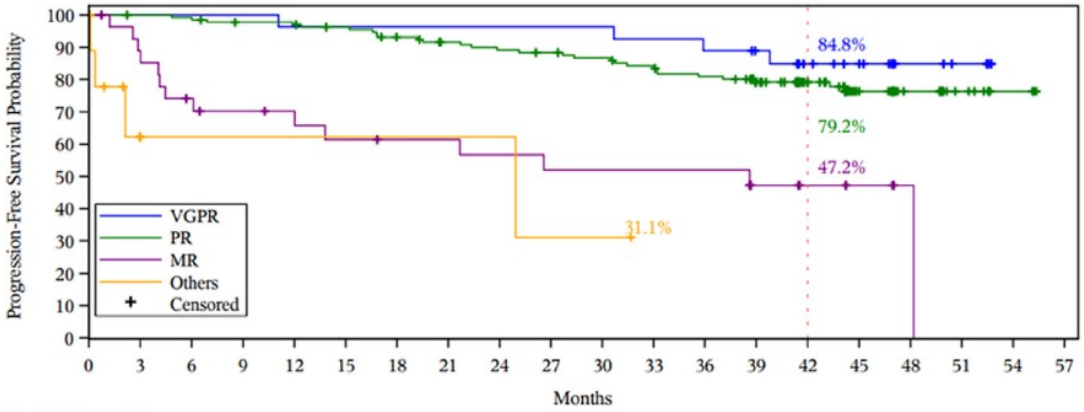
Steven P. Treon[a,*], Alessandra Tedeschi[b], Jesus San-Miguel[c], Ramon Garcia-Sanz[d], Kenneth C. Anderson[e], Eva Kimby[f], Monique C. Minnema[g], Giulia Benevolo[h], Lugui Qiu[i,j], Shuhui Yi[i,j], Evangelos Terpos[k], Constantine S. Tam[l], Jorge J. Castillo[a], Pierre Morel[m], Meletios Dimopoulos[k], Roger G. Owen[n]

Table 5
IWWM-11 response criteria (also referred to as simplified IWWM-6 response criteria) for assessment of disease response in Waldenstrom's macroglobulinemia.

		Serum Monoclonal IgM	Serum IgM Level	Bone Marrow Aspirate and Trephine Biopsy	Extramedullary disease
Complete response	CR	Absence of monoclonal IgM protein by SPEP and IFX.	Within normal range	Normal morphology; no evidence of LPL involvement.	Absence of extramedullary disease if present at baseline. See criteria for determination of resolution of extramedullary disease.*
Very good partial response	VGPR		≥90% reduction in serum IgM levels or within normal range		
Partial response	PR		≥50% to <90% reduction in serum IgM levels		
Minor response	MR		≥25% to <50% reduction in serum IgM levels		
Stable disease	SD		<25% reduction to <25% increase in serum IgM levels		
Progressive disease	PD		≥ 25% increase in serum IgM levels with a minimum increase of 500 mg/dL from nadir. Reconfirmation is required by 2 sequential (back-to-back) measurements if the serum IgM is being used to support PD. Demonstration of PD by imaging does not require re-confirmation.†,‡		Any new lesion (>1.5 cm in any axis) or unequivocal evidence of an increase by >50% in any axis to >1.5 cm in size of previously involved extramedullary disease sites from their nadir measurements. Any new lesion consistent with transformed disease.
Nonevaluable	NE		Suspected IgM flare or IgM rebound, absence of data or suspected error in data reporting§		

Comparison Standard vs Simplified Response Criteria

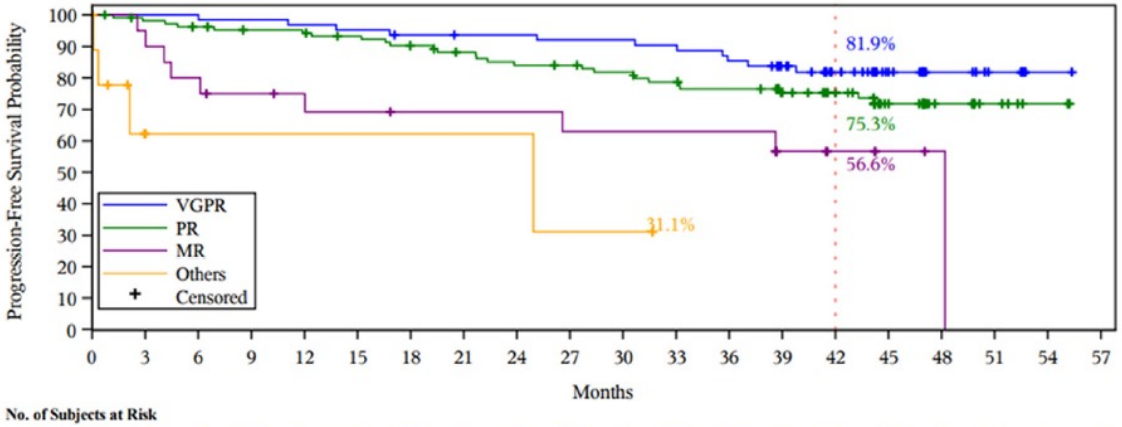
A. Standard IWWM-6



No. of Subjects at Risk

VGPR	27	27	27	27	26	26	26	26	26	26	26	25	24	22	17	14	7	5	0
PR	135	134	133	129	128	125	119	114	111	109	106	102	97	83	62	35	18	9	3	0
MR	28	24	19	17	16	14	13	13	12	11	11	11	11	7	5	3	1	0		
Others	11	3	2	2	2	2	2	2	2	1	1	0								

C. Simplified IWWM-6/New IWWM-11



No. of Subjects at Risk

VGPR	63	63	63	62	61	60	58	57	57	56	56	55	52	46	33	22	13	8	1	0
PR	107	103	100	97	96	93	89	85	81	80	77	73	70	60	47	28	12	6	2	0
MR	20	19	16	14	13	12	11	11	11	10	10	10	10	6	4	2	1	0		
Others	11	3	2	2	2	2	2	2	2	1	1	0								

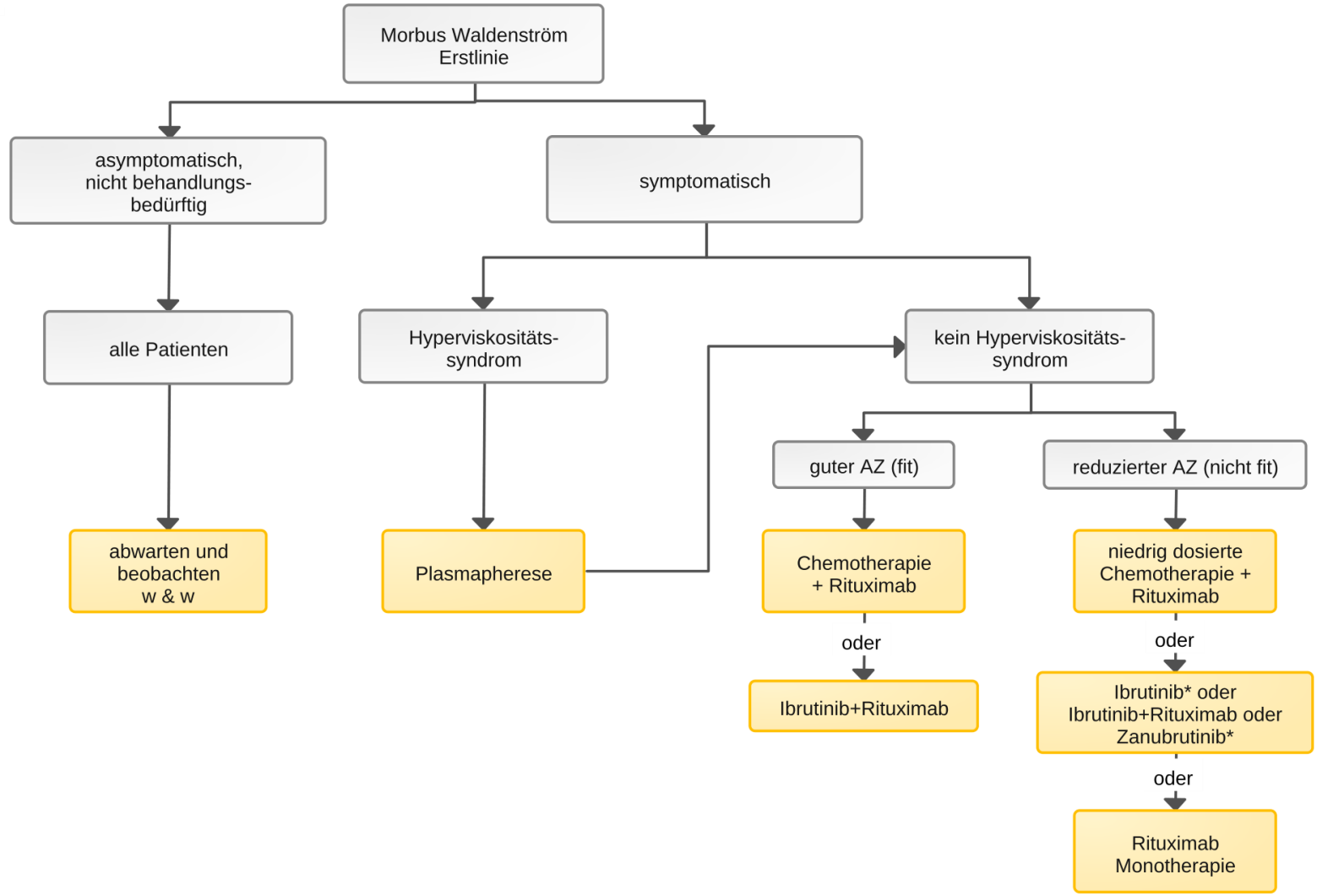
Treon et al., 2022 Sem Haem

Agenda

1. **Wie alles begann…, und wo stehen wir heute**
2. **Der Morbus Waldentström – eine komplexe Erkrankung**
   - Definition
   - molekulare Alterationen: Diagnostik und klinische Implikatonen
   - Definitionen Ansprechen
3. **Behandlung**
   - Immunchemotherapie
   - Stellenwert Erhaltungstherapie
   - Ibrutinib
   - Zanubrutinib
4. **Zukünftige Entwicklungen**
5. **Fallbeispiel**

Therapierichtlinie - Erstlinie

Algorithmus für die Primärtherapie

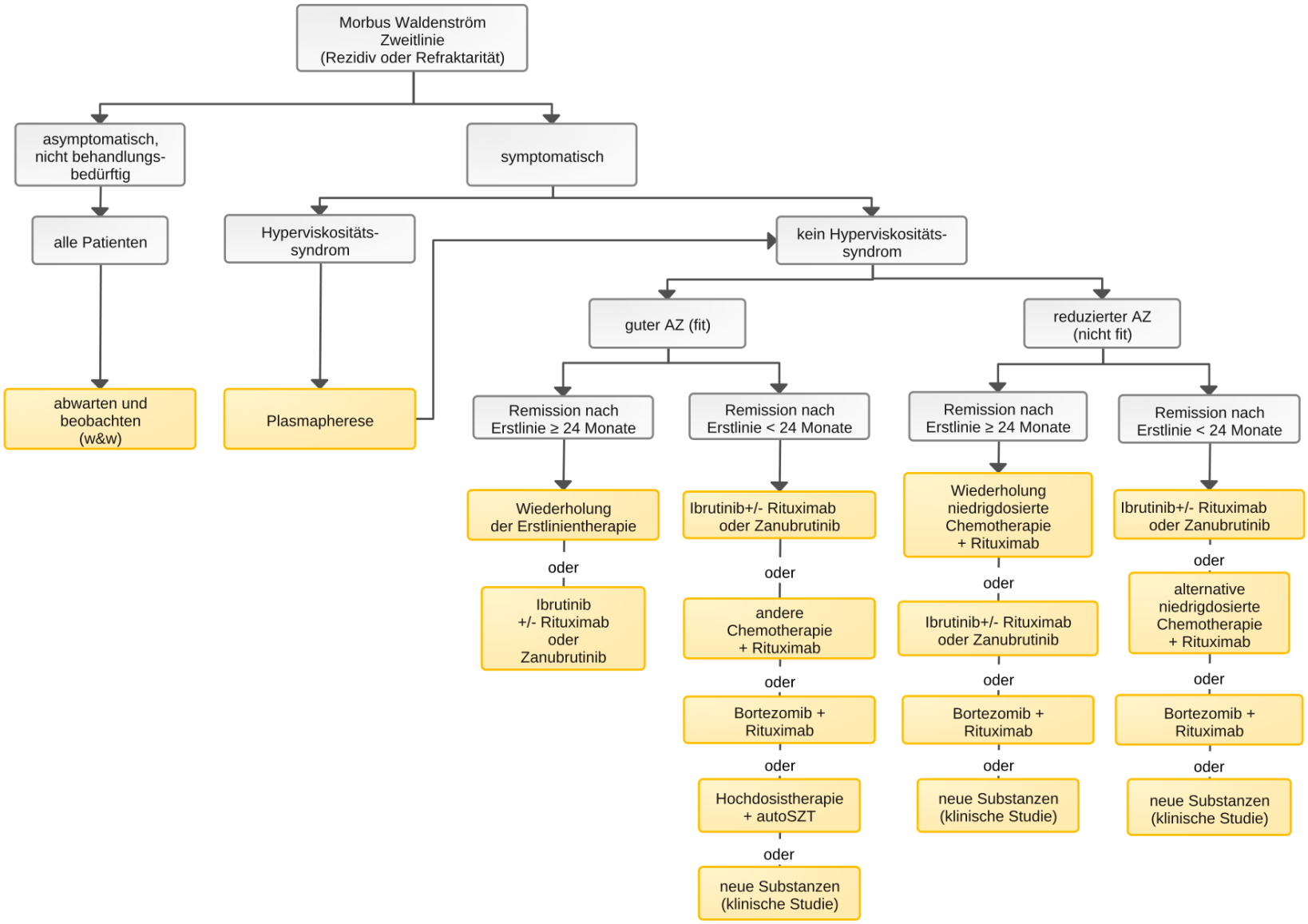


Legende:

kurative Intention; palliative Intention;
*AZ – Allgemeinzustand, * nicht geeignet für Immunchemotherapie*

Therapierichtlinie - Rezidiv

Algorithmus für die Therapie im Rezidiv oder bei Refraktärität



Legende:

kurative Intention; palliative Intention; Bortezomib nur als „off-label use“ einsetzbar

What about R-chemotherapy?

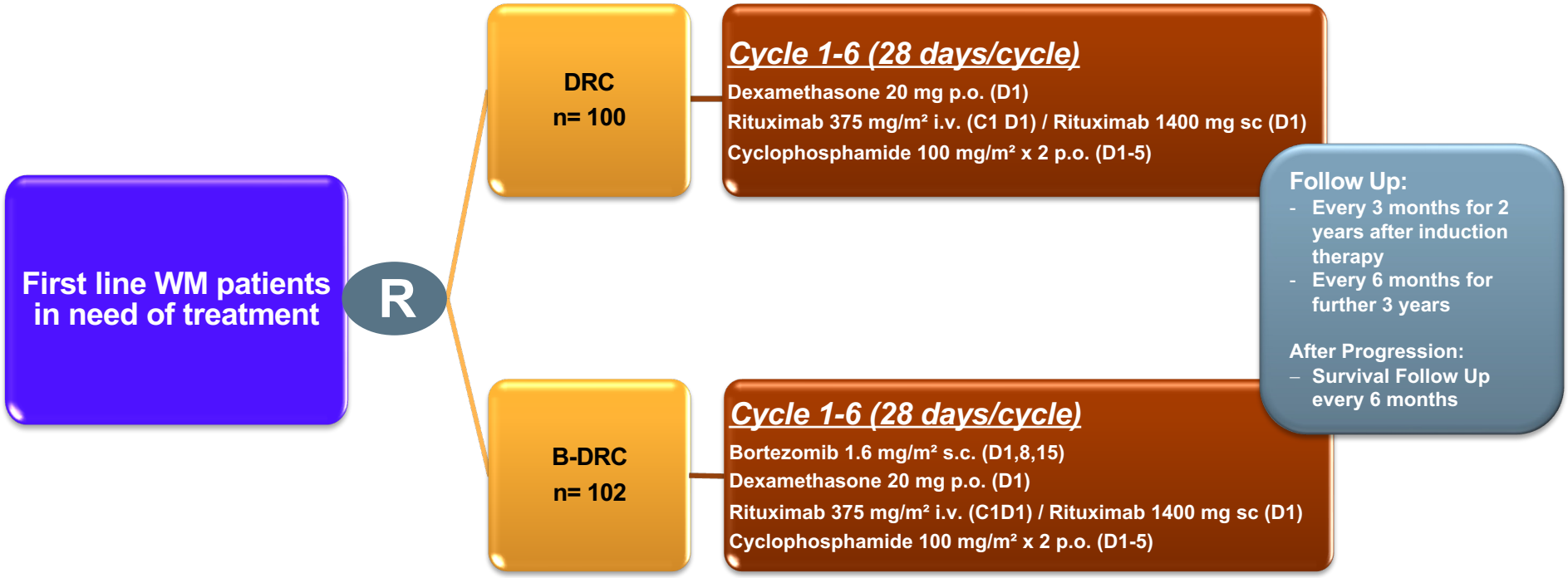
A dinosaur?

Bortezomib in combination with Dexamethasone, Rituximab and Cyclophosphamide (B-DRC) as first – line treatment of Waldenström's Macroglobulinemia: results of a prospectively randomized multicenter European phase II trial.

Christian Buske, MD[1], Meletios A Dimopoulos, MD[2], Alexander Grunenberg, MD[3]*, Efstathios Kastritis, MD[4]*, Cecile Tomowiak, MD[5]*, Béatrice Mahé, MD[6]*, Xavier Troussard, MD[7], Roman Hajek, MD, PhD[8], Andreas Viardot, MD[9], Olivier Tournilhac, MD[10]*, Therese Aurran, MD[11], Stephane Lepretre, MD[12], Hacene Zerazhi, MD[13], Benedicte Hivert, MD[14], Veronique Leblond, MD, PhD[15], Sophie de Guibert, MD[16], Lena Brandefors[17], Ramon Garcia-Sanz, MD[18], Maria Gomes da Silva, MD[19], Eva Kimby, MD, PhD[20], Jens Dreyhaupt, PhD[21], Rainer Muche, PhD[22] and Pierre Morel, MD[23]

[1]Comprehensive Cancer Center Ulm, Institute of Experimental Cancer Research, University Hospital of Ulm, Ulm, Germany; [2]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [3]Concord Hospital, University of Sydney, Sydney, NSW, Australia; [4]Hospital Universitario de Salamanca, Salamanca, Spain; [5]The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; [6]Département d' Hématologie Hôpital Pitié-Salpêtrière APHP, UPMC Université Paris, Paris, France; [7]Centre Hospitalier Universitaire de Nantes, Nantes, France; [8]Centre Hospitalier Régional Universitaire de Lille, Institute of Hematolog-Tranfusion, Lille, France; [9]Colorado Blood Cancer Institute, Denver, CO, USA; [10]Peter MacCallum Cancer Centre, St. Vincent's Hospital, and the University of Melbourne, Melbourne, VIC, Australia; [11]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [12]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [13]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [14]Royal Victoria Hospital at McGill University Health Centre, Montreal, QC, Canada; [15]National and Kapodistrian University of Athens School of Medicine, Athens, Greece; [16]Dana-Farber Cancer Institute, Boston, MA, USA; [17]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA

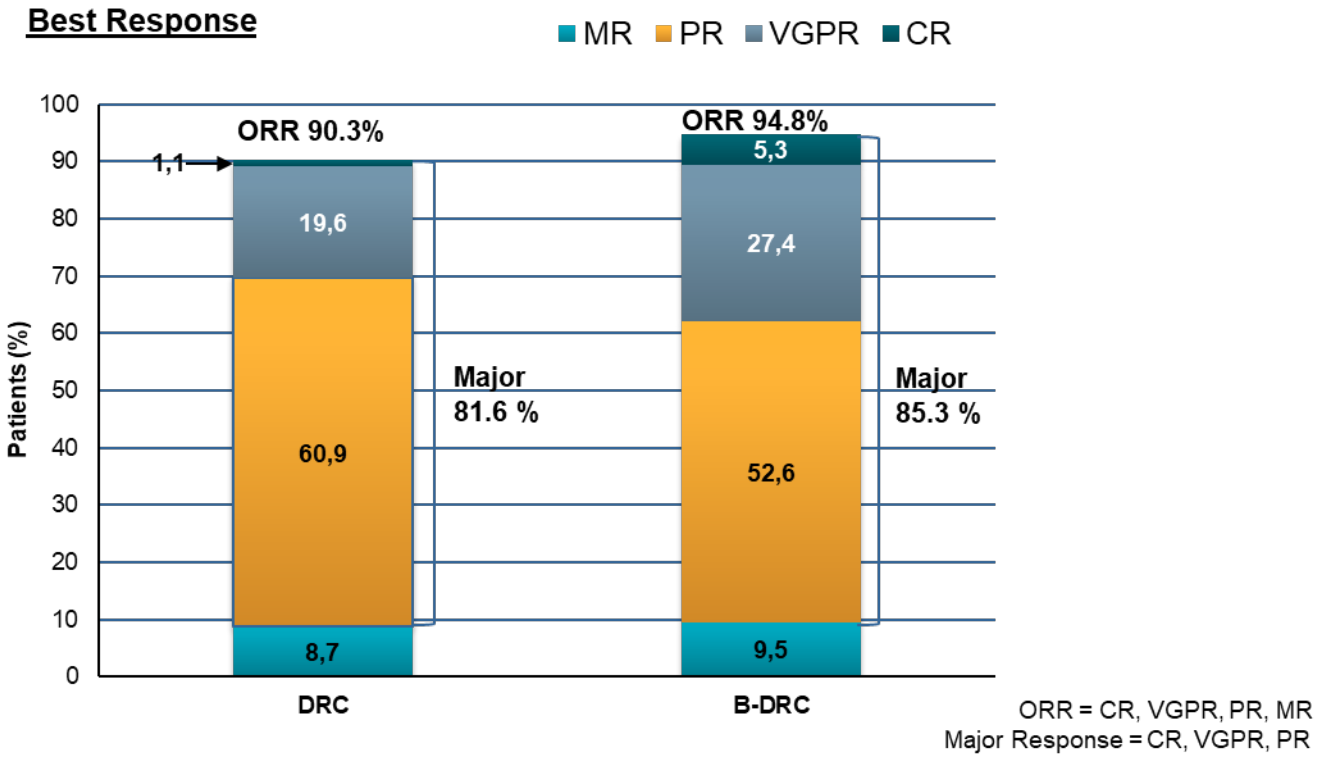
ECWM-1 Study Design



Randomized Phase II
Endpoints: PFS, response rates, OS, safety

Buske et al., JCO, 2023

Response Rates

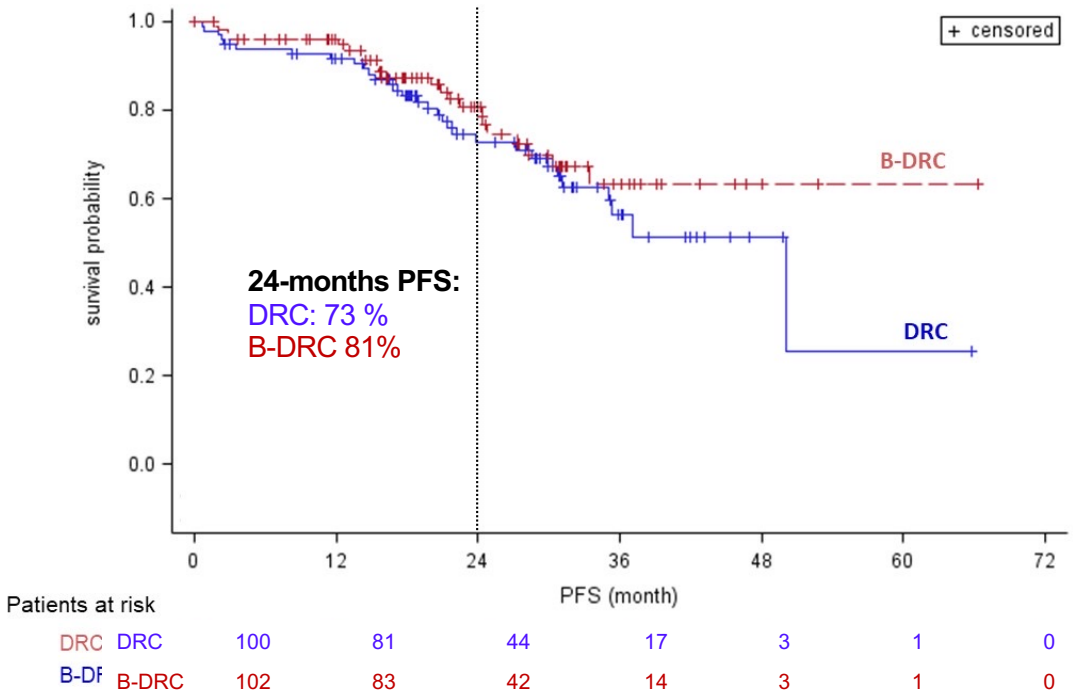


	DRC	B-DRC
Median time to first response, mo (range)	5.5 (2.3-8.5)	3.0 (2.3-15.8)

Buske et al., JCO, 2023

Progression-Free Survival

Median follow-up was 27.5 months at the time of the data cut.



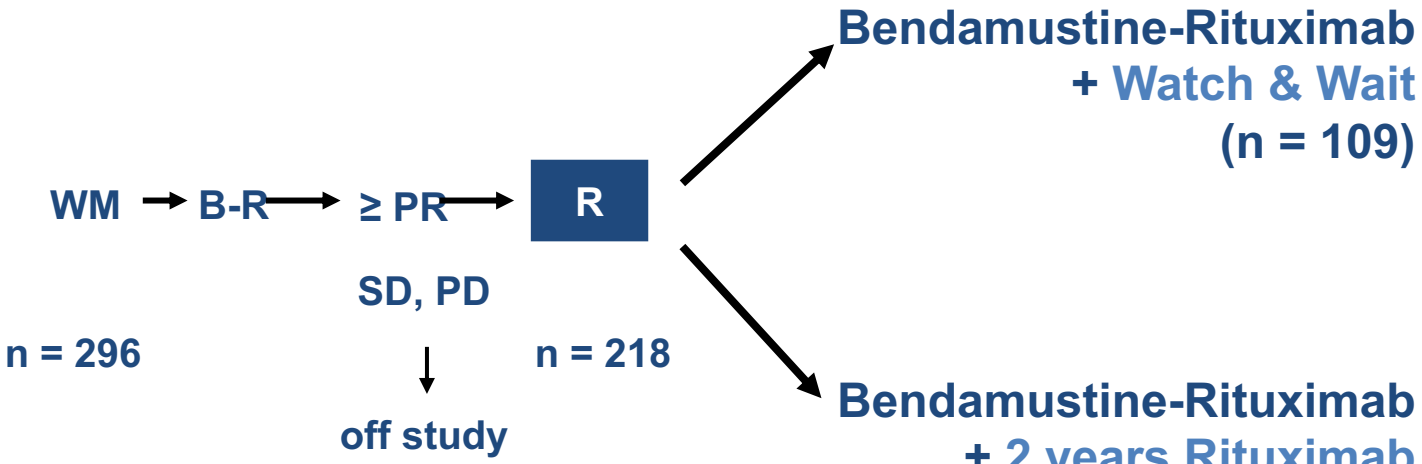
	DRC	B-DRC
Median PFS, months (95% CI)	50.1 (31.2-n.a.)	n.a. (33.5-n.a.)
HR (95% CI)	0.759 (95% CI: 0.439; 1.311)	
Logrank p-value	P=0.32	

Buske et al., JCO, 2023

To maintain or not to maintain?

B-R + observation vs B-R + 2 years rituximab

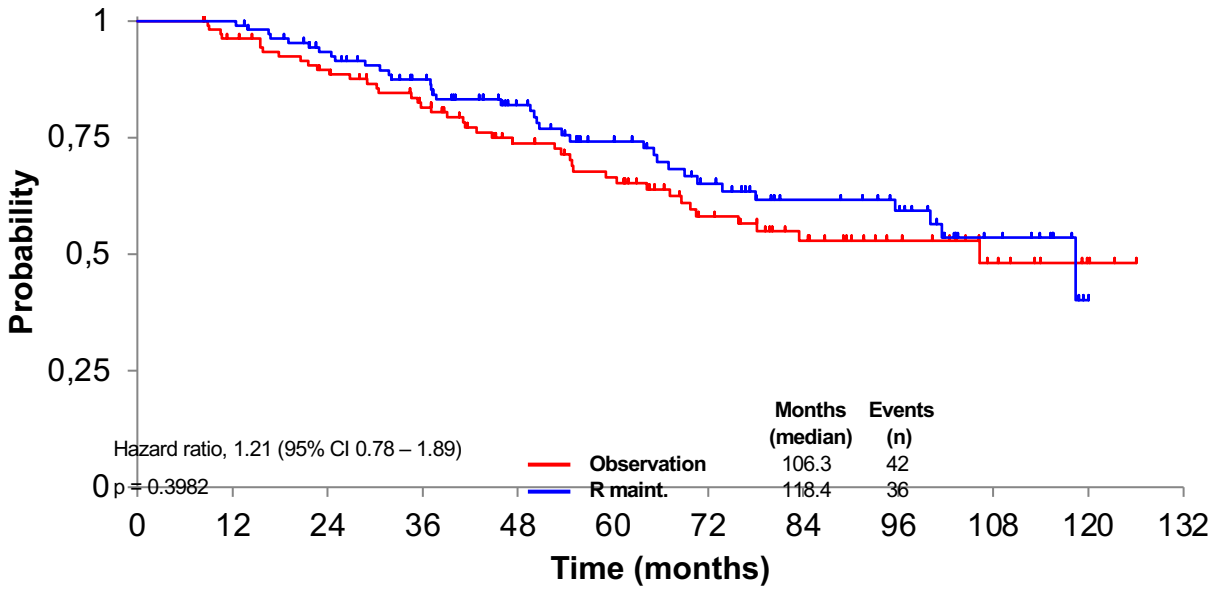
StiL NHL 7-2008 - MAINTAIN



Rummel MJ, et al., ASH 2019; Abstract 343.

B-R + watch & wait vs B-R + 2 years rituximab

Progression free survival (80 months median follow-up)

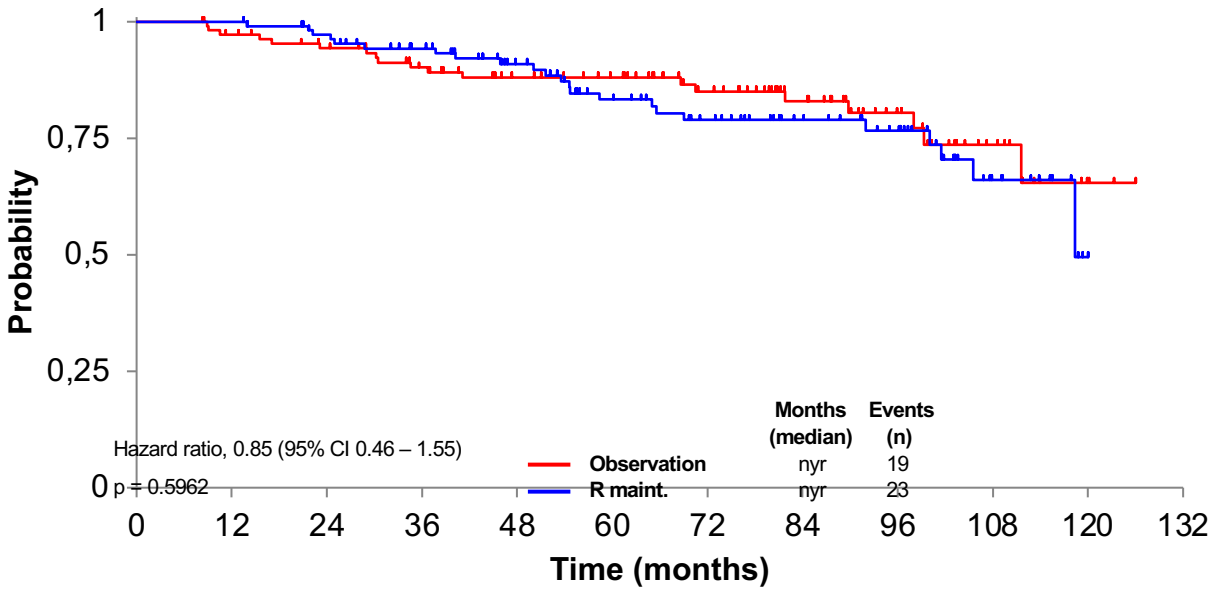


Pts at risk											
Observ.	109	102	92	79	62	54	39	27	18	9	3
R maint.	109	109	96	83	65	52	41	30	25	11	1

Rummel MJ, et al., ASH 2019; Abstract 343.

B-R + observation vs B-R + 2 years rituximab

Overall survival (80 months median follow-up)



Pts at risk											
Observ.	109	103	96	86	75	69	55	40	26	12	3
R maint.	109	109	101	91	75	61	51	40	32	12	1

Rummel MJ, et al., ASH 2019; Abstract 343.

Contents lists available at ScienceDirect

Seminars in Hematology

journal homepage: www.elsevier.com/locate/seminhematol

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

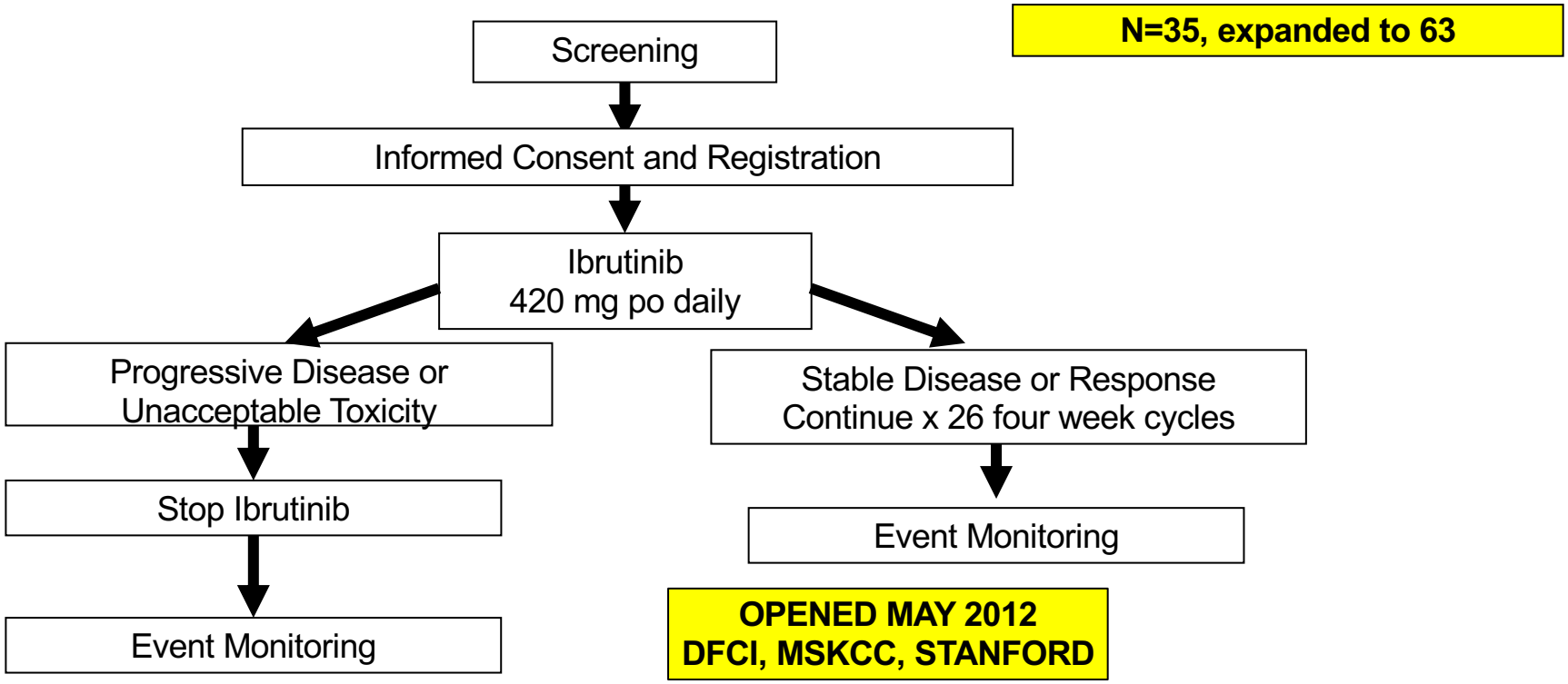
Christian Buske[a,*], Jorge J. Castillo[b], Jithma Prasad Abeykoon[c], Ranjana Advani[d], Suzanne O. Arulogun[e], Andrew R. Branagan[f], Xinxin Cao[g], Shirley D'Sa[e], Jian Hou[h], Prashant Kapoor[c], Efstathios Kastritis[i], Marie J. Kersten[j], Veronique LeBlond[k], Merav Leiba[l], Jeffrey V. Matous[m], Jonas Paludo[c], Lugui Qiu[n], Constantine S. Tam[o], Alessandra Tedeschi[p], Sheeba K. Thomas[q], Ibrahim Tohidi-Esfahani[r], Marzia Varettoni[s], Josephine M. Vos[j], Ramon Garcia-Sanz[t], Jesus San-Miguel[u], Meletios A. Dimopoulos[i], Steven P. Treon[b], Judith Trotman[r]

„For first-line treatment, chemoimmunotherapy (CIT) regimens such as DRC, or Benda-R continue to play a central role in managing WM, as they are effective, of fixed duration, generally well-tolerated, and affordable."

Rituximab/Chemotherapy still a valid treatment option

But *BTK inhibition sets the standard!*

Schema for multicenter Phase II study of ibrutinib in relapsed/refractory WM



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

Clinical responses to ibrutinib: Median of 9 (range 1-18) cycles

	(N= 63)	(%)
VGPR	10	15.9
PR	36	57
MR	11	17.5

Response criteria adapted from 3rd International Workshop on WM (Treon et al, BJH 2011)

ORR: 90.5% Major RR (≥ PR): 73%

Treon et al, NEJM 2015; 372(15):1430-40

What about Ibrutinib?

What can we achieve (and what not) with Ibrutinib?

Challenges!

Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations

	$MYD88^{MUT}$ $CXCR4^{WT}$	$MYD88^{MUT}$ $CXCR4^{WHIM}$	$MYD88^{WT}$ $CXCR4^{WT}$	p-value
N	36	21	5	
Overall RR	100%	85.7%	60%	<0.01
Major RR	91.7%	61.9%	0%	<0.01

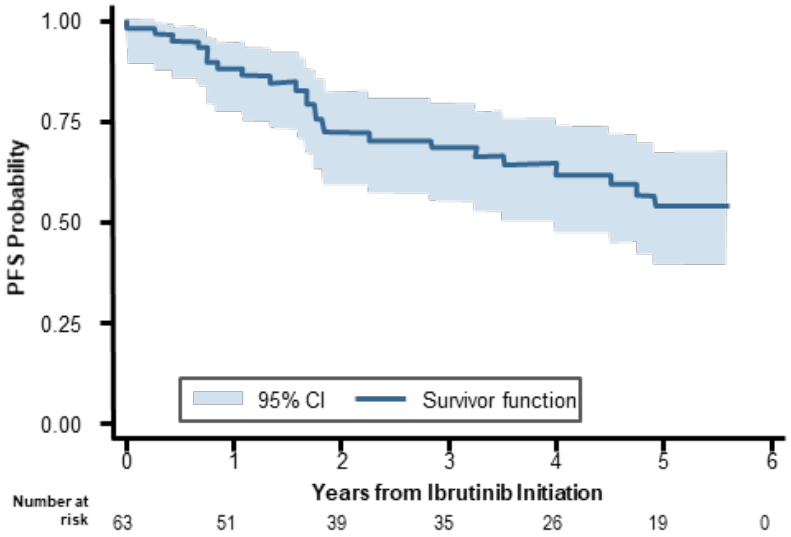
2 patients subsequently found to have other MYD88 mutations not picked up by AS-PCR

AS-PCR: Allele-specific polymerase chain reaction

Treon et al, N Engl J Med. 2015; 372(15):1430-40; NEJM 2015; Letter, August 6, 2015

Ibrutinib Activity in Previously Treated WM:
Updated PFS of the Pivotal Trial (median f/u 59 mos)

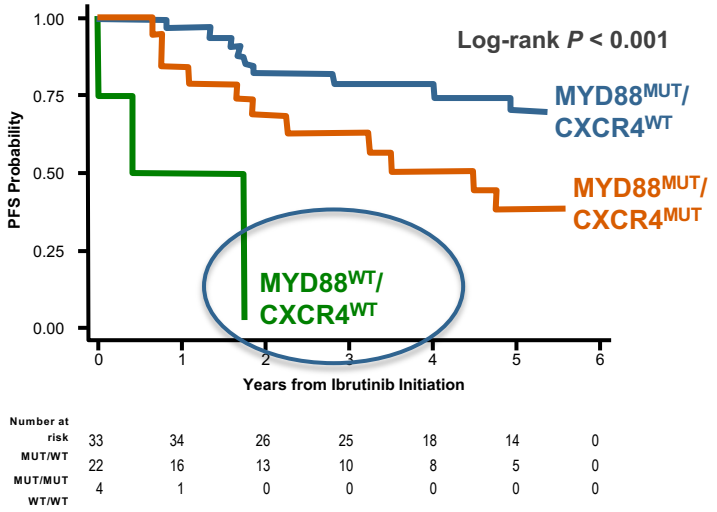
All patients



5-year PFS: 54%

5-year OS: 87%

MYD88 and CXCR4 Mutation Status



Treon, et al. *N Engl J Med*. 2015;372(15):1430-1440.; Updated in Treon, et al. *J Clin Oncol*. 2021;39(6):565-575.

Waldenström's macroglobulinemia - an Update

Quo Vadis?

What are the key challenges?

Dealing with CXCR4 mutated patients

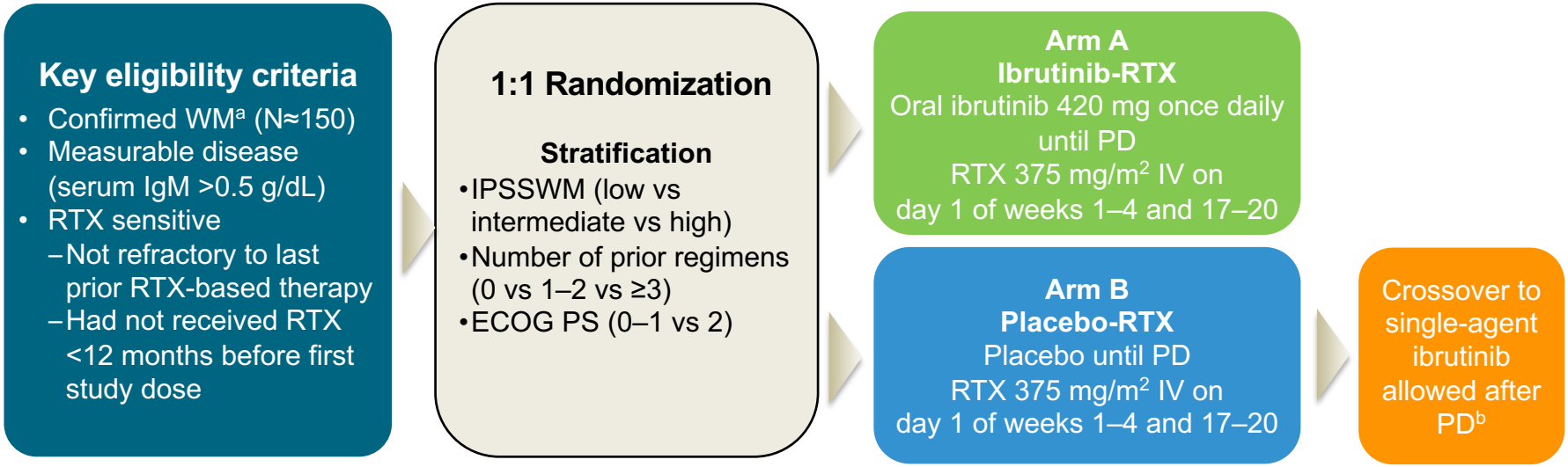
What comes next?

Improving Ibrutinib (Ibrutinib as a backbone)!

Major goal: Break through genotype-dependent efficacy

→ Two concepts: anti-CD20 and Proteasome Inhibitors

iNNOVATE (PCYC-1127) study design



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

Hgb, hemoglobin; IPSSWM, International Prognosis Scoring System for Waldenström's Macroglobulinemia; IRC, independent review committee; TTNT, time to next treatment.
[a]Treatment-naive patients were allowed to enroll following a protocol amendment (November 2015); therefore, their enrollment started later than relapsed patients.
[b]Patients in the placebo-RTX arm could receive next-line single-agent ibrutinib in crossover following IRC-confirmed PD.
iNNOVATE Study; ClinicalTrials.gov ID: NCT02165397

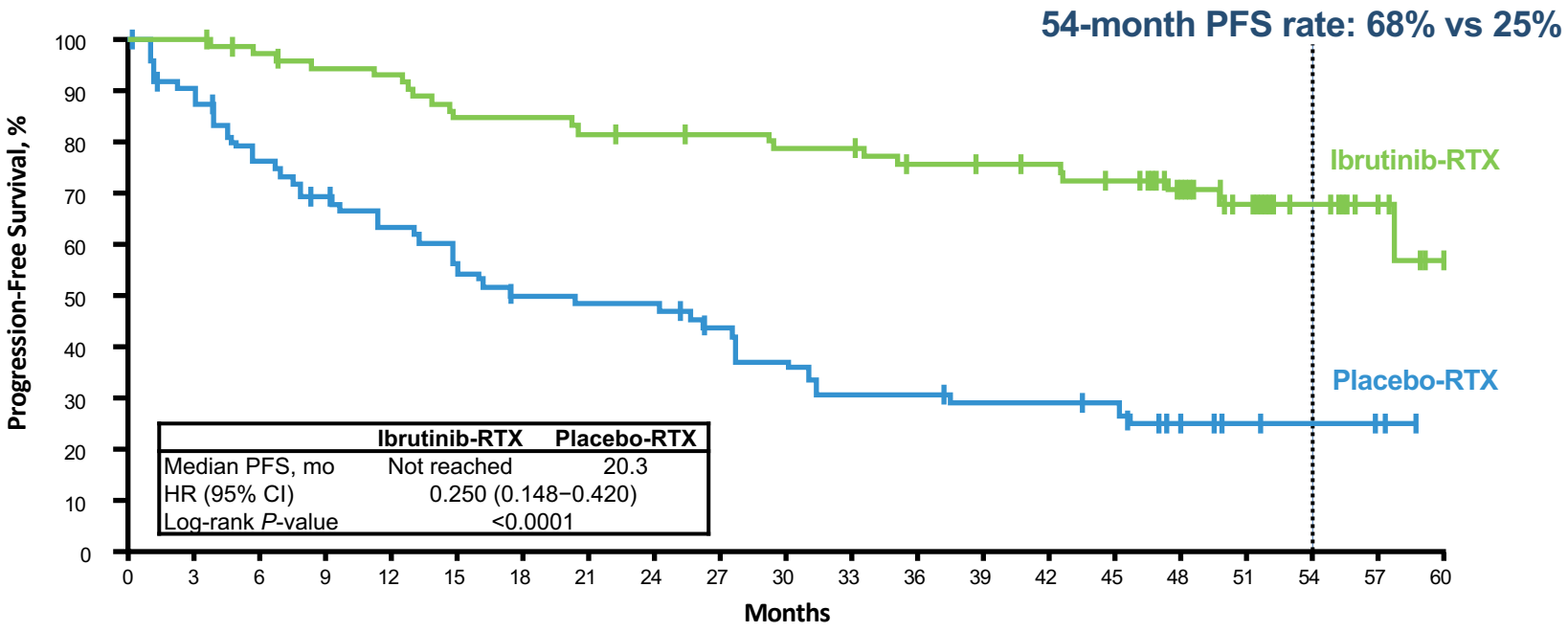
Buske et al., J Clin Oncol 2022; 40(1): 52-62

Demographics and clinical characteristics – were well balanced at baseline

Characteristic at Randomization	Ibrutinib-RTX (n=75)	Placebo-RTX (n=75)
Median age, years (range)	70 (36–89)	68 (39–85)
Male, n (%)	45 (60)	54 (72)
IPSSWM, n (%)		
Low	15 (20)	17 (23)
Intermediate	33 (44)	28 (37)
High	27 (36)	30 (40)
Median Hgb, g/L (range)	105 (69−155)	100 (66−161)
Baseline Hgb ≤110 g/L, n (%)	44 (59)	50 (67)
Median serum IgM, g/L (range)	33 (6−78)	32 (6−83)
Number of prior systemic therapies, n (%)		
0	34 (45)	34 (45)
1–2	34 (45)	36 (48)
≥3	7 (9)	5 (7)
Genotype, n (%)		
$MYD88^{L265P}/CXCR4^{WT}$	32 (43)	35 (47)
$MYD88^{L265P}/CXCR4^{WHIM}$	26 (35)	23 (31)
$MYD88^{WT}/CXCR4^{WT}$	11 (15)	9 (12)
Unknown	6 (8)	8 (11)
Bone marrow infiltration: % cellularity, mean (range)	73 (25−100)	75 (2−100)

Buske et al., J Clin Oncol 2022; 40(1): 52-62

Median progression free survival was not reached with 5 years of ibrutinib-RTX – ITT Population

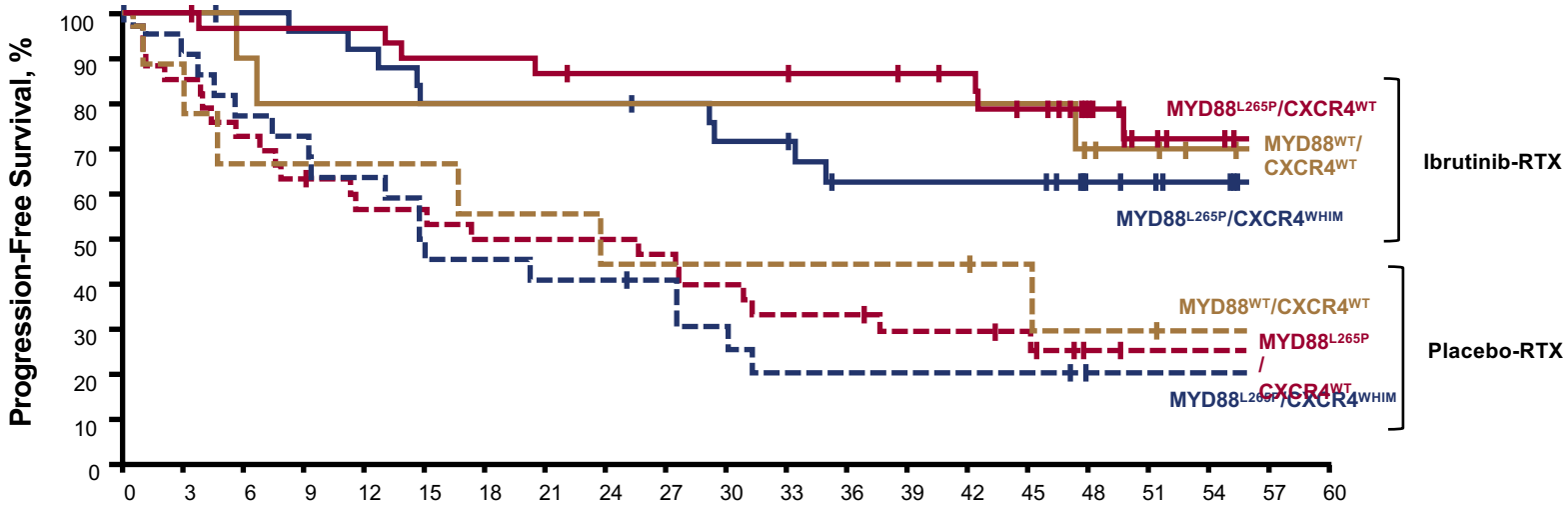


Patients at risk

Ibrutinib-RTX	75	73	69	67	66	60	60	58	57	56	54	54	46	48	47	44	32	22	15	7
Placebo-RTX	75	64	54	48	43	39	33	32	31	27	23	19	19	17	17	15	7	4	3	2

Buske et al., J Clin Oncol 2022; 40(1): 52-62

Progression-free survival benefit with ibrutinib-RTX was independent of genotype



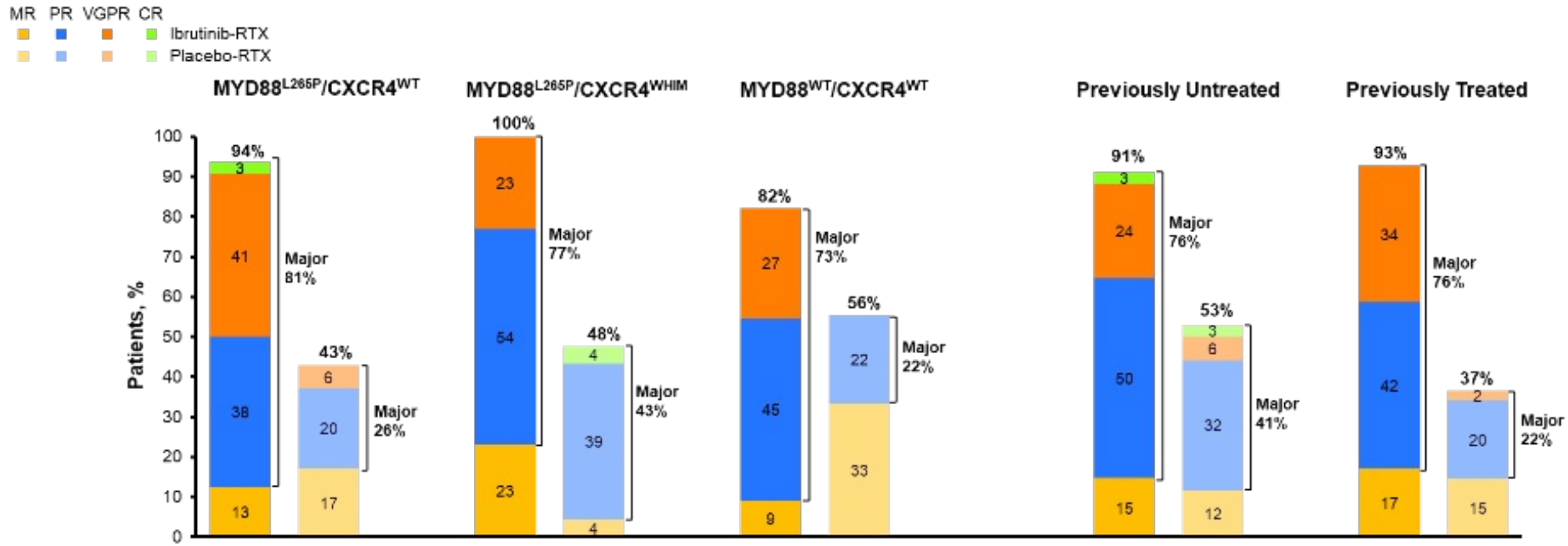
Patients at risk

Ibrutinib-RTX MYD88^{L265P}/CXCR4^{WHIM}	26	26	25	24	23	20	20	20	20	19	17	17	13	13	13	13	8	7	5
Ibrutinib-RTX MYD88^{L265P}/CXCR4^{WT}	32	31	29	29	29	27	27	26	25	25	25	25	24	23	22	19	15	8	5
Ibrutinib-RTX MYD88^{WT}/CXCR4^{WT}	11	10	9	8	8	8	8	8	8	8	8	8	8	8	8	8	6	5	3
Placebo-RTX MYD88^{L265P}/CXCR4^{WHIM}	23	20	17	16	14	11	10	9	9	8	6	4	4	4	4	4	2	1	1
Placebo-RTX MYD88^{L265P}/CXCR4^{WT}	35	28	23	20	17	17	15	15	15	14	12	10	10	8	8	7	3	1	1
Placebo-RTX MYD88^{WT}/CXCR4^{WT}	9	8	6	6	6	6	5	5	4	4	4	4	4	4	4	3	2	2	1

Kaplan-Meier curves are shown for timepoints with ≥10 patients at risk.

Buske et al., J Clin Oncol 2022; 40(1): 52-62

Higher response rates with ibrutinib-RTX independent of genotype or prior treatment status



Median time to ORR, months (range)	1 (1-18)	3 (1-22)	2 (1-11)	3 (1-7)	3 (1-21)	3 (2-17)	1 (1-21)	2 (1-22)	1 (1-11)	3 (1-17)
Median time to major response, months (range)	2 (1-41)	5 (2-17)	3 (1-38)	9 (4-18)	7 (1-46)	5 (5-6)	3 (1-46)	5 (2-18)	3 (1-41)	7 (5-41)

Buske et al., J Clin Oncol 2022; 40(1): 52-62

ECWM-2 - „iNNOVATE plus Bortezomib“ fully recruited

Key eligibility criteria

- Confirmed WM (N=53)
- Measurable disease (serum IgM > 0.5 g/dL)
- In need of treatment
- ECOG PS status of 0–2
- Genotyped for MYD88/CXCR4

Treatment

Induction

- Bortezomib SC 1.6/m^2 d1,8,15 cycle 1-6
- Rituximab 375 mg/m2 IV cycle 1, 1400 SC cycle 1-6
- Ibrutinib 420 mg PO continuously

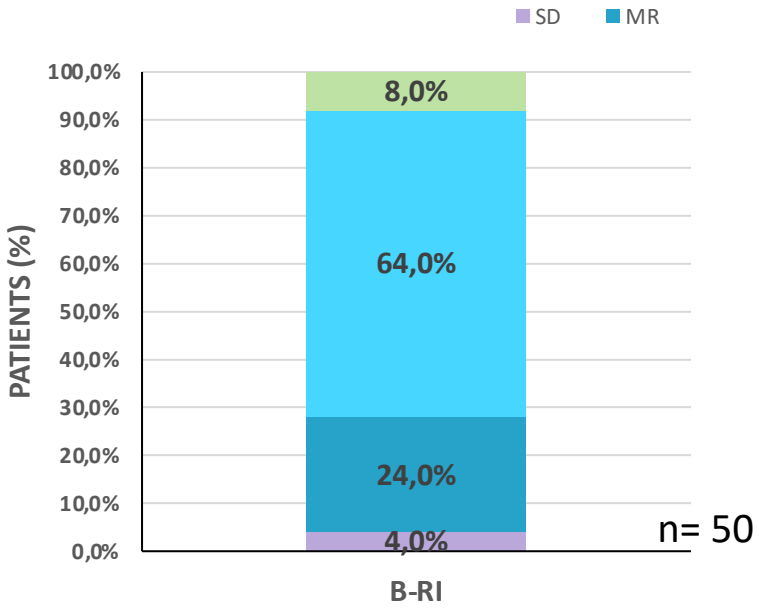
Maintenance

- Rituximab 1400 SC every 2nd month x 12
- Ibrutinib 420 mg PO continously

http://www.ecwm.eu/clinical_trials/__Clinical-Trials.html

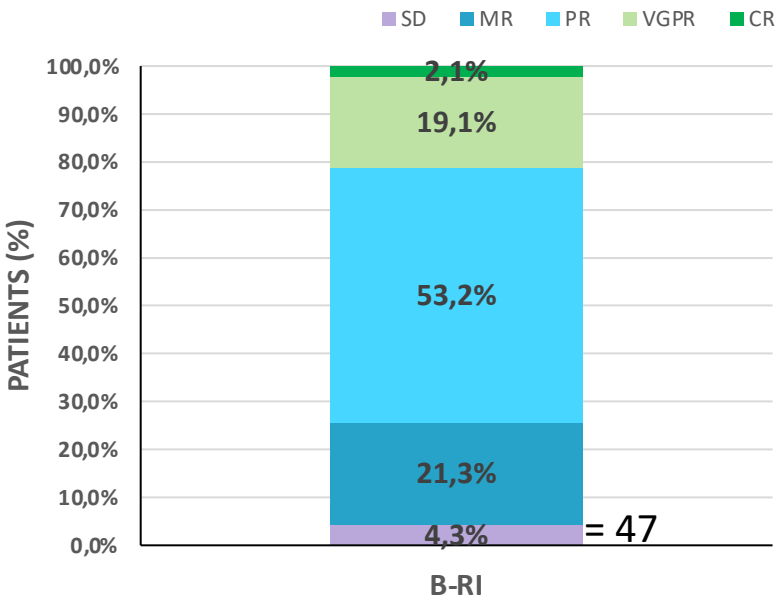
Response at interim Staging (C4) and End of Induction

Response at End of Cycle 3



ORR	96.0%
Major Resp.	72.0%

Response at End of Induction



ORR	95.7%
Major Resp.	74.5%

CZAR-1 | Study design

Study design

- Phase II, international
- CR / VGPR rate of 35% in patients Carfilzomib and Ibrutinib
- 94 patients required to reach a power of 80% at an one-sided type one error of 0.10
- Withdrawal rate < 5%, maximum enrolment 99.

1:1 Randomization (N=99)

Stratification

- MYD88/CXCR4 mutations
- Number of prior regimens (0 vs ≥1)

Arm A: Carfilzomib/Ibrutinib

Ibrutinib	420 mg p.o. once daily until PD or non-tolerable toxicities*
Carfilzomib	20 mg/m² i.v. C1 d1, 70 mg/m² i.v. C1 d8, 15 70 mg/m² i.v C2-C12 d1, 8, 15 70 mg/m² i.v C13-24 d1, 15

Arm B: Ibrutinib

Ibrutinib 420 mg p.o. once daily until PD or non-tolerable toxicities*

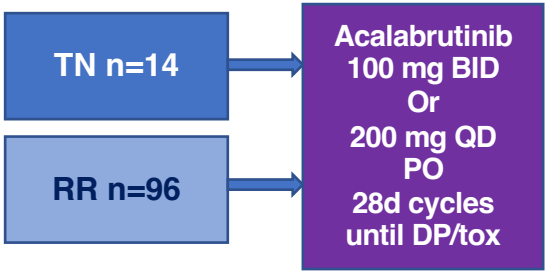
Follow Up

- 2 years every 3 months
- 3 years every 6 months
- after PD every 6 months for survival until year 7 after first patient in

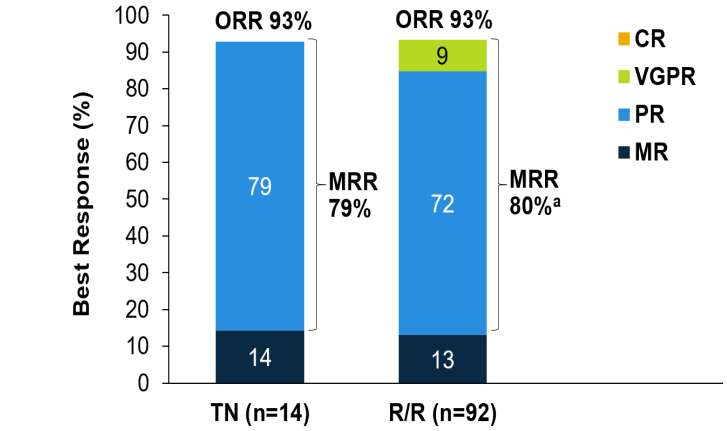
79 Patienten rekrutiert

2nd generation BTKi

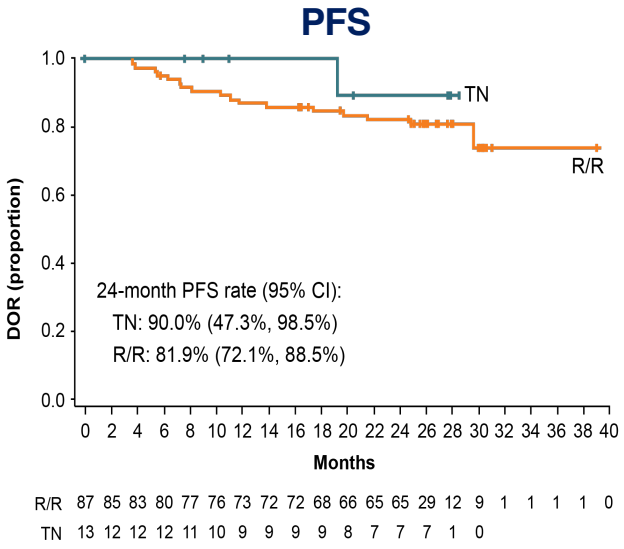
Acalabrutinib monotherapy in patients with WM: a Phase 2 study



Characteristic	TN (n=14)	R/R (n=92)
Median age (range), y	73 (48-86)	69 (39-90)
Median n prior tx	-	2 (1-7)
≥3 previous tx	-	41 (45%)
Refractory disease n (%)		33 (36)



Median time to best response (range), mo: 4.9 (1.8-16.6) 1.9 (0.9-23.2)



Owen et al., Lancet Haematol 2019

ASPEN: Long-Term Follow-Up Results of a Phase 3 Randomized Trial of Zanubrutinib versus Ibrutinib in Patients With Waldenström Macroglobulinemia

Meletios Dimopoulos,[1] Stephen Opat,[2] Shirley D'Sa,[3] Wojciech Jurczak,[4] Hui-Peng Lee,[5] Gavin Cull,[6] Roger G. Owen,[7] Paula Marlton,[8] Bjorn E. Wahlin,[9] Ramon Garcia-Sanz,[10] Helen McCarthy,[11] Stephen Mulligan,[12] Alessandra Tedeschi,[13] Jorge J. Castillo,[14] Jaroslaw Czyż,[15] Carlos Fernández de Larrea Rodriguez,[16] David Belada,[17] Edward Libby,[18] Jeffrey Matous,[19] Marina Motta,[20] Tanya Siddiqi,[21] Monica Tani,[22] Marek Trněný,[23] Monique Minnema,[24] Christian Buske,[25] Véronique Leblond,[26] Steven P. Treon,[14] Judith Trotman,[27] Wai Y. Chan,[28] Jingjing Schneider,[28] Heather Allewelt,[28] Aileen Cohen,[28] Jane Huang,[28] and Constantine S. Tam[29]

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Presented at the 11th International Workshop on Waldenström Macroglobulinemia on October 27-30, 2022
Session XI: Plenary Session II – Presentation WM042

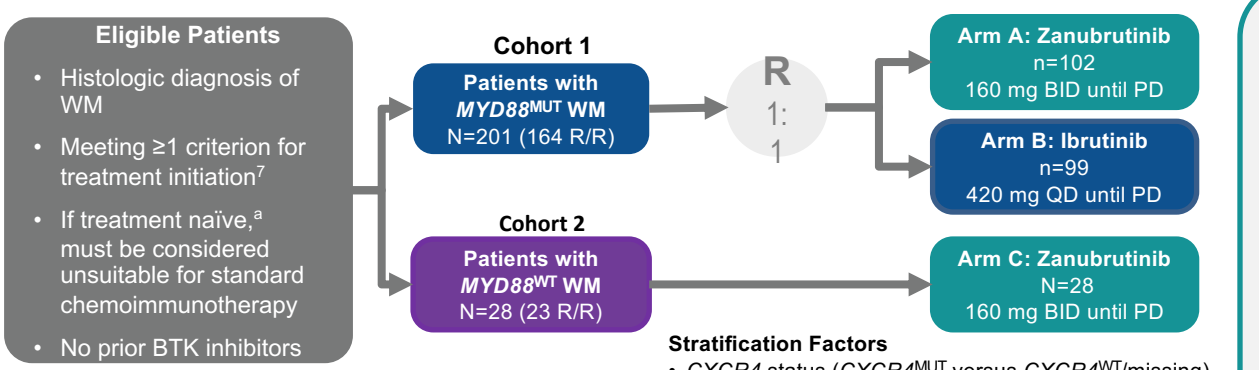
INTRODUCTION

- Zanubrutinib is a potent, selective, and irreversible next-generation Bruton tyrosine kinase (BTK) inhibitor designed to maximize BTK occupancy and minimize inhibition of off-target kinases[1]
- Zanubrutinib has demonstrated a complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes[2]
- Zanubrutinib has shown equipotency against BTK compared with ibrutinib.[1]
- Zanubrutinib has high selectivity for BTK and minimal off-target inhibition of TEC- and EGFR-family kinases[1]
- Favorable drug interaction properties allow zanubrutinib to be co-administered with strong or moderate CYP3A inhibitors (eg, antifungals) at a reduced dose, as well as PPIs, acid-reducing agents, and antithrombotic agents[3,4]

CYP3A, cytochrome P450 3A; EGFR, epidermal growth factor receptor; PPI, proton pump inhibitor; TEC, tyrosine kinase expressed in hepatocellular carcinoma.

1. Guo et al. *J Med Chem* 2019;62:7923-7940. 2. Tam et al. *Blood* 2019;134:851-859. 3. Mu et al. *Cancer Chemother Pharmacol* 2020;85:391-399. 4. Ou et al. *Clin Transl Sci* 2021;14:764-77.

ASPEN: Phase 3 Study of Zanubrutinib Versus Ibrutinib in WM[1,2]



ClinicalTrials.gov: NCT03053440
EU Clinical Trial Register: EUDRACT 2016-002980-33

Primary objectives
- Efficacy of zanubrutinib versus ibrutinib in patients with activating *MYD88*^{MUT} WM
- Primary endpoint was CR+VGPR rate

Secondary objectives
- Efficacy, clinical benefit, and anti-lymphoma effects of zanubrutinib versus ibrutinib
- Safety and tolerability of zanubrutinib versus ibrutinib

Exploratory objectives
- Efficacy and safety of zanubrutinib in patients with *MYD88*^{WT} WM
- Efficacy of zanubrutinib versus ibrutinib according to *CXCR4* gene mutation in patients with *MYD88*^{MUT} WM

- At median follow-up of nearly 4 years, 66% of patients remained on treatment with zanubrutinib versus 52% with ibrutinib

[a]Up to 20% of the overall population.
BID, twice a day; BTK, Bruton tyrosine kinase; CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; PD, progressive disease; QD, once a day; R, randomization; R/R. relapsed/refractory; VGPR, very good partial response; WM, Waldenström macroglobulinemia; WT, wild type.
1. Tam et al. *Future Oncol* 2018;14(22):2229-2237. 2. Tam et al. *Blood* 2020;136(18):2038-2050.

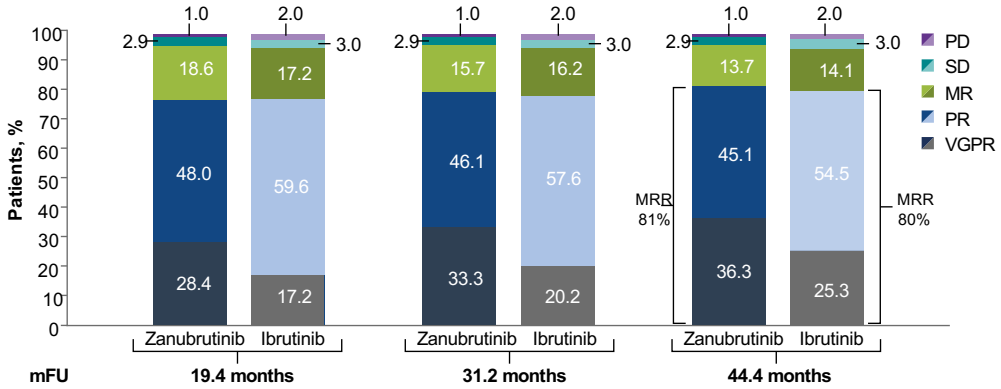
Baseline Characteristics

Characteristics	Cohort 1		Cohort 2
	Ibrutinib (n=99)	Zanubrutinib (n=102)	Zanubrutinib (N=28)
Age, median (range), years	70 (38-90)	70 (45-87)	72 (39-87)
>65, n (%)	**70 (70.7)**	61 (59.8)	19 (67.9)
>75, n (%)	22 (22.2)	**34 (33.3)**	12 (42.9)
Sex, n (%)			
Male	65 (65.7)	69 (67.6)	14 (50.0)
Prior lines of therapy, n (%)			
0	18 (18.2)	19 (18.6)	5 (17.9)
1-3	74 (74.7)	76 (74.5)	20 (71.4)
>3	7 (7.1)	7 (6.9)	3 (10.7)
Genotype by NGS, n (%)			
CXCR4^{WT}	72 (72.7)	65 (63.7)	27 (96.4)
CXCR4^{MUT} / *CXCR4*^{NS}	20 (20.2) / 13 (13.1)	**33 (32.4)** / 14 (13.7)	1 (3.6) / 0
Unknown	7 (7.1)	4 (3.9)	0
IPSS WM high score, n (%)	44 (44.4)	47 (46.1)	12 (42.9)
Hemoglobin ≤110 g/L, n (%)	53 (53.5)	**67 (65.7)**	15 (53.6)
Baseline IgM (central lab), median (range), g/L	34.2 (2.4-108.0)	31.8 (5.8-86.9)	28.5 (5.6-73.4)
Bone marrow involvement, median (range), %	60 (0-90)	60 (0-90)	22.5 (0-50)
Extramedullary disease by investigator, n (%)	66 (66.7)	63 (61.8)	16 (57.1)

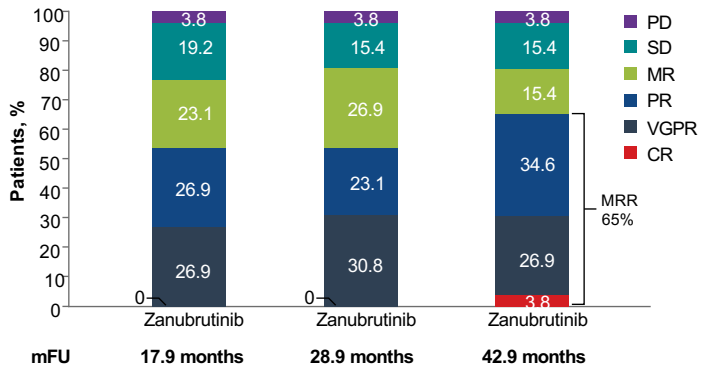
Bold blue text indicates >10% difference between arms in cohort 1.
CXCR4, C-X-C chemokine receptor type 4 gene; IPSS, International Prognostic Scoring System; MUT, mutant; NGS, next-generation sequencing; NS, nonsense mutation; WM, Waldenström macroglobulinemia; WT, wild type.

Best Overall Response by Investigator Over Time

Responses Over Time in Patients With *MYD88*^{MUT}



Responses Over Time Observed in *MYD88*^{WT}

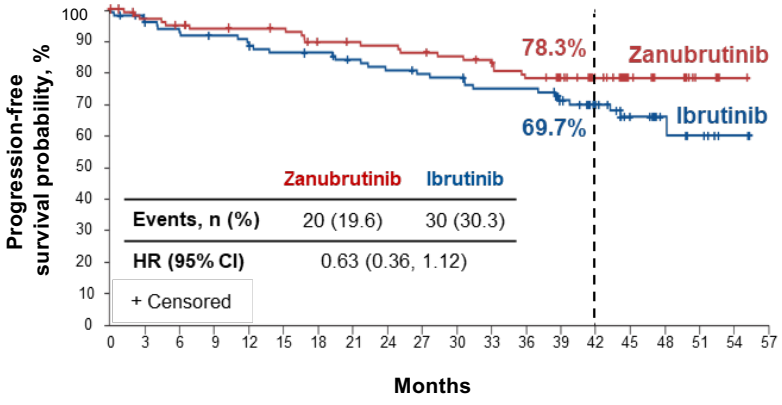


- At 44.4-month median follow-up, CR+VGPR rates by investigator were 36.3% (zanubrutinib) versus 25.3% (ibrutinib)

Data cutoff: October 31, 2021.
CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; mFU, median follow-up; MR, major response; MRR, major response rate; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild type.

PFS and OS in ITT population (Cohort 1)

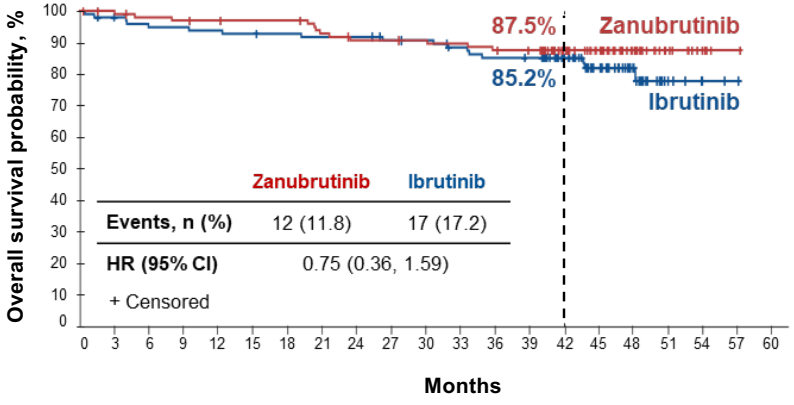
Progression-Free Survival[a]



No. of Patients at Risk:

Zanubrutinib	102	96	93	90	89	88	82	81	80	78	76	74	68	60	43	25	15	8	1	0
Ibrutinib	99	92	88	85	83	79	78	74	71	69	68	64	64	52	41	27	11	6	2	0

Overall Survival[a]



No. of Patients at Risk:

Zanubrutinib	102	100	97	96	95	94	94	89	86	86	85	84	82	80	65	49	27	13	5	1	0
Ibrutinib	99	96	93	92	91	90	89	88	88	85	84	80	77	76	62	43	21	7	3	1	0

- In patients with *MYD88*^{MUT} WM, median PFS and median OS were not yet reached, with hazard ratio estimates favoring zanubrutinib

Data cutoff: October 31, 2021.
[a]By investigator assessment.
HR, hazard ratio; MUT, mutation; *MYD88*, myeloid differentiation primary response 88 gene; PFS, progression-free survival; OS, overall survival; WM, Waldenström macroglobulinemia; WT, wild type.

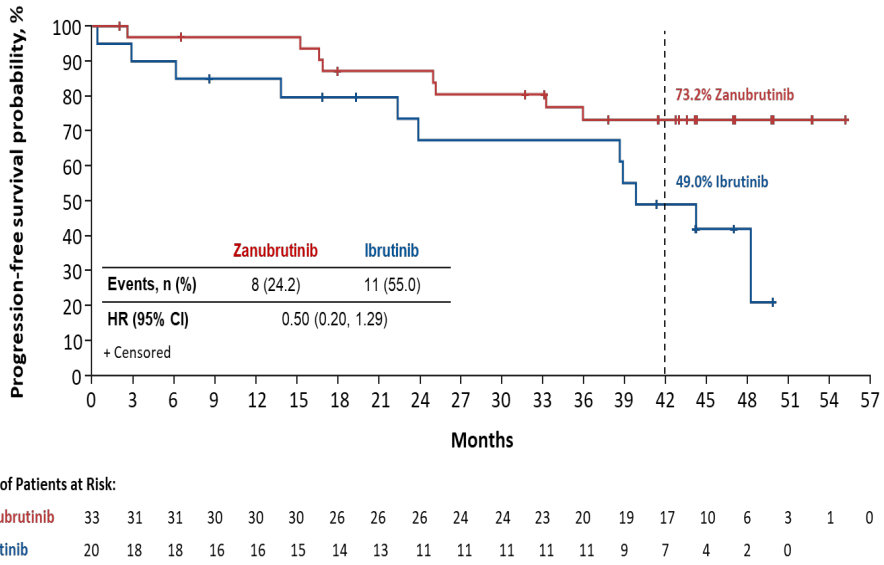
Response and PFS in Patients With *MYD88*^{MUT} by *CXCR4*^{MUT} Status

Response Assessment by *CXCR4* Status[a]

Response	*CXCR4*^{MUT} Ibrutinib (n=20)	*CXCR4*^{MUT} Zanubrutinib (n=33)	*CXCR4*^{WT} Ibrutinib (n=72)	*CXCR4*^{WT} Zanubrutinib (n=65)
VGPR or better, n (%)	2 (10.0)	**7 (21.2)**	22 (30.6)	**29 (44.6)**
Major response, n (%)	13 (65.0)	**26 (78.8)**	61 (84.7)	**54 (83.1)**
Overall response, n (%)	19 (95.0)	30 (90.9)	68 (94.4)	63 (96.9)
Median time to major response, median (months)	6.6	3.4	2.8	2.8
Median time to VGPR, median (months)	31.3	11.1	11.3	6.5

Bold blue text indicates >10% difference between arms.

PFS in Patients With *MYD88*^{MUT}*CXCR4*^{MUT}



Data cutoff: October 31, 2021.

[a]*CXCR4* mutation determined by NGS. Ninety-two ibrutinib patients and 98 zanubrutinib patients had NGS results available.

CXCR4, C-X-C chemokine receptor type 4 gene; HR, hazard ratio; MR, major response; MUT, mutant; PFS, progression-free survival; VGPR, very good partial response.

Overall Safety Summary

Category, n (%)	Cohort 1		Cohort 2
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Zanubrutinib (n=28)
Patients with ≥1 AE	98 (100.0)	100 (99.0)	26 (92.9)
Grade ≥3	71 (72.4)	75 (74.3)	20 (71.4)
Serious	49 (50.0)	57 (56.4)	14 (50.0)
AE leading to death	5 (5.1)[a]	3 (3.0)[b]	3 (10.7)[c]
AE leading to treatment discontinuation	20 (20.4)	9 (8.9)	6 (21.4)
Cardiac AEs[d]	4 (4.1)	1 (1.0)	1 (3.6)
AE leading to dose reduction	26 (26.5)	16 (15.8)	2 (7.1)
AE leading to dose held	62 (63.3)	63 (62.4)	18 (64.3)
COVID-19–related AE	4 (4.1)	4 (4.0)	2 (7.1)

- Most common AEs that led to discontinuation were cardiac disorder (n=4 [4%], includes 2 due to atrial fibrillation) and infection (4%) with ibrutinib, versus second malignancy (4%) with zanubrutinib

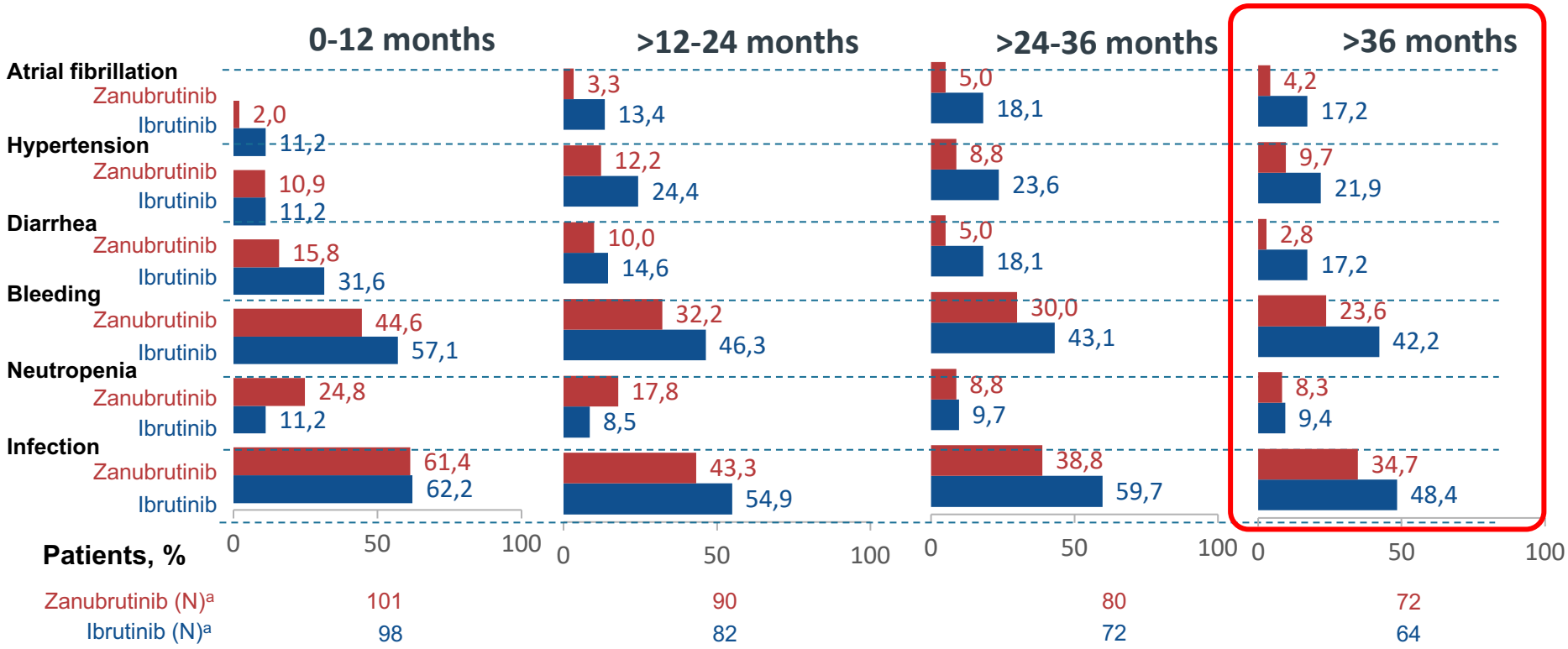
Data cutoff: October 31, 2021.
[a]Cardiac failure acute, death (unexplained), pneumonia, sepsis (n=2). [b]Cardiomegaly (cardiac arrest after plasmapheresis), metastatic malignant melanoma, subdural hematoma (after a fall). [c]Cardiac arrest, COVID-19 infection, lymphoma transformation. [d]Cardiac disorder system organ class. AE, adverse event

Adverse Events of Interest (Cohort 1)

AEs,[a] n (%)	Any grade		Grade ≥3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Infection	78 (79.6)	80 (79.2)	**27 (27.6)**	22 (21.8)
Bleeding	61 (62.2)	56 (55.4)	10 (10.2)	9 (8.9)
Diarrhea	**34 (34.7)**	23 (22.8)	2 (2.0)	3 (3.0)
Hypertension*	**25 (25.5)**	15 (14.9)	**20 (20.4)***	10 (9.9)
Atrial fibrillation/ flutter*	**23 (23.5)***	8 (7.9)	**8 (8.2)***	2 (2.0)
Anemia	22 (22.4)	18 (17.8)	6 (6.1)	**12 (11.9)**
Neutropenia*[b]	20 (20.4)	**35 (34.7)***	10 (10.2)	**24 (23.8)***
Thrombocytopenia	17 (17.3)	17 (16.8)	6 (6.1)	11 (10.9)
Second primary malignancy/ nonskin cancers	17 (17.3)/ 6 (6.1)	17 (16.8)/ 6 (5.9)	3 (3.1)/ 3 (3.1)	6 (5.9)/ 4 (4.0)

Bol
Data cutoff: October 31, 2021.
*Descriptive purposes only, 1-sided $P < 0.025$ in rate difference in all grades and/or grade ≥3. [a]Grouped terms. [b]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.
AE, adverse event.

Prevalence Analysis for Adverse Events of Interest (Cohort 1)



Zanubrutinib (N)[a]	101	90	80	72
Ibrutinib (N)[a]	98	82	72	64

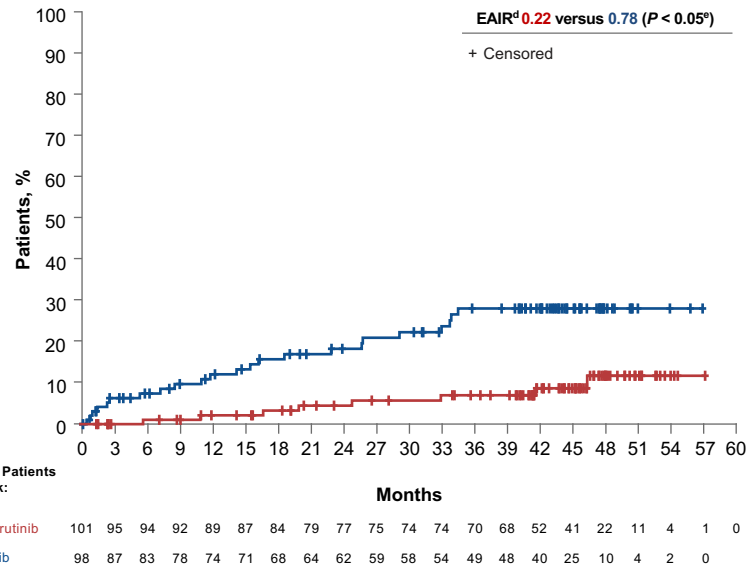
Data cutoff: October 31, 2021. Percentage is based on N. [a]N is the number of patients who are on treatment in each time interval or who discontinued treatment but on the time from first dose date to the earliest date (last dose date +30 days, initiation of new anticancer therapy, end of study, death or cutoff date) is within the time interval.

Cardiovascular Disorders

Cardiovascular AEs

Cardiovascular Disorders, n (%)	ASPEN cohort 1 WM		Pooled analysis B-cell malignancies	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (N=422)	Zanubrutinib (N=1550)
Median treatment duration, months	42.23	43.37	19.96	26.64
Any Cardiovascular AE				
Atrial fibrillation/flutter*	23 (23.5)	8 (7.9)	60 (14.2)	60 (3.9)
Ventricular arrhythmia (VA)[a] Grade ≥2	1 (1.0)	0	6 (1.4)	11 (0.7)
Symptomatic idiopathic VA[b]	1 (1.0)	0	6 (1.4)*	5 (0.3)*
Hypertension[c,*]	25 (25.5)	15 (14.9)	85 (20.1)	225 (14.5)
Any Cardiovascular Medical History				
Atrial fibrillation/flutter	8 (8.2)	10 (9.9)	26 (6.2)	101 (6.5)
Ventricular arrhythmia[a]	0	1 (1.0)	1 (0.2)	14 (0.9)
Hypertension[c]	45 (45.9)	39 (38.6)	206 (48.8)	669 (43.2)

Atrial Fibrillation/Flutter



[a]Ventricular arrhythmia including ventricular tachyarrhythmia (SMQ narrow), ventricular arrhythmias and cardiac arrest (High Level Term MedDRA version 24.0). [b]Symptomatic idiopathic ventricular arrhythmia is defined as a ventricular arrhythmia occurring in structurally normal hearts in the absence of myocardial scarring and active infections and were grade ≥2 per CTCAE. [c]Including hypertension (SMQ narrow). [d]EAIR, as incidence per 100 person-month. [e]Descriptive 2-sided *P* value. **P* <0.05 for EAIR difference between treatments.
AE, adverse event; EAIR, exposure-adjusted incidence rates; SMQ, Standardized MedDRA (Medical Dictionary for Regulatory Activities) queries; VA, ventricular arrhythmia.

CONCLUSIONS

- With long-term follow-up, zanubrutinib continued to demonstrate clinically meaningful efficacy in patients with WM
  - Although not statistically significant at primary analysis, a consistent trend of deeper, earlier, and more durable responses (CR+VGPR) compared with ibrutinib was observed over time
  - PFS and OS continued to favor zanubrutinib treatment compared with ibrutinib
- Zanubrutinib provided faster and deeper responses in patients with *MYD88*^{MUT} *CXCR4*^{MUT} compared to ibrutinib, and responses to zanubrutinib in patients with *MYD88*^{WT} (cohort 2) continued to deepen over time
- Safety advantages of zanubrutinib remained consistent with less off-target activity compared with ibrutinib
  - Fewer patients discontinued zanubrutinib owing to AEs
  - Cardiovascular adverse events were less common in patients receiving zanubrutinib

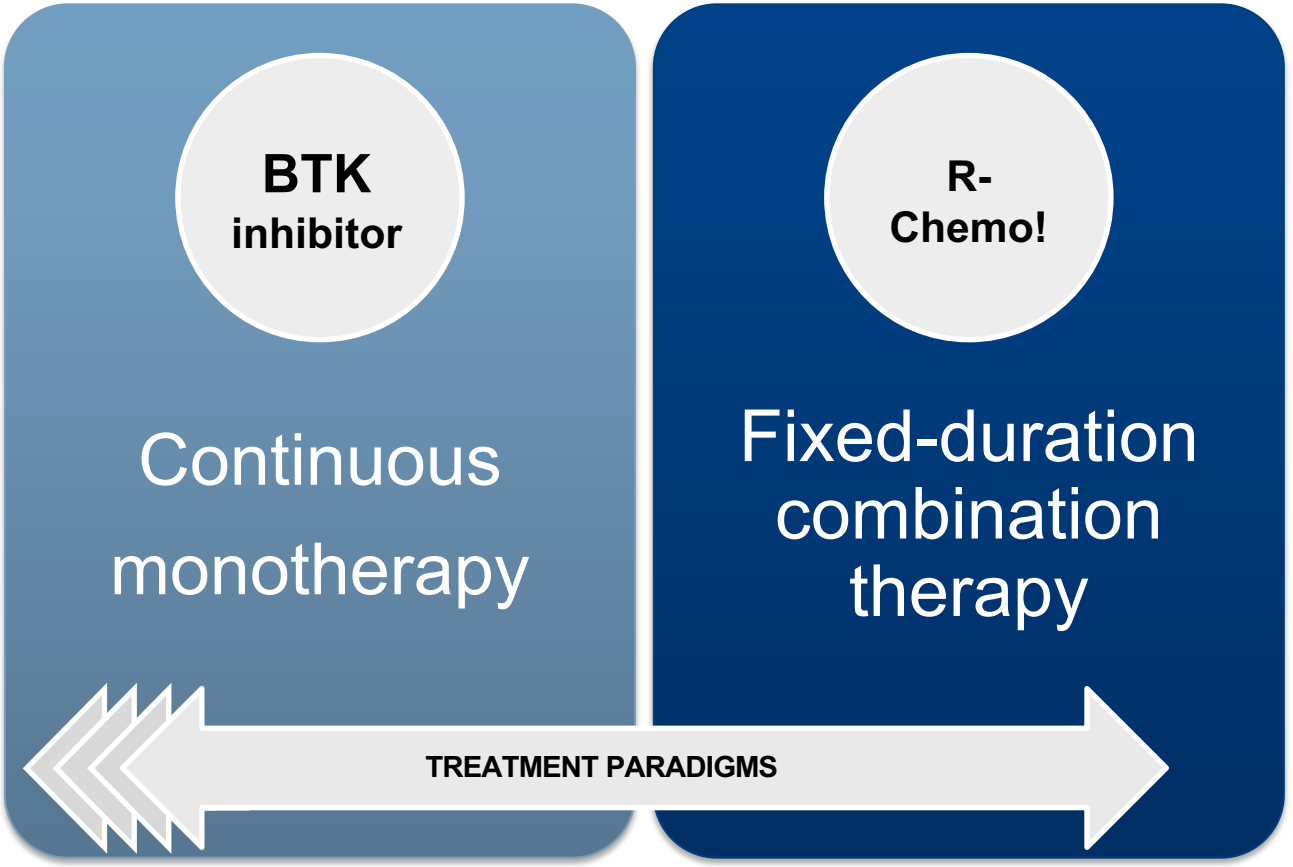
AE, adverse event; CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; *MYD88*, myeloid differentiation primary response 88 gene; VGPR, very good partial response; MUT, mutant; OS, overall survival; PFS, progression-free survival; WM, Waldenström macroglobulinemia; WT, wild type.

Agenda

1. **Wie alles begann…, und wo stehen wir heute**
2. **Der Morbus Waldentström – eine komplexe Erkrankung**
   - Definition
   - molekulare Alterationen: Diagnostik und klinische Implikatonen
   - Definitionen Ansprechen
3. **Behandlung**
   - Immunchemotherapie
   - Stellenwert Erhaltungstherapie
   - Ibrutinib
   - Zanubrutinib
4. **Zukünftige Entwicklungen**
5. **Fallbeispiel**

Waldenström's macroglobulinemia - an Update

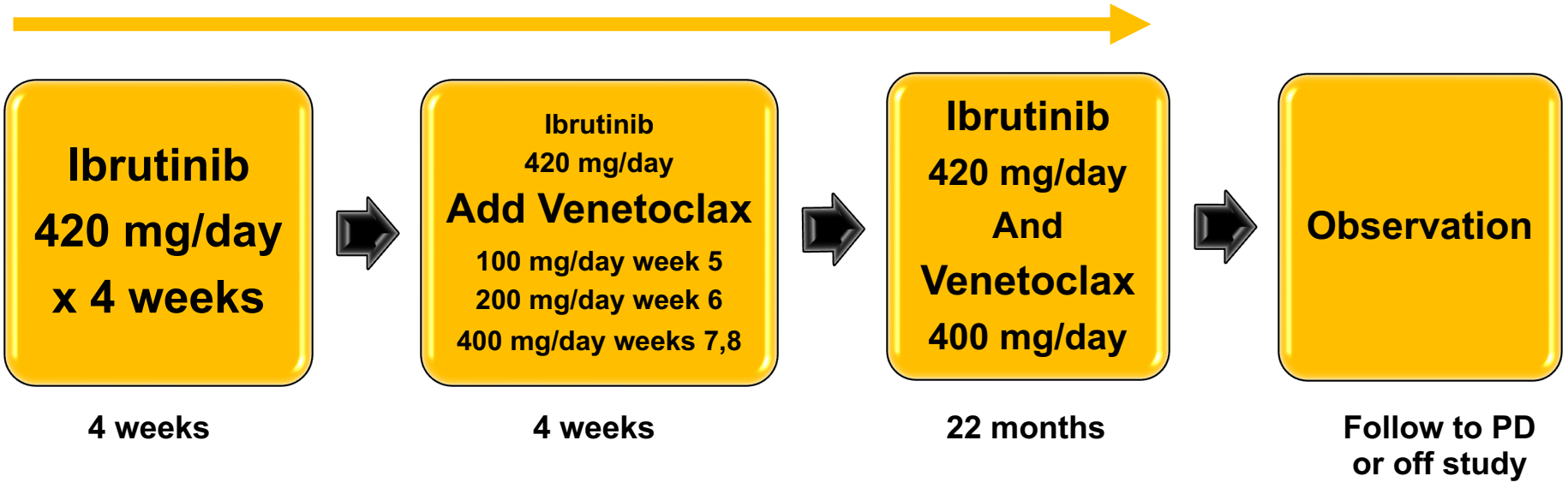
Quo Vadis?



Timely fixed duration chemofree approaches!

Ibrutinib/venetoclax in treatment naïve WM

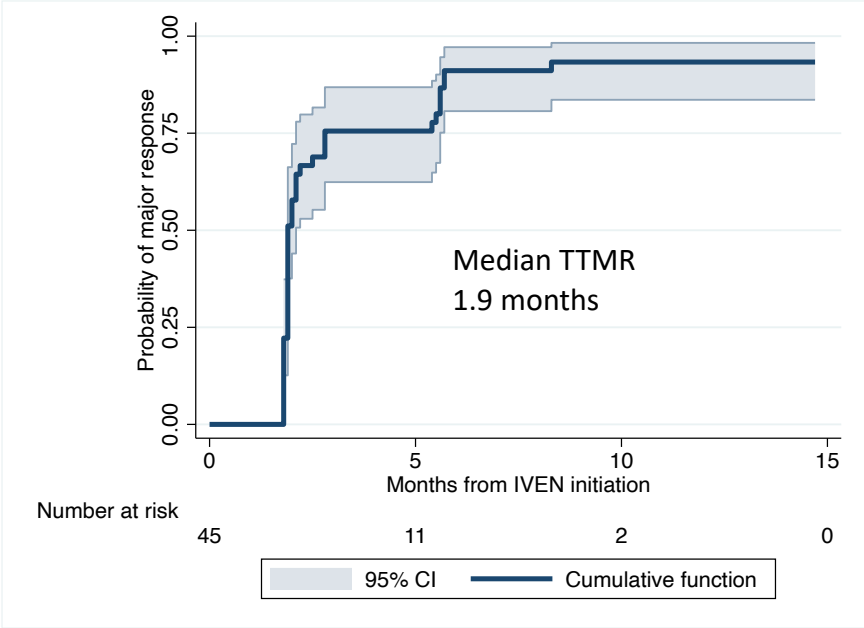
24 months

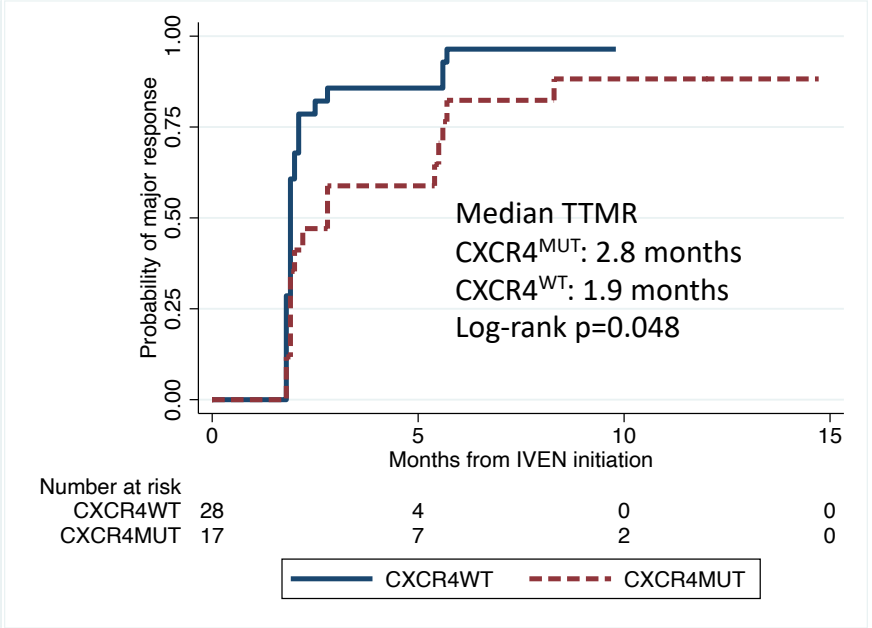


Jorge Castillo, PI (DFCI)

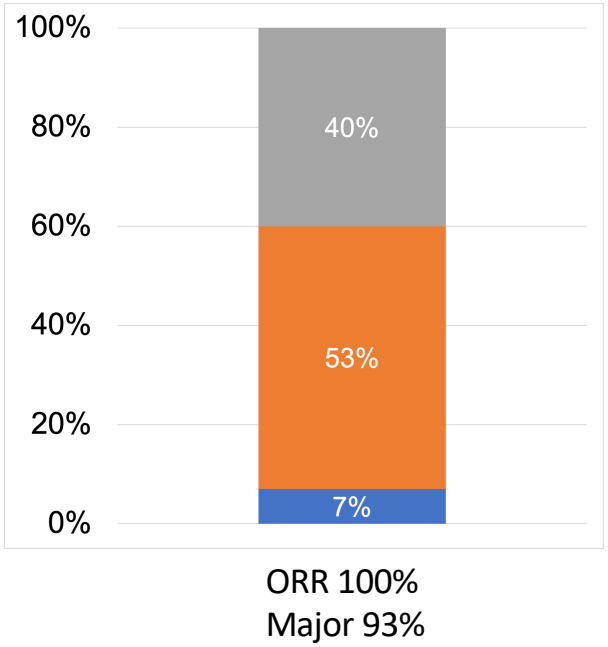
Clinicaltrials.Gov: NCT04273139

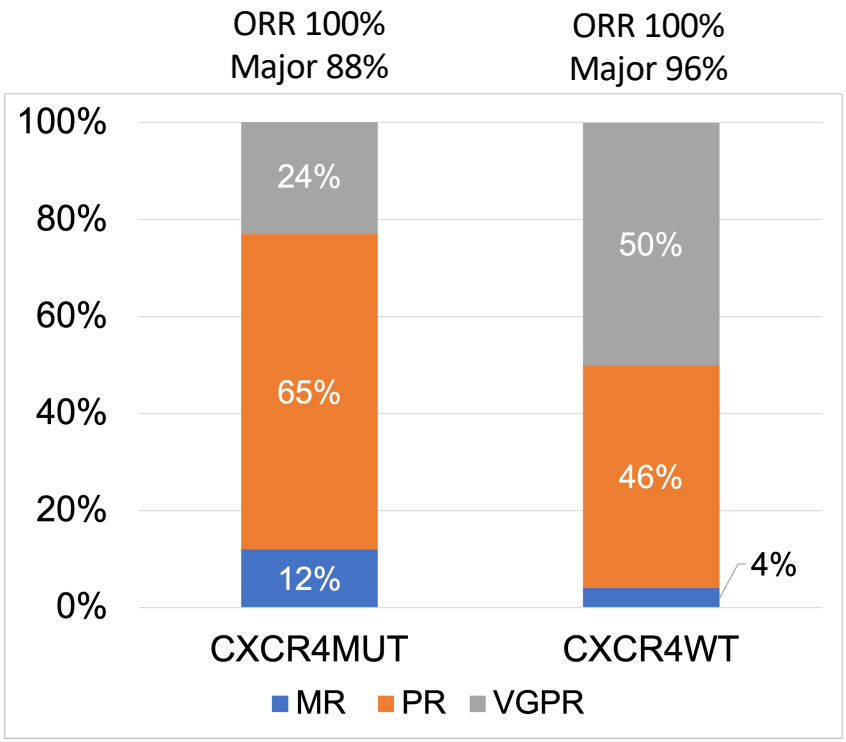
Time to major response





Response to therapy



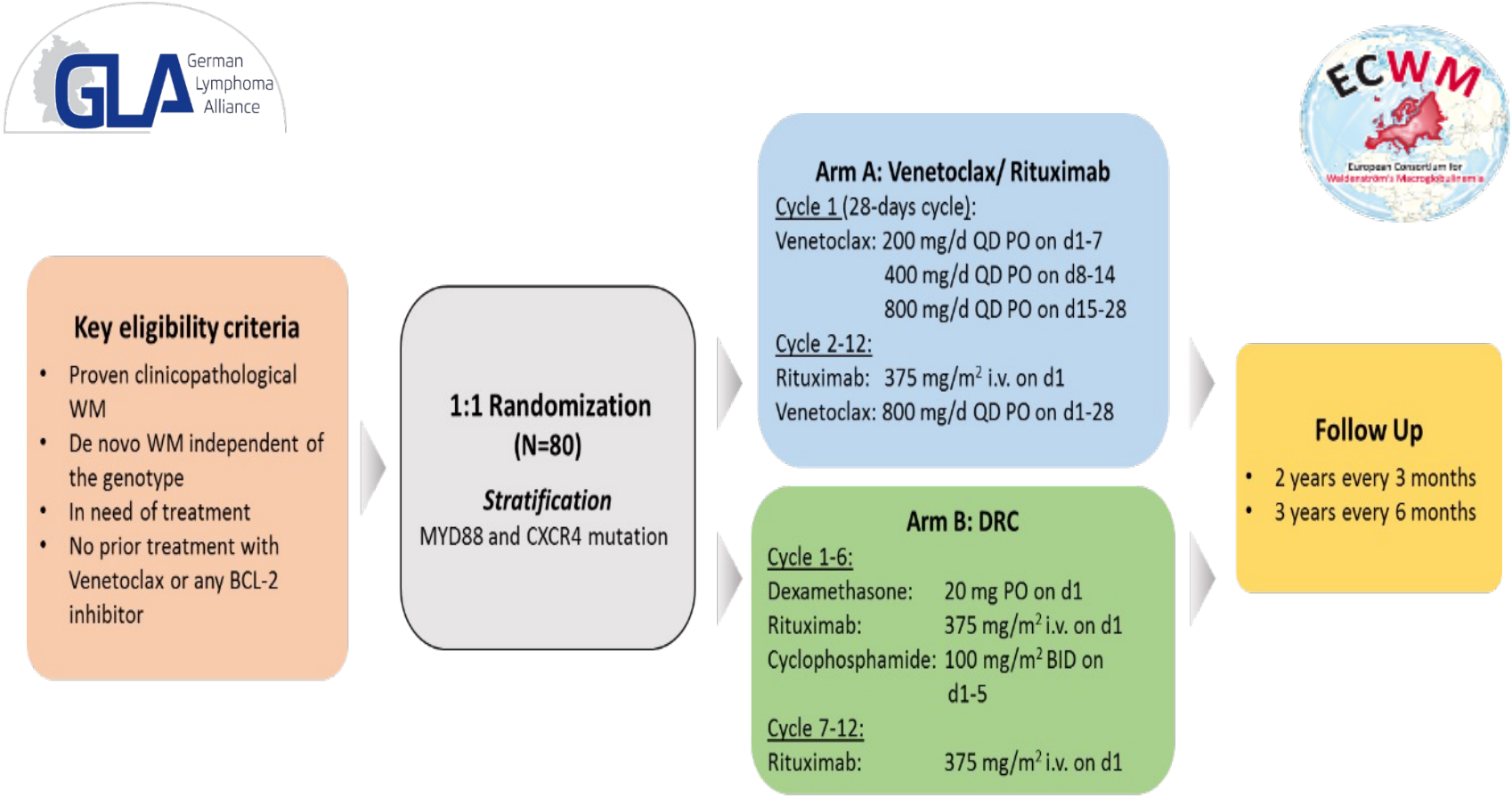


Safety

Adverse events observed in ≥3 patients and of clinical importance

Adverse events	Grade 2	Grade 3	Grade 4	Grade 5	Total
Anemia	1	2			3
Atrial fibrillation	1	2	1		4
Diarrhea	8	1			9
Reflux	10				10
Mucositis	7	2			9
Nausea	5				5
Neutropenia	1	10	3		14
Hyperphosphatemia	8				8
Muscle/joint pain	14	2			16
Skin rash	6				6
Ventricular arrhythmia	***1***		***1***	***2***	***4***
Laboratory TLS		2			2

VIWA-1 trial | Study design



Waldenström's macroglobulinemia - an Update

Quo Vadis?

What are the key challenges?

Sequencing of treatment – development of resistance

Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed/Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study

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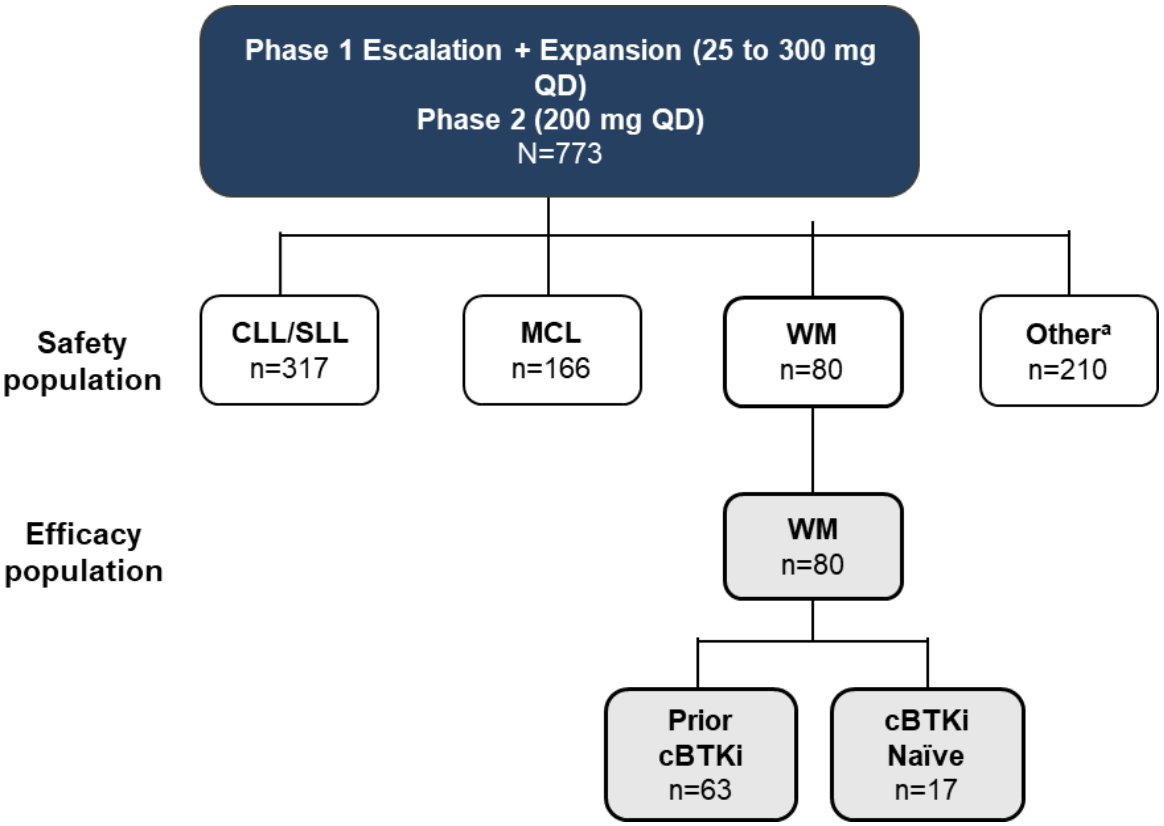
Phase 1/2 BRUIN Study

Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

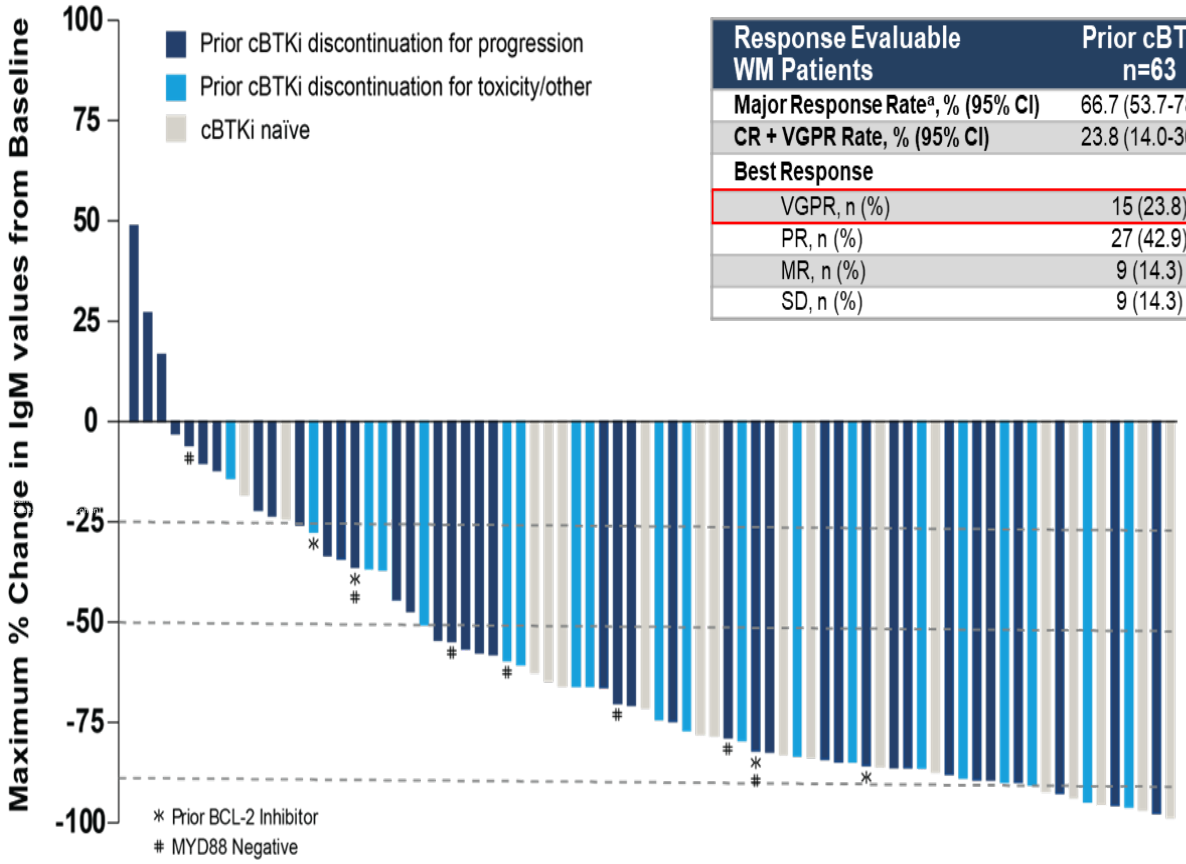
- Safety/tolerability
- Determine MTD and recommended Phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DoR (IWWM6/Modified IWWM6) as assessed by Investigator

Data cutoff date of 29 July 2022.
[a]Other includes DLBCL, Richter transformation, FL, MZL, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation

Patient Characteristics

Characteristics	Prior cBTKi n=63	cBTKi Naïve n=17
Median age (range), years	69 (42-84)	68 (47-83)
Male, n (%)	42 (67)	10 (59)
ECOG PS, n (%)		
0	34 (54)	9 (53)
1	28 (44)	8 (47)
2	1 (2)	0 (0)
Median number prior lines of systemic therapy (range)	3 (1-11)	2 (1-4)
Prior therapy, n (%)		
cBTK inhibitor	63 (100)	0 (0)
Chemotherapy	52 (83)	17 (100)
Anti-CD20 antibody	58 (92)	16 (94)
CIT + BTK inhibitor	50 (79)	0 (0)
PI3K inhibitor	3 (5)	0 (0)
Immunomodulator	6 (10)	2 (12)
BCL2 inhibitor	4 (6)	0 (0)
Autologous stem cell transplant	4 (6)	0 (0)
Other systemic therapy	31 (49)	6 (35)
Reason discontinued any prior BTK inhibitor[a,b], n (%)		
Progressive disease	41 (65)	-
Toxicity/Other	21 (33)	-

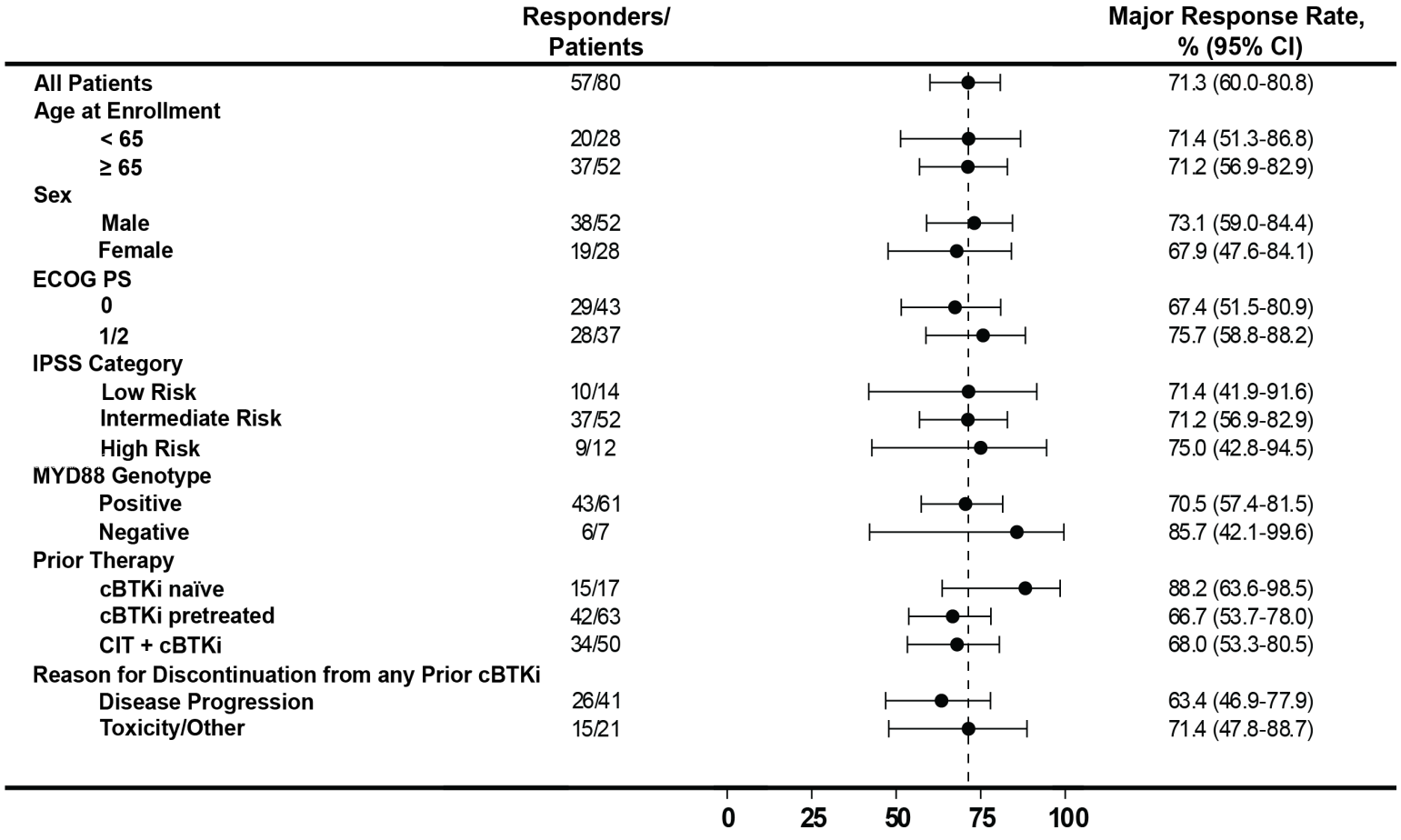
Pirtobrutinib Efficacy in WM Patients



Response Evaluable WM Patients	Prior cBTKi n=63	cBTKi Naïve n=17
Major Response Rate[a], % (95% CI)	66.7 (53.7-78.0)	88.2 (63.6-98.5)
CR + VGPR Rate, % (95% CI)	23.8 (14.0-36.2)	29.4 (10.3-56.0)
Best Response		
VGPR, n (%)	15 (23.8)	5 (29.4)
PR, n (%)	27 (42.9)	10 (58.8)
MR, n (%)	9 (14.3)	0 (0)
SD, n (%)	9 (14.3)	2 (11.8)

Data cutoff date of 29 July 2022. Data for 4 patients are not shown in the waterfall plot due to missing IgM values at baseline or response assessment. Response as assessed by investigator based on Modified IWWM6 (Owen's) criteria. Under modified IWWM6 criteria, a PR is upgraded to VGPR if corresponding IgM is in normal range or has at least 90% reduction from baseline. [a]Major response includes subjects with a best response of CR, VGPR, or PR. Total % may be different than the sum of the individual components due to rounding.

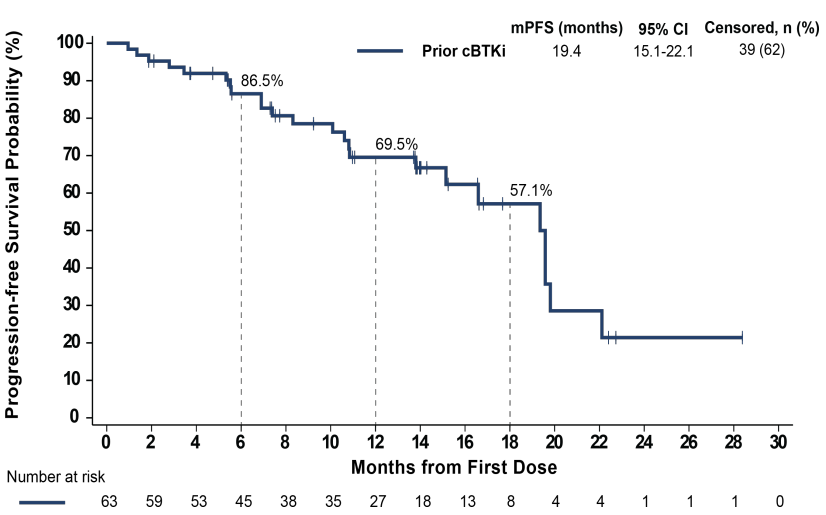
Major Response Rate in WM Subgroups



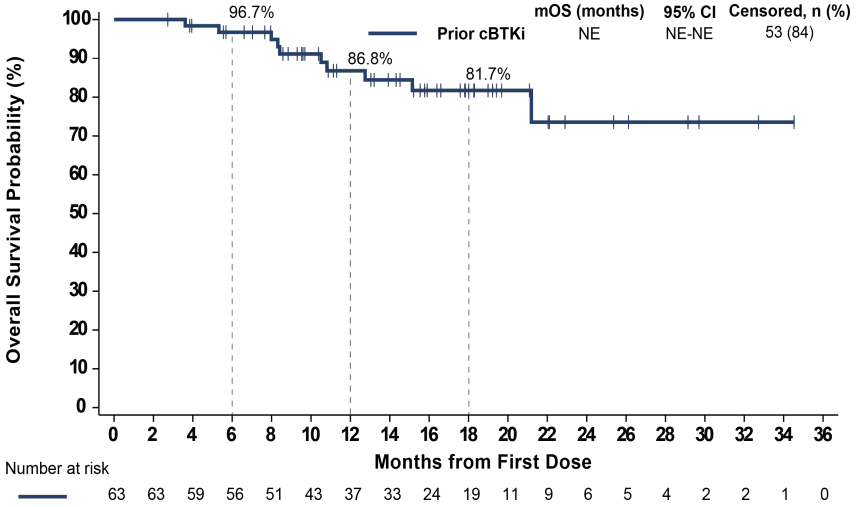
Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.

Progression-Free Survival and Overall Survival in Prior cBTKi Patients

Progression-Free Survival



Overall Survival



- The median follow-up for PFS and OS in patients who received prior cBTKi was 14 and 16 months, respectively
- 55.6% (35/63) of patients who received prior cBTKi remain on pirtobrutinib

Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.

Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

Median time on treatment for the overall safety population was 9.6 months
Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
Overall and WM safety profiles are generally consistent[h]

Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]WM safety population data can be found via QR code. Constipation is more commonly seen as a TEAE in the WM population than in all patients.

Phase II study of Pirtobrutinib plus Venetoclax in WM

- Single-arm, open-label phase II study
- DFCI/MGH
- 42 patients
- 24 cycles, 1 cycle just Pirtobrutinib

Jorge Castillo, PI (DFCI)
Shayna Sarosiek, Co-Inv. (DFCI)

ClinicalTrials.gov Identifier: NCT03740529

Agenda

1. **Wie alles begann…, und wo stehen wir heute**
2. **Der Morbus Waldentström – eine komplexe Erkrankung**
   - Definition
   - molekulare Alterationen: Diagnostik und klinische Implikatonen
   - Definitionen Ansprechen
3. **Behandlung**
   - Immunchemotherapie
   - Stellenwert Erhaltungstherapie
   - Ibrutinib
   - Zanubrutinib
4. **Zukünftige Entwicklungen**
5. **Fallbeispiel**

WM Case 1 - Introduction

2012: 51 years

1. arterial hypertension, IgM kappa “MGUS” (no marrow assessment)
2. Hb=12,7 g/dL, WBC=6.2 $10^9/mm^3$, PMN=3.16 $10^9/mm^3$, Platelet=289 $10^9/mm^3$. IgM concentration: 9g/L

May 2020: 59 years

1. Epistaxis, BP=160/90 mmHg, systolic BP: sometimes 190 mmHg,
2. No lymph nodes
3. Hb=10.2 g/dL WBC=3.7 $10^9/mm^3$, PMN=2.07 $10^9/mm^3$,Platelet=198 $10^9/mm^3$.
4. IgM concentration: 60,9 g/L; β_2-microglobulin: 2,4 *mg/L*

5. Bone marrow biopsy:
    1. diffuse lymphoid infiltration (>80%),
    2. MYD88 (L265P) positive
    3. CXCR4 mutated
6. Cryoglobulin: positive, high titer, preventing the identification of the type
7. Fundoscopic:
    1. February 2011: central retinal hemorrhages, tortuous blood vessels, good control of BP
    2. May 2011: small blot-like retinal hemorrhages, tortuous blood vessels with venous sausaging

June 2020

1. Hb=9.1 g/dL, Platelet=214 $10^9/mm^3$, WBC=3.9 $10^9/mm^3$, PMN=1.99 $10^9/mm^3$,

Weiterer Verlauf

December 4, 2020: **60 years**

1. Weight loss (7 kg), asthenia (ECOG=3)
2. Epistaxis, no lymph node
3. Hb=7.8 g/dL, Platelet=134 $10^9/mm^3$, WBC=3.6 $10^9/mm^3$, PMN=2.23 $10^9/mm^3$
4. IgM concentration: 94,5 g/L, viscosity 7,11 Cst
5. dizziness

6. **Fundoscopy:**
   -- multiple retinal hemorrhages, tortuous blood vessels

6. **Bone marrow biopsy:**
   -- Diffuse infiltrate of B-cells (50%)
   -- Mastocytes
   -- Eosinophil deposit (light chain deposit?)

Welche Therapie würden Sie in dieser Situation zunächst wählen?

1. DRC (Dexamethason, Rituximab, Cyclophosphamide)
2. R-Bendamustin
3. Ibrutinib
4. Ibrutinib/Rituximab
5. Zanubrutinib
6. Notfall - Plasmapherese

Wie würden Sie zunächst vorgehen?

1. **December 4, 2020**:
    1. Weight loss (7 kg), asthenia (ECOG=3)
    2. *Epistaxis, no lymph node*
    3. Hb=7.8 g/dL, Platelet=134 $10^9/mm^3$, WBC=3.6 $10^9/mm^3$, PMN=2.23 $10^9/mm^3$
    4. *IgM concentration: 94,5 g/L, viscosity 7,11 Cst*
    5. *dizziness*
    6. **Fundoscopy:**
        -- *multiple retinal hemorrhages, tortuous blood vessels*
    6. **Bone marrow biopsy:**
        -- Diffuse infiltrate of B-cells (50%)
        -- Mastocytes
        -- Eosinophil deposit (light chain deposit?)
    7. **Prognostic assessment**
        -- β2-microglobulin: 3 mg/L

→ Emergency procedure: plasmapheresis

Was würden Sie nach der Plasmapherese machen?

- DRC
- Bortezomib plus Rituximab
- R – Bendamustin
- Ibrutinib plus/minus Rituximab
- Zanubrutinib

Klinischer Verlauf

1. **Patient was treated with DRC**

Patient follow – up 9/2022 in PR

→ **Progression, Anemia, rising IgM, Fatigue**

Welche Therapie würden Sie in dieser Situation wählen?

1. Erneut DRC (Dexamethason, Rituximab, Cyclophosphamide)
2. R-Bendamustin
3. Ibrutinib
4. Ibrutinib/Rituximab
5. Zanubrutinib

Klinischer Verlauf

1. **Patient was treated with Zanubrutinib**

Last Patient follow – up 8/2023 in PR

The journey will go on……

Acta Medica Scandinavica. Vol. CXVII, fasc. III—IV, 1944.

(From Med. Clin. Akad. Hospital, Upsala (Sweden). Chief: Prof. G. Bergmark).

Incipient myelomatosis or «essential« hyperglobulinemia with fibrinogenopenia — a new syndrome?

By

JAN WALDENSTRÖM.

Submitted for publication September 2, 1943.

The real nature of myelomatosis.


Bi-specifc antibodies?


CAR-T‘s everywhere!
CAR-T cells attacking cancer cells
Photo Source: Sloan Kettering Cancer Center; courtes


The future looks bright!