Relapsed/refractory Waldenström's macroglobulinemia: Key considerations for managing pre-treated patients

Wednesday, March 10, 2021 | 17:00–18:30 (CET)

Welcome and introductions

Chair: Professor Véronique Leblond

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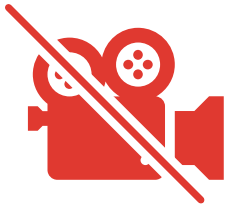
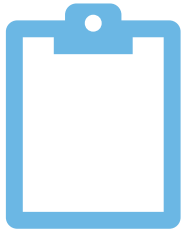
- Prescribing information (PI) may vary depending on local approval in each country. Therefore, before prescribing any product, always refer to local materials such as the PI and/or the summary of product characteristics (SPC).
- Zanubrutinib is not approved for the treatment of Waldenström’s macroglobulinemia outside Canada.

Housekeeping



Please note that personal recording of this meeting is not permitted

Exit full screen view at any time to submit a question for the panel to answer during the Q&A session



A post-meeting survey will be shared at the end of the webinar;
we would greatly appreciate your feedback

Introducing the speakers

Christian Buske
University Hospital of Ulm, Germany

Ramón García-Sanz
University Hospital of Salamanca, Spain

Véronique Leblond
Pitié-Salpêtrière Hospital, France

Alessandra Tedeschi
Niguarda Cancer Center, Italy

Disclosures

- **Speaker bureau:** Roche, Gilead, Janssen, AbbVie, BeiGene, GSK
- **Board:** Roche, Pharmacyclics, Janssen-Cilag, GSK, Gilead, AstraZeneca, AbbVie
- **Honoraria:** Roche, Pharmacyclics, Janssen-Cilag, GSK, Gilead, Lilly, Amgen, AstraZeneca, BeiGene

Agenda

17:00	**Welcome and introductions**	Véronique Leblond
	Plenary presentation	
17:05	What is the current approach for patients that are refractory to or experience relapse following first-line treatment?	Christian Buske
	Case studies	
17:25	A patient refractory to first-line treatment	Ramón García-Sanz
17:35	A patient with relapsed WM	Alessandra Tedeschi
17:45	Case study panel discussion	**Moderator**: Véronique Leblond
	Open panel discussion	
17:55	What are the greatest difficulties in the treatment of patients with refractory or relapsed WM and what does the future hold?	**Moderator**: Christian Buske **Panel**: All
	Audience Q&A	**Moderator**: Véronique Leblond
18:15	What challenges do you face in treating WM?	**Panel**: All
18:25	**Summary**	Véronique Leblond

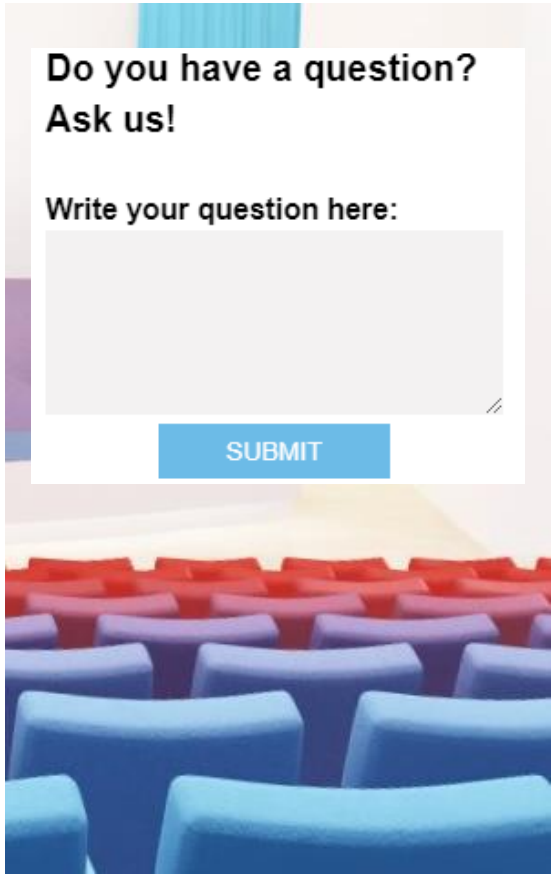
WM, Waldenström's macroglobulinemia.

A guide to the meeting platform

Please exit full screen view to submit a question for the panel

Audience questions:

- Please enter your question in the submission box
- Because of the volume of questions expected today, some questions received might not be answered during the session



What is the current approach for patients that are refractory to or experience relapse following first-line treatment?

Professor Christian Buske
University Hospital of Ulm, Germany

Disclosures

- **Honoraria**: Roche, Janssen, BeiGene, Celltrion, Pfizer, AbbVie, Bayer
- **Research funding**: Roche, Janssen, Celltrion, AbbVie, Bayer, MSD

Waldenström's macroglobulinemia

- First described by Jan Gosta Waldenström in 1944
- IgM protein or paraprotein
- Bone marrow infiltration by lymphoplasmacytic lymphoma

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

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

By

JAN WALDENSTRÖM.

Submitted for publication September 2, 1943.

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 these two patients but also shows other signs, that do not fit in so well with the picture.

IgM, immunoglobulin M.

Waldenström J. *Acta Med Scand* 1944; 117 (3–4): 216–247.

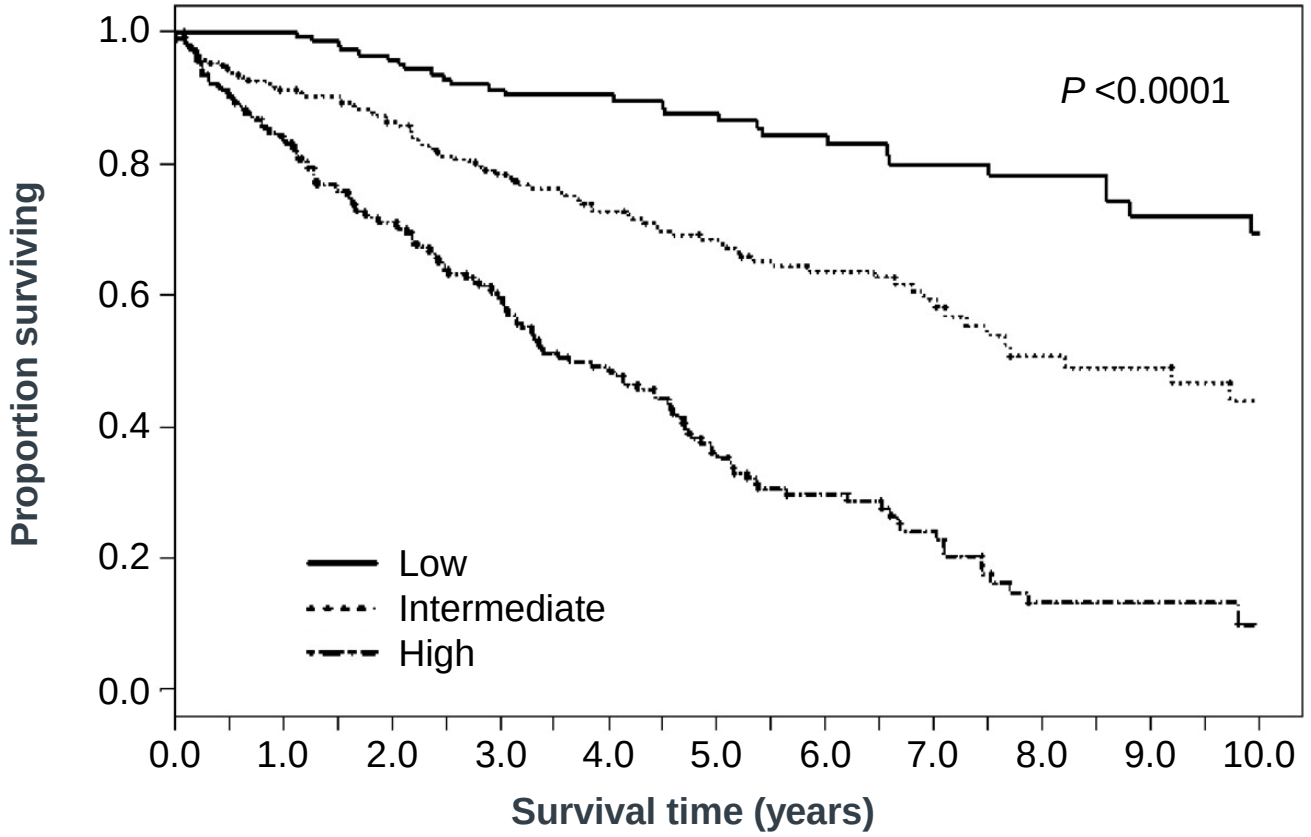
Waldenström's macroglobulinemia is an incurable disease and with this a disease of the 'relapsed patient'!

Thus, developing strategies for optimal care of relapsed patients is vital!

Patients are relapsing…

The International Prognostic Scoring System for WM

Survival after treatment initiation according to the IPSSWM



- Age >65 years
- Hemoglobin ≤11.5 g/dL
- Platelets ≤100 × 10^9/L
- β_2-microglobulin >3 mg/L
- M protein >7.0 g/dL

Low risk = 0 or 1 (except age)

Intermediate risk = age or 2

High risk = ≥3

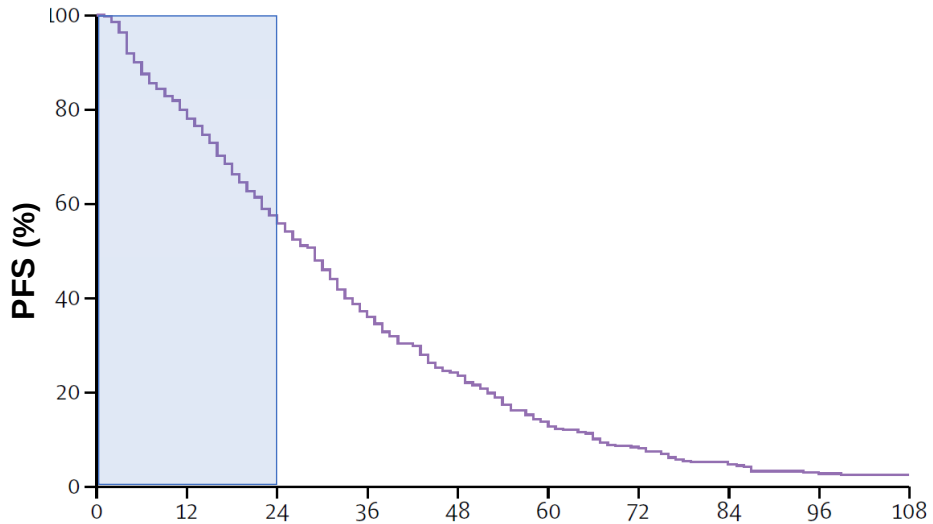
IPSSWM, International Prognostic Scoring System for Waldeström's macroglobulinemia; WM, Waldenström's macroglobulinemia.

Morel P *et al*. *Blood* 2009; 113 (18): 4163–4170.

How many patients are at risk of progression?

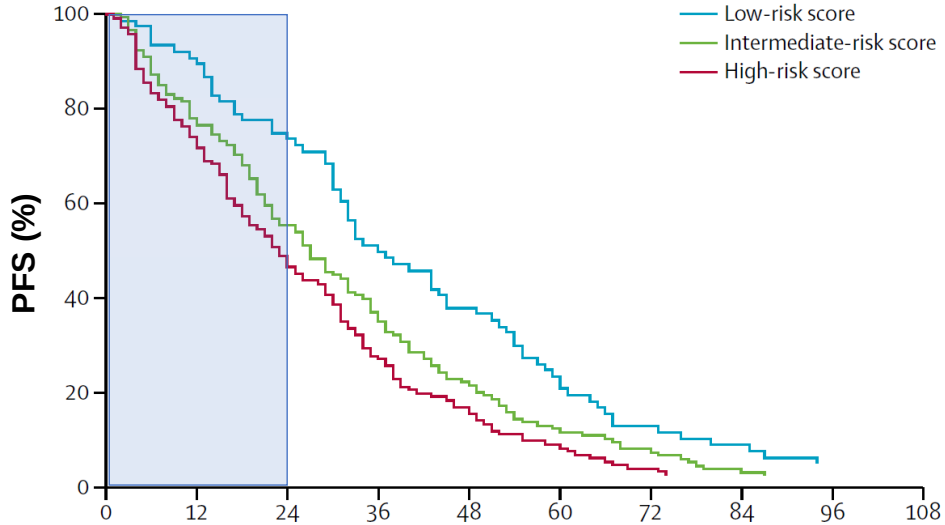
- The group of high-risk patients is not small
  - A significant proportion of ‘low’ and ‘intermediate’ risk patients will experience progression or relapse within 24 months (‘POD24’ patients)

PFS for all patients with WM (N = 454)



Number at risk	454	363	261	169	111	63	39	24	15	12

PFS by IPSSWM risk score (N = 357)



Number at risk										
Low-risk score	76	69	57	39	29	18	10	7	.	..
Intermediate-risk score	142	111	79	53	32	18	12	6	..	..
High-risk score	139	103	68	39	24	13	6	..	..	..

IPSSWM, International Prognostic Scoring System for Waldeström’s macroglobulinemia; PFS, progression-free survival; POD24, progression of disease within 24 months; WM, Waldenström’s macroglobulinemia.
Buske CB *et al. Lancet Haematol*. 2018; 5 (7): e299–e309.

Relapsed and refractory WM and when to treat

All patients with WM will ultimately relapse

- The indications to treat outlined in the ESMO guidelines apply to patients with R/R WM

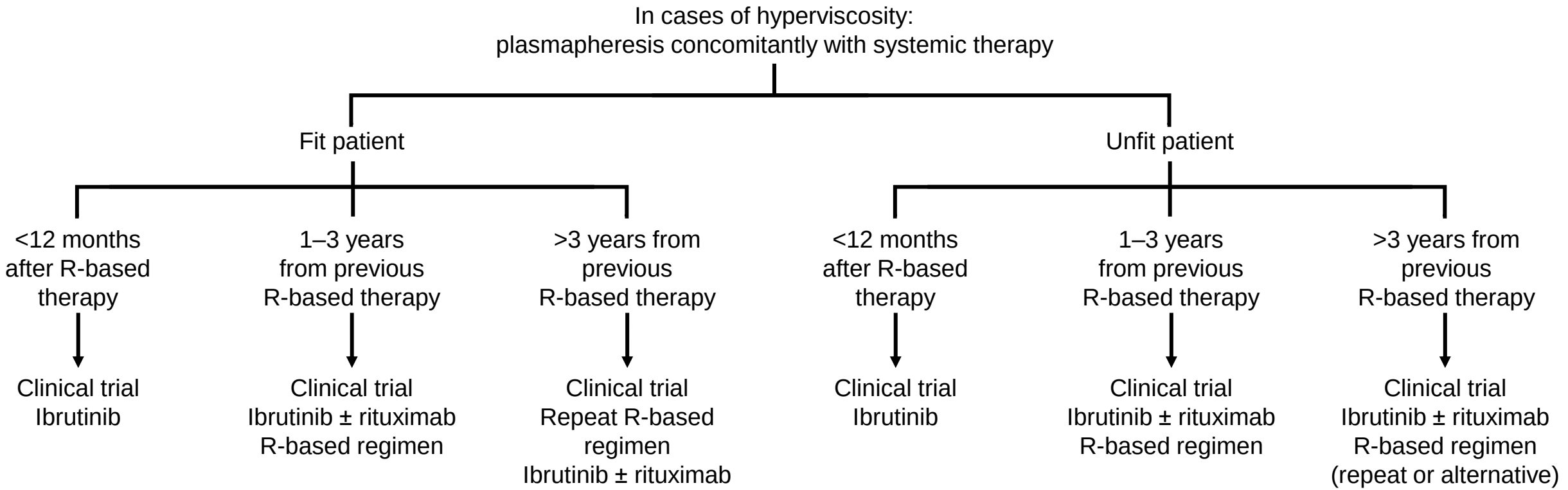
Clinical indications
Recurrent fever, night sweats, weight loss, fatigue
Hyperviscosity
Lymphadenopathy: either symptomatic or bulky (≥5 cm in maximum diameter)
Symptomatic hepatomegaly and/or splenomegaly
Symptomatic organomegaly and/or organ or tissue infiltration
Peripheral neuropathy due to WM

Laboratory indications
Symptomatic cryoglobulinemia
Symptomatic cold agglutinin anemia
Autoimmune hemolytic anemia and/or thrombocytopenia
Nephropathy related to WM
Amyloidosis related to WM
Hemoglobin ≤10 g/dL
Platelets <100 × 10^9/L
IgM levels >60 g/L

ESMO, European Society for Medical Oncology; IgM, immunoglobulin M; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

Kastritis E *et al*. *Ann Oncol* 2018; 29 (Suppl 4): iv41–iv50.

ESMO guidelines for relapsed WM (adapted)[1,2]



ESMO, European Society for Medical Oncology; IgM, immunoglobulin M; R, rituximab; WM, Waldenström's macroglobulinemia.

1. Kastritis E *et al*. *Ann Oncol* 2018; 29 (Suppl 4): iv41–iv50. 2. Grunenberg A and Buske C. *Hemasphere* 2019; 3: 65–67.

Do we obey our own guidelines?

- **There is no standard treatment for relapsed patients!**

- Even in a relapsed setting, a watch-and-wait strategy is preferred for patients not meeting ESMO guideline treatment criteria
- The choice of treatment for a relapsed patient is based on:
  - Fitness of the patient (consider specific risk factors)
  - Previous therapy
  - Duration of response after the last treatment
- Well-tolerated and effective options in patients with relapsed WM include:
  - Rituximab-based regimens
  - Bortezomib-containing regimens
  - Ibrutinib

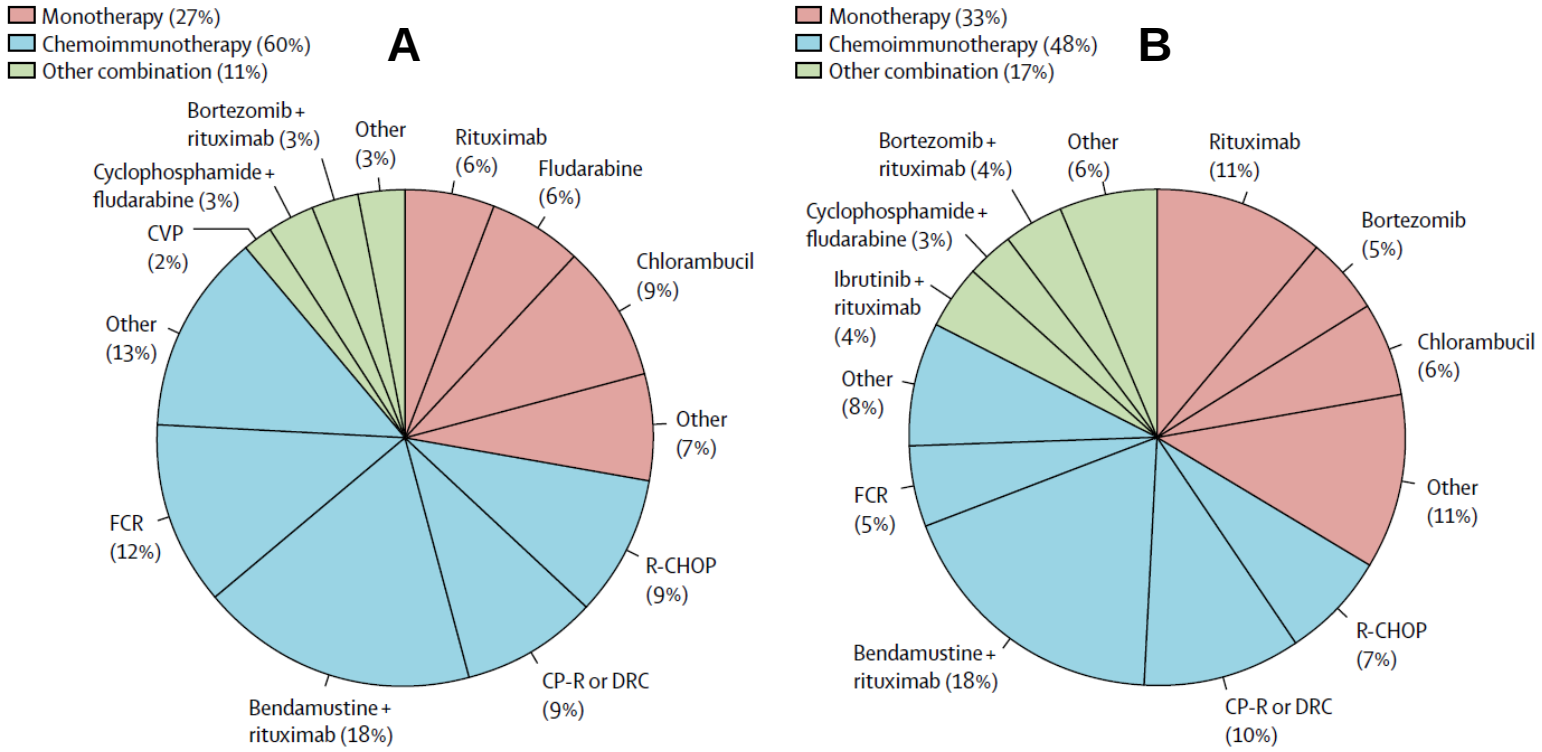
→ **In daily practice, there is a clear trend towards chemotherapy-free approaches and with this towards BTK inhibitors!**

BTK, Bruton's tyrosine kinase; ESMO, European Society for Medical Oncology; WM, Waldenström's macroglobulinemia.
Grunenberg A and Buske C. *Hemasphere* 2019; 3: 65–67.

Treatment choices in R/R WM before the era of BTK inhibitors

- Chemoimmunotherapy and chemotherapy regimens were the most common choice for patients with R/R WM treated between January 2000 and January 2014

(A) Second-line (N=397) and (B) third-line setting (N=160) treatment choices in European patients with WM



BTK, Bruton's tyrosine kinase; CP-R, cyclophosphamide, prednisone, and rituximab; CVP, cyclophosphamide, vincristine, and prednisone; DRC, dexamethasone, rituximab, and cyclophosphamide; FCR, fludarabine, cyclophosphamide, and rituximab; IWWM-10, 10th International Workshop on Waldenström's macroglobulinemia; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

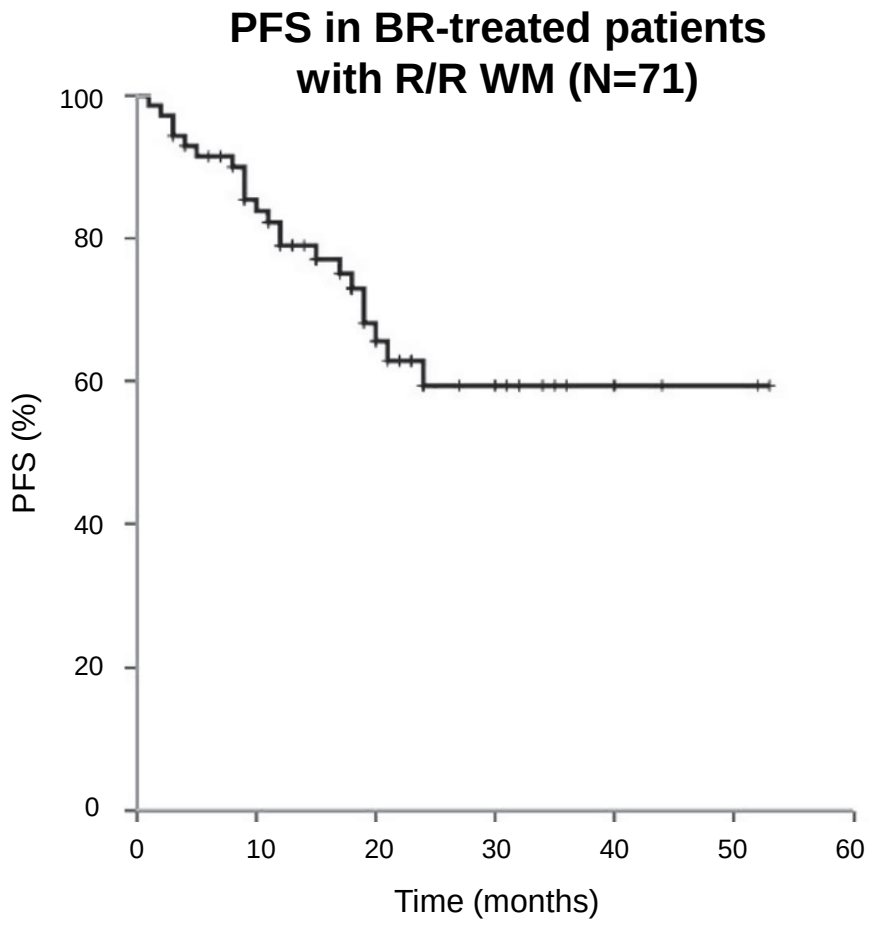
Buske CB *et al. Lancet Haematol*. 2018; 5 (7): e299–e309.

Classical chemotherapy

Bendamustine and rituximab

At 19 months:

- Median PFS not reached
- ORR = 80.2%
- MRR = 74.6%
- Grade ≥3 neutropenia = 13%



BR, bendamustine and rituximab; MRR, major response rate; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

Tedeschi A *et al*. *Leuk. Lymphoma* 2015; 56 (9): 2637–2642.

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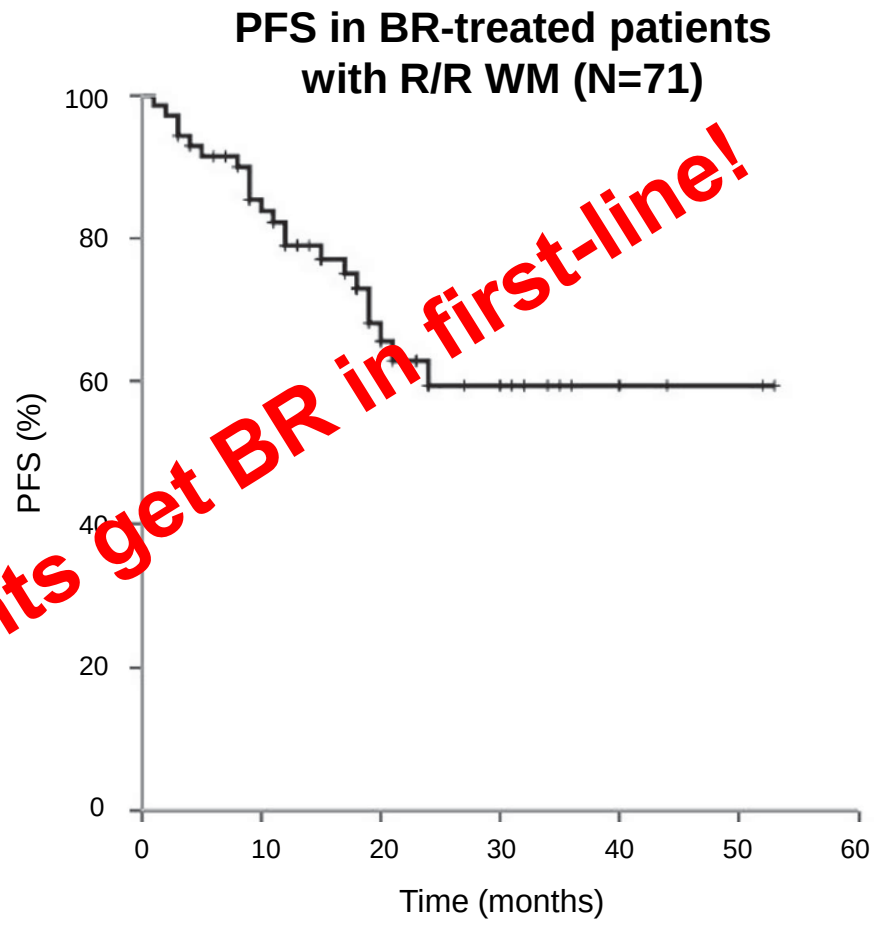


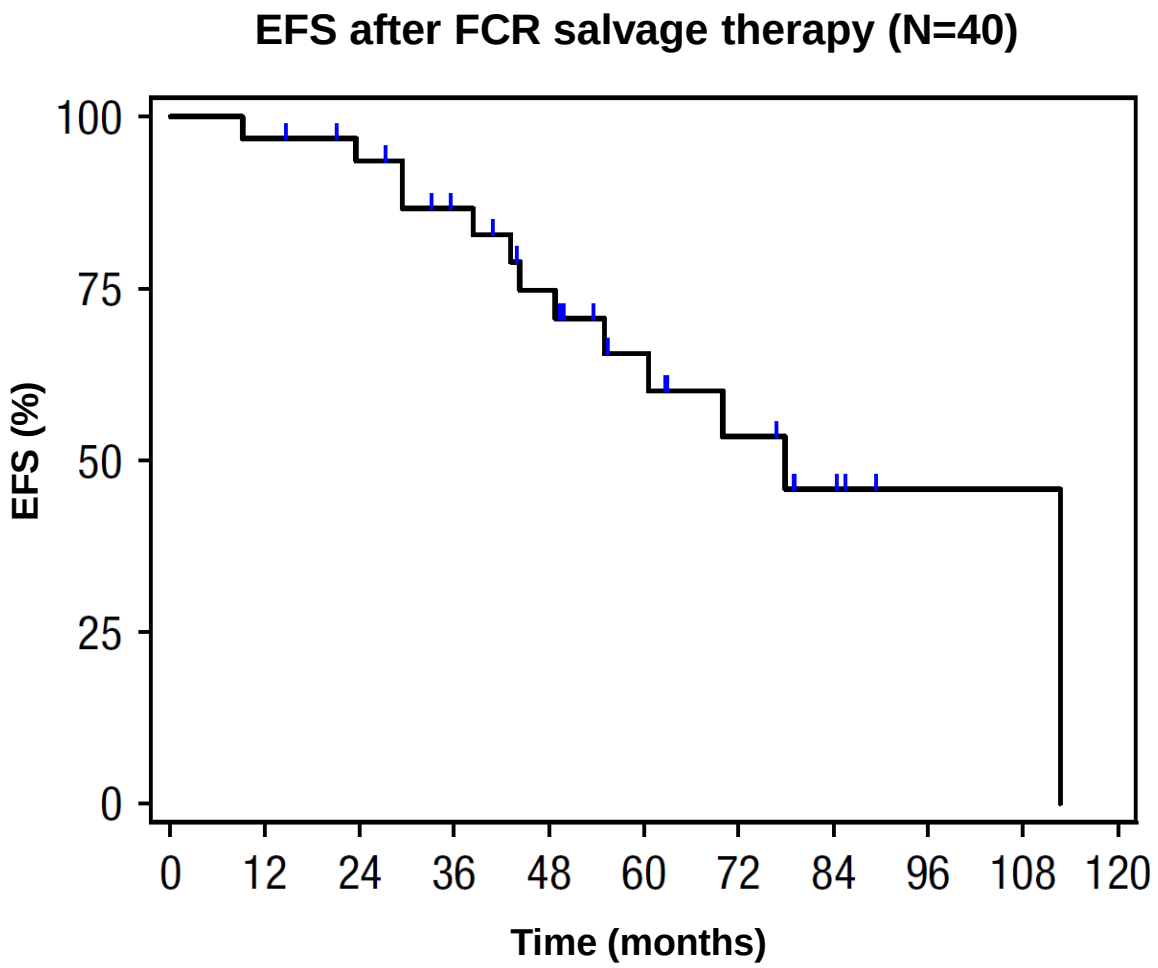
Many patients get BR in first-line!

BR, bendamustine and rituximab; MRR, major response rate; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.
Tedeschi A *et al*. *Leuk. Lymphoma* 2015; 56 (9): 2637–2642.

Fludarabine, cyclophosphamide, and rituximab

Retrospective study:

- ORR = 80%
- MRR = 80%
- Grade ≥3 neutropenia = 61%
- Discontinued because of myelosuppression and infection = 30%



EFS, event-free survival; FCR, fludarabine, cyclophosphamide, and rituximab; MRR, major response rate; ORR, overall response rate; WM, Waldenström's macroglobulinemia.
Tedeschi A *et al*. *Clin. Lymphoma Myeloma Leuk.* 2013; 13 (2): 231–234.

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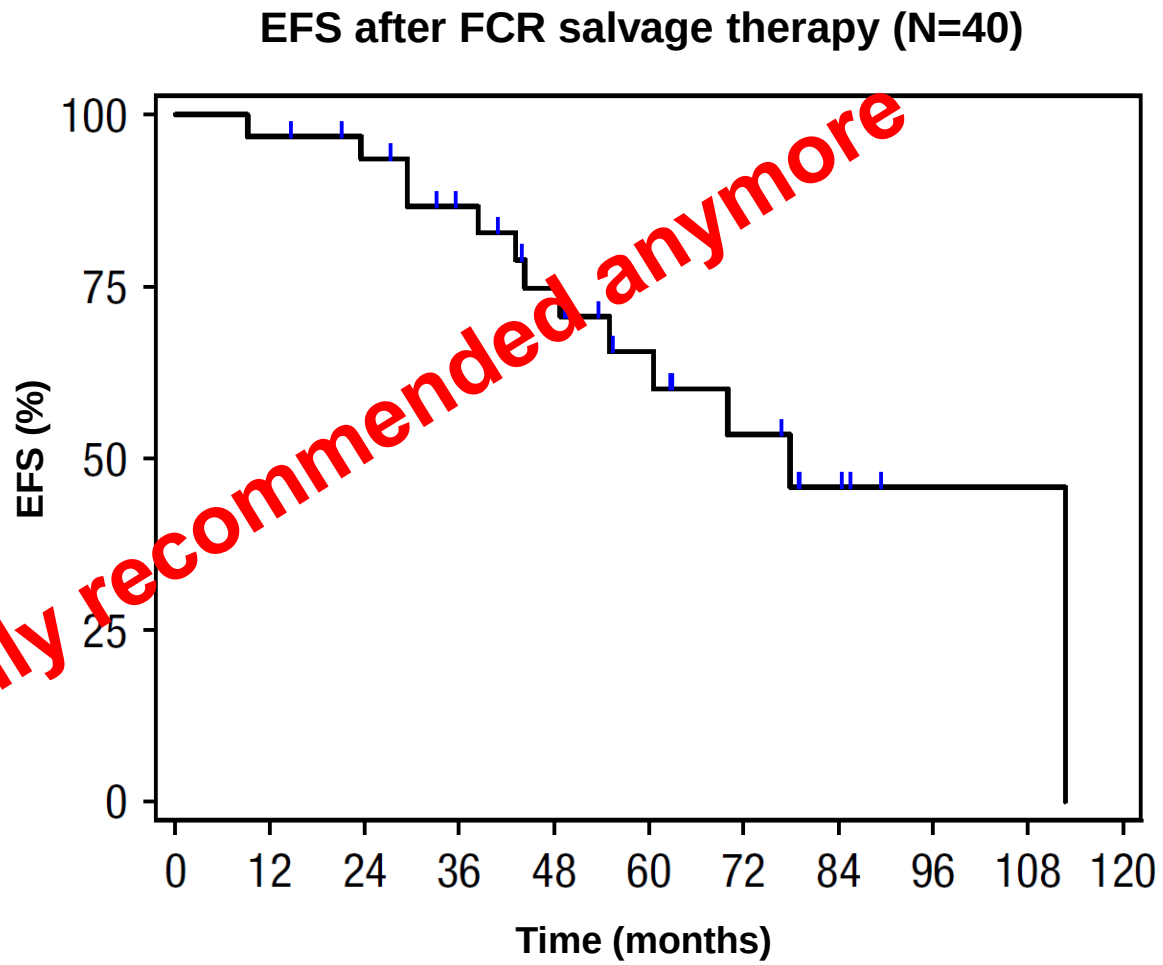


Not generally recommended anymore

EFS, event-free survival; FCR, fludarabine, cyclophosphamide, and rituximab; MRR, major response rate; ORR, overall response rate; WM, Waldenström's macroglobulinemia.

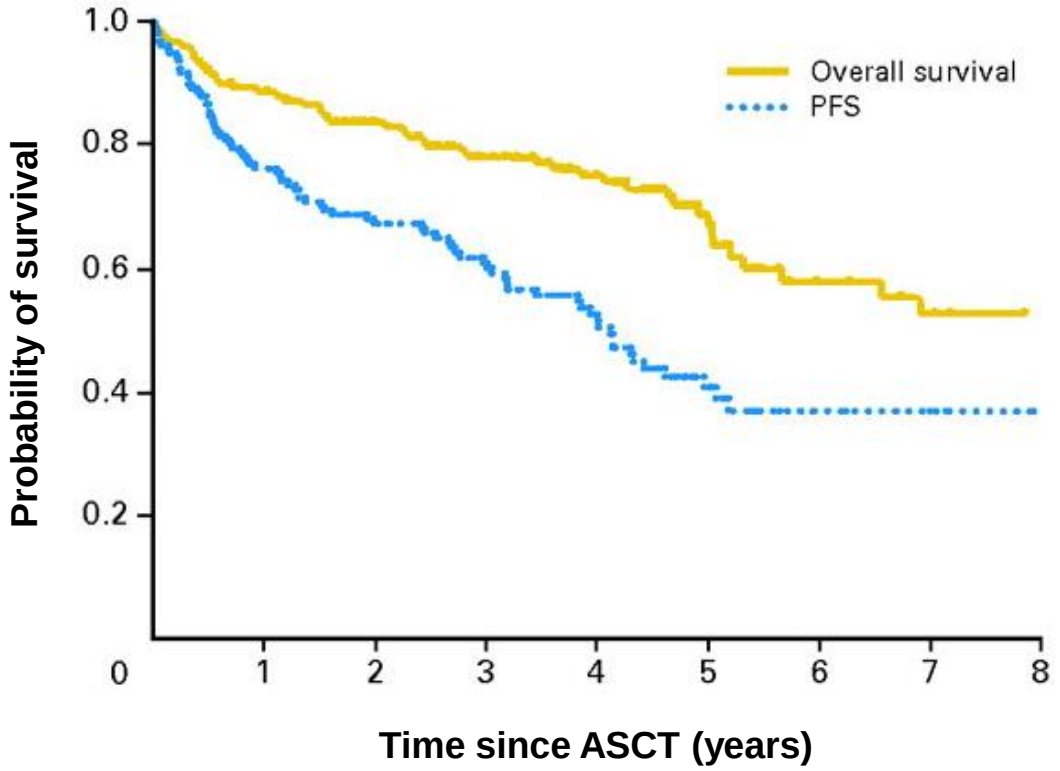
Tedeschi A *et al*. *Clin. Lymphoma Myeloma Leuk.* 2013; 13 (2): 231–234.

High-dose therapy with autologous stem cell transplantation

At 5 years:

- PFS = 39.7%
- OS = 68.5%
- Relapse rate = 52.1%

PFS and OS for patients with WM receiving ASCT (N=158)



ASCT, autologous stem cell transplantation; OS, overall survival; PFS, progression-free survival; WM, Waldenström's macroglobulinemia.
Kyriakou C *et al*. *J Clin Oncol* 2010; 28 (13): 2227–2232.

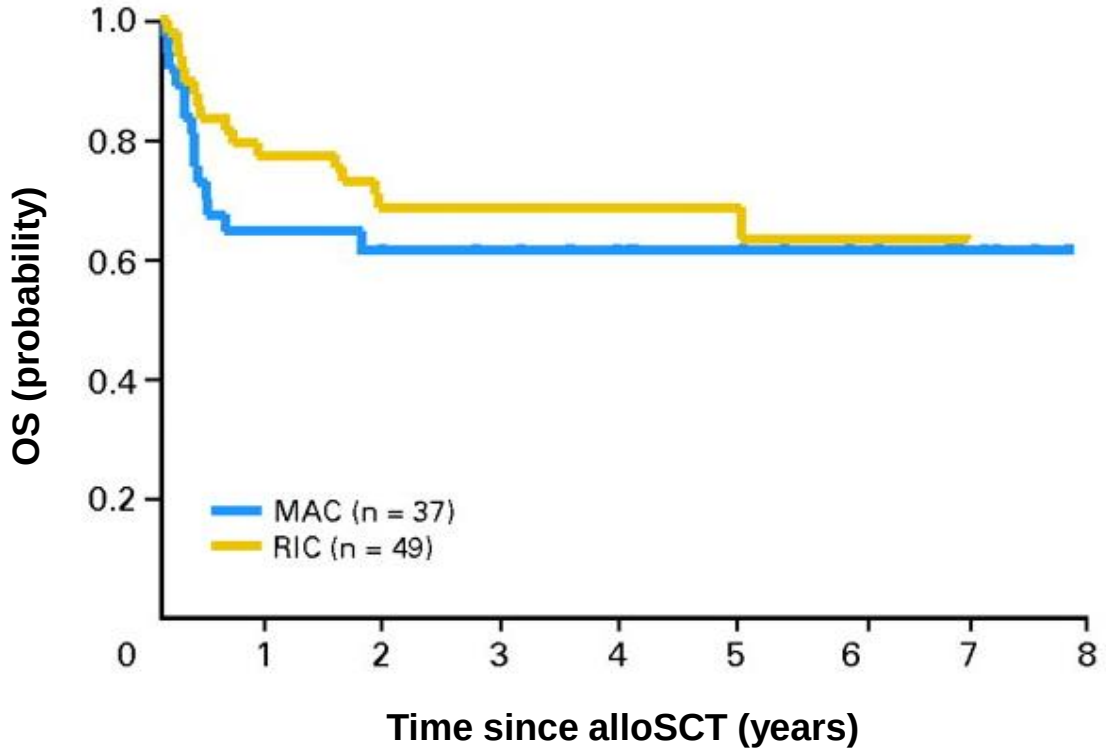
Allogeneic stem cell transplantation

At 3 years:

- PFS = 56% (MAC), 49% (RIC)
- OS = 62% (MAC), 64% (RIC)
- Relapse rates
  - 11% (MAC)
  - 25% (RIC)

- Non-relapse mortality at 3 years was 33% for MAC and 23% for RIC

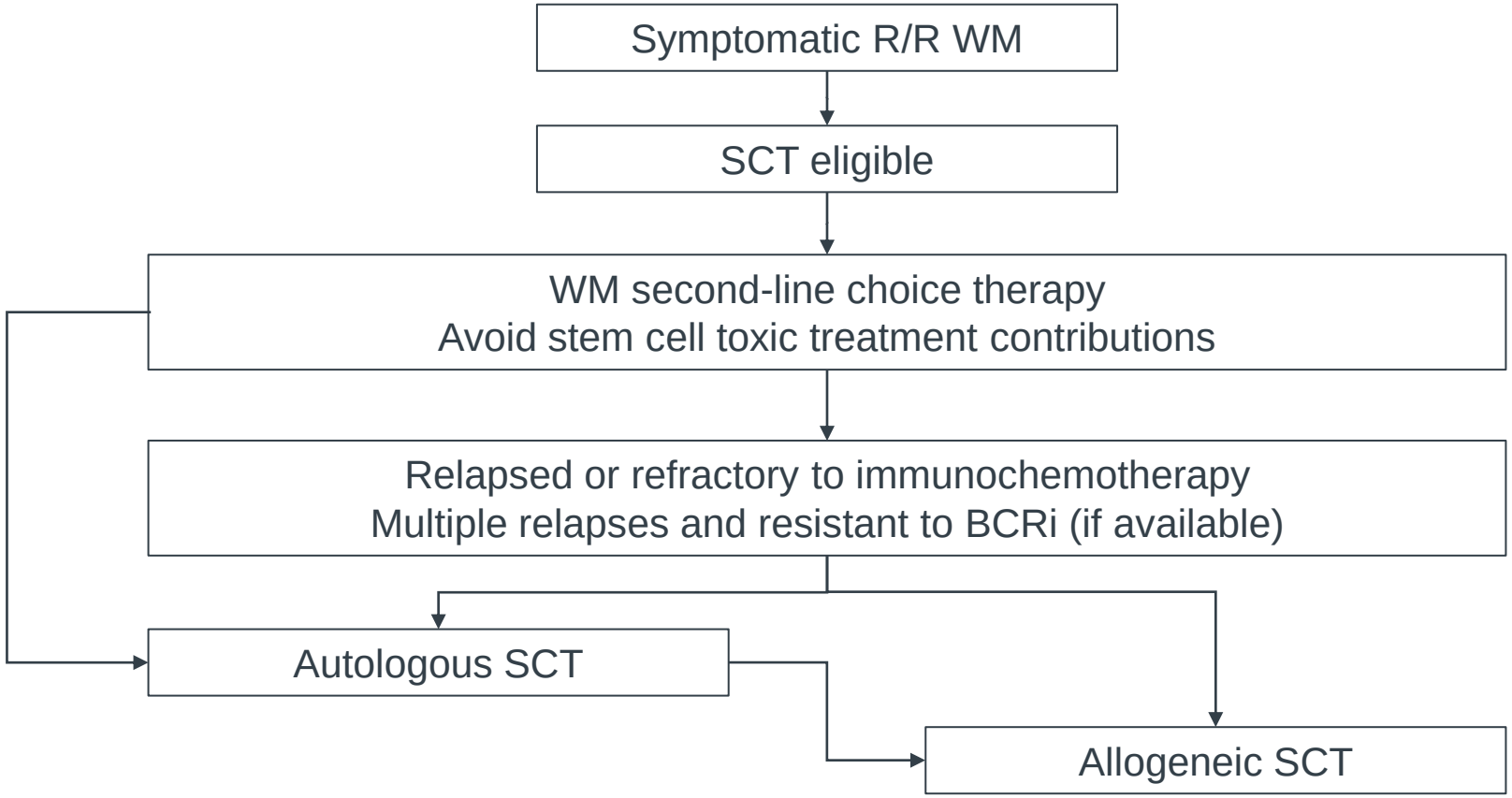
OS for patients with WM who received MAC and RIC regimens (N=86)



alloSCT, allogeneic stem cell transplantation; MAC, myeloablative conditioning; OS, overall survival; PFS, progression-free survival; RIC, reduced-intensity conditioning; WM, Waldenström's macroglobulinemia.
Kyriakou C *et al. J. Clin. Oncol.* 2010; 28 (33): 4926–4934.

The EBMT/ECWM/IWMG international consensus project on the role of autologous and allogeneic stem cell transplantation in patients with Waldenstrom's Macroglobulinemia

Dr Charalampia Kyriakou [1], Prof Ranjana Advani [2], Prof Stephen Ansell [3], Prof Christian Buske [4], Dr Jorge Castillo[5], Prof Peter Dreger [6], Prof Morie Gertz [7], Prof Sergio Giralt [8], Prof Veronique Leblond [9], Prof David G. Maloney[10], Prof Olivier Tournilhac [11], Dr Silvia Montoto [12]



BCRi, B-cell receptor inhibitor; R/R, relapsed/refractory; SCT, stem cell transplantation; WM, Waldenström's macroglobulinemia.
Kyriakou C, *et al*. 2021. In submission.

CLINICAL TRIALS & OBSERVATIONS

Comment on Flinn et al, page 3406; and Kahl et al, page 3398; and Brown et al, page 3390

CLL and NHL: the end of chemotherapy?

Bruce D. Cheson GEORGETOWN UNIVERSITY HOSPITAL

"The times they are a changin'"—Bob Dylan

– **Proteasome inhibitors?**

– BTK inhibitors?

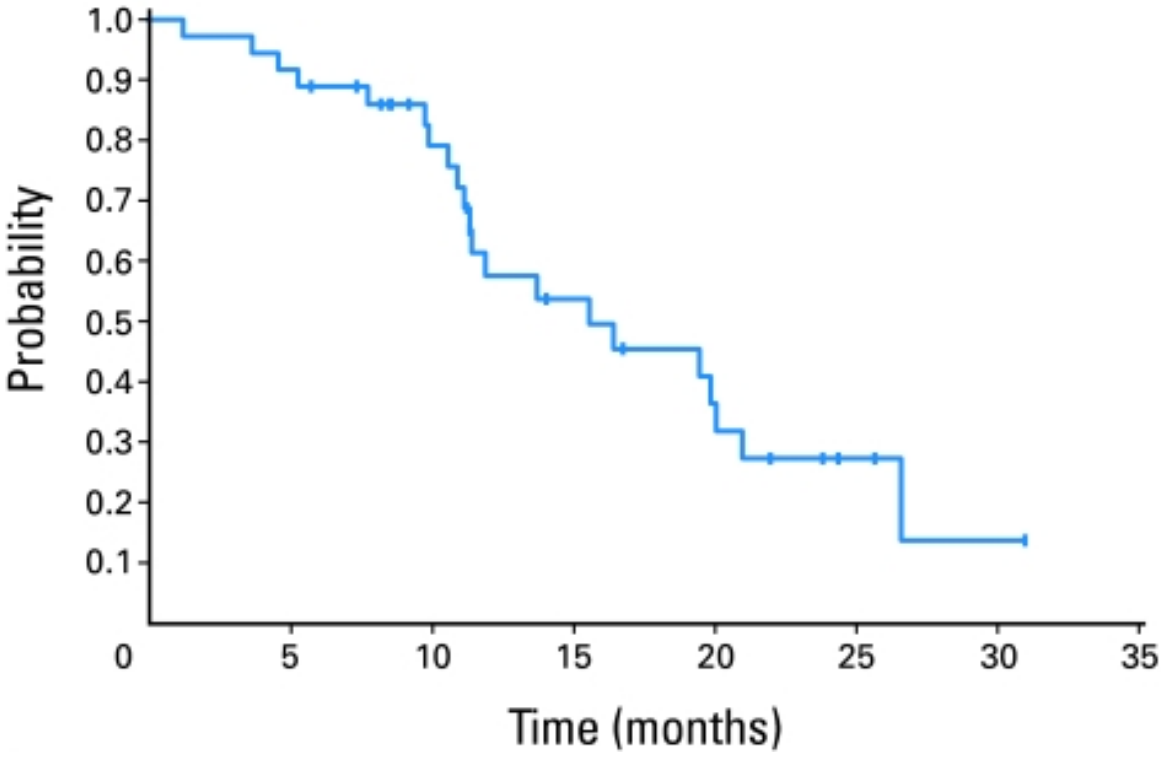
BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukaemia; NHL, non-Hodgkin lymphoma.
Cheson BD. *Blood* 2014; 123 (22): 3368–3370.

Bortezomib with rituximab in R/R WM

At 33 months:

- ≥ minor response = 78%
- Median PFS = 15.6 months
- Median DoR = 19.5 months
- Grade ≥3 neutropenia = 16%

PFS in patients with R/R WM (N=37)



DoR, duration of response; PFS, progression-free survival; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

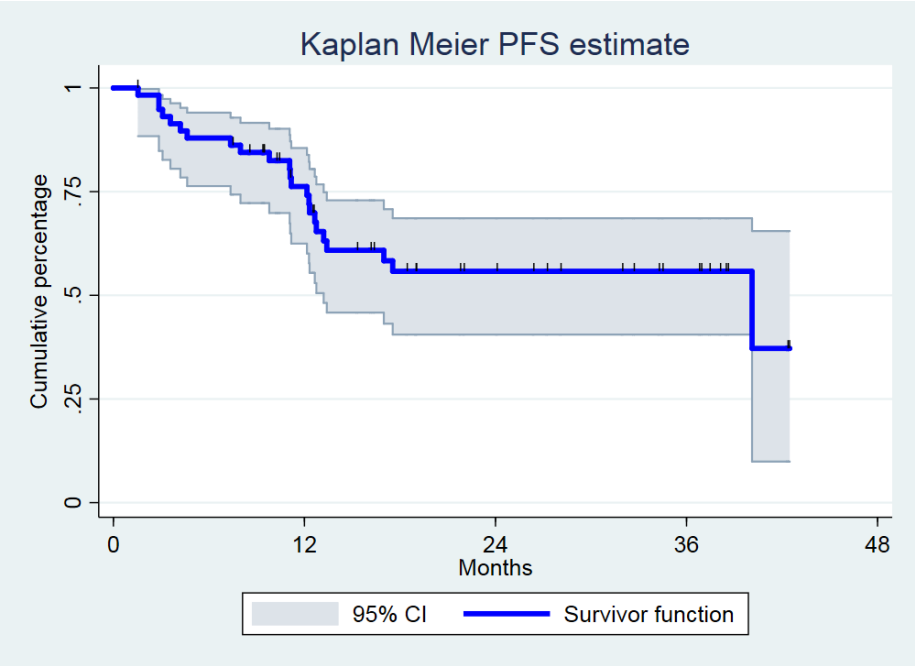
Ghobrial IM *et al*. *J Clin Oncol* 2010; 28 (8): 1422–1428.

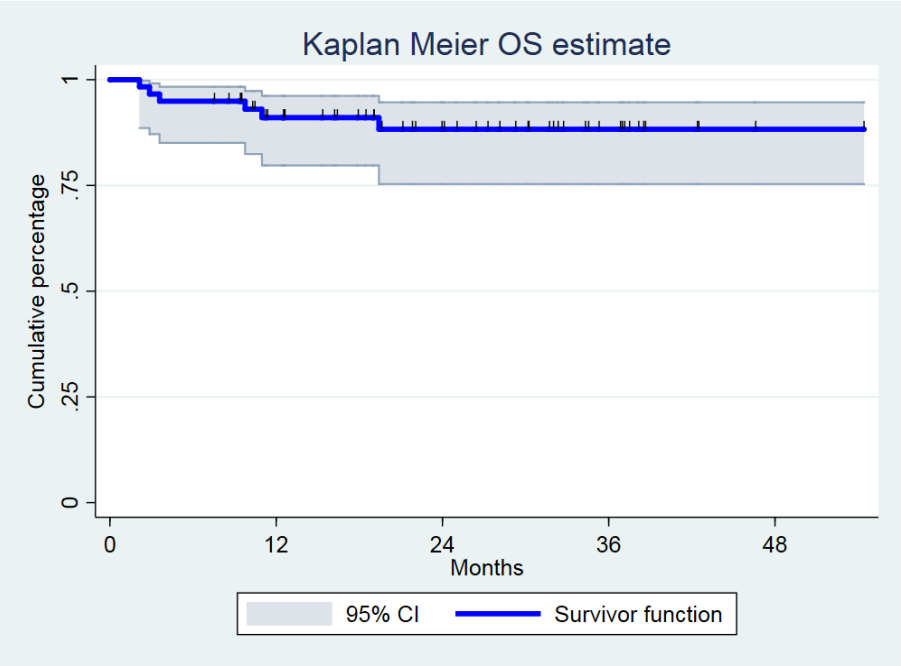
Oral proteasome inhibitor plus rituximab

Ixazomib, rituximab, and dexamethasone in R/R WM: Median follow-up at 24 months

At 24 months:

- PFS = 56%
- DoR = 60%
- OS = 88%





CI, confidence interval; DoR, duration of response; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

Kersten MJ, *et al. Blood* 2019; 134(Supplement_1):344. Presented at the American Society of Hematology (ASH) annual meeting; December 7–10, 2019.

CLINICAL TRIALS & OBSERVATIONS

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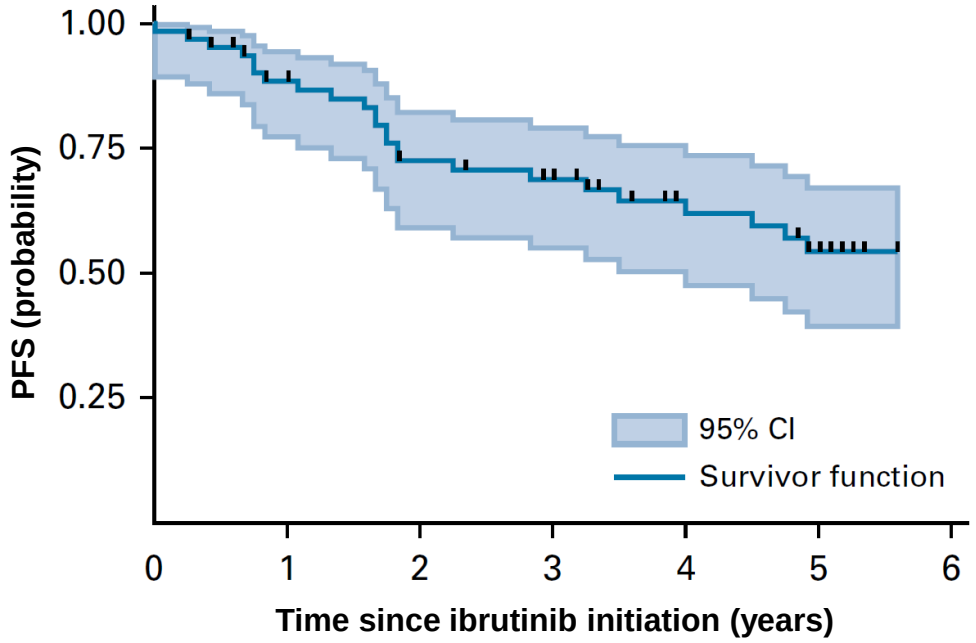
BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukaemia; NHL, non-Hodgkin lymphoma.
Cheson BD. *Blood* 2014; 123 (22): 3368–3370.

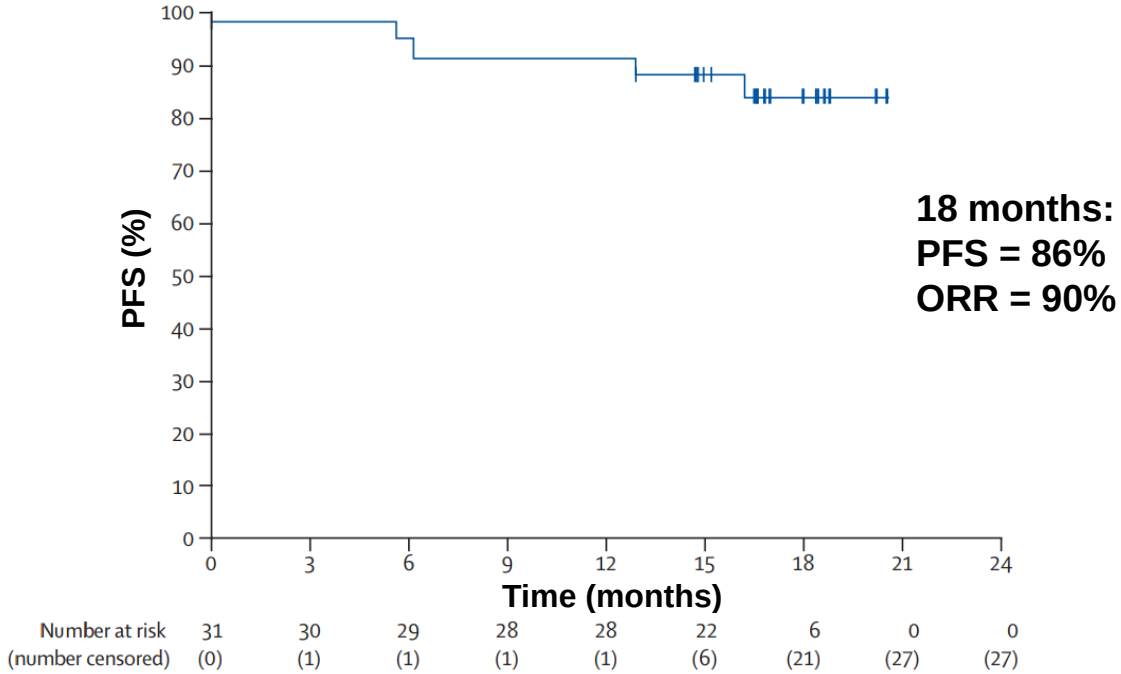
Ibrutinib monotherapy

At 59 months: ORR = 90.5%, MRR= 79.4%, Grade ≥3 neutropenia = 15.9%[1]

PFS in patients with R/R WM (N=63)[1]



PFS in patients with rituximab-refractory WM (N=31)[2]



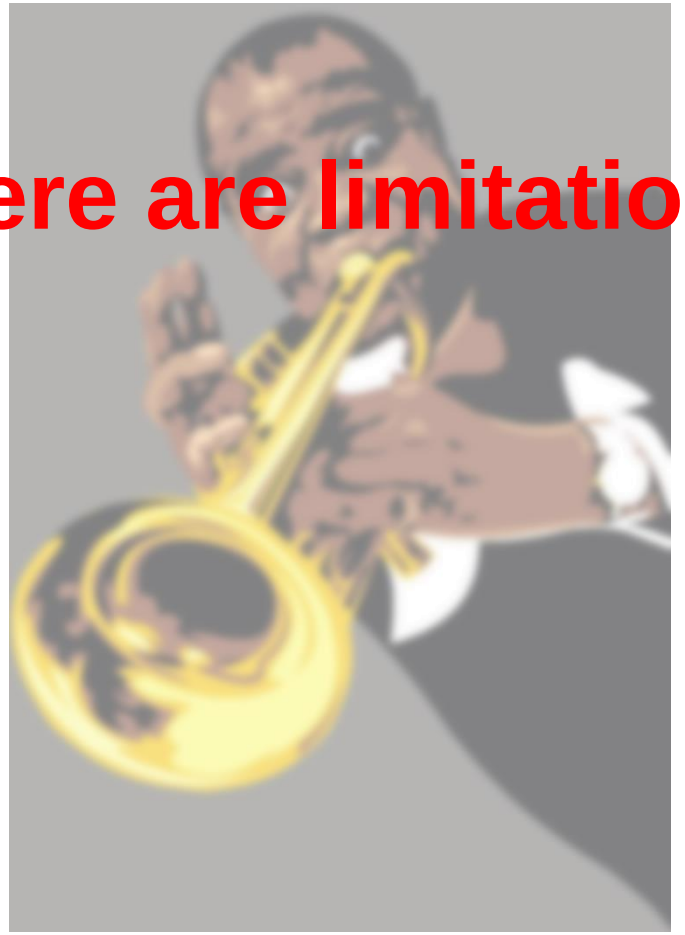
18 months:
PFS = 86%
ORR = 90%

CI, confidence interval; MRR, major response rate; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

1. Treon SP *et al. J Clin Oncol* 2021; 39 (6): 565–575. 2. Dimopoulos *et al. Lancet Oncol* 2017; 18 (2): 241–250.

“What a wonderful world”

“What a wonderful world”



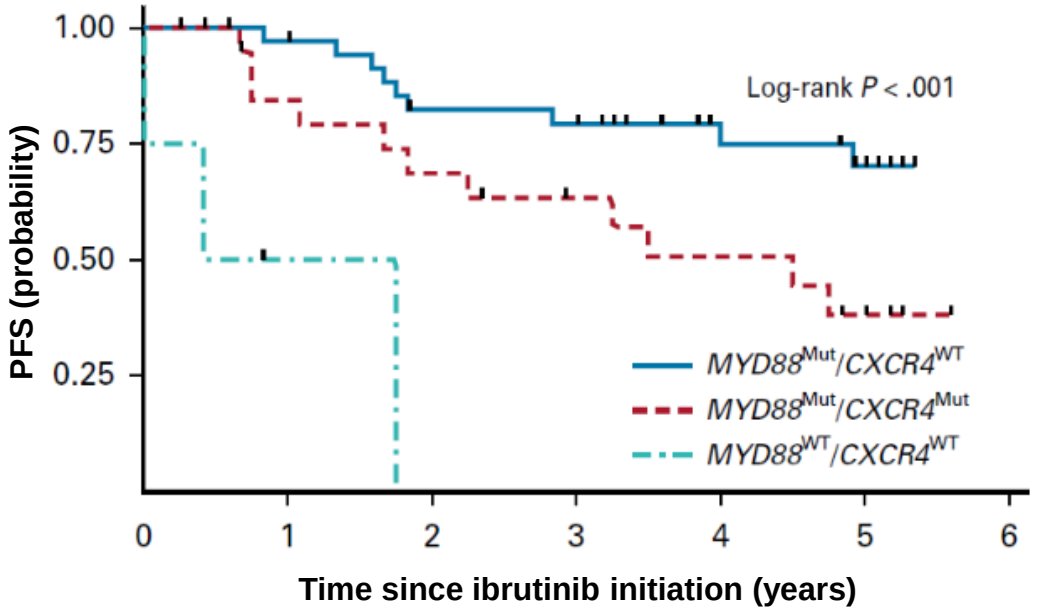
There are limitations!

Ibrutinib monotherapy

Most common Grade ≥2 AEs associated with ibrutinib therapy (N=63)

Adverse event	No.			
	Grade 2	Grade 3	Grade 4	Total
Neutropenia	5	6	4	15
Thrombocytopenia	1	5	2	8
Atrial fibrillation	5	1	0	6
Infection or infestation: lung	3	2	0	5
Gastroesophageal reflux disease	5	0	0	5
Infection or infestation: skin	3	1	0	4
Hypertension	4	0	0	4
Anemia	2	1	0	3
Mucositis oral	3	0	0	3

PFS with ibrutinib monotherapy in patients with R/R WM by genotype (N=62)

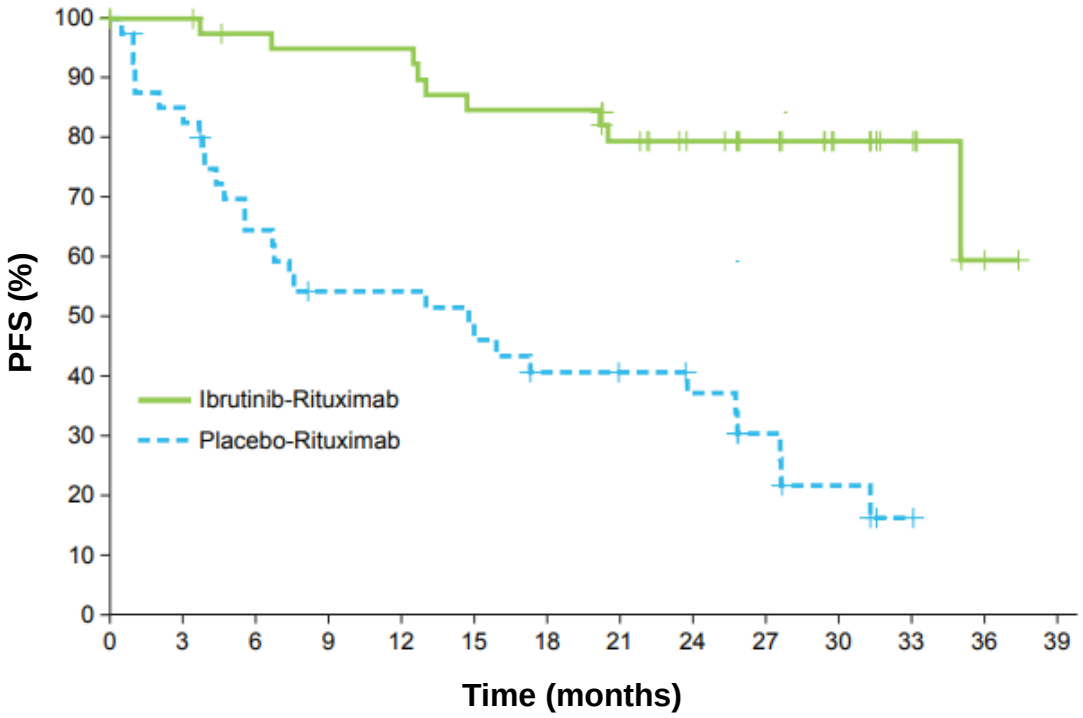


AE, adverse event; Mut, mutated; PFS, progression-free survival; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia; WT, wild type.
Treon SP *et al. J Clin Oncol* 2021; 39 (6): 565–575.

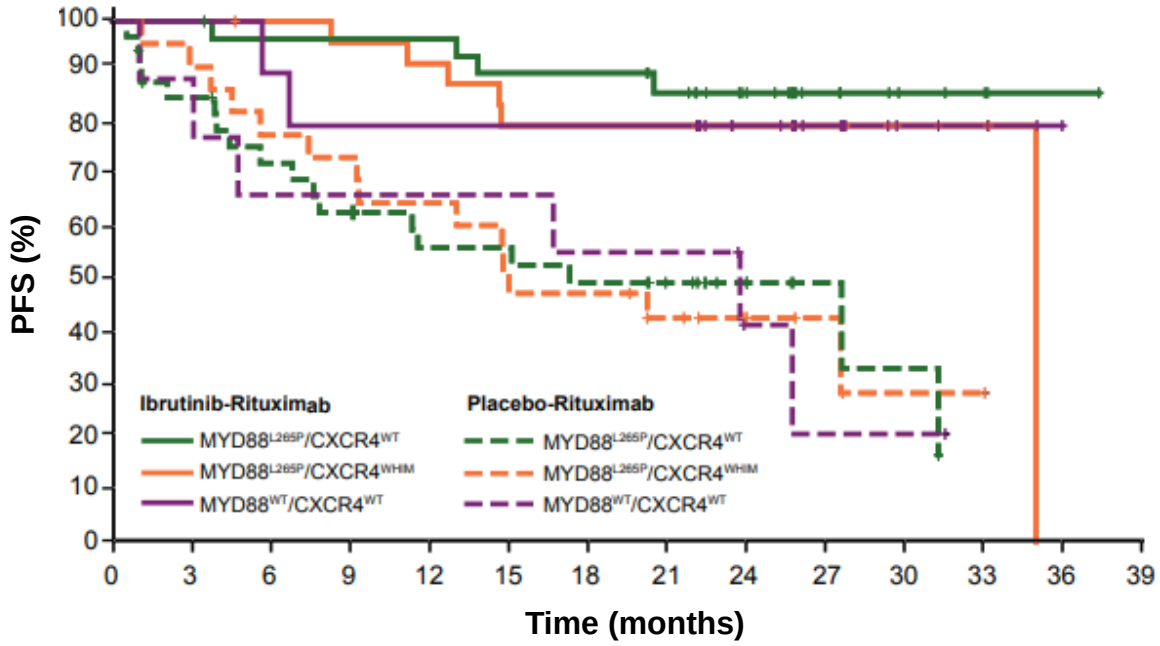
Ibrutinib with rituximab in relapsed WM

At 30 months: PFS = 82%, MRR = 72%

PFS in patients with relapsed WM (N=150)

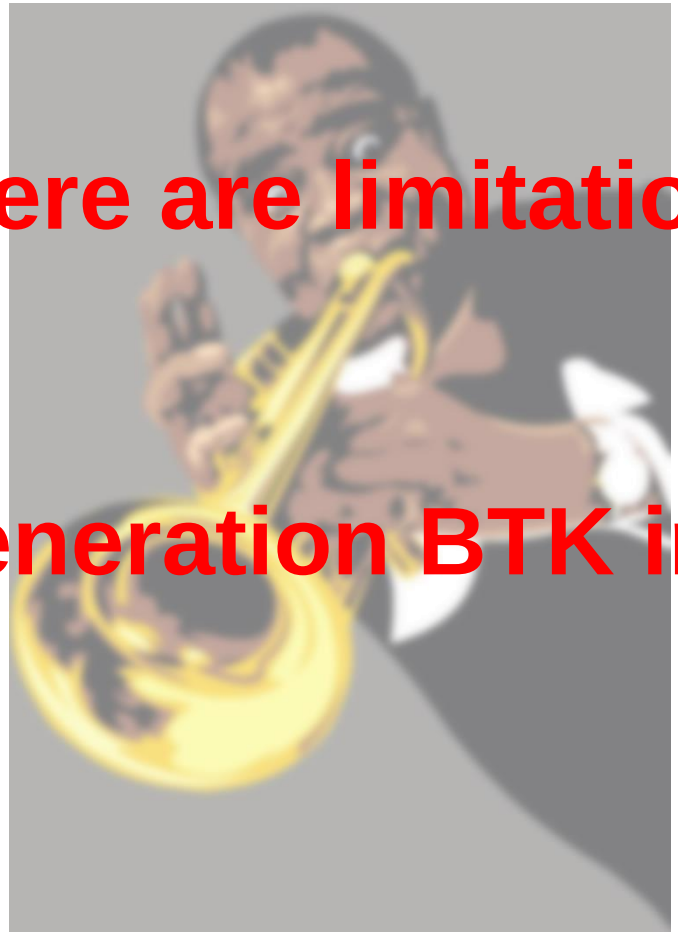


PFS by genotype (N=150)



MRR, major response rate; MUT, mutant; PFS, progression-free survival; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; WM, Waldenström's macroglobulinemia; WT, wild type.
Dimopoulos MA, *et al. N Engl J Med* 2018; 378 (25): 2399–410.

“What a wonderful world”

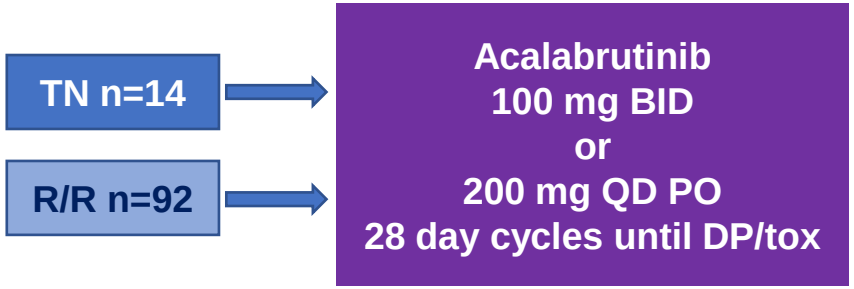


There are limitations!

Second-generation BTK inhibitors?

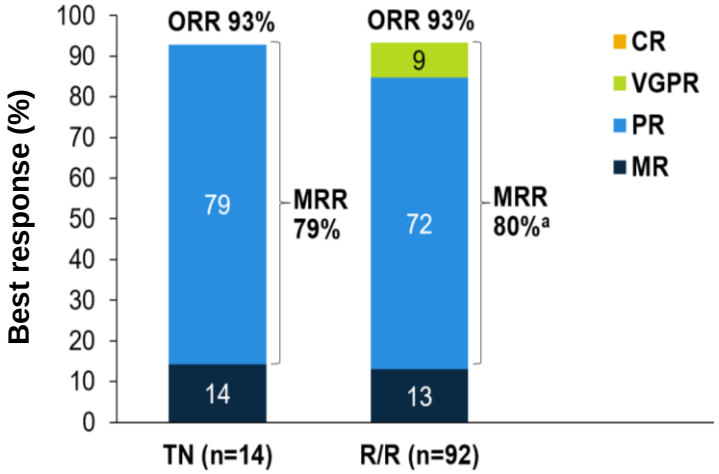
BTK, Bruton’s tyrosine kinase.

Acalabrutinib monotherapy in patients with WM: A Phase II study



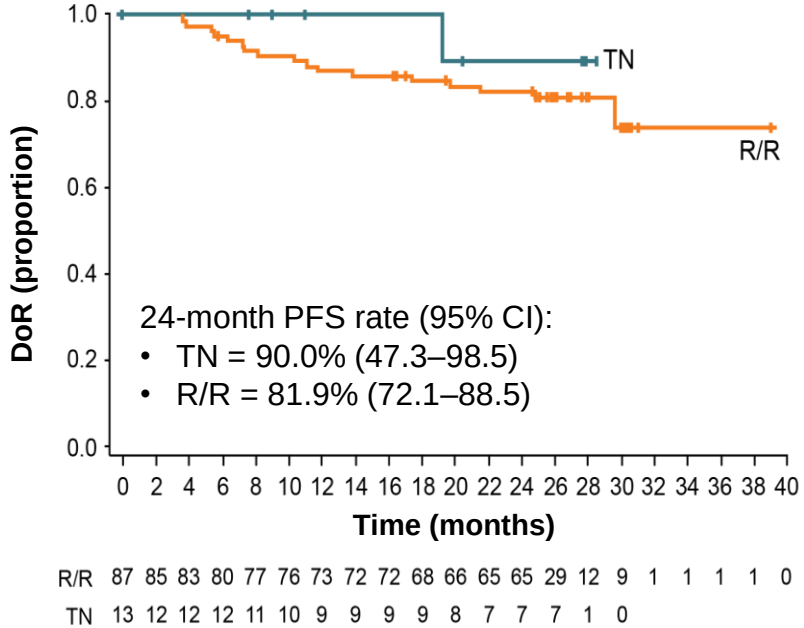
Characteristic	TN (n=14)	R/R (n=92)
Median age (range), y	73 (48–86)	69 (39–90)
Median n prior tx (range)	-	2 (1–7)
≥3 previous tx, n (%)	-	41 (45)
Refractory disease, n (%)	-	33 (36)

Best responses by treatment status



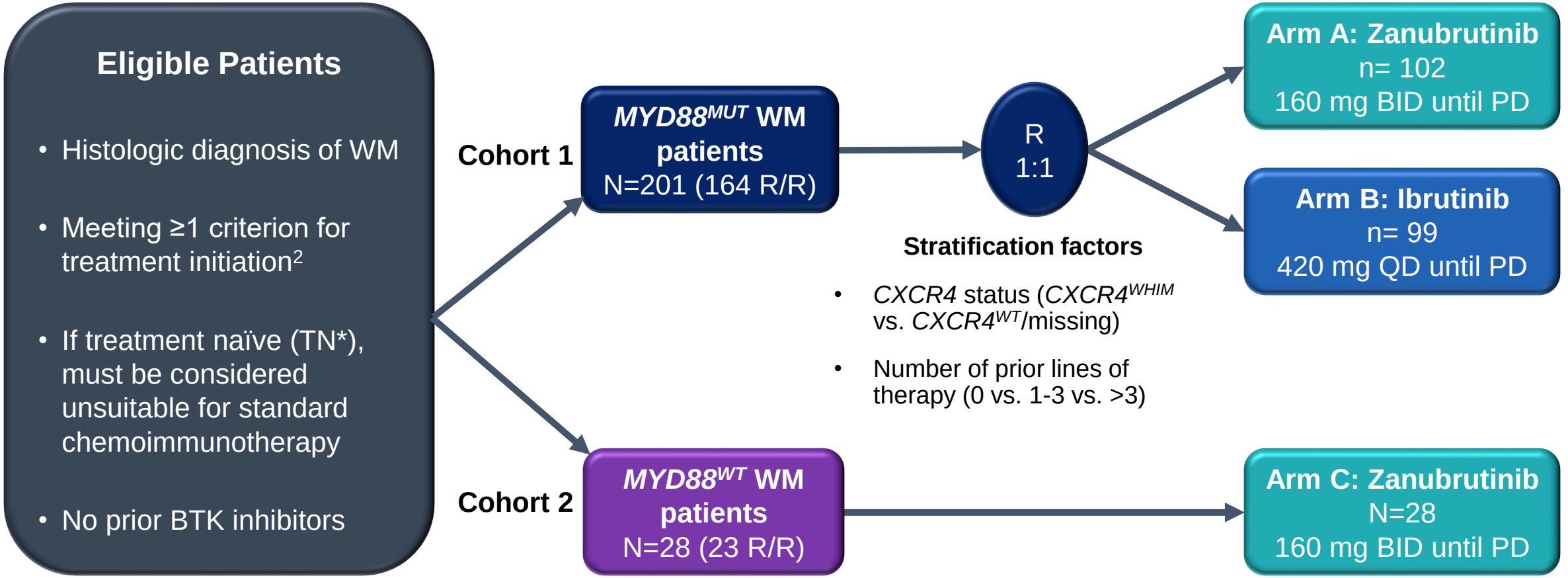
	TN (n=14)	R/R (n=92)
Median time to best response (range), mo:	4.9 (1.8-16.6)	1.9 (0.9-23.2)

DoR by treatment status



BID, twice a day; CI, confidence interval; CR, complete response; DoR, duration of response; DP, disease progression; MRR, major response rate; MR, minor response; ORR, overall response rate; PD, progressive disease, PFS, progression-free survival; PO, by mouth; PR, partial response; QD, every day; R/R, relapsed/refractory; SD, stable disease; TN, treatment naive; tox, toxicity; tx, treatment; VGPR, very good partial response; WM, Waldenström's macroglobulinemia. Owen RG *et al. Lancet Haematol* 2020; 7(2): e112–e121.

ASPEN study design: Zanubrutinib vs. ibrutinib in *MYD88*^{MUT} WM[1]



Poster: EP1180

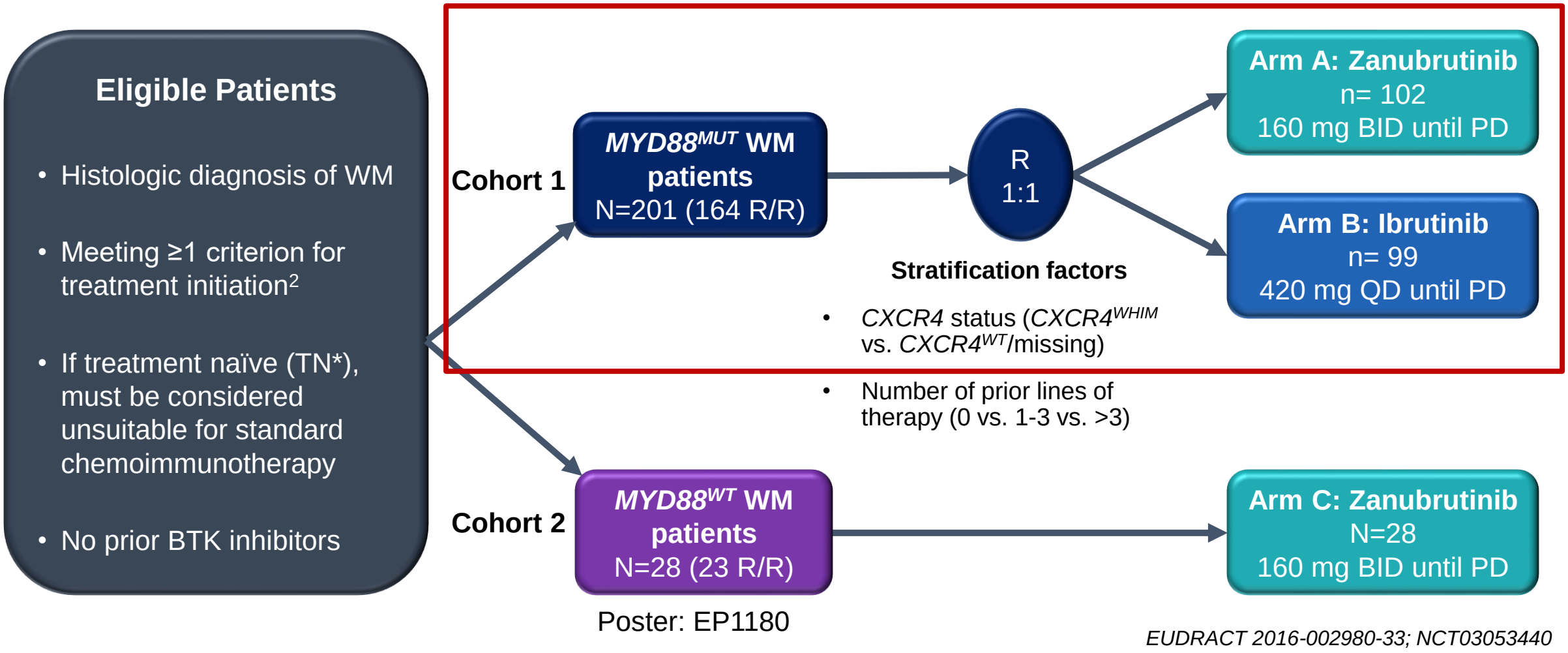
EUDRACT 2016-002980-33; NCT03053440

*Up to 20% of the overall population.

BID, twice a day; BTK, Bruton's tyrosine kinase; MUT, mutated; PD, progressive disease; QD, every day; R, randomization; R/R, relapsed/refractory; TN, treatment naive; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; WM, Waldenström's macroglobulinemia; WT, wild-type.

1. Tam CS *et al*. Abstract 8007. Oral presentation at the 2020 Annual Meeting of the American Society of Clinical Oncology (ASCO), May 29–May 31, 2020. 2. Dimopoulos MA, *et al. Blood* 2014; 124: 1404–1411.

ASPEN study design: Zanubrutinib vs. ibrutinib in *MYD88*^{MUT} WM[1]



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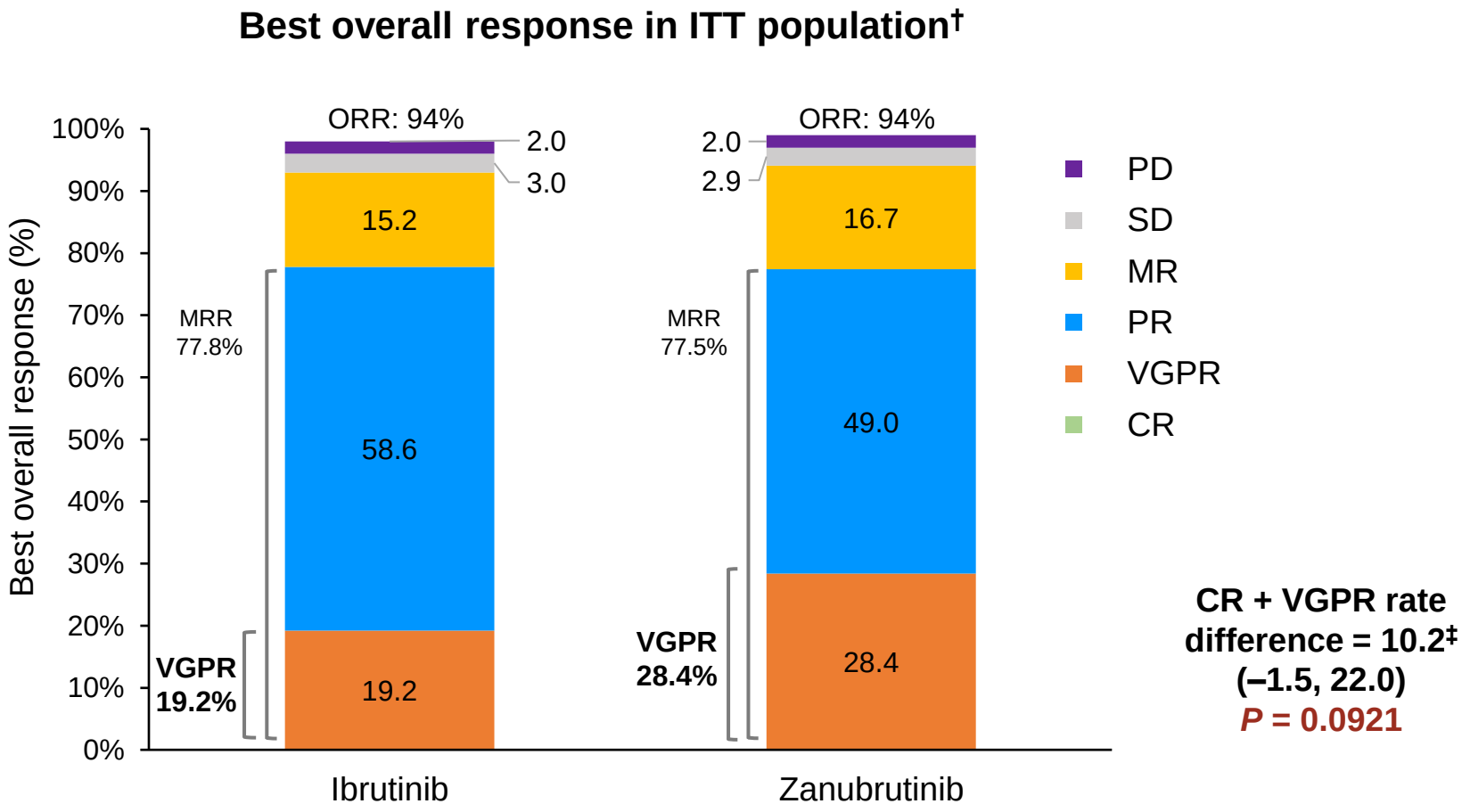
BID, twice a day; BTK, Bruton's tyrosine kinase; MUT, mutated; PD, progressive disease; QD, every day; R, randomization; R/R, relapsed/refractory; TN, treatment naive; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; WM, Waldenström's macroglobulinemia; WT, wild-type.

1. Tam CS *et al*. Abstract 8007. Oral presentation at the 2020 Annual Meeting of the American Society of Clinical Oncology (ASCO), May 29–May 31, 2020. 2. Dimopoulos MA, *et al. Blood* 2014; 124: 1404–1411.

ASPEN study: IRC-assessed efficacy in overall population

- Superiority in CR + VGPR rate compared with ibrutinib in R/R population (primary study hypothesis) was not significant*

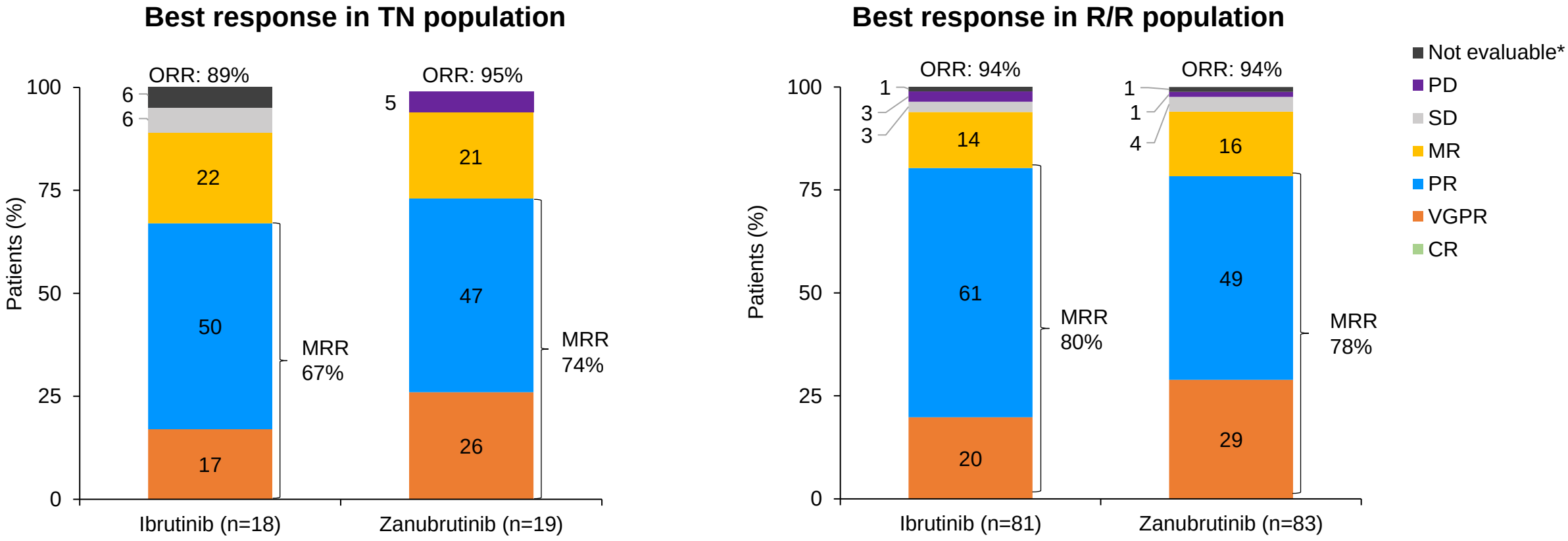


CR + VGPR rate difference = 10.2‡ (–1.5, 22.0)
***P* = 0.0921**

Overall concordance between independent review committee and investigators = 94%. *All other p-values are for descriptive purposes only. †Data cutoff: 31 August 2019. ‡Adjusted for stratification factors and age group.
CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MRR, major response rate; MR, minor response; ORR, overall response rate; PD, progressive disease, PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good partial response.

Tam CS *et al*. Abstract 8007. Oral presentation at the 2020 Annual Meeting of the American Society of Clinical Oncology (ASCO), May 29–May 31, 2020.

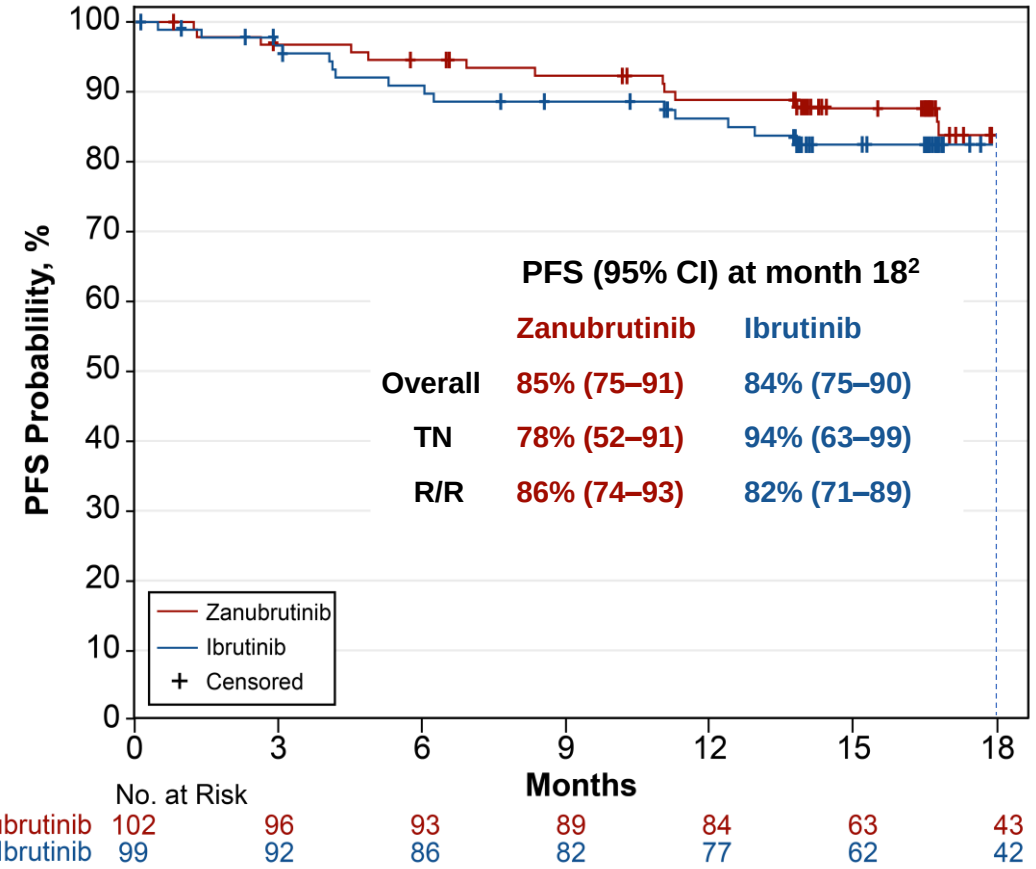
ASPEN study: IRC-assessed efficacy in TN and R/R populations



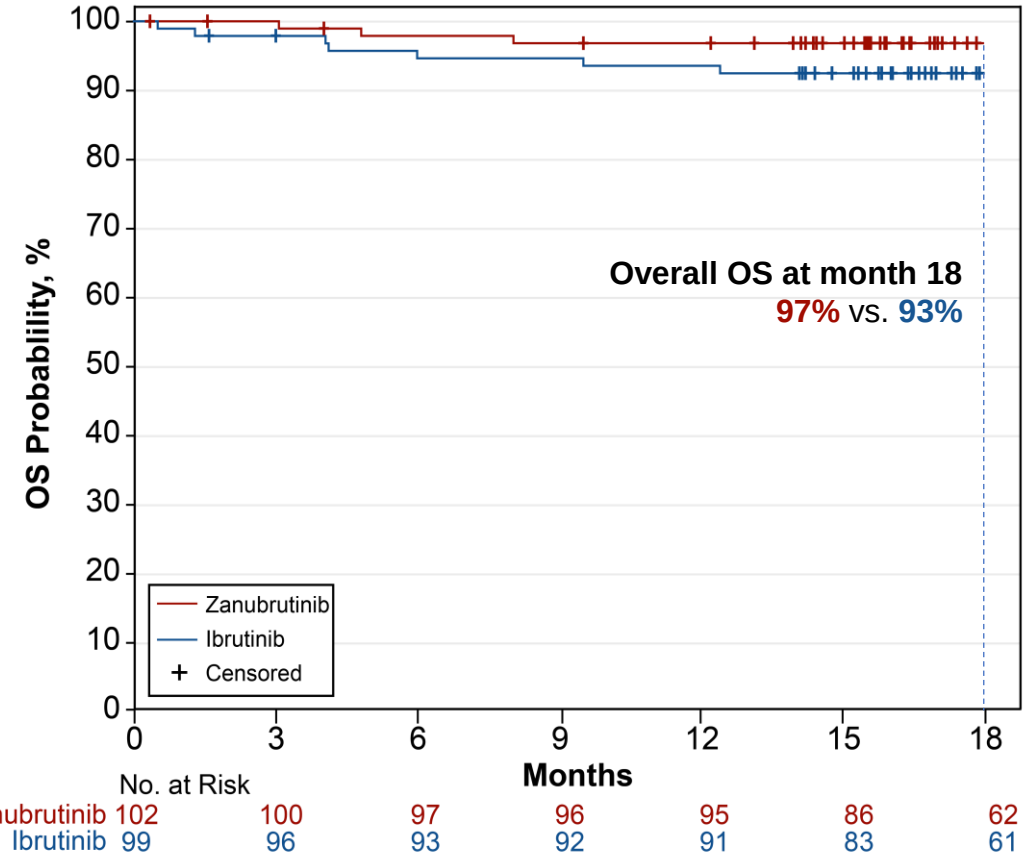
*includes patients with unknown response, disease flare, and study discontinuation prior to first disease assessment.
CR, complete response; IRC, independent review committee; MR, minimal response; MRR, major response rate; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good partial response.
Tam CS *et al*. *Blood* 2020; 136 (18): 2038–2050.

ASPEN study: PFS and OS in ITT population

PFS[1]



OS[1]



CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival; OS, overall survival.

1. Tam CS *et al*. Abstract 8007. Oral presentation at the 2020 Annual Meeting of the American Society of Clinical Oncology (ASCO), May 29–May 31, 2020. 2. Tam CS *et al*. *Blood* 2020; 136 (18): 2038–205.SS

ASPEN study: Adverse event categories of interest

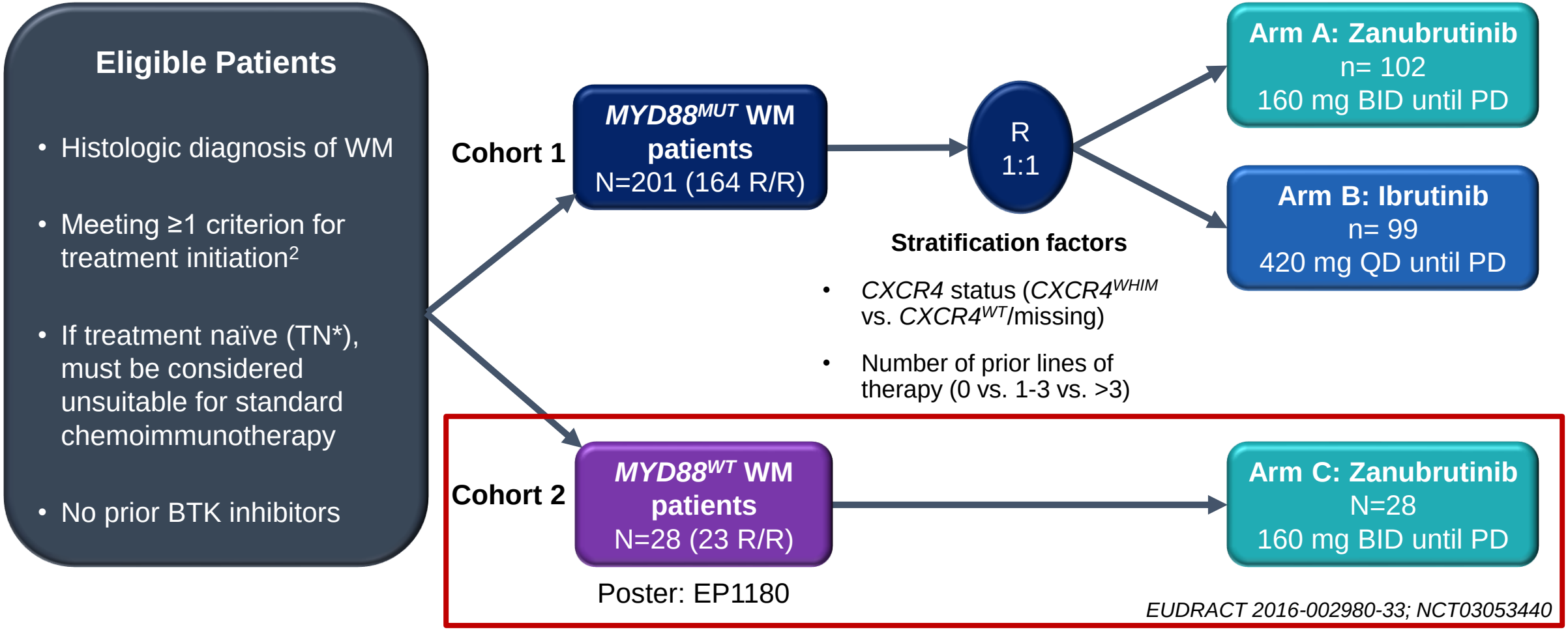
5-month follow-up

- An additional 5 patients had discontinued ibrutinib treatment because of AEs vs. 0 patients in the zanubrutinib arm
- Total discontinuation rate
  - Ibrutinib = 14.3%
  - Zanubrutinib = 4.0%

AE categories, n (%) *(pooled terms)*	All grades		Grade ≥3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	**18 (18.4%)**	3 (3.0%)	**7 (7.1%)**	0
Diarrhea (PT)	**32 (32.7%)**	22 (21.8%)	2 (2.0%)	3 (3.0%)
Hemorrhage	**59 (60.2%)**	51 (50.5%)	9 (9.2%)	6 (5.9%)
Major hemorrhage†	10 (10.2%)	6 (5.9%)	9 (9.2%)	6 (5.9%)
Hypertension	20 (20.4%)	13 (12.9%)	**15 (15.3%)**	8 (7.9%)
Neutropenia*‡	15 (15.3%)	**32 (31.7%)**	8 (8.2%)	**23 (22.8%)**
Infection	70 (71.4%)	70 (69.3%)	23 (23.5%)	19 (18.8%)
Second malignancy	12 (12.2%)	13 (12.9%)	1 (1.0%)	3 (3.0%)

Data cutoff: 31 January 2020.
Higher AE rate in bold with ≥10% difference in any grade AE, or ≥5% difference in grade ≥3 AEs.
*Descriptive two-sided *p*-value <0.05. †Defined as any grade ≥3 hemorrhage or any grade central nervous system hemorrhage. ‡Including PTs of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.
AE, adverse event; PT, preferred term.
Tam CS *et al*. Oral presentation at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting; May 29–31, 2020. This study is registered at ClinicalTrials.gov (NCT03053440).

ASPEN study design: Zanubrutinib vs. ibrutinib in *MYD88*^{WT} WM[1]



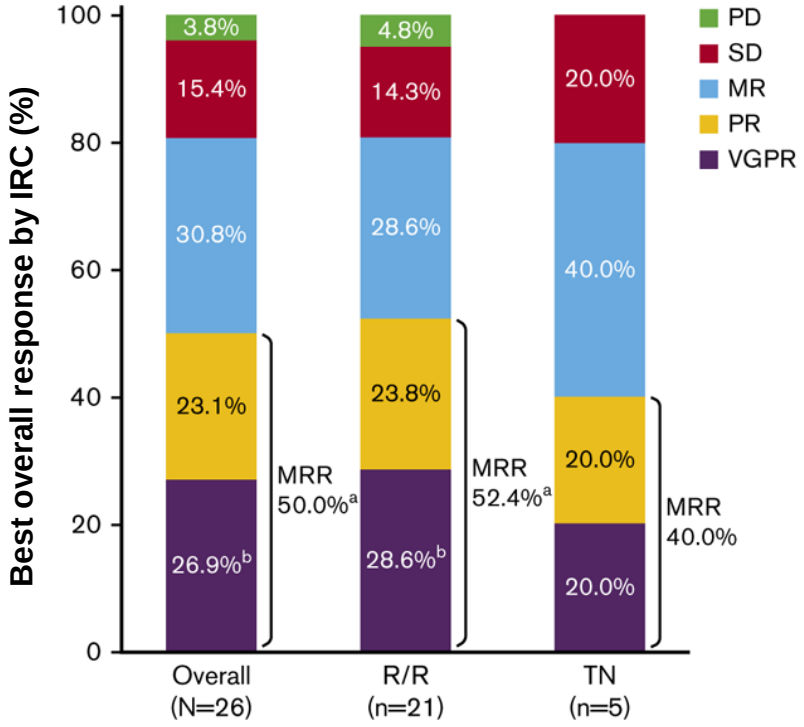
*Up to 20% of the overall population.

BID, twice a day; BTK, Bruton's tyrosine kinase; MUT, mutated; PD, progressive disease; QD, every day; R, randomization; R/R, relapsed/refractory; TN, treatment naive; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; WM, Waldenström's macroglobulinemia; WT, wild-type.

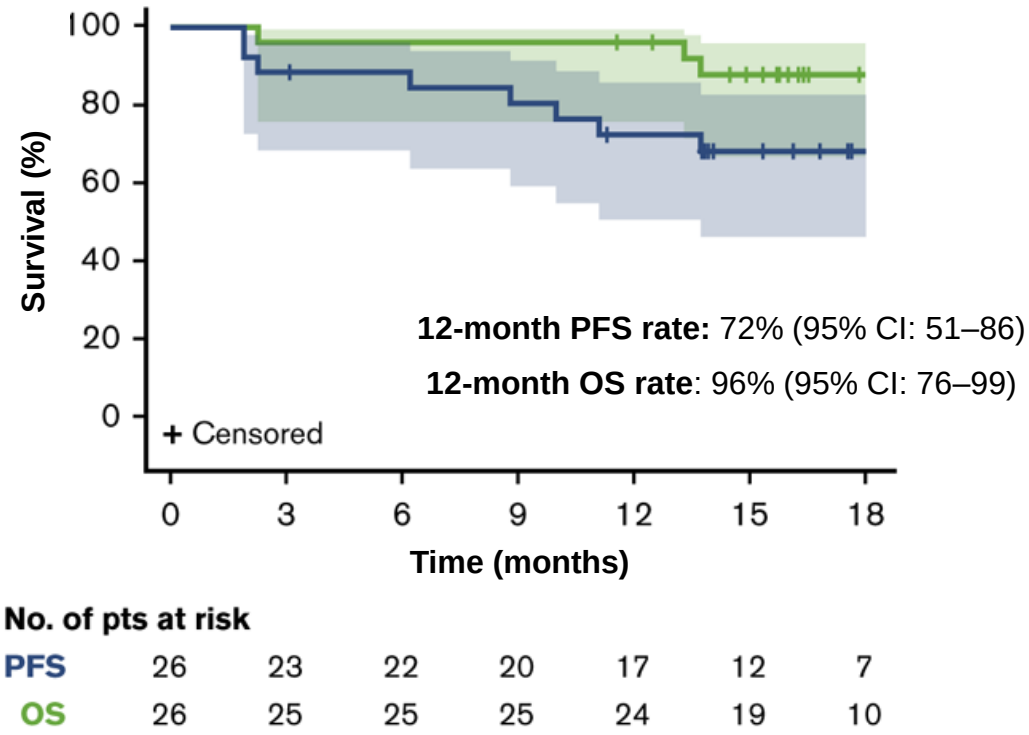
1. Tam CS *et al*. Abstract 8007. Oral presentation at the 2020 Annual Meeting of the American Society of Clinical Oncology (ASCO), May 29–May 31, 2020. 2. Dimopoulos MA, *et al. Blood* 2014; 124: 1404–1411.

ASPEN study: Zanubrutinib in *MYD88*^{WT} WM

Best overall response* in R/R or TN† WM



Survival in R/R or TN† WM



*Determined by an Independent Review Committee;†Unsuitable for standard immunochemotherapy.
CI, confidence interval; IRC, independent review committee; MR, minimal response; MRR, major response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; pts, patients; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive; VGPR, very good partial response; WM, Waldenström's macroglobulinemia; WT, wild type.
Dimopoulos MA *et al*. Abstract 2022 presented at the European Hematology Association (EHA) Annual Meeting; June 11–22, 2020.

Treatment of WM

What comes next?

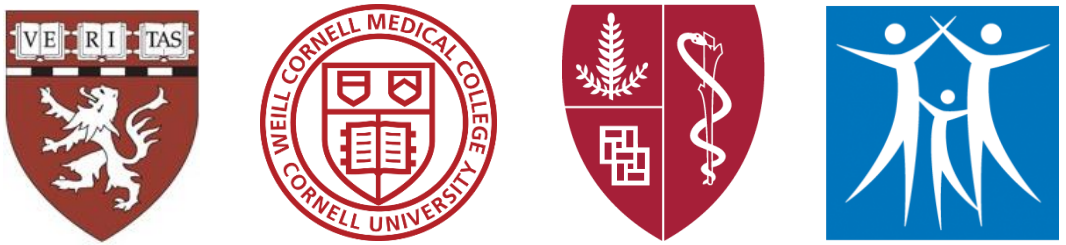
Beyond BTK inhibitors?

BTK, Bruton's tyrosine kinase; WM, Waldenström's macroglobulinemia.

DANA-FARBER CANCER INSTITUTE

HARVARD MEDICAL SCHOOL

Multicenter Prospective Phase II Study of Venetoclax in Patients with Previously Treated Waldenstrom Macroglobulinemia

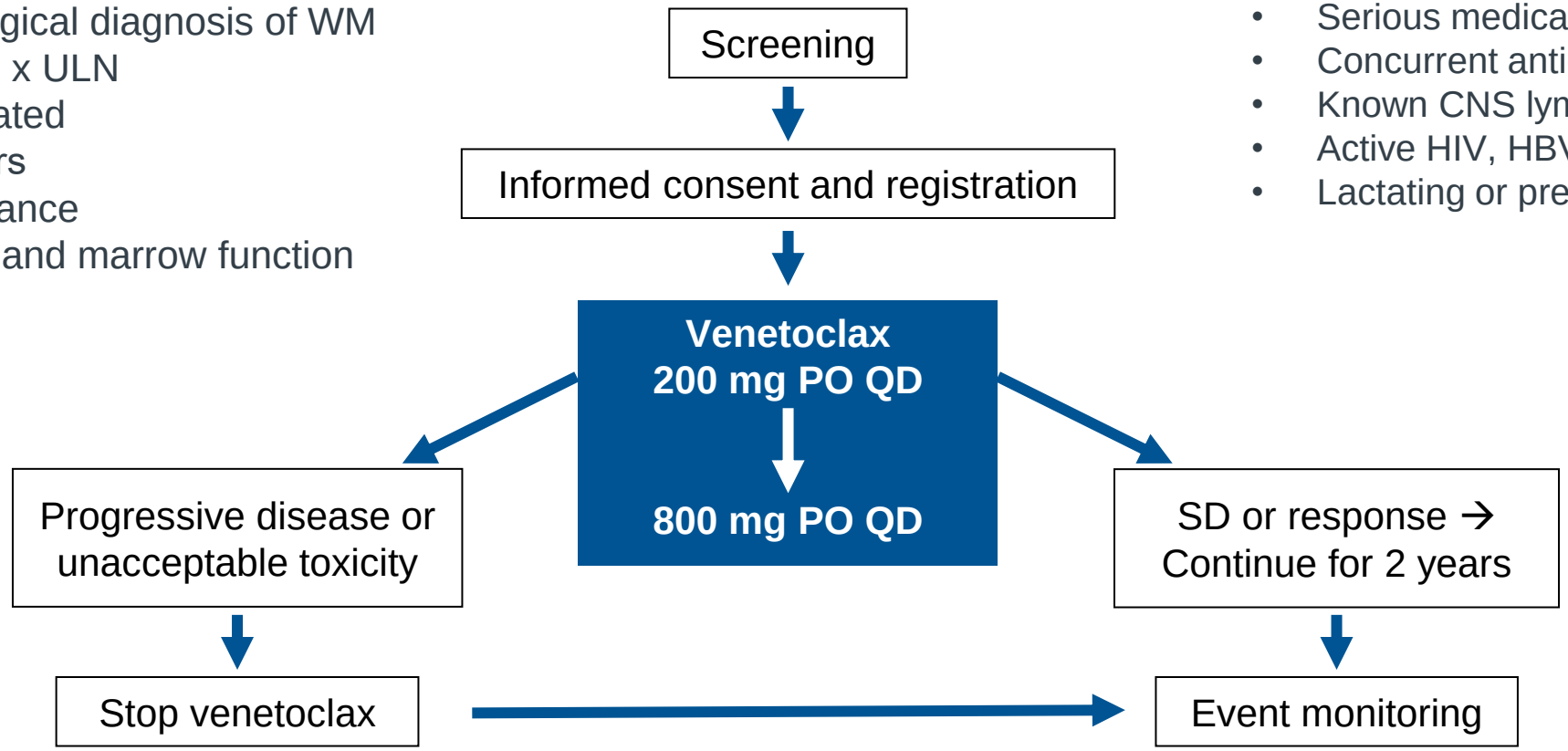


Castillo JJ, Gustine J, Meid K, Dubeau T, Keezer A, Allan JN, Furman RR, Siddiqi T, Advani R, Lam J, Hunter ZR, Yang G, Xu L, Davids MS, Treon SP

Castillo JJ *et al. Blood* 2018; 132 (Suppl 1):2888.

Phase II study of venetoclax in R/R WM
Study design

Selected inclusion criteria:
- Clinicopathological diagnosis of WM
- Serum IgM >2 x ULN
- Previously treated
- Aged ≥18 years
- Good performance
- Normal organ and marrow function



Selected exclusion criteria:
- Serious medical condition
- Concurrent anticancer agent
- Known CNS lymphoma
- Active HIV, HBV, HCV infection
- Lactating or pregnant women

CNS, central nervous system; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgM, immunoglobulin M; PO, by mouth; QD, every day; SD, stable disease; ULN, upper limit of normal; WM, Waldenström's macroglobulinemia.

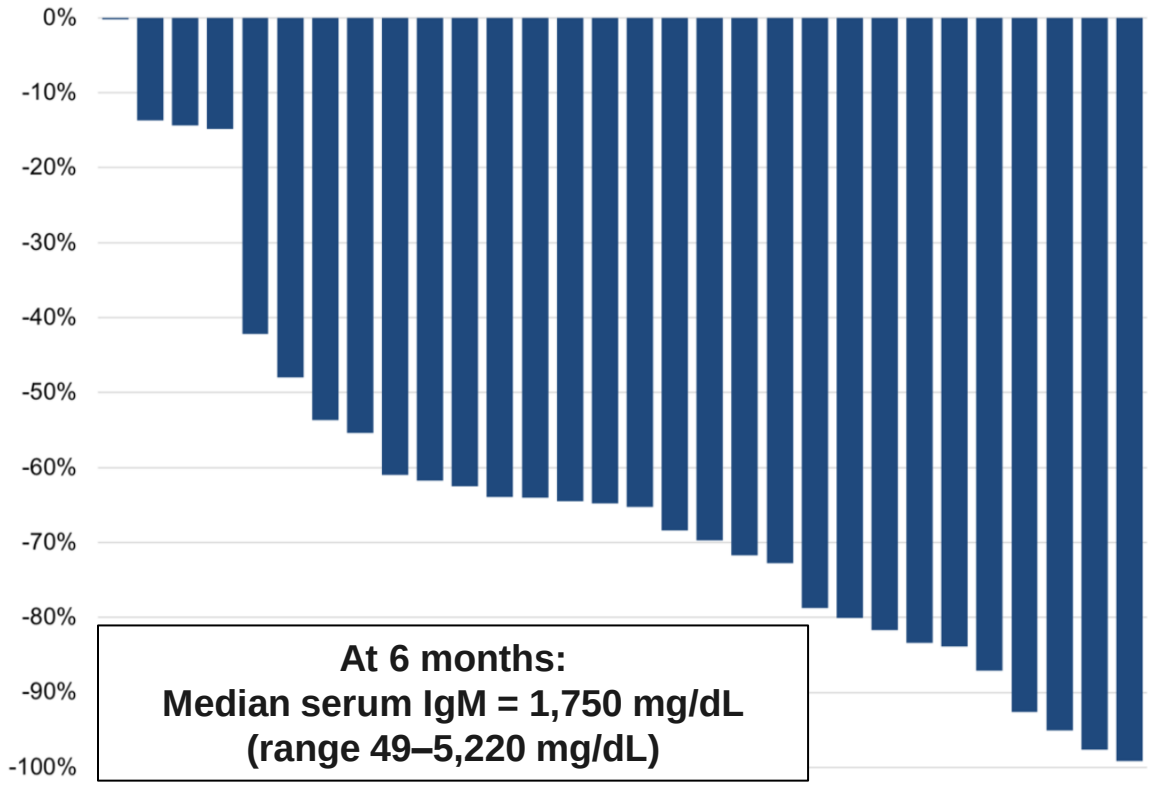
Castillo JJ *et al. Blood* 2018; 132 (Suppl 1): 2888; ClinicalTrails.gov NCT02677324. Available at: https://clinicaltrials.gov/ct2/show/NCT02677324. Accessed March 2021.

Phase II study of venetoclax in R/R WM
Efficacy

At 6 months, at best response:

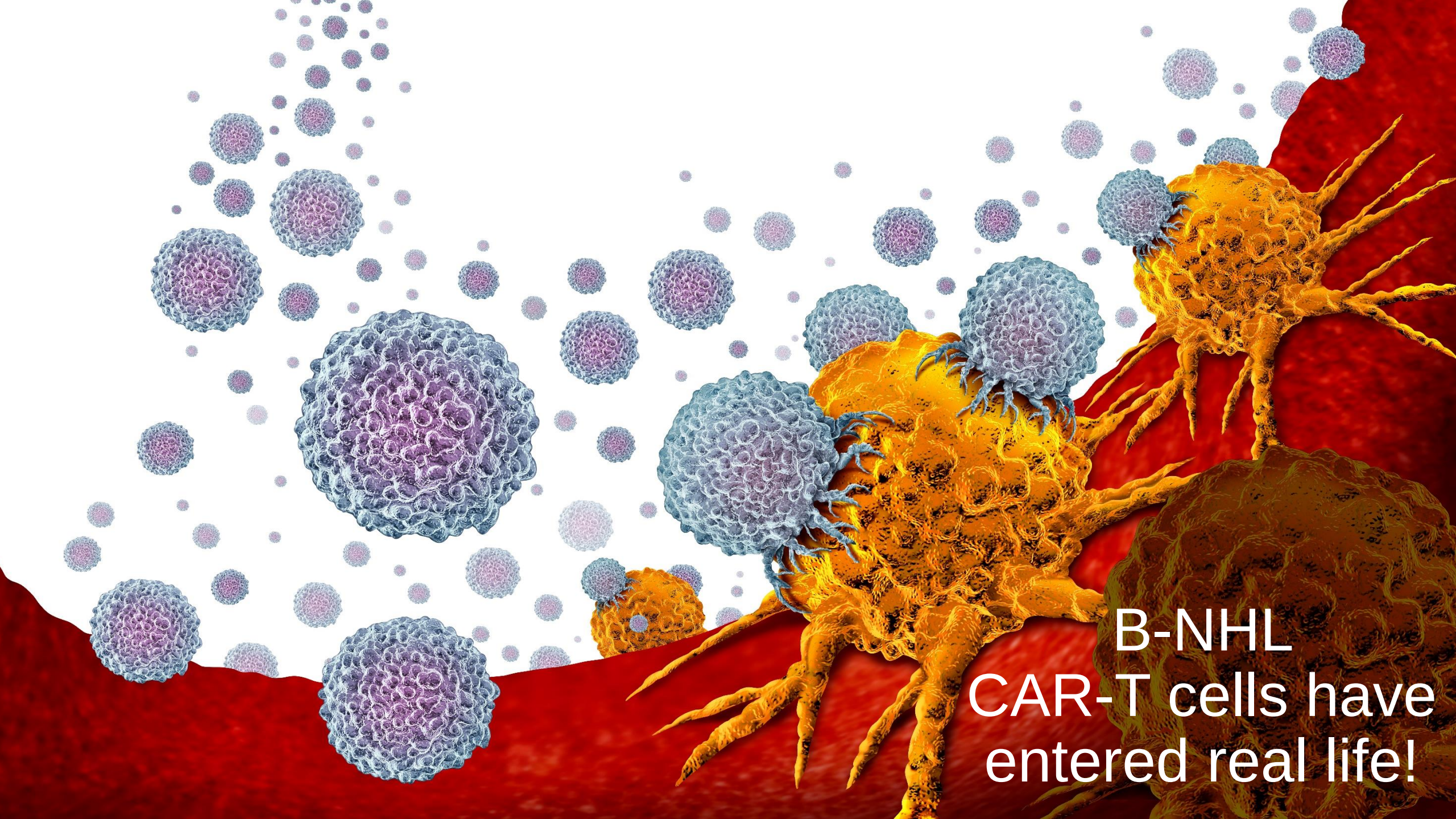
- ORR = 87%
- MRR = 80%
- Median DoR = 19.5 months
- Grade 3 neutropenia = 23%
- Activity lower in patients previously treated with ibrutinib

Serum IgM level reduction at best response (N=30)



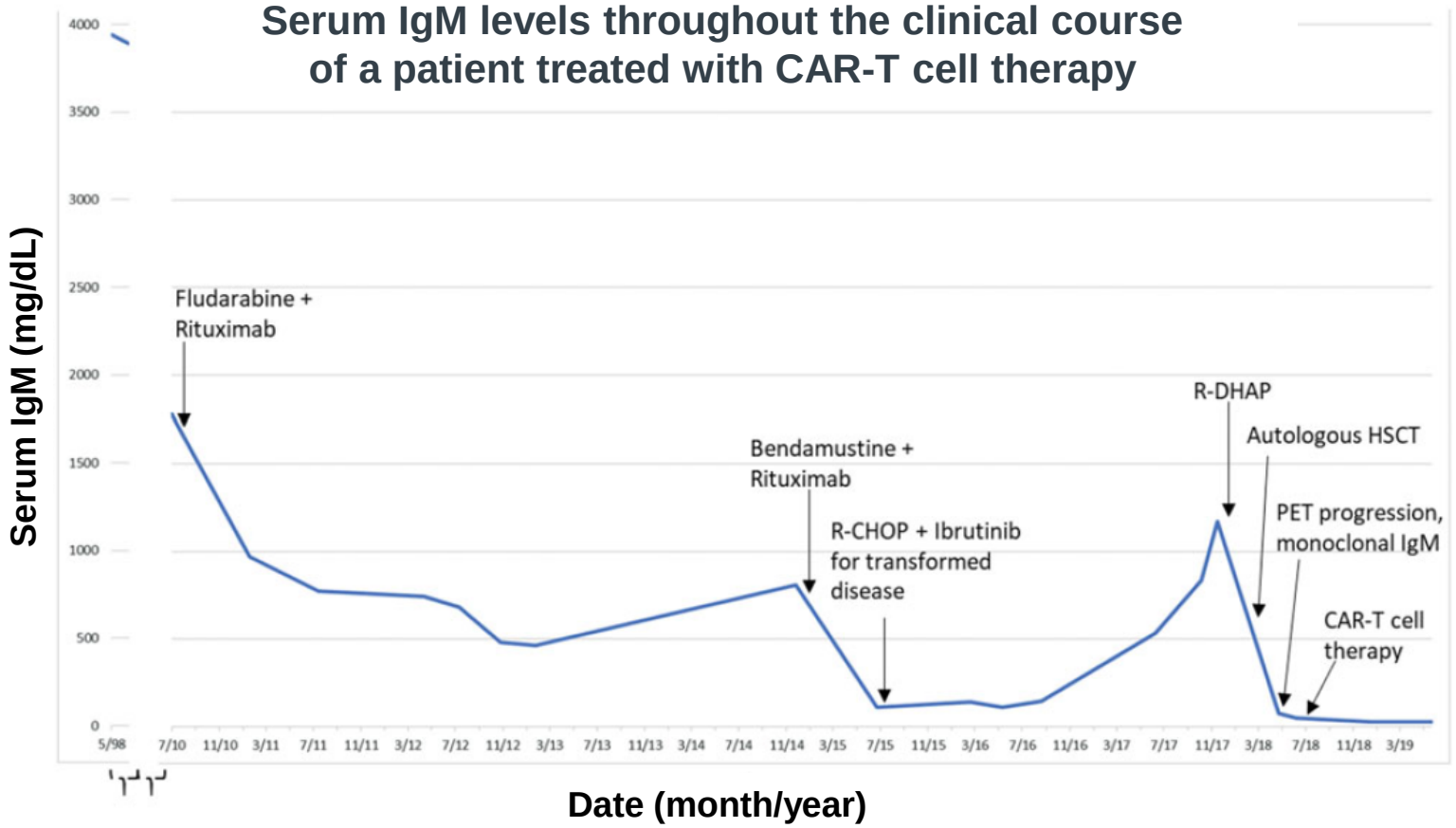
DoR, duration of response; IgM, immunoglobulin M; MRR, major response rate; ORR, overall response rate; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

Castillo JJ *et al. Blood* 2018; 132 (Suppl 1): 2888.


B-NHL
CAR-T cells have
entered real life!

CD19-targeted CAR-T cell therapy in transformed WM

- Complete response reported for a 71-year-old male patient with transformed WM who had experienced multiple relapses



CAR-T cell, chimeric antigen receptor T cell; HSCT, hematopoietic stem cell transplantation; IgM, immunoglobulin M; PET, positron emission tomography; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; WM, Waldenström's macroglobulinemia.

Bansal R *et al. Leuk Lymphoma* 2020; 61 (2): 465–468.

Summary and key challenges

- Relapse of WM is inevitable; a watch-and-wait strategy is preferred until patients meet the guideline criteria for treatment initiation

- There is no standard approach to treatment of patients with R/R WM
  - Immunochemotherapy can be an effective salvage therapy
  - BTK inhibitor therapy with ibrutinib has transformed the treatment landscape
    - Specific toxicity issues
    - Reduced efficacy in patients with *MYD88*^{WT} genotype vs. *MYD88*^{L265P}

- Patients who relapse on ibrutinib and/or discontinue because of toxicity have limited options
  - Major challenge is to find chemotherapy-free approaches that act in all genotypes, have good toxicity profiles, and do not need permanent application

- Emerging treatments: Second-generation BTK inhibitors, BCL2 inhibition, cellular therapies

BTK, Bruton's tyrosine kinase; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia; WT, wild type.


The future
looks bright!

Case studies

Dr. Ramón García-Sanz
Dr. Alessandra Tedeschi

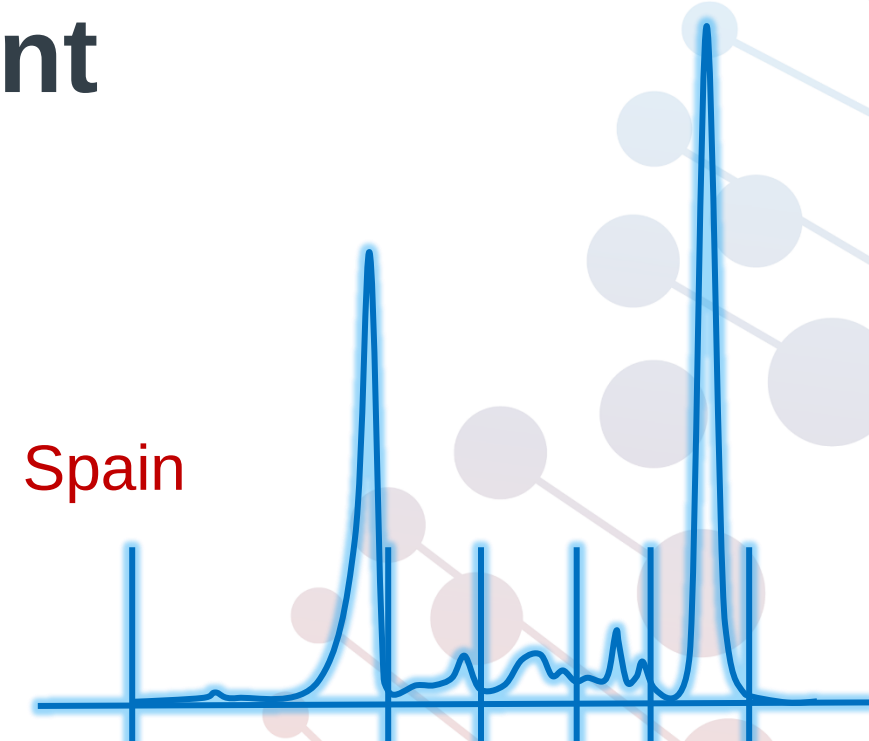
Sacyl

Hematología
HOSPITAL UNIVERSITARIO
SALAMANCA

SEHH Sociedad Española de Hematología y Hemoterapia

A patient refractory to first-line treatment

Dr. Ramón García-Sanz
University Hospital of Salamanca, Spain



Disclosures

- **Honoraria**
  - Amgen, Astellas, Beigene, BMS, Janssen, Takeda

- **Speakers bureau / scientific advisory board**
  - Takeda

Initial presentation (1)

Patient characteristics

- Male, 41-years-old
- No prior pathology
- Progressive asthenia, several months, certain sensitivity to low temperature, no B symptoms, no lymphadenopathy, no organomegaly
- Many failed biological studies
- High ESR, hyperproteinemia not very high

Review of systems

- Fatigue: No anemia
- Occasional headache
- No somnolence, no visual alterations
- No fever, weight loss or night sweats
- No bleeding
- No Raynaud's disease, no acrocyanosis

Laboratory studies

- Hemoglobin 12.9 g/dL
- Platelets 320 x 10^9/L
- WBC 5.8 x 10^9/L
  - ANC: 3.01, ALC: 1.21, AMC: 0.8 × 10^9/L
- Serum creatinine 0.81 mg/dL
- LDH 207 U/L (max. 260)
- β_2-microglobulin 2.32 µg/mL (max. 2.6)
- Albumin 4.1 g/L
- Serum monoclonal IgM 3.1 g/dL
- sFLC (mg/dL), k/l: **400/**23.

ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; sFLC, serum free light chains; WBC, white blood cells.

Initial presentation (2)

Laboratory studies

- Serum Fe: 59.3 mg/dl
- Ferritin: 86 ng/ml
- Transferrin: 429 mg/dl (Sat: 11%)

Bone marrow examinations

- Bone marrow biopsy: paratrabecular interstitial infiltration by lymphocytes, lymphoplasmocytes and plasma cells (33%); abundant mastocytes
- Flow cytometry:
  - Bone marrow: **48%** monoclonal lymphoid B cells with phenotype: $CD19^{+}$, $CD5^{-}$, $CD20^{++}$, $FMC7^{\pm}$, $CD22^{w+}$, $sIgk^{+}$, $CD25^{+}$, $CD10^{-}$, $CD103^{-}$
    0.98% kappa plasma cells, with no aberrancies
  - Peripheral blood: 0.015% monoclonal B cells
- BM FISH studies: 6q21, *TP53* & IgH, normal
- BM molecular studies:
  - $MYD88^{L265P}$: positive (Ct: 30.3^{MUT}; vs. 28.1^{WT})
  - *CXCR4* ($CD19^{+}$ cells & Sanger): normal

Total body CT scan

- No organomegaly
- Several lymph nodes between 1 & 2 cm

Funduscopy

- Normal

Cryoagglutinins

- Positive

Cryoglobulins

- Negative

BM, bone marrow; CT, computed tomography; Ct, 1st cycle threshold; FISH, fluorescence in situ hybridization; IgH, immunoglobulin heavy-chain; MUT: mutated; WM, Waldenström's macroglobulinemia; WT: wild type.

Disease progression

- In one year, progressive increase of the M component
- Anemia: Hb 8.4 g/dL, without the appearance of lymphadenopathy or B symptoms
- Almost impossible to perform analytics due to tube agglutination
- Very frequent headaches
- In the last visit incipient signs of bloating, slow thinking, prolonged sleep
  - Funduscopy: Small isolated hemorrhages, which were not seen previously

- Action needed! Very young patient (42-years-of-age), symptomatic disease, quick progression

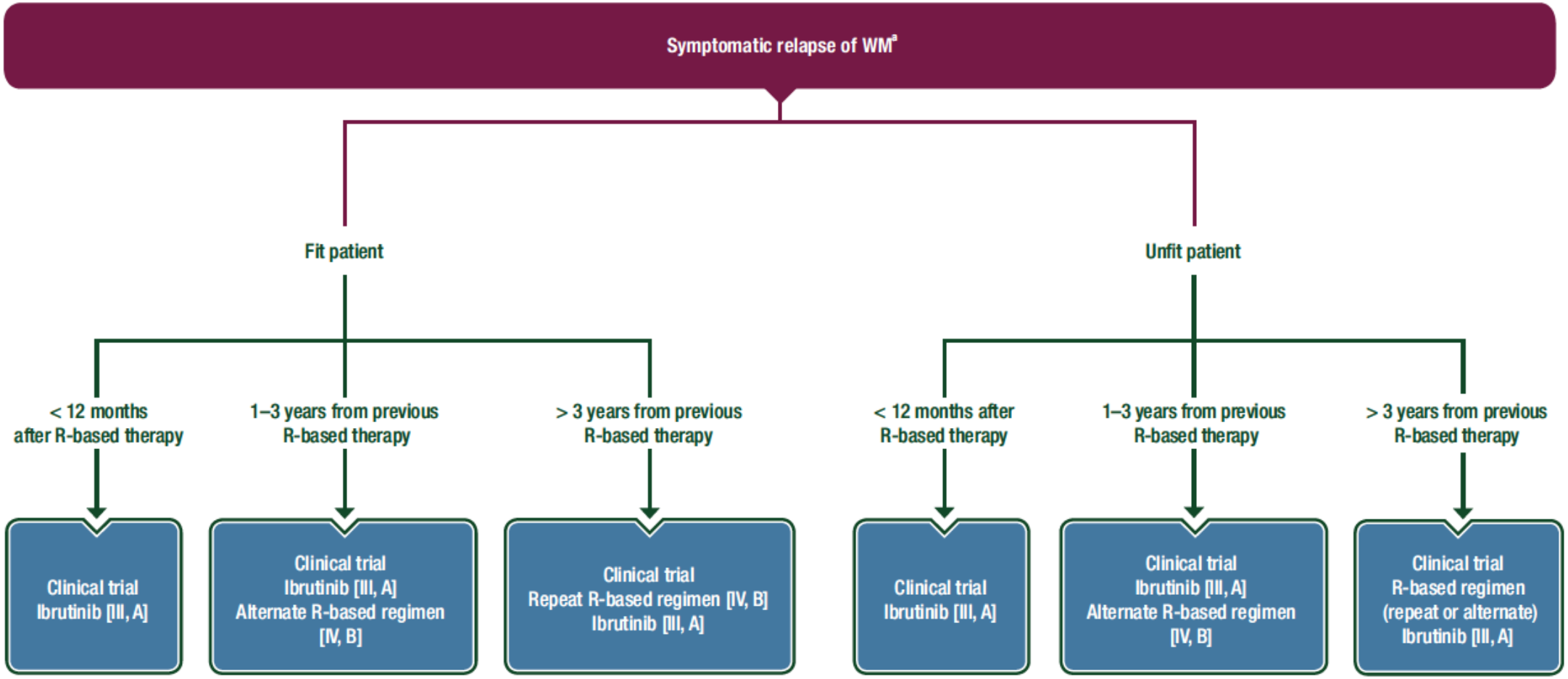
Hb, hemoglobin.

Patient treatment and outcome

- BDR, European protocol
- Well tolerated: completion of the protocol, no delays, no dose reductions
- Minor response, low symptomatic improvement
- Early progression
- Refractory disease

BDR, bortezomib, dexamethasone, and rituximab.
Dimopoulos MA *et al*. *Blood* 2013; 122 (19): 3276–82.

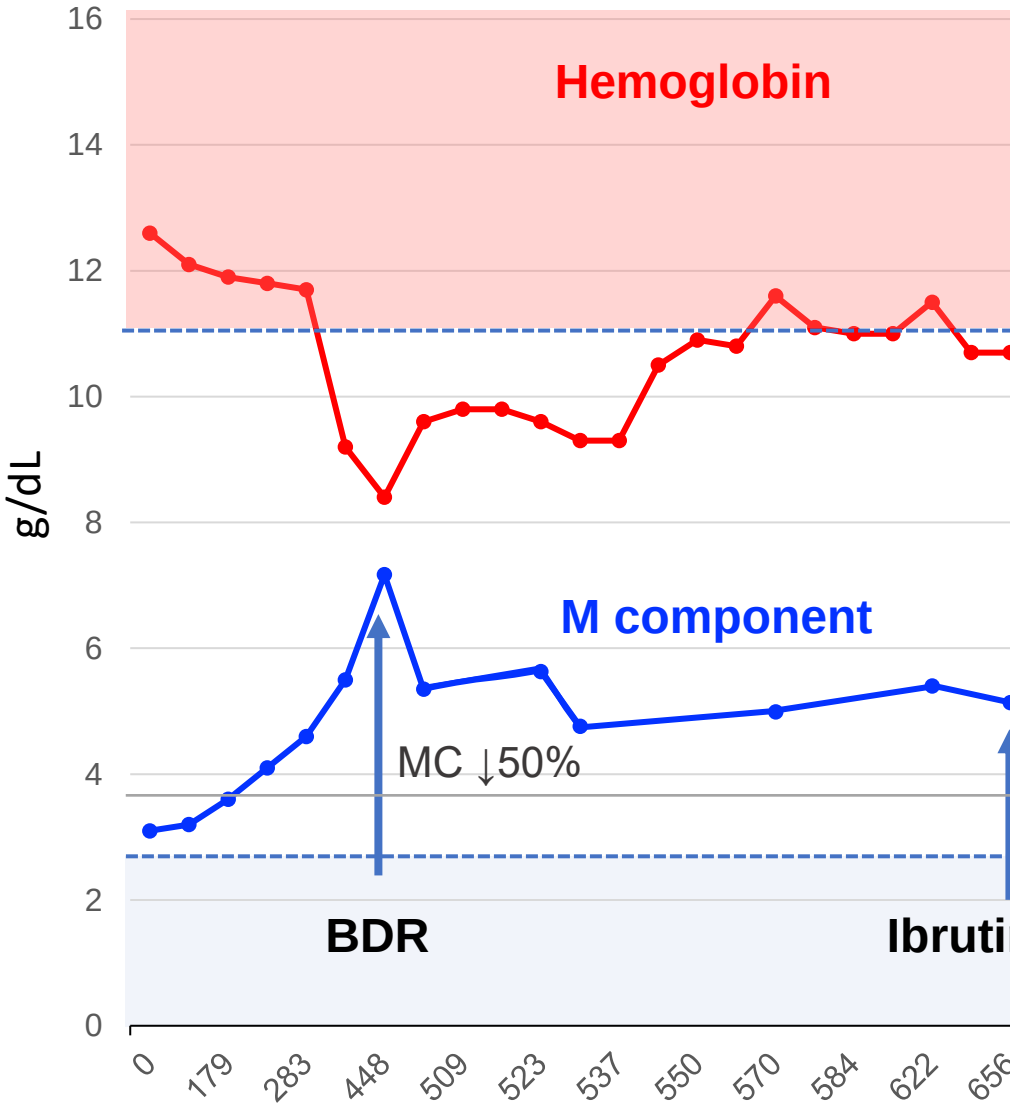
ESMO guidelines: Treatment of patients with R/R WM



[a]In case of hyperviscosity, plasmapheresis should be used concomitantly with systemic therapy [IV, A]. In case of high IgM levels and at risk for IgM-related complications, plasmapheresis may be used pre-emptively [IV, A]. ESMO, European Society for Medical Oncology; IgM, immunoglobulin M; R, rituximab; WM, Waldenström's macroglobulinemia.

Kastritis E *et al*. *Ann Oncol* 2018; 29 (Suppl 4): iv41–iv50.

Patient outcome: Hb and M component



A patient with relapsed WM

Dr. Alessandra Tedeschi
Niguarda Cancer Center, Italy

Disclosures

- Consulting services for AbbVie, AstraZeneca, BeiGene and Janssen-Cillag SpA

Initial case presentation

Patient characteristics

- 62-year-old male
- Fatigue, shortness of breath
- Good overall health, no comorbidities
- No medications

Physical examination

- 2 small palpable adenopathies (~2 cm, LC)
- Splenomegaly (16 cm)

Laboratory studies

• Hemoglobin	8.9 g/dL
• Platelets	120 × 10^9/L
• WBC	3.7 × 10^9/L
• PMN	62%
• Serum creatinine	1.3 mg/dL
• LFTs	Normal
• M spike	5.3 g/dL
• IgM	5,700 mg/dL
• Bence Jones κ	Positive
• 24h urinary protein	Normal

IgM, immunoglobulin M; κ, kappa; LC, laterocervical; LFT, liver function test; PMN, polymorphonuclear leukocyte; WBC, white blood cell.

Next steps

Bone marrow examination

Bone marrow biopsy

- 80% lymphoplasmacytic lymphoma infiltrate

Genotype

- *MYD88*^{mut}

Flow cytometry

- CD19^{+}, CD22^{low+}, CD20^{+}, CD25^{+}, CD27$^{+/-}$, CD5^{-}, CD23^{--}, CD10^{-}, CD11^{c-}, CD38$^{-/+}$, sIgM^{bright}

CT scan

- Confirmed splenomegaly (16 cm)
- Abdominal adenopathies (2 cm)

Ocular funduscopic inspection

- Normal

CT, computed tomography; mut, mutated; sIgM, serum immunoglobulin M.

WM in need of treatment for anemia

Patient characteristics

- 62-years-old
- Fit, no comorbidities

Disease characteristics

- Mucosal bleeding
- Anemia
- High IgM level

First-line

Immunochemotherapy
- DRC
- Benda-R

Bortezomib–rituximab
Not reimbursed in Italy; bortezomib in first-line

Ibrutinib
Consider benefit of continuous therapy… not reimbursed in Italy

Benda-R, bendamustine and rituximab; DRC, dexamethasone, rituximab, and cyclophosphamide; IgM, immunoglobulin M.

WM in need of treatment for anemia

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Disease characteristics

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First-line

Immunochemotherapy
- DRC
- Benda-R

Bortezomib–rituximab
Not reimbursed in Italy; bortezomib in first-line

Ibrutinib
Consider benefit of continuous therapy… not reimbursed in Italy

Benda-R, bendamustine and rituximab; DRC, dexamethasone, rituximab, and cyclophosphamide; IgM, immunoglobulin M.

First-line treatment: Bendamustine and rituximab

First course: Bendamustine 90 mg/m^2; rituximab postponed (to avoid flare)

→ Grade 4 neutropenia

Second course: Bendamustine 70 mg/m^2 and rituximab

→ Long-lasting grade 3–4 neutropenia (third course postponed for 15 days)

Third course: Bendamustine 70 mg/m^2 and rituximab

→ Long-lasting grade 3–4 neutropenia: more than 3 weeks
Pneumonia: Ceftriaxone IM

→ **Treatment discontinued**

↓

Partial remission
Hb: 11.5 g/dL
IgM: 1,900 mg/dL
Splenomegaly (14 cm)
No adenopathies

Hb, hemoglobin; IgM, immunoglobulin M; IM, intramuscular.

First progression after bendamustine and rituximab

+28 months:
Progressive disease → IgM: 2,380 mg/dL
Hb: 10.8 g/dL
Splenomegaly (14 cm)
Adenopathies (2 cm, LC)

+38 months:
Progressive disease in need of treatment → Mucosal bleeding
IgM: 6,100 mg/dL
Hb: 9.6 g/dL
Splenomegaly (14 cm)
Adenopathies (max. 2 cm, LC)
CT scan: Abdominal adenopathies (2 cm)

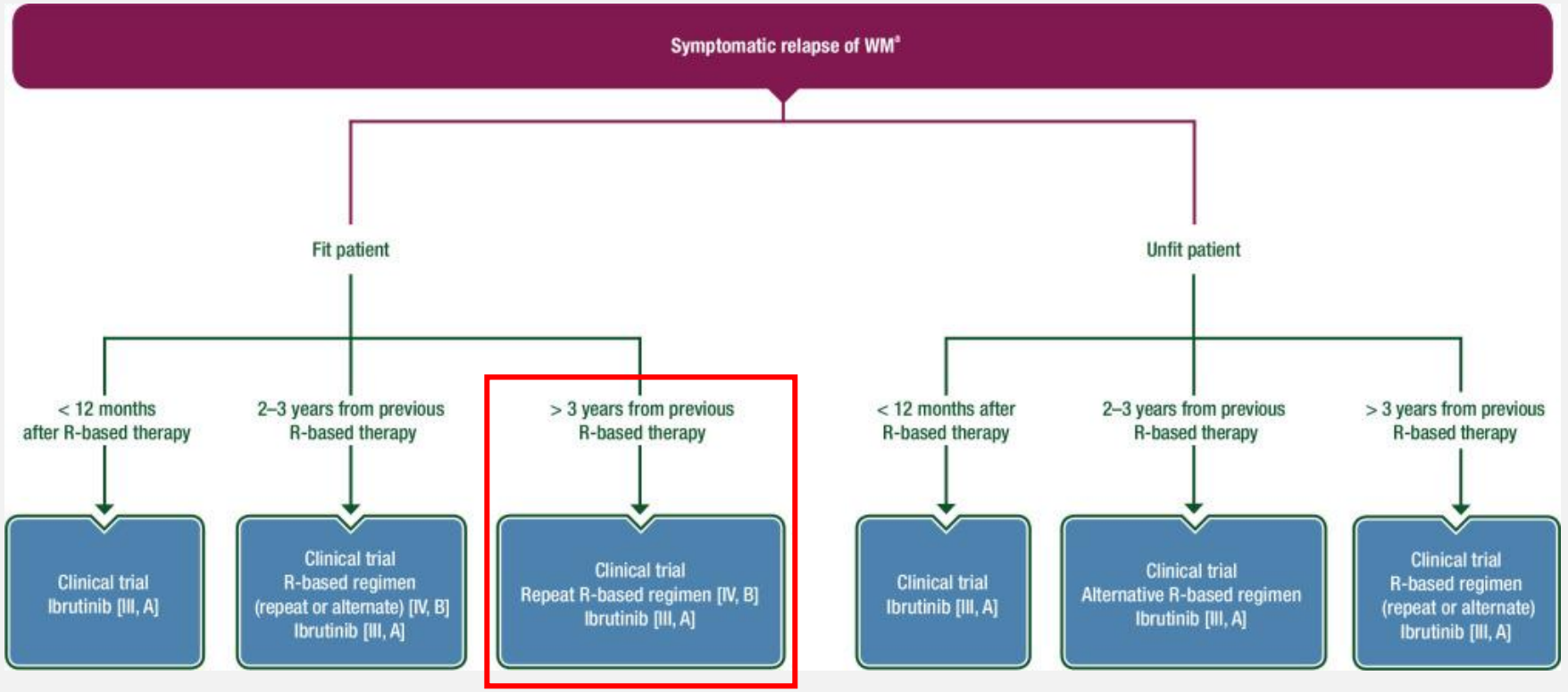
CT, computed tomography; Hb, hemoglobin; IgM, immunoglobulin M; LC, laterocervical.

Second-line treatment after bendamustine and rituximab

Patient characteristics
- 65-years-old
- Fit, no comorbidities

Disease characteristics
- Mucosal bleeding
- Anemia, splenomegaly (15 cm), adenopathies (max. 3 cm)
- High IgM level
- *MYD88*^{mut}, *CXCR4*^{mut}

Disease history
- PR after first-line Benda-R; reduced tolerance
- Progression: 38 months



[a]In case of hyperviscosity, plasmapheresis should be used concomitantly with systemic therapy [IV, A]. In case of high IgM levels and at risk for IgM-related complications, plasmapheresis may be used pre-emptively [IV, A].
Benda-R, bendamustine and rituximab; IgM, immunoglobulin M; mut, mutated; PR, partial remission; R, rituximab; WM, Waldenström's macroglobulinemia.
Kastritis E *et al*. *Ann Oncol* 2018; 29 (Suppl 4): iv41–iv50.

Second-line treatment after bendamustine and rituximab

Second-line options:

1. Immunochemotherapy: DRC or Benda-R
2. Ibrutinib
3. Bortezomib–rituximab

Benda-R, bendamustine and rituximab; DRC, dexamethasone, rituximab, and cyclophosphamide.

Second-line treatment after bendamustine and rituximab

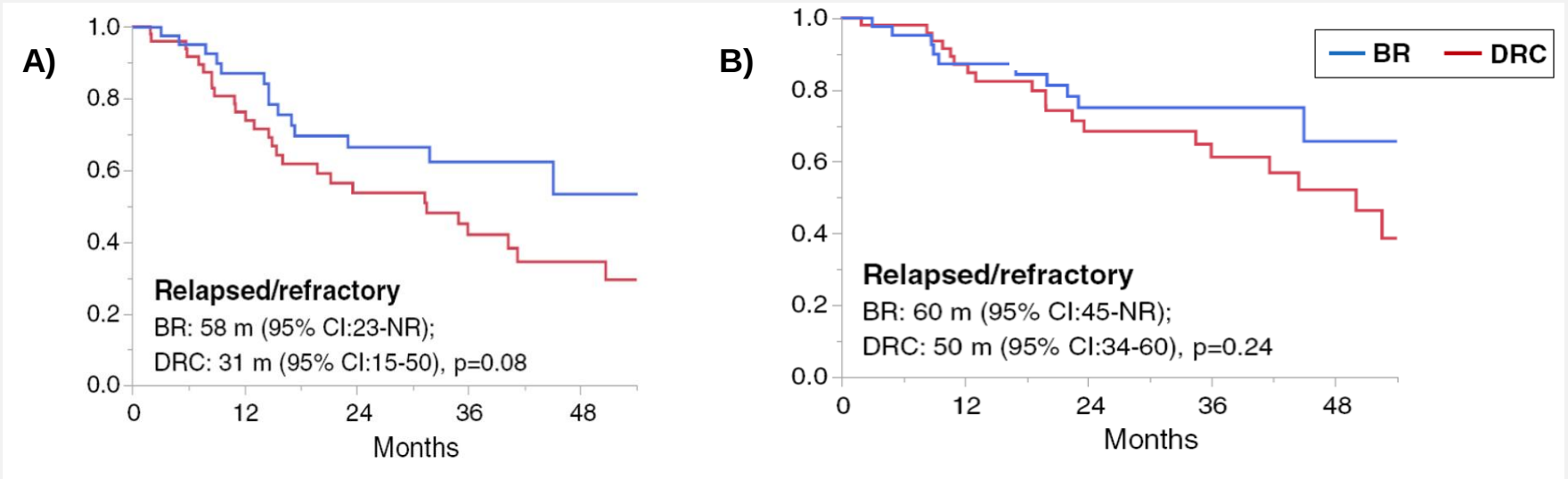
Second-line options:

1. Immunochemotherapy: DRC or Benda-R

2. Ibrutinib

3. Bortezomib–rituximab

A) PFS and B) TTNT in patients with R/R WM treated with Benda-R or DRC (N=160)[1]



BR/Benda-R, bendamustine and rituximab; CI, confidence interval; DRC, dexamethasone, rituximab, and cyclophosphamide; m, months, NR, not reported; PFS, progression-free survival; R/R, relapsed/refractory; TTNT, time to next treatment; WM, Waldenström's macroglobulinemia.

1. Paludo J *et al*. *Ann Hematol* 2018; 97 (8): 1417–1425.

Second-line treatment after bendamustine and rituximab

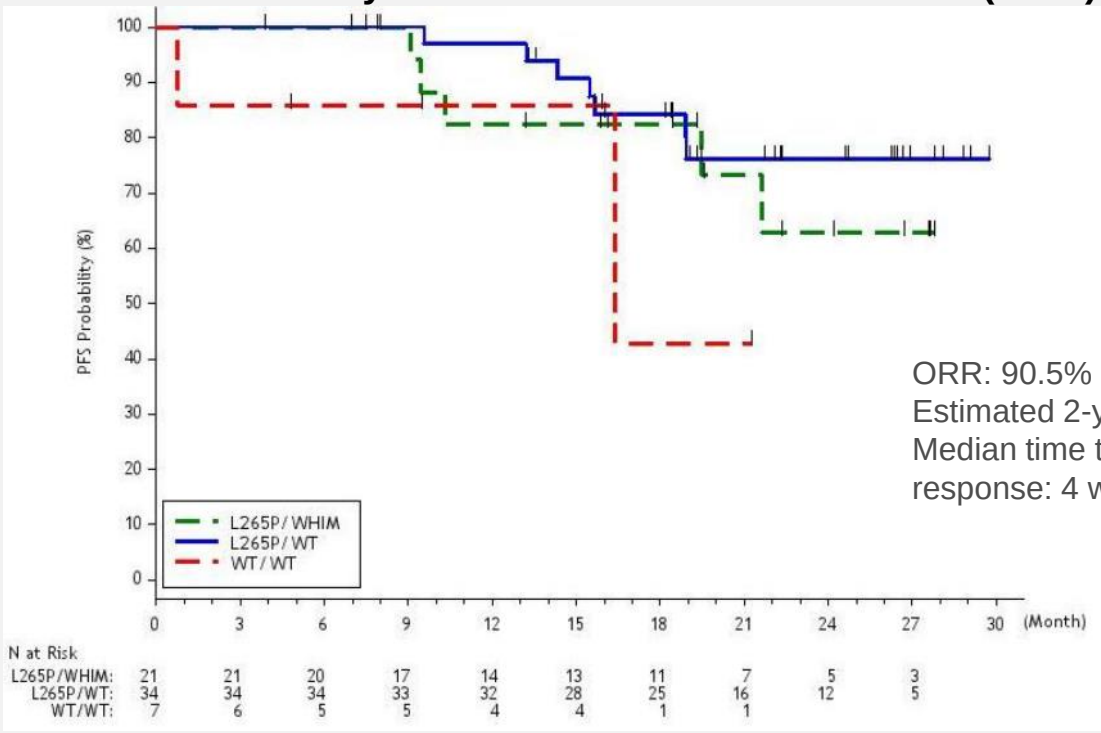
Second-line options:

1. ~~Immunochemotherapy: DRC or Benda-R~~

2. Ibrutinib

3. Bortezomib–rituximab

PFS by *MYD88/CXCR4* mutational status (N=63)[1]



ORR: 90.5%
Estimated 2-year PFS: 69%
Median time to a minor response: 4 weeks

Benda-R, bendamustine and rituximab; DRC, dexamethasone, rituximab, and cyclophosphamide; ORR, overall response rate; PFS, progression-free survival; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; WT, wild-type.

1. Treon SP *et al*. *N Engl J Med* 2015; 372 (15): 1430–1440.

Second-line treatment after bendamustine and rituximab

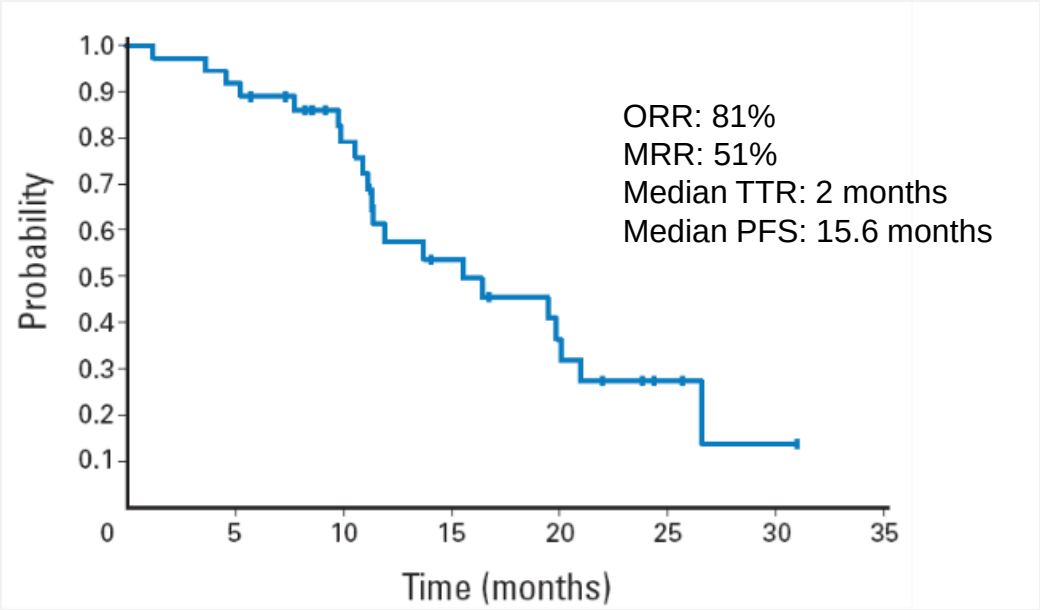
Second-line options:

1. ~~Immunochemotherapy: DRC or Benda-R~~

2. ~~Ibrutinib~~

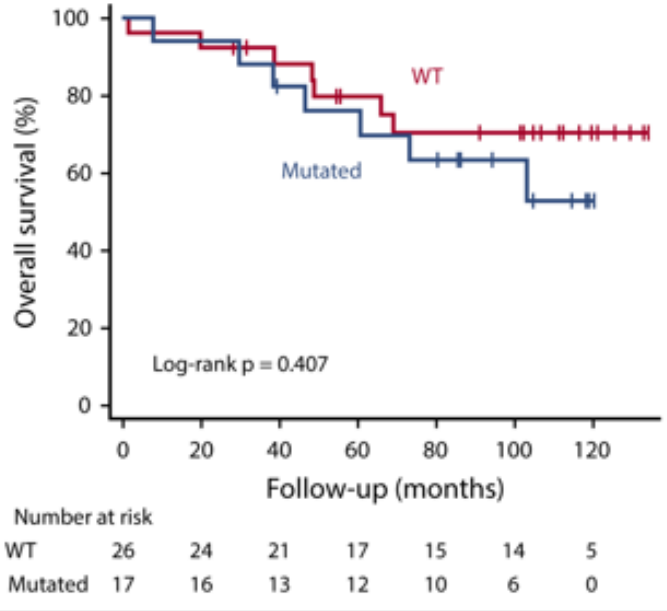
3. Bortezomib–rituximab

PFS in patients with R/R WM (N=37)[1]



ORR: 81%
MRR: 51%
Median TTR: 2 months
Median PFS: 15.6 months

Overall survival according to *CXCR4* mutational status (N=43)[2]



Benda-R, bendamustine and rituximab; DRC, dexamethasone, rituximab, and cyclophosphamide; MRR, major response rate; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; TTR, time to (first) response; WT, wild-type.

1. Ghobrial IM *et al*. *J Clin Oncol* 2010; 28 (8): 1422–1428. 2. Sklavenitis-Pistofidis R *et al*. *Blood* 2018; 132 (24): 2608–2612.

Second-line treatment: Bortezomib and rituximab

Patient characteristics
- 65-years-old
- Fit, no comorbidities

Disease characteristics
- Mucosal bleeding
- Anemia, splenomegaly (15 cm), adenopathies (max. 3 cm)
- High IgM level
- *MYD88*^{mut}, *CXCR4*^{mut}

Disease history
- PR after Benda-R; reduced tolerance
- Progression: 38 months

Bortezomib–rituximab: Six courses
- Weekly schedule bortezomib 1.6 mg (Days 1, 8, and 15)
- Rituximab weekly cycle 1–4

Grade 2 neuropathy after the third course
- Reduced dosage of bortezomib (1.2 mg)
- VZV reactivation after cycle 2

Minor response

IgM: 3,900 mg/dL
Hb: 10.8 g/dL

Benda-R, bendamustine and rituximab; Hb, hemoglobin; IgM, immunoglobulin M; mut, mutated; PR, partial remission; VZV, varicella-zoster virus.

Progression after second-line bortezomib–rituximab

Third-line treatment

+16 months
Progressive disease
in need of treatment

→ Mucosal bleeding
IgM: 5,100 mg/dL
Hb: 9.5 g/dL
Splenomegaly (16 cm)
Adenopathies (max. 4 cm, LC)
CT scan: Abdominal adenopathies (6 cm)

Third-line treatment

~~Immunochemotherapy~~

~~Bortezomib–rituximab~~

BTK inhibitors

BTK, Bruton's tyrosine kinase; CT, computed tomography; Hb, hemoglobin; IgM, immunoglobulin M; LC, laterocervical.

Third-line treatment: Zanubrutinib, April 2018

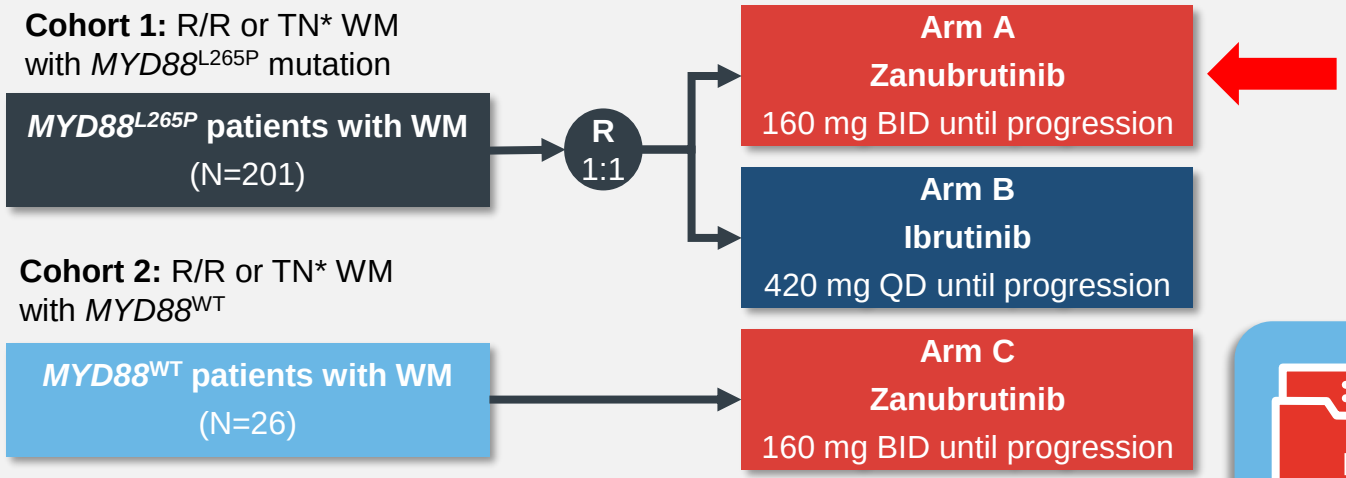
Patient characteristics
- 67-years-old
- Fit
- Concomitant medication: aspirin (non-critical carotid artery stenosis)

Disease characteristics
- Mucosal bleeding
- Anemia, abdominal bulky disease
- High IgM level
- *MYD88*^{mut}, *CXCR4*^{mut}

Disease history
- PR after Benda-R; reduced tolerance
- Minor response after bortezomib–rituximab

Clinical Study Protocol

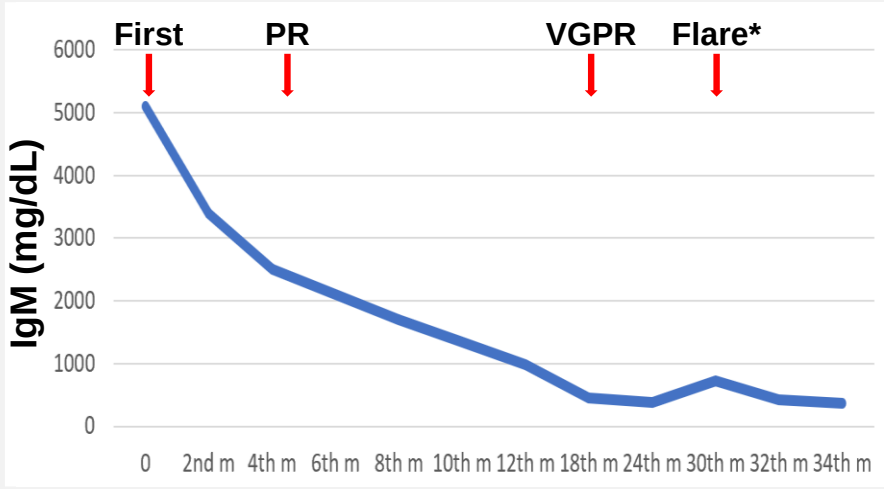
Protocol Title:	**A Phase 3, Randomized, Open-Label, Multicenter Study Comparing the Efficacy and Safety of the Bruton's Tyrosine Kinase (BTK) Inhibitors BGB-3111 and Ibrutinib in Subjects with Waldenström's Macroglobulinemia (WM)**
Protocol Number:	**BGB-3111-302**



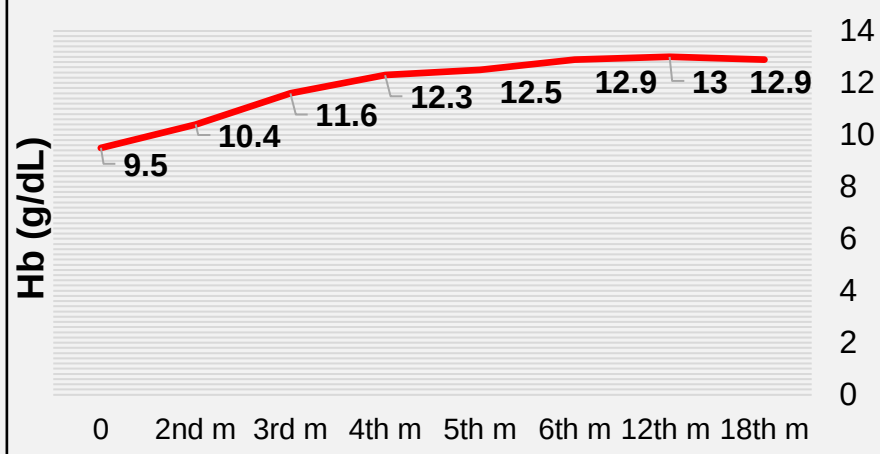
*Unsuitable for standard immunochemotherapy because of comorbidities and/or other risk factors.
Benda-R, bendamustine and rituximab; BID, twice a day; IgM, immunoglobulin M; mut, mutated; PR, partial remission; QD, every day; R, randomized; R/R, relapsed/refractory; TN, treatment-naive; WM, Waldenström's macroglobulinemia; WT, wild-type.
Dimopoulos MA *et al*. Abstract 2022 presented at the European Hematology Association (EHA) Annual Meeting; June 11–22, 2020.

Third-line treatment: Zanubrutinib, April 2018

IgM



Hb



CT scan

0	Adenopathies	6 cm
	Splenomegaly	16 cm
+3 m	Adenopathies	2.5 cm
	Splenomegaly	15 cm
+6 m	Adenopathies	2 cm
	Splenomegaly	15 cm
+12 m	Adenopathies	<1.5 cm
	Splenomegaly	13 cm

Adverse events:

- Grade 3–4 neutropenia
- Musculoskeletal diffuse pain (Grade 2) managed with low-dose steroids
- No major or minor infections

Response at 18 months: VGPR
Still ongoing +34 months

*Flare for discontinuation (surgical programmed intervention).
CT, computed tomography; Hb, hemoglobin; IgM, immunoglobulin M; m, month; PR, partial response; VGPR, very good partial response.

Case study panel discussion

- Criteria to change therapy
- Influence of age in therapeutic decision-making
- Secondary effects
- Considerations about stem cell transplantation
- Considerations about clinical trials

Open panel discussion

Moderator: Professor Christian Buske
Panel: All

Open panel discussion

1. Impact of COVID-19, including vaccination programs, on treatment decisions

2. Patients with early relapse (‘POD24’ patients) or refractory patients

3. Guidelines vs. daily practice

POD24, progression of disease within 24 months.

Audience Q&A: What challenges do you face in treating WM?

Moderator: Professor Véronique Leblond
Panel: All

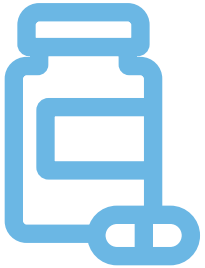
WM, Waldenström’s macroglobulinemia.

Summary

Chair: Professor Véronique Leblond

Summary

Relapse is inevitable in WM and a substantial proportion of patients are at risk of relapse within 24 months



The panelists consider immunochemotherapy to be a suitable treatment for many patients with R/R WM, but BTK inhibitors are also highly effective and may be particularly appropriate for early relapsing and unfit patients

As with first-line treatment of WM, a major challenge in the R/R setting is to develop chemotherapy-free approaches that act in all genotypes, have low toxicity, and do not need permanent application

BTK, Bruton's tyrosine kinase, R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

Save the date!

Multidisciplinary management of Waldenström's macroglobulinemia: Providing specialist care beyond hematology

Join us in **May 2021** for the fourth installment in the BeiGeneius webinar series in which we will consider multidisciplinary management of WM, with a focus on neuropathy and cardiotoxicity

WM, Waldenström's macroglobulinemia.

We would appreciate your feedback!

Please complete the post-meeting survey.

Thank you for your attention

BeiGeneius