Second-generation BTK inhibitors for patients with WM: What is the potential for improving outcomes?

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

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First-generation BTK inhibitors in WM

Ibrutinib is approved by the EMA for patients with WM who have relapsed after primary therapy and for the first-line treatment of patients who are not eligible for chemoimmunotherapy[1]

Oral, irreversible BTK inhibitor that covalently binds to cysteine at position 481 in the kinase domain and thereby blocks kinase activity[2]	**iNNOVATE phase III study[1]** • Ibrutinib with rituximab vs rituximab monotherapy in patients who had received no previous treatment or in pretreated, rituximab-sensitive patients • PFS at 30 months: - 82% with ibrutinib/rituximab - 28% with placebo/ rituximab - HR, 0.2; 95% CI, 0.11–0.38	**Effectiveness of ibrutinib depends on the mutational status of the *MYD88* and *CXCR4* genes[1]** **Number of off-target effects and can inhibit other tyrosine kinases[3]** **Known to cause bleeding and atrial fibrillation[3]**

CI, confidence interval; EMA, European Medicines Agency; HR, hazard ratio; PFS, progression-free survival.

1. Kastritis E, et al. *Annals of Oncology* 2018;29:iv41–50; 2. Singh P, et al. *Mol Cancer* 2018;17:57; 3. Owen C, et al. *Curr Oncol* 2019;26:e233–40.

Why mutational status matters

Common mutations

- *MYD88* L265P is found in over 90% of patients with WM
- Patients with wild-type *MYD88* have a higher risk of aggressive transformation to DLBCL and a worse survival rate
- Recurrent mutations in *CXCR4* have been detected in 30–40% of patients with WM
- Patients with *CXCR4* mutations tend to have higher serum IgM levels, a higher risk of developing symptomatic hyperviscosity and lower rates of extramedullary disease

Response to ibrutinib

- Patients with *MYD88* L265P tend to have deeper and more sustained responses to ibrutinib with major response rate of 97% and 5-year PFS rate of 75%
- Patients with WM with concurrent *MYD88* and *CXCR4* mutations had major response rate of 64% and median PFS of 42 months
- None of the patients with WM and wild-type *MYD88* or *CXCR4* mutations achieved a partial response, and the median PFS was reached at 5 months

CXCR4, CXC chemokine receptor 4; DLBCL, diffuse large B-cell lymphoma; IgM, immunoglobulin M.

1. Castillo JJ, Treon SP. *Leukemia* 2019;33:2555–62; 2. Treon SP, et al. *Hematol Oncol* 2019;37(S2):184–5.

Limitations of first-generation BTK inhibitor led to active development of second-generation BTK inhibitors

Second-generation, more specific BTK inhibitors, have fewer off-target effects and are more potent than ibrutinib[1]

Zanubrutinib

- Forms irreversible covalent bond at Cys481 in the adenosine triphosphate-binding pocket of the BTK active site
- Potent BTK inhibitor with greater selectivity than ibrutinib, with minimal off-target inhibition[2,3]
- In phase I trials, the C_{max} and AUC were the same for:
  - zanubrutinib at 80 mg
  - ibrutinib at 560 mg[3,4]
- Complete and continuous BTK occupancy observed in peripheral blood mononuclear cells of patients with advanced B-cell malignancies[3]

Acalabrutinib

- Orally administered second-generation, small-molecule irreversible inhibitor of BTK that covalently binds to Cys481
- Selective BTK inhibitor without the off-target effects on other kinases[5–7]
- In human whole blood, acalabrutinib had equipotent BTK inhibition compared with ibrutinib but less of an effect on healthy T cells likely due to its selectivity[8,9]
- In murine models, acalabrutinib caused a significant reduction in proliferating cells and total tumour burden in the spleen[10]

AUC, area under the curve; C_{max}, maximum concentration of drug in plasma.

1. Wang Q, et al. *Proc Natl Acad Sci USA* 2019;116:9390–9; 2. Li N, et al. *Cancer Res* 2015;75(15 Suppl.):2597; 3. Tam C, et al. *Blood* 2015;126:832; 4. Advani RH, et al. *J Clin Oncol* 2013;31:88–94; 5. Bryd JC, et al. *N Engl J Med* 2016;374:323–2; 6. Covey T, et al. *Cancer Res* 2015;75(15 Suppl):2596; 7. Barf T, et al. *J Pharmacol Exp Ther* 2017;363:240–252; 8. Covey T, et al. *Blood* 2017;130(Suppl. 1):1741; 9. Patel V, et al. *Clin Cancer Res* 2017;23:3734–43; 10. Herman SEM, et al. *Blood* 2015;126:2920.

ASPEN: Phase III randomized trial shows efficacy of zanubrutinib vs ibrutinib for patients with WM

- WM with *MYD88* mutation
- Assigned 1:1 to receive zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily)
- Randomization was stratified by *CXCR4* mutational status and the number of lines of prior therapy (0 vs 1–3 vs >3)

VGPR (%)
Zanubrutinib: **28**
Ibrutinib: **19**

CR, complete response; VGPR, very good partial response.
Tam CS, et al. Blood. 2020. doi: 10.1182/blood.2020006844. Online ahead of print.

ASPEN: Phase III study shows efficacy of zanubrutinib in *MYD88^{wt}* patients with WM

Best response, n (%)	Total (N=26)
ORR	21 (80.8%)
MRR (PR or better)	13 (50.0%)
VGPR	7 (26.9%)
PR	6 (23.1%)
MR	8 (30.8%)
SD/PD	4 (15.4%)/1 (3.8%)
Time to major response (≥PR), median (range), months	2.9 (1.9–7.4)
Study follow-up time, median months	17.9

BID, twice daily; MR, major response; MRR, major response rate; ORR, overall response rate; PD, progression of disease; PR, partial response; R/R, relapsed/refractory; SD/PD, stable disease/progression of disease.

Garcia-Sanz R, et al. *J Clin Oncol* 2020;38:Abstract e20056.

Single-arm, phase II study demonstrates OR of acalabrutinib monotherapy in patients with WM

- Patients were either treatment naive (n=14; declined or not eligible for chemoimmunotherapy) or relapsed/refractory (n=92; at least one previous therapy)
- Acalabrutinib (100 mg twice daily) in 28-day cycles until disease progression or unacceptable toxicity

Treatment-naive
OR: **93% (CI 66–100)**
CR/VGPR: **0/0**

Relapsed/refractory
OR: **93% (CI 86–98)**
CR/VGPR: **0/9%**

Acalabrutinib is active as single-agent therapy
Additional trials needed to compare efficacy with other treatment options

OR, overall response.
Owen RG, et al. *Lancet Haematol* 2020;7:e112–21.

Ongoing studies of investigational therapies, including BTK inhibitors, in WM

Ulocuplumab
(monoclonal antibody against CXC chemokine receptor 4 [CXCR4])

- Under investigation in combination with ibrutinib in a single arm phase I/II study of symptomatic patients with mutated *CXCR4* WM (NCT03225716)[1]
  - Ibrutinib administered orally once daily
  - Ulocuplumab administered IV 2–4 times per cycle for Cycles 1–6
- Primary outcome measures:
  - Maximum tolerated dose of ulocuplumab
  - Major response rate
- Secondary outcome measures include: time to MMR, time to progression, ORR

Mavorixafor
(selective *CXCR4* chemokine receptor allosteric antagonist)

- Planned phase Ib study: in combination with ibrutinib in patients with *MYD88* and *CXCR4* mutated WM (NCT04274738)
- This is an intrapatient dose-escalation study:
  - Mavorixafor 200 mg once daily, 400 mg once daily and 600 mg once daily
  - Ibrutinib will be administered at the labelled dose for patients with WM, 420 mg orally once daily
  - Each treatment cycle will be 28 days

IV, intravenous.

1. ClinicalTrials.gov. A Study of Ulocuplumab And Ibrutinib in Symptomatic Patients With Mutated CXCR4 Waldenstrom's Macroglobulinemia. [Cited 9 July 2020] Available from: https://clinicaltrials.gov/ct2/show/NCT03225716; 2. ClinicalTrials.gov. A Study of Mavorixafor in Combination With Ibrutinib in Participants With Waldenstrom's Macroglobulinemia (WM) Whose Tumors Express Mutations in MYD88 and CXCR4. [Cited 9 July 2020] Available from: https://clinicaltrials.gov/ct2/show/NCT04274738.

Summary

- **First-generation BTK inhibitor ibrutinib approved for patients with WM who have relapsed after primary therapy and first-line in patients not eligible for chemoimmunotherapy**
  - Mutational status of *MYD88* and *CXCR4* genes affects effectiveness
  - Off-target effects
  - Associated with bleeding and atrial fibrillation

- **Second-generation, more specific BTK inhibitors (e.g. zanubrutinib and acalabrutinib)**
  - Fewer off target effects
  - Better PK/PD than ibrutinib
  - Zanubrutinib active in *MYD88*^{wt} patients

- **Studies of investigational therapies in WM are ongoing, including:**
  - Ulocuplumab (monoclonal antibody against CXCR4)
  - Mavorixafor (selective CXCR4 chemokine receptor allosteric antagonist)

PD, pharmacodynamics; PK, pharmacokinetics

Maximizing outcomes for patients with WM: Adverse events associated with second-generation BTK inhibitors

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

Adverse events with ibrutinib

Bleeding[1]
Ibrutinib + rituximab: **51%**
Rituximab + placebo: **21%**

Atrial fibrillation[1]
Ibrutinib + rituximab: **15%**
Rituximab + placebo: **3%**

Hypertension[1]
Ibrutinib + rituximab: **13%**
Rituximab + placebo: **4%**

Dimopoulous MA, et al. *N Engl J Med* 2018;378:2399–10.

Mechanisms for ibrutinib-related adverse events

Atrial fibrillation:
inhibition of PI3K

Bleeding:
inhibition of platelet aggregation via glycoprotein VI

Infection:
inhibition of ITK and/or macrophages

Stephens DM, Byrd JC. *Blood* 2019;133:1298–307.

Zanubrutinib equipotent against BTK compared with ibrutinib and higher selectivity for EGFR, ITK, JAK3, HER2, and TEC

Targets	Assays	Ibrutinib IC_{50} (nM)	Zanubrutinib IC_{50} (nM)	Ratio (Zanu:Ibrutinib)
BTK	BTK-pY223 cellular assay	3.5	1.8	0.5
	Rec-1 proliferation	0.34	0.36	1.1
	BTK occupation cellular assay	2.3	2.2	1.0
	BTK biochemical assay	0.20	0.22	1.1
EGFR	p-EGFR HTRF cellular assay	101	606	6.0
	A431 proliferation	323	3210	9.9
ITK	ITK occupancy cellular assay	189	3265	17
	p-$PLC_{\gamma 1}$ cellular assay	77	3433	45
	IL-2 production cellular assay	260	2536	9.8
	ITK biochemical assay	0.9	30	33
JAK3	JAK3 biochemical assay	3.9	200	51
HER2	HER2 biochemical assay	9.4	661	70
TEC	TEC biochemical assay	0.8	1.9	2.4

EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IC50, half-maximal inhibitor concentration; JAK3, Janus kinase 3; TEC, tyrosine-protein kinase Tec.

Tam CS, et al. *Blood* 2019;134(11):851–9.

ASPEN: safety profile of zanubrutinib vs ibrutinib for patients with WM

Adverse events	Zanubrutinib (%)	Ibrutinib (%)
Grade ≥3	58.4	63.3
Leading to dose reduction	13.9	23.5
Leading to discontinuation	4.0	9.2
Leading to death	1.0	4.1
Adverse events of interest		
Atrial fibrillation or flutter	2.0	15.3
Haemorrhage	48.5	59.2
Major haemorrhage	5.9	9.2

Zanubrutinib arm reported a safer and more tolerable adverse event profile

Dimopoulos MA, et al. Abstract presented at 25th European Haematology Association Annual Congress. June 11-21, 2020. Abstract S225; Tam CS, et al. Blood. 2020. doi: 10.1182/blood.2020006844. Online ahead of print.

ASPEN: frequently occurring adverse events with zanubrutinib vs ibrutinib for patients with WM

Event preferred term*, n (%)	All grades (≥20%)		Grade ≥3 (≥5%)	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Diarrhoea	**31 (32)**	21 (21)	1 (1)	3 (3)
Upper respiratory tract infection	28 (29)	24 (24)	1 (1)	0
Contusion	**23 (24)**	13 (13)	0	0
Muscle spasms†	**23 (24)**	10 (10)	1 (1)	0
Peripheral oedema†	**19 (19)**	9 (9)	0	0
Hypertension	16 (16)	11 (11)	**11 (11)**	6 (6)
Atrial fibrillation†	**15 (15)**	2 (2)	4 (4)	0
Neutropenia†	13 (13)	**29 (29)**	8 (8)	**19 (20)**
Pneumonia†	**12 (12)**	2 (2)	**7 (7)**	1 (1)
Anaemia	10 (10)	12 (12)	5 (5)	5 (5)
Thrombocytopenia	10 (10)	10 (10)	3 (3)	6 (6)

*Including most common adverse events and adverse events with ≥10% or ≥5% differentials, respectively (higher frequency in bold red). †Descriptive 2-sided $p<0.05$

Tam CS, et al. Blood. 2020. doi: 10.1182/blood.2020006844. Online ahead of print.

ASPEN: adverse event categories of interest (BTKi class adverse events)

Adverse event categories, n (%) (pooled terms)	All grades		Grade ≥3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter†	**15 (15.3)**	2 (2.0)	4 (4.1)	0 (0.0)
Diarrhoea (PT)	**31 (31.6)**	21 (20.8)	1 (1.0)	3 (3.0)
Haemorrhage	**58 (59.2)**	49 (48.5)	8 (8.2)	6 (5.9)
Major haemorrhage*	9 (9.2)	6 (5.9)	8 (8.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)	**12 (12.2)**	6 (5.9)
Neutropenia†,‡	13 (13.3)	**30 (29.7)**	8 (8.2)	**20 (19.8)**
Infection	66 (67.3)	67 (66.3)	19 (19.4)	18 (17.8)
Second malignancy	11 (11.2)	12 (11.9)	1 (1.0)	2 (2.0)

BTKi, Bruton's tyrosine kinase inhibitor. Higher adverse event (AE) rate in bold red with ≥10% difference in any grade or ≥5% difference in grade 3 or above.
No tumour lysis syndrome was reported. Opportunistic infection ibrutinib (n=2), zanubrutinib (n=1). *Defined as any grade ≥3 haemorrhage or any grade central nervous system haemorrhage. ‡Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.
†Descriptive 2-sided $p<0.05$. Dimopoulos MA, et al. Abstract presented at 25th European Haematology Association Annual Congress. June 11-21, 2020. Oral Presentation: p425-1.

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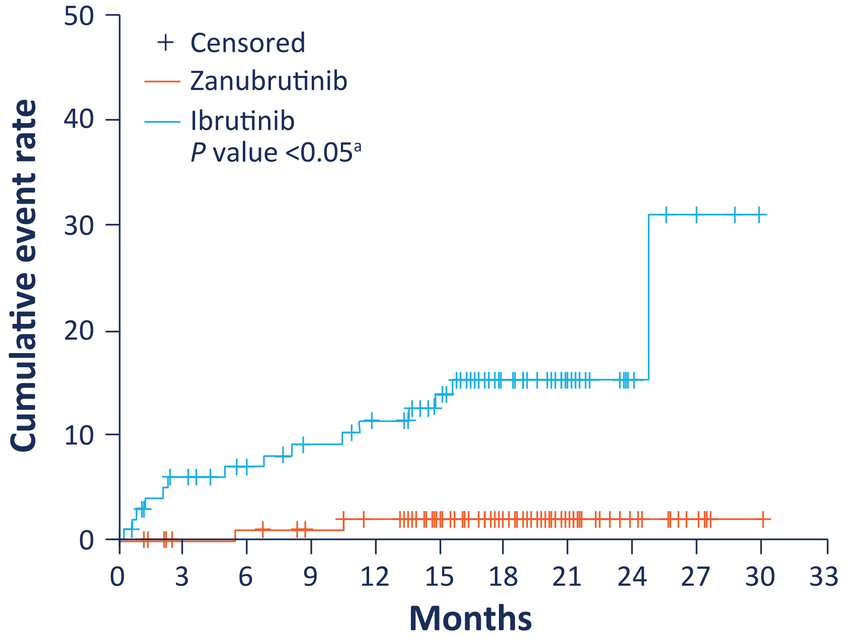
ASPEN: Time to adverse event – risk analysis over duration of treatment

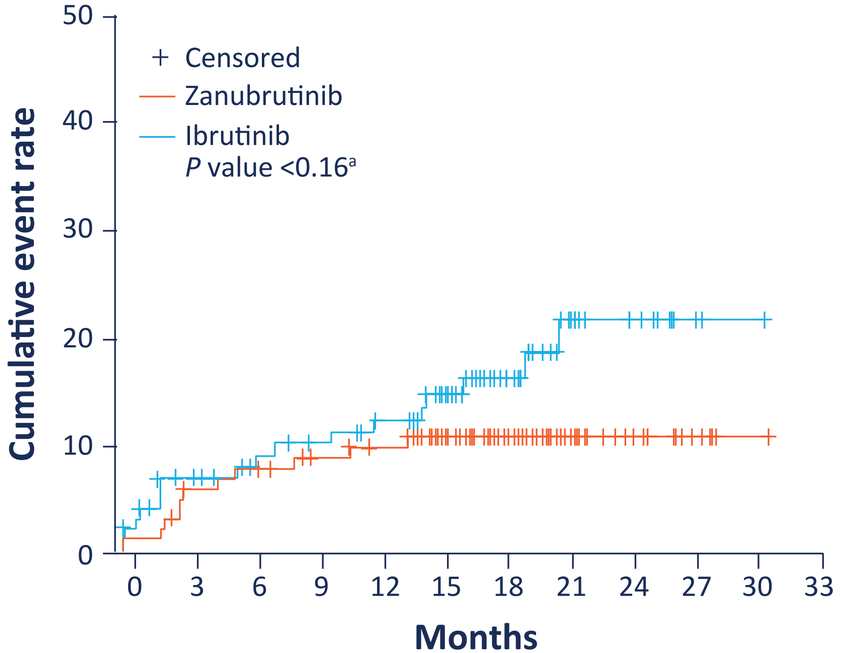
Kaplan-Meier curve: time to **atrial fibrillation/flutter**



Number at risk

Zanubrutinib	101	95	94	92	89	81	57	34	15	7	1	0
Ibrutinib	98	87	83	78	74	66	46	28	13	3	1	0

Kaplan-Meier curve: time to **hypertension**



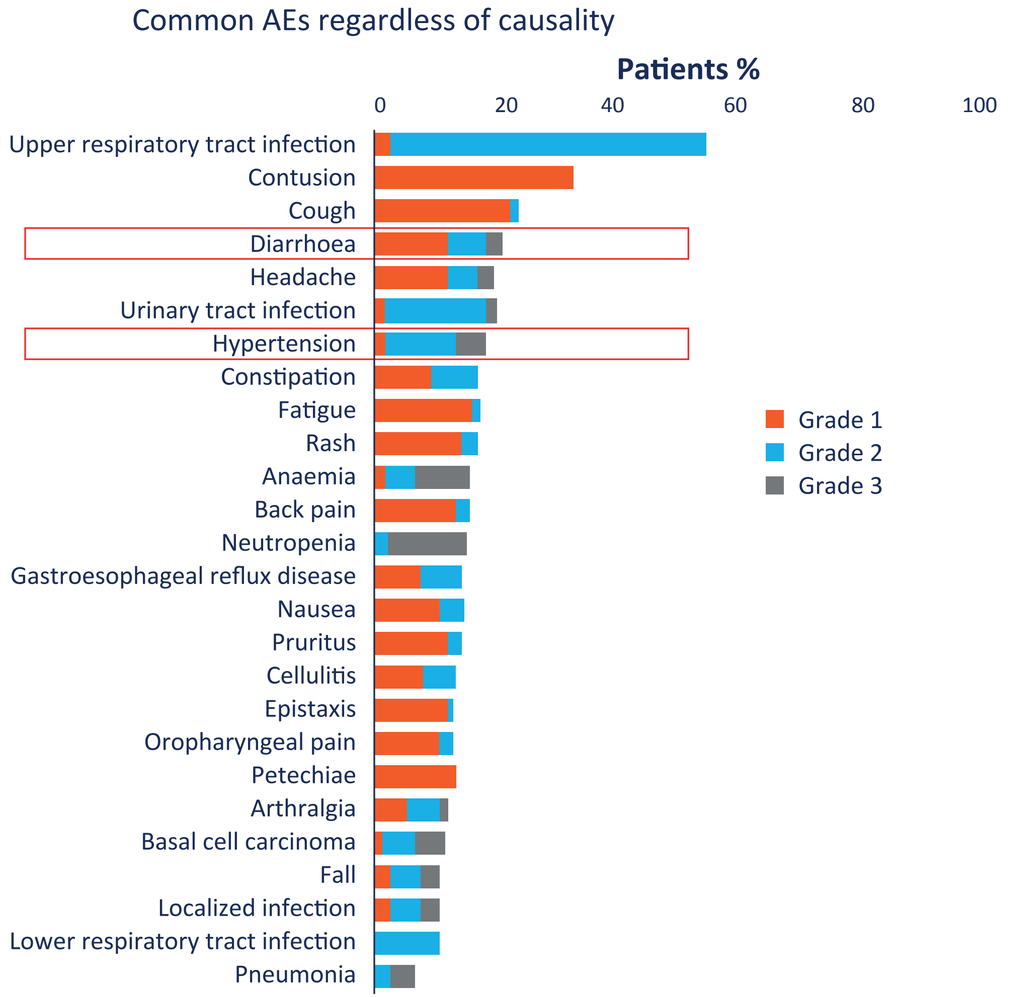
Number at risk

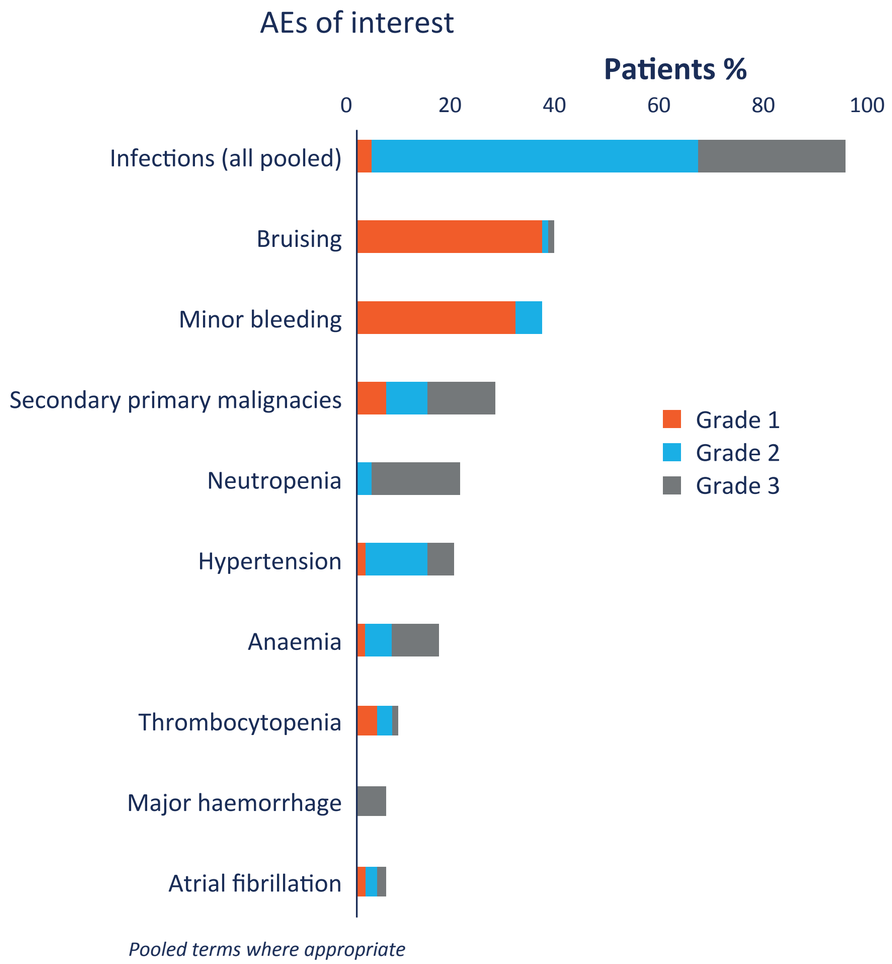
Zanubrutinib	101	90	88	84	81	73	51	28	14	7	1	0
Ibrutinib	98	84	80	75	71	61	42	24	11	3	1	0

[a]Descriptive purpose only.

Dimopoulos MA, et al. Abstract presented at 25th European Haematology Association Annual Congress. June 11-21, 2020. Oral Presentation: p425-1.

Phase I/II BGB-3111-AU-003 study: WM cohort long-term follow up





Pooled terms where appropriate

AEs, adverse events.

Tam CS, et al. American Society of Clinical Oncology Annual Meeting, May 29–31, 2020: Abstract 304709; Trotman J, et al. Blood. 2020. doi: 10.1182/blood.2020006449. Online ahead of print.

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Acalabrutinib has higher selectivity than ibrutinib across a range of kinases, including EGFR, ITK and TEC

Kinase assay	Ibrutinib IC_{50} (nM)	Acalabrutinib IC_{50} (nM)	Ratio (Acal:Ibrutinib)
BTK	1.5	5.1	3.4
TEC	7.0	93	13.3
BMX	0.8	46	57.5
TXK	2.0	368	184
ERBB2	6.4	~1000	~156.3
EGFR	5.3	>1000	>188.7
ITK	4.9	>1000	>204.1
JAK3	32	>1000	>31.25
BLK	0.1	>1000	>10,000

BMX, bone marrow kinase on chromosome X; BLK, B lymphoid kinase; ERBB2, erb-b2 receptor tyrosine kinase 2; TXK, tyrosine-protein kinase

Byrd JC, et al. *N Engl J Med* 2016; 374(4):323–32.

Safety profile of acalabrutinib monotherapy in patients with WM

Adverse events	Grade 1–2 (%)	Grade ≥3 (%)
Bleeding (contusion, epistaxis, etc)	58	3
Hypertension	2	3
Atrial fibrillation	4	1
Headache	39	0
Neutropenia	1	16

Owen RG, et al. *Lancet Haematol* 2020;7:e112–21.

Strategies to reduce impact of AEs in patients with WM

Key principles of clinical management in patients with WM prior to ibrutinib therapy	For patients developing AF	For patients experiencing bleeding or requiring procedures that increase the risk of bleeding
• Comprehensive pretreatment assessment to identify patients who are at a higher risk of complications • Careful choice of concomitant drugs • Regular monitoring • Multispecialist approach	• Anticoagulant and antiarrhythmic therapy where appropriate (guided by considerations about efficacy, safety, and risk of PK interactions	• Considerations about platelet turnover, ibrutinib-related platelet dysfunctions, and bleeding worsening by concomitant anticoagulants or antiplatelet agents

AF, atrial fibrillation.
Boriani G, et al. *Hematol Oncol* 2018;36:624–32.

Summary

- **Management of adverse events in patients receiving ibrutinib requires careful planning and recognition of the reported safety profile**

- **Zanubrutinib has higher selectivity for EGFR, ITK, JAK3, HER2, and TEC**
  - Safer and more tolerable adverse event profile
  - Atrial fibrillation/flutter and hypertension cumulative event rate decreased over time
  - Majority of patients remain on zanubrutinib over the long term

- **Acalabrutinib has higher selectivity than ibrutinib across a range of kinases, including EGFR, ITK and TEC**

Using BTK inhibitors in clinical practice: How is the landscape changing?

BTK, Bruton's tyrosine kinase.

When should treatment be initiated in patients with WM?

Patients with symptoms related to tissue infiltration by neoplastic cells treatment should be started upon:[1]

- Fatigue
- Recurrent fever
- Night sweats
- Cytopenias
- Lymphadenopathy
- Organomegaly
- Bulky extramedullary disease
- **IgM-related complications**

Patients with IgM level >60 g/L should receive treatment based on imminent risk of symptomatic hyperviscosity[2]

- Considered a clinical emergency, with plasma exchange followed by systemic treatment
- Avoid rituximab in case of hyperviscosity syndrome and introduce when the serum IgM is <4000 mg/dL[3]

IgM, immunoglobulin M; WM, Waldenström's macroglobulinemia.

1. Tedeschi A, Frustaci AM. *HemaSphere* 2019;3:S2. 2. Kastritis E, et al. *Ann Oncol* 2018;29(Suppl 4):iv41– iv50. 3. Gustine JN, et al. *Br J Haematol* 2017;177:717–25.

Factors for consideration when deciding treatment options for people with WM

Patient

- Age
- Performance status
- Comorbidities

Therapy

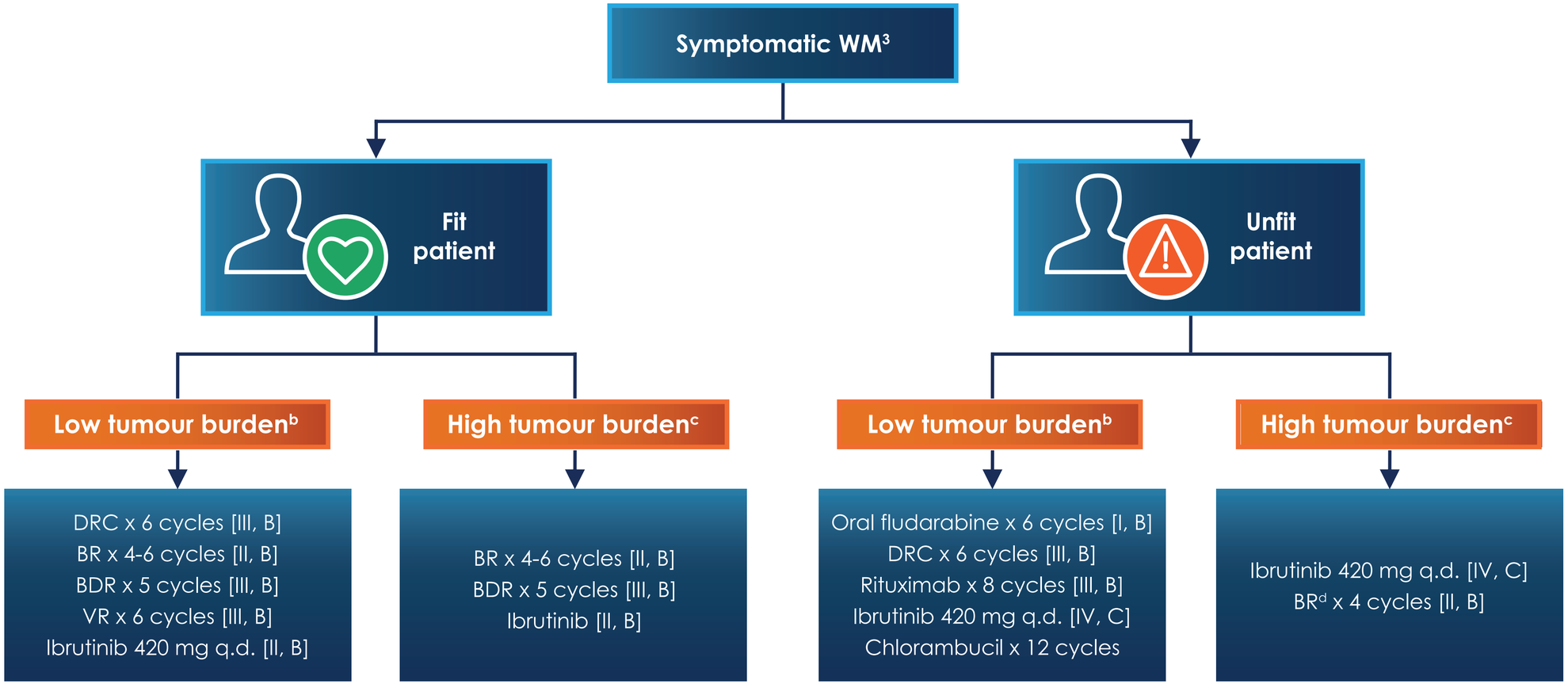
- Treatment goals
- Treatment concerns

Disease presentation

- Need for rapid disease control
- Cytopenia
- Neuropathy
- Bulky disease/extramedullary disease
- Cryoglobulinemia/cold agglutinin

MYD88 & *CXCR4* status (?)

European guidelines for newly diagnosed symptomatic 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]. [b]No major cytopaenias, hyperviscosity or organomegaly. [c]Presence of any of the following: severe cytopaenias, hyperviscosity, organomegaly. [d]BR for unfit patients may require dose reductions for bendamustine and use of G-CSF and/or antibacterial/antiviral prophylaxis. BDR, bortezomib/rituximab/dexamethasone; BR, bendamustine/rituximab; DRC, rituximab/cyclophosphamide/dexamethasone; G-CSF, granulocyte colony-stimulating factor; q.d., once a day; VR, bortezomib/rituximab. Kastritis E, et al. *Ann Oncol* 2018;29(Suppl 4):iv41– iv50.

Suggested therapy in treatment-naive patients with WM

Therapy	Indications
Rituximab monotherapy	Elderly with comorbidities not suitable for immune-chemotherapy Disease presenting with IgM related symptoms, not high tumor burden
Fludarabine monotherapy	Elderly with comorbidities not suitable for immune-chemotherapy
Chlorambucil monotherapy	
DRC	Disease with low tumor burden Patients with poor marrow reserve Disease presenting with IgM related symptoms
BR	Disease with high tumor burden Need of rapid disease control
Bortezomib rituximab ± DXM	High IgM level Need of rapid disease control
Purine analogues rituximab ± CTX	Possibly avoid in first line treatment
Ibrutinib monotherapy	Elderly not suitable for immunochemotherapy Rapid disease control
Ibrutinib rituximab	Elderly not suitable for immunochemotherapy

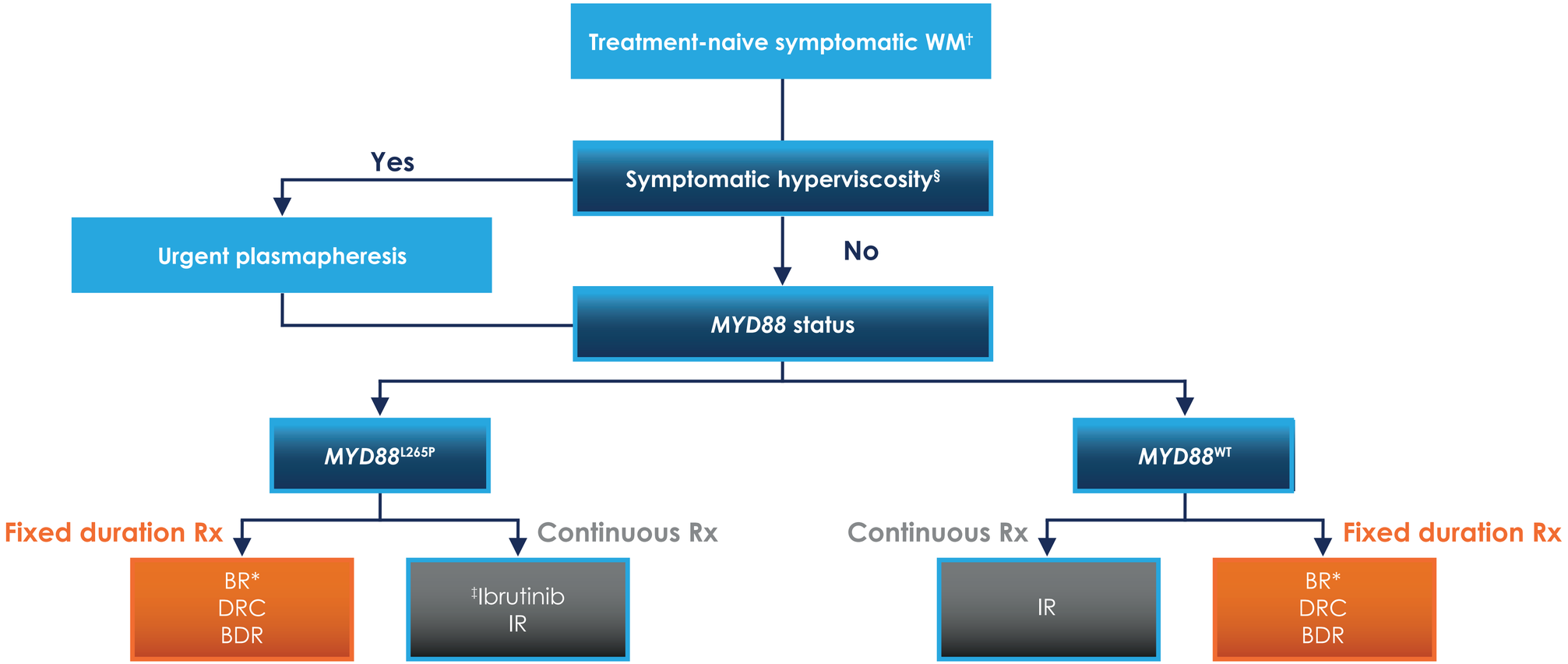
CTX, cyclophosphamide.
Tedeschi A, Frustaci AM. *HemaSphere* 2019;3:S2.

Suggested therapy in treatment-naive patients with WM

Therapy	Indications	Limitations
Rituximab monotherapy	Elderly with comorbidities not suitable for immune-chemotherapy Disease presenting with IgM related symptoms, not high tumor burden	IgM "flare", plasmapheresis indicated if IgM>4000 mg/dL Low response rates Slow disease control
Fludarabine monotherapy	Elderly with comorbidities not suitable for immune-chemotherapy	Slow disease control
Chlorambucil monotherapy		Myelotoxicity Secondary malignancies
DRC	Disease with low tumor burden Patients with poor marrow reserve Disease presenting with IgM related symptoms	Slow disease control
BR	Disease with high tumor burden Need of rapid disease control	Possible immunosuppression Need of long-term follow-up to define late toxicities
Bortezomib rituximab ± DXM	High IgM level Need of rapid disease control	Neuropathy
Purine analogues rituximab ± CTX	Possibly avoid in first line treatment	Myelotoxicity Immunosuppressive Secondary malignancies
Ibrutinib monotherapy	Elderly not suitable for immunochemotherapy Rapid disease control	CXCR4 may have an impact on outcome Continuous treatment
Ibrutinib rituximab	Elderly not suitable for immunochemotherapy	Continuous treatment

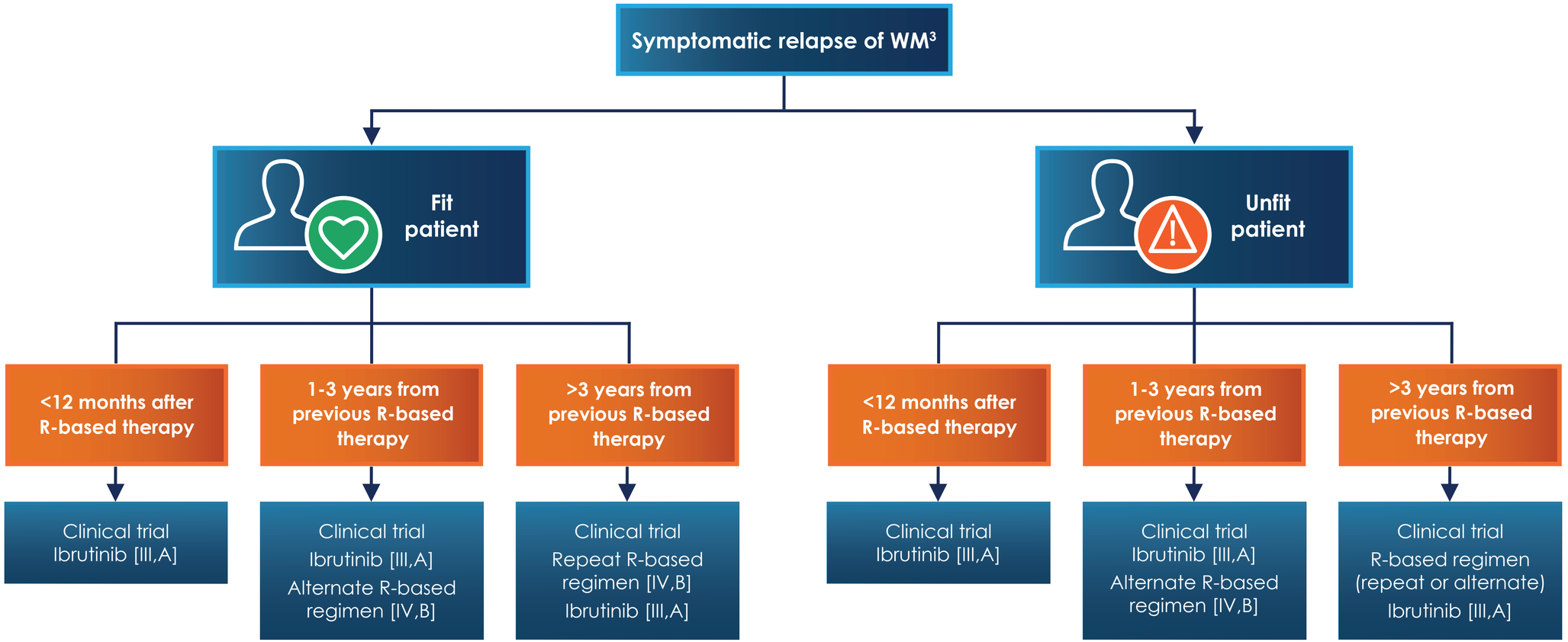
Tedeschi A, Frustaci AM. *HemaSphere* 2019;3:S2.

Choice of frontline therapy for symptomatic WM according to MYD88 status



BDR, bortezomib, dexamethasone, rituximab; BR, bendamustine rituximab; IR, ibrutinib plus rituximab; Rx, prescription. †Patients meeting the 2002 Consensus criteria for treament initiation; §Presence of one or more hyperviscosity-related clinical symptoms such as bleeding, blurry vision, headache, vertigo, dizziness, nystagmus, deafness, slow mentation, changes in retinal blood vessels, or ataxia in patients with WM that was otherwise not attributable to another cause; *Our preferred regimen is BR (over DRC or BDR); ‡No prospective study comparing ibru versus BR/DRC/BDR; BDR to be avoided in patients with pre-existing neuropathy Zanwar S, et al. *Oncol Hematol Rev* 2019;15:39–47.

European guidelines for relapsed or refractory symptomatic WM treatment



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

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Summary

- **Treatment should be offered only to symptomatic patients and selected according to individual patient characteristics and disease presentation**
- **Rituximab in combination with cyclophosphamide and dexamethasone or bendamustine are considered standard first-line treatment options**
- **Ibrutinib monotherapy or in combination is effective and may be a valid option in patients unfit for immunochemotherapy**
- **Re-treatment with immunochemotherapy should be reserved only for fit patients after a long response duration**
  - Ibrutinib monotherapy or in combination allows for better outcomes in the relapsed/refractory setting
- **Treatment outcome may be affected by *MYD88* and *CXCR4* mutations**
  - A better understanding of their impact on treatment outcome may lead to a more targeted approach