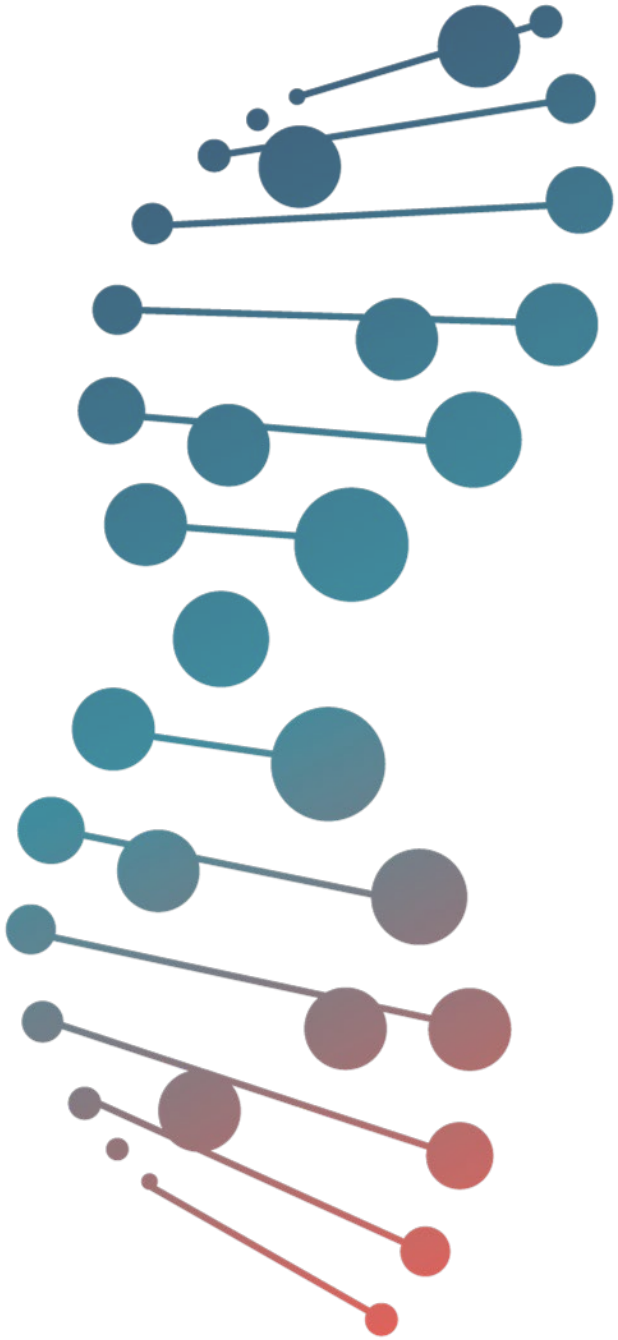
EHA and Beyond:
Post-Congress Season
Insights on CLL and WM

Monday, September 1, 2025 | 17:30–18:30 (CEST)

BeGenius



Welcome and introductions

Chair: Christian Buske

Disclosures

- **Research support**: AbbVie, Amgen, Bayer, Celltrion, Janssen, MSD, Roche
- **Honoraria**: AbbVie, Bayer, BeOne Medicines Ltd, Celltrion, Hexal, Janssen, MorphoSys, Novartis, Pfizer, Regeneron, Roche

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- The views expressed in the presentations are those of the speakers and may not necessarily reflect the opinion of BeOne. BeOne does not guarantee the accuracy or reliability of the information provided herein and expressly disclaims liability for any errors or omissions in this information.
- Zanubrutinib is approved in the EU as monotherapy for adults with chronic lymphocytic leukemia (CLL), for adults with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20–based therapy, for adults with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy or in first-line treatment for patients unsuitable for chemoimmunotherapy, and in combination with obinutuzumab for adults with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least two prior lines of systemic therapy.[1]
- Prescribing information (PI) may vary depending on local approval in each country. Therefore, before prescribing any product, always refer to local authorities concerning reimbursement status and to local materials such as the PI and/or the summary of product characteristics (SPC) for guidance on prescribing.

CD, cluster of differentiation.

1. BeiGene Ireland Ltd. BRUKINSA 80 mg hard capsules – summary of product characteristics; May 2025.

Introducing the panel

Christian Buske (Chair)
University Hospital Ulm, Germany

Anna Maria Frustaci
ASST Niguarda Great Metropolitan Hospital, Italy

Romain Guièze
University Hospital Center of Clermont-Ferrand, France

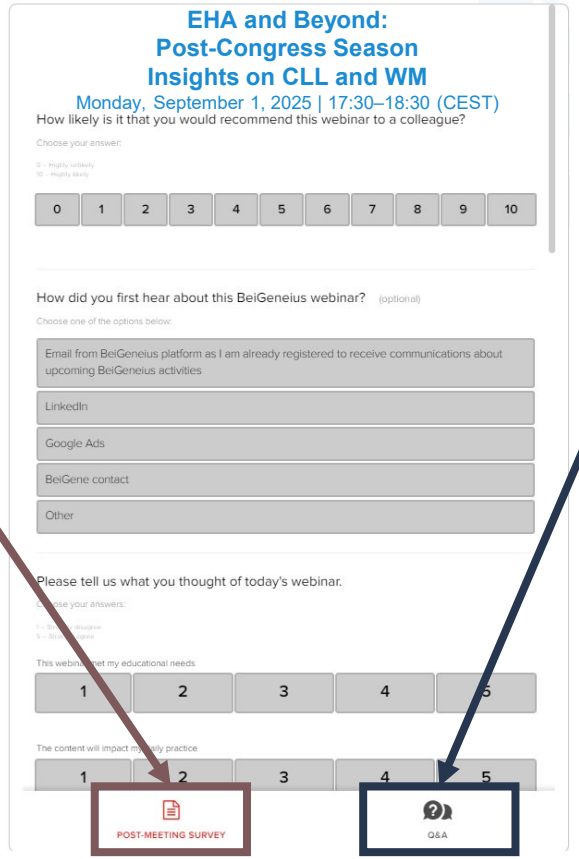
Agenda

Time	Session	Speaker
5 min	Welcome	Christian Buske
20 min	Expert digest: Chronic lymphocytic leukemia	Romain Guièze
15 min	Expert digest: Waldenström's macroglobulinemia	Anna Maria Frustaci
15 min	Discussion and audience Q&A	All faculty
5 min	Summary	Christian Buske

Q&A, question and answer.

We want to hear from you!

Exit full-screen view to have your say



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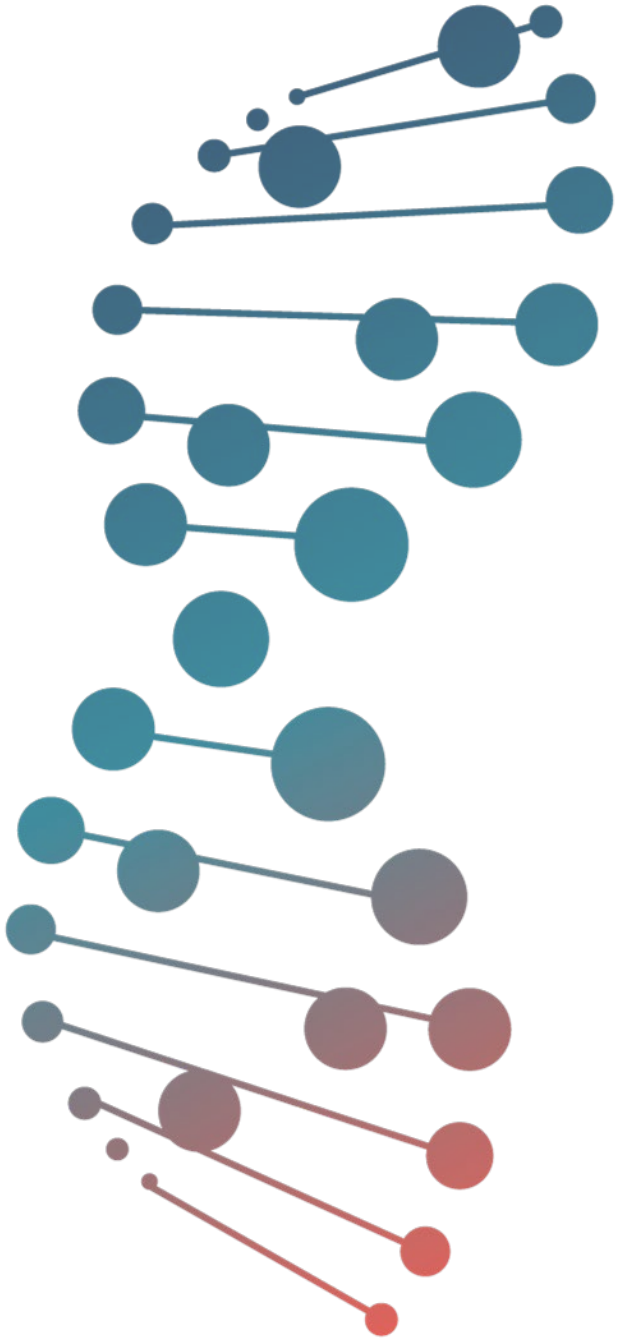
Please submit your questions to the faculty here

Meeting objective

To share and explore important data and expert discussions on **CLL** and **WM** from the 2025 summer meetings and congresses

ASCO, American Society of Clinical Oncology; CLL, chronic lymphocytic leukemia; ECWM, European Consortium for Waldenström's Macroglobulinemia; EHA, European Hematology Association; ICML, International Conference on Malignant Lymphoma; WM, Waldenström's macroglobulinemia.



Expert digest: Chronic lymphocytic leukemia

Romain Guièze
University Hospital Center of Clermont-Ferrand, France

Disclosures

- **Honoraria:** AbbVie, AstraZeneca, BeOne Medicines Ltd, Johnson & Johnson, Lilly
- **Research funds:** AbbVie, AstraZeneca, BeOne Medicines Ltd, Johnson & Johnson, Lilly

First-line treatment

FILO guidelines: The key choice in first-line therapy is between continuous BTKi monotherapy and fixed-duration therapies

April 2025

Symptomatic CLL (iwCLL criteria)

No *TP53* alterations / no complex karyotype*

Mutated IGHV

1. Ven-Obi

2. If Ven-Obi is not preferentially indicated:

Ibr-Ven
In the absence of CV comorbidities

OR

Continuous cBTKi
Selection criteria in associated text

Unmutated IGHV

Fixed-duration targeted therapy

- **Ven-Obi**
- **Ibr-Ven**

In the absence of CV comorbidities

Continuous cBTKi

Selection criteria in associated text

TP53 alterations and/or complex karyotype*

1. Continuous cBTKi
Selection criteria in associated text

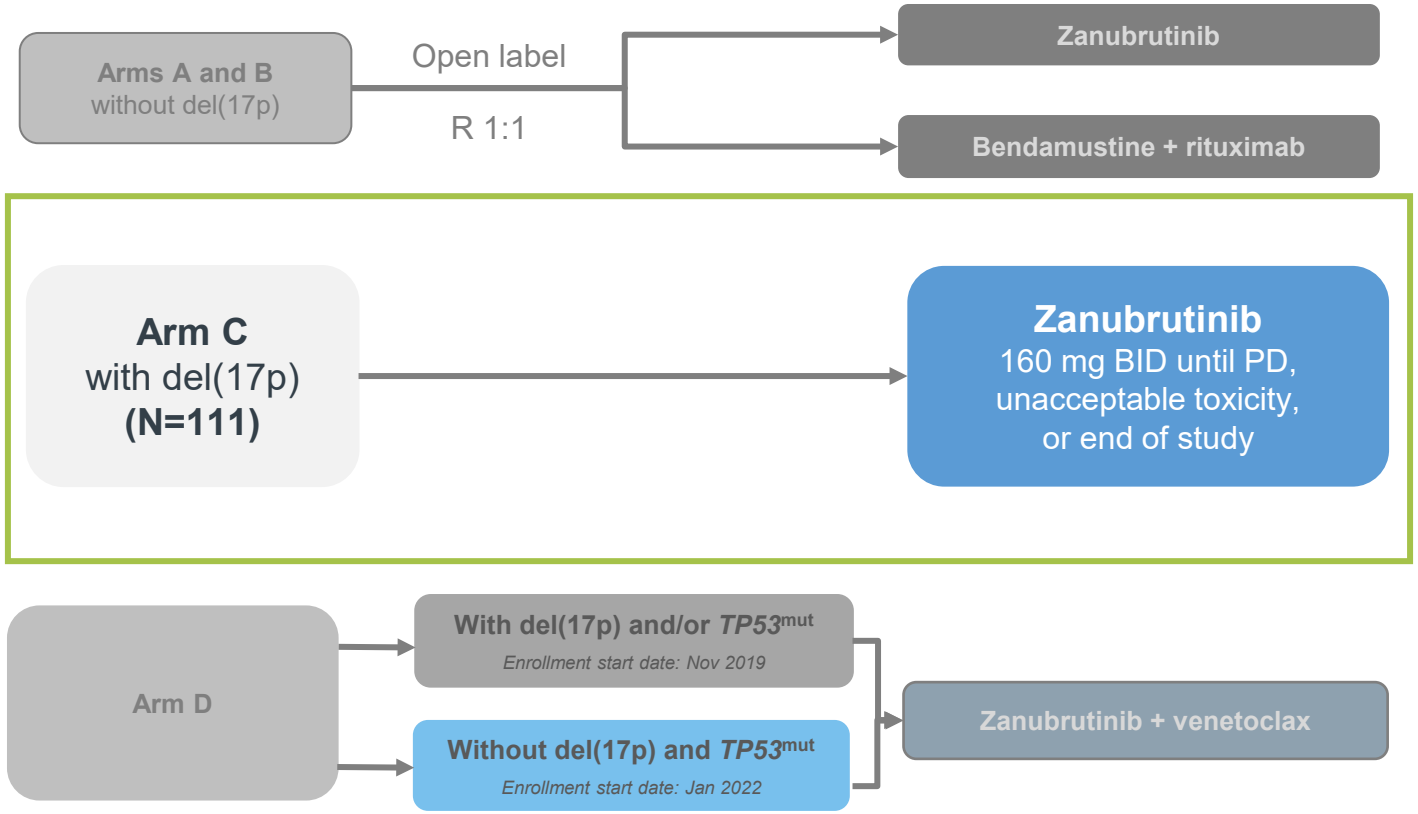
2. Ven-Obi
If cBTKi is contraindicated

*≥5 anomalies.
(c)BTKi, (covalent) BTK inhibitor; CLL, chronic lymphocytic leukemia; CV, cardiovascular; FILO, French Innovative Leukemia Organization; Ibr, ibrutinib; IGHV, immunoglobulin heavy chain variable; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; Obi, obinutuzumab; Ven, venetoclax.
FILO recommendations for CLL. Available at: www.filo-leucemie.org/page/filo-llc-mw/recommandations-llc. Accessed August 2025.

SEQUOIA Arm C: Long-term follow-up data for patients with del(17p) were shared at ASCO[1]

Key eligibility criteria

- Untreated CLL/SLL
- Met iwCLL criteria for treatment
- Measurable disease by CT/MRI
- Unsuitable for FCR



Key endpoints for Arm C

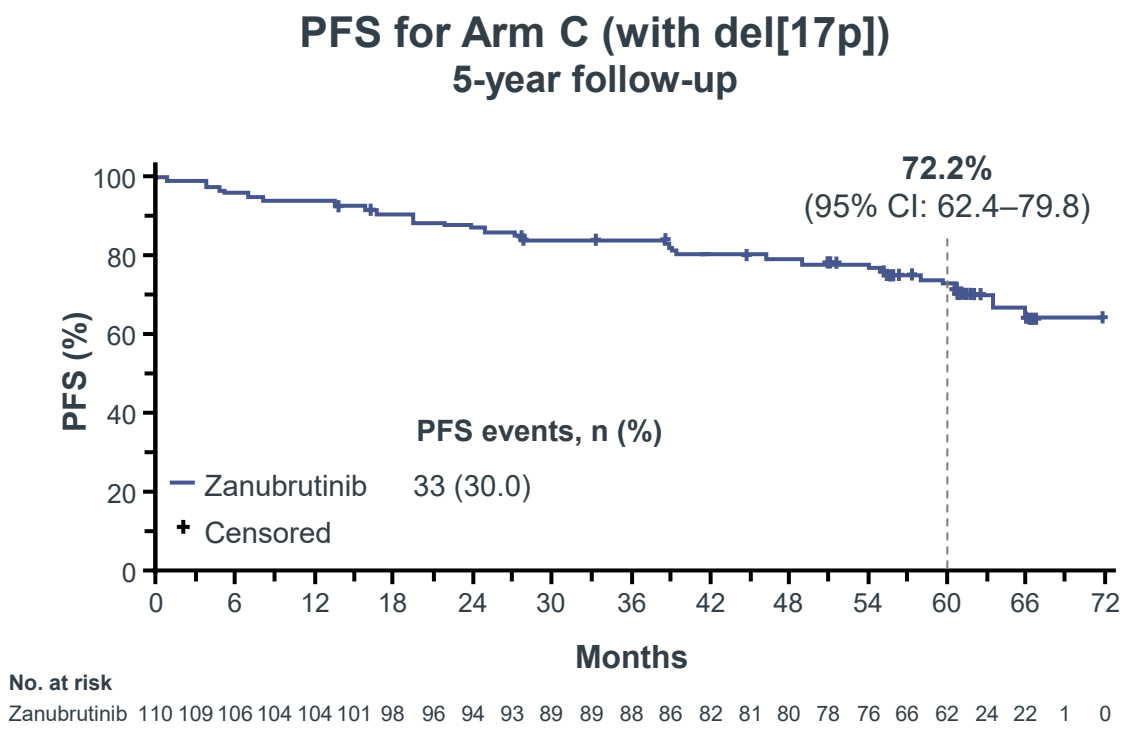
- PFS (INV)
- ORR (INV)*
- OS
- Safety per CTCAE

*Responses were assessed by investigator per the 2008 iwCLL guidelines[2] with modification for treatment-related lymphocytosis[3] for patients with CLL and per Lugano criteria[4] for patients with SLL. ORR was defined as achievement of PR-L or better.

ASCO, American Society of Clinical Oncology; BID, twice daily; CLL, chronic lymphocytic leukemia; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; del, deletion; FCR, fludarabine, cyclophosphamide, and rituximab; INV, investigator-assessed; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; mut, mutation; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR-L, partial response with lymphocytosis; R, randomized; SLL, small lymphocytic lymphoma.

1. Tam CS *et al*. Oral presentation at ASCO 2025; Chicago, IL, USA, May 30 – June 3, 2025. 2. Hallek M *et al*. *Blood* 2008; 111 (12): 5446–5456. 3. Cheson BD *et al*. *J Clin Oncol* 2012; 30 (23): 2820–2822.
4. Cheson BD *et al*. *J Clin Oncol* 2014; 32 (27): 3059–3068.

SEQUOIA Arm C: PFS outcomes in the high-risk cohort were consistent with outcomes of patients in the lower-risk cohort[1]



5-year OS: 85.1% (95% CI: 76.9–90.6)

Estimated 5-year PFS in patients treated with zanubrutinib in the SEQUOIA study

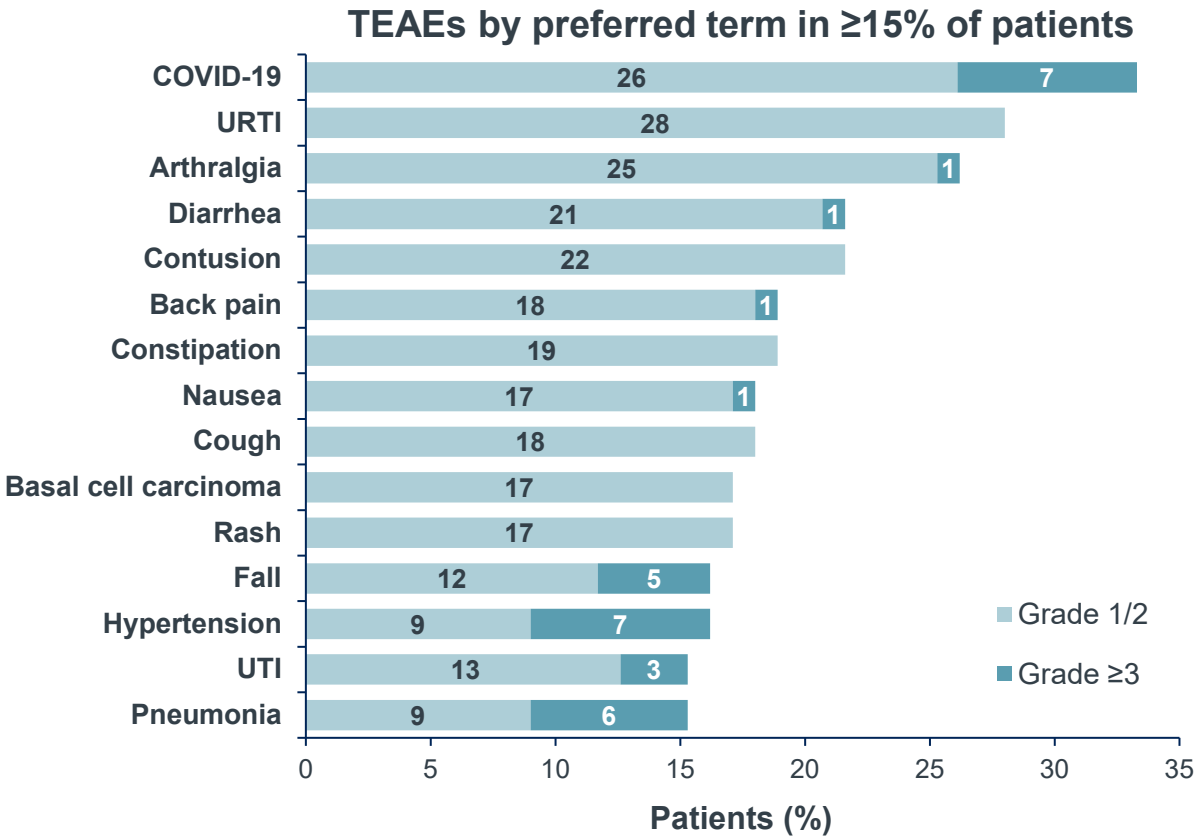
- Del(17p)-negative: 76%[2]
- Del(17p)-positive: 72%

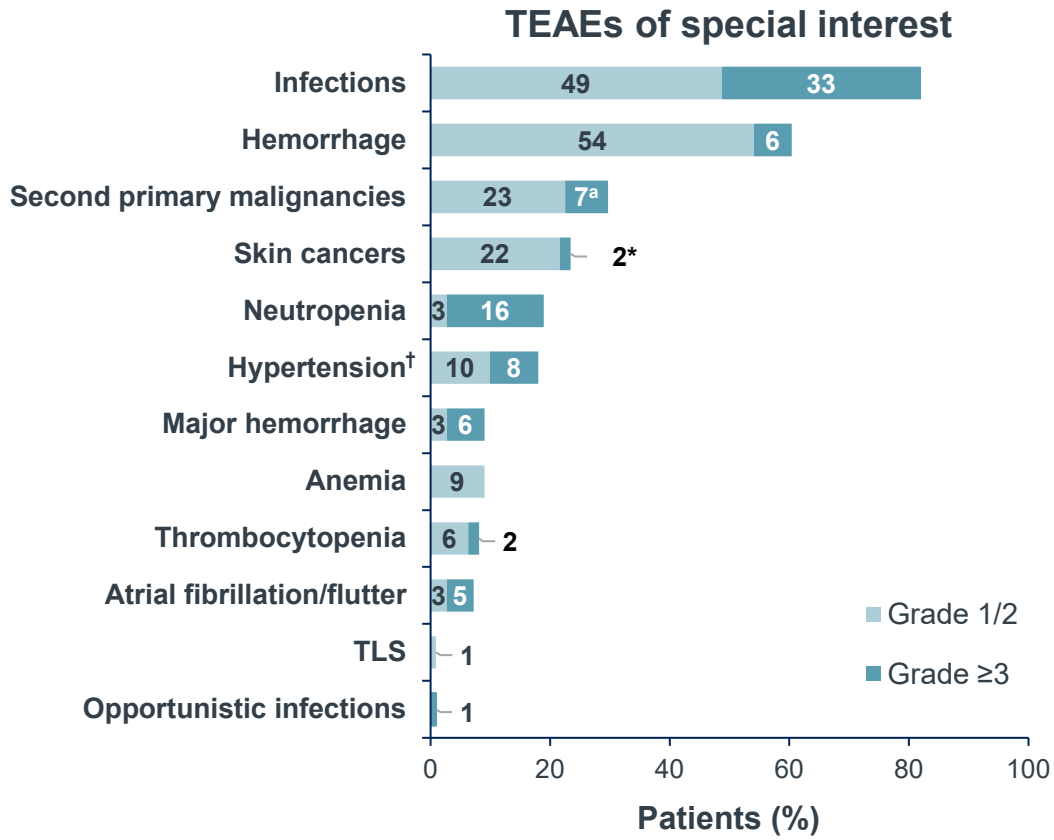
Median PFS was not reached with zanubrutinib

CI, confidence interval; del, deletion; OS, overall survival; PFS, progression-free survival.

1. Tam CS *et al*. Oral presentation at ASCO 2025; Chicago, IL, USA, May 30 – June 3, 2025. 2. Shadman M *et al*. *J Clin Oncol* 2025; 43 (7): 780–787.

SEQUOIA Arm C: No new safety signals were identified with zanubrutinib





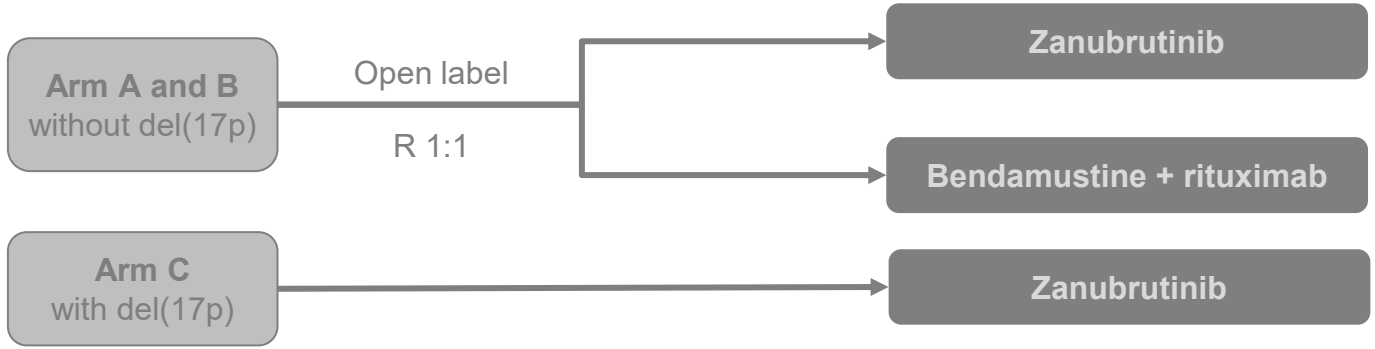
→ AEs led to death in 6 patients (5.4%)

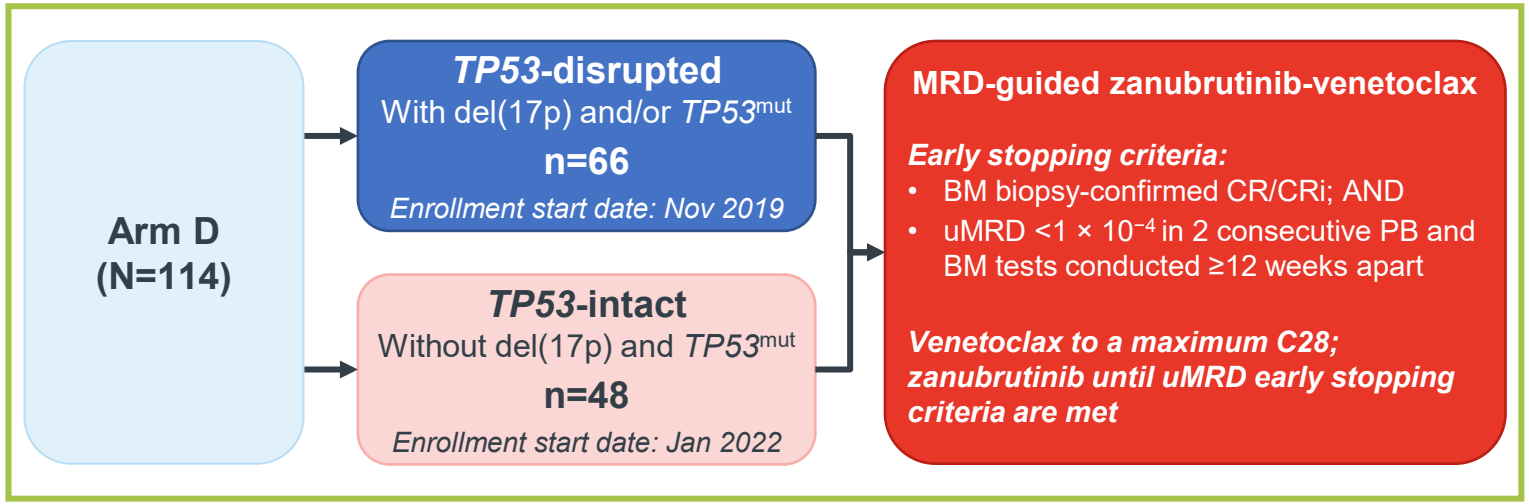
*Includes two patients with malignant melanoma. †Includes hypertension, increased blood pressure, hypertensive crisis, and hypertensive heart disease.
AE, adverse event; COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; URTI, upper respiratory tract infection; UTI, urinary tract infection.
Tam CS *et al*. Oral presentation at ASCO 2025; Chicago, IL, USA, May 30 – June 3, 2025.

SEQUOIA Arm D: Data with MRD-guided zanubrutinib-venetoclax were shared at ASCO[1]

Key eligibility criteria

- Untreated CLL/SLL
- Met iwCLL criteria for treatment
- Measurable disease by CT/MRI
- Unsuitable for FCR





Endpoints for Arm D

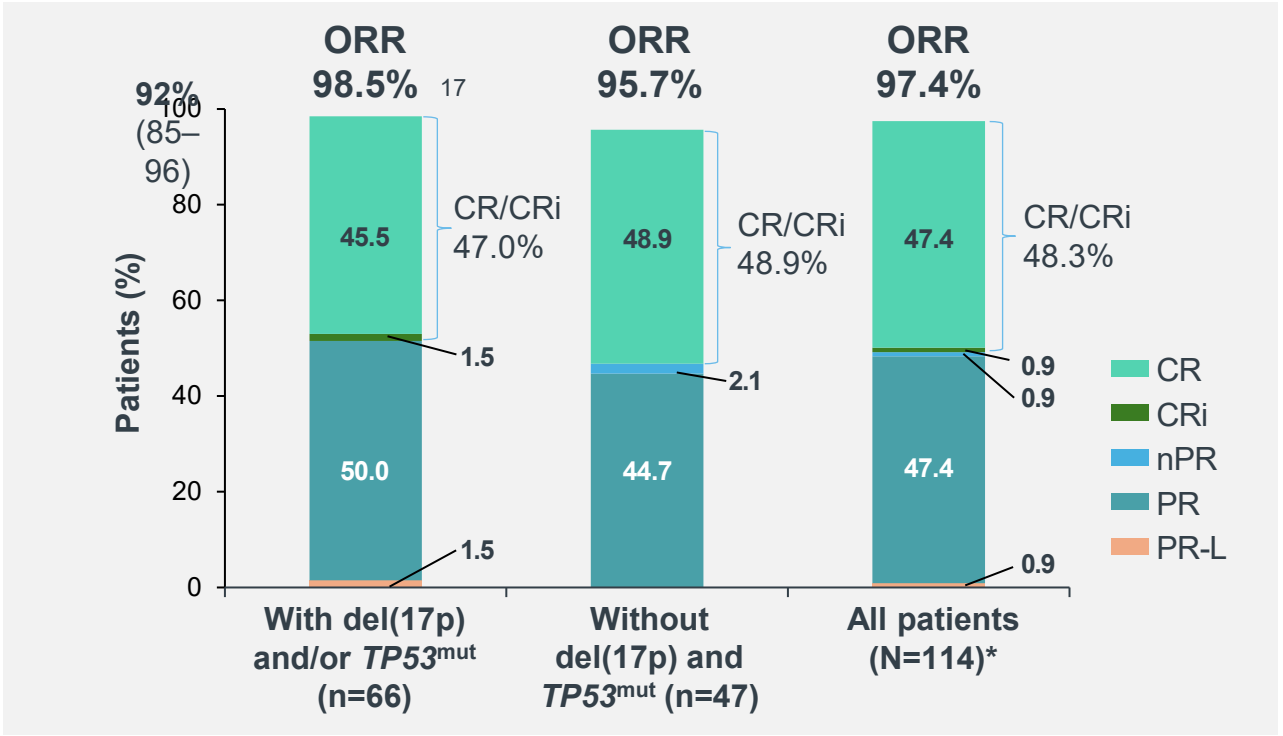
- PFS (INV)*
- ORR (INV)†
- OS*
- uMRD4 rate ($<10^{-4}$ sensitivity)
- Safety per CTCAE

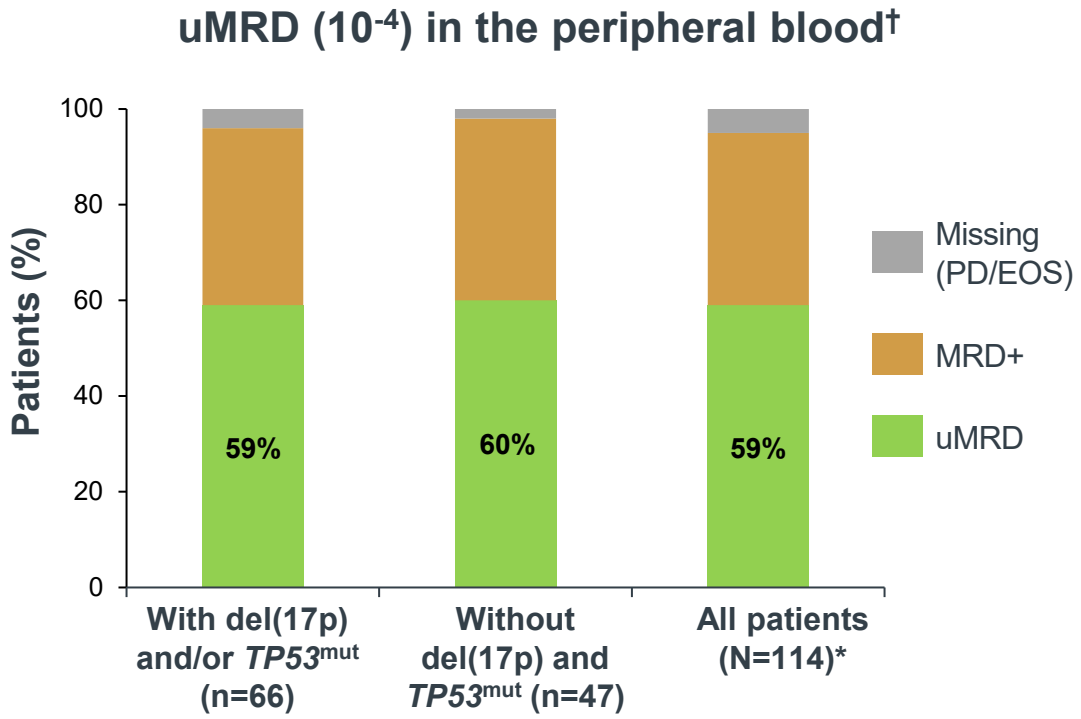
*PFS and OS were assessed in the intention-to-treat population. †Responses were assessed by investigator per the 2008 iwCLL guidelines[2] with modification for treatment-related lymphocytosis[3] for patients with CLL and per Lugano criteria[4] for patients with SLL. ORR was defined as achievement of PR-L or better.

ASCO, American Society of Clinical Oncology; BM, bone marrow; C, Cycle; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete bone marrow recovery; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; del, deletion; FCR, fludarabine, cyclophosphamide, and rituximab; INV, investigator-assessed; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRI, magnetic resonance imaging; mut, mutation; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PR-L, partial response with lymphocytosis; R, randomized; SLL, small lymphocytic lymphoma; (u)MRD, (undetectable) minimal residual disease.

1. Shadman M *et al*. Oral presentation at ASCO 2025; Chicago, IL, USA, May 30 – June 3, 2025. 2. Hallek M *et al*. *Blood* 2008; 111 (12): 5446–5456. 3. Cheson BD *et al*. *J Clin Oncol* 2012; 30 (23): 2820–2822.
4. Cheson BD *et al*. *J Clin Oncol* 2014; 32 (27): 3059–3068.

SEQUOIA Arm D: PFS, response and best PB-uMRD rates were high and consistent across subgroups

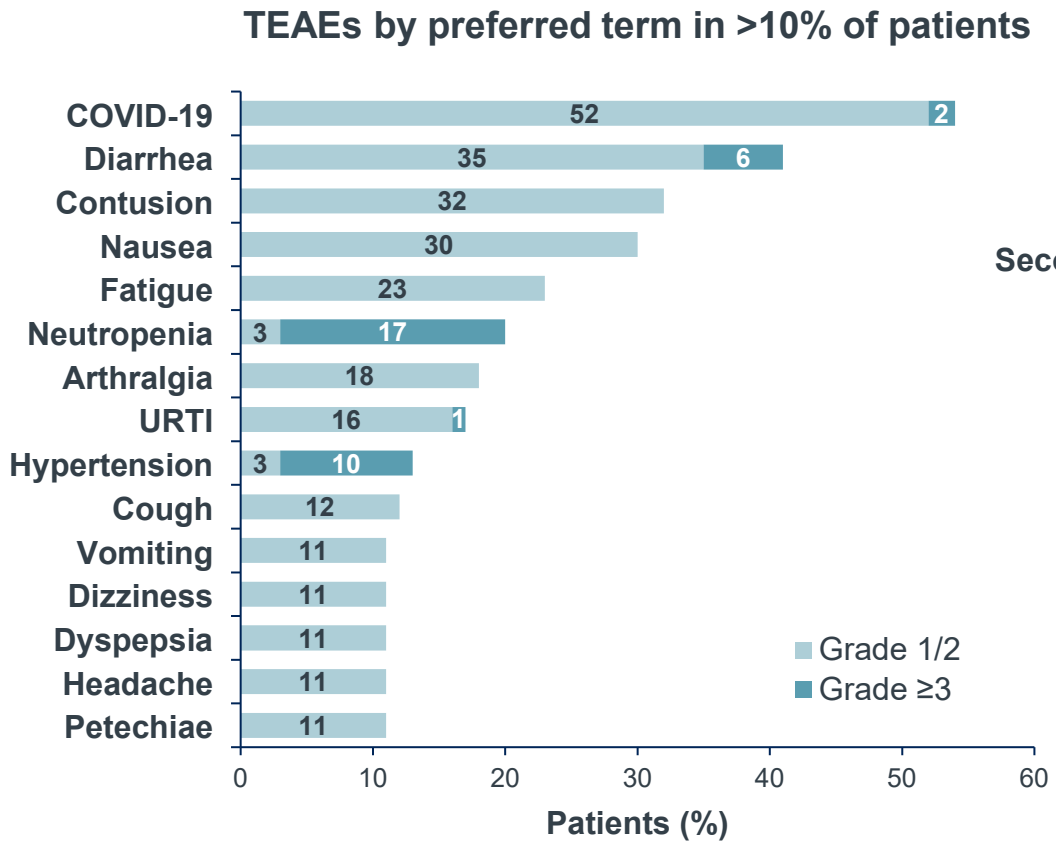


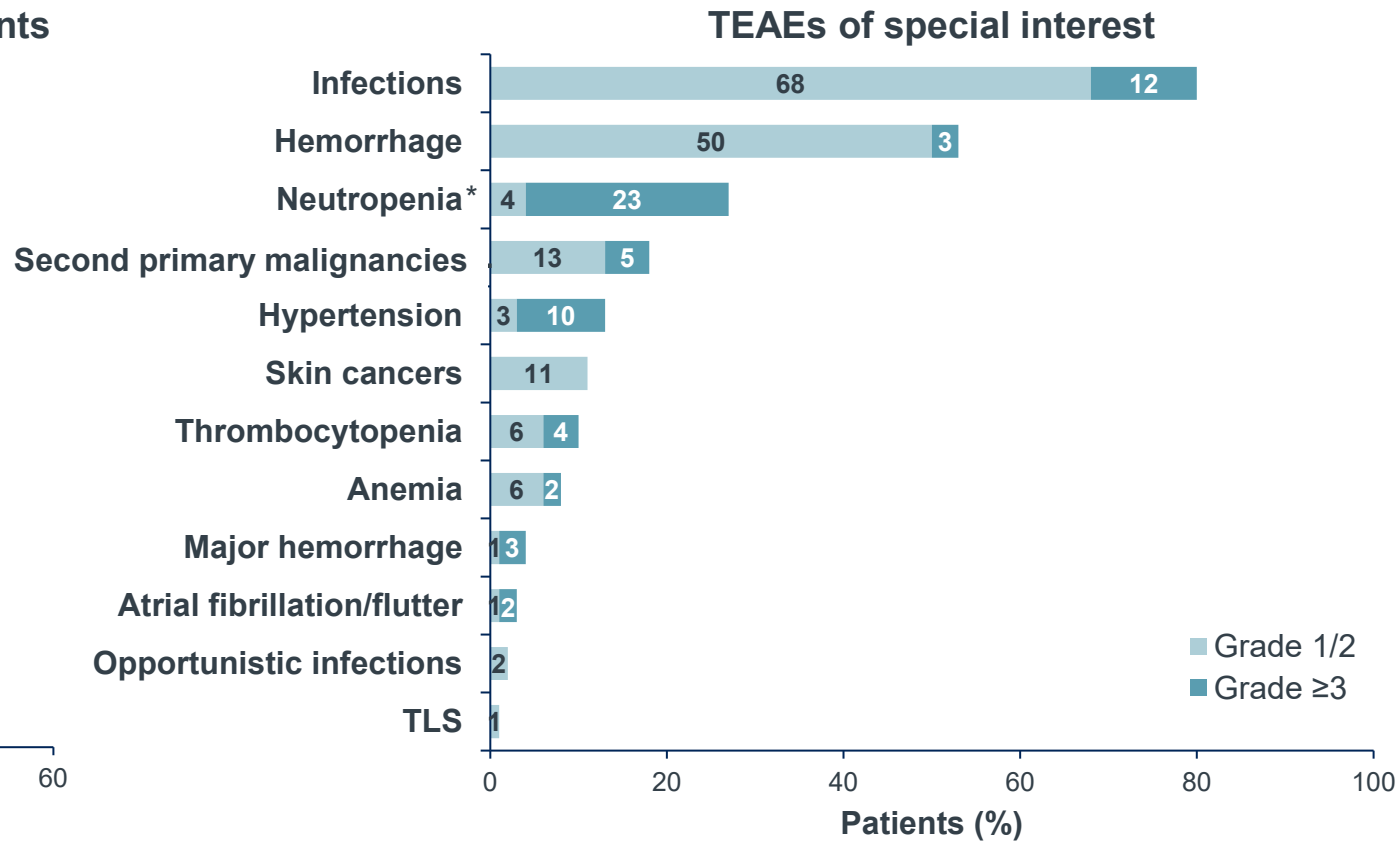


2-year PFS (95% CI)	**94%** (85–98)	**89%** (76–95)	
Median FU, months (range)	**38.7** (0.4–58.0)	**29.6** (0.6–31.9)	**31.2** (0.4–58.0)

*Central laboratory findings on del(17p) and *TP53* mutation status were missing for one patient. †Best uMRD in the peripheral blood defined as achieving uMRD in the peripheral blood at ≥1 timepoint.
CI, confidence interval; CR, complete response; CRi, complete response with incomplete hematopoietic recovery; del, deletion; EOS, end of study; FU, follow-up; (n)PR, (nodular) partial response; ORR, overall response rate; PB, peripheral blood; PD, progressive disease; PFS, progression-free survival; PR-L, partial response with lymphocytosis; (u)MRD, (undetectable) minimal residual disease.
Shadman M *et al*. Oral presentation at ASCO 2025; Chicago, IL, USA, May 30 – June 3, 2025.

SEQUOIA Arm D: MRD-guided zanubrutinib-venetoclax had a favorable safety profile overall





→ AEs led to death in 5 patients (4.4%)†

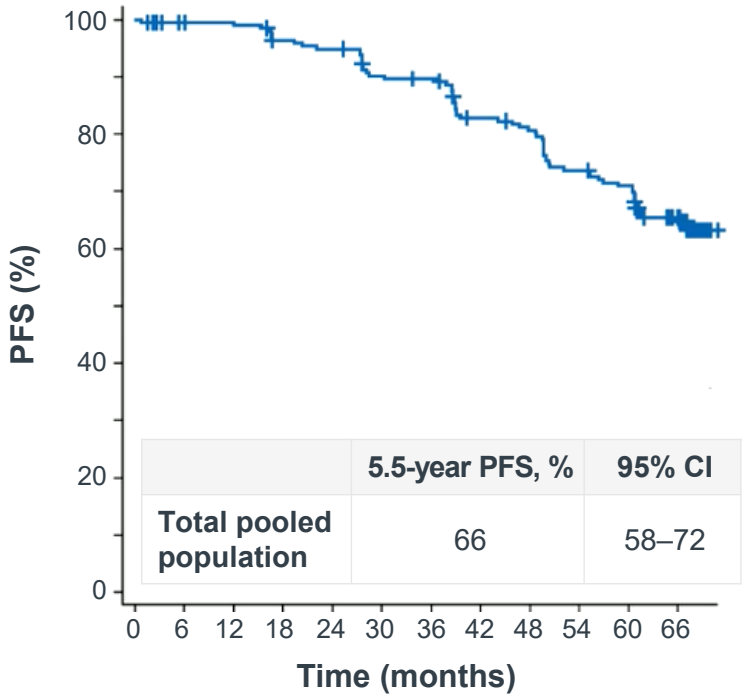
*Included neutropenia, neutrophil count decreased, and agranulocytosis. †One patient experienced a fatal road traffic accident leading to intracranial hemorrhage and intra-abdominal hemorrhage. One patient experienced death due to pneumonia and septic shock. Other TEAEs leading to death included lung carcinoma, gallbladder carcinoma, and intracranial hemorrhage in a patient with concomitant direct oral anticoagulant use and prior zanubrutinib discontinuation.

AE, adverse event; COVID-19, coronavirus disease 2019; MRD, minimal residual disease; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; URTI, upper respiratory tract infection.

Shadman M *et al*. Oral presentation at ASCO 2025; Chicago, IL, USA, May 30 – June 3, 2025.

CAPTIVATE study: Fixed-duration Ibr-Ven produces durable responses in fit patients with CLL with some differences between subgroups

Overall PFS (N=202)



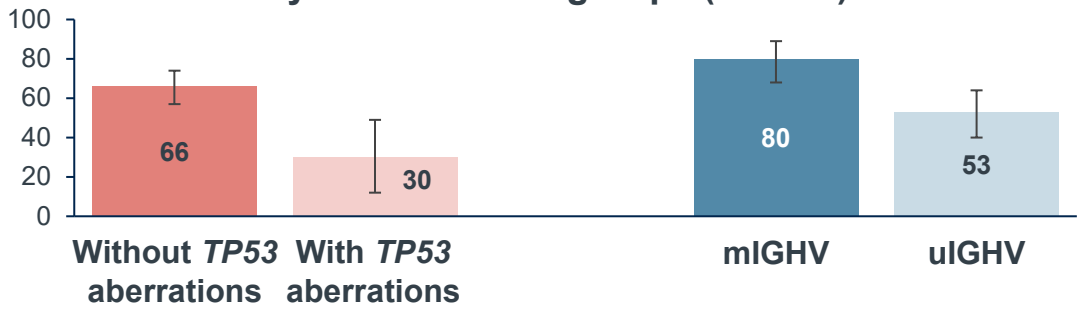
	5.5-year PFS, %	95% CI
Total pooled population	66	58–72

Patients at risk

Total	202	196	195	187	184	173	171	155	150	137	131	112

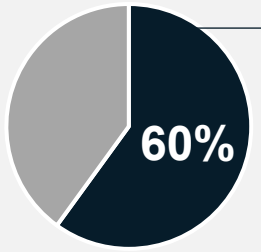
Overall 5.5-year OS: 97% (95% CI: 93–99)

5.5-year PFS in subgroups (95% CI)



Patients with high-risk features had reduced PFS

uMRD in BM and PB at EOT



uMRD status at EOT was strongly associated with long-term PFS regardless of high-risk genomic features

0 resistance mutations were detected in *BTK* or *PLCG2* in samples from 53 patients with PD after Ibr-Ven

Ibrutinib-based retreatment	PFS, %	OS, %	Median follow-up, months
Ibrutinib alone (n=25)	91	96	28.4
Ibr-Ven (n=11)	100	100	15.2

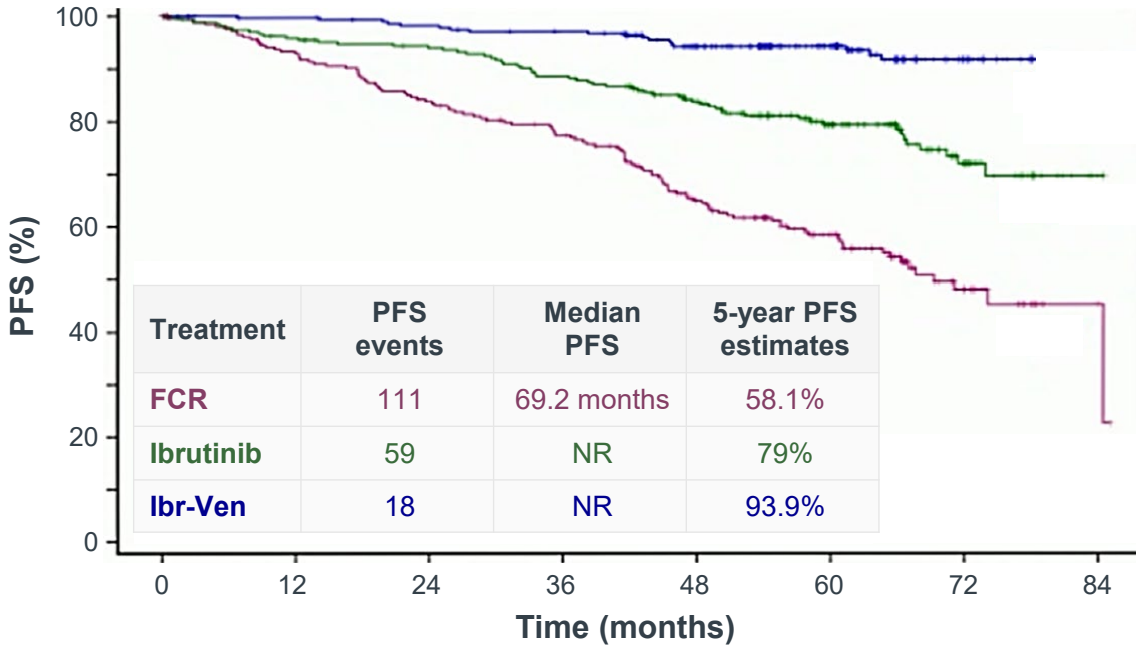
BM, bone marrow; CI, confidence interval; CLL, chronic lymphocytic leukemia; EOT, end of treatment; Ibr-Ven, ibrutinib-venetoclax; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable; OS, overall survival; PB, peripheral blood; PD, progressive disease; PFS, progression-free survival; uMRD, undetectable minimal residual disease.

Wierda WG *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.

FLAIR: MRD-guided Ibr-Ven is superior to ibrutinib monotherapy and FCR, and it has a manageable safety profile in patients ≤75 years of age

PFS

Median follow-up: 62.2 months



Treatment	PFS events	Median PFS	5-year PFS estimates
FCR	111	69.2 months	58.1%
Ibrutinib	59	NR	79%
Ibr-Ven	18	NR	93.9%

5-year OS

	FCR	Ibrutinib	Ibr-Ven
Overall	86.5	90.5	95.9
mIGHV	85.9	89.5	92.2
uIGHV	88.9	93.2	97.4

Ibrutinib and Ibr-Ven could be administered for a maximum of 6 years

Median duration of Ibr-Ven	
uIGHV: 25 months	mIGHV: 48 months

uMRD up to 2 years

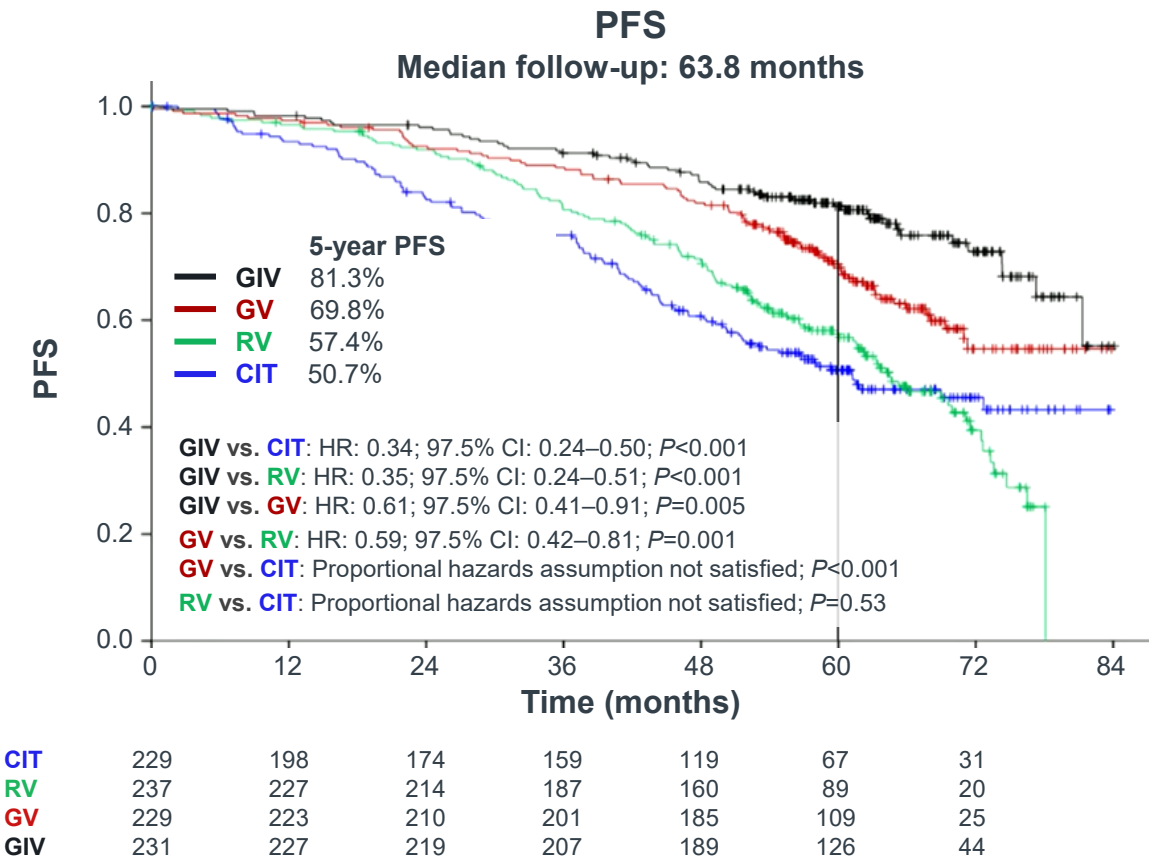
n (%) [exact 95% CI]	FCR (n=263)	Ibrutinib (n=263)	Ibr-Ven (n=260)
uMRD in bone marrow	127 (48.3) [42.1–54.5]	0 [0–1.39]	172 (66.2) [60.1–71.9]
uMRD in blood	160 (60.8) [54.7–66.7]	0 [0–1.39]	190 (73.1) [67.3–78.4]

SAEs

Category, n (%)	FCR (n=239)	Ibrutinib (n=260)	Ibr-Ven (n=257)
Infections and infestations	65 (29.1)	87 (39.0)	79 (37.4)
Blood and lymphatic system disorders	96 (43.0)	12 (5.4)	17 (8.1)
Cardiac disorders	1 (0.4)	32 (14.3)	29 (13.7)
Gastrointestinal disorders	19 (8.5)	7 (3.1)	10 (4.7)
Nervous system disorders	2 (0.9)	14 (6.3)	5 (2.4)
Respiratory, thoracic, and mediastinal disorders	8 (3.6)	7 (3.1)	4 (1.9)
Eye disorders	0	5 (2.2)	7 (3.3)

CI, confidence interval; FCR, fludarabine, cyclophosphamide, and rituximab; Ibr-Ven, ibrutinib-venetoclax; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable; NR, not reached; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event; (u)MRD, (undetectable) minimal residual disease. Munir T *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.

GAIA/CLL13 final analysis: Superior PFS with GIV vs. GV or RV, but no OS benefit and increased toxicity



→ There were no OS differences between groups

Independent prognostic factors*

	HR	95% CI	*P*
GV			
ECOG PS (≥1 vs. 0)	1.72	1.08–2.72	0.02
IGHV (unmutated vs. mutated)	2.68	1.60–4.49	<0.001
RV			
B symptoms (yes vs. no)	1.47	1.01–2.12	0.04
Complex karyotype (≥3 vs. <3)	1.64	1.05–2.55	0.03
IGHV (unmutated vs. mutated)	2.17	1.45–3.26	<0.001
CIT			
Age (>65 vs. ≤65 years)	2.16	1.43–3.26	<0.001
Bulky disease (yes vs. no)	1.55	1.01–2.37	0.046
Complex karyotype (≥3 vs. <3)	1.69	1.09–2.61	0.02
IGHV (unmutated vs. mutated)	3.55	2.20–5.75	<0.001

Grade ≥3 infections (events per 1,000 patients)
CIT (33) > GIV (20) > GV (14) > RV (10)

Cardiac AEs (events per 1,000 patients)
GIV (15) > CIT (12) > GV (7) ≈ RV (7)

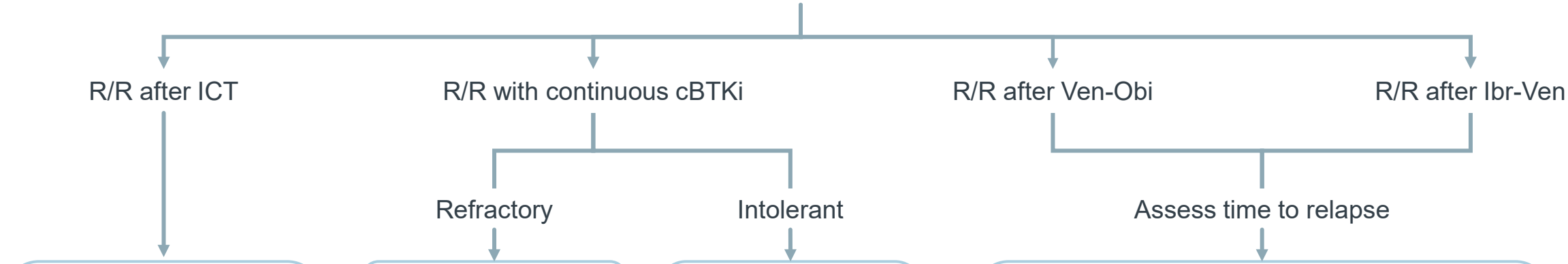
*No independent prognostic factors were identified with GIV.
AE, adverse event; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GIV, obinutuzumab-ibrutinib-venetoclax; GV, obinutuzumab-venetoclax; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable; OS, overall survival; PFS, progression-free survival; RV, rituximab-venetoclax.
Fürstenau M *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.

Relapsed or refractory disease

FILO guidelines: Treatment history is critical to selection in the relapsed setting

April 2025

First symptomatic relapse
(in the absence of eligibility for a clinical trial)



- **Ven-R**

Preferred for mutated IGHV disease in the absence of *TP53* alterations

- **Continuous cBTKi**
  1. Acala, Zanu
  2. Ibr

Preferred for patients with *TP53* alterations

Ven-R

1. Ven-R

2. Switch cBTKi

In the absence of resistance mutations

Relapse ≤36 months

- **Continuous cBTKi**
  1. Acala, Zanu
  2. Ibr

In the absence of resistance mutations

Relapse >36 months

1. **Continuous cBTKi**
   1. Acala, Zanu
   2. Ibr
2. **Ven-R**

In the absence of resistance mutations

Acala, acalabrutinib; cBTKi, covalent BTK inhibitor; FILO, French Innovative Leukemia Organization; Ibr, ibrutinib; ICT, immunochemotherapy; IGHV, immunoglobulin heavy chain variable; Obi, obinutuzumab; R, rituximab; R/R, relapsed/refractory; Ven, venetoclax; Zanu, zanubrutinib.

FILO recommendations for CLL. Available at: www.filo-leucemie.org/page/filo-llc-mw/recommandations-llc. Accessed August 2025.

FILO guidelines: Treatment options narrow in second and subsequent lines of therapy

April 2025

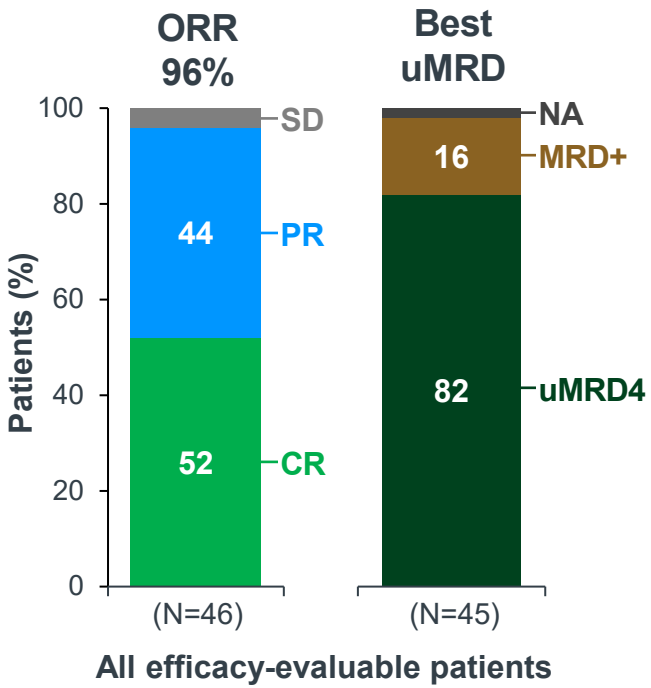
Subsequent relapses
(in the absence of eligibility for a clinical trial)

Patient not double-exposed (2^{nd} relapse after ICT)	Patient double-exposed **but not** refractory to BTKi or venetoclax	Double refractory to BTKi and venetoclax **or** refractory with a resistance mutation
Prioritize the therapeutic class to which the patient has not been exposed	If no resistance mutation: • Resume BTKi • Resume venetoclax ± anti-CD20	• Clinical trial • Pirtobrutinib (when available) • Idelalisib + rituximab • Allogeneic stem cell transplant

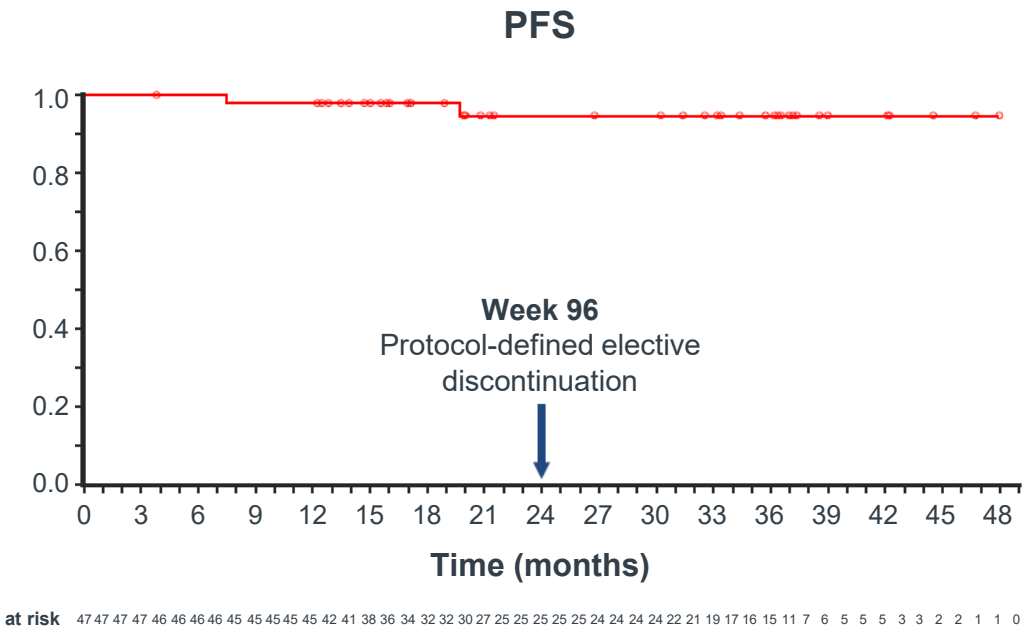
BTKi, BTK inhibitor; CD, cluster of differentiation; FILO, French Innovative Leukemia Organization; ICT, immunochemotherapy.
FILO recommendations for CLL. Available at: www.filo-leucemie.org/page/filo-llc-mw/recommandations-llc. Accessed August 2025.

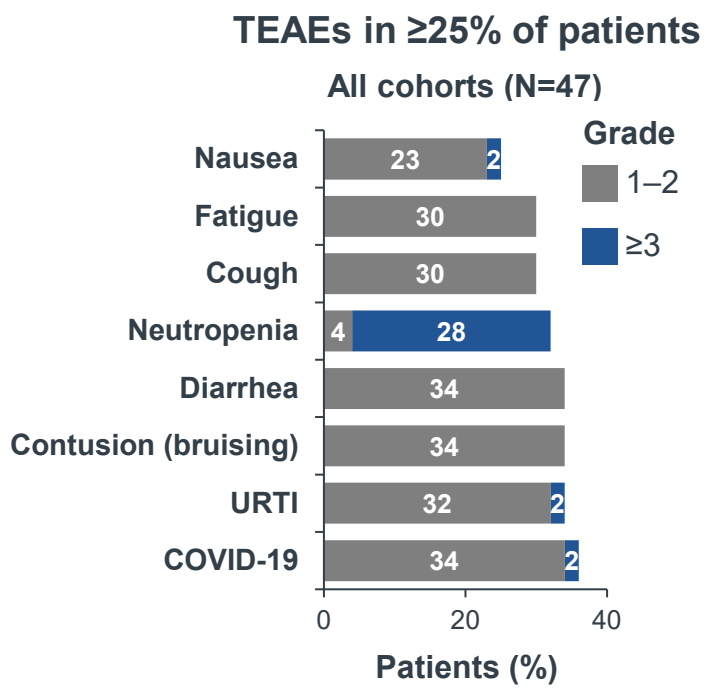
Phase 1/1b study: Sonrotoclax-zanubrutinib demonstrates deep responses with a manageable safety profile in R/R CLL

Median age: 65 years	Del(17p) and/or *TP53*^{mut}: 38% (16/42)	uIGHV: 73% (30/41)	Median prior lines of therapy: 1	Prior BTKi: 15% (7/47)



Median study follow-up of 32.2 months





BTKi, BTK inhibitor; CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; CR, complete response; del, deletion; mut, mutation; ORR, overall response rate; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TEAE, treatment-emergent adverse event; uIGHV, unmutated immunoglobulin heavy chain variable; (u)MRD, (undetectable) minimal residual disease; URTI, upper respiratory tract infection.

Cheah CY *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.

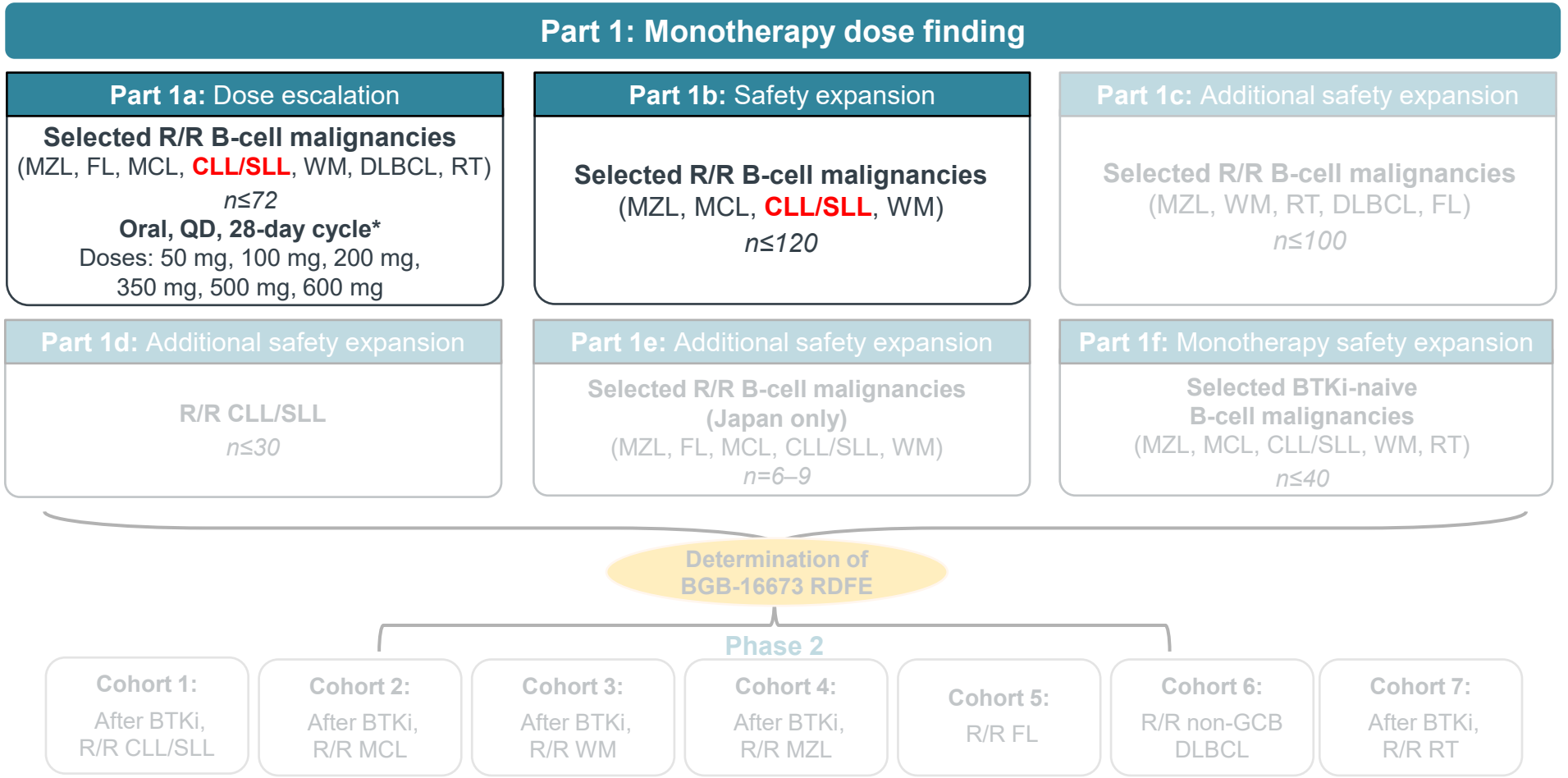
BGB-16673, a chimeric degradation activation compound (CDAC), is being trialled in CLL within the CaDAnCe-101 trial

Key eligibility criteria for CLL/SLL

- Meets iwCLL 2018 criteria for treatment
- ≥2 prior therapies, including cBTKi if approved for disease
- ECOG PS 0–2
- Adequate end-organ function

Key objectives: Part 1

- **Primary:** Safety† and tolerability; MTD; and RDFE
- **Secondary:** PK, PD, and preliminary antitumor activity‡



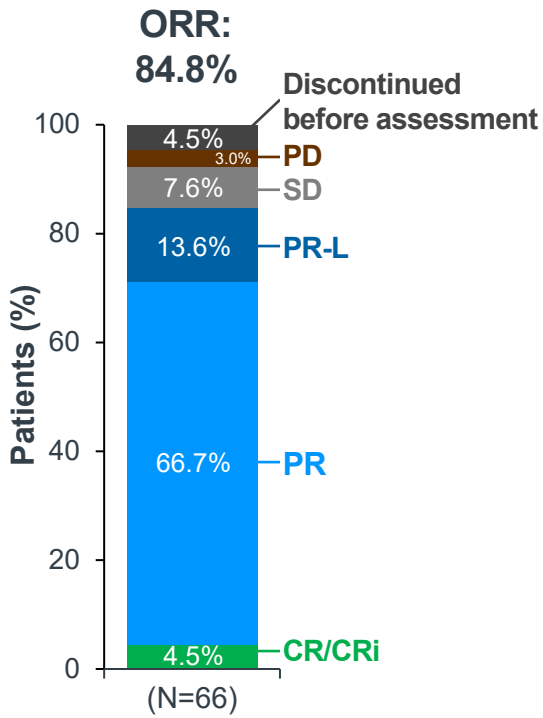
Data from gray portions of the figure are not included in this presentation.
*Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. †Safety was assessed according to CTCAE v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL. ‡Response was assessed per iwCLL 2018 criteria after 12 weeks in patients with CLL. (c)BTKi, (covalent) BTK inhibitor; CLL, chronic lymphocytic leukemia; CTCAE, Common Terminology Criteria for Adverse Events; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; GCB, germinal center B-cell; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; QD, daily; RDFE, recommended dose for expansion; R/R, relapsed/refractory; RT, Richter transformation; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.
Scarfò L *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.

CaDAnCe-101: BGB-16673 was well tolerated and displayed significant antitumor activity in a high-risk, heavily pretreated population

Median age: 70 years	Del(17p) and/or *TP53*^{mut}: 65% (43/66)	uIGHV*: 78% (38/49)	Complex karyotype (≥3)*: 50% (22/44)	Median prior lines of therapy: 4 (2–10)	Prior cBTKi: 94% (62/66)

All patients

Median exposure: 12.9 months (range: 0.2–29.6)



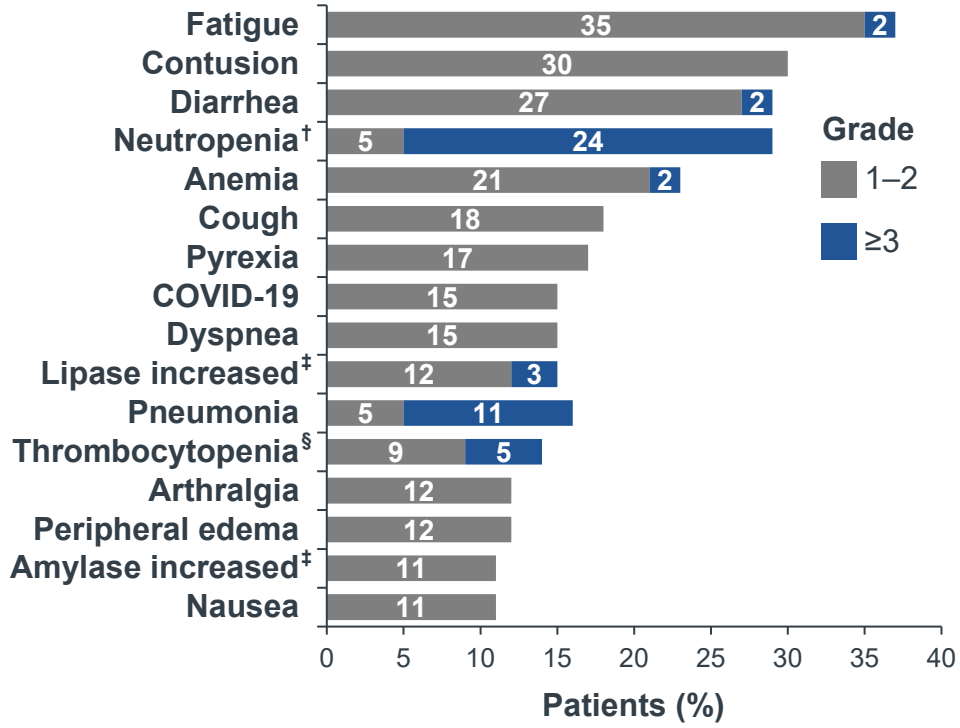
ORR in subgroups

- Prior cBTKi + BCL2i: 90.5% (38/42)
- Prior cBTKi + BCL2i + ncBTKi: 75.0% (9/12)

Responses occurred regardless of baseline mutations

1-year PFS: 77.4% (95% CI: 63.1–86.8)

All-grade TEAEs in ≥10% of all patients



Treatment-related AEs leading to death: 0

Treatment-related AEs leading to treatment discontinuation: 3% (2/66)

*Includes patients with known status only. †Neutropenia combines preferred terms neutrophil count decreased and neutropenia. ‡All events were laboratory findings and were transient, mostly occurring during the first 1–3 cycles of treatment, with no clinical pancreatitis. §Thrombocytopenia combines preferred terms platelet count decreased and thrombocytopenia.

AE, adverse event; BCL2i, B-cell lymphoma 2 inhibitor; CI, confidence interval; c/ncBTKi, covalent/non-covalent BTK inhibitor; COVID-19, coronavirus disease 2019; CR, complete response; CRi, complete response with incomplete marrow recovery; del, deletion; mut, mutation; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; TEAE, treatment-emergent adverse event; uIGHV, unmutated immunoglobulin heavy chain variable. Scarfò L *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.

Summary

TN setting

- **SEQUOIA[1–3]**
  - Arm C: Zanubrutinib monotherapy achieved efficacy outcomes in patients with del(17p) comparable to outcomes in patients without this high-risk feature, supporting its use in treating patients with *TP53* aberrations
  - Arm D: Robust efficacy was demonstrated with MRD-guided zanubrutinib-venetoclax across patient subgroups
- **Durable long-term outcomes reported with 15-cycle Ibr-Ven**, but with reduced efficacy in high-risk patients[4]
- MRD-guided **Ibr-Ven found to be superior to ibrutinib monotherapy** in terms of MRD and survival[5]
- **Obi-Ibr-Ven did not improve OS** vs other arms in GAIA/CLL13 **and was associated with significant toxicity[6]**

R/R setting

- Promising results with **sonrotoclax-zanubrutinib**[7]
- **BTK degraders are an exciting novel therapeutic class**[8,9]
  - BGB-16673 yielded prolonged PFS in heavily pretreated patients and has the potential to significantly improve outcomes for patients exposed to BTKis and BCL2is

BCL2i, B-cell lymphoma 2 inhibitor; BTKi, BTK inhibitor; del, deletion; Ibr-Ven, ibrutinib-venetoclax; MRD, minimal residual disease; Obi-Ibr-Ven, obinutuzumab-ibrutinib-venetoclax; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment-naive. 1. Tam CS *et al*. Oral presentation at ASCO 2025; Chicago, IL, USA, May 30 – June 3, 2025. 2. Shadman M *et al*. *J Clin Oncol* 2025; 43 (7): 780–787. 3. Shadman M *et al*. Oral presentation at ASCO 2025; Chicago, IL, USA, May 30 – June 3, 2025. 4. Wierda WG *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025. 5. Munir T *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025. 6. Fürstenau M *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025. 7. Cheah CY *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025. 8. Scarfò L *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025. 9. Speaker's opinion.

Thank you for your attention

Expert digest: Waldenström's macroglobulinemia

Anna Maria Frustaci
ASST Niguarda Great Metropolitan Hospital, Italy

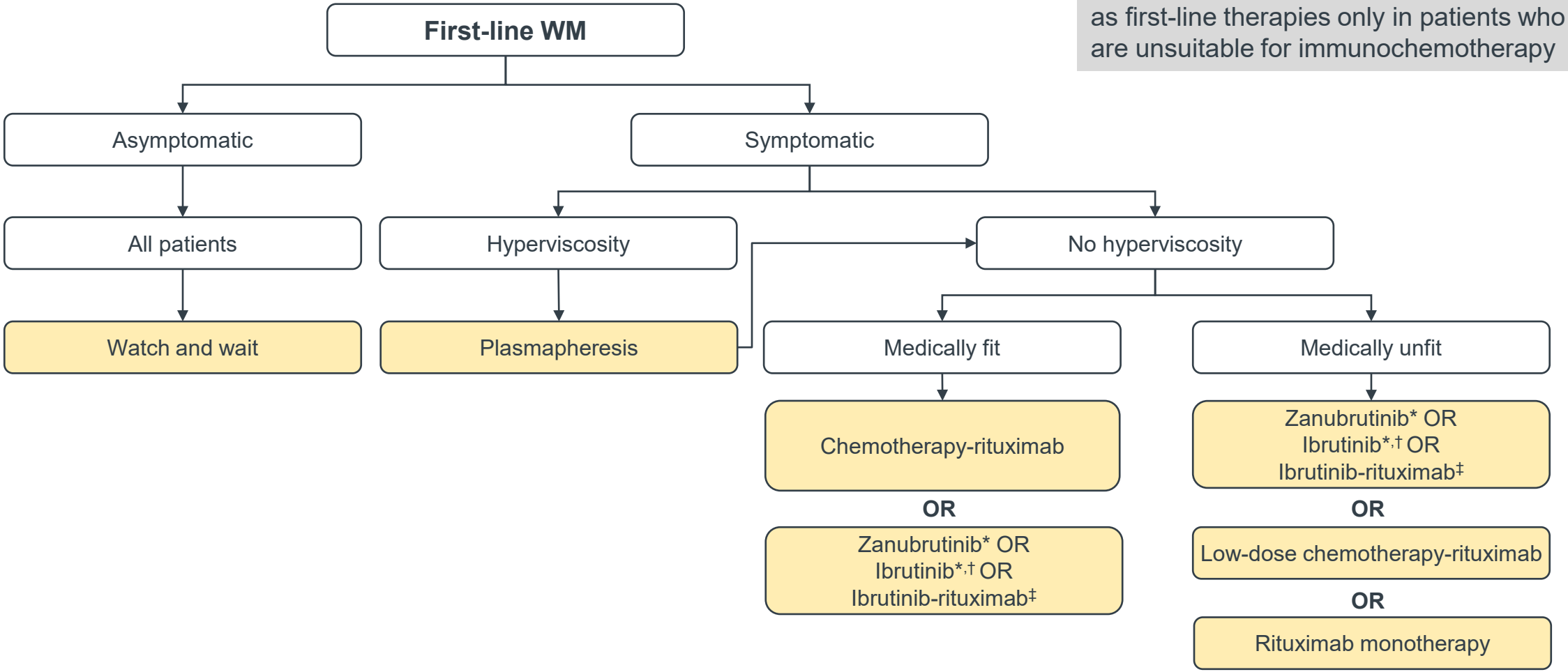
Disclosures

- **Honoraria, consulting, or advisory role:** AbbVie, AstraZeneca, BeOne Medicines Ltd, Janssen
- **Travel, accommodation, and expenses:** AbbVie, AstraZeneca, BeOne Medicines Ltd

The current treatment landscape for WM

Onkopedia first-line WM[1]

*Zanubrutinib and ibrutinib are approved as first-line therapies only in patients who are unsuitable for immunochemotherapy



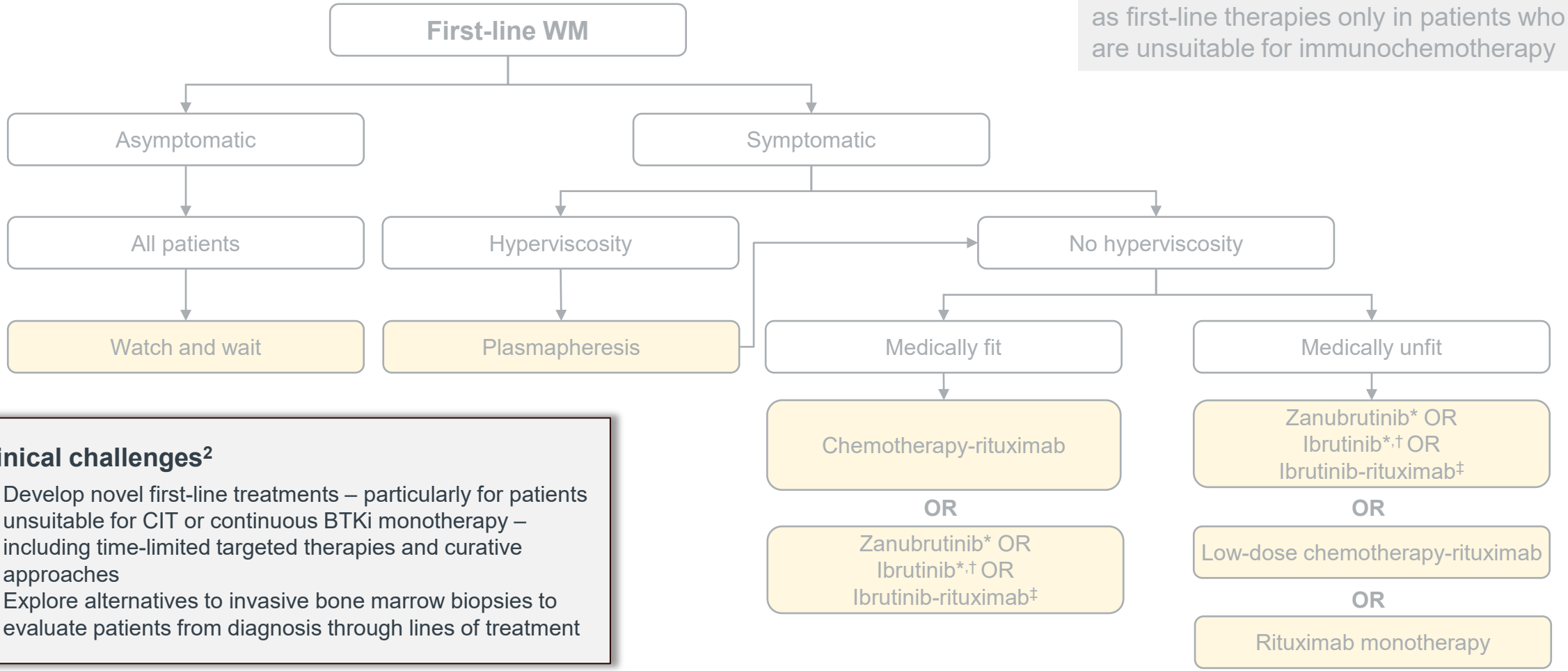
†Especially in *MYD88* mutated patients. ‡Especially in *CXCR4* mutated or *MYD88* wild-type patients.

BTKi, BTK inhibitor; CIT, chemoimmunotherapy; WM, Waldenström's macroglobulinemia. 1. Buske C *et al*. Waldenström's disease (lymphoplasmocytic lymphoma). Available at: https://www.onkopedia.com/de/onkopedia/guidelines/morbus-waldenstroem-lymphoplasmozytisches-lymphom/@@guideline/html/index.html. Accessed August 2025. 2. Speaker's opinion.

The current treatment landscape for WM

Onkopedia first-line WM[1]

*Zanubrutinib and ibrutinib are approved as first-line therapies only in patients who are unsuitable for immunochemotherapy



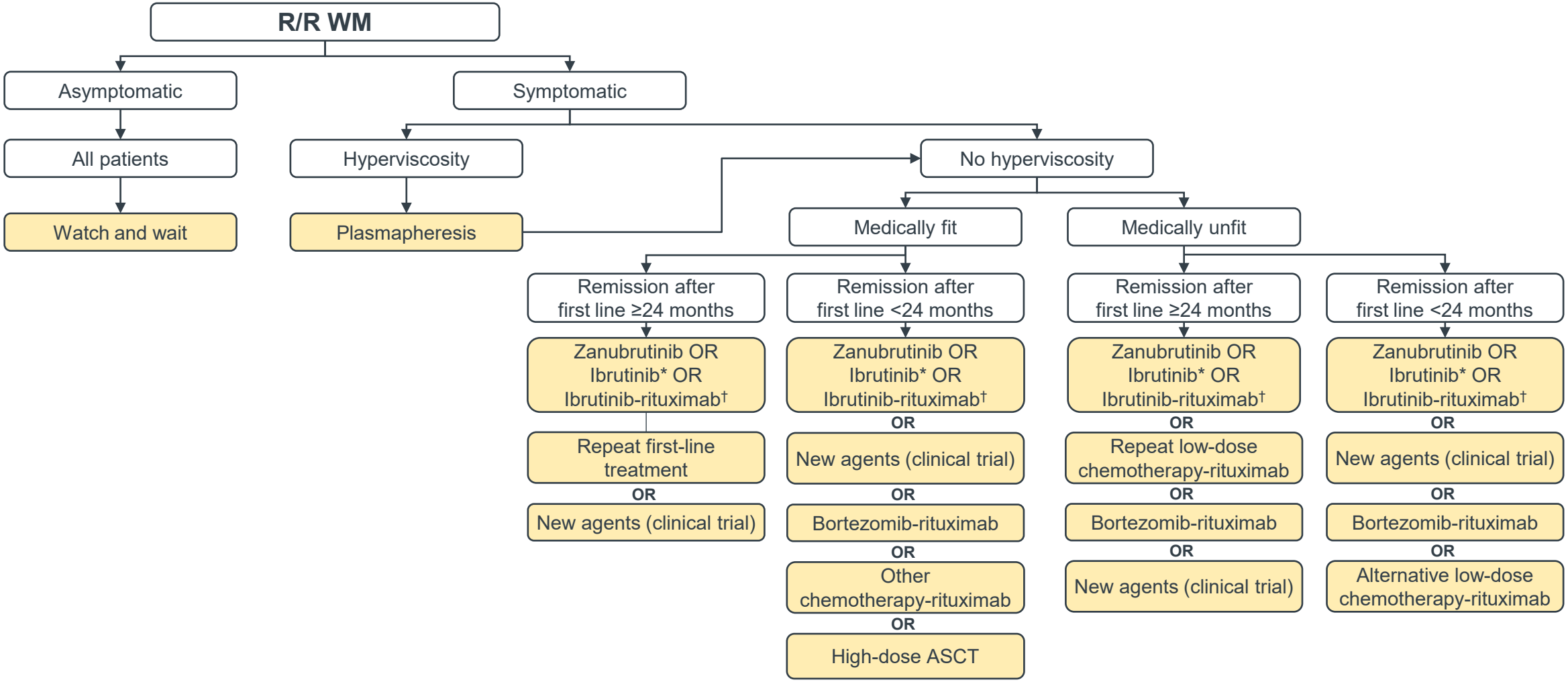
Clinical challenges[2]

- Develop novel first-line treatments – particularly for patients unsuitable for CIT or continuous BTKi monotherapy – including time-limited targeted therapies and curative approaches
- Explore alternatives to invasive bone marrow biopsies to evaluate patients from diagnosis through lines of treatment

†Especially in *MYD88* mutated patients. ‡Especially in *CXCR4* mutated or *MYD88* wild-type patients.
BTKi, BTK inhibitor; CIT, chemoimmunotherapy; WM, Waldenström's macroglobulinemia. 1. Buske C *et al*. Waldenström's disease (lymphoplasmocytic lymphoma). Available at: https://www.onkopedia.com/de/onkopedia/guidelines/morbus-waldenstroem-lymphoplasmozytisches-lymphom/@@guideline/html/index.html. Accessed August 2025. 2. Speaker's opinion.

The current treatment landscape for WM

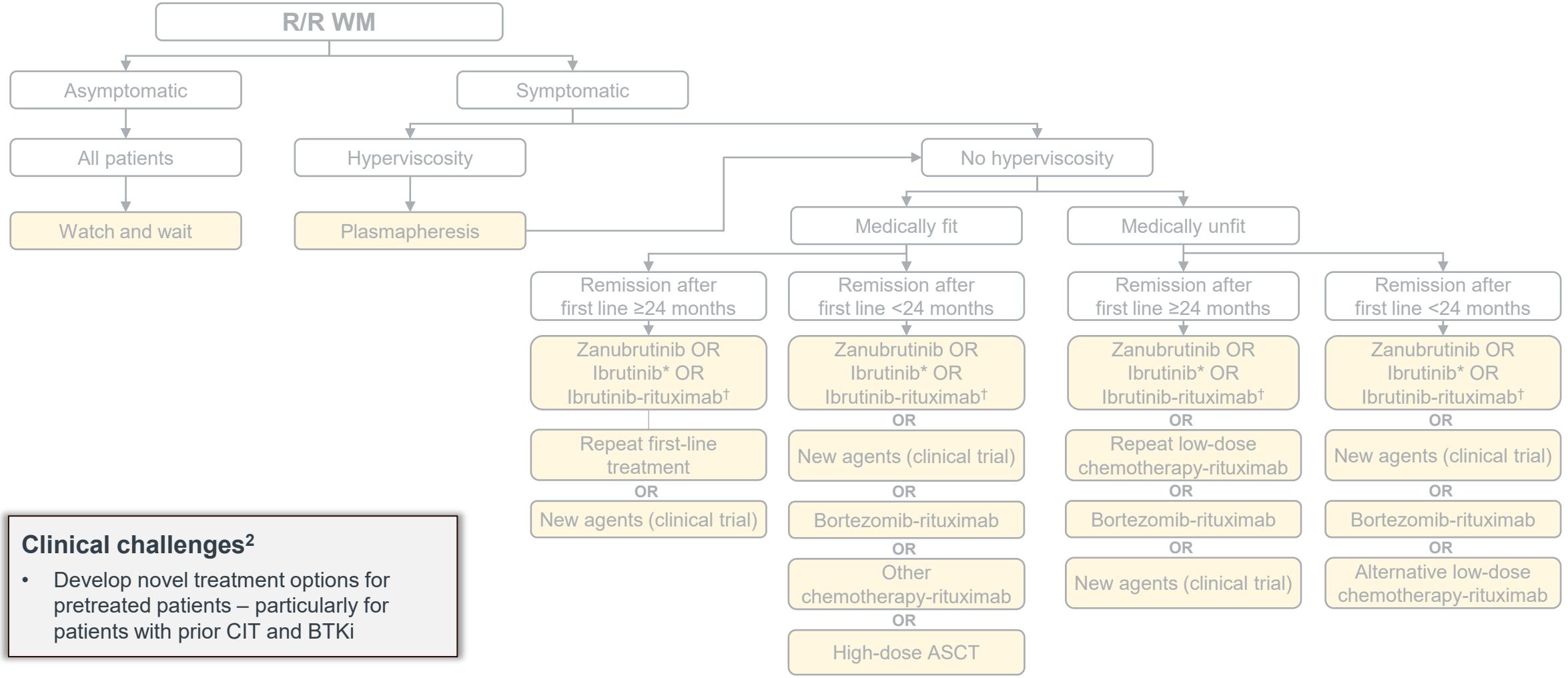
Onkopedia R/R WM[1]



*Especially in *MYD88* mutated patients. †Especially in *CXCR4* mutated or *MYD88* wild-type patients. ASCT, autologous stem cell transplant; BTKi, BTK inhibitor; CIT, chemoimmunotherapy; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia. 1. Buske C *et al*. Waldenström's disease (lymphoplasmocytic lymphoma). Available at: https://www.onkopedia.com/de/onkopedia/guidelines/morbus-waldenstroem-lymphoplasmozytisches-lymphom/@@guideline/html/index.html. Accessed August 2025. 2. Speaker's opinion.

The current treatment landscape for WM

Onkopedia R/R WM[1]



Clinical challenges[2]

- Develop novel treatment options for pretreated patients – particularly for patients with prior CIT and BTKi

*Especially in *MYD88* mutated patients. †Especially in *CXCR4* mutated or *MYD88* wild-type patients. ASCT, autologous stem cell transplant; BTKi, BTK inhibitor; CIT, chemoimmunotherapy; R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia. 1. Buske C *et al*. Waldenström's disease (lymphoplasmocytic lymphoma). Available at: https://www.onkopedia.com/de/onkopedia/guidelines/morbus-waldenstroem-lymphoplasmozytisches-lymphom/@@guideline/html/index.html. Accessed August 2025. 2. Speaker's opinion.

Patient evaluation

Evaluation of circulating clonal B cells could eliminate the need for frequent invasive bone marrow assessments in WM

EHA2025 POSTER

Prognostic value and mutational profile of circulating clonal B cells in Waldenström macroglobulinemia patients undergoing ibrutinib therapy, Bagratuni T *et al*.

Aims: Determine the potential to detect and characterize circulating clonal B cells (CCBCs) in patients with IgM monoclonal gammopathies, especially in patients undergoing ibrutinib therapy

Methods: Multi-parametric FC was used to detect CCBCs from 110 patients with IgM MGUS (35), asymptomatic WM (19), and symptomatic WM (56) – the molecular profile of matched CCBCs and BM tumor cells was compared by WES

Results: CCBCs were detectable in 86% of patients with sWM (47/56), 63% of patients with aWM (12/19), and 40% of patients with IgM MGUS (14/35)

WES analysis of matched samples from 14 patients showed similar mutation patterns in CCBCs and clonal B cells from the BM, with shared mutations seen in genes such as *MYD88*, *CXCR4*, *ARID1A*, and *CD79B*

Conclusions:

- Evaluation of CCBCs is feasible in IgM monoclonal gammopathies
- Levels of CCBCs may reflect BM tumor load

(a/s)WM, (asymptomatic/symptomatic) Waldenström's macroglobulinemia; BM, bone marrow; CCBC, circulating clonal B cell; EHA, European Hematology Association; FC, flow cytometry; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; WES, whole exome sequencing.

Bagratuni T *et al*. Poster presentation at EHA2025; Milan, Italy, June 12–15, 2025.

Ongoing trials in WM

Active clinical trials in WM are exploring novel approaches to treating patients with TN and R/R WM

	TN setting			R/R setting
Trial	ECWM-1 (Phase 2)[1]	ECWM-2 (Phase 2)[2,3]	RAINBOW (Phase 2/3)[4]	CZAR-1 (Phase 2)[5]
Arms	DRC vs. B-DRC	Bortezomib + IR	IR vs. DRC	Carfilzomib + Ibrutinib
Primary endpoint	PFS	1-year PFS rate	Overall response rate at Week 24 and 2-year PFS rate	CR or VGPR rate after 1 year of treatment
Status	Final analysis pending	Study completion: Sep 2029	Primary completion: Mar 2030	Primary completion: Aug 2028
Results	**Median follow-up: 27.5 months** **2-year PFS** B-DRC: 80.6%, DRC: 72.8% **MRR** B-DRC: 80.6%, DRC: 69.9% **Grade ≥3 AEs:** B-DRC: 49.5%; DRC: 49.0% **Deaths:** 5/99 patients in the B-DRC arm and 6/96 patients in the DRC arm	**Median follow-up: 37 months** **1-year PFS:** 93% **2-year PFS:** 88% **MRR:** 70% **Treatment-related Grade ≥3 AEs:** 45% **Deaths:** 8/53 patients (5 related to COVID-19 and 3 to respiratory tract infection)		

This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

AE, adverse event; (B-)DRC, (bortezomib,) dexamethasone, rituximab, and cyclophosphamide; CIT, chemoimmunotherapy; COVID-19, coronavirus disease 2019; CR, complete response; ECWM, European Consortium for Waldenström's Macroglobulinemia; IR, ibrutinib and rituximab; MRR, major response rate; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment-naive; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.

1. Buske C *et al*. *J Clin Oncol* 2023; 41 (14): 2607–2616. 2. Buske C *et al*. *Blood* 2024; 144 (Suppl 1): 859. 3. ECWM-2. Available at: https://www.ecwm.eu/research-and-trials/ecwm-2-155.html. Accessed August 2025. 4. ClinicalTrials.gov RAINBOW. Available at: https://clinicaltrials.gov/study/NCT04061512. Accessed August 2025. 5. ClinicalTrials.gov CZAR-1. Available at: https://clinicaltrials.gov/study/NCT04263480. Accessed August 2025.

EHA2025
ORAL

R/R setting

Updated Efficacy & Safety of the Bruton Tyrosine Kinase Degrader BGB-16673 in Patients With Relapsed/Refractory Waldenström Macroglobulinemia: Ongoing Phase 1 CaDAnCe-101 Study Results

Anna Maria Frustaci,[1] John F. Seymour,[2] Chan Y. Cheah,[3-5] Ricardo D. Parrondo,[6] John N. Allan,[7] Judith Trotman,[8] Mazyar Shadman,[9,10] Ranjana Advani,[11] Herbert Eradat,[12] Pier Luigi Zinzani,[13] Masa Lasica,[14] Emmanuelle Tchernonog,[15] Steven P. Treon,[16] Linlin Xu,[17] Kunthel By,[17] Shannon Fabre,[17] Motohisa Takai,[17] Amit Agarwal,[17] Constantine S. Tam[18]

[1]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [2]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia; [3]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [4]Medical School, University of Western Australia, Crawley, WA, Australia; [5]Linear Clinical Research, Nedlands, WA, Australia; [6]Mayo Clinic - Jacksonville, Jacksonville, FL, USA; [7]Weill Cornell Medicine, New York, NY, USA; [8]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [9]Fred Hutchinson Cancer Center, Seattle, WA, USA; [10]University of Washington, Seattle, WA, USA; [11]Stanford Cancer Institute, Stanford, CA, USA; [12]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [13]Institute of Hematology "Seràgnoli", University of Bologna, Bologna, Italy; [14]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [15]CHRU Montpellier - Hôpital St Eloi, Montpellier, France; [16]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [17]BeOne Medicines Ltd, San Carlos, CA, USA; [18]Alfred Hospital and Monash University, Melbourne, VIC, Australia

EHA, European Hematology Association; R/R, relapsed/refractory.

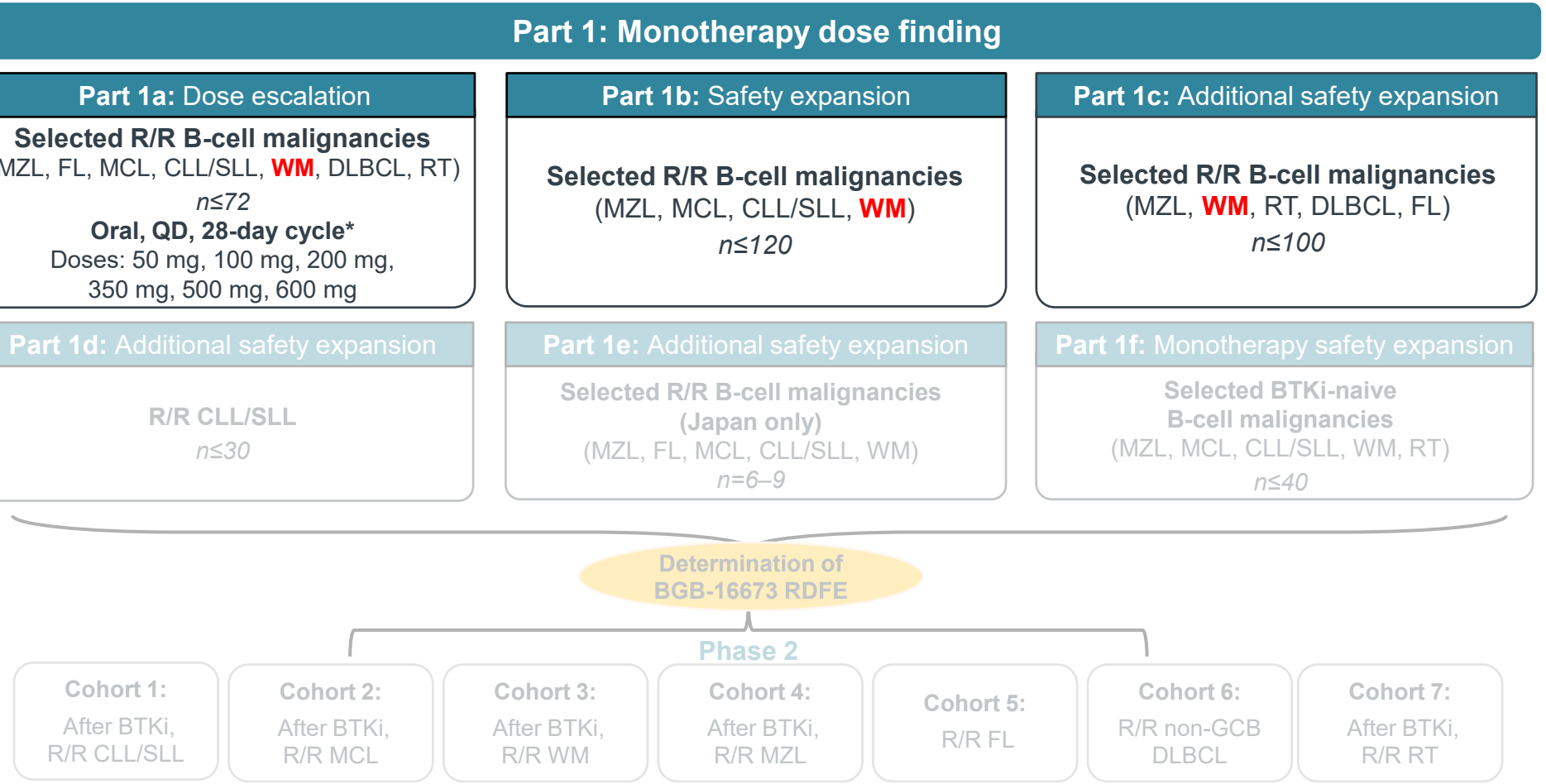
BGB-16673, a chimeric degradation activation compound (CDAC), is being trialled in WM within the CaDAnCe-101 trial

Key eligibility criteria for WM

- Met IWWM-7 criteria for treatment
- ≥2 prior therapies, including anti-CD20 monoclonal antibody and cBTKi (US and EU only)
- ECOG PS 0–2
- Adequate organ function

Key objectives: Part 1

- **Primary:** Safety† and tolerability; MTD; and RDFE
- **Secondary:** PK, PD, and preliminary antitumor activity‡



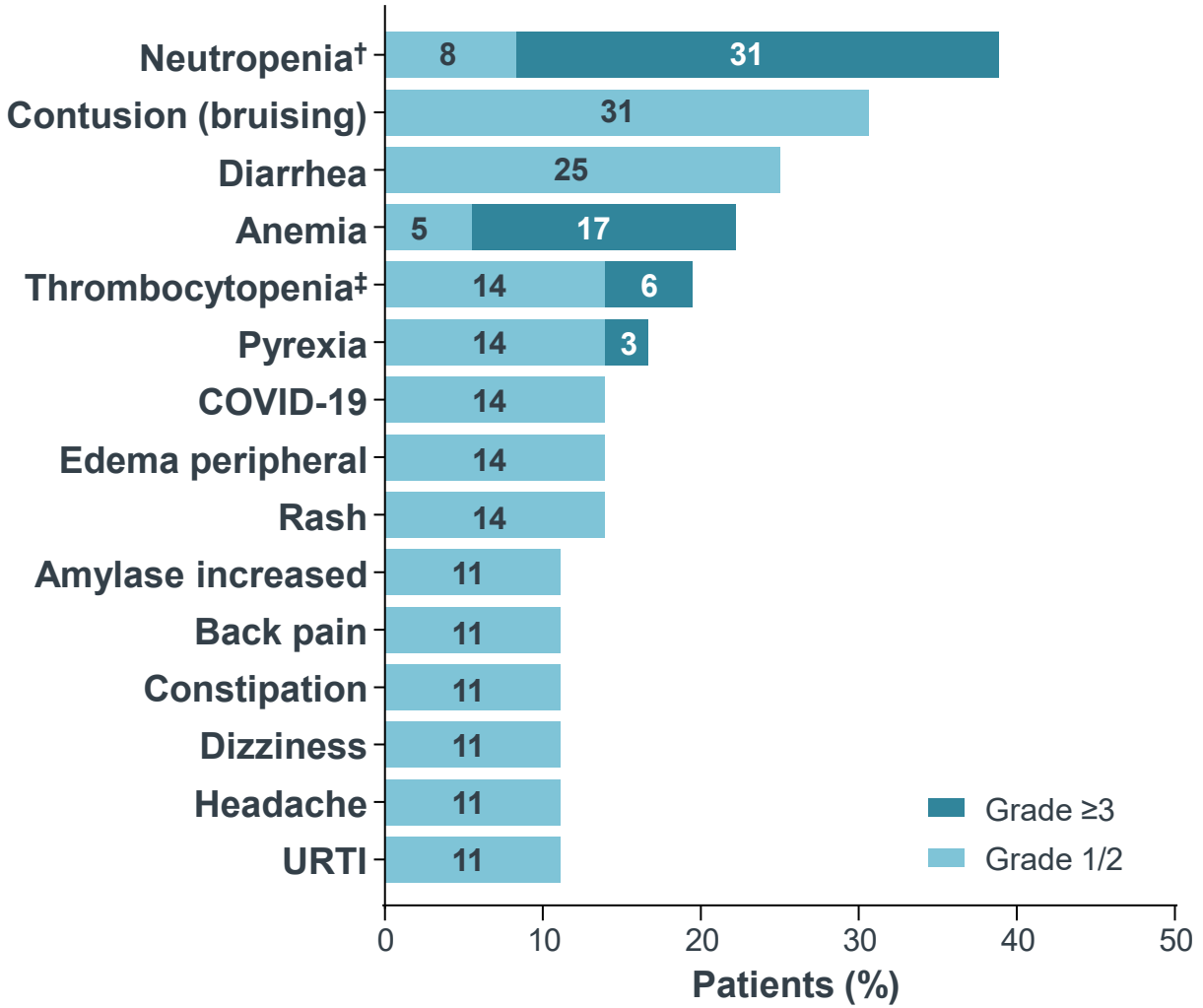
Data from gray portions of the figure are not included in this presentation.
*Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. †Safety was assessed according to CTCAE v5.0. ‡Responses were assessed per IWWM-6, modified Owen 2013 criteria after 4 weeks. (c)BTKi, (covalent) BTK inhibitor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; CTCAE, Common Terminology Criteria for Adverse Events; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; GCB, germinal center B-cell; IWWM, International Workshop on Waldenström's Macroglobulinemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; QD, daily; RDFE, recommended dose for expansion; R/R, relapsed/refractory; RT, Richter transformation; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.
Frustaci AM *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.

BGB-16673 was well tolerated in a heavily pretreated population

N=36

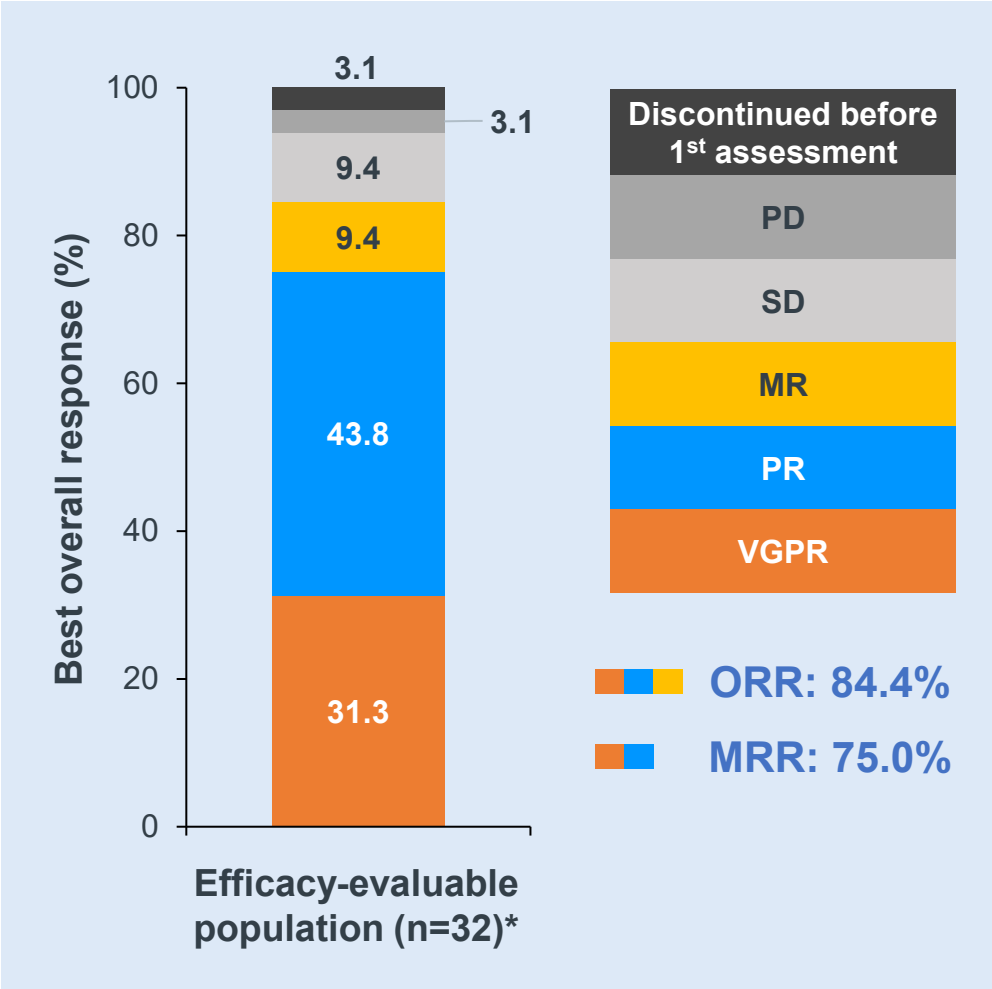
- Age, median (range): 72 years (49–81)
- Prior lines of treatment, median (range): 3 (1–11)
- Prior cBTKi, n (%): 36 (100)
- Discontinued prior BTKi owing to PD, n (%): 30 (88.3)

Patients, n (%)	Total (N=36)
Any TEAE	32 (88.9)
Any treatment-related	25 (69.4)
Grade ≥3	22 (61.1)
Treatment-related Grade ≥3	14 (38.9)
Serious	12 (33.3)
Treatment-related serious	4 (11.1)
Leading to death*	1 (2.8)
Treatment-related leading to death	0
Leading to treatment discontinuation	2 (5.6)



Data cut-off: March 3, 2025. Median follow-up: 8.2 months (range: 0.6–30.6 months). *Septic shock (200 mg dose level), note in the context of PD. †Neutropenia combines preferred terms neutrophil count decreased and neutropenia. ‡Thrombocytopenia combines preferred terms platelet count decreased and thrombocytopenia.
(c)BTKi, (covalent) BTK inhibitor; COVID-19, coronavirus disease 2019; PD, progressive disease; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.
Frustaci AM *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.

Promising antitumor activity was observed, including in patients with BTKi-resistant mutations



Responses occurred regardless of baseline mutations, with an ORR 100% (n=11/11) in patients with *BTK* mutations

Rapid and significant cytopenia improvement was observed in patients who responded to treatment

IgM levels decreased in all patients, with a rapid and sustained decline in most cases

Based on the data available, BGB-16673 is being evaluated in an ongoing Phase 2 study in R/R WM

*Four patients were too early in the treatment course to be response-evaluable.
BTKi, BTK inhibitor; IgM, immunoglobulin M; MR, minor response; MRR, major response rate (PR or better); ORR, overall response rate (MR or better); PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.
Frustaci AM *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.

Hot topics from the 10th Meeting of the European Consortium for Waldenström's Macroglobulinemia

Researchers at the 10th ECWM addressed some of the biggest unanswered questions in WM

What role does the tumor microenvironment play?

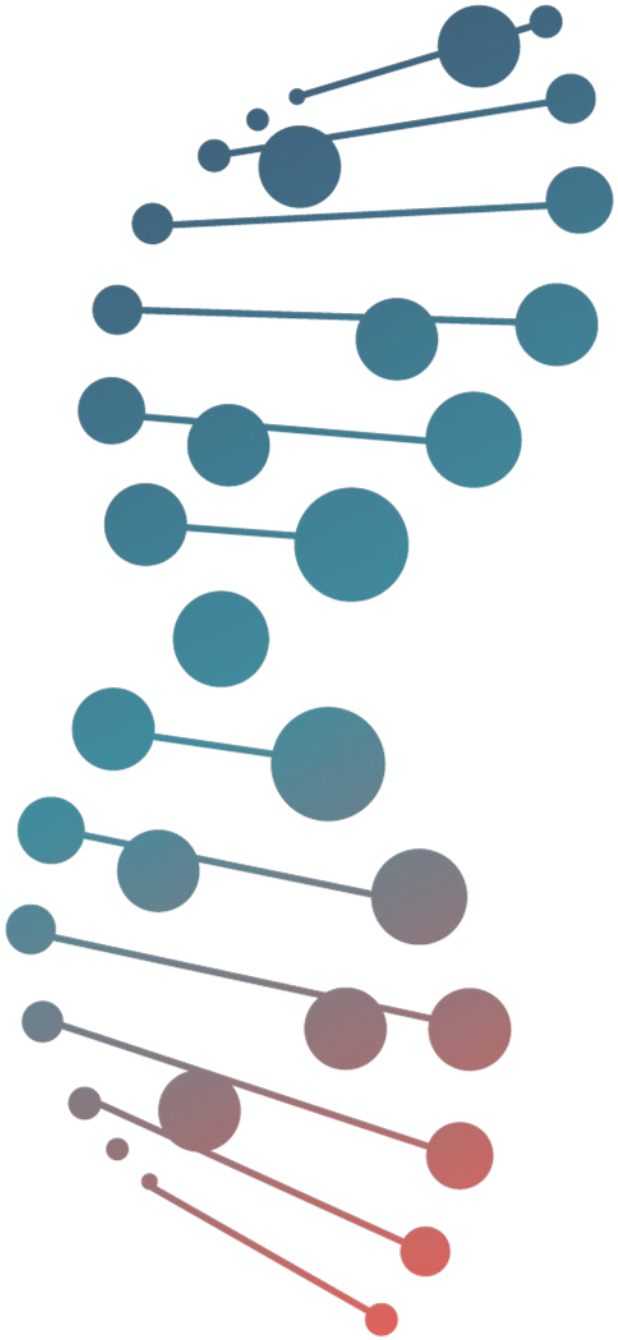
What WM subtypes exist (if any) and what is their clinical relevance?

What are the possibilities for time-limited chemotherapy-free approaches in WM?

What is the best approach to sequencing therapies in WM, and how should we treat BTKi-exposed patients?

How should a cure for WM be defined, and what approaches offer the greatest potential?

BTKi, BTK inhibitor; ECWM, European Consortium for Waldenström's Macroglobulinemia; WM, Waldenström's macroglobulinemia.
Speaker's opinion.



Summary

Chair: Christian Buske

Summary

CLL

Highlights in CLL included pivotal updates from mature clinical trials across approved and investigational regimens, along with early-stage data spotlighting novel combinations and emerging assets

- Outcomes from the SEQUIOA trial Cohorts 1 and 2 confirm the efficacy and tolerability of first-line zanubrutinib monotherapy regardless of disease features – while Cohort 3 and ongoing trials demonstrate the future potential of zanubrutinib-based combinations[1–4]
- The CAPTIVATE follow-up reinforces the clinical value of fixed-duration Ibr-Ven, while data from the FLAIR trial highlight the promise of MRD-guided Ibr-Ven – although MRD-guided strategies are not yet approved in CLL and there may be practical barriers to widespread clinical adoption[5–7]

WM

While the use of continuous BTK inhibitors is a cornerstone in the treatment of WM, experts explore novel approaches, including strategies for characterizing and treating patients, optimizing sequencing, developing time-limited targeted treatments, and pursuing curative strategies

BTK degraders are a novel therapeutic class showing encouraging evidence of activity and tolerability in CLL and WM – with particular promise for heavily pretreated patients[8,9]

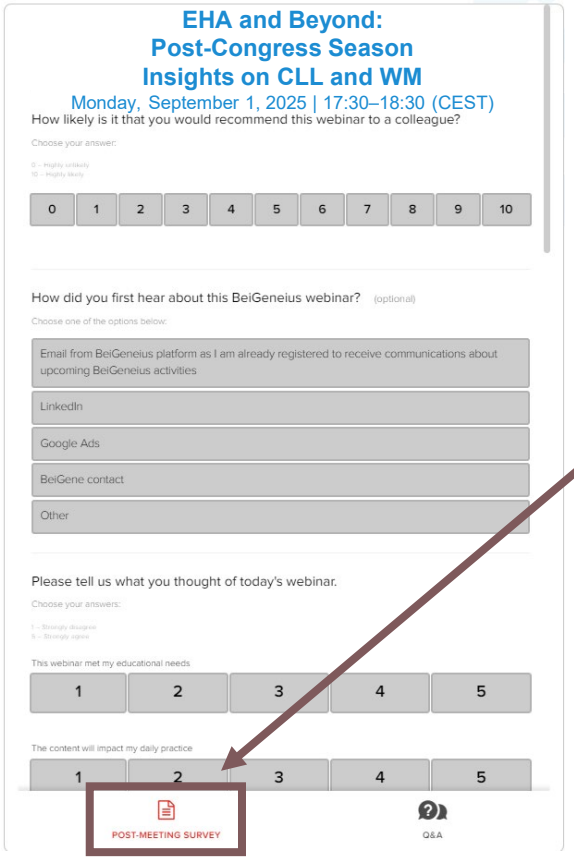
BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; Ibr-Ven, ibrutinib-venetoclax; MRD, minimal residual disease; WM, Waldenström's macroglobulinemia.

1. Tam CS *et al*. Oral presentation at ASCO 2025; Chicago, IL, USA, May 30 – June 3, 2025. 2. Shadman M *et al*. Oral presentation at ASCO 2025; Chicago, IL, USA, May 30 – June 3, 2025. 3. Shadman M *et al*. *J Clin Oncol* 2025; 43 (7): 780–787. 4. Cheah CY *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025. 5. Wierda WG *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025. 6. Munir T *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025. 7. Speaker's opinion. 8. Scarfò L *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.
9. Frustaci AM *et al*. Oral presentation at EHA2025; Milan, Italy, June 12–15, 2025.

We want to hear from you!

Exit full-screen view to have your say

Exit full-screen view to have your say



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