Navigating Treatment Selection and Infection Management in CLL

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WELCOME AND INTRODUCTION

Clemens-Martin Wendtner

Ludwig Maximilian University, Munich, Germany

✦ ✦ ✦

BeOne

BeiGene

is now

BeOne

Our name change to BeOne Medicines reaffirms our commitment
to develop innovative medicines to eliminate cancer
by partnering with the global community
to serve as many patients as possible.

Faculty disclosures

Clemens-Martin Wendtner

- **Advisory boards**: AbbVie, Amgen, AstraZeneca, BeOne Medicines, BioNTech, Cilag-Janssen, F. Hoffmann-La Roche, Genentech, Gilead, GSK, Moderna, MorphoSys
- **Honoraria**: AbbVie, Amgen, AstraZeneca, BeOne Medicines, BioNTech, Cilag-Janssen, F. Hoffmann-La Roche, Genentech, Gilead, GSK, Moderna, MorphoSys
- **Research funding**: AbbVie, AstraZeneca, BeOne Medicines, Cilag-Janssen, F. Hoffmann-La Roche, Genentech, Gilead, GSK, MorphoSys

Anne-Sophie Michallet

- **Honoraria**: AbbVie, AstraZeneca, BeOne Medicines, Janssen
- **Consultancy/advisory role**: Lilly

Faculty disclosures

Helen Parry

- **Advisory board honorarium/participation**: AbbVie, AstraZeneca, BeOne Medicines, GSK
- **Scientific conference support**: AbbVie, BeOne Medicines, Janssen
- **Speaker fees**: AbbVie, AstraZeneca, BeOne Medicines, CSL Behring, Janssen, Takeda

Alessandra Tedeschi

- **Advisory board**: AbbVie, AstraZeneca, BeOne Medicines, Johnson & Johnson, Lilly
- **Speaker bureau**: AbbVie, BeOne Medicines, Johnson & Johnson, Lilly

Talha Munir

- **Advisor/consultant**: Alexion, AstraZeneca, BeOne Medicines, Janssen, Lilly, MorphoSys, Roche, Sobi, Sunesis
- **Honoraria/travel support**: AbbVie, Alexion, AstraZeneca, BeOne Medicines, Gilead, GlaxoSmithKline, Janssen, Novartis, Pharmacyclics, Roche, Sobi

Disclaimers

- The views expressed are those of the speakers and may not necessarily reflect the opinion of BeOne Medicines
- The material may contain information about products or indications that have not yet been approved in your country; for prescriptions, always refer to the product information approved in your country, as well as, where applicable, the reimbursement conditions
- The speakers' opinions are those of experts and do not necessarily reflect those of BeOne Medicines

Disclaimers

- Zanubrutinib▼* is indicated in the European Union (EU) for the treatment of adult patients as:
  - Monotherapy for: patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemoimmunotherapy; patients with chronic lymphocytic leukemia (CLL); and patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy
  - Combination therapy with obinutuzumab in patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies
- Indications may differ outside of the EU. Prescribing information may vary depending on local approval in each country. For the country where you practice medicine, consult the zanubrutinib prescribing and reimbursement information and the local materials, such as the PI and/or the SmPC for guidance on prescribing.

*▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; EU, European Union; FL, follicular lymphoma; MZL, marginal zone lymphoma; PI, prescribing information; SmPC, summary of product characteristics; WM, Waldenström's macroglobulinemia.

Learning objectives

By the close of this session, participants will be able to:

- Assess individual patient and disease characteristics to inform and apply personalized treatment strategies for CLL
- Implement effective strategies to prevent and manage infections in patients with CLL, based on current best practices
- Evaluate emerging challenges and trends in CLL to adapt and enhance future clinical management approaches
- Understand the role of zanubrutinib in the treatment of patients with CLL

Faculty

Chair

Clemens-Martin Wendtner
Ludwig Maximilian University,
Munich, Germany

Speakers

Anne-Sophie Michallet
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Lyon, France

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Milan, Italy

Helen Parry
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University Hospitals
Birmingham, UK

Agenda

Time	Session	Speaker
5 min	Welcome and introductions	Clemens-Martin Wendtner
20 min	Factors influencing individualized treatment selection in CLL	Anne-Sophie Michallet
20 min	Managing infection risks in CLL	Helen Parry
40 min	Panel discussion: Addressing key questions in CLL management	All faculty
5 min	Summary and close	Clemens-Martin Wendtner

CLL, chronic lymphocytic leukemia.

FACTORS INFLUENCING INDIVIDUALIZED TREATMENT SELECTION IN CLL

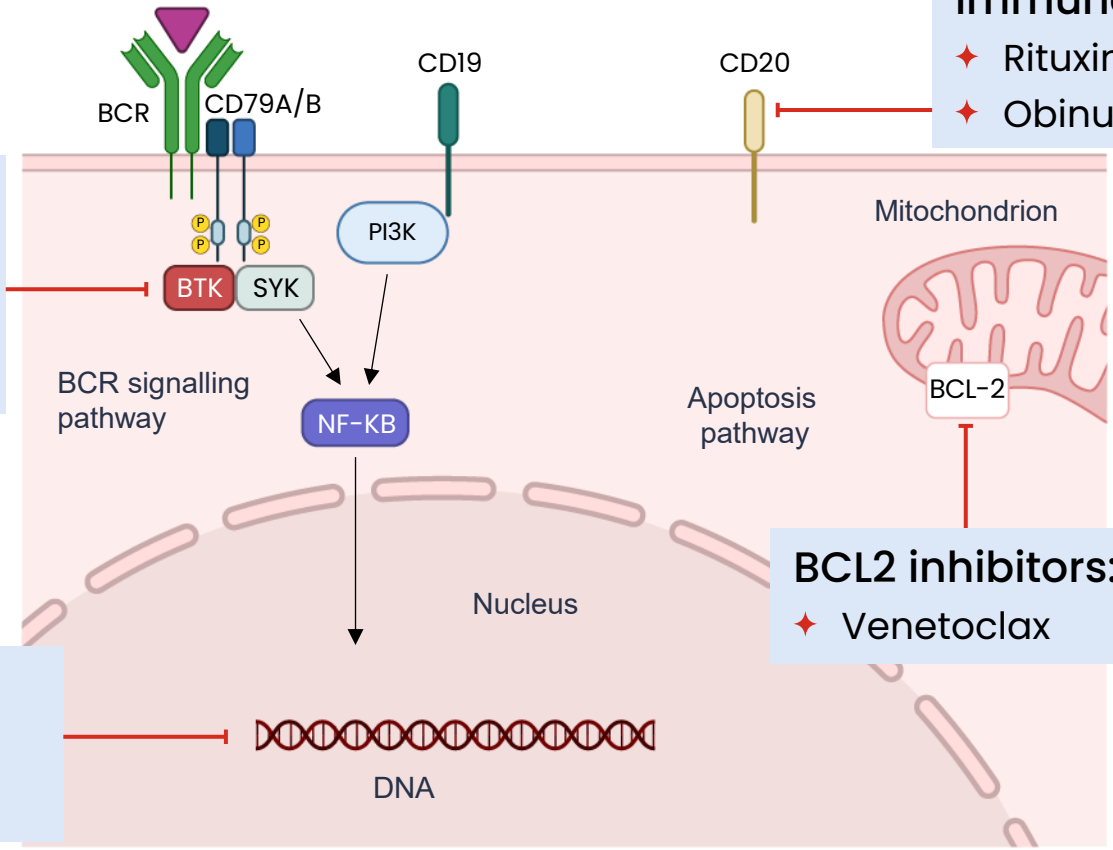
Anne-Sophie Michallet

Léon Bérard Centre,
Lyon, France

The CLL treatment landscape

Many options are now available

Covalent BTK inhibitors:
- Ibrutinib (1st generation)
- Zanubrutinib (2nd generation)
- Acalabrutinib (2nd generation)



Immunotherapy:
- Rituximab
- Obinutuzumab

BCL2 inhibitors:
- Venetoclax

Chemotherapy:
- Fludarabine
- Bendamustine

Indications for use may vary from country to country. Therefore, please always refer to the product information approved in your country.
BCL2, B-cell lymphoma 2; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; DNA, deoxyribonucleic acid; NF-κB, nuclear factor kappa B; PI3K, phosphoinositide 3-kinase; SYK, spleen tyrosine kinase.
Speaker's opinion.

First-line CLL treatment

The treatment selection process is multi-dimensional

Patient-related factors	Disease-related factors	Treatment-related factors	Other factors
✦ Fitness/age	✦ Biology	✦ Cardiotoxicity	✦ Treatment sequence
✦ Comorbidities	✦ Presentation	✦ TLS / renal function	✦ Resistance
✦ Patient preference	✦ Infections	✦ TEAEs (e.g. infections, diarrhea, headaches)	✦ Cost
✦ Logistics/caregivers		✦ Co-medications	

CLL, chronic lymphocytic leukemia; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome.
Speaker's opinion.

Predictive biomarkers

To date, there are no dedicated trials of prognostic biomarkers

Difficult to achieve the required statistical power

Only post hoc analyses are available

	BTKi monotherapy[1–5]	Obi-Ven[6,7]	Ibr-Ven[8,9]
IGHV status	–	★★	★★
TP53 abnormality	★	★★	?
Complex karyotype	★	★★	?

★★ Predictive in multivariate analysis

★ Predictive in univariate analysis or real-world data

– Not predictive

? No mature data

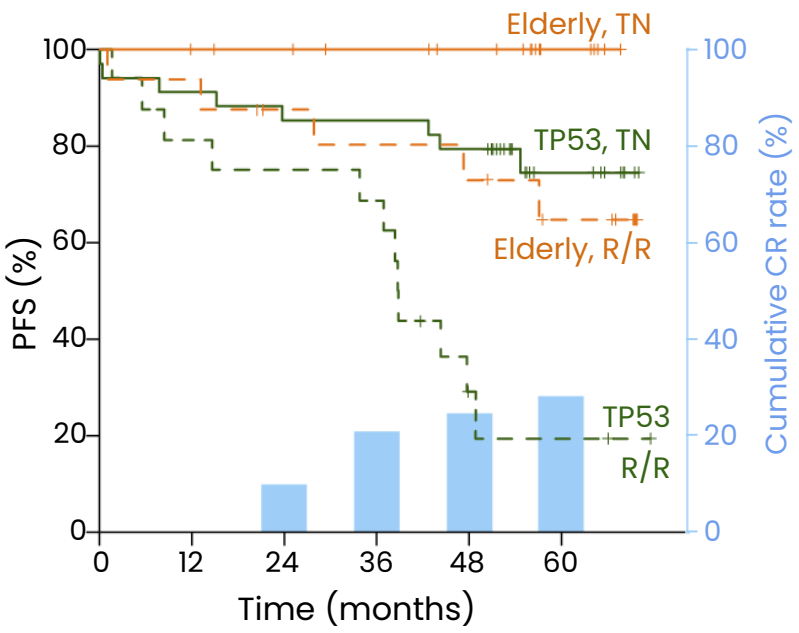
BTKi, Bruton's tyrosine kinase inhibitor; IGHV, immunoglobulin heavy chain variable region genes; Obi, obinutuzumab; Ven, venetoclax.

1. Shadman M *et al. J Clin Oncol* 2024; 43 (7): 780–787. 2. Barr PM *et al. Blood Adv* 2022; 6 (11): 3440–3450. 3. Sharman JP *et al. Lancet* 2020; 395 (10232): 1278-1291. 4. Ahn IE *et al. Blood* 2018; 131 (21): 2357–2366. 5. Kittai S *et al. Blood* 2021; 138 (23): 2372–2382. 6. Fürstenau M *et al. Lancet Oncol* 2024; 25 (6): 744–759. 7. Al-Sawaf O *et al. Blood* 2024; 144 (18): 1924–1935. 8. Niemann C *et al. Lancet Oncol* 2023; 24 (12): 1423–1433. 9. Wierda WG *et al.* Oral presentation at ASCO 2024; Chicago, IL, USA, May 31-June 4, 2024.

CLL disease profile

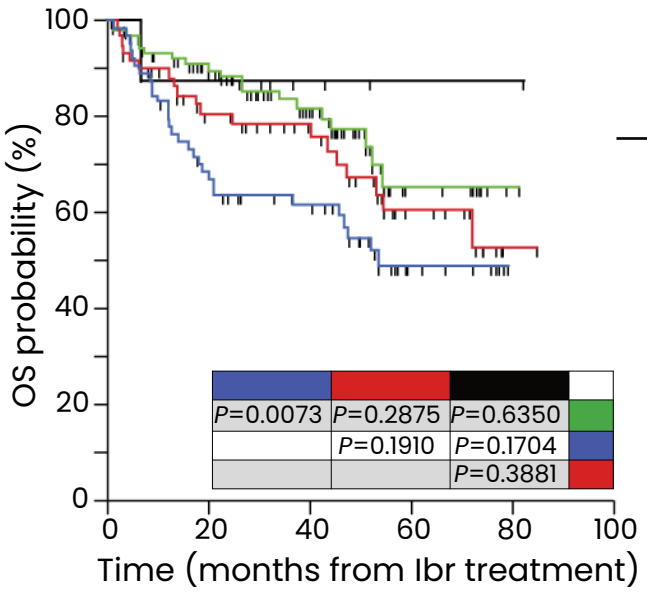
TP53 mutation status is a prognostic biomarker independent of del(17p)

NIH Phase 2 ibrutinib study[1]



≠ between 1L and relapse

Campus CLL study of patients receiving ibrutinib[2]



Non del(17p)/*TP53* mut	95	68	40	9	1	0
Del(17p)/*TP53* WT	8	7	3	1	1	0
Non del(17p)/*TP53* mut	60	39	39	12	1	0
Del(17p)/*TP53* mut	66	41	31	8	0	0

Non del(17p)/*TP53* mut (n=95)
Del(17p)/*TP53* WT (n=8)
Non del(17p)/*TP53* mut (n=60)
Del(17p)/*TP53* mut (n=66)

Similar outcomes were reported for PFS

OS outcomes numerically worse for *TP53* mut VAF >10% and *TP53* mut VAF <10% vs. *TP53* wild type

This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison.
1L, first line; CLL, chronic lymphocytic leukemia; CR, complete response; del, deletion; Ibr, ibrutinib; mut, mutation; NIH, National Institutes of Health; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment naïve; VAF, variant allele frequency; WT, wild type.
1. Ahn IE *et al. Blood* 2018; 131 (21): 2357–2366. 2. Bomben R *et al. Leukemia* 2023; 37 (4): 914–918.

CLL disease profile

FILO recommendations for 'high-risk' patients

FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

APRIL 2025[1]

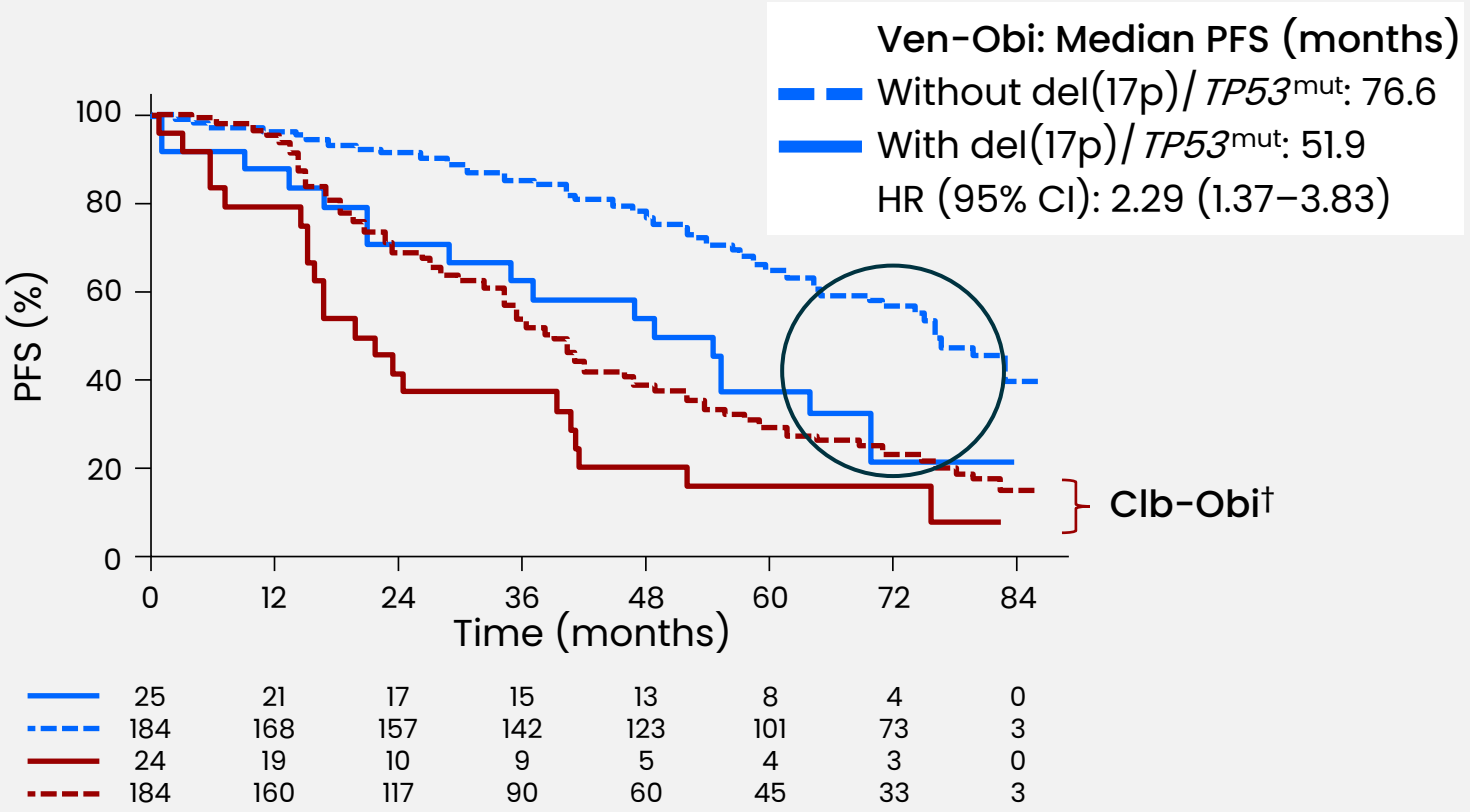
TP53 mutation and/or complex karyotype*

1. Continuous cBTKi

2. Ven-Obi

CLL14 study:[2]

Poorer outcomes with Ven-Obi in patients with *TP53* del/mut

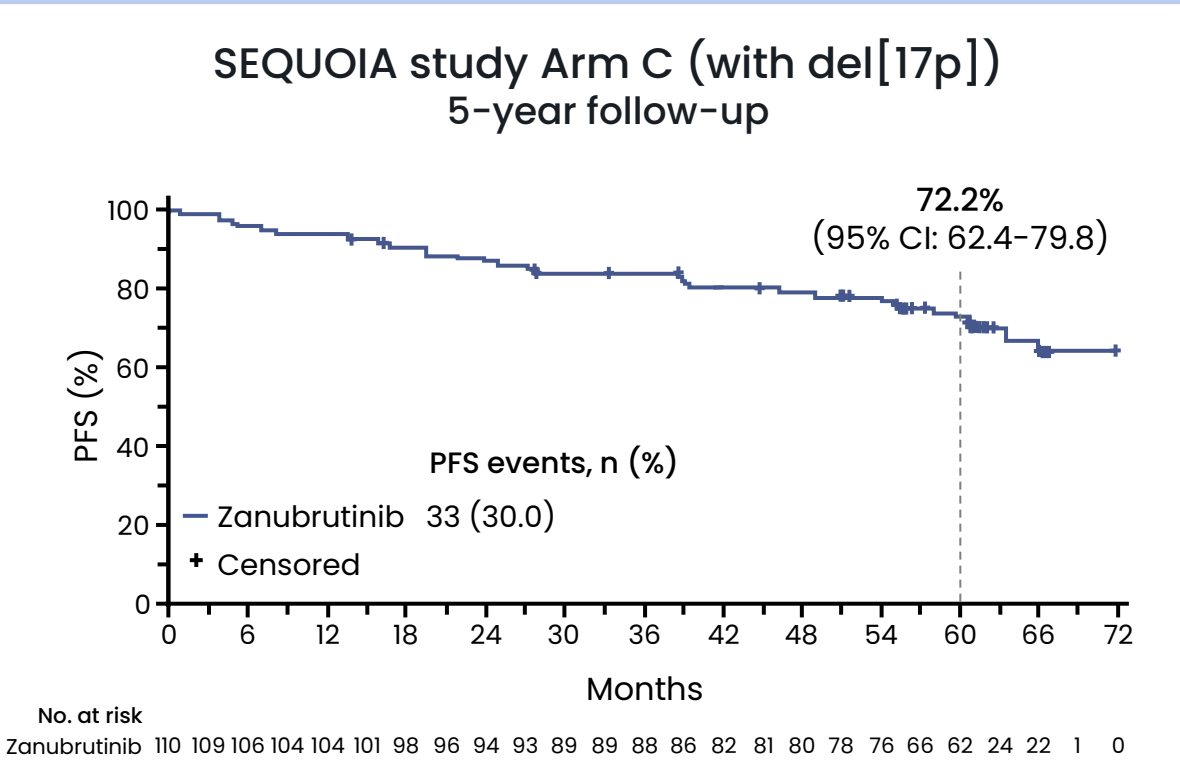


*≥5 anomalies. †Clb-Obi without *TP53* del/mut: 38.9 months; Clb-Obi with *TP53* del/mut: 20.8 months; HR: 1.66; 95% CI: 1.05–2.63; *P*=0.03.
cBTKi, covalent Bruton's tyrosine kinase inhibitor; CI, confidence interval; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; del, deletion; FILO, French Innovative Leukemia Organization; HR, hazard ratio; mut, mutation; Obi, obinutuzumab; PFS, progression-free survival; Ven, venetoclax.

1. FILO recommendations for CLL. Available at: www.filo-leucemie.org/page/filo-llc-mw/recommandations-llc. Accessed May 2025. 2. Al-Sawaf O *et al. Blood* 2024; 144 (18): 1924–1935.

CLL disease profile

Consistent efficacy with zanubrutinib in patients with and without del(17p)[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%

EAIRs for select AEs[3]	Patients with del(17p)
	Arm C: zanubrutinib (n=111)
Atrial fibrillation and flutter	0.15
Hemorrhage	2.73
Major hemorrhage	0.20
Hypertension	0.35

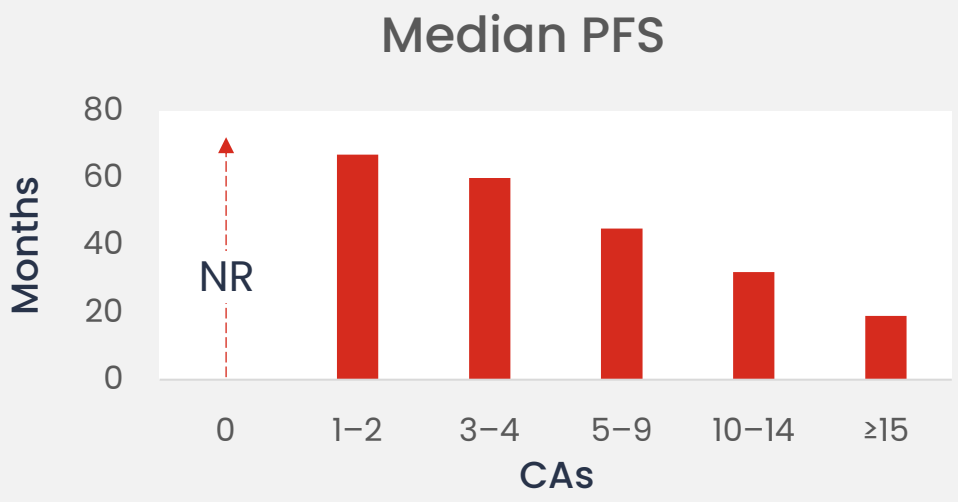
Consistent efficacy with zanubrutinib across low- and high-risk CLL while maintaining a favorable safety profile

AE, adverse event; CI, confidence interval; CLL, chronic lymphocytic leukemia; del, deletion; EAIR, exposure-adjusted incidence rate; HR hazard ratio; 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* 2024; 43 (7): 780–787. 3. Munir T *et al.* Poster presentation at EHA 2023; Frankfurt, Germany, June 8–11, 2023.

Disease profile
Impact of complex karyotype

Ibrutinib therapy:
Retrospective analysis (N=456)[1]

All-comer Tx. Ibr Ibr-αCD20



Increasing karyotypic complexity was an independent predictor of inferior PFS/OS with ibrutinib

GAIA/CLL13 study (N=926)[2]

TP53 normal Tx. Ven-R Ven-Obi Ven-Obi-Ibr FCR BR

PFS in pooled venetoclax arms: ≥5 CAs vs. ≤2 CAs
HR (95% CI): 3.72 (2.03-6.82); $P<0.001$

≥5 cytogenetic abnormalities (but not ≥3) was an independent prognostic factor for inferior PFS in pooled venetoclax arms

SEQUOIA study (N=479)[3]

No del(17p) Tx. Zanubrutinib BR

PFS with zanubrutinib: ≥3 CAs vs. ≤2 CAs
HR (95% CI): 1.85 (0.75-4.55); $P=0.18$

≥3 cytogenetic abnormalities was not associated with inferior PFS with zanubrutinib

This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison.
BR, bendamustine and rituximab; CA, cytogenetic abnormality; CD, cluster of differentiation; CI, confidence interval; del, deletion; FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio; Ibr, ibrutinib; Obi, obinutuzumab; NR, not reached; OS, overall survival; PFS, progression-free survival; R, rituximab; Tx, treatment; Ven, venetoclax.
1. Kittai S *et al. Blood* 2021; 138 (23): 2372–2382. 2. Fürstenau M *et al. Blood* 2023; 142 (5): 446-459. 3. Xu L *et al.* Poster 1902 presented at ASH 2023; San Diego, CA, USA, December 9–12, 2023.

CLL treatment selection recommendations

FILO first-line treatment algorithm

APRIL 2025

Symptomatic CLL (iwCLL criteria)

No *TP53* mutation / 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 mutation and/or complex karyotype*

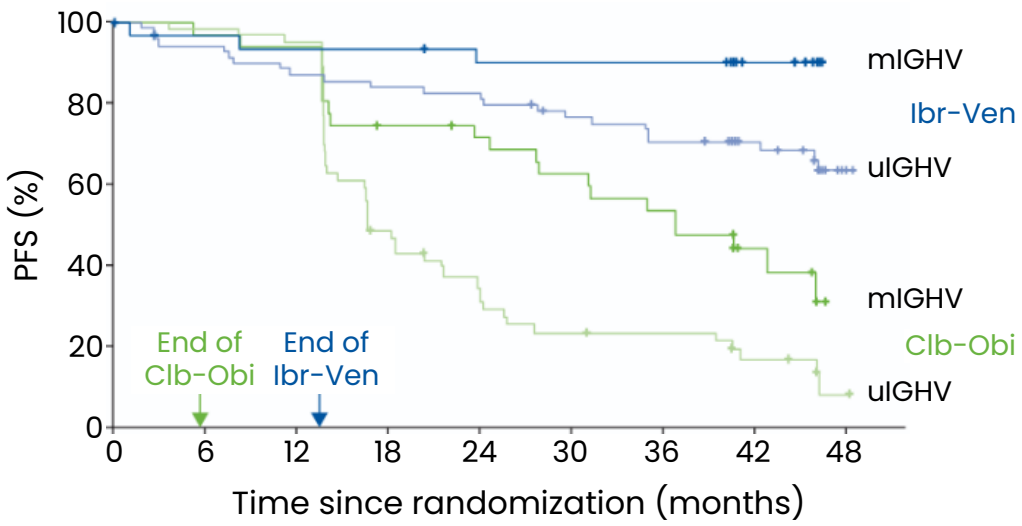
1. Continuous cBTKi
Selection criteria in associated text

2. Ven-Obi
If cBTKi is contra-indicated

*≥5 anomalies.
cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CV, cardiovascular; FILO, French Innovative Leukemia Organization; Ibr, ibrutinib; IGHV, immunoglobulin heavy chain variable region genes; 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 May 2025.

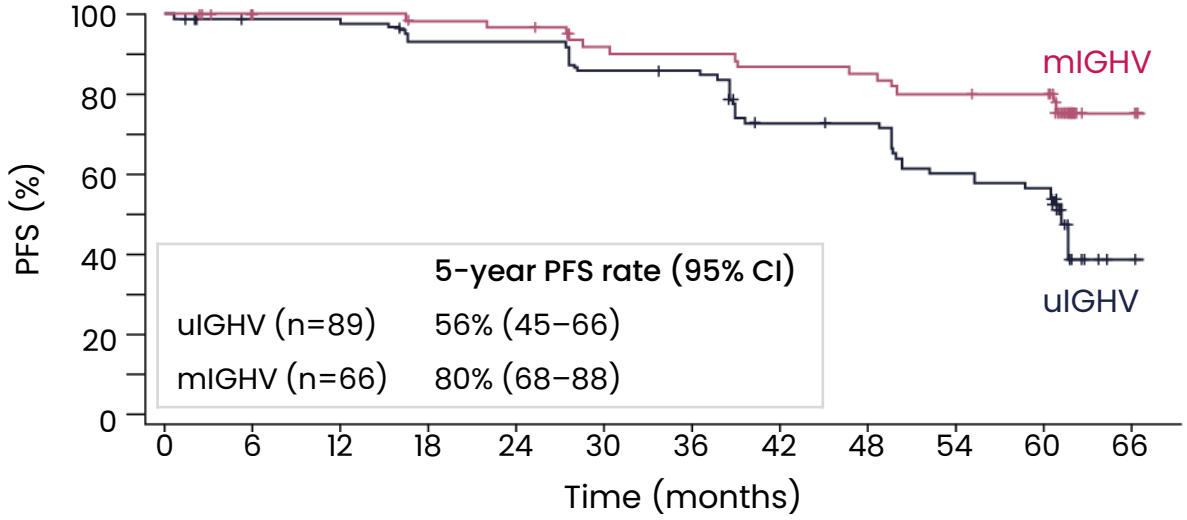
CLL disease profile
Impact of IGHV mutation status

Phase 3 randomized GLOW study[1,2]
Ibr-Ven vs. Clb-Obi in unfit patients



- Median 71 years of age with NO *TP53* anomalies*
- Overall 42-month estimated PFS: 74.6% (vs. 24.8%)

Phase 2 CAPTIVATE study (FD cohort)[3]
Ibr-Ven in fit patients by IGHV status

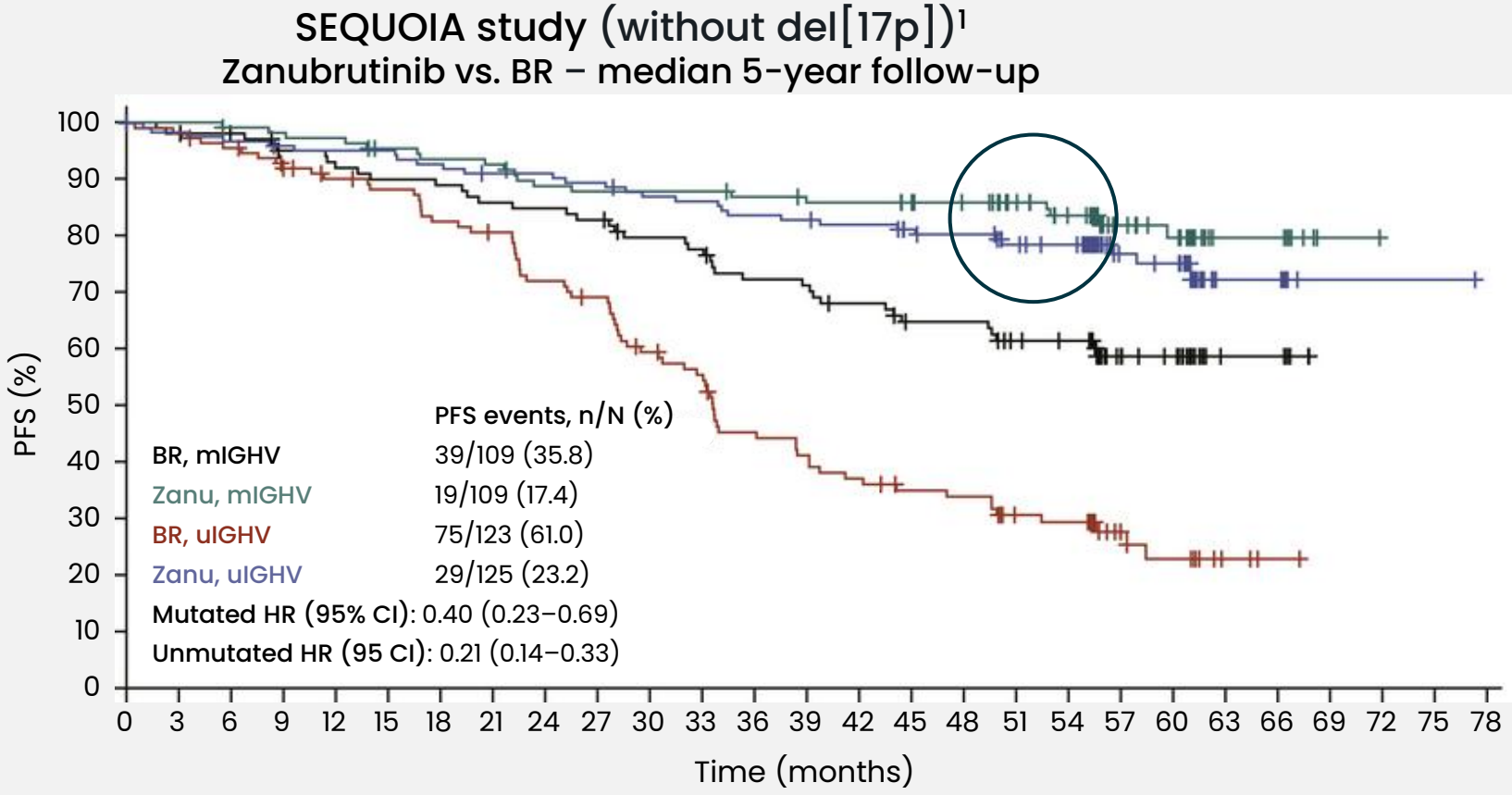


- Mean 60 years of age, 17% *TP53* anomalies
- Overall PFS at 5 years: 67%
- PFS at 5 years depending on IGHV status: 80% (mIGHV) vs. 56% (uIGHV)

This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison.
*Patients with *TP53* mutations at baseline were excluded from the study; however, *TP53* mutational status was subsequently assessed centrally for all randomly assigned patients and seven patients with mutated *TP53* were included in efficacy and safety analyses.
CI, confidence interval; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; FD, fixed-duration; Ibr, ibrutinib; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable region genes; Obi, obinutuzumab; PFS, progression-free survival; Ven, venetoclax.
1. Niemann C *et al. Lancet Oncol* 2023; 24 (12): 1423–1433. 2. Kater AP *et al. NEJM Evid* 2022; 1 (7): EVIDoa2200006. 3. Wierda WG *et al.* Oral presentation at ASCO 2024; Chicago, IL, USA, May 31-June 4, 2024.

CLL disease profile

Impact of IGHV mutation status



- Zanubrutinib 5-year PFS rate:
  - 75.8%
- No significant difference in PFS for mIGHV vs. uIGHV with zanubrutinib
  - HR (95% CI): 1.35 (0.76–2.40)

PFS outcomes independent of IGHV status have also been reported for ibrutinib and acalabrutinib[2,3]

BR, bendamustine and rituximab; CI, confidence interval; CLL, chronic lymphocytic leukemia; del, deletion; HR, hazard ratio; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable region genes; PFS, progression-free survival; Ven, venetoclax; Zanu, zanubrutinib.

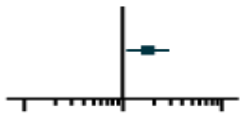
1. Shadman M *et al. J Clin Oncol* 2024; 43 (7): 780–787. 2. Barr PM *et al. Blood Adv* 2022; 6 (11): 3440–3450. 3. Sharman JP *et al. Lancet* 2020; 395 (10232): 1278-1291.

CLL disease profile
Impact of bulky disease

Bulky disease affected PFS outcomes with Ven-Obi

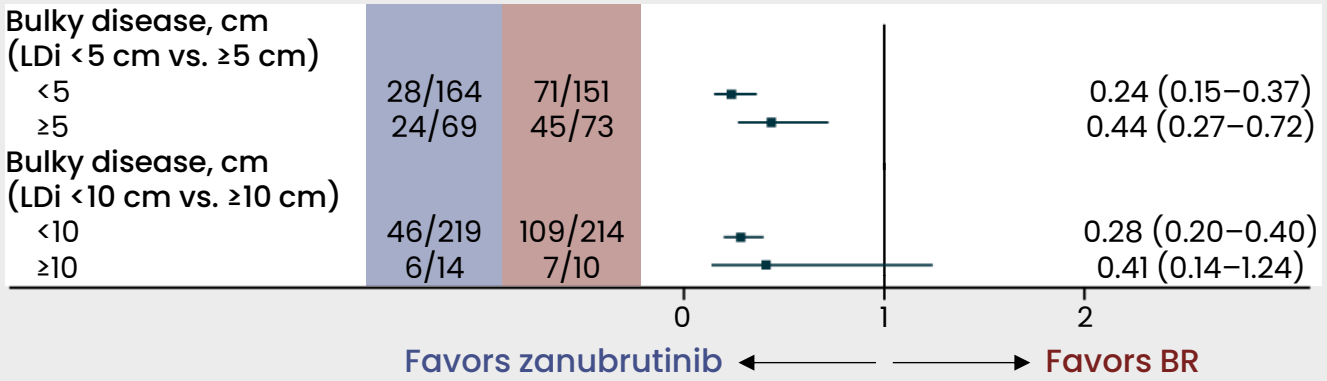
CLL14 study: Ven-Obi[1]

Lymph node size			
≥5 cm	vs. <5 cm	1.768	1.114–2.808

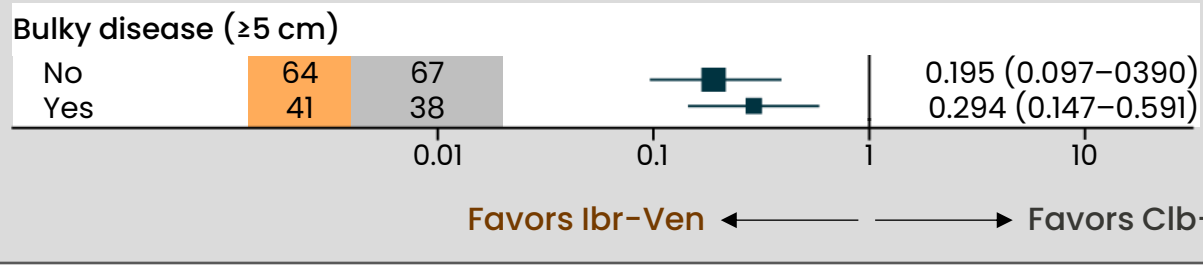


Consistent PFS benefit vs. CIT with zanubrutinib and Ibr-Ven with or without ≥5 cm lymph node size

SEQUOIA study: Zanu vs. BR[2]



GLOW study: Ibr-Ven vs. Clb-Obi[3]

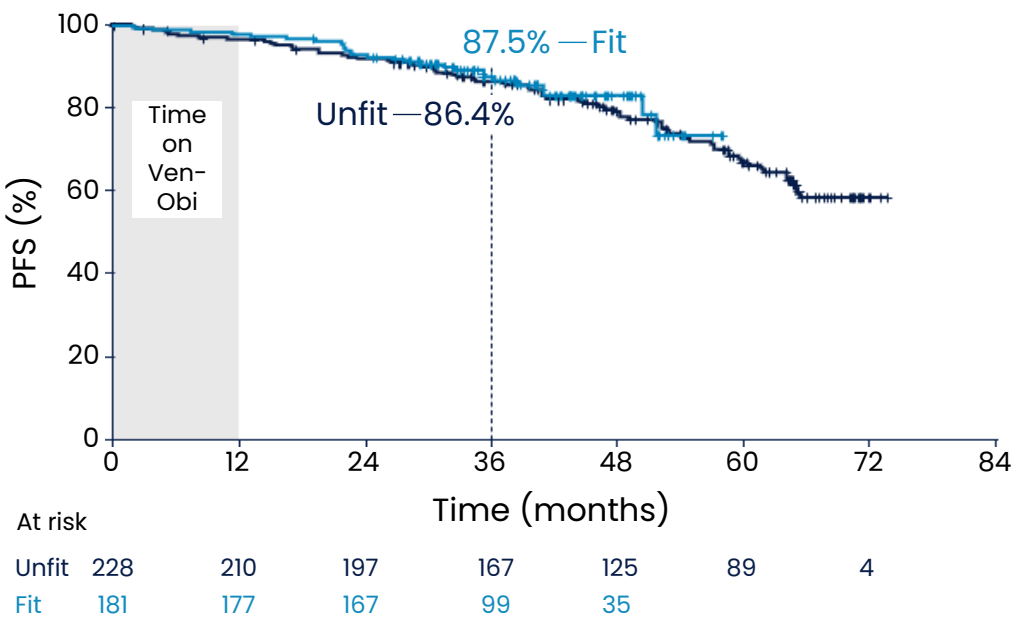


This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison.
BR, bendamustine and rituximab; CIT, chemoimmunotherapy; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; Ibr, ibrutinib; LDi, longest transverse diameter; Obi, obinutuzumab; PFS, progression-free survival; Ven, venetoclax; Zanu, zanubrutinib.
1. Al-Sawaf O *et al. Blood* 2024; 144 (18): 1924–1935. 2. Shadman M *et al. J Clin Oncol* 2024; 43 (7): 780–787. 3. Kater AP *et al. NEJM Evid* 2022; 1 (7): EVIDoa2200006.

CLL patient profile
Impact of fitness

No impact of fitness on PFS with venetoclax + obinutuzumab[1]

Ven-Obi in pooled analysis, by patient fitness, of the CLL13 and CLL14 studies[1,*]



Ibrutinib + venetoclax was better tolerated by fit vs. unfit patients in cross-trial comparison[2,3]

	CAPTIVATE study (Fit)[2]	GLOW study (Unfit)[3]
Median age	60 years	71 years
Completed 12 cycles	92%	77%
Discontinued treatment owing to toxicity	5%	10%
AE Grade 5 (death)	1%	7%

CAPTIVATE: aged ≥18 **and** ≤70 years; ECOG PS: ≤2; adequate hepatic, renal, and hematologic function

GLOW: ≥65 years **or** 18–64 years with a CIRS score >6 **or** creatinine clearance <70 mL/min

This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison.
*The median follow-up was 66.7 months for CLL14 and 38.9 months for CLL13.
AE, adverse event; CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Obi, obinutuzumab; PFS, progression-free survival; Ven, venetoclax.
1. Al-Sawaf O *et al. Blood* 2023; 142 (Suppl 1): 4639. 2. Tam CS *et al. Blood* 2022; 139 (22): 3278–3289. 3. Kater AP *et al. NEJM Evid* 2022; 1 (7): EVIDoa2200006.

CLL patient profile

Comorbidities and the importance of medical history

Be vigilant in monitoring risk factors, such as:[1]

Cardiac health
Especially with BTKis

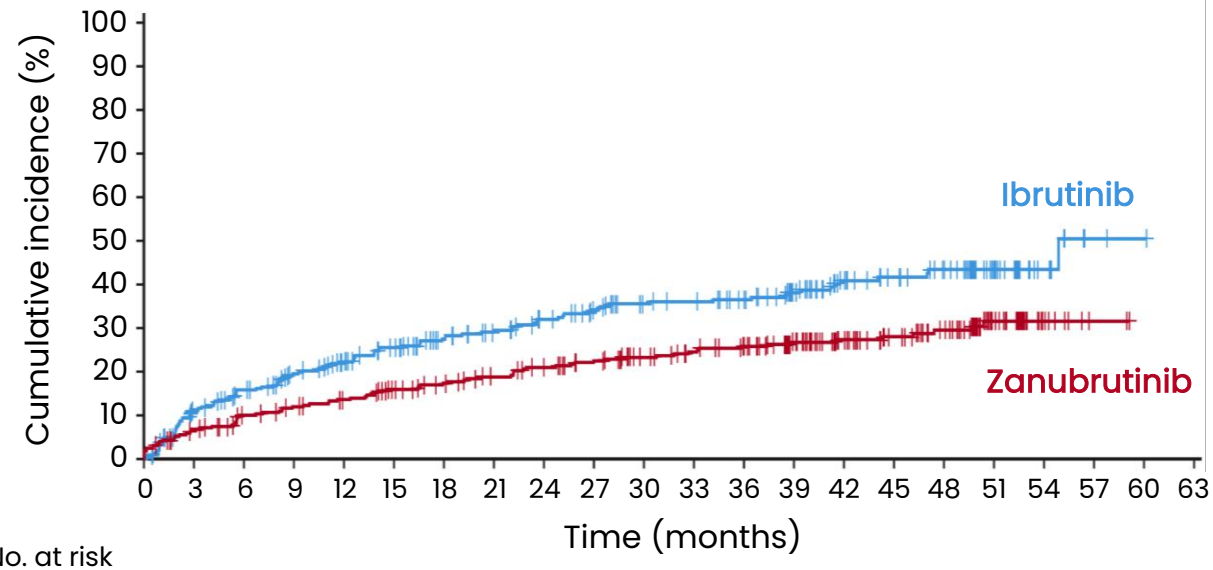
Vascular health

Infection

Renal function
Especially with BCL2is

ALPINE study: Zanubrutinib vs. ibrutinib[2]

Time to occurrence of cardiac disorders at 42.5 months median follow-up



No. at risk

Zanu	324	295	277	268	259	244	233	223	211	201	189	179	168	143	118	102	90	46	12	2	0	0
Ibr	324	276	255	235	220	201	182	170	158	146	136	133	125	101	77	68	60	35	11	2	1	0

Atrial fibrillation/flutter
Ibrutinib: 17%
Zanubrutinib: 7.1%

Fatal cardiac AEs
Ibrutinib: 2%
Zanubrutinib: 0%

Based on outcomes from head-to-head trials, zanubrutinib or acalabrutinib are generally recommended over ibrutinib for patients with CV risk[3,4]

AE, adverse event; BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CV, cardiovascular; Ibr, ibrutinib; Zanu, zanubrutinib.
1. Speaker's recommendation. 2. Brown JR *et al. Blood* 2024; 144 (26): 2706–2717. 3. Eichhorst B *et al. Ann Oncol* 2024; 35 (9): 762-768. 4. Awan FT *et al. Blood Adv* 2022; 6 (18): 5516-5525.

CLL patient profile

Treatment selection on the basis of distinct safety profiles

Bayesian network meta-analysis to assess the relative safety profile of first-line targeted therapies in patients with CLL of advanced age and/or with comorbidities
AEs Grade 3–5*

-	CLB+OBI										
CLB	**0.38 [0.24, 0.6]**	CLB									
CLB+RTX	**0.47 [0.32, 0.69]**	1.25 [0.8, 1.96]	CLB+RTX								
BEND+RTX	0.79 [0.44, 1.45]	**2.11 [1.12; 4.01]**	**1.69 [1.08; 2.68]**	BEND+RTX							
ZAN	**0.22 [0.11; 0.46]**	0.59 [0.28; 1.26]	**0.47 [0.26; 0.87]**	**0.28 [0.18; 0.42]**	ZAN						
CLB+OFA	**0.5 [0.28, 0.91]**	1.33 [0.92, 1.94]	1.07 [0.59, 1.92]	0.63 [0.3, 1.32]	2.26 [0.97, 5.32]	CLB+OFA					
IBR	0.69 [0.35, 1.36]	**1.82 [1.11, 3]**	1.46 [0.75, 2.85]	0.86 [0.38, 1.93]	**3.1 [1.24, 7.72]**	1.37 [0.74, 2.56]	IBR				
ACA+OBI	1.02 [0.64, 1.61]	**2.7 [1.4, 5.19]**	**2.17 [1.18, 3.96]**	1.28 [0.6, 2.71]	**4.58 [1.94, 10.83]**	2.03 [0.95, 4.29]	1.48 [0.65, 3.38]	ACA+OBI			
ACA	**0.42 [0.27, 0.66]**	1.13 [0.59, 2.14]	0.9 [0.5, 1.62]	0.53 [0.25, 1.11]	1.91 [0.81, 4.48]	0.85 [0.4, 1.78]	0.62 [0.27, 1.4]	**0.42 [0.27, 0.64]**	ACA		
IBR+VEN	1.35 [0.74, 2.51]	**3.59 [1.69, 7.76]**	**2.88 [1.41, 5.95]**	1.7 [0.73, 3.99]	**6.11 [2.39, 15.76]**	**2.7 [1.16, 6.36]**	1.97 [0.79, 4.96]	1.33 [0.62, 2.88]	**3.19 [1.51, 6.85]**	IBR+VEN	
IBR+OBI	1.35 [0.74, 2.47]	**3.59 [1.69, 7.66]**	**2.88 [1.41, 5.88]**	1.7 [0.73, 3.94]	**6.1 [2.39, 15.57]**	**2.69 [1.16, 6.29]**	1.97 [0.79, 4.9]	1.33 [0.63, 2.85]	**3.18 [1.52, 6.74]**	1 [0.42, 2.35]	IBR+OBI
VEN+OBI	1.1 [0.7, 1.75]	**2.93 [1.53, 5.63]**	**2.35 [1.29, 4.28]**	1.39 [0.65, 2.93]	**4.98 [2.12, 11.7]**	**2.2 [1.04, 4.67]**	1.6 [0.71, 3.65]	1.08 [0.57, 2.09]	**2.6 [1.38, 4.92]**	0.81 [0.38, 1.75]	0.82 [0.38, 1.73]	VEN+OBI
SUCRA	29%	86%	72%	42%	98%	68%	50%	28%	78%	13%	13%	23%

10 RCTs

4,171 patients

- Targeted therapies had distinct relative safety profiles
- Therapies appear to be safer as monotherapy rather than in combination with immunological agents in patients with advanced age and/or comorbidities
- Next-generation BTKis had the most favorable safety profile
- Zanubrutinib was associated with the lowest risk of AEs leading to treatment discontinuation

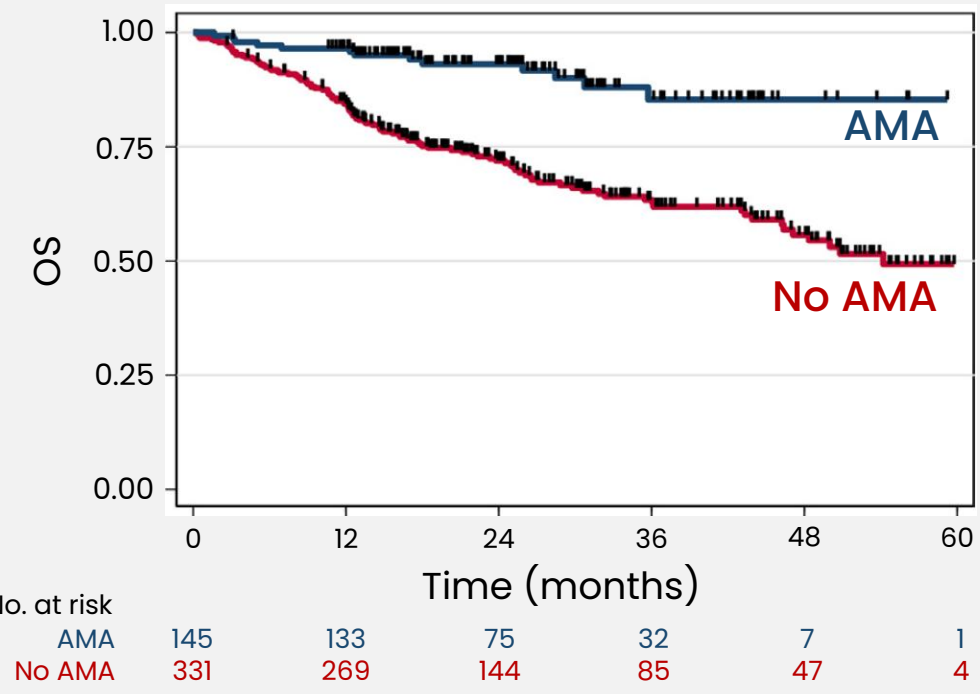
*Data presented as OR (95% CI).
ACA, acalabrutinib; AE, adverse event; BEND, bendamustine; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLB, chlorambucil; CLL, chronic lymphocytic leukemia; IBR, ibrutinib; OBI, obinutuzumab; OFA, ofatumumab; OR, odds ratio; RCT, randomized controlled trial; RTX, rituximab; SUCRA, surface under the cumulative ranking curve; VEN, venetoclax; ZAN, zanubrutinib.
Stożek-Tutro A *et al. Crit Rev Oncol Hematol* 2024; 201: 104428.

A secure patient care pathway

Outpatient medical assistance

- Secure outpatient care and education
- Screen for frailty
- Manage comorbidities
- Detect side effects early
- Monitor treatment adherence
- Reinforce links with homecare providers

AMA weekly telephone monitoring program
N=476 patients on BTKi (11 French centers)



50%
Reduction in early Ibr discontinuation

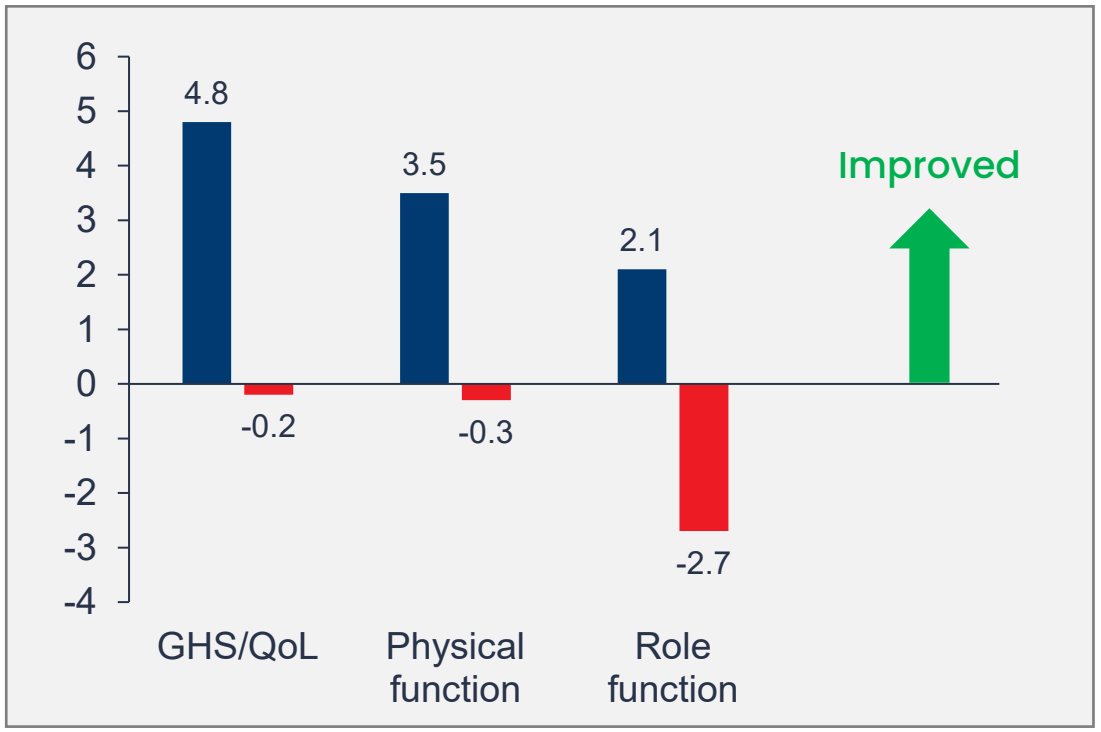
30%
Reduction in toxicity-related Ibr withdrawal

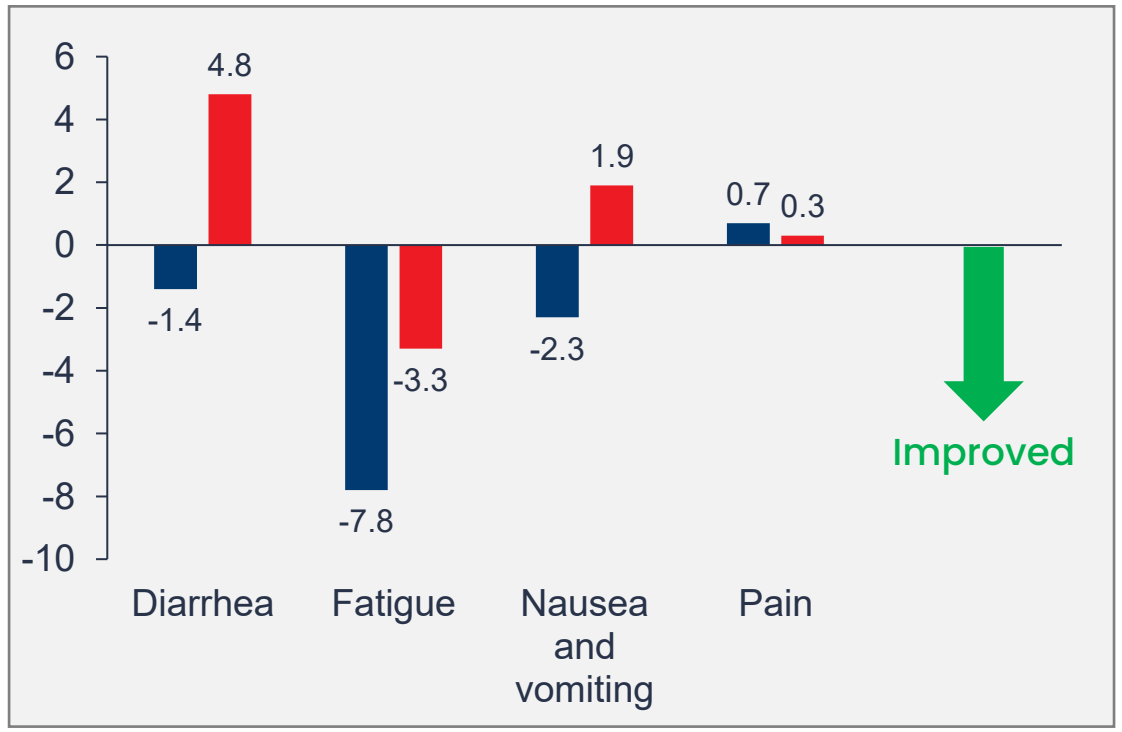
AMA, assistance medical ambulatoire (outpatient medical assistance); BTKi, Bruton's tyrosine kinase inhibitor; Ibr, ibrutinib; OS, overall survival.
Ysebaert L *et al. Eur J Cancer* 2020: 135: 170-172.

CLL patient profile

Improved quality of life with zanubrutinib vs. BR

SEQUOIA study: LS mean change from baseline to Week 24 in QLQ-C30 scales





BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; GHS, global health status; LS, least squares; QLQ-C30, Quality of Life Questionnaire - Core 30; QoL, quality of life.

Ghia P *et al. Curr Med Res Opin* 2023; 39 (11): 1505–1511.

CLL treatment selection recommendations

FILO relapse treatment algorithm

APRIL 2025

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

R/R post ICT

- **Ven-R**

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

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

Preferred for patients with *TP53* mutation

R/R with continuous cBTKi

Refractory

Ven-R

Intolerant

1. **Ven-R**
2. **Switch cBTKi**

In the absence of resistance mutations

R/R post Ven-Obi / R/R post Ibr-Ven

Assess time to relapse

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

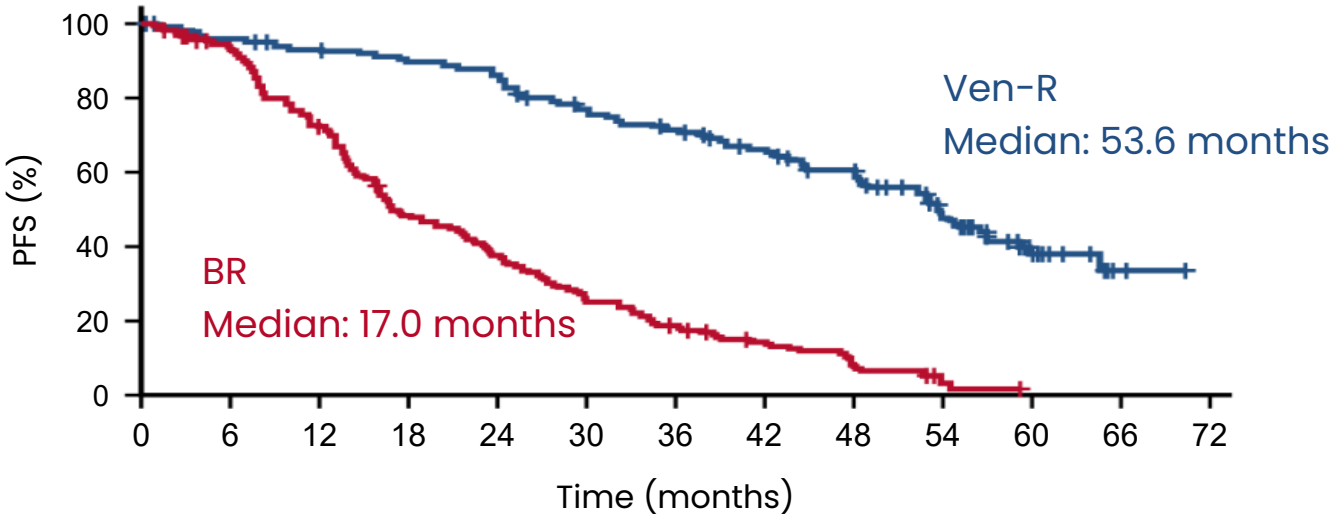
In the absence of resistance mutations

Acala, acalabrutinib; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; FILO, French Innovative Leukemia Organization; Ibr, ibrutinib; ICT, immunochemotherapy; IGHV, immunoglobulin heavy chain variable region genes; 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 May 2025.

R/R CLL treatment selection
Venetoclax-rituximab

The MURANO study: PFS



Ven-R	194	185	176	170	161	142	132	116	99	57	15	3
BR	195	165	128	84	65	44	31	21	11	2		

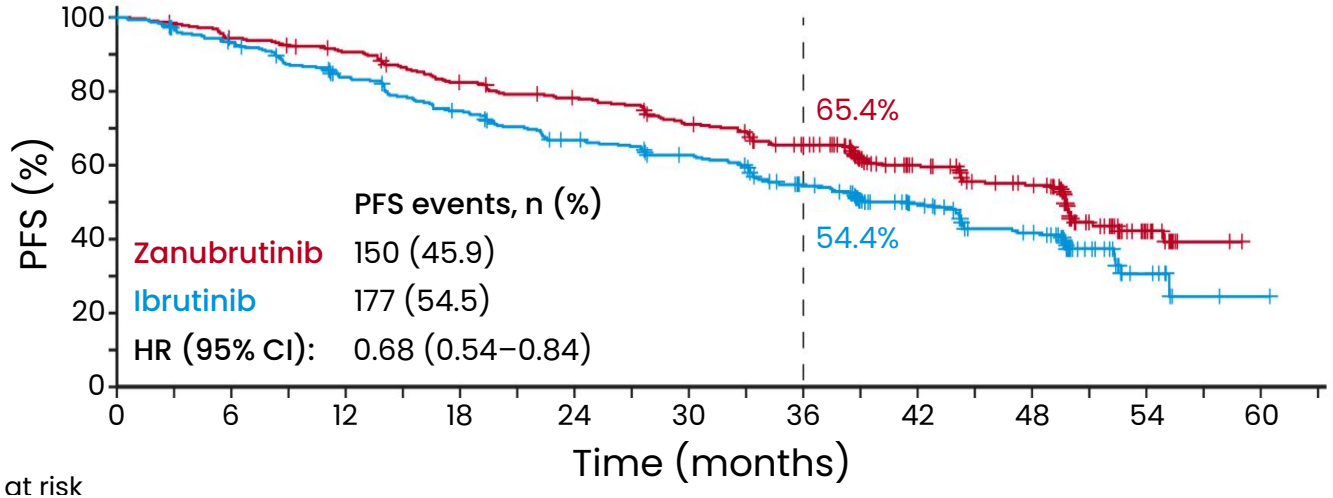
- Patients with prior exposure to venetoclax were excluded
- Median TTNT
  - Ven-R: 57.8 months
  - BR: 23.9 months
- Ven-Obi is not currently approved in the relapsed setting

BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; Obi, obinutuzumab; PFS, progression-free survival; R, rituximab; R/R, relapsed/refractory; TTNT, time to next treatment; Ven, venetoclax.
Seymour JF *et al. Blood* 2022; 140 (8): 839–850.

R/R CLL treatment selection

Head-to-head trials of BTKis in the relapsed setting

ALPINE study[1]
Zanubrutinib vs. ibrutinib
Median follow-up: 42.5 months

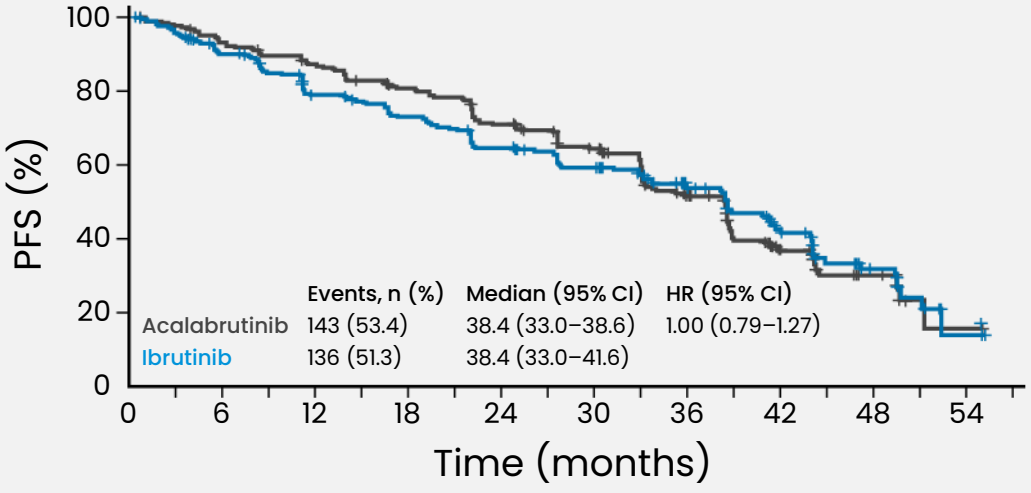


No. at risk

Zanu	327	315	302	295	287	272	258	247	242	236	218	210	189	151	128	109	104	43	19	2	0	0
Ibr	325	305	293	273	258	242	229	212	200	194	183	173	148	116	101	77	74	30	10	2	1	0

Sustained PFS benefit with zanubrutinib over ibrutinib, consistent across sensitivity analyses[1]

ELEVATE-RR[2]
Acalabrutinib vs. ibrutinib in patients with del(17p) and/or del(11q)
Median follow-up: 40.9 months



Median PFS with acalabrutinib with del(11q) or del(17p): 38.4 months[2]

This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison.
BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; del, deletion; HR, hazard ratio; Ibr, ibrutinib; PFS, progression-free survival; R/R, relapsed/refractory; Zanu, zanubrutinib.
1. Brown JR *et al. Blood* 2024; 144 (26): 2706–2717. 2. Byrd JC *et al. J Clin Oncol* 2021; 39 (31): 3441–3452.

Summary

- Most patients with previously untreated CLL will have multiple viable treatment options
- Treatment strategies can be broadly categorized into fixed-duration therapies and continuous BTKi regimens
- Finding an appropriate treatment for a patient involves evaluation of multiple factors, including:
  - Patient profile (fitness, age, comorbidities) and preferences (shared medical decision)
  - Disease profile (bulky or infiltrative, prognostic factors: IGHV status, *TP53* status, complex karyotype)
  - Treatment profile (including the risk of cardiotoxicity, TLS, infections)
  - Possible therapeutic sequences
  - The cost to society

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain variable region genes; TLS, tumor lysis syndrome.
Speaker's opinion.

MANAGING INFECTION RISKS IN CHRONIC LYMPHOCYTIC LEUKEMIA

Helen Parry
University of Birmingham,
University Hospitals Birmingham,
UK

✦ ✦ ✦

BeOne

Objectives

Review the burden of disease- and therapy-related immune suppression and infection risk in CLL

Outline approaches to assessing and diagnosing secondary immune deficiency in CLL patients

Review current strategies and best practice in infection prevention management

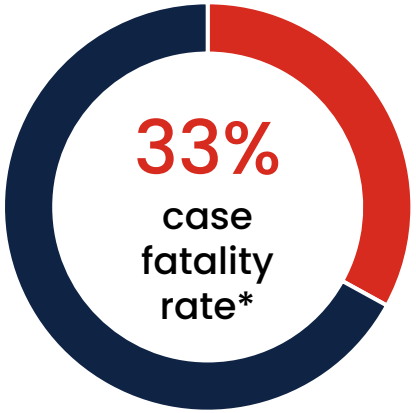
CLL, chronic lymphocytic leukemia.

Infection-related mortality is a major risk in CLL

- Up to 80% of patients with CLL will develop a serious infection at some point[1]
  - 30%–50% die from infection

International cohort study of patients with CLL and symptomatic COVID-19[2]

N=198



39% naive to CLL treatment and 45% receiving CLL treatment at COVID-19 diagnosis

ERIC/CLL Campus joint study of patients with CLL and symptomatic COVID-19[3]

N=190

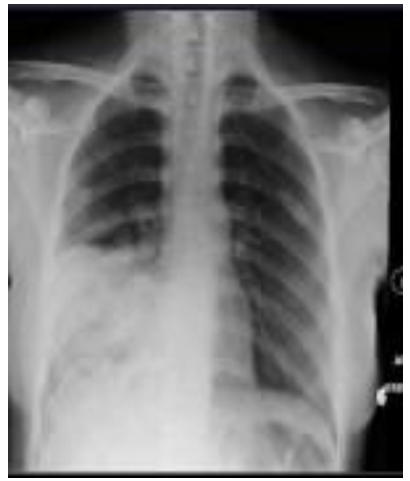
40% of patients with severe COVID-19 received current or recent (≤12 months) treatment for CLL

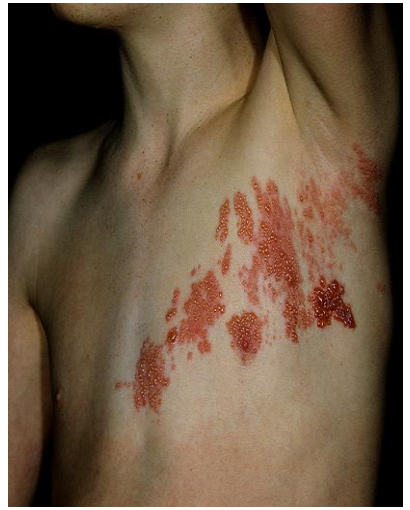
*After median follow-up of 16 days. †After median follow-up of 23 days.
CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019.
1. Murru R *et al. Ann Hematol* 2024; 103 (5): 1655–1664. 2. Mato A *et al. Blood* 2020; 136 (10): 1134–1143. 3. Scarfò L *et al. Leukemia* 2020; 34: 2354–2363.

Immune impairment can be multifactorial in CLL

Infection manifestations can provide insights

- **Hypogammaglobulinemia**
  - Low IgG present in ~25% of patients at diagnosis[1]
  - Increased risk of infection from encapsulated bacteria (e.g. Pneumococcus)[2]
- **Cellular immune dysfunction**
  - VZV reactivation in 28% (133/473); median age: 61 years[3]
  - Often on >1 occasion[3]
- **Combined deficiency**[2,4]
  - Influenza, COVID-19, common cold viruses
- **Neutrophil, macrophage, $CD4^+$ T-cell depletion**
  - Opportunistic infections (e.g. Pneumocystis, Aspergillus)[5]



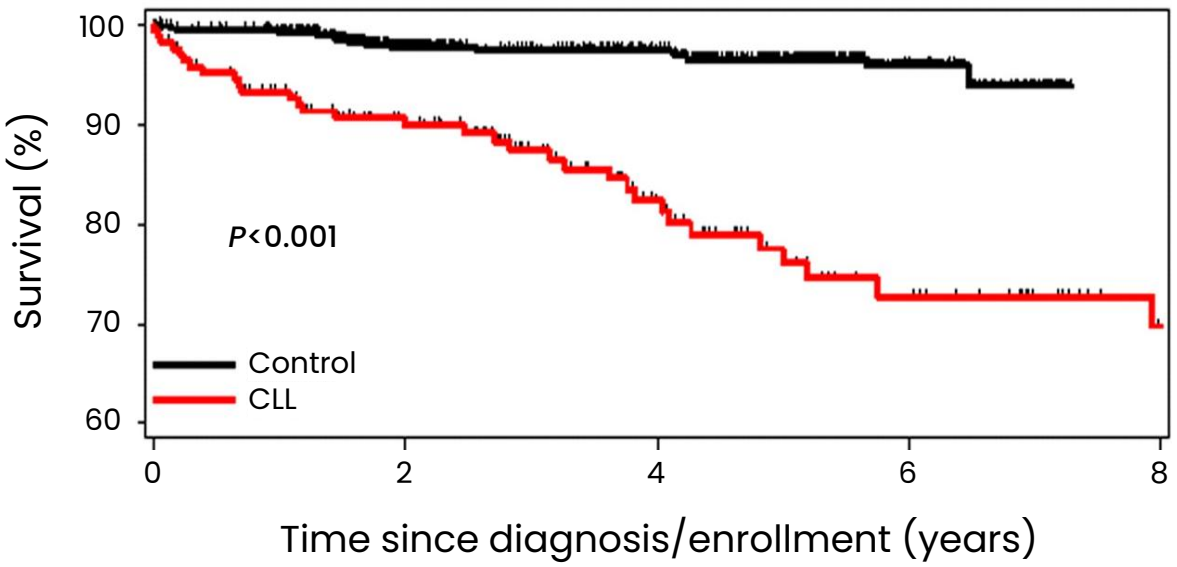


Images provided with patient consent.
CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; VZV, varicella zoster virus.
1. Parikh SA *et al. Cancer* 2015; 121 (17): 2883–2891. 2. Jolles S *et al. Blood Rev* 2023: 58: 101020. 3. Parry *et al.* unpublished data. 4. Kwok M *et al. BMJ Case Rep* 2021; 14: e235981. 5. Langerbeins P, Eichhorst B. *Acta Haematol* 2021; 144 (5): 508–518.

Infection morbidity is apparent early in the disease course

Early-stage CLL

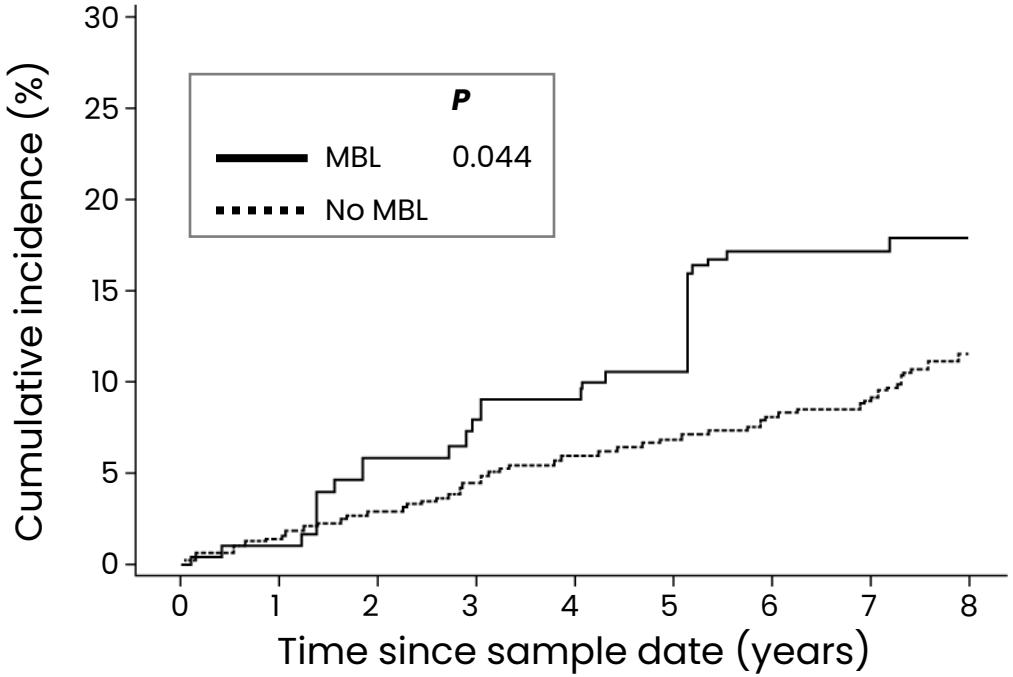
Survival-free hospitalizations for infection versus controls*,[1]



Control	689	500	338	105	0
CLL	174	122	72	41	22

Monoclonal B-cell lymphocytosis

Cumulative incidence of hospitalization for infection versus controls*,[2]



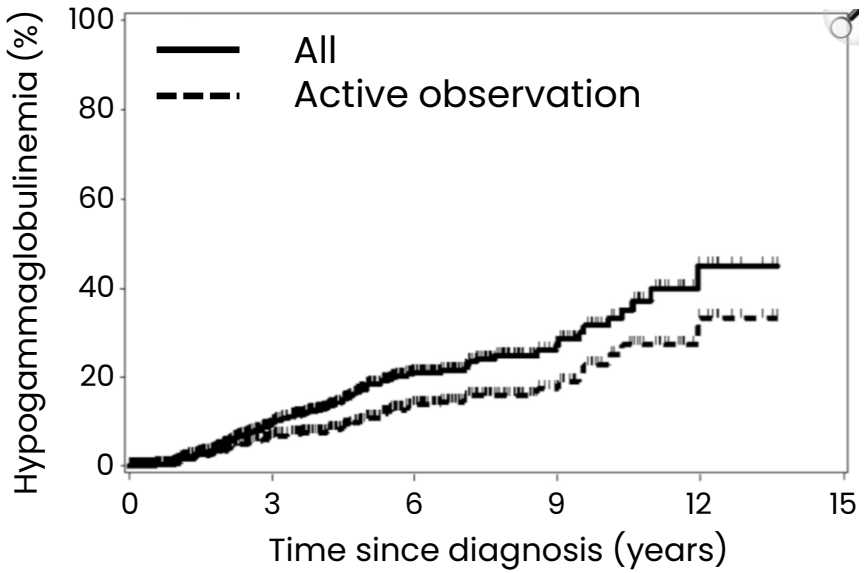
MBL	106	101	96	81	67	63	49	47	28
No MBL	865	839	821	753	690	677	505	490	189

*Adjusted for age and sex.
CLL, chronic lymphocytic leukemia; MBL, monoclonal B-cell lymphocytosis.
1. Moreira J *et al. Blood* 2011; 118 (21): 4610. 2. Shanafelt TD *et al. Leukemia* 2021; 35 (1): 239–244.

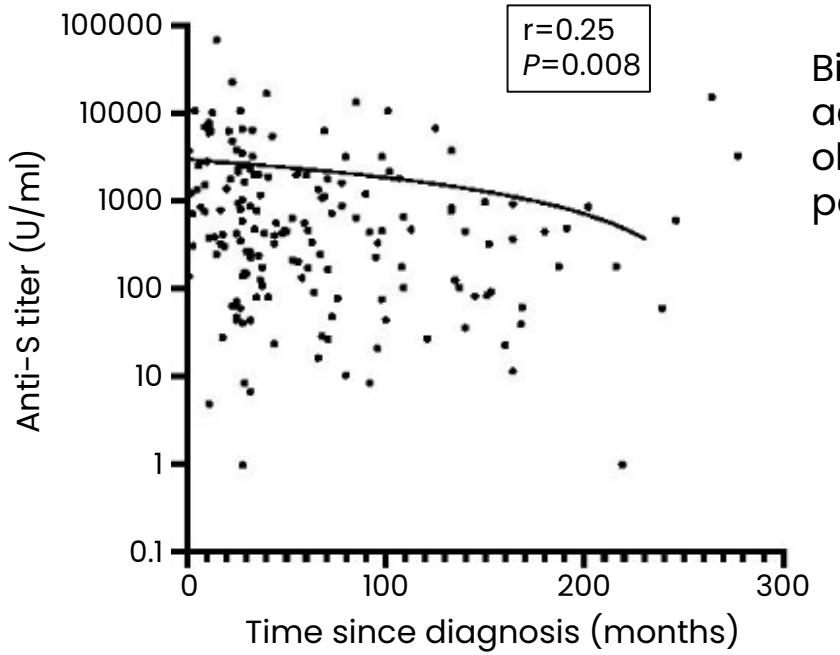
Active observation in CLL

Watching the immune system decline

Risk of acquired hypogammaglobulinemia[1]



Antibody titers following primary vaccine course compared to time since diagnosis[2]



Binet A, active observation participants

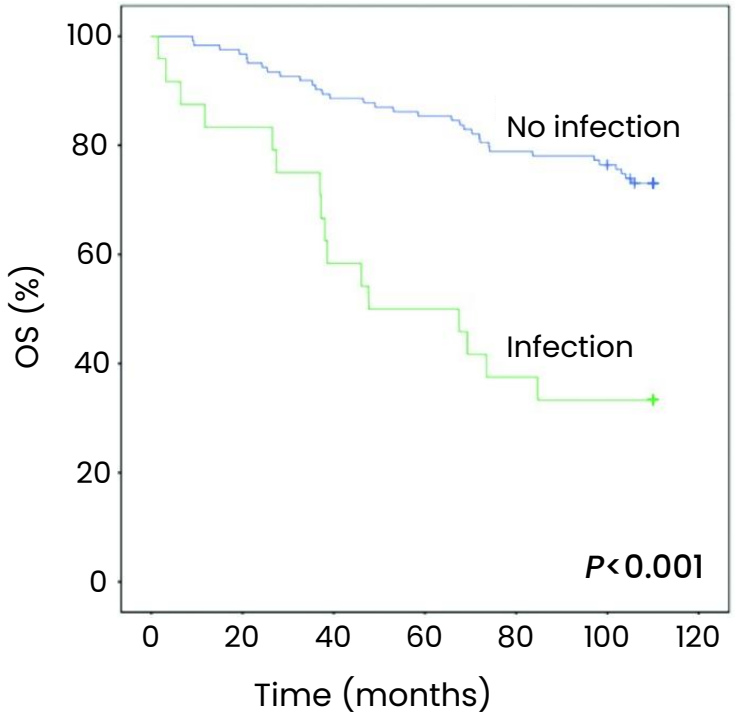
- The 5-year cumulative incidence of severe infection in treatment-naive patients is 31%[3]
- Hypogammaglobulinemia is the most well-recognized immune defect; however, others arise, such as: T-cell and/or NK-cell suppression, complement system deficiencies, and innate immunity supported by the tumor microenvironment[4]

CLL, chronic lymphocytic leukemia; NK, natural killer.

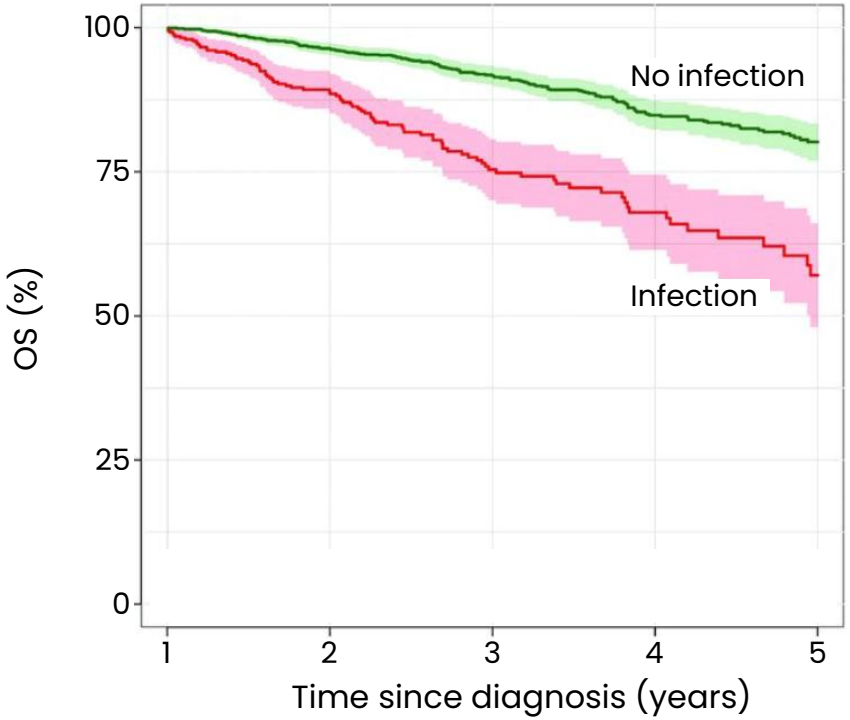
1. Parikh SA *et al. Cancer* 2015; 121 (17): 2883–2891. 2. Parry H *et al. J Hematol Oncol* 2022; 15 (1): 3. 3. Andersen MA *et al. Haematologica* 2018; 103 (7): e300–e303. 4. Langerbeins P, Eichhorst B. *Acta Haematol* 2021; 144 (5): 508-518.

The mortality associated with infection from diagnosis

OS in CLL patients with or without physician-documented infection in the first year of observation (N=147)[1]



Danish registry: OS in patients with CLL with or without infection within a year of diagnosis[2]



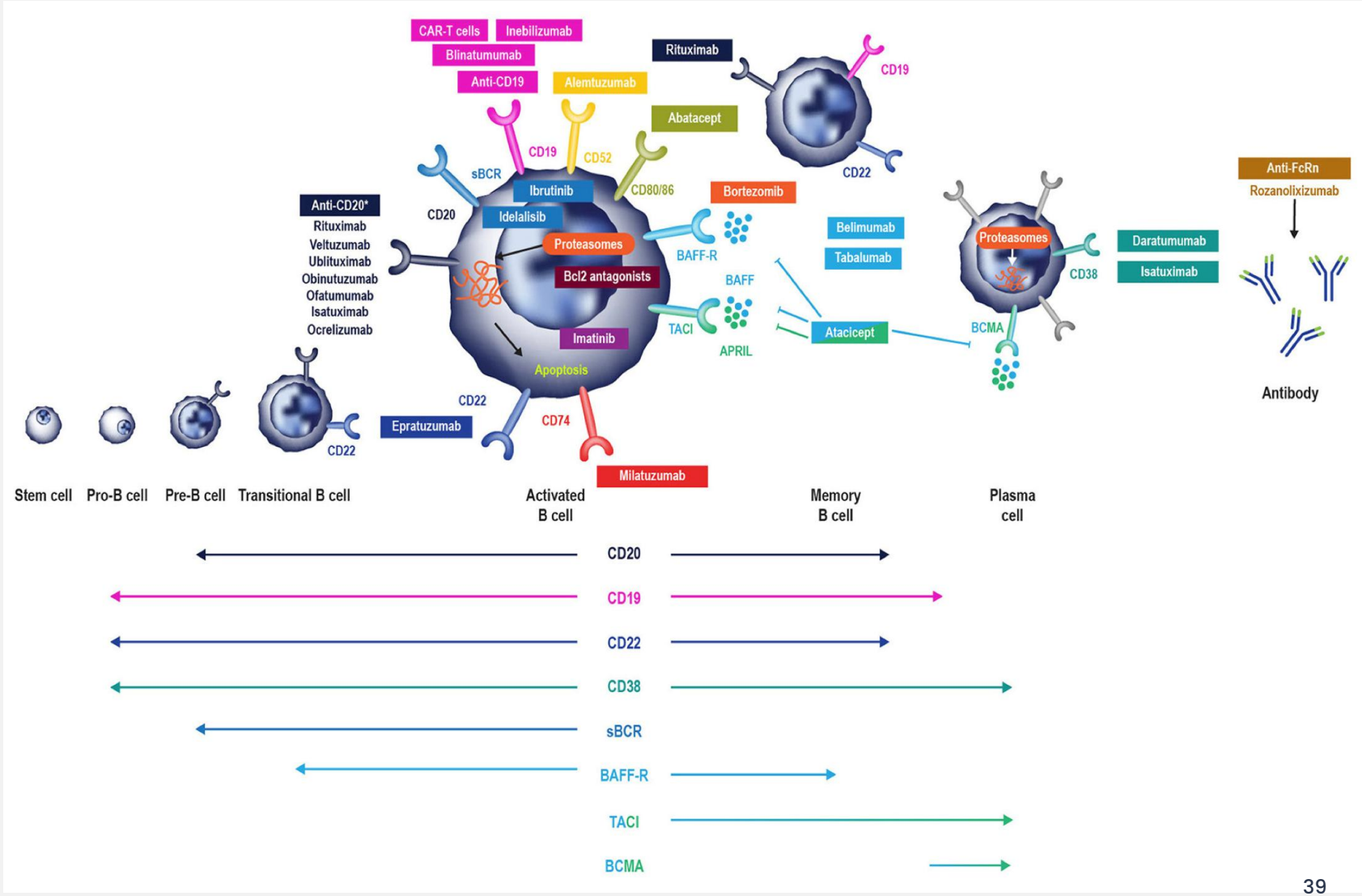
No infection	1505	1133	773	451	196
Infection	397	247	136	71	32

CLL, chronic lymphocytic leukemia; OS, overall survival.
1. Crassini KR *et al. Haematologica* 2018; 103 (7): e329. 2. Andersen MA *et al. Haematologica* 2018; 103 (7): e330.

Impact of therapy

- There is a differential impact of novel antigen exposure compared with historical infection with therapy type
- Paradoxically, these drugs are helping us to unravel more information about B-cell immunology[2]

B cell-specific chemotherapeutic causes of secondary antibody deficiency[1]



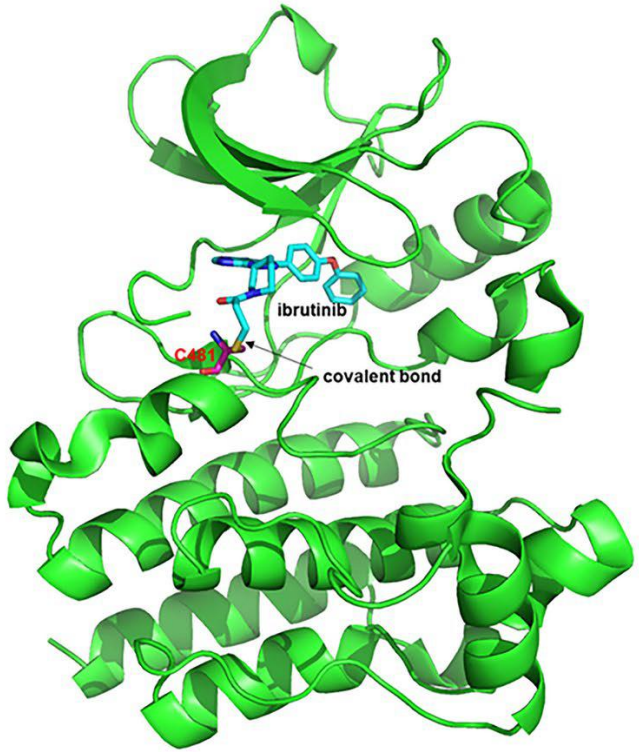
APRIL, A proliferation-inducing ligand; BAFF(-R), B-cell activating factor (receptor); BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; sBCR, stereotyped B-cell receptor; TACI, transmembrane activator, calcium modulator and cyclophilin ligand interactor.

1. Patel SY *et al. Front Immunol* 2019; 10: 33 (reproduced with permission from Srivastava S, Wood P. *Clin Med* 2016; 16: 571–576). 2. Speaker's opinion.

Covalent BTKi and infection risk

- Pooled data from 10 trials, involving 15 BTKi regimens* and 2,672 patients: 1 in 5 had a high-grade infection with up to 40.9 months of follow-up[1]
- Cumulative incidence of 20.7% from eight studies with BTKi monotherapy[1]
  - RWD cumulative infection incidence likely higher owing to a longer exposure to therapy[2]
- Treatment-naive 16.2% vs. relapsed/refractory 25.8%[1]
  - Pneumonia: 2.2%–10%
  - URTI: 0.4%–2.9%
  - UTI: 0%–4%
- Rarely invasive fungal infection and Pneumocystis jirovecii[3]
- Similar rates of infection among different BTKi by cross-trial comparison[4]
- Prophylaxis with antibiotic – no clear guidance:[2]
  - Up to 30% of patients are at risk of severe infection following BTKi-based therapy; however, more work is needed to identify those at risk[5]
  - Hepatitis B prophylaxis for those at risk[2]

BTK inhibition with ibrutinib[6]



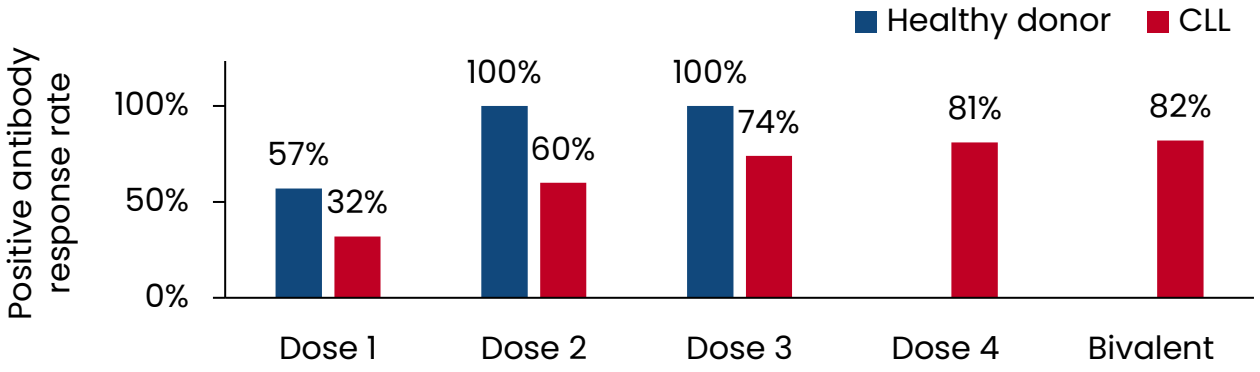
*Patients received regimens including the BTKis ibrutinib or acalabrutinib.

BTKi, Bruton's tyrosine kinase inhibitor; RWD, real-world data; URTI, upper respiratory tract infection; UTI, urinary tract infection.

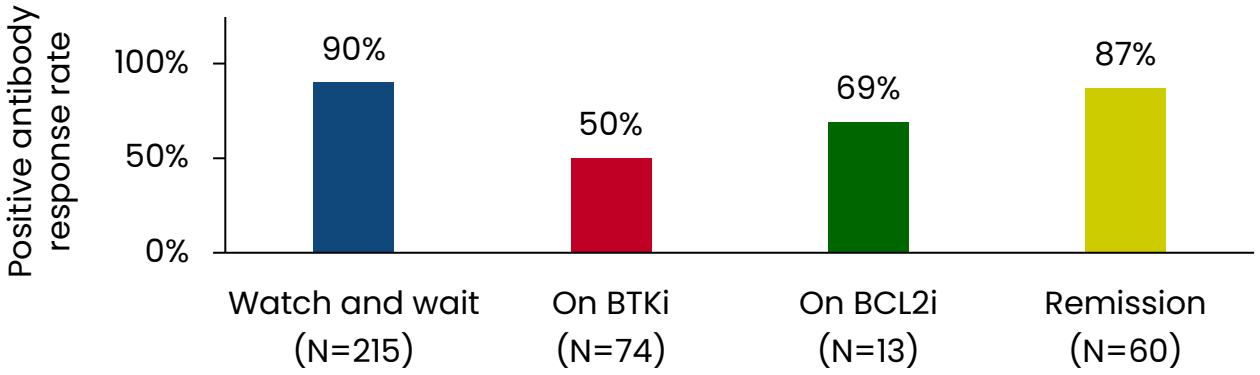
1. Vassipoulos S *et al. Clin Lymphoma Myeloma Leuk* 2022; 22_Suppl 2: S264. 2. Speaker's opinion. 2. Speaker's opinion. 3. Higuita NIA *et al. Open Forum Infect Dis* 2024; 11 (6): ofae115. 4. Yin S *et al. Ann Hematol* 2023; 103 (7): 2231–2244.
5. Mauro FR *et al. Crit Rev Oncol Hematol* 2024; 201: 104408. 6. Gu D *et al. J Hematol Oncol* 2021; 14: 40.

Patients treated with ibrutinib or acalabrutinib continue to have impaired responses despite multiple doses of vaccination*

500 patients vaccinated against SARS-CoV-2[1,2]

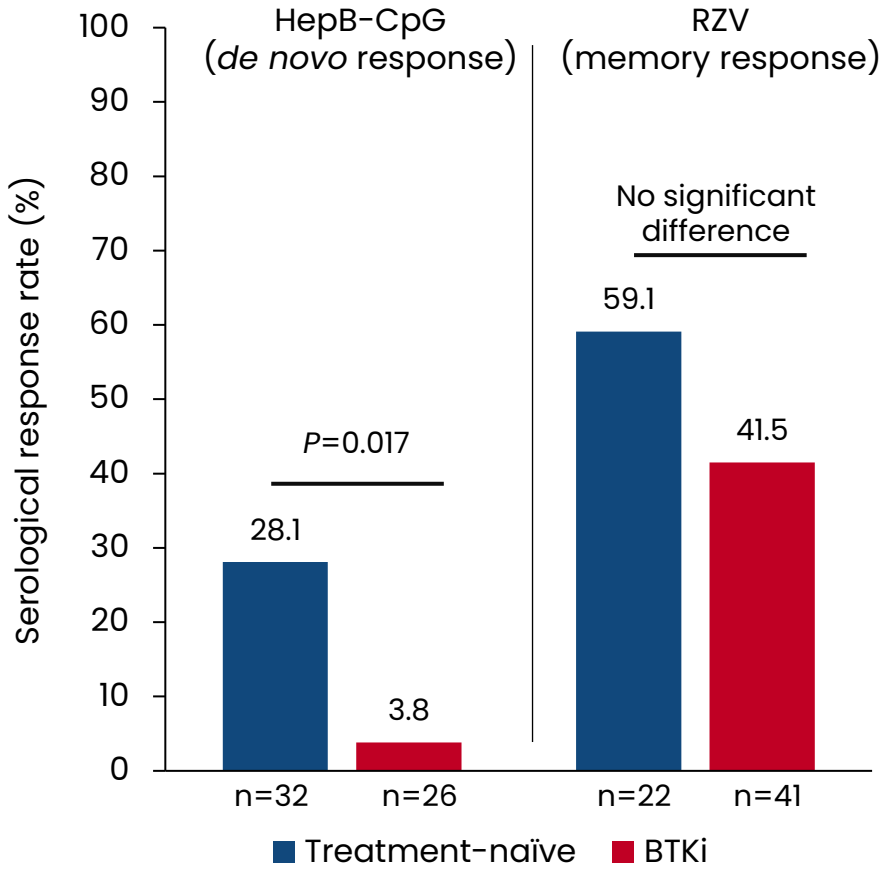


Lower response rate to SARS-CoV-2 vaccination on BTKi[1,2]



✦ Cellular immunity improves on BTKi therapy

Recall of memory responses may be more favorable than *de novo* responses on BTKi[3]



*Patients in these trials were treated with either ibrutinib or acalabrutinib.
BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; RZV, recombinant zoster virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
1. Parry H *et al. J Hematol Oncol* 2022; 15 (1): 3. 2. Parry *et al.* unpublished data. 3. Pleyer C *et al. Blood* 2021; 137 (2): 185–189.

Could pausing therapy work and if so, for how long?

IMPROVE study: RCT to assess the impact of pausing BTKi* around the time of vaccination

3-week pause of BTKi treatment, with vaccination on Day 7 **vs.** Continue BTKi treatment as normal

Primary outcome
S1-RBD antibody titers 3 weeks after COVID-19 booster vaccine†

Primary outcome at baseline, 3 weeks and 12 weeks‡

	Continue with BTKi group		Pause BTKi group		Geometric mean ratio, mixed-effects model§	*P*-value, mixed-effects model
	n	Geometric mean, U/mL	n	Geometric mean, U/mL		
Baseline	49	133.0 (82.2)	50	76.8 (97.1)	-	-
3 weeks	48	218.8 (122.9)	47	153.4 (103.2)	1.104 (0.565–2.158)	0.77
12 weeks	46	177.6 (95.3)	47	122.4 (92.5)	1.037 (0.529–2.035)	0.91

- No evidence pausing BTKi at the time of vaccination improves the immune response
- ~1/3 on BTKi will not develop an antibody response, even if treatment is paused ('at-risk' group)

*51 (52%) participants were taking ibrutinib therapy whereas 48 (48%) were taking acalabrutinib at 100 mg twice daily. †Assessed by quantitative Elecsys immunoassay (Roche Diagnostics). ‡Data are n, mean (SD), ratio (95% CI), or *P*.
§Presenting a model adjusted for baseline values to account for the difference between groups at baseline, BTKi treatment line (first or subsequent), COVID-19 infection status at baseline, and booster type as fixed effects, and with a treatment by time interaction.
BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; COVID-19, coronavirus disease 2019; RBD, receptor-binding domain. RCT, randomized controlled trial.
Cook JA *et al. Lancet Haematol* 2025; 12: e294–303.

BCL2i and infection

Typically combined with other immunosuppressive medication

Rates of neutropenia and infection events in the CLL13 trial*,[1]

Event	CIT (N=216)			Ven-R (N=237)			Ven-Obi (N=228)			Ven-Obi-Ibr (N=231)		
	G1/2, %	G3, %	G4, %	G1/2, %	G3, %	G4, %	G 1/2, %	G3, %	G4, %	G1/2, %	G3, %	G4, %
Neutropenia	3.2	15.7	29.6	5.9	23.6	16.0	3.5	22.4	22.8	6.1	16.9	24.2
Febrile neutropenia	0	10.6	0.5	0	4.2	0	0.4	3.1	0	0	6.5	1.3
Infections	41.2	17.6	0.9	47.7	10.1	0.4	53.1	13.2	0	53.2	20.8	0.4
URTI	19.4	0.9	0	30.8	2.1	0	36	2.2	0	33.8	0.9	0
UTI	4.2	0.9	0	5.5	2.1	0	6.1	1.3	0	10.4	3.9	0
Pneumonia	2.8	5.6	0	1.7	1.7	0	3.9	5.3	0	6.1	6.1	0.4
Infection, NOS	5.1	2.3	0	2.1	0.4	0	3.1	1.8	0	2.2	1.7	0
Influenza	0.9	2.3	0	3.4	1.3	0	3.9	0	0	2.2	1.3	0

- Rates of infections, particularly pneumonia in first-line setting, were higher with Ven-Obi and Ven-Obi-Ibr than Ven-R[1]
- Neutropenia can be problematic but usually does not translate into febrile neutropenia[1]
- Elimination of CLL cells by Ven-Obi treatment can reverse T-cell dysfunction, restoring T-cell activation and proliferation[2]
- Currently, there are insufficient data to support prophylaxis in fixed-duration treatment[3]
  - Hepatitis B prophylaxis should be mandated for patients who are hepatitis B-positive[4]

*Excluding rates of anemia, leukopenia and thrombocytopenia.
BCL2i, B-cell lymphoma 2 inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; Ibr, ibrutinib; NOS, not otherwise specified; Obi, obinutuzumab; R, rituximab; URTI, upper respiratory tract infection; UTI, urinary tract infection; Ven, venetoclax.
1. Eichorst B *et al. New Engl J Med* 2023; 388: 1739–1754. 2. van Bruggen JAC *et al. Blood Adv* 2022; 6 (14): 4185–4195. 3. Mauro FR *et al. Crit Rev Oncol Hematol* 2024; 201: 104408. 4. Speaker's opinion.

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Neutropenia	3.2	15.7	29.6	5.9	23.6	16.0	3.5	22.4	22.8	6.1	16.9	24.2
Febrile neutropenia	0	10.6	0.5	0	4.2	0	0.4	3.1	0	0	6.5	1.3
Infections	41.2	17.6	0.9	47.7	10.1	0.4	53.1	13.2	0	53.2	20.8	0.4
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1. Eichorst B *et al. New Engl J Med* 2023; 388: 1739–1754. 2. van Bruggen JAC *et al. Blood Adv* 2022; 6 (14): 4185–4195. 3. Mauro FR *et al. Crit Rev Oncol Hematol* 2024; 201: 104408. 4. Speaker's opinion.

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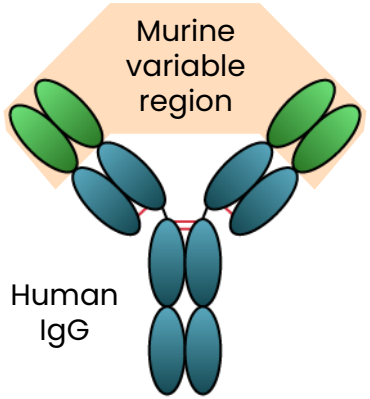
Anti-CD20 treatment

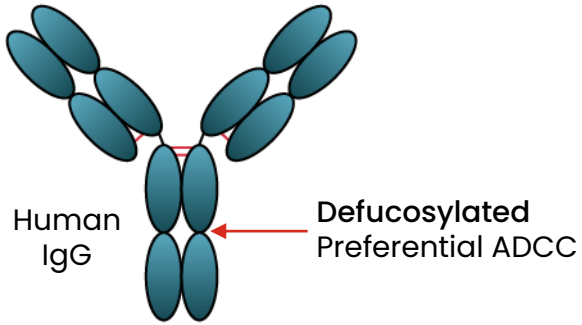
Rituximab



Type I	
Direct killing	+
CDC	+++
ADCC	++
ADP	++

Engineered differences between anti-CD20 mAbs[1]

Obinutuzumab



Type II	
Direct killing	+++
CDC	+
ADCC	+++
ADP	+++

- Profound and lasting suppression of B-cell populations – may be heterogeneous across patients[2,3]
- Counseling should be considered for patients exposed to Ven-Obi and Ven-R – as they are at risk of B-cell depletion until reconstitution[2–4]

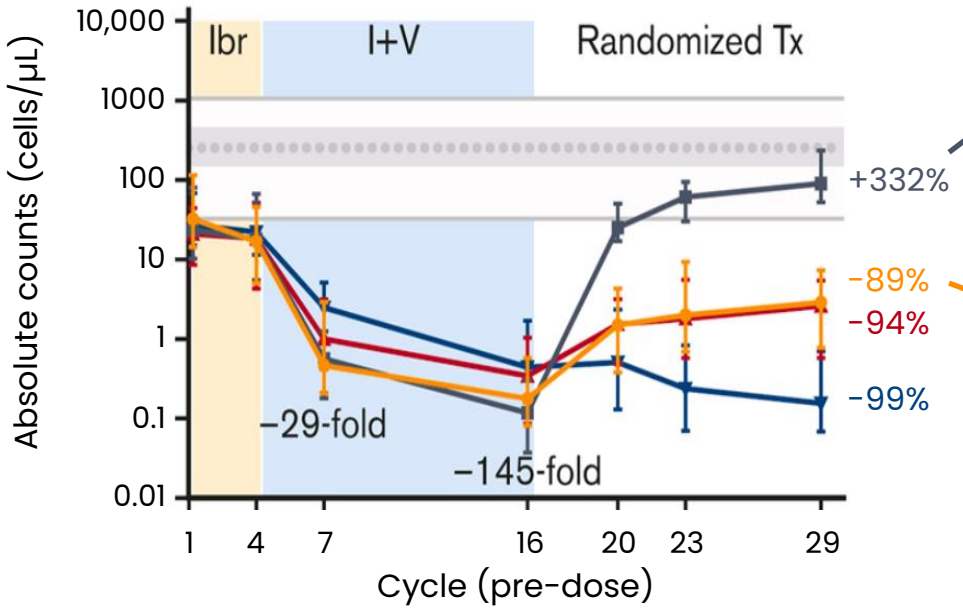
Should we be re-vaccinating upon reconstitution or are long-lived plasma cells sufficiently repleted?

ADCC, antibody-dependent cell-mediated cytotoxicity; ADP, antibody-dependent phagocytosis; CD, cluster of differentiation; CDC, complement-dependent cytotoxicity; IgG, immunoglobulin G; mAb, monoclonal antibody; Obi, obinutuzumab; R, rituximab; Ven, venetoclax.

1. Pierpont TM *et al. Front Oncol* 2018; 8: 163. 2. Moser T *et al. Ther Adv Neurol Disord* 2022; 15: 17562864221092092. 3. Shields AM *et al. Clin Exp Immunol* 2021; 207 (1): 3–10. 4. Speaker's opinion.

Fixed-duration ibrutinib + venetoclax and immune reconstitution

Absolute counts of normal B cells in the CAPTIVATE study*



- Patients with confirmed uMRD randomized to placebo showed ‘normal’ B-cell counts 4 months after finishing active therapy
- Patients with uMRD who continued on BTKi monotherapy showed improvement on stopping venetoclax
  - But B-cell numbers remain below the ‘normal’ range
- **Will this influence clinical practice in the longer term?**

*Data points represent median values, and error bars represent the interquartile range. For GLOW data, samples at Cycle 28 were available only for patients with a best overall response of complete response (n=6 per arm).
BTKi, Bruton’s tyrosine kinase inhibitor; Ibr, ibrutinib monotherapy; IQR, interquartile range; I+V, ibrutinib + venetoclax; MRD, minimal residual disease; uMRD, undetectable minimal residual disease.
Moreno C *et al. Blood Adv* 2023; 7 (18): 5294–5303.

How can we identify patients at risk?[1]

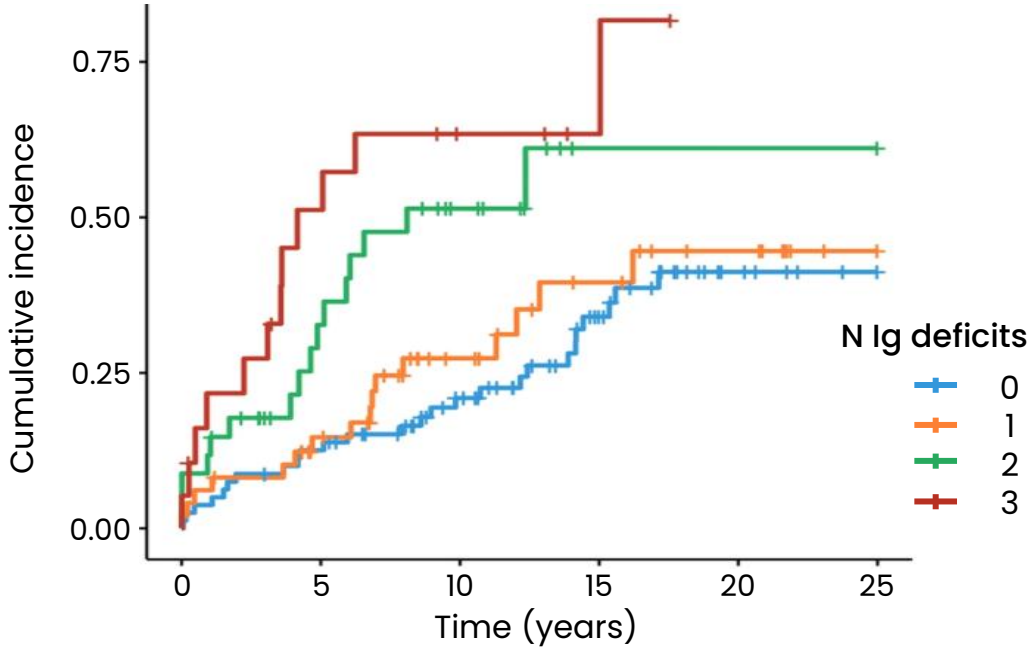
Medical history factors:

- Recurrent infections
- Grade 3 infection / ITU stay
- CLL treatment history[2]

Biological disease factors:

- Low serum Igs (IgA/IgG pan-hypogammaglobulinemia) +/- bronchiectasis[2–4]
- Increasing age / frailty[2,4]
- Unmutated IGHV[2,4]
- B2M[4]

Increased numbers of deficient Ig classes are associated with increased infection risk[2]



- CLL Treatment Infection Model (CLL-TIM) identifies patients at risk of infection or CLL treatment within 2 years of diagnosis[5]
  - Ensemble algorithm composed of 28 machine learning algorithms based on data from 4,149 patients with CLL (used in the PreVent-ACaLL study)
- **Current iwCLL criteria do not include serious infection as an indication for treatment[6]**

B2M, beta-2 macroglobulin; CLL, chronic lymphocytic leukemia; Ig, immunoglobulin; IGHV, immunoglobulin heavy chain variable; ITU, intensive treatment unit; iwCLL, International Workshop on Chronic Lymphocytic Leukemia.

1. Speaker's opinion. 2. Murru R *et al. Ann Hematol* 2024; 103 (5): 1655–1664. 3. Wand O *et al. Eur Resp J* 2023; 62 (Suppl 67): Abstract PA387. 4. Andersen MA. *et al. Haematologica* 2018; 103 (7): e300–e303.
5. Agius R *et al. Nat Comm* 2020; 11: 363. 6. Hallek M *et al. Blood* 2018; 131 (25): 2745–2760.

Identifying those at high risk in clinical practice

1. Establish previous infection history – previous hospitalization, types of infection and number of antibiotics per year. Any bronchiectasis? CT scan
2. Check serum immunoglobulins – which and number of subtypes are deficient?
3. Consider CD4 T-cell count (lymphocyte subsets <200)
4. Age and comorbidity

*If infection history is significant, check FNABs and document vaccine response

CD, cluster of differentiation; CT, computed tomography; FNAB, functional antibody.
Speaker's opinion.

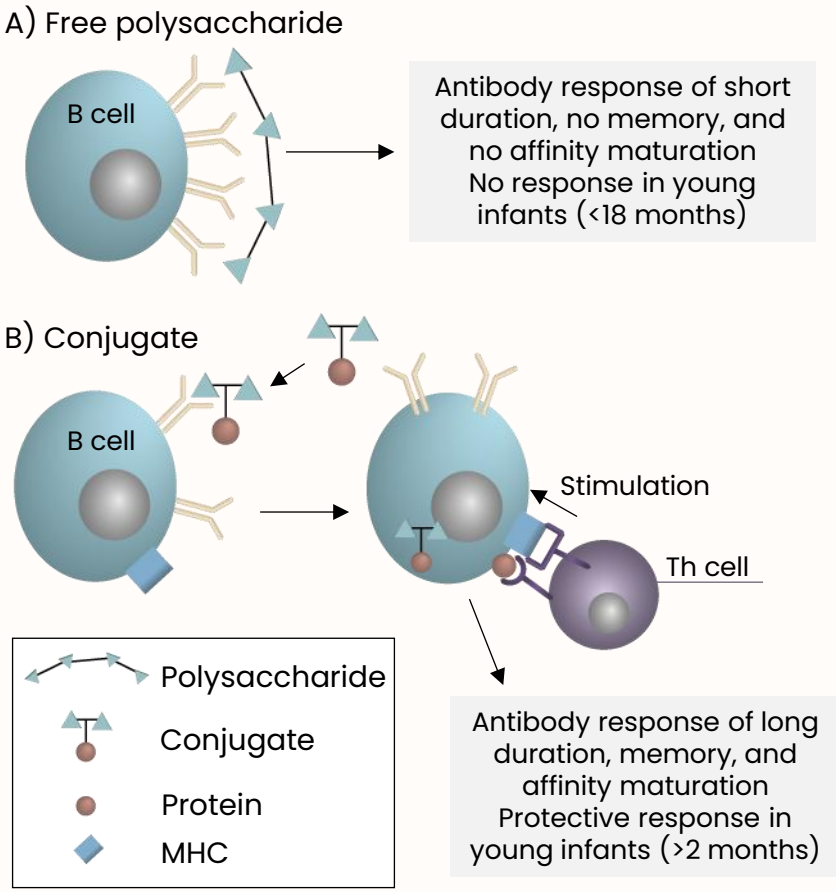
Vaccination – when and which?

- At diagnosis[1] – the earlier the better and before treatment[2]
- Conjugate pneumococcal vaccine ± Hemophilus influenzae B*,[1,3]
- ≥2 months later – polysaccharide vaccine[1]
- Recombinant varicella vaccine[1]
  - Not live so can be given to immunocompromised patients[1,4]
  - Shows 87.2% efficacy (95% CI: 44.2%–98.6%) in patients with hematologic malignancies†,[4]
    - Consider even if patient has prior history of shingles[2]
- Influenza[1] / COVID-19[1] / RSV (if eligible and aged >50 years)[5]
- Remember household members[1]

Assess response with functional antibody testing in patients at risk[2]

Allows response assessment and insight into underlying immune impairment

T cell-independent and -dependent responses to polysaccharide and glycoconjugate vaccines[6]

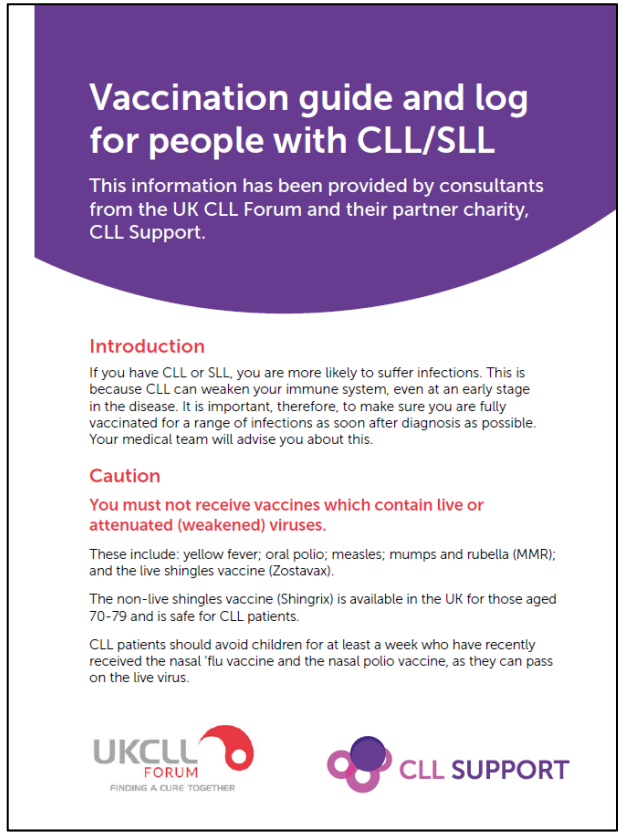


*Depending on local recommendations. †During or following a cancer therapy course; antiviral prophylaxis in line with local standard of care was permitted.
CI, confidence interval; COVID-19, coronavirus disease 2019; MHC, major histocompatibility complex; RSV, respiratory syncytial virus.

1. Walewska R *et al. Br J Haematol* 2022; 197: 544–557. 2. Speaker's opinion. 3. Guarana M, Nucci M. *Hematol Transfus Cell Ther* 2023; 45 (3): 387–393. 4. GlaxoSmithKline Biologicals s.a. Herpes zoster vaccine (recombinant, adjuvanted) – summary of product characteristics; April 2025. 5. GlaxoSmithKline Biologicals s.a. Respiratory Syncytial Virus (RSV) vaccine (recombinant, adjuvanted) – summary of product characteristics; October 2024. 6. Poolman J, Borrow R. *Expert Rev Vaccines* 2011; 10 (3): 307–322.

Avoid live vaccines

- Often the advice to avoid live vaccines is overlooked[1]
  - Measles, mumps, rubella (MMR combined vaccine) – IVIG if exposure and at risk[2]
  - Rotavirus[2]
  - Smallpox (relevant for Mpox)[2]
  - Chickenpox and live shingles vaccine – acyclovir if exposure and at risk[2]
  - Yellow fever[2]
- Vaccination booklet associated with the British Society of Haematology guidelines[3]



Vaccination guide and log for people with CLL/SLL

This information has been provided by consultants from the UK CLL Forum and their partner charity, CLL Support.

Introduction

If you have CLL or SLL, you are more likely to suffer infections. This is because CLL can weaken your immune system, even at an early stage in the disease. It is important, therefore, to make sure you are fully vaccinated for a range of infections as soon after diagnosis as possible. Your medical team will advise you about this.

Caution

You must not receive vaccines which contain live or attenuated (weakened) viruses.

These include: yellow fever; oral polio; measles; mumps and rubella (MMR); and the live shingles vaccine (Zostavax).

The non-live shingles vaccine (Shingrix) is available in the UK for those aged 70-79 and is safe for CLL patients.

CLL patients should avoid children for at least a week who have recently received the nasal 'flu vaccine and the nasal polio vaccine, as they can pass on the live virus.

UKCLL FORUM
FINDING A CURE TOGETHER

CLL SUPPORT

What vaccinations should I have?

Your medical team will advise you, but the most useful vaccines you should consider are:

'Flu vaccine

This may not work for you as well as for people without CLL, but it should offer at least some protection. You should have this vaccine annually. Your close family should be vaccinated too as this will protect them from getting 'flu and from passing it on to you.

Pneumonia

For pneumococcus, modern practice for CLL patients is to give two vaccines some time apart. These are known as Prevnar 13® (child vaccine) and the usual Pneumovax 23. You should talk to your CLL consultant about having these. Your G.P. may not be aware of this. This can be repeated every 5 years. Your doctor will advise when you may need to renew it.

Coronavirus vaccine

It is important to remain up to date with the recommended doses of vaccination because protection wanes. You should have three primary doses plus two further boosters 3 to 6 months apart. It is likely that further booster doses will be recommended in future.

Shingrix vaccine

Protects against shingles. Available for those aged 70–79 years old.

Adapted from Walewska, R, Parry-Jones, N, Eyre, TA, Follows, G, Martinez-Calle, N, McCarthy, H, et al. (2022). Guideline for the treatment of chronic lymphocytic leukaemia. Br J Haematol. 2022; 00: 1– 14. https://doi.org/10.1111/bjh.18075

Useful resources for CLL/SLL patients and their families

UK CLL Forum

The main body representing CLL consultants, connecting CLL clinicians, scientists and researchers.
www.ukcllforum.org/

CLL Support

The charity partner of the UKCLL Forum. Managed by people directly affected by CLL and provide trusted guidance, support, free conferences and webinars.
www.cllsupport.org.uk/

Our sister charities also have lots of expertise and information:

Leukaemia Care:
www.leukaemiacare.org.uk/

Lymphoma Action:
www.lymphoma-action.org.uk

Blood Cancer UK:
www.bloodcancer.org.uk/

Macmillan:
www.macmillan.org.uk

Cancer research UK:
www.cancerresearchuk.org

Maggies:
www.maggies.org/

CLL Support on-line forum:
www.healthunlocked.com/cllsupport

NHS number:			Date of diagnosis:		
Treatment centre:			Specialist:		
Vaccine	Location/date MM/DD/YY	Location/date MM/DD/YY	Location/date MM/DD/YY	Location/date MM/DD/YY	Comments
Annual 'flu					Recommended annually
Prevnar 13 or 15® (whichever your GP stocks)					Once only- recommended at diagnosis*
Pneumovax® 23 (at least 2 months after Prevnar®)					Once only** - recommended at least 2 months after Prevnar®.***
Shingrix® vaccine x2					Once only course which includes 2 doses for those >50 years old, given 2-6 months apart. Recommended at diagnosis.
COVID-19					As recommended by Department of Health for immunocompromised
RSV vaccine					As recommended by Department of Health for those aged 75-79

CLL, chronic lymphocytic leukemia; IVIG, intravenous immunoglobulin; SLL, small lymphocytic lymphoma.
1. Speaker's opinion. 2. CLL Support and UKCLL Forum. Vaccination guide and log for people with CLL/SLL. Available at: https://cll1prod.wpengine.com/wp-content/uploads/2024/11/Vaccination-leaflet-v04-NOV-24-1.pdf. Accessed May 2025.
3. Walewska R *et al. Br J Haematol* 2022; 197: 544–557.

For those at higher risk with significant infection history

- Poor FNAB following Pneumovax 23 – but controversial especially when IgG is very low[1,2]
- Low serum immunoglobulins[1,2]
- 6 months of prophylactic antibiotics and no improvement documented[1,2]
- Persisting infections and hypogammaglobulinemia, co-manage with immunology and consider IGRT (SC vs. IV)[2,3]

FNAB, functional antibody; IgG, immunoglobulin G; IGRT, immunoglobulin replacement therapy; IV, intravenous; SC, subcutaneous.

1. NHS England. Updated Commissioning Criteria for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England (November 2019). Available at: https://igd.mdsas.com/wp-content/uploads/NHSE_Commissioning_Criteria_for_the_use_of_Ig_V1.4_November_2019.pdf. Accessed May 2025. 2. Speaker's opinion. 3. Noto A *et al. Front Immunol* 2023; 14: 1062376.

Alternative strategies

- To date, the focus has been on COVID-19[1]
  - Initial results with tixagevimab + cilgavimab showed a relative reduced risk of COVID-19 by 77% (95% CI: 46%–90%) in patients at increased risk for inadequate response to active immunization; however, these data were produced prior to newer variants (e.g. Omicron) emerging[2]
  - Sipavibart demonstrated prophylactic efficacy against pre–November 2024 variants but lacks activity against dominant strains circulating since[3]
- Likely to see more developments in this arena[4,5]

Phase 3 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

Authors: James D. Chalmers, M.B., Ch.B., Ph.D., Pierre-Régis Burgel, M.D., Ph.D., Charles L. Daley, M.D., Anthony De Soyza, M.B., Ch.B., Ph.D., Charles S. Haworth, M.B., Ch.B., M.D., David Mauger, Ph.D., Michael R. Loebinger, M.D., Ph.D., +11 , for the ASPEN Investigators* Author Info & Affiliations

Brensocatib in Bronchiectasis — A New Sheriff in Town?

Authors: Scott C. Bell, M.B., B.S., M.D., and Keith Grimwood, M.B., Ch.B., M.D. Author Info & Affiliations

CI, confidence interval; COVID-19, coronavirus disease 2019; DPP-1, dipeptidyl peptidase 1; IVIG, intravenous immunoglobulin.
1. Speaker's opinion. 2. AstraZeneca AB. Tixagevimab 150 mg + cilgavimab 150 mg solution for injection – summary of product characteristics; October 2024. 3. Haidar G *et al. Lancet Infect Dis* 2025: S1473-3099(24)00804-1.
4. Chalmers JD *et al. New Engl J Med* 2025; 392 (16): 1569–1581. 5. Bell SC *et al. New Engl J Med* 2025; 392 (16): 1647–1648.

Summary

- Secondary immune deficiency is common in patients with CLL
- Managing patients relies on awareness and early recognition
- Early vaccination is important to optimize patient outcomes
- Stepwise pathway can be used for those at risk and may include prophylaxis and IGRT
- **More research is required on risk stratification, particularly for patients around the time of treatment**

CLL, chronic lymphocytic leukemia; IGRT, immunoglobulin replacement therapy.
Speaker's opinion.

PANEL DISCUSSION: ADDRESSING KEY QUESTIONS IN CLL MANAGEMENT

Clemens-Martin Wendtner
Ludwig Maximilian University, Munich, Germany

All faculty

For discussion

How does IGHV status influence your choice of therapy and when might it be a decisive factor?

What differences may be anticipated in the management of patients receiving different continuous and fixed-duration therapies?

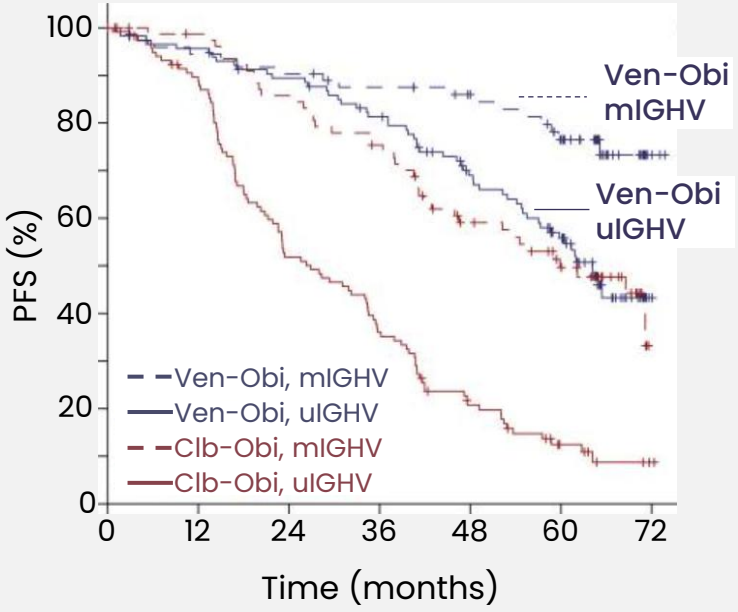
How does the risk of infections in CLL change as patients age and progress through different lines of therapy?

What role should MRD evaluation have in the management of CLL – and how should it be measured and defined?

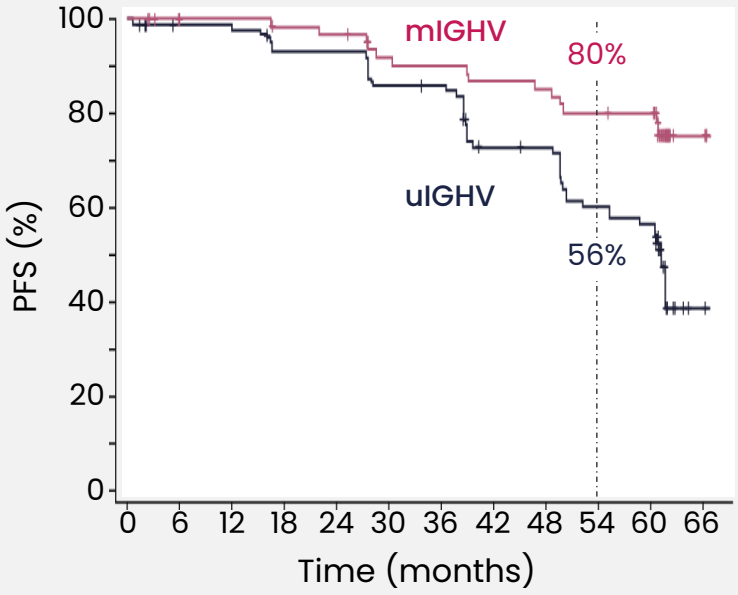
CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain variable region genes; MRD, minimal residual disease.

How does IGHV status influence your choice of therapy and when might it be a decisive factor?

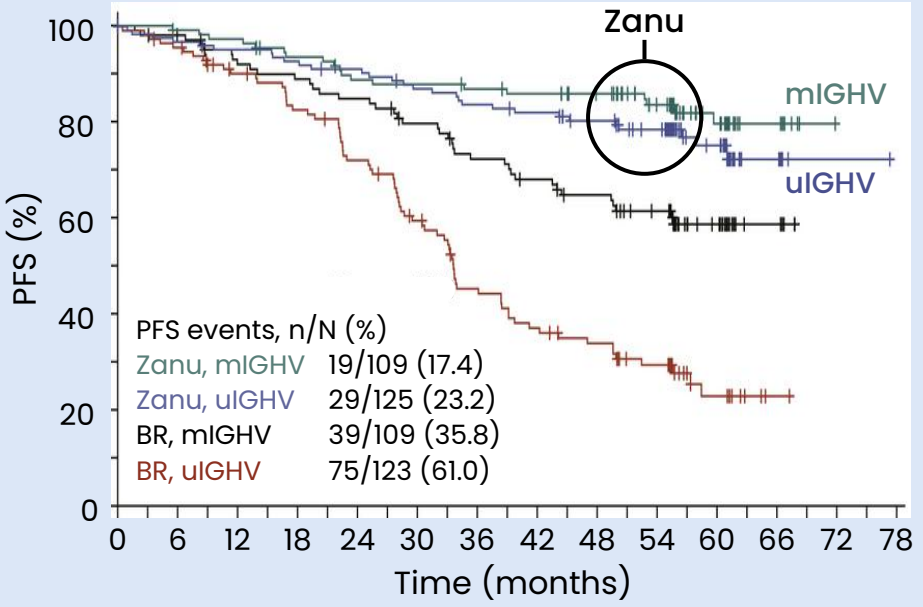
CLL14: Ven-Obi
5-year follow-up[1]



CAPTIVATE: Ibr-Ven
5-year follow-up[2]



SEQUOIA: Zanubrutinib
5-year follow-up[3]



Shorter PFS in patients with uIGHV vs. mIGHV with Ven-Obi and Ibr-Ven

Consistent PFS in patients with uIGHV and mIGHV with zanubrutinib

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

BR, bendamustine and rituximab; Clb, chlorambucil; Ibr, ibrutinib; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable region genes; Obi, obinutuzumab; PFS, progression-free survival; Ven, venetoclax; Zanu, zanubrutinib.

1. Al-Sawaf O *et al. Nat Commun* 2023; 14 (1): 2147. 2. Wierda WG. *et al.* Oral presentation at ASCO 2024; Chicago, IL, USA, May 31-June 4, 2024. 3. Shadman M *et al. J Clin Oncol* 2025; 43 (7): 780-787.

What differences may be anticipated in the management of patients receiving different continuous and fixed-duration therapies?

Continuous therapies[1]

- Sustained disease control in low- and high-risk disease[2–5]
- Safety profile favorable for elderly, unfit, or frail patients[6]
- Convenient administration and monitoring

Fixed-duration therapies[1]

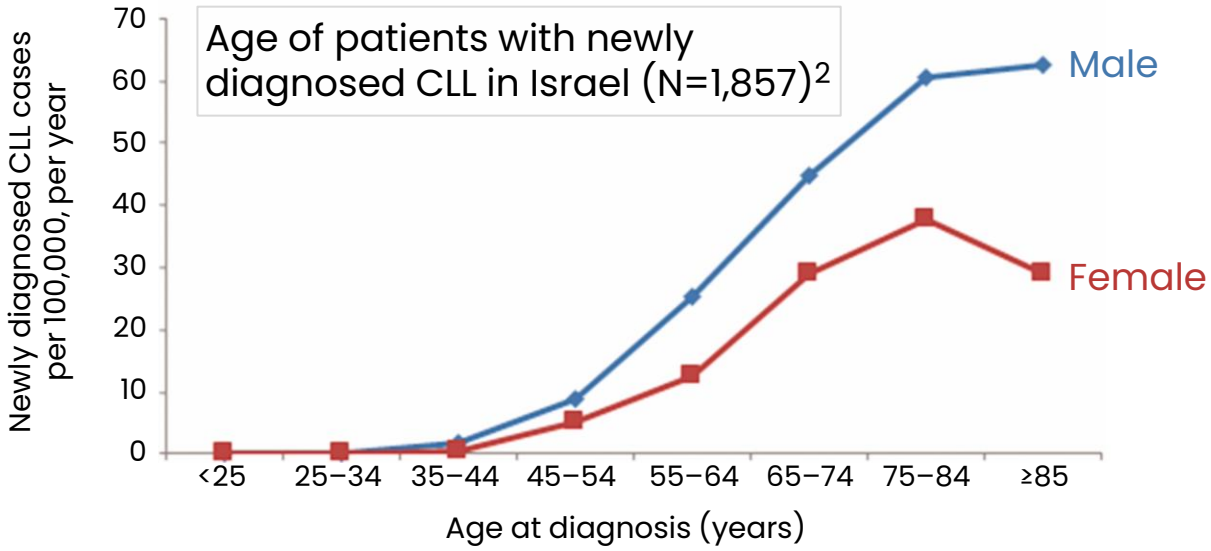
- Sustained disease control in some patients[7–9]
- May be preferred for fitter, younger patients able to better tolerate higher toxicity
- Logistically complex administration and monitoring

1. Speaker's opinion. 2. Tam CS *et al.* Oral presentation at ASCO 2025; Chicago, IL, USA, May 30–June 3, 2025. 3. Shadman M *et al. J Clin Oncol* 2024; 43 (7): 780–787. 4. Barr PM *et al. Blood Adv* 2022; 6 (11): 3440–3450. 5. Sharman JP *et al. Lancet* 2020; 395 (10232): 1278-1291. 6. Stożek-Tutro A *et al. Crit Rev Oncol Hematol* 2024; 201: 104428. 7. Al-Sawaf O *et al. Blood* 2024; 144 (18): 1924–1935. 8. Kater AP *et al. NEJM Evid* 2022; 1 (7): EVIDoa2200006. 9. Wierda WG *et al.* Oral presentation at ASCO 2024; Chicago, IL, USA, May 31-June 4, 2024.

How does the risk of infections in CLL change as patients age and progress through different lines of therapy?

Immune senescence is a feature of human ageing[1]

- Thymic degeneration
- 'Inflammageing' and cellular senescence
- Decline in T-cell populations
- Metabolic changes



Infections remain a key challenge in the targeted therapy era – and are more common in the relapsed setting[3]

Grade ≥3 infection rates in CLL prospective trials

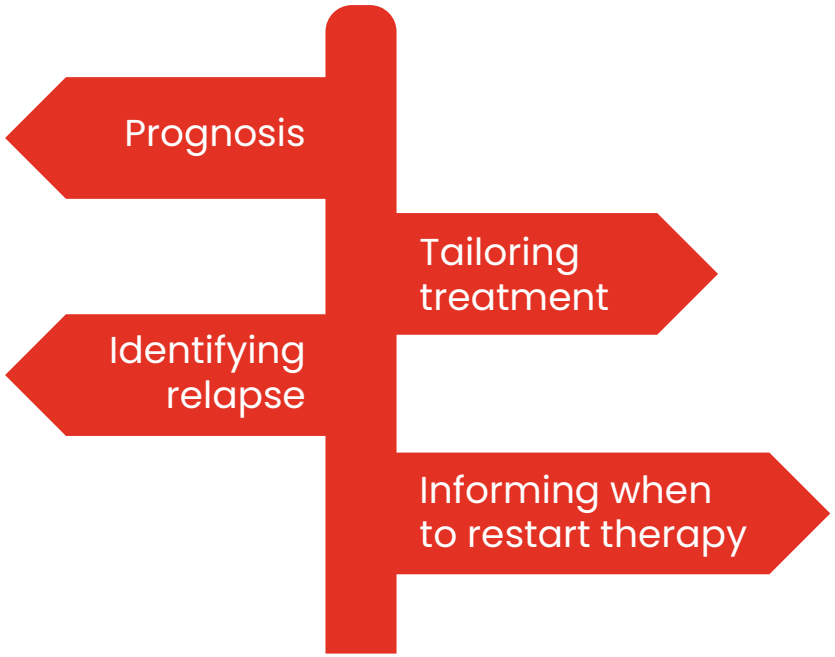
	TN patients	R/R patients
BTKi	11.4%–27.4%	~30%
Ven-based	≤20%	≤20%

- Cumulative toxicity from prior chemotherapy and anti-CD20 therapy makes it challenging to interpret infection rates in relapsed patients

BTKi, Bruton's tyrosine kinase inhibitor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory; TN, treatment-naïve; Ven, venetoclax.
1. Liu Z *et al. Signal Transduct Target Ther* 2023; 8 (1): 200. 2. Weil C *et al. Leuk Lymphoma* 2021; 62 (5): 1136-1145. 3. Mauro FR *et al. Crit Rev Oncol Hematol* 2024; 201: 104408.

MRD in the management of CLL

What role should MRD evaluation have in the management of CLL?



What do we think about stopping therapy when a patient has detectable MRD?

Do we need MRD after fixed-duration therapy?

How should MRD be measured and defined in CLL?

Compartment?	Peripheral blood Bone marrow
Technique?	Cell-based (FLOW) Molecular (NGS)
Depth?	1×10^{-4} 1×10^{-5} 1×10^{-6}
Approach?	Static Dynamic

CLL, chronic lymphocytic leukemia; FLOW, flow cytometry; MRD, minimal residual disease; NGS, next-generation sequencing.
Speaker's opinion.

SUMMARY AND CLOSE

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Summary & conclusions[1]

- Most newly diagnosed patients with CLL have multiple treatment options – finding an appropriate treatment involves evaluating multiple factors, including the patient profile and preferences, disease characteristics, treatment profile, possible therapeutic sequences, and cost

- Continuous BTKi monotherapy is a viable option for almost all patients with CLL, including those with high-risk disease and those who are elderly or unfit
  - Zanubrutinib monotherapy delivers long-term disease control with a manageable safety profile – as well as flexible dosing and convenient administration – across patient populations[2]
  - Data presented at 2025 ASCO demonstrate robust and sustained efficacy with zanubrutinib in treatment-naive patients with del(17p)[3]
  - In the relapsed setting, zanubrutinib demonstrated consistent efficacy across patient subgroups and superior PFS overall versus ibrutinib in the ALPINE study[4]

- Secondary immune deficiency is common in CLL, requiring a management approach including patient education, early vaccination, and pathways for managing those most at risk – such as prophylaxis and IGRT
  - Further research is needed on risk stratification, particularly for patients around the time of treatment

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; IGRT, immunoglobulin replacement therapy; MRD, minimal residual disease.
1. Speaker's opinion. 2. BeOne Medicines. Zanubrutinib 80 mg hard capsules – summary of product characteristics; May 2025. 3. Tam CS *et al.* Oral presentation at ASCO 2025; Chicago, IL, USA, May 30–June 3, 2025. 4. Brown JR *et al. Blood* 2024; 144 (26): 2706–2717

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