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The data behind your treatment selection in CLL & indolent lymphomas

BeiGene

Introduction

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- **Research funding:** F. Hoffmann-La Roche, GSK, Cilag-Janssen, Gilead, Genentech, Morphosys, AbbVie, AstraZeneca, BeiGene

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Disclaimers (2)

- Zanubrutinib ▼*. Refer to Brukinsa SmPC (MAH: BeiGene Ireland Ltd)
  - as **monotherapy** is indicated in the European Union (EU) for the treatment of adult patients with:
    - Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemoimmunotherapy
    - Chronic lymphocytic leukaemia (CLL)
    - Marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy
  - in **combination** with obinutuzumab is indicated in the EU for the treatment of adult patients with:
    - Refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies (FL is not reimbursed in Spain)

  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.

- Sonrotoclax is an experimental orally bioavailable inhibitor of the anti-apoptotic protein B-cell lymphoma 2 (BCL-2), with potential pro-apoptotic and antineoplastic activities. It is currently under Phase 1-3 clinical investigation.

* ▼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.
CLL, chronic lymphocytic leukemia; EU, European Union; FL, follicular lymphoma; MAH, marketing authorization holder; MZL, marginal zone lymphoma; PI, prescribing information; SmPC, summary of product characteristics; WM, Waldenström's macroglobulinaemia.

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- Chlorambucil. Refer to Chlorambucil SmPC (MAH: Aspen Pharma Trading Limited)
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- Obinutuzumab. Refer to Gazyvaro SmPC (MAH: Roche Registration GmbH)
- Pirtobrutinib ▼*. Refer to Jaypirca SmPC (MAH: Eli Lilly Nederland B.V)
- Rituximab. Refer to MabThera SmPC (MAH: Roche Registration GmbH)
- Venetoclax. Refer to Venclyxto SmPC (MAH: AbbVie Deutschland GmbH Co. KG)

* ▼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.
MAH, marketing authorization holder; SmPC, summary of product characteristics.

Learning Objectives

- New therapies such as next-generation BTKis are increasing the options available to treat patients with CLL and indolent lymphomas, in both TN and R/R disease
- Treatment choices need to be made between monotherapy vs combination therapy, continuous vs fixed duration, and oral vs parenteral therapy
- These decisions should be based on patient preferences, as well as patient and disease characteristics

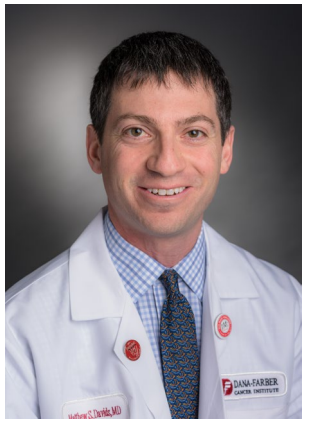
After this session, participants should have increased understanding of:

- The data supporting therapy selection and use in **TN and R/R CLL**
- The data supporting BTKi selection and use in **indolent lymphomas**

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory; TN, treatment naive.

Chair and Speakers

Prof. Clemens Wendtner –
Department of Internal Medicine III,
Ludwig-Maximilian University, Munich,
Germany



Dr. Matthew Davids –
Dana-Farber Cancer Institute,
Boston, USA

Prof. Renata Walewska –
University Hospitals Dorset,
Bournemouth, UK

Prof. Pier Luigi Zinzani –
Institute of Hematology,
«L. e A. Seràgnoli»
University of Bologna, Italy

The data behind your treatment selection in CLL & indolent lymphomas

Timing (60 minutes)	Topic	Speaker
12.30 – 12.35 (5 mins)	Welcome and introduction	Clemens Wendtner (Chair), Munich, Germany
12.35 – 13.00 (25 mins)	Treatment selection in TN CLL	Renata Walewska, Bournemouth, UK
13.00 – 13.25 (25 mins)	Treatment selection in R/R CLL	Matthew Davids, Boston, USA
13.25 – 13.45 (20 mins)	BTKis in indolent lymphomas (WM, MZL, FL)	Pier Luigi Zinzani, Bologna, Italy
13.45 – 14.00 (15 mins)	Panel discussion, audience Q&A	ALL

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MZL, marginal zone lymphoma; Q&A, question & answer; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström's macroglobulinemia.

SCAN QR CODE NOW!

Allows you to:

- Answer poll questions
- Ask your questions to the faculty
- Provide your feedback and help BeiGene to better meet your educational needs in the future

Treatment selection in TN CLL

Renata Walewska, MB ChB, PhD
University Hospitals Dorset,
Bournemouth, UK

Disclosures

- **Janssen**: Speaker, advisory board, meeting sponsorship
- **AstraZeneca**: Speaker, advisory board, meeting sponsorship
- **SecuraBio**: Advisory board
- **AbbVie:** Speaker, advisory board, meeting sponsorship
- **BeiGene**: Speaker, advisory board, meeting sponsorship
- **Medscape, Limbic**: Educational material development

Audience poll question

- What is the one most important consideration when choosing CLL treatment?
  - Genetic characteristics of CLL ☐
  - Age ☐
  - Frailty ☐
  - Comorbidities ☐
  - Other medications ☐
  - Patient's preference ☐

CLL, chronic lymphocytic leukemia.

First-line pivotal targeted clinical trials

FIT → FRAIL

CLL13
(Ven-R vs Ven-Obi vs Ibru-Ven-Obi vs CIT)
NCT02950051

ECOG1912
(Ibru-R vs CIT)
NCT02048813

FLAIR
(Ibru-R vs CIT)
2013-001944-76

CAPTIVATE
(Ven-Ibru)
NCT02910583

ALLIANCE
(Ibru vs Ibru-R vs BR)
NCT01886872

SEQUOIA
(Zanu vs BR)
NCT03336333

RESONATE-2
(Ibru vs Clb)
NCT01722487

CLL14
(Ven-Obi vs Clb-Obi)
NCT02242942

iLLUMINATE
(Ibru-Obi vs Clb-Obi)
NCT02264574

ELEVATE-TN
(Acala vs AO vs Clb-Obi)
NCT02475681

GLOW
(Ven-Ibru vs Clb-Obi)
NCT03462719

A or Acala, acalabrutinib; B, bendamustine; CIT, chemoimmunotherapy; Clb, chlorambucil; Ibru, ibrutinib; O or Obi, obinutuzumab; R, rituximab; Ven, venetoclax; Zanu, zanubrutinib.

TN CLL – Patient case 1

Patient presentation

- 72-year-old woman, night sweats and unexplained weight loss
- Labs: ALC 50 × 10^9/L, Hb 89 g/L, platelets 78 × 10^9/L
- Physical exam: bilateral 4 cm mobile axillary lymph nodes
- Diagnosis: CLL at Binet C/Rai stage IV
- Molecular testing: *IGHV*^{UNMUT} and del(11q), with no *TP53* aberrations
- Medical history: impaired renal function (CrCl 45 mL/min), recurrent DVT (on apixaban), ECOG PS 1
- Patient preferences: difficulty adhering to medications and did not want to add another daily medication; anxious about potential side-effects of another medication taken for an indefinite period, so preferred a fixed-duration regimen; comfortable with receiving infusions; intermediate TLS risk and lives near monitoring facilities

This is a hypothetical case provided by the Speaker for educational purposes only.
ALC, absolute lymphocyte count; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; del(11q), deletion of the long arm of chromosome 11; del(17p), deletion of the short arm of chromosome 17; DVT, deep vein thrombosis; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; *IGHV*^{UNMUT}, unmutated immunoglobulin heavy chain variable region; TLS, tumor lysis syndrome; TN, treatment naïve; *TP53*, tumor protein p53.

Case 1 – Therapy options considered

- Fixed-duration Ven-Obi
- Fixed-duration Ven-Ibru

(BTKi are given as continuous therapy and so are not considered for this patient)

This is a hypothetical case provided by the Speaker for educational purposes only.
BTKi, Bruton's tyrosine kinase inhibitor; Ibru, ibrutinib; Obi, obinutuzumab; Ven, venetoclax.

Ven-Obi supportive trials

- 1L fixed-duration Ven-Obi provides durable remissions with a safety profile that is manageable in fit and unfit patients with untreated CLL[1,2]
- The CLL14 trial established the superiority of Ven-Obi vs Clb-Obi in patients older than 70 years of age and/or with clinically relevant coexisting medical conditions[1]
  - The results are particularly relevant for this patient who is 72 years old with multiple comorbidities

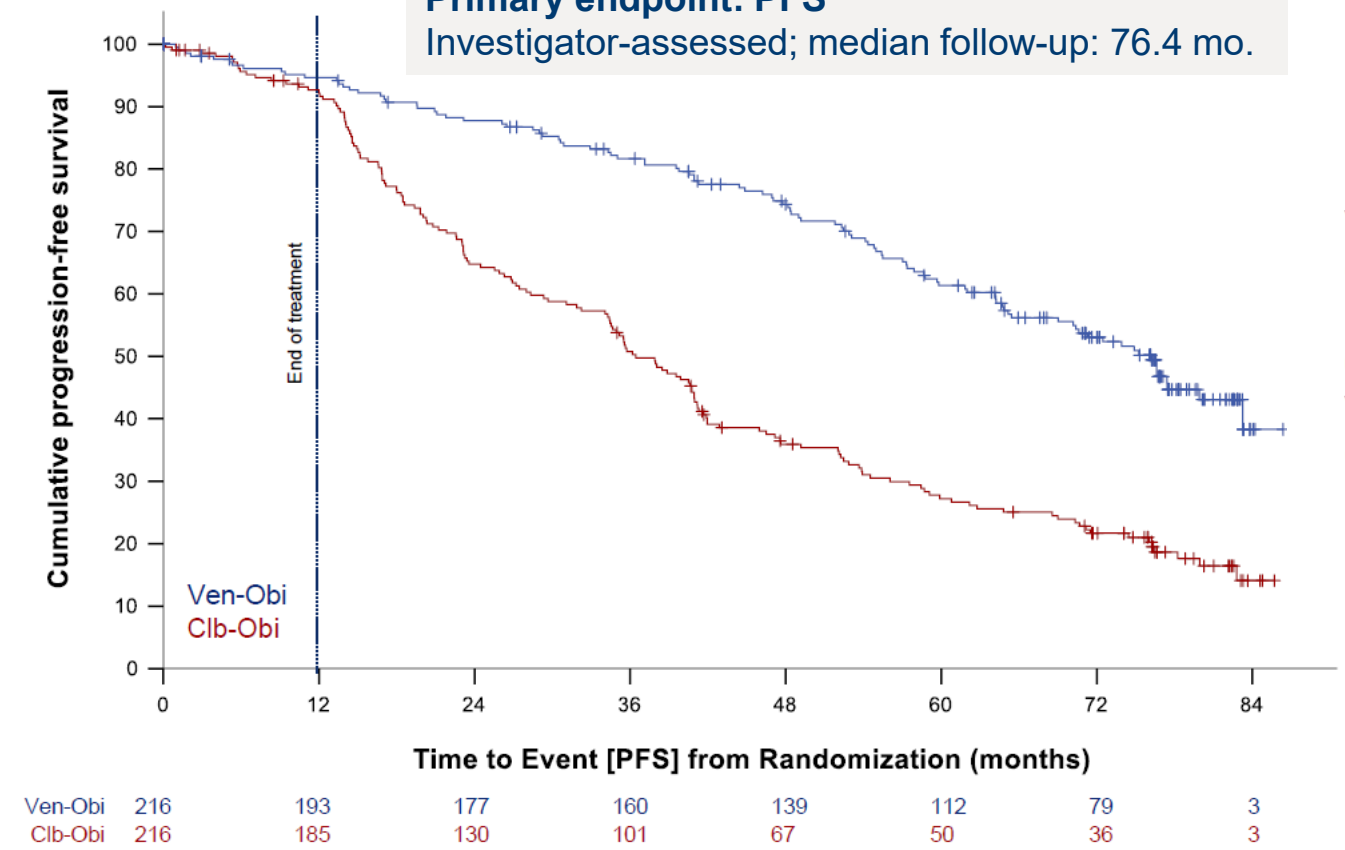
IL, first line; CLL, chronic lymphocytic leukemia; Obi, obinutuzumab; Ven, venetoclax.

1) Fischer K et al, N Engl J Med. 2019;380:2225-2236; 2) Eichhorst B et al. N Engl J Med. 2023;388(19):1739-54.

Ven-Obi in TN CLL

- **CLL14 trial (Ven-Obi vs Clb-Obi)**

Primary endpoint: PFS[1]
Investigator-assessed; median follow-up: 76.4 mo.



Summary:
- PFS was significantly higher with Ven-Obi vs Clb-Obi at 6-year follow-up[1]

Median PFS
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

6-year PFS rate
Ven-Obi: 53.1%
Clb-Obi: 21.7%

HR 0.40, 95% CI [0.31-0.52]
P<0.0001

Key baseline characteristics[2]
- *IGHV* unmutated: 60%
- del(17p): 8%
- Median age: 72 years

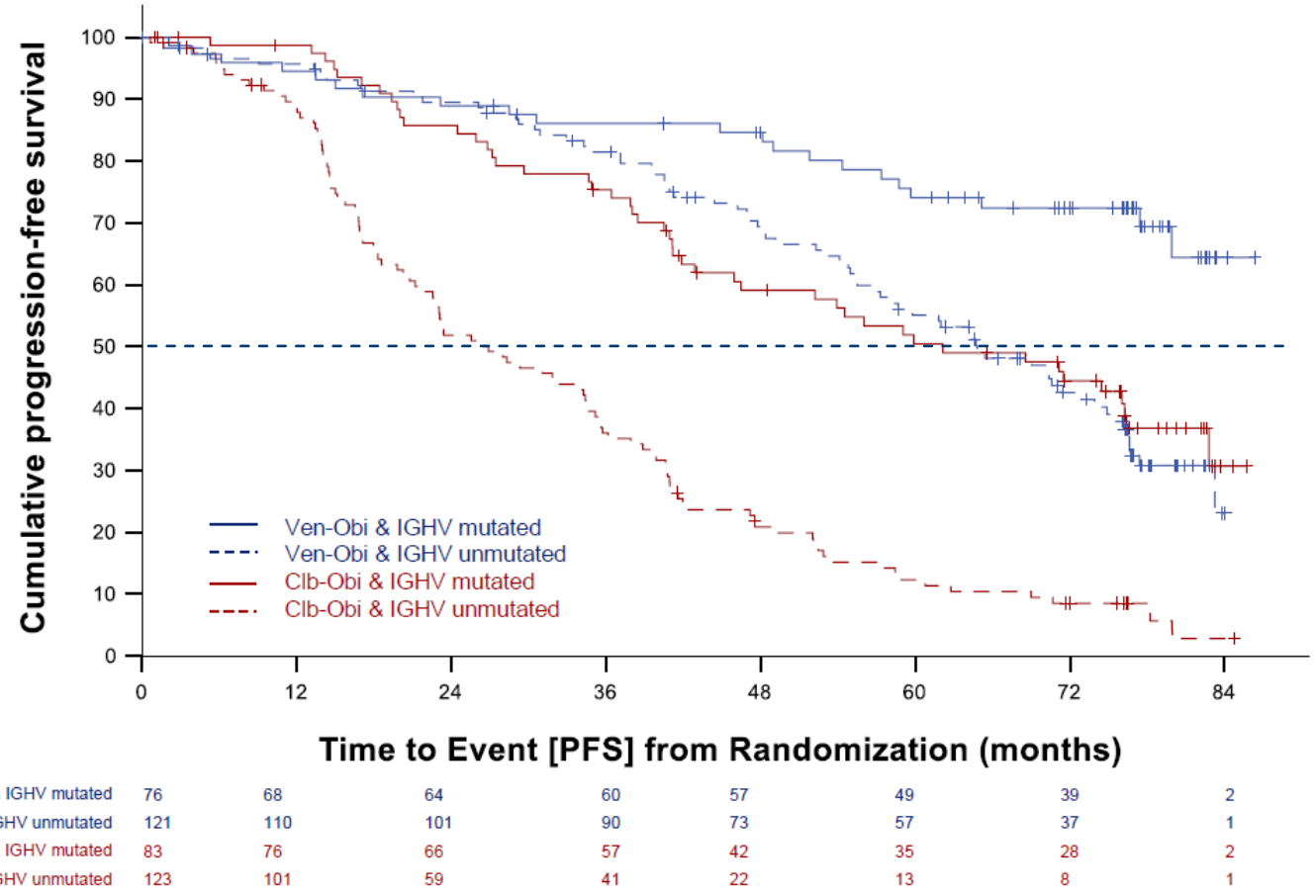
CI, confidence interval; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; HR, hazard ratio; *IGHV*, immunoglobulin heavy chain variable region; mo., months; Obi, obinutuzumab; PFS, progression-free survival; TN, treatment naïve; Ven, venetoclax.

1) Al-Sawaf O et al. ICML June 15 2023. Abstract N.025 Session 4 (Accessed 04 June 2024). Available at: https://medically.gene.com/content/dam/pdmahub/restricted/oncology/icml-2023/ICML-2023-presentation-ai-sawaf-venetoclax-obinutuzumab-for-previously-untreated-chronic.pdf; 2) Fischer K et al. N Engl J Med 2019;380:2225–36.

CLL14: Although IGHV^{UNMUT} was associated with poorer outcomes than IGHV^{MUT}, Ven-Obi still provided prolonged benefit

Secondary endpoint: PFS by *IGHV* status

Median observation time 76.4 months



Ven-Obi & IGHV mutated	76	68	64	60	57	49	39	2
Ven-Obi & IGHV unmutated	121	110	101	90	73	57	37	1
Clb-Obi & IGHV mutated	83	76	66	57	42	35	28	2
Clb-Obi & IGHV unmutated	123	101	59	41	22	13	8	1

Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.8 m

HR 0.38, 95%CI [0.23-0.61], p<0.001

Clb-Obi & IGHVmut: 62.2 m

Clb-Obi & IGHVunmut: 26.9 m

HR 0.33, 95% CI [0.23-0.47], p<0.001

Safety: No new safety signals observed

CI, confidence interval; Clb, chlorambucil; *IGHV*, immunoglobulin heavy chain variable region; mo., months; MUT, mutated; NR, not reached; Obi, obinutuzumab; PFS/mPFS, progression-free survival/median PFS; UNMUT, unmutated; Ven, venetoclax.

Extracted from Al-Sawaf O et al. ICML June 15 2023. Abstract N.025 Session 4 (Accessed 04 June 2024). Available at: https://medically.gene.com/content/dam/pdmahub/restricted/oncology/icml-2023/ICML-2023-presentation-ai-sawaf-venetoclax-obinutuzumab-for-previously-untreated-chronic.pdf

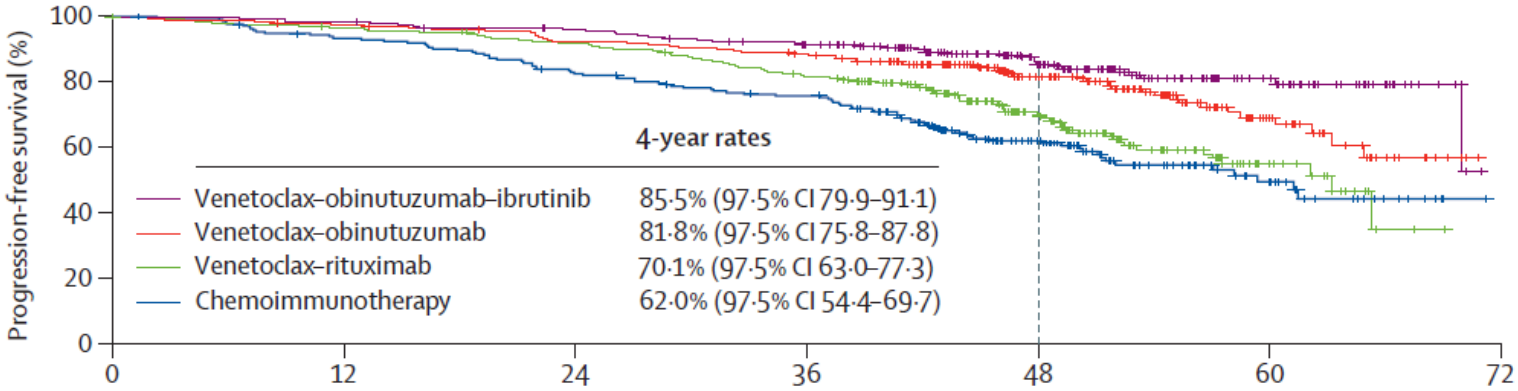
Ven-Obi supportive trials

- 1L fixed-duration Ven-Obi provides durable remissions with a safety profile that is manageable in fit and unfit patients with untreated CLL.
- The CLL14 trial established the superiority of Ven-Obi vs Clb-Obi in patients older than 70 years of age and/or with clinically relevant coexisting medical conditions.
  - The results are particularly relevant for this patient who is 72 years old with multiple comorbidities.
- The GAIA (CLL13) trial was a head-to-head study of venetoclax-based time-limited combinations versus CIT (FCR or BR) in 926 fit patients that established the superiority of Ven-Obi versus CIT.

BR, bendamustine-rituximab; CIT, chemoiummotherapy; FCR, fludarabine, cyclophosphamide and rituximab; Obi, obinutuzumab; Ven, venetoclax.
Eichhorst B et al, N Engl J Med. 2023;388(19):1739-1754.

Ven-based regimens in TN CLL

- **CLL13 trial: Ven-Obi significantly better PFS than CIT**



Number at risk (number censored)							
Chemoimmunotherapy	229 (0)	197 (18)	173 (19)	156 (22)	84 (68)	24 (117)	.. (..)
Venetoclax–rituximab	237 (0)	227 (2)	214 (4)	188 (6)	106 (67)	21 (135)	.. (..)
Venetoclax–obinutuzumab	229 (0)	222 (1)	209 (3)	198 (5)	121 (69)	32 (146)	.. (..)
Venetoclax–obinutuzumab–ibrutinib	231 (0)	227 (0)	218 (4)	201 (10)	130 (71)	44 (152)	.. (..)

Summary:

- PFS was significantly higher with Ven-Obi or Ven-Obi-Ibru vs CIT at 4-year follow-up
- Some of the benefits of the triplet therapy were neutralized by the need for dose reductions and early treatment discontinuation for AEs

AE, adverse event; CI, confidence interval; CIT, chemoiummotherapy; CLL, chronic lymphocytic leukemia; Ibru, ibrutinib; Obi, obinutuzumab; PFS, progression-free survival; TN, treatment naïve; Ven, venetoclax.
Extracted from Fürstenau M et al, Lancet Oncol. 2024;25(6):744-759.

Ven-Ibru considerations

If patient:

- Favours time-limited therapy (*this patient does favour FD*)
- Does not want lengthy appointments for IV therapy and so prefers all-oral therapy (*this patient does not mind infusions*)
- Has low genetic risk CLL (*this patient has IGHV^{UNMUT} and del(11q)*)
- Is young (*this patient is 72 years old*)
- Is fit (*this patient has comorbidities*)

This is a hypothetical case provided by the Speaker for educational purposes only.
CLL, chronic lymphocytic leukemia; del(11q), deletion of the long arm of chromosome 11; FD, fixed-duration; Ibru, ibrutinib; *IGHV^{UNMUT}*, unmutated immunoglobulin heavy chain variable region; IV, intravenous; Ven, venetoclax.

Ven-Ibru trials

- CAPTIVATE[1]
  - Phase 2: Ven-Ibru (FD and MRD-guided cohorts)
  - FD cohort (n=159): 3 cycles Ibru lead-in then 12 cycles Ven-Ibru

- GLOW[2]
  - Phase 3: Ven-Ibru vs Clb-Obi

Clb, chlorambucil; FD, fixed-duration; Ibru, ibrutinib; MRD, minimal residual disease; Obi, obinutuzumab; Ven, venetoclax.

1) Tam CS et al, Blood. 2022;139(22):3278-3289; 2) Kater AP et al, NEJM Evid. 2022;1(7):EVIDoa2200006.

CAPTIVATE FD Cohort: Overall mPFS was NR with up to 5 years of follow-up

	54-Month PFS Rate, % (95% CI)
All patients (n=159)	70 (62–77)
del(17p)/mutated *TP53* (n=27)	45 (25–64)
Complex karyotype (n=31)[a]	60 (41–79)
Unmutated IGHV (n=40)[b]	68 (50–80)
del(11q) (n=11)[b]	64 (30–85)

Summary: With up to 5 years of follow-up, fixed-duration Ven-Ibru continues to provide deep remissions with clinically meaningful PFS, including in patients with high-risk genomic features

[a]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics. [b]Excluding patients with del(17p)/mutated *TP53* or complex karyotype.
CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete bone marrow recovery; del(11q), deletion of the long arm of chromosome 11; del(17p), deletion of the short arm of chromosome 17; EOT, end of treatment; FD, fixed duration; Ibru, ibrutinib; *IGHV*, immunoglobulin heavy chain variable region; NR, not reached; OS, overall survival; ORR, overall response rate; PD, progressive disease; PFS/mPFS, progression-free survival/median PFS; *TP53*, tumor protein p53; Ven, venetoclax.
Ghia P et al, Blood. 2023;142(Supplement 1):633.

CAPTIVATE (FD cohort): In a fit population, Ven-Ibru was well tolerated

AEs	All treated patients (n = 159), n (%)	
	Any grade	Grade 3/4
Most common AEs*		
Diarrhea	99 (62)	5 (3)
Nausea	68 (43)	2 (1)
Neutropenia	66 (42)	52 (33)
Arthralgia	53 (33)	2 (1)
Hypertension	25 (16)	9 (6)
Neutrophil count decreased	16 (10)	8 (5)
Other AEs of clinical interest		
Atrial fibrillation	7 (4)	2 (1)
Major hemorrhage†	3 (2)	2 (1)
Laboratory safety parameters		
Hematology		
Neutrophils decreased	115 (72)	60 (38)
Platelets decreased	94 (59)	20 (13)
Hemoglobin decreased	31 (19)	0
Chemistry		
Corrected calcium decreased	61 (38)	1 (1)
Potassium increased	39 (25)	4 (3)
Uric acid increased	34 (21)	34 (21)
Creatinine increased	27 (17)	0

- Other AEs [not shown in table]
  - Grade ≥3 infections in 13 patients
- Serious AEs: 36 patients
- Fatal AEs:
  - Sudden death in 1 patient

*AEs of any grade occurring in ≥30% of patients or grade 3/4 occurring in ≥5% of patients. †Major hemorrhage was identified using the Standardized MedDRA Query for Hemorrhage, excluding laboratory terms.
AE, adverse event; FD, fixed-duration; Ibru, ibrutinib; PFS, progression-free survival; Ven, venetoclax.
Extracted from Tam CS et al, Blood. 2022;139(22):3278-3289.

GLOW: ≥Grade 3 adverse events occurring in >5% of either arm, and Grade 5 AEs occurring in any patient

Table 2. Grade 3 or 4 Adverse Events Occurring in 5% or More of Either Arm and Grade 5 Adverse Events Occurring in Any Patient (Safety Population).*

	Ibrutinib-Venetoclax (n=106)		Chlorambucil-Obinutuzumab (n=105)	
Treatment exposure — mo, median (range)	13.8 (0.7–19.5)		5.1 (1.8–7.9)	
Adverse events — n (%)	**Grade 3/4**	**Grade 5**	**Grade 3/4**	**Grade 5**
Patients with ≥1 adverse events	73 (68.9)	7 (6.6)	71 (67.6)	2 (1.9)
Neutropenia†	37 (34.9)	0	52 (49.5)	0
Infections and infestations‡	16 (15.1)	2 (1.9)§	11 (10.5)	1 (1.0)
Diarrhea	11 (10.4)	0	1 (1.0)	0
Hypertension	8 (7.5)	0	2 (1.9)	0
Atrial fibrillation	7 (6.6)	0	0	0
Thrombocytopenia	6 (5.7)	0	21 (20.0)	0
Hyponatremia	6 (5.7)	0	0	0
Cardiac failure	3 (2.8)	1 (0.9)§	0	0
Sinus node dysfunction	1 (0.9)	1 (0.9)§	0	0
Cholestasis	1 (0.9)	0	0	1 (1.0)
Sudden death	0	2 (1.9)	0	0
Ischemic stroke	0	1 (0.9)	0	0
Malignant neoplasm	0	1 (0.9)	0	0
Cardiac arrest	0	1 (0.9)	0	0
Tumor lysis syndrome	0	0	6 (5.7)	0

4 cardiac/sudden deaths

- **All in patients with CIRS score ≥10 or PS ≥2 and a history of hypertension, CV disease or diabetes**

50% all grade diarrhoea

Efficacy summary: Ven-Ibru demonstrated superior PFS and deeper and better sustained responses vs Clb-Obi as IL CLL treatment in older patients and/or those with comorbidities

*Fifteen 28-day cycles are equivalent to 13.8 months for I+V, and six 28-day cycles are equivalent to 5.5 months for Clb+O. Patients may have treatment exposure times exceeding these limits due to cycle holds.
†Includes "neutrophil count decreased." Rates of febrile neutropenia (grade ≥3): 1.9% for I+V versus 2.9% for Clb+O; ‡Includes multiple preferred terms. Only pneumonia (grade ≥3) occurred in 5% or more of patients in the I+V (7 [6.6%]) and Clb+O (6 [5.7%]) arms; §Both grade 5 adverse events were pneumonia (one patient experienced three grade 5 adverse events: pneumonia, cardiac failure, and sinus node dysfunction).
In the I+V arm, 3 diarrhoea (grade ≥3) resolved or improved after a median of 9.0 days.
AE, adverse event; CIRS, cumulative illness rating score; Clb, chlorambucil; CV, cardiovascular; Ibru, ibrutinib; Obi, obinutuzumab; PS, performance score; Ven, venetoclax.
Kater AP et al, NEJM Evid. 2022;1(7) + supplementary appendix.

Case 1 treatment considerations and choice

- Ven-Obi was chosen, as it is likely to provide long treatment-free intervals without the need for ongoing therapy.
- The patient did not have high genetic risk CLL with del(17p)/*TP53*^{MUT} that would lead to a recommendation for a BTKi.
- Drug-drug interactions: apixaban (anticoagulant for her DVT) can increase bleeding risk with BTKi, and she would require monitoring for bleeding.
- Reduced renal function can increase TLS risk with venetoclax, but no dose adjustments needed for mild/moderate renal impairment (CrCl ≥30 ml/min), and the therapy can be safely administered with appropriate precautions.

This is a hypothetical case provided by the Speaker for educational purposes only.
BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; del(17p), deletion of the short arm of chromosome 17; DVT, deep vein thrombosis; Obi, obinutuzumab; TLS, tumor lysis syndrome; *TP53*^{MUT}, mutated tumor protein p53; Ven, venetoclax.

BCL2i-BTKi trials

Look out for EHA 2024 abstract P702 (Munir et al):

EFFICACY AND SAFETY OF ZANUBRUTINIB VS. VENETOCLAX+IBRUTINIB IN THE TREATMENT-NAÏVE (TN) CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A MATCHING-ADJUSTED INDIRECT COMPARISON (MAIC)

See also ASCO 2024 poster #TPS7087 (Shadman et al):

CELESTIAL-TNCLL: Sonrotoclax-Zanubrutinib vs Ven-Obi – Phase 3 trial *in progress*

†Nominal p-value.
AE, adverse event; HR, hazard ratio; UTI, urinal-tract infection.

TN CLL – Patient case 2

TN CLL – Patient case 2

Patient presentation

- 55-year-old man, fatigue and shortness of breath
- Labs: ALC 129 × 10^9/L, Hb 85 g/L, Platelets 95 × 10^9/L, B2M 4 mg
- Physical exam: 3 cm lymph nodes and spleen/liver enlargement
- Diagnosis: CLL at Binet C/Rai IV
- High-risk features: *IGHV*^{UNMUT}, del(17p), *TP53*^{MUT}
- Past medical history: atrial fibrillation (on atenolol and dabigatran); gastroesophageal reflux disease (on omeprazole); history of migraines; otherwise, healthy (ECOG PS 1)
- No preference for continuous versus fixed-duration therapy nor for all-oral therapy versus regimens requiring infusions.

This is a hypothetical case provided by the Speaker for educational purposes only.
ALC, absolute lymphocyte count; B2M, beta 2 microglobulin; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; *IGHV*, immunoglobulin heavy chain variable region; MUT, mutated; TN, treatment naïve; *TP53*, tumor protein p53; UNMUT, unmutated.

Case 2 – Therapy options considered

- Continuous BTK inhibitor
- Fixed-duration with Ven-Obi or Ven-Ibru

This is a hypothetical case provided by the Speaker for educational purposes only.
BTK, Bruton's tyrosine kinase; Ibru, ibrutinib; Obi, obinutuzumab; Ven, venetoclax.

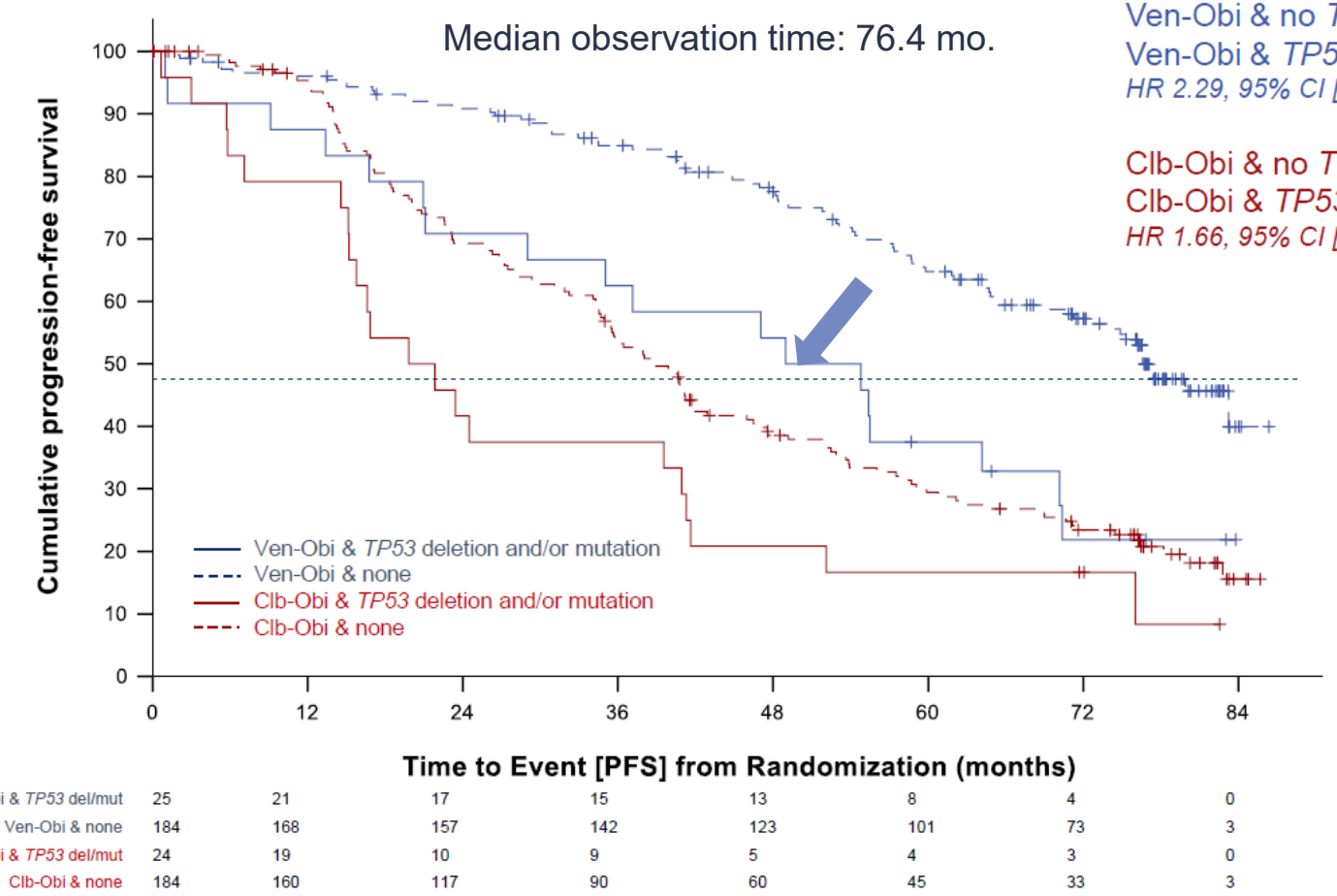
Case 2 – Special considerations for this patient: high risk

- High-risk: del(17p) with mutated *TP53*
  - In 1L, BTKi outcomes for patients with del(17p) and/or *TP53*^{MUT} are comparable to those without these features[1-3]
  - With Ven-Obi, patients with del(17p) and/or *TP53*^{MUT} have shorter PFS than lower genetic risk patients[4]

This is a hypothetical case provided by the Speaker for educational purposes only.
1L, first line; BTKi, Bruton's tyrosine kinase inhibitor; del(17p), deletion of the short arm of chromosome 17; MUT, mutated; Obi, obinutuzumab; PFS, progression-free survival; *TP53*, tumor protein p53; Ven, venetoclax.
1) Sharman JP et al, Leukemia. 2022;36(4):1171-5; 2) Shadman M et al. Presented at the EHA 2023 Hybrid Congress; June 8-15, 2023; Frankfurt, Germany. Abstract P639 (Accessed 04 June 2024). Available at: Shadman_BGB-3111-304_ICML_Presentation_2023.pdf; 3) Burger JA et al. Leuk Lymphoma. 2022;63(6):1375-86; 4) Tausch E et al. Blood. 2020;135(26):2402-12.

Ven-Obi in high-risk TN CLL

- **CLL14 – PFS by *TP53* del/mut status[1]**



Ven-Obi & *TP53* del/mut	25	21	17	15	13	8	4	0
Ven-Obi & none	184	168	157	142	123	101	73	3
Clb-Obi & *TP53* del/mut	24	19	10	9	5	4	3	0
Clb-Obi & none	184	160	117	90	60	45	33	3

Median PFS

Ven-Obi & no *TP53*del/mut: 76.6 m
Ven-Obi & *TP53*del/mut: 51.9 m
HR 2.29, 95% CI [1.37-3.83], p=0.001

Clb-Obi & no *TP53*del/mut: 38.9 m
Clb-Obi & *TP53*del/mut: 20.8 m
HR 1.66, 95% CI [1.05-2.63], p=0.03

Summary[2]:

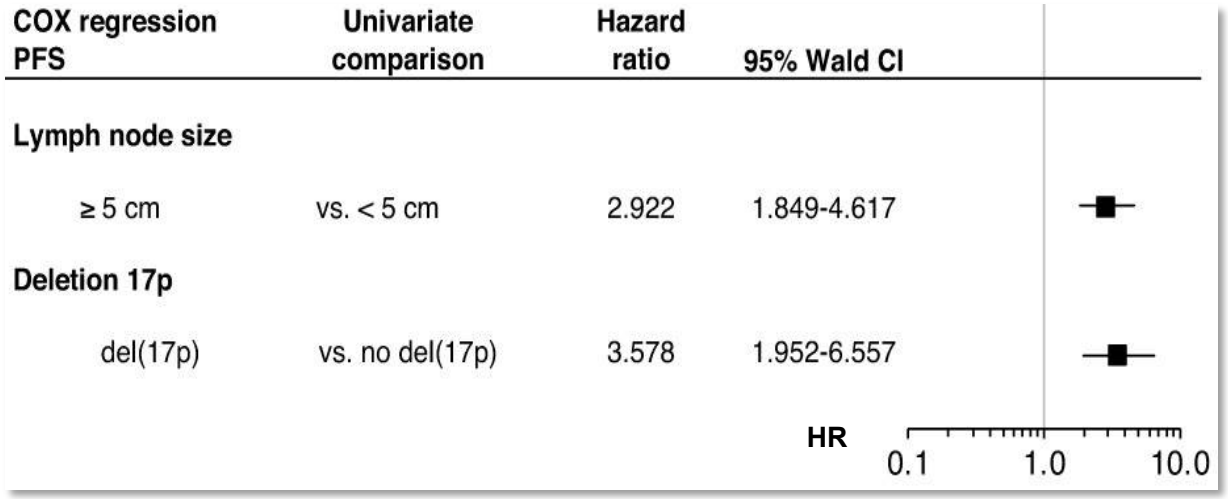
- These data confirm a long-term PFS benefit of fixed-duration Ven-Obi treatment compared with Clb-Obi, including patients with high-risk CLL.
- No new safety signals were observed.
- Secondary malignancy rate under continued observation

Clb, chlorambucil; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; mo.; months; MUT, mutated; Obi, obinutuzumab; PFS/mPFS, progression-free survival/median PFS; TN, treatment naïve; *TP53*, tumor protein p53; Ven, venetoclax.

1) Extracted from Al-Sawaf O et al. ICML June 15 2023. Abstract N.025 Session 4 (Accessed 04 June 2024). Available at: https://medically.gene.com/content/dam/pdmahub/restricted/oncology/icml-2023/ICML-2023-presentation-ai-sawaf-venetoclax-obinutuzumab-for-previously-untreated-chronic.pdf; 2) Al-Sawaf O et al, Hemasphere. 2023;7(Suppl):e064430a.

CLL14: del(17p) and lymph node size were poor prognostic factors

- **Multivariable analyses of PFS in Ven-Obi arm (n = 194)**



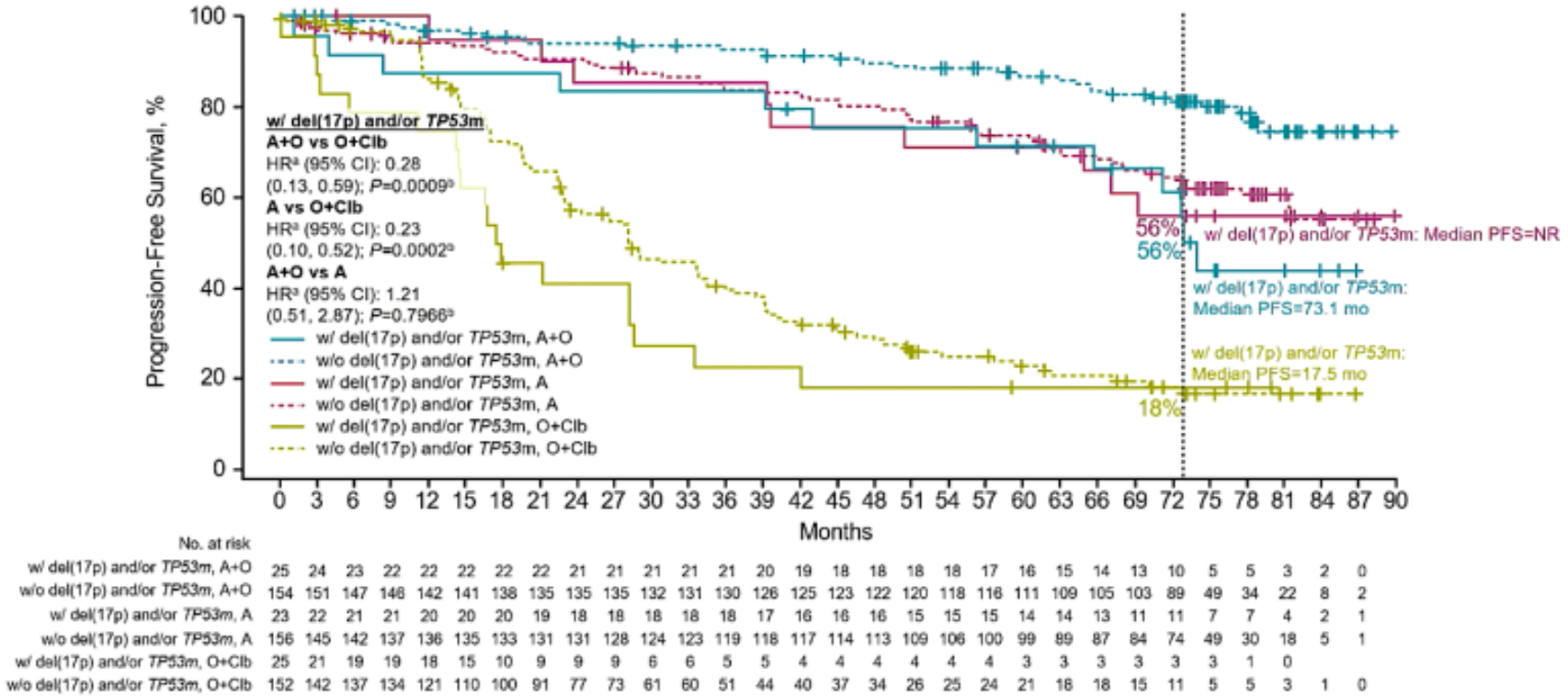
Summary:

- For patients treated with Ven-Obi, a multivariable analysis suggested presence of **del(17p)**, irrespective of *TP53* mutational status, and **LN ≥5 cm**, as independent prognostic factors for PFS

CI, confidence interval; del(17p), deletion of the short arm of chromosome 17; HR, hazard ratio; LN, lymph node; Obi, obinutuzumab; PFS, progression-free survival; *TP53*, tumor protein p53; Ven, venetoclax.
Extracted from Al-Sawaf O et al, Nat Commun. 2023;14(1):2147.

BTKi in high-risk TN CLL

- **ELEVATE-TN (acalabrutinib) – PFS by del(17p)/*TP53*^{MUT} and treatment arm**



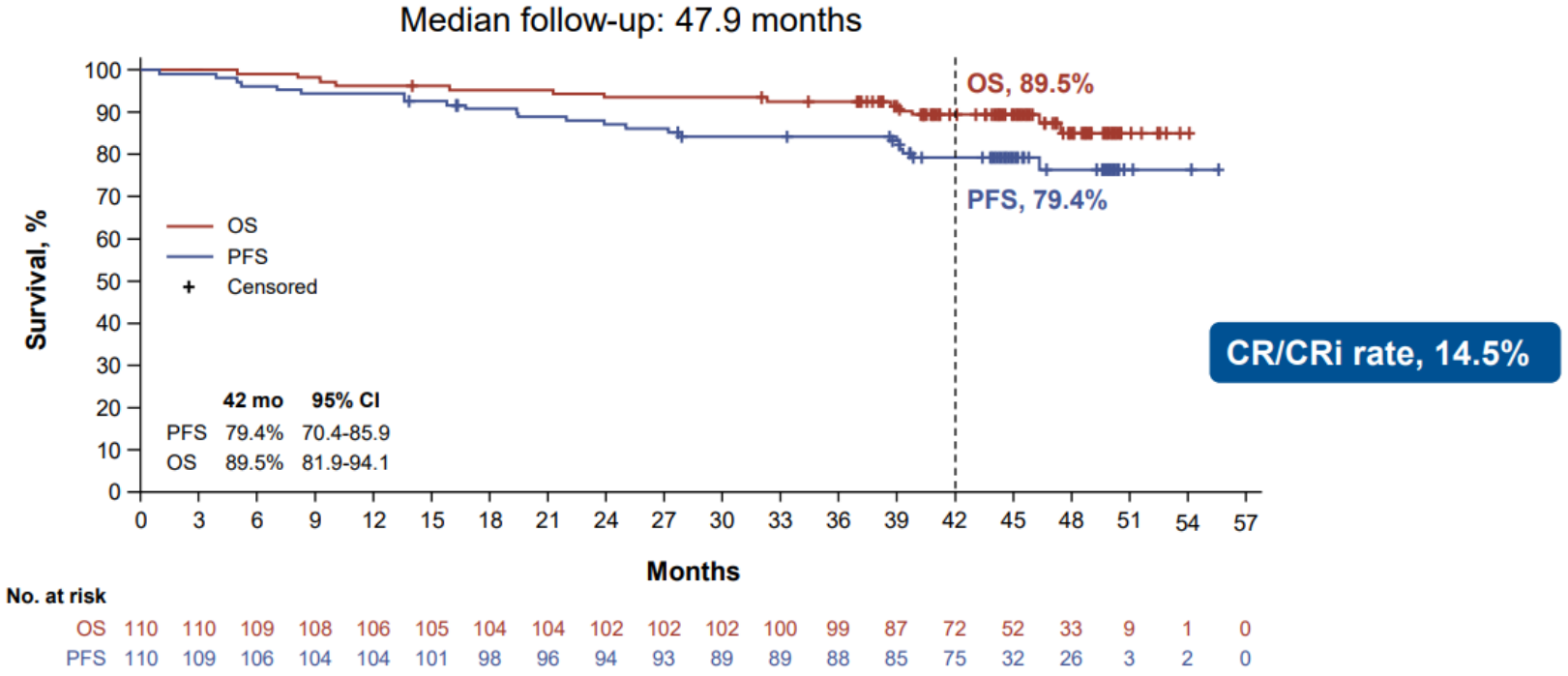
Summary:
In patients with del(17p) and/or *TP53*^{MUT}:

- Significantly longer PFS for Acala-Obi vs Clb-Obi (and for Acala vs Clb-Obi)
- Longer PFS for Acala-Obi vs Acala, but study not powered for comparison
- No new safety signals were observed with Acala-containing treatment with longer-term follow-up.

Acala, acalabrutinib; BTKi, Bruton's tyrosine kinase inhibitor; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; mo., months; MUT, mutated; NR, not reached; Obi, obinutuzumab; PFS/mPFS, progression-free survival/median PFS; TN, treatment naïve; *TP53*, tumor protein p53.
Extracted from Sharman et al. Blood. 2023;142:636–639.

BTKi in high-risk TN CLL

- **SEQUOIA (zanubrutinib), cohort 2: PFS and OS in patients with del(17p)**



CR/CRi rate, 14.5%

Summary:

- Patients *without* del(17p):
  - ✓ PFS longer for Zanu vs BR independent of *IGHV* status
- Patients *with* del(17p) (largest studied cohort):
  - ✓ All received Zanu
  - ✓ PFS was similar to those without del(17p)
- Zanu was well tolerated over this extended treatment period and aligned with the known profile of BTK inhibitors; Afib events remained low

Afib, atrial fibrillation; BR, bendamustine-rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; mo., months; OS, overall survival; PFS, progression-free survival; TN, treatment naïve; Zanu, zanubrutinib.

Shadman M et al. Presented at the EHA 2023 Hybrid Congress; June 8-15, 2023; Frankfurt, Germany. Abstract P639 (Accessed 04 June 2024). Available at: Shadman_BGB-3111-304_ICML_Presentation_2023.pdf.

BTKi in high-risk TN CLL

Oral presentation on Friday, 14 June at 14:45-15:00 CEST: Ghia et al, S160.

- **SEQUOIA (zanubrutinib), Cohort 2 (Arm D): EHA2024 update**

COMBINATION OF ZANUBRUTINIB + VENETOCLAX FOR TREATMENT-NAÏVE (TN) CLL/SLL WITH DEL(17P) AND/OR TP53: PRELIMINARY RESULTS FROM SEQUOIA ARM D

Table. Efficacy Outcomes in Patients With del(17p) and/or *TP53* Mutation

Median study follow-up 28.6 mo.	del(17p)+ or *TP53*+ (n=66)
Response evaluable, n (%)[a]	65 (98)
Best overall response, n (%)	
CR+CRi	29 (45)
Nodular PR	0
PR	35 (54)
PR with lymphocytosis	1 (2)
SD	0
ORR, n (%)	65 (100)
Best uMRD rate at any time in PB, n (%)	32 (48)

[a] Patients who received ≥1 dose of zanu with ≥1 post-baseline disease assessment.

ARM D (Zanu + Ven) is the nonrandomized cohort of patients with TN del(17p) CLL/SLL

Summary:

- Preliminary data demonstrate promising efficacy and tolerability of Zanu + Ven in patients with high-risk TN CLL/SLL with del(17p) and/or *TP53* mutation.
- The safety profile of Zanu + Ven was consistent with results of prior Zanu studies, and no new safety signals were identified.

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete blood count recovery; del(17p), deletion of the short arm of chromosome 17; ORR, overall response rate; PB, peripheral blood; PR, partial response; SD, stable disease; SLL, small lymphocytic leukemia; TN, treatment naïve; *TP53*, tumor protein p53; uMRD, undetectable minimal residual disease; Ven, venetoclax; Zanu, zanubrutinib.

Shuo MA et al. Oral presentation at EHA 2024; June 13-16, 2024; Madrid, Spain (Abstract S160). Available at: https://library.ehaweb.org/eha/2024/eha2024-congress/422264.

Case 2 – Special considerations for this patient: cardiac history

- Patient has a cardiac comorbidity
  - Next-generation BTKis have reduced risk of cardiac AEs compared with Ibru[1,2]
- Patient history of Afib:
  - Ven-Obi would avoid the bleeding risk associated with concomitant dabigatran and a BTKi; however, patients with del(17p) treated with Ven-Obi have shorter PFS than patients without del(17p)[3,4,5]

This is a hypothetical case provided by the Speaker for educational purposes only.
AE, adverse event; Afib, atrial fibrillation; BTKi, Bruton's tyrosine kinase inhibitor; del(17p), deletion of the short arm of chromosome 17; Ibru, ibrutinib; Obi, obinutuzumab; PFS, progression-free survival; Ven, venetoclax.
1) Byrd JC et al. J Clin Oncol, 2021;39:3441-3452; 2) Brown JR et al, N Engl J Med. 2023;388(4):319-332 3) Al-Sawaf O et al, Nat Commun. 2023;14(1):2147; 4) Dabigatran etexilate SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf; 5) von Hundelshausen P & Siess W. Cancers (Basel). 2021;13(5):1103.

BTKi safety – next generation vs 1st generation
ALPINE Cardiovascular AEs

- Head-to-head BTKi safety data are only available from R/R CLL trials:

AESI, n (%)	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	Ibrutinib (n=324)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 AESI	**294 (90.7)**	**300 (92.6)**	**186 (57.4)**	**184 (56.8)**
Anemia	50 (15.4)	53 (16.4)	7 (2.2)	8 (2.5)
Atrial fibrillation and flutter	17 (5.2)	43 (13.3)	8 (2.5)	13 (4.0)
Hemorrhage	137 (42.3)	134 (41.4)	11 (3.4)	12 (3.7)
Major hemorrhage	12 (3.7)	14 (4.3)	11 (3.4)	12 (3.7)
Hypertension	76 (23.5)	74 (22.8)	49 (15.1)	44 (13.6)
Infections	231 (71.3)	237 (73.1)	86 (26.5)	91 (28.1)
Opportunistic infection	7 (2.2)	10 (3.1)	5 (1.5)	5 (1.5)
Neutropenia†	95 (29.3)	79 (24.4)	68 (21.0)	59 (18.2)
Secondary primary malignancies	40 (12.3)	43 (13.3)	22 (6.8)	17 (5.2)
Skin cancers	21 (6.5)	28 (8.6)	7 (2.2)	4 (1.2)
Thrombocytopenia	42 (13.0)	50 (15.4)	11 (3.4)	17 (5.2)
Tumor lysis syndrome	1 (0.3)	0	1 (0.3)	0

* Specific related MedDRA preferred terms were pooled for each AESI category and summarized.
†Febrile neutropenia was reported in 4(1.2%) vs 3(0.9%) patients treated with zanubrutinib and ibrutinib, respectively.

AE, adverse event; BTKi, Bruton's tyrosine kinase inhibitor; AESI, AEs of special interest; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory.
Extracted from Brown JR et al, N Engl J Med. 2023;388:319-32 (supplement).

BTKi safety – next generation vs 1st generation
ELEVATE-RR Cardiovascular AEs

- Head-to-head BTKi safety data are only available from R/R CLL trials:

	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
Event	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Diarrhea[a,b]	92 (34.6)	3 (1.1)	**121 (46.0)**	**13 (4.9)**
Headache[a,b]	**92 (34.6)**	**4 (1.5)**	53 (20.2)	0
Cough[a]	**77 (28.9)**	2 (0.8)	56 (21.3)	1 (0.4)
Upper respiratory tract infection	71 (26.7)	5 (1.9)	65 (24.7)	1 (0.4)
Pyrexia	62 (23.3)	8 (3.0)	50 (19.0)	2 (0.8)
Anemia	58 (21.8)	31 (11.7)	49 (18.6)	34 (12.9)
Neutropenia	56 (21.1)	52 (19.5)	65 (24.7)	60 (22.8)
Fatigue[b]	54 (20.3)	**9 (3.4)**	44 (16.7)	0
Arthralgia[a]	42 (15.8)	0	**60 (22.8)**	2 (0.8)
Hypertension[a,b]	23 (8.6)	11 (4.1)	**60 (22.8)**	**23 (8.7)**
Nausea	47 (17.7)	0	49 (18.6)	1 (0.4)
Pneumonia	47 (17.7)	28 (10.5)	43 (16.3)	23 (8.7)
Thrombocytopenia	40 (15.0)	26 (9.8)	35 (13.3)	18 (6.8)
Dyspnea	37 (13.9)	6 (2.3)	23 (8.7)	1 (0.4)
Bronchitis	34 (12.8)	3 (1.1)	23 (8.7)	2 (0.8)
Constipation	31 (11.7)	0	37 (14.1)	2 (0.8)
Contusion[a]	31 (11.7)	0	**48 (18.3)**	1 (0.4)
Nasopharyngitis	29 (10.9)	0	27 (10.3)	0
Dizziness	28 (10.5)	0	26 (9.9)	0
Vomiting	28 (10.5)	1 (0.4)	36 (13.7)	3 (1.1)
Peripheral edema	26 (9.8)	0	38 (14.4)	1 (0.4)
Rash	26 (9.8)	2 (0.8)	33 (12.5)	0
Myalgia	25 (9.4)	2 (0.8)	27 (10.3)	1 (0.4)
Atrial fibrillation[a]	24 (9.0)	12 (4.5)	**41 (15.6)**	9 (3.4)
Urinary tract infection[a]	22 (8.3)	3 (1.1)	**36 (13.7)**	6 (2.3)
Back pain[a]	20 (7.5)	0	**34 (12.9)**	2 (0.8)
Epistaxis	19 (7.1)	1 (0.4)	28 (10.6)	1 (0.4)
Muscle spasms[a]	16 (6.0)	0	**35 (13.3)**	2 (0.8)
Dyspepsia[a]	10 (3.8)	0	**32 (12.2)**	0

AE, adverse event; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory.
Extracted from Byrd JC et al. J Clin Oncol, 2021;39:3441-3452.

BTKi safety – next generation vs 1st generation

- Pooled analyses and meta-analyses have provided additional insight:

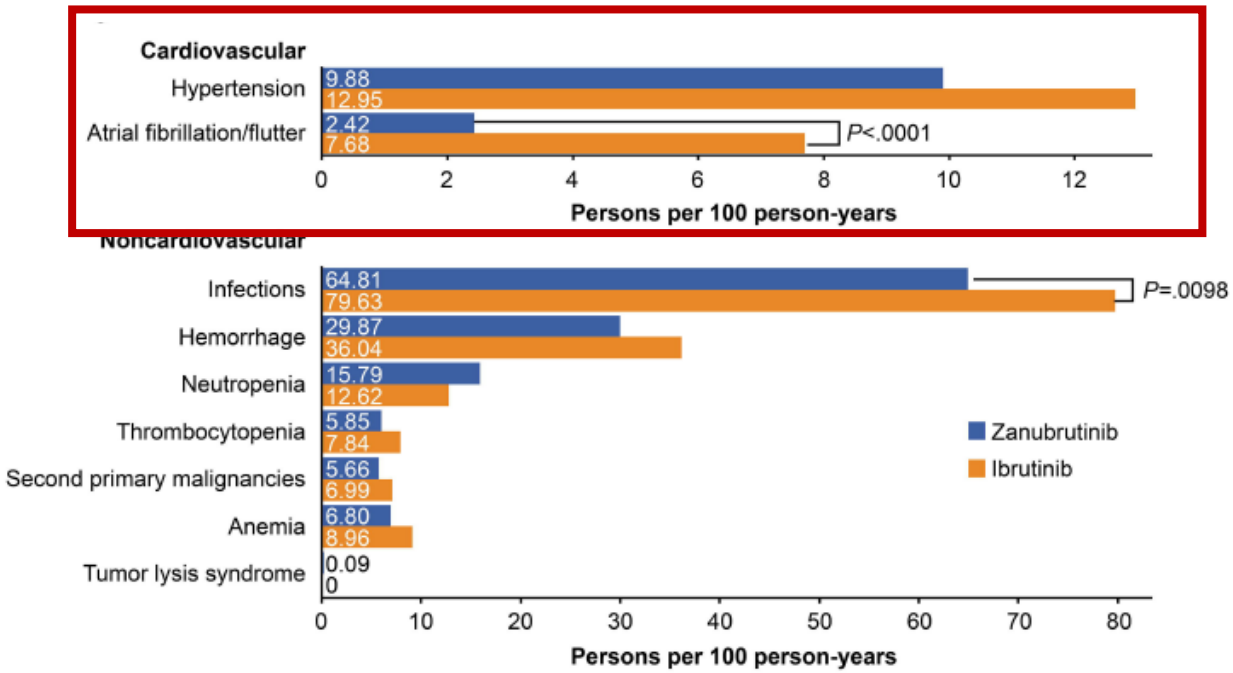
Mayo Clinic meta-analysis[1]

- 61 trials, 6959 patients, CLL/WM/MCL
- 84 AE types analysed for Ibru, Zanu, Acala
- All AEs (all-grade & ≥Grade 3):
  Zanu & Acala similar, both < Ibru
- CV AEs (all-grade only):
  Afib Acala>Zanu; HT Zanu>Acala
- AEs affecting daily QoL: Acala > Zanu
  (fatigue, nausea, vomiting, diarrhea, myalgia, headaches)

Pooled analysis 10 Zanu studies[2]

- Overall and exposure-adjusted incidence of Afib, hypertension & symptomatic VA were lower with Zanu vs Ibru

Zanu pooled safety (1,550 patients)[3]



Acala, acalabrutinib; AE, adverse event; Afib, atrial fibrillation; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CV, cardiovascular; HT, hypertension; Ibru, ibrutinib; MCL, mantle cell lymphoma; QoL, quality of life; VA, ventricular arrhythmia: WM, Waldenström's macroglobulinemia; Zanu, zanubrutinib.

1) Hwang S et al, HemaSphere. 2023;7(S3); 2) Moslehi JJ et al, Blood Adv. 2024;bloodadvances.2023011641; 3) Brown JR et al, Haematologica 2024 [Epub ahead of print].

Case 2 – Recommendation

- Continuous therapy with a next-generation BTK inhibitor for this patient with del(17p) and *TP53*^{MUT}
- In line with Onkopedia & NCCN guidelines, zanubrutinib or acalabrutinib are favoured for better safety profile vs ibrutinib[1,2]
- Decision: due to patient's history of migraine, patient opted to start on zanubrutinib

This is a hypothetical case provided by the Speaker for educational purposes only.
BTK, Bruton's tyrosine kinase; del(17p), deletion of the short arm of chromosome 17; *TP53*^{MUT}, mutated tumor protein p53.
1) Onkopedia guidelines. Chronic Lymphocytic Leukemia (CLL), 2023. Available at: https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll/@@guideline/html/index.html
2) Stephens DM, J Natl Compr Canc Netw. 2023;21(5.5):563–566.

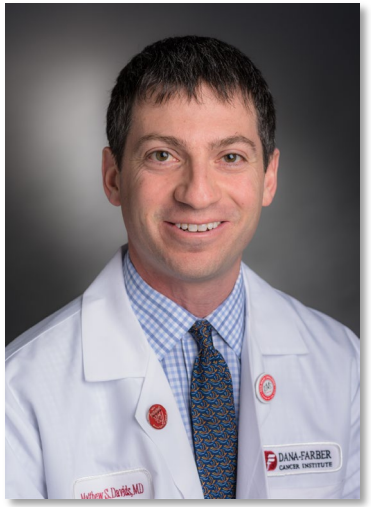
Conclusions (Speaker's own)

- These two cases illustrate:
  - A patient who would be suitable for continuous BTKi
  - A patient who would be suitable for fixed duration Ven-based therapy
- Treatment choice should be based on patient preferences and disease characteristics
- Both choices provide good options for subsequent therapy

BTKi, Bruton's tyrosine kinase inhibitor; Ven, venetoclax.

Treatment selection in R/R CLL

Matthew Davids, MD, MMSc
Dana-Farber Cancer Institute,
Boston, USA



Disclosures

- **Consulting**: AbbVie, Ascentage Pharma, AstraZeneca, BeiGene, Eli Lilly, Genentech, Genmab, Janssen, MEI Pharma, Merck, Nuvalent, Secura Bio, Takeda, TG Therapeutics
- **Research funding**: Ascentage Pharma, MEI Pharma, Novartis

Audience poll question (optional)

- Assuming approval or reimbursement for these drugs, what is your preferred regimen for BTKi-naïve R/R CLL?
  - Ibrutinib ☐
  - Zanubrutinib or acalabrutinib ☐
  - Non-covalent BTKi ☐
  - BTKi + venetoclax ☐
  - Venetoclax + anti-CD20 ☐

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory.

Patient case 1: original presentation

Patient presentation

- 72-year-old woman, night sweats and unexplained weight loss
- Labs: ALC 50 × 10^9/L, Hb 89 g/L, platelets 78 × 10^9/L
- Physical exam: bilateral 4 cm mobile axillary lymph nodes
- Diagnosis: CLL at Binet C/Rai stage IV
- Molecular testing: *IGHV*^{UNMUT} and del(11q), with no *TP53* aberrations
- Medical history: impaired renal function (CrCl 45 mL/min), recurrent DVT (on apixaban), ECOG PS 1
- Patient preferences: difficulty adhering to medications and did not want to add another daily medication; anxious about potential side-effects of another medication taken for an indefinite period, so preferred a fixed-duration regimen; comfortable with receiving infusions; intermediate TLS risk and lives near monitoring facilities

Patient opted for 1L Ven-Obi

This is a hypothetical case provided by the Speaker for educational purposes only.
1L, first-line treatment; ALC, absolute lymphocyte count; B2M, beta-2 macroglobulin; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; DVT, deep vein thrombosis; CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemaglobin; Ibru, ibrutinib; IGHV, immunoglobulin heavy chain variable region; IV, intravenous; TLS, tumor lysis syndrome; *TP53,* tumor protein 53; unmut, unmutated; Ven-Obi, venetoclax + obinutuzumab.

Case 1 – good response to Ven-Obi but progressed after 2 years

- She tolerated treatment well and completed the one-year therapy
- Achieved a CR, though still with low-level detectable MRD in the blood
- Two years later, she developed progressive CLL and now requires 2L therapy
- *TP53* status re-tested and is still wildtype
- You ask whether she has had any changes in life circumstances and discuss:
  - Venetoclax-based re-treatment

    vs.
  - Continuous therapy with cBTKi

    vs.
  - Clinical trial with novel agents

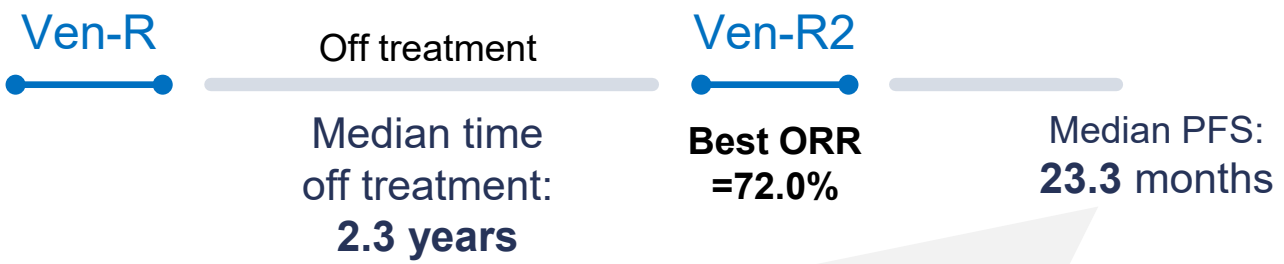
This is a hypothetical case provided by the Speaker for educational purposes only.
2L, second-line treatment; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; MRD, minimal residual disease; *TP53,* tumor protein 53; Ven-Obi, venetoclax + obinutuzumab.

Re-treatment with venetoclax-based regimens after a previous venetoclax-based regimen (1/2)

MURANO substudy (N=25)

Re-treatment with Ven-R after Ven-R

Median prior LOT before first Ven-R: 2
92% high-risk features



Re-treatment 3-year OS rate: 53.1%

Safety: No new safety findings were observed since the 5-year data cut

These data suggest that re-treatment with Ven-R is a viable option for Ven-R pre-treated R/R CLL patients

cBTKi, covalent Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; LOT, line of therapy; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ven-R, venetoclax + rituximab

Kater A at al. Hemasphere. 2023;7(Suppl):e492813f (S201).

Re-treatment with venetoclax-based regimens after a previous venetoclax-based regimen (2/2)

Multicenter, retrospective study(N=46)

Re-treatment with venetoclax-based regimens

Median prior LOT: 2 (0–10)
Prior BTKi: 40%

Ven1 — Off treatment — Ven2

ORR =95.7%

Median time off treatment: **16 months**

ORR =79.5%

Median PFS: **25** months

Ven1:
Ven mono 37%
Ven-R 48%
Ven-Obi 4%
Ven-Ibru 2%
Other 9%

Ven2:
Ven mono 46%
Ven-R 28%
Ven-Obi 11%
Ven-Ibru 4%
Other 11%

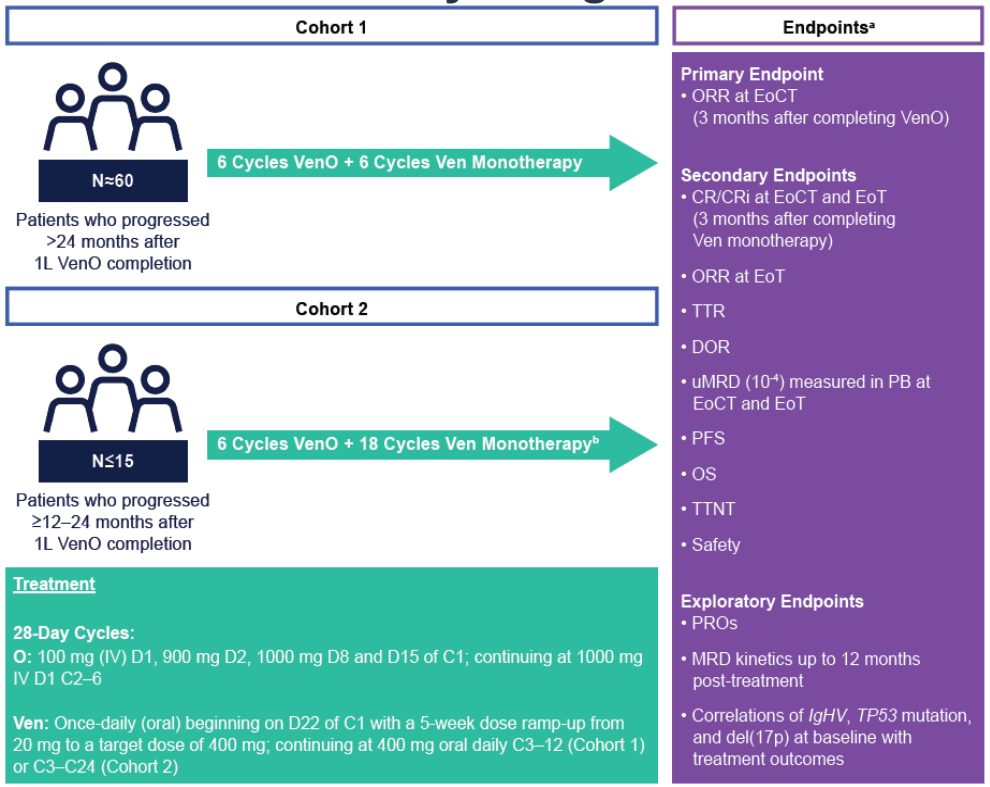
Safety: Data supported re-treatment with venetoclax with 3 patients experiencing TLS

The high ORR and durability of observed remissions support venetoclax re-treatment

CLL, chronic lymphocytic leukemia; LOT, line of therapy; mono, monotherapy; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TLS, tumor lysis syndrome, Ven-Ibru, venetoclax + ibrutinib; Ven-Obi, venetoclax + obinutuzumab; Ven-R, venetoclax + rituximab
Thompson MC et al. Blood Adv 2022;6:4553–4557.

A Phase 2 study of venetoclax plus obinutuzumab retreatment in patients with relapsed CLL (*actively accruing*)

Study design



Objectives

The ReVenG study will assess whether patients with chronic lymphocytic leukemia who completed first-line venetoclax + obinutuzumab (VenO) can derive clinical benefit with VenO retreatment following disease progression

1. The primary objective is to evaluate the overall response rate of VenO retreatment in patients who progressed >24 months after first-line VenO
2. The secondary objective is to quantify time-to-event efficacy endpoints and to assess the safety of VenO retreatment in patients who progressed >24 months after first-line VenO

STUDY OVERVIEW

Multicenter	International	Open-Label	Phase 2	Up to 75 Patients Are Planned for Enrollment	NCT04895436 Planned Initiation in December 2021

DEUTSCHE STUDIENGRUPPE

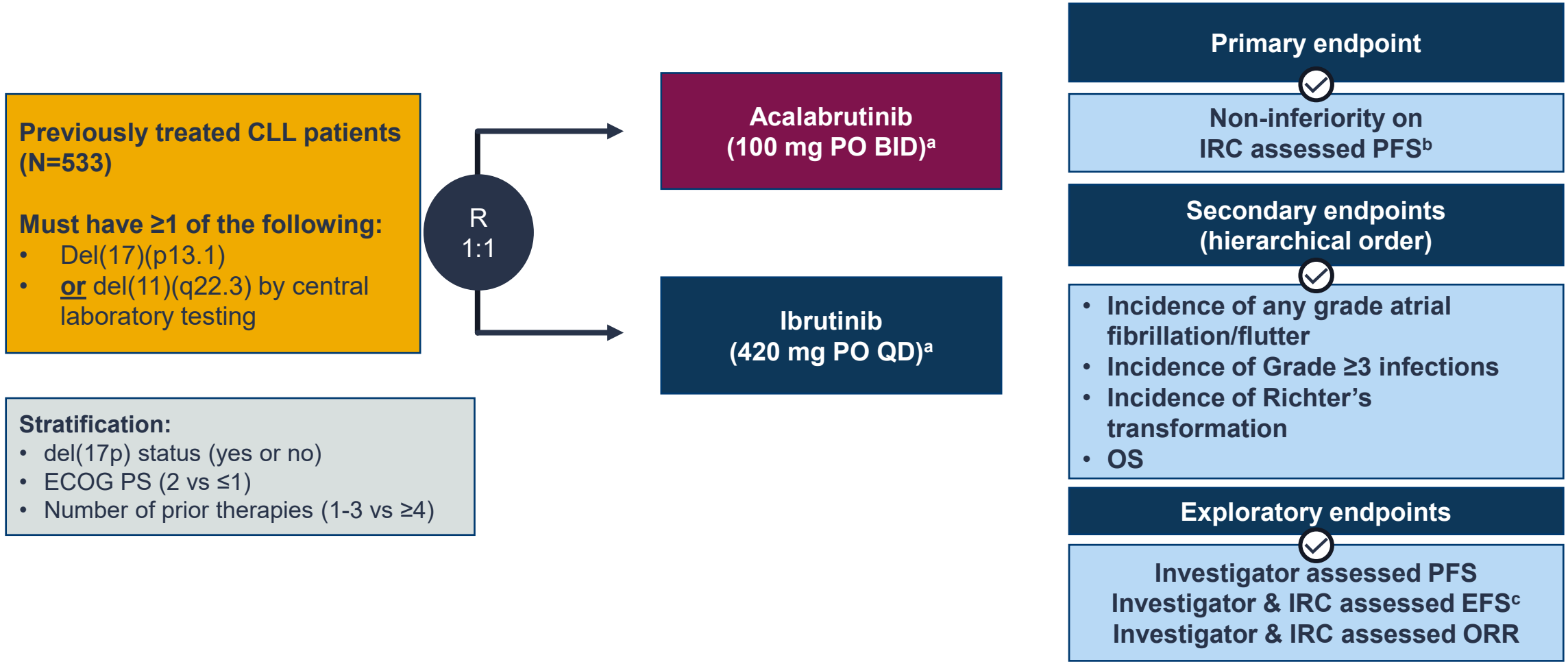
Dana-Farber Cancer Institute

[a]Primary and secondary endpoints are for Cohort 1. Assessments for Cohort 2 are exploratory; [b]Patients in Cohort 2 with detectable MRD (MRD ≥10-4) may continue Ven monotherapy beyond 24 cycles until progressive disease per the investigator's discretion.

1L, first-line; C, cycle; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete marrow recovery; D, day; DOR, duration of response; EoCT, end of combination treatment; EoT, end of treatment; IgHV, immunoglobulin heavy chain; IV, intravenous; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PRO, patient-reported outcome; TTNT, time to next treatment; TTR, time to response; uMRD, undetectable MRD; VenO, venetoclax and obinutuzumab.

Davids MS et al. Blood 2021;138(Supplement 1):2634 (Accessed 06 June 2024). Available at: https://medically.gene.com/content/dam/pdmahub/restricted/haematology/ash-2021/ASH-2021-poster-davids-ReVenG-a-phase-2-study-of-venetoclax-plus-obinutuzumab-retreatment.pdf.

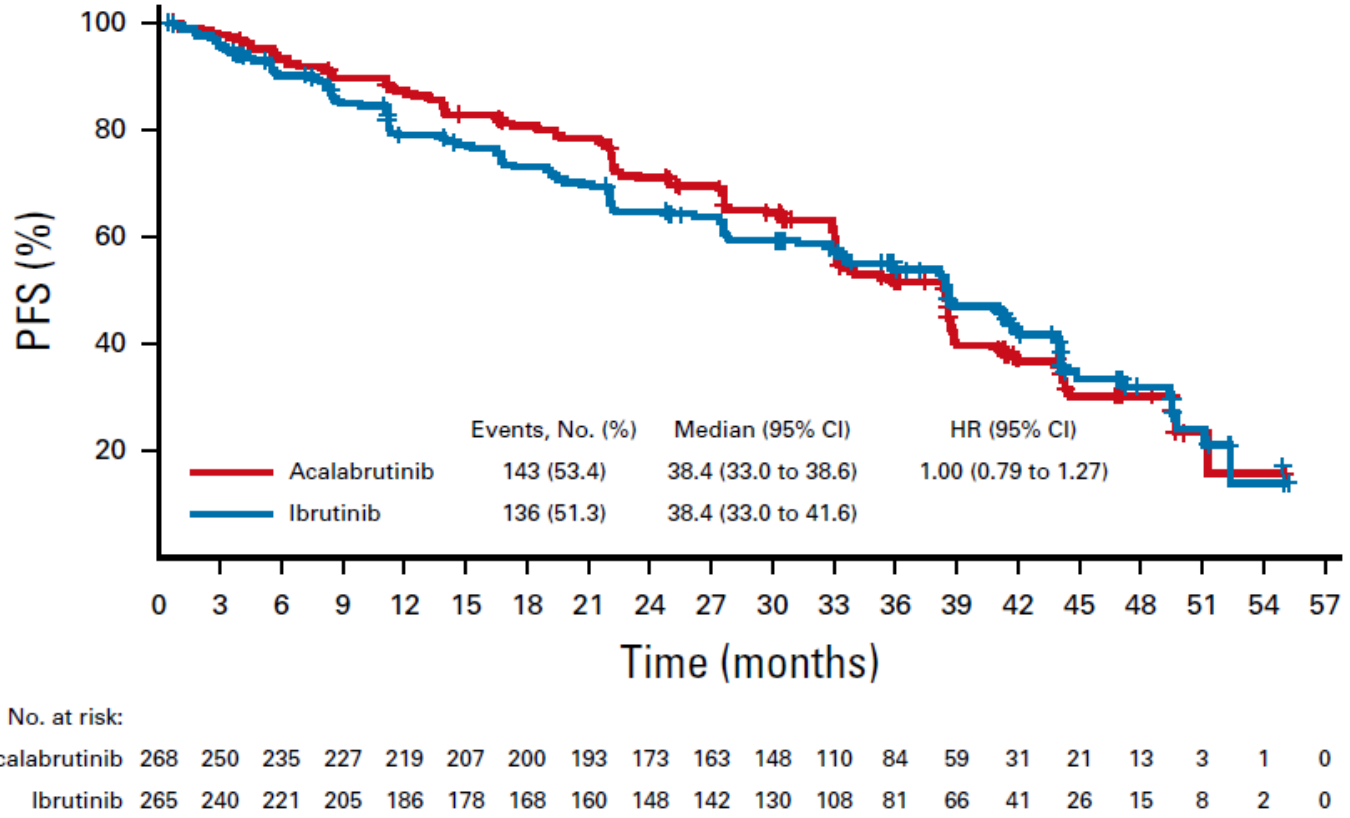
ELEVATE-RR: Study schema



[a]Continued until disease progression or unacceptable toxicity; [b]Conducted after enrollment and accrual of ~250 IRC-assessed PFS events;
[c]Defined as the time from date of randomization to the date of first disease progression, any-cause death, start of subsequent anti-cancer therapy, or discontinuation of treatment due to adverse events
BID, twice daily; CLL, chronic lymphocytic leukemia; ECOG PS, eastern cooperative oncology group performance status; EFS, event-free survival; IRC, independent review committee;
OS, overall survival; PFS, progression-free survival; PO, orally; R, randomization, QD, once daily.
Byrd JC et al. J Clin Oncol, 2021;39:3441-3452.

ELEVATE-RR: Acalabrutinib non-inferior to ibrutinib for PFS

- At a median follow-up of 40.9 months (range 0.0–59.1), acalabrutinib was **non-inferior** to ibrutinib with a median PFS of 38.4 months in both arms (HR: 1.00; 95% CI: 0.79–1.27)



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; RR, relapsed/refractory.
Byrd JC et al. J Clin Oncol. 2021; 39:3441-3452.

ELEVATE-RR: AEs of special interest

	Acalabrutinib (n=266)		Ibrutinib (n=263)	
Events	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Hypertension events[a]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Events/100 person-months	0.444	0.133	1.243	0.435
Patients with a history of hypertension	16 (64.0)	9 (81.8)	30 (49.2)	16 (66.7)
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
Ventricular arrhythmia or cardiac arrest	1 (0.4)	1 (0.4)	5 (1.9)	3 (1.1)
Cardiorespiratory arrest	1 (0.4)	1 (0.4)	0	0
Cardiac arrest	0	0	2 (0.8)	2 (0.8)
Ventricular arrhythmia	0	0	1 (0.4)	0
Ventricular extrasystoles	0	0	1 (0.4)	0
Ventricular fibrillation	0	0	1 (0.4)	1 (0.4)
Atrial fibrillation[b]	25 (9.4)[c]	13 (4.9)	42 (16.0)	10 (3.8)
Events/100 person-months	0.366	0.155	0.721	0.124
Age 75 years or older	8 (32.0)	6 (46.2)	11 (26.2)	4 (40.0)
Patients with a history of atrial fibrillation	10 (40.0)	6 (46.2)	5 (11.9)	2 (20.0)
Patients with risk factors[d]	23 (92.0)	12 (92.3)	32 (76.2)	8 (80.0)
Hypertension	15 (60.0)	6 (46.2)	23 (54.8)	6 (60.0)
Diabetes mellitus[e]	10 (40.0)	5 (38.5)	4 (9.5)	2 (20.0)
Myocardial infarction/ischemia	3 (12.0)	3 (23.1)	4 (9.5)	0
Cardiac disease[f]	2 (8.0)	2 (15.4)	5 (11.9)	2 (20.0)
Time to atrial fibrillation onset, median (range), months	28.8 (0.4–52.0)	22.3 (0.4–45.1)	16.0 (0.5–48.3)	4.8 (0.5–28.2)
Treatment discontinuations because of atrial fibrillation	0	0	7 (16.7)	2 (20.0)
Interventional procedures for atrial fibrillation	4 (16.0)	3 (23.1)	6 (14.3)	1 (10.0)
Cardioversion	4 (16.0)	2 (15.4)	5 (11.9)	1 (10.0)
Cardiac pacemaker insertion	1 (4.0)	1 (7.8)	0	0
Cardiac ablation	0	0	1 (2.4)	0
Implantable defibrillator insertion	0	0	1 (2.4)	0
Atrial fibrillation or flutter incidence in patient subgroups				
Age 75 years or older	8 of 44 (18.2)	6 of 44 (13.6)	11 of 42 (26.2)	4 of 42 (9.5)
Without previous history of atrial fibrillation or flutter	15 of 243 (6.2)	7 of 243 (2.9)	37 of 249 (14.9)	8 of 249 (3.2)
Without risk factors[d]	2 of 99 (2.0)	1 of 99 (1.0)	10 of 99 (10.1)	2 of 99 (2.0)

- Acala had fewer CV events than Ibru:
  - Afib (all-grade) 9.4% vs 16.0%
  - Fewer total cardiac events (24.1% vs 30.0%) and hypertension (9.4% vs 23.2%)
- Grade ≥3 infections (30.8% v 30.0%), RT (3.8% v 4.9%), and major bleeding events (4.5% vs 5.3%) comparable between groups
- Discontinuations due to AEs numerically fewer with Acala vs Ibru (14.7% vs 21.3%)

Acala, acalabrutinib; AE, adverse event; CV, cardiovascular; HR, hazard ratio; Ibru, ibrutinib; RT, Richter's transformation.
[a]Includes events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased; two-sided P value on the basis of Barnard's exact test without multiplicity adjustment, P -value<0.001 (any-grade) and P-value = 0.0214 (Grade 3 or higher); [b]Includes events with the preferred terms of atrial fibrillation and atrial flutter (a patient was only counted once if he or she experienced both types of events); atrial flutter was reported in one patient in the acalabrutinib arm and two patients in the ibrutinib arm (one of the two ibrutinib patients also had an atrial fibrillation event and was counted only once for the combined atrial fibrillation or flutter term). [c]Part of the multiple testing procedure; difference in any-grade incidence rates was –6.6% (95% CI: 212.2–20.9), P-value = 0.02; [d]Risk factors for atrial fibrillation were based on medical review; [e]Includes patients with a history of diabetes mellitus or type 2 diabetes mellitus; [f]Includes patients with a history of coronary artery bypass, coronary artery disease, cardiomyopathy, cardiac failure chronic, or cardiac failure congestive.
Byrd JC et al. J Clin Oncol. 2021;39(31):3441-3452.

ALPINE: Study Design

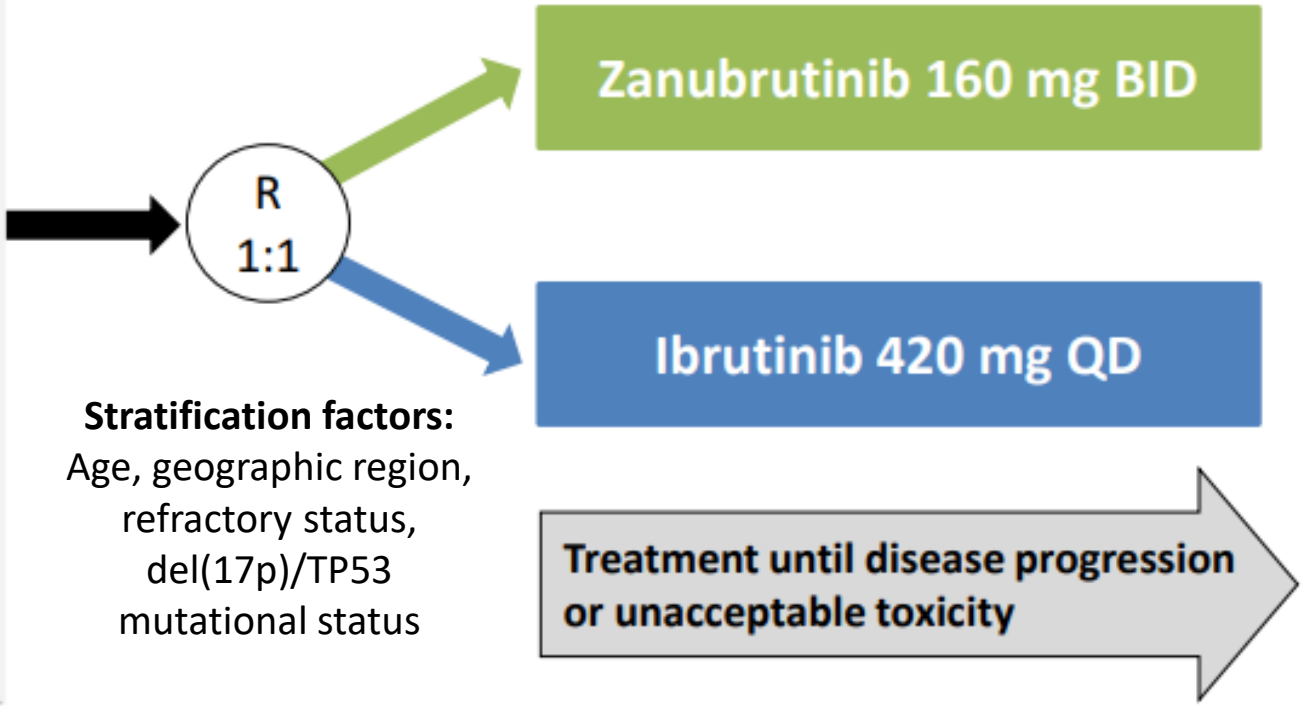
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria

- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

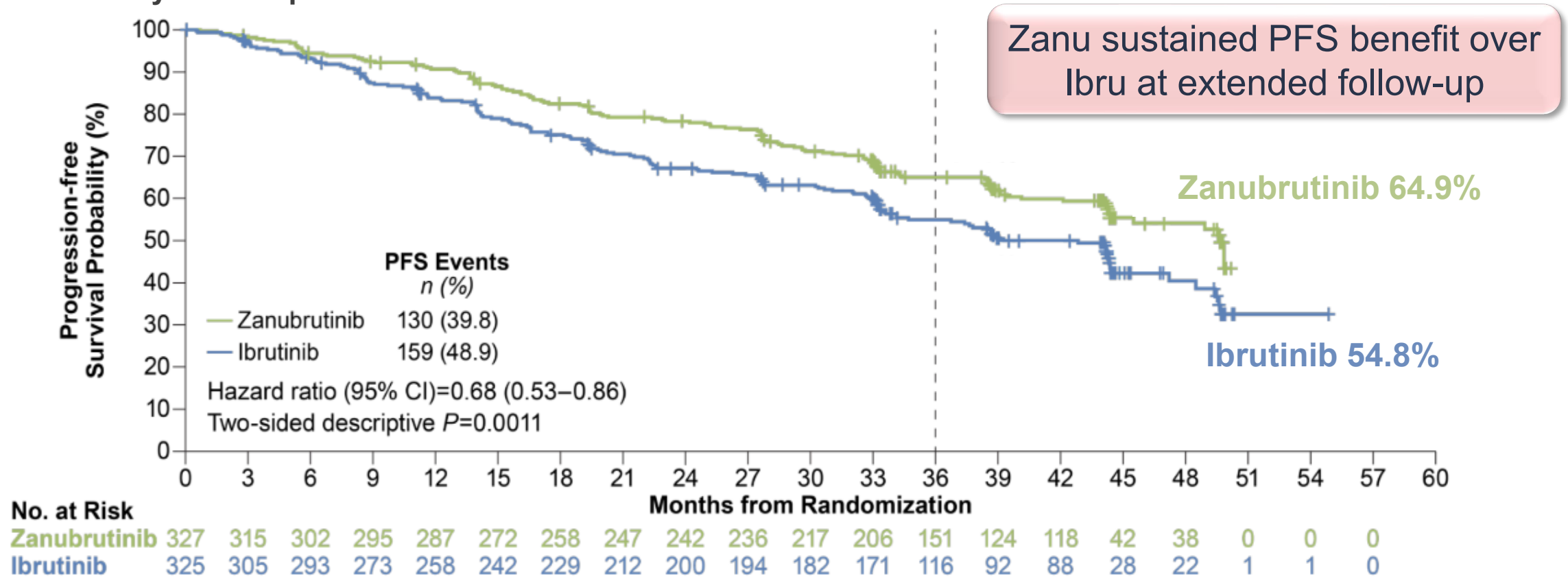


BID, twice daily; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CT, computed tomography; EFS, event-free survival; MRI, magnetic resonance imaging; IRC, independent review committee; R, randomization, QD, once daily; SLL, small lymphocytic leukemia; *TP53*, tumor protein 53

Extracted from Brown JR, Eichhorst B, Lamanna N, O'Brien SM, Tam CS, Qiu L et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA (Accessed 05 June 2024). Available at: Brown_BGB-3111-305_ASH_Presentation_2023.pdf.

ALPINE: Zanubrutinib sustains PFS benefit vs ibrutinib

Median study follow-up of 39.0 months



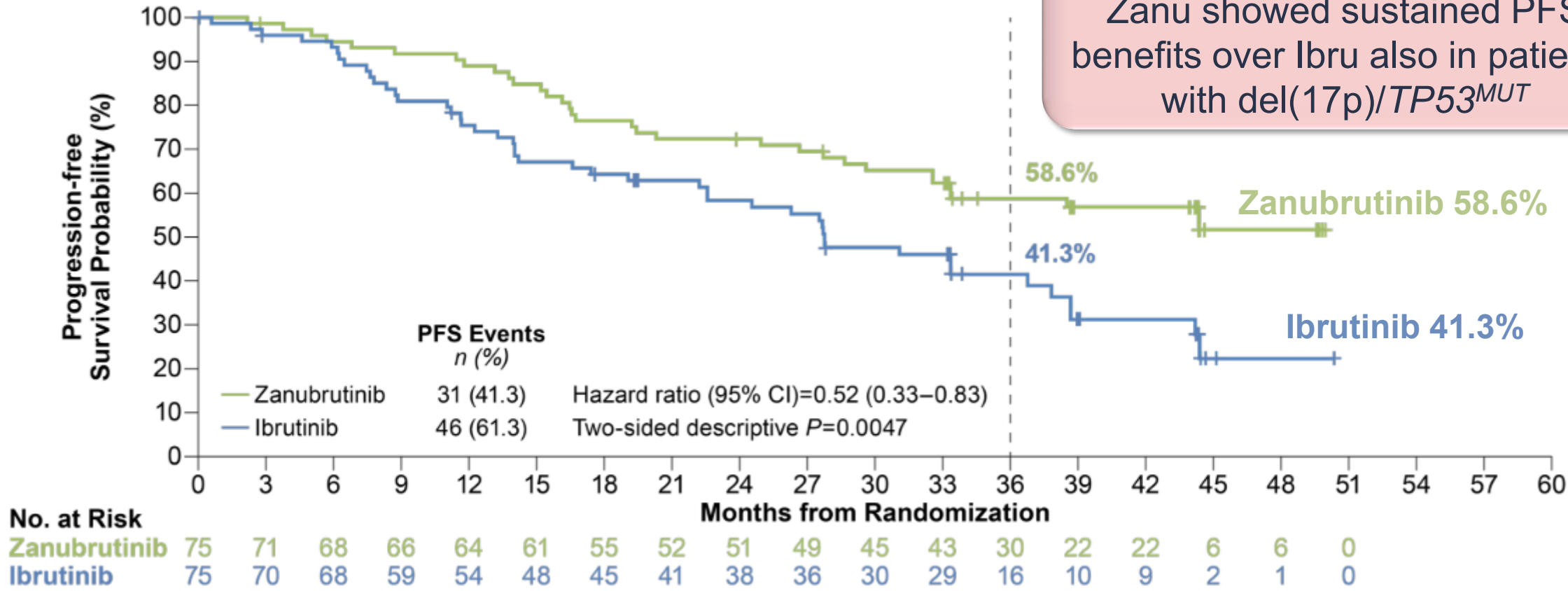
- The durable PFS benefits with Zanu were observed across major subgroups, including multiple sensitivity analyses

Data cutoff: 15 Sep 2023.
CI, confidence interval; HR, hazard ratio; Ibru, ibrutinib; PFS, progression-free survival; Zanu, zanubrutinib.
Extracted from Brown JR, Eichhorst B, Lamanna N, O'Brien SM, Tam CS, Qiu L et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA (Accessed 05 June 2024). Available at: Brown_BGB-3111-305_ASH_Presentation_2023.pdf.

ALPINE: PFS del(17p)/*TP53*^{MUT} subgroup, extended follow-up

Median study follow-up of 39.0 months

At a median follow-up of 3 years, Zanu showed sustained PFS benefits over Ibru also in patients with del(17p)/*TP53*^{MUT}

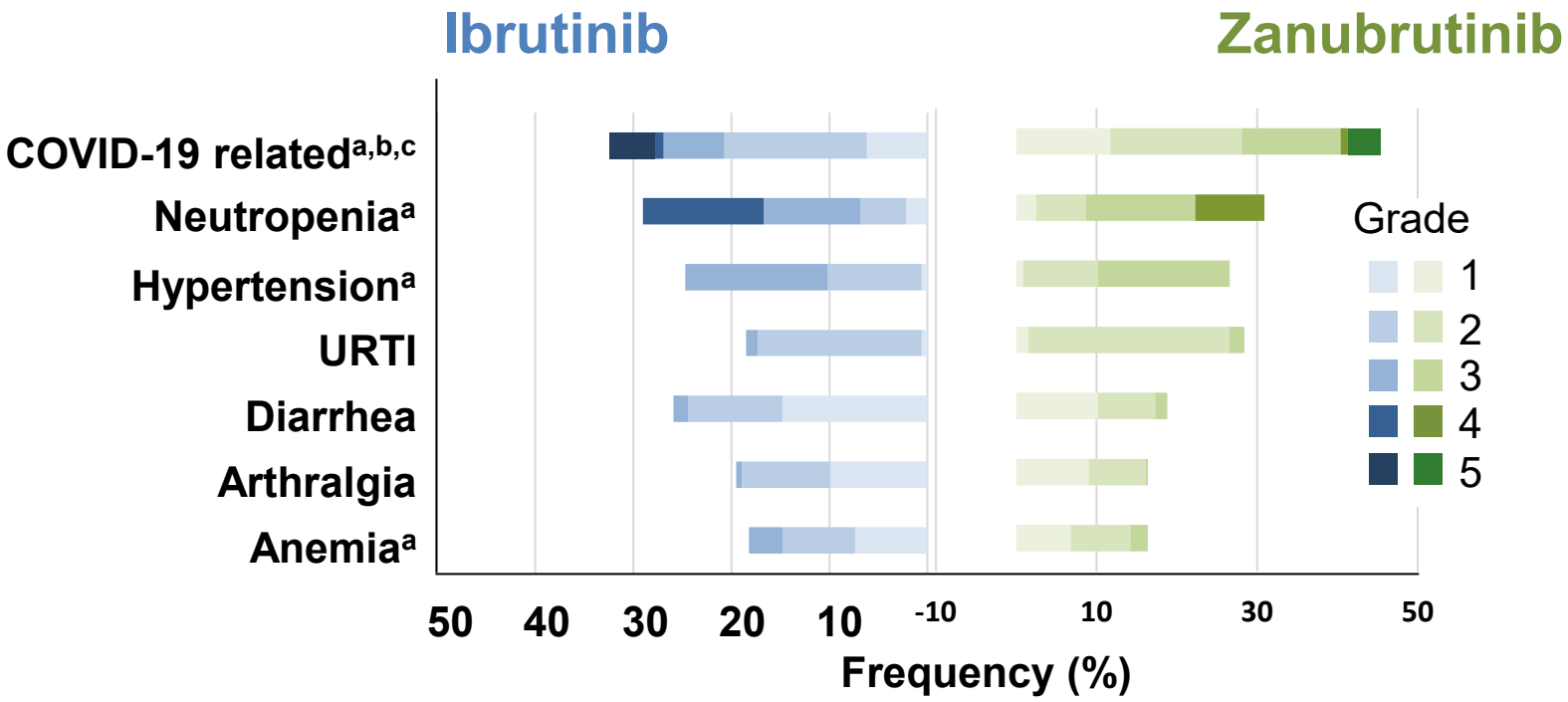


Data cutoff: 15 Sep 2023.

CI, confidence interval; HR, hazard ratio; Ibru, ibrutinbi; mut, mutated; PFS, progression-free survival; TP53, tumor protein 53; Zanu, zanubrutinib.

Extracted from Brown JR, Eichhorst B, Lamanna N, O'Brien SM, Tam CS, Qiu L et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA (Accessed 05 June 2024). Available at: Brown_BGB-3111-305_ASH_Presentation_2023.pdf.

ALPINE: most common AEs by grade occurring ≥15% of patients in both arms

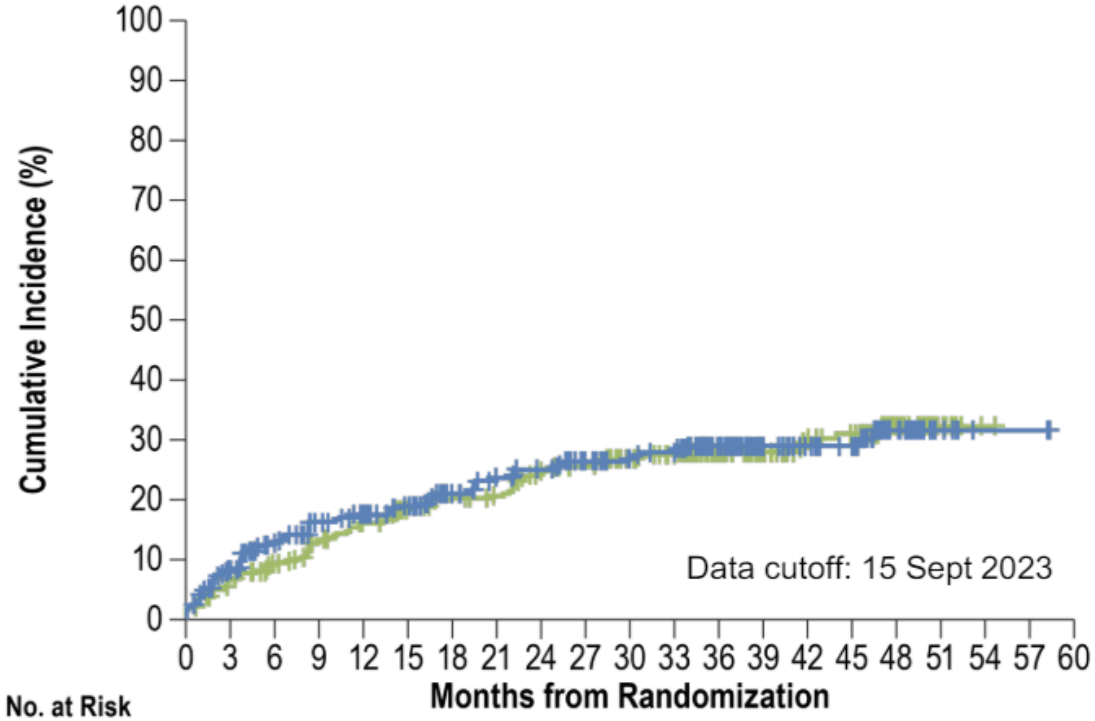


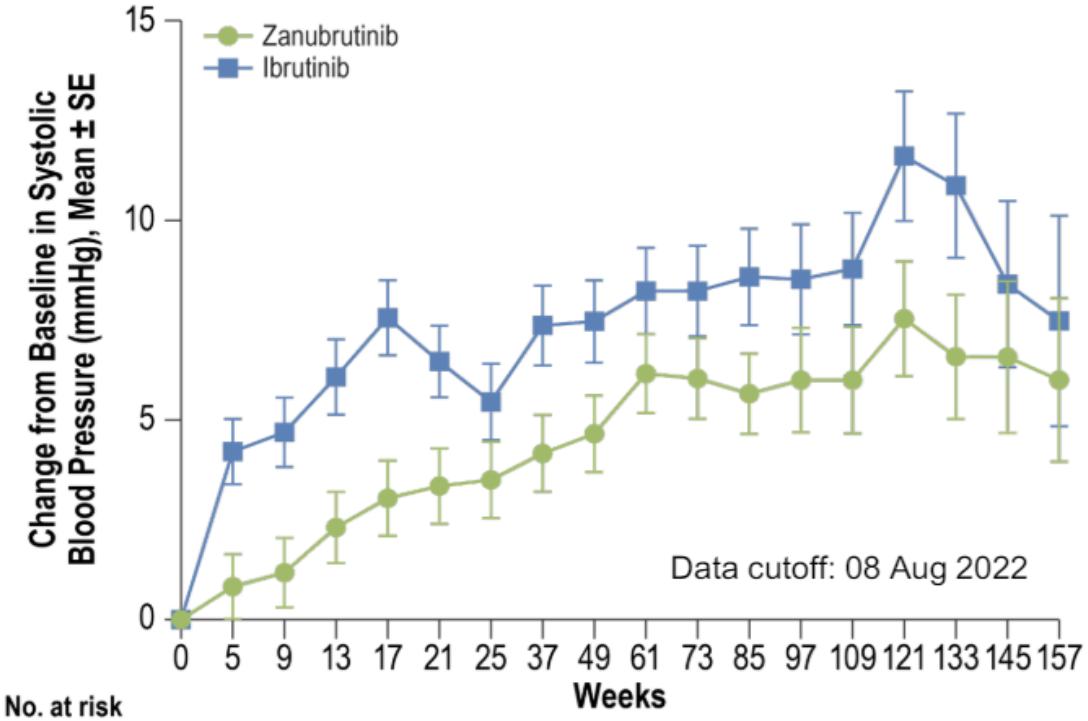
With over 3 years of treatment, Zanu continues to be more efficacious and better tolerated vs Ibru

- No new safety signals emerging with longer follow-up
- The cardiac safety profile remained favorable

Data cutoff: 15 Sep 2023.
[a]Pooled MedDRA preferred terms.
[b]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.
[c]Grade 5 COVID-related events: 13 (4.0%) with zanubrutinib and 15 (4.6%) with ibrutinib.
AE, adverse events; COVID-19, Coronavirus disease-19; Ibru, ibrutinib; URTI, upper respiratory tract infection; Zanu, zanubrutinib.
Extracted from Brown JR, Eichhorst B, Lamanna N, O'Brien SM, Tam CS, Qiu L et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA (Accessed 05 June 2024). Available at: Brown_BGB-3111-305_ASH_Presentation_2023.pdf.

ALPINE: despite similar overall hypertension rates, changes in systolic blood pressure and EAIR of hypertension were lower with zanubrutinib[1,2]





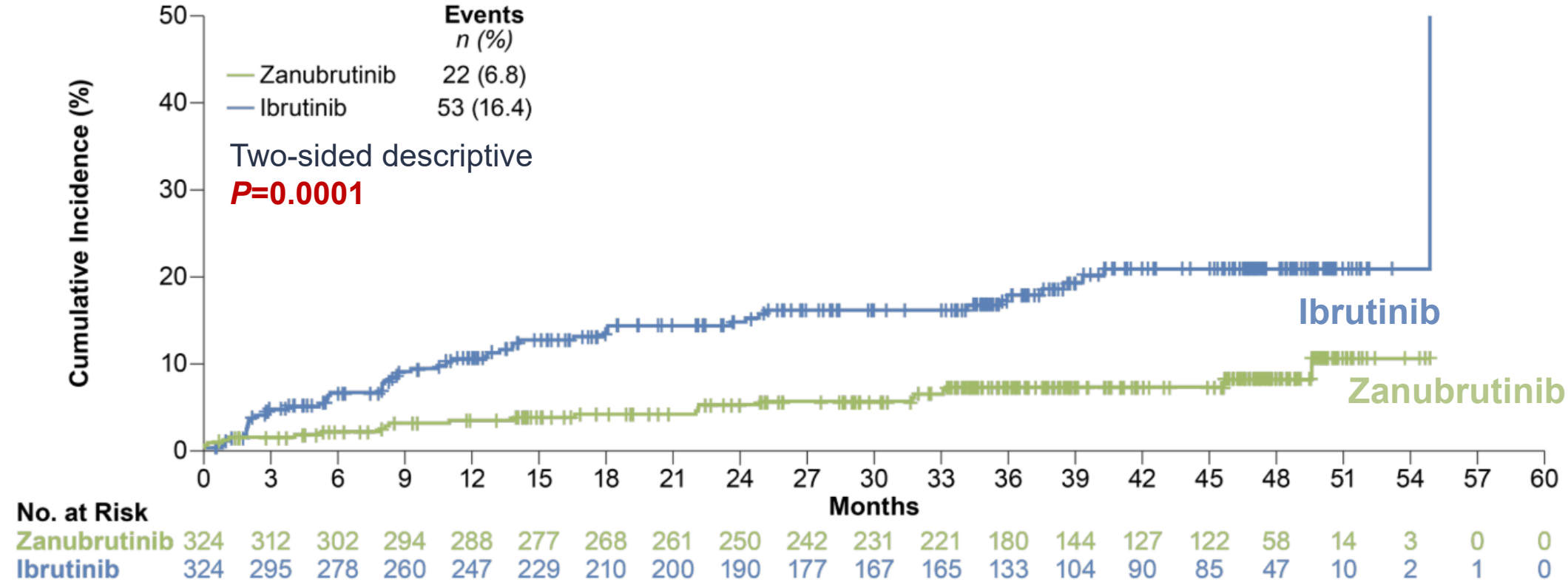
- In ALPINE, initiation of new anti-HTN or a new class of anti-HTN occurred less frequently in the Zanu arm vs the Ibru arm in patients with CLL/SLL[3]
- Adoption of anti-HTN occurred sooner with Ibru than Zanu[3]

Anti-HTN, antihypersensitives; CLL, chronic lymphocytic leukemia; EAIR, exposure-adjusted incidence rate; Ibru, ibrutinib; SE, standard error; SLL, small lymphocytic leukemia; Zanu, zanubrutinib.

1. Extracted from Brown JR, Eichhorst B, Lamanna N, O'Brien SM, Tam CS, Qiu L et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA (Accessed 05 June 2024). Available at: Brown_BGB-3111-305_ASH_Presentation_2023.pdf; 2. Moslehi J et al. Blood Adv. 2024;8(10):2478–2490; 3. Ramirez D et al. ASCO 2024. Abstract e19016. Available at: https://ascopubs.org/doi/pdf/10.1200/JCO.2024.42.16_suppl.e19016.

ALPINE: significantly fewer atrial fibrillation/flutter events with zanubrutinib than ibrutinib

Median study follow-up of 39.0 months



Data cutoff: 15 Sep 2023.

Extracted from Brown JR, Eichhorst B, Lamanna N, O'Brien SM, Tam CS, Qiu L et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA (Accessed 05 June 2024). Available at: Brown_BGB-3111-305_ASH_Presentation_2023.pdf.

ALPINE: Cardiac adverse events, extended follow-up

- Serious cardiac adverse events were lower with zanubrutinib vs ibrutinib
  - Atrial fibrillation/flutter (3 vs 13)
  - Ventricular fibrillation (0 vs 2)
  - MI[a]/acute coronary syndrome (3 vs 3)
- **Fatal cardiac events[b]:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

Zanubrutinib continues to demonstrate a more favorable cardiac safety profile than ibrutinib

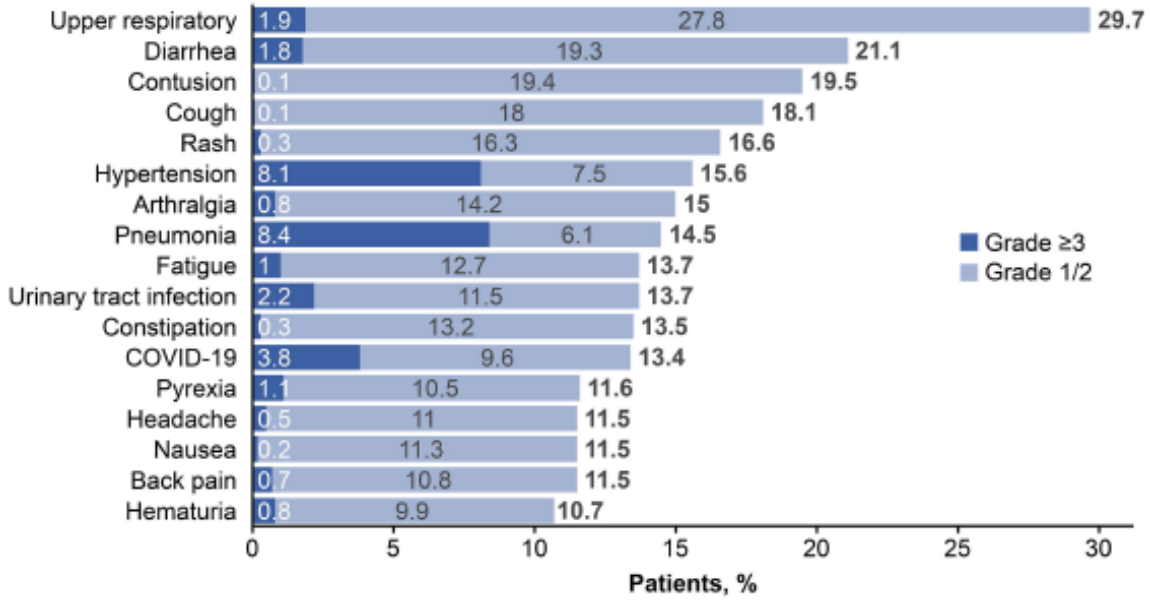
	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**80 (24.7)**	**112 (34.6)**
Serious cardiac adverse events	**11 (3.4)**	**31 (9.6)**
Cardiac adverse events leading to treatment discontinuation	**3 (0.9)**	**15 (4.6)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation/flutter	1 (0.3)	6 (1.9)
Cardiac failure	1 (0.3)	2 (0.6)
Cardiac arrest	0	2 (0.6)[b]
Cardiac failure acute	0	1 (0.3)[b]
Congestive cardiomyopathy	0	1 (0.3)[b]
Myocardial infarction	0	1 (0.3)[b]
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

[a]Including acute MI; [b]Fatal cardiac event (n=6); 1 death (myocardial infarction with ibrutinib) was not listed due to discontinuation due to diarrhea 14 days prior to the fatal event.
MI, myocardial infarction.

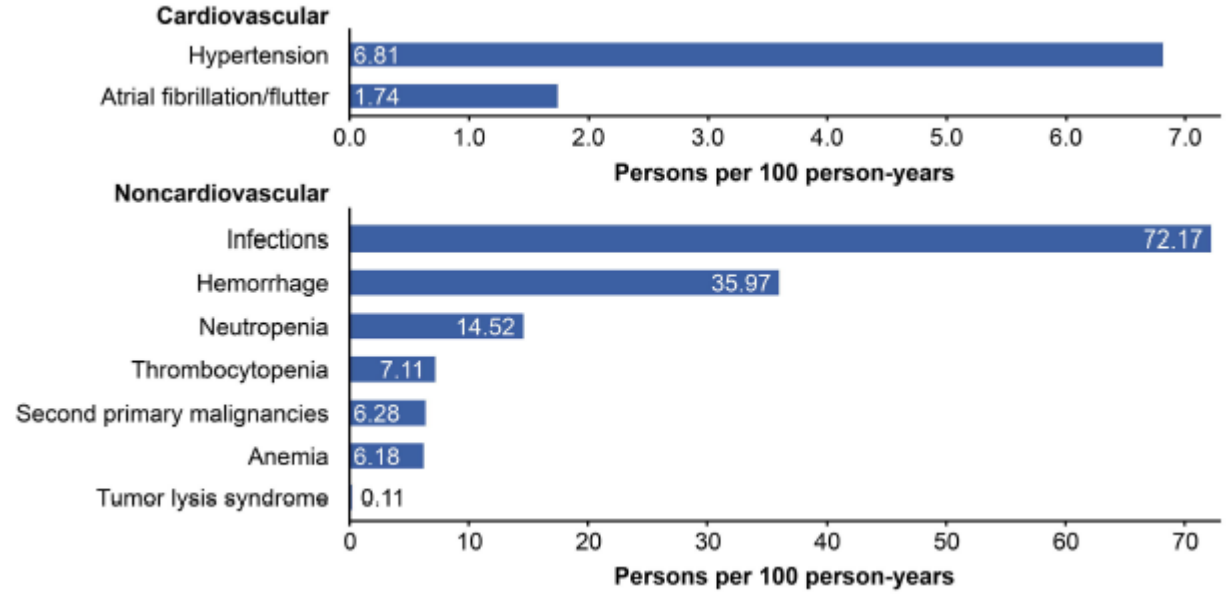
Extracted from Brown JR, Eichhorst B, Lamanna N, O'Brien SM, Tam CS, Qiu L et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA (Accessed 05 June 2024). Available at: Brown_BGB-3111-305_ASH_Presentation_2023.pdf.

Zanubrutinib Pooled Safety Analysis: n=1,550, median follow-up 34.4 mo. (1/2)

TEAEs in ≥10% or Grade ≥3 TEAEs in ≥5% of patients treated with zanubrutinib (N=1550)[1]



AESIs in total pooled zanubrutinib population (N=1550)[1]

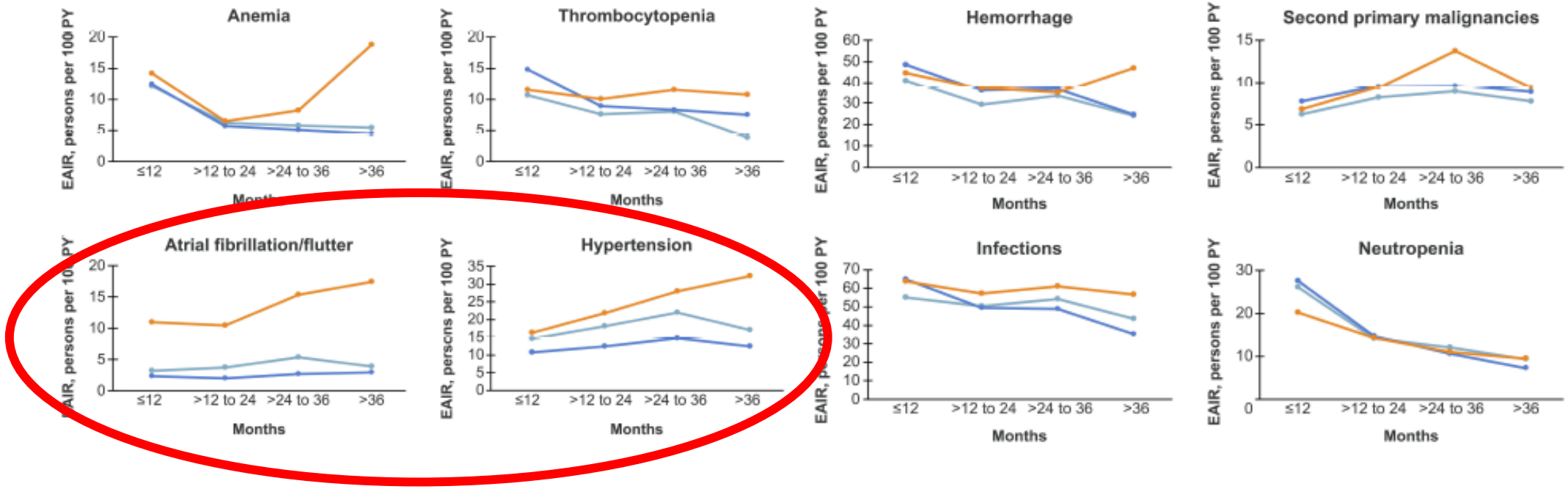


In this analysis, zanubrutinib remained well tolerated, consistent with the previous analysis[2], with no emergence of new safety signals, even at a median treatment duration of approximately 3 years.

AESI, adverse event of special interest; mo., month; TEAE, treatment emergent adverse event.

1) Brown JR et al. Haematologica, 2024; doi: 10.3324/haematol.2023.283846; 2) Tam CS et al. Blood Adv. 2022;6(4):1296-1308.

Zanubrutinib Pooled Safety Analysis: AESI EAIRs over time were relatively constant or decreased with Zanu (2/2)



No. at risk (person-years at risk)

All zanubrutinib (N=1,550)	1550 (1399.9)	1282 (1179.0)	1040 (912.0)	698 (913.8)	1550 (1399.9)	1282 (1179.0)	1040 (912.0)	698 (913.8)	1550 (1399.9)	1282 (1179.0)	1040 (912.0)	698 (913.8)	1550 (1399.9)	1282 (1179.0)	1040 (912.0)	698 (913.8)
Zanu in ASPEN/ALPINE (n=425)	425 (403.0)	384 (353.1)	268 (223.9)	125 129.1)	425 (403.0)	384 (353.1)	268 (223.9)	125 129.1)	425 (403.0)	384 (353.1)	268 (223.9)	125 129.1)	425 (403.0)	384 (353.1)	268 (223.9)	125 129.1)
Ibru in ASPEN/ALPINE (n=422)	422 (381.8)	348 (306.8)	240 (182.1)	107 (74.4)	422 (381.8)	348 (306.8)	240 (182.1)	107 (74.4)	422 (381.8)	348 (306.8)	240 (182.1)	107 (74.4)	422 (381.8)	348 (306.8)	240 (182.1)	107 (74.4)

AESI, adverse event of special interest; EAIR, exposure-adjusted incidence rate; Ibru, ibrutinib; PY, patient-years; Zanu, zanubrutinib.

Brown JR et al. Haematologica, 2024; doi: 10.3324/haematol.2023.283846.

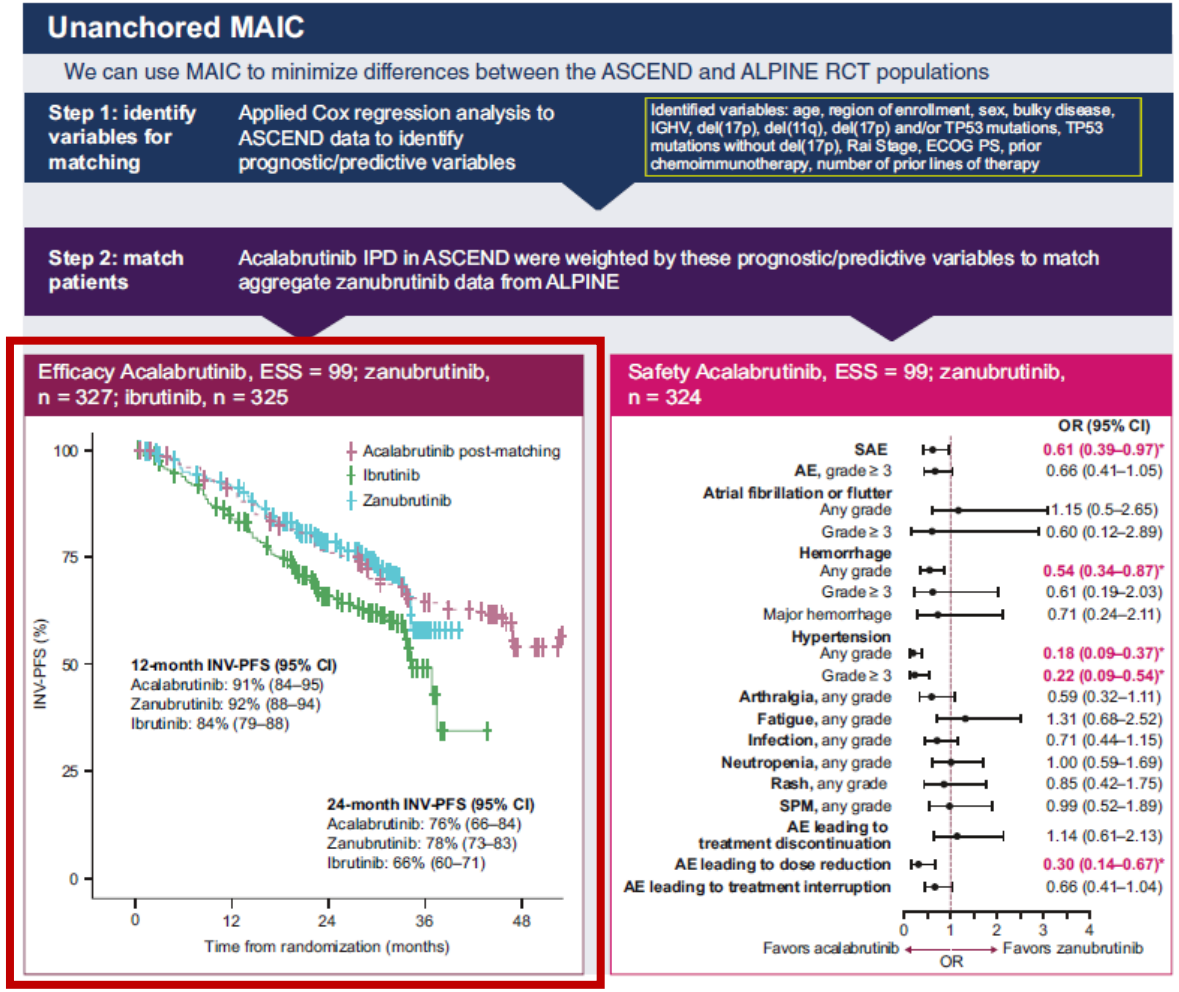
Matching-adjusted indirect comparisons and meta-analyses: context and limitations

- **Randomized Controlled Trials** (RCTs) are the gold standard in clinical evidence-based decision-making[1]
- **Matching-adjusted indirect comparisons** are a methodology to compare data across clinical trials and represent a lower level of evidence than RCTs[1-3]
  - The results of the comparisons should be interpreted with caution and should not drive treatment decisions for individual patients
  - Based on the variables selected for matching, outcomes of the comparisons may differ
- **Meta-analyses** may also provide valuable information across multiple clinical trials, especially on safety[1,2]

RCT, randomized controlled trial.

1) Signorovitch JE et al, Value Health. 2012;15(6):940-7; 2) Signorovitch JE et al, J Dermatolog Treat. 2023;34(1):2169574; 3) Jiang T et al, Adv Ther. 2023;40(7):2985-3005.

Comparison #1: acalabrutinib vs zanubrutinib

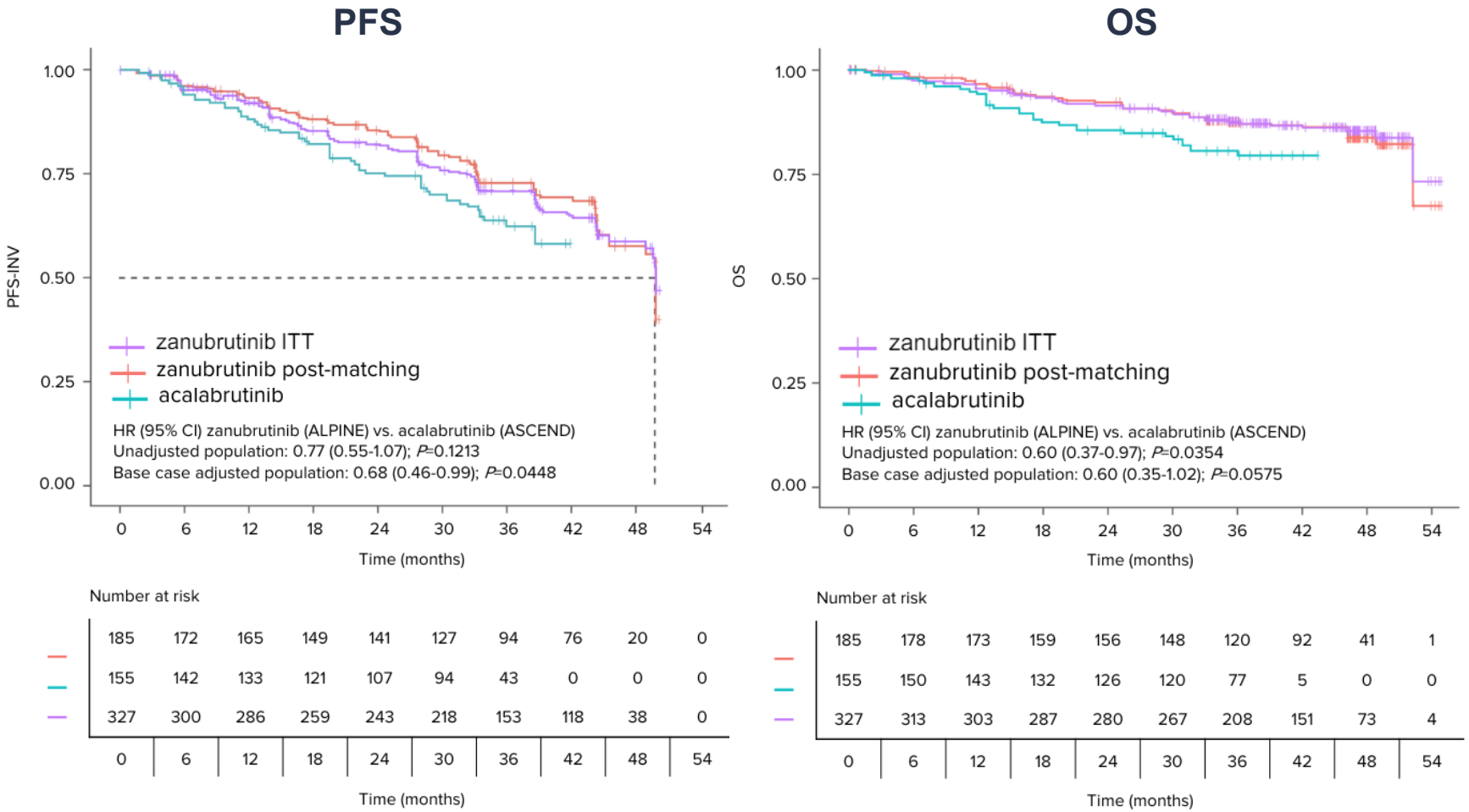


This comparison showed that, when matching on patient baseline characteristics known to be prognostic and/or predictive of INV-PFS, Acala and Zanu have a similar efficacy in the treatment of R/R CLL when evaluated using INV-PFS

Acala, acalabrutinib; CI, confidence interval; CLL, chronic lymphocytic leukemia; H2H, head-to-head; MAIC, matching-adjusted indirect comparison; ESS, ESS, effective sample size; INV, investigator-assessed; OR, odds ratio; RCT, randomized controlled trial; R/R, relapsed/refractory; Zanu, zanubrutinib.

Kittai AS et al. Am J Hematol. 2023;98:E387–E390.

Comparison #2: zanubrutinib vs acalabrutinib – PFS and OS



- This comparison aimed to address the limitations of the comparison on the previous slide (impact of COVID, chosen follow-up timepoints being compared)
- This comprehensive comparison showed a significant PFS and CR advantage, and potentially improved OS for Zanu compared with Acala
- Results were robust across multiple sensitivity analyses

Acala, acalabrutinib; CI, confidence interval; CR, complete response; HR, hazard ratio; INV, investigator-assessed; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; Zanu, zanubrutinib.
Extracted from Shadman M, et al. Poster presentation at the 28th ICHM 2024; February 29 - March 3, 2024, Miami, FL. Available at: https://www.onclive.com/view/efficacy-of-zanubrutinib-versus-acalabrutinib-in-the-treatment-of-relapsed-or-refractory-chronic-lymphocytic-leukemia-r-r-cll-a-matching-adjusted-indirect-comparison-maic-.

Next-generation BTKis – efficacy

Zanubrutinib versus acalabrutinib in R/R CLL (Network Meta-Analysis: ALPINE, ELEVATE, ASCEND)[1]

Zanubrutinib vs. acalabrutinib	High-risk with COVID-19 adjustment	High-risk without COVID-19 adjustment
HR [95% CrI] Probability Better (%)		
PFS	0.54 (0.32, 0.92), 98.6	0.58 (0.34,0.98), 98.0
OS	0.72 (0.35, 1.48), 81.7	0.84 (0.43, 1.65), 69.1
OR [95% CrI] Probability Better (%)		
ORR	1.91 (0.75, 5.00), 91.7	1.69 (0.61, 4.97), 84.4
CR	2.07 (0.50, 9.67), 84.4	1.84 (0.50, 7.20), 81.6

Zanubrutinib compared with acalabrutinib demonstrated:

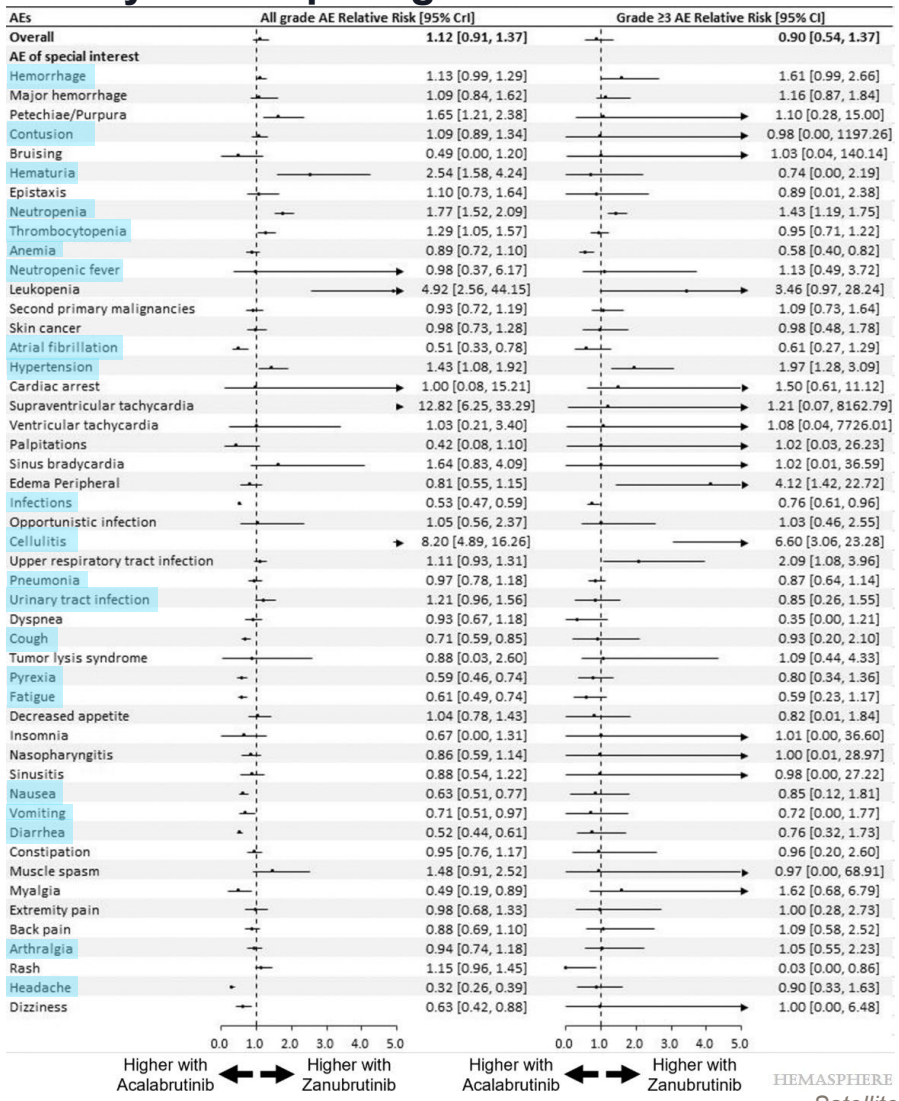
- A statistically significant **improvement in PFS** in **high-risk** patients
- A trend towards improvement in OS, ORR, and CR

CLL, chronic lymphocytic leukemia; CrI, credible interval; CR, complete response; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory

Shadman M et al. Poster presented at ASCO 2024; Abstract 7048 (Accessed 05 June 2024). Available at: Shadman_RR_CLL_NMA_Zanu_vs_Acala_ASCO_Abstract_2024.pdf.

Next-generation BTKis – safety

Meta-analysis comparing TEAEs of acalabrutinib vs zanubrutinib



A meta-analysis showed that zanubrutinib and acalabrutinib have distinct safety profiles:

- Zanubrutinib had lower rates of Afib/flutter and infections, and lower rates of AEs that limit activities of daily living including GI toxicities (diarrhea, nausea, vomiting), headache and fatigue
- Acalabrutinib had lower rates of hypertension and neutropenia

Grade ≥3 AEs of Interest are highlighted in blue.
Afib, atrial fibrillation; AE, adverse events; GI, gastrointestinal;TEAE, treatment emergent adverse event.
Hwang S et al. EHA 2023; Abstract P632. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10428881/.

Patient case 1: treatment decision and rationale

- A covalent BTK inhibitor would be suitable for this patient who progressed on Ven-Obi
- Following discussion with the patient, zanubrutinib was chosen based on PFS superiority results from ALPINE
- Entry of the patient into a clinical trial (such as ReVenG, Ven-Obi re-treatment) would have been an alternative option

This is a hypothetical case provided by the Speaker for educational purposes only.
BTK, Bruton's tyrosine kinase; PFS, progression-free survival; Ven-Obi, venetoclax + obinutuzumab.

RR CLL – Patient case 2

Patient case 2: original presentation

Patient presentation

- 55-year-old man, fatigue and shortness of breath
- Labs: ALC 129 × 10^9/L, Hb 85 g/L, platelets 95 × 10^9/L, B2M 4 mg
- Physical exam: 3 cm lymph nodes and spleen/liver enlargement
- Diagnosis: CLL at Binet C/Rai IV
- High-risk features: *IGHV*^{UNMUT}, del(17p), *TP53*^{MUT}
- Past medical history: atrial fibrillation (on atenolol and dabigatran); gastroesophageal reflux disease (on omeprazole); history of migraine; otherwise, healthy (ECOG PS 1)
- No preference for continuous versus fixed-duration therapy nor for all-oral therapy versus regimens requiring infusions.

Patient opted for 1L zanubrutinib

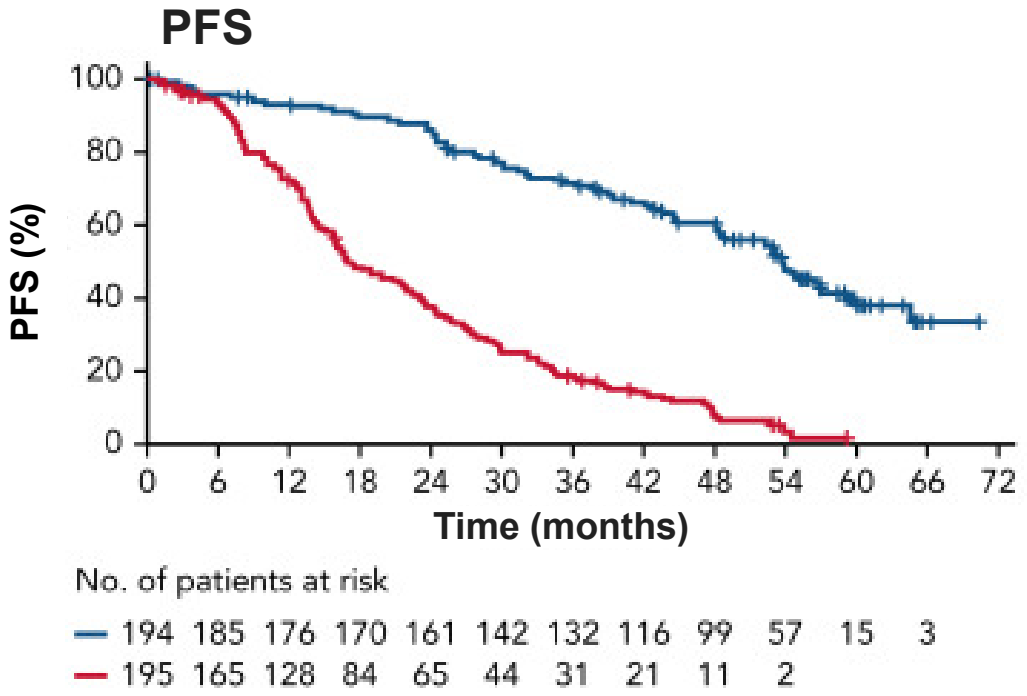
This is a hypothetical case provided by the Speaker for educational purposes only.
1L, first-line treatment; ALC, absolute lymphocyte count; B2M, beta-2 macroglobulin; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemaglobin; Ibru, ibrutinib; IGHV, immunoglobulin heavy chain variable region; IV, intravenous; mut, mutated; TP53, tumor protein 53.

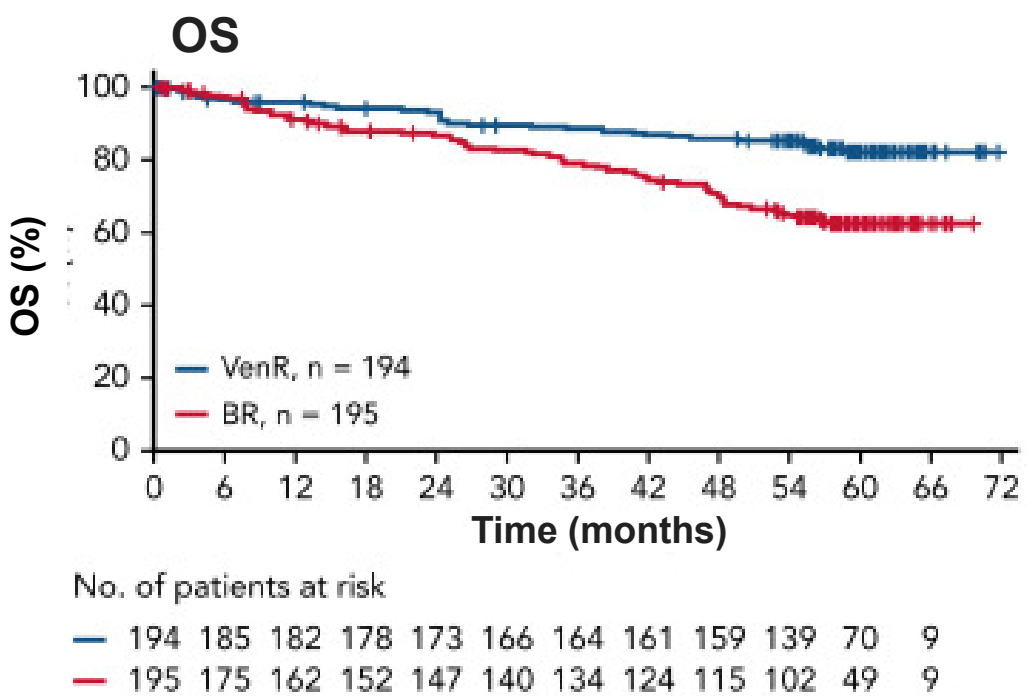
Case 2 – good response to zanubrutinib but eventual progression

- He tolerated this well and achieved PR after about 6 months on treatment
- Continued on zanubrutinib in good remission for about 4 years, but subsequently developed disease progression
- Sequencing reveals a *BTK* C481S mutation
- He asks about other CLL treatment options

This is a hypothetical case provided by the Speaker for educational purposes only.
BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; PR, partial response.

MURANO study of Ven-R in R/R CLL – 5-year analysis





Treatment arm	Median PFS, months (95% CI)	HR (95% CI); P value*	5-year PFS, % (95% CI)
Ven-R	53.6 (48.4, 57.0)	0.19 (0.15, 0.26)	37.8 (28.8, 46.8)
BR	17.0 (15.5, 21.7)	<0.0001	NE

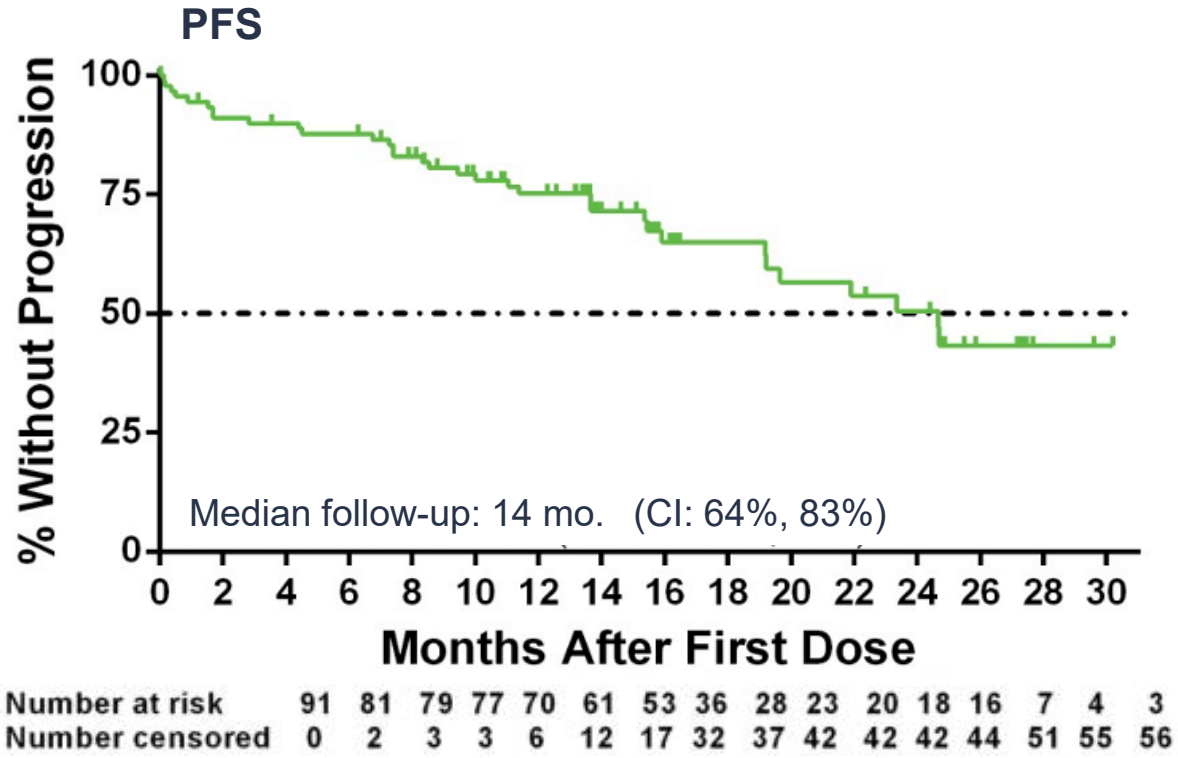
Treatment arm	Median OS, months (95% CI)	HR (95% CI); P value*	5-year OS, % (95% CI)
Ven-R	NE	0.40 (0.26, 0.62)	82.1 (76.4, 87.8)
BR	NE	<0.0001	62.2 (54.8, 69.6)

Safety: No new safety signals were identified

BR, bendamustine + rituximab; CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival; Ven-R, venetoclax + rituximab.
Seymour JF et al., Blood. 2022;140(8):839–850.

Venetoclax is active post-ibrutinib

- **M14-032 was the first prospective study of any treatment for patients progressing on a KI**



Summary:

- 91 pts progressed after ibrutinib and were treated with venetoclax
- Median 4 prior therapies (range 1-15)
- del(17p) in 47%
- ORR: 65%, CR/CRi rate: 9%
- 12-month PFS estimate: 75% (95% CI 64%, 83%)

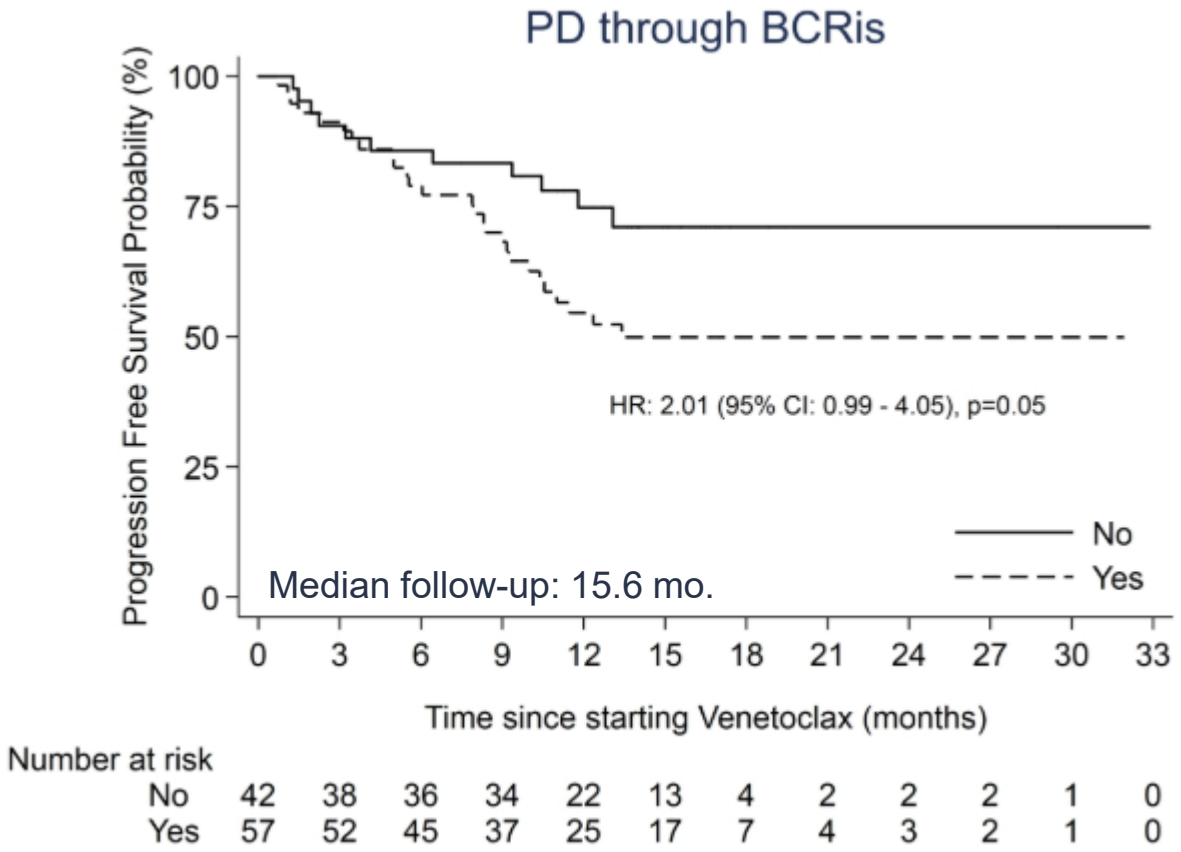
Safety: Venetoclax had an acceptable safety profile, which was consistent with other clinical studies of venetoclax monotherapy

CR, complete response; CRi, CR with incomplete blood count recovery; KI, kinase inhibitor; ORR, overall response rate; PFS, progression-free survival

Jones JA et al. Lancet Oncol. 2018;19(1):65-75.

Venetoclax after BTKi

- **Multicenter retrospective study in UK**

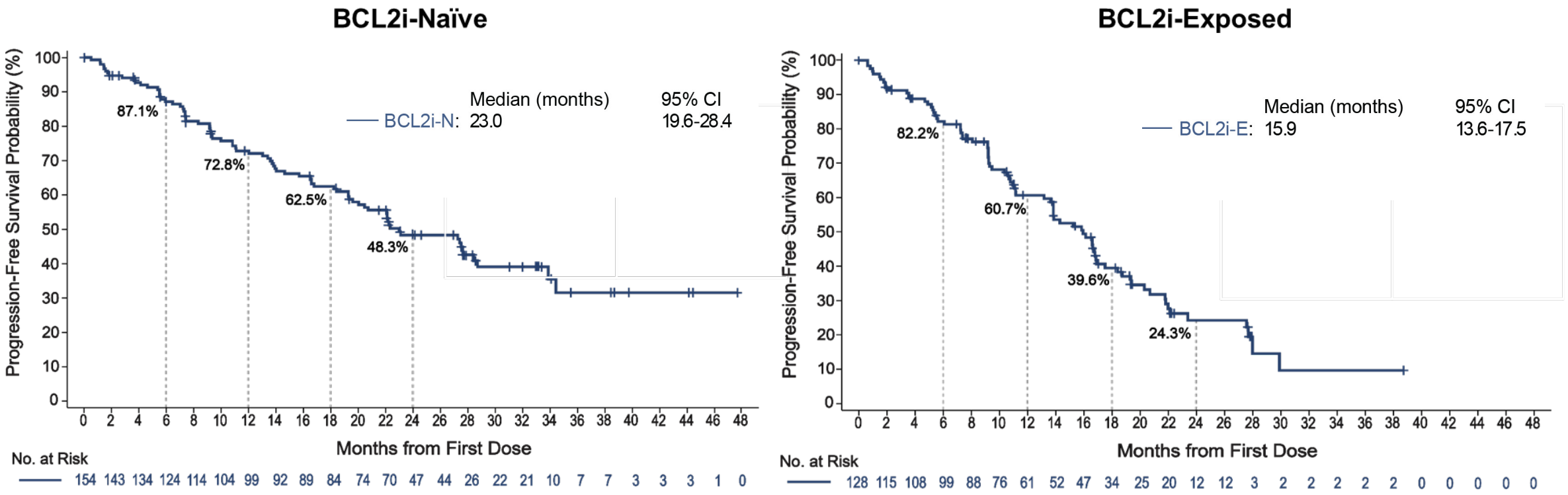


Summary:

- 98 R/R CLL patients received venetoclax after BCRi (72 BTKi)
- ORR 85% in BTKi-exposed patients
- Venetoclax was active and well tolerated in R/R CLL post ≥1 BCRi

BCRi, B cell antigen receptor inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; mo., months; ORR, overall response rate; PD, progressive disease; R/R, relapsed/refractory.
Extracted from Eyre TA et al. Br J Haematol. 2019;185:656-669. Available at: https://discovery.ucl.ac.uk/id/eprint/10077738/1/VEN%20CLL%20proof.pdf.

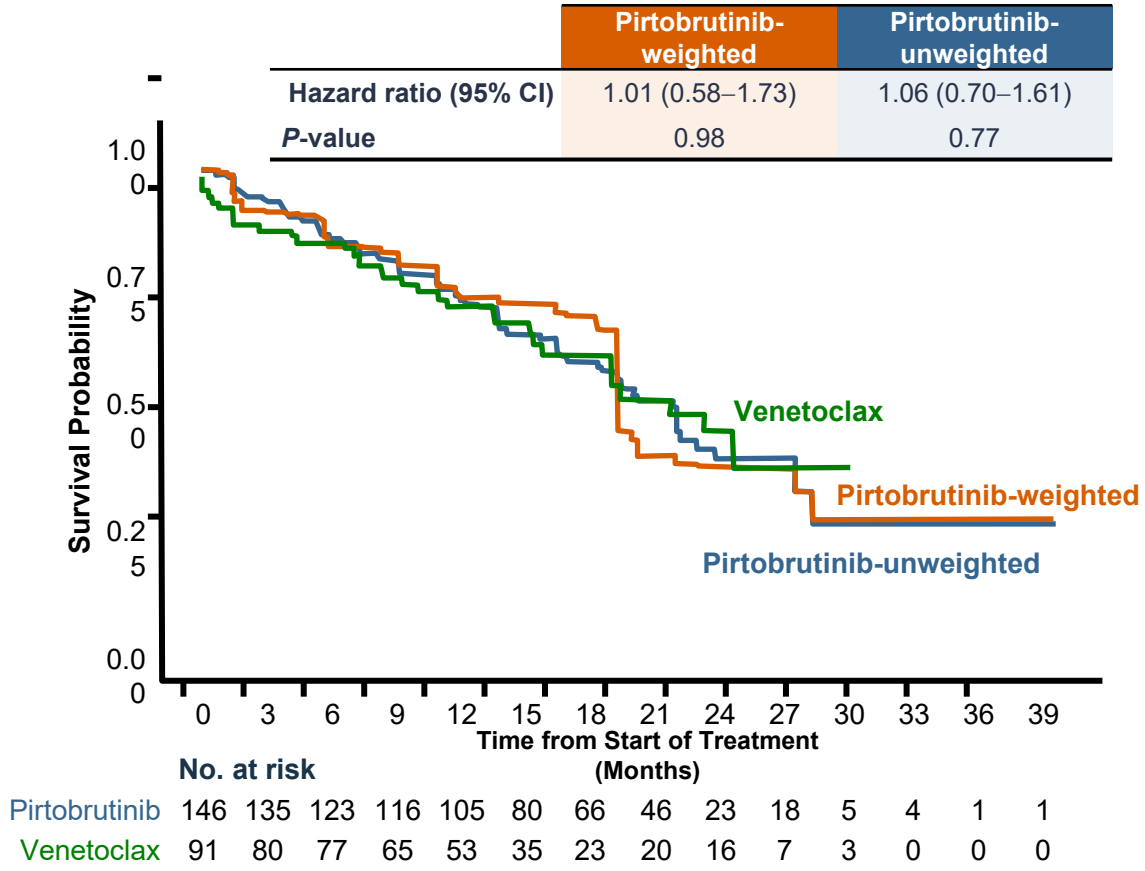
Pirtobrutinib PFS with prior cBTKi, with or without prior BCL2i



Safety: Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity among both BTKi-naïve and -exposed patients

BCL2i, B-cell lymphoma-2 inhibitor; BCL2i-E, BCL2i-exposed; BCL2i-N, BCL2i-naive; BTKi, Bruton's tyrosine kinase inhibitor; C, covalent; CI, confidence interval; PFS, progression-free survival.
Woyach JA et al. Blood 2023;142(Supplement 1):325. Available at: https://ashpublications.org/blood/article/142/Supplement.

Pirtobrutinib vs venetoclax in BTKi-pretreated CLL



Adverse event	Venetoclax (n = 91)	Pirtobrutinib (unweighted) (n = 146)	Unweighted OR (95% CI), *P*-value	Pirtobrutinib (weighted)*	Weighted OR (95% CI), *P*-value
Anemia	28.6%	5.5%	0.15 (0.05–0.35), *P* < 0.001	1.3%	0.04 (0.004–0.16), *P* < 0.001
Febrile neutropenia	13.2%	1.4%	0.09 (0.01–0.43), *P* < 0.001	1.4%	0.10 (0.01–0.47), *P* < 0.001
Neutropenia	50.5%	19.9%	0.24 (0.13–0.45), *P* < 0.001	20.3%	0.25 (0.13–0.47), *P* < 0.001
Thrombocytopenia	28.6%	1.4%	0.04 (0.004–0.15), *P* < 0.001	1.1%	0.02 (0.00–0.12), *P* < 0.001
Pneumonia	6.6%	5.5%	0.82 (0.24–2.98), *P* = 0.78	1.2%	0.22 (0.02–1.25), *P* = 0.06
Treatment discont. due to AEs	6.6%	7.5%	1.15 (0.37–3.95), *P* = 1.00	2.9%	0.44 (0.09–1.92), *P* = 0.32

This comparison of pirtobrutinib versus venetoclax in covalent BTKi-pretreated CLL suggests either can be effective

*All patients were included in the weighted analyses; however, reweighting resulted in an effective sample size of 61
AE, adverse event; CI, confidence interval; OR, odds ratio.
Al-Sawaf O et al. Haematologica. 2024;109:6:1866-73.

Patient case 2: treatment decision and rationale

- **Ven-R** was chosen, based on the results of the MURANO trial, and the patient being willing to have therapy that includes infusions
- In US, Ven-Obi would be an alternative choice, or pirtobrutinib

This is a hypothetical case provided by the Speaker for educational purposes only.
US, United States (of America); Ven-Obi; venetoclax + obinutuzumab; Ven-R, venetoclax + rituximab.

Conclusions (1/2) [Speaker's own]

- For patients who progress on 1L cBTKi, venetoclax-based therapy is current standard of care[1]
- The ncBTKi pirtobrutinib is also active post-cBTKi, and may have a role in this space[1]
- For patients who progress on 1L Ven-Obi, re-treatment with Ven-Obi can be considered, though prospective data are limited[1]
- Next-generation cBTKi including Zanu and Acala represent an excellent option post Ven-Obi[1]
- Both next-generation cBTKi have an improved safety profile compared with Ibru[2,3]

1L, first-line treatment, Acala, acalabrutinib; BTKi, Bruton's tyrosine kinase inhibitor; c, covalent; nc, non-covalent; Ibru, ibrutinib; Ven-Obi, venetoclax + obinutuzumab; Zanu, zanubrutinib.

1) Speaker's own; 2) Byrd JC et al. J Clin Oncol. 2021;39(31):3441-3452; 3) Brown JR, Eichhorst B, Lamanna N, O'Brien SM, Tam CS, Qiu L et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA (Accessed 05 June 2024). Available at: Brown_BGB-3111-305_ASH_Presentation_2023.pdf.

Conclusions (2/2) [Speaker's own]

- Acala showed non-inferiority to Ibru in a high-risk R/R CLL population[1]
- Zanu showed confirmed superiority vs Ibru at extended follow-up in a Phase 3 trial in both all-comers and in those with del(17p)/*TP53*^{MUT} [2]
- No H2H data are available comparing Acala and Zanu; for safety, meta-analyses are valuable tools[3]
- Decisions about therapy of R/R CLL need to be individualized based on patient characteristics and individual preferences[4]

Acala, acalabrutinib; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; H2H, head-to-head; Ibru, ibrutinib; mut, mutated; R/R, relapsed/refractory; *TP53*, tumor protein 53; Zanu, zanubrutinib.

1) Byrd JC et al. J Clin Oncol. 2021;39(31):3441-3452; 2) Brown JR, Eichhorst B, Lamanna N, O'Brien SM, Tam CS, Qiu L et al. Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL). Presented at: 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA (Accessed 05 June 2024). Available at: Brown_BGB-3111-305_ASH_Presentation_2023.pdf;
3) Kittai AS et al. Am J Hematol. 2023;98:E387–E390 ; 4) Speaker's own.

BTKis in indolent lymphomas (WM, MZL, FL)

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University of Bologna, Italy

Disclosures

- **Advisory boards:** Secura Bio, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, MSD, TG Therapeutics, Takeda, Roche, EUSA Pharma, Kyowa Kirin, Novartis, ADC Therapeutics, Incyte, BeiGene
- **Speakers' bureau:** Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, TG Therapeutics, Takeda, Roche, EUSA Pharma, Kyowa Kirin, Novartis, Incyte, BeiGene
- **Consultant:** MSD, EUSA Pharma, Novartis

BTKi regulatory approvals

Indolent lymphomas

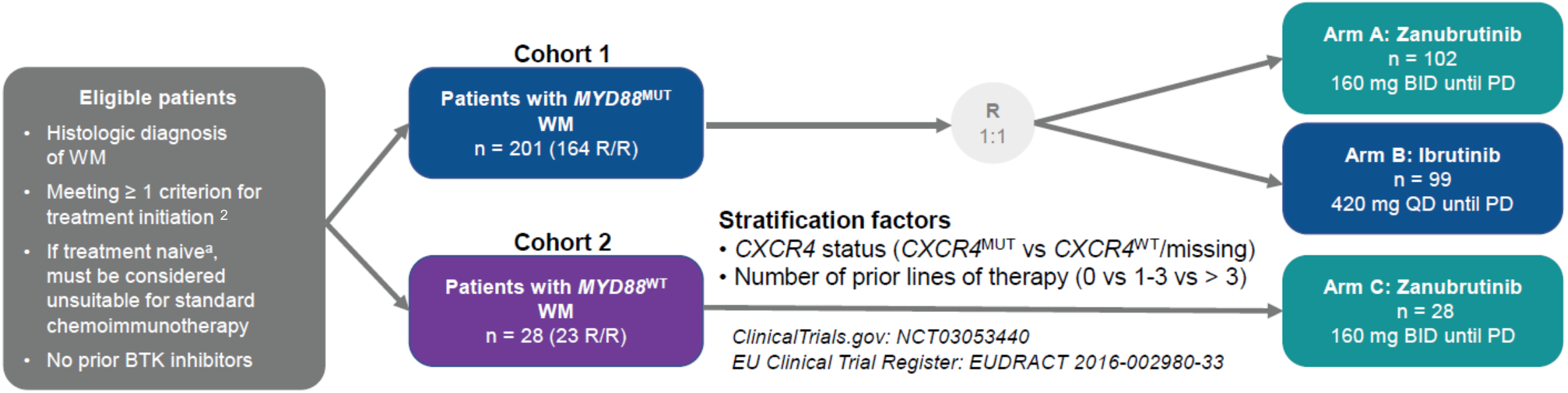
	CLL		WM		MZL		FL		MCL	
	EU	US	EU	US	EU	US	EU	US	EU	US
Zanubrutinib[1]	✓	✓	✓	✓	✓	✓	✓	✓	planned	✓
Ibrutinib[2]	✓	✓	✓	✓		withdrawn			✓	withdrawn
Acalabrutinib[3]	✓	✓								✓

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; EU, European Union; FL, follicular lymphoma; MZL, marginal zone lymphoma; US, United States (of America); WM, Waldenström's macroglobulinemia.

1) Brukinsa SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/brukinsa; 2) Imbruvica SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/imbruvica; 3) Calquence SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/calquence.

Waldenström’s macroglobulinemia

Phase 3 ASPEN study design[1]: Zanubrutinib vs. Ibrutinib in WM



- **Primary endpoint**: CR + VGPR rate in cohort 1
- **Secondary endpoints**: Efficacy, clinical benefit, antilymphoma effects, safety and tolerability of zanubrutinib vs ibrutinib
- **Exploratory endpoints**: Efficacy and safety of zanubrutinibin cohort 2, and efficacy of zanubrutinib vs ibrutinib according to *CXCR4* status

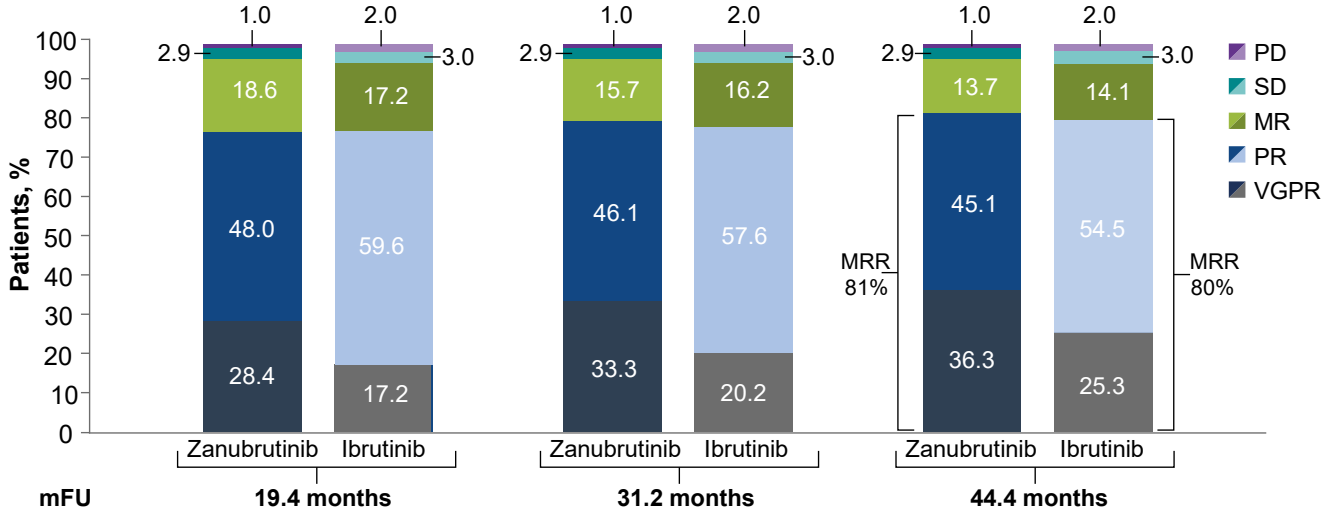
[a]Up to 20% of the overall population.

BID, twice daily; BTK, Bruton's tyrosine kinase; CR, complete response; *CXCR4*, C-X-C chemokine receptor 4; MUT, mutated; *MYD88*, myeloid differentiation primary response 88; PD, progressive disease; QD, once daily; R/R, relapsed/refractory; VGPR, very good partial response; WM, Waldenström's macroglobulinemia; WT, wild type.

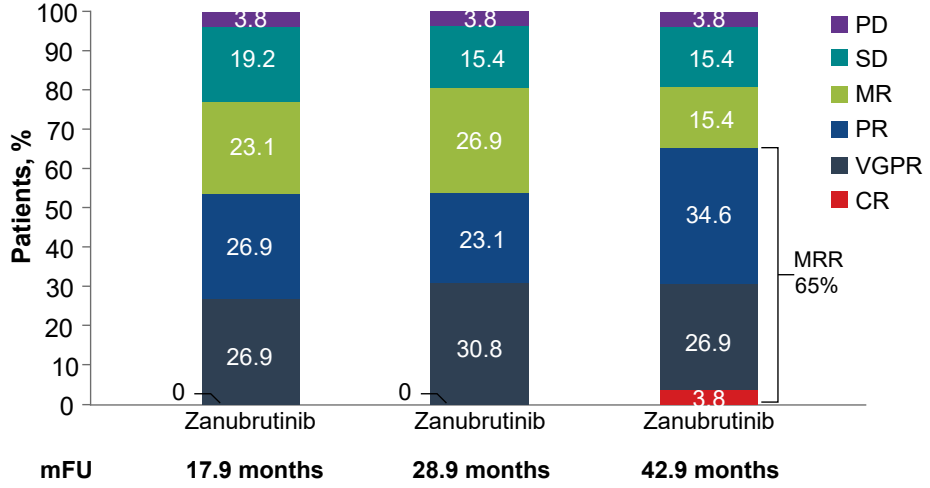
1) Extracted from Garcia-Sanz R, Tam CS, Opat S, D'Sa S, Jurczak W, Lee H et al. ASPEN: Long-Term Follow-Up Results of a Phase 3 Randomized Trial of Zanubrutinib vs Ibrutinib in Patients with Waldenström Macroglobulinemia (WM). Presented at the 38th World Congress of the ISH; October 6-8, 2022; Barcelona, Spain (Accessed 04 June 2024). Available at: Garcia-Sanz_BGB-3111-302_SEHH_Presentation_2022.pdf; 2) Dimopoulos MA et al, Blood. 2014;124(9):1404-1411.

ASPEN: Best overall response by investigator assessment

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



[1]Responses Over Time Observed in *MYD88^{WT}*



- Cohort 1 (*MYD88^{MUT}*): no CRs; at all time points, CR + VGPR rate numerically higher with zanubrutinib vs ibrutinib.
- Cohort 2 (*MYD88^{WT}*): for zanubrutinib, 1 CR and 31% CR + VGPR overall.

CR, complete response; mFU, median follow-up; MR, major response; MUT, mutated; OS, overall survival; PD, progressive disease; PFS, progression-free survival; SD, stable disease; PR, partial response; VGPR, very good partial response; WT, wild type.

1)) Extracted from Garcia-Sanz R, Tam CS, Opat S, D'Sa S, Jurczak W, Lee H et al. ASPEN: Long-Term Follow-Up Results of a Phase 3 Randomized Trial of Zanubrutinib vs Ibrutinib in Patients with Waldenström Macroglobulinemia (WM). Presented at the 38th World Congress of the ISH; October 6-8, 2022; Barcelona, Spain (Accessed 04 June 2024). Available at: Garcia-Sanz_BGB-3111-302_SEHH_Presentation_2022.pdf.

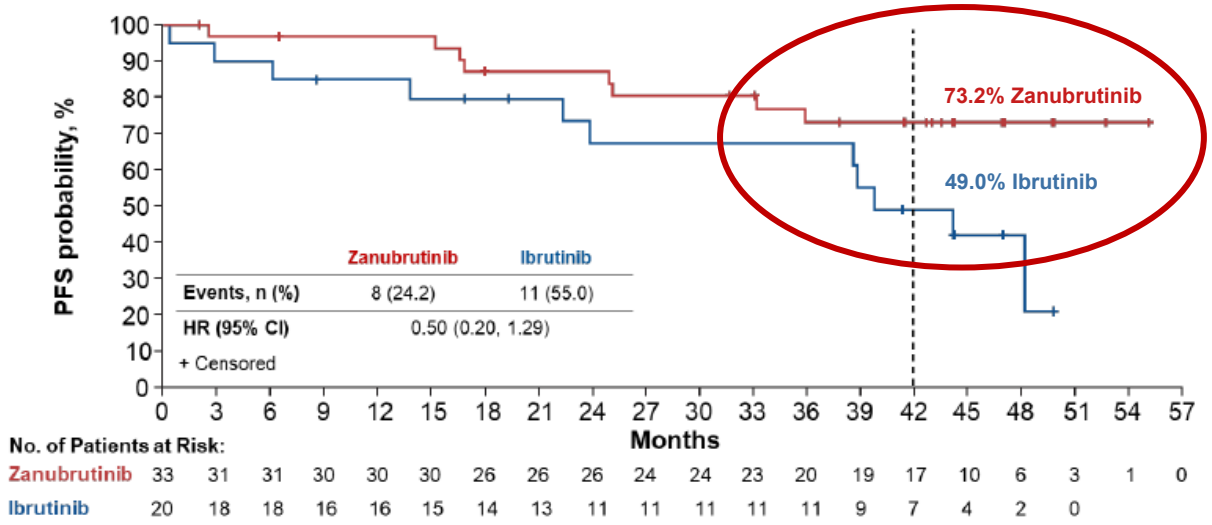
Response and PFS in patients with *MYD88*^{MUT} by *CXCR4*^{MUT} status

[1]Responses Assessment by *CXCR4* Status[a]

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

Bold values indicate >10% differences between arms.

[1]PFS in Patients with *MYD88*^{MUT} *CXCR4*^{MUT}



[a]CXCR4 mutation determined by NGS. 92 ibrutinib patients and 98 zanubrutinib patients had NGS results available.

CI, confidence interval; *CXCR4*, C-X-C chemokine receptor 4; HR, hazard ratio; MUT, mutated; *MYD88*, myeloid differentiation primary response 88; PFS, progression-free survival; VGPR, very good partial response; WT, wild type.

1)) Extracted from Garcia-Sanz R, Tam CS, Opat S, D'Sa S, Jurczak W, Lee H et al. ASPEN: Long-Term Follow-Up Results of a Phase 3 Randomized Trial of Zanubrutinib vs Ibrutinib in Patients with Waldenström Macroglobulinemia (WM). Presented at the 38th World Congress of the ISH; October 6-8, 2022; Barcelona, Spain (Accessed 04 June 2024). Available at: Garcia-Sanz_BGB-3111-302_SEHH_Presentation_2022.pdf;
2) Dimopoulos MA et al, J Clin Oncol. 2023;41(33):5099-5106.

ASPEN: Adverse Events of Interest (Cohort 1)

AEIs (Grouped Terms),[a] No. (%)	Any grade		Grade ≥3	
	Ibrutinib (n = 98)	Zanubrutinib (n = 101)	Ibrutinib (n = 98)	Zanubrutinib (n = 101)
Infection	78 (79.6)	80 (79.2)	**27 (27.6)**	22 (21.8)
Bleeding	61 (62.2)	56 (55.4)	10 (10.2)	9 (8.9)
Diarrhea	**34 (34.7)**	23 (22.8)	2 (2.0)	3 (3.0)
Hypertension[b]	**25 (25.5)**	15 (14.9)	**20 (20.4)[b]**	10 (9.9)
Atrial fibrillation/flutter[b]	**23 (23.5)[b]**	8 (7.9)	**8 (8.2)[b]**	2 (2.0)
Anemia	22 (22.4)	18 (17.8)	6 (6.1)	**12 (11.9)**
Neutropenia[b]	20 (20.4)	**35 (34.7)[b]**	10 (10.2)	**24 (23.8)[b]**
Thrombocytopenia	17 (17.3)	17 (16.8)	6 (6.1)	11 (10.9)
Second primary malignancy/ Non-skin cancers	17 (17.3)/ 6 (6.1)	17 (16.8)/ 6 (5.9)	3 (3.1)/ 3 (3.1)	6 (5.9)/ 4 (4.0)

AEI, adverse event of interest
[a]Categories (grouped terms) of preferred terms by Medical Dictionary for Regulatory Activities v24.0;
[b]Descriptive purposes only, 1-sided $P < 0.025$ in rate difference in any grade and/or Grade ≥ 3.
Extracted from Dimopoulos MA et al, J Clin Oncol. 2023;41(33):5099-5106 (supplement).

High rates of *TP53*^{MUT} and *TERT*^{MUT} were found in ASPEN study[a] and more often detected in patients with *MYD88*^{MUT} or *CXCR4*^{MUT}

Mutation rate, % (n)	*MYD88*^{WT} (n=20)	*MYD88*^{MUT} (n=190)	*CXCR4*^{WT} (n=156)	*CXCR4*^{MUT} (n=54)	CXCR4^{FS} (n=27)	CXCR4^{NS} (n=27)
TP53	4 (20%)	48 (25.3%)	33 (21.2%) *	**19 (35.2%)** *	8 (29.6%)	**11 (40.7%)** *
TERT	0	**19 (10%)**	6 (3.9%) *	**13 (24.1%)** *	**4 (14.8%)** *	**9 (33.3%)** *
ARID1A	1 (5%)	**31 (16.3%)**	9 (5.8%) *	**23 (42.6%)** *	**11 (40.7%)** *	**12 (44.4%)** *

Bold text indicates >10% difference between MUT and WT in 210 NGS-evaluable patients with WM. *P value <0.05, based on Fisher's exact test, WT is the reference group.
[a] Including 190 patients with *MYD88*^{MUT} (98 treated by zanubrutinib, and 92 treated by ibrutinib) and 20 patients with *MYD88*^{WT} (all zanubrutinib), *MYD88* status was assessed by a PCR-based assay which was used for patients' enrollment. CXCR4 status was evaluated by NGS.
CXCR4, C-X-C chemokine receptor type 4 gene; FS, frameshift; MUT, mutated; *MYD88*, myeloid differentiation primary response 88 gene; NGS, next-generation sequencing; NS, nonsense; *TERT*, telomerase reverse transcriptase gene; *TP53*, tumor protein P53 gene; WT, wild type.
Extracted from Dimopoulos MA, Opat S, D'Sa S, Jurczak W, Lee H-P, Cull G et al. ASPEN Biomarker Analysis: Response to BTK Inhibitor Treatment in Patients With Waldenström Macroglobulinemia Harboring *CXCR4, TP53, and TERT* Mutations. Presented by Constantine Tam at the 11th International Workshop on Waldenström Macroglobulinemia on October 27-30, 2022; Presentation WM041 (Accessed 04 June 2024). Available at: Dimopoulos_BGB-3111-302_Biomarker_IWWM_Presentation_2022.pdf.

Marginal zone lymphoma

Acalabrutinib for R/R MZL

MZL cohort of a Phase 1b/2 study of acalabrutinib monotherapy (NCT02180711)

- 42 patients with R/R MZL (≥1 prior therapy including ≥1 anti-CD20)
  - Extranodal 43%
  - Nodal 31%
  - Splenic 26%
- Primary endpoint: ORR, median follow-up: 10.7 months
- 16 patients discontinued acalabrutinib, mainly due to disease progression
- 37 patients evaluable for response: ORR 54% (CR: 16%, PR: 38%)
- Median PFS: 27.4 months; 12-month PFS: 66%; median OS: NR
- Safety: consistent with prior profile; Grade ≥3 AE: 16/42 (38%); AESI: hypertension: 2/42 (4.8%)

AE, adverse event; AESI, adverse event of interest; CR, complete response; MZL, marginal zone lymphoma; NR, not reached; ORR, overall response rate; OS overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory.
Extracted from Budde LE et al, J Clin Oncol. 2022;40(16_suppl):7549.

American Society of Hematology
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Long-Term Efficacy and Safety of Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma (MZL): Final Analysis of the MAGNOLIA (BGB-3111-214) Trial

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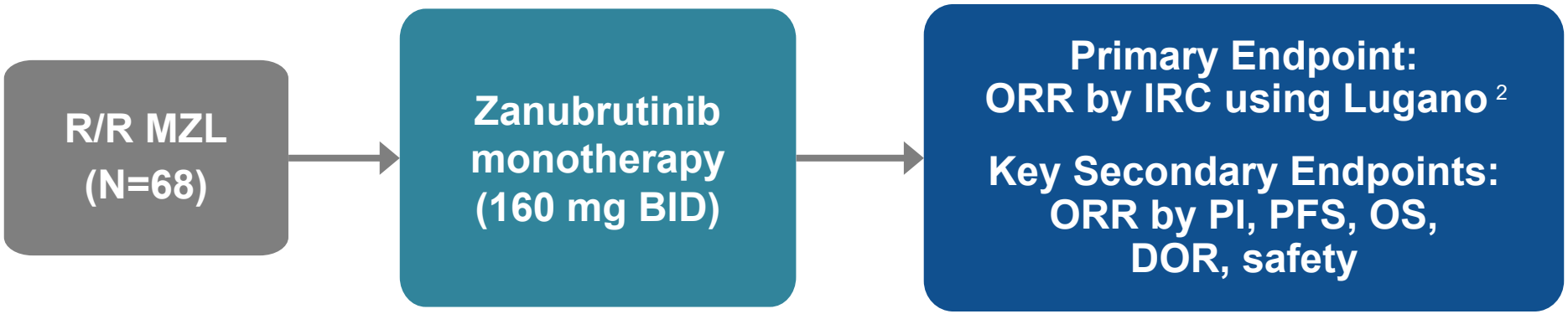
Saturday, December 10, 2022 (2:00 PM - 3:30 PM)
623. Mantle Cell, Follicular, and Other Indolent B Cell Lymphomas: Clinical and Epidemiological

Extracted from Opat S, Tedeschi A, Hu B, Linton KM, McKay P, Leitch S et al. Long-Term Efficacy and Safety of Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma (MZL): Final Analysis of the MAGNOLIA (BGB-3111-214) Trial. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, LA; Abstract 234 (Accessed 04 June 2024).
Available at: Opat_BGB-3111-214_ASH_Presentation_2022.pdf.

MAGNOLIA (BGB-3111-214)[1]: Phase 2, Multicenter, Open-Label, Single-Arm Study



- 68 patients with R/R MZL who received ≥1 CD20-directed regimen
- Median age 70 (37-95), ECOG PS 0/1 93%, median prior therapy lines 2 (1-6)
- MZL subtypes: extranodal 38%, nodal 38%, splenic 18%, unknown 6%

BID, twice a day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS overall survival; PFS, progression-free survival; PI, principal investigator; PR, partial response; R/R, relapsed/refractory.

1) Extracted from Opat S, Tedeschi A, Hu B, Linton KM, McKay P, Leitch S et al. Long-Term Efficacy and Safety of Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma (MZL): Final Analysis of the MAGNOLIA (BGB-3111-214) Trial. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, LA; Abstract 234 (Accessed 04 June 2024). Available at: Opat_BGB-3111-214_ASH_Presentation_2022.pdf; 2) Cheson BD et al, J Clin Oncol. 2014;32(27):3059-3067.

Consistent response across IRC and between PET & CT with high CR rates of 24–29%

Efficacy	(N=66)[a]		
	IRC		INV
	PET and/or CT (primary endpoint)[b]	CT only (sensitivity analysis)[f]	PET and/or CT
ORR, n (%) [95% CI] *p*-value	45 (68) [55.6, 79.1] <0.0001[c]	44 (67) [54.0, 77.8]	50 (76) [63.6 85.5]
Best response, n (%)			
CR	17 (26)	16 (24)	19 (29)
PR	28 (42)	28 (42)	31 (47)
SD	14 (21)[d,e]	16 (24)	10 (15)
PD	6 (9)	5 (8)	5 (8)
Discontinued study prior to 1st assessment, n (%)	1 (1)	1 (1)	1 (1)
Median time to response (range), months	2.8 (1.7-11.1)	3.0 (1.8-22.2)	2.8 (1.7-16.6)

[a]Two patients were excluded from the efficacy population owing to lack of central confirmation of MZL.
[b]Patients with IRC-confirmed FDG-avid disease were assessed by PET-based criteria; non–FDG-avid patients were assessed by CT-based Lugano criteria.
[c]P-value for the primary endpoint was computed with the binomial exact test against the null hypothesis of ORR = 30% with alternative of ORR > 30%.
[d]Five (7.6%) patients with stable disease are remaining on study treatment (after 12-18 cycles).
[e]Includes one patient with FDG-avid disease who missed the PET scan at cycle 3 and was assessed as non-PD; CT showed stable disease at cycle 3.
[f]Additional sensitivity analysis using CT-based Lugano criteria for all 66-evaluable patients regardless of PET status at baseline.
CI, confidence interval; CR, complete response; CT, computed tomography; INV, investigator; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.
Extracted from Opat S, Tedeschi A, Hu B, Linton KM, McKay P, Leitch S et al. Long-Term Efficacy and Safety of Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma (MZL): Final Analysis of the MAGNOLIA (BGB-3111-214) Trial. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, LA; Abstract 234 (Accessed 04 June 2024).
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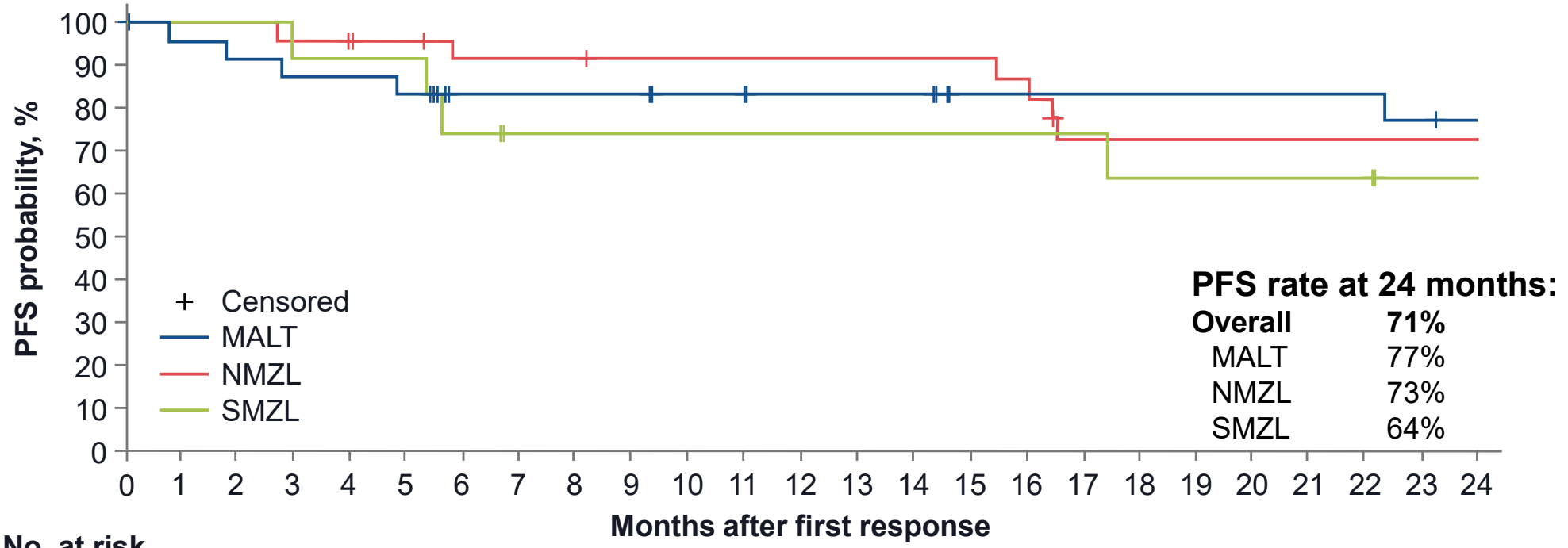
PFS by MZL Subtypes by IRC Assessment

Median follow-up of 28 months



No. at risk

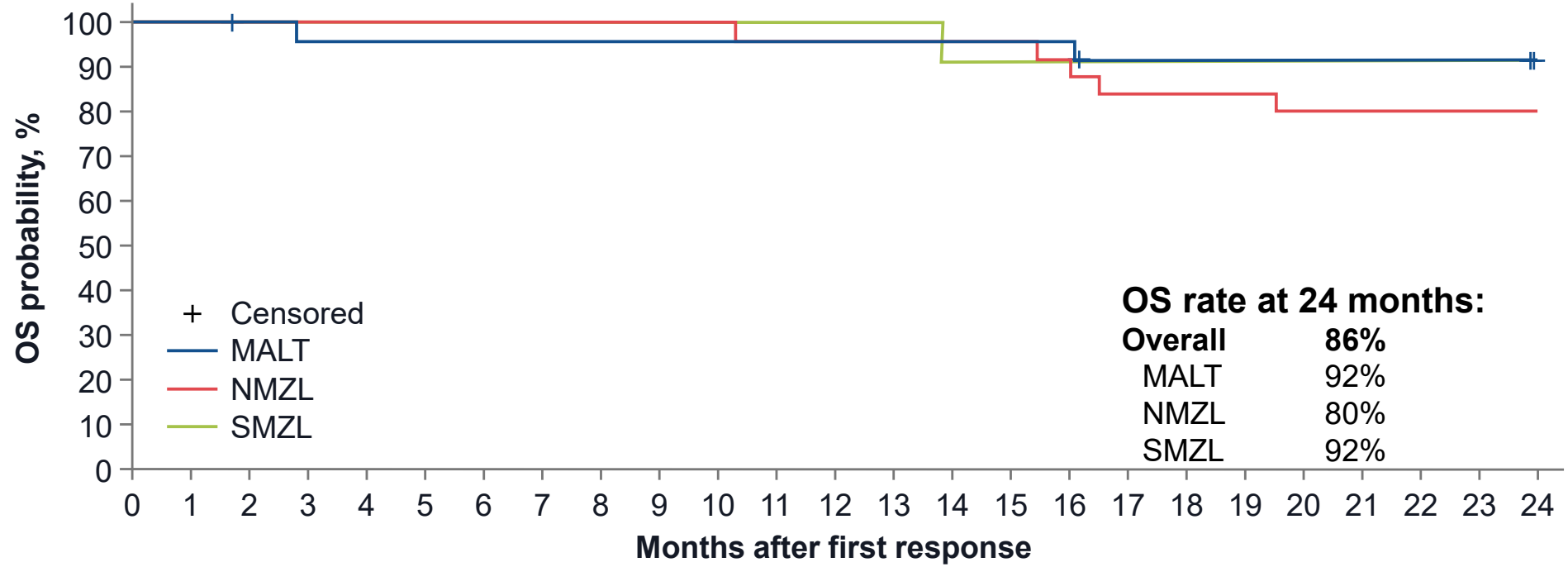
MALT	25	23	22	21	21	20	18	18	18	18	17	17	16	16	16	14	14	14	14	14	14	14	14	13	12
NMZL	25	25	25	24	24	23	21	21	21	20	20	20	20	20	20	20	19	15	15	15	15	15	15	15	15
SMZL	12	12	12	11	11	11	8	7	7	7	7	7	7	7	7	7	7	7	6	6	6	6	6	4	4

IRC, independent review committee; MALT, mucosa associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; PFS, progression-free survival; SMZL, splenic MZL.

Extracted from Opat S, Tedeschi A, Hu B, Linton KM, McKay P, Leitch S et al. Long-Term Efficacy and Safety of Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma (MZL): Final Analysis of the MAGNOLIA (BGB-3111-214) Trial. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, LA; Abstract 234 (Accessed 04 June 2024). Available at: Opat_BGB-3111-214_ASH_Presentation_2022.pdf.

Overall Survival by MZL Subtypes

Median follow-up of 28 months



No. at risk

MALT	25	25	24	23	23	23	23	23	23	23	23	23	23	23	23	23	23	21	21	21	21	21	21	21	21
NMZL	25	25	25	25	25	25	25	25	25	25	25	24	24	24	24	24	23	21	21	21	20	20	20	20	20
SMZL	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	10

MALT, mucosa associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; OS, overall survival; SMZL, splenic MZL.

Extracted from Opat S, Tedeschi A, Hu B, Linton KM, McKay P, Leitch S et al. Long-Term Efficacy and Safety of Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma (MZL): Final Analysis of the MAGNOLIA (BGB-3111-214) Trial. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, LA; Abstract 234 (Accessed 04 June 2024).
Available at: Opat_BGB-3111-214_ASH_Presentation_2022.pdf.

TEAEs of Clinical Interest

TEAEs of interest, n (%)	N=68	
	All grade	Grade ≥3
Infections	38 (56)	15 (22)[a]
Hemorrhage	28 (41)	1 (1.5)[b]
Cardiac		
Hypertension	3 (4)[c]	2 (3)
Atrial fibrillation/flutter	2 (3)[d]	1 (1.5)
Ventricular extrasystole	1 (1.5)[e]	0
Second primary malignancy	5 (7)[f]	3 (4)

[a]Fatal infection: COVID-19 pneumonia (n=2);
[b]Gastrointestinal hemorrhage (day 862) in a patient who also received anticoagulant for pulmonary embolism; patient continued zanubrutinib with no recurrent bleeding episode.
[c]Two 2 patients had new-onset hypertension; none led to treatment reduction or discontinuation;
[d]Atrial fibrillation in a patient with preexisting atrial fibrillation (21 days after end of treatment owing to disease progression). Patient with atrial flutter recovered spontaneously and continued zanubrutinib;
[e]Ventricular extrasystole in an 83-year-old patient with no known cardiac history, was non-serious, transient, resolved on the same day, and did not lead to treatment modification or discontinuation;
[f]Includes basal cell and squamous cell carcinoma and basal cell carcinoma (with history of skin cancer); papillary thyroid carcinoma; (with preexisting thyroid nodule); recurrent bladder cancer and prostate cancer (with history of bladder cancer); and acute myeloid leukemia (with prior chemotherapy with alkylating agent).
TEAE, treatment-emergent adverse event.
Extracted from Opat S, Tedeschi A, Hu B, Linton KM, McKay P, Leitch S et al. Long-Term Efficacy and Safety of Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma (MZL): Final Analysis of the MAGNOLIA (BGB-3111-214) Trial. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, LA; Abstract 234 (Accessed 04 June 2024).
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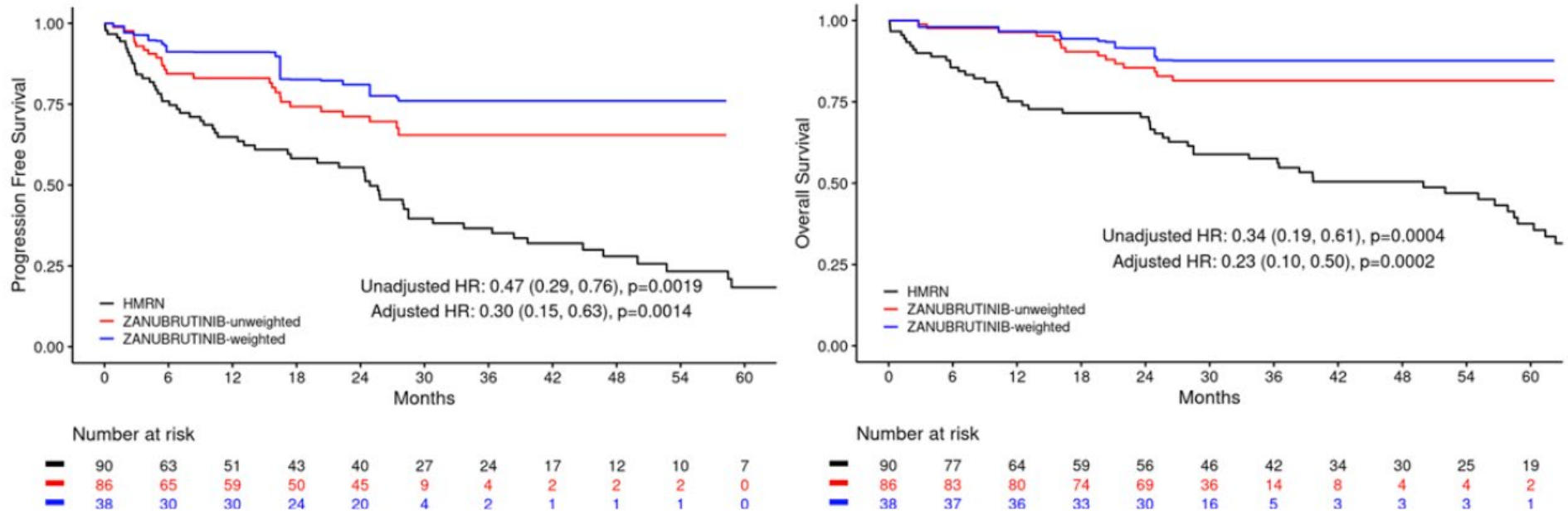
Matching-adjusted indirect comparison of zanubrutinib versus Real-World CIT or chemotherapy in R/R MZL

Poster presentation in Hall 7 on Friday, 14 June at 18:00-19:00 CEST: Walewska et al. P1123.

- **Matching-adjusted indirect comparison using aggregate data from HMRN and pooled individual patient-level data from MAGNOLIA and BGB-3111-AU-003**

Summary: This comparison shows significant PFS and OS benefits for zanubrutinib over CIT or chemo in R/R MZL

PFS and OS Kaplan-Meier results in comparison of MAGNOLIA/BGB-3111-AU-003 (Zanu) and HMRN (CIT or chemo*)



*CIT or chemo included the following regimen in order of most to least common: bendamustine/rituximab (30%), single agent rituximab (13%), cyclophosphamide/rituximab+/-steroid (13%), R-CVP (11%), chlorambucil (8%), R-CHOP (4%), FCR (2%), other rituximab (7%), and other non-rituximab (11%).

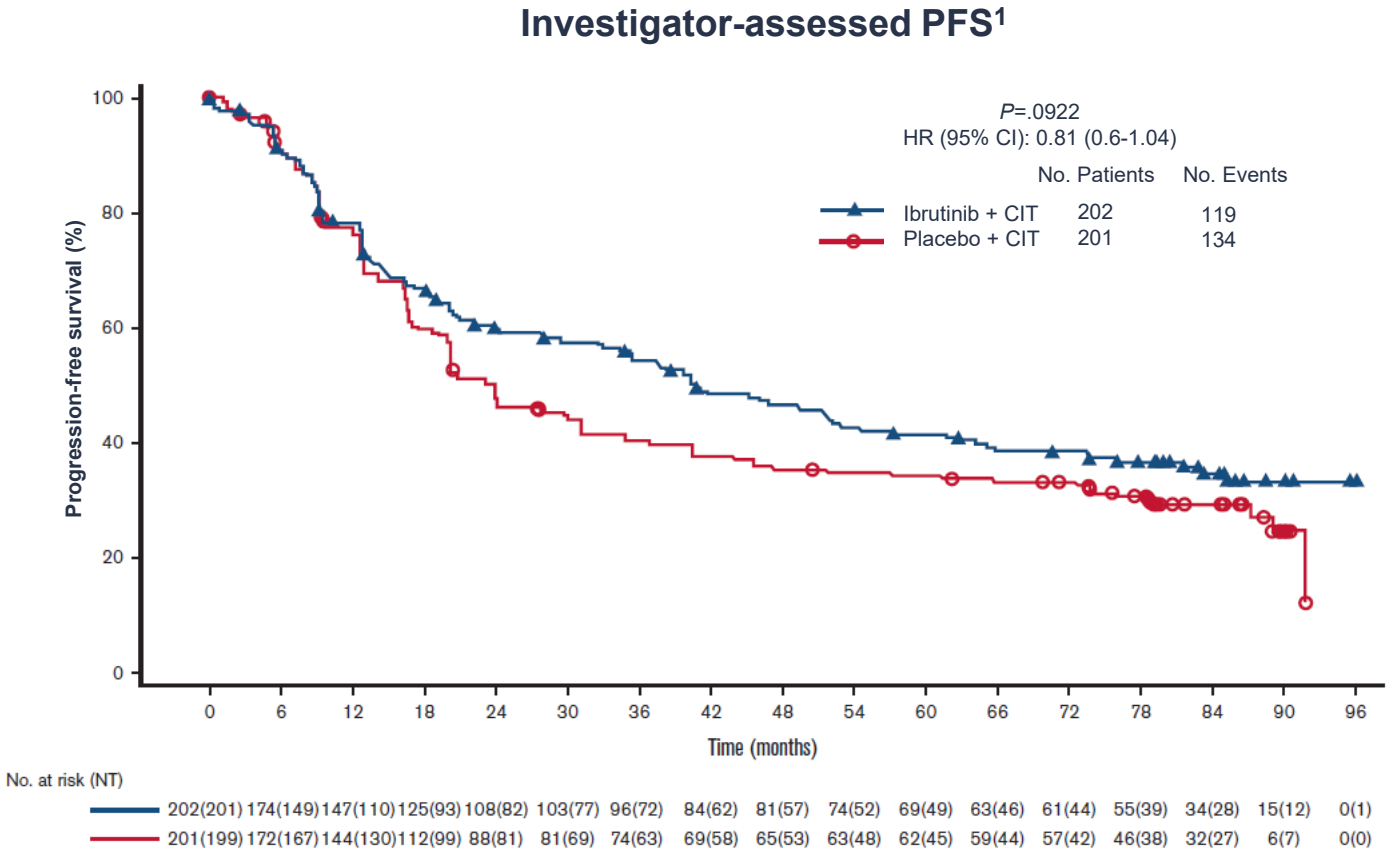
CIT, chemoimmunotherapy; HMRN, Haematological Malignancy Research Network; HR, hazard ratio; MZL, marginal zone lymphoma; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

Extracted from Walewska R, Wang K, Smare C, Zhang I, Mohseninejad L, Mardiguian S et al. Matching-adjusted indirect comparison (MAIC) of zanubrutinib versus real-world chemoimmunotherapy (CIT) or chemotherapy (chemo) in relapsed/refractory marginal zone lymphoma (R/R MZL). EHA 2024. Abstract P1123 (Accessed 04 June 2024). Available at: https://library.ehaweb.org/eha/2024/Abstract P1123.

Follicular lymphoma

Ibrutinib for R/R FL or MZL

SELENE: Phase 3 study of Ibru + CIT vs CIT



Ibru-monotherapy:

- Phase 2 DAWN trial[2]: ORR 20.9%, CR 11%
- Phase 2 consortium[3]: ORR 37.5%, CR 12.5%

Summary[1]

- Most patients had FL (86.1%)
- CIT was BR (90.3%) or R-CHOP
- The addition of Ibru to CIT did not significantly improve PFS compared with placebo + CIT
- The safety profile was consistent with known profiles of ibrutinib and CIT

BR, bendamustine and rituximab; CIT, chemoimmunotherapy; FL, follicular lymphoma; HR, hazard ratio; Ibru, ibrutinib; MZL, marginal zone lymphoma; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory.

Extracted from 1) Nastoupil LJ et al, Blood Adv. 2023;7(22):7141–7150; 2) Gopal AK et al, J Clin Oncol. 2018;36(23):2405-2412; 3) Bartlett NL et al, Blood. 2018;131(2):182-190.

Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With R/R Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study

PL Zinzani,[1] J Mayer,[2] J Trotman,[3] F Bijou,[4] AC de Oliveira,[5] Y Song,[6] Q Zhang,[7] M Merli,[8] K Bouabdallah,[9] PS Ganly,[10] H Zhang,[11] R Johnson,[12] AM Garcia-Sancho,[13] M Provencio Pulla,[14] M Trněný,[15] S Yuen,[16] SE Assouline,[17] R Auer,[18] E Ivanoa,[19] P Kim,[19] A Greenbaum,[19] S Huang,[19] R Delarue,[20] CR Flowers[21]

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R/R, relapsed/refractory.

Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024).
Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf.

ROSEWOOD: Background

- In a Phase 1b/2 study that included patients with R/R FL, the combination of zanubrutinib[a] + obinutuzumab was generally well tolerated, with an ORR of 72% and a CR rate of 39%
- The ROSEWOOD trial (BGB-3111-212; NCT03332017) examined zanubrutinib + obinutuzumab vs obinutuzumab in patients with R/R FL who received ≥2 prior lines of therapy
- At the primary analysis, the trial met its primary endpoint of ORR
  - Zanubrutinib + obinutuzumab, 68.3%
  - Obinutuzumab, 45.8%

P=0.0017

Here we report an updated analysis of the ROSEWOOD trial with a median follow-up of 20.2 months

[a]Zanubrutinib monotherapy is approved in the US and EU for the treatment of adult patients with CLL; marginal zone lymphoma after ≥1 prior anti-CD20–based therapy; WM (in EU: after ≥1 prior therapy, or as 1L treatment if unsuitable for chemoimmunotherapy); and MZL after ≥1 prior therapy (US only).
CR, complete response; FL, follicular lymphoma; ORR, objective response rate; R/R, relapsed/refractory.
Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024).
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ROSEWOOD: Study design[1]

Key eligibility criteria

- Age ≥18 years
- Grade 1-3A R/R FL
- Previous treatment with ≥2 lines of therapy, including an anti-CD20 antibody and an alkylating agent
- Measurable disease
- ECOG PS of 0-2
- Adequate organ function
- No prior BTK inhibitor

127 sites; 17 countries/regions
Randomized November 2017 to June 2021

Arm A
Zanubrutinib[a] + obinutuzumab[b] (N=145)
Until PD or unacceptable toxicity

Randomization 2:1
Stratification factors
- Number of prior lines of treatment
- Rituximab-refractory status
- Geographic region

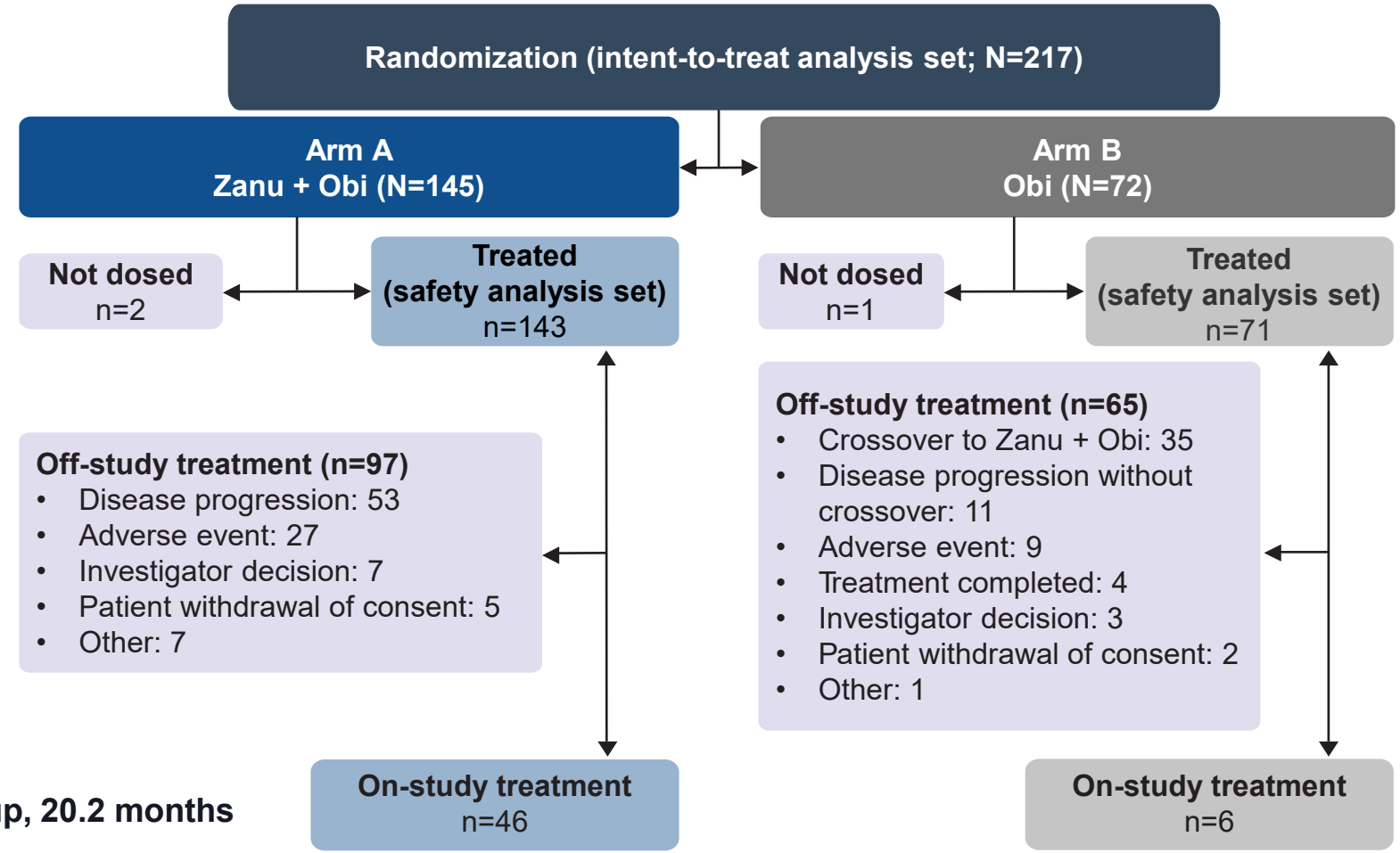
Arm B
Obinutuzumab[b] (N=72)
Option to cross over to combination if PD is centrally confirmed or if there is no response at 12 months

Primary endpoint
- ORR by IRC according to Lugano 2014 classification[2]

Other endpoints
- DOR by IRC[c]
- PFS by IRC[c]
- OS[c]
- TTNT
- Safety (AEs)[c]

[a]Zanubrutinib was given orally at 160 mg twice daily; [b]Obinutuzumab was given intravenously at 1000 mg in both arms on days 1, 8, and 15 of cycle 1, day 1 of cycles 2-6, and then every 8 weeks up to a maximum of 20 doses; [c]Secondary endpoint.
AE, adverse event; BTK, Bruton tyrosine kinase; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R/R, relapsed or refractory; TTNT, time to next treatment.
1) Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024). Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf; 2) Cheson BD et al, J Clin Oncol. 2014;32(27):3059-3067.

ROSEWOOD: 1/3 patients still receiving Zanu-Obi at the time of this updated analysis



Median follow-up, 20.2 months

Obi, obinutuzumab; Zanu, zanubrutinib.

Extracted from Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024). Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf.

ROSEWOOD: Study population was heavily pretreated and had refractory disease

Characteristics	Zanu + Obi (n=145)	Obi (n=72)
Age, median (range), years	63.0 (31-84)	65.5 (32-88)
ECOG PS of ≥1, n (%)	59 (40.6)	41 (57.0)
FLIPI score of ≥3, n (%)	77 (53.1)	37 (51.4)
Ann Arbor stage III-IV, n (%)	119 (82.1)	60 (83.3)
Bulky disease (≥7 cm), n (%)	23 (15.9)	12 (16.7)
High LDH level (>ULN), n (%)	49 (33.8)	29 (40.3)
High tumor burden per GELF criteria, n (%)	83 (57.2)	40 (55.6)
No. of prior lines of therapy, median (range)	3 (2-11)	3 (2-9)
Refractory to rituximab, n (%)	78 (53.8)	36 (50.0)
Refractory to most recent line of therapy, n (%)	47 (32.4)	29 (40.3)
PD ≤24 months after starting first line of therapy, n (%)	50 (34.5)	30 (41.7)
Prior therapy, n (%)		
Chemoimmunotherapy	143 (98.6)	71 (98.6)
Anthracyclines	118 (81.4)	57 (79.2)
Cyclophosphamide	136 (93.8)	68 (94.4)
Bendamustine	79 (54.5)	40 (55.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; LDH, lactate dehydrogenase; Obi, obinutuzumab; PD, progressive disease; ULN, upper limit of normal; Zanu, zanubrutinib.

Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024). Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf.

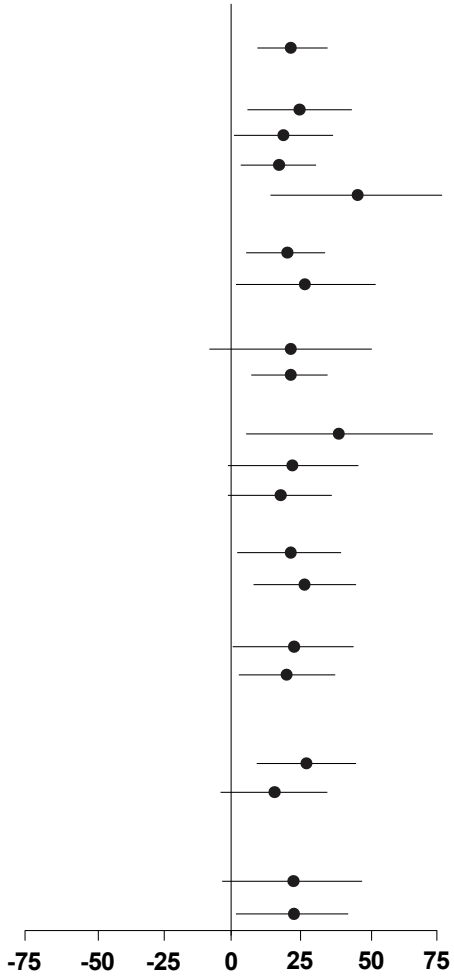
ROSEWOOD: ORR difference by IRC was 22.7% in favor of Zanu-Obi at median study follow-up of 20.2 months

Endpoint	Zanu + Obi (n=145)	Obi (n=72)	2-sided *P* value
ORR by IRC[a] (95% CI), %	69.0 (60.8-76.4)	45.8 (34.0-58.0)	.0012
CR	39.3	19.4	.0035
PR	29.7	26.4	–
DOR by IRC			
Median (95% CI), months	NE (25.3-NE)	14.0 (9.2-25.1)	–
18-month DOR rate (95% CI), %	69.3 (57.8-78.2)	41.9 (22.6-60.1)	–
DOCR by IRC			
Median (95% CI), months	NE (26.5-NE)	26.5 (2.7-NE)	–
18-month DOCR rate (95% CI), %	87.4 (73.8-94.2)	51.1 (21.0-74.9)	–

[a]ORR difference by IRC was 22.7%; 95% CI, 9.0%–36.5%.
CR, complete response; DOCR, duration of CR; DOR, duration of response; IRC, independent review committee; NE, not estimable; Obi, obinutuzumab; ORR, objective response rate; PR, partial response; Zanu, zanubrutinib.
Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024). Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf.

ROSEWOOD: Zanu-Obi showed consistent benefit over Obi alone across prespecified subgroups

Subgroups	Response/patients		Risk difference (95% CI), %
	Obinutuzumab	Zanubrutinib + obinutuzumab	
All patients in ITT	33/72	100/145	22.7 (9.0-36.5)
Age, years			
<65	14/32	58/83	26.1 (6.3-45.9)
≥65	19/40	42/62	20.2 (0.9-39.6)
<75	30/60	89/130	18.5 (3.5-33.4)
≥75	3/12	11/15	48.3 (15.2-81.5)
No. of prior lines of therapy			
2-3	27/54	77/108	21.3 (5.5-37.1)
>3	6/18	23/37	28.8 (2.0-55.6)
Bulky disease: any target lesion longest diameter ≥7 cm			
Yes	3/12	11/23	22.8 (−9.1 to 54.7)
No	30/60	89/122	23.0 (8.0-37.9)
FLIPI risk category			
Low (0-1)	3/9	21/29	39.1 (4.3-73.9)
Intermediate (2)	13/24	26/34	22.3 (−2.2 to 46.8)
High (≥3)	17/37	49/77	17.7 (−1.6 to 37.0)
Rituximab-refractory status			
Refractory	14/36	47/78	21.4 (2.1-40.6)
Not refractory	19/36	53/67	26.3 (7.3-45.3)
Refractory status to most recent line of therapy			
Refractory	11/29	29/47	23.8 (1.3-46.2)
Not refractory	21/42	66/93	21.0 (3.3-38.7)
Progression of disease ≥6 months of completion of the most recent line of therapy			
Yes	12/39	42/71	28.4 (9.9-46.8)
No	19/30	53/67	15.8 (−4.0 to 35.6)
Progression of disease ≥24 months of starting the first line of chemoimmunotherapy			
Yes	9/22	25/39	23.2 (−2.3 to 48.7)
No	14/31	40/59	22.6 (1.4-43.8)

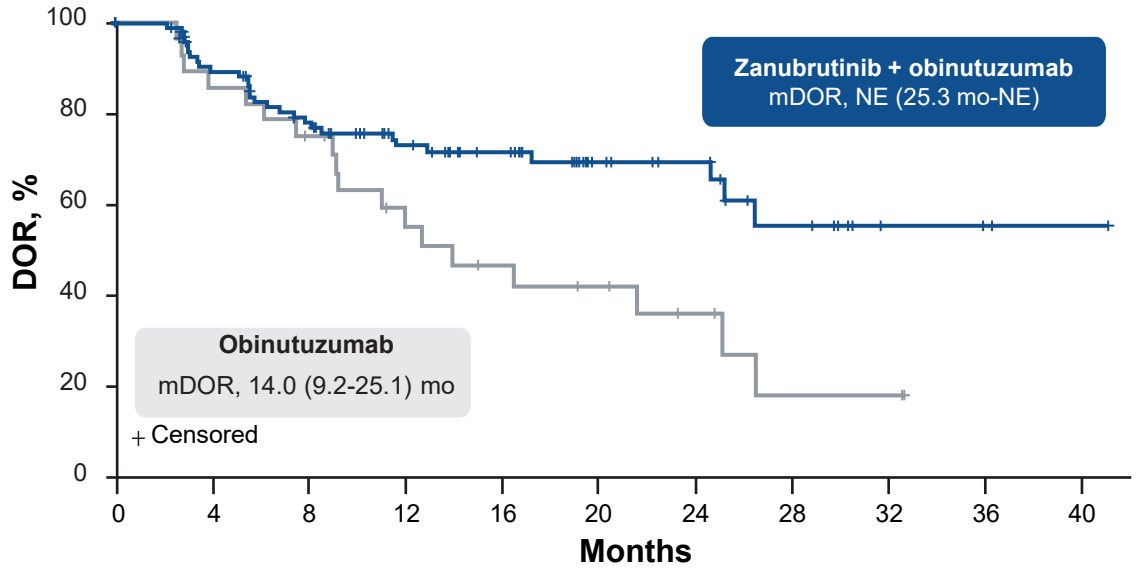


FLIPI, Follicular Lymphoma International Prognostic Index; ITT, intent to treat; Obi, obinutuzumab; zanu, zanubrutinib.

Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024). Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf.

ROSEWOOD: DOR and PFS were longer with Zanu-Obi

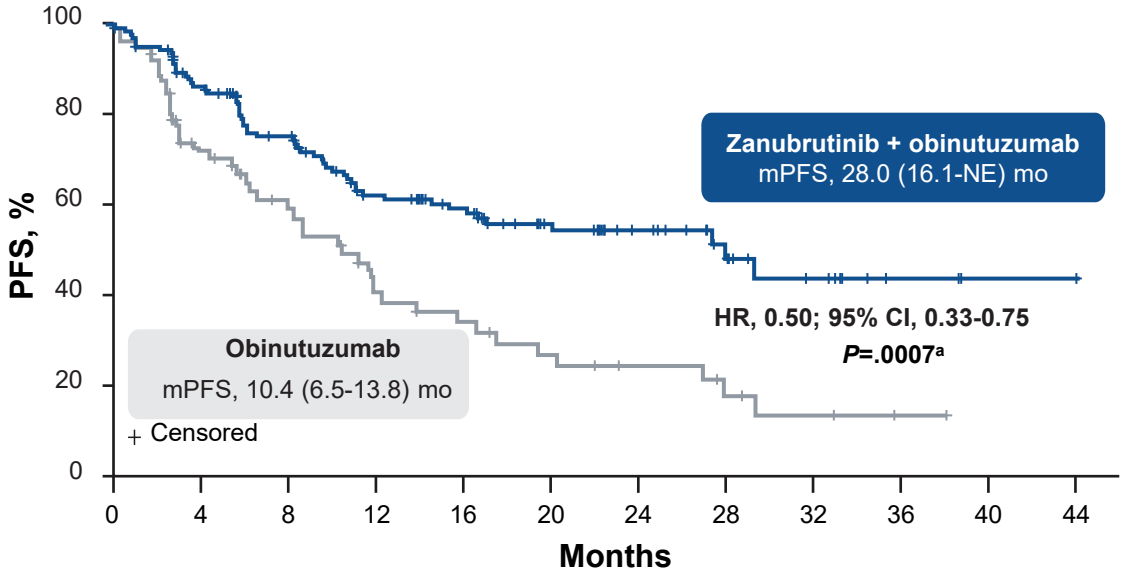
DOR by IRC



No. at risk

Zanubrutinib + obinutuzumab	100	97	82	73	68	59	51	43	40	33	23	21	19	12	10	7	3	3	2	1	1	0
Obinutuzumab	33	29	24	23	20	16	13	11	10	9	8	6	5	3	2	2	2	0				

PFS by IRC



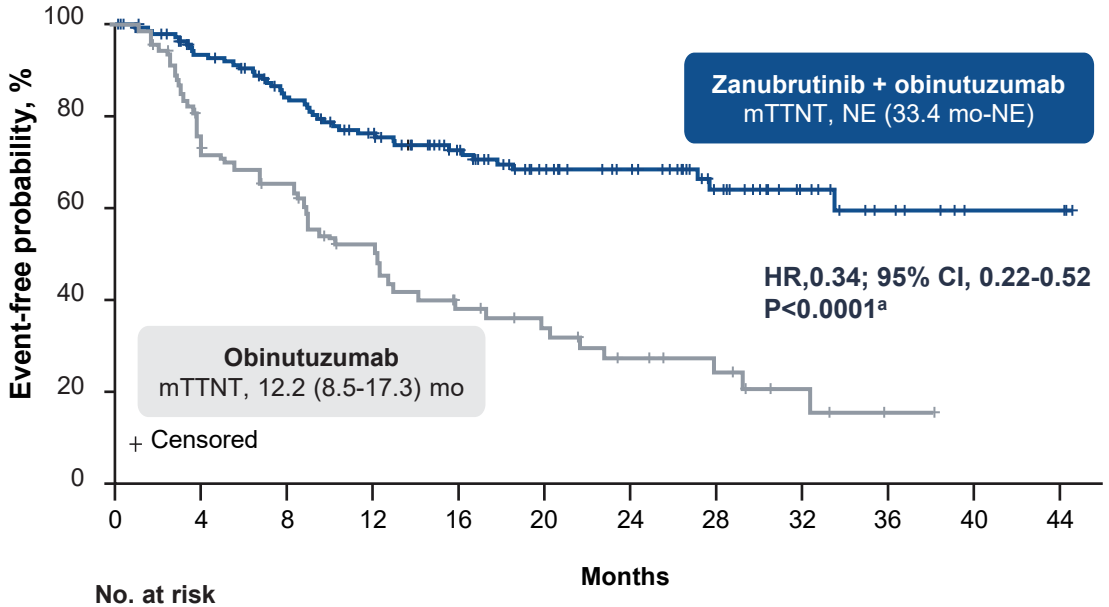
No. at risk

Zanubrutinib + obinutuzumab	145	135	116	96	92	79	67	62	56	45	38	35	25	22	15	10	9	5	3	3	1	1	0
Obinutuzumab	72	63	42	34	30	27	19	16	15	12	11	9	8	8	5	3	3	2	1	1	0		

[a]Descriptive 2-sided P value.
DOR, duration of response; HR, hazard ratio; IRC, independent review committee; mDOR, median DOR; mPFS, median progression-free survival; NE, not estimable; Obi, obinutuzumab; zanu, zanubrutinib.
Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024).
Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf.

ROSEWOOD: TTNT and OS were prolonged with Zanu-Obi

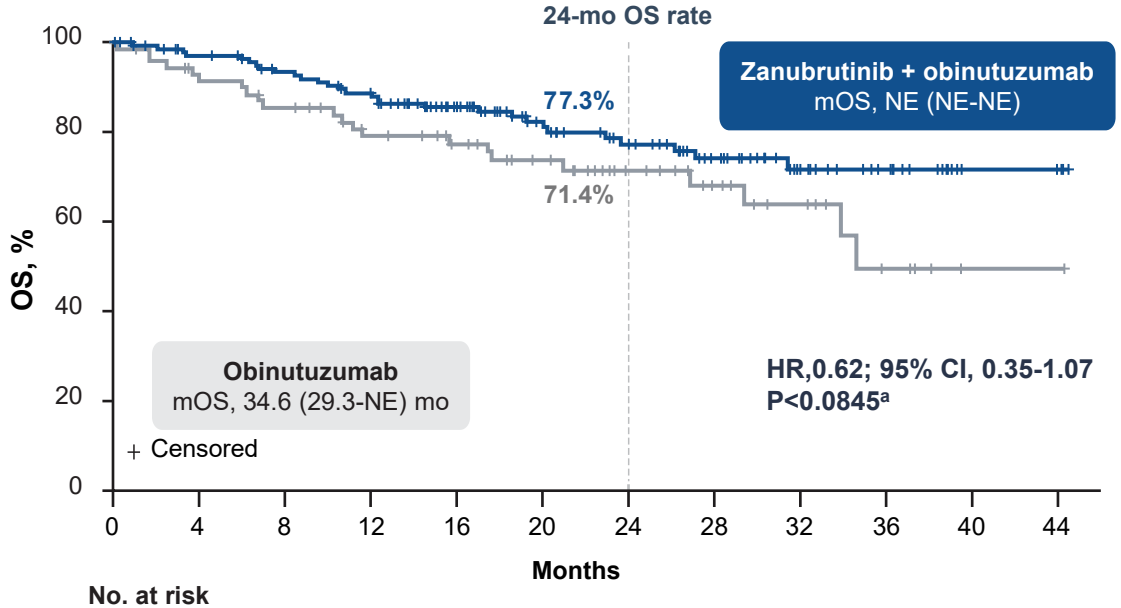
TTNT



No. at risk

Zanubrutinib + obinutuzumab	145	137	125	118	107	98	91	80	71	62	53	47	44	40	29	22	17	12	10	6	3	3	3	0
Obinutuzumab	72	65	49	44	41	32	30	24	20	18	16	13	11	9	8	5	4	2	1	1	0			

OS



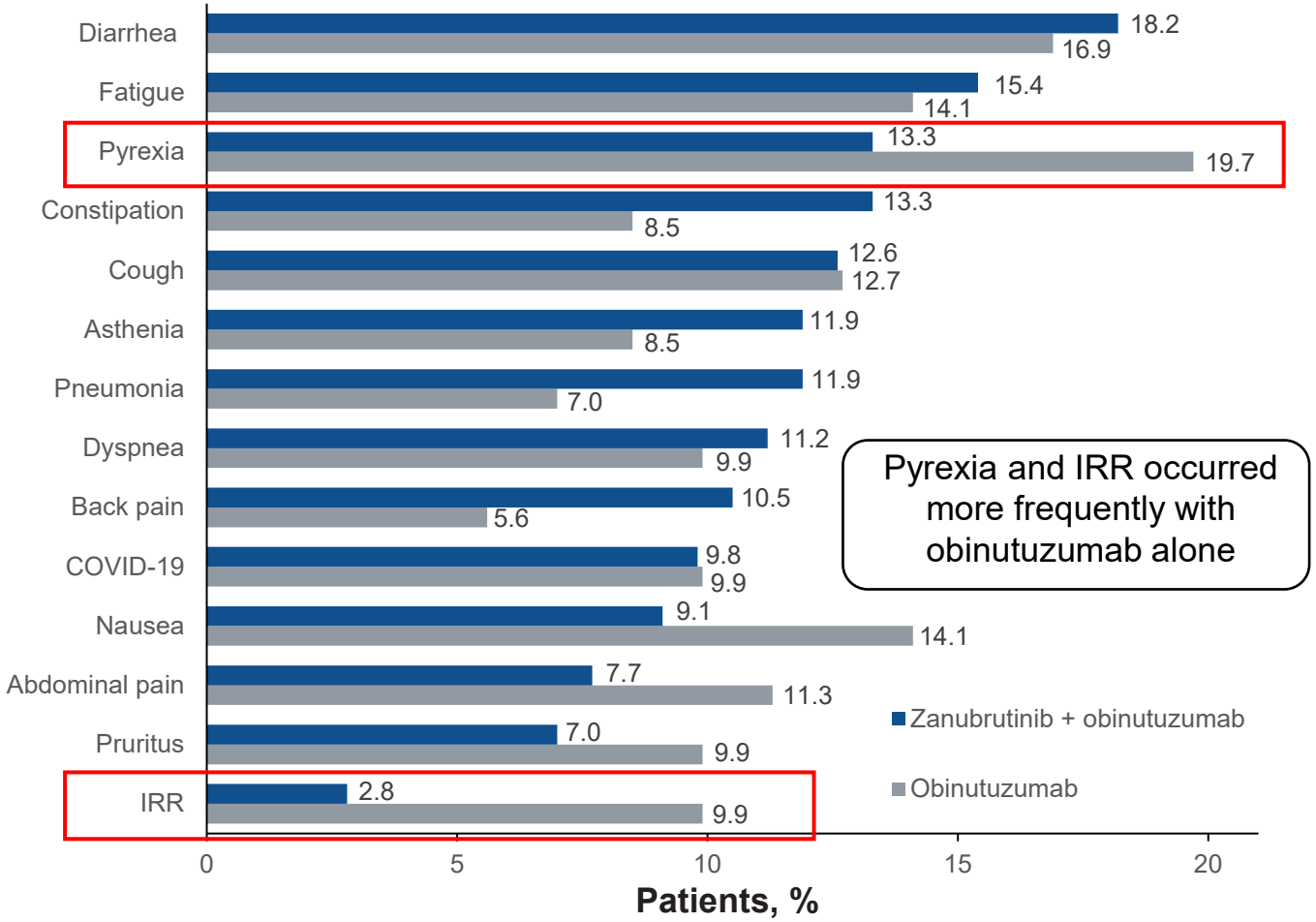
No. at risk

Zanubrutinib + obinutuzumab	145	139	133	129	123	119	113	102	92	81	70	62	56	51	41	33	26	20	17	11	4	4	3	0
Obinutuzumab	72	67	63	62	57	54	49	48	43	39	36	32	25	23	18	14	13	8	5	3	1	1	1	0

[a]Descriptive 2-sided P value.
HR, hazard ratio; m, median; mo, months; NE, not estimable; Obi, obinutuzumab; OS, overall survival; TTNT, time to next treatment; Zanu, zanubrutinib.
Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024).
Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf.

ROSEWOOD: There were no unexpected safety findings with Zanu-Obi

Common nonhematologic TEAEs (any grade)



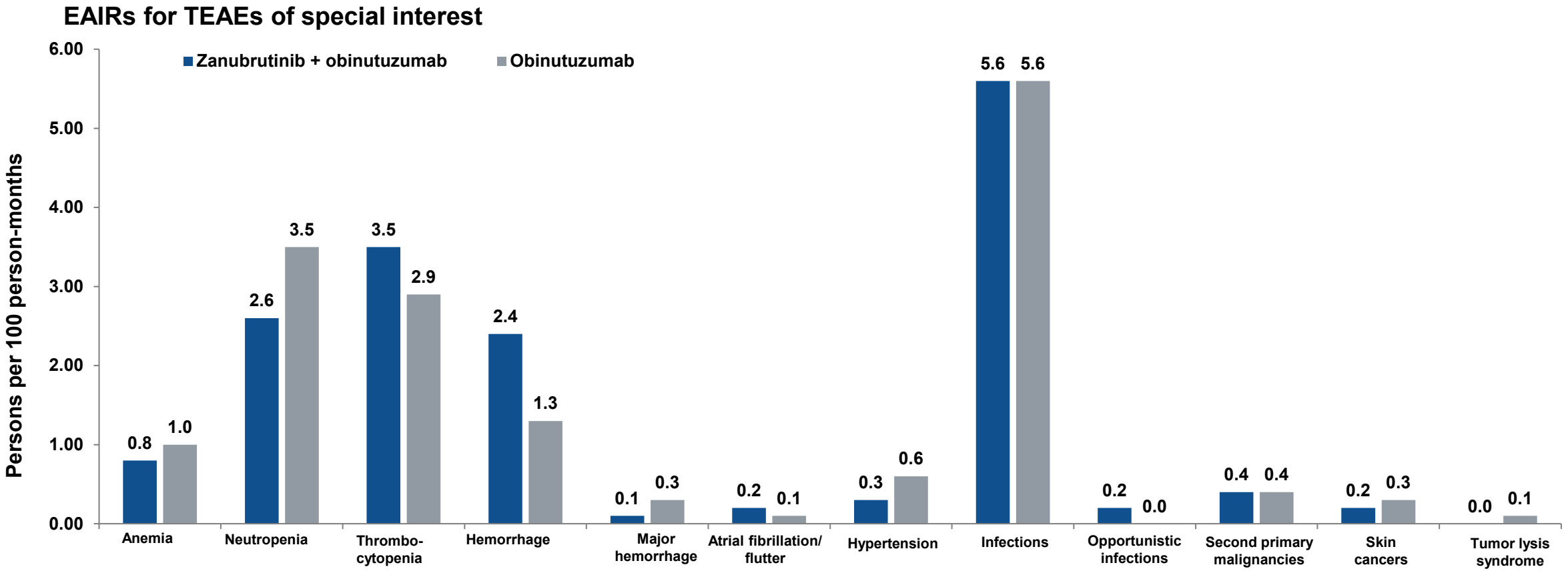
Grade ≥3 non-hematologic TEAEs

n (%)	Zanu + Obi (n=143)	Obinutuzumab (n=71)
Pneumonia	14 (9.8)	3 (4.2)
COVID-19	8 (5.6)	2 (2.8)
COVID-19 pneumonia	5 (3.5)	2 (2.8)
Diarrhea	4 (2.8)	1 (1.4)
Febrile neutropenia	3 (2.1)	1 (1.4)
Atrial fibrillation	2 (1.4)	0
IRR	1 (0.7)	3 (4.2)
Hypertension	1 (0.7)	1 (1.4)

IRR, injection-related reaction; Obi, obinutuzumab; TEAE, treatment-emergent adverse event; Zanu, zanubrutinib.

Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024). Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf.

ROSEWOOD: EAIRs for TEAEs of special interest were similar in both arms, except for any-grade hemorrhage



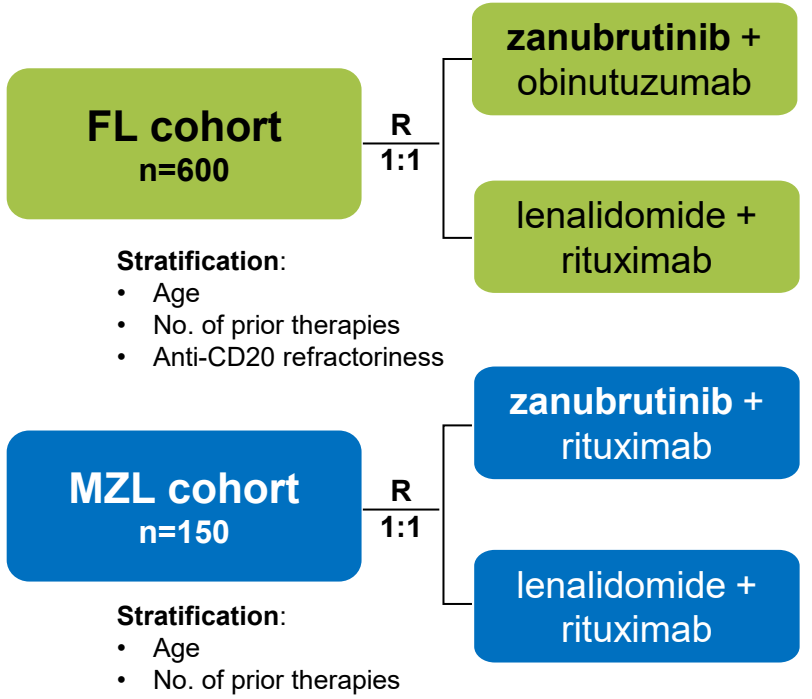
EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event.
Extracted from Zinzani PL, Mayer J, Trotman J, Bijou F, de Oliveira AC, Song Y, Zhang Q et al. Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024).
Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf.

MAHOGANY: Phase 3 study design

- MAHOGANY (BGB-3111-308; NCT05100862) is a randomized, open-label, multicenter phase 3 trial of **zanubrutinib + anti-CD20 antibody** in R/R FL and with R/R MZL

Key eligibility criteria

- Age ≥18 years
- Histologically confirmed R/R FL (grade 1-3A) or MZL (extranodal, nodal, or splenic)
- Previous treatment with ≥1 prior line of systemic therapy, including an anti-CD20–based regimen
- In need of treatment according to modified GELF criteria[1]
- Adequate bone marrow and organ functions
- No prior treatment with BTK inhibitor
- Prior lenalidomide treatment allowed unless no response or short remission (DOR <24 months)
- No clinically significant cardiovascular disease, severe or debilitating pulmonary disease, or history of a severe bleeding disorder



Primary endpoint
PFS

Secondary endpoints
ORR
OS
TTNT
HR-QoL
Safety

BTK, Bruton tyrosine kinase; DOR, duration of response; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; HR-QoL; health-related quality of life; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; TTNT, time to next treatment.

Extracted from Sehn LH, Sarkozy C, Song Y, Salar A, Trotman J, Zinzani PL et al. MAHOGANY: A Phase 3 Trial of Zanubrutinib Plus Anti-CD20 Antibodies vs Lenalidomide Plus Rituximab in Patients With Relapsed or Refractory Follicular or Marginal Zone Lymphoma. Presented at 17th International Conference on Malignant Lymphoma, June 13-17, 2023; Lugano, Switzerland; Abstract 994 (Accessed 04 June 2024). Available at: Sehn_BGB-3111-308_ICML_Presentation_2023.pdf.

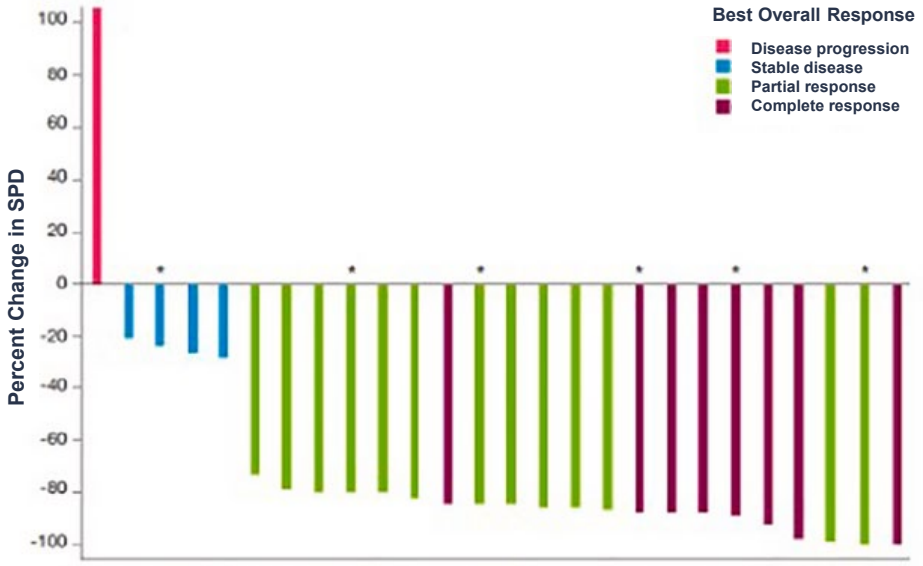
Phase 1 study: acalabrutinib and R^2 in patients with relapsed FL

Summary of Safety Profile and Efficacy Results

Patients, n (%)	Part 1			Part 3
	R/R cohort		TN cohort	R/R cohort
	Arm A n=12	Arm A+rituximab-R/R n=13	Arm A+rituximab-TN n=13	Arm A+R^2 n=29
Safety				
Any TEAE	12 (100)	13 (100)	13 (100)	29 (100)
Grade ≥3 TEAE	5 (41.7)	9 (69.2)	8 (61.5)	19 (65.5)
Grade 5 TEAE	0	0	0	1 (3.4)[a]
Any serious TEAE	2 (16.7)	5 (38.5)	3 (23.1)	10 (34.5)
Efficacy-evaluable patients, n	12	12	13	26
ORR, n (%) [95% CI]	4 (33.3) [9.9, 65.1]	4 (33.3) [9.9, 65.1]	12 (92.3) [64.0, 99.8]	21 (80.8) [60.6, 93.4]
CR, n (%)	1 (8.3)	2 (16.7)	5 (38.5)	8 (30.8)
PR, n (%)	3 (25.0)	2 (16.7)	7 (53.8)	13 (50.0)
SD, n (%)	5 (41.7)	6 (50.0)	1 (7.7)	4 (15.4)
PD, n (%)	3 (25.0)	2 (16.7)	0	1 (3.8)
Landmark K-M estimate of duration of response, % (95% CI)	75.0 (12.8, 96.1)[b]	75.0 (12.8, 96.1)[b]	52.1 (19.8, 76.9)[b]	88.2 (59.9, 97.0)[c]

[a] Death occurred 7 days after treatment was interrupted for febrile neutropenia; the cause of death was noted as secondary to follicular lymphoma. Two additional patients died from AEs (septicemia and aortic aneurysm) which occurred outside of the treatment-emergent period (>30 days after last dose of treatment).
[b] 60-month K-M estimate. [c] 12-month K-M estimate.

Best percent change from baseline in sum of product diameters in Part 3 (A+R^2 in R/R FL)



* Indicates patient who received lenalidomide 15 mg. All other patients received lenalidomide 20 mg.

Summary:

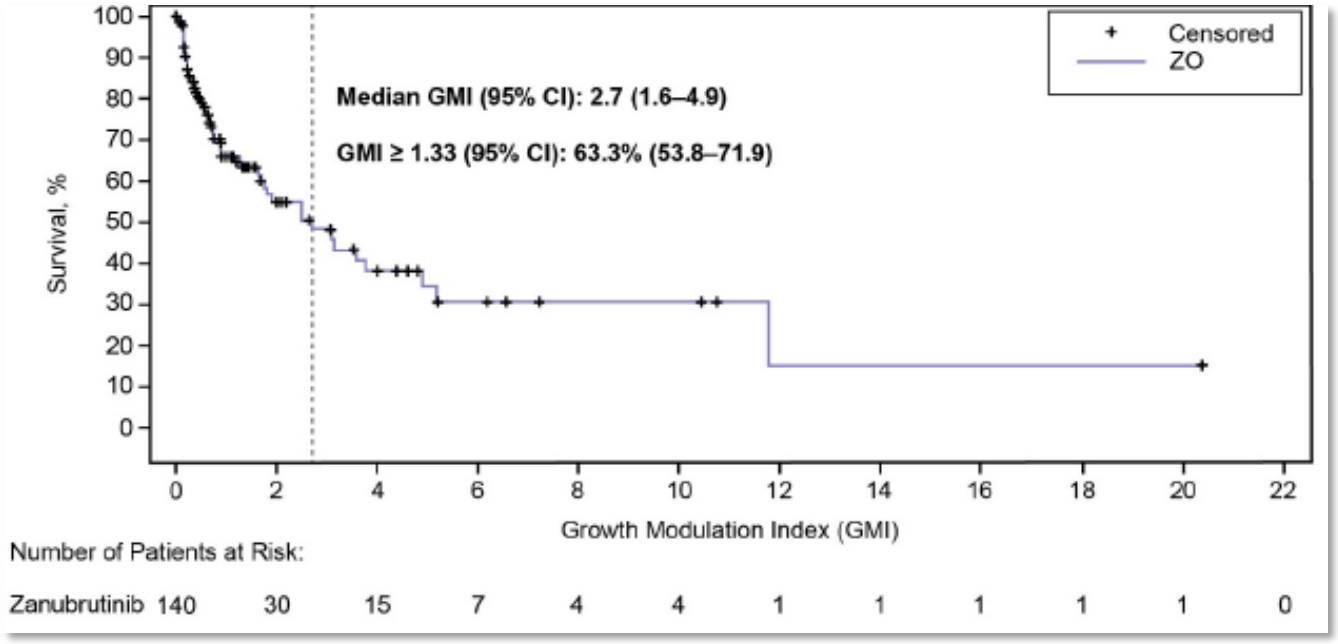
- The combination of A+rituximab was well tolerated in TN FL and R/R FL.
- The addition of lenalidomide 20 mg suggests improved ORR in R/R FL compared with A alone.
- Further studies of this regimen in FL are needed.

A, acalabrutinib; AE, adverse event; CI, confidence interval; CR, complete response; K-M, Kaplan-Meier; ORR, overall response rate; PD, progressive disease; PR, partial response; R^2, lenalidomide and rituximab; R/R, relapsed/refractory; SD, stable disease; SPD, sum of product diameters; TEAE, treatment-emergent AE; TN, treatment naïve.
Extracted from Strati P et al, Blood. 2022;140(Supplement 1):3606–3608.

Growth Modulation Index (GMI) analysis of Zanu-Obi efficacy in R/R FL

Poster presentation in Hall 7 on Friday, 14 June at 18:00-19:00 CEST: Bouabdallah et al. P1143.

INTRAPATIENT COMPARATIVE ANALYSIS OF ZANUBRUTINIB PLUS OBINUTUZUMAB EFFICACY IN RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA USING THE GROWTH MODULATION INDEX



- Post hoc GMI analysis of data from ROSEWOOD showed that most (>60%) of patients with R/R FL receiving Zanu-Obi had a significant (GMI ≥1.33) improvement in PFS vs their last prior treatment, irrespective of the number of prior treatments
- In the overall population, the median GMI of 2.7 was more than double the 1.33 threshold for meaningful clinical activity compared with the last prior treatment

Summary:
These data further support the benefit of Zanu-Obi as a novel treatment option for patients with R/R FL.

CI, confidence interval; GMI, growth modulation index; R/R, relapse or refractory; FL, follicular lymphoma; O or Obi, obinutuzumab; Z or Zanu, zanubrutinib.

Bouabdallah K, Liao S, Delarue R, Dima L, Weber D, Dumartin L. EHA 2024; Abstract P1143 (Accessed 04 June 2024). Available at: Bouabdallah_BGB-3111-212_GMI_EHA_Abstract_2024.pdf.

Conclusions (Speaker's own)

- Patients with indolent lymphomas now have effective next-generation BTKi-based treatment options[1]
- In WM (ASPEN study), Zanu delivered sustained responses regardless of line of therapy or mutation status; 44-month CR/VGPR 36% (Zanu) vs 25% (Ibru) and for patients with *CXCR4*^{MUT}, 21% (Zanu) vs 10% (Ibru)[2]
- In R/R MZL (MAGNOLIA study), Zanu showed high response rates and durable disease control, with responses in all MZL subtypes and in difficult-to-treat subgroups[3]
- In R/R FL (ROSEWOOD study), Zanu + Obi demonstrated meaningful efficacy in heavily pretreated patients; at 20 months, ORR was 69% (Zanu + Obi) vs 46% (Obi) (p=0.0012)[4]
- Across these studies, Zanu had a consistent and manageable safety profile[2-4]

Approval status[5-7]:

Indolent lymphomas

	CLL		WM		MZL		FL		MCL	
	EU	US	EU	US	EU	US	EU	US	EU	US
Zanubrutinib[1]	✓	✓	✓	✓	✓	✓	✓	✓	planned	✓
Ibrutinib[2]	✓	✓	✓	✓		withdrawn			✓	withdrawn
Acalabrutinib[3]	✓	✓								✓

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; *CXCR4*, C-X-C chemokine receptor 4; EU, European Union; FL, follicular lymphoma; Ibru, ibrutinib; MUT, mutated; MZL, marginal zone lymphoma; Obi, obinutuzumab; ORR, overall response rate; R/R, relapsed/refractory; US, United States (of America); VGPR, very good partial response; WM, Waldenström's macroglobulinemia; Zanu, zanubrutinib.

1) Speaker's own; 2) Extracted from Garcia-Sanz R et al. Presented at the 38th World Congress of the ISH; October 6-8, 2022; Barcelona, Spain (Accessed 04 June 2024). Available at: Garcia-Sanz_BGB-3111-302_SEHH_Presentation_2022.pdf; 3) Sehn LH et al. Presented at 17th International Conference on Malignant Lymphoma, June 13-17, 2023; Lugano, Switzerland; Abstract 994 (Accessed 04 June 2024). Available at: Sehn_BGB-3111-308_ICML_Presentation_2023.pdf; 4) Extracted from Zinzani PL et al. Presented at the 17th International Conference on Malignant Lymphoma; June 13-17, 2023; Lugano, Switzerland; Abstract 81 (Accessed 04 June 2024). Available at: Zinzani_BGB-3111-212_ICML_Presentation_2023.pdf; 5) Brukinsa SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/brukinsa; 6) Imbruvica SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/imbruvica; 7) Calquence SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/calquence.

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