Between ASH and EHA: Updates, Trends & New Directions in CLL & Indolent Lymphomas

Wednesday, May 7, 2025 | 17:30–18:30 (CEST)

Welcome and introductions

Chair: Catherine Thieblemont

Disclosures

- **Research funding**: Gilead, Janssen
- **Advisory boards**: AbbVie, Amgen, Bayer, BMS/Celgene, Gilead, Incyte, Janssen, Kite, Novartis, Roche, Takeda
- **Education activities**: BeiGene, Janssen, Roche

Disclaimers

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- Zanubrutinib is approved in the EU as monotherapy for adults with chronic lymphocytic leukemia (CLL), for adults with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20–based therapy, for adults with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy or in first-line treatment for patients unsuitable for chemoimmunotherapy, and in combination with obinutuzumab for adults with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least two prior lines of systemic therapy.[1]
- Prescribing information (PI) may vary depending on local approval in each country. Therefore, before prescribing any product, always refer to local authorities concerning reimbursement status and to local materials such as the PI and/or the summary of product characteristics (SPC) for guidance on prescribing.

CD, cluster of differentiation.

1. BeiGene Ireland Ltd. BRUKINSA 80 mg hard capsules – summary of product characteristics; February 2024.

Introducing the panel

Catherine Thieblemont (Chair)
Saint-Louis Hospital, France

Raúl Córdoba
Jiménez Díaz Foundation University Hospital, Spain

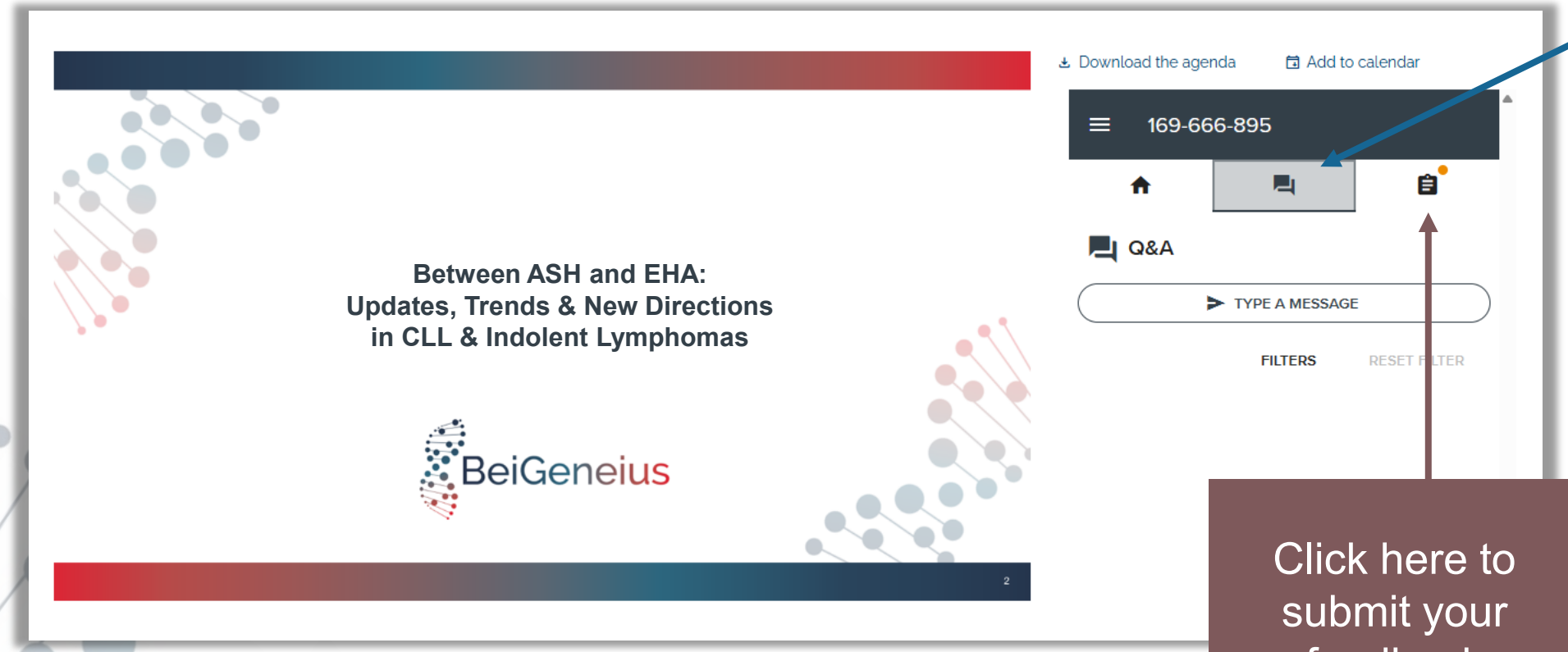
Stefano Luminari
University of Modena and Reggio Emilia, Italy

Agenda

Time (CEST)	Session	Speaker
17:30	Welcome and introductions	Catherine Thieblemont
17:35	Updates, trends & new directions in CLL	Raúl Córdoba
17:55	Updates, trends & new directions in indolent lymphomas	Stefano Luminari
18:15	Audience Q&A	All faculty
18:25	Summary and close	Catherine Thieblemont

CLL, chronic lymphocytic leukemia; Q&A, question and answer.

Exit full-screen view to have your say

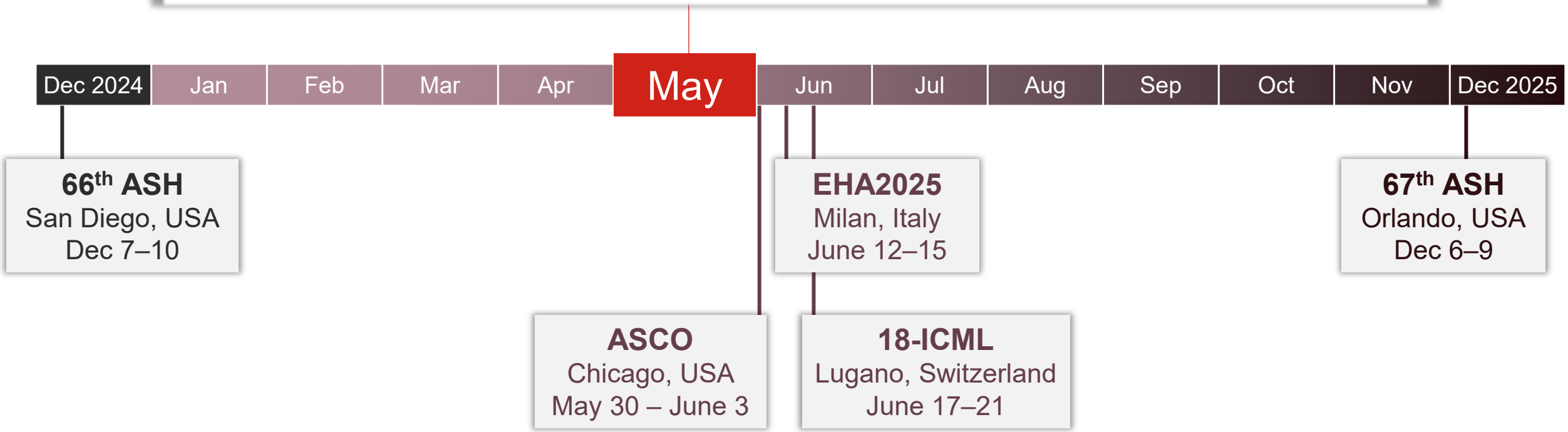


Click here to submit your questions to the faculty

Click here to submit your feedback

Meeting objective

Provide an overview of recent developments in **chronic lymphocytic leukemia**, **follicular lymphoma**, and **marginal zone lymphoma**, and highlight the key trends and research directions likely to feature prominently in the upcoming summer congress season



ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; EHA, European Hematology Association; ICML, International Conference on Malignant Lymphoma.

Updates, Trends & New Directions in CLL

Raúl Córdoba, MD, PhD
Fundación Jiménez Díaz, University Hospital, Spain

Disclosures

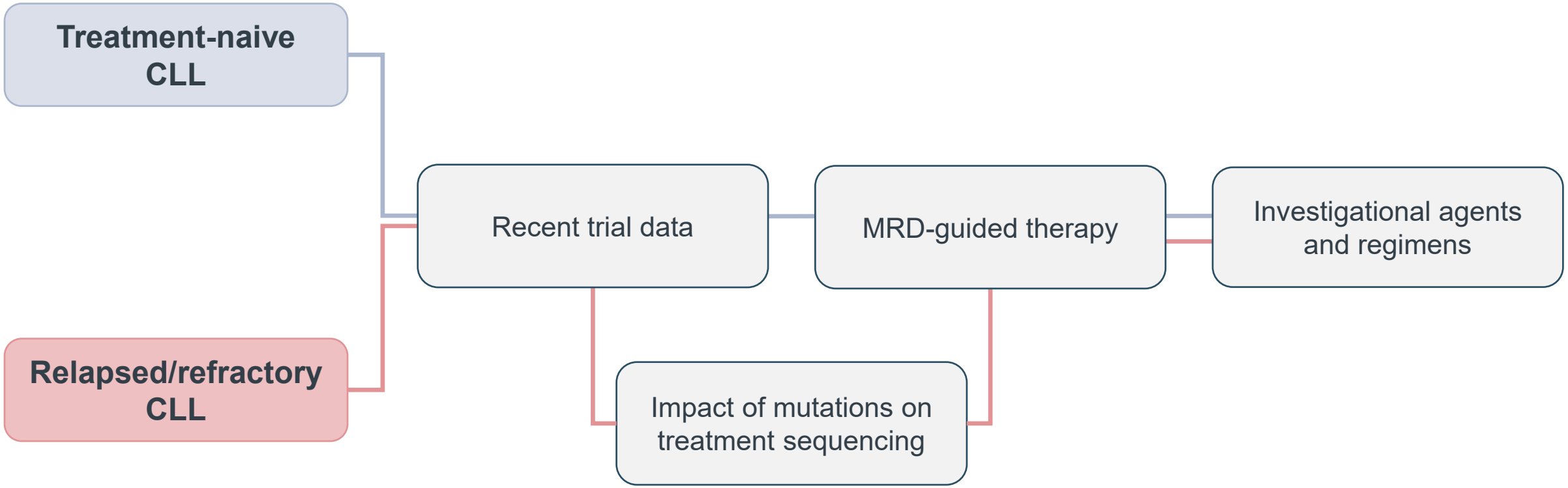
- **Consultancy and advisory role:** AbbVie, AstraZeneca, BeiGene, BMS, Genmab, Incyte, Kite, Kyowa Kirin, Lilly, Regeneron, Roche, Takeda

- **Faculty:** AbbVie, AstraZeneca, BeiGene, BMS, Incyte, Kite, Kyowa Kirin, Lilly, Roche

- **Research grants:** Pfizer

BMS, Bristol Myers Squibb.

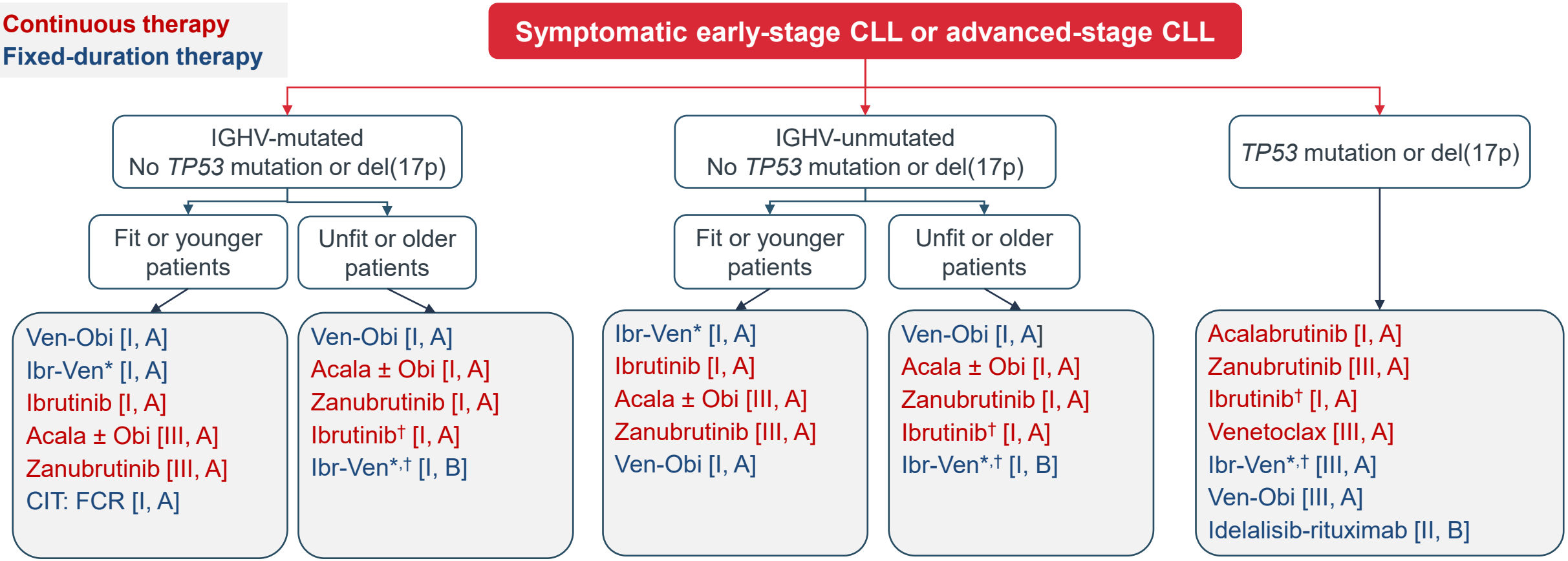
What we will discuss



CLL, chronic lymphocytic leukemia; MRD, minimal residual disease.

ESMO clinical practice guidelines for first-line CLL

Continuous therapy
Fixed-duration therapy



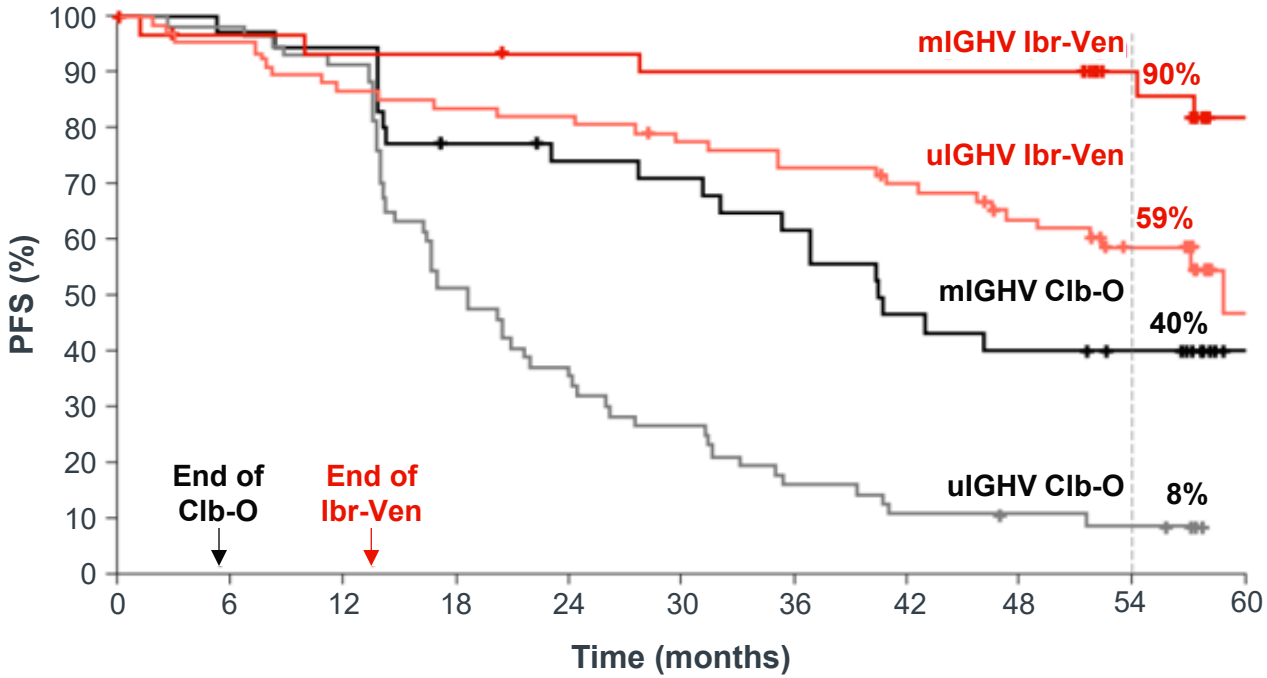
I: Evidence from at least one large randomized, controlled trial of good methodological quality (low potential of bias) or meta-analyses of well-conducted randomized trials without heterogeneity. II: Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity. III: Prospective cohort studies.
A: Strong evidence for efficacy with a substantial clinical benefit; strongly recommended. B: Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended.
*Ibrutinib-venetoclax with a 15-month fixed duration or with an MRD-guided duration. †Ibrutinib or ibrutinib-venetoclax should be considered carefully in older patients with cardiac comorbidities.
Acala, acalabrutinib; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del, deletion; ESMO, European Society for Medical Oncology; FCR, fludarabine, cyclophosphamide, and rituximab; Ibr, ibrutinib; IGHV, immunoglobulin heavy chain variable; MRD, minimal residual disease; Obi, obinutuzumab; Ven, venetoclax. Eichhorst B *et al*. *Ann Oncol* 2024; 35 (9): 762–768.

GLOW study: Fixed-duration Ibr-Ven

Durable efficacy but with serious cardiac side effects

GLOW: Ibr-Ven vs. Clb-O by IGHV status (N=211)[1]

Superior outcomes for mIGHV vs. uIGHV patients with Ibr-Ven



Eligible patients[2]

- Elderly (≥65 years) or comorbidities (CIRS >6 or creatinine clearance <70 mL/min)
- No del(17p) or *TP53* mutation

No difference in TTNT for patients with mIGHV vs. uIGHV
HR (95% CI): 1.20 (0.31–4.60); *P*=0.7878

uMRD status at EOT+3 predicted a PFS benefit for patients with uIGHV but not for patients with mIGHV

AEs with Ibr-Ven at a median 27.7 months of follow-up[2]

- Any-grade atrial fibrillation: 14.2% (15/106)
- Cardiac or sudden deaths: 4% (4/106)

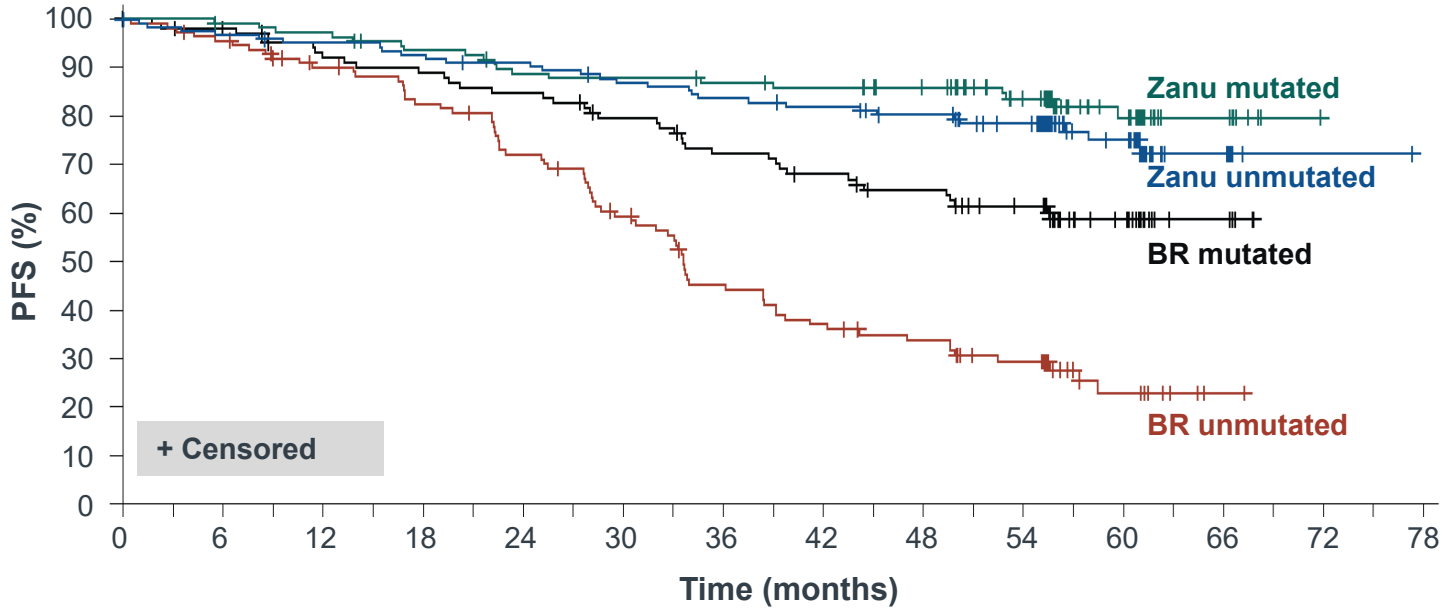
AE, adverse event; CI, confidence interval; CIRS, Cumulative Illness Rating Scale; Clb, chlorambucil; del, deletion; HR, hazard ratio; EOT+3, 3 months after end of treatment; Ibr, ibrutinib; (m/u)IGHV, (mutated/unmutated) immunoglobulin heavy chain variable; O, obinutuzumab; PFS, progression-free survival; TTNT, time to next treatment; uMRD, undetectable minimal residual disease; Ven, venetoclax.

1. Moreno C *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023. 2. Kater AP *et al*. *NEJM Evid* 2022; 1 (7): EVIDoa2200006.

SEQUOIA long-term follow up[1]

Consistent efficacy with zanubrutinib across low- and high-risk disease

PFS with mutated and unmutated IGHV (no del[17p])



Zanu mIGHV	109	109	107	106	105	101	99	98	93	92	92	92	90	88	88	86	83	77	69	41	36	11	11	1	0	
Zanu uIGHV	125	122	120	118	117	117	114	111	111	109	105	104	101	100	98	93	91	84	81	45	43	8	8	1	1	1	0
BR mIGHV	109	100	98	93	90	88	87	84	83	81	76	74	68	67	63	58	58	52	50	25	22	5	5	0			
BR uIGHV	123	112	108	102	96	93	87	84	75	71	60	55	44	40	36	32	31	24	23	12	9	3	1	0			

Overall PFS in patients without del(17p)

Estimated 60-month PFS rate (95% CI)

- Zanu (Arm A): 75.8% (95% CI: 69.0–81.3)
- BR (Arm B): 40.1% (95% CI: 32.7–47.3)

Zanubrutinib mIGHV vs. uIGHV

HR (95% CI): 1.35 (0.76–2.40); *P*=0.5194

Estimated 42-month PFS in patients treated with zanubrutinib with/without del(17p)*,[2]

Del(17p) negative: 82.4%
Del(17p) positive: 79.4%

At a median follow-up of 26.4 months, 85% of patients in Arm A remained on zanubrutinib[3]

Any-grade atrial fibrillation occurred in 3%

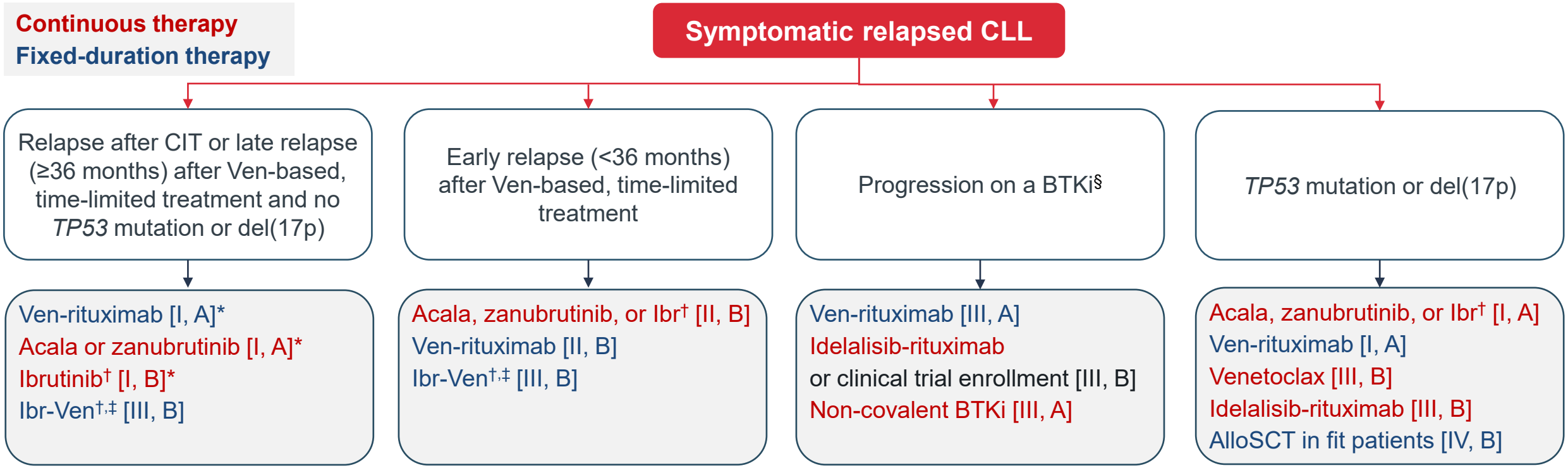
*Patients with del(17p) were treated with open-label zanubrutinib.

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

1. Shadman M *et al*. Oral presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024. 2. Munir T *et al*. Poster presentation at EHA 2023; Frankfurt, Germany, June 8–11, 2023. 3. Tam CS *et al*. *Lancet Oncol* 2022; 23 (8): 1031–1043.

Therapeutic Sequencing

ESMO clinical practice guidelines for relapsed CLL



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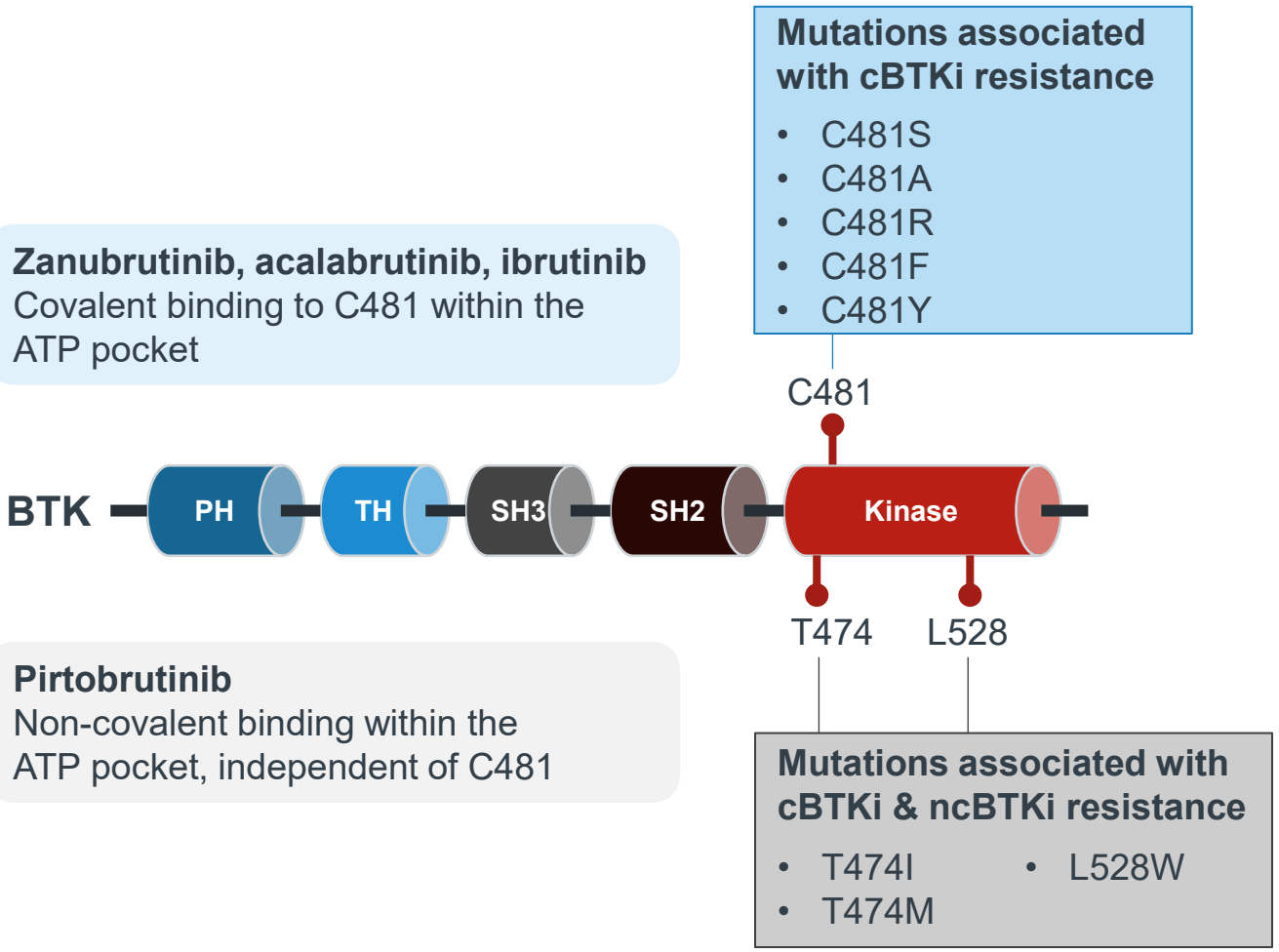
A: Strong evidence for efficacy with a substantial clinical benefit; strongly recommended. B: Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended.
*For relapse after CIT, BTKis or venetoclax-rituximab should be considered equally, depending on comorbidities, comedication, access, and preference. †Ibrutinib should be considered carefully in older patients with cardiac comorbidities. ‡Not EMA approved, not FDA approved in relapse. §If a patient relapses after prior treatment with a BTKi that was stopped owing to side effects, changing to a different BTKi or rechallenge could be considered [III, B].
Acala, acalabrutinib; alloSCT, allogeneic stem cell transplantation; BTKi, BTK inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del, deletion; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; Ibr, ibrutinib; Ven, venetoclax.
Eichhorst B *et al*. *Ann Oncol* 2024; 35 (9): 762–768.

Data suggest mutations leading to cBTKi–ncBTKi cross-resistance are rare following cBTKi use in the relapsed setting[1,2]

Zanubrutinib, acalabrutinib, ibrutinib
Covalent binding to C481 within the ATP pocket

Pirtobrutinib
Non-covalent binding within the ATP pocket, independent of C481



ELEVATE-RR: Acquired BTK mutations in patients with PD[3]

- Acalabrutinib: 66% (31/48)
- Ibrutinib: 37% (11/36)

Acalabrutinib PD (n=48)		Ibrutinib PD (n=36)	
C481S	60%	**C481S**	58%
T474I	19%	**T474I**	0%
L528W	0%	**L528W**	3%

ALPINE: Acquired BTK mutations in patients with PD[4]

- Zanubrutinib: 23% (6/26)
- Ibrutinib: 6% (2/31)

Zanubrutinib PD (n=26)		Ibrutinib PD (n=31)	
C481S	15%	**C481S**	6%
L528W	3%	**L528W**	0%

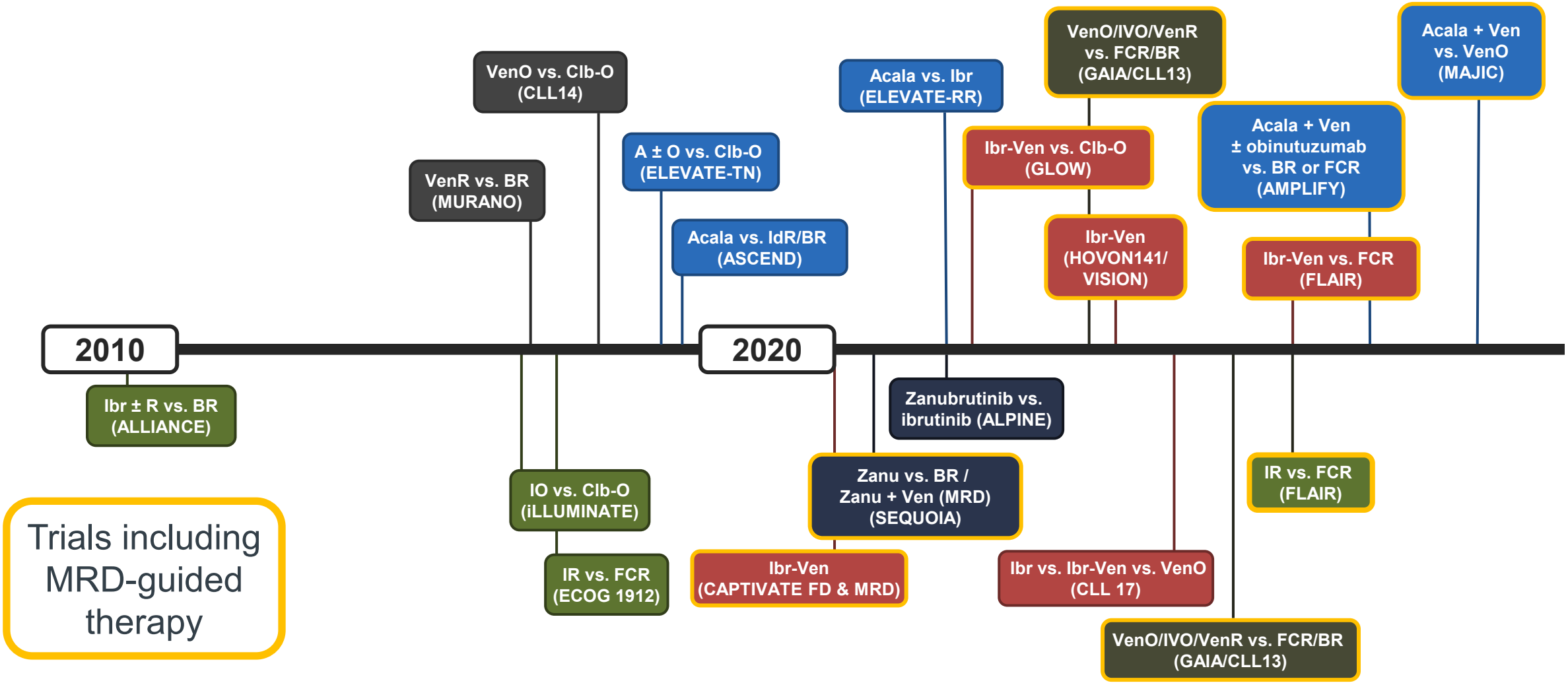
This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

ATP, adenosine triphosphate; c/ncBTKi, covalent/non-covalent BTK inhibitor; PD, progressive disease.

1. Stephens DM *et al*. *Blood* 2021; 138 (13): 1099–1109. 2. Wang E *et al*. *N Engl J Med* 2022; 386 (8):735–743. 3. Woyach J *et al*. Poster presentation at ICML 2023; Lugano, Switzerland, June 13–17, 2023.
4. Brown JR *et al*. Poster presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023.

MRD-guided Therapy

MRD-guided therapy is a feature of several active trials in CLL



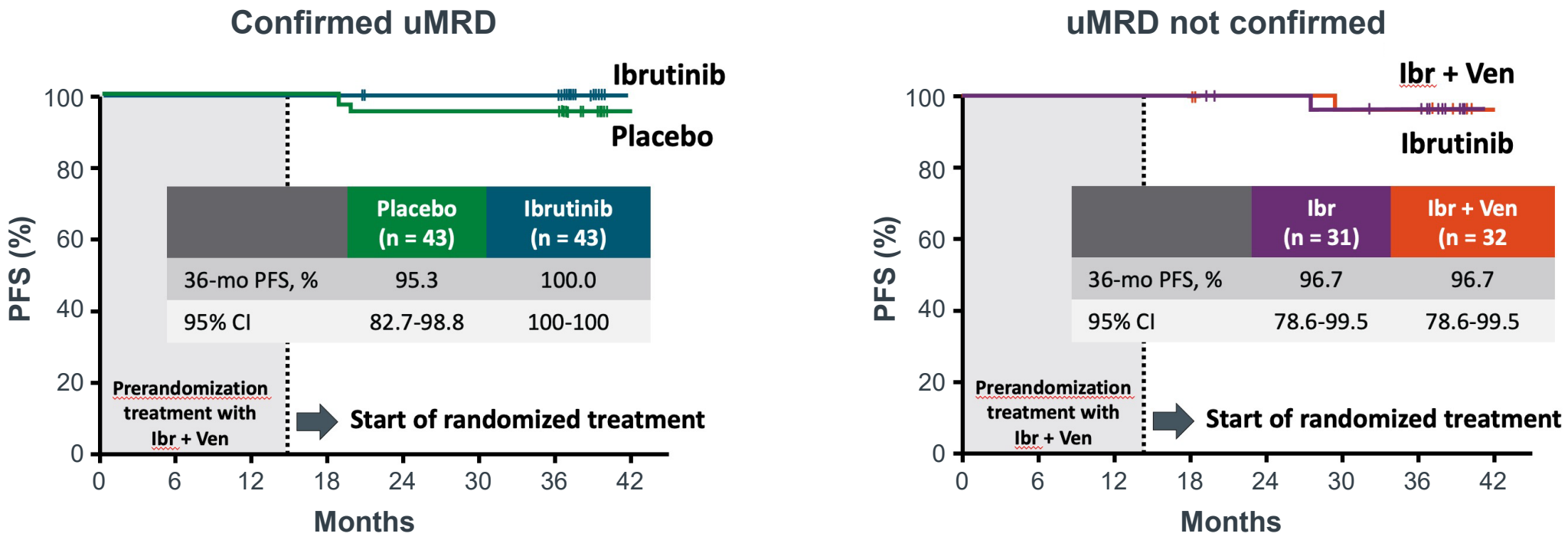
A/Acala, acalabrutinib; B, bendamustine; C, cyclophosphamide; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; F, fludarabine; I/Ibr, ibrutinib; Id, idelalisib; MRD, minimal residual disease; O, obinutuzumab; R, rituximab; V/Ven, venetoclax; Zanu, zanubrutinib.
Slide courtesy of Raúl Córdoba.

CAPTIVATE: MRD-guided Ibr-Ven in TN CLL

Very few PFS events in MRD cohort at 3 years

MRD cohort – after 12 cycles of Ibr-Ven

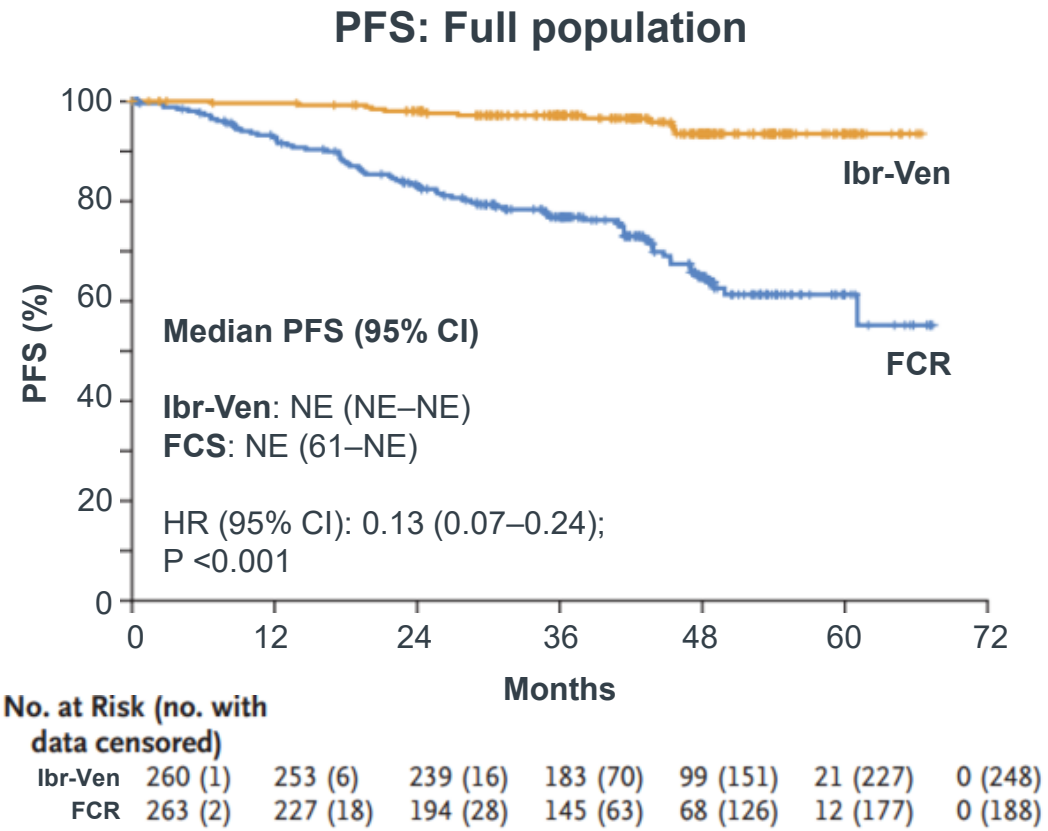
- Patients with confirmed uMRD were randomly assigned to receive placebo or continuous ibrutinib
- Patients with uMRD not confirmed were randomly assigned to ibrutinib or Ibr-Ven (max. 2 years of venetoclax)



CI, confidence interval; CLL, chronic lymphocytic leukemia; Ibr, ibrutinib; mo, month; PFS, progression-free survival; TN, treatment-naive; (u)MRD, (undetectable) minimal residual disease; Ven, venetoclax.

Moreno C *et al*. Poster presented at EHA 2022; Vienna, Austria, June 9–12, 2022 (Poster P669).

FLAIR: MRD-guided Ibr-Ven improved PFS vs. FCR in TN CLL



MRD-guided Ibr-Ven

Ibr-Ven duration was double the time taken to achieve uMRD, defined by assessment in PB and BM

PFS favored Ibr-Ven vs. FCR for uIGHV patients

- HR (95% CI): 0.07 (0.02–0.19)

But not mIGHV patients

- HR (95% CI): 0.54 (0.21–1.38)

3-year OS of the full population

- Ibr-Ven: 98% (95% CI: 95.2–99.2)
- FCR: 93% (95% CI: 88.9–95.6)

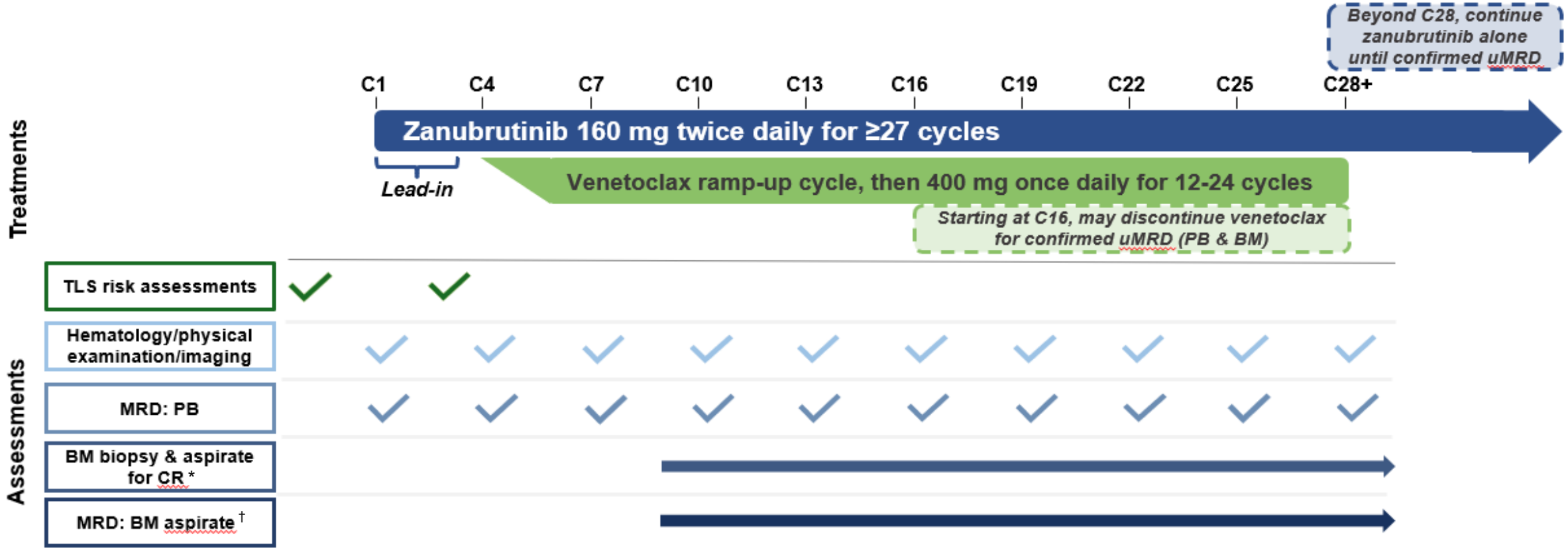
AEs with Ibr-Ven at a median 27.7 months of follow-up

- Any-grade atrial fibrillation: 4.8% (12/252)
- Cardiac or sudden unexplained deaths: 1% (3/252)

AE, adverse event; BM, bone marrow; CI, confidence interval; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio; I/Ibr, ibrutinib; NE, not estimable; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; TN, treatment-naive; uIGHV, unmutated immunoglobulin heavy chain variable; (u)MRD, (undetectable) minimal residual disease; V, venetoclax.

Munir T *et al. N Engl J Med* 2024; 390 (4): 326–337.

SEQUOIA Arm D: Zanubrutinib-venetoclax in TN del(17p) and/or *TP53*-mutated CLL



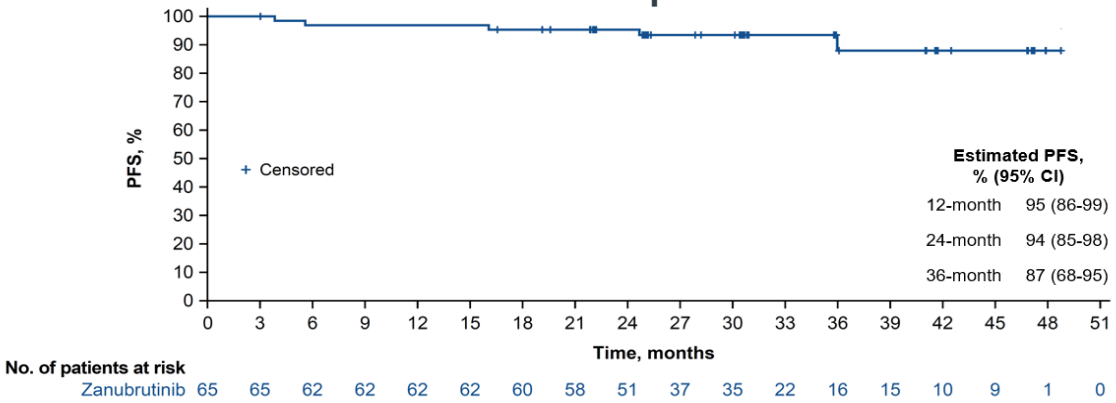
*BM biopsy and aspirate are required to confirm a suspect CR/CRi (BM collection time point not defined per protocol), starting after Cycle 9 and then annually if needed. †Patients with confirmed CR/CRi and two consecutive PB MRD tests with results that meet uMRD requirements for dose stopping.

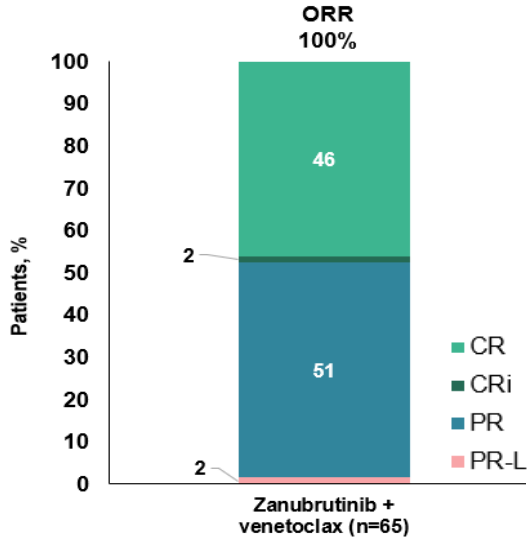
BM, bone marrow; C, Cycle; CLL, chronic lymphocytic leukemia; CR(i), complete response (with incomplete recovery); del, deletion; PB, peripheral blood; TLS, tumor lysis syndrome; TN, treatment-naive; (u)MRD, (undetectable) minimal residual disease.

Shuo MA *et al*. Oral presentation at EHA 2024; Madrid, Spain, June 13–16, 2024.

SEQUOIA Arm D: Zanubrutinib-venetoclax in TN del(17p) and/or *TP53*-mutated CLL

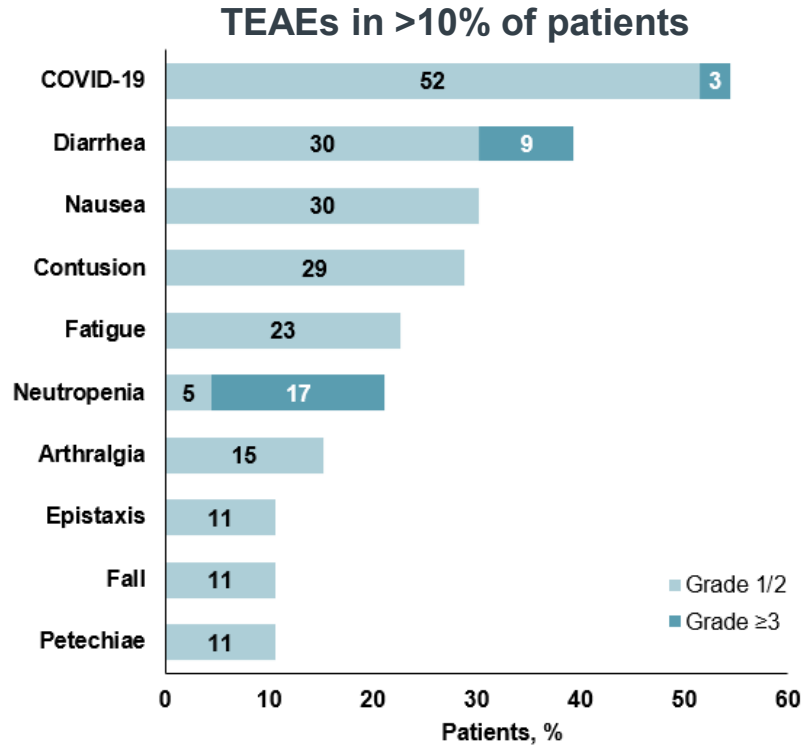
Median follow-up: 31.6 months





Best uMRD rate:
59% (39/66) in ≥1 PB;
37% (13/35) in ≥1 BM sample

Preliminary data demonstrate promising efficacy and tolerability with first-line zanubrutinib-venetoclax in high-risk CLL



BM, bone marrow; CI, confidence interval; CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; CR(i), complete response (with incomplete recovery); del, deletion; ORR, overall response rate; PB, peripheral blood; PFS, progression-free survival; PR(-L), partial response (with lymphocytosis); TEAE, treatment-emergent adverse event; TN, treatment-naive; uMRD, undetectable minimal residual disease.
Shuo Ma *et al*. Oral presentation at EHA 2024; Madrid, Spain, June 13–16, 2024.

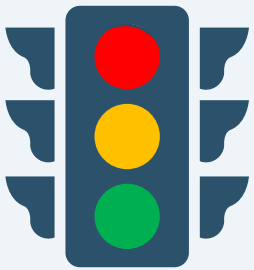
Questions with MRD in CLL

What technique should you use to measure MRD?

How should you define MRD?

What compartment should you monitor?

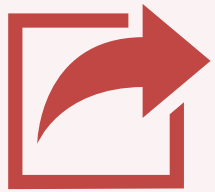
Should you use static or dynamic MRD evaluation?



When should you stop treatment?

When should you extend treatment?

When should you re-treat?



When and how should you alter treatment?

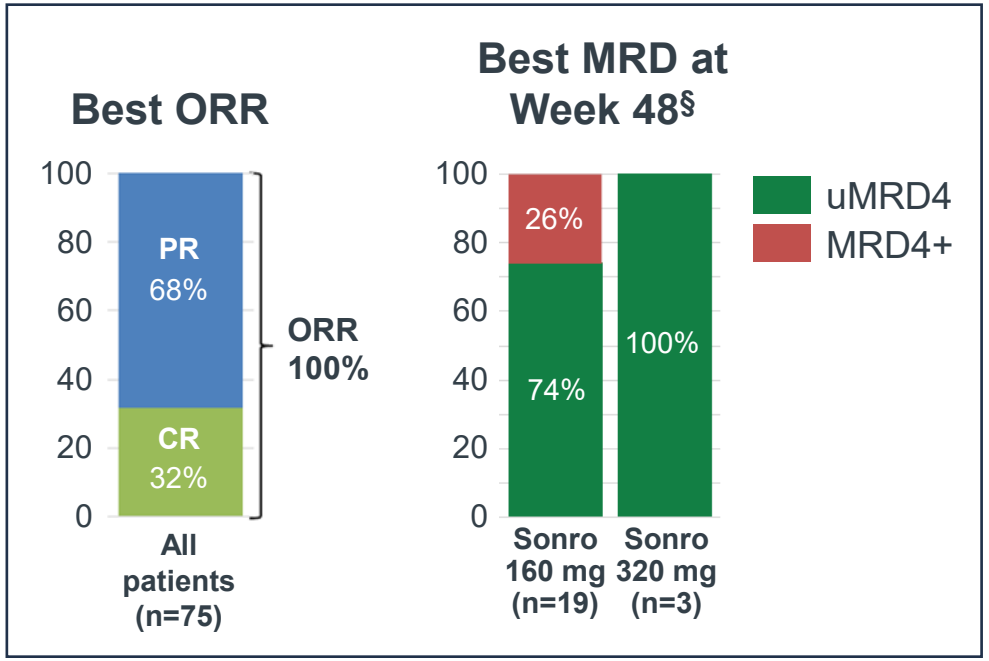
CLL, chronic lymphocytic leukemia; MRD, minimal residual disease.
Slide courtesy of Raúl Córdoba.

New Agents and Combinations

Sonrotoclax-zanubrutinib: Phase 1/2 study in B-cell malignancies

Early data have been presented for the TN CLL/SLL cohort

	Sonro 160 mg + Zanu (n=51)*,†	Sonro 320 mg + Zanu (n=56)‡
Any AEs, n (%)	47 (92.2)	49 (87.5)
Grade ≥3 AEs, n (%)	22 (43.1)	21 (37.5)
Serious AEs, n (%)	7 (13.7)	8 (14.3)
Leading to death	0	0
Leading to dose reduction of zanubrutinib	1 (2.0)	2 (3.6)
Leading to discontinuation of zanubrutinib	1 (2.0)	0
Treated with sonrotoclax, n (%)	41 (80.4)	53 (94.6)
Leading to hold of sonrotoclax	11 (26.8)	10 (18.9)
Leading to dose reduction of sonrotoclax	2 (4.9)	3 (5.7)
Leading to discontinuation of sonrotoclax	1 (2.4)	0



Based on the promising efficacy and safety data from this study, first-line Sonro-Zanu 320 mg will be tested in a Phase 3 head-to-head study vs. Ven-Obi (CELESTIAL-TNCLL)

*One patient stopped both sonrotoclax and zanubrutinib owing to fungal infection. †Median follow-up (range): 7.2 months (0.3–21.1 months). ‡Median follow-up (range): 9.8 months (0.5–17.4 months). §MRD was measured by ERIC flow cytometry with 10^{-4} sensitivity. uMRD4 is defined as the number of CLL cells of total nucleated cells $<10^{-4}$. MRD4+ is defined as the number of CLL cells of total nucleated cells $>10^{-4}$; MRD is best reported within a 2-week window following the Week 24 Day 1 and Week 48 Day 1 MRD assessment time points.

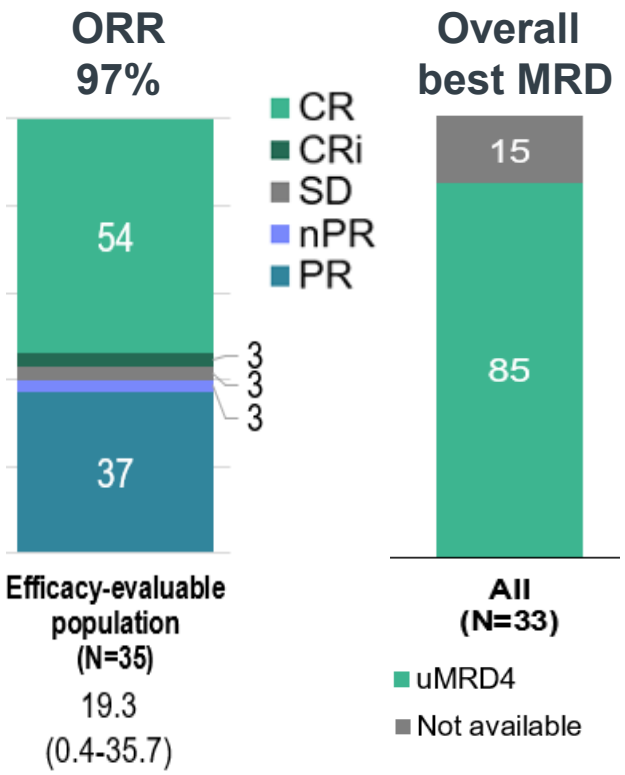
AE, adverse event; CLL, chronic lymphocytic leukemia; CR, complete response; ERIC, European Research Initiative on CLL; MRD, minimal residual disease; Obi, obinutuzumab; ORR, overall response rate; PR, partial response; SLL, small lymphocytic lymphoma; Sonro, sonrotoclax; TN, treatment-naive; (u)MRD, (undetectable) minimal residual disease; Ven, venetoclax; Zanu, zanubrutinib.

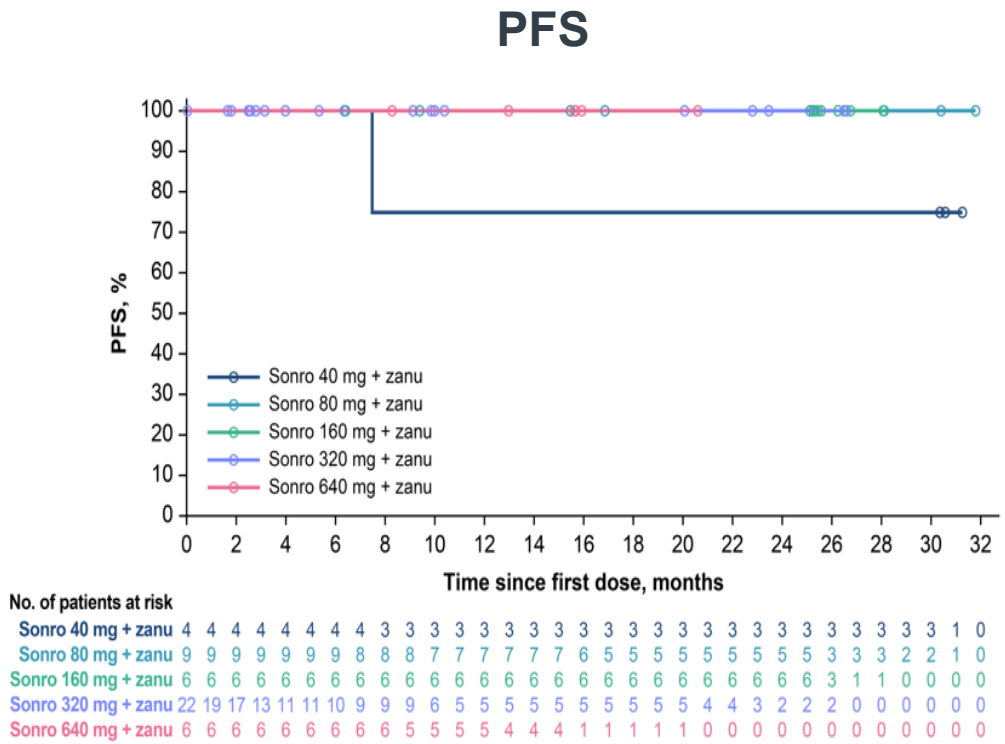
Patten P *et al*. Oral presentation at BSH 2024; Liverpool, UK, April 28–30, 2024.

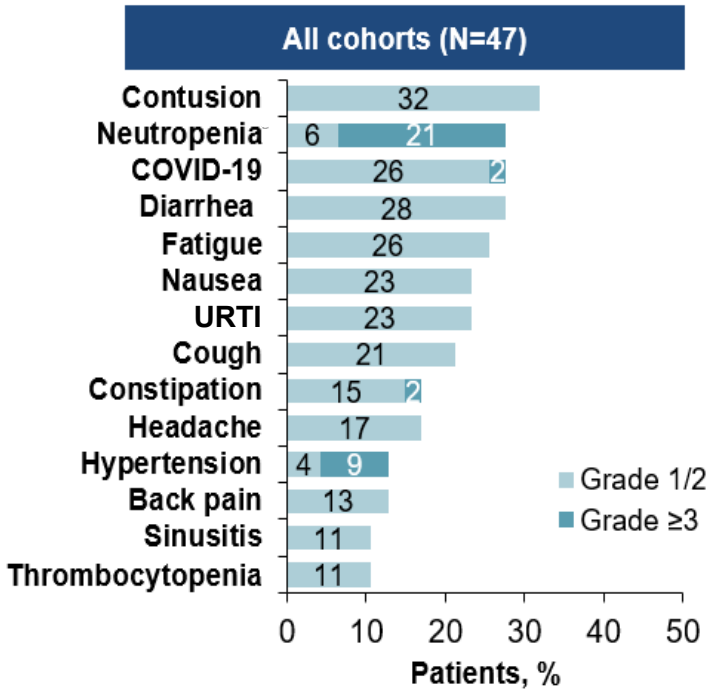
Sonrotoclax-zanubrutinib: Phase 1/1b study in R/R CLL

Tolerable safety profile and deep responses with the next-generation regimen in the relapsed setting

Median study follow-up of 19.3 months







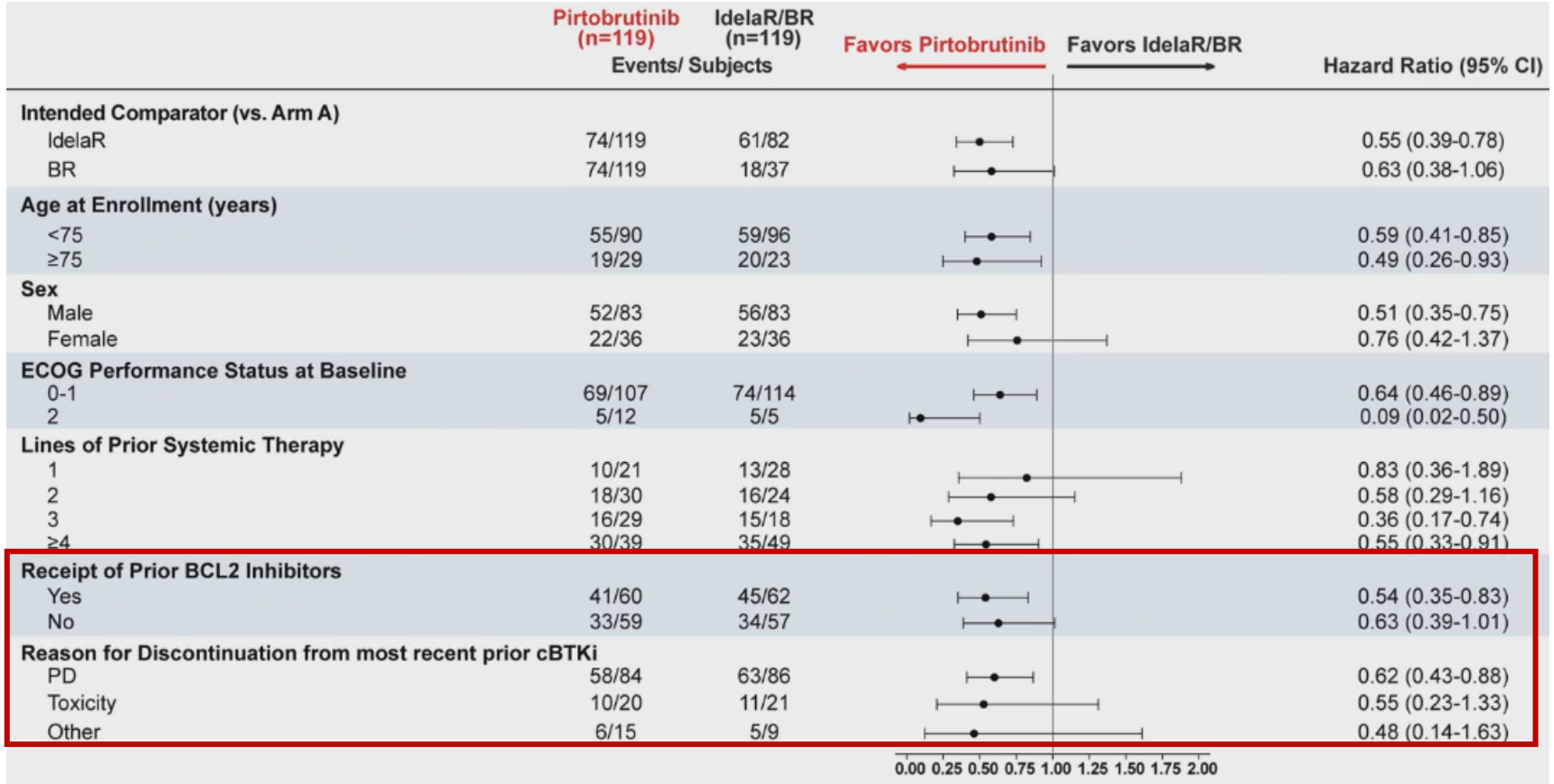
CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; CR(i), complete response (with incomplete recovery); (n)PR, (nodular) partial response; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; SD, stable disease; Sonro, sonrotoclax; (u)MRD, (undetectable) minimal residual disease; URTI, upper respiratory tract infection; Zanu, zanubrutinib.

Opat S *et al*. Oral presentation at EHA 2024; Madrid, Spain, June 13–16, 2024.

Non-covalent BTKis

BRUIN study[1]

IRC-assessed PFS among patient subgroups



Patients

High-risk: >50% del(17p) and/or *TP53*^{MUT}, and complex karyotype

Heavily pretreated population: all with prior cBTKi; 33% with ≥4 prior lines of therapy, ~50% received prior BCL2i

Median PFS

- **Pirtobrutinib:** 14.0 months
- **IdelaR/BR:** 8.7 months

HR (95% CI): 0.54 (0.39–0.75); *P*=0.0002

Safety outcomes

Discontinuations

- **Pirtobrutinib:** 6/116 (5.2%)
- **IdelaR/BR:** 23/109 (21.1%)

BCL2(i), B-cell lymphoma 2 (inhibitor); BR, bendamustine and rituximab; (c)BTKi, (covalent) BTK inhibitor; CI, confidence interval; del, deletion; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IdelaR, idelalisib-rituximab; IRC, independent review committee; MUT, mutated; PD, progressive disease; PFS, progression-free survival.

Sharman JP *et al*. Oral presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024.

Non-covalent BTKis

BRUIN study[1]

Pirtobrutinib in patients with CLL intolerant to prior BTKi[2]

Patients

High-risk: >50% del(17p) and/or *TP53*^{MUT}, and complex karyotype

Heavily pretreated population: all with prior cBTKi; 33% with ≥4 prior lines of therapy, ~50% received prior BCL2i

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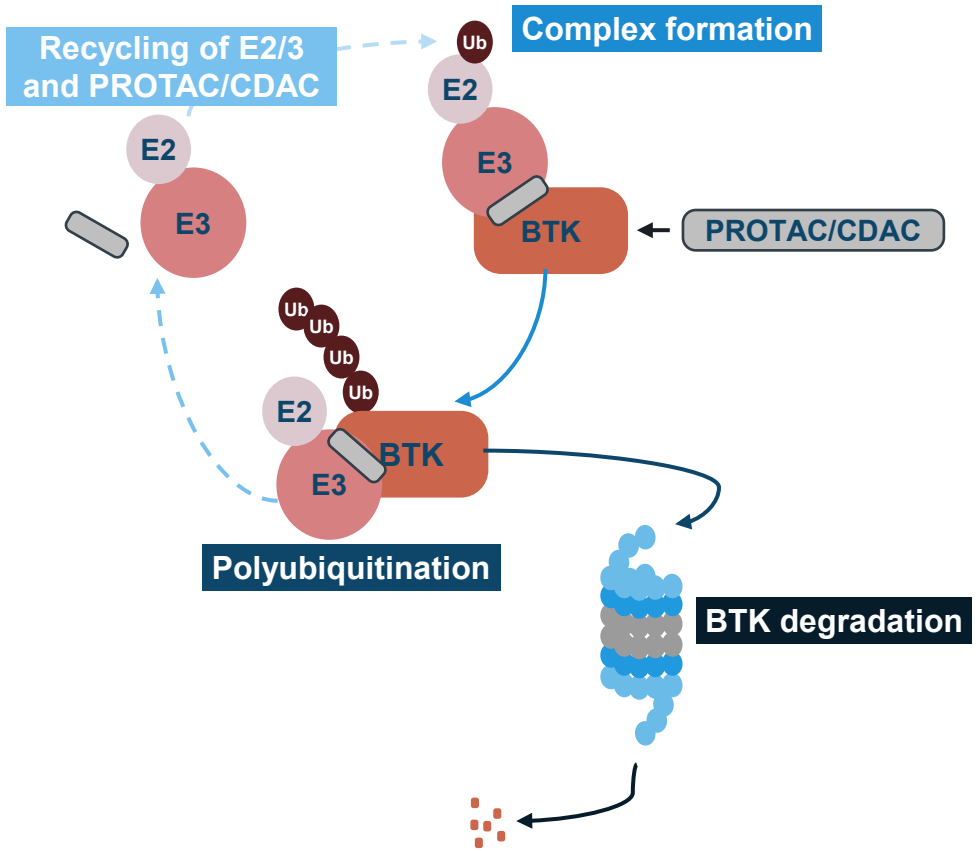
BCL2i, B-cell lymphoma 2 inhibitor; BR, bendamustine and rituximab; (c)BTKi, (covalent) BTK inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; del, deletion; HR, hazard ratio; IdelaR, idelalisib-rituximab; MUT, mutated; PFS, progression-free survival; SPD, sum of the product of the diameters.

1. Sharman JP *et al*. Oral presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024. 2. Shah NN *et al*. *Haematologica* 2025; 110 (1): 92–102.

BTK degraders are a potential future therapeutic option in the R/R setting

Targeting BTK for proteasomal degradation



Phase 1
CaDAnCe-101 study of BTK degrader BGB-16673[1]

60 patients with R/R CLL/SLL enrolled
Median 4 prior lines of therapy

Safety
- Well tolerated
- No AF

ORR (n=49)
- Overall: 77.6%
- Prior cBTKi + BCL2i: 86.7%
- Prior cBTKi + BCL2i + ncBTKi: 58.3%

Phase 1a/b study of BTK degrader NX-5948[2]

60 patients with R/R CLL/SLL enrolled
Median 4 prior lines of therapy

Safety
- Well tolerated
- One case of Grade 1 AF in a patient with pre-existing AF

ORR (n=49)
- Overall: 75.5%

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

AF, atrial fibrillation; BCL2i, B-cell lymphoma 2 inhibitor; (c/nc)BTKi, (covalent/non-covalent) BTK inhibitor; CDAC, chimeric degradation activation compound; CLL, chronic lymphocytic leukemia; ORR, overall response rate; PROTAC, proteolysis-targeting chimera; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; Ub, ubiquitin.

1. Thompson MC *et al*. Oral presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024. 2. Shah NN *et al*. Oral presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024.

Thank you for your attention

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Click here to submit your questions to the faculty

Click here to submit your feedback

Updates, Trends & New Directions in Indolent Lymphomas

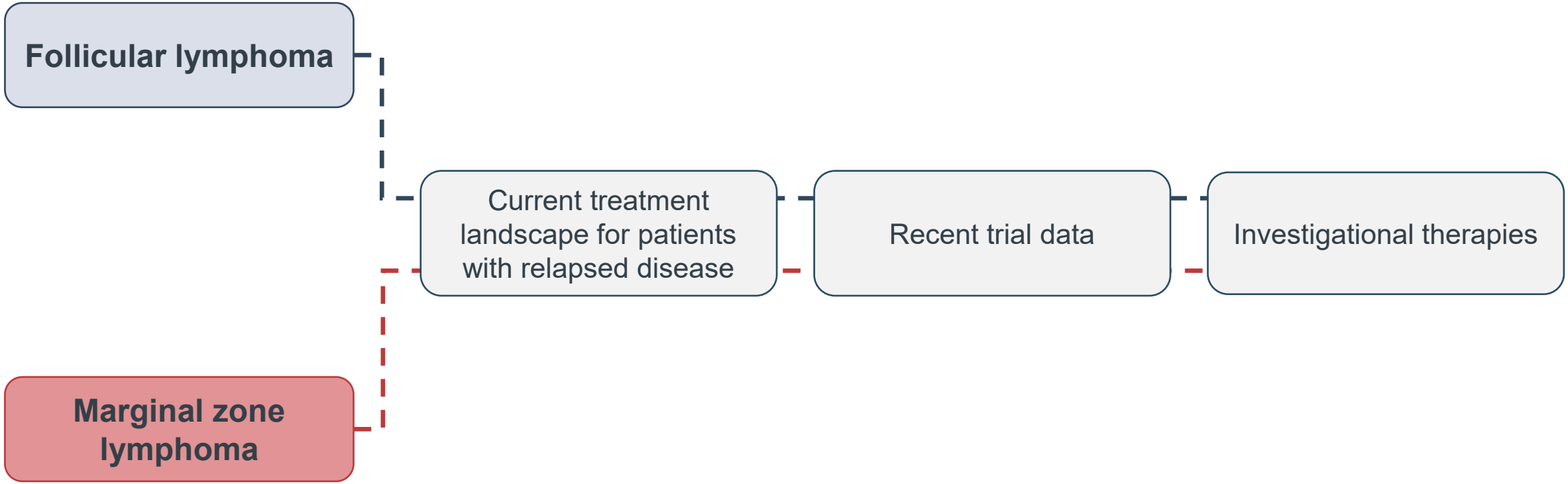
Stefano Luminari
University of Modena and Reggio Emilia, Italy

Disclosures

- **Advisory board:** AbbVie, BeiGene, BMS, Gilead/Kite, Incyte, Novartis, Regeneron, Roche
- **Research support:** BeiGene
- **Speakers bureau:** BeiGene, BMS, Gilead/Kite, Incyte, Regeneron, Roche

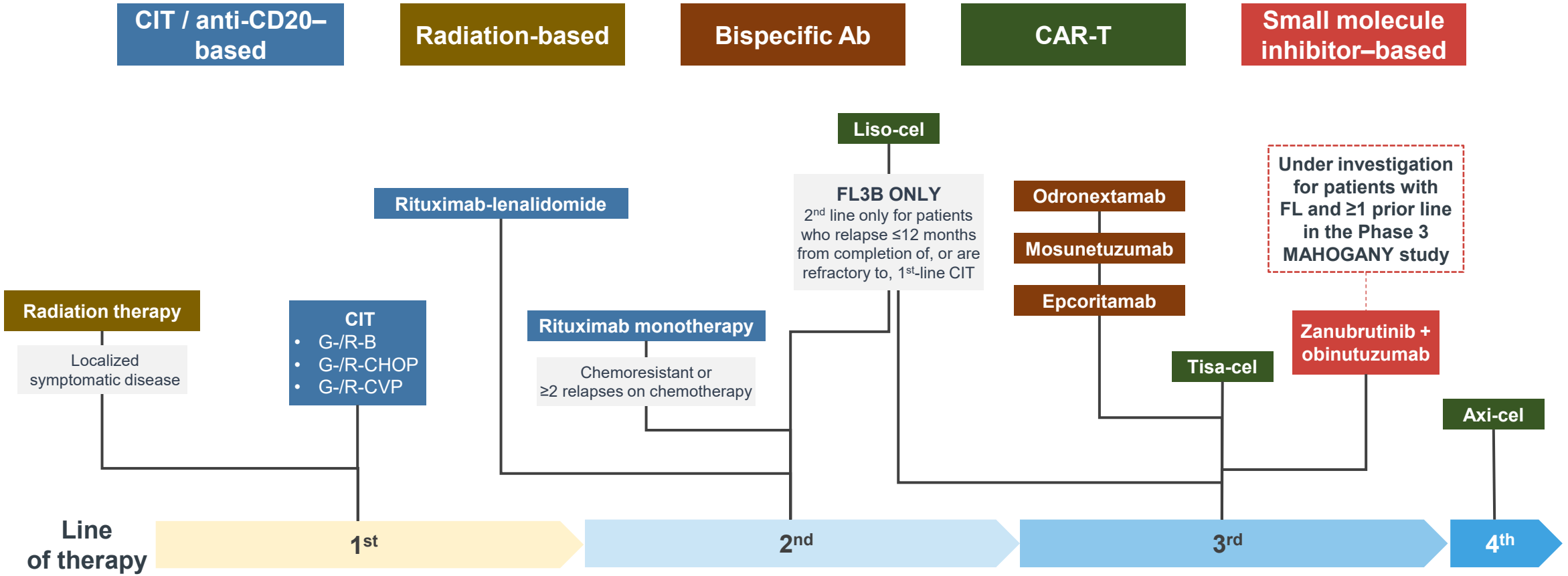
BMS, Bristol Myers Squibb.

What we will discuss



Follicular Lymphoma

Overview of the FL treatment landscape*



Please consult local guidance for details on licensed indications and reimbursement criteria.

*Information collated from the relevant Summary of Product Characteristics hosted on the EMA website (available at: https://www.ema.europa.eu, accessed May 2025).

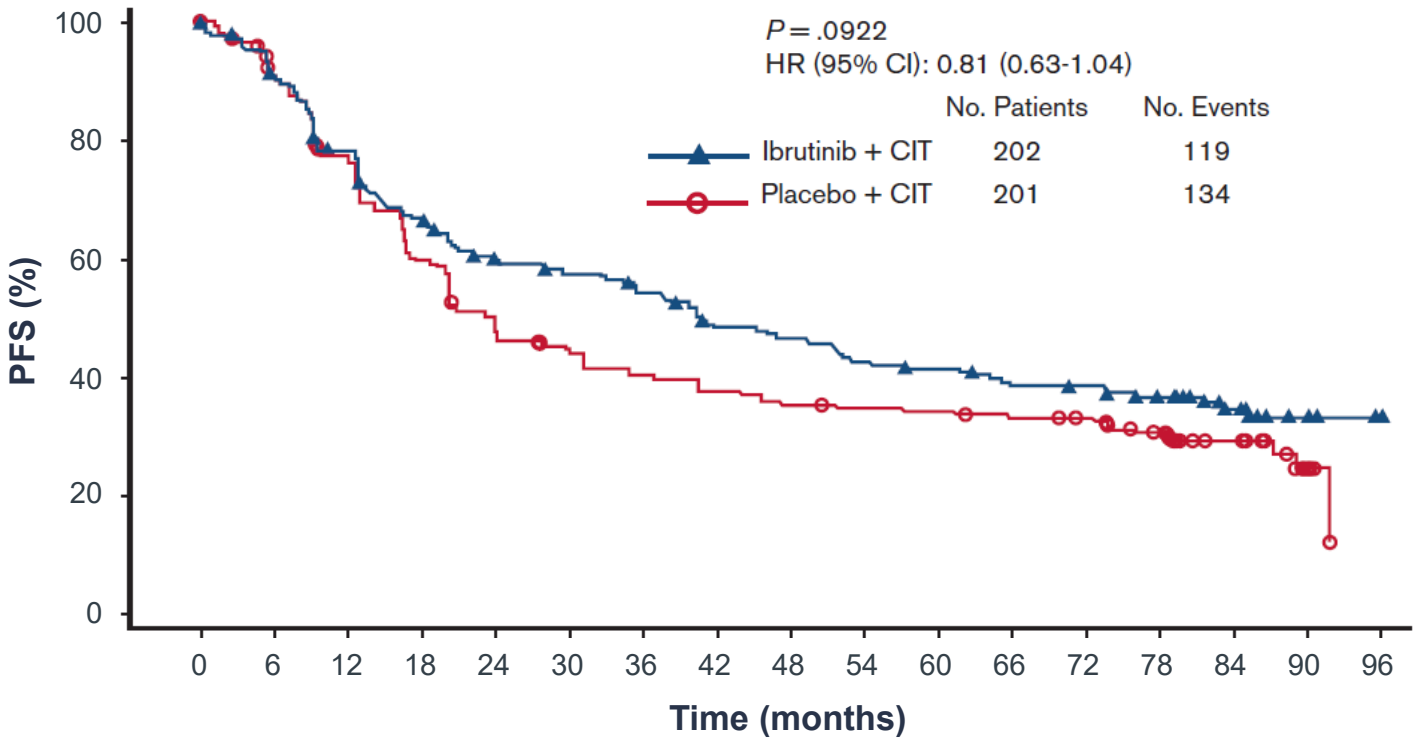
Ab, antibody; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell; CD, cluster of differentiation; CIT, chemoimmunotherapy; FL, follicular lymphoma; FL3B, FL Grade 3B; G-/R-B, obinutuzumab/rituximab, bendamustine; G-/R-CHOP, obinutuzumab/rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; G-/R-CVP, obinutuzumab/rituximab, cyclophosphamide, vincristine, prednisone; liso-cel, lisocabtagene maraleucel; tisa-cel, tisagenlecleucel.

Slide courtesy of speaker.

SELENE: No improvement with ibrutinib + CIT in R/R FL or MZL

BTKi monotherapy
≥1 prior CIT

Investigator-assessed PFS[1]



Study summary

- Most patients (86.1%) had FL
- CIT was BR (90.3%) or R-CHOP
- **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; BTKi, BTK inhibitor; CI, confidence interval; 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.

Nastoupil LJ *et al*. *Blood Adv* 2023; 7 (22): 7141–7150.

ROSEWOOD: Randomized, Phase 2 study of zanubrutinib + obinutuzumab vs. obinutuzumab in R/R FL[1]

BTKi + anti-CD20
≥2 prior Tx

Response by ICR	Zanubrutinib + obinutuzumab (n=145)	Obinutuzumab (n=72)
ORR, % (95% CI)	**68.3 (60.0–75.7)**	**45.8 (34.0–58.0)**
Risk difference, % (95% CI)	**22.0 (8.3–35.8)**	
2-sided *P*-value	**0.0017**	
BOR, n (%)		
CR	54 (37.2)	14 (19.4)
PR	45 (31.0)	19 (26.4)
SD	25 (17.2)	14 (19.4)
Non-progressive disease	3 (2.1)	4 (5.6)
PD	13 (9.0)	15 (20.8)
Discontinued prior to first tumor assessment	4 (2.8)	6 (8.3)
NE	1 (0.7)	0

Median follow-up: 12.5 months

Primary endpoint
ORR per ICR was significantly higher with zanubrutinib + obinutuzumab, with a risk difference of 22%

PFS[2]
- Zanubrutinib + obinutuzumab: 28 months
- Obinutuzumab: 10.4 months

HR (95% CI): 0.50 (0.33 to 0.75); *P*<0.001

The **safety profile of zanubrutinib + obinutuzumab was consistent with the safety profile of each drug**[2]

Incidences of atrial fibrillation and hypertension were low and similar between both treatment arms

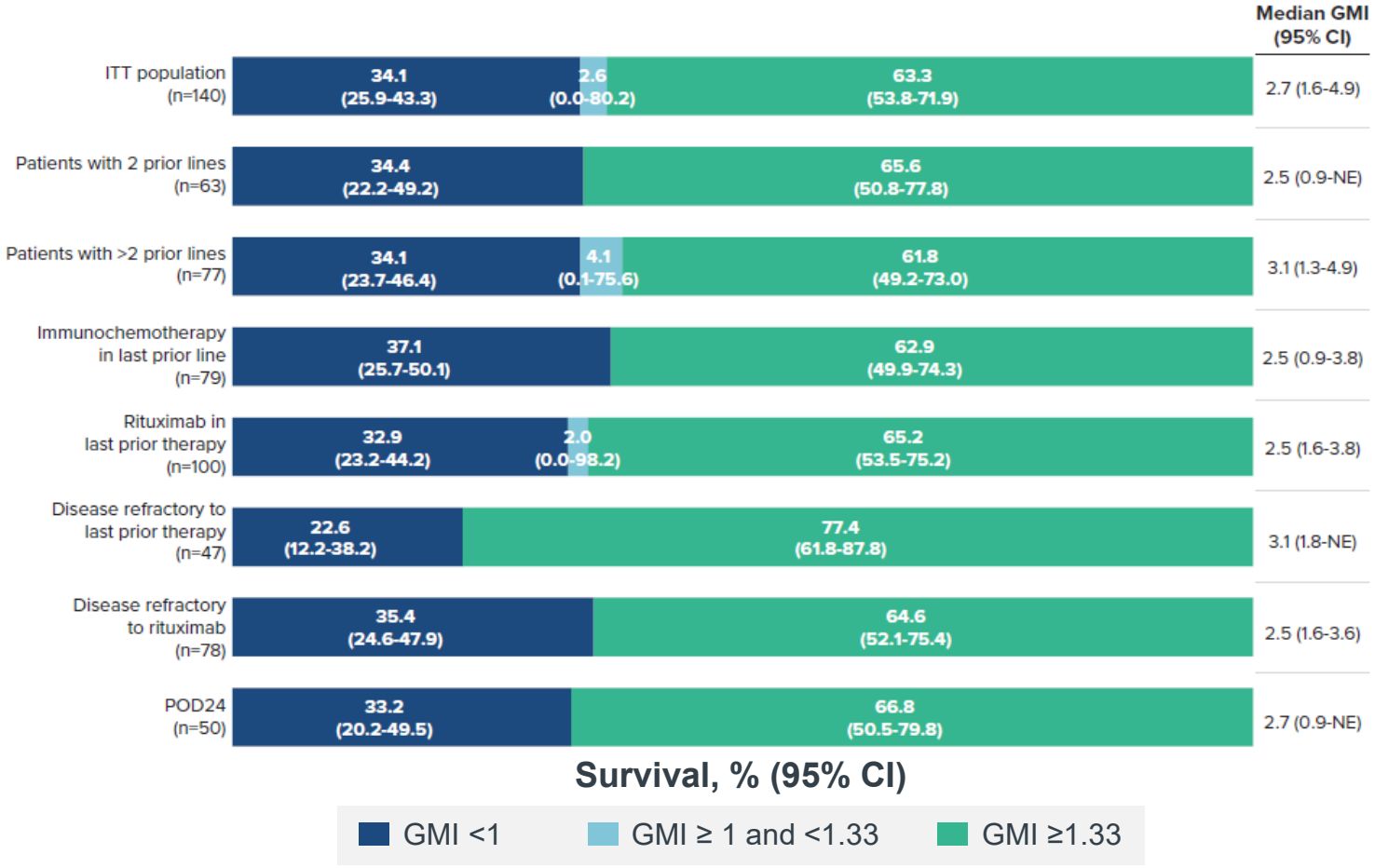
BOR, best overall response; BTKi, BTK inhibitor; CD, cluster of differentiation; CI, confidence interval; CR, complete response; FL, follicular lymphoma; HR, hazard ratio; ICR, independent central review; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; SD, stable disease; Tx, treatment.

1. Zinzani PL *et al.* Oral presentation at ASCO 2022; Chicago, IL, USA, June 3–7, 2022. 2. Zinzani PL *et al*. *J Clin Oncol* 2023; 41 (33): 5107–5117.

Growth modulation index analysis of ROSEWOOD

BTKi
+ anti-CD20
≥2 prior Tx

Median GMI and distribution of GMI in subgroups of interest with zanubrutinib-obinutuzumab[1]



$$\text{GMI} = \frac{\text{PFS with current treatment}}{\text{PFS with previous treatment}}$$

>60% of patients receiving Zanu-Obi had a significant **(GMI ≥1.33) improvement in PFS vs. their last prior treatment**, irrespective of the number of prior treatments[1]

In the overall population, **the median GMI was 2.7, more than double the 1.33 threshold** for meaningful clinical activity vs. the last prior treatment[1,2]

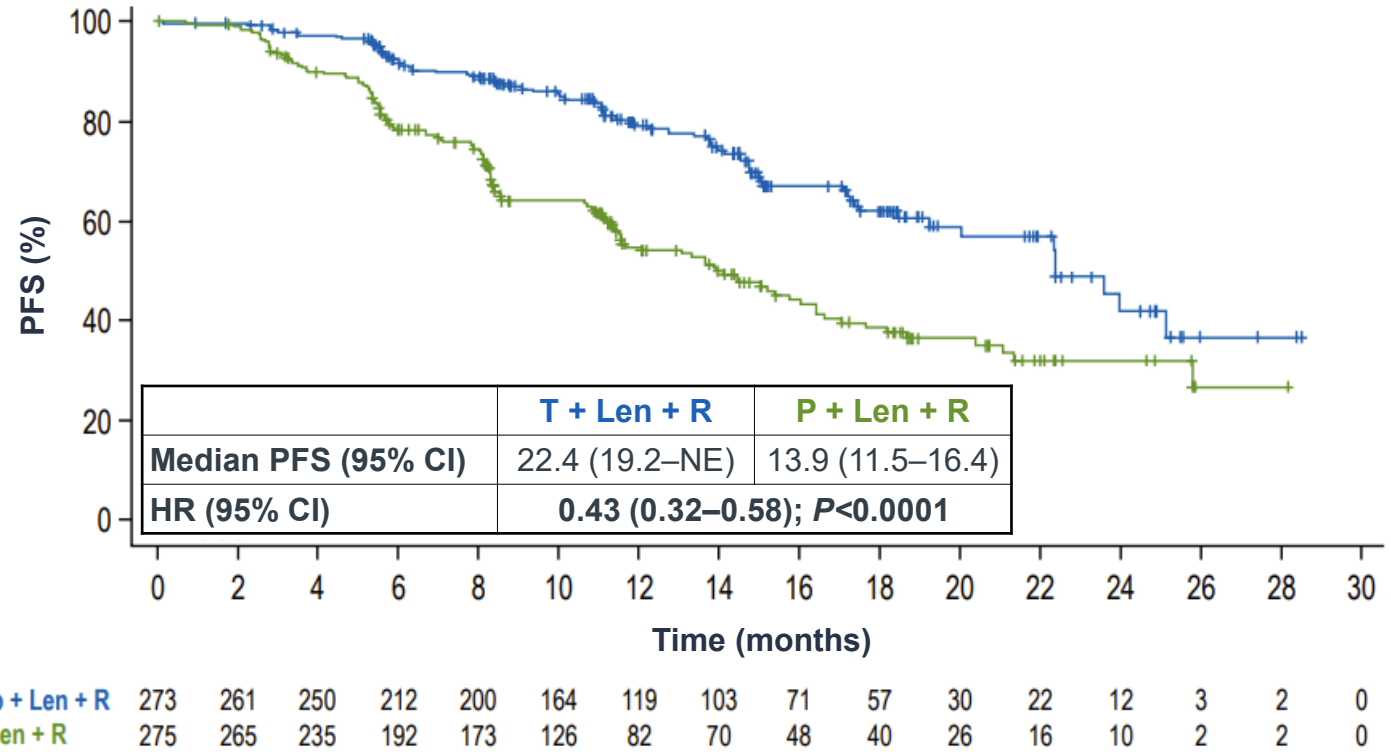
BTKi, BTK inhibitor; CD, cluster of differentiation; CI, confidence interval; GMI, growth modulation index; ITT, intention-to-treat; NE, not evaluable; Obi, obinutuzumab; POD24, progression of disease within 24 months; Tx, treatment; Zanu, zanubrutinib.

1. Trotman J *et al*. Poster presentation at ASH 2024; San Diego, CA, USA, December 7–10, 2024. 2. Penel N *et al*. *Ann Oncol* 2013; 24 (2): 537–542.

inMIND: Tafasitamab + lenalidomide + rituximab in R/R FL

Anti-CD19 + anti-CD20
≥1 prior Tx

Primary endpoint: PFS by investigator assessment
Median follow-up: 14.1 months



	T + Len + R	P + Len + R
Median PFS (95% CI)	22.4 (19.2–NE)	13.9 (11.5–16.4)
HR (95% CI)	**0.43 (0.32–0.58); *P*<0.0001**	

PFS was superior with tafasitamab + Len + R vs. placebo + Len + R in the overall population and in clinically relevant subgroups

- POD24
- Anti-CD20 refractory
- 1 prior line of therapy
- ≥2 prior lines of therapy

Key secondary endpoint, PET-CR rate

T + Len + R = 49.4% (95% CI: 43.1–55.8)
P + Len + R = 39.8% (95% CI: 33.7–46.1)

OR (95% CI): 1.5 (1.04–2.13)

Nominal *P*=0.03

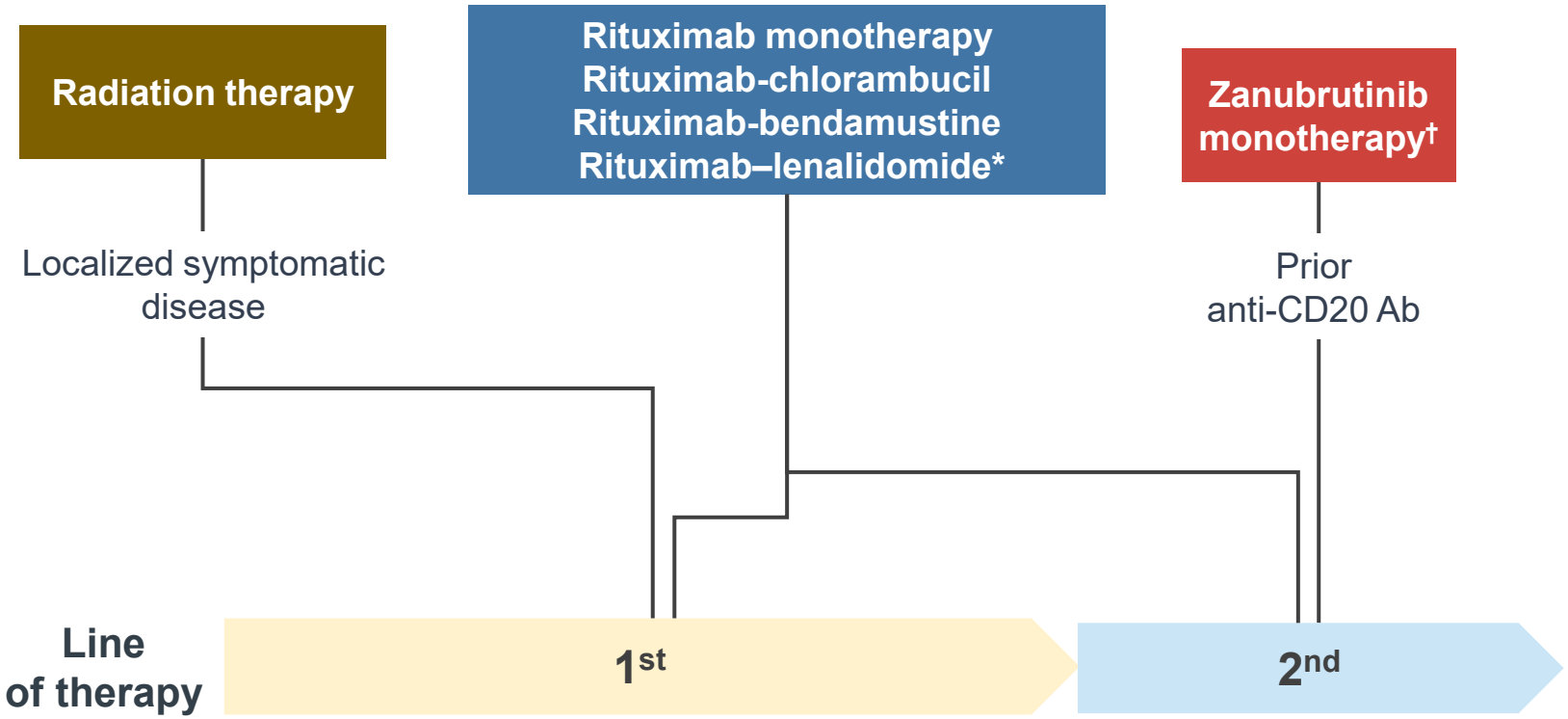
The **safety profile was manageable and consistent with the safety profile of each drug**

CD, cluster of differentiation; CI, confidence interval; CR, complete response; FL, follicular lymphoma; HR, hazard ratio; Len, lenalidomide; NE, not evaluable; OR, odds ratio; P, placebo; PET, positron emission tomography; PFS, progression-free survival; POD24, progression of disease within 24 months; R, rituximab; R/R, relapsed/refractory; T, tafasitamab; Tx, treatment.

Sehn LH *et al*. Abstract presented at ASH 2024; San Diego, CA, USA, December 7–10, 2024 (Abstract #LBA-1).

Marginal Zone Lymphoma

Overview of the R/R MZL treatment landscape



Compared with FL, **there are relatively few therapies specifically approved for MZL**

MZL is a heterogeneous disease, with different subtypes requiring different therapeutic approaches

Please consult local guidance for details on licensed indications and reimbursement criteria.

*Rituximab-based therapies are commonly used in clinical settings for MZL, but none have specific EMA-approved indications in MZL. †Zanubrutinib monotherapy is approved by the EMA for the treatment of adult patients with MZL who have received at least one prior anti-CD20–based therapy.

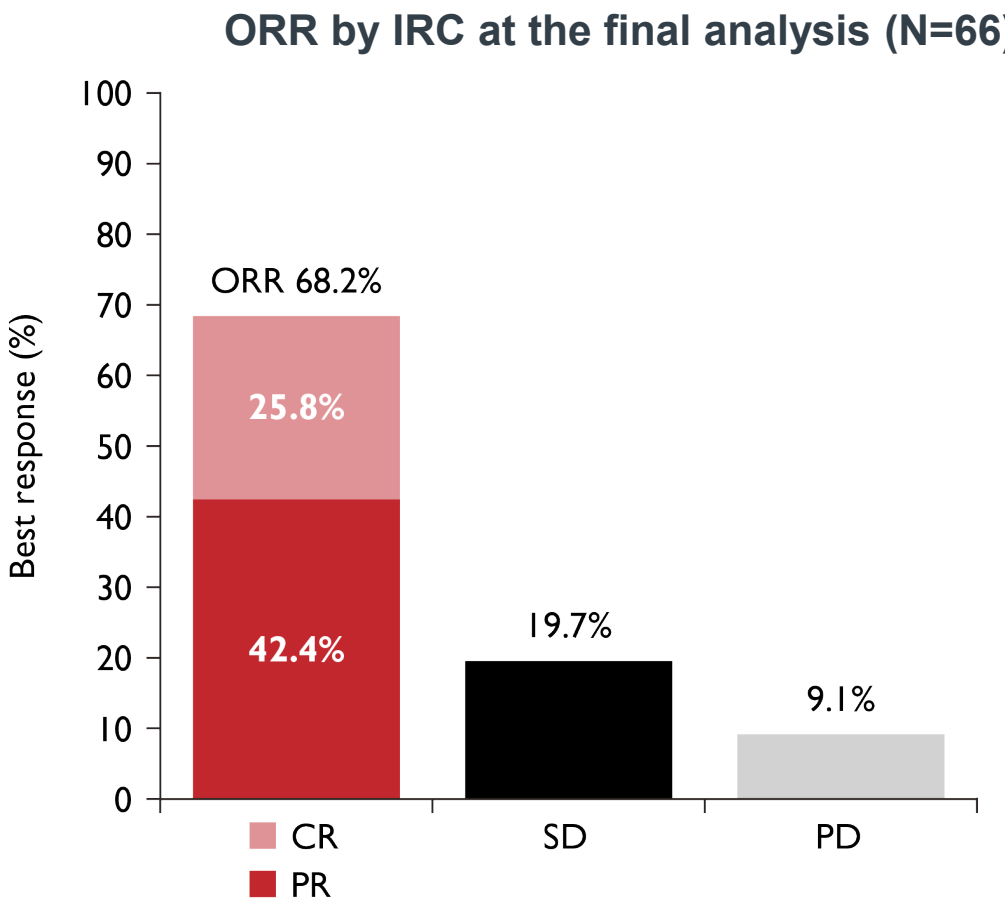
Ab, antibody; CD, cluster of differentiation; EMA, European Medicines Agency; FL, follicular lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory.

Walewska R *et al*. *Br J Haematol* 2024; 204 (1): 86–107.

Slide courtesy of speaker.

MAGNOLIA: A multicenter, open-label, Phase 2 study of zanubrutinib monotherapy in R/R MZL

BTKi monotherapy
≥1 prior Tx



Primary endpoint of ORR by IRC was met in the primary analysis

In the final analysis (median follow-up: 28 months), **ORR was 68% by PET and/or CT and 67% by CT only**

24-month PFS (95% CI): 70.9% (57.2–81.0)
24-month DoR (95% CI): 72.9% (54.4–84.9)

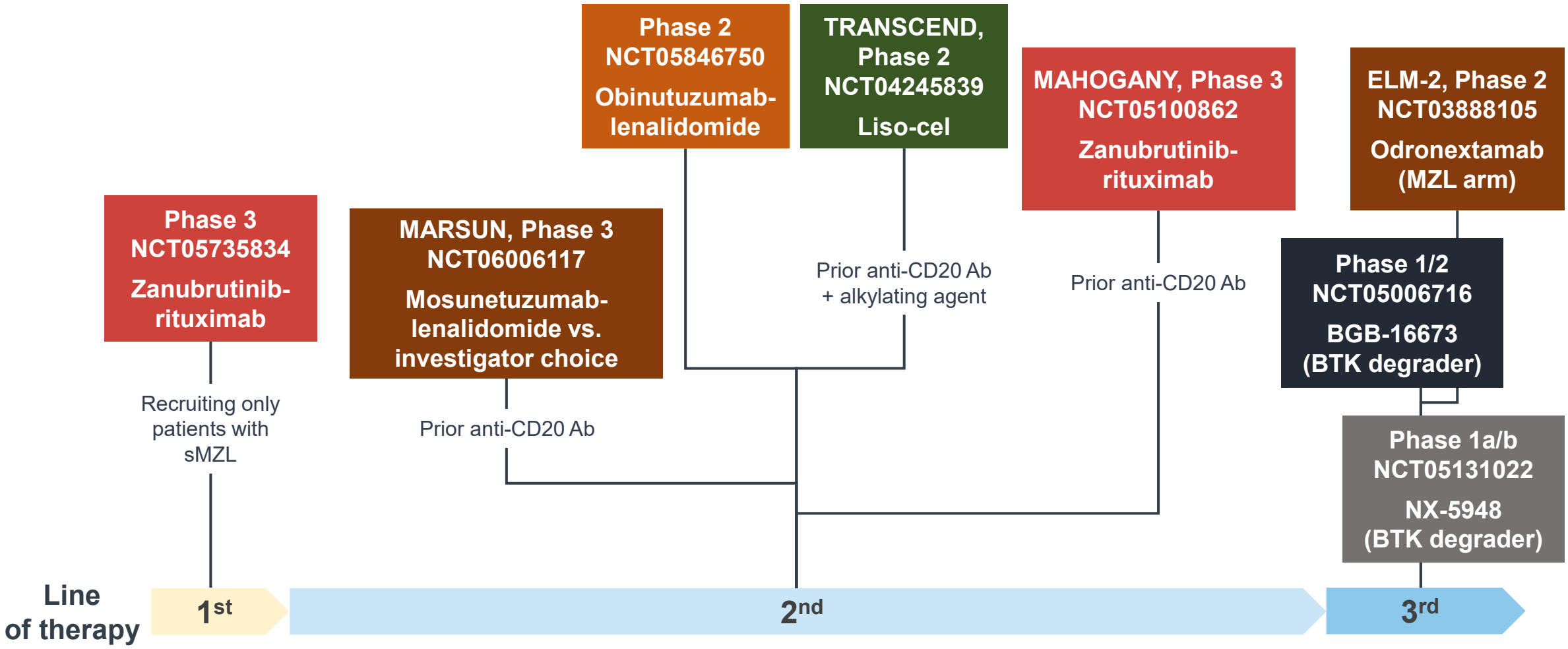
Efficacy was observed across all MZL subtypes, including nodal MZL, splenic MZL, and extranodal mucosa-associated lymphoid tissue

No unexpected safety signals were observed; atrial fibrillation/flutter and hypertension were uncommon

BTKi, BTK inhibitor; CI, confidence interval; CR, complete response; CT, computed tomography; DoR, duration of response; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; SD, stable disease; Tx, treatment.

Opat S *et al. Blood Adv* 2023; 7 (22): 6801–6811.

Investigational agents and regimens in MZL



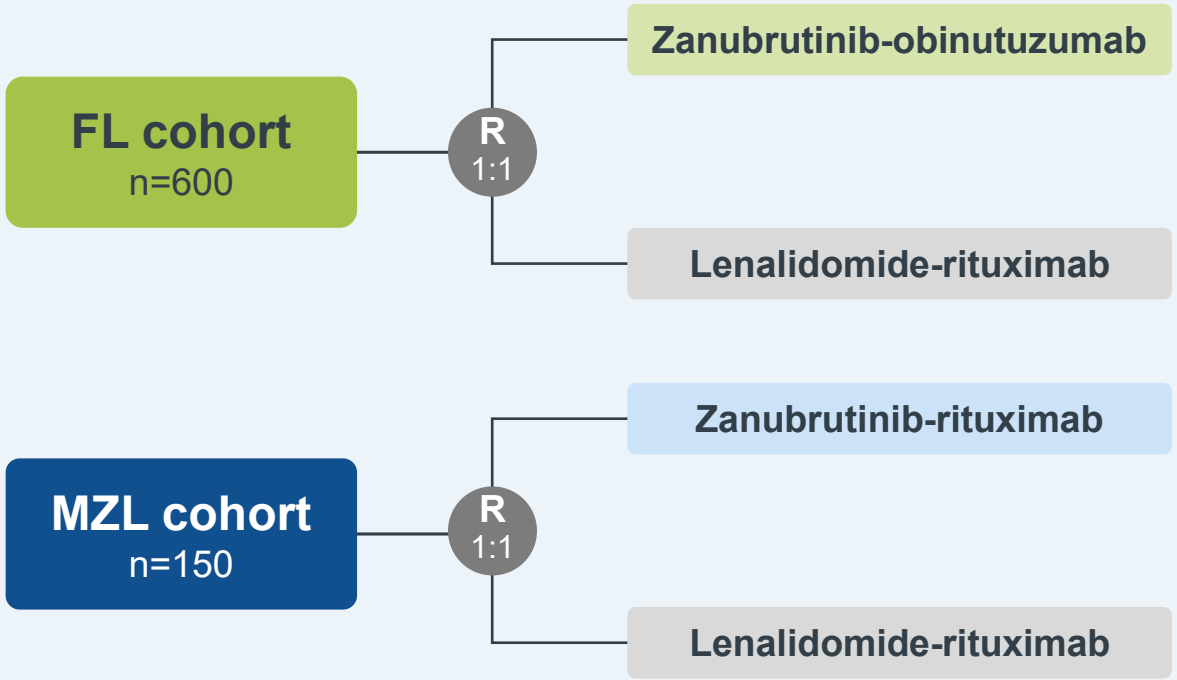
Ab, antibody; CD, cluster of differentiation; liso-cel, lisocabtagene maraleucel; MZL, marginal zone lymphoma; sMZL, splenic MZL.
Slide courtesy of speaker.

MAHOGANY: Randomized, open-label, Phase 3 trial of zanubrutinib + anti-CD20 in patients with FL or MZL with one prior systemic therapy

Key eligibility criteria

- Age ≥18 years
- Histologically confirmed R/R FL (Grade 1–3A) or MZL (eMZL, nMZL, or sMZL)
- Previous treatment with ≥1 prior line of systemic therapy, including an anti-CD20–based regimen
- In need of treatment according to modified GELF criteria[2]
- Adequate bone marrow and organ functions
- No prior treatment with BTKi
- 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

Two independent cohorts



BTKi, BTK inhibitor; CD, cluster of differentiation; DoR, duration of response; eMZL, extranodal MZL; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; MZL, marginal zone lymphoma; nMZL, nodal MZL; R, randomized; R/R, relapsed/refractory; sMZL, splenic MZL.

1. Sehn LH *et al.* Oral presentation at ICML 2023; Lugano, Switzerland, June 13–17, 2023 (Abstract 994). 2. Brice P *et al*. *J Clin Oncol* 1997; 15 (3): 1110–1117.

Thank you for your attention

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Click here to submit your questions to the faculty

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Audience Q&A

All faculty

Summary

Chair: Catherine Thieblemont

Take-home messages

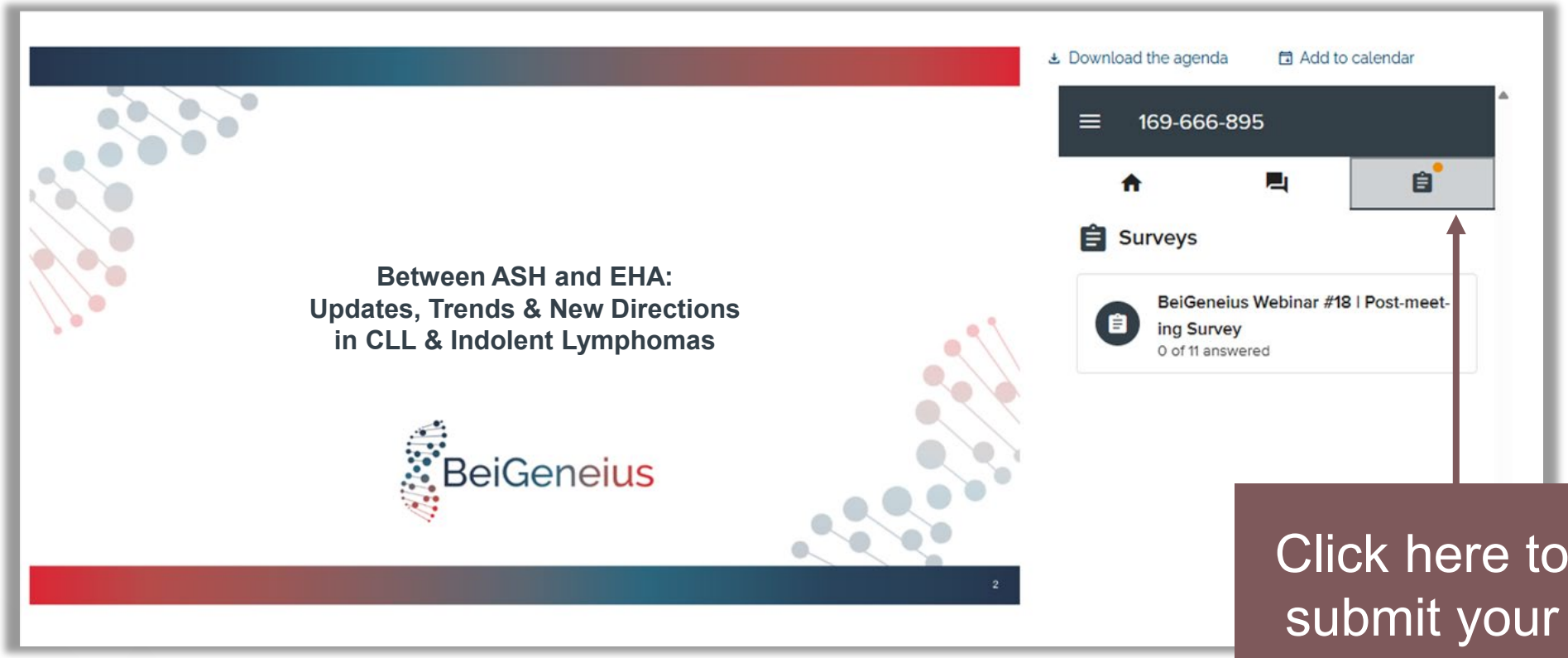
Current treatment options for CLL are divided between continuous and fixed-duration targeted therapies, with new agents and regimens being explored in both approaches – and fixed-duration combinations often incorporating MRD-guided strategies

The treatment landscape for follicular zone lymphoma is rapidly evolving in the relapsed setting, with BTK inhibitors, CAR-T therapy, and bispecific antibodies expanding patient options – and raising important questions about optimal sequencing

Specific approvals in marginal zone lymphoma are currently limited, but several ongoing trials are investigating regimens that include BTK inhibitors, CAR-T therapy, bispecific antibodies, and BTK degraders

BTK, Bruton's tyrosine kinase; CAR-T, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukemia; MRD, minimal residual disease.
Speaker's own slide.

Exit full-screen view to have your say



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