BEONE-SPONSORED SATELLITE SYMPOSIUM AT THE
18TH INTERNATIONAL CONFERENCE ON MALIGNANT LYMPHOMA

BTK targeting across lymphomas: The key to effective treatment today and tomorrow

17th June 2025, 14.00 – 15.30 CEST
Lugano, Switzerland

✦ ✦ ✦

Introduction

Professor Catherine Thieblemont
Hôpital Saint-Louis
(Hôpitaux Universitaires Saint-Louis, Laboisière, Fernand-Widal)
Paris, France

BeOne

Disclosures

Honoraria for advisory boards	BeOne, Abbvie, BMS, Novartis, Kite-Gylead, Incyte, Amgen

BeiGene

is now

BeOne

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

Learning objectives

After this session, participants should have an increased understanding of:

- The role of BTKis in improving treatment outcomes for patients with B-cell lymphomas, including CLL, WM, MCL, and MZL
- The differences in safety and efficacy among available BTKis
- Emerging and future therapeutic strategies targeting BTK, including novel BTKi-based combinations and BTK protein degraders as a promising new approach to the treatment of lymphomas

Today’s speakers

Prof. John Gribben

Hamilton Fairley Chair of Medical Oncology, Barts Cancer Institute, Queen Mary, University of London (QMUL), London, UK

Prof. Shirley D’Sa

University College London Hospitals NHS Foundation Trust, London, UK

Prof. Markus Raderer

Medical University Vienna, Vienna, Austria

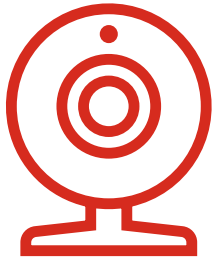
Prof. Carlo Visco

University of Verona, Verona, Italy

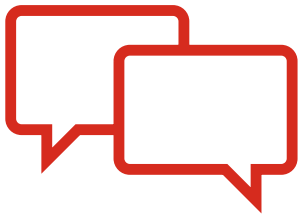
Agenda

Time	Presentation	Speaker
14.00 h	Welcome and introduction	Catherine Thieblemont Paris, France
14.05 h	CLL therapy - Navigating the continuous BTKi landscape	John Gribben London, UK
14.25 h	BTKis in WM - Where are we now and where are we going?	Shirley D'Sa London, UK
14.40 h	BTKis in MCL and MZL - Current insights and future directions	Markus Raderer Vienna, Austria
15.00 h	BTK protein degraders - Experiences with a novel approach to treating lymphomas	Carlo Visco Verona, Italy
15.15 h	Audience Q&A	Catherine Thieblemont Paris, France

Some notes



This session is being recorded for on-demand viewing on beonemedaffairs.com



We value your active participation. Please use the microphones in the hall to ask questions or scan the QR code.

Please also use the QR code to leave your feedback after the session so BeOne can even better meet your educational needs.

Disclaimers

- This presentation is intended for Healthcare Professionals for scientific information exchange purposes only, not for advertising purposes, and does not constitute commercial promotion of any product or recommendation on diagnosis and treatments.
- The speakers' opinions are those of experts and do not necessarily reflect those of BeOne.
- As part of scientific exchange, patient cases prepared by healthcare professionals will be presented. Generalized conclusions should never be drawn from individual patient cases.
- The presentations may contain information about products or indications not yet approved in your country.
- Indications of approved products may differ outside of the European Union. Zanubrutinib is authorized under different conditions (e.g., different government-approved professional information: indications, warnings, etc.) in Switzerland. For country-specific information, refer to the prescribing information for the country in which you practice medicine.

BTKi regulatory approvals

	CLL		WM		MZL		MCL		FL	
	EU	US	EU	US	EU	US	EU	US	EU	US
Zanubrutinib[1]	✓	✓	✓	✓	✓	✓	planned	✓	✓	✓
Ibrutinib[2]	✓	✓	✓	✓		withdrawn[5]	✓	withdrawn[5]		
Acalabrutinib[3]	✓	✓					✓	✓		
Pirtobrutinib[4]	✓	✓					✓	✓		

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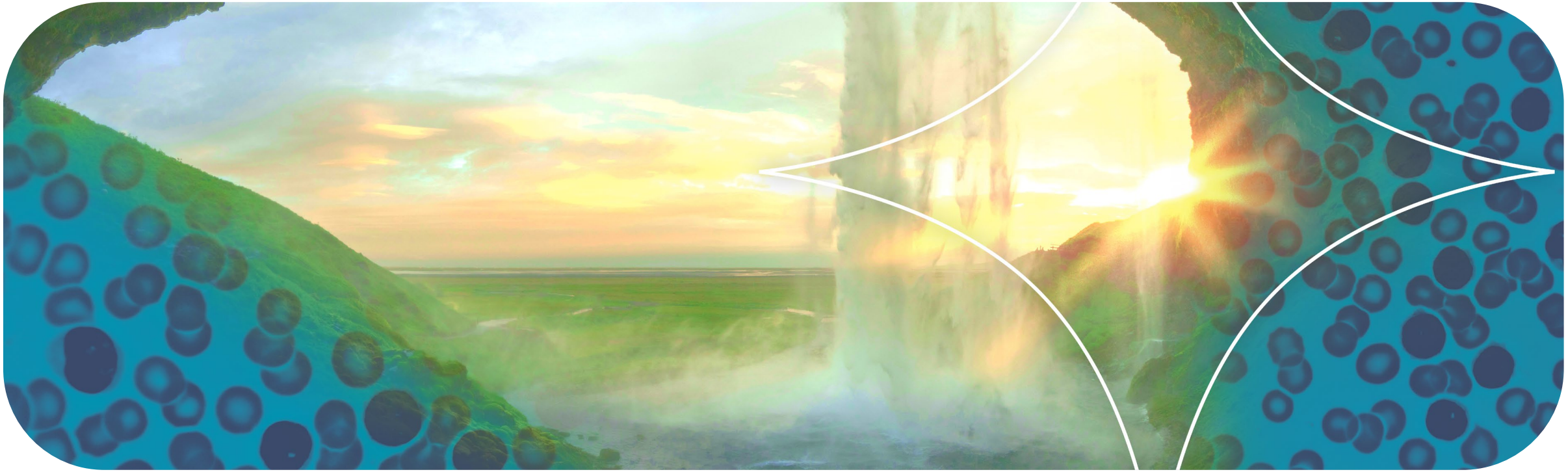
BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; EU, European Union; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; US, United States (of America); WM, Waldenström's macroglobulinemia.
1. Brukinsa SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/brukinsa. 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. 4. Jaypirca SmPC. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/jaypirca. 5. J&J Press release, 06 April 2023. Available at: https://www.jnj.com/media-center/press-releases/update-on-imbruvica-ibrutinib-u-s-accelerated-approvals-for-mantle-cell-lymphoma-and-marginal-zone-lymphoma-indications.



Continuous BTKi therapy for treatment of CLL

Professor John Gribben
Barts Cancer Institute
Queen Mary University of London, UK

BeOne

Disclosures

I have the following disclosures to declare	
AstraZeneca	research funding and honoraria for advisory boards
Amgen	honoraria for advisory boards
BeOne	honoraria for speaking
Kite-Gilead	honoraria for advisory boards and speaking

Learning objectives

Understand how

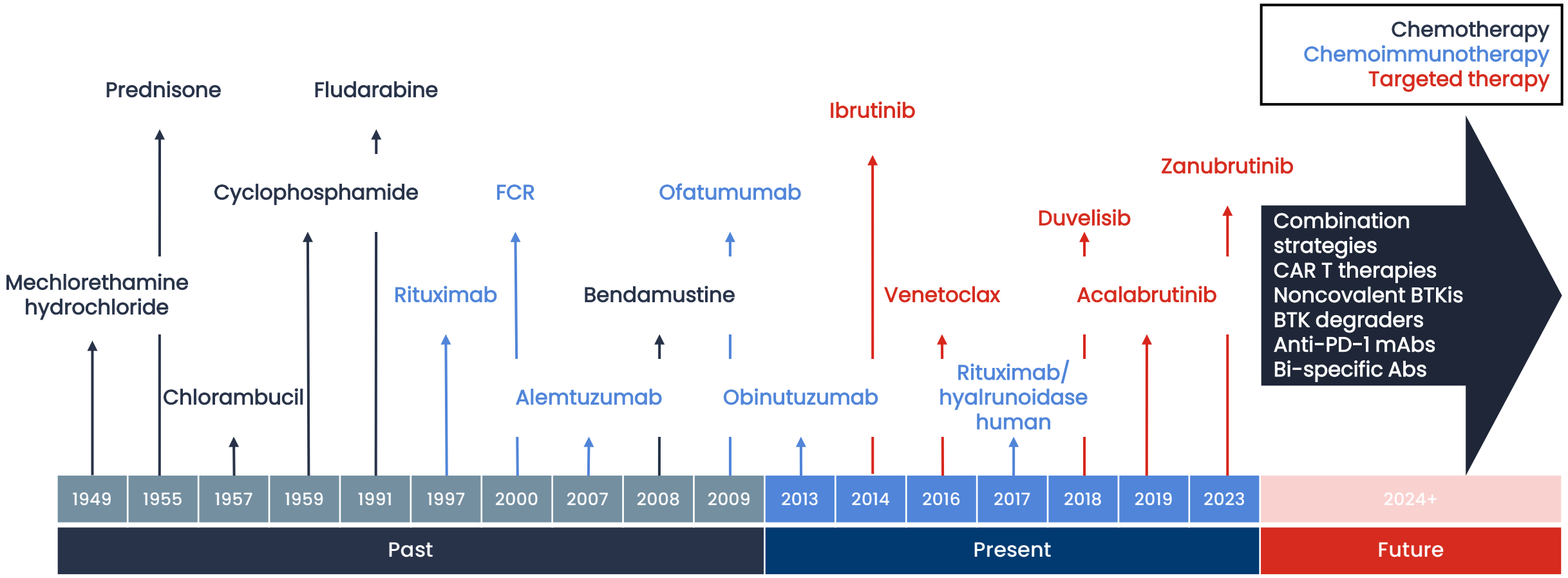
the importance of B-cell receptor signaling in CLL is demonstrated by the efficacy of BTKis

BTKis have impacted treatment in CLL

the efficacy and safety profile of the available BTKis suggest that zanubrutinib is a treatment of choice in TN and relapsed CLL patients

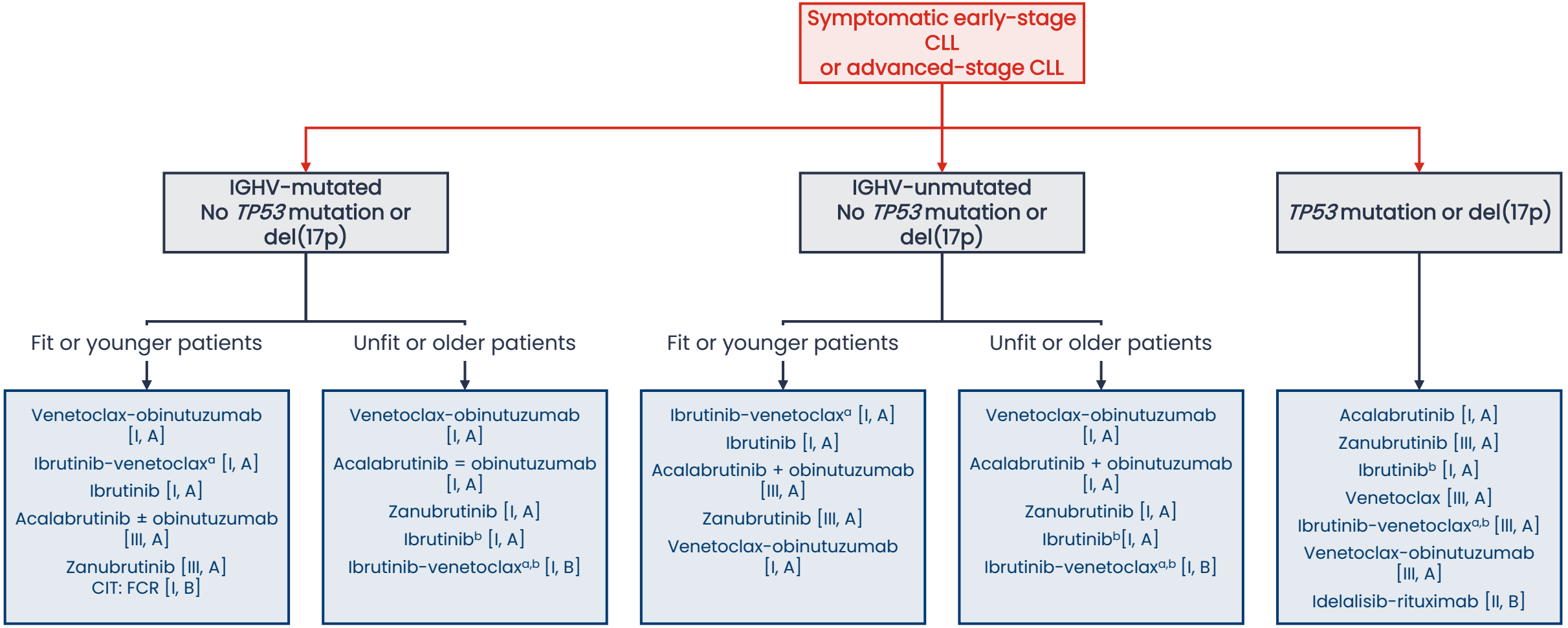
BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; TN, treatment-naïve.

Treatment evolution in CLL – targeted therapies are now the treatment of choice



Abs, antibodies; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; mAbs, monoclonal Abs; PD-1, programmed cell death protein 1.
Adapted from Tam CS, et al. *Blood Cancer J.* 2023;13:141.

2024 ESMO guidelines for first-line CLL treatment



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[a]Ibrutinib-venetoclax with a 15-month fixed duration or with an MRD-guided duration. [b]Ibrutinib or ibrutinib-venetoclax should be considered carefully in older patients with cardiac comorbidities.
CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del, deletion; ESMO, European Society for Medical Oncology; FCR, fludarabine, cyclophosphamide, rituximab; IGHV, immunoglobulin heavy chain variable region; MRD, minimal residual disease; TN, treatment naïve.
Adapted from Eichhorst B, et al. *Ann Oncol.* 2024;35(9):762-768.

Targeted therapies are now treatment of choice for CLL

Chemotherapy and chemoimmunotherapy approaches are no longer recommended in the latest guidelines

Treatment approaches

- Venetoclax-based therapy given as fixed-duration therapy in combination with either obinutuzumab or ibrutinib
- BTK inhibitor therapy as continuous treatment

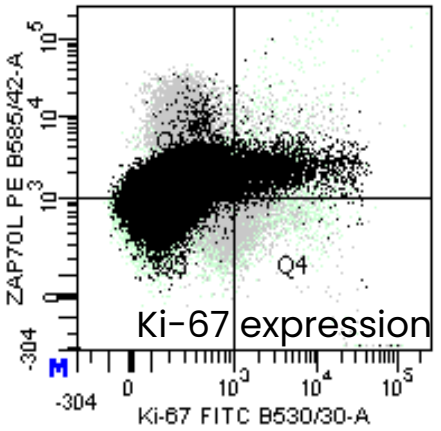
Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia.

CLL results from an imbalance of life and death signals

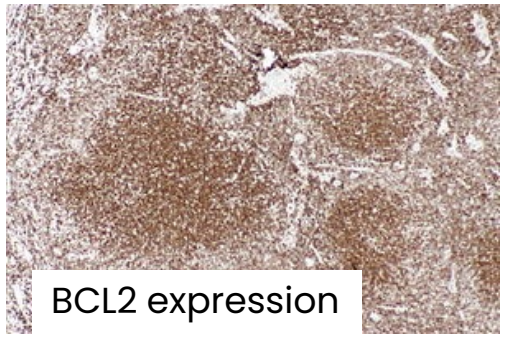
Inhibitors

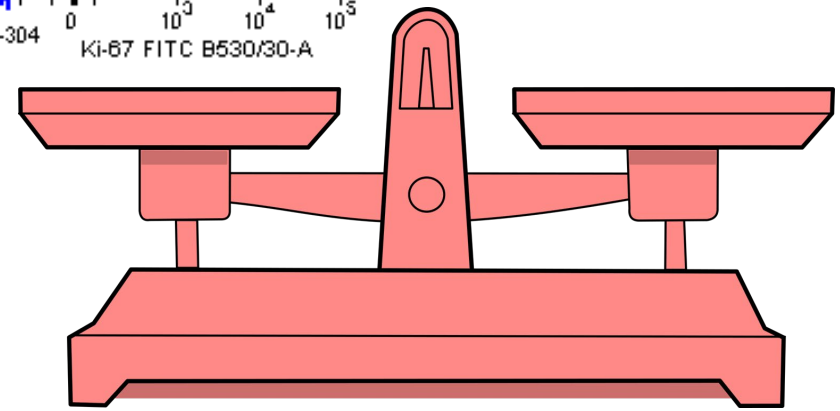
- **BTKi**
  - Ibrutinib
  - Acalabrutinib
  - Zanubrutinib
  - Pirtobrutinib
  - Other BTKi in development
- PI3Ki
  Effective but limited use because of toxicity

Proliferation
driven by BCR signaling and NFKb activation



Apoptosis
driven by balance of pro- and anti-apoptotic members of the BCL2 family





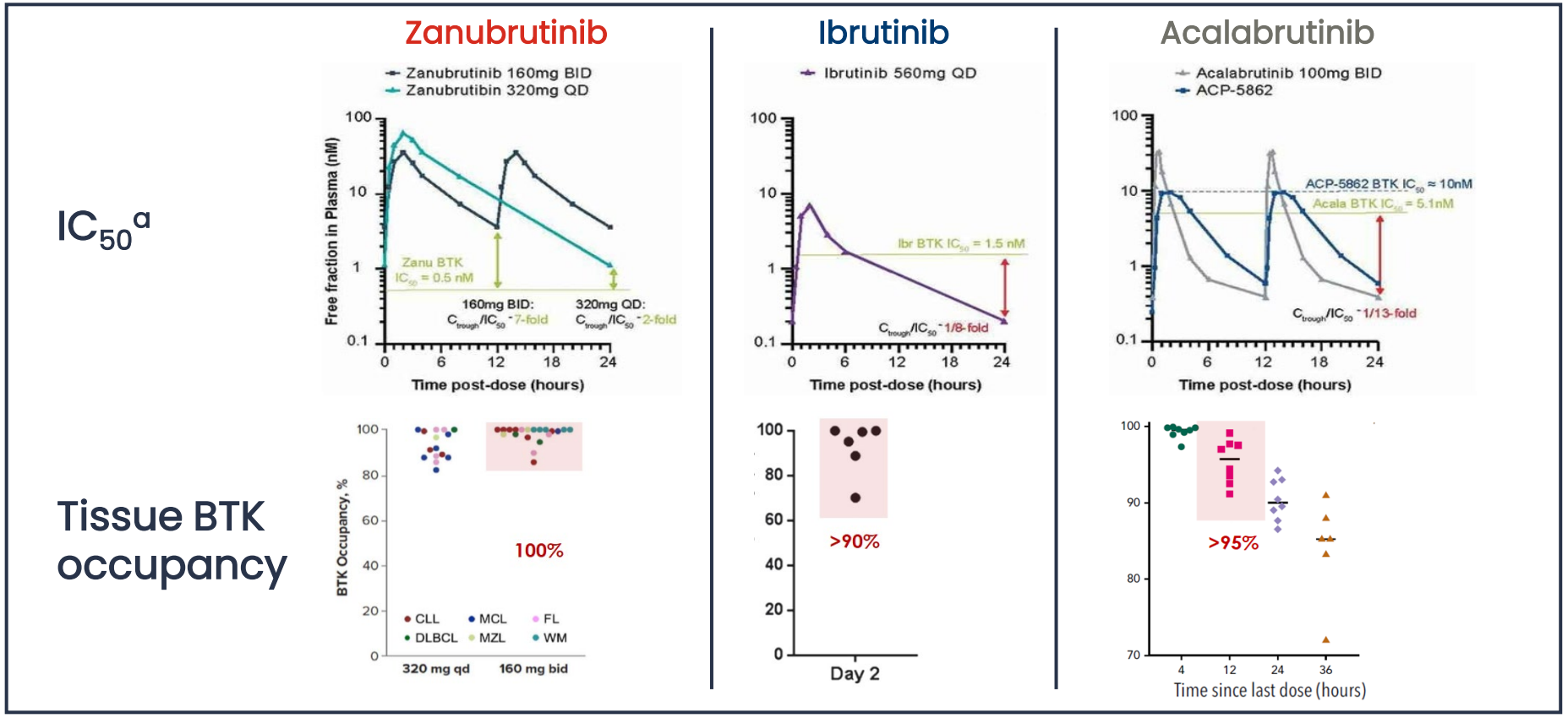
Inhibitors

- **Venetoclax**
- Other BCL2 inhibitors in development

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BCR, B-cell receptor; BCL2, B-cell lymphoma 2; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; PI3Ki, phosphoinositide 3-kinase inhibitor; TN, treatment-naïve.

Targeting BTK – How do we select the best agent?

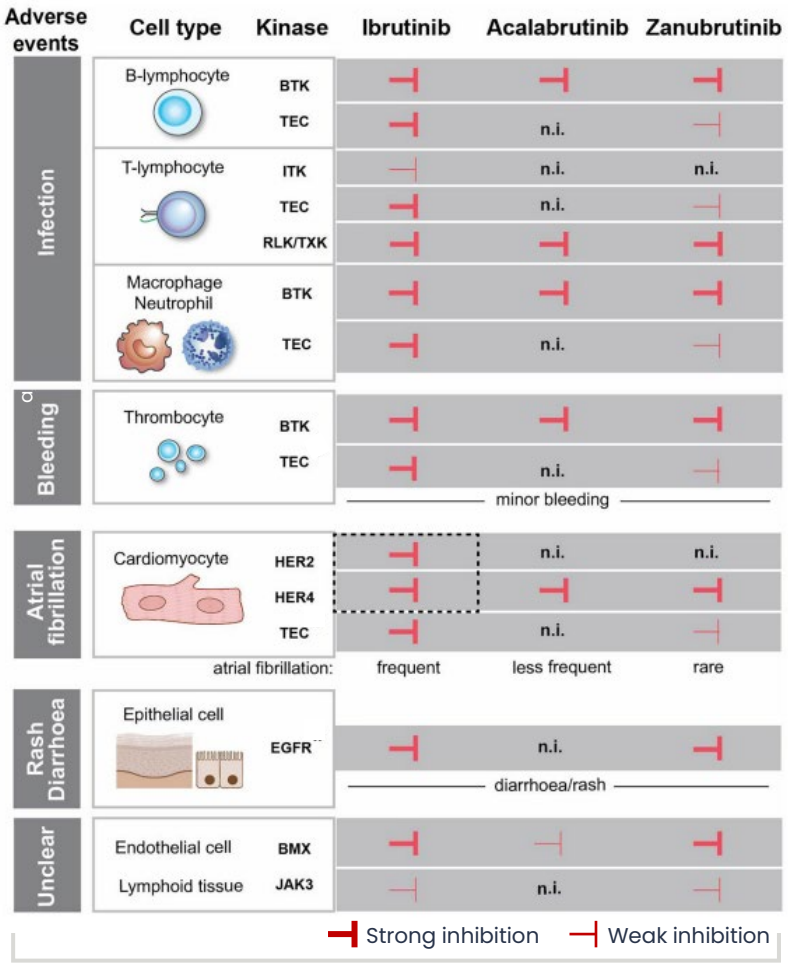
Three important factors: oral bioavailability, plasma levels and BTK occupancy



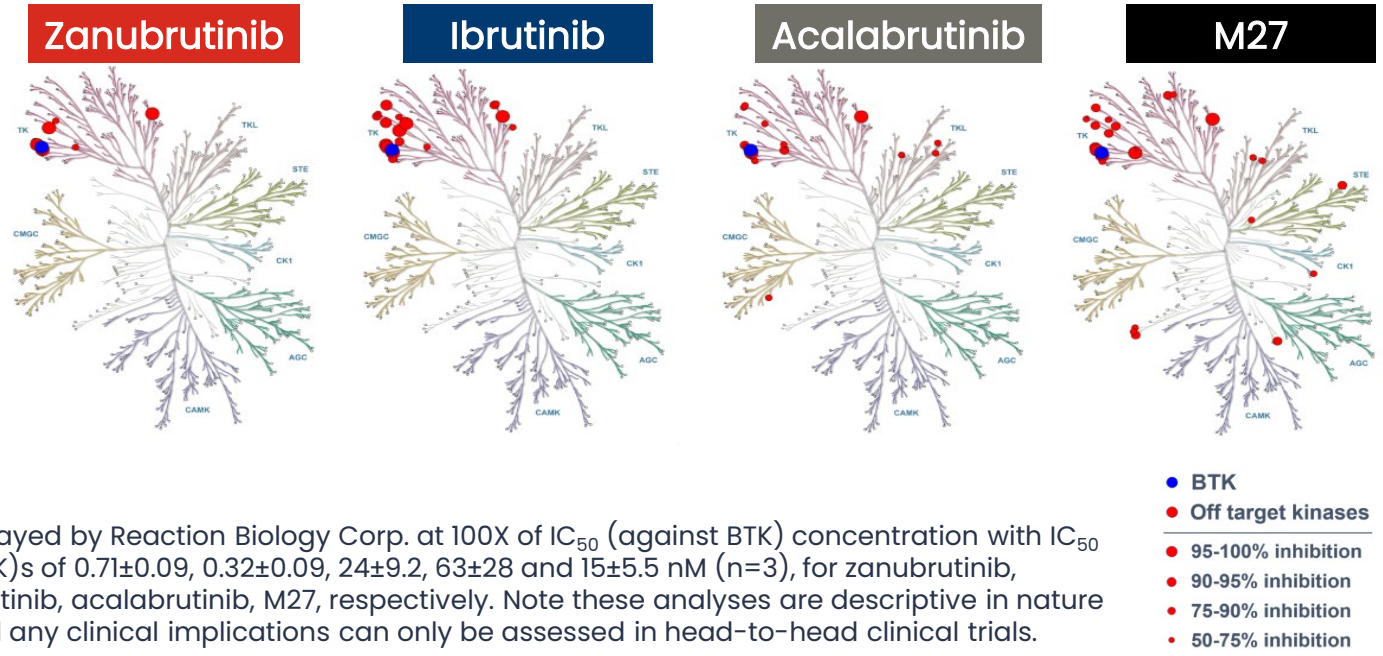
- With BTKi, need to weigh impact of dose reduction on CV ADRs with risk of reduced BTK occupancy in LN
- LN biopsy studies suggest **BTK occupancy:** Zanubrutinib > Acalabrutinib > Ibrutinib

[a]IC_{50} was measured using the LanthaScreen™ TR-FRET binding assay (Thermo Fisher Scientific) as reported by Kaptein et al. (2018)[1]
ADR, adverse drug reaction; BID, twice daily; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; CLL, chronic lymphocytic leukemia; C_{trough}, trough concentration; CV, cardiovascular; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; IC_{50}, half maximal inhibitory concentration; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; LN, lymph node; QD, once daily; TR-FRET, time-resolved fluorescence energy transfer; WM, Waldenström's macroglobulinemia.
Figures adapted from Tam CS, et al. *Expert Review of Clinical Pharmacology.* 2021;14(11):1329-1344. 1. Kaptein A, et al. *Blood.* 2018;132(suppl 1):1871.

Kinase selectivity
Impact of off-target inhibition and potential AEs



Kinase selectivity of zanubrutinib, ibrutinib, acalabrutinib, and acalabrutinib metabolite M27



Assayed by Reaction Biology Corp. at 100X of IC_{50} (against BTK) concentration with IC_{50} (BTK)s of 0.71±0.09, 0.32±0.09, 24±9.2, 63±28 and 15±5.5 nM (n=3), for zanubrutinib, ibrutinib, acalabrutinib, M27, respectively. Note these analyses are descriptive in nature and any clinical implications can only be assessed in head-to-head clinical trials.

Less selective BTK inhibitors have more off-target effects, which contribute to more toxicity compared with more selective agents[2]

[a]Major bleedings are more frequent upon ibrutinib treatment versus more selective BTKi.
AE, adverse event; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; EGFR, epidermal growth factor receptor; IC_{50}, half maximal inhibitory concentration; HER2, human epidermal growth factor receptor 2; ITK, interleukin-2-inducible T-cell kinase; JAK3, Janus kinase 3; n.i.; no inhibition; TEC, non-receptor protein-tyrosine kinase.
Figures adapted from: 1. Estupinan HY, et al. *Front Cell Dev Biol.* 2021;9:630942. 2. Shadman M, et al. *Blood.* 2021;138(1):1410.

Zanubrutinib is highly selective for BTK

Equipotent against BTK compared with ibrutinib; higher selectivity for BTK vs. EGFR, ITK, JAK3, HER2, and TEC[1]

Targets	Ibrutinib, IC_{50} (nM)	Zanubrutinib, IC_{50} (nM)	Ratio (zanubrutinib:ibrutinib)
BTK	3.5	1.8	0.5
	0.34	0.36	1.1
	2.3	2.2	1.0
	0.20	0.22	1.1
EGFR	101	606	**6.0**
	323	3210	**9.9**
ITK	189	3265	**17**
	77	3433	**45**
	260	2536	**9.8**
	0.9	30	**33**
JAK3	3.9	200	51
HER2	9.4	661	**70**
TEC	0.8	1.9	**2.4**

Off-target inhibition has been associated with:

- **6.0** and **9.9** → Diarrhea[2]
- **17**, **45**, **9.8**, and **33** → Infection[2]
- **70** and **2.4** → Cardiotoxicities (both) and bleeding (TEC only)[2]

BTK, Bruton's tyrosine kinase; EGFR, epidermal growth factor receptor; IC_{50}, half maximal inhibitory concentration; ITK, interleukin-2-inducible T-cell kinase; JAK3, Janus kinase 3, HER2, human epidermal growth factor receptor 2; TEC, non-receptor protein-tyrosine kinase.
Adapted from: 1. Tam CS, et al. *Blood.* 2019;134:851–859. 2. Tam CS, et al. *Expert Review of Clinical Pharmacology.* 2021;14:1329-1344.

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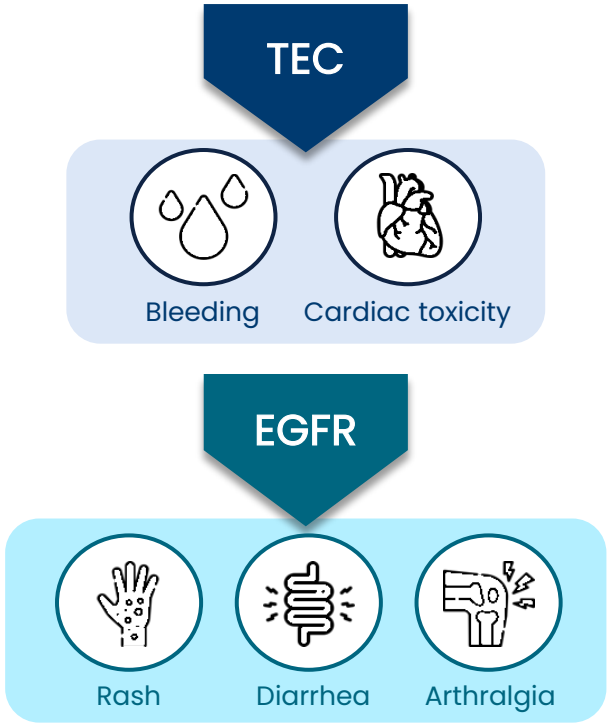
Potential off-target effects include[2]



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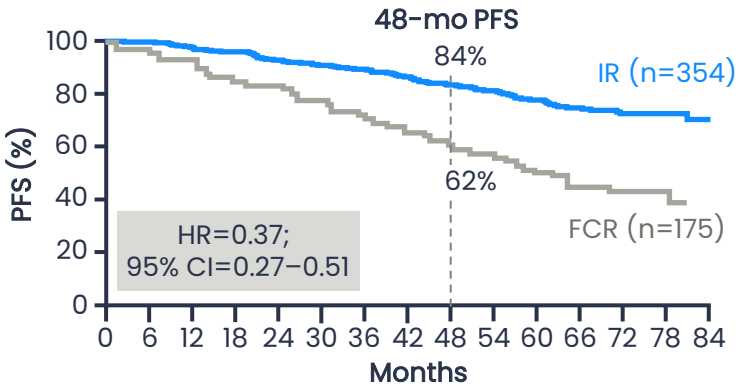
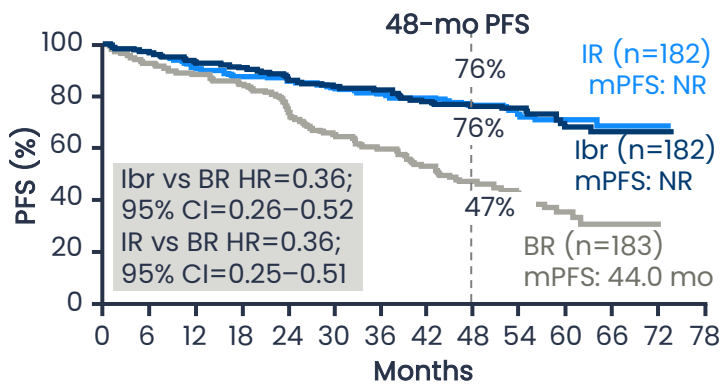
Adapted from: 1. Tam CS, et al. *Blood.* 2019;134:851–859. 2. Tam CS, et al. *Expert Review of Clinical Pharmacology.* 2021;14:1329-1344.

BTKi therapy has replaced chemotherapy based upon results of numerous clinical trials of BTKi vs CT/CIT

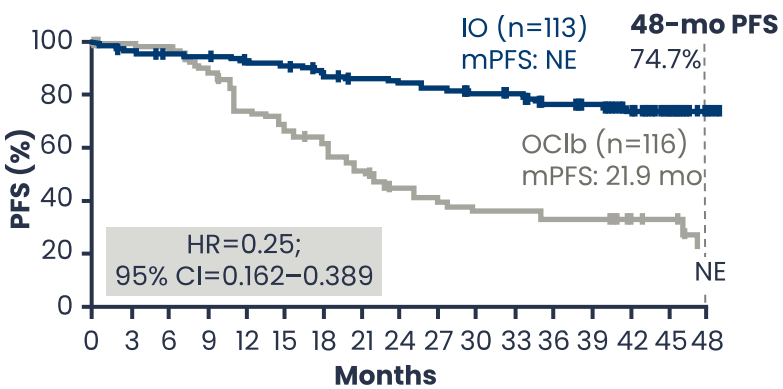
ECOG-1912: IR vs FCR
(median follow-up: 70 months)[1]



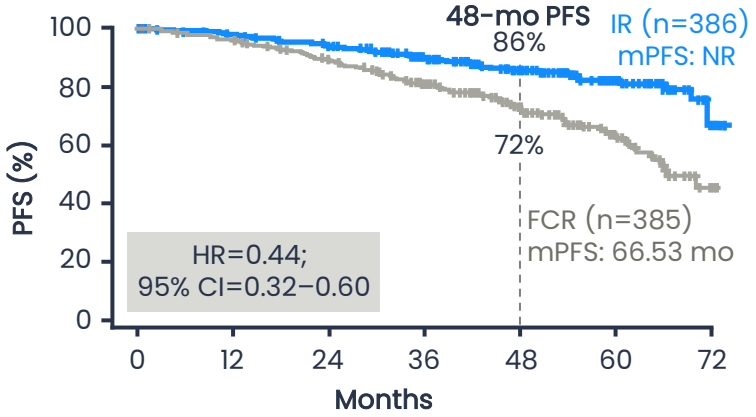
Alliance A041202: Ibr/IR vs BR
(median follow-up: 55 months)[2]



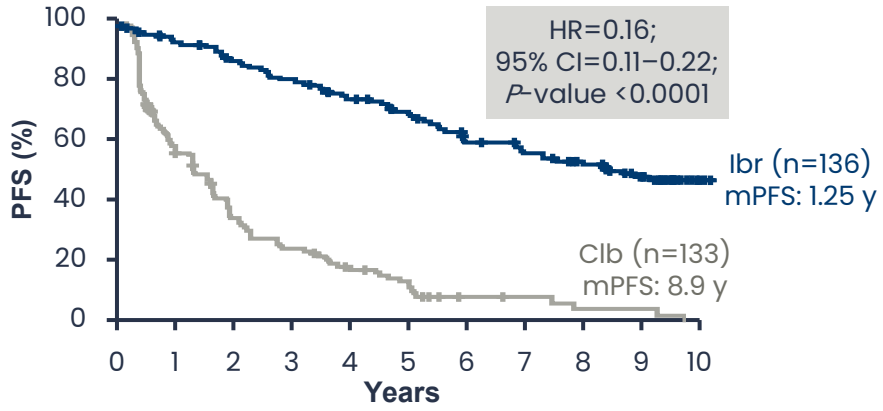
iLLUMINATE: IO vs OClb
(median follow-up: 45 months)[3]



FLAIR: IR vs FCR
(median follow-up: 52.7 months)[4]



RESONATE-2: Ibr vs Clb
(median follow-up: 10 years)[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.

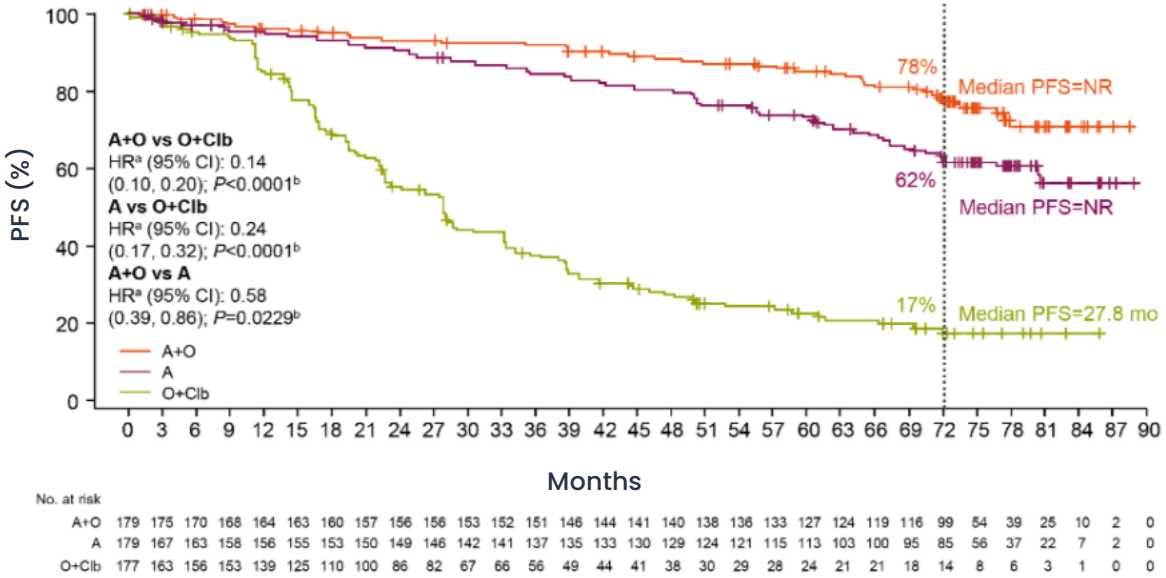
BR, bendamustine + rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; Clb, chlorambucil; CT/CIT, chemo(immuno)therapy; FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio, Ibr, Ibrutinib; IO, ibrutinib + obinutuzumab; IR, ibrutinib + rituximab; mo: month(s); mPFS, median progression-free survival; NE, not evaluable; NR, not reached; OClb: obinutuzumab + chlorambucil; PFS, progression-free survival; Y, years.

Figures adapted from: 1. Shanafelt TD, et al. *Blood.* 2022;140(2):112-120. 2. Woyach J, et al. *Blood.* 2021;138(suppl 1):639. 3. Moreno C, et al. *Haematologica.* 2022;107(9):2108-2120. 4. Hillmen P, et al. *Blood.* 2021;138(suppl 1):642. 5. Burger J, et al. Poster presented at EHA 2024. Abstract #P670.

Next-generation cBTKis

Acalabrutinib and zanubrutinib also outperform chemo-immunotherapy

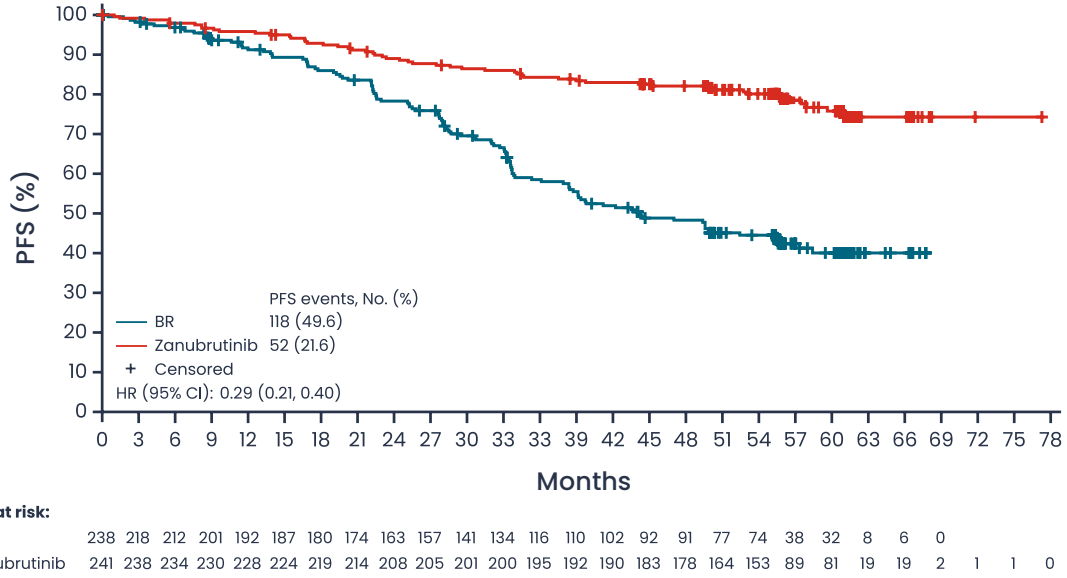
ELEVATE-TN[1]: A vs AO vs O-chlorambucil
Median FU: 6 y



No. at risk

A+O	179	175	170	168	164	163	160	157	156	156	153	152	151	146	144	141	140	138	136	133	127	124	119	116	99	54	39	25	10	2	0
A	179	167	163	158	156	155	153	150	149	146	142	141	137	135	133	130	129	124	121	115	113	103	100	95	85	56	37	22	7	2	0
O+Clb	177	163	156	153	139	125	110	100	86	82	67	66	56	49	44	41	38	30	29	28	24	21	21	18	14	8	6	3	1	0	0

SEQUOIA[2]: Z vs BR
Median FU: 5 y



No. at risk:

BR	238	218	212	201	192	187	180	174	163	157	141	134	116	110	102	92	91	77	74	38	32	8	6	0					
Zanubrutinib	241	238	234	230	228	224	219	214	208	205	201	200	195	192	190	183	178	164	153	89	81	19	19	2	1	1	0		

No head-to-head comparison trials of different BTKis in TN CLL
Different patient selection in different trials

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.
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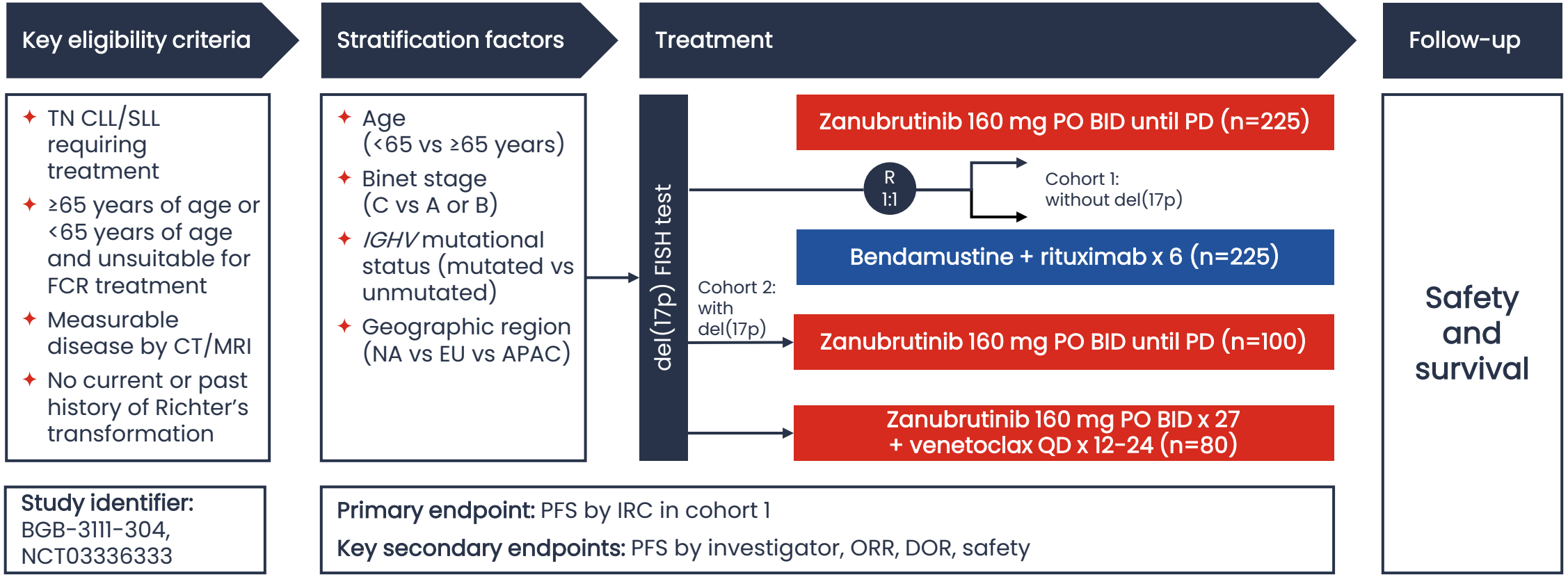
A, acalabrutinib; BR, bendamustine+rituximab; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent BTKi; CI, confidence interval; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; HR, hazard ratio; FU, follow-up; mo, months; NR, not reached; O, obinutuzumab; PFS, progression-free survival; TN, treatment-naïve; y, years; Z, zanubrutinib.
Figures adapted from: 1. Sharman JP, et al. *Blood.* 2023;142(suppl 1):636. 2. Shadman M, et al. *J Clin Oncol.* 2025; 43(7):780-787.

SEQUOIA: Study design

Zanubrutinib in TN CLL/SLL



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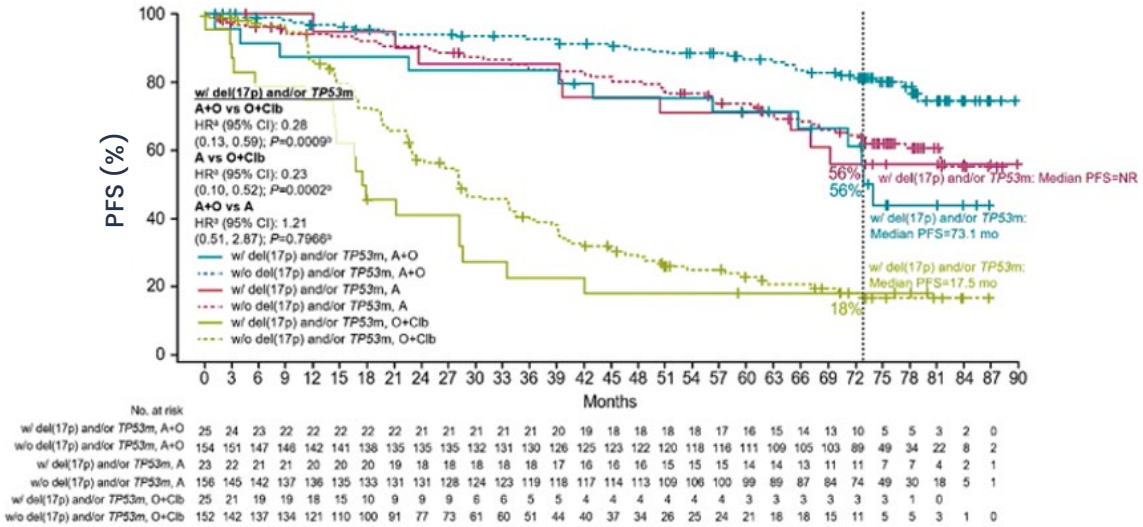
APAC, Asia/Pacific; BID, twice daily; CLL, chronic lymphocytic leukemia; CT, computed tomography; del, deletion; DOR, duration of response; EU, European Union; FCR, fludarabine, cyclophosphamide, and rituximab (chemotherapy regimen); FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain variable region gene; IRC, independent review committee; MRI, magnetic resonance imaging; NA, North America; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PO, per oral; QD, once daily; R, randomized; SLL, small lymphocytic lymphoma; TN, treatment-naïve.
Adapted from Tam, C. Abstract 396 presented at ASH 2021.

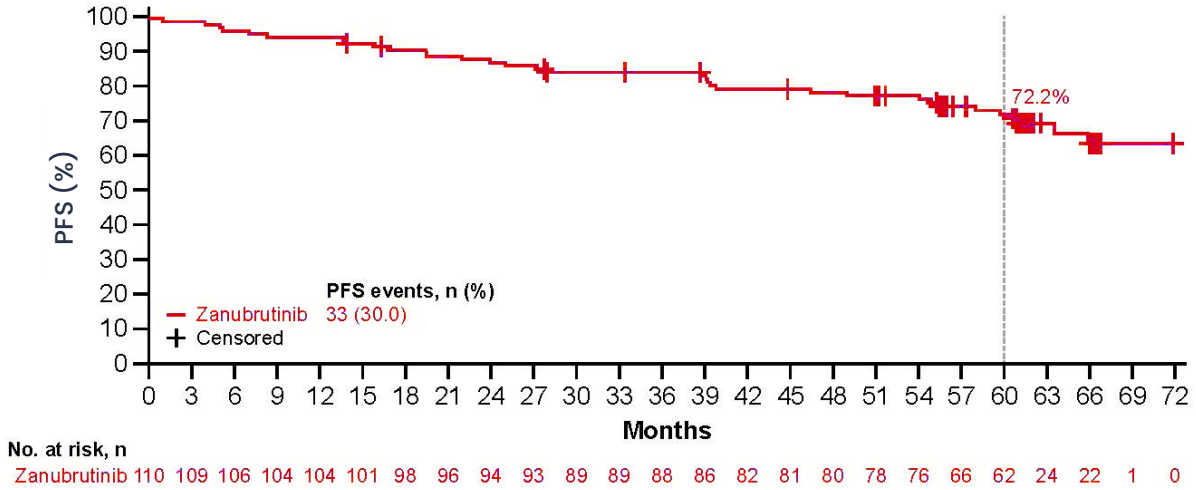
BTKi in high-risk CLL

High-risk subgroups are most in need of continuous BTKi therapy: del(17p)

ELEVATE-TN[1]: A vs AO vs O-chlorambucil
Median FU: 6 y



SEQUOIA[2]: Zanubrutinib (Arm C)
Median FU: 65.8 mo



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.
Indications of approved products may differ outside of the European Union. Zanubrutinib is authorized under different conditions (e.g., different government-approved professional information: indications, warnings, etc.) in Switzerland. For country-specific information, refer to the prescribing information for the country in which you practice medicine.

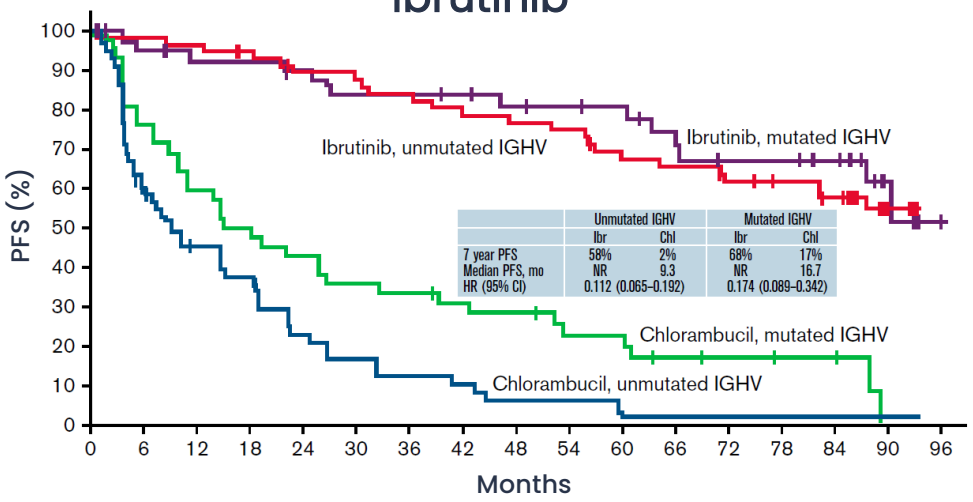
A, acalabrutinib; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; del, deletion; HR, hazard ratio; FU, follow-up; mo, months; m, mutated; NR, not reached; O, obinutuzumab; PFS, progression-free survival; y, years; Z, zanubrutinib.

1. Sharman JP, et al. *Blood*. 2023;142(suppl 1):636. 2. Adapted from Shadman M, et al. Poster presented at EHA 2025; abstract PS1565.

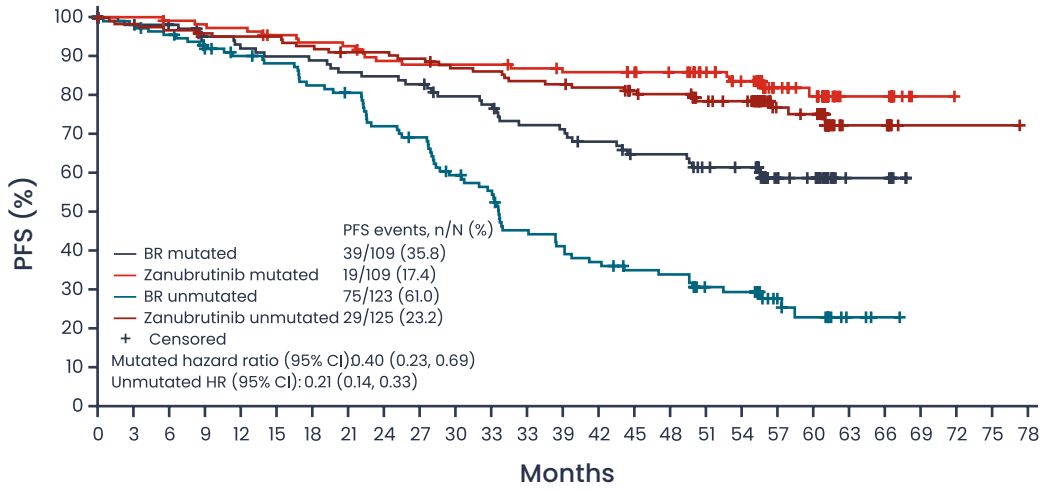
BTKi in high-risk CLL

High-risk subgroups are most in need of continuous BTKi therapy: uIGHV

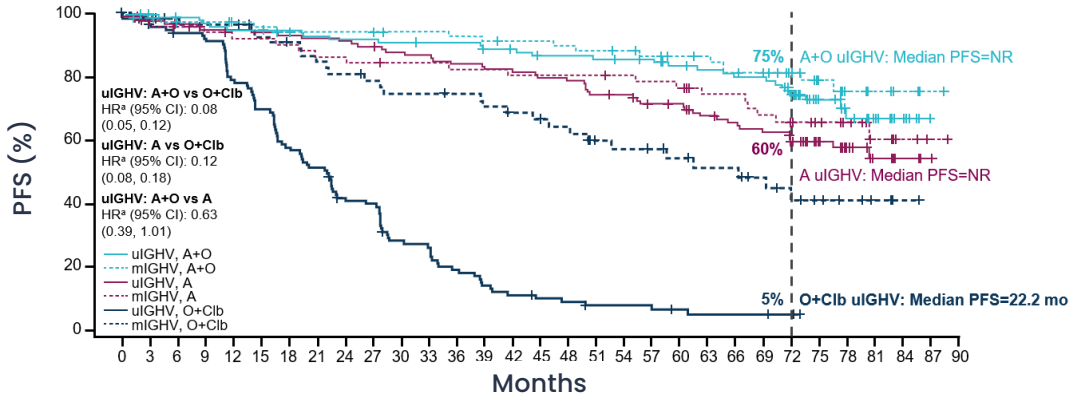
Ibrutinib[1]



Zanubrutinib[3]



Acalabrutinib[2]



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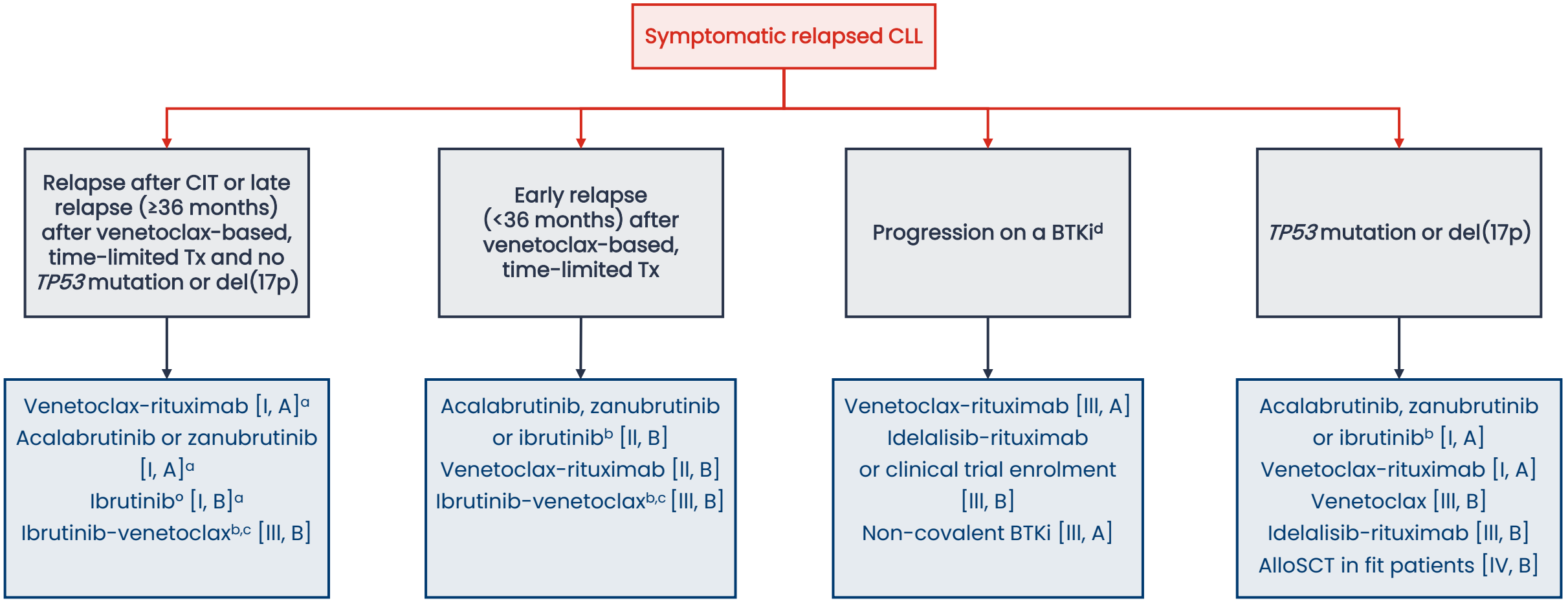
A, acalabrutinib; BR, bendamustine+rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; Clb/Chl, chlorambucil; CLL, chonic lymphocytic leukemia; HR, hazard ratio; Ibr, ibrutinib; IGHV, immunoglobulin heavy chain variable region gene; mIGHV, mutated IGHV; mo, months; NR, not reached; O, obinutuzumab; PFS, progression-free survival; TN, treatment naïve; uIGHV, unmutated IGHV.

Figures adapted from: 1. Barr PM, et al. *Blood Adv.* 2022. 6(11):3440-3450. 2. Sharman JP, et al. *Blood.* 2023;142(suppl 1):636. 3. Shadman M, et al. *J Clin Oncol.* 2025; 43(7):780-787.

2024 ESMO guidelines for R/R CLL

Treatment decisions should be based on previous therapy given and response and duration of response to that therapy

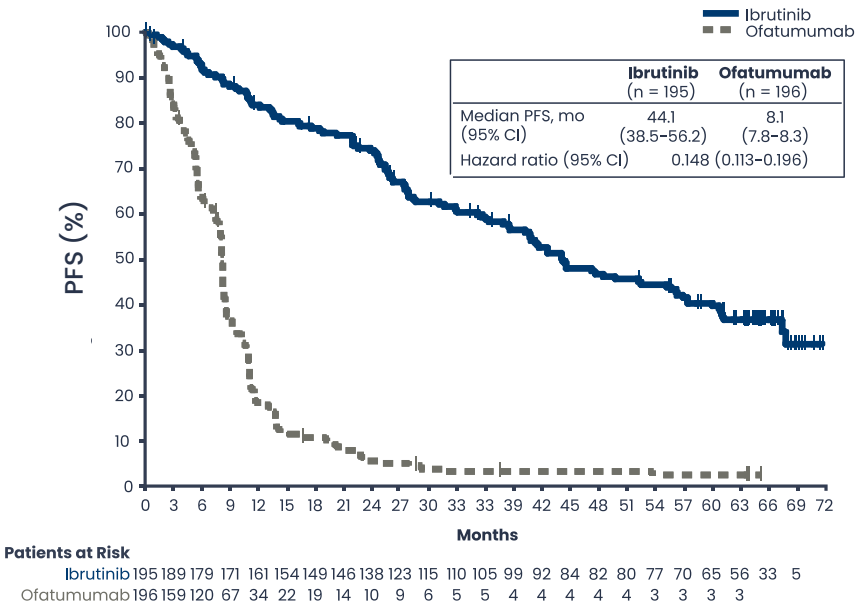


[a]For relapse after CIT, BTKis or venetoclax–rituximab should be considered equally, depending on comorbidities, comedication, access, and preference. [b]Ibrutinib should be considered carefully, particularly in older patients with cardiac comorbidities. [c]Not EMA approved, not FDA approved in relapse. [d]If a patient relapses after prior treatment with a BTKi, which was stopped due to side effects, changing to a different BTKi or rechallenge could be considered.
AlloSCT, allogeneic stem cell transplant; BTKi, Bruton's tyrosine kinase; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del, deletion; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; R/R, relapsed/refractory; Tx, treatment.
Adapted from Eichhorst B, et al. *Ann Oncol* 2024;35(9):762-768.

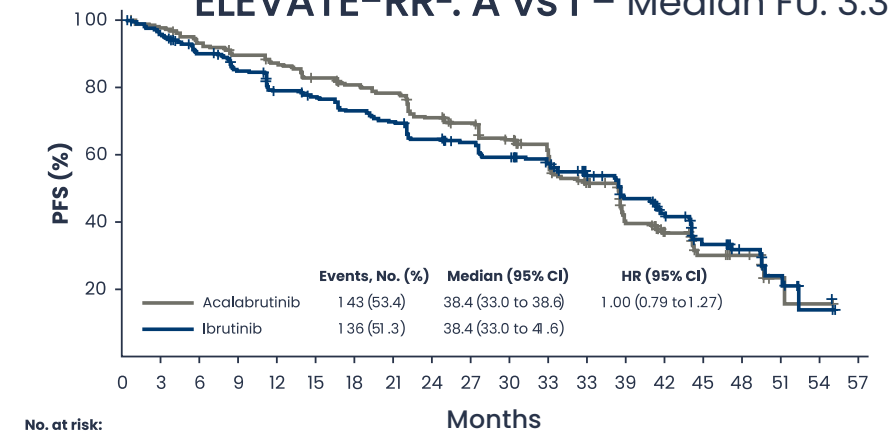
cBTKis in R/R CLL

RESONATE[1]: I vs ofatumumab – Median FU: 6 y

Median number of prior therapies: 3

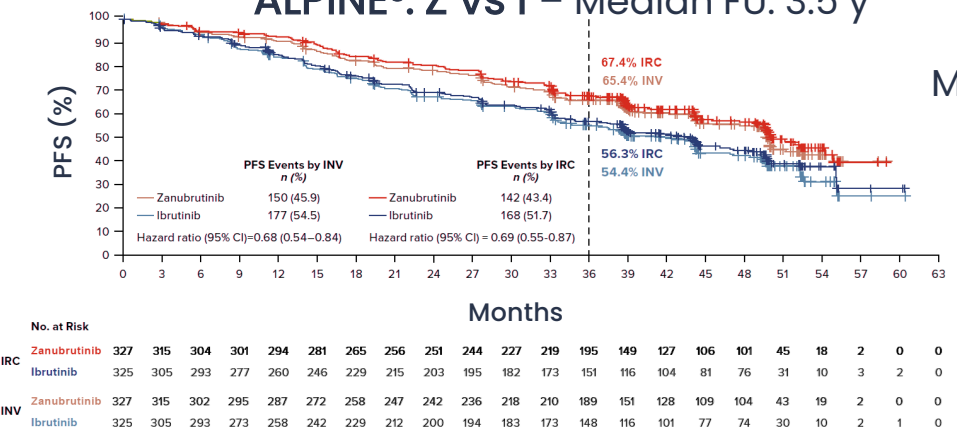


ELEVATE-RR[2]: A vs I – Median FU: 3.3 y



Median number of prior therapies: 2

ALPINE[3]: Z vs I – Median FU: 3.5 y



Median number of prior therapies: 1

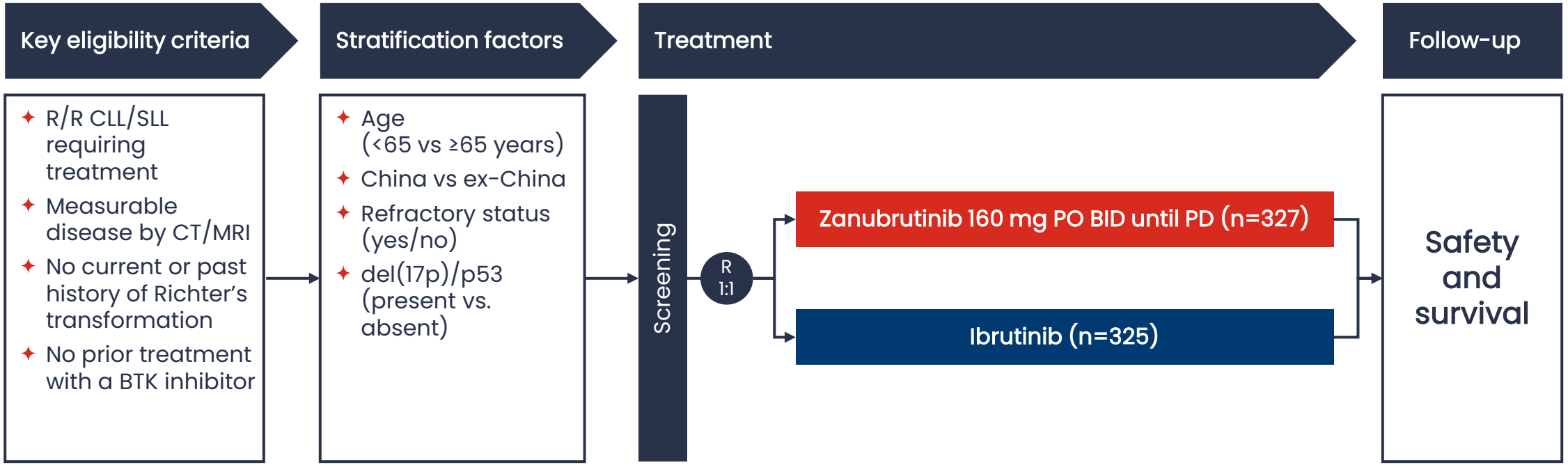
This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.
A, acalabrutinib; cBTKi, covalent Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; FU, follow-up; HR, hazard ratio; I, ibrutinib; INV, investigator; IRC, independent review committee; mo, months; PFS, progression-free survival; R/R, relapsed/refractory; y, years; Z, zanubrutinib.
Figures adapted from: 1. Munir T, et al. *Am J Hematol.* 2019;94(12):1353-1363. 2. Byrd JC, et al. *J Clin Oncol.* 2021; 39(31):3441-3452. 3. Brown JR, et al. Abstract PB2631 presented at EHA2025.

ALPINE: Study design

In R/R CLL we have head-to-head comparative studies

Study identifier:
BGB-3111-305, NCT03734016

Primary endpoint: ORR
Key secondary endpoints: PFS, OS, safety

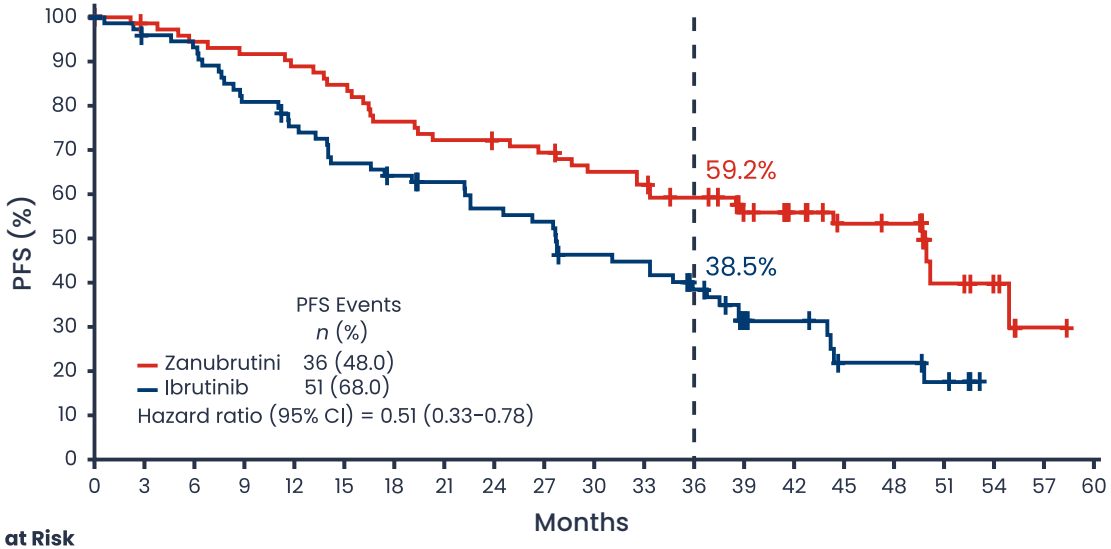


BID, twice daily, BTK, Bruton's tyrosine kinase, CLL, chronic lymphocytic leukemia, CT, computed tomography, MRI, magnetic resonance imaging, ORR, objective response rate, OS, overall survival, PD, progressive disease, PFS, progression-free survival, PO, per oral, QD, once daily, R, randomized, R/R, relapsed/refractory, SLL, small lymphocytic lymphoma.
Brown JR, et al. *Blood*. 2024;144(26):2706-2717.

R/R CLL – Head-to-head comparative studies

High-risk subgroups: del(17p)/ *TP53*^{mut}

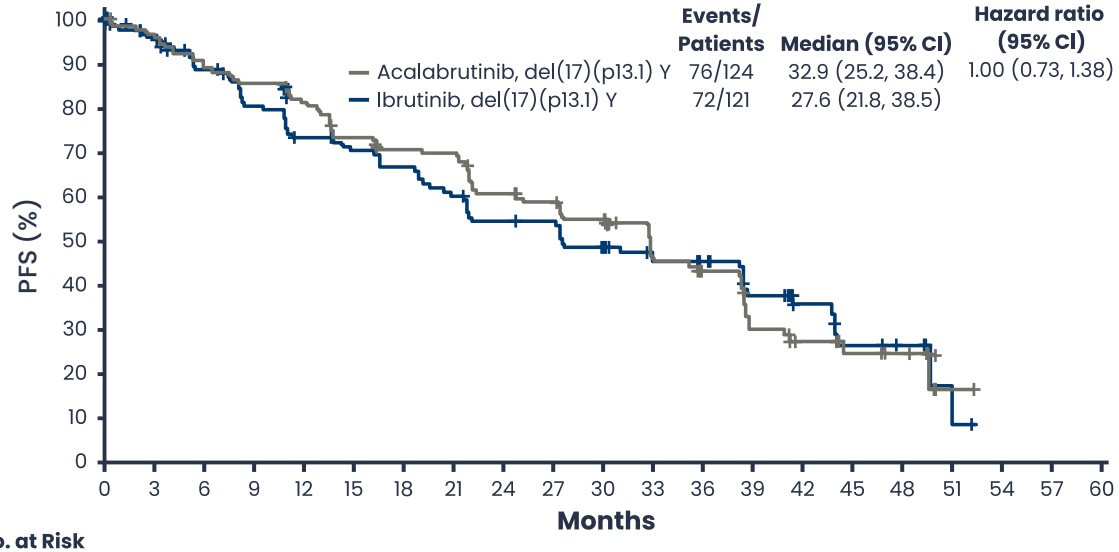
ALPINE[1]: Ibrutinib vs zanubrutinib



No. at Risk

Zanubrutinib	75	71	68	66	64	61	55	52	51	49	45	43	39	31	25	20	19	8	5	1	0
Ibrutinib	75	70	68	59	54	48	45	41	38	36	30	29	23	13	11	6	6	4	0	0	0

ELEVATE RR[2]: Ibrutinib vs acalabrutinib



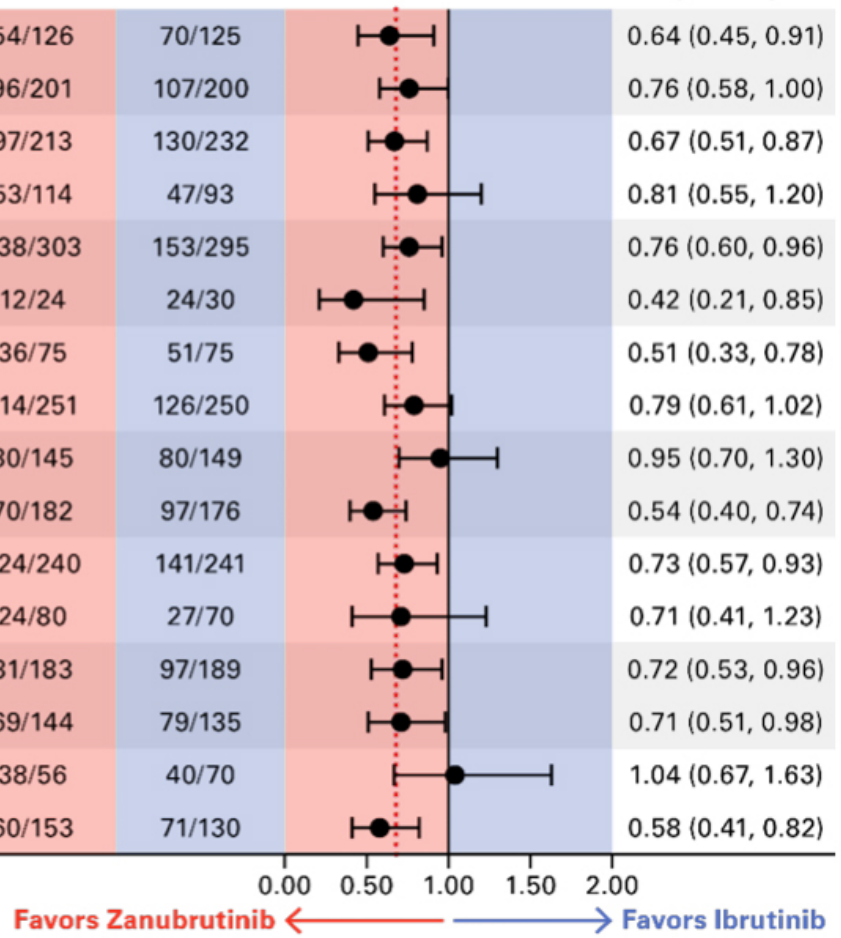
No. at Risk

Acalabrutinib	124	113	104	100	94	84	79	78	66	63	58	43	35	23	14	10	7	1	0		
Ibrutinib	121	112	100	89	80	75	71	64	57	56	49	43	38	29	16	11	7	2	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.
CI, confidence interval; CLL, chronic lymphocytic leukaemia; del, deletion; mut, mutated; PFS, progression-free survival; R/R, relapsed/refractory.
Figures adapted from: 1. Brown JR, et al. *Blood.* 2024;144(26):2706-2717. 2. Byrd JC et *al. J Clin Oncol.* 2021;39(31):3441-3452.

ALPINE: PFS favored zanubrutinib across subgroups

Subgroup		Zanubrutinib Events/Patients	Ibrutinib Events/Patients	Hazard Ratio (95% CI)
Age group	<65 years	54/126	70/125	0.64 (0.45, 0.91)
	≥65 years	96/201	107/200	0.76 (0.58, 1.00)
Sex	Male	97/213	130/232	0.67 (0.51, 0.87)
	Female	53/114	47/93	0.81 (0.55, 1.20)
Prior lines of therapy	1-3	138/303	153/295	0.76 (0.60, 0.96)
	>3	12/24	24/30	0.42 (0.21, 0.85)
Baseline del(17p)/ TP53 mutation status	Present	36/75	51/75	0.51 (0.33, 0.78)
	Absent	114/251	126/250	0.79 (0.61, 1.02)
Bulky disease	Yes	80/145	80/149	0.95 (0.70, 1.30)
	No	70/182	97/176	0.54 (0.40, 0.74)
Baseline IGHV mutation status	Unmutated	124/240	141/241	0.73 (0.57, 0.93)
	Mutated	24/80	27/70	0.71 (0.41, 1.23)
Disease stage	Binet stage A/B or Ann Arbor stage I/II bulky	81/183	97/189	0.72 (0.53, 0.96)
	Binet stage C or Ann Arbor stage III/IV	69/144	79/135	0.71 (0.51, 0.98)
Complex karyotype	Yes	38/56	40/70	1.04 (0.67, 1.63)
	No	60/153	71/130	0.58 (0.41, 0.82)



Data cutoff: 15 Sep 2023. Hazard ratio and 95% CI were unstratified for subgroups.
CI, confidence interval; del, deletion; IGHV, immunoglobulin heavy chain variable region; ITT, intent-to-treat.
Adapted from Brown JR, et al. *Blood.* 2024;144 (26):2706–2717.

Eligibility criteria differ –

Different methodology required to attempt to compare outcomes
R/R CLL: ALPINE vs ASCEND Matching-Adjusted Indirect Comparison (MAIC)

ALPINE (n=327)

Individual patient-level data (IPD)
(DCO: September 2023;
median follow-up: 39 months)[1]

ASCEND (n=155)

Published aggregate data
(DCO: October 2020;
median follow-up: 36 months)[2,3]

Adjustment for impact of COVID-19 within ALPINE

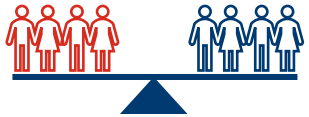
Variables identified as prognostic factors or predictors of treatment effect for matching adjustments

Age, gender, ECOG PS, geographic region, mutated IGHV, del(17p), del(11q), *TP53* mutation status, complex karyotype,[a] bulky disease, cancer type, $beta_2$-microglobulin,[a] Rai/Binet stage, number and type of prior therapies, absolute lymphocyte and neutrophil counts, and platelet count

Sensitivity analyses of scenarios to consider impact of matching for different sets of variables

Matching, reweighting, and adjusting for variables

- Zanubrutinib unadjusted (ITT) population (ALPINE), n=327
- Zanubrutinib ITT population filtered to patients with existing data on the selected baseline characteristics and excluding patients with SLL, n=308
- After population adjustment, ESS=184.8 for zanubrutinib (60% of the starting filtered population)



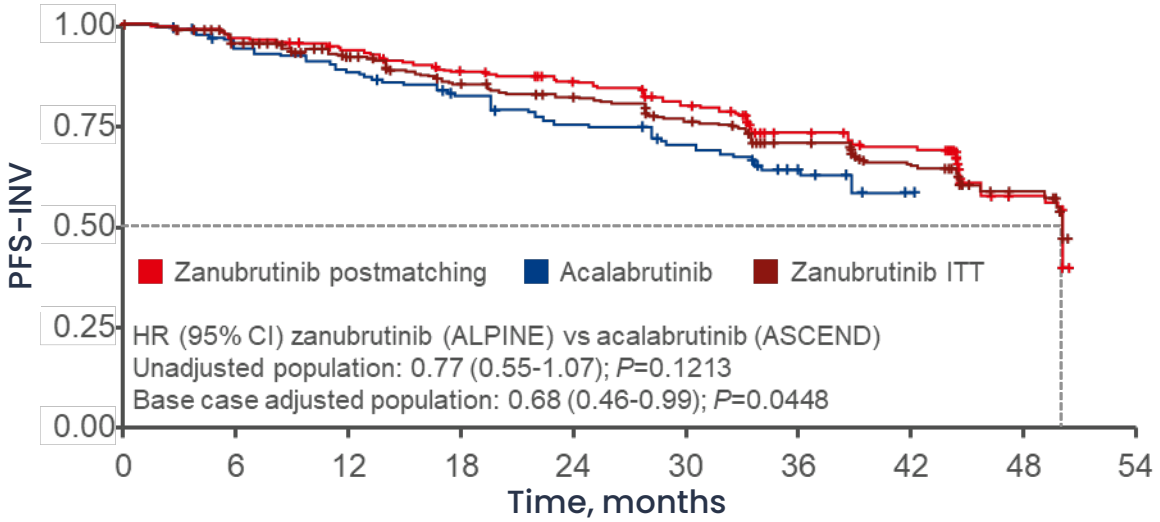
Outcomes

- **PFS-INV**[b] HR: Weighted Cox proportional hazard model
- **OS**[b] HR: Weighted Cox proportional hazard model
- **CR** OR: Weighted logistic regression model

[a]Covariates not matched in the base case. [b]Pseudo IPD for PFS and OS in the acalabrutinib Arm of ASCEND were reconstructed from the digitized Kaplan-Meier curves reported in the ASCEND publication using the algorithm by Guyot et al.[4]
CR, complete response; DCO, data cut-off; del, deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable region; IPD, individual patient-level data; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; OR, odds ratio; OS, overall survival; PFS-INV, investigator-assessed progression-free survival; SLL, small lymphocytic lymphoma.
1. Brown JR, et al. *N Engl J Med.* 2023; 388: 319-332. 2. Ghia P, et al. *J Clin Oncol.* 2020; 38: 2849-2861. 3. Ghia P, et al. *Hemasphere.* 2022; 6(12):e801. 4. Guyot P, et al. *BMC Med Res Methodol.* 2012;12:9.
Adapted from Shadman et al. Abstract #P700 presented at EHA2024.

MAIC outcomes

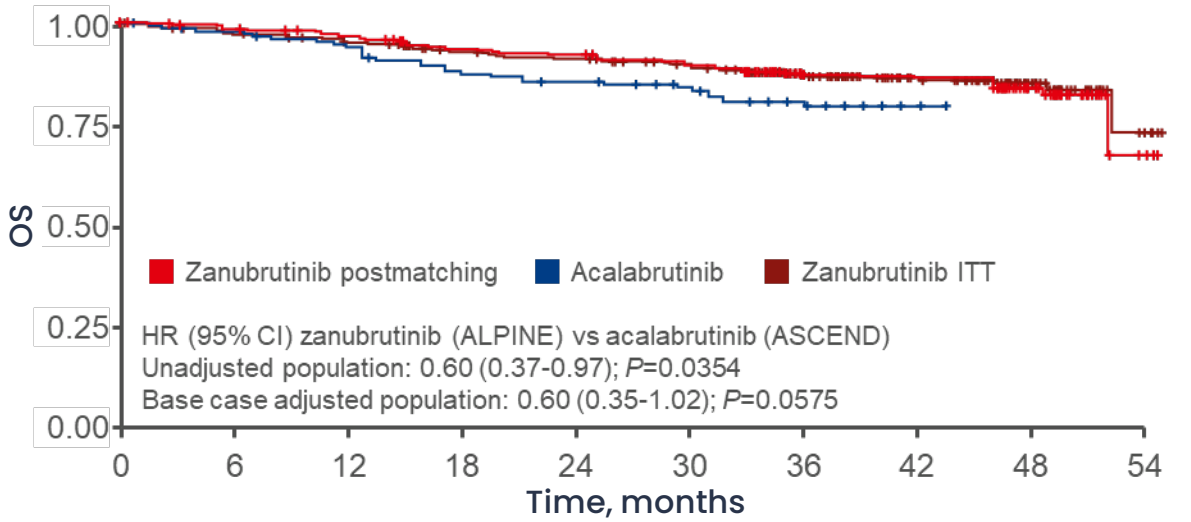
PFS-INV



No. at risk										
	185	172	165	149	141	127	94	76	20	0
	155	142	133	121	107	94	43	0	0	0
	327	300	286	259	243	218	153	118	38	0

PFS-INV was significantly improved for zanubrutinib postmatching

OS



No. at risk										
	185	178	173	159	156	148	120	92	41	1
	155	150	143	132	126	120	77	5	0	0
	327	313	303	287	280	267	208	151	73	4

OS was potentially improved for zanubrutinib postmatching

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS-INV, investigator-assessed progression-free survival.
Adapted from Shadman et al. Abstract #P700 presented at EHA2024.

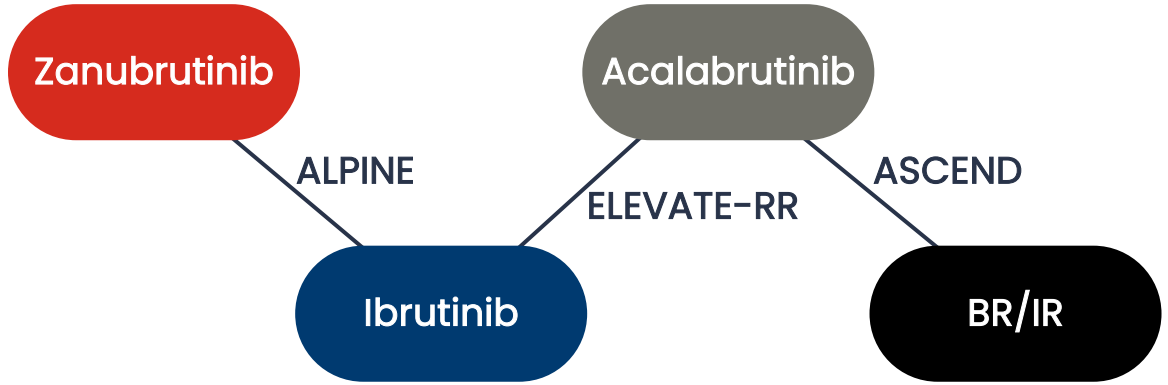
NMA: Comparative efficacy of BTKis in R/R CLL

Baseline characteristics of studies included in Network Meta Analysis (NMA) methods

Key trial and patient characteristics at baseline

Trial Name	ALPINE	ELEVATE-RR	ASCEND
Study arms	Zanubrutinib vs Ibrutinib	Acalabrutinib vs Ibrutinib	Acalabrutinib vs BR/IR
Median follow-up in months	39	40.9	46.5 (acalabrutinib) 45.3 (BR/IR)
Sample size	652	533	310
Median age (range)	67 (35–90)	66 (28-89)	67 (32–90)
% male	68	71	67
ECOG (%)	0-1: 97 2: 3	0-1: 92 2: 8	0: 36 1: 51 2: 13
Rai stage III–IV (%)	NR	50	42
del(11q) (%)	27	64	27
del(17p) (%)	15	46	16
TP53 (%)	15	40	24
del(17p) and/or *TP53*	23	51	28
Unmutated *IGHV* (%)	73	86	74
Median number of prior lines (range)	1 (1-8)	2 (1-12)	2(1-10)
No. prior lines (%)	1: 59 2: 24 3: 10	1-3: 88	1: 48 2: 27 3: 13
Prior anti-CD20 Ab (%)	83	86	80

- Fixed effect Bayesian NMA models:
  Relative treatment effects observed in each trial (i.e., HRs) and obtain estimates
- Survival outcomes: HR (95% CI)
- Response outcomes: OR (95% CI),
- Probability of zanubrutinib superiority was assessed
- Data were analyzed with and without adjustment for COVID-19-related deaths



Ab, antibody; BR/IR, bendamustine + rituximab or idelalisib + rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CD, cluster of differentiation; COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IGHV, immunoglobulin heavy-chain variable region gene; NMA, network meta-analysis; OR, odds ratio; R/R, relapsed/refractory.
Adapted from Shadman M et al. Poster presented at EHA2024; abstract P701.

Data inputs used for NMA: Outcomes for high-risk population

Available data inputs used for the analyses, presented by high-risk population of interest

Trial	Comparators	High Risk*					Del(17p)		*TP53 mutation*	
		N	OR [95% CI]		HR [95% CI]		N	HR [95% CI]	N	HR [95% CI]
			ORR-INV	CR-INV	PFS-INV	OS		PFS-INV		PFS-INV
ALPINE COVID-adjusted	Zanubrutinib	75	3.02 [1.35, 6.73]	1.89 [0.53, 6.75]	0.49 [0.31, 0.78]	0.59 [0.31, 1.12]	45	0.49 [0.27, 0.89]	50	0.49 [0.28, 0.86]
	Ibrutinib	75	Ref	Ref	Ref	Ref	50	Ref	45	Ref
ALPINE COVID-unadjusted	Zanubrutinib	75	2.64 [1.07, 6.54]	1.67 [0.52, 5.37]	0.52 [0.33, 0.82]	0.69 [0.38, 1.24]	45	0.53 [0.30, 0.94]	50	0.52 [0.30, 0.90]
	Ibrutinib	75	Ref	Ref	Ref	Ref	50	Ref	45	Ref
ELEVATE-RR	Acalabrutinib	268	1.61 [1.01, 2.56]	0.95 [0.53, 1.68]	0.90 [0.70, 1.16]	0.82 [0.58, 1.15]	124	1.00 [0.73, 1.37]	100	0.95 [0.68, 1.33]
	Ibrutinib	265	Ref	Ref	Ref	Ref	121	Ref	112	Ref
ASCEND	Acalabrutinib	44	NR	NR	0.22 [0.12, 0.40]	0.90 [0.45, 1.79]	28	0.13 [0.06, 0.29]	39	0.25 [0.14, 0.45]
	BR/IR	42	NR	NR	Ref	Ref	21	Ref	34	Ref

Response findings

- Zanubrutinib versus ibrutinib: Favorable ORR-INV and a trend favoring improvement in CR-INV
- Zanubrutinib versus acalabrutinib: Trends favoring zanubrutinib but not statistically significant

PFS findings

- **Zanubrutinib more efficacious** than ibrutinib, acalabrutinib, and BR/IR, representing risk reductions of 51%, 45%, and 88% respectively
- del(17p): Zanubrutinib more efficacious than all other treatments in the network and all treatments except acalabrutinib when unadjusted data were used
- *TP53* mutations: Zanubrutinib more efficacious than ibrutinib and BR/IR, with trends in favor of zanubrutinib compared with acalabrutinib

OS findings

- Numerical benefit with zanubrutinib compared with other treatments
- Less favorable for zanubrutinib when not adjusted for COVID-19-related deaths

*Trial-defined definition of high risk.
BR/IR, bendamustine + rituximab or idelalisib + rituximab; CI, confidence interval; CR, complete response; HR, hazard ratio; INV, investigator assessed; NMA, network meta-analysis; NR, not reported; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ref, reference for the HR.
Adapted from Shadman M et al. Poster presented at EHA2024; abstract P701.

NMA: Limitations and conclusions

- Comparative efficacy of BTKis in R/R CLL
- Structure of the network (indirect evidence)
- Sample size issue
- Definition of "high risk" varied between the studies

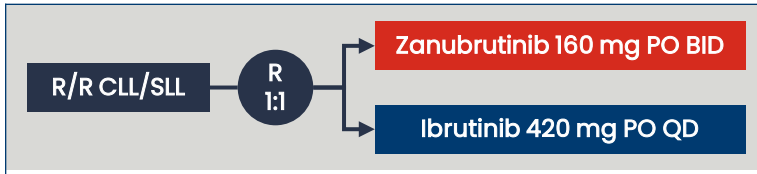
However,
these findings suggest that zanubrutinib is likely to be the most efficacious BTKi for patients with genetic high-risk features such as the presence of *TP53* mutations and/or del(17p)

BR/IR, bendamustine + rituximab or idelalisib + rituximab; CLL, chronic lymphocytic leukemia, NMA, network meta-analysis.
Shadman M et al. Poster presented at EHA2024; abstract P701.

BTKi safety – Next-generation vs 1st generation

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

ALPINE: Overall safety summary



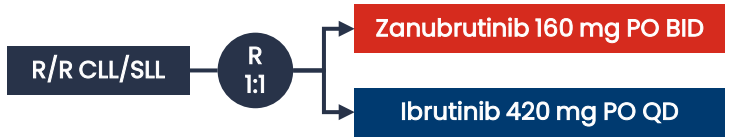
	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**38.3 (0.4, 54.9)**	**35.0 (0.1, 58.4)**
Any grade adverse event	**320 (98.8)**	**323 (99.7)**
Grade 3 to 5	235 (72.5)	251 (77.5)
Grade 5	41 (12.7)	40 (12.3)
Serious adverse event	**165 (50.9)**	**191 (59.0)**
Adverse events leading to		
Dose reduction	47 (14.5)	59 (18.2)
Dose interruption	196 (60.5)	201 (62.0)
Treatment discontinuation	64 (19.8)	85 (26.2)
Hospitalization	150 (46.3)	180 (55.6)

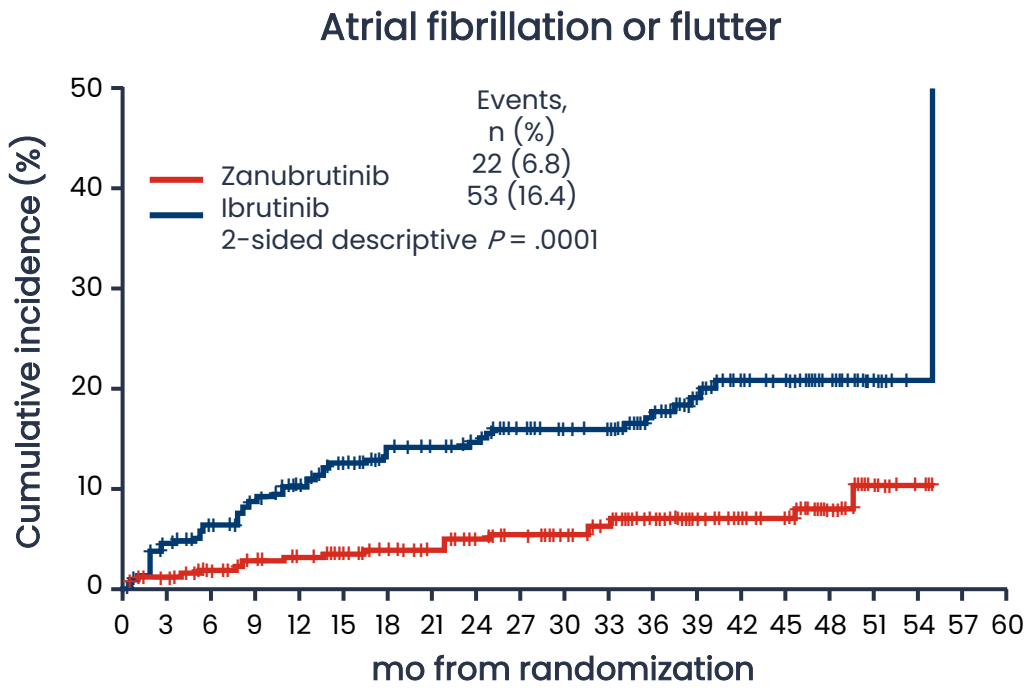
Data cutoff: 15 Sep 2023
BID, twice daily; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; PO, per oral; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.
Adapted from Brown, JR et al. Oral Presentation at ASH 2023; abstract number 202.

BTKi safety – Next-generation vs 1st generation

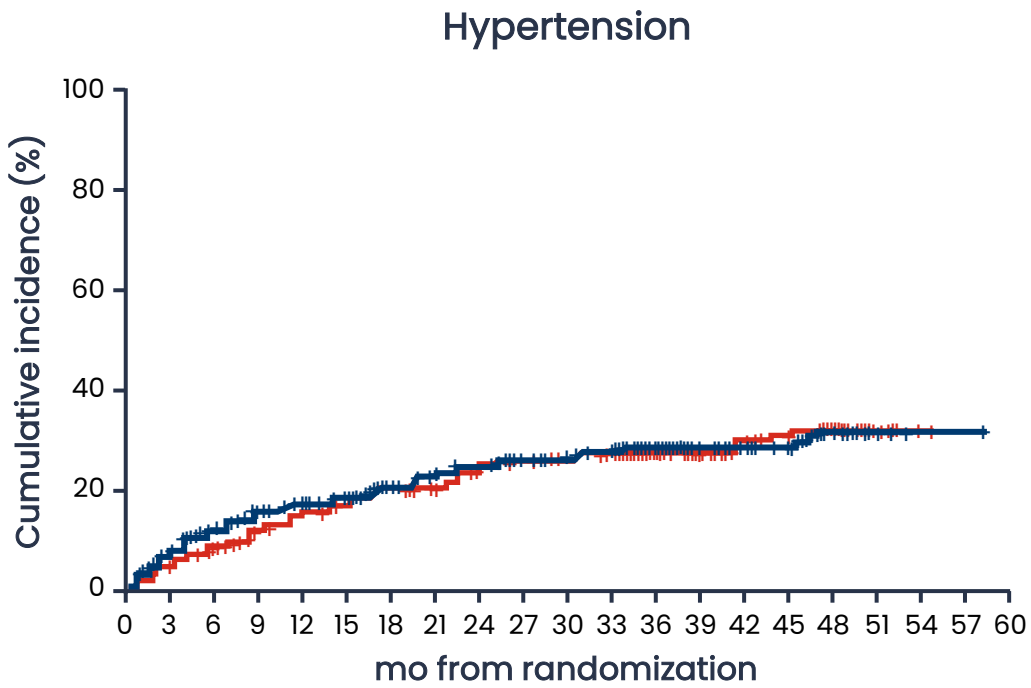
Head-to-head BTKi safety data are only available from R/R CLL trials

ALPINE: Cumulative incidence of any-grade AF and hypertension





Patients at risk, n																				
Zanubrutinib	324	312	302	294	288	277	268	261	250	242	231	221	180	144	127	122	58	14	3	0	0
Ibrutinib	324	295	278	260	247	229	210	200	190	177	167	165	133	104	90	85	47	10	2	1	0



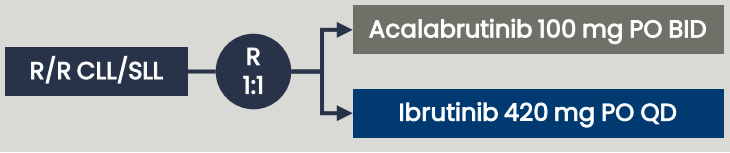
Patients at risk, n																				
Zanubrutinib	324	296	279	262	247	232	220	215	196	188	175	165	133	108	91	86	37	10	1	0	0
Ibrutinib	324	280	253	231	221	207	185	172	164	150	140	136	108	79	69	64	32	7	2	2	0

Data cutoff: 15 Sep 2023
AF, atrial fibrillation; BID, twice daily; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; mo, month(s); PO, per oral; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.
Adapted from Brown, JR et al. Oral Presentation at ASH 2023; abstract number 202.

BTKi safety – Next-generation vs 1st generation

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

Adverse events of clinical interest[a] in ELEVATE-RR



	Acalabrutinib (n = 266)		Ibrutinib (n=263)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
▪ Atrial fibrillation/flutter[a]	25 (9.4)	13 (4.9)	42 (16.0)	10 (3.8)
▪ Ventricular arrhythmia	0	0	1 (0.4)	0
Bleeding events	101 (38.0)	10 (3.8)	135 (51.3)	12 (4.6)
▪ Major bleeding events[b]	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Hypertension[c]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
ILD/pneumonitis	7 (2.6)	1 (0.4)	17 (6.5)	2 (0.8)
SPMs, excluding NMSC	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

[a]Includes preferred terms of atrial fibrillation and atrial flutter. [b]Any hemorrhagic event that was serious, grade ≥3, or a central nervous system hemorrhage (any grade). [c]Includes preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
AE, adverse event; BID, twice daily; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; PO, per oral; QD, once daily; R/R, relapsed/refractory; SPMs, second primary malignancies.
Adapted from Hillmen P et al, Abstract S145 presented at EHA 2021.

BTKi safety – Next-generation vs 1st generation

Pooled analyses have provided additional insights

Mayo Clinic meta-analysis[1]

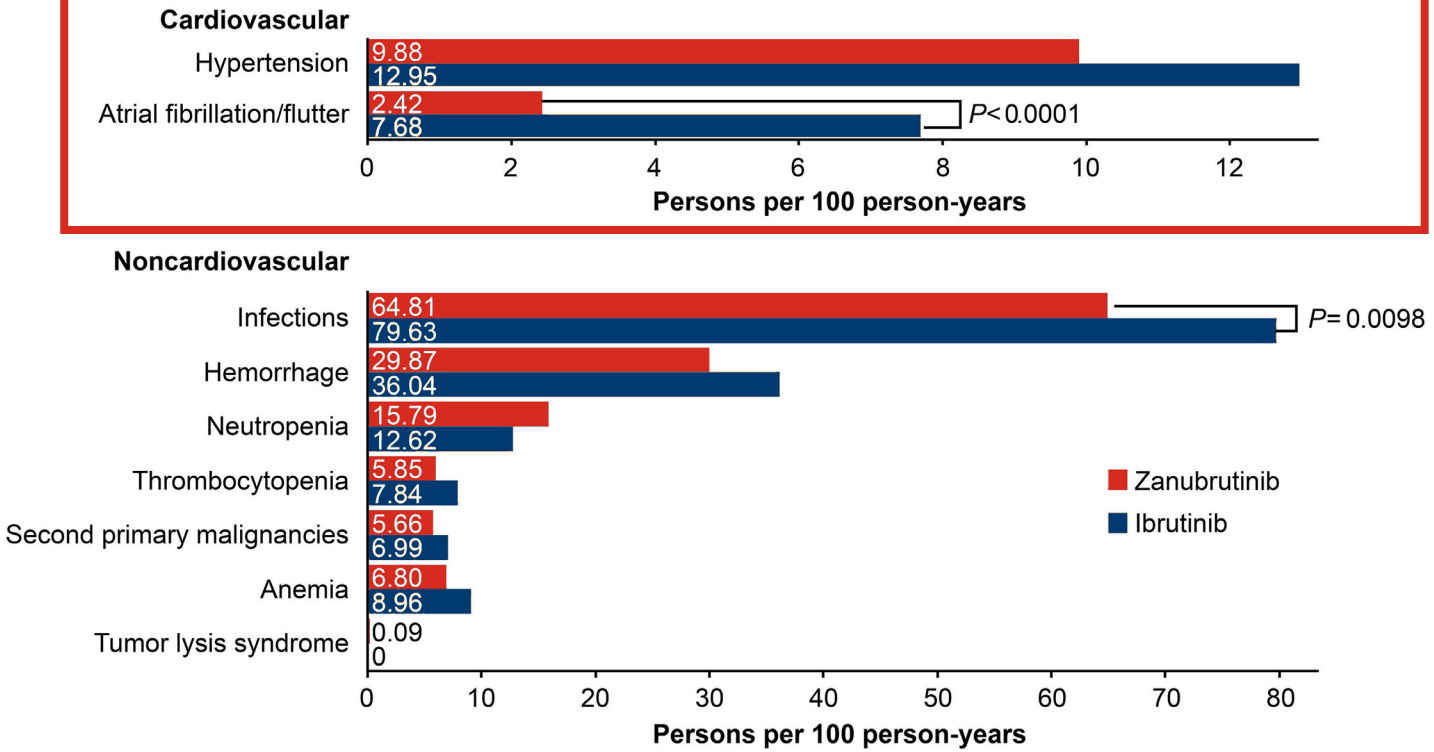
- 61 trials, 6,959 patients, CLL/WM/MCL
- Comparison of TEAEs of Ibru, Zanu, Acala
- All AEs (all-grade & ≥Grade 3): Zanu & Acala similar, both lower than Ibru
- **Zanubrutinib and acalabrutinib have distinct safety profiles:**
  - Zanubrutinib had lower rates of Afib/flutter and infections, and lower rates of AEs affecting daily QoL including GI toxicities (diarrhea, nausea, vomiting), headache and fatigue
  - Acalabrutinib had lower rates of hypertension and neutropenia

Pooled analysis 10 zanubrutinib trials[2]

- Overall and exposure-adjusted incidence of cardiac events, including Afib, hypertension & symptomatic VA, were lower with Zanu vs Ibru across trials

Comparative analysis of pooled safety data from ASPEN and ALPINE (1,550 patients)[3]

- Zanubrutinib demonstrated improved CV tolerability over ibrutinib



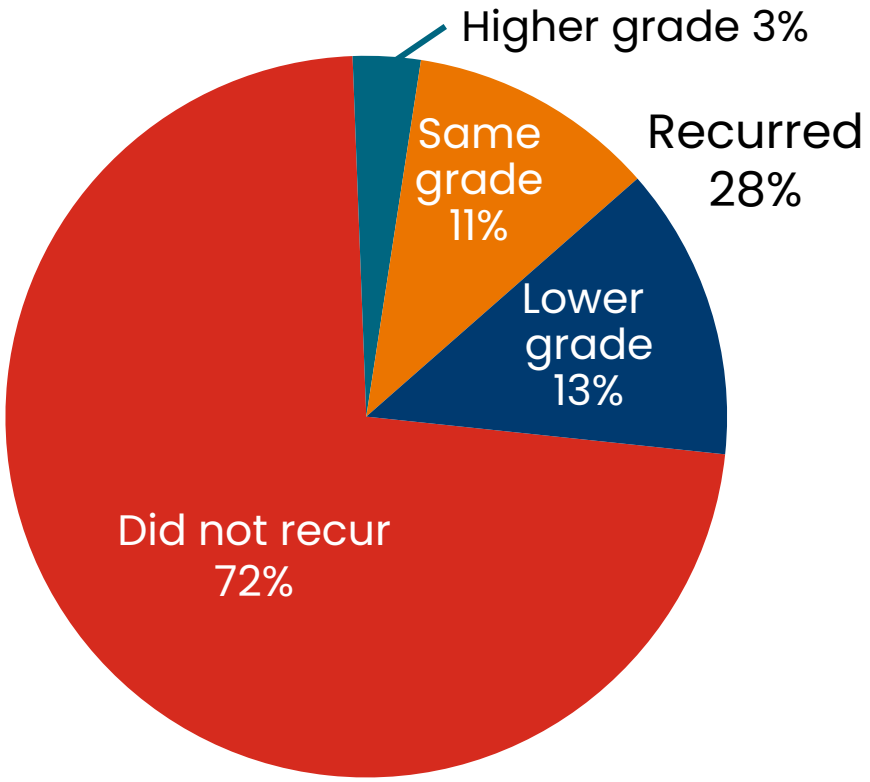
Acala, acalabrutinib; AE, adverse event; Afib, atrial fibrillation; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CV, cardiovascular; GI, gastrointestinal; HT, hypertension; Ibru, ibrutinib; MCL, mantle cell lymphoma; QoL, quality of life; VA, ventricular arrhythmia: WM,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

1. Hwang S, et al. *HemaSphere*. 2023;7(S3): e47546cf. 2. Moslehi JJ, et al. *Blood Adv*. 2024;2023011641. 3. Adapted from Brown JR, et al. *Haematologica*. 2024;109(7):2277-2283.

Replacing BTKi because of toxicity
ACE-CL-001: Results in ibrutinib-intolerant cohort

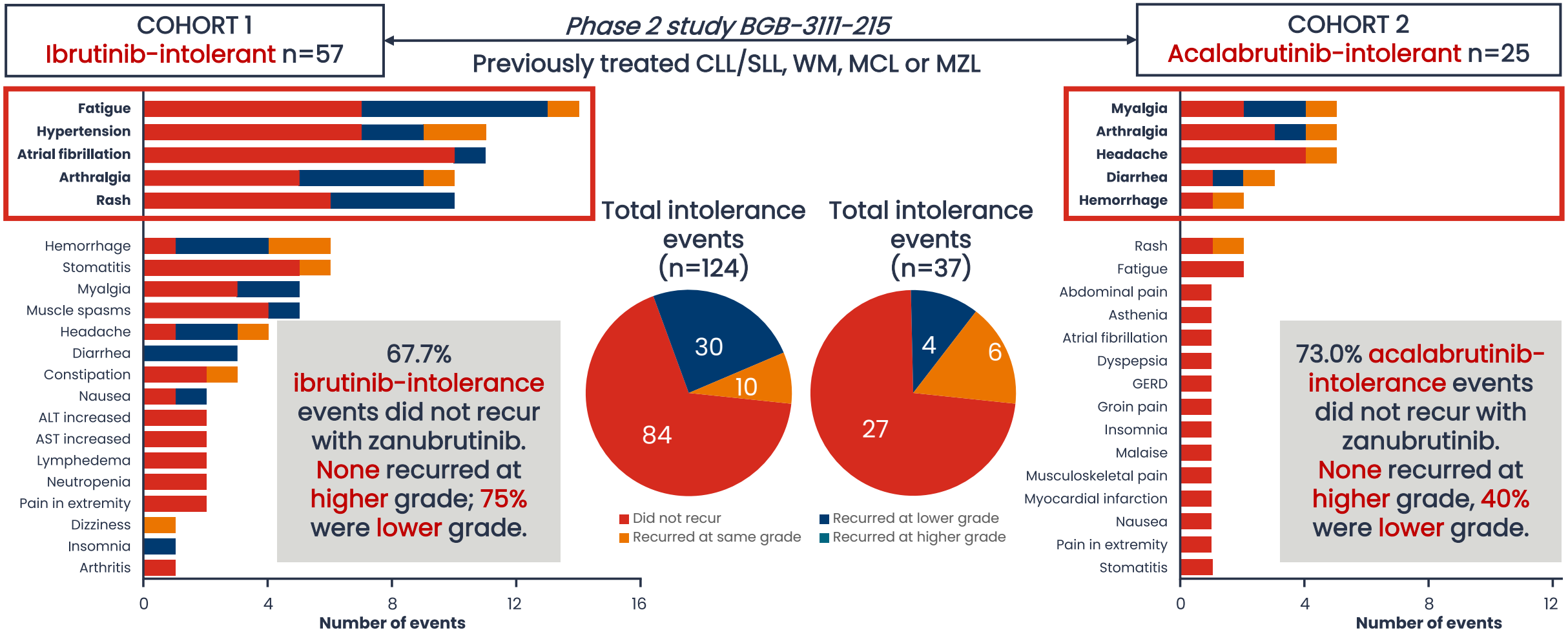
- N=33 heavily pretreated patients with CLL treated with acalabrutinib
  - 23 remained on acalabrutinib at median of 19 months on treatment
  - No acalabrutinib dose reductions
- 61 ibrutinib-related AEs associated with intolerance at study entry
  - No recurrence: 72%
  - Recurrence at lower grade than with acalabrutinib: 13%
- ORR: 76%
- Median PFS: not reached
  - 1-year PFS rate: 83.4%

Recurrence of ibrutinib-related AEs (n=61) during acalabrutinib treatment



AE, adverse event; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ORR, overall response rate; PFS, progression-free survival..
Awan FT, et al. *Blood Adv.* 2019;3(9):1553-1562.

Zanubrutinib in ibrutinib- and/or acalabrutinib-intolerant patients with B-cell malignancies



Intolerance is defined as an unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care as a result of: Grade ≥2 non-hematologic toxicities for >7 days; Grade ≥3 non-hematologic toxicity of any duration; Grade 3 neutropenia with infection or fever; or Grade 4 hematologic toxicity that persists until ibrutinib therapy is discontinued due to toxicity NOT until progression.
ALT, alanine transaminase; AST, aspartate transaminase; CLL, chronic lymphocytic leukemia; GERD, gastroesophageal reflux disease; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; SLL, small lymphocytic leukemia.
Adapted from Shadman M et al. Poster presented at EHA 2023; Abstract P633.

Mechanisms of resistance to BTKi – Acquisition of resistance mutations

Drug	Resistance mutations	Has *in vitro* activity against
Ibrutinib	C481S in >90% (Rare – D43H, C481 kinase dead*, A428D, L528W, T474I)	L528W, T474I/L, C481 kinase dead (via HCK), V416L/M, A428D
Acalabrutinib	C481S, C481 kinase dead*, T474I, E41V	L528W
Zanubrutinib	C481S, C481 kinase dead*, L528W, A428D	T474I, V416L/M
Pirtobrutinib	C481 kinase dead*, L528W, V416L, T474I/F/L/Y, A428D, M477I, M437R, D539G/H, Y545N	C481S

*C481 kinase dead = C481F, C481Y, C481W, C481G, C481R. C481T is catalytically active.

BTKi, Bruton's tyrosine kinase inhibitor; HCK, hematopoietic cell kinase.

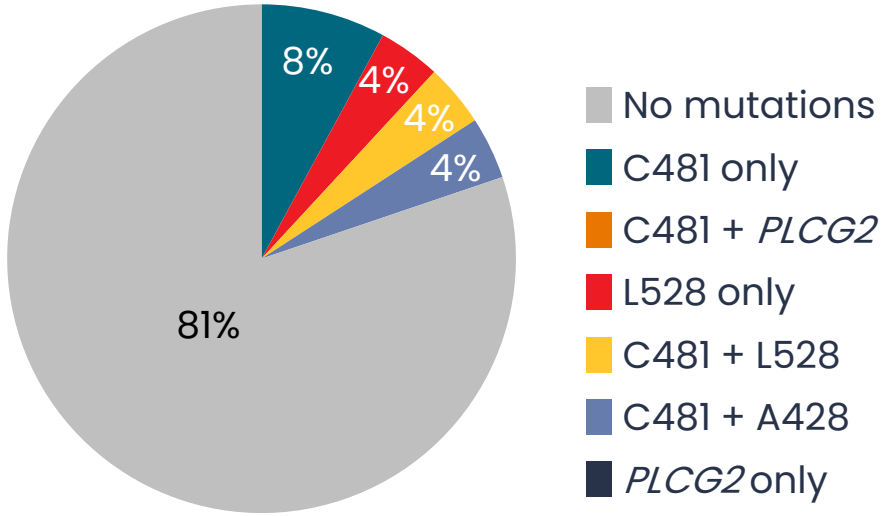
1. Woyach JA, et al. *Blood.* 2019;134(Suppl_1):504. 2. Rogers KA, et al. *Haematologica.* 2021;106(9):2364-2373. 3. Sun C, et al. *Blood.* 2023;142(Suppl_1):1891. 4. Blombery P, et al. *Blood Adv.* 2022;6(20):5589-5592. 5. Wang E, et al. *N Engl J Med.* 2022;386(8):735-743. 6. Dhami K, et al. *Sci Signal.* 2022;15(736):eabg5216. 7. Woyach JA, et al. *J Clin Oncol.* 2017;35(13):1437-1443. 8. Landau DA, et al. *Nat Commun.* 2017;8(1):2185. 9. Quinquenel A, et al. *Blood.* 2019;134(7):641-644. 10. Estupinán HY, et al. *Leukemia.* 2021;35(5):1317-1329. 11. Byrd JC, et al. *N Engl J Med.* 2013;369(1):32-42. 12. Song Y, et al. *Br J Haematol.* 2022;198(1):62-72. 13. Mato AR, et al. *Lancet.* 2021;397(10277):892-901. 14. Naeem AS, et al. *Blood Adv.* 2023;7(9):1929-1943. 15. Gomez EB, et al. *Blood.* 2023;142(1):62-72. 16. Brown JR, et al. *Blood.* 2023;142(Suppl 1): 1890-1892. 17. Woyach JA, et al. Poster presented at ICML 2023; Abstract #163. 18. Qi J, et al. *Blood Adv.* 2023;7(19):5698-5702. 19. Hamasy A, et al. *Leukemia.* 2017;31(1):177-185.

Acquired mutations in patients with R/R CLL who progressed in the ALPINE study

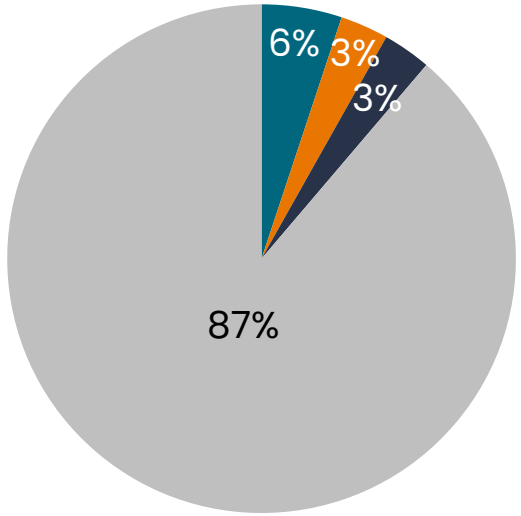
BTK and/or *PLCG2* mutation distribution at progression[a]

Overall median treatment duration was 17.0 m (range, 5.0-34.5 m)

Zanubrutinib arm (n=24)



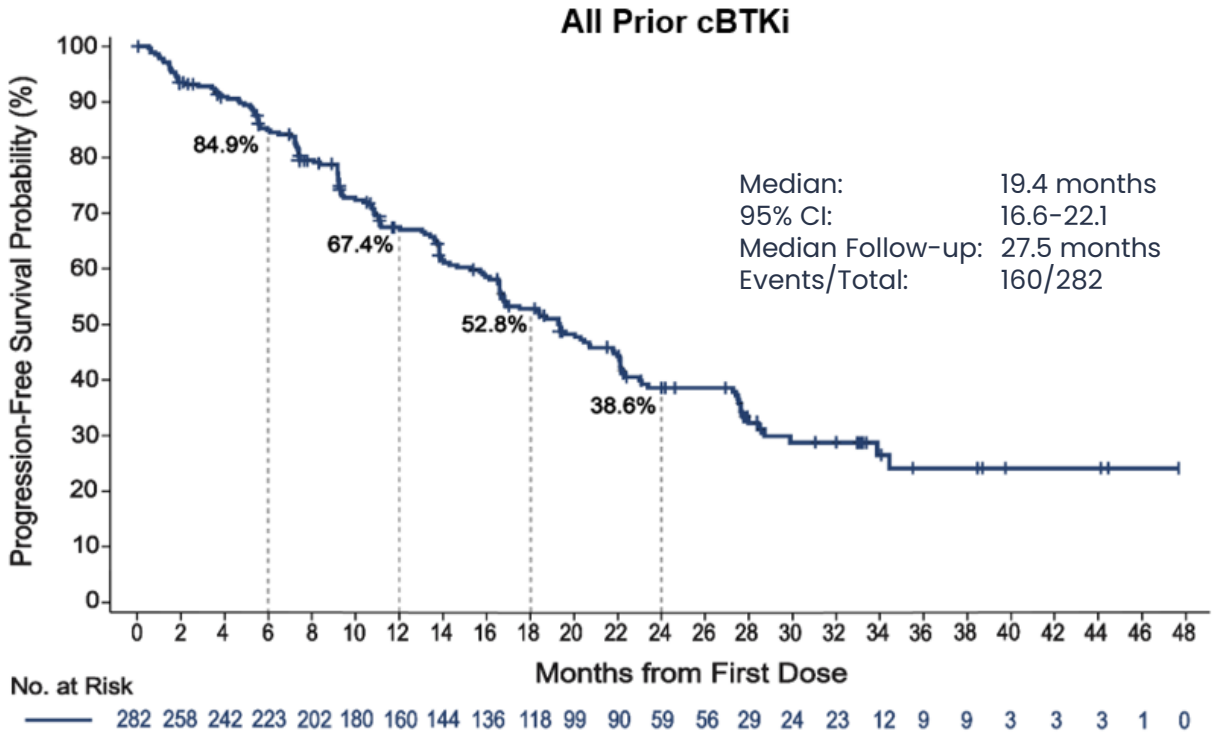
Ibrutinib arm (n=28)

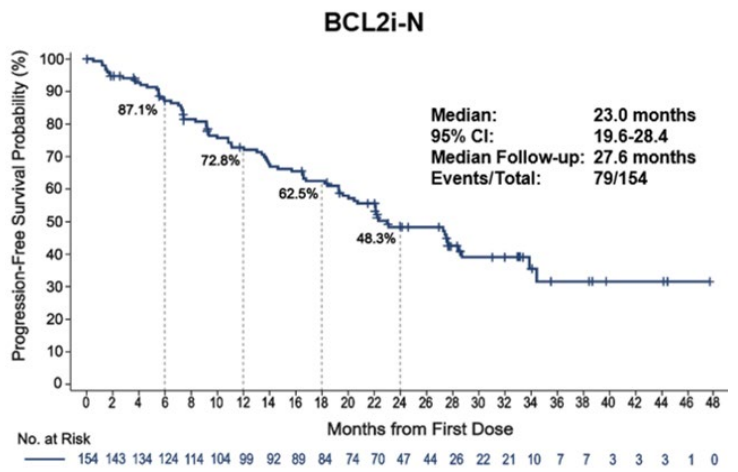


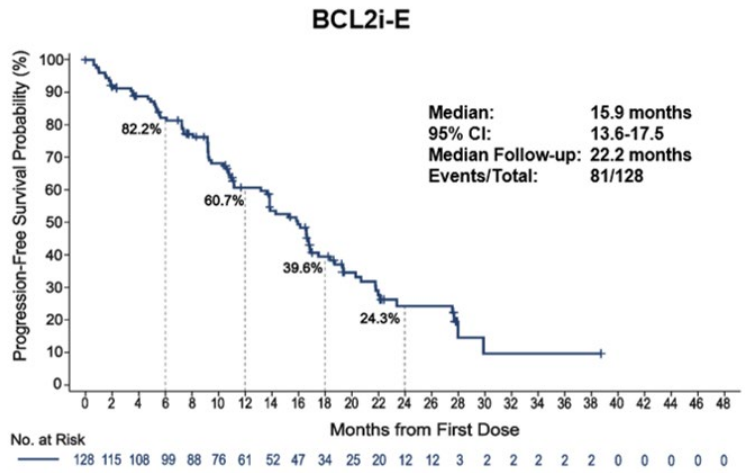
- No ***BTK* mutations** were identified **at baseline**
- Of **patients who progressed** in ALPINE and were included in this analysis, **most** (82.6%) **did not acquire *BTK* or *PLCG2* mutations**
- 5/24 patients who progressed on zanubrutinib acquired BTK mutations
- These data suggest that ***BTK* and/or *PLCG2* mutations** are **not the main factors driving PD** in this population
- **Progression** on BTKi therapy (particularly that due to ***BTK* mutations**) is **rare**
- Limited data are available to make clinical decisions

[a]Excluding patients without paired baseline and PD blood samples (ibrutinib arm, n=1) and patients with Richter's transformation (n=2 from each of the zanubrutinib and ibrutinib arms).
BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PD, progressive disease; PLCG2, phospholipase C gamma 2; R/R, relapsed/refractory.
Adapted from Brown JR et al. Poster presented at ASH 2023. Abstract #1890.

Non-covalent BTKi
BRUIN trial: Pirtobrutinib in R/R CLL patients pretreated with cBTKi[1]







Characteristics	N=282
Median age, y	69 (36-88)
Median N of prior Tx	4 (1-11)

Pre-existing T474x and L528W mutations do not impact pirtobrutinib response[2]

BCL2i, B-cell lymphoma 2 inhibitor; BCL2i-E, BCL2i experienced; BCL2i-N, BCL2i naive; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent BTKi; CI, confidence interval; Tx, treatment.
1. Woyach JA, et al. *Blood.* 2023;142(suppl 1):325. 2. Brown JR, et al. *Blood.* 2023;142(Suppl 1):326.

Speaker's own conclusions

- Targeted therapies are the treatment of choice in both TN and R/R CLL
- Compared with fixed-duration venetoclax combinations, continuous therapy with covalent BTKi is indicated particularly in patients with high-risk features including *TP53*^{mut}/del(17p) and uIGHV
- The second-generation BTKis, acalabrutinib and zanubrutinib, appear to have decreased toxicity compared with first-in-class ibrutinib. This has been confirmed in head-to-head studies in R/R CLL
- Zanubrutinib has demonstrated improved efficacy vs ibrutinib in a head-to-head trial in R/R CLL
- Favorable BTK occupancy and MAIC and NMA analyses support zanubrutinib as the BTKi with most efficacious activity with lowest toxicity profile among currently available covalent BTKi
- Pirtobrutinib has now been licensed for R/R CLL in patients who have been previously treated with covalent BTKi
- Ongoing clinical trials look to address potential combination partners for zanubrutinib

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
Indications of approved products may differ outside of the European Union. Zanubrutinib is authorized under different conditions (e.g., different government-approved professional information: indications, warnings, etc.) in Switzerland. For country-specific information, refer to the prescribing information (PI) for the country you practice medicine in.
BTK, Bruton tyrosine kinase; BTKi, BTK inhibitor; CLL, chronic lymphocytic leukemia; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; R/R, relapsed/refractory; TN, treatment-naive.

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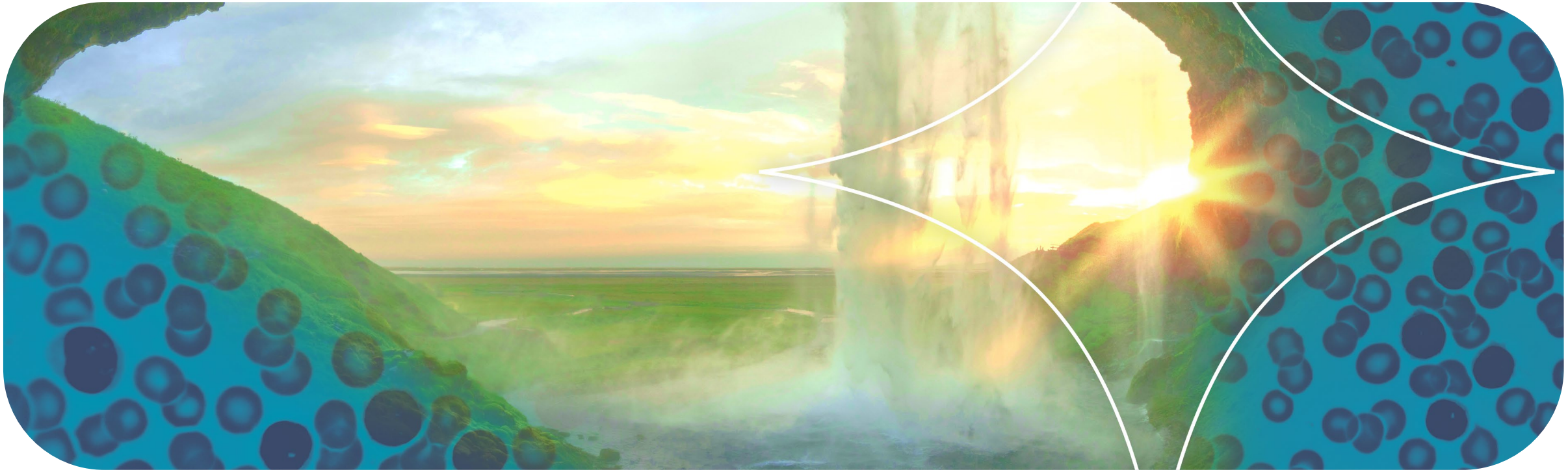

BTKis in WM – Where are we now and where are we going?

Professor Shirley D'Sa FRCP FRCPath MD(Res)
University College London Hospitals NHS Foundation Trust
UCL Cancer Institute, London, UK

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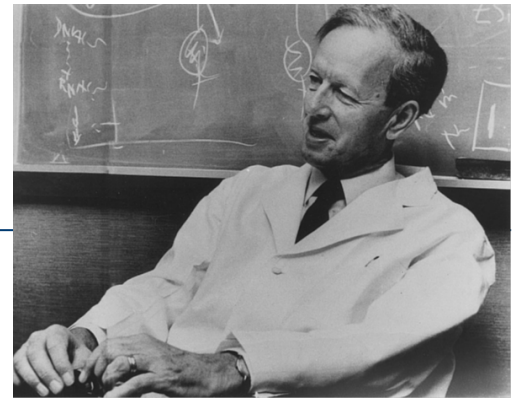
Disclosures

Disclosures	
BeOne	honoraria, speaker fees, congress expenses, grant funding
Sanius Health Ltd	consultancy
Cellectar	advisory board
Ouro Medicines	advisor
Janssen	honoraria for preceptorship

The plasma cell compartment adds a unique dimension to WM



- IgM paraprotein
- Bone marrow infiltration by lymphoplasmacytic lymphoma (LPL)

Clonal B cells
CD19, CD20, CD22, CD24, Sig
Kappa:lambda = 5:1
CD10 is negative
One-fifth are positive for CD5 and CD23
BCL2 present in most cases
Plasma cells
CD38++
CD19++/-
CD56-
CD45++
CD20(+)

WM/LPL - simple model

B cell compartment

- Symptoms related to tumour bulk
- Anaemia
- B symptoms
- Lymph nodes
- Spleen

Plasma cell compartment

- Symptoms attributable to M protein
- Hyperviscosity syndrome
- Neuropathy
- Haemolytic anaemia
- Cryoglobulinaemia
- Immunodeficiency

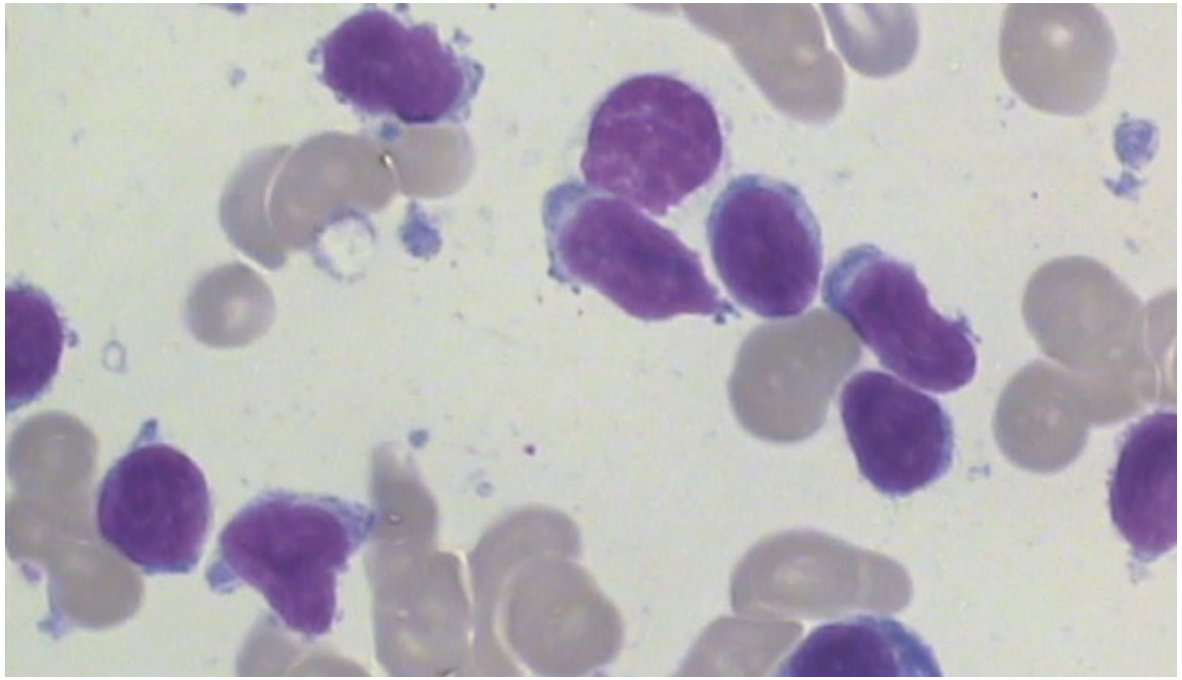
Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BCL2, B-cell lymphoma 2; CD, cluster of differentiation; IgM, immunoglobulin M; LPL, lymphoplasmacytic lymphoma; WM, Waldenström's macroglobulinaemia.

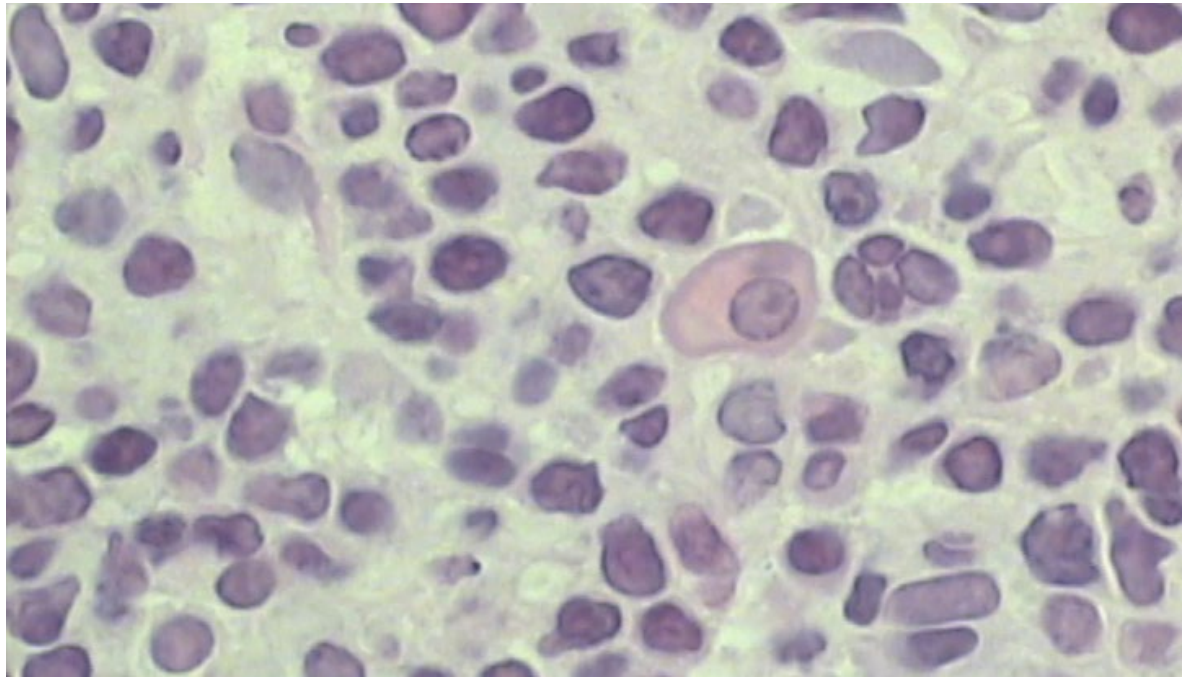
Waldenström's macroglobulinemia: A chronic, incurable paradigm

Indolent lymphoplasmacytic lymphoma associated with IgM paraprotein

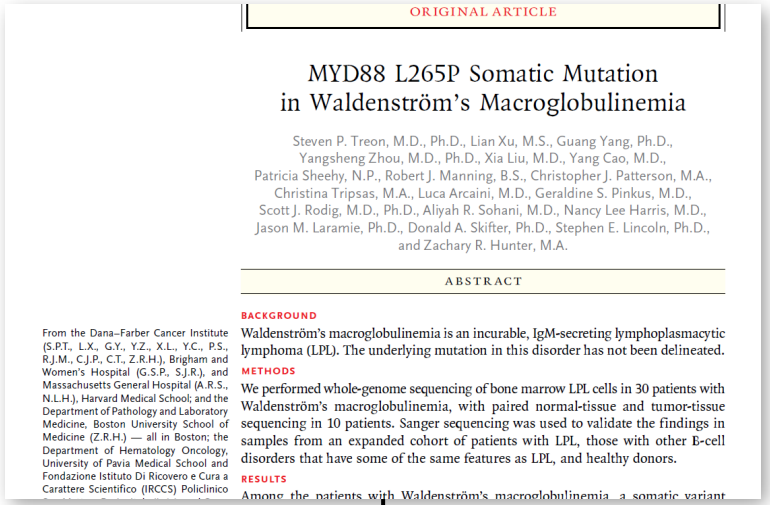
Historically managed as a relapsing–remitting condition

Treatment goals: symptom control and progression delay, not cure





Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
IgM, immunoglobulin M.



ORIGINAL ARTICLE

MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

From the Dana–Farber Cancer Institute (S.P.T., L.X., G.Y., Y.Z., X.L., Y.C., P.S., R.J.M., C.J.P., C.T., Z.R.H.), Brigham and Women's Hospital (G.S.P., S.J.R.), and Massachusetts General Hospital (A.R.S., N.L.H.), Harvard Medical School; and the Department of Pathology and Laboratory Medicine, Boston University School of Medicine (Z.R.H.) — all in Boston; the Department of Hematology Oncology, University of Pavia Medical School and Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico

ABSTRACT

BACKGROUND

Waldenström's macroglobulinemia is an incurable, IgM-secreting lymphoplasmacytic lymphoma (LPL). The underlying mutation in this disorder has not been delineated.

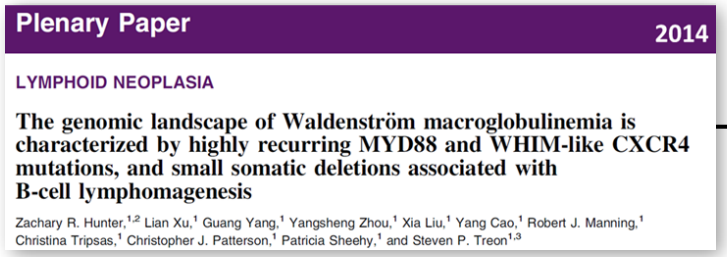
METHODS

We performed whole-genome sequencing of bone marrow LPL cells in 30 patients with Waldenström's macroglobulinemia, with paired normal-tissue and tumor-tissue sequencing in 10 patients. Sanger sequencing was used to validate the findings in samples from an expanded cohort of patients with LPL, those with other B-cell disorders that have some of the same features as LPL, and healthy donors.

RESULTS

Among the patients with Waldenström's macroglobulinemia, a somatic variant

- ***MYD88*** L265P is a commonly recurring mutation in WM (~90% of cases)
- Most patients heterozygous, but UPD at 3p22.2 in a minority
- Present in BCWM.1 and MWCL-1 WM cell lines
- Absent or rarely expressed in MM, MZL (7%), or IgM MGUS (10%)



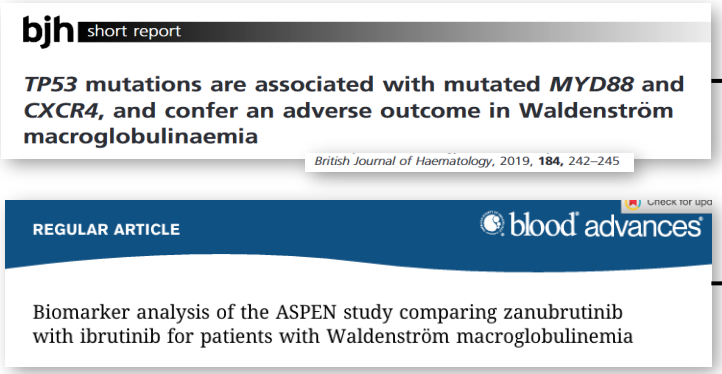
Plenary Paper 2014

LYMPHOID NEOPLASIA

The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis

Zachary R. Hunter,[1,2] Lian Xu,[1] Guang Yang,[1] Yangsheng Zhou,[1] Xia Liu,[1] Yang Cao,[1] Robert J. Manning,[1] Christina Tripsas,[1] Christopher J. Patterson,[1] Patricia Sheehy,[1] and Steven P. Treon[1,3]

- ***CXCR4*** is the second most frequently mutated gene (~30% of cases)
- Almost exclusively present in *MYD88*^{mut} WM
- Associated with pro-survival signalling and possible development of drug resistance, including BTKis



bjh short report

***TP53* mutations are associated with mutated *MYD88* and *CXCR4*, and confer an adverse outcome in Waldenström macroglobulinaemia**

British Journal of Haematology, 2019, **184**, 242–245

REGULAR ARTICLE

blood advances

Biomarker analysis of the ASPEN study comparing zanubrutinib with ibrutinib for patients with Waldenström macroglobulinemia

- ***TP53*** mutations are associated with more aggressive disease
- Patients with *TP53*^{mut} show response to BTKis

BTKi, Bruton's tyrosine kinase inhibitor; MGUS, monoclonal gammopathy of unknown significance; mut, mutated; MZL, marginal zone lymphoma; UPD, uniparental disomy; WM, Waldenström's macroglobulinaemia.

1. Treon SP, et al. *N Engl J Med.* 2012;367(9):826-833. 2. Hunter ZR, et al. *Blood.* 2014;123(11):1637-1646. 3. Gustine JN, et al. *Br J Haematol.* 2019;184(2):242-245. 4. Tam CS, et al. *Blood Adv.* 2024;8(7):1639-1650.

Current treatment landscape

Chemoimmunotherapy works as a frontline treatment and in relapse

Limitations for patients: side effects, toxicity, limited tolerance, prolonged immunosuppression, risk of secondary malignancies/MDS

Limitations in the setting of WM: chemotherapy works on dividing cells

Prominent IgM levels or risk of flares with rituximab

BTK inhibitors: a transformative therapeutic class

BTK inhibitors (ibrutinib, zanubrutinib) target BCR signalling in *MYD88*^{L265P} WM

High response rates and durable disease control in treatment-naïve and relapsed settings

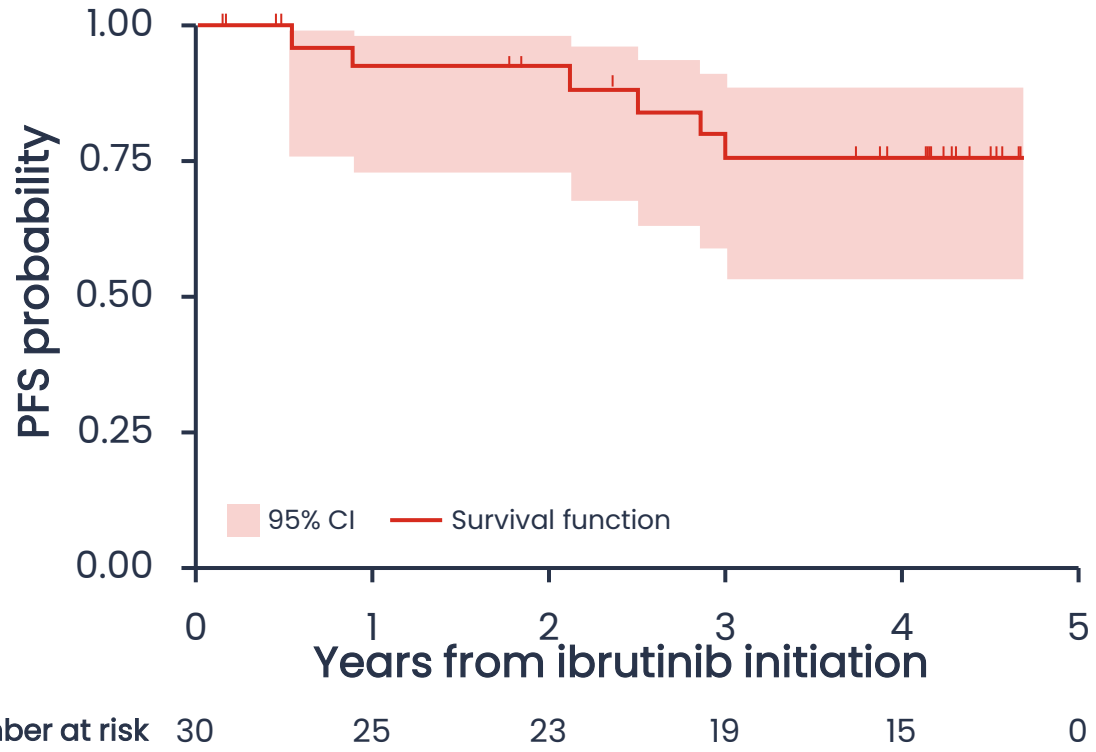
Favourable tolerability enables long-term use

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; IgM, immunoglobulin M; MDS, myelodysplastic syndrome; WM, Waldenström's macroglobulinaemia.

BTK inhibitors overview

- BTKis have demonstrated significant efficacy in the frontline treatment of WM, with PFS outcomes varying based on the specific BTKi used and patient characteristics
  - **Ibrutinib:** Durable efficacy was demonstrated, with a median PFS of approximately 4.5 years[1]
  - **Zanubrutinib:** Deeper and more durable responses versus ibrutinib were observed in the ASPEN study[2]
- **Bing-Neel syndrome:** BTKis cross the BBB[3]
- PFS may be influenced by genetic mutations (e.g., *MYD88/CXCR4/TP53* [?]), patient comorbidities, prior treatments and drug intolerance[2]

PFS with ibrutinib monotherapy[1]



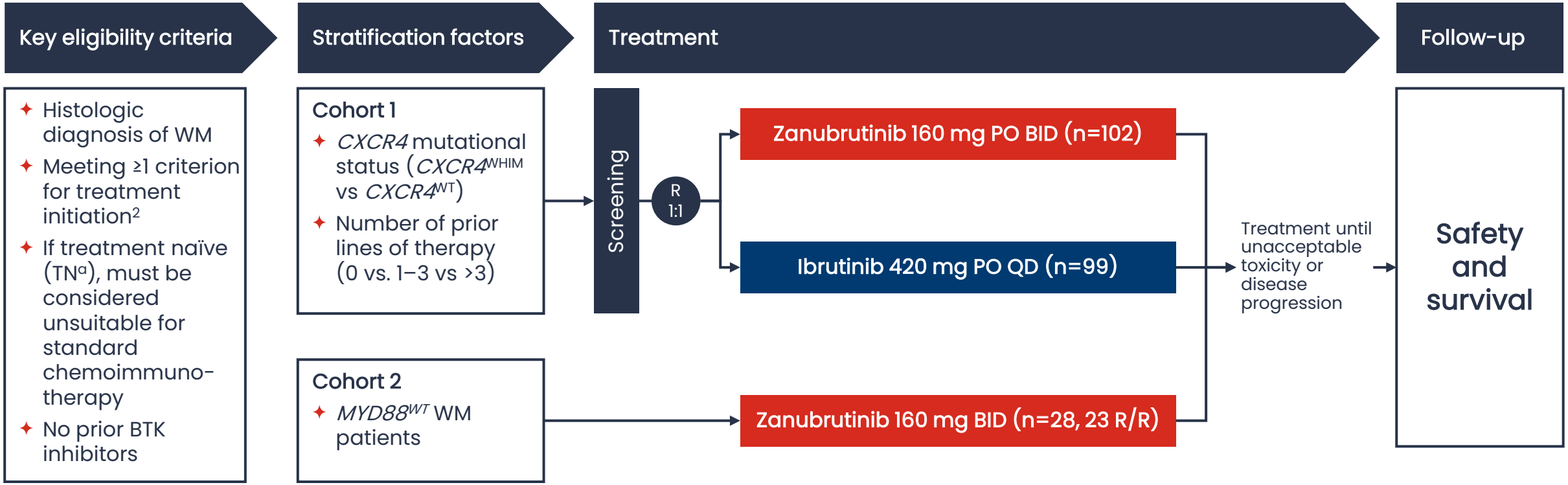
BBB, blood-brain barrier; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; PFS, progression-free survival; WM, Waldenström's macroglobulinaemia.
1. Castillo JJ, et al. *Leukemia.* 2021;36(2):532-539. 2. Dimopoulos MA, et al. *J Clin Oncol.* 2023;41(33):5099-5106. 3. Minnema MC, et al. *Haematologica.* 2017;102(1):43-51.

ASPEN: Trial design

Phase 3 study of zanubrutinib vs ibrutinib in WM

Study identifier:
BGB-3111-302, NCT03053440

Primary endpoint: CR/VGPR rate
Key secondary endpoints: MRR (≥PR), PFS, OS, DOR, symptom resolution, safety
Exploratory endpoints: PK, QoL



Data cutoff: 31 January 2020. Median Follow-up: 19.4 months.
[a]Up to 20% of the overall population.
BID, twice daily, BTK, Bruton tyrosine kinase, CR, complete response; CXCR4, C-X-C motif chemokine receptor 4; DOR, duration of response; MRR, major response rate; MYD88, myeloid differentiation primary response gene 88; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PO, per oral; PR, partial response; QD, once daily; QoL, quality of life; R, randomized; R/R, relapsed/refractory; TN, treatment-naïve; VGPR, very good partial response; WM, Waldenström's macroglobulinemia; WT, wild-type.
1. Tam CS et al. *Blood.* 2020;136(18):2038-2050. 2. Dimopoulos MA et al. *Blood.* 2014;124:1404-1411.

ASPEN: Baseline demographics and disease characteristics

Long-term follow-up

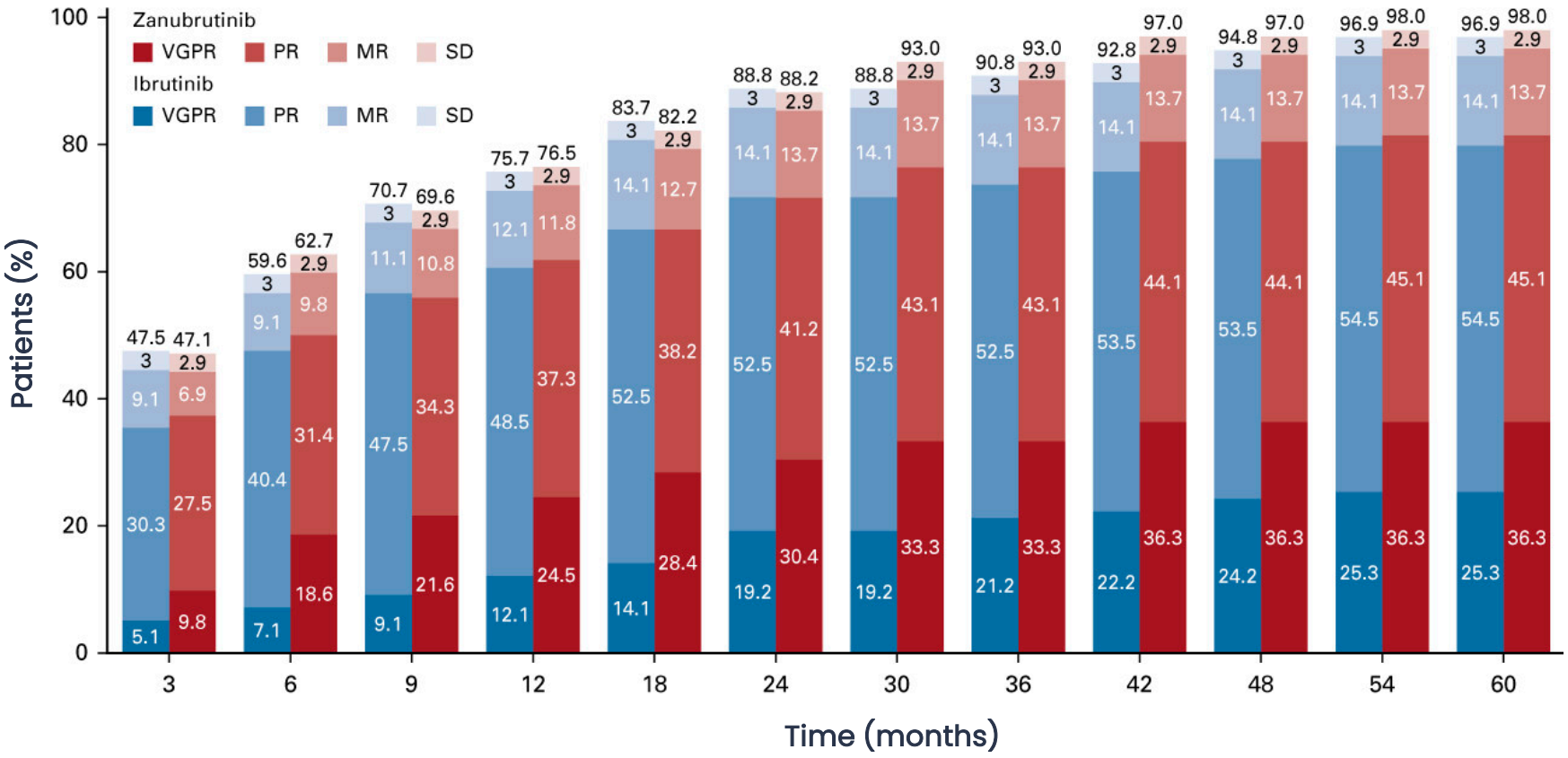
Characteristics	Cohort 1		Cohort 2
	Ibrutinib (n=99)	Zanubrutinib (n=102)	Zanubrutinib (N=28)
Age, years median (range)	70 (38-90)	70 (45-87)	72 (39-87)
>65 years, n (%)	**70 (70.7)**	61 (59.8)	19 (67.9)
>75 years, n (%)	22 (22.2)	**34 (33.3)**	12 (42.9)
Sex, n (%)			
Male	65 (65.7)	69 (67.6)	14 (50.0)
Prior lines of therapy, n (%)			
0	18 (18.2)	19 (18.6)	5 (17.9)
1-3	74 (74.7)	76 (74.5)	20 (71.4)
>3	7 (7.1)	7 (6.9)	3 (10.7)
Genotype by NGS, n (%)			
$CXCR4^{WT}$	72 (72.7)	65 (63.7)	27 (96.4)
$CXCR4^{MUT}$	20 (20.2)	**33 (32.4)**	1 (3.6)
Unknown	7 (7.1)	4 (3.9)	0
IPSS WM, n (%)			
Low	13 (13.1)	17 (16.7)	5 (17.9)
Intermediate	42 (42.4)	38 (37.3)	11 (39.3)
High	44 (44.4)	47 (46.1)	12 (42.9)
Hemoglobin ≤110 g/L, n (%)	53 (53.5)	**67 (65.7)**	15 (53.6)
Baseline IgM (g/L, central lab), median (range)	34.2 (2.4-108.0)	31.8 (5.8-86.9)	28.5 (5.6-73.4)
Bone marrow involvement (%), median (range)	60 (0-90)	60 (0-90)	22.5 (0-50)
Extramedullary disease by investigator, n (%)	66 (66.7)	63 (61.8)	16 (57.1)

- Both arms in cohort 1 were balanced except for patients aged >75 years, patients with *CXCR4*^{MUT} by NGS, and patients with hemoglobin ≤110 g/L, which were higher on the zanubrutinib arm
- In cohort 2, patients aged >75 years were more frequent (42.9%)

Data cutoff: October 31, 2021.
Bold text indicates >10% difference between arms in cohort 1.
CXCR4, C-X-C motif chemokine receptor 4; IgM, immunoglobulin M; IPSS, international prognostic scoring system; MUT, mutant; NGS, next-generation sequencing; WM, Waldenström's macroglobulinemia; WT, wild-type.
Adapted from Dimopolous MA, et al. J *Clin Oncol.* 2023;41(33):5099-5106.

ASPEN: Best overall response by investigator over time

Long-term follow-up



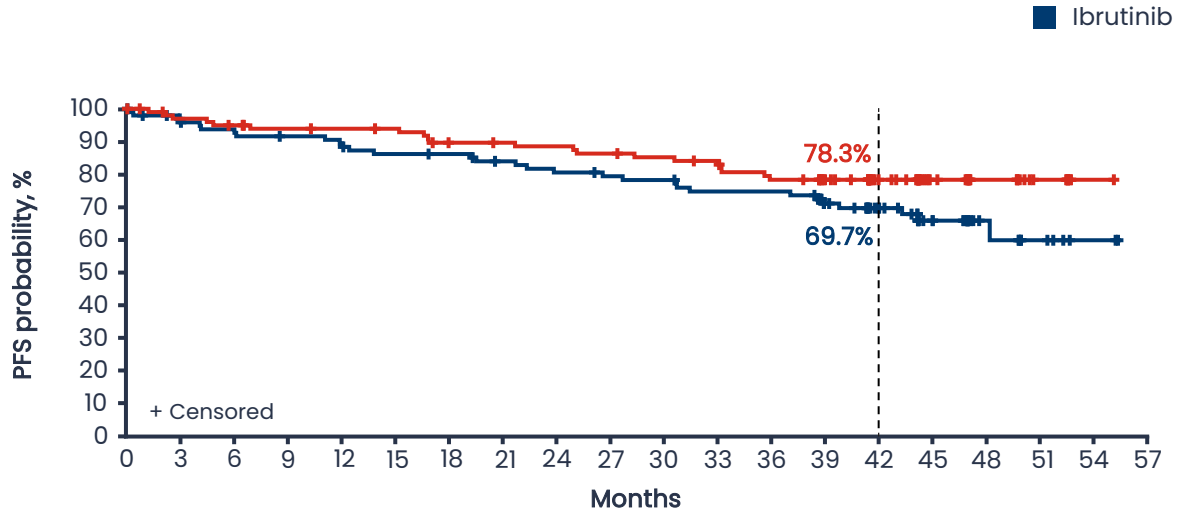
- VGRPR rates increased over time and were numerically higher with zanubrutinib than ibrutinib at all time points
- In *MYD88*^{WT} patients (cohort 2), zanubrutinib demonstrated a CR in 1 patient with MRR of 65% overall (including 31% CR+VGPR)[2]

Data cutoff: October 31, 2021.
CR, complete response; MR, minimal response; MRR, major response rate; MYD88, myeloid differentiation primary response gene 88; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild-type.
1. Dimopoulos MA, et al. *J Clin Oncol.* 2023;41(33):5099-5106. 2. Tam CS. et al. Poster presented at ASCO 2022. Abstract 7521.

ASPEN: Progression-free and overall survivals in ITT population

Long-term follow-up

Progression-free survival[a]

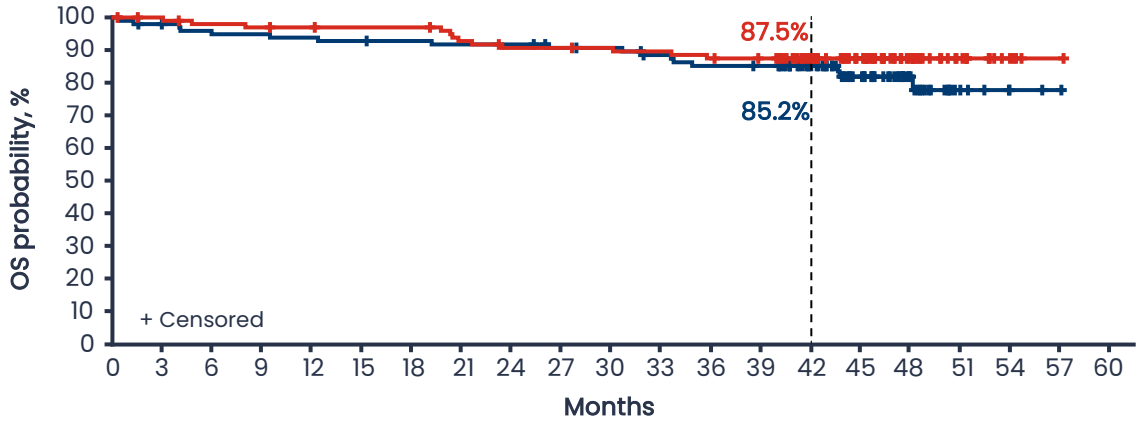


No. of patients at risk:

Zanubrutinib	102	96	93	90	89	88	82	81	80	78	76	74	68	60	43	25	15	8	1	0
Ibrutinib	99	92	88	85	83	79	78	74	71	69	68	64	64	52	41	27	11	6	2	0

	Zanubrutinib	Ibrutinib
Events, n (%)	20 (19.6)	30 (30.3)
HR (95% CI)	0.63 (0.36, 1.12)	

Overall survival[a]



No. of patients at risk:

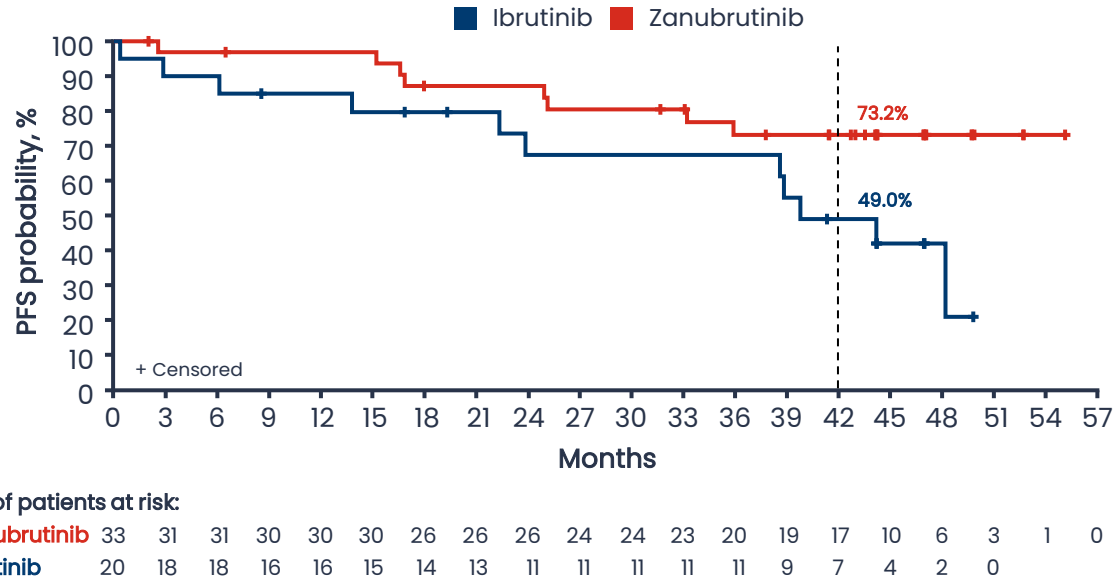
Zanubrutinib	102	100	97	96	95	94	94	89	86	86	85	84	82	80	65	49	27	13	5	1	0
Ibrutinib	99	96	93	92	91	90	89	88	88	85	84	80	77	76	62	43	21	7	3	1	0

	Zanubrutinib	Ibrutinib
Events, n (%)	12 (11.8)	17 (17.2)
HR (95% CI)	0.75 (0.36, 1.59)	

Data cutoff: October 31, 2021.
[a]By investigator assessment.
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.
Adapted from Dimopolous MA, et al. *J Clin Oncol.* 2023;41(33):5099-5106.

ASPEN: PFS in *CXCR4*^{MUT} and response assessment by *CXCR4* status

Long-term follow-up



	Zanubrutinib	Ibrutinib
Events, n (%)	8 (24.2)	11 (55.0)
HR (95% CI)	0.50 (0.20, 1.29)	

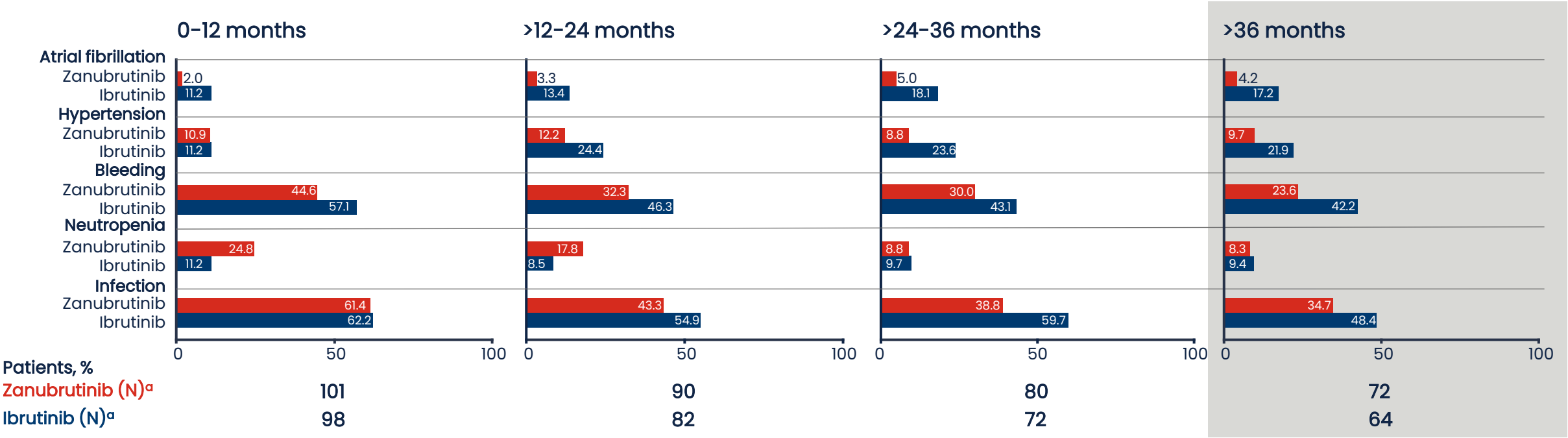
	CXCR4^{MUT}		*CXCR4*^{WT}	
	Ibrutinib (n=20)	Zanubrutinib (n=33)	Ibrutinib (n=72)	Zanubrutinib (n=65)
VGPR or better	2 (10.0)	**7 (21.2)**	22 (30.6)	**29 (44.6)**
Major response	13 (65.0)	**26 (78.8)**	61 (84.7)	54 (83.1)
Overall response	19 (95.0)	30 (90.9)	68 (94.4)	63 (96.9)
Time to major response,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

- In patients with *CXCR4*^{MUT} by NGS, zanubrutinib demonstrated deeper and faster responses, as well as favorable PFS, compared with ibrutinib
- In patients with *TP53*^{mut}, higher VGPR and CR rates, numerically improved MRR, and longer PFS were observed with zanubrutinib vs ibrutinib[2]

Data cutoff: October 31, 2021.
Bold text indicates >10% difference between arms.
[a]*CXCR4* mutation determined by NGS. 92 ibrutinib patients and 98 zanubrutinib patients had NGS results available.
CI, confidence interval; CR, complete response; CXCR4, C-X-C motif chemokine receptor 4; HR, hazard ratio; ITT, intention-to-treat; MRR, major response rate; MUT, mutant; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; VGPR, very good partial response; WT, wild-type.
1. Adapted from Tam CS. et al. Poster presented at ASCO 2022. Abstract 7521. 2. Tam CS, et al. *Blood Adv.* 2024;8(7):1639-1650.

ASPEN: Prevalence analysis for AEs of interest

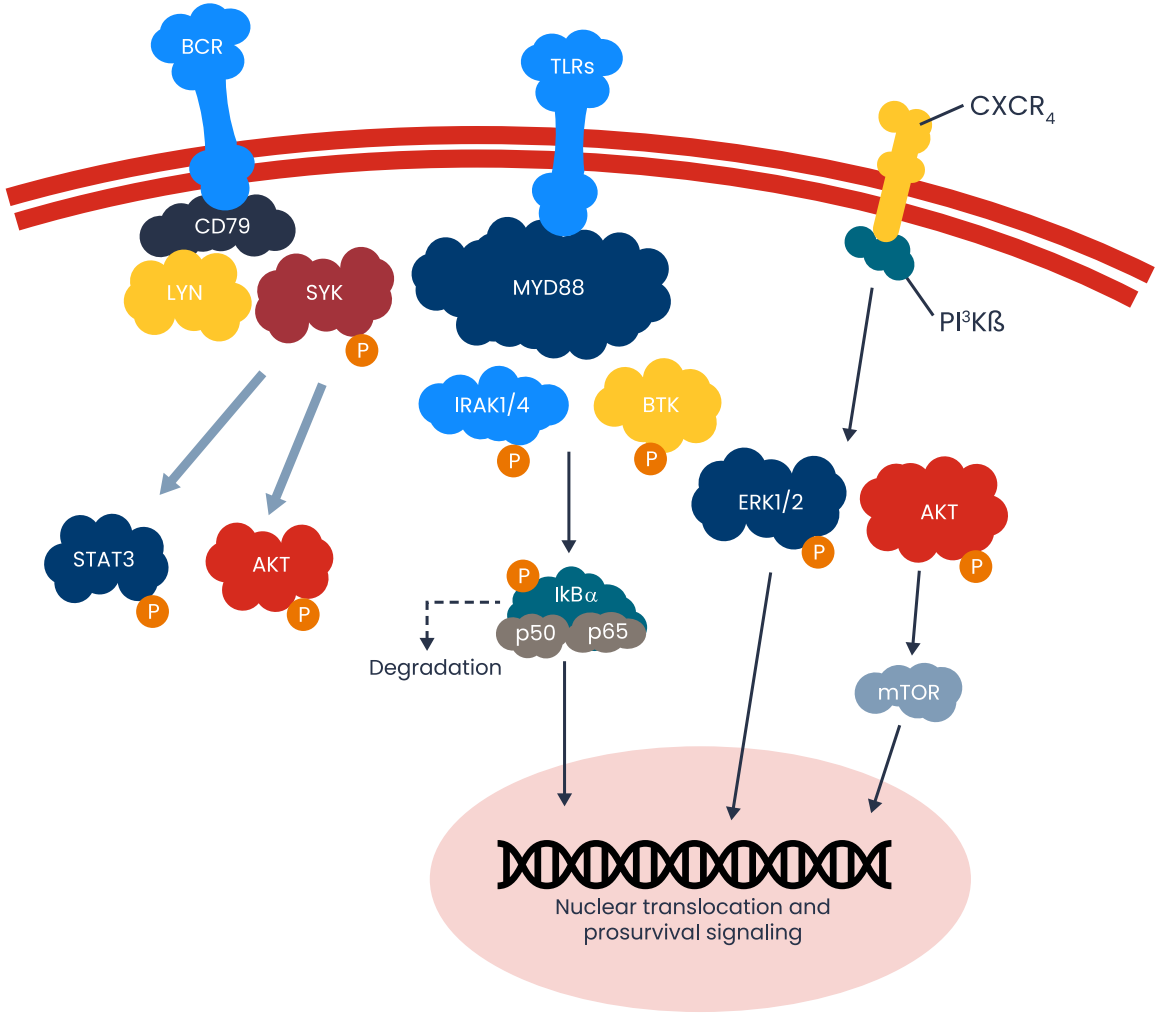
Long-term follow-up



Data cutoff: October 31, 2021.
[a]N is the number of patients who are on treatment in each time interval or who discontinued treatment but the time from first dose date to the earliest date (last dose date +30 days, initiation of new anticancer therapy, end of study, death or cutoff date) is within the time interval.
AE, adverse event.
Adapted from Dimopolous MA, et al. *J Clin Oncol.* 2023;41(33):5099-5106.

Covalent BTK inhibitors – Key considerations in WM

- ***BTK* C481 and *PLCγ2* mutations** affect cBTKi binding or BTK signalling, respectively
- **Alternative pathway upregulation** (PI3K/AKT) promotes survival when BTK is inhibited
- **BCL2 pathway activation** increases expression of anti-apoptotic proteins to evade cell death
- **Clonal evolution and selection of resistance clones** even if WM is more genetically stable than CLL
- ***CXCR4* mutations** (especially nonsense) lead to delayed or reduced responses to BTKis



BCL2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; cBTKi, covalent BTKi; CLL, chronic lymphocytic leukemia; CXCR4, chemokine receptor 4; PLCγ2, phospholipase C γ2; WM, Waldenström's macroglobulinemia.
Image adapted from Treon SP, et al. *J Clin Oncol.* 2020;38(11):1198-1208.

Covalent BTK inhibitors – Emerging opportunities in WM

Non-covalent BTK inhibitors target BTK without requiring covalent binding to C481 - Effective against C481-mutant resistant cases

PROTACs/CDACs mark proteins for destruction through the cell's natural protein degradation system, providing a potentially powerful and selective approach to eliminate disease-causing proteins

BTKi-based combinations with other agents, such as BCL2 or PI3K inhibitors, may help overcome resistance by targeting multiple survival pathways

Targeted therapies inhibiting downstream effectors such as PLCγ2 or pathways parallel to BTK, such as PI3K/AKT, may provide alternative approaches in resistant cases

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BCL2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; CDAC, chimeric degradation activation compound; PROTAC, proteolysis-targeting chimera; WM, Waldenström's macroglobulinaemia.

Non-covalent BTK inhibitors (ncBTKi)

Binding dynamics: ncBTKis bind reversibly to BTK and interact with BTK independently of the C481 site

Efficacy in resistant mutations: ncBTKis can bind to BTK despite resistance mutations, inhibiting B-cell receptor signalling and tumour growth[1]

Safety profile: Fewer side effects, particularly cardiovascular toxicity (e.g., atrial fibrillation and hypertension) and bleeding risks, compared to covalent BTK inhibitors

Future directions: Exploring combinations with anti-CD20 antibodies and BCL2 inhibitors

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BCL2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CD20, cluster of differentiation 20; ncBTKi, non-covalent BTK inhibitor.
1. Palomba LP, et al. Oral presentation at IWWM-12 2024.

Combination therapy with BTK inhibitors

Enhance efficacy:
Chemotherapy can rapidly reduce tumour burden, while BTKis target signalling pathways critical for WM cell survival[1]

Overcome resistance:
Combination therapies prevent or delay the development of resistance mechanisms that can occur with single-agent treatments

Toxicity:
Combining BTKis with chemotherapy may increase the risk of adverse events, including myelosuppression and infections

Patient selection:
Identifying patients who would benefit is crucial, considering factors such as disease burden, genetic mutations, and overall health status

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; WM, Waldenström's macroglobulinaemia.
1. Shuhua YS, et al. Oral presentation at IWWM-12 2024.

Potential options for fixed-term BTKi treatment

1. Combination with anti-CD20 antibodies

- BTKi-naïve patients, including *MYD88*^{WT}, respond well to these agents
- Anti-CD20 Abs induce deeper and faster responses, allowing BTKi discontinuation after a defined period (e.g., 6-12 months)

2. Combination with BCL2 Inhibitors

- BCL2is induce rapid tumour reduction and deep responses, allowing BTKi discontinuation after a set period (e.g., 12 months)[2]

3. Non-covalent BTKis (e.g., pirtobrutinib)

- Suitable for short-term, high-intensity regimens (e.g, 6-9 months)
- Lower toxicity profile
- Re-treatment option upon PD

4. Intermittent dosing regimens

- Potentially reduce cumulative side effects (e.g., CV toxicity)
- Promising activity of "on-and-off" dosing in other B-cell malignancies

5. Sequential therapy with planned discontinuation

- Leverages the initial depth of response achieved after a short BTKi course (e.g., 6–12 months) reducing continuous exposure

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BCL2, B-cell lymphoma 2; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent BTKi; CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; CV, cardiovascular; IgM, immunoglobulin M; PD, progressive disease; WM, Waldenström's macroglobulinemia; WT, wild-type.
1. Buske C, et al. Oral presentation at IWWM-12 2024. 2. Castillo JJ, et al. *J Clin Oncol.* 2022;40(1):63-71.

Operational cure: Reframing the narrative

Median PFS exceeds 5–7 years[1]

In selected patients, disease becomes clinically silent and functionally irrelevant

Raises questions around the conventional boundaries of 'incurable'

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
PFS, progression-free survival.
1. Dimopolous MA, et al. *J Clin Oncol.* 2023;41(33):5099-5106.

Challenges and future opportunities

- Complete eradication of the clonal population remains rare
- MRD negativity uncommon and not yet validated as a surrogate endpoint
- Need for longitudinal data to support operational cure as a meaningful endpoint

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
MRD, minimal residual disease.

Conclusion: Operational cure as a viable therapeutic horizon

BTK inhibitors enable redefinition of success in WM

For a subset of patients, WM may become a biologically dormant condition

Operational cure provides a pragmatic and hopeful reframing of therapeutic goals

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BTK, Bruton's tyrosine kinase; WM, Waldenström's macroglobulinaemia

References

- Buske C, et al. Final analysis of iNNOVATE study: IR vs placebo. Oral presentation at IWWM-12 2024.
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Thank you for your attention

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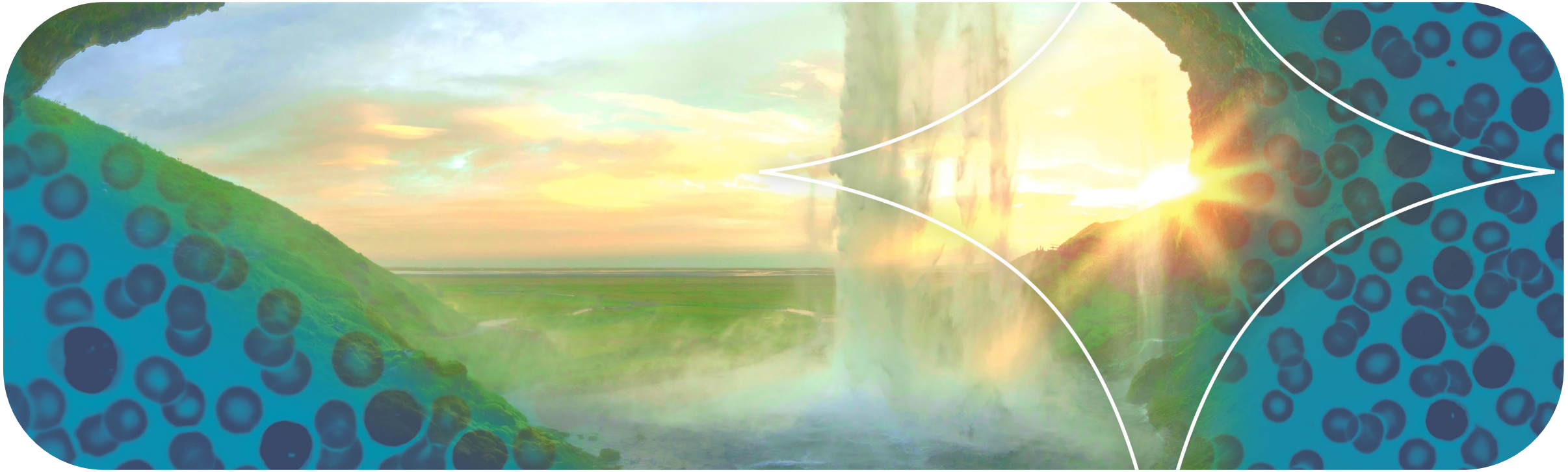


BTKis in MZL and MCL: Current insights and future directions

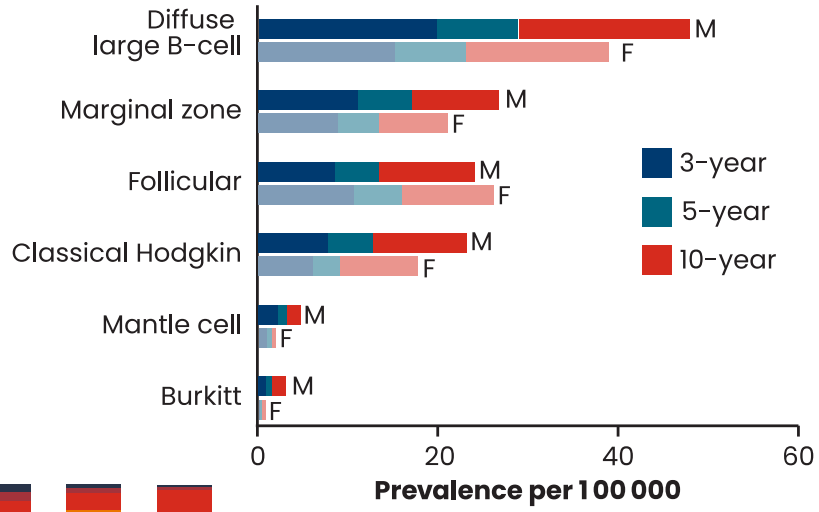
Professor Markus Raderer
Medical University Vienna
Internal Med I, Oncology

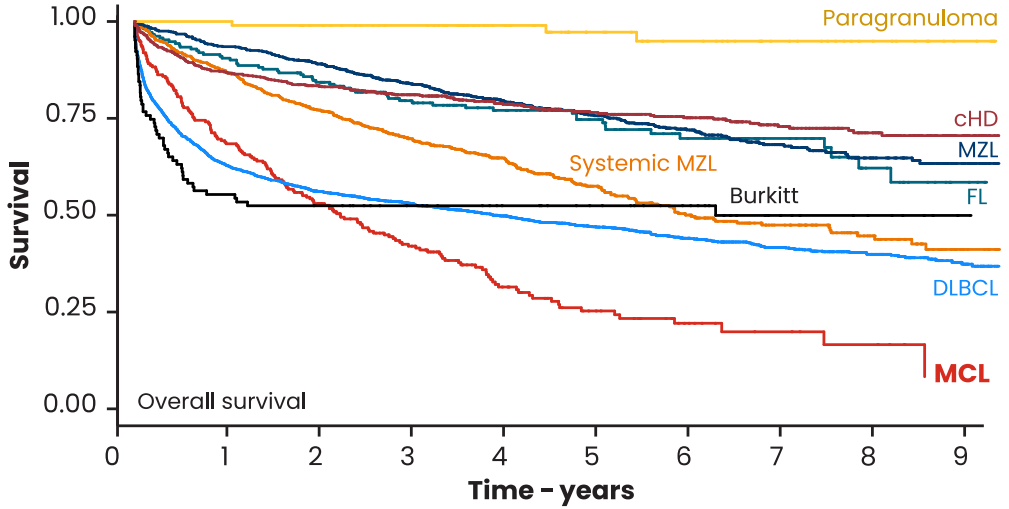
BeOne

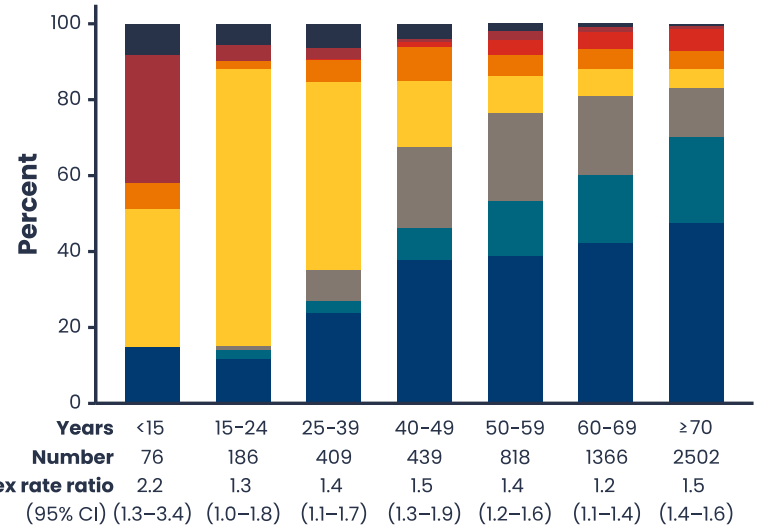
Disclosures

Honoraria	Bayer, BeOne, Eisai, Eli Lilly, Gilead, Ipsen, Johnson + Johnson, Novartis, Pfizer, Roche

"...and now to something completely different..."







Years	<15	15–24	25–39	40–49	50–59	60–69	≥70
Number	76	186	409	439	818	1366	2502
M/F sex rate ratio (95% CI)	2.2 (1.3–3.4)	1.3 (1.0–1.8)	1.4 (1.1–1.7)	1.5 (1.3–1.9)	1.4 (1.2–1.6)	1.2 (1.1–1.4)	1.5 (1.4–1.6)

cHD, classical Hodgkin's disease; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; M/F, male/female; MZL, marginal zone lymphoma.
Adapted from Smith A, et al. *Br J Cancer.* 2015;112(9):1575-1584.

WHO classification 2022

REVIEW ARTICLE OPEN

Check for updates

LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

Rita Alaggio[1], Catalina Amador[2], Ioannis Anagnostopoulos[3], Ayoma D. Attygalle[4], Igu
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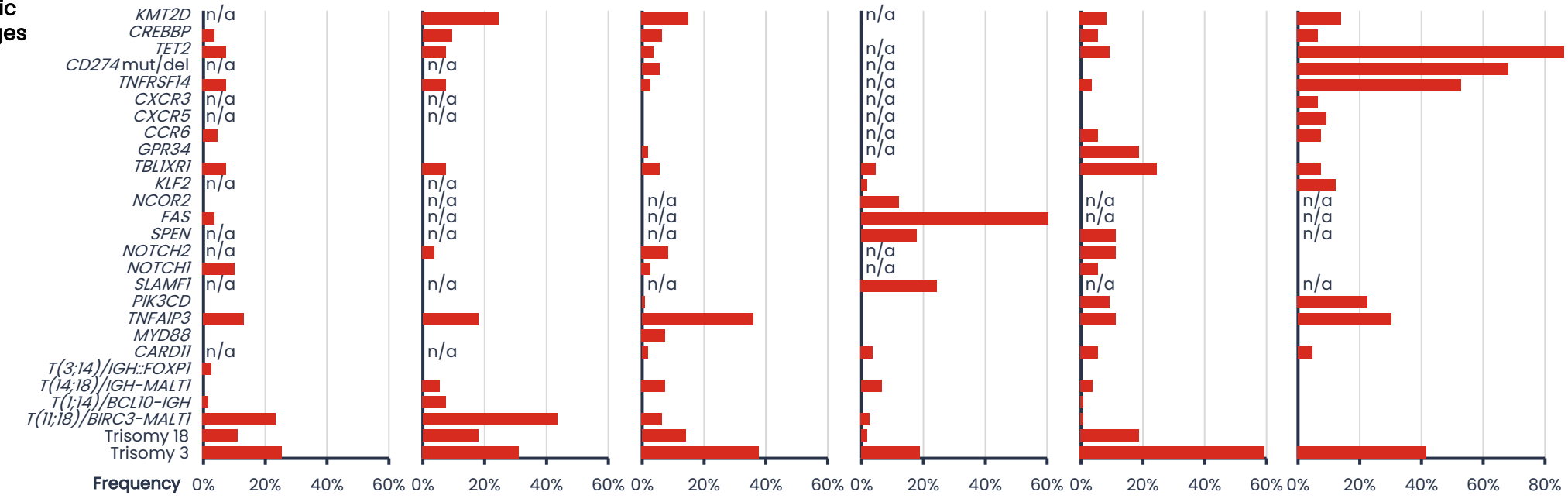
Ashutosh D. Wechalekar[66], Brent Wood[36], Luc Xerri[67] and Wenbin Xiao[53]

Mature B-cell neoplasms	
Pre-neoplastic and neoplastic small lymphocytic proliferations	
Monoclonal B-cell lymphocytosis	(Same)
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	(Same)
(Entity deleted)	B-cell prolymphocytic leukaemia
Splenic B-cell lymphomas and leukaemias	
Hairy cell leukaemia	(Same)
Splenic marginal zone lymphoma	(Same)
Splenic diffuse red pulp small B-cell lymphoma	(Same)
Splenic B-cell lymphoma/leukaemia with prominent nucleoli	*Not previously included* (encompassing hairy cell leukaemia variant and some cases of B-cell prolymphocytic leukaemia)
Lymphoplasmacytic lymphoma	
Lymphoplasmacytic lymphoma	(Same)
Marginal zone lymphoma	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	(Same)
Primary cutaneous marginal zone lymphoma	*Not previously included (*originally included under "extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue")
Nodal marginal zone lymphoma	(Same)
Paediatric marginal zone lymphoma	(Same)

WHO, World Health Organization.
Alaggio R, et al. *Leukemia.* 2022;36(7):1720-1748.

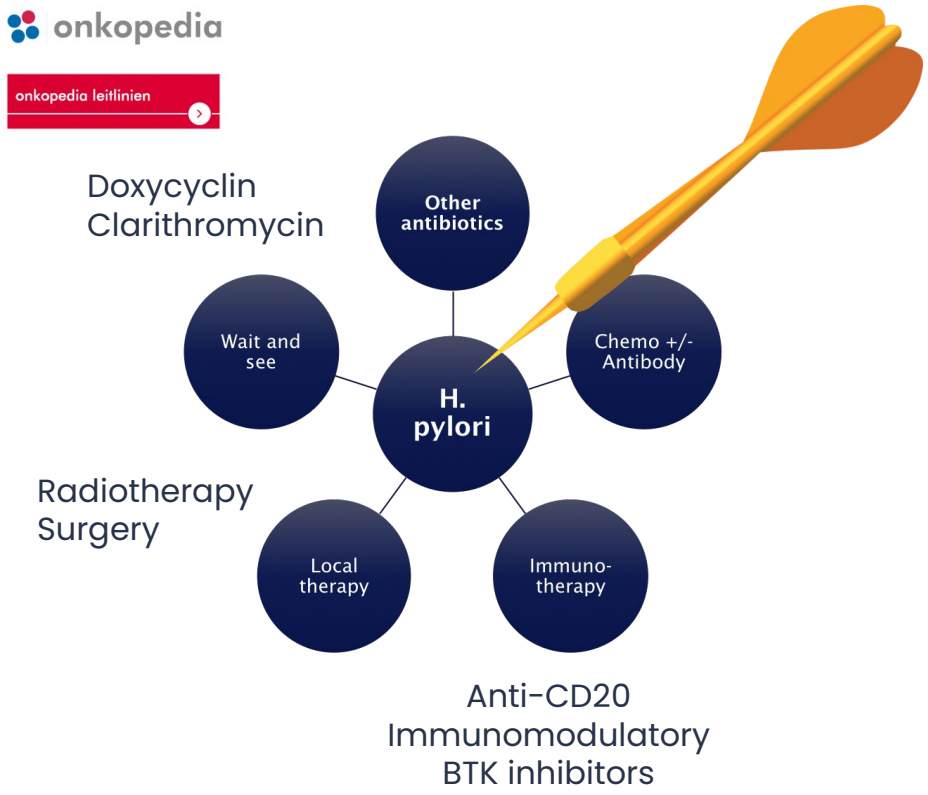
EMZL at various mucosal sites

	Stomach	Lung	Ocular adnexa	Skin	Salivary gland	Thyroid
Aetiology	*Helicobacter pylori*	*Achromobacter xylosoxidans?*	*Chlamydia psittaci*	*Borrelia burgdorferi*	Sjogren syndrome	Hashimoto thyroiditis
IG gene usage	IGHV3-7 IGHV1-69 IGHV1-2 IGHV3-23	IGHV4-34	IGHV4-34 (18%) IGHV3-7 (9%) IGHV3-23 (14%) IGHV3-30 (12%)	IGHV3-23 (12%) IGHV3-30 (12%) IGHV4-59 (12%)	IGHV1-69 (55%) IGHV3-7 (15%) IGHV4-59 IGHV3-30	IGHV3-23 (29%) IGHV3-30 (12%)
Genetic changes						
Association			IGHV4-34 & *TNFAIP3* mut/del IGHV3-23 & *TBL1XR1* mut		*GPR34* mut/trans & *TBL1XR1* mut	*CD274* & *TNFRSF14*

Del, deletion; EMZL, extranodal marginal zone lymphoma; IG, immunoglobulin; IGHV, immunoglobulin heavy chain variable region gene; mut, mutation; n/a, not available; trans, translocation.
Adapted from Raderer M, et al. *Ther Adv Oncol.* 2023;15:17588359231183565.

Treatment strategies in MZL

MALT lymphoma (Onkopedia 2025)[1]

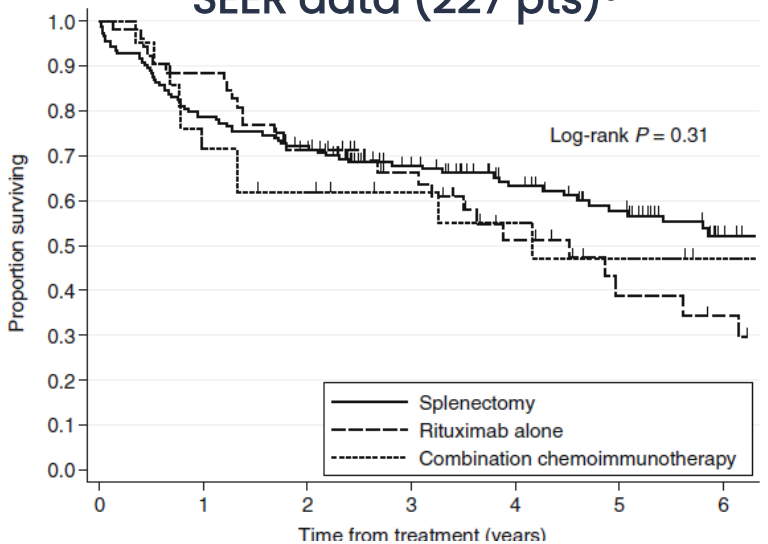


"treatment only in the presence of symptomatic disease"

Splenic MZL (ESMO 2020)[2]

The main criteria for initiating treatment in SMZL are the presence of progressive or symptomatic splenomegaly and/or any progressive cytopenias (hemoglobin <10 g/dl, platelets <80000/µl, neutrophils <1000/µl). Autoimmune disorders such as AIHA or idiopathic thrombocytopenic purpura, if present, should be specifically treated.
Level of evidence: V
Grade of recommendation: B

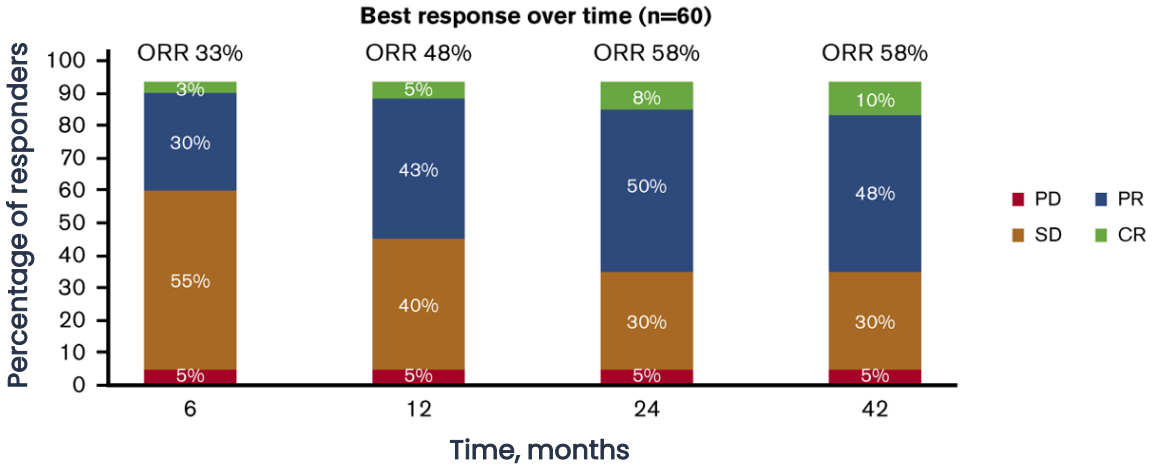
SEER data (227 pts)[3]

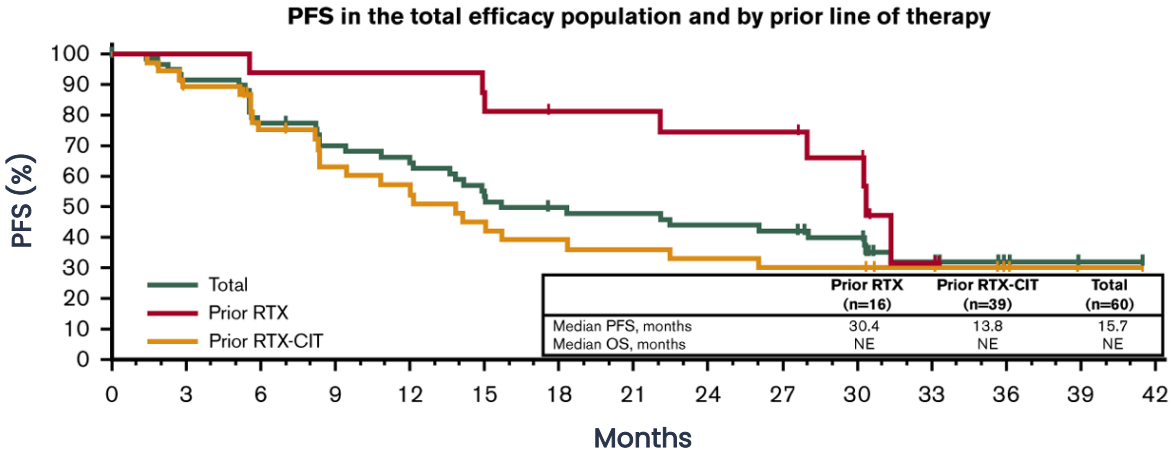


AIHA, autoimmune hemolytic anemia; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; ESMO, European Society for Medical Oncology; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; SMZL, splenic MZL.
1. Raderer M, et al. *Onkopedia.* 2025. 2. Zucca E, et al. *Ann Oncol.* 2020;31(1):17-29. 3. Olszewski AJ, Ali S. *Ann Hematol.* 2014;93(3):449-58.

Durable ibrutinib responses in R/R MZL: Long-term follow-up

Single-agent ibrutinib (560 mg) for R/R MZL





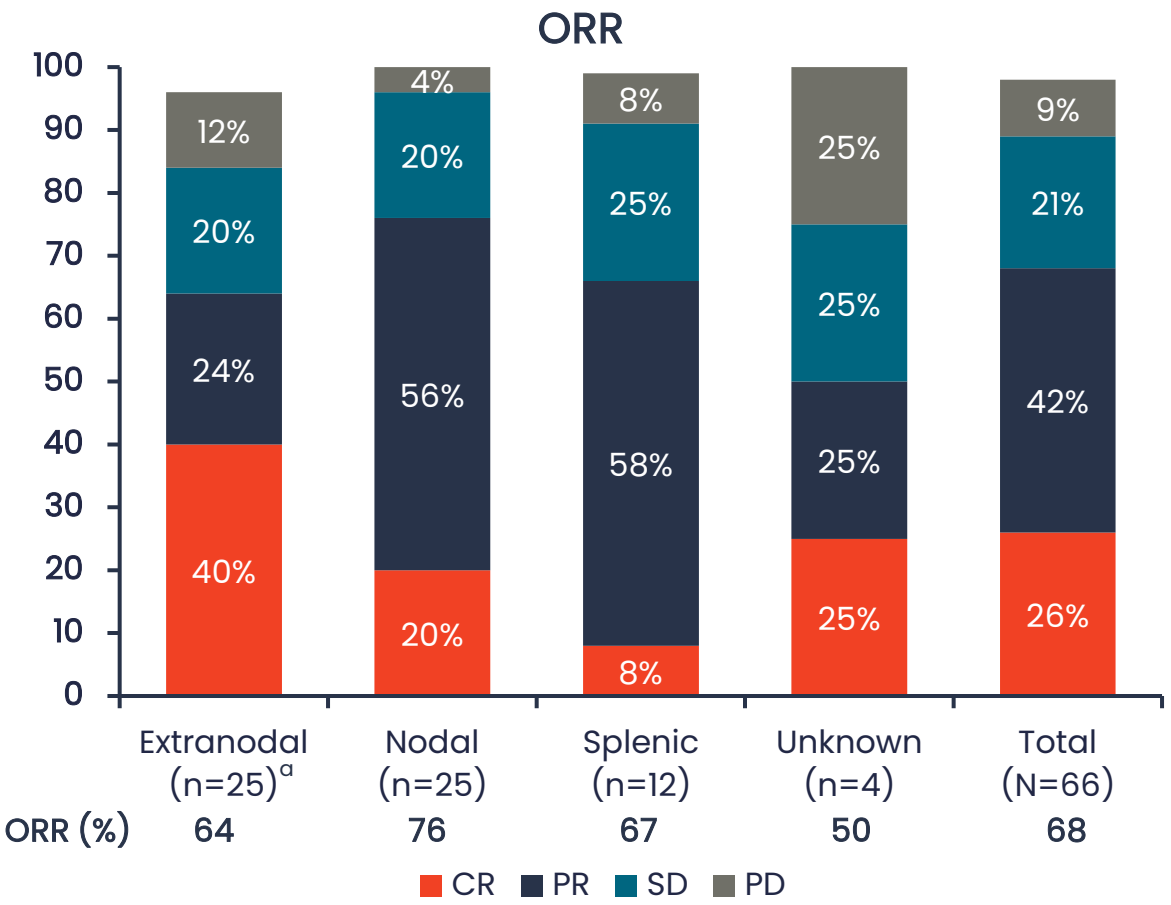
ORR:

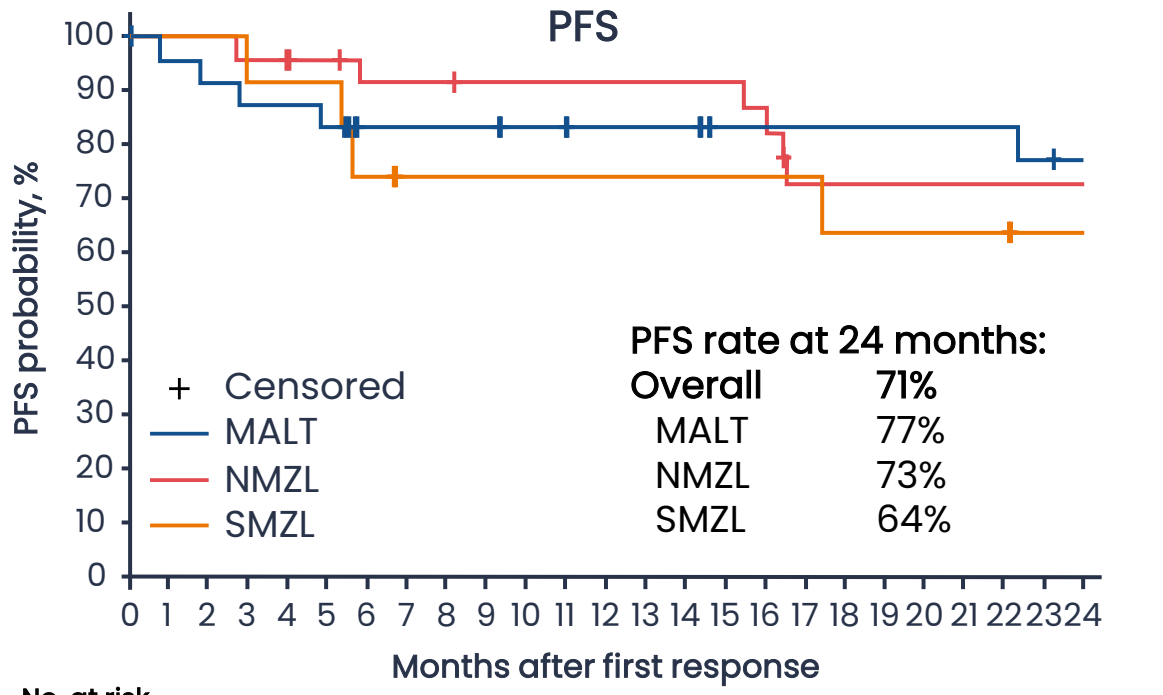
- **EMZL:** 63%
- **nMZL:** 47%
- **sMZL:** 62%

CIT, chemoimmunotherapy; CR, complete response; EMZL, extranodal MZL; MZL, marginal zone lymphoma; NE, not estimable; nMZL, nodal MZL; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; RTX, rituximab; SD, stable disease; SMZL, splenic MZL..
Adapted from Noy A et al. *Blood Adv.* 2020;4(22):5773-5784.

Zanubrutinib in R/R MZL: Phase 2 study (MAGNOLIA)

ORR and PFS by MZL subtypes by IRC assessment





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

Approved after anti-CD20 therapies!

Indications of approved products may differ outside of the European Union. Zanubrutinib is authorized under different conditions (e.g., different government-approved professional information: indications, warnings, etc.) in Switzerland. For country-specific information, refer to the prescribing information for the country in which you practice medicine.

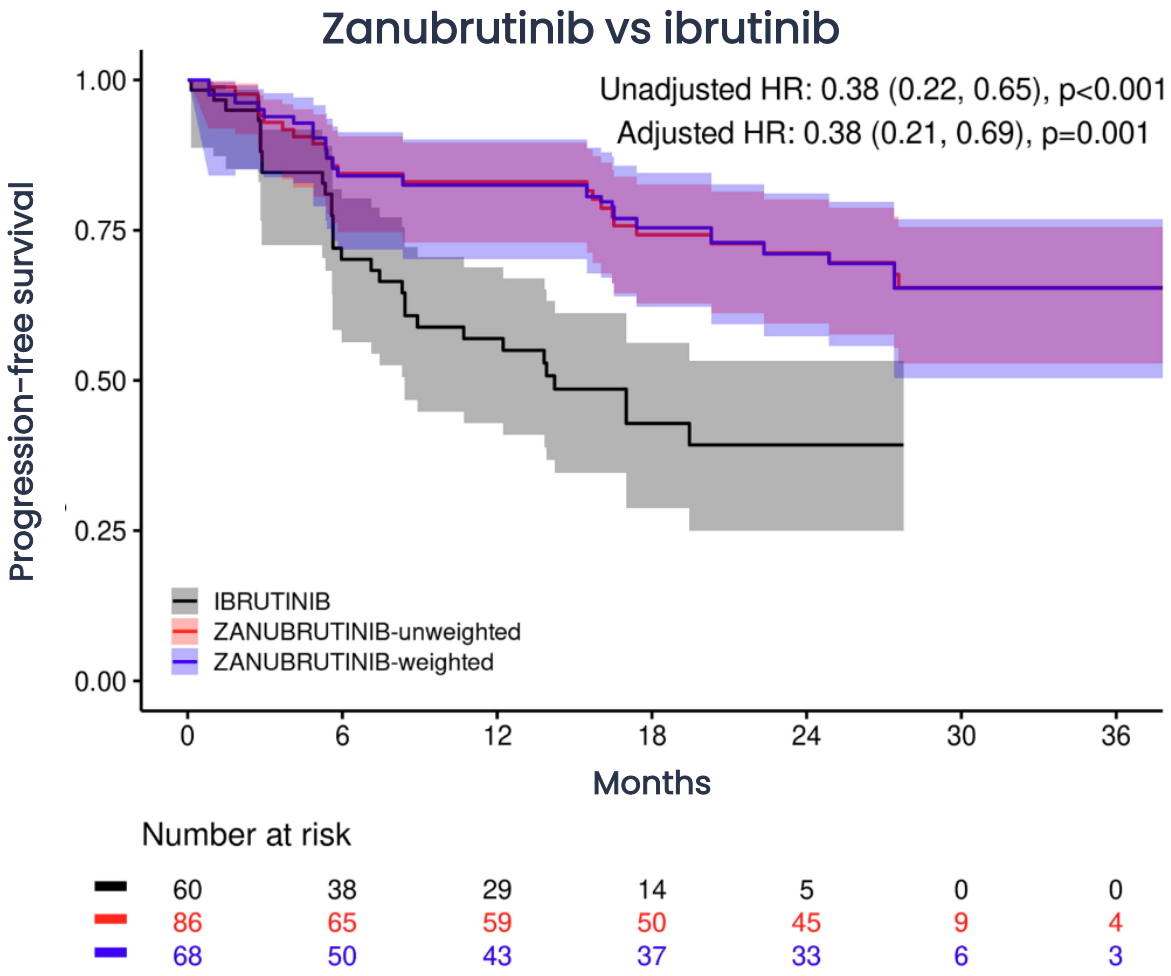
[a]One patient (extranodal MZL) who withdrew consent prior to the first disease assessment was not shown in the graph.

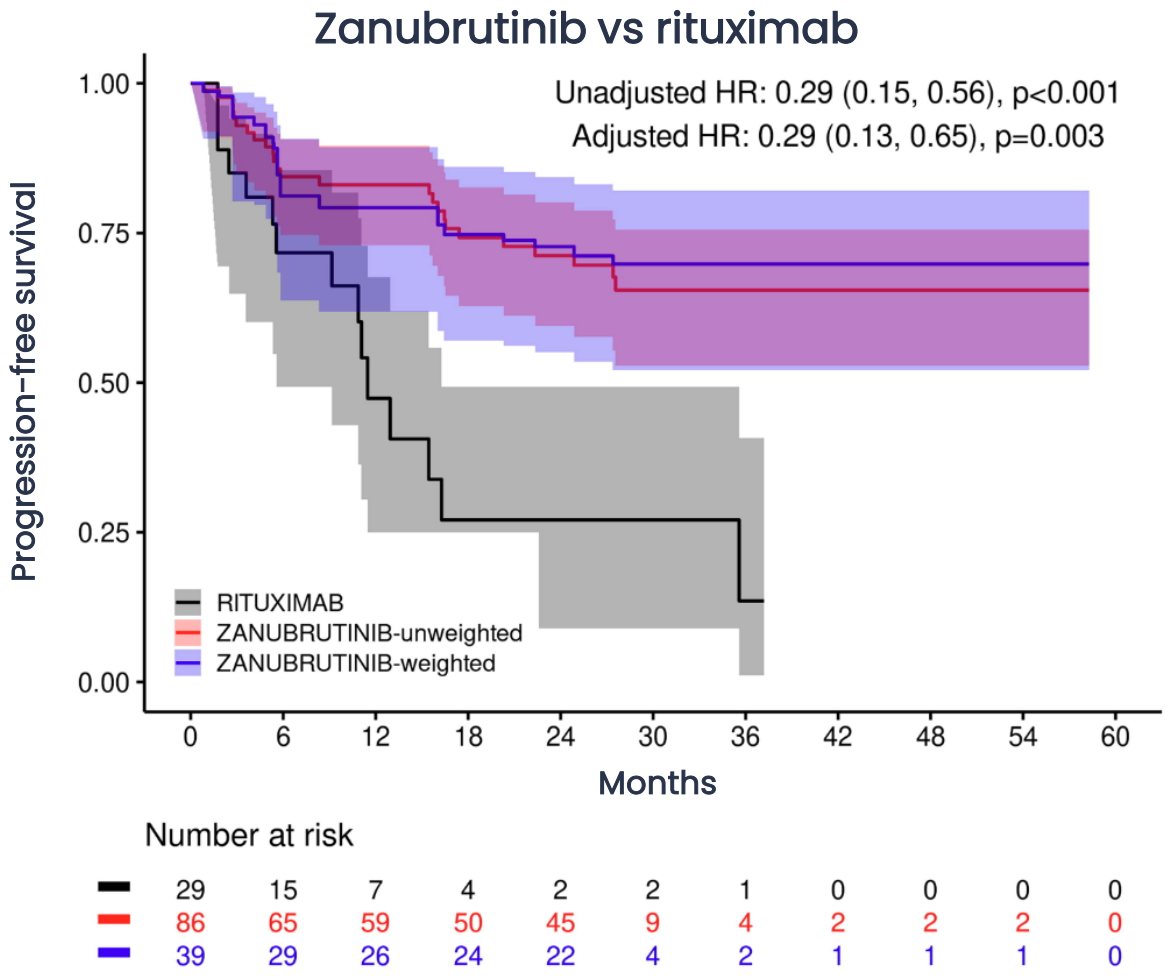
CD, cluster of differentiation; CR, complete response; IRC, independent review committee; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; ORR, overall response rate; PD, progressive disease; PR, partial response; PFS, progression-free survival; R/R, relapsed/refractory; SD, stable disease; SMZL, splenic MZL.

Adapted from Opat S, et al. Oral presentation at ASH 2022. Abstract #234.

Matching-adjusted indirect comparisons of zanubrutinib versus ibrutinib and rituximab in R/R MZL

IRC-assessed PFS before and after matching adjustment





Indications of approved products may differ outside of the European Union. Zanubrutinib is authorized under different conditions (e.g., different government-approved professional information: indications, warnings, etc.) in Switzerland. For country-specific information, refer to the prescribing information for the country in which you practice medicine.

HR, hazard ratio; IRC, independent review committee; MZL, marginal zone lymphoma; PFS, progression-free survival; R/R, relapsed/refractory.

Thieblemont C, et al. *Leuk Lymphoma.* 2025;66(2):240-249.

MCL: "The old standard is dead…."

MCL therapeutic algorithm

Young patient (≤65 years)	Elderly patient (>65 years)	Compromised patient
First-line treatment		
Dose-intensified immunochemotherapy (e.g. R-CHOP, high dose Ara-C) → ASCT → Rituximab maintenance	Conventional immunochemotherapy (e.g. R-CHOP, VR-CAP, BR, R-BAC) → Rituximab maintenance	Best supportive care? R-chlorambucil BR (dose-reduced) R-CVP
Relapse		
Immunochemotherapy (e.g. R-BAC, BR) or **targeted approaches** → Discuss: → AlloSCT	Immunochemotherapy (e.g. BR, R-BAC) or **targeted approaches** → Discuss: → Rituximab maintenance / Radioimmuno-theraphy	Immunochemotherapy (e.g. BR, dose-reduced) or **targeted approaches**
Higher relapse		

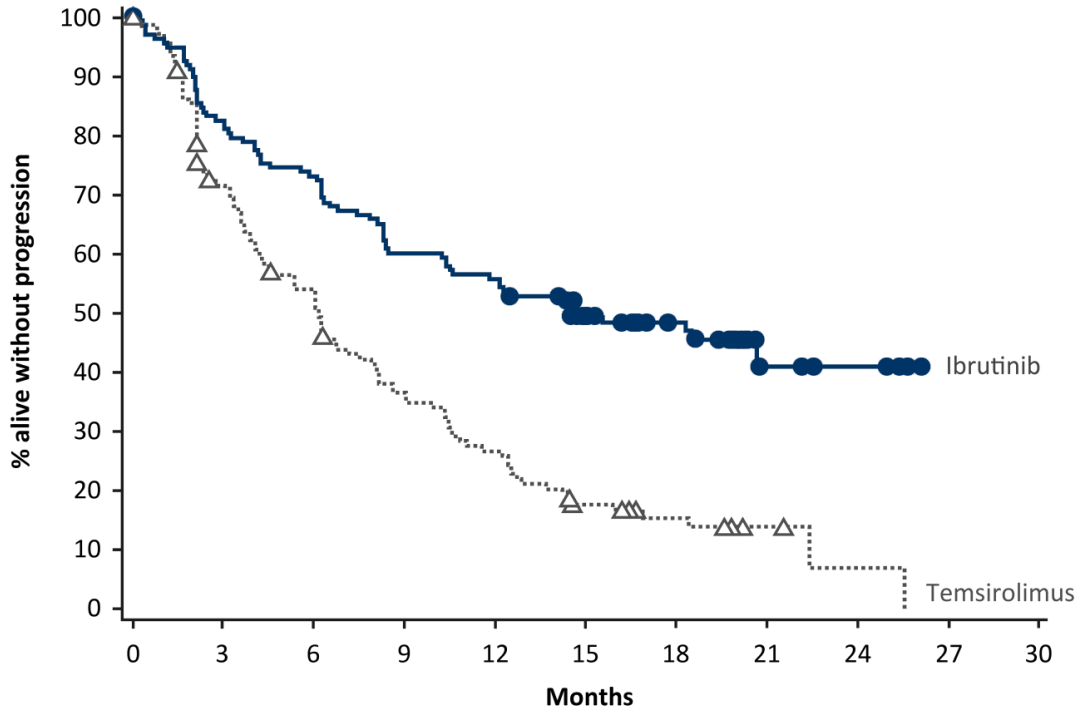
Targeted approaches: ibrutinib, lenalidomide
Temsirolimus, bortezomib (preferable in combination with chemotheraphy)
Alternatively: repeat previous therapy (long remission)

"..hit them hard.....?"

AlloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; BAC, bendamustine and cytarabine; BR, bendamustine and rituximab; Ara-C, cytarabine; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CVP, cyclophosphamide, vincristine and prednisone; R, rituximab; VR-CAP, rituximab, cyclophosphamide, doxorubicin and prednisone with bortezomib.
Adapted from Dreyling M, et al. *Ann Oncol.* 2017;28(suppl_4):iv62-iv71.

Ibrutinib vs temsirolimus in R/R MCL: Phase 3 study (RAY)

Primary endpoint: IRC-assessed PFS



Patients at risk

Ibrutinib	139	114	101	83	77	45	34	8	5	0	0
Temsirolimus	141	93	69	45	33	19	11	3	1	0	0

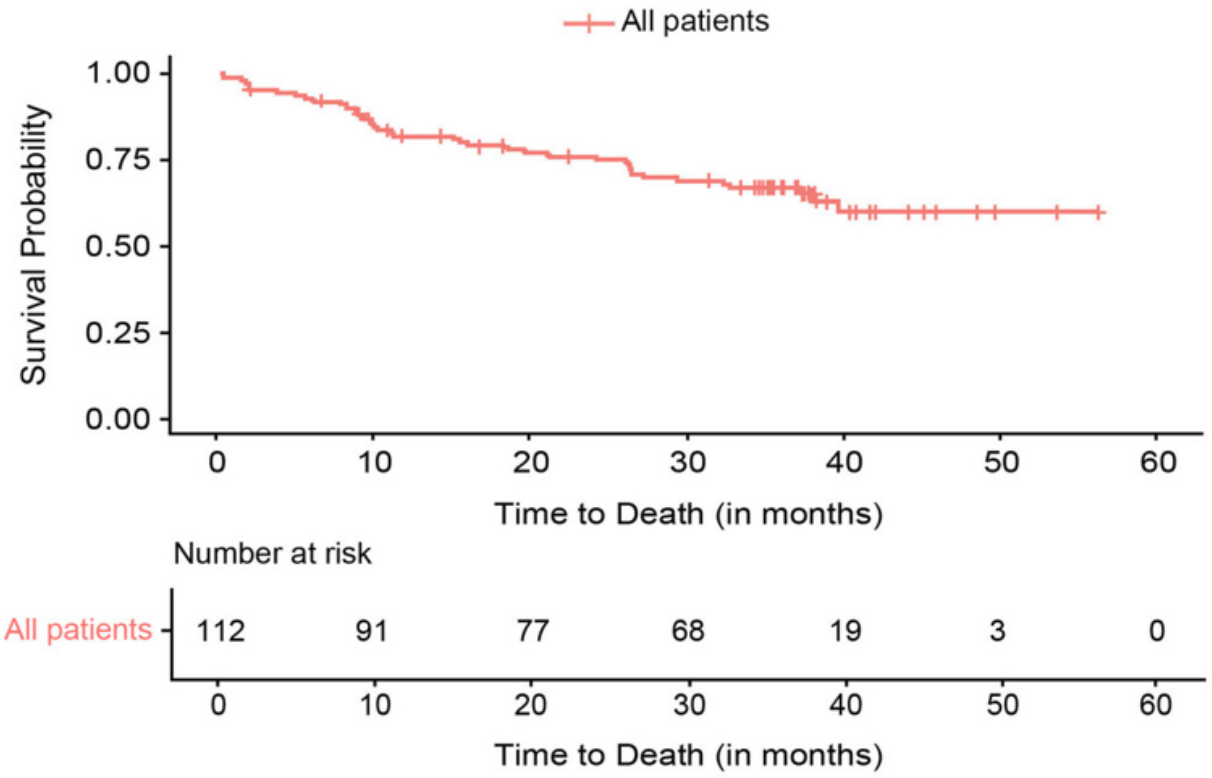
	Ibrutinib	Temsirolimus
Median PFS (months)	14.6	6.2
HR (investigator-assessed)	0.43	
95% CI	0.32–0.58	
Log-rank *p* value	<0.0001	

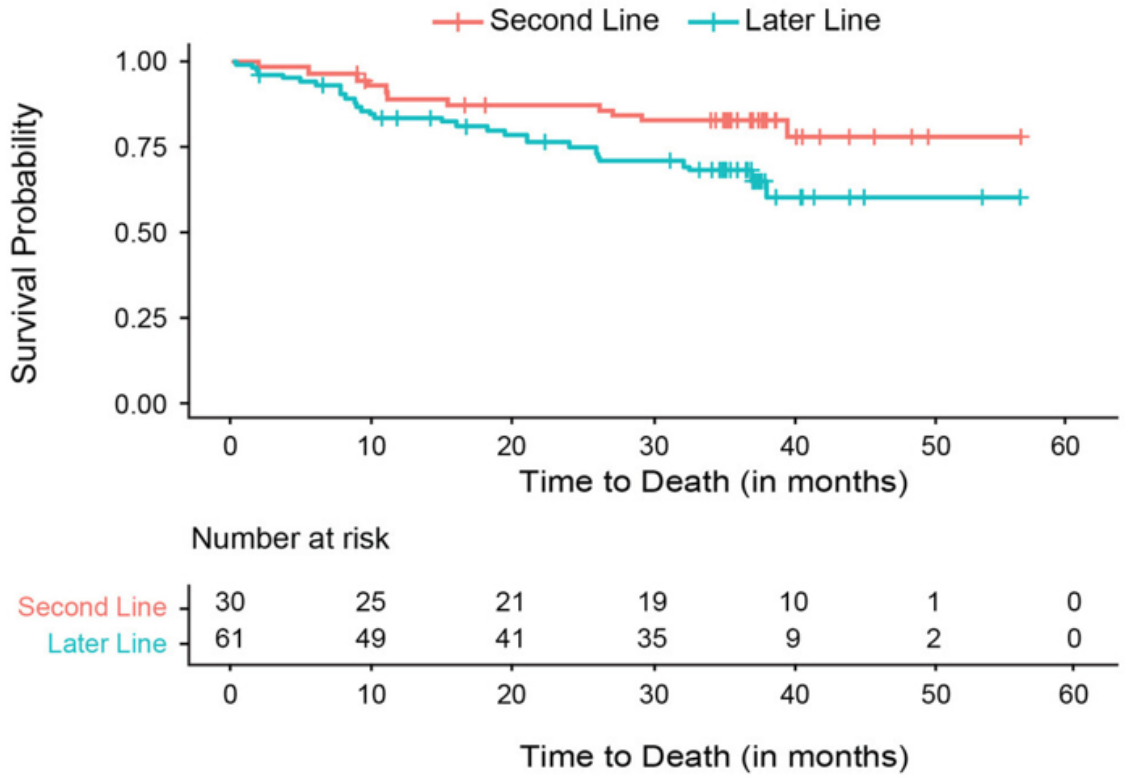
At 2-year landmark: PFS rate 41% (Ibru) vs 7% (Tem)

CI, confidence interval; HR, hazard ratio; Ibru, ibrutinib; IRC, independent review committee; ITT, intention-to-treat; MCL, mantle cell lymphoma; mFU, median follow-up; PFS, progression-free survival; R/R, relapsed/refractory; Tem, temsirolimus.
Adapted from Dreyling M, et al. *Lancet.* 2016;387(10020):770–778.

2L vs 3L+ zanubrutinib in R/R MCL: Pooled analysis

Overall survival





Zanubrutinib in 2L treatment was associated with significantly improved OS compared with later-line treatment (HR, 0.459 [95% CI: 0.215-0.98]; *p*=0.044)

Indications of approved products may differ between countries. Zanubrutinib is authorized under different conditions (e.g., different government-approved professional information: indications, warnings, etc.) in Switzerland. For country-specific information, refer to the prescribing information for the country in which you practice medicine.

2L, second-line; 3L, third-line; CI, confidence interval; HR, hazard ratio; MCL, mantle cell lymphoma; R/R, relapsed/refractory.

Song Y, et al. *Cancer Med.* 2023;12(18):18643-18653.

"…nothing works after BTKi…?"

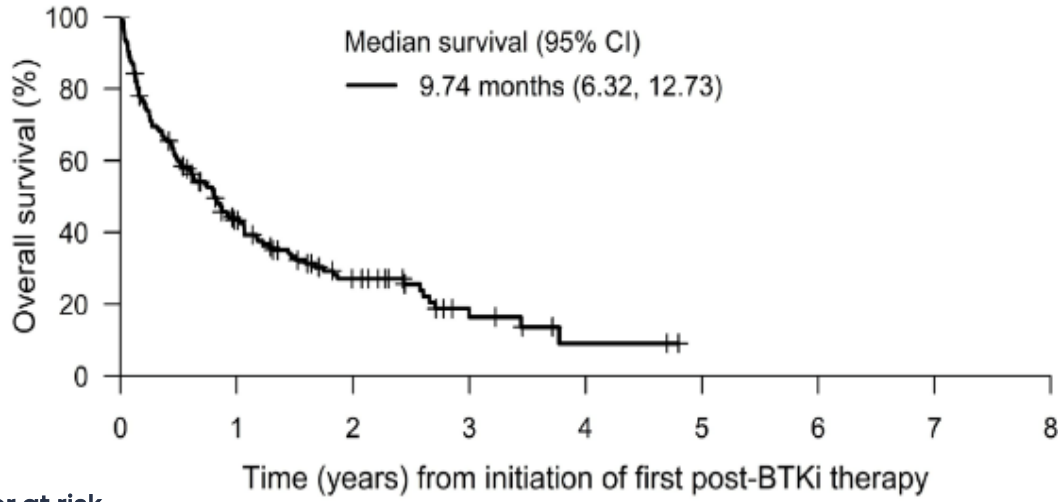
Received: 14 June 2022 | Accepted: 5 October 2022
DOI: 10.1111/bjh.18519

BJHaem

ORIGINAL PAPER

Real-world experience among patients with relapsed/refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor failure in Europe: The SCHOLAR-2 retrospective chart review study

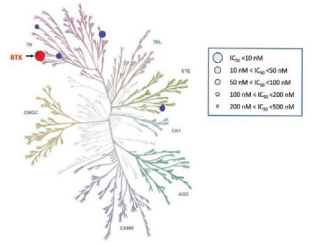
Georg Hess[1] | Martin Dreyling[2] | Lucie Oberic[3] | Eva Gine[4] | Pier Luigi Zinzani[5] | Kim Linton[6] | Adam Vilmar[7] | Mats Jerkeman[8] | Jenny M. H. Chen[9] | Anke Ohler[1] | Stephan Stilgenbauer[10] | Catherine Thieblemont[11] | Jonathan Lambert[12] | Vittorio Ruggero Zilioli[13] | Juan-Manuel Sancho[14] | Ana Jiménez-Ubieto[15] | Luca Fischer[2] | Toby A. Eyre[16] | Sam Keeping[9] | Julie E. Park[9] | James J. Wu[17] | Rubina Siddiqi[17] | John Reitan[18] | Sally Wade[19] | Gilles Salles[20]



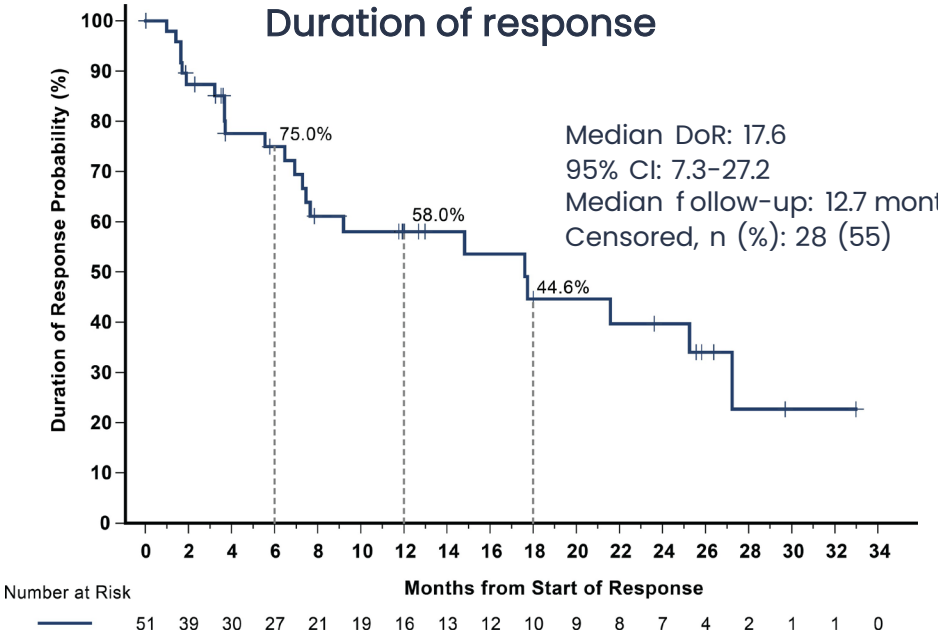
Number at risk (number censored) 149 (0) 54 (15) 24 (27) 7 (38) 2 (41)

BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval.
Hess G, et al. *Br J Haematol.* 2023; 202(44):749-759.

Non-covalent BTKi: Pirtobrutinib (BRUIN)

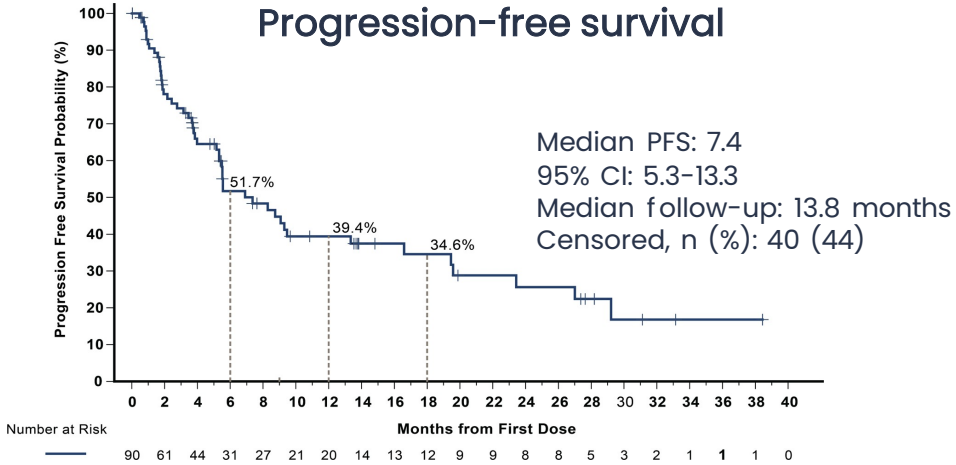


Duration of response

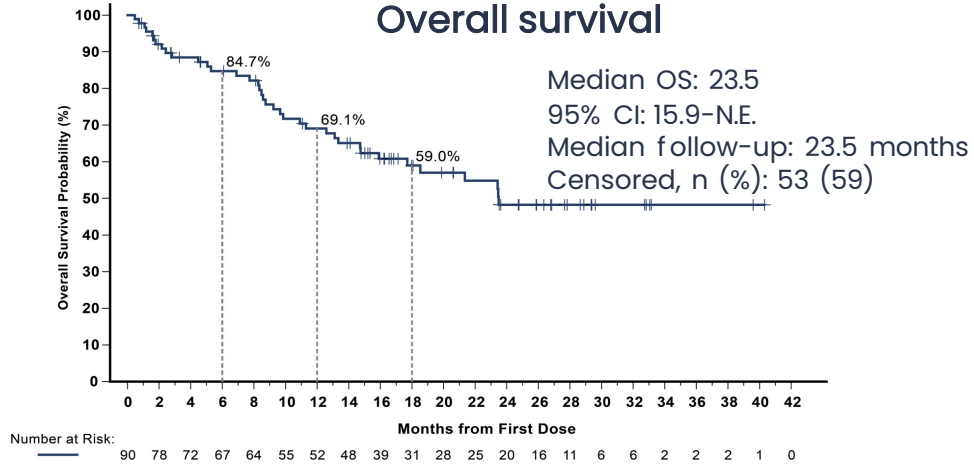


Overall response rate, % (95% CI)	56.7% (45.8-67.1)
CR, n (%)	17 (18.9)
PR, n (%)	34 (37.8)
SD, n (%)	16 (17.8)
PD, n (%)	14 (15.6)

Progression-free survival



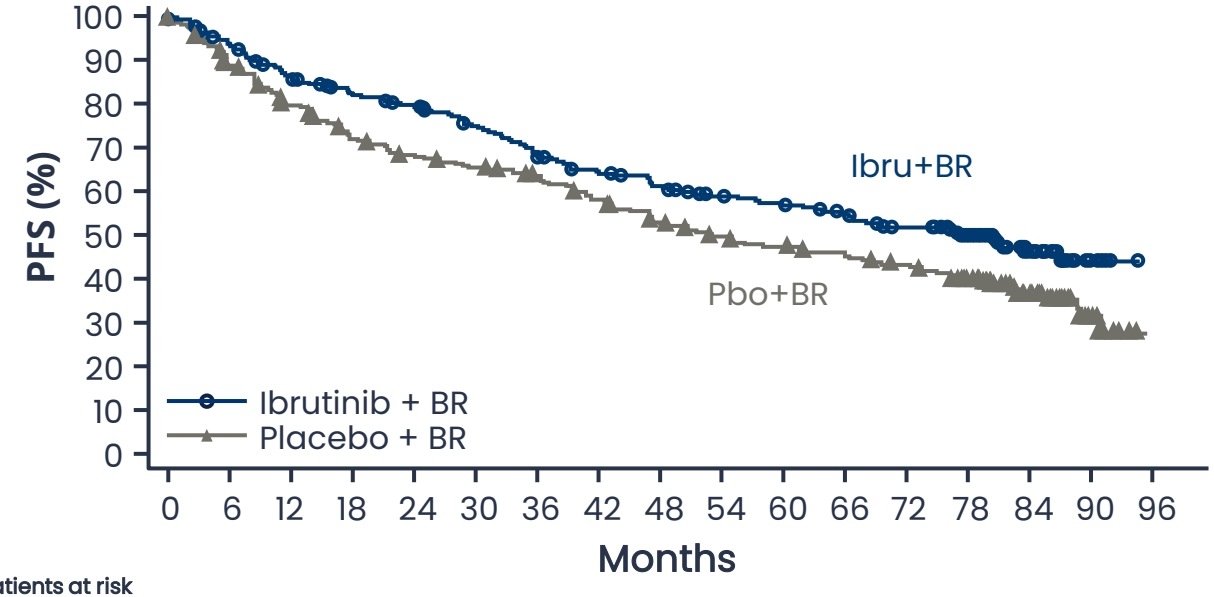
Overall survival



Data cutoff date of 29 July 2022. Response status per Lugano 2014 criteria based on IRC assessment.
BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CR, complete response; DoR, duration of response; IRC, independent review committee; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; OS, overall survival; SD, stable disease.
Shah NN, et al. *J Clin Oncol.* 2023; 41(suppl 16):7514.

SHINE: Phase 3 study of ibrutinib+BR vs BR in TN MCL

- Ibrutinib + BR and R maintenance showed 25% reduction in risk of PD or death[1]
- Significant improvement in median PFS by 2.3 years (6.7 vs 4.4 years)[1]



Patients at risk

Ibrutinib + BR	261	228	207	191	182	167	152	139	130	120	115	106	95	78	39	11	0
Placebo + BR	262	226	199	177	166	158	148	135	119	109	103	98	90	78	41	11	0

	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median PFS, months (95% CI)	80.6 (61.9-NE)	52.9 (43.7-71.0)
Stratified HR (95% CI)	0.75 (0.59-0.96)	
p value	0.011*[2]	

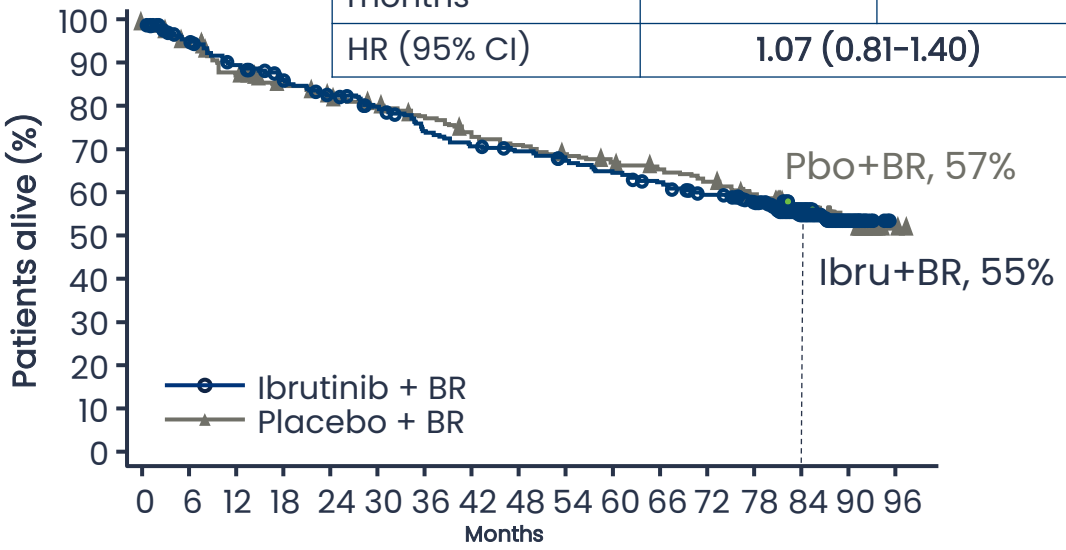
*Significance boundary for superiority was $p < 0.023$.

Primary endpoint of improved PFS was met

BR, bendamustine+rituximab; CI, confidence interval; HR, hazard ratio; Ibru, ibrutinib; NE, not evaluable; Pbo, placebo; PD, progressive disease; PFS, progression-free survival; R. rituximab.
Adapted from: 1. Wang M et al. *N Engl J Med.* 2022;386(26):2482-2494. 2. Wang M et al. *J Clin Oncol.* 2022;40(17_suppl):LBA7502.

SHINE: No OS benefit for addition of ibrutinib to BR

	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median OS, months	NR	NR
HR (95% CI)	1.07 (0.81-1.40)	



Patients at Risk

Ibrutinib + BR	261	239	221	208	197	187	171	163	158	152	145	138	128	118	70	25	0
Placebo + BR	262	244	223	212	203	197	188	177	171	165	159	154	147	137	90	31	2

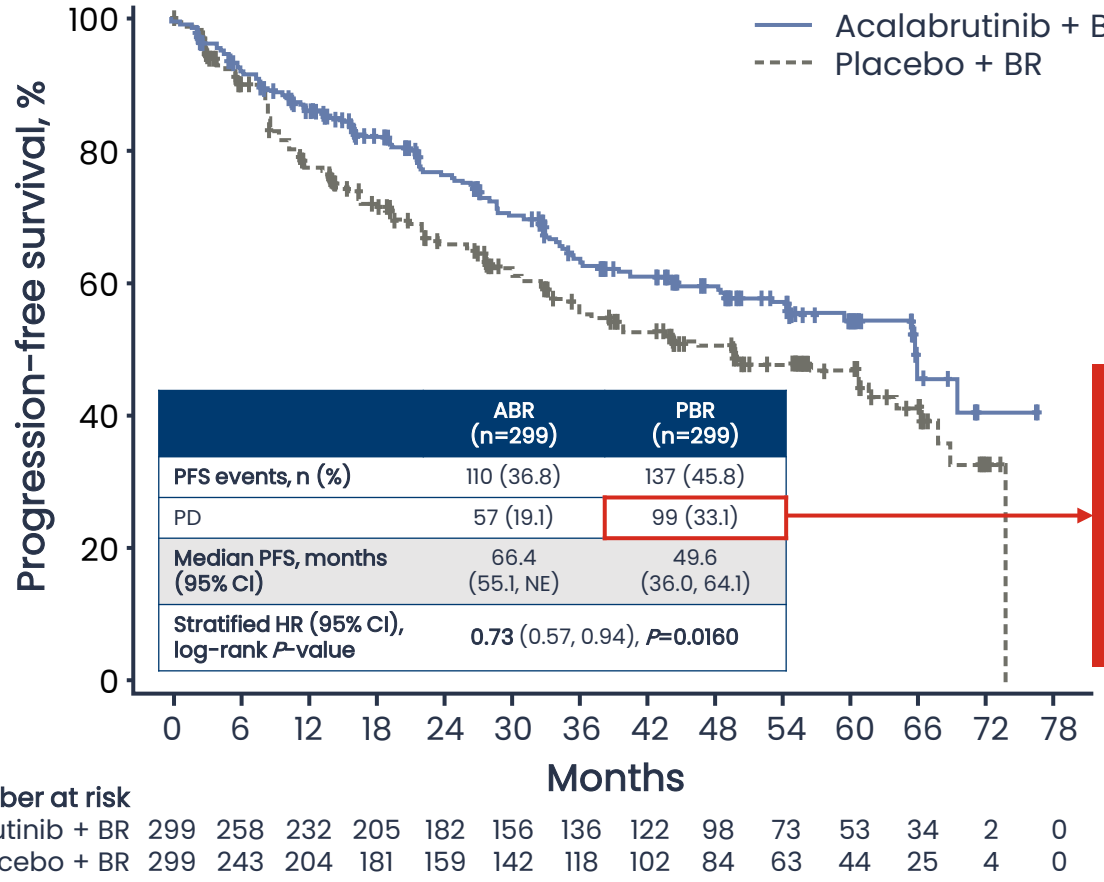
Cause of death	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Death due to PD and TEAE	58 (22.2%)	70 (26.7%)
Death due to PD	30 (11.5%)	54 (20.6%)
Death due to TEAEs	28 (10.7%)	16 (6.1%)
Death during post-treatment follow-up period excluding PD	46 (17.6%)	37 (14.1%)
Total deaths	104 (39.8%)	107 (40.8%)

- Death due to COVID-19 occurred in 3 patients in the ibrutinib arm during the TEAE period and in 2 patients in the placebo arm after the TEAE period
- The most common Grade 5 TEAE was infections in the ibrutinib and placebo arms: 9 versus 5 patients. Grade 5 TEAE of cardiac disorders occurred in 3 versus 5 patients, respectively
- **Exploratory analysis of cause-specific survival including only deaths due to PD or TEAEs showed an HR of 0.88**

BR, bendamustine+rituximab; CI, confidence interval; HR, hazard ratio; Ibru, ibrutinib; NR, not reached; OS, overall survival; Pbo, placebo; PD, progressive disease; TEAE, treatment-emergent adverse event.
Adapted from Wang M et al. *N Engl J Med.* 2022;386(26):2482-2494.

ECHO: BR + acalabrutinib vs BR + placebo in TN MCL

Primary endpoint: PFS



	ABR (n=299)	PBR (n=299)
PFS events, n (%)	110 (36.8)	137 (45.8)
PD	57 (19.1)	99 (33.1)
Median PFS, months (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
Stratified HR (95% CI), log-rank *P*-value	**0.73** (0.57, 0.94), ***P*=0.0160**	

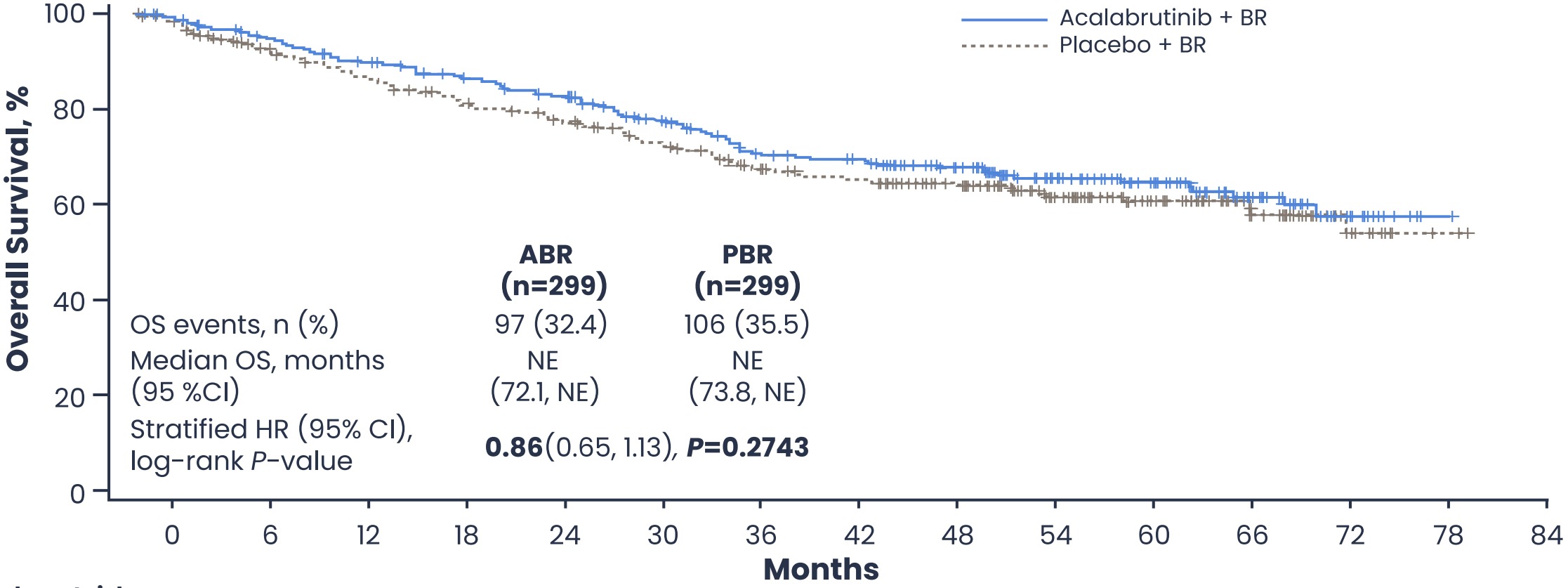
69% received a **BTKi** as a **subsequent treatment**

- Significant improvement in median PFS by ~17 mo with acalabrutinib + BR
- 27% reduction in risk of PD or death[a]

[a]At a median follow-up of 45 months.
ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; CI, confidence interval; BTKi, Bruton's tyrosine kinase inhibitor; HR, hazard ratio; MCL, mantle cell lymphoma; mo, month(s); NE, not estimable; PBR, placebo + bendamustine + rituximab; PD, progressive disease; PFS, progression-free survival; TN, treatment-naïve.
Adapted from Wang M et al. EHA 2024; Abstract LB3439.

ECHO: BR + acalabrutinib vs BR + placebo in TN MCL

Overall survival including crossover



Median follow-up of 45 months.
ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; CI, confidence interval; HR, hazard ratio; MCL, mantle cell lymphoma; NE, not estimable; OS, overall survival; PBR, placebo + bendamustine + rituximab; PD, progressive disease; TN, treatment-naïve.
Adapted from Wang M et al. EHA 2024; Abstract LB3439.

TRIANGLE

AUTOLOGOUS TRANSPLANTATION AFTER A RITUXIMAB/IBRUTINIB/ARA-C CONTAINING INDUCTION IN GENERALIZED MANTLE CELL LYMPHOMA – A RANDOMIZED EUROPEAN MCL NETWORK TRIAL

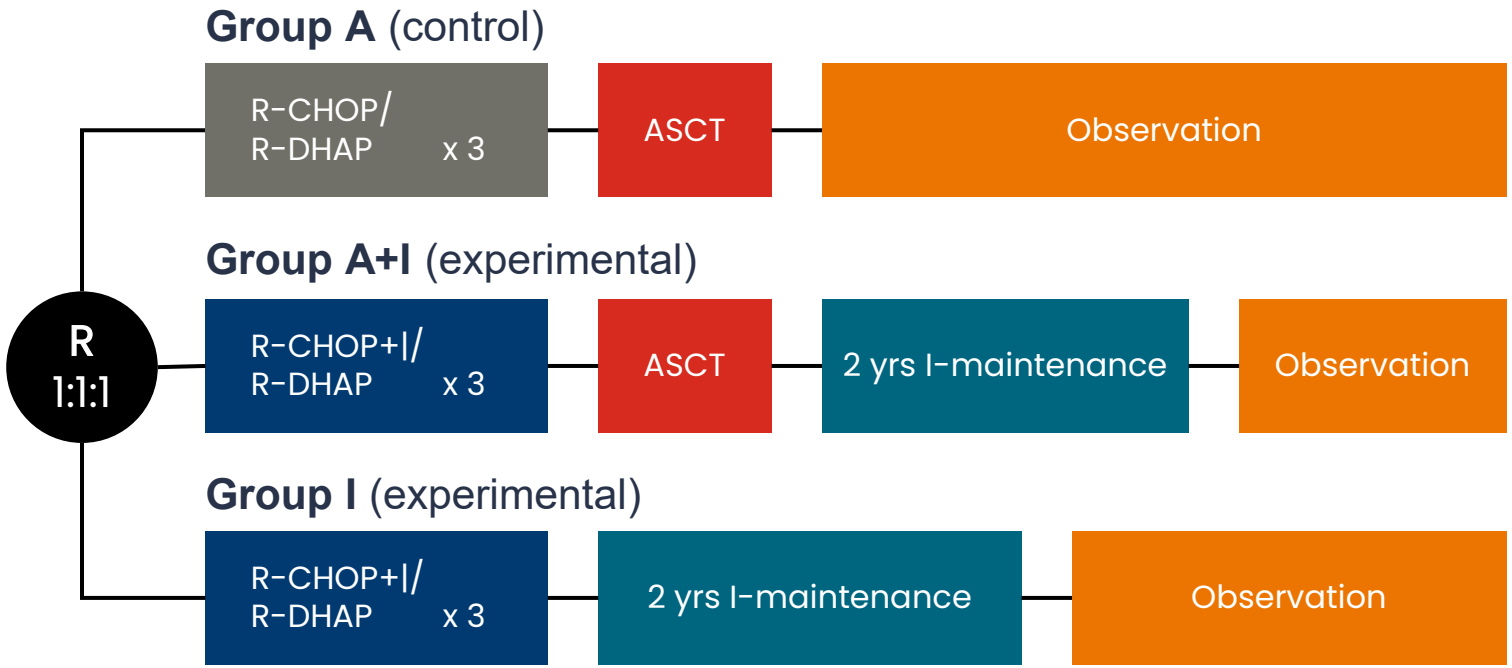
Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network

Martin Dreyling, Jeanette Doorduijn, Eva Giné, Mats Jerkeman, Jan Walewski, Martin Hutchings, Ulrich Mey, Jon Riise, Marek Trneny, Vibeke Vergote, Ofer Shpilberg, Maria Gomes da Silva, Sirpa Leppä, Linmiao Jiang, Stephan Stilgenbauer, Andrea Kerkhoff, Ron D Jachimowicz, Melania Celli, Georg Hess, Luca Arcaini, Carlo Visco, Tom van Meerten, Stefan Wirths, Pier Luigi Zinzani, Urban Novak, Peter Herhaus, Fabio Benedetti, Kristina Sonnevi, Christine Hanoun, Matthias Hänel, Judith Dierlamm, Christiane Pott, Wolfram Klapper, Döndü Gözel, Christian Schmidt, Michael Unterhalt, Marco Ladetto, Eva Hoster**

Dreyling M, et al. *Lancet.* 2024;403(10441):2293-2306.

TRIANGLE: Trial design

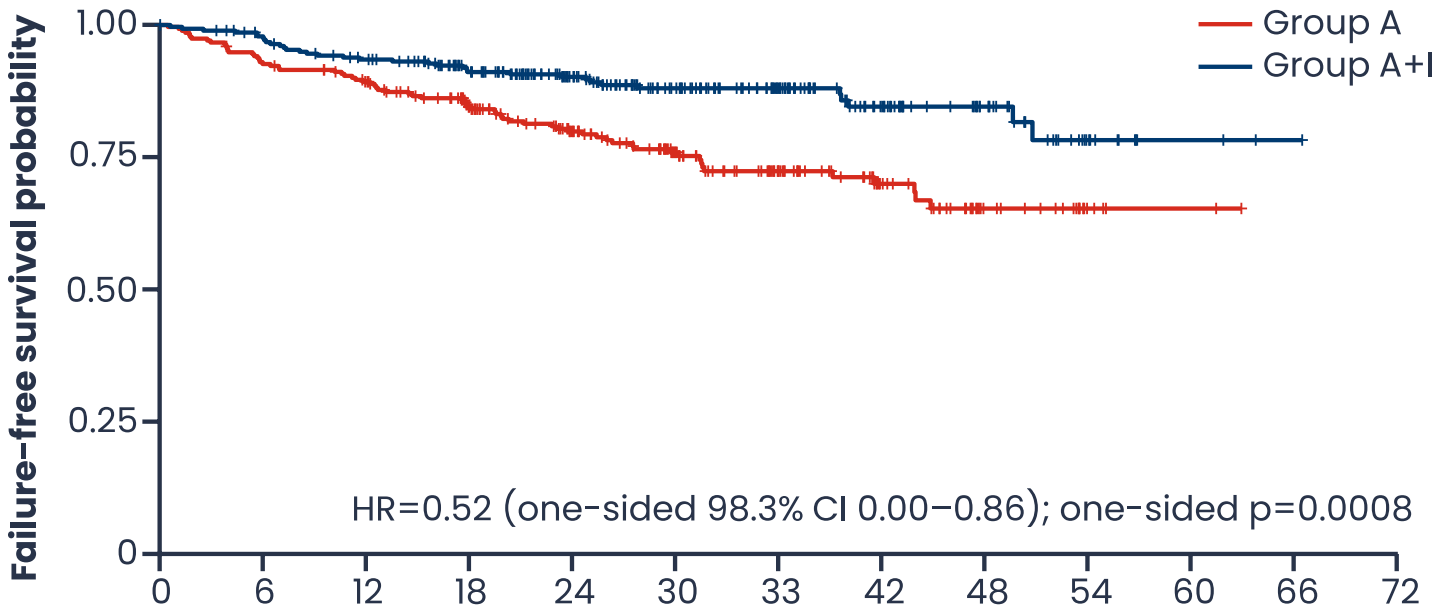
- MCL patients
- Previously untreated
- Stage II-IV
- Younger than 66 years
- Suitable for HA and ASCT
- ECOG 0-2
- **Primary outcome:** FFS
- **Secondary outcomes:**
  - Response rates
  - PFS, RD
  - OS
  - Safety



- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with ibrutinib) was started in 168 (58%)/165 (57%)/158 (54%) of A/A+I/I randomized patients

ACST, autologous stem cell transplantation; FFS, failure-free survival; HA, high-dose Ara-C; I, ibrutinib; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone; R, randomized; RD, duration of remission; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; yrs, years.
Adapted from Dreyling M, et al. *Lancet.* 2024;403(10441):2293-2306.

TRIANGLE: FFS superiority of A+I vs A



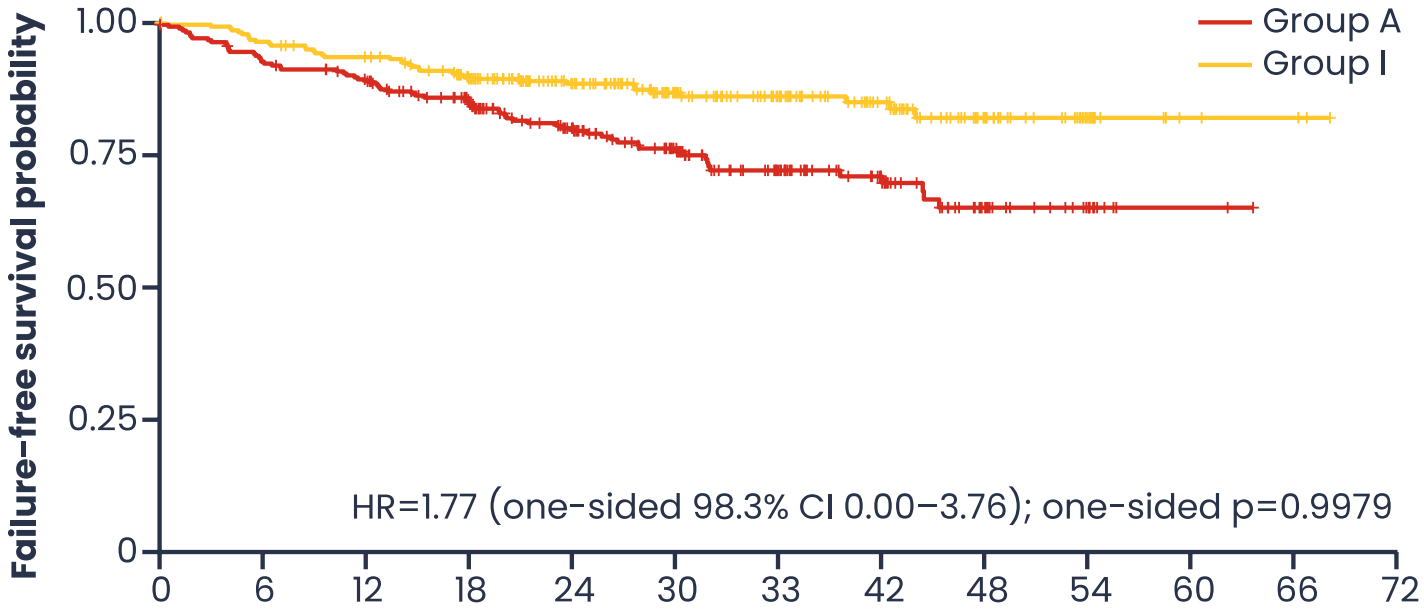
Number at risk (number censored)

Group A	288	252	237	206	162	126	85	54	27	12	2	0	0
	(0)	(17)	(22)	(43t)	(76)	(105)	(140)	(169)	(193)	(208)	(218)	(220)	(220)
Group A+I	292	270	253	226	184	137	109	65	41	17	3	1	0
	(0)	(16)	(21)	(44)	(82)	(125)	(153)	(194)	(219)	(240)	(254)	(256)	(257)

- Superiority of A+I vs. A (FFS) was confirmed
- 3-year FFS A+I: 88%
- 3-year FFS A: 72%

Median follow-up of 31 months.
A, R-CHOP/R-DHAP+ASCT; ACST, autologous stem cell transplantation; A+I, IR-CHOP/IR-DHAP+ASCT; CHOP, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone; CI, confidence interval; DHAP, dexamethasone, cytarabine, cisplatin; FFS, failure-free survival; HR, hazard ratio; IR, ibrutinib, rituximab; R, rituximab.
Adapted from Dreyling M et al. *Lancet.* 2024;403(10441):2293-2306.

TRIANGLE: No FFS superiority of A vs I



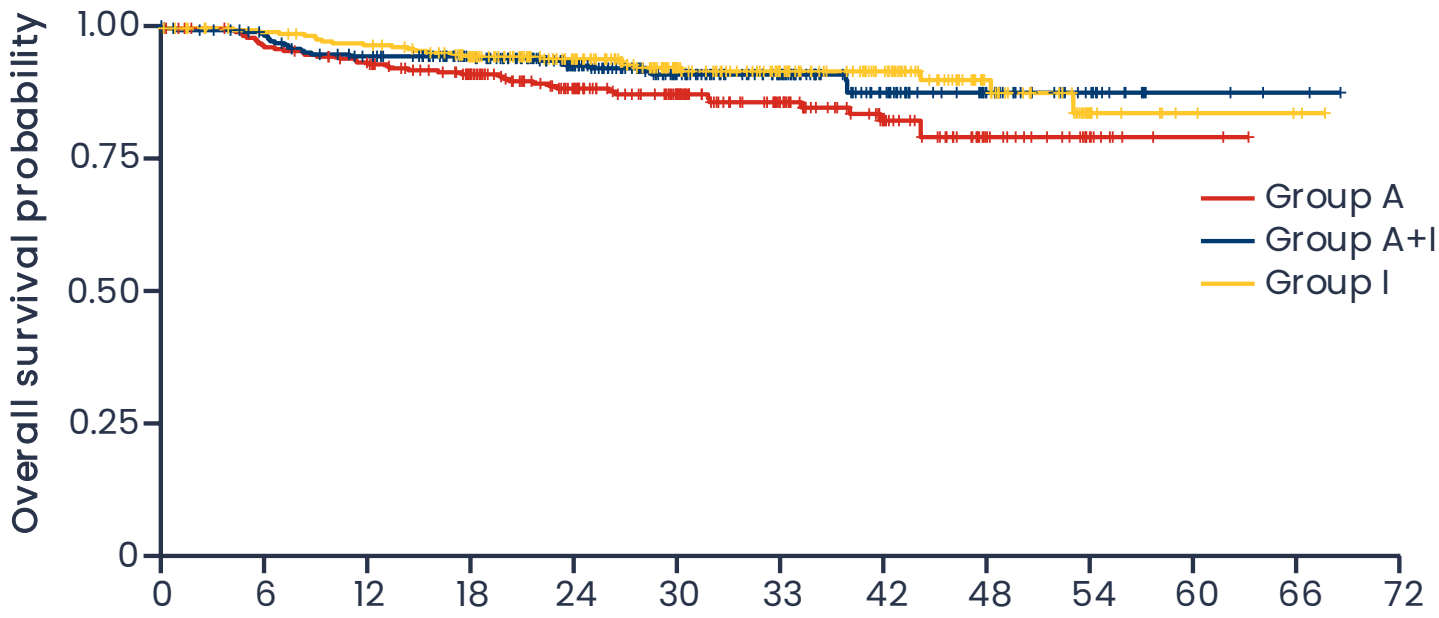
Number at risk (number censored)

Group A	290	269	257	229	180	133	100	68	35	16	4	3	0
	(0)	(12)	(16)	(33)	(80)	(124)	(156)	(187)	(219)	(237)	(249)	(250)	(253)
Group I	288	252	237	206	162	126	85	54	27	12	2	0	0
	(0)	(17)	(22)	(43)	(76)	(105)	(140)	(169)	(193)	(208)	(218)	(220)	(220)

- Superiority of A vs. I (FFS) was rejected
- Kaplan-Meier plots:
  - 3-year FFS A: 72% (MCL Younger: 75%)
  - 3-year FFS I: 86%
- *p*-value corrected for sequential design: *p*=0.9979
- HR (A vs. I): HR=1.77

Median follow-up of 31 months.
A, R-CHOP/R-DHAP+ASCT; ACST, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone; CI, confidence interval; DHAP, dexamethasone, cytarabine, cisplatin; FFS, failure-free survival; HR, hazard ratio; I, IR-CHOP/IR-DHAP; IR, ibrutinib, rituximab; MCL, mantle cell lymphoma; R, rituximab.
Adapted from Dreyling M et al. *Lancet.* 2024;403(10441):2293-2306.

TRIANGLE: Overall survival



Number at risk (number censored)

Group A	288 (0)	270 (8)	256 (13)	230 (34)	181 (77)	145 (111)	97 (157)	63 (188)	32 (217)	15 (234)	2 (247)	0 (249)	0 (249)
Group A+I	292 (0)	280 (8)	262 (15)	238 (38)	195 (78)	142 (128)	113 (157)	67 (200)	43 (225)	19 (248)	4 (263)	2 (265)	0 (267)
Group I	290 (0)	281 (7)	272 (9)	248 (27)	197 (77)	145 (126)	109 (161)	77 (193)	39 (231)	16 (251)	4 (263)	3 (264)	0 (267)

3-year OS:

- Group I: 92%
- Group A+I: 91%
- Group A: 86% (MCL younger exp.: 84%)

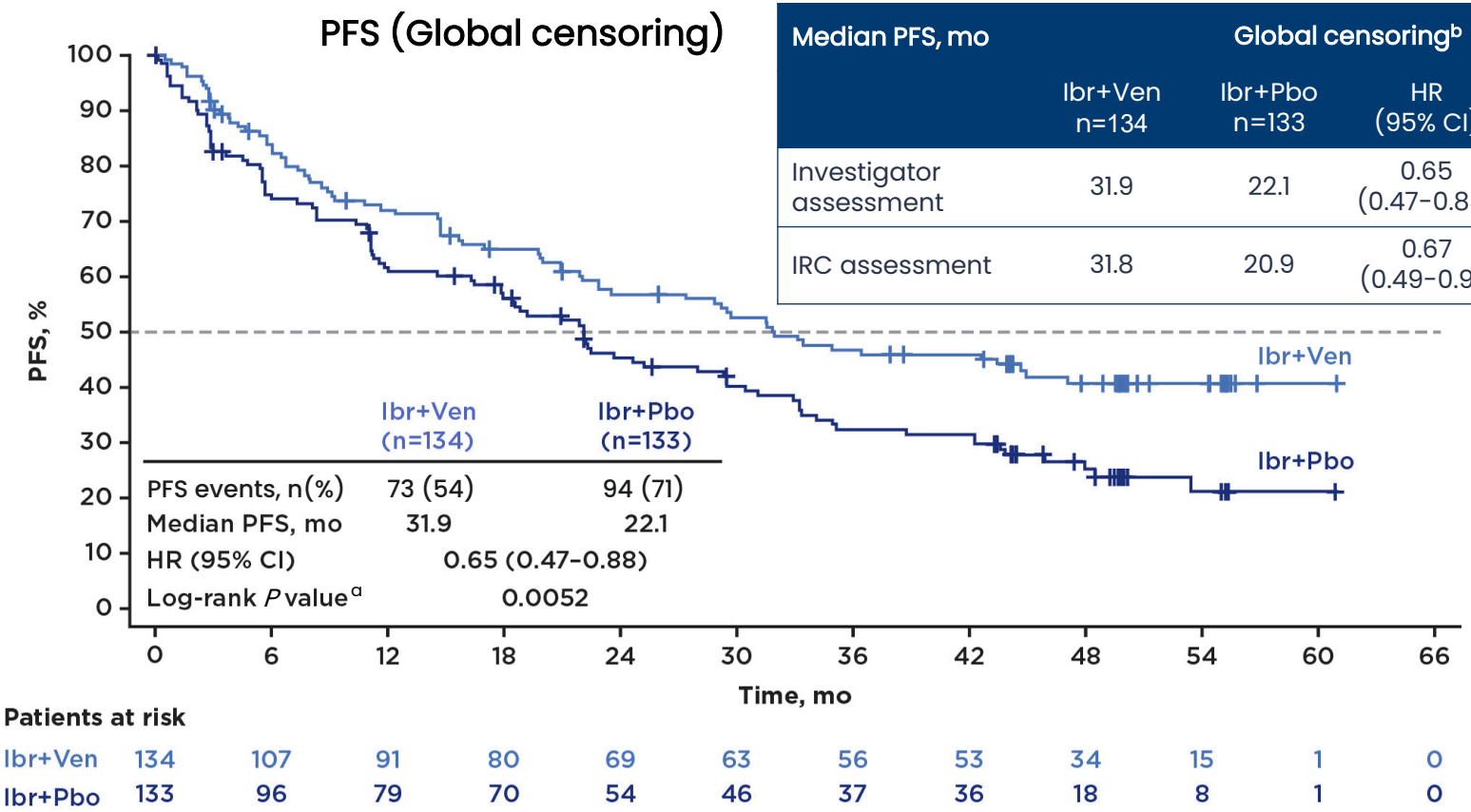
Too early to evaluate statistical significance

Median follow-up of 31 months.
A, R-CHOP/R-DHAP+ASCT; ACST, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone; DHAP, dexamethasone, cytarabine, cisplatin; HR, hazard ratio; I, IR-CHOP/IR-DHAP; IR, ibrutinib, rituximab; MCL, mantle cell lymphoma; OS, overall survival; R, rituximab.
Adapted from Dreyling M et al. *Lancet.* 2024;403(10441):2293-2306.

"... Impossible to see, the future is....."

Master Yoda

Joining forces: BTK + BCL2 inhibition
Ibrutinib + venetoclax in R/R MCL (SYMPATICO)



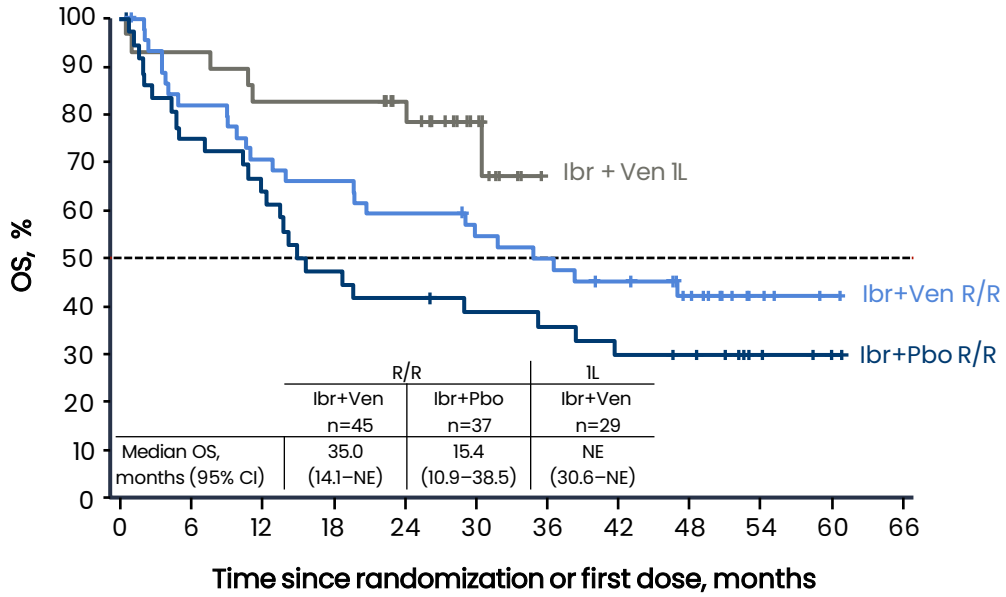
Median PFS, mo	Global censoring[b]				US FDA censoring[c]			
	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank P value[a]	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank P value[a]
Investigator assessment	31.9	22.1	0.65 (0.47-0.88)	0.0052	42.6	22.1	0.60 (0.44-0.83)	0.0021
IRC assessment	31.8	20.9	0.67 (0.49-0.91)	0.0108	43.5	22.1	0.63 (0.45-0.87)	0.0057

Investigator-assessed PFS was significantly improved with ibrutinib+venetoclax vs ibrutinib+placebo

[a]*P*-values were determined by stratified log-rank test (stratification factors: prior lines of therapy [1-2 vs ≥3] and TLS risk category [low vs increased risk]). [b]Censoring at last non-PD assessment for patients without PD or death. [c]Patients were censored at last non-PD assessment before start of subsequent anticancer therapy or missing ≥2 consecutive visits prior to a PFS event, whichever occurred first.
BCL2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CI, confidence interval; HR, hazard ratio; Ibr, ibrutinib; IRC, independent review committee; MCL, mantle cell lymphoma; mo, months; Pbo, placebo; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory; TLS, tumor lysis syndrome; Ven, venetoclax.
Adapted from Wang M et al. *Blood.* 2023;142(Supplement 2):LBA-2.

Joining forces: BTK + BCL2 inhibition
Ibrutinib + venetoclax in R/R MCL (SYMPATICO)

Patients with *TP53* mutations

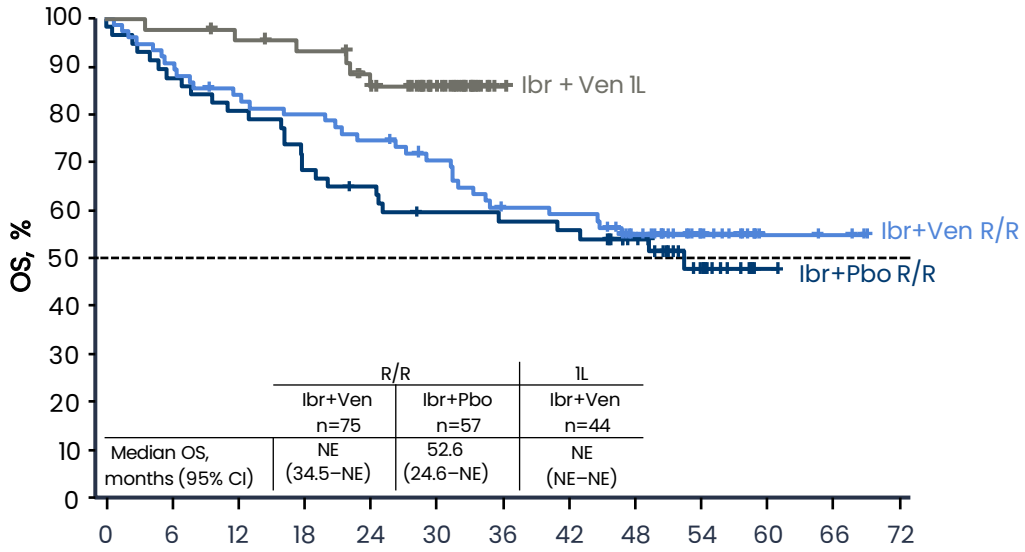


Time since randomization or first dose, months

Patients at risk

Ibr+Ven R/R	45	36	31	29	26	24	21	18	13	5	1	0
Ibr+Pbo R/R	37	27	23	17	15	13	12	10	9	4	2	0
Ibr+Ven 1L	29	27	24	24	19	10	0	0	0	0	0	0

Patients without *TP53* mutations



Time since randomization or first dose, months

Patients at risk

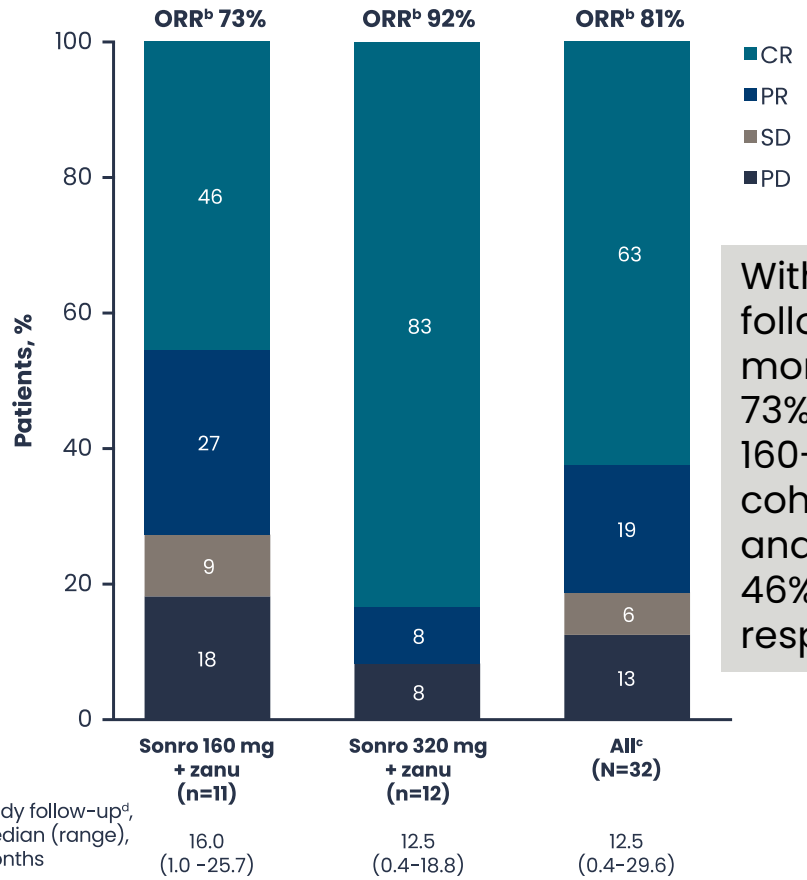
Ibr+Ven R/R	75	68	62	59	55	50	42	41	29	15	4	3	0
Ibr+Pbo R/R	57	50	46	39	36	32	31	30	24	12	1	0	0
Ibr+Ven 1L	44	43	41	39	35	23	1	0	0	0	0	0	0

Ibrutinib+venetoclax demonstrated an OS benefit in patients with and without *TP53* mutations

1L, first line; BCL2, B-cell lymohoma 2; BTK, Bruton's tyrosine kinase; CI, confidence interval; Ibr, ibrutinib; MCL, mantle cell lymphoma; NE, not evaluable; OS, overall survival; Pbo, placebo; R/R, relapsed/refractory; Ven, venetoclax.
Adapted from Wang M, et al. Oral presentation at ASCO 2024. Abstract #7007.

Joining forces: BTK + BCL2 inhibition
Zanubrutinib + sonrotoclax in R/R MCL (BGB-11417-101)

Response rates[a]

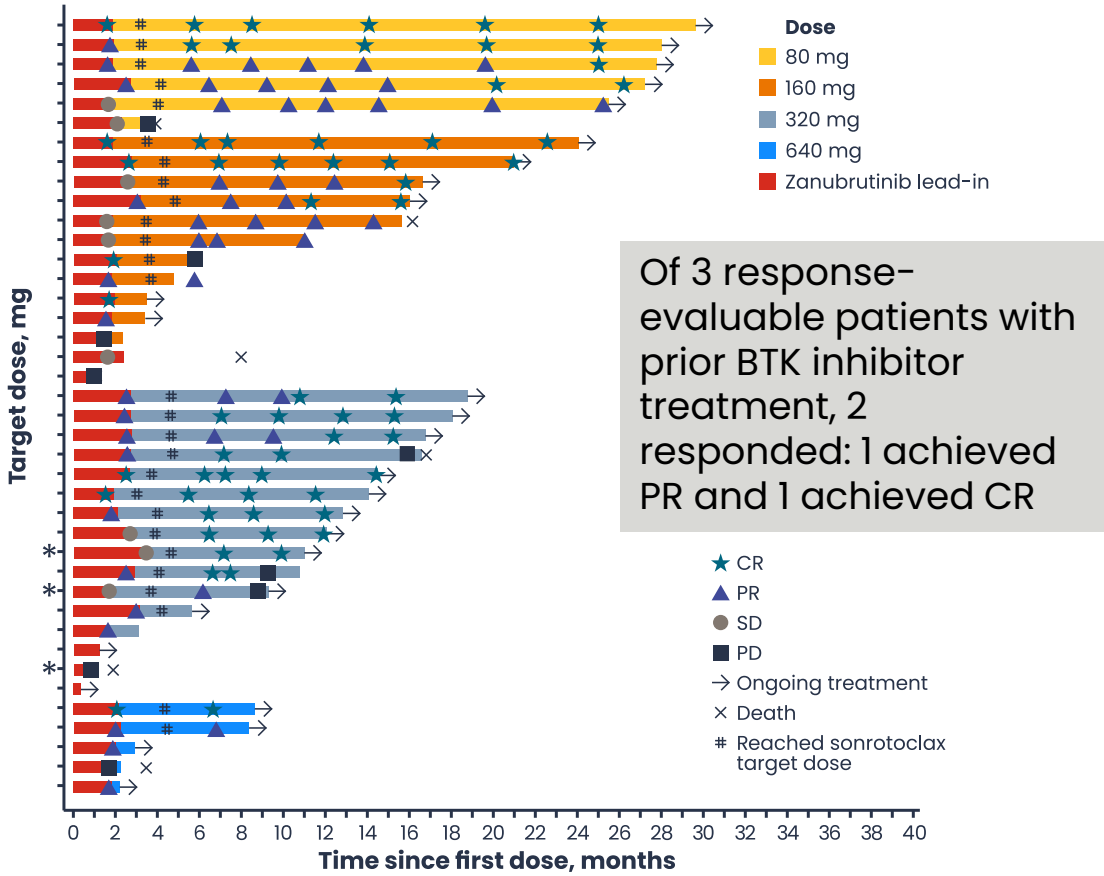


Study follow-up[d], median (range), months

Sonro 160 mg + zanu (n=11)	Sonro 320 mg + zanu (n=12)	All[c] (N=32)
16.0 (1.0 -25.7)	12.5 (0.4-18.8)	12.5 (0.4-29.6)

With a median study follow-up of 12.5 months, ORRs were 73% and 92% in the 160- and 320-mg cohorts, respectively, and CR rates were 46% and 83%, respectively

Duration and investigator-assessed responses[e]



Of 3 response-evaluable patients with prior BTK inhibitor treatment, 2 responded: 1 achieved PR and 1 achieved CR

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[a]Responses were assessed per Lugano 2014 criteria. [b]ORR was defined as PR or better. [c]For all dose levels. [d]For all patients as treated (N=40). sonro, sonrotoclax; zanu, zanubrutinib. [e]Red bar indicates duration of zanubrutinib lead-in.

BCL2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CR, complete response; MCL, mantle cell lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; sonro, sonrotoclax; zanu, zanubrutinib.

Adapted from Tam C, et al. Poster Presentation at EHA 2024;P1112.

Joining forces: BTK + BCL2 inhibition in R/R MCL
BGB-11417-302: Study design

Phase 3 study of sonrotoclax + zanubrutinib vs. placebo + zanubrutinib in R/R MCL

Study identifier: BGB-11417-302, NCT06742996

Study population

- R/R MCL
- Previously received 1-5 lines of treatment
- BTKi-naive/intolerant

n=300

R 1:1

Zanubrutinib 160 mg BID/320 mg QD (C1[a]-PD/intolerance)
+ sonrotoclax[b] (BIW ramp-up) 320 mg QD x 2 years (C2-C25)

Zanubrutinib 160 mg BID/320 mg QD (C1-PD/intolerance)
+ placebo (BIW ramp-up) QD x 2 years (C2-C25)[c]

Primary endpoint
- PFS by IRC

Key secondary endpoints
- Overall survival

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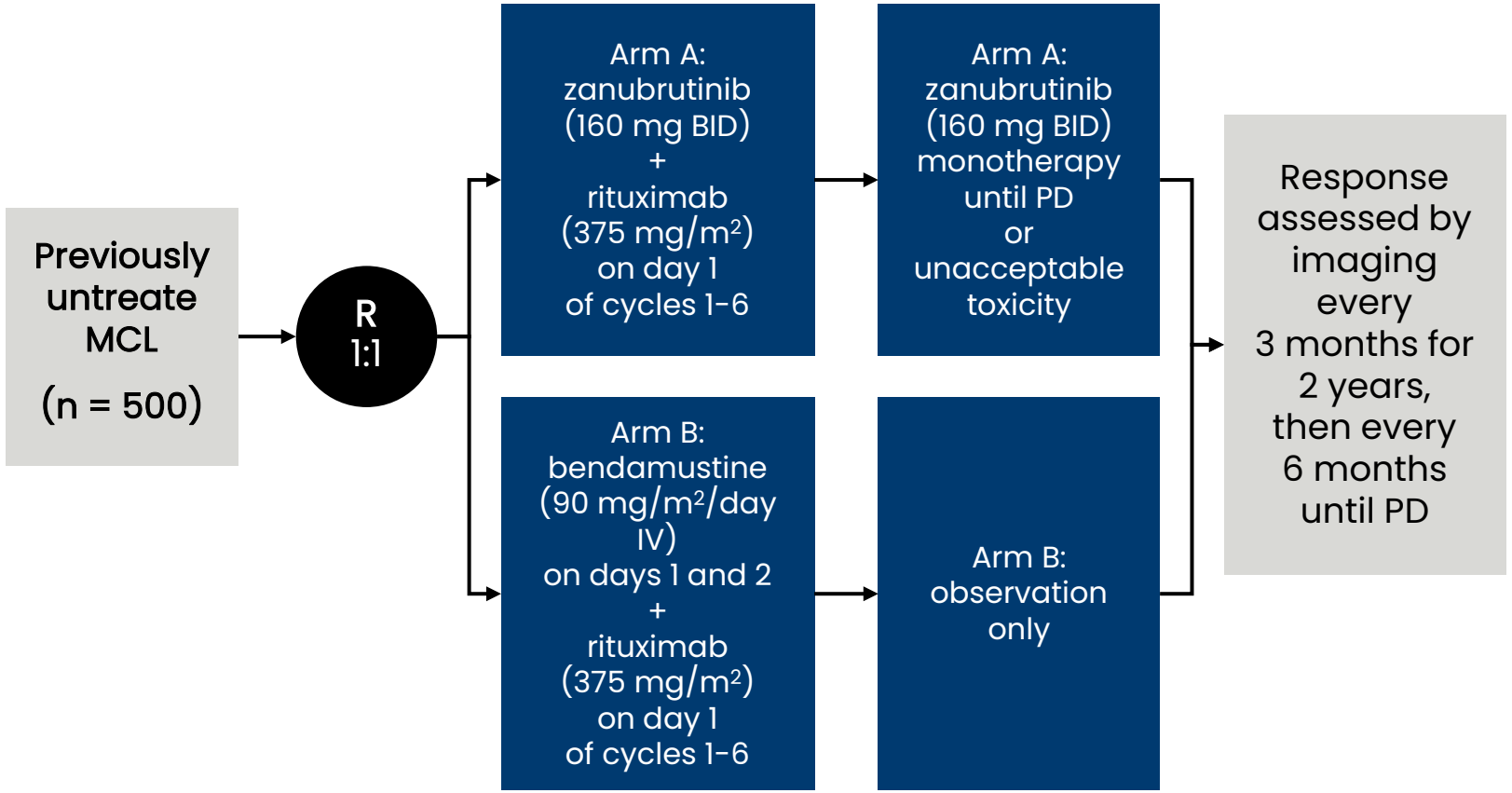
[a]1 cycle=28 days. [b]One cycle of zanubrutinib lead-in before starting sonrotoclax. [c]No crossover allowed.
BCL2, B-cell lymphoma 2; BID, twice daily; BIW, twice a week; BTKi, Bruton's tyrosine kinase inhibitor; C, cycle; IRC, independent review committee; MCL, mantle cell lymphoma; PFS, progression-free survival; QD, once daily; R, randomized; R/R, relapsed/refractory.
BGB-11417-302. NCT06742996. Available from: https://clinicaltrials.gov/study/NCT06742996. Accessed June 2025.

Chemo-free?
Zanubrutinib plus rituximab in TN MCL: Phase 3 study (MANGROVE)

Phase 3 study of zanubrutinib + rituximab vs bendamustine + rituximab in transplant-ineligible, untreated MCL



"....the future is bright...

I've got to wear shades...."

Indications of approved products may differ between countries. Zanubrutinib is authorized under different conditions (e.g., different government-approved professional information: indications, warnings, etc.) in Switzerland. For country-specific information, refer to the prescribing information for the country in which you practice medicine.
BID, twice daily; IV, intravenous; MCL, mantle cell lymphoma; PD, progressive disease; R, randomized; TN, treatment-naïve.
Adapted from Dreyling M et al. *Future Oncol.* 2021;17(3):255-262.

Speaker's own conclusions

- In R/R MZL, zanubrutinib showed high response rates and durable disease control in all subtypes

- BTKis have defined the standard of care in R/R MCL
  - Highest benefit in second line

- BTKis are moving into first line
  - TRIANGLE has defined the standard of care in younger patients
  - BTKi + BR – possible standard of care for older patients?
  - BTKi + rituximab as chemo-free options? MANGROVE will provide further evidence

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BR, bendamustine+rituximab; BTKi, Bruton's tyrosine kinase inhibitor; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed/refractory

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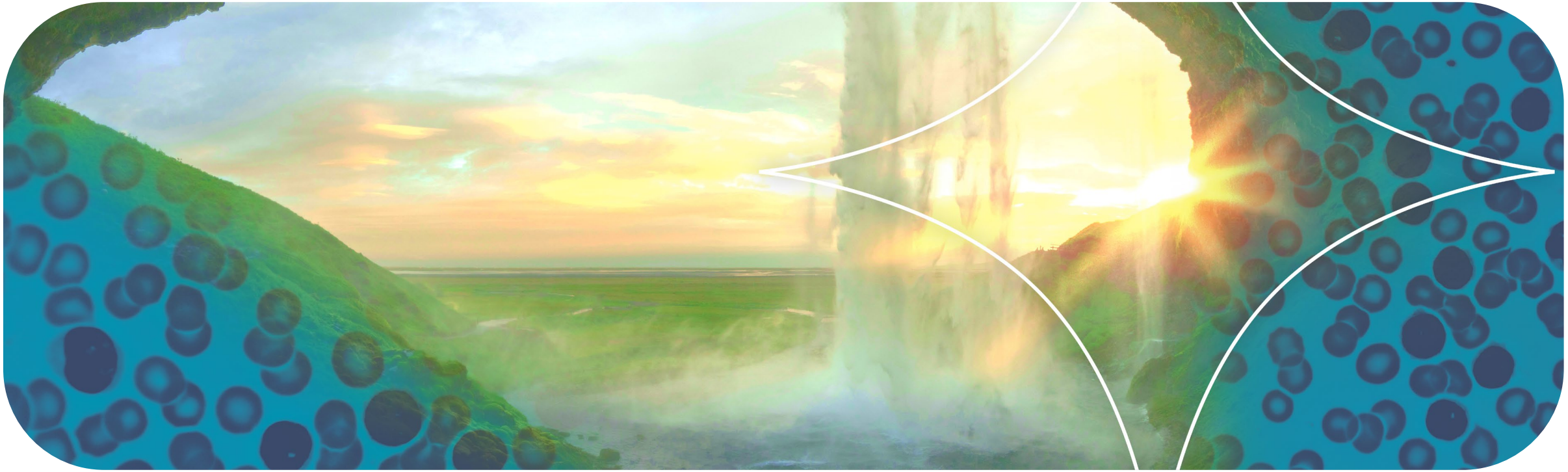


BTK protein degraders – Experiences with a novel approach to treating lymphomas

Professor Carlo Visco
Verona, Italy

BeOne

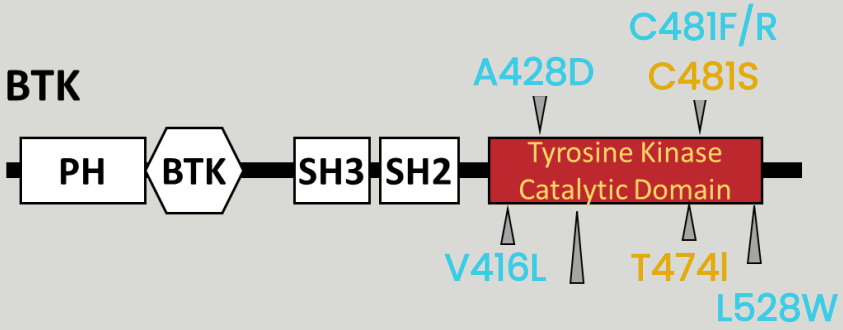
Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	X				X	X	
Kite-Gilead					X	X	
Janssen	x		x		X	X	
Gentili					X	X	
Novartis						X	
Pfizer			x		x	x	
Roche					X	X	
Incyte					x	x	
Servier					x		
Astra Zeneca					X		
BMS						X	
Kyowa Kirin					x		
BeOne					X		
Lilly			X		X	X	

Emerging BTK mutations confer resistance to BTKi

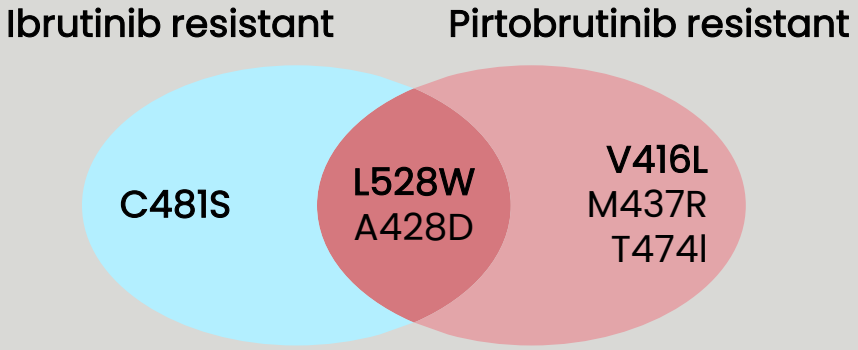
Drug	Resistance mutations
Ibrutinib	C481S in >90% (Rare – D43H, C481 kinase dead*, A428D, L528W, T474I)
Acalabrutinib	C481S, C481 kinase dead*, T474I, E41V
Zanubrutinib	C481S, C481 kinase dead*, L528W, A428D
Pirtobrutinib	C481 kinase dead*, L528W, V416L, T474I/F/L/Y, A428D, M477I, M437R, D539G/H, Y545N

- Targeting BTK via an **alternative mechanism** may overcome the current challenges of BTKis and may allow continued targeting of a key pathway in B-cell malignancies[9]



Kinase proficient

Kinase impaired



*C481 kinase dead = C481F, C481Y, C481W, C481G, C481R. C481T is catalytically active.[19]
BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; HCK, hematopoietic cell kinase.
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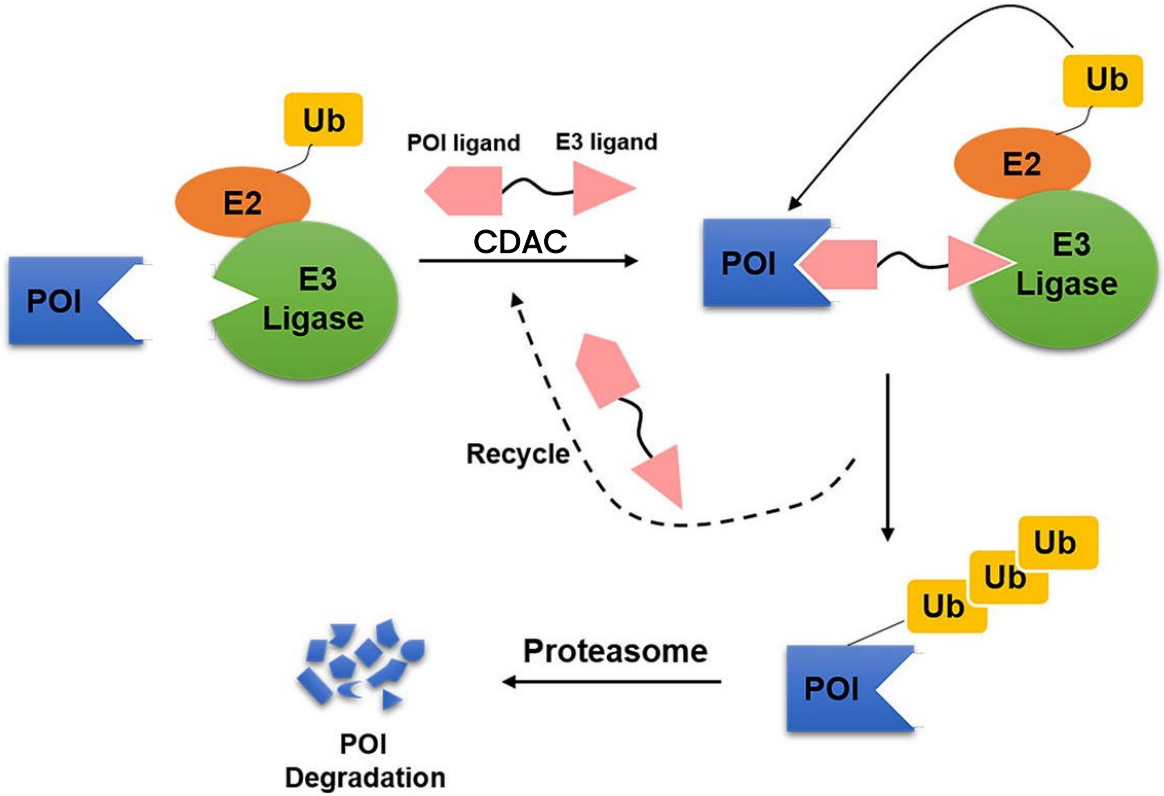
Chimeric Degradation Activation Compound (CDAC)

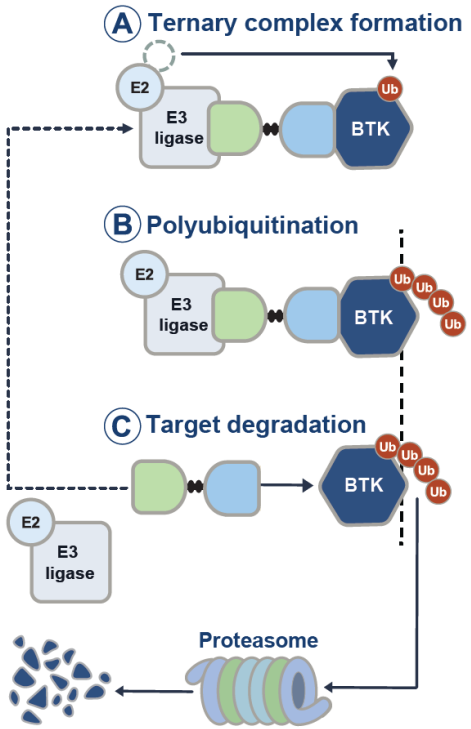
- Bifunctional molecule with two active domains and a linker
  - E3 ubiquitin ligase binder
  - Target protein binder
- Capable of removing specific unwanted proteins
- Induces selective intracellular proteolysis
- VHL and CRBN in use, but many E3 ligases



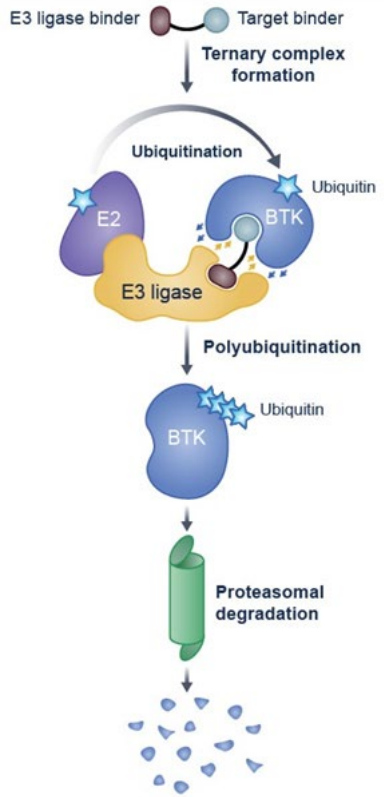
CDAC, chimeric degradation activation compound; CRBN, cereblon; POI, protein of interest; Ub, ubiquitin; VHL, von Hippel-Lindau.
1. Sakamoto KM, et al. *PNAS.* 2001;98(15):8554-9. 2. Image adapted from Xi JY, et al. *Bioorganic Chemistry.* 2022;125:105848.

Utilize the ubiquitin-proteasome pathway to degrade BTK

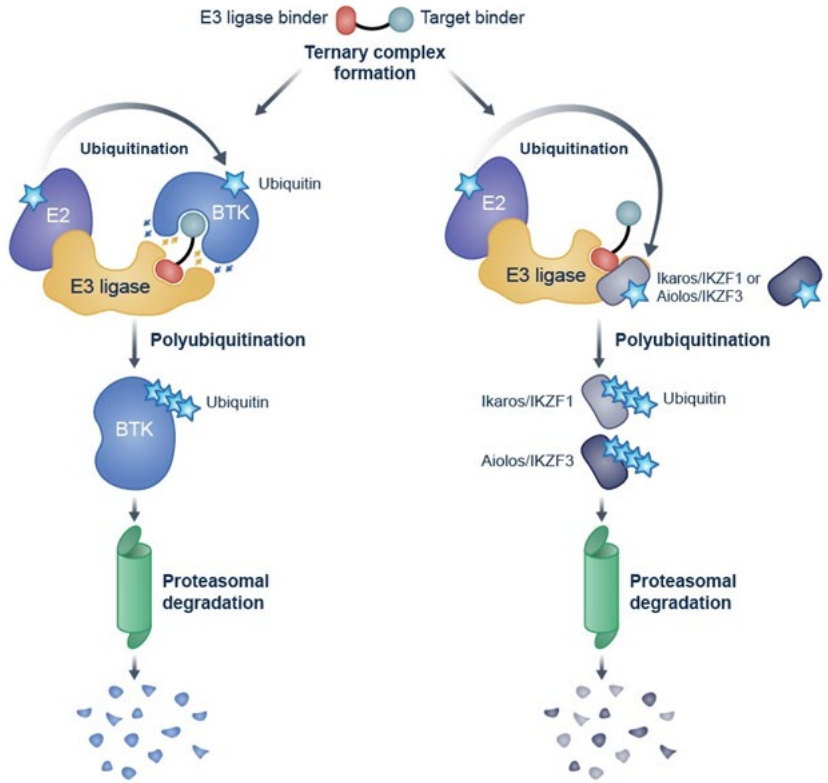
BGB-16673 MOA[1]



NX-5948 MOA[2]



NX-2127 MOA[2]

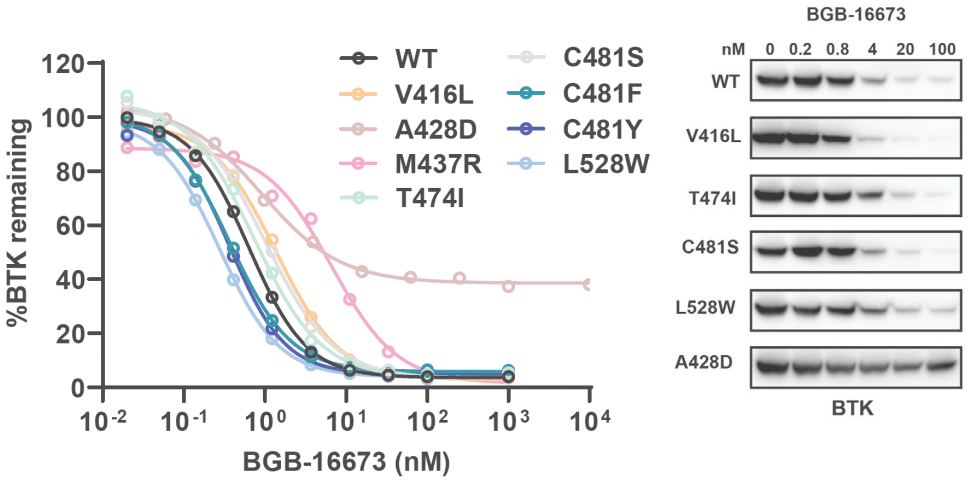


- BTK degraders can overcome treatment-emergent resistance mutations on both cBTKi and ncBTKi[1,2]
- BTK degraders address BTK scaffolding function[1,2]

BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; cBTKi, covalent BTKi; MOA, mechanism of action; ncBTKi, non-covalent BTKi; Ub, ubiquitin.
Adapted from: 1. Cheah CY, et al. Poster presented at the EHA 2024; Abstract #P1119. 2. Noviski M, et al. Poster presented at iwCLL 2023; Abstract #2020.

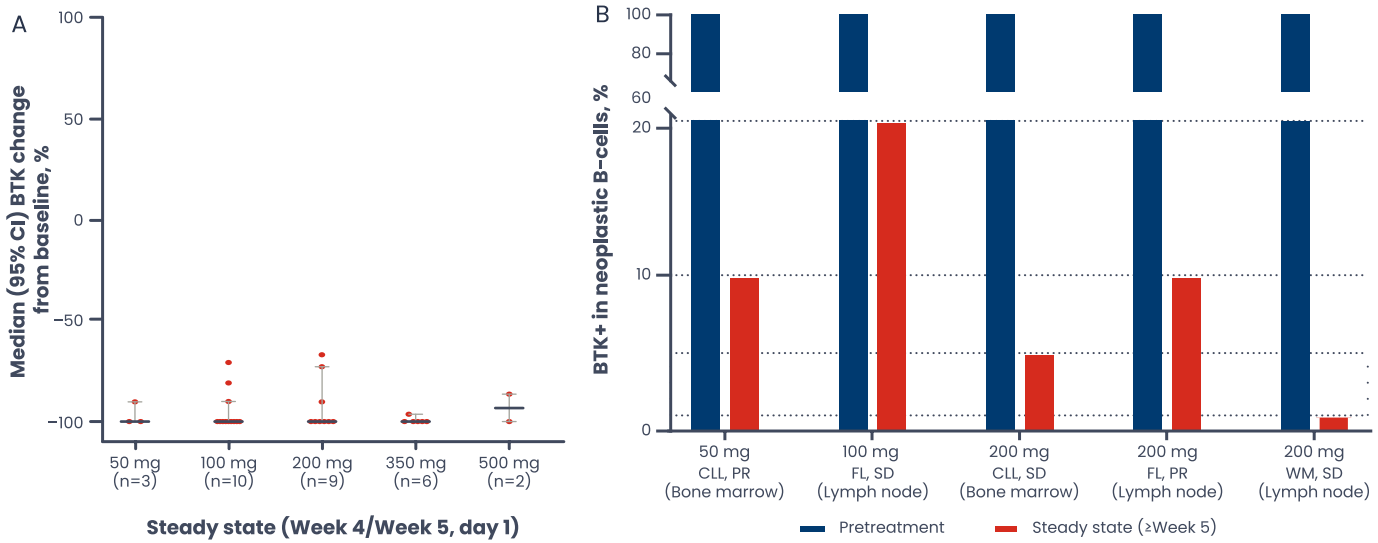
BGB-16673: BTK degrader (CDAC)

Active against mutants in the lab[1]



Active in pts with cBTKi-refractory disease[2]

Reduction of BTK protein levels in A. Peripheral blood and B. Tumor tissue



BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; cBTK, covalent BTKi; CI, confidence interval; CDAC, chimeric degradation activating compound; CLL, chronic lymphocytic leukemia; del, deletion; FL, follicular lymphoma; ncBTK, non-covalent BTK; ORR, overall response rate; PR, partial response; pts, patients; SD, stable disease; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia; WT, wild-type.
Adapted from: 1. Feng X, et al. Poster presentation at EHA 2023; Abstract #P1239. 2. Munir T, et al. Poster presentation at BSH 2024; Abstract #PO143.

CaDAnCe-101: Study design

CLL/SLL WM

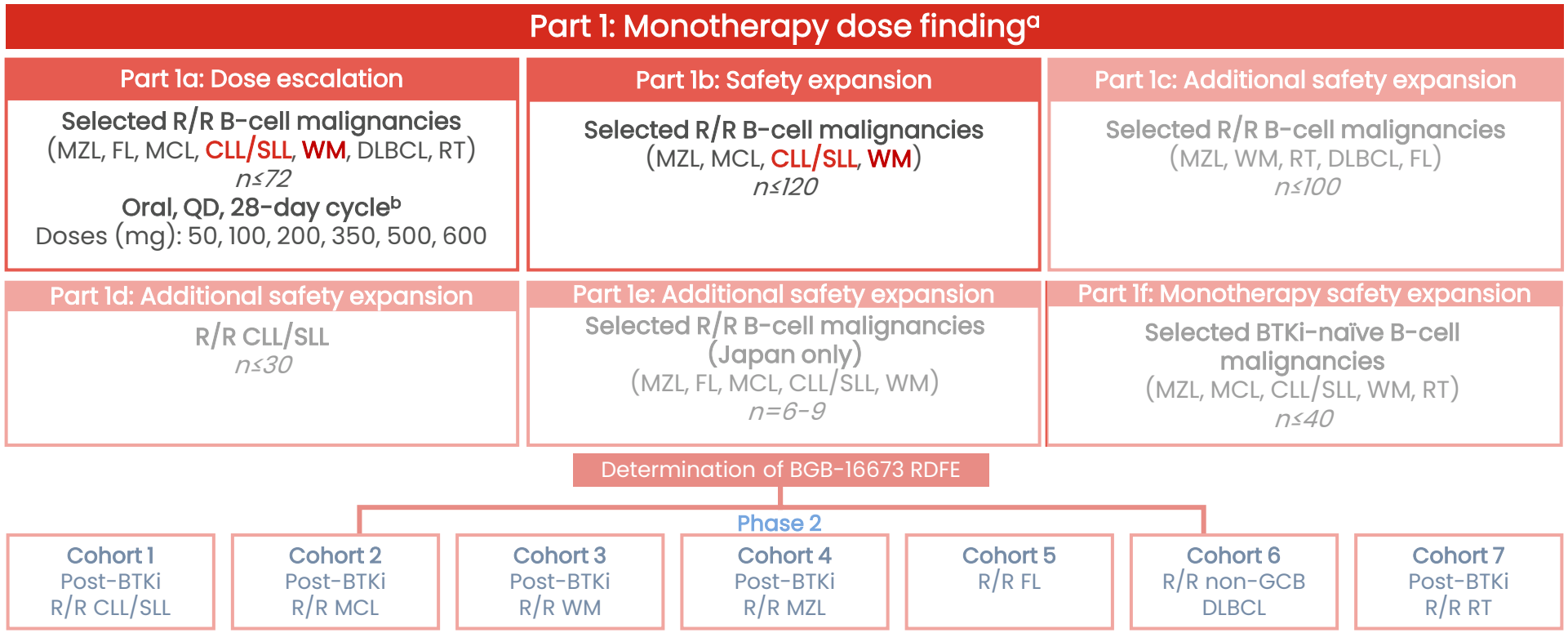
CaDAnCe-101 (BGB-16673-101, NCT05006716) is a phase 1/2, open-label, dose-escalation and dose-expansion study evaluating the BTK degrader BGB-16673 in R/R B-cell malignancies

Key eligibility criteria for CLL/SLL

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

Key study objectives for part 1

Primary: safety[c] and tolerability, MTD, and RP2D
Secondary: PK, PD, and preliminary antitumor activity[d]



[a]Data from gray portions of figure are not included in this presentation. [b]Treatment was administered until progression, intolerance, or meeting criteria for treatment discontinuation. [c]Safety was assessed according to CTCAE v5.0 in all patients and iwCLL hematologic toxicity criteria in patients with CLL; DLTs were assessed during the first 4 weeks. [d]Response was assessed per iwCLL 2018 criteria after 12 weeks for patients with CLL; response was assessed per Lugano criteria after 12 weeks in patients with RT; responses were assessed per IWWM-6, modified Owen 2013 criteria after 4 weeks for patients with WM.
BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; cBTKi, covalent BTKi; CLL, chronic lymphocytic leukemia; CTCAE, Common Terminology Criteria for Adverse Events; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B cell; iwCLL, International Workshop on CLL; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; RDFE, recommended dose for expansion; RP2D, recommended Phase 2 dose; R/R, relapsed/refractory; RT, Richter transformation; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.
Adapted from Thompson MC, et al. Oral presentation at ASH 2024; Abstract #885.

Baseline patient characteristics

CLL/SLL

BGB-16673-101 – CaDAnCe-101 (R/R CLL/SLL): Heavily pretreated, with high-risk CLL features

	Total (N=60)
Median age, years (range)	70 (50-91)
Male, n (%)	39 (65.0)
ECOG PS, n (%)	
0	34 (56.7)
1	25 (41.7)
2	1 (1.7)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	27/56 (48.2)
Unmutated IGHV	38/46 (82.6)
Del(17p) and/or *TP53* mutation	40/60 (66.7)
Complex karyotype (≥3 abnormalities)	19/38 (50.0)

	Total (N=60)
Mutation status, n/N (%)	
BTK	18/54 (33.3)
PLCG2	8/54 (14.8)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	43 (71.7)
cBTKi	56 (93.3)
ncBTKi	13 (21.7)
BCL2i	50 (83.3)
cBTKi + BCL2i	38 (63.3)
cBTKi + ncBTKi + BCL2i	12 (20.0)
Discontinued prior BTKi due to PD, n(%)[a]	50/56 (89.3)

- Patients had a median of 4 (range, 2-10) prior lines of therapy
- Of patients with available data, high-risk characteristics were prevalent, such as:
  - Unmutated IGHV locus (83%)
  - Del(17p) or *TP53* mutation (67%)
  - Complex karyotype (50%)

Data cutoff: September 2, 2024.
[a]Remaining 6 patients discontinued prior BTKi due to toxicity (n=3), treatment completion (n=2), and other (n=1).
BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; cBTKi, covalent BTKi; CLL, chronic lymphocytic leukemia; del, deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; ncBTKi, non-covalent BTKi; PD, progressive disease; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.
Adapted from Thompson MC, et al. Oral presentation at ASH 2024; Abstract #885.

Overall safety summary

BGB-16673-101 – CaDAnCe-101 (R/R CLL/SLL)

CLL/SLL

- No treatment-related TEAEs leading to death occurred
- One DLT[a] was reported at 200 mg dose level (Grade 3 maculopapular rash; patient continued on treatment after a 5-day hold)

TEAE, n (%)	Total (N=60)
Any TEAE	56 (93.3)
Any treatment-related	41 (68.3)
Grade ≥3	33 (55.0)
Treatment-related	16 (26.7)
Serious	27 (45.0)
Treatment-related	6 (10.0)
Leading to death	3 (5.0)
Treatment-related	0
Leading to treatment discontinuation	7 (11.7)
Treatment-related	2 (3.3)

Median follow-up for safety-evaluable patients: 10.2 months (range 0.3-26.4+).
aDLTs were only assessed during the first 4 weeks of part 1a.
CLL, chronic lymphocytic leukemia; DLT, dose-limiting toxicity; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event.
Adapted from Thompson MC, et al. Oral presentation at ASH 2024; Abstract #885.

CLL/SLL

Most frequent adverse events

BGB-16673-101 – CaDAnCe-101 (R/R CLL/SLL)

TEAE, n (%)	Total (N=60)	
	Any Grade	Grade ≥3
Fatigue	18 (30.0)	1 (1.7)
Contusion (bruising)	17 (28.3)	0
Neutropenia[a]	15 (25.0)	13 (21.7)
Diarrhea	14 (23.3)	1 (1.7)
Anemia	11 (18.3)	0
Lipase increased[b]	10 (16.7)	2 (3.3)
Cough	9 (15.0)	0
Pneumonia	8 (13.3)	5 (8.3)
Pyrexia	8 (13.3)	0
Arthralgia	7 (11.7)	0
COVID-19	7 (11.7)	0
Dyspnea	7 (11.7)	0
Peripheral edema	7 (11.7)	0
Thrombocytopenia[c]	7 (11.7)	2 (3.3)
Amylase increased[b]	6 (10.0)	0
Nausea	6 (10.0)	0
Sinusitis	6 (10.0)	0

- No atrial fibrillation
- No pancreatitis[b]
- Major hemorrhage[d]: 3.3% (n=2; Grade 1 subarachnoid hemorrhage [n=1] and Grade 3 subdural hemorrhage [n=1])
- Febrile neutropenia: 1.7%

Median follow-up: 10.2 months (range, 0.3-26.4+).
[a]Neutropenia combines preferred terms neutrophil count decreased and neutropenia. [b]All events were lab findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. [c]Thrombocytopenia combines preferred terms platelet count decreased and thrombocytopenia. [d]Grade ≥3, serious, or any central nervous system bleeding.
CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event.
Adapted from Thompson MC, et al. Oral presentation at ASH 2024; Abstract #885.

CLL/SLL

Overall response rate

BGB-16673-101 – CaDAnCe-101 (R/R CLL/SLL)

- The ORR was 77.6% (38/49) in response-evaluable patients with CLL/SLL
- The ORR for the 200-mg group was 93.8%

	50 mg (n=1)	100 mg (n=5)	200 mg (n=16)	350 mg (n=15)	500 mg (n=12)	Total[a] (N=49)
Best overall response, n (%)						
CR/CRi	0	1 (20.0)	1 (6.3)	0	0	**2 (4.1)**
PR[b]	1 (100)	3 (60.0)	12 (75.0)	10 (66.7)	7 (58.3)	33 (67.3)
PR-L	0	0	2 (12.5)	0	1 (8.3)	3 (6.1)
SD	0	1 (20.0)	0	1 (6.7)	4 (33.3)	6 (12.2)
PD	0	0	1 (6.3)	1 (6.7)	0	2 (4.1)
Discontinued prior to first assessment	0	0	0	3 (20.0)	0	3 (6.1)
ORR, n (%)[c]	1 (100)	4 (80.0)	**15 (93.8)**	10 (66.7)	8 (66.7)	**38 (77.6)**
Disease control rate, n (%)[d]	1 (100)	5 (100)	15 (93.8)	11 (73.3)	12 (100)	44 (89.8)
Median time to first response, mo (range)[e]	2.9 (2.9–2.9)	4.2 (2.8–6.2)	2.9 (2.6–8.3)	2.8 (2.6–8.3)	2.8 (2.6–8.3)	2.8 (2.6–8.3)
Median time to best response, mo (range)	2.9 (2.9–2.9)	5.6 (2.8–11.1)	3.4 (2.6–13.8)	5.6 (2.6–8.3)	4.2 (2.6–8.6)	3.6 (2.6–13.8)
Median duration of exposure, mo (range)	26.4 (26.4–26.4)	13.8 (13.6–18.6)	10.6 (2.9–18.9)	10.3 (0.2–16.8)	9.3 (6.8–15.4)	10.4 (0.2–26.4)

[a]Efficacy-evaluable patients. [b]Out of 33 patients with PR, 8 achieved all nodes normalized. [c]Includes best overall response of PR-L or better. [d]Includes best overall response of SD or better.
[e]In patients with a best overall response of PR-L or better.
CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete marrow recovery; mo, months; ncBTKi, non-covalent BTKi; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; R/R, relapsed/refractory; SD, stable disease; SLL, small lymphocytic lymphoma.
Adapted from Thompson MC, et al. Oral presentation at ASH 2024; Abstract #885.

CLL/SLL

Overall response rate

BGB-16673-101 – CaDAnCe-101 (R/R CLL/SLL)

- The ORR was high in patients who had:
  - Double exposure (previous cBTKi + BCL2i): 26/30 (86.7%)
  - Triple exposure (previous cBTKi + ncBTKi + BCL2i): 7/12 (58.3%)
  - Del(17p) or *TP53* mutation: 23/31 (74.2%)
  - Complex karyotype: 11/15 (73.3%)
- Responses have been observed in patients with *BTK* mutations, as well as patients with *PLCG2* mutations

BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton's tyrosine kinase; cBTKi, covalent BTK inhibitor; CLL, chronic lymphocytic leukemia; del, deletion; ncBTKi, non-covalent BTKi; ORR, overall response rate; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.
Thompson MC, et al. Oral presentation at ASH 2024; Abstract #885.

WM

Baseline patient characteristics

BGB-16673-101 – CaDAnCe-101 (WM): Heavily pretreated with high rate of mutations

	Total (N=27)
Median age, years (range)	73.0 (56-81)
Male, n (%)	15 (55.6)
ECOG PS, n (%)	
0	14 (51.9)
1	12 (44.4)
2	1 (3.7)
Median hemoglobin, g/dL (range)	10.3 (6.0-13.5)
Median neutrophils, 10^9/L (range)	2.7 (0.21-7.43)
Median platelets, 10^9/L (range)	157 (14-455)
Mutation status, n/N with known status (%)[a]	
MYD88	24/26 (92.3)
CXCR4	12/25 (48.0)
BTK	11/25 (44.0)
TP53	13/25 (52.0)

	Total (N=27)
Median IgM, g/L (range)	37.4 (2.8-74.4)
No. of prior lines of therapy, median (range)	3.0 (2-11)
Prior therapy, n (%)	
cBTKi	27 (100)
Chemotherapy	25 (92.6)
Proteasome inhibitor	9 (33.3)
BCL2i	5 (18.5)
ncBTKi[b]	4 (14.8)
Discontinued prior BTKi due to PD, n(%)	21 (77.8)

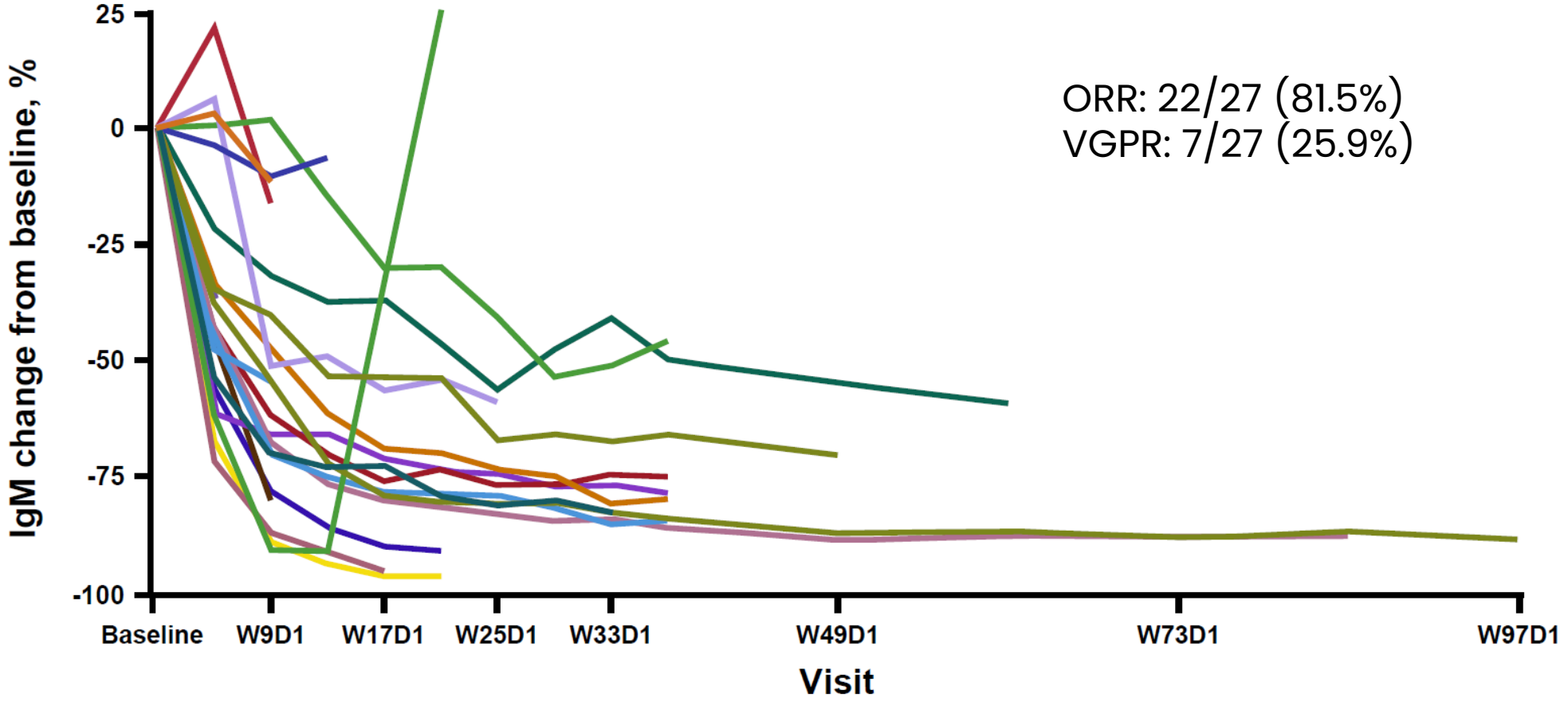
Data cutoff: September 2, 2024.
[a]Confirmed by central laboratory. [b]All 4 patients with ncBTKi exposure were exposed to a cBTKi.
BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; cBTKi, covalent BTKi; ECOG PS, Eastern Cooperative Oncology Group performance status; IgM, immunoglobulin M; ncBTKi, non-covalent BTKi; PD, progressive disease; WM, Waldenström's macroglobulinemia.
Adapted from Seymour JF, et al. Oral presentation at ASH 2024; Abstract #860.

WM

IgM decreased in all patients

BGB-16673-101 – CaDAnCe-101 (WM)

Rapid decline in IgM at all dose levels



ORR: 22/27 (81.5%)
VGPR: 7/27 (25.9%)

Patient with rapid IgM increase had WM mutations in *BTK, MYD88, CXCR4*, and *TP53* at baseline, paused treatment for 2-3 weeks due to COVID-19 infection, and developed rapid progression shortly after restarting treatment.
IgM, immunoglobulin M; ORR, overall response rate; VGPR, very good partial response; WM, Waldenström's macroglobulinemia; WxDx, week x day x.
Adapted from Seymour JF, et al. Oral presentation at ASH 2024; Abstract #860.

Patient case: Double refractory CLL

2014 — Jun 2024 — Mar 2025

Initial presentation
- 77-year-old female patient
- B-CLL diagnosis: U-IGHV, trisomy 12

Progression (IV)
- Ly: 26.340/mmc; LDH: 944 U/L
- CT scan: axillar lymphadenopathies (22x6 mm, 10x6 mm); spleen 14,3 cm; interaortocaval lymphadenopathy (31x26 mm)

Response assessment (W37)
- Ly: 3.590/mmc; LDH: 133 U/L
- CT scan: no lymphadenopathy;
- spleen 10,5 cm
- Treatment-related AE: skin rash G1

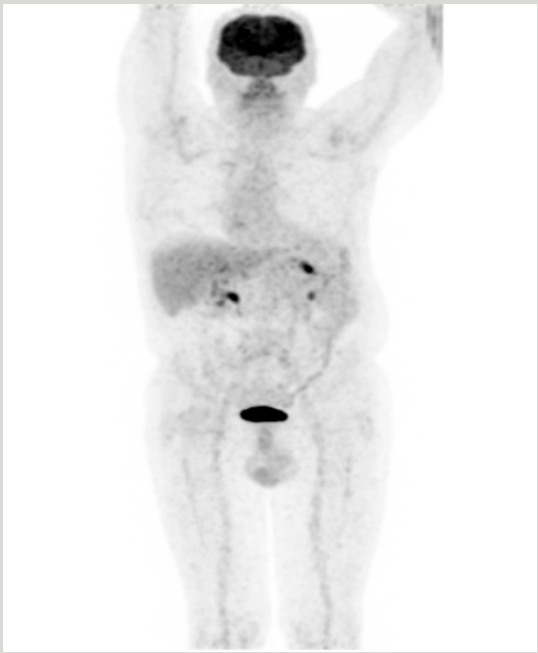
- I: R-bendamustine x6 (Jan-Jun 2017)
- II: Ibrutinib 420 mg (Oct 2019-Sept 2021)
  - Sept 2021: *TP53*^{mut}
- III: R-venetoclax (Sept 2021-Oct 2023)

Jul 3, 2024: Enrolled in BGB-16673-101 (Part 1b, safety expansion)

- Dose: 100 mg QD

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
AE, adverse event; B-CLL, B-cell chronic lymphocytic leukemia; CLL, chronic lymohocytic leukemia; CT, computed tomography; G1, grade 1; LDH, lactate dehydrogenase; Ly, lymphocytes; mut, mutated; QD, once daily; R, rituximab; U-IGHV, unmutated immunoglobulin heavy chain variable region; W37, week 37.

Patient case: Double refractory CLL with RT

2008	Aug 2023	Oct 2024	Jun 2025
Initial presentation ✦ 68-year-old male patient ✦ B-CLL diagnosis	**Richter's syndrome** ✦ DLBCL, GCB type	**Progression** ✦ CT scan: right axillar lymphadenopathy (17x25 mm); carinal lymphadenopathy (20x16 mm); spleen 14,3 cm; retroperitoneal conglomerate 1,8x1x7,5 cm (PET/CT not available); s.c IIIA	**Response assessment (W16)** ✦ PET/CT: CR
✦ I: Ibrutinib (May-Jul 2022) ✦ III: R-venetoclax (Aug 2022-Aug 2023)	✦ I: R-CHOP x6 (Aug 2023-Jan 2024) → PD ✦ II: Glofitamab x12 (Mar-Oct 2024) → PD	**Dec 17, 2024: Enrolled in BGB-16673-101** (Part 1c, additional safety expansion) ✦ Dose: 350 mg QD ✦ AE (Feb 2025): transaminase increase G3 (unrelated)	

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.

AE, adverse event; B-CLL, B-cell chronic lymphocytic leukemia; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CLL, chronic lymphocytic leukemia; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; G3, grade 3; GCB, germinal center B-cell-like; PD, progressive disease; PET, positron emission tomography; QD, once daily; R, rituximab; RT, Richter's transformation; W13, week 13.

Speaker's own conclusions

- In the results from the ongoing first-in-human study CaDAnCe-101, the novel BTK degrader **BGB-16673** showed a generally **tolerable safety profile** in heavily pretreated patients with **R/R CLL and WM**
- There was **promising antitumor activity**, including in patients with BTKi-resistant mutations and those previously exposed to cBTKi, ncBTKi, and BCL2i
- The speaker's experience with double refractory CLL and a RT with 4 prior lines of treatment confirms general observations on the activity of BGB-16673
- These data support further investigation of BGB-16673 clinical activity in patients with CLL/SLL and WM

Speaker's own slide. The opinions expressed here are those of the speaker and do not necessarily reflect those of BeOne.
BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; cBTKi, covalent BTKi; CLL, chronic lymphocytic leukemia; DLT, dose-limiting toxicity; IgM, immunoglobulin M; MTD, maximum tolerated dose; ncBTKi, non-covalent BTKi; ORR, overall response rate; R/R, relapsed/refractory; RT, Richter's transformation; SLL, small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.

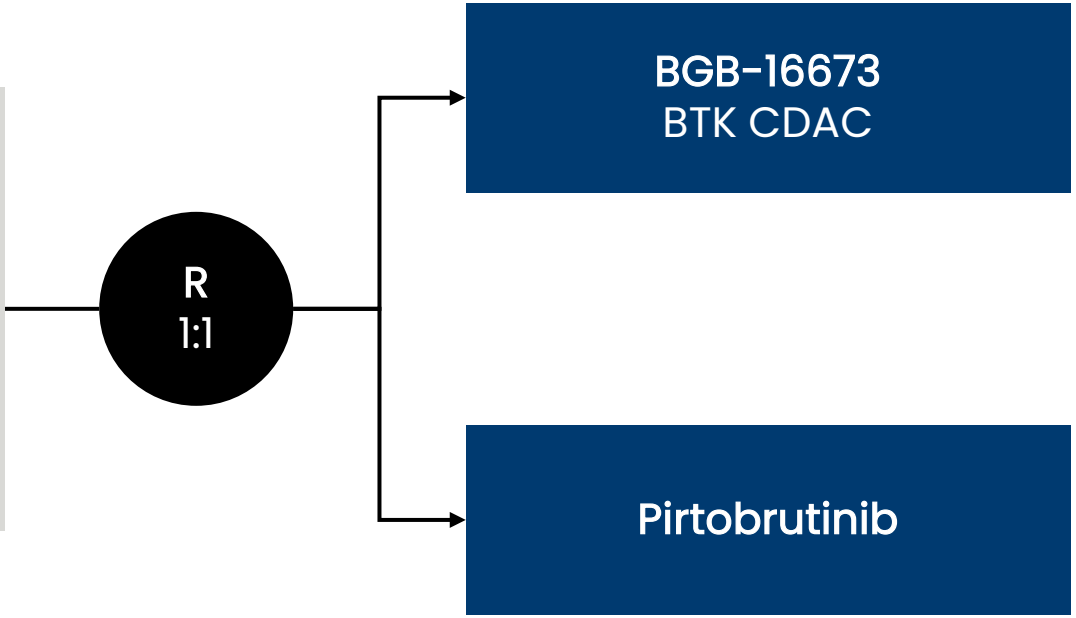
Planned head-to-head study of BGB-16673 vs. pirtobrutinib

BGB-16673-304 is a Phase 3 study of BGB-16673 vs. pirtobrutinib in patients with R/R CLL previously exposed to a cBTKi

Study identifier: BGB-16673-304, NCT06973187

Study population

- R/R CLL/SLL per iwCLL 2018
- Previously received one line of treatment with a **cBTKi**



Primary endpoint

- **PFS superiority** by IRC

Key secondary endpoints

- Complete response rate
- Overall survival

BTK, Bruton's tyrosine kinase; cBTKi, covalent BTK inhibitor; CDAC, chimeric degradation activation compound; CLL, chronic lymphocytic leukemia; IRC, independent review committee; PFS, progression-free survival; R, randomized; R/R, relapsed/refractory.
BGB-16673-304. NCT06973187. Available from: https://clinicaltrials.gov/study/NCT06973187. Accessed June 2025.

BGB-16673 in double/triple-exposed patients

BGB-16673-302 is a Phase 3 study of BGB-16673 vs. investigator's choice in patients with R/R CLL previously exposed to both BTKi and BCL2i

Study identifier: BGB-16673-302, NCT06846671

Study population

- R/R CLL SLL per iwCLL 2018
- Previously received treatment with **BTK and BCL2 inhibitors**
  - Require **≥80 pt triple-exposed** (post-pirto)

N = 250

R
3:2

Stratification:
- Prior ncBTKi
- del(17p)/ *TP53*
- Tx choice

BGB-16673
200mg PO QD

Investigator's choice
- *Idelalisib + rituximab*
- *Bendamustine + rituximab*
- *Ven + R retreatment*

Primary endpoint
- PFS by IRC

Key secondary endpoints
- PFS by IRC in post-pirto pts
- OS

Secondary endpoints
- PFS by Inv
- Safety
- DOR/TTNT
- ORR, PRL+
- PROs

BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; del, deletion; DOR, duration of response; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; mo, months; ncBTKi, non-covalent BTKi; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; pirto, pirtobrutinib; PO, orally; PRL, partial response with lymphocytosis; PRO, patient-reported outcomes; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TTNT, time to next treatment; Ven+R, venetoclax-rituximab.

BGB-16673-302. NCT06846671. Available from: https://clinicaltrials.gov/study/NCT06846671. Accessed May 2025.

Latest updates on BGB-16673 will be presented at 18-ICML

You have the opportunity to learn more about BGB-16673 from Prof. Bertoni at his talk **'The BTK degrader BGB-16673 and the BCL2 inhibitor sonrotoclax show anti-tumor activity as single agents and in combination in marginal zone lymphoma models'**

SESSION

Focus on EXPERIMENTAL THERAPEUTICS

DATE and TIME

June 18th at 17:00

ROOM

Polivalente, East Campus USI

References

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- Brown JR, et al. Genomic evolution and resistance during pirtobrutinib therapy in covalent BTK-inhibitor (cBTKi) pre-treated chronic lymphocytic leukemia patients: Updated analysis from the BRUIN study. *Blood.* 2023;142(Suppl 1):326.
- Cheah CY, et al. Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB -16673 in patients with relapsed or refractory indolent NHL: Results from the Phase 2 BGB-16673-101 study. Poster presented at the EHA 2024; Abstract #P1119.
- Estupinán HY, et al. BTK gatekeeper residue variation combined with cysteine 481 substitution causes super -resistance to irreversible inhibitors acalabrutinib, ibrutinib and zanubrutinib. *Leukemia.* 2021;35(5):1317-1329.
- Feng X, et al. Bruton tyrosine kinase (BTK) protein degrader BGB -16673 is less apt to cause, and able to overcome variable BTK resistance mutations compared to other BTK inhibitors. Poster presentation at EHA 2023; Abstract #P1239.
- Hamasy A, et al. Substitution scanning identifies a novel, catalytically active ibrutinib -resistant BTK cysteine 481 to threonine (C481T) variant. *Leukemia.* 2017;31(1):177-185.
- Munir T, et al. First results from a Phase 1, first-in-human study of BGB-166873 in patients with relapsed/refractory B-cell malignancies. Poster presentation at BSH 2024; Abstract #PO143.
- Naeem AS, et al. Pirtobrutinib targets BTK C481S in ibrutinib-resistant CLL but second-site BTK mutations lead to resistance. *Blood Adv.* 2023;7(9):1929-1943.
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- Seymour JF, et al. Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB -16673 in patients with relapsed or refractory Waldenström macroglobulinemia: Results from the Phase 1 CaDAnCe-101 study. Oral presentation at ASH 2024; Abstract #860.
- Song Y, et al. A two-part, single-arm, multicentre, phase I study of zanubrutinib, a selective Bruton tyrosine kinase inhibitor, in Chinese patients with relapsed/refractory B-cell malignancies. *Br J Haematol.* 2022;198(1):62-72.
- Thompson MC, et al. Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB -16673 in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: Results from the Phase 1 CaDAnCe-101 study. Oral presentation at ASH 2024; Abstract #885.
- Wang E, et al. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors.*N Engl J Med.* 2022;386(8):735-743.
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Q&A

All faculty

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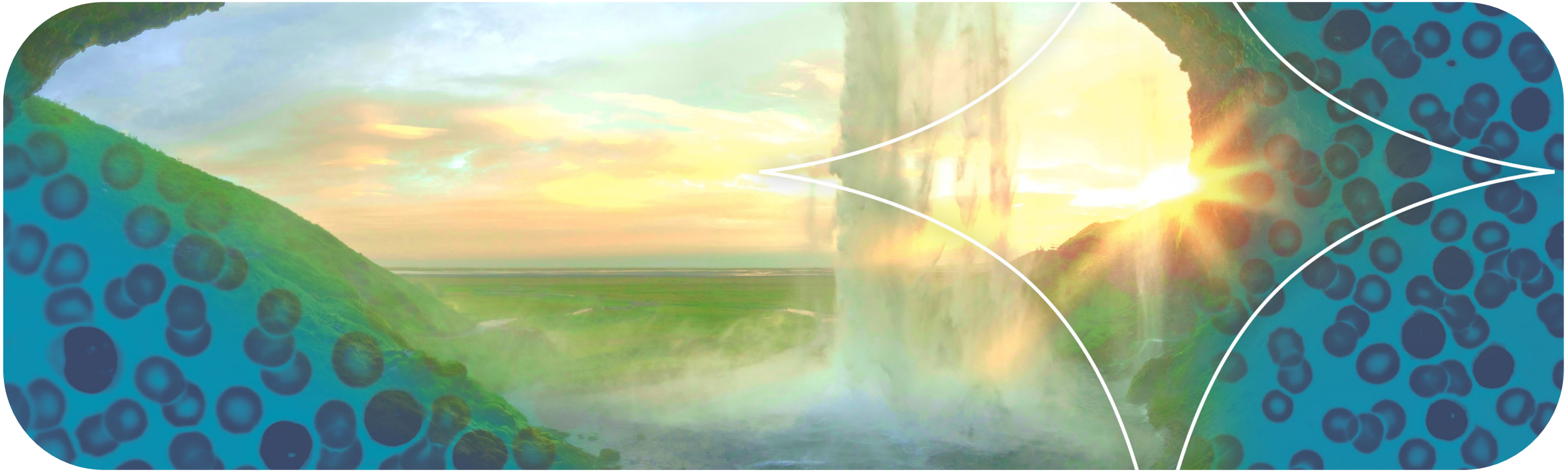

Closing remarks

Professor Catherine Thieblemont
Hôpital Saint-Louis
(Hôpitaux Universitaires Saint-Louis, Laboisière, Fernand-Widal)
Paris, France

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Take-home messages

By improving outcomes, BTKis have significantly transformed the treatment landscape of CLL and other B-cell lymphomas

Zanubrutinib is the only BTKi registered for use in CLL, WM, MZL, MCL*, and FL[1]

First- and second-generation BTKis provide effective treatment options for lymphoma patients

Zanubrutinib:

is the only BTKi with demonstrated superior efficacy to ibrutinib in R/R CLL[2]

overcomes the negative prognostic impact of del(17p), as shown in the largest cohort of uniformly treated patients with del(17p) TN CLL[3]

Second-generation cBTKis have an improved safety profile compared to ibrutinib, which is associated with cardiovascular AEs

A meta-analysis showed that zanubrutinib had lower rates of AEs that limit daily activities compared to acalabrutinib[4]

The future of lymphoma care is bright, with new BTKi-based combinations and novel BTK-degrading agents on the horizon

The BTK degrader BGB-16673 has demonstrated promising clinical benefit in CLL and WM[5,6]

**Indications of approved products may differ between countries. Zanubrutinib is authorized under different conditions (e.g., different government-approved professional information: indications, warnings, etc.) in Switzerland. For country-specific information, refer to the prescribing information for the country in which you practice medicine.*

AE, adverse event; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; cBTKi, covalent BTKi; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma;R/R, relapsed/refractory; WM, Waldenström's macroglobulinemia.

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