NOVEL THERAPIES FOR RELAPSED CLL 2026

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EMORY WINSHIP CANCER INSTITUTE
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DISCLOSURES

Consulting: AstraZeneca, BeOne Medicines, BMS

Research Funding: Abbvie, BeOne Medicines

OUTLINE

Review of current treatment paradigms in relapsed/refractory CLL

- Double-exposed (cBTKi, Bcl-2i)
- Triple-exposed (cBTKi, Bcl-2i, ncBTKi)

Discuss future management of R/R CLL

- Bispecific T cell engagers
- BTK degraders
- Other agents under study

Main Tools for the Treatment of CLL (6-2026)

Obinutuzumab (Obin)

Rituximab (Ritux)

Ibrutinib (Ib)

Acalabrutinib (acala)

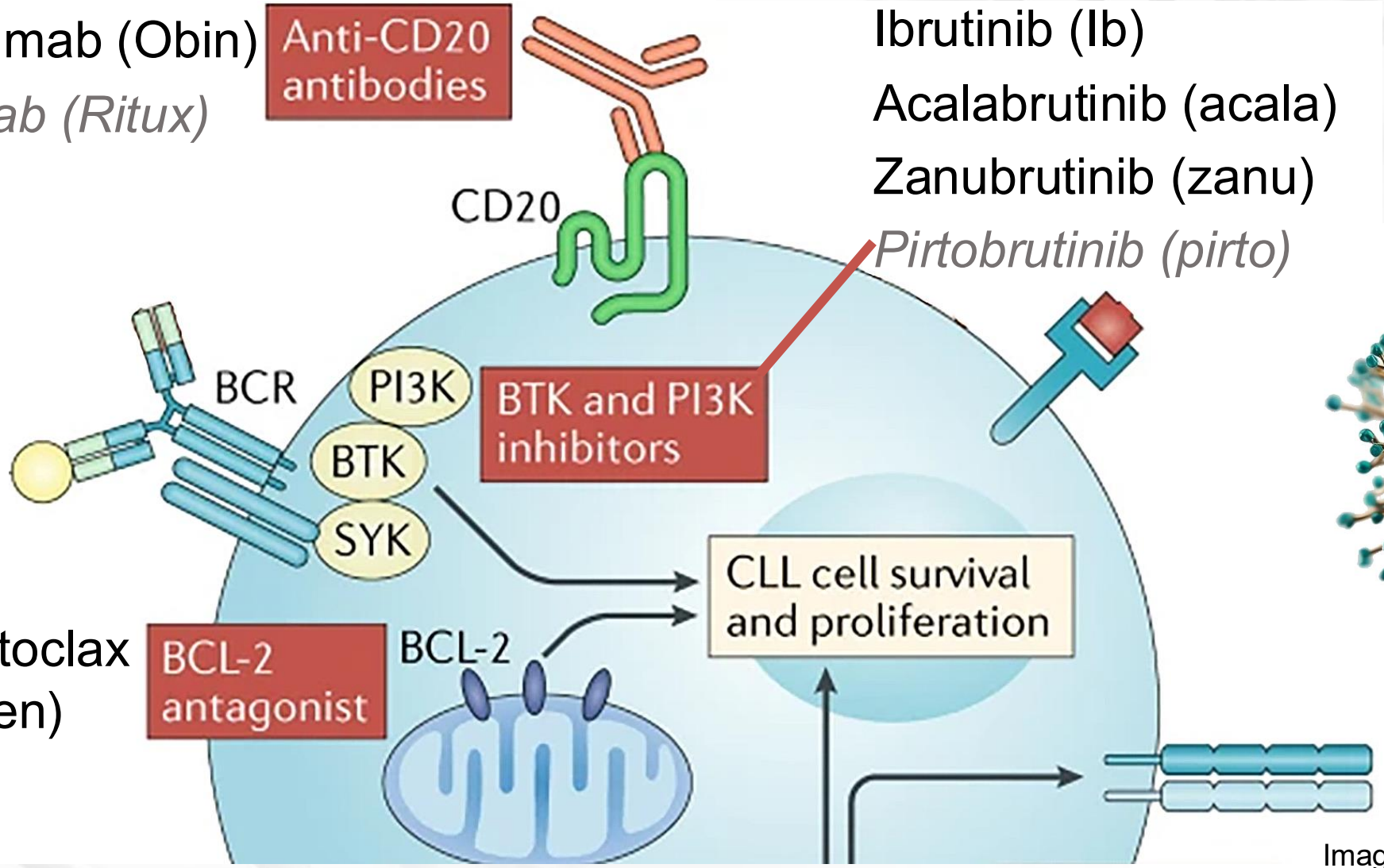
Zanubrutinib (zanu)

Pirtobrutinib (pirto)

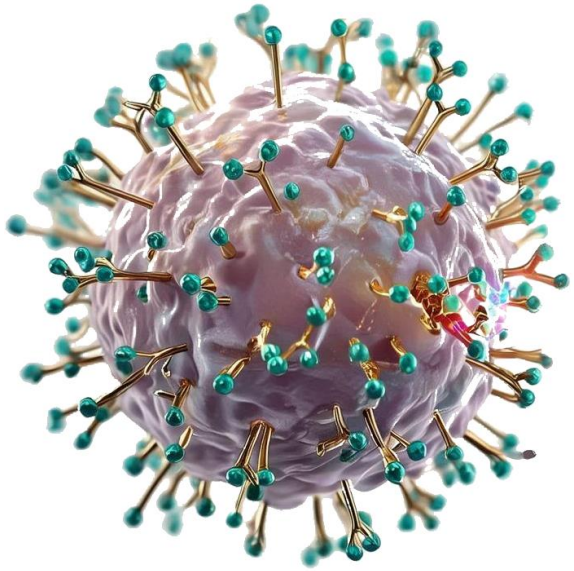
Duvelisib

Idelalisib

Chemotherapy



Venetoclax (ven)



Liso-cel

Image generated from Bing images

Adapted from Burger and O'Brien, Nat Rev Clin Onc, 2018

NCCN Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL with or without del(17p)/*TP53* Mutation
(alphabetical by category)

SECOND-LINE OR SUBSEQUENT THERAPY[e,f]	
Preferred	**Other Recommended**
• BCL2i-containing regimen[*] ▸ Venetoclax + Obinutuzumab • cBTKi-based regimens[i,j,x] ▸ Acalabrutinib (continuous) (category 1) ▸ Zanubrutinib (continuous) (category 1) • ncBTKi-based regimen: ▸ Pirtobrutinib (continuous) (category 1) (resistance or intolerance to prior cBTKi-based regimens)	• BCL2i-containing regimens[*] ▸ Venetoclax + Rituximab (category 1) ▸ Venetoclax[*] ▸ Venetoclax/Ibrutinib[j,y,z] (category 2B) • cBTKi-based regimen[i,j] ▸ Ibrutinib[n] (continuous) (category 1)

[*] Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) or venetoclax + cBTKi is a treatment option for relapse after a period of remission. Single agent venetoclax (continuous) can also be considered a treatment option for relapse after a period of remission.

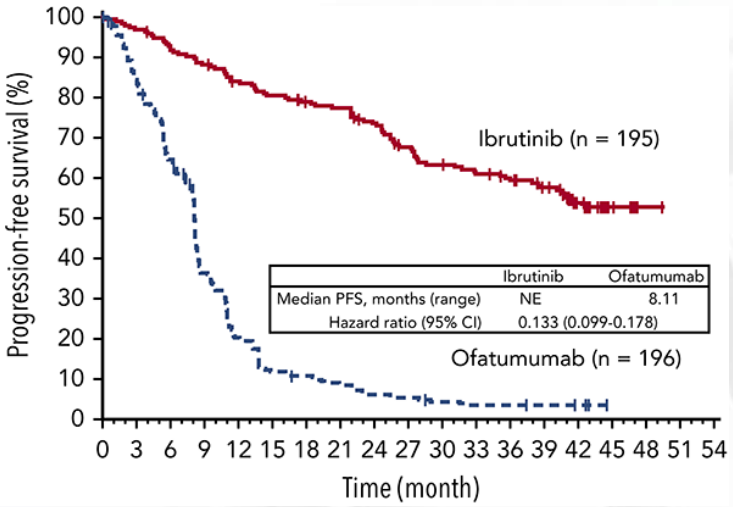
THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR cBTKi-BASED AND BCL2i-CONTAINING REGIMENS[e,f]	
Preferred	**Other Recommended**
• Chimeric antigen receptor (CAR) T-cell therapy ▸ Lisocabtagene maraleucel (CD19-directed)[aa] ± Ibrutinib[j] • ncBTKi-based regimen: ▸ Pirtobrutinib (continuous) (category 1) (if not previously given)	• PI3Ki-based regimens ▸ Duvelisib ▸ Idelalisib[bb] + Rituximab • FC + Rituximab[s,t,**] • Lenalidomide[cc] ± Rituximab • Obinutuzumab • Alemtuzumab[dd] ± Rituximab (with del(17p)/*TP53* mutation) • Bendamustine[p] + Rituximab[q,**] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities) • HDMP + anti-CD20 mAb[δ] (category 2A with del[17p]; category 2B without del[17p])

[**] Not recommended for CLL/SLL with del(17p)/*TP53* mutation.

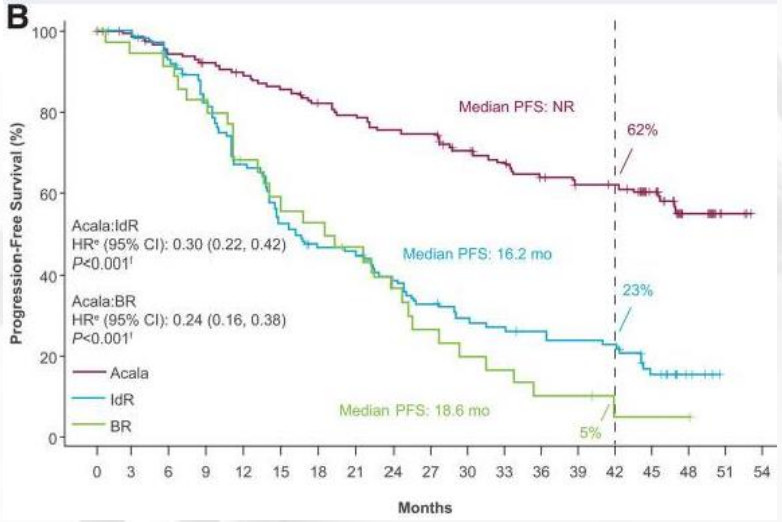
Relapse alone is not an indication for treatment, follow iwCLL criteria

Covalent BTK Inhibitors for R/R CLL

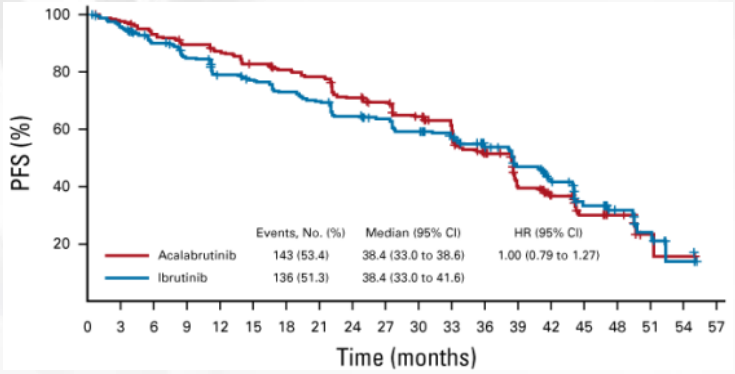
RESONATE
Phase 3, ibrutinib vs ofatumumab



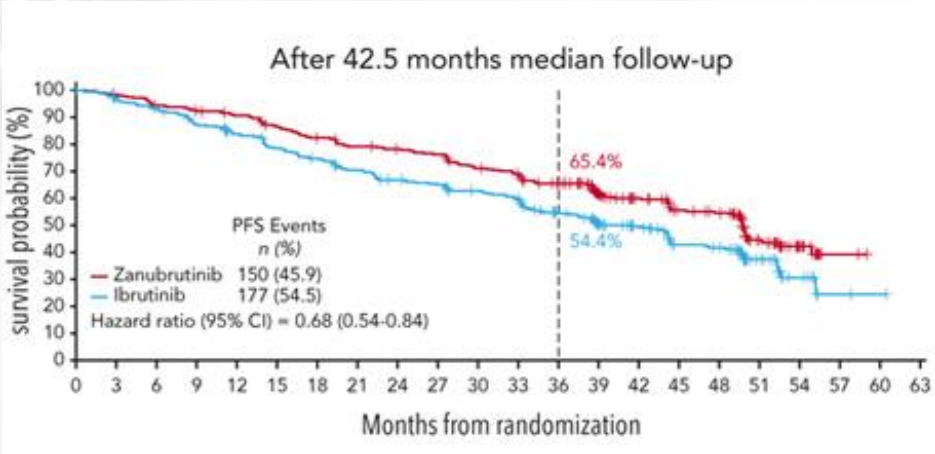
ASCEND
Randomized, open-label, Phase 3
Acalabrutinib vs BR or idelaR



ELEVATE R/R, noninferiority
Phase 3, ibrutinib vs acalabrutinib



ALPINE
Randomized, open-label, Phase 3
Zanubrutinib vs Ibrutinib



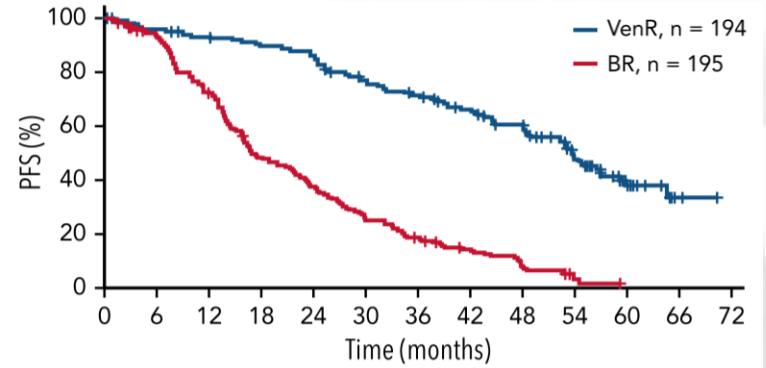
Byrd, et al, NEJM 2014
Byrd, et al, Blood 2019
Ghia et al, Hemasphere 2022
Byrd, et al, JCO 2021
Brown, et al, NEJM 2023
Brown et al, Blood 2024

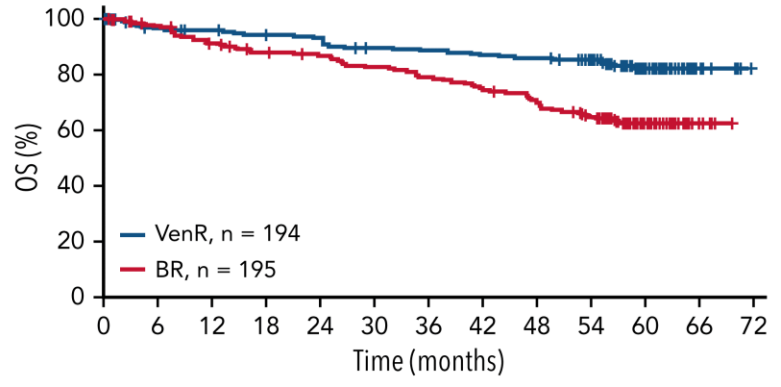
Venetoclax-based Regimens for R/R CLL

MURANO

Randomized, phase 3 N=389

Ven-R x 6 cycles then Ven monotherapy for total 2 years vs BR x 6 cycles

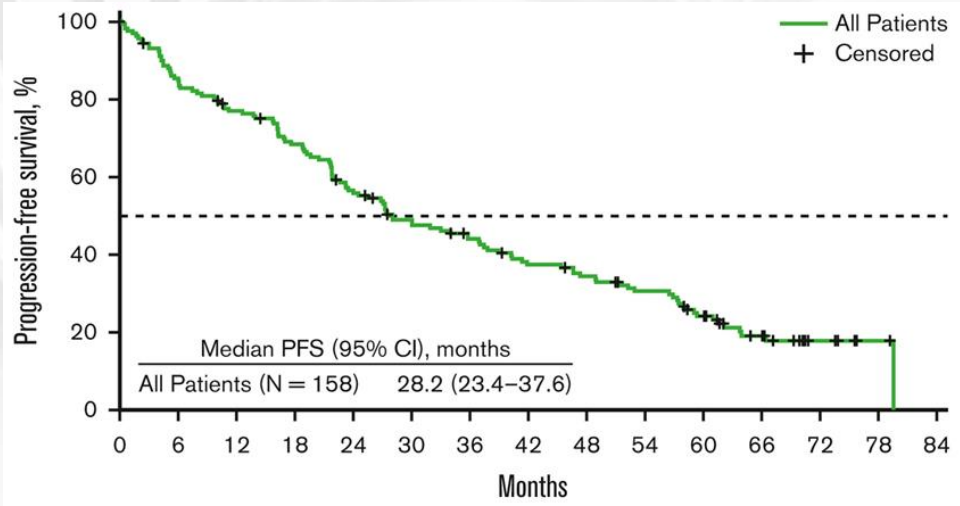




Seymour et al, NEJM 2018; Blood 2022

M13-982

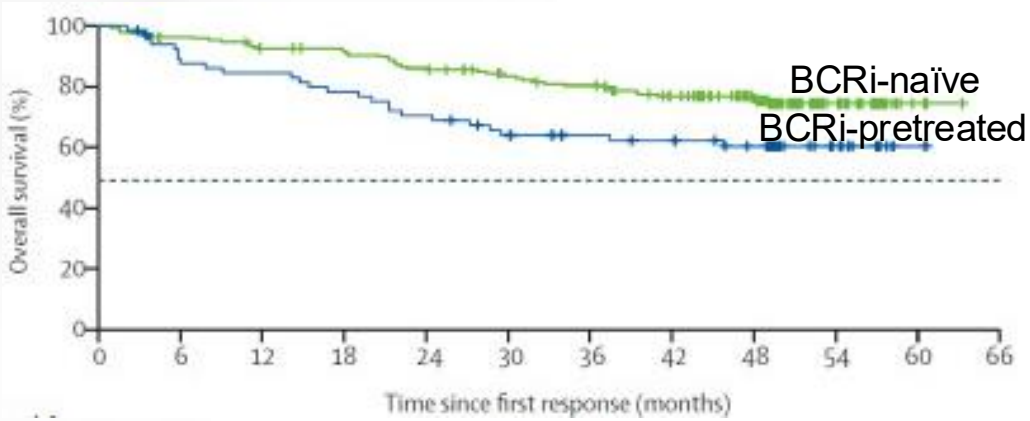
Venetoclax, Phase 2, R/R (mostly) CLL with del17p



Stilgenbauer et al, Lancet Onc 2016; Blood Adv 2024

VENICE-1

phase 3b single arm **Ven** x 2 yr

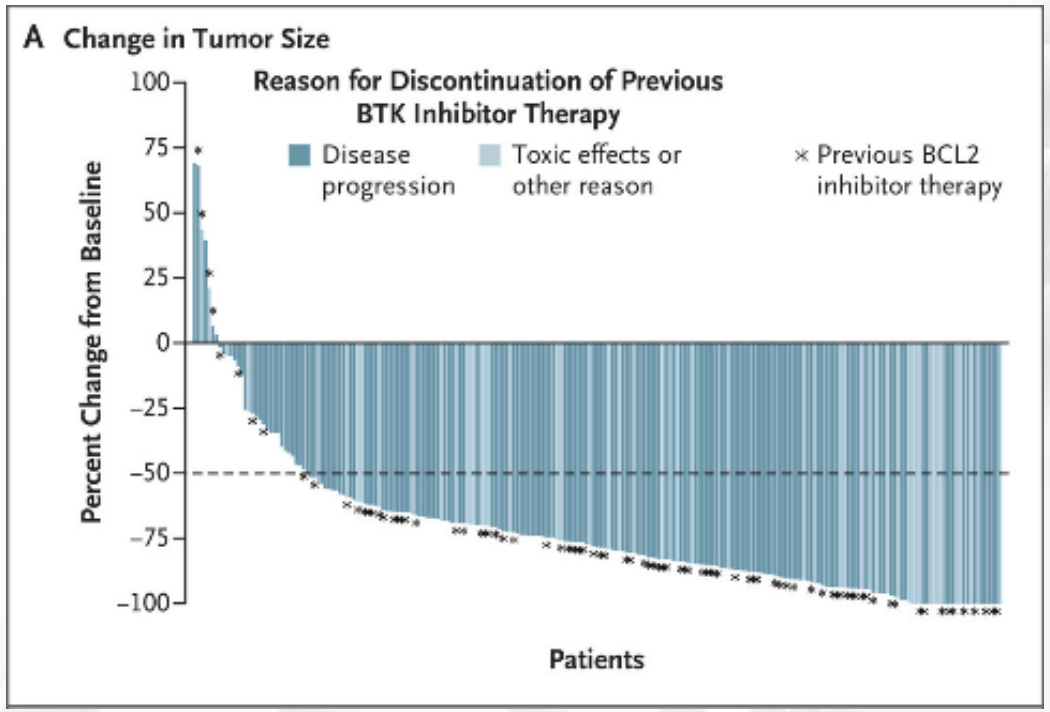


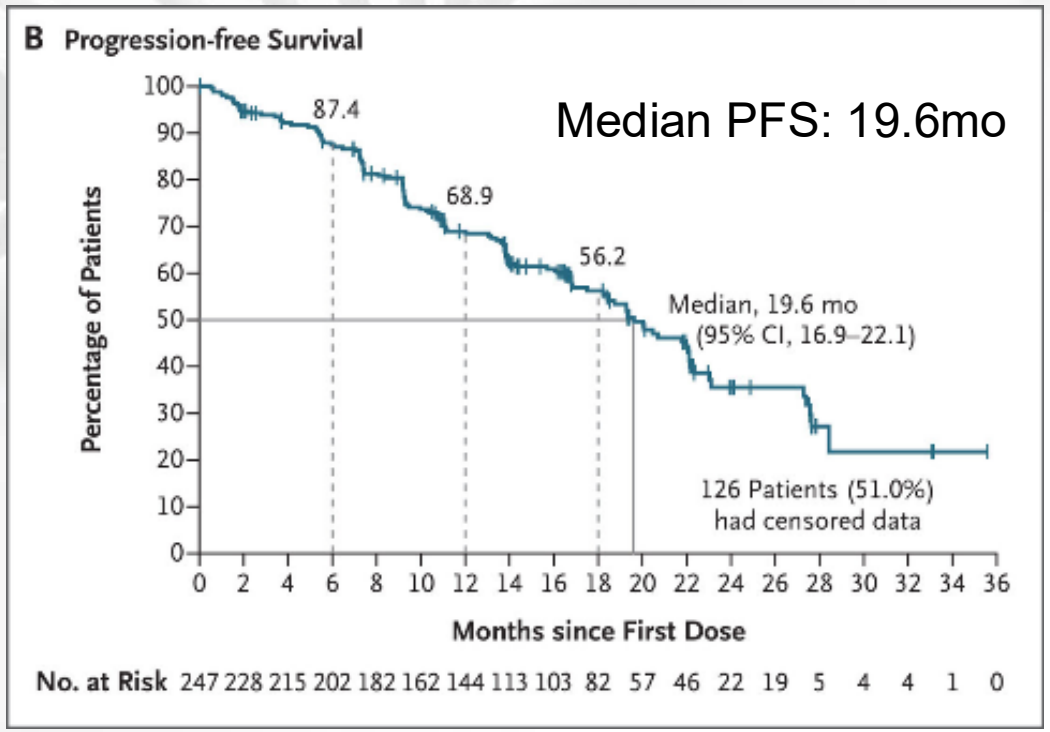
Kater, et al, Lancet Onc 2024

Double Refractory: Pirtobrutinib – non-covalent BTKi

Inhibits WT and C481S mutated BTK

Phase 1/2 BRUIN Trial





ORR:

Prior BTKi: 82.2%

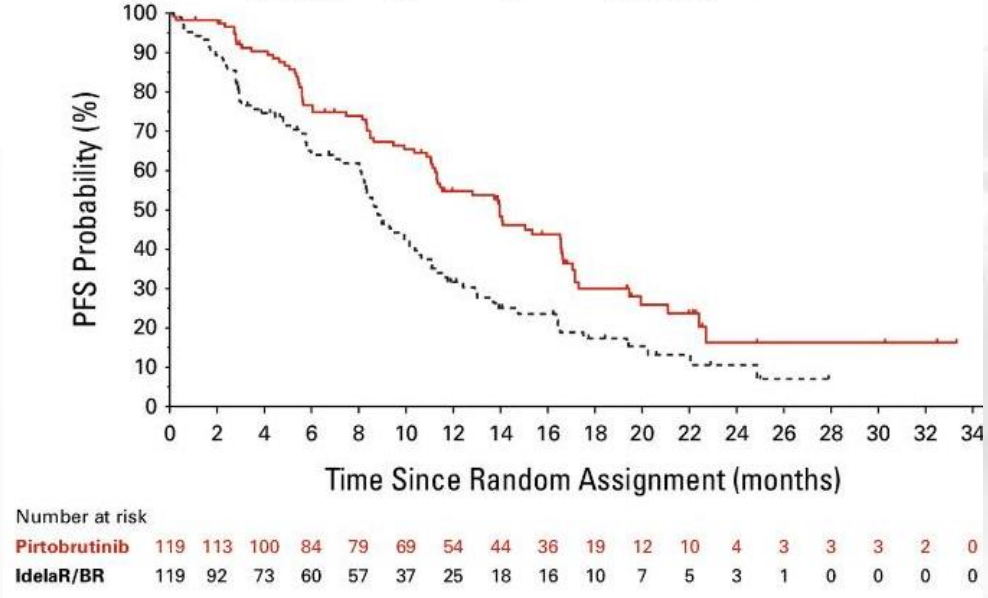
Prior BTKi and Bcl2i: 79.0%

Mato et al, NEJM 2023

Pirtobrutinib – Phase 3 Data

BRUIN 321: Phase 3

	No. of Patients	No. of Events	Median, Months (95% CI)	HR (95% CI)	P*
Pirtobrutinib	119	74	14.0 (11.2-16.6)	0.54 (0.39-0.75)	.0002
IdelaR/BR	119	79	8.7 (8.1-10.4)		



Number at risk

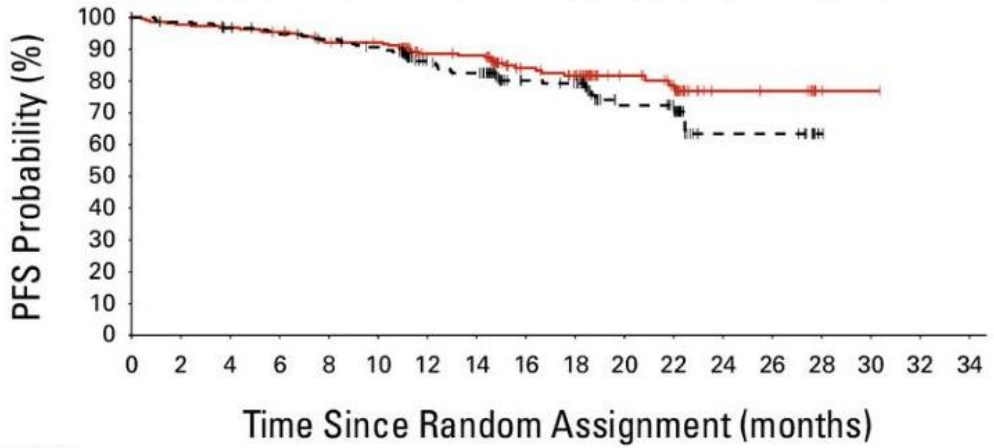
Pirtobrutinib	119	113	100	84	79	69	54	44	36	19	12	10	4	3	3	3	2	0
IdelaR/BR	119	92	73	60	57	37	25	18	16	10	7	5	3	1	0	0	0	0

Pirtobrutinib vs <u>Idela/R or BR</u>
Median lines of therapy: 3
100% previous cBTKi
~50% prior Bcl-2i
mPFS: 14 vs 8.7mo

Sharman et al, JCO 2025

BRUIN 314: Phase 3

	No. of Patients	No. of Events	18-Month PFS Rates (95% CI)	HR (95% CI)	P*
Pirtobrutinib	219	37	81.7 (75.1 to 86.7)	0.729 (0.471 to 1.128)	.1563
Ibrutinib	218	45	79.2 (72.3 to 84.6)		



Number at risk
(number censored)

Pirtobrutinib	219 (0)	212 (2)	209 (3)	205 (4)	197 (5)	195 (7)	157 (38)	155 (39)	106 (82)	99 (86)	56 (129)	46 (137)	13 (169)	12 (170)	3 (179)	2 (180)	0 (182)	0 (182)
Ibrutinib	218 (0)	205 (10)	198 (13)	192 (15)	186 (18)	179 (20)	138 (53)	131 (54)	87 (95)	84 (97)	43 (133)	37 (139)	12 (161)	12 (161)	1 (172)	0 (173)	0 (173)	0 (173)

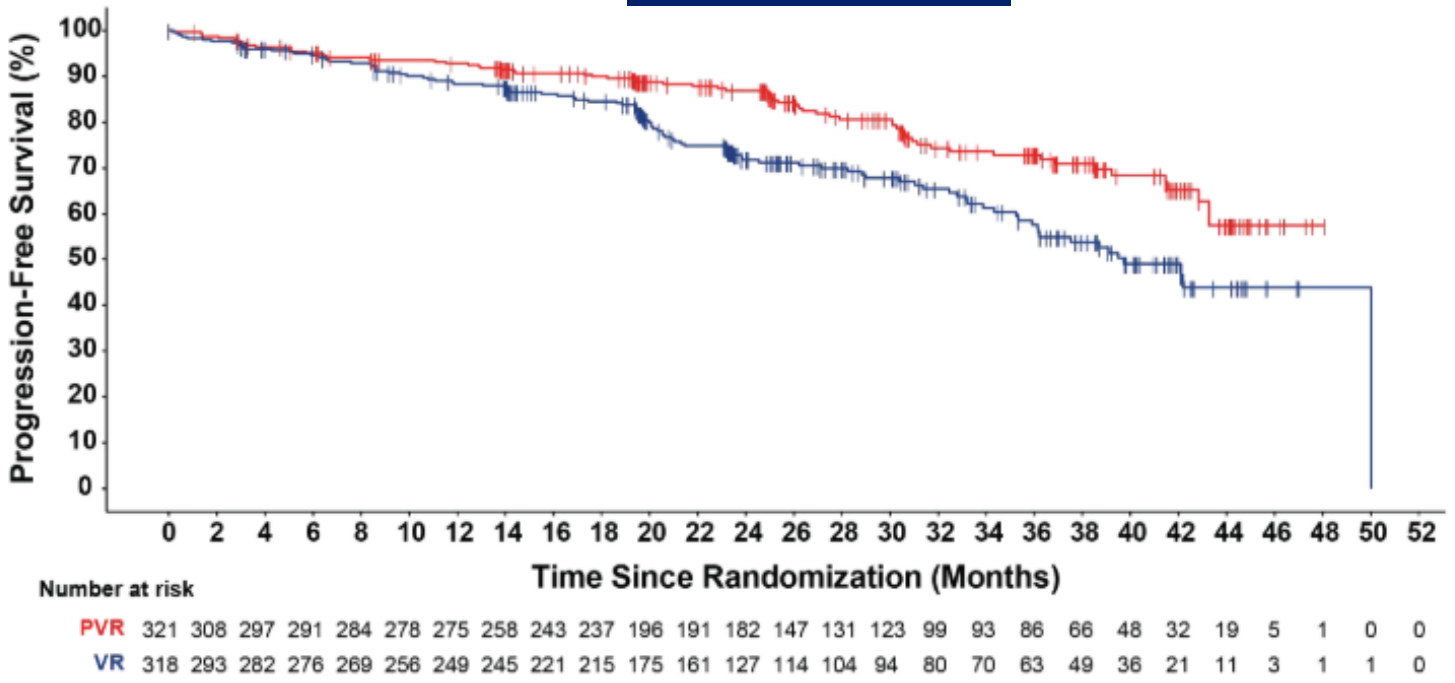
Pirtobrutinib vs <u>Ibrutinib</u>
In R/R CLL arm (n = 437):
Median lines of therapy: 1 (no prior BTKi)
ORR 84% vs 74.8%
18mo PFS: 81.7% vs 79.2%

Woyach et al, JCO 2025

Pirtobrutinib + Venetoclax + Rituximab

Figure: Kaplan–Meier estimate of IRC-assessed PFS in ITT population and efficacy overview in BRUIN CLL-322

	No. of Patients	No. of Events	24-month PFS rate (95% CI)	HR (95% CI)	p-value*
PVR	321	68	86.9 (82.3, 90.4)	0.547 (0.400, 0.748)	0.0001
VR	318	101	71.8 (65.7, 77.0)		

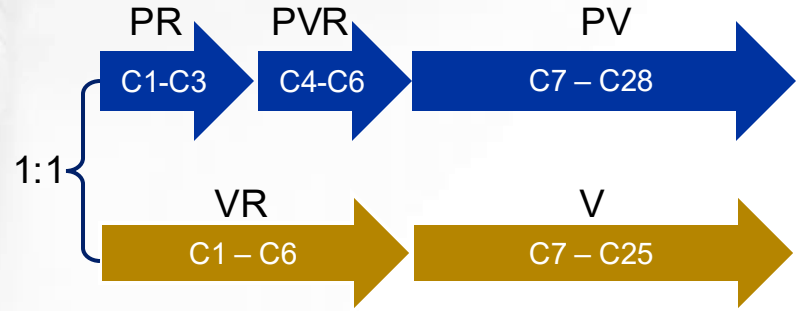


BRUIN-322

Randomized, Phase 3 (N=639)

PVR vs VR

No prior Bcl-2i



Tested superiority

Median prior lines: 2

No prior Bcl2i or ncBTKi

uMRD4: 86% vs 61%

Similar rates of AEs

TLS 0.9% vs 3.9%

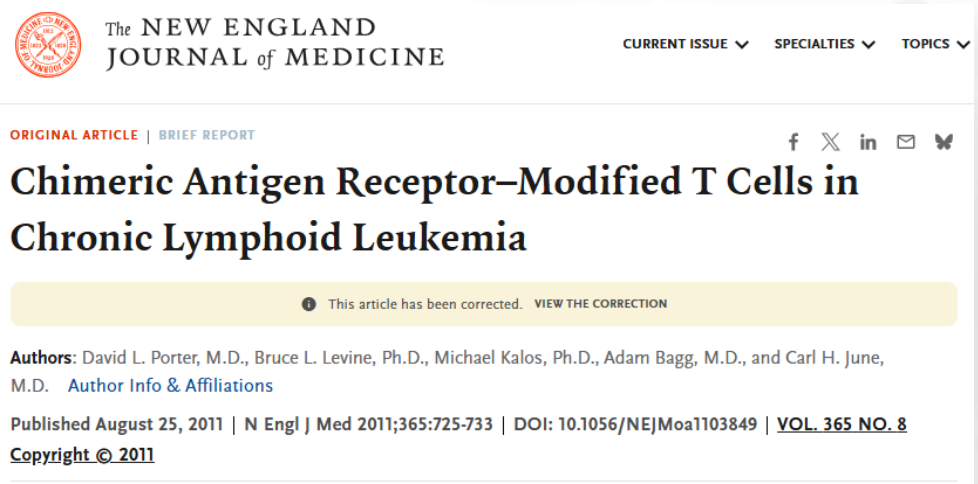
Davids et al, EHA 2026

Double/Triple Refractory: Lisocaptagene maraleucel

TRANSCEND CLL 004

Multicenter, open-label, single-arm, phase 1/2

137 patients underwent pheresis, 117 infused



The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE | BRIEF REPORT

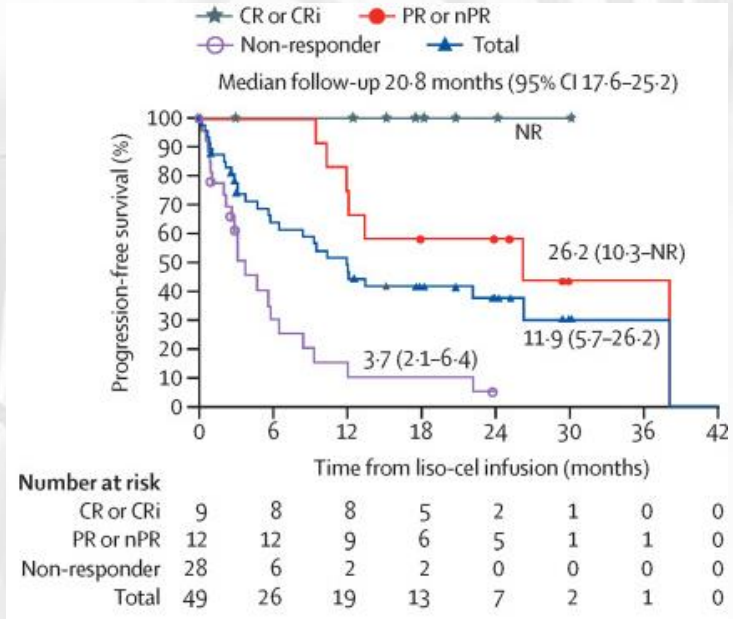
Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

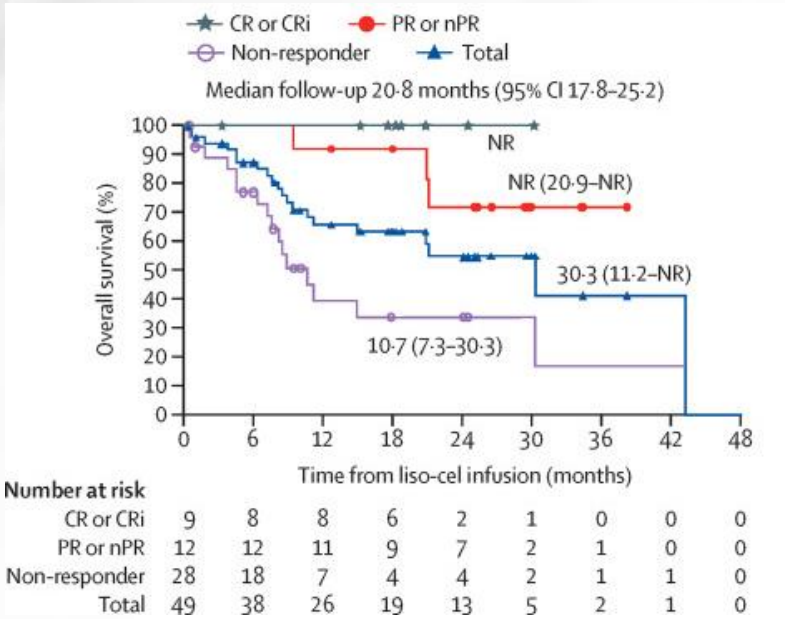
This article has been corrected. VIEW THE CORRECTION

Authors: David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D. Author Info & Affiliations

Published August 25, 2011 | N Engl J Med 2011;365:725-733 | DOI: 10.1056/NEJMoa1103849 | VOL. 365 NO. 8

Porter et al, NEJM 2011





Primary end point CR: **18%**

ORR: 43%

Median PFS **11.9 mo**

Median OS 30.3 mo

AEs: any grade / Grade 3+

CRS	85%/9%
ICANS	45%/18%

Siddiqi et al, Lancet 2023

Liso-cel: Updated Data and Real-World Evidence

TRANSCEND CLL 004: Efficacy (Median Follow-up 31.7 mo)

ORR
44%
95% CI 32–57%

CR / CRi Rate
20%
Heavily pretreated

uMRD Peripheral Blood (10^{-4})
64%
CR+uMRD → PFS Not Reached

uMRD Bone Marrow (10^{-4})
60%
Strong predictor of durability*

CR/CRi + uMRD → Median PFS Not Reached
Estimated 36-mo DOR Rate: 61%

- uMRD- (any response): median PFS 26.2 mo vs MRD-positive: 2.8 mo vs unknown: 0.8 mo
- Median OS 43.2 months | High-risk: del17p 42%, TP53mut 47%, unmut IGHV 47% of patients
- CRS Gr≥3 9%, ICANS Gr≥3 18% (Higher than DLBCL)

Real-World Evidence: CIBMTR

N=45 | Tomasulo E et al. ASCO 2026

- ORR 84% | CR 55% (81% uMRD) | mPFS: NR
- Among responders: 6mo DOR 89%, 6mo PFS: 77%
- CIBMTR (liso-cel, all indications): CRS Gr≥3 4%, ICANS Gr≥3 13%

Real-World Evidence: CARE CAR-T CLL

N=41 evaluable | 19 US centers | Huang J et al. TCT 2026

- ORR 85% | CR 44% | CRi 7% (6-mo PFS: 92%)
- **Prior pirtobrutinib → CR/CRu 72% vs 28% (no pirto)**
- CIBMTR (liso-cel, all indications): CRS Gr≥3 3%, ICANS Gr≥3 7%

Siddiqi T et al. Lancet. 2023;402(10402):641–654; Siddiqi T et al. Blood. 2022;139(12):1794–1806; Blood. 2024;144(Suppl 1):4633 (ASH 2024 updated FU); Huang J et al. TCT 2026 (CARE CAR-T CLL RW analysis); Blood. 2024;144(Suppl 1):470 (CIBMTR real-world liso-cel); Tomasulo E et al. ASCO 2026

Coming Soon: New Combinations, More Potent Inhibitors

Other BTKi

Nemtabrutinib
Orelabrutinib
Rocbrutinib
Docirbrutinib

Other Bcl-2i

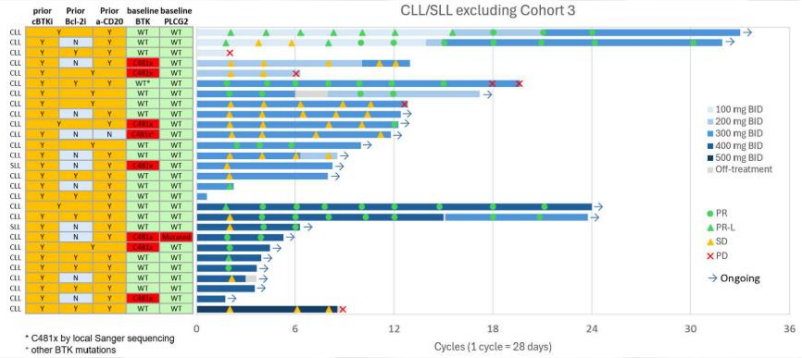
Sonrotoclax
Lisaftoclax
Mesutoclax

UPDATED RESULTS FROM A PHASE 1B STUDY OF NON-COVALENT PAN-MUTANT BTK INHIBITOR DOCIRBRUTINIB (AS-1763) IN PATIENTS WITH PREVIOUSLY TREATED B-CELL MALIGNANCIES

Nitin Jain

Author(s): Nitin Jain, Catherine Coombs, Nirav N Shah, Jonathan S. Goldberg, Seung Tae Lee, Jacqueline Barrientos, Sunil Babu, John Nemunaitis, Shuo Ma, Andrew Gillis-Smith, Danielle M. Brander, Julio Peguero, Shirou Kirita, Koji Yoshida, Masaaki Sawa, Kyoko Miyamoto, Akinori Arimura, William Wierda, Varsha Gandhi, Javier Pinilla

(Abstract release date: 05/12/26) EHA Library. Jain N. 06/11/2026; 4208242; PS1690;



Jain et al, EHA 2026

New Combinations: ASH 2025, EHA 2026

A phase 3, randomized, open-label, multicenter study of sonrotoclax (BGB-11417) plus anti-CD20 antibody therapies vs venetoclax plus rituximab in patients with **relapsed**/refractory **chronic lymphocytic leukemia**/small **lymphocytic** lymphoma (CLL-RR1/CELESTIAL-RRCLL)

Othman Al-Sawaf, Sandra Robrecht, Matthew S Davids, Mary Ann Anderson, Romain Guieze, Valeria Buccheri, Celso Arrais-Rodrigues, Francesc Bosch Albareda, Ruth Clifford, Michael Doubek, Krzysztof Jamroziak, Arnon Kater, Mattias Mattsson, Carsten Niemann, Miguel Pavlovsky, Lydia Scarfo, Renata Walewska, Peng Liu, Ki-Seong Eom, Karl Kreuzer, Eugen Tausch, Christof Schneider, Stephan Stilgenbauer, Kirsten Fischer, Michael Hallek, Kenneth Wu, Marcus Lefebure, Wei Ding, Remus Vezan, Barbara Eichhorst

Mutation-guided finite-duration acalabrutinib plus venetoclax for **relapse** after first-line finite-duration COVALENT Bruton tyrosine kinase inhibitor plus venetoclax–based combination therapy in patients with **chronic lymphocytic leukemia**/small **lymphocytic** lymphoma: Phase 2 MAVRiC study

Matthew S Davids, Alen Ostojic, Susana Wargo, Moana Hodari, Jiefen Munley, Richard Hermann

NEMTABRUTINIB PLUS VENETOCLAX IN PARTICIPANTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA: PART 1 OF THE PHASE 3 BELLWAVE-010 STUDY

Dr. Paolo Ghia

Author(s): Paolo Ghia, Mauricio Chandía, Vernon Louw, Maria Carmen Martinez Chamorro, Gonzalo Garate, Valeria Buccheri, Raimundo Gazitua, Alejandro Berkovits, Michael Africa-Cass, Eva Gonzalez Barca, Jose Sandoval-Sus, Muhit Ozcan, Sven Erik Ojavee, Ima Paydar, Mohammed Farooqui, Ohad Benjamini

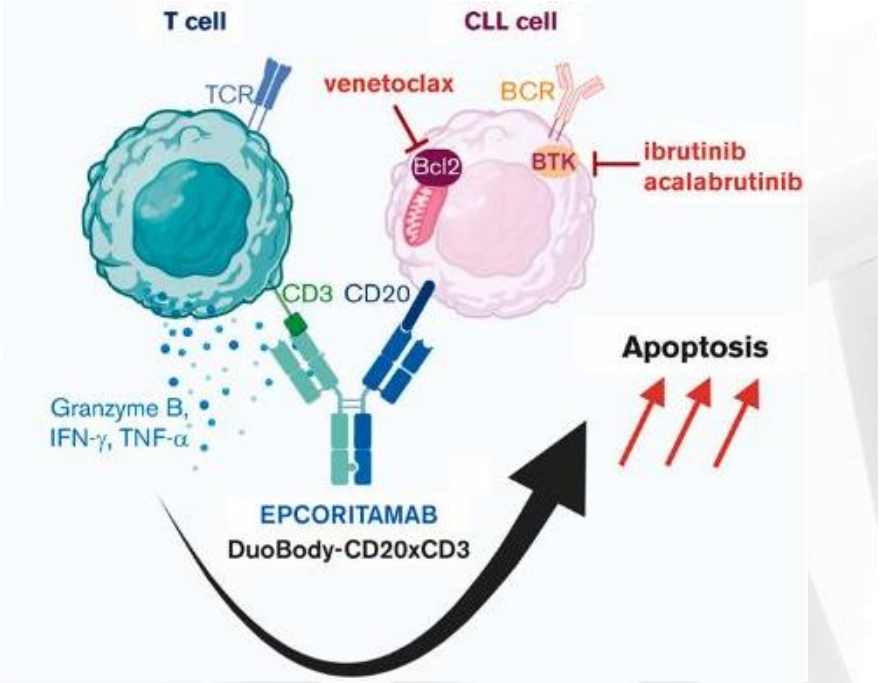
UPDATED SAFETY AND EFFICACY OF ALL-ORAL SONROTOCLAX + ZANUBRUTINIB IN RELAPSED/REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL), INCLUDING PATIENTS WITH DEL(17P)/TP53

Stephen Opat

Author(s): Stephen Opat, Constantine S. Tam, Mary Anderson, Alessandra Tedeschi, Emma Verner, Masa Lasica, Alejandro Arbelaez, Stephan Stilgenbauer, Peter Browett, Sophie Leitch, Eva Gonzalez Barca, Mazyar Shadman, Jing-Zhou Hou, Herbert Eradat, David Westerman, Binghao Wu, Gabriel Man, Yiqian Fang, Sheel Patel, Remus Vezan, Chan Y. Cheah

Coming Soon: New Agents

Bispecific T cell Engagers



Mhibik et al, Blood adv 2023
Kater et al, iWCLL 2023

BTK Degraders

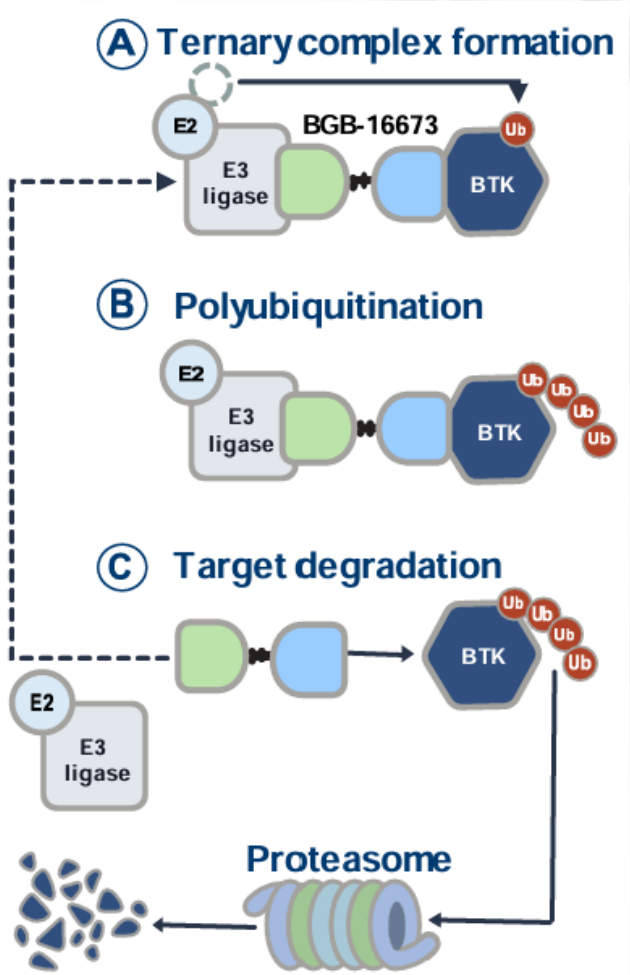


Figure courtesy of BeOne Medicines

New targets

BCLxL/BCL2 – (LP-118)
PKCβ inhibitor – (MS-553)
MALT1 (ABBV-525, SGR-1505)
MCL-1/CDK9
Bcl-2 degraders
BTK/IKZF (NX-2127)
BTK/Lyn inhibitors (DZD8586)
Pi3k inhibitors (roginolisib)
ROR1xCD3 bispecific
Zilovertamab vedotin (ROR1 ADC)
New CAR-T and CAR-NK

Bispecific T Cell Engagers (BiTES)

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 5, 2024

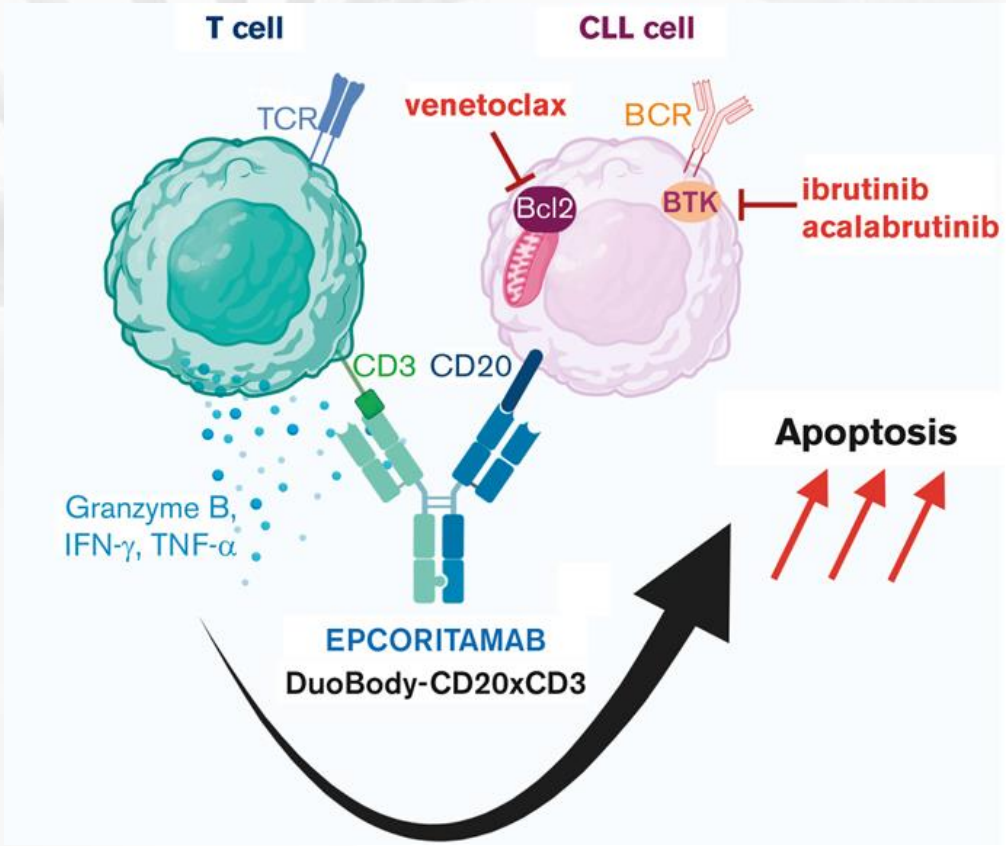
Epcoritamab Monotherapy in Patients (Pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL): Results from CLL Expansion and Optimization Cohorts of Epcore CLL-1

Alexey Danilov, Bita Fakhri, Farrukh T. Awan, Hans Herluf Bentzen, Herbert A. Eradat, Carsten Utoft Niemann, Fritz Offner, Christian Bjørn Poulsen, Thor Hoeyer, Mar Bellido, Damien Roos Weil, Alessandra Ferrajoli, Meghan C. Thompson, Jacob Haaber Christensen, Ann Janssens, Tamar Tadmor, Mazyar Shadman, Pegah Jafarinasabian, Jimin Zhang, Marcia Rios, Alexandra Kuznetsova, Rebecca Valentin, Arnon P. Kater

All pts had prior BTKi
TP53 aberrations: 63%
u*IGHV*: 70%
Double exposed to BTKi and BCL2i: 85%

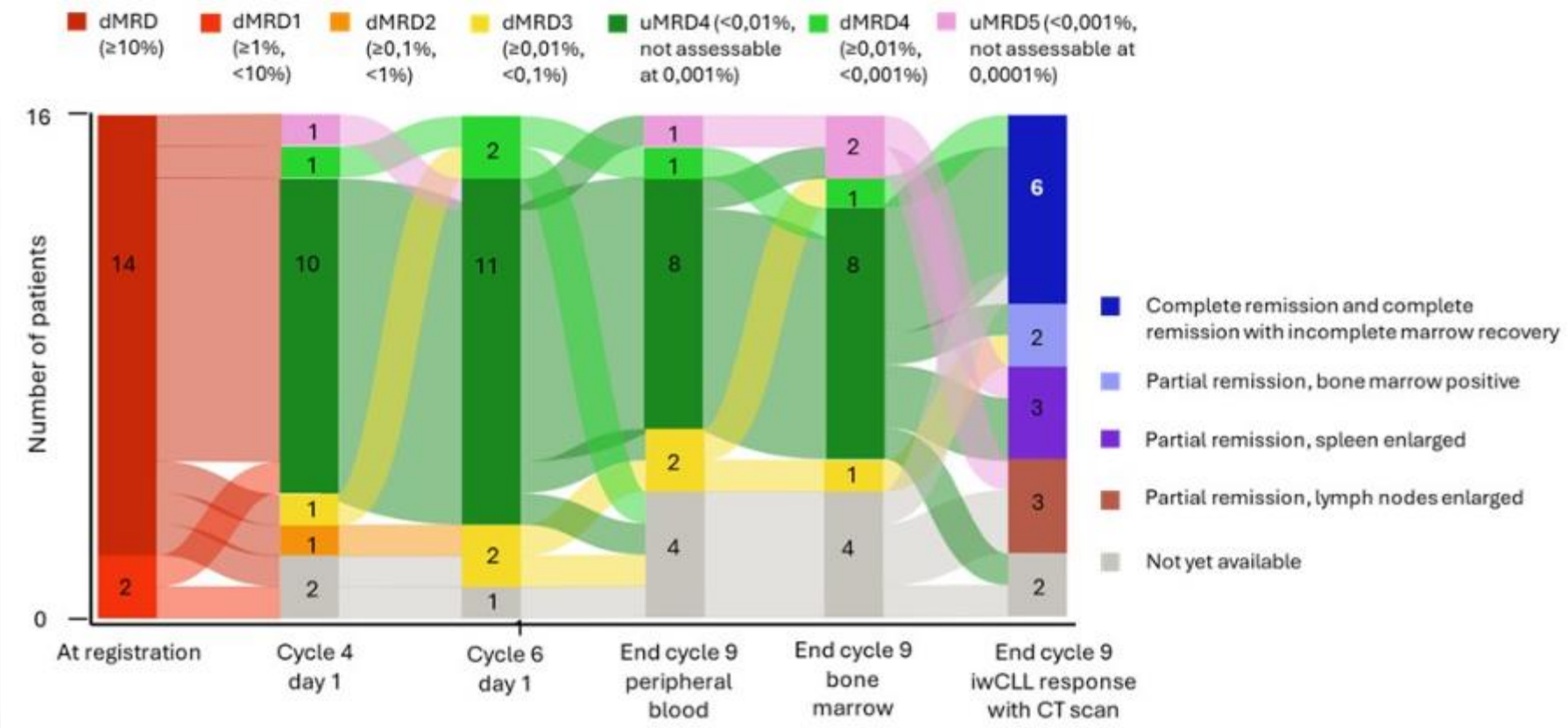
ORR was 61% and CR rate was 39%.
uMRD4: 75%
mPFS: 12.8 mo
mOS: NR

AEs:
CRS: 96% (17% G3 in expansion cohort)
Diarrhea: 48%
Peripheral edema: 48%



Mhibik et al, Blood adv 2023
Kater et al, iWCLL 2023
Danilov et al, ASH 2024

Venetoclax + Epcoritamab



HOVON 165/AETHER
Phase 1/2 (N=47)
Primary Endpoint: uMRD4

Venetoclax lead in, then 6 or 12 cycles of Epcoritamab

Pts: 74% with previous targeted therapy, 49% with prior venetoclax

uMRD4: 87.5% at C4
90% at C6

Kater A et al, EHA 2026

Proteolysis-Targeting Chimeras (PROTACs)

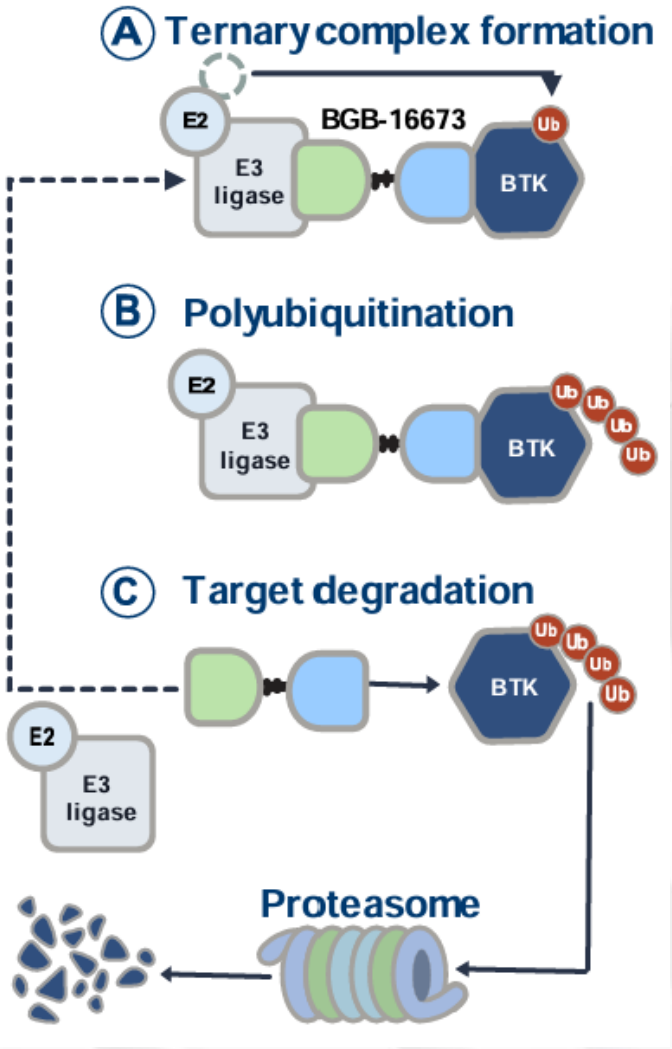


Figure courtesy of BeOne Medicines

AKA: protein degraders

Remove the target protein from the cell

Do not require sustained binding

Potential to work in patients with acquired treatment resistance mutations

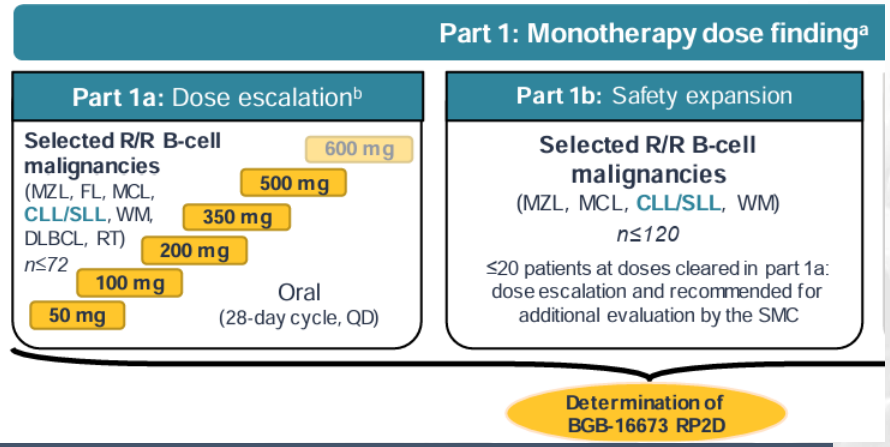
Affect kinase and scaffolding functions

Possible different side effect profile

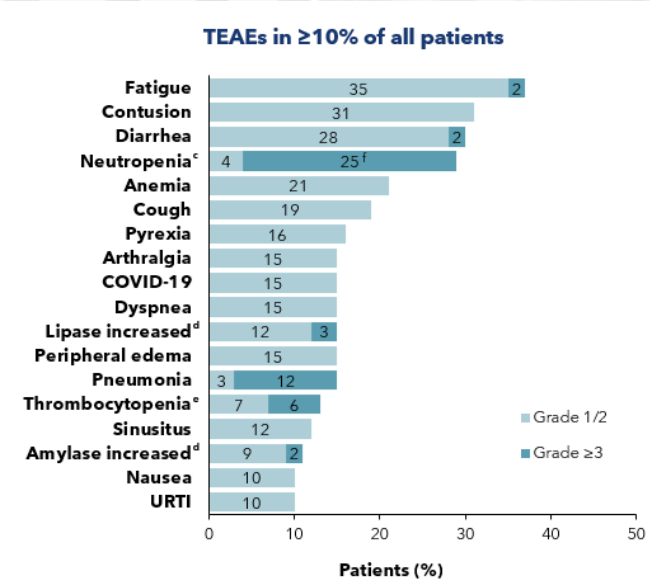
BTK Degraders – BGB-16673/Tacabrutideg, CaDAnCe-101

Key eligibility criteria for CLL/SLL
- Meets iw CLL 2018 criteria for treatment
- ≥2 prior therapies, including cBTKi if approved for disease
- ECOG PS 0-2 & adequate end-organ function

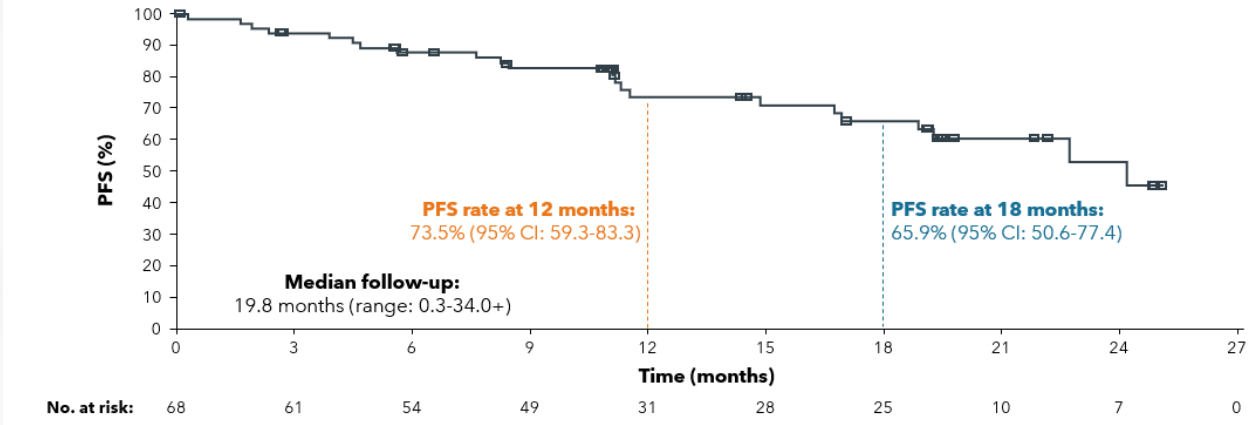
Key study objectives for part 1
- **Primary:** safety[c] and tolerability, MTD, and RP2D
- **Secondary:** PK, PD, and preliminary antitumor activity[d]



Characteristic	Total (n=68)
Mutation status, n/N (%)	
BTK mutation present	26/66 (39.4)
PLCG2 mutation present	10/66 (15.2)
BTK and *PLCG2* mutation present	5/66 (7.6)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	49 (72.1)
cBTK inhibitor	64 (94.1)
ncBTK inhibitor	14 (20.6)
BCL2 inhibitor	56 (82.4)
cBTK + BCL2 inhibitors	44 (64.7)
cBTK + ncBTK + BCL2 inhibitors	12 (17.6)
Discontinued prior BTK inhibitor owing to PD, n/N (%)[a]	57/64 (89.1)



Progression Free Survival



Ahn et al, ASH 2025

CaDAnCe-302 – Open at Winship

BGB-16673 vs. Investigator's Choice in Patients with R/R CLL/SLL After BTKi and BCL2i

CaDAnCe-302

Phase 3

Study identifier: BGB-16673-302, CaDAnCe-302, NCT06846671

Primary endpoint: PFS (IRC)

Key secondary endpoints: OS, PFS (prior ncBTKi; IRC), PFS (investigator), ORR, DoR , (IRC, investigator), PR-L or higher (investigator), TTNT, safety, QoL

Key eligibility criteria

- Age ≥18 years
- Confirmed diagnosis of CLL/SLL and requiring treatment
- Previous treatment with both a BTKi and a BCL2i
- Measurable disease by CT/MRI (SLL only)
- ECOG PS 0-2
- Adequate liver and blood-clotting function
- No prior ASCT or CAR T-cell therapy in the last 3 months
- No PLL or RT
- No CNS involvement or CVD

Treatment

N~250

R 1:1

Arm A
BGB-16673

Arm B (investigator's choice)
Idelalisib + rituximab[a]
OR
Bendamustine + rituximab
OR
Venetoclax + rituximab retreatment

Start date:
April 2025

Estimated primary completion date:
May 2028

Slide courtesy of BeOne Medicines

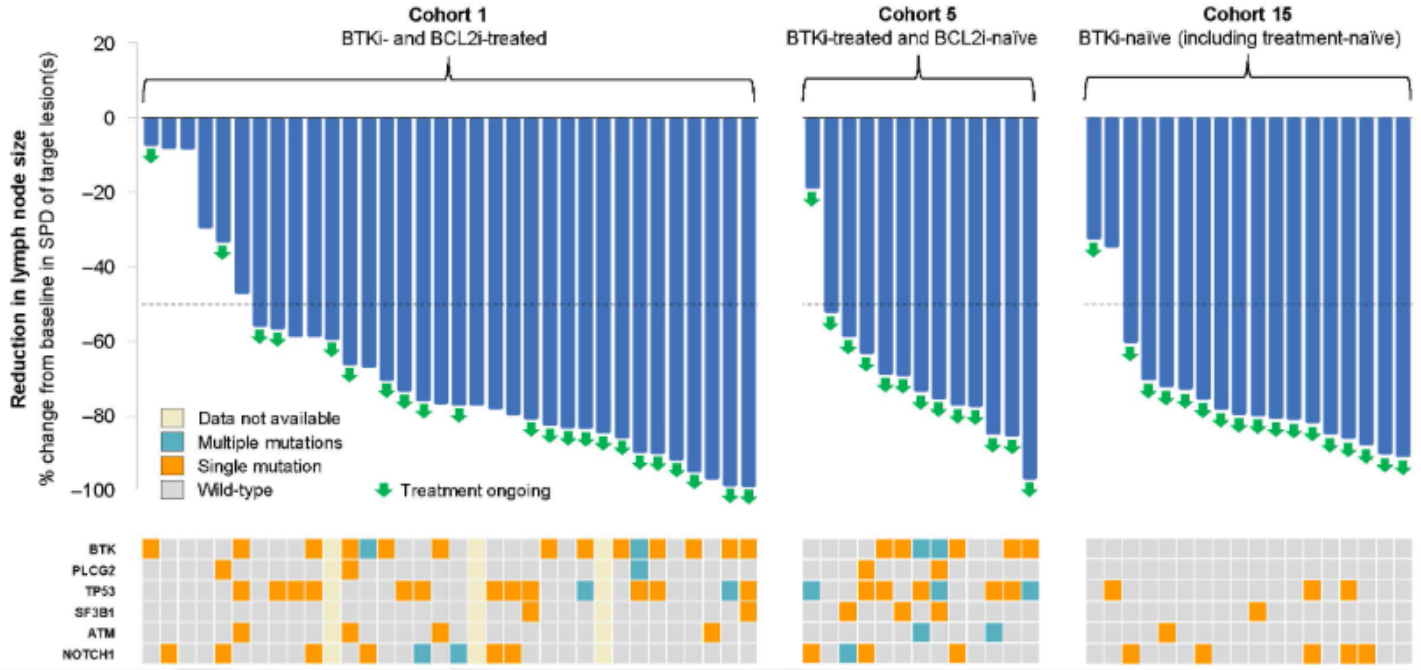
BTK Degraders - Bexobrutideg

642A. CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 3, 2025

Bexobrutideg (NX-5948), a novel Bruton's tyrosine kinase (BTK) degrader, demonstrates rapid and durable clinical responses in Relapsed/Refractory chronic lymphocytic leukemia (CLL): New and updated findings from an ongoing Phase 1a/b trial

Zulfa Omer, Alexey Danilov, Francesco Forconi, Talha Munir, Mary Gleeson, Nirav Shah, Graham Collins, Alvaro Alencar, Jane Robertson, Jonathon Cohen, Karan Dixit, Danielle Brander, John Byrd, Allison Winter, Jeffery Smith, Dima El-Sharkawi, Michal Kwiatek, Iwona Hus, Prioty Islam, Sebastian Grosicki, Michael Tees, Thorsten Zenz, Joanna Romejko-Jarosinska, Sarah Injac, Wojciech Jurczak

Figure. Lymph node reduction in select cohorts of Ph1b with different ranges of prior treatments and associated mutational burden levels at baseline



Double exposed: 73%
ORR: >80%
Median DOR: NR

Omer et al, ASH 2025

Responses observed with CNS involvement

Responders included those with BTK resistance mutations

Munir et al EHA 2026

Conclusions - 2026

Limited role for chemotherapy in R/R CLL

BTKi and Bcl-2i treatments remain favored options, when not previously exposed to these agents

Pirtobrutinib is only approved nc-BTKi for 2L+ after cBTKi

Liso-cel approved for double refractory population

PI3Ki may be useful under certain circumstances

Many new agents and combinations in the horizon