Recent advances in relapsed/refractory CLL

Professor Vincent Lévy
Clinical Research Department, Avicenne Hospital APHP, Bobigny
INSERM UMR U1153, CRESS, ECSTRRA team, Hôpital Saint Louis, Paris, France

CLL, chronic lymphocytic leukemia.

February 2024 | 0124--MRC-083

Disclosures

- **Honoraria, advisory boards, and travel support:** AbbVie, AstraZeneca, BeiGene, CSL Behring, and Janssen

Selecting treatment for patients with R/R CLL

- Looking at the treatment of patients with R/R disease means looking at the profile of these patients and how they evolve
  - Older
  - More severe molecular and cytogenetic characteristics
  - Greater heterogeneity than in 1L, even if only because of the treatments used

- In 2024, what types of treatment do patients receive when they relapse?
  - Currently, there are no clear epidemiological data but there are treatment recommendations (US/Europe)[1–4]

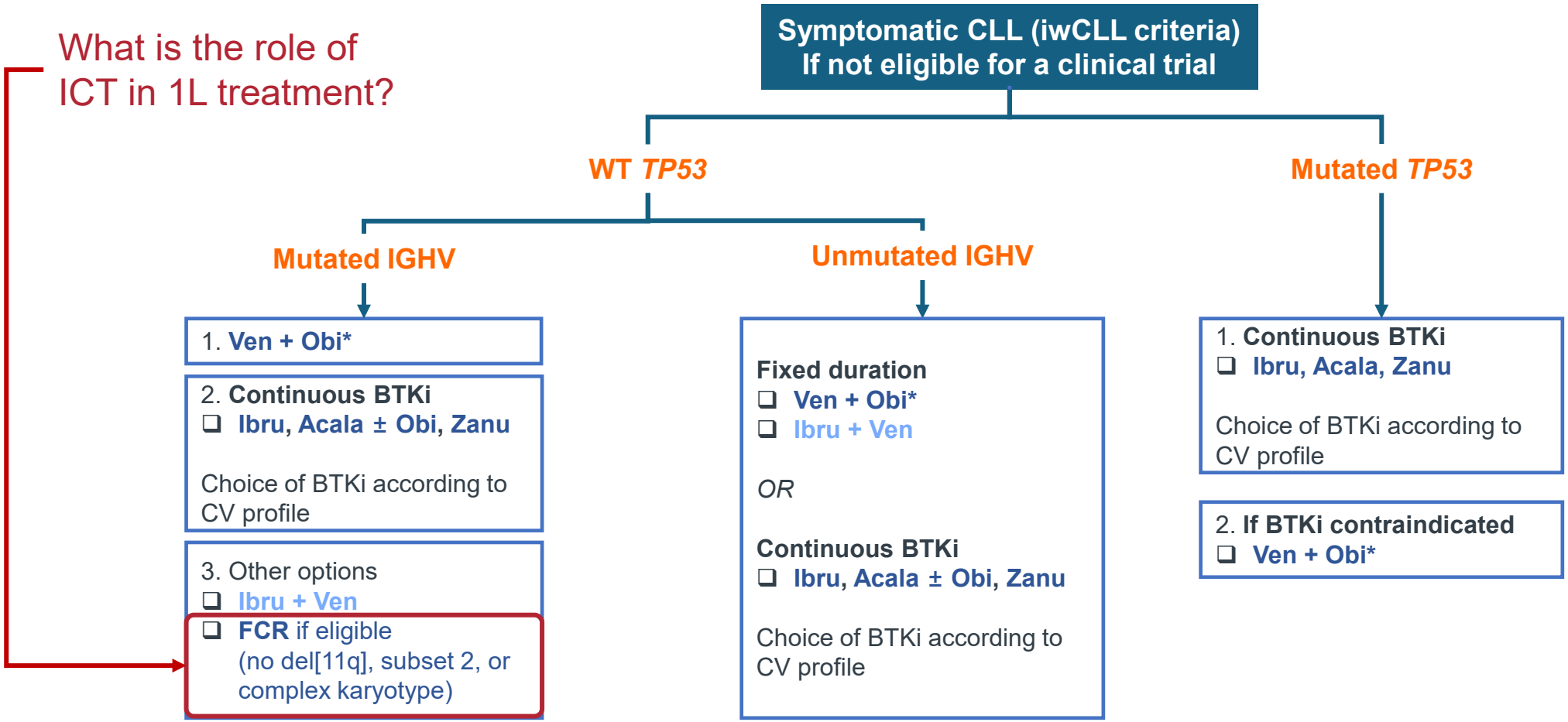
1L, first-line; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory.

1. NCCN Guidelines. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma - Version 1.2024. 2. Eichhorst B *et al*. *Ann Oncol* 2021; 32 (1): 23–33. 3. FILO-CLL recommendations. Available at: https://www.filo-leukemia.org/content/filo-cll/recommandations-llc. Accessed February 2024. 4. Chronic lymphocytic leukemia (CLL) [in German]. Available at: https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll. Accessed February 2024.

FILO-CLL guidelines: Algorithm for 1L CLL

FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

What is the role of ICT in 1L treatment?



- Treatment reimbursed
- Marketing authorization but no reimbursement

*Marketing authorization in France if ineligible for FCR and contraindicated for BTKi.

1L, first-line; Acala, acalabrutinib; BTKi, BTK inhibitor; CLL, chronic lymphocytic leukemia; CV, cardiovascular; del, deletion; FCR, fludarabine, cyclophosphamide, and rituximab; Ibru, ibrutinib; ICT, immunochemotherapy; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; Obi, obinutuzumab; Ven, venetoclax; WT, wild-type; Zanu, zanubrutinib.

FILO-CLL recommendations. Available at: https://www.filo-leukemia.org/content/filo-cll/recommandations-llc. Accessed January 2024.

Assessments to make at the time of relapse and before treatment

Standard karyotype / FISH panel[1]

TP53 mutational status if previously WT[1]

Resistance mutations to targeted therapies[2]

IGHV mutational status[1]

Vaccination status: Influenza[1], COVID-19[3], pneumococcal[1], herpes zoster[4]

Possible Richter's transformation[1]

FISH, fluorescence *in situ* hybridization; WT, wild-type.

1. Eichhorst B *et al*. *Ann Oncol* 2021; 32 (1): 23–33. 2. Moreno C. *Hematology Am Soc Hematol Educ Program* 2020; 2020 (1): 33–40. 3. Shadman M *et al*. *Hemasphere* 2022; 7 (1): e811.
4. Muchtar E *et al*. *Am J Hematol* 2022; 97 (1): 90–98.

CLL relapse or Richter's transformation?

- Richter's transformation should be considered in patients with CLL who present with rapidly progressive disease

- Different prognosis and treatment
  - Patients with Richter's transformation have a dismal prognosis

- A tissue biopsy of the suspected site of transformation is required to confirm Richter's transformation
  - Selected based on markedly increased SUV on ^{18}FDG PET/CT scan

Differentiating between Richter's transformation and R/R CLL

- ❑ More symptomatic CLL with greater morbidity
- ❑ Elevated LDH
- ❑ Asymmetric, rapid increase of lymph nodes
- ❑ Hypercalcemia

CLL, chronic lymphocytic leukemia; CT, computed tomography; FDG, fluorodeoxyglucose; LDH, lactate dehydrogenase; PET, positron emission tomography; R/R, relapsed/refractory; SUV, standardized uptake value.

Odetola O *et al*. *Curr Hematol Malig Rep* 2023; 18 (5): 130–143.

Confirmed R/R CLL

- Assess the need for treatment using the iwCLL 2018 criteria[1,2]

Three simplified situations[1]

1	2	3
Patient previously treated with 1L ICT	Patient previously treated with BTKi ± anti-CD20	Patient previously treated with Ven + anti-CD20

1L, first-line; BTKi, BTK inhibitor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; ICT, immunochemotherapy; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; R/R, relapsed/refractory; Ven, venetoclax.

1. Odetola O *et al*. *Curr Hematol Malig Rep* 2023; 18 (5): 130–143. 2. Hallek M *et al*. *Blood* 2018; 131 (25): 2745–2760.

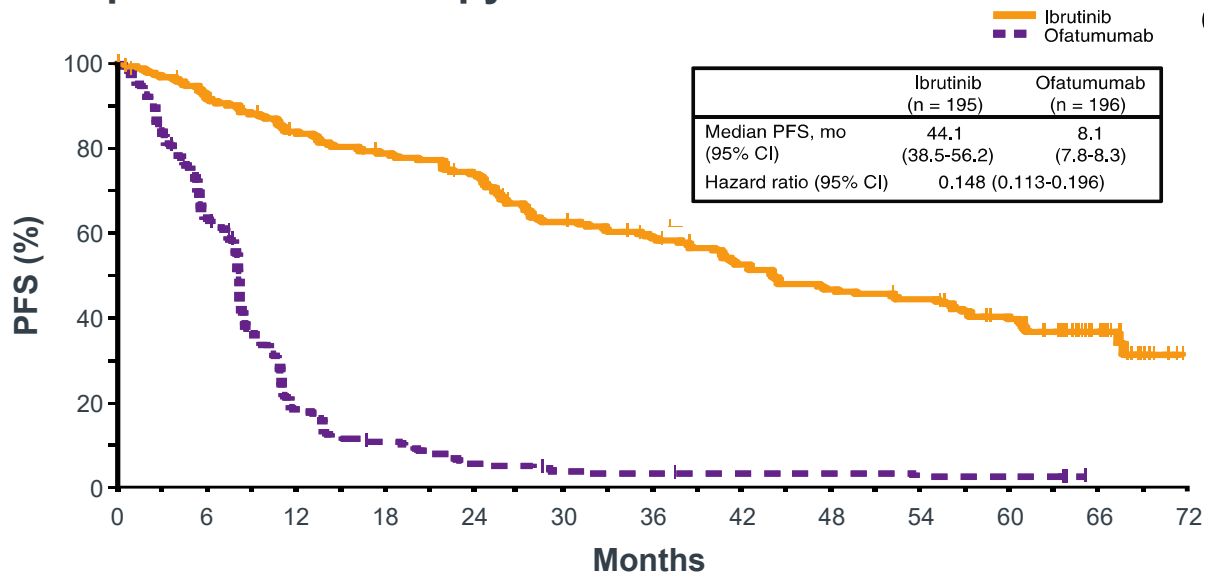
Trials in R/R CLL

CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory.

Trial data: BTKi monotherapy vs. historic SoC therapies

Ibrutinib

- RESONATE[1]
- Ibrutinib vs. ofatumumab
- N=391
- **≥1 prior line of therapy**



Median PFS with ibrutinib: 44.1 mo

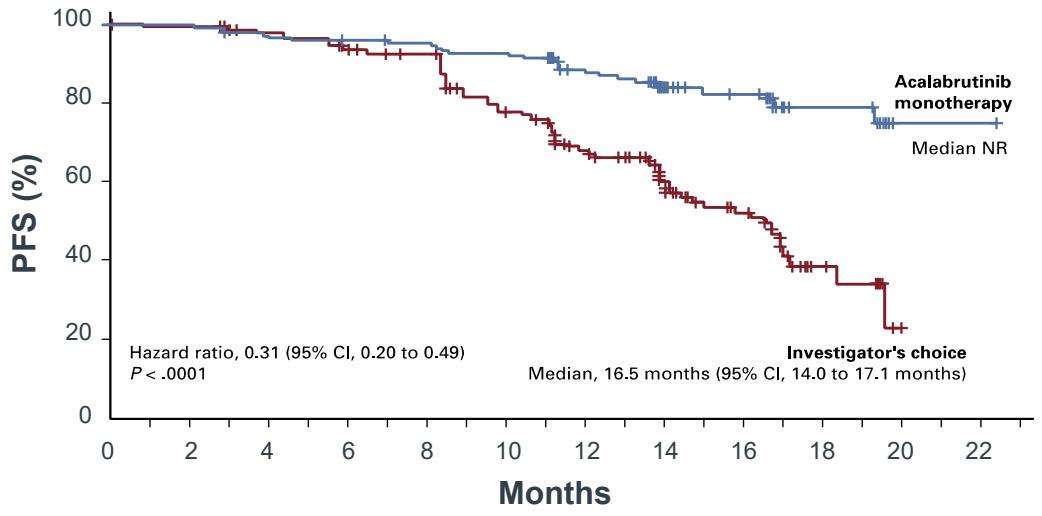
BTKi, BTK inhibitor; CI, confidence interval; mo, months; PFS, progression-free survival; SoC, standard of care.

1. Munir T *et al*. *Am J Hematol* 2019; 94 (12): 1353–1363.

Trial data: BTKi monotherapy vs. historic SoC therapies

Acalabrutinib

- ASCEND[1]
- Acalabrutinib vs. IdR or BR
- N=398
- **≥1 prior line of therapy**



Median PFS with acalabrutinib: NR

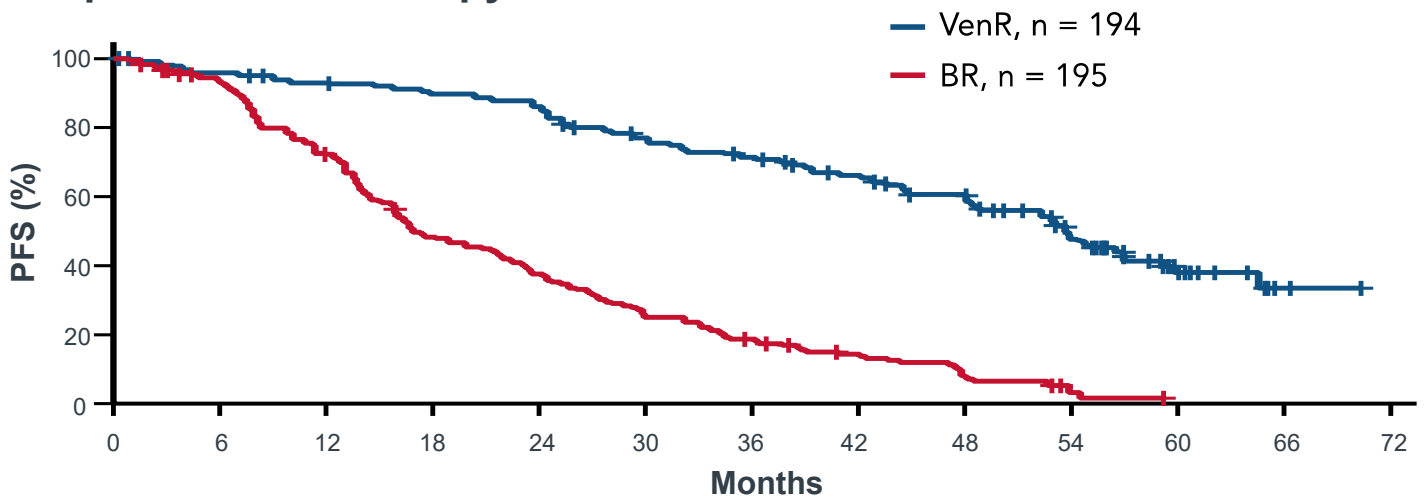
BR, bendamustine and rituximab; BTKi, BTK inhibitor; CI, confidence interval; IdR, idelalisib and rituximab; mo, months; NR, not reached; PFS, progression-free survival; SoC, standard of care.

1. Ghia P *et al*. *J Clin Oncol* 2020; 38 (25): 2849–2861.

Trial data: Venetoclax + anti-CD20 vs. historic SoC therapies

Venetoclax + anti-CD20

- MURANO[1]
- VenR vs. BR
- N=389
- **1–3 prior lines of therapy[2]**



Median PFS with VenR: 59.2 mo

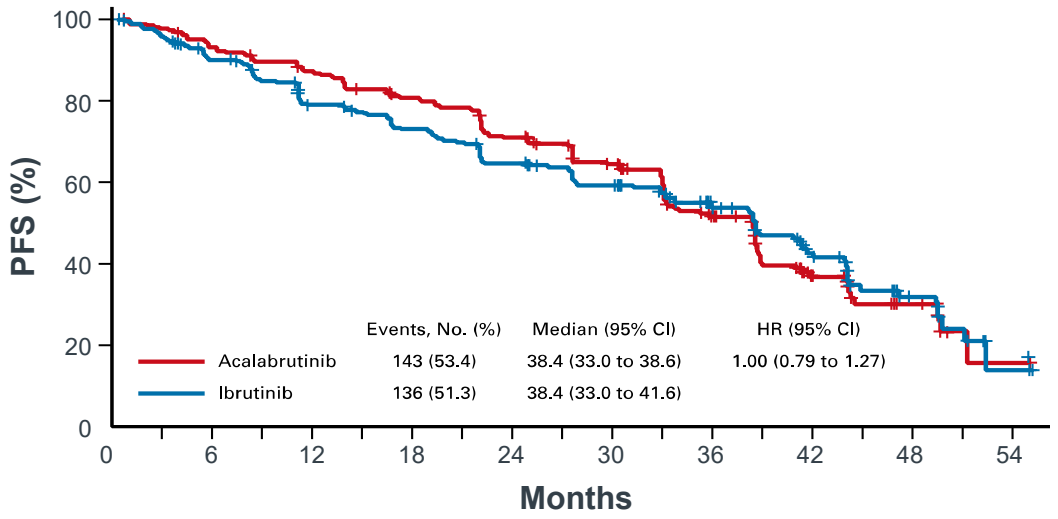
BR, bendamustine and rituximab; CD, cluster of differentiation; mo, months; PFS, progression-free survival; VenR, venetoclax and rituximab.

1. Seymour JF *et al*. *Blood* 2022; 140 (8): 839–850. 2. Seymour JF *et al*. *Blood* 2022; 140 (8): 839–850 – data supplement.

Trial data: Next-generation BTKis vs. ibrutinib

Acalabrutinib

- ELEVATE-RR[1]
- Non-inferiority trial vs. ibrutinib
- N=533
- **≥1 prior line of therapy**



Median PFS with acalabrutinib with del(11q) or del(17p): 38.4 mo

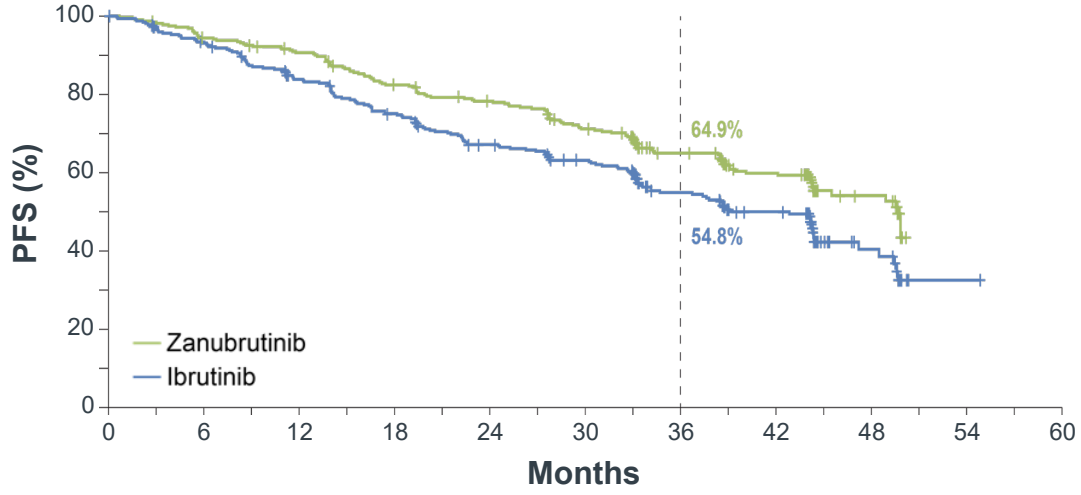
BTKi, BTK inhibitor; CI, confidence interval; del, deletion; HR, hazard ratio; mo, months; PFS, progression-free survival.

1. Byrd JC *et al*. *J Clin Oncol* 2021; 39 (31): 3441–3452.

Trial data: Next-generation BTKis vs. ibrutinib

Zanubrutinib

- ALPINE[1]
- Zanubrutinib vs. ibrutinib
- N=652
- **≥1 prior line of therapy**



36-month PFS with zanubrutinib: 64.9%[2]

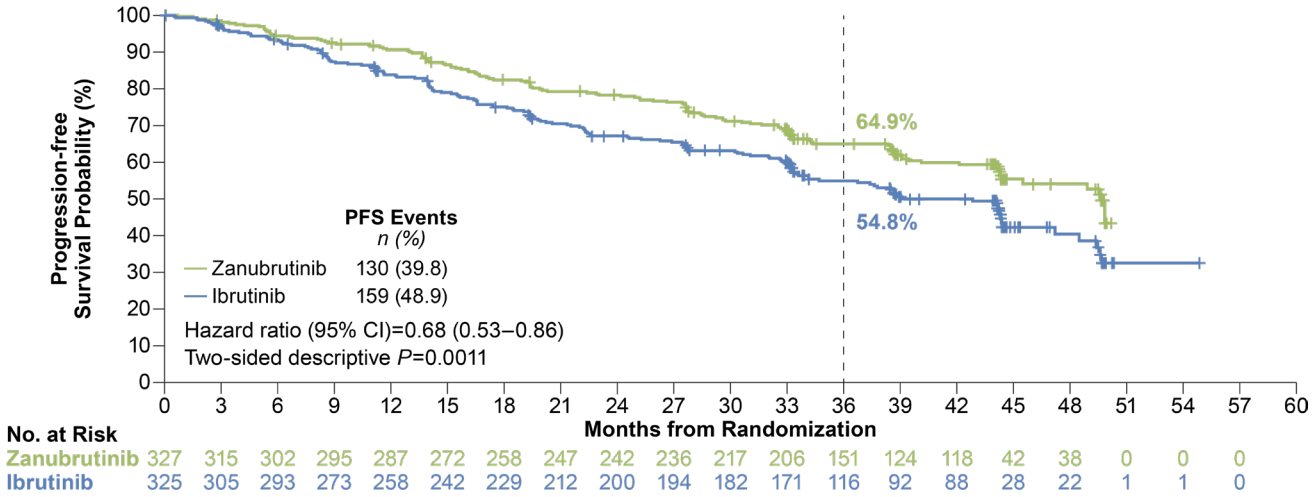
BTKi, BTK inhibitor; CI, confidence interval; del, deletion; HR, hazard ratio; mo, months; PFS, progression-free survival.

1. Brown JR *et al*. *N Engl J Med* 2023; 388 (4): 319–332. 2. Brown JR *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 202).

ALPINE: Zanubrutinib vs. ibrutinib in R/R CLL/SLL

Extended follow-up (median: 39.0 months)

Significant PFS benefit with zanubrutinib over ibrutinib is sustained with extended follow-up over 3 years



PFS benefit with zanubrutinib was consistent across multiple sensitivity analyses

Sensitivity analysis	Zanu, n (%)	Ibr, n (%)	HR (95% CI)	Two-sided *P*-value
Accounting only for PD and death events that occurred during active treatment	76 (23.2)	85 (26.2)	0.69 (0.50–0.95)	0.0206
Censoring for new CLL/SLL therapies	129 (39.4)	157 (48.3)	0.68 (0.54–0.86)	0.0014
Censoring for death due to COVID-19	115 (35.2)	142 (43.7)	0.66 (0.52–0.85)	0.0013

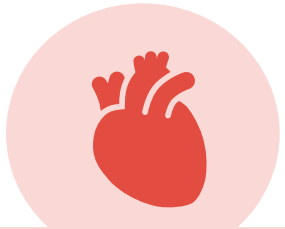
CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; Ibr, ibrutinib; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; Zanu, zanubrutinib.

Brown JR *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 202).

ALPINE: Zanubrutinib vs. ibrutinib in R/R CLL/SLL

Extended follow-up (median: 39.0 months)

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



Cardiac AEs

- Zanubrutinib: 24.7%
- Ibrutinib: 34.6%

Serious cardiac AEs

- Zanubrutinib: 3.4%
- Ibrutinib: 9.6%

Fatal cardiac events

- Zanubrutinib: 0% (n=0)
- Ibrutinib: 1.9% (n=6)

AE, adverse event; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.
Brown JR *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 202).

ALPINE: Acquired mutations in patients who progressed

High-sensitivity NGS was performed on blood samples from patients with PD*

Given the low incidence of non-C481 mutations, the data suggest that patients treated with covalent BTKis are likely to remain sensitive to other BTK-targeting therapies

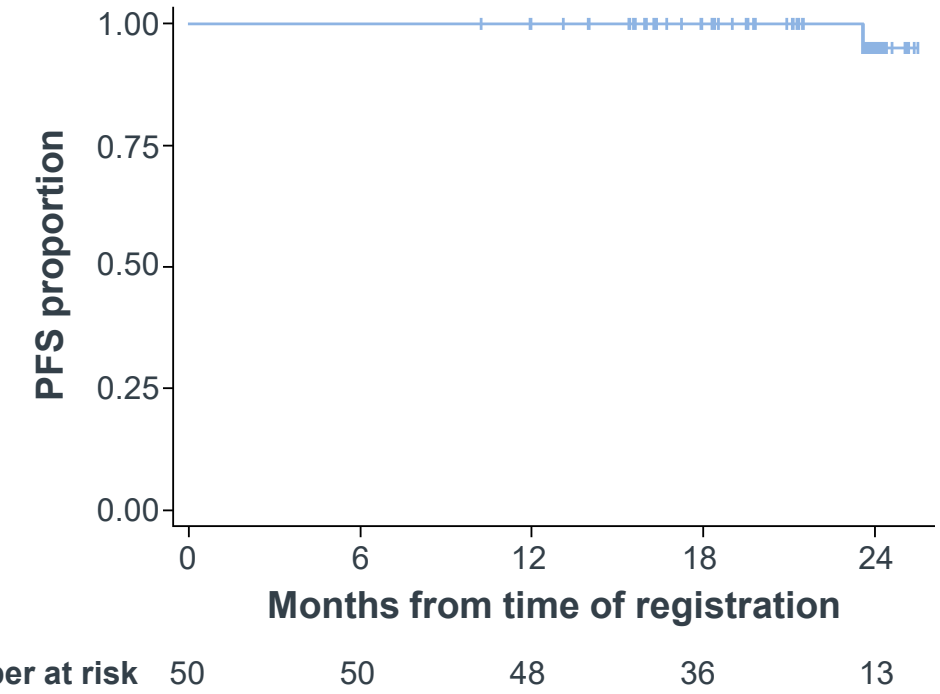
*Excluding patients without paired baseline and PD blood samples (ibrutinib arm, n=1) and patients with Richter's transformation (n=2 from each of the zanubrutinib and ibrutinib arms).
BTKi, BTK inhibitor; NGS, next-generation sequencing; PD, progressive disease.
Brown JR *et al*. Poster 1890 at ASH 2023; San Diego, CA, USA, December 9–12, 2023.

CLARITY: Ibrutinib + venetoclax in R/R CLL[1]

- Phase II trial
- 12-month treatment with ibrutinib + venetoclax
- Primary endpoint: MRD-negative BM
  - MRD in PB: 53%
  - MRD in BM: 36%
- CR: 51%

	Ibrutinib + venetoclax (N=54)
Median (range) prior lines of therapy	1 (1–6)
Previous FCR or BR, n (%)	45 (83)
Previous idelalisib, n (%)	11 (20)

PFS[2]



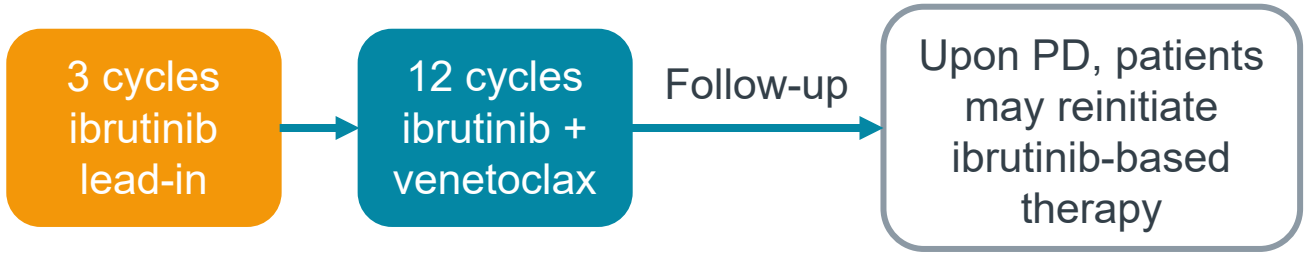
At 21 months' median follow-up, only 1 patient had experienced disease progression

BM, bone marrow; BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; CR, complete response; FCR, fludarabine, cyclophosphamide, and rituximab; MRD, minimal residual disease; PB, peripheral blood; PFS, progression-free survival; R/R, relapsed/refractory.

1. Hillmen P *et al*. *J Clin Oncol* 2019; 37 (30): 2722–2729. 2. Hillmen P *et al*. *J Clin Oncol* 2019; 37 (30): 2722–2729 – data supplement 3.

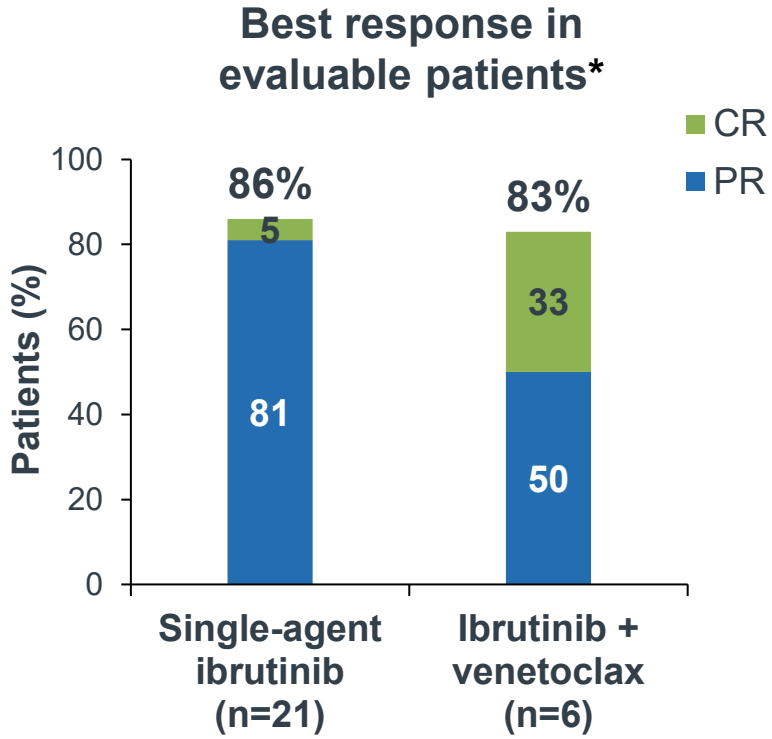
CAPTIVATE: Retreatment with ibrutinib-based therapy after 1L fixed-duration ibrutinib + venetoclax in CLL/SLL

- Phase II trial
- Patients were ≤70 years old
- Median (range) time on retreatment:
  - Single-agent ibrutinib (n=22): 17 (0–45) months
  - Ibrutinib + venetoclax (n=6): 14 (5–15) months



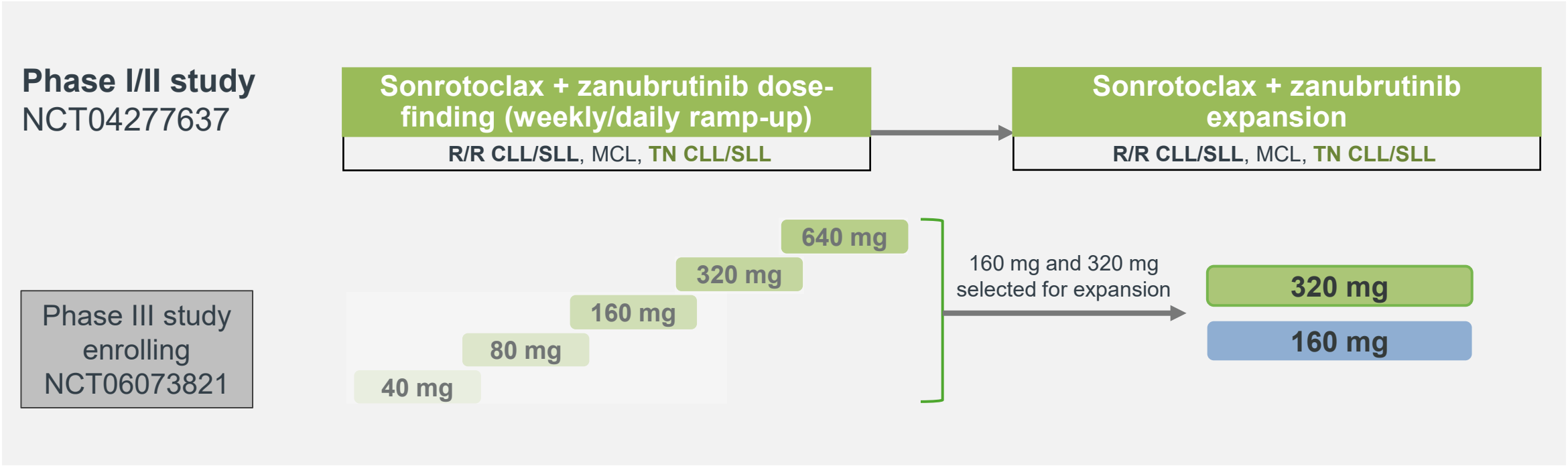
40 patients were evaluated for mutations at PD:
- 1 patient acquired a resistance-associated *BCL2* mutation
- No other clinically relevant mutations in *BTK*, *BCL2*, or *PLCG2* were observed

Ibrutinib-based retreatment demonstrated promising response rates in patients who progressed after fixed-duration ibrutinib + venetoclax



*One patient who initiated single-agent ibrutinib retreatment had not yet undergone response assessment. Patients who did not respond included 1 patient who experienced PR with lymphocytosis (5%), 1 patient who was diagnosed with Richter's transformation (5%), and 1 patient who was not evaluable because of therapy interruption (5%).
1L, first-line; CLL, chronic lymphocytic leukemia; CR, complete response; PD, progressive disease; PR, partial response; SLL, small lymphocytic lymphoma.
Ghia P *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 633).

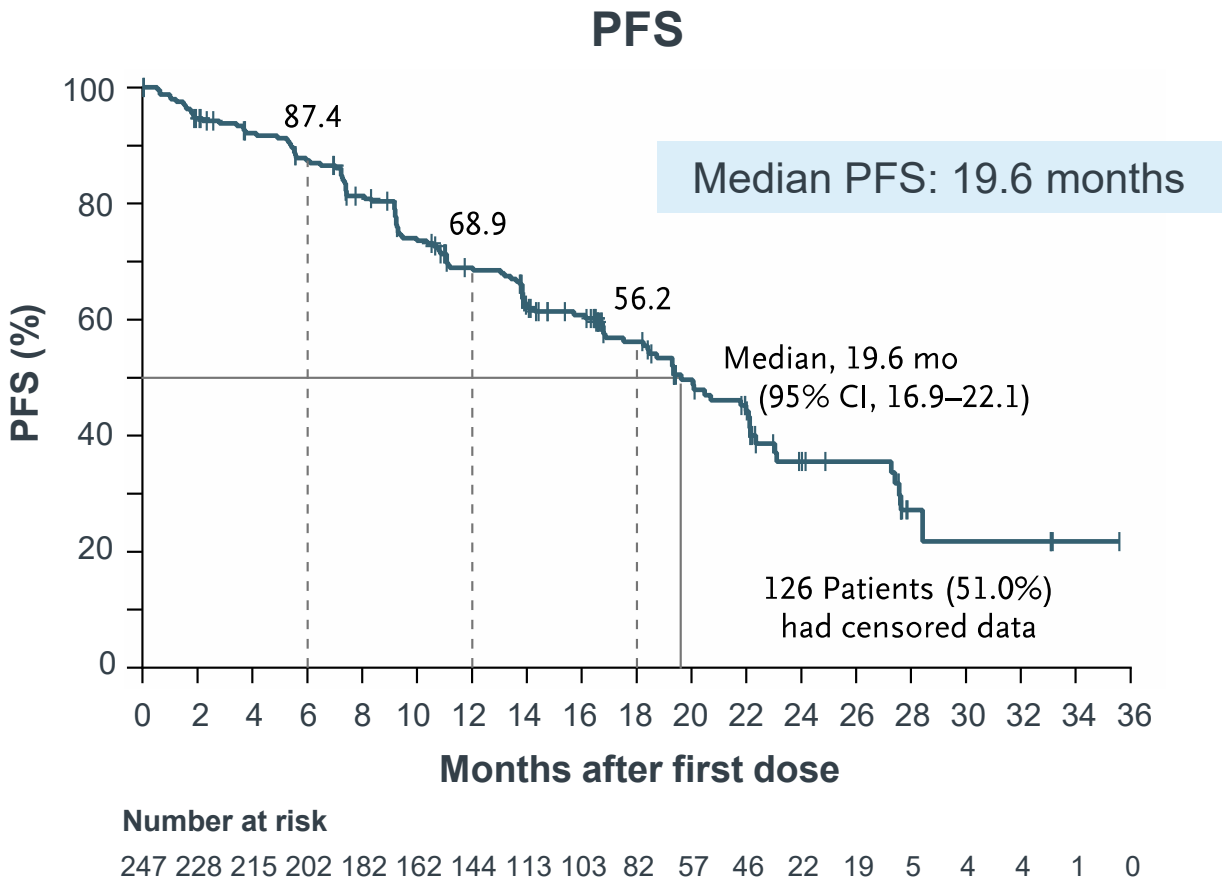
Next-generation combinations of BTK and BCL2 inhibitors



AE, adverse event; ASH, American Society of Hematology; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival; QD, every day; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TLS, tumor lysis syndrome; TN, treatment-naive.
Tam CS *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 327).

BRUIN: Pirtobrutinib

- Non-covalent, reversible BTKi
  - Covalent BTKis bind directly to C481
  - Non-covalent BTKis interact with BTK via hydrogen bonds, ionic bonds, and hydrophobic interactions, inhibiting both WT and C481-mutant BTK
- Phase I/II trial
- N=317
- Median number of prior lines of therapy: 3
  - 78% of patients previously received a BTKi
  - 40% of patients previously received a BCL2i
- ORR: 73%



Median PFS: 19.6 months

Pirtobrutinib demonstrated clinical efficacy in patients with CLL/SLL who had previously received a covalent BTKi

CI, confidence interval; CLL, chronic lymphocytic leukemia; BCL2i, BCL2 inhibitor; BTKi, BTK inhibitor; mo, months; ORR, overall response rate; PFS, progression-free survival; SLL, small lymphocytic lymphoma; WT, wild-type.
Mato AR *et al*. *N Engl J Med* 2023; 389 (1): 33–44.

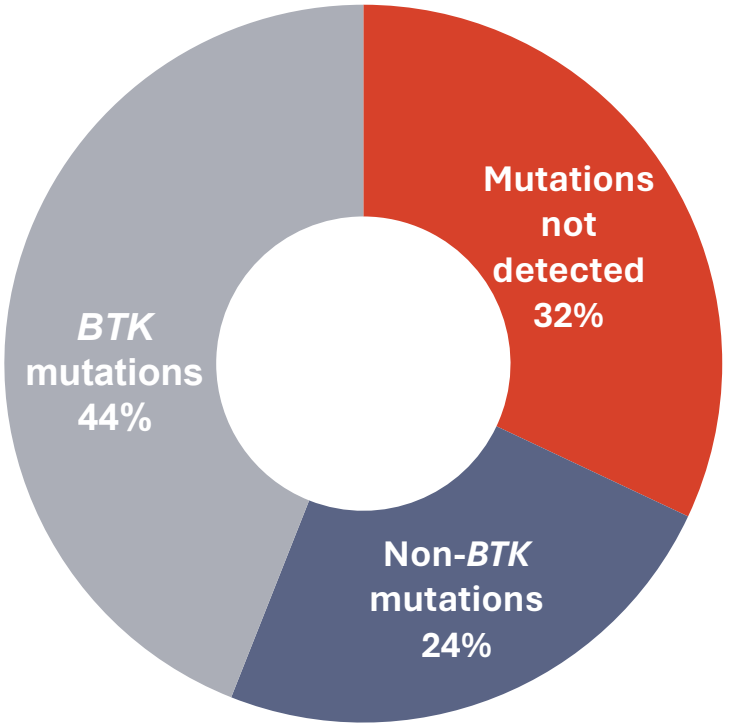
BRUIN: Genomic evolution and resistance during pirtobrutinib therapy in covalent BTKi–pretreated CLL

- 88 patients developed PD while on pirtobrutinib
- Discontinuation of prior covalent BTKi therapy was due to:
  - PD in 75 patients (85%)
  - Toxicity in 13 patients (15%)
- Median (range) time on pirtobrutinib: 16 (1.2–39) months

Among the 43 patients with C481 mutations, a decrease or complete clearance of C481 clones was observed at PD in most patients (84%)

The most common baseline alterations were mutations in *BTK* (53%), *TP53* (49%), *SF3B1* (34%), *ATM* (23%), *NOTCH1* (20%), *PLCG2* (14%), and *BCL2* (9%)

Of 88 patients who progressed on pirtobrutinib, 68% acquired ≥1 mutation



BTKi, BTK inhibitor; CLL, chronic lymphocytic leukemia; PD, progressive disease.
Brown JR *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 326).

Bispecific mAbs

RECRUITING

1

A Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Mosunetuzumab and a Combined Regimen of Mosunetuzumab and Venetoclax in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia

ClinicalTrials.gov ID NCT05091424

2

028 | **GLOFITAMAB MONOTHERAPY INDUCES DURABLE COMPLETE REMISSIONS AND HAS A MANAGEABLE SAFETY PROFILE IN PATIENTS WITH RICHTER'S TRANSFORMATION**

C. Carlo-Stella[1], M. Hutchings[2], F. Offner[3], E. Mulvihill[4], J. Relf[5], B. Byrne[5], L. Lundberg[4], M. Dickinson[6]

[1]*Humanitas University and IRCCS Humanitas Research Hospital, Milan, Italy,* [2]*Rigshospitalet, Copenhagen, Denmark,* [3]*Universitair Ziekenhuis Gent, Ghent, Belgium,* [4]*F. Hoffmann-La Roche Ltd, Basel, Switzerland,* [5]*Roche Products Ltd, Welwyn Garden City, UK,* [6]*Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Victoria, Australia*

3

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 5, 2021

Subcutaneous Epcoritamab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Preliminary Results from the Epcore CLL-1 Trial

Arnon P. Kater, Jacob Haaber Christensen, Hans Herluf Bentzen, Carsten Utoft Niemann, Martin Hutchings, Jenny Chen, Marcia Rios, Tammy Palenski, Tommy Li, Anthony R. Mato

Blood (2021) 138 (Supplement 1): 2627.

https://doi.org/10.1182/blood-2021-146563

4

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 15, 2022

Subcutaneous Epcoritamab in Patients with Richter's Syndrome: Early Results from Phase 1b/2 Trial (EPCORE CLL-1)

Arnon P. Kater, J Christine Ye, Jose Sandoval-Sus, Mar Bellido, Jacob Haaber Christensen, Anthony R. Mato, Ann Janssens, Toshihiko Oki, Daniela Hoehn, Marcia Rios, Alexandra Kuznetsova, Rebecca Valentin, Herbert Eradat

Blood (2022) 140 (Supplement 1): 850–851.

https://doi.org/10.1182/blood-2022-158298

CLL, chronic lymphocytic leukemia; mAb, monoclonal antibody.

1. ClinicalTrials.gov NCT05091424. Available at: https://clinicaltrials.gov/study/NCT05091424. Accessed February 2024. 2. Carlo-Stella C *et al*. *Hematol Oncol* 2023; 41 (Suppl 2): 63–65.
3. Kater AP *et al*. *Blood* 2021; 138 (Suppl 1): 2627. 4. Kater AP *et al*. *Blood* 2022; 140 (Suppl 1): 850–851.

CAR-T therapy: TRANSCEND study of liso-cel in R/R CLL/SLL

24-month median follow-up

- Patients who were previously treated with, or ineligible for, BTKi therapy
- ≥2 prior lines of therapy

Efficacy outcomes	BTKi progression / venetoclax failure subset at DL2 (n=50)
CR/CRi, %	20
uMRD rate in the blood, % (95% CI)	64 (49–77)
Median (95% CI) DoR, months	35.3 (12.4–NR)
Median (95% CI) OS, months	30.3 (15.0–NR)

Liso-cel demonstrated a clinical benefit with a manageable safety profile in patients after BTKi progression / venetoclax failure and in the full study population

BTKi, BTK inhibitor; CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete marrow recovery; DL, dose level; DoR, duration of response; liso-cel, lisocabtagene maraleucel; NR, not reached; OS, overall survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; uMRD, undetectable minimal residual disease.

Siddiqi T *et al*. Oral presentation at ASH 2023; San Diego, CA, USA, December 9–12, 2023 (Abstract 330).

Allogeneic SCT

- One of the few curative options
  - Use has declined over the past decade[1]

- Difficult to interpret the data
  - No RCTs[1]
  - Only very high-risk patients[1]

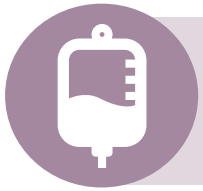
- Long-term results of the GCLLSG CLL3X trial:[2]
  - N=100, of whom 90 were allografted
  - 10-year PFS: 34%
  - OS: 51%

Allogeneic SCT should be reserved for rare cases of young patients who have exhausted all therapeutic options[1,3]

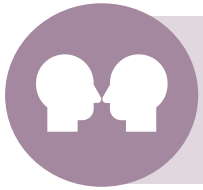
OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; SCT, stem cell transplantation.

1. Gribben JG. *Blood* 2018; 132 (1): 31–39. 2. Krämer I *et al*. *Blood* 2017; 130 (12): 1477–1480. 3. Puckrin R *et al*. *Front Oncol* 2023; 12: 1105779.

What can we conclude for the treatment of R/R CLL?

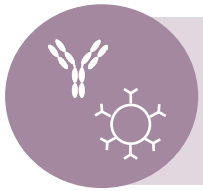


Most trials evaluating targeted therapies in R/R CLL have been carried out in patients treated with first-line ICT



Head-to-head trials have demonstrated better safety profiles of next-generation BTKis vs. ibrutinib, and superior efficacy with zanubrutinib vs. ibrutinib in R/R CLL

The role of ibrutinib + venetoclax in treating these patients is not clear



Bispecific mAbs are likely to be a promising avenue of research, whereas CAR-T therapy has yet to prove its value in randomized trials

BTKi, BTK inhibitor; CAR-T, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukemia; ICT, immunochemotherapy; mAb, monoclonal antibody; R/R, relapsed/refractory.
Slide courtesy of Vincent Lévy.