Chronic Lymphocytic Leukemia: Evaluating Targeted Therapeutic Strategies and Optimizing Outcomes Throughout the Cancer-Care Continuum

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Great Debates Hematologic Malignancies
from Lymphoma · Leukemia & Myeloma Congress

Disclosures

- **Callie Coombs, MD:** Advisory Board—AbbVie Inc., AstraZeneca, Beigene, Genentech, Lilly; consultant—AbbVie Inc., AstraZeneca, Beigene, Lilly, Octapharma; grant/research support—AbbVie Inc., Beigene, Lilly; honoraria—AbbVie Inc., AstraZeneca, Beigene, Genentech, Lilly, Allogene, BMS, Janssen, Pharmacyclics; Speaker's Bureau—AbbVie Inc., AstraZeneca, Beigene, Lilly; institutional research funding—AbbVie, AstraZeneca, Beigene, CarnaBio, Lilly

Program Information

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Learning Objectives

- Interpret the most recent clinical data and real-world evidence associated with approved and emerging novel targeted therapies to inform evidence-based treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Evaluate the latest guidelines, patient selection criteria, and adverse event (AE) management strategies associated with available monotherapies and combination regimens for CLL/SLL
- Summarize the importance of molecular profiling for risk stratification and MRD evaluation for optimized treatment selection and sequencing in CLL/SLL

CLL/SLL Epidemiology

- Most prevalent leukemia in Western world
- More common in men vs women, more common in White people vs other races
- American Cancer Society's estimates for chronic lymphocytic leukemia (CLL) in the United States for 2025 are
  - About 23,690 new cases of CLL
  - About 4,460 deaths from CLL

Nasnas P, et al. *Hematol Rep*. 2023;15(3):454-464. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program [seer.cancer.gov]. Last updated April 16, 2025. https://seer.cancer.gov/statistics-network/explorer/application.html. American Cancer Society (ACS) [www.cancer.org]. Last updated March 20, 2025. https://www.cancer.org/cancer/types/chronic-lymphocytic-leukemia/about/key-statistics.html.

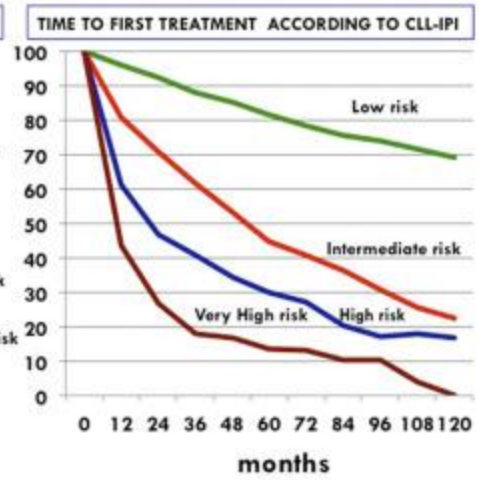
CLL Prognostic Variables

CLL- IPI Prognostic Model

1) TP53 status (no abnormalities v/s del[17p] or TP53 mutation or both)
2) IGHV mutational status (mutated v/s unmutated)
3) Serum β2-microglobulin concentration (≤3.5 mg/L v/s >3.5 mg/L)
4) Clinical stage (Binet A or Rai 0 v/s Binet B–C or Rai I–IV)
5) Age (≤65 years v/s >65 years)

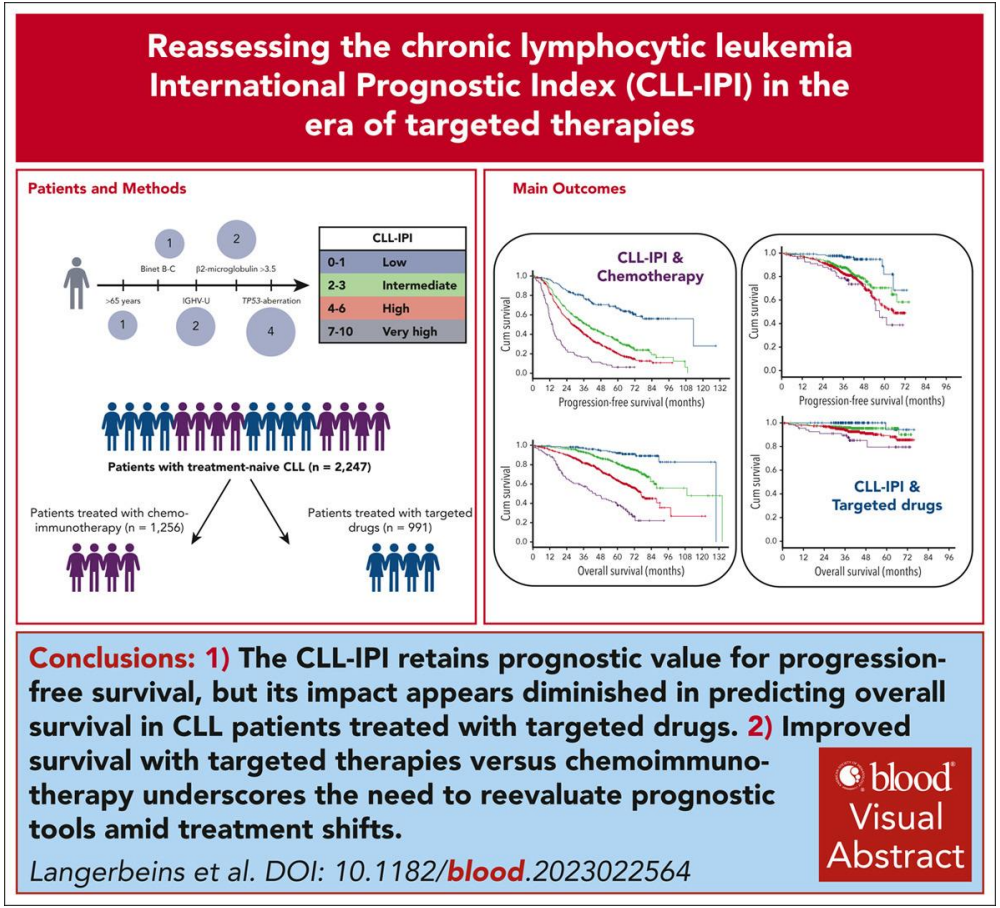
Risk Group	CLL-IPI risk score
Low-risk	0-1
Intermediate-risk	2-3
High-risk	4-6
Very High-risk	7-10

TP53 status	-	Deleted or mutated	1·434	4·2 (3·2–5·5)	<0·0001	4
IGHV mutational status	-	Unmutated	0·950	2·6 (2·1–3·2)	<0·0001	2
β_2-microglobulin concentration	-	>3·5 mg/L	0·678	2·0 (1·6–2·4)	<0·0001	2
Clinical stage	-	Rai I–VI or Binet B–C	0·464	1·6 (1·3–1·9)	<0·0001	1
Age	-	>65 years	0·555	1·7 (1·4–2·1)	<0·0001	1



IPI = International Prognostic Index.
Molica S, et al. *Blood*. 2017;130(Suppl 1):1739. International CLL-IPI Working Group. *Lancet Oncol*. 2016;17(6):779-790.

Are Prognostic Tests Still Relevant in the Novel Agent Era?



IGHV-U = unmutated immunoglobulin heavy-chain variable region gene.
Langerbeins P, et al. *Blood*. 2024;143(25):2588-2598.

Is There a Role for “Early” Treatment

- Not at this time
- Standard of care remains to pursue active surveillance (“watch and wait”) until an iwCLL indication for therapy develops
- Reasons
  - Disease is typically indolent
  - Treatment can carry toxicities
  - There is no cure for the disease
- That being said, trials are ongoing to determine whether there is a role for early intervention using novel agents in pts with higher-risk CLL
  - SWOG S1925 “EVOLVE” trial of early vs delayed ven/obi

iwCLL = International Workshop on Chronic Lymphocytic Leukemia; ven/obi = venetoclax, obinutuzumab.

SWOG Cancer Research Network [www.swog.org]. https://www.swog.org/clinical-trials/s1925.

Frontline Therapy

Treat-to-progression
or
Fixed-duration regimens

2025: There is no one-size-fits-all approach

What Do the Guidelines Say?

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

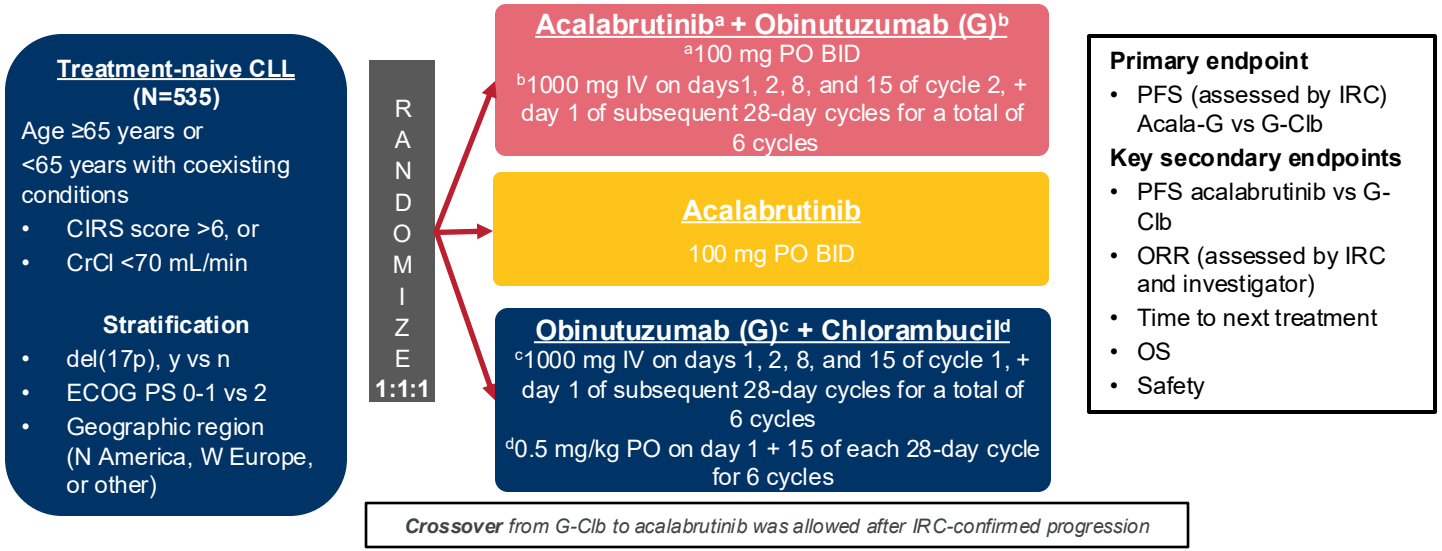
FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• BCL2i-containing regimens ▸ Venetoclax[f,h] + obinutuzumab (category 1) ▸ Venetoclax[f,h] + acalabrutinib ± obinutuzumab (category 1) • cBTKi-based regimens ▸ Acalabrutinib[f,g] ± obinutuzumab (category 1) ▸ Zanubrutinib[f,g] (category 1)	• BCL2i-containing regimen ▸ Venetoclax[f,h] + ibrutinib[f,g] • cBTKi-based regimen ▸ Ibrutinib[f,g,i] (category 1)	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ▸ FCR (fludarabine, cyclophosphamide, rituximab)[j,k] • cBTKi-based regimen ▸ Ibrutinib[f,g] + anti-CD20 mAb (category 2B)[l] • Consider when cBTKi and BCL2i are not available or contraindicated or rapid disease debulking needed ▸ Bendamustine[m] + anti-CD20 mAb[l,n] ▸ Obinutuzumab ± chlorambucil[o] ▸ High-dose methylprednisolone (HDMP) + anti-CD20 mAb[l] (category 2B; category 3 for patients <65 y without significant comorbidities)

Guidelines for patients *with* 17p/TP53 mutation are similar but advise *against* CIT (and no category 1 regimens in first-line).

BCL2i = BCL2 inhibitor; cBTKi = Covalent Bruton's tyrosine kinase inhibitor; mAb = monoclonal antibody; CIT = chemoimmunotherapy.

National Comprehensive Cancer Network (NCCN) [www.nccn.org]. Last updated March 2025. Accessed May 24, 2025. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

ELEVATE TN: Study Design

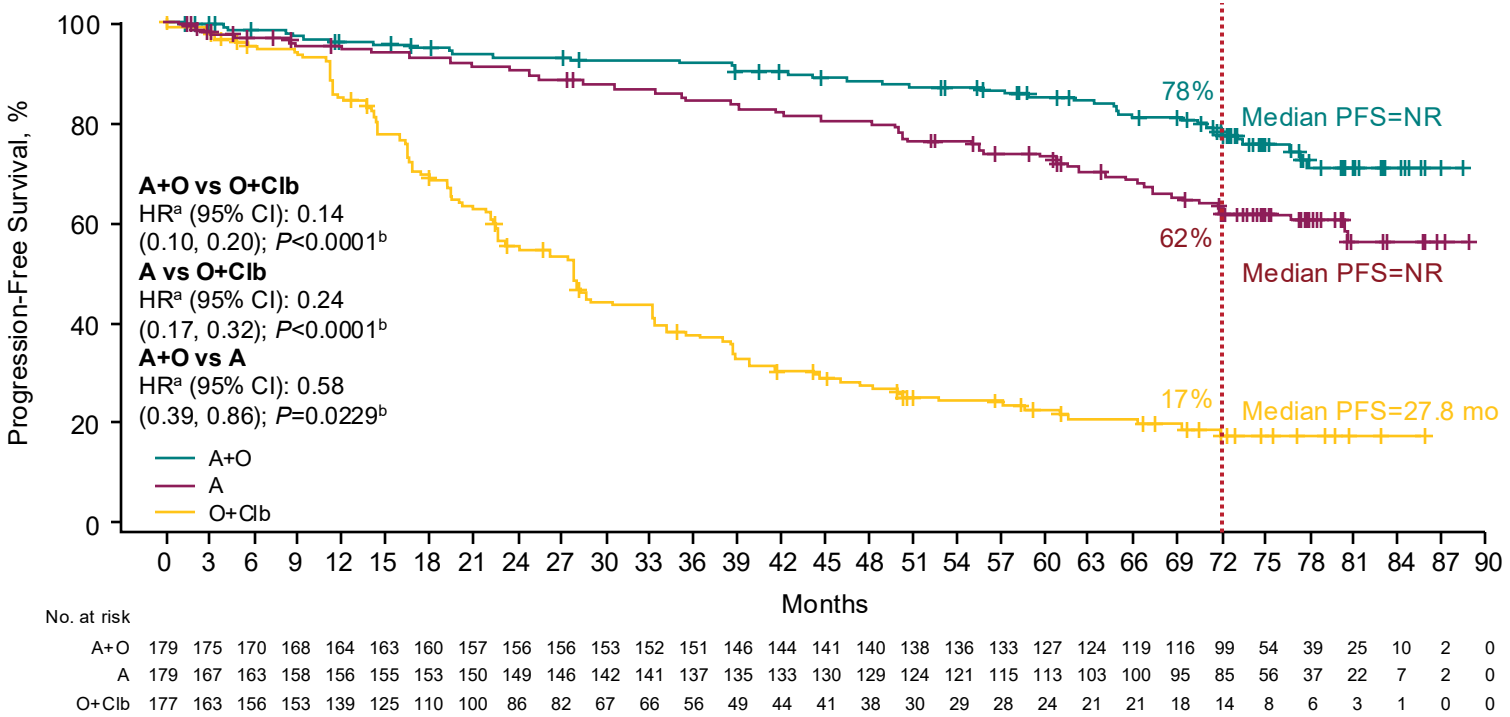


- Interim analysis was planned based on events (after occurrence of ~111 IRC-assessed PFS events in the combination therapy arms) or after 24 months if the required number of events was not met by this time

CIRS = Cumulative Illness Rating Scale; CrCl = creatinine clearance; ECOG PS = Eastern Cooperative Oncology Group performance status; IRC = independent review committee; PFS = progression-free survival; ORR = objective response rate; OS = overall survival.

Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291.

Median PFS Was Significantly Higher for A-Containing Arms vs O+Clb

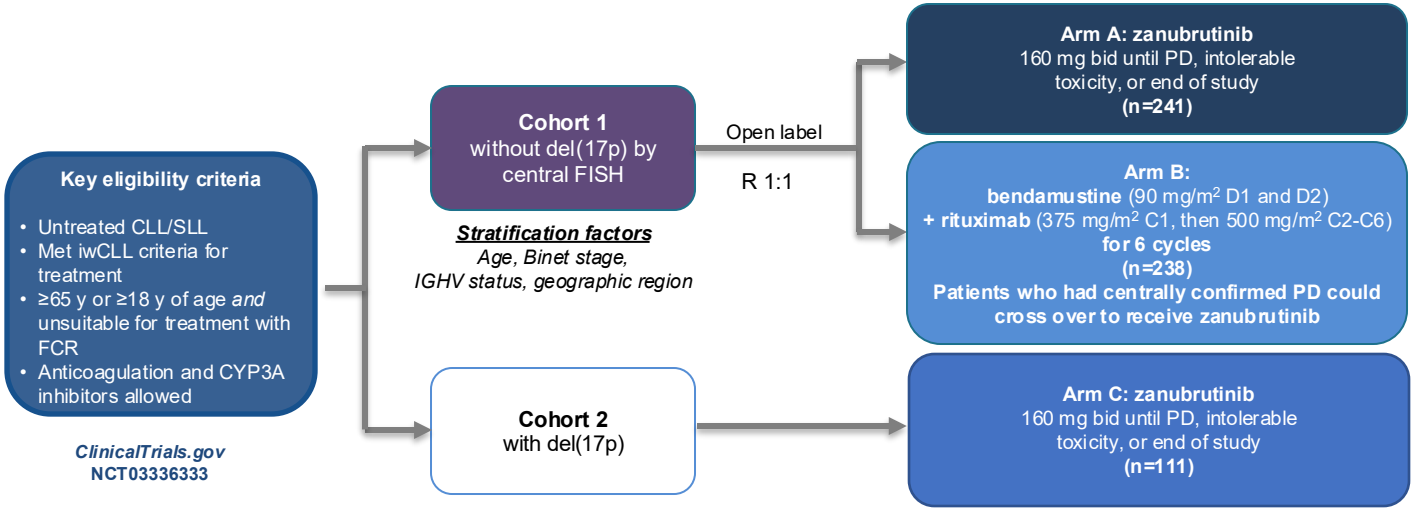


Median PFS was significantly higher for A+O vs A.

[a]Hazard ratio based on stratified Cox proportional-hazards model. [b]*P*-value based on stratified log-rank test.

Sharman JP, et al. *Blood*. 2023;142(Suppl 1):636.

SEQUOIA Study Design



Assessments
- Response assessments were conducted every 12 weeks from start of C1 for 96 weeks and every 24 weeks until PD
- CR/CRi confirmed via bone marrow biopsy
- AEs documented until PD or start of next CLL therapy

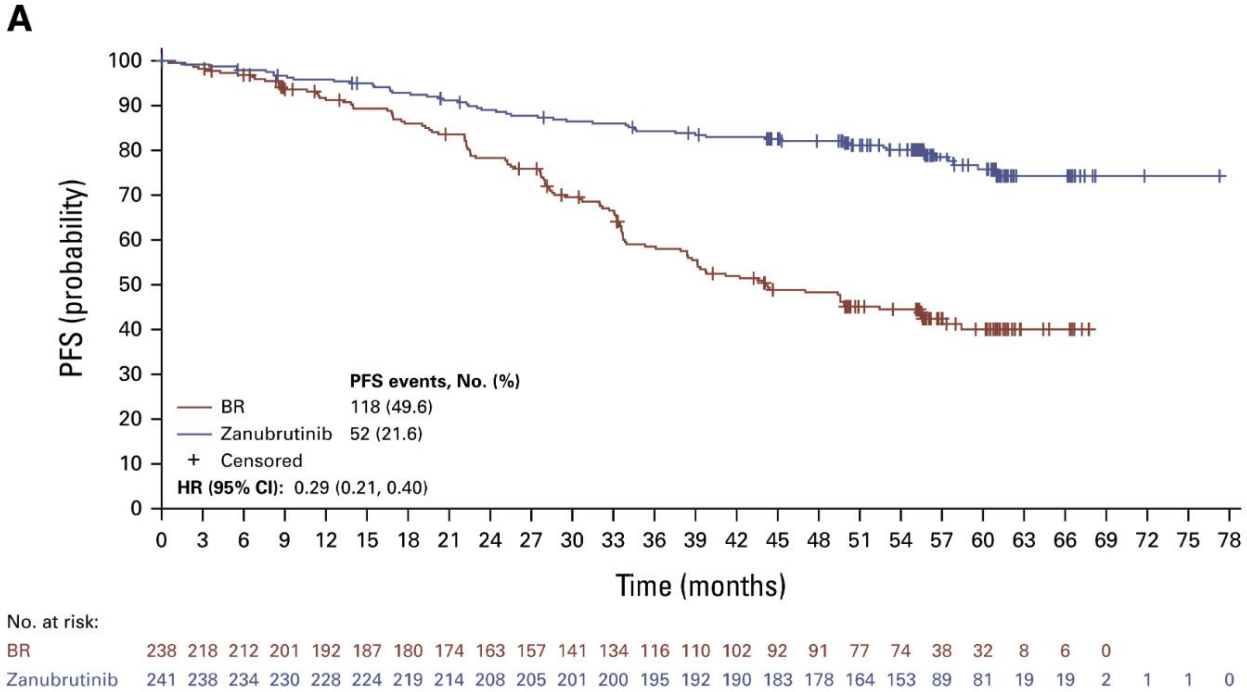
Statistical analysis
- Efficacy endpoints analyzed using ITT analysis and the per-protocol analysis set
- Safety was assessed in all pts who received ≥1 dose of treatment

Outcomes
- PFS assessed by investigator
- OS in cohorts 1 and 2
- PFS 2
- Clinical outcomes (correlated with baseline prognostic and predictive markers)
- Safety

FCR = fludarabine, cyclophosphamide, rituximab; FISH = fluorescence in situ hybridization; PD = progressive disease; CR = complete response; CRi = CR with incomplete hematopoietic recovery; ITT = intention-to-treat.

Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043.

5-Year SEQUOIA Follow-Up



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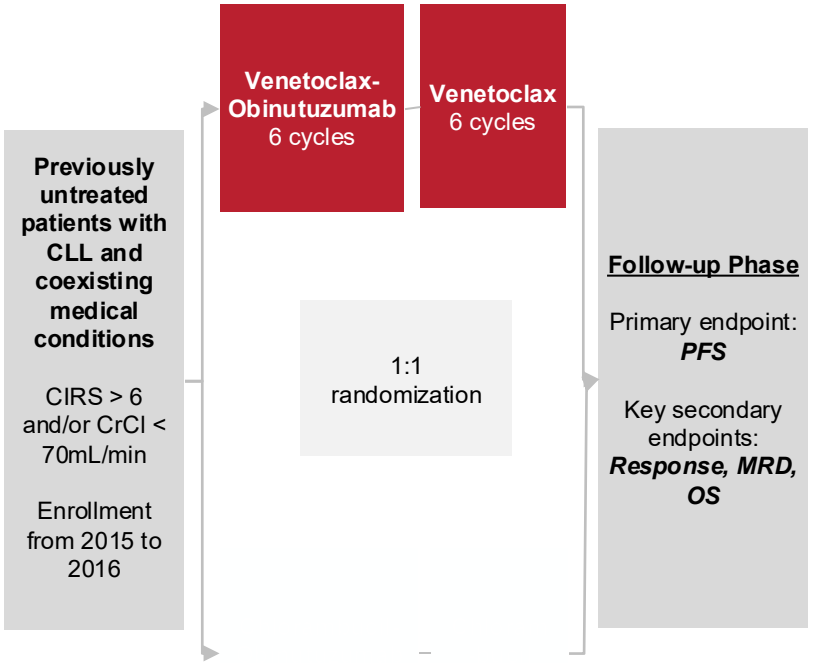
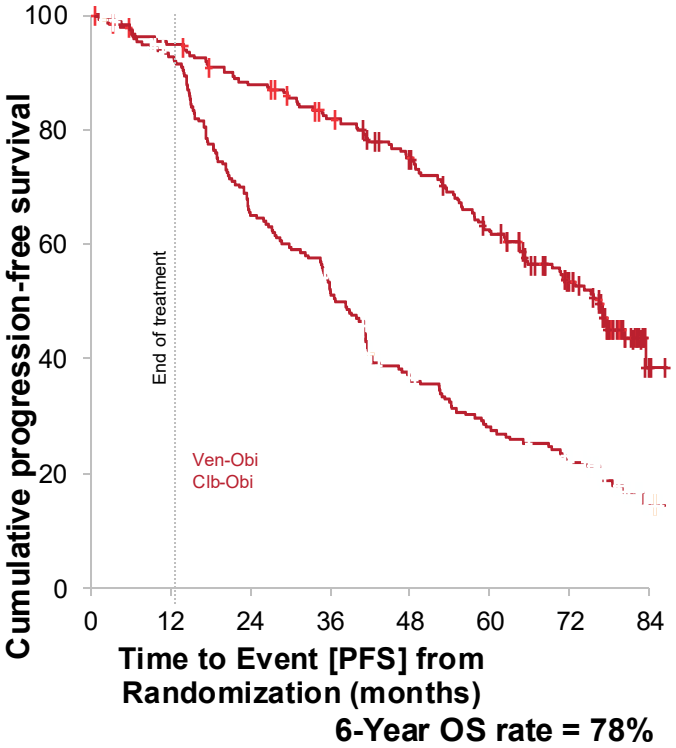
Shadman M, et al. *J Clin Oncol*. 2025;43(7):780-787.

Phase III CLL14 Study: 6-Year Update

Study Design



Investigator Assessed Progression-Free Survival



Median PFS
Ven-Obi: 76.2 months

6-year PFS rate
Ven-Obi: 53.1%

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

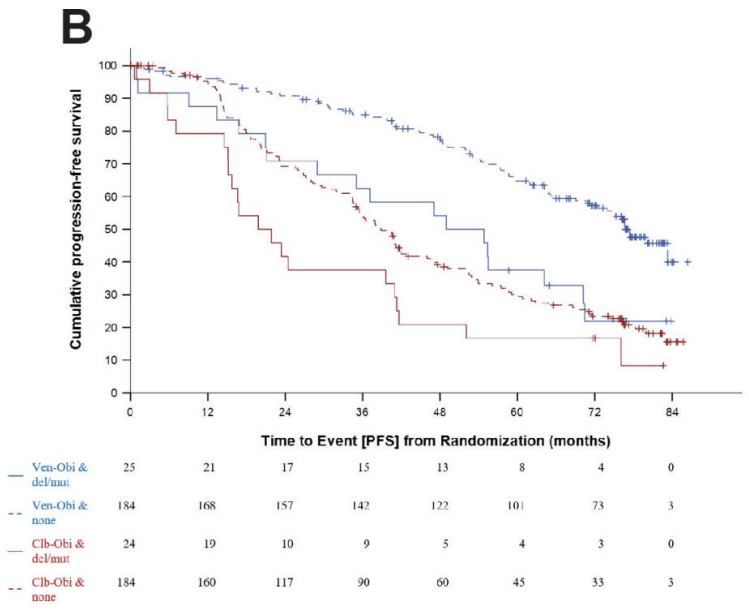
6-Year OS rate = 78%

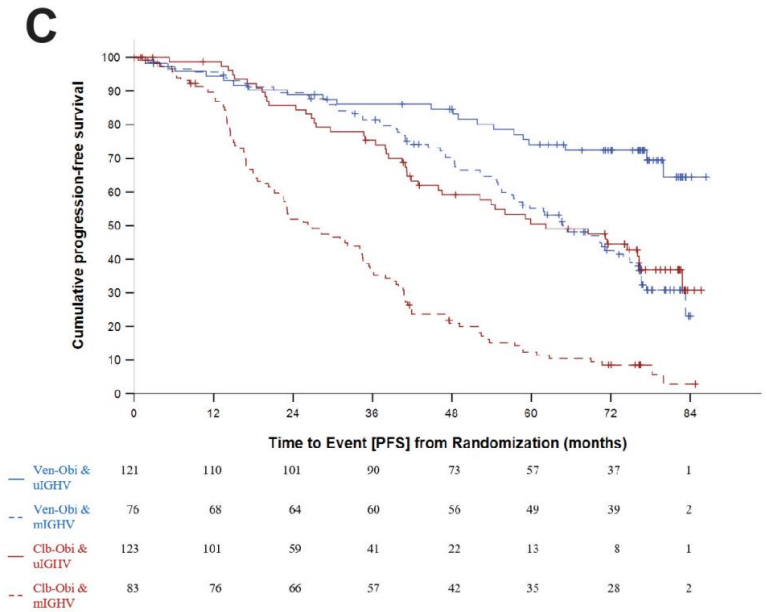
MRD = measurable residual disease.

Reformatted from Al-Sawaf O, et al. Presented at: European Hematology Association (EHA) 2023 Congress; June 8-11, 2023; Frankfurt, Germany. Abstract S145.

Updates from 6-Year CLL14 Follow-Up

- Higher-risk pts have shorter remissions
  - Median PFS for TP53 aberrant pts: 51.9 months
  - Median PFS for unmut IGHV pts: 64.8 months





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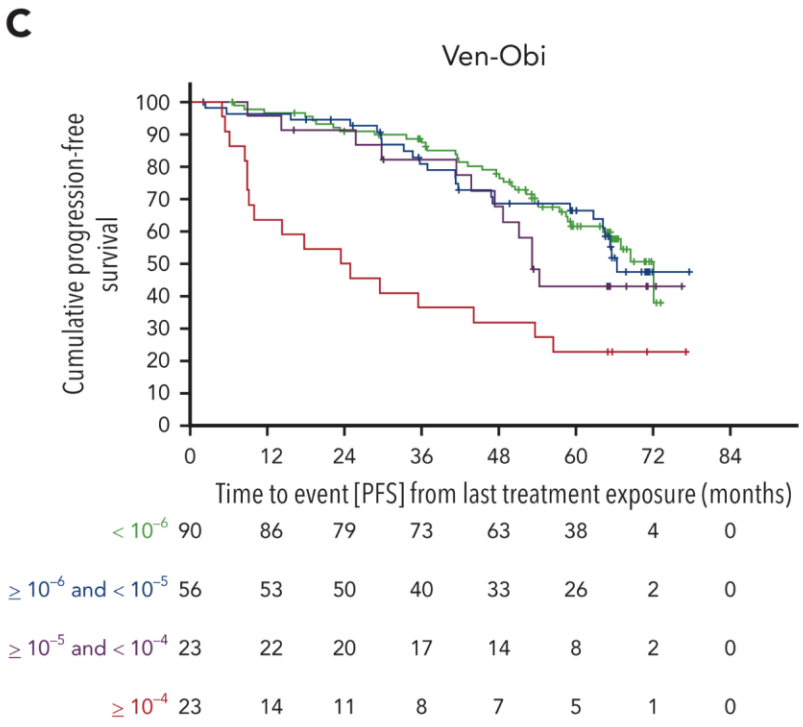
Al-Sawaf O, et al. *Blood*. 2024;144(18):1924-1935.

Prognostic Implications for MRD at EOT

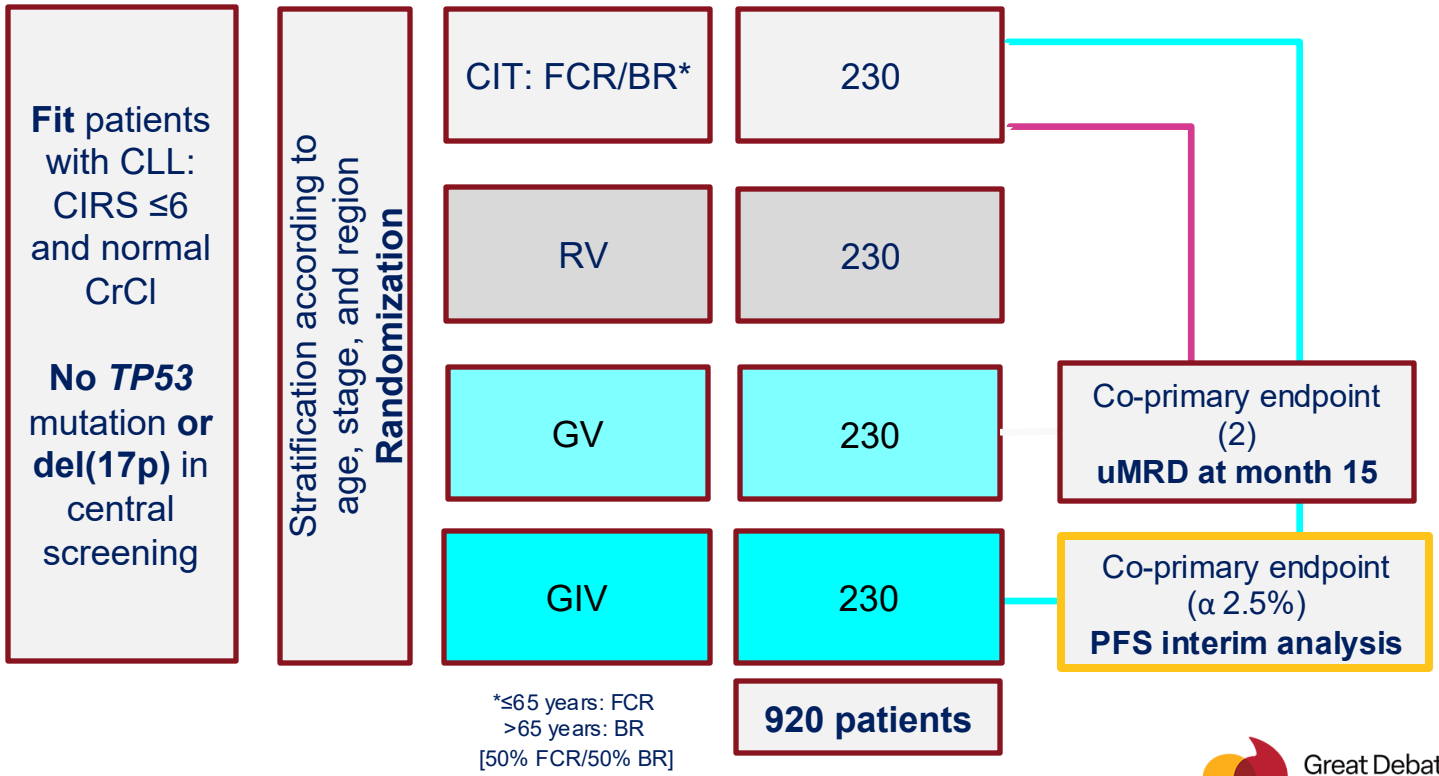


EOT = end of treatment.

Al-Sawaf O, et al. *Blood*. 2024;144(18):1924-1935.

GAIA/CLL13 Study Design for Fit Patients with CLL

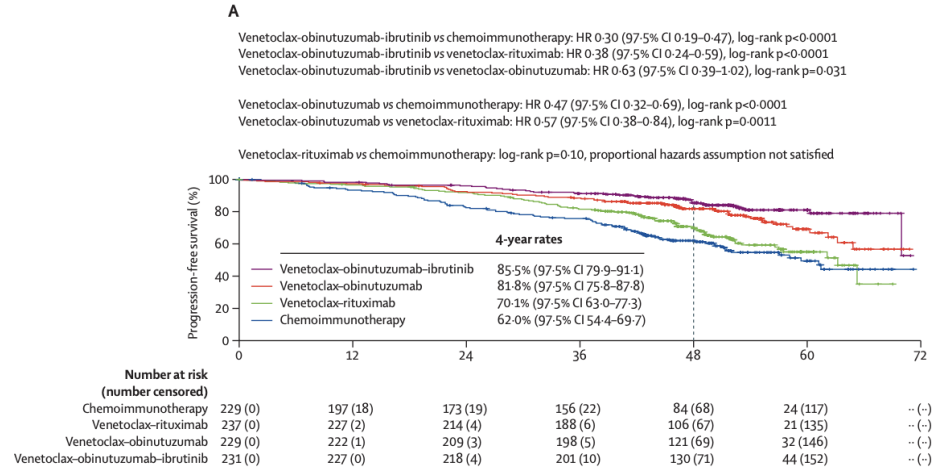
- Chemoimmunotherapy (**FCR/BR**) vs **R**ituximab + **V**enetoclax vs Obinutuzumab (**G**) + **V** vs **G** + **I**brutinib + **V**
- Recruitment in 10 countries (DE, AT, CH, NL, BE, DK, SE, FI, IE, IL)



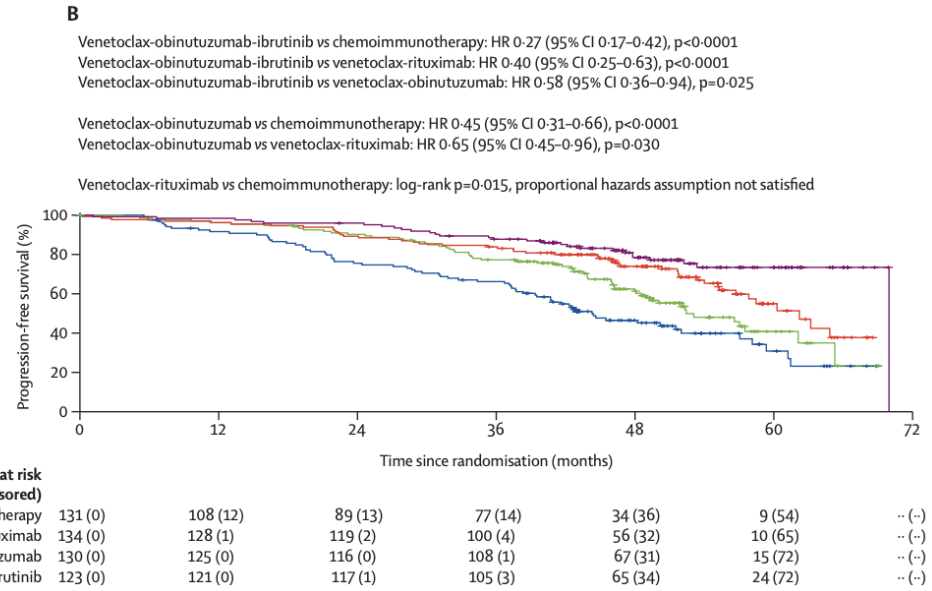
uMRD = undetectable MRD; BR = bendamustine, rituximab.

Eichhorst B, et al. Presented at: EHA2022 Congress; June 9-12, 2022; Vienna, Austria. Abstract LB2365.

4-Year Follow-Up of CLL13 Trial Support VO-Containing Regimens



Unmutated IGHV only



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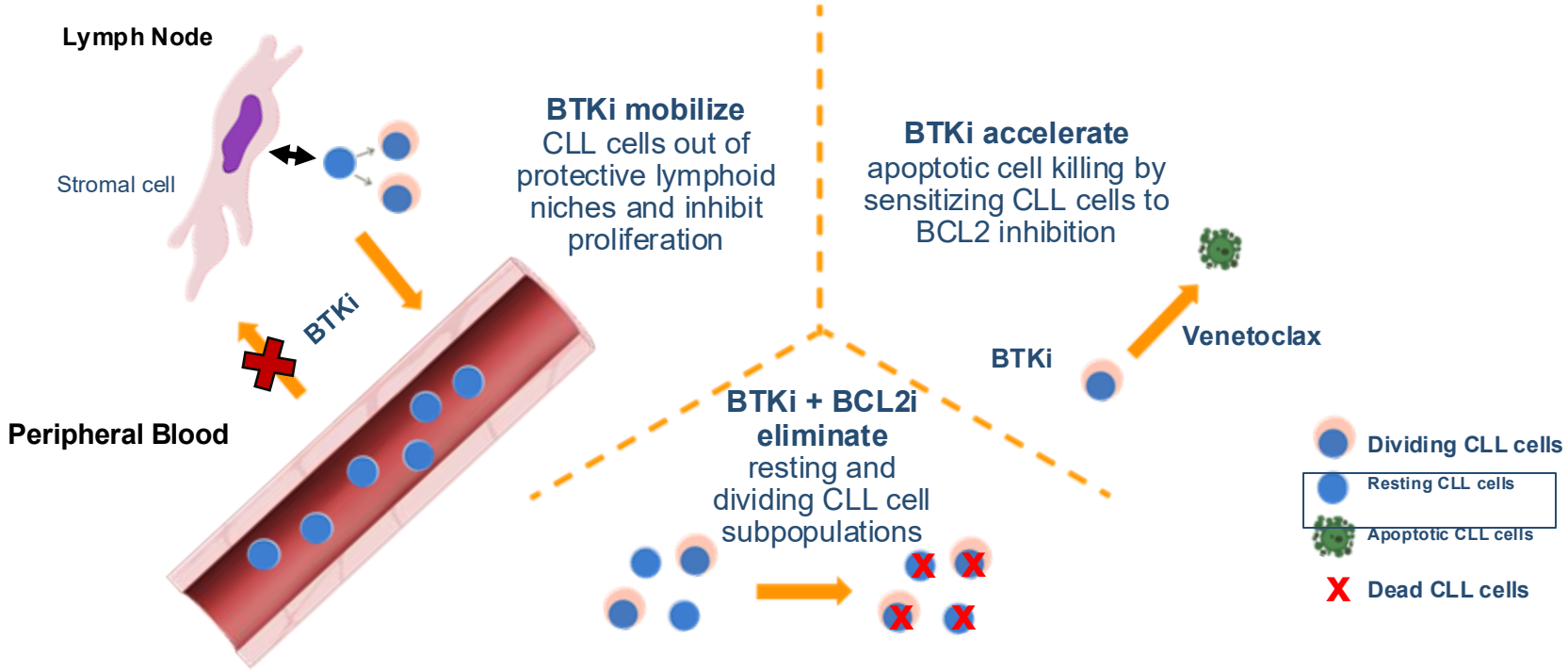
Fürstenau M, et al. *Lancet Oncol.* 2024;25(6):744-759.

Rationale to Combine BTKi with BCL2i



Lu P, et al. *Blood Cancer J*. 2021;11(2):39. Deng J, et al. *Leukemia*. 2017;31(10):2075-2084. Herman SEM, et al. *Clin Cancer Res*. 2015;21(20):4642-4651. Burger JA, et al. *Leukemia*. 2020;34(3):787-798. Shanafelt TD, et al. *N Engl J Med*. 2019;381(5):432-443. Cervantes-Gomez F, et al. *Clin Cancer Res*. 2015;21(16):3705-3715. Slinger E, et al. *Blood*. 2017;130(Suppl 1):3018-3018. Haselager MV, et al. *Blood*. 2020;136(25):2918-2926. Slinger E, et al. *Leukemia*. 2017;31(12):2601-2607.

AMPLIFY Trial Design and Primary Endpoint

Treatment-naive CLL
- Age ≥ 18y/o
- ECOG: 0-2
- Active disease per iwCLL 2018 criteria

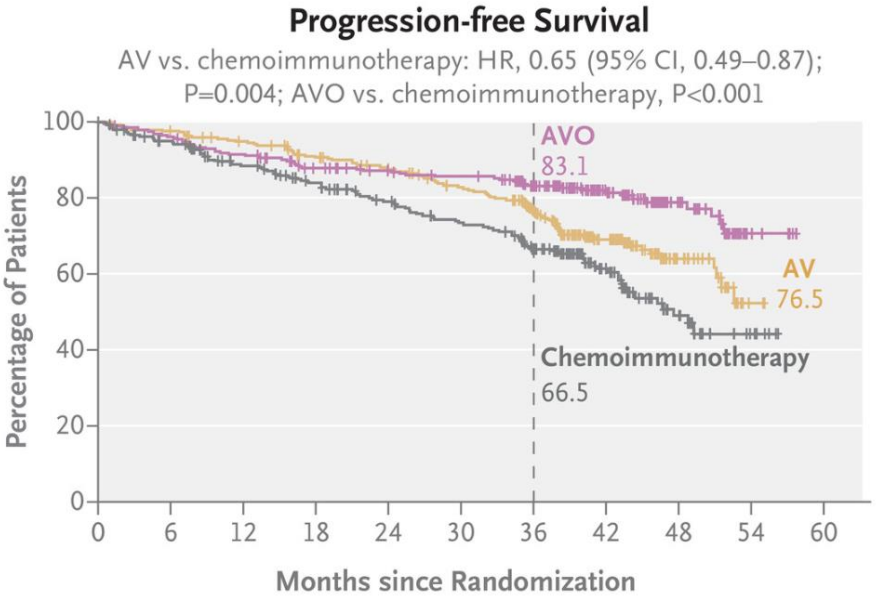
Exclusion
- del(17p), TP53

Randomized 1:1:1 to receive

Acalabrutinib + Venetoclax (2 cycles A then 12 cycles A+V)

Acalabrutinib + Venetoclax + Obinutuzumab

Chemoimmunotherapy (FCR or BR)



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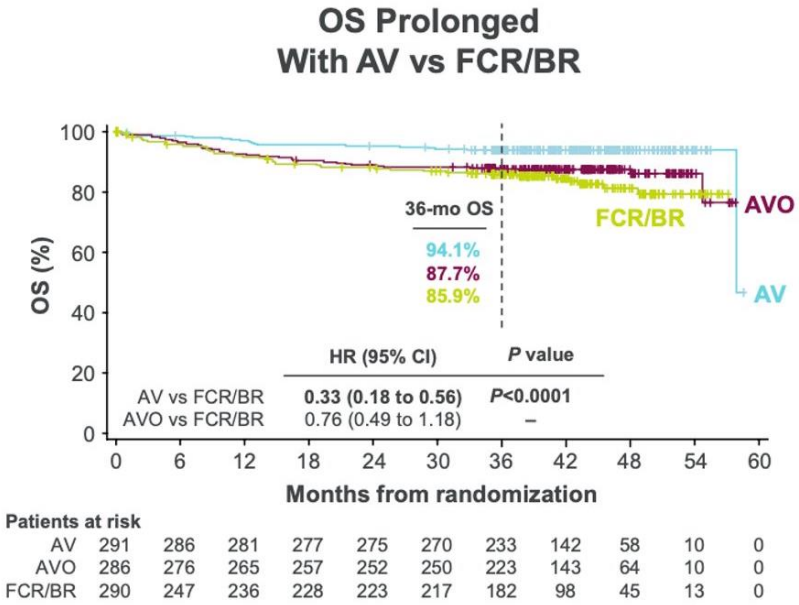
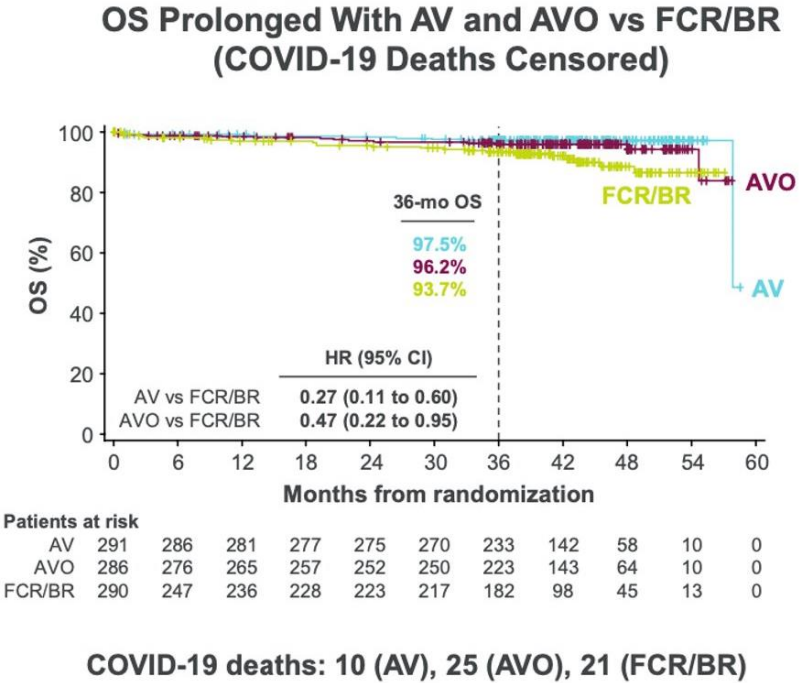
Brown JR, et al. *N Engl J Med*. 2025;392(8):748-762.

Overall Survival for AMPLIFY





COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)

ITT population. Hazard ratio (95% CI) computed using a Cox proportional-hazards model stratified by the randomization strata. *P*-value based on stratified log-rank test.

Brown JR, et al. *Blood*. 2024;144(Suppl 1):1009.

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How to Choose When So Many Effective Options Are Available

A **Patient preference is often the most important factor**

Key features of acalabrutinib or zanubrutinib
1. Therapy until progression or intolerance
2. Only oral therapy
3. Limited visits/laboratory monitoring

Key features of venetoclax and obinutuzumab:
1. Time-limited therapy
2. Includes intravenous therapy (obinutuzumab)
3. Frequent visits/labs over the first 8 weeks

B **Strongly recommend against acalabrutinib or zanubrutinib if:**
1. Concomitant dual antiplatelet therapy (check with cardiologist if DAPT is necessary)
2. Concomitant warfarin (check if non-warfarin anticoagulation is acceptable)
3. History of major bleeding with ongoing risk
4. History of ventricular arrhythmia with ongoing risk

C **Influences toward acalabrutinib or zanubrutinib**
1. Presence of a 17p deletion by FISH or a *TP53* mutation by NGS

Influences toward venetoclax and obinutuzumab:
1. Concomitant single antiplatelet therapy
2. Concomitant anticoagulation (non-warfarin)
3. History of atrial fibrillation or flutter

While these factors influence our treatment selection, all factors should be taken into account, and either therapeutic approach is reasonable

DAPT = dual antiplatelet therapy; NGS = next-generation sequencing.
Soumerai JD, et al. *Blood Adv*. 2025;9(5):1213-1229.

Relapsed Disease

Factors to consider when selecting therapy in relapse

- Response to and tolerance of prior therapy
- Biologic features of CLL
  - FISH, karyotype, TP53 mutations, IGHV
  - BTK mutations?
- Age and comorbidities
- Patient preferences
- Availability of clinical trial

What Do the Guidelines Say?

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

SECOND-LINE OR SUBSEQUENT THERAPY[e]	
Preferred Regimens	**Other Recommended Regimens**
• BCL2i-containing regimen ▸ Venetoclax[f,h] + obinutuzumab • cBTKi-based regimens ▸ Acalabrutinib[f,g,p] (category 1) ▸ Zanubrutinib[f,g,p] (category 1) • ncBTKi-based regimen:[f] ▸ Pirtobrutinib (resistance or intolerance to prior cBTKi-based regimens)	• BCL2i-containing regimens ▸ Venetoclax[f,h] + rituximab (category 1) ▸ Venetoclax[f,h,*] ▸ Venetoclax[f,h] + ibrutinib[f,g,q] (category 2B) • cBTKi-based regimen ▸ Ibrutinib[f,g,i] (category 1)

[*] Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) is a treatment option for relapse after a period of remission.

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi-BASED AND BCL2i-CONTAINING REGIMENS[e]	
Preferred Regimens	**Other Recommended Regimens**
• Chimeric antigen receptor (CAR) T-cell therapy ▸ Lisocabtagene maraleucel (CD19-directed)[r] • ncBTKi-based regimen:[f] ▸ Pirtobrutinib (if not previously given)	• PI3Ki-based regimens[f] ▸ Duvelisib ▸ Idelalisib[s] ± rituximab • FCR[k,t] • Lenalidomide[u] ± rituximab • Obinutuzumab • Bendamustine[m] + rituximab[n] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities) • HDMP + anti-CD20 mAb[l] (category 2B)

ncBTKi = non-covalent BTKi; HDMP = high-dose methylprednisolone.
NCCN [www.nccn.org]. Last updated March 2025. Accessed June 6, 2025.
https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

ELEVATE-RR Trial Design

Patients (N=533)

Key Inclusion Criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria[3])
- Presence of del(17p) or del(11q)[a]
- ECOG PS ≤2

Key Exclusion Criteria

- Significant CV disease
- Concomitant treatment with warfarin or equivalent vitamin K antagonist
- Prior treatment with ibrutinib, a BCR inhibitor (eg, BTK, PI3K, or Syk inhibitors), or a BCL-2 inhibitor (eg, venetoclax)

RANDOMIZE

- Acalabrutinib[b] 100 mg PO BID
- Ibrutinib[b] 420 mg PO QD

Primary endpoint

- Non-inferiority on IRC-assessed PFS

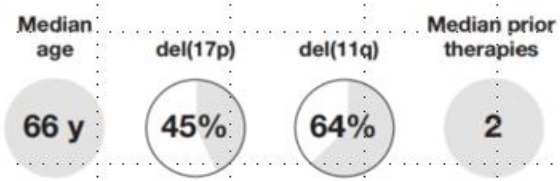
Secondary endpoints (hierarchical order):

- Incidence of any-grade afib/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

***Post hoc* analysis[c]: AE burden score**

- Assessed for 1) AEs overall, 2) most common BTK inhibitor–associated AEs, and 3) ECIs afib/flutter, hypertension, hemorrhage, and infections
- The AE burden score was also analyzed by key baseline characteristics, time interval (yearly),[d] and polypharmacy status (surrogate for comorbidities)

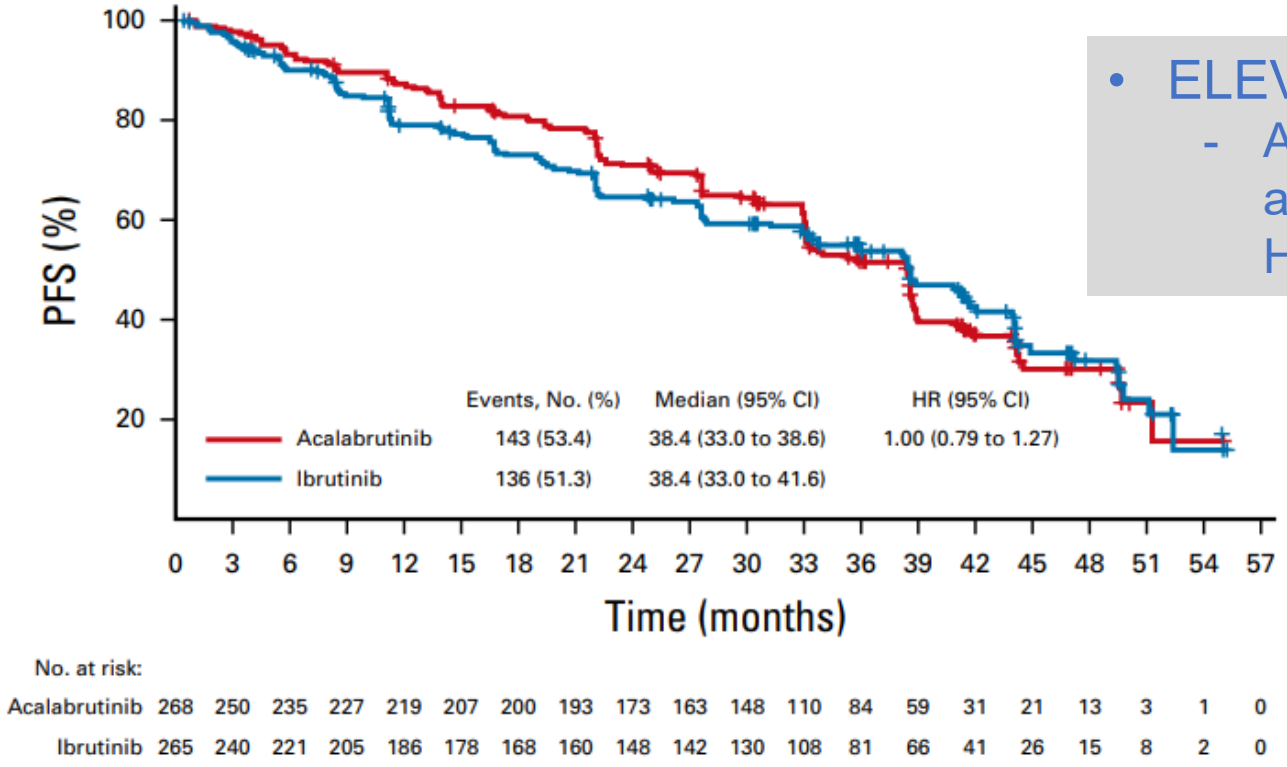
[a]By central laboratory testing. [b]Continued until disease progression or unacceptable toxicity. [c]Data cutoff date for the *post hoc* analysis was the same as that used in the primary publication (September 15, 2020).[2] [d]For the analysis of AE burden score by time interval, for each yearly interval, the end of the AE was defined as the earliest of the end of the AE, end of follow-up year, or end of treatment-emergent period; patients had to be exposed to treatment within the specific year of follow-up to be included in the analysis for that year.



CV = cardiovascular; BCR = B-cell receptor; ECI = event of clinical interest.

Seymour JF, et al. Presented at: 64th American Society of Hematology (ASH) Annual Meeting and Exposition; December 10-13, 2022; New Orleans, Louisiana. Abstract 3133.

ELEVATE-RR Results



- ELEVATE-RR safety
  - Acala had less afib/flutter and less HTN than ibrutinib

HTN = hypertension.

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

ALPINE Trial Design

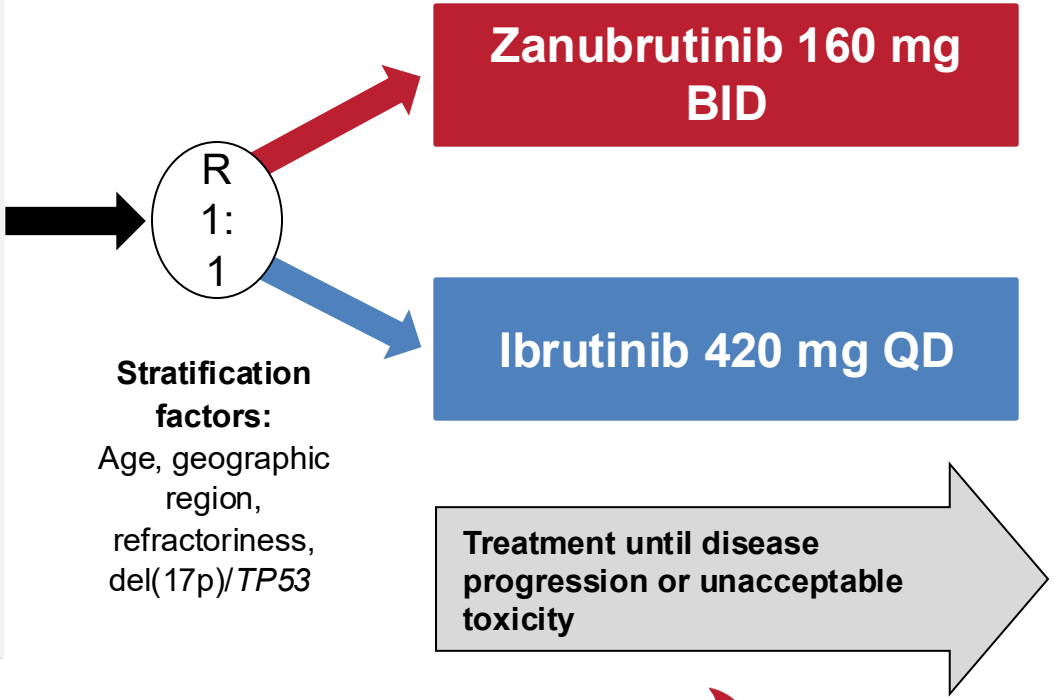
R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

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

Key Exclusion Criteria

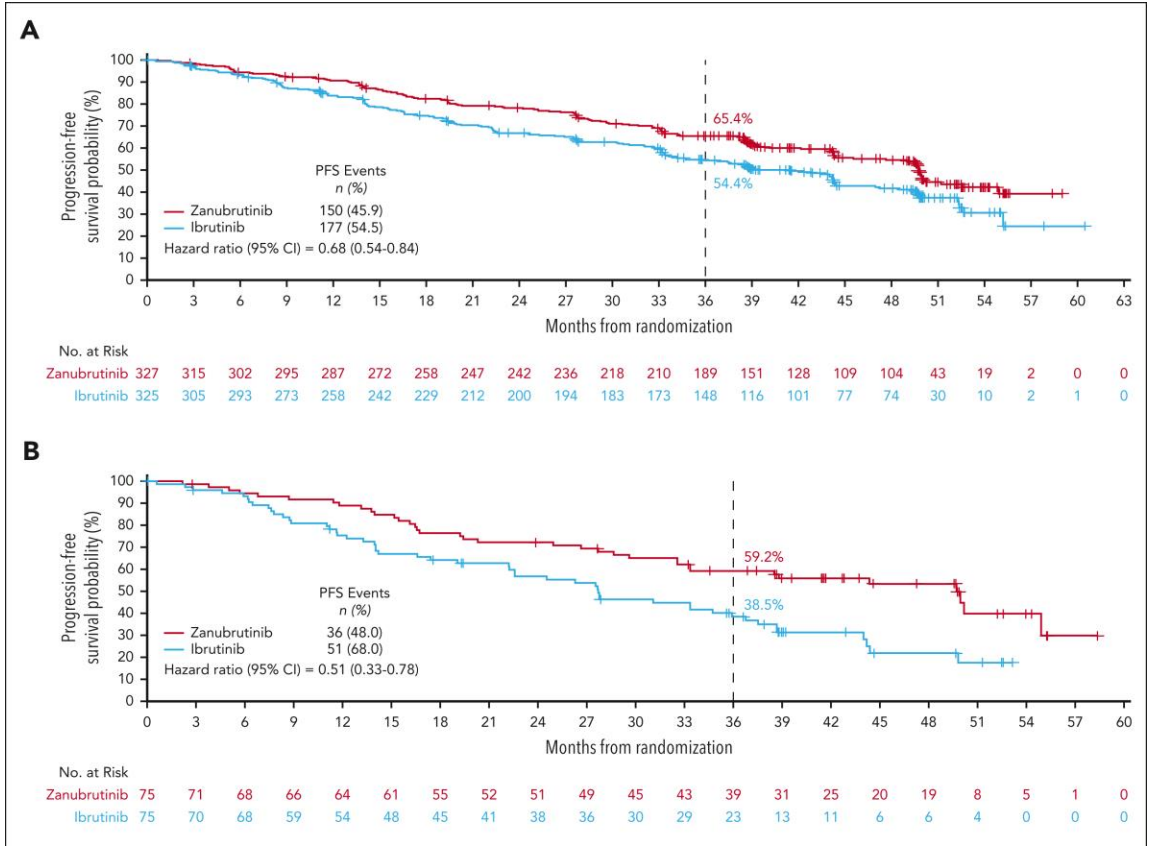
- Prior BTK inhibitor therapy
- Treatment with warfarin/VKA



R/R = relapsed/refractory; CT = computed tomography; MRI = magnetic resonance imaging.

Brown JR et al. *Blood*. 2024;144(26):2706-2717.

ALPINE Results



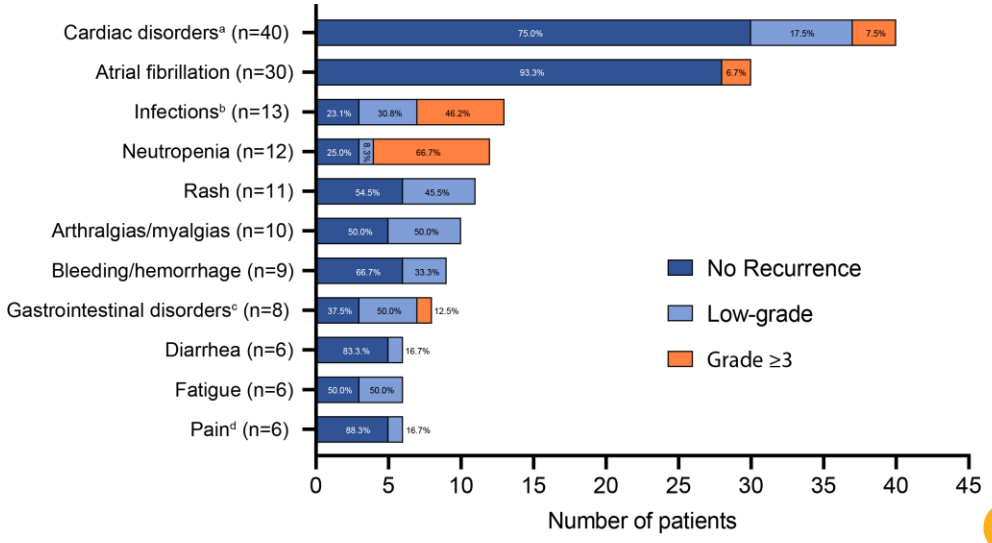
Zanu remains superior to ibrutinib in both all patients (A) and among del 17p patients (B).

Cardiac safety favors zanu which had less afib (though similar HTN).

Brown JR, et al. *Blood*. 2024;144(26):2706-2717.

Can Consider Changing BTKi in Setting of Intolerance

- Data for acalabrutinib: Awan, et al., *Blood Advances,* 2019, and Rogers, et al., *Haematologica,* 2021
- Data for zanubrutinib: Shadman M, et al., *Blood Advances,* 2025
- Data for pirtobrutinib: Shah N, et al., *Haematologica,* 2025



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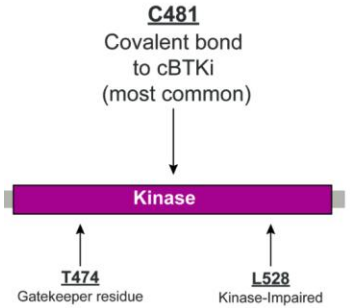
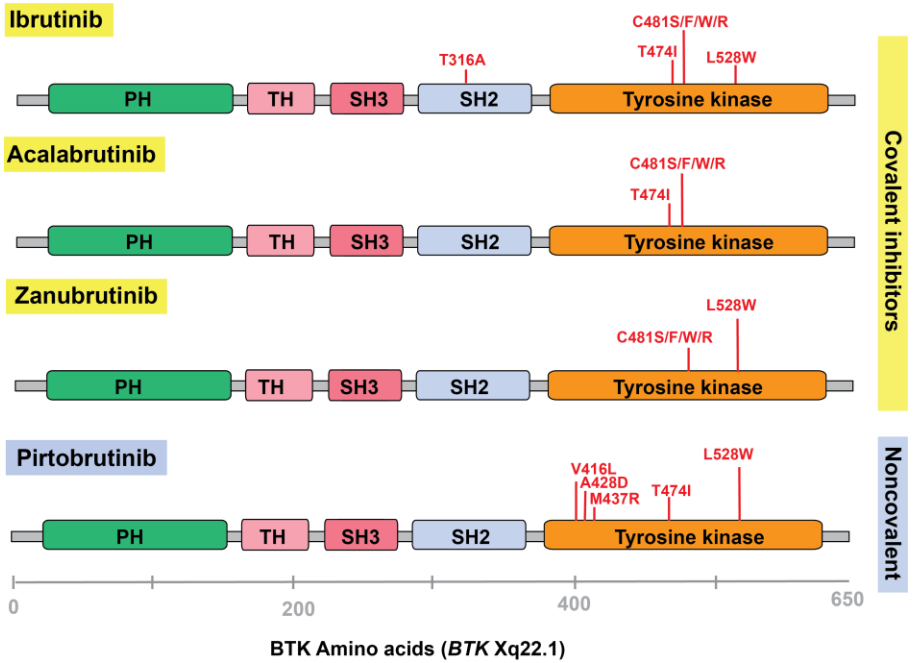
Shah NN, et al. *Haematologica*. 2025;110(1):92-102.

Diverse BTK Mutations Cause Resistance to Covalent (and Non-Covalent) BTK Inhibitors

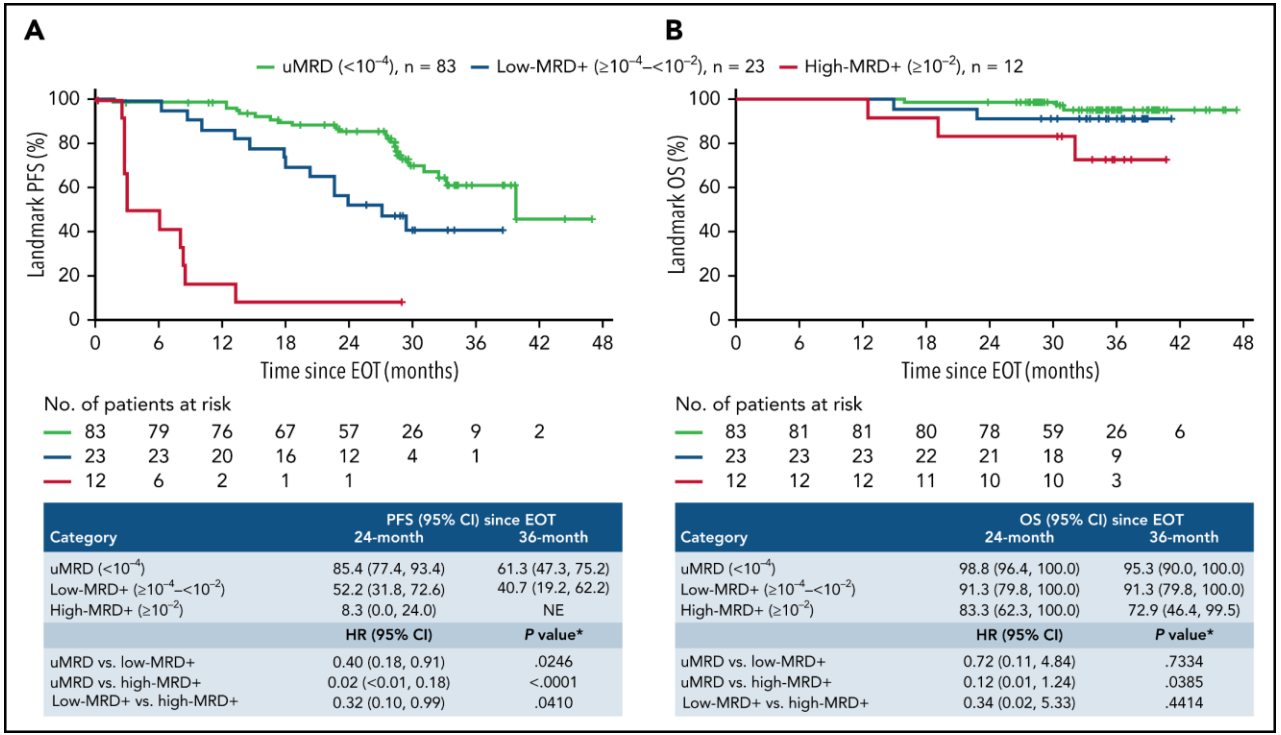
- The majority of patients discontinue covalent BTK inhibitors (cBTKi) due to intolerance or progression
- Should not change from one cBTKi to another in setting of resistance due to shared resistance mechanisms
- BTK C481 substitutions are the most common resistance mechanism to cBTKi





Adapted from Montoya S, et al. *Blood*. 2022;140(Suppl 1):1811-1813. Montoya S, et al. *Hematol Oncol*. 2023;41(S2):542-544. Brown JR, et al. Presented at: EHA2023 Congress; June 8-11, 2023; Frankfurt, Germany. Abstract S146.

MURANO Trial Showed Superior PFS and OS for VenR over BR



Category	PFS (95% CI) since EOT 24-month	36-month
uMRD (<10⁻⁴)	85.4 (77.4, 93.4)	61.3 (47.3, 75.2)
Low-MRD+ (≥10⁻⁴–<10⁻²)	52.2 (31.8, 72.6)	40.7 (19.2, 62.2)
High-MRD+ (≥10⁻²)	8.3 (0.0, 24.0)	NE
	HR (95% CI)	***P* value***
uMRD vs. low-MRD+	0.40 (0.18, 0.91)	.0246
uMRD vs. high-MRD+	0.02 (<0.01, 0.18)	<.0001
Low-MRD+ vs. high-MRD+	0.32 (0.10, 0.99)	.0410

Category	OS (95% CI) since EOT 24-month	36-month
uMRD (<10⁻⁴)	98.8 (96.4, 100.0)	95.3 (90.0, 100.0)
Low-MRD+ (≥10⁻⁴–<10⁻²)	91.3 (79.8, 100.0)	91.3 (79.8, 100.0)
High-MRD+ (≥10⁻²)	83.3 (62.3, 100.0)	72.9 (46.4, 99.5)
	HR (95% CI)	***P* value***
uMRD vs. low-MRD+	0.72 (0.11, 4.84)	.7334
uMRD vs. high-MRD+	0.12 (0.01, 1.24)	.0385
Low-MRD+ vs. high-MRD+	0.34 (0.02, 5.33)	.4414

Note only 2% of pts assigned to venR had prior BCRi exposure

Seymour JF, et al. *Blood*. 2022;140(8):839-850.

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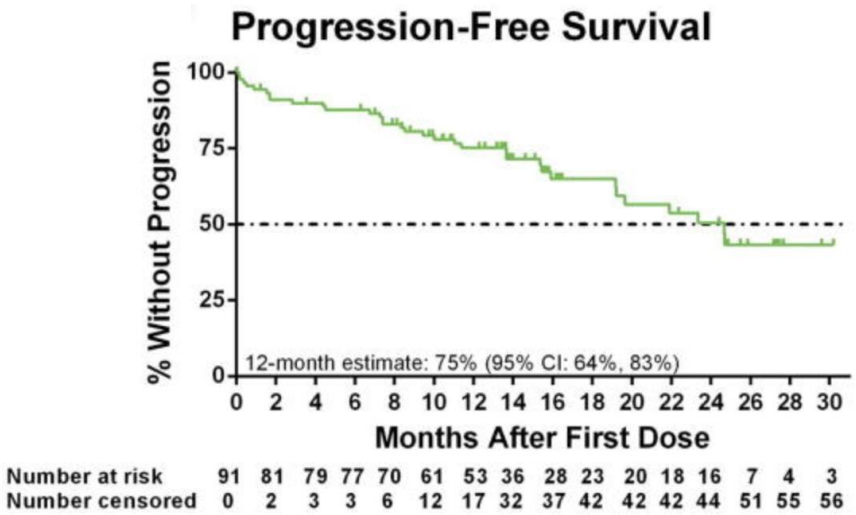
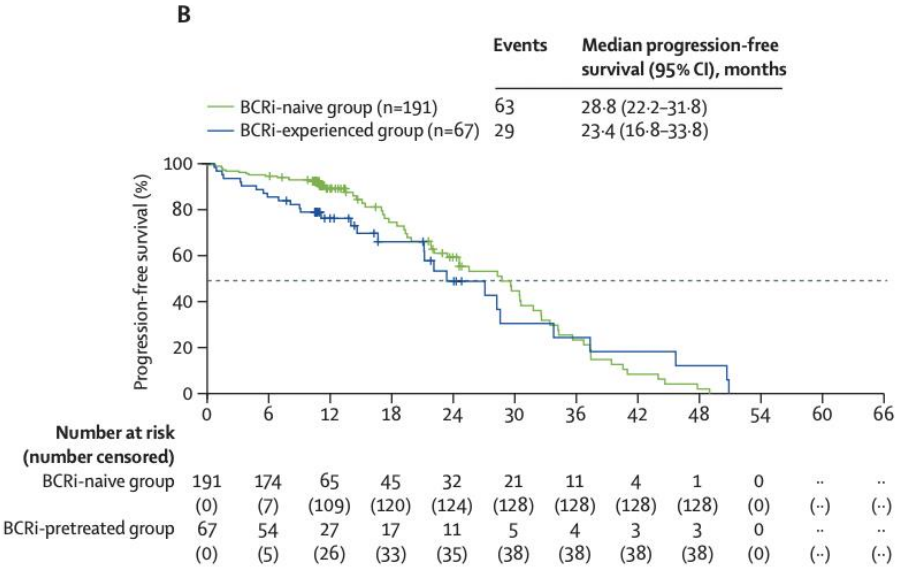
Prospective Data for Ven after cBTKi



- Jones, et al., *Lancet Oncology,* 2017
- N=91 pts
- 4 prior LOT, 47% del 17p, 33% *TP53* mut
- ORR 65% with 9% CR/CRi
- Median PFS 24.7 mo



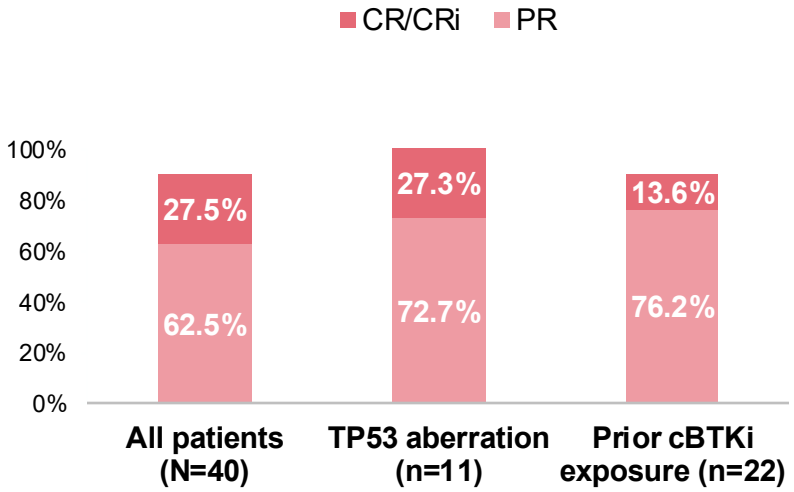
- Phase 3b VENICE trial: Kater, et al., *Lancet Onc*, 2024
- 3 prior LOT for the BCRi experienced
- Median PFS 23.4 mo

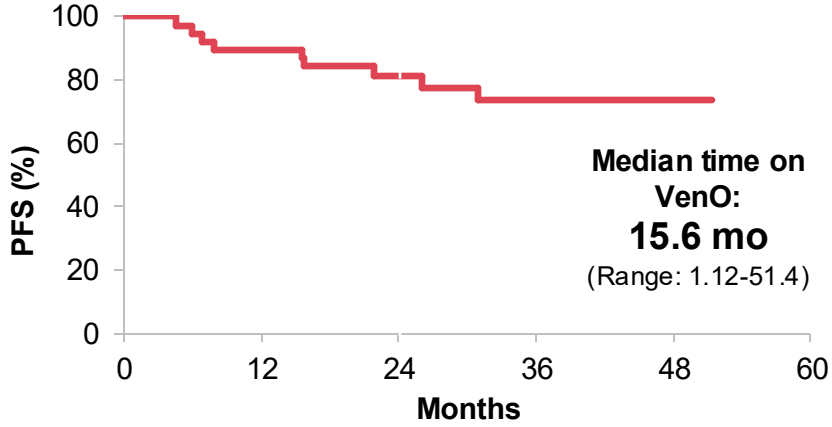
LOT = line of therapy.

Jones JA, et al. *Lancet Oncol*. 2018;19(1):65-75. Kater AP, et al. *Lancet Oncol*. 2024;25(4):463-473.

Venetoclax and Obinutuzumab in Relapsed Setting

- Venetoclax and obinutuzumab are now listed as “preferred” in the relapsed setting in NCCN
- Real-world study of ven/obi in rel/ref CLL with 40 pts, 1 median prior LOT
- ORR was 90% (CR/CRi in 27.5%), and 2-year PFS was 81.2%





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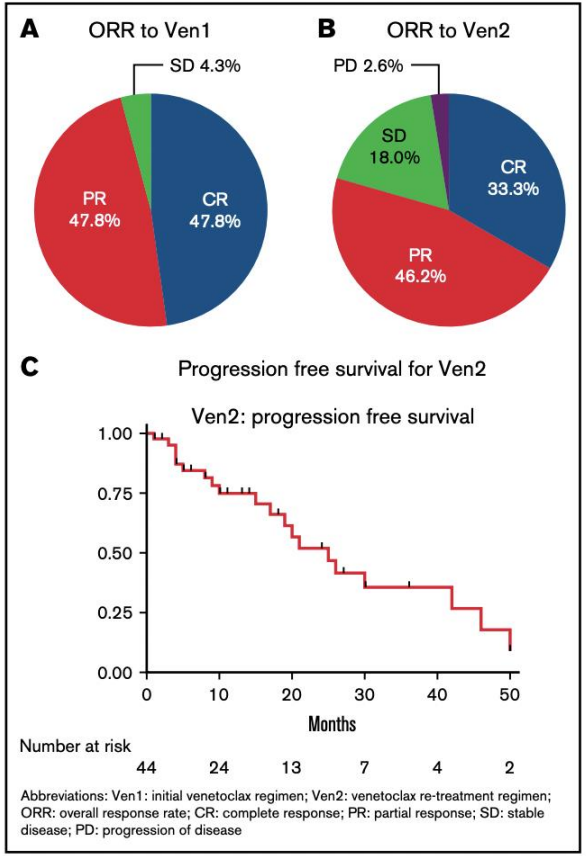
Lei MM, et al. *Leuk Lymphoma*. 2024;65(5):653-659.

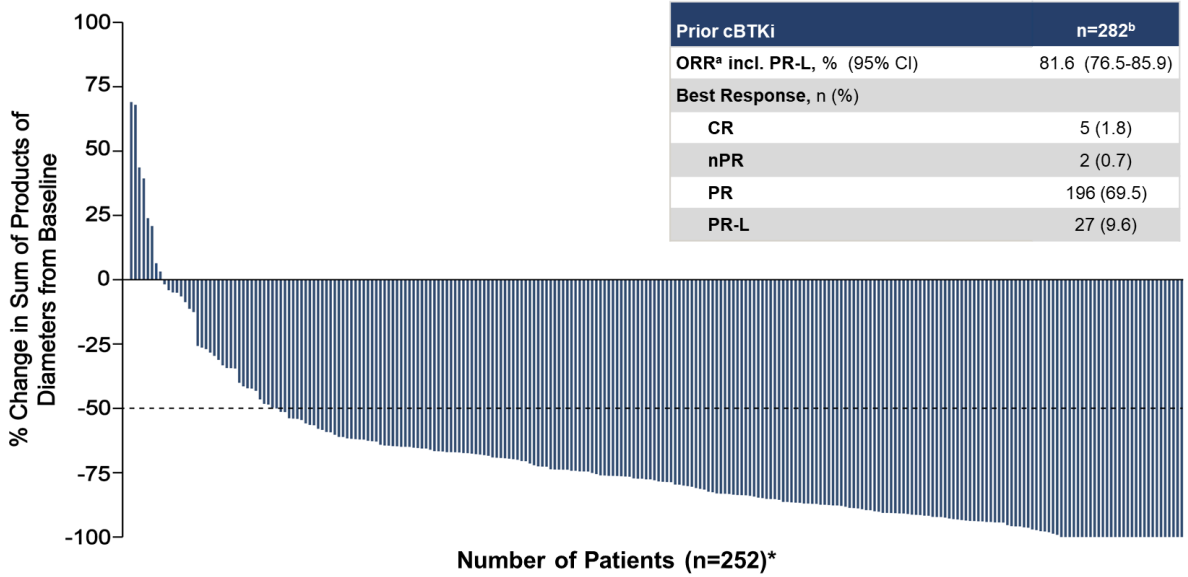
What Do We Know about Venetoclax Retreatment?



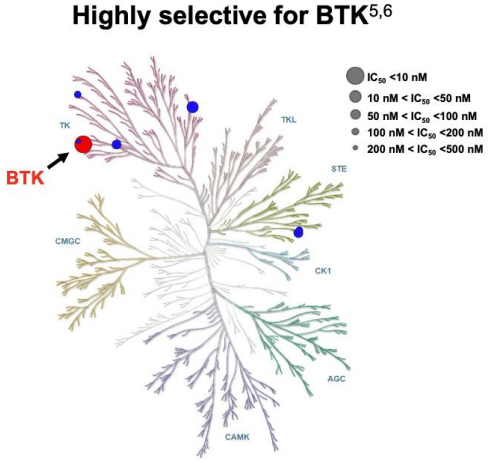
- 46 pts with ven retreatment
- 2 prior LOT
- Median of 16 months between the completion of ven1 and the start of ven2
- Median ven2 PFS for the overall cohort was 25 months
- Prospective trial of venO retreatment in 2nd line (after frontline ven regimen)
  - ReVenG trial, NCT04895436

Thompson MC, et al. *Blood Adv*. 2022;6(15):4553-4557.

Pirtobrutinib in Post-cBTKi CLL: Phase ½ BRUIN Trial



Prior cBTKi	n=282[b]
ORR[a] incl. PR-L, % (95% CI)	81.6 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
nPR	2 (0.7)
PR	196 (69.5)
PR-L	27 (9.6)



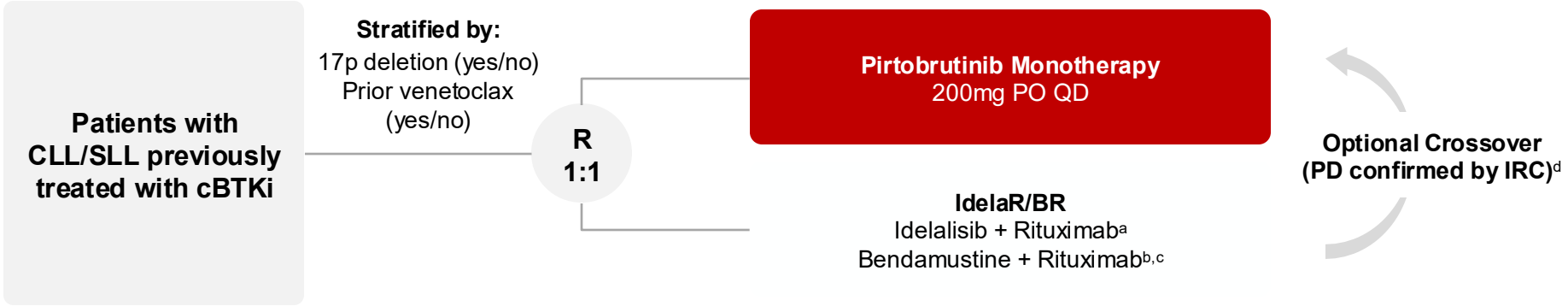
Pirto inhibits wild-type and C481 mutant BTK

Median PFS was 23.0 months for BCL2i-naïve and 15.9 months for BCL2i-exposed

PR-L = partial response with lymphocytosis.

Woyach JA, et al. *Blood*. 2023;142(Suppl 1):325.

BRUIN CLL-321 Study Design



Key Eligibility

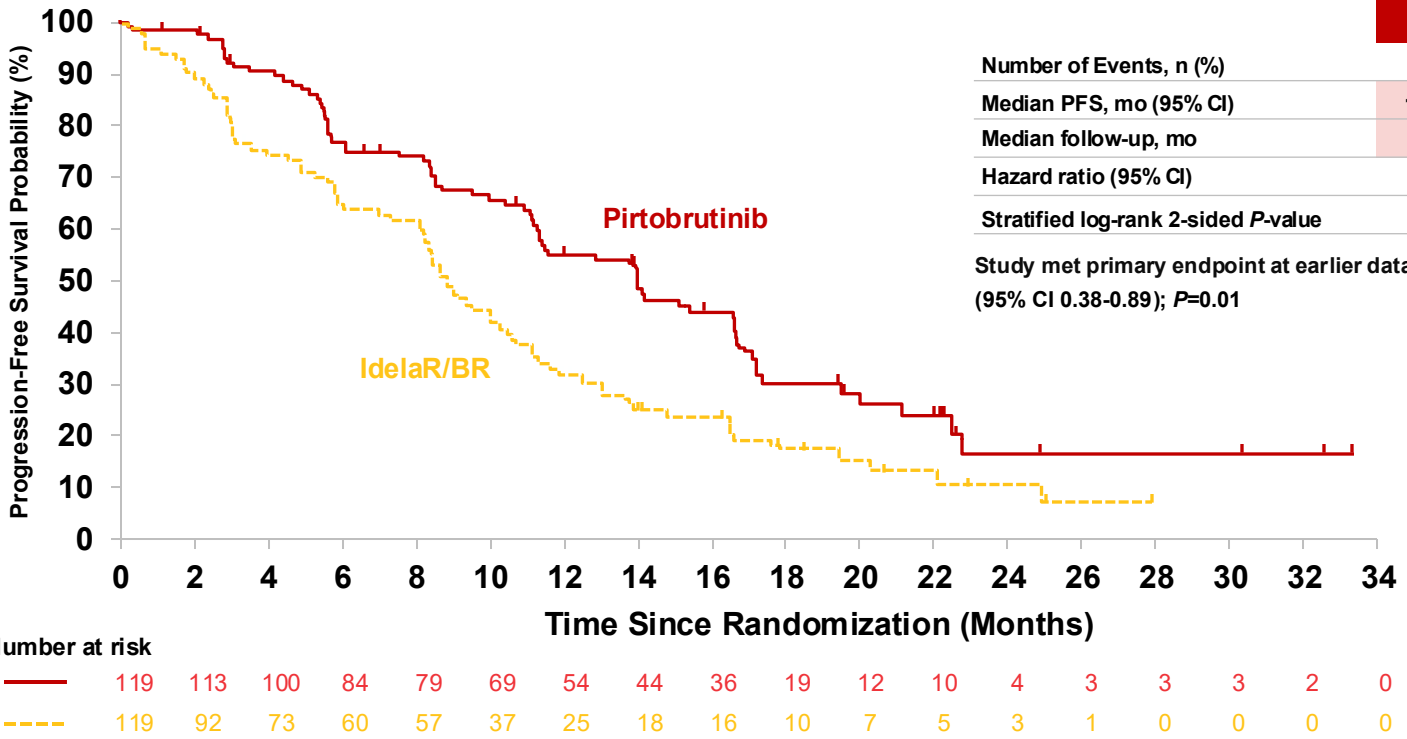
- Age ≥18
- ECOG PS 0-2
- Confirmed CLL/SLL requiring treatment per iwCLL 2018
- **Prior cBTKi required**
- **No limit on prior lines of therapy**
- **Prior history of atrial fibrillation allowed**

Key Endpoints

- **Primary endpoint: PFS assessed by IRC**
- PFS assessed by investigator
- Event-free survival
- Time to next treatment
- Overall survival
- Safety

Treatment was given in 28-day cycles. PFS assessed based on iwCLL2018. [a]Idelalisib dosed at 150 mg PO BID. Day 1 of cycle 1, first dose of rituximab at 375 mg/m2, next 4 infusions at 500 mg/m2 every 2 weeks, next 3 infusions at 500 mg/m2 every 4 weeks. [b]Bendamustine (70 mg/m2) administered IV D1, D2 of cycles 1-6. [c]Day 1 of cycle 1, first dose of rituximab at 375 mg/m2, next 5 infusions day 1 of cycle 2 through cycle 6 at 500 mg/m2. [d]Eligible patients receiving investigator's choice of IdelaR/BR could cross over to receive pirtobrutinib monotherapy upon confirmation of PD by IRC per protocol.
IdelaR = idelalisib + rituximab; R = randomized.
Sharman JP, et al. Presented at: 66th ASH Annual Meeting; December 7-10, 2024; San Diego, California. Abstract 886.

BRUIN CLL-321: IRC-Assessed PFS



	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	**0.54 (0.39-0.75)**	
Stratified log-rank 2-sided *P*-value	0.0002*	

Study met primary endpoint at earlier data cut (Aug 2023) IRC HR=0.58 (95% CI 0.38-0.89); *P*=0.01

Pirtobrutinib reduced risk of progression or death by 46% according to IRC assessment.

***nominal *P*-value.**

Sharman JP, et al. Presented at: 66th ASH Annual Meeting; December 7-10, 2024; San Diego, California. Abstract 886.

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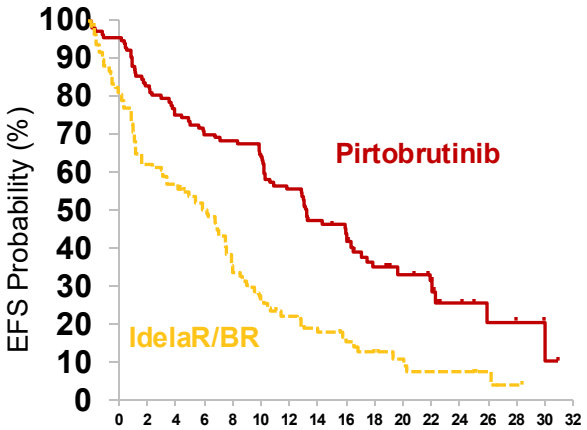
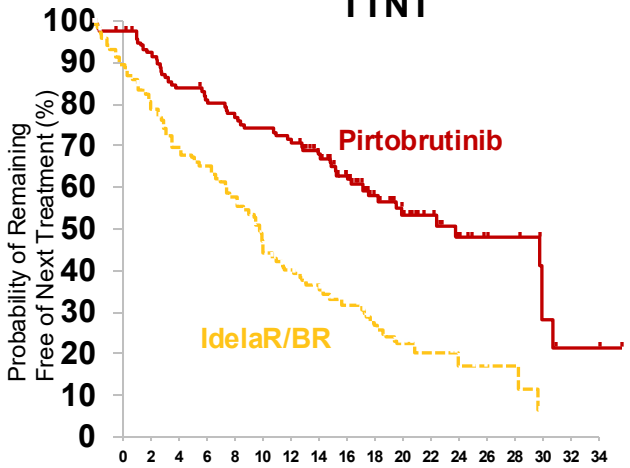
BRUIN CLL-321: Key Secondary Endpoints

EFS



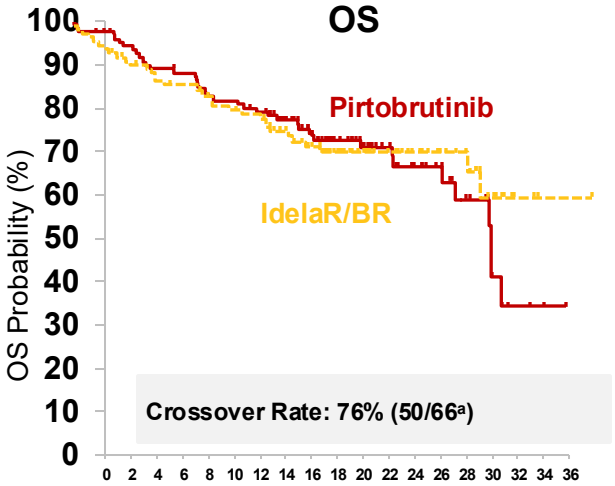
	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	77 (65)	94 (79)
mEFS, mo (95% CI)	**14.1** (11.4-17.0)	**7.6** (4.8-8.8)
m follow-up, mo	19.4	18.7
Hazard ratio (95% CI)	**0.39 (0.28-0.53)**	
Stratified log-rank 2-sided *P*-value	<0.0001*	

TTNT



	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	54 (45)	82 (69)
mTTNT, mo (95% CI)	**24.0** (17.8-29.7)	**10.9** (8.7-12.5)
m follow-up, mo	20.0	20.2
Hazard ratio (95% CI)	**0.37 (0.25-0.52)**	
Stratified log-rank 2-sided *P*-value	<0.0001*	

OS



	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	38 (32)	32 (27)
18-mo OS rate, % (95% CI)	**73.4** (63.9-80.7)	**70.8** (60.9-78.7)
m follow-up, mo	20.4	19.2
Hazard ratio (95% CI)	**1.09 (0.68-1.75)**	
Stratified log-rank 2-sided *P*-value	0.7202	

EFS = event-free survival; m = median; TTNT = time to next treatment.

Sharman JP, et al. Presented at: 66th ASH Annual Meeting; December 7-10, 2024; San Diego, California. Abstract 886.

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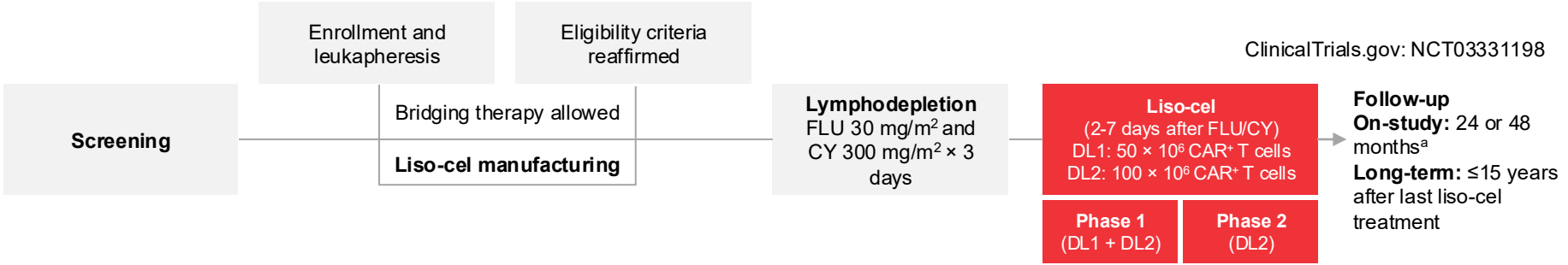
TRANSCEND CLL 004 Study Design: Phase 1/2, Open-Label, Multicenter Study of Liso-Cel



Key patient eligibility criteria

- Age ≥18 years
- R/R CLL/SLL with an indication for treatment
- Previously failed or ineligible for BTKi therapy
- Failure of ≥2 (high risk) or ≥3 (standard risk) lines of prior therapy
- ECOG PS ≤ 1
- Adequate bone marrow, organ, and cardiac function
- No Richter transformation nor active CNS involvement by malignancy

Primary endpoint (PEAS at DL2)

CR/CRi rate per iwCLL 2018 by IRC assessment

Key secondary endpoints (PEAS at DL2)

ORR, uMRD rate in blood

Other secondary endpoints

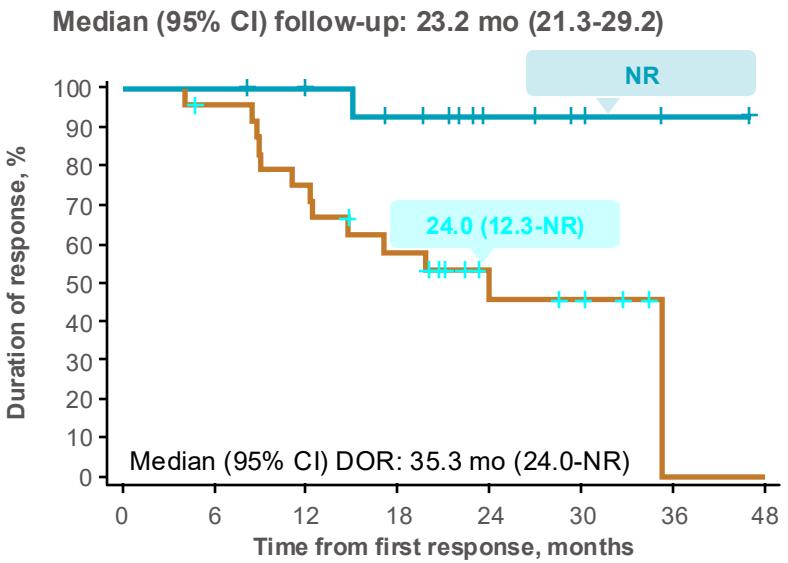
DOR, DOCR, PFS, TTR, TTCR per IRC assessment, OS, uMRD CR rate in blood, and safety

Primary and key secondary endpoints were tested in a prespecified subset of patients with BTKi progression and venetoclax failure (PEAS) at DL2 by the following hierarchy: CR/CRi rate ($H_0 \leq 5\%$), ORR ($H_0 \leq 40\%$), and uMRD rate in blood ($H_0 \leq 5\%$).

[a]Duration of follow-up was increased to 48 months in protocol amendment 5 (February 16, 2021). Patients still in ongoing response per iwCLL 2018 criteria after the 2-year follow-up were followed for safety, disease status, additional anticancer therapies, and survival for an additional 2 years or until progression.
CY = cyclophosphamide; DL = dose level; DOCR = duration of complete response/remission; DOR = duration of response; FLU = fludarabine; H0 = null hypothesis; PEAS = primary efficacy analysis set; TTCR = time to complete response/remission; TTR = time to response; CNS = central nervous system.
Siddiqi T, et al. *J Clin Oncol*. 2023;41(Suppl 16):7501.

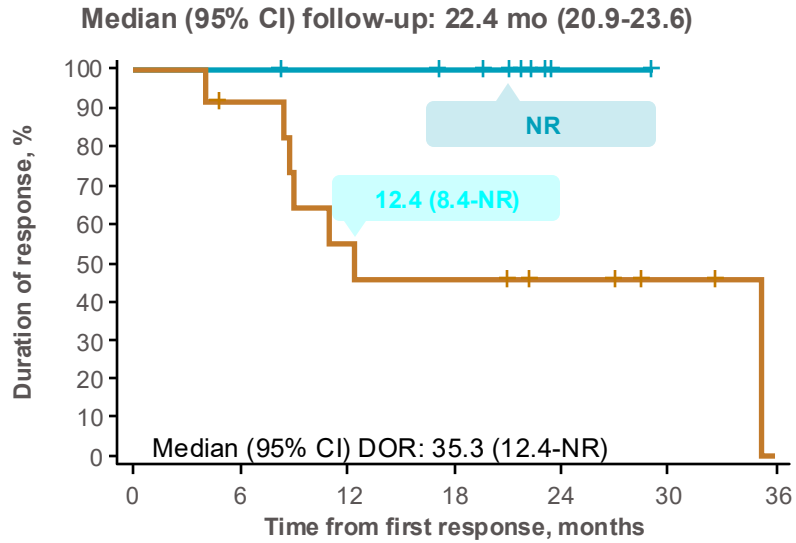
Liso-Cel Monotherapy Efficacy Data

(A) Full study population at DL2 (n=88)



No. at risk								
CR/CRi	17	17	14	12	5	3	1	0
PR/nPR	25	23	18	13	6	5	0	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n=50)

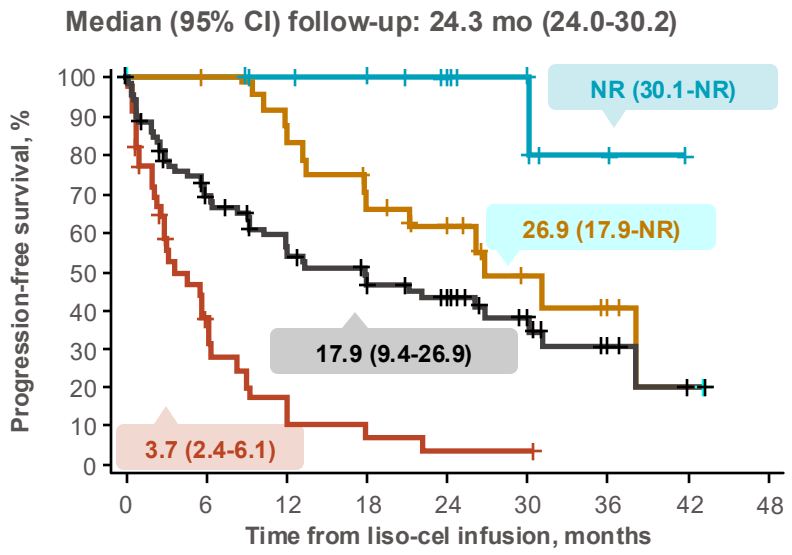


No. at risk								
CR/CRi	10	10	9	8	1	0	0	
PR/nPR	12	10	6	5	3	2	0	

Data on Kaplan-Meier (KM) curves are expressed as median (95% CI, if available).
NR = not reached; PR = partial remission; nPR = nodular partial remission.
Siddiqi T, et al. *Blood*. 2023;142(Suppl 1):330.

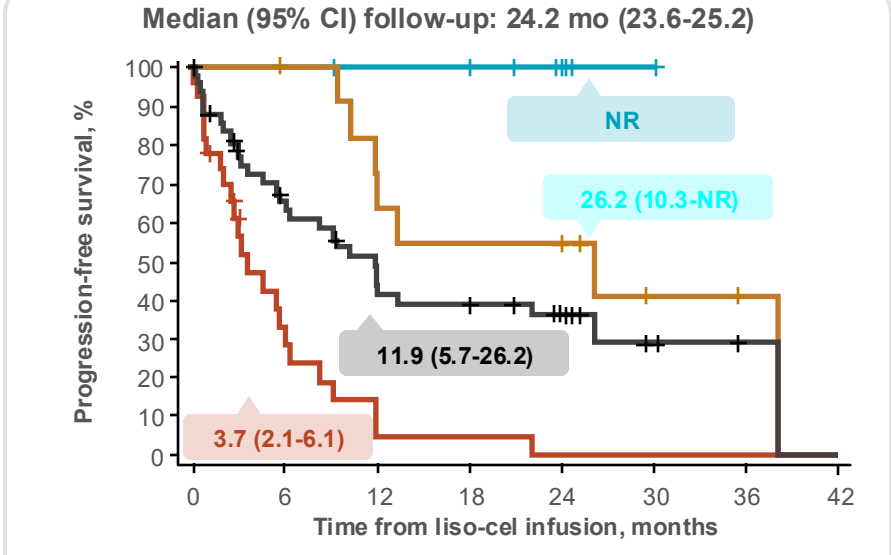
Progression-Free Survival by Best Overall Response

(A) Full study population at DL2 (n=88)



No. at risk									
CR/CRi	17	17	15	14	10	5	2	0	0
PR/nPR	25	24	21	15	11	6	3	1	0
Nonresponder	46	12	4	2	1	1	0	0	0
Total	88	53	40	31	22	12	5	1	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n=50)



No. at risk									
CR/CRi	10	10	9	9	5	1	0	0	
PR/nPR	12	11	8	6	5	2	1	0	
Nonresponder	28	7	2	1	0	0	0	0	
Total	50	28	19	16	10	3	1	0	

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Siddiqi T, et al. *Blood*. 2023;142(Suppl 1):330.

Key Learning Points

- Increasing options for patients in the frontline setting, with current preference for continuous use of a second-generation cBTKi (acala or zanu) or a time-limited regimen (venO only FDA-approved option, but acala, ven +/- obi is now in NCCN guidelines)
- Most important factor in relapsed setting therapy decision-making is what the patient got previously, how he/she responded to it, and reason for discontinuation
- IGHV mutational status and TP53 mutation status are considered essential for initial risk stratification before treatment selection in CLL/SLL
- In cBTKi intolerance, can switch to both different cBTKi or ncBTKi
- Acalabrutinib plus obinutuzumab demonstrated significantly longer PFS compared to chlorambucil plus obinutuzumab for treatment-naïve CLL/SLL
- Fixed-duration acalabrutinib plus venetoclax with or without obinutuzumab demonstrated superior PFS compared to standard chemoimmunotherapy in treatment-naïve CLL patients without TP53 disruption or del(17p)
- In patients progressing after time-limited venetoclax, evidence is emerging regarding retreatment
- Third-line and beyond, favored regimens are pirtobrutinib and liso-cel but with many new options under investigation (BTK degraders, bispecifics)

FDA = US Food and Drug Administration.