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CLL

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THE 2nd ANNUAL HemOnc Pulse LIVE AUSTIN 2025

Recent Updates and Future Directions in CLL

Outline:

CLL 14 Long-Term Follow-Up

AMPLIFY

BRUIN – 321

BTK Degraders

TRANSCEND – CLL

EPCORE – CLL

Presenter

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Fixed Duration vs. Indefinite Therapy

- Chemoimmunotherapy – Fixed Duration
- BTKi Monotherapy – Indefinite
- BCL2i (venetoclax) + Obinutuzumab – Fixed Duration
- BCL2i (venetoclax/sonrotoclax) + BTKi +/- Obinutuzumab – Fixed Duration

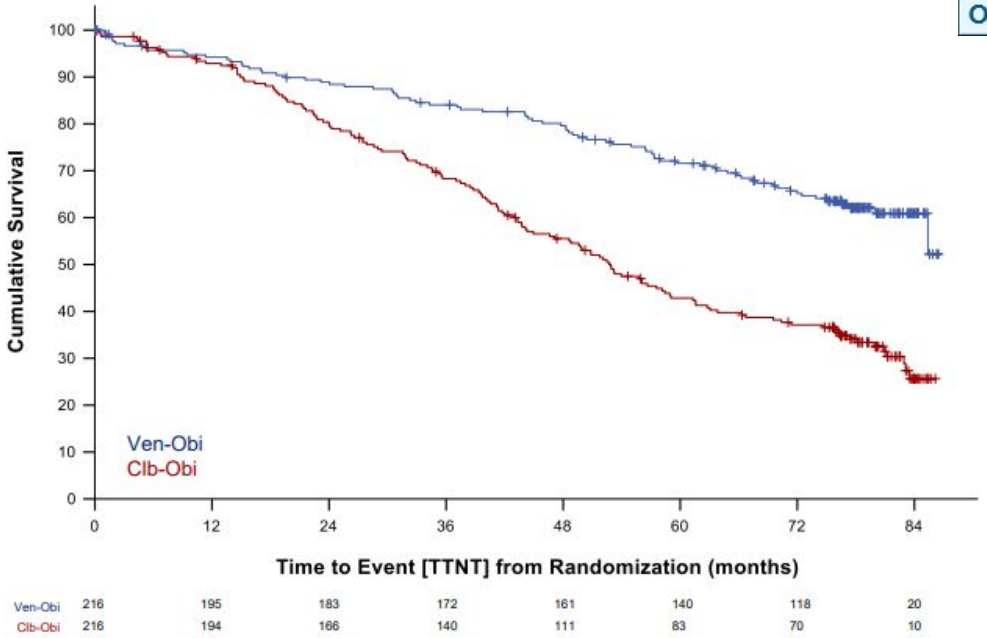
Fixed Duration vs. Indefinite Therapy

Indefinite Therapy: Marathon

Time-Defined Therapy: Sprint

TIME TO NEXT TREATMENT

Defined as time to death or next-antileukemic treatment



Patients negative for MRD		
	Peripheral blood	Bone marrow
Venetoclax + obinutuzumab	75.5%	56.9%
Obinutuzumab + chlorambucil	35.2%	17.1%

Median TTNT
Ven-Obi: not reached
Clb-Obi: 52.9 m

6-year TTNT rate
Ven-Obi: 65.2%
Clb-Obi: 37.1%

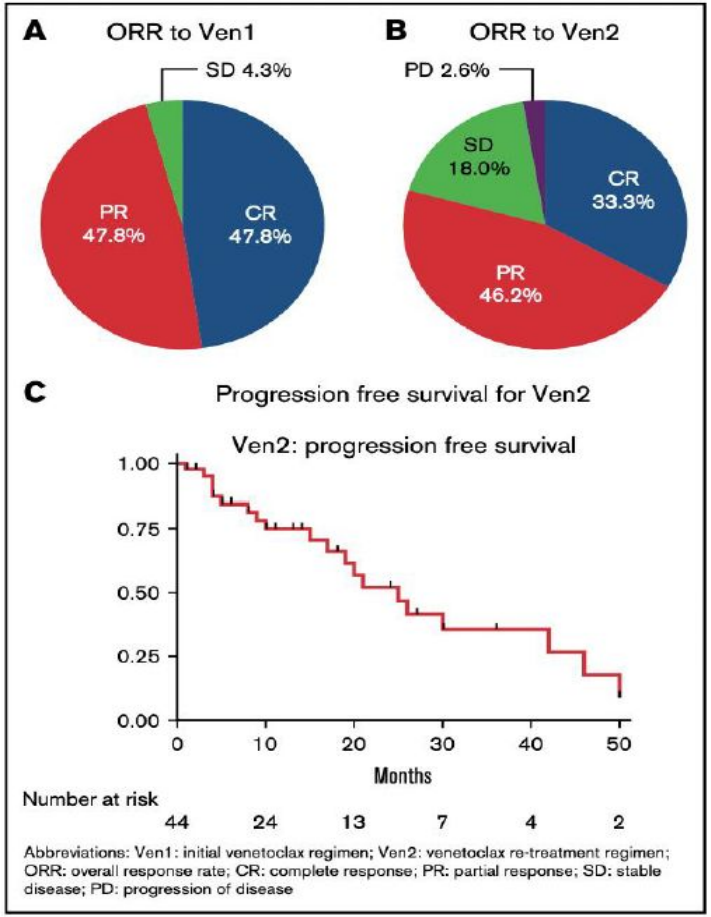
Next anti-leukemic therapy:
Ven-Obi: 67 PDs – 39 NLT
Clb-Obi: 141 PDs – 103 NLT

HR 0.44, 95% CI [0.33-0.58]
P<0.0001

Fischer K et al. *N Engl J Med*. 2019.

Venetoclax Retreatment

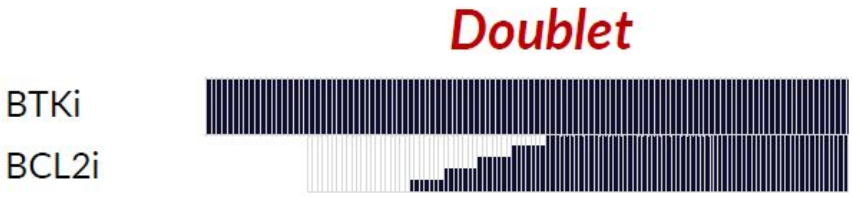
- 46 patients with venetoclax retreatment
- Median 2 prior lines of therapy
- Median of 16 months between the completion of Ven1 and start of Ven2
- Median Ven2 PFS for the overall cohort was 25 months



Thompson MC et al. *Blood Advances*. 2022.

Hybrid Treatment Approaches

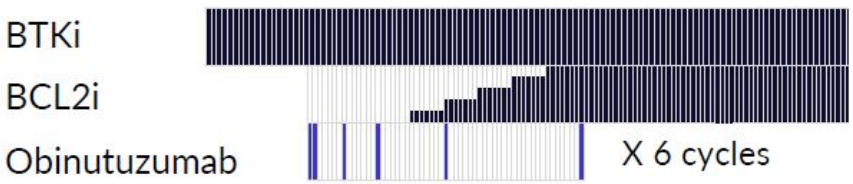
Doublet



IV (Many including CAPTIVATE and GLOW, approved in Europe)
AV (MAJIC)
ZV (Ghia et al, 2024 EHA)
ZS (CELESTIAL)

Fixed duration
OR
MRD guided treatment cessation

Triplet



IVO (CLL13, Rogers et al. JCO 2020, etc.)
AVO (Davids et al, JCO 2024)
ZVO (Soumerai et al, Lacnet Haematol 2021)
PVO (Jain et al. 2024 ASH)

AMPLIFY Study Design

TN CLL (N=867)

Key inclusion criteria
- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria[1]
- Without del(17p) or *TP53*[a]
- ECOG PS ≤2

Key exclusion criteria
- CIRS-Geriatric >6
- Significant cardiovascular disease

Stratification
- Age (>65 vs ≤65 years)
- IGHV mutational status
- Rai stage (≥3 vs <3)
- Geographic region

AMPLIFY: randomized, multicenter, open-label, Ph 3 trial

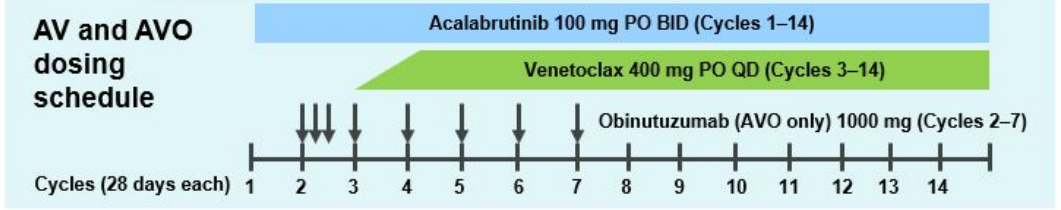
RANDOMIZE 1:1:1

- AV (14 cycles)
- AVO (14 cycles)
- FCR/BR (6 cycles)

Crossover not built into protocol

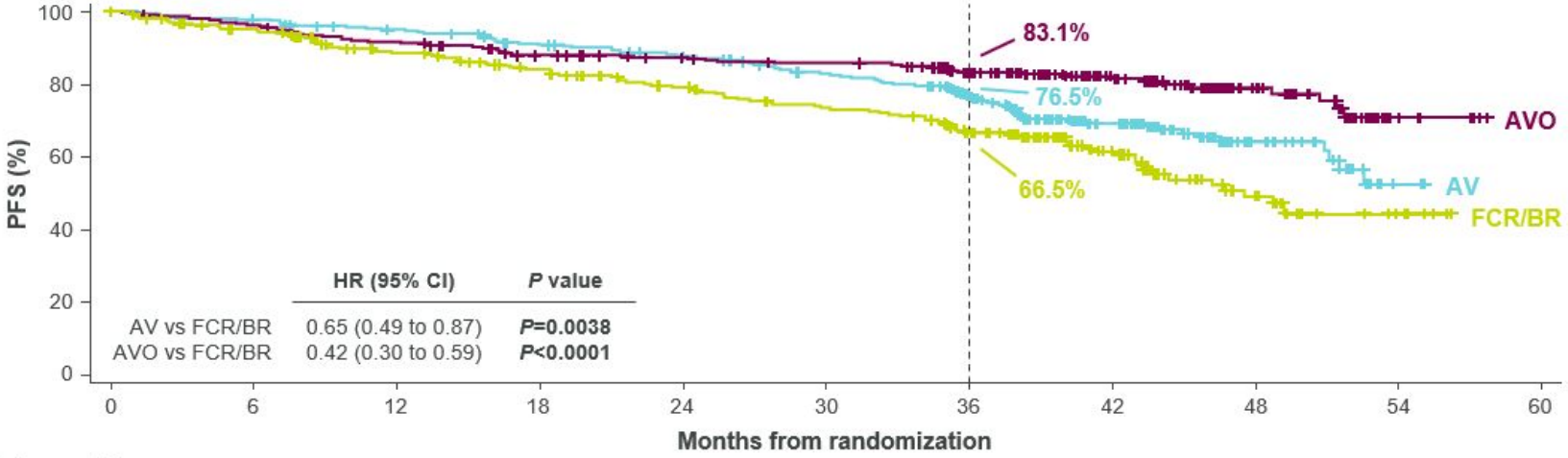
Primary endpoint: IRC-assessed PFS (AV vs FCR/BR)

If primary endpoint met, secondary endpoints tested in fixed sequential hierarchy:
1) IRC-PFS (AVO vs FCR/BR)
2) uMRD (AV vs FCR/BR)
3) uMRD (AVO vs FCR/BR)
4) OS (AV vs FCR/BR)
5) OS (AVO vs FCR/BR)



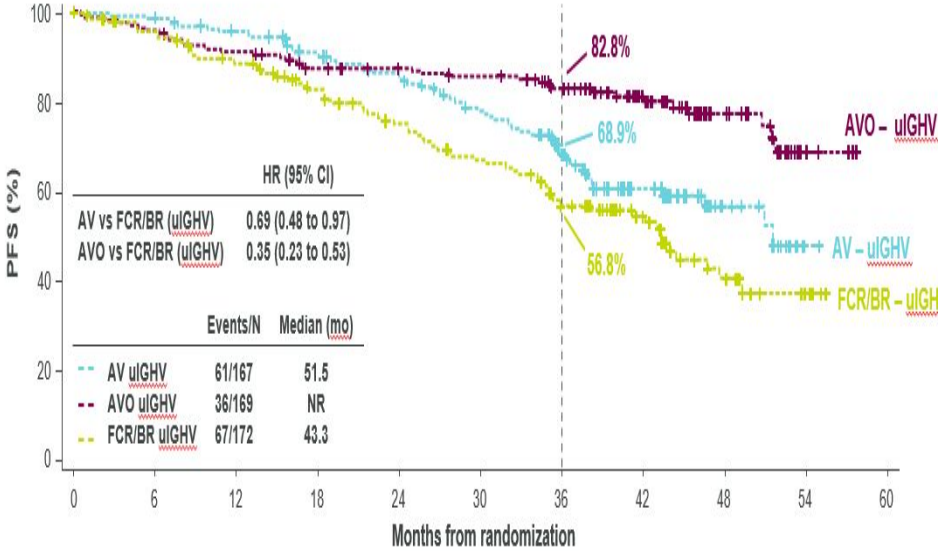
Brown J et al. *N Engl J Med*. 2025.

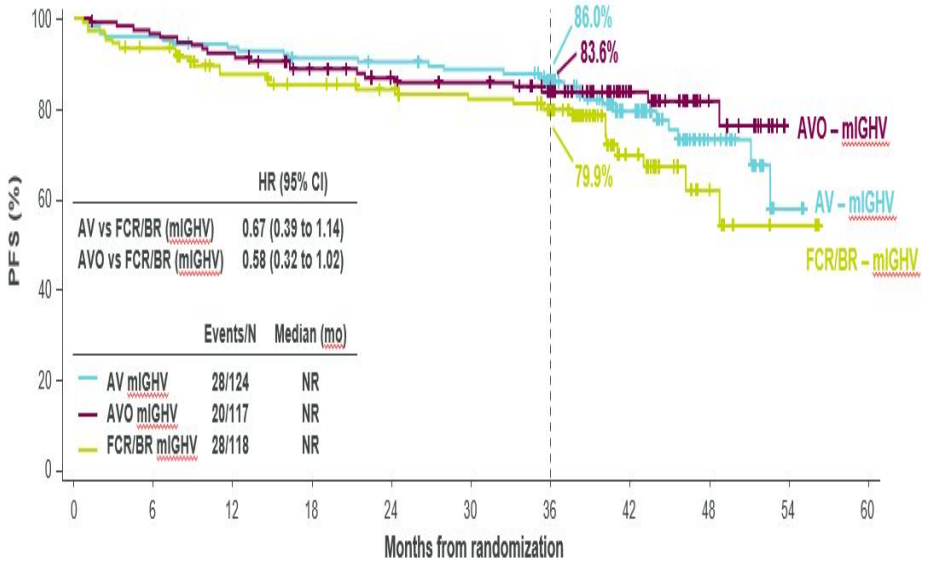
IRC-assessed PFS



Brown J et al. *N Engl J Med*. 2025.

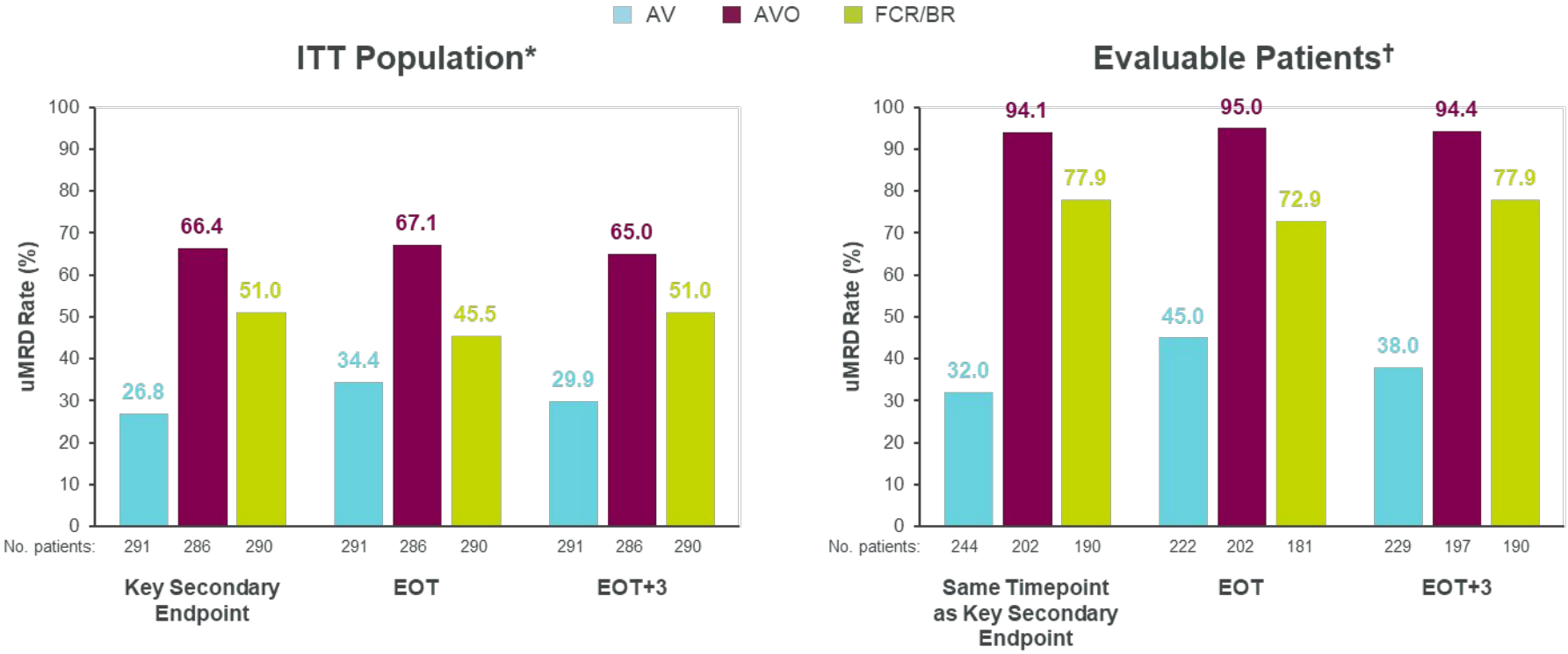
PFS by IGHV Subgroup





Brown J et al. *N Engl J Med*. 2025.

uMRD Rates (Flow Cytometry [$<10^{-4}$] in PB)



Brown J et al. *N Engl J Med*. 2025.

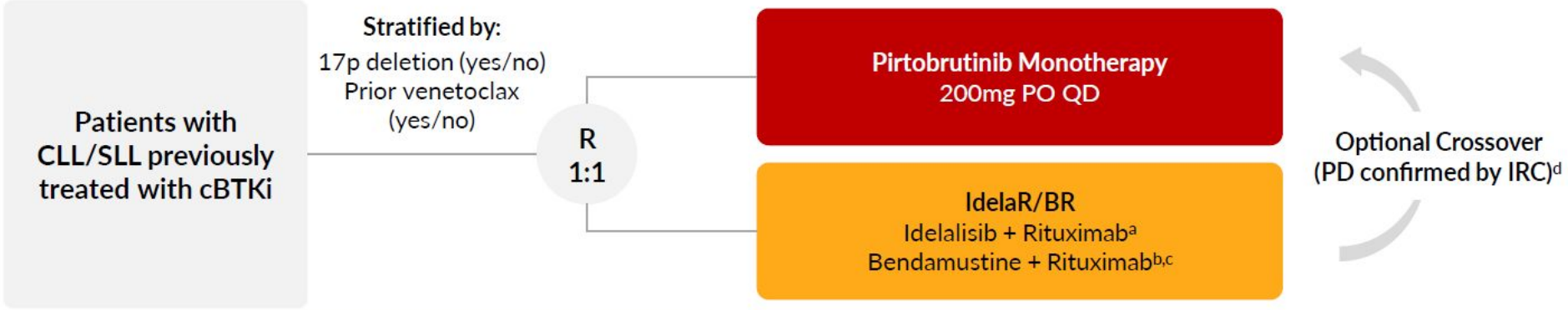
Safety Summary

	AV (n=291)	AVO (n=284)	FCR/BR (n=259)
Duration of exposure, median (range), mo	12.9 (1–18)	12.9 (0–18)	5.6 (1–11)
Summary of AEs			
Any AE	270 (92.8)	269 (94.7)	236 (91.1)
Any AE grade ≥3	156 (53.6)	197 (69.4)	157 (60.6)
Any serious AE	72 (24.7)	109 (38.4)	71 (27.4)
Serious AEs leading to death	10 (3.4)	17 (6.0)	9 (3.5)
AE leading to treatment discontinuation	23 (7.9)	57 (20.1)	28 (10.8)

Data are n (%) unless otherwise noted.

Brown J et al. *N Engl J Med*. 2025.

BRUIN CLL-321



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**

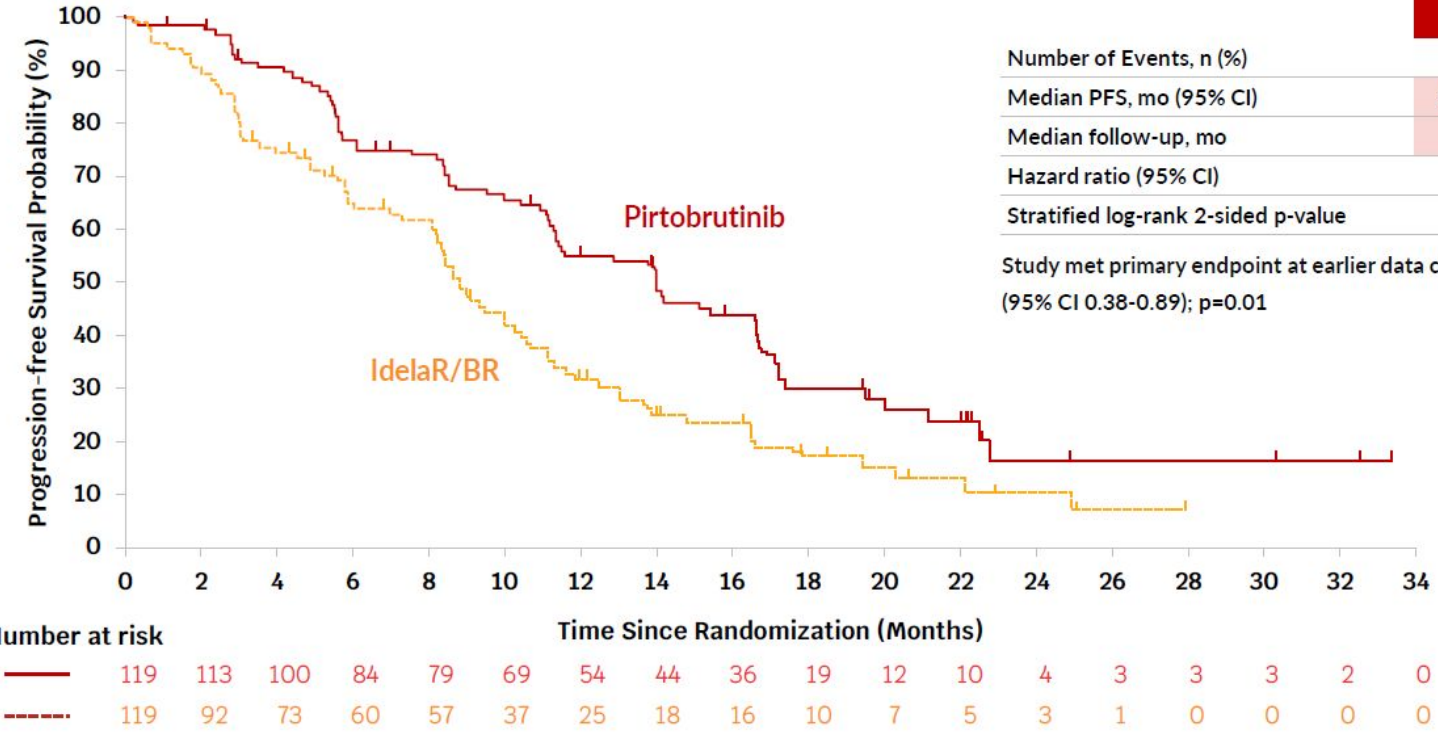
Key Endpoints

- **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 150mg PO BID. Day 1 of cycle 1, first dose of rituximab at 375 mg/m^2, next 4 infusions at 500 mg/m^2 every 2 weeks, next 3 infusions at 500 mg/m^2 every 4 weeks. [b]Bendamustine (70 mg/m^2) administered IV D1, D2 of cycles 1-6. [c]Day 1 of cycle 1, first dose of rituximab at 375 mg/m^2, next 5 infusions day 1 of cycle 2 through cycle 6 at 500 mg/m^2. [d]Eligible patients receiving investigator's choice of IdelaR/BR could crossover to receive pirtobrutinib monotherapy upon confirmation of PD by IRC per protocol. Abbreviations: BID, twice daily; BR, bendamustine + rituximab; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IdelaR, idelalisib + rituximab; IRC, Independent Review Committee; iwCLL, international workshop on chronic lymphocytic leukemia; mg, milligram; PD, progressive disease; PFS, progression-free survival; PO, by mouth; QD, once daily; R, randomized; SLL, small lymphocytic lymphoma.

Sharman et al. ASH 2024. Abstract 886.

BRUIN CLL-321



	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

Sharman et al. ASH 2024. Abstract 886.

BTK Degraders in Relapsed/Refractory CLL

- There is an increasing number of recognized cBTKi resistant mutations in CLL (including to noncovalent BTKis)
- Cell survival can be mediated by BCR signaling through the kinase-independent scaffolding function of BTK (ie, bypassing BTKi inhibitory effects)
- There is a need for new mechanisms of action to block BTK other than kinase inhibition
- BTK degraders induce specific degradation of both wild-type and mutant BTK through ubiquination via the cereblon E3 ligase complex and tagging for protein degradation
- 2 trials presented at ASH with BTK degraders in CLL
  - NX–5948–301 – Shah et al.
  - BGB–16673 (CaDAnCe-101 trial) – Thompson et al.

NX-5948

NX-5948	
Number of CLL pts	34
Median Age	68 (35-88)
Median prior LOT	4 (2-14)
Prior therapies	BTKi (97%) Pirtobrutinib (23.5%) BCL2i (91.2%) BTKi+BCL2i (88.2%)
Mutations	TP53 (48.4%) BTK (41.9%) PLCG2 (19.4%) BCL2 (16.1%)

NX-5948 safety	All/Grade 3+
Purpura/contusion	44%/0%
Thrombocytopenia	23.5%/2.9%
Petechiae	29.4%/0%
Fatigue	20.6%/0%
Neutropenia	17.6%/14.7%
Rash	23.5%/0
Headache	23.5%/0%
New onset Afib/Aflutter	None

NX-5948 Outcomes	
Overall response rate	76.7% (no CR)

Shah N et al. ASH 2024.

BGB-16673

BGB-16673	
Number of patients with CLL	49
Median age	70 (50-91)
Median prior LOT	4 (2-10)
Prior therapies	cBTKi (92%) BCL2i (86%) ncBTKi (24%)
Mutations	17p del and/or TP53 mut (63%) uIGHV (82%)

Safety	All/Grade 3+
Fatigue	35%/2%
Contusion	29%/0%
Diarrhea	27%/2%
Neutropenia	--/20%
Pneumonia	--10%
New Afib	None

BGB-16673 Outcomes	
Overall response rate	78% (CR/CRi 4%)

Thompson et al. ASH 2024.

Liso-cel in CLL: TRANSCEND CLL 004

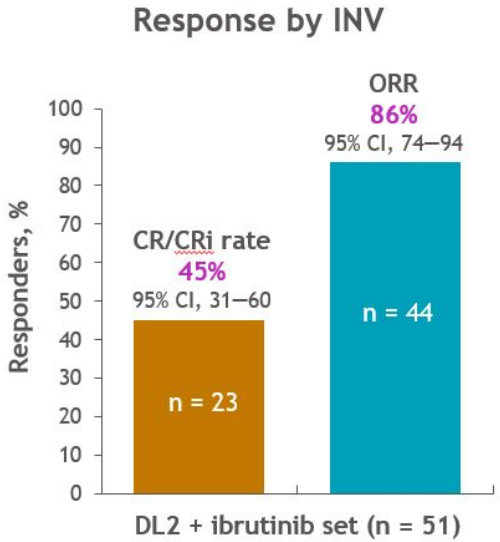
Demographics and baseline characteristics

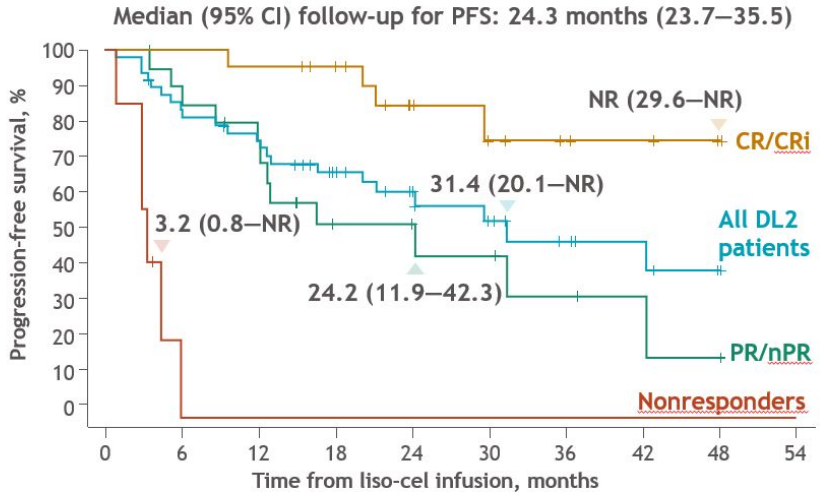
	DL2 + ibrutinib set (n = 51)	Total liso-cel + ibrutinib combination set (n = 56)
Median (range) age, y	65 (44–77)	65 (44–77)
Median (range) prior lines of systemic therapy	5 (1–13)	5 (1–13)
≤ 3 prior therapies, n (%)	19 (37)	20 (36)
Prior BTKi, n (%)	51 (100)	56 (100)
Prior venetoclax, n (%)	39 (76)	42 (75)
Prior BTKi and venetoclax, n (%)	39 (76)	42 (75)
BTKi progression/venetoclax failure,[a] n (%)	28 (55)	31 (55)
High-risk cytogenetics, n (%)	50 (98)	55 (98)
Del(17p)	23 (45)	25 (45)
Mutated *TP53*	23 (45)	24 (43)
Unmutated IGHV	37 (73)	39 (70)
Complex karyotype[b]	25 (49)	29 (52)
Bulky disease (≥ 5 cm) per INV before LDC,[c] n (%)		
Yes	18 (35)	18 (32)
Unknown	4 (8)	5 (9)
Median (range) SPD per INV before LDC,[d] cm^2	29 (1–218)	27 (1–218)
LDH ≥ ULN before LDC, n (%)	22 (43)	24 (43)
Received bridging therapy (in addition to ibrutinib),[e] n (%)	13 (25)	16 (29)

- Median (range) ibrutinib exposure was 34 days (15–188) before and 95 days (6–1517) after liso-cel in the total combination-treated set
- Liso-cel was manufactured for 63/65 (97%) patients in the leukapheresed set
  - Median (range) time from leukapheresis to liso-cel availability was 25 (17–79) days (n = 62)

Wierda W et al. Presented at: 66th ASH Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA. Abstract 887.

Liso-cel in CLL: TRANSCEND CLL 004





	% progression free (95% CI)	
	12 months	24 months
All DL2 patients (n = 51)	76 (61–85)	62 (46–74)
Patients with CR/CRi (n = 23)	96 (73–99)	85 (60–95)

Wierda W et al. Presented at: 66th ASH Annual Meeting and Exposition; December 7-10, 2024; San Diego, CA. Abstract 887.

Epcortimab for R/R CLL (Epcore CLL–1)

- Epcortimab is a CD3xCD20 bispecific antibody
- All patients receive subcutaneous epcortimab 48 mg in 28-day cycles little B-cell population
  - Weekly cycles 1–3
  - Every 2 weeks cycles 4–9
  - Monthly for cycle 10+
- 40 patients total–median age 71, median number of prior LOT was 4 (2–10)
- Chromosome 17 aberrations in 63%, IGHV unmutated 70%
- 85% double exposed to BTKi/Bcl-2i
- **ORR 61%, CR 39% (ORR/CR double-exposed patient is 53%/37%)**
- **CRS 96% (grade 3; 17%), 3 total ICANS events (none grade 3)**

Danilov et al. ASH 2024.

THANK YOU

PANEL DISCUSSION

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Q & A

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