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Multidisciplinary Approaches to Cancer Symposium

Treatment Update In Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Disclosures

- Consultant for AstraZeneca, Abbvie, BeiGene, Bristol Myers Squibb, and Gilead/Kite.
- On the Speakers Bureau for AstraZeneca, BeiGene, and Bristol Myers Squibb.
- Other Financial/Material Interests in BeiGene (Data Safety & Monitoring Committee).

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Liso-cel, Epcoritamab, Bruton's tyrosine kinase (BTK) degrader, Pirtobrutinib will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon must contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Ethnicity and gender differences in treatments/trials.*

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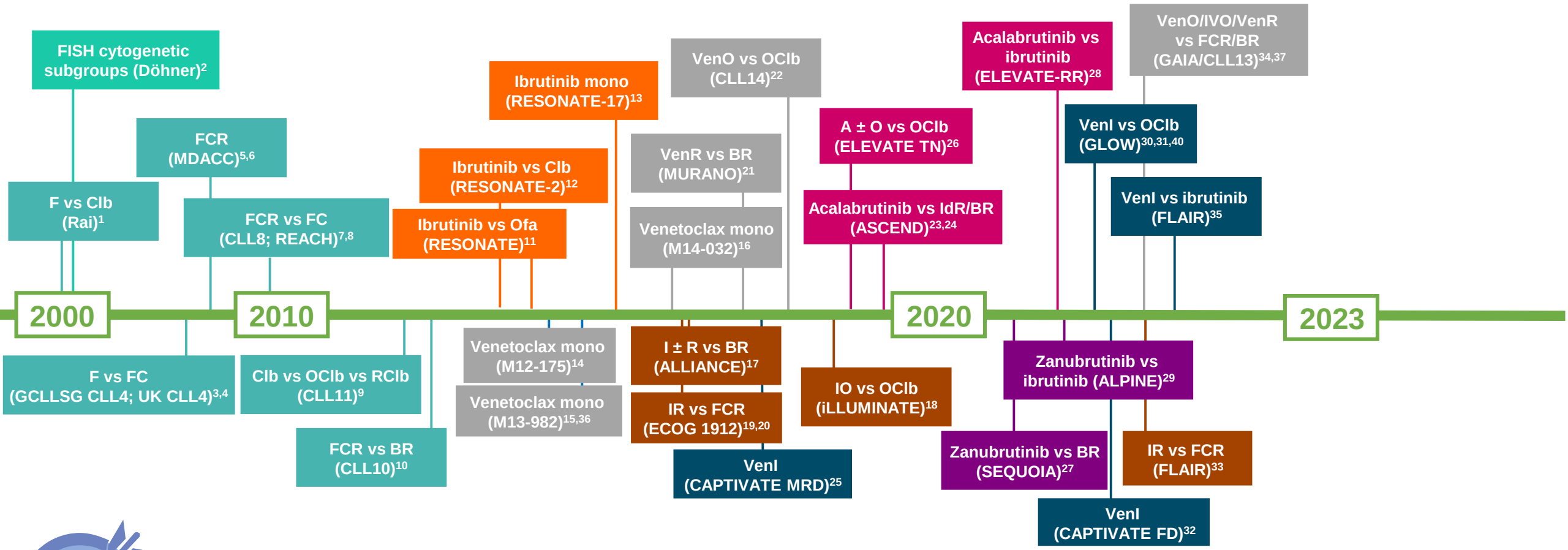
Agenda

- Targeted therapy
  - Ibrutinib
  - Frontline management
    - Newer BTKis
    - BCL2i
    - BTKi+Bcl2i combinations
  - Relapsed setting
- Latest therapies
  - BTK degraders
  - Bispecific antibodies
  - CAR T cells

Development of CLL therapy



Goals of therapy

Alleviating symptoms → Improving response rates and quality of response → Improving long-term outcomes and tolerability → Improving outcomes in more patients, increasing OS

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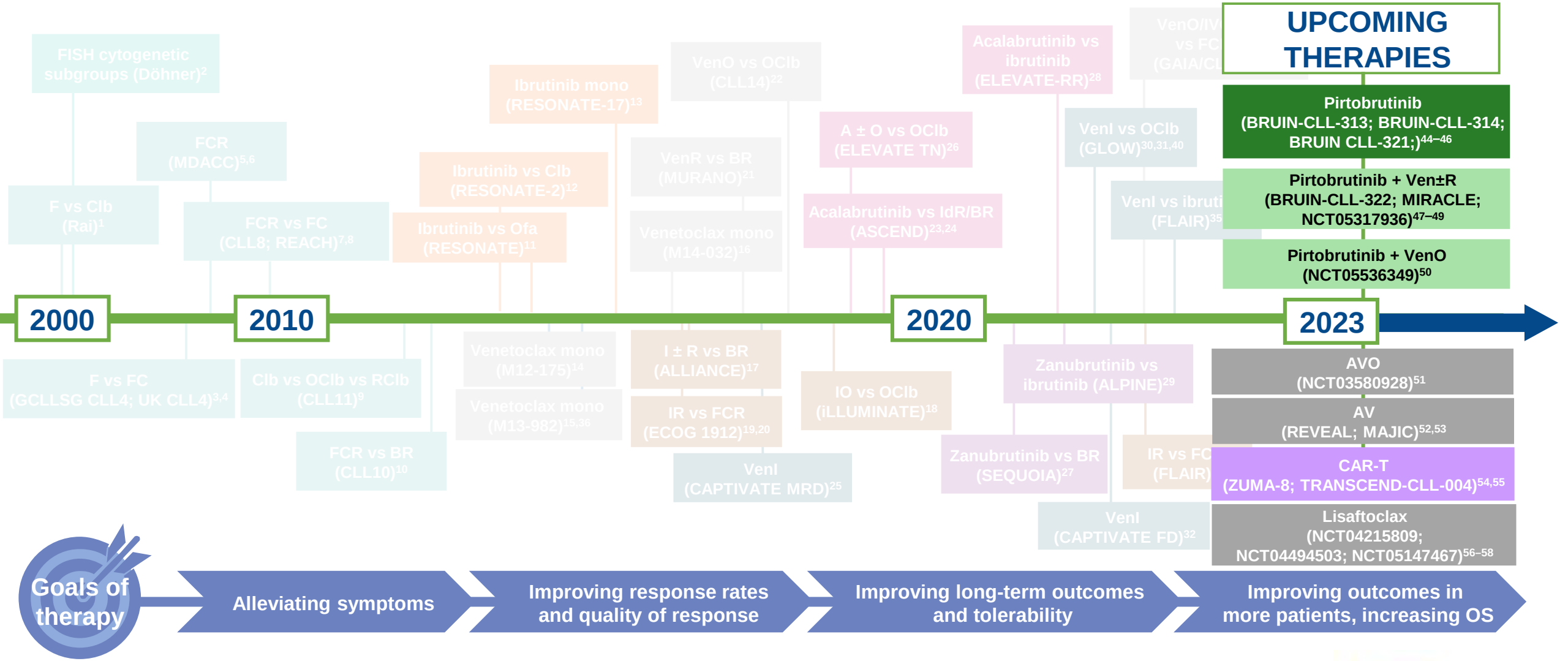
Development of CLL therapy



Goals of therapy

- Alleviating symptoms
- Improving response rates and quality of response
- Improving long-term outcomes and tolerability
- Improving outcomes in more patients, increasing OS

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Key Clinical Trials of 1st-Generation BTKi Ibrutinib in TN CLL

RESONATE-2[1]	iLLUMINATE[2]	ECOG E1912[3-4]	Alliance (A041202)[5]
• Aged ≥65 years • Non-del(17p) • **Ibrutinib vs Clb** • With up to 8 years of follow-up, median PFS was not reached vs 15.0 months (HR 0.154; 95% CI, 0.108-0.220) • 7-year PFS: 59% vs 9% • 7-year PFS by *IGHV* status – Mut: 68% vs 17% – Unmut: 58% vs 2% • 7-year PFS by del(11q) status – With: 52% vs 0% – Without: 61% vs 12%	• Aged >65 years or ≤65 years with comorbidities • **Ibrutinib + G vs Clb + G** • With a median follow-up of 31.3 months, median PFS was significantly longer with Ibr+G vs Clb+G (NR vs 19.0 months; HR 0.23; *P*<0.0001) • 30-month PFS was 79% vs 31%	• Aged ≤70 years • Non-del(17p) • **Ibrutinib + R (IR) vs FCR** • With a median follow-up of 70 months, 5-year PFS was 78% vs 51%, respectively (*P*<0.0001) • PFS with IR vs FCR was statistically significant in *IGHV*mut (HR 0.27, *P*=0.001) and -unmut (HR 0.27, *P*<0.001) patients • 5-year OS was 95% vs 89%, respectively (*P*=0.018)	• Aged ≥65 years • **BR (Arm 1) vs Ibr (Arm 2) vs Ibr + R (Arm 3)** • With a median follow-up of 55 months, median PFS was 44 months with Arm 1 and not reached with the others – Arm 2 vs 1: HR 0.36, 95% CI 0.26-0.52, *P*<0.0001 – Arm 3 vs 1: HR 0.36, 95% CI 0.25-0.51, *P*<0.0001 – Arm 3 vs 2: HR 0.99, 95% CI 0.66-1.48, *P*=0.96 • There were no significant differences in OS among the arms (*P*=0.49)

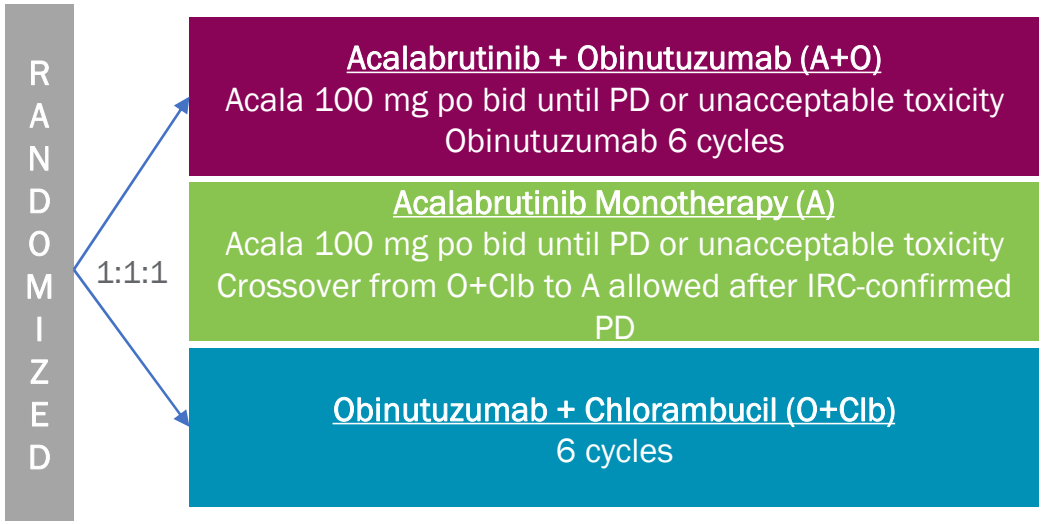
1. Barr PB, et al. *Blood Adv*. 2022;6(11):3440-3450. 2. Moreno C, et al. *Lancet Oncol.* 2019;20(1):P43-56. 3. Shanafelt TD, et al. ASH 2019. Abstract 33. 4. Shanafelt TD, et al. *Blood*. 2022;140(2):112-120. 5. Woyach JA, et al. ASH 2021. Abstract 639.

Newer covalent BTK inhibitors: acalabrutinib, zanubrutinib

5-Year Follow-Up of ELEVATE-TN: Study Design and Patient Characteristics

Key Eligibility Criteria

- Aged ≥65 years or >18 to <65 years with comorbidities (defined as CrCl 30-69 mL/min and CIRS-G >6)
- Untreated CLL requiring treatment per iwCLL 2008 criteria
- ECOG PS ≤2
- No significant cardiovascular disease



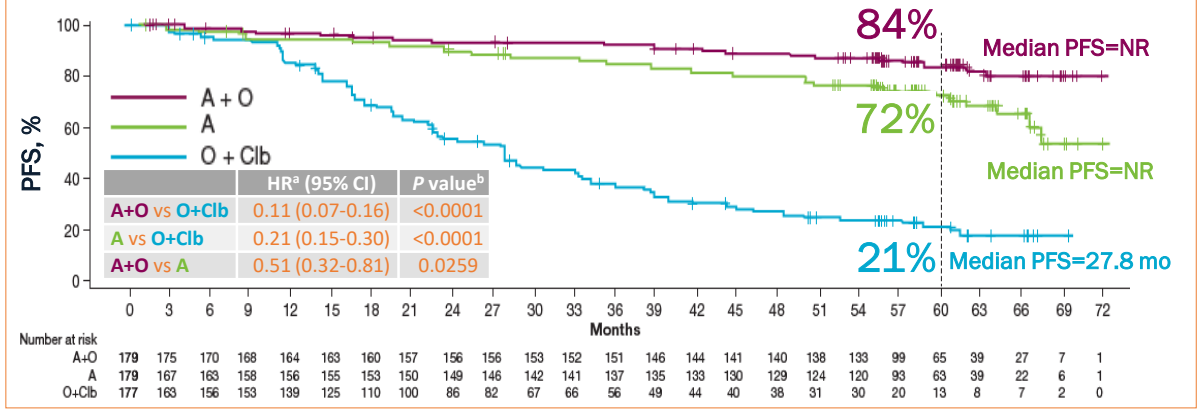
Primary endpoint: IRC-assessed PFS (A+O vs O+Clb)
Secondary endpoints: IRC-assessed PFS (A vs O+Clb), INV-assessed PFS, IRC- and INV-assessed ORR, TTNT, OS, uMRD, safety

Patient Characteristics		A+O (n=179)	A (n=179)	O+Clb (n=177)
Median age (range), years		70 (41-88)	70 (44-87)	71 (46-91)
ECOG PS, n (%)	0-1	169 (94.4)	165 (92.2)	167 (94.4)
	2	10 (5.6)	14 (7.8)	10 (5.6)
Bulky disease ≥5 cm, n (%)		46 (25.7)	68 (38.0)	54 (30.5)
Rai stage, n (%)	III	47 (26.3)	51 (28.5)	40 (22.6)
	IV	38 (21.2)	37 (20.7)	38 (21.5)
Cytogenetics, n (%)	del(17p)	17 (9.5)	16 (8.9)	16 (9.0)
	del(17p) and/or mutated *TP53*	25 (14.0)	23 (12.8)	25 (14.1)
Mutated *TP53*, n (%)		21 (11.7)	19 (10.6)	21 (11.9)
Unmutated *IGHV*, n (%)		103 (57.5)	119 (66.5)	116 (65.5)
Treatment ongoing, n (%)		116 (64.8)	107 (59.8)	0

Data cutoff: October 1, 2021.
Sharman JP, et al. EHA 2021. Abstract S148; Sharman JP, et al. ASCO 2022. Abstract 7539; Sharman JP, et al. EHA 2022. Abstract P666.

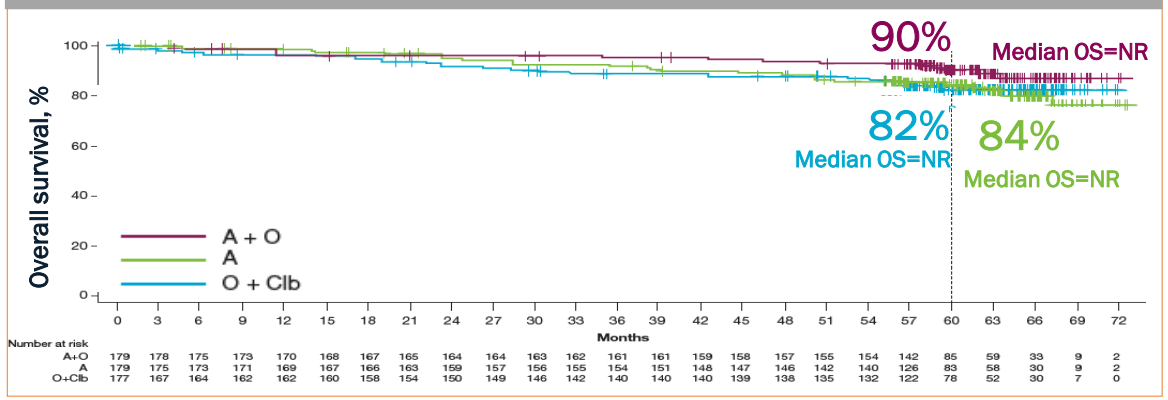
5-Year Follow-Up of ELEVATE-TN: PFS and OS

INV-Assessed PFS (Median Follow-Up: 58.2 Months)[1]



- At a median follow-up of 58.2 months (range, 0.0-72.0), OS data were immature, and medians were not reached in any treatment arm
- Relative risk for death was lower in the A+O vs O+Clb arm (HR=0.55, 95% CI: 0.30-0.99); crossover from O+Clb to A occurred after disease progression in 72 patients (41%)

Overall Survival (Median Follow-Up: 58.2 Months)[1]



Sharman JP, et al. ASCO 2022. Abstract 7539; Sharman JP, et al. *Leukemia*. 2022;36(4):1171-1175.

5-Year Follow-Up of ELEVATE-TN: Safety

AEs of Clinical Interest, n (%)	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	43 (24.2)	17 (9.6)	39 (21.8)	18 (10.1)	13 (7.7)	3 (1.8)
Atrial fibrillation	11 (6.2)	2 (1.1)	13 (7.3)	2 (1.1)	1 (0.6)	0
Bleeding	88 (49.4)	8 (4.5)	78 (43.6)	6 (3.4)	20 (11.8)	0
Major bleeding[a]	12 (6.7)	8 (4.5)	8 (4.5)	6 (3.4)	2 (1.2)	0
Hypertension	17 (9.6)	8 (4.5)	16 (8.9)	7 (3.9)	6 (3.6)	5 (3.0)
Infections	140 (78.7)	50 (28.1)	135 (75.4)	35 (19.6)	75 (44.4)	14 (8.3)
Secondary primary malignancies	31 (17.4)	14 (7.9)	27 (15.1)	7 (3.9)	7 (4.1)	3 (1.8)
Excluding nonmelanoma skin	17 (9.6)	12 (6.7)	13 (7.3)	5 (2.8)	3 (1.8)	2 (1.2)

[a] Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system.

Sharman JP, et al. ASCO 2022. Abstract 7539; Sharman JP, et al. EHA 2022. Abstract P666.

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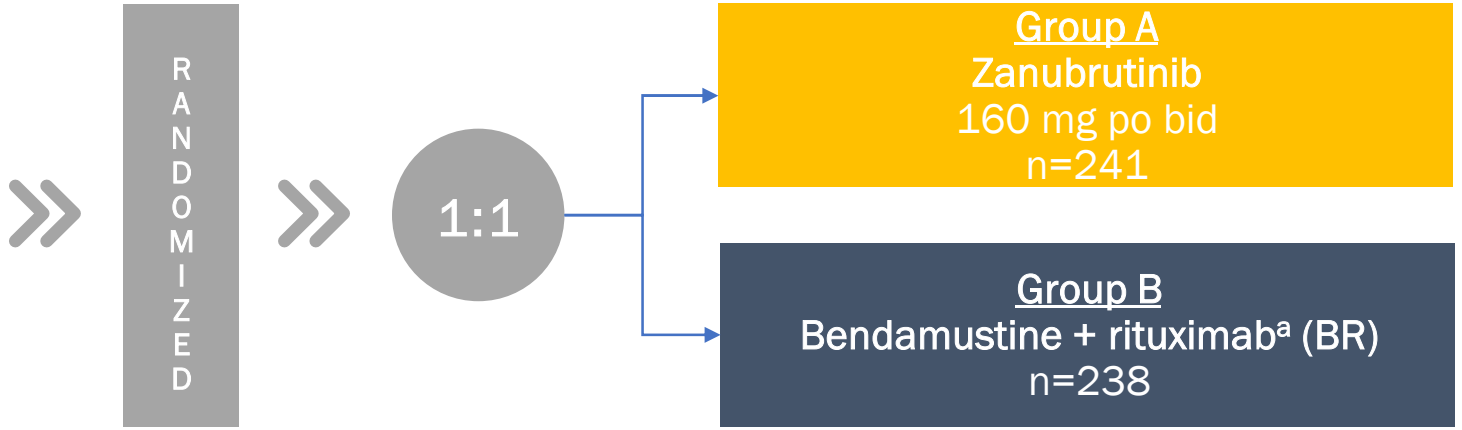
SEQUOIA trial: Study Design

Key Eligibility Criteria

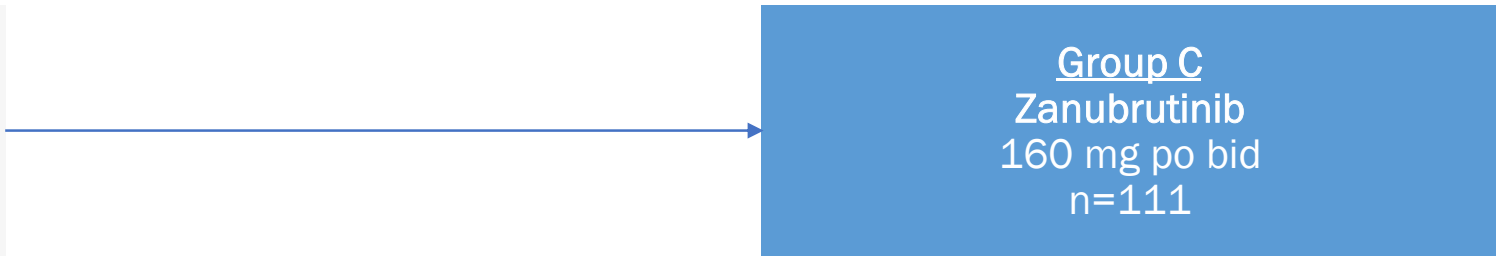
Cohort 1

- TN CLL/SLL
- Without del(17p)
- ≥65 years of age or unsuitable for FCR treatment



Cohort 2

- TN CLL/SLL
- With del(17p)



Primary endpoint

- PFS (IRC assessed) for group A vs group B

Key secondary endpoints

- PFS (IRC assessed) for group C
- PFS (INV assessed) for all groups
- ORR
- OS
- Safety

[a] Bendamustine 90 mg/m^2 on day 1 and 2 and rituximab 375 mg/m^2 in cycle 1, 500 mg/m^2 in cycles 2-6 for 6 × 28-day cycles.

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

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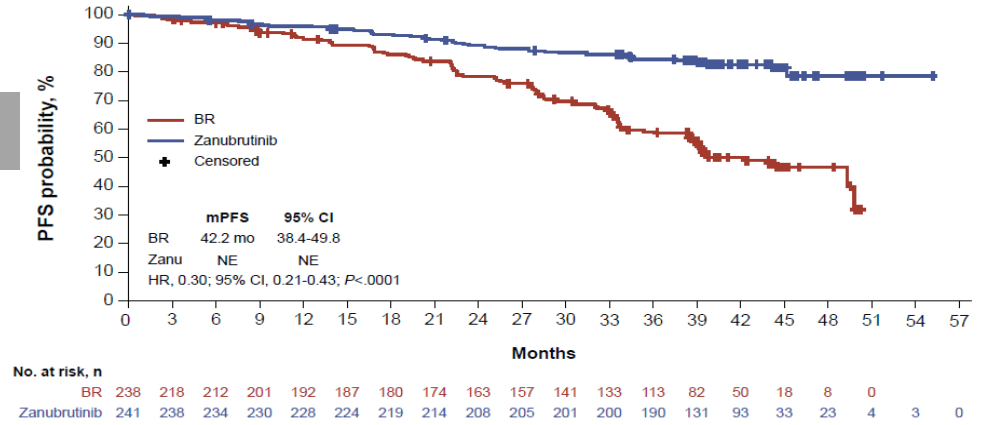
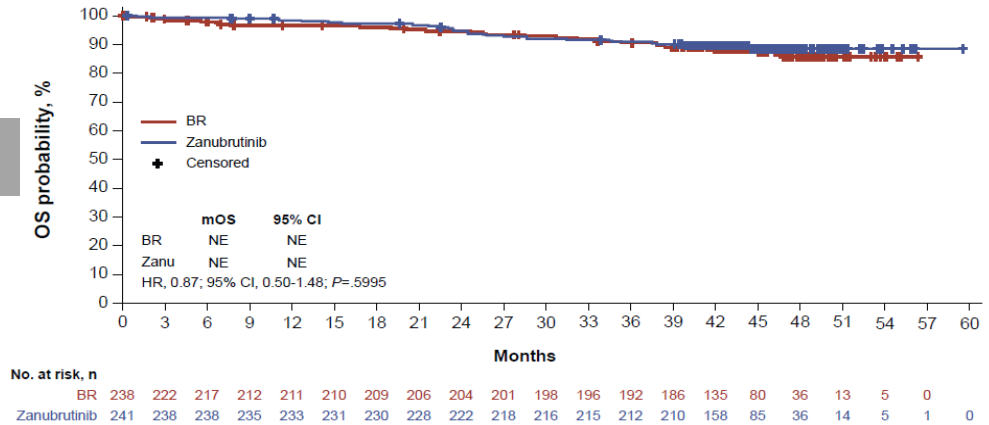
SEQUOIA trial: Efficacy

Cohort 1: Without del(17p) [Median Follow-Up: 43.7 Months]

PFS

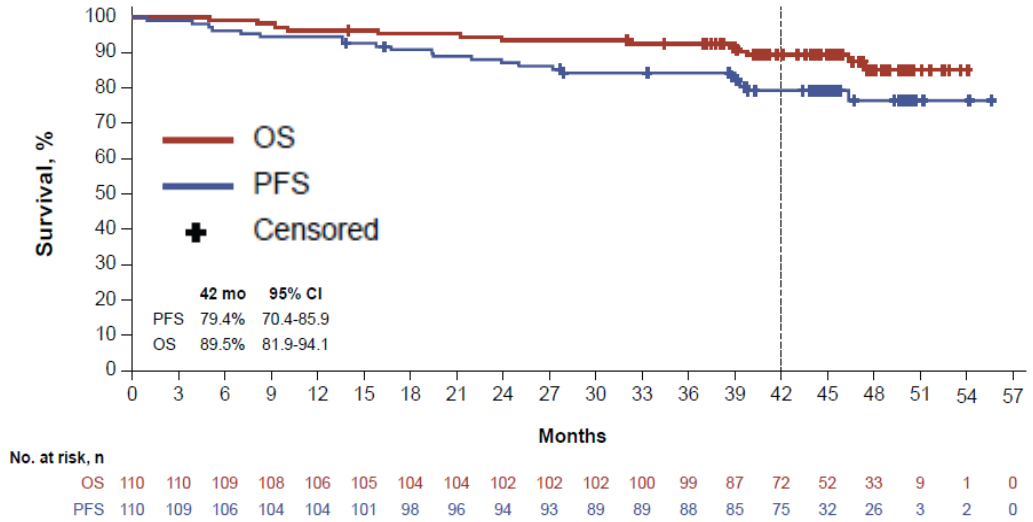


OS



Cohort 2: With del(17p) [Median Follow-Up: 47.9 Months]

PFS and OS



Shadman M, et al. ICML 2023. Abstract 154.

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SEQUOIA trial: Safety

AESIs, %	Cohort 1 – Without del(17p)				Cohort 2 – With del(17p)	
	Group A Zanubrutinib (n=240[a])		Group B BR (n=227[b])		Group C Zanubrutinib (n=111)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Infections	72.9	23.8	62.6	22.0	80.2	27.0
Bleeding	48.8	5.8	12.3	1.8	57.7	5.4
Other malignancies	18.8	9.2	12.3	4.8	24.3	7.2
Hypertension	17.5	9.2	13.7	6.6	13.5	6.3
Diarrhea	17.1	1.7	14.1	2.2	19.8	0.9
Neutropenia	16.7	12.5	56.8	51.1	18.9	16.2
Arthralgia	15.4	0.8	10.1	0.4	23.4	0.9
Anemia	7.1	0.4	20.7	2.2	6.3	0
Thrombocytopenia	6.3	2.1	18.1	7.9	8.1	1.8
Atrial fibrillation/flutter	5.0	1.3	2.6	1.3	6.3	4.5
Myalgia	3.8	0	1.8	0	7.2	0.9
Opportunistic infection	2.5	0.4	1.8	1.3	0.9	0.9
Exposure-Adjusted Incidence Rates for Select AESIs						
Atrial fibrillation and flutter	0.13		0.08		0.15	
Hemorrhage	2.02		0.40		2.73	
Major hemorrhage	0.20		0.05		0.20	
Hypertension	0.49		0.45		0.35	

[a] Patients who did not receive zanubrutinib are not included in the safety analysis. [b] Patients who did not receive BR are not included in the safety analysis.
Shadman M, et al. ICML 2023. Abstract 154.

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BCL2 inhibitor: venetoclax

CLL14 trial (6-Year Follow-Up): Study Design and Efficacy

Key Eligibility Criteria

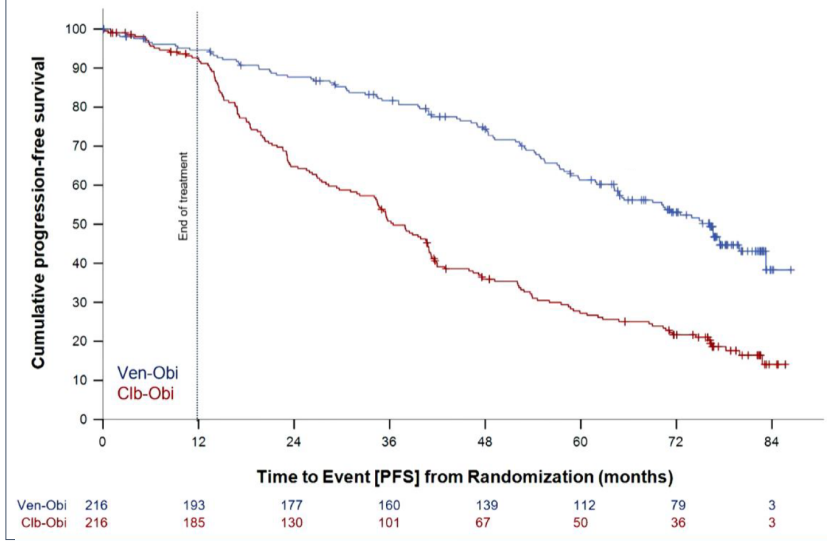
- Patients with TN CLL and coexisting medical conditions
- CIRS >6 and/or CrCl <70 mL/min

RANDOMIZED → 1:1

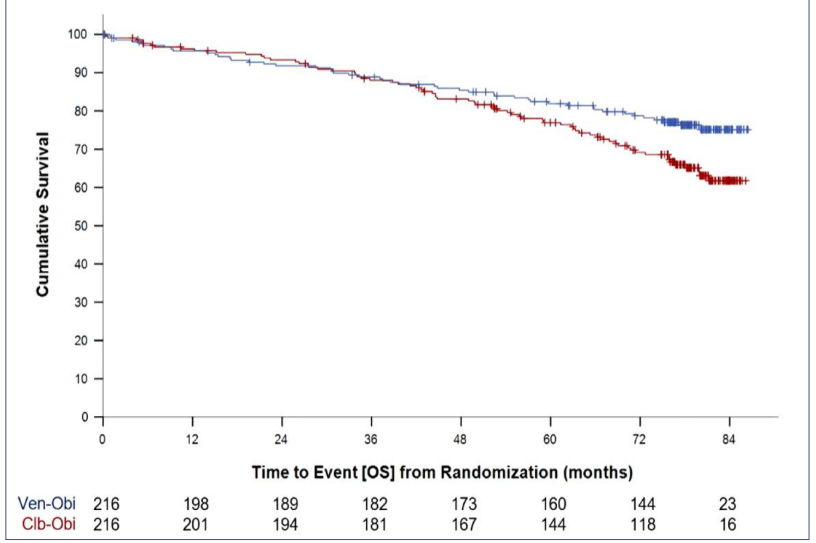
- **Venetoclax-Obinutuzumab (Ven-G)** (6 cycles) followed by venetoclax (6 cycles)
- **Chlorambucil-Obinutuzumab (Clb-G)** (6 cycles) followed by chlorambucil (6 cycles)

Primary endpoint	Secondary endpoints
▪ PFS	▪ Response ▪ MRD ▪ OS

PFS



OS



Median Follow-Up: 76.4 mo

Median PFS	6-year PFS rate	Median OS	5-year OS rate
Ven-G: 76.2 months Clb-G: 36.4 months	Ven-G: 53.1% Clb-G: 21.7%	Ven-G: not reached Clb-G: not reached	Ven-G: 78.7% Clb-G: 62.9%
HR 0.40 (95% CI: 0.31-0.52) *P*<0.0001		HR 0.69 (95% CI: 0.48-1.01) *P*=0.052	

Al-Sawaf O, et al. EHA 2023. Abstract S145.

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CLL14 trial (6-Year Follow-Up): Safety

Most Frequent Grade ≥3 AEs,%	Ven-G (n=212)		Clb-G (n=214)	
	During treatment	After treatment	During treatment	After treatment
Neutropenia	51.9	3.8	47.2	1.9
Thrombocytopenia	14.2	0.5	15.0	0
Anemia	7.5	1.9	6.1	0.5
Febrile neutropenia	4.2	0.9	3.3	0.5
Leukopenia	2.4	0	4.7	0
Pneumonia	3.8	3.3	3.7	1.4
Infusion-related reaction	9.0	0	9.8	0.5
TLS	1.4	0	3.3	0

Secondary Primary Malignancies (SPM)	Ven-G (n=212)	Clb-G (n=214)
Overall total number of events,[a] n	**31**	**20**
Number of pts with ≥1 SPM, n (%)	30 (14.2)	18 (8.4)
Melanoma	8 (3.8)	4 (1.9)
Solid organ tumors	17 (8.0)	11 (5.1)
Hematological malignancies	3 (1.4)	2 (0.9)
Other	2 (0.9)	1 (0.5)

[a] Excluding non-melanoma skin cancers.
Al-Sawaf O, et al. EHA 2023. Abstract S145.

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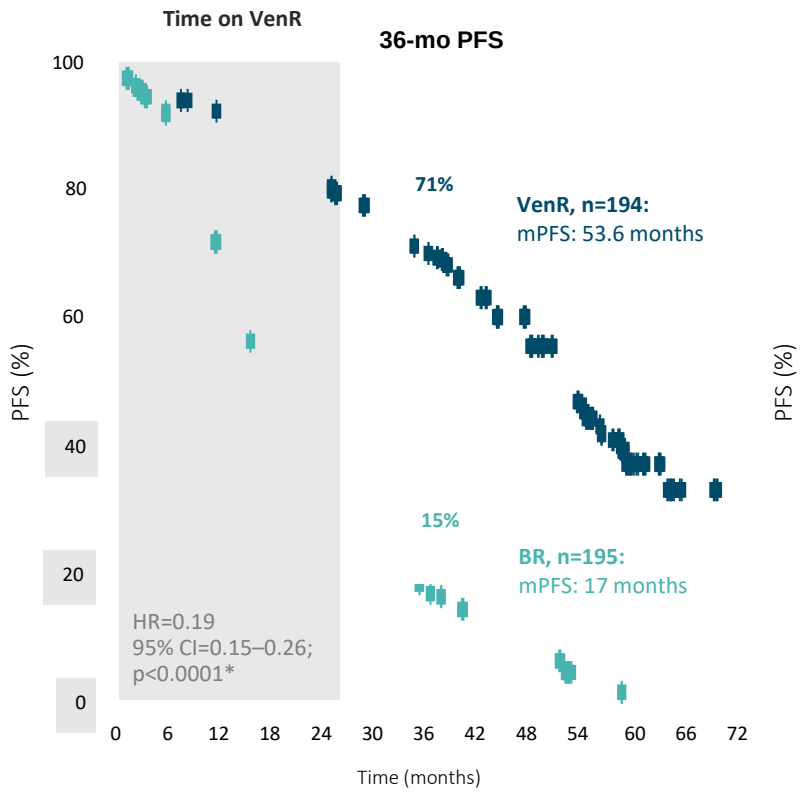
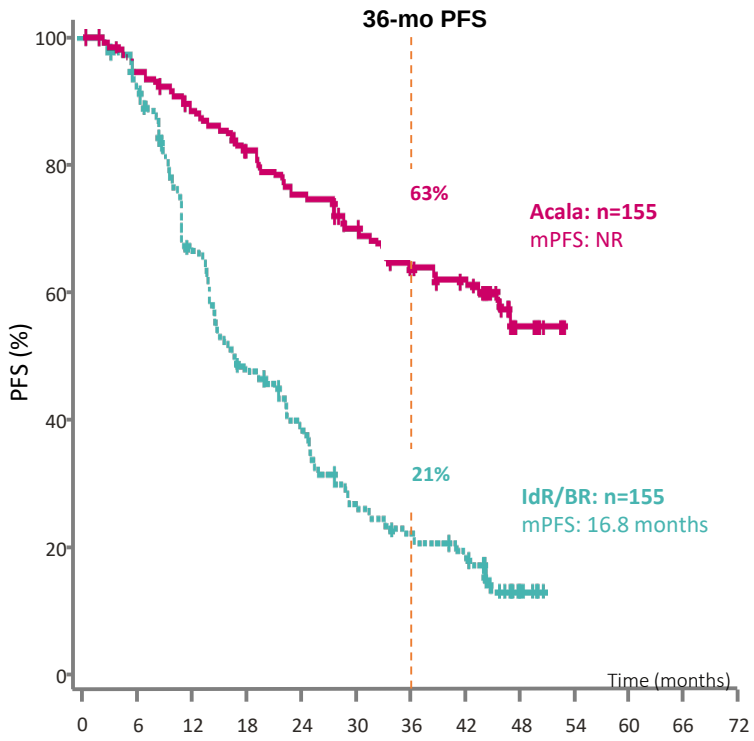
Relapsed setting

PFS in patients with R/R CLL

MURANO: PFS VenR vs BR
59.2-month median follow-up[1]



ASCEND: PFS acalabrutinib vs IdR/BR
46.5-month median follow-up[5]



Seymour JF, *et al. Blood* 2022; 140:839–850; 77; Ghia P, *et al. Hemasphere* 2022; 6:e801

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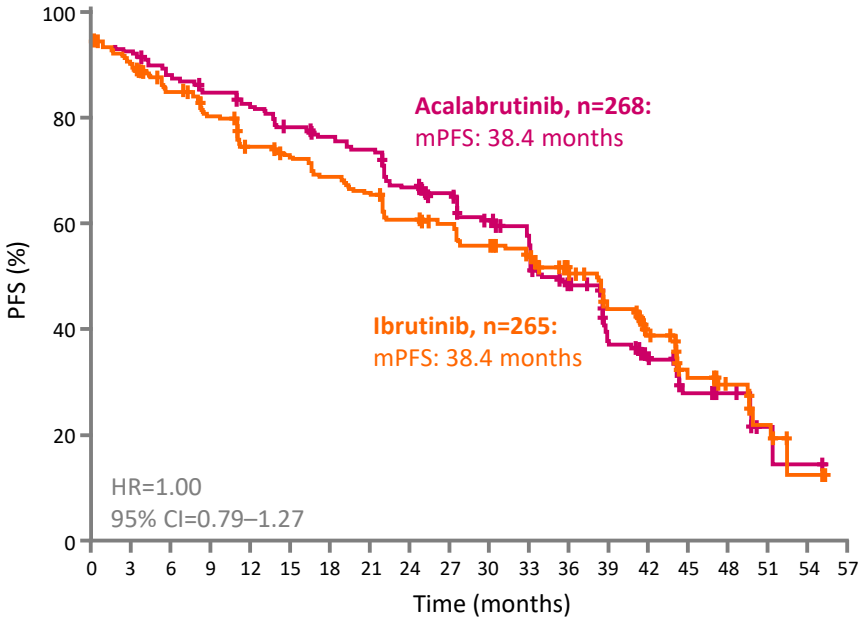
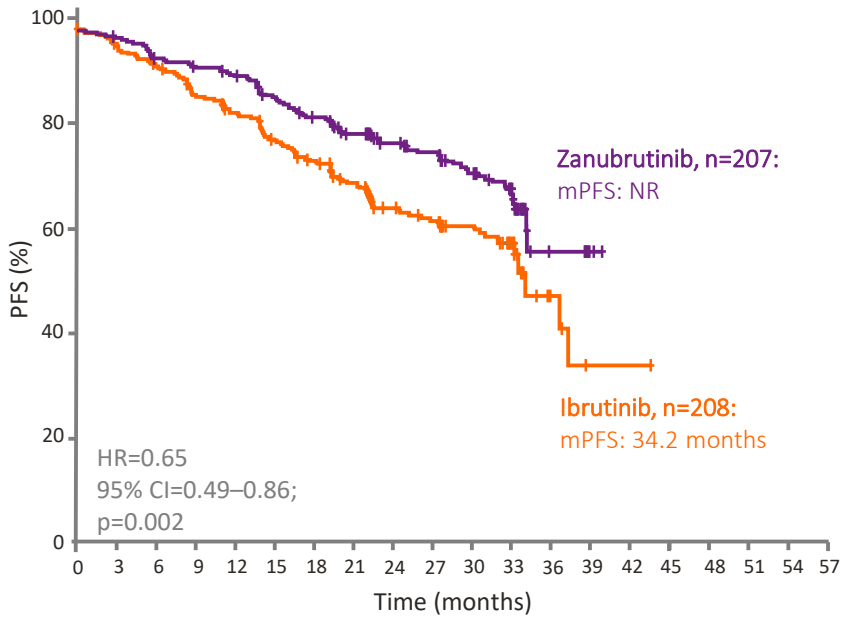
Comparing BTKis

ELEVATE R/R: IRC-assessed PFS with acala vs ibrutinib
40.9-month median follow-up[2,3]



ALPINE: PFS with zanubrutinib vs ibrutinib
29.6-month median follow-up[1]



Brown JR, *et al. N Engl J Med* 2022; doi:10.1056/NEJMoa2211582
Byrd JC, *et al. J Clin Oncol* 2021; **39**:3441–3452;
Hillmen P, *et al.* EHA 2021; Abstract S145 (Oral).

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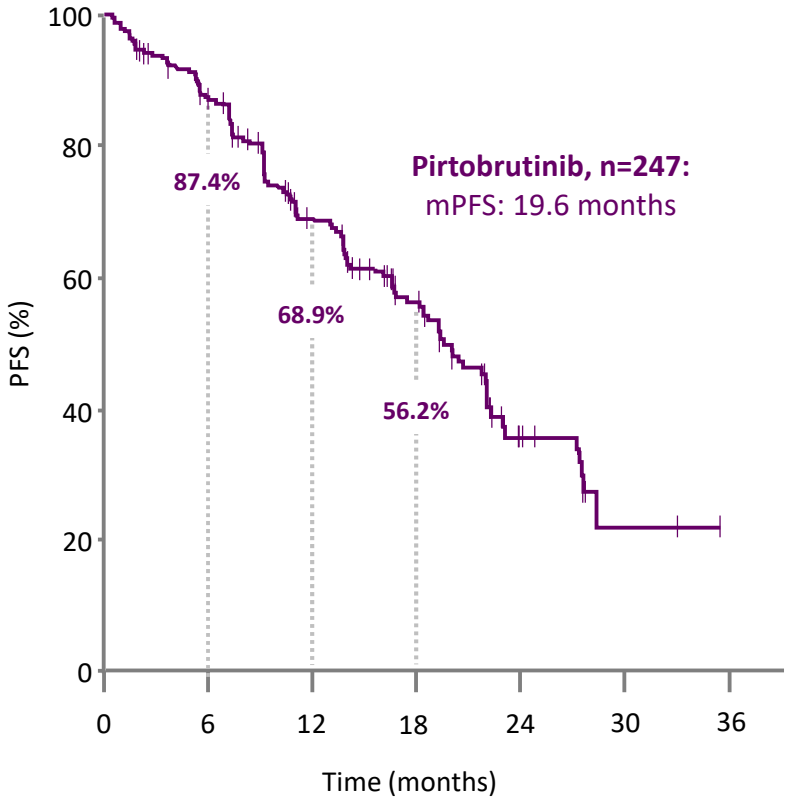
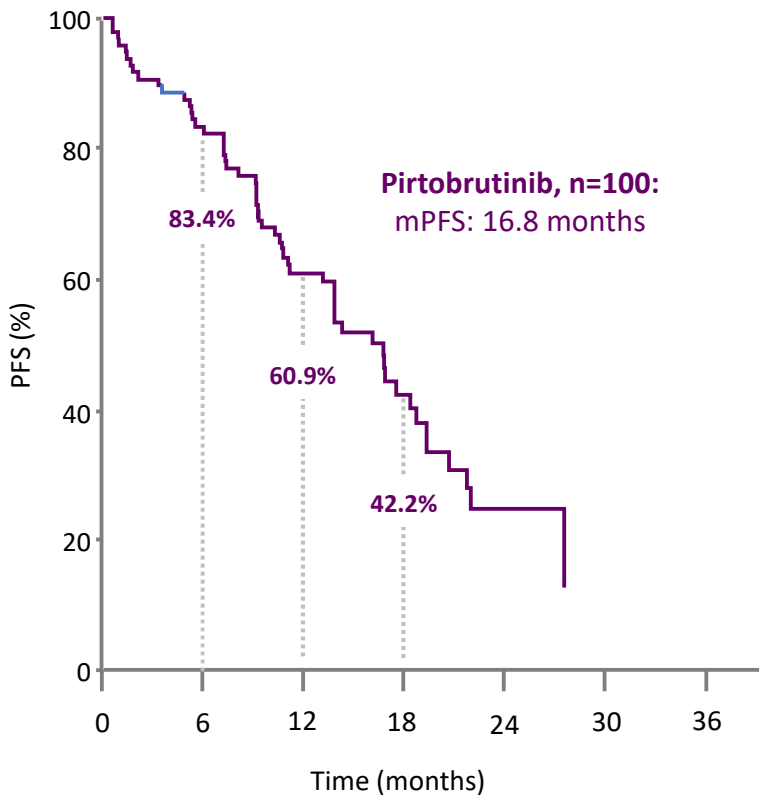
Non-covalent BTKi pirtobrutinib in BTKi pre-treated patients: BRUIN Ph 1/2 study (N=247)

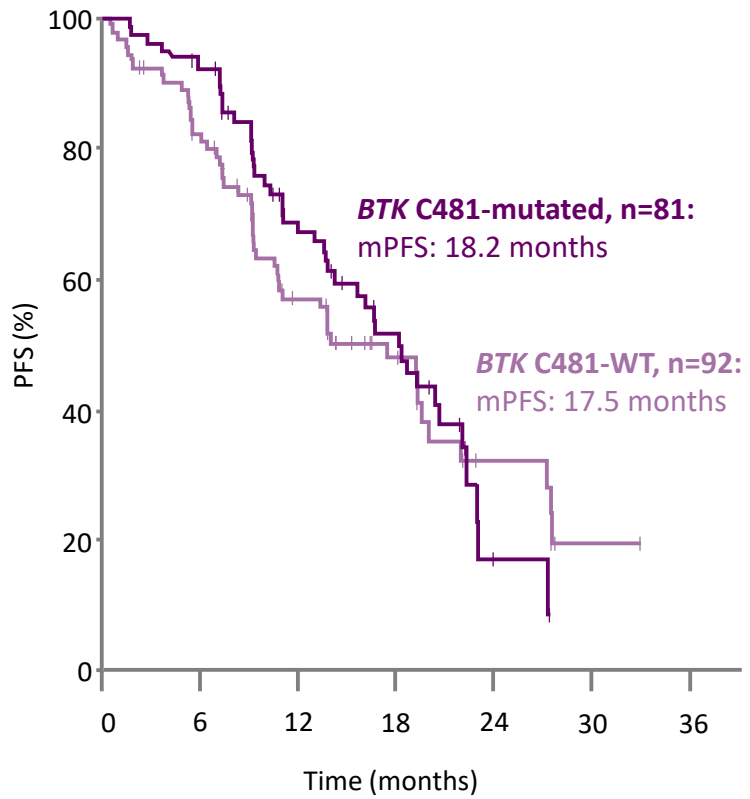
PFS in BTKi pre-treated patients
19.4-month median follow-up
(median prior lines of therapy: 3)



PFS in BTKi and BCL-2i pre-treated patients
16.8-month median follow-up
(median prior lines of therapy: 5)



PFS by *BTK C481* mutation status* in patients with PD on a prior BTKi
18.2-month median follow-up



* *BTK C481* mutation status was centrally determined and based on pre-treatment strategies

Mato AR, *et al.* ASH 2022. Abstract 961 (Oral)

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BTKi + BCL2i combinations

CAPTIVATE trial: Study Design and 4-Year Follow-Up From the Fixed-Duration Cohort

Key Eligibility Criteria
- TN CLL
- Aged ≤70 years
- ECOG PS 0-2

Fixed-duration cohort[1,2]
N=159

Ibrutinib lead-in
Ibr 420 mg qd (3 cycles)

Year 1

Ibrutinib + venetoclax
Ibr 420 mg qd + venetoclax 5-week ramp-up to 400 mg qd (12 cycles)

Year 2

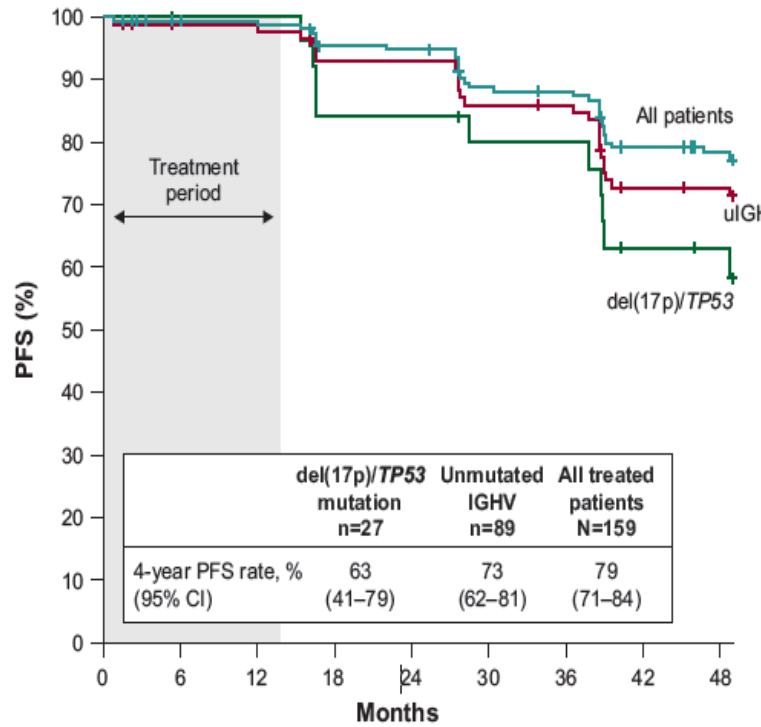
End of Treatment

Follow-up
On PD, patients could be retreated with single-agent Ibr (or FD Ibr+Ven if they had durable response)

Primary endpoint: CR rate, including CRi, per INV, in patients without del(17p)

Secondary endpoints: ORR, DOR, uMRD rates ($<10^{-4}$ by flow cytometry), PFS, OS, reduction in TLS risk category and safety

PFS[1]



	del(17p)/*TP53* mutation n=27	Unmutated IGHV n=89	All treated patients N=159
4-year PFS rate, % (95% CI)	63 (41–79)	73 (62–81)	79 (71–84)

Patients at risk

del(17p)/*TP53* mutation	27	26	26	21	21	19	19	14	13
Unmutated IGHV	89	85	85	79	79	73	72	59	58
All treated patients	159	153	152	144	143	132	130	115	111

[a] CR rate is inclusive of patients achieving CRi. [b] PR rate is inclusive of patients achieving an nPR.

Wierda WG, et al. ASCO 2022. Abstract 7519; Moreno C, et al. EHA 2022. Abstract P669; Tedeschi A. et al. EHA 2023. Abstract P617.

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GLOW trial: Study Design and Results

Key Eligibility Criteria

- Previously untreated CLL
- ≥65 years of age or <65 years with CIRS >6 or CrCl <70 mL/min
- No del(17p) or known *TP53* mutation
- ECOG PS ≤2

R 1:1

Ibrutinib 420 mg po qd lead-in (3 cycles) followed by **ibrutinib + venetoclax (Ibr+Ven)** (12 cycles; venetoclax ramp-up 20-400 mg over 5 weeks beginning C4) n=106

Chlorambucil (Clb) 0.5 mg/kg on D1 & D15 x 6 cycles + **Obinutuzumab (O)** 1000 mg D1-2, D8, D15 of C1, and D1 of C2-6 n=105

Primary endpoint

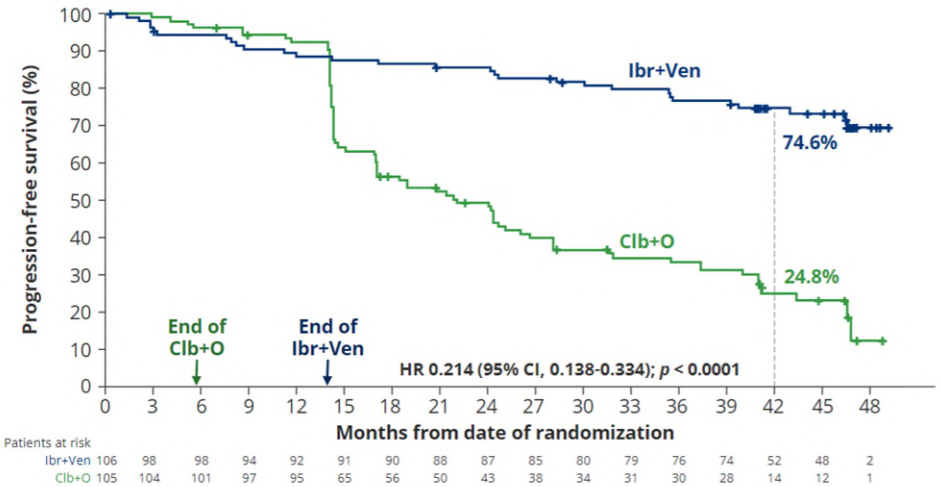
- IRC-assessed PFS

Key secondary endpoints

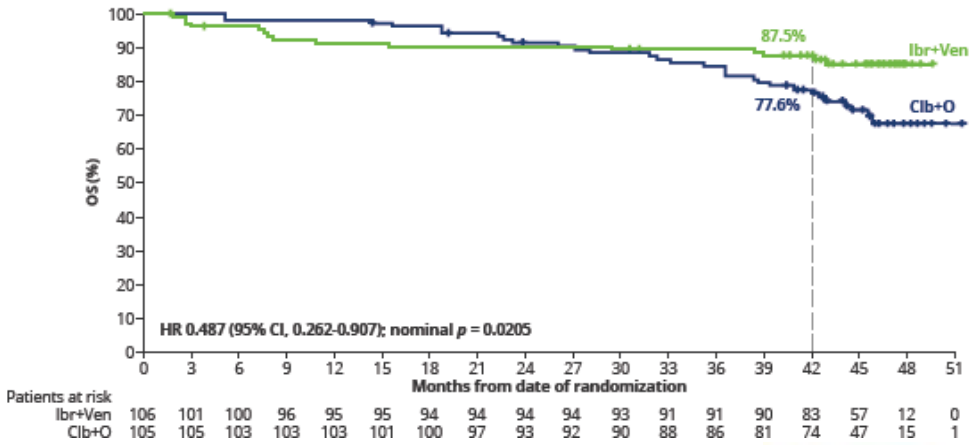
- uMRD rates, OS, TTNT, safety

Safety (Median Follow-Up of 27.7 Months)[1]	Ibr+Ven (N=106)	Clb+O (N=105)
Median exposure (range), mo	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Grade 3 or higher AEs in ≥5% of patients, %	75.5	69.5
Neutropenia[a]	34.9	49.5
Infections[b]	17.0	11.4
Thrombocytopenia	5.7	20.0
Diarrhea	10.4	1.0
Hypertension	7.5	1.9
Atrial fibrillation	6.6	0
Hyponatremia	5.7	0
TLS	0	5.7
There were 4 deaths due to cardiac disorders/sudden death in the Ibr+Ven arm (0 with Clb+O)		

IRC-Assessed PFS (Median Follow-Up: 46 Months)[2]



OS (Median Follow-Up: 46 Months)[2]



[a] Includes neutrophil count decreased; grade ≥3 febrile neutropenia: 1.9% for Ibr+Ven vs 2.9% for Clb+O. [b] Includes multiple preferred terms.

Kater AP, et al. *NEJM Evid*. 2022;1(7); Niemann C, et al. ASH 2022. Abstract 93; Tedeschi A. et al. EHA 2023. Abstract P617.

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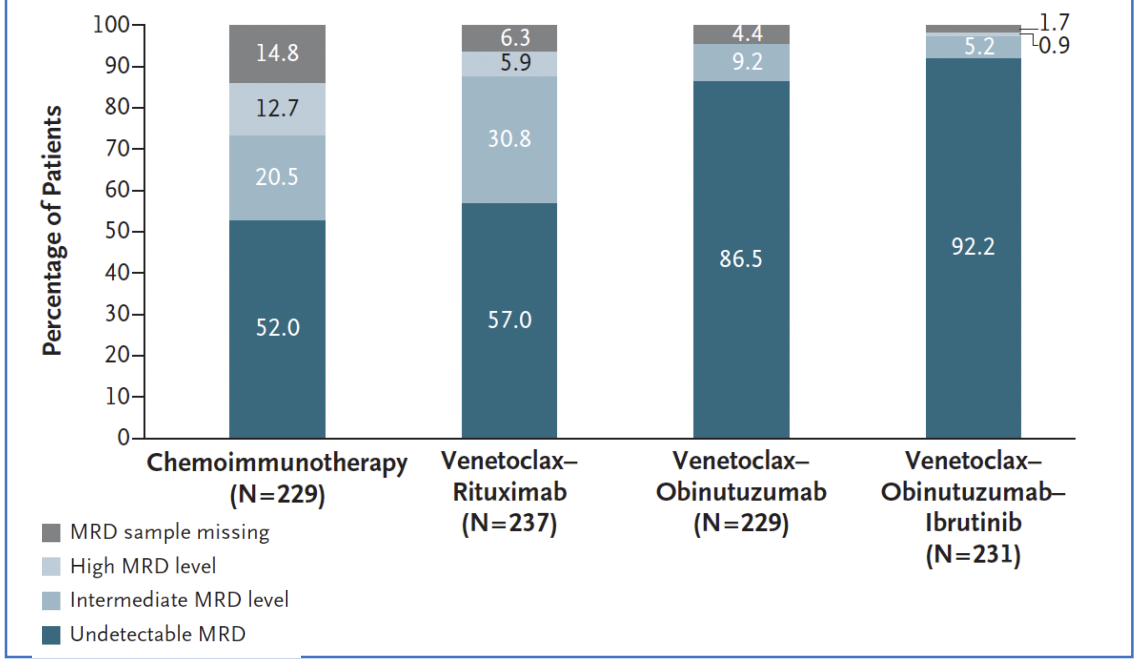
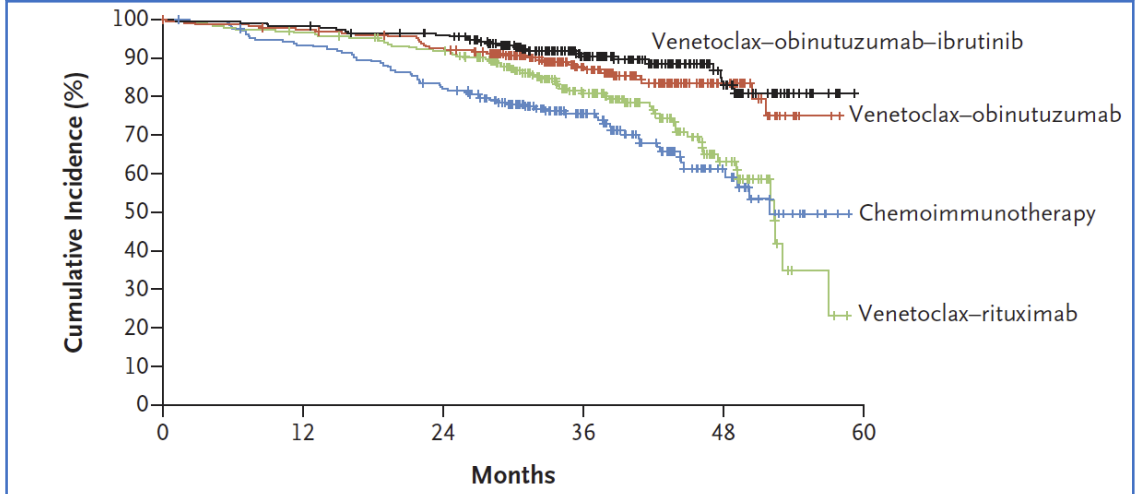
GAIA-CLL13 Trial: Ph 3 Trial of 1L Ven Combinations in Fit Patients With CLL Without *TP53* Aberrations

MRD in PB at Month 15 (Primary Endpoint)



- uMRD in PB at month 15
  - VO was superior to CIT (86.5% [97.5% CI, 80.6-91.1] vs 52.0% [97.5% CI, 44.4-59.5]; *P*<0.001)
  - VOI was superior to CIT (92.2% [97.5% CI, 87.3-95.7); *P*<0.001)
  - No significant difference between VR and CIT (57.0% [97.5% CI, 49.5-64.2]; *P*=0.32)

PFS



CIT	229	197	172	98	28	0
VenR	237	226	212	119	32	0
VenG	229	221	208	125	42	0
Ibrutinib	231	227	217	132	44	0

- PFS after a median follow-up of 38.8 months (IQR, 32.7-46.1)
  - VOI was superior to CIT (HR 0.32 [97.5% CI, 0.19-0.54]; *P*<0.001)
  - VO was superior to CIT (HR 0.42 [97.5% CI, 0.26-0.68]; *P*<0.001)
  - No significant difference between VR and CIT (HR 0.79 [97.5% CI, 0.53-1.18]; *P*=0.18)

Eichhorst B, et al. N Engl J Med. 2023;388:1739-1754.

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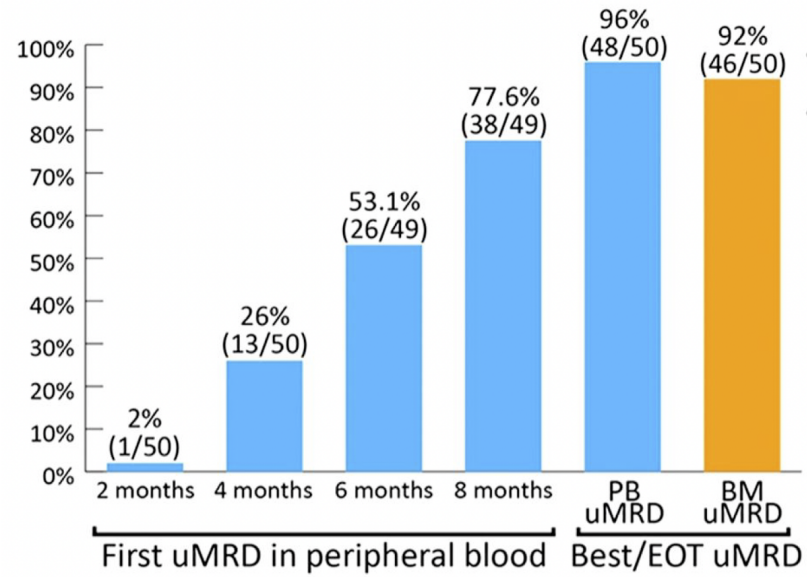
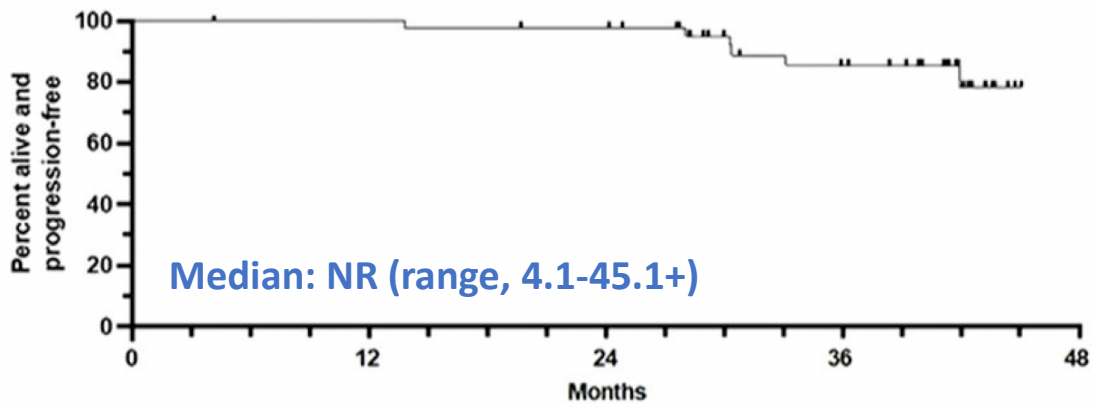
BOVen trial (40-month f/u): Ph 2 Trial of Zanubrutinib, Obinutuzumab, and Venetoclax in TN CLL/SLL

MRD Outcomes

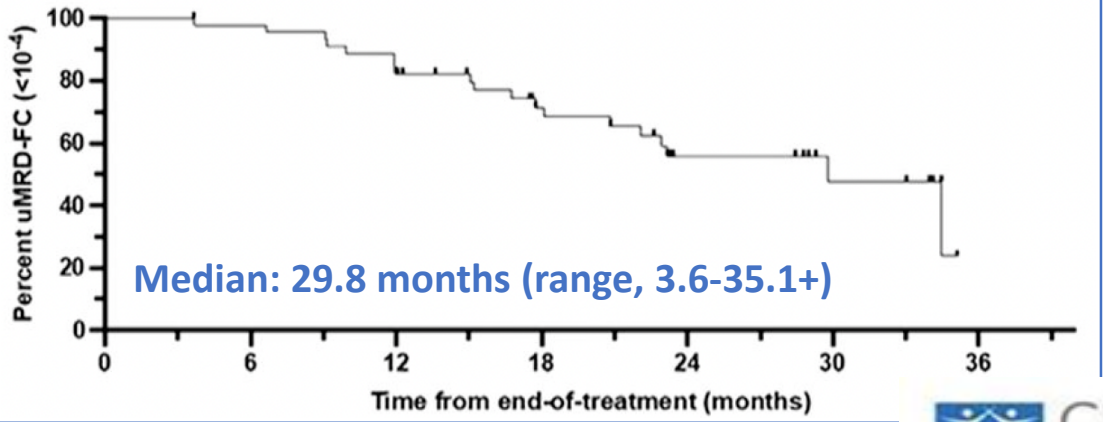


- 96% (48/50) uMRD ($<10^{-4}$) in PB
- 92% (46/50) uMRD in both PB and BM
  - All met prespecified MRD endpoint/treatment discontinuation criterion and stopped therapy after median of 10 months (IQR 8-12 months)
- 400-fold MRD reduction at C5D1 associated with 100% MRD-neg at 8 months

PFS in All Patients (n=50)



MRD-Free Survival in BM uMRD Patients (n=46)



Soumerai J, et al. ICML 2023. Abstract 153.

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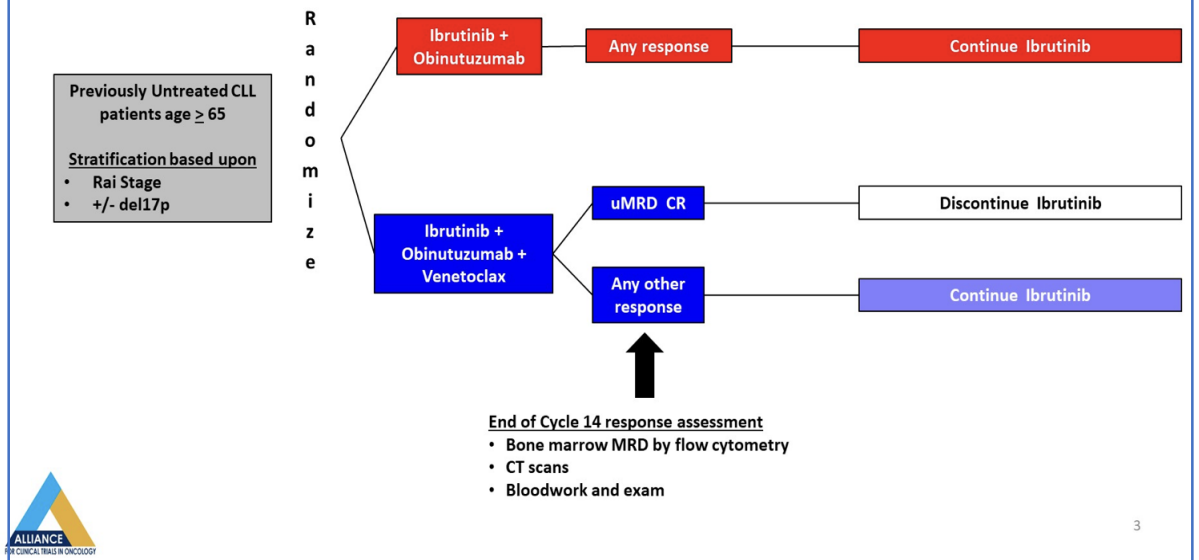
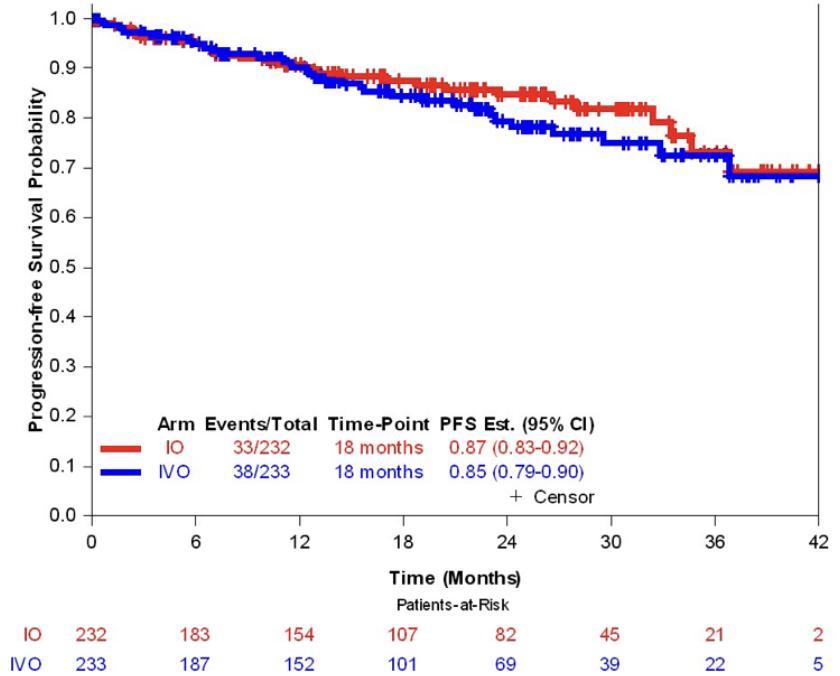
Alliance A041702 trial: Phase 3 Trial of IO±V in Patients With TN CLL (≥70 years of age)

Study Schema



PFS



IVO vs IO:
Hazard Ratio 1.12
95% CI: 0.70-1.79

9

Conclusions:

- IVO not superior to IO in this trial
- COVID19 may have significantly altered these results, with data suggesting death imbalance for patients on venetoclax
- PFS not impacted by MRD or response thus far
- Long term f/u needed

Woyach JA, et al. ASCO 2023. Abstract 75

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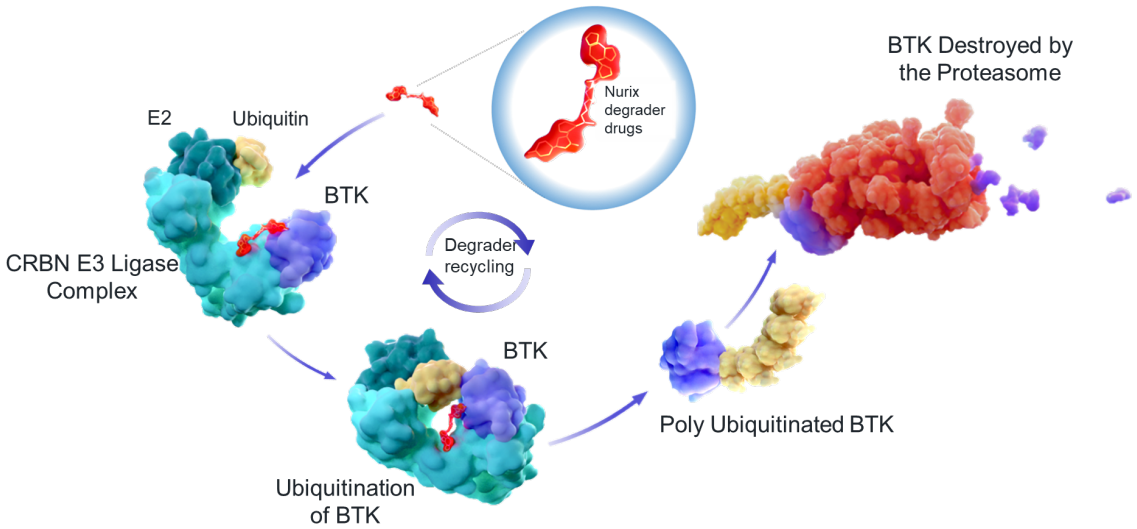
Latest treatments: BTK degraders, bispecific antibodies, CAR T cells

NX-2127: first-in-class targeted protein BTK degrader

Utilizing the ubiquitin-proteasome pathway to degrade BTK, a well-validated target in hematological malignances



Characteristics	CLL (n=23)	Overall population (N=36)
Median age, years (range)	75 (61–90)	75 (50–92)
Female, n (%)	9 (39.1)	13 (36.1)
Male, n (%)	14 (60.9)	23 (63.9)
Lines of prior therapy, median (range)	5 (2–11)	4 (2–11)
BTKi, n (%)	23 (100)	31 (86.1)
Pirtobrutinib, n (%)	8 (34.8)	11 (30.6)
BTKi and BCL2i, n (%)	16 (69.6)	16 (44.4)
cBTKi, ncBTKi, and BCL2i, n (%)	6 (26.1)	6 (16.7)
***BTK* mutation present**[a], n (%)	10 (48)	11 (35)
C481	5 (24)	5 (16)
L528W	4 (19)	4 (13)
T474	3 (14)	4 (13)
V416L	1 (5)	1 (3)
***BCL2* mutation present**[a], n (%)	4 (19)	4 (13)
***PLCG2* mutation present**[a], n (%)	0 (0)	1 (3.2)

NX-2127 has the potential to address emerging *BTK* mutations

Mato A, et al. ASH annual meeting 2022

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NX-2127 safety summary (TEAEs >15% in all patients)

Treatment-emergent AEs occurring in >15% of total population, n (%)	Any grade (N=36)	Grade 3+ (N=36)	SAE (N=36)
Fatigue	19 (52.8)	–	-
Neutropenia[a]	14 (38.9)	13 (36.1)	-
Contusion	10 (27.8)	–	1 (2.8)
Thrombocytopenia[b]	9 (25)	3 (8.3)	-
Anemia	8 (22.2)	4 (11.1)	1 (2.8)
Hypertension	9 (25.0)	1 (2.8)	-
Constipation	7 (19.4)	–	-
Dyspnea	7 (19.4)	1 (2.8)	-
Pruritis	7 (19.4)	–	-
Atrial fibrillation/Atrial flutter[c]	6 (16.7)	3 (8.3)	2 (5.6)
Diarrhea	6 (16.7)	–	-
Petechiae	6 (16.7)	–	-
Rash	6 (16.7)	–	-

1 DLT of cognitive disturbance was observed at 300 mg (CLL); MTD not reached

[a]Aggregate of "neutropenia" and "neutrophil count decreased" [b]Aggregate of "thrombocytopenia" and "platelet count decreased" [c]Cases were confounded by risk factors such as: age >80 years (4 cases), history of hypertension (4 cases), male sex (3 cases), and history of prior AF on ibrutinib (2 cases)

Data cutoff: September 21, 2022

Mato A, et al. ASH annual mtg 2022

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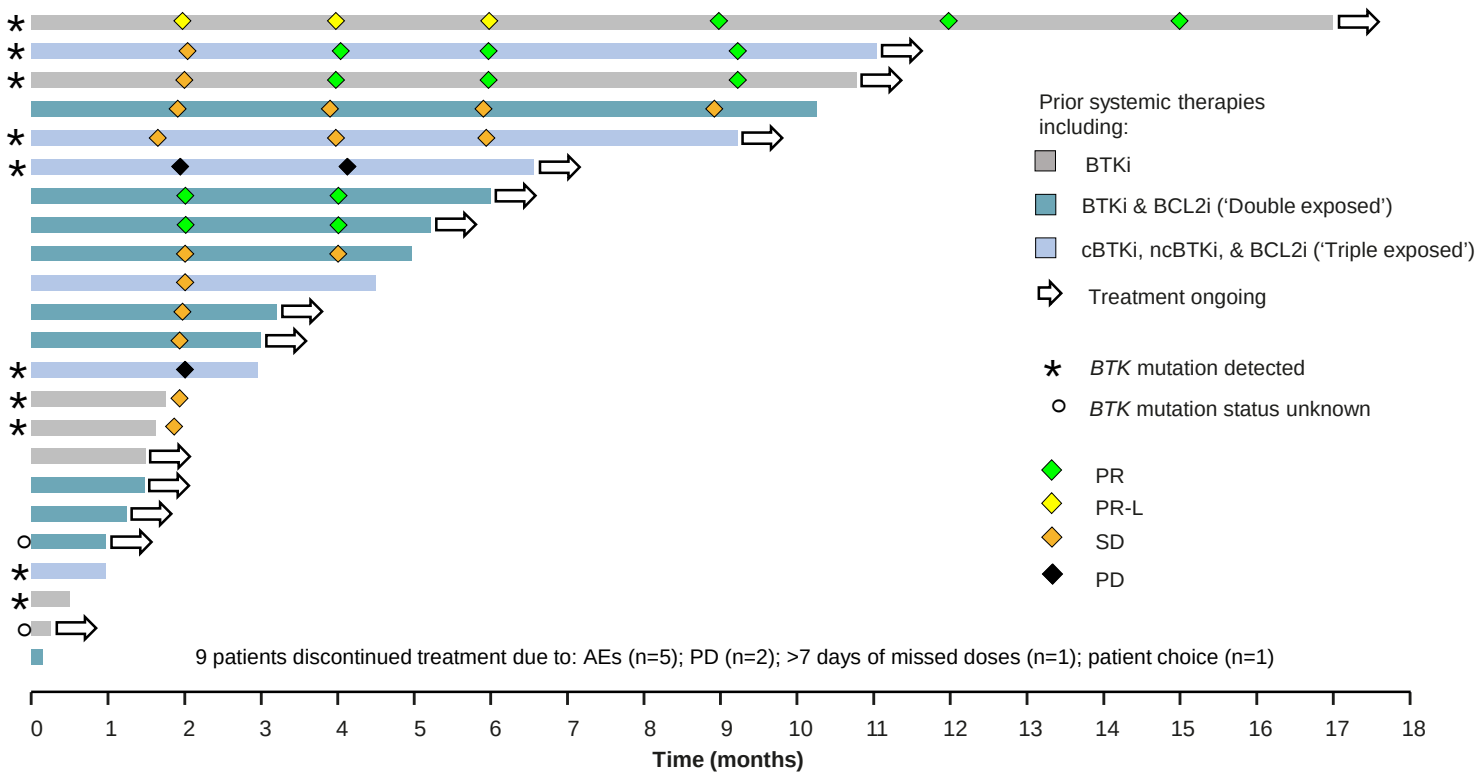
Outcomes and time on therapy with NX-2127 (patients with CLL): Responses seen in double and triple exposed patients



Data cutoff: September 21, 2022

Mato A, et al. ASH annual mtg 2022

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Study Design: EPCORE CLL-1 Expansion Cohort

Key inclusion criteria

- CD20^{+} R/R CLL
- ≥2 prior lines of systemic therapy, including treatment with or intolerance to a BTK inhibitor
- ECOG PS 0–2
- Requiring treatment per iwCLL criteria
- Measurable disease with ≥5×10^{9}/L B lymphocytes or measurable lymphadenopathy or organomegaly
- No minimum life expectancy required

Median follow-up: 12.1 mo (range, 0.1+ to 19.2)

R/R CLL expansion, N=23 (fully enrolled)

Step-up dosing[a]

Epcoritamab SC[b]
RP2D 48 mg

QW C1–3
Q2W C4–9
Q4W C10+

→

Efficacy assessment[c] by CT/MRI obtained Q8W through C6, and Q24W thereafter

→

Treatment until disease progression

- **Primary endpoint:** Overall response rate (ORR)
- **Key secondary endpoints:** Complete response (CR) rate, time to response, safety/tolerability, and measurable residual disease (MRD) in PBMCs using the clonoSEQ next-generation sequencing (NGS) assay

Data cutoff: July 5, 2023. Epcoritamab was administered in 28-d cycles. [a]Patients received epcoritamab SC with step-up dosing (ie, 0.16 mg priming and 0.8 mg intermediate doses before first full dose) and corticosteroid prophylaxis as previously described to mitigate CRS. [b]To ensure patient safety and better characterize CRS, inpatient monitoring was required for the first 4 doses of epcoritamab. [c]Based on iwCLL guidelines. PBMCs, peripheral blood mononuclear cells.

Kater A, et al. iwCLL conference 2023

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Patient Characteristics and Treatment History

Characteristic	Total N=23
Median age, y (range)	72 (55–83)
Male, n (%)	17 (74)
CLL characteristic, n (%)	
IGHV unmutated[a]	16 (70)
TP53 aberrations[b]	15 (65)
Lab abnormalities at baseline, n (%)	
Thrombocytopenia	21 (91)
Anemia	20 (87)
Neutropenia	3 (13)
Beta-2 microglobulin >3.5 mg/L	18 (78)

Treatment History	Total N=23
Median time from initial diagnosis to first dose, y (range)	13 (5.5–19.5)
Median number of prior lines of therapy (range)	**4 (2–10)**
≥4 prior lines of therapy, n (%)	15 (65)
Prior therapy, n (%)	23 (100)
Chemoimmunotherapy	23 (100)
Small molecules	23 (100)
BTK inhibitor	23 (100)
Discontinuation due to progression	17 (74)
BCL-2 inhibitor	19 (83)
Discontinuation due to progression	11 (58)
Relapsed <12 months from last dose	4 (21)
CAR T-cell therapy	1 (4)
Median time from last treatment to first dose, mo (range)	1.0 (0.1–49.4)

Prior therapies and key CLL characteristics reflect a high-risk R/R CLL patient population

Data for CLL characteristics were obtained from local laboratories. [a]*IGHV* status mutated for 4 patients and unknown for 3 patients. [b]*TP53*/del17p status unmutated/negative for 6 patients and unknown for 2 patients.

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High Overall and Complete Response Rates

Response, n (%)[a]	Total Efficacy Evaluable n=21	*TP53* Aberration n=14	Double-Exposed[b] n=17	*IGHV* Unmutated n=15
Overall response[c]	**13 (62)**	**9 (64)**	**9 (53)**	**9 (60)**
Complete response	7 (33)	4 (29)	5 (29)	6 (40)
Partial response	6 (29)	5 (36)	4 (24)	3 (20)
Stable disease	4 (19)	2 (14)	4 (24)	3 (20)
Progressive disease	1 (5)	1 (7)	1 (6)	1 (7)

Encouraging overall and complete response rates observed, including in difficult-to-treat, high-risk R/R CLL patients

Three patients were not evaluable or had no assessment, including 2 patients who died without postbaseline assessment. [a]Based on response-evaluable population, defined as patients who received ≥1 full dose of epcoritamab, had ≥1 postbaseline response evaluation, or died within 60 d of first dose. [b]Patients previously treated with both a BTK inhibitor and a BCL-2 inhibitor. [c]Response assessment according to iwCLL criteria.

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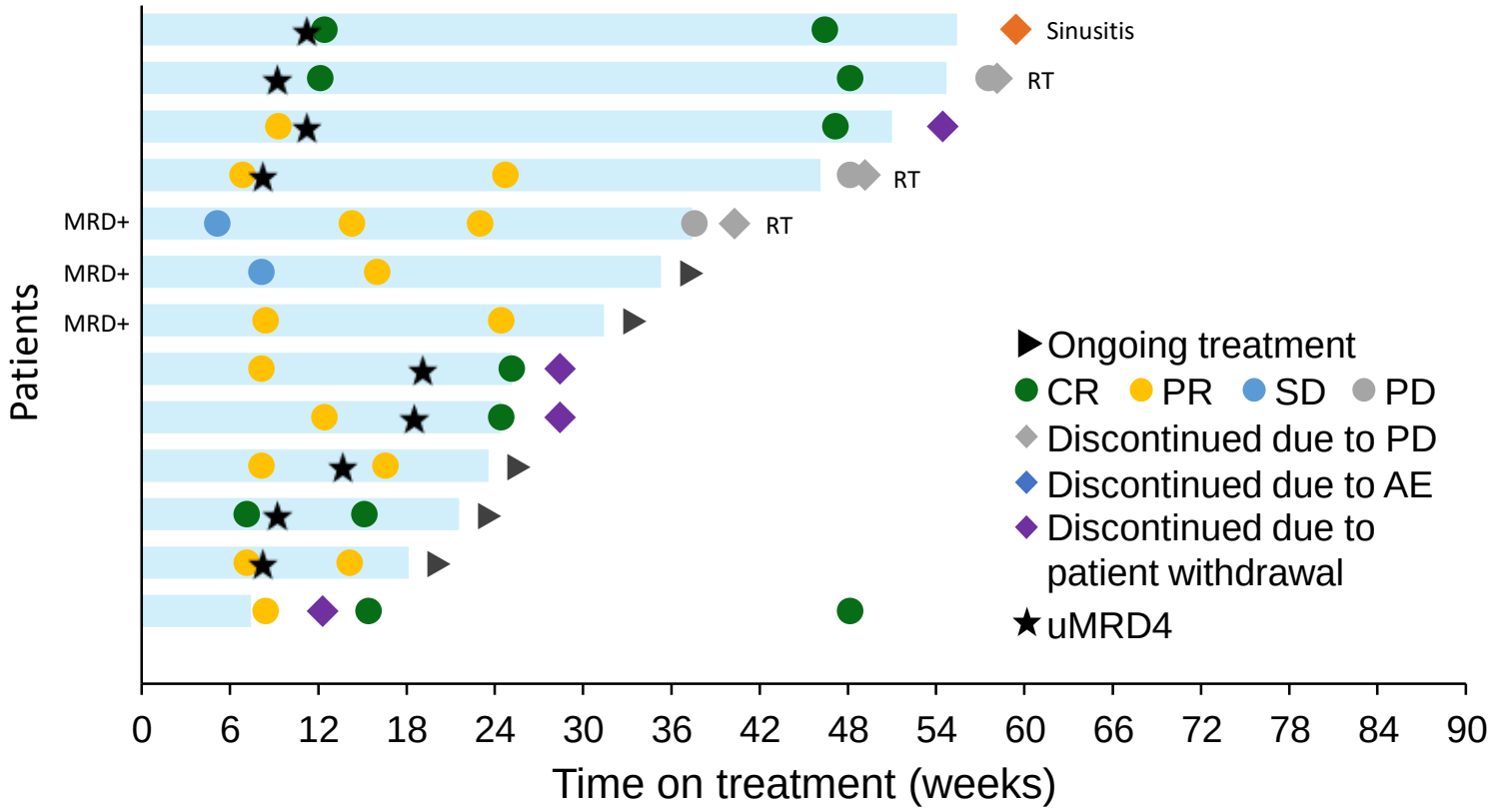
Depth and Duration of Response



	Assessed for MRD n=12
Patients with uMRD4,[a,b] n/n (%)	9/12 (75)
CR with uMRD4	6/6
PR with uMRD4	3/6
MRD-positive patients,[a] n/n (%)	3/12 (25)
> uMRD4 to uMRD2	1/3
MRD > uMRD2	2/3

MRD was evaluated in PBMCs using the clonoSEQ next-generation sequencing assay. [a]Among responders who were tested for MRD. [b]Eight of 12 patients had uMRD6.

uMRD4 was achieved by most responders, including all patients with CR who were tested for MRD

Median follow-up, mo (range): 12.1 (0.1+ to 19.2). Median number of treatment cycles initiated (range): 5 (1–14). Median duration of treatment, mo (range): 5.0 (0.03–12.7). RT, Richter's transformation; uMRD, undetectable MRD.

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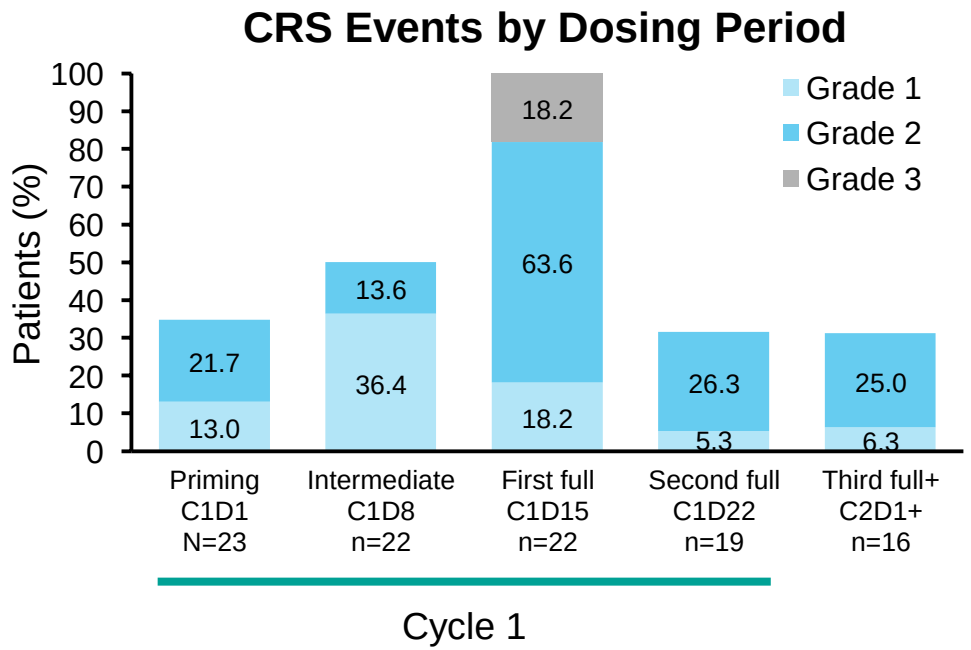
AEs of Special Interest

CRS[a]	Total, N=23
Median time to onset after first full dose, h (range)	7.3 (1–99)
Median time to resolution, d (range)[b]	3 (1–16)
Treated with tocilizumab, n (%)	19 (83)
CRS resolution, n/n (%)	22/22 (100)



ICANS & Clinical Tumor Lysis Syndrome	Total, N=23
ICANS, n (%)[c]	**3 (13)**
Grade 1	1 (4)
Grade 2	2 (9)
Median time to resolution, d (range)	3 (3–4)
ICANS resolution, n/n (%)	3/3 (100)
Tumor lysis syndrome, n (%)	**1 (4)**
Laboratory only	0
Clinical – grade 2	1 (4)
Time to resolution, d	11
Clinical tumor lysis syndrome resolution, n/n (%)	1/1 (100)

- CRS occurrence was predictable, with most cases following the first full dose
- No AEs of special interest led to discontinuation, and all resolved

[a]Graded by Lee et al 2019 criteria. [b]Median is Kaplan–Meier estimate based on longest CRS duration in patients with CRS. [c]All ICANS events occurred with grade 2 CRS.

Kater A, et al. iwCLL conference 2023

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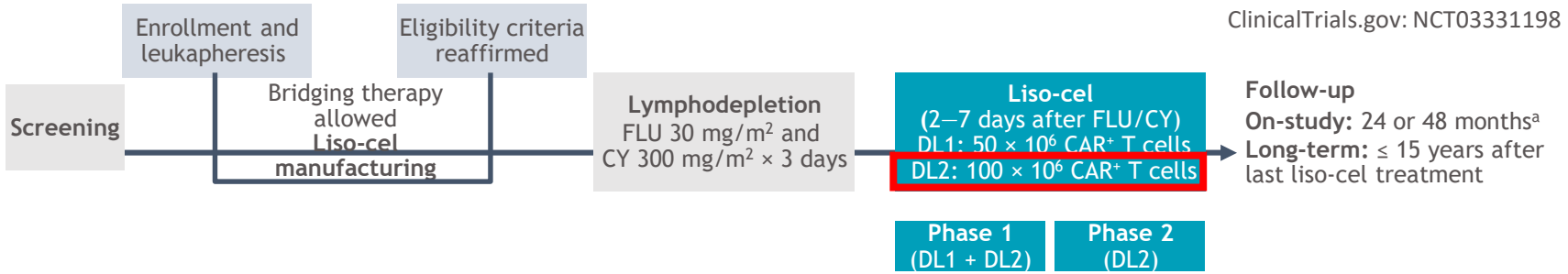
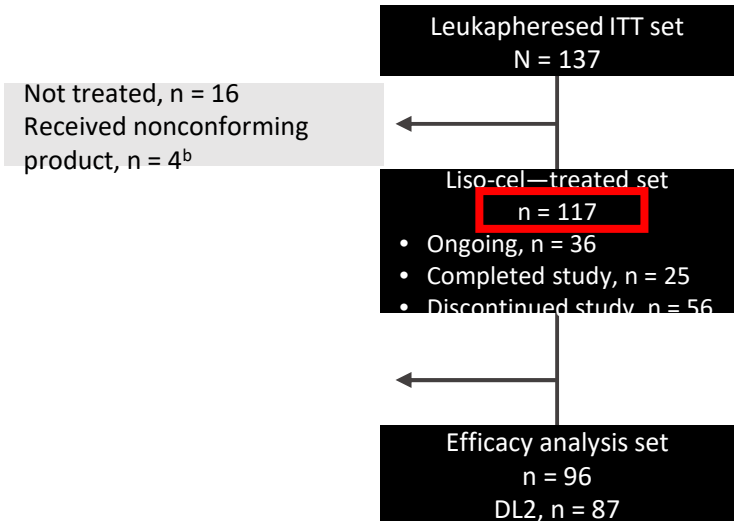
TRANSCEND CLL 004: Ph 1/2, open-label, multicenter study

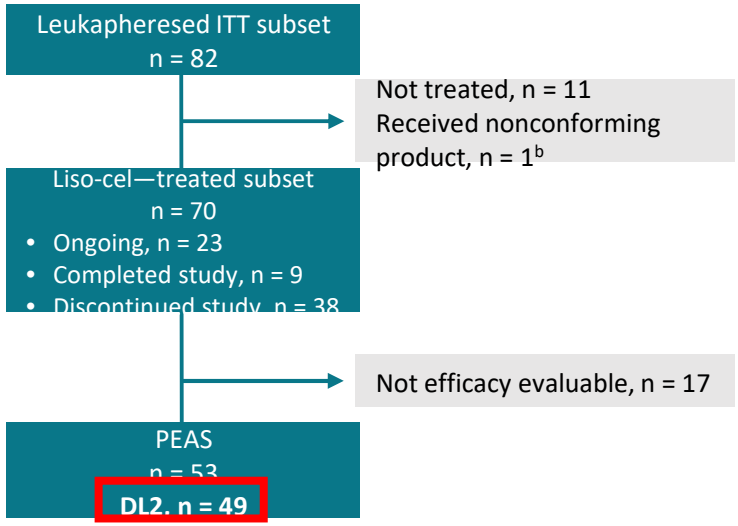


ClinicalTrials.gov: NCT03331198

Full study population



BTKi progression/venetoclax failure[a] subset



- 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 ($H_0 \leq 5\%$)

Siddiqi T, et al. ASCO 2023 and ICML 2023

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Demographics and baseline characteristics

Characteristic	Full study population (n = 117)	BTKi progression/venetoclax failure subset (n = 70)
Median (range) age, y	65.0 (49—82)	66.0 (49—78)
Median (range) prior lines of systemic therapy	5 (2—12)	5 (2—12)
Bulky lymph nodes,[a] n (%)		
Yes	52 (44)	32 (46)
Unknown	9 (8)	8 (11)
High-risk cytogenetics, n (%)	97 (83)	60 (86)
Prior BTKi, n (%)	117 (100)	70 (100)
BTKi refractory[b]	103 (88)	70 (100)
BTKi relapsed[c]	2 (2)	0
BTKi intolerant only	12 (10)	0
Prior venetoclax, n (%)	94 (80)	70 (100)
Venetoclax refractory[b]	89 (76)	67 (96)
Venetoclax relapsed[c]	0	0
Venetoclax intolerant only	4 (3)	3 (4)
Prior BTKi and venetoclax, n (%)	94 (80)	70 (100)
BTKi progression/venetoclax failure,[d] n (%)	70 (60)	70 (100)
Received bridging therapy, n (%)	89 (76)	55 (79)

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Efficacy outcomes

Efficacy	Full study population at DL2 (n = 87)	BTKi progression/venetoclax failure subset at DL2 (n = 49)
Primary endpoint: IRC-assessed CR/CRi rate (95% CI) per iwCLL 2018, %	18 (11—28)	**18 (9—32); *P* = 0.0006[a]**
Key secondary endpoints		
IRC-assessed ORR (95% CI), %	47 (36—58)	43 (29—58); *P* = 0.3931[a]
uMRD rate in blood (95% CI), %	64 (53—74)	63 (48—77)[b]
Exploratory endpoint: uMRD rate in marrow (95% CI), %	59 (48—69)	59 (44—73)
Other secondary endpoints		
Best overall response, n (%)		
CR/CRi	16 (18)	9 (18)
PR/nPR	25 (29)	12 (24)
SD	34 (39)	21 (43)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Median (range) time to first response, months	1.5 (0.8—17.4)	1.2 (0.8—17.4)
Median (range) time to first CR/CRi, months	4.4 (1.1—17.9)	3.0 (1.1—6.1)

- **All MRD-evaluable responders were uMRD in blood and marrow** and 12 of 20 MRD-evaluable patients with SD were uMRD in blood; majority of patients achieved uMRD by day 30

Siddiqi T, et al. ASCO 2023 and ICML 2023

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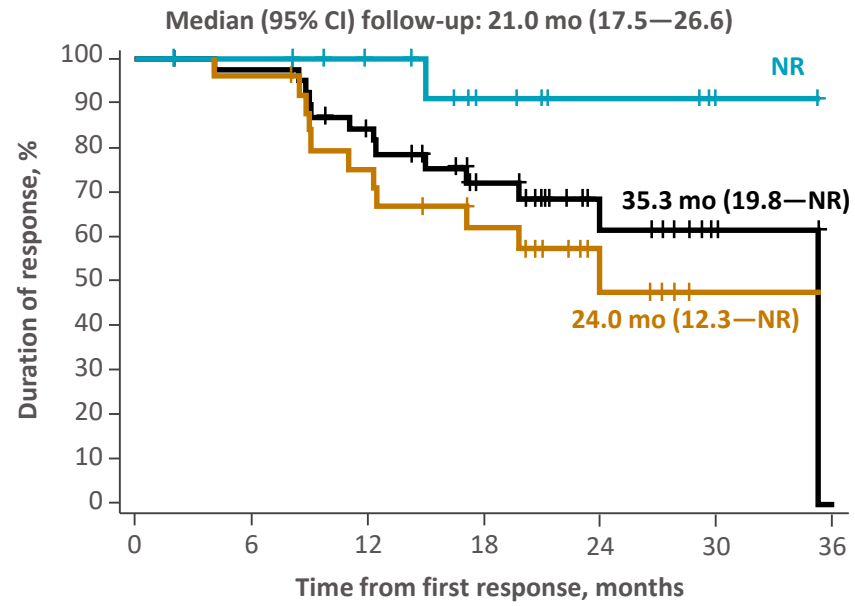
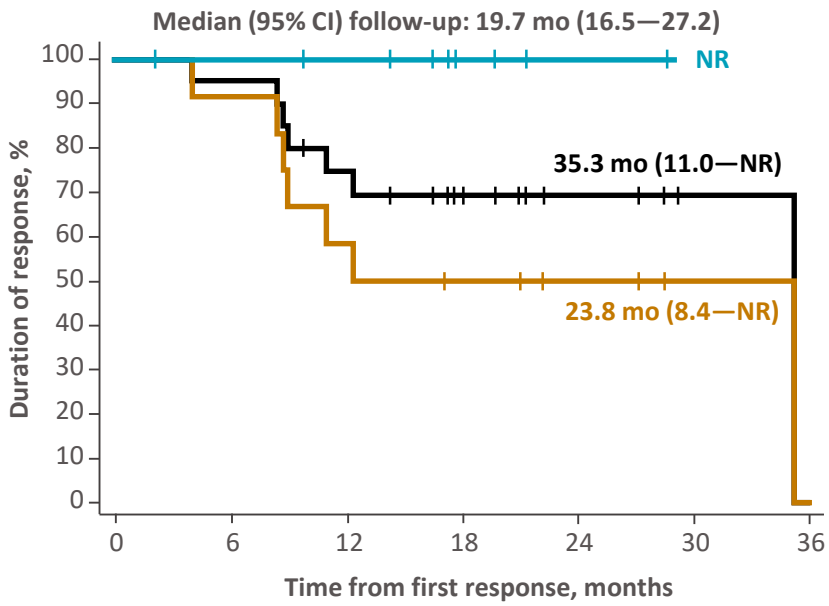
Duration of response by best overall response

(A) Full study population at DL2 (n = 87)



No. at risk							
CR/CRi	16	15	12	7	4	2	0
PR/nPR	25	24	18	13	5	1	0
Responder	41	39	30	20	9	3	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 49)



CR/CRi	9	8	7	3	1	0	0
PR/nPR	12	11	7	5	3	1	0
Responder	21	19	14	8	4	1	0

Data on Kaplan-Meier curves are expressed as median (95% CI, if available). NR, not reached.

Siddiqi T, et al. ASCO 2023 and ICML 2023

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Safety: TEAEs, AESIs, and management of CRS and NEs

- The most common grade ≥ 3 TEAEs (≥ 40%) were neutropenia (61%), anemia (52%), and thrombocytopenia (41%)

Patients with CRS and Nes	Full study population (n = 117)
CRS,[a] n (%)	99 (85)
Grade 1/2	43 (37)/46 (39)
Grade 3	10 (9)
Grade 4/5	0
Median (range) time to onset/resolution, days	4.0 (1—18)/6.0 (2—37)
NE,[b] n (%)	53 (45)
Grade 1/2	13 (11)/18 (15)
Grade 3	21 (18)
Grade 4	1 (1)
Grade 5	0
Median (range) time to onset/resolution, days	7.0 (1—21)/7.0 (1—83)

- 81 (69%) patients received tocilizumab and/or corticosteroids for management of CRS and/or NEs

Other AESIs, n (%)	Full study population (n = 117)
Prolonged cytopenia[c]	63 (54)
Grade ≥ 3 infections[d]	20 (17)
Hypogammaglobulinemia[e]	18 (15)
Tumor lysis syndrome	13 (11)
Second primary malignancy[e]	11 (9)
Macrophage activation syndrome	4 (3)

- 5 deaths due to TEAEs were reported
  - 4 considered unrelated to liso-cel by investigators (respiratory failure, sepsis, *Escherichia coli* infection, and invasive aspergillosis)
  - 1 considered related to liso-cel by investigators (macrophage activation syndrome)

Siddiqi T, et al. ASCO 2023 and ICML 2023

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Overall Conclusions

- Explosion of novel therapies for CLL in recent years, including monoclonal and bispecific antibodies, small molecule inhibitors of various kinases (like BTK and PI3K) and the antiapoptotic pathway (especially Bcl2), BTK degraders, as well as CD19-specific CAR-T cells

- These novel, non-chemotherapeutic agents seem to have done away with the need for standard chemoimmunotherapy in CLL

- Combination studies are underway to improve outcomes further and find a cure

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Thank you for your attention!

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