

Fixed-Duration Frontline Therapy in CLL: Are Two Drugs Enough?

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Evolution of CLL Treatment Landscape

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1960

S

Alkylating Agents

- Chlorambucil
- Cyclophosphamide

1970

S

Purine Nucleosides

- Fludarabine
- Pentostatin

1980

S

1990

S

Purine Nucleosides and Alkylators

2000

S

- CIT (FCR, BR)
- Alemtuzumab
- Lenalidomide

2014 Marked a New Era of CLL Therapy

- **BCL-2 inhibitor** (Venetoclax)
- **Novel CD20 mAb** (Obinutuzumab)
- **BTK inhibitors** (Ibrutinib, Acalabrutinib)
- **PI3K inhibitors** (Idelalisib, Duvelisib)

2023

Novel BTK inhibitors
(Zanubrutinib, Pirtobrutinib)

2024

CD19 CAR T (Liso-cel)

2025+

BTK degraders, novel CD20 BsAbs, novel BCL2i, novel BTKi, etc...

FD Ibrutinib + Venetoclax:

- First approval: EU, August 2022
- Approved in 78 countries (as of 2025)
- Off-label in the United States per NCCN Guidelines

Suggested Frontline Therapy

Preferred Regimens per NCCN Guidelines*

BCL2i-containing regimens

- **Venetoclax/Acalabrutinib +/- Obinutuzumab** (fixed duration)(category 1)
- **Venetoclax + Obinutuzumab** (fixed duration)(category 1)

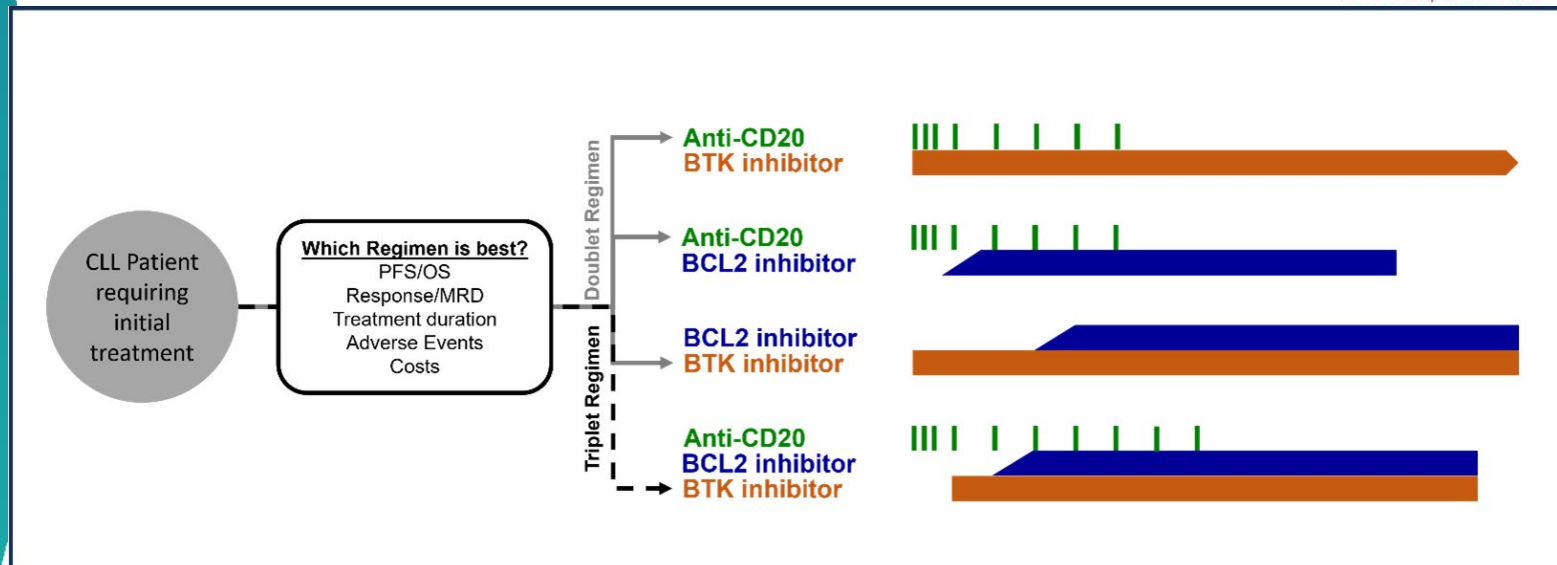
cBTKi-based regimens

- **Acalabrutinib (continuous) +/- Obinutuzumab** (category 1)
- **Zanubrutinib (continuous)**(category 1)



FDA Approves Combo of Acalabrutinib and Venetoclax in CLL

February 21, 2026



*NCCN Guidelines, Chronic Lymphocytic Leukemia, Version 2.2026

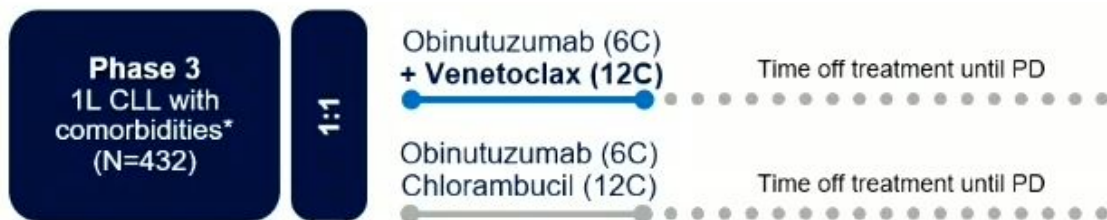
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Rogers K.A., Woyach J.A, Hematology 2024.

Pivotal Frontline Trials of Fixed-Duration Therapy

CLL14

Older / with comorbidities

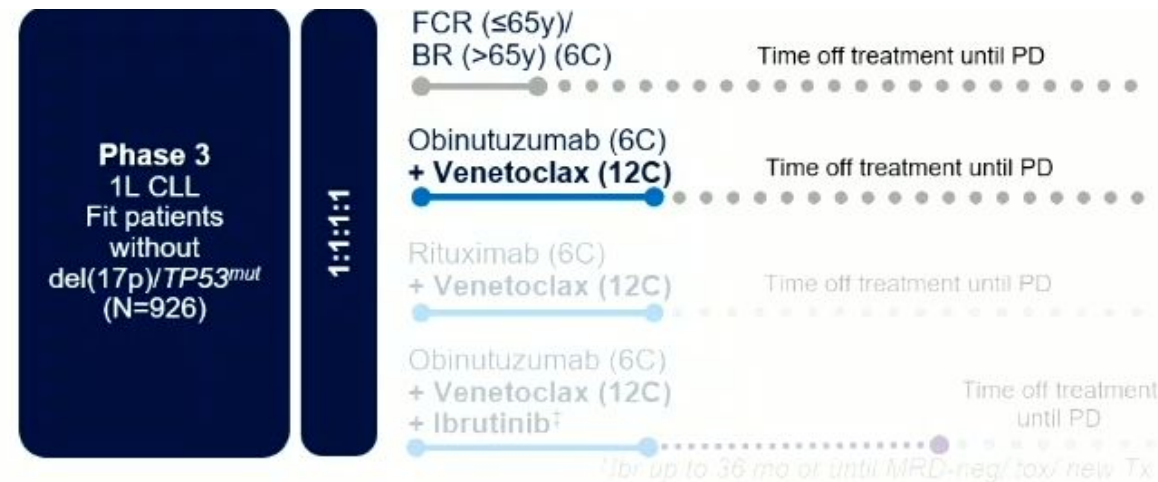


*CIRS score >6 and/or
ClCr <70mL/min

	mIGHV	No del(17p)	WT TP53
VO (n=216)	38.0%	91.5%	88.9%
OC1b (n=216)	39.9%	92.7%	91.7%

CLL13

Fit, No del(17p)/TP53



	mIGHV	No del(17p)	WT TP53
VO (n=229)	39.0%		
CIT (n=229)	41.5%	100%	100%

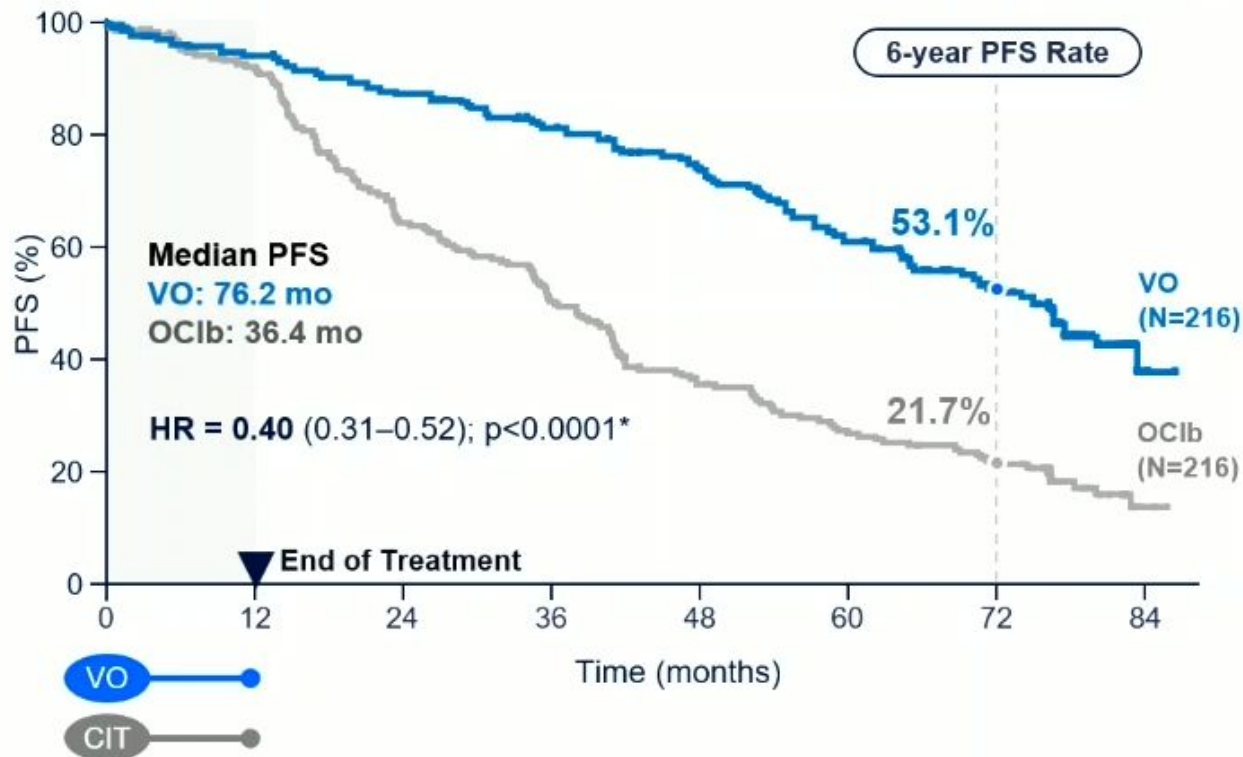
PFS with Fixed-Duration VO

CLL14

Older / with comorbidities

PFS (median follow-up: 76.4 months)

ITT

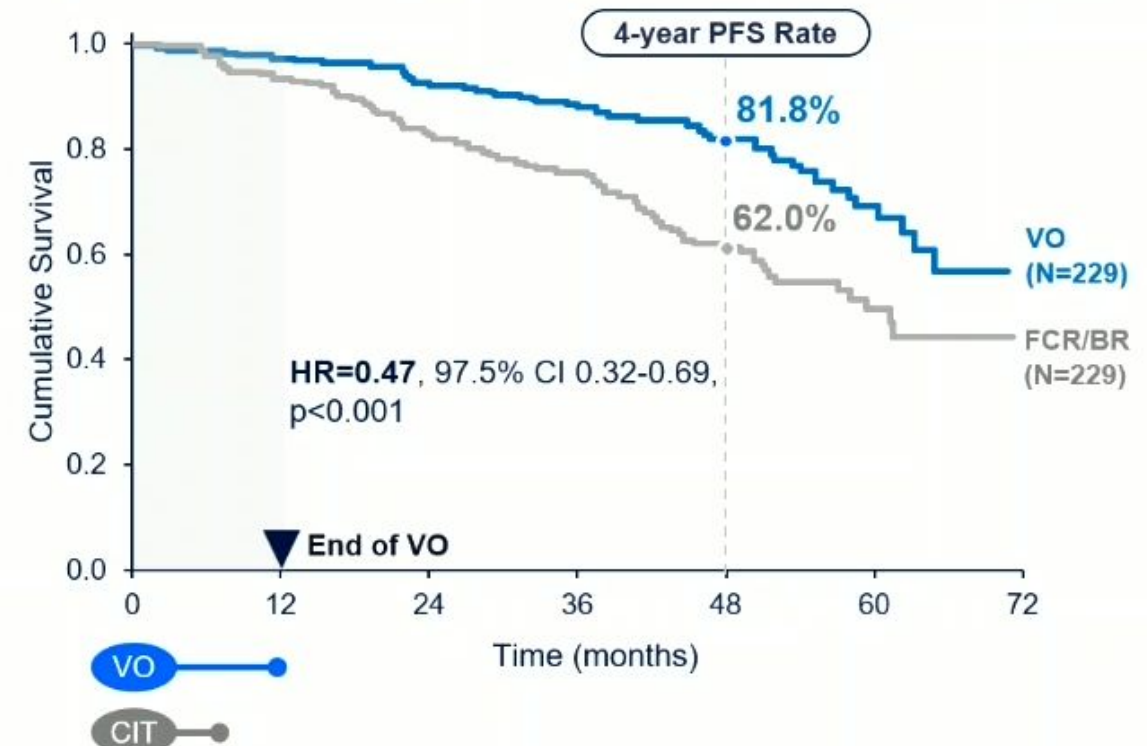


CLL13

Fit, No del(17p)/TP53

PFS (median follow-up: 50.7 months)

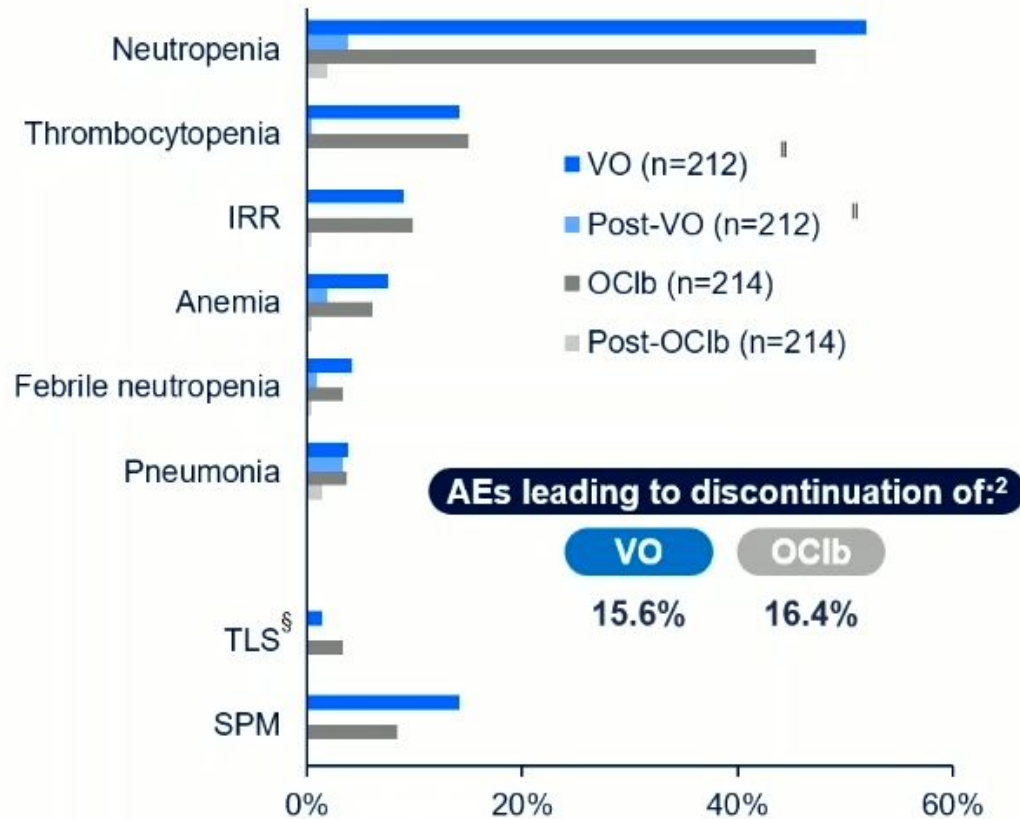
ITT



Safety with Fixed-Duration VO

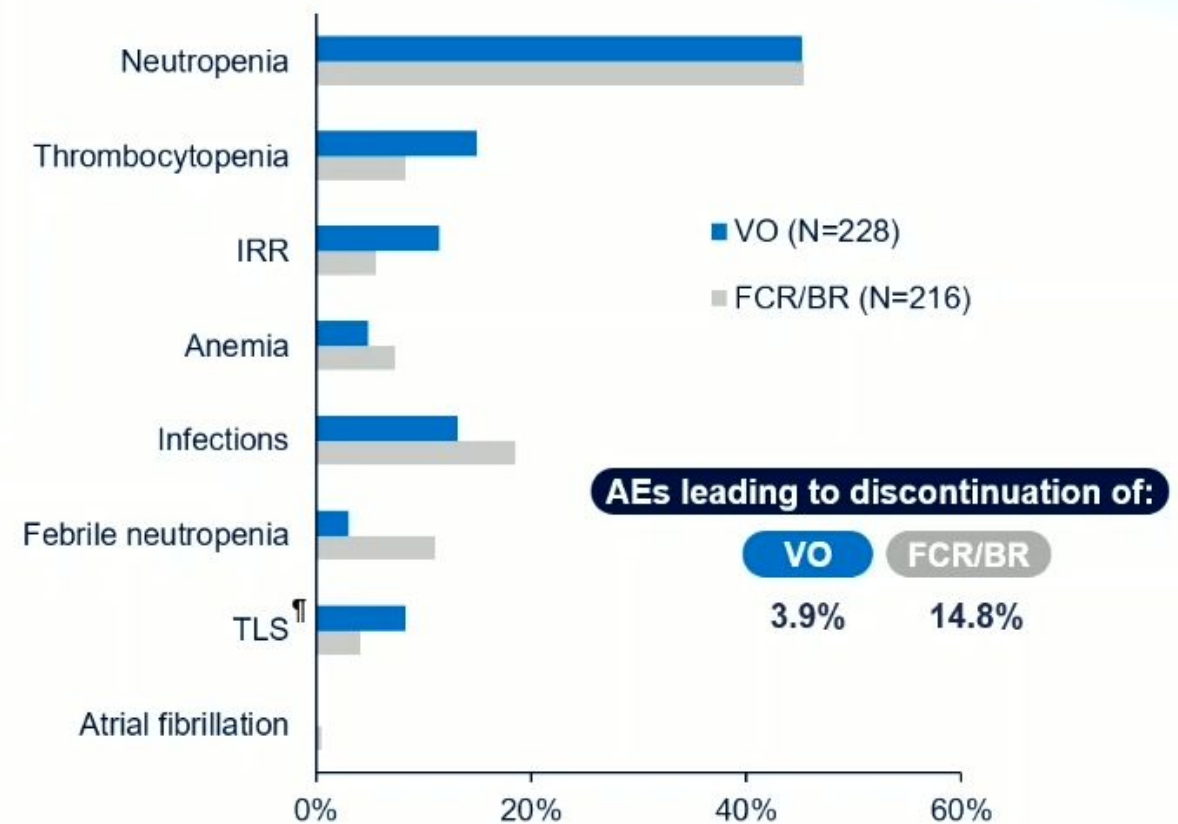
CLL14

Older / with comorbidities



CLL13

Fit, No del(17p)/TP53



AMPLIFY – Study Design

TN CLL (N=867)

Key inclusion criteria

- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria¹
- Without del(17p) or TP53
- 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

NCT03836261. Data cutoff: April 30, 2024.

*FCR/BR administered in cycles 1 to 6.

AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CIRS-Geriatric, Cumulative Illness Rating Scale-Geriatric; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; FCR, fludarabine-cyclophosphamide-rituximab; IGHV, immunoglobulin heavy-chain variable region gene; IRC, independent review committee; iwCLL, International Working Group on CLL; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TN, treatment-naïve; uMRD, undetectable measurable residual disease.

1. Hallek M. et al. *Blood*. 2018;131:2745-60.

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

RANDOMIZE 1:1:1

AV (14 cycles)

AVO (14 cycles)

FCR/BR^a (6 cycles)

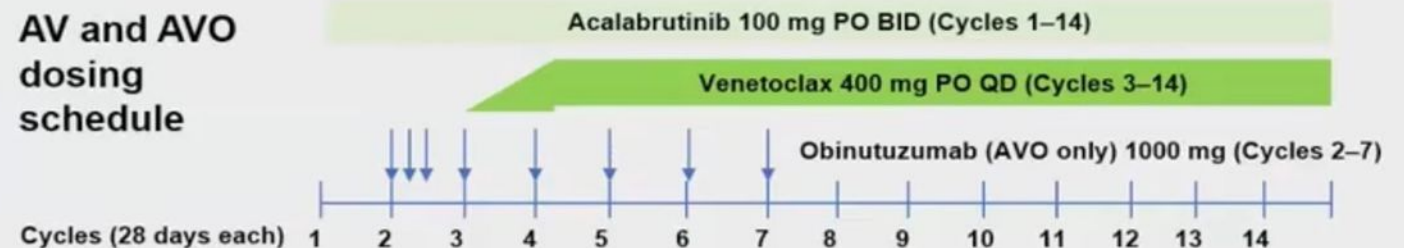
Crossover was not allowed

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)

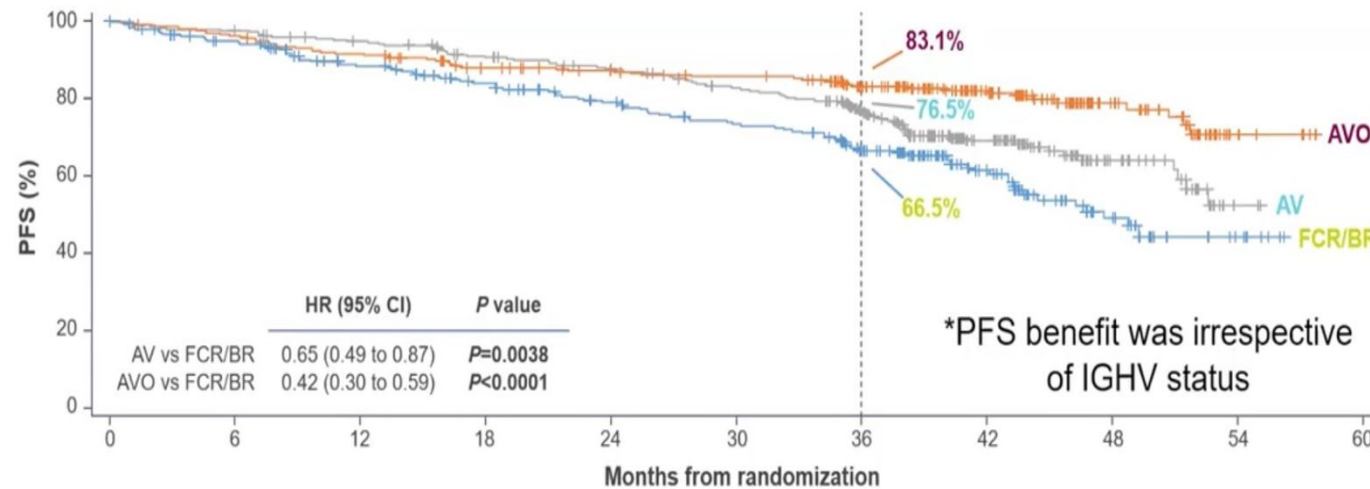
AV and AVO dosing schedule



Abstract #1009

Jennifer Brown, ASH 2024

AMPLIFY – PFS Assessed by BICR and OS



Patient at risk										
AV	291	282	269	251	237	219	177	102	35	3
AVO	286	272	258	237	225	219	191	116	51	7
FCR/BR	290	236	208	189	170	154	127	66	28	6

Median PFS was NR for AV and AVO, and was 47.6 mo for FCR/BR

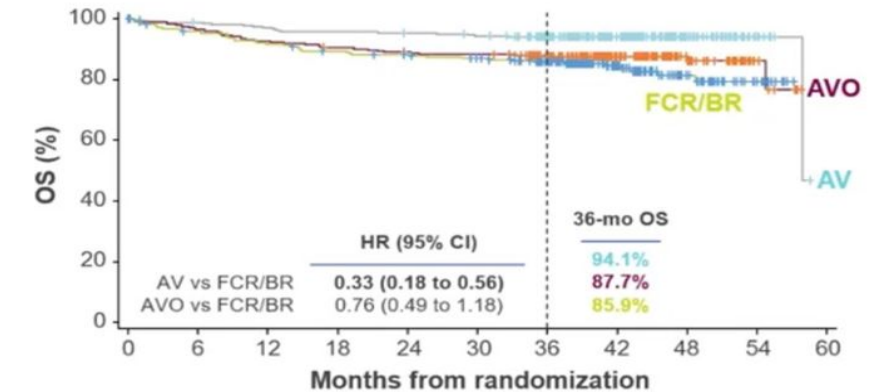
uMRD rates ($<10^{-4}$) in peripheral blood at EOT (evaluative patients): 45.0% (AV), 95.0% (AVO), 72.9% (FCR/BR)

PFS was assessed by IRC; median follow-up from randomization: 40.8 months (range, 0–59 months).

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

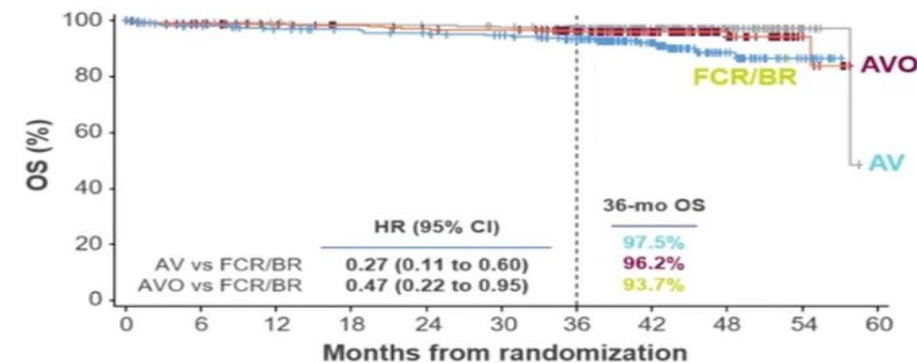
AV, acalabrutinib-venetoclax; AVO, acalabrutinib-venetoclax-obinutuzumab; BR, bendamustine-rituximab; CI, confidence interval; EOT, end of therapy; FCR, fludarabine-cyclophosphamide-rituximab; HR, hazard ratio; NR, not reached; IRC, independent review committee; PFS, progression-free survival; uMRD, undetectable measurable residual disease.

With AV vs FCR/BR (ITT)



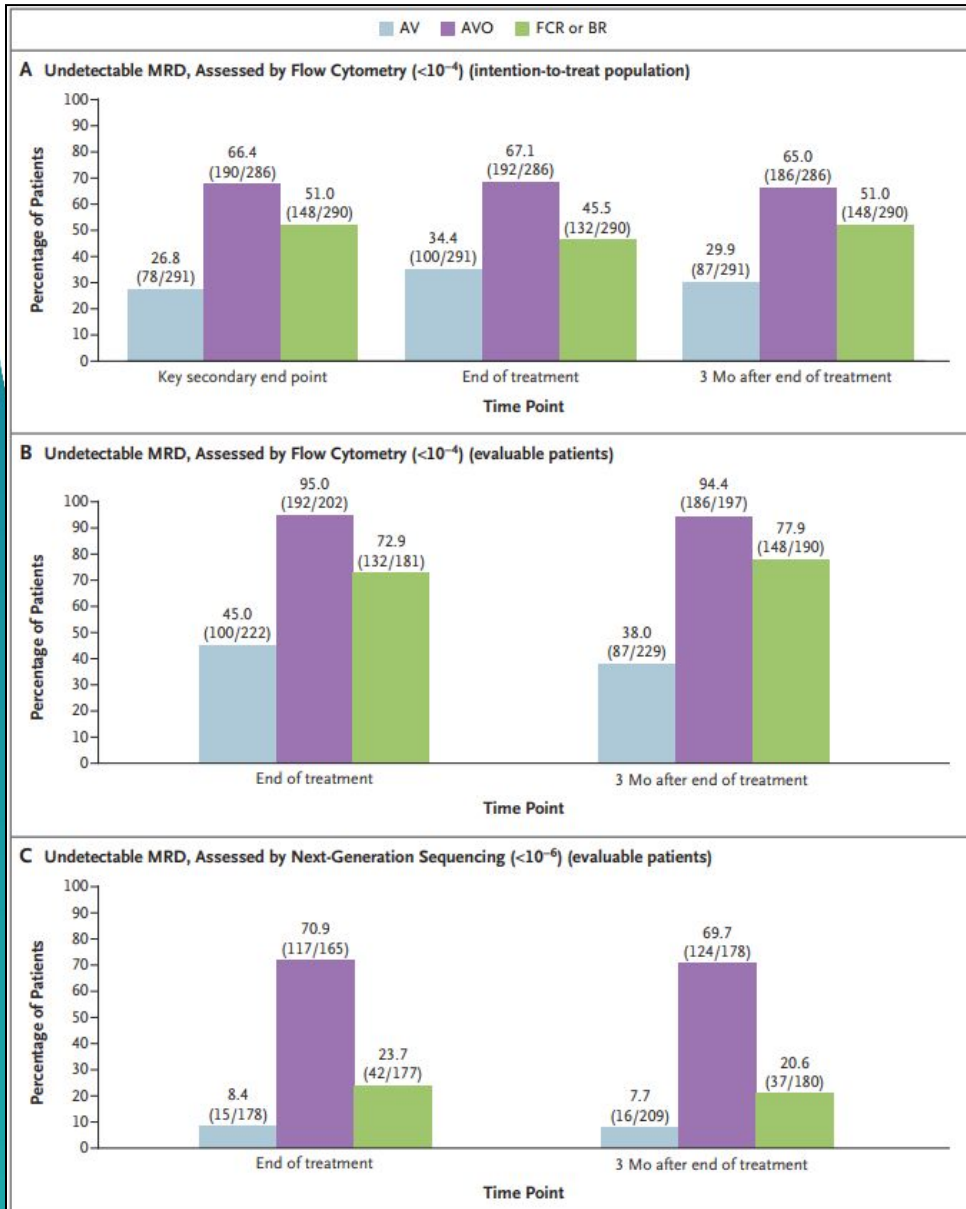
Patient at risk										
AV	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	64	10
FCR/BR	290	247	236	228	223	217	182	98	45	13

With AV and AVO vs FCR/BR (COVID-19 Deaths Censored)



Patient at risk										
AV	291	286	281	277	275	270	233	142	58	10
AVO	286	276	265	257	252	250	223	143	64	10
FCR/BR	290	247	236	228	223	217	182	98	45	13

MRD Responses □ Depth Matters, but Context is Key



Despite lower MRD rates, the doublet achieved 76.5% PFS at 36 mo

Supporting evidence from FLAIR trial (MRD-guided therapy):

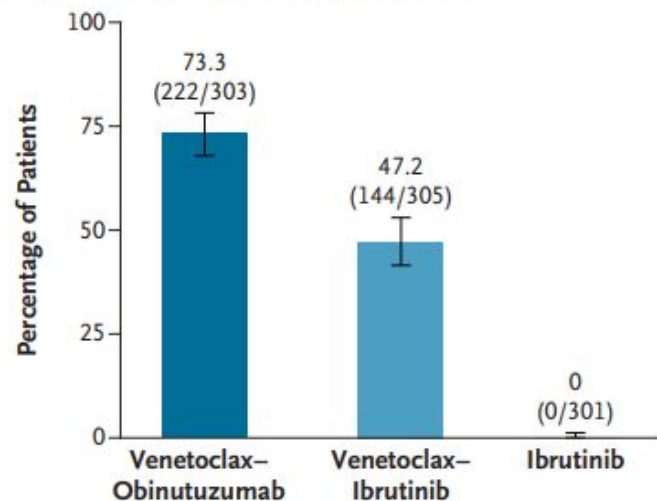
- 47.5% uMRD at 12 months.
- 92.7% uMRD with continued therapy
- 5-year PFS: 93.9%

AMPLIFY – Safety Profile

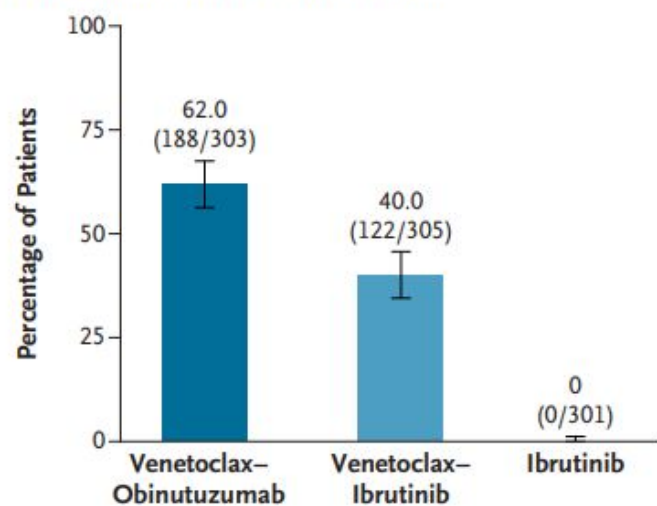
Adverse Event	Grade ≥ 3		
	AV (%)	AVO (%)	Chemoimmunotherapy (%)
Any event of clinical interest	46.7	66.2	54.4
Atrial fibrillation	0.3	0.7	0.8
Major hemorrhage	1.0	2.1	0.4
Neutropenia	32.3	 46.1	43.2
Infection	12.4	 23.6	10.0
TLS	0.3	0.4	3.1
Any serious AE	24.7	38.4	27.4
AE leading to treatment discontinuation	7.9	 20.1	10.8
Serious AE leading to death	3.4	6.0	3.5

CLL 17

A Undetectable MRD in Peripheral Blood



B Undetectable MRD in Bone Marrow



Patients with
previously
untreated CLL

1:1:1
randomization
Stratification
according to fitness,
del17p/TP53, IGHV



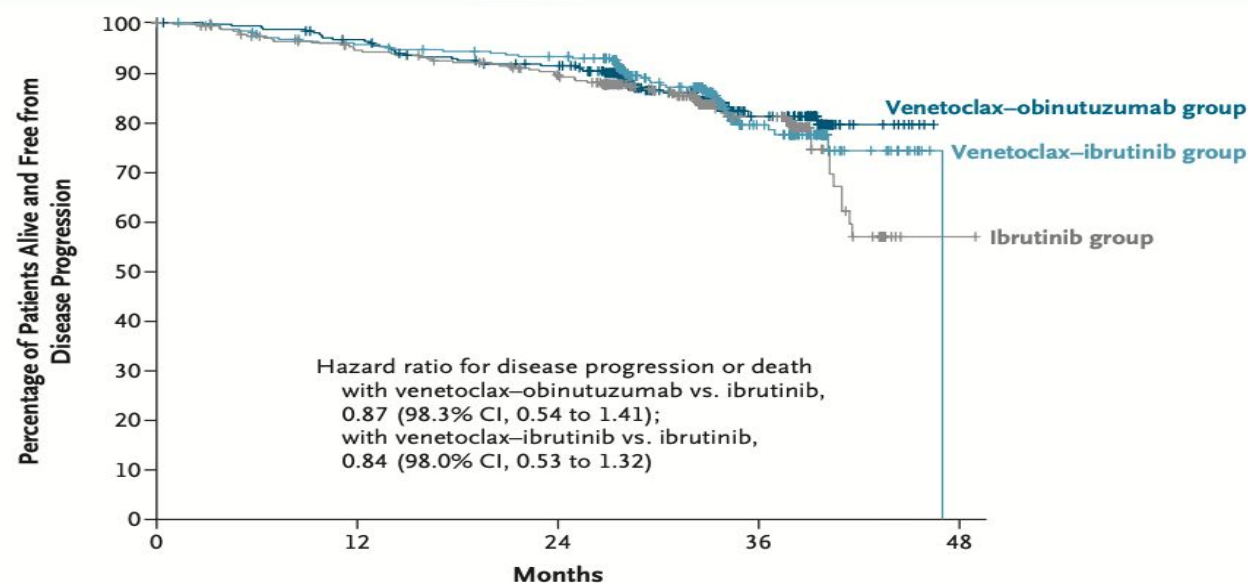
Ibrutinib 420 mg po daily until PD



Venetoclax 400 mg po daily (c1 d22 – c12)
Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c 2-6 d1)



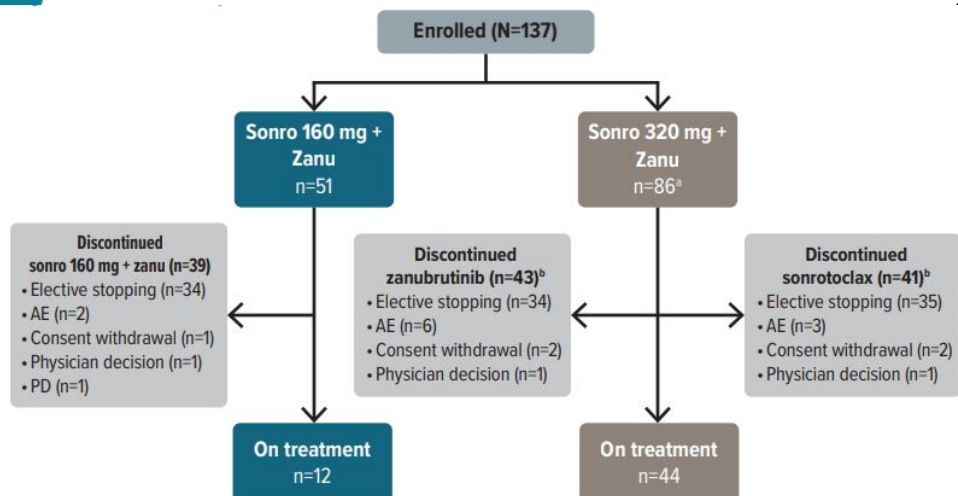
Venetoclax 400 mg po daily (c4 d1 – c15)
Ibrutinib 420 mg po daily (c1 d1 – c15)



No. at Risk

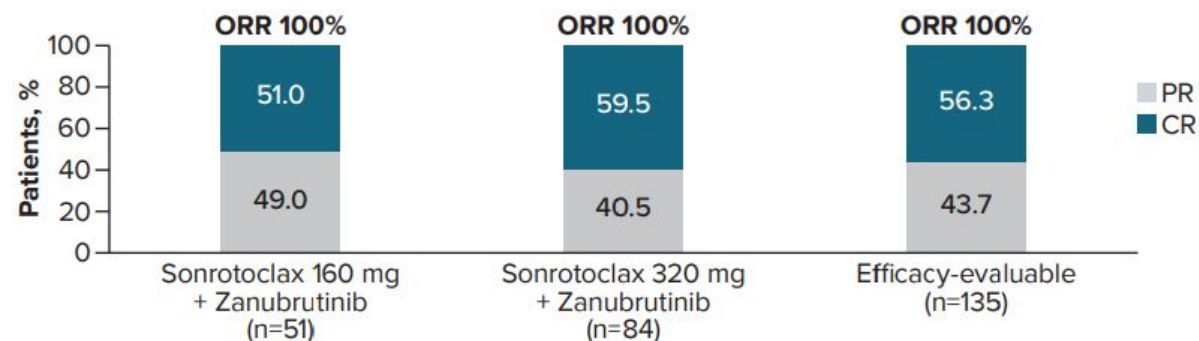
Venetoclax-obinutuzumab	303	278	256	77	0
Venetoclax-ibrutinib	305	278	267	82	0
Ibrutinib	301	267	243	94	1

All-Oral Combination of Sonrotoclax and Zanubrutinib



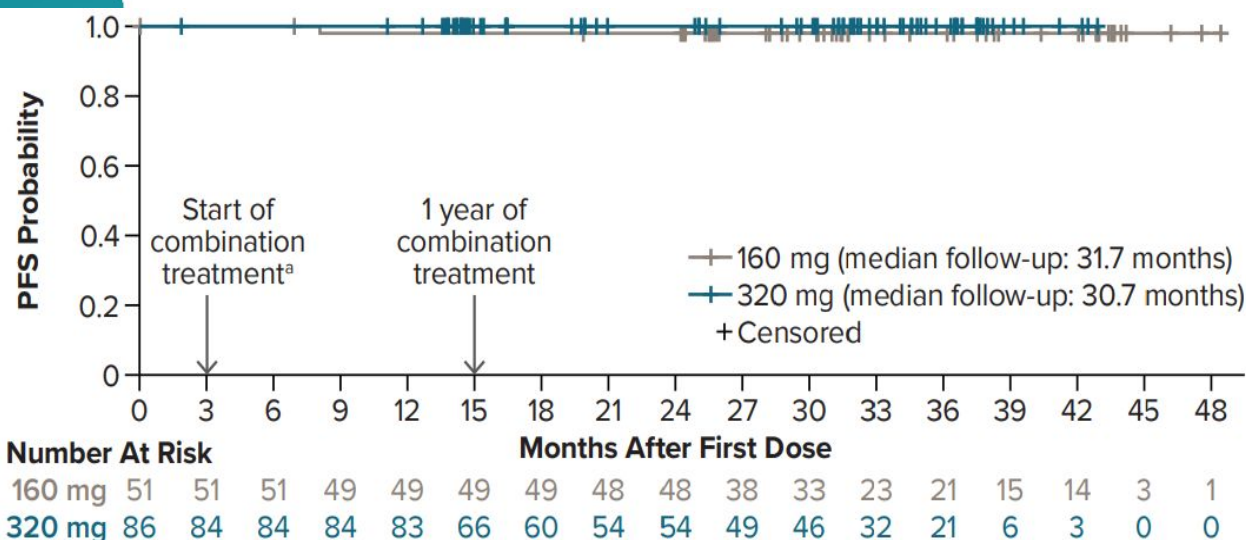
^aOne patient received zanubrutinib but had not received sonrotoclax treatment. ^bIn the 320-mg cohort, 43 participants discontinued any study drug (sonrotoclax and/or zanubrutinib). Per-drug numbers differ due to one patient who did not receive sonrotoclax and one who discontinued only zanubrutinib.

Abbreviations: AE, adverse event; PD, progressive disease; sonro, sonrotoclax; zanu, zanubrutinib.



Treatment-Emergent Adverse Events and Safety Data

	Sonro 160 mg + Zanu (n=51)	Sonro 320 mg + Zanu (n=86) ^a	All Patients (N=137)
Patients, n (%)			
Any TEAEs	51 (100.0)	85 (98.8)	136 (99.3)
Grade ≥3	35 (68.6)	52 (60.5)	87 (63.5)
Serious TEAEs	20 (39.2)	27 (31.4)	47 (34.3)
Leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of zanu	2 (3.9)	6 (7.0)	8 (5.8)
Treated with sonro			
Leading to discontinuation of sonro	2 (3.9)	3 (3.5)	5 (3.6)
Relative dose intensity of sonro, median, %	98.9	99.0	99.0
Duration of exposure, median (range), mo	29.1 (5.8-48.8)	26.2 (0.8-45.2)	26.7 (0.8-48.8)



^aZanubrutinib lead-in was 8-12 weeks.

Summary

- Fixed-duration therapy has become a frontline standard in CLL.
- BTKi+BCL2 inhibitor doublets achieve excellent long-term disease control with favorable tolerability.
- Although triplets consistently deepen MRD responses, they have not yet demonstrated superior PFS or OS.
- Better biomarkers are needed to identify the minority of patients who may truly benefit from treatment intensification.

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