

DEBATE FLASCO 2026 · FRONTLINE CLL

Depth Wins

The Case for Fixed-Duration Triplet Therapy:
BTK Inhibitor + BCL2 Inhibitor + Anti-CD20

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Framing the Debate: What We Agree On — and What We Don't

The doublet side must defend leaving efficacy on the table

SHARED GROUND

- Chemoimmunotherapy is obsolete — AMPLIFY and GAIA/CLL13 both beat FCR/BR decisively
- Fixed duration is a legitimate standard — CLL17: fixed-duration venetoclax regimens are noninferior to continuous ibrutinib (3-yr PFS ~81%)
- BTKi + BCL2i synergy is real: compartment clearance (nodes + blood/marrow) and complementary resistance profiles
- Treatment-free remission is the goal our patients care about

THE ONLY QUESTION

Does adding anti-CD20 to the BTKi + BCL2i backbone earn its place?

My claim — the triplet delivers:

- Deeper remissions (uMRD 95% vs 45% at end of treatment)
- More durable PFS (HR 0.42 vs 0.65 in AMPLIFY; GIV > GV randomized in CLL13)
- Risk-agnostic efficacy — it erases the unmutated-IGHV penalty that caps the doublet

The Evidence Base: Triplets Are Not a Data-Free Zone

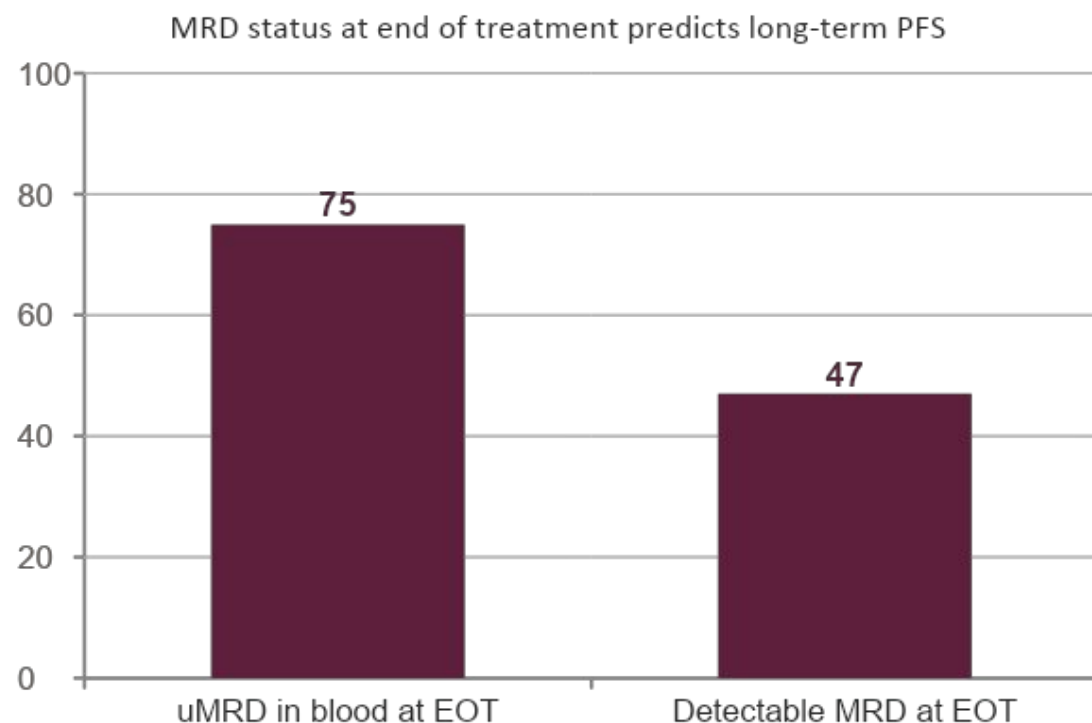
Two randomized phase 3 trials plus mature MRD-guided phase 2 programs

AMPLIFY (Ph 3, N=867)	Acala + Ven ± Obinutuzumab vs FCR/BR	AVO: 3-yr PFS 83.1% (HR 0.42) · uMRD 95% at EOT (evaluable)
GAIA/CLL13 (Ph 3, N=926)	GIV vs GV vs RV vs CIT — randomized triplet vs doublet	5-yr PFS: GIV 81.3% vs GV 69.8% (p=0.0046)
BOVen / “ZVO” (Ph 2, N=52)	Zanu + Obi + Ven, MRD-guided duration (8–24 cycles)	uMRD: 96% blood / 92% marrow at 5-yr follow-up
AVO high-risk (Ph 2, N=72)	Dauids et al. — MRD-guided AVO, 63% TP53-aberrant	BM-uMRD 71%; 4-yr PFS 70% in TP53-aberrant CLL
Doublet comparators	CAPTIVATE (Ibr+Ven), AMPLIFY AV arm, GLOW	The ceiling we are debating against

First Principle: In Fixed-Duration Therapy, Depth = Durability

When treatment stops, uMRD is what keeps working

Continuous therapy suppresses disease as long as you take the pill. Fixed-duration therapy has one currency: **the depth of remission you bank before you stop.**



1

CLL14 — End-of-treatment uMRD → landmark PFS advantage (HR ≈ 0.10 vs high MRD); uMRD status outperforms iwCLL response as a predictor

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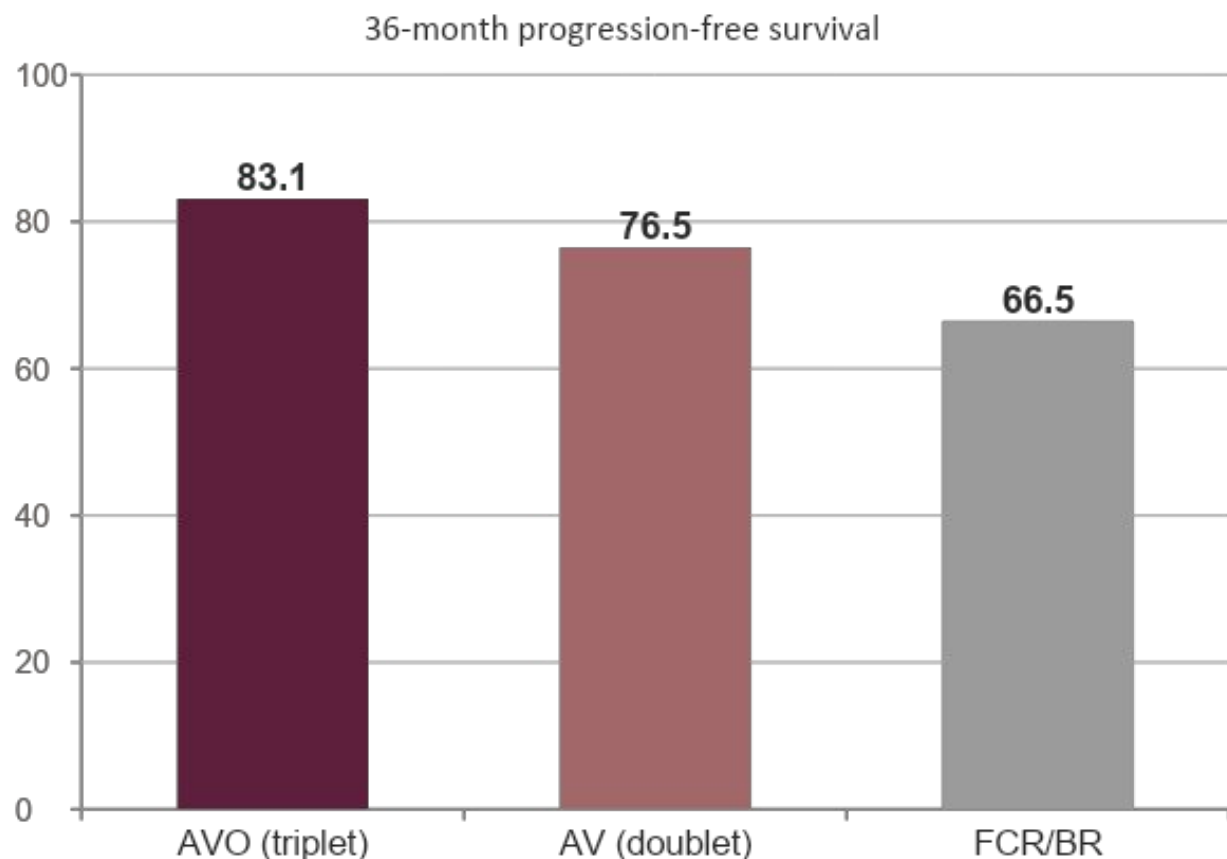
CAPTIVATE — 5.5-yr PFS 75% with blood uMRD at EOT vs 47% without — a 28-point gap from a single biomarker

3

Regulatory & guideline traction — MRD endpoints now drive trial design (BOVen, MAJIC, CELESTIAL) — the field has voted

AMPLIFY: The Triplet Sets the Efficacy Bar

Phase 3, N=867, treatment-naïve fit CLL without del(17p)/TP53mut · median follow-up ~41 mo



0.42

AVO vs CIT
hazard ratio

0.65

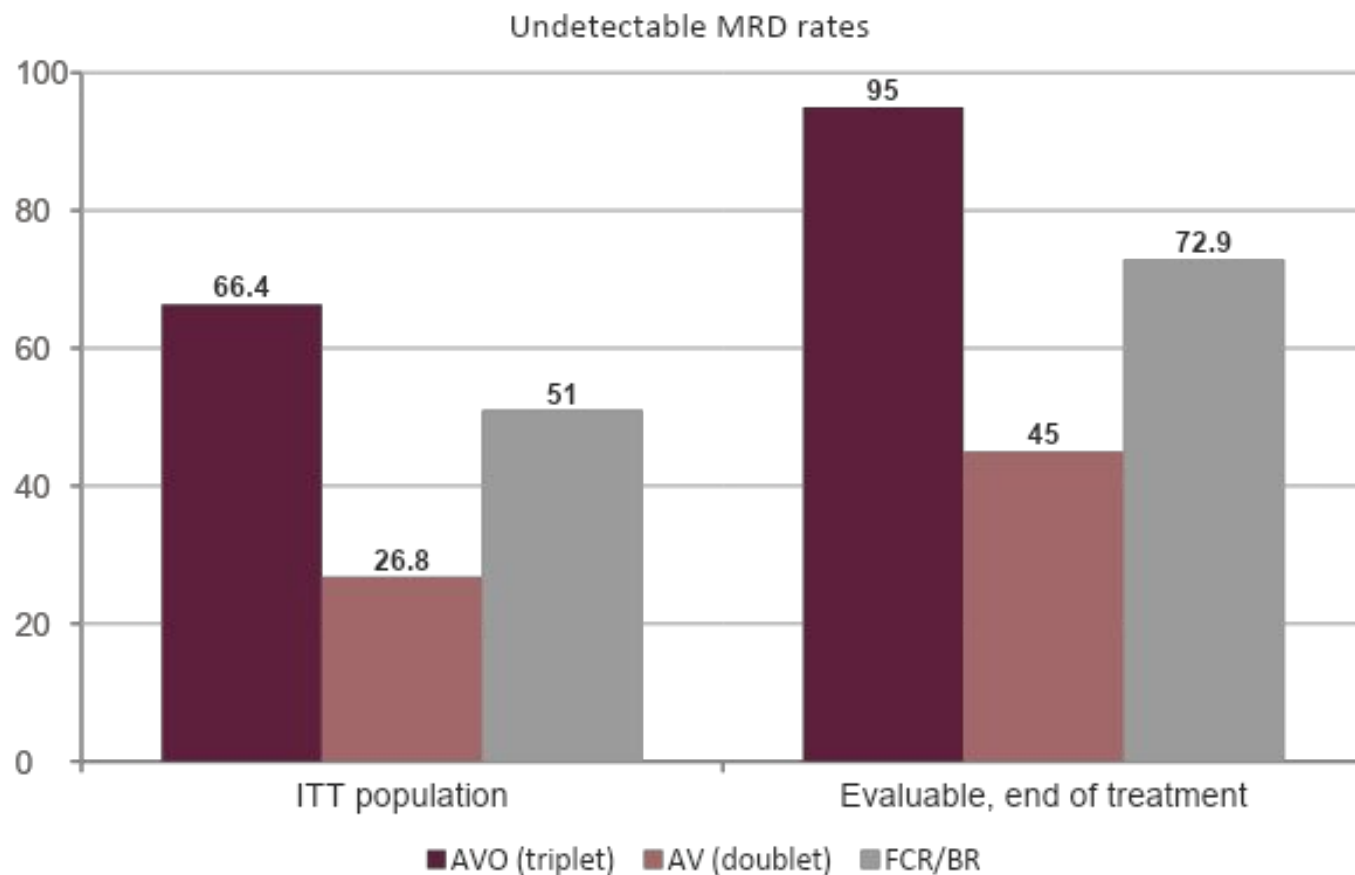
AV vs CIT
hazard ratio

A 35% relative risk reduction (AV) vs a 58% relative risk reduction (AVO) against the same control arm, in the same trial, in the same population.

Sensitivity analysis censoring COVID-19 deaths: AVO HR $\approx$ 0.30 vs AV HR $\approx$ 0.57 — the gap widens, not narrows.

AMPLIFY MRD: The Antibody Doubles the Depth

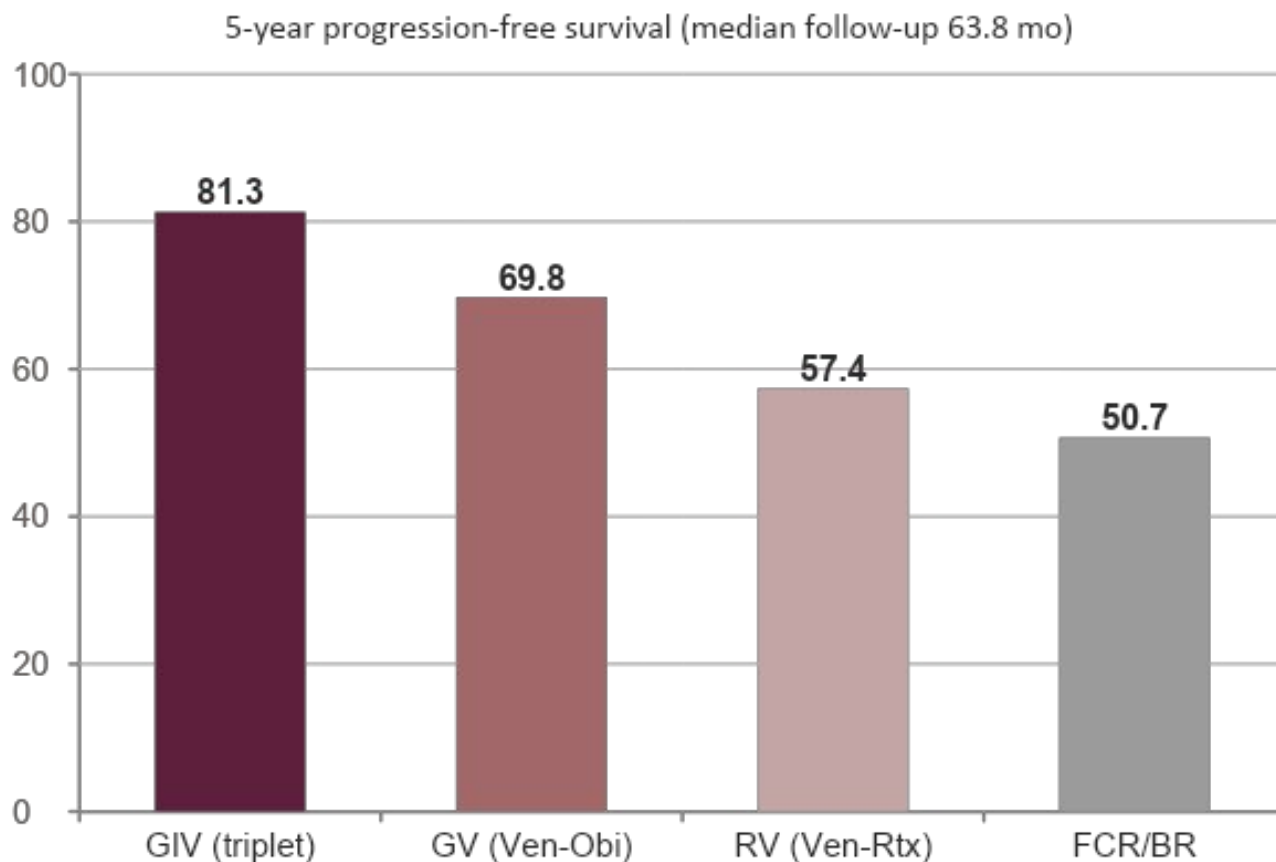
uMRD ($<10^{-4}$, peripheral blood, flow cytometry)



- The doublet leaves a majority of patients MRD-positive at end of 14 cycles of treatment
- AVO at 95% uMRD is among the deepest remissions ever recorded in a phase 3 frontline CLL trial

GAIA/CLL13: Randomized Proof the Third Drug Matters

5-year final analysis — the only phase 3 with a direct randomized triplet-vs-doublet PFS comparison



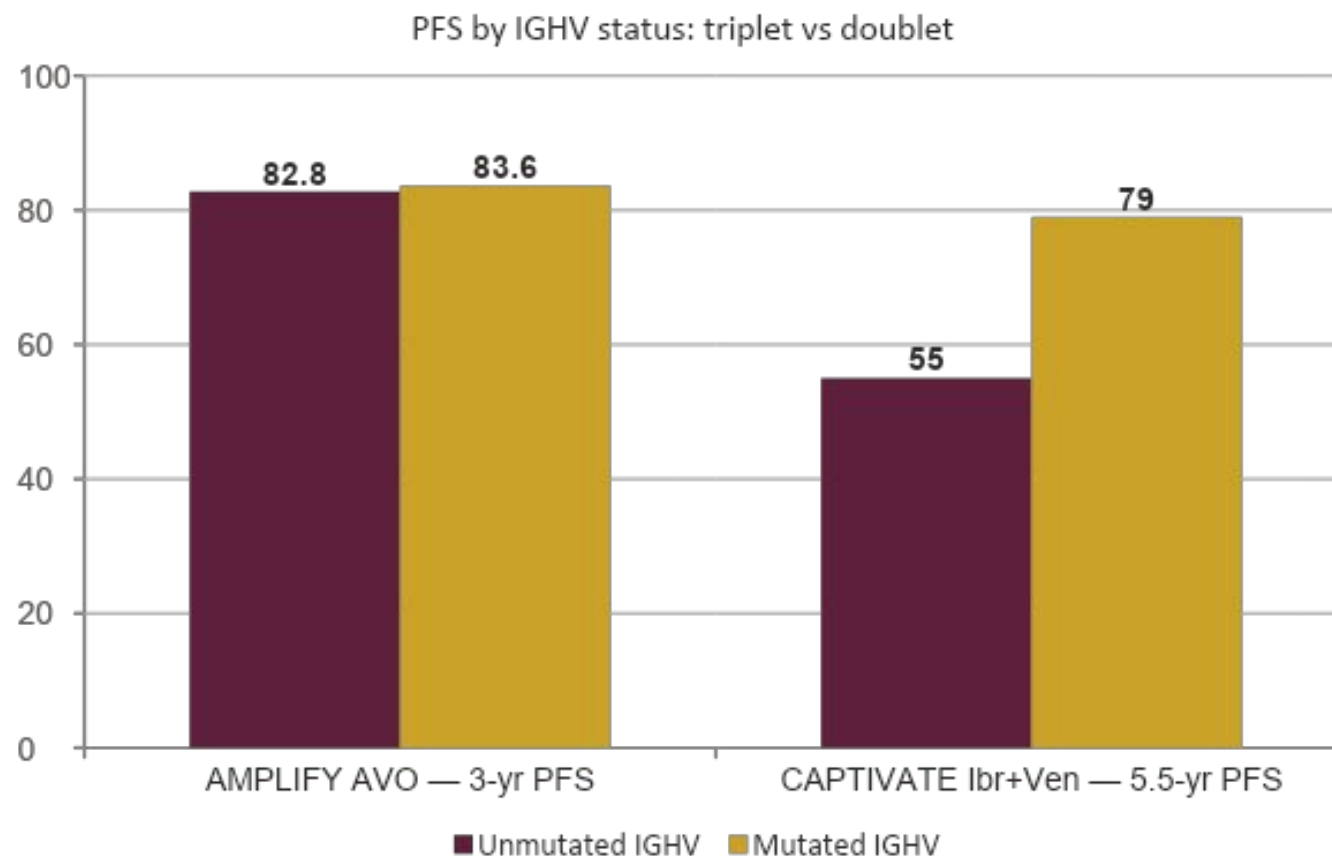
GIV > GV, $p = 0.0046$

Adding the BTKi to the Ven-CD20 backbone significantly extends PFS — randomized, prospective, 5 years out

- uMRD in blood after treatment: 92.2% with GIV — mirroring AMPLIFY's 95% with AVO
- An 11.5-point absolute PFS gap at 5 years vs the best doublet in the trial
- 5-yr OS 93–94% in every targeted arm — deeper therapy costs nothing in survival, and venetoclax-based retreatment works (2-yr treatment-free survival >80% after relapse)

The Triplet Erases Biology; the Doublet Is Capped by It

Unmutated IGHV — the majority of patients who need therapy



AMPLIFY AVO: 0.8-point gap.

Obinutuzumab's benefit was “most apparent” in unmutated IGHV — the triplet makes high-risk biology perform like low-risk biology.

Doublet: a 24-point gap.

CAPTIVATE at 5.5 years: uIGHV 55% vs mIGHV 79%.
Fixed-duration BTKi+BCL2i alone does not neutralize uIGHV — and uIGHV is ~55–60% of frontline trial populations.

High-Risk Disease: Where Depth Is Not Optional

TP53-aberrant and del(17p) CLL — the triplet has the data

71%

Bone-marrow uMRD in TP53-aberrant CLL with MRD-guided AVO (Davids phase 2, 63% TP53-aberrant)

70%

4-year PFS in TP53-aberrant patients on AVO — with 96% OS, on time-limited therapy

36%

5.5-yr PFS with the Ibr+Ven doublet in del(17p)/TP53-mutated CLL (CAPTIVATE) — the doublet's floor

- BOVen enrolled 17% del(17p) and delivered 92% marrow uMRD — depth held in high-risk genomes
- CLL2-GIVe (obinutuzumab + ibrutinib + venetoclax) was built specifically for del(17p)/TP53 frontline disease with durable remissions
- AMPLIFY excluded del(17p)/TP53 — but AVO's NCCN listing and the Davids study extend the triplet to precisely the patients the doublet serves worst
- **In AMPLIFY's mutation analysis, ATM / SF3B1 / NOTCH1 mutations were NOT associated with poorer outcomes in the AVO arm — unlike the AV arm, where uIGHV + NOTCH1 underperformed**

ZVO / BOVen: The Triplet Can Mean LESS Therapy, Not More

MRD-guided zanubrutinib + obinutuzumab + venetoclax · 5-year follow-up, N=52

96%

uMRD in peripheral blood

92%

uMRD in bone marrow

~10 mo

median treatment duration —
MRD-guided stop

92%

ORR on zanu-ven retreatment at relapse
(11/12)

Turn the toxicity argument on its head:

- Fast responders (Δ MRD400 by cycle 5) stopped after a median of 8 cycles — LESS total drug exposure than the 14-cycle AMPLIFY doublet or 15-month CAPTIVATE regimen
- Δ MRD400 achievers enjoyed a median MRD-free survival of 51 months off therapy despite the shorter course — early depth from the antibody buys durable freedom
- The antibody front-loads cytoreduction: rapid debulking also collapses TLS risk before venetoclax ramp-up (>80% of high-risk patients downstaged in AMPLIFY AVO)

Safety: A Manageable, Front-Loaded Cost — Honestly Accounted

AMPLIFY post-hoc safety analysis (ASH 2025), median follow-up 40.8 mo

WHAT WE CONCEDE

- Grade ≥ 3 neutropenia: 46.1% (AVO) vs 32.3% (AV) — vs 43.2% with FCR/BR
- More discontinuations for AEs (20.1% vs 7.9%) and infusion logistics for 6 cycles
- COVID-era mortality hit the antibody arm hardest — a real signal of infection vulnerability during B-cell depletion, concentrated in an unvaccinated pandemic window

WHAT THE DATA ACTUALLY SHOW

- Exposure-adjusted rates of infections and cardiac events were similar across all three arms
- Discontinuation did not cost efficacy: 24-mo post-treatment PFS 91.2% even in AVO patients who discontinued early — the depth was already banked
- Neutropenia is protocol-manageable (G-CSF, holds); no new safety signals at 40.8 months
- **Timing is tunable: MDACC trial — obinutuzumab added after 1 yr of AV kept uMRD4 at 90% while cutting Gr ≥ 3 neutropenia to 12% and infections to 2%**

Pre-Emptying the Rebuttals

What the doublet side will say — and why it doesn't hold

“AV had better OS than AVO (94.1% vs 87.7%)”

Descriptive, immature, and pandemic-confounded: excess AVO deaths were dominated by COVID-19 in unvaccinated patients. Censor COVID and AVO's PFS HR improves to ~0.30. CLL13: identical 5-yr OS (93–94%) across all targeted arms — depth costs no survival.

“AV is all-oral — no chairs, no infusions”

Six months of infusions vs a lifetime-relevant gain in remission depth. Patients accepted obinutuzumab in CLL14/CLL13 at scale; convenience is a preference conversation, not an efficacy argument.

“mIGHV patients do fine on the doublet”

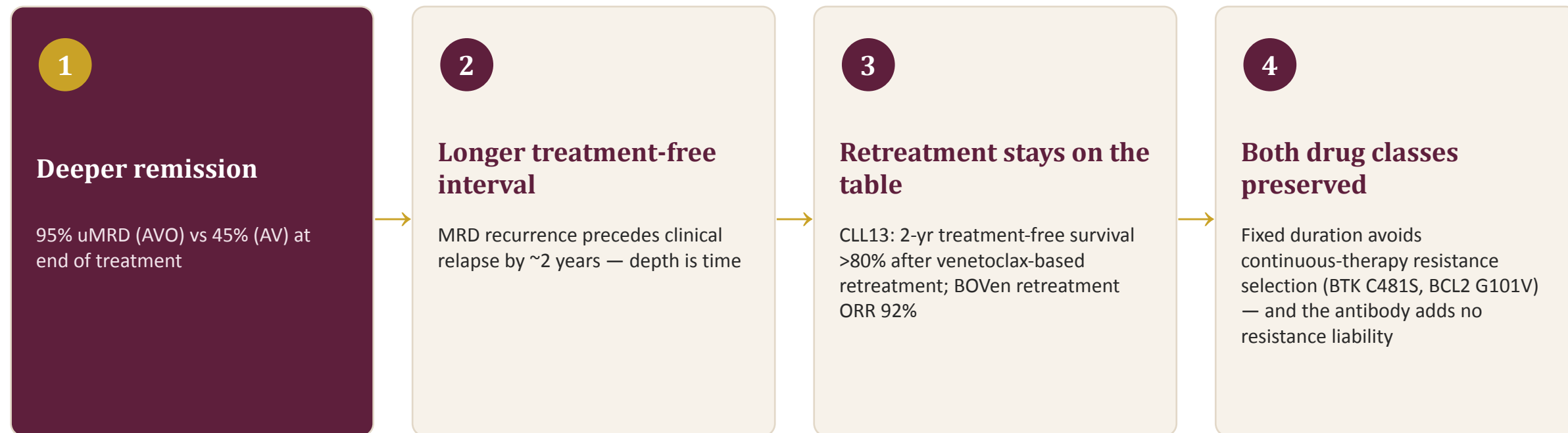
Agreed — and that's a minority of treated patients. Debate resolution says frontline CLL, not frontline favorable-biology CLL. For uIGHV (~55–60%), NOTCH1-mutated, and high-risk genomes, the doublet demonstrably underperforms.

“FDA approved AV, not AVO”

Regulatory sequencing, not a verdict: AVO met its key secondary endpoint (HR 0.42, $p < 0.001$), is NCCN-listed, and is in the EC label (May 2026). Guidelines already treat the triplet as standard.

The Long Game: Remission One Protects Every Future Line

CLL is a multi-decade disease — deeper first remission preserves all options downstream



Every month of treatment-free remission is a month of preserved marrow reserve, preserved quality of life, and preserved future options — including BTKi retreatment, pirtobrutinib, and CAR-T for the few who need them.

THE VERDICT

**If you believe in fixed duration,
you believe in depth.
The added antibody is where the depth comes from.**

95% vs 45%

uMRD at end of treatment — AMPLIFY, same trial, same population

HR 0.42 vs 0.65

vs the same control arm; ~0.30 vs ~0.57 once COVID noise is censored

81.3% vs 69.8%

5-yr PFS, randomized triplet vs doublet — GAIA/CLL13, $p=0.0046$

82.8% $\approx$ 83.6%

AVO erases the unmutated-IGHV penalty that caps every doublet

Fixed-duration BTKi + BCL2i + anti-CD20: the deepest remission, for every biology, once.

Key References

Backup

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