

SINTOMA 2026

Flash Clinical Cases

Chronic Lymphocytic Leukemia

Day 1 · Thursday May 14, 2026

CLL · SLL · Richter Transformation

5 Cases · 3–5 min discussion each

Ibrutinib + Venetoclax Fixed-Duration Frontline: Who Is the Right Patient?

PATIENT

- 62F, CLL — newly diagnosed, treatment-naïve
- Symptomatic: fatigue, progressive LAD, night sweats
- ECOG PS 1; no significant comorbidities
- Well-informed; asks about 'the combination approach'

DIAGNOSTICS

- FISH: del(11q); IGHV: Unmutated; TP53: WT
- CLL-IPI: High risk
- Beta-2 MG: 4.8 mg/L; CT: Diffuse LAD, spleen 17cm
- No del(17p); BTK/PLCG2: WT

PRIOR THERAPY

- Treatment-naïve
- Discussed with patient: ibrutinib + venetoclax fixed-duration (GLOW) · zanubrutinib continuous · VenO (CLL14)

CLINICAL DILEMMA

High-risk, unmutated IGHV CLL requiring frontline treatment. Three credible approaches available. Does fixed-duration ibrutinib + venetoclax offer a meaningful advantage — or is the added complexity justified only in specific patients?

MANAGEMENT OPTIONS — no single correct answer

- A. Ibrutinib + venetoclax fixed-duration (GLOW) — uIGHV**
- B. Zanubrutinib or acalabrutinib monotherapy continuous — simpler**
- C. Venetoclax + obinutuzumab (VenO) — fixed-duration**
- D. Ibrutinib + venetoclax then MRD-guided extension — adapt duration to MRD response depth**

PATIENT

- 58M, CLL on ibrutinib × 30 months
- Rapidly enlarging neck mass × 3 weeks; B symptoms
- ECOG PS 1 (acute improvement); ECOG PS 0 at baseline
- No significant comorbidities; MUD donor

DIAGNOSTICS

- PET: right neck 7cm (SUVmax 18); multiple SUVmax 5–8
- Biopsy: DLBCL GCB, clonally related to CLL
- MYC+, BCL2+, TP53 mutant (new); BTK C481S+
- IPI: 3/5

PRIOR THERAPY

- CLL L1: Ibrutinib × 30 mo → PR (never CR)
- BTK C481S confirmed at Richter biopsy
- R-CHOP × 3 cycles completed → PR (Deauville 3)
- No prior venetoclax; no prior SCT; no prior CAR-T

CLINICAL DILEMMA

58-year-old with Richter transformation achieving PR after R-CHOP × 3. Clonally related, MYC+, TP53 mutant. MUD donor available. What is the consolidation strategy — autologous SCT, allogeneic SCT, or CAR-T?

MANAGEMENT OPTIONS — no single correct answer

- Autologous SCT** — PR achieved
- Allogeneic SCT (MUD)** — clonally related Richter: GVL effect may be essential
- CAR-T (CD19) then reassess SCT** — deeper response before committing to transplant modality
- Continue R-CHOP to CR then decide** — PR after 3 cycles is insufficient
- Goals-of-care discussion** — clonally related MYC+ Richter

 PATIENT

- 58M, CLL — newly diagnosed, symptomatic (treatment indication met)
- Fatigue, progressive splenomegaly, night sweats
- ECOG PS 1; no significant comorbidities
- Asking: 'Is the 12-month treatment a good option for me?'

 DIAGNOSTICS

- FISH: del(13q) only; IGHV: Mutated; TP53: WT
- CLL-IPI: Intermediate
- Beta-2 MG: 3.2 mg/L; CT: Multiple LAD, spleen 15cm
- No del(17p), no del(11q)

 PRIOR THERAPY

- Treatment-naïve
- IGHV mutated — favorable biology
- Discussed with patient: VenO (CLL14) · ibrutinib continuous · acalabrutinib continuous
- Patient strongly prefers fixed-duration therapy

 CLINICAL DILEMMA

IGHV-mutated CLL, favorable biology, patient prefers fixed-duration therapy. VenO is the natural choice — but what happens if he relapses within 24 months (POD24)? Does the potential for early relapse change your upfront recommendation?

 MANAGEMENT OPTIONS — no single correct answer

- VenO (CLL14)** — IGHV-mutated ideal VenO candidate
- Ibrutinib or acalabrutinib continuous** — avoid any relapse risk
- Acalabrutinib + venetoclax fixed-duration** — deepest MRD in mutated IGHV
- VenO then MRD-guided extension** — if MRD positive at cycle 12
- VenO with explicit POD24 plan** — proceed with VenO

 PATIENT

- 61M, CLL — ibrutinib + venetoclax + pirtobrutinib refractory (CR × 14 months)
- ECOG PS 1; no autoimmune disease; spleen 19cm
- No Richter by PET

 DIAGNOSTICS

- FISH: del(17p) + del(11q); TP53 mut (VAF 58%); IGHV unmutated
- BTK C481S+; BCL2 G101V+ (resistance mutations confirmed)
- CD4/CD8 1.1; PHA stimulation normal

 PRIOR THERAPY

- L1: Ibrutinib × 24 mo → BTK C481S resistance
- L2: Venetoclax + obinutuzumab × 12 mo → BCL2 G101V resistance
- L3: Pirtobrutinib 200mg QD × 14 mo → CR, now progressing

 CLINICAL DILEMMA

Ibrutinib, venetoclax, and pirtobrutinib all exhausted. Del(17p)/TP53 triple-refractory CLL. Pirtobrutinib achieved CR lasting 14 months before progression. What comes after pirtobrutinib failure — and is CAR-T the right next step?

 MANAGEMENT OPTIONS — no single correct answer

- Liso-cel CAR-T (TRANSCEND CLL 004)** — FDA-approved post-BTKi+venetoclax failure
- Pirtobrutinib re-challenge after treatment holiday** — some responses after brief off-treatment interval
- Venetoclax re-challenge** — BCL2 G101V confirmed
- Novel CAR-T trial** — dual-targeting or armored constructs
- Goals-of-care discussion first** — ibrutinib + venetoclax + pirtobrutinib exhausted

 PATIENT

- 68M, CLL — started acalabrutinib 30 months ago
- Excellent response; feels well, returned to normal life
- No comorbidities; ECOG PS 0
- Now asking: 'Can I take a break or stop completely?'

 DIAGNOSTICS

- FISH: del(13q) only; IGHV: Mutated; TP53: WT
- CLL-IPI: Intermediate
- Current assessment: lymphocytes normalized; CT: minimal residual LAD
- PB MRD by flow: undetectable ($<10^{-4}$)

 PRIOR THERAPY

- Acalabrutinib 100mg BID \times 30 months — continuous
- Best response: CR by CT criteria
- PB MRD: undetectable at month 24 and 30
- BM MRD: not yet assessed

 CLINICAL DILEMMA

68-year-old with IGHV-mutated CLL in sustained PB MRD-negative CR on acalabrutinib \times 30 months. Patient wants to stop. Is MRD-guided discontinuation of continuous BTKi safe — and what is the evidence?

 MANAGEMENT OPTIONS — no single correct answer

- A. Continue acalabrutinib indefinitely** — no prospective discontinuation data
- B. BM MRD assessment first** — if BM MRD also undetectable
- C. Discontinue acalabrutinib now** — PB uMRD \times 6+ months in IGHV-mutated CLL
- D. Switch to venetoclax + obinutuzumab (fixed-duration)** — consolidate MRD negativity