CLL — Clinical Pearls, Practical Points & Key Facts

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Quickref aligned to CLL guideline v1.9 · April 2026

1. CLL vs MBL · When to Treat — iwCLL Criteria

CLL vs MBL	Treat if present	Do NOT treat for
CLL: clonal B cells ≥5×10⁹/L. MBL high-count: 0.5–5×10⁹/L, no features → 6–12 monthly review. MBL low-count: <0.5×10⁹/L → no follow-up needed. SLL: any count + nodal/organ/cytopenia.	• Hb <10 or plt <100 (marrow failure). • Spleen >6 cm or symptomatic. • Node >10 cm or progressive. • Lymphocyte DT <6 months. • AIHA/ITP poorly controlled. • B-symptoms (weight loss / fever / sweats).	• Lymphocyte count alone (>100×10⁹/L). • del(17p) / TP53 mutation alone in asymptomatic disease. • IGHV-unmutated alone. • Hypogammaglobulinaemia alone. • Patient / GP anxiety. • MBL (not CLL).

2. Molecular Work-up — Treatment-Predictive, Not Just Prognostic

Test	Treatment-predictive role	Common pitfall
TP53 seq + del(17p) FISH	del(17p) / TP53 → targeted agents only. Mandates BTKi or venetoclax regardless of fitness. FISH alone misses ~40% — always sequence too.	Do not use FISH alone. Mnemonic: *"17 and TP — always together"*.
IGHV mutation status	Mutated (≥2%): deepest remissions with fixed-duration venetoclax (TA1119). Unmutated: shorter remissions but all NICE options still work.	IGHV does NOT determine when to treat — only informs treatment choice once criteria met.
Repeat at relapse	Clonal evolution: del(17p)/TP53 emerges in 20–30% at R/R. Repeat mandatory.	Never assume same molecular profile at relapse as at diagnosis.
HBV core Ab	Positive = mandatory antiviral prophylaxis before anti-CD20. Fatal reactivation risk.	Check HBcAb — easy to miss; required before obinutuzumab / rituximab.

3. First-line Treatment Selection — BSH 2025 / NICE (★ = Preferred)

Clinical scenario	Preferred UK option	NICE TA	Practical tip
TP53-aberrant + cardiac risk	★ Zanubrutinib — lowest AF (~2%); ALPINE HR 0.51 in del(17p)/TP53	TA931	BSH 2025 Grade 1A preferred; check Blueteq.
TP53-aberrant + any fitness	★ Acalabrutinib (AF 6%) or Venetoclax+Obi (12 cycles, fixed-duration)	TA689 / TA1119	No cytotoxic agents — targeted only.

Clinical scenario	Preferred UK option	NICE TA	Practical tip
Non-TP53 + IGHV-mutated + fit	Venetoclax+Obi (deepest uMRD 86%; treatment-free remission)	TA1119	GAIA/CLL13 supports; CLL14 median PFS 76 months.
Non-TP53 + cardiac risk / AF	★ Zanubrutinib or acalabrutinib (preferred over ibrutinib, BSH 2025)	TA931 / TA689	Ibrutinib AF 11% vs zanubrutinib 2%.
Non-TP53 + unfit / elderly	★ Zanubrutinib or acalabrutinib or Venetoclax+Obi	TA931 / TA689 / TA1119	All suitable; BTKi avoids IV clinic visits.
Already on ibrutinib, tolerating	Continue — no need to switch if no notable AEs	TA429	Switch only if AEs develop.
R/R after BTKi	Venetoclax monotherapy (ORR 65–80% post-BTKi)	TA796	Ramp-up protocol required; TLS monitoring.
R/R post-CIT or BTKi-naive	Venetoclax + rituximab (MURANO 7-year OS 69.6%)	TA561	Fixed-duration to cycle 24; retreatment feasible.

4. Clinical Pearls

- CLL is chronic and treatable — most patients live **with** it, not **from** it.
- MBL is NOT CLL — do not treat clonal B cells $<5\times10^9$/L without disease features.
- Watch and wait can last years — treat **criteria**, not numbers.
- TP53 / IGHV are treatment-predictive — they change **what** you use, not **when**.
- Zanubrutinib and acalabrutinib preferred over ibrutinib for new patients (BSH 2025 Grade 1A).
- Fixed-duration venetoclax = treatment-free remission — IGHV-mutated benefits most.
- At relapse: repeat TP53 + FISH — clonal evolution in 20–30%.
- CMV monitoring: alemtuzumab-era protocol — NOT routine for BTKi / venetoclax.
- Richter's: PET-CT + biopsy of **hottest** node — not re-biopsy of known site.

5. Common Pitfalls

- Treating MBL or raised ALC alone — early treatment does not improve survival.
- FISH alone for TP53 — misses ~40% of mutations; always sequence together.
- Not repeating TP53 / FISH at relapse — 20–30% evolve to TP53-aberrant.
- Omitting HBV core Ab before anti-CD20 — fatal reactivation possible.
- Ordering weekly CMV PCR — alemtuzumab-era protocol; not current practice.
- Venetoclax ramp-up without TLS risk stratification and monitoring protocol.
- IGHV-unmutated → treating early — IGHV informs choice, not timing.
- Missing Richter's — biopsy the FDG-hottest PET node, not the most accessible.

6. Key Numbers

- **RESONATE-2 (10 yr):** ibrutinib median PFS 8.9 yr vs 1.3 yr; OS HR 0.45.
- **ELEVATE-TN (4 yr):** acalabrutinib+Obi PFS superior; AF 6% vs 11% ibrutinib.
- **CLL14 (6 yr):** Ven-Obi PFS median 76.2 m vs 36.4 m; uMRD 78% EOT; HR 0.40.
- **GAIA/CLL13:** Ven-Obi uMRD 86.5% EOT; superior to all comparators.
- **ALPINE final:** zanubrutinib vs ibrutinib PFS HR 0.65; del(17p)/TP53 HR 0.51.
- **SEQUOIA arm C (5 yr):** zanubrutinib del(17p) PFS 72.2%, OS 85.1%.
- **MURANO (7 yr):** Ven-R OS 69.6% vs 51.0%; uMRD 62% EOT; retreatment ORR 72–89%.
- **BRUIN:** pirtobrutinib ORR 73.3% in covalent BTKi-refractory CLL.

Clinical decision-support only. Not for direct patient use. Use alongside local policy, senior clinical judgement, and patient-specific context. BSH 2025 and NICE-commissioned regimens apply for UK clinical practice. Verify current NICE TA commissioning before prescribing. Full guideline: https://mohsinhaemacademy.com/guidelines/cll/