CLL — Clinical Pearls, Practical Points & Key Facts (v1.4)

1. CLL vs MBL | WHEN TO TREAT — iwCLL Criteria

CLL vs MBL	Treat if present	Do NOT treat for
CLL: clonal B cells ≥5×10■/L MBL high-count: 0.5-5×10■/L, no features → 6-12 monthly review MBL low-count: <0.5×10■/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 (>100×10■/L) • del(17p)/TP53 mutation alone in asymptomatic • 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 (12cx, fixed-duration)	TA689 / TA1119	No cytotoxic agents — targeted only
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 significant 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 7yr OS 69.6%)	TA561	Fixed-duration to cycle 24; retreatment feasible

4. CLINICAL PEARLS | 5. PITFALLS | 6. KEY NUMBERS

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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 <5×10■/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

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 — this is the 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 most accessible

Key Numbers (v1.4)

- RESONATE-2 10yr: ibrutinib median PFS 8.9yr vs 1.3yr; OS HR 0.45
- ELEVATE-TN 4yr: acalabrutinib+Obi PFS superior; AF 6% vs 11% ibrutinib
- CLL14 6yr: Ven-Obi PFS median 76.2m vs 36.4m; 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 5yr: zanubrutinib del(17p) PFS 72.2%, OS 85.1%
- MURANO 7yr: 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