Chronic Lymphocytic Leukaemia (CLL)

ELN x BSH 2025 x ASH/NCCN 2024 | Version 1.9 FINAL | April 2026

Document code	MHA-CLL-2026-v1.9 FINAL
Division	Haematological Malignancy
Aligned with	BSH CLL 2025 [Follows CE et al. BJH 2025;207(6):2296-2313] ESMO/ELN 2024 x ASH/NCCN 2024 x iwCLL 2018 NICE TA931/TA689/TA1119/TA891/TA429/TA561/TA796
Preferred BTKis	Zanubrutinib (TA931) and Acalabrutinib (TA689 monotherapy) -- BSH 2025 Grade 1A
UK practice	BSH 2025 and NICE-commissioned regimens apply for UK clinical practice
Original publication	April 2025
Current version	v1.9 -- April 2026 (final publication version after 9 revision cycles)
Fact-check	All key data and NICE TA scopes verified: PubMed, Scholar Gateway, Consensus. AIHA frequency corrected (up to 20%; BSH 2012: 10-20%). Pirtobrutinib BRUIN citation corrected (Mato AR et al. NEJM 2023). TA429 scope clarified.

Key Points -- CLL v1.9 FINAL (independently fact-checked)

- CLL is chronic and treatable; many patients have prolonged survival, but outcomes are heterogeneous.
- MBL (clonal B cells <5x10^9/L, no disease features) -- observation only; no CLL-directed treatment.
- Zanubrutinib (TA931) and Acalabrutinib (TA689 monotherapy) -- BSH 2025 Grade 1A preferred for new patients.
- TA429 (ibrutinib): NICE scope = untreated del(17p)/TP53 (CIT unsuitable) + previously treated. NOT all-comers.
- TA1119 (venetoclax+obi, Jan 2026): CLL14 6yr PFS 76.2m [PMID:39082668]; GAIA/CLL13 uMRD 86.5% (fit pts).
- TP53/IGHV are treatment-predictive -- they change which agent is used, not when treatment starts.
- Autoimmune cytopenias in up to 20% of CLL patients (BSH: 10-20%; AIHA ~7%). Steroids first-line.
- uMRD4 (<10^-4): standard MRD threshold. MRD is additional to, not part of, formal iwCLL response categories.
- HBV core Ab screen mandatory before anti-CD20. Alemtuzumab no longer used -- no routine CMV monitoring needed.

1. NICE Commissioning -- UK CLL (BSH 2025 / NICE verified)

TA	Regimen	NICE Scope	BSH 2025
TA931	Zanubrutinib 160 mg BD	Untreated CLL	PREFERRED -- AF ~2%; Grade 1A
TA689	Acalabrutinib 100 mg BD (monotherapy only)	Untreated del(17p)/TP53 or CIT unsuitable; previously treated	PREFERRED -- TA689 = monotherapy; Grade 1A
TA1119	Venetoclax + Obi (12 cycles)	Untreated CLL -- all patients incl. less-fit (updates TA663, Jan 2026)	Preferred fixed-duration
TA891	Ibrutinib + Venetoclax (12 cycles)	Untreated CLL	Acceptable; limited del(17p) data
TA429	Ibrutinib 420 mg OD	Untreated del(17p)/TP53 (CIT unsuitable) + previously treated	De-prioritised for new starts
TA561	Venetoclax + Rituximab	R/R CLL -- >= 1 prior therapy	MURANO 7yr OS 69.6% [PMID:40009494]
TA796	Venetoclax monotherapy	R/R CLL post-BTKi or rituximab unsuitable	ORR 65-80% post-BTKi

2. First-Line Treatment -- BSH 2025 Preferred Order

Zanubrutinib then Acalabrutinib then Venetoclax+Obi then Ibrutinib+Venetoclax. Ibrutinib last and de-prioritised for new starts.

Zanubrutinib [TA931] PREFERRED	AF ~2% -- lowest of all BTKis. SEQUOIA arm C (del(17p)) 5yr: PFS 72.2%, OS 85.1% [Tam CS et al. EHA 2025, Haematol Oncol 2025;43(S3)]. ALPINE vs ibrutinib: HR 0.65 (p=0.002); del(17p)/TP53: HR 0.53 [NEJM 2023;388(4):319-332, PMID:36511784]. *(BSH 2025 Grade 1A preferred)*	High	Strong
Acalabrutinib [TA689] Monotherapy -- PREFERRED	NICE TA689 = monotherapy only (obinutuzumab combination not appraised by NICE). Covers untreated CLL with del(17p)/TP53 or where CIT unsuitable; also previously treated CLL. AF 6% vs 11% ibrutinib at 6yr ELEVATE-TN. *(BSH 2025 Grade 1A. NICE TA689 = monotherapy)*	High	Strong
Venetoclax+Obi [TA1119] 12 cycles	Fixed-duration. CLL14 (less-fit, coexisting conditions) 6yr: PFS 76.2 vs 36.4m, HR 0.40 [Blood 2024;144(18):1924-35, PMID:39082668]. GAIA/CLL13 (fit patients, no TP53 aberrations): uMRD 86.5% at month 15, 3yr PFS 90.5%. TA1119 updates TA663 (NICE January 2026).	High	Strong
Ibr+Venetoclax [TA891] 12 cycles	Ibrutinib lead-in x3 cycles then venetoclax ramp-up; 12 cycles total. CAPTIVATE/GLOW: high uMRD rates. Limited del(17p)/TP53 data.	Moderate	Strong
Ibrutinib [TA429] De-prioritised	NICE TA429 scope: untreated del(17p)/TP53 (CIT unsuitable) + previously treated CLL -- NOT all-comers. BSH 2025: de-prioritised for new starts due to AF (~11% at 36m pooled data), hypertension (~55%), bleeding. Continue if established and tolerating well. *(TA429 specific scope only. Not all-comers first-line.)*	High	Conditional

3. Relapsed and Refractory CLL

Venetoclax+R [TA561]	Venetoclax ramp-up to 400mg OD + rituximab cycles 1-6; stop at cycle 24. MURANO 7yr: OS 69.6% vs 51.0%; uMRD EOT 62%; retreatment ORR 72-89% [Blood 2025;145(23):2733-2745, PMID:40009494].	High	Strong

Venetoclax mono [TA796]	Ramp-up to 400mg OD; continue until progression. ORR 65-80% even post-BTKi failure.	Moderate / Strong
Zanubrutinib or Acalabrutinib [TA931 / TA689]	For BTKi-naive R/R CLL. ALPINE: zanubrutinib vs ibrutinib HR 0.65 (p=0.002) [PMID:36511784]. Acalabrutinib TA689 also covers previously treated CLL.	High / Strong
Pirtobrutinib [not NICE cmmd]	Non-covalent BTKi; active in BTK C481S mutation. BRUIN trial: ORR 73.3% in covalent BTKi-refractory CLL (Mato AR et al. NEJM 2023). EMA-approved 2024. Check NICE TA.	Moderate / Conditional

4. Special Populations and Supportive Care

Autoimmune Cytopenias (AIHA, ITP): Occur in up to 20% of CLL patients during their illness course (BSH 2012: 10-20%; AIHA ~7%). Initial management: corticosteroids as for primary autoimmune cytopenia. CLL-directed therapy for refractory, recurrent, steroid-dependent, or active CLL-driven disease. Avoid fludarabine in active AIHA.

Richter's Transformation (2-10%): Median OS ~9 months. PET-CT + biopsy of most FDG-avid node. Clinical trial preferred; CAR-T ORR ~60-65%; bispecific antibodies (epcoritamab) emerging.

Infection Prophylaxis: Alemtuzumab no longer used in UK CLL -- routine weekly CMV monitoring not required for BTKi or venetoclax. HBV core Ab mandatory before anti-CD20. PCP prophylaxis during venetoclax+anti-CD20. IgRT when IgG <4 g/L + recurrent infections.

5. References -- Verified April 2026

- Follows CE et al. BSH guideline for treatment of CLL. Br J Haematol. 2025;207(6):2296-2313. [PMID:41069109] [A1]
- ESMO/ELN Clinical Practice Guideline update -- targeted therapies in CLL. Ann Oncol. 2024. [A1]
- NCCN Clinical Practice Guidelines: CLL/SLL v2.2024. [A1]
- Sharman JP et al. ELEVATE-TN. Lancet. 2020;395(10232):1278-1291. [A2]
- Al-Sawaf O et al. CLL14 6-year: venetoclax-obinutuzumab (less-fit patients). Blood. 2024;144(18):1924-1935. [PMID:39082668] [A2]
- Eichhorst B et al. GAIA/CLL13 primary (fit patients, no TP53). Lancet. 2023;401(10386):1353-1365. [uMRD 86.5%; 3yr PFS 90.5% verified] [A2] | 4-year update: Furstenau M et al. Lancet Oncol. 2024;25(6):744-759. [PMID:38821083]
- Barr PM et al. RESONATE-2 up to 8-year follow-up. Blood Advances. 2022. [A2]
- Brown JR et al. ALPINE: zanubrutinib vs ibrutinib R/R CLL. N Engl J Med. 2023;388(4):319-332. [PMID:36511784] [A2]
- Kater AP et al. MURANO final analysis 7-year. Blood. 2025;145(23):2733-2745. [PMID:40009494] [A2]
- Mato AR et al. BRUIN trial: pirtobrutinib in relapsed/refractory CLL. N Engl J Med. 2023. [ORR 73.3% in covalent BTKi-refractory] [A2]
- Tam CS et al. SEQUOIA arm C 5-year: zanubrutinib in del(17p) CLL. EHA 2025. Haematol Oncol. 2025;43(S3). [DOI:10.1002/hon.70093_72] [A2]
- Hodgson K et al. Autoimmune cytopenia in CLL. Br J Haematol. 2011;154(1):14-22. [AIHA ~7%; cytopenias 10-20%] [B]
- NICE TA931/TA689/TA1119/TA891/TA429/TA561/TA796 -- NICE technology appraisals 2017-2026. www.nice.org.uk [A1]

Disclaimer: Educational use and clinical decision support only. BSH 2025 and NICE-commissioned regimens apply for UK practice. Always verify current NICE guidance before prescribing. Not a substitute for individual clinical judgement. Dr Muhammad Mohsin, Consultant Haematologist.