

Consensus guidelines for the management of treatment-naïve chronic lymphocytic leukaemia in Singapore (2024)

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ABSTRACT

Introduction: Chronic lymphocytic leukaemia (CLL) has a heterogeneous disease course and a variable prevalence across populations. Appropriate management for achieving optimal outcomes requires consideration of multiple factors, including disease-related factors like genomic alterations, patient characteristics and fitness, availability and access to treatments, and logistics/cost. This review aims to provide comprehensive and pragmatic recommendations for the management of treatment-naïve (TN) CLL that are relevant to Singapore's clinical context.

Method: Clinical consensus statements were developed by an expert panel of haematologists from Singapore through a 2-round modified Delphi process. Statements were drafted using recent evidence-based guidelines and published literature. Panel members reviewed draft statements, provided anonymised feedback and proposed modifications where relevant. A physical meeting was held to facilitate discussion, voting and endorsement of the final consensus statements.

Results: The final consensus included 15 statements covering major TN CLL patient subsets. The recommendations highlight the importance of molecular testing for key biomarkers, where available/accessible, to guide initial therapy. Due to the superior efficacy of targeted agents (Bruton's tyrosine kinase inhibitors [BTKis] and B-cell lymphoma 2 inhibitors [BCL2is]) these are favoured over standard chemotherapy or chemotherapy-immunotherapy, especially for patients with del(17p) or TP53 mutation, and less fit patients.

Conclusion: These consensus statements provide practical recommendations for the current management of TN CLL patients in Singapore and similar healthcare systems based on up-to-date evidence. Regular updates to treatment guidelines are important to ensure responsiveness to emerging evidence and evolving clinical practices and to improve patient outcomes and quality of life.

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CLINICAL IMPACT

What is New

- This comprehensive, up-to-date clinical consensus for treatment-naïve chronic lymphocytic leukaemia in Singapore emphasises a balanced approach to therapy selection, integrating patient preferences, side-effect profile, cost, accessibility and logistics for informed decision-making.

Clinical Implications

- These recommendations offer a practical treatment algorithm that aligns with Singapore's healthcare system.
- Treatment decision-making requires consideration of multiple factors and this should be recognised when adapting recommendations for different resource settings.

INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is a lymphoid neoplasm characterised by clonal expansion of mature B-lymphocytes and has a characteristic immunophenotypic pattern. CLL prevalence varies considerably across populations. Although CLL is the most common leukaemia in adults in Western

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countries (25–30% of all leukaemia cases), it is much less common among individuals of Asian and Middle Eastern ancestry.^{1,2} As most CLL patients are older adults, with median age of onset ranging from 65 to >70 years,^{3,4} many will have coexisting conditions that increase their risk of morbidity and mortality from treatment. When selecting the optimal regimen for an individual patient, these factors and other disease and patient-related features (e.g. clinical/disease characteristics, symptoms, genetic risk factors and fitness) should be considered.^{5,6}

In Singapore, an estimated 20–30 new cases of CLL are diagnosed annually.⁷ Patients may receive treatment at public or private institutions, including specialised haematology centres. Singapore's healthcare system offers a mix of insurance-paid, subsidised, co-pay and self-paying options for patients; thus, treatment decision-making involves consideration of several factors, including availability/access to approved or investigational drugs, companion diagnostics, the experience of the specific treatment centre or team, financial considerations and patient preferences. In terms of access to important diagnostic tests for CLL, this is relatively uniform across the public and private sectors. Financing of outpatient cancer treatment in Singapore is determined by a drug's local approval status, and its inclusion in the Ministry of Health's Cancer Drug List (CDL) based on evaluations of its clinical effectiveness and cost-effectiveness.⁸ Patients can receive subsidised access to drugs included in the CDL. With a complex and rapidly evolving treatment landscape, clinicians require practical guidance incorporating up-to-date and emerging clinical evidence. Guidelines from various sources are available but may have greater or lesser applicability to local clinical populations and health systems.^{5,6,9,10} This clinical consensus from a panel of experts in Singapore seeks to offer pragmatic recommendations for the management of treatment-naïve (TN) CLL, considering factors relevant to the local clinical population and healthcare setting. Although the panel's recommendations were developed for a primary audience of haemato-oncologists in the Singapore setting, the practice discussed here may be relevant to specialists practising in similar healthcare settings or systems.

METHOD

Two-round modified Delphi process for consensus generation

A modified Delphi process was used to generate consensus for the management of TN CLL. This consensus aims to provide guidance on contempo-

rary treatment options for TN CLL, with consideration of specific patient subpopulations and important clinical outcomes, including but not limited to treatment efficacy. The expert panel comprised 8 haematology oncology specialists with extensive experience in CLL, practising in Singapore's public healthcare institutions (with all 3 public healthcare administrative clusters represented) or in private specialist centres. The modified Delphi process consisted of 2 rounds. A set of provisional statements on CLL management was developed based on a targeted review of recent clinical guidelines for CLL management and available published literature. A steering committee provided guidance and input for drafting the consensus statements and revising them based on the panel's feedback.

The evidence base for these recommendations includes pivotal studies on CLL management, as identified in recent evidence-based guidelines (European Society for Medical Oncology [ESMO], Canadian evidence-based guidelines for CLL [2022 update], and National Comprehensive Cancer Network [NCCN] Guidelines version 3.2023).^{10–13} Literature relevant to first-line CLL treatment was considered, including primary and follow-up publications for key trials. An adapted version of the evidence grading system employed for the Pan-Asian adapted ESMO clinical practice guidelines for non-small-cell lung cancer¹⁴ was used to define the level of evidence available for each statement proposed (I: at least 1 large randomised controlled trial of good methodological quality—low potential for bias—or meta-analyses of well-conducted randomised trials without heterogeneity; II: small randomised trials or large randomised trials with a suspicion of bias—low methodological quality—or meta-analyses of such trials or of trials with demonstrated heterogeneity). Following the development of this consensus in 2023, updates to guidelines from ESMO and NCCN (2024) became available and are summarised in Supplementary Table S1.^{15,16}

The 17 statements covered 5 major areas: (1) general principles of management for TN CLL; (2) treatment of patients with deletion 17p [del(17p)] or tumour protein 53 (*TP53*) mutation; (3) treatment of fit, immunoglobulin heavy chain (*IGHV*) mutated patients without del(17p) or *TP53* mutation; (4) Treatment of unfit, *IGHV*-mutated patients without del(17p) or *TP53* mutation; and (5) treatment of *IGHV*-unmutated patients without del(17p) or *TP53* mutation.

Data collection and consensus classification

In round 1, the statements and supporting evidence were presented to panel members for input. Responses were collected anonymously using an

electronic survey form. Panel members were asked to respond within 2 weeks, with email reminders as required. For each statement, panel members rated their level of agreement on a 5-point Likert scale: (1) “accept completely”; (2) “accept with minor changes”; (3) “accept with major changes required”; (4) “reject with major changes required”; (5) “reject completely”. If panel members selected options 2–5, they were asked to elaborate on the reasoning for their response and their suggestions for modifying the statement and could propose the addition of other relevant supporting references. A statement was deemed to have achieved consensus when $\geq 80\%$ of the panel voted “1” or “2” (accept completely or with minor changes). Statements that did not achieve consensus in round 1 were modified based on panel members’ input and presented for discussion and voting in round 2.

Round 2 consisted of a moderated face-to-face meeting in Singapore on 26 October 2023. The round 1 voting results and the panel’s consolidated input on the statements were presented. This was followed by a moderated discussion to clarify the clinical reasoning for different viewpoints and provide opportunities for alignment. Statements that did not achieve consensus in round 1 were refined after the discussion and presented for a final round of voting and endorsement by the panel members.

RESULTS AND DISCUSSION

Seventeen provisional statements were presented for the panel’s input and voting in round 1. Consensus was reached on 14 out of 17 statements (82.3%) in round 1. The 3 statements that did not reach consensus were presented for discussion and refinement before the final voting process in round 2. After discussion, the panel agreed to omit 1 statement from consideration for the consensus. The remaining 2 statements were refined based on the panel’s input, and consensus was reached on both modified statements (2 out of 2, 100.0%) during round 2. Overall, consensus was achieved on 15 statements ($\geq 80\%$ voted “1” or “2” to accept completely or with minor changes). The final consensus statements are shown in Table 1. The corresponding algorithm for TN CLL is illustrated in Fig. 1. The following sections cover the clinical reasoning and supporting evidence for the final consensus statements.

General principles of treatment

Early-stage and asymptomatic CLL

CLL is a heterogenous disease with a variable clinical course. A subset of CLL patients can live with their disease without needing any active

treatment over the course of their life, while other patient subsets require treatment and exhibit poor overall survival (OS) and progression-free survival (PFS) even with multiple therapeutic interventions.¹⁷ Only 5% of CLL patients require treatment at diagnosis.¹⁷ Table 2 provides an overview of the suggested clinical workup for newly diagnosed CLL in routine practice settings, as per iwCLL criteria.¹⁸ For most patients, active surveillance (i.e. watchful waiting) is considered appropriate until there are signs of active disease, as defined by iwCLL criteria.¹⁸ In line with iwCLL criteria, the authors recommend initiating treatment only for symptomatic patients.¹⁸ For asymptomatic patients or those not meeting iwCLL treatment criteria, any concurrent conditions, such as autoimmune haemolytic anaemia or immune thrombocytopenia, should be investigated and addressed prior to considering CLL-specific therapy. All international guidelines support this approach of watchful waiting in asymptomatic disease.

Several clinical trials have sought to address whether active treatment with monotherapy or combinations offers meaningful benefit for early-stage asymptomatic patients with CLL, particularly those at a higher risk of disease progression. These include trials of fludarabine monotherapy (CLL-1),¹⁹ fludarabine, cyclophosphamide and rituximab (FCR; CLL7)¹⁹ and ibrutinib (CLL12).²⁰ However, none of these trials demonstrated OS benefit with active treatment versus (vs) active surveillance for asymptomatic early-stage CLL in patients with high-risk genetic profiles, i.e. *TP53* mutation or *del*(17p). With the continuing development of additional novel targeted agents, there has been interest in re-evaluating the benefits of early therapeutic intervention. Several phase II/III trials comparing early intervention using newer targeted agents with watchful waiting are ongoing, including acalabrutinib-venetoclax (PreVent-ACaLL, NCT03868722),²¹ acalabrutinib with or without obinutuzumab (NCT03516617)²² and venetoclax-obinutuzumab (EVOLVE, NCT04269902).²³ Considering the available evidence, the authors favour the current standard approach of monitoring early-stage asymptomatic patients with CLL until there is evidence of disease progression and/or symptoms¹⁸ (see statement 1 in Table 1).

Pre-treatment testing

Due to the heterogeneous characteristics of CLL, pre-treatment testing of molecular biomarkers is considered valuable for guiding patient counselling, prognosticate disease and subsequent disease management.^{9,18} Cytogenetic aberrations (assessed using fluorescence in situ hybridisation, or FISH) and the somatic hypermutation (SHM) status of the *IGHV*

Table 1. Final list of consensus statements.

Statement no.	Statement	Level of evidence ^a	Evidence	% agreement (voted "1" or "2") ^b	Consensus achieved in
General principles of treatment					
1	For treatment-naïve CLL patients who do not meet the iwCLL 2018 criteria for initiation of therapy, a watchful waiting approach is recommended.	I	CLL12, iwCLL guidelines 2018	100.0%	Round 1
2	Besides FISH testing for del(17p), it is important to evaluate TP53 and IGHV mutational status to guide appropriate treatment choices.	N.A.	iwCLL guidelines 2018, NCCN CLL/SLL guidelines version 3.2023, ESMO guidelines, ERIC recommendations	100.0%	Round 1
3	In general, and where equally available, novel targeted agents are preferred over CIT. CIT may be a reasonable option for patients who are fit, IGHV-mutated, without del(17p) or TP53 mutation after appropriate counselling on increased risk of acute haematological toxicity, infection and small increased risk of secondary myeloid malignancies. Note: applies to all subpopulations; subpopulation-specific statements included under respective sections	I	CLL14, E1912, ELEVATE-TN, Alliance A041202, ECOG ACRIN	100.0%	Round 1
4	In general, where novel agents are to be used, the choice between continuous (e.g. BTKi therapy) or time-limited therapy (e.g. V+O or upcoming combinations) should be based on careful consideration of factors including genomic alterations, side-effect profile, patient preferences, comorbidities and medications, logistics and cost, as well as physician judgement.	N.A.	NCCN CLL guidelines version 3.2023	100.0%	Round 1
5	Where continuous treatment is selected, second-generation BTKis (acalabrutinib or zanubrutinib) may be preferred to first-generation BTKis (ibrutinib) based on their side effect profile. Where acalabrutinib is selected, it can be used alone or combined with obinutuzumab. Notes: This statement applies to the following subpopulations: - patients with del(17p) or TP53 mutation - unfit, IGHV-mutated patients without del(17p) or TP53 mutation - IGHV-unmutated patients without del(17p) or TP53 mutation	II	ELEVATE-TN, SEQUOIA, NCCN CLL/SLL guidelines version 3.2023, ESMO guidelines 2020 Note: No head-to-head comparisons in the TN setting.	100.0%	Round 1

Table 1. Final list of consensus statements. (Cont'd)

Statement no.	Statement	Level of evidence ^a	Evidence	% agreement (voted "1" or "2") ^b	Consensus achieved in
Treatment in patients with del(17p) or TP53 mutation					
6	Novel targeted agents (within either continuous or time-limited treatment regimens) are recommended for patients with del(17p) or TP53 mutation; the choice of novel agent(s) should be based on careful consideration of factors including patient preferences, side effect profile, comorbidities and medications, logistics and cost, as well as physician judgement.	I	iLLUMINATE, CLL14	100.0%	Round 1
7	For time-limited treatment for young patients with del(17p) or TP53 mutation, a BTKi+BCL2 inhibitor combination may be considered, accepting heightened risks of hypertension and low but not insignificant risk of cardiac arrhythmia. <i>Note: The only currently approved combination is I+V in Singapore, Europe and Canada. More evidence on other BTKi+BCL2i combinations are expected as survival data from ongoing trials mature (e.g. A+V±O: AMPLIFY, Z+V: SEQUOIA).</i>	I	CAPTIVATE	100.0%	Round 1
8	Time-limited V+O combination is less preferred for patients with del(17p) or TP53 mutation, but may be an option for patients preferring time-limited treatment, after careful counselling of higher risk of progression after time-limited treatment.	I	CLL14, CLL14 follow-up	100.0%	Round 1
Treatment in IGHV-mutated patients without del(17p) or TP53 mutation					
9	Recommended treatment options for fit, IGHV-mutated patients without TP53 mutation, del(17p) are single agent BTKi (first gen), FCR [patients with no del(11q)], V+O or BTKi+BCL2 inhibitor combination, the choice of which should be based on careful consideration of factors including patient preferences, side effect profile, comorbidities and medications, logistics and cost, as well as physician judgement, after appropriate counselling on high rates of haematological toxicity, infection, and small increased risk of secondary myeloid malignancies.	I	CLL8, CLL13 (GAIA), RESONATE-2, ECOG, ALLIANCE, E1912 and E1912 long-term follow-up	87.5%	Round 1
10	If CIT is selected, FCR is the preferred CIT regimen in fit patients without TP53 mutation, del(17p) or del(11q) and IGHV mutated.	I	CLL10, CLL8 and follow-up data	100.0%	Round 2

Table 1. Final list of consensus statements. (Cont'd)

Statement no.	Statement	Level of evidence ^a	Evidence	% agreement ("1" or "2") ^b	Consensus achieved in
12	If time-limited treatment is selected, V+O or I+V is the preferred treatment option in unfit, <i>IGHV</i> -mutated patients without del(17p), or <i>TP53</i> mutation.	I	CLL14	100.0%	Round 1
13	After V+O or I+V, the next preferred time-limited treatment options for unfit, <i>IGHV</i> -mutated patients without del(17p), or <i>TP53</i> mutation include B+R, Clb+O, single-agent rituximab, single-agent obinutuzumab or single-agent chlorambucil.	I	RO5072759 [GA101], CLL14, GAGE, CLL5, Rituximab Phase II trial, NCCN CLL/SLL guidelines Version 3.2023	100.0%	Round 2
Treatment in <i>IGHV</i>-unmutated patients without del(17p) or <i>TP53</i> mutation					
14	Novel targeted agents (continuous or time-limited) are recommended for <i>IGHV</i> -unmutated patients without <i>TP53</i> mutation, or del(17p); the choice of novel agent(s) should be based on careful consideration of factors including patient preferences, side effects, comorbidities and medications, logistics and cost, as well as physician judgement.	I	RESONATE-2, ELEVATE-TN, SEQUOIA, CLL 14 and follow-up data, GLOW	100.0%	Round 1
15	If time-limited treatment is selected, V+O or I+V combination is preferred for <i>IGHV</i> -unmutated patients without del(17p) or <i>TP53</i> mutation.	I	CLL14	100.0%	Round 1

^a Level of evidence: I — Evidence from at least 1 large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity; II — Small randomised trials or large randomised trials with a suspicion of bias (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity

^b Level of agreement: 1 — "accept completely", 2 — "accept with minor changes"

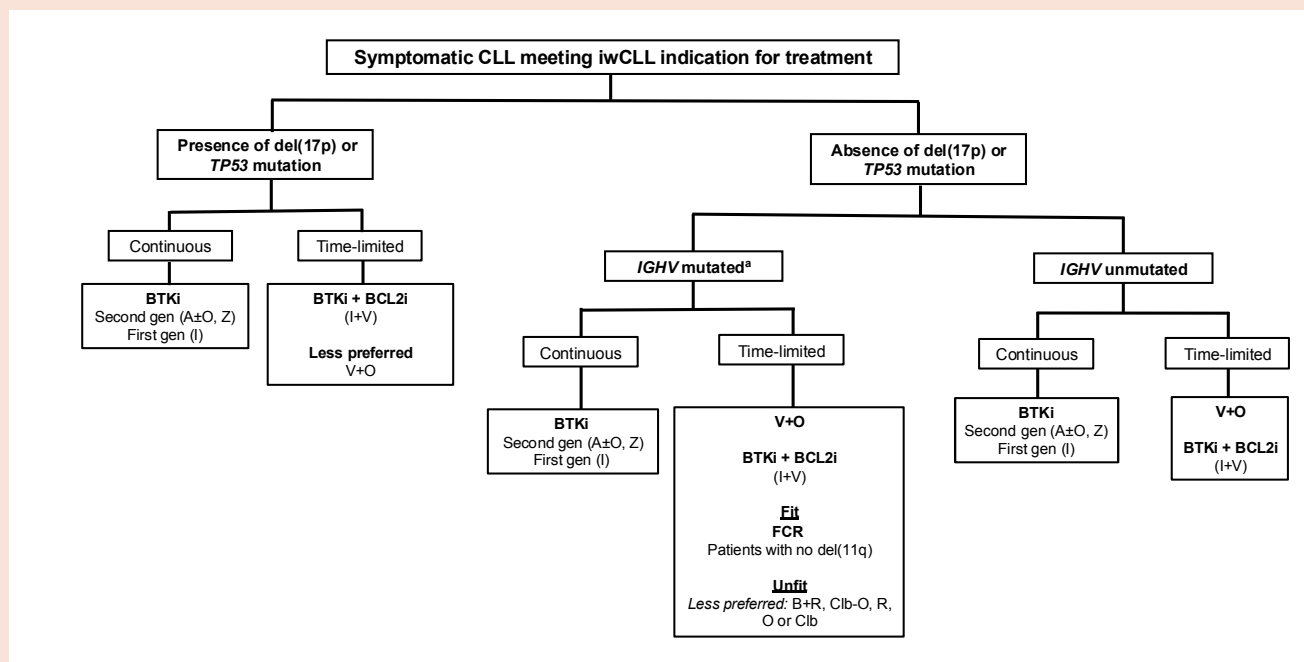
A: acalabrutinib; B: bendamustine; BCL2: B-cell lymphoma 2; BTKi: Bruton's tyrosine kinase inhibitor; C: cyclophosphamide; CIT: chemioimmunotherapy; Chl: chlorambucil;

CLL: chronic lymphocytic leukaemia; ESMO: European Society for Medical Oncology; ERIC: European Research Initiative on CLL; F: fludarabine; FISH: fluorescence in situ hybridisation; I: ibrutinib;

IGHV: immunoglobulin heavy chain gene; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; O: obinutuzumab; R: rituximab; R1: Round 1; R2: Round 2;

SLL: small lymphocytic lymphoma; TN: treatment-naïve; *TP53*: tumour protein p53; V: venetoclax; Z: zanubrutinib

Fig. 1. Algorithm for treatment-naïve CLL.



Treatment should be initiated for symptomatic patients who meet iwCLL criteria. For patients with a high-risk profile—e.g. del(17p)/TP53 mutation, unmutated *IGHV*—regimens containing active targeted agents should be prioritised. The choice of treatment regimen should be based on careful consideration of a range of factors including genomic alterations, side-effect profile, patient preference, comorbidities and medications, logistics and cost, as well as physician judgement.

* A subset of *IGHV*-mutated patients (stereotyped B-cell receptor (BCR) Subset 2) exhibit an aggressive clinical course and poor prognosis and should be treated similarly to patients with high-risk genetic profiles, i.e. TP53 mutation or del(17p).

A: acalabrutinib; B: bendamustine; BCL2i: B-cell lymphoma 2 inhibitor; BTKi: Bruton's tyrosine kinase inhibitor; Clb: chlorambucil; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; CrCl: creatinine clearance; gen: generation; I: ibrutinib; *IGHV*: immunoglobulin heavy chain gene; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; O: obinutuzumab; R: rituximab; V: venetoclax; Z: zanubrutinib

gene (assessed using Sanger sequencing or next-generation sequencing) are important biomarkers that provide both prognostic and predictive information in CLL.^{18,24-26} Patients with del(17p) or TP53 mutation show poor responses to chemoimmunotherapy (CIT) but respond better to targeted agents.^{18,27-29} In general, patients with unmutated *IGHV* (defined as <2% somatic hypermutation relative to the germline sequence) have a poorer prognosis than those with mutated *IGHV* due to faster tumour cell regrowth kinetics.^{9,30} An exception is the B-cell receptor (BCR) stereotyped subset 2, representing 3% of CLL cases; although appearing *IGHV*-mutated in terms of SHM status, this subset is characterised by an aggressive clinical course and a poor prognosis.^{31,32}

The authors acknowledge the key factors of availability, accessibility and affordability in facilitating the uptake of molecular testing. A recent Asian consensus highlighted that resources for *IGHV* mutation testing are scarce in several Asian countries.⁹ As *IGHV* mutational status does not change over time, *IGHV* mutational testing can be done at the time of diagnosis. In contrast, cytogenetic

testing should be conducted pre-treatment, as these aberrations may accumulate over the course of the disease¹⁸ (see statement 2 in Table 1).

Patient fitness

Patient fitness has been an important consideration for treatment selection, notably in the context of chemotherapy and CIT regimens. In clinical trials, the Cumulative Illness Rating Scale (CIRS) and creatine clearance (CrCl) are often used in combination to define patients' fitness to receive CIT.^{33,34} Fit patients are commonly defined as those aged <65 years with a CIRS score <6 and CrCl ≥70 mL/min.

In real-world practice, the assessment of fitness has evolved from focusing on chronological age to considering the patient's physical condition and comorbidities. As such, comprehensive geriatric assessments and frailty indices may support a more nuanced evaluation of fitness and may be helpful in specific cases. That said, the CIRS remains practical and highly relevant in clinical settings as a well-established, standardised approach and judgements based on the CIRS and CrCl criteria are easily aligned with clinical trial data.

Table 2. Overview of clinical workup for newly diagnosed chronic lymphocytic leukaemia in routine practice settings.

Recommendations (as per iwCLL 2018 guidelines) ¹⁸ and notes	
Diagnosis	
Blood tests	CBC with different count • ($\geq 5 \times 10^9/L$ B lymphocytes in the peripheral blood for at least 3 months)
Immunophenotyping	Flow cytometry analysis of peripheral blood to confirm • Expression of CD19, CD20, CD23 • CD5 co-expression • Expression of kappa or lambda immunoglobulin light chains
Before treatment	
Medical history and physical examination	• Complete physical examination, including evaluation of lymph nodes, liver and spleen • Performance status (ECOG) • Comorbidities
Laboratory studies	• CBC with differential count • Serum chemistry (liver and kidney function) • Serum immunoglobulin levels • Direct antiglobulin test • Infectious disease status (e.g. cytomegalovirus, hepatitis B virus or hepatitis C virus)
Imaging	• Chest radiograph
Other tests	
Cytogenetics and molecular genetics studies	• Interphase FISH tests for del(13q), del(11q), del(17p), trisomy 12 in peripheral blood lymphocytes • TP53 mutation analysis • IGHV mutational status

CBC: complete blood count; CLL: chronic lymphocytic leukaemia; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescence in situ hybridisation; iwCLL: International Workshop on CLL; TP53: tumour protein p53; IGHV: Immunoglobulin heavy chain gene

Treatment with novel targeted agents

Multiple studies have demonstrated the superior efficacy of novel targeted agents for TN symptomatic CLL, and these agents are now considered the standard of care in several healthcare systems.^{5,6,10,11,35} Targeted agents include Bruton's tyrosine kinase inhibitors (BTKis, such as ibrutinib, acalabrutinib and zanubrutinib) and B-cell lymphoma 2 inhibitors (BCL2is, such as venetoclax).³⁶ CIT, the previous standard of care, may be a reasonable treatment option under certain circumstances, as discussed in later sections. However, CIT would not be considered for subgroups expected to show poor response to CIT, including patients with del(17p), TP53 mutations and the BCR stereotyped subset 2 (i.e. poor prognosis CLL subset characterised by IGHV3-21 gene expression with a short immunoglobulin heavy chain complementarity determining region 3, and a progressive phenotype regardless of IGHV mutational status³⁷). Pivotal randomised controlled trials (RCTs) of frontline therapies for CLL are summarised in Table 3. Most of these RCTs enrolled patients aged ≥ 65 years or unfit patients aged ≥ 18 years to < 65 years, except for ALLIANCE A041202, which included only patients aged ≥ 65 years.³⁸

Clinical trials of first-generation (i.e. ibrutinib) and second-generation BTKis (i.e. acalabrutinib and zanubrutinib) have demonstrated the superior efficacy of these targeted agents over standard CIT regimens for TN CLL. In the E1912 trial, the ibrutinib-rituximab combination demonstrated superior PFS (hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.22–0.56) and OS (HR 0.17, 95% CI 0.05–0.54) compared with the FCR regimen in fit, young patients (< 70 years) with TN CLL without del(17p).³⁹ In the ALLIANCE A041202 trial, ibrutinib alone (HR 0.39, 95% CI 0.26–0.58) and ibrutinib-rituximab (HR 0.38, 95% CI 0.25–0.59) both demonstrated superior PFS to bendamustine-rituximab (BR) in TN CLL patients ≥ 65 years; however, the OS duration was similar across the treatment arms.⁴⁰ Notably, the incidence of grade ≥ 3 hypertension and atrial fibrillation adverse events (AEs) was significantly higher with ibrutinib-containing regimens than with CIT ($P < 0.05$) in ALLIANCE.⁴⁰ The ELEVATE-TN trial showed that acalabrutinib, with or without obinutuzumab, significantly prolonged PFS vs obinutuzumab-chlorambucil in elderly and generally less fit patients (CIRS score > 6 or reduced creatinine clearance).³⁸ No cardiac AEs were reported with acalabrutinib-containing regimens in ELEVATE-

Table 3. Pivotal studies for treatment-naïve CLL.

Study	Population ^a	Design	PFS benefit for experimental arm?	OS benefit for experimental arm?
Alliance A041202 (phase 3) ⁴⁰	Fit, older patients (>65 years), del(17p) allowed	BR vs lbru vs IR	YES, IR superior 2-year PFS rate: 74% (BR) vs 87% (I) vs 88% (IR)	NO 2-year OS rate: 95% (BR) vs 90% (I) vs 94% (IR)
CLL5 (phase 3) ⁶⁶	Treatment-naïve, ≥65, Binet stage C, ECOG 0–2	F vs Clb	NO 19 months for F vs 18 months for Clb	NO 46 months for F vs 64 months for Clb
CLL8 (phase 3) ²⁹	Treatment-naïve, physically fit, age 30–80, CD20+	FC vs FC+R	YES, FC+R superior 3-year PFS rate: 65% (FCR) vs 45% (FC)	NO not reached for FCR vs 86.0 months for FC
CLL10 (phase 3) ⁷⁶	Treatment-naïve, physically fit, age 30–80, no del(17p)	FCR vs BR	YES, FCR superior PFS 41.7 months BR and 55.2 months	NO
CLL12 (phase 3) ²⁰	Treatment-naïve, Binet stage A, ECOG 0–2	Observational: no treatment Treatment: I vs placebo	YES 3-year PFS rate: 80.9% (lbru) vs 28.5%	-
CLL13 (GAIA) (phase 3) ⁵⁷	Fit, no TP53 aberrations	CIT: FCR or BR V combinations: VR vs VO vs VO+I	YES, VO+I most superior 3-year PFS rate: 90.5% (VO+I) vs 87.7% (VO) vs 80.8% (VR) vs 75.5% (CIT)	NO 3-year OS rate: 95.3% (VO+I) vs 96.3% (VO) vs 96.5% (VR) vs 95.0% (CIT)
CLL14 (phase 3) ⁴⁷	Unfit (CIRS > 6 or CrCl <70)	VO vs Clb-O	YES, VO superior 3-year PFS rate: 82% (VO) vs 50% (Clb-O)	NO 24-month OS rate 92% (VO) vs 93% (Clb-O)
CAPTIVATE (phase 2) ⁵⁵	Treatment-naïve, ≥70 years	I+V	YES 24-month PFS rate 95%	YES 24-months OS rate 98%
E1912 (phase 3) ^{39,59}	Fit, no del(17p)	FCR vs I+R	YES, IR superior 3-year PFS rate: 73% (FCR) vs 89% (IR)	YES 3-year OS rate: 92% (FCR) vs 99% (IR)
GAGE ⁷⁷	Treatment-naïve CLL	O 1000 mg vs 2000 mg	YES, but not superior	-
ELEVATE-TN (phase 3) ^{38,41}	Unfit (CIRS > 6 or CrCl <70)	A vs A+O vs Clb-O	YES, A+O superior Estimated 24-month PFS rate: 93% (A+O) vs 87% (A) vs 47% (Clb-O)	YES Estimated 24-month OS rate: 95% (A+O) vs 95% (A) vs 92% (Clb-O)

Table 3. Pivotal studies for treatment-naïve CLL. (Cont'd)

Study	Population ^a	Design	PFS benefit for experimental arm?	OS benefit for experimental arm?
FLAIR (phase 3) ⁵⁸	Treatment-naïve, fit to receive FCR, age 18–75, WHO performance status ≤2, and treatment required from iwCLL criteria	I+V vs I vs FCR	YES, I+V superior to FCR. Estimated 3-year PFS rate: 97.2% (I+V) vs 76.8% (FCR)	YES 3-year OS rate: 98.0% (I+V) vs 93.0% (FCR)
GLOW (phase 3) ⁴⁸	≥65 years OR CIRS >6	I+V vs Clb-O	YES, I+V superior Estimated 30-month PFS rate 80.5% (I+V) vs 35.8% (Clb-O)	NO
HDMP+R ⁷⁸	Treatment-naïve	HDMP+R	YES PFS 30.5 months	YES 3-years OS rate 96%
iLLUMINATE (phase 3) ⁶¹	Unfit (CIRS>6 or CrCl<70) or TP53 del/mut	I+V vs Clb-O	YES Estimated 30-month PFS rate 79% (I+V) vs 31% (Clb-O)	NO Estimated 30-month OS rate: 86% (I+V) vs 85% (Clb-O)
RESONATE-2 (phase 3) ⁶⁰	≥65 without del(17p)	I vs Clb	YES 5-year PFS rate: 70% (I) vs 12% (Clb)	YES 5-year OS rate: 83% (I) vs 68% (Clb)
Rituximab (phase 2) ⁶⁵	Treatment-naïve	R	YES 1- and 2-year PFS rates were 62% and 49%, respectively	YES
RO5072759 [GA101] (phase 3) ⁶⁴	Treatment-naïve, CIRS >6	Clb-O vs Clb vs Clb-R	YES, Clb superior Median PFS 26.7 months (Clb-O) vs 11.1 months (Clb) vs 16.3 months (Clb-R)	YES OS rate 9% (Clb-O) vs 20% (Clb) vs 15% (Clb-R)
SEQUOIA (phase 3) ⁴²	Untreated, ≥65 years, ECOG 0–2	Z vs BR	Median PFS not reached in either arm. Z showed longer PFS.	NO Estimated 24-month OS rate 94.3% (Z) vs 94.6% (BR)

^a Fit patients are defined as those aged <65 years with a CIRS score <6 and CrCl ≥70 mL/min

A: acalabrutinib; B: bendamustine; Clb: chlorambucil; CLL: chronic lymphocytic leukaemia; ClT: chemoimmunotherapy; CrCl: creatinine clearance; CIRS: Cumulative Illness Rating Scale; C: cyclophosphamide; ECOG: Eastern Cooperative Oncology Group; F: fludarabine; HDMP: high-dose methylprednisolone; FCR: fludarabine + cyclophosphamide + rituximab; I: ibrutinib; iwCLL: International Workshop on CLL; PFS: progression-free survival; O: obinutuzumab; OS: overall survival; R: rituximab; V: venetoclax; WHO: World Health Organization; Z: zanubrutinib

TN.³⁸ The efficacy and safety of acalabrutinib, with or without obinutuzumab, were maintained at 6 years of follow-up. Estimated 72-month PFS rates were 78% for acalabrutinib-obinutuzumab, 62% for acalabrutinib monotherapy and 17% for obinutuzumab-chlorambucil.⁴¹ The median OS was not reached in any treatment arm and was significantly longer on acalabrutinib-obinutuzumab vs obinutuzumab-chlorambucil.⁴¹ The SEQUOIA study demonstrated superior PFS for zanubrutinib vs BR in TN CLL patients >65 years, with the rates of grade ≥ 3 cardiac events being similar across treatment arms.⁴² BTKis carry a possible risk for cardiac toxicity, as noted in studies on ibrutinib, although this risk is lower with second-generation agents (e.g. acalabrutinib, zanubrutinib). Clinicians should weigh the risks and benefits accordingly. Recent analyses, including a 3-year real-world study, reported a more favourable cardiovascular safety profile including lower rates of atrial flutter, hypertension and sepsis in patients treated with acalabrutinib vs ibrutinib.⁴³ Safety analyses using FDA Adverse Event Reporting System (FAERS) data highlighted that ibrutinib carries a higher incidence of severe cardiovascular events, notably atrial fibrillation, cardiac failure, pericardial effusion or haemorrhage, underscoring the need for careful patient selection and toxicity monitoring with long-term therapy.^{44,45}

Similarly, BCL2i-containing regimens were superior to CIT comparator regimens in TN CLL patients with coexisting conditions. In the CLL14 study, unfit patients with CIRS score >6 venetoclax-obinutuzumab for a fixed duration of 1 year demonstrated a significantly lower risk of progression than those receiving chlorambucil-obinutuzumab (HR 0.35, 95% CI 0.23–0.453).⁴⁶ The reduced risk of progression with venetoclax-obinutuzumab was maintained at 2 years after treatment cessation (HR 0.31, 95% CI 0.22–0.44).⁴⁷ Several trials, including CAPTIVATE and GLOW, have assessed the effects of combining a BCL2i with a BTKi.^{48,55} In GLOW, treatment with a fixed-duration combination of venetoclax plus ibrutinib significantly reduced the risk of progression compared with chlorambucil-obinutuzumab (HR 0.22; 95% CI 0.13–0.36; $P < 0.001$).⁴⁸

Targeted agents are now generally preferred over CIT because of their superior efficacy (see statement 3 in Table 1). In higher-risk TN CLL patients, i.e. unmutated or with del(17p) or *TP53* mutation, CIT is generally not recommended, given the significantly inferior outcomes compared with BTKi or BCL2i-based therapy. CIT may be considered for TN CLL patients who are fit and have low-risk disease, i.e. mutated *IGHV*, without del(17p) or *TP53* mutation, after careful consideration of side-effects side effects

associated with CIT—such as increased risk of acute haematological toxicity and infection, and a small increased risk of secondary myeloid malignancies.^{49,50}

Important considerations for selecting initial therapy in CLL include genetic risk, side-effect profile, clinical characteristics in a patient (overall fitness/performance, organ function, comorbidities), patient preference (e.g. if there is a choice between continuous or time-limited therapy, or method of administration, such as intravenous injections), cost, accessibility and logistical concerns. Additionally, physician and centre experience managing treatment-related side effects may influence treatment selection. Resource availability at the system level, including access to specific drugs and diagnostic tests, may also be a relevant consideration. Treating physicians should consider all these aspects and carefully counsel their patients to support informed decision-making as appropriate within their local context (see statement 4 in Table 1).

Treatment in patients with del(17p) or *TP53* mutation

The presence of *TP53* aberrations or del(17p) has historically been associated with poor prognosis,^{27,29} with a median PFS of 11.3 months on FCR therapy.⁵¹ The introduction of small-molecule inhibitors (BTKis and BCL2is) significantly improved PFS among previously untreated patients with del(17p) or *TP53* mutation,^{38,40,46} and these targeted agents are now considered the standard of care for this patient subset.

A pooled analysis of 4 trials (PCYC-1122e, RESONATE-2, iLLUMINATE and E1912) included 89 patients with del(17p) or *TP53* mutation receiving single-agent ibrutinib ($n=45$) or ibrutinib in combination with an anti-CD20 antibody ($n=44$). In this analysis, median PFS was not reached at 4 years of follow-up, and the estimated 4-year PFS and OS rates were 79% and 88%, respectively.⁵² Direct comparisons between continuous BTKi therapy vs time-limited targeted agent-based combinations are not available as the head-to-head trials are ongoing (e.g. CLL17/NCT04608318). However, there are indications that continuous BTKi therapy may confer longer PFS than time-limited regimens. While exercising caution in drawing inferences from cross-trial comparisons, at 76.4 months of follow-up in the CLL14 study for 10% of patients with del(17p) or *TP53* mutation,⁴⁶ patients treated with fixed-duration venetoclax-obinutuzumab had a median PFS of 51.9 months.⁵³ The 5-year PFS for del(17p) or *TP53* mutated patients was 40.6%, and the approximate 4-year estimated PFS was 52%.⁵⁴ Other highly-anticipated readouts include longer-term follow-up data for ibrutinib-venetoclax

time-limited treatment regimens. Several factors are relevant when choosing between continuous BTKi-based therapy and time-limited therapy with venetoclax combinations. Time-limited therapy can potentially produce complete responses⁴² and allows for treatment-free intervals, which some patients may prefer. With finite treatment duration, there may be reduced risk of toxicity and potentially lower drug-related costs. However, these potential advantages must be weighed against additional requirements for safety monitoring (risk of tumour lysis syndrome) and dose ramp-up, which have logistical implications.

Available evidence indicates that second-generation BTKis are as effective as ibrutinib for the del(17p) or TP53-mutated patient subset. ELEVATE-TN randomised patients to receive acalabrutinib monotherapy, acalabrutinib-obinutuzumab, or obinutuzumab-chlorambucil.³⁸ A pre-specified subgroup analysis of ELEVATE-TN showed that the PFS benefit with acalabrutinib therapy was consistent across subgroups, including patients with del(17p) and TP53 mutation (14% of patients).³⁸ As for zanubrutinib, Arm C of the SEQUOIA trial includes patients with del(17p13.1) receiving zanubrutinib monotherapy.⁴² At the 24-month follow-up, the PFS and OS rates for Arm C were 88.9% and 93.6%, respectively.⁴² Given the accruing evidence for both first- and second-generation BTKis, continuous BTKi therapy is preferred over time-limited regimens for patients with del(17p) or TP53 mutation^{42, 52} (see statement 6 in Table 1).

Although continuous therapy is preferred in TP53 patient group, a BTKi + BCL2i time-limited regimen could be considered in the case of cardiac or bleeding concerns. Evidence supporting the use of venetoclax-BTKi combinations for patients with del(17p) or TP53 mutation has been limited, as trials have included few of these patients. However, the ongoing CAPTIVATE trial includes patients with del(17p) or TP53 mutation (17% of patients with known mutational status).⁵⁵ A follow-up analysis of CAPTIVATE data estimated the 4-year PFS and OS rates in this patient population at 63% and 96%, respectively.⁵⁶ In the venetoclax-obinutuzumab arm of CLL14, the grade ≥ 3 AE rates were 78.8% for all AEs, 52.8% for neutropenia and 6.6% for vascular AEs (i.e. hypertension and hypotension).⁴⁶ Of note, the incidence of grade ≥ 3 tumour lysis syndrome was lower with venetoclax-obinutuzumab than with chlorambucil-obinutuzumab (1% vs 3%).⁴⁶ In view of the available evidence, a BTKi-BCL2i combination is preferred over a combination of BCL2i plus an anti-CD20 monoclonal antibody for patients with del(17p) or TP53 mutation who prefer time-limited treatment (see statements 7 and 8 in Table 1).

However, it should be noted that the follow-up of trials using BTKi and BCL2i combination regimens are relatively short.

Treatment in fit, IGHV-mutated patients without del(17p), TP53

The choice of treatment for TN CLL patients with mutated IGHV depends on their age, physiological fitness, presence of comorbidities, and FCR eligibility. As discussed above, younger patients (<65 years) with a CIRS score of <6 and CrCl ≥ 70 mL/min are considered fit to receive a more intensive CIT regimen in clinical trials.^{33,34} In clinical practice, physicians may consider older patients (≥ 65 years) with good functional capacity or without comorbidities fit for treatment. Notably, the clinical trials discussed in this section included a substantial proportion of fit older patients, including 41% of patients in the E1912 trial,³⁹ 84% of those in ELEVATE-TN,³⁸ and 34% of patients enrolled in GAIA (CLL13).⁵⁷

For several years, fixed-duration CIT or chemotherapy was the standard treatment for previously untreated fit patients. FCR therapy in TN CLL was associated with significant PFS benefit over FC across several prognostic subgroups, including patients with mutated IGHV.⁵¹ A 5.9-year follow-up analysis of the CLL8 trial confirmed significant OS and PFS benefit with FCR over FC across several prognostic subgroups, including patients with mutated IGHV (HR [progression] 0.47, 95% CI 0.33–0.68; HR [death] 0.62, 95% CI 0.34–1.11).⁵¹ Median PFS and OS were not reached among IGHV-mutated patients who received FCR.⁵¹ In CLL10, frontline FCR therapy was associated with a higher PFS rate than BR at 31.7 months of follow-up. Although patients aged ≤ 65 years derived significant PFS benefit from FCR in CLL10, there was no significant PFS difference between FCR and fludarabine-cyclophosphamide (FC) for physically fit older patients aged >65 years (median PFS not reached vs 48.5 months; $P=0.172$).

Some studies have demonstrated the superiority of ibrutinib-based therapy over FCR in unselected CLL patient populations, including E1912 and FLAIR. Approximately 29% of patients in E1912 and 33.1% of those in FLAIR had mutated IGHV.^{39,58} Although the planned interim analysis for E1912 (ibrutinib-rituximab vs FCR) showed a similar 3-year PFS rate in both treatment arms for patients with mutated IGHV (87.7% vs 88.0%; HR 0.44, 95% CI 0.14–1.36),³⁹ a long-term follow-up analysis (median follow up of 70 months) showed a significantly better 5-year PFS rate with ibrutinib-rituximab vs FCR (83% vs 68%; HR 0.27, 95% CI 0.11–0.62).⁵⁹ In FLAIR, a randomised trial (minimal residual disease-guided therapy comparing ibrutinib

monotherapy with ibrutinib-venetoclax for up to 6 years vs FCR), ibrutinib-venetoclax therapy showed significantly higher efficacy than standard FCR.⁵⁸ After a median follow-up of 44 months, the 3-year PFS rate was 97.2% for ibrutinib-venetoclax vs 76.8% for FCR (HR [progression] 0.13, 95% CI 0.07–0.24), with OS benefit (HR 0.31, 95% CI 0.15–0.67), in the overall trial population.⁵⁸ However, the PFS results in the *IGHV*-mutated subgroup did not favour ibrutinib-venetoclax over FCR at the time of the analysis (HR 0.54, 95% CI 0.21–1.38). The OS results favoured ibrutinib-venetoclax in *IGHV*-unmutated patients (HR 0.23, 95% CI 0.06–0.81) but not in *IGHV*-mutated patients (HR 0.61, 95% CI 0.20–1.82).⁵⁸ It remains to be seen how and whether longer follow-up will impact these results as in the E1912 trial.

The GAIA trial showed that venetoclax-based combinations (venetoclax-rituximab vs venetoclax-obinutuzumab vs venetoclax-obinutuzumab-ibrutinib) were superior to CIT (FCR or BR) in physically fit patients with TN CLL. At 38.8 months of follow-up, among patients with unmutated *IGHV*, PFS rates were 86.6% in the venetoclax-obinutuzumab-ibrutinib group, 82.9% in the venetoclax-obinutuzumab group, 76.4% in the venetoclax-rituximab group and 65.5% in the CIT group, as compared with 96.0%, 93.6%, 87.0% and 89.9%, respectively, in patients with mutated *IGHV*. In the prespecified subgroup analysis, this benefit of venetoclax-obinutuzumab therapy with or without ibrutinib was observed in all groups except for those with mutated *IGHV*, trisomy 12, normal karyotype and intermediate CLL-IPI scores. OS rates at 3 years were comparable across all treatment arms.⁵⁷ Overall grade ≥ 3 SAEs were numerically higher in the venetoclax-obinutuzumab-ibrutinib arm compared with CIT or other venetoclax arms.⁵⁷

Based on available evidence, first-generation BTKi-based or venetoclax-based regimens or FCR are reasonable options for fit patients with mutated *IGHV*. Expected toxicity profiles, medical comorbidities, patient preference, cost, accessibility and logistical concerns all play an important role in guiding treatment decisions (see statements 9 and 10 in Table 1). As for FCR, the availability of data on long-term outcomes of BTKi-based and venetoclax-based therapy trials will help clarify their comparative “curative” potential in this patient subset.

Treatment in unfit, *IGHV*-mutated patients without del(17p) or TP53 mutation

Several targeted agents have been investigated for the treatment of unfit patients with mutated *IGHV*. In the ALLIANCE study, ibrutinib with or without rituximab was superior to BR with respect to PFS

in unfit older patients (note that *IGHV* mutation status was not reported).⁴⁰ Both RESONATE-2 and iLLUMINATE assessed the efficacy of ibrutinib-containing regimens in FCR-ineligible older patients. Up to 44% of the patients in RESONATE-2 had mutated *IGHV*; in this study, ibrutinib therapy was associated with significantly longer PFS (HR 0.16, 95% CI 0.09–0.28) and OS (HR 0.16, 95% CI 0.05–0.56) compared with chlorambucil. The PFS benefit with ibrutinib was consistently demonstrated across prespecified subgroups, including patients with mutated *IGHV* (HR 0.15, 95% CI 0.05–0.43).⁶⁰ Similarly, iLLUMINATE demonstrated PFS benefit with ibrutinib-obinutuzumab over chlorambucil-obinutuzumab (HR 0.25, 95% CI 0.16–0.39) at 45 months of follow-up. PFS benefit with ibrutinib-obinutuzumab was also observed in patients with mutated *IGHV* (HR 0.20, 95% CI 0.07–0.59).⁶¹

Clinical trials of second-generation BTKis (ELEVATE-TN and SEQUOIA) have enrolled FCR-ineligible older patients aged ≥ 65 years or unfit younger patients aged ≥ 18 years. Of 535 patients in ELEVATE-TN randomised to acalabrutinib or acalabrutinib-obinutuzumab or obinutuzumab-chlorambucil, there were 338 patients (63.1%) with unmutated *IGHV* and 191 (35.7%) patients with mutated *IGHV*.³⁸ Acalabrutinib-obinutuzumab significantly improved PFS vs obinutuzumab-chlorambucil in both *IGHV*-mutated patients (HR 0.15, 95% CI 0.04–0.52) and *IGHV*-unmutated patients (HR 0.08, 95% CI 0.04–0.16).³⁸ In SEQUOIA, PFS in *IGHV*-mutated patients who received zanubrutinib-rituximab was not significantly different from that in BR-treated patients (HR 0.67, 95% CI 0.36–1.22).⁴²

The results of CLL14 support a role for BCL2i-containing regimens in treating older or unfit younger patients with mutated *IGHV*. In CLL14, 39% of patients with known mutation status had mutated *IGHV*.⁶² In this *IGHV*-mutated subset, fixed-duration venetoclax-obinutuzumab significantly improved PFS relative to chlorambucil-obinutuzumab (HR 0.36, 95% CI 0.19–0.68) at 4 years of follow-up.⁶² In GLOW (26% with mutated *IGHV*), PFS was significantly longer with fixed-duration ibrutinib-venetoclax than with chlorambucil-obinutuzumab (HR 0.233, 95% CI 0.065–0.839) at 27.7 months, although with higher rates of cardiac toxicity related to ibrutinib.⁴⁸

Less intensive chemotherapy or CIT regimens for treatment-naïve unfit patients include bendamustine-rituximab,⁶³ chlorambucil-obinutuzumab,⁶⁴ single-agent rituximab,⁶⁵ obinutuzumab or chlorambucil.⁶⁶ As for fit *IGHV*-mutated patients, treatment selection for unfit patients should also consider expected toxicity profiles, presence of comorbidities, patient preference, cost, availability and logistical concerns (see statements 11–13 in Table 1).

Treatment in *IGHV*-unmutated patients without del(17p)

The presence of unmutated *IGHV* is consistently associated with poor prognosis in CLL, and it is one of the biomarkers included in the CLL-IPI.^{30,67,68} As for other patient subsets, including those with mutated *IGHV*, targeted therapies have shown notable efficacy for unfit patients with unmutated *IGHV*, and are thus recommended (see statements 14 and 15 in Table 1). Across trials of targeted agents, the proportions of patients with unmutated *IGHV* (known mutational status) were 44% in RESONATE-2, 58% in iLLUMINATE, 63% in ELEVATE-TN and 51% in SEQUOIA.^{38,42,60,61} In RESONATE-2, single-agent ibrutinib therapy significantly improved PFS vs chlorambucil (HR 0.13, 95% CI 0.06–0.31) at 18.4 months follow-up in older patients with unmutated *IGHV*.⁶⁰ Similarly, among patients with unmutated *IGHV* in E1912, ibrutinib-rituximab showed superior 3-year PFS compared with FCR (90.7% vs 62.5%; HR 0.26, 95% CI 0.14–0.50).³⁹ In a 48-month analysis of iLLUMINATE data, PFS outcomes in unfit patients with unmutated *IGHV* favoured ibrutinib-obinutuzumab over chlorambucil-obinutuzumab (HR 0.17, 95% CI 0.10–0.29). Similar trends have been noted with second-generation BTKi therapy in unfit patients with unmutated *IGHV*. In ELEVATE-TN, the 24-month PFS rate was higher in patients receiving acalabrutinib-obinutuzumab than those receiving obinutuzumab-chlorambucil (91% vs 31%; HR 0.08, 95% CI 0.04–0.16).³⁸ This was maintained at 6 years of follow-up, with the PFS rates in the *IGHV*-unmutated subgroup being 75% (acalabrutinib-obinutuzumab), 60% (acalabrutinib monotherapy) and 5% (obinutuzumab-chlorambucil).⁴¹ In the SEQUOIA study, zanubrutinib treatment was associated with improved PFS vs BR (HR 0.24; 95% CI 0.13–0.43) at 26.2 months follow-up.⁴²

BCL2i-containing regimens have shown superior PFS to standard CIT in patients with unmutated *IGHV*. In CLL14 (60% *IGHV*-unmutated patients), PFS outcomes at 24 months strongly favoured venetoclax-obinutuzumab over chlorambucil-obinutuzumab in patients with unmutated *IGHV* (HR 0.22, 95% CI 0.12–0.38).⁴⁶ In GLOW (52% *IGHV*-unmutated patients), PFS was also significantly longer with ibrutinib-venetoclax compared with chlorambucil-obinutuzumab (HR 0.269, 95% CI 0.148–0.488) at 27.7 months follow-up.⁴⁸

CONCLUSION

The clinical consensus developed through this modified Delphi process offers practical guidance for clinicians managing TN CLL patients in Singapore and similar healthcare systems. The recommendations made for different patient subsets are based on

a range of factors, from biomarker profiles to comorbidities, fitness and treatment preferences. For early-stage asymptomatic CLL patients, active surveillance is recommended, along with pre-treatment molecular biomarker testing to guide treatment selection. In general, targeted agents are prioritised over chemotherapy/CIT, especially for unfit patients, while chemotherapy/CIT may remain relevant for selected patients, e.g. young/fit and without del(17p) or *TP53* mutations. Although the use of targeted agents has improved outcomes in patients with del(17p) or *TP53* mutation, more effective regimens are needed to extend survival and preserve quality of life. Emerging strategies such as minimal residual disease (MRD)-guided adaptive approaches offer a promising way to tailor treatment duration to improve outcomes.⁵⁸ Although discussed in recent guideline updates,^{15,16} MRD-guided approaches are not considered sufficiently mature for routine adoption; moreover, these assessments require specialised flow cytometry capabilities and expertise that may not be widely available—an important practical consideration.¹¹ However, once adequately validated in clinical trials, MRD-guided approaches could help rationalise treatment choices and duration.

While this clinical consensus focuses primarily on guiding frontline management, it is relevant to consider the potential implications of initial treatment selection for subsequent therapy in the relapsed/refractory setting. Patients who relapse after treatment with a novel agent (BTKi or BCL2i) may show a response to an agent of the other class. Patients achieving remission on time-limited regimens (BCL2i combinations) can be re-treated if their remission lasted 3–5 years, while treatment with a BTKi remains an option irrespective of the duration of remission.^{10,11} On the other hand, patients relapsing after treatment with covalent BTKis (e.g. ibrutinib, acalabrutinib, zanubrutinib) are unlikely to respond to another covalent BTKi, and require alternatives such as BCL2i-based therapy. As more patients receive targeted agents earlier in the disease course, options to overcome resistance or intolerance will be increasingly important. Emerging options include non-covalent BTK inhibitors, such as pirtobrutinib, which have demonstrated promise in re-establishing BTK inhibition and clinical responses.^{69,70,71} Of note, ongoing pirtobrutinib trials have recruited Asian participants; these include head-to-head studies with covalent BTKis (NCT05254743, BRUIN-CLL-314).⁷² Such studies should provide valuable Asian-specific CLL outcome data, which have hitherto been very limited. Other agents like nemtabrutinib and vecabrutinib are being studied in ongoing trials, although resistance to non-covalent BTKis is also emerging.^{73,74} BTK protein

degraders may represent another emerging option in cases of BTKi resistance.⁷⁵

The main motivation of this consensus is to promote clinical practice improvement and standardisation, based on the best available evidence. As an additional benefit, the exercise of regularly updating clinical guidelines facilitates consultation and dialogue among funders, regulatory bodies, local experts and national societies. These interactions are important to guide selection and implementation of appropriate interventions, which may include tiered pricing or expanded access programmes, depending on the characteristics of the health system. Effective collaboration among all stakeholders is critical for securing appropriate access to effective therapies, and achieving sustainable improvement in outcomes for patients and healthcare systems. Moving forward, regular updates will ensure these clinical recommendations remain responsive to emerging evidence and clinical practice.

Supplementary Material

Supplementary Table S1. Comparison of recommendations for first-line treatment with NCCN (ver 3.2024), ESMO CPG interim update (2024) and BSH (2022) guidelines.

Ethics statement

These consensus guidelines did not involve the collection or analysis of patient data. As such, ethics review and patient informed consent were not applicable.

Declaration

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