

## REVIEW ARTICLE

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# First-line treatment for CLL in the era of targeted therapy

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In the decade since FDA approval of the first-generation Bruton's tyrosine kinase (BTK) inhibitor ibrutinib, the treatment landscape for chronic lymphocytic leukemia (CLL) has transformed. Targeted agents, as monotherapy or in combination regimens, have decisively replaced chemoimmunotherapy as the standard of care. In national CLL guidelines updated from 2023 through 2025 – including those from France, Germany, and the US – chemoimmunotherapy is considered a treatment option in only exceptional cases, reflecting broad consensus among experts that targeted therapies should be used universally in the management of previously untreated CLL. The primary first-line treatment options for CLL comprise continuous therapies based on the BTK inhibitors ibrutinib, zanubrutinib, or acalabrutinib, or fixed-duration regimens combining the BCL2 inhibitor venetoclax with obinutuzumab or the BTK inhibitors ibrutinib or acalabrutinib (with or without obinutuzumab). Selecting the appropriate targeted therapy requires careful evaluation of a multitude of factors, including molecular disease features (especially *del[17p]/TP53* and *IGHV* mutational status), comorbidities, comediations, and the patient's preferences. Focusing on primary treatment options, we review data from the key controlled trials that support the first-line use of targeted therapies for patients with CLL, consider ongoing trials that may support clinical decision-making in the future, and assess the potential to personalize treatment regimens in CLL based on minimal residual disease status.

*Blood Cancer Journal* (2026)16:19; <https://doi.org/10.1038/s41408-025-01434-2>

## INTRODUCTION

The treatment landscape for chronic lymphocytic leukemia (CLL) has changed dramatically since FDA approval of the first-generation Bruton's tyrosine kinase (BTK) inhibitor ibrutinib for CLL in 2014. In the subsequent decade, targeted therapies have supplanted the role of chemoimmunotherapy (CIT) as preferred first-line therapy. In national guidelines from 2023 to 2025, recommended treatments for previously untreated CLL comprise continuous therapy with the selective BTK inhibitors acalabrutinib or zanubrutinib, or fixed-duration regimens combining the BCL2 inhibitor venetoclax with obinutuzumab or the BTK inhibitor ibrutinib [1–3]. Following approval in some regions, venetoclax combinations with acalabrutinib (with or without obinutuzumab) are expected to be incorporated into treatment guidelines where authorized.

BTK and BCL2 inhibitor-based regimens provide durable responses with manageable safety profiles for most patients [4–13]. However, in the absence of head-to-head data comparing continuous BTK inhibitor-based regimens with fixed-duration venetoclax-based regimens, physicians face a challenge in selecting between these options to optimize first-line treatment outcomes for each patient.

Focusing on the first-line setting, where all approved therapies are viable options for many patients with CLL, we review important clinical trial data with continuous BTK inhibitor therapy, venetoclax-obinutuzumab (Ven-Obi), ibrutinib-venetoclax (Ibr-Ven), and acalabrutinib-venetoclax with or without obinutuzumab (Acal-Ven±Obi). Looking to the future, we consider the potential

for CLL treatment regimens to be individualized based on minimal residual disease (MRD) status—an as-yet unapproved strategy in the management of CLL.

In our discussions, we focus on pivotal studies and/or those that provide influential clinical data shaping treatment selection strategies. We also include selected studies of investigational regimens with the potential to inform future standards of care.

## FIRST-LINE TREATMENT SELECTION

Treatment selection for previously untreated patients with CLL has historically been based on evaluation of a patient's molecular disease characteristics (*IGHV* and *TP53/del[17p]*) and fitness [14–17]. Several clinical trials have demonstrated superior outcomes with targeted therapies versus CIT in patients with unmutated *IGHV* (uIGHV) and/or mutated *TP53/del[17p]* [6–8, 11, 18].

Historically, treatment algorithms have often incorporated the German CLL Study Group concept of patients being "go-go," "slow-go," or "no-go" based on how well patients are expected to tolerate purine analogs and/or anti-CD20 monoclonal antibodies [19]. This approach is no longer relevant in healthcare systems where targeted therapies are widely available. CIT regimens are no longer recommended or have a very minor role in current guidelines for CLL from the US (National Comprehensive Cancer Network), Germany (Onkopedia), and France (French Innovative Leukemia Organization), making the "go-go" and "slow-go" concepts less relevant [1–3]. Recent algorithms retain the

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Received: 5 September 2024 Revised: 25 November 2025 Accepted: 12 December 2025

Published online: 08 January 2026

		Key determinants of treatment selection	Secondary influences on treatment selection
PATIENT PREFERENCES		Attitude toward fixed-duration vs continuous therapy Willingness to visit hospital for treatment and follow-ups	Attitude to intravenous therapy Attitude to side effects
DISEASE FEATURES		Del(17p)/TP53 status IGHV status	Tumor burden* Complex karyotype
PATIENT CHARACTERISTICS & COMORBIDITIES		Age and fitness Cardiovascular status Renal status History of infections or immunosuppression	Potential for DDIs with existing medications Bleeding risk
LOGISTICS		Drug availability Patient's suitability for hospital-based treatment and monitoring Hospital capacity to provide TLS monitoring	Anticipated adherence to treatment

**Fig. 1 Key factors to evaluate in first-line treatment selection for patients with CLL.** \*Particularly relevant when considering venetoclax-based regimens, owing to TLS risk. DDI drug–drug interaction, IGHV immunoglobulin heavy chain variable, TLS tumor lysis syndrome.

molecular-guided basis for treatment selection, but all BTK and BCL2 inhibitor-based regimens are viable options for most patients [1–3, 20].

With targeted therapies preferred, physicians cannot rely on generalized treatment algorithms. Instead, selecting the optimal treatment for a patient requires evaluation and weighting of many factors (Fig. 1). The key decision point is now continuous therapy with a BTK inhibitor versus fixed-duration therapy with a BCL2 inhibitor in combination with obinutuzumab or ibrutinib/acalabrutinib. For most patients, the process starts with a discussion of their treatment preferences.

### FIRST-LINE BTK INHIBITOR THERAPY

Several clinical trials have established that first-line monotherapy with ibrutinib, acalabrutinib, or zanubrutinib provides durable responses with manageable safety profiles in patients with low- and high-risk disease (Table 1). Ibrutinib and acalabrutinib are also approved for use in combination with the anti-CD20 monoclonal antibodies rituximab or obinutuzumab, although the benefit of this combination therapy versus monotherapy has not been proven [21]. In ELEVATE-TN (NCT02475681), acalabrutinib–obinutuzumab (Acala-Obi) led to prolonged progression-free survival (PFS) versus acalabrutinib monotherapy, but the study was not sufficiently powered for this comparison and, critically, there was no benefit from obinutuzumab addition for patients with del(17p13.1) and/or mutated TP53 [6].

Very long-term data are available for ibrutinib, the first approved BTK inhibitor for CLL. Durable responses were demonstrated in patients followed on continuous ibrutinib for up to 10 years in RESONATE-2 (NCT01722487; ibrutinib versus chlorambucil), 8 years in the single-arm PCYC-1102 trial (NCT01105247 and NCT01109069), and a median of 4.5 years in the Alliance A041202 trial (NCT01886872; ibrutinib with or without rituximab versus bendamustine-rituximab [BR]) [8,22–25].

### BTK inhibitors versus BCL2 inhibitors in high-risk patients

Continuous BTK inhibitor-based therapies are typically recommended for patients with high-risk disease. In the first-line setting, outcomes with BTK inhibitor therapy for patients with del(17p)

and/or mutated TP53 are comparable to outcomes for patients without these features [6, 26, 27]. By contrast, for patients receiving Ven-Obi, those with del(17p) and/or mutated TP53 have shorter PFS compared with lower genetic risk patients [18].

The benefit of ibrutinib versus CIT regimens for high-risk disease has been demonstrated in several trials. In the Alliance A041202 trial of ibrutinib versus ibrutinib–rituximab (IR) versus BR, the 48-month PFS with ibrutinib and IR was 76% versus 47% with BR [22, 28]. The benefit of ibrutinib regimens (with no additional benefit of rituximab) versus BR was consistent for patients with or without TP53 abnormalities (mutated TP53/del[17p]), del(11q), complex karyotype, and uIGHV [22]. Among patients treated with ibrutinib regimens, the presence of TP53 abnormalities was not associated with a worse PFS outcome than in the absence of these abnormalities (HR: 0.99; 95% CI: 0.51–1.91;  $P = 0.98$ ) [22].

In the iLLUMINATE trial (NCT02264574) of ibrutinib–obinutuzumab (Ibr-Obi) versus chlorambucil–obinutuzumab (Clb-Obi), 42-month PFS was 74% for patients treated with Ibr-Obi, and outcomes were independent of del(17p)/TP53 mutation status (HR: 0.93; 95% CI: 0.32–2.69;  $P = 0.895$ ) [5]. A pooled analysis of RESONATE-2 and iLLUMINATE demonstrated similar outcomes with ibrutinib regimens in patients with or without high-risk genomic features, including del(17p) and mutated TP53 but also del(11q), uIGHV, and single-gene mutations in *BIRC3*, *NOTCH1*, *SF3B1*, and *XPO1* [27].

Results from an investigator-initiated trial of ibrutinib monotherapy–treated patients ( $N = 34$ ) with TP53 abnormalities underscore the durability of responses that can be achieved in this high-risk population. At 6 years, the estimated PFS and overall survival (OS) were 61% and 79%, respectively [29]. Although only one of 34 patients achieved undetectable minimal residual disease (uMRD) ( $< 10^{-4}$ ), the survival data indicate that deep responses are not a prerequisite for durable remission with ibrutinib [29].

### Second-generation BTK inhibitors

The second-generation BTK inhibitors acalabrutinib and zanubrutinib have also demonstrated durable responses in patients with low- and high-risk disease features [6, 26]. In ELEVATE-TN (NCT02475681), 72-month PFS rates with Acala-Obi and acalabrutinib monotherapy for the overall population were 78.0% and

**Table 1.** Outcomes from selected phase II and III trials evaluating continuous BTK inhibitor regimens in untreated CLL [5–7, 9, 10, 20, 22, 30, 31, 26, 23].

Trial	N	Patients	Outcomes
RESONATE-2 [23, 70]	229	Untreated CLL, >65 years without del(17p)	<ul style="list-style-type: none"> <li>Ibrutinib</li> <li>Chlorambucil</li> </ul> <p>9-year PFS: 49.7% versus 4.4%, favoring ibrutinib. 9-year OS: 68.0% for ibrutinib. OS was significantly longer for patients treated with ibrutinib versus chlorambucil in patients with <math>\geq 1</math> high prognostic risk factor, including mutated <i>TP53</i>, <i>ulIGHV</i>, and <i>del(1q)</i>.</p>
Alliance A041202 [22]	547	Untreated CLL, ≥65 years	<ul style="list-style-type: none"> <li>Ibrutinib</li> <li>• IR</li> <li>• BR</li> </ul> <p>Median PFS at a median follow-up of 55 months: Ibrutinib/IR: NR. BR: 44 months.</p>
ILLUMINATE [5]	229	Untreated CLL, ≥65 years or <65 years with one of: a CIRS score >6, CrCl <70 ml/min, del(17p), or mutated <i>TP53</i>	<ul style="list-style-type: none"> <li>Ibr-Obi</li> <li>• Clb-Obi</li> </ul> <p>Median PFS at a median follow-up of 45 months: Ibr-Obi: NR. Clb-Obi: 22 months.</p> <p>No difference in PFS for patients treated with Ibr-Obi with or without <i>del(17p)</i> or <i>TP53<sup>mut</sup></i> (HR: 0.99; 95% CI: 0.51–1.91; <math>P = 0.98</math>).</p>
E1912 [9]	529	Untreated CLL, ≤70 years without del(17p)	<ul style="list-style-type: none"> <li>• IR</li> <li>• FCR</li> </ul> <p>5-year PFS rates: IR: 78%. FCR: 51%.</p> <p>Superior PFS with IR compared with FCR in patients with <i>mlIGHV</i> and <i>ulIGHV</i>.</p>
FLAIR [10]	771	Untreated CLL, 18–75 years with a WHO performance status of ≤2; patients with del(17p) in >20% of their CLL cells were excluded	<ul style="list-style-type: none"> <li>• IR</li> <li>• FCR</li> </ul> <p>4-year PFS rates: IR: 85.6%. FCR: 73.0%.</p> <p>Superior PFS with IR compared with FCR in patients with <i>ulIGHV</i> but not <i>mlIGHV</i>.</p>
ELEVATE-TN [6, 30]	535	Untreated CLL, ≥65 years or 18–65 years with comorbidities (CIRS-G score >6, CrCl 30–69 ml/ min by Cockcroft–Gault)	<ul style="list-style-type: none"> <li>Acalabrutinib</li> <li>• Acal-Obi</li> <li>• Clb-Obi</li> </ul> <p>72-month PFS (all patients): Acalabrutinib: 61.5%. Acal-Obi: 8.0%. Clb-Obi: 17.2%.</p> <p>No difference in PFS with acalabrutinib and Acal-Obi for <i>ulIGHV</i> versus <i>mlIGHV</i>. With Acal-Obi, PFS was numerically lower in patients with versus without <i>del(17p)</i> and/or <i>TP53</i> mutations, but similar across groups with acalabrutinib.</p>
SEQUOIA [7, 31, 26]	479	Untreated CLL, ≥65 years or <65 years with one of: a CIRS score >6, CrCl <70 ml/min, or history of severe or frequent infections	<ul style="list-style-type: none"> <li>Zanubrutinib</li> <li>• BR</li> </ul> <p>Patients without <i>del(17p)</i> – randomized: 60-month PFS: 75.8% versus 40.1%, favoring zanubrutinib. Patients with <i>del(17p)</i> – zanubrutinib: 60-month PFS: 72.2%.</p>

<sup>a</sup>OS follow-up in the chlorambucil arm was discontinued after a median of 5 years of follow-up for patients with progressive disease.  
Acal-Obi acalabrutinib-obinutuzumab, BR bendamustine-rituximab, BTK Bruton's tyrosine kinase, CIRS Cumulative Illness Rating Scale, CIRS-G CIRS-Geriatric, Clb-Obi chlorambucil-obinutuzumab, CLL chronic lymphocytic leukemia, CrCl creatinine clearance, FCR fludarabine-cyclophosphamide-rituximab, HR hazard ratio, Ibr-Obi ibrutinib-rituximab, IGHV immunoglobulin heavy chain variable, IR ibrutinib-rituximab, mlIGHV mutated IGHV, mut mutated, NR not reached, OS overall survival, PFS progression-free survival, ulIGHV unmutated IGHV, WHO World Health Organization.

61.5%, respectively, compared with 17.2% for Clb-Obi. PFS at 72 months was not significantly different for patients with mutatedIGHV (mIGHV) versus uIGHV treated with acalabrutinib monotherapy or Acal-Obi. PFS outcomes with acalabrutinib monotherapy were similar regardless of del(17)(p13.1) and/or *TP53* mutation status. In contrast, patients with these features had numerically worse outcomes with Acal-Obi, appearing to derive no additional benefit from combination therapy versus acalabrutinib monotherapy [30].

In SEQUOIA (NCT03336333), at a median study follow-up time of 61.2 months in patients without del(17)(p13.1), there was an overall PFS benefit with zanubrutinib versus BR (HR: 0.29; 95% CI: 0.21–0.40). Similar PFS outcomes were reported with zanubrutinib in patients with uIGHV versus mIGHV (HR: 1.35; 95% CI: 0.76–2.40) [26, 31], in contrast to the CLL14 trial with Ven-Obi, where uIGHV was identified as an adverse prognostic factor [32].

Patients with del(17)(p13.1) were not randomized in SEQUOIA because of poor outcomes with CIT in previous trials—these patients ( $n = 111$ ) were instead treated with open-label zanubrutinib and analyzed separately [26]. Notably, the 60-month PFS in this high-risk population (72.2%) was comparable to outcomes of patients without del(17)(p13.1) randomized to receive zanubrutinib (75.8%) [26].

### Ibrutinib, acalabrutinib, or zanubrutinib?

Based on safety outcomes from head-to-head trials in the relapsed setting [1, 2, 33, 34], current treatment guidelines for CLL favor second-generation BTK inhibitors over ibrutinib across all lines of therapy [1–3, 35, 36]. Direct comparisons with acalabrutinib (ELEVATE-RR; NCT02477696) and zanubrutinib (ALPINE; NCT03734016) have demonstrated that their greater selectivity versus ibrutinib translates into overall improved safety profiles in CLL [33, 34]. In relapsed/refractory CLL, discontinuation rates due to adverse events (AEs) were lower with acalabrutinib versus ibrutinib in ELEVATE-RR (14.7% versus 21.3% at a median follow-up of 40.9 months) and with zanubrutinib versus ibrutinib in ALPINE (21.4% versus 28.3% at a median follow-up of 42.5 months) [33, 34, 37].

Real-world rates of side effects and discontinuations are likely to be higher than in controlled trials and can contribute to a significant proportion of patients needing to change therapy. For example, in a retrospective, real-world analysis of 616 patients with CLL treated with ibrutinib, 21% of patients discontinued ibrutinib because of toxicity at a median follow-up of 17 months [38]. Switching to a second-generation BTK inhibitor is a viable option for patients with CLL who develop intolerance to ibrutinib [39, 40]. In a study of zanubrutinib monotherapy (NCT04116437), 54% of ibrutinib-intolerant patients with CLL ( $n = 28/52$ ) and 70% of acalabrutinib  $\pm$  ibrutinib-intolerant patients with CLL ( $n = 19/27$ ) experienced no recurrence of intolerance-related AEs after switching to zanubrutinib. Additionally, 94% of efficacy-evaluable patients ( $n = 63/67$ ) achieved disease control with zanubrutinib [39].

An important difference between the second-generation BTK inhibitors and ibrutinib is a reduced risk of cardiac AEs. All-grade atrial fibrillation/atrial flutter was reduced with acalabrutinib versus ibrutinib (9.4% versus 16.0%;  $P = 0.02$ ) and zanubrutinib versus ibrutinib (7.1% versus 17.0%) in ELEVATE-RR and ALPINE, respectively [33, 34, 37]. As with overall side effects, the rate of atrial fibrillation with ibrutinib is likely to be higher outside of clinical trials. In one study, which used systematic cardiac monitoring before and after initiation of therapy, 26% of patients with B-cell malignancies ( $n = 14/53$ ) developed ibrutinib-associated atrial fibrillation after a median of 13 months [41].

In the absence of head-to-head data, it is difficult to differentiate the clinical properties of acalabrutinib and zanubrutinib, although there are indications of differences between these agents from outcomes across trials. In relapsed/refractory CLL, the

ALPINE trial demonstrated a statistically significant PFS advantage for zanubrutinib over ibrutinib, with clear and sustained separation of the PFS curves. In contrast, the ELEVATE-RR trial showed acalabrutinib to be non-inferior to ibrutinib, with overlapping PFS curves and no evidence of separation over time [33, 34, 37]. However, further research is needed to determine whether efficacy outcomes in the relapsed setting will be consistent with outcomes in the first-line setting.

Outcomes for patients with versus without *TP53* aberrations in the relapsed setting with zanubrutinib and acalabrutinib were consistent with findings with these agents in the first-line setting from SEQUOIA and ELEVATE-TN. In this high-risk subgroup, PFS and response rates with zanubrutinib and acalabrutinib were comparable to the overall study populations in ALPINE and ELEVATE-RR, respectively [6, 26, 33, 34, 37].

In terms of comparative safety of the next-generation BTK inhibitors, the absence of head-to-head trials means that only indirect comparative data are available. A systematic review of 61 trials across different B-cell malignancies and lines of therapy found similar overall rates of treatment-emergent AEs between the two agents, with variations of the relative incidence of specific AEs. Neutropenia, leukopenia, thrombocytopenia, hypertension, hematuria, and cellulitis occurred more frequently with zanubrutinib, whereas atrial fibrillation, infections, pyrexia, cough, fatigue, nausea, vomiting, diarrhea, myalgias, headaches, and dizziness were more frequent with acalabrutinib [42]. A separate network meta-analysis in treatment-naïve CLL patients of advanced age and/or with comorbidities supported the favorable tolerability of second-generation BTK inhibitors. Acalabrutinib and zanubrutinib had the most favorable safety profiles (Grade  $\geq 3$  and special AEs) of first-line targeted therapies in CLL, with zanubrutinib monotherapy associated with the lowest risk of AE-related treatment discontinuation [43]. While such data may be considered in individual cases where no other factors are decisive, cross-trial comparisons should be interpreted with caution.

### FIRST-LINE VEN-OBI

First-line fixed-duration Ven-Obi provides durable remissions with a manageable safety profile in fit and unfit patients with previously untreated CLL (Table 2) [44, 45]. The CLL14 trial (NCT02242942) established the superiority of Ven-Obi versus Clb-Obi in patients older than 70 years of age and/or with clinically relevant coexisting medical conditions [44]. At 5 years after randomization in CLL14, the estimated PFS rate was 62.6% versus 27.0% in favor of Ven-Obi [44]. uMRD ( $< 10^{-4}$ ) in the peripheral blood 2 months after treatment was more common with Ven-Obi versus Clb-Obi (74.5% versus 32.9%), as were MRD remissions below  $10^{-5}$  and  $10^{-6}$  (66.2%/19.0% versus 39.8%/6.5%). In both arms, uMRD status at the end of therapy was associated with longer PFS and OS [11].

### Genetic markers and patient outcomes

A multivariable analysis of the CLL14 study at 6 years identified del(17p), uIGHV, and lymph node size  $\geq 5$  cm as independent prognostic factors for PFS in patients treated with Ven-Obi [32]. Patients with *TP53* abnormalities had a shorter median PFS (51.9 months versus 76.6 months) and 6-year OS rate (60.0% versus 81.9%) than those without *TP53* abnormalities [32]. Although uIGHV was associated with poorer outcomes versus mIGHV, survival outcomes were still good with Ven-Obi in the uIGHV subgroup (median PFS: 64.8 months; 6-year OS: 77.7%), and with the benefit of long treatment-free intervals (median time to next treatment: 85.4 months) [32]. Similarly, although del(17p) and *TP53* mutations are negative prognostic markers with Ven-Obi, this high-risk group achieved a median PFS of 51.9 months in CLL14 [32]. Therefore, while treatment with continuous BTK inhibitors may be generally favored for these high-risk patients,

**Table 2.** Outcomes from selected phase II and III trials evaluating time-limited targeted therapies in previously untreated CLL [11–13, 45, 49, 50, 54, 55, 71, 51, 57, 66, 72, 52, 73, 59].

Study name	Patients	Therapies	Outcomes
GAIA (CLL13) [45]	<i>N</i> = 926 Fit for FCR; no del(17p) or <i>TP53</i> mutations	• CIT (FCR or BR) • Ven-R • Ven-Obi • Ven-Obi-Ibr	3-year PFS: • CIT: 75.5% • Ven-R: 80.8% (uIGHV: 76.4%; mIGHV: 87.0%) • Ven-Obi: 87.7% (uIGHV: 82.9%; mIGHV: 93.6%) • Ven-Obi-Ibr: 90.5% (uIGHV: 86.6%; mIGHV: 96.0%) PB-uMRD4: • Chemoimmunotherapy: 52.0% • Ven-R: 57.0% • Ven-Obi: 86.5% • Ven-Obi-Ibr: 92.2% SAEs: • Chemoimmunotherapy: 47.7% • Ven-R: 40.1% • Ven-Obi: 44.7% • Ven-Obi-Ibr: 50.2%
CLL14 [11]	<i>N</i> = 432 ≥70 years of age and/or with clinically relevant coexisting medical conditions	• Ven-Obi • Clb-Obi	5-year PFS: • Ven-Obi: 62.6% (with <i>TP53</i> aberrations: 40.6%; without <i>TP53</i> aberrations: 65.8%) • Clb-Obi: 27.0% PB-uMRD4 at EOT +2 months • Ven-Obi: 74.5% • Clb-Obi: 32.9% SAEs: • Ven-Obi: 59.9% • Clb-Obi: 47.7%
MD Anderson (NCT02756897) [72, 52, 73]	<i>N</i> = 120 Patients had at least one of: del(17p), mutated <i>TP53</i> , del(11q), uIGHV, or ≥65 years	Ibrutinib for 3 cycles; Ibr-Ven for 24 cycles Initially, patients with BM MRD4+ after 24 cycles could continue ibrutinib monotherapy; later, the protocol was amended to allow an additional 12 cycles of Ibr-Ven	5-year PFS: 90.1% 5-year OS: 95.6% BM-uMRD4 (within 2 years): 64% Grade ≥3 AEs: 60%
FLAIR [49, 56]	<i>N</i> = 786 Fit for FCR	FCR versus MRD-guided Ibr-Ven or ibrutinib monotherapy. All Ibr-Ven-treated patients received ibrutinib (420 mg once daily) for two cycles before initiation of venetoclax at a dose of up to 400 mg per day. Starting at the 12-month assessment, once uMRD was reached, Ibr-Ven was continued for the same duration it had been administered before being stopped. uMRD was assessed again after 3 and 6 months. Treatment was re-commenced for patients with MRD relapse up to a total of 6 years of treatment.	5-year PFS: • Ibr-Ven: 93.9% (uIGHV: 94.9%; mIGHV: 90.1%) • Ibrutinib: 79% (uIGHV: 79.9%; mIGHV: 79.9%) • FCR: 58.1% 5-year OS: • Ibr-Ven: 95.9% • Ibrutinib: 90.5% • FCR: 86.5% BM-uMRD4 (within 2 years): • Ibr-Ven: 66.2% • Ibrutinib: 0% • FCR: 48.3% Treatment-related deaths: • Ibr-Ven: 0.4% • FCR: 2.5% • Ibrutinib: 2.3%
GLOW [13, 50, 54]	<i>N</i> = 211 ≥65 years or 18–64 years with a CIRS score >6 and/or CrCl <70 ml/min	Clb-Obi versus fixed-duration Ibr-Ven administered as three cycles of ibrutinib pre-treatment (420 mg once daily), followed by 12 cycles of Ibr-Ven.	5-year PFS: • Ibr-Ven: 59.9% (uIGHV: 52.2%; mIGHV: 82.5%) • Clb-Obi: 17.8% BM-uMRD4 at a median follow-up of 27.7 months: • Best: Ibr-Ven, 55.7%; Clb-Obi, 21.0% • 3 months after treatment: Ibr-Ven, 51.9%; Clb-Obi, 17.1% in BM PB-uMRD4 at 38 months after treatment: Ibr-Ven: 32.1% SAEs:

Table 2. continued

Study name	Patients	Therapies	Outcomes
CAPTIVATE [12, 55, 51]	Fixed-duration Ibr-Ven cohort, $n = 159$ MRD-guided Ibr-Ven cohort, $n = 164$ 18–70 years	Fixed-duration Ibr-Ven: three-cycle ibrutinib pre-treatment (420 mg once daily), followed by 12 cycles of Ibr-Ven. MRD-guided Ibr-Ven: patients with confirmed uMRD after cycle 12 randomized (1:1) to double-blind placebo or ibrutinib maintenance.	<ul style="list-style-type: none"> <li>Ibr-Ven: 46.2%</li> <li>Clb-Obi: 27.6%</li> </ul> <p>Fixed-duration cohort<sup>a</sup></p> <ul style="list-style-type: none"> <li>5.5-year PFS: 66%</li> <li>With <i>TP53</i> aberrations: 36%; without <i>TP53</i> aberrations: 70%</li> <li>uIGHV: 53%; mIGHV: 80%</li> <li>5.5-year OS: 97%</li> <li>PB-uMRD4:</li> <ul style="list-style-type: none"> <li>End of treatment: 69%</li> <li>Best response: 77% (PB), 60% (BM)</li> <li>SAEs: 23%</li> </ul> <p>MRD-guided cohort</p> <ul style="list-style-type: none"> <li>1-year DFS: 95%</li> <li>Best uMRD4: 75% (PB), 68% (BM)</li> <li>SAEs: 21%</li> </ul> </ul>
AMPLIFY [57]	$N = 867$ Fit for FCR; no del(17p) or <i>TP53</i> mutations	<ul style="list-style-type: none"> <li>CIT (FCR or BR)</li> <li>Acal-Ven (14 cycles)</li> <li>Acal-Ven-Obi (14 cycles)</li> </ul>	<p>3-year PFS:</p> <ul style="list-style-type: none"> <li>CIT (FCR or BR): 66.5%</li> <li>Acal-Ven: 76.5% (uIGHV: 68.9%; mIGHV: 86.0%)</li> <li>Acal-Ven-Obi: 83.1% (uIGHV: 82.8%; mIGHV: 83.6%)</li> </ul> <p>EOT PB-uMRD4 = in evaluable patients:</p> <ul style="list-style-type: none"> <li>CIT (FCR or BR): 72.6%</li> <li>Acal-Ven: 45.0%</li> <li>Acal-Ven-Obi: 95.0%</li> <li>SAEs:</li> <ul style="list-style-type: none"> <li>CIT (FCR or BR): 27.4%</li> <li>Acal-Ven: 24.7%</li> <li>Acal-Ven-Obi: 38.4%</li> </ul> </ul>
Phase II AVO Trial (Dana-Farber Study) [59]	$N = 72$	Cycle 1: acalabrutinib; cycles 2–3: Acal-Obi; cycles 4–7: Acal-Ven-Obi; cycles 8–15: Acal-Ven Therapy was stopped at cycle 16 for patients with CR and BM-uMRD4, and at cycle 25 for patients with BM-uMRD and at least PR	<ul style="list-style-type: none"> <li>4-yr PFS, <i>TP53</i> wild-type: 96%</li> <li>With <i>TP53</i> aberrations: 70%</li> <li>4-yr OS, <i>TP53</i> wild-type: 100%</li> <li>With <i>TP53</i> aberrations: 88%</li> <li>BM-uMRD at cycle 25, overall: 68.1%</li> <li>With <i>TP53</i> aberrations: 57.1%</li> <li>SAEs: 28%</li> </ul>
SEQUOIA, Arm D [66]	$N = 114$	MRD-guided zanubrutinib-venetoclax	<p>2-year PFS: 92% (with <i>TP53</i> aberrations: 94%; without <i>TP53</i> aberrations: 89%)</p> <p>ORR: 97.4%</p> <p>CR/CRI: 47.4%</p> <p>Best PB-uMRD4: 59%</p> <p>Deaths due to AEs: 4.4%</p>

<sup>a</sup>A total of 202 patients were included in the 5.5-year PFS and OS analyses, comprising 159 from the fixed-duration cohort and 43 randomized to the placebo arm within the MRD cohort.

*Acal-Ven* acalabrutinib-venetoclax, *Acal-Ven-Obi* acalabrutinib-venetoclax-obinutuzumab, *AE* adverse event, *BM* bone marrow, *BR* bendamustine-rituximab, *CIRS* Cumulative Illness Rating Scale, *CIT* chemoimmunotherapy, *Clb-Obi* chlorambucil-obinutuzumab, *CLL* chronic lymphocytic leukemia, *CrCl* creatinine clearance, *CR/CRI* complete response / complete response with incomplete marrow recovery, *DFS* disease-free survival, *EOT* end of treatment, *FCR* fludarabine-cyclophosphamide-rituximab, *Ibr-Ven* ibrutinib-venetoclax, *IGHV* immunoglobulin heavy chain variable, *mIGHV* mutated IGHV, *MRD* minimal residual disease, *MRD4+* minimal residual disease at  $10^{-4}$  sensitivity, *ORR* overall response rate, *OS* overall survival, *PB* peripheral blood, *PFS* progression-free survival, *SAE* serious adverse event, *uIGHV* unmutated IGHV, *uMRD* undetectable minimal residual disease, *uMRD4* undetectable MRD at  $10^{-4}$  sensitivity, *Ven-Obi* venetoclax-obinutuzumab, *Ven-Obi-ibr* venetoclax-obinutuzumab-ibrutinib, *Ven-R* venetoclax-rituximab.

*Ven-Obi* may be a viable option depending on other disease and patient factors.

The GAIA (CLL13) trial (NCT02950051) was a head-to-head study of venetoclax-based, time-limited combination treatments versus CIT (fludarabine, cyclophosphamide, and rituximab [FCR] or BR) in 926 fit patients that established the superiority of *Ven-Obi* versus venetoclax-rituximab [45]. At Month 15, significantly higher rates of uMRD ( $<10^{-4}$ ) were achieved in the peripheral blood with *Ven-Obi* (86.5%; 97.5% CI: 80.6%–91.1%) and *Ven-Obi-ibrutinib* (92.2%; 97.5% CI: 87.3%–95.7%) versus CIT (52.0%; 97.5% CI: 44.4%–59.5%; both  $P < 0.001$ ) but not with venetoclax-rituximab versus CIT (57.0%; 97.5% CI: 49.5%–64.2%;  $P = 0.32$  versus CIT) [45].

In the final analysis, 5-year PFS rates were superior with *Ven-Obi-ibrutinib* (81.3%; HR: 0.34; 97.5% CI: 0.24–0.50;  $P < 0.001$ ) versus CIT (50.7%) and numerically higher with *Ven-Obi* (69.8%)

and venetoclax-rituximab (57.4%). The study was not powered to make further comparisons between groups, but subgroup comparisons indicate that IGHV status did not affect PFS outcomes in the *Ven-Obi-ibrutinib* group, whereas *uIGHV* was associated with poorer prognosis in the other treatment arms [46].

#### Tolerability of *Ven-Obi*

*Ven-Obi* was generally well tolerated across CLL14 and GAIA (CLL13). Discontinuation rates reflected differences in age and fitness of the study populations, with rates in CLL14 (16.0%,  $n = 34/212$ ) almost three times higher than those in GAIA (CLL13) (5.7%,  $n = 13/228$ ) [44, 45]. Common AEs also occurred more frequently in CLL14 than in GAIA (CLL13), including Grade 3–4 neutropenia (52.8% versus 45.2%), infections (17.5% versus 10.5%), and diarrhea (8.4% versus 1.8%) [44, 45]. These common

**Table 3.** TLS risk assessment and management with venetoclax [48, 74–76].

Risk group	Criteria	Management
Low	All lymph nodes <5 cm and ALC < $25 \times 10^9/l$	Prophylaxis: Allopurinol 2–3 d prior to venetoclax intake; rasburicase if uric acid is elevated Hydration: Oral (1.5–2 l/d from 2 d prior to dose ramp-up) Hospitalization: Outpatient, check TLS parameters and CrCl at least 6–8 h and 24 h after each ramp-up step
Intermediate	Any lymph node 5–10 cm or ALC $\geq 25 \times 10^9/l$	Prophylaxis: Allopurinol 2–3 d prior to venetoclax intake; rasburicase if uric acid is elevated Hydration: Oral or intravenous Hospitalization: Outpatient, check TLS parameters and CrCl at least 6–8 h and 24 h after each ramp-up step or inpatient if pre-existing abnormalities or relevant coexisting conditions (CrCl <80 ml/min)
High	Any lymph node $\geq 10$ cm or Any lymph node $\geq 5$ cm and ALC $\geq 25 \times 10^9/l$	Prophylaxis: Rasburicase 2–3 d prior to venetoclax intake Hydration: Oral and intravenous Hospitalization: Admission to an inpatient or day hospital with intensified laboratory monitoring

ALC absolute lymphocyte count, CrCl creatinine clearance, d days, h hours, TLS tumor lysis syndrome.

AEs with Ven-Obi are manageable for most patients with supportive measures. For example, Grade 3 neutropenia accompanied by infection or fever, or Grade 4 neutropenia, may initially be managed with dose interruptions and/or reductions. In cases of recurrence, the use of granulocyte colony-stimulating factor (G-CSF), either reactively or prophylactically, may be considered in accordance with institutional guidelines [47].

Tumor lysis syndrome (TLS), a potentially fatal side effect, requires special attention with venetoclax regimens (Table 3). In the GAIA (CLL13) trial in patients with a low burden of coexisting conditions, all-grade TLS (defined by the Cairo–Bishop criteria) occurred in 11% of patients treated with Ven-Obi, with no fatalities [45]. In the CLL14 trial, TLS (defined by the more stringent Howard criteria) occurred in 0.5% of patients treated with Ven-Obi, with all cases occurring after obinutuzumab and before venetoclax initiation. In a patient population with coexisting conditions and in which most patients had some form of renal impairment, there were no clinical or life-threatening TLS events [48–51]. These outcomes highlight that the risk of TLS with Ven-Obi can be managed effectively for patients for whom TLS monitoring is logically feasible, and this regimen should not be discounted for patients with disease features associated with an increased risk of TLS.

## FIRST-LINE VENETOCLAX–BTK INHIBITOR COMBINATION THERAPIES

### Ibr-Ven

Ibr-Ven was the first all-oral, fixed-duration regimen for CLL, and there are several ongoing trials with this regimen [12,13,49–53]. The GLOW study (NCT03462719) in older patients and/or those with comorbidities demonstrated significantly enhanced PFS with Ibr-Ven ( $n = 106$ ) versus Clb-Obi ( $n = 105$ ) (HR: 0.27; 95% CI: 0.18–0.39;  $P < 0.0001$ ) at a median follow-up of 64 months, with a benefit reported across prespecified subgroups [50, 54].

The phase II CAPTIVATE study (NCT02910583) is investigating Ibr-Ven in patients aged 70 years or younger assigned to two cohorts: fixed-duration treatment ( $n = 159$ ) or MRD-guided treatment ( $n = 164$ ), with a primary endpoint of complete response (CR) rates [12, 51]. At 4 years' follow-up, the best CR rate in the fixed-duration cohort was 58% [51]. The overall 5.5-year PFS rate was 66% (95% CI: 58%–72%), with PFS rates numerically lower in patients with uIGHV versus mIGHV (55% versus 63%) and with versus without TP53 aberrations (70% versus 36%) [55]. Unmutated IGHV was also associated with higher rates of CR (62% versus 47%) and uMRD (peripheral blood: 84% versus 67%; bone marrow: 64% versus 53%) [51]. OS at 5.5 years was 97%, and a subgroup analysis at 4 years demonstrated consistently high OS across all patient subgroups [55].

In the group receiving MRD-guided therapy—a strategy that is not currently approved in any context for the treatment of CLL—patients who achieved uMRD ( $<10^{-4}$ ) after three cycles of ibrutinib pre-treatment and 12 cycles of Ibr-Ven were randomly assigned to placebo or continuous ibrutinib until confirmed MRD relapse [12]. At a median follow-up of 31.3 months, best uMRD response rates were 75% ( $n = 123/164$ ) in peripheral blood and 68% ( $n = 112/164$ ) in bone marrow after 12 cycles of Ibr-Ven [12]. The addition of maintenance ibrutinib did not increase 1-year disease-free survival compared with placebo in patients who had achieved uMRD [12].

As in the fixed-duration cohort, rates of uMRD were higher for patients with uIGHV versus mIGHV (77% versus 56%) [12]. Rates of uMRD with or without del(17p) were similar (69% versus 68%) but numerically lower for patients with del(17p) or mutated TP53 compared with patients without either high-risk feature (66% versus 72%) [12].

FLAIR (ISRCTN01844152) is a large, UK-based, adaptive, multi-arm trial that in its most recent phase compares MRD-guided Ibr-Ven or ibrutinib monotherapy (each administered for up to 6 years) with FCR in previously untreated CLL—excluding patients with Richter's transformation, symptomatic cardiac disease, or those with del(17p) in more than 20% of their CLL cells [49, 56].

With a median follow-up of 62.2 months, Ibr-Ven has demonstrated improved outcomes across multiple efficacy endpoints compared with ibrutinib monotherapy and FCR. Estimated 5-year PFS rates were 93.9% with Ibr-Ven, 79.0% with ibrutinib, and 58.1% with FCR. PFS was markedly superior with Ibr-Ven compared with both arms in patients with uIGHV, and numerically highest across all other genetic subgroups (mIGHV, ATM deletion, trisomy 12, del[13q], normal karyotype). OS rates showed the same trend, with Ibr-Ven superior compared with ibrutinib and FCR overall (95.9% versus 90.5% versus 86.5%, respectively) and numerically higher than ibrutinib and FCR in patients with uIGHV and mIGHV [56].

Ibr-Ven treatment also resulted in higher rates of uMRD ( $<10^{-4}$ ) within 2 years compared with FCR in bone marrow (66.2% vs. 48.3%) and peripheral blood (73.1% vs. 60.8%). No patients receiving ibrutinib monotherapy achieved uMRD [56]. The proportion of patients treated with Ibr-Ven meeting the MRD stopping rules increased from Years 2 to 4, with 48.3% stopped at 2 years, 56.3% at 3 years, and 68.1% at 4 years. These findings suggest that responses to Ibr-Ven may deepen over time but also indicate that MRD-guided treatment with Ibr-Ven can lead to prolonged therapy durations for many patients [56]. However, it is important to note that the FLAIR study was designed to compare ibrutinib monotherapy with Ibr-Ven, rather than to formally evaluate the clinical utility of MRD-guided treatment decisions.

This MRD-guided approach is currently unlicensed and further investigation is needed to determine how it can best guide decisions around Ibr-Ven treatment duration and discontinuation, and whether a uniform approach is appropriate for patients with differing disease characteristics. Despite these considerations, MRD-guided combinations of venetoclax with ibrutinib, zanubrutinib, or acalabrutinib with or without obinutuzumab are included as suggested first-line therapies for some patients in the most recent NCCN guidelines [2]. While there may be potential benefit in offering these regimens off-label in specific clinical scenarios, the best available evidence currently supports the use of fixed-duration BTK inhibitor–venetoclax combinations in accordance with their approved labels.

### Tolerability of Ibr-Ven

Common AEs across the GLOW, CAPTIVATE, and FLAIR trials included diarrhea, nausea, fatigue, neutropenia, and arthralgia, all usually low-grade [12, 13, 49, 51]. In common with other ibrutinib-containing regimens, rates of atrial fibrillation were notable. At a median treatment duration of ~14 months, all-grade atrial fibrillation occurred in 7% ( $n = 12/164$ ) and 4% ( $n = 7/159$ ) of patients in the CAPTIVATE MRD and fixed-duration cohorts, respectively [12, 51]. Rates in the FLAIR study within 1 year of randomization were similar, with all-grade atrial fibrillation in 4% ( $n = 10/252$ ) and Grade 3 in 0.8% ( $n = 2/252$ ) of patients [49]. The GLOW trial, which included older and/or more comorbid patients compared with CAPTIVATE and FLAIR, reported atrial fibrillation in 14% of patients ( $n = 15/106$ ) at a median treatment duration of 13.8 months and led to discontinuation of ibrutinib in two patients (2%) [13].

Additional cardiovascular events of concern were reported across these trials, with four on-treatment cardiac or sudden deaths (4%,  $n = 4/106$ ) in the Ibr-Ven arm of the GLOW trial [13]. These patients had a CIRS score of 10 or greater or an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 2, and a history of hypertension, cardiovascular disease, and/or diabetes [13]. In the younger and fitter population enrolled in CAPTIVATE ( $\leq 70$  years and ECOG PS 0–2), there was one sudden death in the MRD cohort (0.6%,  $n = 1/164$ ) and one in the fixed-duration cohort (0.6%,  $n = 1/159$ ), which occurred during the ibrutinib pre-treatment phase [12, 51]. In the FLAIR study, which enrolled patients considered fit enough to receive FCR, there were three sudden unexplained or cardiac deaths (1.2%,  $n = 3/252$ ) in patients treated with Ibr-Ven [49].

As with other ibrutinib regimens, it is essential to evaluate a patient's risk of developing cardiovascular AEs before initiation of Ibr-Ven. Based on the safety outcomes across the trials considered here, clinicians may prefer therapies with a more favorable cardiovascular safety profile over Ibr-Ven for patients who meet the GLOW enrollment criteria, with Ibr-Ven reserved for younger and fitter patients [13].

### Acal-A-Ven±Obi

Fixed-duration Acal-A-Ven and Acal-A-Ven-Obi are the most recent additions to the first-line treatment landscape for CLL. EMA approval was based on results of the AMPLIFY study (NCT03836261) comparing outcomes with fixed-duration Acal-A-Ven±Obi versus CIT (BR or FCR) in a fit and relatively young cohort (median age 61 years) of previously untreated patients with CLL without *TP53* abnormalities [57, 58].

A prespecified interim analysis (median follow-up 40.8 months;  $N = 867$ ) reported significantly improved PFS with either Acal-A-Ven (primary analysis;  $P = 0.004$ ) or Acal-A-Ven-Obi ( $P < 0.001$ ) compared with CIT (36-month PFS: 76.5%, 83.1%, and 66.5%, respectively) [57].

Undetectable MRD in the peripheral blood at the end of treatment (EOT)—an outcome associated with longer PFS—was achieved in 34.4% of the intention-to-treat population receiving

Acal-A-Ven and 67.1% with Acal-A-Ven-Obi. Twelve weeks after EOT, these rates declined slightly to 29.9% and 65.0%, respectively [57]. These findings raise questions about the durability of response achievable with the AMPLIFY regimens, particularly with Acal-A-Ven. While acknowledging the limitations of cross-trial comparisons, uMRD rates of 34.4% in the intention-to-treat population (45.0% in evaluable patients) treated with Acal-A-Ven are markedly lower than the best peripheral blood uMRD rate of 77% reported in the CAPTIVATE study [51, 57]. In the GLOW study, 84.5% of patients treated with Ibr-Ven sustained uMRD in peripheral blood from 3 to 12 months after EOT—again, substantially higher than what was achieved with Acal-A-Ven in the AMPLIFY study [13, 57].

Analysis of safety outcomes showed relatively low incidences of Grade  $\geq 3$  cardiac AEs or hypertension that were comparable across the treatment groups, whereas rates of Grade  $\geq 3$  neutropenia or hemorrhage were higher with Acal-A-Ven-Obi versus Acal-A-Ven [57]. Rates of AEs leading to treatment discontinuation were notably higher with Acal-A-Ven-Obi (20.1%) compared with Acal-A-Ven (7.9%) or CIT (10.8%). Similarly, serious AEs leading to death were more frequent with Acal-A-Ven-Obi (6.0%) versus Acal-A-Ven (3.4%) or CIT (3.5%) [57]. Based on these early findings, Acal-A-Ven-Obi may be best suited to younger, fitter patients who are able to tolerate an increased toxicity, with a modest efficacy benefit offered by this regimen compared with Acal-A-Ven [57].

Longer follow-up of AMPLIFY will determine the durability and tolerability of Acal-A-Ven and Acal-A-Ven-Obi combination regimens in this patient population [57]. Further studies are also needed to evaluate the efficacy and safety of these regimens in older patients and those with high-risk disease features.

A phase II study (NCT03580928) is investigating first-line Acal-A-Ven-Obi in previously untreated CLL, including patients with *TP53* aberrations. Treatment may be discontinued after 15 or 24 cycles for patients with complete remission (as defined by iwCLL criteria) and uMRD4 in the bone marrow. After a median follow-up of 55.2 months, the median duration of treatment was 25 cycles (~25 months). Depth of response with MRD-guided Acal-A-Ven-Obi appeared independent of *TP53* status, with no difference in the uMRD bone marrow rates at cycle 16, day 1 in patients with *TP53* aberrations (42%;  $n = 19/45$ ) compared with the overall population (42%;  $n = 30/72$ ). Four-year PFS outcomes showed durable efficacy in patients with *TP53* aberrations (70%), although this was numerically lower than for patients without *TP53* aberrations (96%) [59].

### IS THERE STILL A ROLE FOR CIT?

Multiple trials have shown that CIT regimens produce inferior outcomes in patients with *TP53* abnormalities and miGHV, but young and fit patients without these genomic features can experience durable remissions [6–8, 11, 18]. Nevertheless, in health systems where targeted therapies are available, CIT regimens have a very limited role in current guidelines, including for patients with miGHV [1, 2]. The authors of this review would not identify any clinical scenario where first-line CIT would be recommended when targeted therapies are available and accessible.

This unequivocal position is primarily driven by the long-term risks associated with CIT, such as secondary neoplasia, leukemias/myelodysplastic syndromes, and infections, as well as the similarly favorable outcomes with targeted therapy suggested in multiple trials despite shorter follow-up. In the Thompson et al. study of FCR, 6.3% of patients ( $n = 19/300$ ) developed therapy-related myeloid neoplasms, which were fatal in 84% of patients ( $n = 16/19$ ) [60].

Although the follow-up for targeted therapies discussed in this review, including BTK inhibitor and venetoclax-based combinations, is still relatively short compared with that for CIT, it is reassuring that there has been no signal of increased risk of

myeloid malignancies with these regimens, beyond the elevated baseline risk associated with CLL itself [4]. However, it is worth noting that the AMPLIFY study reported a numerically higher incidence of any-grade second primary malignancies with Acal-A-Ven (5.2%;  $n = 15/222$ ) and Acal-A-Ven-Obi (4.2%;  $n = 12/242$ ) compared with FCR/BR (0.8%;  $n = 2/185$ ). This emerging signal warrants longer follow-up and continued vigilance [57].

## FUTURE OUTLOOK

As illustrated earlier, treatment selection for previously untreated patients with CLL requires integration of evidence from different clinical trials with individual patient characteristics and preferences. Several ongoing trials will help to shape these conversations in the future through additional data on several areas of current uncertainty. To address the question of continuous versus fixed-duration therapy, the CLL17 trial (NCT04608318) will examine first-line ibrutinib monotherapy as a continuous therapy until time of progression or unacceptable toxicity, or fixed-duration therapy with either Ven-Obi for 1 year or Ibr-Ven for 15 months. The primary endpoint of the trial is PFS, with several secondary endpoints focused on MRD outcomes [61].

To better understand the optimal combination partner for a first-line venetoclax-based doublet, the MAJIC trial (NCT05057494) is comparing first-line Acal-A-Ven versus Ven-Obi [62]. MRD assessment is a co-primary endpoint of MRD-driven finite Acal-A-Ven versus MRD-driven finite Ven-Obi, with patients able to receive 1 or 2 years of venetoclax-based therapy depending on whether they achieve uMRD at the end of the first year. The second co-primary endpoint is PFS [62].

Looking further ahead, the ongoing CELESTIAL-TNCLL study (NCT06073821) is comparing zanubrutinib plus the second-generation BCL2 inhibitor sonrotoclax with Ven-Obi in patients with previously untreated CLL with or without mutated *TP53*/del(17p) [63]. This phase III study will build on promising findings from a phase I study of zanubrutinib-sonrotoclax in patients with various B-cell malignancies (NCT04277637) [64, 65]. Preliminary data at a median follow-up of 19.4 months for 137 patients with previously untreated CLL suggested zanubrutinib-sonrotoclax was well tolerated. Neutropenia was the most common Grade  $\geq 3$  AE (23%–24% of patients), but these events were mostly transitory and were not associated with a higher rate of Grade  $\geq 3$  infection; no patients experienced TLS. Efficacy was extremely promising, with 48-week best blood uMRD4 rates of 79% ( $n = 27/34$ ) with 160 mg and 90% ( $n = 43/48$ ) with 320 mg, and only one PFS event, which was in the lower dose cohort [64, 65]. Zanubrutinib has also been assessed in combination with venetoclax as MRD-guided treatment in arm D of the SEQUOIA trial ( $n = 114$ ) [66]. With a median follow-up of 31.2 months, best peripheral blood uMRD ( $<10^{-4}$ ) rates were similar for patients with and without *TP53* aberrations (59% and 60%, respectively). Estimated 2-year PFS rates were also similar, at 94% (95% CI: 85%–98%) in patients with *TP53* aberrations and 89% (95% CI: 76%–95%) in patients without. The safety profile was in line with expectations from previous studies [66].

Finally, two MRD-guided approaches using zanubrutinib, venetoclax, and obinutuzumab are being evaluated in patients with previously untreated CLL [67–69]. In the BOVen study (NCT03824483), the triple therapy is administered until progressive disease, unacceptable toxicity, or uMRD ( $<10^{-4}$ ), with a minimum of 8 months and a maximum of 24 months of treatment based on MRD status. At a median follow-up of 57 months, 92% of patients ( $n = 46/50$ ) achieved the primary endpoint of uMRD in both peripheral blood and bone marrow [67, 68]. Patients who reverted to MRD positivity were eligible for retreatment. At a median follow-up of 14 months, 92% of evaluable patients ( $n = 11/12$ ) achieved an overall response and 46% ( $n = 6/13$ ) regained uMRD status. The BOVen regimen was generally well

tolerated, with no unexpected safety signals observed during long-term follow-up [67, 68]. In the BruVenG study (NCT05650723), from which interim results are expected in late 2025, patients are treated initially with zanubrutinib-venetoclax, and obinutuzumab is added only for patients who remain MRD-positive [69].

## SUMMARY

Targeted therapies have dramatically improved outcomes for patients with CLL, particularly for patients unsuitable for CIT because of poor fitness and comorbidities or because of higher genetic risk markers, such as *TP53* abnormalities and/or miGHV. In this review, we have assessed the key evidence supporting the use of first-line single-agent zanubrutinib/acalabrutinib, Ven-Obi, and venetoclax-BTK inhibitor combinations. With these regimens, it is more difficult to provide a generalized treatment algorithm than it was in the CIT era. For most patients, particularly those with miGHV and no high-risk disease features or confounding comorbidities/comedications, there will be more than one viable treatment option in the first-line setting. Consequently, several factors require evaluation, and weight should be given to the patient's preferences. With effective shared decision-making, there has never been a better opportunity for prescribers to provide patients with CLL with a therapy that meets their individual therapeutic goals.

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## ACKNOWLEDGEMENTS

Editorial support was provided by Luke Smith, PhD, of Porterhouse Medical, to collate and incorporate author input on the manuscript, all carried out under the authors' direction. Editorial support was funded by BeOne Medicines Ltd.

## AUTHOR CONTRIBUTIONS

MSD, SS, and CST contributed equally as co-first authors through the conception, drafting, critical review, and final approval of the manuscript.

## COMPETING INTERESTS

MSD: Research funding from Ascantage Pharma, MEI Pharma, and Novartis; honoraria from AbbVie, Adaptive Biotechnologies, Ascantage Pharma, AstraZeneca, BeOne Medicines Ltd, BMS, Eli Lilly, Genentech, Genmab, Janssen, Merck, Nuvalent, Secura Bio, Takeda Pharmaceuticals, and TG Therapeutics. SS: Honoraria from AbbVie, Acerta Pharma, Amgen, AstraZeneca, BeOne Medicines Ltd, BMS, Celgene, Eli Lilly, F. Hoffmann-La Roche, Gilead Sciences, GSK, Janssen, Novartis, and Sunesis Pharmaceuticals. CST: Research funding from AbbVie, BeOne Medicines Ltd, and Janssen; honoraria from AbbVie, AstraZeneca, BeOne Medicines Ltd, Janssen, and Merck.

## ADDITIONAL INFORMATION

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