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by Mathias Castonguay and John F. Seymour

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Current frontline management of chronic lymphocytic leukemia: balancing efficacy, toxicity, and treatment duration

Mathias Castonguay[1], John F. Seymour[1*]

1. Department of Clinical Haematology, Peter MacCallum Cancer Centre, The Royal Melbourne Hospital, and The University of Melbourne, Melbourne, Australia

* Corresponding author: John.Seymour@petermac.org

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Abstract

The treatment landscape for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has been profoundly transformed over the past decade. Chemoimmunotherapy, once the cornerstone of frontline management, has been supplanted by novel targeted agents demonstrating superior efficacy and improved tolerability. Initial application of covalent Bruton tyrosine kinase inhibitors (cBTKi) and the BCL-2 inhibitor (BCL2i) venetoclax utilised continuous, indefinite therapy paradigms, which established durable disease control but were associated with cumulative toxicity, financial burden, and the risk of acquired on-target resistance mutations.

Recognizing these limitations, subsequent trials explored fixed-duration (FD) regimens combining venetoclax with CD20 monoclonal antibodies or cBTKi, demonstrating that deep and durable remissions, including high rates of undetectable measurable residual disease (uMRD), are achievable with defined treatment durations. Landmark trials have established FD combinations as viable and effective frontline options across diverse patient populations, including those with high-risk genomic features where longer treatment durations appear beneficial.

More recently, MRD-guided approaches have emerged as a strategy to individualize treatment duration, permitting early cessation in rapid responders while allowing extended therapy in those with persisting residual disease. However, MRD-guided regimens have not uniformly resulted in shorter treatment exposure, and optimal stopping rules are not yet standardized.

Selecting between continuous BTKi therapy, FD combinations, and MRD-guided strategies now requires careful integration of disease biology, patient comorbidities, and individual preferences, underscoring the increasing complexity of frontline treatment decisions in CLL/SLL.

1. Introduction

Novel agents, including the BCL2i venetoclax and cBTKi, ± CD20 mAb, have demonstrated superior efficacy and safety compared with chemoimmunotherapy (CIT) in treatment-naïve (TN) CLL/SLL(1, 2). Initially used as continuous monotherapy, these agents are now increasingly combined in FD regimens, achieving deep and durable remissions. As multiple time-limited combinations emerge, selecting the optimal frontline regimen has become increasingly complex.

2. Risk stratification

Diagnosis and treatment initiation for CLL/SLL should follow the 2018 recommendations of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL)(3).

We endorse assessment of immunoglobulin heavy chain variable region (IGHV) somatic hypermutation (SHM) status in all patients showing progressive lymphocytosis or lymphadenopathy, as it is a key predictor for both time-to-first-treatment (TTFT) and duration of response, and can guide treatment selection. IGHV SHM analysis should be performed using next-generation sequencing (NGS); CD38 and ZAP-70 should not be used as surrogate markers given their limited accuracy and variable expression over time(4, 5). Patients with mutated IGHV (mIGHV) CLL typically exhibit slower disease growth kinetics and can therefore be observed for longer before requiring treatment than those with unmutated IGHV (umIGHV) CLL (median TTFT, 95 vs. 36 months), which may help inform clinicians on the appropriate frequency of follow-up.(6). IGHV mutated subset #2 (characterized by IGHV3-21/IGHJ6) is the exception, with a shorter TTFT and traditionally a shorter duration of response to CIT, similar to that observed with umIGHV(7, 8). Another emerging prognostic factor is immunoglobulin light chain variable region (IGLV) mutational status, although not all laboratories report it with IGHV sequencing. Patients with both mutated IGHV (mIGHV) and mutated IGLV and without high risk cytogenetics may remain stable for many years(9). Other prognostic factors, such as mutations in *ATM,*

NOTCH1, and *SF3B1*, may also impact TTFT, but less so than IGHV mutational status and conventional cytogenetics, and their clinical utility remains investigational(6)

For patients meeting treatment criteria, conventional karyotype, FISH for del(17p), *TP53* mutational analysis by NGS and karyotype should be performed to guide treatment decisions. FISH for del(11q) or del(13q), other NGS-detected mutations, complex karyotype, and unbalanced translocations provide additional prognostic information but do not currently influence treatment selection, with the possible exception of patients with high-complexity karyotype (≥5 chromosomal abnormalities), who may be managed as having high-risk CLL, similarly to patients with TP53-aberrant CLL(10).

3. Evidence for frontline therapies in CLL.

Key clinical trials evaluating novel agents in TN CLL (Table 1) are discussed below.

Chemoimmunotherapy

CIT was the standard treatment for TN CLL/SLL before the advent of novel agents. In young (e.g., ≤65 years) and fit patients, fludarabine-cyclophosphamide-rituximab (FCR) was preferred, demonstrating superior progression-free survival (PFS) compared with bendamustine-rituximab (BR)(11). IGHV mutational status is an important predictor of disease control with FCR, and long-term data showed a 19-year PFS of 63% among patients with mutated IGHV, with some patients remaining MRD-6 undetectable, suggesting the possibility of cure(12, 13). However, therapy-related myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) occurred in up to 5-10% of patients, compromising long-term safety(12). For older but fit patients, BR was traditionally preferred, whereas obinutuzumab-chlorambucil (O-chlorambucil) was commonly used in older and unfit patients, as it demonstrated superior OS compared CIT and rituximab-chlorambucil(14, 15).

Venetoclax and CD20 mAbs combinations

Initial trials focused on indefinite venetoclax monotherapy in relapsed/refractory (RR) CLL but were limited by low CR rates and the cumulative risk of *BCL2* mutation development beyond 3 years of drug exposure(16). Venetoclax was subsequently combined with rituximab (VR) in a phase 1b/2 study achieving a high rate of deep (uMRD) remissions and establishing the feasibility of treatment cessation which was then explored in the MURANO phase-3 RR trial and demonstrated improved PFS compared to BR (median PFS of 54.7 vs 17.0 months)(17-19). The MURANO trial also included a re-treatment component, confirming the feasibility of Ven-combination re-treatment after relapse and further highlighting the importance of long-term follow-up(20).

After refinement of sequencing and scheduling with Obinutuzumab as the CD20 mAb partner (VO), this fixed-duration combination (total 14 months) was investigated in TN CLL versus O-Chlorambucil in CLL14 in patients with coexisting conditions (Cumulative Illness Rating Scale score >6)(21). VO demonstrated superior efficacy with a similar safety profile (median PFS 76.2 vs. 36.4 months). Among prognostic factors, disease bulk >5cm, umIGHV, and *TP53* aberrations were associated with shorter PFS and TTNT(2, 21, 22).

The CLL13/GAIA trial evaluated FCR/BR, FD VO, VR, and Venetoclax-Obinutuzumab-Ibrutinib (IVO) in fit patients without *TP53* aberrations. Ibrutinib was administered for a minimum of 12 months and discontinued after two consecutive uMRD assessments or, if uMRD was not achieved, after a maximum of 36 cycles. VO and IVO achieved higher 15-month uMRD rates compared with FCR (86.5% and 92.2% vs. 52.0%), whereas VR did not (57.0%; p=0.32). With longer follow-up, IVO and VO maintained superior PFS compared with FCR/BR, establishing obinutuzumab as the preferred CD20 mAb partner for venetoclax, despite its current approval being limited to TN CLL(23, 24).

Resistance to venetoclax

Resistance to continuous venetoclax is largely driven by acquired on target *BCL2* mutations, with G101V being the most common. Although often detected at low variant

allele frequencies (VAF: 1–2%), multiple distinct *BCL2*-mutant subclones are frequently present, suggesting that resistance is typically oligoclonal(25). In contrast, CLL relapsing after FD venetoclax regimens does not display such a resistance pattern, with *BCL2* mutations rarely observed and limited evidence of therapy-induced clonal evolution, with persistence of the baseline genetic profile(26, 27). Upregulation of alternative pro-survival proteins MCL1 and BCL-XL, associated with NF-κB activation, has been described after both continuous and FD venetoclax therapy. This can be caused by Cr1 amplification (locus for *MCL1* gene), but more commonly by reversible epigenetic changes which may dissipate after venetoclax discontinuation, potentially supporting preserved sensitivity to venetoclax re-exposure, although data remain limited(28-30).

BTKi monotherapy or in combination with CD20 mAb

Ibrutinib with or without a CD20 mAb

Ibrutinib was the first cBTKi to demonstrate superiority over chlorambucil in the phase-3 RESONATE-2 trial, with significantly improved PFS and OS which was consistent among all subgroups. Longer-term follow-up highlighted the durability of ibrutinib, with a median PFS of 8.9 years(1, 31).

Ibrutinib was combined with rituximab (IR) in patients with high-risk features, demonstrating encouraging efficacy, with an 18-month PFS of 78%(32). Subsequently, IR was compared to FCR in the ECOG 1912 trial in patients ≤70 years old and demonstrated improved 3-year PFS.(33). In older patients, the ALLIANCE trial assessed Ibrutinib and IR vs. BR in TN patients ≥65yo. Ibrutinib arms had a better 2-year PFS than BR,but the addition of rituximab provided no PFS benefit (Ibrutinib: 87%, IR: 88%, BR: 74%)(34).

In iLLUMINATE, ibrutinib and obinutuzumab (IO) was compared with O-chlorambucil in patients aged ≥65 years or younger patients with coexisting conditions. Obinutuzumab was given for 6 cycles in both arms, while ibrutinib continued until progression or

unacceptable toxicity. At 45 months' median follow-up, IO improved PFS (median not reached vs. 22 months), with benefit maintained in high-risk patients and across mutated and umIGHV(35, 36). However, there is no phase-3 data to prove the addition of Obinutuzumab truly improves the outcomes relative to Ibrutinib alone.

Acalabrutinib with or without obinutuzumab

Acalabrutinib and acalabrutinib-obinutuzumab (AO; 6 cycles of obinutuzumab with indefinite acalabrutinib) demonstrated improved PFS compared with O-chlorambucil in the ELEVATE-TN trial (72-month PFS: 61.5% and 78.0% vs. 17.2%, respectively). Benefit was observed across all subgroups, including patients with mIGHV CLL. The addition of obinutuzumab to acalabrutinib provided a consistent benefit across IGHV mutational subgroups but did not appear to improve disease control in patients with *TP53* aberrations or complex karyotype. This benefit came at the cost of higher rates of neutropenia, pneumonia, and COVID-19(37, 38). There is no head-to-head trial comparing acalabrutinib with ibrutinib in patient with TN CLL. However, the ELEVATE-RR trial, conducted in patients with previously treated high-risk CLL (del(17p) or del(11q)), demonstrated non-inferiority of acalabrutinib to ibrutinib, with an improved safety profile, including lower rates of atrial fibrillation (AF; 9.4% vs 16.0%), hypertension (9 vs. 23%) and major hemorrhage (~2% vs ~4%)(39, 40).

Zanubrutinib

The SEQUOIA trial compared zanubrutinib with BR in TN patients aged ≥65 years or younger patients with comorbidities. Patients with *TP53* aberrations were non-randomly assigned to zanubrutinib (arm C/D). At 5 years, PFS was 75.8% with zanubrutinib vs. 40.1% with BR, with benefit across all subgroups(41, 42). In patients with *TP53* aberrations (arm C, including 111 patients), the 5-year PFS was 72%(43). Zanubrutinib was compared with ibrutinib in the phase 3 ALPINE trial in RR CLL, demonstrating superior PFS and a more favourable safety profile, with lower rates of AF but similar rates of hypertension (1.9% vs. 3.7% and 14.8% vs. 11.1%, respectively, at 30 months of follow-up)(44).

Pirtobrutinib

Pirtobrutinib is the first non-covalent BTKi (ncBTKi) assessed in TN CLL. The BRUIN CLL-313 trial compared pirtobrutinib with BR and demonstrated improved 2-year PFS (93.4% vs. 70.7%) across all subgroups leading to its approval by the EMA. More deaths occurred in the BR group (10 vs. 3), despite crossover in 52% of patients progressing on BR. Pirtobrutinib was well tolerated, with lower rates of AF and infections compared with BR(45). Pirtobrutinib was compared with ibrutinib in the phase 3 BRUIN CLL-314 trial in patients with TN and RR CLL. Pirtobrutinib was non-inferior to ibrutinib, with superior 18-month PFS in TN CLL (95.3 vs. 87.6%). AF and hypertension were less frequent with pirtobrutinib(46). It is too early to define the frontline role of pirtobrutinib. However, these studies demonstrate a favourable safety profile in this setting. As with all continuous BTKi-based approaches, cumulative infection risk remains a concern, with grade ≥3 infections reported in 13.6% and 17.0% of patients treated with pirtobrutinib in BRUIN CLL-313 and CLL-314, respectively.

Resistance to continuous therapy with BTKi

Resistance to continuous cBTKi therapy is mainly driven by acquired on-target BTK mutations, with *BTK* C481S being the most common mechanism by disrupting irreversible drug binding. Other *BTK* kinase-domain mutations (e.g., T474 and L528W) and gain-of-function downstream *PLCG2* mutations often co-occur with C481S. Resistance patterns may differ according to the frontline cBTKi used, which, if confirmed in larger cohorts, may impact sensitivity to subsequent ncBTKi therapy(27, 47, 48). However, in a subset of patients their disease may progress without detectable *BTK/PLCG2* alterations, suggesting alternative mechanisms involving pathways such as NF-κB, MAPK, and PI3K/AKT signaling(27). Resistance to ncBTKi is also largely driven by acquired, but a different repertoire of *BTK* mutations (e.g., T474, V416L, and L528W), with frequent alterations in non-BTK genes, including *TP53, SF3B1, PLCG2*, and *NOTCH1.* Using highly sensitive assays,

up to 37% of resistance-associated mutations have been detected at very low VAF (range 0.2-5.6%) at baseline from previous exposure to a cBTKi(49, 50).

Venetoclax and cBTKi fixed-duration combinations with or without CD20 monoclonal antibody

BTKi and venetoclax target complementary survival pathways, providing a strong rationale for their combination. BTKi inhibit BCR signalling, disrupting CLL cell interactions with the marrow and lymph node microenvironment and mobilising cells into the peripheral blood, where loss of stromal support increases apoptotic susceptibility. Venetoclax then inhibits BCL-2, releasing pro-apoptotic proteins such as BIM and inducing cell death, resulting in deep cytoreduction and high uMRD rates(51).

Venetoclax with Ibrutinib

The phase-2 CAPTIVATE trial evaluated IV using FD and MRD-guided regimens in TN patients aged <70yo, including those with *TP53* aberrations. In the FD cohort, patients received 3 cycles of ibrutinib lead-in followed by 12 cycles of IV. Patients with PD after >24 months could be retreated with IV, while all patients could restart ibrutinib monotherapy after PD. Best uMRD-4 rates were 77% in PB and 60% in BM, including high rates in *TP53* aberrancy (PB 81%, BM 41%). uMRD-4 rates were higher in umIGHV than mIGHV CLL (PB 84% vs. 67%; BM 64% vs. 53%). With 68.9 months follow-up, 5-year PFS was 66%; among patients with umIGHV CLL and intact *TP53*, 5-year PFS was 55% compared with 79% in those with mIGHV(52-54).

The GLOW trial assessed FD IV versus O-chlorambucil in patients aged ≥65 years or with comorbidities, including those with *TP53* aberrations. IV demonstrated superior PFS across all subgroups, with 42-month PFS rates of 74.6% vs. 24.8%, and high uMRD rates (uMRD-4 in PB by NGS: 54.7%; by flow cytometry at month 3 post-treatment: 61.3%). Any-grade AF occurred in 15.6% of patients.(55, 56).

The CLL17 trial compared FD VO, FD IV, and continuous ibrutinib, without restriction on age or high-risk genomic features. After a median follow-up of 34.2 months, 3-year PFS with both FD regimens was non-inferior to continuous ibrutinib (VO: 81.1%, IV: 79.4%, ibrutinib: 81.0%). In patients with *TP53* aberrations, a trend favouring ibrutinib was observed (VO: 62.0%, IV: 69.0%, ibrutinib: 79.4%), with a similar pattern in complex karyotype (VO: 62.2%, IV: 82.3%, ibrutinib: 80.1%). PB uMRD rates were highest with VO (73.2% vs. 47.2% with IV and 0% with ibrutinib). Safety profiles were consistent with known toxicities; severe infections, especially CoVID-19 were more frequent with the Obinutuzumab-containing regimen, while AF occurred in 12.5% of IV and 16.8% of ibrutinib patients(57). While no major differences are evident with current short follow-up, this is insufficient to establish equivalence, as clinically meaningful divergence in outcomes may only emerge with longer follow-up, as observed in CLL13.

Venetoclax with acalabrutinib

In fit patients with *TP53*-intact CLL, FD acalabrutinib-venetoclax (AV) and acalabrutinib-venetoclax-obinutuzumab (AVO) were compared with FCR or BR (age stratified) in the AMPLIFY trial. AV and AVO improved 3-year PFS compared with FCR/BR (AV: 76.5%, AVO: 83.1% vs. FCR: 68.9%, BR: 64.5%), driven mainly by patients with umIGHV CLL, as no superiority was observed in mIGHV CLL. Three-year OS was improved with AV (94.1% vs. 85.9%) but not AVO, likely due to COVID-19-related deaths (AV: 3.4%, AVO: 8.7%, FCR/BR: 2.7%). This highlights the increased severe infection risk associated with Obinutuzumab, although the impact may be less relevant in the post-COVID era. End-of-treatment PB uMRD-4 was highest with AVO (AV: 45.0%, AVO: 95.0%, FCR/BR: 72.9%); notably, AV achieved longer disease control despite lower uMRD rates than FCR/BR(58).

Resistance to FD venetoclax and BTKi combinations

FD combinations of venetoclax with cBTKi appear to be associated with lower rates of *BTK* or *BCL2* resistance mutations at relapse, likely due to shorter treatment exposure and deeper remissions. In CAPTIVATE, after a median follow-up of 38.9 months, 15% of

patients developed PD, with no *BTK* or *PLCG2* mutations detected. An uncommon *BCL2* mutation (A113G) was identified, although its role in venetoclax resistance remains unknown(59, 60).

Venetoclax and cBTKi MRD-guided combinations

MRD-guided therapy may enable shorter treatment in patients achieving rapid responses while allowing prolonged therapy in slower responders to optimize disease control. It may reduce cumulative toxicity and limit emergence of *BCL2* or *BTK* resistance mutations associated with continuous exposure. However, treatment duration remains individualized and difficult to predict. Importantly, whether uMRD is required for durable disease control remains uncertain, as many patients, particularly those with mIGHV disease, achieve prolonged remissions despite not attaining uMRD with FD regimens.

uMRD is defined as the absence of detectable CLL cells in blood or bone marrow, corresponding to <1 CLL cell per 10,000 leukocytes (10^{-4}), assessed by high-sensitivity flow cytometry, PCR, or NGS. Some therapies, particularly CD20 mAbs, achieve high PB uMRD rates but less effective marrow clearance(3). uMRD is associated with longer PFS compared with patients who do not achieve MRD negativity within the same treatment arm, as well as longer OS among patients treated with CIT. This association is particularly evident with time-limited therapy, supporting the potential role of uMRD as a predictive biomarker to guide treatment duration and intensity(61, 62). However, its prognostic value varies according to the treatment regimen and the depth and compartment assessed (e.g., PB vs BM)(63, 64). Definitive phase 3 evidence demonstrating that MRD-guided treatment improves clinical outcomes over fixed-duration is still awaited, and such approaches are currently not recommended outside clinical trials.

Continuous BTKi monotherapy rarely achieves high uMRD rates; therefore, uMRD is not a relevant endpoint for this approach.

Venetoclax with ibrutinib

In the MRD-guided cohort of the phase-2 CAPTIVATE trial, patients received a 3-cycle ibrutinib lead-in followed by 12 cycles of IV. Patients achieving uMRD4 in PB and BM were randomized to placebo or ibrutinib until confirmed MRD relapse or PD. uMRD4 was achieved in 75% and 68% of patients in PB and BM, respectively. At 30 months, PFS and PB uMRD4 were 95% and 84% with placebo versus 100% and 77% with ibrutinib. (65). Similarly, the phase-2 HOVON141/VISION trial included patients with or without del(17p) treated with frontline ibrutinib-venetoclax, who discontinued therapy upon achieving uMRD-4 after 15 cycles or continued ibrutinib maintenance. The 12-month PFS rate was 98% in the treatment discontinuation group(66).

As previously introduced, the CLL13/GAIA trial demonstrated encouraging efficacy for VO plus ibrutinib in fit patients without *TP53* aberrancies (5-year PFS 81.3%). Patients with umIGHV appeared to derive particular benefit from the triplet regimen, with 5-year PFS rates of 75.9% for IVO, 59.0% for VO, 48.3% for Ven-R, and 33.6% for FCR/BR(24). However, this improved efficacy was associated with increased toxicity. Grade 3–5 infections were modestly higher with IVO than VO (19.8 vs. 14.2 events per 1000 patient-months), while cardiovascular events were substantially increased with IVO.

Extended follow-up of the phase-3 FLAIR trial demonstrated an OS benefit with MRD-guided IV compared with ibrutinib (± rituximab) or FCR in patients ≤75 years without del(17p) in >20% of cells . In the IV arm, treatment could be discontinued after sustained MRD response, defined as uMRD-4 in PB at +3 months and in both PB and BM at +6 months after initial uMRD documentation. Despite this strategy, treatment duration remained substantial (median 27 cycles; range, 2–79), and was longer in mIGHV than umIGHV CLL, with >30% of patients with mIGHV remaining on treatment at 60 months. Few deaths were CLL-related, suggesting the OS benefit may partly reflect reduced treatment-related or disease-associated complications compared with continuous ibrutinib. IV was restarted upon MRD-5 re-emergence, although retreatment was not considered a PFS event(67).

Venetoclax with zanubrutinib

The SEQUOIA Arm D cohort was a non-randomized trial evaluating zanubrutinib plus venetoclax in patients with del(17p) and/or *TP53* mutation. Venetoclax was administered for 24 cycles after a 3-cycle zanubrutinib lead-in. Zanubrutinib was continued until PD, intolerance, or achievement of uMRD-4 in PB on two samples ≥12 weeks apart after at least 12 cycles of venetoclax and 27 cycles of zanubrutinib. The 2-year PFS was 92%, with median PFS and OS not reached after 31.2 months follow-up. Overall, 7% discontinued zanubrutinib based on MRD-guided criteria(68).

Zanubrutinib-venetoclax-obinutuzumab (ZVO) was assessed in the phase 2 BOVen trial in TN CLL. Treatment was administered for 8–24 cycles, with discontinuation 2 months after achieving uMRD-4 in PB and BM. Retreatment with ZV was permitted for MRD resurgence. Most patients had umIGHV CLL and 17% had *TP53* aberrations. Among patients meeting MRD stopping criteria, median treatment duration was 10 cycles, with 92% and 96% achieving uMRD-4 in PB and BM, respectively. Median uMRD-4 duration was 34 months, with a 48-month MRD-free survival rate of 36.1% and median PFS of 53.2 months. Among patients retreated for detectable MRD (56.5% without progression and 43.5% with iwCLL PD), all responded, with a 12-month PFS of 100%.(69, 70).

4. Selecting the appropriate frontline treatment

The following section addresses commonly encountered questions regarding optimal treatment selection and provides practical insights to inform clinical decision-making. Society guidelines, including the 2026 European Hematology Association (EHA) and British Society for Haematology (BSH) guidelines, may also provide useful guidance when selecting treatment(71, 72).

Should we still offer FCR for young patients with mIGHV CLL?

FCR is a potentially curative option for patients with mIGHV(12). However, it is associated with an increased risk of infections and long-term immunosuppression, and a 5–10% risk of MDS/AML. As both BCL2i and BTKi have demonstrated similar PFS in phase 3 randomized trials against FCR in patients with mIGHV CLL (ECOG 1912, CLL13, FLAIR), we believe novel agents should be prioritized when available(23, 33, 67, 73).

Should we use a continuous BTKi approach or a time-limited venetoclax-based approach?
This key question is being assessed by the CLL17 trial, which compared FD VO and IV with continuous ibrutinib. CLL17 was designed to test for non-inferiority of 3-year PFS (margin set at >8%), and no significant difference was observed. However, these data remain premature for definitive conclusions. Although MRD rates were higher with VO, this has not yet translated into improved PFS. As discussed, FD treatment allows potential retreatment with a BTKi (either continuous BTKi or an FD with venetoclax regimen), and cBTKi-class refractoriness may represent a more clinically relevant outcome. Limiting treatment duration reduces cumulative BTKi toxicity (particularly immunosuppression and arrhythmias), while also reducing financial and logistical burdens and potentially improving quality of life(74). However, venetoclax is associated with a higher burden of hospital visits during ramp-up, and some patients may find the logistics challenging. Patient and caregiver related factors, including individual preferences, values, and priorities, should remain fundamental to treatment selection and central to the shared decision-making process(75). The ongoing EA9161 trial (NCT03701282), assessing IVO vs. IO, will also likely provide further insights.

When using a continuous BTKi, which BTKi should be used?
Second generation cBTKi (acalabrutinib or zanubrutinib) are favoured over Ibrutinib, as they have less off-target toxicity and better safety profile, and zanubrutinib have also demonstrated improved PFS when compared to ibrutinib(39, 46, 76). Among cBTKi, acalabrutinib is associated with a lower incidence of hypertension than ibrutinib, whereas zanubrutinib has rates comparable to ibrutinib. A potential advantage of acalabrutinib is

the established combination with Obinutuzumab, which may provide additional benefit in patients with umIGHV CLL. Conversely, the strongest efficacy data supporting a cBTKi in *TP53*-aberrant CLL currently come from zanubrutinib.

If using a continuous BTKi, should a CD20 mAb be added?

The ALLIANCE trial demonstrated no benefit from adding rituximab to continuous ibrutinib; therefore, rituximab should not routinely be added to this regimen(34). However, in the ELEVATE-TN trial AO achieved longer PFS and higher rates of deep uMRD compared with acalabrutinib monotherapy(37). This came at the cost of higher rates of neutropenia and slightly increased rates of infections, including pneumonia and COVID-19. Consequently, when adding an anti-CD20 antibody to a continuous BTKi regimen, we favour obinutuzumab over rituximab and generally reserve this approach for younger, fitter patients with umIGHV in whom maximizing PFS is a key treatment priority. There is no randomised data to support adding a CD20 mAb to zanubrutinib.

If combining venetoclax with a CD20 mAb, should we use obinutuzumab or rituximab?

The CLL13 GAIA study directly compared VR with VO in the frontline setting and demonstrated higher rates of uMRD, CR and PFS with VO, albeit with a higher incidence of infections in the obinutuzumab-containing arm. Therefore, for most patients, obinutuzumab would be favoured as the preferred monoclonal antibody partner given its superior efficacy outcomes(23).

Should venetoclax be combined with a CD20 mAb or a cBTKi?

The CLL17 trial is addressing the question of the optimal partner for venetoclax (a cBTKi or obinutuzumab). With available follow-up, no PFS difference has been observed between VO and VI, despite the higher uMRD rates achieved with VO, as expected with obinutuzumab(57). In practice, the choice between a cBTKi and a monoclonal antibody should be individualized, with patient comorbidities and practical considerations representing major determinants of treatment selection. Compared with a mAb, a cBTKi

is associated with a higher risk of cardiovascular events and bleeding, whereas mAbs, particularly obinutuzumab, are associated with an increased risk of viral infections. Additionally, because obinutuzumab requires infusion-center visits and carries a risk of infusion-related reactions, a cBTKi partner may be logistically simpler for many patients and treatment centers. In some jurisdictions Obinutuzumab is only funded frontline, so omission would remove its beneficial role from disease management. Ongoing trials may provide further insights, including CELESTIAL-TNCLL (NCT06073821), evaluating Zanubrutinib-Sonrotoclax vs. VO (with 1-year FD in both arms), and MAJIC (NCT05057494), evaluating MRD-guided AV vs. VO.

Should we use a triplet regimen?

Triplet regimens (venetoclax-cBTKi-obinutuzumab) achieved deeper and more durable responses than venetoclax-cBTKi or VO doublets in both the AMPLIFY (AVO vs. AV) and CLL13/GAIA (IVO vs. VO) trials(23, 58). However, this benefit came at the cost of increased toxicity, particularly viral infections (including COVID-19), and no OS benefit was observed in AMPLIFY, partly due to excess COVID-related deaths. The benefit of triplet therapy appears to be driven primarily by patients with umIGHV CLL, with an absolute PFS improvement of approximately 10-15% at 3–5 years (3-year PFS: AVO 82.8% vs. AV 68.9%; 5-year PFS: IVO 69.8% vs. VO 57.4%). Careful patient selection is therefore essential. We believe triplet therapy should be considered for fit, younger patients with umIGHV disease but intact *TP53* who are willing to adhere to public health recommendations regarding vaccination and infection prevention measures(77).

If combining venetoclax with a cBTKi, which cBTKi should we use?

There are no head-to-head trials comparing venetoclax combinations with different cBTKis. In indirect comparisons, IV was associated with higher EOT uMRD-4 rates (GLOW: 54.7%; CAPTIVATE: 77%) than AV (AMPLIFY: 45%)(55, 58, 65). However, this difference was not observed in CLL17, where IV achieved a comparable uMRD-4 rate of 47.2%(57). Although cross-trial comparisons are fraught, a matched indirect comparison of IV and AV

using data from CAPTIVATE and AMPLIFY, while censoring for early COVID-related deaths, suggests that IV may provide more durable disease control than AV(78). This observation has been hypothesized to reflect more vigorous and unidirectional mobilization of CLL cells from the lymph nodes, greater BIM upregulation, which enhances sensitivity to venetoclax, and off-target inhibition of kinases other than BTK by ibrutinib(79). For example, inhibition of interleukin-2-inducible T-cell kinase (ITK) may promote Th1 differentiation and enhance cytotoxic T-cell responses, potentially restoring immune surveillance(80, 81). However, ibrutinib is associated with a higher risk of cardiovascular adverse events, and careful patient selection is essential. Older patients and those with significant baseline cardiovascular comorbidities may have reduced tolerance. The incidence of AF was higher in GLOW, which enrolled patients aged ≥65 years (14%), than in the younger CAPTIVATE population (~4%), highlighting the importance of age and comorbidities when selecting a cBTKi. Sudden cardiac death due to ventricular arrhythmia is rare but may occur in 0.3–3% of treated patients and is poorly correlated with baseline cardiovascular risk factors, limiting prediction(82). Regimen selection should be individualized based on patient characteristics, comorbidities, risk tolerance, and clinician experience. Given the potential for rare but serious cardiovascular toxicity, IV should generally be used with caution in patients >65–70 years, even without conventional cardiovascular risk factors.

If combining venetoclax and a cBTKi, should we use FD or MRD-guided regimen?

No direct trial has assessed FD versus MRD-guided duration of IV in CLL, and MRD-guided treatment is not approved in any jurisdiction. Ghia et al. compared 5-year OS from pooled GLOW and CAPTIVATE FD cohort data with an age-matched general European population, demonstrating similar 5-year OS irrespective of age (<65 or ≥65 years) and IGHV SHM status(83). While MRD-guided duration of IV may theoretically individualize therapy by allowing early cessation in rapid responders and prolonged treatment in patients with high-risk disease, overall treatment duration may remain substantial. Moreover, it remains uncertain whether achieving uMRD is necessary for durable remissions, as treatment

duration was paradoxically longer in patients with favourable-risk IGHV-mutated CLL than in those with umIGHV. Moreover, MRD stopping rules are also heterogeneous and lack standardization. Therefore, definitive conclusions regarding FD versus MRD-guided I+V strategies cannot yet be drawn. MRD-guided approaches may be less attractive in patients with favourable-risk mIGHV CLL but may provide effective disease control in high-risk CLL, including those with umIGHV, mIGHV subset 2, complex karyotype, or *TP53* aberration(73).

How should I approach CLL with TP53 aberrations?

Continuous disease suppression with cBTKi has been advocated by many guidelines and experts, largely based on longer PFS observed with cBTKi compared with Ven-O/R in indirect comparisons. (37, 42, 84). Moreover, adverse prognostic features such as *TP53* aberrations, umIGHV, and del(11q) are generally not associated with shorter duration of response with BTKi therapy, supporting its use as a durable treatment strategy across high-risk subgroups(31, 85). In recent years, trials evaluating FD or MRD-guided cBTKi-venetoclax combinations have demonstrated that deep and durable responses are achievable in patients with *TP53* aberrations. However, outcomes remain inferior compared with patients with intact *TP53* (52, 54). In the CLL17 trial, 3-year PFS appeared to favor continuous ibrutinib over fixed-duration VI or VO in patients with *TP53* aberrations (79% with ibrutinib vs. 69% with VI and 62% with VO)(57). Assuming disease retains sensitivity to BTKi or venetoclax at relapse after an FD regimen, time to BTKi-refractoriness may represent a more relevant endpoint than PFS for assessing the long-term impact of FD strategies compared with continuous BTKi therapy. However, safety of treatment cessation and response to retreatment remain unestablished in *TP53* aberrant CLL and are largely extrapolated from lower-risk subsets. MRD-guided duration may represent a promising approach in this population. In FLAIR, del(17p) was an exclusion criterion; however, retrospective *TP53* sequencing identified 70 patients with *TP53*mut (without del(17p)). Of these, 11 received IV, all remained in remission at 5 years, and 50% discontinued treatment at 3 years after meeting the MRD stopping rule(73). However, this

requires validation in larger cohorts, as few patients were evaluated and this was not a prespecified analysis. In conclusion, continuous BTK inhibitor treatment remains preferred in *TP53*-mutated CLL, except in young patients seeking a time-limited approach, for whom Venetoclax-cBTKi for more than 12 months could be considered, if available. The ongoing CLL16 trial (NCT05197192) is evaluating AVO (with 24 cycles of acalabrutinib) vs. VO in high-risk TN CLL and will likely provide important insights into the role of fixed-duration regimens in *TP53*-mutated CLL.

5. Conclusion

The frontline management of CLL/SLL has been fundamentally transformed by novel targeted agents. The shift from continuous monotherapy toward time-limited combinations of BTKi and venetoclax, with or without CD20 mAbs, reflects growing evidence supporting deep and durable remissions within defined treatment windows. MRD-guided strategies offer a promising approach to further individualize treatment duration, although optimal stopping rules remain to be standardized. Despite the expanding range of effective options, treatment selection remains nuanced, requiring integration of disease biology, particularly IGHV mutational status and *TP53* aberration, patient comorbidities, and individual preferences. With strong evidence supporting FD regimens and emerging data on retreatment with BTKi-BCL2i combinations, treatment class refractoriness may represent a more meaningful endpoint than PFS alone. Preserving sensitivity to both drug classes should therefore guide frontline treatment sequencing strategies in contemporary CLL/SLL management.

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Table 1: Landmark clinical trials evaluating frontline treatment regimens for CLL

Study/treatment	Key inclusion & population characteristics.	Median Follow up	Best response and MRD	PFS and OS	Cytopenias and infection (any grade, unless specified).	Adverse events of special interest.
CLL14, 2019 VO vs. O-Chlorambucil(2, 22)	TN CLL, patients with comorbidities Age ≥75 yr 33.3 vs. 36.1% umIGHV: 60.5 vs. 59.1% Del(17)p: 8.5 vs. 7.3% *TP53*mut: 11.1 vs. 8.3%	76 months	ORR: 84.7 vs. 71.3%, p < 0.001 CR 49.5 vs. 23.1%, p < 0.001 uMRD PB: 75.5 vs. 35.2%, p < 0.001	PFS 6-year PFS for VO: 53% PFS for mIGHV Median PFS NR vs. 62.2 months (HR, 2.66; 95% CI, 1.63-4.34) PFS for umIGHV Median PFS 64.8 vs. 26.9 months vs. 62.2 months (HR, 0.30; 95% CI, 0.22-0.42) OS 6-year OS 78.7 vs. 69.2% (HR, 0.69; 95% CI, 0.48-1.01; *P* = .052).	With VO Neutropenia grade ≥3: 52.8% Thrombocytopenia grade ≥3: 13.7% Anaemia grade ≥3: 8.0% All infection grade ≥3: 17.5%	TLS Laboratory: 1.4 vs. 2.3% TLS clinical: 0 vs. 0
GAIA/CLL13 VO vs. MRD-guided IVO vs. VR vs. BR/FCR(23, 24)	TN CLL, ECOG 0-2, no *TP53* or del(17)p Median age: 62 vs. 60 vs. 62 vs. 61 umIGHV: 57 vs. 53.2 vs. 56.5 vs. 57.2%	63 months	ORR: 96.1 vs. 94.4 vs. 93.3 vs. 80.8% CR: 56.8 vs. 61.9 vs. 49.4 vs. 31.0% uMRD PB: 86.5 vs. 92.2 vs. 57.0 vs. 52.0%	PFS 5-year PFS: 69.8 vs. 81.3 vs. 57.4 vs. 50.7% PFS for mIGHV 5-year PFS 82.9 vs. 89.1 vs. 71.0 vs. 75.3% PFS for umIGHV 5-year PFS 59.0 vs. 75.9 vs. 48.3 vs. 33.6% OS	Neutropenia grade 45.2 vs. 41.1 vs. 39.6 vs. 45.3% Thrombocytopenia grade ≥3: 14.9 vs. 11.3 vs. 3.4 vs. 8.4% Anaemia grade ≥3: 3.9 vs. 4.8 vs. 3.8 vs. 7.4% Pneumoniae ≥grade 3: 5.3 vs. 6.4 vs. 1.7 vs. 5.6%	Atrial fibrillation/flutter: 0.9 vs. 7.8 vs. 0.8 vs. 1.9% Hypertension: 9.3 vs. 12.5 vs. 6.7 vs. 2.4% TLS laboratory: 6.8 vs. 6 vs. 10.1 vs. 1.4% TLS clinical: 1.7 vs. 0.9 vs. 2.7 vs. 0.5%

				5-year OS 93.6 vs. 94.3 vs. 94.7 vs. 90.7%	All infection grade ≥3: 13.2 vs. 21.2 vs.10.5 vs. 18.5%	
GLOW FD IV vs. Chlorambucil-obinutuzumab(55, 56)	TN CLL ≥65yr or with comorbidities ≥75yr: 71 vs. 71% umIGHV: 51.9 vs. 51.4% *TP53*mut: 6.6 vs. 1.9%	64 months	ORR 86.8 vs. 84.8%/ CR 38.7 vs. 11.4% uMRD PB: 54.7 vs. 39.0%	PFS 60mo-PFS 59.9 vs. 17.8% PFS for mIGHV with IV 60-mo PFS for mIGHV: 82.5% PFS for umIGHV with IV 60-mo PFS for umIGHV: 52.2% OS 60mo-OS: 81.6 vs. 60.8%	Neutropenia grade ≥3: 34.9 vs. 49.5% Thrombocytopenia grade ≥3: 5.7 vs. 20.0% Infection grade ≥3: 17.0 vs. 11.5%	Atrial fibrillation/flutter: 14.2 vs. 1.9%
CLL17, 2026 VO vs. FD IV vs. I(57)	TN CLL Median age: 61 vs. 62 vs. 61 yr umIGHV: 56.4 vs. 56.4 vs. 56.8% Del(17)p: 6.3 vs. 3.9 vs. 5.0% *TP53*mut: 7.6 vs. 8.2 vs. 7.0%	34 months	ORR 84.2 vs. 88.5 vs. 86.0%. CR 51.5 vs. 46.2 vs. 8.3%. uMRD PB: 73.2 vs. 47.2 vs 0%.	PFS 3-year PFS 81.1 vs. 81.0 vs. 79.4% PFS for mIGHV 3-year PFS 87.6 vs. 80 vs. 83.5% PFS for umIGHV 3-year PFS 75.8 vs. 78.9 vs. 79.7% OS 5-year OS 91.5 vs. 96.0 vs. 95.7%	Neutropenia grade ≥3: 36.6 vs. 22.1 vs. 8.4%. Febrile neutropenia: 4.7 vs. 2.3 vs. 0% Thrombocytopenia grade ≥3: 9.2 vs. 2.4 vs. 0.7% Anaemia grade ≥3: 6.1 vs. 4.0 vs. 4.4% Infection grade ≥3: 34.9 vs. 22.8 vs. 24.8%	Atrial fibrillation/flutter: 3.1 vs. 12.5 vs. 16.8% Hypertension: 11.5 vs. 16.8 vs. 24.2%
AMPLIFY FD AV vs. FD AVO vs. FCR/BR(58)	TN CLL, no *TP53*mut or del(17p) Median age: 61 vs. 61 vs. 61 yr	40 months	uMRD PB: 45.0 vs. 95.0 vs 72.9%.	PFS 3-year PFS 76.5 vs. 83.1 vs. 66.5% PFS for mIGHV	Neutropenia grade ≥3: 32.3 vs. 46.1 vs. 43.2%. Infection grade ≥3: 12.4 vs. 23.6 vs. 10.0%	Atrial fibrillation/flutter: 1 vs. 2.8 vs. 1.6% Hypertension grade ≥3: 2.7 vs. 2.1 vs. 0.8% Tumor lysis syndrome: 0.6 vs. 0.8 vs. 6.2%

	umIGHV: 57.4 vs. 59.1 vs. 59.3% Del(17)p: 0% *TP53*mut: 0%			3-year PFS 86.0 vs. 83.6 vs. 79.9% PFS for umIGHV 3-year PFS 68.9 vs. 82.8 vs. 56.8% OS 3-year OS: 94.1 vs. 87.7 vs. 85.9%		
RESONATE-2 Ibrutinib vs. chlorambucil(1, 31)	TN CLL, ≥65yr Median age: 61 vs. 61 vs. 61 yr umIGHV: 43 vs. 45% Del(17)p: NR *TP53*mut: NR	9.6 years	For ibrutinib ORR: 92% CR: 36%	PFS Median PFS 8.9 vs. 1.3 years PFS for mIGHV 9-year PFS 51% for ibrutinib PFS for umIGHV 9-year PFS 56% for ibrutinib OS 9-year OS 68% for ibrutinib	At 18 months of median follow-up Neutropenia grade ≥3: 10 vs. 18% Anemia grade ≥3: 6 vs. 8% Febrile neutropenia grade ≥3: 2 vs. 2% Pneumonia grade ≥3: 4 vs. 2%	For Ibrutinib Atrial fibrillation/flutter: 9% Hypertension grade ≥3: 26% Major hemorrhage: 2%
ALLIANCE I vs. IR vs. BR(34, 86)	TN CLL, ≥65yr Median age: 71 vs. 71 vs. 70 yr umIGHV: 61 vs. 63 vs. 58% Del(17)p: 6 vs. 5 vs. 8% *TP53*mut: 12 vs. 9 vs. 9%	55 months	ORR: 94 vs. 93 vs. 81% CR: 12 vs. 7 vs. 26%. uMRD: 4 vs. 1 vs. 8%	PFS 48-months PFS 76 vs. 76 vs. 47%. OS 48-months OS 86 vs. 85 vs. 84%.	At 38 months of median follow-up Neutropenia grade ≥3: 27 vs. 33 vs. 35% Anemia grade ≥3: 6 vs. 11 vs. 12% Febrile neutropenia grade ≥3: 1 vs. 2 vs. 7% Infection grade ≥3: 15 vs. 16 vs. 10%	Atrial fibrillation/flutter: 18% for I/IR and 3% for BR Hypertension grade ≥3: 29 for I/IR vs. 12% for BR.
ILLUMINATE IO vs. O-Chlorambucil(35, 36)	TN CLL, ≥65yr or with comorbidities Median age: 70 vs. 72yr	45 months	ORR: 91 vs. 81% CR: 40 vs. 16%	PFS 42-months PFS 74 vs. 33% PFS for umIGHV for IO	For IO Neutropenia grade ≥3: 36% Thrombocytopenia grade ≥3: 19%	Atrial fibrillation/flutter: 15% Hypertension grade ≥3: 23 vs. 7%

	umIGHV: 62 vs. 53% Del(17)p: 12 vs. 16% *TP53*mut: 12 vs. 15%		uMRD: 38 vs. 25%	48-months PFS: 67% <u>PFS for mIGHV for IO</u> 48-months PFS: 89%	Anemia grade ≥3: 4 vs. 8% Pneumonia grade ≥3: 9% Upper respiratory tract infection: 18 vs. 6%	
ELEVATE TN A vs. AO vs. O-Chlorambucil(37, 38)	TN CLL, ≥65yr or with comorbidities or with creatinine clearance of 30-69 mL/min Median age: 70.0 vs. 90.0 vs. 71.0yr umIGHV: 66.5 vs. 57.5 vs. 65.5% Del(17)p: 8.9 vs. 9.5 vs. 9.0% *TP53*mut: 10.6 vs. 11.7 vs. 11.9%	74 months	ORR: 86 vs. 94 vs. 79% CR: 1 vs. 13 vs. 5% uMRD among patients with CR: 7 vs. 49 vs. 69%	<u>PFS</u> 72-months PFS: 61.5 vs. 78.0 vs. 17.2% <u>PFS for umIGHV</u> 72-months PFS: 60 vs. 75 vs. 5% <u>PFS for mIGHV:</u> Not precisely available	<u>For A and AO:</u> Neutropenia grade ≥3: 11.7 and 30.9% Thrombocytopenia grade ≥3: 3.4 and 8.4% Anemia grade ≥3: 8.9 and 7.3% Pneumonia grade ≥3: 6.1 and 7.3% Infection grade ≥3: 27.9 and 35.4%	<u>For A and AO:</u> Atrial fibrillation/flutter: 8.9 and 7.3% Hypertension grade ≥3: 5 and 4.5%
SEQUOIA arm A and B Z vs. BR(41, 42)	TN CLL, ≥65yr or with comorbidities. Patients with del(17)p enrolled in single arm D. Median age: 70 vs. 70yr umIGHV: 53 vs. 53% Del(17)p: 1 vs. 0% *TP53*mut: 6 vs. 6%	61 months	ORR: 97.5 vs. 89% CR: 21 vs. 15%	<u>PFS</u> 60-months PFS 75.8 vs. 40.1% <u>PFS for umIGHV</u> Median PFS: NR vs. 33.6 months <u>PFS for mIGHV</u> Median PFS for mIGHV: NR vs. NR. <u>OS</u> 60-months PFS 85.8 vs 85.0%.	Neutropenia grade ≥3: 2.1 vs. 10.6% Thrombocytopenia grade ≥3: 1.4 vs. 7.5% Anemia grade ≥3: 0.8 vs. 2.6% Pneumonia grade ≥3: 6.3 vs. 5.3%	<u>For zanubrutinib</u> Atrial fibrillation/flutter: 7.3% Hypertension grade ≥3: 12.1%
SEQUOIA arm C Zanubrutinib(43, 87)	TN CLL with del(17)p, ≥65yr or unsuitable for FCR Median age: 70yr	65 months	ORR: 94.5% CR: 2.8%	60-months PFS 72.2% 60-month OS 85.1%	<u>After 18 months of follow up</u> Neutropenia grade ≥3: 9.2%	Atrial fibrillation/flutter: 5% Hypertension grade ≥3: NR

	umIGHV: 65% Del(17)p: 100% *TP53*mut: 42%				Thrombocytopenia grade ≥3: 0.9% Anemia grade ≥3: 0 Infection grade ≥3: 13.8%	
SEQUOI arm D MRD-guided ZV(68)	TN CLL Median age: 67yr umIGHV: 75% Del(17)p: 52% *TP53*mut: 43%	31 months Median duration of ZV: 22 months	ORR: 97% CR: 48% uMRD 59%	PFS 24-month PFS 94% 36-month PFS for TP53mut CLL: 88% OS 24-month OS 96%	Neutropenia grade ≥3: 17% Thrombocytopenia grade ≥3: 4% Anemia grade ≥3: 2% Infection grade ≥3: 7%	Atrial fibrillation/flutter: 5% Hypertension grade ≥3: 10% TLS clinical: <1%
BRUIN CLL-313 Pirtobrutinib vs. BR(45)	TN CLL without del(17)p Median age: 65 vs. 66yr umIGHV: 56 vs. 56% Del(17)p: 0 *TP53*mut: 8 vs. 10.1%	32 months	ORR: 94.3 vs. 80.9% CR: 13.5 vs. 20.6%	PFS 24-months PFS 93.4 vs. 70% PFS for umIGHV 24-months PFS: 90.8 vs. 58.6% PFS for mIGHV 24-months PFS: 96.7 vs. 86.1% OS 24-months OS 97.8 vs. 93.0%	Neutropenia grade ≥3: 7.1 vs. 34.8% Thrombocytopenia any grade: 3.5 vs. 43.1% Anemia any grade: 4.1 vs. 43.1% Infection grade ≥3: 13.6 vs. 8.3%	Atrial fibrillation/flutter: 1.4 vs. 1.5% Hypertension any grade: 7.9 vs. 4.5%
BRUIN CLL-314 Pirtobrutinib vs. Ibrutinib(46)	TN and RR CLL For TN CLL Median age: 67 vs. 67yr umIGHV: 58 vs. 58% Del(17)p: 12.5 vs. 15% *TP53*mut: 11.6 vs 20.2%	22 months for TN CLL	For TN CLL ORR: 92.9 vs. 85.8% CR: 7.1 vs. 3.5%	For TN CLL 18-months PFS: 95.3 vs. 87.6% 18-months OS: 97.5 vs. 97.5%	Neutropenia grade ≥3: 25.3 vs. 17.5% Thrombocytopenia grade ≥3: 3.6 vs. 4.0% Anemia grade ≥3: 6.1 vs. 3.7% Infection grade ≥3: 17.0 vs. 16.6%	For TN CLL Atrial fibrillation/flutter: 0.9 vs. 4.0% Hypertension grade ≥3: 3.3 vs. 4.9%

FLAIR MRD-guided IV vs. Ibrutinib vs. FCR(67)	TN CLL ≤75 yr and considered FIT for FCR, del(17)p included if ≤20% of cells. Median age: 62 vs. 62 vs. 62yr umIGHV: 47.3 vs. 49.0 vs. 52.9% Del(17)p: 0.4 vs. 0 vs. 0 *TP53*mut: NR.	62 months Median duration of MRD-guided IV: 35 months (mIGHV: 48 months, umIGHV: 25 months).	uMRD in BM: 66.2 vs. 0 vs. 48.3% 2-year uMRD in PB: 73.1 vs. 0 vs. 60.8%.	PFS 5-year PFS: 93.9 vs. 79.0 vs. 58.1% HR for PFS IV vs. I in mIGHV: 0.51 (0.24-1.08) HR for PFS IV vs. I in umIGHV: 0.20 (0.08-0.48) OS 5-year OS: 95.9 vs. 90.5 vs. 86.5%	Neutropenia grade ≥3: 27.3 vs. 6.5 vs. 47.3% Thrombocytopenia grade ≥3: 5 vs. 0.8 vs. 4.2% Anemia grade ≥3: 7 vs. 4.6 vs. 14.9% Infection grade ≥3: %	Atrial fibrillation/flutter: 8.2 and 4.2% for IV and I Hypertension grade ≥3: 3.9 and 3.1% for IV and I. TLS laboratory: 5% for IV TLS clinical: <1% for IV
CAPTIVATE MRD-guided IV and FD IV(52, 54, 65) Source.	TN CLL, ≤70 yr Median age: 58 and 60yr umIGHV: 60 and 56% Del(17)p: 16 and 13% *TP53*mut: 12 and 10%	68.9 months	ORR: 97 and 96% CR: 46 and 56% uMRD: 75 and 69%	MRD-guided IV 30-months PFS: 95% for treatment cessation vs. 100% for continuing ibrutinib in patients with uMRD. FD IV 5-year PFS: 66% 5-year PFS in umIGHV: 55% 5-year PFS in mIGHV: 79% 5-year OS: 97%	At 27.9 months of median follow-up of FD IV Neutropenia grade ≥3: 5% Thrombocytopenia grade ≥3: 13% Anemia grade ≥3: 0% Infection grade ≥3: 8%	For FD IV Atrial fibrillation/flutter: 1% Hypertension grade ≥3: 6%

A: Acalabrutinib
AO: Acalabrutinib-Obinutuzumab
AV: Acalabrutinib-Venetoclax
AVO: Acalabrutinib-Venetoclax-Obinutuzumab
BR: Bendamustine-Rituximab
CR: complete response
FD: fixed duration

I: Ibrutinib
IO: Ibrutinib-Obinutuzumab
IR: Ibrutinib-Rituximab
IVO: Ibrutinib-Venetoclax-Obinutuzumab
mIGHV: mutated IGHV
mIGHV: mutated IGHV somatic hypermutation status
NR: not reported
O-Chlorambucil: Obinutuzumab-Chlorambucil
ORR: overall response rate
OS: Overall survival
PFS: Progression-free survival
TN CLL: treatment-naïve chronic lymphocytic leukemia
umIGHV: Umutated IGHV somatic hypermutation status
uMRD: Undetectable measurable residual disease
VO: Venetoclax-Obinutuzumab
VR: Venetoclax-Rituximab
P: Pirtobrutinib
Z: Zanubrutinib
ZV: Zanubrutinib-Venetoclax