HHS Public Access

Author manuscript

Blood Neoplasia. Author manuscript; available in PMC 2025 February 13.

Published in final edited form as:

Blood Neoplasia. 2024 September ; 1(3): . doi:10.1016/j.bneo.2024.100034.

Ibrutinib and venetoclax in combination for chronic lymphocytic leukemia: synergy in practice

Natalia Timofeeva[1], **Nitin Jain**[2], **Varsha Gandhi**[1,2]

[1]Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

[2]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Abstract

The combination of ibrutinib and venetoclax has emerged as a promising therapeutic strategy for patients with chronic lymphocytic leukemia (CLL). Preclinical investigations demonstrated a synergistic antitumor effect through multiple mechanisms, providing a robust foundation for translating this regimen into clinical trials. Beyond the dual inhibition by 2 small molecules, another innovative concept being tested with this combination is the use of measurable residual disease (MRD)–driven treatment vs fixed-duration treatment to meet the escalating demand for oral, convenient, cost-effective, and time-limited therapeutic approaches. The clinical translation of this combination has yielded remarkable outcomes with significant improvements in the progression-free survival and overall survival rates for both treatment-naïve patients and those with relapsed/refractory CLL. Notably, a substantial proportion of patients achieved undetectable MRD. Clinical trial updates following the initial published results have shown consistency and durability of responses over time. In this review, the initial investigator-initiated trial results for ibrutinib and venetoclax are discussed, several multicenter clinical trial designs and outcomes are examined, variables such as chromosome 17p deletion that influence treatment responses are addressed, and the safety of the regimen is discussed. In addition, we reviewed the usage of this combination in other B-cell malignancies and discussed how current knowledge can be used for shaping the future CLL treatment regimens.

Introduction

Pathophysiology studies of chronic lymphocytic leukemia (CLL) have identified 2 primary pathways responsible for production, proliferation, survival, and migration of CLL cells, namely B-cell receptor (BCR) pathway signaling and abundance of B-cell lymphoma 2 (BCL-2) family antiapoptotic proteins. These biologic features of CLL were instrumental for identifying and establishing targeted therapies in CLL.

Correspondence: Varsha Gandhi, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Unit 1950, 1901 East Rd, Houston, TX 77054; vgandhi@mdanderson.org.

Authorship

Contribution: N.T. and V.G. researched the literature, outlined the review, and wrote the review; and N.J. reviewed the manuscript.

To mitigate BCR pathway signaling, targeting the Bruton tyrosine kinase (BTK) node has proved to be the most successful strategy. Ibrutinib, a small molecule inhibitor, is a first-in-class oral irreversible inhibitor of BTK that binds covalently to cysteine 481 in its kinase domain. This binding prevents the activation of BTK by hindering its autophosphorylation at tyrosine 223 and consequently suppressing the downstream BCR signaling required for B-cell proliferation, migration, and survival.[1] The phase 1 and 2 trials and the RESONATE trial series demonstrated the high efficacy and safety of ibrutinib monotherapy in patients with both treatment-naïve[2–4] and relapsed/refractory (R/R)[4–9] disease. Ibrutinib is continued until disease progression or the emergence of serious adverse effects (AEs). Despite its success, especially in reducing lymph node tumor burdens, the need for continuous treatment, the lower rates of achieving complete remission (CR)[4,8–10] and undetectable minimal residual disease (uMRD) status, the accrual of undesirable toxicity events,[11–15] and the development of drug resistance over time[4,11,16–19] have underscored the necessity for alternative approaches. Ibrutinib toxicity, rather than disease progression, is a predominant reason for discontinuation of the drug. AEs include bleeding, hypertension, cytopenia, and atrial fibrillation.[11–16] Death analysis using VigiBase (the World Health Organization global database of adverse drug reaction) revealed that ibrutinib is associated with severe and sometimes fatal cardiovascular adverse drug reactions, including supraventricular and ventricular arrhythmias, heart failure, conduction disorders, and central nervous system events.[20,21] Limited-time ibrutinib treatment and second-generation of BTK inhibitors, such as acalabrutinib[22] and zanubrutinib, along with the new noncovalent BTK inhibitor pirtobrutinib, provide an alternative approach for a favorable safety profile.[23,24]

Among the BCL-2 family of antiapoptotic proteins, the most pronounced member in CLL biology is BCL-2 itself. The BCL-2 inhibitor venetoclax has emerged as a promising monotherapy, demonstrating impressive results, especially in peripheral blood (PB) and bone marrow (BM).[25–27] The potent effect of venetoclax and its rapid reduction of tumor burden have presented challenges, notably tumor lysis syndrome (TLS), which is managed through a carefully administered ramp-up period to reach the full therapeutic dose.[28–30] The risk for TLS and hematologic toxicities have emerged as limiting factors for the use of venetoclax.[31–33]

Despite the advantages and drawbacks of ibrutinib and venetoclax as single agents, the combination of these 2 distinct drugs may enable a potential synergistic approach in the evolving landscape of CLL treatment. This review first describes the rationale for ibrutinib plus venetoclax combination treatment. We then synthesized the clinical trial results obtained thus far (Table 1). We examined various trial designs, the results for genetic sub-populations, the safety of the combination, and the molecular findings at disease progression. Finally, we discussed ongoing trials and novel drug combinations.

Rationale for combining ibrutinib and venetoclax

The lymph node creates a supportive microenvironment for CLL cells, offering protection against proapoptotic signals. Figure 1 illustrates cell signaling and activity within and outside the lymph nodes. Within proliferation niches, various cell types, including T cells, natural killer cells, leukemia-associated macrophages, endothelial cells, and mesenchymal

stem cells, provide essential stimulation, whereas CLL cells suppress antitumor immune responses.[34–36] Not only does BCR stimulation sustain survival signaling, but the interaction with T cells through CD40-CD40L engagement also induces the upregulation of antiapoptotic BCL-2 family proteins such as B-cell lymphoma-extra large (BCL-XL) and myeloid cell leukemia-1 (MCL-1).[36–41] This interconnected relationship was further highlighted in in vitro and ex vivo experiments in which primary samples from patients with CLL demonstrated that Toll-like receptor stimulation and CD40 overexpression collectively diminish the sensitivity to pharmacologic BCL-2 inhibition by venetoclax.[42,43] In CLL cells, BCL-2 protein levels are upregulated because of the loss of microRNA cluster miR-15a/miR-16–1 (miR-15/16). These micro-RNAs normally act as tumor suppressors by directly targeting BCL-2 messenger RNA for degradation. This dysregulation promotes the survival and accumulation of CLL cells by inhibiting apoptosis.[44]

The ibrutinib-venetoclax combination exhibits clinically complementary activity with ibrutinib effectively inducing CLL cells to undergo a compartment shift from the lymph nodes to PB and venetoclax addressing all 3 compartments, namely PB, BM, and lymph nodes. Ibrutinib treatment leads to a reduction in the cell surface levels of CXCR4, which leads to the rapid redistribution of CLL cells from the spleen and lymph nodes to PB circulation, thereby inducing transient lymphocytosis in treated patients.[45] Although CLL cells that have recently migrated from lymph nodes have higher MCL-1 and BCL-XL expression, the levels change after treatment with ibrutinib.[37] Ibrutinib was shown to decrease MCL-1 protein levels and to make CLL cells highly dependent on BCL-2 signaling, thereby reinforcing the efficacy of its combination with venetoclax.[46–48]

Recent studies have shown that tyrosine 223 phosphorylation is not fully critical for maintaining BCR signaling; kinase-deficient or dead BTK mutants still play an integral role in BCR signaling through their scaffolding function.[49–52] The L528W mutation of BTK prevents adenosine triphosphate (ATP) binding, thereby making it kinase-dead; however, it was shown to contribute to ibrutinib, zanubrutinib, and pirtobrutinib resistance in patients with CLL.[53,54] CLL cells lacking BTK catalytic activity are still capable of activating phospholipase C γ2 through alternative signaling such as phospha-tidylinositol 3-kinase, hematopoietic cell kinase, and Toll-like receptor 9. [51,55,56] It has been demonstrated that ibrutinib treatment leads to a reduction in the BTK transcript and protein levels, which would also decrease the intensity of the BTK scaffolding function.[57] Patients who developed the L528W mutation were responsive to subsequent venetoclax treatment.[53] Thus, BTK inhibition by ibrutinib may be complemented by the proapoptotic effect of venetoclax. [57]

Ex vivo drug profiling of primary CLL lymphocytes from patients treated with ibrutinib demonstrated enhanced sensitivity to venetoclax. Furthermore, the levels of MCL-1 and BCL-XL were reduced in these samples. In primary CLL cells from treatment-naïve patients, the combination of ibrutinib and venetoclax showed a synergistic effect on the apoptosis rate.[48] Incubation of isolated CLL cells with ibrutinib demonstrated increased BCL-2 dependence, revealed through BCL-2 homology-3 (BH3) profiling.[47]

Ibrutinib and venetoclax synergism was confirmed in in vivo studies in the T-cell leukemia/lymphoma 1 (TCL1) mouse model.[58] Furthermore, ibrutinib and venetoclax selectively

act on different CLL subpopulations with distinct proliferative capacities; the proliferating subset of CLL cells displays a more favorable response to ibrutinib, whereas the quiescent subpopulation responds more to venetoclax.[59] This comprehensive approach, backed by preclinical evidence of synergism and nonoverlapping toxicity profiles, underlies the promising therapeutic potential of the ibrutinib-venetoclax combination in CLL.

Clinical trials and outcomes to date

MD Anderson Cancer Center trial—Based on preclinical findings, the first investigator-initiated clinical trial in CLL was initiated in 2016 at the MD Anderson Cancer Center for high-risk treatment-naïve (N = 120)[60–62] and previously treated (N = 80) patients,[63] (NCT02756897). High risk was defined as the presence of a *TP53* aberration, chromosome 11q deletion (del(11q)), unmutated *IGHV*, or age >65 years. The treatment regimen (Figure 2) started with ibrutinib (420 mg/d) for 3 cycles to achieve debulking, lower MCL-1 protein levels, and enable migration of cells from lymph nodes to the blood and then venetoclax was commenced with a weekly dose escalation up to a target dose of 400 mg daily. The combination therapy spanned 24 cycles with MRD measurements performed (assessed in BM by flow cytometry) at regular intervals. uMRD was defined as <0.01%, low MRD was defined as 0.01% to <1%, and high MRD was defined as ≥1%.[60] The study applied the concept of MRD-driven treatment duration in which patients with uMRD concluded treatment at 24 cycles, whereas MRD-positive patients continued the combination of ibrutinib and venetoclax for another 12 cycles.

Initially, the combination of ibrutinib and venetoclax was tested in a cohort of patients with R/R CLL. After 12 cycles of the combination, 29 of 60 patients (48%) achieved BM uMRD, and among 24 patients who completed 24 cycles, 16 (67%) achieved uMRD remission. Limited data are published on the long-term results; however, the median progression-free survival (PFS) and overall survival (OS) durations were not reached by month 36 of follow-up.[63]

Subsequently, treatment-naïve patients with high-risk CLL demonstrated a 69% CR rate (n = 55) or CR with incomplete BM recovery (CRi) by cycle 12 and a 69% (n = 55) CR rate by cycle 24. In the BM, the rates of uMRD were 56% at 12 cycles and 66% at 24 cycles. The best response was uMRD in 72% (86/120) of patients. One patient experienced Richter transformation, and another had disease progression within the first 2 years of therapy.[61] Data on the trial's 5-year follow-up were presented at the 2023 American Society of Hematology Annual Meeting[62]; at a median of 61.5 months, PFS was 90.1% and OS was 95.6%. In summary, the administration of 24 cycles of fixed-duration ibrutinib and venetoclax demonstrated its efficacy, characterized by a high rate of uMRD and a substantial rate of response retained even after treatment discontinuation.

CAPTIVATE trial—The international industry-sponsored trial, CAPTIVATE, investigated the combination of venetoclax and ibrutinib in 323 treatment-naïve patients with CLL. Patients were stratified into 2 cohorts, namely fixed duration (N = 159) and MRD-driven duration (N = 164).[64,65] Ibrutinib was administered for 3 cycles, followed by a 5-week ramp-up of venetoclax, after which a full-dose combination regimen of both agents was

continued for 12 cycles (Figure 2). After 12 cycles, uMRD status was achieved in the PB in 75% of patients and in the BM in 68% of patients.[65]

In the MRD cohort, patients with flow cytometry–confirmed uMRD after 12 cycles of combination therapy were randomized 1:1 to either receive ibrutinib (n = 43) or a placebo (n = 43). Patients without confirmed uMRD continued either ibrutinib (n = 31) or ibrutinib with venetoclax (n = 32). The fixed-duration cohort received the combination for 12 cycles or until disease progression or toxicity if either occurred earlier. The main variables studied in the CAPTIVATE trial were fixed-duration treatment and the impact of MRD on disease-free survival.

For the MRD cohort, in the uMRD subgroup, the 1-year disease-free survival rates were similar between the placebo and the ibrutinib groups (95% vs 100%, respectively; $P = .15$). This result emphasizes the favorable impact on uMRD status. Continuing treatment may not confer a substantial additional benefit in terms of maintaining disease-free status in patients with uMRD. Patients who remained MRD positive after 12 cycles continued treatment with either ibrutinib alone or a combination of ibrutinib and venetoclax. Both groups had similar 30-month estimated PFS rates (95% vs 97%, respectively). Among patients who achieved a partial remission (PR) as their best response during the initial 12 cycles of combination treatment, nearly half experienced a deepening of their response to CR with continued treatment (8/15 in the ibrutinib group and 10 of 24 in the combination group).[65]

For the fixed-duration cohort, with a median follow-up of 27.9 months, the efficacy observed with the combination regimen was remarkable with a 56% rate of CR and 76% and 62% rates of uMRD in the PB and BM, respectively.[66]

The significance of achieving uMRD was evident in this cohort. Based on the MRD status after 12 cycles of combination treatment, there was minimal difference in the PFS rates at 24 months (100% for uMRD vs 91% for MRD positive). However, by the 4-year follow-up time, there was a substantial difference in the PFS rates (90% for uMRD vs 66% for MRD positive).[67] This result serves as a compelling illustration of how a prolonged follow-up period unveils the impact of prognostic factors. By the 5-year follow-up, the PFS and OS rates for the fixed-duration cohort were 70% and 97%, respectively. Overall, 58% achieved CR or CRi as their best response, which in most cases lasted >12 cycles. [68]

CLARITY trial—The UK CLARITY trial explored a modified approach to the ibrutinib-venetoclax combination by administering ibrutinib as a monotherapy for 2 cycles before introducing the combination in patients with R/R CLL (Figure 2). A unique aspect of the study design was the definition of therapy duration based on the pace of achieving remission and MRD status, which was evaluated using highly sensitive, multiparameter flow cytometry. Patients who achieved uMRD in the PB and BM at 6 months of combination therapy ceased ibrutinib-venetoclax treatment at cycle 12. Those who attained uMRD later (by cycle 12 or 24) ceased combination treatment at cycle 24. Patients with persistent MRD at the final assessment continued ibrutinib therapy.[69]

Of 50 patients with CLL who completed the combined treatment, 14 achieved MRD negativity in the PB and BM at the early time point of 6 cycles.[70] Remarkably, MRD responses showed ongoing improvement beyond the initial 12 cycles with 40% (n = 20) achieving uMRD in the BM at cycle 14 and increasing to 48% (n = 24) by cycle 26. Of the 23 patients who discontinued treatment before 36 months, 17 did so because of achieving uMRD. At the 36-month mark, 18 patients who stopped therapy because of uMRD still had uMRD. Notably, 90% of patients who attained uMRD achieved this status within the initial 24 cycles of combination therapy. Finally, 1 case of progressive disease occurred at month 38.

Patients who achieved uMRD at cycle 24 demonstrated better CLL depletion during the initial 4 cycles than MRD-positive patients; however, from cycles 4 to 8, disease depletion rates were slower across all groups. The 2-log reduction in MRD levels at 2 months of combined ibrutinib-venetoclax therapy emerged as a strong predictor for long-term response in R/R CLL.[71]

FLAIR trial—Following the favorable outcomes of the CLARITY trial, the UK CLL group investigated the combination of ibrutinib and venetoclax in 260 patients with untreated CLL in the FLAIR trial. Initially comparing the gold standard of FCR (fludarabine, cyclophosphamide, and rituximab) with the combination of ibrutinib and rituximab,[72] the trial's design was later adapted to include 2 additional arms, namely ibrutinib monotherapy and the ibrutinib-venetoclax combination. The duration of ibrutinib-venetoclax therapy was determined by flow cytometry assessment of MRD in PB and BM and lasted up to 6 years for patients without a uMRD response.[73] The results of the interim analysis of the ibrutinib-venetoclax cohort indicated a high rate of uMRD in the BM (65.4%), which was superior to the absence of a uMRD response among patients who received ibrutinib alone.[74] After 27 cycles of ibrutinib and venetoclax, 49.9% stopped therapy because of achieving uMRD; the rate increased to 72.9% by 51 months.[73,75]

Ultimately, the ibrutinib-venetoclax arm (N = 260) was compared with the FCR arm (N = 263). MRD-guided venetoclax and ibrutinib therapy demonstrated superiority over FCR in terms of PFS (93.5% vs 64.8% at 4 years) and OS (94.9% vs 87.3% at 3 years).[75] In addition, there was a difference in the association between *IGHV* mutational status and PFS at the 3-year follow-up; PFS for patients with unmutated *IGHV* who received ibrutinib and venetoclax was 98.3% vs 70.9% for patients who received FCR ($P < .001$).A total of 42 patients had disease progression on FCR therapy in comparison with only 5 patients on ibrutinib-venetoclax therapy.[73]

GLOW trial—The European multicenter GLOW trial[76,77] compared the efficacy and safety of 24 cycles of fixed-duration ibrutinib-venetoclax therapy (N = 106) with those of chlorambucil and obinutuzumab (N = 105) in untreated patients who were older than 65 years and/or who had comorbidities. Patients with del(17p) were excluded from this study. MRD was assessed using next-generation sequencing (clonoSEQ) and flow cytometric assays. The ibrutinib-venetoclax combination demonstrated superiority in terms of PFS with the median PFS not reached by 46 months of follow-up, whereas the chlorambucil and obinutuzumab arm had a median PFS of 21.7 months. After 12 cycles of ibrutinib and

venetoclax combination therapy, 55% achieved uMRD in PB 3 months after treatment, but the rate decreased to 38% after 24 months.[76]

Following the results of the phase 3 GLOW trials, the European Commission granted approval in August 2022 for ibrutinib in combination with venetoclax as an oral fixed-duration regimen for untreated CLL.

Optimal duration of treatment

The discussed clinical trials can be broadly categorized into 2 subgroups, namely those that employed 12 cycles of fixed-duration treatment and those that employed 24 cycles. Although reducing the number of cycles may seem appealing to minimize potential adverse events, the risk for acquiring drug resistance, and therapy costs, it is essential to weigh these benefits against treatment efficacy. Although most uMRD responses typically manifest within the initial 12 cycles of treatment, distinct dynamics emerge across various studies depending on the duration of treatment. For instance, the MD Anderson[60,62] and FLAIR[73] trials have observed an increase in MRD rates between 12 and 24 cycles if treatment is prolonged. In the CAPTIVATE trial, the MRD rates remained stable without a distinct increase in uMRD after 12 cycles of treatment.[64] Notably, the GLOW trial exhibited a decrease in uMRD rates over time, particularly in the cohort of patients with unmutated *IGHV*, after 12 months of fixed-duration treatment.[76]

The MD Anderson trial amendment allowed for the administration of an additional 12 cycles of venetoclax if MRD persisted at the 24th cycle of combined treatment. Overall, 101 patients completed 24 cycles, and 77 patients achieved BM uMRD, whereas 24 patients remained MRD positive. Ultimately, 18 patients with MRD positivity opted to resume venetoclax, leading to 11 patients who achieved uMRD remission during the third year of the combined therapy.[71]

The MD Anderson trial for the R/R population demonstrated an increase in uMRD rates in the BM from 48% (29/60 patients) at 12 cycles to 67% (16/24 patients) by cycle 24 of combination treatment.[63] Similarly, for the CLARITY trial, there was ongoing improvement in MRD dynamics with 36% achieving BM uMRD and 53% achieving PB uMRD after 12 cycles of combination therapy, and this increased to 44% of patients who achieved uMRD by cycle 24.[69]

However, MRD is not the sole criterion used to define the optimal treatment duration. Disease progression while on ibrutinib and venetoclax time-limited treatment predominantly occurred during the off-therapy phase, regardless of the treatment duration.[62,76,78] Therefore, sustained response emerges as one of the primary considerations for determining therapy duration.

Patient populations and responses

Diverse outcomes are noted among distinct CLL subgroups, including those with *TP53*/del(17p) and *IGHV*-mutated vs -unmutated CLL. The ibrutinib-venetoclax combination demonstrated promising effectiveness in patients with *TP53* abnormalities, although outcomes remain less favorable than those in standard-risk patients with CLL. In the MD

Anderson trial, in which all untreated patients exhibited high-risk features, the 5-year PFS was 90.1%, whereas patients with *TP53* abnormalities had a numerically lower PFS of 86.1%.[62]

The CAPTIVATE trial included 129 patients with at least 1 higher-risk feature (*IGHV*-unmutated status, n = 119; del[17p] and/or *TP53* mutated, n = 29).[79] Patients with del(17p) displayed a 4-year follow-up PFS of 63% as opposed to 79% among those without *TP53* abnormalities[79]; however, at the 54-month mark among those with del(17p)/mutated *TP53*, there was a decline to 45%.[78] Patients with CLL with *TP53* abnormalities had a lower rate of uMRD in the BM (45%) than patients without del(17p) mutations (72%), suggesting increased resistance to therapy when these mutations are present.

Noteworthy findings emerged during the analysis of MRD and *IGHV* status. There was a trend among patients with unmutated *IGHV* toward a higher likelihood of achieving uMRD. In the MD Anderson trial for treatment-naïve patients, patients without an *IGHV* mutation had a uMRD rate of 60% (n = 38) at 12 cycles and 67% (n = 42) at 24 cycles as opposed to 38% (n = 5) and 54% (n = 7), respectively, among patients with a mutation. Notably, this trial primarily recruited patients with high-risk features, and 86% had unmutated *IGHV*.

In the CAPTIVATE analysis, among patients with *IGHV*-unmutated CLL, the rates of uMRD in the PB and BM were 88% and 73%, respectively as opposed to 72% and 60% among those with *IGHV*-mutated CLL. Patients with *IGHV*-unmutated CLL had a 36-month PFS of 88%, whereas those with *IGHV*-mutated CLL had a PFS of 92%.[79]

More uMRD cases were observed among patients with *IGHV*-unmutated CLL in the FLAIR trial. Within the ibrutinib and venetoclax arm, patients with unmutated *IGHV* achieved uMRD rates of 83% in the PB and 80% in the BM at 24 months. In contrast, patients with mutated *IGHV* had uMRD rates of 64% in the PB and 56% in the BM.[73]

Similar results were observed in the GLOW trial. Patients with *IGHV*-unmutated CLL achieved higher uMRD rates earlier (60% at 12 months). However, this rate decreased to 36% at the 24-month follow-up. Patients with *IGHV*-mutated CLL had a stable uMRD rate of 41% up to the 24-month follow-up. However, in patients with mutated IGHV, the 2-year PFS was 92.3% among those with detectable MRD (n = 14) and 100% among those with uMRD (n = 13), whereas in patients with unmutated *IGHV*, PFS was 67% with detectable MRD (n = 16) and 89.9% with undetectable MRD (n = 40).[76]

Generally, uMRD is considered a favorable prognostic marker, and its status is frequently used as a surrogate end point for PFS.[79] Despite higher initial rates of uMRD during ibrutinib-venetoclax therapy, the PFS was shorter among patients with unmutated *IGHV*, highlighting that higher uMRD rates do not necessarily translate into improved PFS for this CLL subgroup. Conversely, this phenomenon may suggest that the MRD status has a minor impact on the survival outcomes among patients with mutated *IGHV*.

Safety of ibrutinib-venetoclax combination

In terms of side effects, the ibrutinib-venetoclax regimen seems to have a combination of the AE profiles of each of the drugs. Ibrutinib is known for its unfavorable cardiovascular

events, including hypertension and atrial fibrillation, which often necessitate the withdrawal of BTK inhibitors.[15] Venetoclax can lead to TLS, necessitating close monitoring of laboratory results during venetoclax ramp-up[28,29] and hematologic toxicity, particularly grade 3 to 4 neutropenia.[31,32] The limited treatment duration of the ibrutinib-venetoclax regimen aims to mitigate the occurrence of these adverse events, which tend to increase over prolonged drug exposure. However, despite these efforts, infections and cardiovascular events were still observed across the discussed studies, but no new toxicities were observed with this drug combination.

AEs noted in the fixed-duration ibrutinib-venetoclax trials occurred at varied rates with the most common grade 3 to 4 AEs being neutropenia (10.3%−51%), atrial fibrillation (0.8%−16%), and hypertension (6%−16%).[62,64,73] Drug discontinuations and interruptions because of AEs remained a significant concern in the clinical trials. In the MD Anderson trial for treatment-naïve patients, therapy discontinuation owing to AEs occurred in 8 (10%) patients, and 2 patients discontinued during ibrutinib monotherapy because of pneumonia and a severe skin rash, and 7 patients discontinued during the combination treatment.[61] In the CAPTIVATE trial, within the MRD cohort, dose reductions were necessary for 24 patients (15%) on ibrutinib and for 16 patients (10%) on venetoclax. In addition, 10 patients (6%) discontinued ibrutinib, and 4 patients (4%) discontinued venetoclax.[65] In the fixed-duration cohort, AEs led to dose reductions for 9 patients (6%) on ibrutinib, 18 patients (11%) on venetoclax, and 6 patients (4%) on both drugs. Of the 33 patients with AEs that led to dose reductions, 88% saw resolution at the time of analysis. Discontinuation because of AEs occurred in 5 patients (3%) on ibrutinib, 1 patient (1%) on venetoclax, and 2 patients (1%) on both drugs.[66] The CLARITY trial reported 4 discontinuations during ibrutinib monotherapy but none during combination treatment. Ibrutinib treatment was interrupted in 28 of 50 patients (56%) and reduced in 8 patients (16%), whereas venetoclax treatment was interrupted in 23 patients (46%) and reduced in 11 patients (22%). Most treatment modifications were because of toxicity with diarrhea and neutropenia being the most common AEs.[69] In the FLAIR trial, early discontinuation of treatment was reported in 58 of 252 patients (23.0%), mostly because of toxicity, including 21 cases treated with ibrutinib and 11 treated with venetoclax. Dose modifications, including reductions, delays, and omissions, were reported for 143 patients (55.0%) in the ibrutinib-venetoclax group.[73] The GLOW trial that specifically involved patients with older age and/or comorbidities showed a discontinuation rate of 10.4% for the ibrutinib-venetoclax combination with 2 patients (1.9%) discontinuing ibrutinib because of atrial fibrillation while continuing venetoclax. Fifteen deaths were reported with 3 attributed to posttreatment infections and 4 to cardiac events.[76,77]

As an alternative to fixed-duration treatment aimed at reducing AEs, clinical trials and real-world practice have explored the use of low-dose single-agent ibrutinib. A pilot study (NCT02801578) investigated whether lower doses of ibrutinib could maintain biologic activity in patients with CLL. After an initial cycle of 420 mg/d, the dose was systematically and preemptively reduced to 280 mg/d in cycle 2 and then to 140 mg/d in cycle 3. The results showed that the lowest dose of ibrutinib was sufficient to suppress >95% of BTK protein. BTK downstream signaling inhibition was maintained, and biomarkers of ibrutinib response were similar across the cycles. This suggests that after 1 full-dose

cycle, ibrutinib can be safely reduced without losing efficacy.[80] Real-world practice studies reported more frequent dose reductions than clinical trials, ranging from 11% to 31.3%, mostly because of the AEs of ibrutinib.[81] As part of this exploration, the TAILOR clinical trial (NCT05963074) aimed to assess the efficacy and safety of ibrutinib plus venetoclax and ibrutinib monotherapy regimens and incorporated proactive or reactive modifications of ibrutinib dosing in response to adverse events.

Investigating the impact of fixed-duration ibrutinib-venetoclax therapy on immune restoration revealed interesting patterns in various immune cell subsets. The MD Anderson trial found stable immunoglobulin G (IgG) and IgM levels, whereas IgA levels increased during the ibrutinib monotherapy phase. Absolute T-cell and natural killer– cell numbers decreased during combination treatment and remained low at the 12-month follow-up. [61] Immune cell subsets were evaluated in the CAPTIVATE and GLOW trials, and, despite a decrease in the normal B cells during the first 12 cycles of combined treatment, healthy B cells recovered to normal levels after 16 cycles. Within 6 months, T-cell, monocyte, and dendritic cell counts returned to normal levels and resembled those of a healthy donor.[82] Over time, infections showed a general decrease, regardless of the randomized treatment, with the lowest frequency observed in patients assigned to the placebo group after cycle 16. Integrating 2 to 3 debulking cycles of ibrutinib before venetoclax has led to a reduction in the TLS risk, thereby allowing patients to avoid hospitalization for venetoclax initiation. Clinical TLS has not been reported, and predominantly laboratory TLS has occurred in the range of 1% to 4% of cases.[60,64,75,83,84]

Disease progression

In patients with CLL, mutations in *BTK, PLCG2,* and *BCL-2* have been observed in those with progressive disease during continuous, single-agent BTK or BCL-2 inhibitor treatment.[85] In the MD Anderson and CAPTIVATE trials, among patients who completed fixed-duration treatment, no evidence of *BTK, PLCG2,* and *BCL-2* mutations was observed at disease progression.[62,85] One patient in the CAPTIVATE trial developed a *BCL-2* (A113G) mutation.[78] Targeted next-generation sequencing panels were employed; however, it was noted that their sensitivity might be insufficient, and ultradeep sequencing techniques, capable of detecting subclonal variants, were suggested.[86] Nevertheless, clinically, these patients remained responsive to covalent BTK inhibitors (ibrutinib, acalabrutinib), ibrutinib-venetoclax or venetoclax-rituximab, or obinutuzumab combination treatment.[62,78,85] Notably, retreatment with single-agent ibrutinib proved effective, yielding an overall response rate of 85% (21/22 patients), predominantly comprising PR in 81% of cases.[78]

Ongoing trials and novel combinations

The CLL17 trial is an ongoing German CLL Study group phase 3 trial (NCT04608318) that is comparing 3 treatment regimens for previously untreated CLL. Patients receive either continuous ibrutinib, a fixed-duration combination of obinutuzumab and venetoclax, or a fixed-duration combination of venetoclax and ibrutinib. In the latter, ibrutinib is given for 3 cycles, followed by the addition of venetoclax starting at cycle 4, with combination treatment given for 12 cycles. Although the results have not been published yet, the trial

builds on previous evidence to optimize treatment combinations and durations for patients with CLL. The SAKK 34/17 trial from the Swiss Group for Clinical Cancer Research is investigating ibrutinib and venetoclax combination with flexible TLS risk–based ibrutinib lead-in duration in R/R CLL (NCT03708003).

The success of ibrutinib-venetoclax treatment has spurred a diverse range of clinical trials that explored venetoclax treatment in combination with new generations of BTK inhibitors. Notably, the REVEAL trial (NCT04523428) is investigating the efficacy of venetoclax retreatment in combination with acalabrutinib following fixed-duration venetoclax therapy. The PreVent-ACaLL trial (NCT03868722) aims to study short-term acalabrutinib and venetoclax for newly diagnosed patients with CLL with a high risk for infection. Similarly, the MAJIC clinical trial explores MRD-driven fixed-duration treatment with acalabrutinib plus venetoclax in comparison with venetoclax plus obinutuzumab in previously untreated CLL. In addition, zanubrutinib and venetoclax are under investigation for treatment-naïve (NCT05650723) and R/R cases (ZANU-VEN trial, NCT05168930). The noncovalent BTK inhibitor pirtobrutinib is also being explored in clinical trials for both treatment-naïve (NCT05677919) and R/R CLL (NCT04965493).

As research ventures into new combinations with BTK inhibitors, investigations into BCL-2 inhibitors are also gaining momentum and expanding the horizon of CLL treatment options. In an ongoing phase 1/2 trial, the novel BCL-2 inhibitor sonrotoclax, in combination with zanubrutinib and obinutuzumab, is being investigated for patients with treatment-naïve CLL with the *BCL-2* G101V mutation (NCT04277637).[87] Sonrotoclax, classified as a BH3 mimetic with >10-fold increase in potency when compared with venetoclax and higher selectivity,[88] will be further studied in a global phase 3 trial (NCT06073821). Another BCL-2 inhibitor, lisaftoclax,[89] will be combined with a BTK inhibitor in the NCT06104566 trial. These trials represent a comprehensive effort to advance treatment options in the management of CLL.

Beyond CLL

The combination of ibrutinib and venetoclax shows promising efficacy beyond CLL. In the recent SYMPATICO trial of 267 patients with R/R mantle cell lymphoma, the combination achieved superior 24-month PFS (57%) and CR rates (54%) when compared with ibrutinib alone (45% and 32%, respectively).[90,91] In addition, in a study of 45 patients with treatment-naïve *MYD88*-mutated Waldenström macroglobulinemia, the combination demonstrated effectiveness in 19 patients, yielding a 42% very good PR rate. Moreover, this regimen clinically improved hemoglobin levels, hyperviscosity symptoms, and extramedullary disease. However, within this trial, ibrutinib treatment was linked to a higher-than-expected incidence of ventricular arrhythmia, prompting an early discontinuation of the study.[92] The combination of ibrutinib and venetoclax demonstrated efficacy in patients with activated B-cell-like (ABC) subtype and BCL-2-overexpressing diffuse large B-cell lymphoma with a median PFS of 5.6 months, an overall response rate of 61%, and a CR rate of 21.1%. Although the PFS and CR rates were relatively low when compared with those in CLL cases, they represent a significant improvement over current therapies for R/R diffuse large B-cell lymphoma.[93]

Conclusions

Several mature clinical trials of ibrutinib and venetoclax have demonstrated the feasibility and efficacy of fixed-duration combination therapy, showcasing high rates of PFS and OS, even with long-term follow-up, in high-risk CLL. Despite these advancements, there remains a lack of consensus regarding the optimal treatment duration with many trials using the MRD status as a guide for therapy cessation. However, although achieving uMRD is associated with improved survival outcomes, as observed, it does not necessarily correlate with a better prognosis for high-risk CLL. Testing of the MRD-driven approach indicates that prolonged treatment can lead to increased MRD rates, even during the third year of combination administration. This result underscores the need for a nuanced understanding of the impact of uMRD and the implications of extended treatment duration on CLL outcomes.

A significant number of patients who maintained uMRD status for 4 or 5 years after ibrutinib-venetoclax treatment were observed in the discussed clinical trials. A longer follow-up, as seen for the FCR regimen (median of 19 years),[94] is crucial for revealing the potential risk for late relapse and for highlighting the possibility of a functional CLL cure.

Acknowledgments

The authors thank Sunita Patterson, a senior scientific editor in the Research Medical Library, MD Anderson Cancer Center, for providing editorial assistance.

This work was supported by a CLL Global Research Foundation Grant (#00011311), an Alliance Grant, and MD Anderson Cancer Center's Moon Shots Program.

Conflict-of-interest disclosure:

N.J. reports receiving research funding from Pharmacyclics, AbbVie, Genentech, AstraZeneca, Bristol Myers Squibb (BMS), Pfizer, Antibody Drug Conjugates (ADC) Therapeutics, Cellectis, Adaptive Biotechnologies, Precision Biosciences, Fate Therapeutics, Kite/Gilead, MingSight, Takeda, Medisix, Loxo Oncology, NovalGen, Dialectic Therapeutics, Newave, Novartis, Carna Biosciences, Sana Biotechnology, and KisoJi Biotechnology; and receiving honoraria from Pharmacyclics, Janssen, AbbVie, Genentech, AstraZeneca, BMS, Adaptive Biotechnologies, Kite/Gilead, Precision Biosciences, BeiGene, Cellectis, Marshall Edwards, Inc Pharma, Ipsen, CareDx, MingSight, Autolus, and NovalGen. V.G. reports receiving research grants from Pharmacyclics, Acerta Pharma, AbbVie, Gilead Sciences, Sunesis Pharmaceuticals, Infinity Pharmaceuticals, Loxo Oncology, and Clear Creek Bio; and receiving honoraria from AbbVie. N.T. declares no competing financial interests.

References

1. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci USA. 2010;107(29):13075–13080. [PubMed: 20615965]
2. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. Lancet Oncol. 2014;15(1):48–58. [PubMed: 24332241]
3. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015;373(25): 2425–2437. [PubMed: 26639149]
4. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. Blood. 2018;131(17):1910–1919. [PubMed: 29437592]

5. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol. 2013;31(1):88–94. [PubMed: 23045577]
6. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369(1):32–42. [PubMed: 23782158]
7. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3):213–223. [PubMed: 24881631]
8. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016;17(10):1409–1418. [PubMed: 27637985]
9. Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood. 2019;133(19):2031–2042. [PubMed: 30842083]
10. Strati P, Schlette EJ, Solis Soto LM, et al. Achieving complete remission in CLL patients treated with ibrutinib: clinical significance and predictive factors. Blood. 2020;135(7):510–513. [PubMed: 31895947]
11. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. Haematologica. 2018;103(5):874–879. [PubMed: 29419429]
12. Zhou Y, Lu H, Yang M, Xu C. Adverse drug events associated with ibrutinib for the treatment of elderly patients with chronic lymphocytic leukemia: a systematic review and meta-analysis of randomized trials. Medicine (Baltim). 2019;98(33):e16915.
13. Caldeira D, Alves D, Costa J, Ferreira JJ, Pinto FJ. Ibrutinib increases the risk of hypertension and atrial fibrillation: systematic review and meta-analysis. PLoS One. 2019;14(2):e0211228.
14. Hilal T, Hillegass WB, Gonzalez-Velez M, Leis JF, Rosenthal AC. Adverse events in clinical trials of ibrutinib and acalabrutinib for B-cell lymphoproliferative disorders: a systematic review and network meta-analysis. Blood. 2020;136(suppl 1):23.
15. Gordon MJ, Jones JE, George B, et al. Long-term outcomes in patients with chronic lymphocytic leukemia treated with ibrutinib: focus on hypertension and cardiovascular toxicity. Cancer. 2023;129(14):2192–2200. [PubMed: 37016930]
16. Furman RR, Cheng S, Lu P, et al. Ibrutinib resistance in chronic lymphocytic leukemia. N Engl J Med. 2014;370(24):2352–2354. [PubMed: 24869597]
17. Liu TM, Woyach JA, Zhong Y, et al. Hypermorphic mutation of phospholipase C, γ2 acquired in ibrutinib-resistant CLL confers BTK independency upon B-cell receptor activation. Blood. 2015;126(1):61–68. [PubMed: 25972157]
18. Burger JA, Landau DA, Taylor-Weiner A, et al. Clonal evolution in patients with chronic lymphocytic leukaemia developing resistance to BTK inhibition. Nat Commun *7*. 2016;7:11589. [PubMed: 27199251]
19. Woyach JA, Ruppert AS, Guinn D, et al. BTK(C481S)-mediated resistance to ibrutinib in chronic lymphocytic leukemia. J Clin Oncol. 2017;35(13): 1437–1443. [PubMed: 28418267]
20. Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. J Am Coll Cardiol. 2019;74(13):1667–1678. [PubMed: 31558250]
21. Bergler-Klein J. Real-life insight into ibrutinib cardiovascular events: defining the loose ends. J Am Coll Cardiol. 2019;74(13):1679–1681. [PubMed: 31558251]
22. Wan Q, Li Q, Lai X, Xu T, Hu J, Peng H. Data mining and safety analysis of BTK inhibitors: a pharmacovigilance investigation based on the FAERS database. Front Pharmacol. 2022 Nov;13:995522.
23. Christensen BW, Zaha VG, Awan FT. Cardiotoxicity of BTK inhibitors: ibrutinib and beyond. Expert Review of Hematology. 2022;15(4):321–331. [PubMed: 35437106]
24. Quartermaine C, Ghazi SM, Yasin A, et al. Cardiovascular toxicities of BTK inhibitors in chronic lymphocytic leukemia: JACC: cardiooncology state-of-the-art review. JACC CardioOncol. 2023;5(5):570–590. [PubMed: 37969643]
25. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374(4): 311–322. [PubMed: 26639348]

26. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016;17(6):768–778. [PubMed: 27178240]
27. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol. 2018;19(1):65–75. [PubMed: 29246803]
28. Fischer K, Al-Sawaf O, Hallek M. Preventing and monitoring for tumor lysis syndrome and other toxicities of venetoclax during treatment of chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2020;2020(1):357–362. [PubMed: 33275717]
29. Wierda WG, Tambaro FP. How I manage CLL with venetoclax-based treatments. Blood. 2020;135(17):1421–1427. [PubMed: 32076705]
30. Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. Blood. 2018;131(15):1704–1711. [PubMed: 29305552]
31. Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the MURANO phase III study. J Clin Oncol. 2019;37(4):269–277. [PubMed: 30523712]
32. Seymour JF, Kipps TJ, Eichhorst BF, et al. Four-year analysis of murano study confirms sustained benefit of time-limited venetoclax-rituximab (VenR) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). Blood. 2019;134(suppl 1):355.
33. Lew TE, Anderson MA, Lin VS, et al. Undetectable peripheral blood MRD should be the goal of venetoclax in CLL, but attainment plateaus after 24 months. Blood Adv. 2020;4(1):165–173. [PubMed: 31935286]
34. Herishanu Y, Katz BZ, Lipsky A, Wiestner A. Biology of chronic lymphocytic leukemia in different microenvironments: clinical and therapeutic implications. Hematol Oncol Clin North Am. 2013;27(2):173–206. [PubMed: 23561469]
35. Burger JA, Ghia P, Rosenwald A, Caligaris-Cappio F. The microenvironment in mature B-cell malignancies: a target for new treatment strategies. Blood. 2009;114(16):3367–3375. [PubMed: 19636060]
36. Haselager MV, Kater AP, Eldering E. Proliferative signals in chronic lymphocytic leukemia; what are we missing? Front Oncol. 2020;10:592205.
37. Haselager MV, Kielbassa K, ter Burg J, et al. Changes in Bcl-2 members after ibrutinib or venetoclax uncover functional hierarchy in determining resistance to venetoclax in CLL. Blood. 2020;136(25):2918–2926. [PubMed: 32603412]
38. Haselager M, Thijssen R, West C, et al. Regulation of Bcl-XL by non-canonical NF-κB in the context of CD40-induced drug resistance in CLL. Cell Death Differ. 2021;28(5):1658–1668. [PubMed: 33495554]
39. Pascutti MF, Jak M, Tromp JM, et al. IL-21 and CD40L signals from autologous T cells can induce antigen-independent proliferation of CLL cells. Blood. 2013;122(17):3010–3019. [PubMed: 24014238]
40. Tromp JM, Tonino SH, Elias JA, et al. Dichotomy in NF-kappaB signaling and chemoresistance in immunoglobulin variable heavy-chain-mutated versus unmutated CLL cells upon CD40/TLR9 triggering. Oncogene. 2010;29(36):5071–5082. [PubMed: 20581863]
41. Smit LA, Hallaert DYH, Spijker R, et al. Differential Noxa/Mcl-1 balance in peripheral versus lymph node chronic lymphocytic leukemia cells correlates with survival capacity. Blood. 2006;109(4):1660–1668. [PubMed: 17038534]
42. Kielbassa K, Haselager MV, Bax DJC, et al. Ibrutinib sensitizes CLL cells to venetoclax by interrupting TLR9-induced CD40 upregulation and protein translation. Leukemia. 2023;37(6):1268–1276. [PubMed: 37100883]
43. Thijssen R, Slinger E, Weller K, et al. Resistance to ABT-199 induced by microenvironmental signals in chronic lymphocytic leukemia can be counteracted by CD20 antibodies or kinase inhibitors. Haematologica. 2015;100(8):e302–e306. [PubMed: 25957396]

44. Pekarsky Y, Balatti V, Croce CM. BCL2 and miR-15/16: from gene discovery to treatment. Cell Death Differ. 2018;25(1):21–26. [PubMed: 28984869]
45. Chen SS, Chang BY, Chang S, et al. BTK inhibition results in impaired CXCR4 chemokine receptor surface expression, signaling and function in chronic lymphocytic leukemia. Leukemia. 2016;30(4):833–843. [PubMed: 26582643]
46. Jayappa KD, Gordon VL, Morris CG, et al. Extrinsic interactions in the microenvironment in vivo activate an antiapoptotic multidrug-resistant phenotype in CLL. Blood Adv. 2021;5(17):3497–3510. [PubMed: 34432864]
47. Deng J, Isik E, Fernandes SM, Brown JR, Letai A, Davids MS. Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia. Leukemia. 2017;31(10):2075–2084. [PubMed: 28111464]
48. Cervantes-Gomez F, Lamothe B, Woyach JA, et al. Pharmacological and protein profiling suggests venetoclax (ABT-199) as optimal partner with ibrutinib in chronic lymphocytic leukemia. Clin Cancer Res. 2015;21(16):3705–3715. [PubMed: 25829398]
49. Wist M, Meier L, Gutman O, et al. Noncatalytic Bruton's tyrosine kinase activates PLCγ(2) variants mediating ibrutinib resistance in human chronic lymphocytic leukemia cells. J Biol Chem. 2020;295(17):5717–5736. [PubMed: 32184360]
50. Estupiñán HY, Bouderlique T, He C, et al. In BTK, phosphorylated Y223 in the SH3 domain mirrors catalytic activity, but does not influence biological function. Blood Adv. 2024;8(8):1981–1990. [PubMed: 38507738]
51. Yuan H, Zhu Y, Cheng Y, et al. BTK kinase activity is dispensable for the survival of diffuse large B-cell lymphoma. J Biol Chem. 2022;298(11).
52. Middendorp S, Dingjan GM, Maas A, Dahlenborg K, Hendriks RW. Function of Bruton's tyrosine kinase during B cell development is partially independent of its catalytic activity 1. J Immunol. 2003;171(11):5988–5996. [PubMed: 14634110]
53. Blombery P, Thompson ER, Lew TE, et al. Enrichment of BTK Leu528Trp mutations in patients with CLL on zanubrutinib: potential for pirtobrutinib cross-resistance. Blood Adv. 2022;6(20):5589–5592. [PubMed: 35901282]
54. Wang E, Mi X, Thompson Meghan C, et al. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase Inhibitors. N Engl J Med. 2022;386(8): 735–743. [PubMed: 35196427]
55. Dhami K, Chakraborty A, Gururaja TL, et al. Kinase-deficient BTK mutants confer ibrutinib resistance through activation of the kinase HCK. Sci Signal. 2022;15(736):eabg5216.
56. Montoya S, Bourcier J, Noviski M, et al. Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127. Science. 2024;383(6682):eadi5798.
57. Cervantes-Gomez F, Kumar Patel V, Bose P, Keating MJ, Gandhi V. Decrease in total protein level of Bruton's tyrosine kinase during ibrutinib therapy in chronic lymphocytic leukemia lymphocytes. Leukemia. 2016;30(8):1803–1804. [PubMed: 27198052]
58. Kater AP, Slinger E, Cretenet G, et al. Combined ibrutinib and venetoclax treatment vs single agents in the TCL1 mouse model of chronic lymphocytic leukemia. Blood Adv. 2021;5(23):5410–5414. [PubMed: 34555843]
59. Lu P, Wang S, Franzen CA, et al. Ibrutinib and venetoclax target distinct subpopulations of CLL cells: implication for residual disease eradication. Blood Cancer J. 2021;11(2):39. [PubMed: 33602908]
60. Jain N, Keating M, Thompson P, et al. Ibrutinib and venetoclax for first-line treatment of CLL. N Engl J Med. 2019;380(22):2095–2103. [PubMed: 31141631]
61. Jain N, Keating M, Thompson P, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: a nonrandomized phase 2 trial. JAMA Oncol. 2021;7(8):1213–1219. [PubMed: 34110383]
62. Jain N, Keating MJ, Thompson PA, et al. Combined ibrutinib and venetoclax for first-line treatment of patients with chronic lymphocytic leukemia (CLL): 5-year follow-up data. Blood. 2023;142(suppl 1):4635.
63. Jain N, Keating MJ, Thompson PA, et al. Combined ibrutinib and venetoclax in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) [abstract]. Blood. 2019;134(suppl_1):359.

64. Tam CS, Siddiqi T, Allan JN, et al. Ibrutinib (Ibr) plus venetoclax (Ven) for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): results from the MRD cohort of the phase 2 CAPTIVATE study [abstract]. Blood. 2019;134(suppl_1):35.

65. Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE study. J Clin Oncol. 2021;39(34):3853–3865. [PubMed: 34618601]

66. Tam CS, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. Blood. 2022;139(22):3278–3289. [PubMed: 35196370]

67. Barr PM, Allan JN, Siddiqi T, et al. Fixed-duration ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 4-y follow-up from the FD cohort of the phase 2 CAPTIVATE study. J Clin Oncol. 2023;41(suppl 16):7535.

68. Ghia P Fixed-duration ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): up to 5 years of follow-up from the FD cohort of the phase 2 CAPTIVATE study. Oral presentation at ASH Annual Meeting; December 10, 2023; San Diego, CA, USA.

69. Hillmen P, Rawstron AC, Brock K, et al. Ibrutinib plus venetoclax in relapsed/refractory chronic lymphocytic leukemia: the CLARITY study. J Clin Oncol. 2019;37(30):2722–2729. [PubMed: 31295041]

70. Munir T, Cherrill L-R, Webster N, et al. MRD4 eradication at 6 months and early clearance of MRD with combination of ibrutinib plus venetoclax results in sustained clinical and MRD responses: exploratory analysis of the blood cancer UK TAP clarity study. Blood. 2022;140(suppl 1):222–223. [PubMed: 34986238]

71. Hillmen P, Boucher RH, Webster N, et al. Continued long term responses to ibrutinib + venetoclax treatment for relapsed/refractory CLL in the blood cancer UK TAP clarity trial. Blood. 2020;136(suppl 1):17–18.

72. Hillmen P, Pitchford A, Bloor A, et al. Ibrutinib and rituximab versus fludarabine, cyclophosphamide, and rituximab for patients with previously untreated chronic lymphocytic leukaemia (FLAIR): interim analysis of a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2023;24(5):535–552. [PubMed: 37142374]

73. Munir T, Cairns DA, Bloor A, et al. Chronic lymphocytic leukemia therapy guided by measurable residual disease. N Engl J Med. 2024 Jan 25;390(4): 326–337. [PubMed: 38078508]

74. Hillmen P, Pitchford A, Bloor A, et al. The combination of ibrutinib plus venetoclax results in a high rate of MRD negativity in previously untreated CLL: the results of the planned interim analysis of the phase III NCRI FLAIR trial. HemaSphere. 2022;S145;6(S3):46–47.

75. Hillmen P, Cairns DA, Bloor AJC, et al. Ibrutinib plus venetoclax with MRD-directed duration of treatment is superior to FCR and is a new standard of care for previously untreated CLL: report of the phase III UK NCRI FLAIR study. Blood. 2023;142(suppl 1):631.

76. Niemann CU, Munir T, Moreno C, et al. Fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in previously untreated chronic lymphocytic leukaemia (GLOW): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2023;24(12):1423–1433. [PubMed: 37944541]

77. Kater AP, Owen C, Moreno C, et al. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. NEJM Evidence. 2022;1(7):EVIDoa2200006.

78. Ghia P, Wierda WG, Barr PM, et al. Relapse after first-line fixed duration ibrutinib + venetoclax: high response rates to ibrutinib retreatment and absence of BTK mutations in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with up to 5 years of follow-up in the phase 2 captivate study [abstract]. Blood. 2023;142(suppl 1):633.

79. Rogers KA. A CAPTIVATEing analysis for higher-risk CLL. Clin Cancer Res. 2023;29(14):2561–2562. [PubMed: 37289004]

80. Chen LS, Bose P, Cruz ND, et al. A pilot study of lower doses of ibrutinib in patients with chronic lymphocytic leukemia. Blood. 2018;132(21): 2249–2259. [PubMed: 30254130]

81. Hardy-Abeloos C, Pinotti R, Gabrilove J. Ibrutinib dose modifications in the management of CLL. J Hematol Oncol. 2020;13(1):66. [PubMed: 32503582]
82. Moreno C, Solman IG, Tam CS, et al. Immune restoration with ibrutinib plus venetoclax in first-line chronic lymphocytic leukemia: the phase 2 CAPTIVATE study. Blood Adv. 2023;7(18):5294–5303. [PubMed: 37315225]
83. Sharman JP, Biondo JML, Boyer M, et al. A review of the incidence of tumor lysis syndrome in patients with chronic lymphocytic leukemia treated with venetoclax and debulking strategies. eJHaem. 2022;3(2):492–506. [PubMed: 35846043]
84. Barr PM, Tedeschi A, Wierda WG, et al. Effective tumor debulking with ibrutinib before initiation of venetoclax: results from the CAPTIVATE minimal residual disease and fixed-duration cohorts. Clin Cancer Res. 2022;28(20):4385–4391. [PubMed: 35939599]
85. Jain N, Croner LJ, Allan JN, et al. Absence of BTK, BCL2, and PLCG2 mutations in chronic lymphocytic leukemia relapsing after first-line treatment with fixed-duration ibrutinib plus venetoclax. Clin Cancer Res. 2024;30(3):498–505. [PubMed: 37955424]
86. Al-Sawaf O, Davids MS. Overcoming resistance in chronic lymphocytic leukemia—maybe less is more? Clin Cancer Res. 2024;30(3):471–473. [PubMed: 38055246]
87. Tam CS, Anderson MA, Lasica M, et al. Combination treatment with sonrotoclax (BGB-11417), a second-generation BCL2 inhibitor, and zanubrutinib, a Bruton tyrosine kinase (BTK) inhibitor, is well tolerated and achieves deep responses in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma (TN-CLL/SLL): data from an ongoing phase 1/2 study. Blood. 2023;142(suppl 1):327.
88. Liu J, Li S, Wang Q, et al. Sonrotoclax overcomes BCL2 G101V mutation-induced venetoclax resistance in preclinical models of hematologic malignancy. Blood. 2024;143(18):1825–1836. [PubMed: 38211332]
89. Deng J, Paulus A, Fang DD, et al. Lisaftoclax (APG-2575) is a novel BCL-2 inhibitor with robust antitumor activity in preclinical models of hematologic malignancy. Clin Cancer Res. 2022;28(24):5455–5468. [PubMed: 36048524]
90. Wang M, Ramchandren R, Chen R, et al. Concurrent ibrutinib plus venetoclax in relapsed/refractory mantle cell lymphoma: the safety run-in of the phase 3 SYMPATICO study. J Hematol Oncol. 2021;14(1):179. [PubMed: 34717692]
91. Wang M, Jurczak W, Trněný M, et al. Ibrutinib Combined with Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study. Oral presentation at ASH Annual Meeting; 12 December 2023, San Diego, CA, USA.
92. Castillo JJ, Branagan AR, Sermer D, et al. Ibrutinib and venetoclax as primary therapy in symptomatic, treatment-naïve Waldenström macroglobulinemia. Blood. 2024;143(7):582–591. [PubMed: 37971194]
93. Zhou Z, Zhang L, Wang X, et al. Ibrutinib combined with venetoclax for the treatment of relapsed/refractory diffuse large B cell lymphoma [abstract]. Ann Hematol. 2021;100(6):1509–1516. [PubMed: 33900450]
94. Thompson PA, Bazinet A, Wierda WG, et al. Sustained remissions in CLL after frontline FCR treatment with very-long-term follow-up. Blood. 2023; 142(21):1784–1788. [PubMed: 37595283]

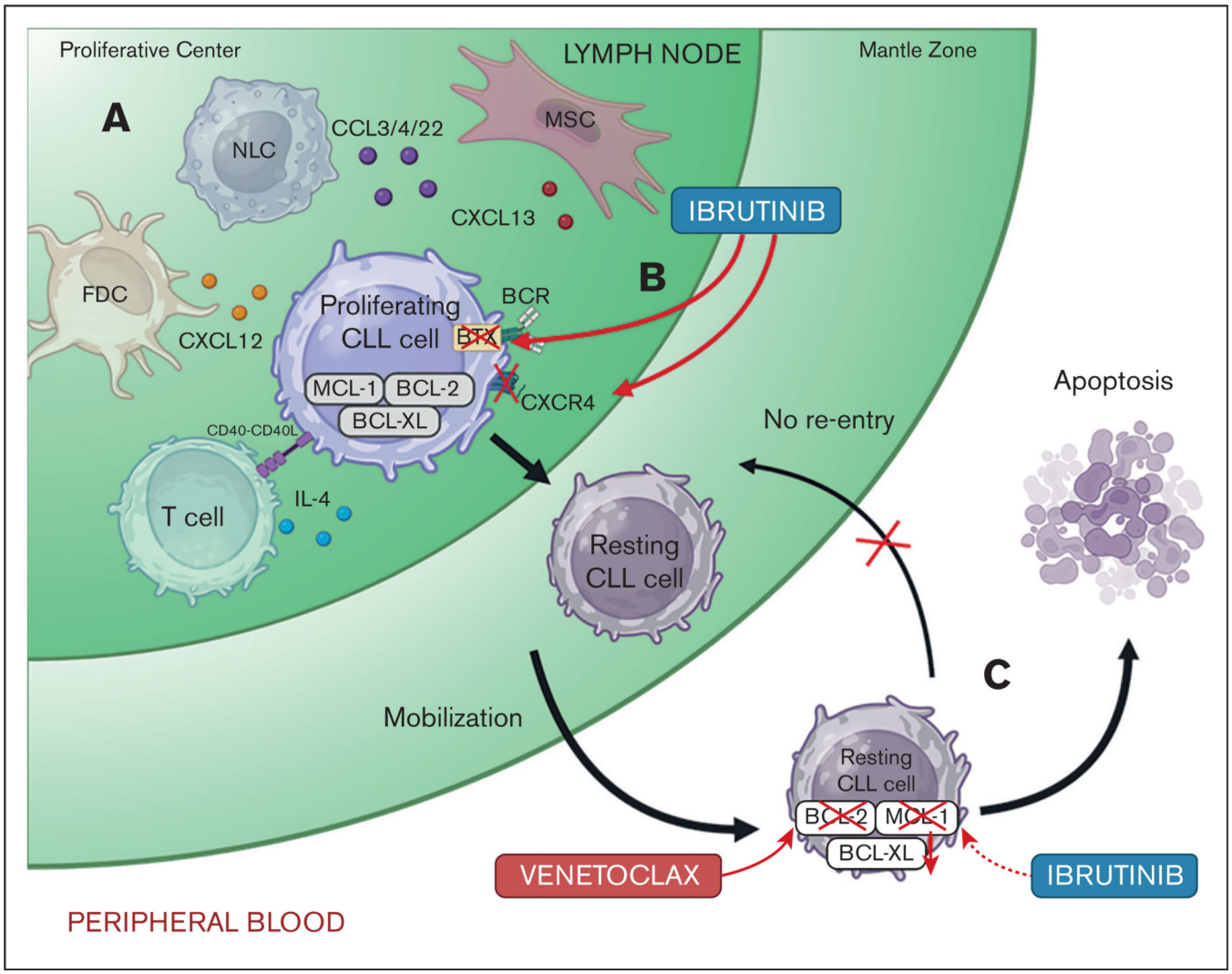
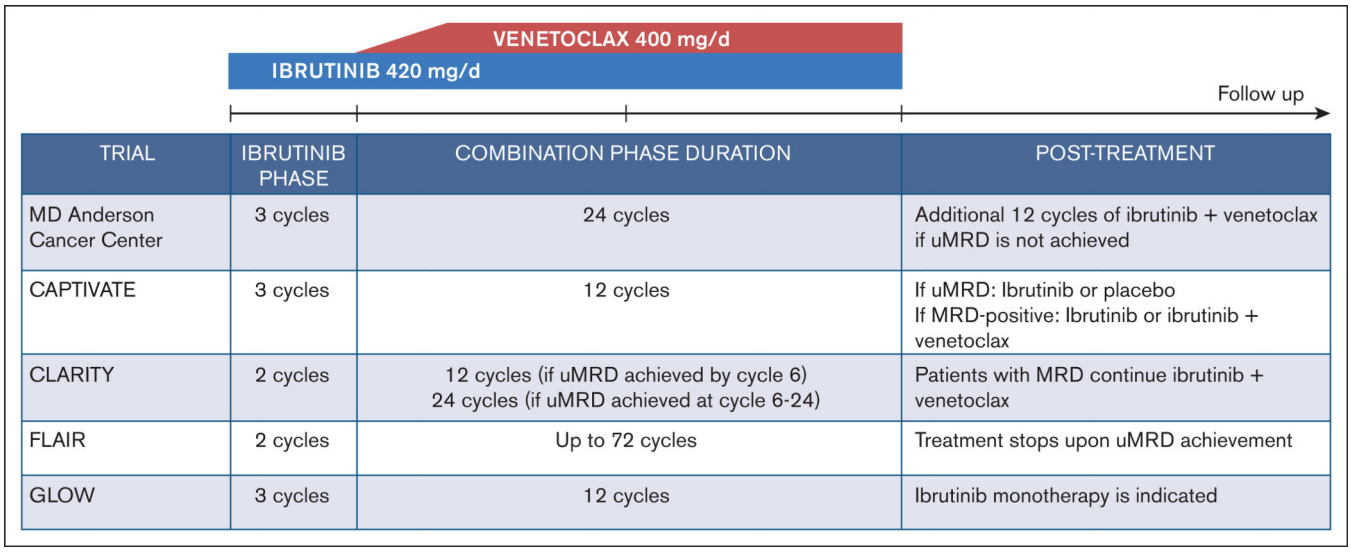


Figure 1. The effects of ibrutinib and venetoclax on CLL cells in different microenvironments.

(A) The lymph node provides a favorable microenvironment for CLL cells in which they receive survival signals from various stromal cells and immune cells via cell-cell interactions and soluble factors. BCL-2 family proteins, such as MCL-1 and BCL-XL, are upregulated, conferring resistance to venetoclax. (B) Ibrutinib covalently binds and inactivates BTK, leading to inhibition of BCR signaling. In addition, ibrutinib reduces chemokine receptor CXCR4, causing CLL cells to be released in the PB and impeding their homing back to the lymph nodes. (C) In the PB, recently emigrated CLL cells lose the supportive microenvironment, have reduced BCL-XL expression, and become dependent on BCL-2 signaling. Venetoclax directly targets BCL-2 (red arrow), whereas ibrutinib indirectly inhibits MCL-1 prosurvival protein (red dashed arrow), causing apoptosis of CLL cells. CCL3/4/22, C-C motif chemokine ligands 3, 4, and 22; CXCL12/13, chemokine C-X-C motif ligands 12 and 13; CXCR4, C-X-C chemokine receptor type; FDC, follicular dendric cell; MSC, mesenchymal stem cell; NLC, nurse-like cell. Figure created with BioRender.com.



TRIAL	IBRUTINIB PHASE	COMBINATION PHASE DURATION	POST-TREATMENT
MD Anderson Cancer Center	3 cycles	24 cycles	Additional 12 cycles of ibrutinib + venetoclax if uMRD is not achieved
CAPTIVATE	3 cycles	12 cycles	If uMRD: Ibrutinib or placebo If MRD-positive: Ibrutinib or ibrutinib + venetoclax
CLARITY	2 cycles	12 cycles (if uMRD achieved by cycle 6) 24 cycles (if uMRD achieved at cycle 6-24)	Patients with MRD continue ibrutinib + venetoclax
FLAIR	2 cycles	Up to 72 cycles	Treatment stops upon uMRD achievement
GLOW	3 cycles	12 cycles	Ibrutinib monotherapy is indicated

Figure 2. Ibrutinib plus venetoclax combination trial designs.

Ibrutinib was administered for 2 to 3 cycles, each lasting for 28 days, to induce a debulking effect, disrupt the protective microenvironment of CLL cells in the lymph node, and complementarily reduce MCL-1 levels to enhance sensitivity to venetoclax. Venetoclax was then added. Following venetoclax dose ramp-up, the combination of ibrutinib and venetoclax was given for 12 or 24 cycles or until uMRD was achieved.

Table 1.
Ibrutinib and venetoclax clinical trials for patients with CLL

Clinical trial	Cohort	Combination regimen duration	CR/CRi response rate	MRD rate	PFS rate
MD Anderson[60–62]	TN high-risk CLL, N = 120; del 17p/*TP53* mutation, n = 27	IBR, 3 cycles; IBR + VEN, 24 cycles ± additional 12 cycles	59% at cycle 12 69% at cycle 24	52% (BM) at cycle 12 64% (BM) at cycle 24	90.1% at 5 y
MD Anderson[63]	R/R, N = 80	IBR, 3 cycles; IBR + VEN, 24 cycles ± additional 12 cycles	Not reported	48% (BM) at cycle 12 67% (BM) at cycle 24	~75% at 3 y
CAPTIVATE[66,78]	TN FD, N = 159; MRD, N = 164; del 17p/*TP53* mutation, n = 23	IBR, 3 cycles; IBR + VEN, 12 cycles	FD cohort: 56% MRD cohort: 46%	FD cohort: 68% (PB) and 75% (PB) at cycle 12 MRD cohort: 75% (PB) and 68% (BM) at cycle 12	FD cohort: 70% at 5 y uMRD cohort: 95% placebo vs 100% ibrutinib at 1 y
CLARITY[69,71]	R/R, N = 50; del 17p/*TP53* mutation, n = 10	IBR 2, cycles; IBR + VEN, 12 cycles (if uMRD at 6 mo of combination) or 24 cycles (if uMRD achieved after 6 mo)	51%	40% (BM) at cycle 12 48% (BM) at cycle 24	98% at median FU of 21.1 mo
FLAIR[75]	TN, N = 260; no del17p	IBR, 2 cycles; IBR + VEN, up to 72 cycles, defined by MRD	59.2%	52.4% (BM) at cycle 24 49.8% (BM) at 5 y	97.2% at 3 y
GLOW[76]	TN patients, >65 y or with comorbidities, N = 106; no del17p	IBR 3, cycles; IBR + VEN, 12 cycles	45%	55% (PB) at cycle 12	74.6% at 3.5 y

CR/CRi, complete remission/CR with incomplete BM recovery; FD, fixed duration; FU, follow-up; IBR, ibrutinib; TN, treatment naïve; VEN, venetoclax.