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Diagnosis and Treatment of Chronic Lymphocytic Leukemia
A Review

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IMPORTANCE Chronic lymphocytic leukemia (CLL), defined by a minimum of 5×10^9/L monoclonal B cells in the blood, affects more than 200 000 people and is associated with approximately 4410 deaths in the US annually. CLL is associated with an immunocompromised state and an increased rate of complications from infections.

OBSERVATIONS At the time of diagnosis, the median age of patients with CLL is 70 years, and an estimated 95% of patients have at least 1 medical comorbidity. Approximately 70% to 80% of patients with CLL are asymptomatic at the time of diagnosis, and one-third will never require treatment for CLL. Prognostic models have been developed to estimate the time to first treatment and the overall survival, but for patients who are asymptomatic, irrespective of disease risk category, clinical observation is the standard of care. Patients with symptomatic disease who have bulky or progressive lymphadenopathy or hepatosplenomegaly and those with a low neutrophil count, anemia, or thrombocytopenia and/or symptoms of fever, drenching night sweats, and weight loss (B symptoms) should be offered treatment. For these patients, first-line treatment consists of a regimen containing either a covalent Bruton tyrosine kinase (BTK) inhibitor (acalabrutinib, zanubrutinib, or ibrutinib) or a B-cell leukemia/lymphoma 2 (BCL2) inhibitor (venetoclax). There is no evidence that starting either class before the other improves outcomes. The covalent BTK inhibitors are typically used indefinitely. Survival rates are approximately 88% at 4 years for acalabrutinib, 94% at 2 years for zanubrutinib, and 78% at 7 years for ibrutinib. Venetoclax is prescribed in combination with obinutuzumab, a monoclonal anti-CD20 antibody, in first-line treatment for 1 year (overall survival, 82% at 5-year follow-up). A noncovalent BTK inhibitor, pitobrutinib, has shown an overall response rate of more than 70% after failure of covalent BTK inhibitors and venetoclax. Phosphoinositide 3′-kinase (PI3K) inhibitors (idelalisib and duvelisib) can be prescribed for disease that progresses with BTK inhibitors and venetoclax, but patients require close monitoring for adverse events such as autoimmune conditions and infections. In patients with multiple relapses, chimeric antigen receptor T-cell (CAR-T) therapy with lisocabtagene maraleucel was associated with a 45% complete response rate. The only potential cure for CLL is allogeneic hematopoietic cell transplant, which remains an option after use of targeted agents.

CONCLUSIONS AND RELEVANCE More than 200 000 people in the US are living with a CLL diagnosis, and CLL causes approximately 4410 deaths each year in the US. Approximately two-thirds of patients eventually need treatment. Highly effective novel targeted agents include BTK inhibitors such as acalabrutinib, zanubrutinib, ibrutinib, and pirtobrutinib or BCL2 inhibitors such as venetoclax.

Multimedia

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Chronic lymphocytic leukemia (CLL) is the most common type of leukemia, affects approximately 200 000 people in the US, and represents 1.1% of all new cancers diagnosed in the US. The median age at diagnosis is 70 years, with a slight male predominance (1.7:1).[1] In 2022, it was estimated that approximately 20 160 people would be newly diagnosed with CLL and that approximately 4410 patients with a CLL diagnosis would die in the US.[2] Approximately 90% of patients with CLL will be alive 5 years after diagnosis, and approximately 82% will be alive 10 years after diagnosis.[1] Most patients (70%-80%) do not require anti-CLL treatment at the time of diagnosis, and the time to first treatment ranges from months to decades, depending on the clinical and molecular features of the disease.[3,4] This review summarizes current evidence regarding the diagnosis and treatment of CLL.

Box 1. Presenting Signs and Symptoms of Chronic Lymphocytic Leukemia

Asymptomatic at diagnosis with incidental finding of lymphocytosis (70%)

Symptomatic (30%)
- Enlarged lymph nodes (≈50%)
- Enlarged spleen or liver (≈20%-50%)
- Constitutional (or B) symptoms: drenching night sweats, unintentional weight loss (≥10% body weight within 6 months), fever (5%-10%)
- Autoimmune cytopenia: hemolytic anemia (up to 10%) or immune thrombocytopenia (up to 2%)
- Hypogammaglobinemia leading to frequent infections (particularly sinus or lung) (up to 10%)

Methods

A PubMed search was performed for articles published between January 2014 and January 2023 on the diagnosis and treatment of CLL. The start of the search was selected because it coincided with the availability of targeted therapy agents such as ibrutinib. Larger randomized clinical trials were prioritized for inclusion. Clinical trials for the approved medications, or those with expected approvals, were included. Of 654 identified articles, 89 were included, consisting of 28 randomized trials, 9 single-group trials, and 14 longitudinal studies.

Discussion

Pathophysiology

CLL is characterized by accumulation of immunologically dysfunctional mature B lymphocytes with a typical immunophenotype that includes expression of CD5, CD23, and CD19 and dim surface expression of immunoglobulin, CD20, CD22, and CD79b.[5] Impaired apoptosis (programmed cell death) due to overexpression of proteins such as B-cell leukemia/lymphoma 2 (BCL2) and increased proliferation of lymphocytes via antigen-independent and constitutional activation of the B-cell receptor (BCR) pathway are important components of CLL pathobiology.[6] These biological pathways led to drugs targeting BCL2 and the downstream enzymes in the BCR pathway.[7,8] An important factor in the pathophysiology of CLL is the mutation status of the immunoglobulin heavy chain variable region gene (*IGHV*). Approximately one-half of patients with CLL have an unmutated-*IGHV* status (<2% deviation from the germline sequence). These patients typically have a shorter interval between diagnosis and progression of disease and more adverse clinical outcomes. In contrast, patients who have CLL with a mutated-*IGHV* status (≥2% deviation) experience a more indolent clinical course.[9-11] Patients with CLL have abnormal humoral and cellular immune responses to infections or vaccination.[12]

Clinical Presentation and Diagnosis

Approximately 70% of patients with CLL are diagnosed based on an unexplained lymphocytosis discovered incidentally and have no symptoms at the time of diagnosis (**Box 1**).[13] Among symptomatic patients, approximately 50% present with symptoms due to lymphadenopathy, about 20% to 50% present with symptoms from hepatosplenomegaly, and approximately 5% to 10% present with unintentional weight loss of 10% or more body weight within a 6-month period, fever, drenching night sweats, or extreme fatigue (B symptoms). Patients can also present with cytopenia, either as a result of bone marrow involvement by CLL cells or because of an immune-mediated complication like autoimmune hemolytic anemia (<10%) or immune thrombocytopenia (<2%).[14,15] A flow cytometry test of the peripheral blood is necessary and often adequate for making a CLL diagnosis.[16] In asymptomatic patients, additional imaging and bone marrow biopsy are not necessary, and further assessments can be delayed until treatment.[16,17] CLL is defined by a minimum number of monoclonal B cells of 5×10^9/L. Patients with a monoclonal B-cell count less than 5×10^9/L who have a CLL immunophenotype with evidence of lymphadenopathy or extranodal involvement are diagnosed with small lymphocytic lymphoma. Monoclonal B lymphocytosis (MBL) refers to fewer than 5×10^9/L monoclonal B cells and no evidence of lymphadenopathy or extranodal involvement; patients with MBL do not meet the diagnostic criteria for CLL. In patients with MBL, the rate of transformation to CLL is 1% to 2% per year.[16,18,19] The biology and therapies for CLL and small lymphocytic lymphoma are identical, and the term CLL will be used in this review for both conditions.

Staging and Risk Categories

CLL staging is performed using the Rai and Binet systems, which rely on clinical variables including the presence and degree of cytopenia and the presence of large lymph nodes, splenomegaly, or hepatomegaly (**Table 1**).[15,20] Molecular information is increasingly used for prognostic purposes. The most commonly defined cytogenetic abnormalities in CLL are del(13q14), trisomy 12, del(17p12), and del(11q22). The presence of aberrations (deletion or sequence variation) in the tumor-suppressor gene *TP53* (tumor protein p53), located in the short arm of chromosome 17, is the most important adverse prognostic marker in CLL.[21] Cytogenetic abnormalities can change with treatments. For example, while del(17) is detected in less than 10% of untreated patients, the incidence is up to 23% to 50% in patients with disease that has relapsed, highlighting the importance of repeating the test before each line of treatment.[22,23] A useful clinical tool to estimate the time to first treatment for newly diagnosed asymptomatic patients is the International Prognostic

Table 1. Clinical Staging Systems in Chronic Lymphocytic Leukemia

Rai staging			Binet staging	
Stage	Risk category	Findings	Stage	Findings
0	Low	Lymphocytosis[a]	A	No cytopenia and ≤2 lymphoid area involvement
1	Intermediate	Lymphadenopathy[b]	B	No cytopenia and >3 lymphoid area involvement
2	Intermediate	Hepatosplenomegaly[b]	C	Presence of anemia or thrombocytopenia
3	High	Anemia[c]		
4	High	Thrombocytopenia[d]		

[a] Lymphocyte count greater than 5×10^9/L.

[b] On physical examination.

[c] Hemoglobin level less than 11 g/dL.

[d] Platelet count less than 100 000/μL

Table 2. Prognostic Scoring Systems in Chronic Lymphocytic Leukemia

Variable	Points	Risk group (total points)	5-y cumulative risk of treatment start, %	
International Prognostic Score for Asymptomatic Early-stage Disease (IPS-E)				
Unmutated *IGHV*	1	Low (0)	8.4	
ALC ≥15 × 10^9/L	1	Intermediate (1)	28.4	
Palpable lymphadenopathy	1	High (2-3)	61.2	
CLL International Prognostic Index (CLL-IPI)			5-y overall survival, %	10-y overall survival, %
Del(17p12) or *TP53* variant	4	Low (0-1)	93	79
β_2 microglobulin >3.5 mg/L	2	Intermediate (2-3)	79	39
Unaltered *IGVH*	2	High (4-6)	63	22
Rai stage 1-4	1	Very high (7-10)	23	4
Age >65 y	1			

Abbreviations: ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukemia; *IGHV*, immunoglobulin heavy chain gene.

Score (range, 0-3; higher scores are worse) for Asymptomatic Early-stage Disease (IPS-E) (**Table 2**). This model assigns a score to unmutated *IGHV*,[1] an absolute lymphocyte count of 15 × 10^9/L or greater,[1] and lymphadenopathy.[1] Using this model, the 5-year rates for requiring treatment were 8.4% in patients with low risk (score 0), 28.4% in those with intermediate risk (score 1), and 61.2% in those with high risk (scores 2-3).[3]

Management of Newly Diagnosed CLL

Questions commonly asked about the approach to CLL are provided in **Box 2**; information related to preventive care for patients with CLL is provided in **Box 3**. Approximately 30% to 50% of newly diagnosed and asymptomatic patients with CLL have low-risk disease by IPS-E score. Of these patients, only approximately 8% require treatment in the first 5 years after diagnosis.[13] Therefore, given the median age of CLL diagnosis (70 years), many patients (approximately 30%) never require treatment. Patients with CLL should be advised that they have an increased risk of infection due to impaired cellular and humoral immune function. While live vaccines such as live attenuated influenza vaccine (nasal influenza vaccine) should be avoided, all patients with CLL should receive the recombinant zoster vaccine, the COVID-19 vaccine, and inactivated (killed) influenza vaccine, delivered intramuscularly, annually.[24,25] Pneumococcal vaccination is recommended for all patients with CLL. The 20-valent pneumococcal conjugate vaccine (PCV20) is recommended in previously unvaccinated patients or those who had received a 23-valent pneumococcal polysaccharide vaccine (PPSV23), at least 1 year after the PPSV23 dose. For patients with no prior PPSV23 vaccine, some expert guidelines recommend the administration of PPSV23 at least 8 weeks after PCV20.[26-28] Patients should be informed that their immune response to vaccinations is lower than that of the general population, and protective measures such as masks and avoiding exposure should be continued in high-risk conditions like viral pandemics.[12,29] Patients with frequent sinus or lung infections who have hypogammaglobulinemia (IgG level <500 mg/dL) benefit from intravenous immunoglobulin infusions every 6 to 8 weeks if the levels remain low. Patients with CLL have a higher risk for recurrence of basal cell carcinoma (hazard ratio, 14 [95% CI, 1.6-115.1]; absolute rates not provided) and squamous cell carcinoma (hazard ratio, 7 [95% CI, 2.0-25.3]; absolute rates not provided) of the skin compared with those without CLL.[30,31]

Indications for Treatment

Observation without treatment is the standard of care for asymptomatic patients without anemia, neutropenia, or thrombocytopenia; therefore, most patients do not require treatment at the time of diagnosis. There is no evidence that treating patients with asymptomatic CLL improves survival. For example, a clinical trial of 201 patients with asymptomatic CLL showed no benefit from treatment with fludarabine, cyclophosphamide, and rituximab, compared with observation without treatment at 5 years (82.9% vs 79.9%; $P = .86$). In another clinical trial, 363 asymptomatic patients were randomized to ibrutinib or placebo. At 31 months of follow-up, ibrutinib was associated with improved event-free survival (event defined as progression, starting new CLL therapy, or death), compared with placebo (3-year event-free survival, 87.3% vs 60.4%; $P < .001$). However, unless overall survival is improved with longer follow-up, that study did not provide evidence to support treating asymptomatic patients.[24,25] Patients require treatment if they experience CLL-related complications, including significant anemia or cytopenia (hemoglobin level <10 g/dL or platelet count <100 000/μL), massive progressive or symptomatic lymphadenopathy or hepatosplenomegaly (≥10 cm for lymph nodes and ≥6 cm below the left costal

Box 2. Commonly Asked Questions

- Should all patients with lymphocytosis, defined by a minimum of 5×10^9/L, be referred to a hematologist for further workup?
  - Reactive causes like infections (such as viral etiologies like cytomegalovirus, Epstein-Barr virus, mumps, rubella, measles, HIV, and influenza or nonviral infections like pertussis, toxoplasmosis, rickettsiosis, and cat scratch disease), drugs (phenytoin as an example), and autoimmune disorders (rheumatoid arthritis) should be ruled out. A flow cytometry test of peripheral blood confirms a clonal lymphocytosis (CLL or non-CLL) and should prompt referral to a hematologist
- In patients with CLL who are being followed up without therapy, which findings during history taking, physical examination, or blood tests should prompt an appointment with a hematologist?
  - Report of fever or unintentional weight loss (10% of body weight or more in 6 months)
  - A rapidly enlarging lymph node or palpable spleen or liver on physical examination
  - Any new finding of neutropenia, anemia, or thrombocytopenia should be investigated, but an increasing lymphocyte count in the absence of cytopenia should not be a reason for referral
- Are patients with CLL at increased risk of infection even if they are not receiving active therapy for CLL?
  - Patients with CLL should be regarded as moderately or severely immunocompromised regardless of their current treatment status. For example, recommendations for the "immunocompromised" group applies to all CLL patients during pandemics. All patients should be vaccinated against influenza, pneumococcal pneumonia, COVID-19, and varicella zoster.

Abbreviation: CLL, chronic lymphocytic leukemia.

Box 3. Preventive Medicine Considerations and Chronic Lymphocytic Leukemia

Avoid live vaccines

Patients should receive annual influenza vaccine and recombinant zoster vaccine

The 20-valent pneumococcal conjugate vaccine (PCV20) is recommended in previously unvaccinated patients or those with prior receipt of 23-valent pneumococcal polysaccharide vaccine (PPSV23), 1 year apart

Patients should be informed that their immune response to vaccinations is lower than that of the general population

For COVID-19 vaccination, follow the Centers for Disease Control and Prevention recommendations for patients with moderate and severe immunocompromised state, and protective measures should be continued in high-risk conditions such as viral pandemics

Patients with frequent sinus or lung infections who have hypogammaglobulinemia (IgG level <500 mg/dL) benefit from intravenous immunoglobulin infusions every 6 to 8 weeks if the levels remain low

Age-specific cancer screening guidelines should be followed in patients with CLL

Patients with CLL have a higher risk for recurrence of basal cell carcinoma and squamous cell carcinoma of skin compared with those without CLL; routine examinations and skin protection measures are recommended

There is no indication for screening or genetic testing in family members

Abbreviation: CLL, chronic lymphocytic leukemia.

margin for spleen), recurrent infections, or refractory autoimmune thrombocytopenia/anemia related to CLL.[16,17]

Treatment

Remission refers to a decrease or disappearance of CLL after treatment, and cure refers to a permanent resolution of disease. Durable remissions are attainable in CLL, and approximately 80% of patients were reported to be in remission at 5 years in 1 study (N = 529).[32] However, CLL is not curable except after an allogeneic hematopoietic cell transplant, and repeat treatments are often necessary.[33] Standard treatment options for CLL include the following 5 classes (**Table 3** and **Table 4**; **Box 4**).

Inhibitors of the BCR Pathway

The BCR signaling pathway is involved in the pathogenesis of CLL, and drugs that inhibit the enzymes involved in the BCR pathway, specifically Bruton tyrosine kinase (BTK) and phosphoinositide 3'-kinase (PI3K), are standard of care to treat CLL.[51] BTK inhibitors, such as ibrutinib, acalabrutunib, and zanubrutinib, are used indefinitely as monotherapy because continuous inhibition of the target enzyme is essential for their antiproliferative effect. Covalent BTK inhibitors such as ibrutinib, acalabrutunib, and zanubrutinib irreversibly inhibit the BTK enzyme, and more than 90% of patients respond to these treatments.[33] Approximately 66% to 80% of patients with disease progression taking ibrutinib had sequence variations in the BTK binding site (C481S) or gain-of-function variation in the downstream gene phospholipase C gamma 2 (*PLCG2*).[52,53] The noncovalent BTK inhibitor, pirtobrutinib, reversibly inactivates BTK. Resistance to pirtobrutinib occurs due to sequence variations in non-C481S kinase domains of *BTK* and *PLCG2*.[54] Ibrutinib was the first BTK inhibitor identified and was associated with 60% PFS at 7 years when used as first-line therapy and 40% PFS at 5 years when used in patients who had relapse (Table 2 and Table 3), but adverse events such as arthralgia (42%), atrial fibrillation (25%), and rash (16.7%) are common and may lead to drug discontinuation. This is a limiting factor in approximately 23% of patients and leads to dose discontinuation.[33,43,55] Second-generation BTK inhibitors, such as acalabrutinib or zanubrutinib, selectively target the BTK enzyme. In clinical trials that directly compared these drugs with ibrutinib, lower incidences of grade 3 or greater adverse events have been observed with both acalabrutinib (68.8% vs 74.9%) and zanubrutinib (67.3% vs 70.4%) compared with ibrutinib.[46,47]

All BTK inhibitors are associated with increased rates of atrial fibrillation. Randomized clinical trials have demonstrated a higher incidence with ibrutinib compared with acalabrutinib (15.6% vs 9% with 41 months of follow-up) or zanubrutinib (3.7% vs 1.9% with 29 months of follow-up). Ventricular arrhythmias have been reported with BTK inhibitors, and clinicians should consider a cardiology evaluation in patients with signs or symptoms suggesting a possible arrhythmia.[56,57] Patients receiving treatment with a BTK inhibitor who require a surgical procedure should not take the drug for 3 to 7 days before and after the procedure because of increased bleeding risk due to an association of these drugs with platelet dysfunction.[58]

PI3K inhibitors inhibit the δ isoform of PI3K, an effective treatment strategy for patients with indolent B-cell lymphomas. Idelalisib

Table 3. Randomized Clinical Trials Testing BTK Inhibitors, and Venetoclax-Based Regimens for Initial Treatment of CLL

Source	Investigational group(s)	Standard group	Study participants	Primary end point	Median follow-up, mo	Findings (investigational vs standard)	Selected grade 3-4 adverse events (investigational vs standard)	Significance/notes
Ibrutinib								
RESONATE-2[33,34]	Ibrutinib	Chlorambucil	N = 269 ≥65 y Patients with del(17p) excluded Crossover allowed	PFS by IRC	8 y	7-y PFS: 59% vs 9%[a] Median PFS: NR vs 15 mo[a]	Neutropenia (10% vs 18%) Anemia (6% vs 8%) Thrombocytopenia (2% vs 6%) Pneumonia (4% vs 2%) Rash (3% vs 2%) Diarrhea (4% vs 0)	Study led to the approval of ibrutinib for first-line treatment
iLLUMINATE[35,36]	Ibrutinib-obinutuzumab	Chl-O	N = 229 ≥65 or <65 y with comorbidities Patients with del(17p)/*TP53* variations included Crossover allowed	PFS by IRC	45	42-mo PFS: 74% vs 33%[a] Median PFS: NR vs 22 mo[a]	Neutropenia (37% vs46%) Thrombocytopenia (19% vs 10%) Pneumonia (4% vs 4%) Atrial fibrillation (5% vs 0) Febrile neutropenia (5% vs 6%)	Not clear if the addition of obinutuzumab to ibrutinib is superior to ibrutinib, given the study design and lack of a monotherapy group
ECOG1912[32,37]	Ibrutinib-rituximab	FCR	N = 529 Age ≤70 y and fit Patients with del(17p) excluded	PFS	6 y	5-y PFS: 78% vs 51%[a] in both unmutated *IGHV* (75% vs 33%)[a] and mutated *IGHV* (83% vs 68%)[a] 5-y OS: 95% vs 89%[a]	Neutropenia (36% vs 45%) Thrombocytopenia (4.3% vs 15%) Infection (12.% vs 8.9%) Hypertension (18.5% vs 8.2%) Atrial fibrillation (3.2% vs 1.2%)	The study showed the OS advantage of ibrutinib + rituximab over FCR Providing a rationale for using ibrutinib in young/fit patients in first-line treatment
Alliance A041202[38]	Ibrutinib; ibrutinib-rituximab	BR	N = 547 Age ≥65 y Patients with del(17p) not excluded	PFS	38	24-mo PFS: 87% vs 88% vs 74%[a] No OS difference	Neutropenia (15% vs 40% vs 21%) Thrombocytopenia (7% vs 15% vs 5%) Atrial fibrillation (9% vs 3% vs 6%) Hypertension (29% vs 15% vs 34%) Infections (20% vs 15% vs 20%)	Study showed no benefit of adding rituximab to ibrutinib
Acalabrutinib								
ELEVATE TN[39]	Acalabrutinib-obinutuzumab; acalabrutinib	Chl-O	N = 535 Age ≥65 or <65 y with comorbidities Patients with del(17p)/*TP53* variations included Crossover allowed	PFS by IRC	48	48-mo PFS: 87% vs 78% vs 25%[a] Median PFS: NR vs NR vs 27.8 mo[a]	Neutropenia (29.8% vs 9.5% vs 41.4%) Diarrhea (4.5% vs 0.6% vs 1.8%) Arthralgia (1.1%vs 0.6% vs1.2%) Thrombocytopenia (8.4% vs 2.8% vs 11.8%) Pneumonia (5.6% vs 2.2% vs 1.8%)	Study led to the approval of acalabrutinib for first-line treatment Post hoc analysis shows a PFS improvement in the acalabrutinib + obinutuzumab group over acalabrutinib monotherapy group

(continued)

Table 3. Randomized Clinical Trials Testing BTK Inhibitors, and Venetoclax-Based Regimens for Initial Treatment of CLL (continued)

Source	Investigational group(s)	Standard group	Study participants	Primary end point	Median follow-up, mo	Findings (investigational vs standard)	Selected grade 3-4 adverse events (investigational vs standard)	Significance/notes
Zanubrutinib								
SEQUOIA[40]	Zanubrutinib	BR	N = 479 Age ≥65 y Patients without del(17p) included Crossover allowed	PFS by IRC	26.2	24-mo PFS: 85.5% vs 69.5%[a] Median PFS: NR vs NR[a]	Neutropenia (12% vs 51%) Hypertension (6% vs 5%) Thrombocytopenia (<2% vs 7%) Pneumonia (2% vs 4%) Bleeding events (3% vs <2%)	Study led to the approval of zanubrutinib in first-line treatment
Venetoclax								
CLL14[41]	Venetoclax-obinutuzumab	Chl-O	N = 432 Patients with comorbidities	PFS by IRC	39.6	5-y PFS: 62.6% vs 27%[a] Median PFS: NR vs 36.4 mo[a]	Neutropenia (53% vs 48%) Thrombocytopenia (14% vs 15%) Febrile neutropenia (5% vs 4%) Pneumonia (4% vs 4%)	Study led to the approval of venetoclax + obinutuzumab in first-line treatment as the first nonchemotherapy and fixed-duration therapy: venetoclax (12 mo) and obinutuzumab (6 mo)
Combination								
GLOW[42]	Ibrutinib-venetoclax	Chl-O	N = 211 Age ≥65 or <65 y with comorbidities Patients had no del(17p) or known *TP53* variation	PFS by IRC	27.7	24-mo PFS: 84.4 vs 44.1%[a] Median PFS: NR vs 21.0 mo[a]	Neutropenia (35% vs 50%) Thrombocytopenia (6% vs 20%) Infections (15% vs 10.5%) Diarrhea (10% vs 15%) Hypertension (7.5% vs 2%) Atrial fibrillation (6.6% vs 0) Cardiac failure (3% vs 0) Diarrhea (4% vs 0.5%) Infections (17.5% vs 15%)	Study may lead to the approval of ibrutinib + venetoclax in first-line treatment in the US

Abbreviations: BR, bendamustine-rituximab; Chl-O, chlorambucil-obinutuzumab; CLL, chronic lymphocytic leukemia; FCR, fludarabine-cyclophosphamide-rituximab; IRC, independent review committee; *IGHV*, immunoglobulin heavy chain gene; NR, not reached; OS, overall survival; PFS, progression-free survival.

[a] Statistically significant.

Table 4. Randomized Clinical Trials That Used Novel Agents for the Treatment of CLL in Patients With Relapsed/Refractory Disease

Source	Investigational group(s)	Standard group	Population	Primary end point	Median follow-up, mo	Findings with the most recent follow-up	Selected grade 3-4 adverse events (investigational vs standard)	Significance/notes
Ibrutinib								
RESONATE[43,44]	Ibrutinib	Ofatumumab	N = 391 ≥1 prior line of treatment Crossover allowed mid study	PFS investigator-assessed	65.3	60-mo PFS: 40% vs 3%[a] Median PFS: 44.1 vs 8.1 mo[a]	Neutropenia (16% vs 14%) Thrombocytopenia (6% vs 4%) Urinary tract infections (4% vs 1%)	Benefit of ibrutinib was observed irrespective of the del(17p) status Expanded approval for ibrutinib for del(17p)
Acalabrutinib								
ASCEND[45]	Acalabrutinib	Idelalisib-rituximab or BR (investigator choice)	N = 398 ≥1 prior line of treatment	PFS by IRC	16.1	12-mo PFS: 88% vs 75%[a] Median PFS: NR vs 16.6 mo[a]	Neutropenia (15% vs 39% vs 31%) Diarrhea (1% vs 24% vs 0) Thrombocytopenia (4% vs 8% vs 3%) Pneumonia (5% vs 8% vs 3%) Headache (1% vs 0 vs 0)	Study led to the acalabrutinib in previously treated CLL
ELEVATE R/R[46]	Acalabrutinib	Ibrutinib	N = 533 Previously treated with del(17p) or del(11q)	PFS by IRC (noninferiority) Secondary safety end points	40.9	Median PFS: 38.4 mo in both groups (acalabrutinib was non- inferior) Atrial fibrillation/flutter (9.4% vs 16%)[a] was significantly lower with acalabrutinib	Neutropenia (19.5% vs 23%) Diarrhea (1% vs 5%) Headache (1.5% vs 0) Arthralgia (0 vs 0.8%) Hypertension (4.1% vs 8.7%) Pneumonia (10.5% vs 8.7%) Thrombocytopenia (9.8% vs 6.8%) Rash (9.8% vs 0) Myalgia (0.8% vs 0.4%) Atrial fibrillation (4.5% vs 3.4%) Contusion (0% vs 0.4%)	Study confirmed better safety profile of acalabrutinib compared to ibrutinib Acalabrutinib was noninferior to ibrutinib from the efficacy (PFS) standpoint
Zanubrutinib								
ALPINE[47]	Zanubrutinib	Ibrutinib	N = 625 Previously treated	ORR (noninferiority and superiority) by the investigator Secondary: PFS and safety end points	29.6	ORR: 86.2% vs 75.7%[a] 24-mo PFS: 78.4% vs 65.9%[a]	Neutropenia (16% vs 14%) Hypertension (15% vs 11%) COVID-19-related pneumonia (7% vs 4%) COVID-19 (7% vs 5%) Pneumonia (6% vs 8%) Thrombocytopenia (3% vs 4%) Atrial fibrillation (1.9% vs 3.7%) Increased blood pressure (1.2% vs 3%)	Study led to the approval of zanubrutinib in relapsed CLL First study showing higher efficacy (OR and PFS) of a next-generation BTK inhibitor (zanubrutinib) compared with ibrutinib PR-L was not included in the ORR definition

(continued)

Table 4. Randomized Clinical Trials That Used Novel Agents for the Treatment of CLL in Patients With Relapsed/Refractory Disease (continued)

Source	Investigational group(s)	Standard group	Population	Primary end point	Median follow-up, mo	Findings with the most recent follow-up	Selected grade 3-4 adverse events (investigational vs standard)	Significance/notes
GS-US-312-0116[48]	Idelalisib-rituximab	Placebo + rituximab	N = 220 Progressed within 24 mo Not eligible for cytotoxic agents	PFS	18	Median PFS: 19.4 vs 6.5 mo[a]	Diarrhea (9% vs 0) Colitis (4.5% vs 0) Rash (3.6% vs 1%) Pneumonitis (3.6% vs 1%) *Pneumocystis jirovecii* infection (3.6% vs 1%)	Study led to approval of idelalisib + rituximab in relapsed CLL
DUO[49]	Duvelisib	Ofatumumab	N = 319 Previously treated	PFS by IRC	22.4	12-mo PFS: 60% vs 39%[a] Median PFS: 13.3 vs 9.9 mo[a]	Neutropenia (30% vs 17%) Anemia (13% vs 5%) Thrombocytopenia (8% vs 2%) Diarrhea (15% vs 1%) Pneumonia (14% vs 1%) Colitis (12% vs 1%) Rash (12% vs 1%) Asthenia (11% vs 3%)	Study led to approval of duvelisib in relapsed CLL
Venetoclax								
MURANO[50]	Venetoclax-rituximab	BR	N = 382 Previously treated (1-3 lines)	PFS investigator-assessed	59.2	5-y PFS: NR vs 37.8%[a] Median PFS: 53.6 vs 17 mo[a]	Neutropenia (58% vs 39%) Infections (17.5% vs 22%) Anemia (11% vs 14%) Thrombocytopenia (6% vs 10%) Pneumonia (5.2% vs 8%) Tumor lysis syndrome (3.1% vs 1.1%) Pneumonia (8.2% vs 8%)	Study led to approval of venetoclax + rituximab for relapsed CLL with fixed-treatment-duration therapy: venetoclax (24 mo) and rituximab (6 mo)

Abbreviations: BR, bendamustine-rituximab; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; IRC, independent review committee; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PR-L, partial response with lymphocytosis.

[a] Statistically significant.

Box 4. Practical Points for General Practitioners About Commonly Used CLL Drugs

BTK inhibitors (ibrutinib, acalabrutinib, zanubrutinib, pirtobrutinib)

Atrial fibrillation/flutter
- Low threshold for an ECG with concerning signs or symptoms
- Patients with controlled atrial fibrillation are often able to continue BTK inhibitors

Hypertension
- Multiple antihypertensive drugs may be needed for management of BTK inhibitor–induced hypertension
- No specific class of antihypertensives is preferred for BTK inhibitor–induced hypertension, and general guidelines for management of blood pressure should be followed

Bleeding
- Hold the drug 3 to 7 days before and after procedures
- Consult with hematologist before starting anticoagulants. Patients taking warfarin or vitamin K antagonists were excluded from most BTK inhibitor trials

Infections
- Consult the hematologist about holding the BTK inhibitors during the infection episodes
- Concurrent use with corticosteroids may lead to an increased risk for fungal infections

BCL2 inhibitor (venetoclax)

Tumor lysis syndrome
- Venetoclax should *only* be initiated under the direct supervision of a hematologist as it requires a slow dose increase and close monitoring at the beginning because of risk for tumor lysis syndrome
- If the drug is held more than 1 week, consult the hematologist before restarting as there may be a need for a slow dose increase depending on the disease burden (lymphocyte count or size of the lymph nodes)

Infections
- Consult the hematologist about holding venetoclax during the infection episodes

PI3K inhibitors (idelalisib, duvelisib)

Pneumonitis
- The drug should be discontinued in the setting of cough, hypoxia, or shortness of breath; notify a hematologist and refer to a pulmonologist.

Diarrhea/colitis
- The drug should be discontinued. A hematologist should be notified and the patient referred to a gastroenterologist.
- Can occur as a direct adverse event or as a presentation of cytomegalovirus infection

Transaminitis
- Hold the drug and contact a hematologist

Infections
- Patients are at risk of *Pneumocystis jirovecii* infections and cytomegalovirus reactivation, and *P jirovecii* prophylaxis is recommended

Abbreviations: BCL2, B-cell leukemia/lymphoma 2; BTK, Bruton tyrosine kinase; ECG, electrocardiogram; PI3K, phosphoinositide 3'-kinase.

(a δ isoform inhibitor) and duvelisib (a δ and γ isoform inhibitor) are approved for the treatment of CLL.[59] PI3K inhibitors are associated with higher rates of all infections and several immune-mediated adverse events. Patients taking idelalisib should be monitored every month for elevated liver enzyme levels (39%), pneumonitis (cough, dyspnea, and hypoxemia) (5.5%), diarrhea (29%), and colitis (4.5%).[60] Routine monitoring for cytomegalovirus activation (0.9%) using a blood polymerase chain reaction test and prophylactic use of antibiotics such as sulfamethoxazole/trimethoprim for *Pneumocystis jirovecii* pneumonia (3.6%) is recommended for patients taking a PI3K inhibitor.

Inhibitor of B-Cell Leukemia/Lymphoma 2

BCL2 proteins inhibit the mitochondrial pathway of apoptosis. Overexpression of the BCL2 family proteins is an essential component of the pathophysiology of CLL.[61] Limited duration treatment with venetoclax, the only clinically available BCL2 inhibitor, induces complete responses without detectable, measurable disease in the blood or marrow of approximately 70% of patients with CLL, an effect that is durable in more than 60% of patients after the drug is discontinued. The initiation of venetoclax requires a weekly dose increase over 5 weeks because of the potential for tumor lysis syndrome. While receiving treatment, patients should be monitored for cytopenia, because they may require supportive treatment such as granulocyte colony–stimulating factor. Venetoclax is a substrate of CYP3A4 and P-glycoprotein, and consultation with a clinical pharmacist before starting any new medication (eg, moderate and strong CYP3A4 inducers and inhibitors such as phenytoin, carbamazepine, voriconazole, posaconazole) is necessary to avoid adverse drug-drug interactions.

Monoclonal anti-CD20 antibodies, including chimeric (rituximab) and humanized (obinutuzumab and ofatumumab), bind to the extracellular portion of the CD20 antigen and result in cell death via a direct effect, complement-dependent cell toxicity, or antibody-dependent cell toxicity. Monoclonal antibodies are combined with novel agents such as venetoclax.[62] Infusion reactions (ie, fever, chills, flushing, changes in blood pressure or heart rate) occur in up to 67% of patients, especially with the initial doses. Given the risk for reactivation of viral hepatitis, testing for B surface antigen and core antibody should be performed before starting treatment. If a patient is a chronic carrier of hepatitis B, concurrent antiviral therapy should be initiated after consultation with a hepatologist.[28]

Chemoimmunotherapy was the mainstay of therapy before the introduction of novel agents. Purine analogues (fludarabine, pentostatin) and alkylating agents (cyclophosphamide, bendamustine chlorambucil) were used in combination with monoclonal anti-CD20 antibodies. It should be noted that the fludarabine-cyclophosphamide-rituximab (FCR) regimen is associated with an approximately 7% risk of a secondary myeloid malignancy over a median follow-up of 58 months.[63] Currently, chemoimmunotherapy has a limited, if any, role in the treatment of CLL, because this class of drugs is inferior to BTK inhibitors and venetoclax-based regimens in different clinical settings (Table 2 and Table 3).

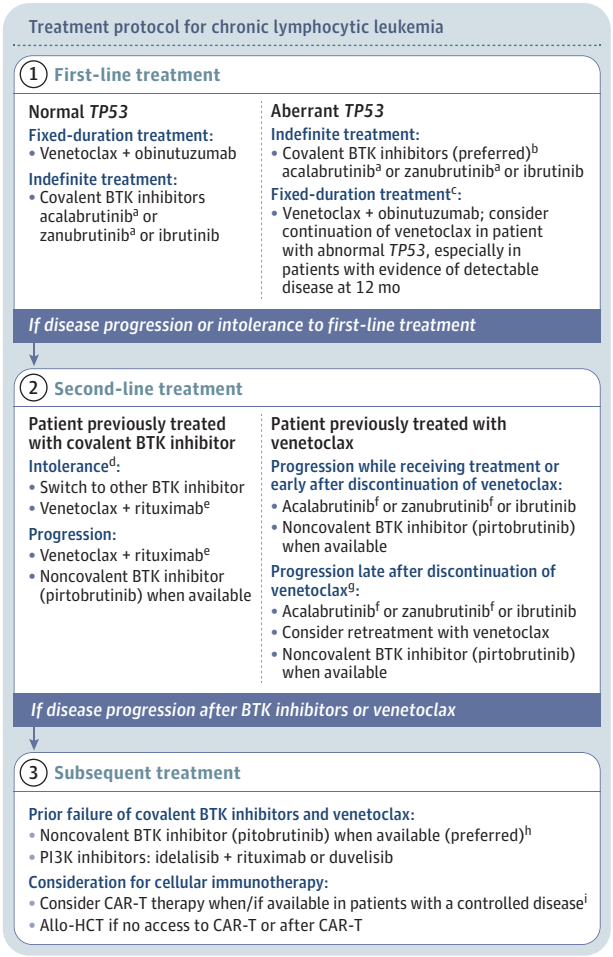
Choice of Treatment

Figure 1 shows the approach to treatment for CLL; **Figure 2** shows the mechanisms of action of several CLL treatments.

First-Line Treatment

Chemoimmunotherapy consisting of FCR, (bendamustine-rituximab (BR), and chlorambucil-obinutuzumab (Chl-O) was previously the first-line therapy for CLL. FCR was used for young (<65 years) and fit

Figure 1. The Treatment Approach to Chronic Lymphocytic Leukemia



Allo-HCT indicates allogeneic hematopoietic cell transplant; BTK, Bruton tyrosine kinase; CAR-T, chimeric antigen receptor T cell; PI3K, phosphoinositide 3'-kinase; *TP53*, tumor protein p53.

[a] Second-generation BTK inhibitors (acalabrutinib, zanubrutinib) preferred, given improved safety extrapolating from head-to-head trials in patients with relapse. Zanubrutinib had superior efficacy compared with ibrutinib.

[b] BTK inhibitors are preferred based on data using cross-trial comparisons.

[c] Some experts consider the continuation of venetoclax in patients with aberrant *TP53*, especially in those with evidence of detectable measurable residual disease at the end of 12 months.

[d] In patients with controlled disease who are intolerant to ibrutinib, watch and wait can be considered until there is an indication for treatment.

[e] In patients with rapidly progressive disease, consider inpatient care with rapid dose escalation.

[f] Second-generation covalent BTK inhibitors (acalabrutinib, zanubrutinib) preferred, given improved safety based on randomized clinical trials. Zanubrutinib had superior efficacy compared with ibrutinib.

[g] Two years is generally accepted as the cutoff, although confirmatory studies are needed.

[h] Pirtobrutinib is preferred over PI3K inhibitors, as its efficacy has been shown in a clinical trial, including after receipt of BTK inhibitor and venetoclax.

[i] Referral for CART-T therapy is recommended while patients are responsive to treatment.

(Cumulative Illness Rating Scale [CIRS] score <6)]) patients.[64] Patients older than 65 years or those with CIRS scores greater than 6 were candidates for BR or Chl-O.[65,66]

In the US E1912 clinical trial of 529 previously patients with untreated CLL, FCR was less effective than the combination of ibrutinib (indefinite) and rituximab (6 months) for the outcome of PFS at 45 months follow-up, irrespective of the IGHV status (5-year PFS, 78% for ibrutinib-rituximab group, compared with 51% for the FCR group; $P < .001$). Ibrutinib-rituximab regimen was also associated with a superior 3-year overall survival compared with FCR (98.8% vs 91.5%; $P < .001$).[32,37] In the A041202 clinical trial of 364 patients randomized to ibrutinib, ibrutinib-rituximab, or BR, PFS was associated with better outcomes, with the indefinite use of ibrutinib (2-year PFS, 87% vs 74%; $P < .001$) and ibrutinib-rituximab (2-year PFS, 88% vs 74%; $P < .001$) compared with BR. In that study, there was no improvement in the PFS by adding rituximab to ibrutinib ($P = .49$).[38] In the SEQUOIA study of 590 participants, monotherapy with zanubrutinib (indefinite) was associated with a better PFS compared with BR (2-year PFS, 85.5% vs 69.5%; $P < .001$).[40]

Chl-O has been used as the standard-treatment group in several clinical trials that enrolled patients with high CIRS scores (>6) or older age (>65 years). In the randomized iLLUMINATE trial that included 229 patients, ibrutinib-obinutuzumab use was associated with improved PFS compared with Chl-O (42-month PFS, 74% vs 33%; $P < .001$) and in the 3-group randomized ELEVATE TN trial (n = 535), patients who received acalabrutinib-obinutuzumab or acalabrutinib had a better PFS compared with the patients treated with Chl-O (4-year PFS, 87% vs 78% vs 25%; $P < .001$).[35,39] Together, these studies led to the approval of ibrutinib, acalabrutinib, and zanubrutinib for first-line treatment of CLL.

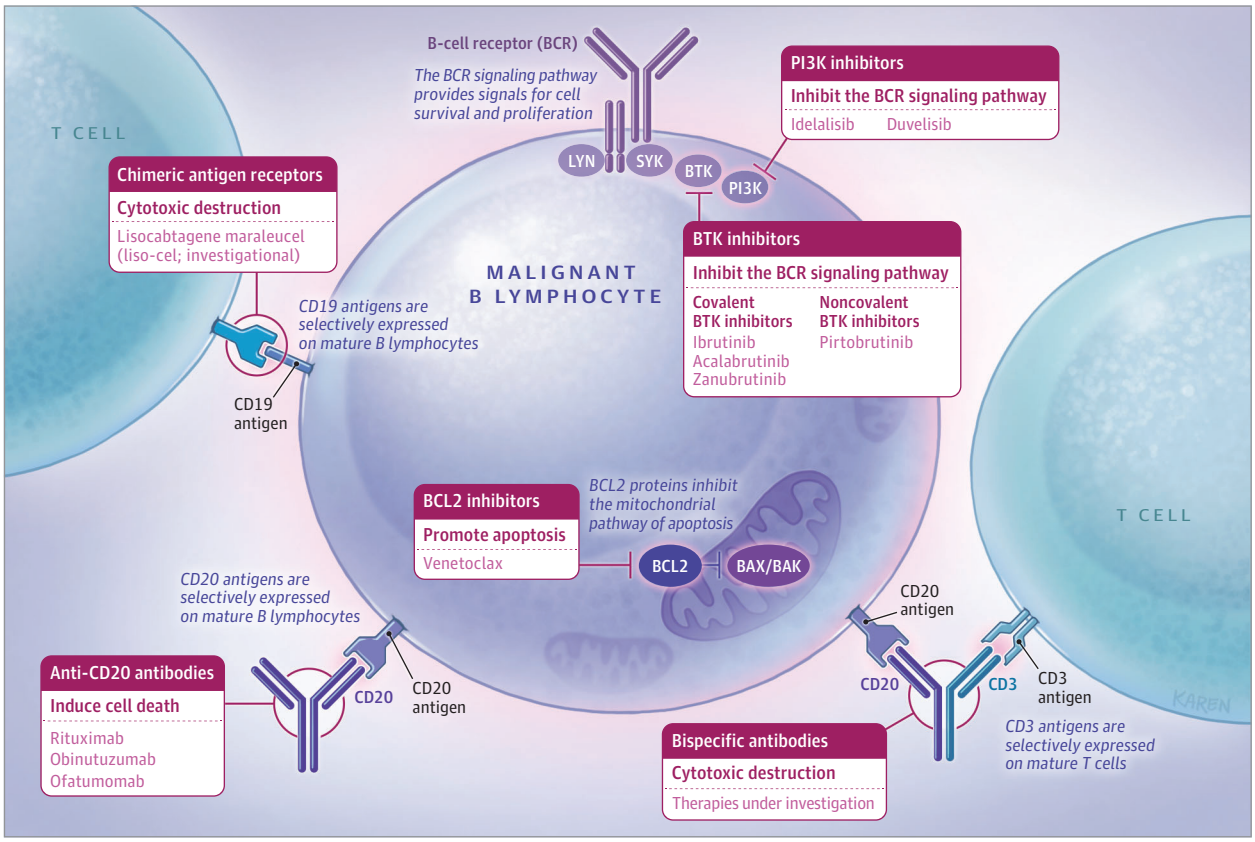
The CLL-14 study randomized 423 patients to either venetoclax-obinutuzumab or Chl-O for 12 months and showed a significant improvement in 3-year PFS (81.9% vs 49.5%; $P < .001$). Among 216 patients treated with venetoclax-obinutuzumab, there was no evidence of detectable CLL cells in the blood samples of 75.5% using allele-specific oligonucleotide polymerase chain reaction. Also, with more than 4 years of follow-up after finishing treatment, 63% of patients treated with venetoclax-obinutuzumab remained in remission.[41] The CLL-14 study established a time-limited and chemotherapy-free regimen (venetoclax for 12 months and obinutuzumab for 6 months) as a first-line therapy.

Combining antiproliferative agents, such as BTK inhibitors, and proapoptotic drugs, such as venetoclax, is biologically reasonable because of the distinct mechanism of action and toxicities of the 2 classes. In the GLOW randomized trial, 211 patients (aged >65 years or with impaired organ function determined by CIRS score) were randomized to receive ibrutinib-venetoclax (12 cycles) or Chl-O (6 cycles); the 2-year PFS rate was better with ibrutinib-venetoclax compared with Chl-O (84.4% vs 44.1%; $P < .001$). There was no detectable disease by next-generation sequencing at the end of treatment in 54.7% of patients treated with ibrutinib-venetoclax.[42]

Patients With Aberrant *TP53*

Details of studies enrolling patients with aberrant (deleted or altered) *TP53* are reported in **Table 5**; common features of approved BTK inhibitors compared with venetoclax are reported in **Table 6**. *TP53* is a proapoptotic gene located in the short arm of chromosome 17. Aberrancies, either in form of deletion—del(17p)—or sequence variation of the gene (present in 10% of patients with untreated CLL), resulted in a short remission after chemotherapy with a median PFS of only 11 months after treatment with the fludarabine, cyclophosphamide, and

Figure 2. Mechanisms of Action: Chimeric Antigen Receptors, PI3K Inhibitors, BTK Inhibitors, Bispecific Antibodies, BCL2 Inhibitors, and Anti-CD20 Antibodies



BAK indicates BCL2 antagonist/killer 1; *BAX*, BCL2-associated X-protein; BCL2, B-cell leukemia/lymphoma 2; BTK, Bruton tyrosine kinase; LYN, Lyn tyrosine kinase; PI3K, phosphoinositide 3'-kinase; SYK, Syk kinase.

Table 5. Efficacy of BTK Inhibitors and Venetoclax-Based Regimens for Patients With CLL and *TP53* Aberrancy—Data From Prospective Clinical Trials

				%				
					TP53 aberrancy			
Source	Drug	No.	Median follow-up, mo	Concurrent use of anti-CD20 antibody	del(17p) or *TP53* altered	del(17p)	*TP53* altered	PFS
Pooled analysis of 4 prospective clinical trials[67]	Ibrutinib	89	49.8	49	100	53	59	48 mo: 79% Median: NR
ELEVATE TN[39]	Acalabrutinib	48	46.9	48	100	68-69	83-84	48 mo: 76% Median: NR
SEQUOIA[68]	Zanubrutinib	109	35	0	100	100	Not reported	24 mo: 88.9% Median: NR
CLL14[41]	Venetoclax-obinutuzimab	25	39.6	100	100	68	76	36 mo: 60.4% Median: NR

Abbreviations: BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; NR, not reached; PFS, progression-free survival.

rituximab, compared with 9.1 months with fludarabine and cyclophosphamide (P = .03).[69] In a pooled analysis of randomized and nonrandomized clinical trials that used ibrutinib in 89 patients with aberrant *TP53*, a 4-year PFS rate of 79% was reported.[67] The SEQUOIA trial included 109 previously untreated patients with del(17p), and treatment with zanubrutinib in these patients was associated with a 2-year PFS rate of 89%.[68] Forty-eight patients with aberrant *TP53* were treated with acalabrutinib (with or without obinutuzumab) in the ELEVATE TN study and had a 4-year PFS of 76%.[39] In the CLL-14 study, 49 patients had an aberrant *TP53* and were treated with venetoclax-obinutuzumab for 12 months. For these patients, the 3-year PFS was 60.4%.[41] Based on these studies and in the absence of head-to-head clinical trials comparing BTK inhibitors with venetoclax, BTK inhibitors are preferred for patients with *TP53* aberrancy, but venetoclax-obinutuzumab remains a reasonable option if BTK inhibitors cannot be used due to potential for adverse events (eg, major cardiac or bleeding disorders). If venetoclax is used in patients with an aberrant *TP53*, indefinite therapy can be considered.[70]

In summary, for first-line treatment, both BTK inhibitors (acalabrutinib, zanubrutinib and ibrutinib) or the combination of venetoclax-obinutuzumab are acceptable choices. Treatment with venetoclax-obinutuzumab provides the opportunity for a fixed duration of treatment (for 1 year) in contrast with indefinite therapy until progression or intolerance with the BTK inhibitors. Patients with multiple comorbidities can still be candidates for treatment with these agents, but medical comorbidities may influence the choice of treatment. For example, BTK inhibitors can be associated with adverse outcomes in patients with an increased risk of bleeding or poorly controlled cardiac arrhythmias. When there is access to BTK inhibitors or venetoclax, chemoimmunotherapy regimens should be avoided due to inferior efficacy (Table 3).

Previously Treated Patients

Patients with a progression of disease after a response for at least 6 months are considered to have relapsed CLL. Patients who have not responded to treatment or who relapse within 6 months of the last dose of therapy are considered to have refractory CLL. For both patients with relapse and those with refractory disease, and depending on the previous treatment that they received, either venetoclax-rituximab (if they previously received chemoimmunotherapy or BTK inhibitors) or BTK inhibitors (if they previously received chemoimmunotherapy or venetoclax) are preferred treatments.[71,72] In the ASCEND trial, 398 patients with relapsed or refractory CLL were randomized to receive acalabrutinib or investigator's choice of agent (BR or idelalisib and rituximab), and acalabrutinib treatment was associated with a better 1-year PFS (88% vs 75%; $P < .001$).[45] In the MURANO trial, 389 patients with relapsed CLL were randomized to fixed-duration therapy with venetoclax (24 months) in combination with rituximab (6 months) or BR. Venetoclax-rituximab regimen was associated with superior PFS (median, 53.6 vs 17 months; $P < .001$) and overall survival (82.1% vs 62.2% at 5 years) compared with BR.[50,73] Treatment should be started promptly in patients who progress with a BTK inhibitor, and patients may require rapid increases in venetoclax dose in the inpatient setting and continuation of BTK inhibitor until or after a therapeutic target dose of venetoclax is achieved.[71,74]

For patients with disease progression after first-line venetoclax-based therapy, the timing of progression is important to consider when selecting subsequent treatment. Progressive disease while taking venetoclax indicates the need to switch to BTK inhibitors as an alternative class, whereas patients who relapse after finishing the planned treatment duration may benefit from the reintroduction of venetoclax.[75] In patients with relapse, PI3K inhibitors, idelalisib (in combination with rituximab), and duvelisib are approved for CLL. Close monitoring for immune-mediated events and infections is recommended.[76] These drugs should not be used as first-line treatments because of the higher incidence of idelalisib-induced grade 3 or greater elevations in liver enzyme levels in patients receiving first-line treatment (54%) compared with previously treated patients (13%).[77] Noncovalent (reversible) inhibitors of BTK, such as pirtobrutinib, represent a new class of effective drugs for CLL. Pirtobrutinib has demonstrated efficacy in patients with CLL relapse who had prior treatment with covalent BTK inhibitors (100%) and venetoclax (41%) and has demonstrated efficacy irrespective of prior treatment history, including in patients with mutant *C481S* gene with overall responses in 50% to 70% of patients.[78]

Table 6. Common Features of Approved BTK Inhibitors Compared With Venetoclax

Class	BTK inhibitors (acalabrutinib, zanubrutinib, and ibrutinib)	BCL2 inhibitor (venetoclax)
Mechanism of action	Inhibit BTK, a critical enzyme in the B-cell receptor pathway	Inhibit BCL2, antiapoptotic protein
Duration of treatment	Indefinite therapy until progression or intolerance	Fixed duration (12 or 24 mo in first and released setting)
Efficacy		
Feasibility	No need for initial intense monitoring	Requires frequent monitoring and visits at the start of treatment (first 4-8 wk)
Adverse events	Cardiovascular (cardiac arrhythmias, hypertension), musculoskeletal symptoms, infections, hematologic events Less common with acalabrutinib and zanubrutinib	Tumor lysis syndrome, gastrointestinal symptoms, hematologic events Tumor lysis syndrome risk is minimized with ramp-up and debulking with anti-CD20 antibodies
Effect on other treatment options	Venetoclax can be used subsequently after progression Can be used peri (before or after) CAR-T	BTK inhibitors can be used subsequently after progression No data on possible effect of venetoclax on safety/efficacy of CAR-T

Abbreviations: BCL2, B-cell leukemia/lymphoma 2; BTK, Bruton tyrosine kinase; CAR-T, chimeric antigen receptor T cell.

Selecting a Covalent BTK Inhibitor

Zanubrutinib and acalabrutinib are newer covalent BTK inhibitors that are more selective for BTK (with less effect on non-BTK enzymes) than ibrutinib and were originally expected to have a better safety profile. Two clinical trials tested this hypothesis by comparing acalabrutinib with ibrutinib (ELEVATE R/R study) and zanubrutinib with ibrutinib (ALPINE study) in patients with relapse. In the ELEVATE R/R study, 533 patients with previously treated high-risk CLL—del(17p) or del(11q)—were randomized to either acalabrutinib or ibrutinib; acalabrutinib was noninferior to ibrutinib with regard to PFS (median, 38.4 months in both groups) but showed lower rates of atrial fibrillation/flutter (9.4% vs 16%; $P = .02$) and hypertension (9.4% vs 23.2%) and a higher incidence of headache (34.6% vs 20%) than treatment with ibrutinib. Discontinuation rates due to adverse events were 14.7% with acalabrutinib and 21.3% with ibrutinib. In the ALPINE study, 652 patients with previously treated CLL were randomized to zanubrutinib or ibrutinib. Treatment with zanubrutinib was associated with an improved overall response (86.2% vs 75.7%; $P < .001$) and PFS (24-month PFS, 78.4% vs 65.9%; $P = .002$) compared with ibrutinib. The improved efficacy also occurred in patients with aberrant *TP53* (24-month PFS, 72.6% vs 54.6%; $P = .01$). Zanubrutinib was associated with a lower cumulative incidence of atrial fibrillation/flutter (5.2% vs 13.3%), but there was an increased rate of neutropenia (29.3% vs 24.4%) without an increased rate of infection (71.3% vs 73.1%). Events leading to treatment discontinuation were less common with zanubrutinib vs ibrutinib (14.5% vs 22.2%).[47] The mechanism of resistance is similar among the covalent BTK inhibitors. Switching between drugs in this category (acalabrutinib, zanubrutinib, or ibrutinib) after disease progression should be avoided.[53,79] When BTK inhibitors are discontinued because of intolerance due to adverse effects, treatment indications should be assessed before additional treatments are initiated, particularly in patients who have taken BTK inhibitors for

2 years or more. Data from the E1912 study indicated that the median time between stopping ibrutinib due to adverse effects and the time to initiating new therapy was 25 months.[32] If treatment is indicated, clinical trials have shown that acalabrutinib or zanubrutinib can be used effectively in ibrutinib-intolerant patients, and zanubrutinib can be used in ibrutinib- or acalabrutinib-intolerant patients.[80-82] Based on the results of these studies, zanubrutinib and acalabrutinib are preferred over ibrutinib because of their favorable safety profile and the superior efficacy of zanubrutinib compared with ibrutinib.

Cellular Immunotherapy

Allogeneic Hematopoietic Cell Transplant

Allogeneic hematopoietic cell transplant is the only potentially curative treatment for CLL, with an approximate 5-year PFS rate of 40%. In this procedure, healthy hematopoietic donor cells genetically matched to the patient are infused after a conditioning regimen that includes a combination of chemotherapy, total body irradiation, or both. Despite the efficacy, approximately 30% to 50% of patients experience complications such as graft-vs-host-disease, which is associated with mortality in approximately 10% to 20% of patients.[83,84] Allogeneic transplants should be discussed with patients after progression with BTK inhibitors, venetoclax, or both, while CLL is in complete or partial remission (Figure 1).

Chimeric Antigen Receptor T-Cell Therapy

Chimeric antigen receptor T-cell (CAR-T) therapy is considered the standard of care for several B-cell lymphoid malignancies but remains investigational for CLL.[85] In the phase 1 portion of the TRANSCEND study, 23 patients with high-risk CLL who progressed after BTK inhibitors (91%), venetoclax (65%), or both (48%) all received lisocabtagene maraleucel, an autologous CD19-directed CAR-T therapy, with or without ibrutinib. The response rate was 82% by the International Workshop on CLL criteria, and there was no detectable disease by flow cytometry in the peripheral blood (75%) or the bone marrow (64%) of most patients at 24-month follow-up. CAR-T therapy is associated with cytokine release syndrome, which is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction. In the TRANSCED study, 74% of patients developed cytokine release syndrome (9% grade 3). Neurologic events are also associated with CAR-T therapy, and 39% of patients in this study experienced temporary neurologic events (21% grade 3 or 4). These adverse effects may limit the clinical utility of CAR-T therapy for some patients, but if approved, it will be an important option for patients who experience disease progression after BTK inhibitors or venetoclax.[86]

Richter Transformation

Richter transformation, which is CLL transformation to high-grade lymphoma (large B-cell lymphoma [90%] and Hodgkin lymphoma [10%]), occurs in up to 10% of patients with CLL, at a rate of about 0.5% to 1% per year. Median overall survival is about 3 to 4 months in patients with CLL and Richter transformation.[87] For this reason, these patients should be referred for clinical trials using investigational treatments. Less than 15% of patients achieve a complete response to initial chemotherapy regimens like the standard-of-care R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine, and prednisone), and consolidation with allogeneic or autologous stem cell transplant should be considered for these patients. Patients with Richter transformation to Hodgkin lymphoma have a 2-year overall survival of approximately 72% with standard chemotherapy regimens, and consolidation with a transplant is reserved for patients with relapsed disease who are not in the first remission.[88]

Limitations

This review has several limitations. First, it is not a systematic review, and the quality of evidence was not evaluated. Second, some relevant publications may not have been included. Third, some important but still investigational drugs, combinations, and procedures were not included. Fourth, some cited studies did not include long-term follow-up data.

Conclusions

More than 200 000 people in the US are living with a CLL diagnosis, and CLL causes approximately 4410 deaths each year in the US. Approximately two-thirds of patients eventually need treatment. Highly effective novel targeted agents include BTK inhibitors such as acalabrutinib, zanubrutinib, ibrutinib, and pirtobrutinib or BCL2 inhibitors such as venetoclax.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Cancer Stat Facts: Leukemia—chronic lymphocytic leukemia (CLL). National Cancer Institute. Published 2022. Accessed February 21, 2023. https://seer.cancer.gov/statfacts/html/clyl.html

2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7-33. doi:10.3322/caac.21708

3. Condoluci A, Terzi di Bergamo L, Langerbeins P, et al. International prognostic score for asymptomatic early-stage chronic lymphocytic leukemia. *Blood*. 2020;135(21):1859-1869. doi:10.1182/blood.2019003453

4. Brieghel C, Galle V, Agius R, et al. Identifying patients with chronic lymphocytic leukemia without need of treatment: end of endless watch and wait? *Eur J Haematol*. 2022;108(5):369-378. doi:10.1111/ejh.13743

5. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. 2022;36(7):1720-1748.

6. Zhang S, Kipps TJ. The pathogenesis of chronic lymphocytic leukemia. *Annu Rev Pathol*. 2014;9:103-118. doi:10.1146/annurev-pathol-020712-163955

7. Burger JA. Treatment of chronic lymphocytic leukemia. *N Engl J Med*. 2020;383(5):460-473. doi:10.1056/NEJMra1908213

8. García-Muñoz R, Roldan Galiacho V, Llorente L. Immunological aspects in chronic lymphocytic leukemia (CLL) development. *Ann Hematol*. 2012;91(7):981-996. doi:10.1007/s00277-012-1460-z

9. Delgado J, Nadeu F, Colomer D, Campo E. Chronic lymphocytic leukemia: from molecular pathogenesis to novel therapeutic strategies. *Haematologica*. 2020;105(9):2205-2217. doi:10.3324/haematol.2019.236000

10. Bosch F, Dalla-Favera R. Chronic lymphocytic leukaemia: from genetics to treatment. *Nat Rev Clin Oncol*. 2019;16(11):684-701. doi:10.1038/s41571-019-0239-8

11. Crombie J, Davids MS. *IGHV* mutational status testing in chronic lymphocytic leukemia. *Am J Hematol*. 2017;92(12):1393-1397. doi:10.1002/ajh.24808

12. Shadman M, Liu C, Eakle K, et al. COVID-19 vaccination response and its practical application in patients with chronic lymphocytic leukemia. *Hemasphere*. 2022;7(1):e811. doi:10.1097/HS9.0000000000000811

13. Abrisqueta P, Pereira A, Rozman C, et al. Improving survival in patients with chronic lymphocytic leukemia (1980-2008): the Hospital Clinic of Barcelona experience. *Blood*. 2009;114(10):2044-2050. doi:10.1182/blood-2009-04-214346

14. Nabhan C, Rosen ST. Chronic lymphocytic leukemia: a clinical review. *JAMA*. 2014;312(21):2265-2276. doi:10.1001/jama.2014.14553

15. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. *Blood*. 1975;46(2):219-234. doi:10.1182/blood.V46.2.219.219

16. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760. doi:10.1182/blood-2017-09-806398

17. Wierda WG, Brown J, Abramson JS, et al. NCCN Guidelines Insights: chronic lymphocytic leukemia/small lymphocytic lymphoma, version 3.2022. *J Natl Compr Canc Netw*. 2022;20(6):622-634. doi:10.6004/jnccn.2022.0031

18. Fazi C, Scarfò L, Pecciarini L, et al. General population low-count CLL-like MBL persists over time without clinical progression, although carrying the same cytogenetic abnormalities of CLL. *Blood*. 2011;118(25):6618-6625. doi:10.1182/blood-2011-05-357251

19. Parikh SA, Rabe KG, Kay NE, et al. The CLL International Prognostic Index predicts outcomes in monoclonal B-cell lymphocytosis and Rai 0 CLL. *Blood*. 2021;138(2):149-159. doi:10.1182/blood.2020009813

20. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer*. 1981;48(1):198-206. doi:10.1002/1097-0142(19810701)48:1<198::AID-CNCR2820480131>3.0.CO;2-V

21. Baliakas P, Espinet B, Mellink C, et al. Cytogenetics in chronic lymphocytic leukemia: ERIC perspectives and recommendations. *Hemasphere*. 2022;6(4):e707. doi:10.1097/HS9.0000000000000707

22. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med*. 2000;343(26):1910-1916. doi:10.1056/NEJM200012283432602

23. Guièze R, Robbe P, Clifford R, et al. Presence of multiple recurrent mutations confers poor trial outcome of relapsed/refractory CLL. *Blood*. 2015;126(18):2110-2117. doi:10.1182/blood-2015-05-647578

24. Langerbeins P, Zhang C, Robrecht S, et al. The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage chronic lymphocytic leukemia. *Blood*. 2022;139(2):177-187. doi:10.1182/blood.2021010845

25. Herling CD, Cymbalista F, Groß-Ophoff-Müller C, et al. Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk chronic lymphocytic leukemia (CLL): a randomized phase 3 trial. *Leukemia*. 2020;34(8):2038-2050. doi:10.1038/s41375-020-0747-7

26. Pneumococcal vaccine timing for adults. Centers for Disease Control and Prevention Published February 8, 2022. Accessed February 22, 2023. https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf

27. COVID-19 vaccines for people who are moderately or severely immunocompromised. Centers for Disease Control and Prevention. Updated January 31, 2023. Accessed February 22, 2023. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html

28. Chronic lymphocytic leukemia/small lymphocytic lymphoma (version 1.2023) National Comprehensive Cancer Network. Published 2023. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf

29. Greenberger LM, Saltzman LA, Gruenbaum LM, et al. Anti-spike T-cell and antibody responses to SARS-CoV-2 mRNA vaccines in patients with hematologic malignancies. *Blood Cancer Discov*. 2022;3(6):481-489. doi:10.1158/2643-3230.BCD-22-0077

30. Mehrany K, Weenig RH, Pittelkow MR, Roenigk RK, Otley CC. High recurrence rates of squamous cell carcinoma after Mohs' surgery in patients with chronic lymphocytic leukemia. *Dermatol Surg*. 2005;31(1):38-42. doi:10.1097/00042728-200501000-00008

31. Mehrany K, Weenig RH, Pittelkow MR, Roenigk RK, Otley CC. High recurrence rates of basal cell carcinoma after Mohs surgery in patients with chronic lymphocytic leukemia. *Arch Dermatol*. 2004;140(8):985-988. doi:10.1001/archderm.140.8.985

32. Shanafelt TD, Wang XV, Hanson CA, et al. Long-term outcomes for ibrutinib-rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. *Blood*. 2022;140(2):112-120. doi:10.1182/blood.2021014960

33. Barr PM, Owen C, Robak T, et al. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv*. 2022;6(11):3440-3450. doi:10.1182/bloodadvances.2021006434

34. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437. doi:10.1056/NEJMoa1509388

35. Moreno C, Greil R, Demirkan F, et al. First-line treatment of chronic lymphocytic leukemia with ibrutinib plus obinutuzumab *versus* chlorambucil plus obinutuzumab: final analysis of the randomized, phase III iLLUMINATE trial. *Haematologica*. 2022;107(9):2108-2120. doi:10.3324/haematol.2021.279012

36. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(1):43-56. doi:10.1016/S1470-2045(18)30788-5

37. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381(5):432-443. doi:10.1056/NEJMoa1817073

38. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379(26):2517-2528. doi:10.1056/NEJMoa1812836

39. Sharman JP, Egyed M, Jurczak W, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. *Leukemia*. 2022;36(4):1171-1175. doi:10.1038/s41375-021-01485-x

40. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2022;23(8):1031-1043. doi:10.1016/S1470-2045(22)00293-5

41. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(9):1188-1200. doi:10.1016/S1470-2045(20)30443-5

42. Kater AP, Owen C, Moreno C, Follows G, Munir T, Levin M-D, et al. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. NEJM Evidence. Published May 13, 2022. Accessed February 22, 2023. https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200006

43. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94(12):1353-1363. doi:10.1002/ajh.25638

44. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223. doi:10.1056/NEJMoa1400376

45. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2020;38(25):2849-2861. doi:10.1200/JCO.19.03355

46. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol*. 2021;39(31):3441-3452. doi:10.1200/JCO.21.01210

47. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2023;388(4):319-332. doi:10.1056/NEJMoa2211582

48. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997-1007. doi:10.1056/NEJMoa1315226

49. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. 2018;132(23):2446-2455. doi:10.1182/blood-2018-05-850461

50. Seymour JF, Kipps TJ, Eichhorst BF, et al. Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab. *Blood*. 2022;140(8):839-850. doi:10.1182/blood.2021015014

51. Byrd JC, Jones JJ, Woyach JA, Johnson AJ, Flynn JM. Entering the era of targeted therapy for chronic lymphocytic leukemia: impact on the practicing clinician. *J Clin Oncol*. 2014;32(27):3039-3047. doi:10.1200/JCO.2014.55.8262

52. 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. doi:10.1200/JCO.2016.70.2282

53. Bonfiglio S, Sutton LA, Ljungström V, et al. *BTK* and *PLCG2* remain unmutated in one third of patients with CLL relapsing on ibrutinib. *Blood Adv*. 2023;bloodadvances.2022008821. doi:10.1182/bloodadvances.2022008821

54. Wang E, Mi X, Thompson MC, et al. Mechanisms of resistance to noncovalent bruton's tyrosine kinase inhibitors. *N Engl J Med*. 2022;386(8):735-743. doi:10.1056/NEJMoa2114110

55. 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. doi:10.3324/haematol.2017.182907

56. Bhat SA, Gambril J, Azali L, et al. Ventricular arrhythmias and sudden death events following acalabrutinib initiation. *Blood*. 2022;140(20):2142-2145. doi:10.1182/blood.2022016953

57. Lampson BL, Yu L, Glynn RJ, et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. *Blood*. 2017;129(18):2581-2584. doi:10.1182/blood-2016-10-742437

58. Kamel S, Horton L, Ysebaert L, et al. Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation. *Leukemia*. 2015;29(4):783-787. doi:10.1038/leu.2014.247

59. Shouse G, Danilova OV, Danilov AV. Current status of phosphoinotiside-3 kinase inhibitors in blood cancers. *Curr Opin Oncol*. 2022;34(5):540-545. doi:10.1097/CCO.0000000000000871

60. Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. *J Clin Oncol*. 2019;37(16):1391-1402. doi:10.1200/JCO.18.01460

61. Chong SJF, Davids MS. Breaking through BCL-2 inhibition in CLL. *Blood*. 2020;135(10):709-711. doi:10.1182/blood.2019004767

62. Maloney DG. Anti-CD20 antibody therapy for B-cell lymphomas. *N Engl J Med*. 2012;366(21):2008-2016. doi:10.1056/NEJMct1114348

63. Kutsch N, Bahlo J, Robrecht S, et al. Long term follow-up data and health-related quality of life in frontline therapy of fit patients treated with FCR versus BR (CLL10 trial of the GCLLSG). *Hemasphere*. 2020;4(1):e336. doi:10.1097/HS9.0000000000000336

64. Hudon C, Fortin M, Vanasse A. Cumulative Illness Rating Scale was a reliable and valid index in a family practice context. *J Clin Epidemiol*. 2005;58(6):603-608. doi:10.1016/j.jclinepi.2004.10.017

65. Eichhorst B, Fink AM, Bahlo J, et al; International Group of Investigators; German CLL Study Group (GCLLSG). First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17(7):928-942. doi:10.1016/S1470-2045(16)30051-1

66. Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. *Leukemia*. 2015;29(7):1602-1604. doi:10.1038/leu.2015.14

67. Allan JN, Shanafelt T, Wiestner A, et al. Long-term efficacy of first-line ibrutinib treatment for chronic lymphocytic leukaemia in patients with *TP53* aberrations: a pooled analysis from four clinical trials. *Br J Haematol*. 2022;196(4):947-953. doi:10.1111/bjh.17984

68. Tam CS, Robak T, Ghia P, Kahl BS, Walker P, Janowski W, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. *Haematologica*. 2020;106(9):2354-2363.

69. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood*. 2016;127(2):208-215. doi:10.1182/blood-2015-06-651125

70. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a phase II pivotal trial. *J Clin Oncol*. 2018;36(19):1973-1980. doi:10.1200/JCO.2017.76.6840

71. 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. doi:10.1016/S1470-2045(17)30909-9

72. Mato AR, Roeker LE, Jacobs R, et al. Assessment of the efficacy of therapies following venetoclax discontinuation in CLL reveals BTK inhibition as an effective strategy. *Clin Cancer Res*. 2020;26(14):3589-3596. doi:10.1158/1078-0432.CCR-19-3815

73. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2018;378(12):1107-1120. doi:10.1056/NEJMoa1713976

74. Davids MS, Shadman M, Parikh SA, et al. A multicenter, retrospective study of accelerated venetoclax ramp-up in patients with relapsed/refractory chronic lymphocytic leukemia. *Am J Hematol*. 2022;97(3):E105-E109. doi:10.1002/ajh.26444

75. Thompson MC, Harrup RA, Coombs CC, et al. Venetoclax retreatment of patients with chronic lymphocytic leukemia after a previous venetoclax-based regimen. *Blood Adv*. 2022;6(15):4553-4557. doi:10.1182/bloodadvances.2022007812

76. Coutré SE, Barrientos JC, Brown JR, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. *Leuk Lymphoma*. 2015;56(10):2779-2786. doi:10.3109/10428194.2015.1022770

77. Lampson BL, Kasar SN, Matos TR, et al. Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity. *Blood*. 2016;128(2):195-203. doi:10.1182/blood-2016-03-707133

78. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet*. 2021;397(10277):892-901. doi:10.1016/S0140-6736(21)00224-5

79. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370(24):2286-2294. doi:10.1056/NEJMoa1400029

80. Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. *Blood Adv*. 2019;3(9):1553-1562. doi:10.1182/bloodadvances.2018030007

81. Rogers KA, Thompson PA, Allan JN, et al. PHASE 2 study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. *Hematol Oncol*. 2019;37(S2):60-61. doi:10.3324/haematol.2020.272500

82. Shadman M, Flinn IW, Levy MY, et al. Zanubrutinib in patients with previously treated B-cell malignancies intolerant of previous Bruton tyrosine kinase inhibitors in the USA: a phase 2, open-label, single-arm study. *Lancet Haematol*. 2023;10(1):e35-e45. doi:10.1016/S2352-3026(22)00320-9

83. Shadman M, Maloney DG. Immune therapy for chronic lymphocytic leukemia: allogeneic transplant, chimeric antigen receptor T-cell therapy, and beyond. *Hematol Oncol Clin North Am*. 2021;35(4):847-862. doi:10.1016/j.hoc.2021.03.011

84. Roeker LE, Dreger P, Brown JR, et al. Allogeneic stem cell transplantation for chronic lymphocytic leukemia in the era of novel agents. *Blood Adv*. 2020;4(16):3977-3989. doi:10.1182/bloodadvances.2020001956

85. Melenhorst JJ, Chen GM, Wang M, et al. Decade-long leukaemia remissions with persistence of $CD4^+$ CAR T cells. *Nature*. 2022;602(7897):503-509. doi:10.1038/s41586-021-04390-6

86. Siddiqi T, Soumerai JD, Dorritie KA, et al. Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL. *Blood*. 2022;139(12):1794-1806. doi:10.1182/blood.2021011895

87. Smyth E, Eyre TA, Cheah CY. Emerging therapies for the management of Richter transformation. *J Clin Oncol*. 2023;41(2):395-409. doi:10.1200/JCO.22.01028

88. Stephens DM, Boucher K, Kander E, et al. Hodgkin lymphoma arising in patients with chronic lymphocytic leukemia: outcomes from a large multi-center collaboration. *Haematologica*. 2021;106(11):2845-2852. doi:10.3324/haematol.2020.256388