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Modern approaches to the treatment of chronic lymphocytic leukemia: chemoimmunotherapy, targeted therapy, and minimal residual disease assessment

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Abstract: Chronic lymphocytic leukemia (CLL) is one of the most common B-cell lymphoproliferative disorders characterized by the progressive accumulation of monoclonal CD5+, CD19+, and CD23+ lymphocytes in the peripheral blood, bone marrow, lymph nodes, liver, and spleen. Over the past two decades, therapeutic strategies for CLL have evolved significantly, transitioning from conventional chemotherapy to chemoimmunotherapy and, subsequently, to targeted molecular therapies. The fludarabine, cyclophosphamide, and rituximab (FCR) regimen has long remained the standard first-line treatment for fit patients, demonstrating high response rates and prolonged progression-free survival. However, the development of Bruton tyrosine kinase inhibitors, BCL-2 inhibitors, and phosphoinositide 3-kinase inhibitors has substantially changed the therapeutic landscape.

These agents have improved survival outcomes while offering alternative options for elderly and comorbid patients. Despite these advances, treatment-related toxicity, drug resistance, and economic burden remain major challenges. Minimal residual disease (MRD) monitoring and the evaluation of serum free light chains (FLCs) have emerged as promising prognostic and therapeutic monitoring tools. This review summarizes contemporary evidence regarding chemoimmunotherapy, targeted therapy, real-world clinical data, and novel biomarkers in CLL management.

Keywords: chronic lymphocytic leukemia, chemoimmunotherapy, targeted therapy, minimal residual disease, free light chains, immunophenotyping, FCR regimen.

Introduction

Chronic lymphocytic leukemia (CLL) represents a heterogeneous B-cell malignancy characterized by the clonal proliferation and accumulation of mature CD5+, CD19+, and CD23+ lymphocytes. The disease predominantly affects elderly individuals and is associated with variable clinical outcomes ranging from indolent disease requiring only observation to rapidly progressive leukemia requiring intensive treatment.

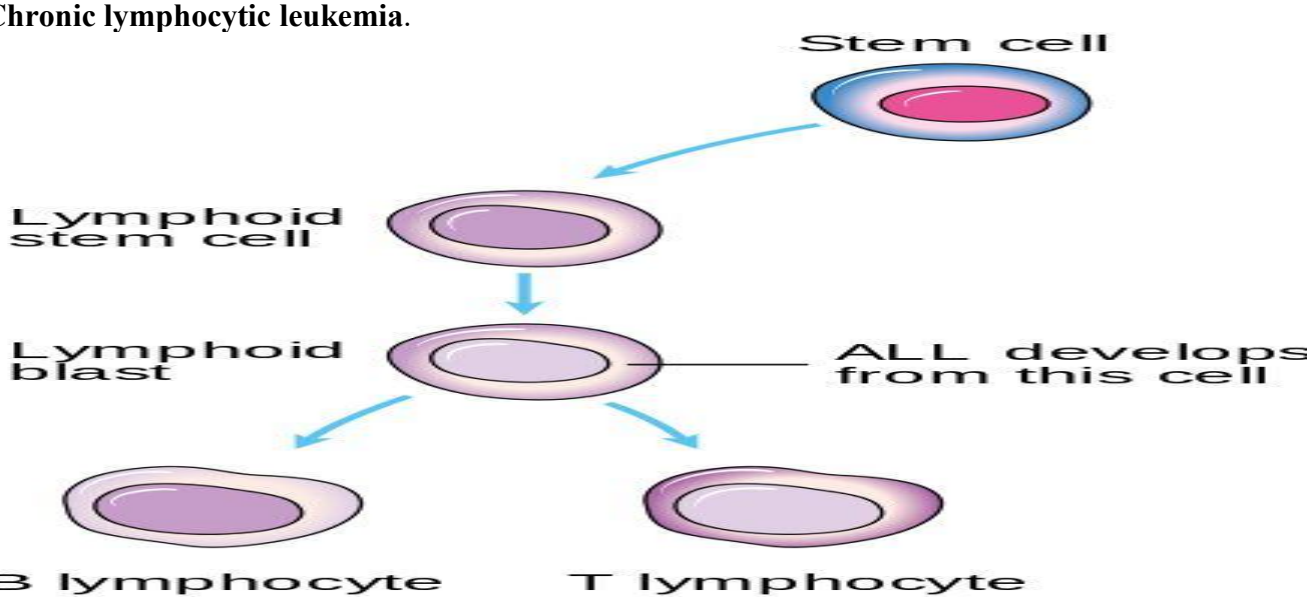
According to current epidemiological data, CLL accounts for approximately 25–30% of all adult leukemias in Western countries. The introduction of modern immunological and molecular

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diagnostic techniques has improved disease characterization and enabled the development of personalized therapeutic strategies.

Historically, chlorambucil-based chemotherapy represented the cornerstone of CLL treatment. Subsequently, purine analogues such as fludarabine demonstrated superior efficacy, particularly when combined with cyclophosphamide. The addition of rituximab, a monoclonal anti-CD20 antibody, established the FCR regimen as a standard first-line therapeutic approach for younger and physically fit patients.

Pic.1
Chronic lymphocytic leukemia.



Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults and is characterized by the progressive accumulation of mature but immunologically dysfunctional B lymphocytes in the peripheral blood, bone marrow, lymph nodes, and spleen. These malignant cells evade apoptosis, survive for prolonged periods, and progressively infiltrate hematopoietic and lymphoid tissues, leading to disease progression and immune dysfunction.

Several molecular and cytogenetic abnormalities significantly influence disease behavior, prognosis, and treatment response, including deletion 17p (del17p), TP53 mutations, unmutated immunoglobulin heavy-chain variable region (IGHV) status, CD38 overexpression, ZAP-70 expression, and chromosomal abnormalities identified by fluorescence in situ hybridization (FISH). Furthermore, interactions between leukemic cells and the tumor microenvironment play a critical role in disease progression. In particular, signaling pathways involving the B-cell receptor (BCR) are central to CLL pathogenesis and have become important therapeutic targets.

Recent years have witnessed revolutionary changes in CLL management due to the development of targeted therapies, including Bruton tyrosine kinase (BTK) inhibitors, BCL-2 inhibitors, and phosphoinositide 3-kinase (PI3K) inhibitors. These novel agents have significantly improved survival outcomes while reducing dependence on traditional cytotoxic chemotherapy. The

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purpose of contemporary therapeutic strategies is to maximize treatment efficacy, prolong progression-free and overall survival, minimize toxicity, and improve patients' quality of life.

Historically, chemotherapy represented the foundation of CLL treatment. Comparative clinical studies demonstrated that fludarabine was more effective than chlorambucil in achieving remission and prolonging progression-free survival. Subsequently, combination therapy with fludarabine and cyclophosphamide (FC regimen) showed superior efficacy compared with fludarabine monotherapy, establishing combination chemotherapy as a standard treatment approach for fit patients.

The introduction of monoclonal antibody therapy further improved treatment outcomes. Alemtuzumab, a monoclonal antibody directed against CD52, was among the first immunotherapeutic agents used in CLL treatment. The drug induces antibody-dependent cellular cytotoxicity and complement-mediated lysis of malignant lymphocytes. Clinical studies demonstrated high response rates among patients with refractory disease. However, significant hematological toxicity, including severe neutropenia and increased susceptibility to viral and opportunistic infections, limited its widespread clinical use.

A major advance in CLL therapy was achieved with the introduction of the FCR regimen, consisting of fludarabine, cyclophosphamide, and rituximab. This combination became one of the most effective treatment strategies for newly diagnosed CLL patients. Large randomized clinical trials demonstrated overall response rates exceeding 90%, complete remission rates above 70%, significant improvements in progression-free survival, and favorable long-term survival outcomes. Despite the relatively low expression of CD20 on malignant CLL cells, the addition of rituximab substantially enhanced antitumor activity and treatment efficacy.

Nevertheless, although FCR remains highly effective, its use is often limited in elderly patients and individuals with significant comorbidities because of considerable toxicity, including prolonged neutropenia, severe infectious complications, and treatment-related immunosuppression. These limitations stimulated the development of targeted therapeutic agents, which have transformed the modern management of CLL and established a new era of personalized treatment based on the molecular and biological characteristics of the disease.

Randomized clinical trials provide optimal conditions for evaluating the efficacy and safety of therapeutic agents; however, they frequently involve highly selected patient populations that may not fully reflect routine clinical practice. Consequently, real-world registry studies have become increasingly important for assessing treatment outcomes in broader and more heterogeneous patient populations. Population-based registries have demonstrated that the fludarabine, cyclophosphamide, and rituximab (FCR) regimen maintains substantial efficacy outside the controlled environment of clinical trials. At the same time, these studies have shown that elderly patients and individuals with significant comorbidities are more likely to receive less intensive treatment regimens. The use of chlorambucil has progressively declined, whereas bendamustine-rituximab combinations have become widely utilized in older patients. Registry data have also revealed that toxicity profiles observed in routine clinical practice may differ from those reported in randomized studies, highlighting the importance of integrating prospective clinical research with observational real-world evidence.

The introduction of targeted therapies has fundamentally transformed the management of chronic lymphocytic leukemia (CLL). Among these agents, Bruton tyrosine kinase (BTK) inhibitors represent one of the most important therapeutic advances. Ibrutinib irreversibly inhibits BTK, thereby blocking B-cell receptor signaling pathways that are essential for the survival and proliferation of

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malignant lymphocytes. Clinical trials have demonstrated significant improvements in progression-free survival and overall survival, as well as substantial efficacy in both treatment-naïve and relapsed or refractory patients, including those with high-risk genetic abnormalities such as deletion 17p. Nevertheless, long-term administration of ibrutinib may be associated with adverse events including atrial fibrillation, hemorrhagic complications, hypertension, and the development of resistance mutations. To overcome these limitations, second-generation BTK inhibitors such as acalabrutinib and zanubrutinib were developed. These agents exhibit greater selectivity for BTK and have demonstrated favorable efficacy together with improved tolerability profiles.

Another major therapeutic advance in CLL management has been the development of BCL-2 inhibition. Venetoclax is a highly selective BCL-2 inhibitor that restores the apoptotic capacity of malignant lymphocytes and promotes programmed cell death. Clinical studies have demonstrated high overall response rates, deep remissions characterized by undetectable minimal residual disease (MRD), and substantial efficacy in relapsed and refractory disease. Furthermore, the combination of venetoclax with anti-CD20 monoclonal antibodies such as rituximab or obinutuzumab has been associated with improved survival outcomes. One of the most important complications of venetoclax therapy is tumor lysis syndrome; however, careful laboratory monitoring and gradual dose escalation have significantly reduced the incidence of this potentially life-threatening adverse event. Despite its remarkable efficacy, long-term treatment may eventually result in resistance due to the emergence of BCL-2 gene mutations.

Phosphoinositide 3-kinase (PI3K) inhibitors constitute another important class of targeted agents in CLL therapy. Idelalisib inhibits PI3K-mediated signaling pathways involved in leukemic cell survival and proliferation. Clinical studies have shown that the combination of idelalisib and rituximab is superior to rituximab monotherapy in relapsed and refractory disease. However, treatment-related toxicities remain a significant limitation and may include severe diarrhea, colitis, hepatotoxicity, opportunistic infections, and immune-mediated complications. Consequently, newer PI3K inhibitors such as duvelisib and umbralisib have been developed with the aim of improving efficacy while reducing treatment-associated toxicity.

Modern therapeutic strategies increasingly focus on rational combination regimens involving targeted therapies and monoclonal antibodies. Examples include combinations of ibrutinib with venetoclax, venetoclax with rituximab, venetoclax with obinutuzumab, and ibrutinib combined with bendamustine and rituximab. These treatment approaches seek to achieve deeper remissions, increase rates of undetectable MRD, reduce treatment duration, and minimize cumulative toxicity. In this context, time-limited therapy has emerged as an important therapeutic concept because prolonged exposure to targeted agents may contribute to treatment resistance and increased adverse effects.

Assessment of minimal residual disease has become one of the most valuable prognostic tools in contemporary CLL management. Numerous studies have demonstrated that MRD negativity is strongly associated with prolonged progression-free survival, improved overall survival, and superior long-term disease control. Flow cytometric immunophenotyping remains the most commonly used method for MRD detection, and a threshold below 0.01% leukemic cells is generally considered indicative of undetectable disease. Nevertheless, MRD assessment has several limitations, including variability between bone marrow and peripheral blood findings, topographic asymmetry of tumor distribution, and dependence on tumor cell adhesion characteristics. Despite these limitations, MRD

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monitoring continues to play a critical role in evaluating therapeutic efficacy and guiding treatment duration.

In addition to MRD assessment, the measurement of serum free light chains (FLCs) has emerged as a promising complementary biomarker in CLL. Abnormal FLC levels are detected in approximately half of patients and may manifest as monoclonal elevation of kappa or lambda chains, polyclonal elevation, or abnormal kappa/lambda ratios. Clinical investigations have demonstrated significant associations between FLC abnormalities and adverse prognostic factors, including absolute lymphocytosis, CD38 expression, unmutated IGHV status, elevated β2-microglobulin concentrations, and renal dysfunction. Unlike MRD assessment based on immunophenotyping, FLC analysis is independent of tumor localization and cellular adhesiveness. Furthermore, the short biological half-life of FLCs, approximately two to four hours, permits rapid assessment of treatment response and tumor sensitivity to therapy. Consequently, serum FLC measurement may serve as an integrated biomarker reflecting overall tumor burden, disease activity, and therapeutic effectiveness.

Taken together, these advances demonstrate that the management of chronic lymphocytic leukemia has evolved from conventional chemotherapy-based approaches toward highly individualized treatment strategies based on molecular characteristics, targeted therapeutic interventions, and sensitive biomarkers of treatment response. The integration of real-world clinical evidence, targeted therapies, MRD monitoring, and serum free light chain assessment has substantially improved prognostic evaluation and clinical outcomes, providing a foundation for increasingly personalized approaches to CLL management.

Materials and Methods

This review article was conducted as a comprehensive narrative and analytical review of the scientific literature devoted to chronic lymphocytic leukemia (CLL), with particular emphasis on chemoimmunotherapy, targeted therapies, minimal residual disease (MRD), and serum free light chain (FLC) assessment. Relevant scientific publications indexed in major international databases, including PubMed, Scopus, Web of Science, and Google Scholar, were systematically analyzed. The review included clinical trials, observational studies, population-based registry analyses, and review articles published between 2000 and 2026.

The literature search was performed using a combination of keywords and Medical Subject Headings (MeSH) terms, including “chronic lymphocytic leukemia,” “CLL targeted therapy,” “FCR regimen,” “minimal residual disease in CLL,” “free light chains in leukemia,” “ibrutinib,” “venetoclax,” “idelalisib,” and “chemoimmunotherapy.” Boolean operators (AND/OR) were used to optimize search sensitivity and specificity. Eligible studies included randomized controlled clinical trials, prospective and retrospective cohort studies, real-world registry analyses, investigations involving adult patients with CLL, and publications available in English or Russian. Studies evaluating treatment efficacy, toxicity profiles, MRD assessment, and prognostic biomarkers were prioritized. Case reports with insufficient clinical information, studies lacking methodological transparency, non-peer-reviewed publications, and duplicate reports were excluded from the analysis.

The review focused on comparative evaluation of treatment efficacy, progression-free survival (PFS), overall survival (OS), toxicity characteristics, and MRD outcomes across different therapeutic approaches. Published findings were synthesized descriptively and interpreted according to contemporary evidence-based principles.

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Analysis of the reviewed literature demonstrated substantial progress in the management of chronic lymphocytic leukemia over the past two decades. Among conventional treatment approaches, the combination of fludarabine, cyclophosphamide, and rituximab (FCR) consistently demonstrated high therapeutic efficacy in newly diagnosed patients. Major clinical trials reported overall response rates exceeding 90%, complete remission rates ranging from 40% to 70%, significant prolongation of progression-free survival, and superior overall survival compared with fludarabine-cyclophosphamide therapy alone. Nevertheless, FCR treatment was associated with considerable hematological toxicity, particularly prolonged neutropenia and infectious complications, which limited its applicability in elderly and comorbid populations.

The introduction of targeted therapies has significantly improved clinical outcomes in CLL. Bruton tyrosine kinase (BTK) inhibitors, particularly ibrutinib, demonstrated substantial efficacy in both treatment-naïve and relapsed or refractory patients. Clinical studies consistently reported prolonged progression-free survival, improved overall survival, and significant activity in high-risk genetic subgroups, including patients with del17p and TP53 mutations. However, long-term administration of ibrutinib was associated with cardiovascular adverse events, most notably atrial fibrillation and hypertension.

Venetoclax-based treatment strategies produced some of the most impressive results among targeted therapies. Clinical investigations demonstrated high response rates, profound reductions in tumor burden, and deep remissions characterized by undetectable minimal residual disease. Furthermore, venetoclax combined with rituximab or obinutuzumab resulted in superior therapeutic outcomes and durable remissions even after completion of time-limited treatment protocols. Tumor lysis syndrome remained the most important treatment-related complication, emphasizing the necessity of gradual dose escalation and careful laboratory monitoring.

PI3K inhibitors, including idelalisib, also demonstrated significant antileukemic activity, particularly in relapsed and refractory disease. However, their clinical use was frequently limited by immune-mediated adverse effects such as severe diarrhea, colitis, hepatotoxicity, and opportunistic infections.

Evaluation of minimal residual disease emerged as one of the most important prognostic tools in modern CLL management. Numerous studies demonstrated a strong association between MRD negativity and prolonged progression-free survival, improved overall survival, and superior long-term disease control. The reviewed evidence indicated that targeted therapies are capable of achieving undetectable MRD with lower toxicity compared with intensive chemoimmunotherapy, thereby improving both efficacy and tolerability.

Serum free light chain analysis was identified as a promising complementary biomarker in CLL. Abnormal FLC concentrations were detected in approximately 50% of patients and were significantly associated with increased tumor burden, absolute lymphocytosis, adverse molecular prognostic markers, and renal dysfunction. Unlike MRD assessment, FLC analysis is independent of tumor localization and may provide a broader reflection of total disease burden. The short biological half-life of free light chains also enables rapid assessment of therapeutic response and disease dynamics.

Overall, the findings of this review demonstrate that contemporary management of chronic lymphocytic leukemia increasingly relies on targeted therapeutic strategies, sensitive methods of treatment response assessment, and novel biomarkers. The integration of chemoimmunotherapy,

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targeted agents, MRD monitoring, and serum free light chain analysis provides a comprehensive framework for individualized treatment planning and improved long-term clinical outcomes in patients with CLL.

Discussion

The findings of this review confirm that therapeutic strategies for chronic lymphocytic leukemia (CLL) have undergone a profound transformation over the past two decades. Advances in molecular biology, immunology, and targeted drug development have significantly expanded treatment options and improved clinical outcomes for patients across different risk categories.

Historically, chemoimmunotherapy represented the standard of care for CLL, with the combination of fludarabine, cyclophosphamide, and rituximab (FCR) demonstrating remarkable efficacy in physically fit patients. Numerous clinical studies have shown that the FCR regimen achieves high overall response rates, durable remissions, and prolonged progression-free and overall survival.

However, despite its effectiveness, the considerable hematological toxicity associated with FCR, particularly prolonged neutropenia and infectious complications, restricts its use in elderly individuals and patients with significant comorbidities.

The emergence of targeted therapies has revolutionized CLL management by selectively inhibiting molecular pathways essential for malignant B-cell survival and proliferation. Bruton tyrosine kinase inhibitors, BCL-2 inhibitors, and phosphoinositide 3-kinase inhibitors have demonstrated superior efficacy in many high-risk patient populations, including those harboring TP53 mutations and deletion 17p. These agents have substantially improved progression-free survival and have provided effective treatment options for patients who were previously considered difficult to treat. In addition, targeted therapies have enabled the development of individualized treatment strategies based on molecular and genetic risk profiles.

Despite these significant advances, several important challenges remain. Long-term administration of targeted therapies may be associated with cumulative toxicity, cardiovascular complications, development of resistance mutations, and substantial economic burden. Continuous treatment requirements for certain therapeutic regimens may further increase healthcare costs and affect patient adherence. Resistance mechanisms involving BTK and BCL-2 mutations have emerged as important clinical concerns that may compromise long-term treatment effectiveness. Furthermore, access to modern targeted therapies remains limited in many low-resource healthcare systems, creating disparities in treatment availability and patient outcomes.

One of the most important developments in contemporary CLL management is the implementation of minimal residual disease (MRD) monitoring. Numerous studies have demonstrated that MRD negativity is strongly associated with prolonged progression-free survival, improved overall survival, and superior long-term disease control. Consequently, MRD assessment has become a valuable prognostic indicator and an important tool for evaluating therapeutic efficacy, guiding treatment duration, and supporting clinical decision-making.

The integration of MRD-guided treatment strategies has contributed to the growing concept of personalized medicine in hematologic oncology.

At the same time, serum free light chain (FLC) analysis has emerged as a promising complementary biomarker. Unlike conventional MRD assessment based on immunophenotyping, FLC analysis is independent of tumor localization, tissue distribution, and cellular adhesion characteristics.

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Clinical investigations have demonstrated significant associations between FLC abnormalities and markers of increased tumor burden, adverse molecular characteristics, and disease activity. The short biological half-life of free light chains allows rapid assessment of treatment response and may provide a more comprehensive evaluation of overall disease burden. Therefore, FLC analysis has the potential to complement existing prognostic and monitoring strategies in CLL.

Future research should focus on optimizing therapeutic sequencing, refining molecular risk stratification, and developing more effective combination treatment strategies. Particular attention should be directed toward personalized medicine approaches that integrate genomic profiling, targeted therapies, MRD monitoring, and novel biomarkers such as serum free light chains. Additional priorities include the development of time-limited treatment strategies capable of achieving deep and durable remissions while minimizing toxicity and reducing treatment-related costs. Large multicenter prospective studies are required to establish the optimal sequencing and combination of therapeutic agents and to further improve long-term patient outcomes.

Conclusion

Modern treatment strategies for chronic lymphocytic leukemia have evolved dramatically due to advances in chemoimmunotherapy and targeted molecular therapies. Although the FCR regimen remains an effective treatment standard for selected physically fit patients, targeted agents such as BTK inhibitors, BCL-2 inhibitors, and PI3K inhibitors have significantly expanded therapeutic opportunities and improved outcomes in diverse patient populations.

Minimal residual disease assessment and serum free light chain analysis represent valuable tools for evaluating treatment response, refining prognostic assessment, and supporting individualized patient management. The future of CLL therapy lies in personalized treatment approaches that integrate molecular diagnostics, targeted therapeutic interventions, and advanced biomarker monitoring while minimizing toxicity, overcoming resistance, and improving quality of life.

References

1. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomized phase III trial. Lancet. 2010;376:1164–1174.
2. Eichhorst B, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil in elderly patients with advanced chronic lymphocytic leukemia. Blood. 2009;114:3382–3391.
3. Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukemia. Lancet. 2007;370:230–239.
4. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019;381:432–443.
5. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2018;378:1107–1120.
6. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371:213–223.
7. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374:311–322.

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HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

8. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;370:997–1007.
9. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in CLL. Blood. 2016;127:303–309.
10. Rawstron AC, Bottcher S, Letestu R, et al. Improving efficiency and sensitivity: European Research Initiative in CLL recommendations for flow cytometric MRD analysis. Leukemia. 2013;27:142–149.