Mediterranean Journal of Hematology and Infectious Diseases

Original Article

# Greek Consensus on Chronic Lymphocytic Leukemia (CLL) Treatment

Sotirios Sachanas[1], Theodoros Vassilakopoulos[2], Maria Angelopoulou[3], Sotirios Papageorgiou[4], Emmanouil Spanoudakis[5], Maria Bouzani[6], Maria Dimou[7] and Panagiotis Panagiotidis[8].

[1] Department of Hematology, Athens Medical Center, Psychikon Branch, Athens, Greece.
[2] Department of Haematology and Bone Marrow Transplantation, Laikon General Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece.
[3] Department of Haematology and Bone Marrow Transplantation, Laikon General Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece.
[4] Second Department of Internal Medicine, Propaedeutic, Hematology Unit, University General Hospital «Attikon», National and Kapodistrian University of Athens, Athens, Greece.
[5] Department of Hematology, Democritus University of Thrace, Alexandroupolis, Greece.
[6] Department of Hematology and Lymphoma, Evangelismos General Hospital, Athens, Greece.
[7] First Department of Internal Medicine, Propaedeutic, National and Kapodistrian University of Athens, School of Medicine, Laikon General Hospital, Athens, Greece.
[8] Department of Haematology and Bone Marrow Transplantation, Laikon General Hospital, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece.

**Competing interests:** The authors declare no conflict of Interest.

**Abstract.** ***Background*: New targeted therapies have revolutionized the treatment landscape in CLL. Biological features, patient characteristics and preferences and the safety profile of each treatment option should be taken into consideration for making the optimal treatment choice. This consensus practice statement on CLL treatment was developed by a group of Greek experts in CLL based on the available evidence for both first-line treatment and the relapsed/refractory setting.**

**Keywords:** Chronic Lymphocytic Leukaemia; Treatment; Consensus.

**Citation:** Sachanas S., Vassilakopoulos T., Angelopoulou M., Papageorgiou S., Spanoudakis E., Bouzani M., Dimou M., Panagiotidis P. Greek consensus on chronic lymphocytic leukemia (CLL) treatment. Mediterr J Hematol Infect Dis 2025, 17(1): e2025014, DOI: http://dx.doi.org/10.4084/MJHID.2025.014

**Published: March 01, 2025** **Received: December 02, 2024** **Accepted: February 07, 2025**



Correspondence to: Sotirios Sachanas. Department of Hematology, Athens Medical Center, Psychikon Branch, Athens, Greece. E-mail: ssachanas@gmail.com

**Introduction.** CLL is a clonal B-cell neoplasm characterized by increased numbers of B cells with a distinct immunophenotype. It typically occurs in elderly patients and is the most common type of leukemia in adults in Western countries, accounting for 30% of all leukemia cases.[1-3] The treatment landscape in CLL has dramatically changed over the last years with the advent of novel targeted therapies, namely Bruton Kinase Inhibitors (BTKis) such as Ibrutinib, Acalabrutinib, and Zanubrutinib, as well as the B-cell leukemia/lymphoma 2 inhibitor (BCL-2), Venetoclax.[4]

Optimal selection of first-line treatment is currently challenging, as the clinician has to choose among almost equally effective treatment options, taking into account both disease and patient factors and preferences and the unique safety profile of each drug. Patients with CLL in Greece have access to all novel therapies pending approval by the official committee overseeing high-cost

drugs.

The scope of this document is to provide recommendations for the treatment of patients with CLL based on the available evidence for both the first-line and the relapsed/refractory setting.

**Methodology.** The Lymphoma Working Group of the Hellenic Society of Haematology invited a panel of Greek hematology experts to consider the treatment landscape of CLL. The experts performed a systematic review of all available data related to the treatment of CLL over the last two decades, focusing on pivotal randomized phase 3 clinical trials of novel agents. The results of the literature search were presented and discussed.

*Pretreatment evaluation of clinically meaningful biological factors.* Screening for *TP53* disruption [(del17p13.1)] and/or *TP53* mutation) is mandatory prior to the first and each subsequent line of treatment. Patients with CLL with *TP53* mutations may or may not have concomitant del (17p).[5] *TP53* abnormalities are associated with poor prognosis, and their evaluation is crucial for making treatment decisions even in the era of targeted therapies.[6-7] Next Generation Sequencing (NGS) allows for the identification of low-burden *TP53* mutations (variant allele frequency, VAF, <10%). *TP53* pathogenic variants identified by NGS should be considered significant for treatment decisions regardless of the VAF, provided that the laboratory undertaking the analysis is certified for this test by a competent authority (ERIC and/or GenQA) and reports the corresponding limit of detection[8] Immunoglobulin heavy variable (IGHV) gene somatic hypermutation (SHM) status also plays a key role in the prognosis of CLL.[9-10] As this biomarker remains stable over time, assessment of IGHV gene SHM status should be performed only once, ideally prior to first-line treatment. Moreover, the study of B-cell receptor (BCR) immunoglobulins (IGs) stereotypy should be included in pretreatment assessment in CLL since patients in certain stereotyped subsets, such as patients in subset 2 display remarkably consistent clinicobiological profiles and should be treated accordingly.[11]

*Consensus:*

1. IGHV gene SHM analysis should be performed once during the disease course, ideally before the first-line treatment. Major stereotyped subsets should be defined before treatment initiation
2. Before each line of treatment, FISH for del (17p) and NGS for *TP53* mutations are required.
3. G-banding analysis for assessing genomic complexity is not generally recommended in routine care, emphasizing, however, that only the presence of at least five chromosomal aberrations is clinically relevant.[12]

**First line therapy.**

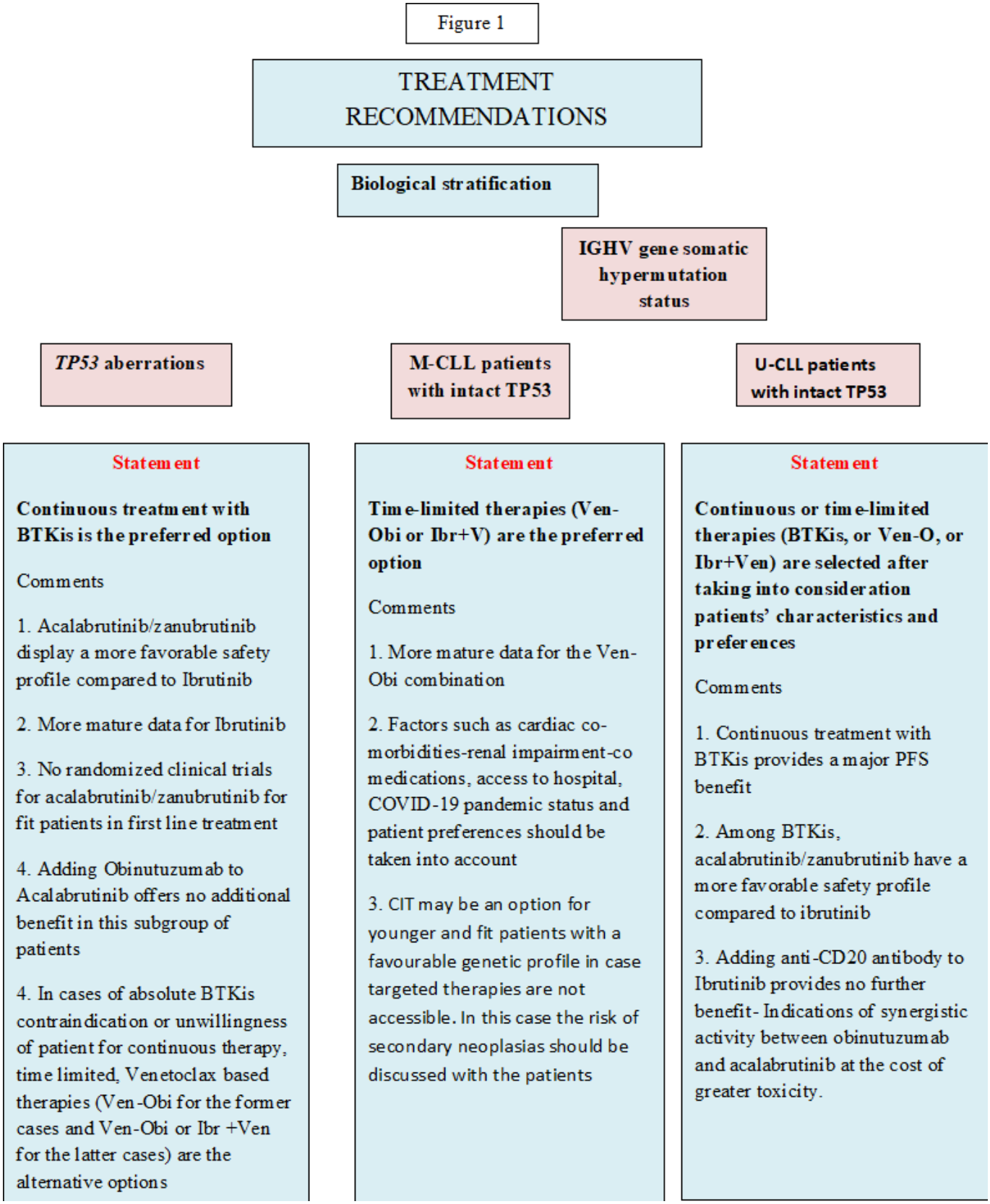
*CLL patients with TP53 aberrations (**Figure 1**).* The detection of del(17p) and *TP53* mutations in patients with no evidence of active disease is not per se a criterion for starting therapy.[3]

In patients meeting the criteria for treatment initiation, the detection of *TP53* is an absolute contraindication to the use of chemoimmunotherapy (CIT) [6,13].

*Continuous therapy.* Continuous therapy with BTKis has shown promising results in the first-line setting. In the National Institutes of Health Clinical Center (NIH) phase 2 trial evaluating only patients with del(17p) or *TP53* mutations treated with Ibrutinib, the Progression Free Survival(PFS) and Overall Survival (OS) medians were not reached and the estimated 6-year PFS and OS rates were 60% and 79% respectively.[14-15] In the ALLIANCE trial comparing Ibrutinib and Ibrutinib-Rituximab (IR) to Bendamustine-Rituximab (BR), after a median follow-up of 38 months, the median PFS for patients with del(17p) was not reached for IR versus 7 months for BR.[16] In the ILLUMINATE trial, the estimated 48-month PFS was 74% for patients with del(17p) or *TP53* mutations and 77% for those without.[17] Similarly, patients with *TP53* aberrations treated with Acalabrutinib with or without Obinutuzumab within the ELEVATE TN trial had a 72-month PFS rate of 56 %. These results suggest that CLL patients with *TP53* aberrations could effectively be treated with Acalabrutinib monotherapy without the need for additional Obinutuzumab.[18] The nonrandomized cohort, Arm C, of the phase 3 SEQUOIA trial, which included 109 patients with centrally confirmed del(17p) that received Zanubrutinib showed that after a median follow-up of 18.2 months, the overall response rate was 94.5% with 3.7% of patients achieving complete response with or without incomplete hematologic recovery. The estimated 18-month PFS rate was 88.6%, and the estimated 18-month OS rate was 95.1%. Moreover, in the SEQUOIA trial, there is also a nonrandomized cohort, Arm D, that includes treatment naïve CLL patients with del(17p) treated with the combination of Zanubrutinib and Venetoclax.[19-20]

*Time-limited therapies.* In the phase III CLL14 trial, 36 and 27 patients displayed TP53 aberrations in the Venetoclax plus Obinutuzumab and in the Chlorambucil-Obinutuzumab arm, respectively.[21] The median PFS for patients with *TP53* aberrations was approximately 18 months in patients treated with Chlorambucil-Obinutuzumab versus almost 4 years for Venetoclax plus Obinutuzumab (Ven-Obi).[21] That notwithstanding, the trial results showed that *TP53* aberrations remained a relatively poor prognosticator also in the context of Ven-Obi treatment with a hazard ratio (HR) of 3.39 (p=0.03).[21] In the

Figure 1




CAPTIVATE phase II trial investigating the effectiveness of the Ibrutinib–Venetoclax (Ibr-Ven) combination in patients aged ≤70 years with previously untreated CLL, 27/159 (17%) pts had *TP53* aberrations. Ibr-Ven resulted in high complete response (CR) and undetectable Minimal Residual Disease (uMRD) rates across patient subgroups, including those with *TP53* aberrations. Specifically, the best overall response rates by investigator assessment were 96% in patients with del(17p) and/or mutated *TP53*, while at 4, the 4-year PFS and OS rates were 63% and 96%, respectively.[22]

*Recommendations for CLL patients with TP53 aberrations.*

- More prolonged disease control achieved with BTKis appears to confer greater benefit to patients with *TP53* aberrations compared to other treatments.
- Fixed-duration treatment with the Ven-Obi combination does not appear to overcome the negative prognostic impact of *TP53* aberrations.
- CIT is not recommended.

*Patients with mutated IGHV genes (M-CLL) without TP53 aberrations (**Figure 1**).* This subgroup displays a favorable risk profile and represents approximately 25-30% of CLL patients at first-line treatment.[2-4] Young and fit M-CLL patients treated with the Fludarabine, Cyclophosphamide, Rituximab combination (FCR) in the CLL-8 trial had a 53.9% PFS at 12.8 years, while similar results have also been reported by the MD Anderson group.[23-25]

Regarding BTKis, subgroup analysis of several studies confirms the high effectiveness of BTKis in M-CLL, mostly in terms of PFS.[16-17,20,26] More mature data was derived from the RESONATE-2 trial for elderly and/or unfit patients in which Ibrutinib was compared to Chlorambucil monotherapy. After a median follow-up of 8 years, PFS at 7 years for M-CLL patients was 68% for Ibrutinib versus 17% for Chlorambucil.[26] The E1912 trial compared the combination of Ibrutinib with Rituximab against FCR for young and fit patients, reporting 5-year PFS rates of 83% for IR vs. 68% for FCR.[27] In the ELEVATE TN trial for elderly and/or unfit patients, the 4-year PFS rates for M-CLL patients were 89%, 81% and 62% for Acalabrutinib plus Obinutuzumab, Acalabrutinib monotherapy and Obinutuzumab plus Chlorambucil respectively; the difference between Acalabrutinib plus Obinutuzumab versus Obinutuzumab plus Chlorambucil was statistically significant ($p=0.0012$).[18]

In the SEQUOIA trial, Zanubrutinib was also particularly effective in M-CLL patients, inducing high PFS rates (median not reached versus 49.9 months for BR, $p<0.00033$).[20] Concerning time-limited approaches, in the CLL14 trial, after a follow-up of 72 months, the median PFS for M-CLL patients was not reached for Ven-Obi whereas it was 62.2 months for Chlorambucil-Obinutuzumab; no OS benefit has been shown yet.[21]

Venetoclax-based combinations were also evaluated in the context of the CLL-13/GAIA trial, which reported that the Ven-Obi combination with or without Ibrutinib was superior to CIT (FCR or BR) in terms of PFS, inducing high rates of undetectable MRD in M-CLL, with 3-year PFS rates of 96%, 93.6%, 87% and 89.9% for Ven-Obi-ibrutinib, Ven-Obi, Ven-Rituximab and CIT respectively[28] In the GLOW trial, the combination of Ibr-Ven led to > 90% 2-year PFS rate for M-CLL patients independent of MRD status.[29]

The role of the FCR regimen for fit M-CLL patients without unfavorable cytogenetic characteristics is questionable for the following reasons:

- Inferior results compared to chemo-free regimens in phase III trials.[27-28]
- The use of FCR is associated with severe complications, including myelosuppression, infections, and secondary malignancies.[30-31]
- Not all M-CLL patients are equivalent, as exemplified by those belonging to stereotyped subset #2 who have a particularly adverse prognosis and respond poorly to CIT, including FCR. Information regarding membership in subset #2 must be provided by the laboratory performing IGHV gene analysis.[11]

*Recommendations for M-CLL patients*

1. Time-limited treatment options with novel agents are the preferred therapy (Ven-Obi, Ibr-Ven)
2. CIT such as FCR should only be considered for fit and younger patients if targeted therapies are not accessible

*Patients with unmutated IGHV (U-CLL) without TP53 aberrations.* Patients with U-CLL experience inferior outcomes with shorter survival rates when treated with CIT [7]. Results from pivotal clinical trials in the first-line comparing BTKis versus chemotherapy or CIT highlighted that BTKis with or without anti-CD20 antibodies are clearly superior in U-CLL.[16-18,20,27] In the RESONATE-2 trial, U-CLL patients treated with Ibrutinib had a PFS of 67% versus 6% for Chlorambucil after 5 years of follow-up.[26] In the ALLIANCE trial, after a median follow-up of 33.6 months in patients with U-CLL, the median PFS was not reached for both the Ibrutinib and Ibrutinib-Rituximab arms, whereas it was only 39 months for the BR arm[16] Likewise, in fit patients within the E1912 trial, the combination of Ibrutinib with Rituximab resulted in a significant PFS advantage in U-CLL patients over FCR (5-year PFS 75% for Ibrutinib vs 33% for FCR).[27]

In the ELEVATE-TN trial, after 7 years of follow-up, the median PFS was not reached for U-CLL patients treated with Acalabrutinib plus Obinutuzumab, whereas it was 22.2 months in Obinutuzumab-Chlorambucil arm.[18]

A treatment benefit was also demonstrated for U-CLL patients treated with Zanubrutinib in the SEQUOIA trial.[20]

Concerning time-limited therapies, in the CLL-14 trial, U-CLL patients had significantly superior PFS when treated with the Ven-Obi combination compared to Chlorambucil-Obinutuzumab.[21] In the GLOW trial, PFS at 3.5 years was higher for U-CLL patients on the Ibr-Ven arm compared to the Chlorambucil-Obinutuzumab arm.[29] In conclusion, there is a clear advantage of novel agents over CIT for U-CLL patients. The final decision

on the treatment choice concerning targeted therapies should depend on patients' profiles and preferences as well as the safety profile of each drug. Regarding the latter, Acalabrutinib and Zanubrutinib have fewer cardiovascular adverse events compared to Ibrutinib. The most common cardiac toxicity associated with BTK inhibitors, particularly with Ibrutinib, is atrial fibrillation, while other types of cardiac events include ventricular arrhythmias, heart failure, and hypertension.[32] BTKis should be avoided in patients with severe cardiac failure (ejection fraction<30%), a family history of sudden cardiac arrest, a past medical history of significant ventricular arrhythmia, and in patients with uncontrolled blood pressure.[32] On the other hand, treatment with Venetoclax requires adequate renal function, and patients with severe renal impairment (creatinine clearance >15 and <30ml/min) should only be considered for Venetoclax if the benefit outweighs the risk.[33] Thus, for patients with high tumor burden and/or chronic renal impairment, BTKis are the preferred option.

*Recommendations:*

1. Targeted therapies are preferred for patients with U-CLL over CIT.
2. Cardiotoxicity is a class effect of BTKis, and alternative treatment options should be considered for patients at increased cardiac risk.
3. Among BTKis, Acalabrutinib and Zanubrutinib show a favorable safety profile compared to Ibrutinib.

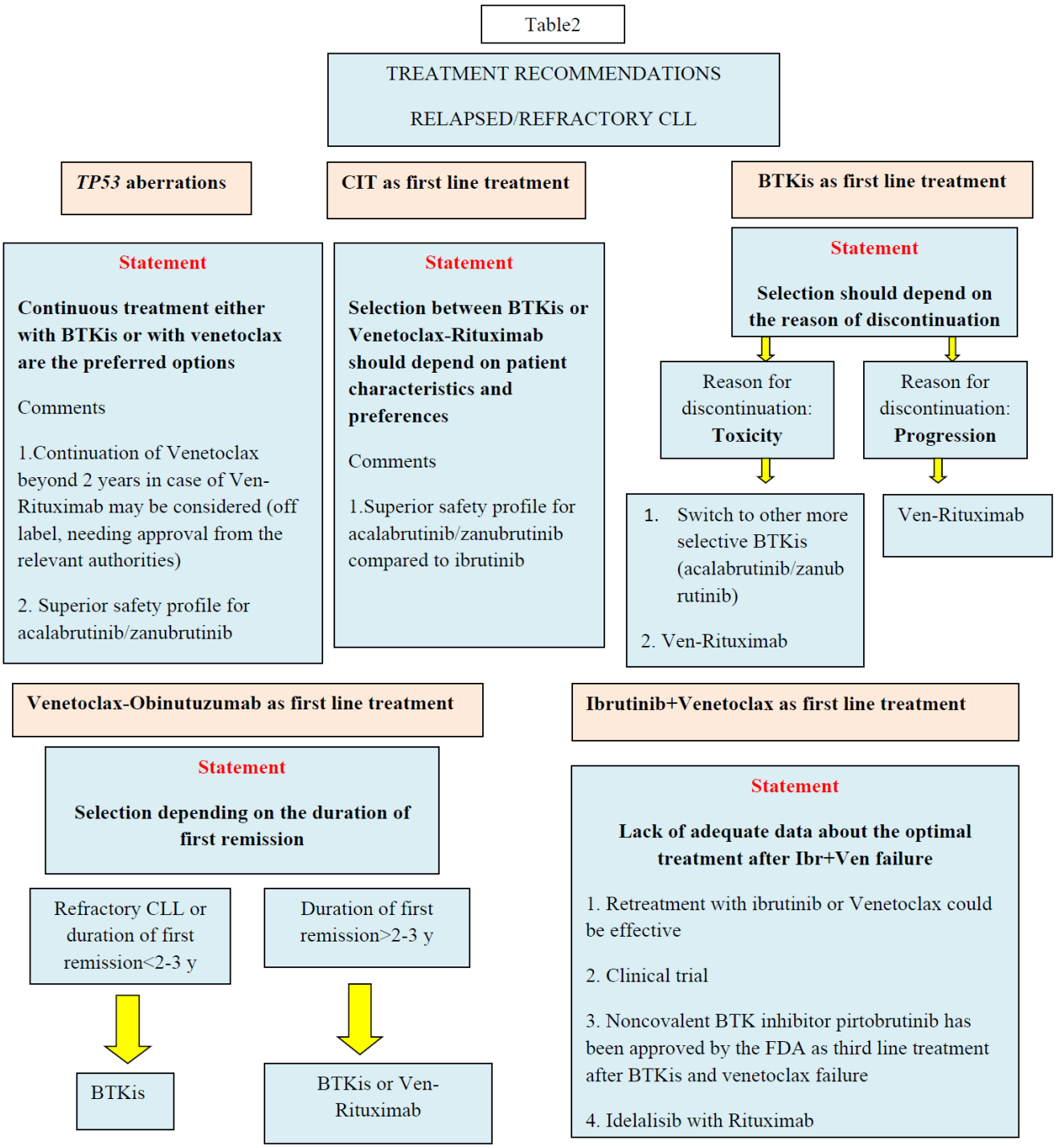
**The role of anti-CD20 in the context of continuous treatment.** No significant difference was seen in terms of PFS between Ibrutinib monotherapy and Ibrutinib - Rituximab in the ALLIANCE trial.[15] In the ELEVATE TN trial, at 6 years of follow-up, PFS was significantly longer in patients treated with Acalabrutinib plus Obinutuzumab versus Acalabrutinib, while median OS was not reached in any treatment arm and was considerably longer in patients treated with Acalabrutinib-Obinutuzumab versus Obinutuzumab-Chlorambucil combination.[18] However, patients in the Acalabrutinib-Obinutuzumab arm experienced more frequently grade ≥3 adverse events, such as neutropenia and thrombocytopenia.[18] Another important issue concerning the addition of Obinutuzumab to Acalabrutinib concerns the increased vulnerability of patients with CLL receiving anti-CD20 antibodies to severe coronavirus disease 2019 (COVID-19) as well as their impaired immune response to vaccination against COVID-19.[34]

**Management of relapsed/refractory CLL (Figure 2).** Crucial issues for deciding on treatment of relapsed/refractory(R/R) CLL are the type of first-line treatment and the duration of response after first-line treatment. *TP53* aberrations remain the most important prognostic factor also in this setting.

There is no role for CIT for patients with R/R CLL as both BTKis and Venetoclax-based regimens proved to be significantly better versus CIT in head-to-head comparisons.[35-39] Regarding continuous treatments, in the RESONATE study, the PFS and OS medians for Ibrutinib were 44 months and 68 months, respectively, compared to 8 and 65 months for Ofatumumab.[35] In the ASCEND trial, 42-month PFS rates were 62% for Acalabrutinib versus 19% for Idelalisib-R and BR, whereas, in the ALPINE study, Zanubrutinib showed a PFS superiority compared to Ibrutinib (12-month PFS rates of 97% vs 93% respectively.[36-38] Regarding time-limited therapies, the phase 3 MURANO trial reported a survival advantage for the combination of Venetoclax plus Rituximab (VR) over BR, with median PFS rates of 53.6 months for VR vs 17 months with BR, and 5-year OS rates of 82% versus 62.2% respectively.[39] Venetoclax monotherapy has also been studied in a phase II study of 158 patients with del(17p), resulting in a median OS of 62 months and a median PFS of 28 months.[40-41] Continuation of Venetoclax beyond 2 years in the case of the VR combination may be considered in patients with *TP53* aberrations.[42]

*Sequence of treatment.* In cases treated with CIT in the first line, the choice of BTKis versus VR critically depends on patient characteristics and preferences. When BTKis are considered, Acalabrutinib or Zanubrutinib are most likely recommended, as they both show similar efficacy and less toxicity compared to ibrutinib.[38,43] In patients exposed to BTKis as first-line, the reason for BTKis discontinuation should be considered.

In case of toxicity, dose reduction or treatment with an alternative, more selective BTK could be an option. In case of disease progression, it is absolutely necessary to provide a different treatment approach, such as the Ven-R.[44] On the other hand, if patients had been exposed to Ven-Obi as first-line therapy, the decision should be made on the basis of the reason for discontinuation and the duration of response after Ven-Obi. In case of unmanageable toxicity related to Venetoclax or disease progression on Venetoclax treatment, covalent BTKis represent the next available treatment option.[44] The decision to re-administer Venetoclax after Ven-Obi depends on the duration of the prior response. Retreatment with a Venetoclax-based regimen could be an option in case the duration of remission is greater than 2-3 years. Patients with shorter remissions are not considered suitable for retreatment and should instead proceed to BTKis.[44] Currently, a new group of patients is emerging, including those who have been exposed upfront to both Ibrutinib and Venetoclax. There are no mature data available to support a specific treatment recommendation for patients who progress after this combination. However, a few patients experiencing




relapse within the CAPTIVATE trial responded to Ibrutinib retreatment.[20-21] Currently, Pirtobrutinib, a noncovalent BTK inhibitor, has been approved by the FDA (12/2023) for patients after 2 lines of treatment, including BTKis and Venetoclax.[45]

In addition, we should also consider the oral first-in-class phosphatidylinositol 3-kinase delta inhibitor idelalisib in combination with Rituximab, which has shown efficacy in heavily pretreated CLL patients.[46]

**Conclusions.** The treatment landscape in CLL has radically changed, and the OS of CLL patients has dramatically improved over the last decade due to the advent of novel agents such as BTK and BCL-2 inhibitors. Among almost equally effective treatment options, the clinician, apart from biological dismal prognostic factors such as TP53 abnormalities and unmutated IGHV status, should also take into account several parameters associated with the patient's characteristics as well as with specific side effects of the different regimens. The most important clinical question on the superiority of continuous over time-limited treatment remains, as we will expect the findings from the CLL17 trial of the German CLL Study Group (NCT04608318), which has been conducted in order to address this question. Additionally, concerns about the

optimal sequencing of therapies or about the treatment alternatives for double refractory patients need to be further investigated.

## References:


1. The Surveillance E, and End Results (SEER) Program of the National Cancer Institute. Cancer Stat Facts: Leukemia-Chronic Lymphocytic Leukemia (CLL). https://seer.cancer.gov/statfacts/html/clyl.html; 2021
2. Hallek M. Chronic lymphocytic leukemia: 2015 update on diagnosis, risk stratification, and treatment. Am J Hematol. 2015;90:446-60. https://doi.org/10.1002/ajh.23979 PMid:25908509
3. Hallek M, Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. Am J Hematol. 2021; 96: 1679-1705. https://doi.org/10.1002/ajh.26367 PMid:34625994
4. Awan FT, al-Sawaf O, Fischer K, Woyach JA. Current perspectives on therapy for chronic lymphocytic leukemia. Am Soc Clin Oncol Educ Book. 2020; 40: 320-329. https://doi.org/10.1200/EDBK_279099 PMid:32239979
5. Zenz T, Eichhorst B, Busch R, Denzel T, Häbe S, Winkler D, Bühler A, Edelmann J, Bergmann M, Hopfinger G, Hensel M, Hallek M, Döhner H, Stilgenbauer S. TP53 mutation and survival in chronic lymphocytic leukemia. J Clin Oncol. 2010;28:4473-4479. https://doi.org/10.1200/JCO.2009.27.8762 PMid:20697090
6. Campo E, Cymbalista F, Ghia P, Jäger U, Pospisilova S, Rosenquist R, Schuh A, Stilgenbauer S. TP53 aberrations in chronic lymphocytic leukemia: an overview of the clinical implications of improved diagnostics. Haematologica 2018; 103: 1956-1968. https://doi.org/10.3324/haematol.2018.187583 PMid:30442727 PMCid:PMC6269313
7. Stilgenbauer S, Schnaiter A, Paschka P, Zenz T, Rossi M, Dohner K, Bühler A , Böttcher S , Ritgen M , Kneba M, Winkler D , Tausch E , Hoth P , Edelmann J , Mertens D , Bullinger L, Bergmann M , Kless S , Mack S, Jäger U , Patten N , Wu L , Wenger MK , Fingerle-Rowson G , Lichter P, Cazzola M , Wendtner CM , Fink AM , Fischer K , Busch R , Hallek M, Döhner H. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood. 2014;123:3247-3254. https://doi.org/10.1182/blood-2014-01-546150 PMid:24652989
8. Malcikova J, Tausch E, Rossi D, Sutton LA, Soussi T, Zenz T, Kater A P, Niemann CU, Gonzalez D, Davi F, Gonzalez Diaz M, Moreno C, Gaidano G, Stamatopoulos K, Rosenquist R, Stilgenbauer S, Ghia P, Pospisilova S. European Research Initiative on Chronic Lymphocytic Leukemia (ERIC) - TP53 network. ERIC recommendations for TP53 mutation analysis in chronic lymphocytic leukemia-update on methodological approaches and results interpretation Leukemia. 2018; 32: 1070-1080. https://doi.org/10.1038/s41375-017-0007-7 PMid:29467486 PMCid:PMC5940638
9. Cramer P, Hallek M. Prognostic factors in chronic lymphocytic leukemia-what do we need to know? Nat Rev Clin Oncol. 2011;8:38-47. https://doi.org/10.1038/nrclinonc.2010.167 PMid:20956983
10. Crombie J, Davids MS. IGHV mutational status testing in chronic lymphocytic leukemia. Am J Hematol 2017; 92: 1393-1397 https://doi.org/10.1002/ajh.24808 PMid:28589701 PMCid:PMC5675754
11. Gerousi M, Laidou S, Gemenetzi K, Stamatopoulos K, Chatzidimitriou A. Distinctive Signaling Profiles With Distinct Biological and Clinical Implications in Aggressive CLL Subsets With Stereotyped B-Cell Receptor Immunoglobulin Front Oncol. 2021;11:771454 https://doi.org/10.3389/fonc.2021.771454 PMid:34804974 PMCid:PMC8595110
12. Baliakas P, Jeromin S, Iskas M, Puiggros A, Plevova K, Nguyen-Khac F, Davis Z , Rigolin GM , Visentin A , Xochelli A, Delgado J, Baran-Marszak F, Stalika E, Abrisqueta P, Durechova K, Papaioannou G, Eclache V, Dimou M, Iliakis T, Collado R, Doubek M, Calasanz MJ, Ruiz-Xiville N, Moreno C, Jarosova M, Leeksma AC, Panayiotidis P, Podgornik H, Cymbalista F, Anagnostopoulos A, Livio Trentin, Stavroyianni N, Davi F, Ghia P, Kater AP, Cuneo A, Pospisilova S, Espinet B, Athanasiadou A, Oscier D, Haferlach C, Stamatopoulos K. Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. Blood. 2019; 133: 1205-1216. https://doi.org/10.1182/blood-2018-09-873083 PMid:30602617 PMCid:PMC6509568
13. Döhner H, Stilgenbauer S, Benner A, Leupolt E, Kröber A, Bullinger L, Döhner K, Bentz M, Lichter P. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343:1910-1916 https://doi.org/10.1056/NEJM200012283432602 PMid:11136261
14. Allan JN, Shanafelt T, Wiestner A, Moreno C, O'Brien SM, Braggio E, Jianling Li, Krigsfeld G , Dean JP, Ahn IE . Long-term efficacy of first-line Ibrutinib treatment for chronic lymphocytic leukemia (CLL) with 4 years of follow-up in patients with TP53 aberrations (del(17p) or TP53 mutation): a pooled analysis from 4 clinical trials. Br J Haematol. 2022 196:947-953. https://doi.org/10.1111/bjh.17984 PMid:34865212 PMCid:PMC9299890
15. Ahn IE, Tian X, Wiestner A. Ibrutinib for chronic lymphocytic leukemia with TP53 alterations. N Engl J Med. 2020; 383: 498-500 https://doi.org/10.1056/NEJMc2005943 PMid:32726539 PMCid:PMC7456330
16. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W Bartlett NL , Brander DM, Barr PM, Rogers KA, Parikh SA, Coutre S, Hurria A, Brown JR, Lozanski G, Blachly JS, Ozer HG, Major-Elechi B, Fruth B, Nattam S, Larson RA, Erba H, Litzow M, Owen C, Kuzma C, Abramson JS, Little RF, Smith SE, Stone RM, Mandrekar SJ, Byrd JC. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. N Engl J Med. 2018; 379: 2517-2528 https://doi.org/10.1056/NEJMoa1812836 PMid:30501481 PMCid:PMC6325637
17. Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, Simkovic M, Samoilova O, Novak J, Ben-Yehuda D, Strugov V, Gill D, Gribben JG, Hsu E, Lih CJ, Zhou C, Clow F, James DF, Styles L, Flinn IW . 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: 43-56. https://doi.org/10.1016/S1470-2045(18)30788-5 PMid:30522969
18. Sharman JP, Egyed M, Jurczak W, Skarbnik A, Patel K, Flinn IW, Kamdar M, Munir T, Walewska R, Hughes M, Fogliatto LM, Herishanu Y, Banerji V, Follows G, Patricia A. Walker, Karlsson K, Ghia P, Janssens A, Cymbalista F, Byrd JC, Ferrant E, Ferrajoli A, Wierda WG, Munugalavadla V, Wachira CW, Wun CC, Woyach JA. Acalabrutinib ± Obinutuzumab Vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of Elevate-TN Blood 2023; 142 (Supplement 1): 636 https://doi.org/10.1182/blood-2023-174750
19. Tam CS, Robak T, Ghia P, Kahl BS, Walker P, Janowski W, Simpson D, Shadman M, Ganly PS, Laurenti L, Opat S, Tani M, Ciepluch H, Verner E, Šimkovič M, Österborg A, Trněný M, Tedeschi A, Paik JC, Kuwahara SB, Feng S, Ramakrishnan V, Cohen A, Huang J, Hillmen P, BrownJR. Zanubrutinib monotherapy for patients with treatment naive chronic lymphocytic leukemia and 17p deletion. Haematologica 2021;106:2354-2363. https://doi.org/10.3324/haematol.2020.259432 PMid:33054121 PMCid:PMC8409041
20. Tam CS, Brown JR, Kahl BS, Ghia P, Giannopoulos K, Jurczak W, Šimkovič M, Shadman M, Österborg A, Laurenti L, Walker P, Opat S, Chan H, Ciepluch H, Greil R, Tani M, Trněný M, Danielle M Brander, Flinn IW, Grosicki S, Verner E, Tedeschi A, Li J, Tian T, Zhou L, Marimpietri C, Paik JC, Cohen A, Huang J, Robak T, Hillmen P. 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: 1031-1043. https://doi.org/10.1016/S1470-2045(22)00293-5 PMid:35810754
21. Al-Sawaf O, Zhang C, Lu T, Michael Z Liao, Panchal A, Robrecht S, Ching T, Tandon M, Anna-Maria Fink, Tausch E, Schneider C, Ritgen M, Böttcher S, Karl-Anton Kreuzer, Chyla B, Miles D, Clemens-Martin

Wendtner, Eichhorst B, Stilgenbauer S, Jiang Y, Hallek M, Fischer K. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off-treatment follow-up from the randomized CLL14 study. J Clin Oncol. 2021; 39: 4049-4060
https://doi.org/10.1200/JCO.21.01181
PMid:34709929 PMCid:PMC8678026

22. Barr PM, Allan JN, Siddiqi T, Wierda WG, Lu Tam CS, Moreno CD, Tedeschi A, Szafer-Glusman E, Zhou C, Abbazio C, Dean JP, Szoke A, Ghia P. Fixed-duration ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): 4-y follow-up from the FD cohort of the phase 2 CAPTIVATE study. J Clin Oncol.Volume 41 Number 16, Suppl 7535
https://doi.org/10.1200/JCO.2023.41.16_suppl.7535
23. Fischer K, Bahlo J, Fink AM, Goede V, Herling CD, Cramer P, Langerbeins P, von Tresckow J, Engelke A, Maurer C, Kovacs G, Herling M, Tausch E, Kreuzer KA, Eichhorst B, Böttcher S, John F Seymour JF, Ghia P, Marlton P, Kneba M, Wendtner CM, Döhner H, Stilgenbauer S, Hallek M. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood. 2016; 127: 208-215
https://doi.org/10.1182/blood-2015-06-651125
PMid:26486789
24. Thompson PA, Tam CS, O'Brien SM, Wierda WG, Stingo F, Plunkett W, Smith SC, Kantarjian HM, Freireich EJ, Keating MJ. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood. 2016; 127: 303-309.
https://doi.org/10.1182/blood-2015-09-667675
PMid:26492934 PMCid:PMC4760129
25. Thompson PA, Tam CS, O'Brien SM, Wierda WG, Stingo F, Plunkett W, Smith SC, Kantarjian HM, Freireich EJ, Keating MJ Fludarabine, cyclophosphamide,and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia.Blood.2016;127:303-309
https://doi.org/10.1182/blood-2015-09-667675
PMid:26492934 PMCid:PMC4760129
26. Barr PM, Owen C, Robak T, Tedeschi A, Bairey O, Burger JA, Hillmen P, Coutre SE, Dearden C, Grosicki S, McCarthy H, Li JY, Offner F, Moreno C, Zhou C, Hsu E, Szoke A, Kipps TJ, Ghia P. Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. Blood Adv. 2022;6:3440-3450
https://doi.org/10.1182/bloodadvances.2021006434
PMid:35377947 PMCid:PMC9198904
27. Shanafelt TD, Wang XV, Hanson CA, Paietta EM, O'Brien S, Barrientos J. Jelinek DF, Braggio E, Leis JF, Zhang CC, Coutre SE, Barr PM, Cashen AF, Mato AR, Singh AK, Mullane MP, Little RF, Erba H, Stone RM, Litzow M, Tallman M, Neil E Kay. Long-term outcomes for ibrutinib-Rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial. Blood. 2022; 140: 112-120
https://doi.org/10.1182/blood.2021014960
PMid:35427411 PMCid:PMC9283968
28. Eichhorst B, Niemann CU, Kater AP, Fürstenau M, von Tresckow J, Zhang C, Robrecht S, Gregor M, Juliusson G, Thornton P, Staber PB, Tadmor T, Lindström V, da Cunha-Bang C, Schneider C, Poulsen CB, Illmer T, Schöttker B, Nösslinger T, Janssens A, Christiansen I, Baumann M, Frederiksen H, van der Klift M, Jäger U, Leys MBL, Hoogendoorn M, Lotfi K, Hebart H, Gaska T, Koene H, Enggaard L, Goede J, Regelink JC, Widmer A, Simon F, De Silva N, Fink AM, Bahlo J, Fischer K, Wendtner CM, Kreuzer KA, Ritgen M, Brüggemann M, Tausch E, Levin MD, van Oers M, Geisler C, Stilgenbauer S, Hallek M; GCLLSG, the HOVON and Nordic CLL Study Groups, the SAKK, the Israeli CLL Association, and Cancer Trials Ireland.First Line Venetoclax Combinations in Chronic Lymphocytic Leukemia.N Engl J Med. 2023;388:1739-1754.
https://doi.org/10.1056/NEJMoa2213093
PMid:37163621
29. Moreno C, Munir T, Owen C, Follows G, Hernandez Rivas JA, Benjamini O, Janssens A, Levin MD, Robak T, Simkovic M, Voloshin S, Vorobyev VI, Yagci M, Ysebaert L, Qi Q, Smith E, Srinivasan S, Schuier N, Baeten K, Caces DB, Niemann CU, Kater AP. First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): 55-Month Follow-up from the Glow Study. Blood. 2023; 142 (Supplement 1): 634.
https://doi.org/10.1182/blood-2023-177713
30. Benjamini O, Jain P, Trinh L, Qiao W, Strom SS, Lerner S, Wang X, Burger J, Ferrajoli A, Kantarjian H, O'Brien S, Wierda W, Estrov Z, Keating M. Second cancers in patients with chronic lymphocytic leukemia who received frontline fludarabine, cyclophosphamide and Rituximab therapy: distribution and clinical outcomes. Leuk Lymphoma. 2015; 56: 1643-1650
https://doi.org/10.3109/10428194.2014.957203
PMid:25308294 PMCid:PMC4437921
31. Kutsch N, Bahlo J, Robrecht S, Franklin J, Zhang C, Maurer C, De Silva N, Lange L, Weide R, Kiehl MG, Sökler M, Schlag R, Vehling-Kaiser U, Köchling G, Plöger C, Gregor M, Plesner T, Herling M, Fischer K, Döhner H, Kneba M, Wendtner CM, Klapper W, Kreuzer KA, Böttcher S, Stilgenbauer S, Fink AM, Hallek M, Eichhorst B. 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:e336.
https://doi.org/10.1097/HS9.0000000000000336
PMid:32072150 PMCid:PMC7000471
32. Awan FT , Addison D, Alfraih F , Baratta SJ , Campos RN , Cugliari MS, Goh YT , Ionin VA , Mundnich S, Sverdlov AL , Tam C, Ysebaert L. International consensus statement on the management of cardiovascular risk of Bruton's tyrosine kinase inhibitors in CLL Blood Adv. 2022 27:6:5516-5525
https://doi.org/10.1182/bloodadvances.2022007938
PMid:35790105 PMCid:PMC9631706
33. Koehler AB, Leung N, Call TG, Rabe KG, Achenbach SJ, Ding W, Kenderian SS, Leis JF, Wang Y, Muchtar E, Hayman SR, Hampel PJ, Finnes HD, Schwager SM, Slager SL, Kay NE, Parikh SA. Incidence and risk of tumor lysis syndrome in patients with relapsed chronic lymphocytic leukemia (CLL) treated with venetoclax in routine clinical practice. Leuk Lymphoma. 2020; 61: 2383-2388
https://doi.org/10.1080/10428194.2020.1768384
PMid:32449401
34. Langerbeins P, Hallek M. COVID-19 in patients with hematologic malignancy.Blood. 2022;140:236-252.
https://doi.org/10.1182/blood.2021012251
PMid:35544585 PMCid:PMC9098396
35. Munir T, Brown JR, O'Brien S, Barrientos JC, Barr PM, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Kipps TJ, Moreno C, Montillo M, Burger JA, Byrd JC, Hillmen P, Dai S, Szoke A, Dean JP, Woyach JA. 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: 1353-1363.
https://doi.org/10.1002/ajh.25638
PMid:31512258 PMCid:PMC6899718
36. Jurczak W, Pluta A, Wach M, Lysak D, Kozak T, Šimkovič M, Kaplan P, Kraychok I, Illes A, de la Serna j, Dolan S, Campbell P, Musuraca G, Jacob A, Avery E, Lee JH, Liang W, Patel P, Quah C, Jurczak W. Three-year follow-up of the ascend trial: acalabrutinib vs Rituximab plus idelalisib or bendamustine in relapsed/refractory chronic lymphocytic leukemia. Blood. 2021; 138:393.
https://doi.org/10.1182/blood-2021-146570
37. Ghia P, Pluta A, Wach M, Lysak D, Kozak T, Simkovic M, Kaplan P, Kraychok I, Illes A, de la Serna J, Dolan S, Campbell P, Musuraca G, Jacob A, Avery E, Lee JH, Liang W, Patel P, Quah C, Jurczak W W. 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: 2849-2861.
https://doi.org/10.1200/JCO.19.03355
PMid:32459600
38. Hillmen P, Eichhorst B, Brown JR, Lamanna N, O'Brien SM, Tam CS, Qiu L, Kazmierczak M, Zhou K, Šimkovič M, Mayer J, Gillespie-Twardy A, Shadman M, Ferrajoli A, Ganly PS, Weinkove R, Grosicki S, Mital A, Robak T, Österborg A, Yimer HA, Salmi T, Ji M, Yecies J, Idoine A, Wu K, Huang J, Jurczak W. Zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma: interim analysis of a randomized phase III. J Clin Oncol 2023; 41: 1035-1045.
https://doi.org/10.1200/JCO.22.00510
PMid:36395435 PMCid:PMC9928683
39. Seymour JF, Kipps TJ, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, Owen C, Gerecitano J, Robak T, De la Serna J, Jaeger U, Cartron G, Montillo M, Humerickhouse R, Punnoose EA, Li Y, Boyer M, Humphrey K, Mobasher M, Kater AP. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med. 2018;378:1107-20.
https://doi.org/10.1056/NEJMoa1713976
PMid:29562156
40. Stilgenbauer S, Eichhorst B, Schetelig J, Hillmen P, Seymour JF, Coutre S, Jurczak W , Mulligan SP, Schuh A, Assouline S, Wendtner CM, Roberts AW, Davids MS, Bloehdorn J, Munir T, Böttcher S, Zhou L, Salem AH, Desai M, Chyla B, Arzt J , Kim SY, Verdugo M, Gordon G,

Hallek M , Wierda WG . 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: 1973-1980.
https://doi.org/10.1200/JCO.2017.76.6840
PMid:29715056

41. Stilgenbauer S, Tausch E, Roberts AW, Davids MS, Eichhorst B, Hallek M, Hillmen P , Schneider C , Schetelig J , Böttcher S , Kater AP , Jiang Y , Boyer M , Popovic R, Ghanim MT , Moran M , Sinai WJ , Wang X , Mukherjee N , Chyla B , Wierda WG , Seymour JF . Six-year follow-up and subgroup analyses of a phase 2 trial of venetoclax for del(17p) chronic lymphocytic leukemia Blood Adv.2024;8:1992-2004
https://doi.org/10.1182/bloodadvances.2023011741
PMid:38290108 PMCid:PMC11024923
42. Hampel PJ, Parikh SA. Chronic lymphocytic leukemia treatment algorithm Blood Cancer J. 2022.; 12:161.
https://doi.org/10.1038/s41408-022-00775-6
PMid:36543762 PMCid:PMC9772411
43. Byrd JC, Hillmen P, Ghia P, Kater AP , Chanan-Khan A , Furman RR , O'Brien S , Yenerel MN , Illés A , Garcia-Marco NK , Mato A, Pinilla-Ibarz J, Seymour JF , Lepretre S , Stilgenbauer S , Robak T , Rothbaum W , Izumi R , Hamdy A , Patel P, Higgins K, Sohoni S, Jurczak W . Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. J Clin Oncol. 2021; 39: 3441-3452.
https://doi.org/10.1200/JCO.21.01210
PMid:34310172 PMCid:PMC8547923
44. Eichhorst B , Ghia P , Niemann CU , Kater AP , M Gregor M , Hallek M, Jerkeman M, C Buske C. ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia .Ann Oncol.2024;35:762-768.
https://doi.org/10.1016/j.annonc.2024.06.016
PMid:38969011
45. Mato AR, Shah NN, Jurczak W, Cheah CY, Pagel JM, Woyach JA, Fakhri B, Eyre TA, Lamanna N, Patel MR, Alencar A, Lech-Maranda E, Wierda WG, Coombs CC, Gerson JN, Ghia P, Le Gouill S, Lewis DJ, Sundaram S, Cohen JB, Flinn IW, Tam CS, Barve MA, Kuss B, Taylor J, Abdel-Wahab O, Schuster SJ, Palomba ML, Lewis KL, Roeker LE, Davids MS, Tan XN, Fenske TS, Wallin J, Tsai DE, Ku NC, Zhu E, Chen J, Yin M, Nair B, Ebata K, Marella N, Brown JR, Wang M. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021;397:892-901.
https://doi.org/10.1016/S0140-6736(21)00224-5
PMid:33676628
46. Furman RR, Sharman JP , Coutre SE , Cheson BD, Pagel JM, Hillmen P , Barrientos JC , Zelenetz AD , Kipps TJ , Flinn I , Ghia P , Eradat H , Ervin T , Lamanna N , Coiffier B , Pettitt AR, Ma S , Stilgenbauer S , Cramer P , Aiello M , Johnson DM , Miller LL , Li D , Jahn TM , Dansey RD , Hallek M , O'Brien SM. Idelalisib and Rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014 13;370:997-1007
https://doi.org/10.1056/NEJMoa1315226
PMid:24450857 PMCid:PMC4161365