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Original Article

Greek Consensus on Chronic Lymphocytic Leukemia (CLL) Treatment

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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.

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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.

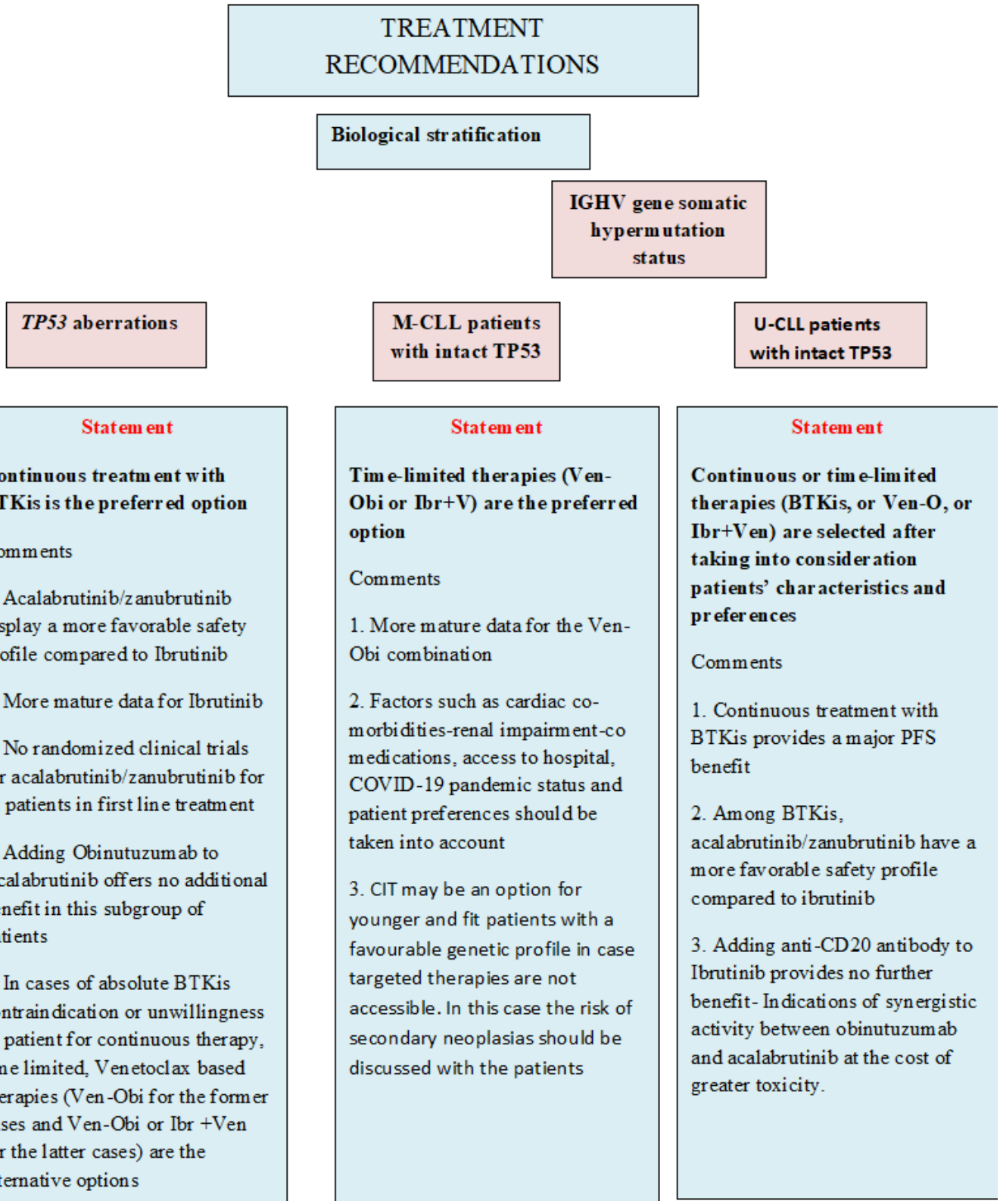
*CLL patients with TP53 aberrations (**Figure 1**).* The detection of del(17p) and *TP53* mutations in patients with no evidence of active disease is not per se a criterion for starting therapy.[3]

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]

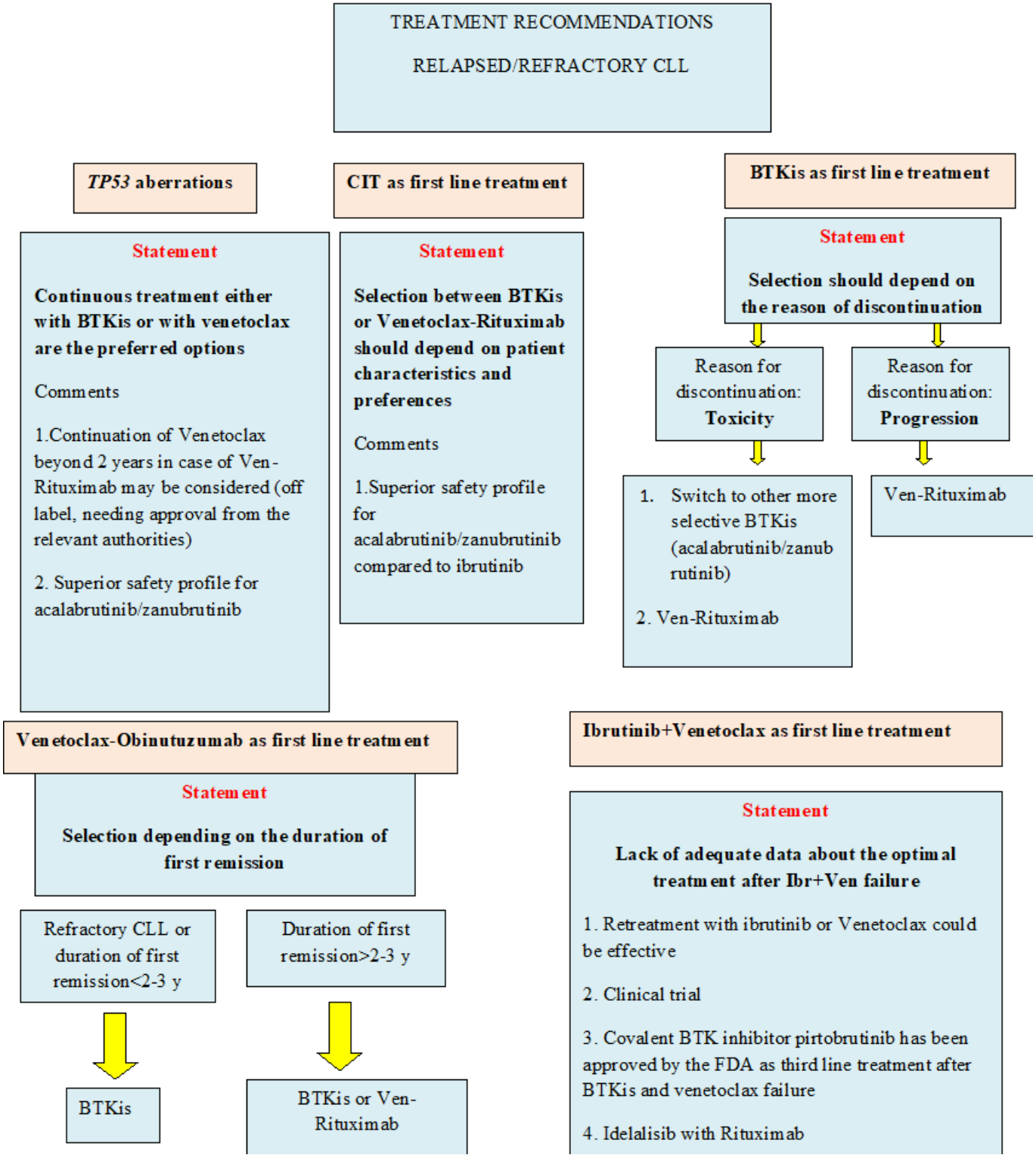
Management of relapsed/refractory CLL (Figure 2). Crucial issues for deciding on treatment of relapsed/refractory(R/R) CLL are the type of first-line treatment and the duration of response after first-line treatment. *TP53* aberrations remain the most important prognostic factor also in this setting.

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

Figure 2



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.

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