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REVIEW ARTICLE

Chronic lymphocytic leukemia following venetoclax treatment failure

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Abstract

Venetoclax (ABT-199) is a highly selective and potent inhibitor of BCL-2, capable of inducing deep remission in chronic lymphocytic leukemia (CLL). The introduction of this compound to the treatment armamentarium of CLL represented a real breakthrough, as the drug is effective in high-risk CLL patients and in the setting of Bruton's tyrosine kinase inhibitors (BTKi) failure. Nevertheless, treatment failure or progression following venetoclax treatment occurs over time. Potential mechanisms of refractoriness, including BCL-2 mutations or activation of alternative anti-apoptotic pathways, have been identified. So far, questions regarding patient management after venetoclax and venetoclax-based regimen failure have yet to be answered, and only a few studies have addressed this problem. With increasing use of venetoclax-based treatment, the optimal sequencing and the most suitable next line treatment should be addressed in upcoming guidelines. In this review, we summarize the possible mechanism of resistance to venetoclax, and explore possible therapeutic options in cases of venetoclax failure.

Key words: chronic lymphocytic leukemia, immunochemotherapy, ibrutinib, venetoclax, resistance

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Introduction

Chronic lymphocytic leukemia (CLL) is an incurable clonal proliferation of CD5/CD19 lymphocytes accumulating in the blood, bone marrow, and lymphoid tissues [1]. It is the most commonly diagnosed leukemia, with an annual age-adjusted incidence of 3–5 per 100,000 persons. It is mostly encountered in older people, with a median age at diagnosis of 72 years [1, 2]. In the last decade, new treatment options have emerged, of which the most notable have been Bruton's tyrosine kinase (BTK) inhibitors (ibrutinib and acalabrutinib), selective phosphatidylinositol-3-kinase (PI3K) inhibitors (idelalisib and duvelisib), the Bcl-2 antagonist venetoclax, and the new anti-CD20 antibodies (obinutuzumab) [1, 3]. Ibrutinib and idelalisib combined with rituximab have shown remarkable efficacy in high-risk patients with defects in the p53 pathway (deletion 17p13 and/or *TP53* mutation) [4–6]. Despite treatment with these agents, clonal evolution with the selection of resistant clones can lead to therapy failure with possibly rapid progression [6–11]. Venetoclax was hailed as a breakthrough in CLL therapy due to the high activity of this small molecule in high-risk CLL patients, as well as in the setting of therapy failure with BTK and PI3K inhibitors [12–22]. Venetoclax is an attractive therapy option in treatment-naïve as well as relapse and refractory settings when combined with anti-CD20 antibodies due to its highly effective, predictable adverse event profile, and the possibility of a time limited therapy as opposed to BTK and PI3K inhibitors [23, 24]. With a broad range of venetoclax use in CLL patients, the development of treatment strategies in case of its failure as therapy is of the utmost importance. In this review, we summarize the current efficacy of venetoclax in CLL and potential future directions in this clinical setting.

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Venetoclax mechanism of action and clinical efficacy

Proteins of the B-cell lymphoma 2 (BCL-2) are capable of regulating the intrinsic apoptosis pathway and, depending on the protein type, may act as proapoptotic or antiapoptotic factors. In normal, stable conditions the impact of both types of proteins is in balance. However, in stress conditions, the balance may be shifted towards the initiation of the apoptotic program [25]. The BCL-2 family of proteins is characterized by the presence of B-cell homology domain (BH) in all of its members. The antiapoptotic members include BCL-2, BCL-X_L, MCL-1, BCL-W, and BFL-1/A1 which poses four BH domains (BH1-4). The proapoptotic members include BAD, BIK, NOXA, HRK, PUMA, BMF, BID, and BIM which are bound to be the antiapoptotic BCL-2 subfamily members (including BCL-2). Once the proapoptotic members are unbound from the antiapoptotic members, they activate the proapoptotic effectors BAK and BAX, which due to allosteric structural changes form hetero- and homodimeric channels leading to mitochondrial outer membrane permeabilization (MOMP), cytochrome C release, and eventually caspase cascade activation [25–27].

BCL-2 is overexpressed in c. 95% of CLL cells. Interestingly, the proportion is higher in lymph node-derived cells than in ones isolated from peripheral blood [28, 29]. In parallel, CLL cells overexpress the proapoptotic BIM protein, which is bound by overexpressed BCL-2. However, such balance renders clonal lymphocytes prone to apoptosis [26, 27]. The use of anti-BCL-2 compounds such as venetoclax shifts the balance towards apoptosis via the activation of the intrinsic apoptosis pathway independently of the p53 pathway status [30, 31].

Venetoclax (ABT-199) is a highly selective and potent inhibitor of BCL-2, capable of neutralizing the antiapoptotic effect in subnanomolar concentrations [32]. Early phase as well as phase III clinical trials have shown that venetoclax can achieve fast, deep, and durable remissions in both treatment-naïve (TN) and relapse and refractory (RR) CLL cases. Its combination with anti-CD20 antibodies has established its importance in international guidelines [1, 33, 34]. A recent metanalysis of 14 clinical trials and real-life observations in RR-CLL showed a pooled overall response rate (ORR) of 82% [95% confidence interval (CI) 77–87%] for venetoclax monotherapy, 89% (95% CI 83–94%) for a combination of venetoclax and anti-CD20 antibody, and 86% (95%CI 78–92%) for a venetoclax-ibrutinib combination [35]. The recently published results of the phase III CLL14 trial showed that a 1-year fixed duration of venetoclax and obinutuzumab (Ven-Obi) treatment of TN-CLL led to an ORR of 86% in patients with coexisting comorbidities [36]. The Ven-Obi protocol showed achievement of durable remissions and at a median follow-up of 52.4 months the median progression-free survival (PFS) was not reached and the estimated 4-year PFS rate was 74.0%. Nevertheless, the analysis of minimal residual disease (MRD) dynamics indicates that disease progression is inevitable over time [37].

Resistance to venetoclax therapy

Data from clinical trials and real-world observations show that venetoclax discontinuation is attributable in most cases to disease progression, while discontinuation due to adverse events is rare [13–18, 21, 36–41]. The retrospective analyses identified that heavy (more than three lines of therapy) pretreatment, previous therapy with BTK inhibitor, fludarabine resistance, bulky disease, complex karyotype, 17p deletion, mutations of *TP53, SF3B1 NOTCH1*, and unmutated *IGHV* status were associated with shorter responses [41–43]. So far, several mechanisms of venetoclax resistance have been identified, although the mutation of target protein and activation of alternative anti-apoptotic or survival pathways seem to be the most important.

Mutation in the binding site of the BH3 grove of BCL-2 protein has been shown to diminish venetoclax binding affinity. Analysis of paired samples before venetoclax initiation and at disease progression in 15 CLL cases identified the presence of *BCL2*p.Gly101Val mutation in seven patients [44]. The mutation was firstly detectable after 19 to 42 months of therapy, but was not present in the pretreatment samples. Its emergence anticipated clinical disease progression by several months, and in the analyzed samples the median time to disease progression was 36 months. Gly101Val mutation reduces the affinity of BCL2 for venetoclax by approximately 180-fold, and prevents the drug from displacing proapoptotic mediators from BCL-2 in CLL cells stopping the apoptosis [44]. Additional mutations in residues 103, 104, 107–110, 113 and 129 of *BCL2* have been detected in patients resistant to venetoclax [45, 46].

The activation of alternative pathways and kinases such as BTK, PI3K, spleen tyrosine kinase (SYK), or B-Raf protooncogene (BRAF) may foster activation of alternative anti-apoptotic signaling independently of BCL-2, shifting the balance by upregulating other anti-apoptotic BCL-2 family members such as MCL-1 and BCL-XL [47–51]. Amplification of CD274 (PD-L1), loss of CDKN2A/B, and/or mutation in *BTG1* have also been observed in patients refractory to venetoclax [51]. In addition, amplification of 1q also confers venetoclax resistance by upregulating MCL-1 expression [49].

The accumulated data indicates that the proper identification of a potential resistance mechanism is important in order to tailor treatment at disease progression under venetoclax treatment.

Efficacy of treatment regimens following venetoclax failure

Questions regarding patient management after venetoclax and venetoclax-based regimen failure have not yet been answered, and only a few studies have addressed this problem (Table I). Treatment of CLL relapse after venetoclax therapy remains to be determined [43, 52].

Immunochemotherapy

Only limited data concerns the use of immunochemotherapy after venetoclax treatment. In one of the first reports of the clinicopathological features and outcomes of patients with CLL progression during venetoclax treatment, only 1 of 8 patients received FCR (fludarabine, cyclophosphamide, rituximab) immunochemotherapy after post-venetoclax relapse, and the response to the treatment is unknown [41]. In their retrospective analysis, Mato et al. [43] identified 41 CLL patients who discontinued venetoclax, just over half, 21 of them, because of disease progression. Three patients treated with anthracycline-based regimens were described, however none of them responded [43]. In the updated analysis of the MURANO trial, 15 patients received immunochemotherapy after a venetoclax-rituximab regimen, although the outcomes of these patients were not presented [53, 54].

The use of anti-CD20 monoclonal antibody monotherapy after venetoclax discontinuation has been mentioned in only one study concerning 19 patients. However, the regimen did not result in durable remissions following venetoclax, with an ORR of 32% and a median PFS of only two months [55].

Novel drugs

While there is reassuring information on venetoclax treatment after BCR inhibitors therapy failure, data regarding the efficacy of BCR inhibitors in the treatment of patients who relapsed after receiving venetoclax is scarce [15, 19, 52, 56, 57]. Several reports have pointed to a response to ibrutinib following venetoclax discontinuation in previously ibrutinib-naïve patients, although the data is limited in terms of patient numbers and follow-up [52]. These were five studies with six, 11, five, 27 and 23 patients [43, 52, 57–59].

One of the first studies of venetoclax-treated patients from early clinical trials reported that 6 of 8 patients with progressive CLL received ibrutinib after venetoclax, and five had a partial remission (PR) [41]. Another retrospective report showed 10 of 11 patients achieved PR under ibrutinib therapy after venetoclax [58]. In the previously mentioned study by Mato et al. [43], 23 patients required therapy after progression following venetoclax treatment. Of them, 20.8% received ibrutinib; however, responses were not satisfying (one patient achieved PR, whereas two had stable disease [SD] and one progressive disease [PD]) [43]. In addition, an analysis of 27 ibrutinib-naïve patients [one patient received another Bruton's tyrosine kinase inhibitors (BTKi)] with progression after venetoclax reported 56.0% ORR to ibrutinib (of the 25 response-evaluable patients, 13 had PR and one achieved CR). Time to progression on ibrutinib ranged from 3 to 53 months, and the median duration of ibrutinib therapy was 18.3 months [60]. In the analysis by Lin et al. [59], BTKi therapy was shown to achieve durable disease control after progression on venetoclax and clinical efficacy for patients with acquired resistance to venetoclax. Among the analyzed group, 23 patients received BTKi and 20 patients had a response (90% ORR), with 16 PR or PR with lymphocytosis (PR-L) and four achieved CR. Median PFS after BTKi initiation was 34 months. Moreover, ≥24 months remission during venetoclax or deep responses (CR or undetectable MRD) during venetoclax therapy were associated with longer PFS after initiation of a BTKi. It is worth mentioning that 8 of 19 tested patients had a BCL2 Gly101Val mutation. At a median follow-up of 33 months, the median PFS while receiving a BTKi had not been reached for these eight patients, suggesting that BTKi is a possible therapeutic modality in such patients [59].

The analysis of the MURANO trial reported follow-up data on 18 patients who received ibrutinib when relapsed after a venetoclax-rituximab combination. The ORR was 100% (7.1% achieved CR, 92.9% PR) [53, 54].

Subsequently, a multicenter retrospective cohort study identified 326 patients who discontinued venetoclax and required treatment. Of the 74 patients treated with BTKi, 44 were BTKi naïve and 30 were previously BTKi-exposed. They received ibrutinib or acalabrutinib, or a noncovalently binding BTKi monotherapy within a clinical trial. The ORR was 84% (9% CR) in the BTKi-naïve patients with a median PFS of 32 months. This was significantly higher compared to outcomes of previously BTKi-exposed pre-venetoclax patients (53.4% ORR, 10% CR, median PFS 12 months) [55]. In the same study, 17 patients received PI3Ki (idelalisib or duvelisib). All of the patients were previously exposed to PI3Ki and BTKi before venetoclax. The ORR was 46.9% (5.9% CR), but the responses were not durable, with a median PFS of only five months [55].

As venetoclax treatment after BCR inhibitors therapy failure is proven to be effective, it is necessary not to forget about the small group of patients who progress on venetoclax, but are ibrutinib- (and other covalent BTKis) resistant [15, 19, 52, 61]. PI3Kis would be the most available next treatment for that group, but the responses are typically short-lived [19, 55]. Resistance to ibrutinib is mostly the result of acquired cysteine-to-serine mutation in BTK [62, 63]. Reversible, noncovalent BTKis, with activity against Cys481-mutated BTK, may overcome BTKi resistance [22]. Although trials of noncovalent BTKis are ongoing and in early phases, preliminary data suggests that these agents have clinical activity in heavily pretreated patients [64–66]. A promising new agent is LOXO-305 (pirtobrutinib). In

Table I. Summary of selected studies assessing subsequent therapies following venetoclax failure

Author	Study	Number of patients	ORR (with CR)	Median PFS (months)	Median OS (months)	Comments
Mato et al. [43]	Retrospective study	Anthracycline-based immunochemotherapy — 3	ORR 0.0% (CR 0.0%)	NA	NA	Short observation time with a median follow-up of 7 months
		Rituximab monotherapy — 3	ORR 66.7% (CR 0.0%)			
		Ibrutinib — 5	ORR 20.0% (CR 0.0%)			
		Idelalisib — 2	ORR 50.0% (CR 50.0%)			
		CAR-T — 2	No assessment			
		allo-HCT — 3	ORR 66.7% (CR 66.7%)			
Anderson et al. [41]	Retrospective study	Immunochemotherapy — 1	Unknown response	NA	NA	
		Ibrutinib — 6	ORR 83.3% (CR 0.0%)			
Harrup et al. [54]	Retrospective study	Immunochemotherapy — 15	Unknown response	NA	NA	Patients treated earlier within phase III MURANO trial
		BTKi — 18	ORR 100.0% (CR 7.1%)			
		Retreatment with venetoclax — 32	ORR 72.2% (CR 5.6%)			
Mato et al. [55]	Retrospective study	BTKI: ibrutinib, acalabrutinib (BTKi-naïve) — 44	ORR 83.9% (CR 9.0%)	32	NA	With a median follow-up of 7.7 months (1–48 months) for patients treated with BTKi post-venetoclax, estimated median PFS to post-venetoclax BTKi was 32 months in BTKi--naive patients, not reached in BTKi-intolerant patients, but was only 4 months in patients who were known to be BTKi resistant
		BTKi: ibrutinib, acalabrutinib, noncovalent BTKi (BTKi-exposed) — 30	ORR 53.4% CR 10.0%)	12	NA	
		PI3Ki — 17	ORR 46.9% (CR 5.9%)	5 9	NA NA	
		CAR-T — 18	ORR 66.6% (CR 33.3%)	2	NA	
		Anti-CD20 — 19	ORR 32.0% (CR 16.0%)			
Brown et al. [58]	Retrospective study	Ibrutinib — 11	ORR 90.9% (CR 0.0%)	NA	NA	Time on ibrutinib therapy ranged from 0.5 to 30 months, with only three patients having discontinued

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Table I (cont.). Summary of selected studies assessing subsequent therapies following venetoclax failure

Author	Study	Number of patients	ORR (with CR)	Median PFS (months)	Median OS (months)	Comments
Brown et al. [60]	Retrospective study	Ibrutinib — 27	ORR 56.0% (CR 4.0%)	NA	NA	Ibrutinib-naïve patients progressing after venetoclax ORRs were 1/25 CR, 13/25 PR. Time to progression on ibrutinib ranged from 3.0 to 53.0 months (n = 10). Median duration of ibrutinib therapy was 18.3 (3.7–53.2) months, and 20.0 (4.9–44.3) months for those remaining on ibrutinib (8/27)
Lin et al. [59]	Retrospective study	BTKi: ibrutinib — 21, zanubrutinib — 2	ORR 90.0% (CR 13.0%)	34	42	
Mato et al. [67]	Phase 1/2 study	LOXO-305 — 121	ORR 62.0% (CR 0.0%)	NA	NA	

allo-HCT — allogeneic hematopoietic cell transplantation; BTKi — Bruton's tyrosine kinase inhibitor; CAR-T — chimeric antigen receptor t-cell; CR — complete remission; NA — not reached; ORR — overall response rate; PFS — progression-free survival; PI3Ki — phosphoinositide 3-kinase inhibitor; PR — partial remission

a I/II study, the ORR in patients with relapsed and refractory CLL was 63% and the response rates were consistent in subgroups previously receiving BTKis, venetoclax, or both drugs [67]. Other noncovalent BTKis, including GDC-0853, ARQ-531, and vecabrutinib, also have activity independent of Cys481-mutated *BTK*, but only limited clinical data is currently available [22, 66, 68, 69].

Allogeneic stem cell transplantation and CAR T-cell therapy

Little is known about the outcomes of allogeneic stem cell transplantation (allo-HCT) in CLL at the time of novel drugs. The number of allo-HCTs performed for CLL has steadily declined, with a 58% decrease in the number of allo-HCTs performed from 2010 to 2018 in the USA [70]. Roeker et al. published an analysis of 65 patients with CLL undergoing allo-HCT after being treated with one or more of the new agents. The PFS and OS were 60% and 82% at 24 months, respectively. Before allo-HCT, patients had received a median of three lines of therapy and one of the selective agents. The three most common new drugs used in any line of therapy prior to allo-HCT were ibrutinib (82%), venetoclax (40%), and idelalisib (20%), while 26% had received both ibrutinib and venetoclax. Only 18 patients were 'chemotherapy-free', receiving exclusively novel drugs before allo-HCT. No significant differences in PFS and OS were shown between patients receiving only/exclusively novel agents. Notably, the groups that received ibrutinib (as opposed to venetoclax) as their line of therapy directly preceding allo-HCT were examined in order to explore the optimal bridging strategy to transplantation. No significant differences in PFS or OS were observed between these groups; however, the 12-month relapse incidence was 20% for ibrutinib-bridged patients vs. 9% for venetoclax-bridged patients [71].

CAR T-cells are also a promising therapeutic approach in CLL in the setting of venetoclax failure. In the largest multicenter study to assess the efficacy of different post-venetoclax therapies, 18 patients received CD19 directed CAR-T therapy resulting in a 66.6% ORR (33.3% CR) with a median PFS of nine months [19]. A phase I/II study in relapsed and refractory CLL patients treated with the anti-CD19–directed CAR T-cell product (TRANSCEND-CLL-004) included 15 patients refractory to BTKi and venetoclax. Eight of these patients had ongoing responses (6 CR and 2 PR) [72]. Additionally, Gauthier et al. [73] presented a study of 19 CLL patients treated with CD19-targeted CAR T-cells with concurrent ibrutinib after ibrutinib failure. The data included 11 patients with previous venetoclax treatment (six had progression during treatment). The outcomes of patients treated with venetoclax were not reported separately. However, the 1-year PFS of 59% suggests that ibrutinib in combination with anti-CD19–directed CAR T-cell therapy could be a promising strategy in the future [57, 73].

Re-treatment with venetoclax

In CLL patients treated with immunochemotherapy, re-treatment with the same regimen should be considered in cases of durable remission and absence of del17p and *TP53* mutations [33]. Similarly, there is still a key unanswered clinical question as to whether re-treatment with venetoclax should be considered. In the original phase Ib study evaluating venetoclax and rituximab, 18 patients

stopped venetoclax in deep response and four patients had progressive disease. They were re-treated with venetoclax and all responded, with second remissions ranging from 19 to over 40 months [18, 74].

In the MURANO update, there were 32 response-evaluable patients treated with venetoclax and rituximab. They were subsequently treated with venetoclax or venetoclax-based regimens. The ORR to retreatment was 72%, with 50% of patients remaining on therapy after a median observation time of 11 months. Compared to the patients who received BTKi for progression after venetoclax-rituximab combination, the ORR was 100%, with 71% of patients continuing therapy at a median observation time of 22 months [53, 54, 75].

Richter transformation during venetoclax therapy

The true Richter transformation (RT) is a recognized manifestation of CLL clonal evolution and typically occurs early in venetoclax therapy (median 7.9 months), particularly among heavily pretreated patients with refractoriness to fludarabine or with complex karyotype [41]. In the study by Anderson et al., in a group of 25 patients with progression on venetoclax, 14 patients developed Richter transformation to diffuse large B-cell lymphoma (DLBCL) and three patients to Hodgkin lymphoma. RT treatments were varied and included high-dose chemotherapy in six cases followed by autologous stem cell transplantation (auto-HCT), allo-HCT, or radiotherapy as a part of a proven treatment procedure [76]. The responses to salvage therapies were 31% CR, and 19% PR; 50% had no response [41]. Patients with Hodgkin lymphoma RT represented a prognostically favorable subgroup (CR 100%) as similarly observed when RT does not emerge on venetoclax [41, 77]. In contrast, DLBCL RT is often associated with dismal outcomes [78]. However, some patients with DLBCL RT emerging on venetoclax can achieve durable responses to salvage therapy. In the described group, three patients who responded to chemotherapy subsequently progressed with CLL and then received BTKi therapy, leading to prolonged survival (with PFS up to 45 months) [41].

BTKi or immune-checkpoint inhibitor monotherapy have achieved modest ORRs in small cohorts of RT patients, but CRs are infrequent and survival is poor [75, 78]. In a phase I/II study of acalabrutinib monotherapy in RT, ORR was 40%, including CR in two (8%) and PR in eight (32%) patients with a median PFS of 3.2 months [79]. In a phase II trial of 23 patients with RT, the combination of nivolumab and ibrutinib achieved an ORR of 43%, although the median remission duration was short (9.3 months) [80]. However, in neither study was the group of RT after venetoclax separately assessed.

Finally, the preliminary results for CAR T-cells therapy for patients with RT after targeted agents are promising [75]. In the study by Benjamini et al. [81], out of eight patients, five received venetoclax as the last CLL treatment before the transformation. After CD19-targeted CAR T-cells therapy, 71% of patients achieved CR [81].

Treatment standard and future perspectives

To date, little data has been published regarding the optimal therapy following venetoclax failure. This clinical issue should be addressed promptly to help find the proper treatment. In the setting of disease progression following venetoclax exposure, several factors should be considered before planning the next therapy i.e. time-limited or continous venetoclax therapy, duration of remission after venetoclax therapy, prior exposure to BTKi, and mechanism of resistance to BTKi or BCL-2 antagonist therapy (Figure 1).

Taking into account the current scarce data, it seems the most plausible to qualify patients to BTK-based next line therapy, especially BTKi-naïve patients. In cases of long-lasting remissions following venetoclax-based therapy, retreatment with the agent is also a suitable option, although there is no strict definition of a long-lasting remission in this treatment scenario. The open question remains whether in the case of repeated venetoclax therapy additional *BCL2* mutation testing before treatment initiation should be performed.

It seems that patients with venetoclax failure and prior resistance to BTKi treatment pose the most difficult clinical pchallenge. In this group, the initiation of another BTKi or a PI3Ki will result in only time-limited responses, while the effects of immunochemotherapy will probably be unsatisfactory. The combination of novel agents with CD20 antibodies is an interesting option in such patients however, and cellular-based therapies (CAR T-cells and allo-HCT) should be strongly considered.

In the case of RT under venetoclax therapy, there have been no specific guidelines published, and such cases should be treated depending on the type of histological transformation and the patient's comorbid status.

Conclusions

The increasing use of venetoclax in CLL treatment and possible therapy-related failures may pose a significant clinical problem in the future. So far, no specific guidelines for this clinical setting have been published. However, an individually tailored treatment approach, based on previous types of therapies and patient comorbidities, seems the most reasonable method of choosing the next line of treatment.

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Authors' contributions

Both authors wrote and revised the manuscript.

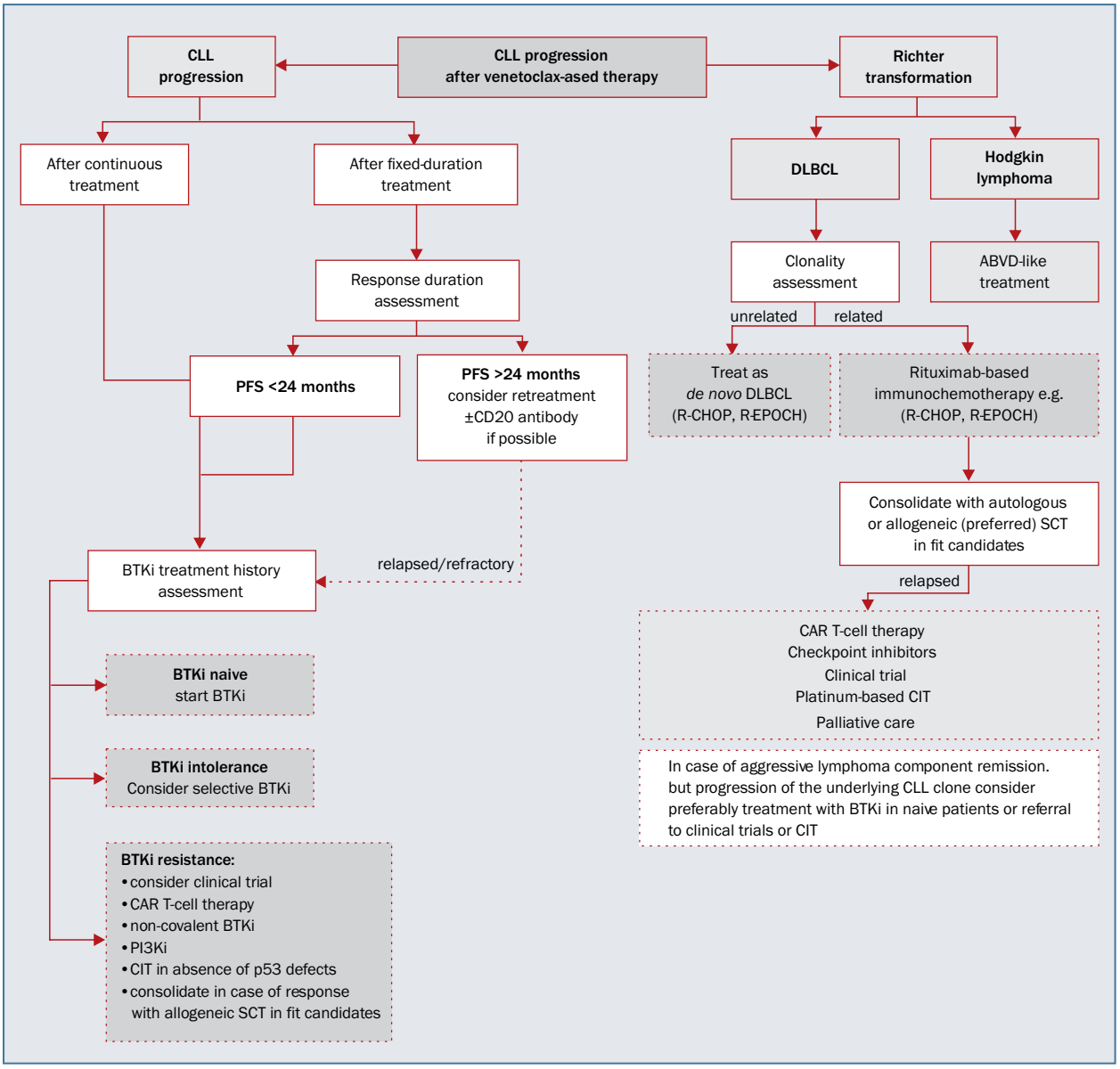

Figure 1. Proposed treatment algorithm in patients with chronic lymphocytic leukemia (CLL) following venetoclax treatment failure; ABVD — adriamycin, bleomycin, vinblastine, dacarbazine; BTKi — Bruton's tyrosine kinase inhibitors; CAR — chimeric antigen receptor; CIT — chemoimmunotherapy; DLBCL — diffuse large B-cell lymphoma; PFS — progression-free survival; PI3Ki — phosphatidylinositol-3-kinase inhibitor; R-EPOCH — rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; SCT — stem cell transplantation

Conflict of interest

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to Biomedical journals.

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