Curr. Treat. Options in Oncol. (2020) 21: 24
DOI 10.1007/s11864-020-0715-5

Leukemia (PH Wiernik, Section Editor)

# Novel Therapies in Chronic Lymphocytic Leukemia: A Rapidly Changing Landscape

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Published online: 13 March 2020


This article is part of the Topical Collection on *Leukemia*

**Keywords** CLL · SLL · Treatment · Ibrutinib · Acalabrutinib · Venetoclax · Idelalisib · Duvelisib

## Opinion statement

Treatment landscape of chronic lymphocytic leukemia (CLL) has changed since 2014 after the introduction of inhibitors of B-cell receptor signaling pathway (ibrutinib, acalabrutinib, idelalisib and duvelisib) and the inhibitor of the anti-apoptotic protein BCL-2 (venetoclax). In 2019, novel agents were upgraded from being a "great treatment option" to the "preferred choice" for all lines of treatment after number of randomized clinical trials proved their superiority compared to conventional chemoimmunotherapy (CIT) regimens. A growing number of next-generation molecules are in clinical trials with a promise of improved efficacy and less toxicity. This includes agents with expected better safety profile (zanubrutinib, umbralisib, etc.) or more importantly with a potential to overcome the resistance mechanism to early generation agents (ARQ-531, LOXO-305, or vecabrutinib). Early intervention has once again become an active topic of research and, if proven to provide an overall survival benefit, will eliminate the "watch and wait" strategy for asymptomatic CLL patients. Until then, treatment should only be offered to patients who meet the standard treatment indication in standard practice. With our upgraded therapeutic toolbox, there are and will be many unanswered questions. CLL field will need to define the optimal treatment sequence and most effective combinations with a goal of having a time-limited and chemotherapy-free regimen that provides longest remissions and potentially cure. Cellular immunotherapy with chimeric antigen receptor T-cell (CAR-T) may become available for high-risk CLL along with allogeneic stem cell transplant (allo-SCT). Financial toxicity of novel agents especially when used in combination will need to be an important aspect of research in coming years to avoid unnecessary overtreatment of patients. As current prognostic models (CLL-IPI, etc.) were developed and validated in the

CIT era, there is ongoing effort to develop new models using clinical and molecular characteristics to accurately define high-risk CLL in the era of novel agents. We all need to keep in mind that access to the novel agents is currently limited to certain developed countries and every effort should be made to make sure patients around the world also benefit from these outstanding drugs.

## Introduction

CLL is the most common leukemia in the western world [1]. It is defined by the presence of $\geq 5 \times 10^9$/L clonal B lymphocytes in the peripheral blood (PB). Small lymphocytic lymphoma (SLL) is considered the nodal form of CLL and is defined as presence of lymphadenopathy with clonal B lymphocyte count of less than $5 \times 10^9$/L [2]. The diagnosis of CLL is made by flow cytometry performed on the PB and by confirming the immunophenotype of CLL (typically positive for CD5/CD19/CD20/CD23+ and negative for CD10/FMC7) [3]. In SLL, the diagnosis is confirmed by histopathological evaluation of a lymph node or tissue biopsy [4]. For this review, we will use the term "CLL" when referring to CLL or SLL as the discussion regarding prognosis and treatment is identical for the two diseases. Monoclonal B-cell lymphocytosis (MBL), defined as the presence of monoclonal B-cell populations in the PB of up to $5 \times 10^9$/L in the absence of other lymphomatous features, can be considered as a pre-malignant stage that precedes virtually all cases of CLL [5]. Recent studies highlighted that "high-count" MBL ($> 2 \times 10^9$/L) requires annual follow-up, showing biological features in common with CLL and higher risk of transformation to CLL [6], whereas with "low-count" MBL ($< 0.5 \times 10^9$/L), there is lower chance of progression [7]. CLL is still considerable as an incurable disease despite effective treatment and the initial indolent course of disease.

CIT regimens have been the mainstay of CLL treatment until recently. Despite the efficacy of CIT for selected patients, outcomes have been inferior in those with high-risk molecular markers, and more importantly, short- and long-term adverse events from the CIT regimens were significant. In recent years, introduction of novel inhibitors of B-cell receptor (BCR) signaling pathway like Bruton's tyrosine kinase (BTK), phosphatidylinositol-3-kinase δ (PI-3kδ), as well as the inhibitor of BCL-2 has dramatically changed the therapeutic landscape of CLL (Table 1). This review will focus on how to choose the best evidence-based therapeutic approach in the exciting and challenging era of new drugs for CLL.

# Risk stratification in CLL: clinical, phenotypic, and molecular markers

Clinical staging is still recognized as an important tool for disease assessment. There are two widely accepted staging systems in CLL, both relying solely on a physical examination and laboratory tests. The Rai staging system [8] considers low-risk disease in patients with asymptomatic lymphocytosis (Stage 0), intermediate-risk in patients with lymph nodes and/or spleen and/or liver enlargement (Stages I–II), and high-risk in patients with anemia or thrombocytopenia (Stages III–IV). The Binet staging system [9] classifies on stage A patients with no cytopenias (Hb ≥10 g/dL and platelets $\geq 100 \times 10^9$/L) and involvement of enlarged lymph nodes (≥1 cm in diameter) in up to two major areas (head and neck; axillae, groins, spleen, liver); patients in stage B should have involvement of three or more of the abovementioned areas without

**Table 1. Efficacy and safety of FDA approved novel agents for CLL**

| | BTKi | BCL-2 inhibitor | PI3K inhibitors |
|---|---|---|---|
| Drugs | Ibrutinib Acalabrutinib | Venetoclax | Idelalisib duvelisib |
| Duration of treatment | Indefinite | Fixed | Indefinite |
| Administration | -Oral | -Oral-given in combination with obinutuzumab or rituximab | -oral-idelalisib is approved in combination with rituximab |
| Adverse events | -Atrial fibrillation*-hypertension *-bleeding issues*-arthralgia *-muscle cramps* | -Tumor lysis syndrome (early)<br>-Cytopenia | -Transaminitis-colitis-pneumonitis-infections (PJP,CMV) |
| Indication for CLL | -All lines of treatment | -All lines of treatment | -Relapsed/refractory setting |

BTK: Bruton's tyrosine kinase; PI3K, phosphatidylinositol-3-kinase
*Adverse events less common with acalabrutinib

showing signs of cytopenia. Patients showing cytopenia are in Stage C regardless the number of lymphoid area. Classical laboratory markers associated with CLL prognosis include simple laboratory tests, such as lactate dehydrogenase and such as beta-2-microglobulin levels on serum [10]. In the CIT era, CLL patients with somatic mutation in the immunoglobulin heavy chain variable gene (IGHV) had better prognosis, showing a median OS 12 years longer that those with unmutated IGHV [11]. When interphase fluorescence in situ hybridization (FISH) became available in the late 1990s, Dohner et al. showed that more than 80% of patients with CLL have cytogenetic lesions [12]. The most common deletions are in the long arm of chromosome 13 [del(13q)]. In this series, patients with del17p13 were shown to have the worst prognosis. Next-generation sequencing (NGS) techniques uncovered the complexity of the mutation landscape in CLL, reporting numerous somatic mutations affecting genes that play key roles in cell function integrity [13]. Among them, NOTCH1 mutations (mostly occurring in patients with trisomy 12), SF3B1 mutations (mostly occurring in patients with del13q14), and TP53 (locus on 17p) mutations were associated with worse prognosis [14–16]. Given this strong association with poor prognosis, patients with del17p13 and TP53 mutation at diagnosis are considered as a separate category that needs a specific therapy. Cumulatively, del17p3 and TP53 mutations are seen in approximately 25% of CLL patients, some patient having a TP53 mutation in absence of del17p13 [17]. These patients were shown to have inferior outcomes with traditional CIT [18]. One of the most important implications of the novel agents is for treatment of this group, and their survival rates have significantly improved in recent years [19]. The CLL international prognostic index (CLL-IPI) was derived from a large meta-analysis and tried to include biological markers in the initial risk stratification. The authors evaluated the combined impact of TP53 deletion and/or mutation, IGHV mutational status, serum b2-microglobulin, clinical stage, and

age at diagnosis. These parameters identified four risk groups with significantly different OS at 5 years [20]. Limitations of the CLL-IPI are its applicability only at the time of first treatment, the exclusion of other important biological factors, and, importantly, the fact that had been developed before the outbreak of novel agents. There is a clear need of novel prognostic models in the era of targeted therapy, and one example is the score developed by the group at National Institutes of Health (NIH) that includes TP53 aberration, Rai stage, and beta-2-microglobulin or relapsed/refractory status [21]. The NIH model did not include complex karyotype which is reported by other groups to be important at least when BTK inhibitors are used [22]. In the era of the novel agents and while waiting for validated prognostic models, presence of TP53 aberrations (del17p or TP53 mutation) is the most important prognostic and predictive marker and is used in clinical decision-making. Minimal residual disease (MRD) at the completion of treatment, evaluated by multiparameter flow cytometry or allele-specific oligonucleotide polymerase chain reaction, is a powerful prognostic tool that predicts time to next therapy and overall survival (OS) in many studies, mainly for CIT and more recently with venetoclax-based treatments [23–25, 26•]. MRD negativity is increasingly being used as one of the endpoints in clinical trials using novel agents where time-limited treatment is being investigated.

# When is the right time to start treatment?

Patients with asymptomatic early-stage CLL should be monitored with a watch and wait (W&W) strategy without starting treatment until disease progression or presence of disease-related symptoms. In the era of chemotherapy, a number of studies were conducted but failed to show a survival benefit in treating asymptomatic patients with early-stage disease [27, 28]. Therefore, the 2018 guidelines from the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) still considers W&W standard for asymptomatic patients [4]. The introduction of novel agents for CLL has led to design of randomized studies investigating the role of early intervention for high-risk patients, based on molecular/cytogenetic profile. The CLL12 study from the German CLL study group randomized high-risk CLL patients to receive either ibrutinib or placebo. The study was positive for the event-free survival (EFS) primary endpoint. While the study is powered to detect an OS difference with longer follow-up, the current results should not change the current W&W practice [29, 30]. An upcoming US intergroup led by the SWOG will investigate potential benefit of early intervention using venetoclax-based treatment in high-risk patients with OS being the primary endpoint.

# Treatment options

## Patients with TP53 aberrations (TP53 ab: del17p or TP53 mutation)

### First-line treatment (for patients with TP53ab)

CIT regimens are not effective in patients with TP53ab [31, 32] and are therefore not recommended. Ibrutinib, a first in class covalent inhibitor of BTK, is constitutively activated and plays an important role in CLL clones [33]. It was

more effective as a single agent than traditional therapy in several studies [34]. In a phase 2 single arm trial, the National Institutes of Health (NIH) group showed efficacy of ibrutinib in a subgroup of 51 therapy-naïve (TN) patients with TP53ab: of the 48 evaluable patients, overall response rate (ORR) was 95.8% after six months of treatment, and 29% obtained complete remission (CR). With a median follow-up of 57 months, the estimated 5-year PFS for TN patients was 74.4%, and the OS was 85.3%, which was superior to the historical results obtained with FCR, BR, and other regimens [35•]. The iLLUMINATE trial compared ibrutinib versus chlorambucil in combination with six cycles of the anti-CD20 antibody obinutuzumab in TN patients. With a median follow-up of 31.3 months, patients with del17p had significantly better PFS in the ibrutinib plus obinutuzumab (median not reached) than in the chlorambucil plus obinutuzumab arm (11.3 months) [36]. The excellent results of these trials made ibrutinib as the treatment of choice in this group of patients. Venetoclax, an inhibitor of BCL-2, is an antiapoptotic protein that is overexpressed in various B-cell cancers, including CLL [37]. For TN naïve patients, the data comes from the phase 3 CLL14 trial that tested venetoclax in combination with obinutuzumab versus chlorambucil + obinutuzumab. Among 63 patients with TP53ab enrolled in the trial, there was a clear benefit for the venetoclax + obinutuzumab group in terms of in ORR, CR rate, and MRD negativity with a median 24-month PFS of 74% [38••].

*In our practice and based on the available data, ibrutinib remains the preferred choice for first-line treatment of CLL patients with a TP53ab status. If BTKis are not a feasible option for medical comorbidities or other reasons, venetoclax in combination with obinutuzumab would be the treatment of choice. Duration of treatment with venetoclax in this population is subject of debate in the CLL community. Authors would only consider discontinuation of venetoclax in TP53ab patients if there is no detectable disease and only after minimum 1 year of treatment.*

## Relapsed/refractory (for patients with TP53ab)

The RESONATE trial compared ibrutinib with ofatumumab and led to the approval of ibrutinib in the relapsed/refractory (R/R) setting [39–41]. With the long-term follow-up of this study and focusing on patients with del17p, the median duration of PFS was 40 months in the ibrutinib group [40–42]. In the NIH study, the 5-year PFS estimate in the relapsed setting for del17p patients was 19% [35]. Lastly, the 5-year median PFS from the PCYC-1102/1103 study was 26 months [34]. Second-generation BTKi acalabrutinib is also approved by FDA for CLL and has shown a promising result in del17p patients with an 18-month PFS of 80% in the ACE-CL-001 study, but a longer follow-up is needed [43, 44]. The anti-BCL2 oral agent venetoclax was initially approved in patients with del17p and after one prior line of treatment. In the M13-982 study, the 24-month PFS was reported to be 54% when venetoclax was used as monotherapy and indefinably [45, 46]. The MURANO study was a randomized study comparing venetoclax + rituximab with bendamustine + rituximab in the R/R setting. One-third of patient had del17p and in those patients the 3-year PFS was in the range of 70% [47•]. Pi3K inhibitors idelalisib and duvelisib are both effective in TP53ab patients [48, 49].

*In our practice and in TP53ab patients and in the R/R setting, we first utilize ibrutinib or acalabrutinib if there was no prior exposure to a BTKi. In patients with R/R*

*disease after treatment with a BTKi, we use venetoclax-based treatment based on the data from Jones* et al. *showing clinical efficacy of venetoclax when it was used in patients after ibrutinib failure* [50•]. *Ibrutinib-intolerant patients will have acalabrutinib as an option* [51, 52]. *In high-risk CLL patients who failed either a BTKi or venetoclax, we strongly recommend cellular therapy with either CAR-T or alloSCT* (see below) [53••]. Idelalisib and duvelisib are reasonable option, but their efficacy in multiple refractory setting is limited [54••] (Fig. 1).

## Patients with an intact TP53 (no deletion or mutation)

### First line of treatment (normal TP53)

Before the introduction of novel agents, young and fit patients were usually treated with fludarabine, cyclophosphamide, and rituximab (FCR), and older (> 65) patients and those with comorbidities had bendamustine and rituximab (BR) as the main option [55]. Older and more frail patients were preferentially treated with chlorambucil plus obinutuzumab [56]. Ibrutinib received an FDA approval for all CLL patients in the first-line setting based on the RESONATE-2 study that showed an OS advantage of ibrutinib over single agent chlorambucil [57]. With CIT and ibrutinib as viable options, disease and patient characteristics and preferences were used to pick the appropriate treatment choice. However, and based on recently published randomized trials comparing each of the abovementioned CIT regimens with ibrutinib, ibrutinib is now considered a preferred option for all patients in the first-line setting. The ECOG1912 trial

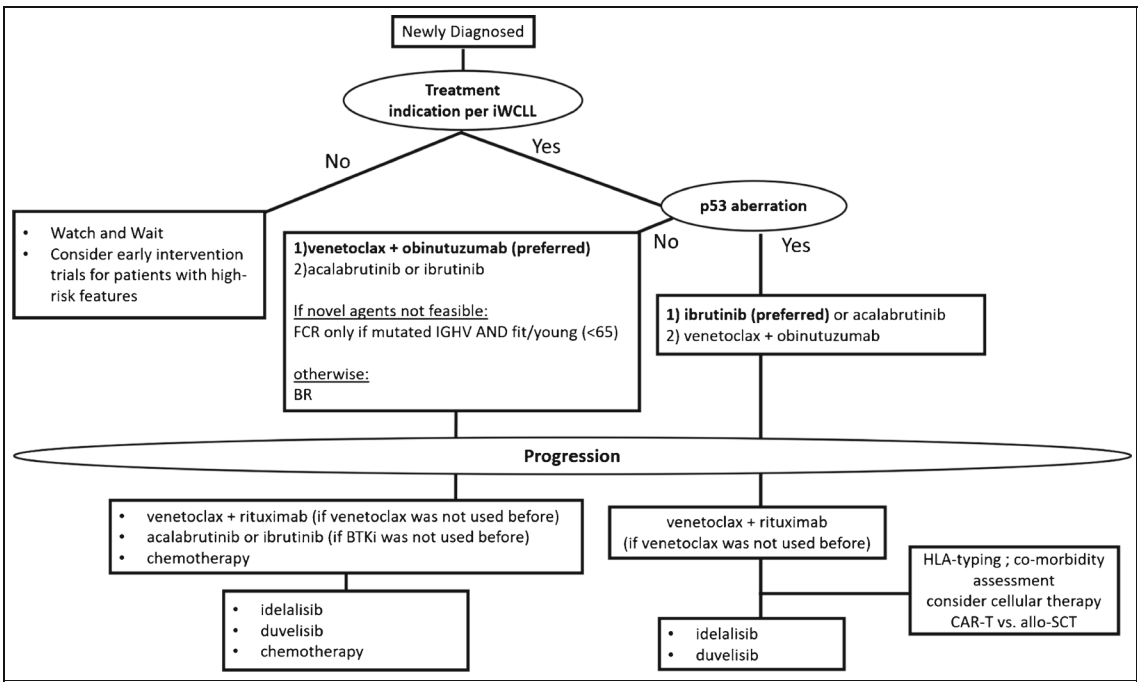


**Fig. 1.** Suggested approach to treatment of CLL. Allo-SCT, allogeneic stem cell transplant; BR, bendamustine, rituximab; CAR-T, chimeric antigen receptor T-cell therapy; FCR, fludarabine, cyclophosphamide, rituximab; iWCLL, International Workshop on Chronic Lymphocytic Leukemia

showed better OS and PFS in favor of the ibrutinib + rituximab over FCR in younger (< 70) patients without del17p and those who were considered to be "FCR candidates." Patients with mutated IGVH are known to have long-term remission from FCR, and it is important to note that with the current follow-up, the E1912 study has not yet provided evidence to support a superiority of ibrutinib in these patients [58••] [59]. The ALLIANCE A041202 trial was a three-arm study that compared BR versus ibrutinib + rituximab versus ibrutinib monotherapy in a population of previously untreated elderly patients. PFS at 2 years was 74% with BR and was significantly higher with ibrutinib alone (87%) and with ibrutinib plus rituximab (88%). The addition of rituximab to ibrutinib did not show a significant benefit [60]. Lastly, the iLLUMINATE study compared ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab in patients ≥ 65 years or ones with comorbidities. A post hoc analysis excluding patients with del17p showed that ibrutinib plus obinutuzumab was associated with a lower risk of progression and superior PFS. Notably, 35% of patients on this treatment had no detectable MRD in the bone marrow or peripheral blood [36]. Differently from the ALLIANCE trial, the iLLUMINATE study did not have an ibrutinib monotherapy arm, this way not making possible to estimate the benefit of adding obinutuzumab to ibrutinib.

In the abovementioned CLL14 study testing venetoclax + obinutuzumab for 1 year in first line for elderly patients with comorbidities, the German group reported that venetoclax + obinutuzumab was significantly superior to chlorambucil + obinutuzumab in terms of 24-month PFS (88.2% vs 64.1%). There was no difference in grade 3–4 neutropenia, grade 3–4 infections, and all-cause mortality [38••]. The study is particularly important because venetoclax received FDA approval for the first-line setting based on this study. If remissions are found to be sustained with longer follow-up, this will be the first "chemo-free" and "fixed-duration" treatment for CLL patients in the frontline setting. Although this study did not include the young and fit population, deep remissions with high rate of MRD negativity (76% in PB and 57% in the marrow) makes it a very reasonable treatment option for all CLL patients as there is no reason to believe that the quality of responses will be inferior in fitter and younger patients. The ELEVATE TN study was also a three-arm study comparing acalabrutinib with or without obinutuzumab with chlorambucil + obinutuzumab. Based on the data presented at the American Society of Hematology (ASH) 2019 meeting, patients who were treated on the acalabrutinib containing arms had a superior PFS. Importantly, acalabrutinib use was associated with lower rates of grade ≥ 3 atrial fibrillation (3–4%), bleeding (2%), or hypertension (2–3%) compared to what has been reported with ibrutinib [61•]. Based on this data, FDA approved acalabrutinib for CLL in November 2019.

*Authors consider both BTKi (acalabrutinib or ibrutinib) and venetoclax + obinutuzumab as reasonable first-line treatment options for CLL. In the absence of head-to-head trials, we prefer venetoclax + obinutuzumab especially when there is an interest in fixed treatment duration (majority of patients, in patients with cardiovascular comorbidities (hypertension and atrial fibrillation), or if there is a higher risk for bleeding). BTKis (ibrutinib or acalabrutinib) are preferred in patients with significant risk of tumor lysis syndrome and if debulking or ramp-up strategies cannot safely be implemented. Also, BTKis are generally easier to initiate and maybe preferred when a quick disease control is planned. We do not consider CIT as a preferred choice for any CLL patient in the first line*

*setting. If novel agents are not available or not preferred by patients, risk and benefit of FCR should be discussed in detail with the patient. The focus should be on risk of AML/MDS which is at least 5% after FCR. We would only consider FCR reasonable for younger (< 65) patients with a mutated IGHV and in the absence of TP53 aberration or del11q. BR is a reasonable choice in all other patients only if novel agents are not used.*

## Relapsed/refractory patients (normal TP53)

Novel agents are superior to CIT regimens in the relapsed/refractory (R/R) setting. In the RESONATE study, ibrutinib showed OS benefit when compared with ofatumumab, leading to its FDA approval for relapsed CLL [40, 42]. A number of other trials and real-world experience support the efficacy of ibrutinib in R/R CLL [62]. Adverse events, however, still represent a barrier in some patients and can lead to drug discontinuation [63]. Acalabrutinib, a second-generation BTK inhibitor, has a different safety profile with less off-target effects and lower rate of adverse events [43]. Acalabrutinib is currently approved for CLL and mantle cell lymphoma [64]. Data from the ACE-CL-001 study showed efficacy in treatment-naïve [44] and R/R CLL [43, 51]. In the ASCEND trial, previously treated patients were randomized to receive acalabrutinib or investigator's choice between BR or idelalisib + rituximab. The study met the primary endpoint of PFS in favor of acalabrutinib which was superior to both BR and idelalisib + rituximab. There is no OS benefit which is not surprising given the short follow-up and also allowance of cross-over in this study [65•]. This data led to the FDA approval for previously treated CLL. Also, NCCN guidelines propose acalabrutinib in ibrutinib-intolerant patients [66].

In the MURANO trial, venetoclax (administered for 2 years) in combination with rituximab (given for 6 months), was shown to have superior PFS and OS in previously treated patients with CLL when compared to BR [47•]. These results are explainable with the higher rates of deep and molecular responses, with undetectable MRD emerging as a predictor of PFS [26•]. With 10-month follow-up after completion of 2 years treatment, only 2 of 83 patients who had undetectable MRD at the end of treatment developed disease progression [26•]. Tumor lysis syndrome (TLS) is the most significant adverse event with venetoclax. Appropriate patient selection, implementation of debulking strategies to lower the TLS risk, and following the standard ramp-up are critical to minimize the TLS risk [67] [68] [66].

Idelalisib and duvelisib are inhibitors of phosphatidylinositol 3-kinases δ. Idelalisib is a selective PI3Kδ inhibitor, whereas duvelisib inhibits PI3K-δ,γ [69] [70]. Both drugs are approved by FDA for treatment of r/r CLL patients. Idelalisib in combination with rituximab was superior to rituximab monotherapy in previously treated patients [49]. Results from the DUO trial showed that R/R patients treated with duvelisib have improved PFS compared to ofatumumab in monotherapy [48]. Despite their efficacy, PI3K inhibitors have fallen out of favor as first- or second-line treatment options mainly because of their toxicity profile. Main adverse events like transaminitis, colitis, and pneumonitis are mainly due to immune-mediated reactions [71]. Importantly, these events are reported to occur more often in treatment-naïve patients [72] and for this reason, these agents should be avoided for first line treatment if possible. Moreover, there is a higher reported risk for certain infections due to T-cell

dysregulation [73], and prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) and close monitoring for cytomegalovirus (CMV) reactivation are recommended in course of treatment [74].

Ongoing studies investigate safety and efficacy of next-generation Pi3Kis (i.e., umbralisib) or alternative scheduling (i.e., weekly) and may make this group of drugs more attractive in future.

*In our opinion, either venetoclax + rituximab or BTKis (ibrutinib or acalabrutinib) are preferred choices for relapsed patients. Obviously, previous failure of these agents in prior lines of treatment would exclude them as a viable option. Potential for time-limited treatment with venetoclax-rituximab makes it a more attractive choice. We strictly follow the standard approach for TLS risk mitigation, and we often try to debulk patients before initiating venetoclax. Patients whose disease progressed on ibrutinib should not receive these covalent BTKi. We use Pi3Ki as third line of treatment.*

# Allogeneic transplant

Allo-SCT was considered the treatment of choice for high-risk patients with CLL in the CIT era and remains to be the only potentially curative treatment for CLL. Due to the higher prevalence of CLL in elderly patients, transplant with reduced-intensity conditioning (RIC) is used for CLL. In general, long-term follow-up studies from different groups show an OS of 50% with PFS of ~ 40%. Non-relapse mortality (NRM) remains significant and affects 15–25% of patients [75, 76]. The Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) is a reliable predictor of NRM. We recently published the results of a prospective trial conducted on 55 patients and showed that the addition of rituximab peri-transplant improved the response rate in comparison to the 157 historical control patients. Including the entire cohort, we showed that in patients with no comorbidities, the NRM rate was less than 12% [77]

In the era of novel agents, Allo-SCT remains an option for high-risk patients who progress after at least a BTKi or venetoclax. It should be noted our current knowledge of allo-SCT efficacy and toxicity is based on the studies that we conducted in the CIT era. Given the small number of patients undergoing allo-SCT today, there is a need for collaborative efforts to understand the efficacy of this approach in the post-novel agent setting. We generally agree with the guidelines provided by the European Society for Blood and Marrow Transplantation (EBMT) and European Research Initiative on CLL (ERIC) [53••]. In patients who progress on either a BTKi or venetoclax, we make an initial assessment of comorbidities and donor availability. If available on a clinical trial, we consider CAR-T cell therapy first given lower mortality and possibility of long-term remissions in some patients (see below). We have shown that allo-SCT can safely be done after CAR-T therapy without additional toxicity above what is expected from allo-SCT [78] (Fig. 1).

# Future directions

## Cellular immunotherapy

CD-19 directed CAR-T cell therapy has shown efficacy in the management of CLL patients who have disease progression including ones who progressed on ibrutinib. CAR-T is not currently FDA approved for CLL and it is only available

through clinical trials. In a study of 27 R/R CLL patients (19 of whom had progression of disease on ibrutinib), anti-CD19 CAR-T cell therapy was associated with an ORR of 74% at 4 weeks, with a CR rate of 21% by iwCLL criteria [79•]. The addition of ibrutinib to CAR-T improved the ORR in a mouse model of mantle cell lymphoma [80]. Clinical data confirmed that ibrutinib does not increase the risk of CRS and other manifestations of toxicity in CLL and in fact provides similar efficacy [81]. Registration trials are currently ongoing and, if led to the approval of CD19 CAR-T for CLL, will add to our CLL toolbox. Further studies are needed to investigate the appropriate timing, and the right sequence of treatment for high-risk CLL is needed in the upcoming years.

## New generation of BCRi

Next generation of drugs targeting the BCR downstream signaling will soon be available for CLL treatment. Acalabrutinib is recently approved for CLL. Zanubrutinib is a potent and highly selective inhibitor of BTK and is currently approved by FDA for treatment of MCL. Similar to acalabrutinib, zanubrutinib has been shown to be effective and probably better tolerated than ibrutinib based on results of single arm study [82]. Results of phase I/II acalabrutinib trials revealed ORR of 96% in treatment-naïve, 93% in R/R and 76% in ibrutinib-intolerant patients with CLL [44]. The safety profile of acalabrutinib is more acceptable than ibrutinib with limited grade 3 or 4 toxicities and lower incidence of cardiac events [51]. As mentioned above, the ELEVATE TN and ASCEND trials have shown efficacy of the agents compared to CIT in the frontline and relapsed setting, respectively [61•, 65•]. In a phase I trial, zanubrutinib was given at different doses. Among 78 efficacy-evaluable CLL/SLL patients, the ORR was 96.2%. Estimated progression-free survival at 12 months was 100%. A low incidence of major toxicities was reported, neutropenia being the only grade 3/4 toxicity observed [82]. In another study conducted on 25 patients with R/R CLL, zanubrutinib was shown to be also active in reverting the exhausted phenotype of T cells [83]. Zanubrutinib has provided high response rates with excellent responses albeit with a relatively short follow-up when used in the frontline setting for patients with del17p [84]. Randomized trials comparing acalabrutinib or zanubrutinib versus ibrutinib have completed enrollment and when published/presented will help us understand the potential benefit of the second generation BTKis compared to ibrutinib. For conventional (covalent) BTKis, mutation in the C481S binding side can confer clinical resistance. Important group of drugs currently in early-phase trials are the third-generation BTKis like vecabrutinib (SNS-062), ARQ-531, and LOXO-305. For these noncovalent BTK inhibitors, binding to cysteine C481is not required which makes them a potential option for patients with resistance to covalent BTKis [85]. The role of these new inhibitors will be clarified in the ongoing and upcoming trials.

Umbralisib (TGR-1202) is a next-generation inhibitor of PI3Kδ, which is structurally distinct from other PI3Kδ inhibitors and shows improved isoform selectivity. Umbralisib also uniquely inhibits casein kinase-1ε, a major regulator of protein translation [86]. A phase I trial showed efficacy in 90 patients with relapsed or refractory NHL and CLL, and more importantly, umbralisib was well tolerated and exhibited fewer autoimmune-like toxicities (such as colitis) than previous PI3Kδ-selective inhibitors. Availability of next-generation BCRis

in the upcoming years with same or better efficacy and will better toxicity profile can potentially change the treatment landscape of CLL.

### Combination studies

Given the efficacy of the novel drugs in monotherapy, the combination of these novel agents is under investigation in number of clinical trials. Because of its distinct mechanism of action, venetoclax is combined with different BCRis to utilize its pro-apoptotic effect in addition to the anti-proliferative mechanism of the BCRis. For example, the MD Anderson group conducted a phase II trial on which 80 treatment-naïve high-risk CLL patients were treated. Patients received ibrutinib monotherapy for three cycles after which venetoclax was added at the standard dose. Eighty-eight percent of the patients had complete remissions, and 61% had undetectable MRD, and the adverse event profile was similar to what has been reported with ibrutinib and venetoclax [87, 88]. Currently, a number of studies investigate combination therapy with different drugs, schedules, and endpoint including MRD-informed stopping rules. While achieving high rates of deep responses is definitely encouraging, combination therapies are considered experimental until randomized trials show meaningful clinical efficacy and safety. Two examples of such phase III trials are the US intergroup studies led my ECOG-ACRIN (NCT03701282) and the Alliance group (NCT03737981) comparing the combination of ibrutinib + obinutuzumab vs venetoclax + ibrutinib + obinutuzumab as first line in patients with previously untreated CLL younger and older than 70-year-olds, respectively.

Treatment of CLL has been revolutionized with the introduction of growing number of novel agents that have relapsed the CIT as preferred choices in all settings. There are still many unanswered questions that will require well-designed and clinically relevant studies in coming years. Issues like appropriate time to start treatment, the optimal treatment sequence or combinations, duration of treatment, and the best approach to treatment of high-risk patients are some of the active areas of research. Cost-effectiveness of different approaches needs to be considered in both research and clinical settings. Lastly, access to these novel agents is still limited to patients in developed countries, and every effort should be made to provide access to CLL patients around the world.

## Funding information

Mazyar Shadman has received research funding from AbbVie, Genentech, Pharmacyclics, Acerta Pharma, Verastem Oncology, Gilead, TG Therapeutics, BeiGene, Sunesis, Celgene, Mustang Bio, and Merck and has received compensation from AbbVie, Genentech, Pharmacyclics, AstraZeneca, Verastem Oncology, Gilead, Sound Biologics, Atara Biotherapeutics, Cellectar Biosciences, and ADC Therapeutics.

## Compliance with Ethical Standards

**Conflict of Interest**

Lorenzo Iovino declares that he has no conflict of interest.

**Human and Animal Rights and Informed Consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance


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