Published in final edited form as:

Expert Opin Pharmacother. 2017 June ; 18(9): 857–873. doi:10.1080/14656566.2017.1324420.

Pharmacotherapy of relapsed/refractory chronic lymphocytic leukemia

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Abstract

Introduction: The treatment of relapsed/refractory (RR) CLL has been revolutionized by the advent of the new oral inhibitors of B-cell receptor (BCR) signaling and the pro-survival protein, B-cell lymphoma 2 (BCL2). Additionally, new and more potent monoclonal antibodies against CD20 have replaced/may replace rituximab in many settings.

Areas covered: Herein, we review the entire therapeutic landscape of RR CLL, with particular attention to the new small-molecule kinase inhibitors and BH3-mimetics. We discuss preclinical data with these agents in CLL, cover available efficacy and safety information, and examine potential resistance mechanisms and possible rational combinations to circumvent them.

Expert opinion: The availability of potent and selective inhibitors of BCR signaling and of the anti-apoptotic functions of BCL2 has enormously enhanced our therapeutic armamentarium, with unprecedented efficacy now observed in patients who historically had poor outcomes with chemoimmunotherapy (CIT), e.g., those with deletion 17p/11q and/or *IGHV*-unmutated disease. The next challenge is to optimally sequence these agents and develop rational combinations that will hopefully lead to deeper and more durable remissions than ever seen before. Indeed, long term relapse free survival, already achievable with CIT in patients with genetically favorable-risk disease, now appears to be a realistic possibility for most patients with CLL.

Keywords

CLL; ibrutinib; idelalisib; venetoclax; BCL2; B-cell receptor; BTK; PI3K; chemoimmunotherapy; rational combinations

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Declaration of Interest

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1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western world, with an estimated 18960 new cases and 4660 deaths in the United States in 2016[1]. The past several years have witnessed an unprecedented increase in the availability of novel, targeted therapies for the treatment of CLL. Indeed, 2012 was declared the year of CLL by the American Society of Clinical Oncology. These developments reflect our improved understanding of CLL biology, in particular the pivotal role of B cell receptor (BCR) signaling and the addition of CLL cells to the BCL2 anti-apoptotic protein for survival (Figure 1)[2]. The availability of novel agents targeting Bruton's tyrosine kinase (BTK), phosphoinositidyl-3-kinase (PI3K), and BCL2 has transformed the therapeutic landscape of relapsed/refractory (RR) CLL, and is poised to dramatically alter the management of previously untreated patients as well (Table 1)[3].

Until very recently, chemo-immunotherapy (CIT) had been the standard of care for most patients with CLL in the frontline setting, with the only exception being patients with deletion 17p, who should receive ibrutinib[4]. However, as alluded to above, the treatment landscape in the frontline setting is also changing, with the approval of ibrutinib for treatment-naïve patients with CLL based on the phase III RESONATE2 trial, which compared it head to head with chlorambucil in older patients[5, 6]. Nonetheless, CIT in the frontline setting still plays an important role since it can result in long-term (approximately 10 years) relapse-free survival, particularly in the subset of patients with favorable genomic features (mutated *IGHV*, absence of del11q and del17p)[7]. At present, there is interest in combining CIT with novel agents upfront so as to induce deeper remissions and minimal residual disease (MRD) negativity, an important predictor of long-term survival in CLL[8, 9]. Such combinations may also permit reducing the duration of exposure to alkylating agents and in-turn, the risk of secondary myeloid malignancies (NCT02629809). While targeted therapy with single agents has significantly improved outcomes of patients in RR setting, these do not induce complete remissions (CRs) in the majority of patients, and MRD-negativity even less so, and do not completely overcome the negative prognostic impact of del17p[10, 11]. Thus, much work remains to be done to further optimize outcomes in RR setting, e.g., defining optimal sequencing of the novel agents and identifying rational combinations of the same, as well as the management of unique treatment-emergent adverse events. A better understanding of the mechanisms of resistance to the new targeted therapies will enable us to design novel drug combinations based on laboratory evidence of synergism.

2. Chemo-immunotherapy

The most frequently used backbone chemotherapy for CLL has been either the combination of an alkylating agent and a purine analog, or the bifunctional agent, bendamustine, which has properties of both[12, 13]. CD20 is a transmembrane protein that is expressed on B-cells, including CLL cells. The addition of rituximab, a first-generation, chimeric CD20 monoclonal antibody, to chemotherapy has significantly improved outcomes in the frontline and RR settings[14, 15]. Before the approval of ibrutinib, there was no "standard" regimen for the management of RR CLL[16]. However, CIT with fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine plus rituximab (BR) was commonly used[15, 17, 18].

Data from a phase 3 study demonstrated improved outcomes for FCR over FC in RR CLL. Progression-free survival (PFS) times were 30.6 and 20.6 months in the FCR and FC arms, respectively[15]. A phase 2 study with BR in RR CLL showed an overall response rate (ORR) of 59% (45.5% in fludarabine refractory patients). The median PFS and overall survival (OS) were 15 and 34 months, respectively[18]. However, patients with del17p do not derive clinical benefit from CIT[15, 18].

In the era of novel agents, the role of CIT in RR CLL is limited. However, it is reasonable to use CIT in patients with late relapses (duration of previous remission > 2–3 years) with functional p53, especially if there is limited access to novel agents. The choice of the chemotherapy backbone in these situations depends on both the degree of fitness of the patient and their previous treatment. CD20 monoclonal antibodies, with or without chemotherapy, can potentially be used for debulking prior to the initiation of highly effective novel agents such as venetoclax to decrease the risk of tumor lysis syndrome (TLS) in patients with high disease burden.

3. Newer anti-CD20 monoclonal antibodies

A phase 1 study demonstrated safety and potential efficacy of higher doses of rituximab in RR CLL[19]. However, responses were short-lived, and this strategy has not been investigated further, in part because of cost, and in part because of the development of anti-CD20 monoclonal antibodies with superior efficacy, e.g., obinutuzumab. Two newer CD20 monoclonal antibodies are approved for the treatment of CLL, ofatumumab and obinutuzumab. In addition to RR CLL, ofatumumab is also approved for frontline and maintenance treatment in CLL[20, 21, 22]. Ofatumumab is a fully human, IgG1 second generation anti-CD20 monoclonal antibody. Ofatumumab binds to an epitope distinct from that bound by rituximab, is slowly released from the epitope and exerts more potent *in vitro* complement-dependent cytotoxicity (CDC) even in the setting of low CD20 expression, a hallmark of CLL[23]. Unlike rituximab, ofatumumab has single agent activity in the RR setting. It was approved in 2009 in the RR setting, primarily for fludarabine and alemtuzumab-refractory (“double refractory”) CLL, based on results of a pivotal trial. In this trial, 138 patients with fludarabine/alemtuzumab refractory CLL (FA-ref) or fludarabine refractory CLL with bulky lymphadenopathy (BF-ref) were enrolled[24]. The ORRs were 58% and 47% in the FA-ref and BF-ref groups, respectively. Median PFS and OS were 5.7 and 13.7 months in the FA-ref group and 5.9 and 15.4 months in the BF-ref group, respectively. Importantly, ofatumumab demonstrated single-agent activity even among patients with rituximab-refractory disease, with ORR of 44%, median PFS of 5.5 months and median OS of 15.5 months in this subgroup[25]. Overall, however, the response rates, PFS and OS to single agent ofatumumab are poor[24, 26, 27]. In order to further improve the outcomes of ofatumumab in the RR setting, it has been combined with chemotherapy, steroids and novel agents[28, 29, 30, 31]. Cross-trial comparison suggests that bendamustine/ofatumumab compares favorably to BR or FCR with an ORR of 72% and a PFS of 23.6 months in the RR setting[31]. Ofatumumab was well tolerated and active across various higher risk groups except for patients with *SF3B1* and *TP53* mutations. However, another study with this combination was closed early because of poorer outcomes and an inferior adverse event (AE) profile, including neurotoxicity[28]. A phase 3 trial

demonstrated improved PFS with ofatumumab, fludarabine, cyclophosphamide (OFC) vs fludarabine and cyclophosphamide; 28.9 vs. 18.8 months respectively[22]. There has not been a direct comparison between OFC and FCR in RR CLL. However, cross trial comparison suggest comparable PFS[15, 22].

Obinutuzumab is a glycoengineered, type II, humanized anti-CD20 monoclonal antibody. It binds to the same epitope as rituximab but has a glycoengineered Fc region that improves its affinity for FcR γ IIIa, enhancing its ability to bind immune effector cells[32]. This leads to enhanced complement-independent programmed cell death, including antibody dependent cell-cell mediated cytotoxicity (ADCC)[33]. Obinutuzumab in combination with chlorambucil is approved for the frontline treatment of CLL in patients deemed unfit for intensive chemotherapy[34]. In the RR setting, a phase 1/2 trial of obinutuzumab demonstrated best overall responses of 62% (8/13) in the dose escalation phase and 30% (6/20) in the dose expansion phase[35]. The median PFS for the expansion cohort was 10.7 months. Obinutuzumab plus bendamustine has been studied in RR indolent lymphomas; however, only 12 patients with small lymphocytic lymphoma (SLL) were enrolled[36]. Infusion-related reactions are the most common AEs with both ofatumumab and obintuzumab; however, the majority are grade < 3 and, at least in the case of obinutuzumab, are predominantly seen only after the first infusion.

Ublituximab is yet another anti-CD20 monoclonal antibody that binds to an epitope which is distinct from the rituximab, ofatumumab or obinutuzuamb binding sites. It also has a glycoengineered Fc region with enhanced ADCC activity[37]. An early phase study demonstrated potential clinical efficacy of ublituximab in the RR setting with responses in 5/11 patients[38]. However, the pharmacokinetics (PK) data suggest that the dose could be further optimized. As such, higher doses of ublituximab monotherapy are currently under evaluation (NCT01647971). Anti-CD20 monoclonal antibodies are being combined with BTK and PI3K inhibitors, as discussed below.

4. Other Monoclonal Antibodies

Monoclonal antibodies against antigens other than CD20, such as CD19, CD23, and CD37 are also being investigated in CLL (reviewed in ref.[39]). MOR00208 is an Fc-engineered humanized anti-CD19 monoclonal antibody. As a single agent, it was relatively well tolerated and effective in RR CLL with an ORR of 67%[40]. It is being investigated in combination with lenalidomide, ibrutinib and idelalisib (NCT02005289, NCT02639910). Antibody-drug conjugates targeting CD19, e.g., SAR-3419, ADCT-402, may hold promise in CLL treatment. NCT02669017 is an ongoing phase 1 trial of ADCT-402 in RR B-cell malignancies. Otlertuzumab is a novel, humanized, anti-CD37 protein therapeutic that exhibited modest activity and good tolerability in a phase 1 trial in previously untreated or RR CLL[3]. In RR CLL, otlertuzumab plus bendamustine was superior to bendamustine alone (ORR 69% vs. 39%, $p = 0.025$; PFS 15.9 vs. 10.2 months, $p = 0.02$, respectively)[41]. It is currently being investigated in combination with anti-CD20 antibodies and targeted therapy (NCT01644253).

Alemtuzumab is an anti-CD52 monoclonal antibody which demonstrated activity in fludarabine-refractory patients, including those with defective p53[42, 43]. However, the risk of opportunistic infections, particularly cytomegalovirus reactivation, with this B- and T-cell depleting agent is substantial, and alemtuzumab is rarely used in the present era of novel agents with proven efficacy in patients with deletion 17p. Also, the drug is no longer marketed for CLL; however, it may be obtained for individual patients through a special manufacturer distribution program.

5. BTK inhibitors

Signaling through the BCR pathway plays an important role in normal B-cell maturation and survival. However, it is also critical in various lymphoproliferative disorders, including CLL[44, 45]. BCR activation leads to activation of PI3K and BTK. In CLL, BCR signaling promotes cell survival and is important for CLL cells' trafficking within the tumor microenvironment[45, 46]. Based on this, targeting BCR signaling has been successfully used as a therapeutic strategy in CLL. Ibrutinib is a first-in-class BTK inhibitor that binds irreversibly to the C481 residue. However, ibrutinib also inhibits other kinases at pharmacologic concentrations including TEC family kinases, interleukin-2 inducible kinase (ITK), epidermal growth factor receptor (EGFR), etc., which may contribute to its off target effects[47, 48].

5.1 Ibrutinib: preclinical and clinical data in CLL

Preclinically, ibrutinib led to a decrease in B cell receptor signaling which, in turn, translated into apoptosis, decreased proliferation of CLL cells and inhibition of tumor growth in xenograft models[49]. Furthermore, ibrutinib disrupts the interaction of CLL cells with the protective tumor microenvironment by decreasing the expression and impairing the signaling of several adhesion molecules, and interferes with their homing to tissue niches, resulting in their egress from lymph nodes into the blood, where they eventually die from the lack of pro-survival signals[50]. [46]. Clinically, this correlates with a treatment-induced "redistribution lymphocytosis" typically seen with inhibitors of BCR signaling that has been shown to not have any adverse impact on long-term outcome[51]. The clinical efficacy of ibrutinib as a single agent is now well-established in both frontline and RR settings, including in the presence of del17p/mutated *TP53* (table 2). A phase Ib/II study in the RR setting demonstrated an identical ORR, 71%, in the 420 mg/d and 840 mg/d cohorts. An additional 20% and 15% of patients, respectively, achieved a partial response (PR) with lymphocytosis (PR_L)[52]. Importantly, response to ibrutinib was independent of risk category, including del17p[5, 52]. The 26-month estimated PFS and OS rates were 75% and 83%, respectively[52]. The clinical efficacy of ibrutinib was further confirmed in a phase III clinical trial comparing it to ofatumumab (RESONATE) in RR CLL[27]. Patients receiving ibrutinib had significantly better OS at one year (90% vs. 81%, respectively (hazard ratio (HR) for survival 0.43, $p = 0.005$)). Data from 5 years of follow-up of 101 patients with RR CLL treated with single agent ibrutinib were recently reported and demonstrated that longer treatment was associated with durable responses and improvement in response quality[53]. After a median time of 39 months on study, the ORR in the RR setting was 86%; however, only 10% of the patients achieved CR. The median PFS was 52 months. At 60 months, the

estimated OS was 57%. However it is important to recognize that ibrutinib does not completely overcome the negative prognostic effect of p53 loss, complex karyotype and del11q[53, 54]. The median PFS was 26 months and not reached among patients with and without del17p, respectively. The median PFS was 33 months and not reached for patients with and without complex karyotype, respectively. Also, at 60 months, the estimated OS times for patients with del17p and complex karyotype were 32% and 46%[53]. On multivariate analysis, del17p was identified as significant predictor of poorer PFS and OS. Interestingly, another study[55] suggests that among patients with del17p receiving ibrutinib, complex karyotype is the main predictor of poorer outcome. The outcomes of patients with del17p without complex karyotype were similar to those of patients without del17p[55]. Several combination strategies are being explored to further improve outcomes with ibrutinib, as discussed below.

5.2 Ibrutinib toxicity and drug-drug interactions

Ibrutinib is currently approved for all patients with CLL at a dose of 420mg once daily. However, it has significant off-target AEs. Ibrutinib inhibits both BTK and TEC kinases in platelets. This leads to impaired platelet function, primarily von Willebrand factor- and collagen-induced platelet activation[48]. Clinically, this translates to increased bleeding complications, with grade 3 bleeding having been reported in up to 8% of cases[10]. The current label recommends avoiding using ibrutinib with warfarin; however, it can be used with the direct oral anticoagulants, and anti-platelet agents. Nevertheless, concomitant use of ibrutinib with direct oral anticoagulants and antiplatelet agents is associated with higher bleeding risk[48]. It is also recommended to stop ibrutinib approximately 7 days before major surgery. This washout period correlated well with improved platelet function as assessed by ristocetin-induced platelet aggregation; however, in some patients there was delayed normalization of ristocetin-induced platelet aggregation[48].

Atrial fibrillation and flutter have been reported in 6–9% of patients treated with ibrutinib[10]. Ibrutinib's inhibition of BTK and TEC kinases in cardiac myocytes down-regulates the cardio-protective signaling mediated by PI3K/AKT which could contribute to the increased risk of atrial arrhythmias[56]. Though idelalisib inhibits PI3K/AKT signaling, it has not been associated with an increased rate of atrial fibrillation[57]. This may be because it selectively inhibits the delta isoform of PI3K, which is primarily expressed in lymphoid cells. Also, ibrutinib inhibits other kinases that are present in myocytes such as human epidermal growth factor receptor (HER) 2 and 4; this could represent an additional mechanism of increased atrial arrhythmias with ibrutinib[58]. In general, hemodynamically stable atrial arrhythmias occurring in patients on ibrutinib are managed with rate control and non-warfarin anticoagulation without discontinuation of ibrutinib.

Diarrhea is reported by approximately 60% of patients receiving ibrutinib; however, the majority of cases are low grade and self-limited[10]. Diarrhea may be attributable to potent inhibition of EGFR by ibrutinib[58]. It is worth noting that ibrutinib allows for partial restoration of humoral immunity, particularly IgA[59]. This is accompanied by a decline in infection rates in CLL patients over time during ibrutinib therapy[59]. However, prolonged treatment with ibrutinib has been associated with a decline in IgG levels. Also,

Pneumocystis jirovecii pneumonia (PJP) has been reported in previously untreated patients who were being treated with single-agent ibrutinib[60]. Cases of disseminated herpes zoster in CLL patients on ibrutinib have been reported as well[61]. Currently, universal PJP or antiviral prophylaxis is not recommended; however, clinicians should be aware of the possible increased risk of opportunistic infections with BTK inhibitors.

Overall, extended administration of ibrutinib is well-tolerated. AEs leading to treatment discontinuation tend to diminish over time, with a 12% discontinuation rate at 3 years[10]. Treatment-related lymphocytosis occurs in the majority of ibrutinib-treated patients (73%) and tends to peak at around 4 weeks. It is generally asymptomatic and does not impact outcomes[10, 51].

Ibrutinib is metabolized through the CYP3A system. Concomitant use of strong inhibitors or inducers of CYP3A with ibrutinib should be avoided. If a moderate inhibitor of CYP3A must be used in conjunction with ibrutinib, the dose of ibrutinib should be reduced to 140 mg daily.

5.3 Newer BTK inhibitors

Acalabrutinib is a second-generation, highly selective BTK inhibitor with fewer off-target effects compared to ibrutinib[62, 63]. Acalabrutinib does not inhibit EGFR, TEC or ITK signaling[63]. It binds covalently at the same C481 residue of BTK as ibrutinib. Data from a phase 1/2 clinical trial that included 61 patients with RR CLL suggest that acalabrutinib is well-tolerated and highly effective[63]. A dose of 100mg bid was used in the expansion cohort. The ORR was 95% (100% in patients with del17p, n = 18). Grade 3/4 AEs were infrequent. Common AEs included headache (43%), diarrhea (39%), weight gain (26%) and pyrexia (23%). Importantly, no major hemorrhage or atrial fibrillation was noted. The discontinuation rate was 13%. A phase 3 non-inferiority trial comparing ibrutinib with acalabrutinib head-to-head in RR CLL is ongoing (NCT02477696).

ONO/GS-4059, CC-292, and BGB-3111 are other selective BTK inhibitors that are in early phase clinical trials. ONO/GS-4059 is a highly selective, irreversible BTK inhibitor. A phase 1 trial of ONO/GS-4059 included 90 patients with RR NHL/CLL (n = 28)[64]. Overall, the treatment was well-tolerated with only one reported case of atrial fibrillation that occurred in the context of an infection. One patient had grade 3 bleeding in the context of CLL progression. None of the 28 patients who were on prophylactic and therapeutic anticoagulation had bleeding complications. Among the CLL patients, ORR was 82%. 2 patients with CLL progressed on study. BGB3111 is another selective, irreversible inhibitor of BTK that has a better pharmacokinetic profile compared to ibrutinib[65]. A phase 1 study demonstrated encouraging safety and efficacy. After a median follow up of 8.6 months, the ORR was 96%. 1 patient discontinued treatment secondary to AEs[65]. CC-292 is another potent, selective, irreversible inhibitor of BTK. A phase 1 study in RR CLL showed an ORR of 63%[66]. The most frequent grade 3/4 AEs included neutropenia (21%), thrombocytopenia (15%), pneumonia (10%), and anemia (8%).

5.4 Ibrutinib resistance

Outcomes post-ibrutinib discontinuation have been reported to be poor[67, 68]; however, most patients in these studies did not have access to newer agents, e.g., venetoclax. In approximately 50% of cases of ibrutinib discontinuation, the reason was CLL progression or Richter's transformation (RT). RTs tended to occur early, while most CLL progressions were relatively late events[68]. Acquired mutations in BTK and phospholipase C gamma 2 (PLC γ 2) contribute to ibrutinib resistance in a significant subset of these patients (85%, with the majority being BTK mutations)[54, 69, 70]. The most commonly reported mutations in BTK include C481S, C481R and T474I. These mutations lead to less effective, reversible BTK inhibition by ibrutinib. PLC γ 2 mutations are gain-of-function mutations that allow for signaling through the BCR pathway independent of BTK[71]. Though initial reports suggest that these mutations are not typically seen in BTK inhibitor-naïve patients, more sensitive sequencing techniques demonstrated that resistant sub-clones may be present pre-treatment[72]. Importantly, BTK and PLC γ 2 mutations may be detected before full clinical relapse, providing an opportunity for earlier intervention with adjunctive non-BTK-dependent treatments to eliminate the mutant clone[54, 73].

Increasing the dose of ibrutinib can inhibit mutated BTK non-covalently; however doing so does not impact signaling in presence of PLC γ 2 mutations[69]. Increasing the dose of ibrutinib to overcome resistance secondary to BTK mutations is unlikely to be feasible clinically, in part because none of the other kinases that are inhibited by ibrutinib (e.g., ITK, BMX, TEC, EGFR, JAK3, HER2, HER4, BLK) acquire mutations. Thus, increasing the dose of ibrutinib is likely to be significantly limited by AEs[69]. Also, it is unlikely that acalabrutinib will overcome resistance secondary to BTK mutations as it also binds covalently at C481. Newer BTK inhibitors that bind non-covalently to BTK and therefore, are not dependent on C481, are being developed[74] [75]. For example, two noncovalent BTK inhibitors, SNS-062 and GNE-431, demonstrated *in vitro* activity against CLL cells with mutations at C481. Strategies to overcome non-BTK-mediated resistance to ibrutinib are in development as well. Approved agents such venetoclax and idelalisib (discussed below) are associated with clinical responses in ibrutinib-resistant patients. Also, Syk inhibitors can potentially overcome resistance conferred by PLC γ 2 mutations[71]. Targeting PLC γ 2 itself is also being investigated. PLC γ 2 mutations lead to a stimulatory effect on its interaction with activator Rac GTPases[76]. Pharmacological interventions at the level of Rac might offer new treatment avenues. It is important to recognize that in some patients, multiple sub-clones with BTK and PLPC γ 2 emerged, highlighting the sub-clonal heterogeneity of ibrutinib-resistant disease[54]. Beyond resistance-conferring mutations in the BCR pathway, resistant sub-clones bearing del8p, leading to haplo-insufficiency of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors, with driver mutations have been described in patients developing ibrutinib resistance[72]. This highlights the importance of developing combination strategies targeting BCR and non-BCR pro-survival pathways.

5.5 Combination strategies involving ibrutinib in RR CLL

BTK-inhibitor-based combination strategies might allow for achieving better quality responses, primarily MRD negativity. This may potentially allow a proportion of patients to

obtain durable treatment-free remissions. Importantly, rational combinations could potentially delay or overcome the development of treatment resistance

The largest clinical study evaluating an ibrutinib-containing combination in RR CLL is a phase 3 study (HELIOS) comparing ibrutinib plus BR to placebo plus BR[77]. The ibrutinib/BR combination was relatively well-tolerated and associated with significant improvement in PFS over BR alone. After a median follow up of 17 months, PFS was not reached in the ibrutinib-containing group vs. 13.3 months in the placebo group. Cross trial comparison does not, however, suggest improvement in PFS with ibrutinib plus BR in comparison to ibrutinib alone or ibrutinib plus rituximab[52, 78]. The rituximab-ibrutinib combination was associated with high response rates in RR CLL[78], and is being further investigated in a randomized trial versus ibrutinib alone (NCT02007044). Early data on the ibrutinib/obintuzumab combination suggest achievement of deeper responses than with either agent alone; however, the reported results on ibrutinib plus ofatumumab or ublituximab do not suggest significant improvements in CR rates[30, 79].

Ibrutinib, through its inhibition of ITK, might enhance T-cell recognition and activity against CLL cells. Thus, combinations of ibrutinib with immune checkpoint inhibitors may be synergistic. Early data from a phase 2 study of ibrutinib plus nivolumab suggest promising clinical efficacy, particularly in high risk patients with Richter's transformation[80].

Another potential therapeutic target in CLL is XPO-1[81], a nuclear export protein that transports various tumor suppressor proteins, e.g., p53, p21 and p27 out of the nucleus. Selinexor is an XPO1 inhibitor that restores the subcellular localization of tumor suppressor proteins, leading to apoptosis of CLL cell lines. Importantly, selinexor is active against ibrutinib-resistant cell lines, including those harboring the BTK C481S mutation. The combination of selinexor and ibrutinib is synergistic *in vitro* and may allow for the eradication of emerging resistant clones, thus preventing or delaying clinical relapse[81].

6. PI3K inhibitors

PI3Ks play important roles in multiple cellular processes such as differentiation, survival, metabolism, and apoptosis, among others[82]. There are 3 classes of PI3Ks in humans, of which class I is most commonly implicated in cancer[83]. Class I PI3K is a heterodimer consisting of regulatory and catalytic subunits, which can have α , β , γ or δ isoforms[84]. Gain of function in PI3K class I has been reported in CLL[85]. Both pan-PI3K inhibitors and isoform-selective PI3K inhibitors have been studied in CLL; however, the activity of pan-PI3K inhibitors has generally been limited by narrow therapeutic windows.

6.1 Idelalisib – efficacy in CLL

Idelalisib is the only PI3K inhibitor currently approved for any therapeutic indication. It is a selective, reversible inhibitor of the δ isoform of the p110 catalytic subunit of class I PI3Ks, which is differentially expressed in lymphatic tissue. Preclinically, idelalisib inhibits survival signals to CLL cells by disrupting BCR signaling and disrupting the interaction of CLL cells with the tumor microenvironment[86, 87]. Importantly it induces apoptosis in CLL cells independent of del17p status[86, 88].

A phase 1 study that included 54 patients with RR CLL demonstrated single agent activity of idelalisib in this heavily pretreated group of patients (median 5 prior therapies) with poor prognostic factors (unmutated *IGHV* (91%), del 11q (28%) and del17p/mutated p53 (24%)) [89]. The ORR was 72%. The PFS was 15.8 months and 3-year OS was 75%. Similar to ibrutinib, single agent idelalisib was associated with a transient redistribution lymphocytosis, most pronounced in the first 8 weeks[89]. In a 7-arm phase 1b study, idelalisib 150mg twice daily was combined with chemotherapy (bendamustine, fludarabine, chlorambucil), CIT (BR, chlorambucil plus rituximab) and monoclonal antibodies (rituximab, ofatumumab)[90]. 114 subjects with RR CLL were enrolled. Two combinations stood out overall. Idelalisib in combination with BR was associated with fewer AEs compared to idelalisib plus bendamustine, particularly pneumonitis, transaminitis and diarrhea. Combining idelalisib with rituximab or ofatumumab was effective without added toxicity compared to idelalisib monotherapy. The ORR for all patients was 83% with a median PFS of 26.1 months. The median OS was not reached. Among patients with p53 mutations or del17p, the ORR was 70% with PFS 20.3 months[90].

Idelalisib plus rituximab was compared to rituximab plus placebo in patients with RR CLL who were candidates for rituximab alone in a phase III trial[57]. Idelalisib plus rituximab was associated with a significantly improved ORR (81 vs. 13% with odds ratio (OR) 29.9; $p < 0.001$), PFS (not reached vs. 5.5 months) and OS at 12 months (92% vs. 80% with HR of 0.28; $p = 0.02$). These benefits were observed regardless of *IGHV* mutation status or p53/del17p status. Based on this study, idelalisib plus rituximab was approved by the Food and Drug Administration (FDA) in RR CLL in 2014. Similar results were seen when comparing idelalisib plus ofatumumab to ofatumumab alone in RR CLL[91]. A third phase III trial compared idelalisib plus BR to BR alone in patients with RR CLL[92]. The idelalisib plus BR combination led to an OS benefit versus BR alone (HR 0.67, $p = 0.036$). However, cross trial comparisons suggest no added benefit of chemotherapy in this setting, similar to the situation with the HELIOS trial, which showed an improvement of PFS with the addition of ibrutinib to BR (versus BR alone) in patients with RR CLL, although the benefit of adding BR to ibrutinib over ibrutinib alone is not clear[77].

Importantly, retrospective analyses suggest that patients with RR CLL treated with ibrutinib as the first kinase inhibitor of choice have a superior PFS compared to those in whom idelalisib is used first (HR 2.8, CI 1.9–4.1 $p < .001$)[93]. Furthermore, idelalisib demonstrated activity post ibrutinib failure with an ORR of 46%.

6.2 Idelalisib toxicity and drug-drug interactions

In the pivotal phase III trial discussed above, the overall rate of treatment cessation because of AEs was not more frequent in the idelalisib-containing arm, being $<10\%$ [57]. The most common causes of treatment cessation were rash, diarrhea (with or without colitis), hepatotoxicity and pneumonitis. Grade 3 neutropenia and thrombocytopenia have been reported in up to 34% and 10% of patients, respectively. AEs of particular interest are hepatotoxicity, colitis and pneumonitis[94]. In RR CLL patients, 3 grade hepatotoxicity has been reported in up to 14%[94]. It usually occurs in the first 12 weeks and is reversible with treatment interruption. Most patients (74%) are able to resume treatment without

recurrence of hepatotoxicity. This is in contrast to the unacceptable rates of hepatotoxicity when idelalisib is used in the upfront setting[95]. The rate of grade 3/4 hepatotoxicity was 52% and in some patients, was not readily reversible with treatment cessation. Hepatotoxicity of idelalisib is believed to be autoimmune in nature, which might explain the higher incidence of grade 3 hepatotoxicity in treatment-naïve, immunocompetent patients[95]. Whether used upfront or in the relapsed setting, the use of concomitant hepatotoxic medications such as statins with idelalisib should be avoided. Liver function tests should be monitored every 2 weeks for first 3 months and management of hepatotoxicity should be performed per the package insert[96]. Pneumonitis has been reported in 3% of cases with a fatality rate of 0.4%[94]. Pneumonitis is usually managed with drug cessation and steroids. However, it is critical to rule out infectious etiologies including *Pneumocystis* and cytomegaloviral infection, particularly in light of a recent safety alert of increased deaths from pneumonia secondary to these organisms in idelalisib-treated patients[96, 97]. Though the increased risk of opportunistic infections has been primarily reported in regimens containing idelalisib and bendamustine, PCP prophylaxis and CMV monitoring are generally recommended in idelalisib-treated patients[97]. Diarrhea secondary to idelalisib has two peaks. Early onset diarrhea, within the first 2 weeks, is usually self-limited and can be managed with anti-motility agents. Late onset diarrhea is usually more severe and is usually secondary to colitis and managed with treatment cessation and prompt initiation of oral steroids[94]. In the United States, the idelalisib label contains a black box warning concerning the occurrence of fatal and/or serious hepatotoxicity, diarrhea/colitis, pneumonitis, infections and intestinal perforation.

Idelalisib is metabolized through the CYP3A system and therefore, concomitant administration of strong CYP3A inducers or inhibitors can substantially alter the exposure to the drug. Concomitant administration of strong CYP3A inducers with idelalisib should be avoided. Idelalisib itself is a strong CYP3A inhibitor.

6.3 Other PI3K inhibitors for CLL

There are other PI3K delta inhibitors that are being investigated in CLL. Duvelisib inhibits both the PI3K delta and gamma isoforms[98]. In a phase 1 trial in 54 patients with RR CLL, duvelisib was relatively well-tolerated, with the grade 3/4 AEs being neutropenia (31%), thrombocytopenia (11%) and infections/febrile neutropenia (26%). The ORR was 55% but with only 1 CR[98]. ORRs were similar regardless of p53 status. Similar to other PI3K and BTK inhibitors, treatment-related lymphocytosis was observed. In a phase 1 trial of duvelisib in RR indolent non-Hodgkin's lymphoma (iNHL), grade 3 transaminitis was observed in 41% of cases and diarrhea in 22%[99]. A phase 2 trial further investigated duvelisib, 25mg orally twice daily, in RR iNHL[100]. 128 patients were enrolled, including 28 with SLL. Treatment was relatively well-tolerated, with no grade 3 transaminits seen. Grade 3 diarrhea was reported by 15% of patients. 17% of patients discontinued the medication because of AEs, including 3 because of pneumonitis. The ORR among patients with SLL was 68% with median PFS of 11.3 months[100]. Duvelisib is currently being evaluated in comparison to ofatumumab in patients with RR CLL in a phase III trial (NCT02049515).

In contrast, copanlisib is a pan-PI3K inhibitor that is administered intravenously. High response rates were reported in a phase 2 pivotal trial in RR indolent NHL, comprising primarily patients with follicular and marginal zone lymphoma[101]. A phase II study showed single agent activity in CLL (n = 13) with an ORR of 38%. It was relatively well-tolerated[102]. TGR-1202 is a second generation PI3K δ inhibitor with a potentially improved toxicity profile compared to idelalisib. It was relatively well-tolerated (alone or in combination with ublituximab) with a discontinuation rate of 8% among patients with RR CLL (n=40) and NHL (n=112)[103]. The ORR (monotherapy or in combination) in RR CLL was 89%. This combination is currently being compared to the obinutuzumab plus chlorambucil combination in frontline and previously treated CLL patients (NCT02612311). A phase 1/1b study showed that TGR-1202 plus ibrutinib is relatively well-tolerated and effective in the RR setting[104]. Ongoing phase 1 and 2 trials are investigating TGR 1202 in various combinations, including with immune checkpoint inhibitors (NCT02006485, NCT02535286). The potential role of the newer PI3K inhibitors in the future treatment paradigm for CLL is not clear yet. However, less toxic PI3K inhibitors might allow for safer combination regimens[104] and enable frontline use of these agents.

7. BCL2 inhibitors

Venetoclax is the latest medication to be approved for CLL, specifically for RR CLL harboring del17p. CLL cells have several perturbations that favor survival by skewing the balance between pro- and anti-apoptotic proteins towards the latter, and are exquisitely dependent upon BCL2 for survival[105]. Deletion of miR15A and miR16A on chromosome 13q14, which is present in 50 to 60% of cases of CLL, leads to constitutive up-regulation of the anti-apoptotic protein BCL2[106, 107]. Despite the up-regulation of BCL-2, the majority of patients with CLL are highly sensitive to CIT. This is, in part, due to p53 activation by chemotherapy, leading to increases in “BH3-only” pro-apoptotic proteins which, in turn, sequester BCL-2[108]. However, defective p53 (del17p or mutant p53) is present in 3 to 10% of treatment-naïve patients and in up to 50% of patients with RR CLL. Importantly, lack of functional p53 is associated with poorer outcomes with CIT and BCR pathway inhibitors alike[10, 14, 18]. Thus, there is a particularly strong biological rationale for BCL2-directed therapy in CLL without functional p53. The first genuine “BH3-mimetic” in the clinic, navitoclax, an antagonist of both BCL2 and BCL-X_L, displayed substantial activity in CLL but caused on-target thrombocytopenia due to inhibition of BCL-X_L, which is critical for platelet survival[109, 110, 111]. On the other hand, venetoclax, a product of reverse engineering of navitoclax, is a highly selective, potent inhibitor of BCL-2 that spares platelets[112]. Venetoclax induces p53-independent apoptosis of CLL cells[108].

7.1 Venetoclax efficacy in RR CLL

Venetoclax demonstrated clinical activity in RR CLL across various dose levels in a first-in-human phase 1 study[11]. Importantly, TLS occurred in the first 3 patients; hence, a dose ramp-up approach was adopted. In this study, 116 heavily pretreated (median 3 prior therapies, range 1–11) CLL patients were enrolled. The majority of patients had poor prognostic factors (unmutated *IGHV* in 45%, del17p in 30%, del 11q in 27%). The pooled ORR was 79% (20% CR with or without count recovery) with a median time to response of

6 weeks. Among patients with del 17p, the ORR was 71% (CR in 16%). The PFS was 25 months in the dose escalation cohort and appeared to be dose-dependent. The 15 month-PFS was 58% in patients who received < 400 mg daily vs 69% in those who received 400 mg daily and 77% for those who received > 400mg per day. The 2-year OS was 84%. Richter's transformation was more common among patients with del17p and PFS in this subgroup was shorter than in patients without del17p (at 15 months, 50% vs 71%, respectively). A phase II pivotal study was then conducted to assess the efficacy of venetoclax in RR CLL with del17p[113]. 107 patients were enrolled. The ORR was 77% and among the 85 responders, 18 (21%) achieved MRD negativity. After a median follow-up of 12 months, the median PFS had not been reached[113]. Importantly, venetoclax has demonstrated activity in patients failing ibrutinib or idelalisib with a ORRs of 70% and 48%, respectively, although only one CR has been reported to date in this ongoing study[114]. After a median follow up of approximately 12 months, the median duration of response, PFS and OS had not been reached for whole group (n = 64). The estimated 12-month PFS and OS were 72 and 90%, respectively[114].

7.2 Venetoclax toxicity and drug-drug interactions

Venetoclax at 400 mg orally daily is usually quite well-tolerated. The major AE of concern that was noted early on was TLS[11]. In the phase I trial, TLS incidence was 12%, including 3 cases with renal failure and 2 fatalities. This was abrogated by adopting a weekly dose ramp-up schedule (20–50–100–200–400 mg daily) and closer monitoring[11]. With these modifications, the TLS incidence decreased to 6% and none of the cases was severe. Patients with high tumor burden are admitted for TLS prophylaxis and monitoring at the initiation of the first and second weeks of the ramp-up. Grade 3/4 neutropenia has been reported in 41% of patients; however, febrile neutropenia was reported in only 5%[11]. Another potential issue with venetoclax is that of drug-drug interactions. Venetoclax is metabolized by CYP3A4/5[115]. Concomitant use of strong inhibitors of CYP3A4/5 is, therefore, contraindicated, particularly at venetoclax initiation and during the ramp-up period. Venetoclax is also an inhibitor of drug transporters such as P-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Therefore, concomitant use of other inhibitors, especially P-gp inhibitors, should be avoided. If a moderate CYP3A or P-gp inhibitor must be used concomitantly, the dose of venetoclax must be reduced by at least 50% (75% if a strong CYP3A inhibitor is used concomitantly). On the other hand, if P-gp substrates have to be used, they should be taken at least 6 hours prior to venetoclax[116].

7.3 Venetoclax resistance

Identifying primary and secondary resistance to venetoclax is an area of active research. *In vitro* sensitivity of CLL cells to venetoclax did not correlate with its clinical efficacy[108]. However, “BH3 profiling”, a technique that uses various BH3-only peptides to identify tumor cell addiction to specific anti-apoptotic proteins of the BCL2 family[117], has the potential to identify potential non-responders to venetoclax[108]. Major mediators of resistance to venetoclax across tumor types include MCL-1 and BCL-X_L[118]. MCL-1 is an important anti-apoptotic protein, the levels of which are regulated by transcription and translation. Since selective pharmacologic inhibitors of MCL-1 are still in early stages of preclinical development, targeting transcription of MCL-1 by inhibiting CDK9 using agents

such as alvocidib and dinaciclib may be synergistic with venetoclax[119]. Targeting the PI3K/AKT/mammalian target of rapamycin (mTOR) axis may represent another way of overcoming resistance secondary to BCL-X_L and MCL-1[120]. Other mechanisms of resistance to venetoclax include BCL2 mutations and post-translational modifications[121, 122]. These post-translational modifications could be induced in part by the CLL stroma or microenvironment[119]. Combining venetoclax with multi-kinase inhibitors such as sunitinib may be more effective than BTK or PI3K inhibitors in abrogating stroma-mediated resistance to venetoclax[119].

Like ibrutinib, venetoclax is being investigated in combination with anti-CD20 monoclonal antibodies and CIT with promising clinical efficacy[123, 124]. A phase 1b study assessed the safety and efficacy of the venetoclax/rituximab combination in 49 patients with RR CLL[124]. Rituximab was added one week after the target dose of venetoclax was achieved. The rate of grade 3/4 AEs was similar to that with venetoclax monotherapy. The ORR was 86% and the CR/CRi rate was 51%. MRD negativity was achieved in 67% (28/42) of cases. Importantly, 8 MRD-negative patients remain in ongoing remission after a median of 9.7 months off venetoclax. The US FDA granted this combination “breakthrough therapy” designation for the treatment of RR CLL[125]. Though the numbers are small and the follow-up is short, this data raises the prospect of MRD-guided, time-limited treatment with targeted agents. Mechanistically, an even more interesting combination is that of venetoclax with BTK inhibitors, with or without anti-CD20 treatment (NCT02756897, NCT02427451). There is strong scientific rationale for combining ibrutinib with venetoclax in CLL. Clinically, the 2 drugs complement each other. Ibrutinib is very effective in controlling lymph node disease; however, very few patients achieve CR, and the drug does not efficiently clear disease in the bone marrow[52]. Venetoclax, on the other hand, is more effective against marrow than nodal disease[11]. Importantly, ibrutinib down-regulates MCL-1, which is not targeted by venetoclax[126]. In a phase 1b/2 study, obintuzumab as a single agent was introduced in cycle 1, followed by ibrutinib in cycle 2 and a venetoclax ramp up beginning in cycle 3[127]. The recommended phase 2 dose of venetoclax was 400 mg/d. This combination was well tolerated and the phase 2 portion of the study is ongoing. Other BCR signaling inhibitors such as idelalisib and SYK inhibitors can down-regulate MCL-1[128]. *In vitro*, SYK inhibitors were more effective than ibrutinib and idelalisib in down-regulating MCL-1 and overcoming venetoclax resistance in CLL[128].

Using direct or indirect MCL-1 inhibitors with venetoclax warrants further clinical investigation, particularly post-ibrutinib failure where treatment options are limited. In the absence of direct pharmacologic inhibitors of MCL-1, pan-CDK inhibitors such as dinaciclib or flavopiridol (alvocidib), which inhibit CDK-9, transcriptionally repress MCL-1[129, 130]. Flavopiridol has demonstrated clinical activity in high risk CLL; however, its use has been limited by a narrow therapeutic index with significant toxicities, including TLS, diarrhea, fatigue and cytokine release syndrome[130]. Data from a phase 1 study of dinaciclib also showed clinical efficacy with an ORR of 64% in the expansion cohort[129]. ORR was not influenced by del17p status. Though dinaciclib was better tolerated than flavopiridol, TLS occurred in 1 of 16 patients in the expansion cohort, highlighting the importance of a ramp-up approach similar to venetoclax and potentially a single-agent lead-in phase to further reduce the risk of TLS.

8. Immune checkpoint inhibitors

Cancer cells can evade immune recognition by activating various immune checkpoints such as CTLA4 and PD1, among others. Targeting immune checkpoints can allow for better recognition of cancer cells by immune surveillance mechanisms and their destruction by the immune system[131]. This strategy has transformed the treatment of various malignancies and is also being investigated in CLL. Higher expression of immune checkpoints such as PD1 and CTLA4 has been observed on T-cells isolated from CLL patients, as well on CLL cells[132]. Furthermore, PDL1, one of the ligands of PD1, is highly overexpressed on CLL cells from bone marrow and peripheral blood[133]. In a CLL mouse model, the use of anti-PDL1 agents led to an increase in the cytotoxic T-cell repertoire and improved anti-leukemia immune surveillance[134]. However, single agent ipilimumab, a CTLA4 inhibitor, was not active clinically[135]. On the other hand, the PD-1 monoclonal antibody pembrolizumab demonstrated single agent activity in a cohort of RR CLL and Richter's transformation with an ORR of 21% [136, 137]. Importantly, 4 of 5 patients with Richter's transformation responded to the treatment[136]. Despite the small number of patients and lack of long term follow up, this treatment approach is potentially promising, especially in Richter's transformation, since outcomes are poor even with intensive chemotherapy regimens such as oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR)[138]. However, patients with Richter's transformation should still undergo allogeneic hematopoietic cell transplantation (allo-HCT) upon achievement of an objective response. The combination of ibrutinib with anti-PDL-1 antibodies demonstrated synergistic activity in mouse models of mature B-lymphomas resistant to either agent[139]. This combination is currently being explored in Richter's transformation and RR CLL (NCT02420912).

9. Lenalidomide

The immunomodulatory drug lenalidomide, while not specifically approved for CLL, has clinical efficacy in both the frontline and maintenance settings, even among high risk subgroups such del11q and unmutated *IGHV*[140, 141]. In the RR setting, the ORR (single agent or combination) ranges from 32% to 66%, with few CRs[142, 143, 144, 145]. Although the drug has some activity in p53-deleted/mutated disease, it is limited and inferior to that of the novel agents discussed above[146]. Also, lenalidomide use in CLL initially was limited by AEs including tumor flare reaction, TLS and myelosuppression. Tumor flare reaction manifests as a transient increase in WBC count, tender lymph node enlargement and/or splenomegaly with or without fever and rash[147]. Steroids and non-steroidal anti-inflammatory drugs can help in the symptomatic management of tumor flare. To circumvent these issues, lower doses of lenalidomide, with or without slow escalation were used. This was associated with a better toxicity profile. However, lower doses were associated with lower response rates[148]. The role of lenalidomide in RR CLL in the era of novel agents is not well-established[147]. However, it is worth investigating it further in combination with new agents, especially in high risk populations. CC-122, a pleiotropic pathway modifier, is currently being investigated in various malignancies, including lymphomas[149]. Like lenalidomide, it promotes the degradation of the Aiolos and Ikaros transcription factors which are frequently up-regulated in CLL. CC-122 exhibits superior anti-proliferative activity *in vitro* compared to lenalidomide[149].

10. Conclusion

The plethora of new agents recently approved for the treatment of RR CLL has greatly enhanced our therapeutic armamentarium against the most common leukemia in the Western hemisphere. The availability of potent drugs directed against diverse targets such as the BCR, BCL2 and CD20 opens up numerous possibilities for rational combinations, such that “cure” may become a realistic possibility for most patients with CLL in the not too distant future. More choices also pose new challenges regarding optimal sequencing and combination of these agents, delineation of mechanisms of resistance, and cost.

11. Expert Opinion

Pharmacotherapy of CLL has come a long way in the last few years. Before 2014, therapeutic options were limited to CIT, monoclonal antibodies such as rituximab, ofatumumab or alemtuzumab, used either singly or in combination with steroids, and the off-label use of lenalidomide, with or without rituximab. The last three years have seen the introduction of three first-in-class, oral small-molecule targeted therapies with unique mechanisms of action, i.e., ibrutinib, idelalisib and venetoclax, for the treatment of patients with relapsed/refractory disease, followed by the approval of ibrutinib for upfront use. Obinutuzumab, while approved only in the frontline setting for patients with CLL at this time, represents the most potent anti-CD20 monoclonal antibody to be licensed yet. Deletion 17p and TP53 aberrations had thwarted CIT for many years before efficacy of the BCR signaling inhibitors[5, 150] and venetoclax[113] was demonstrated, leading to specific regulatory approvals of ibrutinib and venetoclax for patients with these genomic abnormalities, which are significantly more common in the relapsed setting. All these new tools have provided substantial enthusiasm that a cure may now be on the horizon for most patients with CLL, given that CIT already produces long-term treatment-free remissions in the subset of patients with mutated *IGHV* and favorable genomic features such as deletion 13q, trisomy 12 and normal interphase fluorescence in situ hybridization (FISH)[7, 151].

Elimination of MRD is an important therapeutic goal in CLL[152]. While potent frontline combinations such as that of ibrutinib, fludarabine, cyclophosphamide and obinutuzumab (NCT02629809) are attempting to both minimize the duration of exposure to cytotoxic chemotherapy in an MRD-directed manner (thereby mitigating the risk of therapy-related myeloid neoplasms), and achieve deeper and longer-lasting remissions in patients with favorable risk disease, laboratory-based, rational combinations such as that of ibrutinib and venetoclax (e.g., NCT02756897) are being studied in efforts to improve the outcomes of patients with unmutated *IGHV*, deletion 11q and/or deletion 17p, in whom CIT has inevitably led to disease relapses and less than satisfactory outcomes. While ibrutinib has been a remarkable advance for patients with CLL, particularly for those with unmutated *IGHV*[153] and/or deletion 17p[150], the very low rates of CR with ibrutinib monotherapy in the RR setting[52] and its off-target toxicities represent important shortcomings. The former calls for rational combinations and venetoclax is a particularly attractive partner for the reasons discussed earlier in the article. Preclinically, ibrutinib may antagonize the effects of rituximab[154], and while such antagonism is not apparent clinically, it is not clear that the addition of rituximab alone[78] or even CIT[77] to ibrutinib adds meaningful benefit

over rituximab alone in the RR setting. Early results with more specific BTK inhibitors such as acalabrutinib[63] suggest that these agents may avoid off-target toxicities of ibrutinib such as atrial fibrillation and bleeding while retaining similar efficacy. Particularly intriguing in this context is data that BTK levels in CLL patients on ibrutinib diminish over time[155], which might argue for the use of lower doses[156]. Indeed, 95% BTK occupancy was achieved at doses 2.5 mg/kg/day and higher in the phase 1 trial of ibrutinib[157]. Pharmacodynamic correlates of ibrutinib dosing at 420, 280 and 140 mg daily in three consecutive months is being tested in a small pilot study (NCT02801578). Lower doses may be expected to result in reduced binding to off-target kinases, thereby decreasing toxicity, while sufficiently inhibiting BTK, which has been shown to be the principal therapeutic target of ibrutinib in CLL[44] and vindicated by the success of the more selective BTK inhibitor acalabrutinib[63].

While PI3K is a *bona fide* target in the BCR pathway, the toxicity profile of idelalisib has somewhat limited its use, particularly given the availability of ibrutinib. Furthermore, idelalisib is approved in conjunction with rituximab, while ibrutinib is approved as monotherapy. Nevertheless, idelalisib remains a valuable agent, particularly for some patients who fail ibrutinib[93], and its use is likely to increase given increasing adoption of frontline ibrutinib in community practice and also demonstration of a survival benefit with the addition of idelalisib to BR over BR alone in the RR setting[158]. Other PI3K inhibitors with reportedly better toxicity profiles, such as duvelisib and TGR-1202, are in clinical trials, and their availability in the future would be a welcome development.

The approval of venetoclax over a decade after the first genuine BH3-mimetic was characterized[159] represents a landmark development in the history of BCL2 and apoptosis research. While undoubtedly a very exciting agent, data on the clinical efficacy of venetoclax in patients previously exposed to BCR inhibitors is only now emerging[114]. Venetoclax provides a mechanistically distinct (from the BCR pathway inhibitors) option for patients with deletion 17p[113] and produced higher rates of CR/CRi and MRD negativity in the original phase 1/2 trial[11] in patients with RR CLL than have been seen with ibrutinib monotherapy[52]. However, it is likely that the optimal role of this first-in-class agent will ultimately lie in combinations with other targeted drugs. Besides the rational combination with ibrutinib discussed above, combining venetoclax with specific inhibitors of MCL-1[160, 161] or CDK9[162] is particularly appealing. At this time, however, single agent venetoclax represents the main option for patients with or without deletion 17p who fail ibrutinib, idelalisib or both. Recently reported results with the combination of venetoclax and rituximab in patients with RR CLL appear especially encouraging[124].

Although rather early, there is considerable enthusiasm for the use of immune checkpoint inhibitors for the treatment of RS[80, 136], and more mature results from currently ongoing trials (e.g., NCT02420912) are eagerly awaited. Despite early promising data[163], the future role, if any, of chimeric antigen receptor-modified T-cells in the treatment landscape of relapsed CLL is presently unclear[164]. Rates of allo-HCT for RR CLL have expectedly dropped with the introduction of the novel agents discussed in this article[165], but the procedure remains relevant even in the current era of targeted therapies, particularly for young patients with high-risk disease[166, 167]. Specifically, allo-HCT is recommended for

patients with standard-risk CLL who fail to respond to or whose disease progresses after BCR inhibitors. Allo-HCT is also recommended for high-risk patients who fail two lines of therapy and can be “bridged” to allo-HCT using BCR inhibitors or a clinical trial. BCL-2 inhibitors can also serve as a bridge to allo-HCT after the failure of BCR inhibitors – in this situation, allo-HCT is recommended regardless of whether an objective response is achieved. Although never specifically approved for CLL, lenalidomide remains a useful immunomodulatory agent that could potentially be explored further in novel combinations, e.g., with immune checkpoint inhibitors, in patients with RR CLL.

In our practice, we treat patients with RR CLL on clinical trials as much as possible, with regimens such as ibrutinib plus venetoclax, lenalidomide plus obinutuzumab, acalabrutinib, CC-122- or immune checkpoint inhibitor-based combinations (e.g., with ibrutinib or anti-CD20 monoclonal antibodies). Outside of clinical trials, we prefer ibrutinib monotherapy for patients failing frontline FCR. The choice for patients who have received multiple prior therapies depends on the nature and sequence of their previous treatments. As discussed above, data are emerging on the efficacy of venetoclax in patients previously treated with BCR inhibitors[114]; there is also evidence that idelalisib may benefit some patients who fail ibrutinib[93]. In the era of novel, targeted therapies, patients with relapsed CLL post-allo-HCT are approached similarly to those who have not undergone allo-HCT.

According to current treatment paradigms, BCR pathway inhibitors are administered indefinitely, i.e., until disease progression or development of unacceptable toxicity. Combination strategies are being investigated in attempts to improve the quality and depth of responses, which could potentially facilitate treatment discontinuation. This is of particular interest in the light of emerging preclinical data suggesting that PI3K δ and, to a lesser extent, BTK inhibitors increase genomic instability in B-cells via up-regulation of activation-induced cytidine deaminase (AID)[168]. Longer-term follow-up of patients treated with BCR inhibitors is needed to evaluate the clinical impact of these findings.

Last but not the least is the issue of the prohibitive cost of the new targeted therapies for CLL, a problem that would only be compounded by the approval of novel drug combinations which, from a scientific standpoint, are clearly the way forward, unless treatment regimens of defined duration aimed at producing durable treatment-free remissions prove successful and are widely adopted. A recently published simulation model evaluating the evolving management of CLL from 2011 to 2025 that compared the current and predicted future scenarios to one in which CIT remained the standard of care throughout projected a 55% increase in the prevalence of CLL over this period due to improved survival and an increase in the annual cost of CLL management from \$0.74 billion to \$5.13 billion[169]. The per-patient lifetime cost of CLL treatment was estimated to increase from \$147,000 to \$604,000, translating to an increase in out-of-pocket expenditure for Medicare beneficiaries from \$9,200 to \$57,000. Compared with the CIT scenario, oral targeted therapies resulted in an incremental cost-effectiveness ratio of \$189,000 per quality-adjusted life-year[169]. Similar concerns have been raised by experts in chronic myeloid leukemia, another chronic leukemia transformed by the advent of oral targeted therapies[170].

Acknowledgments

Funding:

The authors were supported in part by a MD Anderson cancer centre support grant from the National Cancer Institute P30 CA016672.

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Figure 1.

Signaling through the BCR and anti-apoptotic pathways play critical roles in the survival and proliferation of CLL cells. Activated BCR signaling induces LYN- and SYK-dependent phosphorylation of BTK and PI3K, and activates downstream signal transduction cascades. Additionally, activated BCR signaling, primarily through SYK and PI3K, leads to up-regulation of MCL-1 as shown. Pharmacologic inhibitors of CDK9 suppress MCL-1 via transcriptional inhibition. CLL cells are particularly addicted to BCL-2 for survival, explaining the activity of BH3-mimetics, e.g., venetoclax. MCL-1 and BCL-xL are major mediators of resistance to venetoclax. Mutations in BTK and its immediate downstream effector, PLCγ2, confer resistance to therapeutic BTK inhibition. Drugs targeting the various kinases, surface proteins and anti-apoptotic proteins are shown. *Abbreviations:* BCR, B-cell receptor; SYK, spleen tyrosine kinase; BTK, Bruton's tyrosine kinase; PI3K, phosphatidylinositol-3-kinase; PLCγ2, phospholipase C gamma 2; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor kappa B; PKCδ, protein kinase C delta; GSK3, glycogen synthase kinase 3; BCL-2, B-cell lymphoma 2; BCL-xL, B-cell lymphoma extra long; MCL-1, myeloid cell leukemia 1; CDK9, cyclin dependent kinase 9.

Table 1.

Drugs currently in use or being studied in CLL

Cytotoxic chemotherapy	Anti-CD20 monoclonal antibodies	BTkI	PI3Ki	BCL2 antagonists	Immune checkpoint inhibitors	Immunomodulatory agents	Other monoclonal antibodies
Fludarabine Pentostatin Cyclophosphamide Chlorambucil Bendamustine	Rituximab Obinutuzumab Ofatumumab Ublituximab	Ibrutinib Acicabrutinib CC-292 BGB-3111 SNS-062 GNE-431	Idelalisib Duvelisib Copanlisib TGR-1202	Venetoclax	Nivolumab Durvalumab Pembrolizumab Atezolizumab	Lenalidomide CC-122	Anti-CD19: MOR208 Anti CD37: Oflertuzumab AntiCD52: alemtuzumab

Table 2:

Major clinical trials of novel agents in RR CLL

Phase	Patients	Intervention	ORR (CR/CRi)	PFS/OS
Ibrutinib				
Phase 1b/2[52]	N = 85 Del17p = 28 (33%) Del11q = 31 (36%) Unmutated <i>IGHV</i> = 69 (81%) Median number of prior therapies = 4	Ibrutinib dose 420 – 840 mg/day	91% (2%)	Estimated PFS at 26 months = 75% Estimated OS at 26 months = 83%
Phase 2 (RESONATE-17)[150]	N = 144 Del17p = 144 Median number of therapies = 2	ibrutinib	100% (2%)	Estimated PFS at 12 months = 79.3
Phase 3[27] (RESONATE)	N = 391 Del17p = 127 (32%) Del11q = 122 (31%) Median number of prior therapies in ibrutinib arm = 3	Ibrutinib vs. ofatumumab	Ibrutinib = 63% (0%) Ofatumumab = 4% (0%)	6-month PFS Ibrutinib = 88% Ofatumumab = 65% (p < 0.001) OS at 1 year Ibrutinib = 90% Ofatumumab = 81% HR for death = 0.43 favoring ibrutinib (p=0.005)
Phase 3[77] (HELIOS)	N = 578 Del17p: excluded Del11q = 152(26) Median number of therapies in ibrutinib arm = 2	Ibrutinib + BR vs. Placebo+ BR	Ibrutinib + BR=83% (10%) Placebo + BR=68% (3%)	Median PFS iBR = NR placeb+BR = 13.3 months (p < 0.0001) Median OS NR in both groups, (p = 0.059)
Idelalisib				
Phase 3[57]	N = 220 Del17p/p53 mutation = 87 (39%) Unmutated <i>IGHV</i> = 168 (76%) Median number of prior therapies in idelalisib group = 3	R plus idelalisib vs. R plus placebo	R + idelalisib = 81% (0%) R + placebo = 13% (0%)	Median PFS R+idelalisib = NR R+placebo = 5.5 months (p < 0.001) 1-year OS -R plus idelalisib = 92% -R plus placebo = 80% (p=0.02)
Phase 3[92]	N = 416 Del17p/p53 mutation= 137 (33%) Unmutated <i>IGHV</i> = 345 (83%) Median number of prior therapies in idelalisib + BR arm = 2	Idelalisib + BR vs. BR + placebo		Median PFS Idelalisib + BR = 23 months BR+placebo = 11 months (p = 2.8×10^{-14}) Median OS Idelalisib + BR = NR BR + placebo = 41 months (p value = 0.036)
Venetoclax				
Phase 1[11]	N = 116 Del17p = 31 (30%) Del11q = 28 (27%) Median number of prior therapies = 3	Venetoclax	79% (20%)	PFS at 15 months = 66%
Phase 2[113]	N = 107 Del17p = 107 Median number of prior therapies = 2	Venetoclax	79% (8%)	Estimated 12 months PFS = 72% Estimated 12 months OS = 87%
Phase 1b[124]	N = 49 Del17p = 9 (18%) Del11q = 20 (41%) Unmutated <i>IGHV</i> = 19 (39%)	Venetoclax + rituximab	86% (51%)	Estimated 2 year PFS = 82% Estimated 2 year OS = 94%

Phase	Patients	Intervention	ORR (CR/CRi)	PFS/OS
	Median number of prior therapies = 2			
Otlertuzumab				
Phase 2[41]	N = 65 Del17p/p53 mutation = 17 (26%) Median number of prior therapies in otlertuzumab +bendamustine arm = 6	Otlertuzumab + bendamustine vs. bendamustine alone	Otlertuzumab + bendamustine = 69% Bendamustine = 39%	Median PFS Otlertuzuamb +bendamustine = 15.9 months Bendamustine = 10.2 months p = 0.0192

Abbreviations: BR, bendamustine plus rituximab; NR, not reached; PFS, progression-free survival; OS, overall survival; CR, complete remission; CRi, complete remission with incomplete count recovery; ORR, overall response rate.