Small Molecules in Chronic Lymphocytic Leukemia: Novel Targets, New Challenges

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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Abstract

The treatment of chronic lymphocytic leukemia (CLL) is in a state of transformation owing largely to an improved understanding of the pathways and molecular targets in normal B-cell development, the role aberrant pathways play in the development of B-cell malignancies, and how these aberrations can be exploited for therapeutic benefit. Small-molecule agents are among the new agents recently approved for the treatment of CLL. Understanding the individual mechanisms of action provides a critical foundation for the advanced practitioner (AP) necessary for the safe and effective administration of small-molecule agents. The goals of this paper are to highlight the B-cell receptor and associated pathways, the B-cell lymphoma 2 family of proteins, and the tumor microenvironment with discussion of agents targeting these pathways currently approved for the treatment of CLL. Highlights from pivotal clinical trials including drug properties, specific administration requirements, management and mitigation of adverse events, and application of the experience gained from clinical trials are included. The currently approved small-molecule agents for CLL are oral therapies. Given the significant role APs play in the management of adverse events (AEs) and emergent outpatient visits to avoid emergency department visits or hospitalization, AE management will be highlighted.

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Small-molecule antineoplastic therapy has become a mainstay for the treatment of solid and liquid tumors. Understanding aberrant signaling pathways in cancer cells has enabled the development of small-molecule agents that target protein tyrosine kinases and growth factor receptors, which are both critical to cell proliferation, differentiation, migration, angiogenesis, and cell-cycle regulation in normal cells and tumorigenesis in aberrant cells (Imai & Takaoka, 2006). Small molecules, by definition, have a lower molecular weight, are oral agents, have a shorter half-life than monoclonal antibodies,

and have pharmacokinetic properties that vary between patients (Imai & Takaoka, 2006). Understanding the role of individual pathways and molecular targets in normal B-cell development, the role aberrant pathways play in the development of B-cell malignancies, and how these aberrations can be exploited for therapeutic benefit is critical to the safe and effective administration of agents used to treat chronic lymphocytic leukemia (CLL). In addition, the microenvironment—a network of specialized cells including mesenchymal stromal cells, nurse-like cells, endothelial cells, follicular dendritic cells, T lymphocyte and natural killer cells, chemokines, adhesion molecules, and angiogenic factors—plays a critical role in the pathogenesis of CLL.

The ability to exploit aberrations in the B-cell receptor (BCR) and associated signaling pathways, B-cell lymphoma 2 (Bcl-2) family of proteins, and the tumor microenvironment using novel agents has led to the approval of several new agents, with many others are currently in clinical trials. Small molecules are currently being used as single agents, in combination with monoclonal antibodies, or in combination with chemoimmunotherapy. The safe and effective administration of small-molecule drugs requires a working knowledge of the drug properties, application of the experience gained from clinical trials, and awareness of the underlying principles of oral therapies in cancer treatment.

The purpose of this paper is to provide the advanced practitioner (AP) in oncology with an overview of the pathways and targets relative to small molecules used to treat CLL. Given the significant role APs play in the management of adverse events (AEs) and emergent outpatient visits to avoid emergency department visits or hospitalization, AE management will be highlighted (Kurtin et al., 2015). The focus will be on currently approved agents, as emerging therapies are discussed in the "Emerging Therapies in Chronic Lymphocytic Leukemia: Current Trials" article (by Glode and Babiker) in this supplement.

BCR RECEPTOR SIGNALING AND THE TUMOR MICROENVIRONMENT

Normal B-lymphocyte development relies on both signaling pathways and the microenvironment for the homing, survival, and proliferation of cells. B-cell receptor signaling through both antigen-dependent and antigen-independent mechanisms plays a key role in normal B-lymphocyte development and survival, and when aberrant or upregulated, in the pathogenesis of CLL (Choi, Kashyap, & Kumar, 2016; Gauld, Dal Porto, & Cambier, 2002; Jeyakumar & O'Brien, 2016; ten Hacken & Burger, 2014; Wang, Zhang, Champlin, & Wang, 2015). Antigen-specific membrane-bound immunoglobulins (CD79a/CD79b) and accessory molecules, once activated via ligands or via tonic mechanisms, activate downstream signaling via intracellular kinases and adapter proteins, leading to activation of SRC family kinases, LYN kinases, spleen tyrosine kinase (SYK), Bruton's tyrosine kinase (BTK), phospholipidase Cγ2 (PLCγ2), phosphatidylinositol 3-kinase (PI3K), and other signaling molecules and cascades (Burger et al., 2015; Choi et al., 2016; Figure 1). When combined with elements of the tissue microenvironment, these signaling pathways regulate B-cell selection, differentiation, proliferation, motility, homing, adhesion, chemotaxis, and survival (Scupoli & Pizzolo, 2012).

Chronic lymphocytic cells move continuously between the peripheral blood and lymphatic tissues (ten Hacken & Burger, 2014). Chemokines secreted by stromal cells, together with adhesion molecules on CLL cells and their correlating tissue-ligands, play a role in disrupting the normal migration of B lymphocytes, thereby increasing the homing of abnormal cells to tissues (ten Hacken & Burger, 2014; Figure 1). The improved understanding of each of these elements in both normal and abnormal B-cell development has elucidated actionable targets for the treatment of CLL. Small-molecule agents targeting protein kinases in the BCR pathway, including BTK inhibitors, PI3 kinase inhibitors, and BCL2 inhibitors, have recently been approved for the treatment of CLL, and others are currently in clinical trials. Similarly, agents targeting elements of the tumor microenvironment are in various stages of clinical development.

BTK INHIBITORS

Bruton's tyrosine kinases are constitutively active and expressed at higher levels in CLL cells than on normal B cells, and are involved in the regulation of the migration and adhesion of B cells via chemokines and integrin signaling (Choi

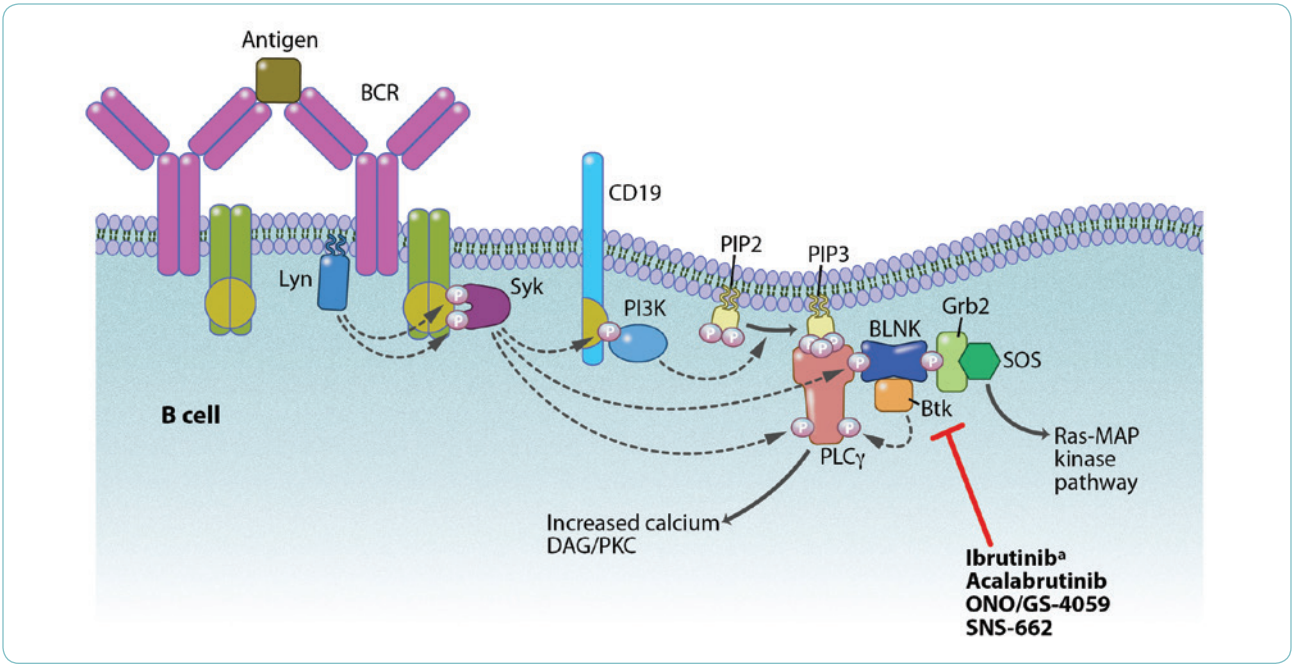

Figure 1. B-cell receptor pathway. BCR = B-cell receptor; Syk = spleen tyrosine kinase; PI3K = phosphatidylinositol 3-kinase; PLCγ = phospholipidase Cγ; Btk = Bruton's tyrosine kinase. [a]FDA approved.

et al., 2016; Ponader et al., 2012). Bruton's tyrosine kinase plays a critical role in BCR signaling, including the activation of transcription factors necessary for B-cell proliferation, differentiation, and survival. In addition, BTK plays a key role in B-cell trafficking and tissue homing via interactions with the tissue microenvironment (Ponader et al., 2012). Inhibition of BTK leads to the disruption of BCR signaling and B-cell apoptosis. Importantly, the disruption of the homing and migration patterns for B lymphocytes in the presence of BTK inhibitors largely explains the common pattern of rapid reduction in lymphadenopathy and an increase in lymphocytosis (Woyach et al., 2014). The presence of lymphocytosis early in the treatment of CLL is not felt to represent disease progression and does not confer inferior survival (Woyach et al., 2014). In fact, in May 2011 the Lymphoma Research Foundation sponsored a workshop to discuss the CLL response criteria relative to novel agents and recommended that in the absence of other objective evidence of progressive disease, such as anemia, thrombocytopenia, lymphadenopathy, or hepatosplenomegaly, treatment should continue (Cheson et al., 2012). Because of these recommendations, a partial response with lymphocytosis (PR-L) category has been added to the response criteria for CLL (Wierda et al., 2017).

Ibrutinib

Ibrutinib, a first-in-class irreversible inhibitor of BTK, has broad indications in the treatment of CLL in treatment-naive (TN), relapsed or refractory (RR), deletion (del[17p]) CLL patients over the age of 65 (Foluso, Glick, Stender, & Jaiyesimi, 2016; Maddocks & Jones, 2016). The three pivotal trials are summarized in Table 1, including the RESONATE trial (Byrd et al., 2014), the RESONATE- 2 trial (Burger et al., 2015), and the HELIOS trial (Chanan-Khan et al., 2016). Among the 656 CLL patients participating in these trials, the overall response rate (ORR) ranged from 63% to 88% in RR CLL and 97% in treatment-naive CLL, including patients with unfavorable attributes such as del(17p), 11q, and unmutated immunoglobulin heavy variable gene (u*IgHV*). Patients with RR CLL (RESONATE and HELIOS trials) had a median of 2 prior therapies (range 1–13), with a median age between 64 and 73 years. Although ORR and progression-free survival (PFS) rates in these trials are promising, complete re-

Table 1. Registration Trials for FDA-Approved Small Molecules Used in the Treatment of Chronic Lymphocytic Leukemia

Agent and target	Trial information	Population	Key outcomes and FDA-approved indication	Indication
Ibrutinib BTK inhibitor	RESONATE phase III (Byrd et al., 2014)	RR CLL N = 391	• PFS: 8% reduction in risk of progression or death vs. ofatumumab (HR, 0.22 [95% CI = 0.15–0.32; $p < .0001$]) • OS: 57% reduction in risk of death vs. ofatumumab (median follow-up of 9.4 months)	CLL and SLL (newly diagnosed or RR CLL); CLL/SLL with del(17p)
	RESONATE-2 phase III (Burger et al., 2015)	TN CLL/SLL age > 65 years n = 269	• PFS: 84% reduction in risk of death or progression vs. chlorambucil (HR, 0.16 [95% CI = 0.09–0.28; $p < .0001$]) • OS: 56% risk of reduction of risk of death; 41% of patients crossed over to ibrutinib arm after progression on chlorambucil • Estimated survival rates at 24 months: 95% for ibrutinib, 84% for chlorambucil	
	HELIOS phase III (Chanan-Khan et al., 2016)	RR CLL n = 578	• PFS: 80% reduction in risk of death or progression in IBR vs. placebo + BR • ORR: 83% for IBR vs. 68% in BR alone	
Idelalisib PI3K inhibitor	Study 116 phase III (Furman et al., 2014)	RR CLL n = 220	• PFS: 85% reduction in risk of death or progression vs. placebo + rituximab (95% CI = 0.08–0.28; unadjusted $p < .001$) • OS: 92% vs. 80% in the placebo + rituximab (HR for death, 0.28 [95% CI = 0.09–0.86; $p = .02$])	• Relapsed CLL in combination with rituximab in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities • Relapsed SLL in patients who have received at least 2 prior systemic therapies • Accelerated approval was granted for follicular lymphoma and SLL based on overall response rate. An improvement in patient survival or disease-related symptoms has not been established. Continued approval for these indications may be contingent upon verification of clinical benefit in confirmatory trials.

Note. BTK = Bruton's tyrosine kinase; RR = relapsed or refractory; CLL = chronic lymphocytic leukemia; TN = treatment naive; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; OS = overall survival; IBR = ibrutinib, bendamustine, and rituximab; BR = bendamustine and rituximab; ORR = overall response rate; SLL = small lymphocytic lymphoma; CR = complete response; PR = partial response; FDA = US Food and Drug Administration.

sponses (CR) were rare, indicating a need to explore other novel combinations (Jain et al., 2017). Several trials evaluating these novel combinations as well as second-generation BTK inhibitors are underway.

Effective utilization of ibrutinib in the treatment of CLL across indications requires a familiarity with anticipated early and late AEs and strategies to prevent or mitigate them. The most common AEs cited for early discontinuation of ibrutinib included

Table 1. Registration Trials for FDA-Approved Small Molecules Used in the Treatment of Chronic Lymphocytic Leukemia (cont.)

Agent and target	Trial information	Population	Key outcomes and FDA-approved indication	Indication
Venetoclax BCL2 inhibitor	Phase II single-arm trial (Roberts et al., 2016)	RR CLL with del(17p) N = 85	• ORR: 80.2% (CR = 5.7%; PR = 72.6%)	• Treatment of patients with CLL with del(17p), as detected by an FDA-approved test, who have received at least 1 prior therapy • This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Note. BTK = Bruton's tyrosine kinase; RR = relapsed or refractory; CLL = chronic lymphocytic leukemia; TN = treatment naive; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; OS = overall survival; IBR = ibrutinib, bendamustine, and rituximab; BR = bendamustine and rituximab; ORR = overall response rate; SLL = small lymphocytic lymphoma; CR = complete response; PR = partial response; FDA = US Food and Drug Administration.

atrial fibrillation (A-fib), infection, pneumonitis, bleeding, and diarrhea (Barr, Robak, & Owen, 2016; Byrd, et al., 2017; Jain et al., 2017; Mato et al., 2016; Table 2). Adverse event profiles in the postmarketing setting are mostly consistent with profiles reported in the clinical trials, with some variations in frequency and severity in patients on long-term treatment, including persistent hypertension and the incidence of A-fib and bleeding episodes (Barr et al., 2016; Gashonia et al., 2017; Kunk et al., 2016; Mato et al., 2016; Shanafelt et al., 2017; Yun, Vincelette, Acharya, & Abraham, 2017; Table 2).

New-onset A-fib was reported in 6%–9%, associated with ibrutinib administration. Factors shown to correlate with an increased risk of treatment-emergent A-fib include older age (> 75), male sex, valvular heart disease, and hypertension (Shanafelt et al., 2017; Yun et al., 2017). One of the pathways regulated by BTK is the PI3K-Akt pathway, a critical regulator of cardiac protection under stress conditions (McMullen et al., 2014). Preclinical studies suggest that activation of this pathway may contribute to the development of A-fib in some patients treated with ibrutinib (McMullen et al., 2014).

Anticoagulation, a proven method for reducing the potential for ischemic stroke in the setting of A-fib, can be safely managed in CLL patients receiving ibrutinib but requires vigilance and engagement of the patient in early reporting of AEs and maintaining safety (Yun et al., 2017). Grade > 2 bleeding events were observed in 6% of patients on ibrutinib; the mechanism is not well understood. Importantly, patients receiving warfarin sodium were excluded from clinical trial participation (Wierda et al., 2017). Although the exact mechanism for the increased bruising and bleeding risk associated with ibrutinib administration is not well understood, preclinical studies suggest that there may be inhibition of platelet adhesion to collagen on von Willebrand factor, integrin signaling, and collagen-mediated platelet aggregation (Levade et al., 2014). Therefore, the risks and benefits of anticoagulation or antiplatelet medications should be evaluated and discussed with individual patients. Ibrutinib should be held 3 days before and after a minor surgical procedure and 7 days before and after a major surgical procedure.

Uncontrolled adverse events continue to be a leading cause of treatment discontinuation in older patients (Barr et al., 2016). Importantly, patients who discontinued ibrutinib due to progression of disease may benefit from other small-molecule agents; however, those who progress with Richter's transformation have an extremely poor prognosis, with an estimated life expectancy of 1.5 years (Mato, Jauhari, & Schuster, 2015). In addition, a change to a new therapy in patients who progress on ibrutinib should be made as soon as possible, as progression may accelerate when ibrutinib is stopped.

Table 2. Common Adverse Events Associated With Small Molecules Used to Treat Chronic Lymphocytic Leukemia

Adverse event (%) (Alphabetical order)	Ibrutinib		Idelalisib		Venetoclax	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
ALT/AST elevation	NR	NR	28–39	11-18 # !	NR	NR
Anemia	33–46	0	NR	NR	29	18
Anorexia	21	2	16	2	NR	NR
Arthralgia/myalgia	16–59	0–2	9	1	10	< 1
Atrial fibrillation	6–16	2–6 #	NR	NR	NR	NR
Bleeding/hemorrhage	44–69	0–6 #	NR	NR	NR	NR
Bruising	20–26	0–2	NR	NR	NR	NR
Colitis	NR	NR	–	14–19 !	NR	NR
Contraindications	None		History of serious allergic reactions		Concomitant use of strong inhibitors of CYP3A at initiation and during ramp-up	
CYP3A interactions	Yes		Yes		Yes	
Diarrhea	36–59	4	32	11 # !	35	< 1
Dose modification	Hepatic/hematologic		Hepatic/hematologic		Hepatic/hematologic/TLS	
Edema	8–29	0–1	NR	NR	11	< 1
Embryofetal toxicity	Possible #		Possible #		Possible #	
Fatigue/lethargy	5–30	0–5	5	0	21	2
Hypertension	11–16	4–8 #	NR	NR	NR	NR
Infections	See pneumonia/URI		5–9	21–36 !	See pneumonia/URI	
Intestinal perforation	NR	NR	Reported		NR	NR
Lymphopenia	NR	NR	21	10	NR	NR
Nausea	16–20	0–2	30	1	33	< 1
Neutropenia	4–24	0–5 #	65	42	45	41 #
Pneumonia/URI	10–26	4–20 #	30	21	30	6
Pneumonitis	NR	NR	–	4 !	NR	NR
Rash	3–47	0–3	27	4	NR	NR
Sepsis	NR	NR	NA	9	NR	NR
SPM	3–16	NA	NR	NR	NR	NR
Laboratory TLS+	Rare; #	0	NR	NR	6	6 #
Thrombocytopenia	16–21	5–10 #	NR	NR	22	15

Note. FDA = US Food and Drug Administration; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NR = not reported; # = warning and precautions; ! = black box warning; URI = upper respiratory infection; SPM = secondary primary malignancies; TLS = tumor-lysis syndrome; + = using ramp-up dosing of venetoclax. Information from AbbVie (2016); Gilead (2017); Pharmacyclics (2016).

Acalabrutinib

Acalabrutinib (ACP-196) is a selective BTK inhibitor developed to minimize off-target effects seen with ibrutinib that has shown promising clinical activity in patients with relapsed/refractory CLL. In a phase I/II multicenter study, 61 patients (median age 62) with RR CLL received acalabrutinib at a dose of 100 to 400 mg once daily in the dose-escalation (phase I) portion of the study and 100 mg twice daily in the expansion (phase II) portion

of the study (Byrd et al., 2016). The study population included patients with unfavorable risk factors, including 17p13.1 deletion (n = 18/59, 31%) and u*IgHV* (n = 38/51, 75%). At a median follow-up of 14.3 months, the ORR was 95%, including 85% with a PR and 10% with a PR-L. Among the 18 patients with a 17p13.1 deletion, the ORR was 100% (PR = 89%, PR-L = 11%). No cases of Richter's transformation and only one case of CLL progression occurred. The most common adverse events observed were headache (43%), diarrhea (39%), weight gain (26%), and pyrexia (23%). Most adverse events were of grade 1 or 2. No major hemorrhage or atrial fibrillation was noted in this dose-finding trial. A phase III trial comparing acalabrutinib with ibrutinib in RR CLL is underway (ClinicalTrials.gov, NCT02477696).

PI3 KINASE INHIBITORS

The PI3K pathway plays a key role in B-cell development, proliferation, metabolism, protein synthesis, and survival (Fruman et al., 2017; Okkenhaug & Burger, 2016; Figure 2). In B lymphocytes, the PI3K pathway is under the control of the BCR. PI3Ks mediate signals from the B-cell receptor that not only facilitate the development of functional B cells but also support the growth and survival of neoplastic B cells, including CLL cells (Okkenhaug, Graupera, & Vanhaesebroeck, 2016). There are several isoforms that exist in cell signaling. The PI3Kδ isoform is unique to leukocytes in B-cell malignancies, specifically CLL. PI3Kδ is a central integrator of signals from the BCR, CD19, and the tissue homing cytokines, CXCR4, CXCR5, in B cells. Class I PI3Ks phosphorylate phosphatidylinositol (4,5) P2 (PIP2) to generate phosphatidylinositol (3,4,5)P3 (PIP3). PIP3 is essential for the activation of Akt and contributes to the activation of Btk. Inhibition of PI3K directly affects stromal elements including vasculature (angiogenesis), infiltrating immune cells, fibroblasts, and connective tissue, essentially disrupting the normal nurturing processes needed for cellular development (Okkenhaug et al., 2016). This growth arrest suggests that inhibition of PI3K is more cytostatic than cytotoxic, rendering the cells dormant in a nutrient-deprived state (Okkenhaug et al., 2016). This is evidenced in the current in-

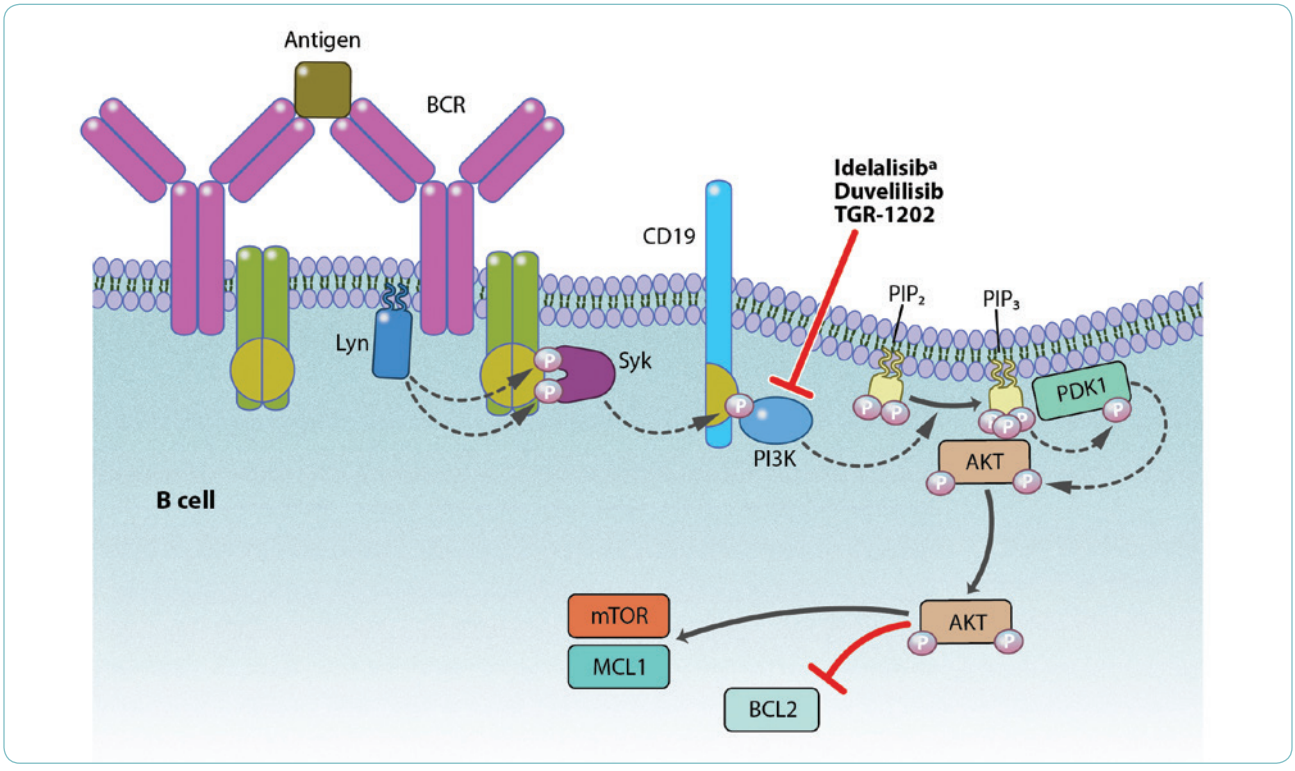

Figure 2. Phosphatidylinositol 3-kinase pathway.
[a]FDA approved.

vestigation of intermittent dosing of idelalisib as well as combination therapies where multiple targets can be exploited simultaneously (Mato et al., 2017). In addition, inhibition of PI3K results in a decreased number of T-regulatory cells, resulting in enhanced antitumor immunity, but also a loss of self-tolerance and enhanced T-effector activity, thought to play a primary role in the increased risk of infections and autoimmune toxicity (Ali et al., 2014; Cheah & Fowler, 2016).

Idelalisib

Idelalisib is a first-in-class PI3K inhibitor that selectively inhibits PI3Kδ. It is currently approved for treatment of relapsed follicular lymphoma and relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic treatments and for the treatment of relapsed CLL in combination with rituximab in patients for whom rituximab alone would be considered appropriate therapy because of other comorbidities (Gilead, 2017).

Preclinical studies and early-phase human trials established the affinity of idelalisib for selective inhibition of PI3Kδ signaling and the preferred dosing of 150 mg twice daily (Flinn et al., 2014). A follow-up phase III randomized, double-blind, placebo-controlled trial of rituximab and idelalisib vs. placebo in 220 patients with RR CLL (median age, 71 years). Patients received rituximab dosed at 375 mg/m^2 for the first dose and then 500 mg/m^2 every 2 weeks for four doses and then 500 mg/m^2 every 4 weeks for three doses. They were then assigned either oral idelalisib at 150 mg twice daily or placebo (Furman et al., 2014). The primary endpoint of the study was PFS, with secondary endpoints including overall survival, ORR, CR, PR, and lymph node response.

An interim analysis performed at 24 weeks revealed increased PFS favoring the idelalisib arm (93% vs. 46%, respectively ($p < .001$). Overall survival in the idelalisib group was 92% vs. the placebo group 80% at 12 months, with a median OS not reached at the time of the analysis. No CR was seen in the study, with PRs seen in 81% of the idelalisib arm vs. 13% in the placebo arm ($p < .001$). Further analysis of poor prognostic factors in a post hoc analysis revealed that 17p deletion, mutation of *TP53*, and u*IgHV* status favored the idelalisib group.

Adverse events were common, with 90% of participants reporting at least one AE. The most common AEs reported in the idelalisib arm vs. the placebo arm included pyrexia (29% vs. 16%), fatigue (24% vs. 27%), nausea (24% vs 21%), chills (22% vs. 6%), and diarrhea (19% vs. 14%). Grade 3 or higher hepatic aminotransferase elevations occurred in six patients (5%) in the idelalisib group, with onset at 8 to 16 weeks, with only one patient having similar toxicity in the placebo group. Discontinuation of therapy was seen in 9 patients (8%) in the idelalisib arm and 11 patients (10%) in the placebo group. Discontinuation in the idelalisib arm was secondary to gastrointestinal and skin disorders in most of these patients (6 patients). Importantly, the diarrhea associated with idelalisib occurs in two phases: early onset within the first 8 weeks, amenable to antimotility agents, and late onset, more characteristic of the immune mediated colitis, which may respond to budesonide.

Several other clinical studies are looking at the combination of idelalisib with other agents in the treatment of CLL (Table 1). A recent phase III study evaluated the combination of idelalisib and ofatumumab for CLL (Jones et al., 2015). The study evaluated 261 patients and showed an increase in the ORR that was significantly higher in the idelalisib plus ofatumumab arm in comparison to ofatumumab monotherapy (75% vs. 18%, $p < .0001$). Similarly, the median PFS was longer (16.3 vs. 8 months, $p < .0001$), and showed improved outcomes in high-risk patients including patients with del(17p) and/or *TP53* mutation (13.7 vs. 5.8 months, $p < .0001$). However, the study did not show an OS difference observed (20.9 vs. 19.4 months, $p = .27$).

Several other studies are looking at combination therapies including bendamustine, rituximab, and idelalisib. Evaluating these combinations in CLL patients will depend on patient risk factors, tolerability to idelalisib combination, and the sequencing of these regimens into a patient's treatment trajectory (Table 2).

Importantly, owing to increased risk of serious infections, idelalisib is not recommended in the front-line setting, and prophylaxis for herpes simplex virus and *Pneumocystis jirovecii* pneumonia (PJP) is recommended (Wierda et al., 2017). Baseline and routine monitoring for cytomegalovirus (CMV) reactivation is also recommended (Wierda et al., 2017). Additionally, late-onset pneumonitis

(median, 7.8 months) may occur requiring differential diagnosis (infection vs. pneumonitis), as steroids are required for treatment.

BCL-2 INHIBITION

Programmed cell death, or apoptosis, is regulated by multiple pathways including both intrinsic (mitochondrial) and extrinsic (cell membrane) elements (Levy & Claxton, 2017). Apoptosis occurs via release of cytochrome C and other caspases (death proteins) that induce permeability of the mitochondrial outer membrane (MOMP) leading to cellular demolition necessary to maintain cellular homeostasis (Levy & Claxton, 2017; Roberts & Huang, 2017). Evasion of apoptosis is considered an oncogenic process (Ortiz-Maldonado, Mozas, & Delgado, 2016). The intrinsic pathway is primarily regulated by the BCL-2 family of proteins (Ortiz-Maldonado et al., 2016; Figure 3). There are at least 19 proteins in the BCL-2 family.

The BAX, BAK and BCL-2 homology 3 (BH3) family of proteins, including the myeloid cell leukemia 1 (MCL1), are particularly important in understanding the role of BCL-2 in CLL (Figure 3). In normal cellular regulation there is a balance between proapoptotic (BH3) and antiapoptotic (BCL2, MCL1) proteins. BH3 proteins can either be activators or sensitizers. When exposed to stressors, cell damage, genomic instability, or activation of oncogenes, this balance is upset, antiapoptotic proteins (BCL2) are overexpressed, and BH3 activator proteins are suppressed and fail to activate death effector molecules (BAX and BAK), leading to increased survival of the abnormal clone (Levy & Claxton, 2017; Ortiz-Maldonado et al., 2016; Roberts & Huang, 2017). BCL-2 overexpression, common in CLL, confers a survival advantage to B lymphocytes, and is associated with lymphomagenesis and resistance to standard chemotherapeutic agents, including DNA-damaging drugs, antimicrotubular drugs, nucleoside analogs, and glucocorticoids (Miyashita & Reed, 1993; Vaux, Cory, & Adams, 1988). Deletions or mutation in the *TP53* gene on chromosome 17 decreases BH3 protein expression, making the CLL cells relatively resistant to DNA-damaging agents. Suppression of BCL2 and other elements of the intrinsic pathway, including BH3, provide an attractive option for the treatment of CLL.

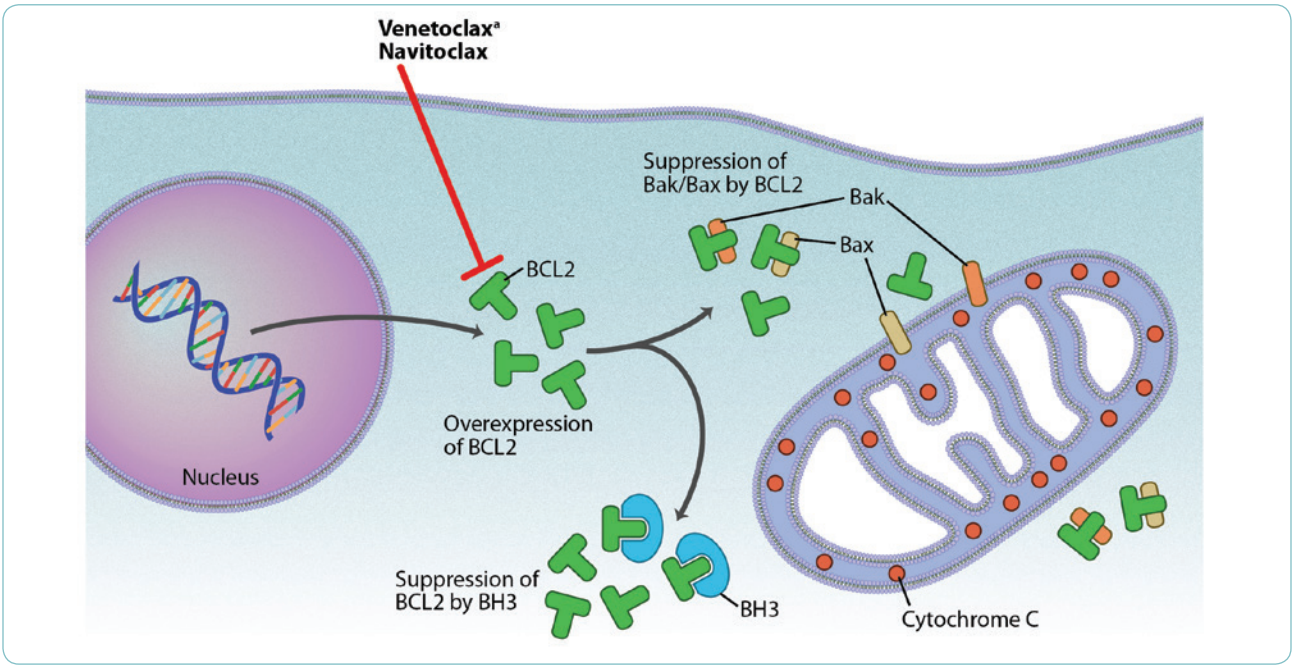

Figure 3. BCL2 pathway. Overexpression of BCL2 prevents proapoptotic Bak and Bax from forming pores in the outer mitochondrial membrane that would release cytochrome C, thus promoting cell survival. BCL2 = B-cell lymphoma 2.
[a]FDA approved.

Venetoclax

Venetoclax, a first-in-class small-molecule inhibitor of BCL2, is approved for the treatment of patients with CLL with 17p deletion, as detected by an FDA-approved test, who have received at least one prior therapy (AbbVie, 2016). Approval was based on data from a phase I and phase II trial, with 79% of all patients (n = 107) in both trials achieving an objective response, regardless of the dose of venetoclax (Roberts et al., 2016; Roberts & Huang, 2017; Table 1). The estimated 12-month PFS (72%) and OS (86.7%), together with ORR (> 70%) in patients with adverse risk features (fludarabine refractory, bulky disease, del(17p), *TP53* mutation) led to the drugs approval. Neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%) were the most common treatment-related AEs (Table 2).

In a phase II, open-label study (n = 54), in patients previously treated and refractory to either ibrutinib (n = 41, arm A) or idelalisib (n = 13, arm B), or both (n = 6, 3 in each arm), venetoclax monotherapy showed an ORR of 70% in patients previously treated with ibrutinib and 48% in those treated with idelalisib (Jones et al., 2016). Subjects in this study had adverse risk factors, including 54% with more than 5 prior therapies, 83% with u*IgHV*, 20% with an absolute lymphocyte count > 100 x 10^9, 35% with del(17p), and 24% with ≥ 1 node ≥ 10 cm. Despite these high-risk features, 42 patients (33%) achieved minimal residual disease negative (MRD–) status. Adverse events were similar to those seen in prior studies, with the most common AEs being neutropenia (48%), diarrhea (37%), nausea (35%), anemia (32%), fatigue (24%), and hyperphosphatemia (20%). Only two patients had laboratory tumor lysis syndrome (TLS). This study (ClinicalTrials.gov, NCT02141282) is ongoing and will assess depth and duration of response.

As with many small molecules, combining venetoclax with monoclonal antibodies or chemoimmunotherapy has been the focus of other studies. The combination of venetoclax with rituximab in patients with RR CLL (n = 49) resulted in an ORR of 86%, including a CR rate of 51%. In addition, the 2-year estimate of PFS was 82% (95% confidence interval [CI] = 66%–91%), and 28 patients (57%) achieved MRD– status (Seymour et al., 2017). Venetoclax is being combined with other agents in ongoing clinical trials (Table 1).

Just as with other small-molecule agents, venetoclax has AEs that require risk assessment and measures for prevention. Tumor lysis syndrome is included in the warnings and precautions. Two fatal events and 3 cases of acute renal failure, 1 requiring dialysis, were reported in the initial phase I trial. Subsequent modification of the dosing using a ramp-up method, together with guidelines for evaluation of TLS risk, prevention, and management, resulted in only 6% of patients on the phase II trial reported as having laboratory TLS. No cases of clinical TLS were noted (Roberts et al., 2016). The time to response with venetoclax is rapid, with a range of 0.1 to 8.1 months. Therefore, careful assessment of the risk of TLS prior to initiating therapy is required for safety. Patients at higher risk require inpatient administration of venetoclax and more intensive prevention and monitoring with the initial ramp-up. These guidelines can be found in the prescribing information for venetoclax, are also included in the National Comprehensive Cancer Network (NCCN) guidelines, and are discussed elsewhere in this supplement (Wierda et al., 2017).

IMMUNOMODULATORY AGENTS: LENALIDOMIDE

Chronic lymphocytic leukemia proliferation and survival depends on the microenvironment. Lenalidomide has been shown to regulate several pathways in the inhibition of CLL including immunomodulation, cytotoxic effects on leukemic cells, and perturbation of the CLL microenvironment (Fecteau et al., 2014; Kater, Tonino, Egle, & Ramsay, 2014). The multifaceted mechanism of action is thought to explain the variability in responses seen in clinical trials to date. Although currently not approved for the treatment of CLL, several studies have established clinical activity. However, nonhematologic toxicities noted in the early trials included TLS with associated cardiac-related deaths and tumor flare reactions, which led to a hiatus in investigations aimed at the treatment of CLL (Badoux et al., 2013; Chanan-Khan et al., 2006; Maffei et al., 2016). Subsequent trials were designed to reduce the potential for these reactions using variable dosing of lenalidomide (Wendtner et al., 2016).

Badoux et al. (2011) investigated the role of lenalidomide in newly diagnosed patients 65 years or older. Lenalidomide was administered at a dose of 5 mg for 56 days with dose escalations allowable to a maximum of 25 mg daily. The median follow-up of the study was 29 months, with 53 patients alive and 32 patients remaining on lenalidomide therapy out of a total of 60 enrolled patients. The overall response rate to lenalidomide was 65%, with a 2-year PFS of 60%. The most common side effect was neutropenia, with grade 3/4 rates of 34%. Other side effects included neutropenic fever and infections, which occurred in 13% of patients during treatment. Of note, there were no grade 3 or 4 tumor flare or TLS reported in the study.

Several combination studies have followed suit with lenalidomide combination therapy. Preclinical data have shown that lenalidomide has been seen to activate natural killer cells and induce antibody-dependent cellular cytotoxicity (ADCC). The utilization of concomitant treatment with both lenalidomide and rituximab in CD20-expressing cells would then warrant further exploration. Thus, lenalidomide would seem an appealing therapeutic agent to add to rituximab treatment, which is known to induce ADCC of CD20-expressing CLL cells (Wu et al., 2008).

Ferrajoli and colleagues (2008) investigated the combination of rituximab and in relapsed or refractory CLL. The treatment consisted of weekly rituximab for 4 weeks and then monthly thereafter, with concomitant lenalidomide at a starting dose of 10 mg starting on day 9 of cycle 1. The ORR was reported at 64% with a CR of 8% seen in 60 patients. The most common toxicity observed was neutropenia, seen in 68% of the patients' treatment. In addition, the most frequently observed toxicity was neutropenia, occurring in 68% of patients. Tumor flare was reported in 37% of patients treated. Several ongoing studies are evaluating the combination in the front-line setting with rituximab and lenalidomide (Chavez et al., 2016).

RESISTANCE TO AND SEQUENCING OF SMALL MOLECULES

Despite the promise of these new agents and the increased understanding of pathways and targets presenting potential therapeutic targets, CLL remains an incurable disease. Most patients will progress at some point with currently available regimens (Woyach, 2015; Woyach & Johnson, 2015). In addition, there are patients who fail to respond to novel agents. Ibrutinib is currently the only targeted agent in CLL therapy where resistance mechanisms have been confirmed in multiple patients undergoing whole-genome sequencing enrolled in clinical trials, elucidating acquired mutations in BTK at the binding site of ibrutinib or in PLCγ2 (Maddocks et al., 2015; Woyach & Johnson, 2015). Chronic lymphocytic leukemia progressions on ibrutinib tend to occur late in therapy (after 12 months) in patients who previously had attained a response, in contrast to Richter's transformations, which tend to occur during the first 1 to 2 years of treatment (Maddocks et al., 2015).

Importantly, progression following treatment with ibrutinib requires rapid planning for the next available treatment, as discontinuation of ibrutinib in this setting is associated with a rapid progression of disease and in some cases difficulty achieving control of the disease (Maddocks et al., 2015). In fact, continuing ibrutinib while planning for the next available therapy despite evidence of progression is employed in some cases. Resistance to idelalisib and venetoclax is also a focus of ongoing trials. Factors proposed to be associated with resistance to small molecules are included in Table 3.

The sequencing of small molecules either as monotherapy or in combination with other agents is a key area for investigation. In a multicenter, retrospective analysis of 683 CLL patients treated with ibrutinib, idelalisib, or venetoclax, ORR to ibrutinib and idelalisib in the front-line setting was 69% and 81%, respectively (Mato et al., 2017). With a median follow-up of 17 months (range, 1–60 months), median PFS and OS for the entire cohort was 35 months for patients treated ibrutinib, and not reached for patients treated with idelalisib. Patients treated with ibrutinib as the first treatment had significantly better PFS in all settings; front-line (hazard ratio [HR], 2.8, CI = 1.3–6.3, $p = .01$), relapsed-refractory (HR, 2.8, CI = 1.9–4.1, $p < .001$), del(17p) (HR, 2.0, CI = 1.2–3.4, $p = .008$), and complex karyotype (HR, 2.5, CI = 1.2–5.2, $p = .02$) when compared to those starting with idelalisib. Patient who progressed on either ibrutinib or idelalisib fared better with venetoclax than with chemoimmunotherapy. For patients progressing

Table 3. Mechanism of Resistance to Small-Molecule Agents Used to Treat Chronic Lymphocytic Leukemia

Agent	Mechanism of resistance	Potential bypass strategies
Ibrutinib	PLCG2 mutation	Targeting a similar pathway (PI3K) Targeting an alternative pathway (BCL2) Downstream targeting of BCR
	BTK mutations	Targeting an alternative pathway (BCL2) Targeting a similar pathway (PI3K) Alternate targeting of BTK protein Alternate targeting of BTK kinase Downstream targeting of BCR
Idelalisib	Myc amplification	Targeting an alternative pathway (BCL2)
	PI3K amplification	Targeting a similar pathway (BTK) Targeting an alternative pathway (BCL2) Less selective or more potent PI3K inhibitors
Venetoclax	BCL2 family upregulation or mutation	PI3K inhibition BCR inhibition CDK9 inhibition

Note. PLCG2 = phospholipase C γ 2; BTK = Bruton's tyrosine kinase. Information from Woyach & Johnson (2015).

while on ibrutinib, a change to venetoclax (ORR 79%) vs. idelalisib (ORR 46%) (PFS HR, 0.6, CI = 0.3–1.0, $p = .06$) was associated with improved outcomes. Ongoing analysis of mechanisms of resistance and sequencing of treatment will be necessary to further characterize these phenomena and provide clinical recommendations.

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

The robust pace of scientific discovery brings hope to patients living with CLL. However, despite the expansion of treatment options, clinicians—including the AP in oncology—must familiarize themselves with the complexity of the underlying pathobiology of CLL, the mechanisms of actions of currently available agents and those in clinical trial, and the nuances of each clinical trial to effectively apply these data to the general CLL population requiring treatment. Applying the principles of precision medicine in implementing the best therapy based on the individual disease profile and the individual patient profile is imperative to achieving the outcomes reported in clinical trials. Continued enrollment of patients into clinical trials at all phases of disease and over extended periods of time will be required to fully understand this very complex and heterogeneous disease (Table 4). The challenge will be to engage in the scientific discussion of the molecular underpinnings of CLL and incorporate the science into everyday practice in a way that can be effectively described to colleagues and patients alike, while employing optimal and individualized strategies for the management of CLL.

Disclosure

Ms. Kurtin has served as a consultant for AbbVie, Celgene, Genentech, and Pharmacyclics; and Dr. McBride has served on speakers bureaus for AbbVie and Incyte.

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Table 4. Selected Clinical Trials Currently Recruiting Using Novel Agents for the Treatment of CLL (clinicaltrials.gov)

Trial ID	Regimens	CLL population	Phase	NCT No.
CLL12	Ibrutinib vs. watch and wait	TN Binet stage A	III	NCT02863718
E1912	FCR + ibrutinib vs. ibrutinib + rituximab	Young, fit, TN		NCT02048813
A041202	BR vs. ibrutinib + rituximab	65 years or older, TN		NCT01886872
150172	Ibrutinib + short-course fludarabine	Fit, TN	II	NCT02514083
CLL2-GIVe	Ibrutinib + venetoclax + obinutuzumab	Fit, TN, with *TP53* del(17p-) and/or mutation	II	NCT02758665
CLL13	FCR/BR vs. rituximab + venetoclax (RVe) vs. obinutuzumab + venetoclax (GVe) vs. obinutuzumab + ibrutinib + venetoclax (GIVe)	Fit, TN, no del(17p) or *TP53* mutation	III	NCT02950051
CLL2-BIO	Bendamustine followed by ofatumumab and ibrutinib followed by ibrutinib and ofatumumab maintenance	All-comer population with indication for treatment	II	NCT02689141
CLL2-BCG	Bendamustine followed by obinutuzumab + idelalisib followed by idelalisib maintenance	All-comer population with indication for treatment	II	NCT02445131
UTX-TGR-304	Ublituximab + TGR-1202 vs. obinutuzumab + chlorambucil	TN or RR, no prior obinutuzumab, PI3K, or chlorambucil	III	NCT02612311
CLLR3	Fludarabine + cyclophosphamide + obinituzumab (FCG) vs. bendamustine + obinituzumab	Fit, RR, no more than 3 prior regimens for CLL	II	NCT02320383
MDA 2015-0860	Venetoclax + ibrutinib	TN with high-risk features RR	II	NCT02756897
141106	Ibrutinib + obinituzumab	All-comer population with indication for treatment	I/II	NCT02315768
ACE-CL-208	ACP-196 (acalabrutinib)	RR	II	NCT02717611

Note. CLL = chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, and rituximab; BR = bendamustine and rituximab; TN = treatment naive; RR = relapsed or refractory.

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