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Targeting the B cell receptor pathway in non-Hodgkin lymphoma

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Abstract

Introduction: Dysregulated B cell receptor (BCR) signaling has been identified as a potent contributor to tumor survival in B cell non-Hodgkin lymphomas (NHLs). This pathway's emergence as a rational therapeutic target in NHL led to development of BCR-directed agents, including inhibitors of Bruton's tyrosine kinase (BTK), spleen tyrosine kinase (SYK), and phosphatidylinositol-3 kinase (PI3K). Several drugs have become valuable assets in the anti-lymphoma armamentarium.

Areas covered: We provide an overview of the BCR pathway, its dysregulation in B cell NHL, and the drugs developed to target BCR signaling in lymphoma. Mechanisms, pharmacokinetics, pharmacodynamics, efficacy, and toxicity of currently available BTK, SYK, and PI3K inhibitors are described.

Expert opinion: While the excellent response rates and favorable toxicity profile of the BTK inhibitor ibrutinib in certain NHL subtypes have propelled it to consideration as front-line therapy in selected populations, additional data and clinical studies are needed before other agents targeting BCR signaling influence clinical practice similarly. PI3K inhibitors remain an option for some relapsed indolent lymphomas and chronic lymphocytic leukemia, but their widespread use may be limited by adverse effects. Future research should include efforts to overcome resistance to BTK inhibitors, combination therapy using BCR-targeted agents, and exploration of novel agents.

Keywords

B cell receptor; fostamatinib; ibrutinib; non-Hodgkin lymphoma

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Declaration of interest

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1. Introduction

The B cell receptor (BCR) signaling pathway represents a crucial constituent involved in the survival of normal B cells throughout their development. In many B cell non-Hodgkin lymphomas (NHLs), dysregulated BCR signaling has been identified as a potent contributor to lymphomagenesis and tumor survival. Accordingly, novel therapies that target this pathway have emerged as valuable assets in the anti-lymphoma armamentarium, with some agents performing well enough to shift the treatment paradigm in certain lymphoma subtypes in recent years. We provide an overview of the BCR pathway, its dysregulation in B cell NHL, and drugs developed to target BCR signaling in lymphoma.

1.1 BCR in normal B cell development

During the process of normal maturation, developing B cells progress through several stages to assemble and modify their immunoglobulin (IG) genes to produce a functionally diverse antibody repertoire. At each stage, gene rearrangement is monitored, and a successfully modified protein chain serves as a signal for progression to the next step. Beginning in the bone marrow, V(D)J recombination of the IG gene ultimately results in extracellular expression of IgM, which consists of two Ig heavy (IgH) and two Ig light (IgL) chains. In addition to binding antigen, surface IgM is coupled to cytoplasmic CD79a and CD79b subunits (Ig α and Ig β , respectively) to form the B cell receptor (BCR), which allows maturing B cells to transmit survival signals throughout development.¹

Failure to produce surface IgM, or production of IgM that binds self-antigen, results in apoptosis (negative selection). In addition, positive-selection survival signals in B cells are thought to derive from antigen-independent, “tonic” tyrosine phosphorylation generated by the BCR and allow migration from the bone marrow.^{2,3} Mature B cells that survive these selection processes are exposed to antigen in the lymph nodes and spleen. Most B cells home to the germinal centers of these secondary lymph organs, where they undergo further IG gene modification via somatic hypermutation to increase the antibody’s affinity for antigen. Those B cells with antibodies exhibiting high affinity receive survival signaling through the BCR; the rest undergo apoptosis. During the next step of class switch recombination, IGHV exons are replaced to produce the secondary Ig isotypes IgG, IgA, and IgE.⁴ B cells that survive to exit the germinal center eventually differentiate into either plasma cells or memory B cells.

1.2 The BCR signaling pathway

Key components of the BCR signaling pathway are depicted in Figure 1. Binding of antigen to extracellular BCR results in phosphorylation of highly conserved immunoreceptor tyrosine-based activation motifs (ITAMs) within CD79a and CD79b, which then act as docking sites for additional adaptor molecules and kinases.⁵ The three SRC-family kinases LYN, FYN, and B lymphocyte kinase (BLK) are essential for downstream survival signal propagation early in B cell development, with some functional redundancy between them.⁶ LYN directly phosphorylates spleen tyrosine kinase (SYK) to continue signal propagation via Bruton’s tyrosine kinase (BTK), and simultaneously activates phosphatases that inhibit BCR signal transduction, thus serving a dual role by both transmitting and checking BCR

signaling.⁷ Tonic BCR signaling refers to the BCR-dependent process observed in normal B cells that does not require antigen binding but is mediated by SYK activation of the pro-survival phosphatidylinositol 3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway.⁸ Thus, SYK is also activated through autophosphorylation when bound directly to the phosphorylated ITAMs of CD79a/b, at which point it amplifies the BCR signal by promoting further ITAM phosphorylation and activating downstream signaling cascades, including those mediated by PI3K.⁹

Two isoforms of PI3K are known to be crucial for B cell development: the ubiquitously expressed PI3K α , and PI3K δ , which is primarily expressed in leukocytes. Activation of either isoform results in generation of PIP3, which complexes with AXL and BLNK to recruit key members of the BCR pathway such as BTK, PLC γ 2, and AKT to the plasma membrane. Activation of PLC γ 2 downstream of BTK leads to subsequent activation of PKC β , which phosphorylates IKK recruited by a complex of MALT1, BCL10, and CARD11. Phosphorylated IKK activates NF- κ B transcription factors that translocate to the nucleus to promote expression of genes associated with survival and proliferation.¹⁰ BTK also affects B cell migration and homing via the chemokine receptors CXCR4 and CXCR5.¹¹ In a separate signaling cascade, AKT and the ubiquitously expressed serine/threonine kinase mTOR propagate PI3K activation to other downstream targets that mediate effects on cell cycle regulation.¹²

2. Dysregulated BCR signaling in non-Hodgkin lymphoma

2.2 Antigen-driven BCR activation

While constitutive BCR activation in lymphoma is often associated with somatic mutations in members of the BCR signaling cascade, binding of the BCR to a cognate antigen can also activate this survival pathway. Antigen recognition as a means of pathologic BCR activation has been implicated in several lymphoma types, most notably in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), but also in follicular lymphoma (FL), several subtypes of marginal zone lymphoma (MZL) and even mantle cell lymphoma (MCL).^{13–23} The association of some lymphoma types with autoimmune diseases posits chronic antigen contact (i.e., with an autoantigen) as a mechanism for lymphomagenic BCR engagement and is exemplified by parotid gland mucosal-associated lymphoid tissue (MALT) lymphoma that develops in the setting of Sjögren's syndrome.²⁴ In large pooled case-control analyses conducted by the International Lymphoma Epidemiology Consortium (InterLymph), a diagnosis of Sjögren's syndrome increased risk of MZL by 30-fold and increased risk of parotid gland MALT lymphoma 1000-fold (OR = 996; 95% CI, 216–4596). Additionally, systemic lupus erythematosus (SLE) was found to increase MZL risk by a factor of 7.5 (OR = 12.9; 95% CI, 4.91–33.8).²⁵

Such a role is also suggested by associations between certain lymphoma types and specific infectious pathogens. For instance, gastric MALT lymphoma is clearly associated with *Helicobacter pylori* infection. Hematologic and gastroenterologic guidelines recommend *H. pylori* eradication as an initial therapeutic step in this subtype, since treatment of the infection alone results in cure of the lymphoma in a significant proportion of cases.^{26–28} However, an explicit link to BCR signaling in gastric MALT lymphomagenesis has yet to be

established. More direct evidence for a relationship between chronic infection, BCR activation and lymphomagenesis is derived from the subset of splenic MZLs associated with hepatitis C virus (HCV) infection, some of which express BCRs that bind the HCV E2 envelope protein.^{29,30} This suggests that some SMZLs may arise from expansion of HCV-reactive B cells. Similar to the phenomenon observed in *H. pylori*-associated MALT lymphomas, antiviral therapy alone has been reported to induce remission in up to 75% HCV-associated lymphoproliferative disorders.³¹ Immunogenetic studies showing biased IG gene usage, restricted BCR sequences (termed “stereotyped” BCRs), and BCR reactivity to foreign and self-antigens in several lymphoma types^{21,23,32,33} lend additional credence to a role for chronic antigenic stimulation in lymphomagenesis and tumor growth and survival. Intriguing data in CLL even suggest the presence of intrinsic epitopes on the BCR itself, thus providing a mechanism for cell-autonomous BCR signaling independent of extrinsic antigen, as well as a possible explanation for the restricted BCR repertoire observed in this disease.^{19,34}

2.2 Chronic active BCR signaling

Genetic alterations that result in constitutive BCR signaling in lymphoma have been described in several BCR pathway members. Chronic active BCR signaling resulting in constitutive NF- κ B activity is a prominent feature in the activated B cell-like (ABC) subtype of diffuse large B cell lymphoma (DLBCL). *In vitro* studies show that most ABC-DLBCL cell lines require expression of functionally intact BCR and signaling components (e.g., SYK, PI3K δ , and BTK) for survival.³⁵ In ABC-DLBCL tumors, constitutive BCR activation appears to be facilitated through a variety of mechanisms, including gain-of-function mutations in the BCR signal-transducing subunits: CD79a and CD79b,³⁵ oncogenic CARD11 mutations that activate NF- κ B,³⁶ and biallelic deletions of A20, a negative regulator of NF- κ B.^{37,38} In fact, *TNFAIP3*, the gene that encodes A20, is inactivated by a variety of mechanisms in several lymphoma subtypes, including Hodgkin lymphoma, primary mediastinal B cell lymphoma, and MALT lymphoma.³⁹ Truncating mutations in *NFKBIE*, which codes for I κ B ϵ , another negative regulator of NF- κ B, have also been described in CLL; such mutations have been associated with inferior prognosis in that disease.⁴⁰

Interestingly, a study of 46 splenic MZLs identified mutually exclusive somatic mutations in several NF- κ B regulators, indicating that mechanisms other than antigenic stimulation may underlie BCR signal activation in these lymphomas.⁴¹ Other mechanisms of NF- κ B activation are also found in MALT lymphomas. Thirty to 50% harbor t(11,18), which causes formation of a c-IAP2/MALT1 fusion protein that activates NF- κ B via aberrant BCL10 expression even though neither c-IAP2 nor MALT1 does so by itself.^{42,43} Less frequently, constitutive BCL expression results from t(1,14) in MALT lymphomas.⁴⁴

2.3 Tonic BCR signaling

Tonic BCR signaling refers to the BCR-dependent process observed in normal B cells that does not require antigen binding but is mediated by SYK activation of the PI3K/AKT pathway, which coordinates downstream pro-survival effectors.⁸ Lymphomas may thus co-opt BCR signaling through perturbations of the PI3K axis. For instance, SYK is amplified in

some MCL, and its inhibition leads to arrest of cell proliferation and apoptosis.⁴⁵ Burkitt lymphoma (BL) is defined by translocations resulting in pathologic overexpression of c-Myc, but since c-Myc can paradoxically exhibit pro-apoptotic properties, it requires activation of pro-survival signaling to exert its oncogenic effect. PI3K activation has been shown to collaborate with c-Myc to fulfill this role and promote lymphomagenesis.⁴⁶ The pro-survival PI3K pathway may be activated in BL via mutations in the transcription factors TCF3 and ID3, which augment tonic activity of the BCR.⁴⁷ In DLBCL (especially in the germinal center B cell-like [GCB] subtype), activating PI3K mutations and disinhibition of PI3K via loss of its negative regulator PTEN have been described.^{48,49} In fact, recent work in GCB-DLBCL cell lines shows variable sensitivity to BCR knockout, but universal sensitivity to AKT knockout, suggesting that tonic BCR signaling is essential to GCB-DLBCL, in contrast to the chronic active BCR signaling shown to be necessary for survival of ABC-DLBCL.⁵⁰ Downstream of PI3K, constitutive activation of AKT has also been implicated in MCL pathogenesis and survival.^{51–53}

3. BCR-directed therapies in NHL

Given the variety of mechanisms by which B cell lymphomas hijack BCR signaling to promote their own survival, targeting the BCR pathway as a potent driver of lymphoma pathogenesis represents a rational treatment approach in B cell NHL. In addition, small molecule agents targeting these signaling pathways are often available as oral therapy. Toxicity profiles of these agents vary, with some side effects specific to the inhibited signaling pathways. In general, patients treated with BCR pathway inhibitors may experience a circulating lymphocytosis shortly after initiation, due to disruption of BCR-mediated chemotaxis and adhesion of malignant cells to the tumor microenvironment. Since this demarginalization phenomenon can persist for months, it is important to recognize that disease response criteria for these agents may include partial response with lymphocytosis. Their direct targeting of B cell proliferation, maturation, and survival also introduces infectious risk as a complication. Mechanism, pharmacokinetics and pharmacodynamics, efficacy, and toxicity of currently available BTK, SYK, and PI3K inhibitors are described.

3.1 Bruton's tyrosine kinase (BTK) inhibitors

Bruton's tyrosine kinase mediates signaling immediately downstream from BCR and is thus an attractive target amenable to inhibition through rational drug design. To date, two orally bioavailable BTK inhibitors have been approved for use in the United States: ibrutinib and acalabrutinib. Both irreversibly inhibit BTK through covalent binding to a cysteine residue (C481) within the ATP-binding pocket of BTK, ultimately impeding B cell proliferation as well as chemotaxis, trafficking, and adhesion.^{54,55} A cysteine-to-serine substitution at this amino acid residue has been associated with resistance to ibrutinib.^{56,57} In addition to reducing ibrutinib's affinity for the receptor binding pocket, the C481S point mutation renders ibrutinib binding reversible. Gain-of-function mutations in PLC γ 2 (R655W and L845F) that allow for autonomous BCR activity have also been described in cases of ibrutinib resistance.^{56,57}

With respect to pharmacokinetics and pharmacodynamics, maximal plasma concentrations are achieved quickly for both agents following oral administration (within 1 – 2 hours for ibrutinib and in approximately 45 minutes for acalabrutinib).^{54,55} Since acid-suppressive therapy affects absorption of acalabrutinib, patients should be advised to avoid proton pump inhibitors and delay other antacids, including H₂-receptor antagonists, for at least 2 hours after administration of acalabrutinib. Both ibrutinib and acalabrutinib undergo hepatic metabolism primarily via the cytochrome P450 enzyme CYP3A4 to less potent, but active metabolites: PCI-45227 and ACP-5862, respectively. Accordingly, dose reductions are recommended in patients on concomitant moderate CYP3A4 inhibitors as well as for patients with hepatic dysfunction. Excretion of these BTK inhibitors is primarily via feces. The elimination half-life is considerably shorter for acalabrutinib, lending itself to a twice-daily dosing schedule. Although this may be viewed as less desirable from a compliance standpoint, it does come with the benefit of consistent BTK inhibition as demonstrated by >95% BTK occupancy across the dosing interval. It has been hypothesized that such maintenance of complete BTK inhibition will reduce the incidence of BTK inhibitor resistance seen with ibrutinib.⁵⁸

Ibrutinib (Imbruvica, Pharmacyclics, LLC) is a first-in-class agent that has received accelerated approval as a second-line therapy for both MCL and MZL in addition to treatment of other B cell NHL such as CLL and Waldenström's macroglobulinemia.⁵⁴ Dosing strategies are different among these indications, with daily doses of 420 mg recommended for CLL and 560 mg for MCL and MZL. While doses up to 840 mg daily have been evaluated in CLL, no added efficacy was noted and more patients experienced adverse effects, whereas a fixed dose of 560 mg daily was recommended for MCL based on a schema of weight bases doses and pharmacokinetic analysis performed in a phase 1 study.^{58,59} Single-agent data in heavily pretreated patients with relapsed or refractory CLL revealed an overall response rate (ORR) of 71%, with a similar response rate in those with certain negative prognostic markers unmutated IGHV.⁵⁸ These responses appear durable, with an estimated progression free survival (PFS) of 75% and overall survival (OS) of 83% at 26 months. In the phase 3 RESONATE study comparing relapsed/refractory CLL patients treated with either ibrutinib or the anti-CD20 monoclonal antibody ofatumumab, ORR was significantly better with ibrutinib treatment (63% with ibrutinib vs 4% with ofatumumab).⁶⁰ At a median follow up of 9.4 months, median PFS was not reached for ibrutinib-treated patients, compared to a median PFS of 8.1 months for those who received ofatumumab. One-year OS also favored ibrutinib (90% vs. 81%, respectively). These responses prompted evaluation of ibrutinib in the frontline setting. In RESONATE II, Burger and colleagues compared ibrutinib to chlorambucil in patients over 65 years of age with untreated CLL.⁶¹ Of note, they did exclude patients with del17p, a known poor prognostic factor, but included other higher-risk patients (e.g., del11q, unmutated IGHV). RESONATE II showed an impressive difference in median PFS after a median follow-up of 18.4 months (not reached vs. 18.9 months). Common adverse effects occurring in approximately 20% or more patients in the aforementioned studies included diarrhea, rash, arthralgia, fatigue, cough, pyrexia, upper respiratory tract infections, and peripheral edema. Neutropenia was the most common hematologic adverse effect among these trials, but was still commonly low grade. In early-phase studies, hemorrhage was recognized as an adverse effect associated with ibrutinib, and

protocols were subsequently amended to exclude patients requiring warfarin-based anticoagulation. Ibrutinib-associated atrial fibrillation was also identified in approximately 3% of patients in RESONATE II. A recent meta-analysis sought to shed light on this unique consequence of ibrutinib therapy, and ultimately concluded that patients incur a 3- to 4-fold increase in the risk of developing atrial fibrillation while taking ibrutinib.⁶²

In a single-arm phase 2 study, Wang and colleagues enrolled 111 patients with relapsed or refractory MCL to receive ibrutinib at a dose of 560 mg daily.⁶³ Patients received a median of 3 prior lines of therapy and were stratified for analysis by receipt of prior bortezomib or not. For the primary endpoint of ORR, the investigators found that 68% of patients responded to ibrutinib (21% CR, 47% PR), and rates were similar regardless of prior bortezomib therapy. Responses were durable, with duration of response (DOR) estimated at 17.5 months and associated PFS of 13.9 months. Though median OS was not reached, an estimated 18-month OS of 58% was reported. Ibrutinib was also well tolerated in this population, with an adverse effect profile similar to that seen in the CLL studies: predominantly grade 1 or 2 non-hematologic toxicities including diarrhea (50% overall, 6% grade 3 or higher), fatigue, low-grade nausea, peripheral edema, dyspnea, constipation, upper respiratory tract infection, vomiting, and decreased appetite representing those occurring in more than 20% of the patients overall. Grade 3 or 4 neutropenia occurred in 16% of patients, also comparable to the rate seen in RESONATE II. A more recent single-center phase 2 trial evaluating combination therapy with ibrutinib and rituximab reported a remarkable 88% ORR, with 44% of patients achieving CR.⁶⁴ Additional study will help elucidate the value of this approach.

Noy and colleagues evaluated ibrutinib as monotherapy in a phase 2 study of 63 patients with MZL of any subtype.⁶⁵ Enrolled patients had received at least 1 prior therapy, with a median of 2 (range 1 – 9); most patients (90%) had prior exposure to rituximab. Patients treated with ibrutinib 560 mg daily had a ORR of 48%, including 2 patients who achieved a CR. Though the response rate in this disease entity is not as impressive as in CLL or MCL, the DOR observed is similar, with a median PFS of 14.2 months and median OS not reached after follow-up of 19.4 months. Response rates were consistent across subtypes, with median PFS by subtype of 13.8 months for extranodal, 19.4 months for splenic, and 8.3 months for nodal MZL. Ibrutinib's known toxicity profile was confirmed in this population. A 6% incidence of atrial fibrillation was noted, though all affected patients were noted to have known risk factors. Fifty-nine percent of patients had bleeding events, the majority of which were not serious, and 46% of affected patients were receiving either anticoagulants or antiplatelet agents. One case of fatal cerebral hemorrhage was reported in a patient receiving concomitant dalteparin.

The second-generation BTK inhibitor acalabrutinib (Calquence, AstraZenica Pharmaceuticals LP) was developed to improve upon the success of ibrutinib by refining BTK selectivity. Ibrutinib is known to interact with kinases other than BTK, including epidermal growth factor receptor (EGFR), tyrosine kinase expressed in hepatocellular carcinoma (TEC), and interleukin-2 inducible T cell kinase (ITK).⁶⁶ Activity at these alternative targets are thought to be responsible for some of the problematic adverse effects that may lead to dose interruption, reduction, or discontinuation of ibrutinib, such as atrial

fibrillation, rash, and hemorrhage. Both BTK and TEC have been identified on cardiac tissues, and EGFR inhibition as a treatment modality is often associated with dermatologic effects.⁶⁷ To date, in a database of 612 patients who have received acalabrutinib, bleeding, bruising, or petechiae of any grade have occurred in 50% of patients, but only 3% of patients experienced a bleeding event of grade 3 or higher.⁵⁵ Like ibrutinib, it is recommended to monitor patients receiving anticoagulant or antiplatelet therapies closely, and to briefly interrupt therapy for patients who are scheduled to undergo procedures with a high risk of bleeding. Atrial fibrillation or flutter of any grade has been reported in 3% of patients receiving acalabrutinib.

Byrd and colleagues conducted a phase 1/2 study of acalabrutinib in 61 patients with CLL in order to assess safety, pharmacokinetics, and pharmacodynamics in two dosing schemas: escalating daily doses up to 400 mg (phase 1), and 100 mg twice daily (phase 2 expansion).⁶⁶ Results validated the hypothesis of consistent BTK occupancy and inhibition at a dose of acalabrutinib 100 mg orally twice daily. Disease responses consisted of either PR (85%) or PR with lymphocytosis (10%), and response rates increased over time. Though the sample size was small, there was 100% response in patients who had received prior idelalisib (n=4). In the only instance of disease progression, the patient was found to have the C481S mutation associated with ibrutinib resistance. The majority of toxicities were grade 1 or 2, with the most frequent being headache (43%), diarrhea (39%), increased weight (26%), pyrexia (23%), and upper respiratory infections (23%). Serious events were infrequent; notably, atrial fibrillation and hemorrhage were not observed in any patients.

On October 31, 2017, the United States Food and Drug Administration (FDA) granted accelerated approval to acalabrutinib for patients with MCL who have received at least one prior line of therapy based on a single-arm open-label phase 2 study (Trial LY-004, NCT02213926).⁶⁸ The 124 patients enrolled had received a median of 2 prior lines of therapy (ranging from 1 – 5), including stem cell transplant (18%), and all received acalabrutinib 100 mg twice daily. An overall response rate of 81% was observed by investigator assessment, with CR reported in 40% of patients. Best response typically occurred within the first 2 months of therapy, and at a median follow up of 15.2 months, median DOR was not reached.⁵⁵ In line with prior studies of acalabrutinib, non-hematologic adverse effects were dominated by grade 1 or 2 headache (39%), diarrhea (31%), and fatigue (28%). Hematologic toxicities including neutropenia (36% overall, 15% grade 3 or higher), thrombocytopenia (44% overall, 12% grade 3 or higher), and anemia (46% overall, 10% grade 3 or higher) occurred in these patients.

3.2 SYK inhibitors

Fostamatinib and entospletinib (GS-9973) are the SYK inhibitors farthest along in clinical development, but others, including cerdulatinib (PRT062070) and TAK-659, are being evaluated in early-phase trials.⁶⁹ Signaling through SYK leads to activation of both BTK and PI3K pathways, making this an attractive target for interruption of survival mechanisms exploited by B cell malignancies as well as autoimmune disorders. SYK inhibition has been shown to impair B lymphocyte development at the transitional stage, but mature B cell populations are unaffected, a phenomenon validated through evaluation of peripheral blood

mononuclear cells (PMBCs) isolated from patients treated with fostamatinib.⁷⁰ Following 2 months of treatment with fostamatinib, a marked decrease in transitional (T1/T2) B cells was seen, but the total number of CD19+ B cells remained consistent. Additionally, SYK is involved with chemotaxis via CXCL12 and CXCL13 and mediates levels of CCL3 and CCL4. These mediators play a role in retaining malignant cells within the tumor microenvironment of secondary lymphoid tissues.⁷¹

Fostamatinib is a prodrug for R406, a potent reversible SYK inhibitor that has been investigated in immune thrombocytopenia purpura, rheumatoid arthritis, and B cell malignancies. The constellation of neutropenia, thrombocytopenia, and diarrhea proved to be dose-limiting in a phase 1/2 study of fostamatinib in various subtypes of B cell NHL.⁷² The phase 2 portion of this study utilized the maximum tolerated dose of 200 mg twice daily in 68 patients who were stratified by histology into 3 cohorts: DLBCL, FL, and other B cell NHLs including MCL, MZL, and CLL/SLL. Objective response in the phase 2 portion of the study was 23.5% in DLBCL, 9.5% in FL, 54.5% in CLL, and 11.1% in MCL. Diarrhea, fatigue, cytopenias, nausea, and hypertension were the most frequently reported adverse effects. Notably, new-onset or worsening hypertension occurred in 24% of patients overall, typically within 1 month of drug initiation. Most patients requiring intervention to reduce blood pressure were controlled with a single antihypertensive agent. Fostamatinib-induced hypertension resolved rapidly upon discontinuation, and is hypothesized to result from off-target inhibition of vascular endothelial growth factor receptor (VEGF).⁷³

Based on the encouraging response rate observed in that initial study, a phase 2 trial focusing on DLBCL patients was performed,⁶⁵ enrolling a total of 68 patients with relapsed or refractory DLBCL. At the study's onset, patients were randomized to compare two different dosing approaches (100 mg twice daily or 200 mg twice daily), but due to limited efficacy with the lower dose, a protocol amendment was drafted to allow for patients receiving the lower dose to increase their dosing to 200 mg twice daily, and all subsequently enrolled patients were started at that dose. Despite the promising responses seen in the phase 1/2 study, the phase 2 trial reported an ORR of only 3%. Interestingly, most responders were among patients receiving the 100-mg dose twice daily. Gastrointestinal toxicities were the most commonly reported adverse effects, and were more frequent at the higher dose. Ultimately, these disappointing results have stalled enthusiasm surrounding this compound.

Like acalabrutinib, entospletinib was designed to maximize its selectivity and reduce adverse effects resulting from unintended, off-target kinase inhibition. In the first-in-human study of entospletinib in healthy volunteers, headache was the most frequently reported adverse effect.⁷⁴ Expanded safety data are available in CLL, indolent NHL, MCL, and DLCL, and early efficacy data has been reported from studies in CLL.⁷¹ At a dose of 800 mg twice daily, entospletinib induced response in 61% of the 41 patients with CLL. Furthermore, 94.5% of patients experienced a reduction of adenopathy, with 2-year PFS of 70.1%. Hypertension was not as prevalent as with fostamatinib treatment, but this appeared to come at the cost of more patients with elevated transaminases or bilirubin. Other notable adverse effects include fatigue and gastrointestinal disturbances. Entospletinib was administered during a fasting state due to the impact of gastric pH on absorption observed in earlier studies, but a newer formulation designed to improve drug absorption at a higher

gastric pH may alleviate this issue. Combination of SYK inhibitors with other agents that target the BCR pathway was explored as a strategy to enhance response rates. However, such study has been limited for now based on results of a phase 2 study combining entospletinib with the PI3K inhibitor idelalisib, where pneumonitis occurred in 12 of 66 patients treated with these two agents.⁷⁵ The majority of pneumonitis cases were severe and were thought to result from excessive inhibition of downstream BCR signaling impacting the mTOR pathway.

3.3 PI3K inhibitors

Idelalisib (Zydelig, Gilead Sciences, Inc.) is an orally bioavailable inhibitor of selective to PI3K δ , whereas the pan-isoform inhibitor copanlisib (Aliqopa, Bayer Healthcare Pharmaceuticals, Inc.) is administered intravenously for three weeks followed by one week of rest.^{76,77} Copanlisib's preferential activity against PI3K δ and PI3K α is proposed to be advantageous in preventing possible resistance that may result from upregulation of the alpha isoform following continuous, selective inhibition of PI3K δ .⁷⁸ In ABC-DLBCL, where PI3K α expression is prevalent, copanlisib shows promise – even in cases of ibrutinib resistance.⁷⁹ In fact, in ibrutinib-resistant ABC-DLBCL models, the combination of copanlisib and ibrutinib has led to sustained complete responses and is of clinical interest. Both idelalisib and copanlisib are currently approved for use in relapsed follicular lymphoma (FL) in the third-line setting; idelalisib has additional indications for CLL/SLL. Though these agents directly induce apoptosis and inhibit malignant cell proliferation, idelalisib impairs function of CXCR4 and CXCR5 and copanlisib interferes with CXCR12 signaling, all of which mediate cell trafficking. While *in vitro* studies suggest that these drugs may also directly induce apoptosis, this effect has only been demonstrated at drug concentrations not reached *in vivo*.⁸⁰

Immune-mediated adverse effects, including diarrhea, transaminitis, and pneumonitis, are reported with PI3K-inhibitor use and are thought to occur as a result of T cell activation. Pneumonitis is a treatment warning for both available agents. Due to concomitant PI3K α inhibition, treatment with copanlisib has also been associated with significant hyperglycemia and hypertension. These effects are often transient, but should be monitored closely, especially during initiation of therapy as well as before and after each infusion. The package insert for copanlisib provides guidance on dose omission and reduction in response to hypertension and hyperglycemia.

Duvelisib (formerly IPI-145, a dual-inhibitor of PI3K δ and PI3K γ) and umbralisib (formerly TGR-1202, a selective inhibitor of PI3K δ as well as casein kinase-1 ϵ) are two newer PI3K inhibitors currently in late-phase study.^{81,82} Thus far, results from the Phase 3 DUO trial comparing duvelisib to the CD20 monoclonal antibody ofatumumab in relapsed and refractory CLL/SLL demonstrated an impressive ORR as well as a 3-month PFS advantage for duvelisib. Priority FDA review is currently underway for CLL/SLL and FL indications. Interestingly, umbralisib, which is being studied primarily as a part of combination therapies in indolent B-cell lymphomas, is thought to result in less immune-mediated toxicities in comparison to other PI3K-inhibitors. A recent review describes the

pharmacology, clinical development, current place in therapy, and future directions for agents within this class.⁸³

4. Expert Opinion

B cell receptor signaling represents a cornerstone in normal B cell development, and B cell lymphomas frequently exploit the BCR pathway to promote their own survival. Targeting the BCR pathway thus represents a rational treatment approach in B cell NHL, and several BCR-directed agents have emerged in recent years as valuable assets in the anti-lymphoma therapeutic arsenal. The BTK inhibitor ibrutinib has shown special promise in the treatment of both indolent and aggressive lymphomas, but eventual development of resistance remains an issue that has yet to be overcome. Inhibition of SYK with fostamatinib was initially attractive, but disappointing response rates in further study abruptly halted clinical development of this agent. Improvements in the pharmacologic properties of entospletinib seem to have reignited enthusiasm for these agents, but high rates of pneumonitis observed when combined with idelalisib has made it difficult to justify potential combinatory regimens involving SYK inhibitors. Exploiting BCR signaling through inhibition of PI3K has led to FDA approval for two agents thus far, but the future success of this class hinges on the ability to limit off-target adverse effects. Clinically significant pneumonitis and gastrointestinal toxicities within this class and among many BCR pathway inhibitors may adversely affect clinical applicability of potentially active combinations. The selectivity of these agents appears to change tolerability, likely related to activity at alternative target kinases (e.g., EGFR, VEGF, and TEC). Future directions should involve efforts to understand and overcome resistance mechanisms to inhibitors of BCR signaling, studies of combination therapy incorporating BCR-targeted agents, strategies aimed at optimizing sequencing of therapy, and exploration of novel agents. Finally, as the treatment paradigm shifts toward chronic therapy with oral BCR pathway inhibitors, pharmacoeconomic considerations of single agents and potential combination regimens become important to ensure uninterrupted access to treatment.

Excellent response rates and favorable toxicity profile of the BTK inhibitor ibrutinib in CLL, MCL, and MZL have propelled its widespread use as an effective single-agent therapy, with front-line indications in selected populations. Given that these oral therapies produce prolonged responses but uncommonly produce CRs, these agents are typically intended to be administered until progressive disease occurs. The long-term use of oral agents also can be associated with financial toxicity. One study examined the financial burden on both patients and payers associated with the increased use of BCR-targeting agents in CLL and projected that the number of people living with CLL in the United States will increase from 128,000 in 2011 to 199,000 by 2025 due to improved OS.⁸⁴ However, the per-patient lifetime cost of CLL treatment is expected to increase from \$147,000 to \$604,000 (based on current drug costs), and the annual societal cost of CLL management is expected to increase to \$5.13 billion by 2025 as oral BCR-directed therapies become routinely used in the frontline setting. For patients enrolled in Medicare, the corresponding total out-of-pocket costs are expected to increase from \$9,200 to \$57,000 per year. Novel payment and reimbursement strategies will be needed as additional agents reach the marketplace in order for the increased cost of these therapies to remain sustainable to payers and patients with B-cell

malignancies, so that patients can continue to have access to these effective and well-tolerated treatments. As additional agents are developed in this class, we will wait to see whether competition leads to reduced drug costs, or whether drug prices will continue to rise even when competitors arrive as was observed for tyrosine kinase inhibitors for chronic myelogenous leukemia.⁸⁵

Moreover, not all patients exhibit a good response to ibrutinib, and drug resistance eventually develops in most cases. Prognosis following relapse on ibrutinib has been shown to be poor in MCL, with subsequent 1-year OS of just 22%.^{86,87} For patients with CLL, one study shows median survival after progression of 17.6 months.⁸⁸ It remains to be seen whether other BTK inhibitors or other novel agents can produce durable response after ibrutinib failure. Future patient management will require treatment pathways that identify mutations associated with resistance for CLL (well characterized) and other B-cell malignancies (poorly characterized), track the rise in mutant clones, and promote strategies such as switching drug classes or adding novel agents to overcome resistance before clinical progression occurs. The availability of cancer personalized profiling deep sequencing (CAPP-Seq), immunoglobulin high-throughput sequencing (Ig-HTS), and other strategies for monitoring disease status using peripheral blood samples could transform treatment paradigms by allowing early intervention for impending relapse and modification of initial treatment strategies for high-risk patients identified during treatment. Preliminary studies using these technologies for detection of molecular disease in the plasma often preceded clinical or radiographic imaging demonstrating relapse.^{89,90} In addition, CAPP-Seq has been used to identify *BTK* C481S resistance mutation in the plasma of a patient with B cell NHL.⁹⁰ Future studies will explore the value of mutation testing for patients receiving agents that address the BCR pathway and examine the associates between allele frequency, relapse, and response to subsequent treatment. Such studies will aid in the design of future trials and treatment pathways.

Other future directions include efforts to overcome resistance to BTK inhibitors, combination therapy using BCR-targeted agents, and exploration of novel agents.

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• *of interest*

•• *of considerable interest*

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Article Highlights

- B cell non-Hodgkin lymphomas (NHLs) frequently exploit dysregulated B cell receptor (BCR) signaling to promote tumor survival.
- Targeting the BCR pathway represents a rational treatment approach in B cell NHL, and several BCR-directed agents have emerged in recent years as valuable assets in the anti-lymphoma therapeutic arsenal.
- The BTK-inhibitor ibrutinib represents an important treatment option in chronic lymphocytic leukemia, mantle cell lymphoma, and marginal zone lymphoma.
- Lower response rates and concerning toxicity profiles have limited the role of SYK inhibitors in NHL.
- Future directions should involve efforts to understand and overcome resistance mechanisms to inhibitors of BCR signaling, studies of combination therapy incorporating BCR-targeted agents, and exploration of novel agents such as next-generation BTK inhibitors.

Figure 1. B cell receptor (BCR) signaling pathways.

BCR may be activated either by antigen binding or via cell-autonomous pathways. Antigen binding to extracellular BCR results in phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) within CD79a and CD79b, which act as intracellular docking sites for additional adaptor molecules and kinases such as LYN. LYN phosphorylates the tyrosine kinase SYK to continue signal propagation. SYK is also activated through autophosphorylation when bound directly to phosphorylated ITAMs, at which point it promotes further ITAM phosphorylation and activates downstream signaling cascades, including those mediated by Bruton's tyrosine kinase (BTK) and phosphatidylinositol 3 kinase (PI3K). PI3K activation generates PIP3, which complexes with AXL and BLNK to recruit BTK, PLCγ2, and AKT to the plasma membrane. Tonic BCR activity is mediated by the PI3K/AKT pathway, which coordinates downstream pro-survival effectors and cell cycle regulators. In a separate pathway, activation of PLCγ2 downstream of BTK activates PKCβ, which phosphorylates IKK recruited by a complex of MALT1, BCL10, and CARD11. Phosphorylated IKK activates NF-κB transcription factors that translocate to the nucleus to promote expression of genes associated with survival and proliferation. A20 acts as a negative regulator of NF-κB, while SHIP-1 and PTEN phosphatases inhibit PI3K signaling by hydrolyzing PIP3.

Table 1.
BCR-targeted agents FDA-approved for single-agent use in non-Hodgkin's lymphoma

(NHL). Abbreviations: Bruton's tyrosine kinase (BTK), chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL), follicular lymphoma (FL) mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), overall response rate (ORR), phosphatidylinositol 3 kinase (PI3K).

Target	Drug	NHL subtype	Study	ORR	Toxicities
BTK	ibrutinib	CLL/SLL	Byrd JC <i>et al.</i> , 2013 ⁵⁸ Phase 2, relapsed/refractory	71%	<i>Common:</i> Diarrhea, nausea/vomiting, rash, arthralgia, fatigue, cough, pyrexia, upper respiratory tract infections, peripheral edema, neutropenia. <i>Notable:</i> hemorrhage, atrial fibrillation.
			RESONATE, Byrd JC <i>et al.</i> , 2014 ⁶⁰ Phase 3, previously treated	63%	
			RESONATE II, Burger JA <i>et al.</i> , 2015 ⁶¹ Phase 3, untreated, age >65 years	86%	
		MCL	Wang ML <i>et al.</i> , 2013 ⁶³ Phase 2, relapsed/refractory	68%	
		MZL	Noy A <i>et al.</i> , 2017 ⁶⁵ Phase 2, relapsed/refractory	48%	
	acalabrutinib	CLL/SLL	Byrd JC <i>et al.</i> , 2016 ⁶⁶ Phase 1/2, relapsed/refractory	95%	Headache, diarrhea, increased weight, fatigue, pyrexia, upper respiratory infections, neutropenia, thrombocytopenia, anemia.
		MCL	Wang ML <i>et al.</i> , 2017 ⁶⁸ Phase 2, relapsed/refractory	81%	
PI3K	idelalisib	FL	Gopal AK <i>et al.</i> , 2014 ⁹¹ Phase 2, relapsed/refractory	54%	<i>Common:</i> Diarrhea, fatigue, nausea, cough, pyrexia, neutropenia, transaminase elevation, pneumonia. <i>Notable [especially in combination regimens]:</i> colitis, hepatitis, pneumonitis
		CLL/SLL		61%	
	copanlisib	FL	Dreyling M <i>et al.</i> , 2013 ⁹² Phase 3, relapsed/refractory	40%	