Published in final edited form as:

Curr Opin Oncol. 2014 September ; 26(5): 469–475. doi:10.1097/CCO.0000000000000113.

Phosphoinositide 3-kinase inhibitors in lymphoma

Emily Curran and Sonali M. Smith

Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, Illinois, USA

Abstract

Purpose of review—The phosphoinositide 3-kinase (PI3K) pathway, with downstream targets including Akt and mammalian target of rapamycin, has been implicated in numerous human cancers, including hematologic malignancies and lymphomas. The development and refinement of PI3K inhibitors directed toward this pathway show promising clinical efficacy. This review will discuss the emerging body of clinical data in lymphoid malignancies and present future directions for research utilizing these inhibitors.

Recent findings—The PI3K δ inhibitor, idelalisib, has been most widely studied in lymphoma, and has shown promising results both as a single agent and in combination with other therapies. IPI-145, a dual inhibitor of PI3K δ and PI3K γ , has also shown efficacy and several clinical trials are underway. Other PI3K inhibitors are in active development, with several entering early phase clinical trials.

Summary—The PI3K pathway appears to be important in lymphoma and targeting this pathway shows promising clinical efficacy.

Keywords

chronic lymphocytic leukemia; indolent non-Hodgkin lymphoma; mantle cell lymphoma; phosphoinositide 3-kinase inhibitors

Introduction

Given the complexity of B-cell lymphoproliferative disorders, there is an urgent need to find common aberrant pathways for therapeutic targeting among lymphoma subtypes. One recently identified key element in lymphomagenesis and pathogenesis is B-cell receptor (BCR) signaling, which is required for both malignant and nonmalignant mature B-cell survival. The BCR is a ubiquitous surface protein complex with a number of intracellular signaling components. One of the most proximal signaling nodes is phosphoinositide 3-kinases (PI3Ks), a highly conserved family of intracellular lipid kinases that regulate critical

© 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins

Correspondence to Sonali M. Smith, MD, Associate Professor, Section of Hematology/Oncology, Director, Lymphoma Program, University of Chicago, 5841 S. Maryland Avenue MC2115, Chicago, IL 60637, USA. Tel: +1 773 702 4400; fax: +1 773 702 0963; smsmith@medicine.bsd.uchicago.edu.

Conflicts of interest: E.C. has no conflicts of interest. S.M.S. has been a consultant for Gilead in 2013. No one other than E.C. and S.M.S. contributed to the design, writing, editing or other aspect of the manuscript.

cellular processes, including proliferation, growth, apoptosis and cytoskeletal rearrangement [1]. In addition to mediating BCR signaling, PI3K integrates signals from a variety of other chemokines and cytokines and has multiple downstream intracellular effects on Akt, mammalian target of rapamycin (mTOR) and NF- κ B.

The PI3K family is categorized into three classes, grouped into classes I, II and III, on the basis of substrate preference and sequence homology. Class I PI3Ks, the most widely implicated in human neoplasia [2], are further divided into two subgroups, class IA and class IB (Fig. 1), with class IA PI3Ks activated by growth factor receptor tyrosine kinases, and class IB PI3Ks activated by G-protein coupled receptors [1,2]. Binding of the class IA p85 regulatory subunit to receptor tyrosine kinases relieves the inhibition of the p110 catalytic subunit, resulting in conversion of phosphatidyl inositol (PIP)2 to PIP3. PIP3 assists in phosphorylation of Akt, which promotes cell growth and survival by a variety of downstream mechanisms, including inhibition of proapoptotic Bcl-2 family members, decreased negative regulation of the NF- κ B transcription factor, inhibition of p53-mediated apoptosis and stimulation of the mTOR [3]. Phosphatase and tensin homolog (PTEN), which removes the 3-phosphate from PIP3 and thus down-modulates Akt signaling, is a major negative regulator of the PI3K/Akt/mTOR pathway [4,5].

The PI3K pathway is constitutively deregulated in multiple malignancies and overexpression of the class I p110 isoforms (p110 α , p110 β , p110 δ , p110 γ) has been shown to induce oncogenic transformation in cell culture [6]. Among the PI3K isoforms, PI3K α mutations are the most widely implicated in human cancer. Gain of function mutations in the gene encoding PI3K α occurs frequently in human tumors [7,8], and cancer cell line models have shown correlation between PI3K α mutations and sensitivity to PI3K inhibitors [9]. The role of PI3K β in human cancers is less clear and PI3K γ , although highly expressed in leukocytes, may play a more crucial role in the immune system than in oncogenesis [9].

Among the PI3K isoforms, PI3K δ may be the most important in hematologic malignancies. PI3K δ and the p110 δ isoform are highly expressed in lymphocytes and lymphoid tissues [10,11]. In B-cell malignancies, aberrant PI3K signaling may be the result of constitutive BCR activation and/or response to proliferation and survival factors present in the bone marrow and lymph node microenvironments [12–16]. PI3K δ signaling appears to be critical for activation, proliferation and survival of B-cells and plays an important role in homing and retention in lymphoid tissues. Pharmacologic approaches that specifically inactivate p110 δ demonstrate its central role in B-cell signaling [17–19], making it an attractive target for treatment of hematologic malignancies, especially B-cell malignancies.

Targeting the Phosphoinositide 3-Kinase Pathway

Emerging awareness of the PI3K pathway's role in hematologic malignancies has prompted a concerted effort to develop targeted PI3K inhibitors. First-generation PI3K inhibitors, wortmannin and LY294002, had broad activity *in vitro* and inhibited all four PI3K isoforms, but due to unfavorable pharmaceutical properties and limited single-agent in-vivo efficacy, were not developed further for clinical use [20]. These compounds were also found to lack specificity and inhibit multiple other kinases [9], fueling the search for more targeted PI3K

inhibitors, including the development of PI3K inhibitors against specific isoforms. There is a robust body of preclinical data of PI3K inhibitors in lymphoid malignancies supporting the proliferation of ongoing single agent and combination clinical trials, with several detailed reviews available. Here, we summarize the clinical data to date of PI3K inhibitors in lymphoid malignancies, focusing mainly on idelalisib, a PI3K δ inhibitor, and IPI-145, a dual PI3K δ or PI3K γ inhibitor, which are furthest along in development.

Chronic lymphocytic leukemia

Idelalisib is, to date, the most well studied of the PI3K δ inhibitors in hematologic malignancies. Previously known as CAL-101 or GS-1101, idelalisib is a potent selective p110 δ inhibitor and, in primary cells from patients with lymphoid and myeloid leukemias, has been shown to block PI3K signaling, resulting in decreased phosphorylation of Akt and induction of apoptosis [21,22]. Chronic lymphocytic leukemia (CLL) tumor cells have higher intrinsic PI3K activity compared with normal B-cells [22], and promising preclinical data of idelalisib in CLL, including dose-dependent cytotoxicity, reduction of survival signals from the BCR, abrogation of protective microenvironment stimuli and sensitization of CLL toward chemotherapy, led to the development of further clinical trials [23].

A recently published pivotal phase I trial in CLL evaluated escalating doses of idelalisib in 54 adult patients with relapsed or refractory CLL requiring therapeutic intervention [24]. The patients had many adverse risk features, including high-risk Rai stage disease at presentation (67%), bulky lymphadenopathy (80%), unmutated IGHV (91%) and del17p or TP53 mutations (24%). Patients were also heavily pretreated, with a median of five prior therapies (range 2–14). All patients had received fludarabine, nearly all patients (96%) had received rituximab, and the majority of the patients (87%) had been treated with alkylating agents. Idelalisib was generally well tolerated, with most adverse events related to the underlying disease or previous therapy. Serious adverse events included pneumonia (20%), febrile neutropenia (9%), colitis (6%), cellulitis (6%) and pseudomonas bacteremia (6%). One fairly unique toxicity is transient transaminase elevation, with transaminase elevations of any grade seen in 28% of patients in this study. Despite the level of elevation, the transaminases typically showed rapid resolution with holding idelalisib. The investigators comment that idelalisib could be safely restarted in most patients with a dose reduction. Other drug-related events included skin rashes and diarrhea. While response was not the main outcome of this study, idelalisib demonstrated promising results, with 44 of 54 patients (81.5%) achieving a lymph node response of greater than 50% and an overall response rate of 72%. The median progression-free survival was 15.8 months and the median overall survival was not reached. Notably, among patients with deletion 17p and/or TP53 mutation, the overall response rate was 54% (7 of 13 patients), with median progression-free survival of 3 months. No dose-limiting toxicities were reached, and the dose for further investigation was determined to be 150mg twice daily.

Given the single-agent activity and overall tolerable side-effect profile, idelalisib has entered a number of combination studies. Preliminary results from a phase I trial of idelalisib, combined with rituximab and/or bendamustine in patients with relapsed or refractory CLL, were initially presented in 2011 [25]. Among 27 patients enrolled at the time, over three-

fourths of patients had a 50% or greater decrease in lymph node area. This decrease in lymphadenopathy occurred on all three regimens and generally within the first two cycles of treatment. In updates presented at both the American Society of Hematology and the American Society of Clinical Oncology annual meetings, over 50 patients had been enrolled. In this group of patients, of which half had refractory disease, the overall response rate was 81%, with a 2-year progression-free survival and overall survival of 62 and 85%, respectively [26,27]. The authors concluded that all three combination regimens were highly active and resulted in durable tumor control in patients with heavily pretreated relapsed or refractory CLL.

A phase III randomized, double-blind, placebo-controlled trial of rituximab in combination with idelalisib versus placebo was recently completed in 220 patients with relapsed CLL [28]. The patients enrolled in the trial had progressed within 24 months of their last treatment and were not able to receive cytotoxic agents because of severe neutropenia or thrombocytopenia, renal insufficiency or significant coexisting illnesses (score on the Cumulative Illness Rating Scale of more than six). The majority (84%) of patients had unmutated IGHV and nearly half (44%) had 17p deletion or TP53 mutation. The study was stopped early because of apparent efficacy and, at the time of analysis, showed significantly increased progression-free survival (5.5 months in placebo group versus not reached in idelalisib group), improved overall response (13% in placebo group versus 81% in idelalisib group) and significantly increased overall survival at 12 months ($P = 0.02$). When patients were stratified according to 17p deletion, TP53 mutation and IGHV mutation status, the improvement in progression-free survival with idelalisib persisted. Similar to the phase I trial, idelalisib was well tolerated, with adverse events including aminotransferase elevations, rash and diarrhea, but there was no overall increase in the rate of adverse events in the group receiving idelalisib as compared with placebo. On the basis of these data, the Food and Drug Administration (FDA) granted idelalisib breakthrough therapy designation and a new drug application for the treatment of CLL was submitted to the FDA in December 2013.

There is also clinical interest in combining idelalisib with other agents. For instance, a phase I study of idelalisib in combination with rituximab or of atumumab in patients with relapsed or refractory CLL demonstrated high activity, with over 80% overall response rate, and acceptable safety profiles [29]. A phase III trial is currently underway in patients with previously treated CLL, randomized to receive ofatumumab, with or without idelalisib (NCT01659021) [30]. In patients with CLL, lenalidomide can induce tumor flare and cytokine release, which may promote CLL survival and is dependent on the PI3K p110 δ pathway [31]. Thus, clinical trials combining lenalidomide and idelalisib are underway.

It is important to note that a transient lymphocytosis was seen across all studies of idelalisib in CLL. For instance, in phase I trials, an increase in peripheral absolute lymphocyte counts of greater than 50% was observed in over half of patients [24,32,33]. This increase peaked at 2 months and then gradually declined. This transient lymphocytosis was similarly noted in the recently published phase III trial of rituximab and idelalisib, although the addition of rituximab appeared to shorten the duration, with the peak of lymphocytosis at week 2 and resolving by week 12 [28]. Prior studies demonstrated that idelalisib normalized plasma

concentrations of CCL3, CCL4 and CXCL13. Because chemokines, especially CXCL13, appear to be important for CLL cells to home to lymphatic tissues, it has been hypothesized that this transient increase in peripheral lymphocytes is related to interference of idelalisib with the normal B-cell migration and homing to lymphatic tissues [23]. Thus, these data suggest that, in clinical use and studies of idelalisib, early transient lymphocytosis should not be confused with progression.

Like idelalisib, IPI-145 is a potent inhibitor of PI3K δ , but is also a potent inhibitor of PI3K γ . A phase I, dose-escalation study of IPI-145 is currently underway in patients with advanced hematologic malignancies, including a subset of 44 patients with relapsed or refractory CLL, and the interim analysis was presented in 2013. IPI-145 was well tolerated, with the most common adverse events being transient neutropenia, anemia and pneumonitis, and in this subgroup of heavily pretreated CLL patients, many (44%) with TP53 mutation and/or 17p deletions, IPI-145 demonstrated promising clinical activity, with an overall response rate of greater than 50% [34].

Indolent non-Hodgkin lymphoma

Idelalisib is also actively being studied as a therapy for indolent non-Hodgkin lymphoma (iNHL), including follicular lymphoma, small lymphocytic lymphoma or leukemia, marginal zone lymphoma and lymphoplasmacytic lymphoma. In a phase I study of 64 patients with relapsed iNHL, idelalisib was well tolerated and clinically active, with an overall response rate of 47% in this patient population [35]. A phase II trial of 125 relapsed patients with iNHL refractory to rituximab and an alkylating agent again showed clinical activity, with an overall response rate of 57%, and an acceptable safety profile, with the most common adverse grade 3 or greater adverse events being neutropenia, aminotransferase elevations, diarrhea and pneumonia [36]. On the basis of this study, a new drug application was submitted to the FDA for the use of idelalisib in refractory iNHL.

Combination studies of idelalisib and other agents are underway in iNHL. A phase I trial of patients with heavily pretreated iNHL combined idelalisib with rituximab and/or bendamustine. The overall response rate was 81%, with 28% of patients overall achieving a complete response (43% complete response in the group receiving all three drugs). Adverse events were similar to those seen with idelalisib as single-agent therapy. The authors concluded that idelalisib-based combination therapy is highly active and well tolerated in patients with relapsed or refractory iNHL [37]. Phase III trials are currently ongoing.

Early reports from phase I trials of IPI-145 in relapsed or refractory lymphoma have shown clinical efficacy and an acceptable safety profile, with the most common adverse events being neutropenia and transaminase elevations, as seen with idelalisib [38]. A large phase II multicenter clinical trial is currently underway (NCT01882803, Table 1). Although PI3K may also be important in aggressive lymphomas, there are no substantial data to date in those subsets.

Mantle cell lymphoma

On the basis of gene expression profiling, the PI3K or AKT signaling pathway appears to be upregulated in mantle cell lymphoma (MCL) cells compared with naïve B cells [39], and

inhibition of PI3K decreases growth and induces apoptosis in MCL cell lines [40]. Thus, this pathway may also be a useful therapeutic target in MCL. A phase I trial of 40 patients with relapsed or refractory MCL demonstrated tolerable adverse effects, with the most common grade 3 or greater effects including diarrhea (18%), decreased appetite (15%), pneumonia (10%) and transaminase elevations (20%). The overall response rate was 40%, with a complete response in two patients (5%) [41■]. A separate phase I study combining idelalisib with everolimus, bortezomib, or rituximab plus bendamustine in 22 patients with relapsed or refractory MCL demonstrated an overall response rate of 46%, with two achieving complete response (9%). All of the combinations appeared to be tolerable [42]. These trials have suggested that idelalisib is a viable treatment strategy in patients with MCL, and further studies are underway.

The dual PI3K δ and PI3K γ inhibitor IPI-145 has also been studied in MCL in the same phase I study mentioned in iNHL [38]. In the small subset of six evaluable patients, there was a 67% overall response rate, with one patient achieving a complete response. Further studies are ongoing.

Other lymphomas

Although most trials have evaluated PI3K inhibitors as a downstream component of BCR signaling, there are clearly important functions of PI3K independent of this role. For instance, high levels of PI3K δ have been detected in Hodgkin lymphoma cell lines and, in preclinical studies, idelalisib resulted in inhibition of Akt phosphorylation and induced dose-dependent apoptosis [43]. Similarly, there are data that PI3K inhibitors may also be effective in T-cell lymphomas as well. Among eight patients with T-cell lymphoma and evaluable disease treated with IPI-145, one had a complete response, and two had partial response [44]. Treatment-related adverse events occurred in half of the patients, with the most common grade 3 or greater adverse events being increased alanine aminotransferase, rash and pneumonia.

Other Phosphoinositide 3-Kinase Inhibitors

In addition to idelalisib and IPI-145, there are multiple other PI3K inhibitors in active development for hematologic malignancies (see Table 1). AMG319, a PI3K δ inhibitor, has demonstrated promising preclinical activity against various lymphoma cell lines [45] and is currently under study in a phase I trial in patients with relapsed or refractory lymphoid malignancies. Another PI3K δ inhibitor, TGR-1202, was designed specifically to attempt to mitigate the hepatotoxicity that occurs with this class of agent. TGR-1202 is also currently being studied in a phase I trial in patients with relapsed or refractory hematologic malignancies and preliminary reports of the 13 patients treated thus far demonstrated minimal toxicity, with no hepatotoxicity aside from a grade 1 elevated gamma-glutamyl transpeptidase [46]. NVP-BKM120, which has been shown to inhibit all four class I PI3K isoforms [47], induces cell death in Burkitt lymphoma [16] and CLL [15] cell lines, as well as sensitizing CLL cells to bendamustine and fludarabine and disturbing the protective effect of the tumor microenvironment [15]. It is being studied in phase I trials both as a single agent and in combination with rituximab.

Conclusion

An unresolved question is whether isoform-specific targeting will be sufficient for treatment of hematologic malignancies, or if dual PI3K or mTOR inhibitors or the combination of PI3K with chemotherapeutic agents will be necessary. Although idelalisib shows activity as a single agent, it may be more effective when combined with standard chemotherapy, as is being demonstrated in current clinical trials. Much less is known about intrinsic or acquired resistance to PI3K inhibitors. Further research will need to focus not only on the design of additional targeted PI3K inhibitors, but also on the ideal combinations of agents that may abrogate resistance.

It is of interest that in both CLL and lymphoma, the PI3K inhibitors appear to exert some of their action through the microenvironment and via blockade of BCR signaling, rather than directly affecting the tumor cells. There is yet much to learn and understand about these pathways, but studies thus far support the microenvironment as an important target for therapeutics. On the basis of the encouraging preclinical and early clinical data, inhibition of the PI3K pathway appears to be a promising new therapeutic target in hematologic malignancies, especially in B-cell malignancies. This field is rapidly expanding, with many new agents currently being developed, and understanding of this pathway will become increasingly important.

Acknowledgments

None.

References and Recommended Reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ ■ of outstanding interest

1. Vivanco I, Sawyers CL. The phosphatidylinositol 3-kinase AKT pathway in human cancer. *Nat Rev Can.* 2002; 2:489–501.
2. Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat Rev Genet.* 2006; 7:606–619. [PubMed: 16847462]
3. Courtney KD, Corcoran RB, Engelman JA. The PI3K pathway as drug target in human cancer. *J Clin Oncol.* 2010; 28:1075–1083. [PubMed: 20085938]
4. Steelman LS, Abrams SL, Whelan J, et al. Contributions of the Raf/MEK/ERK, PI3K/PTEN/Akt/mTOR and Jak/STAT pathways to leukemia. *Leukemia.* 2008; 22:686–707. [PubMed: 18337767]
5. McCubrey JA, Steelman LS, Abrams SL, et al. Targeting survival cascades induced by activation of Ras/Raf/MEK/ERK, PI3K/PTEN/Akt/mTOR and Jak/STAT pathways for effective leukemia therapy. *Leukemia.* 2008; 22:708–722. [PubMed: 18337766]
6. Kang S, Denley A, Vanhaesebroeck B, Vogt PK. Oncogenic transformation induced by the p110beta, -gamma, and -delta isoforms of class I phosphoinositide 3-kinase. *Proc Natl Acad Sci U S A.* 2006; 103:1289–1294. [PubMed: 16432180]
7. Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. *Science.* 2004; 304:554. [PubMed: 15016963]

8. Samuels Y, Velculescu VE. Oncogenic mutations of PIK3CA in human cancers. *Cell Cycle*. 2004; 3:1221–1224. [PubMed: 15467468]
9. Fruman DA, Rommel C. PI3K δ inhibitors in cancer: rationale and serendipity merge in the clinic. *Cancer Discov*. 2011; 1:562–572. [PubMed: 22586681]
10. Chantry D, Vojtek A, Kashishian A, et al. p110delta, a novel phosphatidyli-nositol 3-kinase catalytic subunit that associates with p85 and is expressed predominantly in leukocytes. *J Biol Chem*. 1997; 272:19236–19241. [PubMed: 9235916]
11. Vanhaesebroeck B, Welham MJ, Kotani K, et al. P110delta, a novel phos-phoinositide 3-kinase in leukocytes. *Proc Natl Acad Sci U S A*. 1997; 94:4330–4335. [PubMed: 9113989]
12. Bernal A, Pastore RD, Asgary Z, et al. Survival of leukemic B cells promoted by engagement of the antigen receptor. *Blood*. 2001; 98:3050–3057. [PubMed: 11698290]
13. Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature*. 2010; 463:88–92. [PubMed: 20054396]
14. Munk Pedersen I, Reed J. Microenvironmental interactions and survival of CLL B-cells. *Leuk Lymphoma*. 2004; 45:2365–2372. [PubMed: 15621749]
15. Rosich L, Saborit-Villarroya I, Lopez-Guerra M, et al. The phosphatidylinositol-3-kinase inhibitor NVP-BKM120 overcomes resistance signals derived from microenvironment by regulating the Akt/FoxO3a/Bim axis in chronic lymphocytic leukemia cells. *Haematologica*. 2013; 98:1739–1747. [PubMed: 23850807]
16. Schmitz R, Young RM, Ceribelli M, et al. Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. *Nature*. 2012; 490:116–120. [PubMed: 22885699]
17. Durand CA, Hartvigsen K, Fogelstrand L, et al. Phosphoinositide 3-kinase p110 delta regulates natural antibody production, marginal zone and B-1 B cell function, and autoantibody responses. *J Immunol*. 2009; 183:5673–5684. [PubMed: 19843950]
18. Jou ST, Carpino N, Takahashi Y, et al. Essential, nonredundant role for the phosphoinositide 3-kinase p110delta in signaling by the B-cell receptor complex. *Mol Cell Biol*. 2002; 22:8580–8591. [PubMed: 12446777]
19. Okkenhaug K, Bilancio A, Farjot G, et al. Impaired B and T cell antigen receptor signaling in p110delta PI 3-kinase mutant mice. *Science*. 2002; 297:1031–1034. [PubMed: 12130661]
20. Garcia-Echeverria C, Sellers WR. Drug discovery approaches targeting the PI3K/Akt pathway in cancer. *Oncogene*. 2008; 27:5511–5526. [PubMed: 18794885]
21. Lannutti BJ, Meadows SA, Herman SE, et al. CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. *Blood*. 2011; 117:591–594. [PubMed: 20959606]
22. Herman SE, Gordon AL, Wagner AJ, et al. Phosphatidylinositol 3-kinase-delta inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals. *Blood*. 2010; 116:2078–2088. [PubMed: 20522708]
23. Hoellenriegel J, Meadows SA, Sivina M, et al. The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leukemia. *Blood*. 2011; 118:3603–3612. [PubMed: 21803855]
24. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3 kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014; 123:3390–3397. This study describes phase I results of idelalisib as a single agent in relapsed or refractory CLL. The results demonstrated that idelalisib was well tolerated with promising clinical response, supporting further study as a single agent. [PubMed: 24615777]
25. Sharman, J.; de Vos, S.; Leonard, J., et al. A phase 1 study of the selective phosphatidylinositol 3-kinase-delta inhibitor, CAL-101 (GS-1101), in combination with rituximab and/or bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). San Diego, California, USA: American Society of Hematology; 2011. in press
26. Coutre, S.; Leonard, J.; Furman, R., et al. Combinations of the selective phos-phatidylinositol 3-kinase-delta (PI3K δ) inhibitor GS-1101 (CAL-101) with rituximab and/or bendamustine are tolerable and highly active in patients with relapsed or refractory chronic lymphocytic leukemia (CLL): results from a phase I study. Atlanta, Georgia, USA: American Society of Hematology; 2012.

27. Barrientos, JC.; Furman, RR.; Leonard, J., et al. Update on a phase I study of the selective PI3K-delta inhibitor idelalisib (GS-1101) in combination with rituximab and/or bendamustine in patients with relapsed or refractory CLL. Chicago, Illinois, USA: American Society of Clinical Oncology; 2013.
28. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014; 370:997–1007. This pivotal large, multicenter phase III trial of idelalisib combined with rituximab in patients with relapsed CLL demonstrated improvement in progression-free survival, response rate and overall survival among the patients receiving idelalisib compared with placebo. [PubMed: 24450857]
29. De Vos, S.; Leonard, JP.; Barrientos, JC., et al. A phase I study of the selective PI3K δ inhibitor idelalisib (GS-1101) in combination with therapeutic anti-CD20 antibodies (rituximab or ofatumumab) in patients with relapsed or refractory chronic lymphocytic leukemia. New Orleans, Los Angeles, USA: American Society of Hematology; 2013.
30. Flinn, I.; Kimby, E.; Cotter, FE., et al. A phase III, randomized, controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with ofatumumab for previously treated chronic lymphocytic leukemia (CLL). Chicago, Illinois: American Society of Oncology Annual Meeting; 2013.
31. Herman SE, Lapalombella R, Gordon AL, et al. The role of phosphatidylinositol 3-kinase-delta in the immunomodulatory effects of lenalidomide in chronic lymphocytic leukemia. *Blood*. 2011; 117:4323–4327. [PubMed: 21378270]
32. Coutre, S.; Byrd, J.; Furman, R., et al. Phase I study of CAL-101, an isoform-selective inhibitor of phosphatidylinositol 3-kinase P110 δ , in patients with previously treated chronic lymphocytic leukemia. Chicago, Illinois, USA: American Society of Clinical Oncology; 2011.
33. Brown, J.; Furman, R.; Flinn, I., et al. Final results of a phase I study of idelalisib (GS-1101) a selective inhibitor of PI3K δ , in patients with relapsed or refractory CLL. Chicago, Illinois, USA: American Society of Clinical Oncology; 2013.
34. Patel, M.; Kahl, BS.; Horwitz, SM., et al. Preliminary safety and efficacy of IPI-145, a potent inhibitor of phosphoinositide-3-kinase- δ , γ , in patients with chronic lymphocytic leukemia. New Orleans, Los Angeles, USA: American Society of Hematology; 2013.
35. Flinn IW, Kahl BS, Leonard JP, et al. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-delta, as therapy for previously treated indolent non-Hodgkin lymphoma. *Blood*. 2014; 123:3406–3413. This article describes results from a phase I trial of idelalisib in patients with relapsed iNHL, demonstrating that it was well tolerated and active in this population. [PubMed: 24615776]
36. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014; 370:1008–1018. This phase II study of patients with relapsed or refractory iNHL treated with idelalisib demonstrated clinical activity and acceptable toxicity profile, prompting the company to submit a new drug application submission to the FDA for this indication. [PubMed: 24450858]
37. Leonard, J.; Wagner-Johnston, N.; Coutre, S., et al. Tolerability and activity of combinations of the PI3K δ inhibitor idelalisib (GS-1101) with rituximab and/or bendamustine in patients with previously treated, indolent non-Hodgkin lymphoma (iNHL): updated results from a phase I study. Chicago, Illinois, USA: American Society of Clinical Oncology; 2013.
38. Horwitz, S.; Flinn, I.; Patel, M., et al. Preliminary safety and efficacy of IPI-145, a potent inhibitor of phosphoinositide-3-kinase- δ , γ , in patients with relapsed/refractory lymphoma. Chicago, Illinois, USA: American Society of Clinical Oncology; 2013.
39. Rizzatti EG, Falcao RP, Panepucci RA, et al. Gene expression profiling of mantle cell lymphoma cells reveals aberrant expression of genes from the PI3K-AKT, WNT and TGFbeta signalling pathways. *Br J Haematol*. 2005; 130:516–526. [PubMed: 16098065]
40. Dal Col J, Zancai P, Terrin L, et al. Distinct functional significance of Akt and mTOR constitutive activation in mantle cell lymphoma. *Blood*. 2008; 111:5142–5151. [PubMed: 18339899]
41. Kahl BS, Spurgeon SE, Furman RR, et al. A phase I study of the PI3K δ inhibitor idelalisib in patients with relapsed/refractory mantle cell lymphoma (MCL). *Blood*. 2014; 123:3398–3405. This study reports the outcomes of patients with MCL who were enrolled on a dose escalation and extension phase I trial of idelalisib in patients with relapsed or refractory hematologic

malignancies. Idelalisib was well tolerated and showed promising clinical activity, suggesting that it may be worthwhile of further study in MCL. [PubMed: 24615778]

42. Wagner-Johnston, N.; De Vos, S.; Leonard, J., et al. Preliminary results of PI3K δ inhibitor idelalisib (GS-1101) treatment in combination with everolimus, bortezomib, or bendamustine/rituximab in patients with previously treated mantle cell lymphoma (MCL). Chicago, Illinois, USA: American Society of Clinical Oncology; 2013.
43. Meadows SA, Vega F, Kashishian A, et al. PI3Kdelta inhibitor, GS-1101 (CAL-101), attenuates pathway signaling, induces apoptosis, and overcomes signals from the microenvironment in cellular models of Hodgkin lymphoma. *Blood*. 2012; 119:1897–1900. [PubMed: 22210877]
44. Horwitz, S.; Younes, A.; Flinn, I., et al. Preliminary safety and efficacy of IPI-145, a potent inhibitor of phosphoinositide-3-kinase-delta, gamma, in patients with relapsed/refractory T-cell lymphoma International Conference on Malignant Lymphoma. Lugano, Switzerland: 2013.
45. Herko, A.; Mavis, M.; Czuczman, M.; Hernandez, F. AMG 319, a novel inhibitor of phosphoinositide-3 kinase delta (PI3Kd), demonstrates activity in lymphoma pre-clinical models. Atlanta, Georgia, USA: American Society of Hematology; 2012.
46. Savona, M.; Gutierrez, M.; Lanasa, M., et al. A phase I dose escalation study of TGR-1202, a novel PI3K- δ inhibitor, for patients with relapsed or refractory hematologic malignancies. New Orleans, Los Angeles, USA: American Society of Hematology; 2013.
47. Maira SM, Pecchi S, Huang A, et al. Identification and characterization of NVP-BKM120, an orally available pan-class I PI3-kinase inhibitor. *Mol Cancer Ther*. 2012; 11:317–328. [PubMed: 22188813]

Key Points

- The PI3K pathway appears to be important in lymphoid malignancies, and inhibitors of this pathway show promising preclinical and clinical activity.
- In addition to the direct cellular toxicity of the PI3K inhibitors, they also appear to exert effects through inhibition of BCR signaling and alterations of the microenvironment.
- Idelalisib, a p110 δ inhibitor, has been the most studied in clinical trials to date and demonstrates single agent activity in CLL and iNHL.
- Combination trials of idelalisib and other agents show promising efficacy.
- Further clinical trials are needed to determine the most effective combinations of these agents in lymphoma.

Figure 1.
Schematic description of phosphoinositide 3-kinase family members.

Table 1
Selected ongoing clinical trials of phosphoinositide 3-kinase inhibitors in lymphoma

Agent type	Disease type	Phase study	Treatment	Clinical trial #
PI3K δ inhibitor	CLL, previously treated	3	Idelalisib versus placebo	NCT01539291
	CLL, previously treated	3	Ofatumumab +/- idelalisib	NCT01659021
	CLL, previously treated	3	Rituximab +/- idelalisib	NCT01539512
	CLL, untreated	3	Bendamustine and rituximab +/- idelalisib	NCT01980888
	CLL, untreated	3	Rituximab or chlorambucil +/- idelalisib	NCT01980875
	CLL, previously treated	3	Bendamustine and rituximab +/- idelalisib	NCT01569295
	CLL, untreated elderly patients,	2	Idelalisib +/- rituximab	NCT01203930
	CLL, previously untreated with 17p deletion	2	Idelalisib + rituximab	NCT02044822
	iNHL	3	Bendamustine and rituximab +/- idelalisib	NCT01732926
	iNHL, previously treated	3	Rituximab +/- idelalisib	NCT01732913
	iNHL, refractory to rituximab and alkylating agents	2	Idelalisib	NCT01282424
	iNHL, previously treated	1/2	Idelalisib	NCT01306643
	Mantle cell lymphoma, relapsed or refractory	2	Lenalidomide and rituximab +/- idelalisib	NCT01838434
	Follicular lymphoma, recurrent	1	Lenalidomide + rituximab + idelalisib	NCT01644799
	Hodgkin lymphoma, relapsed or refractory	2	Idelalisib	NCT01393106
	Hematologic malignancies, refractory	2	Idelalisib + GS-9973	NCT01799889
	Lymphoid malignancies, relapsed or refractory	1	AMG-319	NCT01300026
	Hematologic malignancies, relapsed or refractory	1	TGR-1202	NCT01767766
	B-cell malignancies (CLL, NHL), relapsed or refractory	1	TGR-1202 + ublituximab	NCT02006485
	CLL	1	TGR-1202 + obinutuzumab + chlorambucil	NCT02100852
PI3K δ or PI3K γ inhibitor	CLL, relapsed or refractory	3	IPI-145 versus ofatumumab	NCT02004522
	iNHL, refractory to rituximab	2	IPI-145	NCT01882803
	Hematologic malignancies (lymphoma, CLL), refractory	1	IPI-145 + rituximab versus IPI-145 + bendamustine versus IPI-145 + bendamustine + rituximab	NCT01871675
	Hematologic malignancies, advanced	1	IPI-145	NCT01476657
pan-PI3K inhibitor	iNHL, relapsed or refractory	1	BKM120 + rituximab	NCT02049541
	iNHL, relapsed or refractory	Pilot study	BKM120	NCT01719250
	NHL (DLBCL, MCL, FL)	2	BKM120	NCT01693614

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma.

Data obtained from www.clinicaltrials.gov.