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Idelalisib: First-in-Class PI3K Delta Inhibitor for the Treatment of Chronic Lymphocytic Leukemia, Small Lymphocytic Leukemia, and Follicular Lymphoma

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Abstract

Idelalisib (Zydelig[™], also known as CAL-101 and GS-1101) was approved in 2014 in the United States and European Union for the treatment of three indolent B-cell neoplasms: relapsed/refractory chronic lymphocytic leukemia (CLL, in combination with rituximab), relapsed follicular lymphoma, and relapsed small lymphocytic lymphoma (as monotherapy). Furthermore, it was approved in the European Union as first-line therapy for poor-prognosis CLL with 17p deletions or *TP53* mutations and in patients unsuitable for chemo-immunotherapy. Idelalisib is an orally bioavailable ATP-competitive kinase inhibitor that targets the phosphoinositide 3-kinase p110 isoform δ (PI3K δ) with high potency and selectivity. PI3K δ is hyperactivated in B-cell malignancies and plays a pivotal role in the B-cell receptor (BCR) pathway, a key oncogenic driver in B-cell malignancies. The near exclusive expression of the PI3K δ isoform in hematopoietic cells and the selectivity of idelalisib for the PI3K δ isoform are essential for its efficacy and tolerability, even in elderly patients unfit for chemotherapy. Idelalisib is the first PI3K inhibitor approved by the regulatory agencies; this approval will change the treatment landscape of indolent B-cell malignancies.

Introduction

Biochemical, cellular and genetic evidences have accumulated for the past three decades defining the phosphoinositide 3-kinase (PI3K) and downstream signaling as an important oncogenic driver in human cancers and have fueled attempts at targeting this axis by pan-PI3K (targeting all four class I isoforms: PI3K α , PI3K β , PI3K δ , or PI3K γ) or isoform-specific inhibitors (1). Pan PI3K isoforms, although first to be tested in the clinic, have yet

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Note: Q. Yang and P. Modi share first authorship.

Disclosure of Potential Conflicts of Interest

T. Newcomb is an employee of Gilead Sciences. C. Quéva is an employee of, reports receiving a commercial research grant from, and has ownership interest in Gilead Sciences. V. Gandhi reports receiving a commercial research grant from Gilead Sciences. No potential conflicts of interest were disclosed by the other authors.

to demonstrate robust clinical efficacy as single agents. Ubiquitous expression and essential function of PI3K α and PI3K β isoforms may limit the tolerability of these agents. Such limitations were not observed for inhibitors specific for the PI3K catalytic subunit p110 δ (PI3K δ) isoform, an isoform almost exclusively expressed in the hematopoietic lineage, and an important regulator of normal and malignant B-cell survival, proliferation, and homing (2, 3). The clinical evaluation of PI3K δ selective inhibitors recently culminated with the milestone approval of the first of such agent, idelalisib, by the FDA and European Medicines Agency (EMA) for the treatment of relapsed indolent B-cell malignancies.

In 2014, the FDA granted approval of idelalisib for three disease indications: full approval for the treatment of relapsed CLL in combination with rituximab, and accelerated approval as monotherapy for patients with relapsed follicular lymphoma (FL) or small lymphocytic leukemia (SLL) who have received at least two prior systemic therapies. In parallel, the EMA granted marketing authorization for the use of idelalisib in combination with rituximab for patients with CLL who have received at least one prior therapy or as first-line treatment in CLL patients with a 17p deletion or *TP53* mutation unsuitable for chemotherapy. Idelalisib monotherapy was also approved for the treatment of FL that is refractory to two prior therapies.

PI3K isoforms and expression

The PI3K plays a major role in many aspects of cellular biology and is often hyper-activated in human cancers (1, 4). The PI3K family of enzymes have multifunctional roles regulating cellular growth, proliferation, differentiation, motility, intracellular trafficking, and metabolism (4). Three distinct classes of PI3K (class I, II and III) have been characterized and grouped according to their structure and function. The class IA PI3Ks, which have been implicated in many human cancers, are activated downstream of receptor tyrosine kinases and protein G-coupled receptors (GPCR) and via interaction with activated RAS or Rho family of GTPases. Class IA PI3Ks are heterodimers and each consists of a regulatory subunit p85 (p85 α , p55 α or p50 α isoforms encoded by *PIK3R1*, *PIK3R2* or *PIK3R3*, respectively) and a catalytic subunit p110 (p110 α , p110 β , or p110 δ isoforms encoded by *PIK3CA*, *PIK3CB*, or *PIK3CD*, respectively) (1, 4). Class IB comprises a single catalytic subunit, p110 δ that associates with the regulatory subunit p101 (encoded by *PIK3R5*) or p87 (encoded by *PIK3R6*) to form PI3K γ . Similar to class IA PI3Ks, activation of PI3K γ is mediated by chemokine signaling through GPCR and binding to RAS (5).

PI3K catalytic subunit mediates phosphorylation of phosphatidylinositol-4,5-bisphosphate (PIP2) to yield phosphatidylinositol-3,4,5-trisphosphate (PIP3), a second messenger that functions as an anchor at the cellular membrane to assemble and activate downstream signaling complexes, including the protein kinase B (AKT) kinase (6). The class IA PI3K signaling pathway is activated in human cancers due to mutational activation, or amplification of genes encoding the catalytic subunits, or by inactivation of phosphatases such as PTEN that catabolize PIP3 (4, 7).

The PI3K class I catalytic isoforms have non-overlapping functions. Genetic ablation of the ubiquitously expressed p110 α or p110 β results in embryonic lethality, indicating their

essential and non-redundant roles during development (8). In contrast, p110 δ is mostly expressed in the hematopoietic system, including myeloid cells, B- and T-cells and play key roles in leukocyte signaling, proliferation, differentiation, activation, and chemotaxis (9, 10). Mice lacking p110 δ function have severely impaired B-cell development and response (11–13). *PIK3CD* knockout and p110 δ kinase-dead mice show complete impairment in proliferative responses to B-cell receptor (BCR) stimulation, and partial inhibition to CD40, interleukin (IL) -4 receptor or toll-like receptor (TLR) 4 stimulation leading to defects in T-cell-dependent and -independent antigen-stimulated antibody generation (11–13). In addition, mice with a kinase-dead mutation in p110 δ develop progressive inflammatory bowel disease (11). Gain-of-function mutations in p110 δ have been reported in rare cases of diffuse large B-cell lymphomas (DLBCL) but also surprisingly in immune-deficient human patients (7, 14, 15). These activating mutations severely impair the development and function of memory B- and T-cells by increasing activation-induced cell death, senescence and by altering differentiation further supporting an essential role of PI3K δ in the regulation of normal and pathologic immune response (14, 15). Recent evidence suggests a role of PI3K δ in the generation and function of regulatory T-cells (Treg) and myeloid-derived suppressor cells (MDSCs), and PI3K δ inhibitors may stimulate anti-tumor immune responses, providing a rationale for the evaluation of PI3K δ inhibitors in solid tumors in addition to hematologic malignancies (16). Class 1B catalytic subunit p110 δ , is also exclusively expressed in the hematopoietic lineage and has essential functions in chemo-attractant-mediated migration of macrophages and neutrophils, thymocyte survival and mature T-cell activation (5).

Numerous reports have identified the pivotal role of class IA PI3Ks in leukemia and lymphoma. In CLL, the constitutive activation of the PI3K pathway is dependent on p110 δ isoform (17). In this context, p110 δ is generally not mutated, but signals downstream of the BCR pathway, leading to increased expression of anti-apoptotic proteins (17, 18). PI3K δ expression is found at higher levels in Hodgkin's lymphoma (HL) (19) and in mantle cell lymphoma (MCL) (20, 21). It has also been reported that constitutive activation of the PI3K pathway through BCR leads to dysregulation of cell-cycle progression in MCL cell lines and in primary MCL and CLL cells (18, 20).

PI3K δ regulation and function

In normal and malignant B-cells, PI3K δ critically regulates a number of signaling pathways driven by receptors, including BCR, Fc-gamma receptor (Fc γ R), TLR, C-X-C chemokine receptor type 4/5 (CXCR4/5), and the tumor necrosis factor (TNF) receptor family (9, 22). PI3K δ functions to integrate and transduce these signals from the microenvironment, thus promoting malignant B-cell proliferation, growth, survival, adhesion, and homing. BCR, a prominent activator of PI3K δ in B-cells, is chronically activated in various B-cell leukemias and lymphomas, including CLL, DLBCL, and MCL (23–25).

BCR activation recruits and activates the tyrosine kinase Lyn and spleen tyrosine kinase (SYK) at the plasma membrane (25). Phosphorylation of a key tyrosine residue in CD79A recruits the adaptor proteins (Nck) and B-cell PI3K adaptor protein (BCAP) (25, 26). PI3K δ recruitment to the cell membrane is mediated by the association of p85 regulatory subunit to

the phosphorylated tyrosine motifs in the B-cell antigen CD19 and BCAP (25). Both CD19 and BCAP contain YXXM sequences, which, upon phosphorylation on the tyrosine residue, become docking sites for the p85 regulatory subunits and a necessary step to the recruitment and activation of the p110 δ catalytic subunit (27). In addition, PI3K δ regulates B-cell responses to CD40-ligand, B-cell activating factor (BAFF), IL-4, and to the homing chemokines CXCL12/13 (2, 3, 9).

Key pathways orchestrated by PI3K δ and turned on in B-cell malignancies upon BCR activation, include membrane trafficking, AKT/mammalian target of rapamycin (mTOR), mitogen-activated protein kinases (MAPK), and nuclear factor kappa light-chain enhancer of activated B cells (NF- κ B) (12, 23). AKT is the best characterized downstream effector of PI3K δ and is the central modulator of PI3K-regulated oncogenic signaling. Many oncogenic effectors downstream of AKT play critical roles in regulating cell cycle and cell survival (mouse double minute 2 homolog (MDM2), p53, forkhead box O (FOXO)), DNA repair (MDM2, p53), chemoresistance (NF- κ B), and energy metabolism (GSK-3 β , mTOR); many of these targets are inhibited by pan-PI3K or PI3K δ -specific inhibitors (28) (Fig. 1).

Discovery and preclinical development of idelalisib

Following the discovery of p110 δ (10, 29), ICOS corporation identified the first PI3K δ selective inhibitor, IC87114, which has been extensively used *in vitro* and *in vivo* to probe the function of PI3K δ (30). Idelalisib (5-fluoro-3-phenyl-2-[(S)-1-(9H-purin-6-ylamino)-propyl]-3H-quinazolin-4-one) belongs to the same chemotype as IC87114 but has improved potency and metabolic stability. Idelalisib and IC87114 bind the ATP-binding pocket of PI3K δ , which is responsible for the selectivity for PI3K δ (31). The idelalisib IC₅₀ for PI3K δ determined at 2x K_m for ATP is 19 nM. The IC₅₀ for PI3K α , β and γ were 8600 nM, 4000 nM, and 2100 nM, respectively (17, 32). In addition, idelalisib at 10 μ M did not significantly bind or inhibit any other kinases besides the PI3Ks in a broad panel of kinase assays (17).

Idelalisib's selectivity and potency translated to PI3K isoform-selective cellular assays. Human basophil activation by anti-Fc ϵ R1, as measured by the surface expression of CD69, and B-cell proliferation in response to BCR crosslinking provided two read-outs that are potently inhibited by idelalisib with an EC₅₀ of 8.9 nM and 6 nM, respectively. Idelalisib was 281, 159 and >1124 fold less potent in cellular assays dependent on PI3K α , β and γ , respectively (32). In patients treated with the 150mg BID dose, idelalisib's free maximal plasma concentration is 13-fold higher than the p110 δ IC₅₀, but is only 0.12-fold the biochemical IC₅₀ for p110 γ and less than 0.10-fold the biochemical IC₅₀ for p110 α and p110 β , indicating that idelalisib selectivity for PI3K δ is maintained in the clinical setting.

Initial studies demonstrated sensitivity to idelalisib in cell lines and primary cells from patients with B-acute lymphocytic leukemia (ALL) and CLL (17). Phosphorylation of AKT on Ser473 and Thr308, two downstream markers of PI3K pathway activation, was inhibited by idelalisib in primary CLL and MCL and in HL cell lines, demonstrating a role for PI3K δ in the regulation of intrinsic or stimulated AKT activity (17, 19). The understanding of idelalisib's mode of action in CLL originated from seminal work from the laboratories of Byrd and Burger, who demonstrated the key role played by PI3K δ in the transmission of

survival, proliferation and homing signals produced by the tumor microenvironment (2, 3). Idelalisib potently negated the trophic influence of these factors as demonstrated by the inhibition of the survival benefits provided by *ex vivo* stimulation of CLL primary cells with BCR crosslinking, CD40L, BAFF, TNF- α , or fibronectin and co-culture with a stromal cell line or monocyte-derived nurse-like cells. *In vitro* idelalisib reduced CLL migration beneath a layer of bone marrow-derived stromal cells, inhibited CLL adhesion to stromal and endothelial cells, and decreased chemotaxis toward CXCL12 and CXCL13. These observations are consistent with the rapid decrease in lymph node size and increase in lymphocytosis in idelalisib-treated patients and are a possible indication of tumor cells being separated and migrating away from the tumor niche (3, 33, 34). Chemokines such as C-C motif ligand 3 and 4 (CCL3/4), as well as stroma-/T-cell-produced factors including CD40L, TNF α , IL-6 and -10, were also impacted (3, 35). Idelalisib may thus simultaneously target the malignant B-cells by inhibiting their response to stromal factors and the tumor niche by limiting its ability to support the tumor cell growth.

The interplay between transformed B-cells, tumor-associated macrophages, MDSCs, follicular dendritic cells, Tregs, and follicular helper T cells with the tumor stroma is also known to be important for the development and prognosis of FL (36). While most of these cell types predominantly express the PI3K δ isoform (10), their contribution to idelalisib's mode of action in FL remains to be fully characterized.

Pharmacokinetic and pharmacodynamic studies of idelalisib

Initial pharmacokinetic investigation of idelalisib was performed in healthy individuals at ascending doses. Similar pharmacokinetic parameters have been reported in patients with CLL or indolent non-Hodgkin lymphoma (iNHL) receiving doses of idelalisib ranging from 50 mg to 350 mg BID or 150 mg QD (33, 37). Over 28 days of dosing, accumulation was minimal and there was little variation in exposure by age or sex. Plasma exposure was less than dose-proportional above 150 mg BID. Trough exposure levels were markedly lower for QD dosing.

Investigations of pharmacodynamic activity have focused on the effect of idelalisib on AKT activity and plasma concentrations of an array of chemokines, stroma-derived factors, and cytokines often elevated in patients with CLL (33). As expected, baseline levels of phospho-AKT were elevated in B-cells from all patients with CLL who were evaluated (n= 27). Within 7 days of idelalisib dosing, AKT activation was reduced to levels approaching that observed in normal B-cells (33). Likewise, plasma concentrations of CCL3, CCL4, CCL17, CCL22, CD40 ligand, CCL2, CXCL13, and TNF- α also decreased significantly after 4 weeks of treatment with idelalisib.

Clinical studies

CLL

The pivotal trial supporting the approval of idelalisib in combination with rituximab included 220 patients with relapsed CLL who were not suitable for cytotoxic therapy due to myelotoxicity from previous therapy, reduced creatinine clearance, or the presence of

significant co-morbidities not related to CLL(34). This was a multicenter, randomized, double-blind, placebo-controlled, phase 3 comparison of 150 mg BID idelalisib plus rituximab versus rituximab plus an oral placebo. The primary endpoint was progression-free survival (PFS).

Patients in this study had long-standing disease (approximately 9 years median time since initial diagnosis) and a median Cumulative Illness Rating Scale (CIRS) of 8, indicating a high degree of comorbidity. The median age was 71 years and patients had received a median of 3 prior therapies for CLL. A large majority (80%) of patients had unfavorable unmutated *IGHV* status and more than 40% had a 17p deletion or another mutation in *TP53*.

An interim analysis was pre-specified to occur after approximately 50% of 119 anticipated events (disease progression or death) had occurred. At this analysis, the study was stopped early by a safety monitoring board due to overwhelming efficacy in the idelalisib plus rituximab arm of the trial. When the study was stopped, the median duration of progression-free survival had not been reached in patients receiving idelalisib plus rituximab. Median duration of progression-free survival was 5.5 months in those receiving rituximab plus placebo. At 24 weeks, the rate of progression-free survival in the idelalisib plus rituximab arm was 93% versus 46% in the rituximab plus placebo arm ($P < 0.001$). The favorable treatment effect of idelalisib plus rituximab was observed across the pre-specified patient subgroups, with similar benefits being observed regardless of the presence or absence of 17p deletion, other *TP53* mutation or *IGHV* status. Idelalisib plus rituximab also had a superior survival benefit. The median duration of overall survival in the two arms was not reached but the overall survival rate was 92% in the idelalisib plus rituximab arm versus 80% in the rituximab plus placebo arm at 12 months ($P = 0.02$).

The most common adverse events in the idelalisib plus rituximab group were pyrexia, fatigue, nausea, chills, and diarrhea. In the rituximab plus placebo group, the common adverse events were infusion-related reactions, fatigue, cough, nausea, and dyspnea. Among more severe events, grade 3 or higher diarrhea was reported in 4 patients and grade 3 or higher rash was reported in 2 patients in the idelalisib plus placebo groups whereas no such events were reported in the rituximab plus placebo group. Among laboratory abnormalities, grade 3 or higher transaminase elevations occurred in 6 patients (5%) receiving idelalisib plus rituximab versus 1 patient (1%) in the rituximab plus placebo arm. Grade 3 or higher neutropenia was also somewhat more frequent in the idelalisib plus rituximab arm (34%) than in the comparator arm (22%).

NHL

The pivotal trial supporting the accelerated approval of idelalisib as monotherapy in patients with FL and SLL was a single-arm, open-label study in 125 patients with iNHL, all of whom received idelalisib 150 mg BID as oral monotherapy (38). As is common in single-arm oncology trials, the primary endpoint was overall response rate (ORR), with duration of response (DOR) being a key secondary endpoint.

Patients had 1 of 4 subtypes of iNHL: FL ($n = 72$), SLL ($n = 28$), marginal-zone lymphoma ($n = 15$), or lymphoplasmacytic lymphoma with or without Waldenström's

macroglobulinemia (n = 10). Per inclusion criteria, patients were those who were refractory to both rituximab and an alkylating agent, defined as having either no response or a response of limited duration (relapse within 6 months) after prior treatment with these agents.

Consistent with the inclusion criteria, subjects enrolled in the study were heavily pretreated with highly refractory disease. Subjects had received a median of 4 prior therapies; 100% had disease refractory to rituximab and 99% to an alkylating agent, with 91% refractory to both when administered as part of the same regimen. The majority of patients had failed regimens considered cornerstones of therapy, including bendamustine plus rituximab (78% of patients were refractory) and R-CHOP (71% of patients were refractory). The median age of enrolled patients was 64 years.

After a median treatment duration of 6.6 months, patients receiving idelalisib had an ORR of 57% (71 responders among 125 patients), with 6% having a complete response. Responses to idelalisib were rapid (median time to response was 1.9 months) and durable, with a median duration of response of 12.5 months. Median PFS was 11 months. Consistent benefit was observed across patient subgroups, including age, sex, iNHL subtype, number of prior therapies, prior bendamustine use or refractory status, and the presence or absence of bulky disease at baseline.

The most common adverse events of any severity were diarrhea (43%), fatigue (30%), nausea (30%), cough (in 29%), and pyrexia (28%). Among events that were grade 3 or higher, the most common were diarrhea (13%), pneumonia (7%), and dyspnea (3%). Grade 3 or higher rash was reported in 2% of patients. As in patients with CLL, grade 3 or higher elevations in transaminase were reported in some patients (13%). Grade 3 or higher neutropenia was reported in 27% of patients.

Other PI3K Delta or Delta/Gamma Inhibitors

Besides idelalisib, several other PI3K δ -specific inhibitors are in clinical development. INCB40093 (Incyte Pharmaceuticals) entered phase I evaluation for refractory B-cell malignancies and may be further tested in combination with Incyte Pharmaceuticals's Janus kinase 1 (JAK1) inhibitor (NCT01905813; clinicaltrials.gov). TGR-1202 (TG Therapeutics) is in phase I clinical trial with the most notable combinations being with brentuximab vedotin in HL and with chlorambucil and obinutuzumab in CLL (NCT02164006, NCT02100852; clinicaltrials.gov). AMG 319 (Amgen Inc.-Acerta Pharma) is currently in phase 1 trials for patients with relapsed or refractory CLL in combination with Acerta's Bruton's tyrosine kinase (BTK) inhibitor (39). Duvelisib (IPI-145, Infinity Pharmaceuticals), a dual PI3K δ and γ inhibitor, is currently being evaluated as a single agent in phase 3 trials for patients with advanced CLL (40) and indolent NHL (41). It is also a more potent inhibitor of PI3K δ . Duvelisib's activity in primary CLL *ex vivo* is comparable to idelalisib when adjusted for potency (42, 43). However, a head to head comparison of idelalisib and duvelisib is needed to identify role of PI3K gamma inhibition in B-cell neoplasia. Consistent with the presence of PI3K γ in T-cells and with the T-cell phenotype in *PIK3CD PIK3CG* double mutant mice, duvelisib decreases the viability of T- and NK-cells *in vitro* and demonstrates activity in T-cell malignancies (42, 44).

Future

The success of inhibiting the PI3K δ isoform and the approval of idelalisib has opened a new chapter in targeting the PI3K pathway. Already there is a flurry of new PI3K δ or δ/γ inhibitors being evaluated in both the preclinical and clinical settings. Several investigators are probing the mechanisms responsible for the activity of idelalisib (45) as well as the mechanisms that will define resistance to these agents. Idelalisib clinical program encompasses 2 major directions: the evaluation of this agent in first-line CLL and, FL, and novel combinations (32). Remarkably, idelalisib in the EU as well as the BTK inhibitor ibrutinib are already approved for the first-line treatment of CLL with the poor prognosis feature of 17p deletion or p53 mutation. Idelalisib already demonstrated clinical efficacy in combination with anti-CD20 monoclonal antibody rituximab and chemo-immunotherapy such as bendamustine-rituximab (34, 46). The landscape of the treatment of indolent B-cell malignancies is undergoing rapid transformation with the advent of exciting clinically active molecules that include Fc-enhanced anti-CD20 monoclonal antibodies such as obinutuzumab, inhibitors of BTK, SYK, BCL2 and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors. The goal of future clinical research will be to identify the optimal combination regimen for idelalisib and sequence of these novel agents to achieve durable complete remission in chemotherapy fit and unfit patients.

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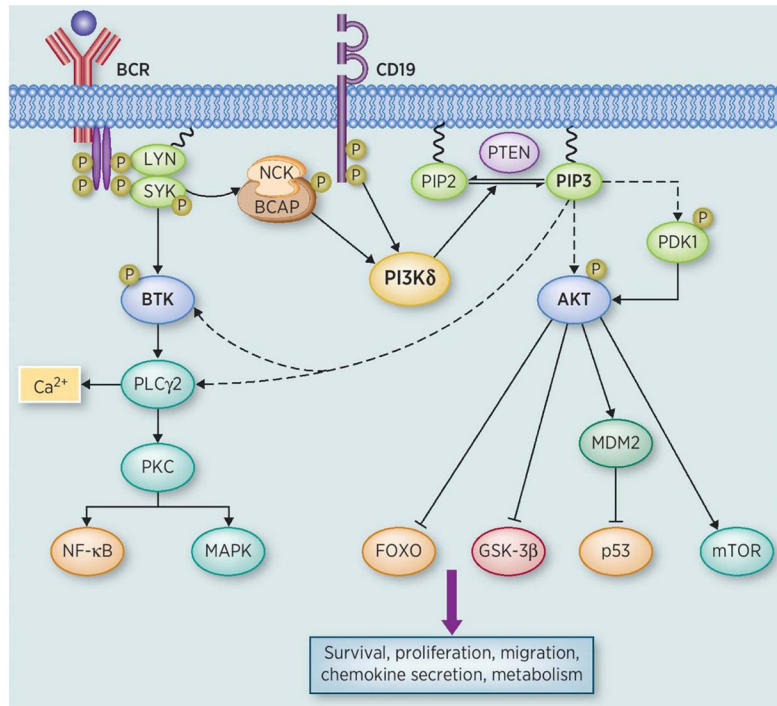


Figure 1. BCR pathway and the role of PI3K

Antigen binding activates the BCR pathway through recruitment and activation of Lyn/Syk, which phosphorylates tyrosine residues on CD19, Nck and BCAP. PI3K regulatory subunit is recruited to the cell membrane by docking to BCAP and CD19 leading to the activation of p110 δ . Activated PI3K phosphorylates PIP2 into PIP3. PIP3 recruits and activates PH domain containing signaling molecules including AKT and PDK1. AKT activates various downstream effectors such as MDM2 and mTOR, whereas it inhibits the functions of FOXO and GSK-3 β upon phosphorylation. Activation of the BCR pathway also leads to BTK and MAPK pathways activation. BTK initiates a transduction cascade leading to the activation of PLC γ 2, intracellular calcium release, PKC activation and initiation of NF- κ B transcriptional program. This process is facilitated through interaction with PIP3 at PH domain to recruit BTK and PLC γ 2 to the cell membrane. P on various molecules indicates that they are phosphorylated. Solid arrows indicates recruitment and/or activation, dotted arrows indicate interaction through PH domain, and inhibitory signs indicates inhibition.