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 (Gilead Sciences, Inc.), 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 chemoimmunotherapy. Idelalisib is an orally bioavailable ATP-competitive kinase inhibitor that targets the PI3K p110 δ (PI3Kδ) with high potency and selectivity. PI3Kδ is hyperactivated in B-cell malignancies and plays a pivotal role in the B-cell receptor pathway, a key oncogenic driver in B-cell malignancies. The near exclusive expression of the PI3Kδ isoform in hematopoietic cells and the selectivity of idelalisib for the PI3Kδ 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. Clin Cancer Res; 21(7); 1537–42. ©2015 AACR. See related article by Miller et al., p. 1525

Introduction

Biochemical, cellular, and genetic evidence has accumulated for the past three decades defining the 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: PI3Kα, PI3Kβ, PI3Kδ, or PI3Kγ) or isoform-specific inhibitors (1). Pan-PI3K isoforms, although first to be tested in the clinic, have yet to demonstrate robust clinical efficacy as single agents. Ubiquitous expression and essential function of PI3Kα and PI3Kβ isoforms may limit the tolerability of these agents. Such limitations were not observed for inhibitors specific for the PI3K catalytic subunit p110δ (PI3Kδ) 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 PI3Kδ-selective inhibitors recently culminated with the milestone approval of the first 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 chronic lymphocytic leukemia (CLL) in combination with rituximab, and accelerated approval as monotherapy for patients with relapsed follicular lymphoma 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 who are unsuitable for chemoimmunotherapy. Idelalisib monotherapy was also approved for the treatment of follicular lymphoma 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 hyperactivated in human cancers (1, 4). The PI3K family of enzymes has 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 IIA PI3Ks, which have been implicated in many human cancers, are activated downstream of receptor tyrosine kinases and G protein–coupled receptors (GPCRs) and via interaction with the activated RAS or RHO family of GTPases. Class IIA PI3Ks are heterodimers, and each consists of a regulatory subunit p85 (p85α, p55γ, or p50δ isoforms encoded by PIK3R1, PIK3R2, or PIK3R3, respectively) and a catalytic subunit p110 (p110α, p110δ, or p110δ isoforms encoded by PIK3CA, PIK3CB, or PIK3CD, respectively; refs. 1, 4). Class IB comprises a single catalytic subunit, p110δ, that associates with the regulatory subunit p101 (encoded by PIK3R5) or

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

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p87 (encoded by PIK3R6) to form PI3Kγ. Similar to class IA PI3Ks, activation of PI3Kγ 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, amplification of genes encoding the catalytic subunits, or inactivation of phosphatases such as PTEN that catalyze PIP3 (4, 7).

The PI3K class I catalytic isoforms have nonoverlapping functions. Genetic ablation of the ubiquitously expressed p110α or p110β results in embryonic lethality, indicating their essential and nonredundant roles during development (8). In contrast, p110δ is mostly expressed in the hematopoietic system, including myeloid cells, B cells, and T cells, and plays key roles in leukocyte signaling, proliferation, differentiation, activation, and chemotaxis (9, 10). Mice lacking p110δ function have severely impaired B-cell development and response (11–13). PIK3CD knockout and p110δ kinase-dead mice show complete impairment in proliferative responses to B-cell receptor (BCR) stimulation, and partial inhibition to CD40, IL4 receptor, or Toll-like receptor 4 (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 p110δ develop progressive inflammatory bowel disease (11). Gain-of-function mutations in p110δ 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 cells and T cells by increasing activation-induced cell death and senescence and by altering differentiation, further supporting an essential role of PI3Kδ in the regulation of normal and pathologic immune response (14, 15). Recent evidence suggests a role of PI3Kδ in the generation and function of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC), and PI3Kδ inhibitors may stimulate antitumor immune responses, providing a rationale for the evaluation of PI3Kδ inhibitors in solid tumors in addition to hematologic malignancies (16). Class II B catalytic subunit p110y is also exclusively expressed in the hematopoietic lineage and has essential functions in chemokine-activated-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 p110δ isoform (17). In this context, p110δ is not mutated, but signals downstream of the BCR pathway, leading to increased expression of antiapoptotic proteins (17, 18). PI3Kδ expression is found at higher levels in Hodgkin lymphoma (19) and in mantle cell lymphoma (MCL; refs. 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).

**PI3Kδ Regulation and Function**

In normal and malignant B cells, PI3Kδ critically regulates a number of signaling pathways driven by receptors, including BCR, Fc-gamma receptor (FcγR), TLR, C-X-C chemokine receptor type 4/5 (CXCR4/5), and the TNF receptor family (9, 22). PI3Kδ 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 PI3Kδ 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; refs. 25, 26). PI3Kδ 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 p110δ catalytic subunit (27). In addition, PI3Kδ regulates B-cell responses to CD40-ligand, B-cell activating factor (BAFF), IL4, and to the homing chemokines CXCL12/13 (2, 3, 9).

Key pathways orchestrated by PI3Kδ and turned on in B-cell malignancies upon BCR activation include membrane trafficking, AKT/mTOR, MAPK, and NF-kB (12, 23). AKT is the best-characterized downstream effector of PI3Kδ 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 [murine double minute 2 homolog (MDM2), p53, forkhead box O (FOXO)], DNA repair (MDM2 and p53), chemotherapy resistance (NF-kB), and energy metabolism (GSK-3β and mTOR); many of these targets are inhibited by pan-PI3K or PI3Kδ-specific inhibitors (ref. 28; Fig. 1).

**Discovery and Preclinical Development of Idelalisib**

Following the discovery of p110δ (10, 29), ICOS Corporation identified the first PI3Kδ-selective inhibitor, IC87114, which has been extensively used in vivo and in vitro to probe the function of PI3Kδ (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 PI3Kδ, which is responsible for the selectivity for PI3Kδ (31). Idelalisib IC50 for PI3Kδ determined at 2x Km for ATP is 19 nmol/L. The IC50 values for PI3Kγ, β, and γ were 8,600 nmol/L, 4,000 nmol/L, and 2,100 nmol/L, respectively (17, 32). In addition, idelalisib at 10 μmol/L did not significantly bind or inhibit any other kinases besides the PI3Kδ 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-FcεR1, 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 nmol/L and 6 nmol/L, respectively. Idelalisib was 281-, 159-, and >1,124-fold less potent in cellular assays dependent on PI3Kα, β, and γ, respectively (32). In patients treated with the 150 mg twice-daily dosage, idelalisib’s free maximal plasma concentration is 13-fold higher than the p110δ IC50 but is only 0.12-fold the biochemical IC50 for p110γ and less than 0.10-fold.
The biochemical IC_{50} for p110α and p110β, indicating that idelalisib selectivity for PI3Kδ 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 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 Hodgkin lymphoma cell lines, demonstrating a role for PI3Kδ 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 PI3Kδ in the transmigration 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, TNFα, or fibronectin and coculture 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 lymphopenia in idelalisib-treated patients and are a possible indication of tumor cells being separated and migrating away from the tumor niche (3, 33, 34). The expression of chemokines such as C-C motif ligand 3 and 4 (CCL3/4), as well as stroma/T-cell–produced factors, including CD40L, TNFα, IL6, and IL10, was also reduced (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 follicular lymphoma (36). Although most of these cell types predominantly express the PI3Kδ isoform (10), their contribution to idelalisib’s mode of action in follicular lymphoma 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 twice a day or 150 mg every day (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 twice a day. Trough exposure levels were markedly lower for every-day 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 INFα also decreased significantly after 4 weeks of treatment with idelalisib.

**Clinical Studies**

**Chronic lymphocytic leukemia**

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 comorbidities not related to CLL (34). This was a multicenter, randomized, double-blind, placebo-controlled, phase III comparison of 150 mg twice-daily 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 of 8, indicating a high degree of comorbidity. The median age was 71 years, and patients had received a median of three prior therapies for CLL. A large majority (80%) of patients had unfavorable unmuted IGHV status, and more than 40% had a 17p deletion or another mutation in TP53.

An interim analysis was prespecified 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 PFS had not been reached in patients receiving idelalisib plus rituximab. The median duration of PFS was 5.5 months in those receiving rituximab plus placebo.

At 24 weeks, the rate of PFS 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 prespecified 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%).

**Non-Hodgkin lymphoma**

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

Patients had one of four subtypes of iNHL: follicular lymphoma (n = 72), SLL (n = 28), marginal-zone lymphoma (n = 15), or lymphoplasmacytic lymphoma with or without Waldenström 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, patients enrolled in the study were heavily pretreated and had highly refractory disease. Subjects had received a median of four 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. The 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 (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 PI3Kδ-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 Pharmaceutical's Janus kinase 1 (JAK1) inhibitor (NCT01905813). TGR-1202 (TG Therapeutics) is being evaluated in a phase I clinical trial with the...
most notable combinations being with bendamustine vedotin in Hodgkin lymphoma and with chlorambucil and obinutuzumab in CLL (NCT02164006, NCT02100852). AMG 319 (Amgen Inc.; Acerta Pharma) is currently in phase I trials for patients with relapsed or refractory CLL in combination with Acerta’s Bruton tyrosine kinase (BTK) inhibitor (39). Duvelisib (IP1-145; Infinity Pharmaceuticals), a dual PI3Kδ and γ inhibitor, is currently being evaluated as a single agent in phase III trials for patients with advanced CLL (40) and indolent NHL (41). It is also a more potent inhibitor of PI3Kδ. Duvelisib’s activity in primary CLL ex vivo is comparable with that of idelalisib when adjusted for potency (42, 43). However, a head-to-head comparison ofidelalisib and duvelisib is needed to identify the role of PI3Kγ inhibition in B-cell neoplasia. Consistent with the presence of PI3Kγ in T cells and with the T-cell phenotype in PIK3CD PIK3CG double-mutant mice, duvelisib decreases the viability of T cells and natural killer cells in vitro and demonstrates activity in T-cell malignancies (42, 44).

Future

The success of inhibiting the PI3Kδ isoform and the approval of idelalisib have opened a new chapter in targeting the PI3K pathway. Already a flurry of new PI3Kδ or δ/γ inhibitors are 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. The clinical program for idelalisib encompasses two major directions: evaluation of this agent in first-line CLL and follicular lymphoma, and evaluation in novel combinations (32). In the EU, idelalisib (in combination with rituximab) and the BTK inhibitor ibritinib are already approved for the first-line treatment of CLL patients with the poor-prognosis feature of 17p deletion or p53 mutation who are unsuitable for chemoimmunotherapy (34, 46). The landscape of treatment for indolent B-cell malignancies is undergoing rapid transformation with the advent of exciting clinically active molecules that include Fe-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 the sequence of these novel agents to achieve durable complete remission in chemotherapy-fit and -unfit patients.

Disclosure of Potential Conflicts of Interest

T. Newcomb and C. Queva are employees of and have ownership interest in Gilead Sciences, Inc. V. Gandhi reports receiving a commercial research grant from Gilead Sciences, Inc. No potential conflicts of interest were disclosed by the other authors.

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Conception and design: Q. Yang, T. Newcomb, C. Queva, V. Gandhi
Development and methodology: V. Gandhi
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Q. Yang, T. Newcomb, C. Queva, V. Gandhi
Writing, review, and/or revision of the manuscript: Q. Yang, P. Modi, T. Newcomb, C. Queva, V. Gandhi
Study supervision: V. Gandhi

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