

## FDA Approval: Idelalisib Monotherapy for the Treatment of Patients with Follicular Lymphoma and Small Lymphocytic Lymphoma

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### Abstract

On July 23, 2014, the FDA granted accelerated approval to idelalisib (Zydelig tablets; Gilead Sciences, Inc.) for the treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma or relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies. In a multicenter, single-arm trial, 123 patients with relapsed indolent non-Hodgkin lymphomas received idelalisib, 150 mg orally twice daily. In patients with follicular lymphoma, the overall response rate (ORR) was 54%, and the median duration of response (DOR) was not evaluable; median follow-up was 8.1 months. In patients with SLL, the ORR was 58% and the

median DOR was 11.9 months. One-half of patients experienced a serious adverse reaction of pneumonia, pyrexia, sepsis, febrile neutropenia, diarrhea, or pneumonitis. Other common adverse reactions were abdominal pain, nausea, fatigue, cough, dyspnea, and rash. Common treatment-emergent laboratory abnormalities were elevations in alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, absolute lymphocytes, and triglycerides. Continued approval may be contingent upon verification of clinical benefit in confirmatory trials. *Clin Cancer Res*; 21(7); 1525-9. ©2015 AACR.

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### Introduction

Although there are several active combinations of cytotoxic chemotherapeutics or radioimmunotherapeutics that can be used for the treatment of relapsed follicular lymphoma (FL) or small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL), response rates range from 40% to 90% with varying durations of response (1, 2). Moreover, repeated administration of intravenous combination chemotherapy is associated with myelosuppression that may limit the amount of treatment that can be given. Therapies currently used for the treatment of patients with relapsed FL or SLL/CLL include single-agent rituximab or

combination regimens; for example, bendamustine, rituximab (BR); rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone (R-CHOP); rituximab, cyclophosphamide, vincristine sulfate, prednisone (RCVP; ref. 3). SEER 5-year relative survival rates for patients with FL and SLL/CLL are estimated to be 86% and 79%, respectively (4). Response rates for regulatory drug approvals in these patient populations range from about 50% to 80% (5-7).

Kinases in the B-cell receptor (BCR) signaling pathway are reasonable targets for treatment in FL and SLL. Phosphatidylinositol-3 kinases (PI3K) are intracellular signal transducer enzymes that are essential for many cellular functions. The delta isoform is generally restricted to hematopoietic cell types.

Upon activation via cell-surface receptor-ligand interactions, PI3K $\delta$  phosphorylates the second messenger phosphatidylinositol to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 enables the transmission of cell-surface receptor signaling by acting as a scaffold for the recruitment and activation of numerous intracellular signaling enzymes, including the serine/threonine protein kinase Akt. Akt is an initiator of specific pathways that ultimately mediate positive pleiotropic effects on cell survival, proliferation, growth, and metabolism. PI3K $\delta$  is a signaling molecule in normal and malignant B lymphocytes (8, 9). PI3K $\delta$  is involved in several signaling pathways, such as the B-cell receptor, CD40, B-cell-activating factor receptor, chemokine receptors CXCR4 and CXCR5, IL6 receptor, and integrins. These pathways may be involved in B-cell proliferation, motility, and in homing to and maintenance of the tumor microenvironment in B-cell malignancies (10).

Herein, we provide a summary of the FDA review and approval of the marketing application for idelalisib as a single-agent

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therapy of FL and SLL. Reported elsewhere is the FDA review of the marketing application for idelalisib for CLL (11).

## Idelalisib

Idelalisib, described chemically as 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-yl-amino)propyl] quinazolin-4(3H)-one, is a lipid kinase inhibitor of the class I phosphatidylinositol-3 kinase p110- $\delta$  (PI3K- $\delta$ ). Inhibition is mediated by competitive inhibition of the ATP binding site of the p110- $\delta$  subunit. In malignant B cells studied *in vitro*, idelalisib inhibited functions of the PI3K- $\delta$  pathway, including secretion of chemokines, chemotaxis, and kinase phosphorylation via receptor signaling, resulting in reduced cell viability and induction of apoptosis. The major metabolite of idelalisib, GS-563117, is inactive against PI3K- $\delta$ , but it does inhibit serine/threonine protein kinase10 (STK10/LOK) and STE20-like kinase (SLK) *in vitro* in some cell lines. Their functions are not well characterized; LOK appears to be involved in lymphocyte migration and SLK in apoptosis. The drug product is available as an oral tablet in 100-mg and 150-mg strengths.

## Clinical Pharmacology

Following oral administration of idelalisib, the median time to maximal concentration was 1.5 hours under fasted conditions. Dose-dependent absorption was observed, but food effects were not statistically significant. The population-apparent central volume of distribution at steady state was 23 L.

Idelalisib is metabolized via aldehyde oxidase and CYP3A and, to a minor extent, by UGT1A4. The population-apparent systemic clearance of idelalisib at steady state was 14.9 L/h, and the population-terminal elimination half-life was 8.2 hours. The population-terminal elimination half-life of GS-563117 was 11.6 hours. A mass balance study with a single 150-mg dose of [<sup>14</sup>C]-labeled idelalisib showed that 78% and 14% of the radioactivity was excreted in feces and urine, respectively. The metabolite GS-563117 accounted for 49% of the radioactivity in the urine and 44% in the feces.

Idelalisib exposure increased in a less-than-dose-proportional manner with doses up to 350 mg. In a population pharmacokinetics analysis, age, gender, race, and weight had no effect on exposure. The mean AUC increased up to 1.7-fold in patients with elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin (Child–Pugh class A and B). Hepatic impairment increased exposure, regardless of the degree of impairment. In studies of volunteers with renal impairment, there was no substantial change in exposure when the creatinine clearance was >15 mL/minute.

## Potential for Drug–Drug Interactions

### Drugs affecting idelalisib exposure

CYP3A can metabolize idelalisib. In healthy volunteers, rifampin (a strong inducer of CYP3A) decreased the idelalisib AUC by 75%; ketoconazole (a strong inhibitor of CYP3A) increased the idelalisib AUC by 1.8-fold.

### Effects of idelalisib on other drugs

Idelalisib or its metabolite inhibited CYP3A, CYP2C19, P-glycoprotein (P-gp), OATP1B1, and OATP1B3 *in vitro*. In healthy volunteers, idelalisib increased midazolam (CYP3A substrate) AUC by 5.4-fold, but no changes in exposure to rosuvastatin

(OAT1B1 and OATP1B3 substrate) or digoxin (P-gp substrate) were observed. There was no formal study of the effect of idelalisib on a CYP2C19 substrate *in vivo*.

## Assessment of Efficacy

### Clinical trial overview

Study 101-09 was an international multicenter, single-arm, open-label trial of idelalisib monotherapy for the treatment of relapsed indolent non-Hodgkin lymphoma (12). Eligible patients had received at least two prior systemic therapies, including rituximab and an alkylating agent. Study subjects were treated with idelalisib, 150 mg orally twice daily, with dose reductions allowed for toxicity. The starting dose was determined by the results of a phase I study, with a dose-expansion phase designed to allow no more than 25% dose-limiting toxicity (DLT; 13). Treatment was to continue until disease progression or intolerable toxicity at the lowest prespecified dose level. The primary efficacy endpoint was overall response rate (ORR) defined as complete (CR) or partial (PR) response; determination of response or progression was defined using the 2007 International Harmonization Project criteria (14). Imaging and laboratory assessments for efficacy were performed at baseline and every 8 to 12 weeks, and responses were assessed by a blinded independent review committee.

The study accrued 123 patients with indolent lymphoma: 72 with FL, 26 with SLL, 15 with marginal zone lymphoma (MZL), and 10 with lymphoplasmacytic lymphoma (LPL). Patients with CLL were not eligible; only patients with SLL defined as an absolute lymphocyte count <5 × 10<sup>9</sup>/L and lymphadenopathy were eligible. At the time of data cutoff, the median follow-up on study was 8 months. Thirty-two percent of patients were still on therapy, and 68% had discontinued. The most common reasons for early discontinuation were lack of efficacy (36%) and adverse event (21%). Given the small number and heterogeneity of patients with MZL and LPL in the study, there were insufficient data to support a meaningful analysis of efficacy for the treatment of these patients.

From the phase I dose-escalation trial, the maximum tolerated dose was not defined during the 28-day DLT observation period. Up to 25% DLT was allowed in the expansion phase of the trial. In patients with indolent lymphomas treated at the dosing regimen used in the trial, the ORR was 20%.

### Efficacy in patients with FL

The demographic characteristics of the 72 subjects with FL are shown in Table 1. The median lymph-node sum of product

**Table 1.** Characteristics of the subjects with FL or SLL from Study 101-09

	FL (n = 72)	SLL (n = 26)
Median age (range), y	62 (33–84)	65 (50–87)
Gender		
Male	39 (54%)	19 (73%)
Female	33 (46%)	7 (27%)
Race		
Caucasian	64 (89%)	21 (81%)
African American	0	2 (8%)
Other	8 (11%)	3 (11%)
Prior therapies, median (range)	4 (2–12)	4 (2–9)
LDH > ULN	21 (29%)	13 (50%)
B-symptoms present	11 (15%)	5 (19%)
ECOG performance score		
0–1	66 (92%)	25 (96%)
2	6 (8%)	1 (4%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactic dehydrogenase; ULN, upper limit of normal.

**Table 2.** Outcomes of the subjects with FL or SLL from Study 101-09

	FL (n = 72)	SLL (n = 26)
Overall responses/ 95% CI	39 (54%) 42%–66%	15 (58%) 37%–77%
Complete responses	6 (8%)	0
Partial responses	33 (46%)	15 (58%)
Median time to response (range), mo	1.9 (1.6–8.3)	1.9 (1.6–8.3)
Median duration of response (range), mo	NE (0+ to 14.8+)	11.9 (0+ to 14.7)

Abbreviations: NE, not evaluable; +, censored data.

diameter (SPD) was 23 cm<sup>2</sup> (range, 3–200 cm<sup>2</sup>). Extranodal organs (33%) or marrow (26%) were involved in a minority of subjects. The median time from diagnosis was 5 years. The most common prior treatments were R-CHOP, BR, and R-CVP; 38% had received radiation and 15% had prior stem cell transplantation. Outcomes are shown in Table 2. A CR or PR was achieved by 54% (95% CI, 42%–66%). CRs occurred in only 8% of the patients. Only 12 responders subsequently had progressive disease by the data cutoff date. The median duration of response could not be calculated, but follow-up of patients with continuing response is short (median, 8 months).

#### Efficacy in patients with SLL

The demographic characteristics of the 26 subjects with SLL are shown in Table 1. The median lymph-node SPD was 56 cm<sup>2</sup> (range, 13–224 cm<sup>2</sup>), and the marrow was involved in the majority of patients (85%). The median time from diagnosis was 7 years. The most common prior treatments were BR, FCR, and R-CHOP. A PR was achieved by 58% (95% CI, 37%–77%), and there were no CRs. The median duration of response was 12 months.

## Assessment of Safety

### Nonclinical toxicology

Nonclinical toxicology studies of idelalisib were conducted in rats and dogs. The duration of drug administration in the studies ranged over 4 to 39 weeks. Inflammation was observed in several tissues, including the gastrointestinal tract, pancreas, lungs, heart, and liver. Target organs for toxicity of idelalisib included the hematopoietic and lymphoid systems (lymphoid depletion, reduced weight of spleen and thymus, thymic hemorrhage and necrosis, myeloid and granulopoietic hyperplasia), liver (increased liver enzymes, increased liver weight, inflammation, and hepatocellular necrosis), gastrointestinal tract (infiltration, hemorrhage, ulceration), heart (myocardium infiltrate, fibrosis, increased heart weight in rats only), skin (erythema, dryness, swelling, and redness), and male reproductive systems (testicular seminiferous tubule degeneration, reduced testicular weight). Additional studies showed that idelalisib was genotoxic and teratogenic.

### Significant safety events in the treated population

The safety of idelalisib was evaluated in 354 adults with hematologic malignancies treated with various dose schedules of idelalisib monotherapy in phase I or II trials. Less than half of the subjects were treated for more than 6 months. An additional 300 subjects without malignancies were treated in studies of pharmacokinetics and drug–drug interactions. The serious and/or fatal adverse drug reactions identified included hepatotoxicity (including 3 potential Hy's law cases), diarrhea or colitis,

intestinal perforation, pneumonitis, neutropenia, and tumor lysis syndrome. Deaths considered at least possibly related to idelalisib included infection with neutropenia, sudden death, respiratory failure, tumor lysis syndrome, and enteropathy.

Biopsy reports were available for several subjects with suspected adverse reactions. A liver biopsy in a healthy volunteer with elevated transaminases showed a granulomatous-type hepatitis with portal mixed-cellular infiltrates. Lower gastrointestinal biopsies from 9 subjects with diarrhea showed cryptitis, crypt abscesses, crypt loss, and apoptotic cells with or without crypt distortion. Skin biopsies from 3 subjects with rash showed a perivascular and interstitial dermal infiltrate of lymphocytes and eosinophils with or without epidermal spongiosis. Lung biopsies from 5 subjects with pneumonitis and no infectious etiology showed organizing pneumonia. In addition, one of the lung biopsy reports noted acute inflammation, one had a mononuclear infiltrate with scattered eosinophils and poorly formed granulomata, and one had a mixed interstitial infiltrate with eosinophils and reactive pneumocytes.

### Adverse events in patients with indolent lymphoma

Common adverse events were reviewed for all 146 subjects with indolent lymphoma (FL, SLL, MZL, and LPL) treated with idelalisib, 150 mg orally twice daily, in phase I and II studies. The median duration of treatment was 6 months (range, <1–26 months). An adverse event was the cause of treatment interruption or permanent discontinuation for 80 (55%) subjects. The most common reasons for interruption or discontinuation were diarrhea (11%), pneumonia (11%), and elevated transaminases (10%).

Table 3 shows the common treatment-emergent adverse reactions and laboratory abnormalities in the subjects with indolent lymphoma. Diarrhea, fatigue, nausea, cough, pyrexia, abdominal

**Table 3.** Treatment-emergent adverse reactions and laboratory abnormalities in 146 patients with indolent lymphoma treated with idelalisib, 150 mg twice daily

	Any grade n (%)	Grade ≥3 n (%)
Adverse reactions ≥10%		
Diarrhea <sup>a</sup>	68 (47)	20 (14)
Fatigue	44 (30)	2 (1)
Nausea	42 (29)	2 (1)
Cough	42 (29)	1 (1)
Pyrexia	41 (28)	3 (2)
Abdominal pain <sup>a</sup>	38 (26)	3 (2)
Pneumonia <sup>a</sup>	37 (25)	23 (16)
Rash <sup>a</sup>	31 (21)	4 (3)
Dyspnea	25 (17)	6 (4)
Decreased appetite	24 (16)	1 (1)
Vomiting	22 (15)	2 (1)
Upper respiratory tract infection	18 (12)	0
Night sweats	18 (12)	0
Asthenia	17 (12)	3 (2)
Insomnia	17 (12)	0
Headache	16 (11)	1 (1)
Peripheral edema	15 (10)	3 (2)
Laboratory abnormalities ≥25%		
Neutrophils decreased	78 (53)	36 (25)
ALT increased	73 (50)	27 (18)
AST increased	60 (41)	18 (12)
Hemoglobin decreased	41 (28)	3 (2)
Platelets decreased	38 (26)	9 (6)

<sup>a</sup>Grouped terms. See Supplementary Table S1 for further information.

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pain, and pneumonia of any grade occurred in  $\geq 25\%$  of the subjects. Grade  $\geq 3$  diarrhea and pneumonia occurred in more than 10% of the subjects. Because it was not always possible to clearly determine the etiology of the pneumonia, the grouped term "pneumonia" included infectious and potentially drug-related pneumonitis (see Supplementary Table S1). The most common grade  $\geq 3$  laboratory abnormalities were neutropenia and elevated transaminases. The maximal ALT elevation was grade 1 for 29% of the subjects, grade 2 for 4%, grade 3 for 14%, and grade 4 for 5%.

## Discussion

No curative treatment exists for relapsed FL and SLL. The standard of care for patients with symptoms is to administer cytoreductive therapies repeatedly until resistant disease occurs. Effective new agents are needed to manage these malignancies. In Study 101-09, the objective response rates were clinically meaningful for the patient with limited or no other treatment options. However, because the single-arm trial was small with limited long-term follow-up, idelalisib was granted accelerated approval. Subpart H regulations, first implemented in 1992 and most recently renewed in 2012, allow an "accelerated" marketing approval for a new drug product provided that it shows a meaningful therapeutic benefit over existing treatments for use in a serious or life-threatening disease or condition (15). This form of approval is subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit.

The FDA review of all available idelalisib safety data revealed several serious risks, including fatal events. The risks were moderated in part by close monitoring and dose interruption and/or dose reduction for toxicities, a strategy that will be needed for safe use of the drug in practice. Because of this, a risk evaluation and mitigation strategy were required, consisting of a communication plan to inform health care professionals about the risks and management of hepatotoxicity, diarrhea and colitis, rash, and pneumonitis in patients taking idelalisib. In addition, a medication guide was written in lay language to inform and educate patients of treatment risks and the need for monitoring. With such controls of risk in place, the FDA concluded that the clinical benefit outweighs the risks for patients with FL or SLL who have limited alternate effective therapy available.

In the patients with indolent lymphoma treated with the approved dose schedule of idelalisib, the most common adverse reactions and laboratory abnormalities affected a range of organs (Table 3). Considering that expression of PI3K- $\delta$  is limited largely to leukocytes, the breadth of the toxicity profile was unexpected. Biopsy results, including those from patients with pneumonitis with no other etiology evident, are consistent at least in part with an inflammatory effect, although it is not clear whether the inflammatory effect was the primary cause or reactive. The cases with eosinophilic infiltrates in the biopsy also raise the possibility of a hypersensitivity reaction. Some reports have suggested that

the toxicities of idelalisib may be mediated by autoreactive T cells due to inhibition of regulatory T cells by idelalisib (16), but a direct toxic effect of GS-563117, the major metabolite of idelalisib *in vivo*, has not been excluded.

It remains to be confirmed in postmarketing studies that idelalisib is efficacious, safe, and tolerable in patients when taken for an extended duration, i.e., 12 months or longer. The optimal idelalisib dosing regimen for chronic administration is also unknown. Postmarketing requirements (PMR) pursuant to the Accelerated Approval regulations include two randomized trials using an add-on design in subjects with previously treated indolent non-Hodgkin lymphomas. One is a comparison of idelalisib plus rituximab versus placebo plus rituximab (17). The other is a comparison of idelalisib in combination with bendamustine and rituximab versus placebo plus bendamustine and rituximab. Clinically meaningful improvement in progression-free survival may satisfy the Accelerated Approval requirement.

A third trial in patients with FL or SLL who achieve a response or stable disease is intended to optimize the safety and efficacy of chronic administration (treatment duration of at least 12 months). Three additional PMRs were needed to further evaluate safety: a study to characterize the incidence, diagnosis, and effective treatment of idelalisib-related pneumonitis and two trials to provide evidence sufficient to characterize the long-term safety of idelalisib with 5 years of follow-up. In summary, idelalisib is an important new treatment option for patients with FL and SLL, but more data are needed to confirm clinical benefit and the safety of long-term administration.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** B.W. Miller, D. Przepiorka, A.T. Farrell, R. Pazdur  
**Development of methodology:** A.T. Farrell  
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** S. Shord, A.T. Farrell  
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