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Phase I Trial of the Pan-PI3K Inhibitor Pilaralisib (SAR245408/XL147) in Patients with Chronic Lymphocytic Leukemia (CLL) or Relapsed/Refractory Lymphoma

Jennifer R. Brown[1], Matthew S. Davids[1], Jordi Rodon[2], Pau Abrisqueta[2], Siddha N. Kasar[1], Joanne Lager[3], Jason Jiang[4], Coumaran Egile[5], and Farrukh T. Awan[6]

Abstract

Purpose: This phase I expansion-cohort study evaluated the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of the pan-PI3K inhibitor pilaralisib (SAR245408/XL147) in patients with chronic lymphocytic leukemia (CLL) or relapsed or refractory lymphoma.

Patients and Methods: Patients were treated with the maximum tolerated dose of pilaralisib previously determined in patients with solid tumors (600 mg capsules once daily). Adverse events (AE) and response were evaluated. Plasma pharmacokinetics and pharmacodynamic effects on cytokines and chemokines were also assessed.

Results: Twenty-five patients were included in the study: 10 with CLL and 15 with lymphoma. The most frequent AEs of any grade were diarrhea (92.0%), pyrexia (52.0%), and fatigue (44.0%). The most frequent grade ≥3 AEs were neutropenia (32.0%), diarrhea (20.0%), and anemia (16.0%). Pilaralisib exposure on cycle 1 day 28 was similar to exposure in patients with solid tumors. In patients with CLL, pilaralisib significantly reduced plasma levels of several cytokines and chemokines involved in B-cell trafficking. Five patients (50.0%) with CLL and 3 patients (20.0%) with lymphoma had a partial response. Six patients (60.0%) with CLL had nodal shrinkage ≥50%. Overall, 14 patients (56.0%; 7 patients with CLL and 7 patients with lymphoma) had progression-free survival ≥6 months.

Conclusions: Pilaralisib demonstrated an acceptable safety profile in patients with CLL and lymphoma, generally consistent with findings in patients with solid tumors. Single-agent pilaralisib showed preliminary clinical activity in patients with CLL and lymphoma, supporting further development. *Clin Cancer Res; 21(14); 3160–9. ©2015 AACR.*

Introduction

B-cell malignancies are heterogeneous diseases, and despite recent therapeutic advances, a high proportion of patients relapse or are refractory to treatment (1). Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world and is characterized by the accumulation of clonal nonfunctional B lymphocytes in blood, bone marrow, lymph nodes, spleen, and liver (2). The clinical course of disease varies significantly; some patients have indolent disease and survive many years without therapy, whereas others experience rapidly fatal disease (3). The emergence of anti-CD20 antibody (rituximab)–based chemoimmunotherapy has led to significant progress in lymphoma and CLL therapy. However, because disease progression is inevitable, novel drugs are needed to improve long-term management (1, 4).

Agents targeting B-cell receptor (BCR) signaling through its downstream effectors phosphoinositide 3-kinase (PI3K) and Bruton's tyrosine kinase (BTK) have emerged as promising treatment options (5). The PI3K enzyme is a heterodimeric lipid kinase that catalyzes the production of phosphatidylinositol 3,4,5-triphosphate (PIP_3) in response to external stimuli, which in turn leads to activation of essential cellular processes, including proliferation, survival, migration, and cellular metabolism (6). PI3K consists of a catalytic PI3K p110 subunit and a regulatory PI3K p85 subunit. In mammalian cells, expression of the catalytic PI3Kα and PI3Kβ isoforms is ubiquitous, whereas expression of PI3Kγ and PI3Kδ is restricted to hematopoietic cells (7, 8). Enhanced PI3K signaling is associated with oncogenesis (8), and constitutive activation of the PI3K pathway has been observed in multiple hematologic malignancies, including lymphoma and CLL (4, 7, 9–11). In CLL, activation of the PI3K pathway is a consequence of activation of the BCR, integrin, and chemokine receptors (4, 9, 11, 12). Activation of the PI3K pathway is associated with poor outcome in patients with diffuse large B-cell lymphoma (DLBCL; refs. 13, 14).

Compared with solid tumors, genetic alterations in components of the PI3K pathway are relatively rare in B-cell malignancies (15, 16). Amplification of *PIK3CA*, the gene encoding PI3Kα, was

[1]Dana-Farber Cancer Institute, Boston, Massachusetts. [2]Val d'Hebron University Hospital and Universitat Autonoma de Barcelona, Barcelona, Spain. [3]Sanofi Oncology, Cambridge, Massachusetts. [4]Sanofi, Bridgewater, New Jersey. [5]Sanofi Oncology, Vitry sur Seine, France. [6]The Ohio State University Comprehensive Cancer Center, Columbus, Ohio.

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Corresponding Author: Jennifer R. Brown, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215. Phone: 617-632-4564; Fax: 617-582-7890; E-mail: jennifer_brown@dfci.harvard.edu

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Translational Relevance

PI3K is a heterodimeric lipid kinase composed of a catalytic and a regulatory subunit. The α and β isoforms are ubiquitously expressed in mammalian cells, and expression of the γ and δ isoforms is restricted to cells of the hematopoietic system. Upregulation of the PI3K pathway is universal in B-cell malignancies, such as CLL and other lymphoma subtypes, and there is preclinical evidence to suggest that inhibition of two or more isoforms of the PI3K catalytic subunit may lead to more complete pathway inhibition. Notably, PI3Kδ-specific, pan-PI3K, and dual PI3K/mTOR inhibitors have all shown preliminary clinical efficacy in B-cell malignancies.

Here, we report results of a phase I expansion-cohort study of pilaralisib, a specific and potent pan-PI3K inhibitor, in patients with CLL or relapsed/refractory lymphoma. Pilaralisib demonstrated an acceptable safety profile, generally consistent with other PI3K inhibitors in development, and showed preliminary clinical activity.

reported in 68% of patients with mantle cell lymphoma (MCL; ref. 10) and 5.6% of patients with CLL (17), and inactivation of PTEN was observed in 14% to 55% of patients with DLBCL (18) and in 16% of patients with MCL (19). Although some studies have reported *PIK3CD* and *PIK3CA* mutations in DLBCL (20, 21), *PIK3CA* mutations in CLL are rare, and in one study were reported in only 1 patient ($n = 61$; ref. 22). Mutations in *PIK3R1*, the gene encoding the p85 regulatory subunit, have been reported in Burkitt's lymphoma (23) but not as yet in CLL.

The PI3Kδ isoform appears to be the most critical for signaling in normal B cells and in CLL cells (11, 12), and knockout mice for p110δ show defective B-cell function (24). Inhibition of PI3Kδ by idelalisib (GS-1101/CAL-101), a selective inhibitor of PI3Kδ, blocks cross talk between CLL cells and protective stromal cells, which in turn prevents chemotaxis toward stroma, and abrogates prosurvival signaling (25–27). Two studies have reported the impressive clinical activity of idelalisib in CLL and indolent non-Hodgkin lymphoma (iNHL; refs. 28, 29). In a randomized phase III trial in relapsed CLL patients unfit to receive standard chemotherapy, administration of idelalisib with rituximab significantly improved progression-free survival (PFS) and overall survival compared with placebo plus rituximab (28). In a phase II, single-arm, registration trial of idelalisib in patients with iNHL, the overall response rate (ORR) was 57%, with documented tumor reduction in 90% of patients (29). Idelalisib was approved in July 2014 for the treatment of patients with CLL, follicular lymphoma, or small lymphocytic lymphoma (30). Several other PI3K inhibitors have also shown promising clinical activity in B-cell malignancies, including the PI3Kγ/δ-specific inhibitor duvelisib (IPI-145), the pan-PI3K inhibitor BAY 80-6946, the PI3Kδ-specific inhibitor TGR-1202, and the mTOR and pan-PI3K inhibitor SAR245409 (XL765; refs. 31–34).

The relative importance of the p110 α, β, and γ isoforms in B-cell malignancies is not clear. *PIK3CA* gene amplification may represent one mechanism contributing to PI3K activation in CLL (17). Notably, the pan-PI3K inhibitor BKM120 has been shown to be more cytotoxic than the PI3Kδ-specific inhibitor idelalisib in primary CLL cells (35). In MCL cell lines and primary tumor samples, inhibition of PI3Kδ was sufficient to block BCR-mediated PI3K activation, but concurrent inhibition of PI3Kα was required to abolish constitutive PI3K activation (19). PI3Kδ was highly expressed early in the course of disease in MCL, whereas PI3Kα expression increased significantly with relapse. The ratio of PI3Kα to PI3Kδ expression identified MCLs that were primarily resistant to a PI3Kδ inhibitor, and this ratio increased at relapse (19). Thus, pan-PI3K inhibitors may offer an advantage in B-cell malignancies.

Pilaralisib (SAR245408/XL147; Sanofi) is a novel, highly selective, reversible and potent inhibitor of class I PI3K α, β, γ and δ isoforms (IC_{50} of 48, 617, 10, and 260 nmol/L, respectively; ref. 36), which has shown activity in preclinical tumor models and in patients with solid tumors (36–38). In the phase I safety, pharmacokinetic (PK) and pharmacodynamic study in patients with solid tumors, the maximum tolerated dose (MTD) and recommended phase II dose of the pilaralisib capsule formation was 600 mg administered orally with continuous once-daily dosing (37). This dose was based on dose-limiting toxicities (DLT) that included grade 2 and 3 rash. Among 57 patients with evaluable tumor assessments, preliminary clinical activity was observed, including a partial response (PR) in 1 patient with advanced non–small cell lung cancer, and 8 patients who were progression free at 6 months (37). Here, we describe safety, PK, pharmacodynamics, and efficacy of pilaralisib in an expansion cohort of the phase I study of pilaralisib, in patients with CLL or relapsed/refractory lymphoma.

Patients and Methods

Study population

Eligible patients were aged ≥18 years, with a histologically confirmed diagnosis of relapsed or refractory aggressive NHL, iNHL (including CLL) or Hodgkin lymphoma, and measurable disease. Patients were also required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2 and adequate organ and hematologic function (including absolute neutrophil count ≥1,000/mm^3, platelets ≥30,000/mm^3, hemoglobin ≥8 g/dL, fasting plasma glucose <160 mg/dL, and glycosylated hemoglobin <8%). Patients were excluded if they had been previously treated with a PI3K inhibitor, had known central nervous system disease involvement, had autoimmune disease requiring immunosuppressive therapy, had autologous stem cell transplantation within 12 weeks before the first dose, or had any history of allogeneic transplantation.

The protocol was approved by regulatory authorities and Independent Ethics Committees at the relevant institutions, and complied with the recommendations of the Helsinki Declaration. All patients provided informed consent before the conduct of any study-related procedure.

Study design

This investigation was part of a phase I, multicohort, multicenter, open-label, single-arm, dose-escalation study (NCT00486135), which established the MTD of pilaralisib capsules in patients with solid tumors at 600 mg once daily in continuous 28-day cycles.

In the CLL and lymphoma expansion cohort, 3 patients were initially enrolled at the starting dose of 600 mg capsules once daily. Following safety review of these initial patients, the cohort was expanded to 6 patients. The preliminary MTD for patients with CLL or lymphoma was based on the safety evaluation of these 6 patients. In the absence of any DLT in cycle 1, up to 9

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additional patients were to be enrolled. The CLL and lymphoma cohort was later expanded to include a total of 25 patients. A DLT was defined as an adverse event (AE) of potential clinical significance such that further dose escalation would expose patients to unacceptable risk, any nonhematologic grade ≥3 AE occurring despite prophylaxis and/or not easily managed by medical intervention, grade ≥3 hyperglycemia not related to corticosteroid treatment and despite treatment with an oral hypoglycemic at standard doses, grade 4 neutropenia for >7 consecutive days duration despite growth factor support, grade 3 febrile neutropenia of ≥3 days duration, grade 4 febrile neutropenia, grade 4 thrombocytopenia for ≥7 days duration, an inability to take 75% or more of the planned number of study doses in cycle 1 due to an AE, or an inability to start cycle 2 within 14 days of the planned start date due to an AE.

Safety assessments

The safety population was defined as all patients who were treated with at least one dose of pilaralisib. Safety evaluations included standard clinical findings, AEs, electrocardiograms, ECOG PS, vital signs, concomitant medications, and laboratory assessments. AEs were graded in accordance with the National Cancer Institute Common Terminology Criteria for AEs version 3.0 (39).

Pharmacokinetic assessments

Blood samples for PK analyses were collected predose on days 1, 2, 8, 15, and 28 of cycle 1, on days 1, 21, and 22 of cycle 2, on day 1 of cycles 3 and 4, then on day 1 every 4 cycles thereafter. In cycle 1, postdose blood samples were collected at 0.5, 1, 2, 4, and 8 hours on days 1 and 28, and at 4 hours on day 8. During cycle 2, postdose blood samples were collected at 4 hours on day 1, and at 2, 4, and 8 hours on day 21. In cycles 3 and 4, blood samples were collected 4 hours after dose on day 1, then every 4 cycles thereafter. Plasma concentrations of pilaralisib were determined using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method (Sanofi, data on file) with a lower limit of quantification of 1.00 ng/mL. Noncompartmental PK analysis and calculation of descriptive statistics were performed using WinNonlin Professional 5.2 (Pharsight Corp.). PK parameters assessed included maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the concentration–time curve up to 24 hours (AUC_{0-24}), concentration before treatment administration (cycle 1 only; C_{trough}) and accumulation ratio.

Pharmacodynamic and molecular profiling evaluation

The pharmacodynamic effects of pilaralisib on cytokines and chemokines important in lymphocyte trafficking and function were evaluated in serial plasma samples from patients with CLL or lymphoma. Blood for pharmacodynamic analysis was collected in tubes with sodium citrate and plasma was snap-frozen in liquid nitrogen or on dry ice, and stored at −70°C. Circulating protein biomarkers (258 analytes) were evaluated using the Human Discovery MAP 250+v1.0 panel and a custom panel (30 analytes), using MAP Technology and a TARC ELISA assay at Myriad RBM. Data were further confirmed in several postdose plasma samples using a commercial ELISA for B lymphocyte chemoattractant (BLC/CXCL13), macrophage-derived chemokine (MDC/CCL22), macrophage inflammatory protein-1α (MIP-1α/CCL3), macrophage inflammatory protein-1β (MIP-1β/CCL4), thymus and activation regulated chemokine (TARC/CCL17), tumor necrosis factor receptor 2 (TNFR2), and interleukin-2 receptor-α (IL2Rα). A postdose increase/decrease was defined as a minimal 2-fold change compared with pretreatment baseline. The statistical significance of the pharmacodynamic change was determined by a pairwise two-tailed *t* test.

Genomic alterations in formalin-fixed paraffin-embedded tumor tissue biopsy sections of patients with lymphoma, or in the peripheral blood of CLL patients, were characterized. Tumor tissue was analyzed on the FoundationOne Next Generation Sequencing platform and T5 gene array ($n = 7$; Foundation Medicine). Matched peripheral blood CLL samples ($n = 4$) and normal DNA (saliva) were sequenced by Dr Brown's laboratory using standard whole-exome sequencing offered by the Genomics Platform at the Broad Institute. Sequence QC and somatic mutation calling were performed as described previously (40).

Efficacy measurements

The efficacy population included all patients in the safety population who had a baseline and at least one postbaseline tumor assessment. Overall disease assessment was based on investigator assessment and was evaluated every 8 weeks. The modified International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Guidelines were used to measure response in CLL patients (41), and the International Working Group Response Criteria were used in patients with other lymphoma subtypes (42). In patients with CLL, nodal response was defined as a ≥50% decrease in lymphadenopathy regardless of change in lymphocytes (43). Partial response was defined by standard IWCLL criteria (41).

Results

Patient population

A total of 25 patients with CLL ($n = 10$) or lymphoma ($n = 15$) were enrolled between April 2010 and December 2012. Among CLL patients, 40% had refractory disease and 60% were from high-risk prognostic subgroups (del17p, del11q); 5 of 8 evaluated patients had unmutated *IGHV*, and 80% were reported to have bulky lymphadenopathy. Patient demographics and disease characteristics are summarized in Table 1. Of 15 patients with lymphoma, 46.7% had refractory disease. The lymphoma cohort included 4 patients (26.7%) with DLBCL, 4 patients (26.7%) with follicular lymphoma, 3 patients (20.0%) with lymphoplasmacytic lymphoma, 2 patients (13.3%) with Hodgkin lymphoma, and 2 patients (13.3%) with transformed lymphoma. Patients with CLL and lymphoma had received a median of one and three prior regimens, respectively. Nine patients (90%) with CLL and 12 patients (80%) with lymphoma had received at least one prior rituximab-containing regimen. Only 1 patient had received a prior BCR pathway signaling inhibitor, a lymphoma patient who had received everolimus.

All patients were treated with pilaralisib 600 mg capsules once daily until disease progression or unacceptable toxicity. In total, 23 patients (92.0%) received >90% of the planned doses of pilaralisib. The median duration of exposure was 280.5 days (range, 118–650) in patients with CLL and 120.0 days (range, 16–721) in patients with lymphoma. Nineteen patients (76.0%)

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Table 1. Patient demographics and baseline disease characteristics

	CLL ($n = 10$)	Lymphoma ($n = 15$)
Age, years, median (range)	64 (57–80)	66 (28–83)
Sex, male, *n* (%)	5 (50.0)	6 (40.0)
ECOG PS, *n* (%)		
0	3 (30.0)	3 (20.0)
1	7 (70.0)	11 (73.3)
2	0	1 (6.7)
Disease type/subtype[a], *n* (%)		
CLL	10 (100)[b]	—
Lymphoma	—	15 (100)
DLBCL	—	4 (26.7)
FL, grades 1–2	—	3 (20.0)
FL, grade 3	—	1 (6.7)
Hodgkin lymphoma	—	2 (13.3)
Lymphoplasmacytic lymphoma	—	3 (20.0)
Transformed lymphoma		2 (13.3)
Disease status, *n* (%)[c]		
Refractory	4 (40.0)	7 (46.7)
Relapsed	6 (60.0)	8 (53.3)
Bulky disease, *n* (%)[d]	8 (80.0)	4 (26.7)
Prior radiation treatments, *n* (%)	2 (20)	4 (26.7)
Prior anticancer regimens within 5 years prior to screening, median (range)	1.0 (1.0–7.0)	3.0 (0–9.0)

Abbreviation: FL, follicular lymphoma.
[a]Diagnosis at baseline.
[b]Six of 10 patients with CLL were from del17p or del11q high-risk prognostic subgroups; 5 of 8 evaluated patients had unmutated IGHV.
[c]Due to the absence of a clear definition of refractory in the protocol, relapsed versus refractory status for lymphoma patients was derived subsequently by two independent observers based on prior treatment data. Refractory was defined as a less than 6 month duration since the most recent prior therapy.
[d]Bulky disease was recorded as determined by investigator.

discontinued study treatment: 12 patients (48.0%) due to disease progression, 2 patients (8.0%) due to AEs, and 2 patients (8.0%) due to withdrawal of consent. Three patients (12.0%) were withdrawn due to investigator decision in the setting of an ongoing AE (diarrhea). Six patients (24.0%) without progressive disease or any grade >2 ongoing AE were enrolled into a treatment extension study (NCT01587040); this included 3 patients (12.0%) with CLL, 2 patients (8.0%) with lymphoplasmacytic lymphoma, and 1 patient (4.0%) with transformed lymphoma. At the time of data cutoff (March 17, 2014), all 3 patients with CLL who were on the extension study had discontinued treatment, and all 3 patients with lymphoma remained on treatment.

Safety and tolerability

All 25 patients were evaluable for safety and experienced at least one AE regardless of causality. The most commonly reported AEs of any grade were diarrhea (92.0%), pyrexia (52.0%), fatigue (44.0%), anemia, cough, and nausea (40.0% each; Table 2). Grade ≥3 AEs were reported in 22 patients (88.0%), most commonly neutropenia (32.0%), diarrhea (20.0%), anemia (16.0%), and hypotension (12.0%; Table 2). One patient (4.0%) with lymphoma experienced a DLT, a nonserious grade 3 rash from days 16 to 22, which was considered treatment related. Treatment was permanently discontinued in this patient due to disease progression on day 16.

Fourteen patients (56.0%; 6 patients with CLL and 8 patients with lymphoma) had ≥1 serious AE (SAE), most frequently pyrexia (20.0%), hypotension (16.0%), diarrhea, and dyspnea (12.0% each). Five patients (20.0%; 3 patients with CLL and 2 patients with lymphoma) had at least one SAE that was assessed as related to study drug. Grade 3 treatment-related SAEs included hypotension, diarrhea and pneumonia (1 patient with follicular lymphoma), pneumonitis (1 patient with CLL), diarrhea (1 patient with CLL, with colonoscopy showing colon ulcers), diarrhea and colitis (1 patient with CLL), and hyponatremia, metabolic encephalopathy, and asthenia (1 patient with follicular lymphoma).

Twenty-three patients (8 patients with CLL and 15 with lymphoma) had diarrhea reported as an AE, many of whom had several episodes. The first episode was generally grade 1, with a median time from treatment start to first episode of 66 days (range, 2–339). Five patients had grade 3 diarrhea (3 patients with CLL and two with lymphoma), with a median time to grade 3 diarrhea of 210 days (range, 91–548). Only 1 patient had grade 3 diarrhea as a first episode. These data are generally consistent with the pattern of later onset of more severe diarrhea, as seen with idelalisib (44, 45). Other AEs of special interest with pilaralisib

Table 2. Most frequent all-grade (>25% of total patients) and grade ≥3 (>10% of total patients) AEs, regardless of causality

Preferred term	CLL ($n = 10$)	Lymphoma ($n = 15$)	Total ($N = 25$)
All-grade AEs, regardless of causality, *n* (%)			
Patients with any AE	10 (100)	15 (100)	25 (100)
Diarrhea	8 (80.0)	15 (100)	23 (92.0)
Pyrexia	6 (60.0)	7 (46.7)	13 (52.0)
Fatigue	4 (40.0)	7 (46.7)	11 (44.0)
Anemia	3 (30.0)	7 (46.7)	10 (40.0)
Cough	3 (30.0)	7 (46.7)	10 (40.0)
Nausea	4 (40.0)	6 (40.0)	10 (40.0)
Back pain	3 (30.0)	5 (33.3)	8 (32.0)
Dyspnea	3 (30.0)	5 (33.3)	8 (32.0)
Neutropenia	5 (50.0)	3 (20.0)	8 (32.0)
Rash	2 (20.0)	6 (40.0)	8 (32.0)
Upper respiratory tract infection	6 (60.0)	2 (13.3)	8 (32.0)
Hyperglycemia	4 (40.0)	3 (20.0)	7 (28.0)
Vomiting	2 (20.0)	5 (33.3)	7 (28.0)
Grade ≥3 AEs, regardless of causality, *n* (%)			
Patients with any grade ≥3 AE	10 (100)	12 (80.0)	22 (88.0)
Neutropenia	5 (50.0)	3 (20.0)	8 (32.0)
Diarrhea	3 (30.0)	2 (13.3)	5 (20.0)
Anemia	1 (10.0)	3 (20.0)	4 (16.0)
Hypotension	2 (20.0)	1 (6.7)	3 (12.0)

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included hyperglycemia, rash, and transaminitis. Treatment-related hyperglycemia of any grade occurred in 6 patients (24.0%; 3 patients with CLL and 3 patients with lymphoma); 1 patient (4.0%) with CLL had grade ≥3 hyperglycemia (this patient had ongoing mild type II diabetes at baseline). Fourteen patients (56.0%) had a rash-related AE of any grade, and 5 of these patients (20.0%; 2 patients with CLL and 3 with lymphoma) experienced eight grade ≥3 rash events, including rash, pruritus, and exfoliation. One patient with follicular lymphoma was reported with treatment-related hepatic grade ≥3 events. This patient temporarily discontinued treatment on study day 71 due to multiple events, including grade 3 pruritus (days 71–79) and maculopapular rash (days 71–92), and grade 2 increases in transaminase levels (days 92–99) and grade 2 lipase (days 92–99). Treatment with pilaralisib was restarted on day 99 at a reduced dose of 400 mg daily, and discontinued on day 121, in response to confusion, weakness, abdominal pain, and hyponatremia, following the SAEs grade 3 hyponatremia and grade 3 metabolic encephalopathy. This patient had treatment-related grade 3 increases in both aspartate aminotransferase (AST; days 120–124) and bilirubin (days 122–127). Due to concurrent increased alkaline phosphatase (ALP), this case did not meet the criteria for Hy's law [i.e., alanine transferase (ALT) ≥3× upper limit of normal (ULN) or AST ≥3× ULN, and ALP <2× ULN in conjunction with an increase in bilirubin ≥2× ULN]. The events resolved after pilaralisib discontinuation.

The most frequent grade ≥3 hematologic abnormalities included neutropenia (36.0%; 6 patients with CLL and three with lymphoma), lymphopenia (32.0%; 1 patient with CLL and 7 patients with lymphoma), and anemia (20.0%; 2 patients with CLL and three with lymphoma).

Five patients (20.0%) had a dose reduction due to AEs (3 patients with CLL and 2 patients with lymphoma). AEs leading to dose reduction were grade 1, 2, and 3 diarrhea and grade 2 pyrexia (all events in 1 patient with CLL), grade 3 pruritic rash (1 patient with CLL), grade 3 macular rash (1 patient with CLL), grade 1 ALT increased (1 patient with lymphoma), and grade 3 neutropenia (1 patient with lymphoma).

Fifteen patients (60.0%) had a total of 23 dose interruptions, the majority (91.3%) due to AEs. AEs leading to dose interruptions in ≥2 patients (regardless of causality) were fever (4 patients), diarrhea (4 patients), neutropenia (1 patient), hyperglycemia (2 patients), increased amylase (2 patients), increased lipase (2 patients), hypotension (1 patient), and rash (2 patients).

Two patients (8.0%) discontinued treatment due to AEs, including grade 2 nausea, grade 2 vomiting, and grade 3 diarrhea in one patient with CLL who discontinued on study day 225, and the patient described above with follicular lymphoma who developed transaminitis and metabolic encephalopathy and discontinued on study day 121. Three additional patients (follicular lymphoma, $n = 2$; CLL, $n = 1$) discontinued due to investigator decision in the setting of an AE (diarrhea). Three deaths occurred within 30 days after the final dose of the study drug, and all were attributed to disease progression.

Pharmacokinetic analysis

Pilaralisib appeared to reach plasma steady state before cycle 1 day 28 and had a median t_{max} of 4.0 hours, with a mean C_{trough} and C_{max} on cycle 1 day 28 of 84,600 ng/mL (156 μmol/L) and 96,700 ng/mL (179 μmol/L), respectively. The mean accumulation ratios (cycle 1 day 28:day 1) for C_{max} and AUC_{0-24} were 8.2 and 9.5, respectively. Exposure on cycle 1 day 28 (mean AUC_{0-24}) in patients with CLL and lymphoma was similar to findings in patients with solid tumors who received pilaralisib 600 mg capsules [mean AUC_{0-24}: 2,090 μg h/mL ($n = 9$) vs. 1,931 μg h/mL ($n = 14$), respectively; Supplementary Fig. S1].

Pharmacodynamic analysis and molecular profiling

The impact of pilaralisib on cytokines/chemokines important in lymphocyte trafficking and function was evaluated in plasma samples collected from 8 patients with CLL (Fig. 1).

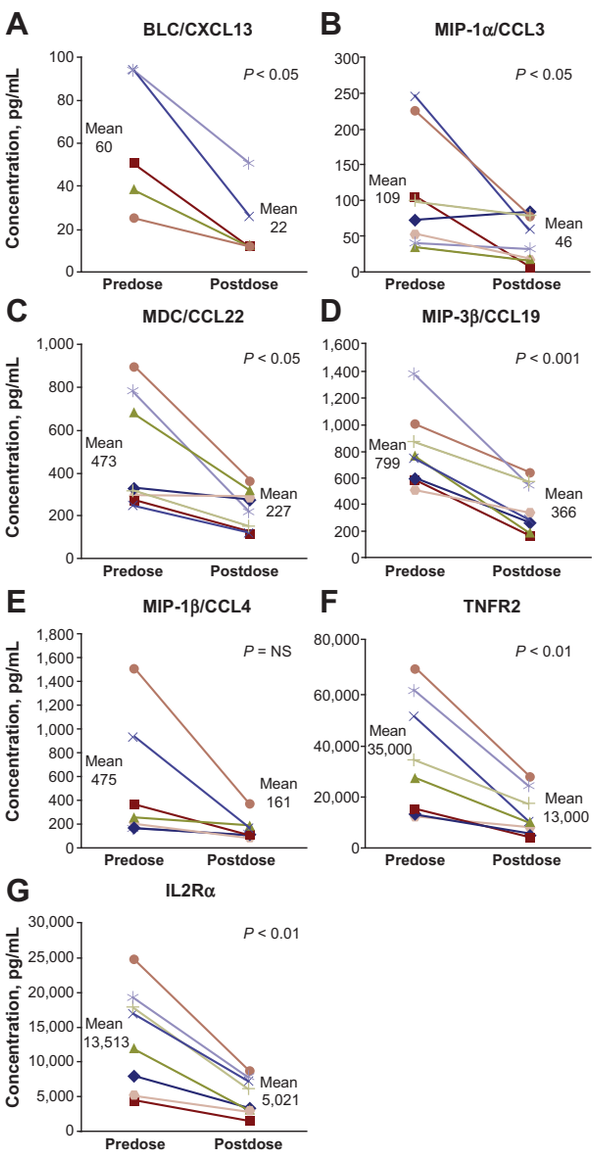

Figure 1.
Effect of pilaralisib 600 mg once daily on the plasma concentration of chemokines involved in B-cell trafficking (A–E) and cytokine receptors (F and G) in patients with CLL. Samples were collected from 8 patients at baseline and post dose (cycle 2 day 1 or later time points), and analyzed using the Myriad RBM Human Discovery MAP 250+v1.0 panel.

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Immunoassay of a panel of >250 protein biomarkers demonstrated that pilaralisib induced a significant reduction in the plasma levels of cytokines and chemokines involved in lymphocyte trafficking, such as B-lymphocyte chemoattractant (BLC/CXCL13; mean reduction ± SD: 63 ± 13%), macrophage inflammatory protein-1 alpha (MIP-1α/CCL3; 48 ± 37%), macrophage inflammatory protein-3 beta (MIP-3-β/CCL19; 54 ± 17%), and macrophage-derived chemokine (MDC/CCL22; 46 ± 24%), and in cytokine receptors, including tumor necrosis factor receptor 2 (TNFR2; 60 ± 14%), and IL2 receptor alpha (IL2Rα; 62 ± 9%). Pilaralisib induced a nonsignificant reduction in the plasma levels of macrophage inflammatory protein-1 beta (MIP-1β/CCL4; 50 ± 25%). No consistent effect on chemokines or cytokines was observed in patients with lymphoma (data not shown).

Peripheral blood samples were collected from 4 patients with CLL, and tumor tissue collected from 7 patients with lymphoma. Data on molecular alterations are summarized in Supplementary Table S1. Of note is a patient with CLL with a high-risk *SF3B1* mutation who had a PR and PFS of 22 months, and a second CLL patient with a high-risk *BIRC3* mutation who had a PR and a PFS of 21 months. The only PI3K pathway mutation in the 11 patients analyzed was found in a patient with DLBCL, who had stable disease and PFS of 9 months.

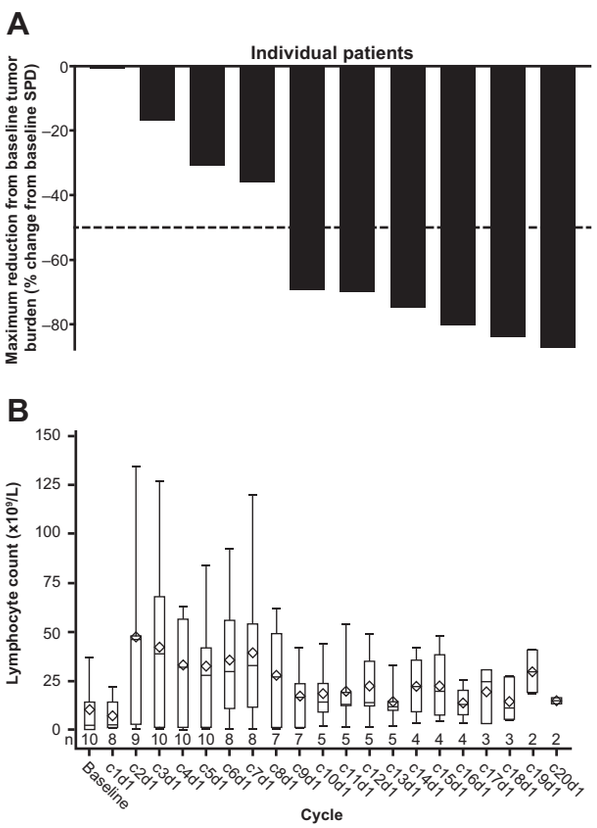

Figure 2.
Effect of pilaralisib 600 mg once daily on lymph nodes and lymphocyte counts in patients with CLL. A, percentage change in lymphadenopathy from baseline in individual patients. B, box and whisker plot of lymphocyte counts at multiple time points from baseline to cycle 20 day 1. Diamonds represent mean, bars represent median, boxes represent quartiles, and vertical lines represent range. Sample size is stated for each time point. SPD, sum of the perpendicular diameters.

Efficacy

All 25 patients were evaluable for efficacy and 8 patients (32.0%) had a PR. Five of 10 patients with CLL had a PR (ORR 50.0%). Six patients with CLL (60.0%) had nodal response (reduced lymphadenopathy ≥50%; Fig. 2A); of these patients, lymphocytosis (absolute increase in lymphocyte count) occurred in 5 patients and subsequently resolved in 4 patients. In 1 patient, reduction in lymphadenopathy was associated with persistent elevated lymphocytosis. In all cases, lymphocyte counts increased after treatment initiation and declined over time (Fig. 2B). The median time to PR in CLL responders was 9.2 months (range, 1.9–12.1).

In the 5 patients (50%) with CLL who had PR, PFS ranged from 7.4 to 22.0 months (Fig. 3A). The chromosomal abnormalities del17p and del11q were observed in 2 (20%) and 5 (50%) patients with CLL, respectively. PRs occurred in 3 patients with high-risk CLL, 1 patient with del17p had a PFS of 15.4 months, 1 patient with del11q had a PFS of 15.6 months, and 1 patient with both del17p and del11q had a PFS of 7.4 months. Three patients with CLL were enrolled onto an extension study and discontinued treatment due to progressive disease ($n = 2$) and secondary malignancy (acute myeloid leukemia; $n = 1$); the total therapy duration on the parent study plus extension trial for these 3 patients was 21.2 + 5.1, 15.4 + 12.0, and 15.6 + 12.7 months, respectively.

Three patients with lymphoma had a PR (ORR 20.0%), including 1 patient with lymphoplasmacytic lymphoma, 1 patient with transformed follicular lymphoma, and 1 patient with follicular lymphoma (Fig. 3B); PFS was 23.7, 18.4, and 4.8 months, respectively. Eight patients with lymphoma (53.3%) had a best response of stable disease, including 3 patients with follicular lymphoma (PFS of 7.6, 3.9, and 3.7 months), 2 patients with lymphoplasmacytic lymphoma (PFS of 12.9 and 3.7 months), and 1 patient each with transformed lymphoma, Hodgkin lymphoma, and DLBCL (PFS of 11.8, 11.4, and 9.0 months, respectively). Three patients with lymphoma were enrolled onto an extension study and all remained on study at the time of data cutoff; as of March 17, 2014, the total therapy duration on the parent plus extension trial was 23.7 + 16.3 months (lymphoplasmacytic lymphoma), 18.4 + 16.3 months (transformed lymphoma), and 12.9 + 17.4 months (lymphoplasmacytic lymphoma). Overall, 14 patients (56%; 7 patients with CLL and 7 patients with lymphoma) had PFS ≥6 months, and 8 patients (32%; 5 patients with CLL and 3 patients with lymphoma) had PFS ≥12 months (Fig. 4).

Discussion

This phase I expansion-cohort study evaluated the safety and preliminary efficacy of the pan-class I PI3K inhibitor pilaralisib at the MTD established in solid tumors (600 mg capsules once daily), in patients with CLL or lymphoma. Given that the PI3Kα isoform is expressed in most B-cell malignancies (10, 17), and has been associated with resistance to PI3Kδ inhibitors in MCL (19), good rationale exists for testing pan-PI3K inhibitors in CLL and lymphoma. Pilaralisib demonstrated an acceptable safety profile consistent with the solid tumor cohort (37), with rash and diarrhea the most common grade 3–4 AEs and the

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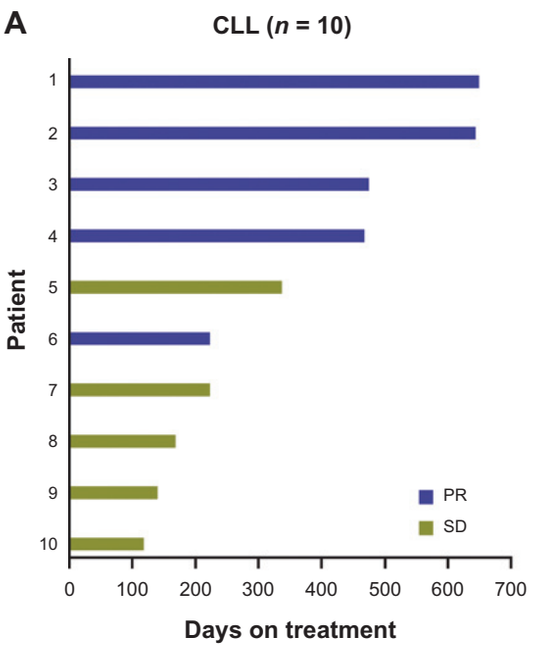
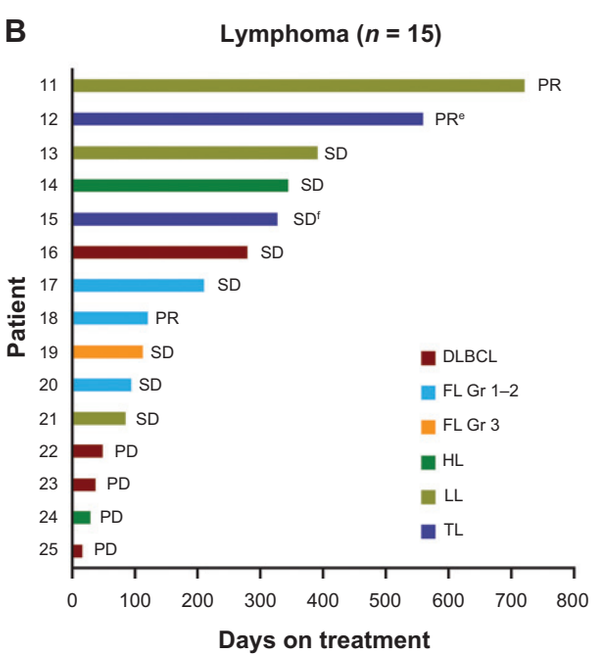


Prior regimens, n	PFS, months	Decrease in lymphadenopathy ≥50%	Lymphocytosis[a]	Prognostic markers	Additional therapy duration in extension trial, months[b]
1	22.0[c]	Y	Y	DEL13Q	-
1	21.2[d]	Y	Y	DEL6Q	Y (5.1)
7	15.6[d]	Y	Y	DEL11Q	Y (12.7)
1	15.4[d]	Y	Y	DEL17P	Y (12.0)
3	12.5[c]	N	N	DEL11Q, DEL13Q	-
1	7.4	Y	N	DEL11Q, DEL13Q, DEL17P, DEL3P, DEL3Q	-
1	9.2[c]	Y	Y	DEL13Q	-
1	5.6	N	N	DEL11Q, DEL13Q	-
5	4.6	N	N	DEL11Q, DEL13Q	-
4	3.6	N	N	INV9	-



Prior regimens, n	PFS, months	Additional therapy duration in extension trial, months[b]
2	23.7[d]	Y (16.3)
1	18.4[d]	Y (16.3)
4	12.9[d]	Y (17.4)
6	11.4	-
0	11.8[c]	-
2	9	-
4	7.6[c]	-
3	4.8[c]	-
3	3.7	-
2	3.9[c]	-
2	3.7[c]	-
2	1.7	-
4	1.4	-
9	0.9	-
4	0.5	-

Figure 3.
Clinical efficacy of pilaralisib 600 mg once daily in individual patients with CLL or lymphoma. A, response in 10 patients with CLL. Discordant nodal response was defined as a ≥50% decrease in lymphadenopathy with stable or increased lymphocyte count [i.e., <50% decrease (or increase) in absolute lymphocyte count]. Prognostic markers indicate those with high-risk disease. B, response in 15 patients with lymphoma. [a]Redistribution lymphocytosis was as expected for drug mechanism. [b]Extension trial = NCT01587040. [c]Censored. [d]Censored; patients continuing treatment to extension trial. [e]TL/DLBCL. [f]TL/B-cell PLL. All 3 patients with CLL on the extension trial discontinued treatment, due to progressive disease ($n = 2$) or secondary malignancy (acute myeloid leukemia; $n = 1$). At the time of data cutoff (March 17), all 3 patients with lymphoma remained on the extension study. FL, follicular lymphoma; Gr, grade; HL, Hodgkin lymphoma; LL, lymphoplasmacytic lymphoma; PD, progressive disease; PLL, prolymphocytic leukemia; SD, stable disease; TL, transformed lymphoma.

most common reason for dose reductions. As expected, a greater proportion of patients in this study had grade ≥3 hematologic-related AEs compared with the solid tumor patients (37), but the rate was similar to what is commonly seen in a relapsed refractory population with B-cell malignancies (29, 33, 34, 46, 47).

Safety findings were otherwise consistent with other PI3K pathway inhibitors in clinical development, with common AEs

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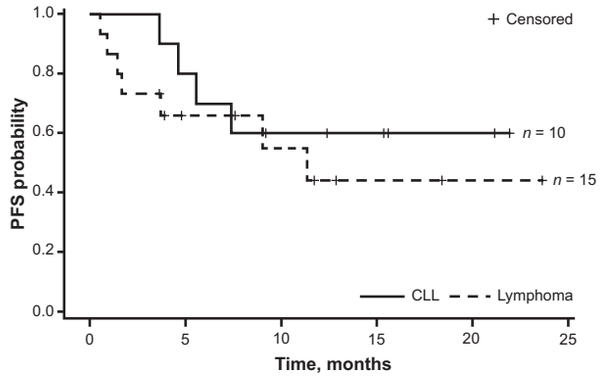

Figure 4.
Kaplan–Meier analysis of PFS in patients with CLL and lymphoma receiving pilaralisib 600 mg once daily.

including fatigue, rash, transaminitis, diarrhea, and hyperglycemia (44, 46–55). Pilaralisib showed higher rates of hyperglycemia and rash than idelalisib, suggesting that these are more related to alpha inhibition. Although low-grade diarrhea was more common with pilaralisib, the frequency of grade 3–4 diarrhea appeared comparable with the rates with idelalisib (44, 45), suggesting that higher-grade diarrhea is related to delta inhibition. Of 5 patients with grade 3 diarrhea, 1 patient resolved with steroid treatment and no change to study drug dosing, 3 patients resolved with interruption, and 1 patient resolved with study drug withdrawal.

The PK profile of pilaralisib in patients with CLL and lymphoma was consistent with the solid tumor cohort who received 600 mg capsules once daily, with similar mean accumulation ratios for cycle 1 for C_{max} and AUC_{0-24}, and exposure on cycle 1 day 28 (mean AUC_{0-24}; ref. 37). At steady state, plasma concentration of pilaralisib was maintained above the cellular IC_{50}. Treatment of CLL patients with PI3Kδ inhibitors has previously been associated with a significant reduction in disease-associated chemokines and cytokines in patients with CLL (44). Pilaralisib treatment also reduced the plasma levels of multiple chemokines/cytokines involved in B-cell trafficking in patients with CLL, suggesting sufficient exposure and pharmacologic activity of pilaralisib on PI3Kδ. Disruption in glucose homeostasis, a class effect of pan-PI3K and PI3Kα inhibitors evidenced by hyperglycemia, was observed in 28% of patients and was manageable.

Single-agent pilaralisib showed clinical activity in patients with both CLL and lymphoma, with observed ORRs of 50% and 20%, respectively, and nodal responses in 60% of patients with CLL, despite most patients being from high-risk prognostic subgroups (del11q or del17p). The observed pattern of response in patients with CLL–a lymph node reduction and an increase in lymphocyte count–was similar to that reported with other inhibitors of the BCR and PI3K pathway (44), and some patients had durable responses. In the lymphoma subgroup, where the ORR was lower, durable responses were observed, including 3 patients with PR who were treated with pilaralisib for approximately 13 to 24 months before continuing on the extension study. The ORR of 32% and the durable responses observed in a subset of patients particularly suggest that pilaralisib has noteworthy clinical activity in lymphoproliferative malignancies.

The clinical activity of pilaralisib in CLL and lymphoma patients in this study supports its continued evaluation as both a single agent and in combination regimens. In particular, given its broader specificity, a study to evaluate the activity of pilaralisib in patients who carry activating mutations of the PI3K pathway or who have progressed on PI3Kδ inhibitor therapies would be warranted. Studies of pilaralisib are ongoing, notably an investigation of a tablet formulation of pilaralisib in patients with lymphoma or solid tumors (NCT01943838).

Disclosure of Potential Conflicts of Interest

J.R. Brown is a consultant/advisory board member for Genentech, Gilead, Janssen, Pharmacyclics, and Sanofi. M.S. Davids reports receiving commercial research grants from Infinity Pharmaceuticals, Pharmacyclics, and TG Therapeutics; and is a consultant/advisory board member for Genentech, Gilead, Infinity Pharmaceuticals, Janssen, and TG Therapeutics. J. Lager and C. Egile hold ownership interest (including patents) in Sanofi. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J.R. Brown, J. Rodon, J. Lager
Development of methodology: J.R. Brown, J. Lager, J. Jiang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.R. Brown, M.S. Davids, J. Rodon, P. Abrisqueta, S.N. Kasar, F.T. Awan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.R. Brown, J. Rodon, S.N. Kasar, J. Lager, J. Jiang, C. Egile, F.T. Awan
Writing, review, and/or revision of the manuscript: J.R. Brown, M.S. Davids, J. Rodon, P. Abrisqueta, S.N. Kasar, J. Lager, J. Jiang, C. Egile, F.T. Awan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.R. Brown, J. Jiang, F.T. Awan
Study supervision: J.R. Brown, J. Lager, J. Jiang, C. Egile, F.T. Awan

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Clinical Cancer Research

Phase I Trial of the Pan-PI3K Inhibitor Pilaralisib (SAR245408/XL147) in Patients with Chronic Lymphocytic Leukemia (CLL) or Relapsed/Refractory Lymphoma

Jennifer R. Brown, Matthew S. Davids, Jordi Rodon, et al.

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