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MONOGRAPH

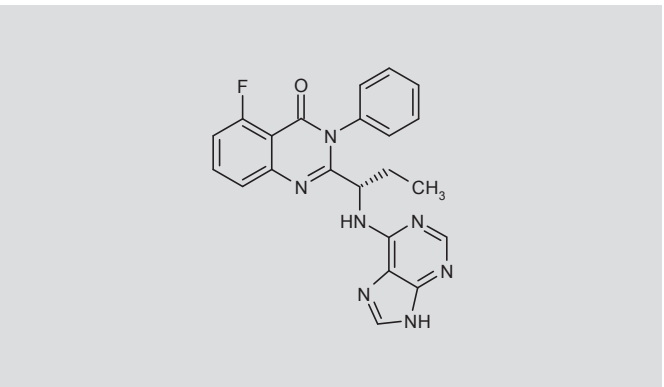
GS-1101

Phosphatidylinositol 3-Kinase p110δ Inhibitor
Oncolytic

CAL-101

5-Fluoro-3-phenyl-2-[1(*S*)-(9*H*-purin-6-ylamino)propyl]quinazolin-4(3*H*)-one

InChI: 1S/C22H18FN7O/c1-2-15(28-20-18-19(25-11-24-18)26-12-27-20)21-29-16-10-6-9-14(23)17(16)22(31)30(21)13-7-4-3-5-8-13/h3-12,15H,2H2,1H3,(H2,24,25,26,27,28)/t15-/m0/s1



$C_{22}H_{18}FN_7O$
Mol wt: 415.423
EN: 414143

SUMMARY

Dysregulation of the phosphatidylinositol 3-kinase (PI3K)–serine/threonine-protein kinase (Akt)–serine/threonine-protein kinase mTOR pathway is important in the etiology of human malignancies. The PI3K p110δ subunit plays a pivotal role in B-cell signaling in response to chemokines and cytokines, and is expressed in many cancers, such as leukemia and lymphoma. GS-1101 is a novel oral p110δ-specific inhibitor that has shown preclinical activity against chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma and multiple myeloma (MM) cells. In vivo and in vitro studies showed that GS-1101 induces apoptosis in malignant lymphoid cells and blocks soluble and tumor microenvironment-mediated survival signals that are key for the development and progression of these malignancies. There is early evidence of clinical efficacy in relapsed/refractory patients with CLL and indolent NHL, where GS-1101 causes rapid lymph node shrinkage and transient lymphocytosis. Studies with GS-1101, as a single agent or in combination with chemo- and immunotherapy, are ongoing in patients with CLL, indolent and aggressive NHL, MM and Hodgkin's lymphoma.

Key words: PI3K p110δ inhibitor – Oncolytic – GS-1101 – CAL-101

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SYNTHESIS*

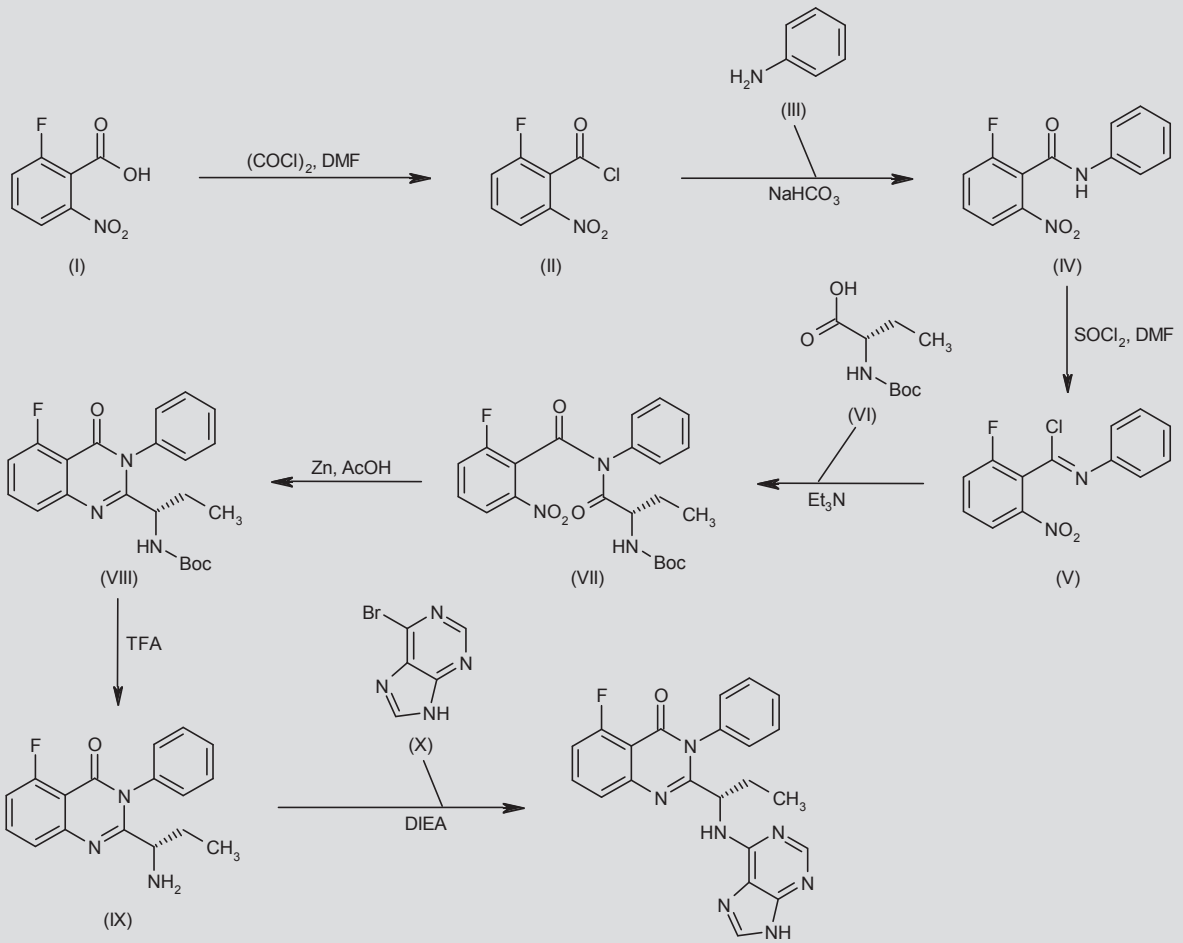
Chlorination of 2-fluoro-6-nitrobenzoic acid (I) with $(COCl)_2$ by means of DMF in CH_2Cl_2 gives 2-fluoro-6-nitrobenzoyl chloride (II), which is then coupled with aniline (III) in the presence of $NaHCO_3$ in dioxane/H_2O to yield 2-fluoro-6-nitro-*N*-phenylbenzamide (IV). Activation of amide (IV) as the corresponding imidoyl chloride (V) by means of $SOCl_2$ and DMF at 85 °C, and subsequent coupling with *N*-Boc-2(*S*)-aminobutyric acid (VI) by means of Et_3N in CH_2Cl_2 affords imide (VII). Reductive cyclization of compound (VII) in the presence of Zn in AcOH affords quinazolinone (VIII), which is *N*-deprotected with TFA in CH_2Cl_2 to obtain amine (IX). Finally, amine (IX) is condensed with 6-bromopurine (X) by means of DIEA in *t*-BuOH at 80 °C (1, 2). Scheme 1.

BACKGROUND

Phosphatidylinositol 3-kinases (PI3Ks) are enzymes that mediate signals from cell surface receptors. PI3Ks are grouped into three classes (I, II and III), with varying structure and substrate preference (3). Class II and III PI3Ks have not been associated with tumorigenesis, while class I PI3Ks have (4, 5).

Class I PI3Ks regulate a variety of cellular functions through the production of phosphatidylinositol (3,4,5)-triphosphate (PIP_3) (6). Generation of PIP_3 activates the downstream serine/threonine protein kinases Akt and mTOR, both of which have positive effects on cell survival, proliferation, growth and metabolism (4, 7, 8). The PI3K/Akt/mTOR pathway is activated by several different mechanisms in cancers, including somatic mutation and amplification of genes encoding key components (4, 5, 7, 9). In addition, PI3K signaling may serve integral functions for noncancerous cells in the tumor microenvironment (5).

Scheme 1. Synthesis of GS-1101



Class IA PI3Ks are heterodimers comprising a regulatory subunit (p85) and a catalytic subunit (p110). There are five p85 isoforms (p85α, p55α, p50α, p85β and p55γ) and three p110 isoforms (p110α, p110β and p110δ). Class IB PI3Ks form a heterodimer between p110γ, a catalytic subunit similar to the class IA p110, and with a distinct regulatory subunit, p101 (3). The p110α and p110β subunits are ubiquitously expressed and influence cellular proliferation and insulin signaling, respectively, whereas p110γ and p110δ, primarily expressed in leukocytes, are involved in immune function and inflammation. The p110α isoform is widely mutated or amplified in human cancer. Interestingly, non-p110α isoforms can induce oncogenic transformation in cultured cells as the wild-type protein, possibly explaining why they are not mutated in human cancer (4, 10). The p110δ isoform has been shown to play a pivotal role in B-cell signaling in response to chemokines and cytokines (11-14).

Development of PI3K inhibitors has been limited because of the requirement of this pathway for many essential cellular functions (10). Identification of the hematopoietic-selective isoform p110δ unlocked a new therapeutic potential for B-cell malignancies (12-14).

GS-1101 is a novel oral PI3K p110δ-specific inhibitor that has shown preclinical activity against chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma and multiple myeloma (MM) cells. There is early evidence of clinical efficacy in CLL and indolent NHL. Studies using GS-1101 alone or in combination are also ongoing in MM, Hodgkin's lymphoma and aggressive NHL.

PRECLINICAL PHARMACOLOGY

Investigation of the in vitro activity profile of GS-1101 against recombinant enzymes showed that the compound was 40- to 300-fold

more selective for p110δ relative to other PI3K class I enzymes. The half-maximal inhibitory concentration (IC_{50}) for GS-1101 for p110δ was 2.5 nM. For p110α, p110β and p110γ, IC_{50} values were 820, 565 and 89 nM, respectively. Greater selectivity (400- to 4,000-fold) was seen against the related kinases PI3K-C2-beta, hVps34, DNA-PK and mTOR, whereas no activity was observed against a panel of more than 400 different kinases at 10 μM. In cell-based assays, GS-1101 showed 240- to 2,500-fold selectivity for p110δ over the other class I PI3K isoforms (12).

Lanutti et al. demonstrated that constitutive PI3K pathway activation is p110δ-dependent in tumor cell lines and primary patient samples representing multiple B-cell malignancies (12). GS-1101 blocked constitutive PI3K signaling, resulting in decreased levels of phosphorylated Akt (pAkt) and other downstream effectors, and increased induction of apoptosis. These effects were observed across a broad range of immature and mature B-cell malignancies, including CLL and B-cell acute lymphoblastic leukemia (B-ALL). In this study, normal peripheral blood mononuclear cells, acute myeloid leukemia (AML) cells and myeloproliferative neoplasm cells were highly resistant to GS-1101. Additionally, GS-1101 downregulated pAkt expression and induced apoptosis in diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and follicular lymphoma (FL) cell lines.

In particular, CLL displays increased PI3K enzymatic activity and PI3K p110δ is expressed in CLL cells. GS-1101 promoted apoptosis in primary CLL cells ex vivo in a concentration- and time-dependent fashion, which was independent of common prognostic markers in the indication. GS-1101-mediated cytotoxicity was caspase-dependent and was not reduced by co-culture on stromal cells. In addition, GS-1101 abrogated protection from spontaneous apoptosis induced by B-cell-activating factors such as CD40L, TNF-α and fibronectin. In contrast to malignant cells, GS-1101 did not promote apoptosis in normal T cells or natural killer cells, nor did it diminish antibody-dependent cell-mediated cytotoxicity. However, GS-1101 did decrease activated T-cell production of various inflammatory and antiapoptotic cytokines (15).

Inhibition of prosurvival pathways in CLL cells did not explain the characteristic pattern of activity of GS-1101 in the clinical setting, where the drug causes rapid lymph node shrinkage and transient lymphocytosis. Therefore, Hoellenriegel et al. tested GS-1101 in assays that model CLL–microenvironment interactions in vitro. GS-1101 inhibited CLL cell chemotaxis towards C-X-C motif chemokine 12 (CXCL12) and C-X-C motif chemokine 13 (CXCL13) and migration beneath stromal cells (13). GS-1101 also downregulated the secretion of chemokines in stromal co-cultures and after B-cell receptor (BCR) triggering. GS-1101 reduced survival signals derived from the BCR or from nurse-like cells, and inhibited BCR- and chemokine receptor-induced Akt and mitogen-activated protein kinase (MAPK) activation. In stromal co-cultures, GS-1101 sensitized CLL cells toward bendamustine, fludarabine and dexamethasone. These results were corroborated by clinical data showing marked reductions in circulating C-C motif chemokine 3 (CCL3), C-C motif chemokine 4 (CCL4) and CXCL13 levels, and a surge in lymphocytosis during GS-1101 treatment. These results demonstrated that GS-1101 displays a dual mechanism of action in CLL, directly decreasing cell survival while reducing interactions that retain CLL cells in protective tissue microenvironments.

Lenalidomide is a drug under development for CLL that has been associated with tumor flare and cytokine release syndrome, which might induce CLL cell survival (16). These CLL-specific events result from increased expression of co-stimulatory molecules on B cells. Herman et al. showed that lenalidomide activation of CLL cells depends on the PI3K p110δ pathway. GS-1101 blocked CLL cell activation, co-stimulatory molecule expression and vascular endothelial growth factor (*VEGF*) and basic fibroblast growth factor (*FGFB*) gene expression induced by lenalidomide (17). GS-1101 reduced lenalidomide-mediated increases in immunoglobulin M production by normal B cells. These results suggested a potential role for the combination of GS-1101 with lenalidomide in the treatment of CLL.

GS-1101 has also shown activity against MM in preclinical studies. PI3K p110δ is expressed and activated in MM. Knockdown of p110δ by small interfering RNA (siRNA) caused significant inhibition of MM cell growth. Similarly, GS-1101 triggered cytotoxicity against LB and INA-6 MM cell lines and primary patient MM cells, associated with inhibition of Akt phosphorylation. GS-1101 overcame MM cell growth conferred by interleukin-6 (IL-6), insulin-like growth factor I (IGF-I) and bone marrow stromal cell co-culture. In addition, combined GS-1101 with the MM-approved drug bortezomib induced synergistic cytotoxicity against LB and INA-6 MM cells. In vivo p110δ inhibition with a GS-1101-related compound, IC-488743, significantly inhibited tumor growth and prolonged host survival in two MM murine xenograft models (18).

To investigate the potential role of PI3K p100δ in Hodgkin's lymphoma, Meadows et al. screened five Hodgkin's lymphoma cell lines and primary samples from patients with Hodgkin's lymphoma for PI3K p110δ expression and constitutive PI3K pathway activation (19). High levels of PI3K p110δ were detected in all cell lines and in 81% of Hodgkin's lymphoma tumor samples. Inhibition of PI3K p110δ by GS-1101 in Hodgkin's lymphoma cell lines resulted in inhibition of Akt phosphorylation. Co-cultures with stromal cells induced Akt activation in Hodgkin's lymphoma cells and this effect was blocked by GS-1101. Conversely, production of the stromal-stimulating chemokine C-C motif chemokine 5 by Hodgkin's lymphoma cells was reduced by GS-1101. GS-1101 also induced cell cycle arrest and concentration-dependent apoptosis of Hodgkin's lymphoma cells. These effects were enhanced when combining GS-1101 with the mTOR inhibitor everolimus.

GS-1101 has also been investigated in non-hematological neoplasms such as glioblastoma. Kashishian et al. showed that PI3K p110δ is expressed and functionally active, inducing high basal levels of pAkt in a wide panel of glioma cell lines (20). Treatment of glioma cells with GS-1101 decreased pAkt, reduced phosphorylation of its downstream target S6 and resulted in G_1 cell cycle arrest and a decrease in cyclin D1 levels. In mice bearing human glioblastoma U-87 MG xenografts, in vivo PI3K p110δ inhibition resulted in statistically significant antitumor effects, delaying time to tumor progression by 30 days.

PHARMACOKINETICS AND METABOLISM

Preliminary evaluation of the disposition, metabolism and elimination of GS-1101 in healthy volunteers was achieved by co-administering a trace amount of [^{14}C]-labeled GS-1101 and unlabeled GS-1101

either orally (p.o.) or intravenously (i.v.). GS-1101 pharmacokinetics were subsequently evaluated in patients with lymphoid malignancies (21). Increases in C_{max} and AUC were less than dose-proportional, revealing minimal gains in plasma exposure at dose levels > 150 mg twice daily. The mean volume of distribution was moderate at 57.7 L. The $t_{1/2}$ was 8 hours across all dose levels and there was no plasma accumulation over 7 or 28 days. The collective data supported twice-daily dosing at 150 mg. Dose levels in this range maintain steady-state trough plasma concentrations that were > 10-fold above the EC_{50} for the in vitro whole-blood assay. In a 7-day, multiple-dose phase I clinical trial in healthy volunteers, GS-1101 plasma concentrations of 500-5000 nM were achieved, which exceeded those required for PI3K p110δ inhibition (22).

In healthy volunteers, [^{14}C]-labeled GS-1101 was metabolized to only one metabolite in plasma and GS-1101-derived materials were primarily excreted in feces (> 65% of total dose), with minimal elimination via urine (< 15% of total dose). A high-fat, high-calorie meal had no effect on C_{max} but slowed absorption, leading to a shift in the observed median t_{max} from 1.5 to 4.5 hours, and a moderate 1.4-fold increase in AUC, suggesting that GS-1101 can be given with or without food (21).

Since GS-1101 is a cytochrome P450 3A4 substrate, the effect of ketoconazole (a potent cytochrome P450 3A4 inhibitor) was evaluated in healthy volunteers. When administered following 4 days of ketoconazole, increases in mean GS-1101 C_{max} and AUC values were 1.3- and 1.8-fold, respectively, suggesting that GS-1101 is not a sensitive substrate for cytochrome P450 3A4. Thus, co-administration of GS-1101 with cytochrome P450 3A4 inhibitors does not appear to be contraindicated (21).

UGT-catalyzed glucuronidation has been shown to be a quantitatively important metabolic clearance mechanism for GS-1101. One major and two minor glucuronides of GS-1101 were identified in human urine and in vitro studies on glucuronidation were then conducted using both unlabeled and [^{14}C]-labeled GS-1101. Activities of 12 human recombinant UGT isoenzymes in catalyzing the glucuronidation of GS-1101 were assessed and categorized as high (UGT1A4), moderate (UGT2B7, 2B17 and 1A1), minimal (UGT1A3, 1A9 and 2B15) and not detectable (UGT1A6, 1A7, 1A8, 1A10 and 2B4). UGT catalytic activity observed in human liver microsomes was approximately four- and sixfold higher than that observed in small intestinal and renal microsomes. Co-incubation of GS-1101 and a specific substrate of UGT1A4 with human liver microsomes resulted in 50-70% inhibition of the reaction. Profound species differences were observed when rates of rat, dog and rabbit liver microsome-catalyzed *N*-glucuronidation of GS-1101 were compared to rates observed in human liver microsomes (23).

SAFETY

In healthy volunteers, GS-1101 was well tolerated at 400 mg (the highest single dose tested) and at 200 mg twice daily through 7 days (the highest multiple dose tested) (21).

GS-1101 has also been symptomatically well tolerated in patients with lymphoid malignancies receiving dose levels up to 350 mg/kg (the highest dose tested) over many months. Monitorable, reversible transaminase elevations have been observed in some patients, most commonly in those with lymphoma (21). In the subset of patients (n = 54) with CLL, grade ≥ 3 pneumonia and neutropenia were seen in 24% of the patients. Other grade 3 adverse events included thrombocytopenia (7%), neutropenic fever (7%), anemia (6%) and ALT/AST increase (6%) (24). In the subset of patients (n = 55) with NHL, grade ≥ 3 hematological adverse events such as anemia, lymphopenia and thrombocytopenia were each observed in 5% of patients. Grade ≥ 3 AST/ALT elevations were observed in 33% of patients 2-8 weeks after initiation of GS-1101, which resolved 2-4 weeks after discontinuation of treatment. Most patients were rechallenged at lower doses of GS-1101 and were able to continue therapy without recurrence (25).

Preliminary data reported from patients receiving GS-1101 in combination with rituximab or bendamustine indicated that the combinations were well tolerated. Patients with indolent NHL (n = 12) and CLL (n = 8) received rituximab or bendamustine and 100 mg GS-1101 twice daily. Grade ≥ 3 neutropenia and thrombocytopenia were each seen in 22% of patients receiving GS-1101 in combination with bendamustine, and increased ALT/AST in 25% of patients with indolent NHL (regimen not specified) (26, 27).

CLINICAL STUDIES

A dose-escalation, open-label phase I study has been conducted in patients with relapsed or refractory hematological malignancies, including CLL, NHL, AML and MM (N = 192) (28). Patients received oral GS-1101 at 50, 100, 150, 200 or 350 mg twice daily or 150 or 300 mg once daily, in 4-week cycles until disease progression or unacceptable toxicity. Preliminary data were reported from CLL patients in this trial. At the study cutoff, 54 patients with resistant/refractory CLL had been included (24). Median age of the patients was 62 years (range: 37-82 years) and they had received a median of 5 prior therapies. Seventy-two percent of patients presented refractory disease, 81% bulky disease and 36% had deletions in 17p. The median of GS-1101 treatment cycles was 8, ranging from 1 to 19. GS-1101 reduced lymphadenopathy by ≥ 50% in 80% of patients. A transient increase of > 50% from baseline in peripheral absolute lymphocyte counts occurred in 58% of patients, probably reflecting redistribution phenomena associated with GS-1101. The overall response rate was 26%. Medians for duration of response and progression-free survival had not been reached, but were ongoing (> 11 months) at publication, with 46% of patients continuing on treatment. GS-1101 reduced constitutive overexpression of pAkt in patient CLL cells and normalized plasma concentrations of CCL3, CCL4 and CXCL13 (13, 24). Dose–response assessments supported the 150-mg twice-daily dose for future single-agent and combination studies in CLL (24).

Results for the subset of patients with NHL have also been reported (n = 55). Twenty-eight of these patients presented indolent NHL, including 15 patients with FL, 6 patients with small lymphocytic lymphoma (SLL), 4 patients with Waldenström's macroglobulinemia and 3 patients with marginal zone lymphoma (MZL). Twenty-seven patients presented aggressive NHL, including 18 MCL and 9 DLBCL cases. The median age was 68 years and patients had received a median of 5 previous therapies. Patients were given a median of four treatment cycles with GS-1101. Partial responses were observed at all dose levels in patients with indolent NHL (62%) and MCL (62%), with no response in any patients with DLBCL. In patients with MCL,

the median duration of response was 3 months, while patients with indolent NHL had not reached the median duration of response at the time of reporting. Greater response rates were observed in patients who had relapsed following prior treatment compared with patients who were previously refractory to treatment. High baseline levels of circulating chemokines C-C motif chemokine 22 and C-C motif chemokine 17 were significantly reduced after one cycle of treatment (25).

Flinn et al. have reported on a phase I study of GS-1101 in combination with rituximab or bendamustine (26, 27). This is an ongoing study in relapsed/refractory indolent NHL and CLL patients (expected number of patients is 126) (29). At data cutoff, patient accrual was 12 for indolent NHL and 8 for CLL. Median age was 64 years (range: 51-87 years). Forty percent of patients presented refractory disease. Median range of prior therapies was three, ranging from one to nine. Fifteen patients received GS-1101 100 mg twice daily (8 in combination with rituximab and 7 in combination with bendamustine) and 5 patients received 150 mg GS-1101 twice daily (3 in combination with rituximab and 2 with bendamustine). Among 18 evaluable patients, there were preliminary overall response rates of 91% in patients with indolent NHL (including 1 complete response) and 71% in patients with CLL. Compared to baseline, on-treatment peripheral lymphocyte counts were stable or decreased in all CLL patients.

An open-label extension phase I study is ongoing with the aim of including patients who have completed prior clinical trials with GS-1101 and for whom treatment was beneficial. Patients were to continue on the dose they had been receiving at completion of their previous trial, with adjustments allowed for enhanced response or toxicity (30). A phase I/II study was recently initiated in treatment-naive patients with low-grade indolent NHL (31).

The combination of GS-1101 with rituximab is under phase II investigation in elderly patients with untreated CLL or SLL (32).

The efficacy and safety of GS-1101 are also being evaluated in a phase II study in patients with relapsed or refractory indolent B-cell NHL, such as FL, SLL, lymphoplasmacytoid lymphoma and MZL (33), as well as in a phase II study in relapsed or refractory Hodgkin's lymphoma patients (34).

A randomized, double-blind phase I trial (35) has been conducted to assess the efficacy of GS-1101 in patients with allergic rhinitis (N = 45). This trial was completed in March 2009, but at the time of publication results had not been reported.

SOURCE

Gilead Sciences, Inc. (US).

DISCLOSURES

The author states no conflicts of interest.

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