CAL-101: a phosphatidylinositol-3-kinase p110-delta inhibitor for the treatment of lymphoid malignancies

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Introduction: The management of lymphoid malignancies has greatly evolved in the last decade with the advent of targeted therapies, which have improved response and survival in patients with Hodgkin’s lymphoma (HL), non-Hodgkin’s lymphoma (NHL), chronic lymphocytic leukemia (CLL) and plasma cell myeloma (PCM). The PI3K pathway seems to play a seminal role in the development of lymphoid malignancies. CAL-101 is a highly selective PI3K p110δ inhibitor currently undergoing clinical development.

Areas covered: The aims of this review are to summarize our understanding of the PI3K pathway, its role in lymphoid malignancies, the preclinical and clinical experience accumulated with CAL-101, a PI3Kδ inhibitor, and potential areas of future development.

Expert opinion: CAL-101 is a novel drug that has shown preclinical activity against CLL, NHL, HL and PCM cells. There is early evidence of clinical efficacy in CLL and indolent NHL. Studies using CAL-101 alone or in combination are also ongoing in PCM, HL and aggressive NHL. However, additional studies are needed to prove CAL-101 is effective and safe as the goals of therapy for patients with lymphoid neoplasms are not only directed towards improving response and cure rates but also prolonging survival without affecting quality of life.

Keywords: CAL-101, chronic lymphocytic leukemia, lymphoma, PI3K inhibitor, plasma cell myeloma

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1. Introduction

The management of lymphoid malignancies has greatly evolved in the last decade with the advent of biological, more targeted therapies. These agents, in conjunction with standard chemotherapy regimens, have improved the response and survival rates in patients with non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukemia (CLL). In other settings, such as the management of plasma cell myeloma (PCM), most would agree that biological agents have replaced chemotherapy as the preferred agents for frontline and even refractory treatment. Not surprisingly, the development of targeted therapies continues to increase with multiple agents undergoing preclinical and clinical evaluation worldwide.

Since its initial description, the PI3K pathway has been an attractive target for anticancer therapy. The PI3K pathway seems to play a seminal role in the development of a series of solid malignancies, such as melanoma, and lung, breast and colorectal cancers. More recently, the role of the PI3K pathway in the pathophysiology of hematological malignancies, such as NHL, CLL and PCM, has begun to be better understood. Parallel to this understanding, the development of novel drugs,
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Article highlights.

- The PI3K pathway plays an important role in the development of B-cell malignancies, mainly through activation of the p110δ subunit.
- Inhibition of p110δ could have a role in the management of B-cell malignancies such as chronic lymphocytic leukemia (CLL), non-Hodgkin’s lymphoma (NHL), plasma cell myeloma (PCM) and Hodgkin’s lymphoma (HL).
- CAL-101 is a PI3K inhibitor with a high specificity for the p110δ subunit.
- Preclinically, CAL-101 has been shown to have cell-killing properties against CLL, NHL, PCM and HL by modulating apoptosis as well as soluble and tumor microenvironment-mediated survival signals.
- Clinically, CAL-101 has shown activity against CLL and indolent NHL with concerns, however, of transient lymphophytosis and elevation of liver transaminases, respectively.
- Additional clinical studies evaluating CAL-101 alone and in combination for the treatment of CLL, NHL, PCM and HL are ongoing.

2. The PI3K pathway

The PI3K/acutely transforming retrovirus (Akt)/mammalian target of rapamycin (mTOR) pathway is a complex cascade of signal transduction phenomena that affects protein synthesis regulating cell survival and differentiation, and has been associated with not only development but also maintenance of a large number of human malignancies (Figure 1).

There are three classes of PI3Ks described: PI3K I, II and III, which mainly function to phosphorylate the 3-OH group of phosphoinositides [1]. PI3K classes II and III have not been associated with tumorigenesis. There are four isoforms of PI3K class I, designated as α, β, γ and δ. While isoforms α and β are ubiquitous, isoforms γ and δ are mainly expressed in leukocytes. PI3K is a heterodimer formed by p85 and p110 subunits. PI3K is activated by receptor tyrosine kinase (RTK) stimulation. The p85 subunit binds to phosphorylated tyrosine residues in the RTK. This binding blocks the inhibition of p85 over p110, allowing the localization of PI3K in the plasma membrane. Similar to several hormones and other pro-inflammatory compounds, p110δ subunits can signal downstream from GPCRs [2,3]. In the membrane, PI3Kδ converts PI(3)P into PI(3,5)P2. PI(3,5)P2 in turn facilitates the phosphorylation of Akt by 3-phosphoinositide-dependent protein kinase-1 (PDK1) and PDK2, with the participation of mTOR-rictor. Akt is a serine/threonine kinase and is the central mediator for several downstream cellular processes. The activation of Akt will in turn modulate the expression of mTOR, p53, c-Myc and cyclin-D1, among other downstream effectors, resulting on dysregulation of metabolism, protein synthesis, and cell growth, proliferation and survival [1].

3. The PI3K pathway in lymphoid malignancies

The potential role of PI3K over-signaling in the development of lymphoid malignancies was initially identified in an experiment by Borlado et al. [4]. In that study, a mouse model with PI3K over-signaling developed an infiltrating lymphoproliferative disorders as well as autoimmune disease. Later work revealed that overactivity of PI3K p110δ is almost exclusive to normal human PBMCs, thymus and spleen [5,6]. Low levels of PI3K p110δ activity were detected in testes, uterus, colon and small intestine but not in heart, prostate, liver or brain. Since then, several experiments have shown over-signaling of PI3K (mainly p110δ) in malignant lymphoid cells. Herman et al. [7] evaluated the activity of PI3K p110δ in primary cells from 20 patients with a diagnosis of CLL and in normal hematopoietic cells. Normal hematopoietic cells and the cells from all the CLL patients expressed PI3K p110δ; however, CLL cells showed statistically significant higher levels of PI3K p110δ activity when compared to normal hematopoietic cells. In a recent experiment, Ikeda et al. [8] showed that p110δ, the catalytic portion of PI3Kδ, was overactive not only on PCM cell lines but also in the malignant cells of 24 patients with a diagnosis of PCM. Additionally, by means of western blotting, there was no correlation between the levels of the p110α, β or γ isoforms and the levels of the p110δ isoform. Similarly, there is mounting evidence of the importance of PI3K expression in NHL. Uddin et al. [9] demonstrated the constitutive activation of the PI3K pathway in diffuse large B-cell lymphoma (DLBCL) cell lines and primary cells from 100 DLBCL patients by evaluating the presence of phosphorylated Akt (p-Akt). p-Akt activation was identified in several DLBCL lines and, importantly, in 52% of primary DLBCL cells. In the survival analysis, Akt-activated DLBCL patients had a trend towards a worse 5-year overall survival rate. A more recent retrospective study showed that the 25% of DLBCL patients with high immunohistochemical expression of p-Akt had worse outcomes then DLBCL with low p-Akt activity even when treated with rituximab-containing regimens [10]. Rudelius et al. [11] demonstrated the constitutive activation of the PI3K pathway, measured by expression of p-Akt, in 4 out of 4 (100%) mantle
cell lymphoma (MCL) cell lines as well as primary cells derived from patients with a diagnosis of blastoid (6 out of 6, 100%) and typical MCL (5 out of 16, 31%). Finally, PI3K activation has also been demonstrated in follicular lymphoma (FL), mediastinal DLBCL and Hodgkin’s lymphoma (HL) [12,13].

4. CAL-101

CAL-101 (5-fluoro-3-phenyl-2-[(S)-1-(9H-purin-6-ylamino)-propyl]-3H-quinazolin-4-one) is a PI3Kδ inhibitor that is available in oral form. In vitro, CAL-101 is highly selective for the p110δ subunit with an IC50 of 2.5 nM [14]. In contrast, the IC50 for the α, β and γ subunits are 820, 565 and 89 nM, respectively [14]. CAL-101 also showed a greater selectivity for mTOR and other related kinases, but no activity was seen against a panel of > 400 diverse kinases [14]. Additionally, in cell-based assays, CAL-101 showed a 240- to 2500-fold specificity for p110δ than for other PI3K class I subunits [14]. Given the high selectivity against PI3K p110δ and other related kinases such as mTOR, CAL-101 is undergoing preclinical and clinical development in a variety of lymphoid malignancies.

4.1 Preclinical development

Herman et al. investigated the potential of CAL-101 as a therapeutic agent for CLL. Blood samples were collected from patients with CLL who had been treatment-free for at least 30 days [7]. CLL cells were then treated with variable concentrations of CAL-101. Several interesting findings derived from this experiment: i) CLL cells expressed PI3Kδ in abundance; ii) the cytotoxic effect of CAL-101 was independent of IgVH mutational status and interphase cytogenetic abnormalities but was dependent on CAL-101 concentration; iii) the cytotoxicity seen with CAL-101 was preferential to CLL cells than to normal cells; iv) the mechanism of action seemed to be associated with induction of apoptosis through caspase activation; and v) CAL-101 antagonized CLL cell survival mechanisms by blocking the protective effect of CD40-ligand (CD40L) and microenvironment stimuli [7]. Additionally, an in vitro experiment demonstrated that CAL-101 inhibits CLL cells
chemotaxis towards CXCL12 and CXCL13, and blocks survival signals mediated by the B-cell receptor (BCR) and nurse-like cells (NLCS), mechanisms associated with immortalization of CLL [15]. Furthermore, CAL-101 decreased the secretion of survival-associated chemokines such as CCL3, CCL4 and CXCL13 mediated by BCR and NLCS, downregulated the secretion of IL-6, TNF and CD40L, and increased the sensitivity of CLL cells to other cytotoxic drugs [15]. Finally, in an in vivo experiment using primary cells derived from CLL patients, CAL-101 decreased the plasma concentration of p-Akt, CCL3, CCL4 and CXCL13, which were parallel to an increase in the number of circulating lymphocytes [15]. In a more recent study, Herman et al. demonstrated that lenalidomide (Revlimid®, Celgene Corp., Summit, NJ, USA), an immunomodulatory drug with clinical activity against CLL, regulates p-Akt via PI3K pathway activation by upregulating p110δ [16]. Lenalidomide has been associated with tumor flare and a cytokine-release syndrome when administered to patients with CLL [17]. The joint administration of CAL-101 and lenalidomide bluntlenalidomide-associated upregulation of p-Akt and other CLL survival pathways such as CD40L, CD68 and CD80, and could presumably decrease the tumor flare seen in these patients while enhancing the cell killing activity [16].

Ikeda et al. sought to identify the efficacy of CAL-101 against PCM cells [8]. Findings from this study showed that: i) all PCM cell lines were shown to express PI3Kδ; ii) CAL-101 was highly selective against p110δ-positive PCM cells inducing caspase-dependent apoptosis in dose-dependent fashion but with minimal cytotoxicity in p110δ-negative cells; iii) CAL-101 inhibited the phosphorylation of Akt in p110δ-positive PCM cells; iv) CAL-101 was shown to have inhibitory effect against PCM cells in the presence of bone marrow stromal cells (BMSCs), and to disrupt cell growth, cytokine regulation and AKT phosphorylation induced by BMSCs; and v) CAL-101 was shown to have anti-angiogenic effect by inhibiting capillary-like tubule formation in human umbilical vein endothelial cells [8]. Furthermore, CAL-101 was observed to have synergistic effect with bortezomib (Velcade®, Millennium Pharmaceuticals, Cambridge, MA, USA) on PCM cells presumably by inhibiting bortezomib-mediated induction of p-Akt [8]. Bortezomib is a proteasome inhibitor approved by the FDA for the treatment of PCM and MCL.

In a more recent report, Lannutti et al. evaluated p110δ inhibition in B-cell tumors [14]. Neoplastic mononuclear cells were isolated from patient samples and cell lines were then cultered and studied. CAL-101 yielded no activity against non-neoplastic mononuclear cells, but it was noted that 26% of CLL and 23% of B-cell acute lymphoblastic leukemia samples were sensitive to CAL-101. In contrast, 3% of acute myeloid leukemia and 0% of myeloproliferative neoplasm samples showed sensitivity to CAL-101, indicating CAL-101 has a greater therapeutic potential for lymphoid malignancies. Additionally, CAL-101 downregulated p-Akt expression in DLBCL, MCL and FL cell lines, and induced a several-fold increase in the levels of apoptotic markers, such as caspase 3 and poly(ADP-ribose) polymerase cleavage [14].

Finally, Meadows et al. evaluated the effect of CAL-101 in HL cell lines [18]. High levels of p110δ and p-Akt were found in five out of five HL cell lines investigated. Exposure to CAL-101 not only decreased levels of p110δ and p-Akt but also disrupted tumor microenvironment-mediated survival signals mediated by CCL5, CCL17 and CCL22 in co-cultures of HL cells and BMSCs.

4.2 Clinical development

4.2.1 Phase I studies

Coutre et al. have reported on a Phase I study using CAL-101 as a single agent for relapsed/refractory (R/R) CLL [19,20]. At the study cutoff, 54 patients with R/R CLL have been included. Doses of CAL-101 were escalated from 50 mg oral (p.o.) twice daily to 300 mg p.o. once daily. CAL-101 was administered continuously at 28-day cycles. The patients' median age was 62 years. The population was heavily pretreated with a median of five previous therapies; 72% were refractory, 81% had bulky disease and 36% had del(17p). Grade ≥ 3 pneumonia and neutropenia were seen in 24% of the patients while other adverse events (AEs) such as anemia, thrombocytopenia, febrile neutropenia and AST/ALT elevation were seen in 6 – 7%. The overall response rate (ORR) was 26% with a median duration of response (DOR) that has not been reached but is ongoing for > 11 months. Pharmacokinetic analyses showed minimal Cmax increases with doses > 150 mg p.o. twice daily. Of note, a transient increase in the absolute lymphocyte count (ALC) of > 50% was seen in 58% of the patients, probably reflecting a lymphocyte redistribution phenomenon associated with CAL-101.

Kahl et al. presented data on 55 patients with R/R NHL enrolled in a Phase I study with CAL-101 at similar escalating doses as the previous study [21]. In all, 28 patients had indolent NHL (15 had FL, 6 small lymphocytic lymphoma (SLL), 4 Waldenstrom macroglobulinemia and 3 marginal zone lymphoma) and 27 had aggressive NHL (18 MCL and 9 DLBCL). The median age was 68 years. This cohort of patients had a median of 5 previous therapies; 44% were refractory and 56% had relapsed disease. Grade ≥ 3 hematological AEs such as anemia, lymphopenia and thrombocytopenia were seen each in 5% of the patients. Grade ≥ 3 AST/ALT elevations were seen in 33% of the patients 2 – 8 weeks after initiation of CAL-101, which resolved 2 – 4 weeks after discontinuation of treatment. Most of the patients were re-challenged at lower doses of CAL-101 and were able to continue therapy without recurrence. The ORRs for indolent NHL, MCL and DLBCL were 62, 62 and 0%, respectively. No complete responses were seen. The median DOR has not been reached for indolent NHL and was 3 months on MCL patients. Similar to the study
by Coutre et al., minimal increases in $C_{\text{max}}$ were seen with doses $> 150$ mg p.o. twice daily [19].

Flinn et al. have reported on a Phase I studies of CAL-101 in combination with rituximab (Rituxan®, Genentech, South San Francisco, CA, USA) or bendamustine (Treanda®, Cephalon, Frazer, PA, USA) in 20 patients with R/R B-cell malignancies [22,23]. CAL-101 was administered at doses of 100 – 150 mg p.o. twice daily continuously at 28-day cycles for 12 cycles. Rituximab was administered weekly starting on day 1 for 8 weeks and bendamustine at 90 mg/m$^2$ intravenously (i.v.) on days 1 and 2 of each cycle for six cycles. At data cutoff, 20 patients had been enrolled (12 indolent NHL and 8 CLL). The median age was 64 years, 40% had refractory disease and the median number of previous therapies was 3. Grade ≥ 3 neutropenia and thrombocytopenia were seen in 22% of patients receiving bendamustine in combination with CAL-101, and increased AST/ALT levels in 25% of patients with indolent NHL. The ORR in patients with indolent NHL was 91%, including one complete response (9%). The ORR in CLL patients was 71%. Interestingly, no increase in the ALC was observed in CLL patients while on treatment. Both rituximab and bendamustine are agents approved by the FDA for the treatment of patients with CLL.

4.2.2 Ongoing studies

4.2.2.1 Single agent CAL-101

An extension study sponsored by Gilead Sciences is aiming to include 100 patients with hematologic malignancies who have completed other CAL-101 studies [24]. Patients will continue on the dose of CAL-101 they were taking at the end of the previously enrolled study with adjustments allowed for enhanced response or toxicity.

Dr Ron Levy of Stanford Cancer Center is conducting a Phase I – II study aiming to enroll 15 previously untreated patients with a diagnosis of indolent NHL [25]. The study contains a single group and patients will be given CAL-101 150 mg p.o. twice daily. The response rate to CAL-101 will be analyzed every 2 months. In compliant patients, treatment with CAL-101 will proceed for twelve 28-day cycles.

Gilead Sciences is also sponsoring a Phase II study evaluating CAL-101 in patients with R/R HL [26]. This study aims to enroll 25 patients 12 years or older who will receive CAL-101 at a dose of 150 mg p.o. twice daily continuously until tumor progression or unacceptable toxicity.

Finally, a Phase II study sponsored by Gilead Sciences will be examining the response rate of CAL-101 in patients older than 18 years with indolent NHL who are refractory to rituximab and alkalyting agents [27]. A total of 150 patients will be accrued who will take CAL-101 at a dose of 150 mg p.o. twice daily, with treatment to continue in subjects provided that safety is maintained and treatment remains beneficial.

4.2.2.2 Combination regimens

A Phase II study sponsored by Gilead Sciences will be evaluating the safety and efficacy of CAL-101 administered at a dose of 150 mg p.o. twice daily for 12 months in conjunction with rituximab 375 mg/m$^2$ weekly i.v. for 8 weeks in patients 65 years or older with a new diagnosis of CLL/SLL [28]. This study is nonrandomized aiming to recruit 60 patients. Response rate will be measured in 2 – 3 month intervals. DOR, plasma levels of CAL-101 and safety of CAL-101 will also be evaluated.

CAL-101 is also being studied as a supportive agent in conjunction with other chemotherapeutic drugs in patients with relapsed or refractory CLL or NHL [29]. In this Phase I study sponsored by Gilead Sciences, 150 patients will be enrolled in five different interventional arms: CAL-101 and rituximab, CAL-101 with rituximab and bendamustine, CAL-101 with bendamustine, CAL-101 with ofatumumab (Arzerra®, GlaxoSmithKline, Research Triangle Park, NC, USA), and CAL-101 and fludarabine (Fludara®, Genzyme Corp., Cambridge, MA, USA); the last two arms will be limited to patients with CLL. Primary outcome measure is safety of CAL-101 with use of other chemotherapeutic agents. Secondary measures include clinical response rate and pharmacodynamic activity of CAL-101.

5. Conclusion

CAL-101 is a promising drug with a novel mechanism of action and early clinical evidence of efficacy in R/R CLL and indolent NHL. Studies using CAL-101 alone or in combination are ongoing in PCM, HL and aggressive types on NHL. However, additional studies are needed not only to prove CAL-101 is effective but also safe as the goals of therapy for patients with lymphoid neoplasms are not only directed towards improving responses and cures but also prolonging survival without decreasing quality of life.

6. Expert opinion

In the last decade, we have witnessed major developments in the therapy of hematological malignancies and more so in the realm of B-cell lymphoid disorders with the use of more targeted biological agents. The use of rituximab in combination with standard chemotherapy regimens has resulted in great improvements in the response and survival rates for patients with indolent and aggressive B-cell NHL [30,31] and CLL [32]. In the PCM world, biological agents with novel mechanisms of action such as lenalidomide and bortezomib have been able to induce deep and prolonged responses never previously reached with chemotherapy agents, improving the survival and quality of life of these patients [33,34]. Last, the recently approved anti-CD30 antibody–drug conjugate brentuximab vedotin (Adcetris®, Seattle Genetics, Bothell, WA, USA) has been shown to induce potent responses in patients with R/R HL [35], and is under current investigation in earlier treatment settings. None of these advances, however, would have been possible without a better knowledge of cell and cancer biology, and they are clear examples of the impact
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the understanding of a cellular pathway can have in the life of our patients.

Based on the reviewed literature, there is accumulating evidence on the importance of the PI3K/Akt/mTOR pathway in the development and maintenance of lymphoid malignancies making this signal transduction pathway an attractive therapeutic target. As seen in Figure 1, multiple approaches for PI3K/Akt/mTOR inhibition, including mAbs, pure PI3K inhibitors, dual PI3K/mTOR inhibitors, Akt inhibitors and mTOR kinase inhibitors, are of great therapeutic potential. The activation of p110\(\delta\) seems to be a key upstream event for the development of lymphoid malignancies as it is overactive in CLL, PCM, NHL and HL, and has been associated with downstream effects such as phosphorylation of Akt and activation of the mTOR pathway. This phosphorylation results in alteration of normal protein synthesis and normal cell cycle, differentiation and survival. Hence, the development of a specific p110\(\delta\) inhibitor is scientifically justified and of great interest.

CAL-101, a highly specific PI3K p110\(\delta\) inhibitor, has shown significant preclinical and clinical activity against several lymphoid malignancies. In vitro and in vivo studies have shown that CAL-101 can attack lymphoid neoplasms by activating apoptotic mechanisms and blocking soluble and tumor microenvironment-mediated survival signals that are key for the development and progression of these tumors. Furthermore, there are early indications of the efficacy that CAL-101 can have in the treatment of patients with CLL and NHL. More importantly, CAL-101 seems to be effective in hard-to-treat CLL patients such as the ones carrying del(17p). However, no drug is without AEs and CAL-101 is not the exception. In early Phase I studies in CLL and NHL patients, CAL-101 was associated with a transient increase in ALC thought to be due to lymphocyte re-distribution and elevation of serum levels of liver transaminases, respectively. Ongoing Phase II studies will provide additional information on the safety, tolerability and efficacy of CAL-101 in CLL, NHL and other lymphoid malignancies either alone or in combination with other effective agents. It is important to note that other PI3K inhibitors are undergoing clinical development for hematological malignancies. Novartis and the MD Anderson Cancer Center are evaluating BKM120, an oral PI3K inhibitor, in patients with advanced leukemia (NCT01396499). Amgen is also evaluating an orally bioavailable PI3K inhibitor, AMG319, in patients with R/R lymphoid malignancies (NCT01300026).

There is wide potential for the clinical development of CAL-101. Similar to any other novel agent, CAL-101 would have to show single-agent activity in heavily pretreated settings, probably in patients already refractory to frontline agents. However, the future for CAL-101 in earlier treatment settings would most likely stand in combination with other effective drugs. In CLL, the combination of CAL-101 and lenalidomide is interesting as both agents can be given orally and the combination appears synergistic in preclinical studies. However, the combination of CAL-101 and anti-CD20 mAbs is also of interest. The combination of CAL-101 and chemotherapy agents such as fludarabine and bendamustine could be of value; however, most likely CLL patients would have been exposed to these agents early in the treatment of their disease. In PCM, CAL-101 in combination with bortezomib and/or lenalidomide seems to be a logical step given preclinical experience. However, it remains to be seen if the synergy observed in the preclinical studies translates to clinically meaningful outcomes.

A similar approach could be taken in patients with indolent NHL, in which the combination of CAL-101 and bendamustine and/or rituximab could be a next step. Unfortunately, the slow-growing nature of these malignancies and the multiplicity of ongoing studies will make accrual for Phase II studies slow and challenging. Multi-institutional efforts are warranted to evaluate novel agents and regimens in a randomized, head-to-head fashion to maximize participation. In in vitro studies on aggressive NHL cell lines, CAL-101 failed to show efficacy in DLBCL, making further development questionable, but the efficacy seen in MCL cell lines is intriguing. An initial multi-institutional effort could be to evaluate the efficacy of single-agent CAL-101 in R/R MCL followed by, if effective, a randomized study comparing bortezomib with or without CAL-101 as bortezomib is effective and already FDA approved in this setting.

CAL-101 is a novel agent with great potential; however, its clinical development in lymphoid malignancies will have to be undertaken through the careful design and execution of randomized controlled studies.

**Declaration of interest**

The authors state no conflict of interest and have received no payment in preparation of this manuscript.
Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


• The first study to show that increased PI3K activity has a malignant lymphoproliferative effect.


• A study showing important preclinical activity of CAL-101 in chronic lymphocytic leukemia.


• A study showing important preclinical activity of CAL-101 in multiple myeloma.


• A study showing the high specificity and selectivity CAL-101 has against p110δ.


• The first study showing CAL-101 is safe in patients with chronic lymphocytic leukemia.


• The first study showing CAL-101 is safe in patients with non-Hodgkin’s lymphoma.


• The first study showing that the combination of CAL-101 with rituximab or bendamustine is safe in patients with B-cell malignancies.
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