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The Role of PI3K Inhibition in Lymphoid Malignancies

Gottfried von Keudell[1] · Alison J. Moskowitz[1]

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Abstract

Purpose of Review The outcome of patients with lymphoid malignancies has markedly improved in recent years which is likely due to a combination of advances in supportive care, and therapeutic options. In this article, we will provide an overview over the role PI3-kinase signalling, one of the most important dysregulated pathways in cancer, and its successful inhibition in lymphoma.

Recent Findings PI3-kinase inhibitors have shown remarkable activity in an increasing subset of patients with non-Hodgkin lymphomas. The first drug to be approved was idelalisib for patients with relapsed/refractory follicular lymphoma and CLL/SLL as monotherapy, or in combination with rituximab, respectively. After an initial setback related to increased toxicity including deaths observed in several upfront studies, there has been a resurgence in interest in this pathway following the promising efficacy of second-generation PI3K inhibitors including in patients with T cell lymphomas.

Summary PI3K inhibition continues to be an invaluable tool in the therapy of patients with lymphoid malignancies if managed cautiously. Preclinical models are helpful in predicting possible side effects and identifying new lymphoma subtypes that may be susceptible to this class of agents. The future will likely involve rationally designed combinatorial approaches to deepen the response rate and prevent the emergence of resistance.

Keywords PI3-kinase · B cell receptor · Tumor microenvironment · Lymphoma · Follicular lymphoma · T cell lymphoma · CLL

Introduction

Non-Hodgkin Lymphoma

The non-Hodgkin lymphomas (NHLs) consist of a diverse group of malignant neoplasms derived from the B cell and T cell lineages. In the USA, B cell lymphomas constitute approximately 90% of NHL cases. Diffuse large B cell lymphoma (DLBCL) is the most common type of NHL accounting for approximately 30–40%, followed by follicular lymphoma (FL) and mantle cell lymphoma (MCL) [1]. The biologic heterogeneity of B cell malignancies is reflected in the clinical course and outcome of the respective disease subtypes. Indolent lymphoid neoplasms such as FL evolve slowly, with a median survival of up to 20 years [2]. In contrast, more aggressive diseases, such as DLBCL, if left untreated have a median survival of several months. Finally, the T cell lymphomas represent a small, yet heterogeneous subset of NHLs which are typically associated with less favorable prognosis [3].

Combination chemoimmunotherapy has traditionally been used in the treatment of these diseases, both in the front-line and relapsed settings; however, with deeper understanding of oncogenic pathways, development of effective targeted agents has been made possible [4, 5]. One such pathway is phosphatidylinositol 3-kinase (PI3K), which has been successfully targeted in indolent B cell lymphomas, such as FL and CLL/SLL, and more recently showing promise for T cell lymphomas. In this review, we provide an overview of this pathway and discuss its current use and future potential in lymphoid malignancies.

This article is part of the Topical Collection on *B-cell NHL, T-cell NHL, and Hodgkin Lymphoma*

✉ Alison J. Moskowitz
moskowia@mskcc.org

Gottfried von Keudell
vonkeudg@mskcc.org

[1] Memorial Sloan Kettering Cancer Center, Lymphoma Service, New York, NY, USA

PI3K Pathway

The PI3K pathway is one of the most commonly altered pathways in cancers [6]. While there are three PI3K classes (I, II, and III), class I is the most relevant to cancer. The class I PI3K has four isoforms: α, β, δ, and γ, each of which consists of a heterodimer that includes a catalytic (p110) and a regulatory (p85) subunit. When phosphorylated, the catalytic subunit dissociates from the regulatory subunit which phosphorylates its target, resulting in the generation of phosphoinositide 3,4,5-triphosphates (PIP_3) from phosphoinositide 4,5-diphosphosphates (PIP_2). PIP_3 activates multiple signalling pathways that regulate cellular functions such as motility, proliferation, and survival (Fig. 1) [7]. PI3K is antagonized by PTEN (phosphatase and tensin homolog), a PIP_3 3-phosphatase, and by SHIP1, a PIP_3 5-phosphatase [8].

PI3K Isoforms

The PI3K p110 α and β isoforms (PI3Kα and PI3Kβ) are expressed ubiquitously; thus, murine knockouts for these isoforms are embryonically lethal [9, 10]. PI3Kα is involved in glucose homeostasis which explains the transient hyperglycemia observed in patients treated with inhibitors affecting this isoform.

The PI3K p110γ and δ isoforms (PI3Kγ and PI3Kδ) are specifically expressed in cells of hematopoietic origin [11]. PI3Kδ expression is particularly important in B cell development, as mice deficient in PI3Kδ show decreased maturation, diminished receptor-induced proliferation, and increased susceptibility to apoptotic cell death within their B cells [12]. Interestingly, these mice have no gross abnormalities or increased susceptibility to infections; however, they tend to develop inflammatory bowel disease, a finding that was significant in the prediction of anticipated side effects of PI3Kδ inhibitor therapy [13].

PI3Kγ expression is crucial for macrophage accumulation and neutrophil migration in inflammation. In addition, PI3Kγ is important for the activation of mature T cells but it does not appear to influence B cell function [14, 15].

Inhibition of PI3Kγ reduces the differentiation and migration of CD4+ T cells and M2 tumor-associated macrophages which may explain the promising activity of PI3Kγ inhibition in T cell lymphomas [16, 17].

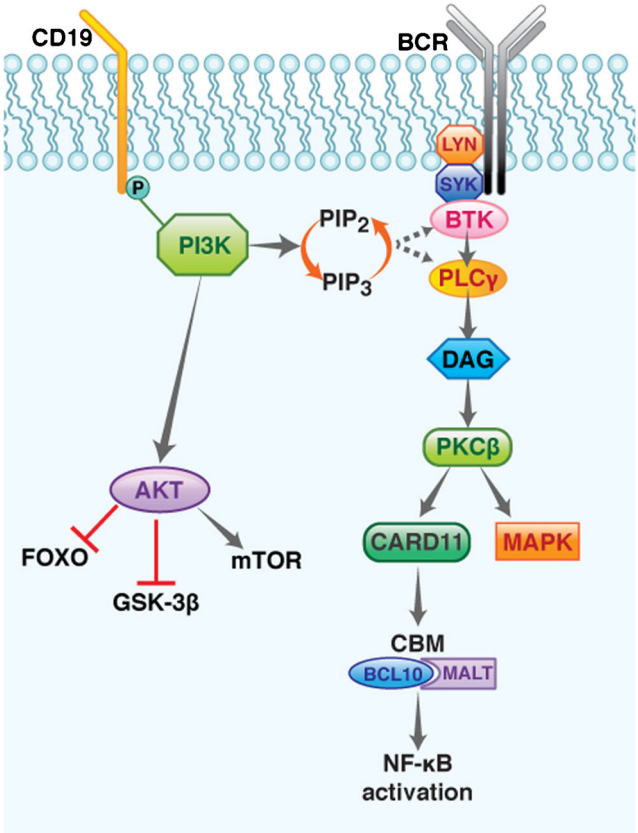

Fig. 1 Upon binding of the antigen by the B cell receptor (BCR) transmembrane protein CD19 is phosphorylated by the SRC family kinase LYN leading to the PI3K recruitment. PI3K phosphorylates PI(4,5)P2 to phosphatidylinositol-3,4,5-trisphosphate (PIP3) which results in recruitment of the Bruton tyorosine kinase (BTK) and AKT. BTK activates phospholipase Cγ2 (PLCγ2) leading to protein kinase Cβ (PKCβ)–mediated NF-κB signalling

Mechanisms of Action of PI3K Inhibition in Lymphomas

There are at least 3 potential mechanisms of action of PI3K inhibition in lymphoma. Healthy B cells as well as their malignant counterparts depend upon b cell receptor (BCR) activation for growth and survival, and in lymphomas, activating mutations such as in CARD11, CD79A, or CD79B play a role in establishing tonic BCR signalling that may contribute to malignant transformation [18]. Since PI3K is an essential protein in BCR signalling, its inhibition can cause apoptosis of tumor cells which are dependent upon BCR signalling for survival. It was shown that treatment with idelalisib (CAL-101) led to a significant increase in annexin V staining which is indicative of apoptosis induction and was accompanied by an increase in both caspase 3 and poly(ADP-ribose) polymerase cleavage. This direct impact on tumor cells represents one mechanism of action of PI3K inhibitors in lymphoid malignancies and was found to be at least partially mediated by inhibition of Akt phosphorylation and a decrease in the prosurvival factor Mcl-1 [19]. Using a BCR knockout mouse model, it was shown that BCR-deficient mature B cells can be rescued by the PI3K pathway which is mediated via the FOXO transcription factor and its target genes BCL-2 and AICDA (encoding activation-induced cytidine deaminase (AID)) and recombination-activating gene 1 (RAG1) [20].

A second potential mechanism of action is through disruption of the tumor microenvironment. In fact, PI3K inhibitors were shown to reduce CLL cell responsiveness to

microenvironment signals including CXCL12 and CXCL13 and decrease secretion of multiple cytokines and chemokines such as CCL3, CCL4, and CXCL13 important for their interaction with the nurse-like cells (NLCs) which are crucial for the CLL cell survival [21, 22]. This mechanism is responsible for the redistribution lymphocytosis typically observed in CLL upon initiation of treatment.

Lastly, PI3K inhibitors may enhance anti-tumor immunity as preclinical data suggests that p110δ inhibition of regulatory T cells (Tregs) leads to increased capacity of cytotoxic T lymphocytes to reject tumor growth [23].

PI3K Inhibitors in B Cell Lymphomas

Idelalisib

Idelalisib, a PI3Kδ-specific inhibitor, was discovered in kinome-wide screening assays using tumor cell lines and primary patient samples representing multiple B cell malignancies. It was found to have a low MIC-50 without significant off target effects on the other isoforms [19].

Idelalisib was first studied in a phase I study with 64 patients with relapsed indolent non-Hodgkin lymphoma (iNHL) including 38 (59%) with follicular lymphoma (FL), 11 (17%) with small lymphocytic lymphoma (SLL), 9 (14%) with lymphoplasmacytic lymphoma (LPL), and 6 (9%) with marginal zone lymphoma (MZL). These patients were heavily pre-treated with a median number of 4 prior therapies and over half of the patients were refractory to their prior line of therapy.

While no clear dose-limiting toxicity was observed, the recommended phase 2 dose was 150 mg twice daily based on the observed efficacy at this dose. Idelalisib showed an overall response rate of 30/64 (47%), with 1 patient having a complete response. Median duration of response was 18.4 months and median progression-free survival was 7.6 months.

Following the phase I study, a single-arm, open-label, phase 2 study was initiated for patients with iNHL. This study ultimately led to the 2014 accelerated FDA approval for patients with relapsed FL and SLL who have received at least two prior systemic therapies [24]. The study enrolled 125 patients who were refractory to rituximab and an alkylating agent or had relapsed within 6 months after receipt of those therapies. The overall response rate was 57% (95% confidence interval (CI), 48–66%) and complete response 6% by the independent review committee. The median progression-free survival was 11 months (range, 0.03–16.6) and the median overall survival (OS) was 20.3 months (range, 0.7–22.0) with similar response rates across all subtypes of iNHL. Idelalisib also received FDA approval for CLL based on the results of an international, multicenter, randomized (1:1), placebo-controlled trial of 220 patients comparing idelalisib 150 mg twice daily in combination with rituximab to placebo in combination with rituximab. The trial was stopped early on the recommendation of the data and safety monitoring board owing to overwhelming efficacy in the interim analysis of 176 evaluable patients out of the total of 220 planned patients in which the median PFS was not reached (95% CI 10.7, NR) in the idelalisib plus rituximab arm and was 5.5 months (95% CI 3.8, 7.1) in the placebo plus rituximab arm (HR 0.18 (95% CI 0.10, 0.32); $p < 0.0001$) [25].

The most common adverse events (AEs) in the study with iNHL were neutropenia, elevations in aminotransferase levels, diarrhea, and pneumonia. The most common serious AEs (≥ 5%) were fever (10%), pneumonia (7%), and diarrhea (7%) with comparable rates in the CLL registration study. AEs led to treatment discontinuation in 25 patients (20%) and a dose reduction (100 mg BID or 75 mg BID) in 42 patients (34%) in the iNHL study.

With longer observation on treatment, the range of side effects for idelalisib became more apparent: treatment-emergent grade 3 or 4 neutropenia was reported in 31% (234/760) and severe diarrhea or colitis occurred in 14% (106/760) across clinical trials [26]. Serious transaminitis occurred in 14% (109/760) and pneumonitis in 3% (24/760). This led to a black box warning on the prescribing information (ZYDELIG full prescribing information, Gilead Sciences, Inc., Foster City, CA, 2018).

Given the promising results from the early trials and its tolerability in combination with rituximab, idelalisib was explored in several studies as a triplet in combination with lenalidomide or with a Syk inhibitor, entospletinib [27–29]. However, these studies had to be terminated early due to overwhelming infectious complications as well as pulmonary and hepatic toxicity which were thought to be immune-mediated [30].

Even so, the response rates were felt to be sufficiently encouraging to warrant exploration of idelalisib in several upfront studies in combination with rituximab with or without bendamustine. However, as reports of increased serious adverse events and deaths emerged, mostly due to *Pneumocystis jiroveci* pneumonia (PJP) and cytomegalovirus (CMV) infections, 3 clinical trials were terminated (NCT01980888, NCT01732913, NCT01732926). Many of these infectious related side effects were, however, potentially avoidable with more rigorous antibiotic prophylaxis and stringent monitoring of the CMV status [31].

Despite this setback in the field if PI3K inhibitors, there were two recent approvals for patients with follicular lymphoma who have received two or more prior therapies: copanlisib and duvelisib.

Copanlisib

Copanlisib is an intravenous pan-class I PI3K inhibitor with preferential inhibition of p110α and p110δ that was identified in high-throughput PI3K inhibitor screenings [32]. It was initially evaluated in a phase I dose-escalation study in patients with advanced solid tumors or NHL [33•]. While a total of 57 patients received treatment, all 6 patients with FL responded (1 CR and 5 PRs). An intermittent dosing schedule on days 1, 8, and 15 of a 28-day cycle was found to be safe and tolerable. AEs possibly related to the study drug occurred in 49 patients (86%) with the most common (≥ 20%) AEs including hyperglycemia (63%), nausea (37%), and hypertension (21%). The most common grade 3 AEs were hyperglycemia (30%), hypertension (14%), and rash (7%). Dose modifications and delays caused by drug-related AEs occurred in 14 patients (25%).

The results of this study led to CHRONOS-1, a phase II study for patients with relapsed or refractory, indolent, or aggressive lymphoma [34•]. It enrolled 142 patients, with a majority of patients having follicular lymphoma (73%; $n = 104$). In a recent update, the objective response rate was 61%, including 24 patients (17%) with a complete response [35]. The median progression-free survival was 12.5 months (range, 0.2 to 24.0 months) and the median overall survival had not yet been reached at 2 years. Of note, a deepening of responses was observed with a conversion of 7 patients from PR to CR.

The most common treatment-emergent AEs (all-grade/≥ grade 3) included transient hyperglycemia (50%/40%) and transient hypertension (30%/24%). Other AEs of interest included neutropenia (29%/24%), diarrhea (35%/8%), pneumonitis (6%/1%), and colitis (one patient with grade 4). Serious AEs (SAEs) were reported in 56% of patients, with 38 patients (27%) discontinuing treatment due to an AE. Overall, AEs were felt to be manageable by investigators. The hyperglycemia was thought to be an on-target effect of insulin receptor signalling by blockade of p110α. Compared with idelalisib, a lower incidence of severe transaminitis, diarrhea, and colitis was seen suggesting that the dosing schedule, differential inhibition if the PI3K catalytic isoforms, and possibly the route of administration may be of importance.

Duvelisib

Duvelisib (formerly IPI-145), a PI3Kγ and PI3Kδ inhibitor, is the latest drug in the class to receive FDA approval for relapsed/refractory CLL/SLL and FL after at least 2 prior lines of therapy. Duvelisib was first explored in a phase I study in patients with advanced hematologic malignancies in which the maximal tolerated dose of 75 mg twice daily was established; however, the recommended phase II dose was 25 mg twice daily based upon equivalent response rates and markers of PI3Kδ inhibition compared with the higher dose [36]. In the expansion phase with 179 patients with indolent non-Hodgkin lymphoma, CLL, and T cell lymphoma (TCL), responses were observed across different disease subtypes with an overall response rate of 58%, 56%, and 50% in relapsed/refractory iNHL, CLL, and peripheral TCL, respectively. Severe, grade ≥ 3 adverse events occurred in 84% of patients with neutropenia (32%), alanine transaminase increase (20%), and aspartate transaminase increase (15%), being the most common followed by anemia and thrombocytopenia (each 14%), diarrhea (11%), and pneumonia (10%).

The results from the FL cohort of the phase II DYNAMO study were sufficient to obtain FDA approval. DYNAMO enrolled 129 patients with indolent B cell NHL including 83 patients with FL who were refractory to rituximab and to either chemotherapy or radio-immunotherapy. Among the FL patients, there was an ORR 42% (95% CI 31, 54) with 43% maintaining responses for at least 6 months and 17% over 12 months [37•]. While the results appeared to be inferior to copanlisib, the authors of the study pointed out that 33% of patients treated with duvelisib were early progressors after front-line R-CHOP (or equivalent) therapy making cross-study comparisons difficult. The ORR in the SLL ($N = 28$) and marginal zone lymphoma ($N = 18$) cohorts were 68% and 39%, respectively.

Within DYNAMO, the most frequent any-grade AEs were diarrhea (49%), nausea (30%), neutropenia (29%), fatigue (28%), and cough (27%). The most frequent grade 3 or greater AEs were neutropenia (25%), diarrhea (15%), anemia (15%), and thrombocytopenia (12%). Colitis and pneumonitis were reported in 10 (8%) and six patients (5%), respectively. Forty patients (31%) discontinued duvelisib as a result of a treatment-related AE.

The approval for patients with relapsed/refractory CLL was based on DUO, a multicenter, randomized, open-label, phase 3 trial comparing the efficacy and safety of duvelisib monotherapy with ofatumumab monotherapy for relapsed or refractory CLL/SLL. In this study, 319 patients were randomized 1:1 to study treatment with duvelisib ($n = 160$) or ofatumumab ($n = 159$). The median PFS by blinded independent review was significantly longer for the duvelisib arm compared with the ofatumumab arm (13.3 months vs 9.9 months, HR = 0.52, $p < 0.0001$) with a median OS that was not reached on either treatment arm [38•]. Of note, about 70% of patients had unmutated IGHV and a third had a 17p deletion in this study.

The side effects were similar to what have been observed with idelalisib and the primary reason for discontinuation of duvelisib in DUO was adverse events, affecting 35% of patients, compared with 22% who discontinued for progressive disease. Transaminitis and pneumonitis were less common in DUO, at 3% each which may be due to the close monitoring and early intervention.

Newer PI3K Inhibitors With Promising Activity

Umbralisib

Umbralisib (TGR-1202) is a novel, highly selective next-generation inhibitor of PI3Kδ and casein kinase-1ε (CK1ε). In addition to causing downregulation of mTOR through PI3K inhibition, it was shown to inhibit phosphorylation of the eukaryotic translation initiation factor 4E (eIF4E)–binding protein 1 (4E-BP1), thereby leading to suppression of c-Myc translation and silencing of the c-Myc-dependent transcription [39]. CK1ε is also important for activating non-canonical Wnt5a signalling which has been implicated in promoting interleukin-12-induced interferon-γ signalling in colitis [40, 41]. Its inhibition was thought to be beneficial in preventing the onset of colitis which has been a troublesome on-target effect observed across PI3Kδ inhibitors.

These results prompted a phase 1, dose-escalation, first-in-human study with umbralisib in relapsed or refractory chronic lymphocytic leukemia and lymphoma [42]. Ninety patients with relapsed or refractory CLL/SLL, B cell and T cell non-Hodgkin lymphoma, or Hodgkin lymphoma, who had received one or more previous lines of therapy, were enrolled in this study. Overall, 37% [33•] had objective responses and 33% [30] had partial responses.

The most common treatment-emergent adverse events were diarrhea in 43%, nausea in 42%, and fatigue in 31%. The most common grade 3 or 4 adverse events were neutropenia in 13%, anemia in 9%, and thrombocytopenia in 7%. Most diarrhea events (77%) were grade 1, and only three patients (3%) had grade 3 diarrhea. The maximum tolerated dose was 1200 mg of the micronized formulation, with 800 mg of this formulation selected as the recommended phase 2 dose for pharmacokinetic reasons. Of note, while the median follow-up was relatively short, only 10% of patients discontinued due to adverse events.

Umbralisib is currently being investigated in a variety of trials as monotherapy, as well as in combination with ublituximab, chemoimmunotherapy, and other targeted agents. The UNITY-NHL trial (NCT02793583) is a phase II study to assess the efficacy and safety of umbralisib alone or in combination with ublituximab with or without bendamustine in patients with previously treated non-Hodgkin lymphoma. Interim results for 69 patients with relapsed marginal zone lymphoma showed that umbralisib was active and well tolerated with a CR rate of 19% and partial response rate of 33%. Based on these results, the FDA granted umbralisib breakthrough therapy designation for the treatment of adults with marginal zone lymphoma who have received at least one anti-CD20 treatment.

The side effects were similar to previously published results with the most common adverse event of any grade being diarrhea, nausea, fatigue, headache, cough, and decreased appetite. The most common grade 3/4 adverse events were neutropenia, febrile neutropenia, and diarrhea, which affected between 5 and 8% of patients. No events of colitis or pneumonitis had been reported.

Two phase I combination trials with ibrutinib have recently been published with promising results. The first of which enrolled 46 patients: 24 in the dose-escalation cohort ($n = 14$ CLL/SLL; $n = 10$ B cell NHL) and 22 in the dose-expansion cohort ($n = 9$ CLL/SLL; $n = 13$ B cell NHL). Of note, this study allowed also patients with untreated CLL/SLL. The recommended dose for the dose-expansion phase was umbralisib 800 mg orally once daily plus ibrutinib (420 mg for patients with chronic lymphocytic leukemia; 560 mg for patients with B cell non-Hodgkin lymphoma) orally once daily and intravenous ublituximab 900 mg administered on days 1, 8, and 15 of cycle 1; on day 1 of cycles 2–6; and on day 1 of cycles 9 and 12. Eighty-four percent ($n = 37$) of patients achieved an overall response and 30% achieved CR. The most common AEs were in line with what have been observed in previous umbralisib trials with the exception of grade 1–2 infusion reactions that occurred in 43% ($n = 20$). The most common grade 3–4 AEs were neutropenia in 22% ($n = 10$), cellulitis in 13% ($n = 6$), and diarrhea and pneumonia in 9% ($n = 4$), each. Stomatitis was observed in 24% ($n = 7$) in the patients who received ibrutinib and was the most common AE leading to dose interruptions in that group. Eight (17%) of 46 patients discontinued study treatment due to adverse events [43].

A separate study evaluating umbralisib plus ibrutinib enrolled 44 patients with relapsed/refractory iNHL, including 21 with CLL and 21 with MCL [44]. No dose-limiting toxicities were observed and the maximum tolerated dose of umbralisib was not reached. The recommended phase 2 dose of umbralisib when given in combination with the standard ibrutinib dose was 800 mg once daily. The most frequent adverse events included diarrhea in 52% patients (10% with grade 3), infection in 50% (17% grades 3–4), and transaminitis in 24% (2% grade 3). Serious adverse events occurred in 12 (29%) patients and included lipase elevation, atrial fibrillation, hypophosphatemia, adrenal insufficiency, transaminitis, and infections. Ninety percent ($n = 19$) of patients with CLL achieved an overall response and 29% ($n = 6$) achieved a complete response. The median time to best response was 2 months (IQR 1.9–12.5) and median time to complete response was 18.4 months (12.5–24.0). All of the patients in complete response had, however, detectable minimal residual disease in the bone marrow by flow cytometry.

A phase I/II dose-escalation (3 + 3 design), multicenter study to assess the safety and efficacy of umbralisib, ublituximab, and pembrolizumab in patients with R/R CLL and Richter transformation (NCT02535286) has shown promising activity with 2 CRs and 1 PR out of 5 patients. While the follow-up was short and the patient number small, this was felt to merit further evaluation.

Additional Emerging PI3K Inhibitors

There is a plethora of new PI3K inhibitors with promising results in development. MEI-401 is a selective p100δ inhibitor that was initially explored in once daily 28-day cycles on a continuous schedule (CS) and found to have the expected side effects of the PI3K inhibition [45]. A novel dosing schedule was subsequently explored that consisted of once daily administration of MEI-401 for 7 out of 28 days, followed by two 28-day cycles of once daily dosing. This dosing scheduling was presented at the ASH meeting in 2018 and showed a lower rate of adverse events while maintaining high response rates [46]. Interestingly, 2 patients with diarrhea on the continuous dosing of MEI-401 were re-challenged with the intermittent dosing schedule without recurrence of their symptoms.

Other PI3K inhibitors in various stages of development include the PI3Kδ inhibitors buparlisib (BKM120), INCB040093, INCB50465, and AMG-319.

Buparlisib, a pan-class I PI3K inhibitor, was studied in an open-label phase II study for patients with relapsed or refractory non-Hodgkin lymphoma and included 3 separate cohorts of patients (with diffuse large B cell lymphoma, mantle cell lymphoma, or follicular lymphoma). Patients received buparlisib 100 mg once daily and the primary endpoint was overall response rate [47]. The response rates were somewhat lower than what was observed with other PI3K inhibitors and the development of the drug was ultimately terminated due to an increased incidence of mood disorders and suicidal ideation. In fact, there were suicide attempts reported in 3 patients with breast cancer treated with the combination of buparlisib plus fulvestrant in phase II and phase III trials, which may be partially due to the drug's ability to cross the blood-brain barrier [48–51].

The results of a study of INCB040093 ± JAK1 inhibitor itacitinib in relapsed/refractory B cell lymphoma has recently been published and showed promising activity especially in Hodgkin lymphoma which will need to be confirmed on future studies [52]. Of note, the patients treated with combination appeared to have lower levels of hepatotoxicity which the authors attributed to the anti-inflammatory effect of the JAK1 inhibitor. However, 5 patients developed pneumocystis pneumonia before mandatory prophylaxis was instituted which suggests that this combination's immunosuppressive effects are similar to what have been observed in patients treated with idelalisib.

CUDC-907 is a novel agent which combines a histone deacetylase and PI3K inhibitor in one pill. Younes and colleagues published the results of a phase 1 safety and dose-escalation study of CUDC-907 in patients with advanced refractory lymphoma and multiple myeloma and found promising activity in patients with DLBCL. The study established that a 60-mg dose administered on a 5 days on, 2 days off (5/2) schedule in a 21-day cycle was tolerable and safe [53].

PI3K Inhibitors in T Cell Lymphomas

The T cell lymphomas encompass more than 20 heterogeneous disease entities, which are broadly classified as peripheral T cell lymphoma (PTCL) and cutaneous T cell lymphoma (CTCL). The PTCLs are typically associated with poor prognosis due to high relapse rates following front-line therapy and limited effective options for relapsed or refractory disease [54]. The heterogeneity and rarity of the T cell lymphomas make testing new drugs difficult and therefore new drug development is clearly an unmet need. The clinical importance of the PI3K pathway in the T cell lymphomas was uncovered in the phase I study with duvelisib, which enrolled 16 patients with PTCL and 19 patients with CTCL [55]. Among the 16 PTCL patients, 8 (50%) achieved objective responses and 3 (18.8%) achieved complete responses. Furthermore, clear efficacy was observed among the CTCL patients, with ORR of 31.6%. The observed activity of duvelisib in T cell lymphoma led to preclinical studies aimed at elucidating its mechanism. Since duvelisib specifically targets the PI3Kγ and PI3Kδ isoforms, studies evaluating the importance of isoform specificity were undertaken. Among 11 T cell lymphoma cell lines studied, all expressed PI3Kγ, while only 7 and 10 expressed PI3Kα and PI3Kδ, respectively. Interestingly, duvelisib induced 2-fold more killing than idelalisib or copanlisib in 2 of the 3 sensitive cell lines, suggesting the important contribution of PI3Kγ inhibition in treatment of T cell lymphomas with PI3K inhibitors. Among the T cell lymphoma cell lines, 4 were characterized by constitutive activity of AKT (identified as expression of phosphorylated AKT [pAKT]). Duvelisib potently induced cell death in 3 of 4 lines with pAKT expression compared with 0 of 7 lines lacking expression, demonstrating that duvelisib acts through targeting the PI3K-AKT pathway within tumor cells. Further preclinical studies provided evidence of the impact of duvelisib on the tumor microenvironment. In particular, evaluation of duvelisib in PTCL patient-derived xenografts demonstrated a shift of tumor-associated macrophages from the immunosuppressive M2-like phenotype to the inflammatory M1-like phenotype. This finding suggests a second mechanism of action of duvelisib in T cell lymphoma through enhancing anti-tumor immunity [55].

The promising activity in PTCL and CTCL observed in the phase I single-agent study led to further clinical trials, including a multicenter, investigator-initiated phase I study evaluating 2 doublets: duvelisib in combination with romidepsin and duvelisib in combination with bortezomib. Preliminary results from this study presented at the 2018 ASH meeting demonstrated encouraging efficacy and tolerability of both doublets and further exploration of duvelisib plus romidepsin is planned [56]. In addition, PRIMO, a multicenter industry-sponsored study, is underway to confirm the single-agent activity and optimal dose of duvelisib in T cell lymphoma (NCT03372057).

Table 1 Response rate of patients with lymphoid malignancies to different PI3K inhibitors

Drug	Disease	Number of subjects	Lines of therapy (median)	ORR %	CR %	PFS in months	Reference
Idelalisib	iNHL	125	4	57	6	11	Gopal et al. [24]
	FL	72		54	8		
	SLL	26		58	0		
Copanlisib	iNHL	142	3	59	12	11	Dreyling et al. [56]
	FL	104		59	14	11	
	MZL	23		70	9		
	DLBCL	40	3	25	13		Lenz et al. [57]
	ABC-DLBCL	16		38	24		
	MCL	11		64	18		Dreyling et al. [34•]
	PTCL	13		21			
Duvelisib	iNHL	129	3	47		9.5	Flinn et al. [37•]
	FL	83		35	1	8.2	
	SLL	28		19			
	MZL	18		33	6		
	PTCL	16	3	50	19	3	Horwitz et al. [55]
	CTCL	19	6	32		3	
Buparlisib	NHL	72	3	12	4		Younes et al. [47]
	DLBCL	26	3	12	15	1.8	
	MCL	22	2	23	32	11.3	
	FL	24	2	25	42	9.8	

Outlook and Future Directions

After an initial setback which was likely at least in part related to the suboptimal management of the adverse events observed in patients treated in the upfront studies with idelalisib, there has been a resurgence of interest and excitement in the field of PI3K inhibition—the two recent FDA approvals for copanlisib and duvelisib pay tribute to this as does the ever-expanding field of second-generation PI3K inhibitors (see Table 1). Even so, significant challenges remain, preventing a broader adoption of these therapies. As with many targeted therapies, a better prediction of the responders is necessary which can only be accomplished if well-designed studies include correlative biomarkers that are obtained longitudinally and are published irrespective of the outcome. Similarly, it will be important to identify the patients who are likely to experience serious adverse events, especially pneumonitis and colitis which can develop late in the treatment. Lastly, even though dramatic shrinkage of the tumor burden has been observed in individuals treated with these agents, the duration of the response has been mostly limited. A combinatorial approach is the logical consequence, ideally with agents with non-overlapping toxicity and synergistic effect. Diligent and prolonged monitoring, as well as implementation of early stopping rules, will be pivotal to try to avoid harm to the patients participating in these studies. With the increased understanding of the differential effect of these agents, the field of the PI3K inhibitors appears, yet again, poised for success in the field of lymphoid malignancies and beyond.

Compliance with Ethical Standards

Conflict of Interest Gottfried von Keudell has received consulting honoraria from Genentech, Pharmacyclics, and Bayer.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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