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CHRONIC LYMPHOCYTIC LEUKEMIAS (N JAIN, SECTION EDITOR)

Exploring a Future for PI3K Inhibitors in Chronic Lymphocytic Leukemia

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Abstract

Purpose of Review Treatment for chronic lymphocytic leukemia has changed substantially in the past decade with an increasing shift towards use of targeted therapies, in particular agents targeting the B cell receptor pathway. Inhibition of PI3K, downstream of the B cell receptor pathway, represents an active therapeutic strategy in CLL. Here, we explore the relevance of PI3K inhibition in CLL, examine efficacy and toxicity of approved PI3K inhibitors in CLL, examine barriers to use of PI3K inhibitors, and explore strategies to optimize use of PI3K inhibitors in CLL.

Recent Findings Current generation PI3K inhibitors are active agents in CLL but their use may be limited by immune-mediated toxicities. Clinical trials of next generation PI3K inhibitors are ongoing and early data suggests these agents are highly active with potentially differentiated toxicity profiles. Furthermore, alternative dosing schedules may reduce toxicities of these agents.

Summary Inhibition of PI3K remains an important strategy in management of CLL and novel approaches to limit toxicities of PI3K inhibitors represent an important area of clinical research in CLL.

Keywords PI3K · CLL · Immune-mediated toxicities · B cell receptor · ME-401 · Umbralisib

Introduction

Chronic lymphocytic leukemia is a cancer of mature CD5+ B-lymphocytes and a common form of hematologic malignancy. In 2019, approximately 21,000 new cases of CLL are expected in the US with greater than 130,000 patients living with CLL. In the last two decades, substantial improvements in therapies have led to a decrease in the death rate of patients with CLL [1]. However, CLL remains largely an incurable disease, with a common pattern of sustained disease control, followed by episodic disease progression. It is a heterogenous disease, with outcomes being dependent on cytogenetic, molecular, and patient-specific characteristics [2]. Furthermore, while initially responsive to treatment, overtime, the disease is marked by the development and dominance of increasingly treatment-resistant clones [3].

Increasing knowledge about the biologic underpinnings of CLL has led to the establishment of several important targeted therapies for CLL. Tonic signaling through the B cell receptor (BCR) pathway plays an important role in the survival, proliferation, migration, and adhesion of CLL cells in the tumor microenvironment. Signaling through the BCR pathway occurs in antigen dependent and antigen independent mechanisms. A number of kinases immediately downstream of the cytoplasmic BCR mediate the pro-survival and pro-proliferative effects of tonic BCR signaling. Amongst these are Bruton's tyrosine kinase (BTK) and phosphatidylinositol-3-kinases (PI3K) [4, 5].

Bruton's Tyrosine Kinase, a cytoplasmic kinase of the TEC family, couples the BCR to activation of the NF-kB pathway. Activation of the NF-kB pathway serves an important role in CLL proliferation [6]. Disruption of BTK signaling, through the use of small molecule inhibitors of BTK (BTKi) in vitro and in vivo, results in significant disruption of CLL proliferation. Additionally, BTKi also results in direct apoptosis of CLL cells and disrupts adhesion of CLL cells to the tumor microenvironment, resulting in significant anti-tumor effect

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[7]. Ibrutinib, an oral irreversible inhibitor of BTK, has been studied in several prospective clinical trials as both an initial therapy and a therapy for patients with relapsed/refractory (R/R) CLL and is an established therapy for CLL with efficacy across different CLL subgroups [8–12]. Recent randomized phase III studies (Alliance A041202, ECOG-ACRIN E1912) demonstrate that ibrutinib as an initial CLL therapy compared to modern chemoimmunotherapy regimens appears to improve disease control across almost all CLL subgroup [13, 14]. These data support a paradigm shift away from broad use of chemoimmunotherapy as initial therapy in CLL. Nevertheless, as reported in the RESONATE-2 trial and both the cooperative group studies, CLL relapse after initial ibrutinib therapy remains a relevant clinical challenge [8, 11, 13, 14]. Numerous other irreversible BTKis (acalabrutinib, zanubrutinib) and reversible BTKis (vecabrutinib, LOXO-305, ARQ531) are being developed currently in clinical trials as additional CLL therapies. Whether such novel BTKis may ultimately further improve CLL therapy remains unknown, and there remains sufficient need to continue development of novel therapies in particular for patients experiencing CLL relapse after initial BTKi.

PI3K inhibitors represent one such class of novel CLL therapies. PI3Ks are a family of heterodimeric kinases, with four Class I isoforms (Table 1), alpha (PI3K p110α or PI3Kα), beta (PI3K p110ß or PI3Kß), delta (PI3K p110δ or PI3Kδ), and gamma (PI3K p110γ or PI3Kγ). The alpha and beta isoforms of PI3K are ubiquitously expressed, with PI3Kα playing a role in insulin signaling pathways. The exact role of PI3Kß is unclear, but inhibitors of PI3Kß appear to impact thrombotic biology as well as result in gastrointestinal toxicities [16, 23]. The delta and gamma isoforms are predominantly expressed in leukocytes and mediate a broad range of immune functions [15•]. Specifically, PI3Kδ mediates proliferation of B lymphocytes in response to BCR activation and inhibition of PI3Kδ by either genomic inactivation or inhibition by small molecule inhibitors results in poor cell proliferation despite BCR activation [24]. Additionally, PI3Kδ also interfaces in signaling from other cell surface proteins including CD40, integrins, and CXCR4 and thus disruption of PI3Kδ also impairs B cell chemotaxis. Pro-proliferative and pro-survival signaling through BCR, CD40, and CXCR4 and other stromal factors are enriched in CLL cells and thus disruption of downstream kinases such as PI3Kδ results in marked anti-tumor activity [25]. PI3Kγ also plays an important role in migration, activation, and proliferation of immune cells, primarily macrophages, neutrophils, and T cells [26]. Furthermore, PI3Kγ may be directly expressed in CLL cells and serve a non-redundant role in cell migration and adhesion [27]. Thus, inhibition of PI3Kγ may exert anti-tumor effect indirectly by disruption of pro-survival signals from T cells in the CLL microenvironment and directly by disrupting the ability of CLL cells to localize to stromal niches. In this review, we will focus on the current evidence regarding therapeutic use of Class I PI3K isoform inhibitors in CLL, limitations of currently approved PI3K inhibitors, and development of novel strategies to overcome these limitations.

Approved PI3K Inhibitors in CLL

Idelalisib

Idelalisib is the first commercially approved PI3K inhibitor for patients with CLL. Formerly known as CAL-101, idelalisib is a potent inhibitor of PI3Kδ (IC50 2.5 nM) with 30–400 times more selectivity for PI3Kδ compared to alpha, beta, and gamma isoforms. Preclinical studies demonstrate significant apoptosis of CLL cells in the presence of idelalisib as well as significant knockdown of AKT phosphorylation, an end point of constitutive PI3K signaling [19].

In a phase 1 study enrolling patients with various hematologic malignancies, 54 CLL patients were treated with idelalisib during dose escalation and a subsequent expansion cohort. All patients had been treated with at least 2 lines of prior therapy, including fludarabine-based therapy, and required treatment for CLL based on iwCLL criteria. Initially, no dose limiting toxicities were noted to an escalated dose of 350 mg twice daily. However, subsequent disease-specific

Table 1 PI3K Class I isoforms

	PI3Kα	PI3Kß	PI3Kγ	PI3Kδ	Reference
Tissue expression	Ubiquitous	Ubiquitous	Leukocytes	Leukocytes	[15•]
Toxicities of inhibition	Hyperglycemia, hypertension, nausea, vomiting	Diarrhea, nausea	Unknown	Transaminitis, diarrhea, colitis, pneumonitis, rash	[15•, 16, 17••, 18••]
IC50 (nM)					
Idelalisib	820	565	89	2.5	[19]
Duvelisib	1602	85	27	2.5	[20]
Umbralisib	> 10,000	1116	1065	22.2	[21]
ME-401	5491	335	2533	0.6	[22]

expansion cohorts revealed a significant rate of Grade 3 or high transaminitis and additional doses were studied. Ultimately, the dose of 150 mg twice daily was determined as the recommend phase 2 dose based on the overall safety profile in all treated cohorts, the identification of a plateau of plasma exposure, and a consistent nodal response at the 150 mg twice daily dose. Overall, 81.5% ($n = 44$ of 54) of treated CLL patients achieved $a > 50\%$ reduction in measured nodal lesions. Nodal responses occurred with concurrent asymptomatic rises in the absolute lymphocyte count (ALC). Such lymphocytosis generally peaked within first 8 weeks of treatment with idelalisib with gradual but sometimes persistent lymphocytosis. Importantly, the study also demonstrated significant improvement in hemoglobin, platelet, and absolute neutrophil counts from baseline for treated patients. Based on observations of asymptomatic lymphocytosis with other BCR inhibitors, namely, ibrutinib, during the course of the study, the iwCLL response guidelines were updated to include a new category of response, partial response with lymphocytosis (PR-L). Applying these updated iwCLL response criteria, the overall response rate (ORR) based on iwCLL criteria was 72%, with 33% PR-I, and 39% partial response (PR). Responses were rapid, with median time to response 1 month, and durable with median duration of response 16.2 months. Importantly, idelalisib was active in patients with del 17p or TP53 mutations with an ORR 54%, where 85% of these patients had been refractory to their last line of therapy. Notable adverse events included diarrhea, transaminitis, neutropenia, and pneumonia [28••].

A number of phase 1b studies of combinations with anti-CD20 monoclonal antibodies (rituximab, ofatumumab) and or chemotherapy (bendamustine) were performed confirming activity and tolerability of idelalisib in combination strategies. Subsequently, a phase III randomized controlled trial, study 116, was conducted to compare efficacy of idelalisib-rituximab vs. placebo-rituximab in patients with R/R CLL who were not candidates for cytotoxic chemotherapy. Idelalisib-rituximab resulted in superior ORR (81% vs. 13%), median progression free survival (PFS; not reached vs. 5.5 months at initial reporting), and overall survival at 12 months (OS; 92% vs. 80%). Notable adverse events in idelalisib-treated patients included neutropenia (all 37%, ≥ Grade 3 34%), thrombocytopenia (all 17%, ≥ Grade 3 10%), transaminitis (all 35%, ≥ Grade 3 5%), or diarrhea (all 19%, ≥ Grade 3 4%). Transaminitis had an onset between 8 and 16 weeks and it did not result in discontinuation in the majority of patients after brief drug hold [29••]. Two additional phase 3 randomized studies of idelalisib-based combinations (idelalisib-bendamustine-rituximab vs. bendamustine-rituximab and idelalisib-ofatumumab vs. ofatumumab) demonstrated additional evidence of efficacy of idelalisib, but importantly demonstrated increased infectious toxicities including serious bacterial infections and opportunistic infections (CMV reactivation, Pneumocystis jiroveccii). A phase II study of idelalisib and ofatumumab in treatment naïve (TN) CLL patients demonstrated an ORR of 89%, but also significant toxicity including transaminitis (all 74%; ≥ Grade 3 52%), colitis (all 48%, ≥ Grade 3 15%), and pneumonitis (all 11%, ≥ Grade 3 3.7%) [30]. A multicenter phase II study of idelalisib and rituximab in TN CLL patients also showed high ORR (100%) but again notable diarrhea/colitis (all 64%, ≥ Grade 3 42%) and transaminitis (all 67%; ≥ Grade 3 23%) [20].

Duvelisib

Duvelisib was approved in 2018 for patients with R/R CLL after at least 2 lines of prior therapy. Duvelisib (formerly IPI-145) is a potent inhibitor of PI3Kδ, but in contrast to idelalisib, is also a potent inhibitor of PI3Kγ, with nanomolar IC50 to both isoforms [31, 32]. While the exact benefit of PI3Kγ inhibition in CLL remains uncertain, duvelisib demonstrates clear anti-proliferative effect in primary CLL cells, with knockdown of phospho AKT similar to that reported for idelalisib, and similar cytotoxicity as idelalisib and ibrutinib preclinically [33].

Clinical studies of duvelisib provide evidence of clinical efficacy in indolent non-Hodgkin lymphomas (iNHL) and CLL/SLL. In a phase 1 trial in patients with numerous hematologic malignancies, the maximum tolerated dose (MTD) determined in the study was 75 mg twice daily; however, maximal and sustained pharmacodynamic effect was established at 25 mg twice daily. Adverse events included transaminitis (all 39%, ≥ Grade 3 19.5%), diarrhea (all 41.9%, ≥ Grade 3 11.4%), infection (all 61%, ≥ Grade 3 10%) and neutropenia (all 38.6%, ≥ Grade 3 20%). Severe colitis (6%) and pneumonitis (4%) were also seen. The initial dose escalation cohort enrolled only R/R CLL patients, but subsequent expansion cohort permitted both TN and R/R CLL patients, including those with prior PI3K inhibitor therapy. Amongst R/R CLL patients, the ORR was 56% ($n = 31$ of 55) and in TN patients the ORR was 83% ($n = 15$ of 18). Amongst all CLL responders, the responses were predominantly PR with a single patient achieving complete response (CR). The median duration of response amongst R/R CLL patients was 21 months [34].

Subsequently, a global phase 3 randomized clinical trial (DUO) was completed. The DUO trial enrolled patients with R/R CLL, having had at least 1 line of prior therapy and requiring further CLL therapy per iwCLL criteria. Patients were randomized 1:1 to either duvelisib 25 mg twice daily until progression or unacceptable toxicity vs. ofatumumab per approved label schedule. The study included patients with high risk disease features such as 17p deletion and/or TP53 mutation (31% duvelisib, 33% ofatumumab) and unmutated IGHV (69% duvelisib, 73% ofatumumab). The primary end

point for the study was PFS, and at a median follow-up of 22.4 months, the independent review committee (IRC) assessment indicated median PFS 13.3 months in the duvelisib arm vs. 9.9 months in ofatumumab arm. The PFS benefit appeared to favor duvelisib in numerous subgroups including del 17p and/or TP53 mutated patients. The median overall survival was not reached in either arm, with an estimated 12-month OS of 86% in both arms. The ORR was higher for duvelisib compared to ofatumumab (73.8% vs. 45.3%), with nearly all responses being PR. Toxicities reported were similar to those in the phase 1 study, with neutropenia, diarrhea, and infection being the predominant AEs reported in patients treated with duvelisib. Overall, the rate of concerning immune-mediated toxicities such as pneumonitis, transaminitis, and colitis seemed to be lower in DUO (3%, 3%, 12%) than that reported in similar patients treated with idelalisib. In addition to interruption of duvelisib, the protocol permitted use of corticosteroids for patients with immune-related toxicities, and 60% of patients with colitis or pneumonitis received corticosteroids. There were 19 patients (12%) with fatal AEs in the duvelisib arm, the majority being infectious AEs, with 4 of these attributed to duvelisib [17••]. Given the positive study result, the FDA has approved duvelisib for R/R CLL patients having had at least 2 lines of prior therapy.

Factors Affecting Current Use of Approved PI3K in CLL

Both idelalisib and duvelisib are approved in the US for use in R/R CLL patients and thus broadly available for use in such patients by prescribers. Yet, use of PI3Ki in R/R CLL is limited. While duvelisib is only recently approved, idelalisib has been approved for use in R/R CLL since 2014. Data from real word practice patterns suggests that uptake of idelalisib is relatively lesser than other kinase inhibitors, namely, BTKi, for CLL. Mato et al. demonstrated that in a cohort of over 600 CLL patients treated off clinical trials, idelalisib represented the first kinase inhibitor therapy for only 9% of patients [18••]. There are likely numerous factors that account for this relatively limited uptake of PI3Ki including unique and substantial toxicities of PI3Kδ inhibitors as well as the increasing availability of other well-tolerated targeted therapies for CLL.

Toxicity

In all studies of idelalisib and duvelisib, there have been occurrences of severe immune-related AEs (irAEs) as well as a relatively high incidence of infectious AEs that have led to addition of black box warnings for such toxicities for both agents. In a real-world data set of idelalisib-treated CLL patients, 24% of patients treated with idelalisib as a first kinase inhibitor required dose modification, 51% required dose interruption, and 42% ultimately discontinued idelalisib due to toxicity. Immune-related AEs such as colitis, hepatitis, dermatitis, and pneumonitis can lead to fatal events and in the case of pneumonitis can be relatively unpredictable in severity, onset, and progression [35]. In practice, given the broad range of these irAEs associated with PI3Ki, prescribers unfamiliar with the onset, grading, and management of these toxicities may be deterred from using these agents despite their significant activity.

Diarrhea can occur early (first 8 weeks) after starting PI3Ki, with median onset of 1.9 months. This early diarrhea tends to mild or moderate and responsive to anti-motility agents. A later occurrence of more severe colitis/diarrhea can be seen 7–8 months later. This tends to be manifested as watery diarrhea that is poorly responsive to anti-motility agents and endoscopic evaluation of the colon often demonstrates features of lymphocytic colitis [36]. Rarely, the colitis can result in intestinal perforation. It is critical to recognize and manage late onset colitis/diarrhea due to PI3Ki promptly. Generally, this includes prompt discontinuation of the PI3Ki and often endoscopic evaluation to help exclude infectious causes of colitis such as CMV colitis. Prompt use of corticosteroids is recommended in patients with severe (≥ Grade 3) or prolonged diarrhea. Either enteral steroids such as budesonide and/or systemic oral corticosteroid such as prednisone are effective in management of PI3Ki-related colitis and steroids should be tapered once symptoms resolve to grade 1 or lesser diarrhea, often within 1–2 weeks of initiation [36]. Re-challenge with reduced dose, PI3Ki may be attempted in patients in whom diarrhea and colitis has resolved, but should be done with careful monitoring for recurrent symptoms. For patients experiencing repeated late colitis despite dose reduction, PI3Ki should be discontinued.

Hepatitis most often occurs in the first 3 months of PI3Ki therapy and can lead to marked elevation of AST and ALT [35, 36]. In patients treated with idelalisib, transaminitis may occur in as many as 35% of patients, with severe hepatitis occurring in ~ 10% of patients [29••, 37]. It often resolves with interruption of PI3Ki, but rarely can be fatal. Frequent early monitoring of hepatic function tests is recommended after initiating PI3Ki and substantial rises in transaminases > 5x ULN should prompt drug hold until improvement before attempting re-challenge. Corticosteroids may be useful in severe hepatitis, with re-challenge appearing to be more successful in those on corticosteroids [38]. Hepatic toxicity is more severe in patients treated with other immunomodulatory agents and as such is not recommended outside of clinical trials [39, 40].

Pneumonitis, manifests as onset of a dry cough, dyspnea, and hypoxia, has been reported in ~ 3–6% of idelalisib- or duvelisib-treated patients in randomized studies [17••, 29••]. Clinical symptoms of pneumonitis are often insidious and accompanied by diffuse bilateral lung infiltrates on radiographic imaging [41]. The time to onset of pneumonitis is less clear and particular caution should be applied in patients with

existing pulmonary disease. Importantly, patients with symptoms suggestive of pneumonitis should undergo careful evaluation of infectious causes of pulmonary symptoms given the increased risk of infection in patients with CLL treated with PI3Ki and the similarity clinically of infectious vs. immune-mediated pneumonitis. Patients with pneumonitis may respond to corticosteroid therapy, but again caution to exclude opportunistic pulmonary infections is critical given corticosteroid-based immunosuppression can worsen certain infections. The safety of re-challenge with PI3Ki after resolution of pneumonitis is unknown and it is generally our practice not to re-challenge.

The toxicities described above are immune-mediated toxicities and are likely explained in part by the differential importance of PI3Kδ in T lymphocytes. The function of PI3Kδ in regulatory T lymphocytes (Tregs) in particular seems to be central to such pathophysiology. Tregs play an important role in immune self-tolerance through suppression of CD4+ and CD8+ effector T lymphocytes [42]. While PI3Kδ is expressed in nearly all T lymphocyte types, inhibition of PI3Kδ seems to preferentially effect Tregs compared to other T cells and results in a loss of suppressive regulation on effector T cells [43•]. This hypothesis is supported by clinical evidence. Colonic biopsies of patients experiencing colitis on clinical trials of idelalisib demonstrated histologic features of lymphocytic colitis [36]. Furthermore, clinically irAEs in idelalisib and duvelisib-treated patients are often responsive to lymphotoxic doses of corticosteroids and peripheral blood cytokine profiles in patients with irAEs have suggested a pro-inflammatory Th1 profile. Furthermore, in patients with irAEs, decreased numbers of Tregs have been noted. This immunomodulatory effect of PI3Kδ inhibitors appears exaggerated in younger or TN patients and those treated in combination with other immunomodulatory drugs affecting Tcells such as lenalidomide [40].

Changing Treatment Landscape

In recent years, the availability of BTKi in CLL patients and the approval of venetoclax, a BCL2 antagonist, have provided additional targeted therapies for use in R/R CLL. Ibrutinib, a first generation BTKi, was also approved for use in R/R CLL in 2014 and subsequently approved for use in TN CLL patients in 2016. Overall, in both settings, ibrutinib demonstrates a high response rate, durable responses, and generally is well tolerated as monotherapy [11]. Acalabrutinb, a novel BTKi with less off target kinase inhibition, currently FDA approved for use in R/R mantle cell lymphoma patients, is under ongoing study in CLL patients and appears to be a highly active agent in CLL [21]. Venetoclax has a high rate of response, rapid time to response, and when carefully used to minimize risk of tumor lysis syndrome, it is generally well tolerated. Venetoclax importantly also has significant activity in high risk CLL patients such as those with 17p deletion/TP53 mutations as well as activity in patients who have progressed on BTKi [18••, 44].

To date there have not been direct comparisons of PI3Ki, BTKi, or venetoclax in R/R CLL clinical trials. Mato et al. demonstrated that CLL patients treated in academic practice settings are most often treated with kinase inhibitors as first targeted therapy. The majority are treated with ibrutinib (90.2%; $n = 616$ of 683). Retrospective analyses of PFS in the ibrutinib vs. idelalisib-treated patients demonstrated superiority of ibrutinib for PFS in the front line, R/R, and 17p deletion patients, despite an apparent higher ORR in idelalisib-treated patients. Additionally, there were proportionally greater discontinuations, dose modification, and dose interruptions in idelalisib-treated patients [18••]. Further, patients treated initially with ibrutinib who experienced disease progression appeared to have higher ORR when subsequently treated with venetoclax (ORR 79%) compared to idelalisib (ORR 49%) with a trend towards improved PFS with venetoclax. These data suggest a tendency to use PI3K inhibitors in later line therapy than BTKi or venetoclax when efficacy of PI3Ki may also be more limited.

Overcoming Barriers to PI3K Use

While toxicities of current generation PI3Ki and the availability of other novel therapies for CLL may represent barriers to use of idelalisib and duvelisib, there remains significant opportunity to optimize use of PI3Ki in CLL. The design of novel PI3Ki and alternative dosing schedules represent ongoing efforts to improve tolerability and application of PI3Ki therapies in CLL.

Novel PI3K Inhibitors

While immune-mediated toxicities of idelalisib and duvelisib might be explained in part due to effect of PI3Kδ inhibition on regulatory T cells, off target kinase inhibition and pharmacokinetic properties of these agents may also factor in toxicity. Structurally differentiated PI3Kδ inhibitors with distinct pharmacokinetic properties might exert less immune-mediated toxicities. Several are currently in clinical trials and are described here.

Umbralisib

Umbralisib, formerly TGR-1202, is a novel oral PI3Kδ inhibitor with > 1000-fold greater selectivity for PI3Kδ compared to alpha and beta isoforms. It is also > 200-fold more selective for PI3Kδ relative to PI3Kγ [45]. Additionally, it has minimal off target binding with casein kinase 1 epsilon (CK1ε), the only other kinase significantly inhibited [46, 47]. CK1ε is expressed ubiquitously and plays a role in the Wnt signaling

pathway. It's exact relevance in CLL is unclear, but preclinical data suggests that inhibition of CK1ε might prevent depletion of Tregs mediated by PI3Kδ [48]. Thus, dual inhibition of PI3Kδ and CK1ε by Umbralisib may allow anti-CLL activity with less immune-mediated toxicities.

In a phase 1 dose escalation study of umbralisib in R/R CLL and other lymphomas, the MTD for umbralisib was 1200 mg of a micronized formulation with a recommended phase 2 dose of 800 mg [22]. Amongst all patients in the safety cohort ($n = 90$), most common treatment emergent AEs included diarrhea (all 43%, ≥ Grade 3 3%), nausea (all 42%, ≥ Grade 3 1%), and fatigue (all 31%, ≥ Grade 3 3%). Most diarrhea occurred early (median onset 50 days after start of therapy) and colitis was rare (all 2%, ≥ Grade 3 2%). Transaminitis was rare, occurring in 8% of patients with 3% ≥ Grade 3. The most common ≥ Grade 3 AEs were neutropenia (10%) and anemia (9%). Overall discontinuation of umbralisib was rare occurring in 7% of patients. Amongst patients with CLL, the ORR per iwCLL criteria was 50% ($n = 17$ of 20).

A subsequent phase 2 study of umbralisib 800 mg daily in R/R CLL patients intolerant to prior BTKi or PI3Ki is ongoing. Safety data were presented at ASCO in 2018. The most common reported ≥Grade 3 toxicities were neutropenia (15%) and thrombocytopenia (9%). Amongst immune-mediated toxicities of interest transaminitis occurred in 2% (0% ≥ Grade 3), diarrhea in 40% (6% ≥ Grade 3), colitis in 6% (4% ≥ Grade 3), and pneumonitis in 6% (2% ≥ Grade 3). Discontinuations due to AE occurred in 13% of patients. The median PFS had not been reached at a median follow-up of 9.5 months [49••]. ORR was not reported and we await further data as the study matures.

Finally, a randomized phase 3 study, UNITY-CLL, comparing umbralisib and ublituximab to chlorambucil and obinutuzumab in TN and R/R CLL patients completed accrual in October 2017 and we await reporting of initial results.

ME-401

ME-401 is an oral PI3Kδ inhibitor with nanomolar range binding of PI3Kδ (IC_{50} 0.6 nM) and 500–1000 times selectivity for PI3Kδ compared to alpha and gamma isoforms [50]. Additionally, ME-401 demonstrates no significant inhibition of other kinases and a longer PI3Kδ occupancy time than idelalisib. ME-401 demonstrated favorable pharmacokinetic and pharmacodynamic characteristics with near maximal inhibition of PI3Kδ after single 60 mg dose in a phase 1 healthy volunteer study [51].

A subsequent phase 1b study of ME401 in R/R NHL and CLL is ongoing. In the dose escalation cohort, transaminitis occurred in 39% (≥ Grade 3 6%), diarrhea in 45% (≥ Grade 3 19%), and no reported pneumonitis. After initial dose escalation at a continuous daily dose of ME-401, a strategy of intermittent dosing (ME-401 daily for 7 days then 21 days off therapy) after Cycle 3 was introduced to study the potential impact on irAEs. During continuous dosing, delayed irAEs ≥ Grade 3 occurred in 34% patients. In the patients undergoing switch to intermittent dosing, delayed irAEs ≥ Grade 3 occurred in 12% patients. All patients with irAEs were able to resume intermittent dosing after initial resolution of the irAE. Regarding efficacy, monotherapy with ME401 at doses ≥ 60 mg has thus far reported significant activity with ORR 100% in R/R CLL ($n = 11$ of 11). Patients experiencing disease progression on intermittent dosing ($n = 3$) were all able to recapture response with switch to intermittent dosing and all patients with ongoing response at a median follow-up of 9.3 months [52••].

Optimizing Dose Schedules

In addition to novel PI3Kδ inhibitor design, novel dosing schemas may improve tolerability and thus impact duration of therapy. As described above, depletion of Tregs plays a role in development of irAEs. Recovery of Tregs after depletion occurs in about 13 days [53]. Thus, strategies incorporating intermittent dosing, as used in the ME401 study, with drug free intervals to allow Treg recovery, may reduce irAEs and improve tolerability of existing PI3Kδ inhibitors.

Appearance of irAEs such as colitis is typically late in onset [36]. Thus, fixed duration therapy with PI3Ki prior to development of irAEs may represent alternate strategies to optimize Pi3Ki use. Such fixed duration use could include rational combinations with other CLL therapies such as venetoclax or BTKi. Careful selection of combination partners is necessary to avoid further irAEs, as evidenced in combination studies of idelalisib with lenalidomide, another immunomodulatory agent [39, 40]. Ibrutinib appears to be a reasonable partner for Pi3Ki combinations as reported in two recent phase 1 studies [54•, 55•]. Combinations of PI3Ki with venetoclax to date have not been reported, but are currently in clinical trials.

Conclusion

Inhibition of PI3Kδ results in meaningful anti-tumor activity in CLL (Table 2). Considering the challenges associated with their use, we believe that PI3Kis remain a relevant therapeutic class for patients with R/R CLL. Despite the successes of BTKi and BCL2 antagonists, subsets of patients treated with both agents still experience disease relapse. Therapeutic options for such patients remain limited. Improved design of novel PI3Kis and the development of novel dosing regimens of both current and next generation PI3Kis may lead to improved tolerability of these agents. Given their significant

Table 2 Summary of select PI3K inhibitor clinical trials in CLL

Agent	Study type	Population	ORR	PFS	Immune-related toxicities	Reference
Idelalisib	Phase 1: monotherapy (multiple malignancies) NCT00710528, NCT01090414	$n = 54$; R/R CLL	72% (33% PR-L, 39% PR)	15.8 months median (all); 32 months (150 mg BID dose)	CLL: transaminitis (28%; ≥ Grade 3 1.9%), diarrhea (29.6%; ≥ Grade 3 5.6%), colitis (7.4%; ≥ Grade 3 5.6%), pneumonitis (5.6%; ≥ Grade 3 5.6%)	[28]
	Phase 3: idelalisib-rituximab vs. rituximab (CLL) NCT01539512	$n = 110$ (per arm); R/R CLL	81% vs. 13% ($p < 0.001$)	19.4 months vs. 6.5 months ($p < 0.001$)	Idelalisib-rituximab: transaminitis (35%; ≥ Grade 3 5%), Diarrhea/colitis* (19%; ≥ Grade 3 4%), pneumonitis (6%; ≥ Grade 3 4%)	[29••]
Duvelisib	Phase 1: monotherapy (CLL and iNHL)	$n = 73$ (CLL); treatment naïve ($n = 18$), R/R CLL ($n = 55$)	Treatment naïve: 83%, R/R CLL: 56%	15.7 months (R/R CLL)	CLL+ iNHL: transaminitis (39%; ≥ Grade 3 19.5%), diarrhea (41.9%; ≥ Grade 3 11.4%), colitis (6%; ≥ Grade 3 6%), pneumonitis (4%; ≥ Grade 3 4%)	[32]
	Phase 3: duvelisib vs. ofatumomab (CLL)	$n = 319$ (duvelisib $n = 160$, ofatumomab $n = 159$); R/R CLL	73.8% vs. 45.3% ($p < 0.0001$)	13.3 months vs. 9.9 months ($p < 0.0001$)	Duvelisib: transaminitis (not reported; ≥ Grade 3 3%), diarrhea (51%; ≥ Grade 3 15%), colitis (13%; ≥ Grade 3 12%), pneumonitis (3%; ≥ Grade 3 3%)	[33]
Umbralisib	Phase 1: monotherapy (CLL and NHL)	$n = 24$, R/R CLL	50% (35% PR-L, 15% SD)	24 months	CLL + NHL: transaminitis (8%; ≥ Grade 3 3%), diarrhea (43%; ≥ Grade 3 3%), colitis (2%; ≥ Grade 3 2%)	[47]
	Phase 2: monotherapy (CLL)**	$n = 47$, R/R CLL, intolerant to prior BTKi or PI3Ki	Not reported	Not reached (median 9.5-month follow-up)	CLL: transaminitis (2%; ≥ Grade 3 0%); diarrhea (40%; ≥ Grade 3 6%); colitis (6%; ≥ Grade 3 4%), pneumonitis (6%; ≥ Grade 3 2%)	[48]
ME-401	Phase1: monotherapy or ME-401-rituximab (CLL and NHL)**	$n = 11$, R/R CLL	100% (response type not reported)	Not reached (median 6.9-month follow-up)	CLL + NHL: transaminitis (39%; ≥ Grade 3 6%); diarrhea (45%; ≥ Grade 3 19%); colitis (6%; ≥ Grade 3 6%)	[50]

*Colitis not reported separately

**Study actively enrolling

anti-CLL activity, we foresee that PI3Ki may evolve an important role in treatment of patients experiencing disease progression after BTKi and BCL2 antagonists or those in whom these agents are not reasonable options due to comorbidities. As an example of the latter, R/R CLL patients with significant cardiac or renal disease may not be candidates for either BTKi (due to arrhythmias) or venetoclax (due to risk of tumor lysis syndrome), whereas the toxicity profile of PI3Ki does not preclude use of these agents in such patients. Given CLL is a disease of primarily older patients where cardiac or renal disease may be common, improved tolerability of PI3Ki would represent an important therapeutic development for CLL patients.

Further, there are few well-established therapies for patients relapsing after BTKi or venetoclax. Chimeric Antigen Receptor T cell (CART) therapies are currently being studied in such patients and appear promising [56]. However, current CART therapies require ex vivo production of autologous T cells and select patients with aggressive CLL relapse may not be able to await production of CART. Allogeneic stem cell transplantation, used more often in the chemoimmunotherapy era of CLL treatment, may be an option for select patients who relapse on BTKi or venetoclax, but issues surrounding donor availability and time to transplant may limit its use. Given the activity of PI3Kis, these therapies may prove useful as bridging therapies in select R/R CLL patients to aid in transition to immunotherapies that cannot be immediately deployed.

Finally, there is an increasing shift towards fixed duration combination of novel therapies in CLL. Such combination therapy may provide greater depth of response, limit toxicity associated with the continuous therapy use of novel agents, and reduce costs associated with use of continuous novel therapies. Given their significant activity and that some toxicities associated with their use are delayed in onset, PI3Kis may serve a useful component of future fixed duration combination therapies. In summary, we believe that despite early barriers to use, ongoing efforts to optimize use of PI3Ki may lead to further improvements in the management options for patients with CLL.

Compliance with Ethical Standards

Conflict of Interest Krish Patel reports grants and personal fees from AstraZeneca; and personal fees from Pharmacyclics/Janssen, Genentech/Roche, Juno Therapeutics/Celgene, Sunesis Pharmaceuticals, and personal fees from Verastem.

John M. Pagel reports being a consultant to Gilead, Pharmacyclics, and TG Therapeutics.

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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