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PI3K Inhibitors: Present and Future

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Abstract

Inhibitors of PI3Kδ hold great potential for the therapy of CLL and B cell malignancies. After initially exciting efficacy results with idelalisib, the first in class inhibitor, the emergence of unexpected and unpredictable autoimmune toxicities, worse in less heavily treated and younger patients, has decreased the use of the currently available inhibitors. Newer drugs in development are attempting to reduce toxicity with novel schedules and/or combinations. This article reviews the clinical data on efficacy and toxicity across the class, and discusses ongoing efforts to understand and mitigate the likely on-target autoimmune toxicity.

Keywords

PI3Kδ; idelalisib; duvelisib; copanlisib

Interest in the phosphatidylinositol 3 kinase (PI3K) as a therapeutic target in B cell malignancies arose from observations that mice with either deletion of the delta isoform of PI3K[1,2], or a kinase dead knock-in[3], had significant B cell immunodeficiency. Specifically, these mice have significant reductions in several types of mature B cells - B1 (peritoneal); B2 (follicular); and marginal zone[1,3,4] – leading to loss of germinal centers throughout lymph nodes, spleen and Peyer's patches[3], reduced immunoglobulin levels and reduced humoral response to antigens. In contrast, individual deletion of the other class 1 isoforms in mice, namely p110α[4], p110β[5], and p110γ[6], has no obvious effect on B cells. This finding is perhaps unsurprising, as the alpha and beta isoforms have ubiquitous expression while expression of the delta isoform is largely limited to hematopoietic cells including B cells. Data from the delta deficient mice show that PI3K activation after B cell receptor (BCR) activation is primarily dependent on p110δ[1,3], as is downstream signaling from cytokine/chemokine receptors and RTKs in B cells.

These observations provided the rationale for the initial development of PI3K delta inhibitors in B cell malignancies, although recent work has further evaluated the impact of PI3Kδ abrogation on CLL development in the TCL1 mouse model of CLL[7]. The $p110\delta^{D910A/D910A}$ kinase dead mouse was crossed with the Eμ–TCL1 mouse model of CLL, and the resulting global inactivation of p110δ profoundly inhibited the onset and severity of leukemia in these mice. The mice also resisted engraftment of TCL1 CLL cells through a T

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cell dependent mechanism, while a subset of those engrafted with a very high leukemia burden were able to clear the disease and resist rechallenge, suggesting an adaptive immune response contributing to disease clearance[7]. These data suggest that both cell autonomous and cell non autonomous mechanisms contribute to the potential potency of PI3Kδ inhibition in CLL. Also of interest, both this study and another[8] demonstrated expansion of regulatory T cells (Tregs) in the setting of the TCL1 disease, with marked reduction in these Tregs with either genetic[7] or pharmacologic[8] inhibition of PI3Kδ. In the genetic model, the mice also developed an autoimmune colitis similar to that seen in patients treated with PI3Kδ inhibitors, suggesting that at least colitis is an on target side effect[7].

Idelalisib: Efficacy

The first in class clinical PI3Kδ inhibitor was idelalisib, which demonstrated potent and specific inhibition of PI3Kδ in isoform-specific cell based assays and was able to induce apoptosis in CLL cells in vitro[5,9] (Table 1). Treatment of CLL cells with idelalisib blocked AKT phosphorylation and downstream signaling from the BCR, chemokine receptors and CD40[5,9]. The phase 1 study of idelalisib enrolled heavily pretreated patients with relapsed refractory B cell malignancies, and no formal DLTs were observed, although 25% of patients did have grade 3 or higher transaminase elevations[10] (Table 2). The recommended phase 2 dose (RP2D) of 150 mg BID was ultimately chosen based on a careful assessment of this toxicity, which tended to be more frequent at higher doses, together with evidence of a plateau in both drug exposure and nodal reduction on CT, at 150 mg BID. The CLL subset of this study enrolled 54 patients with a median of 5 prior regimens, 91% with unmutated IGHV, 80% with bulky lymphadenopathy and 70% with treatment refractory disease – hence a very high risk population. In this study we were among the first to identify the phenomenon of treatment-related lymphocytosis, leading to the definition of partial response with lymphocytosis (PR-L); 81% of patients had a nodal response, with 39% meeting traditional PR criteria and an additional 32% meeting PR-L criteria. The median PFS at all dose levels was 15.8 months, but was 32 months in patients treated at the recommended phase 2 dose (RP2D) or higher.

These very promising results led to three registration trials, all in combination, due to concerns about how the FDA would interpret the persistent redistribution lymphocytosis that was observed with the single agent in the phase 1 study. The first to report was a randomized double-blind placebo-controlled trial comparing idelalisib with rituximab to rituximab with placebo[11], with 110 patients per arm. The patient population included relapsed refractory CLL patients not appropriate for chemoimmunotherapy, with comorbidities (median CIRS comorbidity score 8), who had a median of three prior therapies, 84% with unmutated IGHV and 43.5% with TP53 dysfunction. The study was terminated early for efficacy, with a median time on idelalisib of 3.8 months, due to markedly superior PFS in the idelalisib arm (HR for progression or death, 0.15 (0.08–0.28) $p<0.001$)[11]. An improved OS was also seen at this early timepoint, while toxicity of idelalisib was low, likely due to the short follow-up[11]. This trial led to the 2014 FDA approval of idelalisib rituximab for relapsed refractory CLL patients in whom rituximab would be considered an appropriate therapy.

Recently, the final follow-up of this study has been published, demonstrating a median PFS of 20.3 months (95% CI, 17.3 to 26.3 months) among patients initially assigned to idela-R, with median OS 40.6 months (95% CI, 28.5 to 57.3 months)[12]. Prolonged exposure to idelalisib over a median of eighteen months increased the incidence of diarrhea (all grade, 46.4%; grade 2, 17.3%; and grade 3, 16.4%), colitis (grade 3+, 8.2%) and grade 3 or greater pneumonitis (6.4%).

The second registration trial comparing idelalisib ofatumumab to ofatumumab among 261 CLL patients with a median of 3 prior therapies demonstrated a median PFS of 16.3 mos in the idelalisib-ofatumumab group compared to 8 mos in the ofatumumab alone group ($p<0.0001$)[13]. Excess grade 3 or higher diarrhea and neutropenia were observed in the idelalisib arm, and treatment related deaths were 22 in the idelalisib-ofatumumab group compared to 6 in the ofatumumab group[13]. The final registration trial evaluated the addition of idelalisib to bendamustine rituximab (BR) among 416 relapsed refractory CLL patients with a median of 2 prior regimens, one-third of whom had 17p deletion[14]. At a median follow-up of 14 months, the median PFS was 20·8 months (95% CI 16·6–26·4) in the idelalisib-BR group compared to 11·1 months (8·9–11·1) in the placebo-BR group (HR 0·33, 95% CI 0·25–0·44; $p<0·0001$)[14]. Treatment emergent deaths were 11% on the idelalisib arm compared to 7% on the placebo arm, primarily infection[14].

Idelalisib: Toxicity

These registration trials started to demonstrate a characteristic pattern of idelalisib toxicity, which included a relatively early transaminitis, followed by later events of pneumonitis, rash and diarrhea that could progress to colitis. Although all of these toxicities were seen on the phase 1 study, they became much more frequent in the registration program, possibly because the patient population was less heavily pretreated (Table 2). A pooled analysis of 760 patients with a median of 2-3 prior therapies (i.e. patients from the registration trials) demonstrated a 14% incidence of grade 3 or higher diarrhea and transaminitis, significantly higher than in phase 1[15]. Furthermore, a combined 24 month follow-up analysis of the idelalisib-rituximab and idelalisib-ofatumumab registration trials demonstrated that 41% of patients had discontinued therapy due to adverse events, including infection as well as the above toxicities, with only 22.5% continuing on therapy at two years[16].

Studies that attempted to move idelalisib into the front-line setting demonstrated even higher rates of similar toxicities. A company-sponsored frontline study of idelalisib with rituximab in patients over age 65 demonstrated a 42% incidence of grade 3+ diarrhea, 23% grade 3+ transaminitis, and 13% grade 3+ rash, leading to 45.3% of patients discontinuing therapy for toxicity[17]. Our group performed an investigator initiated frontline study of idelalisib with ofatumumab, among patients of any age, and found early fulminant hepatotoxicity typically at week 3-4, and requiring not just drug hold but usually immunosuppression to resolve[18]. Fifty-two percent of patients ultimately had grade 3-4 hepatotoxicity on this trial, which was associated with an activated CD8 T cell, perforin-positive infiltrate on liver biopsy. Risk factors for developing this toxicity included younger age and mutated IGHV[18]. Immune infiltrates were also found in bowel, and the colitis was also shown to be steroid-responsive[19–21]. The biopsy data as well as the clinical response to immunosuppression

suggested an autoimmune etiology for these toxicities, which could also explain why they were worse in less pretreated and younger patients, both of whom are presumably more immunologically intact.

Despite these higher rates of still poorly understood toxicities particularly in the frontline setting, Gilead embarked on a large frontline / early line phase 3 registration program in both CLL and follicular lymphoma. In March 2016, a combined safety analysis of three of these studies demonstrated worse overall survival in the idelalisib containing arms, at 7.4% compared to 3.5% on the control arms. This observation led to the summary closure of all frontline studies evaluating idelalisib. Interestingly, the deaths were primarily related to bacterial infections, sometimes with neutropenia, which had also been seen previously in the relapsed setting, but were not necessarily flagged as unusual among heavily pretreated CLL patients. Some cases of CMV and PJP were also noted. These findings demonstrate that idelalisib likely has multiple immunomodulatory effects, not only inducing autoimmune toxicity, but also increasing risk of both bacterial and opportunistic infections, as well as neutropenia.

The more unusual pattern of hepatitis and colitis strongly suggests an autoimmune process: delayed onset but rapid reoccurrence on rechallenge with drug, immune infiltrates on biopsy, responsiveness to steroids, and higher frequency among less pretreated and younger (i.e. more immunologically intact) patients. Following our initial observation that younger patients had greater risk of transaminitis in our frontline study, we looked at >750 patients across the Gilead registration program, and demonstrated that the rate of grade 3 or higher transaminitis with idelalisib was higher in untreated patients, and in younger patients, by decile of age[22]. Furthermore, mice with genetic inactivation of PI3K delta develop an autoimmune colitis which is similar to that seen in the patients[3], and the same was seen in the TCL1 mice with the PI3K$\delta^{D910A/D910A}$ kinase dead mutation[7]. Interestingly, both mice and humans with mutations that disrupt regulatory T cell function also develop a syndrome of hepatitis, enteritis and pneumonitis[23,24], similar to patients treated with idelalisib. We therefore investigated the impact of idelalisib on regulatory T cells among patients on our upfront study, and we demonstrated a significant decrease in Tregs by one month of therapy, particularly among patients with early hepatotoxicity[18]. In the TCL1 mouse model, regulatory T cells are expanded, and this expansion is abrogated in the p110δ kinase dead background, demonstrating that p110δ is needed for regulatory T cell survival[7]. Similar results have also been seen with pharmacological inhibition of PI3Kδ in the mouse model[8].

Although idelalisib is a very effective drug, the unpredictable often delayed onset as well as severity of its autoimmune toxicity has markedly decreased its use in CLL and lymphoma. Further scientific work may allow its immunomodulatory properties to be harnessed for the therapy of CLL, lymphoma or solid tumors, particularly given that p110δ inactivation in Tregs in mouse models is both necessary and sufficient to confer resistance to a variety of solid tumors[25]. Meanwhile, however, given the importance of the PI3Kδ target, much ongoing drug development is continuing to target PI3Kδ in CLL and lymphoma.

Duvelisib

Duvelisib, an inhibitor of both the delta and gamma isoforms of PI3K (Table 1), was approved by the FDA in September 2018 for the therapy of relapsed CLL after at least two prior therapies, as well as follicular lymphoma. Duvelisib is about ten-fold more potent in inhibiting the delta isoform compared to gamma[26], and at the 25 mg BID dose ultimately chosen for CLL therapy, maintains blood levels consistently above the IC90 for delta inhibition and the IC50 for gamma inhibition[27]. The importance of additionally inhibiting gamma in CLL is not definitely known, although the gamma isoform does have some expression in CLL cells. Duvelisib is cytotoxic to primary CLL cells in vitro, although this may be mediated primarily by delta isoform inhibition, and also inhibits signaling downstream of the BCR[28,29]. As importantly, however, PI3K gamma is thought to modulate the microenvironment, in particular gamma inhibition decreases myeloid derived suppressor cells (MDSCs) and shifts macrophages toward a more immunostimulatory, anti-cancer phenotype[30].

In a phase 1 study in indolent NHL, dose escalation continued up to 100 mg BID, at which dose two DLTs occurred, one grade 3 transaminitis and one grade 3 rash, such that the MTD was determined to be 75 mg BID[27]. In subsequent expansion at both 25 and 75 mg BID doses, pAKT was substantially inhibited in CLL cells at 25 mg BID, with near complete inhibition of Ki67 seen by cycle 2[27,31]. The ORR in phase 1, not including PR-L, was 56%, with 1 CR, and the median response duration was 21 months[27,31]. Given that response rates and durability appeared similar, and toxicity better, at the lower dose, 25 mg BID was moved forward as the RP2D[27] and the phase 3 DUO trial was launched, randomizing relapsed refractory CLL patients between duvelisib and ofatumumab[32]. The median age of the patients was 69 and they had a median of two prior therapies. One-third had 17p deletion or TP53 mutation. DUO met its primary endpoint of improved PFS by independent review committee, at 13.3 mos compared to 9.9 mos for ofatumumab. The PFS of duvelisib as measured by investigators was 17.6 mos, which is very comparable to that seen in the idelalisib registration trials. About one-third of patients discontinued duvelisib for adverse events which included neutropenia and infections, and diarrhea and colitis, which occurred at similar frequencies to idelalisib, while rash, pneumonitis and transaminitis appeared to be less common (Table 2). This study led to the approval of duvelisib monotherapy for the therapy of CLL, currently the only monotherapy approval for a PI3K inhibitor in CLL. Many studies are ongoing, exploring duvelisib in combination, for example with venetoclax at our institution; on alternative schedules with treatment breaks skipping either days within a week, or weeks within a cycle, in an effort to reduce autoimmune toxicity; and in other disease settings, including T cell lymphomas.

Copanlisib

Copanlisib is an extremely potent pan-PI3K inhibitor with some relative selectivity for the alpha and delta isoforms, in fact often billed as an alpha / delta inhibitor, even though it is actually the most potent gamma inhibitor under investigation in CLL or lymphoma (Table 1). Copanlisib has been primarily developed in lymphoma, and received accelerated approval from the FDA in 2017 for the treatment of follicular lymphoma previously treated

with alkylators and rituximab. In contrast to all other PI3Kδ inhibitors currently in the clinic, copanlisib is given intravenously, weekly for three weeks out of four. Thus copanlisib has several distinguishing features from idelalisib or duvelisib: IV administration; a punctuated schedule; and potency against the alpha isoform of PI3K. These differences are of particular interest because the toxicity profile of copanlisib is also distinct, and includes acute infusional hyperglycemia and hypertension, likely both related to its potency against PI3K alpha[33]. Toxicities thought to be related to delta inhibition, including transaminitis and diarrhea/colitis, are much less common, at 2% and 5% grade 3, respectively, in the lymphoma registration trial[34]. This trial enrolled 8 SLL patients, and in those patients, copanlisib had a 75% response rate, but data in CLL remain very limited. We are launching a study of adding copanlisib to enhance response among CLL patients with partial response on ibrutinib, in order to explore the activity and toxicity of copanlisib among CLL patients.

Investigational PI3K Inhibitors

Umbralisib

Among the as yet unapproved PI3K inhibitors, umbralisib (TGR-1202) is most advanced in clinical trials, having completed enrollment to its potential registration trial, UNITY-CLL. Umbralisib is a very specific inhibitor of the delta isoform of PI3K, but is approximately 10X less potent than idelalisib or duvelisib (Table 1). The structure of umbralisib is significantly different from idelalisib and duvelisib, and it also has in vitro activity against casein kinase 1μ[35], which has been shown recently to be a therapeutic target in CLL[36]. The phase 1 study of umbralisib enrolled patients with advanced B cell malignancies, and required reformulation and extensive dose escalation to achieve adequate exposure and a high response rate[37]. Four DLTs were seen, including a grade 3 rash at the 800 mg initial formulation, a grade 3 hypokalemia at the 1800 mg original formulation, and two events of grade 3 fatigue at 1800 mg of the micronized formulation. The RP2D was ultimately chosen to be 800 mg daily of the micronized formulation in a fed state, which reportedly maintained concentrations above 5.25 μM throughout the 24 hr dosing interval. This concentration is below the EC50 of umbralisib for inhibition of casein kinase 1μ in a cell free kinase assay, which is 6.1 μM[35], and below the 15 μM used to inhibit autophosphorylation in vitro[13], suggesting that inhibition of CK1μ does not play a major role in vivo. To date pharmacodynamic analysis demonstrating inhibition of either potential target in patient samples treated on clinical trials has been lacking.

With a median duration of treatment and follow-up of 4.7 cycles, the ORR was 37% across all enrolled hematologic malignancies and all dose levels, with 50% ORR per iwCLL 2008 criteria plus an additional 35% PR-L among the 18 CLL patients[37]. The mean duration of response was 13.4 months in 16 CLL patients. Patients were eligible for intrapatient dose escalation, and, once the RP2D was determined, all patients transitioned to that dose (800 mg daily in the fed state). At the conclusion of the study, 13 of 90 patients remained on umbralisib, with a median duration of treatment and follow-up among those patients of 29.7 mos. Most patients discontinued for disease progression (56%), and 10% for adverse events[37].

Clinical development of umbralisib moved rapidly into combination studies, with the novel anti-CD20 antibody ublituximab[38], as well as with ibrutinib. In the phase 1 study of umbralisib with ublituximab in B cell malignancies, 22 CLL patients were enrolled, with a median of 3 prior regimens and 41% with 17p deletion[39]. The ORR was 62% (13/21), with 2 CRs and a median duration of response of 26 months. Their median treatment duration was 11 mos, with the majority of discontinuations due to progressive disease[39]. Our group led a multicenter phase 1/1b combination study of ibrutinib with umbralisib in relapsed refractory CLL and MCL, with 42 patients with a median of two prior therapies treated in parallel dose cohorts by disease[40]. No DLTs were observed and the MTD was not reached; umbralisib was given at its full single agent dose in combination with the standard dose of ibrutinib for each disease. ORR in CLL was 90% including 29% CRs, and two year PFS was 90%[40]. The MD Anderson Cancer Center led a similar phase 1 study of the triple-drug combination umbralisib, ibrutinib and ublituximab, and treated 46 patients, including 23 CLL patients[41]. The recommended phase 2 doses were again the full single agent doses of each drug. ORR was 84% across all evaluable patients, and was 100% among 22 CLL patients, including 36% CRs. Seven of the nine CLL patients evaluated for MRD had undetectable MRD. Median duration of response in CLL patients was 22.7 mos.

While the efficacy data with umbralisib are generally encouraging, it is the adverse event profile that has attracted the most attention. In the early studies, rates of grade 3 or higher autoimmune toxicities seen with PI3Kδ inhibitors appeared reduced: 2-3% transaminitis, 2-4% rash and 3-10% diarrhea[39–41]. These initial results were difficult to interpret as many patients had very short follow-up on therapy, and particularly the diarrhea tends to occur later. A recent comprehensive safety analysis was therefore performed and encompassed 347 patients, with a median drug exposure of 6.5 mos, and found that grade 3 or higher transaminitis was seen in 2%, grade 3+ colitis in <1%, and grade 3+ pneumonitis in <0.5%[42]. Given this still relatively short follow-up, a sub-analysis focused particularly on 177 patients who remained on umbralisib for at least 6 months, and identified rates of grade 3 or higher toxicity as follows: transaminitis 3%, rash 0%, pneumonitis 0.6%, diarrhea 8%[42]. Only 1 of the 14 patients with diarrhea had colitis, and most of the patients were managed only with dose interruption, not requiring steroids. These data suggest that umbralisib has some similar autoimmune toxicities to idelalisib and duvelisib, but that these occur less frequently and/or are milder. We still await the results of randomized trials, larger patient populations and longer follow-up to truly clarify this.

The UNITY registration trial in CLL is comparing umbralisib given with ublituximab, to chlorambucil-obinutuzumab, in a patient population which is approximately 60% treatment naïve and 40% relapsed. The study is fully accrued and an announcement that overall response rate (ORR) would not be assessed for potential accelerated approval occurred in September 2018. TG Therapeutics is now awaiting the results of the primary PFS endpoint, for potential filing for full approval.

Parsaclisib

One of two highly potent and specific PI3Kδ inhibitors in advanced clinical development is parsaclisib (INCB050465), which has an IC50 for delta inhibition of 10 nM in whole blood

and is 19000X selective for inhibition of delta compared to the other class 1 isoforms[43]. Parsaclisib was assessed in patients with advanced B cell malignancies in phase 1, both alone and in combination with the JAK1 inhibitor itacitinib, as well as with the chemotherapy regimen RICE[44]. Seventy-two patients (6 with CLL) were treated with the single agent at doses ranging from 5-45 mg daily in phase 1, and expansion cohorts were treated at 20 mg daily, 30 mg daily, and an intermittent schedule of 20 mg daily for 9 weeks, then once weekly. All doses tested led to continuous plasma exposure above the IC90, and no DLTs occurred. The primary adverse events of any grade were diarrhea/colitis in 36% (9% grade 3-4), rash in 31% (6% grade 3-4), transaminitis in 29% (albeit almost all grade 1) and grade 3-4 neutropenia in 19%. There were 3 events each of hypotension and sepsis, as well as 3 fatal AEs in 2 patients (2 respiratory failure and 1 sepsis). Dose interruptions occurred in 42% of patients. An intermittent schedule was piloted in an effort to reduce adverse events, and in fact none of 26 patients who received intermittent dosing discontinued. Furthermore, no grade 4 neutropenia or grade 4 non-heme adverse events occurred on the intermittent schedule, and only 1 case each of grade 3 rash and diarrhea, suggesting that the intermittent dosing did improve tolerability. Objective response rates were 71% in follicular lymphoma, 78% in marginal zone lymphoma, 67% in mantle cell lymphoma, 30% in DLBCL and 33% in CLL (3 of whom had had prior ibrutinib)[44]. Phase 2 studies are ongoing, as well as some phase 1 combination studies, in order to identify an optimal potential registration path.

ME-401

ME-401 is the other highly potent and specific novel delta inhibitor that has been investigated in both CLL and follicular lymphoma and is currently enrolling a potential registration trial in follicular lymphoma. ME-401 inhibits the PI3Kδ isoform with IC50 in the low nM range even in whole blood and in isoform-specific cell based assays (Table 1). The first in human study of this drug was an ascending dose study performed in healthy male volunteers in three groups, with each subject given two doses at least one week apart[45]. No significant or recurrent adverse events were seen. Exposure was dose proportional up to 60 mg, and inhibition of basophil activation, a δ isoform specific assay, was also dose proportional and reached 90% inhibition at 60 mg. Furthermore, dosing at 60 mg was predicted to result in trough plasma concentrations that would maintain 90% inhibition of basophil activation. This dose was therefore selected as the starting dose for patient studies.

ME-401 has now also been studied in patients with CLL/SLL and follicular lymphoma in phase 1, as a single agent and together with rituximab in data that have been reported, and most recently together with zanubrutinib in a cohort that is still enrolling[46]. ME-401 was dosed at 60, 120 and 180 mg without DLTs in a 56 day window, with high response rates and with typical adverse event (AE) rates which were as high as one-third of patients developing grade 3+ diarrhea/colitis or rash. An intermittent schedule was then implemented, with two months continuous dosing at 60 mg, followed by one week on, three weeks off. This schedule is supported by the 28 hour half-life of the drug and was intended to allow recovery of regulatory T cells[47] in the second two weeks. The loss of Tregs with PI3Kδ inhibitors is believed to lead to the autoimmune adverse events of PI3Kδ inhibition. Intermittent dosing reduced the grade 3+ diarrhea rate to 9.7%, and allowed 77% of patients

to remain on therapy, compared to 53% on continuous dosing, albeit with shorter follow-up. Grade 3+ rash was reduced from 10% to 0%, and pneumonia/pneumonitis from 12.5% to 3.2%. Response rates were preserved, and were 80% in 50 FL patients across all dose groups, and 100% in 14 CLL patients (83% overall)[46].

A randomized phase 2 registration trial has been initiated in relapsed follicular lymphoma patients. All patients will receive two months continuous dosing lead-in, and then be randomized in a double blind fashion to continuous vs intermittent dosing. In the event of progression on intermittent dosing, patients may switch to continuous dosing, and in the event of adverse event on either arm, drug is held and patients may resume on intermittent dosing regardless of their original arm. This study should provide high quality data on the true value of the intermittent dose schedule, which currently appears to be the preferred path forward to maximize the clinical use and benefit of PI3Kδ inhibitors.

Summary: The Future

The preponderance of evidence from mouse models as well as clinical trials suggests that the autoimmune toxicities of PI3Kδ inhibitors are a class effect, seen as they are even with the highly specific, highly potent newest agents, parsaclisib and ME-401. Given this, a few options exist for optimizing the use of these drugs in order to harness their efficacy. Preliminary data from intermittent dosing with both parsaclisib and especially ME-401 suggest that these intermittent schedules may reduce toxicity while largely maintaining efficacy. The results of the ME-401 registration trial will provide substantial evidence to address this hypothesis. Correlative studies exploring the impact of these schedules on T cells are also of great interest and are ongoing in the context of clinical trials. Additionally, combination studies that use lower intermittent doses of the PI3K inhibitor as a potentiating agent are also likely to be fruitful; these studies could rely on either the direct anti-B cell effects of the delta inhibitors, or on their immunomodulatory properties, to enhance the efficacy of the combination partner. Umbralisib may see success through this mechanism, as its similar exposure relative to its lower potency likely leads to less overall drug exposure. A better scientific understanding of the immunomodulatory properties of the drugs in vivo would certainly help optimize this approach. Finally, and likely furthest away, would be combinations that prevent the effects of the PI3Kδ inhibitors on T cells. For example, preclinical data suggest that inhibition of histone deacetylases may protect regulatory T cells[48,49], and in fact, a study combining romidepsin with duvelisib provided suggestive evidence for reduced toxicity of the combination[50]. Whether this approach or others would prove clinically viable or helpful depends on the drugs involved and remains for future study. Meanwhile, the PI3Kδ inhibitor class is a very active drug class in lymphoma and CLL, if the toxicity can be managed; while managing this toxicity has proved more challenging than initially expected, ongoing work is now pointing a way forward.

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Table 1.

Isoform Inhibition Profiles of PI3Kδ Inhibitors that are FDA Approved or in Advanced Clinical Development (IC_{50} values, nM)

Drug Name	p110α	p110β	p110δ	p110γ
Idelalisib[9]	820	565	2.5	89
Duvelisib[26]	1602	85	2.5	27
Copanlisib[51]	0.5	3.7	0.7	6.4
Umbralisib[37]	>10000	1116	22	1065
Parsaclisib[43]	>20000	>20000	1	>20000
ME-401[45]	22867	30	0.6	713

Table 2.

Comparison of Rates of Autoimmune Toxicity for Each Drug, Based on Lines of Prior Therapy and Duration on Inhibitor

Drug	Disease / Study	Median Prior Tx	Median Time on Therapy	Grade 3+ Neutropenia	Grade 3+ Diarrhea/ Colitis	Grade 3+ Transaminitis	Grade 3+ Rash	Grade 3+ Pneumonitis
Idelalisib	CLL ph 1[10]	5	15 mos	43%	5.6%	2%	0%	5.6%
	CLL / NHL combined safety analysis[15]	1-2	N.R.	30%	14%	14%	5%	3%
	CLL frontline >65 + R[17]	0	22.4 mos	28%	42%	23%	13%	6%
	CLL frontline > 65[52]	0	10.4 mos	17%	27%	22%	10%	5%
	CLL frontline any age[18]	0	8.1 mos	33%	15%	52%	7%	7%
Duvelisib	CLL, Phase 1[31]	4	6 mos	44%	9.1%; 5.5% colitis	11%	0%	9.1%
	CLL, Duo[32]	2	22.4 mos	30%	15%; 12% colitis	3%	2%	3%
	NHL, Dynamo[53]	3	6 mos	23%	15%	6%	5%	4%
	CLL, Ph 1 frontline cohort[54]	0	15.6 mos	33%	22%	17%	5.6%	11%
	NHL, Contempo + R[55]	0	6.2 mos	10.7%	14%	25%	10.7%	N.R.
	NHL Contempo + G[55]	0	6.1 mos	22.2%	11%	26%	7.4%	N.R.
Umbralisib	CLL / NHL, phase 1[37]	3	4.7 mos	13%	3% diarrhea / 2% colitis	3%	4%	N.R.
	CLL / NHL, integrated safety analysis[42]	3	6.5 mos	16%	4% diarrhea / <1% colitis	2%	N.R.	<0.5%
	CLL/NHL Integrated Analysis, pts c > 6 mos exposure[42]	2	1.3 yrs	9%	8% diarrhea (includes 1 colitis)	3%	0%	0.5%
Copanlisib	NHL Ph 2 registration trial[34]	3	5.5 mos	24%	5% diarrhea	2%	1%	1%
Parsaclisib	NHL, CLL[44]	3	4 mos	19%	9%	3%	6%	0%
ME-401	CS: CLL, FL[46]	CLL 1, FL 2	9.8 mo	NR (<15%)	20%	7.5%	10%	12.5%
	IS: CLL, FL[46]	CLL 1, FL 2	4.8 mos (Ton T)	NR (<15%)	9.7%	3.2%	0%	3.2%