Clinical Commentary Review

PI3Kδ Pathway Dysregulation and Unique Features of Its Inhibition by Leniolisib in Activated PI3Kδ Syndrome and Beyond

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The phosphoinositide 3-kinase (PI3K) pathway regulates diverse cellular processes, with finely tuned PI3Kδ activity being crucial for immune cell development and function. Genetic hyperactivation of PI3Kδ causes the inborn error of immunity activated phosphoinositide 3-kinase δ syndrome (APDS). Several PI3Kδ inhibitors have been investigated as treatment options for APDS, but only leniolisib has shown both efficacy and tolerability. In contrast, severe immune-mediated adverse events such as colitis, neutropenia, and hepatotoxicity have been observed with other PI3Kδ inhibitors, particularly those indicated for hematological malignancies. We propose that leniolisib is distinguished from other PI3Kδ inhibitors due to its structure, specific inhibitory properties selectively targeting the δ isoform without overinhibition of the δ or γ isoforms, and the precise match between APDS mechanism of disease and drug mechanism of action. **(J Allergy Clin Immunol Pract 2023;■:■-■)**

Key words: *Leniolisib; PI3K; PI3Kδ; PI3Kδ inhibitor; Mechanism of action; APDS; Activated PI3Kδ syndrome*

OVERVIEW OF THE PHOSPHOINOSITIDE 3-KINASE PATHWAY

Cell growth, proliferation, survival, motility, differentiation, and metabolism are affected by intracellular signaling cascades often involving AKT, forkhead box O (FOXO), glycogen synthase kinase-3 (GSK3), and mechanistic (or mammalian) target of rapamycin (mTOR).[1,2] These cascades can be initiated by the phosphorylation of membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP_2) to generate phosphatidylinositol 3,4,5-trisphosphate.[3] This reaction—and control of the associated intracellular signaling cascades—is regulated by class I phosphoinositide 3-kinases (PI3Ks).[3] These PI3Ks are heterodimers comprising distinct catalytic and regulatory subunits.[1] The most-studied regulatory subunit, p85α, is encoded by *PIK3R1* and maintains inhibitory contacts with the catalytic subunit. These contacts regulate stability and recruitment of the catalytic subunit to membrane-associated phosphoproteins that relieve its inhibitory activity and position the catalytic subunit near PIP_2.[1,3] The p110 catalytic subunit has 4 isoforms, α, β, γ, and δ, encoded by *PIK3CA*, *PIK3CB*, *PIK3CG*, and *PIK3CD*, respectively.[3] The γ subunit is unique among the class I PI3Ks by binding alternative regulatory subunits.[1] The α and β isoforms are expressed ubiquitously; γ and δ isoforms, mainly in immune cells.[1,4] The γ isoform is primarily involved with innate immunity; the δ isoform, with adaptive immunity, albeit with overlap.[1] B- and T-lymphocyte development and function are regulated partly by the degree of PI3Kδ activity.[3] Activity must be dynamically regulated to permit FOXO-dependent transcription and periods of mTOR signaling.[3] Therefore, homeostatic control of PI3Kδ activity is vital for immune health (Figure 1, *A*).

The PI3Kδ is also expressed at low levels in other cell types, in which its expression can be further induced by specific stimuli. The PI3Kδ is expressed in the central nervous system, where it may be involved with axon regeneration.[10,11] Low levels of PI3Kδ are found in fibroblast-like synoviocytes, with increased expression in synovium of patients with rheumatoid arthritis.[12] Tumor necrosis factor α with glucose can induce further expression of PI3Kδ in endothelial cells, where basal levels are low.[13,14] In the lungs, PI3Kδ is expressed in fibroblasts and bronchial epithelial cells.[15,16]

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Abbreviations used
AE- Adverse event
AID- Activation-induced cytokine deaminase
ALT- Alanine aminotransferase
ANC- Absolute neutrophil count
APDS- Activated phosphoinositide 3-kinase delta syndrome
AST- Aspartate aminotransferase
FOXO- Forkhead box O
GSK3- Glycogen synthase kinase-3
IC_{50}- Half-maximal inhibitory concentration
Ig- immunoglobulin
IRT- Immunoglobulin replacement therapy
mTOR- Mechanistic (or mammalian) target of rapamycin
pAKT- Phosphorylated AKT
PI3K- Phosphoinositide 3-kinase
PIP_2- Phosphatidylinositol 4,5-bisphosphate
pSS- Primary Sjögren syndrome
SAE- Serious adverse event

PI3Kδ PATHWAY DYSREGULATION IN ACTIVATED PI3Kδ SYNDROME

The PI3Kδ hyperactivation from gain-of-function variants in *PIK3CD* or loss-of-regulatory-function variants in *PIK3R1* causes the inborn error of immunity activated PI3Kδ syndrome (APDS), first characterized in 2013.[5,6,17,18] Pathogenic variants in p85α or p110δ that disrupt the inhibitory contacts between the 2 subunits, or in p110δ that promote kinase activity or increased interaction with the plasma membrane and thus access to PIP_2, drive hyperactive PI3Kδ signaling.[5,6,18-21] Constitutively active PI3Kδ causes reduced or absent dynamic tuning of activity, resulting in excessive GSK3/FOXO inhibition and mTOR activation (Figure 1, *B*).[8] Hyperactivity can be approximated by measuring increased downstream phosphorylation of AKT (pAKT) or S6.[5]

The hallmark of APDS is recurrent sinopulmonary infections, often associated with severe bronchiectasis, due to derangement of B- and T-cell development and function, causing both immune deficiency and dysregulation.[5,6,10,22-25] Transitional B-cell levels, often elevated, may be entry points and reservoirs for Epstein-Barr virus.[5,10,23,26,27] In contrast, levels of mature naive and memory B cells are often decreased, along with defects in class-switch recombination.[5,10,23,26,27] Hyperactive PI3Kδ signaling also drives terminal differentiation: immunoglobulin M + (IgM+) plasma cell levels are often increased in patients; many patients with APDS display elevated IgM levels, low IgG and/or IgA levels, and poor specific antibody production.[5,10,23,26-28] The T-cell compartment also displays a shift away from functional cells, with an inverted $CD4^+/CD8^+$ T-cell ratio, decreased naive T-cell levels, and increased $CD8^+$ effector memory and T effector memory cells re-expressing CD45RA at the expense of long-lived central memory cells.[5,6,10,23,26,27,29] These T effector memory cells re-expressing CD45RA cells have characteristics of highly inflammatory senescent ($CD57^+$) $CD8^+$ T cells and generate ineffective responses to infections, particularly Epstein-Barr virus and cytomegalovirus, allowing lifelong infections that can be severe and result in end-organ damage and malignancy.[5,6,22-24]

Lymphadenopathy, due to follicular hyperplasia, can further be driven by B-lymphocyte proliferation associated with increased levels of follicular helper and effector T cells, the latter demonstrating an enhanced proliferative burst on encounter with antigen.[5,10,26] B- and T-cell proliferation also contributes to the splenomegaly and hepatomegaly observed in APDS.[9,10,23,26-28,30] B-cell proliferation may underlie the profound submucosal nodular lymphoid hyperplasia seen in many patients, leading to derangement of gastrointestinal or respiratory tract anatomy and functions.[7,10,26]

Autoimmunity, particularly cytopenias, may be caused partly by elevated levels of plasmablasts secreting autoreactive IgM as well as elevated levels of $CD21^{low}$ transitional B cells, as occurs in patients with other primary immune regulatory disorders, including common variable immune deficiency and monogenic diseases such as nuclear factor kappa-light-chain-enhancer of activated B cells-1 or cytotoxic T-lymphocyte—associated protein 4 haploinsufficiency.[31-34] In addition, studies in a mouse model of APDS show increased plasma cell numbers and elevated levels of natural antibodies, which may also contribute to autoimmunity.[35]

Less well-characterized manifestations of APDS include liver disease, neurodevelopmental delay, seizures, fatigue, and atopy, some of which may be due to PI3Kδ expression in nonimmune cells.[9,10,26,36,37] The more ubiquitous expression of p85α may account for the higher prevalence of failure to thrive and neurodevelopmental delay in patients with *PIK3R1* defects.[10,26,30] Interestingly, bronchiectasis and autoimmune cytopenias have been reported as less prevalent in patients with *PIK3R1* variants.[10,26,30]

Historically, there has been no standard of care and management of APDS has remained largely empirical. Most therapies do not directly target disease pathogenesis nor address the full complexity of APDS. Immune deficiency is treated with prophylactic antimicrobials and immunoglobulin replacement therapy (IRT), while immune dysregulation is generally treated with immunomodulatory therapies such as corticosteroids or mTOR inhibtors, and/or surgical procedures.[10,26,30] Hematopoetic stem cell transplantation may be considered curative but carries the risk of serious complications including increased rates of graft rejection, and may not correct non-immune/hematopoietic manifestations.[37]

PI3Kδ INHIBITORS IN APDS

Because APDS is caused by PI3Kδ overactivity, PI3Kδ inhibitors have been investigated as treatment options, albeit in studies with small sample sizes given the rarity of the disease. A 12-week, open-label, phase 2 trial of the once-daily inhaled PI3Kδ inhibitor nemiralisib for patients with APDS (n = 5) demonstrated no efficacy and tolerable adverse events (AEs).[38] No deaths or severe AEs were reported. The most common AEs were cough, headache, and nasopharyngitis (all n = 3). There were no changes in phosphatidylinositol 3,4,5-trisphosphate or downstream inflammatory markers in induced sputum, nor were there changes in blood inflammatory markers or lymphocyte subsets. The authors speculate that lack of efficacy could be due to nemiralisib not being retained in the lung long enough.

Two trials have studied oral, systemic PI3Kδ inhibition in APDS. A 12-week phase 1b open-label trial of the PI3Kδ inhibitor seletalisib (15—25 mg once-daily) demonstrated moderate efficacy and AEs leading to discontinuation.[39] However, of the 7 patients receiving the drug, only 5 completed the study, with 2 discontinuing because of study drug—related AEs in the liver. Four patients entered the extension study, 3

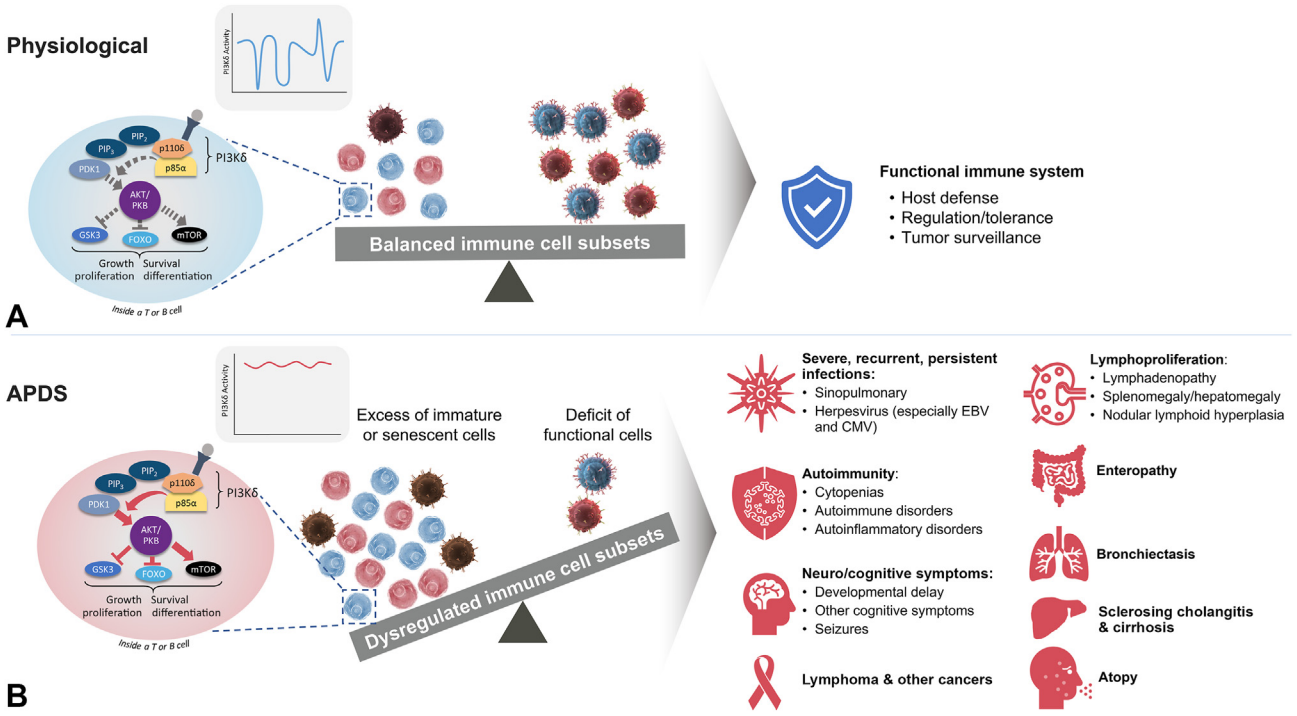

FIGURE 1. The PI3Kδ pathway in lymphocytes under physiological and pathological conditions. (**A**) Under healthy physiological conditions, PI3Kδ activity in B and T cells is dynamically regulated during development and function, with periods of enhanced activity where FOXO and GSK3 are inhibited and mTOR signaling occurs and periods of dampened activity when mTOR is not activated and FOXO/GSK3 are disinhibited. Balanced PI3Kδ activity results in proper lymphocyte development and function.[1-3] (**B**) In APDS, PI3Kδ is hyperactive, resulting in excessive FOXO/GSK3 inhibition and mTOR activation. As a result, lymphocytes do not develop properly, with a general excess of immature or senescent cells and a deficit of functional cells. This deficiency and dysregulation create or contribute to the constellation of clinical manifestations, namely, infections, lymphoproliferation, autoimmunity, enteropathy, bronchiectasis, and an increased risk of malignancy, particularly lymphoma. Patients with APDS may also display neurological or cognitive symptoms, liver disease, and atopy. It is unclear whether some symptoms may be due to PI3Kδ expression in nonimmune cells.[5-9] Please note that PI3Kδ activity levels depicted are for illustrative purposes only and do not represent actual data. *CMV,* Cytomegalovirus: *EBV,* Epstein-Barr virus.

completing 84 weeks or more of treatment (1 withdrew consent at week 36 for personal reasons). Across both parts of the study, aphthous ulcers and deranged liver function were the most common drug-related AEs, including a potentially drug-induced liver injury in 1 patient. One patient also experienced a severe AE of colitis.

The second oral, systemic PI3Kδ inhibitor trial was a 12-week, open-label, within-patient, dose-escalation study of patients with APDS (n = 6) that demonstrated leniolisib treatment inhibited hyperactive PI3Kδ, as assessed by pAKT and phosphorylated S6, ameliorated immune dysregulation, and increased patient well-being.[40] Based on the results of the dose-finding study, a phase 3, randomized 2:1, placebo-controlled trial of 70-mg leniolisib twice-daily was conducted in patients with APDS (n = 31).[41] Both primary end points—increase in the percentage of naive B cells and reduction in lymph node size—were met. Compared with placebo (n = 8), leniolisib (n = 18) significantly reduced lymphadenopathy by day 85, as measured by the decreased $\log_{10}$-transformed sum of product diameters of index lymph nodes ($P = .0006$), and secondary analyses revealed significant reductions in spleen size. Exploratory analyses of baseline cytopenias, which varied among patients and included patients with multiple cytopenias, showed 14 of 17 cytopenias (82%) improved or resolved in patients receiving leniolisib, whereas 3 of 5 (60%) improved or resolved in patients receiving placebo. However, this study was not designed to specifically assess leniolisib efficacy in cytopenias. Leniolisib (n = 8) significantly increased naive B-cell levels versus placebo (n = 5) by day 85 ($P = .0002$), meeting the other primary end point. Exploratory analyses revealed that leniolisib improved other key immune parameters, decreasing levels of IgM, transitional B cells, senescent T cells, and programmed cell death protein 1^+ T cells that are often elevated in APDS.[42] In addition, a reduction in the annualized infection rate by 0.351 ($P = .0040$) was seen in a *post hoc* interim analysis of an open-label extension study (n = 37) that followed patients with exposures up to 5 years (median, ~2 y).[43] During this extension study, immunoglobulin replacement therapy (IRT) use relative to baseline reduced in 10 of 27 patients (37%), including 6 who achieved IRT freedom, of whom 4 had been IRT-free for 1 to 2.5 years at the time of data cut-off in December 2021. The interim analysis also demonstrated durability of effect, with continued improvement in lymphadenopathy, splenomegaly, cytopenias, and regulation of immune cells.[43] Overall, the APDS studies show that leniolisib treatment changed molecular biomarkers and improved clinical manifestations, as well as a reduction in an existing prescribed

TABLE I. FDA-approved or formerly approved PI3Kδ inhibitors

Agent	Target	Current approvals	AEs	Withdrawals of approvals or NDA
Copanlisib (BAY 80-6946)[44]	Pan-PI3K inhibitor, but predominantly PI3Kα and PI3Kδ	Relapsed FL (2017; accelerated approval based on single-arm trial)	Warnings: infections, hyperglycemia, hypertension, noninfectious pneumonitis, neutropenia, and severe cutaneous reactions Other AEs: diarrhea, decreased general strength and energy, and nausea Laboratory abnormalities: leukopenia and thrombocytopenia	NDA for indolent NHL withdrawn December 2021 for additional analyses from ongoing trials[45]
Idelalisib (CAL-101, GS-1101)[46]	PI3Kδ	Relapsed CLL in combination with rituximab (2014)	Fatal and serious toxicities: hepatotoxicity, severe diarrhea or colitis, pneumonitis, infections, and intestinal perforations Warnings: severe cutaneous reactions, hypersensitivity reactions, and neutropenia Other AEs: pyrexia, fatigue, rash, cough, and nausea Laboratory abnormalities: ALT and AST elevations	Relapsed follicular B-cell NHL and relapsed SLL indications also granted accelerated approval based on single-arm trial in 2014, but voluntarily withdrawn February 2022 owing to inability to provide evidence to verify clinical benefit owing to enrollment challenges[47]
Duvelisib (IPI-145)[48]	PI3Kγ and PI3Kδ	Relapsed or refectory: CLL, SLL (2018)	Fatal and serious toxicities: infections, diarrhea or colitis, cutaneous reactions, and pneumonitis Warnings: hepatotoxicity and neutropenia Other AEs: rash, fatigue, pyrexia, cough, nausea, musculoskeletal pain, and anemia FDA drug safety communication June 2022 warning of possible increased risk of death and SAEs[49]	FL indication also granted accelerated approval based on single-arm trial in 2018, but voluntarily withdrawn December 2021 owing to inability to provide evidence to verify clinical benefit owing to trial feasibility issues and commercial reasons[50]
Umbralisib (TGR-1202)[51]	PI3Kδ and CK1ε	None	Warnings: fever, infection, neutropenia, diarrhea or noninfectious colitis, hepatotoxicity, severe cutaneous infections, allergic reactions due to inactive ingredient FD&C yellow No. 5, and embryo-fetal toxicity Other AEs: fatigue, nausea, musculoskeletal pain, anemia, thrombocytopenia, vomiting, abdominal pain, decreased appetite, and rash Laboratory abnormalities: increased creatine and transaminase elevation	Approval withdrawn: was granted accelerated approval based on single-arm studies for relapsed or refractory MZL or FL, both after specific prior therapies (2021). Withdrawn voluntarily by company in April 2022 and by FDA in June 2022 after FDA issued safety alert in February 2022 for possible increased risk of death after review of trial for CLL/SLL NDA[52,53]
Leniolisib (CDZ173)[41]	PI3Kδ	APDS (2023)	Other AEs: headache, sinusitis, and atopic dermatitis	None

CK1ε, Casein kinase 1 epsilon; *CLL,* chronic lymphocytic leukemia; *FDA,* U.S. Food and Drug Administration; *FD&C,* food, drugs, and cosmetics; *FL,* follicular lymphoma; *MZL,* marginal zone lymphoma; *NDA,* New Drug Application; *NHL,* non-Hodgkin lymphoma; *SLL,* small lymphocytic lymphoma.

TABLE II. Summary of AEs of approved or formerly approved PI3Kδ inhibitors when administered as monotherapy for malignancies and leniolisib when administered for APDS*

Measure	Copanlisib (n = 244)[45,†]	Idelalisib (n = 146)[45,‡]	Duvelisib (n = 442)[45,§]	Umbralisib (n = 371)[45,‖]	Leniolisib (n = 38)¶
Median exposure (mo), n (range)	4.3 (0.2–47.2)	6.1 (0.3–26.4)	9.0 (0.1–53.0)	5.9 (0.1–75.1)	23.6 (2.8–60.3)
Toxicity (%)					
Death due to drug-related AE	4	5	4	1	0
Grade ≥ 3 AE	85	71	84	51	29
SAE	51	50	65	26	21
AEs of special interest (%)					
Grade ≥ 3 infection	23	23	27	20	5
Grade ≥ 3 neutropenia#	29	28	43	17	13
Grade ≥ 3 diarrhea/colitis	5	14	23	7	3
Grade ≥ 3 ALT/AST increase#	2	18	8	7	11**
Grade ≥ 3 rash	2	4	9	3	0
Any grade pneumonitis	7	5	7	1	0
Actions due to any AE (%)					
Discontinuation	24	23	35	15	3
Dose reduction	24	41††	23	10	0
Dose interruption	64	41††	64	45	13

DLBCL, Diffuse large B-cell lymphoma; *FL,* follicular lymphoma; *IV,* intravenously; *LPL,* lymphoplasmacytic lymphoma; *MZL,* marginal zone lymphoma; *RCT,* randomized controlled trial; *WM,* Waldenström macroglobulinemia.

*Cross-trial comparisons of safety are not intended.

†n includes 52% FL, 11% MZL, 9% DLBCL, 5% CLL, 4% MCL, 4% SLL, 3% LPL/WM, and 12% other hematological malignancies. Copanlisib was administered 60 mg IV on d 1, 8, and 15 of a 28-d treatment cycle.

‡n includes 60% FL, 21% SLL, 11% MZL, and 8% LPL. Idelalisib was administered orally 150 mg twice-daily in a 28-d treatment cycle.

§n includes 64% CLL, 22% FL, 9% SLL, 4% MZL, and 1% other hematological malignancies. Duvelisib was administered orally 25 mg twice-daily in a 28-d treatment cycle.

‖n includes 40% FL, 22% MZL, 20% DLBCL and MCL, 12% CLL or SLL, and 6% other hematological malignancies. Umbralisib was administered orally 800 mg once-daily in a 28-d treatment cycle.

¶n includes data from a dose-finding study, RCT, and open-label extension. Leniolisib was administered orally 10, 30, or 70 mg twice-daily for 4 wk each in the dose-finding study, 70 mg twice-daily for 85 d in the RCT, and 70 mg twice-daily for ≥ 5 y in the open-label extension.

#Based on analysis of laboratory data.

**Based on investigator-reported grade 3 AEs.

††A dose reduction or interruption due to an AE occurred in 41% of patients.

therapy. In March 2023, leniolisib received U.S. Food and Drug Administration approval for the treatment of APDS in adults and children 12 years of age and older.[41]

Across all 3 studies, leniolisib was well tolerated, and the severe AEs observed with other PI3Kδ inhibitors used to treat malignancy were not seen with leniolisib treatment in patients with APDS (Tables I and II). In the dose-escalating study (n = 6), leniolisib was well tolerated at all doses, with no significant neutropenia, hypertriglyceridemia, hyperglycemia, gastrointestinal disturbances, skin rashes, or liver toxicity reported.[40] In the phase 3 randomized trial (n = 31), study drug–related AEs occurred in 8 patients across both the leniolisib (23.8%) and the placebo (30.0%) arms. Leniolisib-related AEs included transient alopecia (n = 2), aphthous ulcer, taste disorder, vomiting, and vertigo (all n = 1); none were serious. In total, 5 patients reported a serious adverse event (SAE), with none judged as related to study medication. Leniolisib remained well tolerated in the open-label extension study (n = 37).[43] Study drug–related AEs, including weight increase (n = 3), arthralgia, hyperglycemia, and decreased neutrophil count (all n = 1), occurred in 5 patients. The SAEs occurred in 6 patients; none were related to leniolisib treatment. Including non–drug-related AEs, 86.5% of patients with up to 5 years of exposure experienced an AE, 78.4% of which were grade 1 and none of which were grade 4. Across all 3 studies, no discontinuations or interruptions of leniolisib occurred due to treatment-related AE. One death occurred in a patient who had significant baseline comorbidities, including cardiomyopathy, tachycardia, recurrent pneumonia, necrotizing lymphadenitis, disseminated *Mycoplasma* infection, bronchiectasis, pancytopenia, liver disease, and peripheral edema. This patient experienced cardiac arrest resulting in death, determined not related to study drug, at extension day 879.

Skin rash is a known class effect of PI3Kδ inhibitors used for malignancy. Notably, only 1 patient in the leniolisib APDS phase 3 study reported skin rash (grade 1 maculopapular rash), which was deemed fungal and not related to leniolisib by the investigator. Severe gastrointestinal AEs can occur with use of other PI3Kδ inhibitors over time. In the open-label extension study, none were reported related to study treatment, and 85.3% of gastrointestinal AEs that did occur were grades 1 and 2. Furthermore, 10 of the 15 patients in whom these occurred had a prior history of gastrointestinal disease. Transaminitis is another effect of PI3Kδ inhibition. While grade 3 or higher aspartate aminotransferase/alanine aminotransferase (AST/ALT) increase ranged from 2% to 18% with inhibitors used for malignancy, 11% (n = 4) of patients receiving leniolisib had transaminitis. For 3 of these patients, increased AST/ALT resolved; the last patient died from cardiac arrest while levels were elevated. Notably, laboratory values were used to determine grade 3 or higher AST/ALT increase for the malignancy treatments,[45] whereas investigator reports were used for leniolisib.

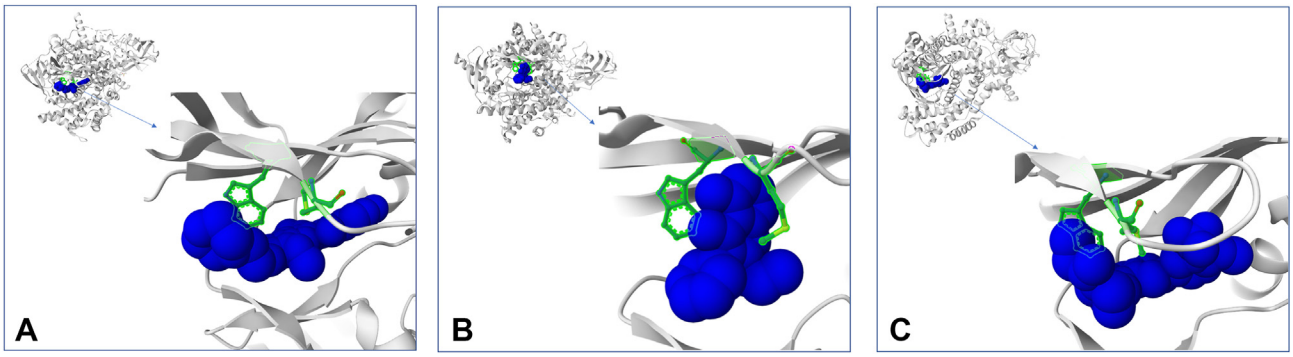

FIGURE 2. Leniolisib binds PI3Kδ differently than other approved inhibitors. (**A**) Copanlisib, a flat, pan-PI3K inhibitor, bound to p110γ. Copanlisib does not wedge between Met804 and Trp812 (lime green), equivalent to Met752 and Trp760 in p110δ, which form the specificity pocket. *PDB ID,* Protein Data Bank identification: 5G2N.[64,68] (**B**) Idelalisib, a propeller-shaped PI3Kδ-specific inhibitor, bound to p110δ. Idelalisib wedges between Met752 and Trp760 (lime green) to open the specificity pocket to achieve specificity for PI3Kδ. PDB ID: 4XE0.[62,69] (**C**) Leniolisib, a PI3Kδ-specific inhibitor, bound to p110δ. Whereas leniolisib does not open the specificity pocket formed by Met752 and Trp760 (lime green), it achieves selectivity by stacking with Trp760, which forms a tryptophan shelf. PDB ID: 5O83.[66,70] *Blue,* Inhibitor; *gray,* p110 protein; *lime green*, key residues. *Dashed lines* indicate hydrogen bonds. (Images from the Research Collaboratory for Structural Bioinformatics PDB [rcsb.org]).

TABLE III. PI3K isoform selectivity of leniolisib vs other (previously) approved PI3Kδ inhibitors

	Biochemical IC_{50} (nM)				
Agent	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ	δ/γ ratio
Copanlisib[72]	0.5	3.7	6.4	0.7	0.1094
Idelalisib[71]	820	565	89	2.5	0.0281
Duvelisib[73]	1602	85	27	2.5	0.0926
Umbralisib[76]	>10,000	1116	1065	22	0.0207
Leniolisib[66]	244	424	2230	11	0.0049

IC_{50}, Half-maximal inhibitory concentration; *PI3Kδ,* phosphoinositide 3-kinase δ.

Severe neutropenia has also been observed with PI3Kδ inhibitor use for malignancies. Across all leniolisib APDS trials (n = 38), transient neutropenia developed in 14 patients: mild ($1.0-1.5 \times 10^9$/L) in 9 patients and moderate ($0.5-1.0 \times 10^9$/L) in 5 patients. In all cases, neutropenia resolved without leniolisib withdrawal. No unresolved or severe infections were concurrent with the neutropenias. Notably, grade 3 neutropenia was observed in 13% of patients, whereas grade 3 or higher neutropenia has been observed in 17% to 43% of patients receiving other PI3Kδ inhibitors for malignancies.[45] Neutropenia has also been observed in healthy volunteers receiving leniolisib (unpublished data). In these studies (leniolisib, n = 118; placebo, n = 70), mean absolute neutrophil count (ANC) remained within normal limits. In the 70-mg twice-daily group, small mean reductions in ANC were observed post-dosing over a 2-week period, with means ranging from 2.66 to 3.17×10^9/L (n = 15–22). Only 3 individuals in this group had levels below normal limits, and only a single ANC was below 1×10^9/L (0.9×10^9/L on d 15; repeat assessment read 1×10^9/L).

IMPACT OF THE PROPERTIES OF PI3Kδ INHIBITORS ON AEs

The causes of PI3Kδ inhibition–associated AEs in APDS and malignancies are poorly understood (Table I).[44,46,48,51,54] These AEs may be due to on-target effects of the agents, and reductions in dosage or cessation of treatment until resolution is advised when treating malignancy.[46,55,56] For instance, autoimmune AEs seen with idelalisib, such as colitis, hepatotoxicity, transaminitis, and pneumonitis, may be mediated by reduced suppressive functions of regulatory T cells leading to a cytotoxic $CD8^+$ T-cell response, as revealed by *ex vivo* human cell models.[57] Another *ex vivo* human cell model suggested neutropenia may be due to inhibition of neutrophil polarization and directional migration, although the precise mechanism leading to neutropenia is unknown.[58] PI3Kδ inhibition potentially contributing to genomic instability has been noted in 1 study of *ex vivo* mouse B cells via increased expression of activation-induced cytokine deaminase (AID).[59] Those experiments were performed in cells not exhibiting the hyperactive PI3Kδ pathway activation seen in APDS; thus, PI3Kδ inhibitor use did not normalize, but rather bluntly suppressed, pathway activity. In fact, B cells expressing the APDS E1021K *PIK3CD* variant showed decreased AID expression and chromosomal translocations, suggesting that use of PI3Kδ inhibitors in patients with APDS may not increase AID to harmful levels.

Toxicities and increased rates of death from other PI3Kδ inhibitors have led to voluntary withdrawal of New Drug Applications and approved malignancy indications (Table I).[45,47,49,50,52,53,60] Many initial malignancy approvals were accelerated and based on single-arm studies. Post-marketing randomized trials revealed SAEs, and increased rates of death led

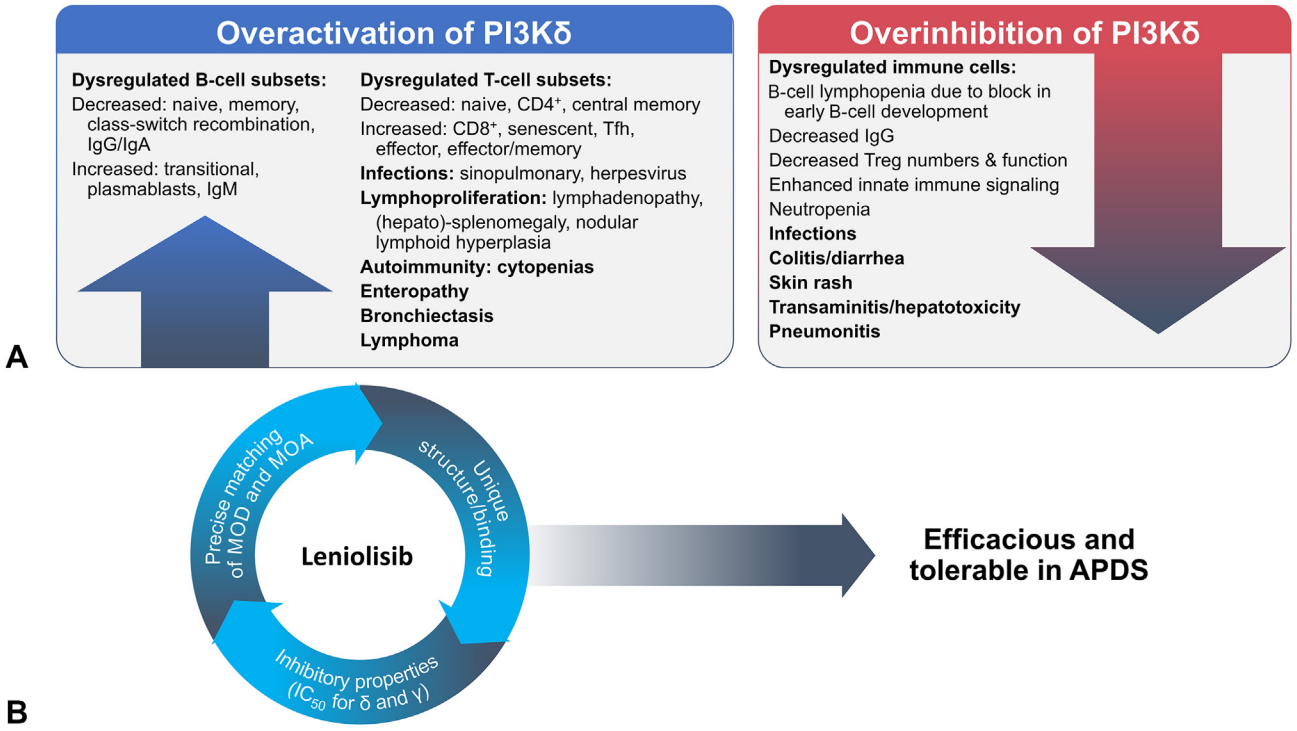

FIGURE 3. Tightly balanced PI3Kδ signaling is required for proper immune development and drug tolerability. (**A**) Both overactivation of PI3Kδ (as seen in APDS) and overinhibition of PI3Kδ (as seen with inhibitor AEs and in patients with PI3Kδ loss-of-function) can disrupt the immune system and result in immune manifestations, highlighting the need for tightly balanced signaling.[55,77,78] (**B**) Leniolisib may be effective and tolerable in APDS by reducing continuous PI3Kδ hyperactivation without overinhibiting the kinase, which may result from lower affinity for the δ isoform than other U.S. Food and Drug Administration (FDA)–approved inhibitors. These inhibitory properties and improved specificity may be due to the unique structure and binding method of leniolisib, which additionally largely spares the γ isoform to avoid off-target immune effects. Combined with precise matching of leniolisib mechanism of action (MOA) with APDS mechanism of disease (MOD), these features may explain why leniolisib demonstrated efficacy and tolerability in the APDS trials. *Tfh,* T-follicular helper cell.

to voluntary withdrawals. Other voluntary withdrawals resulted from additional analyses of ongoing trials, enrollment challenges, or decisions not to pursue further trials.[45,47,49,50,52,53] Consequently, the U.S. Food and Drug Administration is encouraging dose-finding studies, and intermittent dosing schedules are being investigated for many agents.[45] Intermittent dosing regimens in mouse models have recently shown reductions in immune-mediated AEs.[61] These data suggest that excessive inhibition of PI3K activity disrupts homeostasis via PI3Kδ *hypo*activation and yields on-target adverse effects.

In addition, the level of inhibition may be influenced by the chemical structure of the inhibitors (Figure 2). Many PI3Kδ inhibitors, including idelalisib, duvelisib, and umbralisib, are propeller-shaped.[55] They achieve their selectivity by wedging between Met752 and Trp760 in the active site of the catalytic domain of p110δ to open what is known as a specificity pocket.[62,63] In contrast, multi- and pan-selective class I PI3K inhibitors with a flat conformation such as copanlisib do not bind the specificity pocket.[63,64,65] Leniolisib is structurally unique relative to other approved PI3Kδ inhibitors; it is not propeller-shaped. Instead of binding to the specificity pocket, leniolisib uses a tryptophan shelf and stacks with Trp760 in p110δ, whereas the corresponding interaction with Trp780 in p110α is prevented, thus conferring specificity for the δ isoform.[66,67]

On an equimolar basis, leniolisib is less chemically potent at inhibiting PI3Kδ than approved inhibitors targeting PI3Kδ (Table III).[66,71-73] In cell-free assays, the half-maximal inhibitory concentration (IC_{50}; where a lower value indicates that a lower concentration of drug is needed to inhibit 50% of the response) of leniolisib was higher than that of idelalisib, duvelisib, and copanlisib. In addition, leniolisib appears to be much more specific to the δ isoform than the γ isoform, unlike idelalisib, which also appears to inhibit γ, and duvelisib, which is a γ/δ inhibitor. Because both the γ and the δ isoforms are expressed in immune cells, some side effects of idelalisib treatment may be due to dual inhibition.[55,74] Although umbralisib does not appear to bind γ and binds δ less potently than leniolisib, it is also an inhibitor of casein kinase 1 epsilon, which may contribute to AEs. Of note, although seletalisib's IC_{50} for PI3Kδ is similar to that of leniolisib at 12 nM, its IC_{50} for the γ subunit is much lower at 282 nM (compared with leniolisib's 2,230 nM), and the corresponding δ/γ ratio is 0.0426 versus 0.0049 for leniolisib, which may contribute to the differences in outcomes between seletalisib and leniolisib in APDS.[66,75]

The overall lack of toxicity observed with leniolisib treatment in patients with APDS may highlight the benefit of fine-tuning rather than blocking PI3Kδ signaling, because both hyperactive and hypoactive signaling can result in immune deficiency and

dysregulation.[30,41,55,77,78] The unique pathomechanism of APDS, combined with a higher IC_{50} for the δ and γ isoforms than other PI3Kδ inhibitors, may enable leniolisib to generate better balance of high and low activity necessary for appropriate immune cell development and function in patients with APDS (Figure 3).

LENIOLISIB IN OTHER CONDITIONS

Although 70-mg leniolisib twice-daily appears to be safe and effective in APDS, leniolisib at that dose may not be appropriate for conditions in which hyperactive PI3Kδ is involved in, but not the cause of, disease. For instance, in a randomized, double-blind, phase 2 trial for primary Sjögren syndrome (pSS; n = 30), 70-mg leniolisib twice-daily was not effective, and although it had an acceptable safety and tolerability profile, skin rashes occurred in 11 of 20 patients.[79,80] The pSS is an autoimmune condition characterized by B-cell hyperactivation, and although PI3Kδ hyperactivity is observed in patients with pSS, it is not the mechanism of disease.[81,82] Dose range finding will be important in indications in which the level of PI3Kδ activity may be different from that in APDS.

FUTURE DIRECTIONS AND OUTSTANDING QUESTIONS

In APDS, leniolisib normalizes PI3Kδ activity, thereby modifying disease activity through restoring immune function. In the absence of easy ways to measure cellular PI3K activity, it is difficult to know whether PI3Kδ activity is completely normalized. A commercially accessible method to monitor pAKT or other markers of pathway activity or inhibition would be helpful.

The impact of long-term leniolisib use is being investigated. A small number of patients in the APDS open-label extension study have been receiving leniolisib for longer than 6 years with good long-term tolerability. Patient registries such as the European Society for Immunodeficiencies level 3 APDS registry will also be able to provide long-term data on lung function, vaccine responses, and IRT use. The effects of leniolisib on pregnant women, their fetuses, nursing children, and pediatric populations in general also require further study. A pediatric trial is recruiting (NCT05438407).

The emergence of drug resistance is not uncommon in this class of inhibitors when used to treat malignancy and remains to be studied in leniolisib; however, we suspect this concern may be specific to cancer, because in APDS, PI3Kδ hyperactivity is the result of germline variants, whereas cancers can co-opt other non-PI3Kδ pathways to survive.

Because PI3Kδ hyperactivity is not unique to APDS, the potential to use leniolisib, likely with different dosing, in other disease states, needs exploration. Indications to evaluate include those for which mTOR inhibitors are used, because leniolisib targets molecules further upstream in the PI3K-AKT-mTOR pathway. As discussed for pSS, the precise mechanism of PI3Kδ inhibition in these diseases needs careful consideration. The utility of leniolisib in patients with lymphoma who have increased PI3Kδ activity but no germline variants is unknown.

In conclusion, an unmet need exists for PI3Kδ inhibitors that are effective and tolerable in diseases driven by hyperactive PI3Kδ signaling, such as APDS. Leniolisib demonstrates disease-modifying properties in APDS, and by virtue of its novel structure, selectivity, and inhibitory properties, it may confer a more tolerable safety profile than other PI3Kδ inhibitors, particularly when the levels of inhibition by leniolisib are precisely matched to the level of PI3Kδ hyperactivity.

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