

PI3K δ inhibition treatment of APDS: efficacy, safety and tolerability of targeted therapy with leniolisib

Review

Alberto Tommasini^{1,2}, Caterina Cancrini^{3,4}, Antonino Trizzino⁵,
Valentina Drago⁶, Francesca Lazzara⁷, Chiara Bianca Maria Platania⁷,
Vassilios Lougaris⁸

¹ Department of Medical Sciences, University of Trieste, Trieste, Italy; ² Institute for Maternal and Child Health, IRCCS Burlo Garofalo, Trieste, Italy; ³ Research Unit of Primary Immunodeficiency, IRCCS Bambino Gesù Children Hospital, Rome, Italy; ⁴ Department of System Medicine University of Rome Tor Vergata, Rome Italy; ⁵ Department of Pediatric Hematology and Oncology, ARNAS Ospedali Civico Di Cristina Benfratelli Hospital, Palermo, Italy; ⁶ S.C.F. Studio di Consulenza Farmacologica s.r.l. unipersonale, Catania, Italy; ⁷ Department of Biomedical and Biotechnological Sciences, University of Catania, Italy; ⁸ Pediatrics Clinic, Department of Clinical and Experimental Sciences, University of Brescia, Azienda Socio Sanitaria Territoriale Spedali Civili di Brescia, Brescia, Italy

SUMMARY

PI3K δ Activation Syndrome (APDS) is a rare congenital immunodeficiency caused by mutations that result in hyperactivation of the PI3K δ signaling pathway. The persistent activation of the AKT/mTOR signaling pathway leads to impaired survival, proliferation and activation of both B and T lymphocytes. There are two genetic forms of APDS, associated with autosomal dominant transmission. APDS patients face recurrent bacterial and viral infections, frequent respiratory symptoms due to infections or bronchospasm, and persistent benign lymphoproliferations (lymphadenopathies and hepatosplenomegaly) with a high risk of develop lymphomas and/or autoimmune diseases (e.g. cytopenia). APDS treatments are similar to those implemented in management of immunodeficiencies, such as immune prophylaxis and antimicrobial therapies, administration of replacement immunoglobulins and various anti-inflammatory and immunosuppressive drugs. Several PI3K δ inhibitors have been evaluated in clinical trials for the treatment of APDS, but only leniolisib has been approved by the FDA (March 2023) as an orphan drug for APDS due to its good efficacy, safety and tolerability profile. Leniolisib has the high potential to be disease modifying drug for the treatment of APDS patients, also considering its pharmacodynamic properties (selectivity for the δ isoform of PI3K). Further studies and clinical trials have been performed and are ongoing to confirm the long-term effect and safety profile of the drug. Preliminary results show positive data in terms of efficacy, safety and long-term tolerability.

KEYWORDS: leniolisib, PI3K, APDS, immune system

INTRODUCTION

Inborn Errors of Immunity (IEI), or Primary Immunodeficiencies (PID), are a heterogeneous group of diseases caused by mutations in genes encoding proteins with essential functions in the immune system (IS). Although these diseases are rare, the disease's consequences and clinical management is associated to high direct and indirect costs, representing a problem for the sustainability of the healthcare system^{1,2}. PIDs are a group of immune system inherited/

Received: July 23, 2024
Published: January 21, 2025

CORRESPONDENCE

Valentina Drago
valentinadrage@essecieffe.it

How to cite this article: Tommasini A, Cancrini C, Trizzino A, et al. PI3K δ inhibition treatment of APDS: efficacy, safety and tolerability of targeted therapy with leniolisib. Italian Journal of Pediatric Allergy and Immunology 2024;38(04):8-14.
<https://doi.org/10.53151/2531-3916/2024-588>

© Copyright by Italian Society of Pediatric Allergy and Immunology



OPEN ACCESS

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-Non-Commercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: <https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>

congenital diseases, now defined as congenital errors of immunity (IEI), which are characterized by a broad spectrum of clinical manifestations that include, infections susceptibility, and manifestations of immune dysregulation, such as allergy, autoimmunity, autoinflammation, and lymphoproliferation. Approximately, 485 genetic defects associated with IEI are currently known^{3,4}. IEIs are generally diagnosed in childhood, and these diseases are rare (approximate prevalence of 1:10,000), with the exception of immunoglobulin A deficiency (Selective IgA Deficiency, SIgAD), which is found in approximately of every 500 individuals⁵. However, the discovery of new immunodeficiencies and better clinical evaluation of patients has allowed to re-evaluate the frequency of these pathologies, currently considered around 1:1000-1:5000⁶. In severe and combined forms, early diagnosis is crucial for the efficacy of treatment, before the onset of complications or organ damage which characterize disease progression. A delay in diagnosis, and thus delayed correct treatment and prophylaxis, can lead to the development of complications (such as bronchiectasis or chronic otitis/sinusitis), persistent autoimmune manifestations and uncontrolled progression of the lymphoproliferative disease.

Phospholipase 3-kinases delta (PI3K δ) is composed of a catalytic unit p110 δ expressed mainly in lymphocytes, and a ubiquitous p85 α regulatory subunit. APDS (activated PI3K δ syndrome) is a rare disorder due generally to autosomal dominant mutations in one of the two genes encoding for the two subunits. However, autosomal recessive cases have been described, in a total of three relatives⁷.

PI3K δ proteins are crucial for the activation of the PI3K-Akt-mTOR signaling pathway, which is involved in several cellular processes such as metabolism, proliferation, cell survival, differentiation^{8,9}. PI3Ks are heterodimeric proteins consisting of two subunits, a regulatory p85 α and a catalytic p110. The latter has four isoforms (α , β , γ , δ): α and β isoforms are expressed in most cells in the body, while γ and δ isoforms mainly in cells of the immune system. In particular, δ is expressed in B and T lymphocytes, natural killer (NK) cells and monocytes. The most frequent mutations responsible for APDS are localized in the PIK3CD gene, which encodes for the p110 δ catalytic subunit, and those in the PIK3R1 gene, which encodes for the p85 α regulatory subunit. These two mutations characterize respectively: APDS1 (75% of cases) with a kinase hyperactivation, gain of function (GOF) mutation in the PIK3CD gene, and APDS2 (25% of cases) characterized by a loss of function (LOF) of the p85 α subunit, resulting in PI3K δ hyperactivity^{10,11}. There is another germline mutation that induces a syndrome defined as APDS-like, i.e. a LOF related to the activity of phosphatase PTEN (phosphatase and tensin homolog), a phosphatase that does not hydrolyze PIP₃ leading to the activation of AKT^{12,13}. In March 2023, the Food and Drug Administration (FDA) approved leniolisib as an orphan drug for APDS, which inhibits PI3K δ ¹⁴.

The most frequent infections in APDS patients include bacterial infections by *Streptococcus pneumoniae* and *Haemophilus influenzae*^{15,16}. In addition to respiratory infections, patients can be exposed to infections of other organs or systems (eyes, skin, lymph nodes (lymph node abscesses), digestive system (gastroenteritis)), up to severe systemic infections. In addition, viral infections with

Cytomegalovirus (CMV) and Epstein Barr (EBV) can have chronic course in APDS individuals. The chronic replication of EBV in B lymphocytes may favor the development of lymphomas in the long term^{13,17}. In particular, 13% of patients with APDS are prone to develop forms of lymphomas^{15,16,18}. Autoimmune manifestations are also frequent in APDS, such as autoimmune hemolytic anemia or plateletopenia.

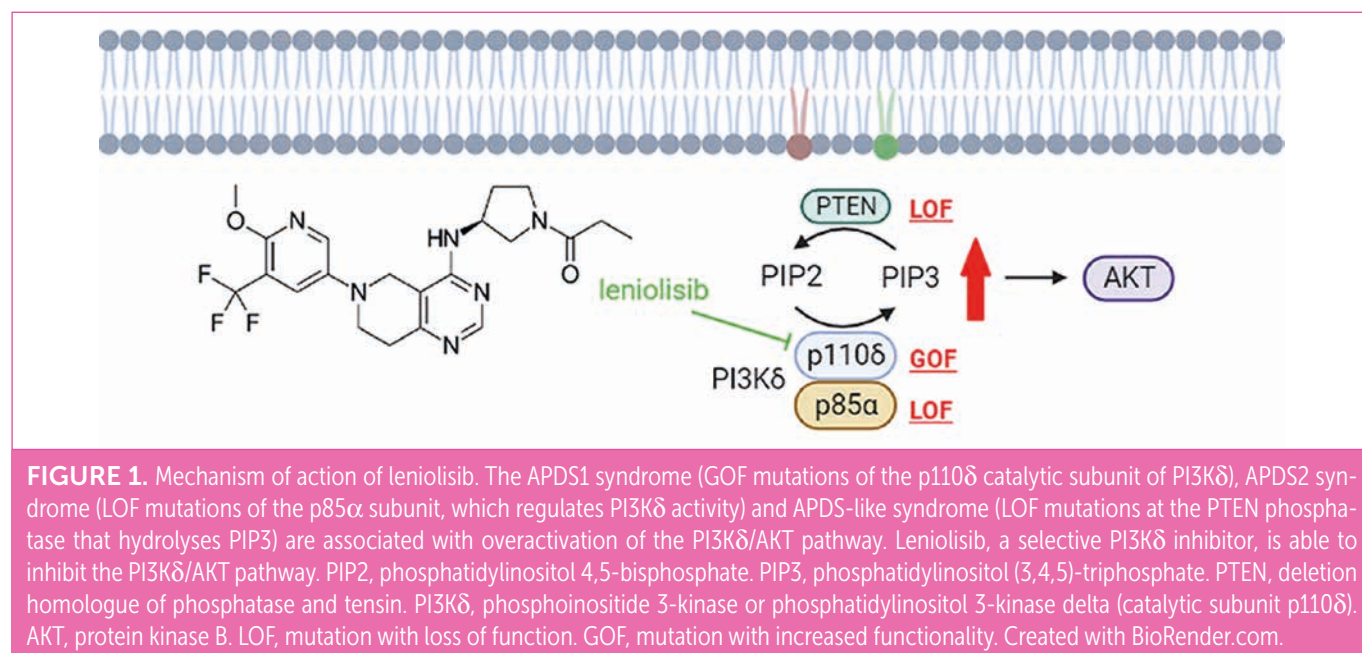
The alteration of the PI3K signaling pathway affects the activation of several molecular targets, including AKT, mTOR, which regulate the differentiation and activity of B and T lymphocytes^{19,20}. Hyperactivation of PI3K δ leads to a reduction in the number of naïve T lymphocytes (both CD4+, T_{helper} and CD8+, T_{cytotoxic}) and increases the proportion of mature T lymphocytes. On the other hand, B lymphocytes remain immature, thus unable to produce immunoglobulins. For these reasons, the immune system in APDS patients is inefficient against infections, given the lack of antibodies (by mature memory B lymphocytes) against antigens, as in the case of autoimmune diseases^{10,17,21}. On the other hand, is possible to find high levels of IgM (produced by immature B lymphocytes) combined with low levels of IgG and IgA (hypogammaglobulinemia). Furthermore, PI3K δ hyperactivation results in hyperproliferation of immature lymphocytes and consequently enlarged lymph nodes (lymphadenopathy)^{15,22,23}.

TREATMENTS FOR APDS

APDS treatment, as for many immunodeficiencies, includes immunosuppressive therapies in order to prevent and treat both bacterial or viral infections, due to the immune deficiency and autoimmune processes^{24,25}. Scientific research has shown that some molecules are effective in reducing the pathological aspects of APDS, as in the case of rapamycin, an mTOR inhibitor, which reduces lymphoproliferation, but which is less effective on other APDS clinical manifestations, such as cytopenias and inflammatory bowel disease²⁴. Moreover, its long-term use at immunosuppressive doses (higher than those used for lymphoproliferative diseases) has been associated with several adverse effects, such as insulin resistance; the target of rapamycin (mTOR) is also involved in the insulin and growth hormone signaling pathway^{13,26}. As mentioned above, the designation of leniolisib as an orphan drug by the FDA²⁷ has revolutionized the treatment of APDS, as this molecule can selectively modulate the hyperactivation of PI3K δ in APDS1 and APDS2 (Fig. 1). Treatment with leniolisib is effective and well-tolerated on the clinical manifestations of the disease and some of its immunological markers^{13,28-30}.

Leniolisib pharmacodynamics and pharmacokinetics

Leniolisib reduces PI3K δ activity by occupying the ATP-binding site on the catalytic site of the p110 δ subunit³⁰. The binding affinity of leniolisib for the PI3K δ isoform is higher than the affinity for the other isoforms: PI3K α subunit (28-fold), β (43-fold) and γ (257-fold)³¹. *In vitro* studies have shown that leniolisib significantly reduces AKT phosphorylation and thus its activation, inhibiting proliferation of B



and T lymphocytes²⁸. By reducing PIP₃ production and regulating the activation of the entire mTOR/AKT pathway, leniolisib is able to reduce the dysregulation of B- and T-cells induced by PI3Kδ hyperactivation. In this way, it has an effect on other cells of the innate immune system, such as neutrophils, monocytes, macrophages³². The systemic drug concentration increases in a dose-dependent manner (AUC and C_{max}); two daily doses (oral administration, 70 mg in adults) are administered every 12 hours, and steady-state (steady-state concentration, C_{ss}) is reached after approximately two/three days. Maximum drug concentration in the blood is reached one hour after administration (T_{max}). Leniolisib binds 94.5% to plasma proteins and the apparent distribution volume is estimated to be 28.5 liters in APDS patients. Approximately 60% of the drug is metabolized by the liver; mainly by CYP3A4 (94.5%), CYP1A2 (0.7%) and CYP2D6 (0.7%). The half-life of leniolisib is approximately 7 hours³³. The selectivity profile of leniolisib towards the different PI3K isoform, which has been accounted to its chemical structure, different from other PI3Kδ inhibitors, which characterizes different interaction modes at the ATP pocket of PI3K^{32,34–37}.

Safety and tolerability of leniolisib

Adverse events associated with pan-PI3K inhibitors are neutropenia, hypertriglyceridemia, hyperglycemia, diarrhea/colitis, and liver problems^{38,39} as well as cardiotoxicity^{40,41}. The most serious adverse events have been associated with inhibition of all four isoforms α, β, δ, γ or in the case of inhibitor therapy (Copanlisib, Idelalisib, Duvelisib, Umbralisib) with a reduced selectivity for the δ isoform^{42,43}. In contrast, leniolisib shows a good safety profile in APDS patients⁴². Notably, the results of the clinical trials NCT02435173

and NCT02859727 show that leniolisib is well tolerated; no adverse events were observed, which are detected with other PI3K inhibitors used for treatment of blood cancers^{28–30}. The trial NCT02435173 included two different designs, referred to part I and part II. Part I included 6 APDS patients in a non-randomized, open-label, dose-finding trial (DFT) design²⁸. Part II had a randomized, controlled study design with a fixed dose of leniolisib (randomized, investigator and sponsor-blinded, placebo-controlled, 70 mg b.i.d.); 31 patients were recruited, including the 6 from part I²⁹. In part I of NCT02435173, no signs of toxicity or serious side effects were observed in the 6 patients recruited and treated with leniolisib (n = 6 patients with the GOF mutation, PIK3CD gene)²⁸. No side effects were observed on the 6 patients, who were subsequently included in part II of the same trial. Rao et al., 2023²⁹, reported the results of part II of the NCT02435173 trial, which included a 12-week treatment with 70 mg leniolisib (o.s., b.i.d.) in the experimental arm. In all, 31 patients with APDS were randomized into two arms: 21 patients treated with leniolisib and 10 patients in the placebo group. In part II of NCT02435173, minor adverse events were reported in 85% of APDS patients treated with leniolisib and in 90% of APDS patients in the placebo group. Drug-related adverse events were reported in 8 patients, with a lower incidence in the leniolisib group (23%) compared to the placebo group (30%). Five patients reported serious adverse events, but none of these were considered to be associated with leniolisib. Skin rash and neutropenia, two of the side effects observed during treatment with PI3K inhibitors used for hematological tumors (idelalisib⁴⁴, duvelisib⁴⁵), were recorded in a very low percentage of APDS patients treated with leniolisib and, if present, were mild and not severe. Grade 1 maculo-papular

TABLE I. PI3K isoform selectivity of leniolisib vs other PI3K δ inhibitors ⁴¹.

Inhibitors	IC ₅₀ (nM)				
	PI3K α	PI3K β	PI3K γ	PI3K δ	δ/γ ratio
Copanlisib	0.5	3.7	6.4	0.7	0.1094
Idelalisib	820	565	89	2.5	0.0281
Duvelisib	1602	85	27	2.5	0.0926
Umbralisib	> 10,000	1116	1065	22	0.0207
Leniolisib	244	424	2230	11	0.0049

IC₅₀: Inhibitory Concentration 50.

rash was recorded in one leniolisib-treated patient, while mild neutropenia, with spontaneous resolution, was recorded in 4 of 21 leniolisib-treated patients ²⁹. Subsequently, the patients involved in part I (dose-finding trial, DFT) and part II (fixed-dose, randomized controlled trial, RCT) (NCT02435173) were involved in an extension trial (NCT02859727), currently ongoing, involving monitoring of patients with maximum exposure to leniolisib for 5 years (open-label extension, single arm extension study; n = 37 patients with APDS) ³⁰. Adverse events were reported in 32 of the 37 patients, and the majority (85.3%) were grade 1 or 2. The most common events were respiratory tract infection (9 patients), migraine (6 patients), external otitis (5 patients), COVID-19 (5 patients), pyrexia (6 patients) and weight gain (5 patients). Additionally, 15 patients reported gastrointestinal problems, 10 of whom had an history of gastrointestinal disorder. Serious adverse events (SAEs) such as vomiting, colitis, sinusitis and abdominal pain were also reported during the trial, but none of these were definitively associated with leniolisib treatment ³⁰.

The causes of the serious adverse events, related to therapy with the PI3K inhibitor class, have been attributed to excessive inhibition of the activity of the PI3K isoforms. This inhibition may result in the disruption of the immune system and PI3K/AKT/mTOR signaling pathways, leading to SAEs ⁴², as reported in hematological patients treated with PI3K inhibitors. An *ex vivo* study on human cells showed that some adverse events related to PI3K inhibition, linked to autoimmune conditions such as colitis or hepatotoxicity, can be determined by the reduced activity of regulatory T cells (T_{reg}), leading to an increased activation and response of CD8⁺ T cells (T_{killer}) ⁴⁶. Another *ex vivo* study, performed in mouse B lymphocytes, demonstrated a relationship between total inhibition of PI3K δ and the over-expression of the AID enzyme (activation-induced cytidine deaminase), a specific enzyme which is crucial for the appropriate production of functional antibodies. A preclinical study has shown that some PI3K δ inhibitors (idelalisib, duvelisib) may increase genomic instability of B cells due to AID upregulation, leading to an increased risk of lymphoma ⁴⁷. However, no data regarding the long-term use of leniolisib are available, but it may lead to low grade adverse events, given its lower

potency toward the PI3K δ isoform (IC₅₀ = 11 nM), compared to high potency PI3K δ inhibitors such as idelalisib (IC₅₀ = 2.5 nM) and duvelisib (IC₅₀ = 2.5 nM) (Tab. I).

Leniolisib and comparison with other PI3K inhibitors

Idelalisib was one of the first PI3K inhibitors whose activity was evaluated both *in vitro* (leukemic patient samples) and *in vivo*, patients with lymphoma. The data demonstrated effective inhibition of all PI3K isoforms, with a poor safety profile characterized by drug-associated adverse events, such as severe neutropenia and increased risk of infections, in oncological patients ⁴⁸⁻⁵⁰. Other inhibitors have been evaluated in the context of APDS, such as nemoralisib. This molecule showed interesting results in animal models, reducing *S. pneumoniae*-induced mortality ⁵¹. However, an open-label, phase II study (NCT02593539) in patients with APDS showed no efficacy and some adverse events that were considered tolerable; accordingly, no further studies were carried out ⁵². In contrast, seletalisib (UCB5857) showed encouraging results, with significant efficacy in APDS, but serious adverse events (liver and kidney dysfunction) were reported in a phase 1b trial (7 recruited APDS patients; European Clinical Trials Database 2015-002900-10) and in the extension study (4 recruited patients, of which 3 completed the study; European Clinical Trials Database 2015-005541) ^{53,54}.

In conclusion, looking at the efficacy and safety profile of leniolisib, the clinical reports on this drug are promising. Both the first clinical trial (NCT02435173) and the extension study (NCT02859727) showed significant efficacy and good tolerability in all patients exposed to the treatment. Typical disease symptoms and clinical signs, such as infection, lymphoproliferation (lymphadenopathy, splenomegaly), cytopenia and immune system alterations were significantly reduced in leniolisib treated APDS patients, along with reduction of lymph node and spleen size. Moreover, reduced levels of CD8⁺ senescent T cells and IgM were detected in leniolisib treated APDS patients ³⁰.

Pharmacodynamic profile of leniolisib and other PI3K inhibitors

As hypothesized by Cant et al., 2024 ⁴², the good tolerability and safety profile of leniolisib observed in clinical trials in APDS may be accounted to: (i) its high selectivity for PI3K δ , compared to the other PI3K isoforms expressed in T- and B-lymphocytes; (ii) modulation of kinase enzyme activity which is restored to a physiological range, due to its low potency (Tab. I). In this light, leniolisib's safety and tolerability profile appears to be better than that of inhibitors used in hemato-oncological patients. Furthermore, PI3K inhibitors studied in clinical trials for treatment of hematological neoplasms were used at high dosages, in order to obtain an antiproliferative effect through complete kinase activity inhibition. Indeed, a comparison between leniolisib and other inhibitors (idelalisib and duvelisib, FDA approved for chronic lymphocytic leukemia) is not useful to infer or predict

SAEs in different populations treated with different drug doses and regimens.

DISCUSSION

Before leniolisib's approval by the FDA, APDS patients were treated only with antibiotics, antivirals, immunosuppressants and Immunoglobulin Replacement Therapy (IRT), in order to control infectious symptoms and immunodysregulation^{16,18,24,25}. However, these therapies are insufficient to control and reduce the symptoms of APDS, and research has focused on PI3K δ inhibitors, which reduce the activation of the PI3K/AKT/mTOR signaling pathway, (hyperactivated in APDS patients due to mutated PI3K δ) thus acting against alterations of immune system functions^{13,25}. Several inhibitors have been evaluated in clinical trials for APDS management; only leniolisib achieved FDA designation as an orphan drug for APDS, based on an initial blinded, randomized, placebo-controlled, 12-week study (NCT02435173)²⁸⁻³⁰. Other PI3K δ inhibitors have been evaluated in clinical trials for the treatment of various lymphomas and different forms of leukemia. However, as mentioned above, the high levels of kinase activity inhibition led to several SAEs^{49,50,52,53}. Leniolisib improved several clinical conditions related to PI3K δ activity such as lymphoproliferation and subsequent differentiation of mature and activated lymphocytes, and also reduced the level of activation of the AKT signaling pathway in T-lymphocytes in patients with APDS, by about 80%⁵⁵. This evidence suggests that leniolisib may have a crucial role preventing the onset of lymphoma in APDS patients. In fact, as reported by Rao et al., 2024³⁰, none of the 3 patients with lymphoma included in the dose-finding trial had relapses or new lymphomas up to the interim analysis cut off. Treatment with leniolisib has also been proposed for other chronic autoimmune diseases, such as Sjögren's syndrome, a connective tissue disease in which the immune system destroys mucous membrane glands (salivary or ocular)^{56,57}. Leniolisib has already been approved for patients with APDS by the FDA in 2023 and is awaiting approval by the EMA. Preliminary results from the open-label extension trial NCT02859727 confirm data on the safety and tolerability of leniolisib in patients with APDS²⁹. Analysis of pharmacodynamic and pharmacokinetic data suggests that leniolisib, compared to other PI3K inhibitors, is safe and well tolerated in APDS patients due to: low PI3K δ potency (high IC₅₀), high selectivity for the mutated PI3K δ expressed in lymphocytes of APDS patients⁴² and low apparent distribution volume that would reduce the risk of drug accumulation and adverse events.

Acknowledgements

The authors acknowledge the Rare Immunodeficiency, AutoInflammatory and AutoImmune Disease (RITA) network. CC was supported by grants PNRRMR1-2022-12376594 and by the Italian Ministry of Health (5x1000 202205_INFETT). CBMP was supported by the funding PON Ricerca e Innovazione D.M. 1062/21–Contratti di ricerca, from the Italian Ministry of University (MUR). [Contract #: 08-I-17629-2]. FL was supported by the funding Missione 4 "Istruzione e

Ricerca" - "Dalla ricerca all'impresa" - NextGenerationUE - "ANTHEM: AdvANced Technologies for Human-centrEd Medicine", Spoke 4, PNC0000003.

Conflicts of interest statement

CC has received consulting fees from Pharminger.

Ethical consideration

Not applicable.

Funding

This research has not been supported by external funding.

Author's contribution

CC: contributed to design the manuscript draft and to write and finalize it; AT: contributed to draw the manuscript draft and finalization. All authors revised the manuscript and approved the final version.

References

- Modell V, Gee B, Lewis DB, et al. Modell, Global study of primary immunodeficiency diseases (PI)--diagnosis, treatment, and economic impact: an updated report from the Jeffrey Modell Foundation. *Immunol Res* 2011;51:61-70. <https://doi.org/10.1007/s12026-011-8241-y>
- Anderson JT, Cowan J, Condino-Neto A, et al. Health-related quality of life in primary immunodeficiencies: Impact of delayed diagnosis and treatment burden. *Clin Immunol* 2022;236:108931. <https://doi.org/10.1016/j.clim.2022.108931>
- Bousfiha A, Moundir A, Tangye SG, et al. The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity. *J Clin Immunol* 2022;42:1508-1520. <https://doi.org/10.1007/s10875-022-01352-z>
- Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2022;42:1473-1507. <https://doi.org/10.1007/s10875-022-01289-3>
- Arkwright PD, Gennery AR. Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century. *Ann NY Acad Sci* 2011;1238:7-14. <https://doi.org/10.1111/j.1749-6632.2011.06206.x>
- Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 2020;40:24-64. <https://doi.org/10.1007/s10875-019-00737-x>
- Swan DJ, Aschenbrenner D, Lamb CA, et al. Immunodeficiency, autoimmune thrombocytopenia and enterocolitis caused by autosomal recessive deficiency of PIK3CD-encoded phosphoinositide 3-kinase δ . *Haematologica* 2019;104:e483-e486. <https://doi.org/10.3324/haematol.2018.208397>
- Fruman DA, Chiu H, Hopkins BD, et al. The PI3K Pathway in Human Disease. *Cell* 2017;170:605-635. <https://doi.org/10.1016/j.cell.2017.07.029>
- Okkenhaug K, Vanhaesebroeck B. PI3K in lymphocyte development, differentiation and activation. *Nat Rev Immunol* 2003;3:317-330. <https://doi.org/10.1038/nri1056>
- Lucas CL, Kuehn HS, Zhao F, et al. Dominant-activating germline mutations

- in the gene encoding the PI(3)K catalytic subunit p110 δ result in T cell senescence and human immunodeficiency. *Nat Immunol* 2014;15:88-97. <https://doi.org/10.1038/ni.2771>
- 11 Preite S, Gomez-Rodriguez J, Cannons JL, et al. T and B-cell signaling in activated PI3K delta syndrome: From immunodeficiency to autoimmunity. *Immunol Rev* 2019;291:154-173. <https://doi.org/10.1111/imr.12790>
 - 12 Tsujita Y, Mitsui-Sekinaka K, Imai K, et al. Phosphatase and tensin homolog (PTEN) mutation can cause activated phosphatidylinositol 3-kinase δ syndrome-like immunodeficiency. *J Allergy Clin Immunol* 2016;138: 1672-1680.e10. <https://doi.org/10.1016/j.jaci.2016.03.055>
 - 13 Vanselow S, Wahn V, Schuetz C. Activated PI3K δ syndrome - reviewing challenges in diagnosis and treatment., *Front Immunol* 2023;14:1208567. <https://doi.org/10.3389/fimmu.2023.1208567>
 - 14 Duggan S, Al-Salama ZT. Leniolisib: First Approval. *Drugs* 2023;83:943-948. <https://doi.org/10.1007/s40265-023-01895-4>
 - 15 Coulter TI, Chandra A, Bacon CM, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: a large patient cohort study., *J Allergy Clin Immunol* 2017;139:597-606.e4. <https://doi.org/10.1016/j.jaci.2016.06.021>
 - 16 Elkaim E, Neven B, Bruneau J, et al. Clinical and immunologic phenotype associated with activated phosphoinositide 3-kinase δ syndrome 2: A cohort study. *J Allergy Clin Immunol* 2016;138:210-218.e9. <https://doi.org/10.1016/j.jaci.2016.03.022>
 - 17 Wentink MWJ, Mueller YM, Dalm VASH, et al. Exhaustion of the CD8+ T Cell Compartment in Patients with Mutations in Phosphoinositide 3-Kinase Delta. *Front Immunol* 2018;9:446. <https://doi.org/10.3389/fimmu.2018.00446>
 - 18 Jamee M, Moniri S, Zaki-Dizaji M, et al. Clinical, Immunological, and Genetic Features in Patients with Activated PI3K δ Syndrome (APDS): a Systematic Review. *Clin Rev Allergy Immunol* 2020;59:323-333. <https://doi.org/10.1007/s12016-019-08738-9>
 - 19 So L, Fruman DA. PI3K signalling in B- and T-lymphocytes: new developments and therapeutic advances. *Biochem J* 2012;442:465-481. <https://doi.org/10.1042/BJ20112092>
 - 20 Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat Rev Genet* 2006;7:606-619. <https://doi.org/10.1038/nrg1879>
 - 21 Wang W, Min Q, Lai N, et al. Cellular Mechanisms Underlying B Cell Abnormalities in Patients With Gain-of-Function Mutations in the PIK3CD Gene. *Front Immunol* 2022;13:890073. <https://doi.org/10.3389/fimmu.2022.890073>
 - 22 Wentink M, Dalm V, Lankester AC, et al. Genetic defects in PI3K δ affect B-cell differentiation and maturation leading to hypogammaglobulinemia and recurrent infections. *Clin Immunol* 2017;176:77-86. <https://doi.org/10.1016/j.clim.2017.01.004>
 - 23 Lucas CL, Zhang Y, Venida A, et al. Heterozygous splice mutation in PIK3R1 causes human immunodeficiency with lymphoproliferation due to dominant activation of PI3K. *J Exp Med* 2014;211:2537-2547. <https://doi.org/10.1084/jem.20141759>
 - 24 Maccari ME, Abolhassani H, Aghamohammadi A, et al. Disease Evolution and Response to Rapamycin in Activated Phosphoinositide 3-Kinase δ Syndrome: The European Society for Immunodeficiencies-Activated Phosphoinositide 3-Kinase δ Syndrome Registry. *Front Immunol* 2018;9:543. <https://doi.org/10.3389/fimmu.2018.00543>
 - 25 Coulter TI, Cant A.. The Treatment of Activated PI3K δ Syndrome. *Front Immunol* 2018;9:2043. <https://doi.org/10.3389/fimmu.2018.02043>
 - 26 Dominguez-Villar M, ed. PI3K and AKT Isoforms in Immunity. Cham: Springer International Publishing 2022. <https://doi.org/10.1007/978-3-031-06566-8>
 - 27 U.S. Food and Drug Administration (n.d.). <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-activated-phosphoinositide-3-kinase-delta-syndrome> (Accessed on: February 23, 2024).
 - 28 Rao VK, Webster S, Dalm VASH, et al. Effective "activated PI3K δ syndrome"-targeted therapy with the PI3K δ inhibitor leniolisib. *Blood* 2017;130:2307-2316. <https://doi.org/10.1182/blood-2017-08-801191>
 - 29 Rao VK, Webster S, Šedivá A, et al. A randomized, placebo-controlled phase 3 trial of the PI3K δ inhibitor leniolisib for activated PI3K δ syndrome. *Blood* 2023;141:971-983. <https://doi.org/10.1182/blood.2022018546>
 - 30 Rao VK, Kulm E, Šedivá A, et al. Interim analysis: Open-label extension study of leniolisib for patients with APDS. *J Allergy Clin Immunol* 2024;153:265-274.e9. <https://doi.org/10.1016/j.jaci.2023.09.032>
 - 31 NIH - National Library of Medicine. Compound summary Leniolisib (n.d.). <https://pubchem.ncbi.nlm.nih.gov/compound/Leniolisib> (Accessed on: February 23, 2024).
 - 32 Hoegenauer K, Soldermann N, Zécri F, et al. Discovery of CDZ173 (Leniolisib), Representing a Structurally Novel Class of PI3K Delta-Selective Inhibitors., *ACS Med Chem Lett* 2017;8:975-980. <https://doi.org/10.1021/acsmedchemlett.7b00293>
 - 33 U.S. Food & Drug Administration. Joenja (leniolisib). FDA Food and Drug Administration - 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217759s000lbl.pdf (Accessed on: February 23, 2024).
 - 34 Vanhaesebroeck B, Perry MWD, Brown JR, et al. PI3K inhibitors are finally coming of age. *Nat Rev Drug Discov* 2021;20:741-769. <https://doi.org/10.1038/s41573-021-00209-1>
 - 35 Miller MS, Thompson PE, Gabelli SB. Structural Determinants of Isoform Selectivity in PI3K Inhibitors. *Biomolecules* 2019;9:82. <https://doi.org/10.3390/biom9030082>
 - 36 Somoza JR, Koditek D, Villaseñor AG, et al. Structural, biochemical, and biophysical characterization of idelalisib binding to phosphoinositide 3-kinase δ . *J Biol Chem* 2015;290:8439-8446. <https://doi.org/10.1074/jbc.M114.634683>
 - 37 Berndt A, Miller S, Williams O, et al. The p110 delta structure: mechanisms for selectivity and potency of new PI(3)K inhibitors. *Nat Chem Biol* 2010;6:117-124. <https://doi.org/10.1038/nchembio.293>
 - 38 Rugo HS. Dosing and Safety Implications for Oncologists When Administering Everolimus to Patients With Hormone Receptor-Positive Breast Cancer. *Clin Breast Cancer* 2016;16:18-22. <https://doi.org/10.1016/j.clbc.2015.09.004>
 - 39 Thompson PA, Stingo F, Keating MJ, et al. Outcomes of patients with chronic lymphocytic leukemia treated with first-line idelalisib plus rituximab after cessation of treatment for toxicity. *Cancer* 2016;122:2505-2511. <https://doi.org/10.1002/cncr.30069>
 - 40 Sadasivan C, Zhabyeyev P, Labib D, et al. Cardiovascular toxicity of PI3K α inhibitors. *Clin Sci (Lond)* 2020;134:2595-2622. <https://doi.org/10.1042/CS20200302>
 - 41 Nunnery SE, Mayer IA. Management of toxicity to isoform α -specific PI3K

- inhibitors. *Ann Oncol* 2019;30(Suppl 10):x21–x26. <https://doi.org/10.1093/annonc/mdz440>
- ⁴² Cant AJ, Chandra A, Munro E, et al. PI3K δ Pathway Dysregulation and Unique Features of Its Inhibition by Leniolisib in Activated PI3K δ Syndrome and Beyond. *J Allergy Clin Immunol Pract* 2024;12:69–78. <https://doi.org/10.1016/j.jaip.2023.09.016>
- ⁴³ Mishra R, Patel H, Alanazi S, et al. PI3K Inhibitors in Cancer: Clinical Implications and Adverse Effects. *Int J Mol Sci* 2021;22. <https://doi.org/10.3390/ijms22073464>
- ⁴⁴ Agenzia Italiana del Farmaco (AIFA). Allegato 1, Caratteristiche del prodotto - 2021. https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_004796_043620_RCP.pdf&retry=0&sys=m0b1l3 (Accessed on: February 23, 2024).
- ⁴⁵ Agenzia Italiana del Farmaco (AIFA). Allegato 1, Caratteristiche del prodotto - 2023. https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_005214_049523_RCP.pdf&retry=0&sys=m0b1l3 (Accessed on: February 23, 2024).
- ⁴⁶ Chellappa S, Kushekhar K, Munthe LA, et al. The PI3K p110 δ Isoform Inhibitor Idelalisib Preferentially Inhibits Human Regulatory T Cell Function. *J Immunol* 2019;202:1397–1405. <https://doi.org/10.4049/jimmunol.1701703>
- ⁴⁷ Compagno M, Wang Q, Pighi C, et al. Phosphatidylinositol 3-kinase δ blockade increases genomic instability in B cells. *Nature* 2017;542:489–493. <https://doi.org/10.1038/nature21406>
- ⁴⁸ Dornan GL, Siempelkamp BD, Jenkins ML, et al. Conformational disruption of PI3K δ regulation by immunodeficiency mutations in PIK3CD and PIK3R1. *Proc Natl Acad Sci USA* 2017;114:1982–1987. <https://doi.org/10.1073/pnas.1617244114>
- ⁴⁹ Coutré SE, Barrientos JC, Brown JR, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. *Leuk Lymphoma* 2015;56:2779–2286. <https://doi.org/10.3109/10428194.2015.1022770>
- ⁵⁰ Condliffe AM, Davidson K, Anderson KE, et al. Sequential activation of class IB and class IA PI3K is important for the primed respiratory burst of human but not murine neutrophils. *Blood* 2005;106:1432–1440. <https://doi.org/10.1182/blood-2005-03-0944>
- ⁵¹ Stark A-K, Chandra A, Chakraborty K, et al. PI3K δ hyper-activation promotes development of B cells that exacerbate *Streptococcus pneumoniae* infection in an antibody-independent manner. *Nat Commun* 2018;9:3174. <https://doi.org/10.1038/s41467-018-05674-8>
- ⁵² Begg M, Amour A, Jarvis E, et al. An open label trial of nemiralisib, an inhaled PI3 kinase delta inhibitor for the treatment of Activated PI3 kinase Delta Syndrome. *Pulm Pharmacol Ther* 2023;79:102201. <https://doi.org/10.1016/j.pupt.2023.102201>
- ⁵³ Diaz N, Juarez M, Cancrini C, et al. Seletalisib for Activated PI3K δ Syndromes: Open-Label Phase 1b and Extension Studies. *J Immunol* 2020;205:2979–2987. <https://doi.org/10.4049/jimmunol.2000326>
- ⁵⁴ EU Clinical Trial Register. An Open-Label, Exploratory, Multicenter, Extension Study to Evaluate the Long-Term Safety, Tolerability, Pharmacokinetics and Efficacy of UCB5857 in Subjects with Activated Phosphoinositide 3 Kinase (PI3K) Delta Syndrome (APDS), n.d. <https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-005541-30/results> (Accessed on: February 23, 2024).
- ⁵⁵ De SK. Leniolisib: a novel treatment for activated phosphoinositide-3 kinase delta syndrome. *Front Pharmacol* 2024;15:1337436. <https://doi.org/10.3389/fphar.2024.1337436>
- ⁵⁶ Nayar S, Campos J, Smith CG, et al. Phosphatidylinositol 3-kinase delta pathway: a novel therapeutic target for Sjögren's syndrome. *Ann Rheum Dis* 2019;78:249–260. <https://doi.org/10.1136/annrheumdis-2017-212619>
- ⁵⁷ Safety, pharmacokinetics, and preliminary efficacy study of CDZ173 in patients with primary Sjögren's syndrome. *ClinicalTrials.gov*. NCT02775916.