Il trapianto nelle immunodeficienze primitive rare: l'esempio paradigmatico dell'APDS

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International Union of Immunological Societies (IUIS) phenotypic classification of IEIs

The 2022 classification includes 485 diverse IEI underlying phenotypes (439 in 2020 classification)

This phenotypic classification is intended to be most useful for physicians to aid in the diagnostic process:

The IUIS recognises that patients with **mutations in the same gene can present with substantial phenotypic and clinical heterogeneity**

Classification	Examples of disorders
I. Immunodeficiencies affecting cellular and humoral immunity	
SCID, defined by CD3 T cell lymphopenia	CD45 deficiency
CID generally less profound than SCID	TCRα deficiency
II. Combined immunodeficiencies with associated or syndromic features	Nijmegen breakage syndrome, Bloom syndrome
III. Predominantly antibody deficiencies	
Hypogammaglobulinemia	**APDS1 and APDS2**
Other antibody deficiencies	Selective IgA deficiency, Isolated IgG subclass deficiency
IV. Diseases of immune dysregulation	
Haemophagocytic Lymphohistiocytosis and EBV susceptibility	ITK deficiency, CD27 deficiency
Syndromes with autoimmunity and others	TGFB1 deficiency

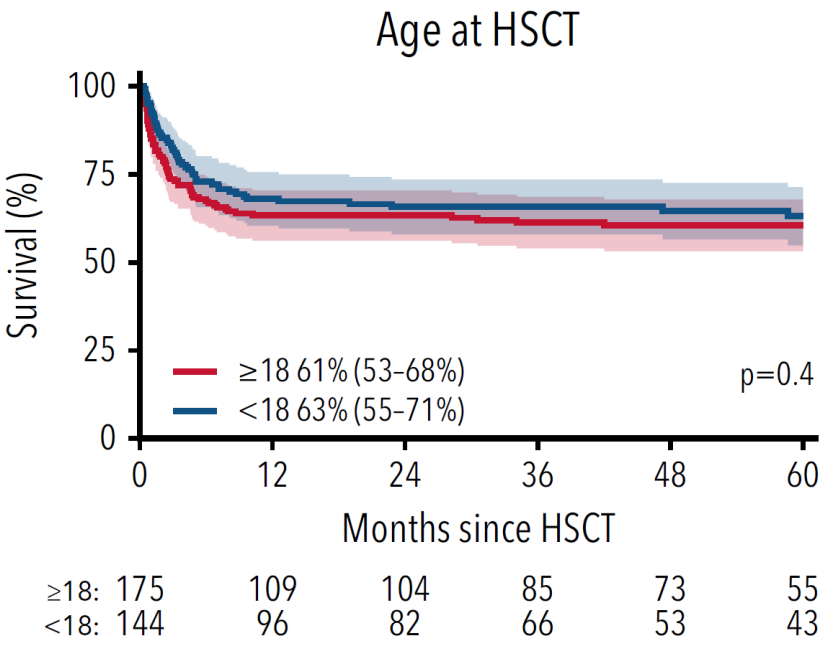
Classification	Examples of disorders
V. Congenital defects of phagocyte number, function or both	
Neutropenia	Cohen syndrome, TLR8 GOF
Functional defects	Leukocyte adhesion deficiency, cystic fibrosis
VI. Defects in intrinsic and innate immunity	
Predisposition to viral infections	STAT1 deficiency, Mollaret's meningitis
Predisposition to bacterial, parasitic and fungal infections	IL-23R deficiency, trypanosomiasis
VII. Auto-inflammatory disorders	Familial Mediterranean Fever, Blau Syndrome
VIII. Complement deficiencies	C6/7/8/9 deficiency, Factor B GOF
IX. Bone marrow failure	Fanconi anaemia Type A-W, osteopetrosis
X. Phenocopies of PID	RAS-associated autoimmune leukoproliferative disease, chronic mucocutaneous candidiasis

References: Bousfiha A *et al. J Clin Immunol.* 2022; 42: 1508–1520. **Abbreviations**: ALPS: autoimmune lymphoproliferative syndrome; APDS: activated PI3K delta syndrome; CD: clusters of differentiation; CID: combined immunodeficiency; EBV: Epstein-Barr virus; GOF: gain of function; ITK: IL2 inducible T cell kinase; IL-23R: interleukin-23 receptor; IUIS: International Union of Immunological Societies; PID: primary immunodeficiency; RAS: rat sarcoma virus; SCID: severe combined immunodeficiency; STAT1: signal transducer and activator of transcription 1; TCRα: T cell receptor alpha; TGFB1: transforming growth factor-beta 1; TLR8: toll-like receptor 8.

TABLE 2 | Indications for HSCT in PID.

HSCT curative	HSCT partially curative	HSCT controversial
SCID	Cartilage Hair Hypoplasia	CVID
CID^	PGM3 deficiency	Agammaglobulinemia
CGD	STAT1-GOF	Complement deficiencies (other than C1q deficiency)
DOCK8 deficiency	STAT3- GOF	DGS
DOCK2 deficiency	Severe congenital neutropenia	IKBA deficiency
IPEX	ADA2 deficiency	NEMO deficiency
WAS	CIQ deficiency	
WIP deficiency	CD25 deficiency	
ARPC1B deficiency	IL-10 deficiency	
CD40 ligand deficiency	IL-10 Receptor deficiency	
CD40 deficiency	DNA double-strand break repair disorders	
XLP1, XLP2		
APDS		
MHC Class II deficiency		
AD Hyper IgE syndrome		
CTLA4 haploinsufficiency		
LRBA deficiency		
Familial HLH types 1–5		
GATA2 deficiency		
RAB27A deficiency		
LAD I		
Reticular Dysgenesis		

HSCT in adolescents and young adults with IEI



Activated PI3Kδ Syndrome

- Is an IEI recently **characterised in 2013**[1]
- Was previously known as PASLI disease (p110d-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency)[2]
- Is rare, affecting 1 to 2 people per 1,000,000
- Is caused by mutations in the genes encoding **subunits of the PI3Kδ enzyme complex** that lead to **hyperactive signalling in the PI3K pathway**[1,4,5]
- Two variants:
  - ***APDS1***: heterozygous GOF mutations in the PIK3CD gene (p110δ protein)
  - ***APDS2***: heterozygous LOF mutations in the PIK3R1 gene (p85α protein)
- **Affects both T and B cells**, and therefore meets the definition of a CID[4]
  - However, APDS is classified by the IUIS as an IEI with 'predominantly antibody deficiencies'[6]

APDS

CHARACTERISED BY

Immune deficiency[7,8]

Causing frequent infections

Immune dysfunction[7,8]

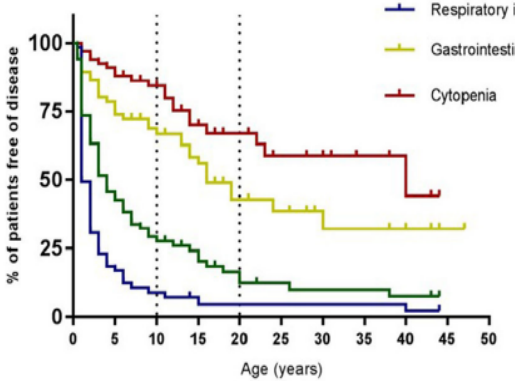
Leading to autoimmune complications and lymphoprolipheration

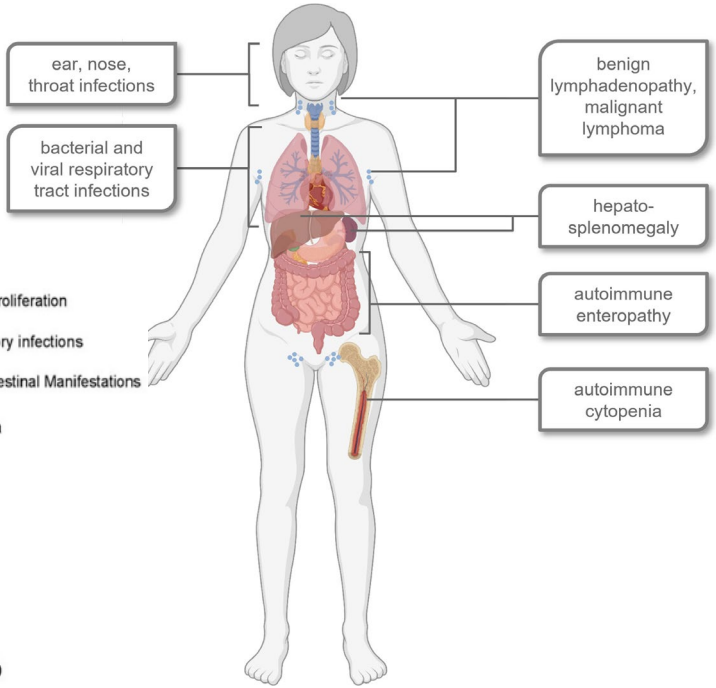
References: 1. Angulo I *et al. Science.* 2013; 342(6160): 866–871. 2. Coulter T *et al. Front Immunol.* 2018; 9: 2043. 3. Plieth J. Evaluate Vantage. Available from: https://www.evaluate.com/vantage/articles/news/deals/novartis-cast-gives-pharming-gap-filler. Last Accessed: April 2023. 4. Lucas CL *et al. Nature Immunology.* 2014; 15: 88–97. 5. Singh A *et al. Genes Dis.* 2019; 7(1): 67–74. 6. Tangye S *et al. J Clin Immunol.* 2022; 42(7): 1473–1507. 7. Elkaim E *et al. J Allergy Clin Immunol.* 2016; 138(1): 210–218. 8. Jamee M *et al. Clin Rev Allergy Immunol.* 2020; 59(3): 323–333. .
Abbreviations: APDS: activated PI3K delta syndrome; CID: combined immunodeficiency; IEI: inborn errors of immunity; IUIS: International Union of Immunological Societies; PASLI: p110d-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency; PI3K: phosphoinositide 3-kinase.

APDS

Activated PI3Kδ syndrome	
Clinical features	**Immunologic features**
• Recurrent respiratory tract infections • Bronchiectasis • Lymphoproliferation • Chronic viral infections (EBV and CMV) • Autoimmune manifestations • Gastrointestinal manifestations • ↑ Risk of lymphoma • Neurologic manifestations • Short stature (APDS2)	• Hypogammaglobulinemia • Increased IgM levels • Impaired vaccination responses • Decreased naive T-cell counts • Increased effector memory, effector, and exhausted T-cell counts • Increased transitional B-cell counts • Decreased memory and switched memory B-cell counts

mTOR-dependent and mTOR-independent effects of activated PI3K and increased AKT signaling	
mTOR dependent	**mTOR independent**
• Increased glucose uptake • Metabolic shift to glycolysis Consequences: • ↓ T_H cell differentiation • ↓ Memory T-cell generation and function • ↑ Effector T-cell numbers • ↓ Memory $CD8^+$ T-cell responses • ↓ Regulatory T-cell homeostasis and function	• Increased FOXO1 phosphorylation • Increased FOXO1 degradation • Decreased FOXO1-dependent transcription Consequences: • ↓ Naive T cells • ↓ B-cell migration during GC reaction • Impaired B-cell maturation • ↑ Transitional B cells • ↓ AID expression • ↓ CSR

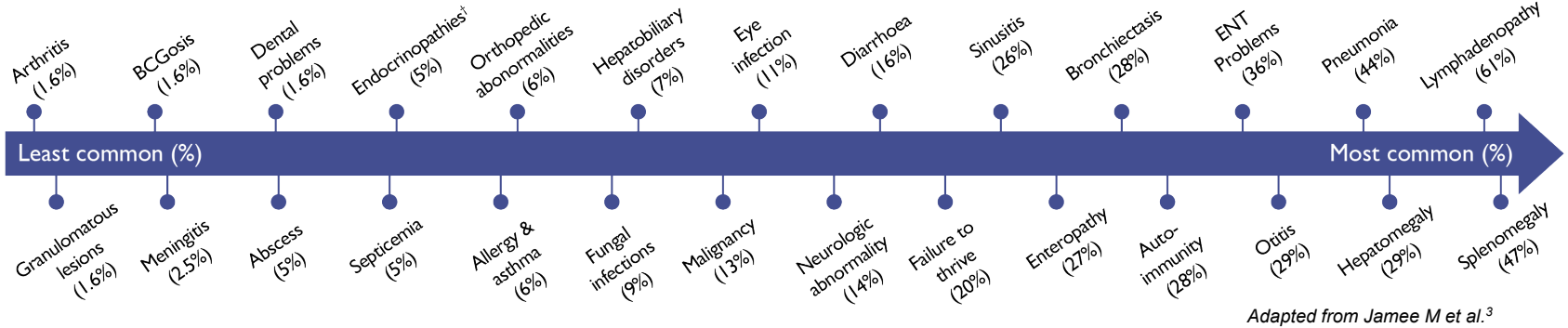




Heterogenous APDS clinical phenotypes

- Clinical phenotypes of APDS vary considerably from asymptomatic adults, to those with profound immunodeficiency causing early death in childhood[1]
- However, there is currently **no immunological marker of disease severity**
- Variability is also seen between APDS1 and APDS2

Proportion of patients with APDS presenting each manifestation (N=243)[3,*]



Adapted from Jamee M et al.[3]

Patients with APDS exhibit great clinical heterogeneity[3]

*Scale is not proportional to the proportion of patients with each manifestation. †Endocrine disorders. **References**: 1. Coulter TI & Cant AJ. *Front Immunol*. 2018. 9: 2043. 2. Coulter TI *et al. J Allergy Clin Immunol*. 2017;139(2):597-606.e4. 3. Jamee M et al. *Clin Rev Allergy Immunol*. 2020;59(3):323-333. **Abbreviations**: APDS1/2: activated PI3K delta syndrome 1/2; BCG: bacillus calmette–guérin; ENT: ear nose throat.

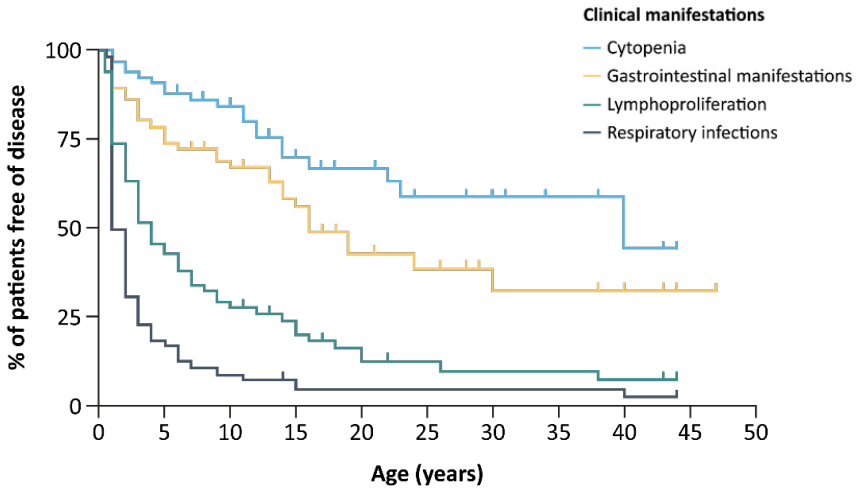
APDS is a progressive disease

Over the disease course, patients develop an **increasing number of manifestations** and can experience greater risk of complications:[1,2]

- Long-term effects of sinopulmonary infections include bronchiectasis, permanent hearing loss and increased susceptibility to RTIs[1,3]
- By late adolescence, people with APDS are at a higher risk of developing lymphomas or persistent and recalcitrant lymphoproliferation[1,2,4]
- Chronic, persistent lymphadenopathy contributes to GI issues which require more serious interventions including surgery[1,4,5]

The time course and **progression of APDS** may be **unpredictable**, which could make it difficult for clinicians to make treatment decisions, allowing **manifestations to accumulate**.

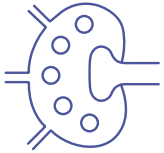
Percentage of people free of disease, from birth to 50 years:[2]



Adapted from Maccari ME et al.[2]

References: 1. Coulter TI *et al. J Allergy Clin Immunol*. 2017;139(2):597-606.e4. 2. Maccari ME *et al. Front Immunol*. 2018; 9:543. 3. What is APDS? Available at: What is APDS | All about APDS. Last Accessed: April 2023. 4. Okano T *et al. J Allergy Clin Immunol*. 2019; 143(1):266:275. 5. Oh J *et al. J Allergy Clin Immunol Pract*. 2021;9(11):4095-4102. **Abbreviations:** APDS: activated PI3K delta syndrome; GI: gastrointestinal; RTI: respiratory tract infections.

Lymphoproliferation in APDS



Lymphoproliferation can be **caused by the uncontrolled increase in numbers of dysfunctional B and T cells**[1], as a result of issues within the physiological mechanisms that control proliferation of these cells in APDS

- Lymphadenopathy can suggest the presence of an infection (commonly seen in APDS). However, it can also indicate the presence of immune dysregulation[2–4]

Lymphoproliferation is seen in **over 70% of patients**,[2,5–8] and was the second most prevalent finding in the largest APDS1 (75%) and APDS2 (89%) cohorts[2,5]

The majority of patients with APDS show signs of lymphoproliferation by age 15 years[6]

Manifestations of lymphoproliferation include:

- **Lymphadenopathy** (58% of people)[1]
- **Splenomegaly** (44%)[1]
- **Hepatomegaly** (24%)[1]
- Lymphoid infiltration of the gut, respiratory tract or ENT (hyperplasia)[2–5]

References: 1. Lymphoproliferative Disorders. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537162/. Last Accessed: April 2023. 2. Coulter TI, *et al. J Allergy Clin Immunol.* 2017; 139(2): 597–606. 3. Lymphadenopathy. Available at: https://www.ncbi.nlm.nih.gov/books/NBK558918/. Last Accessed: April 2023. 4. Costagliola G & Consolini R. *Clin Exp Immunol.* 2021; 205(3): 288–305. 5. Elkaim E, *et al. J Allergy Clin Immunol.* 2016; 138(1): 210–218. 6. Maccari ME, *et al. Front Immunol.* 2018; 9: 543. 7. Okano T, *et al. J Allergy Clin Immunol.* 2019; 143(1): 266–275. 8. Jamee M, *et al. Clin Rev Allergy Immunol.* 2020; 59(3): 323-333. **Abbreviations**: APDS1/2: activated PI3K delta syndrome 1/2.

Lymphoma in APDS

Incidence and onset

- Lymphoma is reported in **13–28%** of patients with APDS,[1-3] and cumulative risk of people with APDS2 developing lymphoma by age 40 is estimated to be 78%[3]
- Median age of onset of lymphoma has been reported to be 23 years old,[3] however, it has also been found to present as early as 18 months[2]

Causes

The elevated frequency of lymphoma in APDS is as a result of:[4]

- Uncontrolled activation of the PI3K/Akt/mTOR pathway in B cells of patients with APDS, resulting in increased B cell survival and malignant transformation
- Elevated T cell counts, impaired cytotoxicity of T and natural killer cells and defects in T regulatory cell activity

Types of lymphoma

The most commonly reported types of lymphoma in APDS are:[1–3,5]

- Diffuse large B cell lymphoma (DLBCL)
- Hodgkin's lymphoma
- Marginal zone lymphoma

Complications

- Lymphoma is one of the major reasons for **early mortality in APDS**[6]
- Around 60% of APDS fatalities are thought to be due to lymphoma[6]

References: 1. Jamee M *et al. Clin Rev Allergy Immunol.* 2020; 59(3): 323-333. 2. Coulter TI *et al. J Allergy Clin Immunol.* 2017; 139(2): 597-606.e4. 3. Elkaim E *et al. J Allergy Clin Immunol.* 2016; 138(1): 210-218. 4. Durandy A *Blood.* 2020; 27; 135(9): 638-643. 5. Maccari ME *et al. Front Immunol.* 2018; 9:543. 6. APDS Features. Available at: https://www.allaboutapds.eu/apds-features/. Last Accessed: April 2023. **Abbreviations**: APDS: activated PI3K delta syndrome; Akt: protein kinase B; DLBCL: diffuse large B cell lymphoma; mTOR: mammalian target of rapamycin; PI3K: phosphoinositide 3-kinase.

Current management for APDS

1. Symptom management

- There are currently **no approved treatment options** for APDS specifically and management is symptom based[1]
- Current supportive therapies target either immune deficiency or immune dysregulation, but do not address the full complexity of APDS:[3]

Immune Deficiency[4–6]

- Immunoglobulin replacement therapy
- Antimicrobial prophylaxis

Immune Dysregulation[6,7]

- Corticosteroids
- Other immunosuppressants including rapamycin, rituximab, tacrolimus and mycophenolate mofetil

- Management aimed at one disease component may exacerbate the other component e.g., increased susceptibility to infection is a clinical challenge when using immunosuppressive therapies[3,7]

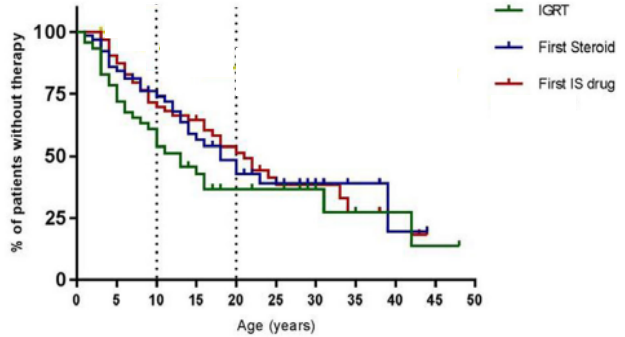
2. Disease modifying therapies

- **HSCT** replaces leukocytes affected by PI3Kδ hyperactivation and is a potentially curative therapeutic option[2]

*By reducing mTOR activation, rapamycin is considered to be a targeted therapy. **References**: 1. What is APDS? Available at: https://www.allaboutapds.eu/what-is-apds/. Last Accessed: April 2023. 2. Coulter TI & Cant AJ. *Front Immunol.* 2018; 9:2043. 3. Walter JE et al. *J Allergy Clin Immunol Pract.* 2016; 4(6): 1089-1100. 4.Coulter TI et al. *J Allergy Clin Immunol.* 2017; 139(2): 597-606. 5. Elkaim E et al. *J Allergy Clin Immunol.* 2016; 138(1): 210-218. 6. Jamee M et al. *Clin Rev Allergy Immunol.* 2020; 59(3): 323-333. 7. Gobert D et al. *Br J Haematol.* 2011; 155(4): 498-508. **Abbreviations**: APDS: activated PI3K delta syndrome; HSCT: haemopoietic stem cell therapy; PI3K: phosphoinositide 3-kinase.

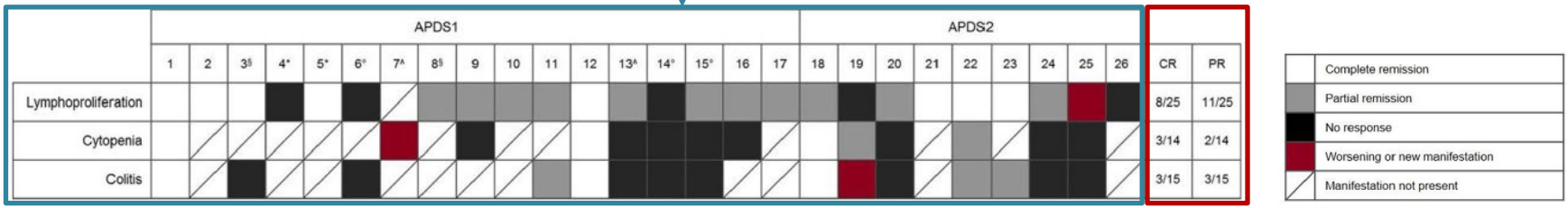
APDS treatments: supportive agents and IS

APDS type	Coulter et al. (2017)	Elkaim et al. (2016)	Maccari et al. (2018)			Tessarin et al. (2020)	Jamee et al. (2020)	Wang et al. (2021)
	APDS1 (n=53)	APDS2 (n=36)	APDS1/2 (n=68)	APDS1 (n=45)	APDS2 (n=23)	APDS1 (n=8)	APDS1/2 (n=240)	APDS1 (n=7)
Antibiotics	33	22	54			1		
IgG	46	32	44	28	16	6	151	
Immunosuppr.	16					3		
Rituximab	8	3	8					
Steroids		5	31			4		



APDS treatment: mTOR inhibitors

APDS type	Coulter et al. (2017)	Elkaim et al. (2016)	Maccari et al. (2018)			Tessarin et al. (2020)	Jamee et al. (2020)	Wang et al. (2021)
	APDS1 (n=53)	APDS2 (n=36)	APDS1/2 (n=68)	APDS1 (n=45)	APDS2 (n=23)	APDS1 (n=8)	APDS1/2 (n=240)	APDS1 (n=7)
Immunosuppr.	16					3		
Rapamycin	6	6	27			2		3
Rituximab	8	3	8					
Steroids		5	31			4		

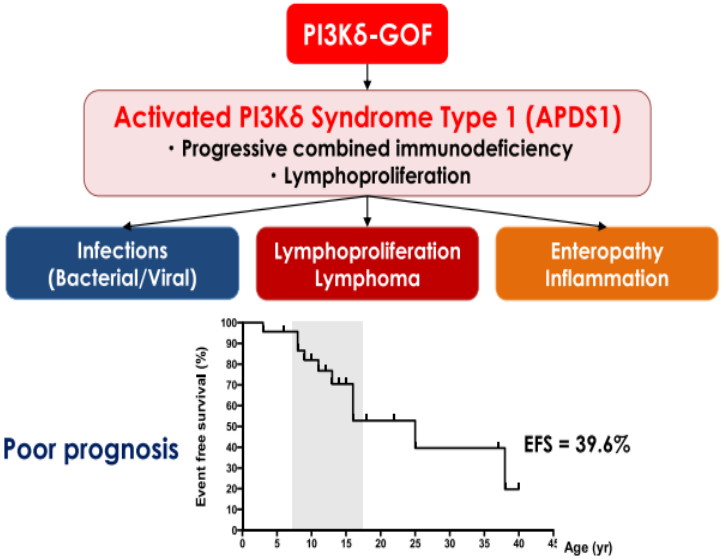


APDS treatment

- Administration of mTOR inhibitors can control immune dysregulation and ameliorate clinical symptoms
  - some patients experience treatment-refractory disease and drug-related adverse events

Events include death, HSCT, and massive lymphoproliferation.

The gray background indicates event-frequent periods between 7 and 17 years of age.



HSCT in APDS

- HSCT is a potentially curative treatment option for people with APDS but there are limited data available[1–3]
- HSCT techniques have improved over time with **overall survival rates now around 80%**[2–4]
- This may be a result of more suitable donor types and donor cell sources, and less toxic conditioning regimens, though there remains variability in these parameters

HSCT use in cohorts of patients with APDS

Characteristics	Nademi *et al.*, 2017[2]	Okano *et al.*, 2019[3]	Dimitrova *et al.*, 2022[4]*
Patients	**11**	**9** (11 transplantations)	**57** (66 transplantations)
Age (years)	5–23	4–17	2–66
Donor type	Matched unrelated (n=5) Sibling (n=4) Mismatched unrelated (n=2)	Matched unrelated (n=5) Mismatched sibling (n=2) Mismatched unrelated (n=2) Mismatched related (n=2)	Matched unrelated (n=41) Matched sibling (n=7) Haploidentical (n=15) Other (n=8)
Source of donor cells	Peripheral blood (n=7) Cord blood (n=1) Bone marrow (n=3)	Bone marrow (n=8) Cord blood (n=2)	Bone marrow (n=32) Peripheral blood (n=31) Cord blood (n=3)
Conditioning regimen	Fludarabine/treosulfan (n=4) Fludarabine/melphalan (n=4) Fludarabine/busulfan (n=1) Busulfan/cyclophosphamide (n=2)	Fludarabine (n=11) Melphalan (n=8) Busulfan (n=2) Cyclophosphamide (n=2) Etoposide (n=2) Antithymocyte globulin (n=9) Total-body irradiation (n=7)**	Myeloablative (n=24) Reduced toxicity myeloablative (n=6) Reduced-intensity (n=35) Nonmyeloablative (n=1)
Overall survival	**81% (n=9)**	**78% (n=7)**	**86% (n=49)**

*Data from Dimitrova et al., 2022 includes data from Nademi et al., 2017 and Okano et al., 2019. **Each patient received more than one therapy as part of their conditioning regimen. **References**: 1. Coulter TI& Cant AJ. *Front Immunol*. 2018; 9: 2043 2. Nademi Z et al. *J Allergy Clin Immunol*. 2017; 139(3): 1046-1049. 3. Okano T et al. *J Allergy Clin Immunol*. 2019; 143(1): 266-275. 4. Dimitrova D et al. *J Allergy Clin Immunol*. 2022; 149(1): 410-421.e7. **Abbreviations**: APDS1: activated PI3K delta syndrome 1; HSCT: haemopoietic stem cell therapy.

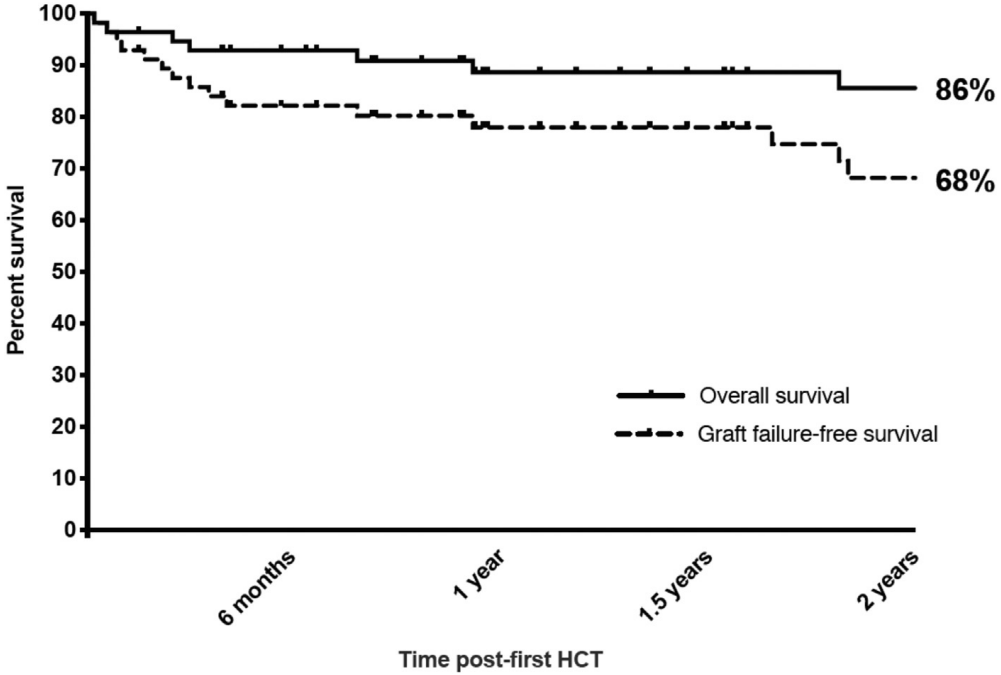
International retrospective study of allogeneic hematopoietic cell transplantation for activated PI3K-delta syndrome

- 57 patients with APDS1/2 (median age, 13 years; range, 2-66 years) treated with allo-HSCT
- Median follow-up: 2.3 years

Indication for HCT, no. of patients	Total (n = 57)
Hematologic malignancy	15 (26)
Nonmalignant lymphoproliferation	28 (49)
Autoimmune cytopenias	8 (14)
Chronic or recurrent infections	26 (46)
End organ damage	24 (42)
Lung	16 (28)
Gastrointestinal tract	9 (16)
Liver	6 (11)
Kidney	2 (4)
Multiple organs	7 (12)
Multiple indications	30 (53)

	Total HCTs (n = 66)	MSD HCTs (n = 7)	8/8 MUD HCTs (n = 36)	Haplo HCTs (n = 15)	Other HCTs (n = 8)
Conditioning intensity					
MAC	24 (36)	7 (100)	11 (31)	5 (33)	1 (13)
RT-MAC	6 (9)	0	6 (17)	0	0
RIC	35 (53)	0	19 (53)	9 (60)	7 (88)
Nonmyeloablative conditioning	1 (2)	0	0	1 (7)	0
Serotherapy use	55 (83)	5 (71)	34 (84)	11 (73)	5 (63)
Antithymocyte globulin	33 (50)	4 (57)	18 (50)	8 (53)	3 (38)
Rabbit	29 (44)	4 (57)	15 (42)	7 (47)	3 (38)
Horse	4 (6)	0	3 (8)	1 (7)	0
Alemtuzumab	22 (33)	1 (14)	16 (44)	3 (20)	2 (25)
Proximal timing (administered day −8 or closer to HCT)	15 (23)	1 (14)	12 (33)	0	2 (25)
Intermediate timing (administered between days −16 and −9)	7 (11)	0	4 (11)	3 (20)	0
Total body irradiation (total dose, 2-4 Gy)	12 (18)	0	6 (17)	3 (20)	3 (38)
GVHD prophylaxis					
Calcineurin inhibitor-based	48 (73)	7 (100)	29 (81)	5 (3)	7 (88)
Posttransplantation cyclophosphamide-based	13 (20)	0	5 (14)	8 (53)	0
Graft manipulation	8 (13)	0	4 (11)	3 (20)	1 (13)
α/β T-cell/CD19$^+$ depletion, with or without CD45RA$^-$ add-back	6 (9)	0	3 (8)	2 (13)	1 (13)
α/β T-cell depletion	1 (2)	0	0	1 (7)	0
CD34$^+$ positive selection	1 (2)	0	1 (3)	0	0
No pharmacologic prophylaxis apart from serotherapy	3 (5)	0	0	2 (13)	1 (13)
Other*/incomplete information	2 (3)	0	2 (6)	0	0

APDS outcome after allo-HSCT

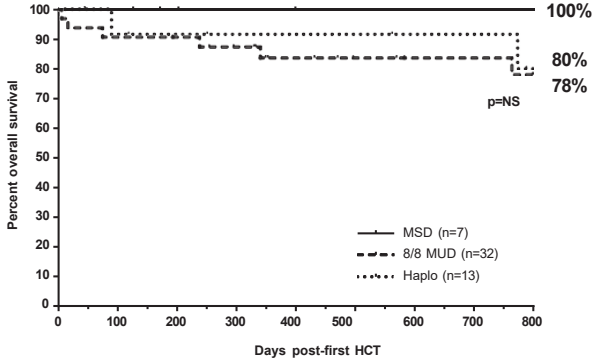


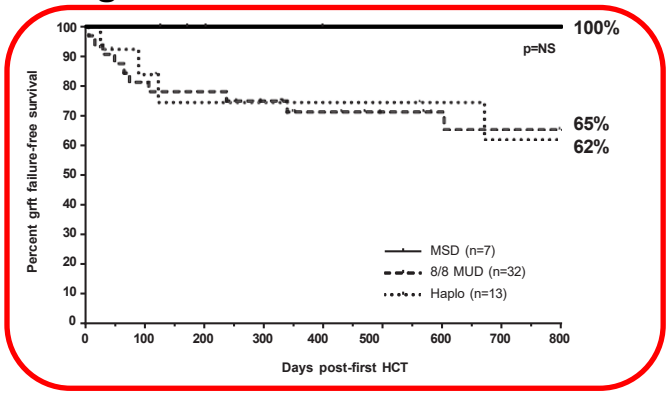
2-year OS and graft failure–free survival did not differ significantly by APDS1 versus APDS2, donor type, or conditioning intensity.

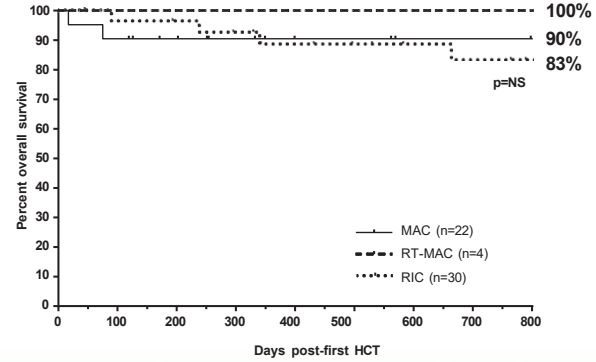
Outcome	Patients (n = 48)
Alive and well with phenotype reversal	41 (85)
Full donor chimerism (>95%)*	33 (69)
Mixed $CD3^+$ donor chimerism only (<95%)†	3 (6)
Mixed donor chimerism in both compartments (<95%)‡	3 (6)
Other§	2 (6)
Alive with phenotype reversal but significant ongoing complications‖	4 (8)
Other	3 (6)
Partial phenotype reversal, mixed donor chimerism¶	2 (4)
Too early to evaluate phenotype reversal (<100 days post-HCT)	1 (2)

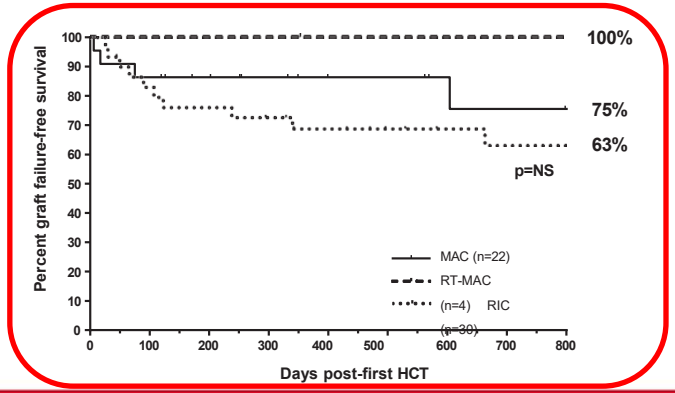
Dimitrova D. et al. J Allergy Clin Immunol 2022; 149:410-421.

APDS outcome after allo-HSCT: OS and graft failure-free survival

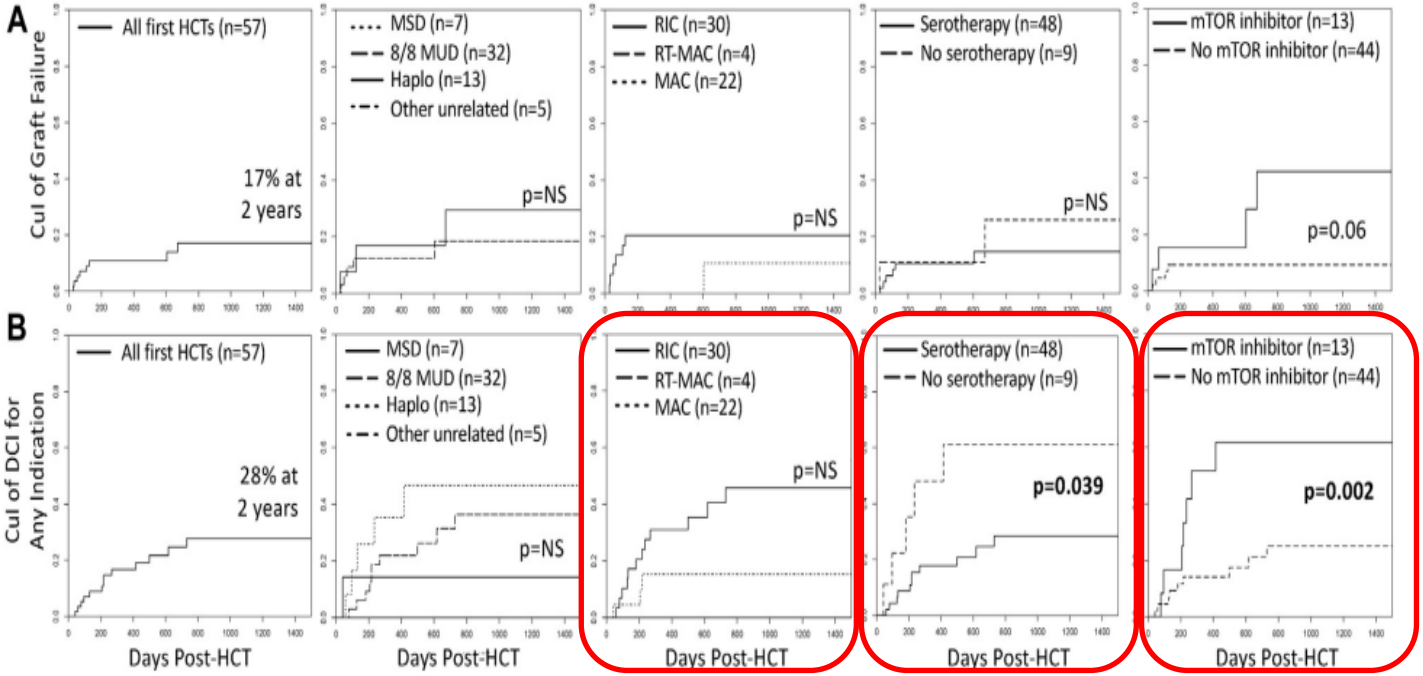








Cumulative incidence of graft failure after first HSCT and subsequent unplanned donor cell infusion (DCI) for any indication after first HSCT



The 2-year CI of graft failure after first HCT was 17% overall **but 42% if mTOR inhibitor(s) were used** in the first year post-HCT, compared with 9% without mTOR.

Serotherapy significantly decreased the risk of graft failure.

APDS treatment: the PI3Kδ inhibitor Leniolisib

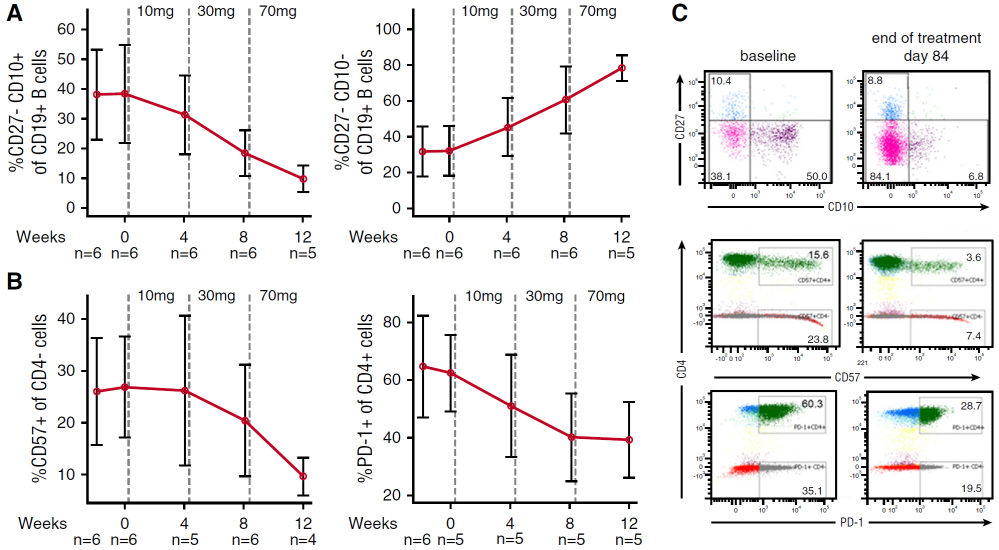
Effective "activated PI3Kδ syndrome"–targeted therapy with the PI3Kδ inhibitor leniolisib

blood

V. Koneti Rao,[1] Sharon Webster,[1] Virgil A. S. H. Dalm,[2,3] Anna Šedivá,[4] P. Martin van Hagen,[2,3] Steven Holland,[1] Sergio D. Rosenzweig,[5] Andreas D. Christ,[6] Birgitte Sloth,[6] Maciej Cabanski,[6] Aniket D. Joshi,[6,7] Stefan de Buck,[6] Julie Doucet,[6] Danilo Guerini,[6] Christoph Kalis,[6] Ilona Pylvaenaeinen,[6] Nicolas Soldermann,[6] Anuj Kashyap,[1] Gulbu Uzel,[1] Michael J. Lenardo,[1] Dhavalkumar D. Patel,[6] Carrie L. Lucas,[1] and Christoph Burkhart[6]

Key Points

- Leniolisib, a novel, potent, selective oral PI3Kδ inhibitor was tested in patients with gain-of-function pathogenic variants in *PIK3CD*.
- Treatment was well tolerated and led to **improvement in cellular immune dysfunction**



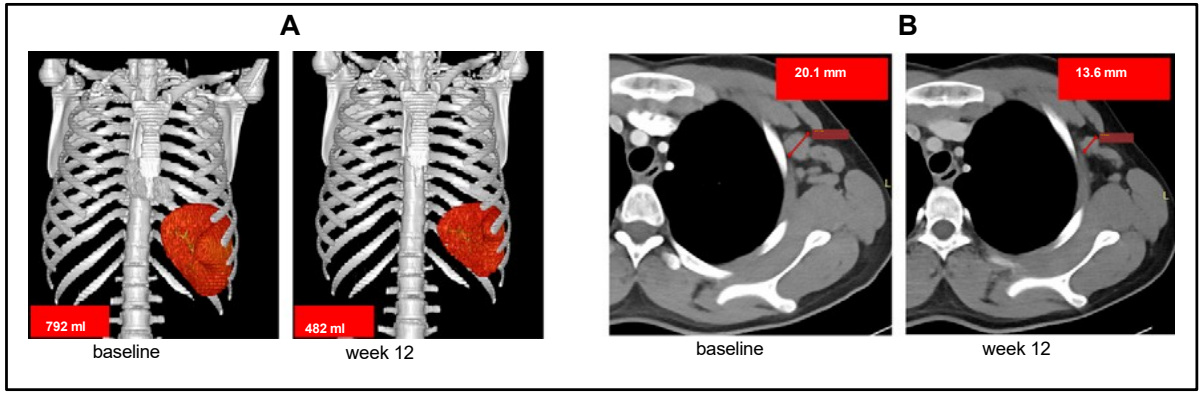
IMMUNOBIOLOGY AND IMMUNOTHERAPY

Effective "activated PI3Kd syndrome"–targeted therapy with the PI3Kd inhibitor leniolisib

V. Koneti Rao,[1] Sharon Webster,[1] Virgil A. S. H. Dalm,[2,3] Anna Šedivá,[4] P. Martin van Hagen,[2,3] Steven Holland,[1] Sergio D. Rosenzweig,[5] Andreas D. Christ,[6] Birgitte Sloth,[6] Maciej Cabanski,[6] Aniket D. Joshi,[6,7] Stefan de Buck,[6] Julie Doucet,[6] Danilo Guerini,[6] Christoph Kalis,[6] Ilona Pylvaenaeinen,[6] Nicolas Soldermann,[6] Anuj Kashyap,[1] Gulbu Uzel,[1] Michael J. Lenardo,[1] Dhavalkumar D. Patel,[6] Carrie L. Lucas,[1] and Christoph Burkhart[6]

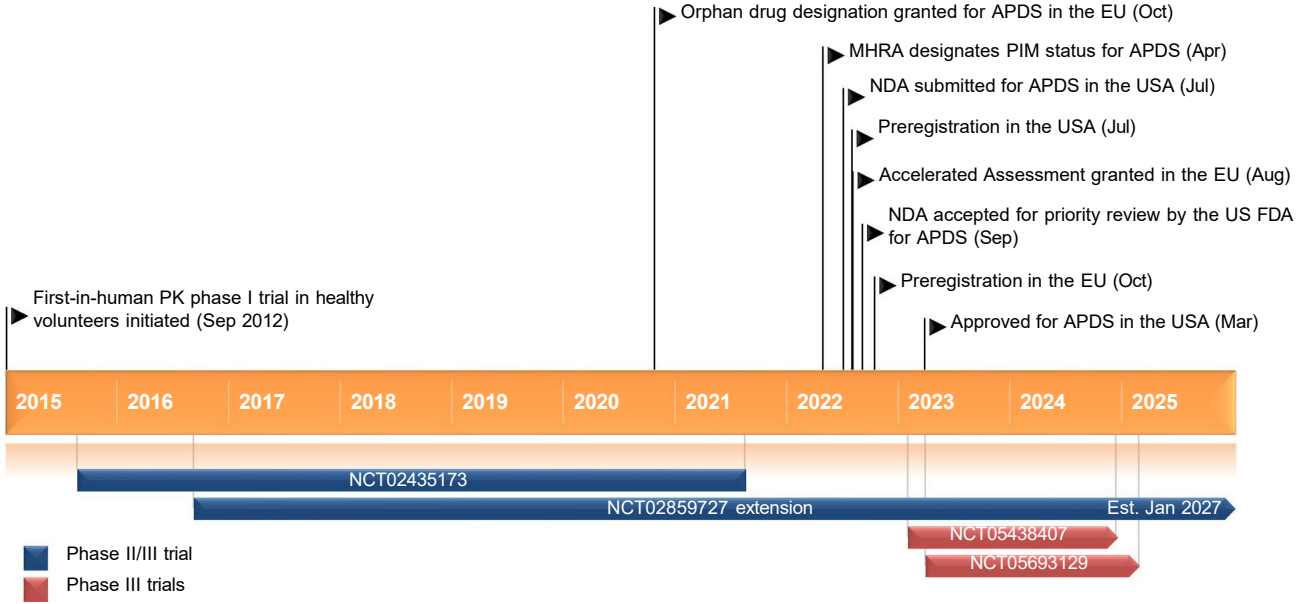
Key Points

- Leniolisib, a novel, potent, selective oral PI3Kδ inhibitor was tested in patients with gain-of-function pathogenic variants in *PIK3CD.*
- Treatment was well tolerated and led to **reduction of lymphoproliferation**.



Leniolisib development key milestone

Leniolisib (JOENJA®): Key Points
A selective PI3Kδ inhibitor is being developed by Pharming Group NV for the treatment of activated PI3Kδ syndrome (APDS).
Received its first approval on 24 March 2023 in the USA
Approved for use in the treatment of APDS in adult and paediatric patients 12 years of age and older.



Key milestones in the development of leniolisib for the treatment of activated phosphoinositide 3-kinase-delta syndrome (ADPS).
MHRA Medicines and Healthcare Products Regulatory Agency, *NDA* new drug application, *PIM* promising innovative medicine, *PK* pharmacokinetics

APDS treatment: use of PI3Kδ inhibitor Leniolisib

- Leniolisib favors abrogation of aberrant PI3K/AKT pathway activity, normalization of immune phenotype, cytokine/chemokine modulation:
  - clinical responses: regression of splenomegaly and lymphadenopathy, improvements in clinical signs and symptoms

- Use of Leniolisib in APDS patients:
  - bridge therapy to allo-HSCT
  - long-term treatment in patients without indication for HSCT

- Ongoing/future clinical research:
  - role in preventing lymphoma
  - use in APDS2
  - broaden application for the treatment of other autoimmune/nonmalignant lymphoproliferative disorders

Take home messages

- Patients with APDS showed variable life-threatening manifestations, like immunodeficiency. autoimmunity and massive lymphoproliferation.
- Treatment with mTOR inhibitors can help control some of the symptoms, but does not eliminate the risk of lymphoma and is associated with an increased risk of graft failure after HSCT.
- Therapy with mTOR inhibitors and, particularly, specific PI3Kδ inhibitors (Leniolisib) can be beneficial, perhaps as a bridge to HSCT.
- HSCT is considered as a valuable option in the treatment of APDS because can reverse phenotype and ameliorated clinical symptoms
  - Transplantation-related complications, including graft failure, still represents the major barrier to successful HSCT.
  - The precise indications, optimal time point for HSCT, and best transplant platform need to be defined.