IPOPI 4TH REGIONAL ASIAN PID MEETING

19-20 NOVEMBER 2022

KUALA LUMPUR, **MALAYSIA**

an **IPOPI** event

CARE FOR RARE

GLOBAL ALLIANCE EDUCATIONAL SEMINAR

Care-for-Rare Foundation

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Looking ahead: advanced therapies in Asia

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Treatment of Primary Immunodeficiencies

How do we treat PID now?

What do we want?

And how do we get there?

An example of primary antibody deficiencies

Common Variable Immune Deficiency (CVID)

Low levels of antibodies (IgG + IgA and/or IgM)
Disturbed response to vaccination
Recurrent (respiratory tract) infections

Autoimmune complications
Autoinflammatory conditions
Hematological diseases

Common Variable Immune Deficiency

Infections

Granuloma, enteropathy

Arthritis,
autoimmune cytopenia

Immunodeficiency

Autoinflammation

Autoimmunity

Common Variable Immune Deficiency

Infections

Granuloma, enteropathy

**Arthritis,
autoimmune cytopenia**

**Antibiotics (on demand, prophylaxis)
Immunoglobulin replacement therapy**

**Immunosuppressive therapies, including
prednisone, azathioprine, Rituximab**

Current treatment is mainly symptomatic

Prevention of infections

Treatment of infections and autoimmune complications

But no prevention of autoimmune disease or hematological disease

Curative treatment options available?

Future perspectives

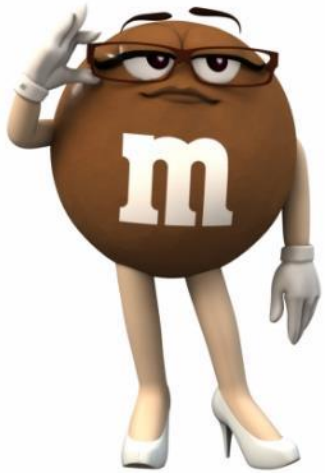
Identification of genetic defects and pathways

APDS

CTLA4

X-MAID

CD27



LRBA

Identification of genetic defects and pathways

APDS

Understanding of the mechanisms involved

Prognosis / complications

Counceling

Therapeutic targets

From CVID to APDS

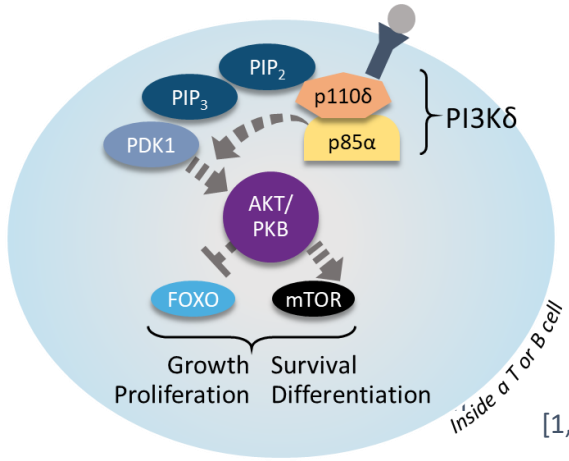
Clinical or immunological manifestation	Patients
Recurrent respiratory and ear infections (*H. influenzae* and *S. pneumoniae*)	P1–17
CT evidence of large (bronchiectasis) or small (mosaic attenuation) airway disease	P1–7, 9, 11–13, 17
Splenomegaly (before the onset of recurrent infections)	P2, 3, 5, 6, 8, 9, 13–16
Skin, salivary gland, lacrimal gland, or dental abscess formation; orbital cellulitis	P1, 3, 5–8, 10
Infection caused by herpes group viruses (HSV, CMV, VZV, and EBV)	P3, 8, 12, 13 (and the deceased sister of P5/P6)
Marginal zone lymphoma	P13
Low/intermittent low-serum IgG2 levels	P2–7, 10–13
High/intermittent high-serum IgM levels	P1–6, 8–11, 13–16
Low levels of antibodies to *S. pneumoniae*	P1–4, 7, 9, 11–13, 17
Low levels of antibodies to *H. influenzae* type B	P1–4, 8, 9, 12, 13
Decreased circulating T cells (total $CD3^+$) and/or $CD4^+$ and/or $CD8^+$ T cells	P1–9, 13, 14, 17
Decreased circulating B cells (total $CD19^+$)	P2–9, 13, 14-16
Increased circulating transitional B cells ($CD19^+CD38^+IgM^+$)	P1–4, 7–14, 16, 17
Decreased circulating class-switched memory B cells ($CD19^+CD27^+IgD^-$)	P1–3, 8, 9, 12, 13, 16

CVID-like phenotype

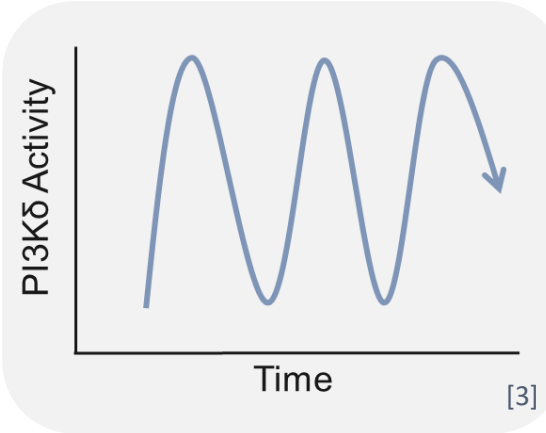
Angelo I et al. 2013 Science

The PI3Kδ Pathway Controls Lymphocyte Development, Trafficking, and Function

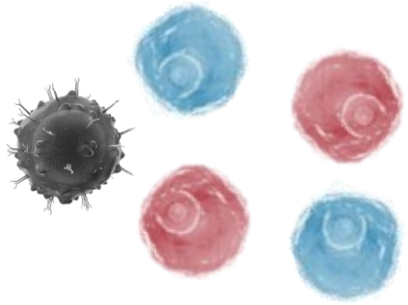
PI3Kδ activity kick-starts cascades that instruct T and B cells to multiply, mature, or undergo apoptosis[1,2]



[1,2]

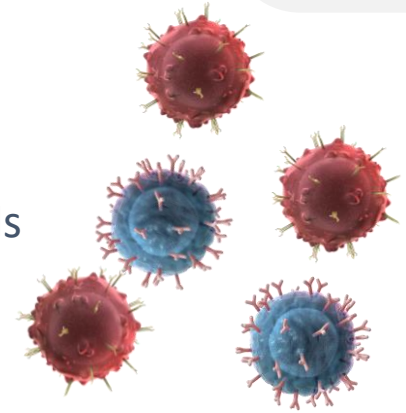


[3]



Immature and senescent cells

Functional cells

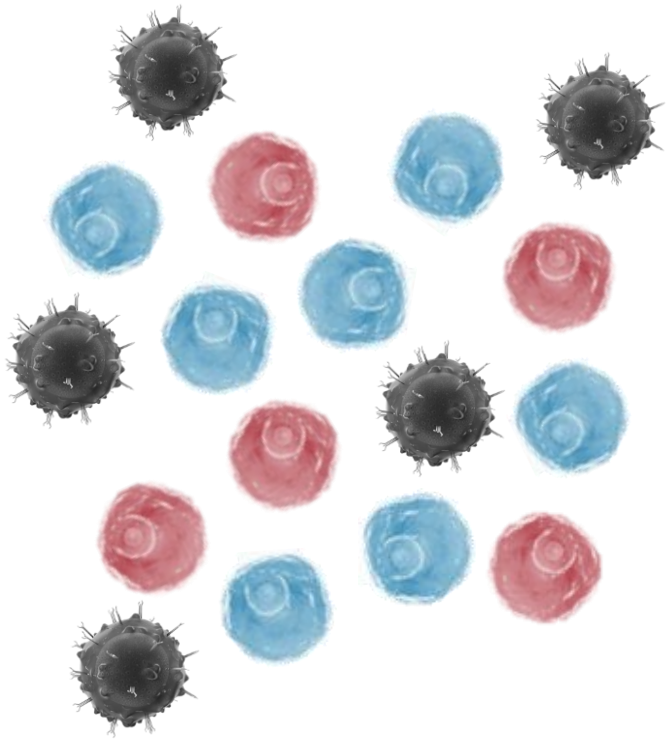


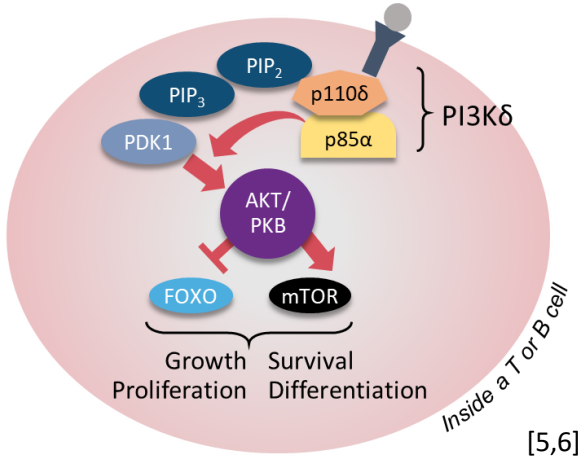
PI3Kδ activity tightly balanced

Fruman D et al. Cell 2017; Okkenhaug K et al. Nat Rev Immunol 2003; Okkenhaug K et al. Ann Rev Immunol 2013

Unbalanced PI3Kδ Pathway Activity Alters T And B Cells

In APDS, PI3Kδ is overactive[1-4]



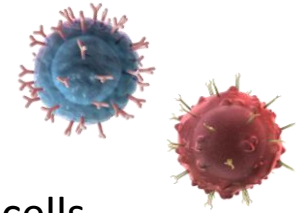


[5,6]

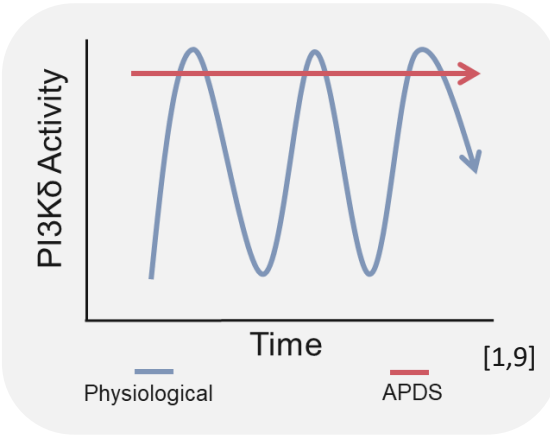
Immature and senescent cells

Hyperactive PI3Kδ

Functional cells



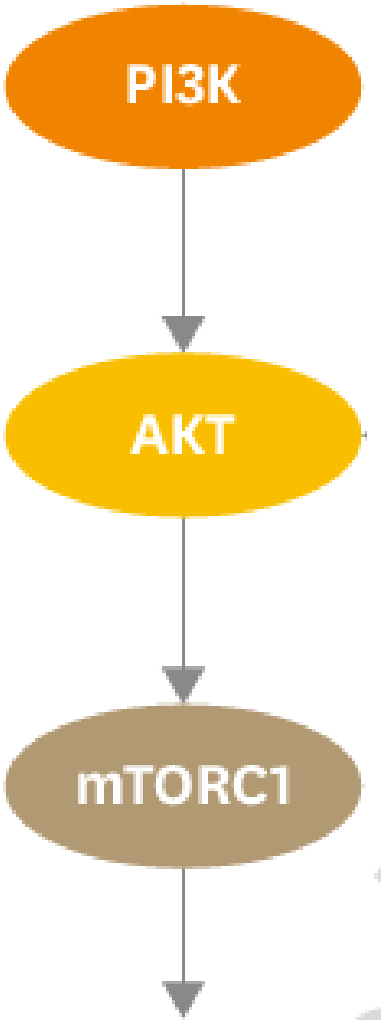
Resulting in unbalanced PI3Kδ activity, leading to altered T and B cell development and function[1,7,8]



[1,9]

Lucas CL et al. Nat Immunol 2014; Angulo I et al. Science 2013; Lucs CL et al. J Exp Med 2014; Deau MC et al. J Clin Invest 2014; Fruman DA et al. Cell 2017; Okkenhaug K et al. Nat Rev Immunol 2003; Coulter TI et al. J Allergy Clin Immunol 2017; Elkaim E et al. J Allergy Clin Immunol 2016; Okkenhaug K et al. Annu Rev Immunol 2013

New insights in treatment

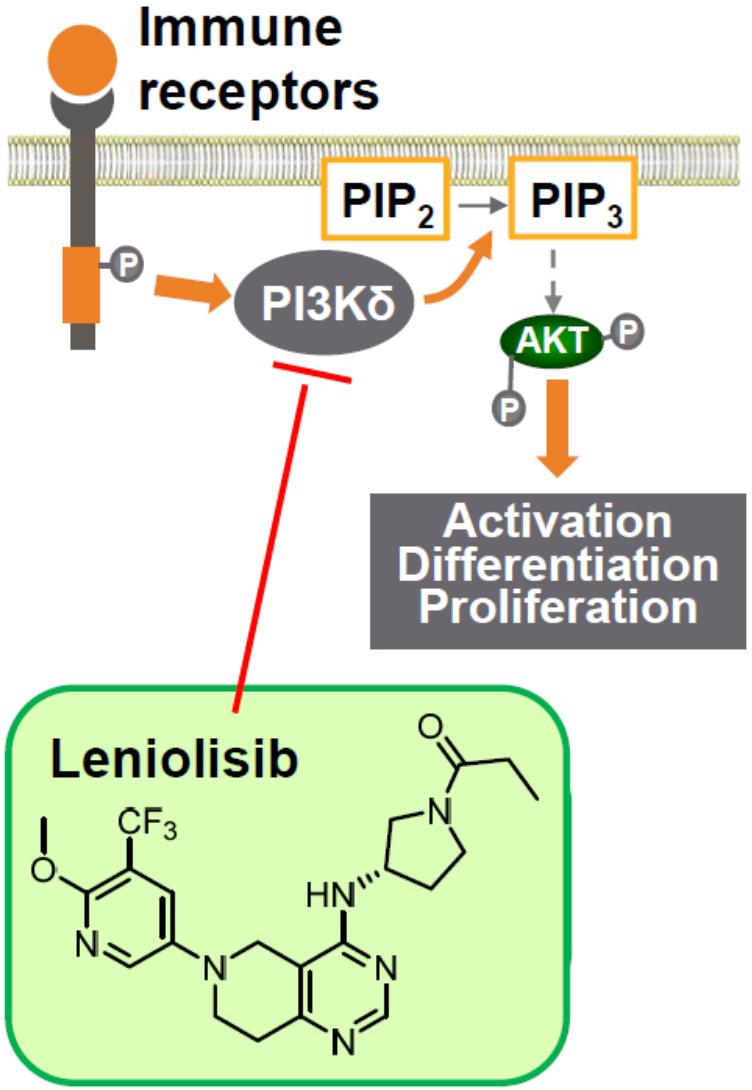


PI3K inhibitors

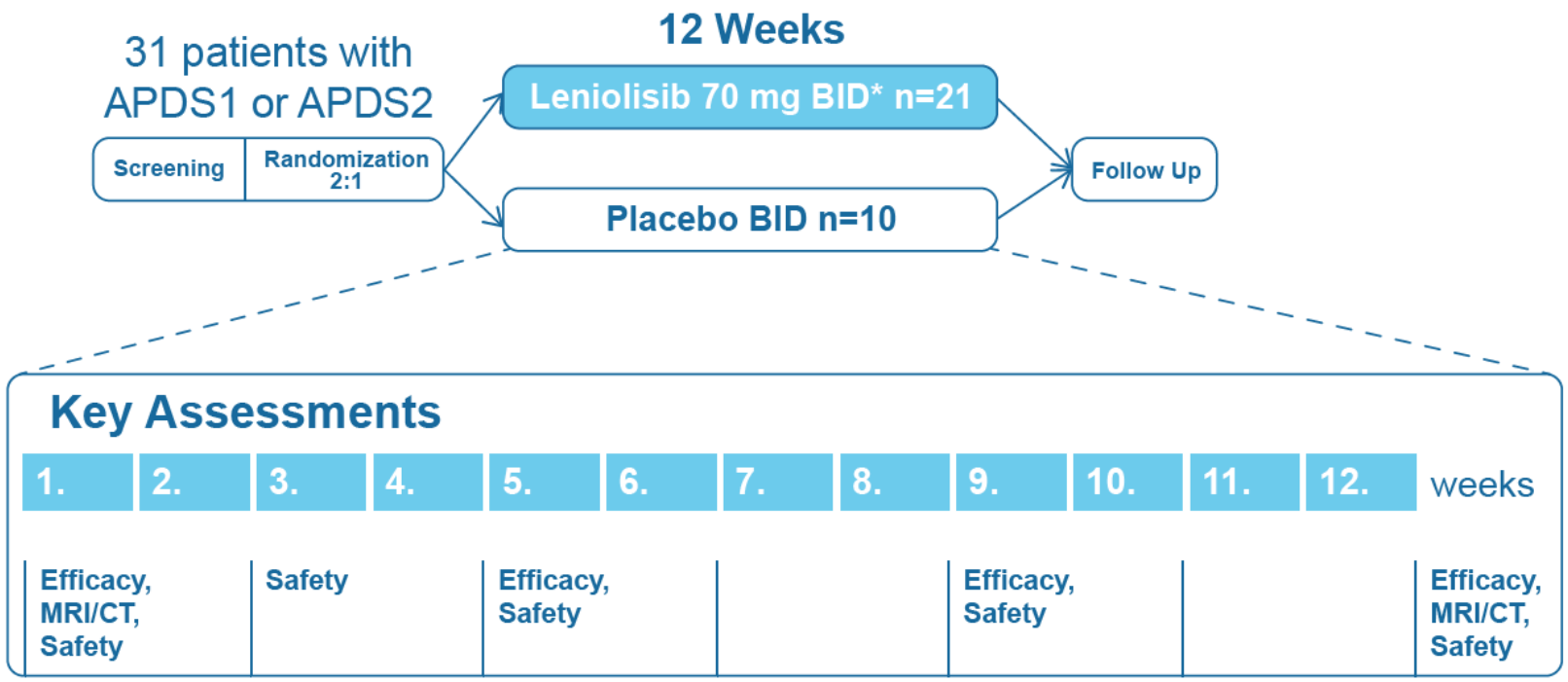
Leniolisib

mTOR inhibitors

Rapamycine



A Multinational, Triple-Blind, Placebo-Controlled, Randomized Clinical Trial



Primary Outcome Measures

Change at 12 weeks from baseline in:

- $\log_{10}$-transformed sum of product of diameters in the index lesions (lymph nodes)
- Percentage of naïve B cells out of total B cells

Analysis[1]

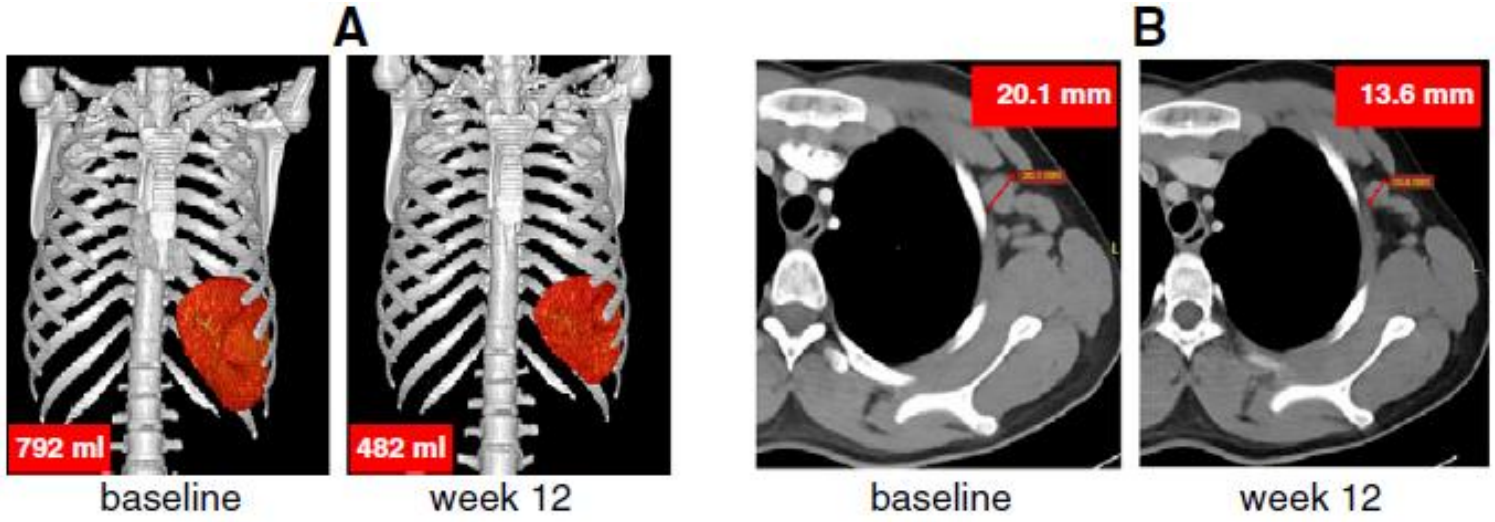
Data were analyzed using ANCOVA model. Use of glucocorticoids and IVIG at baseline were both included as categorical (Yes/No) covariates

Data on file. Pharming Healthcare Inc. 2022. 2. Study of efficacy of CDZ173 in patients with APDS/PASLI. ClinicalTrials.gov identifier: NCT02435173; Rao VK, et al. Blood. 2017.

A Multinational, Triple-Blind, Placebo-Controlled, Randomized Clinical Trial

Table 2. Spleen volumes, lymph node size, and liver volumes

	Spleen 3D volume			Lymph node SPD			Liver 3D volume*		
	Baseline, mm^3	End of study, mm^3	ΔBaseline, %	Baseline, mm^2	End of study, mm^2	ΔBaseline, %	Baseline, mm^3	End of study, mm^3	ΔBaseline, %
Patient 1	978 783	719 915	−26	2453	1194	−51	1 849 588	1 650 823	−11
Patient 2	792 042	482 188	−39	1926	1681	−13	1 438 041	1 413 010	−2
Patient 3	385 832	166 402	−57	1235	427	−65	1 349 165	1 442 528	7
Patient 4	782 213	500 841	−36	748	503	−33	1 398 929	1 332 235	−5
Patient 5	419 843	254 634	−39	258	133	−48	1 396 210	1 359 013	−3
Patient 6	721 831	451 208	−37	858	589	−31	1 817 801	1 904 876	5
Mean ± SD			−39 ± 10			−40 ± 19			−1 ± 6

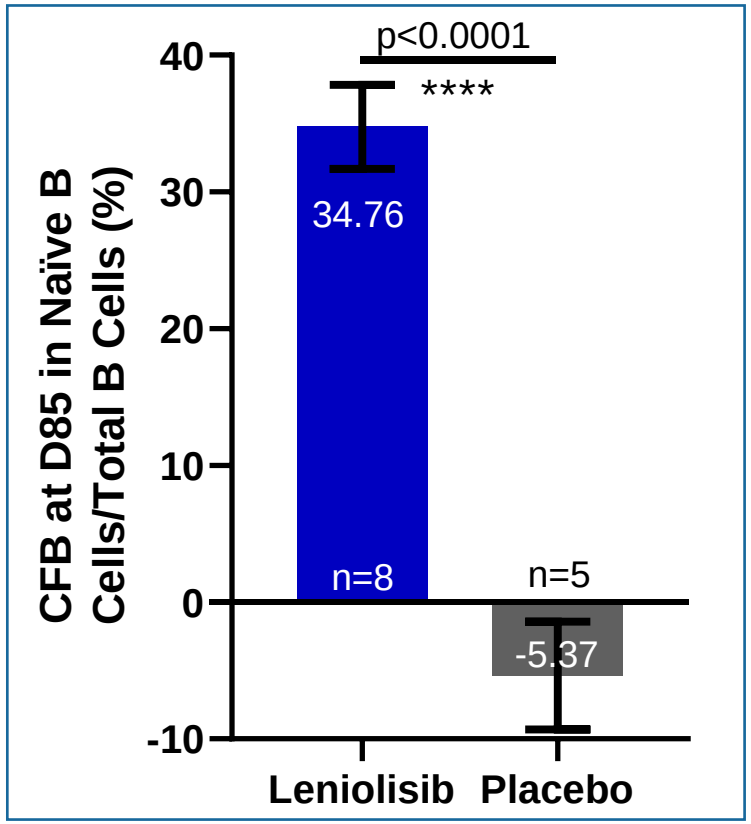


Rao VK, et al. Blood. 2017

A Multinational, Triple-Blind, Placebo-Controlled, Randomized Clinical Trial

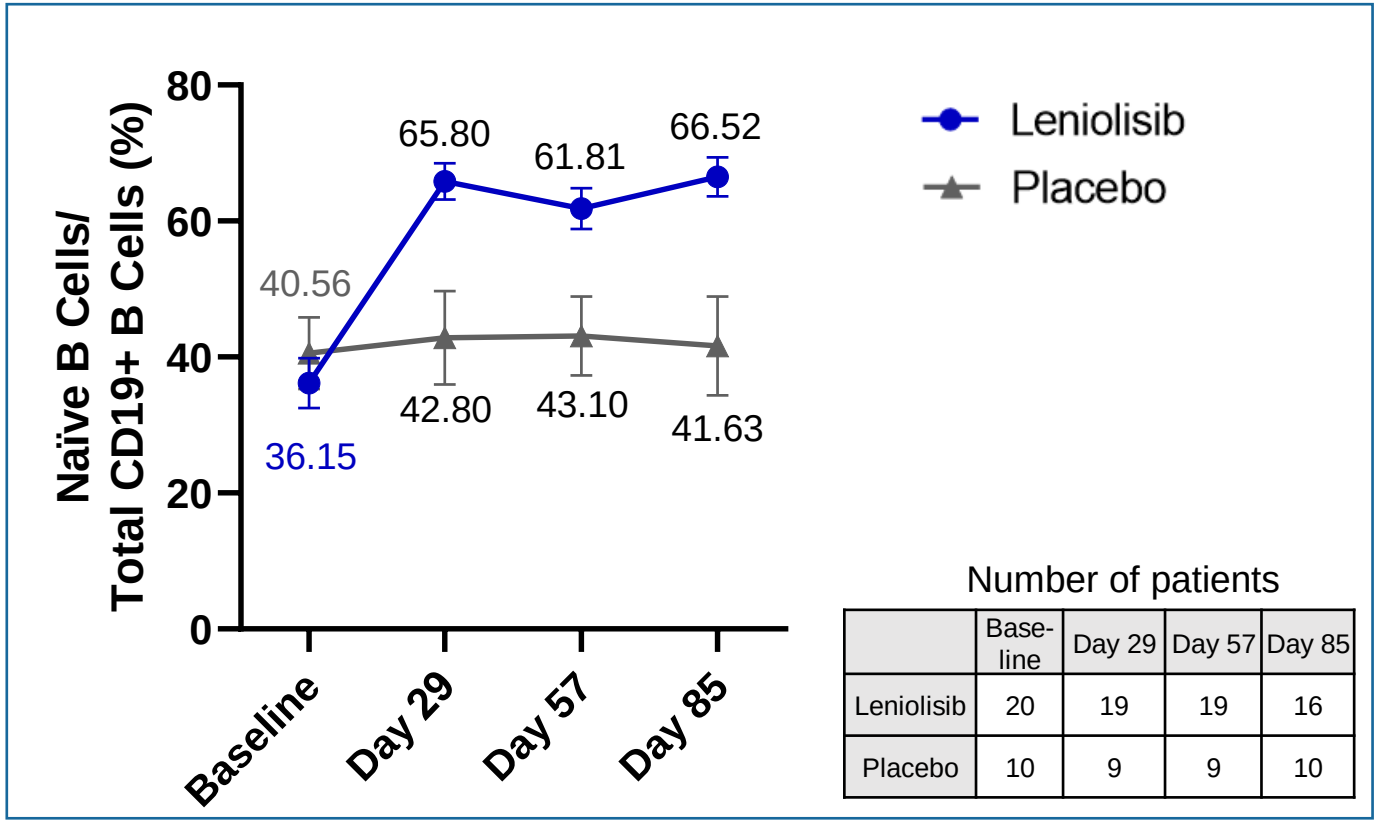
Primary Outcome Analysis*

Change from baseline in naïve B cells



Mean Percentage of Naïve B Cells Over Time

Safety analysis set



Number of patients

	Base-line	Day 29	Day 57	Day 85
Leniolisib	20	19	19	16
Placebo	10	9	9	10

Data on file. Pharming Healthcare Inc. 2022. 2. Study of efficacy of CDZ173 in patients with APDS/PASLI. ClinicalTrials.gov identifier: NCT02435173; Rao VK, et al. Blood. 2017.

Current treatment is mainly symptomatic

“Restoration” of lymphocyte subsets

Less fatigue, increased energy

Increased exercise tolerance
Less infections

Decrease in lymphadenopathy and hepatosplenomegaly

In 2 patients immunoglobulin replacement was stopped

In 3 patients immunoglobulin doses were reduced

From symptomatic to targeted therapy

Limitations

- Availibility / costs

Role of patient orginzations

Role of pharmaceutical companies : societal impact

Towards more personalized treatment, up the ladder?

Thank you

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