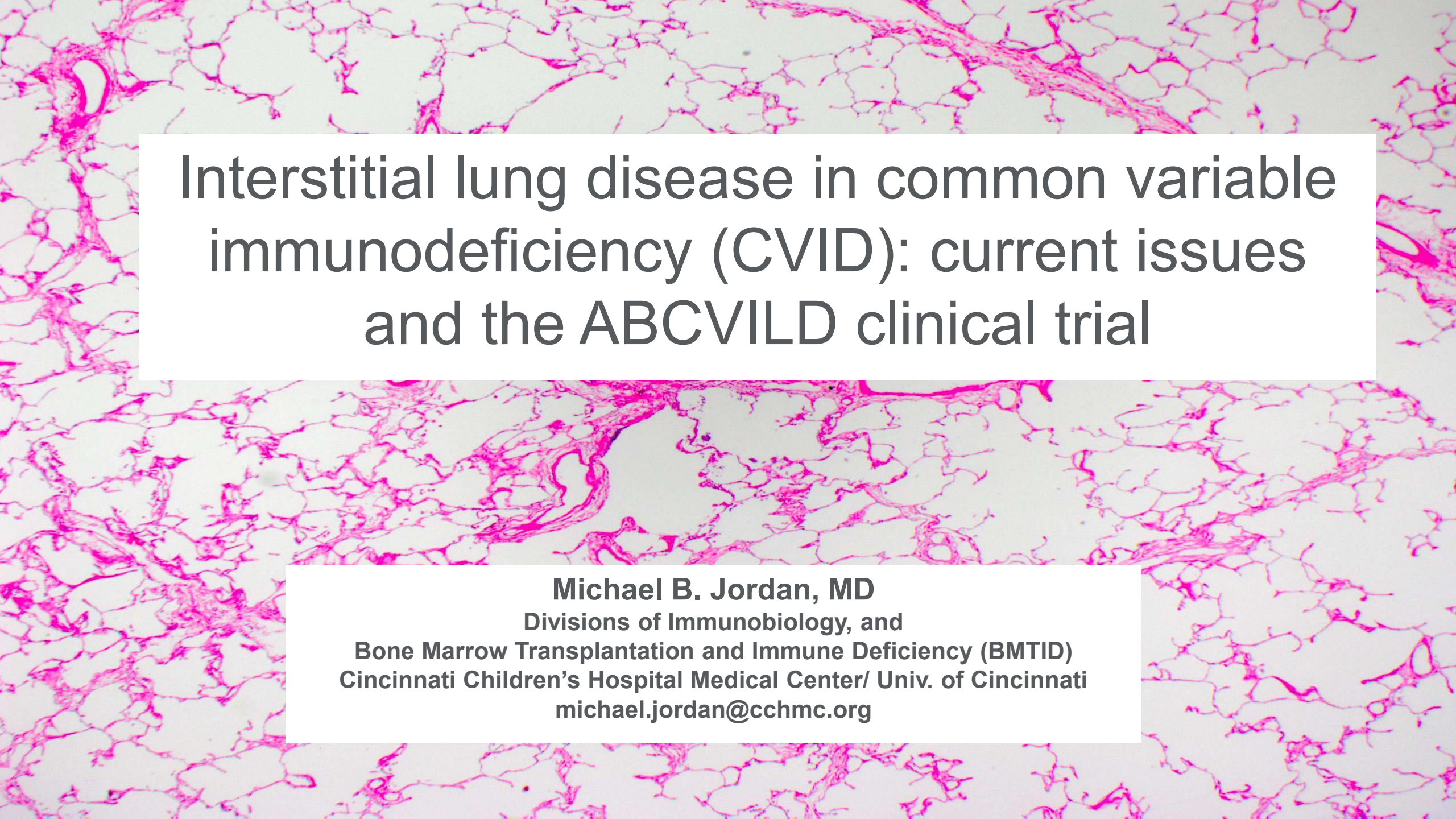

Interstitial lung disease in common variable immunodeficiency (CVID): current issues and the ABCVILD clinical trial

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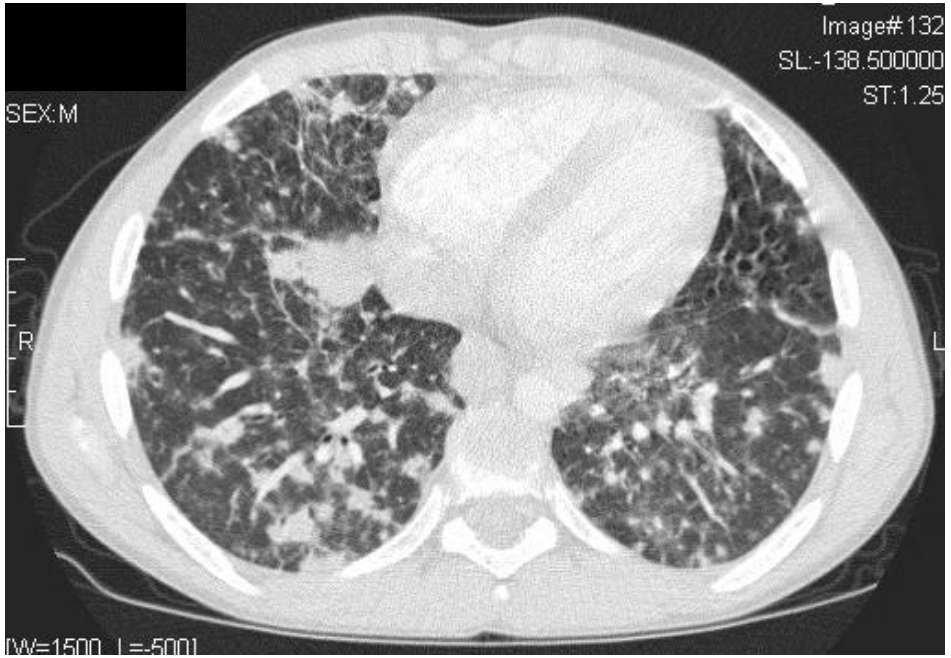
Overview

- The problem of GLILD in CVID
- How is GLILD treated?
- Why Abatacept?; Why the ABCVILD trial?
- Overview of the trial

Disclosures:
The ABCVILD trial is supported by a grant from the FDA and study drug is supplied by Bristol Myers Squibb (the makers of abatacept)

What is GLILD? Why is it a problem?



Common Variable Immunodeficiency (CVID)

- Group of disorders with a variety of known and unknown genetic causes defined by low immunoglobulins leading to recurrent or severe infections
- Immune deficiency can be effectively treated in most with immunoglobulin replacement
- Prevalence around 1:50,000
- Typically diagnosed in 2nd-4th decade of life after secondary causes of hypogammaglobulinemia have been ruled out
- CVID is not *just* an immune deficiency: about 1/3 of patients also have inflammatory complications- including autoimmunity, or accumulation of immune cells in lungs, liver or gut, enlarged spleen, etc
- These ‘complications’ are the major driver of medical difficulties and premature mortality

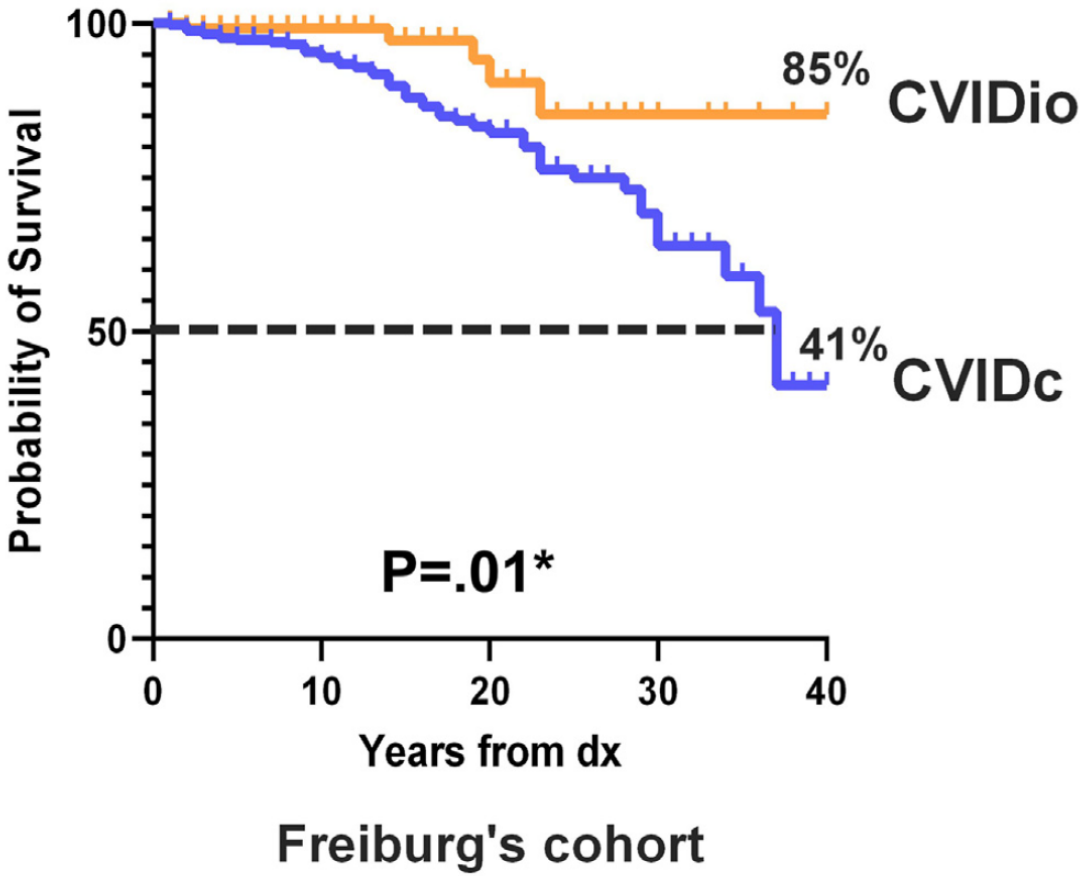


FIGURE 2. Overall survival after CVID diagnosis. The log-rank test was used to compare survival in CVIDio and CVIDc. The time of event was considered time of death and censoring as the loss of follow-up. *CVID*, Common variable immunodeficiency; *CVIDc*, complicated CVID; *CVIDio*, infection-only CVID; *dx*, diagnosis.

Bez et al, 2025

Prevalence of complications in CVID patients

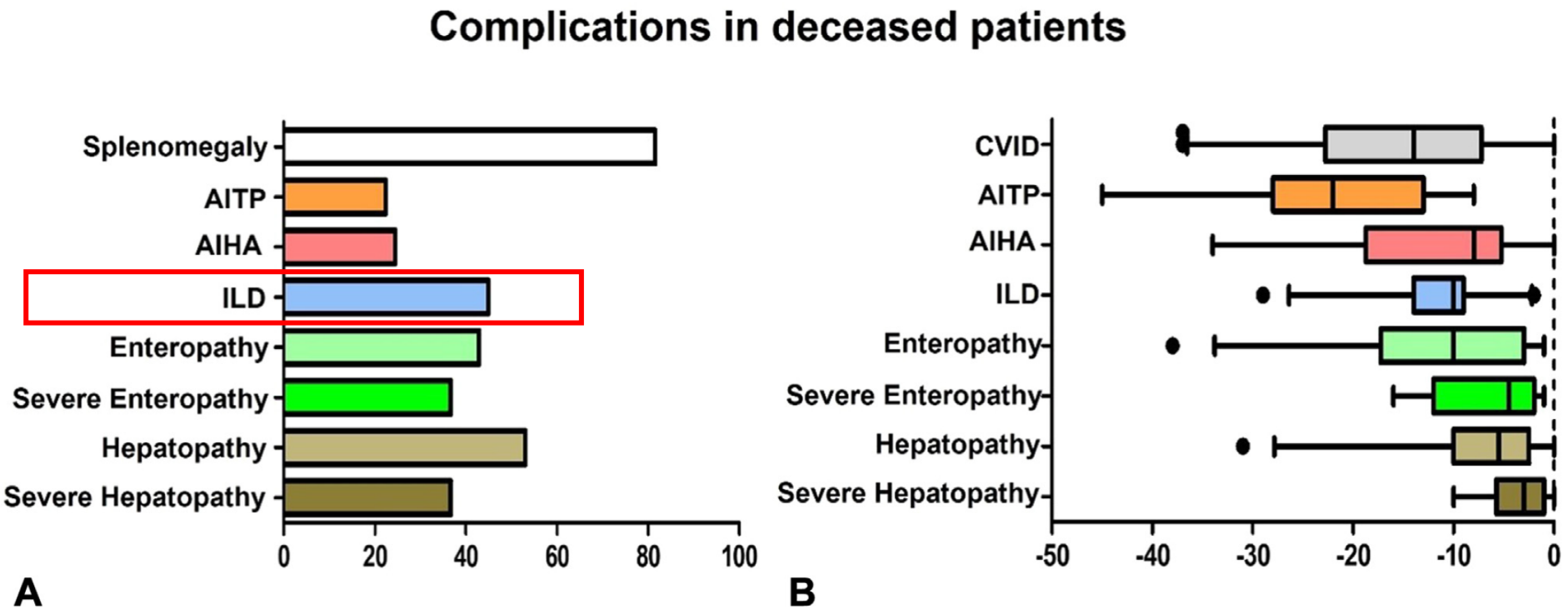


FIGURE E2. Prevalence of various complications and their time interval from death. (**A**) The bar chart displays the prevalence of selected noninfectious complications in percent. (**B**) The box plot shows the time between diagnosis of the respective complication and death (dashed line). The boxes represent the interquartile range, the whiskers the 5th-95th percentiles, and the dots the outliers. Panel **B** refers to the 49 deceased patients (excluding those who had previously undergone HSCT or died for non–health-related conditions). *AIHA*, Autoimmune hemolytic anemia; *AITP*, autoimmune thrombocytopenia; *CVID*, common variable immunodeficiency; *HSCT*, hematopoietic stem cell transplantation; *ILD*, interstitial lung disease.

Bez et al, 2025

CVID patients with immune dysregulation- especially chronic lung disease- have increased mortality risk

Table 8. Cox proportional hazards modeling of complications

	HR	95% CI	*P*
Any complication	10.96	(3.46, 34.69)	< .0001*
Gastrointestinal disease	2.78	(1.44, 3.59)	.0004*
Liver disease/hepatitis	2.48	(1.51, 4.09)	.0003*
Lymphoma	2.44	(1.43, 4.16)	.0010*
Chronic lung disease (structural and functional)	2.06	(1.34, 3.16)	.0010*
Malabsorption	2.06	(1.11, 3.81)	.0218*
Splenectomy	1.69	(0.91, 3.12)	.0957
Cancer	1.51	(0.795, 2.87)	.2084
Autoimmunity	1.36	(0.87, 2.12)	.1735
Granuloma	1.27	(0.65, 2.48)	.4939
Bronchiectasis	0.76	(0.39, 1.48)	.4235

Adjusted for age at diagnosis.
**P* value significant at the .05 level.

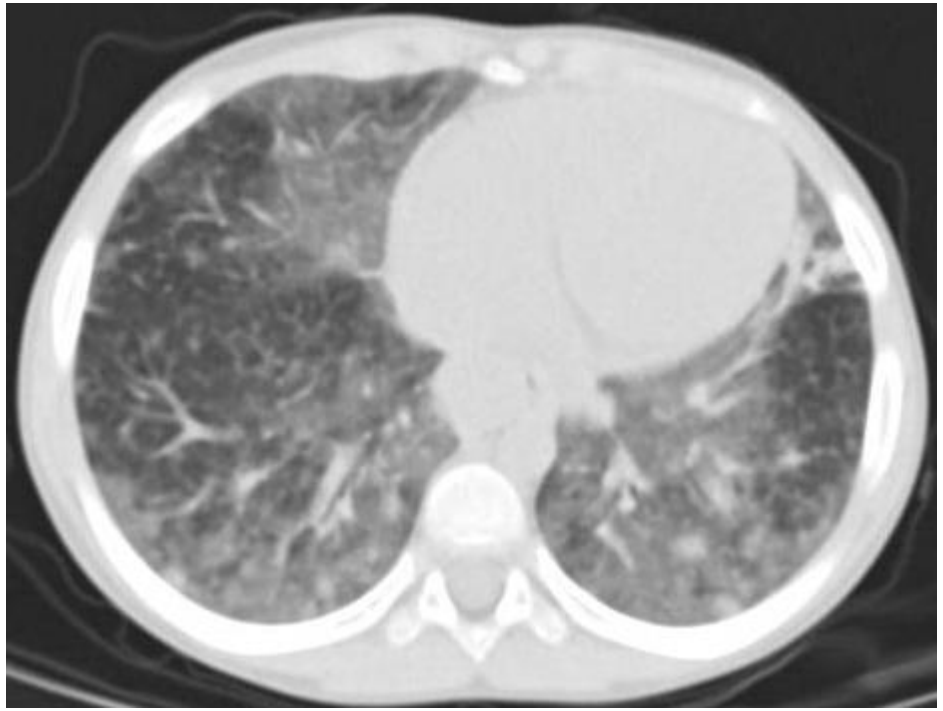
Respiratory failure was number 1 cause of death

HR= Hazards Ratio

Resnick ES et al. Blood 2012;119:1650-1657

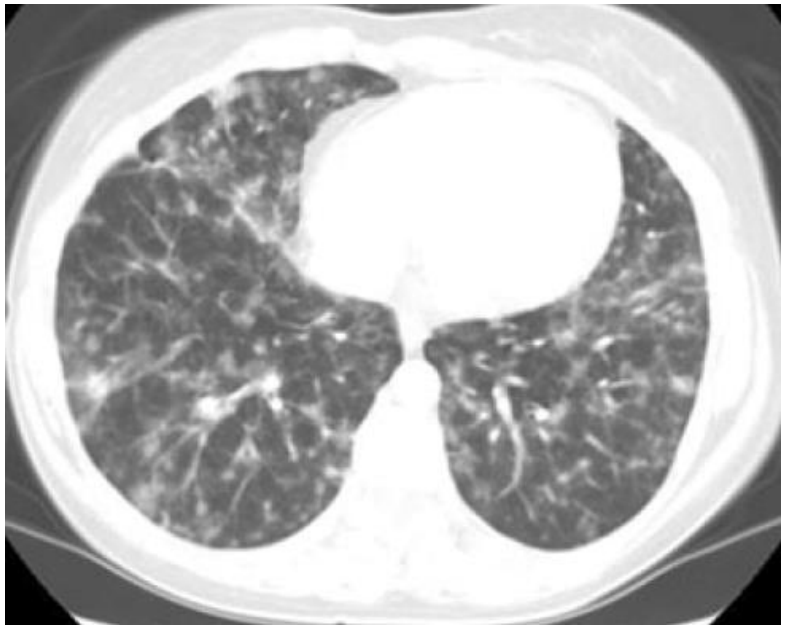
GLILD in CVID

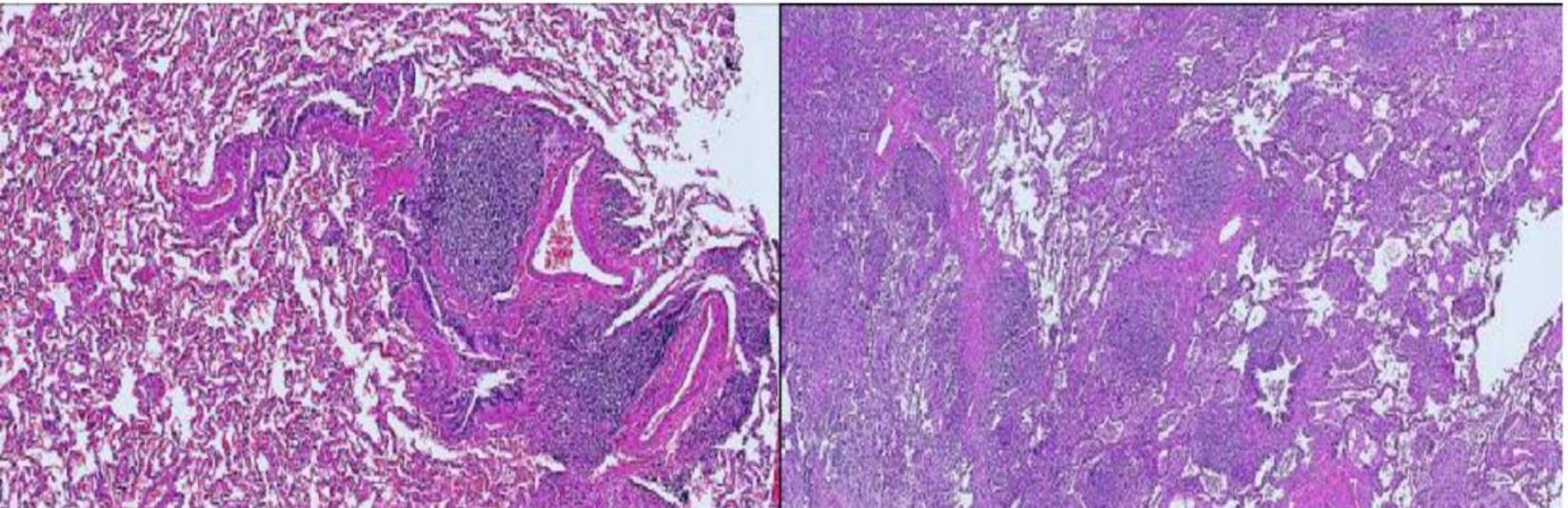
- Granulomatous-lymphocytic interstitial lung disease (GLILD) is a spectrum of ‘interstitial’ lung diseases, and is seen in patients with CVID (different from bronchiectasis or scarring)
- Spectrum – variable on CT scans; most biopsies with immune cells infiltrating the lung tissues; some with more or less ‘granuloma’
- Unknown pathogenesis: apparently non-infectious; non-malignant
- If not effectively treated can cause progressive lung injury / decline in lung function



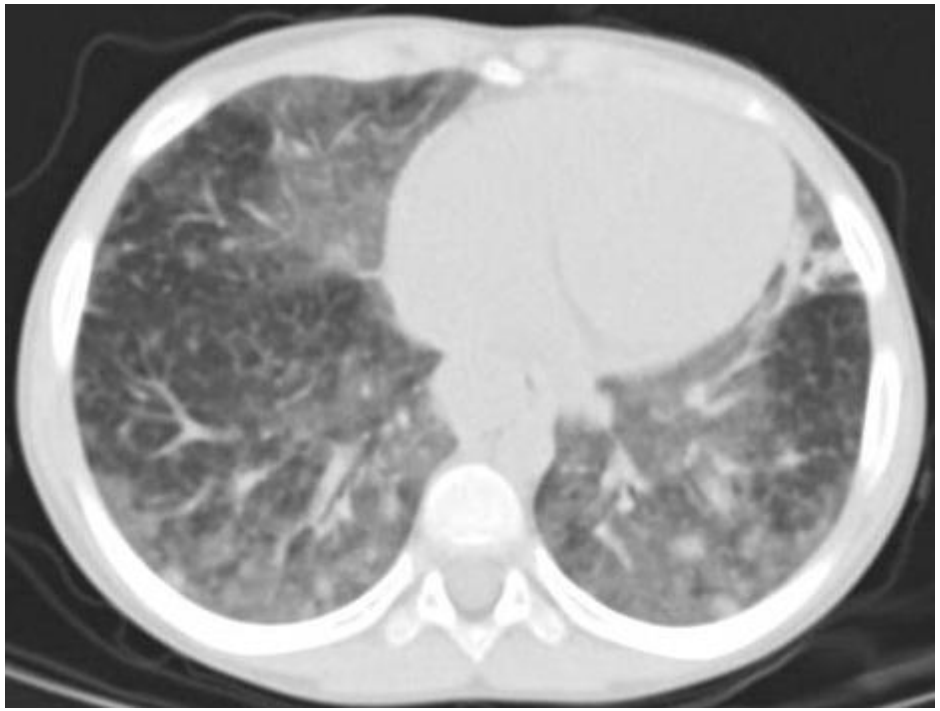
Granulomatous-Lymphocytic Interstitial Lung Disease (GLILD)

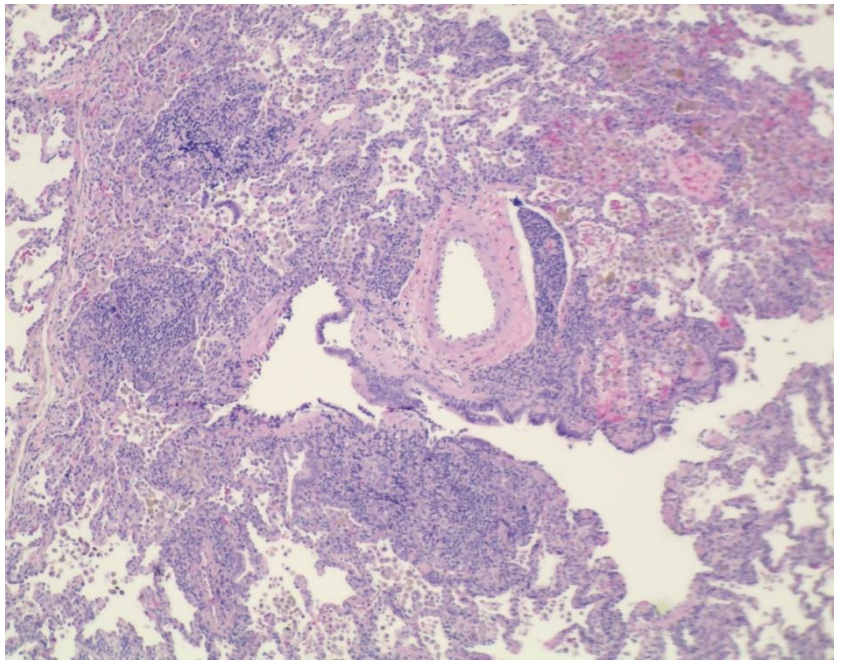
- Clinical-histologic-radiologic diagnosis
  - Nodules
  - Ground glass opacities
  - Consolidation
  - Fibrosis



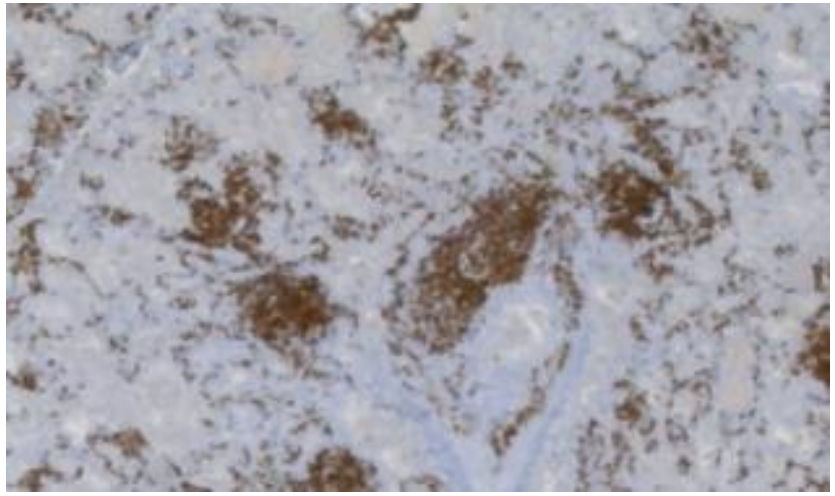


What is in the lesions?





CD3:



Management of GLILD

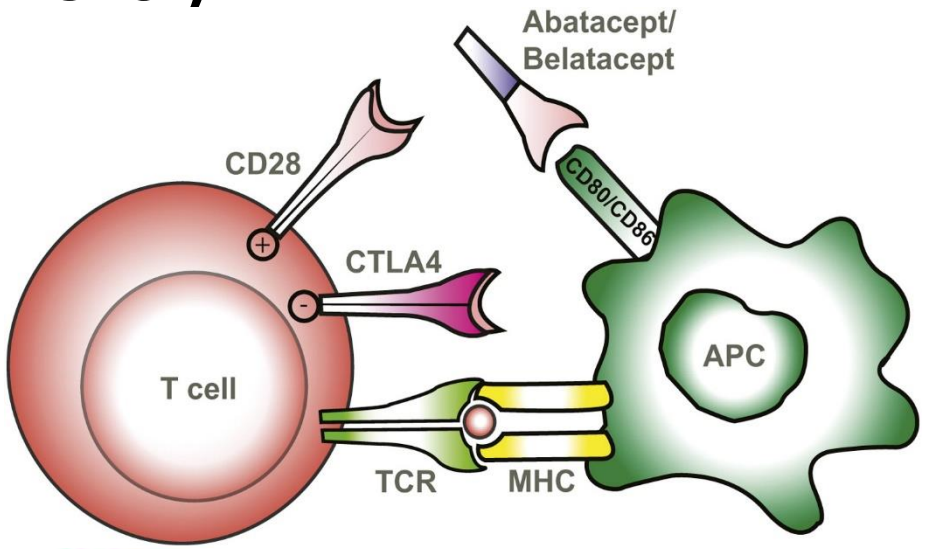
- Consensus that immunoglobulin therapy should be optimized to standard concentrations
- **There is no approved therapy for GLILD**
- Corticosteroids are the most commonly first line agent used, though prolonged use is problematic
- A variety of immune suppressive agents have been described in second line
- The largest study performed to date evaluated treatment of GLILD subjects with rituximab with an antimetabolite (azathioprine or mycophenolate) - most responded, though this approach does not work for all.
- There is a need for more and better therapy options

Hurst et al, J All Clin Immunol Pract 2017 and Verbsky et al. J All Clin Immunol 2020

Why Abatacept? Why the ABCVILD trial?

Abatacept (Orencia)

- Recombinant, human fusion protein of cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and human IgG1 that blocks T cell activation by binding to CD80 and CD86, thereby blocking CD28 engagement
  - Available as IV infusion or preloaded subcutaneous injection



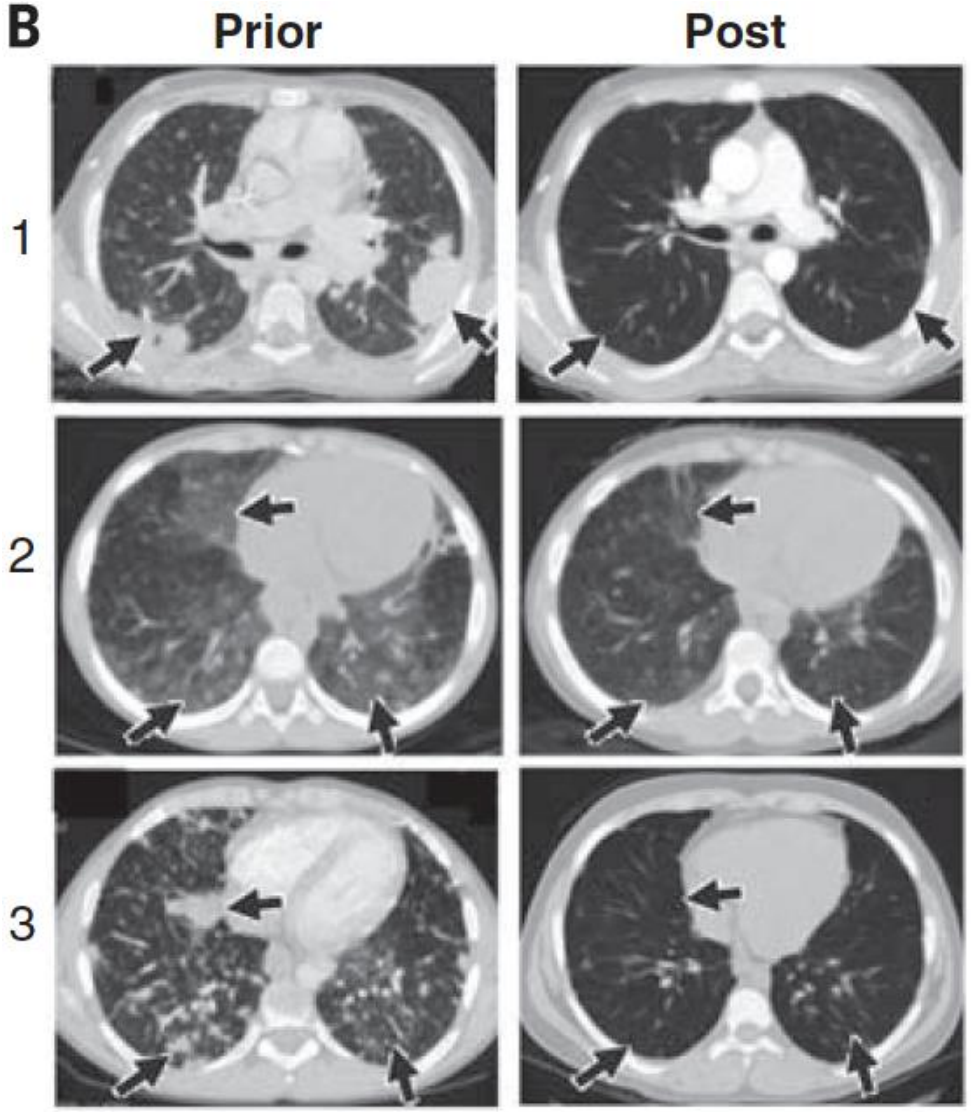
Approved for:

- Rheumatoid arthritis
- Psoriatic arthritis
- Juvenile Idiopathic Arthritis

ORENCIA®
(abatacept)
Injection for Intravenous Use
Injection for Subcutaneous Use

- Principle safety concerns relate to immune suppression and increased incidence of (common) infections
- Long-term follow up (>3 years) has established its efficacy and safety in patients with RA. (Ann Rheum Dis. 2011 Oct;70(10):1826-30.)

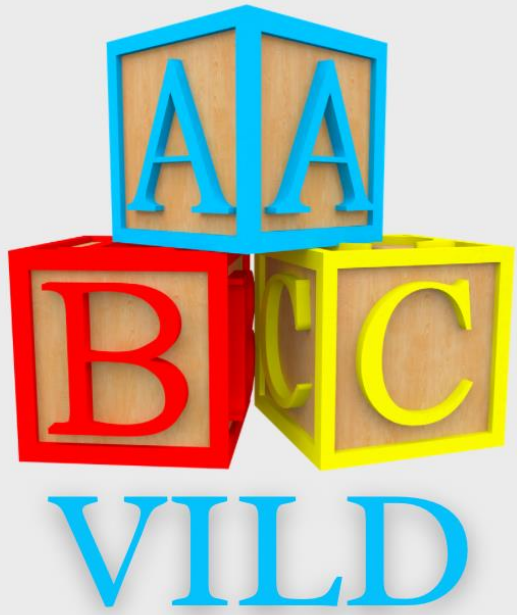
LRBA deficient patients responded to abatacept



Lo et al. Science 2015

DLCO = diffusing capacity of the lungs for carbon monoxide; FVC = forced vital capacity; FEV1 = forced expiratory volume; TLC = total lung capacity.

Abatacept for the treatment of Common Variable Immunodeficiency with Interstitial Lung Disease



Erinn Kellner, MD & Michael Jordan, MD

Cincinnati Children's
changing the outcome together

ABCVILD Study

- **Ab**atacept for the treatment of **C**ommon **V**ariable Immunodeficiency with **I**nterstitial **L**ung **D**isease **(ABCVILD)**

We hypothesize significant radiographic improvement of GLILD (defined as ≥50% decrease of involved lung tissue) will be observed in 66% or more of subjects with CVID after 6 months of treatment with abatacept and that this improvement will be superior to placebo treatment.

Primary Objectives

To determine the efficacy of abatacept compared to placebo for treatment of subjects with GLILD in the context of CVID, as assessed quantitatively on radiologic imaging

Scoring based on nodularity (size and number) and opacities (ground glass opacities and consolidation) within each lobe

Secondary Objectives

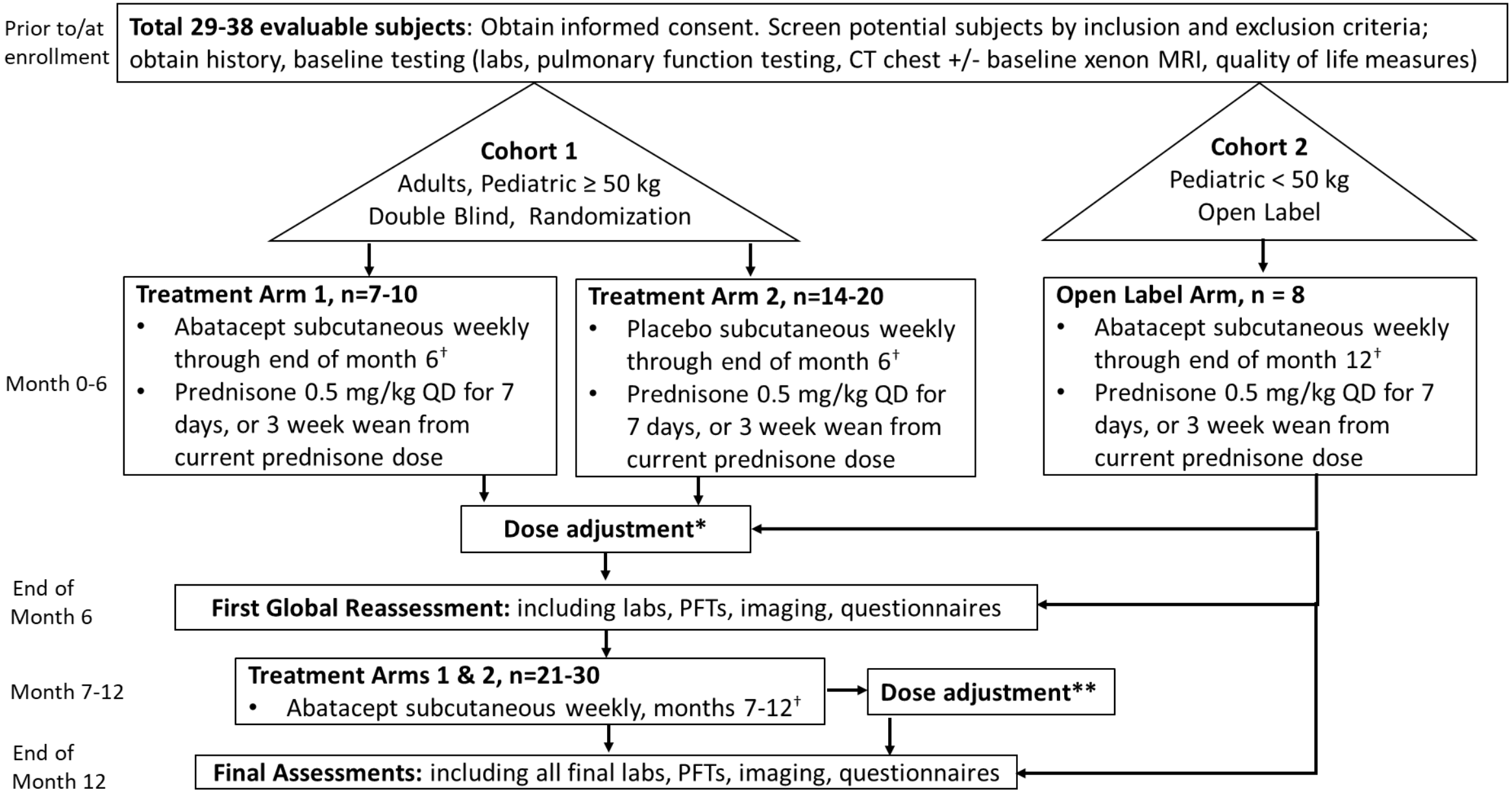
- To determine the efficacy of abatacept for treatment of subjects with GLILD in the context of CVID, as assessed by quantitative pulmonary functional studies
- To assess the impact of abatacept on concurrent autoimmune/inflammatory disorders in subjects with CVID/GLILD
- To compare the response in a limited number of subjects after 12 versus 6 months of abatacept via imaging and pulmonary function testing
- Assess utilization of corticosteroids and cessation of concomitant immune modulators during treatment with abatacept, compared to placebo
- To determine the utility of Xenon MRI imaging for assessment of GLILD compared to HRCT
- To determine the impact of abatacept on infectious complications experienced by subjects with GLILD in the context of CVID
- To evaluate the overall safety and tolerability of abatacept in subjects with GLILD in the context of CVID
- To assess the impact of abatacept on quality of life in subjects with GLILD in the context of CVID

Inclusion Criteria

1. Diagnosis of CVID according to the international consensus document (ICON)
   a. Age 4 years or above
   b. Serum IgG at least 2 standard deviations below the age adjusted normal
   c. Decreased serum IgA and/or serum IgM
   d. Abnormal specific antibody response to immunization
   e. Exclusion of secondary immunodeficiency
2. On replacement immunoglobulin for at least 6 months and willing to maintain throughout study
3. Granulomatous-lymphocytic interstitial lung disease with a lymphocytic component diagnosed by lung biopsy prior to study entry, wedge biopsy preferred.
4. Persistence or worsening of interstitial lung disease measured on serial CT imaging of the lung at least 6 months apart, with the latest assessment within 2 months of study entry.
5. Signed written informed consent
6. Willing to allow storage of biological specimens for future use in medical research.
7. Females of childbearing potential must use a highly effective form of birth control such as hormone-based contraceptive, intrauterine device, or double barrier method.

Exclusion Criteria (paraphrased)

1. History of hypersensitivity to abatacept or any of its components
2. Currently on abatcept
3. Certain recent therapies
4. Uncontrolled specific viral infections
5. Recent malignancy
6. Pregnant or breastfeeding



† First dose is doubled (i.e. loading dose) at the beginning of each phase (blinded or open label)

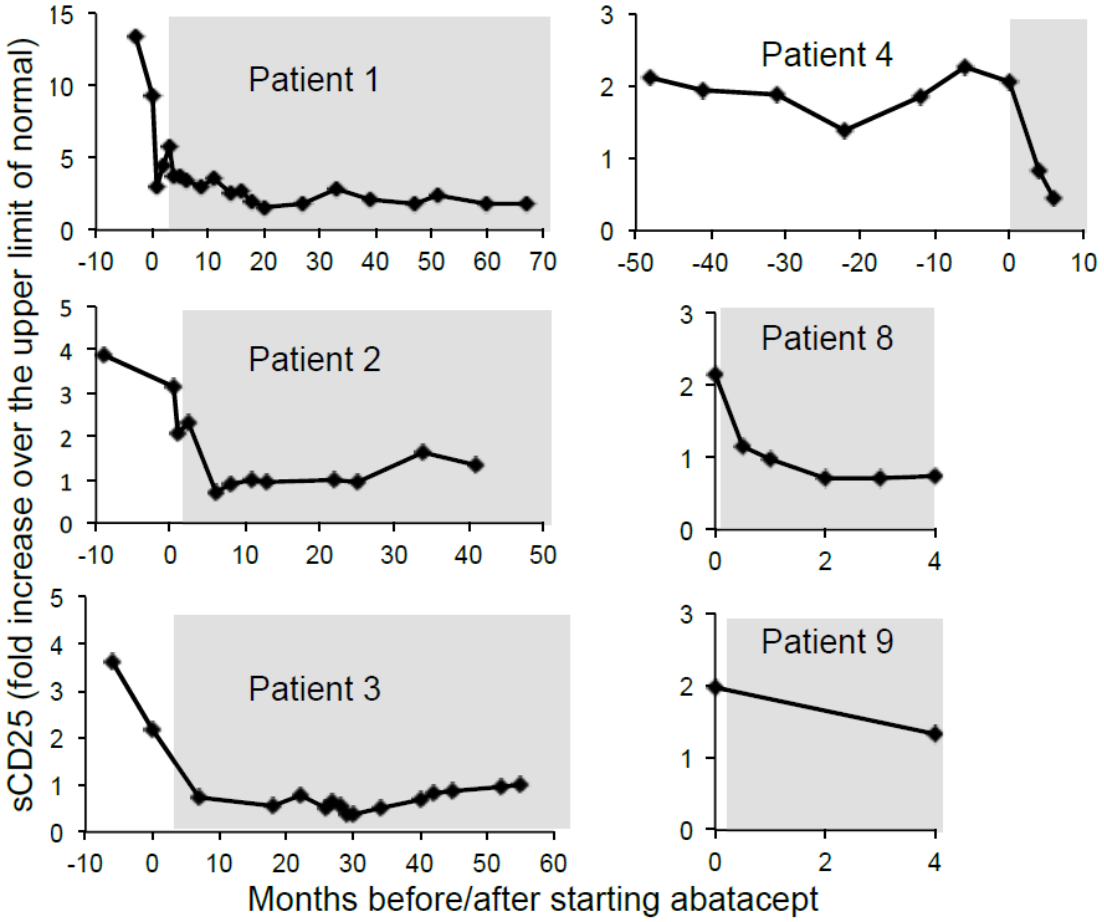
* If sCD25 is elevated at baseline and does not normalize by end of month 2, then double the standard dose of agent at end of month 3.

** If sCD25 is elevated at end of month 6 and does not normalize by end of month 8, then double the standard dose of agent at end of month 9

Mechanistic Studies

- Pharmacokinetics of abatacept
- Assessment of sCD25 for adaptive dosing (pharmacodynamics)
- Flow cytometric profiling of T cells: CD28, activation, differentiation
- Exploratory proteomics

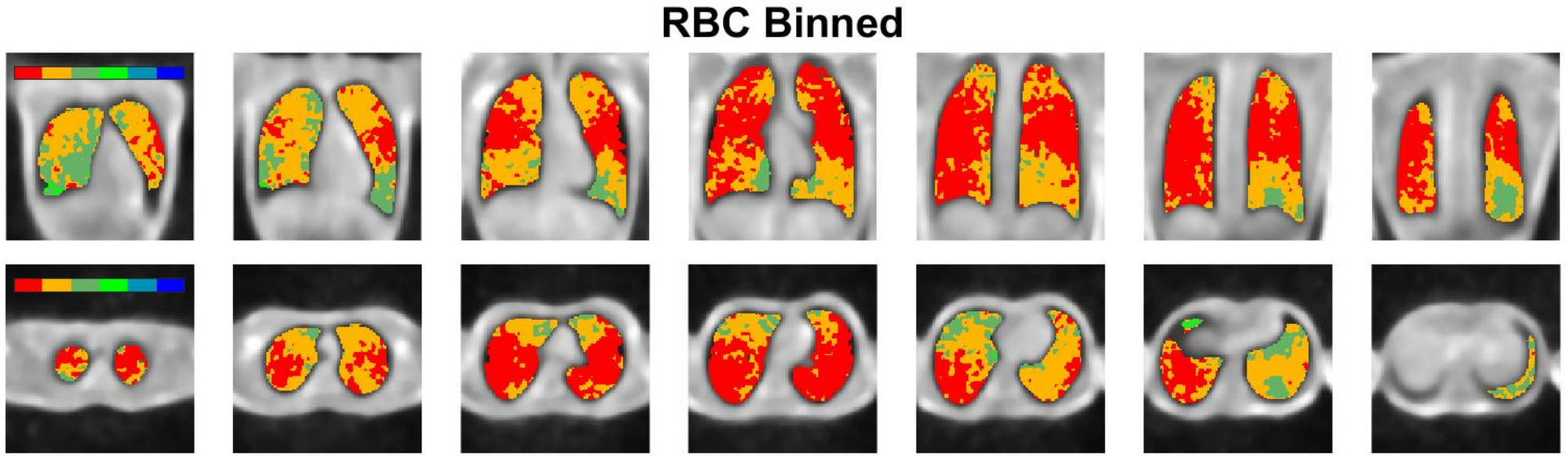
Abatacept Decreases sCD25, a Marker of Immune Activation

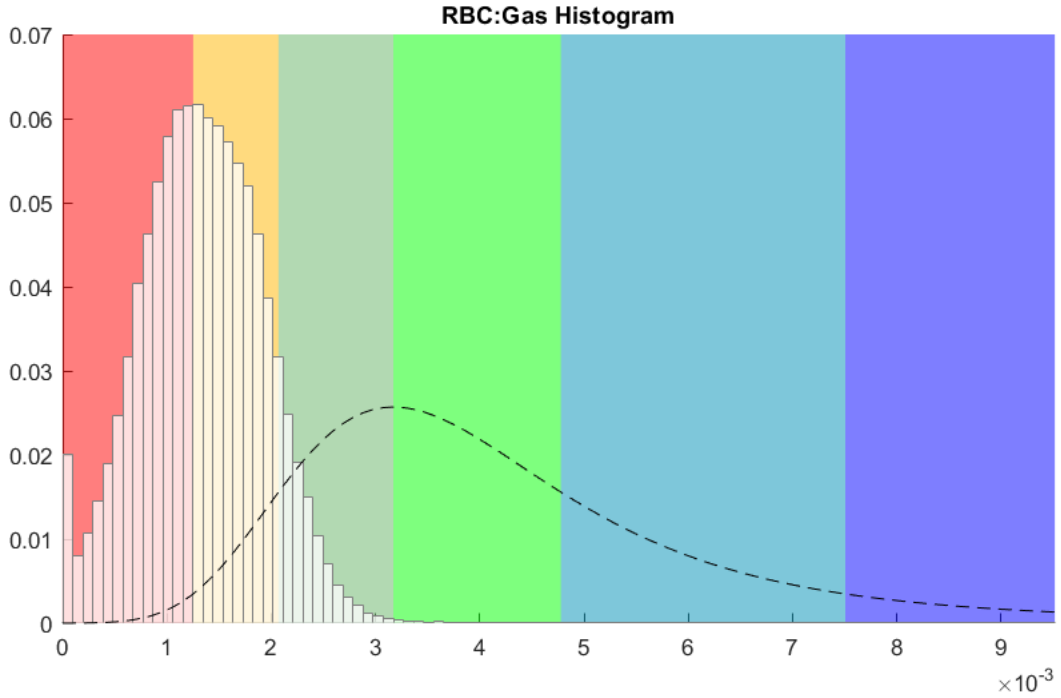


sCD25 = plasma soluble CD25.

Lo B, et al. *Science*. 2015;349:436-440.

Xenon MRI: novel imaging/ functional assay





Mean: 1.335e-03 (Healthy = 3.297e-03±1.350e-03)

	Defect	Low	Healthy	Healthy	High	High
Subject	Bin 1	Bin 2	Bin 3	Bin 4	Bin 5	Bin 6
IRC186H-321	44.96	44.63	10.26	0.16	0.00	0.00
Healthy Cohort	2.96±4.93	18.33±20.09	35.78±21.77	27.02±19.96	13.56±21.76	2.36±5.91

Current Status

- The trial is currently open at :
  - Cincinnati Children's Hospital- Dr Michael Jordan
  - Duke University – Dr. Patricia Lugar/ Dr Peter Bressler
  - Mayo Clinic- Dr. Avni Joshi
  - University of South Florida- Dr. Jolan Walter
  - University of California at San Francisco- Dr. Michele Pham
  - Beth Israel Lahey- Dr Jocelyn Farmer
- We plan to complete enrollment in the next 2 years

Conclusions

- GLILD in patients with CVID remains a significant challenge
- Abatcept has potential for the treatment of GLILD
- The ABCVILD trail is testing the potential of this drug

Adults and children 4 years and above who currently have common variable immunodeficiency with interstitial lung disease are needed for a research study

What

To test the drug abatacept to see what effects it has on interstitial lung disease in patients with common variable immunodeficiency. We will be testing the drugs overall impact, safety, and tolerability.

Who

Adults and children 4 years of age and older

What is involved

Participants will:

- Have 13 study visits (8 over the phone, 5 clinic visits) that take place over 52 weeks
- Subcutaneous injection weekly over 52 weeks
- Monthly blood draws

Interested in finding out more?

Please contact

ABCVILD@cchmc.org

With any questions about the study