DICV ET POUMON

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DÉFINITION **DICV**
ESID/PAGID 1999

- **1)** Diminution des IgG et IgA et/ou IgM
- **2)** Absence de réponse vaccinale et/ou isohemagglutinines
- **3)** Début des symptômes > 2 ans
- **4)** Exclusion des causes connues

- **DEFICIT PRIMITIF HUMORAL de L'ADULTE DE CAUSE INCONNUE**

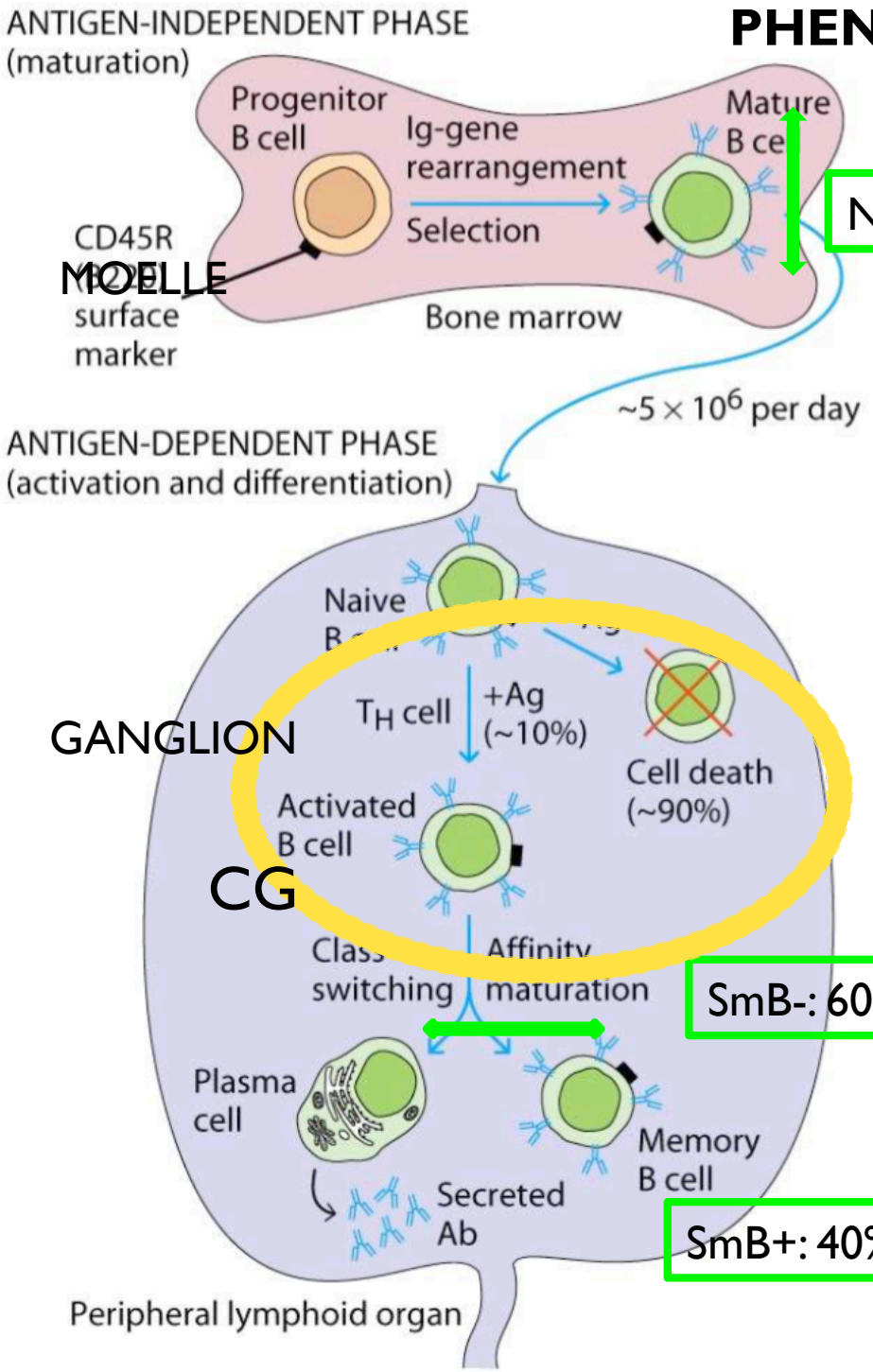
- 1/20 000 à 1/30 000; M=F
- **HETEROGENE**

- **COHORTES**

- Diagnostic: 15-30 ans. **RETARD**
- Formes familiales: 20 à 25%
  Transmission AD>>AR

- **CLASSIFICATIONS**

PHENOTYPE LYMPHOCYTAIRE B



No B:10%

SmB-: 60%

SmB+: 40%

B+:90%

Défaut LB mémoire=SmB-

- Taux bas IgG et IgA
- Infections
- DDB
- SM
- Granulomes

Euroclass, Wehr C, Blood 2008

PHENOTYPE LYMPHOCYTAIRE T

LCD4+ naïfs < 20%

Table 3 Association of Clinical Complications with T-Cell/B-Cell Defects in 285 CVID Patients

	$nT4^-B^-$ (n = 17)	$nT4^-smB^-$ (n=63)	$nT4^-smB^+$ (n=42)	$nT4^+B^-$ (n = 16)	$nT4^+smB^-$ (n=53)	$nT4^+smB^+$ (n = 104)	p
IO (n=93)	3 (18%)	8 (13%)	6 (14%)	6 (38%)	19 (36%)	51 (49%)	< 0.001
LP (n = 138)	14 (82%)	46 (73%)	28 (67%)	4 (25%)	20 (38%)	26 (25%)	< 0.001
AC (n=52)	4 (24%)	18 (29%)	10 (24%)	3 (19%)	7 (13%)	10 (10%)	0.025
CE (n=70)	6 (35%)	16 (25%)	14 (33%)	3 (19%)	12 (23%)	19 (18%)	0.35

Eighteen of the 313 CVID patients had missing phenotypic data and were not classified according to T/B phenotypes.

Percentages refer to the prevalence of the clinical phenomenon indicated in the respective phenotypic subgroup of patients. For each complication, statistical evaluation refers to the distribution of the prevalence of one complication among the different phenotypic groups.

Abbreviations: $nT4^-$ patients with nT4 cells < 20% of $CD4^+$ T cells; $nT4^+$ nT4 cells ≥ 20% of $CD4^+$ T cells; B^- $CD19^+$ cells ≤ 1% of total lymphocytes; smB^- $CD19^+$ cells > 1% of total lymphocytes and smB cells ≤ 2% of total B cells; smB^+ $CD19^+$ > 1% and smB > 2%.

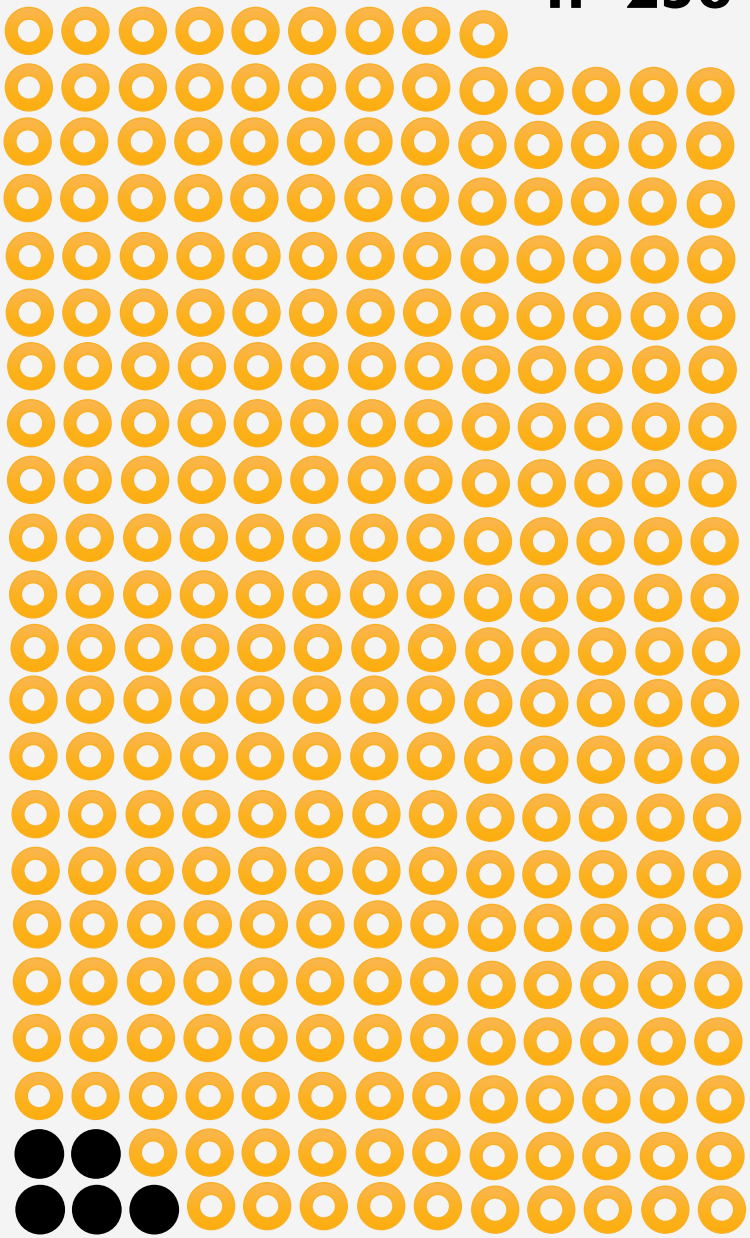
Mouillot et al. 2010

Prolifération lymphoïde corrélée à déficit en TCD4 naïfs

DICV

- **TCD4 ≥ 200**
- **TCD4 naïfs≥ 20**
- **pas O.I.**

n=238



TCD4 naïfs < 20/mm3
n=50

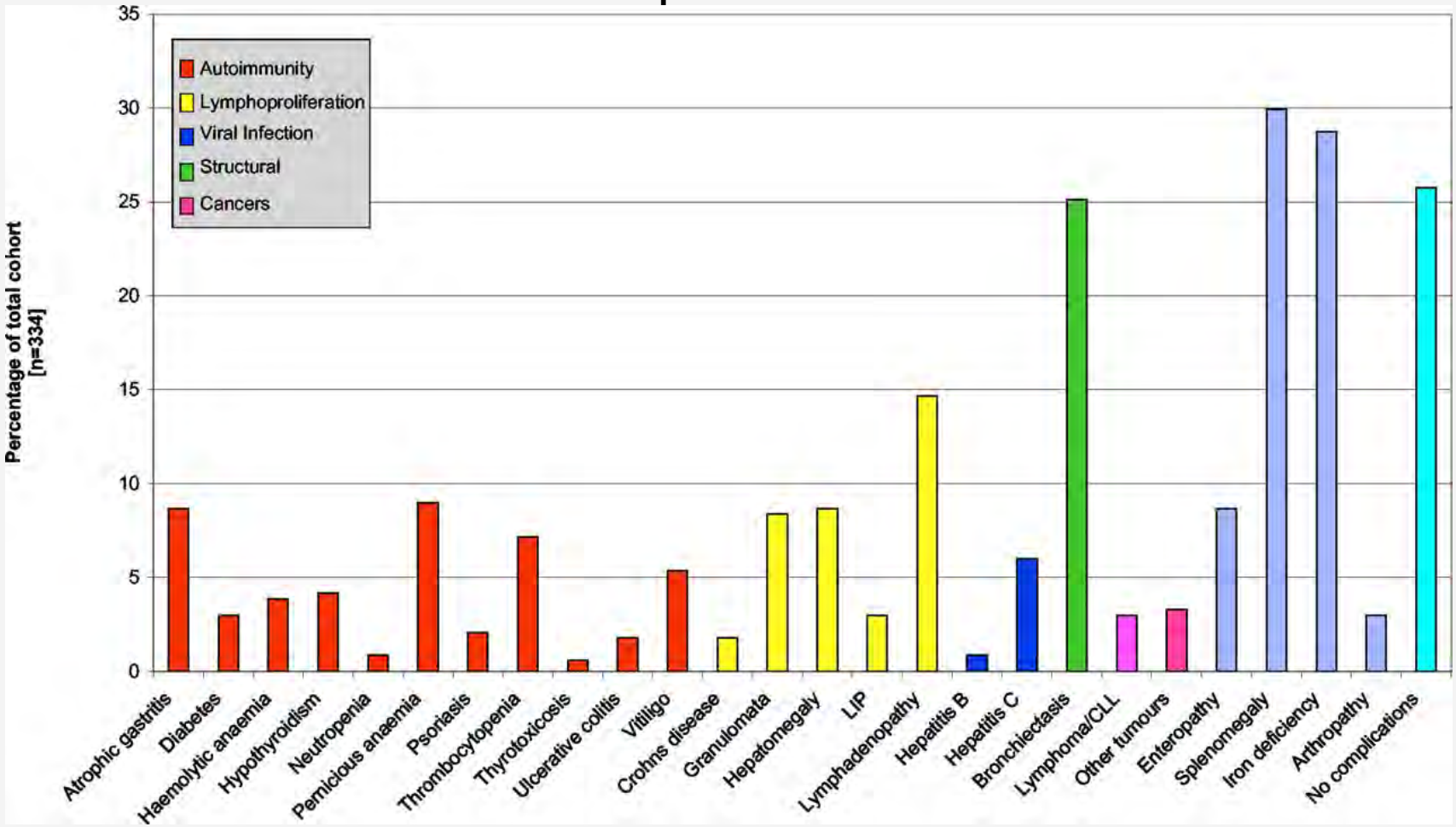
CD4 < 200
n=15

O.I.
n=17

Bertinchamp JACI in Pract, 2016

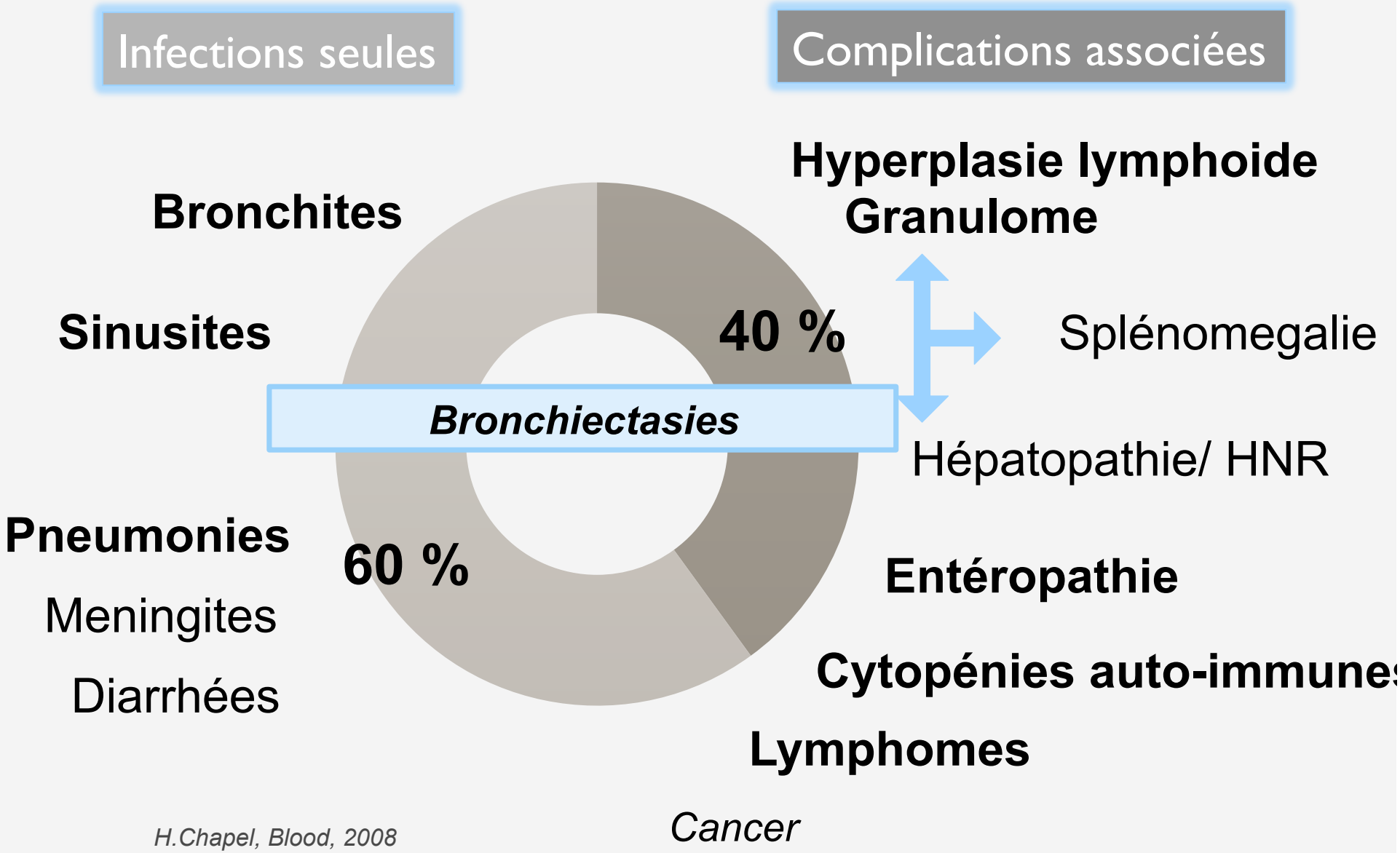
PHENOTYPES CLINIQUES

Individual complications associated with CVIDs across Europe, as a percentage of the all patients.



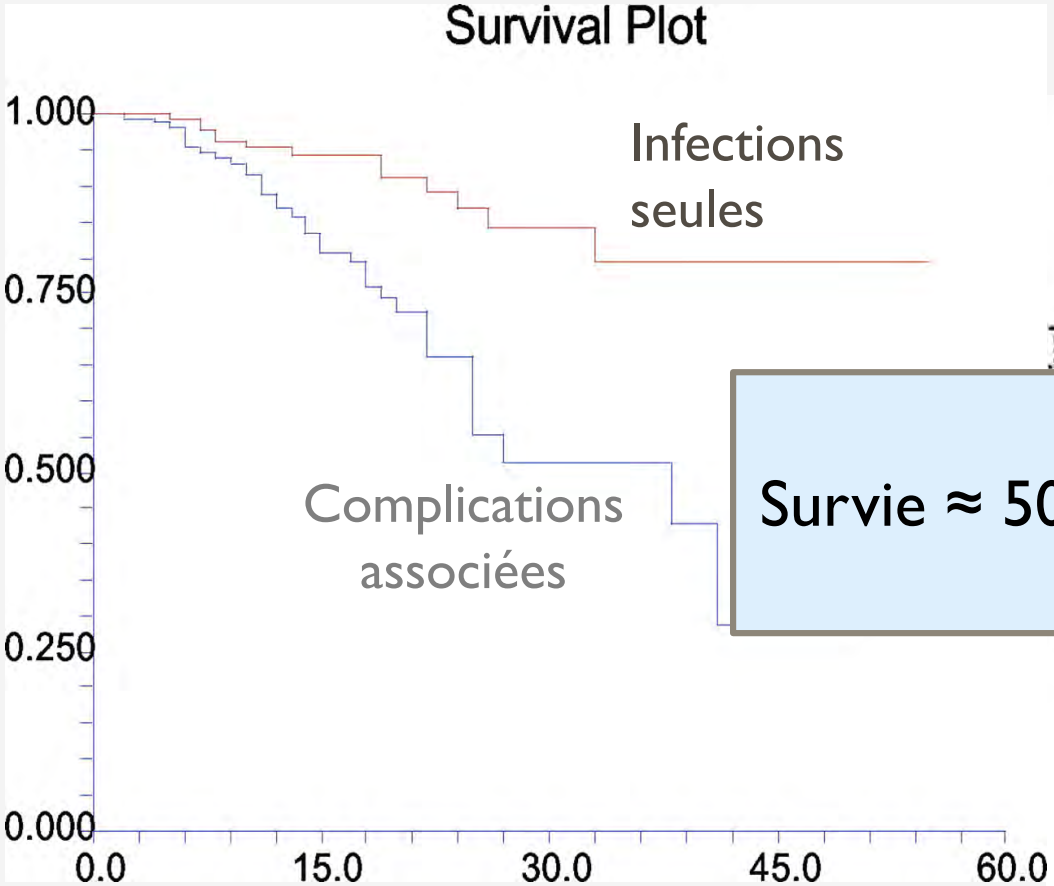
Helen Chapel et al. Blood 2008;112:277-286

PHENOTYPES CLINIQUES

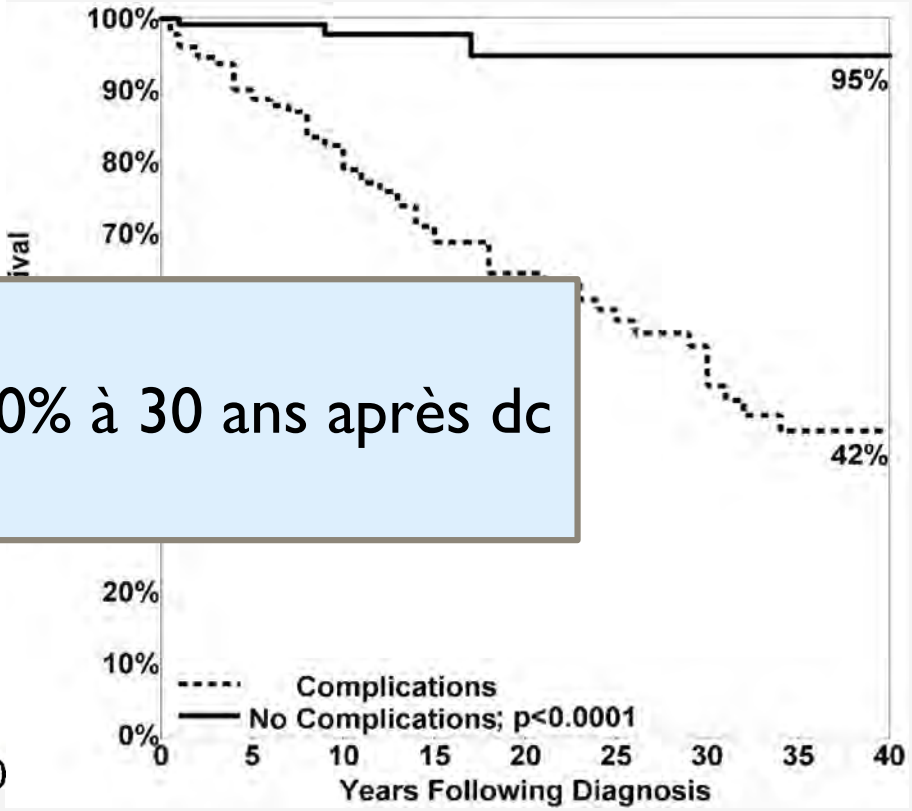


H.Chapel, Blood, 2008

MORTALITE SELON COMPLICATIONS ASSOCIEES



Survie ≈ 50% à 30 ans après dc



Chapel H et al. Blood 2008

Oxford / Northern Europe

Resnick E S et al. Blood 2012

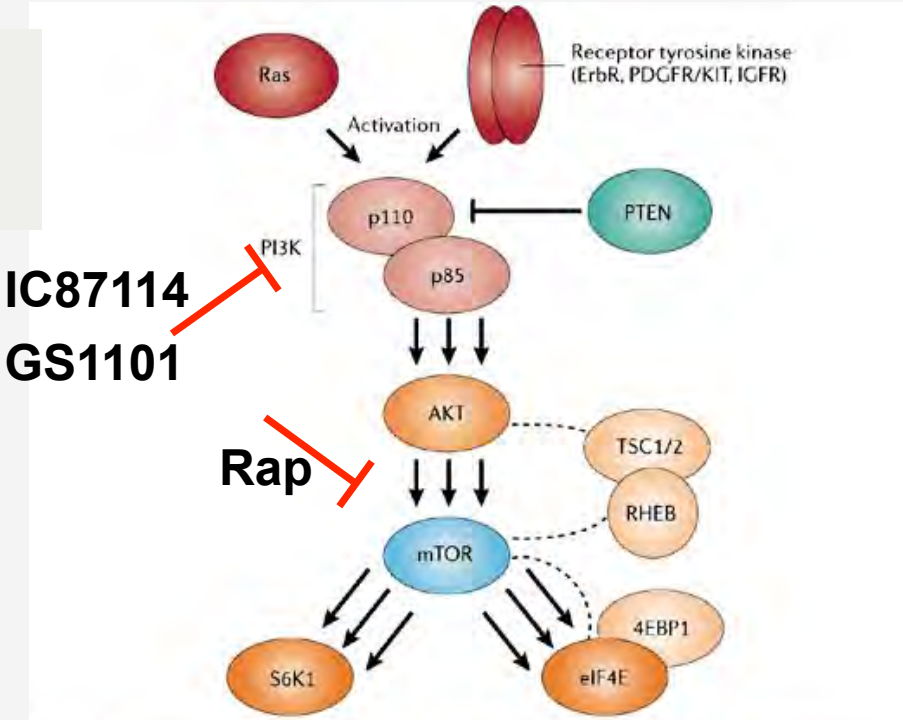
New York city

DICV ESID 2014 "**DYSREGULATION IMMUNITAIRE**"

- **1)** Diminution IgG et IgA et/ou IgM
- **2)** **soit** absence de réponse vaccinale (et/ou isohemagglutinines)
  soit *diminution des lymphocytes B memoires switchés*
- **3)** Age> *4 ans*
- **4)** **soit** *susceptibilité aux infections*
  soit *auto-immunité*
  soit *prolifération (lymphoide, granulome)*
  soit *histoire familiale*
- **5)** *Exclusion déficit T profond (CD4 < 200, · % Naive CD4 < 10%)*
- **6)** Exclusion des causes connues

GÉNÉTIQUE: VOIE PI3K

Mutations activatrices
voie PI3K-AKT-mTOR ➔
lymphoproliferation



Mutation germinale
Autosomique Dominant

- *PIK3CD*_GOF
- *PIK3R1*_LOF

DDB
PROLIFERATION LYMPHOIDE, volumineux centres germinatifs
Herpes virus
IgG normales: 60% → dépistage+++
IgM augmentées ou normales
Lymphopénie TCD4 et B

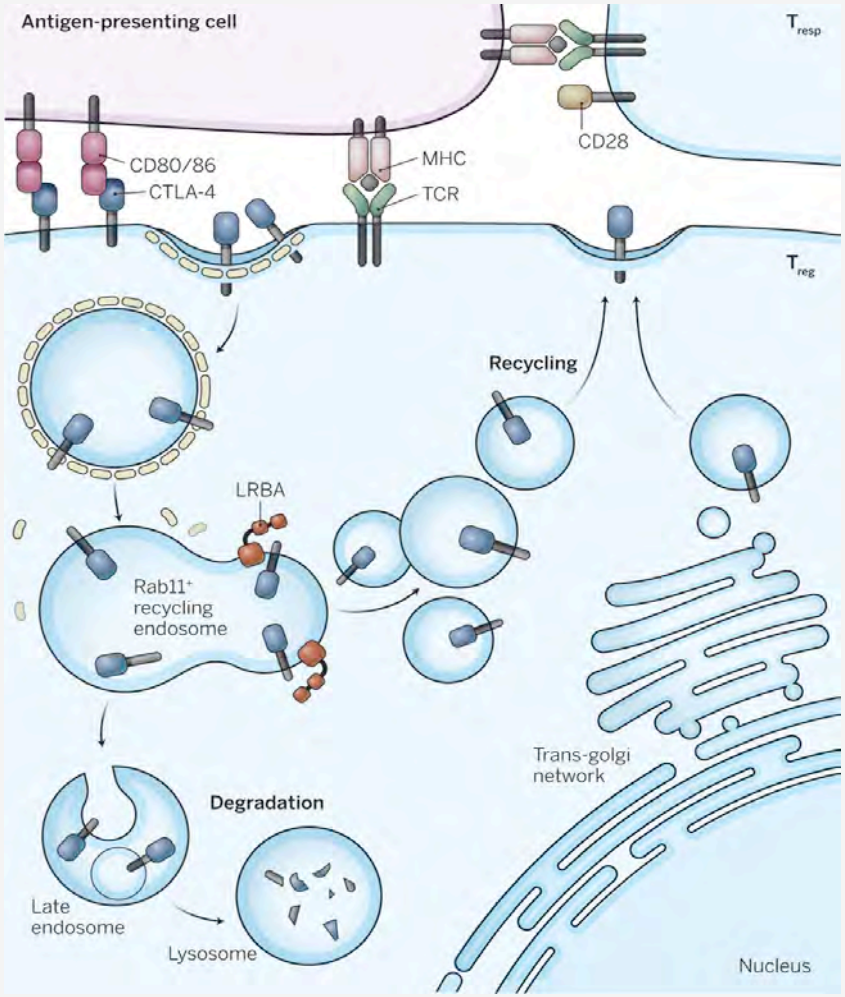
APDS/PASLI

Clinical feature	Frequency (%) in APDS cohort	Frequency (%) in CVID cohort
Pneumonia	85	32-77[E1, E2, E3, E4]
Bronchiectasis	60	23-64[E1, E3, E5, E6, E7]
Splenomegaly	58	15-30[E1, E3, E4, E5, E6]
Autoimmunity	42	22-29[E1, E2, E3]
Enteropathy	25	9[E1, E4, E5]
Granuloma*	0	8-9[E1, E2, E5]
Meningitis/encephalitis	1.9	3-4[E1, E4]
Lymphoma	11	3-8[E1, E2, E5]
Living patients currently receiving immunoglobulin replacement therapy	77	80[E1]

Coulter, JACI 2016

GENETIQUE: CTLA4 LRBA

Mutation autosomique dominante *CTLA4*
Autosomique récessive *LRBA*
→ Défaut LT regulateurs
Activation lymphocytaire T



PROLIFERATION LYMPHOIDE et AUTO-IMMUNITE

DEFAUT CTLA4

	Science 2014	Nat med 2014
Infections	4/6	8/14
Lymphoprolifération **Granulome** **Organes non lymphoïdes**	6/6	8/12
Cytopénies autoImmunes	6/6	6/14
Entéropathie	5/6	11/14
CV CMV/EBV	gg	2/7 / 1/6
IgG ↘	6/6	10/12
↘CD4	3/3	1/12
↘CD4 RA+		9/11
↗CD8 CD57+	3/3	
↘CD19	3/3	7/14
Lymphome	EBVHodgkin 1/6	0

DEFAUT LRBA

	Science 2015
infections	6/9
Lymphoprolifération	8/9
Autoimmunité	6/9
PTI/AHAI	6/9
entéropathie	8/9
IgG ↘	5/9
↘CD4	
↘CD4 RA+	5/9
↗CD8 CD57+	3/9
↘CD19	5/9 (CD27-)
Lymphome	burkitt

Efficacité CTLA4-Ig (Abatacept) et PLAQUENIL

DE LA GÉNÉTIQUE AUX THÉRAPIES CIBLÉES

- PIK3CD
- PIK3R1

→ Rapamune
→ Idelalisib

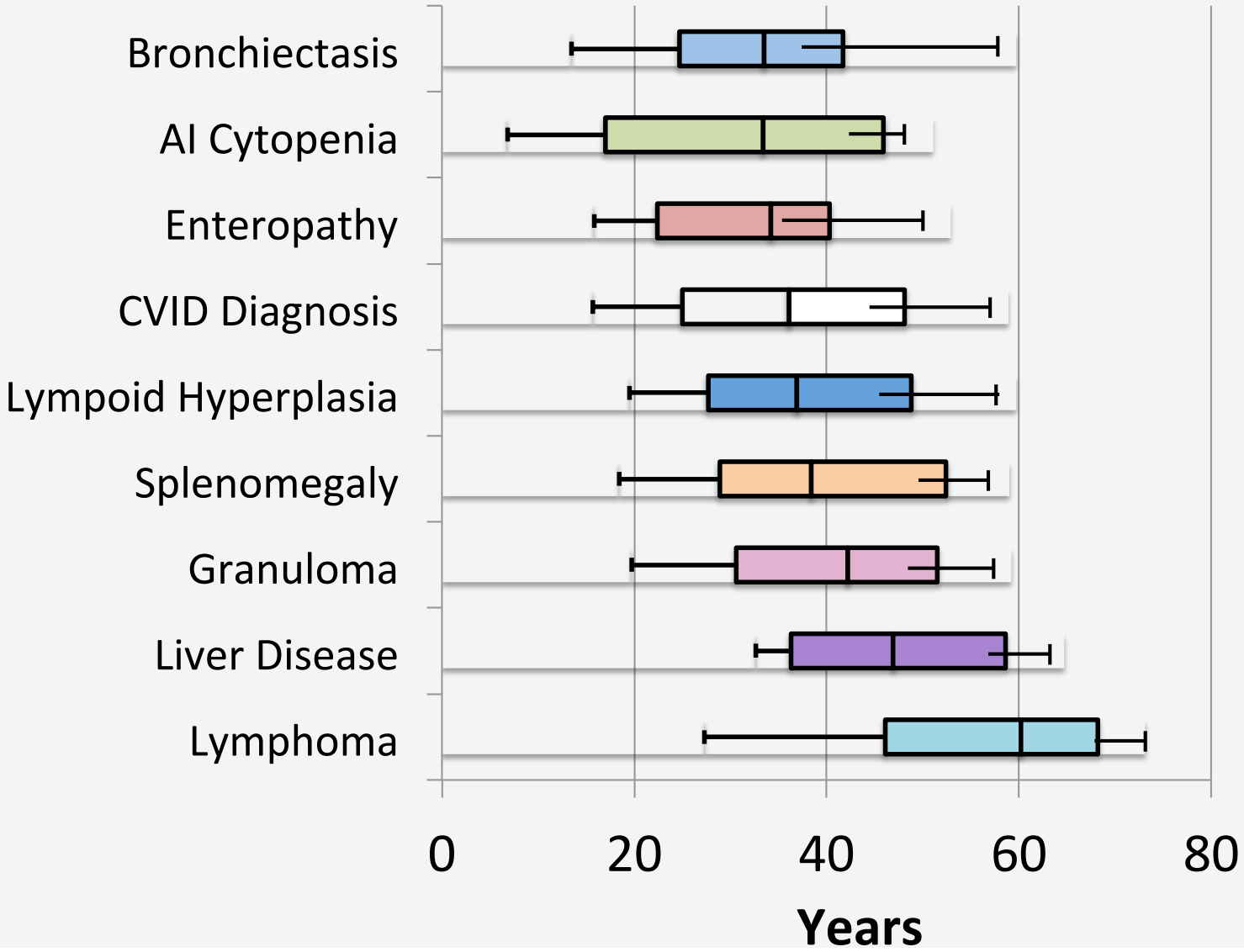
- LRBA
- CTLA4

→ Hydroxychloroquine
→ Abatacept

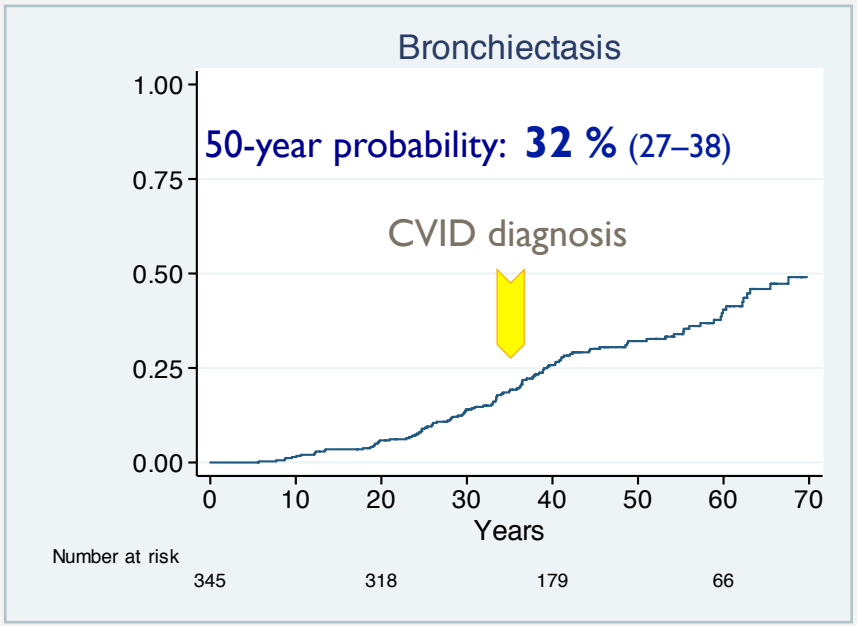
DICV/POUMON

- Impact qualité de vie/mortalité
- Précède parfois dc DICV
- Modification de structure:
  - séquelles des infections aigues
  - déréglement immunologique (lymphoprolifération/ inflammation aberrante)
  +/-facteur déclenchant infectieux
- **DDB**
- **PNEUMOPATHIE INTERSTITIELLE**

HISTOIRE NATURELLE



DILATATIONS BRONCHIQUES



- LM, Linf
- ATCD pneumopathie ?
- Retard diagnostic ?

- Déficit en mannose binding lectin
- Déficit complet IgA (pas IgG)
- Déficit profond LB mémoires

- **Epaississement bronchique**

- **Rôle microbiome respiratoire?**

PNEUMOPATHIE INTERSTITIELLE

- Fréquence: **10** à 30%
  Hyperplasie lymphoïde systémique
- Mortalité (1/3)
- Histologie:
  - granulome
  - bronchiolite folliculaire
  - hyperplasie lymphoïde diffuse
  - LIP
  - lymphome

  Coexistence → GLILD → hyperplasie du tissu lymphoïde BALT

  Pneumopathie organisée

FACTEURS RISQUE PNEUMOPATHIE INTERSTITIELLE

- Cytopénie auto-immunes
- Splénomégalie
- Augmentation des IgM
- Diminution des T CD4 naïfs
- Augmentation des LB CD21 low

La sarcoïdose est-elle un bon modèle?

Granulomatosis-associated common variable immunodeficiency disorder: a case–control study *versus* sarcoidosis

Diane Bouvry, Luc Mouthon, Pierre-Yves Brillet, Marianne Kambouchner, Jean-Pierre Ducroix, Vincent Cottin, Julien Haroche, Jean-Francois Viallard, Romain Lazor, François Lebargy, Abdellatif Tazi, Benoît Wallaert, Amar Smail, Jean-Luc Pellegrin, Hilario Nunes, Zahir Amoura, Jean-François Cordier, Dominique Valeyre, Jean-Marc Naccache and the Groupe Sarcoïdose Francophone

Eur Respir J 2013; 41: 115–122

TABLE 2 Comparison between interstitial lung disease (ILD) in common variable immunodeficiency disorder (CVID)-associated granulomatous disease (GD) and sarcoid controls

	ILD/CVID/GD	Sarcoid controls	p-value
Subjects	20	60	
Age yrs	44±17	43±11.5	0.89
Males/females	11 (55)/9 (45)	18 (30)/42 (70)	0.04
Caucasian/black ethnicity	18/2	49/11	0.5
Recurrent infections	13 (65)	3 (5)	**<0.001**
Autoimmune disease	8 (40)	1 (1.7)	**<0.001**
Crackles	9 (45)	1 (1.7)	**<0.001**
Splenomegaly	15 (75)	5 (8.3)	**<0.001**
Hepatomegaly	10 (50)	5 (8.3)	**<0.001**
Extrathoracic localisation	19 (95)	39 (65)	0.009
Number of extrathoracic localisations	2.4±1.3	1.3±1.3	**0.002**
PFTs			
Normal	5 (25)	11 (18.3)	0.5
Obstructive syndrome	2 (10)	12 (20)	0.4
Restrictive syndrome	7 (35)	11 (18)	0.1
$T_{L,CO}$ impairment	13 (65)	44 (73)	0.6
Blood lymphocyte count cells per mm^3	1498±864	1374±547	0.57
Increased sACE	14 (88)	47 (78)	0.55
BAL			
BAL lymphocyte count %	37.3±15.3	27±21	0.08
CD4/CD8 T-cell ratio	1.6±1.1	5.3±4	**<0.001**

Data are presented as n, mean±SD or n (%), unless otherwise stated. PFT: pulmonary function test; $T_{L,CO}$: transfer factor of the lung for carbon monoxide; sACE: serum angiotensin-converting enzyme; BAL: bronchoalveolar lavage. Bold indicates statistically significant p-values.

PAS D'AMÉLIORATION SPONTANÉE MOINS DE FIBROSE

TABLE 4 Comparison between patients with interstitial lung disease (ILD) in common variable immunodeficiency disorder (CVID)-associated granulomatous disease (GD) and sarcoid controls: treatment and evolution.

	ILD/CVID/GD	Sarcoid controls
Subjects n	20	60
Follow-up months median (range)	80.5 (7–201)	69 (12–188)
Immunoglobulin replacement	17 (85)	0 (0)
Systemic treatment	16 (80)	56 (93)
Oral corticosteroids	15 (75)	46 (77)
Hydroxychloroquine	2 (10)	13 (22)
Immunosuppressive therapy	3 (15)	20 (33)
Fibrosis on follow-up CT scan#	5 (29)	18 (50)
Death***	6 (30)	0 (0)

Data are presented as n (%), unless otherwise stated. CT: computed tomography. #: 17 patients with ILD/CVID/GD and 36 sarcoid controls had a follow-up CT scan. ***: $p<0.001$.

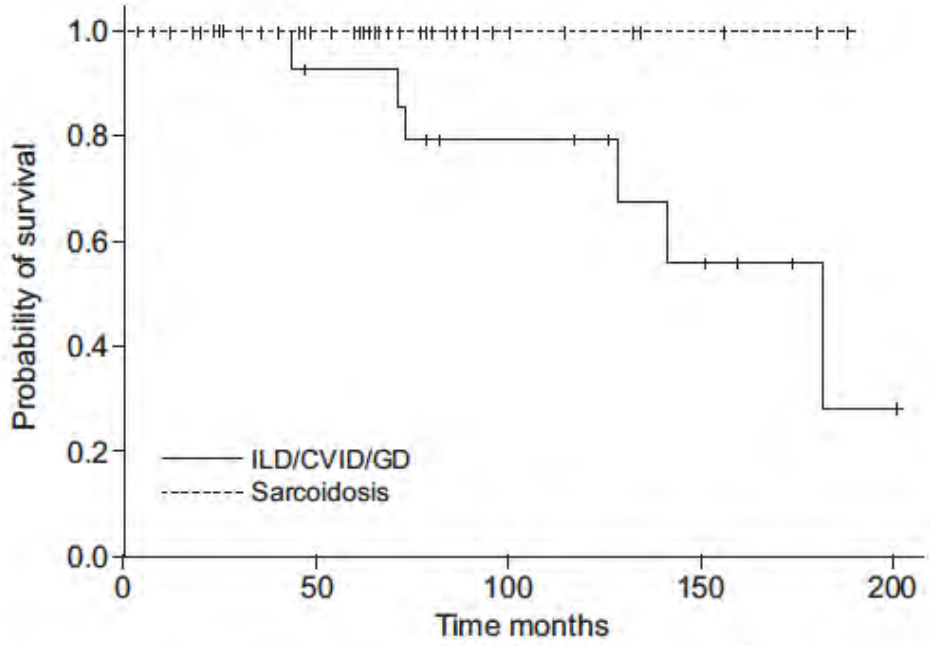


FIGURE 4. Kaplan–Meier overall survival for interstitial lung disease (ILD) in common variable immunodeficiency disorder (CVID)-associated granulomatous disease (GD) patients and sarcoidosis controls.

LAVAGE BRONCHO-ALVÉOLAIRE

- Lymphocytose>20% chez 11/14
  Ratio CD4/CD8: 1,6+/-1,1 (10 patients)
  - 1 patient >3,5
  - 5 patients <1

Bouvry, Eur Respi J,2013

- Lymphocytose>20% chez 11/11
  Ratio CD4/CD8: 6,8+/-7
  - 11 patients>1,5
  - Corrélation négative TCD4/neutrophiles

Kollert, Eur Respir J. 2014

  - Ratio en rapport avec stade inflammation?
  - Haut CD4/CD8 associé à formes stables?

BIOPSIE

- POUR

  - Guide pour traitement (LNH, T versus B, pneumopathie organisée)
  - Granulome extra pulmonaire ne permet pas de préjuger l'histologie pulmonaire

- CONTRE:

  - Intrication différentes histologies
  - Prédominance T (5/6) y compris si hyperplasie folliculaire
  - Efficacité Corticoïdes quelque soit l'histo, efficacité Ritux même si prédominance T

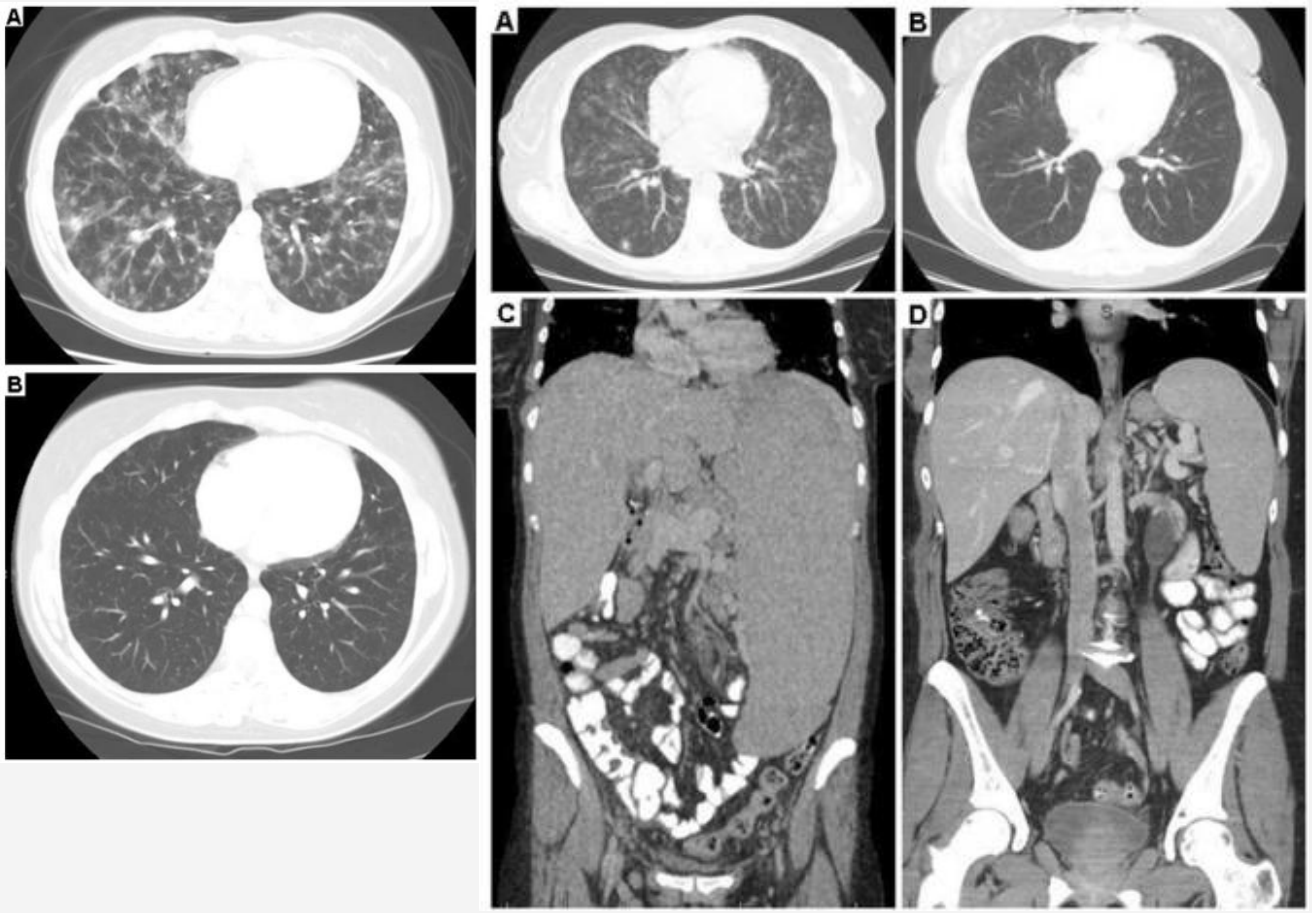
TRAITEMENT

- Quand?
  Retentissement EFR
  Augmentation de taille (LNH)

  Eviter évolution fibrose?
  Eviter transformation en LNH agressif?
- Comment?
  ATB
  Stéroïdes
  Rituximab, Imurel, Cellcept, Ciclosporine, Plaquenil, anti-TNF, Abatacept, Sirolimus

DICV – GLILD
COMBINATION CHEMOTHERAPY

Rituximab: 375 mg/m^2 x4/ week / 3-6 months (12-16 infusions)
Azathioprine: 1-2 mg/kg /day / 18 months



pt	HRCT score pre	HRCT score post
1	15	4
2	16	6
3	17	14
4	18	7
5	23	21
6	12	2
7	15	4

Chase NM. J Clin Immunol, 2013

STILPAD: STUDY OF INTERSTITIAL LUNG DISEASE IN PRIMARY ANTIBODY DEFICIENCY

149 patients adultes

14 centres

Germany:	4 centres
France:	3 centres
UK:	7 centres

Module 2: Clinical Portal for Study Patients - Clinical Trial 10

Study of interstitial lung disease in primary antibody deficiency (STILPAD)

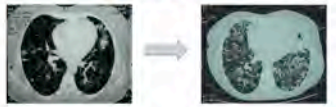
Coordinating Investigator: Klaus Warnatz, Medical Study Coordinator: Sigune Goldacker

RATIONALE

- Severe impact on morbiditiy and mortality of G+LILD
- Lack of evidence

Natural course?

Immunopathology?
Pathogens?



Outcome?
Quality of Life?
Biomarker?

- Basis for randomized interventional trials

Immunosuppressive therapy?

STUDY DESIGN

The study is designed as an observational international multi-centre trial in 200 patients.

CVID according to ESID /PAGID criteria
G+LILD as defined by CT finding of lines, nodules or ground glass
Age > 18yr

Patient Consent and inclusion

Annual visits

Retrospective data documentation | Baseline visit | Prospective observation for 5 years

MILESTONE PLAN

First Patient First Visit	06/2012
End of recruitment	03/2013
Retrospective data analysis final	10/2013
Last Patient Last Visit	03/2018
Study report / publications available	10/2018

Objectives

Objective 1
- To assess the natural course of G+LILD in patients with CVID

Objective 2a
- To explore the pathogenesis of G+LILD

Objective 2b
- To determine Biomarker for disease activity

Objective 3
- To explore efficacy of therapy
- To monitor safety of subjects during therapy

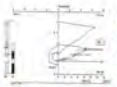
Parameters

- Lung function
- Chest CT
- QoL (SF36, SGRQ, CRDQ)

- Microbiological / immunological / histological evaluation of lung tissue and BAL cells
- Microbiome analysis

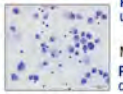
- Serum sIL2R, IL6, IP10, CCL18 and neopterin levels compared to Chest CT and lung function

- Lung function (DLCOcSB)
- Chest CT
- QoL (SF36, SGRQ, CRDQ)
- Overall survival, infections, side effects



Lung function
Prof. A. Prasse
Univ Med Freiburg

Histopathology
Dr. G. Kayser
Univ Med Freiburg



BAL Cytology
Prof. A. Prasse
Univ Med Freiburg

Microbiome
Prof. I. Lipkin
Columbia Univ NY

CT scan
Dr. I. Hartmann
Univ Med Rotterdam

Statistical analysis

- Descriptive and graphical analysis of the course of the disease
- Correlation between CT scores, graded lung involvement and serum biomarker levels
- For the statistical analysis of changes in lung function, patients' data will be divided into periods of specific treatment. The outcome lung function at the end of a period will be analyzed in a linear regression model for repeated measurements (GEE)

Centers and recruitment

Significance for the CCI

- STILPAD addresses one of the most important therapeutic needs in the largest CCI patient cohort
- The trial is designed to be the basis for subsequent prospective randomized interventional trials
- The European CVID network is strengthened contributing also to the visibility of the CCI
- Creation of an interdisciplinary platform for future lung trials in PID

CONCLUSION

1. Fréquent: 30 – 40%
2. Parfois présent avant infections (PID)

   Anomalies subtiles Ig (DDB/Pi3k) → DEPISTAGE
3. Atteinte liée à dérégulation immunologique

   - séquelle infections aigues

   - prolifération lymphoide aberrante

   - microbiote
4. Survie
5. Génétique/Thérapeutique ciblées
6. Déficit immunitaire combiné (B et T) → Allogreffe?