



Refractory Coeliac Disease and malignant complications of Coeliac disease

Prof Christophe CELLIER

European Georges Pompidou Hospital

French Celiac Study Group (CELAC)

Coeliac UK meeting 9 March 2016

Conflict of interest

- **Dr Schar Institute**
- **Thermo-fisher Pharma**
- **Institut du pain**

Malignancy and Coeliac Disease

- High grade lymphoma: EATL
- Refractory Coeliac Disease type 2: intraepithelial lymphoma
- Small Bowel adenocarcinoma

Mortality and CD

Corrao et al, Lancet 2001

1072 CD (1962 - 1994)

Cause Of Death	N of Death	Expected death	overmortality	p
lymphoma	16	9,1	69,3	<0,0001
tumor	8	8,9	0,9	NS
cardiovascular	12	11,3	2	NS
digestive	11	1,8	6,1	<0,0001
others	6	3,7	1,6	NS

T cell lymphoma (EATL)

< 1% of CD
 ≈ 0.2 à 2 / 100 000

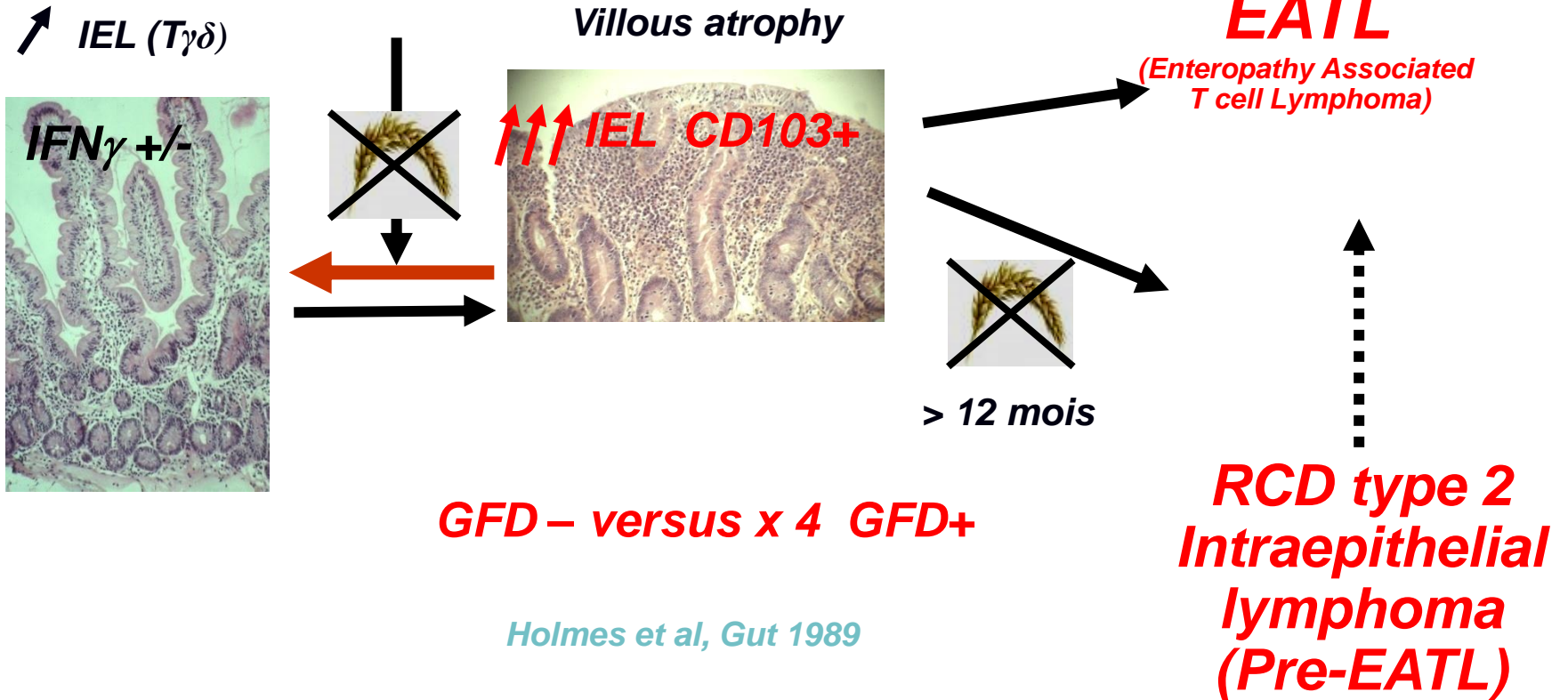
West, Gastroenterology 2009

Enteropathy-Associated T Cell Lymphoma
 (Malignant Histiocytosis of the Intestine) Is
 Recognized by a Monoclonal Antibody (HML-1)
 that Defines a Membrane Molecule on Human
 Mucosal Lymphocytes

HML1= CD103

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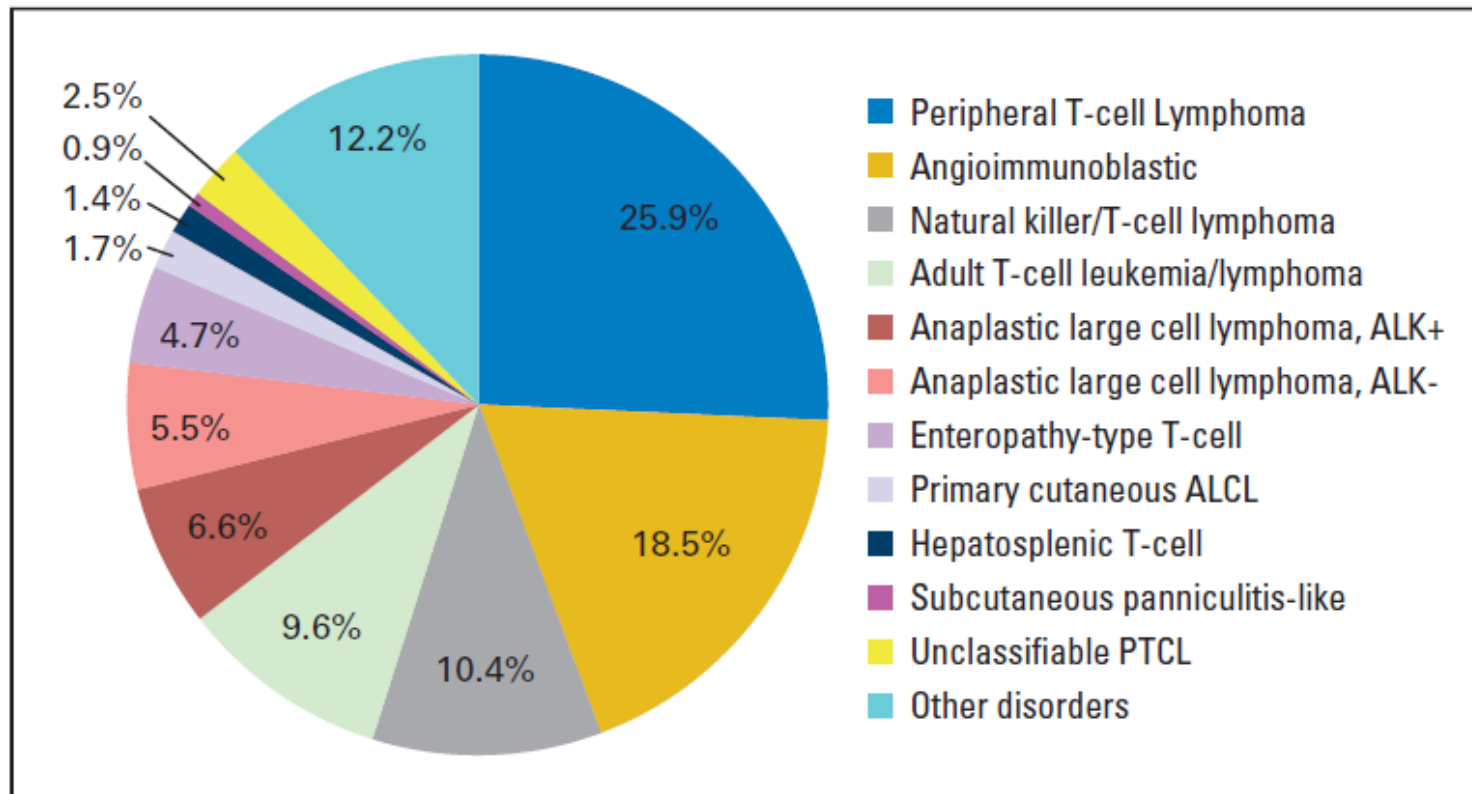
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Lymphoma: RR X 6

Askling, Gastroenterology 2002

EATL in International PTCL project: < 5% of T-cell lymphomas (JCO 2008)



Develops in 4/1000 of CD patients ?

Biagi et al, Dig Liver Dis 2014

EATL Diagnosis and CD

Secondary EATL: CD (or RCD) known before the diagnosis of EATL

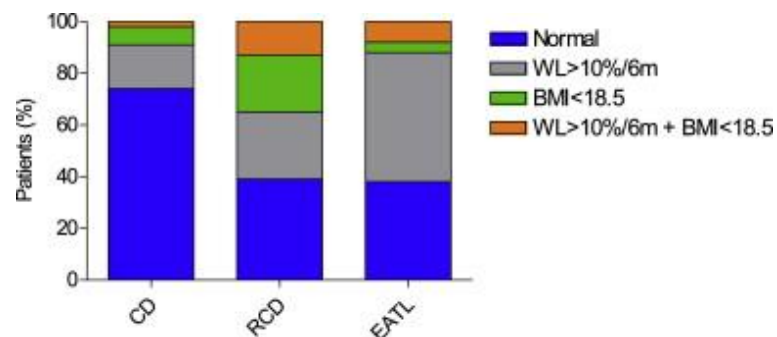
risk factors for EATL

- - **age at diagnosis CD (> 50y/old)**
- - **poor observance of GFD: RRX 4**
- - **RCD type 2 (Pre-EATL)**
- - **lack of mucosal healing**

Primary EATL revealing silent CD (20-50%) : No preceding diagnosis of CD.

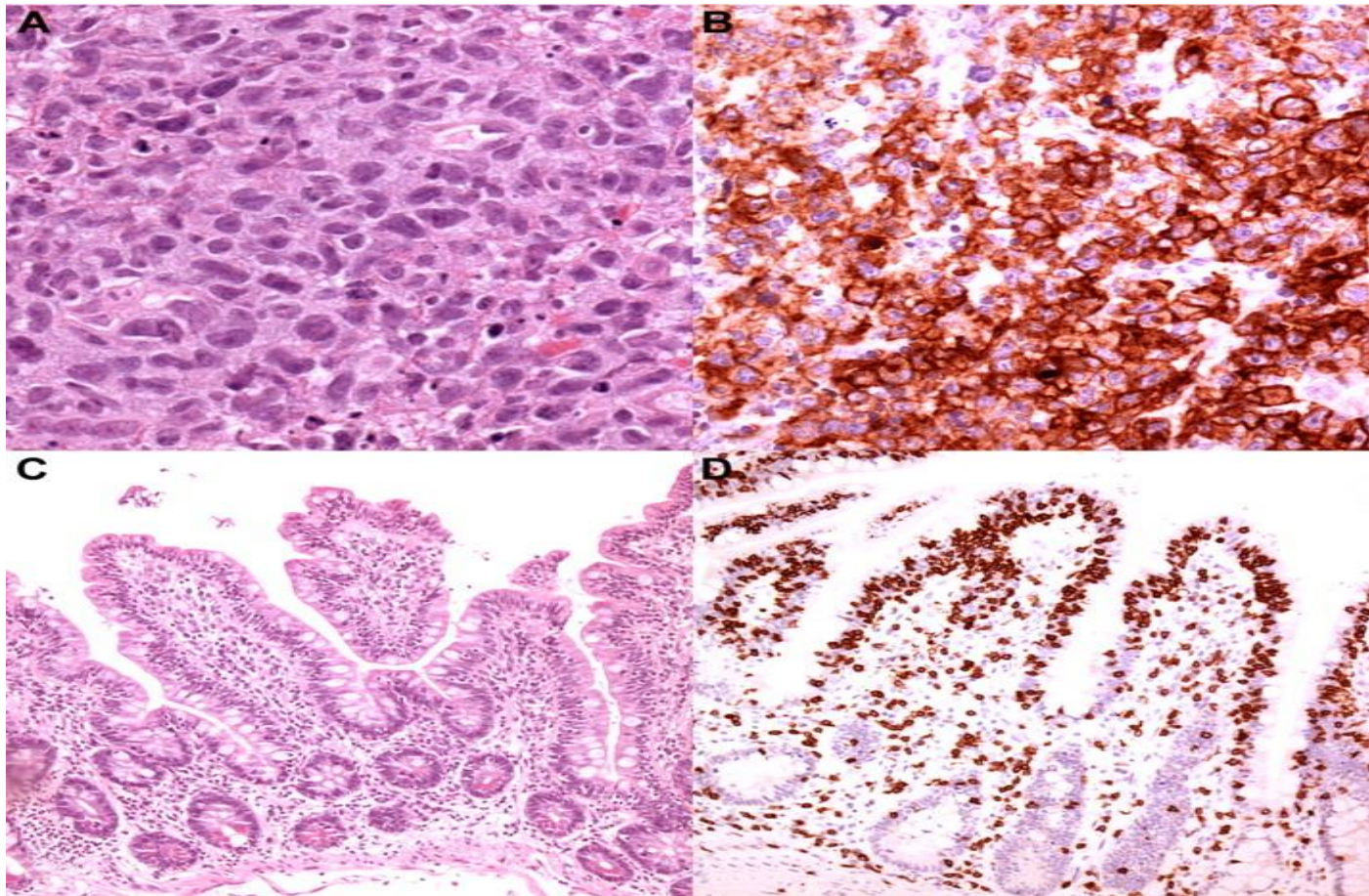
Clinical presentation for EATL

- Abdominal pain 65–100%
- Weight loss 50–80%
- Diarrhea 40–70%
- Fever < 30%
- LDH increased < 30%
- **Complications** 70%: GI perforation (25–50%), GI hemorrhage, intestinal occlusion
- **Malnutrition**: very common. Contributes to the poor tolerance and delay of curative treatment



Enteropathy associated T cell lymphoma in celiac disease: A large retrospective study *

How to obtain histological proof of EATL ?



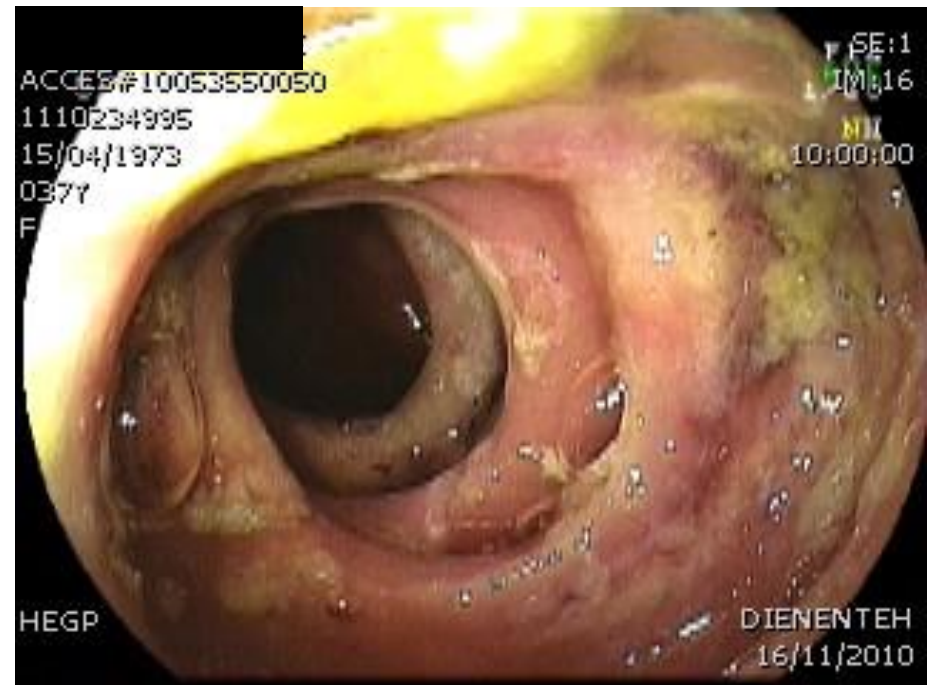
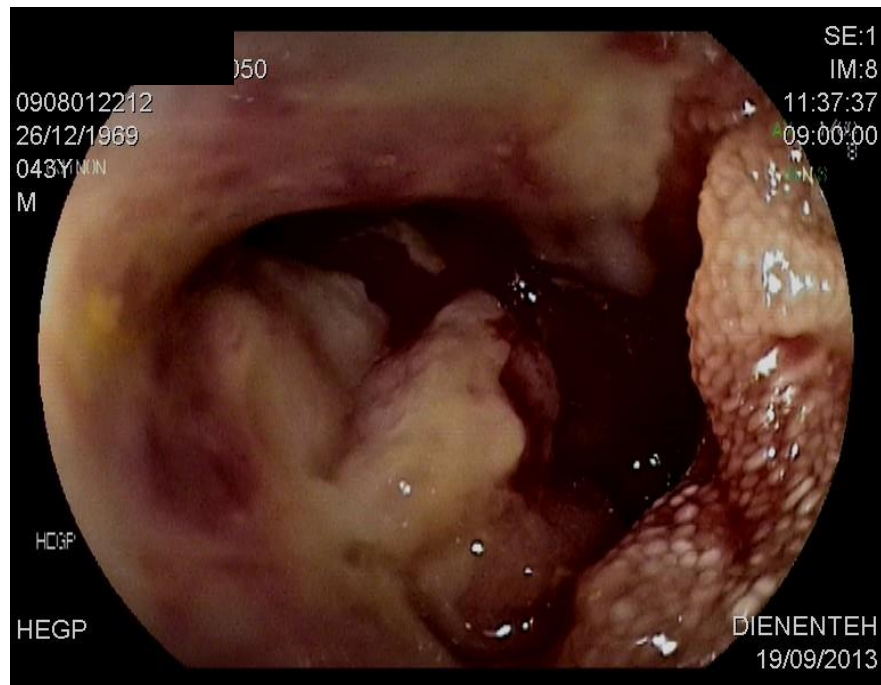
Medium- to large-sized cells with a pleomorphic appearance and an increased mitotic index.

The tumour phenotype is usually sCD3⁻, iCD3⁺, CD4⁻, CD8⁻, CD103⁺, TCR⁻, CD30[±],

CD5[±]. CD8⁺ immunostaining is possible

Enteroscopy (DBE) or surgery (after CT)

- Histological specimens of the distal small bowel, when the lesion can not be reached by standard GI endoscopy



Which treatment for EATL ?

blood

2010 115: 3664-3670
Prepublished online March 2, 2010;
doi:10.1182/blood-2009-07-231324

Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation

Michal Sieniawski, Nithia Angamuthu, Kathryn Boyd, Richard Chasty, John Davies, Peter Forsyth, Fergus Jack, Simon Lyons, Philip Mounter, Paul Revell, Stephen J. Proctor and Anne L. Lennard

Scotland and Newcastle Lymphoma Group
(SNLG)

1994-1998

Data prospectively collected
on all patients with
lymphoma in Scotland and
the Northern region of
England

EATL

- n=54 after review
- median age 57 y (28-82)
- history of CD = 34%

**Surgery
alone**

n=19

CR 11%
5-y OS
0%

**Chemotherapy ±
surgery** n=35
(**anthracycline n=31**)

CR 42%
5-y OS 22%

From 1998

Novel regimen for EATL:

IVE-MTX-ASCT

- EATL
- ≥ 18 y
- eligible for ASCT

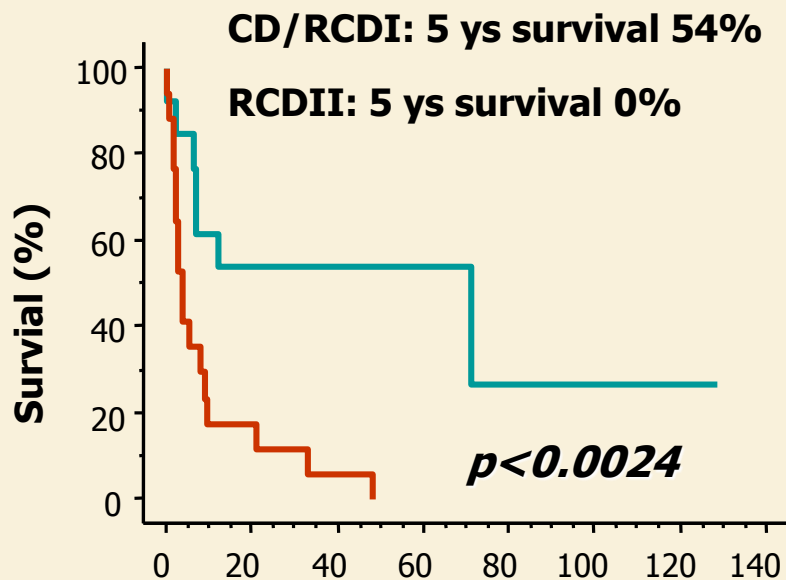
EATL

- n=26
- median age 56 y (36-69)
- history of CD = 42%

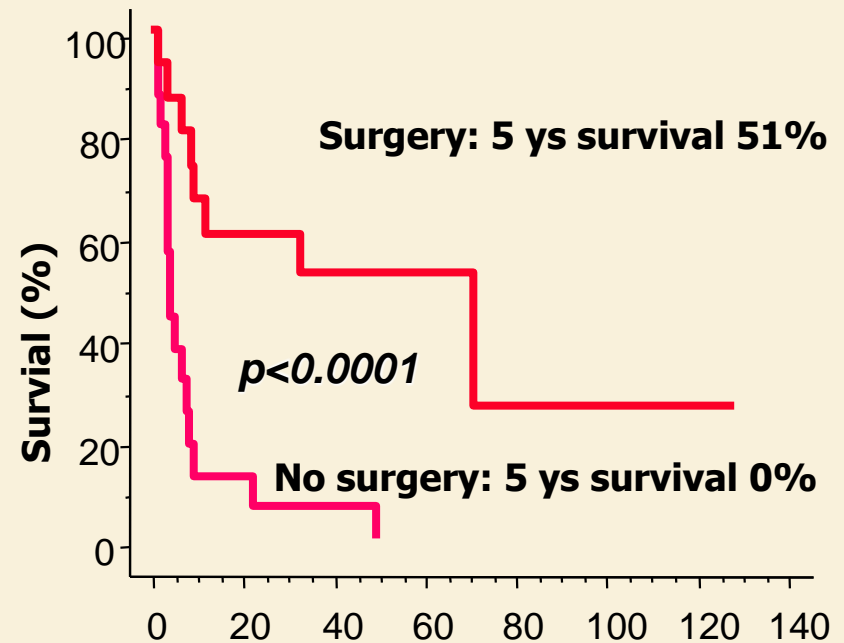
ASCT in 14/26 pts
(54%)
5-y OS 60%

EATL: pronostic factors (malnutrition, stage and age)

Type of enteropathy



Tumour mass reduction surgery



Enteropathy associated T cell lymphoma in celiac disease: A large retrospective study *

Georgia Malamut^{a,b,c}, Olivia Chandesris^{a,d}, Virginie Verkarre^{a,c,e}, Bertrand Meresse^{a,c}, Céline Callens^{a,f}, Elizabeth Macintyre^{a,f}, Yoram Bouhnik^g, Jean-Marc Gornet^h, Matthieu Allez^h, Raymond Jian^b, Anne Berger^{a,i}, Gilles Châtellier^{a,j}, Nicole Brousse^{a,c,e}, Olivier Hermine^{a,d,1}, Nadine Cerf-Bensussan^{a,c},
1, Christophe Cellier^{a,b,c,1}

Summary about EATL treatment

- No consensus for initial treatment
- Surgery (debulking) might be considered in first place but never alone
- A chemotherapy should be considered whenever feasible
- But after CHOP without ASCT:
 - the CR rate is only 40%
 - the 5-y OS is only 20%
- ASCT is feasible and can provide long-term remission
- But only 50% of pts in whom ASCT is initially planned are actually transplanted (toxicities, progression).
- **Need for new drugs (anti CD30)**

EATL: Paris – Amsterdam therapeutic consensus

- Debulking surgery
- EATL CD30-: Scottish regimen

IVE /MTX HD- ASCT

Ifosfamide, Vincristine, Etoposide, Methotrexate

Autologous SCT

- *Sienawski M et al, Blood 2011*

EATL CD30+ (>80%): start 2015

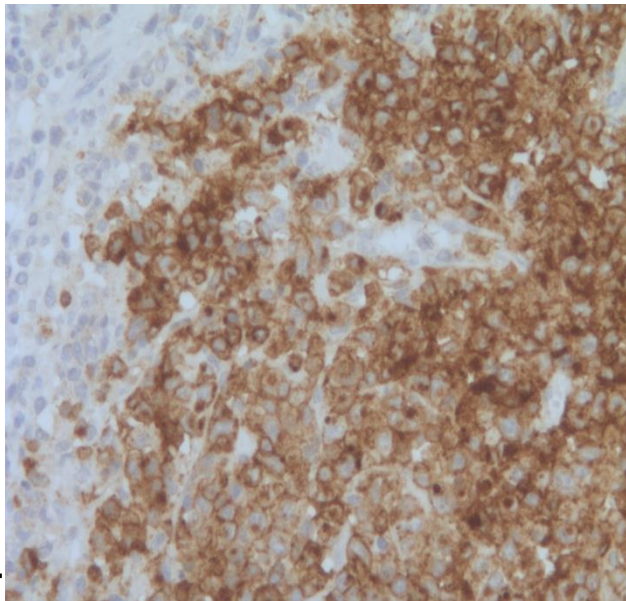
CHP-SGN35

Hermine O, Sibon D (Takeda)

CELAC Network: expression of CD30 in RCD and EATL

New treatment for EATL ?

	RCD I (n=25)	RCD II (n=20)	EATL (n=25)
CD30 expression	CD30-neg in 90% of RCD I and II. Rarely expressed by dispersed atypical lymphocytes (IEL or in lamina propria) in some cases		CD30 strongly expressed by all large tumor cells (25/25)



EATL
CD30+

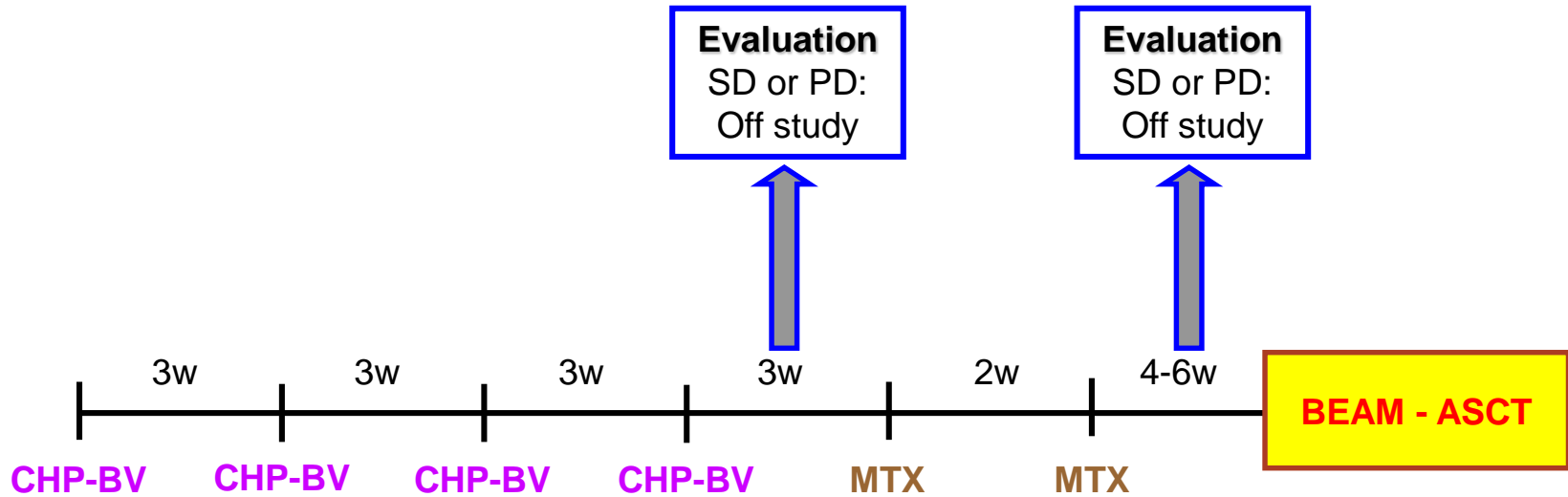
(Sibon D et al, ASH 2013 and T-Cell Lymphoma Forum 2014)

The CELAC experience

- 5 EATL pts
- CHP-Brentuximab Vedotin (BV) (anti CD30)
- good tolerance
- after 4 cycles, 4 patients were in CR and 1 patient in PR
- consolidation with IV MTX (x2) and ASCT

The CHP-BV regimen seems very promising,
both in terms of effectiveness and tolerance

**Phase 2 Study of Brentuximab Vedotin and CHP Followed by Autologous Stem-Cell Transplantation as Frontline Treatment of Enteropathy-Associated T-Cell Lymphoma.
(PI: Prof HERMINE and Dr SIBON)**



CHP-BV (4 cycles):

Brentuximab vedotin 1.8 mg/kg intravenously (IV) on day 1
Cyclophosphamide 750 mg/m² IV on day 1
Doxorubicin 50 mg/m² IV on day 1
Prednisone 40 mg/m² daily orally on days 1-5

MTX (2 cycles):

Methotrexate 3 g/m² IV on day 1

BEAM:

Carmustine 300 mg/m² IV on day -6
Etoposide 100 mg/m² IV twice per day on days -5 through -2
Cytarabine 200 mg/m² IV twice per day on days -5 through -2
Melphalan 140 mg/m² IV on day -1

ASCT: stem-cells reinfused on day 0

→ Enrollment of 25 pts through the CELAC network and LYSA centers (Plus Amsterdam and other?)

Refractory sprue/ refractory CD

- villous atrophy mimicking CD refractory to a strict gluten-free diet

- normal cytological appearance

abnormal IEL phenotype:

CD3+ CD103+ CD8- CD4- TCR-

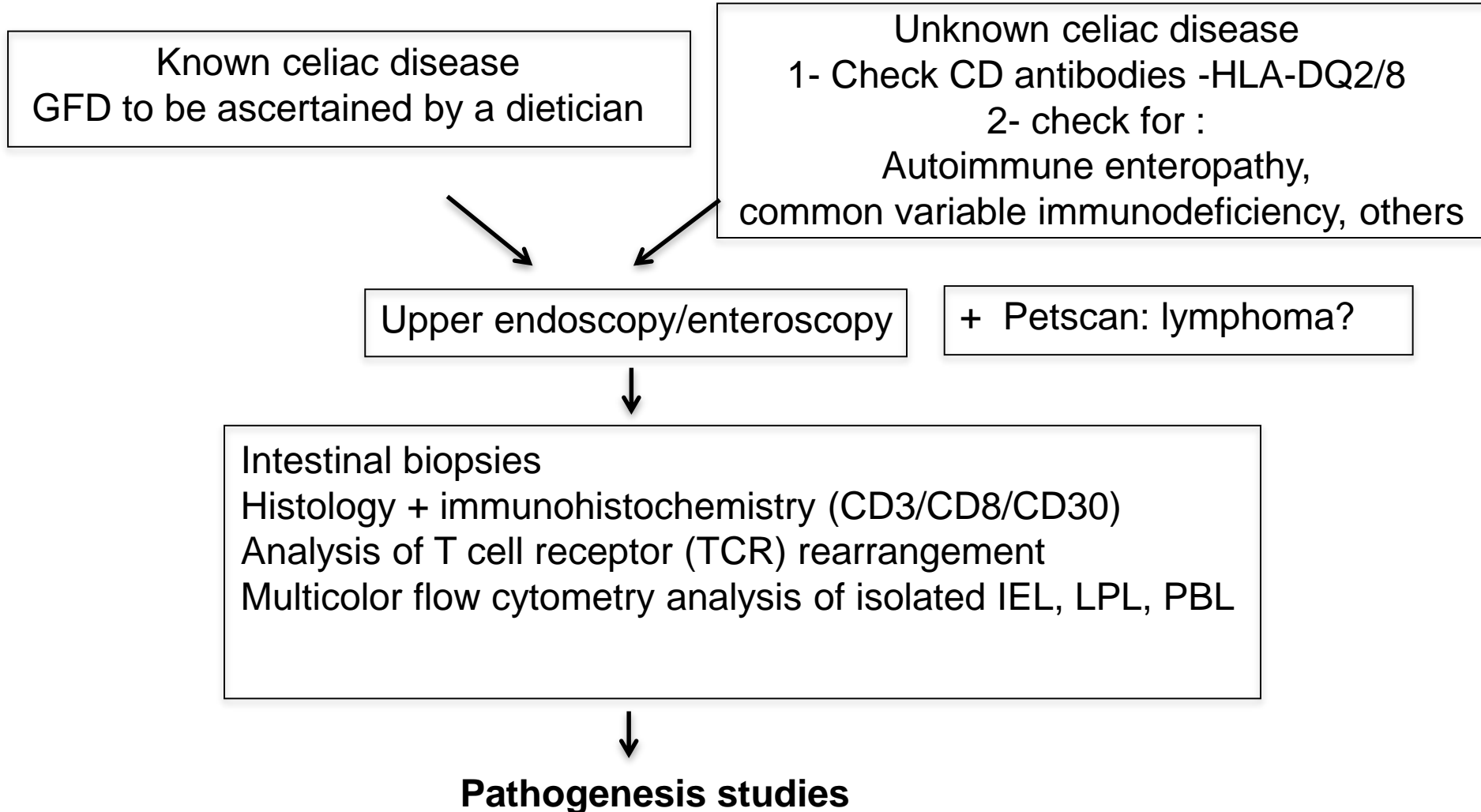
clonal TCR γ rearrangement

Cellier et al, Gastroenterology 1998, Lancet 2000

Carbonnel et al, Blood 1998, Badgi et al, Blood 1999

Daum et al, Gut 2001, Farstadt et al, Gut 2002

Villous atrophy unresponsive to a GFD: a multidisciplinary approach



Epidemiology of Refractory Celiac Disease

- **No clear cut data: rare, but serious disorder (< 1% adult CD)**
- **Paris experience: 95 (70 RCD2 and 25 RCD1) among adult CD over 15 years period (3%)**
- **Adults CD patients (> 50 yrs)**
- **More RCD type 1 in USA**
- **More RCD type 2 in Paris and Amsterdam (different genetic background and diagnostic tools ?)**

REFRACTORY COELIAC DISEASE (RCD)

RCD I (USA)

IEL

Normal T phenotype
Polyclonal repertoire

Villous atrophy



RCD II (Europe)

IEL

Abnormal phenotype
sCD3-TCR- iCD3+ :25-98%
CD8 – or CD8 low

Clonal T γ (T δ)

Malnutrition

more severe

55%

hypoalbuminemia

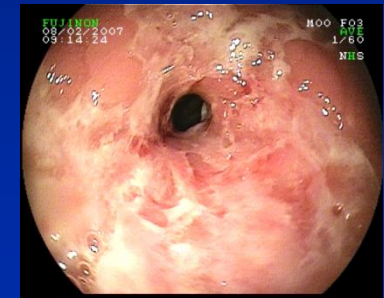
93%

10%

Ulcerative jejunitis

67%

Large ulcerations >1 cm



Malamut et al Gastroenterology 2009

Al Toma et al Gut 2007, Verbeek et al Future drugs 2008

Rubio-Tapia et al Gastroenterology 2009

Cellier et al Gastroenterology 1998

Cellier et al Lancet 2000

REFRACTORY CELIAC DISEASE type 2: GASTROENTEROLOGY 1998;114:471-481 CRYPTIC INTRAEPITHELIAL LYMPHOMA

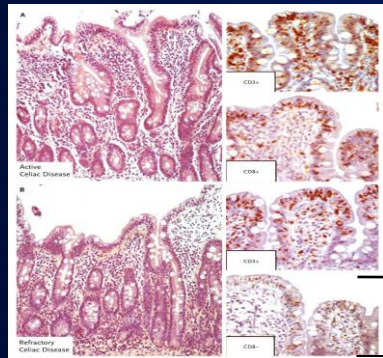
Abnormal Intestinal Intraepithelial Lymphocytes in Refractory Sprue

CHRISTOPHE CELLIER,* NATACHA PATEY,† LAURENT MAUVIEUX,§ BANA JABRI,|| ERIC DELABESSE,§
JEAN-PAUL CERVONI,* MARIE-LAURE BURTIN,§ DELPHINE GUY-GRAND,¶ YORAM BOUHNİK,#
ROBERT MODIGLIANI,# JEAN-PHILIPPE BARBIER,* ELISABETH MACINTYRE,§ NICOLE BROUSSE,†
and NADINE CERF-BENSUSSAN¶

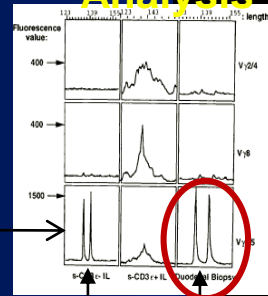
Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma

Christophe Cellier, Eric Delabesse, Christine Helmer, Natacha Patey, Claude Matuchansky, Bana Jabri,
Elizabeth Macintyre, Nadine Cerf-Bensussan, Nicole Brousse, for the French Coeliac Disease Study Group*

THE LANCET • Vol 356 • July 15, 2000



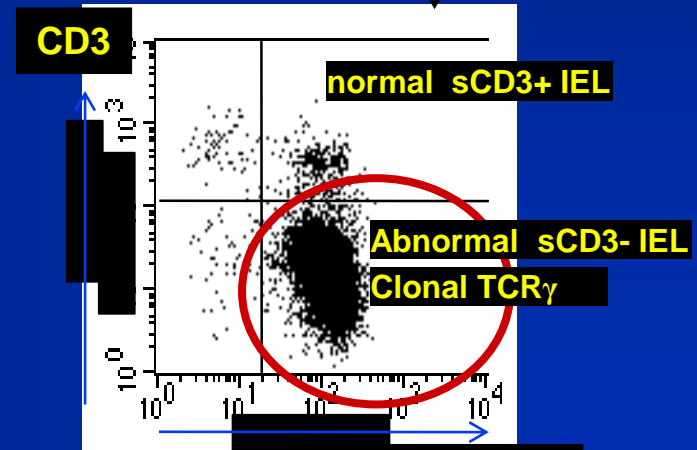
CD3+/CD8-



Analysis of TCR γ clonality

homoduplex

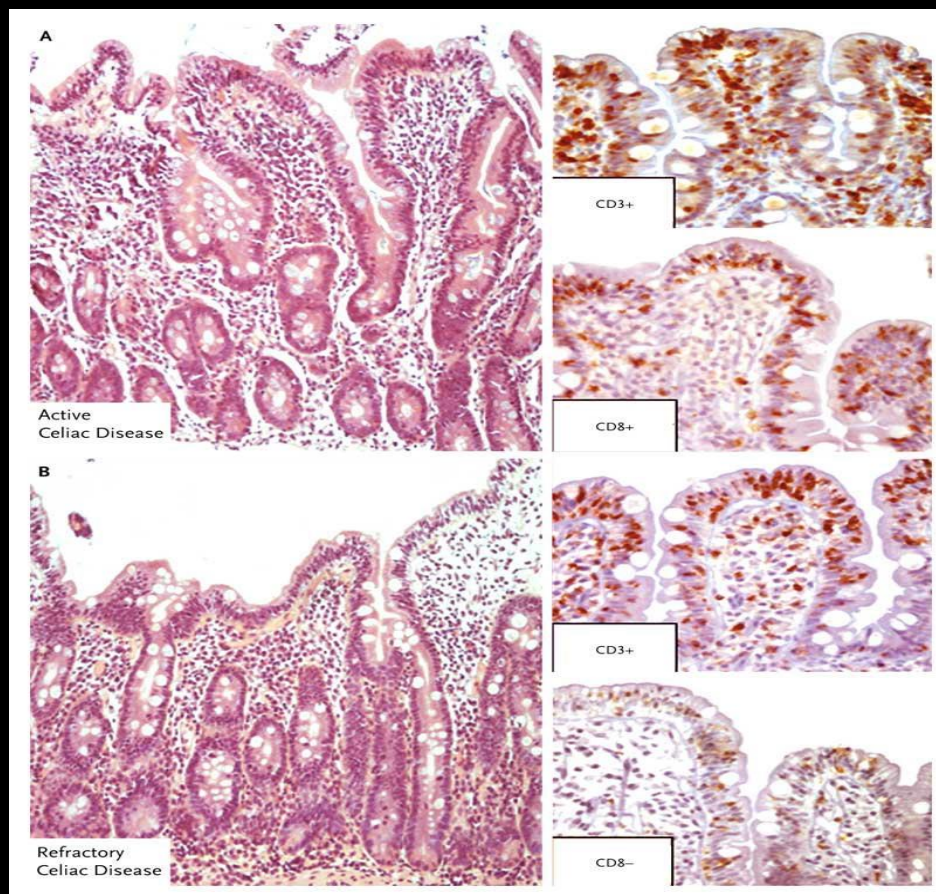
Biopsy



CD103/CD45/CD7

RCD type 2 is a lymphoma (or at least pre-lymphoma)

Phenotyping Intraepithelial Lymphocytes in Active versus Refractory Celiac Disease type 2: a simple screening test (CD3+ /CD8-)



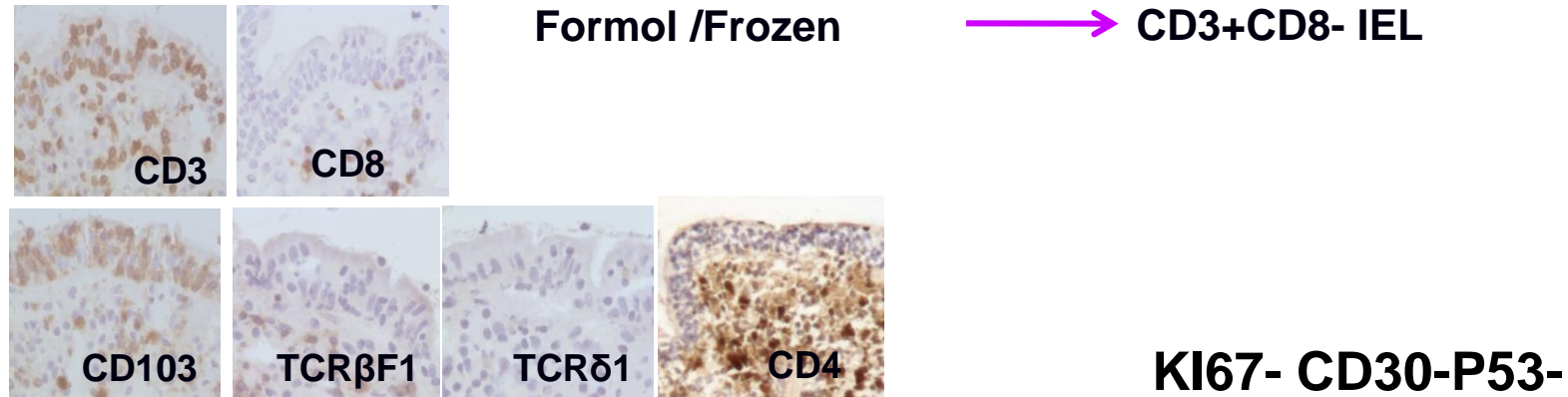
Green P and Cellier C. N Engl J Med 2007;357:1731-1743



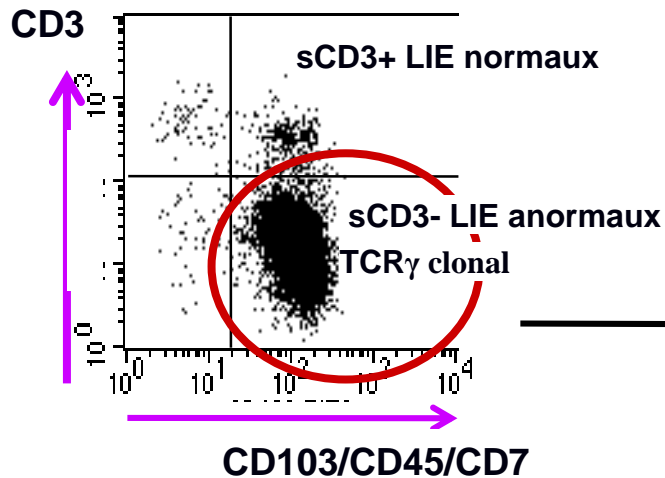
The NEW ENGLAND
JOURNAL of MEDICINE

RCDII : clear diagnostic criteria (FACS is a key point: aberrant C3s- IEL > 20%)

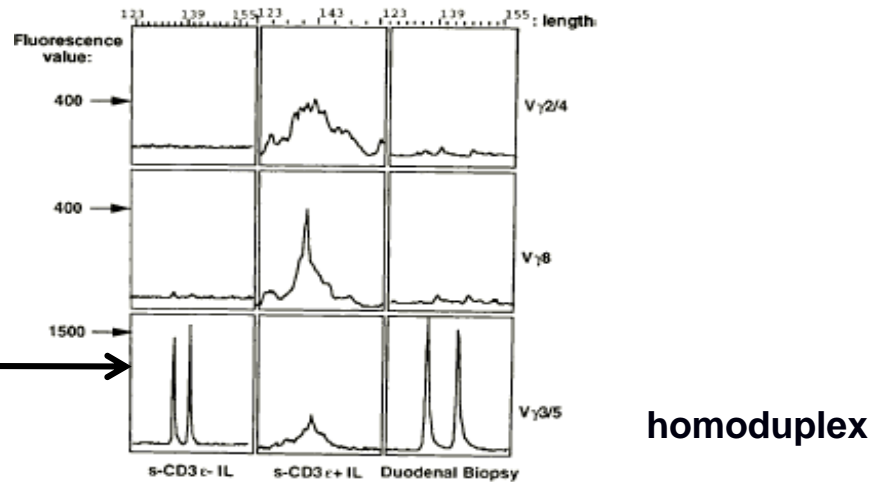
Immunohistochemistry



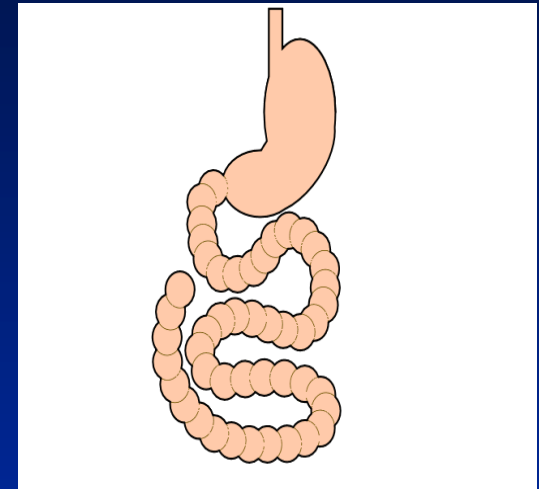
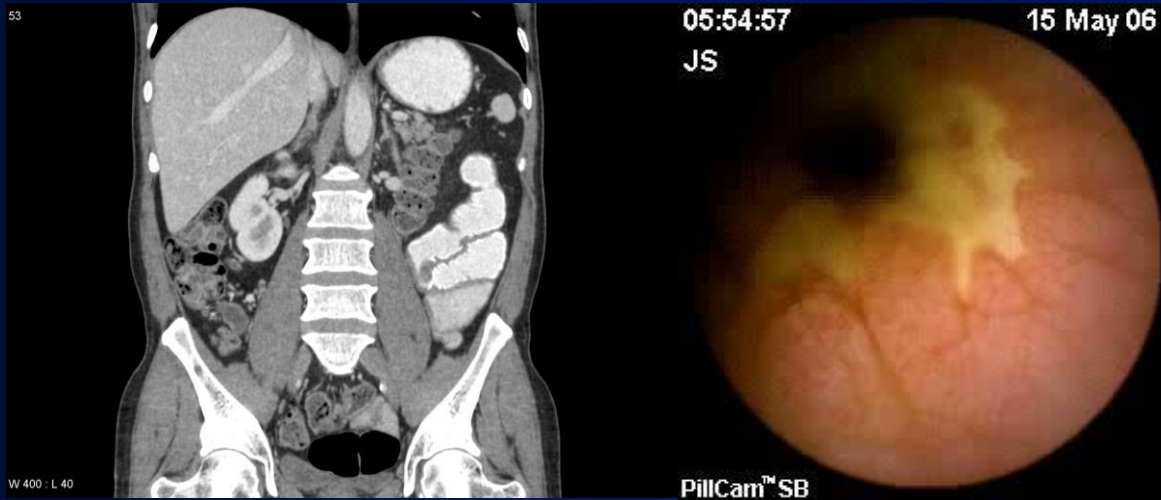
Flow cytometry on IEL isolated from 6-8 biopsies



Analysis of TCR γ clonality par multiplex PCR

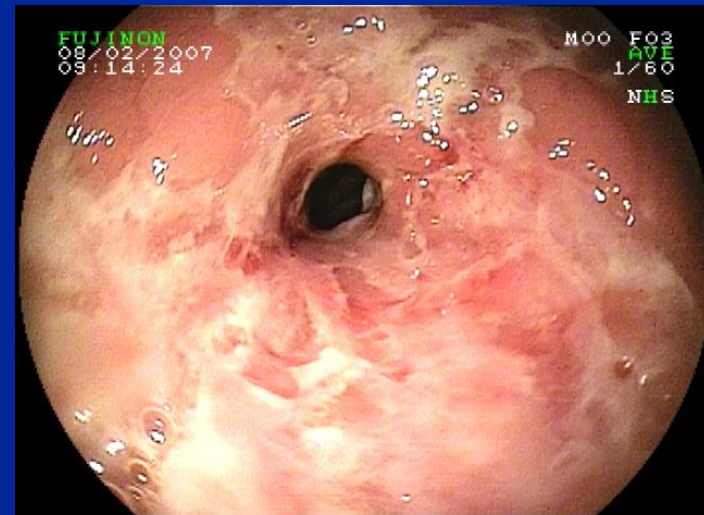


Extensive work-up in order to exclude EATL overt lymphoma: radiology (CT, MRI, TEP), capsule, enteroscopy



Diagnostic Yield of Capsule Endoscopy in Refractory Celiac Disease

Maximilien Barret, MD, MSc^{1,2}, Georgia Malamut, MD, PhD^{1,2,3}, Gabriel Rahmi, MD^{1,2,8}, Elia Samaha, MD^{1,2,8}, Joël Edery, MD¹, Virginie Verkarre, MD, PhD^{2,4}, Elizabeth Macintyre, MD, PhD^{2,5}, Emilie Lenain, MSc^{6,7}, Gilles Chatellier, MD, PhD^{6,7}, Nadine Cerf-Bensussan, MD, PhD^{2,3} and Christophe Cellier, MD, PhD^{1,2}

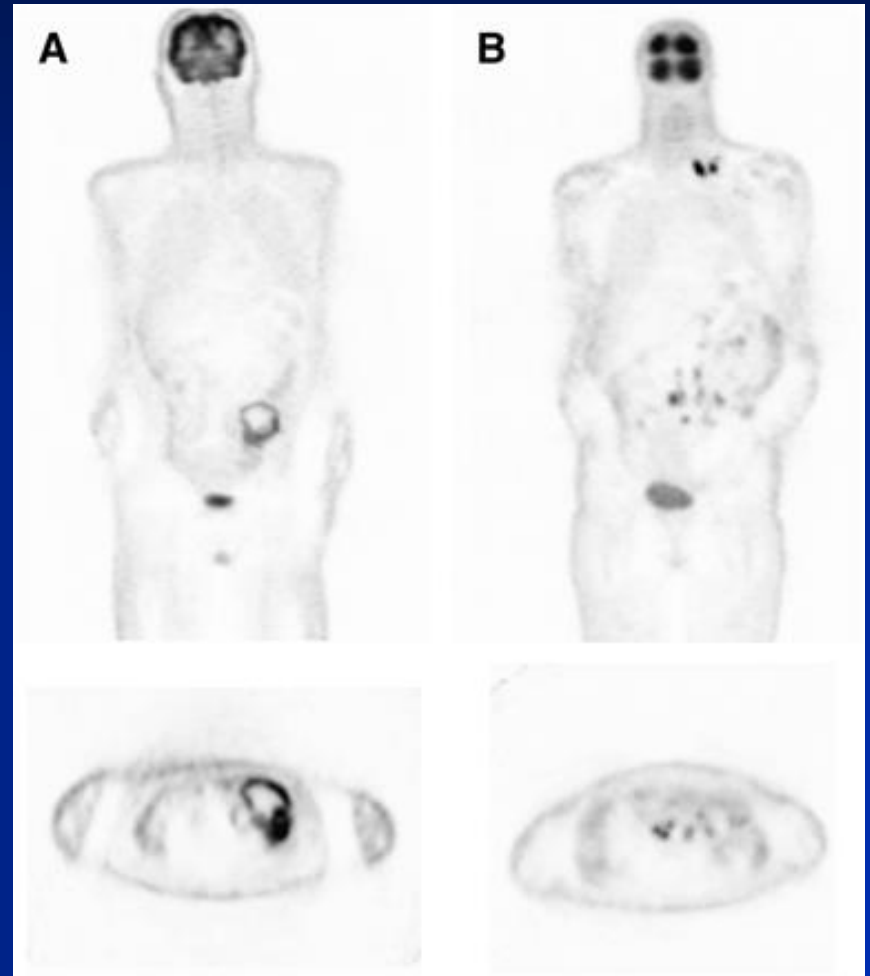


18F-FDG PET for the detection of EATL in Refractory Celiac Disease

- RCD type 2 (clonal) progress to EATL in 50% of cases
- Increased uptake in patients with overt lymphoma (not in RCD)
- Regular follow-up of RCD type 2 with PET ?

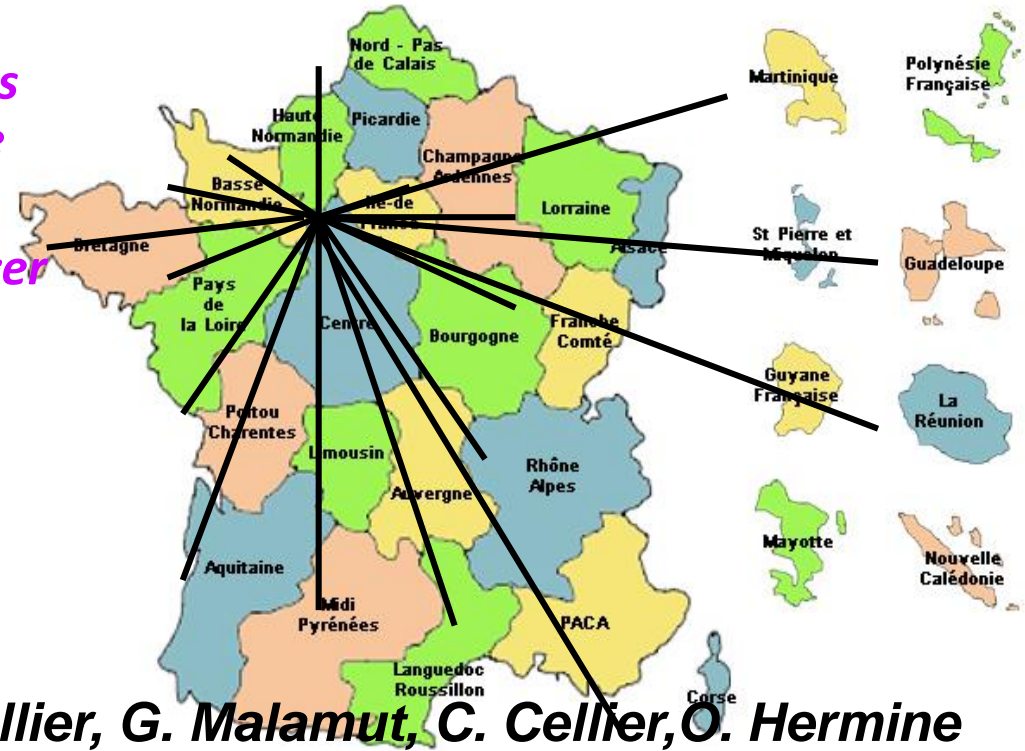
Hoffman et al, Gut 2003

Haditi et al, J Nucl Med 2006



National French Network for malignant complications of CD: CELAC (Future European Network? EUROCELAC)

- *CELAC - Centre Expert national des Lymphomes Associés à la maladie Coeliaque 2011-2015*
- *Labellisation INCa janv 2015 Cancer Rare*



Multidisciplinary meetings: C. Cellier, G. Malamut, C. Cellier, O. Hermine

Pathological centralized review: N. Brousse

Phenotype of intestinal lymphocytes N Cerf Bensussan

TCR rearrangements study: E. Macintyre,

Diagnostic reassessment, research and treatment

RCDII: Paris- Amsterdam therapeutic consensus

Budesonide



< 70 years:

- **Chemotherapy**
Fludarabin or Cladribine
- **Autologous stem cell transplantation (PHRC)**
Conditioning: Fludarabin-Melphalan

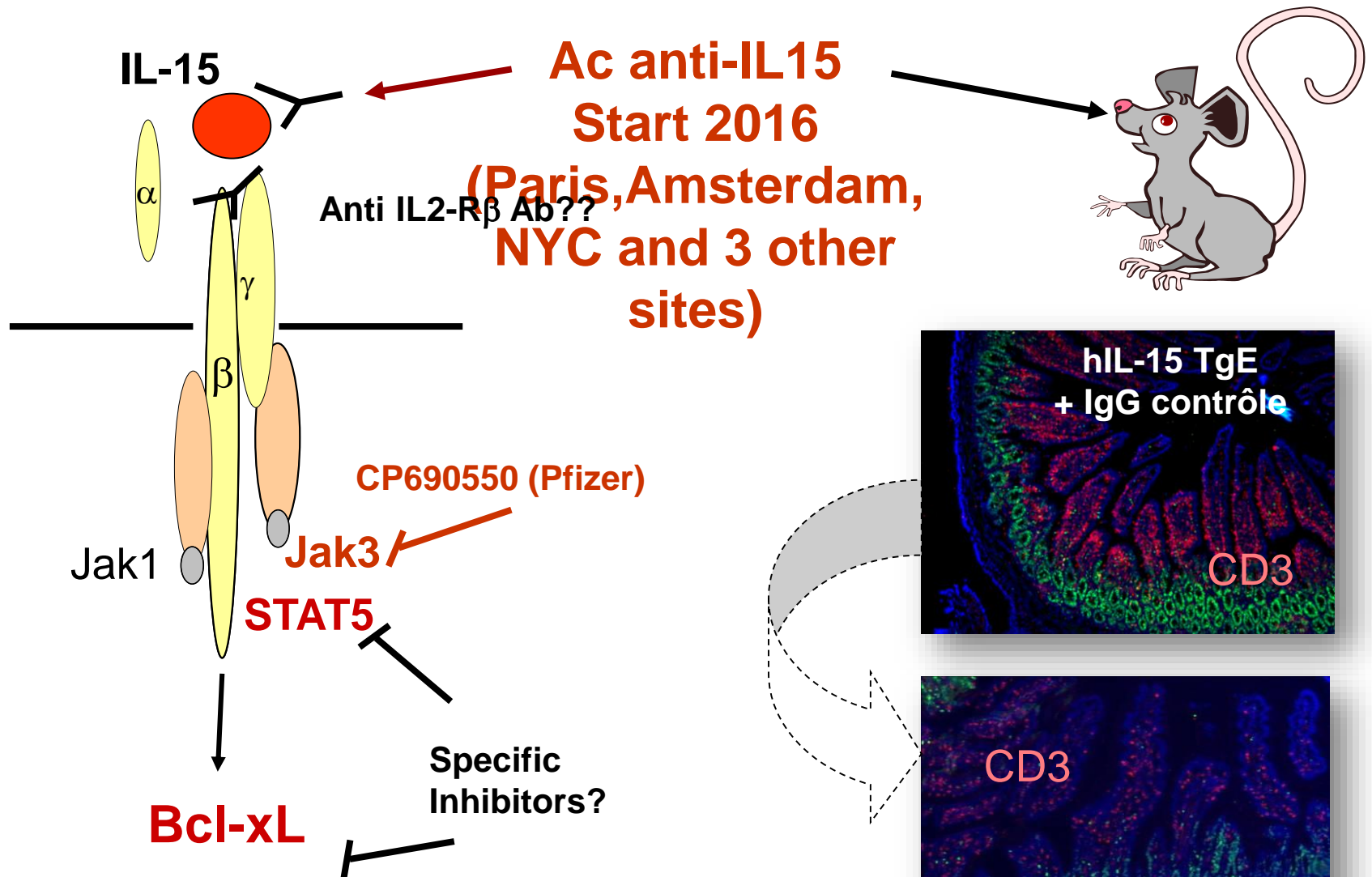
> 70 years:

**Chemotherapy with
Fludarabine-Endoxan
(Cladribine)**

Anti IL 15

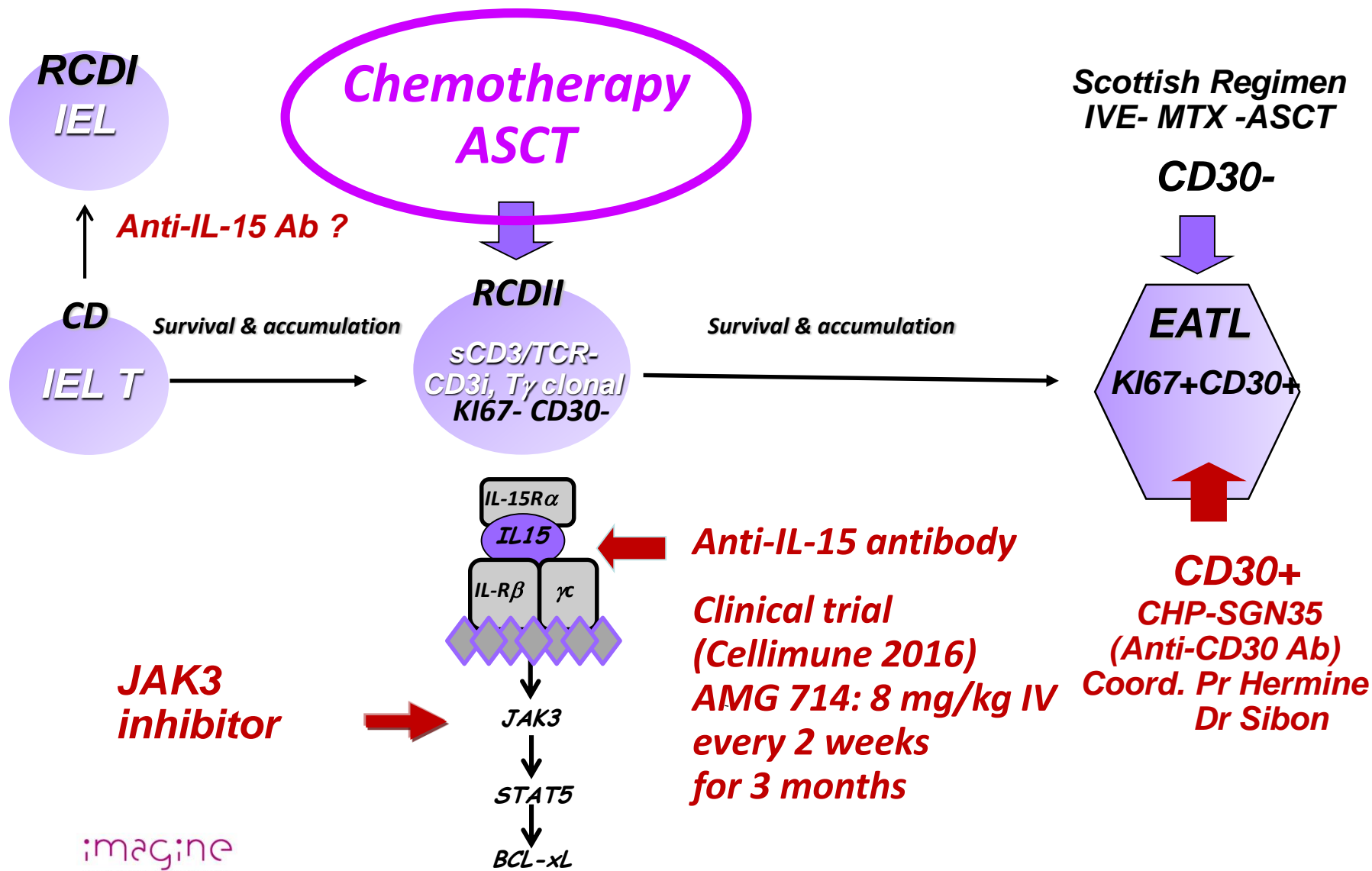
No immunosuppressors because of risk of developing overt lymphoma

RCDII: New targeted therapy?



Staff of Nadine Cerf-Bensussan
INSERM laboratory

Future Treatments of RCDII and EATL: Targeted therapy



European Networking is important

- **Cooperative multicentre trials: RCD:lymphoma/SB adenocarcinoma**
- *Referral centers in Europe*
- *European database and cohort of patients for clinical trial and basic research*
- *Applications to European grants and programs*
- *Excellence networks for rare diseases*

Acknowledgements

The CELAC Network

Gastroenterology

Pr. Georgia Malamut
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Hematology

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Dr. David Sibon

Pathology

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Hematology Lab

Pr. Elizabeth Macintyre
Dr. Coralie Derrieux

Research lab

Dr. Nadine Cerf-Bensussan
Dr. Bertrand Meresse

And all participating centers



Institut national
de la santé et de la recherche médicale



**Thank you for your attention !
SEE YOU AT ISSCD IN DEHLI
2017
and PARIS 2019**

