

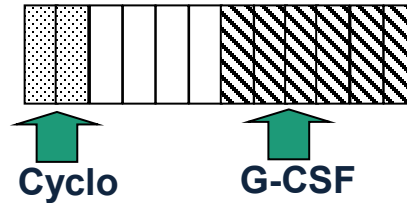
Autogreffe de cellules souches hématopoïétiques *dans la Maladie de Crohn réfractaire*

Matthieu ALLEZ

Xavier TRETON

Autologous HSCT in AID/IBD

Hematopoietic stem cell mobilization

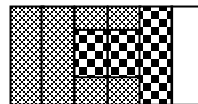


Cyclophosphamide 1.5-2 g/m²
G-CSF 10 µg/kg per day

- Apheresis
- Cryopreservation
- +/- Selection of CD34+ cells

Conditioning
High dose
immunoablation

ATG



Cyclo

Transplant

Autologous HSCT in AID/IBD

Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation

JA Snowden^{1,2}, R Saccardi³, M Allez⁴, S Ardizzone⁵, R Arnold⁶, R Cervera⁷, C Denton⁸, C Hawkey⁹, M Labopin¹⁰, G Mancardi¹¹, R Martin¹², JJ Moore^{13,20}, J Passweg¹⁴, C Peters^{15,21}, M Rabusin^{16,21}, M Rovira¹⁷, JM van Laar¹⁸ and D Farge¹⁹, on behalf of the EBMT Autoimmune Disease Working Party (ADWP) and Paediatric Diseases Working Party (PDWP)

Bone Marrow transplantation 2011

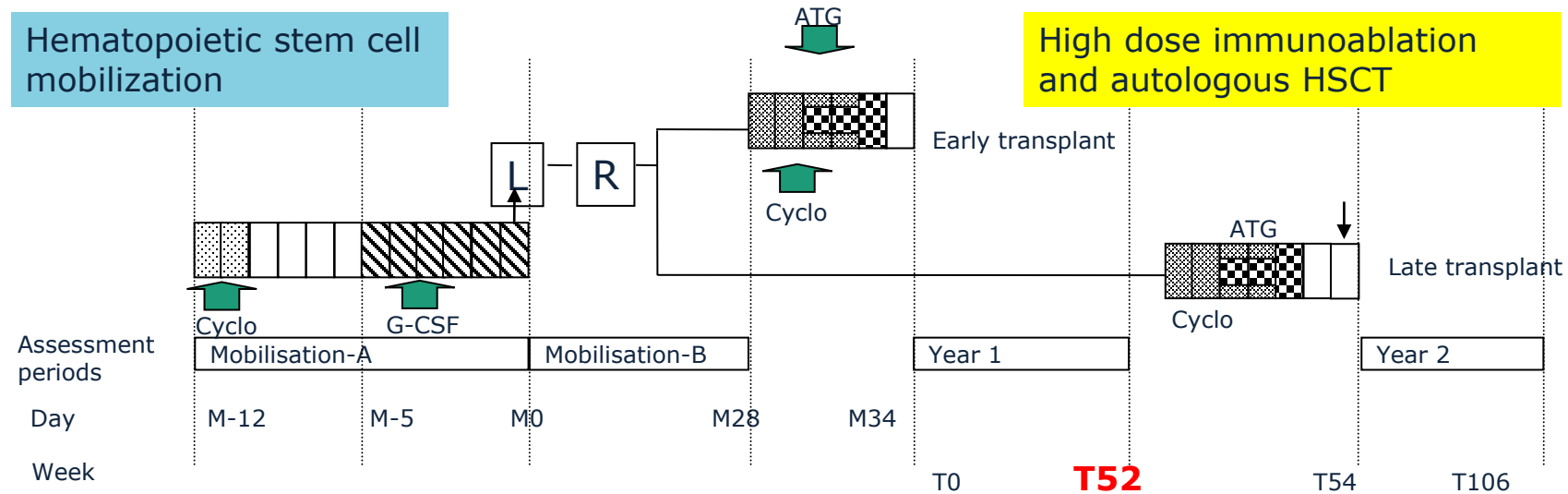
In the absence of results from large studies, autologous HSCT should be ***reserved for patients with severe CD unresponsive to multiple lines of therapy***

Autologous HSCT may be considered for the following situations (level III):

- Active disease, uncontrolled by medical therapies.
- Extensive disease in which surgical resection would expose the patient to the risk of small bowel syndrome.
- Refractory colonic disease and perianal lesions where coloprotection with a definitive stoma not accepted by the patient

Autologous Hematopoietic Stem Cell Transplantation for Refractory Crohn Disease A Randomized Clinical Trial

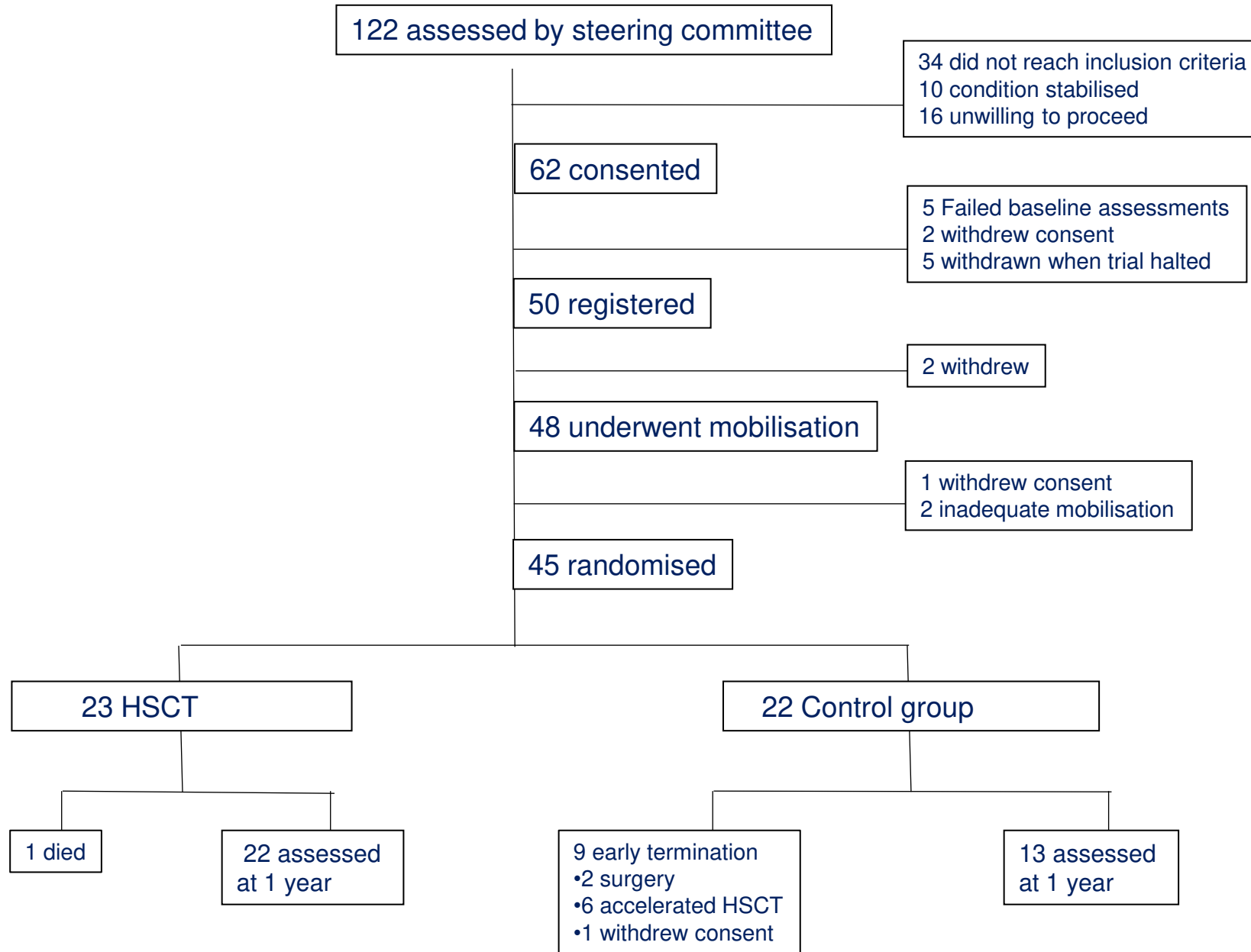
Christopher J. Hawkey, FMedSci; Matthieu Allez, PhD; Miranda M. Clark, BSc(Hons); Myriam Labopin, MD; James O. Lindsay, PhD; Elena Ricart, PhD; Gerhard Rogler, PhD; Montserrat Rovira, MD; Jack Satsangi, DPhil; Silvio Danese, PhD; Nigel Russell, MD; John Gribben, MD; Peter Johnson, MD; Jerome Larghero, MD; Catherine Thieblemont, PhD; Sandro Ardizzone, MD; Daan Dierickx, PhD; Adalberto Ibatici, MD; Timothy Littlewood, MD; Francesco Onida, MD; Urs Schanz, MD; Severine Vermeire, PhD; Jean-Frederic Colombel, MD; Jean-Paul Jouet, MD; Elizabeth Clark, MSc; Riccardo Saccardi, MD; Alan Tyndall, FRACP; Simon Travis, DPhil; Dominique Farge, PhD



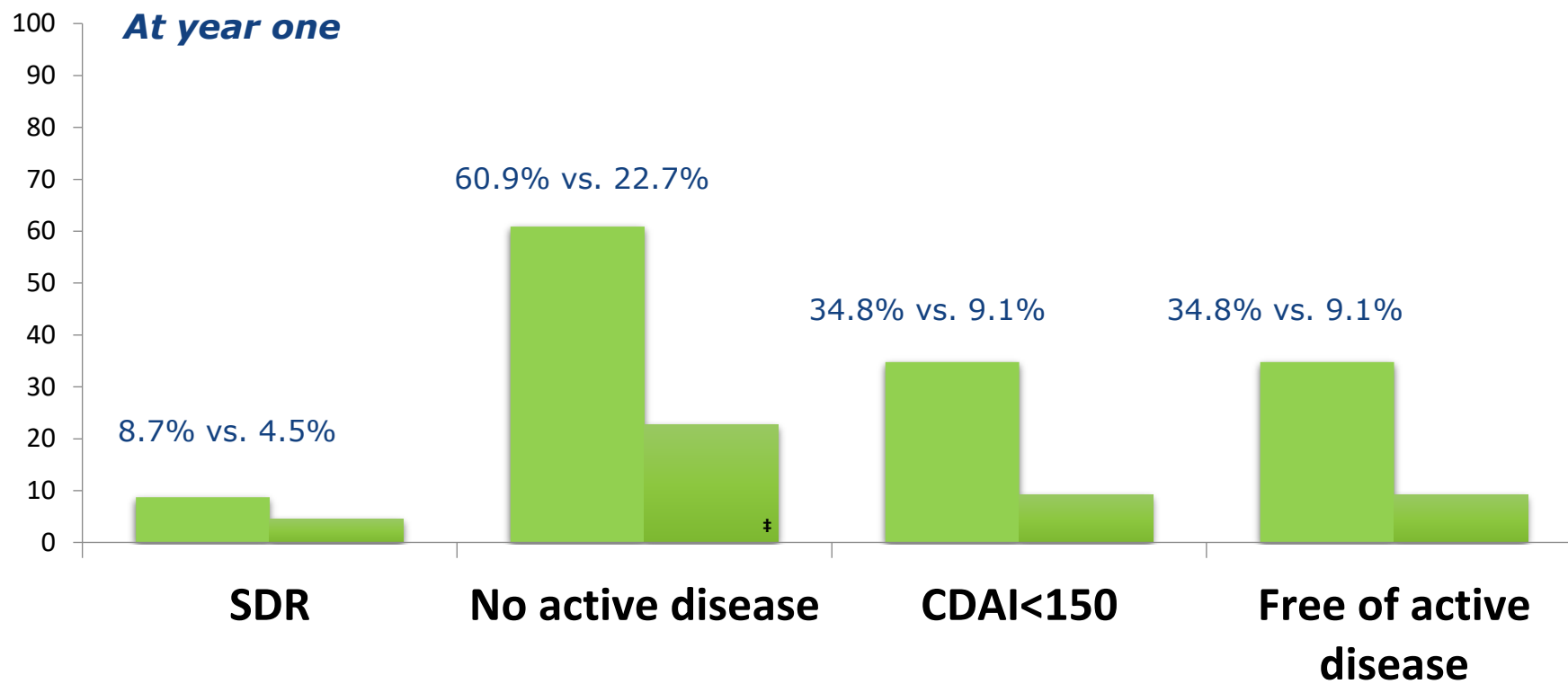
Primary endpoint:

- **Sustained remission 3 month period of CDAI < 150**
- **without treatment (no steroids, no IS, no biologics)**
- **and mucosal healing**

ASTIC trial



Proportion of Subjects (%)



	No. (%)		Difference (95% CI), %	P Value
	HSCT	Control		
Sustained disease remission	2 (8.7)	1 (4.5)	4.2 (-14.2 to 22.6)	.60
Secondary outcomes				
No active treatment	14 (60.9)	5 (22.7)	38.1 (9.3 to 59.3)	.01
CDAI < 150	8 (34.8)	2 (9.1)	25.7 (1.1 to 47.1)	.052
Free of active disease	8 (34.8)	2 (9.1)	25.7 (1.1 to 47.1)	.054

ASTIC trial – Safety: more serious adverse events in the HSCT group

- **76 serious adverse events** in 19 patients of HSCT group

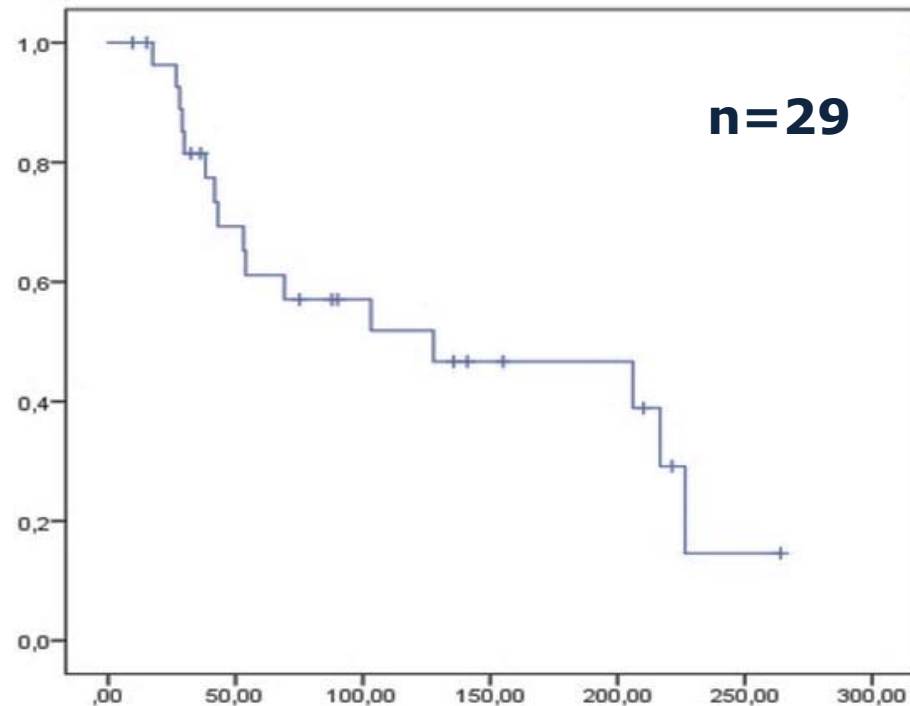
Vs. **38 serious adverse events** in 15 control patients: median difference in number SAE 0 (95%CI -1 to 4; p=0.7)

- **Higher risks in the 100 days following conditioning, mainly infections**
 - **10 viral infections in 5 patients** (none in control patients): EBV reactivation (n= 3), Herpes zoster (n = 1) and cytomegalovirus reactivation (n = 2)
 - 8 presumed neutropenic sepsis
 - 2 pneumonia including Klebsiella (n=1) and pneumocystis (n=1)
 - 3 anal abscesses
- **One patient died 20 days after the start of conditioning** with evidence of the sinusoidal obstructive syndrome at post mortem

HSCT for patients with refractory CD

Hospital Clínic de Barcelona

Proportion of patients with CDAI<150, no ulcers at endoscopy, not restarting CD medication, no surgery [median FU: 12m (3-60m)]

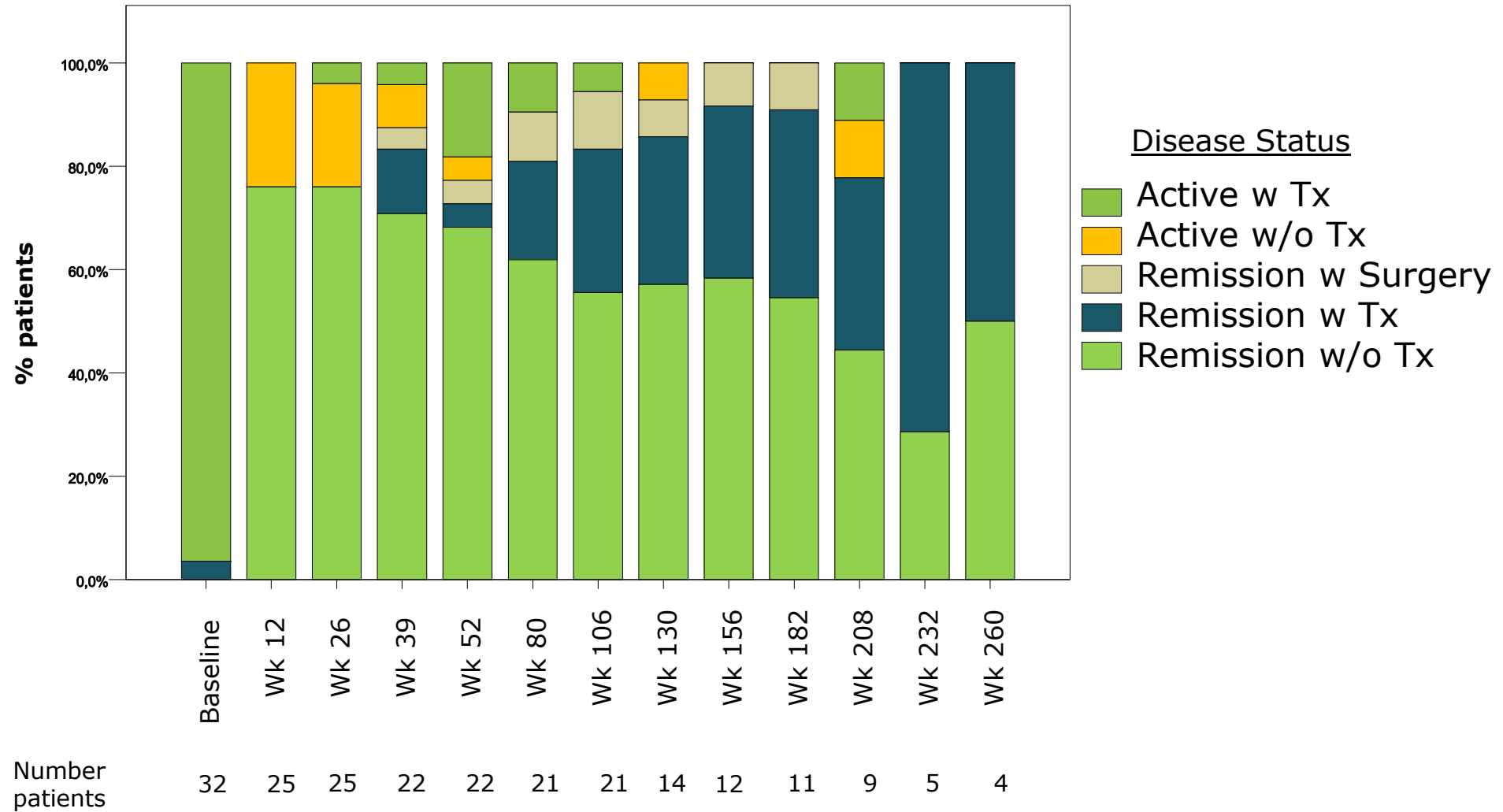


6m: 82%
1 yr: 61%
2 yr: 52%
3 yr: 47%
4 yr: 39%
5 yr: 15%

Relapse: 15/29
12/15 (80%): clinical remission with retreatment
3/15 (20%): non- loss-response, Colectomy

Disease course after HSCT in CD

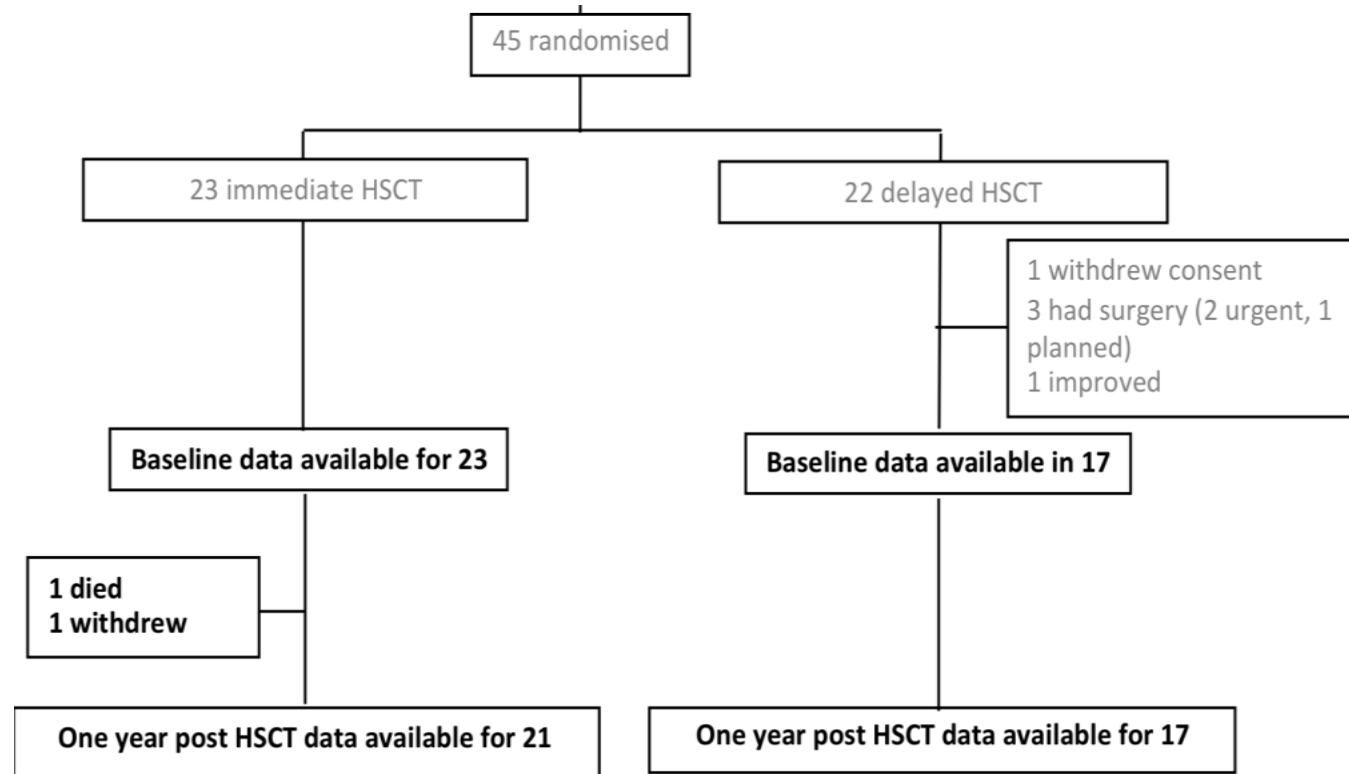
Barcelona cohort



Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial

ASTIC

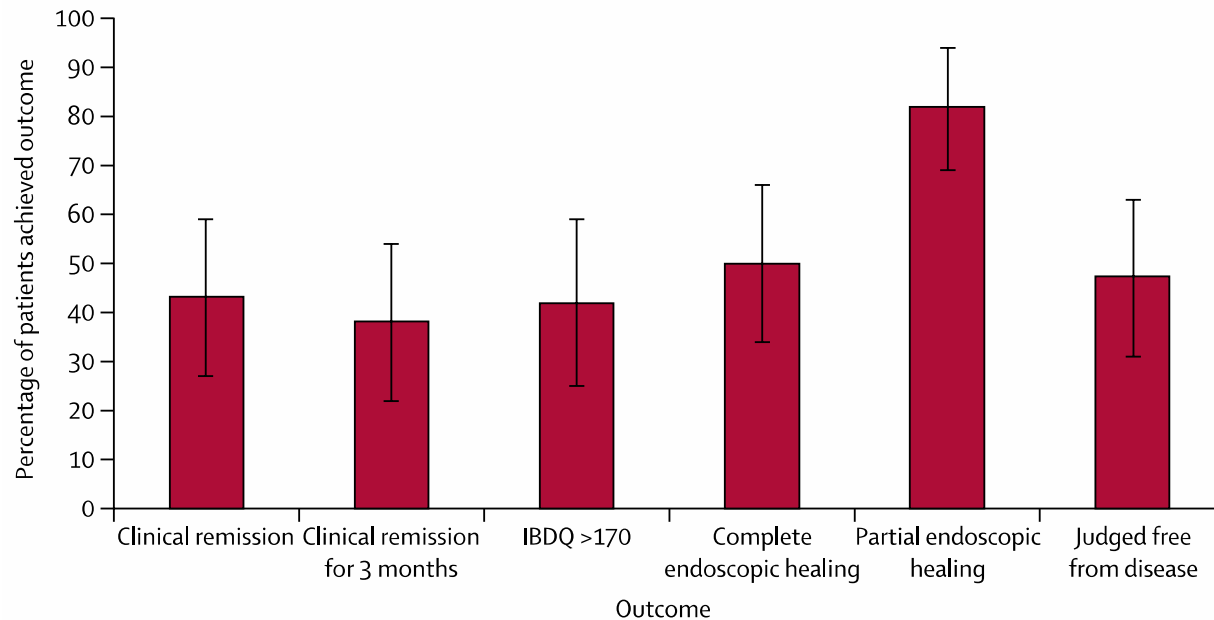
James O Lindsay, Mathieu Allez*, Miranda Clark, Myriam Labopin, Elenor Ricart, Gerhard Rogler, Montserrat Rovira, Jack Satsangi, Dominique Farge, Christopher J Hawkey, on behalf of the ASTIC trial group†, European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party, and European Crohn's and Colitis Organisation*



Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial

James O Lindsay*, Mathieu Allez*, Miranda Clark, Myriam Labopin, Elenor Ricart, Gerhard Rogler, Montserrat Rovira, Jack Satsangi, Dominique Farge, Christopher J Hawkey, on behalf of the ASTIC trial group†, European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party, and European Crohn's and Colitis Organisation

✓ One year outcome



- **Perianal disease: no benefit**

- **Anti TNF therapy: in 7 (18%) patients after 18 (14-39) weeks**
In anti TNF re-treated patients CDAI fell from 319 (55) to 174 (39); $p=0.016$
71.4% patients experienced a clinical response (CDAI fall > 70 points)

Mucosal healing: one year data

Complete endoscopic healing

102	I	RC	TC	LC	R
Baseline	Red	Grey	Green	Green	Green
One year	Green	Green	Green	Green	Green

203	I	RC	TC	LC	R
Baseline	Green	Yellow	Brown	Brown	Green
One year	Green	Green	Green	Green	Green

804	I	RC	TC	LC	R
Baseline	Yellow	Grey	Grey	Grey	Green
One year	Green	Green	Green	Green	Green

805	I	RC	TC	LC	R
Baseline	Green	Green	Green	Yellow	Green
One year	Green	Green	Green	Green	Green

810	I	RC	TC	LC	R
Baseline	Red	Grey	Green	Green	Yellow
One year	Green	Green	Green	Green	Green

902	I	RC	TC	LC	R
Baseline	Blue	Red	Green	Green	Green
One year	Green	Green	Green	Green	Green

101	I	RC	TC	LC	R
Baseline	Blue	Blue	Green	Green	Yellow
One year	Green	Green	Green	Green	Green

702	I	RC	TC	LC	R
Baseline	Red	Green	Green	Green	Green
One year	Green	Green	Green	Green	Green

906	I	RC	TC	LC	R
Baseline	Blue	Blue	Yellow	Brown	Green
One year	Green	Green	Green	Green	Green

911	I	RC	TC	LC	R
Baseline	Brown	Green	Yellow	Yellow	Green
One year	Green	Green	Green	Green	Green

915	I	RC	TC	LC	R
Baseline	Green	Brown	Brown	Brown	Green
One year	Green	Green	Green	Green	Green

1507	I	RC	TC	LC	R
Baseline	Red	Grey	Grey	Grey	Brown
One year	Green	Green	Green	Green	Green

1902	I	RC	TC	LC	R
Baseline	Green	Green	Green	Red	Green
One year	Green	Green	Green	Green	Green

2606	I	RC	TC	LC	R
Baseline	Yellow	Grey	Green	Green	Yellow
One year	Green	Green	Green	Green	Green

No or partial endoscopic healing

802	I	RC	TC	LC	R
Baseline	Blue	Blue	Yellow	Red	Green
One year	Yellow	Green	Green	Green	Green

803	I	RC	TC	LC	R
Baseline	Green	Yellow	Red	Yellow	Brown
One year	Green	Green	Green	Yellow	Green

808	I	RC	TC	LC	R
Baseline	Yellow	Grey	Yellow	Brown	Green
One year	Green	Green	Green	Green	Red

813	I	RC	TC	LC	R
Baseline	Red	Green	Green	Green	Yellow
One year	Yellow	Green	Green	Green	Green

903	I	RC	TC	LC	R
Baseline	Green	Red	Green	Green	Green
One year	Green	Yellow	Yellow	Yellow	Yellow

908	I	RC	TC	LC	R
Baseline	Blue	Red	Brown	Brown	Brown
One year	Blue	Yellow	Green	Red	Yellow

1302	I	RC	TC	LC	R
Baseline	Blue	Grey	Brown	Brown	Red
One year	Yellow	Grey	Brown	Brown	Green

1802	I	RC	TC	LC	R
Baseline	Green	Brown	Brown	Red	Brown
One year	Green	Green	Green	Yellow	Green

1901	I	RC	TC	LC	R
Baseline	Red	Green	Green	Green	Green
One year	Yellow	Green	Green	Green	Green

2504	I	RC	TC	LC	R
Baseline	Brown	Green	Green	Brown	Brown
One year	Yellow	Grey	Grey	Grey	Green

2601	I	RC	TC	LC	R
Baseline	Blue	Green	Yellow	Red	Brown
One year	Green	Green	Yellow	Yellow	Yellow

201	I	RC	TC	LC	R
Baseline	Blue	Blue	Yellow	Green	Yellow
One year	Green	Green	Green	Yellow	Yellow

202	I	RC	TC	LC	R
Baseline	Blue	Blue	Blue	Yellow	Green
One year	Blue	Green	Green	Yellow	Green

801	I	RC	TC	LC	R
Baseline	Green	Green	Green	Yellow	Red
One year	Green	Yellow	Yellow	Red	Red

Patients with stoma

701	I	RC	TC	LC	R
Baseline	Yellow	Green	Red	Grey	Green
One year	Red	Green	Red	Grey	Green

806	I	RC	TC	LC	R
Baseline	Yellow	Grey	Grey	Grey	Green
One year	Yellow	Grey	Grey	Grey	Green

811	I	RC	TC	LC	R
Baseline	Green	Blue	Brown	Green	Green
One year	Yellow	Blue	Yellow	Green	Green

1501	I	RC	TC	LC	R
Baseline	Red	Blue	Blue	Blue	Blue
One year	Green	Blue	Blue	Blue	Blue

1502	I	RC	TC	LC	R
Baseline	Red	Grey	Grey	Grey	Green
One year	Red	Grey	Grey	Grey	Green

2603	I	RC	TC	LC	R
Baseline	Blue	Grey	Yellow	Yellow	Yellow
One year	Blue	Grey	Blue	Green	Green

No ulceration at baseline

1801	I	RC	TC	LC	R
Baseline	Green	Green	Green	Green	Green
One year	Green	Green	Green	Green	Green

905	I	RC	TC	LC	R
Baseline	Green	Green	Green	Green	Green
One year	Green	Green	Green	Green	Green

No endoscopic evaluation at baseline

2502	I	RC	TC	LC	R
Baseline	Blue	Blue	Blue	Blue	Blue
One year	Blue	Yellow	Green	Green	Green

2602	I	RC	TC	LC	R
Baseline	Green	Blue	Blue	Blue	Blue
One year	Green	Grey	Green	Green	Green

No endoscopic evaluation at one year

807	I	RC	TC	LC	R
Baseline	Green	Blue	Blue	Brown	Yellow
One year	Blue	Blue	Blue	Blue	Blue

1505	I	RC	TC	LC	R
Baseline	Red	Green	Green	Green	Green
One year	Blue	Blue	Blue	Blue	Blue

ASTIC trial - Steering committee - 2010

Explanation of why patient should be considered for trial

Mlle C. , **22 years old**

- **Severe refractory Crohn's disease (ileopancolitis and anal)**
- Failures of immunosuppressants (azathioprine, methotrexate)
- Loss of response or intolerance to three anti-TNF (infliximab, adalimumab and certolizumab), loss of response and intolerance to thalidomide (neuropathy).
- Phase 2 trial with Ustekinumab
- May 2010: disease is active and poorly responds to high doses of steroids
- Surgery?

The option of total colectomy with definitive stoma is refused by the patient

C. 22 ans, maladie de Crohn réfractaire sévère (iléopancolite et anale)

Inclus dans l'essai ASTIC en 06/2010

Maladie active :
CDAI > 350,
corticoïdes > 30mg/jour

Fissure anale extensive

Iléo-pancolite avec des lésions très sévères (ulcérations profondes étendues) dans le côlon transverse et gauche.

Juillet 2010 :
Mobilisation

Randomisé dans le bras **transplantation précoce (août 2010)**

Premier mois

Cystite : virus BK

Réactivation EBV => Rituximab

Diarrhée : Adénovirus, coloscopie normale !

Mois 6

Zona, pneumocystose => soins intensifs

A un an: Rémission clinique ; Coloscopie : quelques lésions aphtoïdes

A 2 ans: Rechute clinique, ulcérations superficielles dans le côlon gauche,

Puis Rémission clinique sous adalimumab

Infections ORL, otites / hypoglobulinémie

Cystite, obstruction, JJ

Suivi à 12 ans

Une grossesse menée à terme en 2015

Rémission clinique et endoscopique sous adalimumab

γ globulines SC

Pollakiurie (toutes les 1 à 2 heures), créatinine 110 μmol/l

Bonne qualité de vie

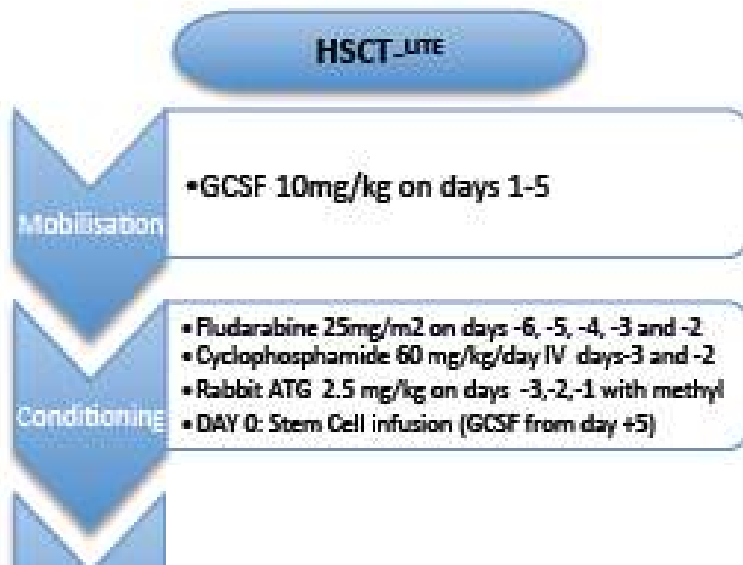
Essai ASTIC Lite

Essai multicentrique contrôlé et randomisé comparant la transplantation de cellules souches autologues (TCS) avec un protocole allégé vs poursuite des traitements conventionnels chez des patients atteints de MC réfractaire.

**CONSENT
SCREENING**

- 1) Standard pre HSCT work (EBMT ADWP guidelines)
- 2) Assessment of clinical disease activity (CDAI / PRO2)
- 3) Ileo-colonoscopy (disease scores using SES CD)
- 4) MRI small bowel
- 5) MRI pelvis in patients with previous perianal disease
- 6) Confirmation of eligibility by TMG

Randomisation 2:1

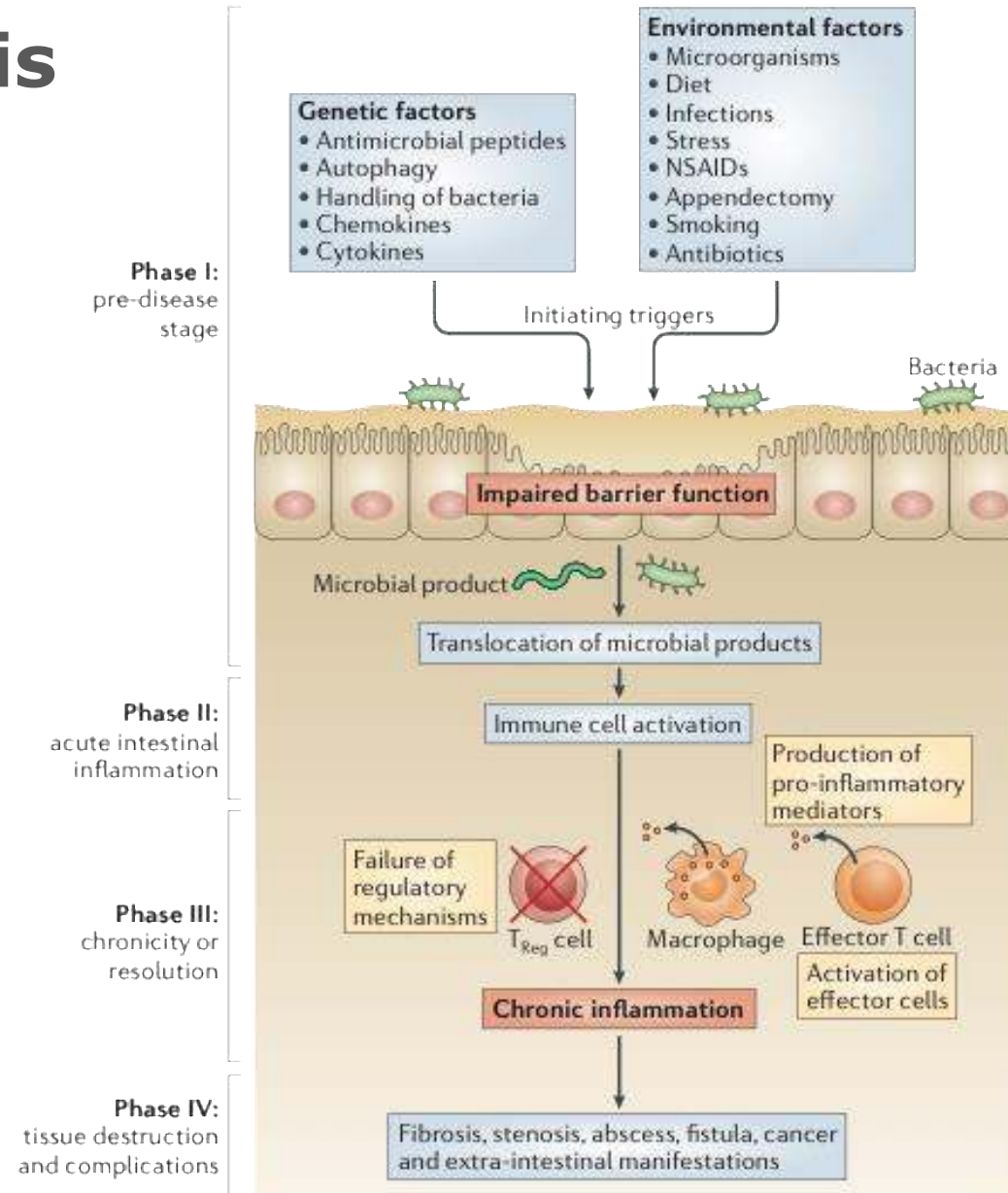


• Résultats

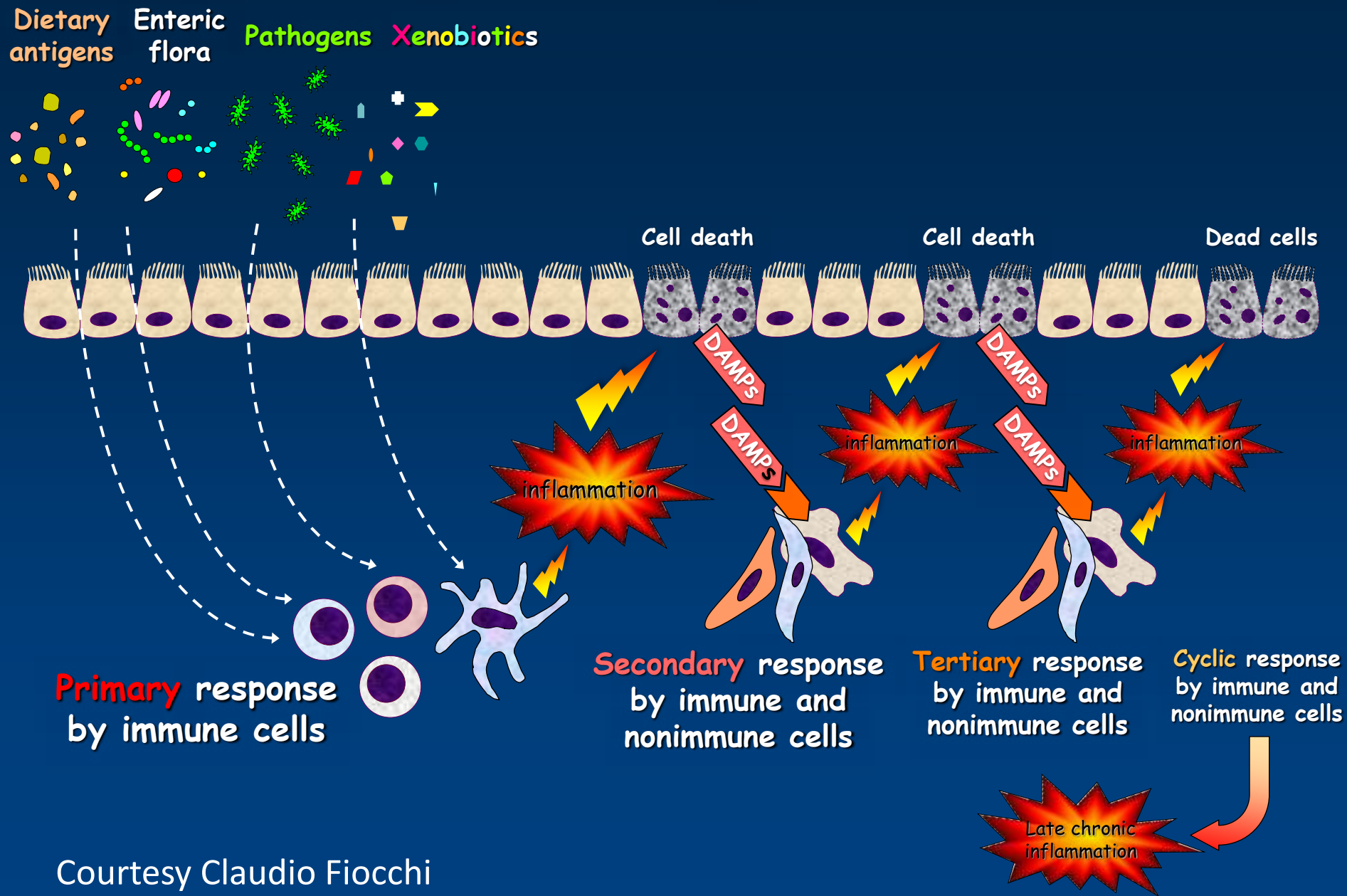
- 23 patients inclus (13 dans le groupe TCS et 10 dans le groupe traitements conventionnels)
- **Essai arrêté précocement du fait de la survenue d'effets indésirables graves dans le groupe TCS : 100 % d'effets indésirables graves (dont 3 MAT), 2 décès**
- Résultats endoscopiques (critère de jugement principal) :

Critère principal, n (%)	TCS (n = 10)	Traitements conventionnels (n = 9)	Tous (n = 19)
Oui	4 (40)	0 (0)	4 (21)
Non	6 (60)	9 (100)	15 (79)

Pathogenesis of IBD



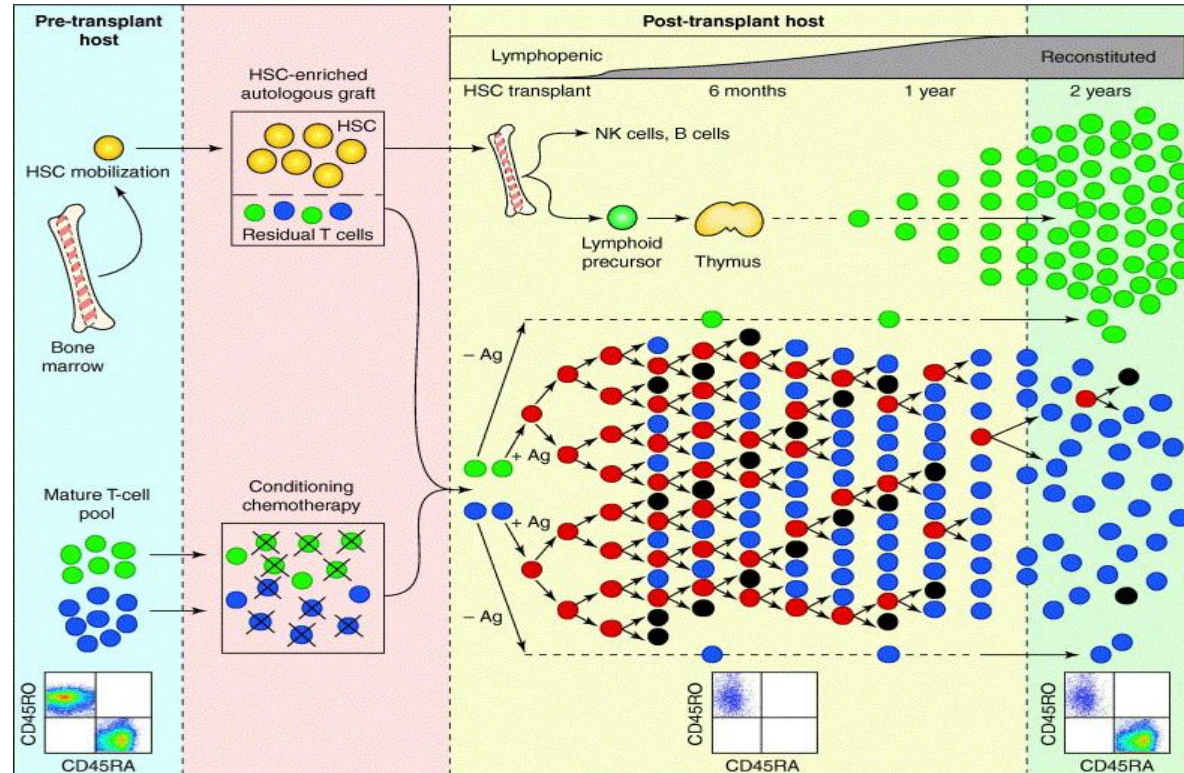
PAMP- and DAMP-mediated non-resolving gut inflammation



Courtesy Claudio Fiocchi

Immune reconstitution after Autologous HSCT

Renewal of the immune repertoire



TRENDS in Immunology

- Replacement of mature T/B memory repertoire with naïve, non-pathogenic cells
- Reinstatement of immune homeostasis
Increased number and/or function of regulatory cells

Integrated microbiota and metabolite profiles link Crohn's disease to sulfur metabolism

Amira Metwaly¹, Andreas Dunkel², Nadine Waldschmitt¹, Abilash Chakravarthy Durai Raj³, Ilias Lagkouravdos⁴, Ana Maria Corraliza⁵, Aida Mayorgas⁵, Margarita Martinez-Medina⁶, Sinah Reiter⁷, Michael Schloter³, Thomas Hofmann⁷, Matthieu Allez⁸, Julian Panes⁵, Azucena Salas⁵ & Dirk Haller^{1,4,8}

NATURE COMMUNICATIONS | (2020)11:4322

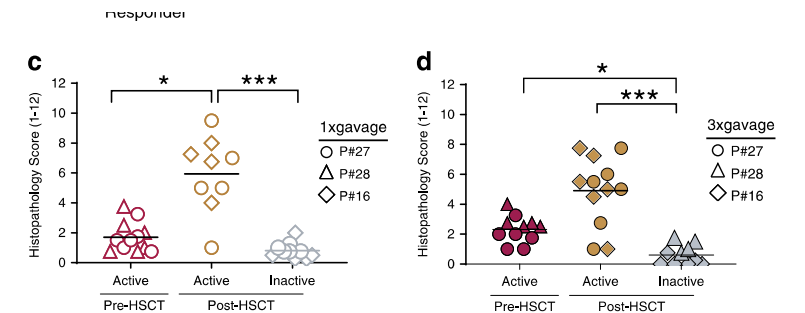
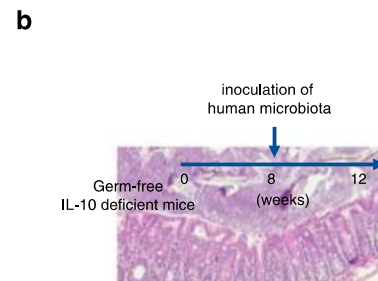
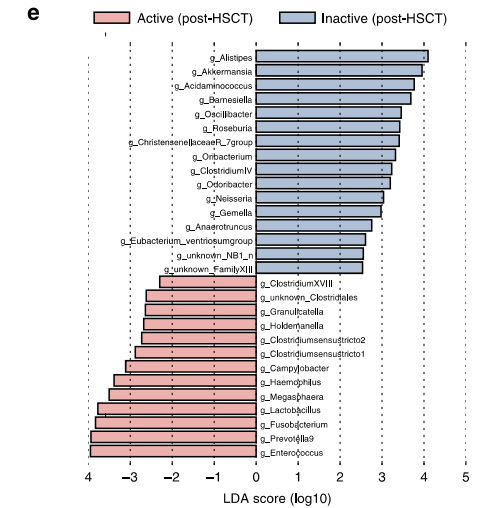
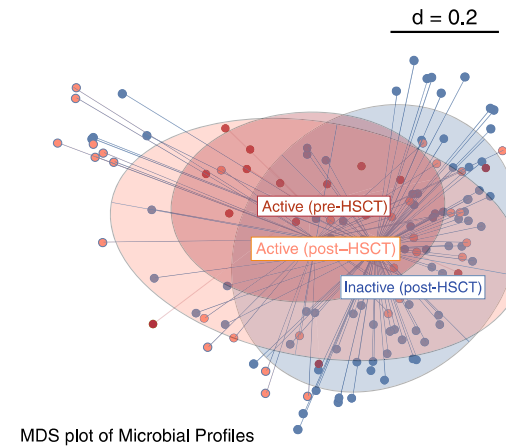
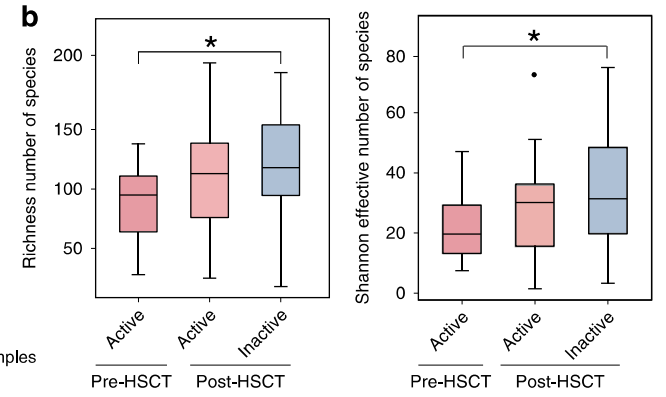
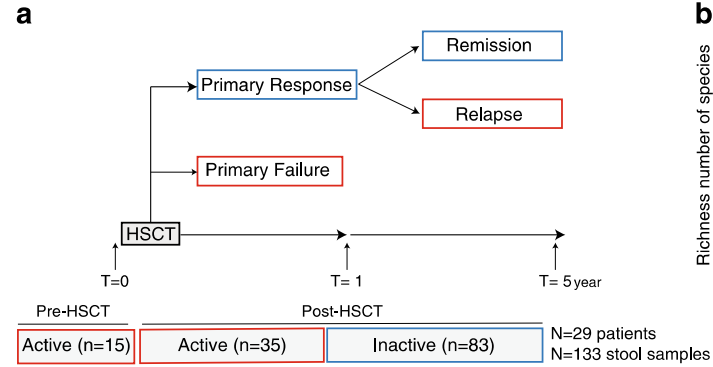
Inflammatory Bowel Disease Over Time (*IBDOT*)

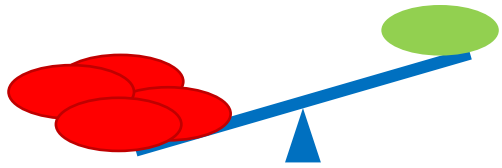
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Health research since 1964

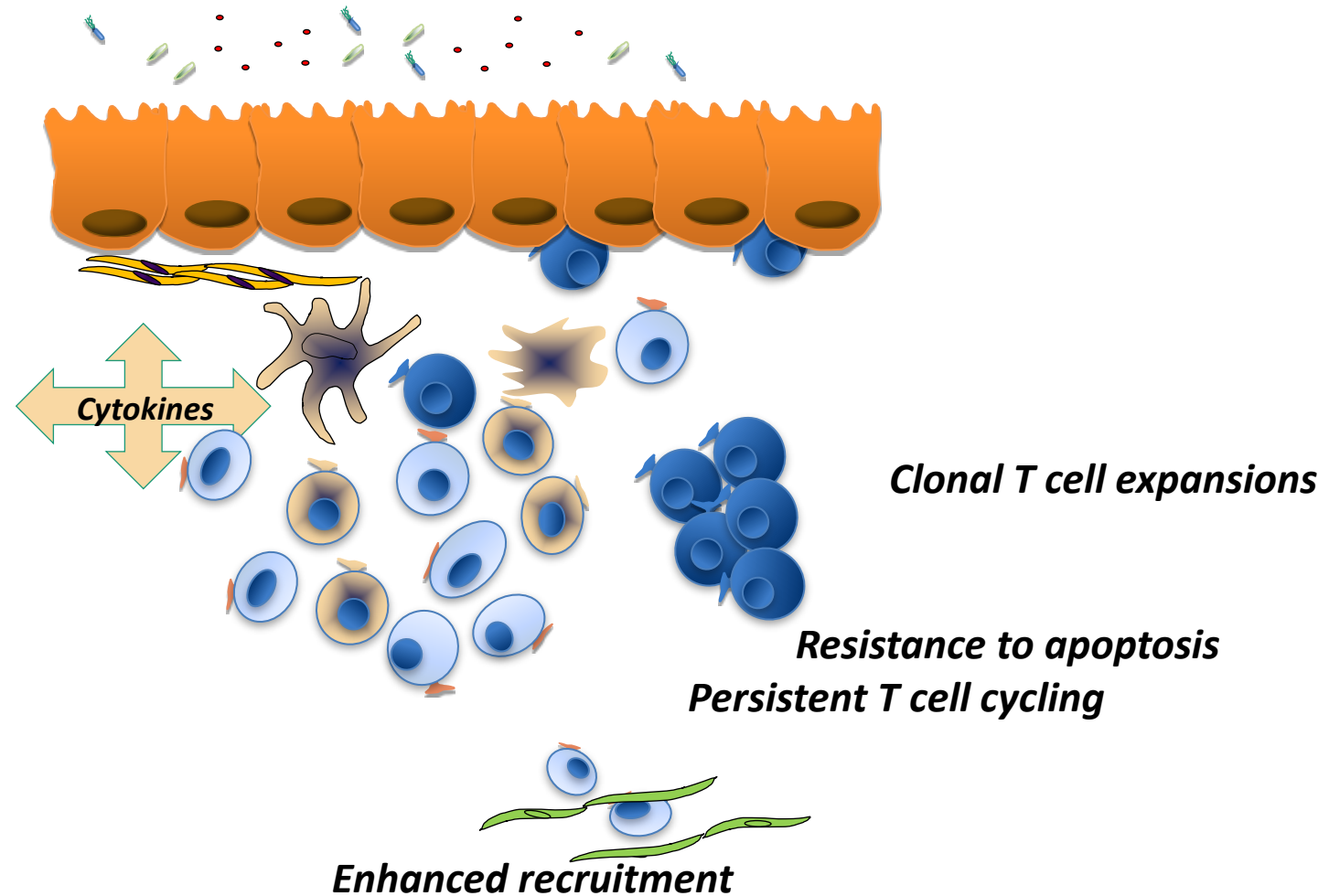
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Technische Universität München

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
IDIBAPS
Institut d'Investigacions Biomèdiques August Pi i Sunyer

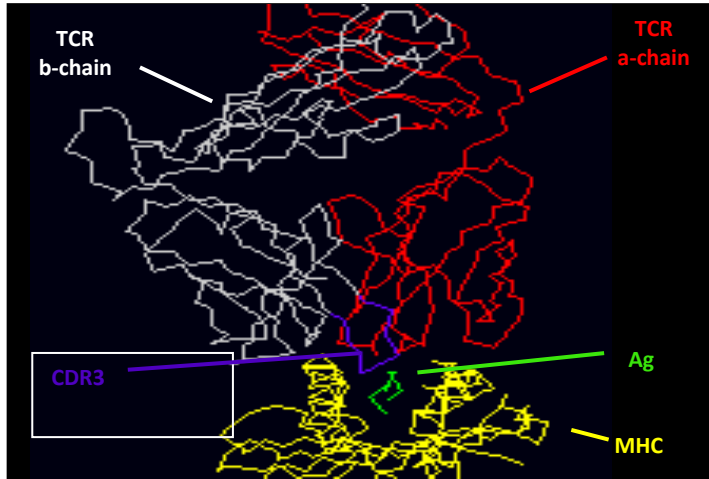




Accumulation of effector T cells in CD



T cell clonal expansions in CD

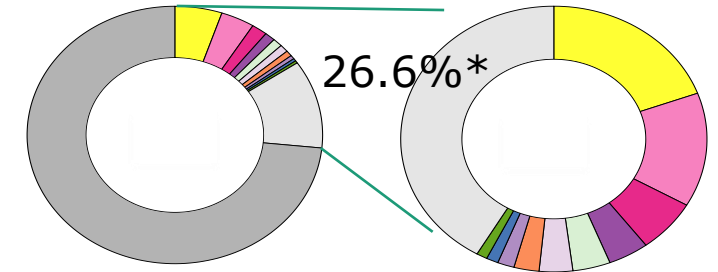


Ileal biopsy CD patient

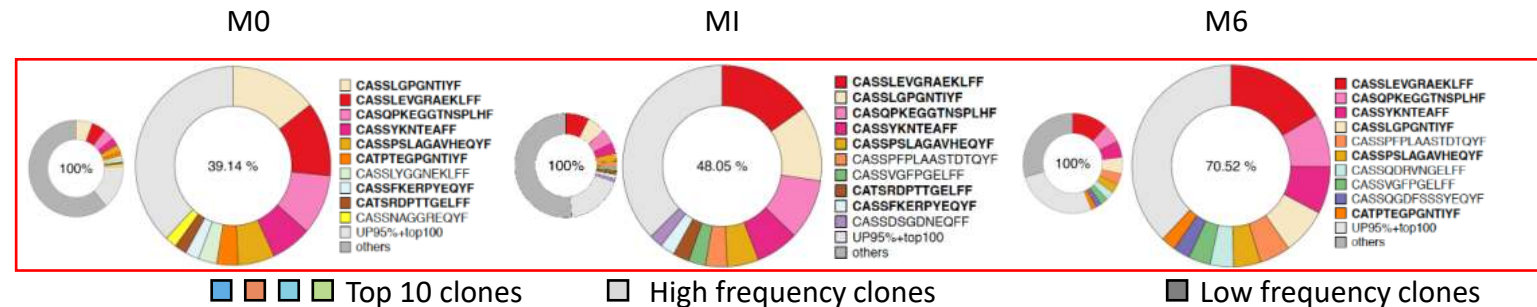
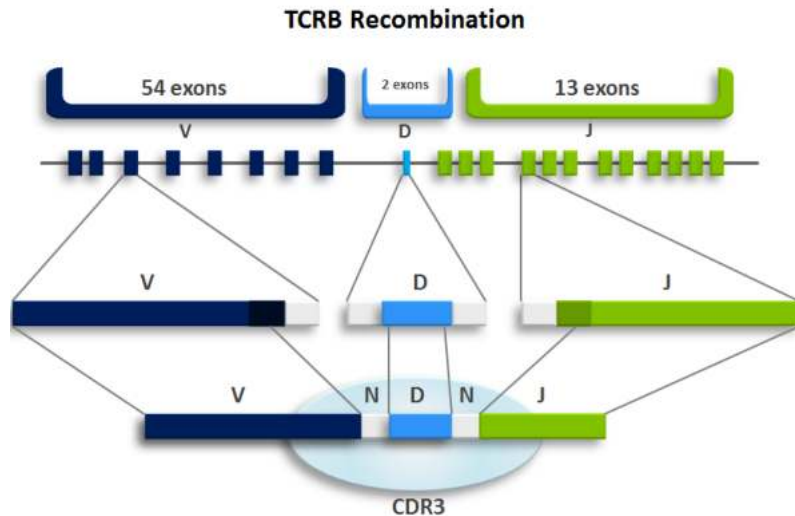
Number of reads in the sample: 7300

Number of unique sequences: 4498

- CASRGGGANEQYF
- CASSDNRDRGPGELFF
- CASSLTRSLYNEQFF
- CASSPTGRVETQYF
- CASLMNTEAFF
- CASSLAGHQPHF
- CASGRDRQSPQHF
- CARSGRVTNTEAFF
- CASSFESRYNEQFF
- CASSPGQNTGELFF
- UP95%+top100
- others

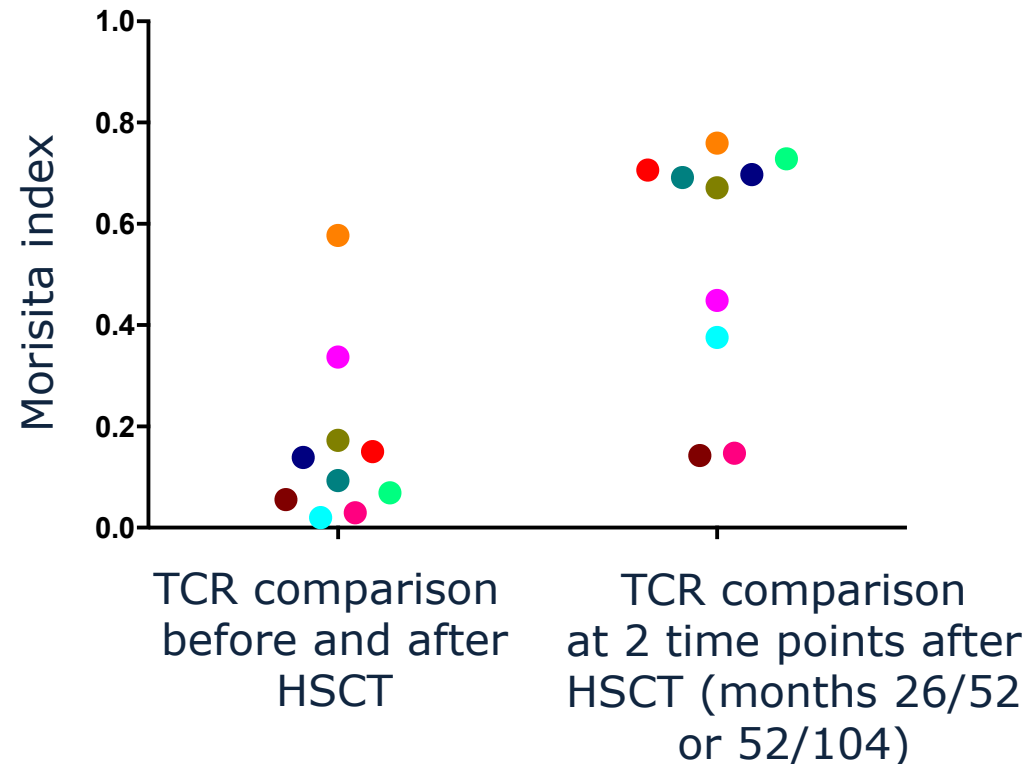


* High frequency clones: top hundred clones in the 95% interval confidence



Resetting of the mucosal T cell repertoire after Hematopoietic Stem Cell Transplantation in refractory Crohn's Disease

Le Bourhis L, Corraliza A, Auzolle C, Ricart E, Hawkey C, Lindsay L, Clark M, Rogler G, Satsangui J, Haller D, Panes J, Salas A, Allez M. ECCO 2017, OP4



**Inflammatory Bowel Disease
Over Time (IBDOT)**

ASSISTANCE
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Health research since 1964

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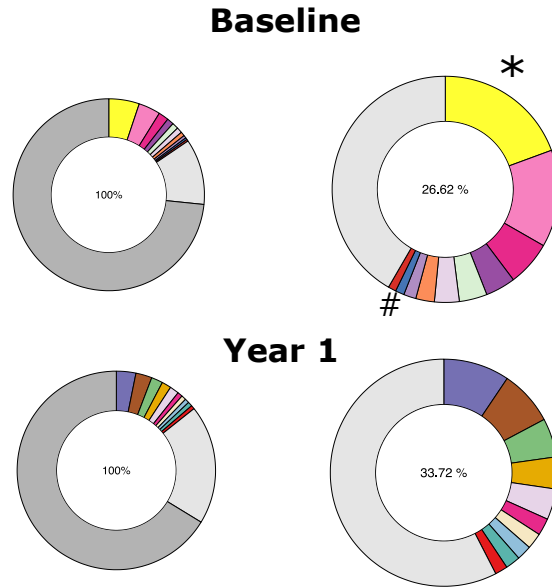
IDIBAPS
Institut
d'Investigacions
Biomèdiques
August Pi i Sunyer

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HELMSLEY
CHARITABLE TRUST

T cell resetting and endoscopic remission (SES-CD: 12 to 0)

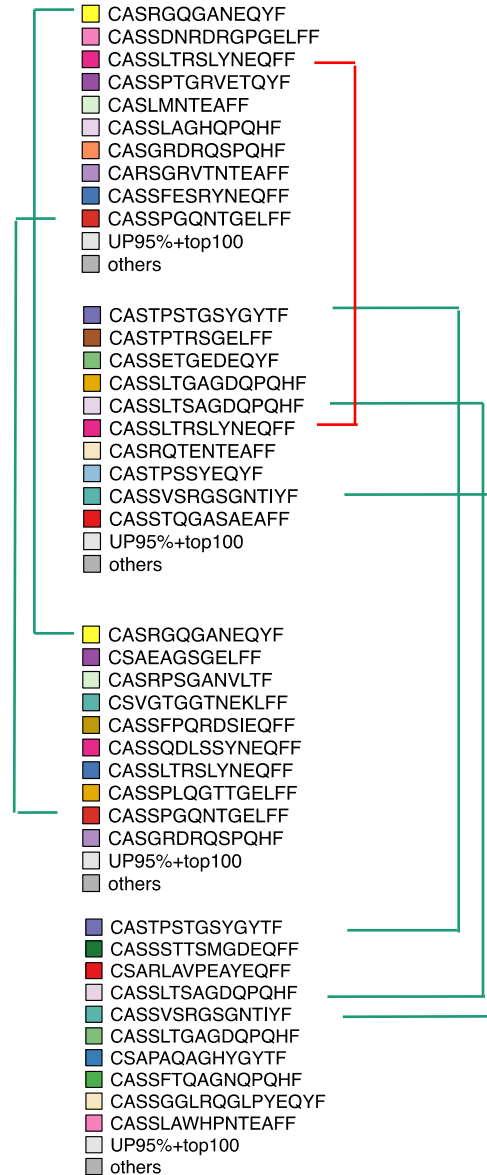
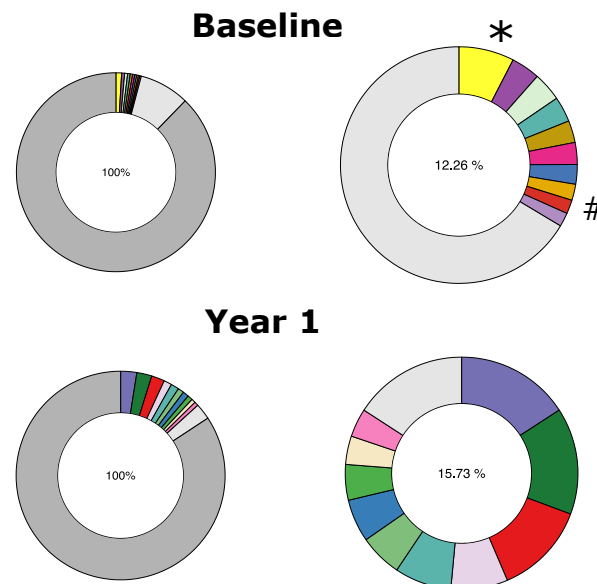
Ileum

810	I
Baseline	Red
One year	Green



Rectum

810	R
Baseline	Yellow
One year	Green



Autologous Haematopoietic Stem Cell Transplantation (AHSCT) in Severe Crohn's Disease: A Review on Behalf of ECCO and EBMT



5 critères pour porter l'indication:

- 1- Maladie de Crohn « certaine »
- 2- Maladie de Crohn active
- 3- Maladie de Crohn réfractaire
- 4- Réponse inadéquate aux traitements disponibles
- 5- Le traitement chirurgical est inapproprié

Les recommandations Françaises 2020



Indications de l'autogreffe de cellules hématopoïétiques dans la Maladie de Crohn : recommandations de la Société francophone de greffe de moelle et de thérapie cellulaire

Mathieu Puyade¹, Xavier Treton², Laurent Alric³, Manuela Badoglio⁴, Cristina Castilla Llorente⁵, Ginette Fotsing⁶, Zora Marjanovic⁷, Montserrat Rovira⁸, Louis Terriou⁹, Miguel Torregrosa Diaz Jose¹⁰, My-Linh Tran-Minh¹¹, Matthieu Allez¹¹, Grégory Pugnet¹², David Laharie¹³, Ibrahim Yakoub-Agha¹⁴, Dominique Farge^{15,16,17}

HAS octobre 2022

Protocole National de Diagnostic et de Soins

Greffe de cellules souches hématopoïétiques dans les maladies auto-immunes



Dominique FARGE¹, Grégory PUGNET², Mathieu ALLEZ³, Cristina CASTILLA LLORENTE⁴, Emmanuel CHATELUS⁵, Pascal CINTAS⁶, Catherine FAUCHER-BARBÉY⁷, Pierre LABAUGE⁸, Céline LABEYRIE⁹, Bruno LIOURE¹⁰, Alexandre MARIA¹¹, David MICHONNEAU¹², Mathieu PUYADE¹³, Marie TALOUARN¹⁴, Louis TERRIOU¹⁵, Xavier TRETON¹⁶, Géraldine WOJTASIK¹⁷, Hélène ZEPHIR¹⁸, Zora MARJANOVIC¹⁴

4.2.2 Indications de la greffe de CSH

La greffe de CSH peut être discutée pour les patients ayant une maladie de Crohn :

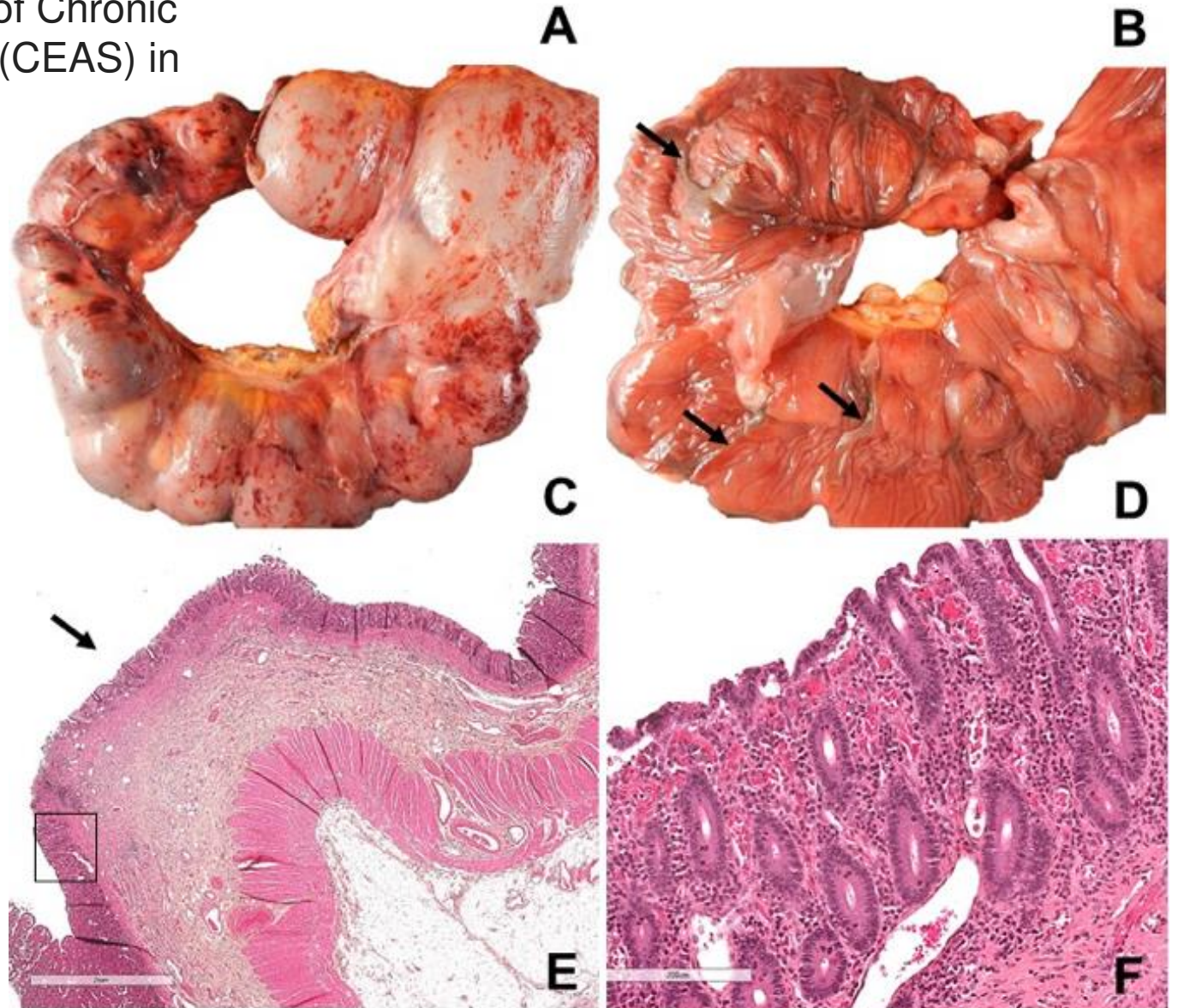
- Avec un diagnostic établi selon des critères cliniques, biologiques, endoscopiques, radiologiques et histologiques définis par l' ECCO (79) ;
- Age \leq 60 ans ;
- Active. L'activité de la maladie doit être objectivée par les examens endoscopiques (iléo-coloscopie et/ou endoscopie oeso-gastro-duodénale) avec la présence d'ulcérations et un SES-CD \geq 2 (76) sur au moins 1 segment et/ou par imagerie (entéro-IRM) avec relecture par un radiologue expert, ainsi que par une élévation des marqueurs biologiques d'inflammation (CRP $>$ 5 mg/L et/ou calprotectine fécale $>$ 150 μ g/g de selles) ;
- Réfractaire comme définie par l'ECCO, c'est-à-dire en cas d'échec, d'intolérance ou de contre-indications aux immunosuppresseurs (thiopurines, méthotrexate ou JAK inhibiteurs), et échec avéré ou contre-indication des biothérapies disponibles sur le marché à des doses optimisées (anti-TNF, ustekinumab/anti-IL23 et vedolizumab) ;
- Non accessible à un traitement chirurgical (75) ou à risque de survenue d'une insuffisance intestinale chronique avec syndrome de grêle court dans les suites de l'intervention chirurgicale.

L'indication de greffe de CSH est discutée au cas par cas en RCP :

- 1) lorsque le patient, informé des risques de morbi-mortalité associés à la procédure de greffe de CSH et ayant donné son accord, refuse catégoriquement une stomie définitive et qu'il existe des lésions inflammatoires intestinales actives et réfractaires ;
- 2) chez certains patients dont l'âge est compris entre 18 et 60 ans.

Génotyper les formes atypiques +++

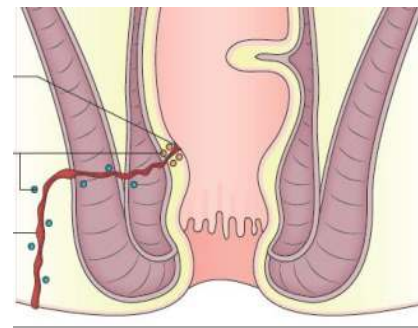
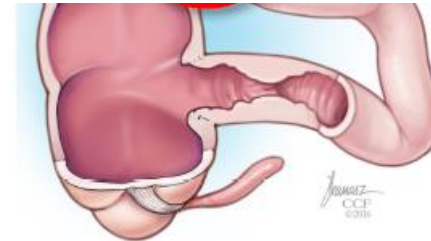
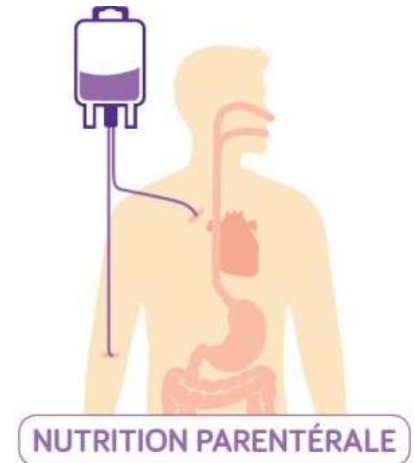
Crohn-like disease affecting small bowel due to monogenic *SLCO2A1* mutations: First cases of Chronic Enteropathy Associated with *SLCO2A1* gene (CEAS) in France



Les contre indications et la préparation

Contre indication :

- ECOG \geq 3.
- Indice de Masse Corporel (IMC) $<$ 18 kg/m².
- Albumine $<$ 20 g/L.
- Tabagisme actif (sevrage de plus de 3 mois nécessaires).
- Abscès intra-abdominaux ou périnéaux non drainés.
- syndrome occlusif
- Fistule péri-anale active non drainée.
- Dysplasie colique de haut grade ou de bas grade multifocale non réséquée.



Bilan digestif $<$ 3 mois:

- endoscopies
- IRMs
- Nutrition

Les critères d'exclusion

-Grossesse ou absence de contraception adaptée

- Comorbidités (non reliées à l'activité de la maladie de Crohn) :

- atteinte respiratoire : anomalie aux épreuves fonctionnelles

- atteinte cardiaque : fraction d'éjection ventriculaire gauche < 50

- Maladie hépatique chronique irréversible documentée non contrôlée ou TP < 60 %.

- néoplasie active ou myélodysplasie concomitante.

- Insuffisance médullaire persistante

- infection aiguë ou chronique non contrôlée, séropositivité VIH1, 2 ou HTLV1, 2 ; hépatite chronique B ou C active.

- Pathologie psychiatrique active ne permettant pas une compliance adaptée du patient au projet thérapeutique.

- Risque de mauvaise compliance du patient.

Le parcours de validation

1 -RCP MICI experte
« staff MICI complexe »

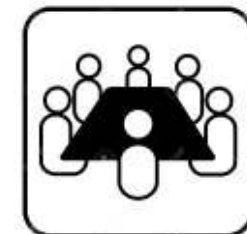


Autogreffe vs
bioTT
Genotypage?
indication



2 -RCP nationale
Autogreffe IMID

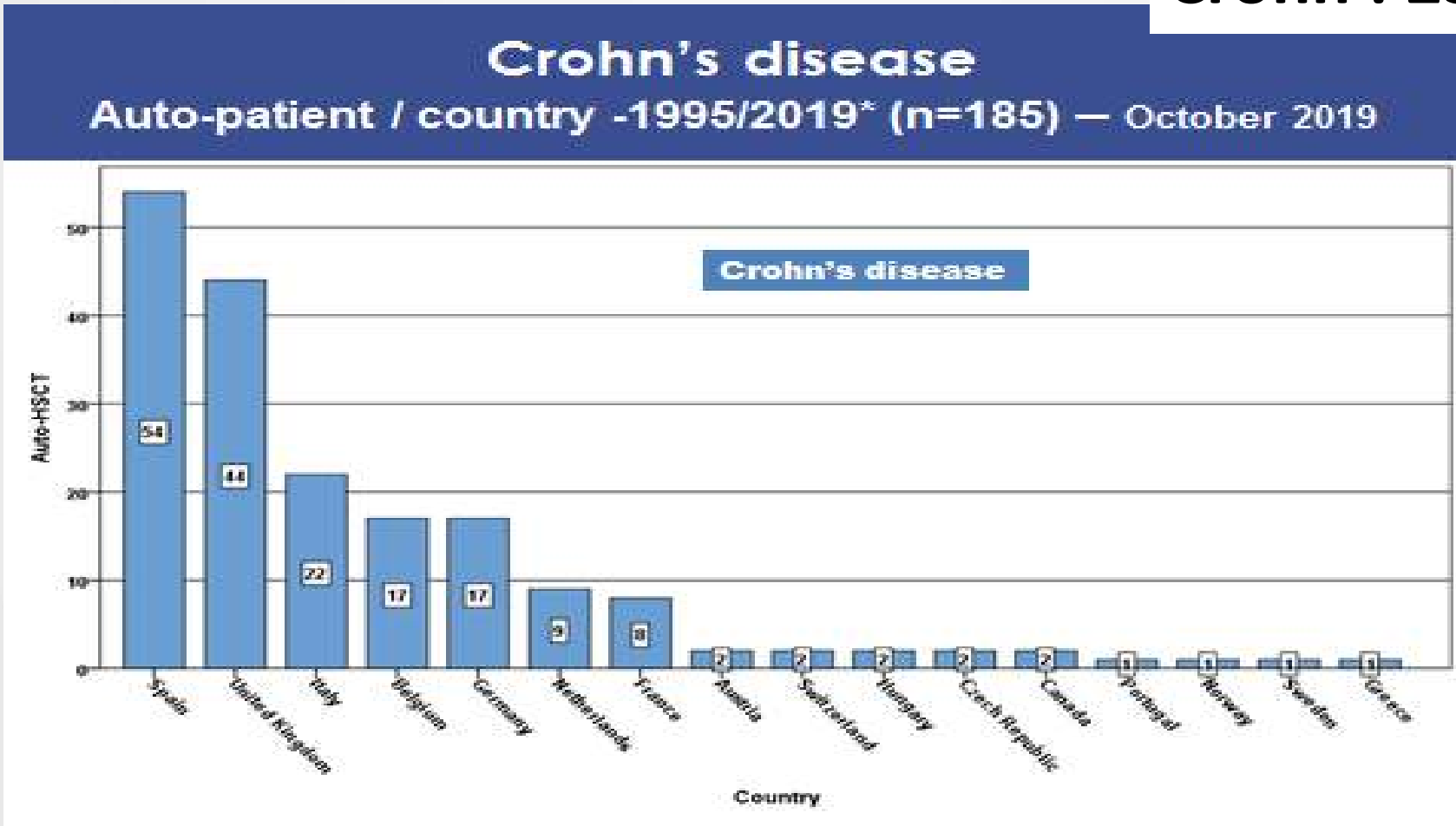
Validation
registre

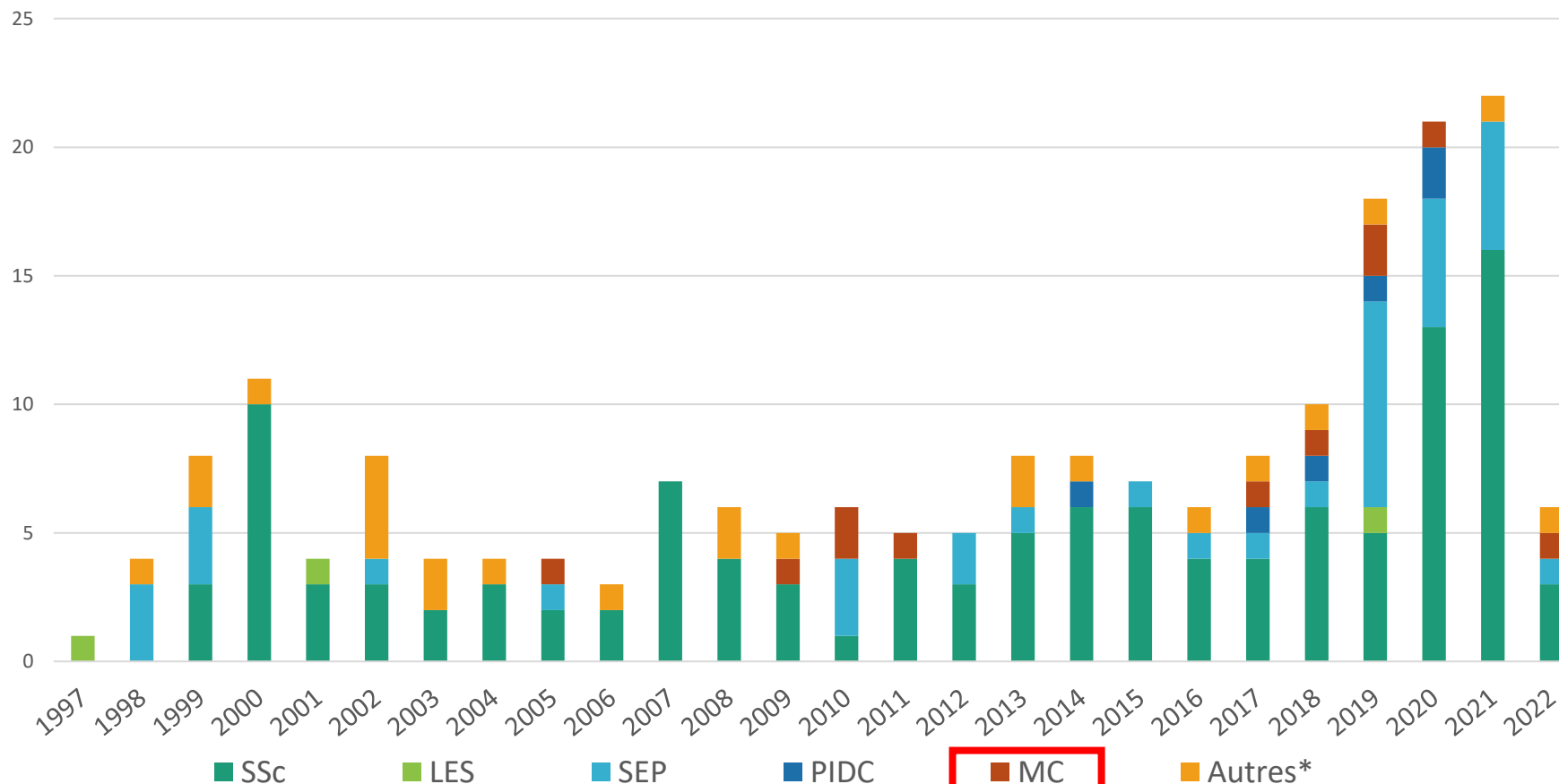


biobanking

3-Traitement dans un service
d'hématologie partenaire

**Europe 2022 :
3947 Autogreffes
Crohn : 232**





Effectifs

123

2

37

7

11

24

Retour 5 patients suivis

- Complications « immédiates » : 1
- Echec =1 (mauvaise indication)
- 4 succès
- 100% de rechute mais modérées

Conclusions

- Indications exceptionnelles pour patients exceptionnels
- Compétition avec les combothérapies, mais pas trop tard...
- Morbidité importante (Crohn > autres IMID), mais effet centre (hématologie) +++
- Parcours de sélection rigoureux et long

