La décroissance thérapeutique dans les MICI

Pourquoi
Quand
Comment

EM-140528

8ème Journée d'échanges cliniques en MICI
Jeudi 21 septembre 2023

Edouard LOUIS

Disclosures

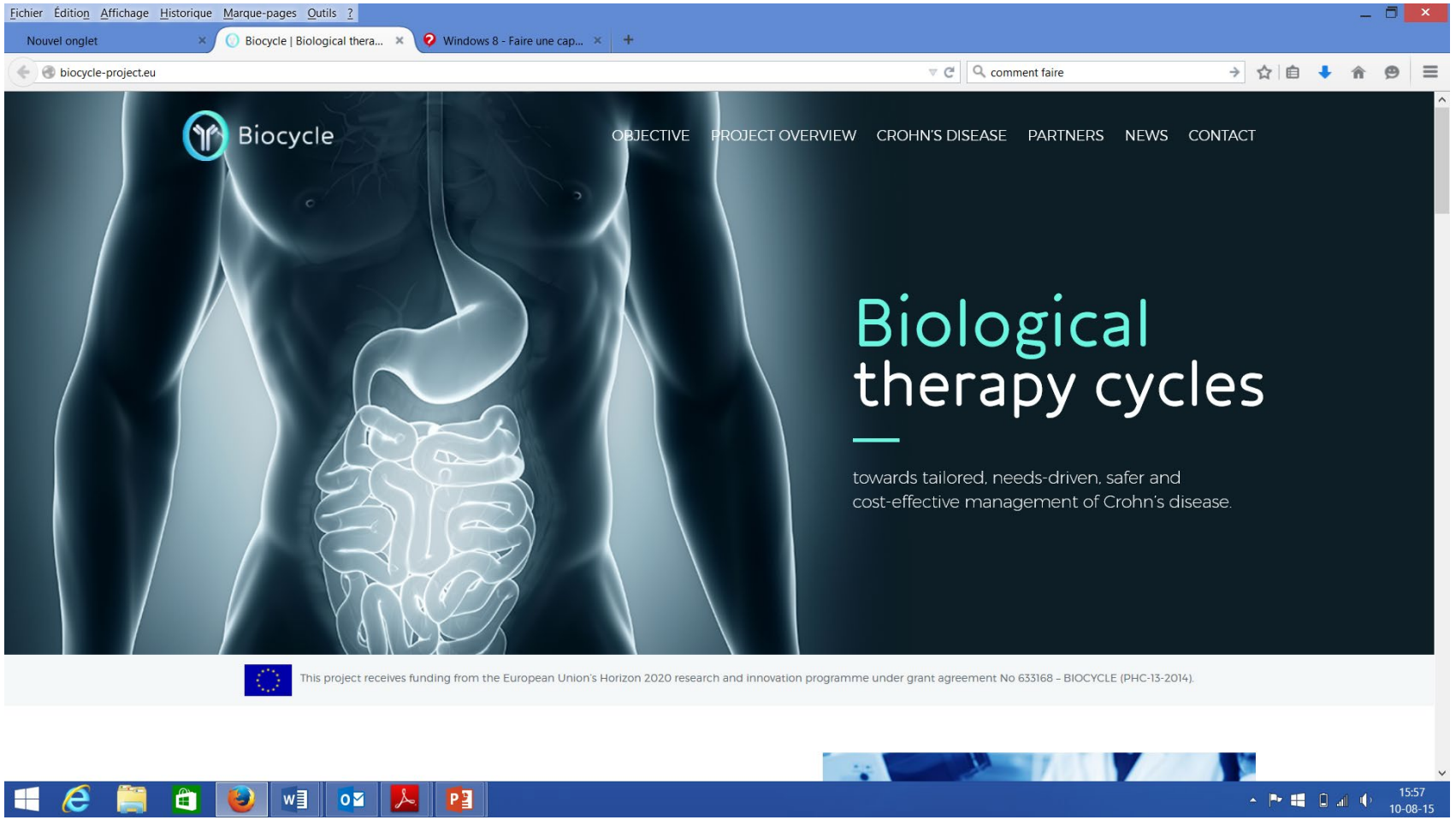
- E Louis has received fees for:

  - **Research Grant:** Takeda, Pfizer
  - **Educational Grant:** Abbvie, MSD, Takeda, Janssen
  - **Speaker Fees:** Abbvie, Ferring, MSD, Falk, Takeda, Hospira, Janssen, Pfizer, Celgene
  - **Advisory Board:** Abbvie, Ferring, MSD, Takeda, Celltrion, Celgene, Hospira, Janssen
  - **Consultant:** Abbvie

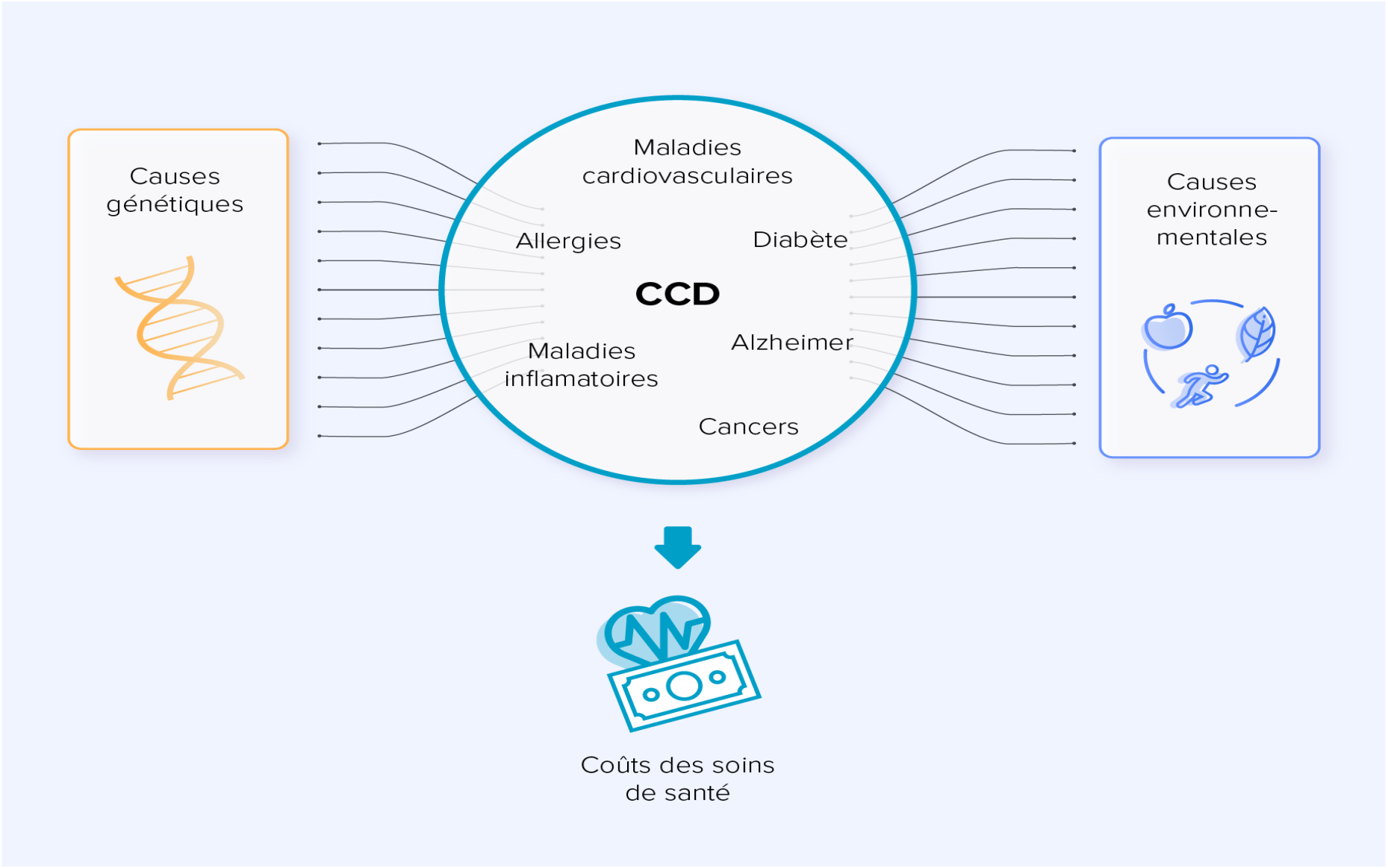
Disclaimer

- This is a medical education event with the support of Janssen-Cilag NV.
- This presentation represents the opinion of the speaker and not necessarily the opinion of Janssen.
- This presentation may include discussions on off-label use of drugs.

Biocycle Website: http://biocycle-project.eu/

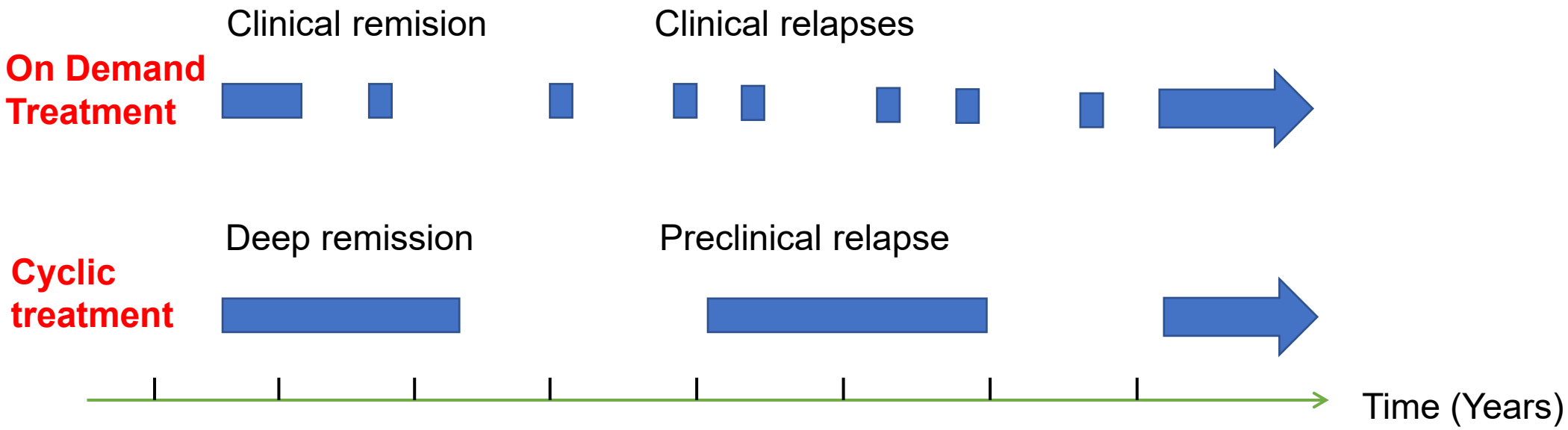


Les maladies résultent d'une rupture de l'homéostasie de l'organisme avec une focalisation préférentielle sur l'un ou l'autre organe



Cyclic treatment **is not** on demand treatment

- First and undisputable aim of IBD treatment is **full disease control**
- The idea of the Cyclic treatment is to aim at the **lowest IS/biological use** still compatible with full disease control



Louis E. Inflamm Bowel Dis 2018;24:725-731

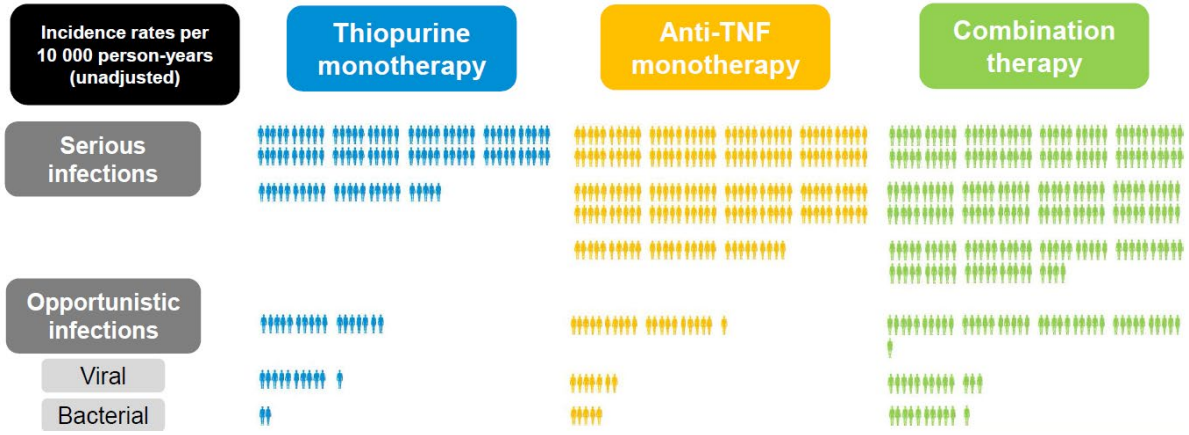
Reasons to contemplate **Treatment de-escalation** in IBD

- Safety
- Specific situations
- Patients concerns
- Adherence
- Cost

Long term side effects with purines and anti-TNF

HRs comparing the risk of lymphoma in patients exposed to thiopurine monotherapy, anti-TNF monotherapy, and combination therapy vs unexposed patients

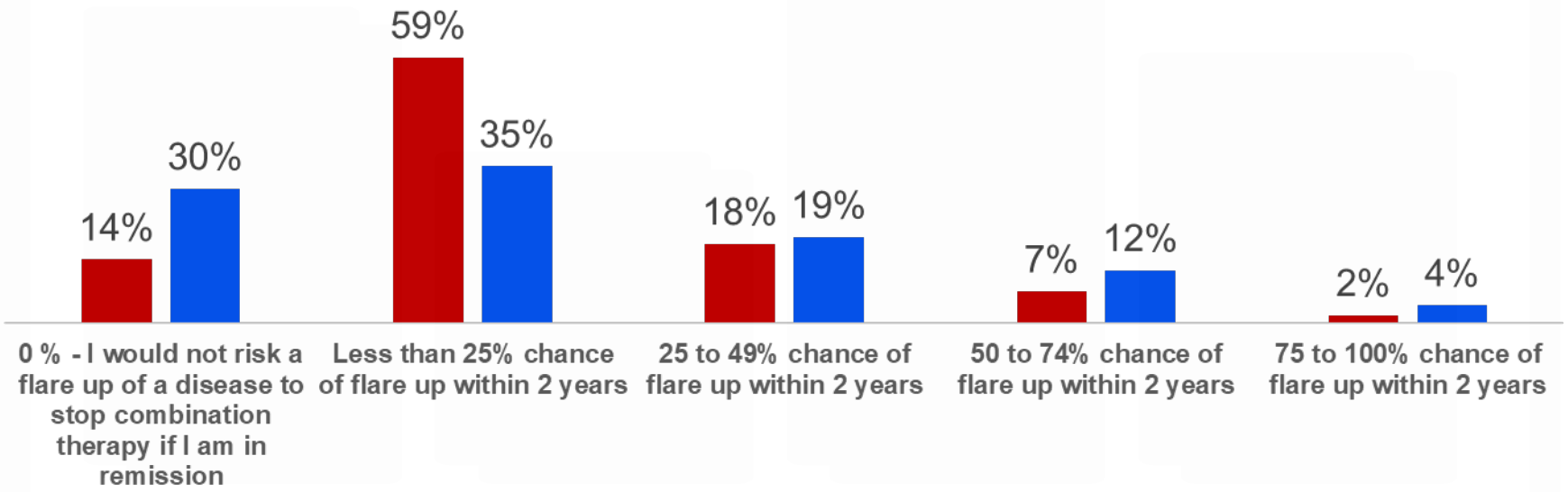
	Exposed to thiopurine monotherapy vs unexposed to thiopurines or anti-TNF agents		Exposed to anti-tnf monotherapy vs unexposed to thiopurines or anti-TNF agents		Exposed to combination therapy vs unexposed to thiopurines or anti-TNF agents	
Lymphoma Type	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)**
All Patients						
All lymphoma	2.06 (1.58-2.70)	2.06 (1.96-3.44)	1.57 (1.08-2.28)	2.41 (1.60-3.64)	3.60 (2.10-6.19)	6.11 (3.46-10.8)
Hodgkin lymphoma	2.78 (1.45-5.33)	2.83 (1.37-5.84)	2.21 (0.92-5.35)	2.23 (0.81-6.13)	11.1 (4.76-27.2)	12.1 (4.46-33.1)
Non-Hodgkin lymphoma	1.95 (1.45-2.62)	2.57 (1.90-3.49)	1.47 (0.97-2.22)	2.48 (1.58-3.89)	2.38 (1.17-4.84)	4.48 (2.15-9.34)



Kirchgesner J, *et al.* Gastroenterology. 2018.
Lemaitre M, *et al.* JAMA 2017;318(17):1679-86.

Acceptance for flare risk among French and American patients

What is the maximum level of risk you are willing to accept that you would experience a flare up (return of symptoms) within 2 years of stopping combination therapy in order to be able to reduce number of treatments you are taking?



United States n=113
France n=297

X^2 (4, N=410) = 22.612 , p=.000

Siegel et al. ECCO 2018

Suivi Crohn - 1 an sans traitement

21 Juillet 2023 10:51

Expéditeur : [redacted]

À: Edouard Louis

Bonjour Monsieur Louis,

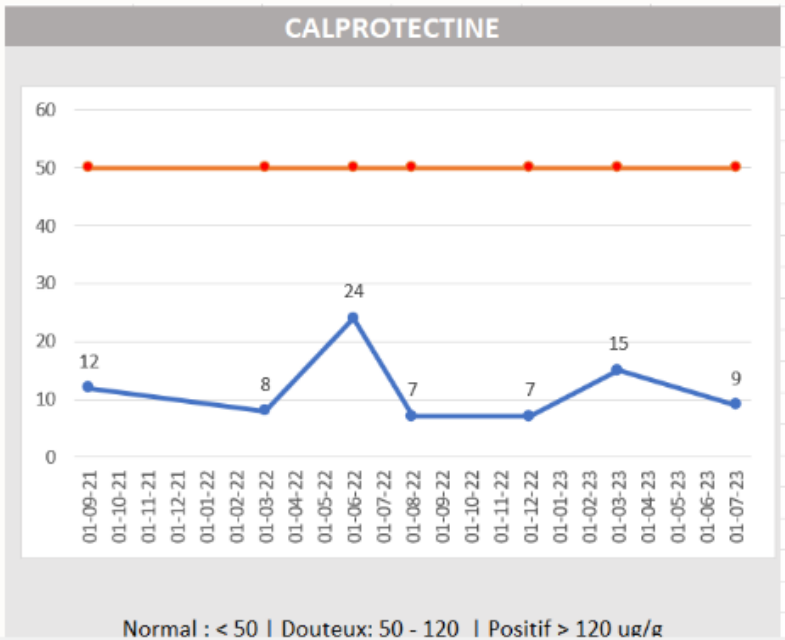
Je me permets de vous adresser un petit message car j'ai reçu cette semaine mes derniers résultats CRP & Calprotectine qui sont excellents. Ceci marque ma première année de vie avec la maladie de Crohn sans traitement. Atteindre cet objectif, 15 ans après le diagnostic, est une réelle victoire pour moi et je souhaitais la partager avec vous!

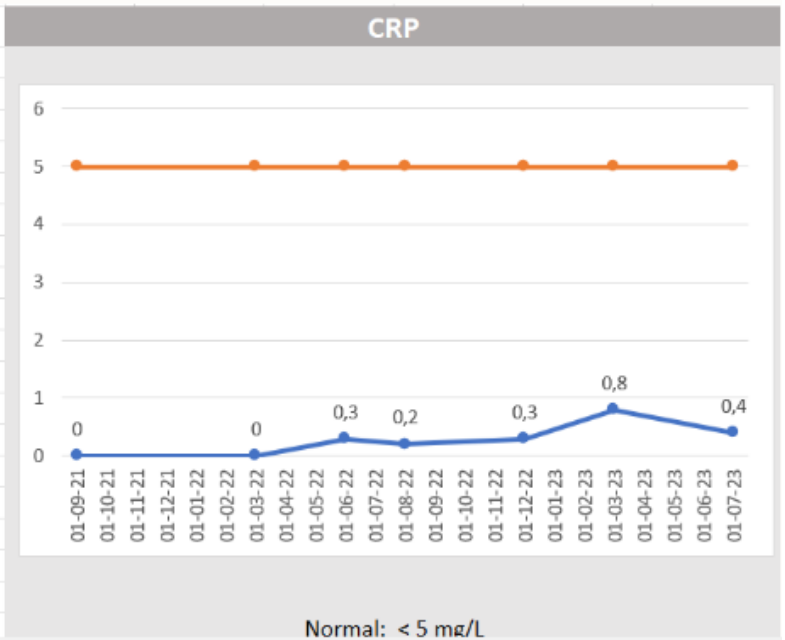
Je tiens à vous remercier sincèrement pour votre prise en charge et votre accompagnement.

Je vous souhaite un bel été et on se revoit en janvier pour ma visite de contrôle.

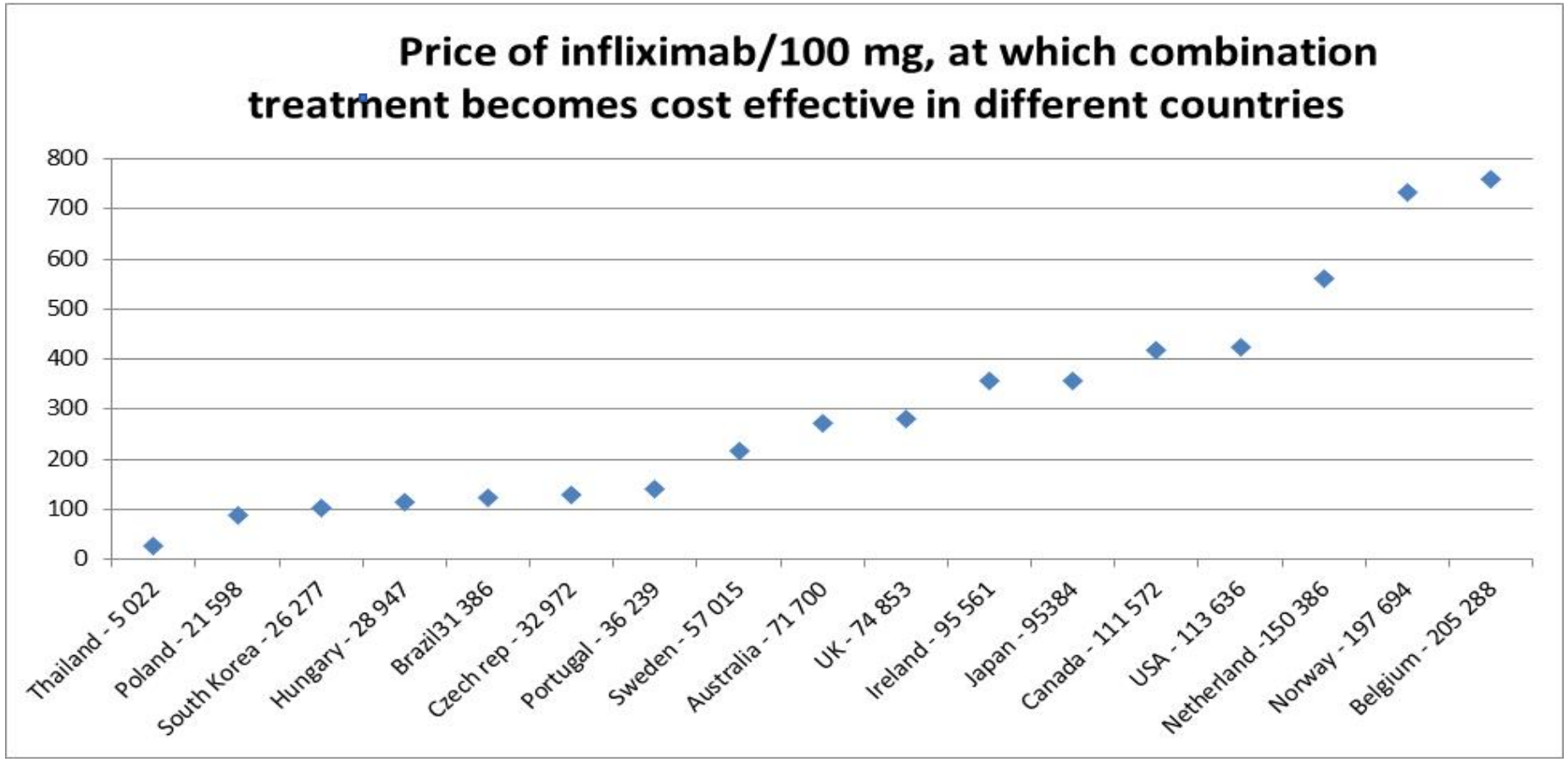
Bien à vous,

[redacted]





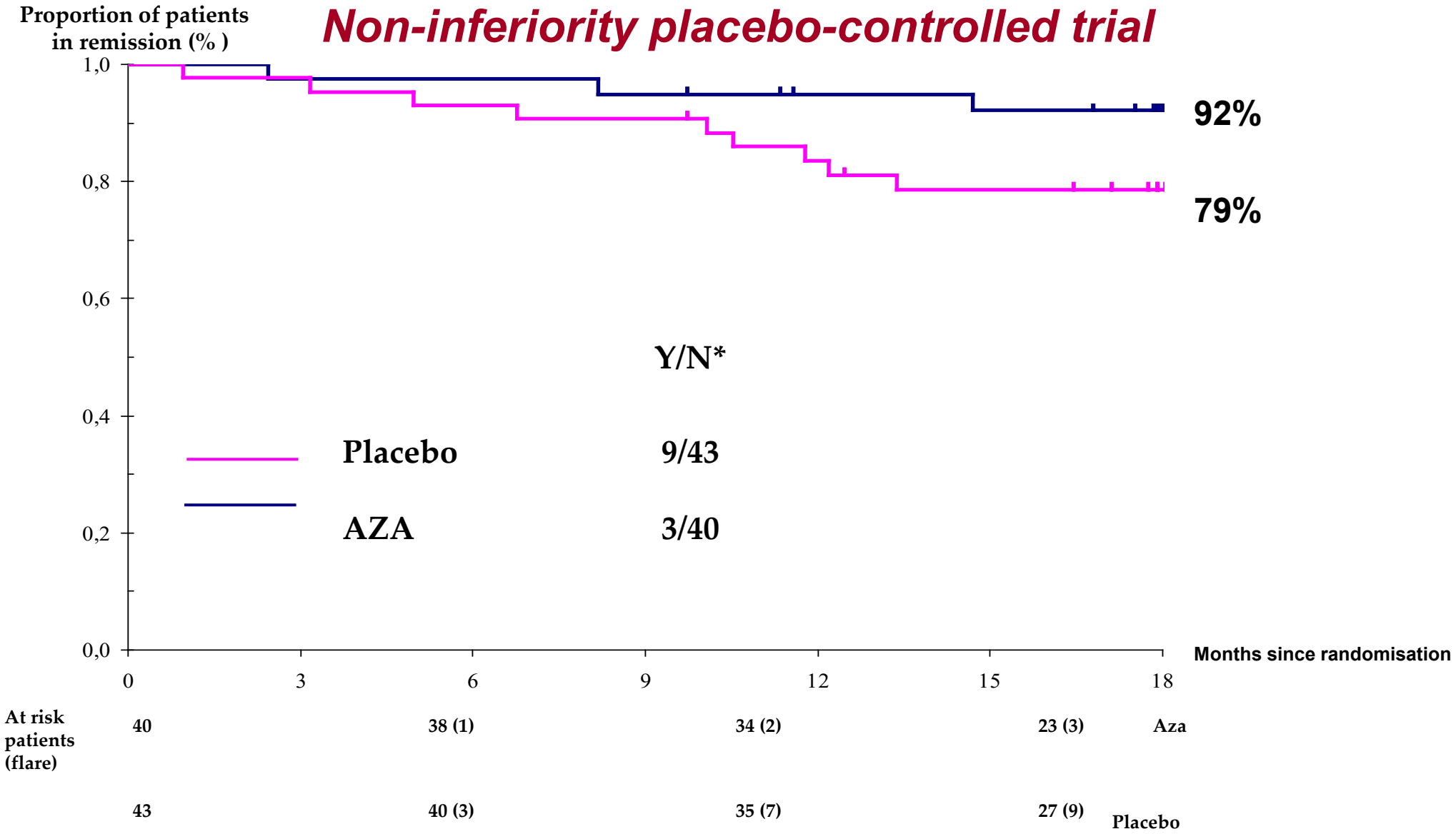
Cost-effectiveness of infliximab combo continuation in sustained remission in CD



K Bolin et al, Biocycle consortium, JCC 2019

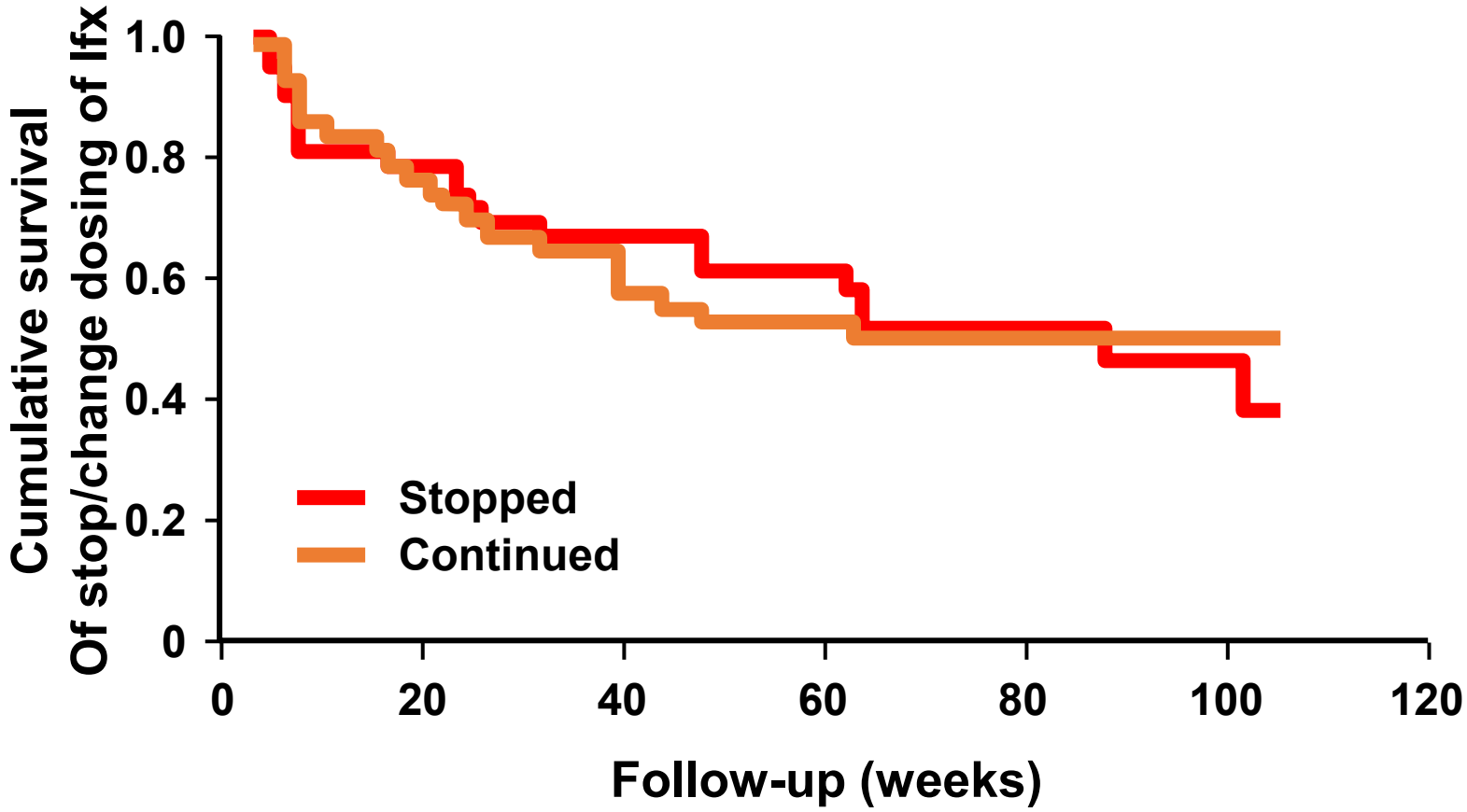
AZA withdrawal

Non-inferiority placebo-controlled trial



Lémann M et al. Gastroenterology 2005;128:1812

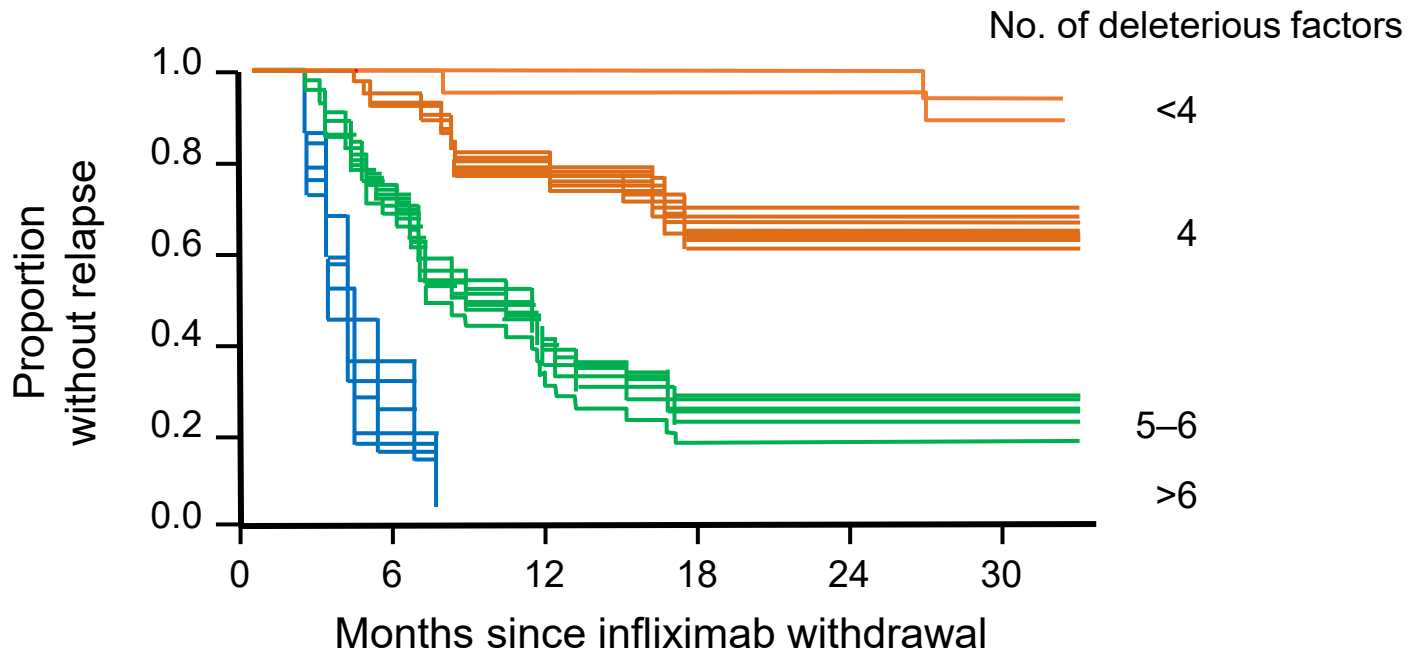
Stopping immunosuppressant **at least 6 months** after starting infliximab



Van Assche G, et al. Gastroenterology 2008; 134: 1861

Time-to-relapse after infliximab withdrawal in patients continuing on IS

Results from the STORI cohort according to predictive model

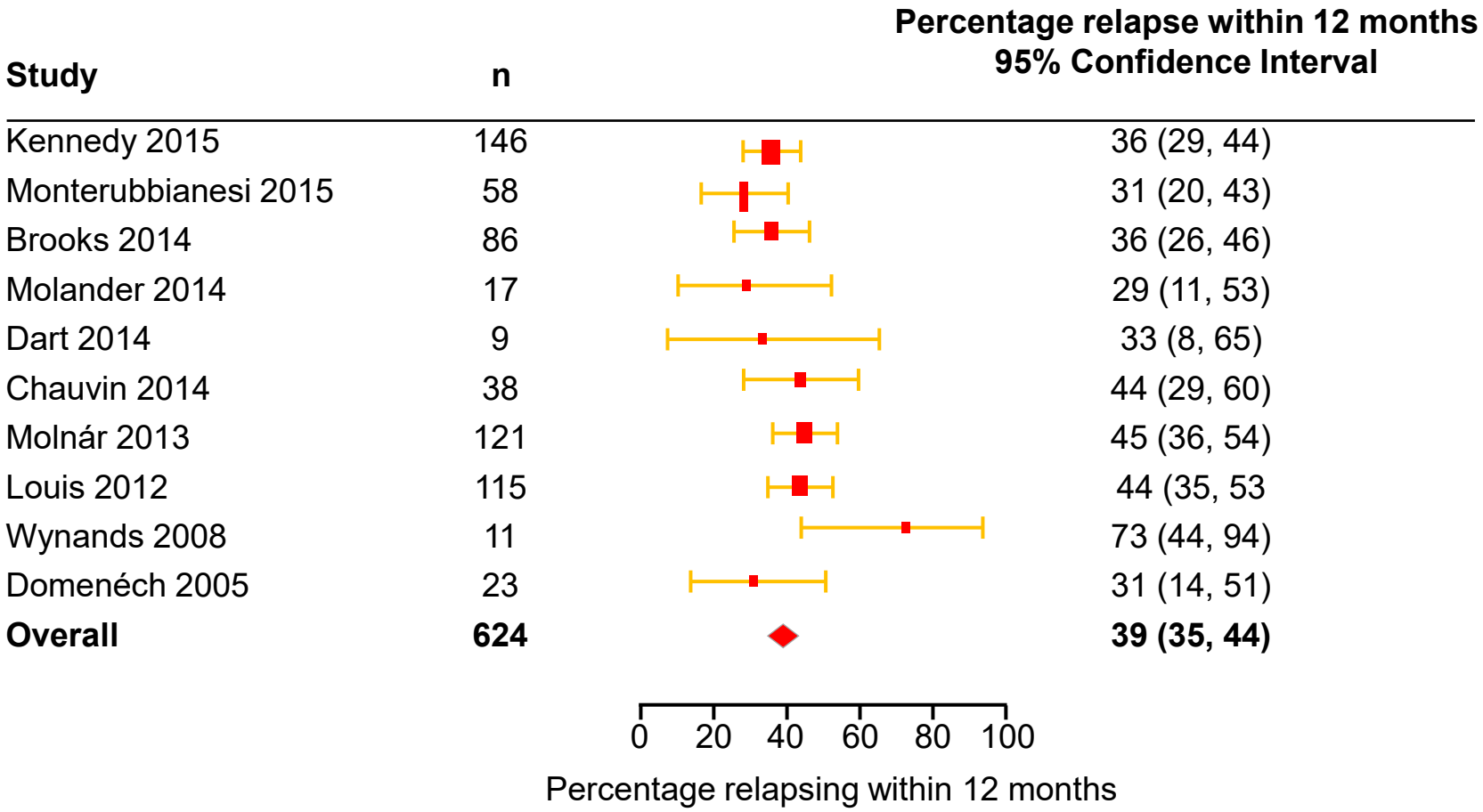


Deleterious factors were:

no previous surgery, steroid use within 12-6 months before infliximab withdrawal, male gender, haemoglobin ≤14.5 g/dl, leukocyte count >6 10^9/l, hsCRP ≥5 mg/l, faecal calprotectin ≥300 µg/g, CDEIS >0, infliximab trough ≥2 mg/l

Louis E and the GETAID, Gastroenterology 2012

Meta-analysis: CD relapse by 12m



Heterogeneity: I^2=12%, p=0.19

Kennedy N, et al. Aliment Pharmacol Ther. 2016

Large Spanish multicenter experience of anti-TNF withdrawal

- 1055 patients
- **CD:**
  - Incidence of relapse: **19%/year**
  - Predictors:
    - Ada vs IFx (HR=1.29; 95% CI= 1.01-1.66)
    - Elective vs Top Down (HR=1.9; 95% CI= 1.07-3.37)
    - Intolerance vs Top Down (HR=2.33; 95% CI=1.27-2.02)
    - Colonic vs Ileal (HR=1.51; 95% CI= 1.13-2.02)
    - B2 vs B1 (HR=1.5; 95% CI=1.09-2.05)
    - No Immunomodulator after stop (HR=1.49; 95% CI=1.15-1.96)
    - Younger age (HR=1.02; 95% CI= 1.01-1.03)
- **UC:**
  - Incidence of relapse: **17%/year**
  - Predictors: No

Casanova MJ et al Am J Gastro 2017

NEJM Evidence

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ORIGINAL ARTICLE

Discontinuation of Infliximab Therapy in Patients with Crohn's Disease

Sine Buhl, M.D.[1], Casper Steenholdt, M.D.[1], Jørn Brynskov, M.D.[1], Katrine Risager Christensen, M.D.[1], Maria Dorn-Rasmussen, M.D.[1], Ole Østergaard Thomsen, M.D.[1], Klaus Bendtzen, M.D.[2], Tobias Wirenfeldt Klausen, M.Sc.[1], Jens Frederik Dahlerup, M.D.[3], Niels Thorsgaard, M.D.[4], ... , for the Stop Infliximab Treatment (STOP-IT) Study Group*

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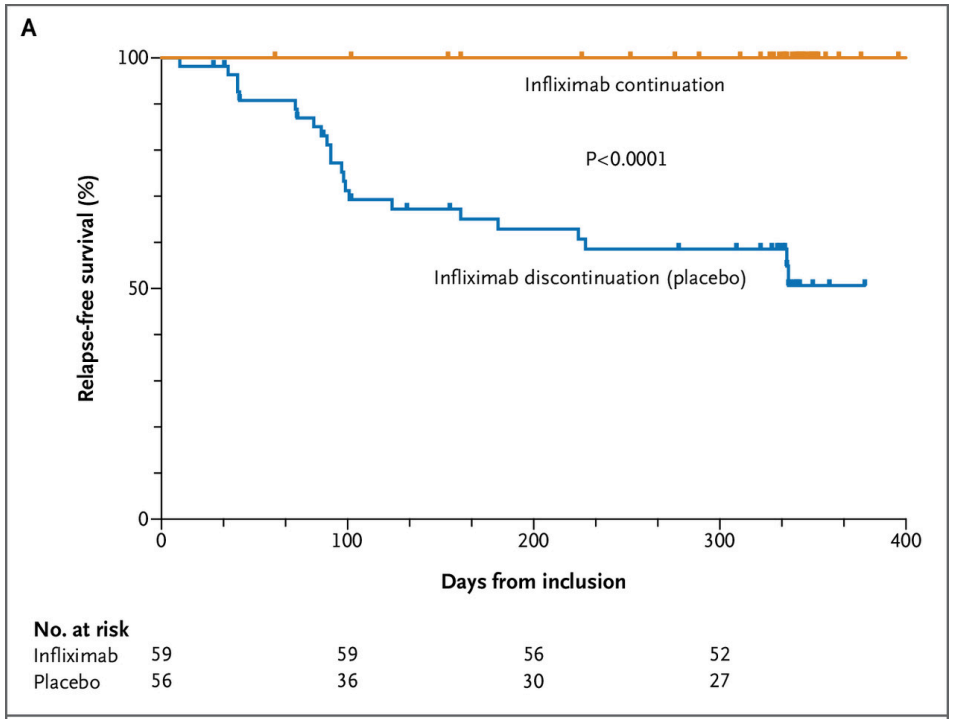
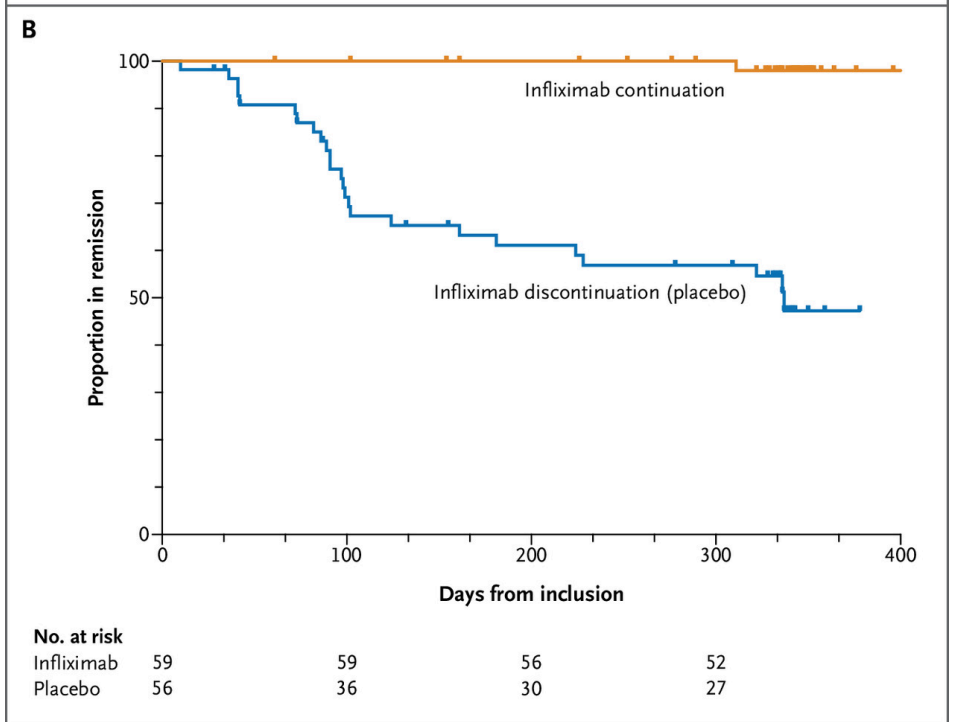
Published June 14, 2022
NEJM Evid 2022; 1 (8)
DOI: https://doi.org/10.1056/EVIDoa2200061

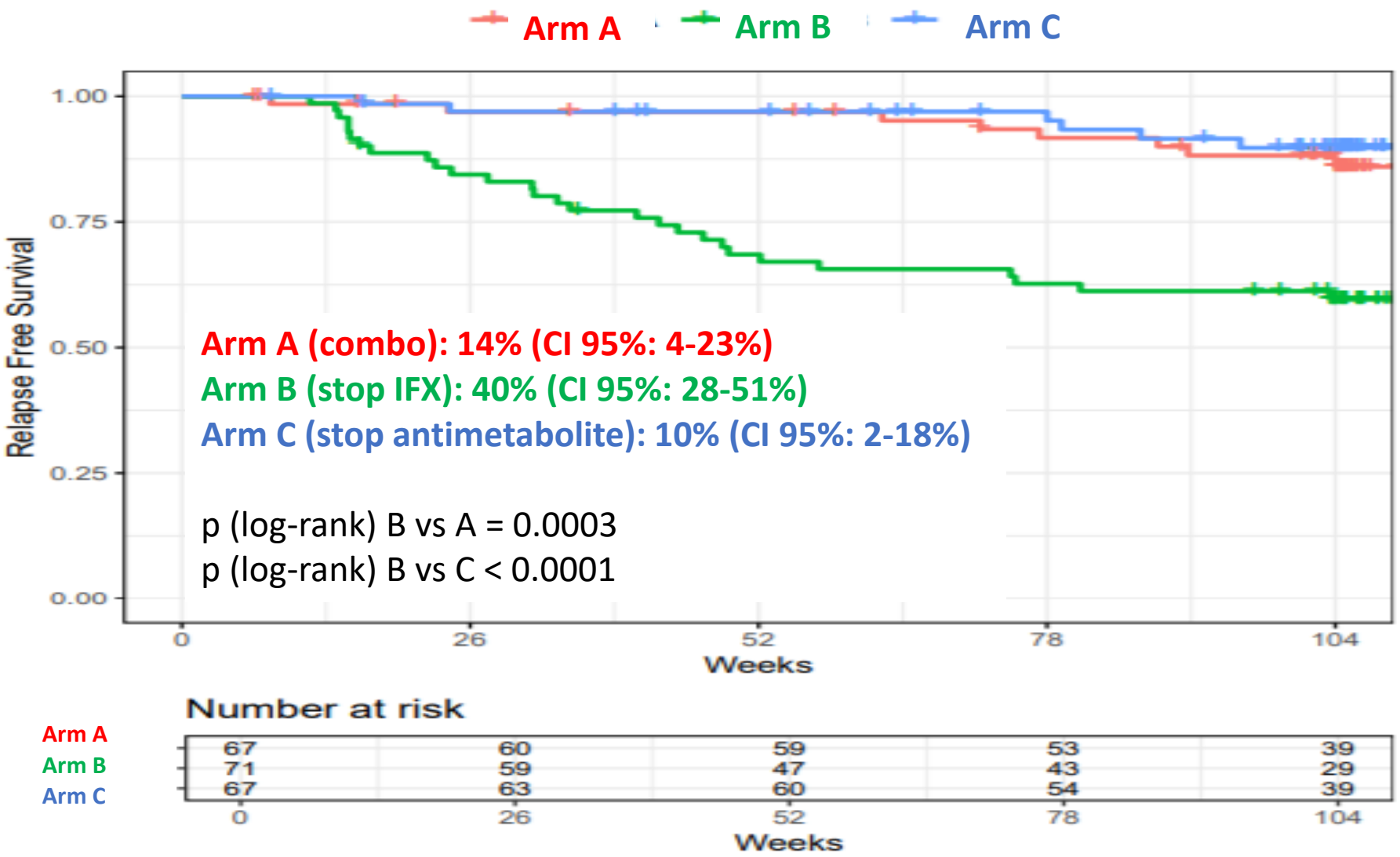
Issue ›





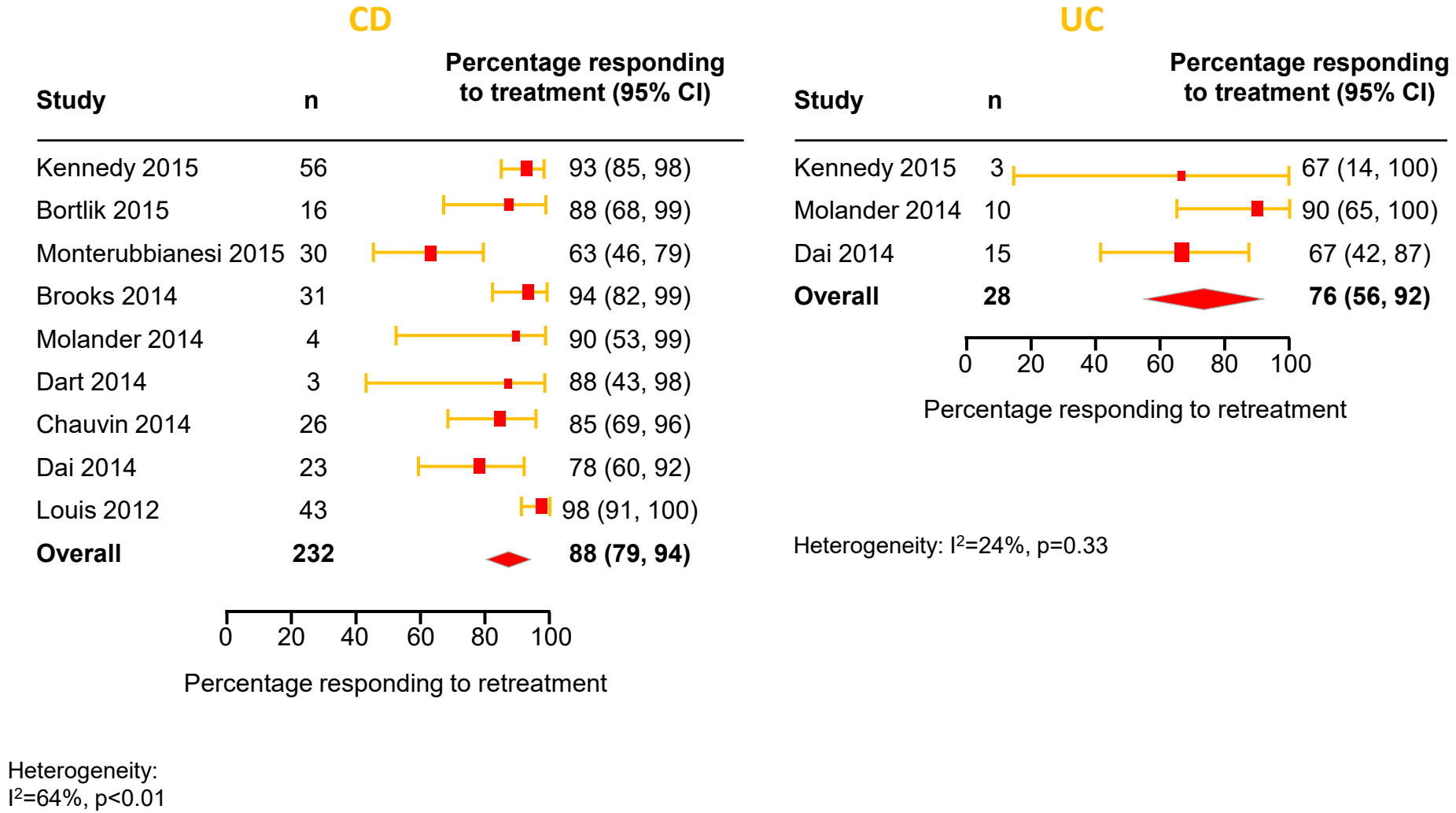
First co-primary endpoint

Time to relapse



Louis E et al, Lancet Gastro 2023

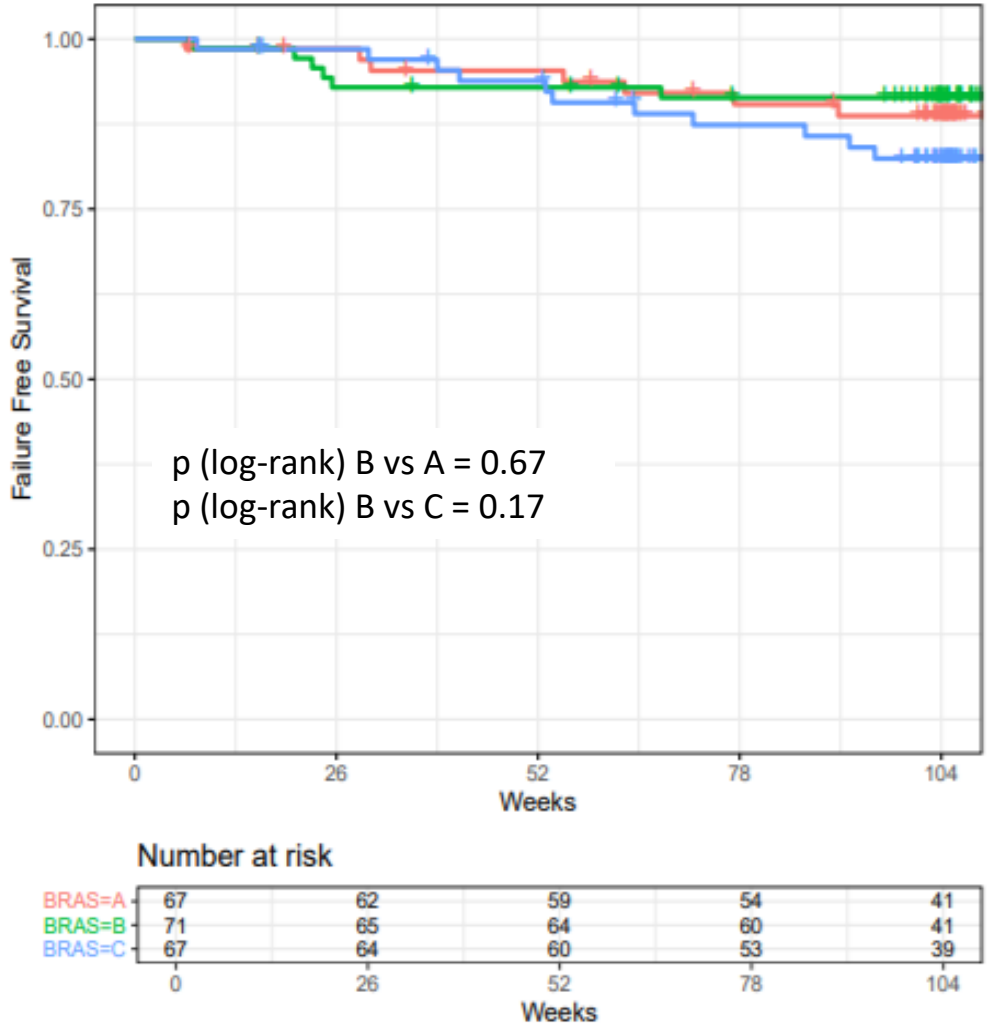
Response to retreatment after infliximab withdrawal



Kennedy N, et al. Aliment Pharmacol Ther. 2016 Feb 19 [E-pub]

Treatment Failure

- A treatment failure was observed in:
  - 7/67 (10.4%) in **arm A** (combo)
  - 6/71 (8.4%) 1 in **arm B** (stop IFX)
  - 11/67 (16.4%) in **arm C** (stop antimet)



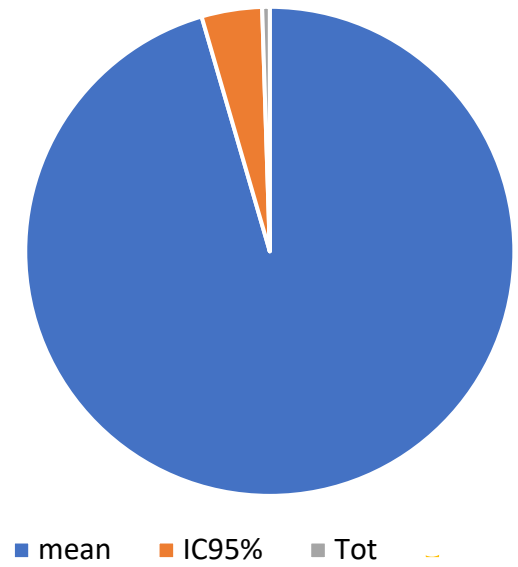
Louis E et al, Lancet Gastro 2023

2nd co-primary endpoint

Mean time spent in remission over 2 years

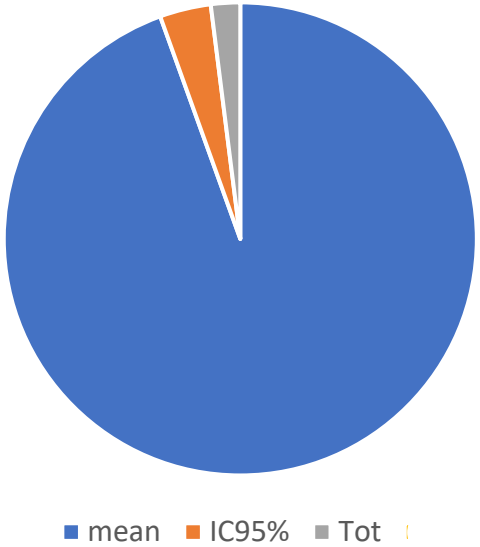
Biocycle

Arm A (combo)



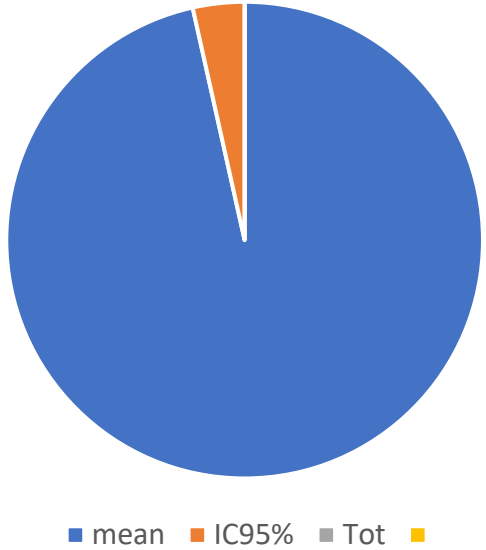
1.91 years (1.83-1.99)

Arm B (stop IFX)



1.89 years (1.82-1.96)

Arm C (stop antimetabolite)



1.93 years (1.86-2.0)

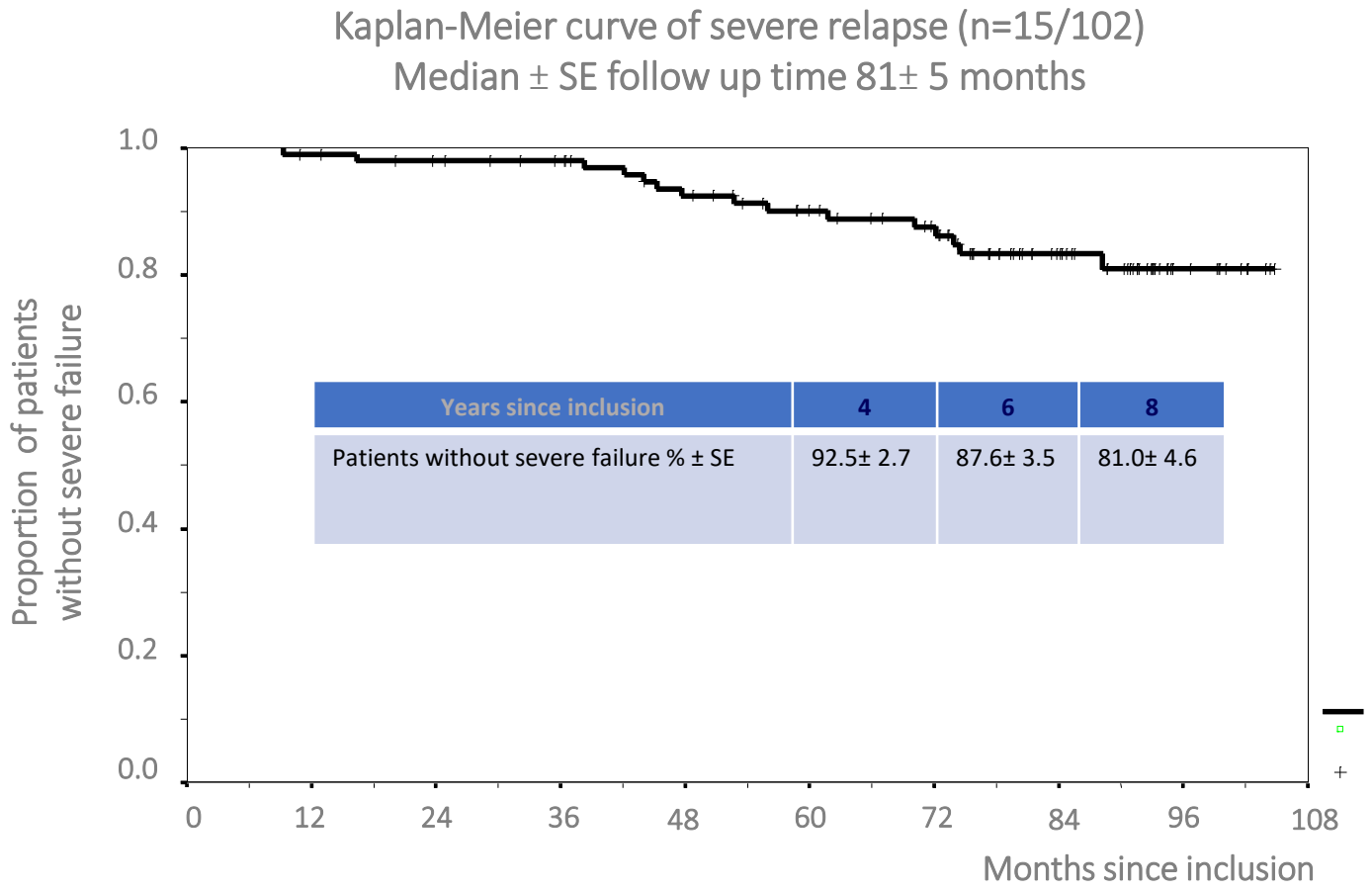
Arm A vs Arm B = **6 days** (95%CI: -33 - **44** days)
Arm C vs Arm B = **14 days** (95%CI: -21 - **69** days)

The prespecified non-inferiority threshold was **34 days.** As the 95%CI overlapped the threshold, the hypothesis was rejected

Louis E et al, Lancet Gastro 2023

GETAID
Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif

Stori long term: Time to surgical resection or new complex perianal disease



# At risk	102	96	83	65	11

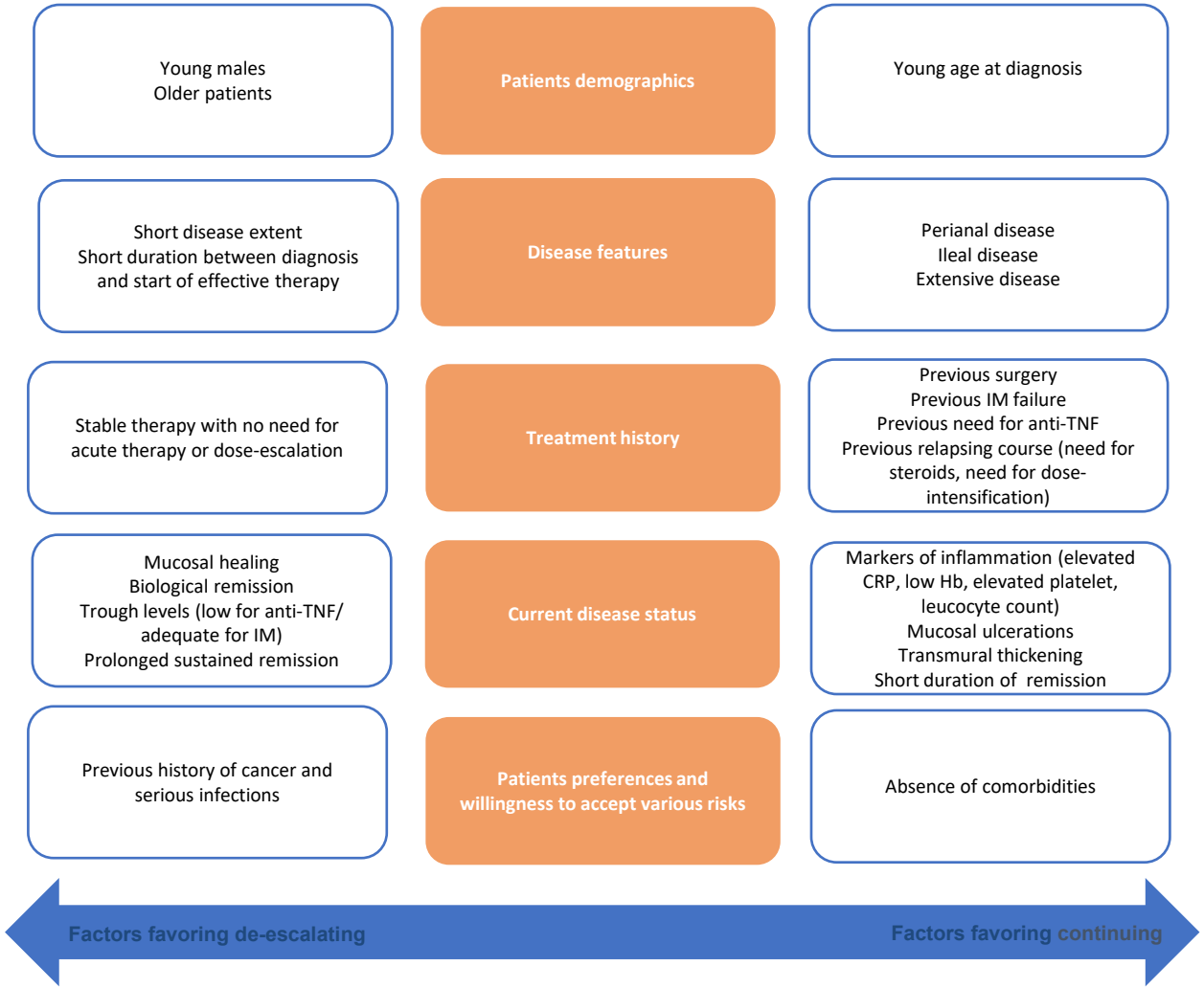
Rennaers et al. CGH 2017

Two important questions

- What is the risk of relapse ?
  - Mainly defined by persisting signs of inflammation/intestinal lesions/immune activation/…
- What could be the consequences in case of relapse ?
  - Mainly defined by previous medical history, previous treatment responses, disease location (including perianal) and previous complications, previous surgeries

A multidimensional decision

- Putting in perspective:
  - Patients wishes and priorities
  - Risk of relapse
  - Potential consequences of a relapse



Torres et al. Gastroenterology 2015 epub

Decision grid fo treatment withdrawal

	Successive interruptions and cycles of biological therapy (Biocycling)	Continuation of current therapy
Clinical characteristics	**Absence of all the following:**	**Presence of at least one of the following:**
	• Absence of perianal disease, AND	• Perianal disease, OR
	First ever anti-TNF agent (or second anti-TNF agent for reasons other than primary non-response or secondary loss of response), AND	• Second anti-TNF agent (after primary non-response or secondary loss of response on the first anti-TNF agent), OR
	• Absence of inflammatory comorbidity requiring biologic treatment, AND	• Any inflammatory comorbidity requiring biologic treatment, OR
	• No use of corticosteroids in the past 6 months, AND	• Treatment with corticosteroids in the past 6 months
	• No history of surgical resection	• Previous surgical resection
Biomarker characteristics	**Sustained remission:**	**Active disease:**
	• Absence of symptoms of active disease, AND	• Symptoms of active disease, OR
	• Two consecutive FC results in the target range in the previous 6 months, OR	• FC out of target range in the previous 6 months, OR
	• Confirmed endoscopic remission in the previous 6 months	• Endoscopically confirmed disease activity in the previous 6 months

Noor N et al, JCC 2023

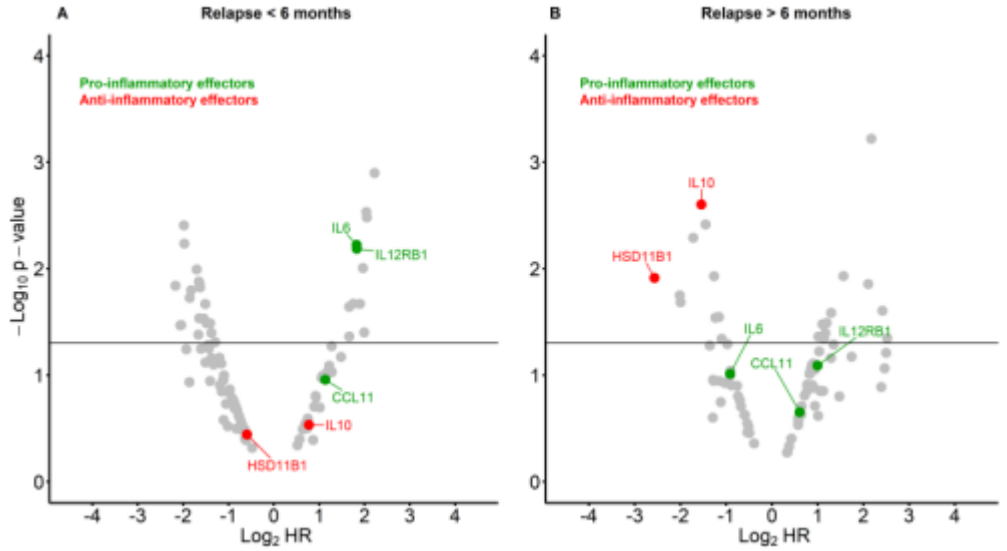
Decision grid fo treatment withdrawal

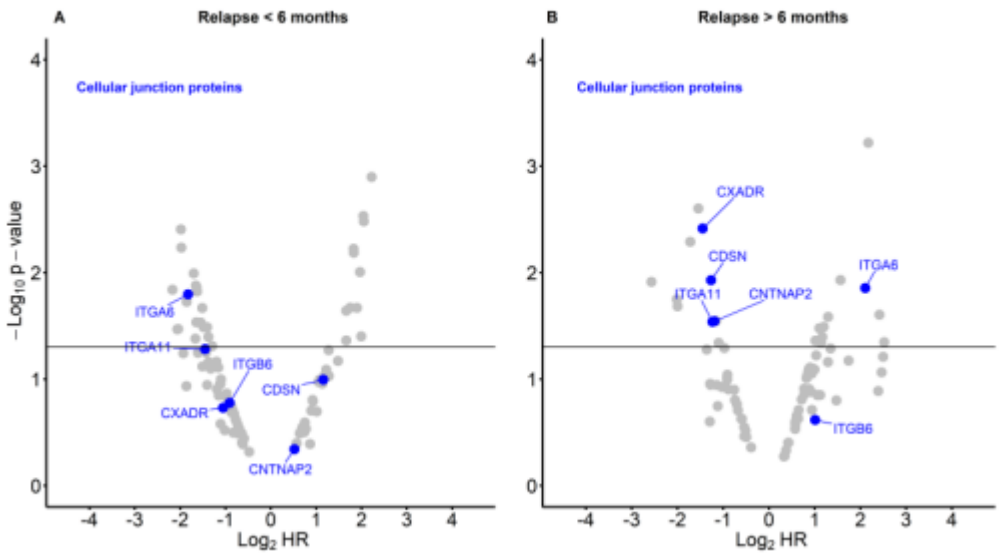
Successive interruptions and cycles of biological therapy (Biocycling)		Continuation of current therapy	
	Interrupted drug exposure		**Unchanged exposure to biological therapy**
Benefits	• One year after discontinuation, no new drug-related skin reactions.		• Among those who do not interrupt their therapy, approximately 10 people out of 100 develop skin reactions.
	• After discontinuation, the susceptibility for infection is reduced.[4]		• Among those who do not interrupt their therapy, the susceptibility for infection remains unchanged.
Safety risks	• One year after discontinuation, approximately 40 people out of 100 experience a clinical relapse.		• Among those who do not interrupt their therapy, approximately 10 people out of 100 experience a clinical relapse over one year .
	• Among the patients who experience a clinical relapse after discontinuation, approximately 90% can be successfully retreated with the same drug.		Among patients who experience relapse despite continuous treatment, approximately 50 out of 100 regain remission with treatment optimisation
	Discontinuation and cycling of biologic therapy		**Continuation of current therapy**
Patient self test Which is the preferred statement?	1 I wish to stop because of potential long term side effects	1	I am more concerned about the risks of stopping than the potential side effects
	2 I accept the risk of a flare and trust that it can be controlled when the medication is reintroduced	2	I do not want to risk a flare of disease
	3 I accept that re-capturing remission may require a course of steroid medication	3	I do not want to receive another course of steroid medication

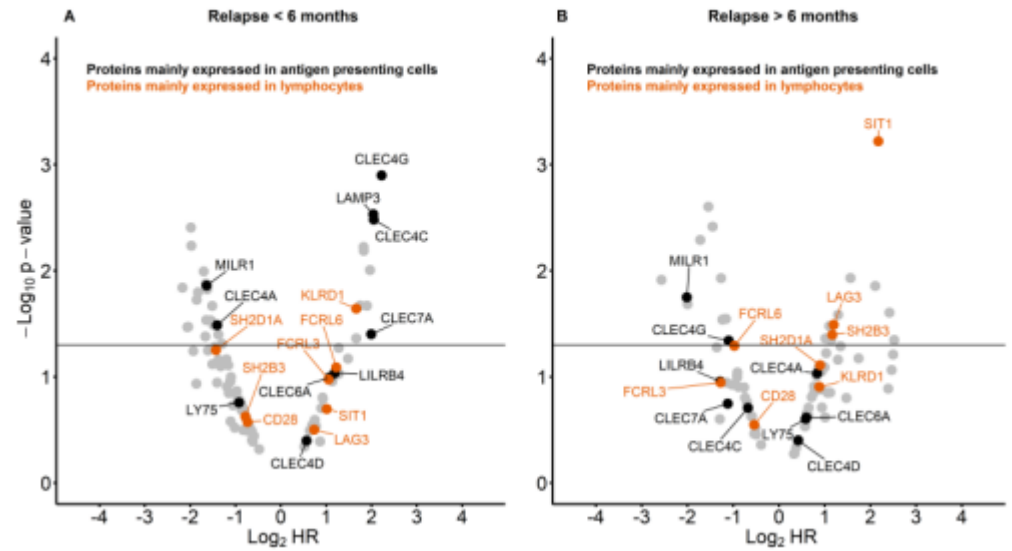
Noor N et al, JCC 2023

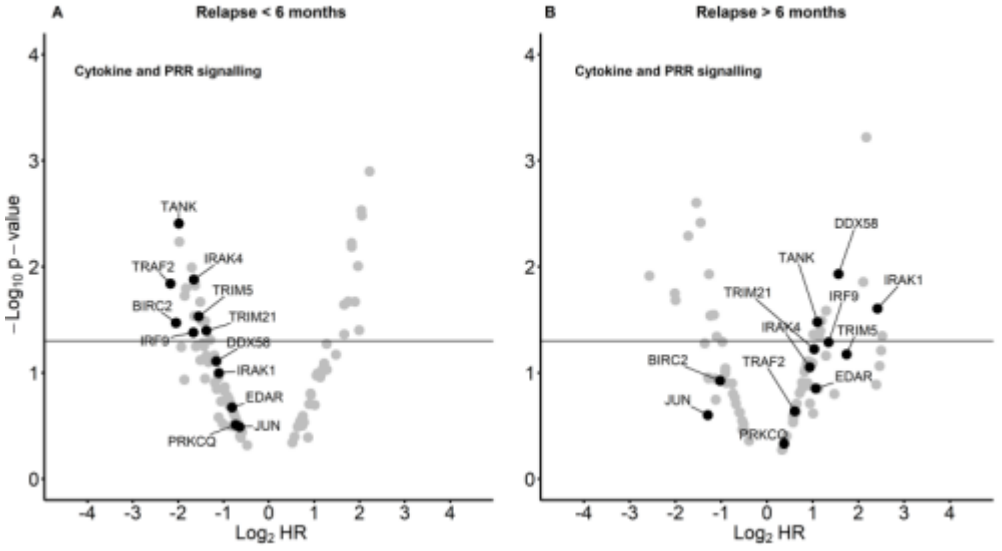
Prédicteurs biologiques de la rechute

Pierre N, et al, Gut 2023

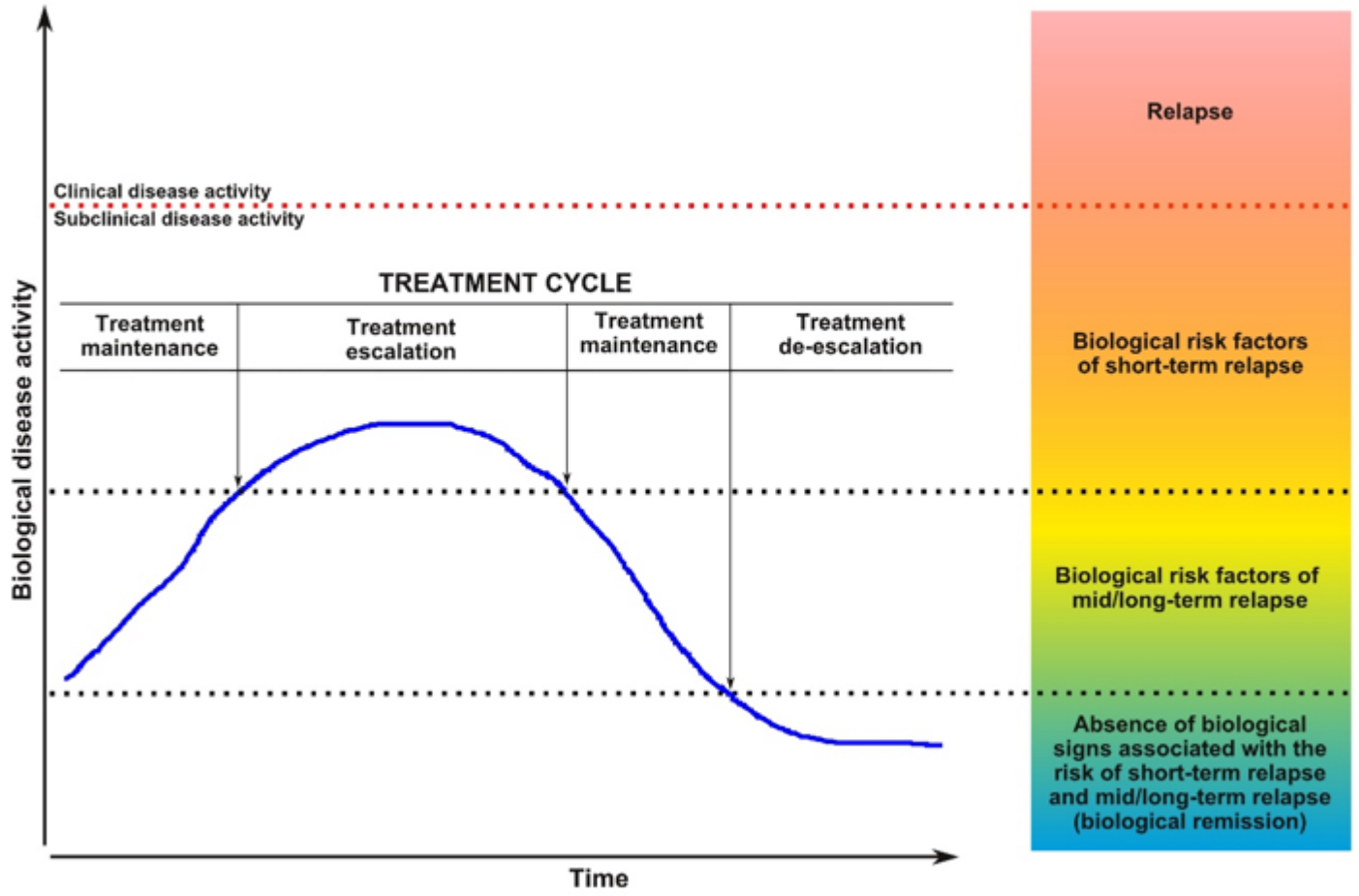








Comprendre la Biologie de la rechute et adapter les traitements



Pierre N, JCC 2023

What follow-up do you plan:

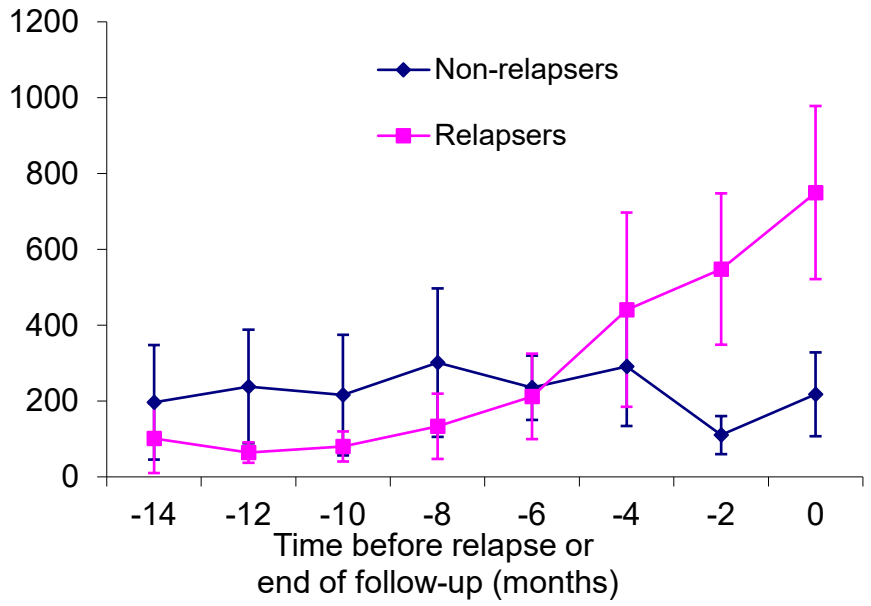
- PRO2
- Weigth
- CRP and blood tests
- Fecal calprotectin
- Ultrasound
- MR-enterography
- Ilecolonoscopy
- Capsule endoscopy
- …

Calpro and CRP monitoring after anti-TNF withdrawal in CD

Preliminary results of an exploratory analysis of longitudinal follow-up of the STORI-GETAID cohort

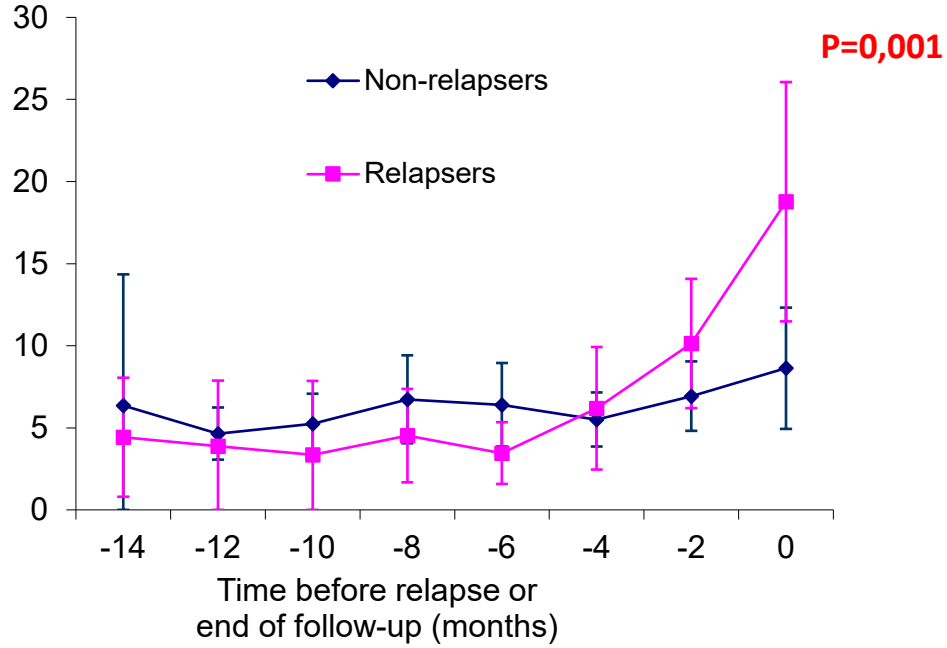
CRP (mg/L)

P<0,001



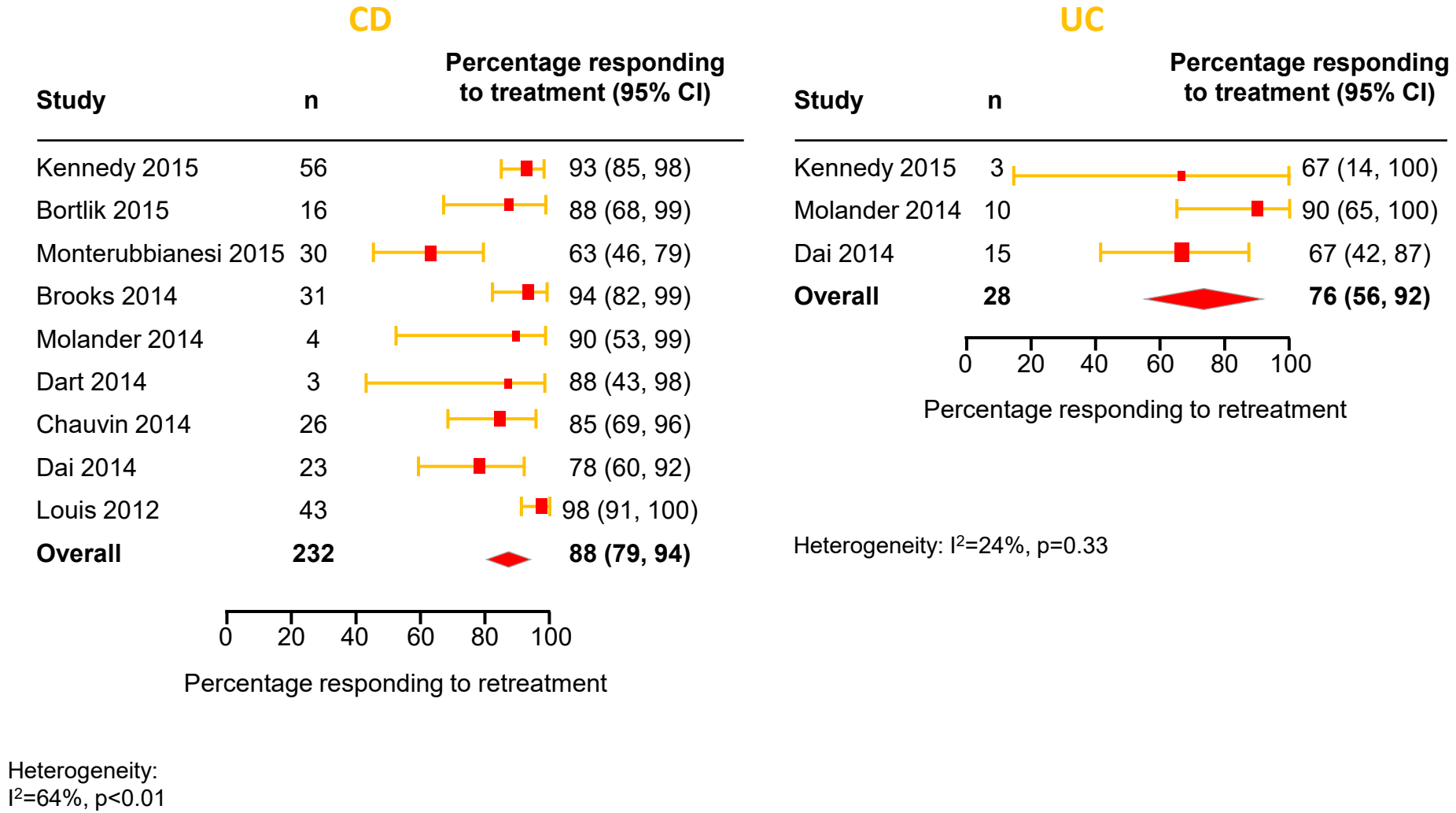
Calpro (µg/g)

P=0,001



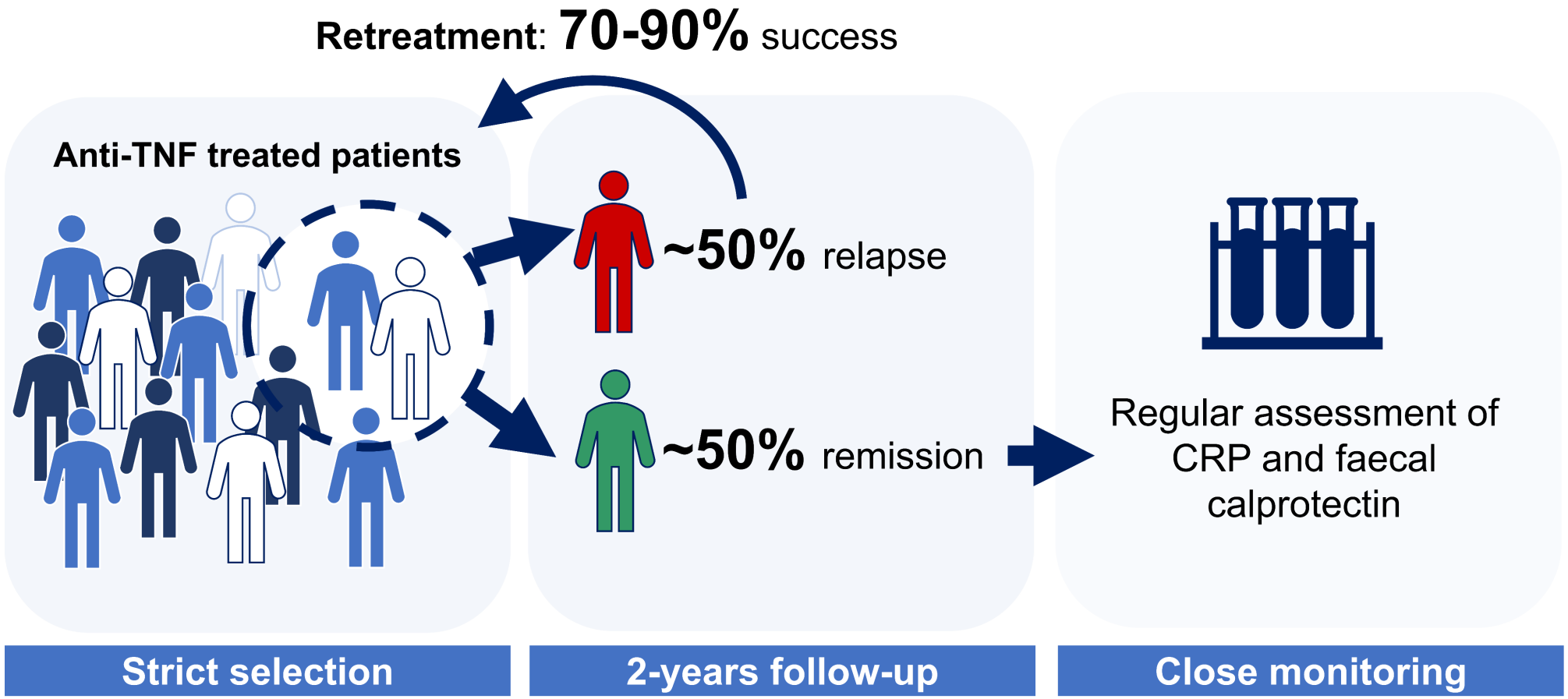
N de Suray, and the GETAID, ECCO2012

Response to retreatment after infliximab withdrawal



Kennedy N, et al. Aliment Pharmacol Ther. 2016 Feb 19 [E-pub]

Summary: anti-TNF withdrawal



Noor N et al, JCC 2023

Clinical outcomes of increased versus conventional adalimumab dose intervals for Crohn's disease : the LADI trial

Matériel et méthodes

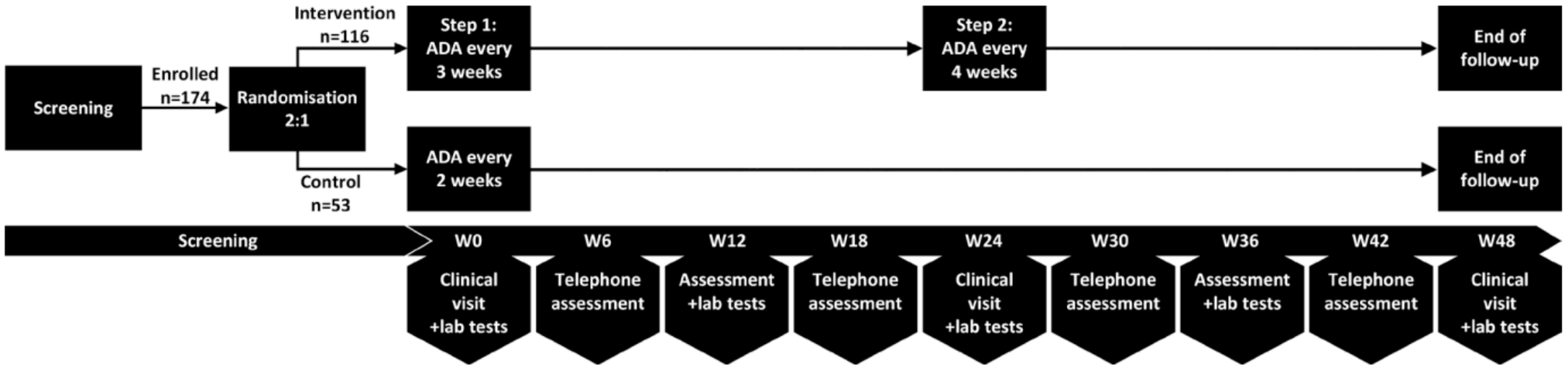


Figure 2 Schematic presentation of the trial design. ADA, adalimumab; W0, week 0; W6, week 6 and so on. Lab tests include haemoglobin, leucocytes, thrombocytes, albumin, C-reactive protein, calprotectin.

Smits LJT, Pauwels RWM, Kievit W, et al. Lengthening adalimumab dosing interval in quiescent Crohn's disease patients: protocol for the pragmatic randomised noninferiority LADI study. *BMJ Open* 2020;10:e035326.

Clinical outcomes of increased versus conventional adalimumab dose intervals for Crohn's disease : the LADI trial

Résultats

Objectif primaire

SCHEMA ALLONGE	3/109 (3 %)	pooled adjusted risk difference (paRD): 1.86%, 90% confidence interval (CI): [-0.36%; + 4.12%]).
SCHEMA CONVENTIONNEL	0/60 (0 %)	

→ Poussées persistantes : non-infériorité du schéma allongé (différence incidence cumulée < 15 %)

Van Linschoten R, et al. UEG 2022.

Clinical outcomes of increased versus conventional adalimumab dose intervals for Crohn's disease : the LADI trial

Résultats

Van Linschoten R, et al. UEG 2022.

Objectifs secondaires

	Poussées transitoires	*Rémission clinique S48*
SCHEMA ALLONGE	2/109 (1,8 %)	74/105 (71 %)
SCHEMA CONVENTIONNEL	0/60 (0 %)	52/57 (91 %)
	paRD: 2.68%, 95% CI: [-0.93%; 6.30%])	paRD: -16.3% 95% CI: [-30.9%; -1.82%]

Le futur de la décroissance thérapeutique

- Agir sur les facteurs environnementaux
- Affiner les prédicteurs de rechute à court terme et à long terme (comprendre la dynamique de la rechute et le retour à m'équilibre homéostatique)
- Privilégier le maintien de traitement de fond les plus sécurisants (vedo, anti-IL23…)
- Monitoring serré et cycles de petites molécules (non immunogènes) très actives (JAKi…)

Conclusions

- La décroissance thérapeutique a du sens dans les maladies chroniques sans destruction d’organe
- Elle correspond à une aspiration des patients
- Elle peut améliorer le coût-bénéfice
- Elle nécessite une meilleure compréhension de la dynamique de la pathologie
- Elle peut s’articuler sur des traitements de maintenance très bien tolérés et des cycles de traitements très efficaces