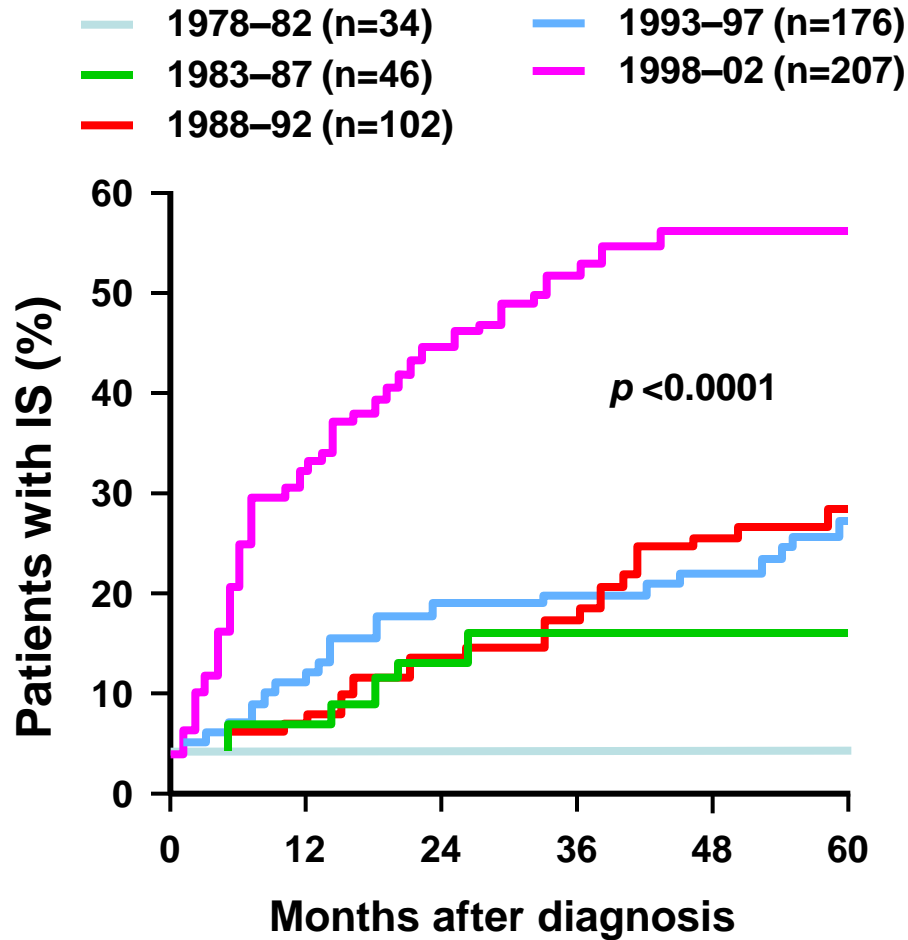


Peut-on **stopper** les  
**immunosuppresseurs** et/ou les  
**anti-TNF** dans la maladie de Crohn?

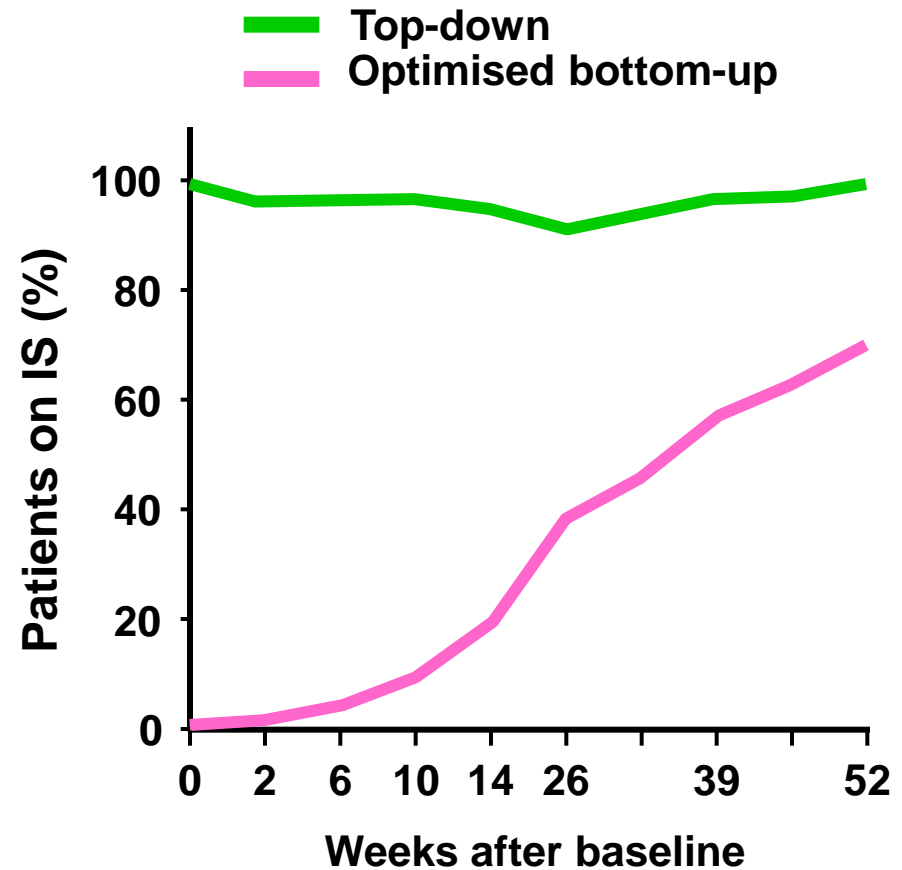


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# Increased use of Immunosuppressant in Crohn's disease

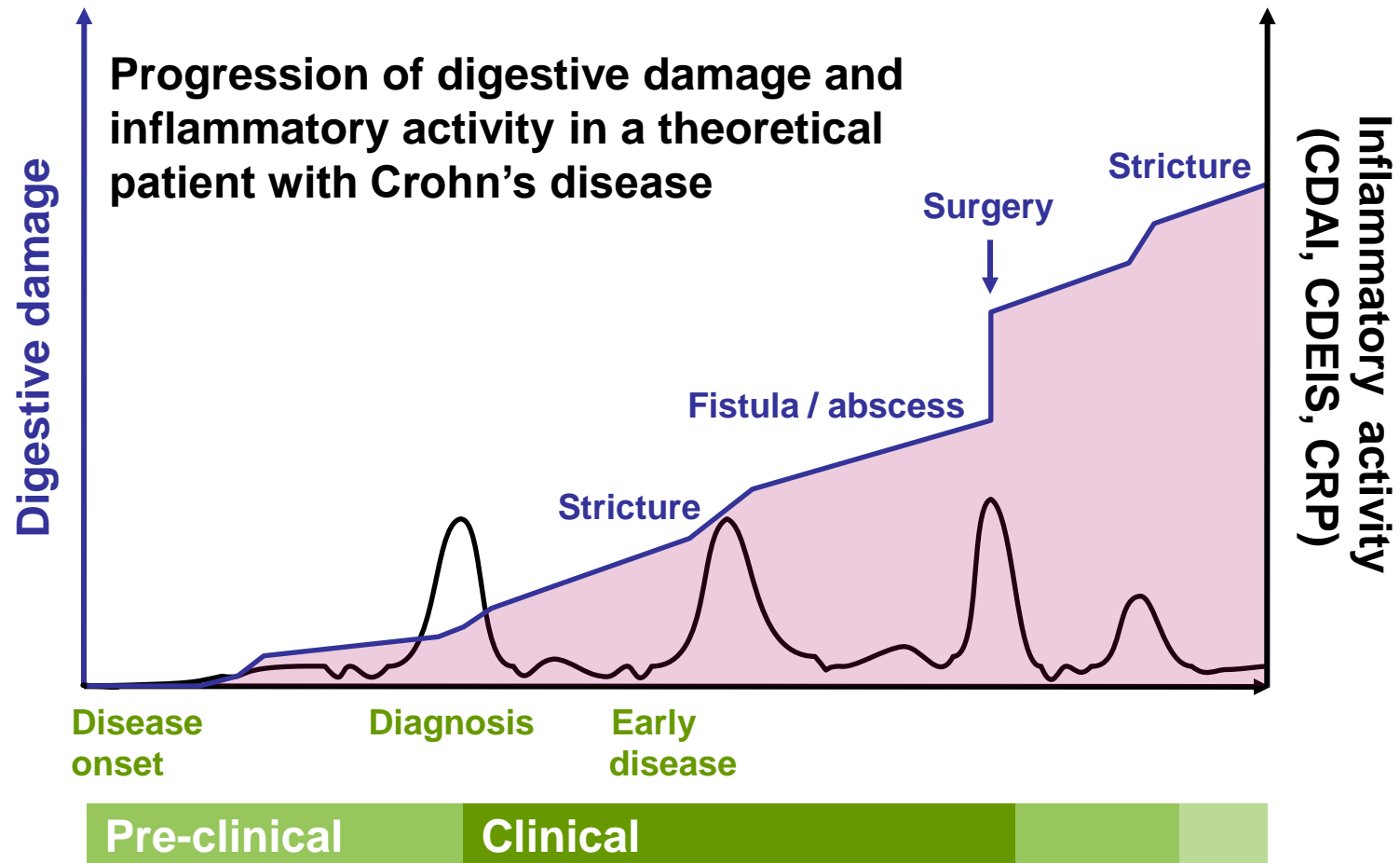


The St-Antoine/Paris experience<sup>1</sup>



The 'Step-up vs. top-down' trial<sup>2</sup>

# Inflammation is ongoing and resulting tissue damage is cumulative



CDAI: Crohn's disease activity index; CDEIS: Crohn's disease endoscopic index of severity; CRP: C-reactive protein

- **Benefits** from long term IS and anti-TNF use
  - Sustained steroid-free remission
  - Mucosal healing
  - Decrease of hospitalisation and surgeries
  - Improved quality of life and ability to work

➤ **Anti-TNF > IS**
  
- **Unsettled issues**
  - Mild side effects
  - Infections
  - Liver toxicity (purines>methotrexate)
  - Lymphomas (purines>anti-TNF>methotrexate)
  - Pregnancy
  - Cost (anti-TNF)

➤ **Combined therapy > Monotherapy**

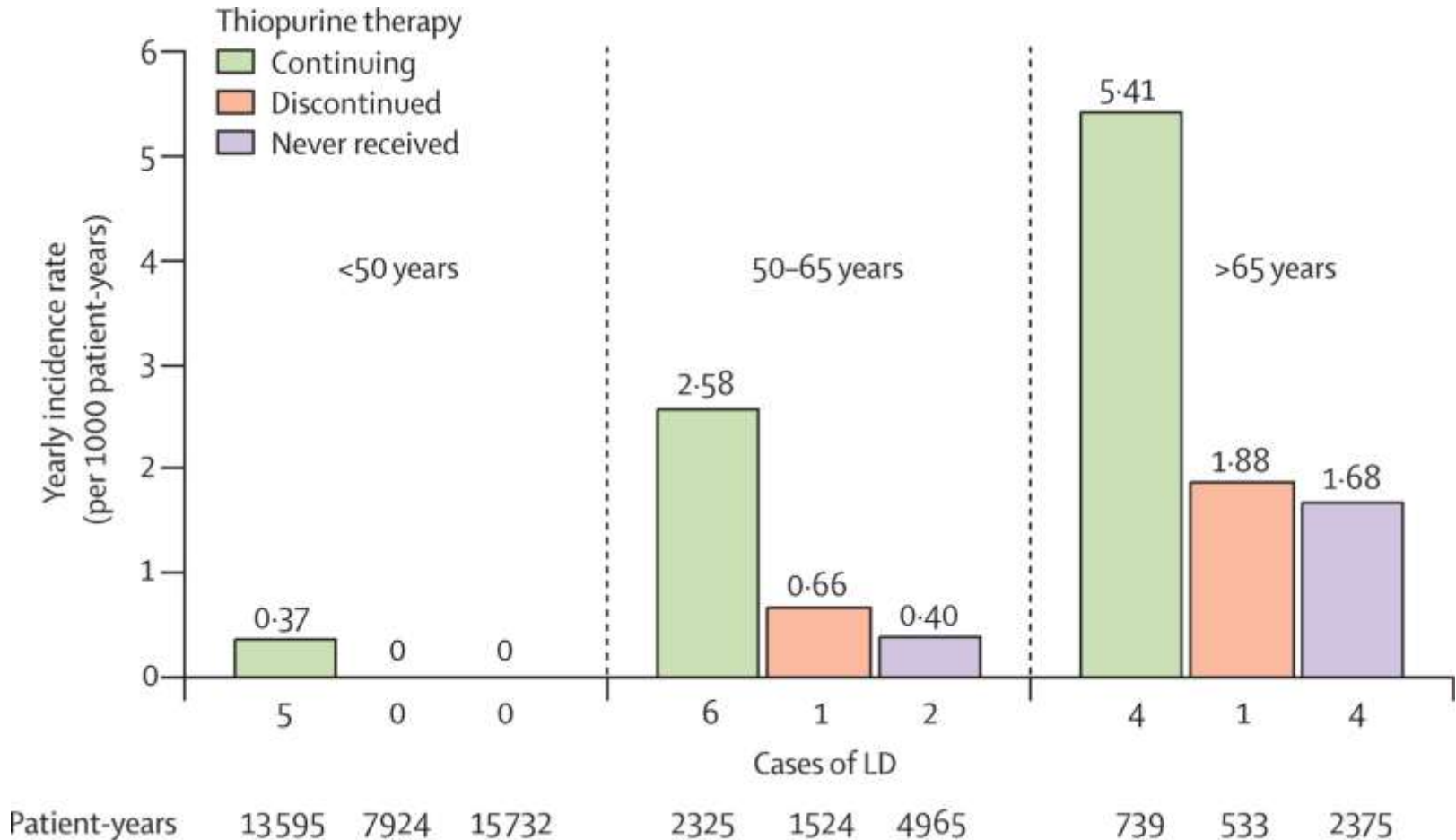
# Different **clinical situations**

- Immunosuppressant monotherapy
- Anti-TNF monotherapy
- Combined IS/anti-TNF therapy

# Different clinical situations

- **Immunosuppressant monotherapy**
- Anti-TNF monotherapy
- Combined IS/anti-TNF therapy

# Lymphomas and thiopurines : CESAME



n= 19486 exposed: 30%+14.5%

23 incident lymphomas

OR= 5.28 (2.01-13.9, p=0.0007)

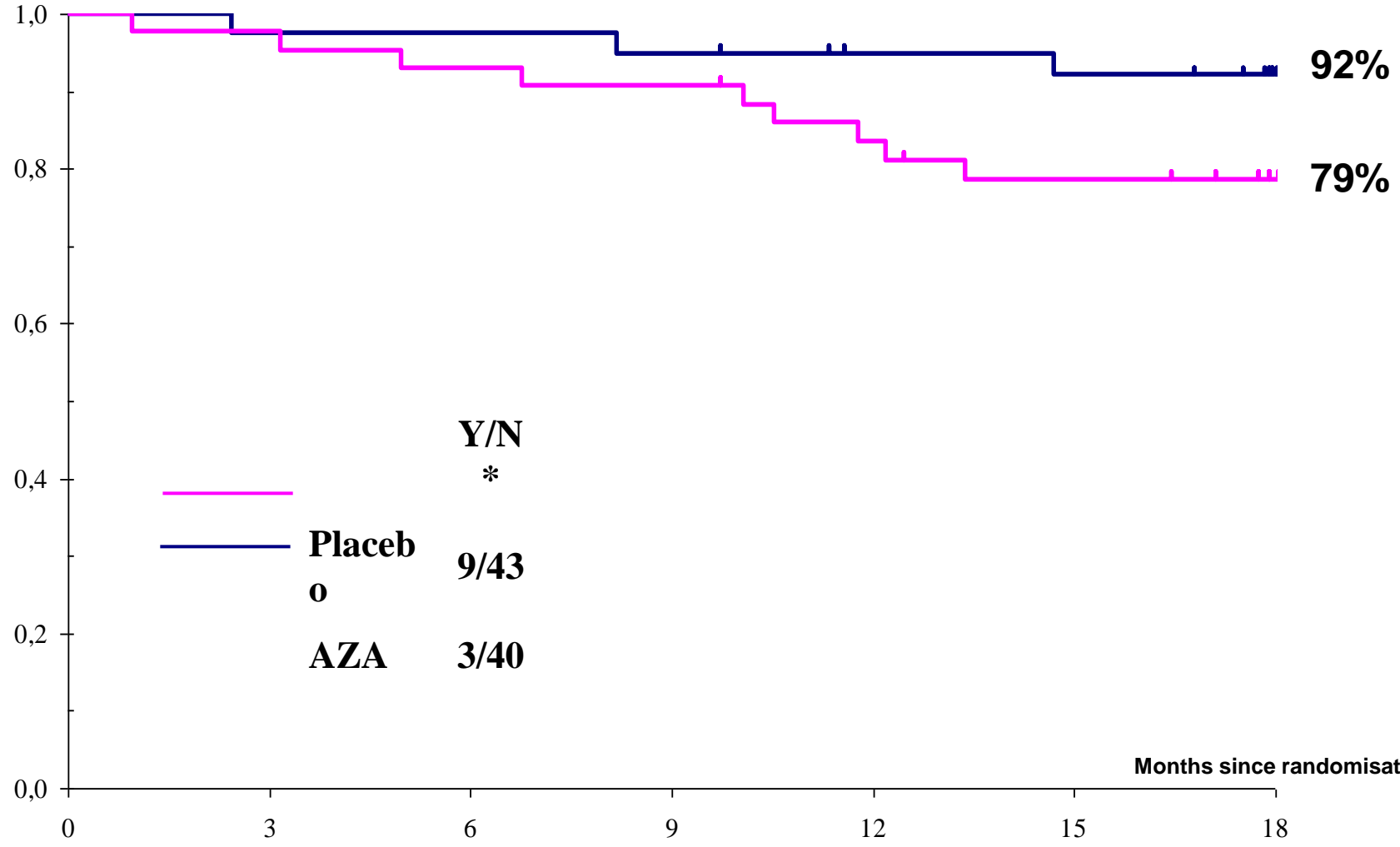
Beaugerie et al. Lancet 2009;374:1617-25



# AZA withdrawal

## Non-inferiority placebo-controlled trial

Proportion of patients in remission (%)



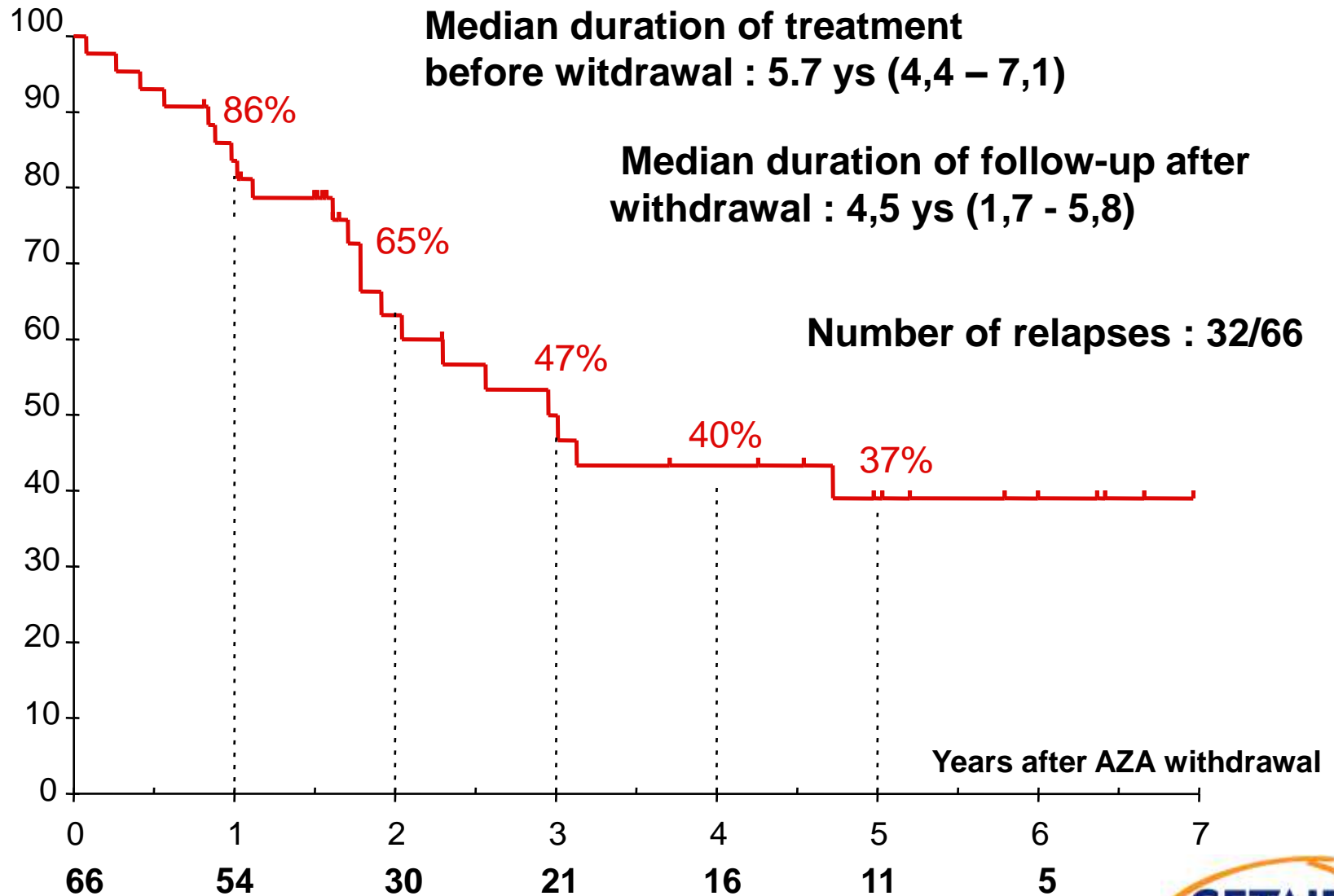
**Y/N**  
 \*  
**Placebo** 9/43  
**AZA** 3/40

At risk patients (flare) 40 38 (1) 34 (2) 23 (3) Aza

\* Y/N number of relapses/number of patients 40 (3) 35 (7) 27 (5) 18 (12) Placebo

# Sustained remission after AZA withdrawal

Patients in remission (%)



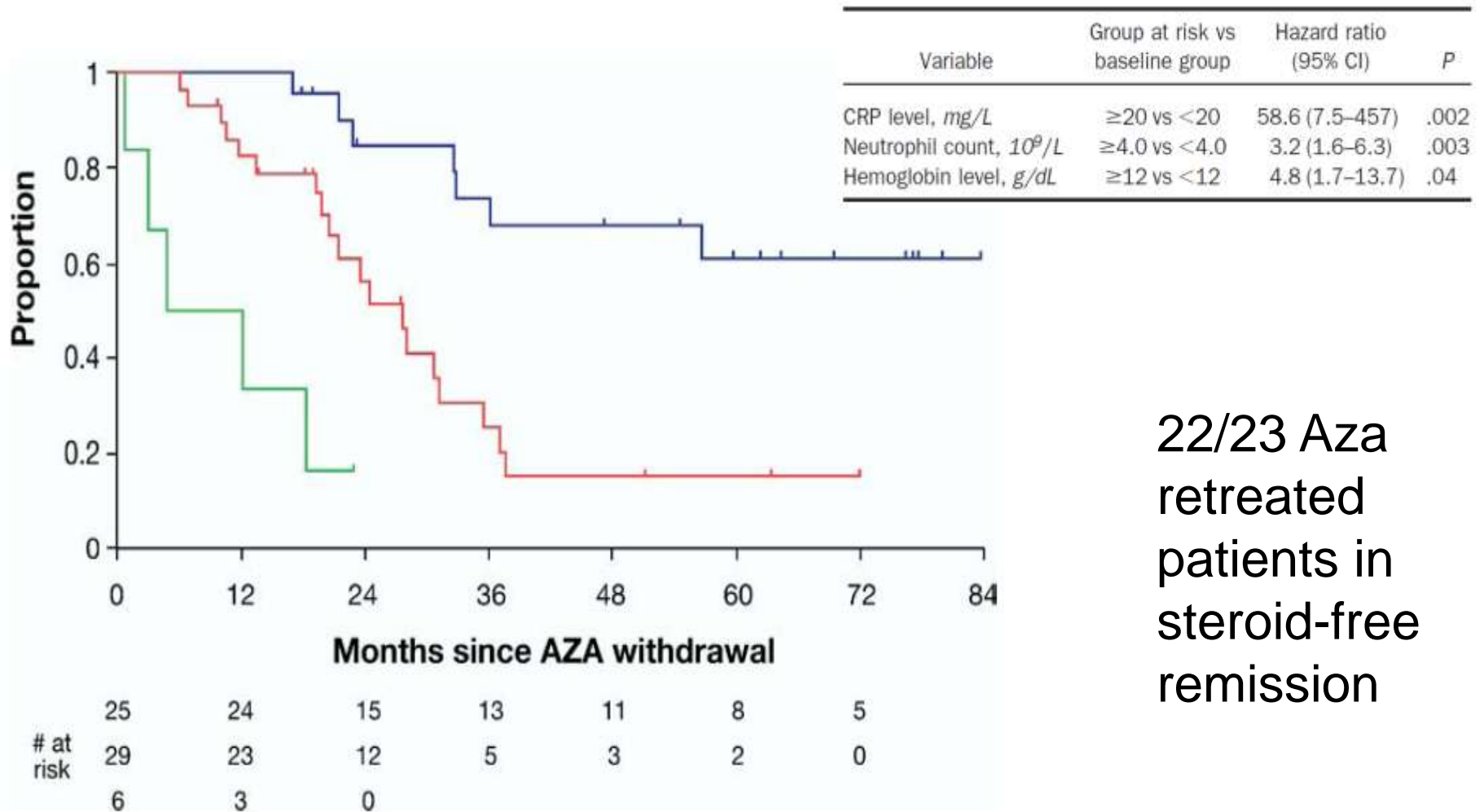
Nb of patients at risk

Treton et al CGH 2009



# Prediction of relapse after AZA withdrawal

*predicting classification according to the presence of risk factors in 66 patients*



22/23 Aza retreated patients in steroid-free remission

# Different clinical situations

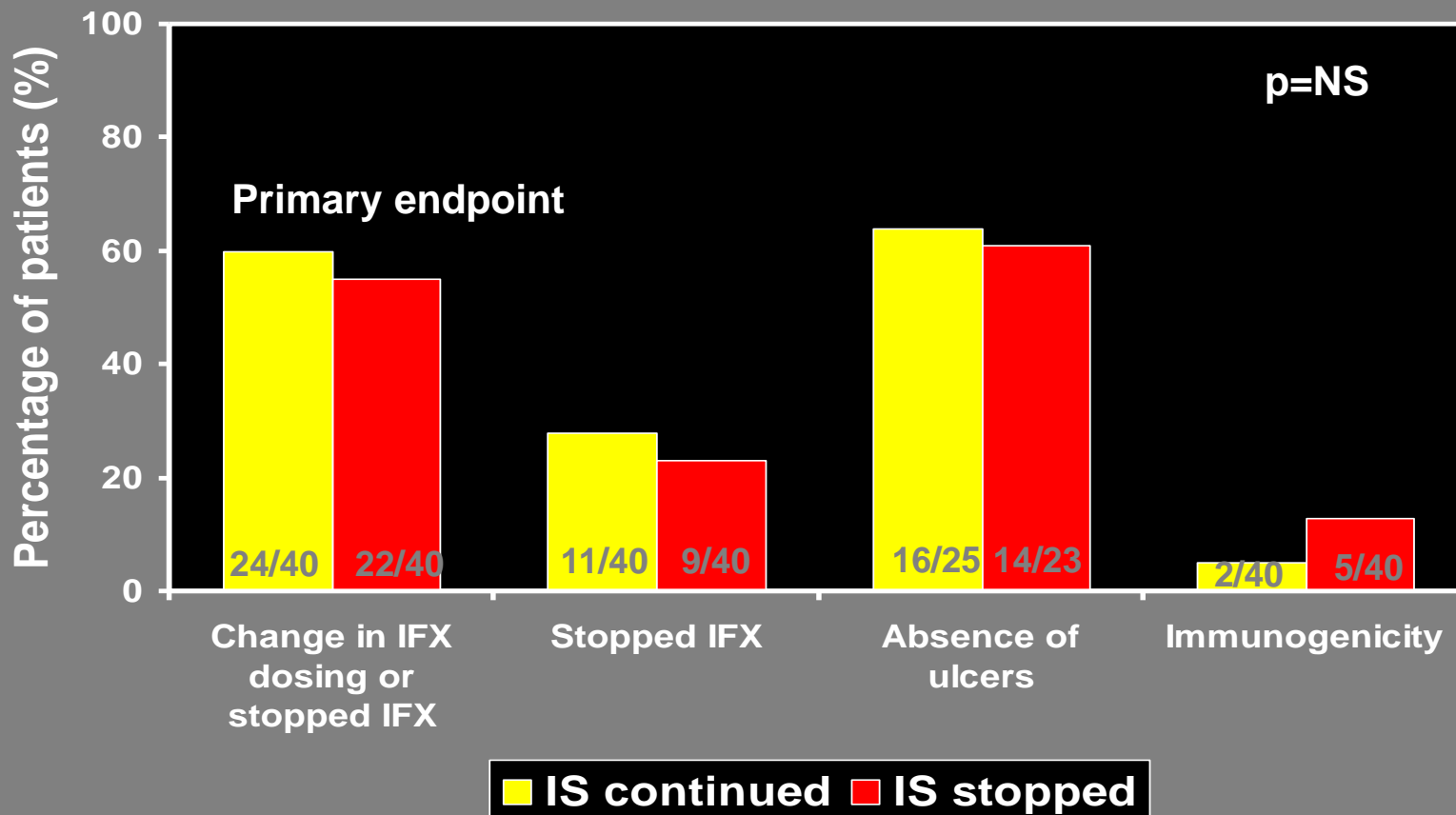
- Immunosuppressant monotherapy
- Anti-TNF monotherapy
- **Combined IS/anti-TNF therapy**

# IS or anti-TNF withdrawal ?

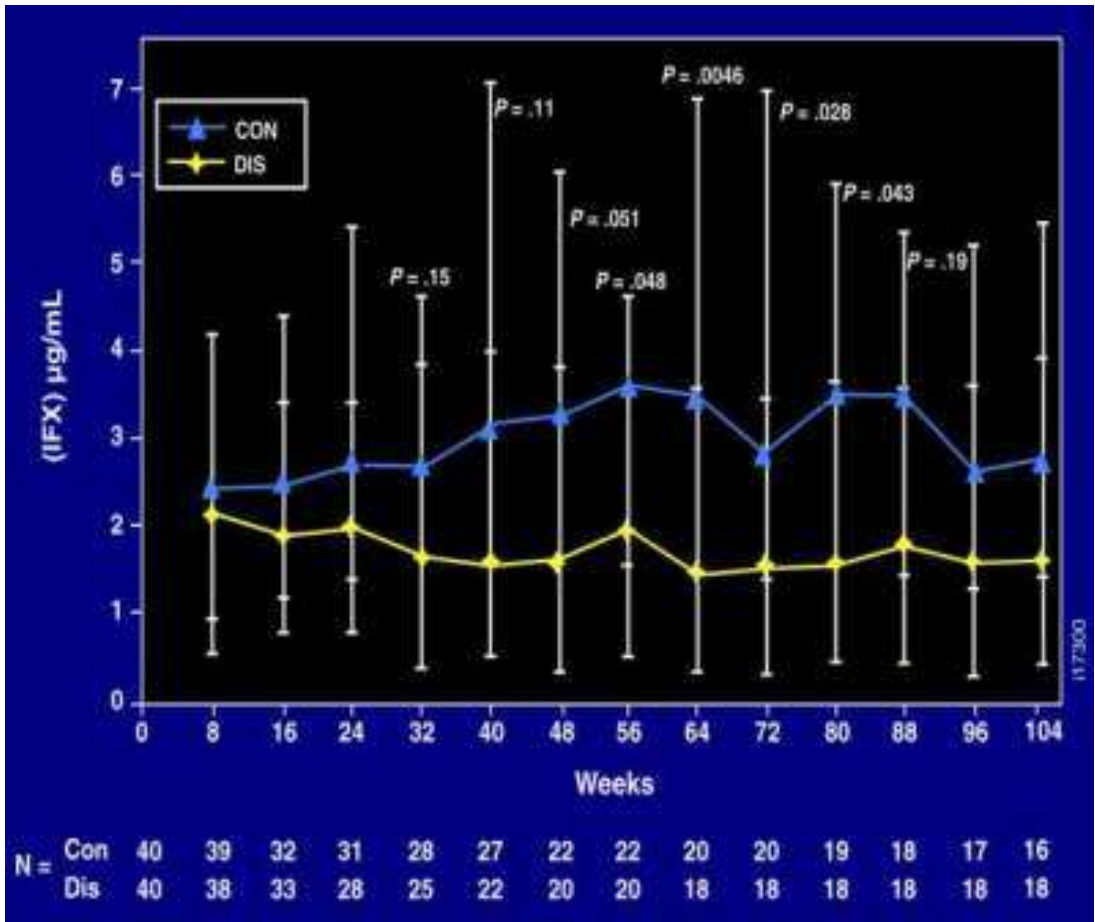
- **Main advantage** of anti-TNF withdrawal is direct cost savings
- **Main drawbacks** of anti-TNF withdrawal are:
  - IS are less efficacious
  - Purine analogues may be less safe (lymphoma, liver toxicity...)
  - Compliance to IS may be lower

# Possibly no benefit continuing IS > 6 months

- Eighty (80) patients, 6 months treatment IFX 5 mg/kg q8+IS
- Randomised (1:1) to continue or discontinue IS; 2 years follow-up
  - Forty-nine (49) underwent a 2 year ileo-colonoscopy



# Evolution of CRP and IFX trough levels may suggest future treatment failure



## After IS withdrawal:

5-15% vs 0% of patients with undetectable trough levels beyond one year

Median CRP level significantly higher (2.8 vs 1.6 mg/l;  $P < 0.005$ )

# Cost-effectiveness of anti-TNF treatment

	Base-case	Range	ICER vs. standard care (per QALY gained)	
			Infliximab	Adalimumab
Relative risk of surgery vs. standard care*	0.45	0.1 0.9	£23 100 £18 600	£9250 £10 450
Annual discount rate of costs and QALYs*	3.5%	0% 6%	£19 750 £19 690	£7560 £7580
Duration of treatment†	1 and 2 years	4 years 34 years Lifetime	£30 000 - Dominated	- £30 000 £181 620
Analytic time horizon‡	Lifetime	1 year 2 years	£155 750 Dominated	£51 270 £60 150

\* Duration of treatment set at 1 year.

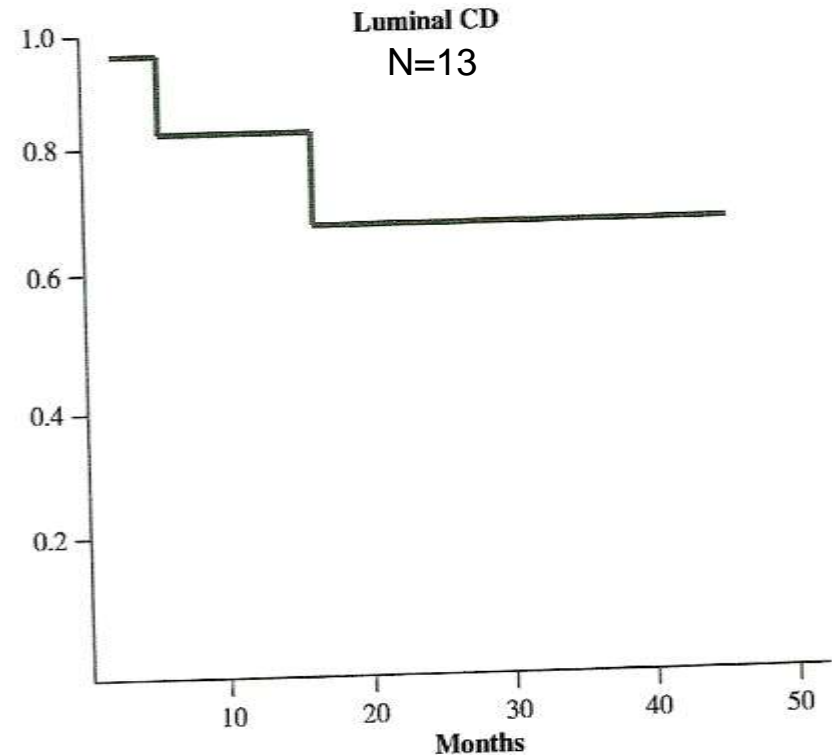
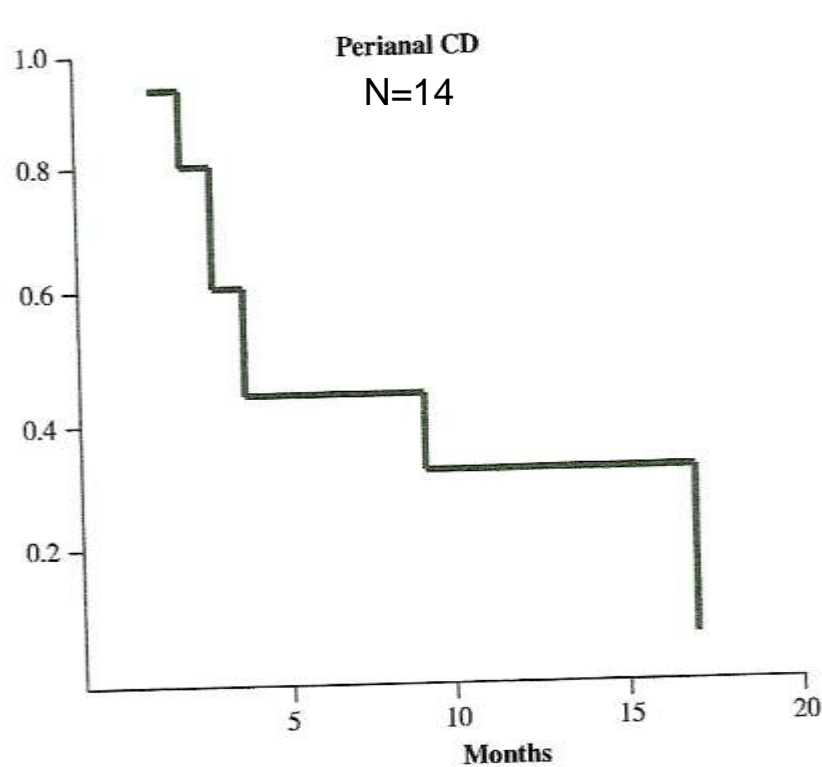
† At which drug is no longer cost-effective at the £30 000 per QALY threshold.

‡ Assuming corresponding duration of treatment in the sensitivity analysis.

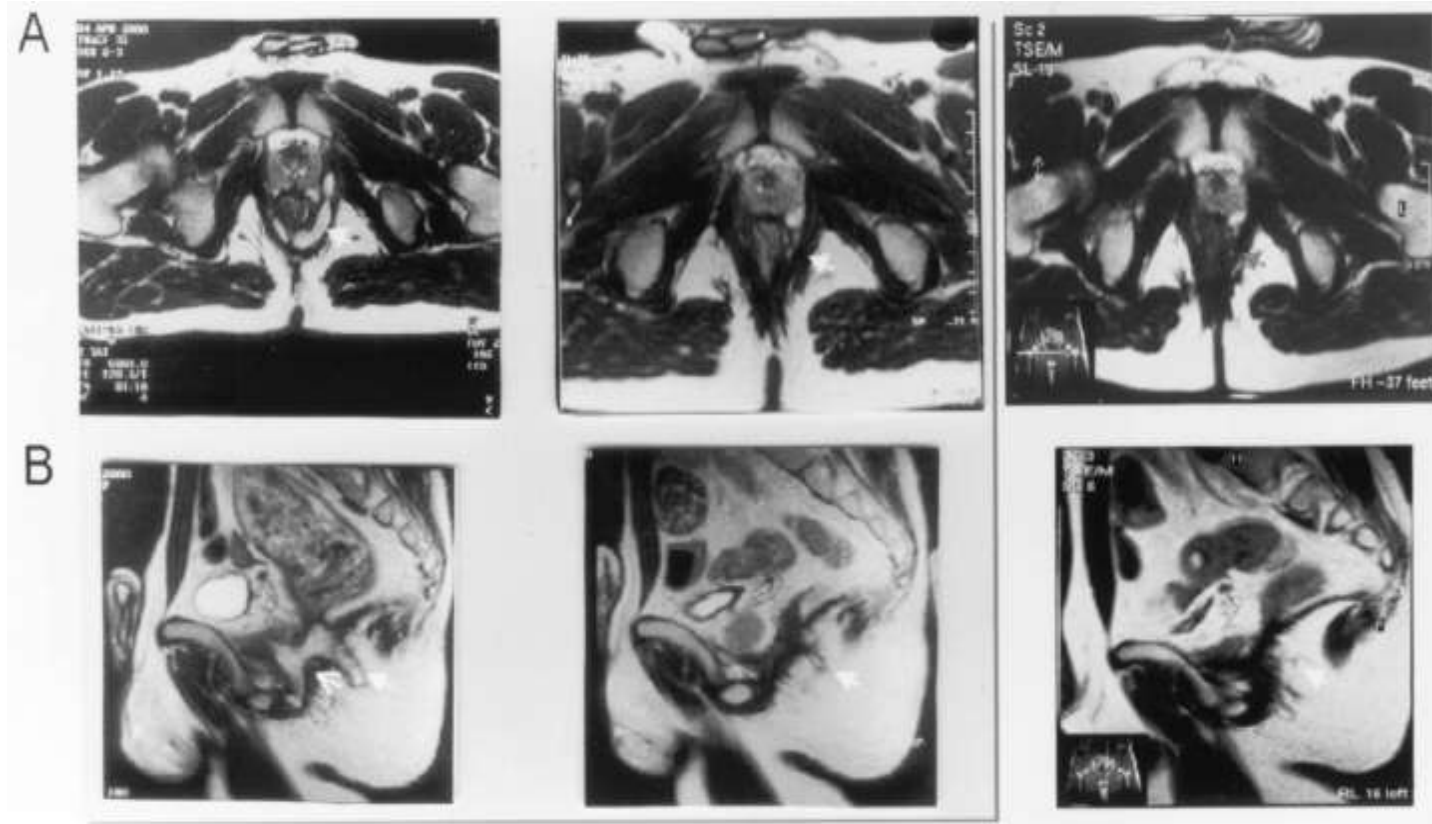
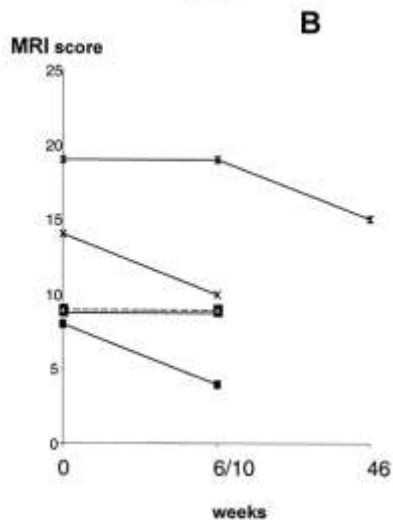
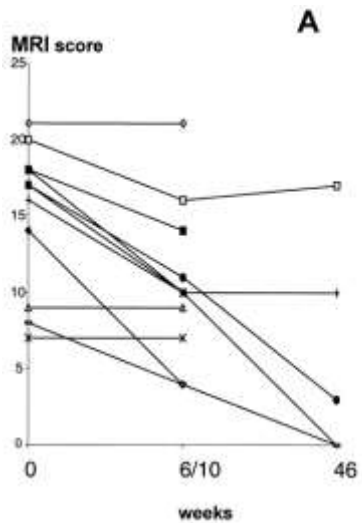
# Preliminary experience of **anti-TNF withdrawal**

*A retrospective Spanish study*

1 yr lfx treatment, concurrent IS, mean f-up=8.8+/-11.2 months



# Anti-TNF: when to stop in **peri-anal Crohn's** disease?

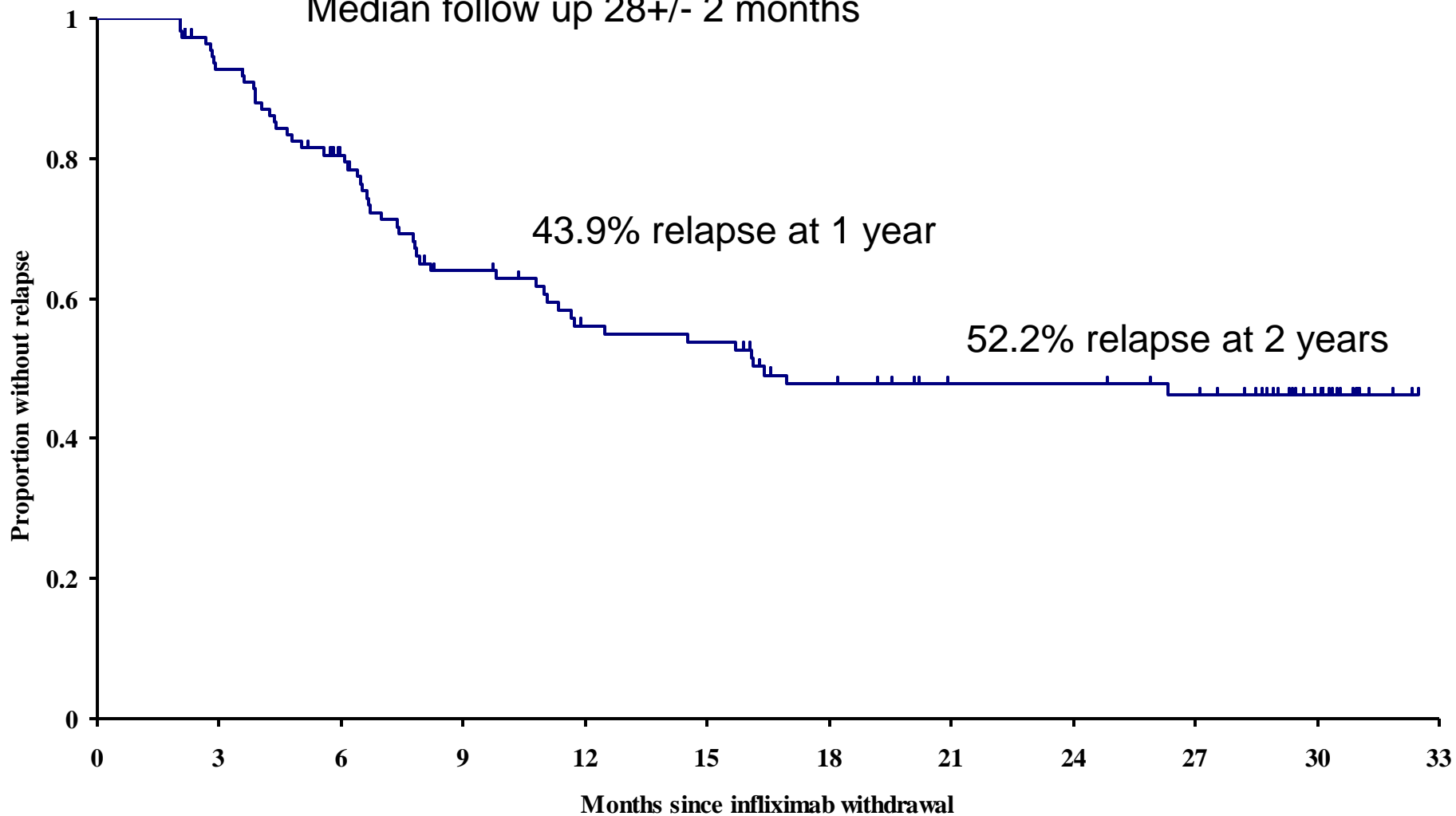


*G Van Assche et al. Am J Gastro 2003; 98: 332*

# Relapse rate after infliximab discontinuation

Kaplan-Meier curve of relapse (n=52/115)

Median follow up 28+/- 2 months



# at  
risk

115

100

79

59

49

47

38

32

32

29

15

# Factors associated with the **time to-relapse**

Association with time-to-relapse in univariate analysis (P value)

<b>Clinical history and characteristics</b>	<b>P value</b>	IFX frequency last 6 months	0.46
Age	0.63	<b>Scores and biological variables</b>	<b>P value</b>
Gender	0.22	<b>CDAI &gt;20</b>	<b>0.045</b>
Disease duration	0.84	<b>CDEIS ≥2</b>	<b>0.002</b>
<b>Current smoker</b>	<b>0.036</b>	<b>CDEIS&gt;0</b>	<b>0.033</b>
Previous surgery	0.07	Presence of ulcers	0.20
Disease location	0.73	ANA	0.81
A-P disease	0.17	ATI	0.39
fistula	0.12	<b>Fecal calprotectin ≥250 microg/g</b>	<b>0.0001</b>
Stricture	0.13	<b>CRP hs ≥5 mg/l</b>	<b>0.0006</b>
Previous steroid treatment	0.067	IFX trough level ≥2 micro/ml	0.25
IS naïve	0.96	ESR >16	0.16
IS type	0.12	Plt count	0.86
IS duration	0.41	WBC > 6000/ml	0.08
IFX duration	0.44	<b>Hemoglobin ≤14.5 g/dl</b>	<b>0.038</b>
IFX scheduled from the start	1.00	6TGN	0.26

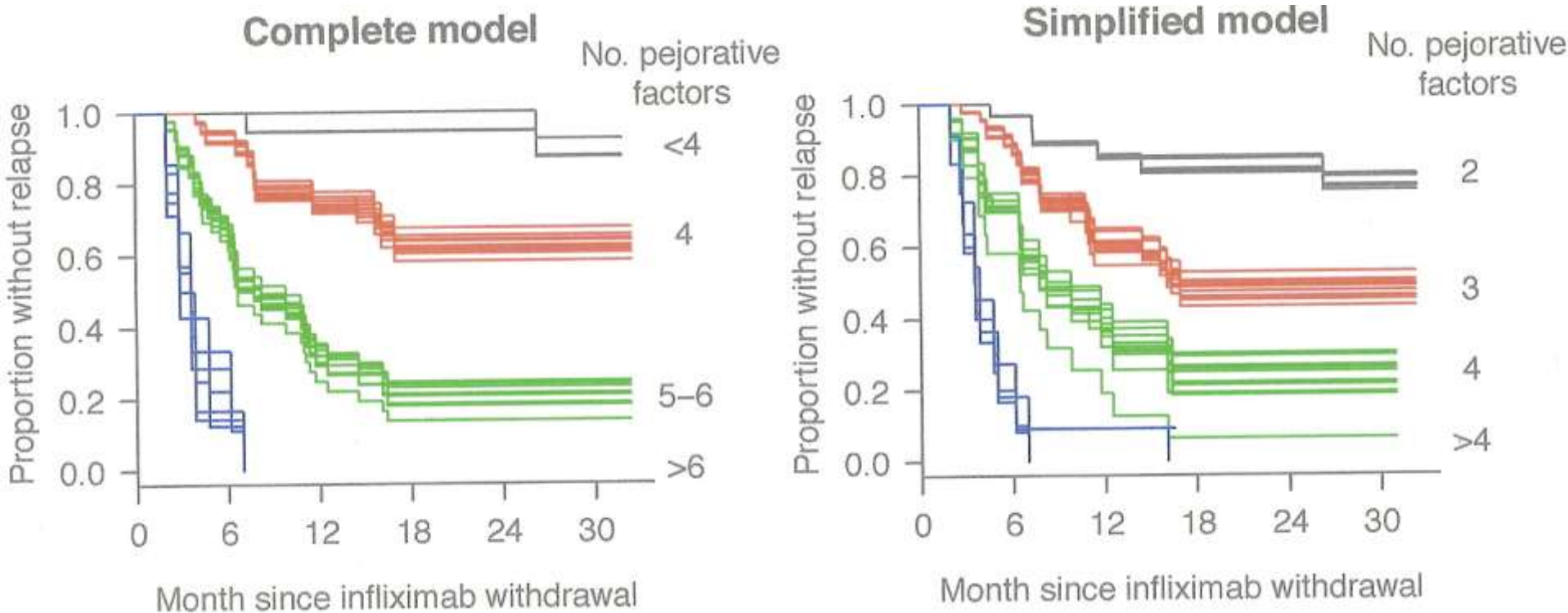
# Predictive model for the **time-to-relapse**

Kaplan Meier time-to-relapse curves according to multivariate models and scores generated through Cox model using multiple imputations method.

**Pejorative factors were:**

**Complete model:** no previous surgery, steroid use within 12-6 months before Ifx withdrawal, male gender, haemoglobin  $\leq 14.5$  g/dl, leukocyte count  $>6 \times 10^9/l$ , hsCRP  $\geq 5$  mg/l, fecal calprotectin  $\geq 300$  mg/g, CDEIS  $>0$ , Ifx trough  $\geq 2$  mg/l

**Simplified model:** the same without steroid use, CDEIS and Ifx trough levels



# Profiles associated with the risk of relapse after Infliximab discontinuation

*Established according to the simplified predictive model derived from the prospective STORI cohort*

## Constitutive risk factors

***Gender and previous surgical resection***

Female with previous surgical resection

Female without previous surgical resection or male with previous surgical resection

Male without previous resection

## Variable risk factors

***hemoglobin, hsCRP, fecal calprotectin, leukocyte count***

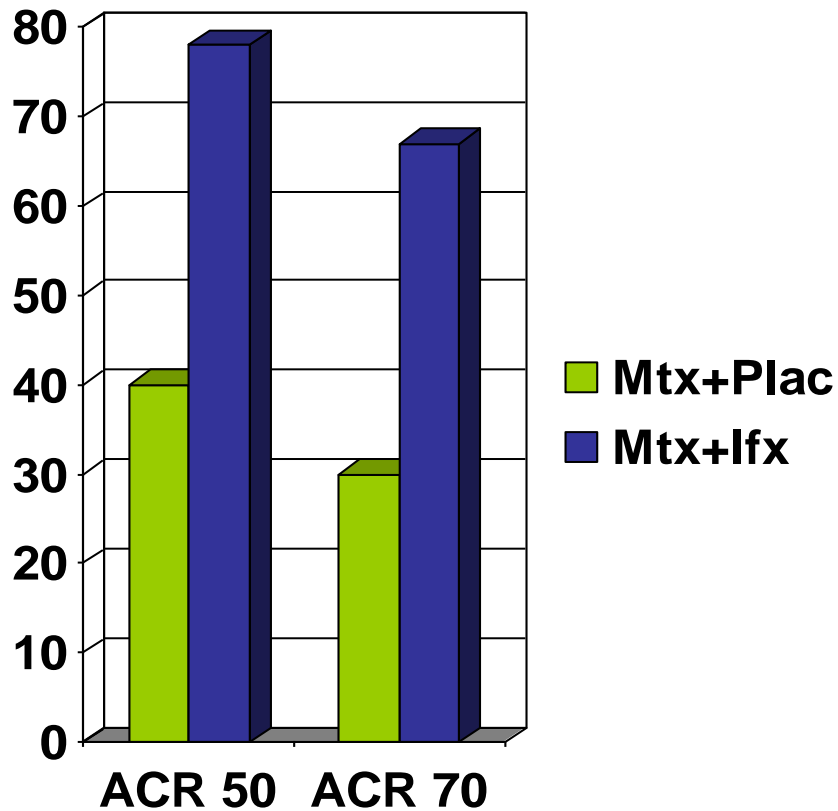
up to 2 other risk factors allowed

only one other risk factor allowed

no other risk factor allowed

- **Earlier introduction** of anti-TNF may increase the possibility of later discontinuation.

# Long term remission without Biologics in early treated Rheumatoid Arthritis



Clinical response  
at one year

- 20 early (<12 months) poor-prognosis RA
- Randomized, double-blind controlled trial: Mtx+Plac vs Mtx+Irx
- At 1 year, better MRI scores with no new erosions in Mtx+Irx
- At 2 yrs: **1 yr after stopping Irx, 70% of sustained response**

Is it possible to **retreat relapsing patients** after anti-TNF discontinuation?

# Retreatment in patients relapsing after Infliximab discontinuation

## *Preliminary experiences*

Disease	Treatment	Treat. duration (months)	Drug holiday (months)	ATI	response	Infusion reaction
<b>AS</b> (n=40)	lfx	36	6	1/40	<b>37/40</b>	0/40
<b>RA</b> (n=15)	lfx/Ada/Eta	19.2	4	-	<b>13/15</b>	0/15
<b>CD</b> (n=61)	lfx	Induction (X3)	9	-	<b>49/61</b>	7/61
<b>CD</b> (n=29)	lfx	Induction (X3)	> 4	-	<b>25/29</b>	5/29

Baraliakos et al. *J Rheumatol* 2007;34:510. Brocq et al. *Joint Bone Spine* 2009;76:350.

Laharie et al. *Aliment Pharmacol Ther* 2009;29:1240. Domènech et al. *J Clin Gastroenterol* 2010;44:34.

# Retreatment in patients relapsing after Infliximab discontinuation

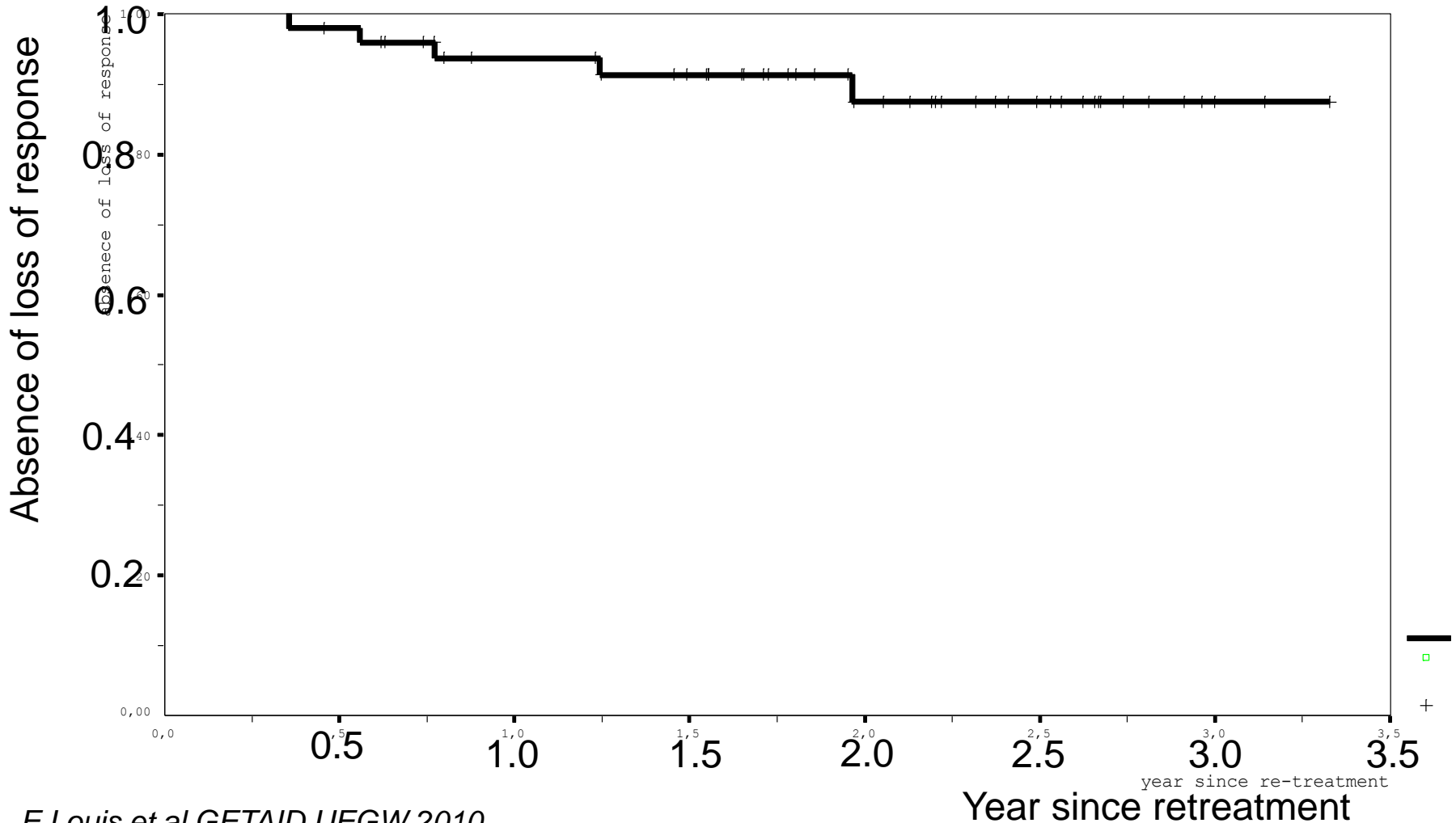
The STORI trial, median time to retreatment=6.6 months (IQR=4.0-10.8)

	<b>1 month</b>	<b>4 months</b>
<b>Remission rate</b>	37/40 (93%) 46/51* (90%)	38/43 (88%) 41/47** (87%)
<b>Response rate</b>	39/40	42/43
<b>Infusion reaction</b>	0/52	0/46

\* Including 11 patients assessed before 20 days or after 40 days (2 not in remission, 9 in remission); excluding 1 patient with rapid consent withdrawal, after 1st infusion.

\*\* Including 4 patients (2 without CDAI evaluation , 1 in remission before, 1 not ; 2 in remission before) ; excluding 4 patients withdrawn around 40 days, all in remission (1 pregnancy, 2 investigator decision, 1 consent withdrawal), 1 patient with rapid consent withdrawal.

# Kaplan Meier **loss of response** over time in infliximab retreated patients in STORI $12 \pm 5\%$ at 2 years



# Conclusions

- Immunosuppressant and/or anti-TNF **withdrawal** is associated with an **increased risk of relapse**
- The risk of relapse is **lower** in patients with **biological and/or endoscopic remission**
- In **combined therapy**,
  - the clinical benefit of a prolonged use of immunosuppressant (>6 months) is not demonstrated
  - For direct cost savings, anti-TNF withdrawal may be considered after 1 year of combined therapy in case of stable steroid-free remission and absence of biological and endoscopic signs of activity
- **Retreatment** with IS and/or anti-TNF is usually effective and well tolerated