Stopping Biologics: A North American Perspective?

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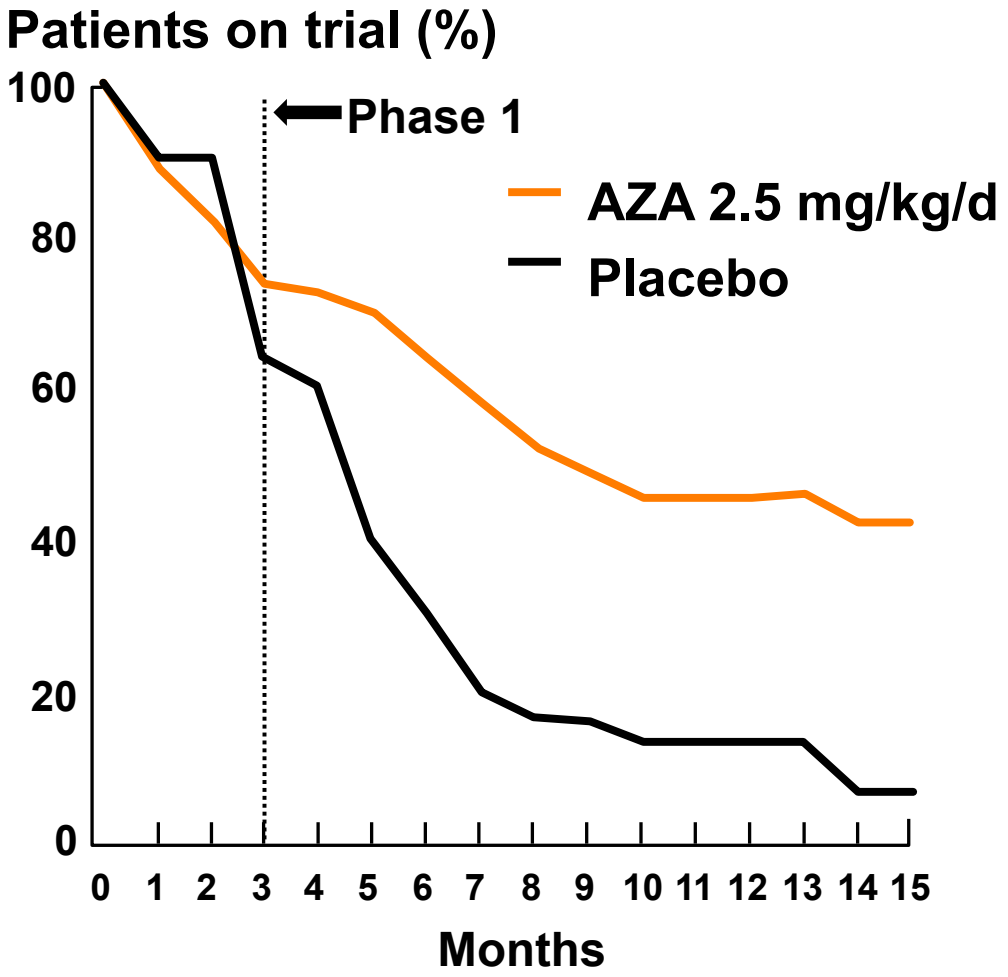
Topics Covered

- The value of combination therapy
- Stopping therapy: Pros vs Cons
- Lessons from RA
- Lessons from CD
- STORI
- Safety considerations
- What do I do in clinical practice?

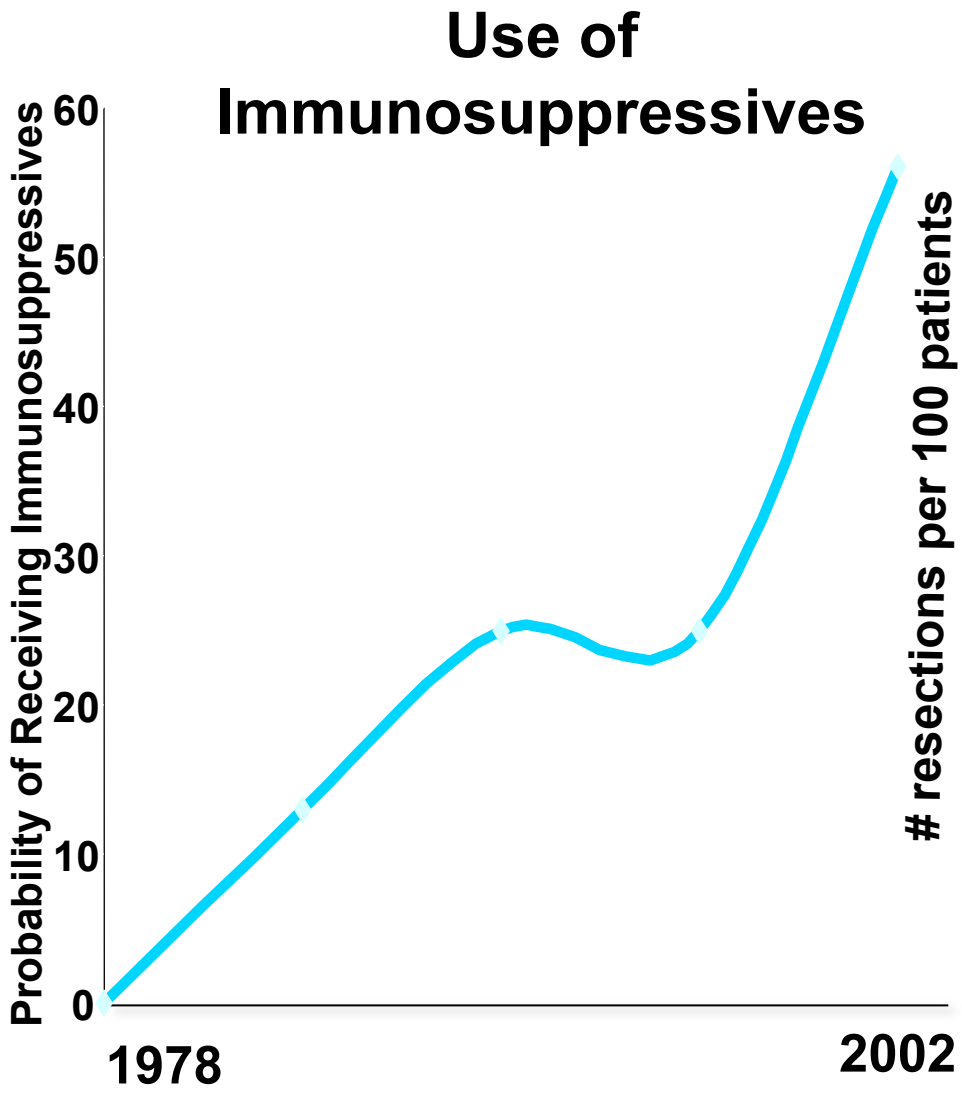
Azathioprine Maintenance Therapy After Corticosteroid-Induction in Crohn's Disease

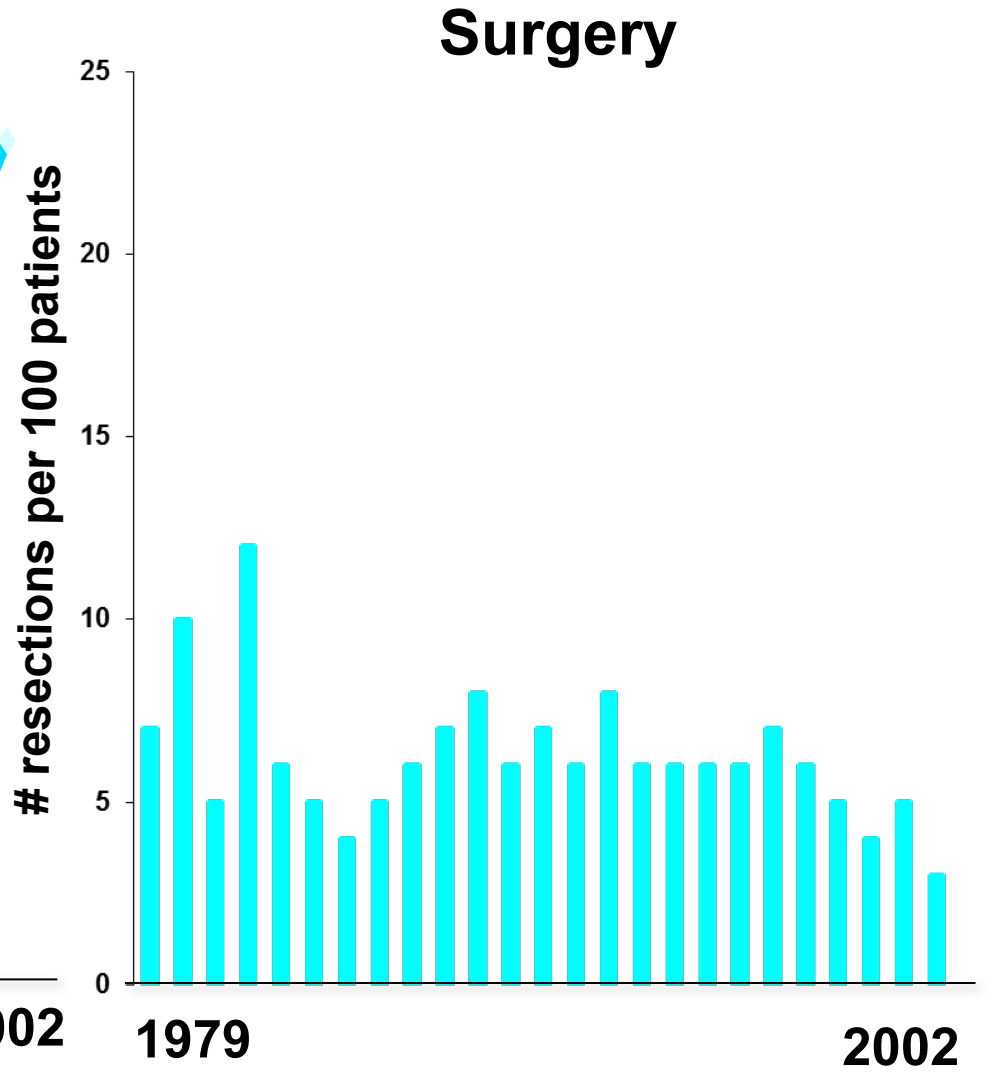
- Single center double-blind placebo controlled trial, n=63
  - Phase 1: combined effect of prednisolone plus AZA *vs* placebo over 12 weeks
  - Phase 2: following completion of phase 1, compared AZA *vs* placebo over 12 months



Candy et al. Gut 1995;37:674

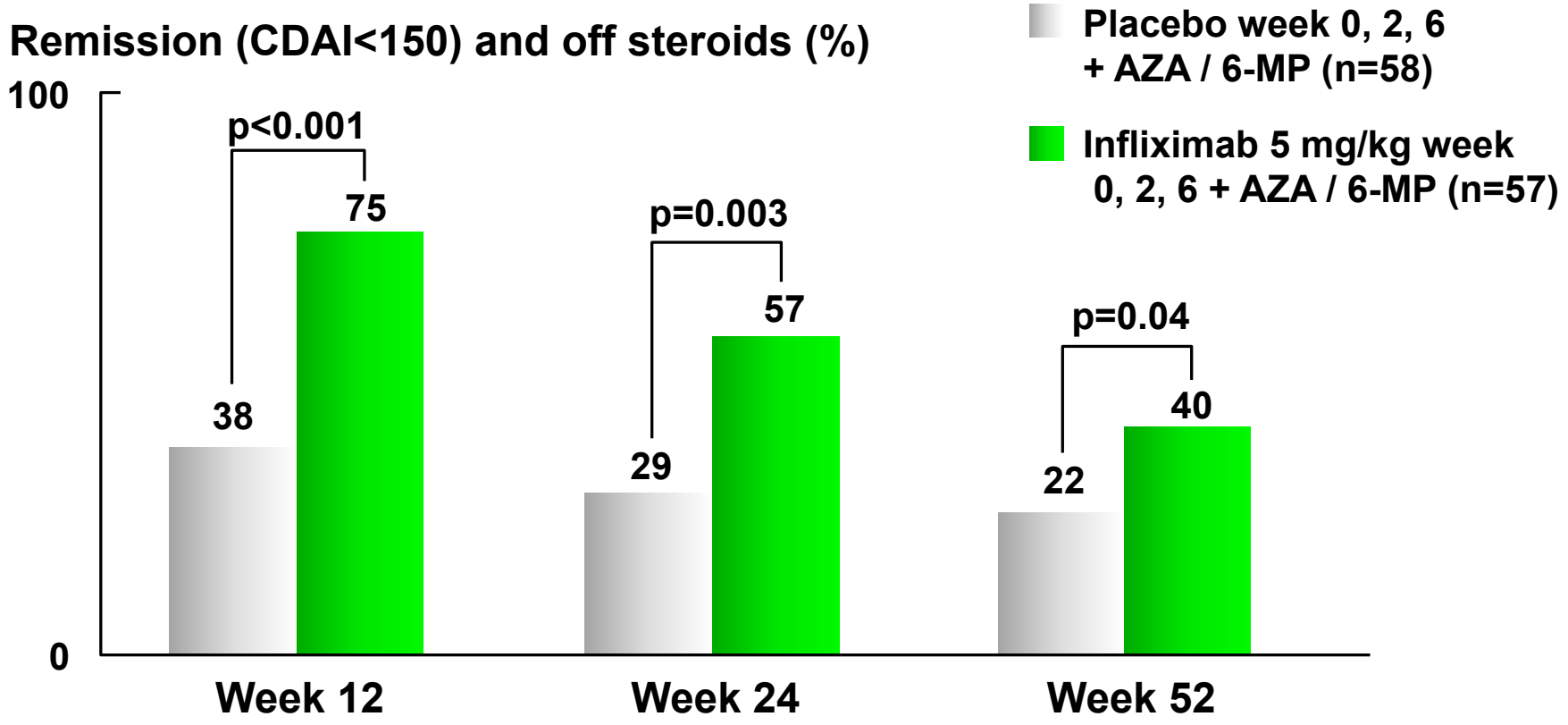
Surgery Rates for CD and the Use of Immunosuppressives over 3 Decades





Cosnes J. et al. Gut 2005:54(2):237-241

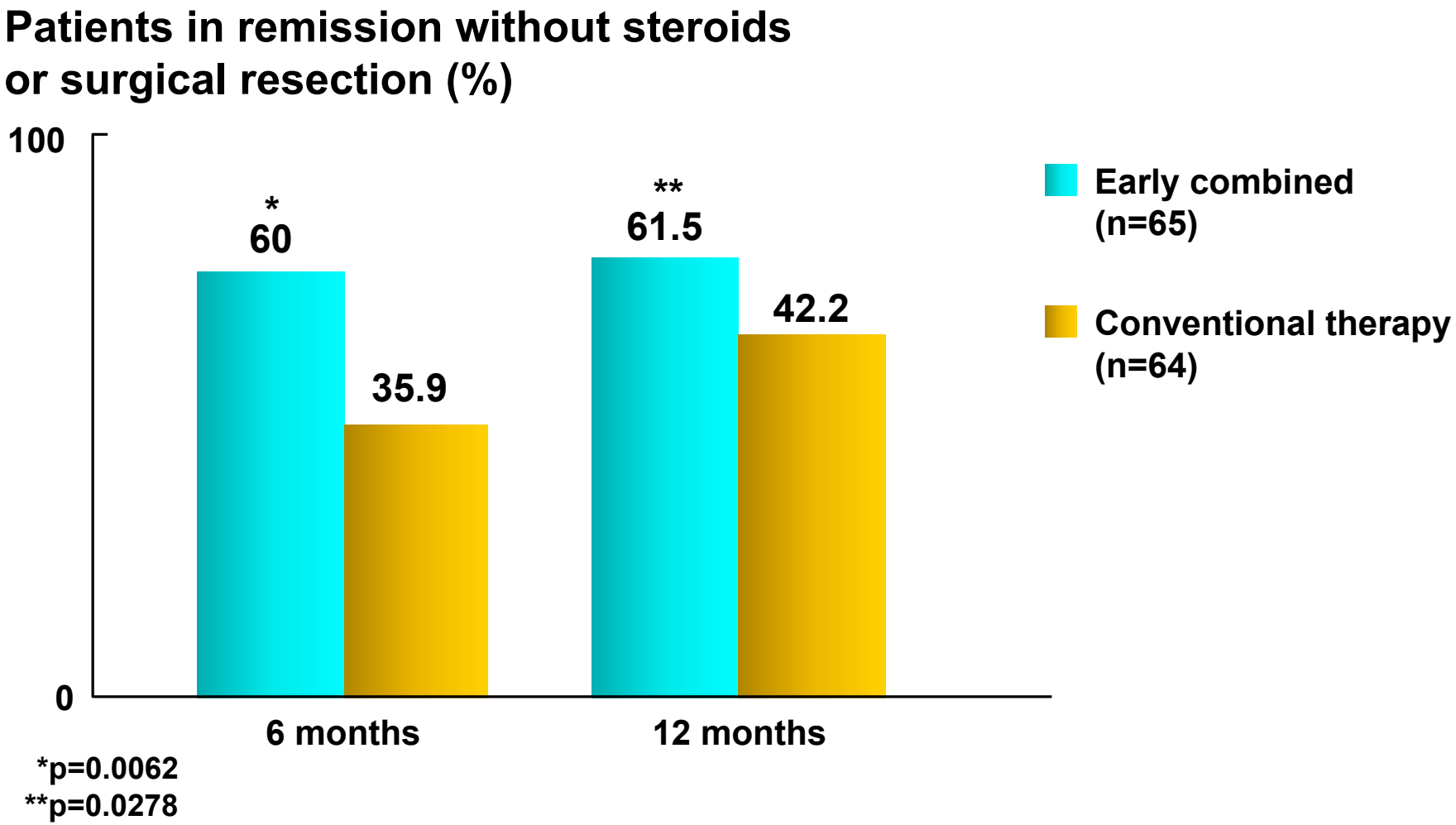
Azathioprine Monotherapy *vs* Infliximab Plus Azathioprine in Steroid-Dependent Crohn's Disease



AZA = Azathioprine
6-MP = 6-Mercaptopurine

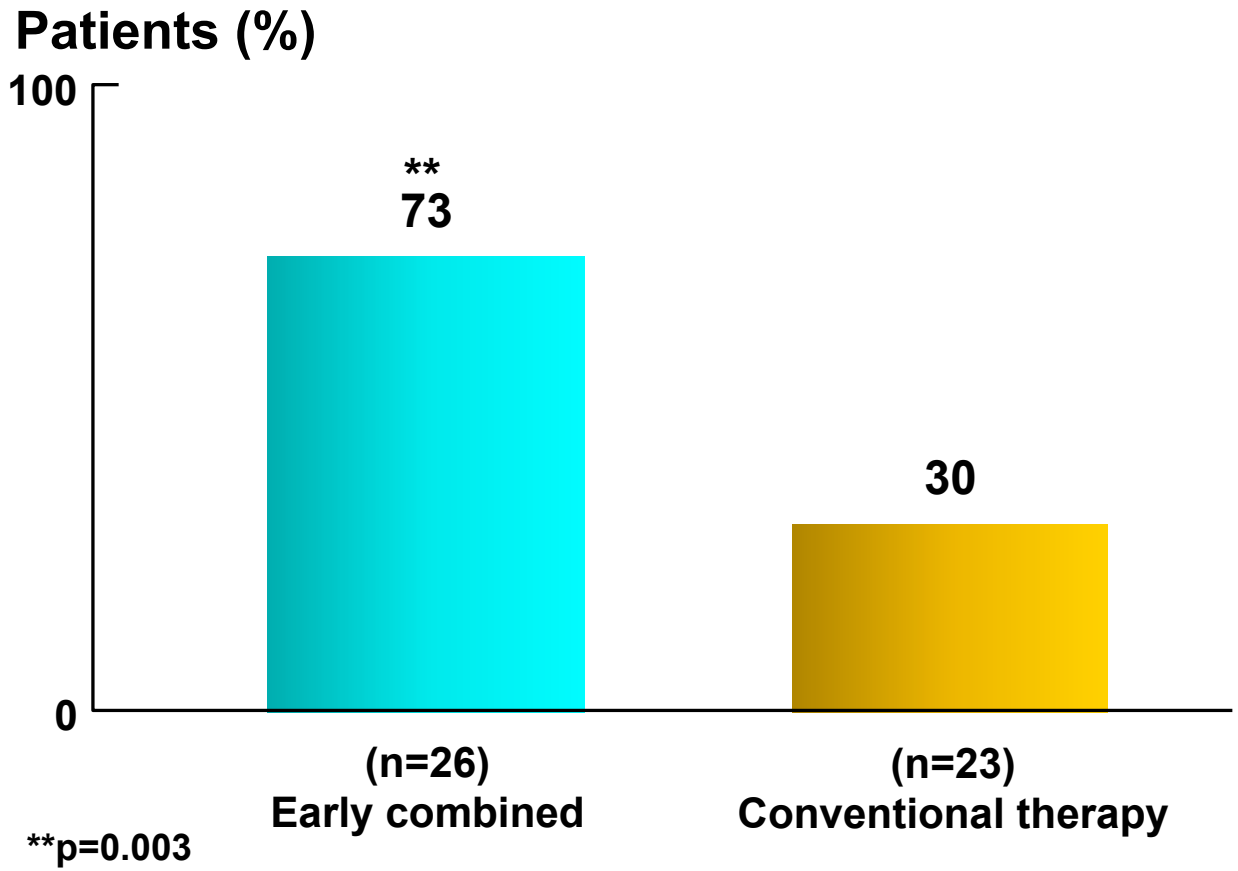
Lemann et al. Gastroenterology 2006;130:1054

Early Combination Therapy *vs* Conventional Management of Crohn's Disease



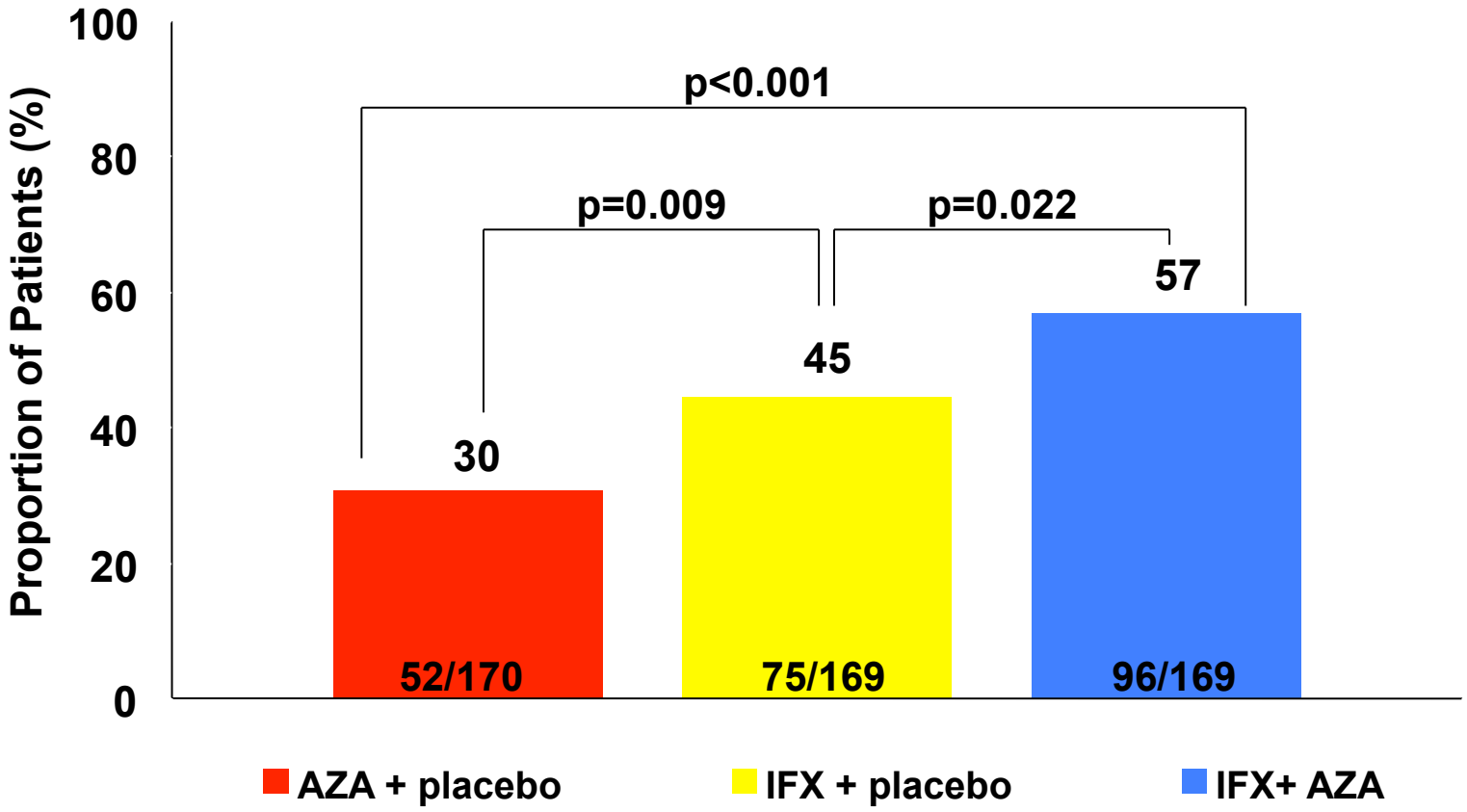
D'Haens et al. Lancet 2008:371:660

Early Combination Therapy *vs* Conventional Management of Crohn's Disease: Complete Ulcer Disappearance



D'Haens et al. Lancet 2008;371:660

SONIC: Clinical Remission Without Corticosteroids at Week 26



Colombel et al., New England J Med 2010

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Stopping Therapy: Pros

- May not be needed for long term efficacy
- Less toxic
- More convenient
- Less costly

Stopping Therapy: Cons

- **May be less effective**
- **Risk of sensitization**
- **May not necessarily be more safe**
- **May lose the opportunity to change the natural history of the disease**

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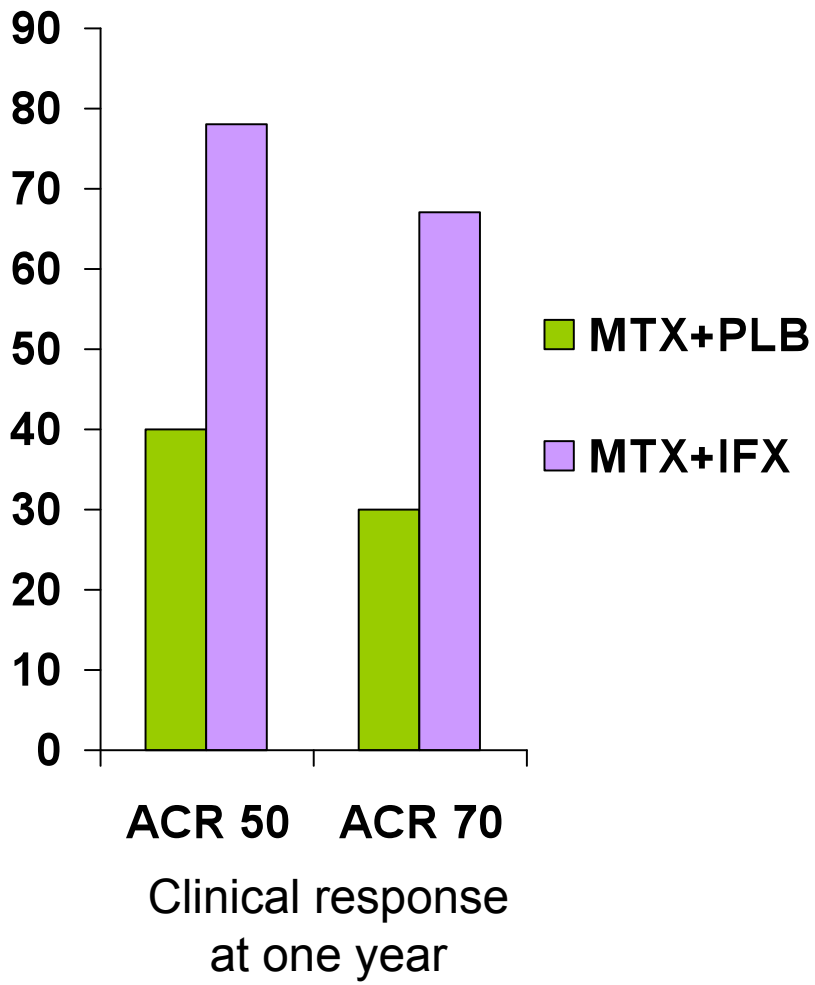
The Seductive Fantasy: Long Term Remission without Biologics in Early RA



Quinn et al. Arthritis Rheum 2005; 52: 27.

- 20 early (<12 months) poor-prognosis RA
- Randomized, double-blind controlled trial evaluating multiple regimens: MTX+PLB vs MTX+IFX – the Winner
- At 1 year, better MRI scores with no new erosions
- At 2 yrs: 1 yr after stopping IFX, 70% sustained response

The Reality (I)

- One half of patients who were carefully monitored by a treat-to-target approach required re-introduction of treatment
- Re-introduction was unsuccessful in ~ 25% of patients
- Risk of sensitization – limited number of biologic drugs
- Can I really risk stopping in my worst patients?

The Reality (II)

- Why should the disease go away?
- IBD results from environmental and genetic factors that you have not altered with short term therapy
- T lymphocytes are long-lived and pathogenic clones are not ablated with conventional treatments

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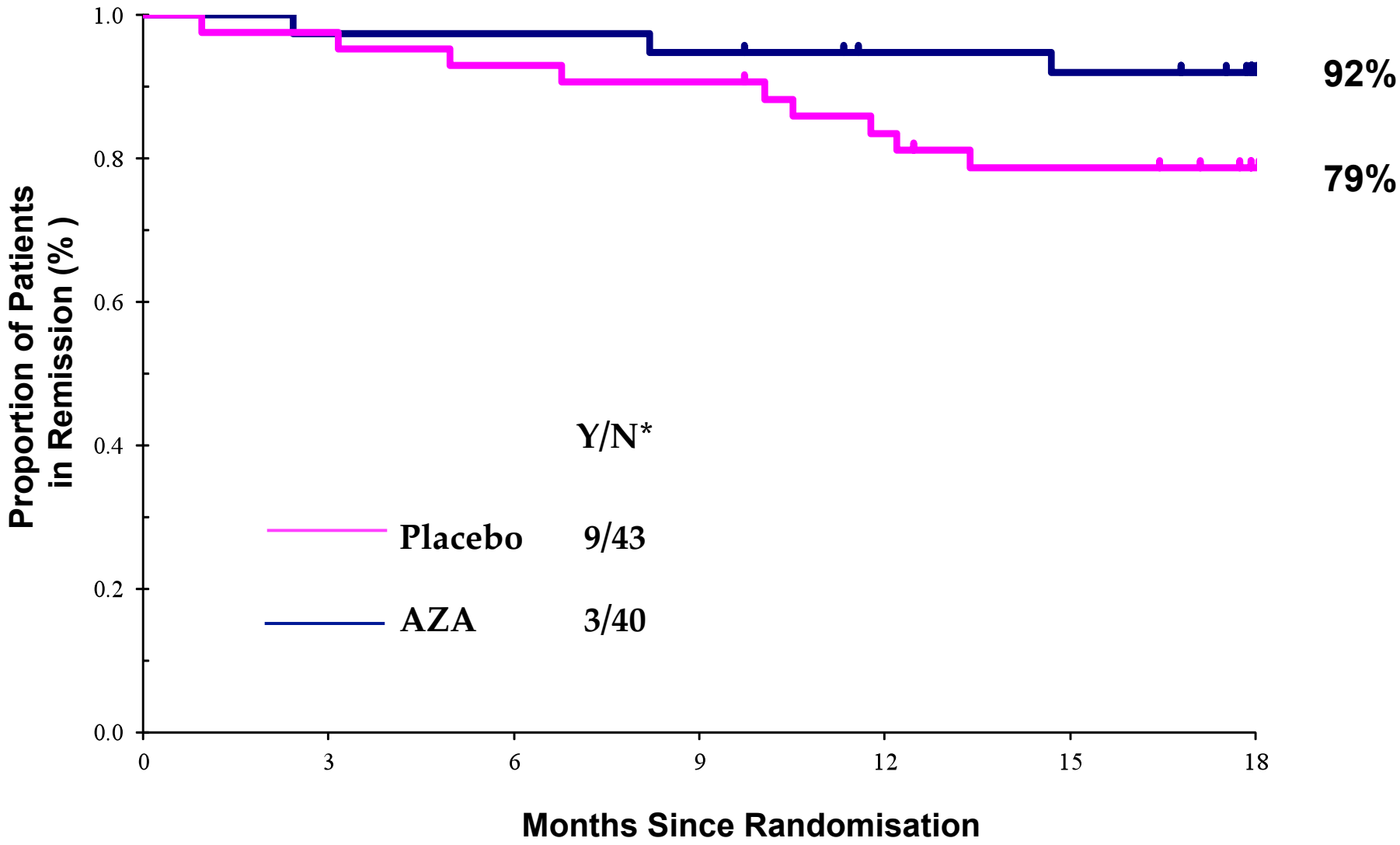
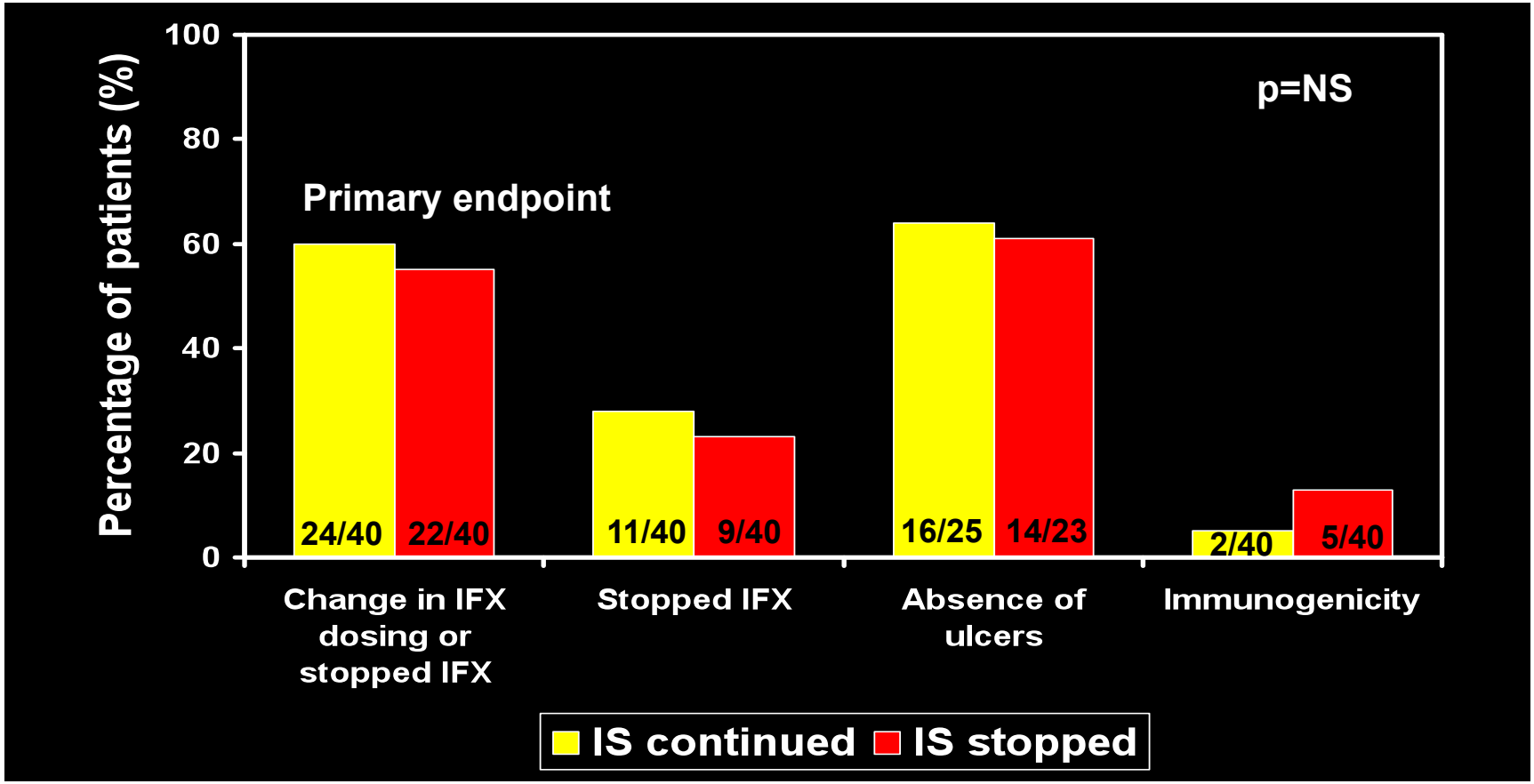
AZA Withdrawal



Lémann M et al. Gastroenterology 2005;128:1812

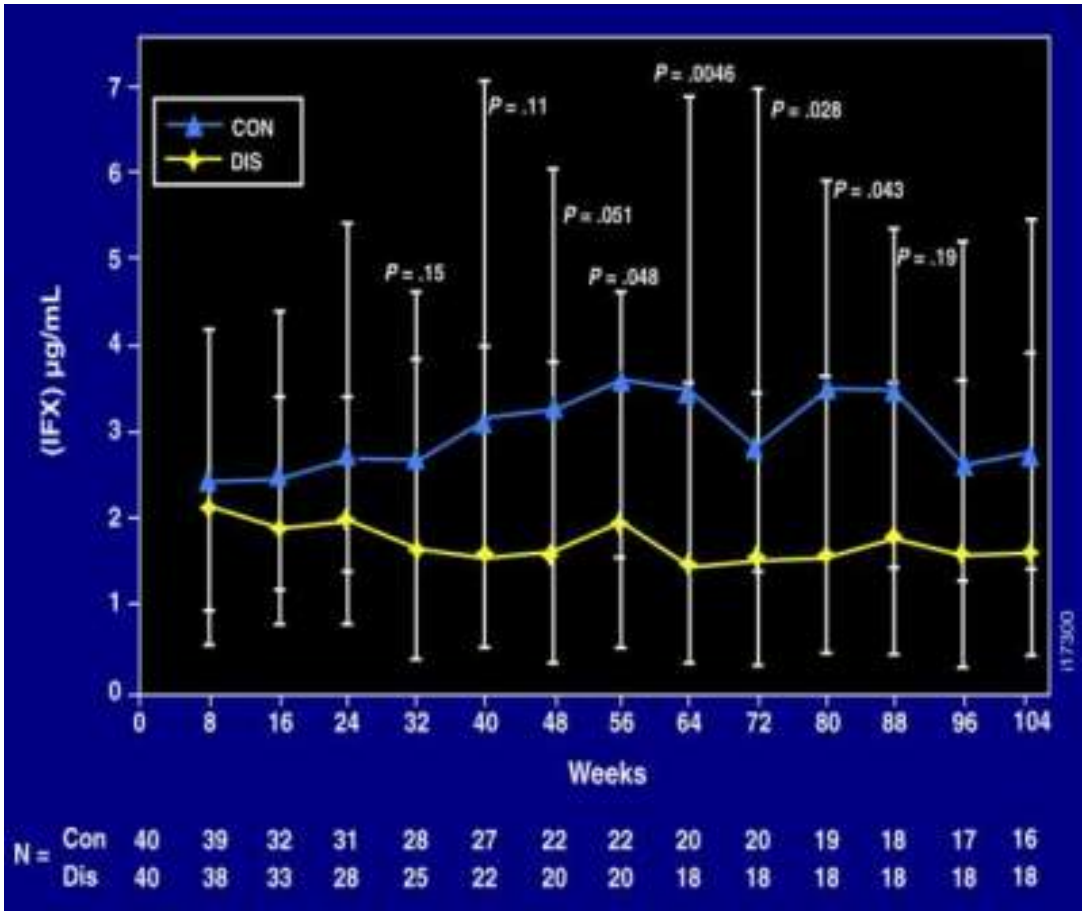
AZA Withdrawal in Patients Treated With Combination Therapy

- 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



Van Assche G et al. Gastroenterology 2008;134(7):1861-8

Potential for Loss of Efficacy



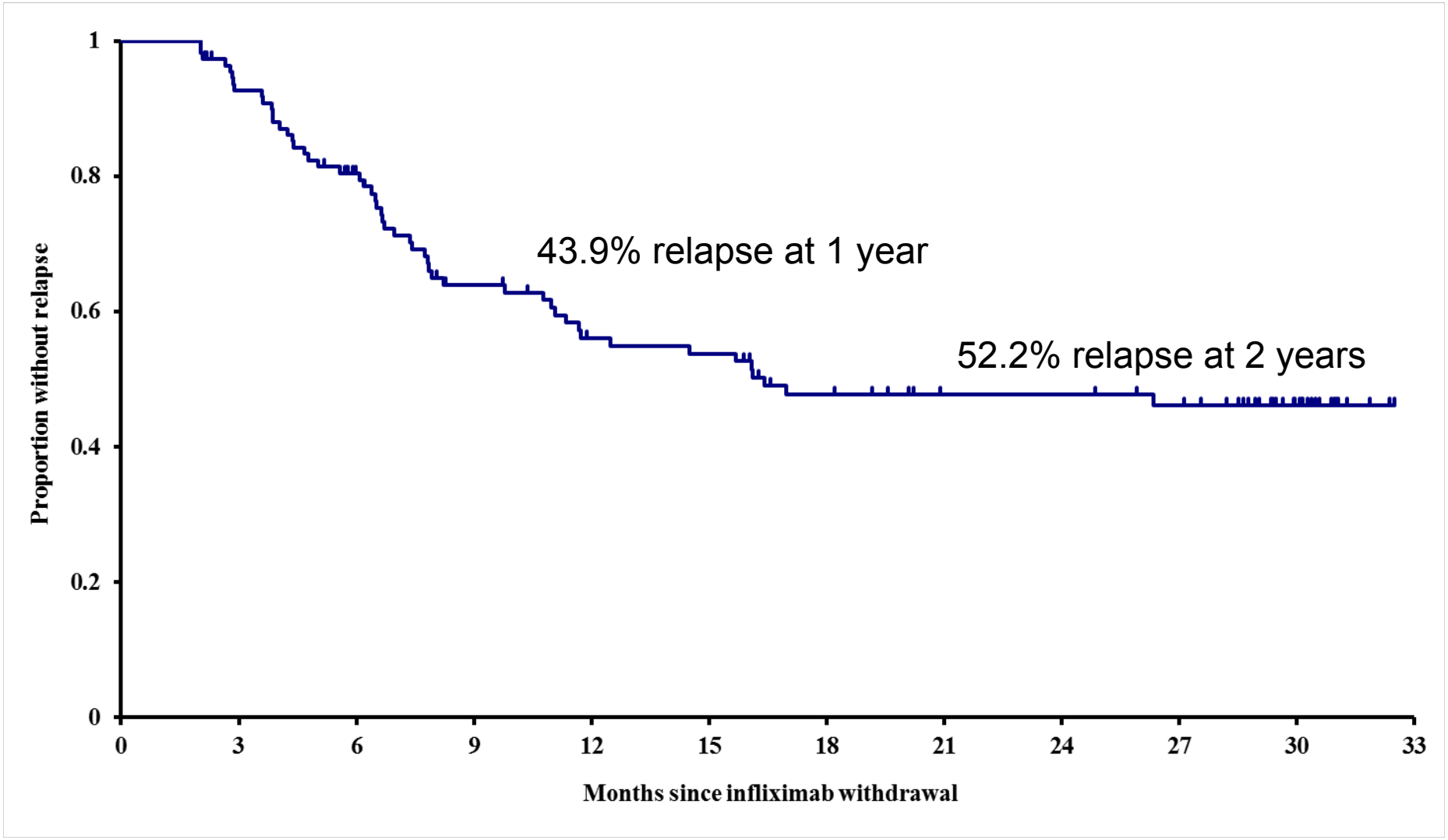
After IS withdrawal:

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)

Van Assche G et al. Gastroenterology 2008;134(7):1861-8.

Relapse Rate after Infliximab Discontinuation



Louis E et al. Gastroenterology. 2012 Jan;142(1):63-70

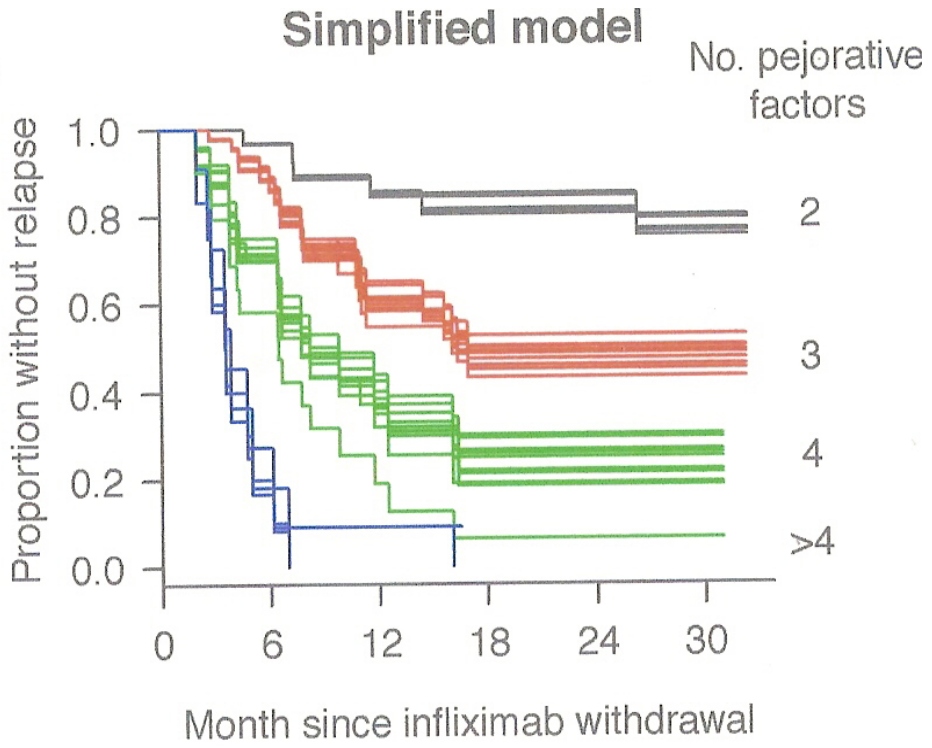
Predictors of Relapse

Clinical history and characteristics	P value	IFX frequency last 6 months	0.46
Age	0.63	Scores and biological variables	P value
Gender	0.22	CDAI >20	0.045
Disease duration	0.84	CDEIS ≥2	0.002
Current smoker	0.036	CDEIS >0	0.033
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	Fecal calprotectin ≥250 microg/g	0.0001
Stricture	0.13	CRP hs ≥5 mg/l	0.0006
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	Hemoglobin ≤14.5 g/dl	0.038
IFX scheduled from the start	1.00	6TGN	0.26

Louis E et al. Gastroenterology. 2012 Jan;142(1):63-70

Predictive Model for the Time-to Relapse: Risk Factors

Simplified Model: the same without steroid use, CDEIS and IFX trough levels



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The Bottom Line on STORI

"Currently there is no good medical reason to stop IFX in patients in stable remission"

E. Louis Principal Investigator STORI, BMJ 2012

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Serious Infection in IBD: The Role of Multidrug Therapy

- Causality difficult to establish
- Mayo Clinic case-control study of opportunistic infection:
  - any *vs* no drug — OR 2.6 (1.4–4.7)
  - infliximab — OR 4.4 (1.2–17.1)
  - corticosteroid — OR 3.4 (1.8–6.2)
  - azathioprine — OR 3.1 (1.7–5.5)
  - 2 drugs — OR 12.9 (4.5–37)
  - 3 drugs — OR- infinite

Toruner et al. Gastroenterology 2008 Apr;134(4):929-36

Summary of Adverse Events Through Week 30

	AZA + placebo n=161	IFX + placebo n=163	IFX + AZA n=179	Total n=503
Mean weeks of treatment	21.1	24.1	24.8	23.4
Subjects with ≥ 1 AE, n (%)	138 (85.7%)	135 (85.3%)	156 (87.2%)	433 (86.1%)
Subjects who d/c study agent due to an AE, n (%)	37 (23%)	19 (11.7%)	25 (14.0%)	81 (16.1%)
Subjects with ≥ 1 SAE, n (%)	39 (24.2%)	26 (16.0%)	25 (14.0%)	90 (17.9%)
Subjects with ≥ 1 infection, n (%)	60 (37.3%)	58 (35.6%)	66 (36.9%)	184 (36.6%)
Subjects with ≥ 1 serious infection, n (%)	8 (5.0%)	4 (2.5%)	6 (3.4%)	18 (3.6%)
Subjects with ≥ 1 infusion rxn, n (%)	8 (5.0%)	22 (13.5%)	9 (5.0%)	39 (7.8%)

Sandborn et al., ACG 2008 annual meeting, abstract #29

Safety Data From the TREAT Registry

Cox proportional hazard regression (multivariate)

Adverse event	Hazard ratio	95% CI
Death		
Current use of IFX	1.1	0.6–1.8
Current use of AZA/6-MP/MTX	0.8	0.5–1.2
Current use of GCS	2.0	1.3–3.0*
Current use of narcotic analgesics	2.1	1.3–3.2†
Serious infection		
Current use of IFX	1.4	1.0–2.1
Current use of AZA/6-MP/MTX	0.9	0.6–1.3
Current use of GCS	2.0	1.4–2.9**
Current use of narcotic analgesics	2.2	1.5–3.1†

*p=0.002; **p<0.001; †p<0.0001

6-MP = 6-mercaptopurine; AZA = azathioprine; CI = confidence interval; GCS = glucocorticoid steroids; IFX = infliximab; MTX = methotrexate

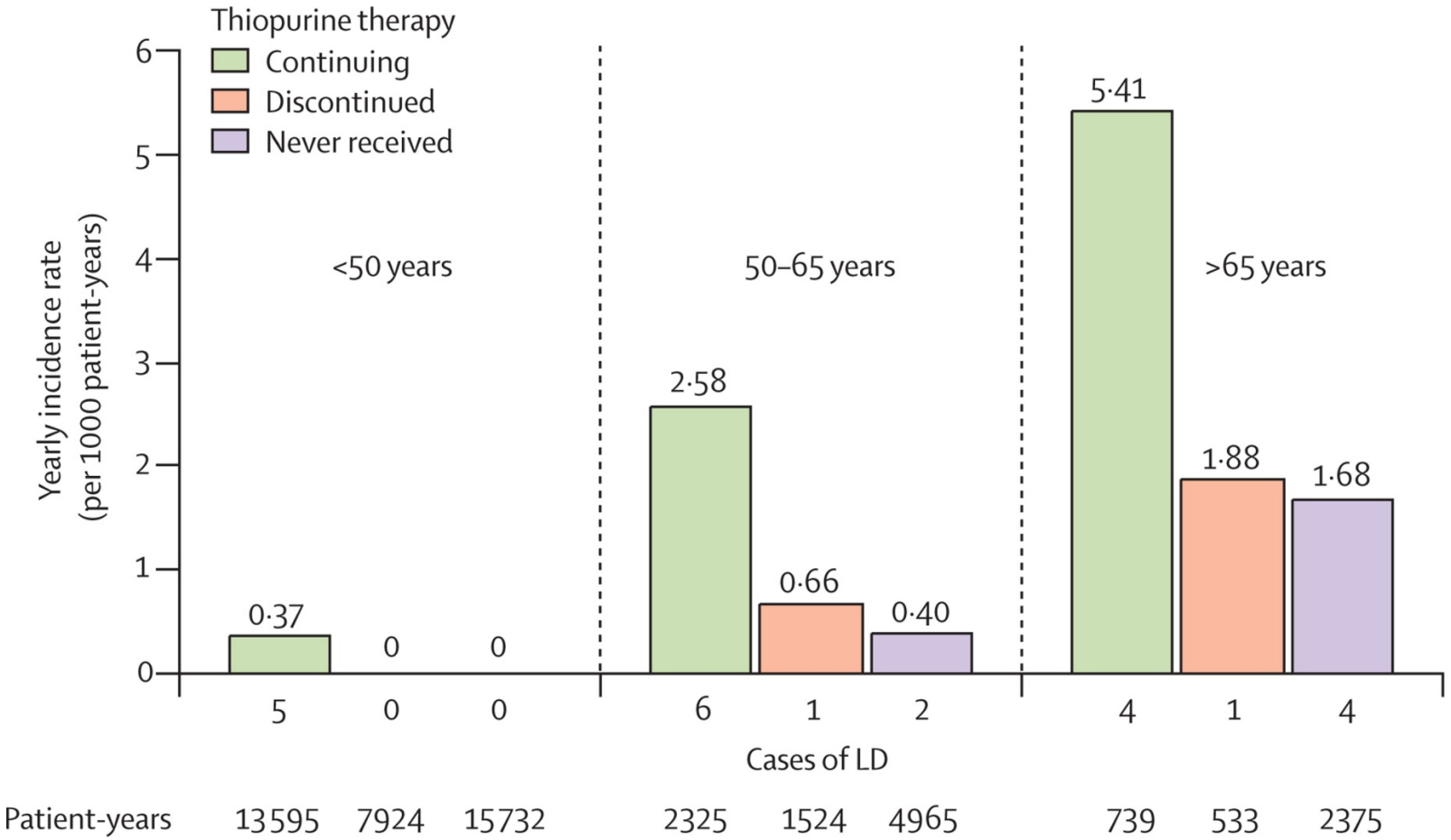
Lichtenstein et al. Gastroenterology 2006;130:A-71
Lichtenstein et al. Gastroenterology 2007;132: A-178

A Pooled Analysis: RCTs of Infliximab in IBD

	Crohn's Disease		Ulcerative Colitis		All Inflammatory Bowel Diseases	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
No. (%) pts with serious infection	9 (5.6%)	55 (4.5%)	6 (2.4%)	26 (5.4%)	15 (3.7%)	81 (4.7%)
Incidence per 100 pt-yrs	8.3	7.63	2.87	5.05	4.72	6.54
95% CI	(3.80,15.76)	(6.10,9.43)	(1.05,6.24)	(3.64,6.83)	(2.64,7.78)	(5.45,7.77)
P-value	0.547		0.085		0.427	

Lichtenstein GR. Am J Gastroenterology. 2012;107(7):1051-63

Lymphoma Risk with Thiopurines: CESAME



n =19486 exposed: 30%+14.5%

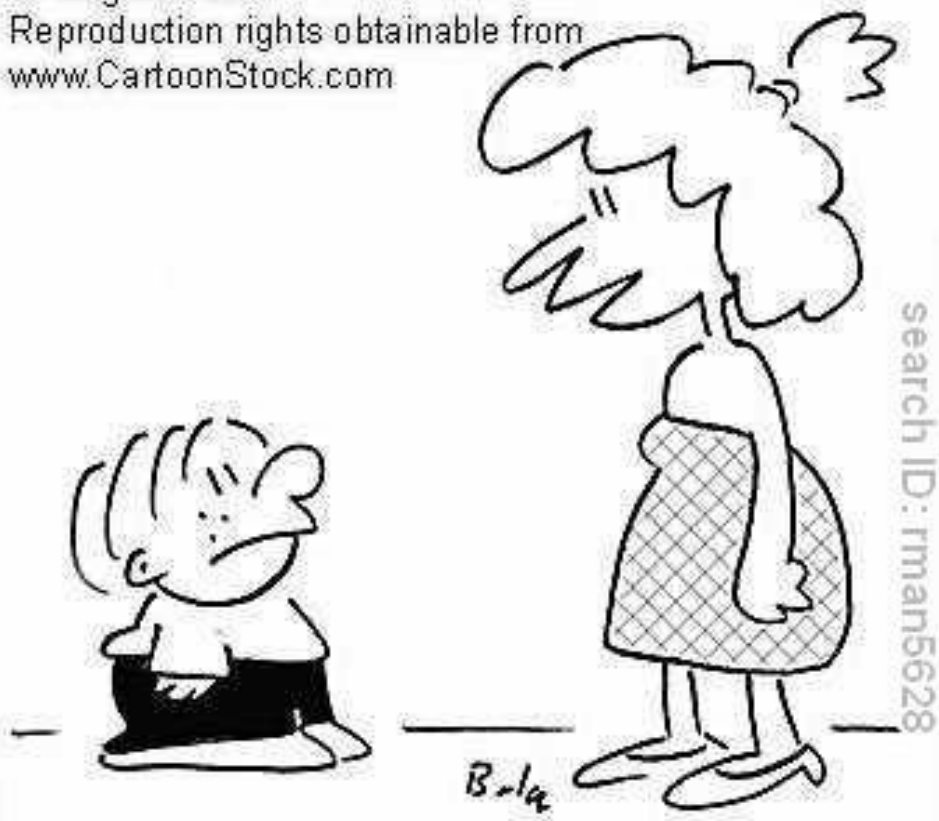
23 incident lymphomas

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

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

Conclusions

- **Discontinuation of our most effective therapy comes at a cost of relapse**
- **No high quality RCTs have examined this issue in CD!**
- **The therapeutic index of stopping is unknown**
- **What do I do in practice?**



"It's nice that you've learned to tie your shoes, but you're really too young to quit while you're ahead."