Οφέλη και Κίνδυνοι των Βιολογικών Θεραπειών

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IBD – Treatment goals

- IBD is a progressive disease that affects patients at a crucial time of their life
- Aim of treating a flare of IBD:
  - control symptoms and try to induce remission
- Aim of therapeutic strategy for IBD:
  - induce long-term control of the disease allowing the patient to lead a normal life

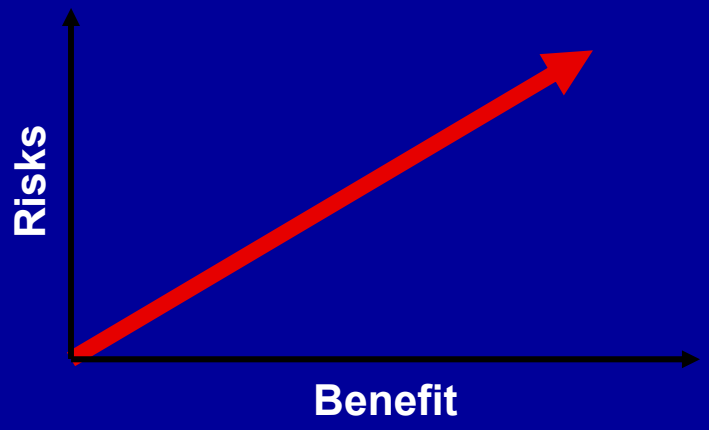
Treatment efficacy and therapeutic strategies

Drugs for IBD

- 5ASA
  - Sulfasalazine, mesalazine
- Probiotics
  - E Coli Nissle, VSL#3
- Antibiotics
  - Metronidazole, ciprofloxacin
- Steroids
  - Prednisolone, budesonide
- Immunosuppressants
  - Azathioprine / 6-MP, methotrexate, ciclosporin
- Anti-TNFs
  - Infliximab, adalimumab, certolizumab pegol

Definition of therapeutic strategies

- When to use a drug (timing, appropriate patient)
- Treatment duration
- Co-treatments
- Objectives of treatment
- Benefit-risk evaluation for various situations



Benefits –What do our patients need:

- Avoid recurrence of flares[1]
- Avoid development of stricturing and fistulising disease[2]
- Avoid development of disabling disease[3]
- Avoid development of severe disease[4]
- Avoid development of disease complications and surgery[5]
- Avoid issues of fertility[6]
- Avoid unemployment[7,8,9]
- Avoid mortality[10]

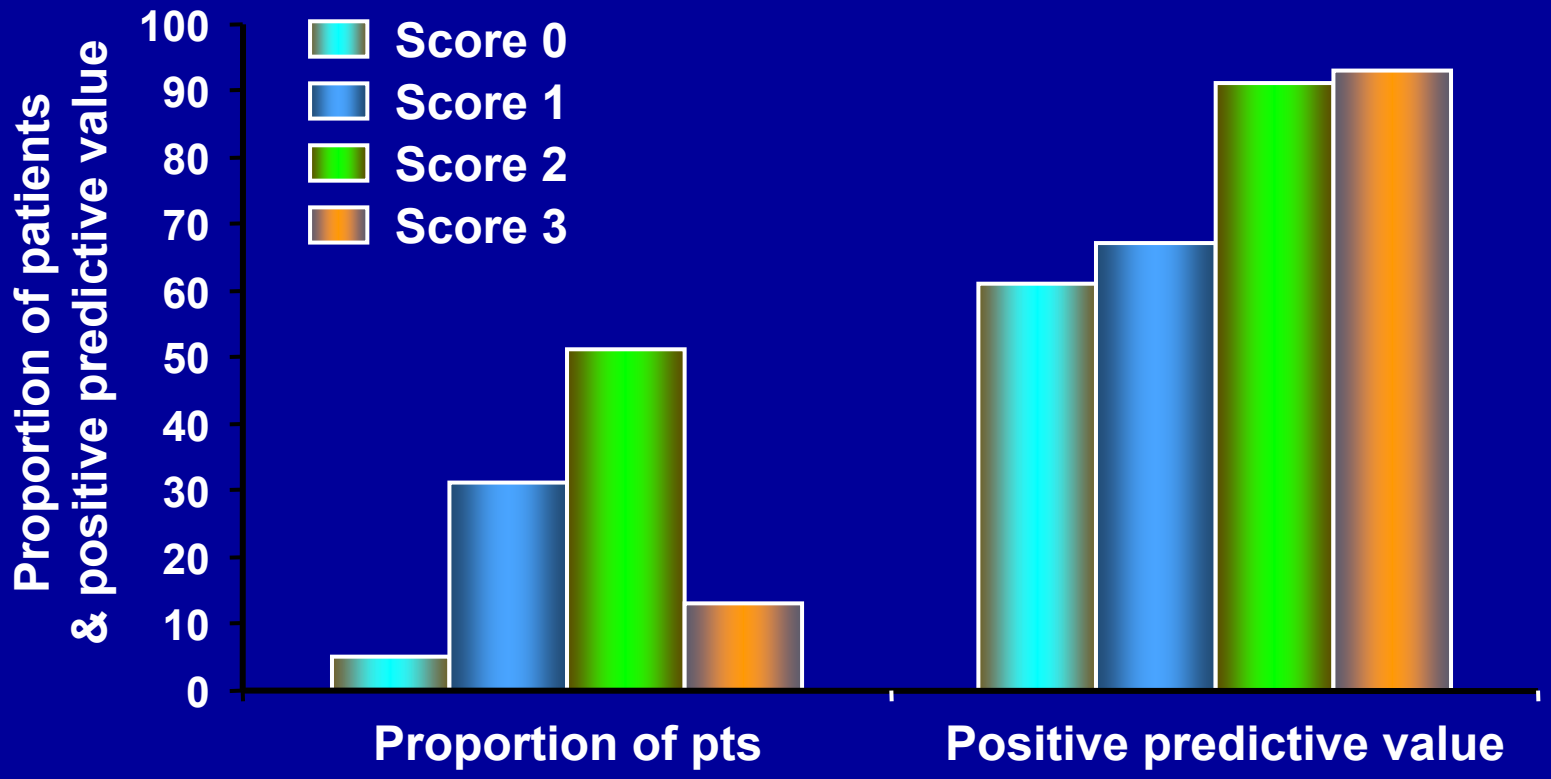
1. Wolters F, *et al. Gut* 2006;55:1124–1130; 2. Louis E, *et al. Gut* 2001;49:777–782;
3. Beaugerie L, *et al. Gastroenterol* 2006;130:650–656 4. Loly C, *et al. Scand J Gastroenterol* 2008;
5. Michener W, *et al. Cleve Clin Q* 1982 ;49:13–16; 6. Mayberry J, *et al. Gut* 1986;27:821–825;
7. Sorensen V, *et al. Gut* 1987;28:382–385; 8. Longobardi T, *et al. Am J Gastroenterol* 2003;98:844–849;
9. Longobardi T, *et al. Am J Gastroenterol* 2003;98:1064–1072; 10. Wolters F, *et al. Gut* 2006;55:510–518

General consideration

There are probably two types of mistakes in defining the treatment strategy for a CD patient:

- Undertreat a patient who will develop disabling, complicated or severe disease
- Overtreat a patient with a benign course of the disease

Predictors of disabling CD
Proportion of patients and positive predictive value of having a disabling CD in the 5-yr period after diagnosis

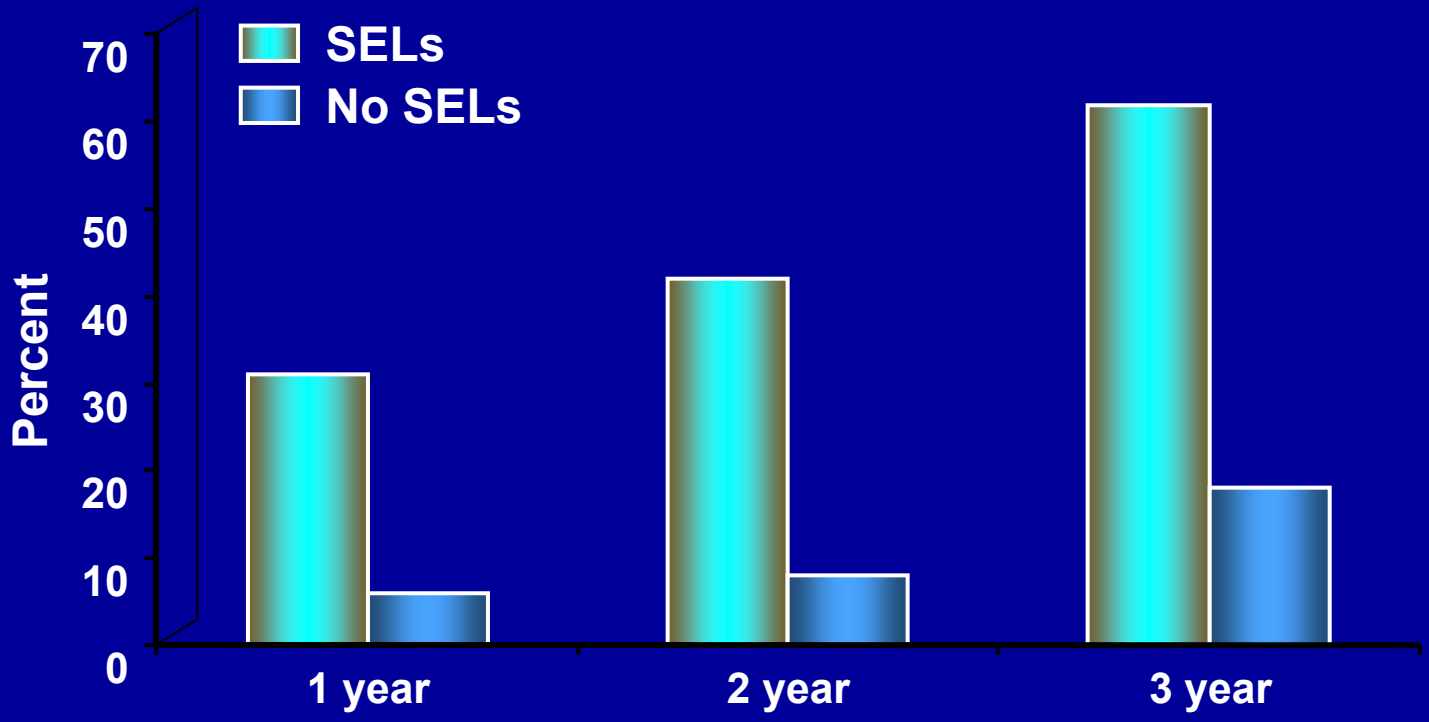


Score is based on the number of predictive factors at diagnosis: age <40, steroid treatment, perianal lesions

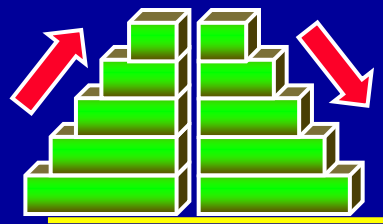
Beaugerie L, *et al. Gastroenterol* 2006;130

Deep colonic ulcers are risk factors for colectomy in CD

Probability of colectomy in patients with or without Severe Endoscopic Lesions (SELs) defined by deep ulcers covering >10% of at least 1 colonic segment

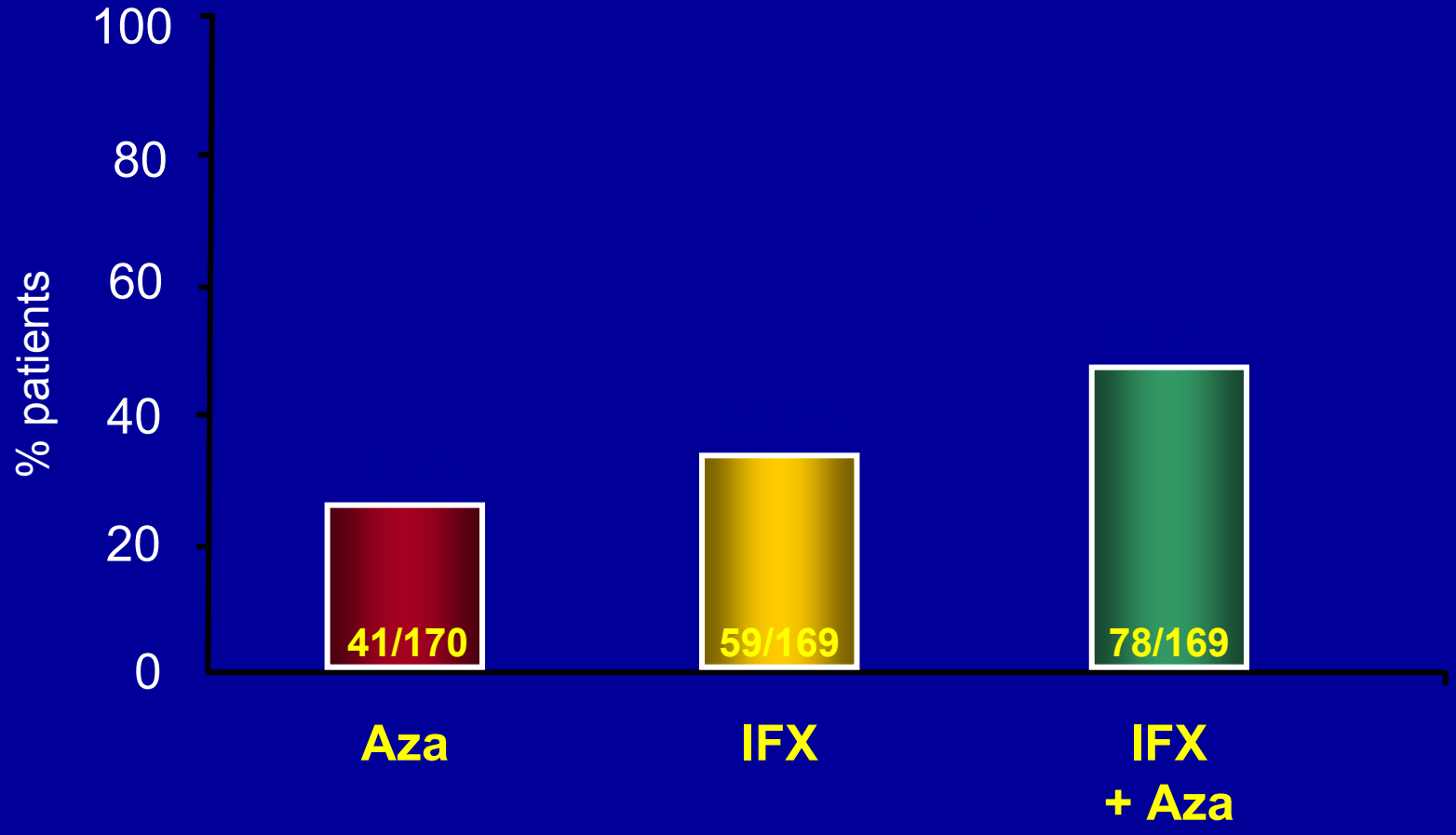


Allez M, *et al. Am J Gastroenterol* 2002;97:947–953

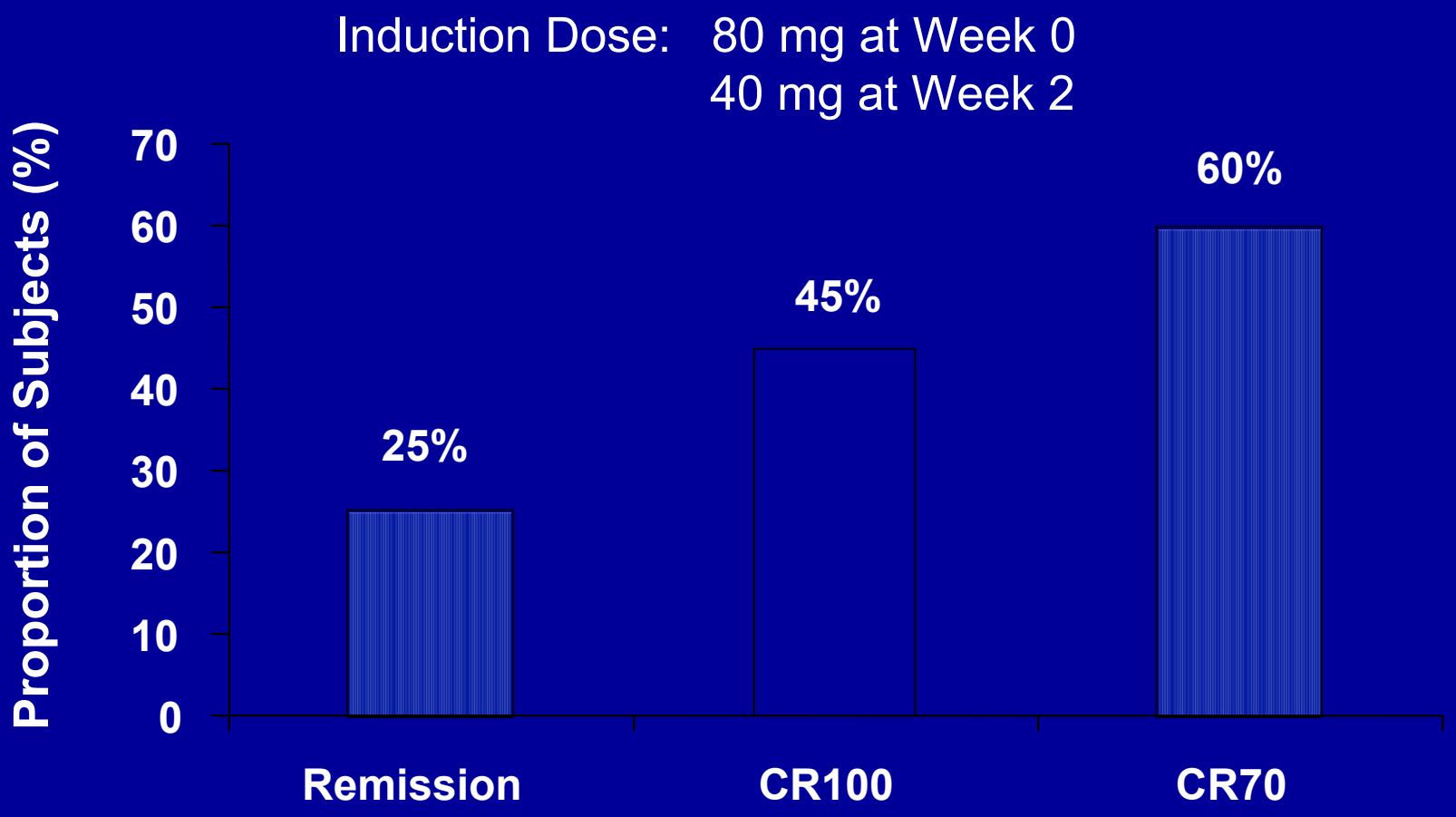


Step-up *vs.* Top-down
The SONIC trial

Steroid-free remission in week 50

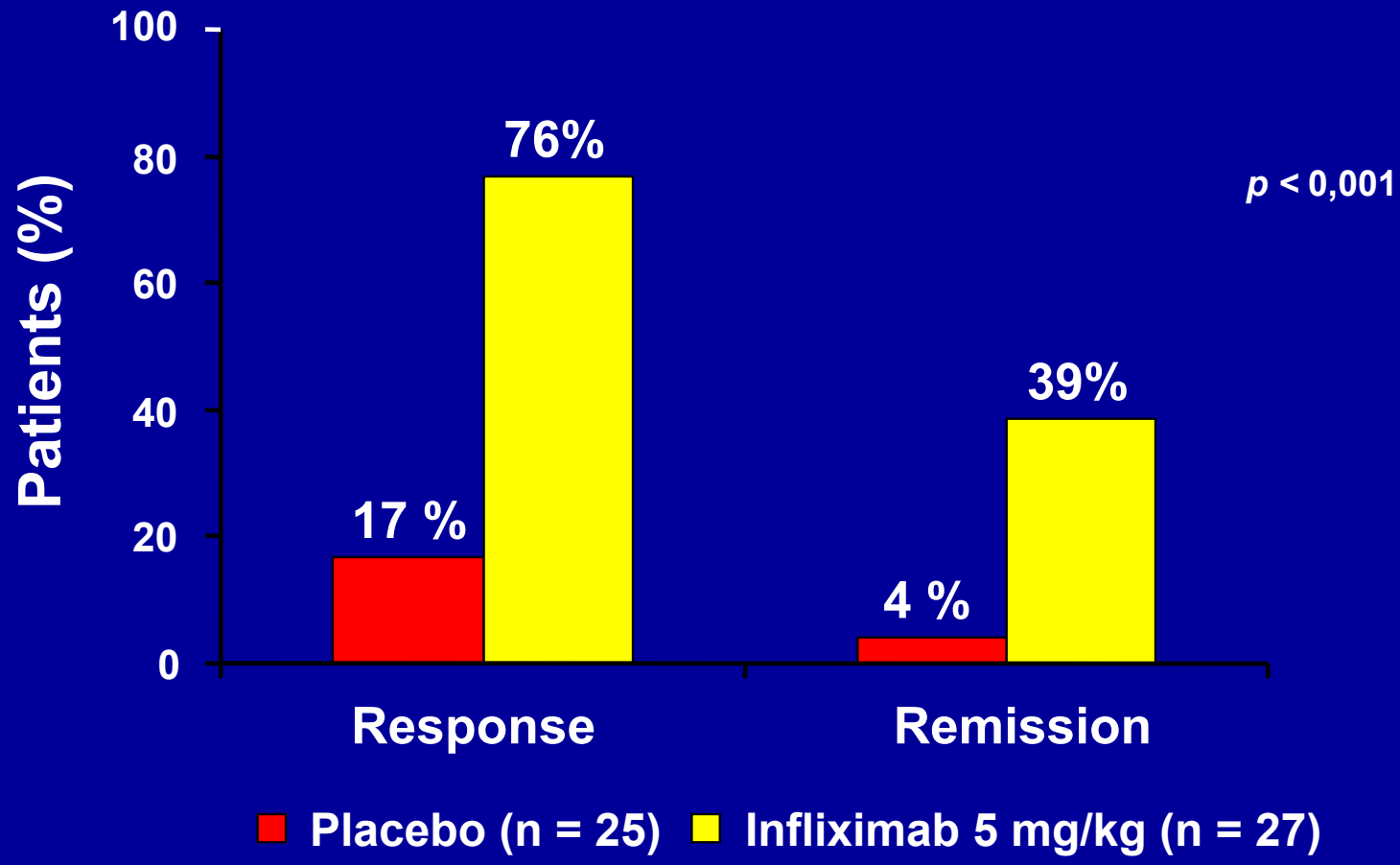


Clinical Responses to Adalimumab Induction (Week 4)



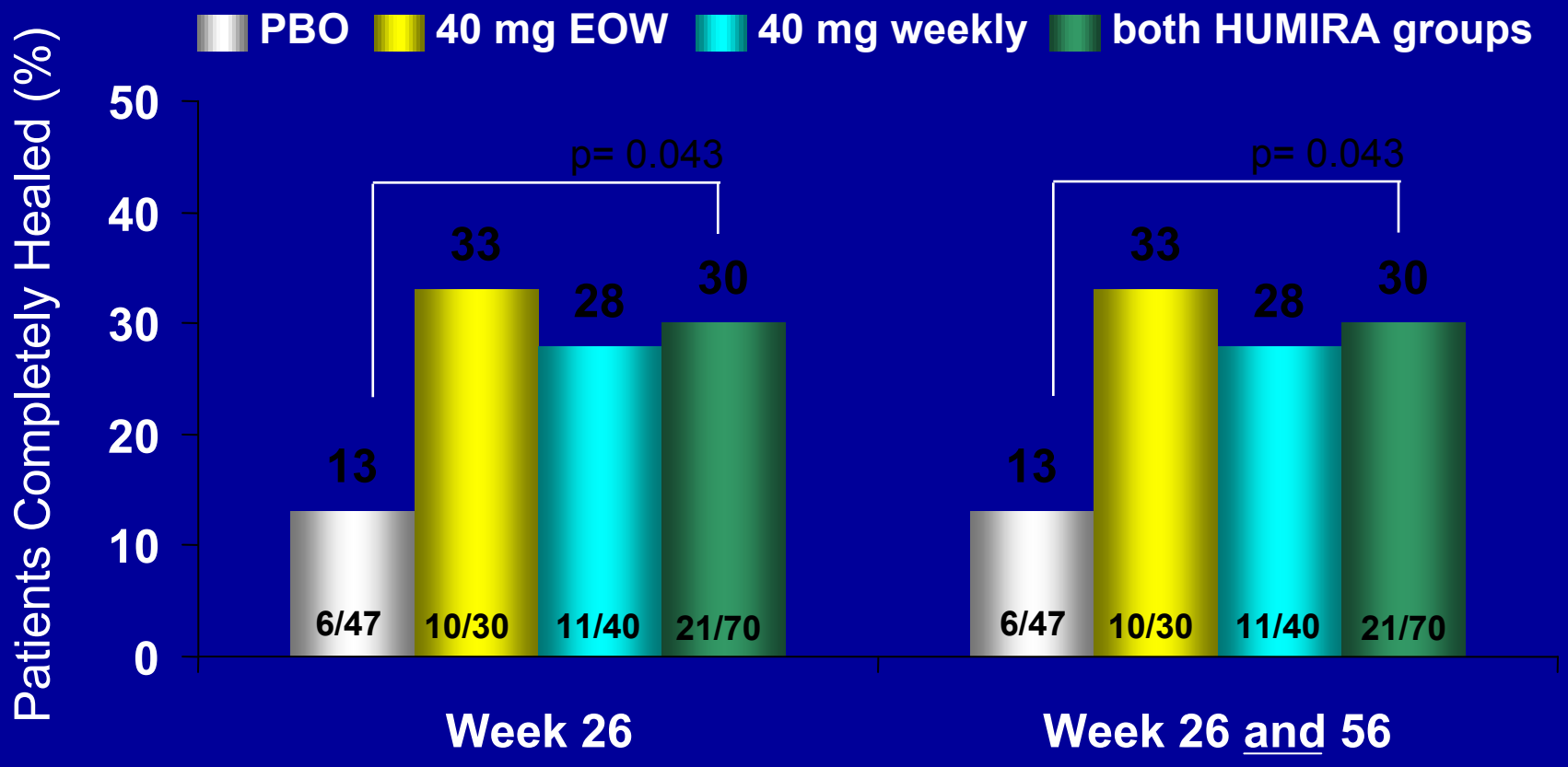
Colombel JF et al. T686d, DDW 2006

Clinical Responses to Infliximab Induction (Week 2)



Targan S *et al. N Engl J Med.* 1997;337:1029-1035.

Maintenance of Healing of Draining Fistulas



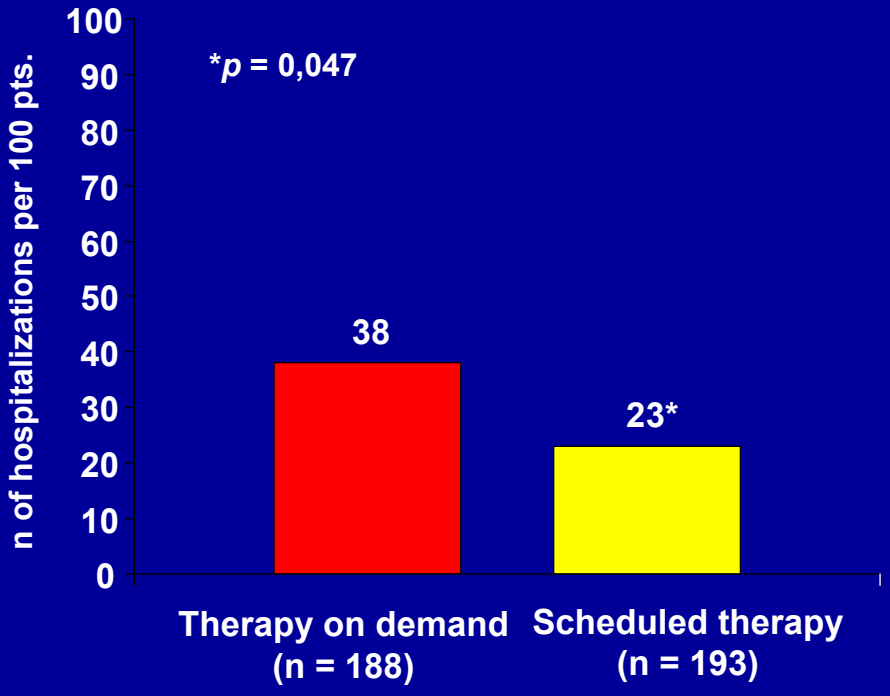
Healing = no draining fistulas

Patients with fistulas: draining fistulas at both screening and baseline

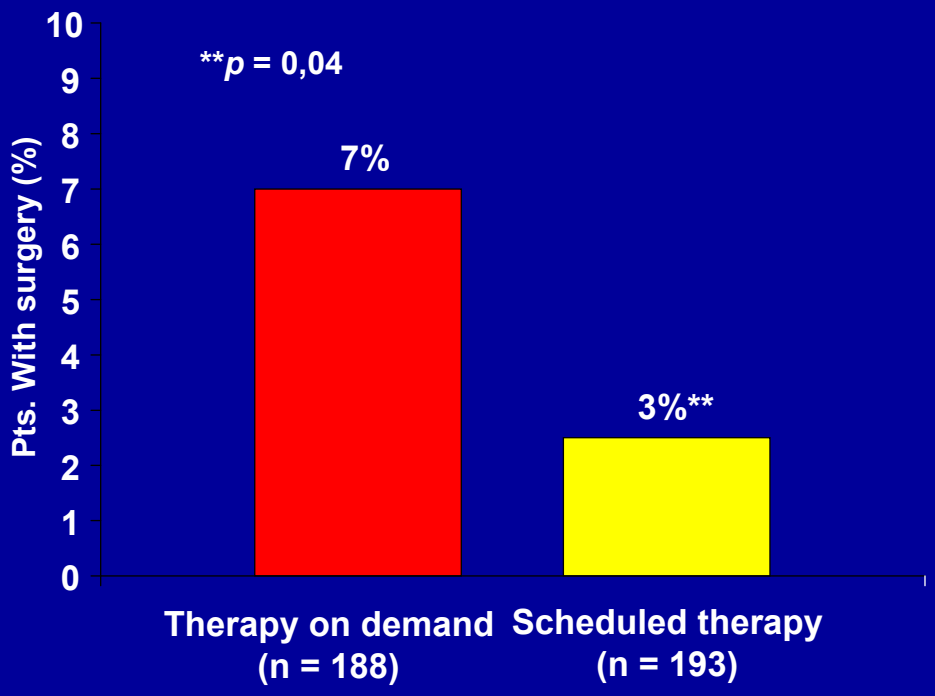
Colombel JF, et al. *Gastroenterol.* 2007;132 (1):52-65

Reduction of Hospitalizations and Surgeries in patients treated with anti TNF-α

Hospitalizations

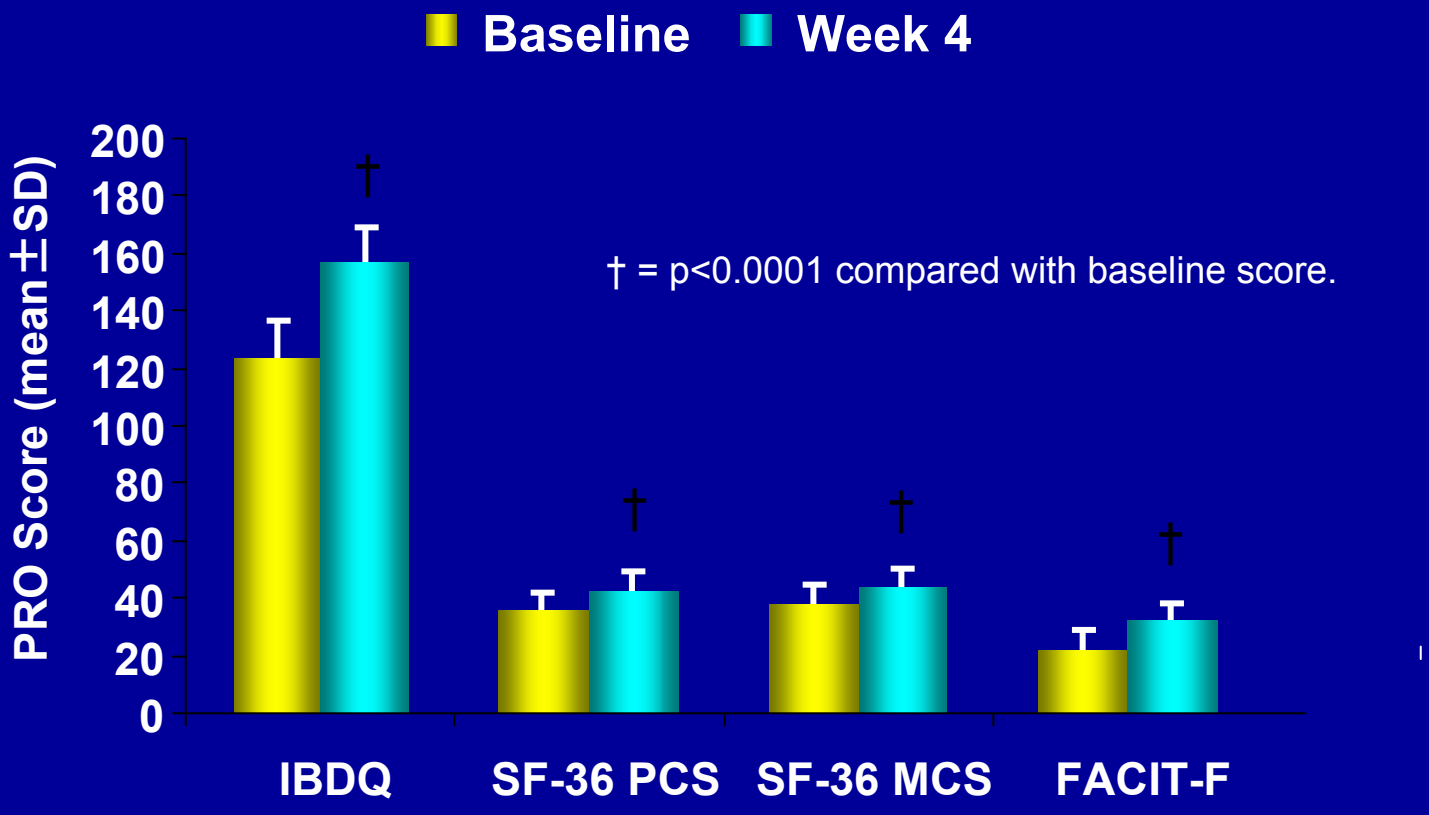


Surgery



Rutgeerts P, *Gastroenterology.* 2004

Health realted Quality of life at Baseline and Week 4 for the Intention-to-Treat Population (N=778)



Loftus, ACG 2008; UEGW 2008

Benefits and risks of biological therapy

So, obviously, there is a benefit in the treatment with biologicals, but

What are the risks?

Side-effects of anti-TNF agents

- Hypersensitivity reactions
  - infusion or injection site reactions
  - serum sickness / delayed hypersensitivity
- Immunogenicity
- Headache
- Rash
- Infections
  - mild and serious
- Demyelinating disorders
- Psoriasis
- Autoantibodies
- Pancytopenia
- Heart failure
- Hepatotoxicity
- Malignancy

Infliximab-associated side effects

- severe side effects: 30/500 (6%)
- acute infusion reaction: 19/500 (3,8%)
- serum disease: 14/500 (2,8%)
- drug-induced Lupus: 3/500 (0,6%)
- infections: 41/500 (8,2%)
  - 2 deadly septicaemiae
  - 8 pneumoniae
  - 6 viral infections
  - 2 abdominale abscesses
  - 1 erysipelas
  - 1 histoplasmosis
- Event of death: 5/500 (1%)
- potential Infliximab-assoziated malignancies: 3/500 (0,6%)

in 500 consecutive CD patients of the Mayo Clinic, Rochester, U.S.A.

Colombel, JF et al. *Gastroenterology* 2004;126:19-31

Adalimumab-associated side effects

AEs of interest	All CD Trials as of February 14, 2006; N=1459 1506.0 PY; E (E/100-PYs)	All CD Trials as of April 15, 2007; N=2228; 2373.7 PY; E (E/100-PYs)
Any AE	12,124 (805.0)	14,991 (631.1)
Any serious AE	487 (32.3)	712 (30.0)
Any AE leading to discontinuation	326 (21.6)	395 (16.6)
Infectious AE	2146 (142.5)	2821 (118.8)
Serious infections	90 (6.0)	123 (5.2)
Malignant neoplasms	17 (1.1)	31 (1.3)
Injection-site related AE	552 (36.7)	592 (24.9)
Opportunistic infections	32 (2.1)	43 (1.8)
Congestive heart failure	1 (<0.1)	1 (<0.1)
Demyelinating disease	2 (0.1)	4 (0.2)
Any fatal AE	1 (<0.1)	2 (0.1)

Colombel JF, et al., Gastroenterology 2008;134

How do you decide who gets early intensive treatment?

18 year old female

- New diagnosis
- Small bowel and perianal disease
- Postprandial abdominal cramping
- 3-4 loose stools/day
- Perianal fistula on exam

18 year old male

- New diagnosis
- Small bowel and colonic disease
- Postprandial abdominal cramping
- 8 diarrheal stools with blood/day

Factors to guide the decision

- Will treatment work?
- What are the risks of biologic therapy?
- Are two drugs better than one?
- Are two drugs riskier than one?
- Are patients willing to take these risks?
- Can we show patients who will benefit most from intensive therapy?

Risk of dying from sepsis with anti-TNFs: systematic review

Reference	Study Design	# Deaths from sepsis thought attributable to infliximab	# of Patients
Ljung *et al.* *Gut* 2004	Population Based Cohort	1	191
Seiderer *et al.* *Digestion* 2004	Single-Center Cohort	0	92
Colombel *et al.* *Gastroenterology* 2004	Single-Center Cohort	5	500
Sands *et al.* *NEJM* 2004	Randomised Controlled Trial	2	282
Hanauer *et al.* *Lancet* 2002	Randomised Controlled Trial	1	573
Rutgeerts *et al.* *Gastroenterology* 1999	Randomised Controlled Trial	0	73

Risk of death from sepsis = 4/1000 pt-yrs

Siegel *et al. Clin Gastroenterol Hepatol.* 2006;4:1017–1024.

Who are the patients who are most at risk for serious infections?

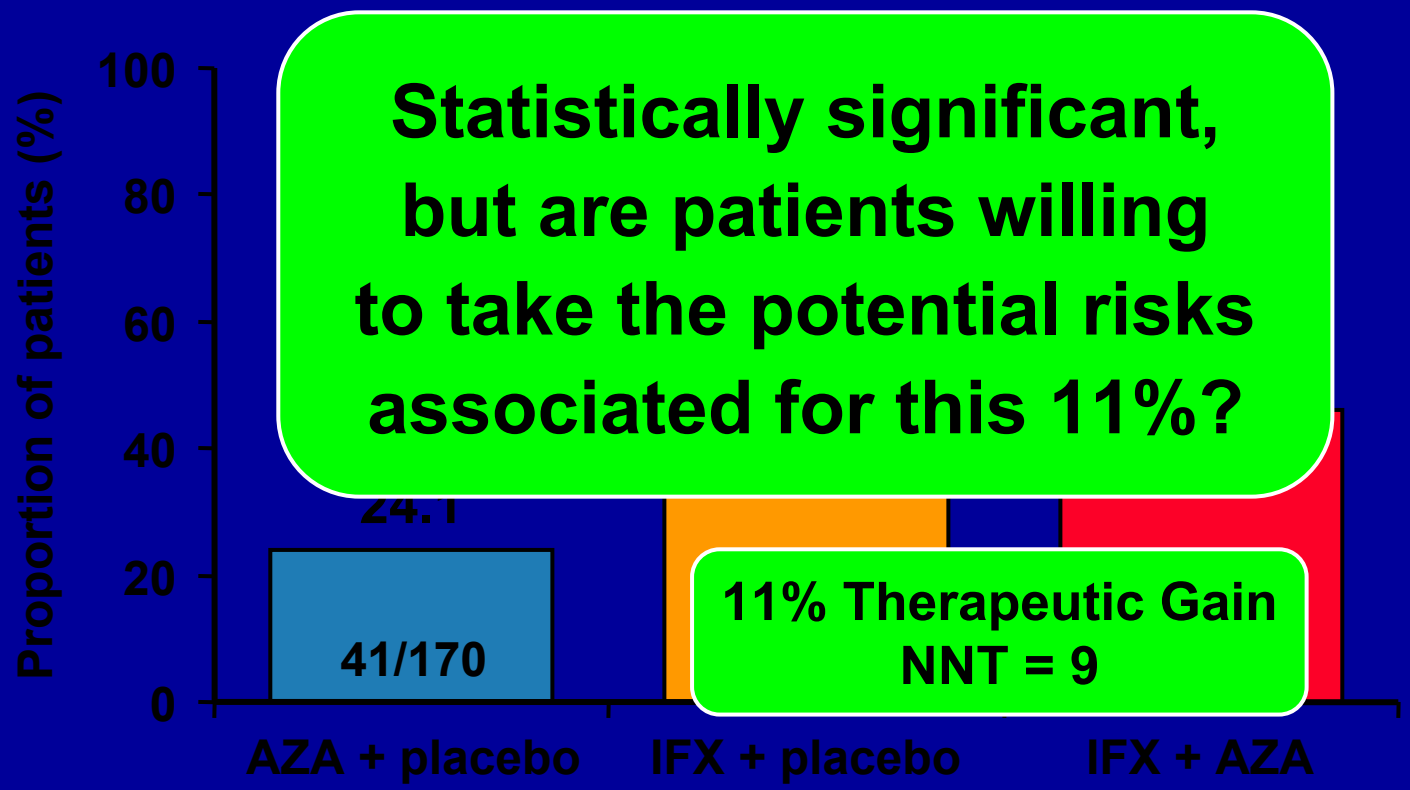
- Older
  - Average age = 63 (systematic review); 67 (Mayo)
  - OR 3.0 (95%CI 1.2–7.2) for >50 yrs versus ≤24
- Multiple co-morbidities
- Concomitant steroids and/or narcotics
- Long-standing disease

Young "healthy" patients are not in the clear, but probably less at risk

Siegel, CGH 2006; Colombel, *Gastro* 2004; Lichtenstein, CGH 2006; Toruner, *Gastro* 2008

Are two drugs better than one? Corticosteroid-free clinical remission at week 50

SONIC: All randomised patients (n=508)*



* Patients who did not enter the Study Extension were treated as non-responders

Late breaking abstract DDW 2009 #751

Are serious infections more common if taking more than 1 medication?

TREAT registry

- Corticosteroids (HR 2.0, 95% CI 1.4–2.9)
- Narcotics (HR 2.7, 95% CI 1.9–4.0)

Opportunistic infections

Prednisone, 6MP/AZA, Infliximab	Odds Ratio (95% CI)
1 medication	2.9 (1.5–5.3)
2 or 3 medications	14.5 (4.9–43)

Lichtenstein, CGH 2006; Toruner, *Gastro* 2008

Closer look at the Mayo experience with opportunistic infections

Herpes zoster	28
Candida albicans	26
Herpes simplex	18
CMW	12
EBV	8
Histoplasmosis	2
Blastomycosis	1
Streptococcus	1
E. Coli	1
Mycobacterium marinum	1
Mycobacterium fortuitum	1
Cryptococcus	1
Mycobaterium gordonae	1

Toruner *et al. Gastro* 2008;134:929

Closer look at the Mayo experience with opportunistic infections

Number of meds	Cases	Controls	OR
0	38	129	1.0 (ref)
1	38	59	2.9 (1.5–5.3)
2 or 3	24*	12	14.5 (4.9–43)
Specific combinations			
Corticosteroids alone	16	27	2.2 (1.0–4.9)
6MP/AZA alone	20	31	3.4 (1.5–7.5)
IFX alone	3	2	11.1 (0.8–148)
AZA/6MP + steroids	16	6	17.5 (4.5–68)
AZA/6MP + IFX	1	5	1.6 (0.1–19)
AZA/6MP + IFX + steroids*	5	0	1.1 (1.0–1.2)

Toruner *et al. Gastro* 2008;134:929

COMMIT and SONIC safety results

	MTX (n=63)	Placebo (n=63)
Blood and lymphatic system disorders	6.3%	11.1%
GI disorders	71.4%	76.2%
Infections	58.7%	61.9%
Connective tissue disorders	44.4%	38.1%
Respiratory disorders	20.6%	23.4%

	AZA + placebo (n=161)	IFX + placebo (n=163)	IFX + AZA (n=179)	Total (n=503)
Pts with ≥1 AE, n (%)	138 (85.7%)	139 (85.3%)	156 (87.2%)	433 (86.1%)
Pts with ≥1 SAE, n (%)	39 (24.2%)	26 (16.0%)	25 (14.0%)	90 (17.9%)
Serious infections	8 (5.0%)	4 (2.5%)	6 (3.4%)	18 (3.6%)

Feagan *et al.* Digestive Disease Week, San Diego, CA 2008.
Sandborn WJ *et al.* ACG 2008.

Risk of NH lymphoma with anti-TNF and immunomodulator treatment for CD

Meta-analysis results

- 8905 patients representing 20,602 pt-years of exposure
- 13 Non-Hodgkin lymphomas → **6.1 per 10,000 pt-years**
- Mean age 52, 62% male
- 10/13 exposed to IM* (so this is really a study of combo Rx)

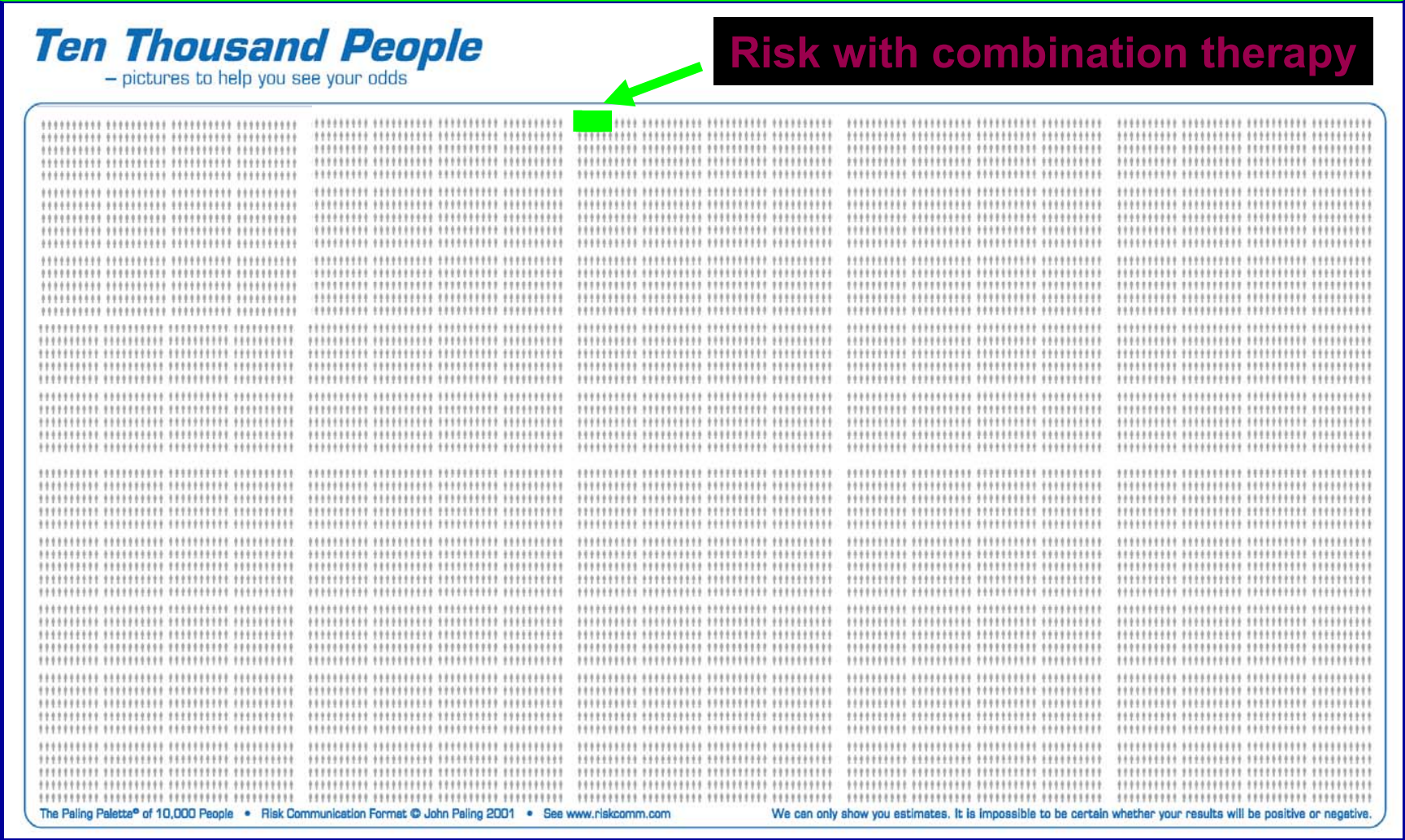
	NHL rate per 10,000	SIR	95% CI
SEER all ages	1.9	–	–
IM alone	3.6	–	–
Anti-TNF + IM vs SEER	6.1	3.23	1.5–6.9
Anti-TNF + IM vs IM alone	6.1	1.7	0.5–7.1

in 2

Siegel *et al.* CGH 2009;7:874

Risk of developing NH lymphoma

20 year old male receiving anti-TNF + immunomodulator therapy for 1 year



Siegel *et al.* CGH 2009;7:874

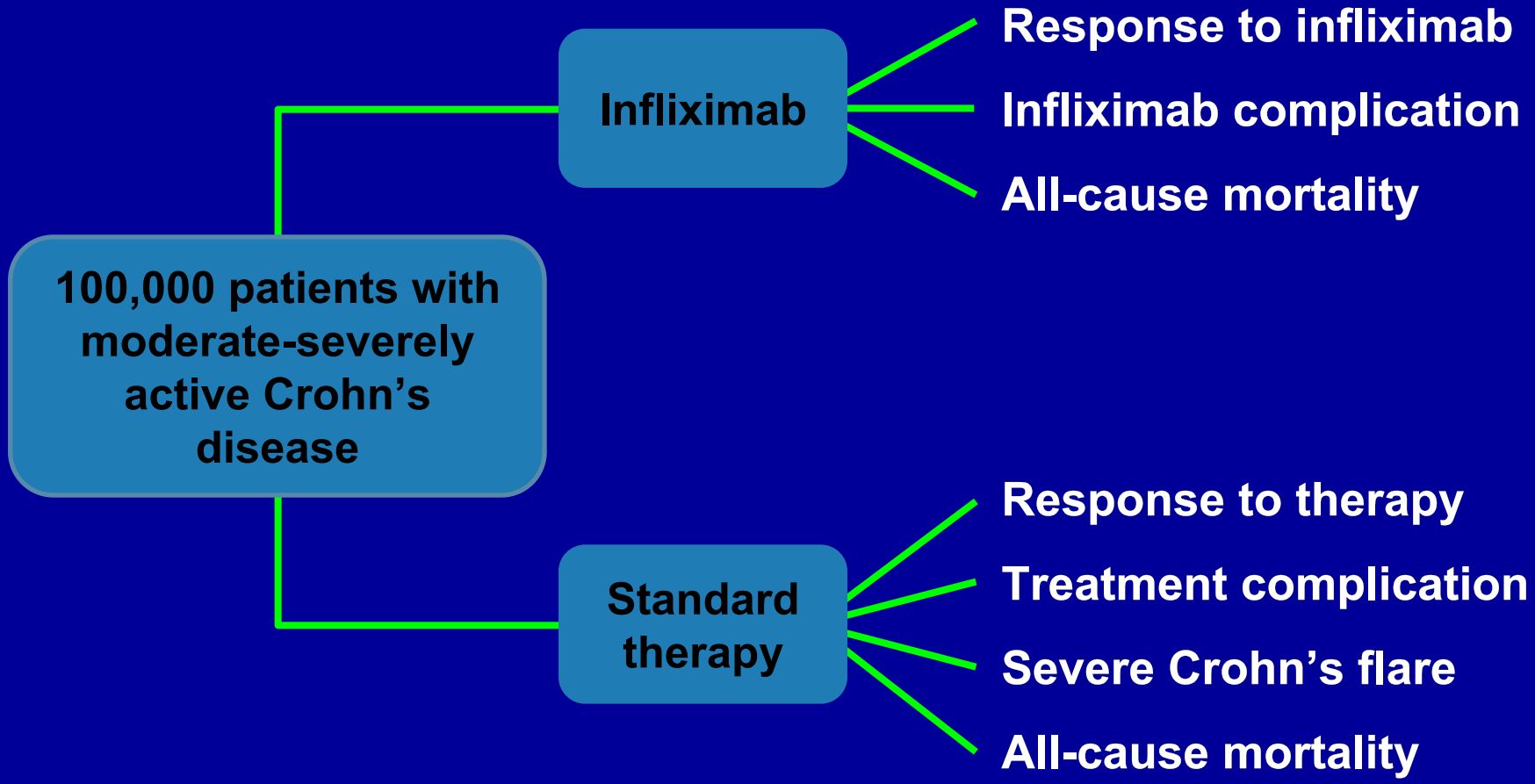
Hepatosplenic T-cell lymphoma

- 9+ cases in IBD with **6MP/AZA** alone
- 18 cases in IBD patients taking **infliximab or adalimumab** with **6MP/AZA**
  - Age range 12–58 years old
  - Average age = 26 years old
  - Almost all are male (17/18)
  - Infusions ranged from 1–24
  - 8 patients had ≤3 infusions
  - Three received adalimumab (after infliximab)

Remember: Over 1 million patients treated with anti-TNFs

Centocor, data on file.

A hypothetical clinical trial: decision analysis



Siegel *et al. Clinical Gastroenterology and Hepatology*. 2006;4:1017–1024.

Decision analysis results*

Outcome of interest	Infliximab	Standard therapy	Difference
Remission without surgery	33394	21121	+12272
Surgery	14101	18332	-4231
Lymphoma	60	30	+30
Death			
Drug side-effect	402	152	+250
Lymphoma	18	9	+9
Disease flare	112	145	-33
Surgery	11	15	-4
All-cause mortality	190	190	0
Total deaths	733	511	+122
Quality adjusted life years	0.77	0.75	+0.02

"+" = more in the infliximab arm

Siegel *et al. Clinical Gastroenterology and Hepatology.* 2006;4:1017–1024.

* Updated with 2009 lymphoma meta-analysis results

Are patients willing to take these risks for the expected benefits?

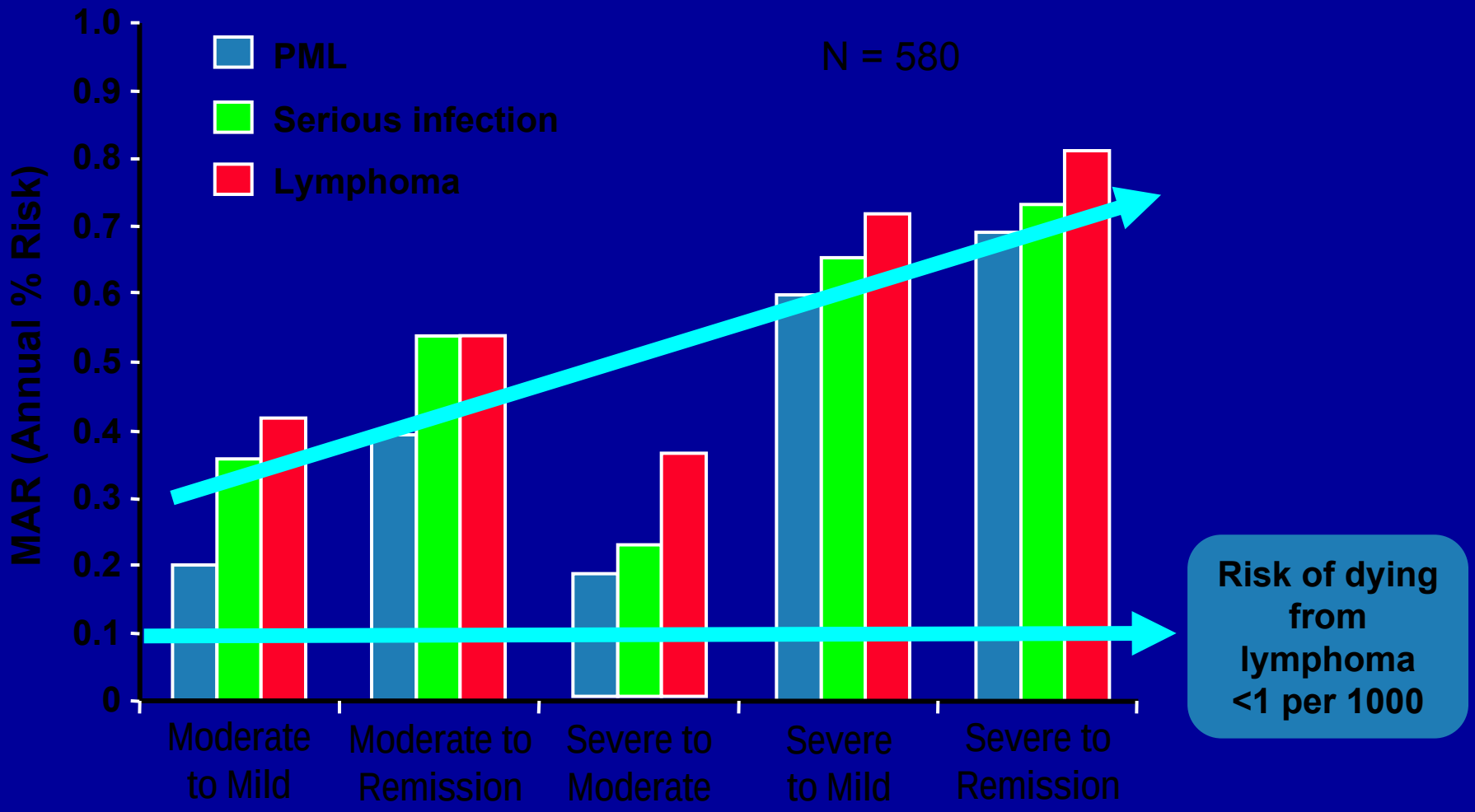
Risk of mortality is highest with uncontrolled disease or steroids

- Retrospective cohort from UK (GPRD)
- 5,539 patients with Crohn's; 41,624 controls
- Hazard ratio for the risk of dying

Exposure	Hazard Ratio	95% CI
Crohn's (mild)	1.27	1.07–1.51
Crohn's (severe)	2.44	1.84–3.25
Current prednisone	2.48	1.85–3.31
Current AZA/6MP	0.83	0.37–1.86

Lewis *et al.* AJG 2008;103:1428.

Patient willingness to take risk



Johnson *et al. Gastroenterology* 2007.

Can we show patients who will benefit most from intensive therapy?

System dynamics modeling to predict and display individual Crohn's disease patient outcomes

- Real data
- Clear presentation
- Individual predictions

Summary

- Earlier intensive therapy is not for everyone
- Immunomodulators and anti-TNFs are associated with real, but small risks of serious infections and lymphoma
- Patients are willing to accept risk, as long as there is substantial benefit
- Predictive models can show physicians and patients who will benefit most from treatment