Università di Palermo
Scuola di Specializzazione in
Gastroenterologia ed Endoscopia Digestiva

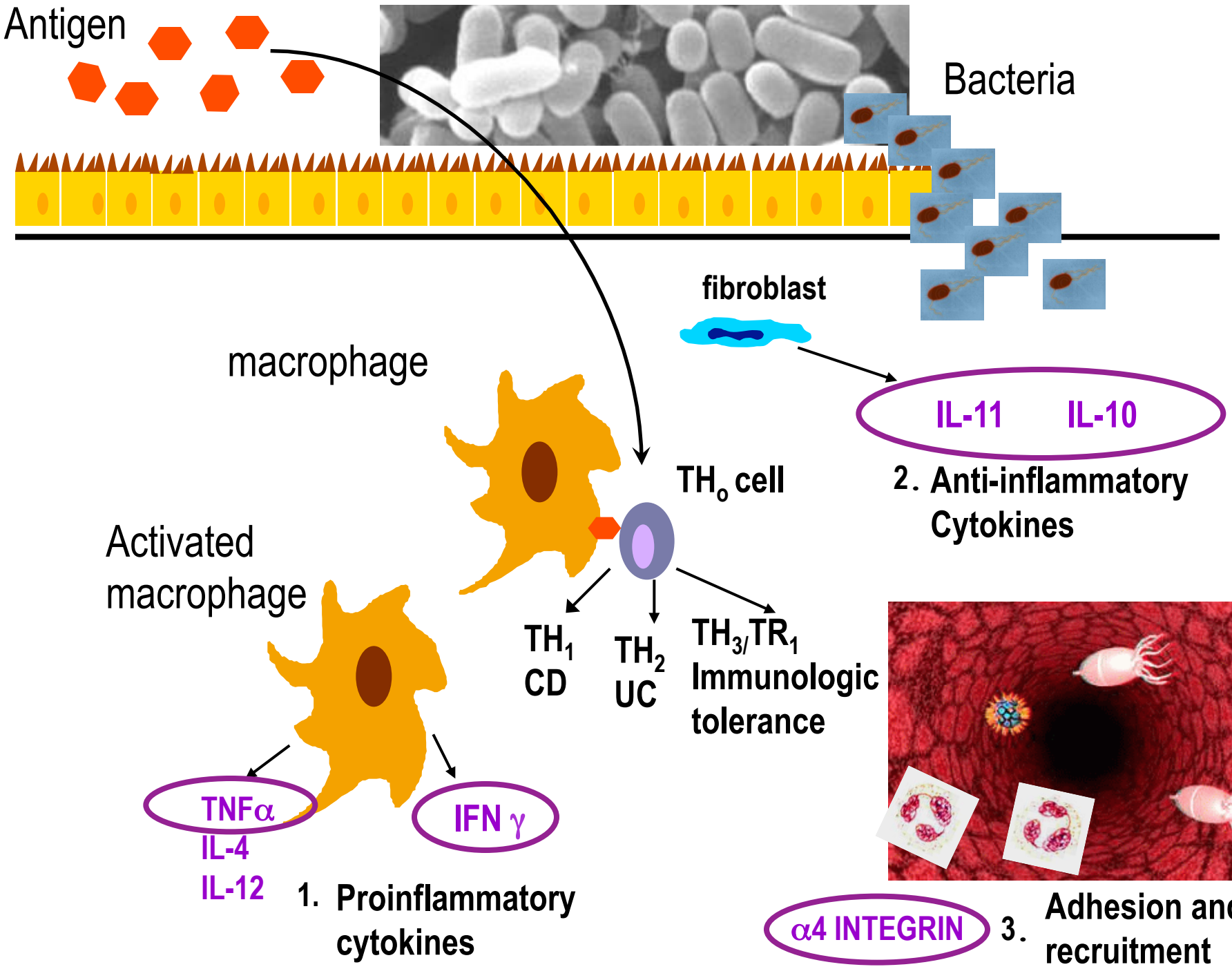
La terapia biologica nelle IBD: Indicazioni attuali e prospettive future

Palermo 18 novembre 2013

Dott.ssa Maria Cappello

Azienda Ospedaliera Universitaria Policlinico Palermo

UOC Gastroenterologia ed Epatologia (Prof. A. Craxì)


Antigen
Bacteria
fibroblast
macrophage
IL-11
IL-10
2. Anti-inflammatory Cytokines
TH_o cell
Activated macrophage
TH_1 CD
TH_2 UC
$TH_{3/}TR_1$ Immunologic tolerance
TNFα
IL-4
IL-12
IFN γ
1. Proinflammatory cytokines
α4 INTEGRIN
3. Adhesion and recruitment

Differenti anticorpi monoclonali anti –TNF

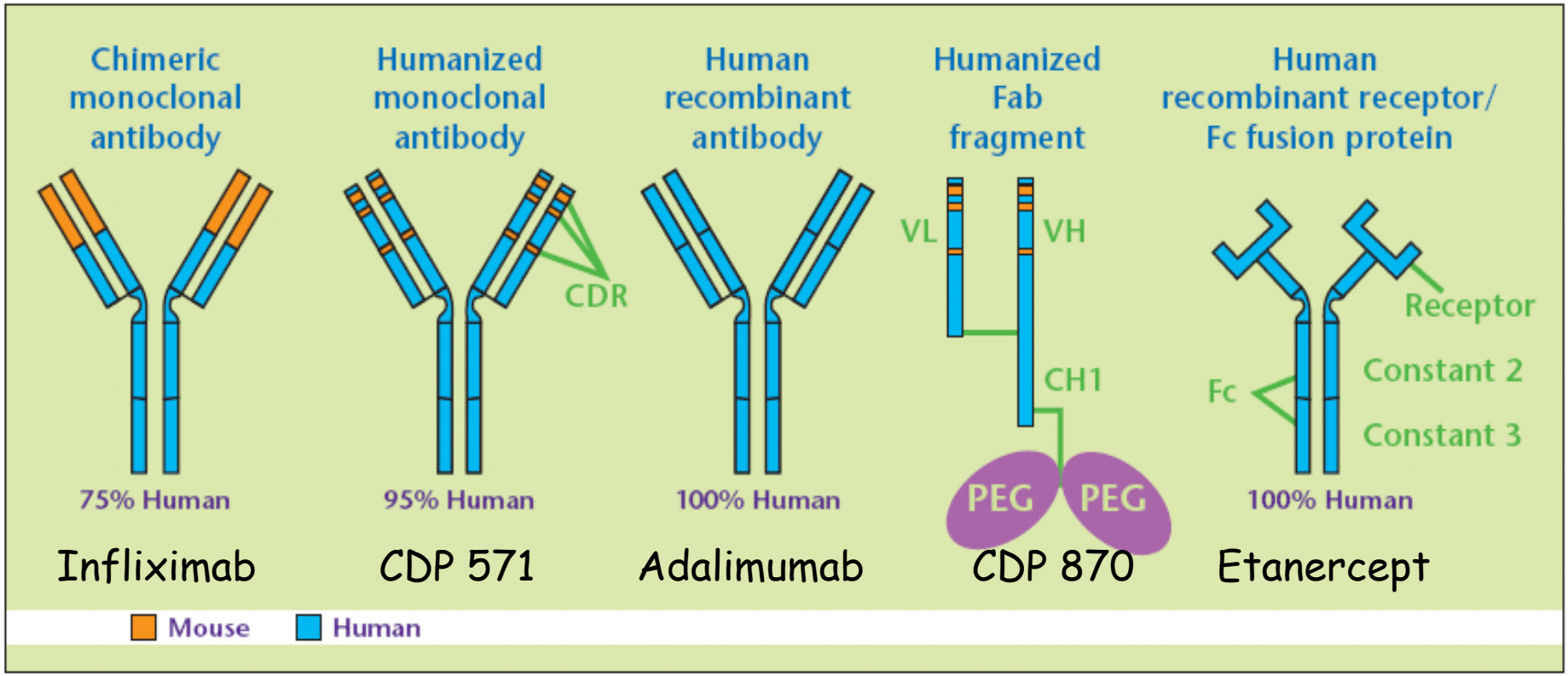
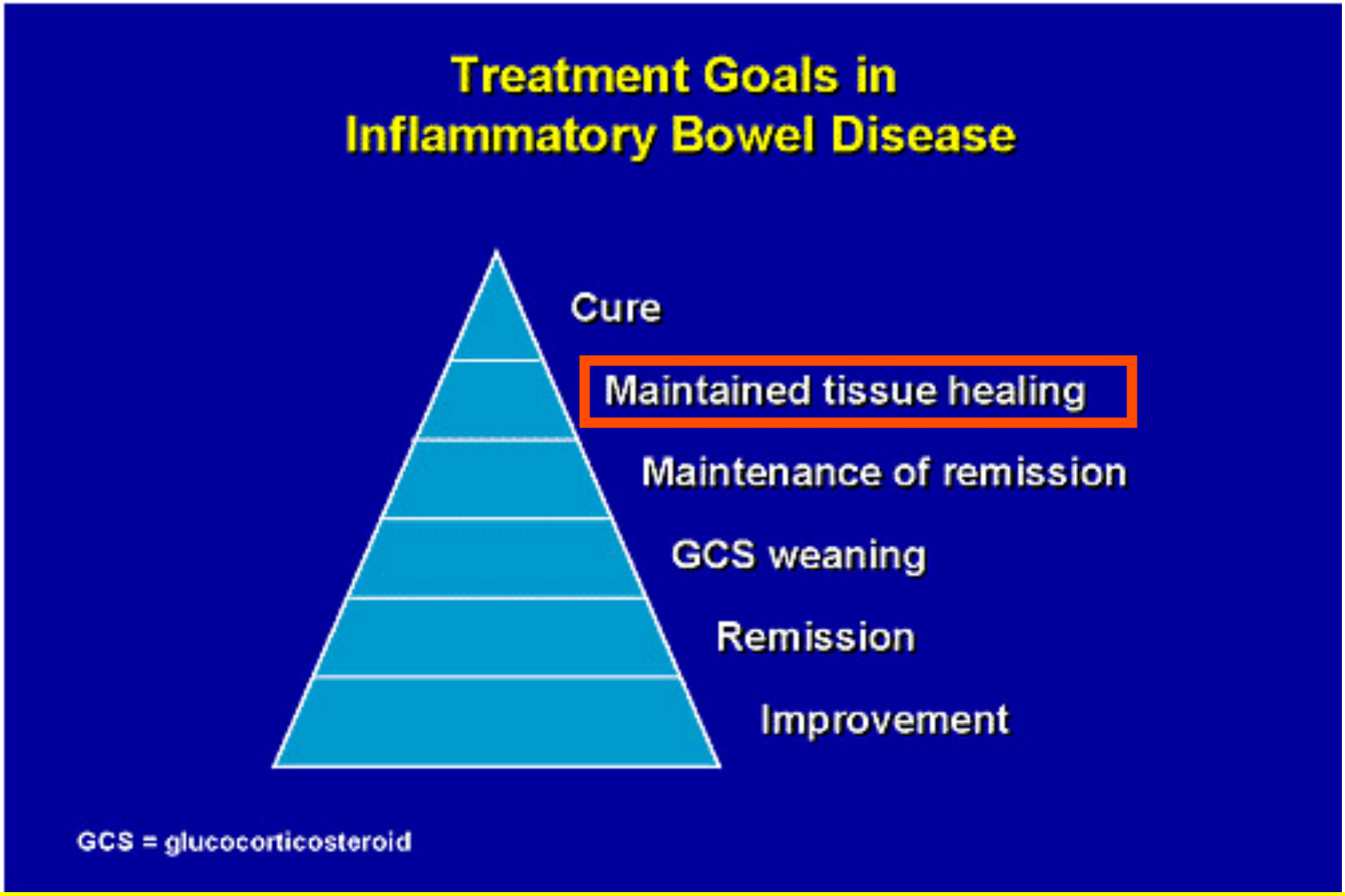


Figure 1. *Protein-engineered antibodies and fusion proteins. CDR, complementarity determining region; VL, immunoglobulin light chain; VH, immunoglobulin heavy chain; CH1, complementary heavy chain; PEG, polyethylene glycol.*

La terapia biologica nelle IBD



N. evacuazioni liquide (somma 7 giorni) x 2

Dolore addominale (0-3) (somma 7 giorni) x 5

Benessere generale (0-4) (somma 7 giorni) x 7

N. complicanze in atto x 20
* artrite/artralgia
* irite/uveite
* eritema nod./pioderma gangr.
* malattia perianale
* altre fistole
* febbre > 38

Farmaci antidiarroici (0-1) x 30

Massa addominale (0-2) x 10

Ematocrito x 6
M= 47-Htc
F = 42-Htc

Peso corporeo x 1
100 x (1 - peso/peso standard)

CDAI < 150
malattia in remissione

CDAI 150- 219
malattie lieve

CDAI 220-450
malattia moderata

CDAI > 450
malattia severa

Table 1. Mayo Scoring System for Assessment of Ulcerative Colitis Activity.*

Stool frequency†
- 0 = Normal no. of stools for this patient
- 1 = 1 to 2 stools more than normal
- 2 = 3 to 4 stools more than normal
- 3 = 5 or more stools more than normal

Subscore, 0 to 3

Rectal bleeding‡
- 0 = No blood seen
- 1 = Streaks of blood with stool less than half the time
- 2 = Obvious blood with stool most of the time
- 3 = Blood alone passes

Subscore, 0 to 3

Findings on endoscopy
- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
- 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)

Subscore, 0 to 3

Physician's global assessment§
- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

Subscore, 0 to 3

* The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Data are from Schroeder et al.[24]

Response : decrease
Of Mayo at least 3 points

Remission: Mayo < 2

Mucosal healing:
endoscopic subscore 0 or 1

MH in IBD

- There is no validated definition of MH in patients with IBD
- The „ideal“ definition of Mucosal Healing (MH) could be complete endoscopic healing of all inflammatory and ulcerative lesions of the gut mucosa in CD and UC
- In CD, an endoscopic response to treatment can be defined as “absence of ulcers” or a significant change of endoscopic disease activity score, such as the CDEIS or the SES-CD
- In UC, an endoscopic response to treatment can be defined as a significant change of endoscopic disease activity score, such as the Baron score or the Mayo endoscopic subscore

Pineton de Chambrun G, et al. Nat Rev Gastroenterol Hepatol 2010; 7: 15-29.

Measurement of Endoscopic Disease Activity in Crohn's Disease

Different scoring systems for different clinical scenarios:

- The Crohn's Disease Endoscopic Index of Severity (CDEIS)
- The Simple Endoscopic Index for Crohn's Disease (SES-CD)
- The Rutgeerts' score for postoperative recurrence

The Simple Endoscopic Score for Crohn's Disease (SES-CD)

	Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Presence and size of ulcers (0÷3)	__+	____+	_____+	____+	___+	+
Extent of ulcerated surface (0÷3)	__+	____+	_____+	____+	___+	+
Extent of affected surface (0÷3)	__+	____+	_____+	____+	___+	+
Presence and type of stenosis (0÷3)	__+	____+	_____+	____+	___+	=
					SUM OF ALL VARIABLES =	**SES-CD**

Gastrointest Endosc 2004

Endoscopic Assessment Following Surgery: Rutgeerts' Score

RUTGEERTS' SCORE

- Developed for lesions in the neoterminal ileum and at the ileocolonic anastomosis
- i0 – i4
- Correlates with clinical behavior in the future

Degree	Endoscopic characteristics
i_0	No lesion in neoterminal ileum
i_1	≤5 aftoid lesions
i_2	>5 aftoid lesions with normal mucosa in-between, or skip areas with larger lesions, or lesions confined to ileocolonic anastomosis
i_3	Diffuse aftous ileitis with extensively inflamed mucosa
i_4	Diffuse inflammation with large ulcers, nodules and/or stenoses

Rutgeerts P, et al. Gastroenterology 1990;99(4): 956-63.

Ulcerative Colitis: Mayo Endoscopic Activity Score

Score 0

normal or healed mucosa

Score 1

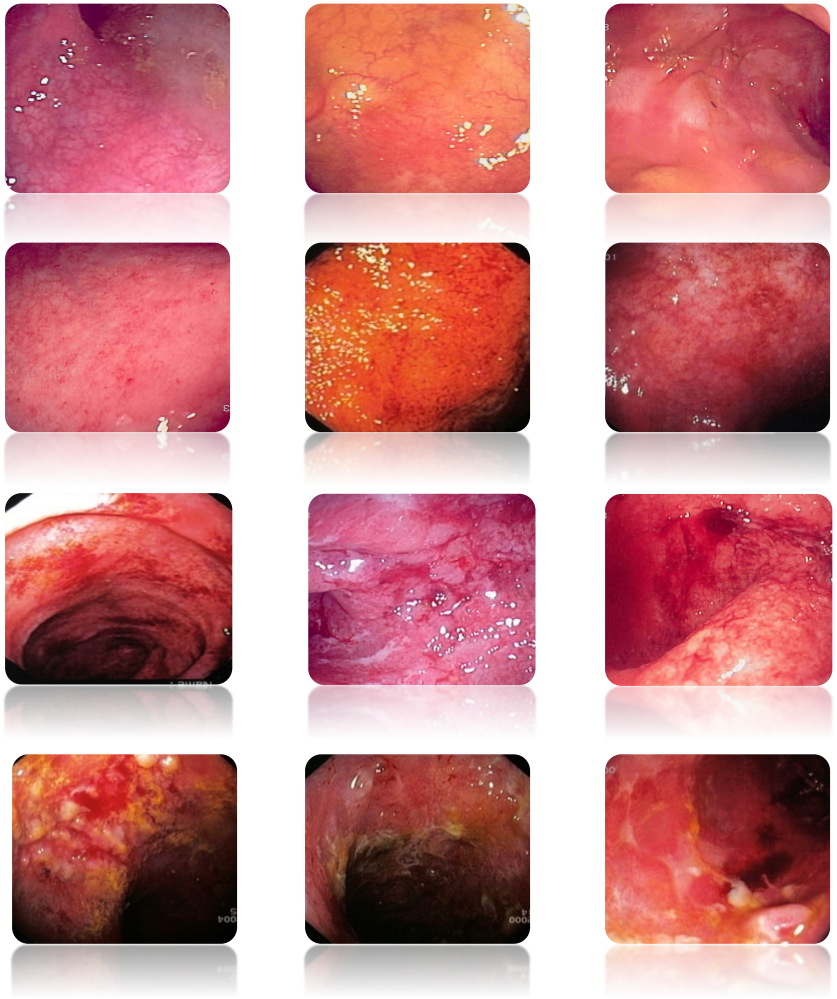
faded vascular pattern
mild friability
erythema

Score 2

absent vascular pattern
marked friability
erosions

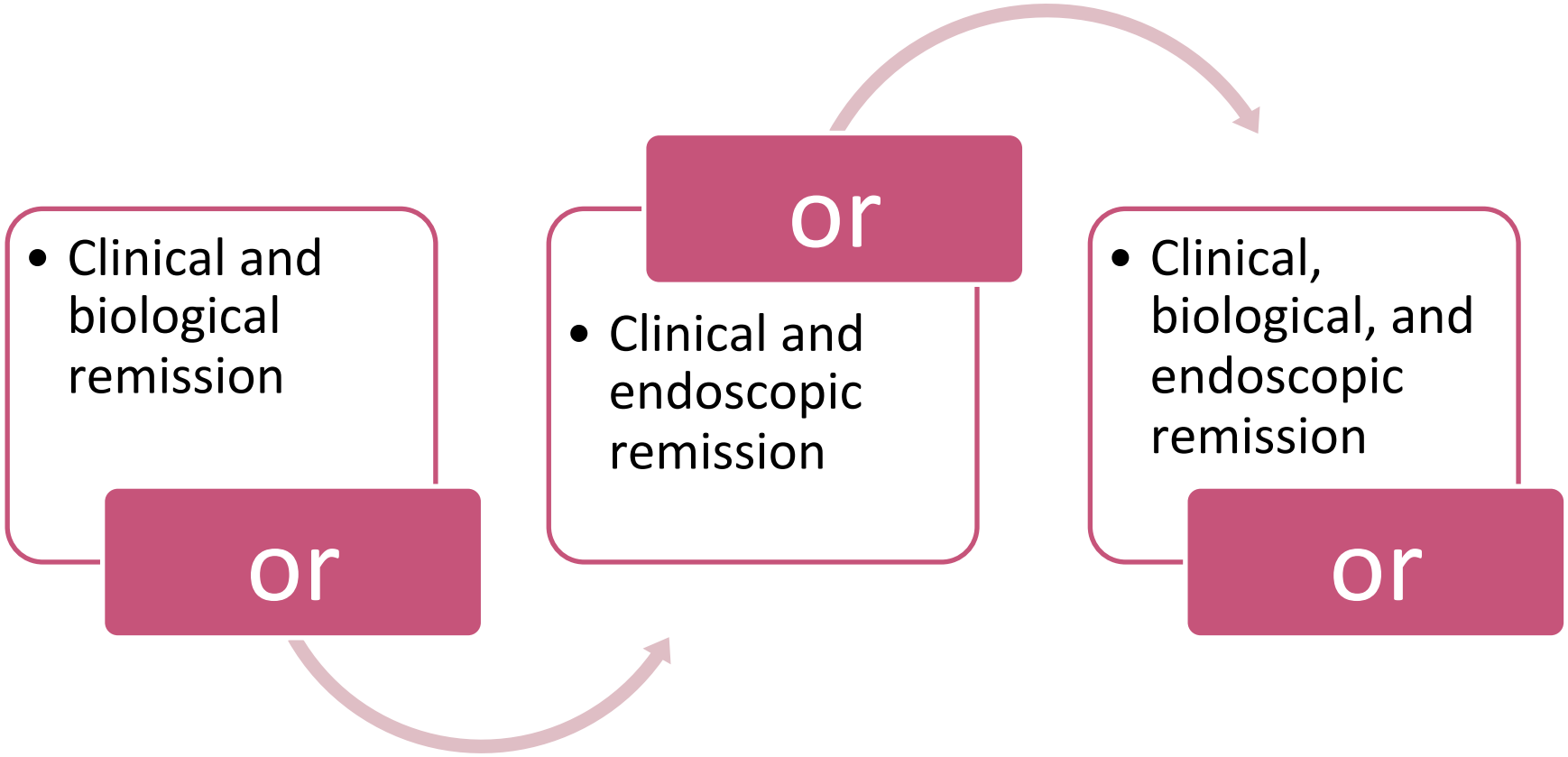
Score 3

spontaneous bleeding
large ulcers

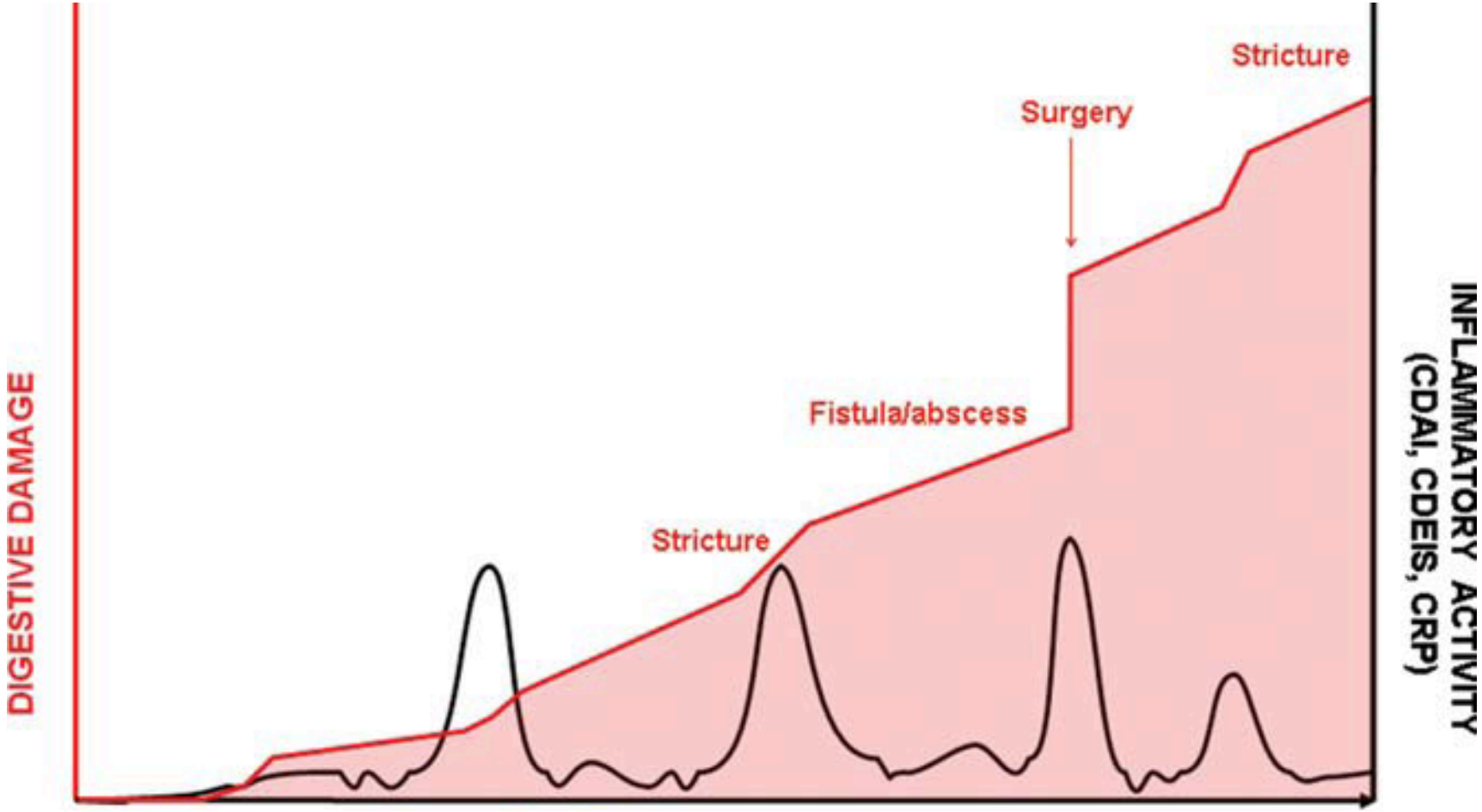


Schroeder KW, et al. N Engl J Med 1987

What is Deep Remission?



Digestive Damage and Lémann score



Pariente B. et al., Inflamm Bowel Dis 2011

Effects of infliximab therapy on transmural lesions as assessed by magnetic resonance enteroclysis in patients with ileal Crohn's disease☆,☆☆,★

Table 3 Correlation of MICD with CRP and CDAI.

	CDAI	CRP
Total MICD	R=0.52 (p=0.0003)	R=0.12 (p=0.4)
Inflammation subscores	R=0.45 (p<0.01)	R=0.13 (p=0.4)

Note: Spearman Rank statistics were used to test for potential correlation between all paired data at different timepoints.

However, normalization of MRE is rare…

Journal of Crohn's and Colitis (2013) **xx**, xxx–xxx

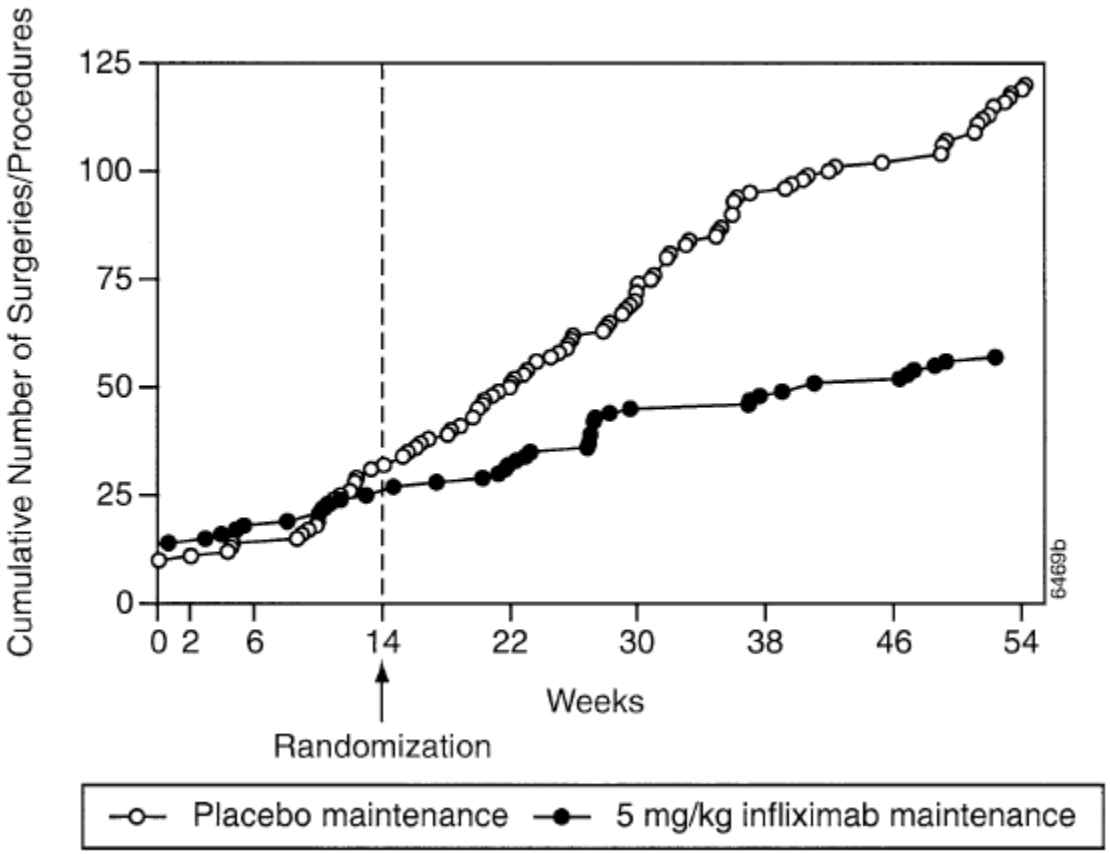
La terapia biologica nelle IBD

- La terapia biologica con infliximab ha consentito di ridurre il tasso di ospedalizzazioni e di interventi chirurgici.
- Questo risultato si riflette in una riduzione di utilizzazione delle risorse.
- Una subanalisi dello studio CHARM ha dimostrato che tali obbiettivi si raggiungono anche con adalimumab.

» Taxonera et al. J Clin Gastroenterol 2009 (Epub)
» Sandborn et al. Gastroenterology 2009 (Epub)
» Lichtenstein et al. Gastroenterology 2005
» Feagan et al. Gastroenterology 2008

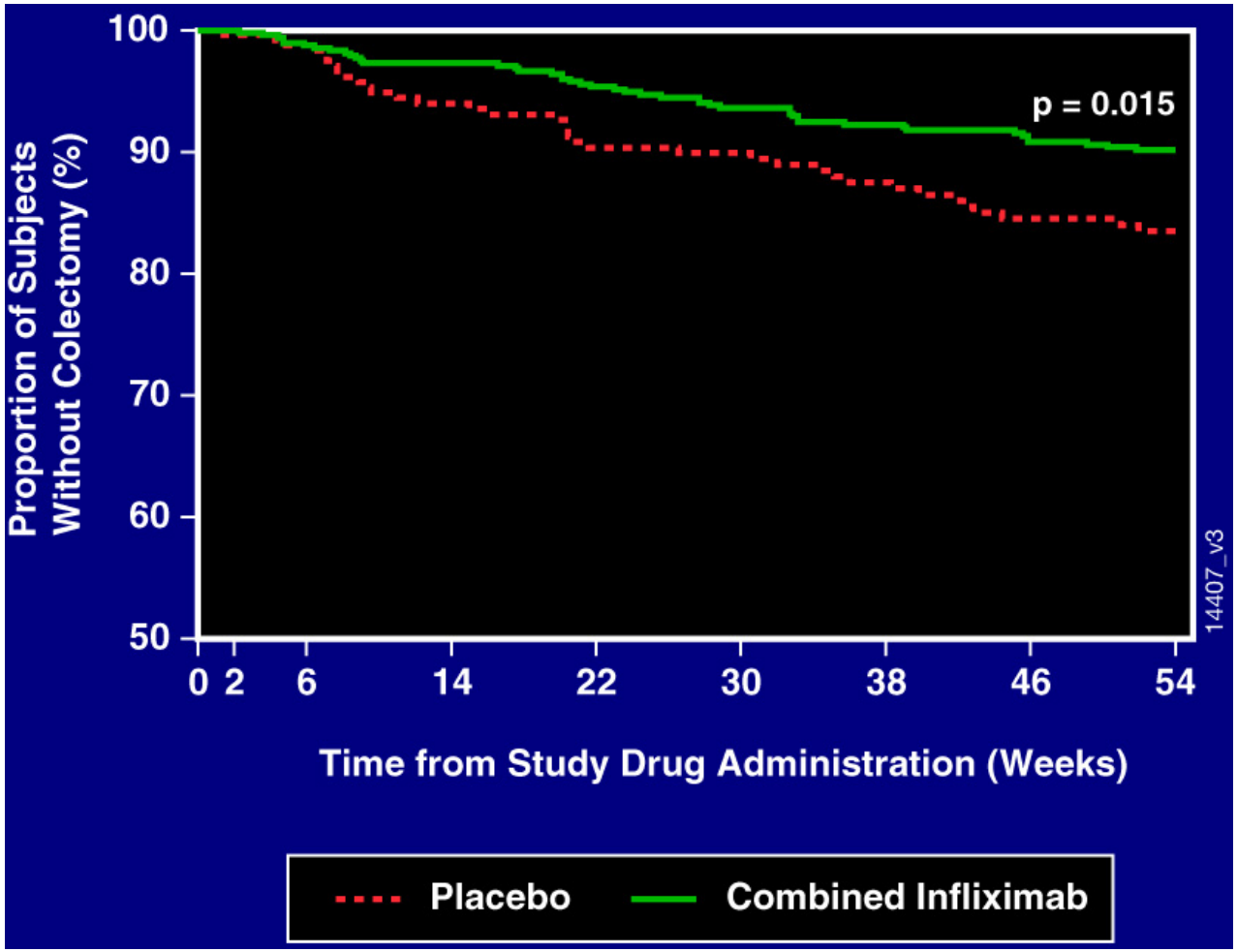
Infliximab Maintenance Treatment Reduces Hospitalizations, Surgeries, and Procedures in Fistulizing Crohn's Disease

GARY R. LICHTENSTEIN,* SONGKAI YAN,† MOHAN BALA,† MARION BLANK,† and BRUCE E. SANDS§

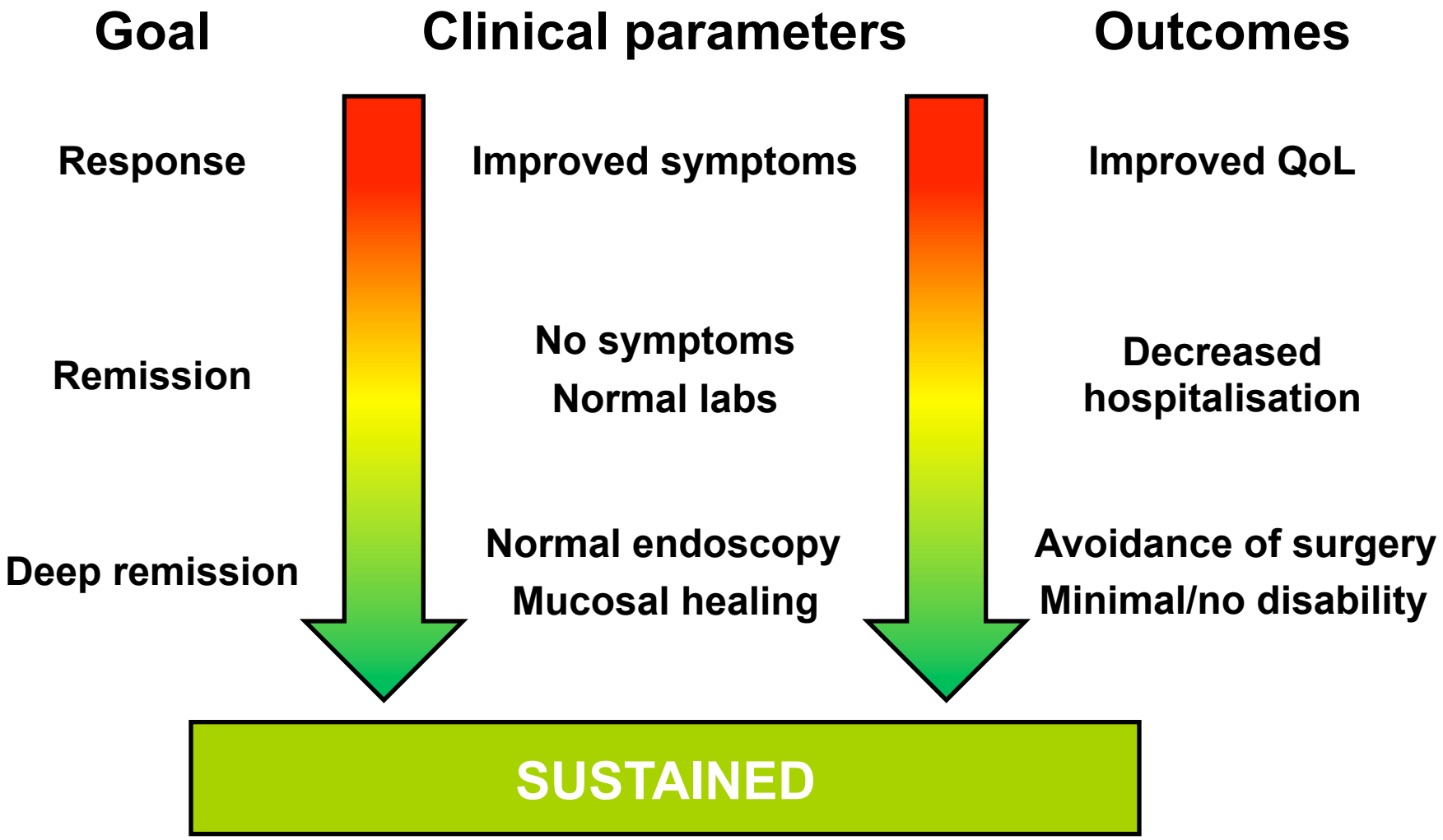


GASTROENTEROLOGY 2005;128:862–869

Time to Colectomy in Subjects With Acute UC



Evolving goals of therapy for Crohn's disease



Panaccione R. Abbott Symposium at ECCO, Prague, Czech Republic; February 2010

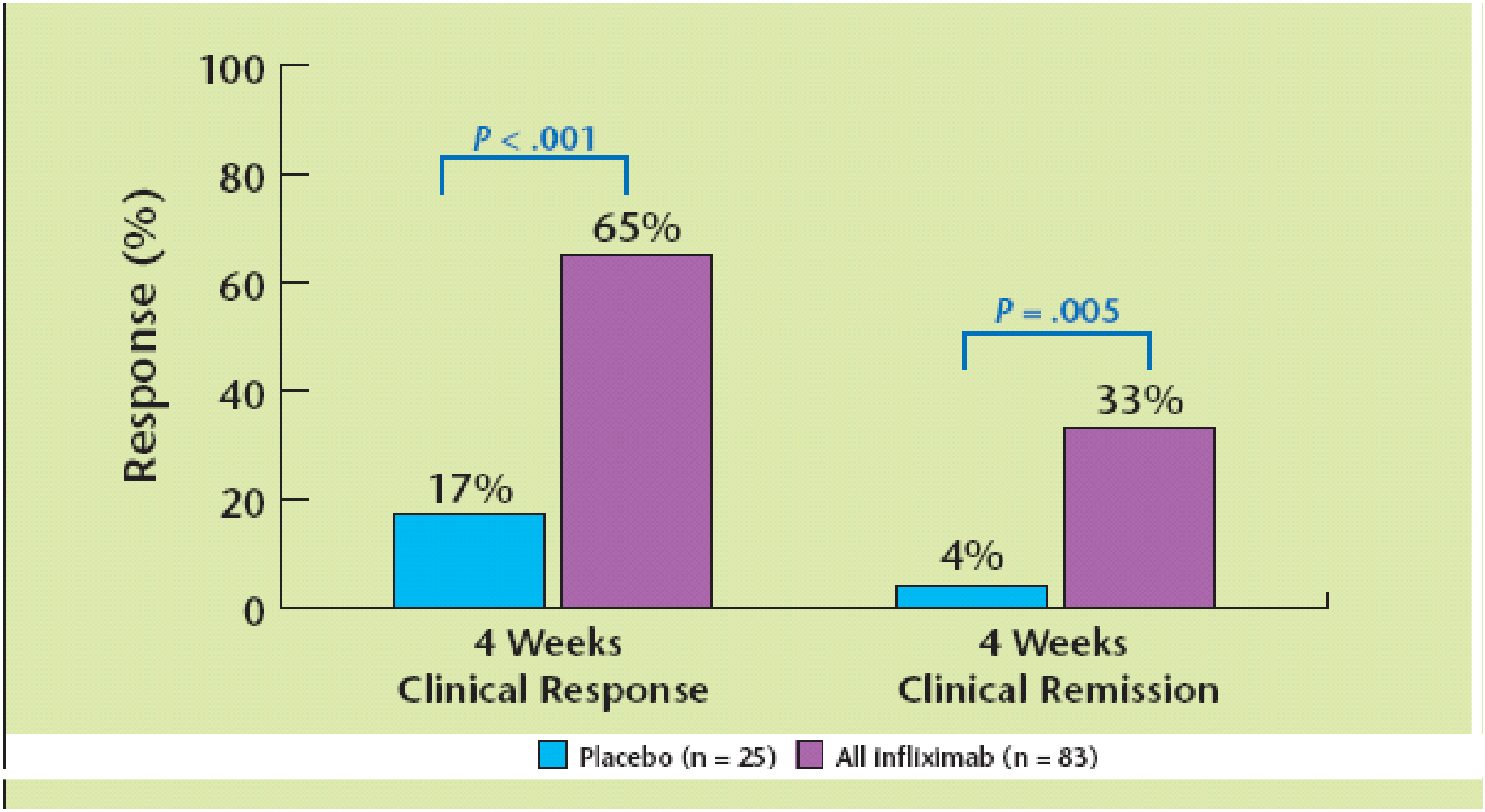
Indicazioni alla terapia biologica nella malattia di Crohn

- Malattia luminale refrattaria
- Le fistole
- La stenosi
- La “early disease”
- La prevenzione delle recidive post-chirurgiche

Indicazioni alla terapia biologica nella malattia di Crohn

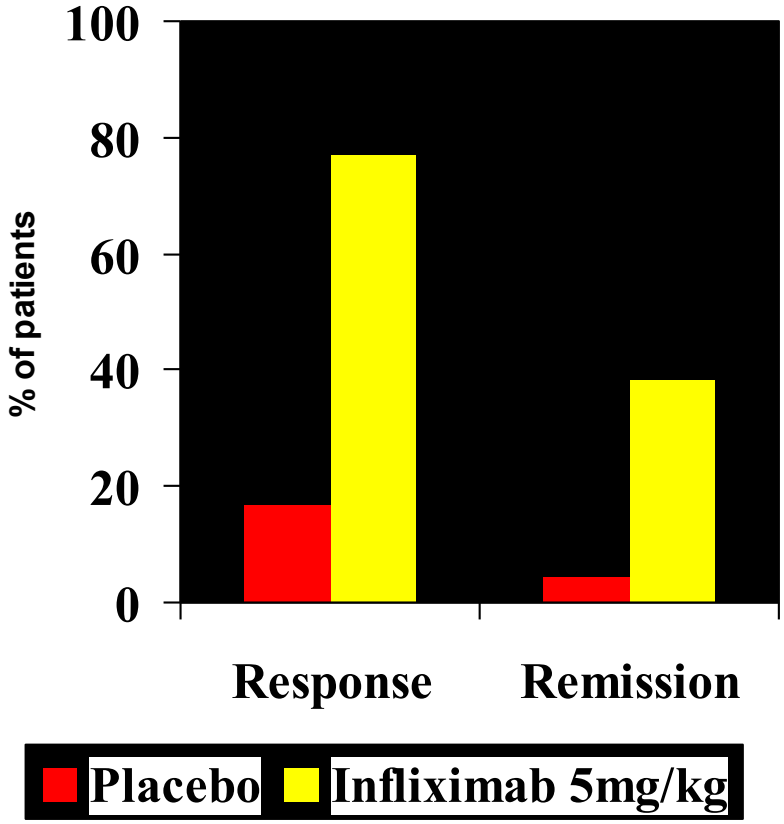
- Malattia luminale refrattaria
- Le fistole
- La stenosi
- La “early disease”
- La prevenzione delle recidive post-chirurgiche

Infliximab nella malattia di Crohn luminale refrattaria



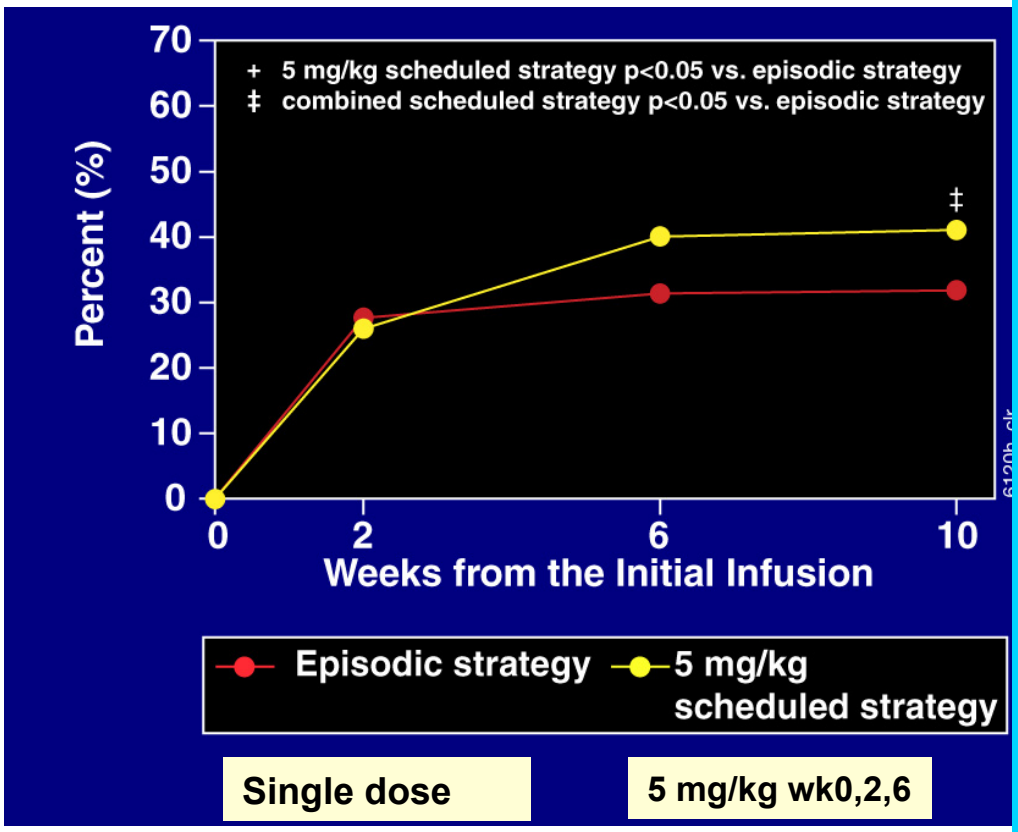
Infliximab
Rapid Induction of Remission

Clinical Response and Remission (Week 2)



Targan et al. NEJM. 1997; 337:1029-35

Clinical Remission through Week 10 Single Dose vs. 3 Dose Induction

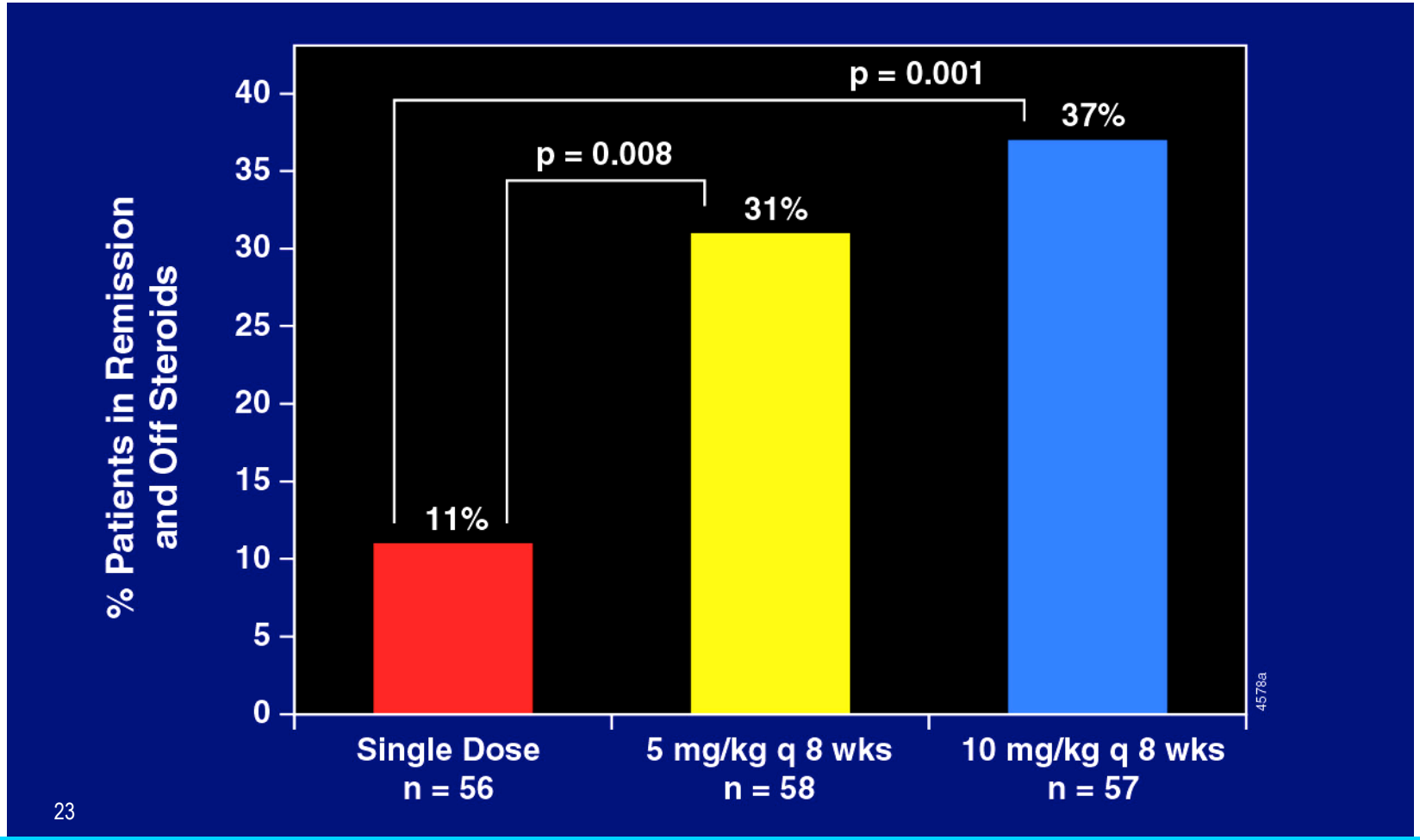


Rutgeerts et al. Gastroenterology 2004;126:402-413

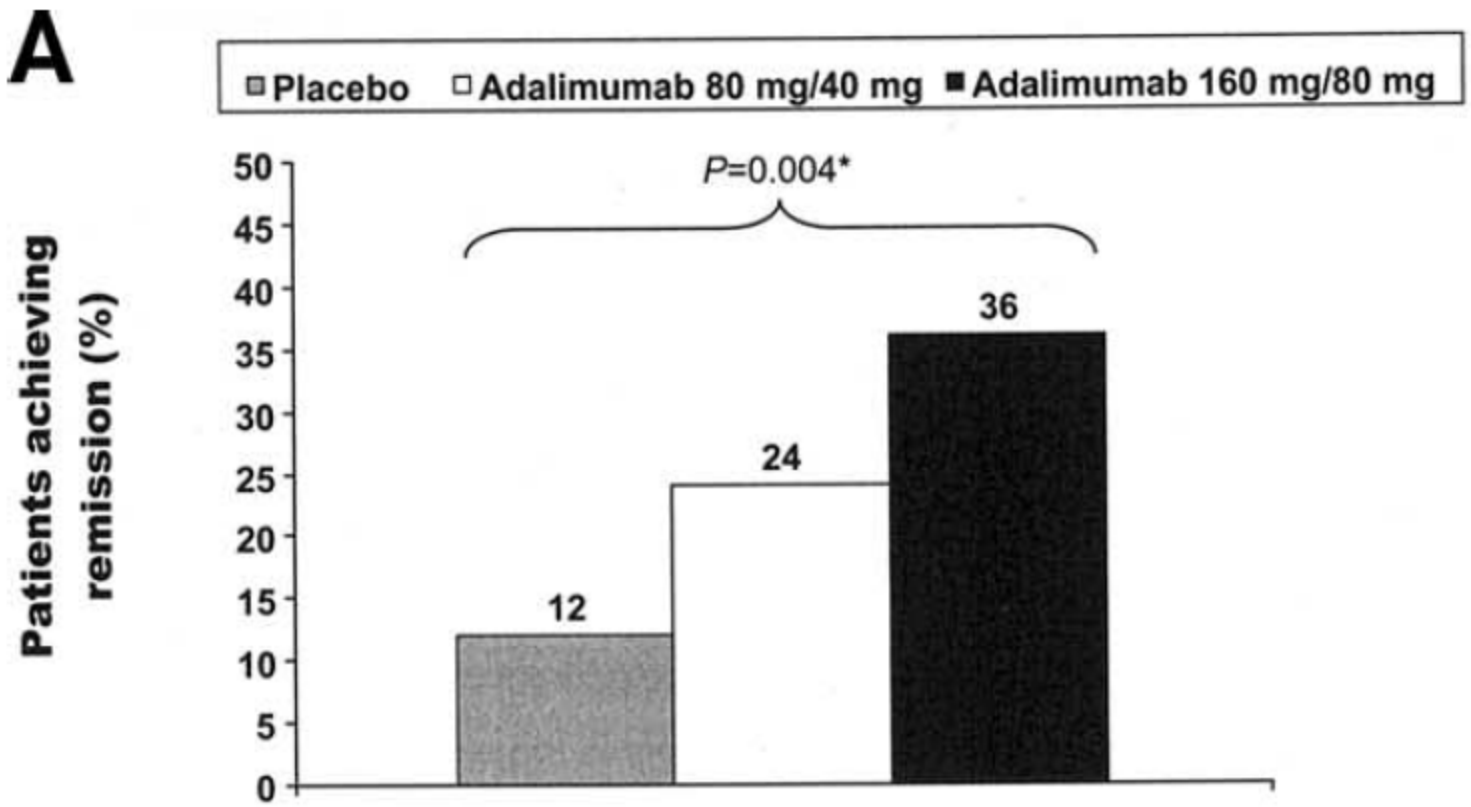
Remissione Clinica e sospensione dei corticosteroidi alla settimana 30

Patients Receiving Steroids at Baseline

ACCENT I

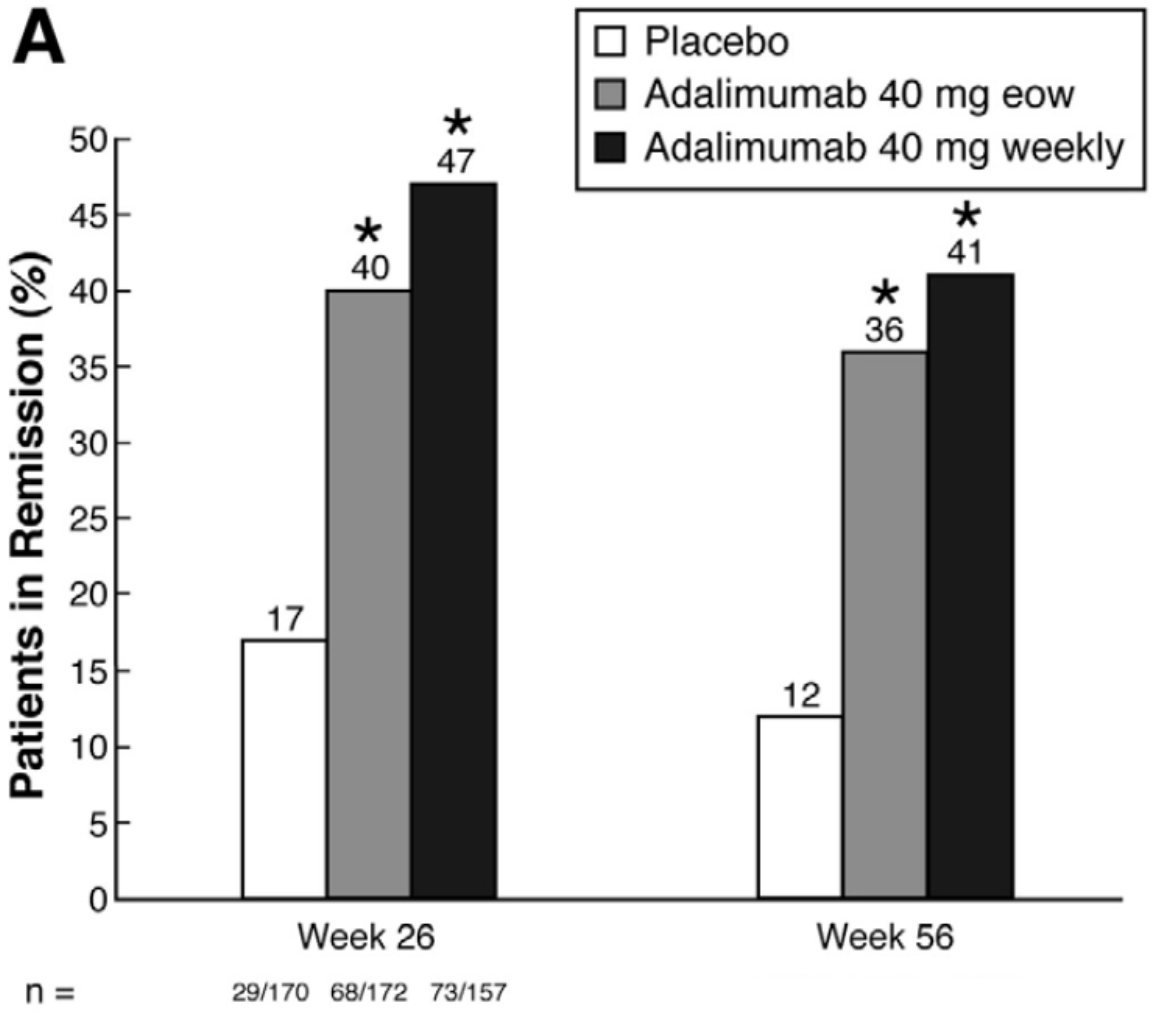


Adalimumab e induzione della Remissione (CLASSIC I)



GASTROENTEROLOGY 2006;130:323–333

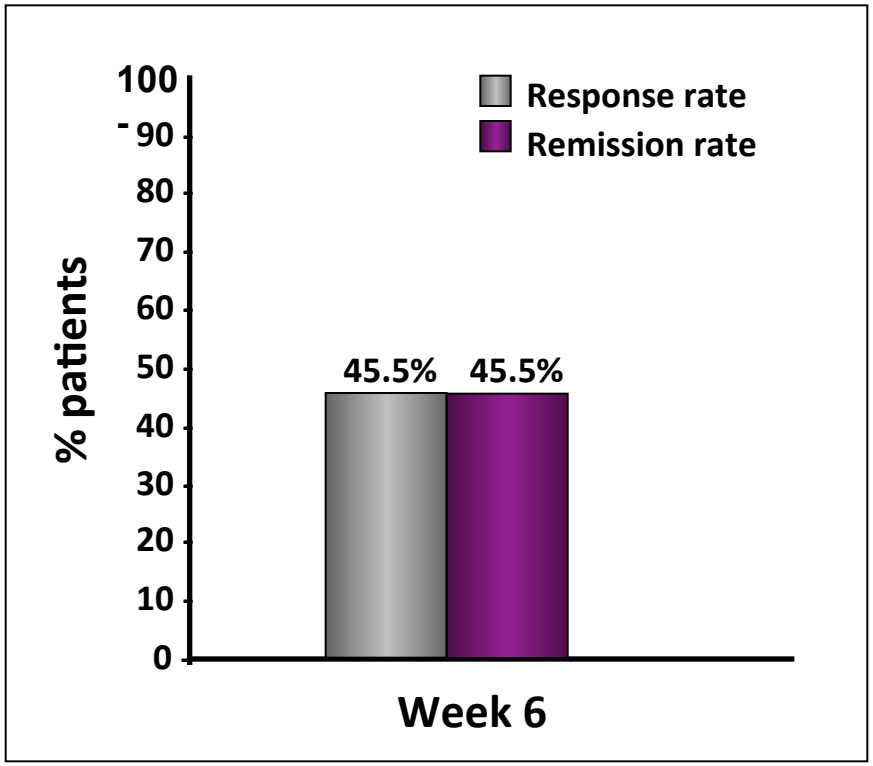
Adalimumab e mantenimento della Remissione (CHARM)

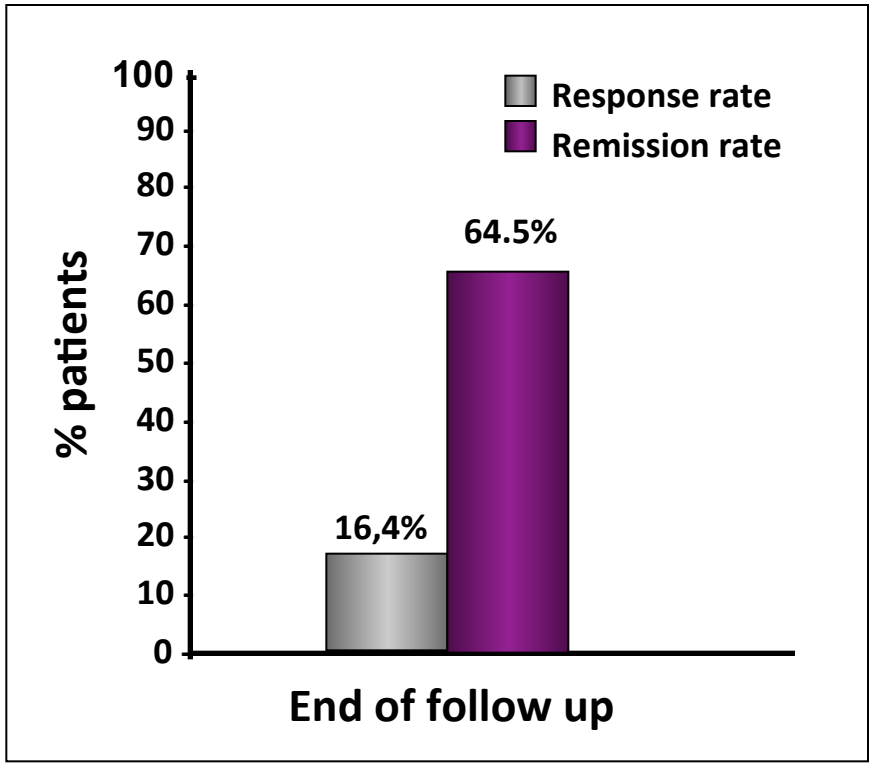


GASTROENTEROLOGY 2007;132:52–65

Efficacy of adalimumab in 110 steroid-dependent Crohn's disease patients

Results





Orlando A et al. Inflamm Bowel Dis 2011

Journal of Crohn's and Colitis (2010) 4, 28–62

ELSEVIER

available at www.sciencedirect.com

ScienceDirect

SPECIAL ARTICLE

The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Current management

All currently available anti-TNF therapies appear to have generally similar efficacy and adverse-event profiles for inflammatory ('luminal') Crohn's disease, so the choice depends on availability, route of delivery, patient preference, cost and national guidelines [EL5, RG D] (Statement 5I).

Le linee guida italiane sull'uso dei biologici nelle IBD (SIGE – IG IBD 2010)

Metodologia

- 15 esperti nazionali (da centri di riferimento) che hanno proposto le raccomandazioni sulla base dell'evidenza scientifica
- 14 esperti nazionali (da centri gastroenterologici e di riferimento) che hanno discusso e condiviso le raccomandazioni
- Un rappresentante dell'associazione AMICI
- Se disaccordo consenso basato su votazione
- 4 incontri
- Documento con statements e testo in italiano ed inglese
- Pubblicazione

Linee guida IG-IBD sull'uso dei biologici nella malattia di Crohn steroido-dipendente

Statement 4A

Anti TNF agents are a valuable option (infliximab **[EL 1a, RG A]**, adalimumab **[EL 1b, RG B]**)

In steroid dependent Crohn's disease thiopurines could be added in naive patients **[EL 4, RG D]**

Although surgical option should be considered for localized disease

Linee guida SIGE – IG IBD 2010

Linee guida IG-IBD sull'uso dei biologici nel mantenimento della remissione nella Malattia di Crohn luminale

Statement 4B

Anti TNF agents (Infliximab and Adalimumab) are effective for maintenance of remission up to one year in patients with clinical response to induction therapy **[EL 1a, RG A]**

Anti TNF agents should be the treatment of choice for patients who have failed maintenance strategies with immunosuppressant **[EL 1b, RG B]**

Linee guida SIGE – IG IBD 2010

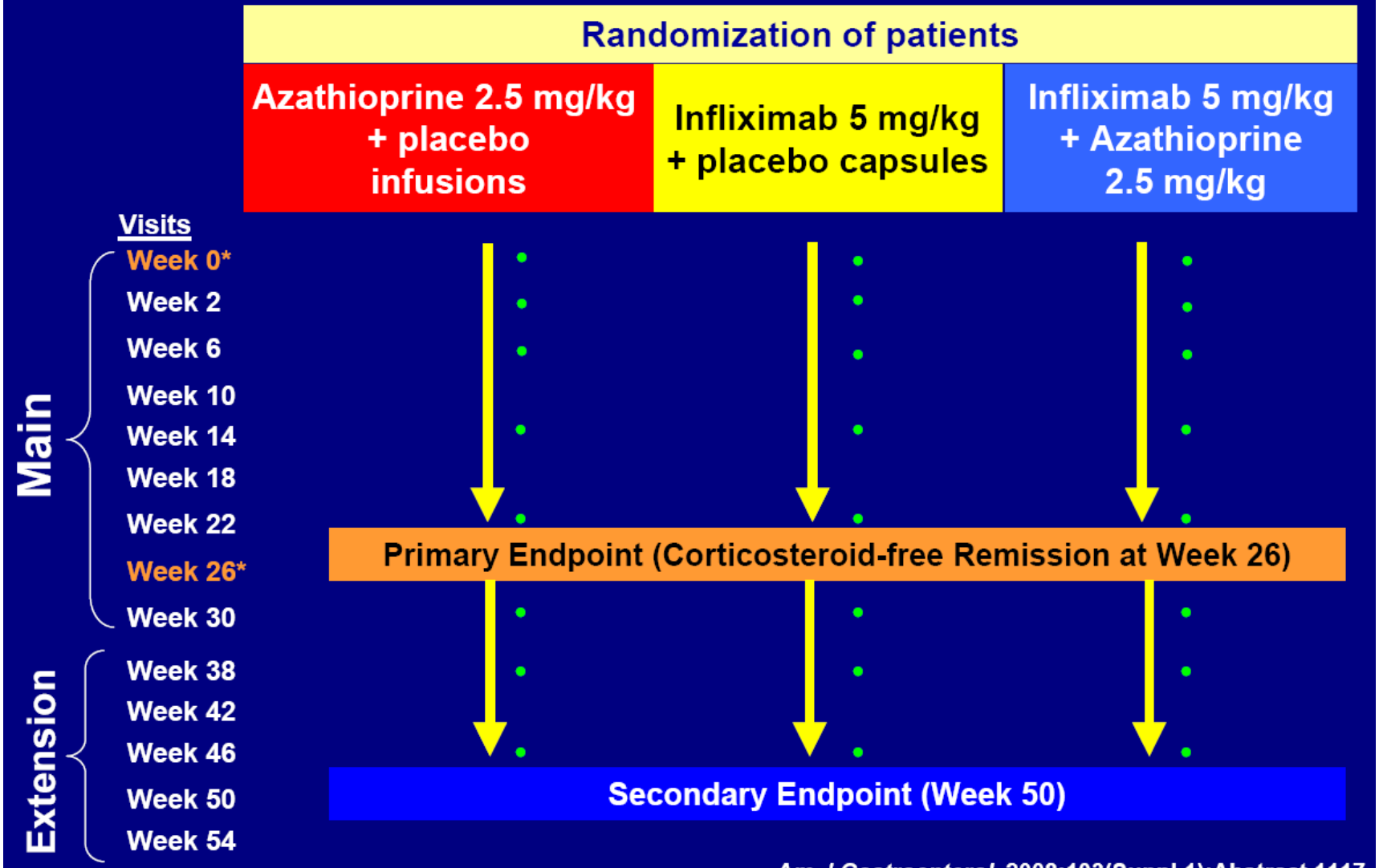
Linee guida IG-IBD sull'uso dei biologici nel mantenimento della remissione nella Malattia di Crohn luminale

Statement 4C

Open experiences have reported long-term effectiveness and safety of anti-TNF agents; however, the duration of the therapy over 1 year should be carefully evaluated on a case-by-case basis **[EL 4, RG C]**

Linee guida SIGE – IG IBD 2010

Study Design



• Infusions

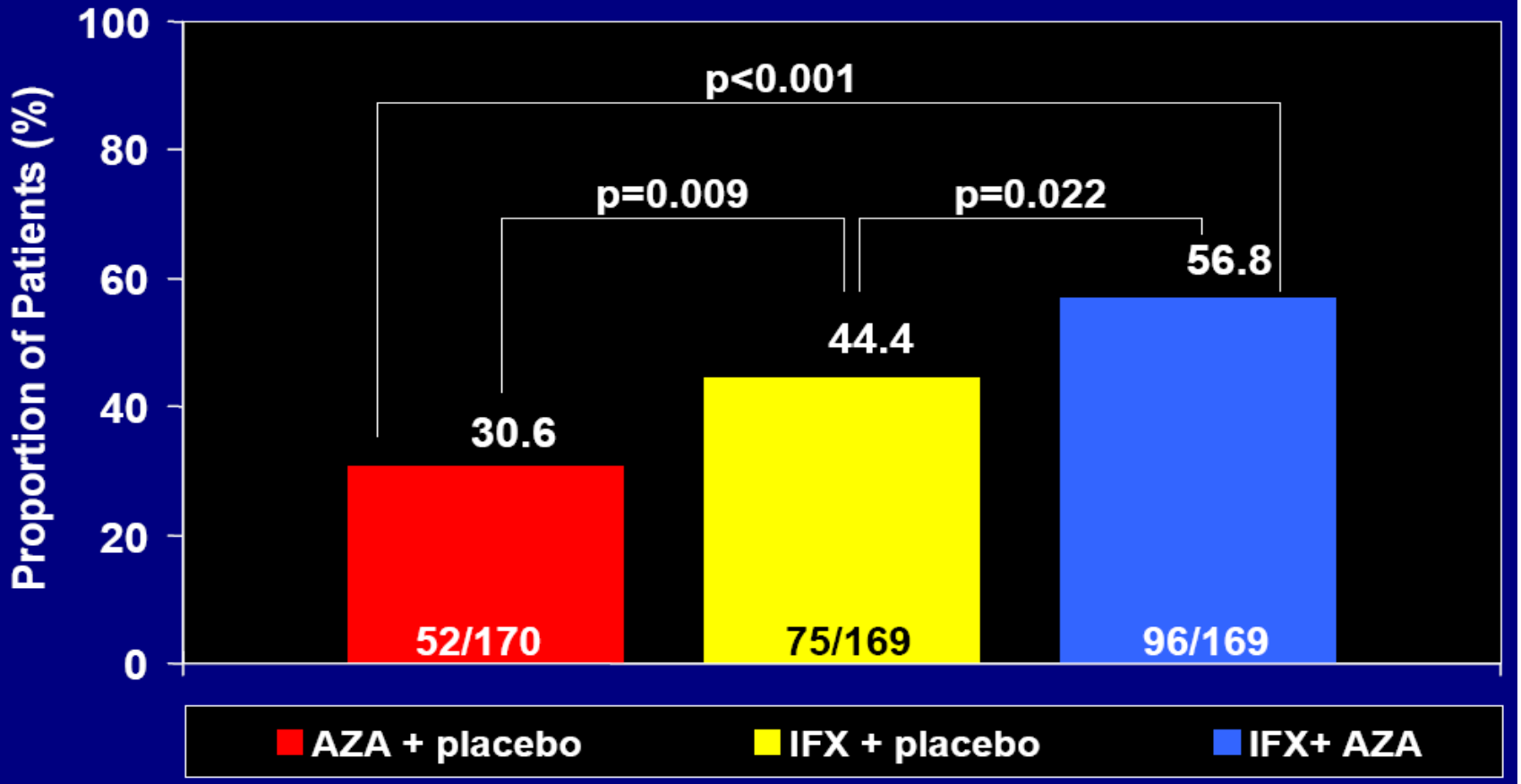
* Endoscopy performed at Weeks 0 & 26

Am J Gastroenterol. 2008;103(Suppl 1):Abstract 1117
Data on File, Centocor

SONIC

Clinical Remission Without Corticosteroids at Week 26

Primary Endpoint



Indicazioni alla terapia biologica nella malattia di Crohn

- Malattia luminale refrattaria
- Le fistole
- La stenosi
- La “early disease”
- La prevenzione delle recidive post-chirurgiche

Le fistole nella malattia di Crohn

- L'incidenza delle fistole nella malattia di Crohn in letteratura varia dal 17 al 43%.

- Schwartz et al. su 176 pazienti con mal. di Crohn della contea di Olmsted, Minnesota, seguiti dal 1976 al 1993, riportavano una incidenza cumulativa di almeno una fistola del 21% a un anno, del 26% a 5 anni, del 33% a 10 anni, del 50% a 20 anni. (Gastroenterology 2002)

Le fistole nella malattia di Crohn

- **Fistole interne**
  - Entero-enteriche, entero-coliche, gastro-coliche
  - Entero-vescicali, entero-vaginali, entero-mesenteriche

- **Fistole esterne**
  - Entero-cutanee
  - Perianali (semplici e complesse)

Infliximab e malattia di Crohn fistolizzante

- Lo studio di Present nel 1999 valutava il ruolo della terapia di induzione con infliximab alla dose di 5 mg/kg e 10 mg/kg a 0, 2 e 6 settimane nella MC con fistole (perianali, entero-cutanee).
- End-point primario era la riduzione del 50% del n° delle fistole attive; end-point secondario la chiusura totale delle fistole.
- Il 68% dei pz trattati con 5 mg/kg e il 56% di quelli con 10 mg/kg vs il 26% dei trattati con placebo ottenevano una risposta parziale; i dati per la chiusura totale erano 55%, 38% e 13%.

N Engl J Med 1999

Infliximab e malattia fistolizzante: lo studio ACCENT II

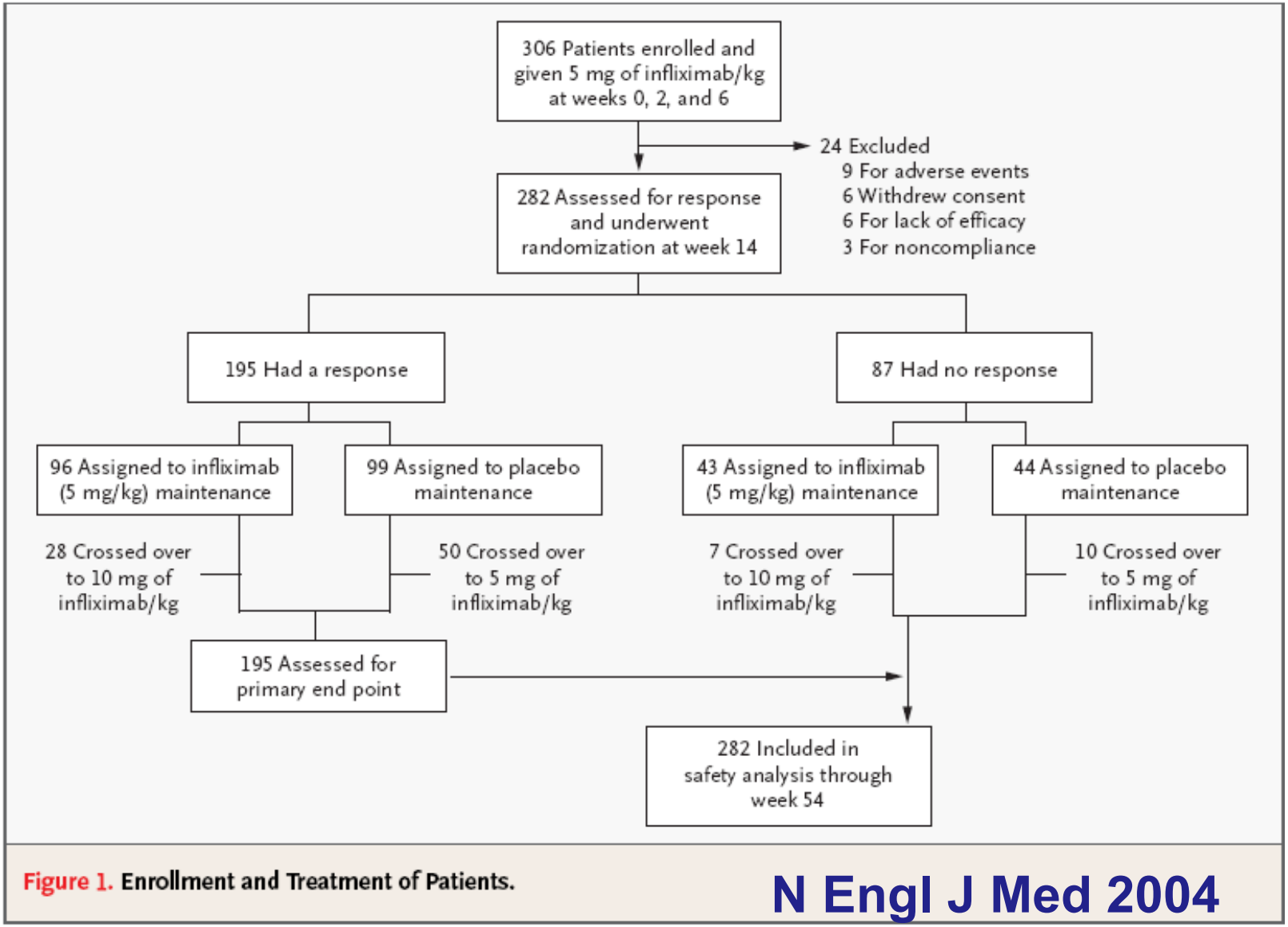
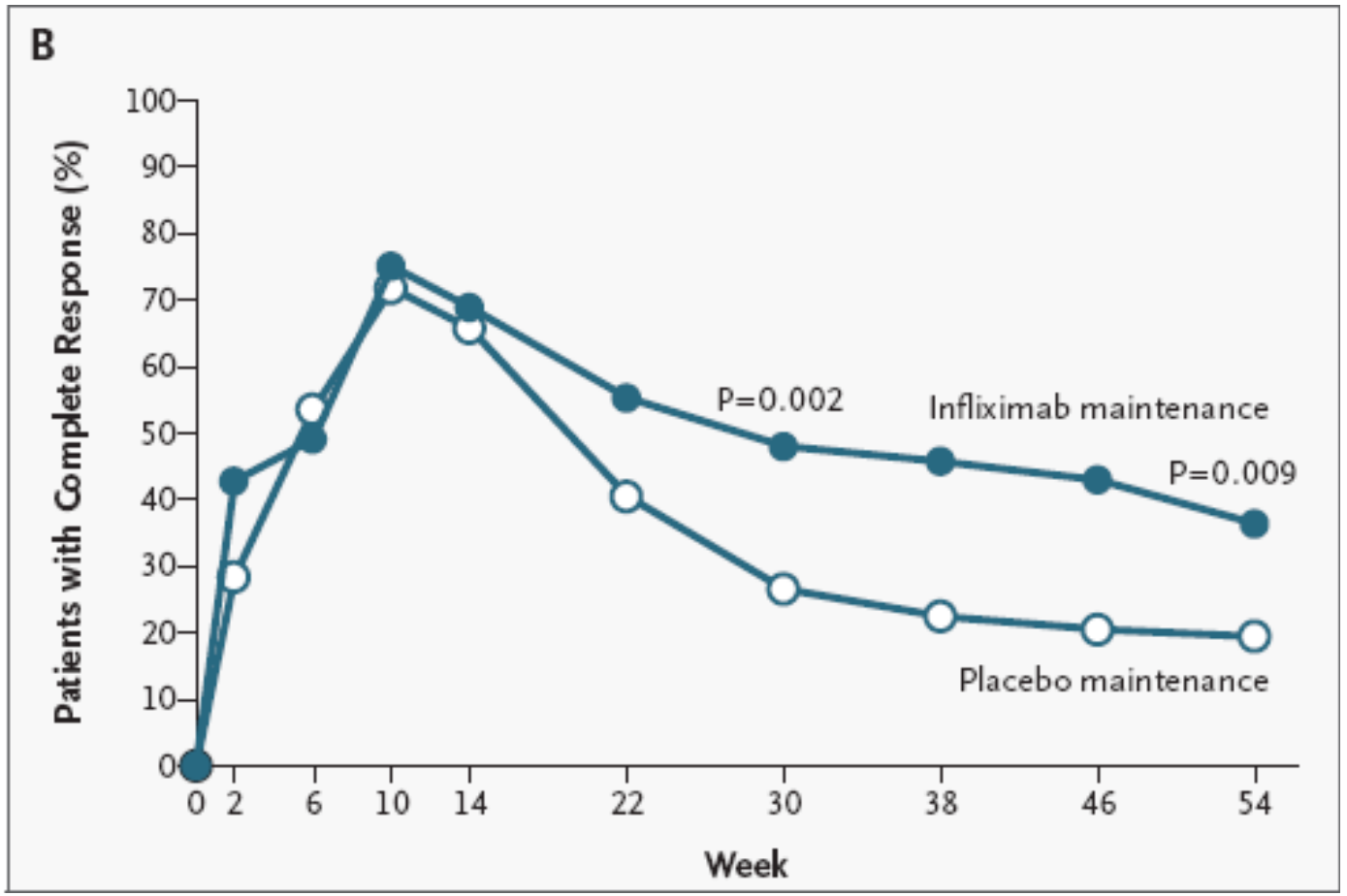


Figure 1. Enrollment and Treatment of Patients.

N Engl J Med 2004

Infliximab e malattia di Crohn fistolizzante: lo studio ACCENT II



N Engl J Med 2004

Tipo di fistola e risposta all'infliximab

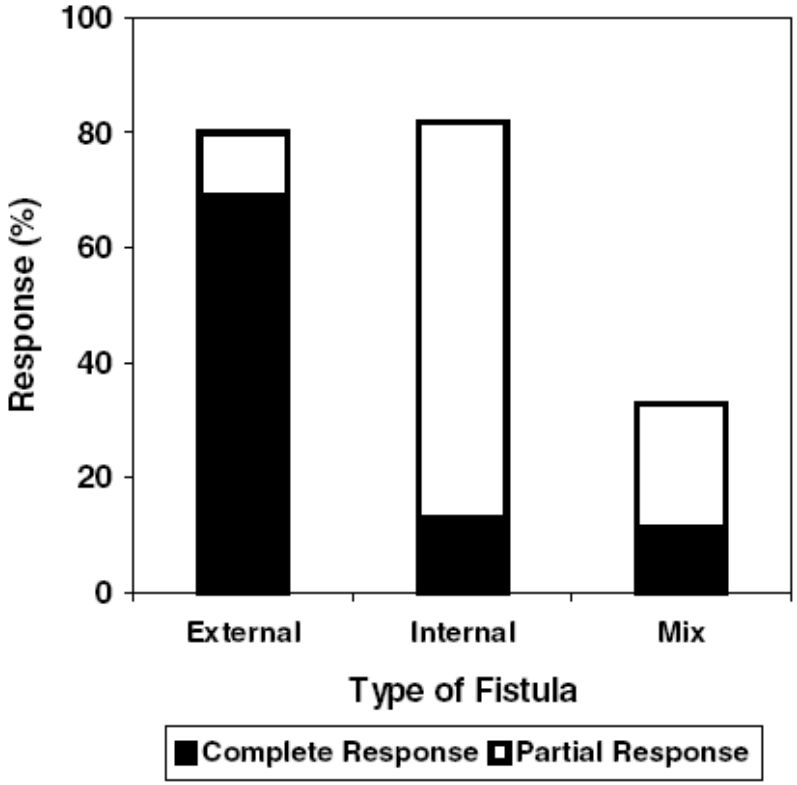


Figure 1. Response to infliximab according to fistula group.

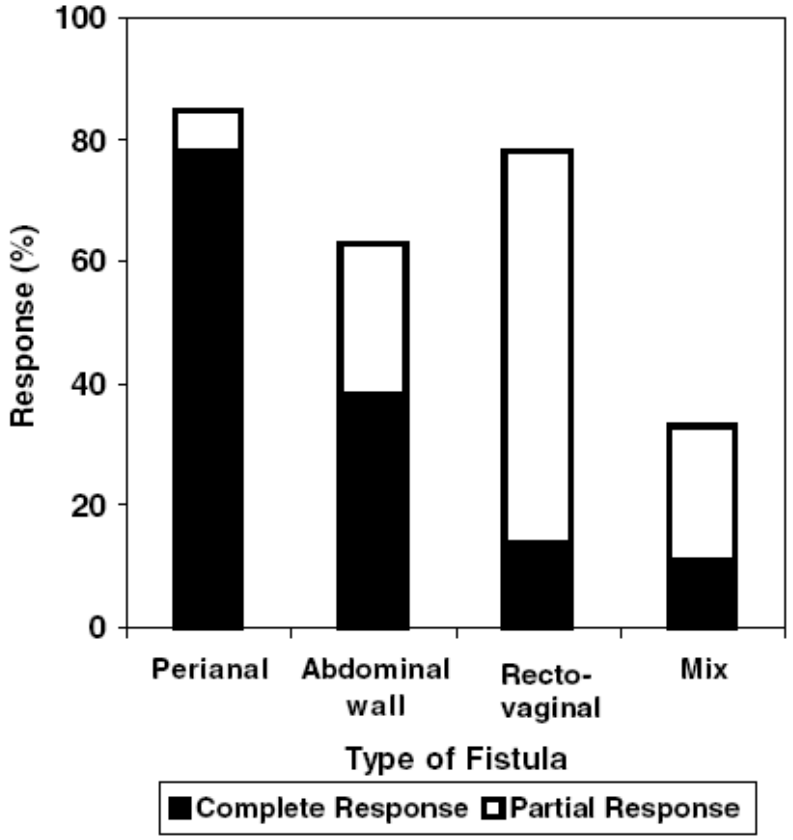


Figure 2. Response to infliximab according to fistula type.

Parsi et al. Am J Gastroenterol 2006

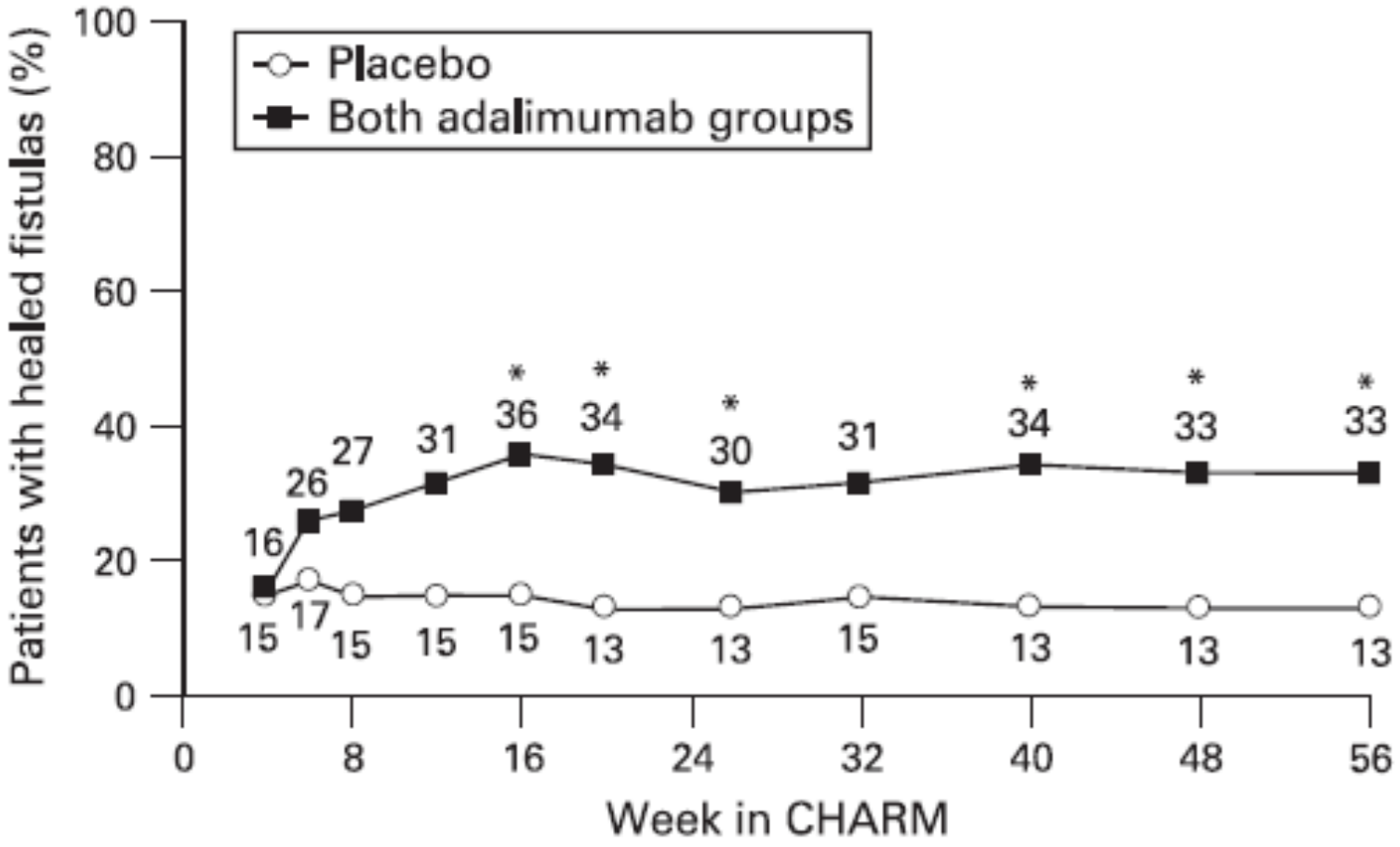
Adalimumab e fistole

- I dati dell'efficacia di adalimumab nel Crohn fistolizzante sono derivati da una subanalisi dello studio CHARM e da una sua estensione in aperto (ADHERE) che valutava il mantenimento della guarigione della fistola a 2 anni.

- A 56 settimane il 33% dei trattati vs il 13% del gruppo placebo otteneva la chiusura completa della fistola. Il 96% dei responders manteneva la chiusura della fistola 1 anno dopo.

Colombel et al. Gut 2009

Adalimumab e malattia fistolizzante (CHARM)



La terapia delle fistole nelle malattia di Crohn

Il trattamento delle fistole richiede un approccio integrato medico-chirurgico.

1. Definizione anatomica (EUA, MRI)
2. Drenaggio degli ascessi
3. Eradicazione dei tratti fistolosi con terapia medica e/o chirurgica
4. Prevenzione delle recidive
5. Preservazione della continenza e della integrità dello sfintere

Terapia combinata medico-chirurgica nelle fistole perianali

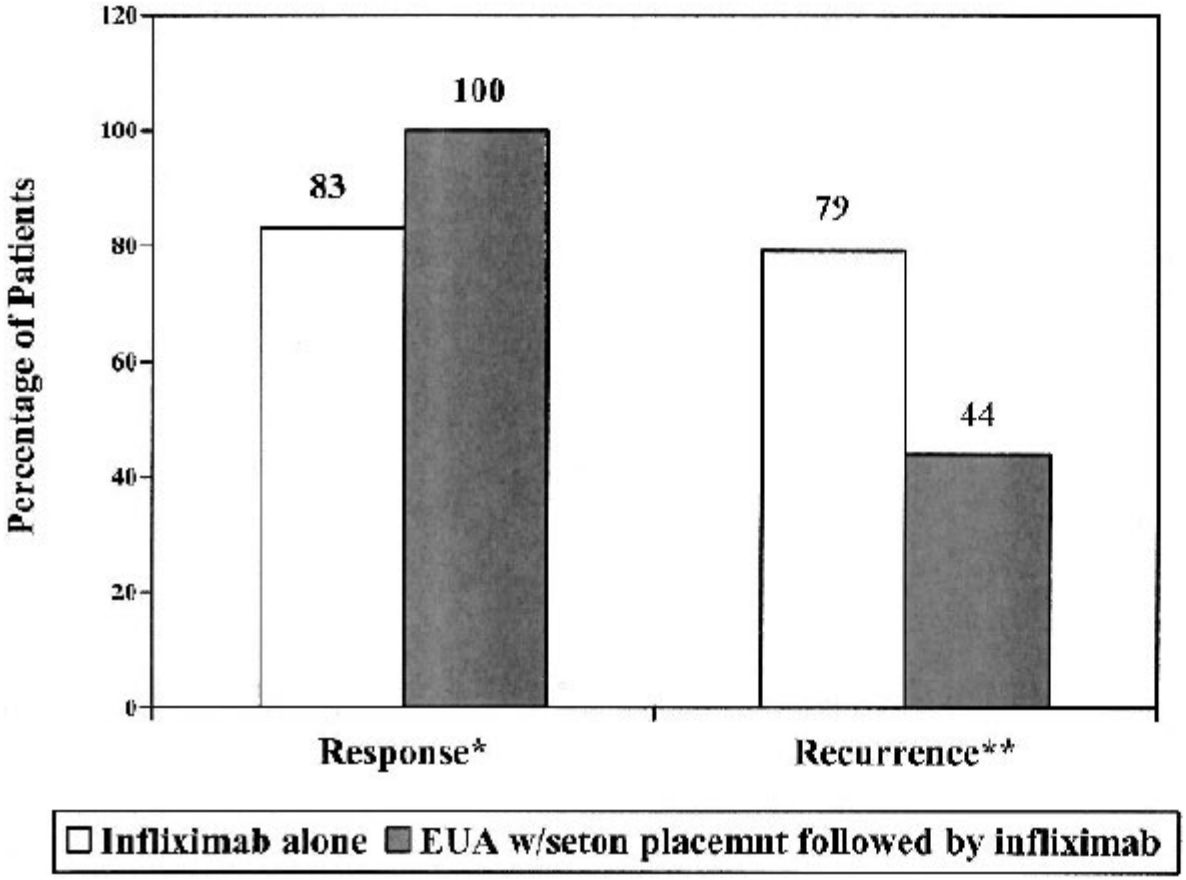


FIG. 1. Response and recurrence rates among patients with fistulizing Crohn's disease. Fistula response was defined as complete closure and cessation of drainage from the fistula. Recurrence was defined as re-opening of the external fistula track with active drainage. *p = 0.014; **p = 0.001.

Regueiro . IBD 2003

Terapia combinata medico-chirurgica nelle fistole perianali

- L'approccio integrato è stato confermato da altri gruppi.
- Non vi è accordo tuttavia sul timing della rimozione dei setoni e sulla tecnica da utilizzare per documentare la chiusura del tragitto fistoloso interno (AE, MRI).
- La chiusura dell'orificio esterno non significa risposta completa e può favorire la comparsa di ascessi.

Linee guida IG-IBD sull'uso dei biologici nelle fistole perianali

- Seton placement should be recommended [EL4, RG D], the timing of removal depending on subsequent therapy. Anti-TNFs should be used as the first choice of therapy for complex perianal Crohn's disease (Infliximab EL1b RG A; Adalimumab EL1b RG B); combination with surgical therapy is recommended despite a lack of clinical trials [EL4, RG D].
- Local Infliximab can be also considered, especially for patients with contraindications for the systemic use, despite the lack of controlled trials (EL5 RG D).
- In rectovaginal or pouch-vaginal fistulae surgery is usually necessary

Linee guida SIGE – IG IBD 2010

Indicazioni alla terapia biologica nella malattia di Crohn

- Malattia luminale refrattaria
- Le fistole
- La stenosi
- La “early disease”
- La prevenzione delle recidive post-chirurgiche

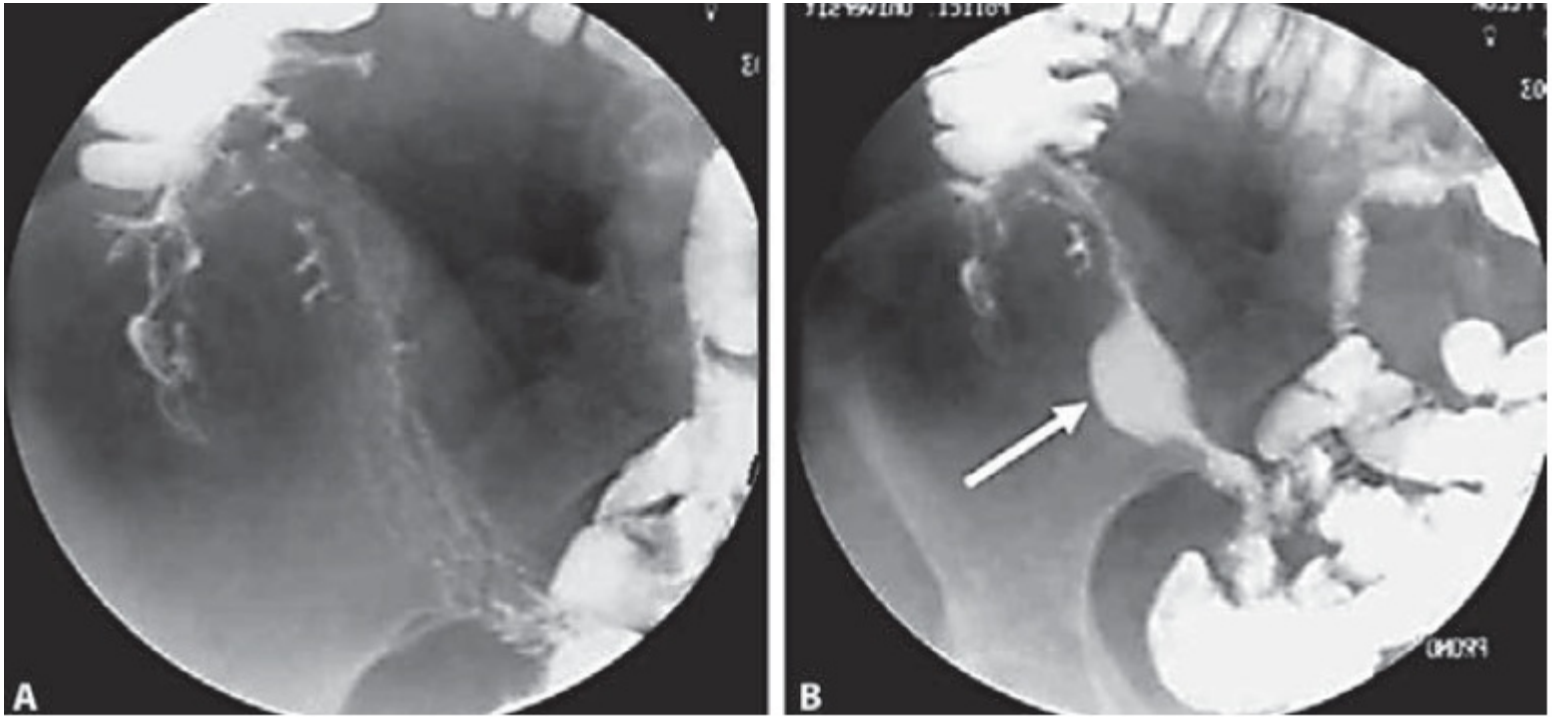
L’infliximab nelle stenosi

- Le stenosi sono le più comuni complicanze nella malattia di Crohn.
- Studi osservazionali hanno riportato la comparsa di nuove stenosi e/o di episodi subocclusivi dopo trattamento con infliximab.
- Nell’ACCENT I il 6% dei trattati sviluppava stenosi sintomatiche.
- Le stenosi intestinali sintomatiche sono considerate una controindicazione all’uso dei biologici (vedi anche scheda tecnica Remicade).

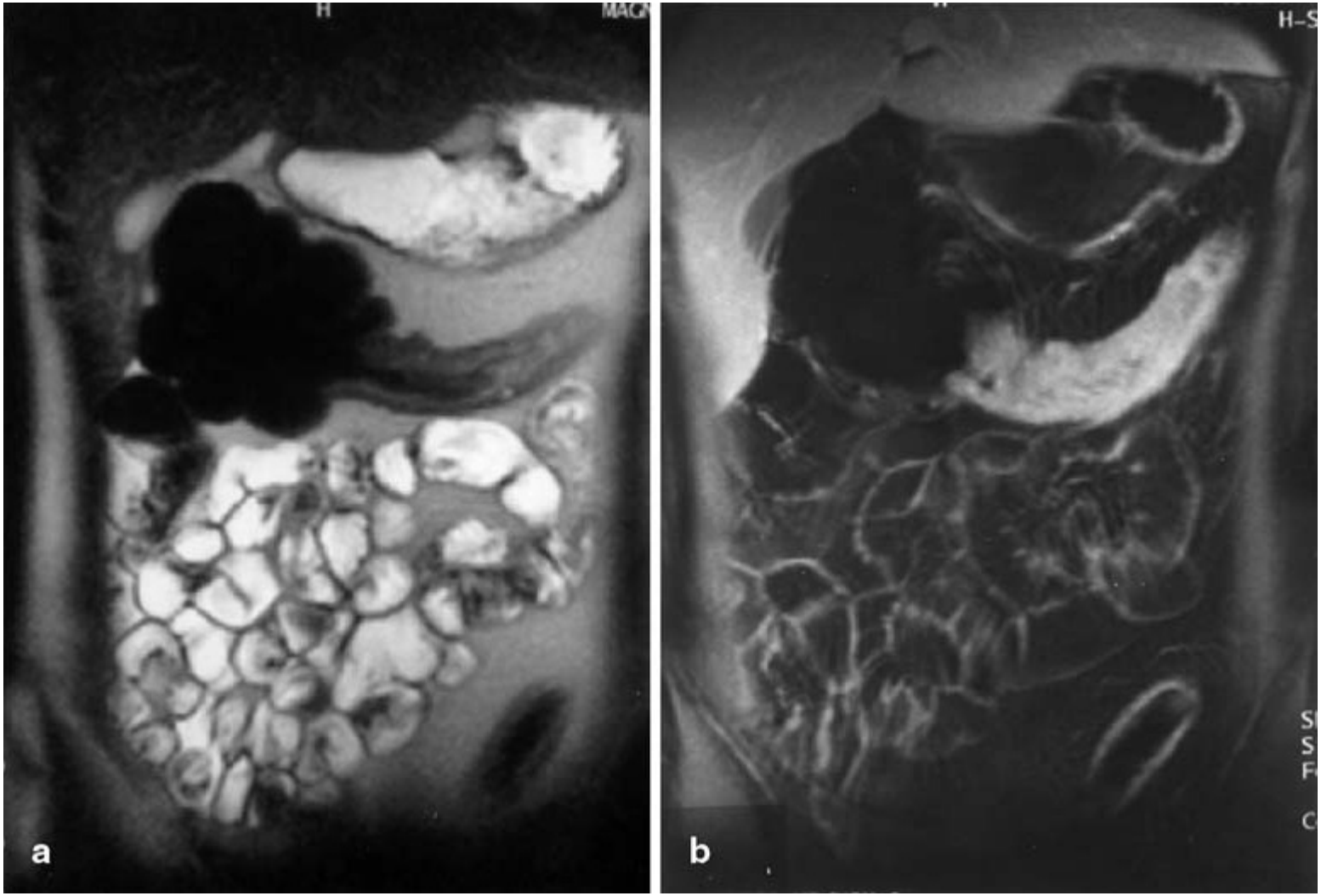
Fig. 2. *Differential diagnosis between an inflammatory stenosis* (**A**) *and a fibrotic stricture* (**B**): *small bowel enteroclysis*. Note the sharp, fixed and narrow lumen and the presence of a pre-stenotic dilation (arrow) in the fibrotic stricture (**B**) compared to the wider, less defined margins as well as with the absence of dilation in the inflammatory stenosis (**A**).

D. Sorrentino

Digestion 2008;77:38–47



RM e stenosi infiammatorie



Uso dei biologici nelle stenosi

- Le evidenze disponibili riguardano solo l'infliximab
- Non vi sono studi controllati ma solo case reports o case series
- Il disegno e la conduzione di tali trials sarebbe limitato dalla capacità di vari centri di classificare le stenosi

Infliximab treatment for symptomatic Crohn's disease strictures

A.-L. PELLETIER, B. KALISAZAN, J. WIENCKIEWICZ, N. BOUARIOUA & J.-C. SOULÉ

Aliment Pharmacol Ther **29**, 279–285

Table 1. Type and duration of obstructive symptoms at day 0. The same patient could have different symptoms ($n > 18$)

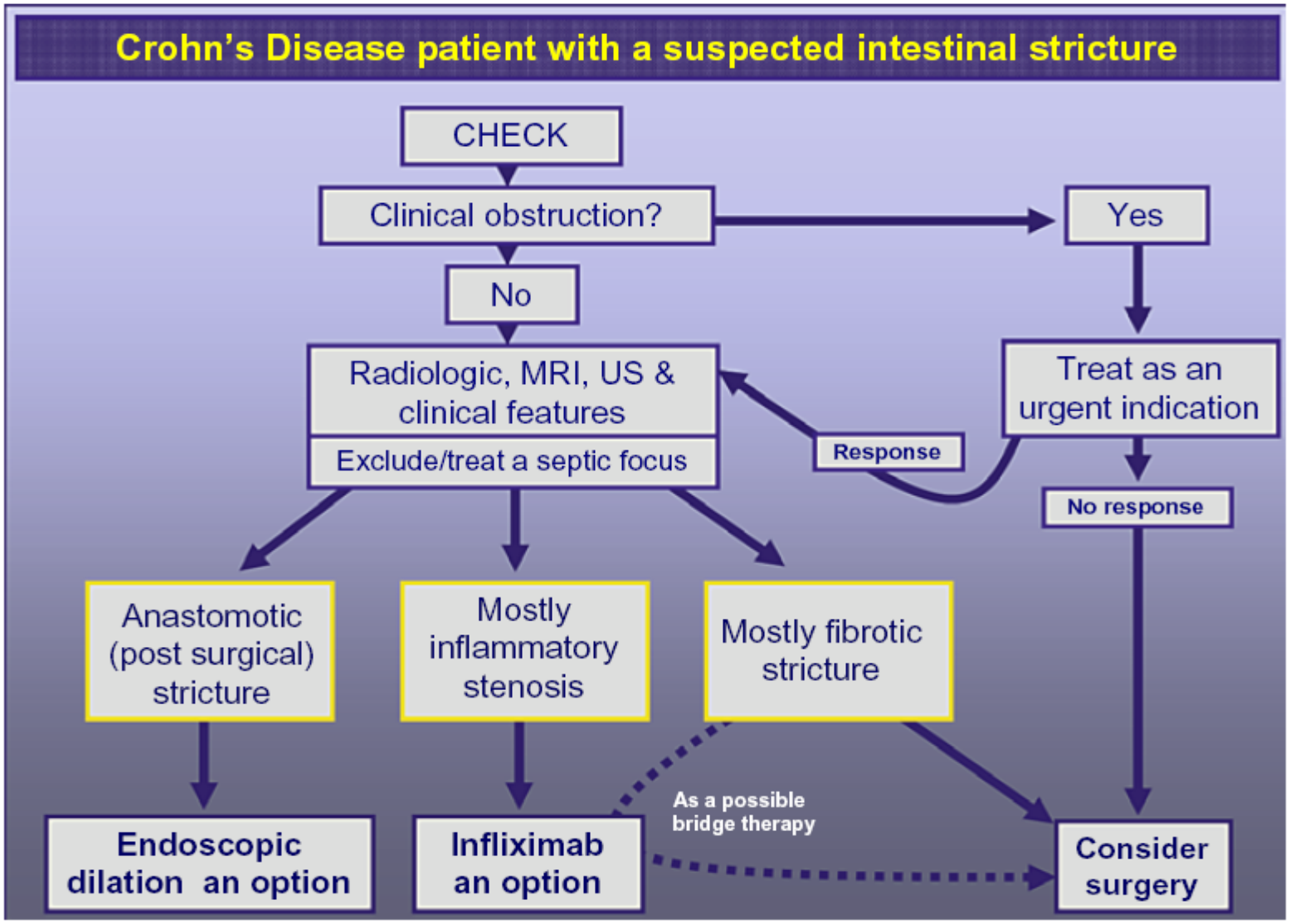
	n	Duration/D0 months (median; range)
Crampy abdominal pain	13	12 (2–120)
Spontaneously self limited obstruction	9	13 (0.3–72)
Complete obstruction	4	2.25 (0.3–2.4)*

* Between day 0 and the last episode of complete obstruction.

Table 4. Therapeutic decisions at week 8 of infliximab

Clinical evaluation	Treatment	*n*
Patients with a complete response ($n = 10$)	Maintenance infliximab infusion	7
	Infliximab interruption	3
Partial response ($n = 7$)	Maintenance infliximab infusion	6
	Infliximab interruption and surgical resection	1
Failure ($n = 1$)	Increased prednisone dosage and maintenance infliximab infusion	1

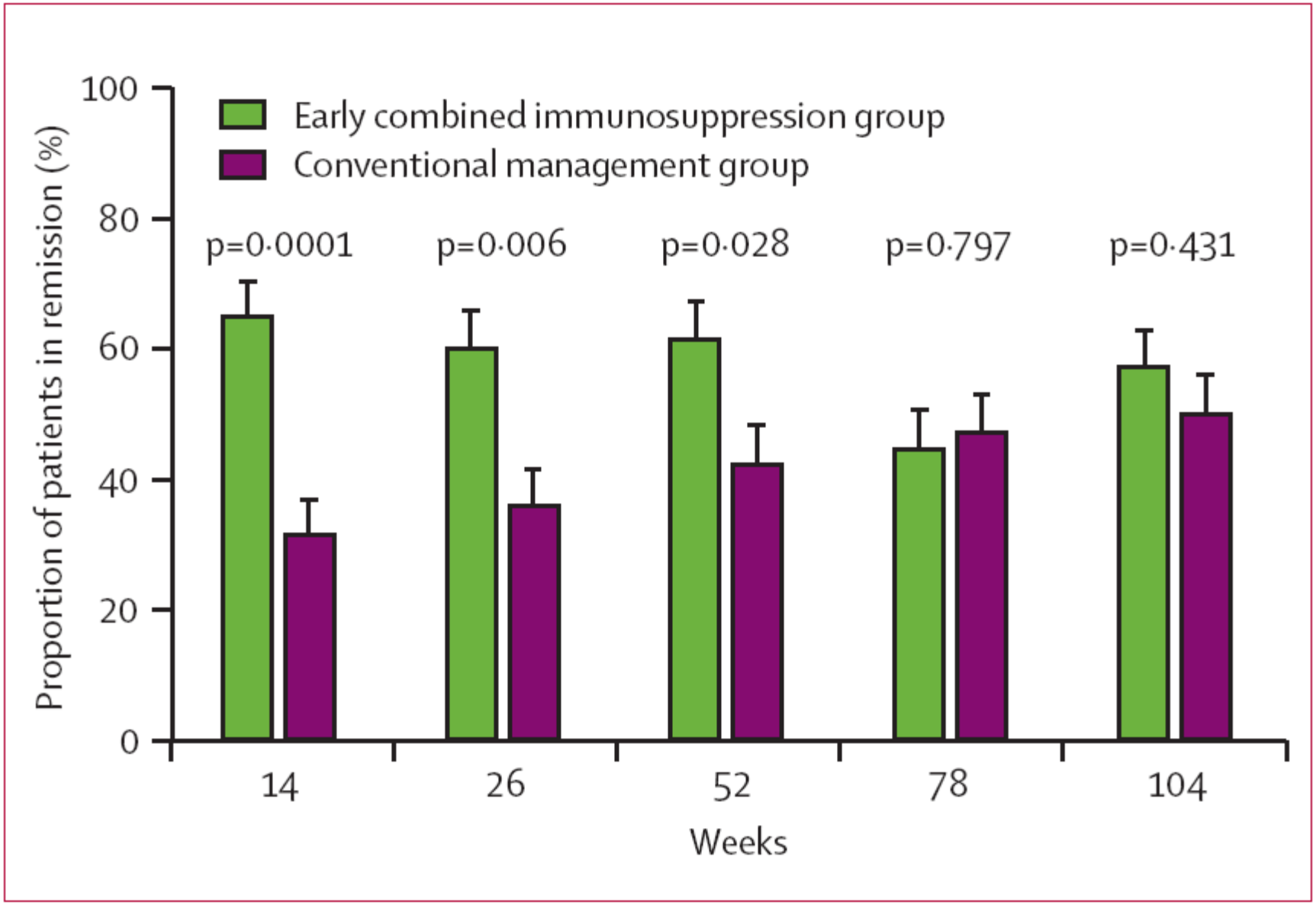
Approccio al paziente con stenosi intestinale



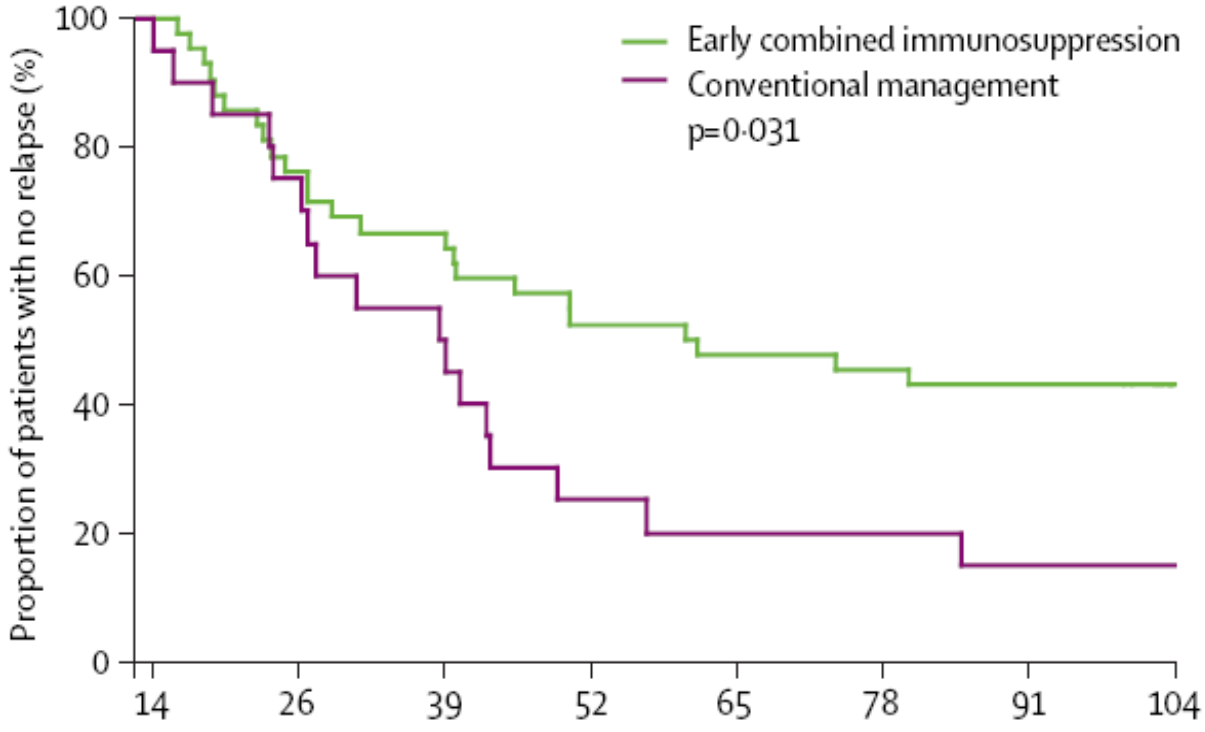
Indicazioni alla terapia biologica nella malattia di Crohn

- Malattia luminale refrattaria
- Le fistole
- La stenosi
- La “early disease”
- La prevenzione delle recidive post-chirurgiche

Terapia di combinazione IFX+IM
Step Up-Top Down trial (Lancet 2008)

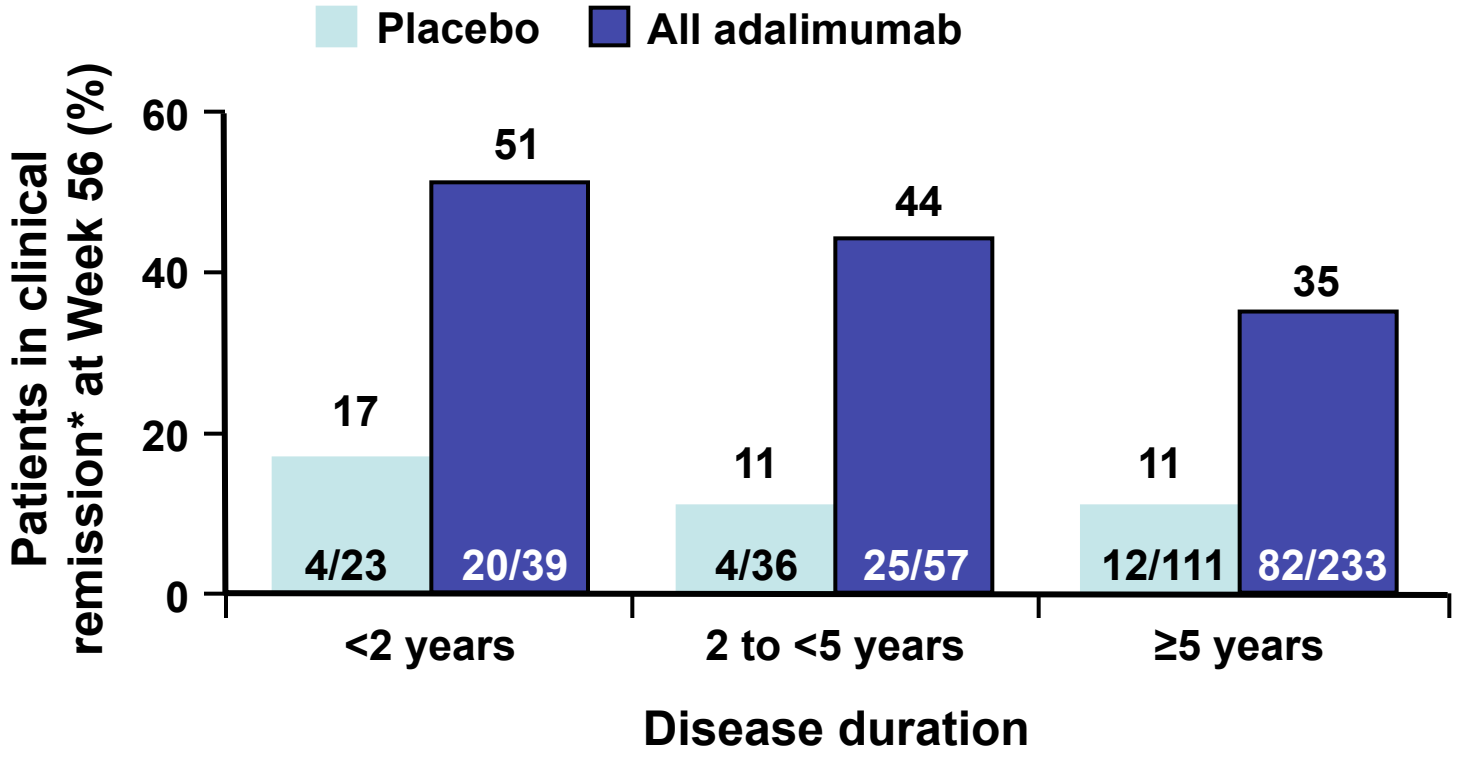


Step-up Top Down Trial (Lancet 2008)



Number at risk								
Early combined immunosuppression	42	33	28	22	20	19	18	7
Conventional management	20	15	10	5	4	4	3	3
Total	62	47	38	27	24	23	21	10

CHARM: disease duration and clinical remission* rates



*Clinical remission defined as CDAI <150
All patients received adalimumab 80/40mg induction therapy, before responders (≥70 decrease in CDAI by Week 4) randomised to adalimumab 40mg either eow or ew or to placebo
Data for randomised responders
CDAI: Crohn's disease activity index; ew: every week; eow: every other week

Schreiber S, *et al. Gastroenterol* 2007;132(Suppl 2):A147

Linee guida IG-IBD sull'uso dei biologici nel trattamento della " early disease"

Statement 5 A

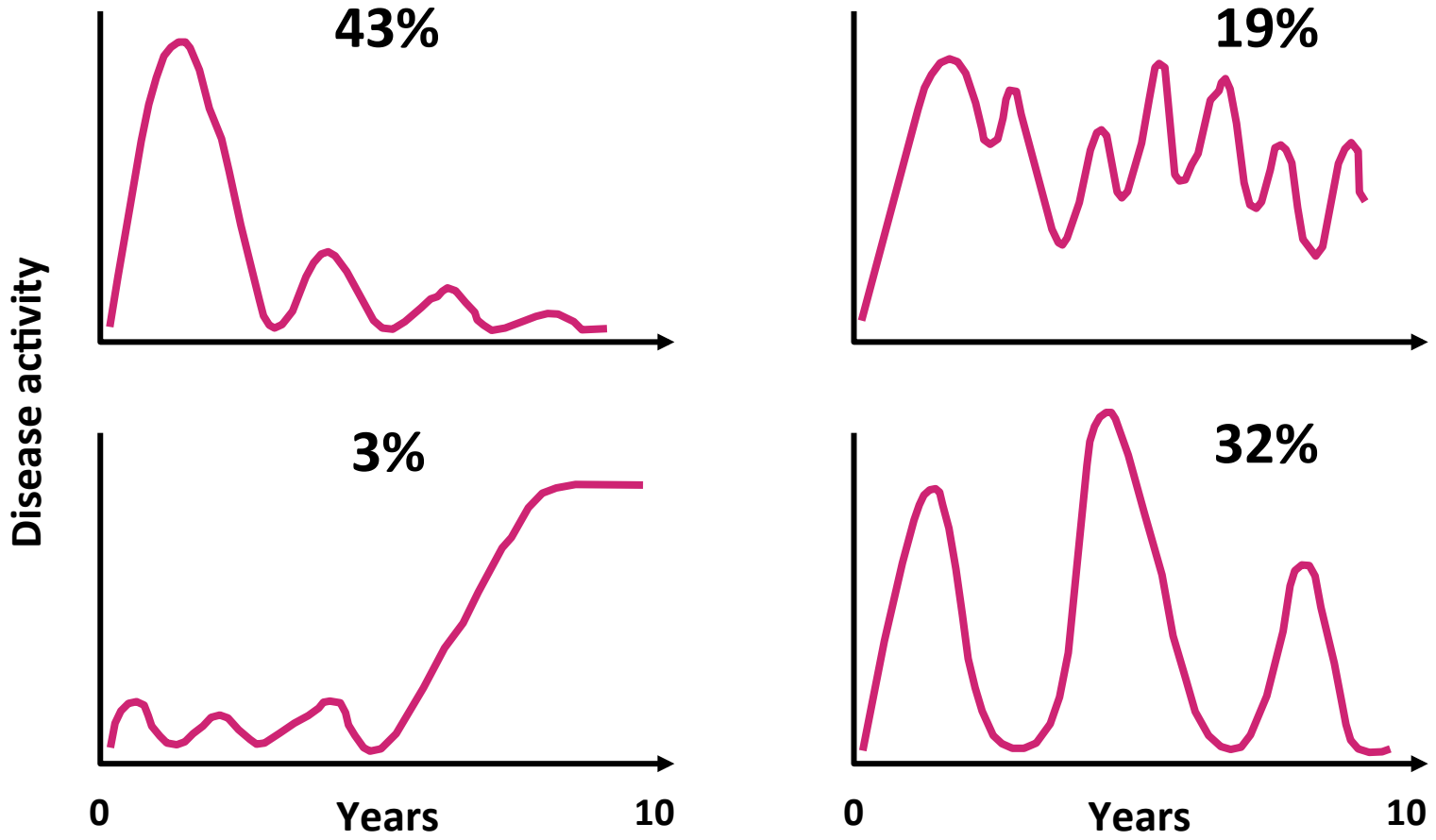
Early use of Biologics can improve patient outcomes in active Crohn's disease **[EL 2b, RGB]**. However, a widespread use of a "top down" approach in all CD patients cannot be recommended

Clinical factors at diagnosis can predict poor outcome in Crohn's disease and should be taken into account when determining the initial therapeutic approach **[EL 2b, RG C**]. However, the benefit of an early treatment with biologics in this patients subgroup is not proven

Linee guida SIGE – IG IBD 2010

However… Management Must Be Tailored to the Individual Patient

IBSEN: disease course in Crohn's disease over 10 years



Solberg IC, et al. Clin Gastroenterol Hepatol 2007;5:1430–8

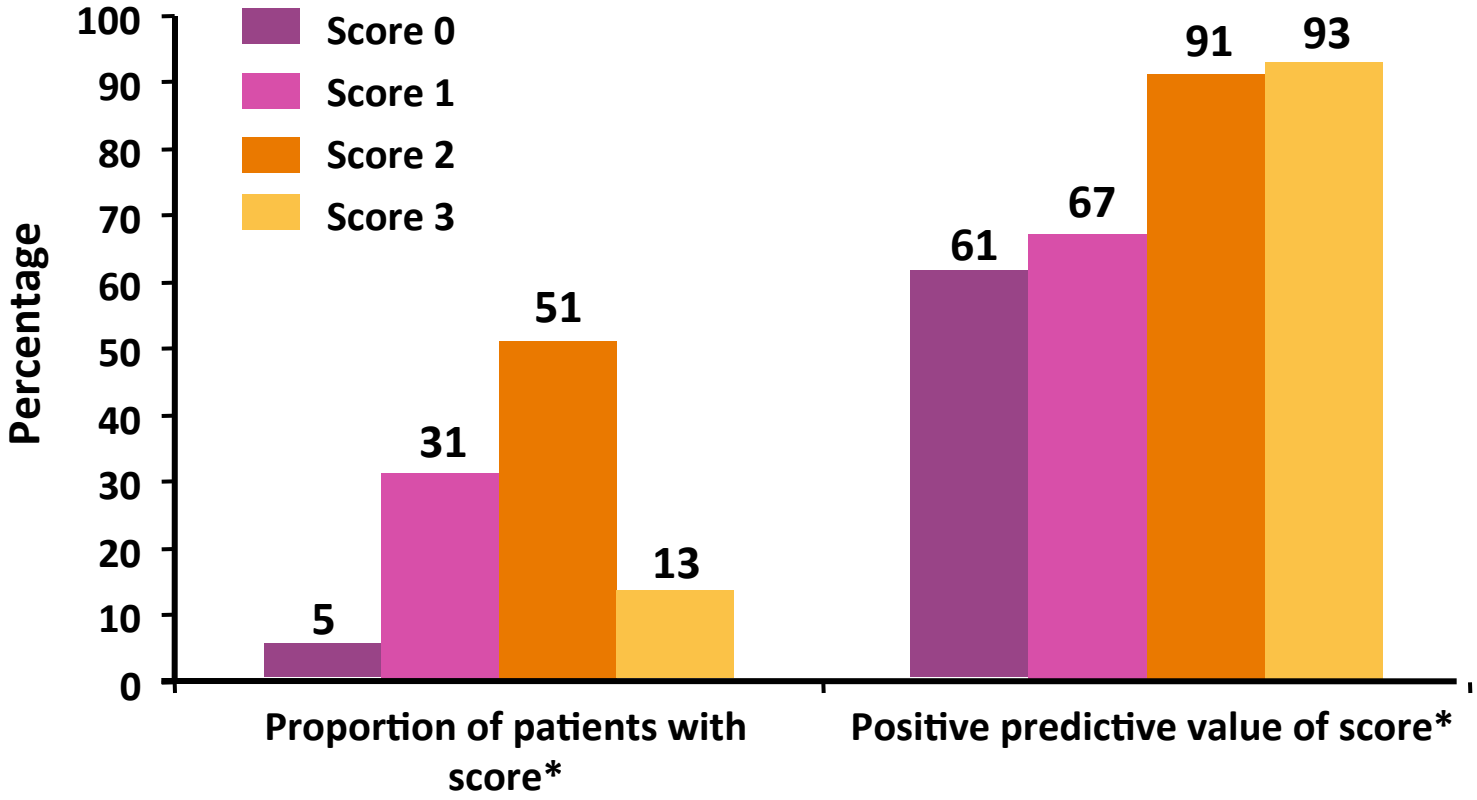
Missing data, 3%

When to Intervene early with anti-TNF Therapy: Poor Prognosis Patients

We must intervene with anti-TNF early in:

- Extensive small bowel disease
- Severe upper GI disease
- Severe rectal disease
- Younger patients
- Patients with perianal lesions
- Patients with early stricturing / penetrating disease
- Patients with deep colonic ulcers

Predictors of Disabling Crohn's Disease in the 5-Year Period after Diagnosis



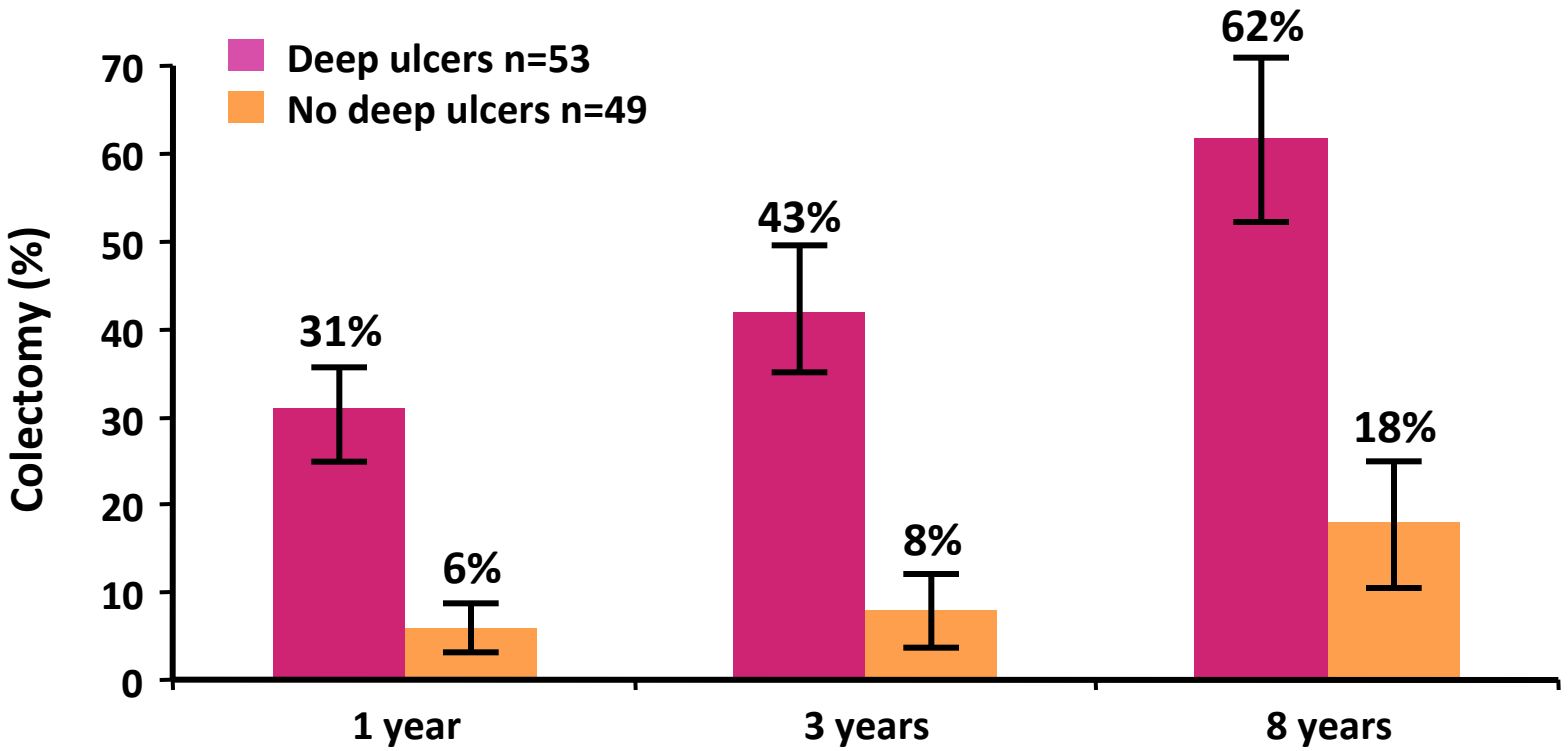
Score is based on the number of predictive factors at diagnosis: age <40 years, steroid treatment, perianal lesions

Beaugerie L, *et al. Gastroenterol* 2006;130:650–6

* Disabling Crohn's disease predictive score

Predicting Severe Crohn's Disease: Deep Ulcers at Colonoscopy

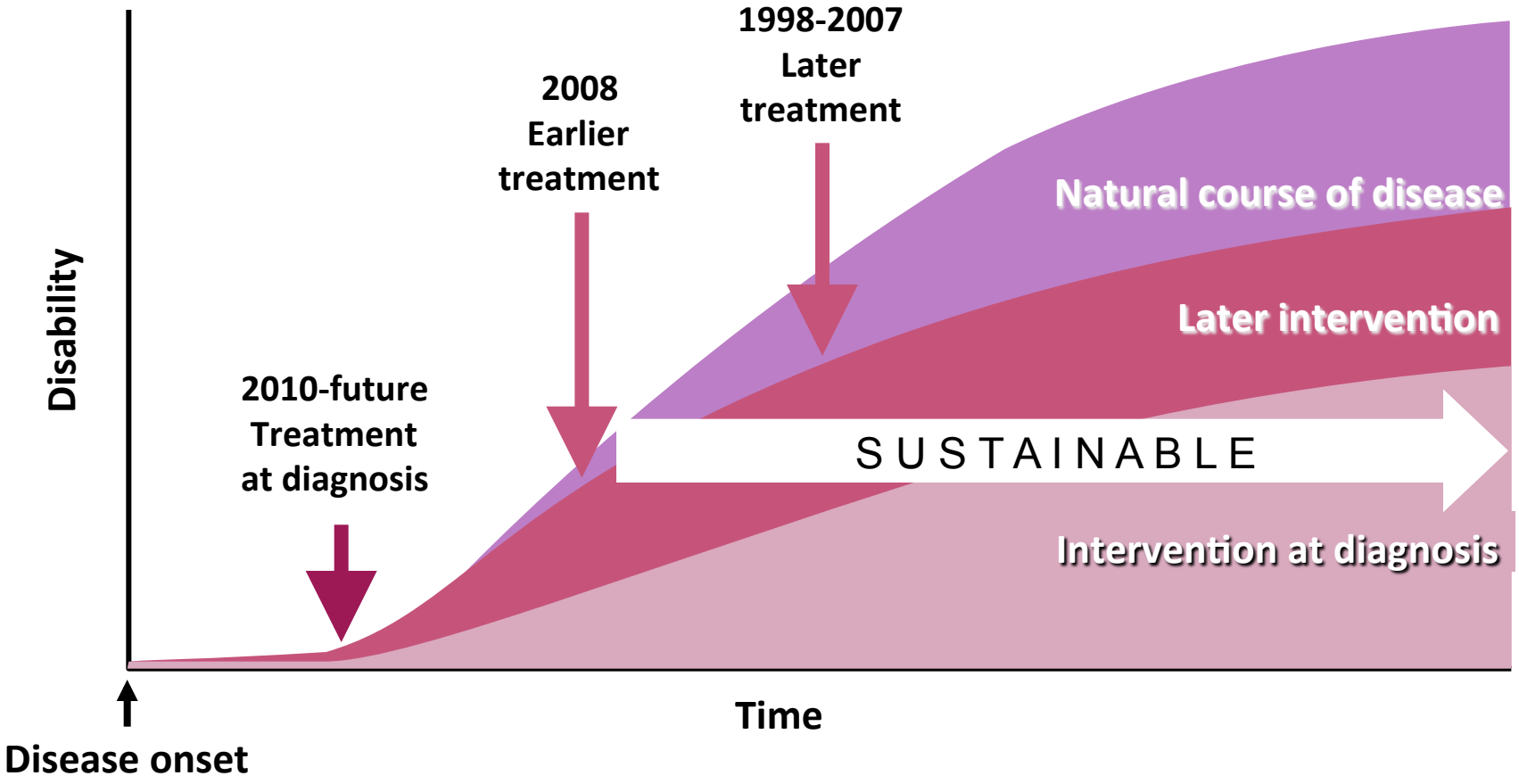
Probability of colectomy in patients with or without deep ulcers covering >10% of at least 1 colonic segment



Bars represent 95% confidence intervals. In univariate analysis, presence of deep ulcers at index colonoscopy were associated with a significantly higher risk of colectomy ($p<0.0001$)

Adapted from Allez M, et al. Am J Gastroenterol 2002;97:947–53

The Window of Opportunity for Intervention



Adapted from Jones J, Panaccione R. Curr Opinion Gastroenterol 2008; 24:475-81

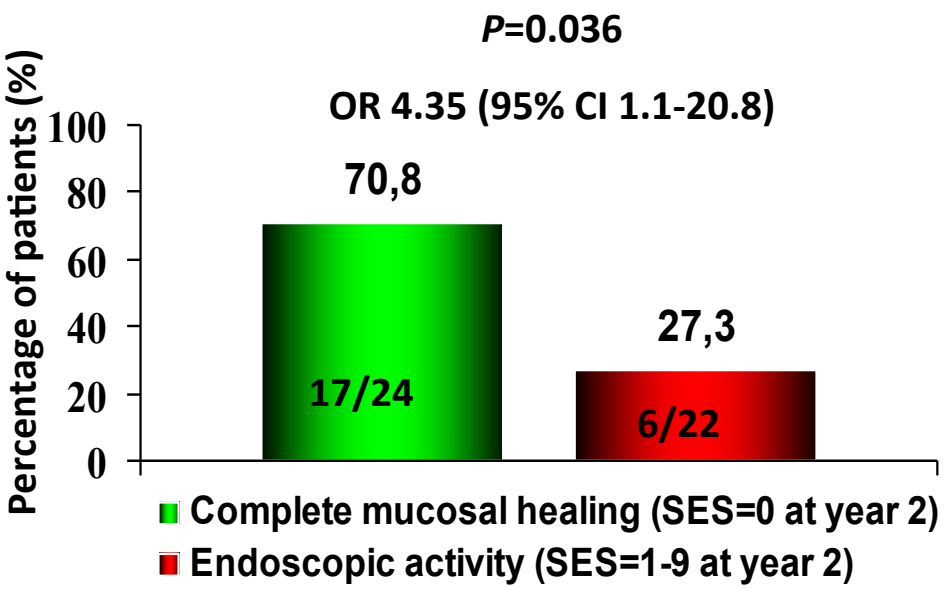
Biologici e guarigione mucosale

- La guarigione mucosale è un end-point secondario riportato nei trial sull'uso dei biologici nella malattia di Crohn
- La rilevanza clinica di questo obbiettivo non era stata finora dimostrata
- Baert et al hanno riportato che la guarigione mucosale predice una maggiore probabilità di remissione sostenuta libera da steroidi (Gastroenterology 2010)
- Si delinea un reale ruolo "disease modifying" dei biologici.

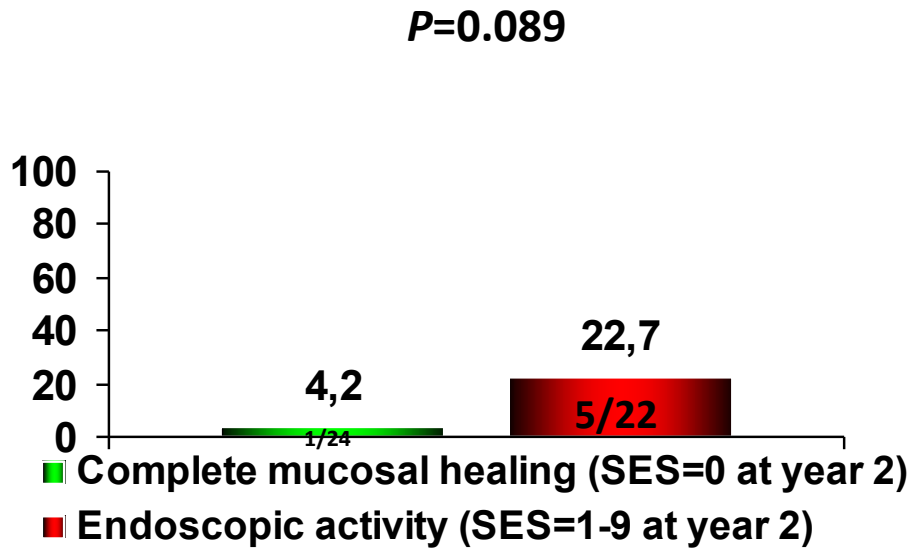
Mucosal healing in CD at year 2 predicts sustained clinical remission through year 3 + 4

49 patients from SUTD trial underwent colonoscopy at year 2

FU through year 3 and 4



Clinical remission (CDAI<150, no steroids, no resections) through Year 3+4

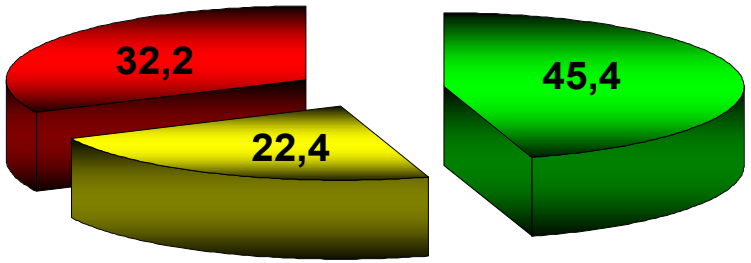


New or active draining fistula through Year 3+4

Baert F, et al. Gastroenterology 2010

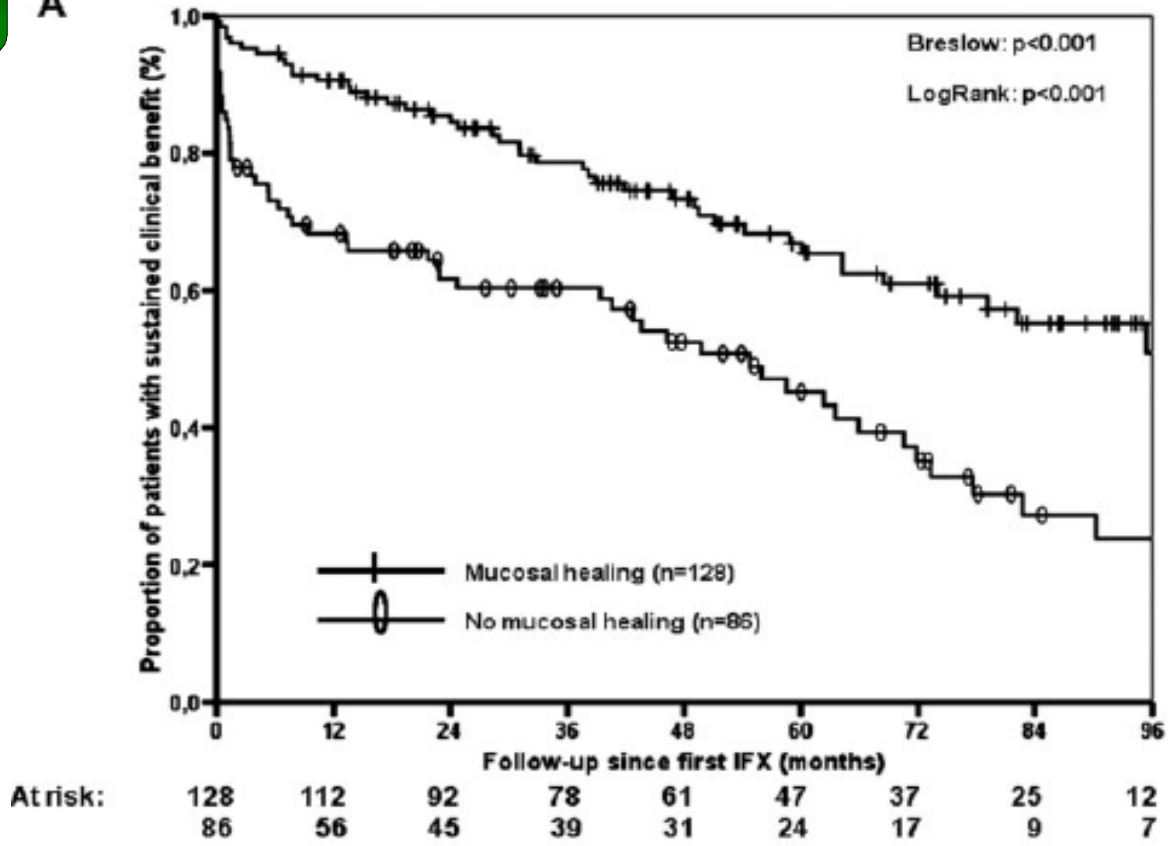
Mucosal healing and long term outcome of infliximab maintenance therapy (Leuven)

MH in 183 responders of 214 CD



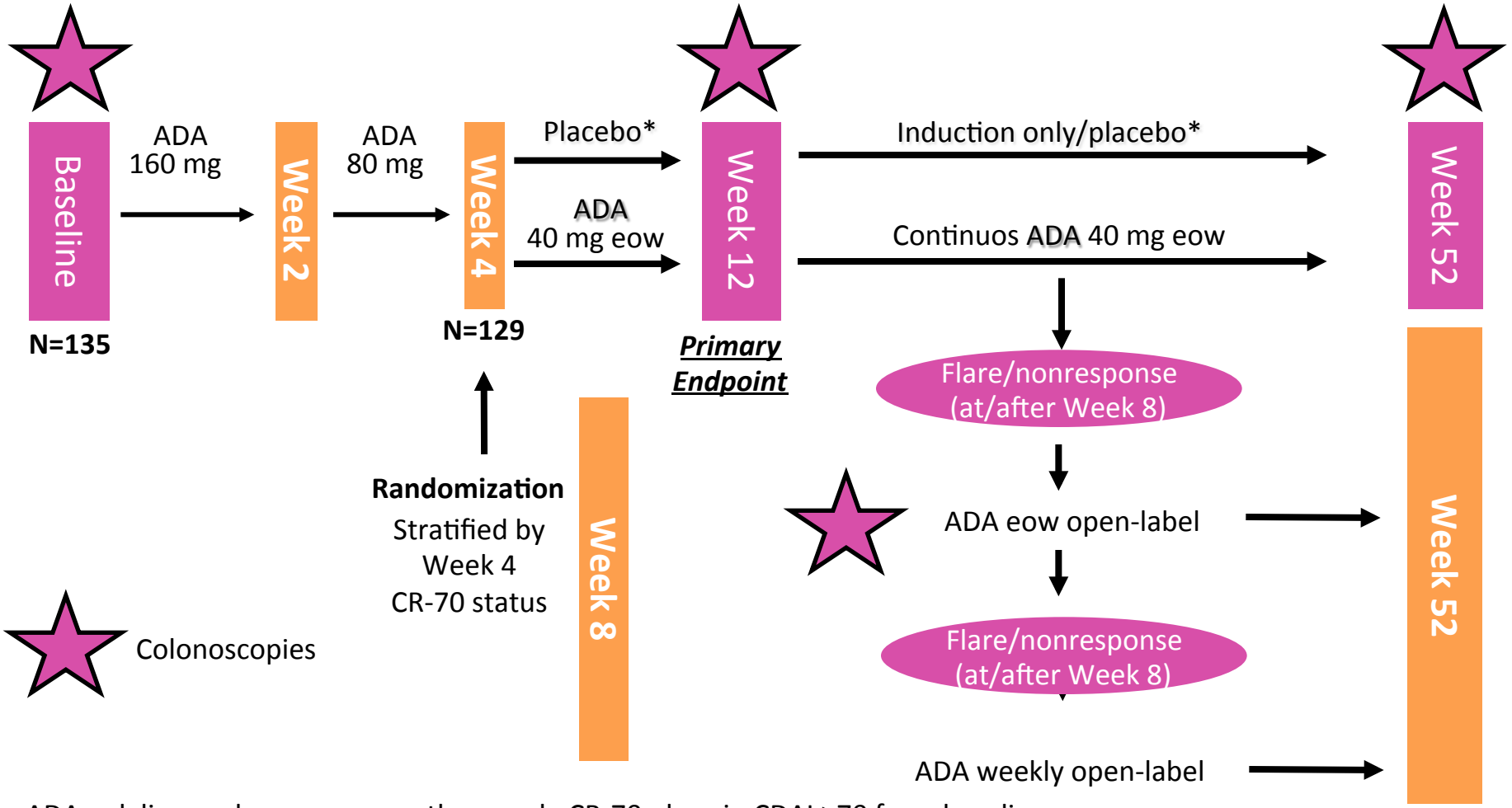
- **Complete MH (n=83)**
- **Partial MH (n=41)**
- **No MH (n=59)**

A



Schnitzler F, et al. IBD 2009

Adalimumab: EXTEND Study Design

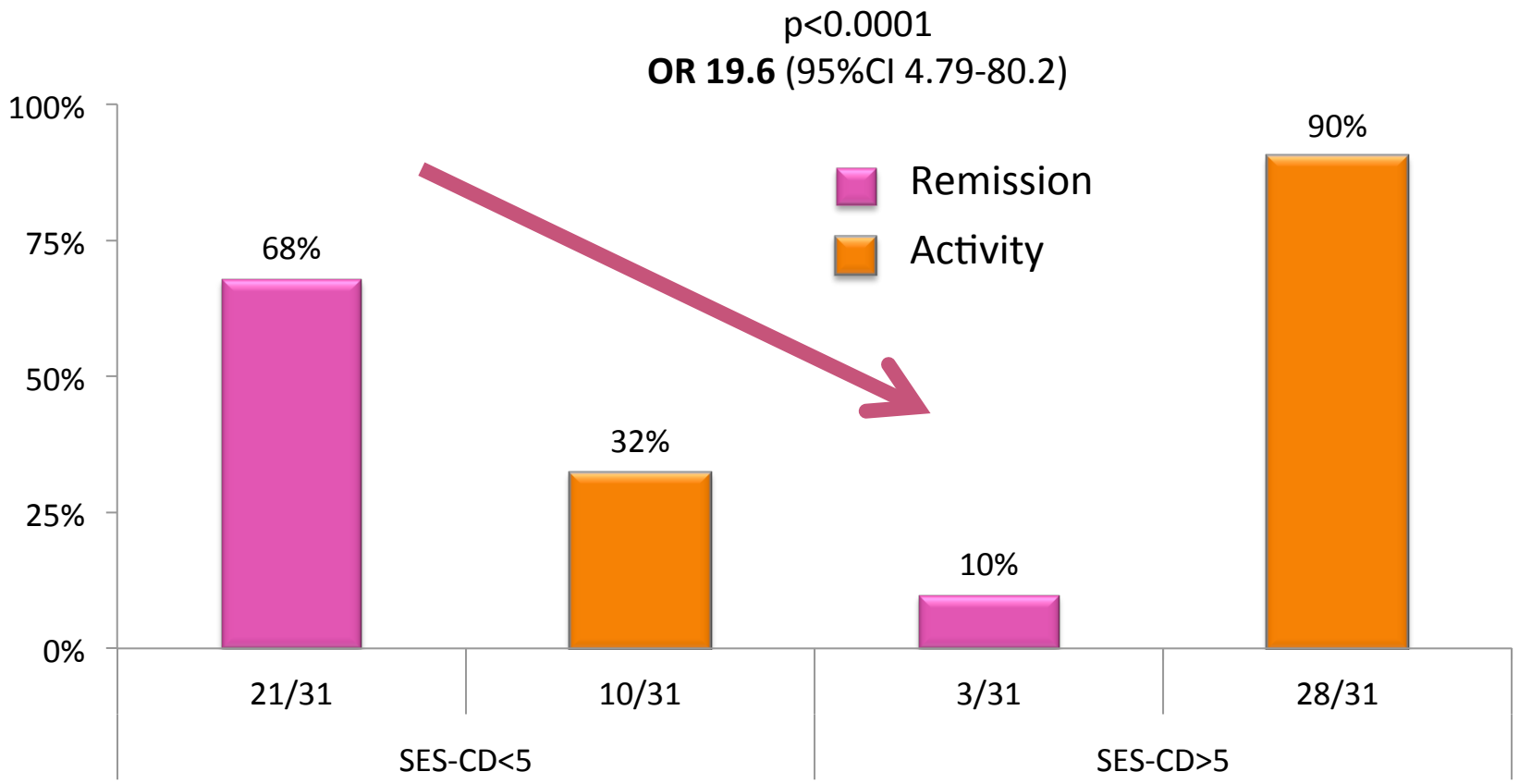


ADA, adalimumab; eow, every other week; CR-70, drop in CDAI ≥70 from baseline.
*ADA induction-only with placebo maintenance; reinitiation of ADA for flare/nonresponse.

Rutgeerts, P. et al. Gastroenterology 2009; 136(Suppl 1): A-116.

Endoscopic Healing & Remission

Among patients treated with anti-TNF, the best endoscopic response at w12 is associated to highest chances of clinical remission at 1 year (CDAI<150 alla w52)



Rutgeerts P, et al. ECCO 2010

Indicazioni alla terapia biologica nella malattia di Crohn

- Malattia luminale refrattaria
- Le fistole
- La stenosi
- La “early disease”
- La prevenzione delle recidive post-chirurgiche

Infliximab e prevenzione delle recidive postchirurgiche (Regueiro et al.)

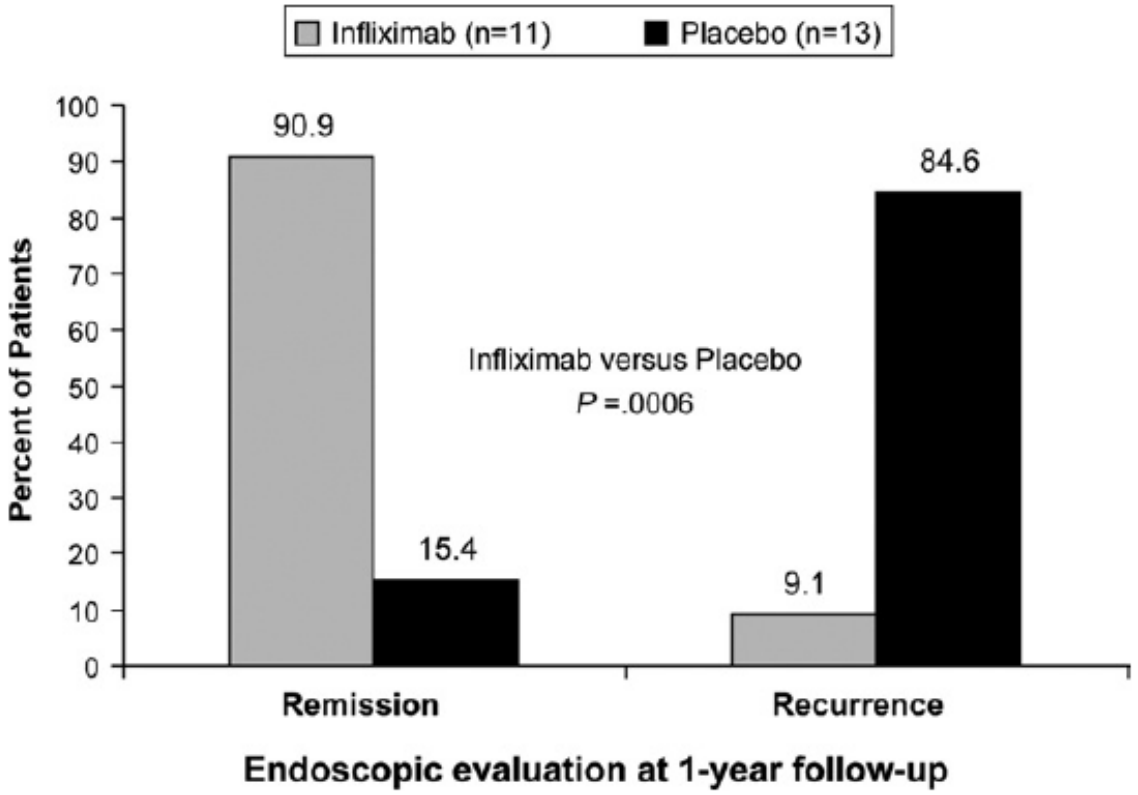


Figure 1. Percentage of patients in remission (endoscopic grade score of i0 or i1) vs recurrence (endoscopic grade score of i2, i3, or i4) of Crohn's disease at the 1-year endoscopic evaluation by random assignment to infliximab or placebo. Infliximab vs placebo: $P = .0006$.

GASTROENTEROLOGY 2009;136:441–450

Linee guida IG-IBD sull'uso dei biologici nella prevenzione della recidiva post-chirurgica

Prevention of post-operative recurrence

Infliximab could be considered in selected high risk patients **[EL2b, RG B]**

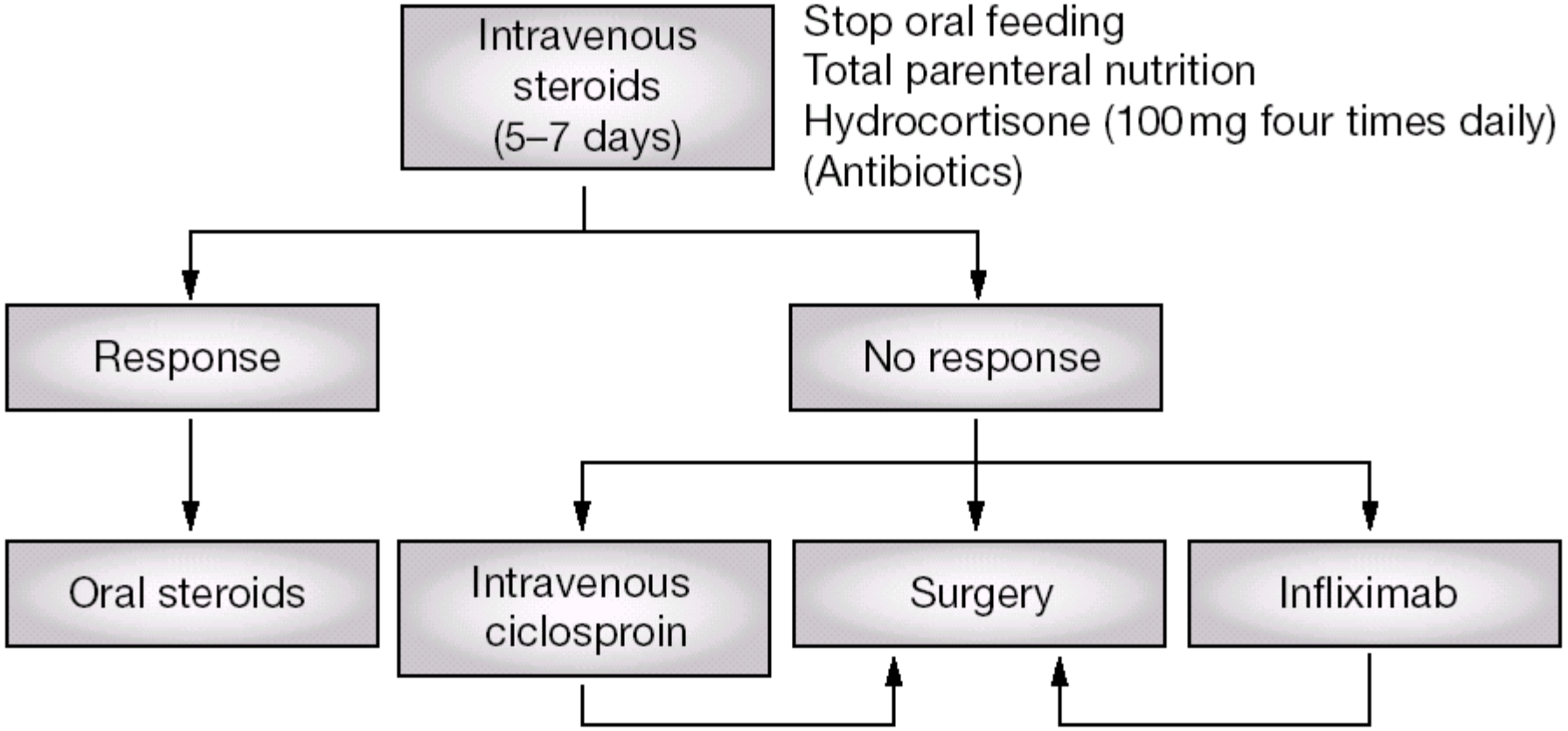
Linee guida SIGE – IG IBD 2010

Indicazioni alla terapia biologica nella rettocolite ulcerosa

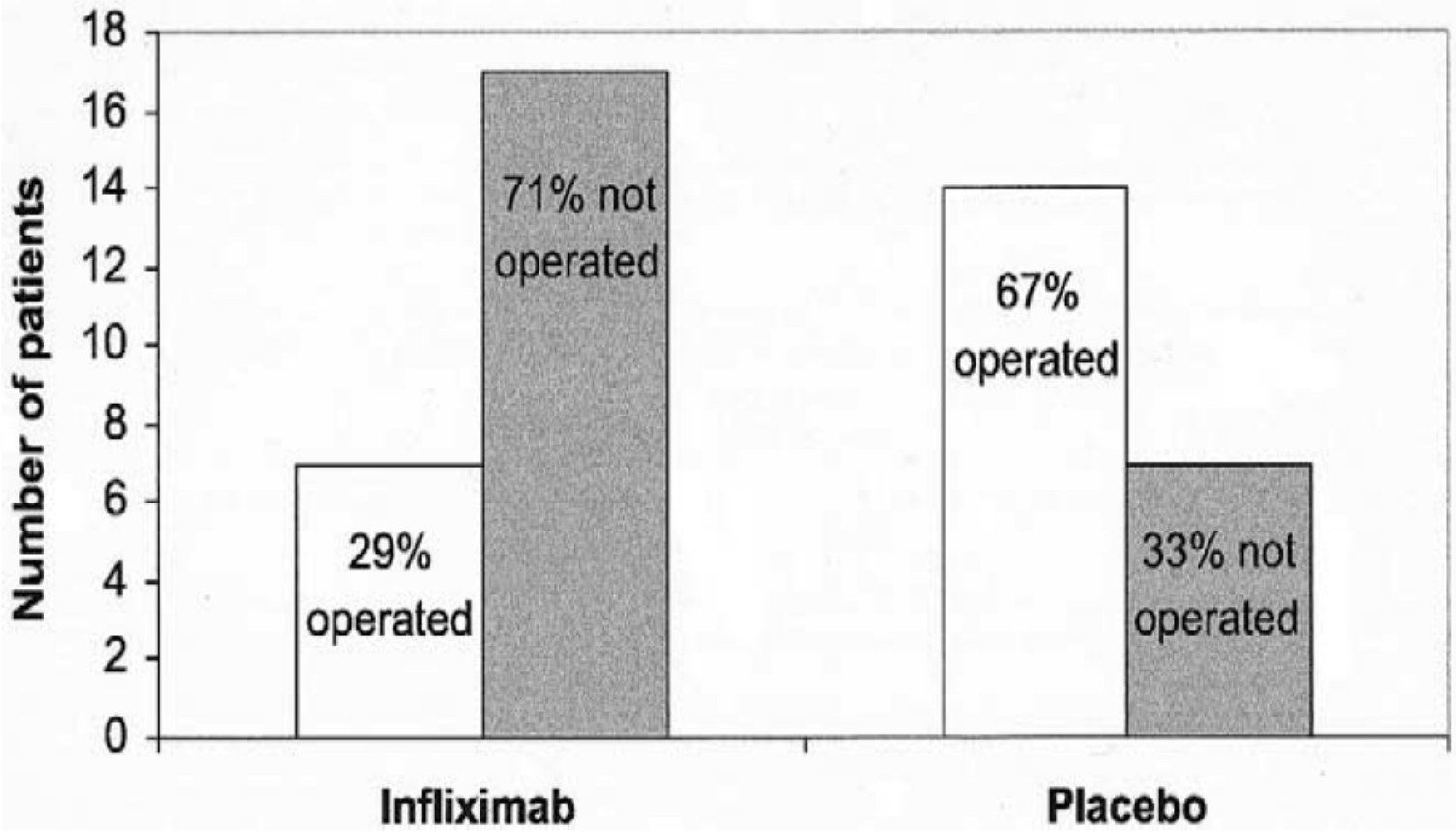
- “Rescue therapy” nella colite severa refrattaria allo steroide

- Malattia cronicamente attiva

Il trattamento della RCU severa



RCTs sull'efficacia dell' anti-TNFα vs placebo in pazienti con RCU severa



Jarnerot et al. Gastroenterology 2005

Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up

A. KOHN[1,*], M. DAPERNO[1,†], A. ARMUZZI‡, M. CAPPELLO§, L. BIANCONE¶, A. ORLANDO**, A. VISCIDO††, V. ANNESE‡‡, G. RIEGLER§§, G. MEUCCI¶¶, M. MARROLLO*, R. SOSTEGNI†, A. GASBARRINI‡, S. PERALTA§ & C. PRANTERA*

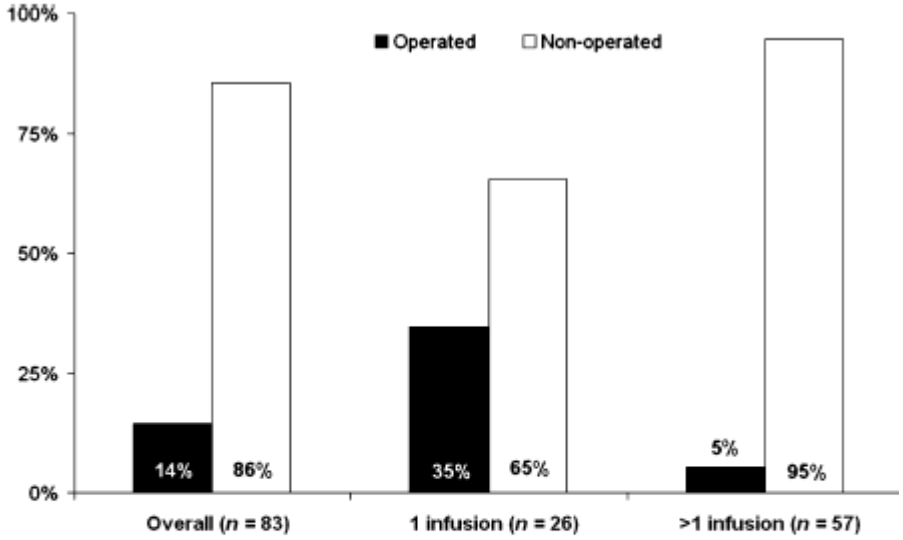


Figure 1. Proportion of surgical/non-surgical patients stratified according to the infusions schedule: one or more than one infusion (two or three infusions). Difference in colectomy rate between one infusion and more than one infusion was highly significant (Fisher's exact test $P = 0.001$; OR = 9.53, 95% CI: 2.31–39.26).

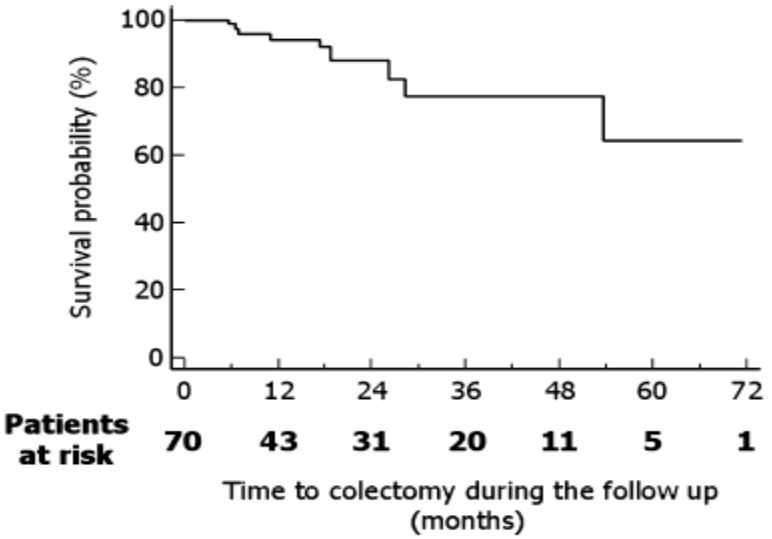


Figure 4. Cox proportional hazards regression of time-to-colectomy after the first 2 months of first infliximab infusion; no covariate was significantly and independently associated with the outcome, and therefore only one solid line is reported. The number of patients at risk at every 12 months time point is reported.

Aliment Pharmacol Ther 26, 747–756

Infliximab e colectomia: l'esperienza di Oxford (Aliment Pharmacol Ther 2007)

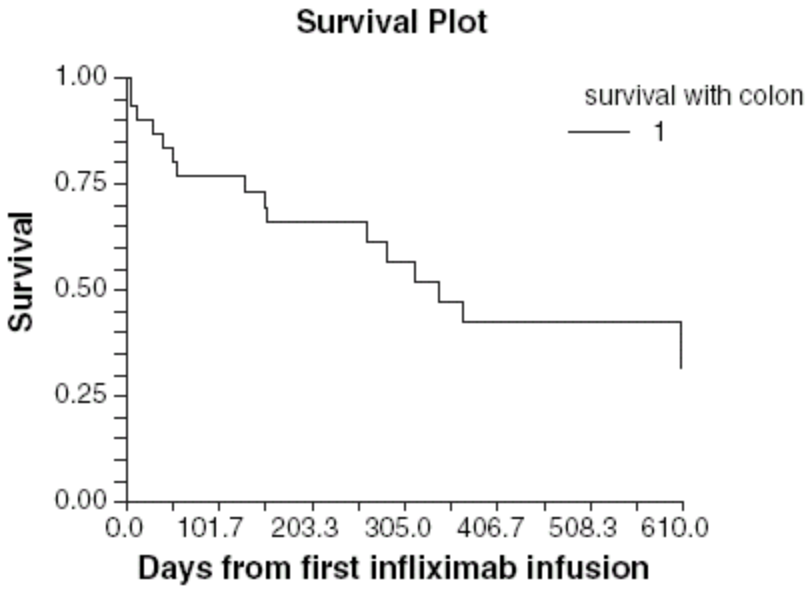
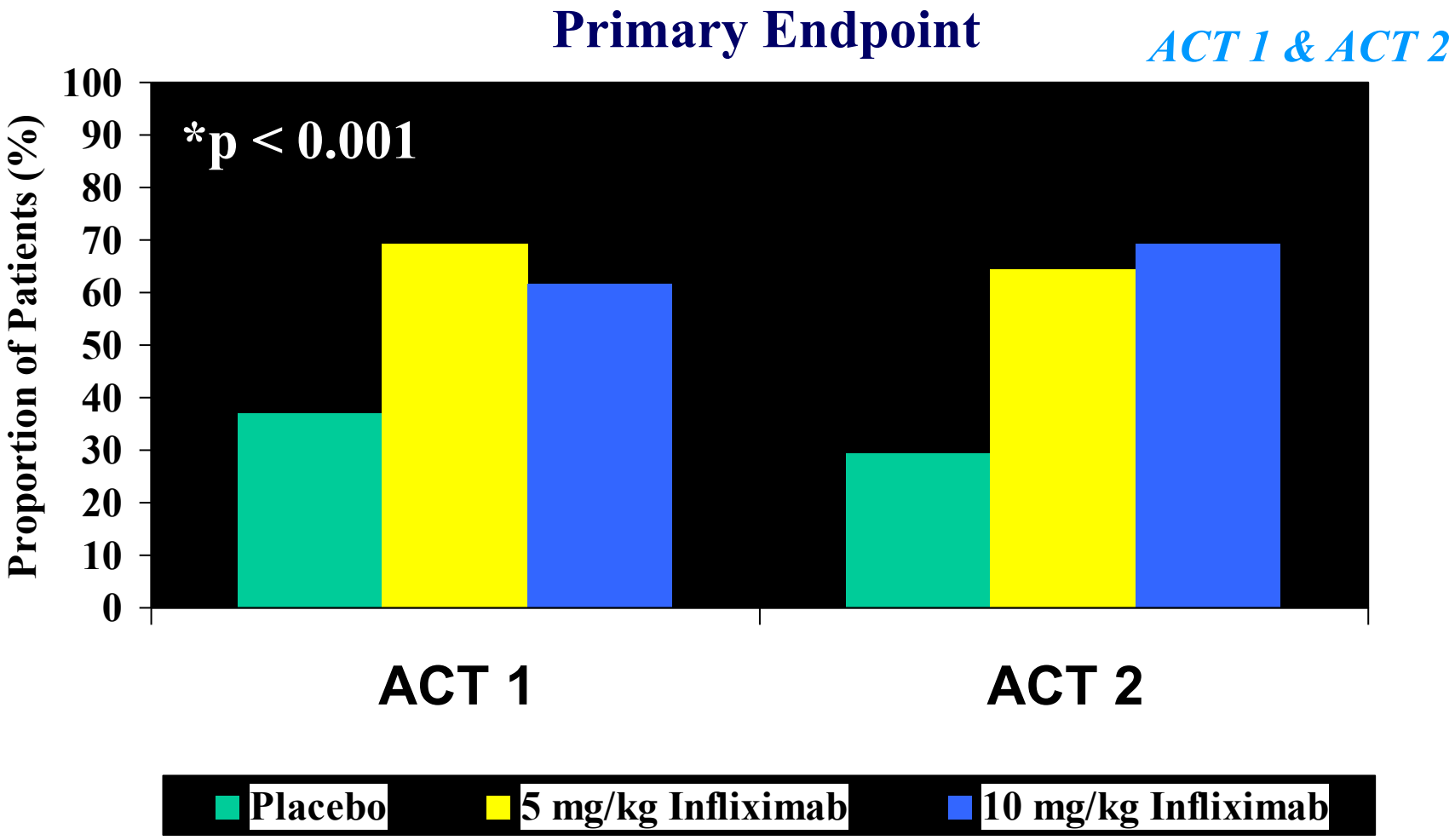


Figure 1. Kaplan–Meir curve showing colectomy-free survival in 30 patients with steroid-refractory ulcerative colitis after treatment with infliximab.

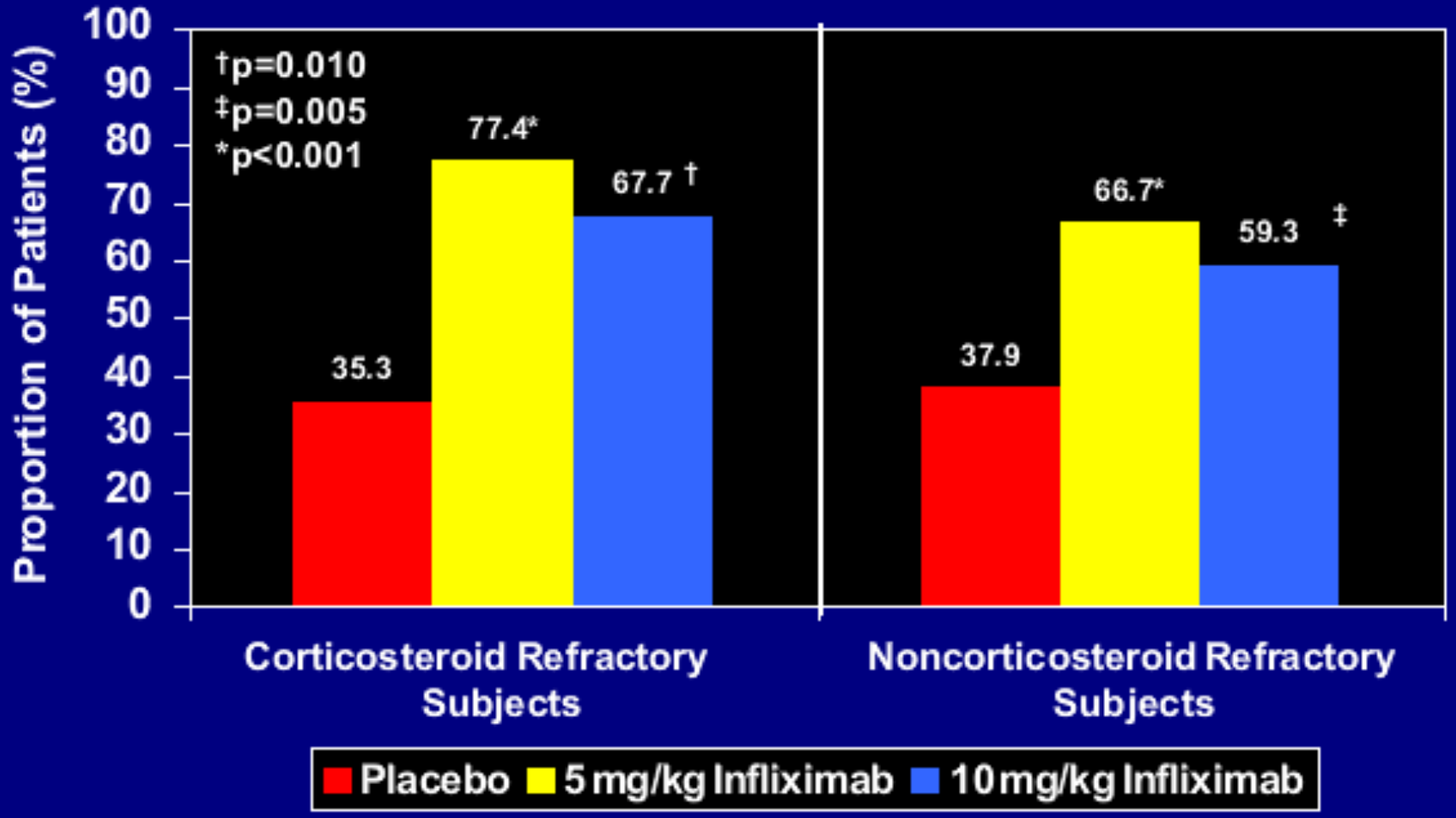
Infliximab in UC: Clinical Response at Week 8



Sandborn et al. Gastroenterology 2005; 128 (suppl 2): A104-A105
Rutgeerts et al. Gastroenterology 2005; 128 (suppl 2): A105

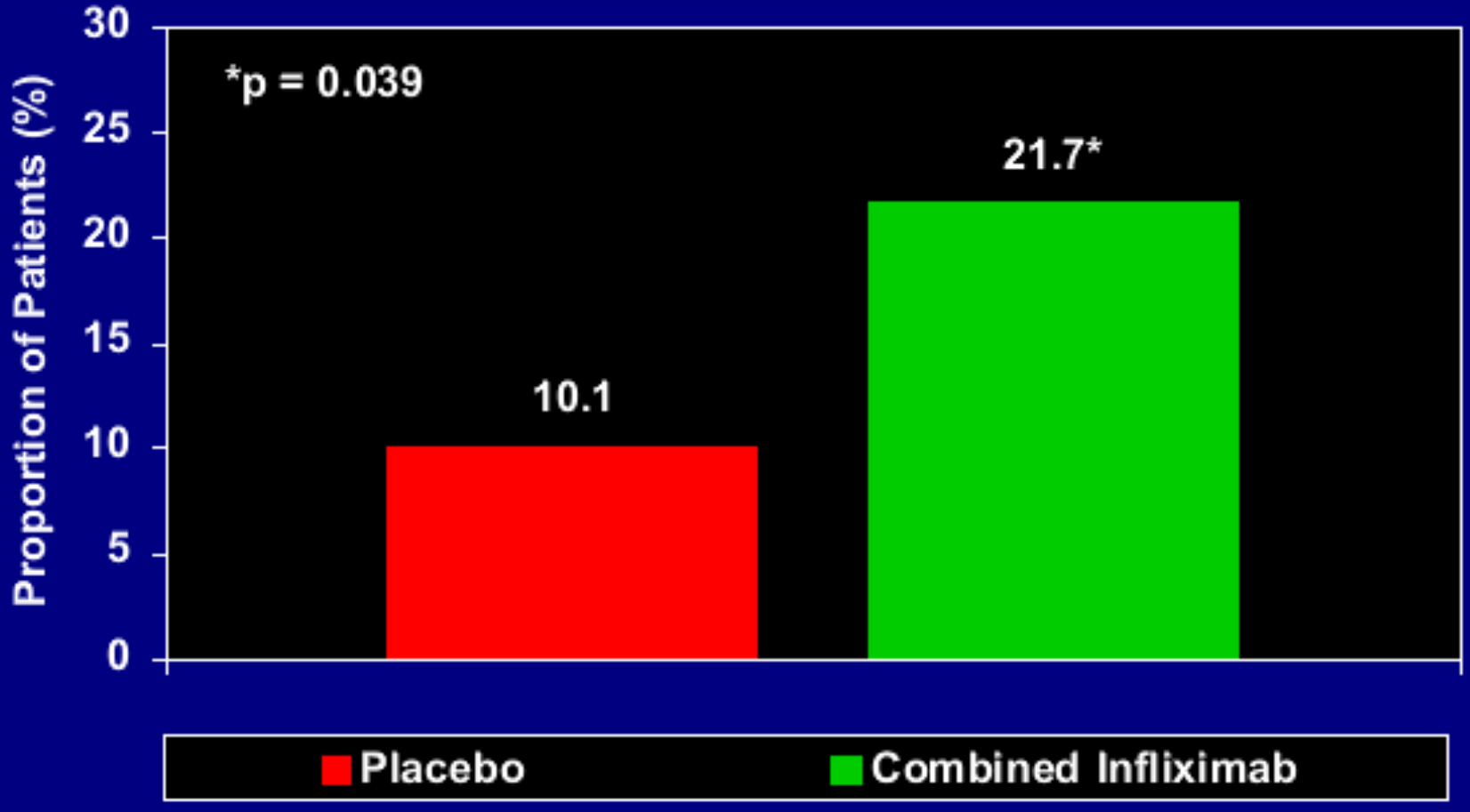
ACT 1

Clinical Response at Week 8 by Corticosteroid Refractory Status

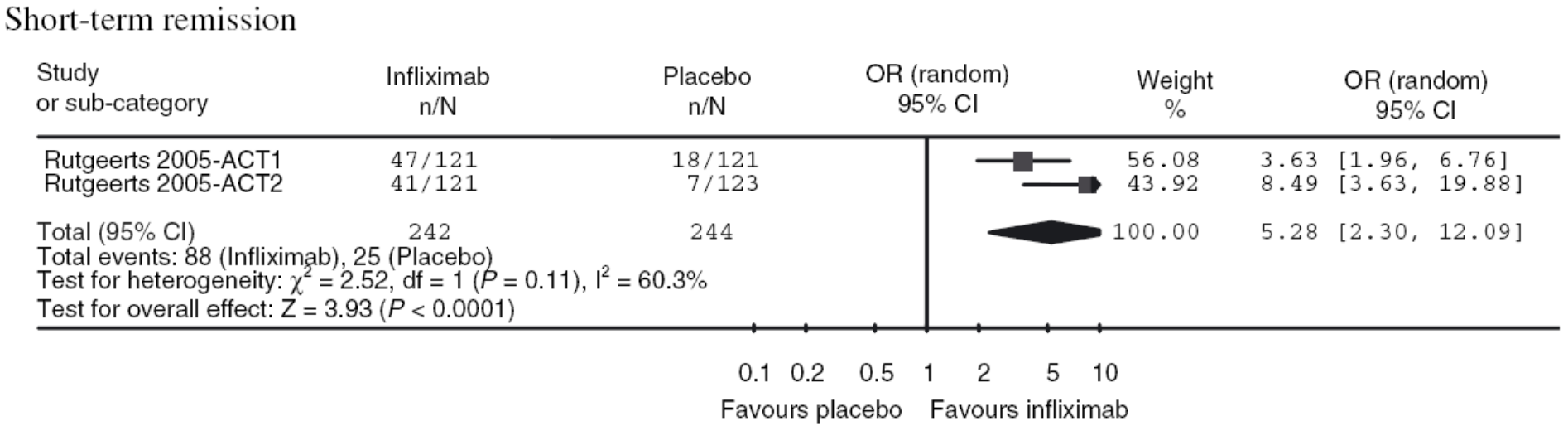


ACT 1

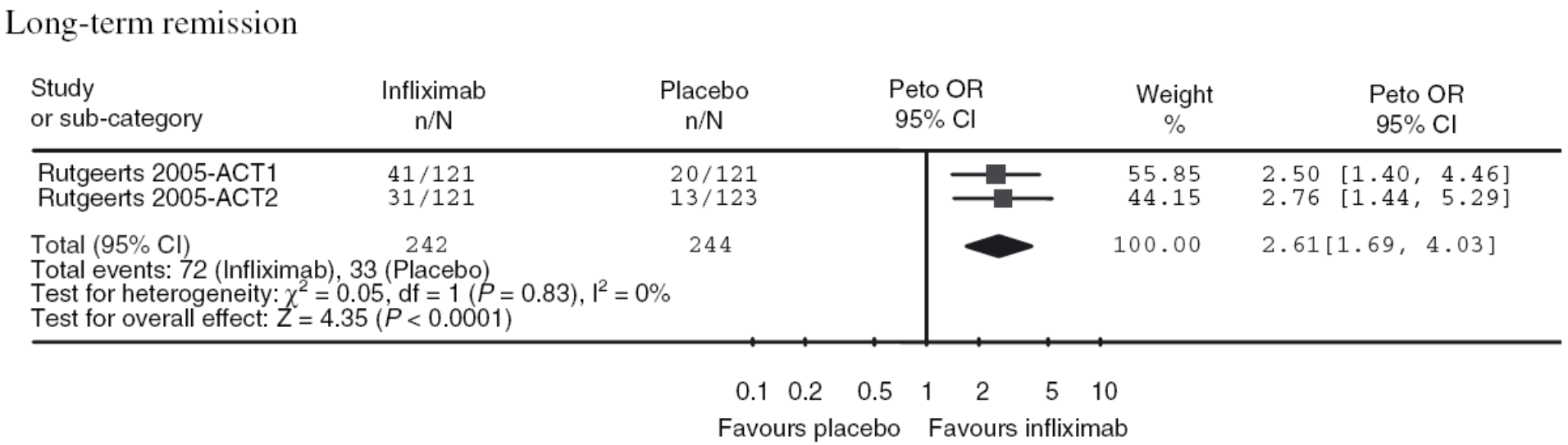
Clinical Remission Without Corticosteroids at Week 30



Infliximab e RCU: la metanalisi di Gisbert



Infliximab e RCU: la metanalisi di Gisbert



Infliximab e RCU: la metanalisi Cochrane

Analysis 1.1. Comparison 1 Infliximab versus placebo, Outcome 1 Clinical Remission at 8 weeks.

Review: Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis

Comparison: 1 Infliximab versus placebo

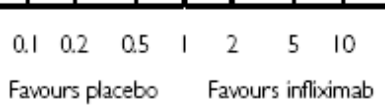
Outcome: 1 Clinical Remission at 8 weeks

Study or subgroup	Infliximab n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rutgeerts 2005 ACT1	86/243	18/121		72.2 %	2.38 [1.50, 3.76]
Rutgeerts 2005 ACT2	74/241	7/123		27.8 %	5.40 [2.56, 11.35]
Total (95% CI)	**484**	**244**		**100.0 %**	**3.22 [2.18, 4.76]**

Total events: 160 (Infliximab), 25 (Placebo)

Heterogeneity: $Chi^2 = 3.52$, df = 1 (P = 0.06); I^2 =72%

Test for overall effect: Z = 5.86 (P < 0.00001)



The Cochrane Library 2009

Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial

ULTRA-1 TRIAL

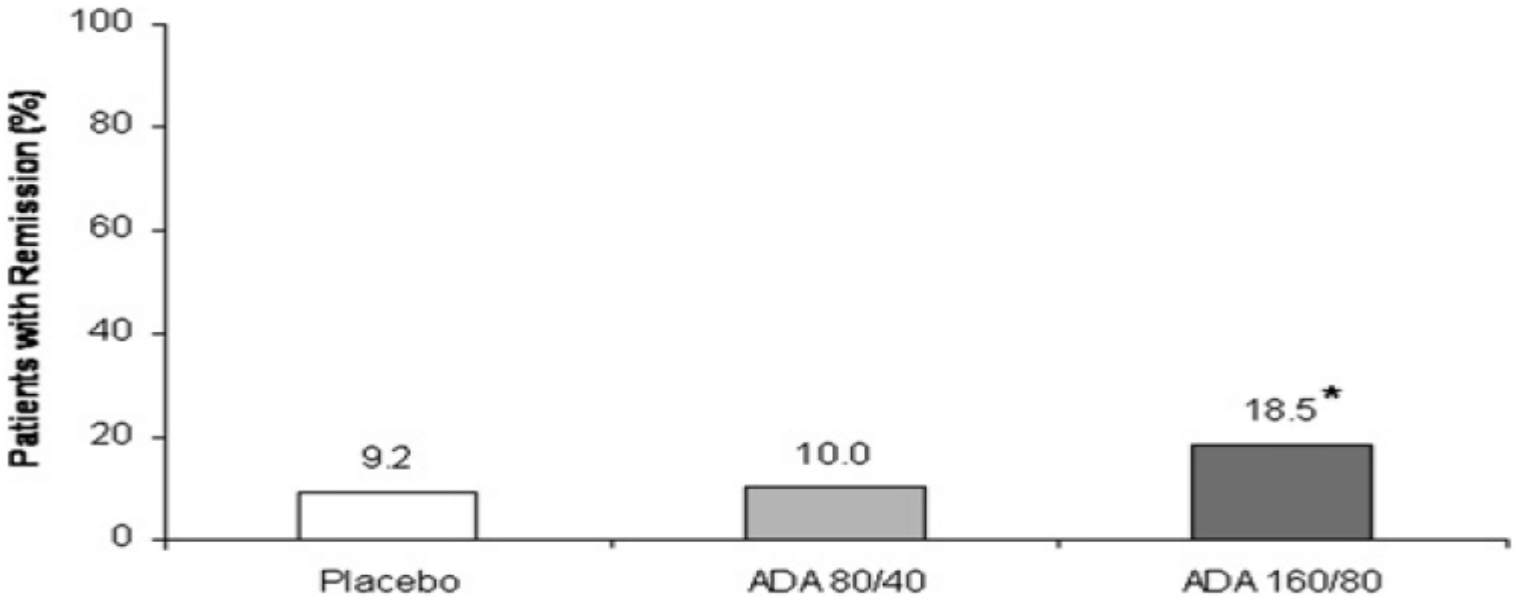


Figure 3 Clinical remission at week 8 in the ITT-A3 population (non-responder imputation). N=130 for each group. *p=0.031 versus placebo.

Gut 2011;**60**:780–787. doi:10.1136/gut.2010.221127

Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial

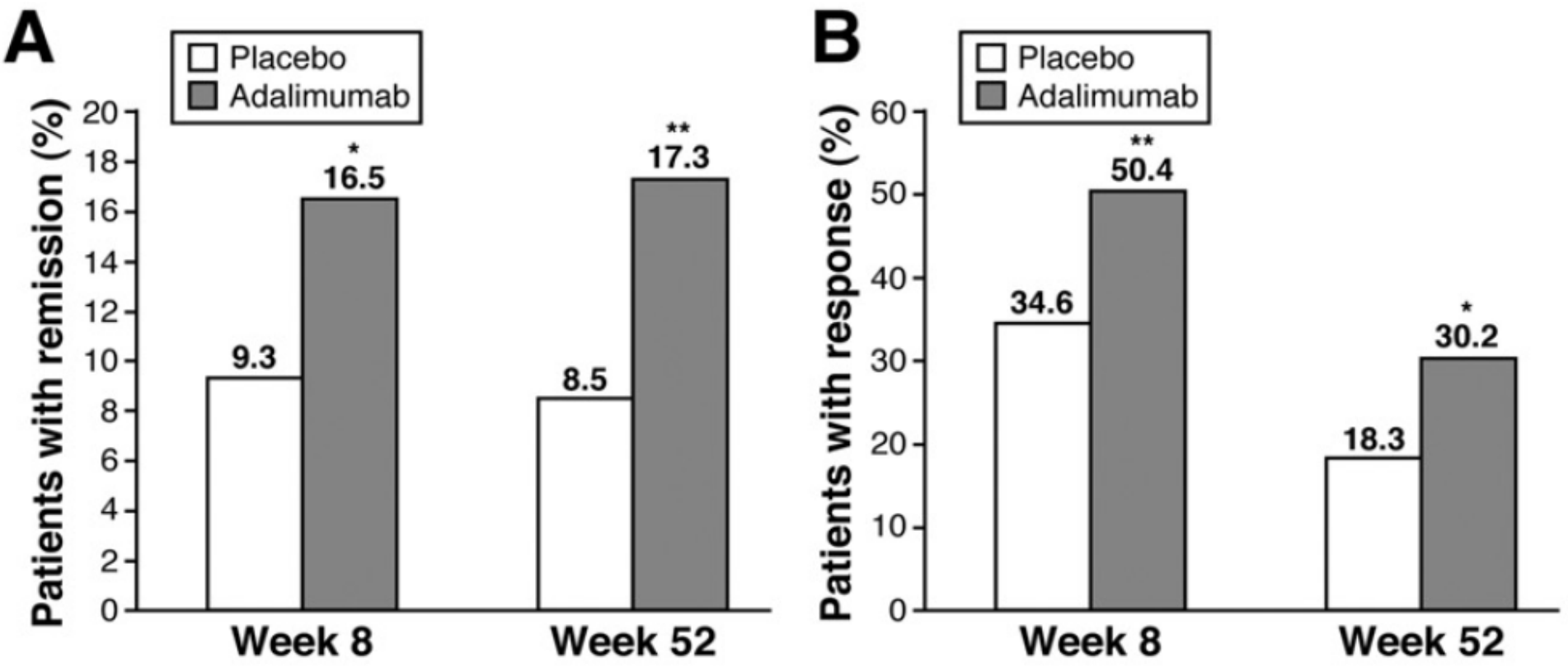
Table 2 Summary of secondary efficacy results

	Placebo (N=130)	ADA 80/40 (N=130)	ADA 160/80 (N=130)
Clinical response	44.6%	51.5%	54.6%
Mucosal healing	41.5%	37.7%	46.9%
Rectal bleeding subscore ≤1	66.2%	70.0%	77.7%*
PGA subscore ≤1	46.9%	53.8%	60.0%†
Stool frequency subscore ≤1	37.7%	36.2%	48.5%

Pitfalls: unusually high placebo response; slow-response; weight –related response

Gut 2011;**60**:780–787. doi:10.1136/gut.2010.221127

Adalimumab Induces and Maintains Clinical Remission in Patients With Moderate-to-Severe Ulcerative Colitis



ULTRA – 2 TRIAL

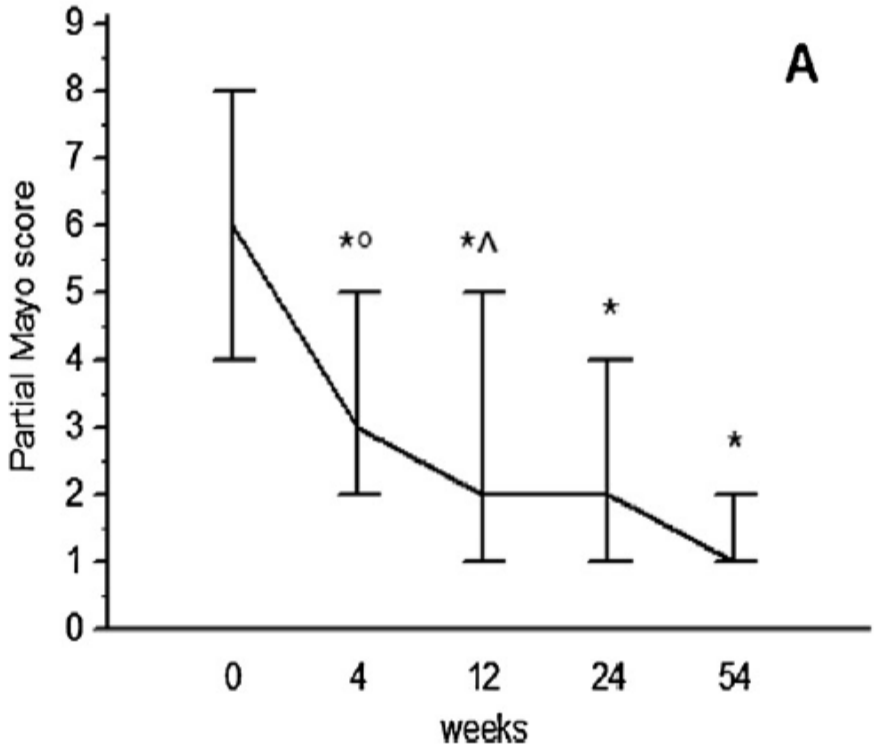
GASTROENTEROLOGY 2012;142:257–265

Adalimumab in active ulcerative colitis: A "real-life" observational study

Italian Group for the Study of Inflammatory Bowel Disease, Alessandro Armuzzi[a,*], Livia Biancone[b], Marco Daperno[b], Alessandra Coli[b], Daniela Pugliese[a], Vito Annese[b], Annalisa Aratari[b], Sandro Ardizzone[b], Paola Balestrieri[b], Fabrizio Bossa[b], Maria Cappello[b], Fabiana Castiglione[b], Michele Cicala[b], Silvio Danese[b], Renata D'Incà[b], Pietro Dulbecco[b], Giuseppe Feliciangeli[b], Walter Fries[b], Stefania Genise[b], Paolo Gionchetti[b], Stefano Gozzi[b], Anna Kohn[b], Roberto Lorenzetti[b], Monica Milla[b], Sara Onali[b], Ambrogio Orlando[b], Luigi Giovanni Papparella[b], Sara Renna[b], Chiara Ricci[b], Fernando Rizzello[b], Raffaello Sostegni[b], Luisa Guidi[a], Claudio Papi[b]

Table 1
Patients' characteristics at baseline.

Patients	Total number 88
Male, *n* (%)	35 (39.8)
Age at diagnosis, years, median (IQR)	27.7 (19.8–35.9)
Duration of disease, years, median (IQR)	8.97 (4.5–15.3)
Extension of disease – E1, E2, E3, *n* (%)	4 (4.5), 27 (30.7), 57 (64.8)
Previous infliximab, *n* (%)	69 (78.4)
Previous immunosuppressants (AZA/6MP, MTX, Cya)[a], *n* (%)	65 (73.9)
Concomitant corticosteroids, *n* (%)	60 (68.1)
Main indication to adalimumab, *n* (%)	
Corticosteroid resistance	23 (26.1)
Corticosteroid dependence	41 (46.6)
EIMs[b]	14 (15.9)
Corticosteroid dependence + EIMs	10 (11.4)
Partial Mayo score, median (IQR)	6.0 (4–8)
CRP[c] (mg/L), median (IQR)	10.9 (4.9–19.6)
Adalimumab induction regimen, *n* (%)	
160/80 mg	77 (87.5)
80/40 mg	11 (12.5)



Induction of response/remission in moderate-to-severe steroid-refractory or dependent ulcerative colitis

Statement 7A

Infliximab induction regimen is effective in patients with moderate-to-severe ulcerative colitis who are refractory to systemic corticosteroids **[EL 1b, RG A]** and corticosteroid-dependent patients who are intolerant/refractory to thiopurines **[EL 2b, RG C]** although surgical options should be considered

Linee guida SIGE-IG IBD 2010

Maintenance of remission in ulcerative colitis

Statement 7B

One year scheduled treatment with Infliximab is effective in patients who have responded to infliximab induction **[EL 1b, RG A]**

In patients who are thiopurine-naïve, maintenance therapy with thiopurines alone is a valuable option **[EL 5, RG D]**

Open experiences have reported long-term effectiveness and safety of infliximab; however, the duration of the therapy over 1 year should be carefully evaluated on a case-by-case basis **[EL 4, RG C]**

Maintenance therapy with infliximab that achieves only response should be carefully evaluated in the face of colectomy **[EL 5, RG D]**

Linee guida SIGE-IG IBD 2010

Indications for Infliximab in Hospitalized severe UC

Statement 8A

Infliximab reduces colectomy rate within 3 months in steroid refractory severe UC **[EL 1b, RG A].** Colectomy is recommended if there is no improvement within five days **[EL 5, RG D].** Long term efficacy is not proven

Infliximab should be avoided in patients with complicated disease **[EL 5, RG D]**

Re-infusions seem more effective than one single infusion to prevent early colectomy **[EL 4, RG C]** but there is insufficient evidence to provide recommendations on the ideal dosing schedule

Antibiotic prophylaxis against opportunistic infections is suggested **[EL 5, RG D]**

Linee guida SIGE-IG IBD 2010

Biologics: Why should we stop?

- **Medical reasons (Benefit/Risk)**
  - Over-treatment of long time remitters
  - Safety concerns
- **Patients may ask for it**
  - Convenience
  - Patients do not like to take drugs
  - Patients may be afraid of complications
  - Specific situations
- **Payor push-back**

STORI Trial: Infliximab Discontinuation in CD Patients in Deep Remission

Aim and Methods

- To assess the risk and **identify factors of CD relapse** in a **prospective cohort** study of 115 pts with luminal CD
- Patients recruited in the GETAID centres
  - Treated with combined **scheduled infliximab + immunosuppressive therapy for ≥1 year**
  - In **stable** steroid-free remission for ≥6 months
- Patients received last infliximab infusion at baseline and were followed up at week 2 and every 2 months
- Immunosuppressor was kept at a stable dosage

Louis E, et al. Gastroenterology 2011

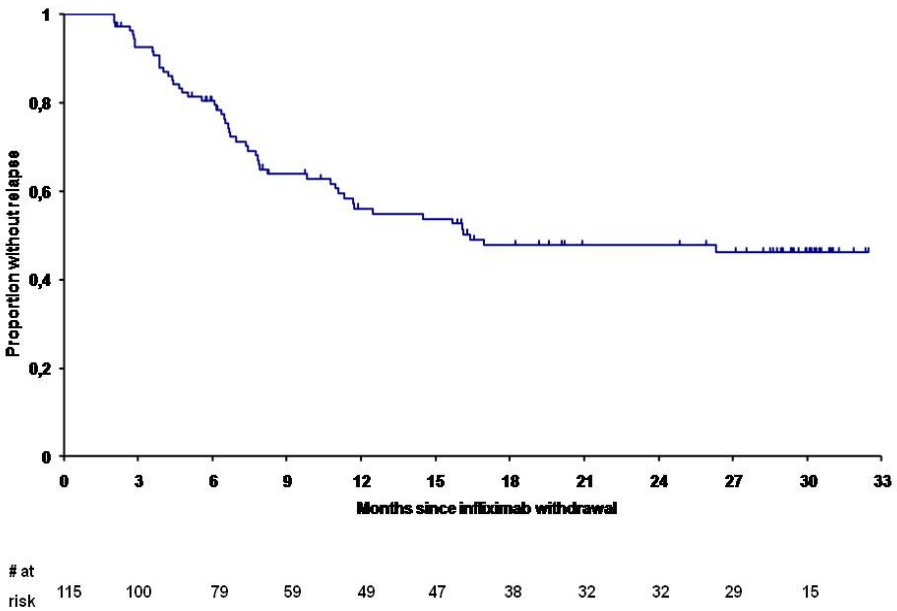
Multivariate analysis of factors predicting time-to-relapse: model on 109 patients

Factor	HR (95%CI)	P
Male	3.6 (1.9-6.9)	0.0001
No previous surgery	4.5 (1.8-11.6)	0.0003
Steroids (month -12 to -6)	4.2 (1.5-11.8)	0.02
Hemoglobin ≤ 14.5 (g/dl)	5.3 (2.1-13.2)	0.0001
WBC > 6 (10^3/ml)	2.2 (1.2-4.2)	0.01
CRP hs > 5 (mg/l)	**3.1 (1.6-5.9)**	**0.0009**
CDEIS > 0	**2.6 (1.3-5.3)**	**0.005**

Louis E, et al. Gastroenterology 2011

Maintenance of remission among patients with CD on anti-metabolite therapy after IFX therapy is stopped

115 CD patients in remission on IFX+AZA (CDAI<150 and steroid free ≥6 months)



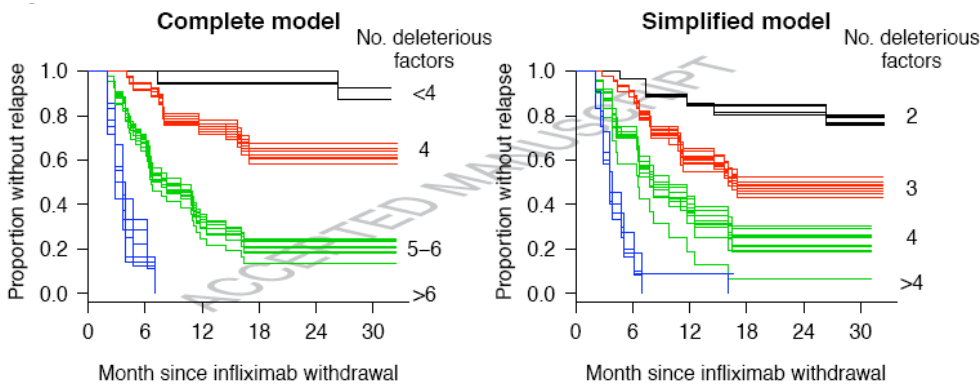
Factor	HR (95%CI)	P
No previous surgery	4.0 (1.4-11.4)	0.01
Steroids (month -12 to -6)	3.5 (1.1-10.7)	0.03
Hemoglobin ≤ 14.5 (g/dl)	6.0 (2.2-16.5)	<0.001
Male Gender	3.7 (1.9-7.4)	<0.001
Fecal calpro ≥ 300 µg/g	2.5 (1.1-5.8)	0.04
Infliximab TL ≥ 2 mg/L	2.5 (1.1-5.4)	0.02
WBC > 6 (10^3/ml)	2.2 (1.2-4.2)	0.01
CRP hs > 5 (mg/l)	3.2 (1.6-6.4)	<0.001
CDEIS > 0	2.3 (1.1-4.9)	0.04

Median follow-up time: 28 ± 2 months

Relapse: 52/115 (45.2%) patients

1-year relapse rate: 43.9% ± 5.0%

2-year relapse rate: 52.2% ± 5.2%



Louis E, et al. Gastroenterology 2011

Possible mechanisms of worsening on anti-TNFs

Non-IBD related inflammation: **(High CRP)**

Infection !

Other (vasculitis, ischemia)

Non-inflammatory mechanisms (Normal CRP)

Fibrostenotic strictures

Cancer

IBS

Miscellaneous (Amyloidosis, BOG, Bile salt diarrhea, etc)

Un-controlled IBD inflammation : (High CRP)

Loss of anti-TNF activity due to anti-drug antibodies

Loss of anti-TNF activity due to non-immune drug clearance

Relentless TNF-mediated flare 'consuming' all anti-TNF Ab

Non-adherence to therapy

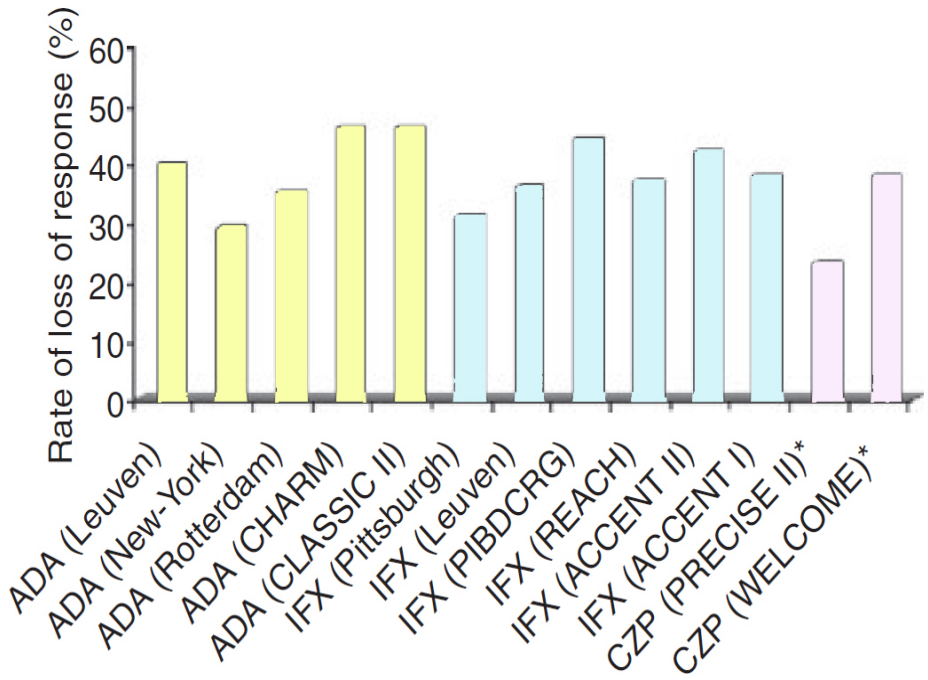
Un-controlled IBD inflammation: (High CRP)

Paradoxical exacerbation of inflammation by anti-TNFs

Shift of disease pathway away from TNF to other mediators

Adapted from Allez M, J Crohn Colitis 2010

Loss of response to anti-TNF alpha



Loss of response (12 months) in case series and in RCTs ranges between 23% and 46%

Infliximab
13% per patient-year of FU
(annual risk)

Adalimumab
18% per patient-year of FU
8% naive vs 22% non-naive
(annual risk)

S. Ben-Horin & Y. Chowers. APT 2011

Gisbert JP, et al. AJG 2009; Chaparro M, et al. IBD 2011

Managing the loss of response to anti-TNFs

- ✓ Optimize: dose escalation or intensification (elective switching leads to loss of tolerance and efficacy and worse outcomes – SWITCH study)); add an immunomodulator
- ✓ Switch to a second anti-TNF (results from GAIN or WELCOME study)
- ✓ Switch to a third anti-TNF (rate of clinical response at wk 20 51%)
- ✓ Switch to another biologic
- ✓ Advice to quit smoking

Managing loss of response: role of trough levels

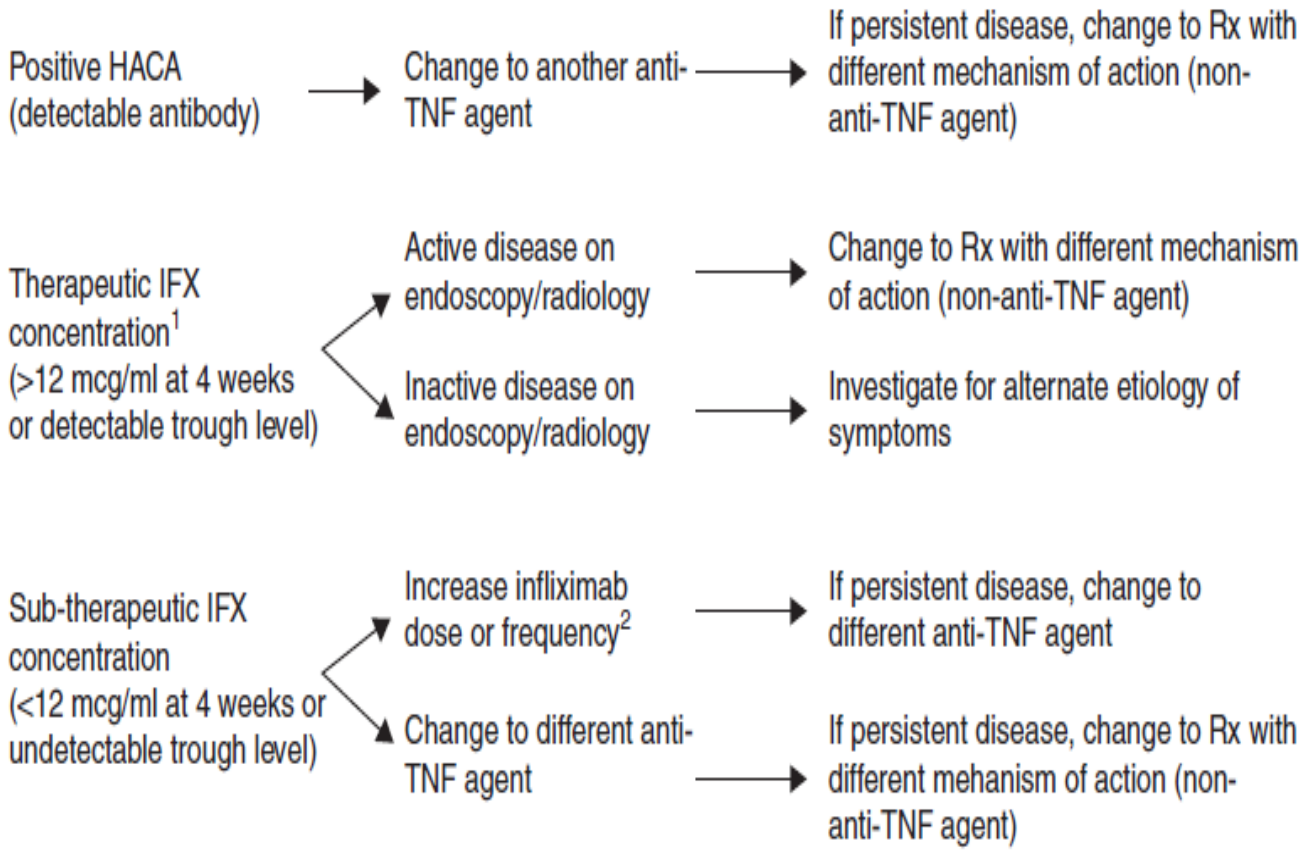
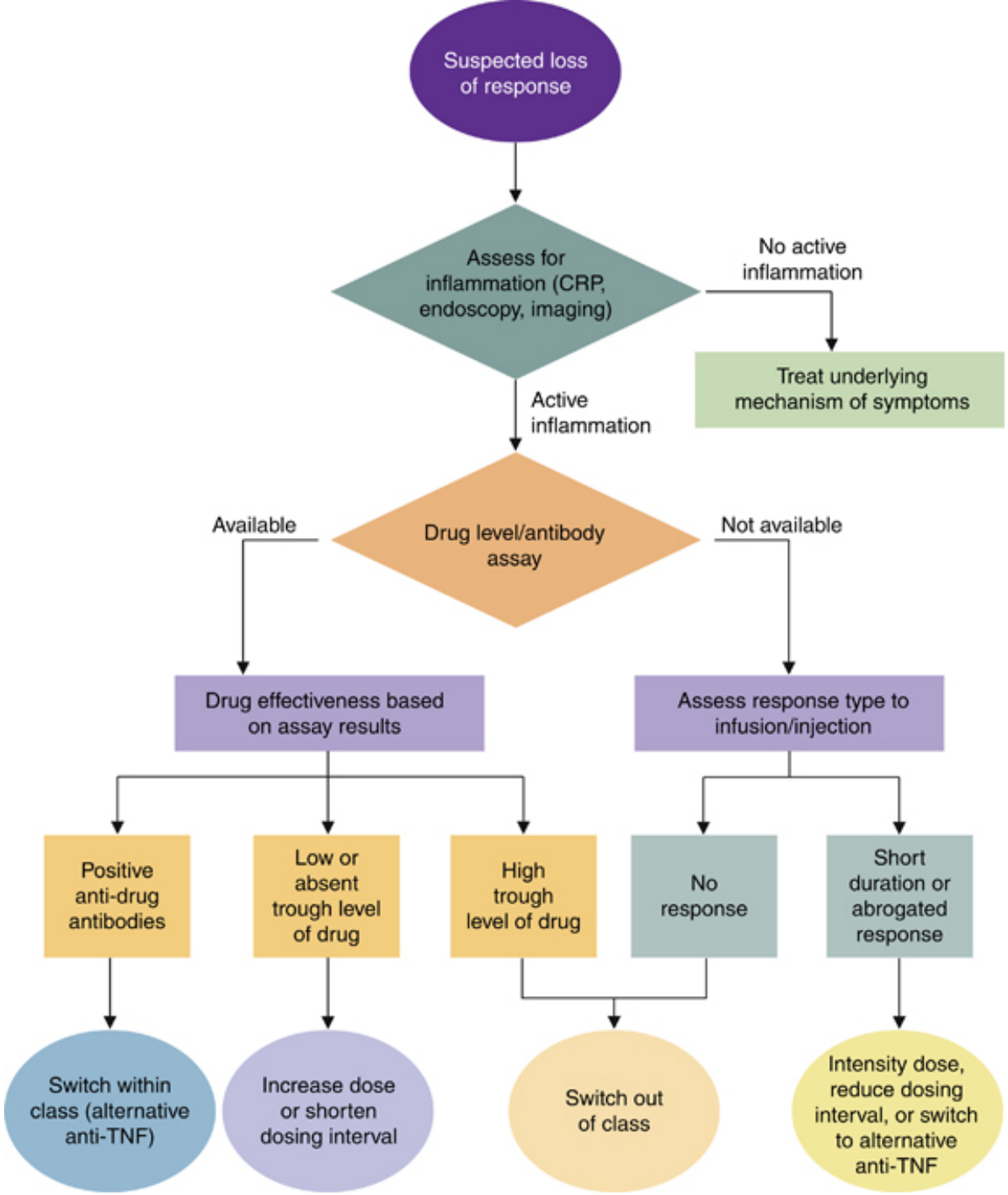


Figure 1. Treatment algorithm in patients with clinical symptoms (infliximab and HACA concentrations). [1]Patients should save endoscopic or radiologic imaging. [2]This strategy may be preferable. HACA, human anti-chimeric antibody; TNF, tumor necrosis factor.



Yanai H, Am J Gastro 2011

Managing loss of response

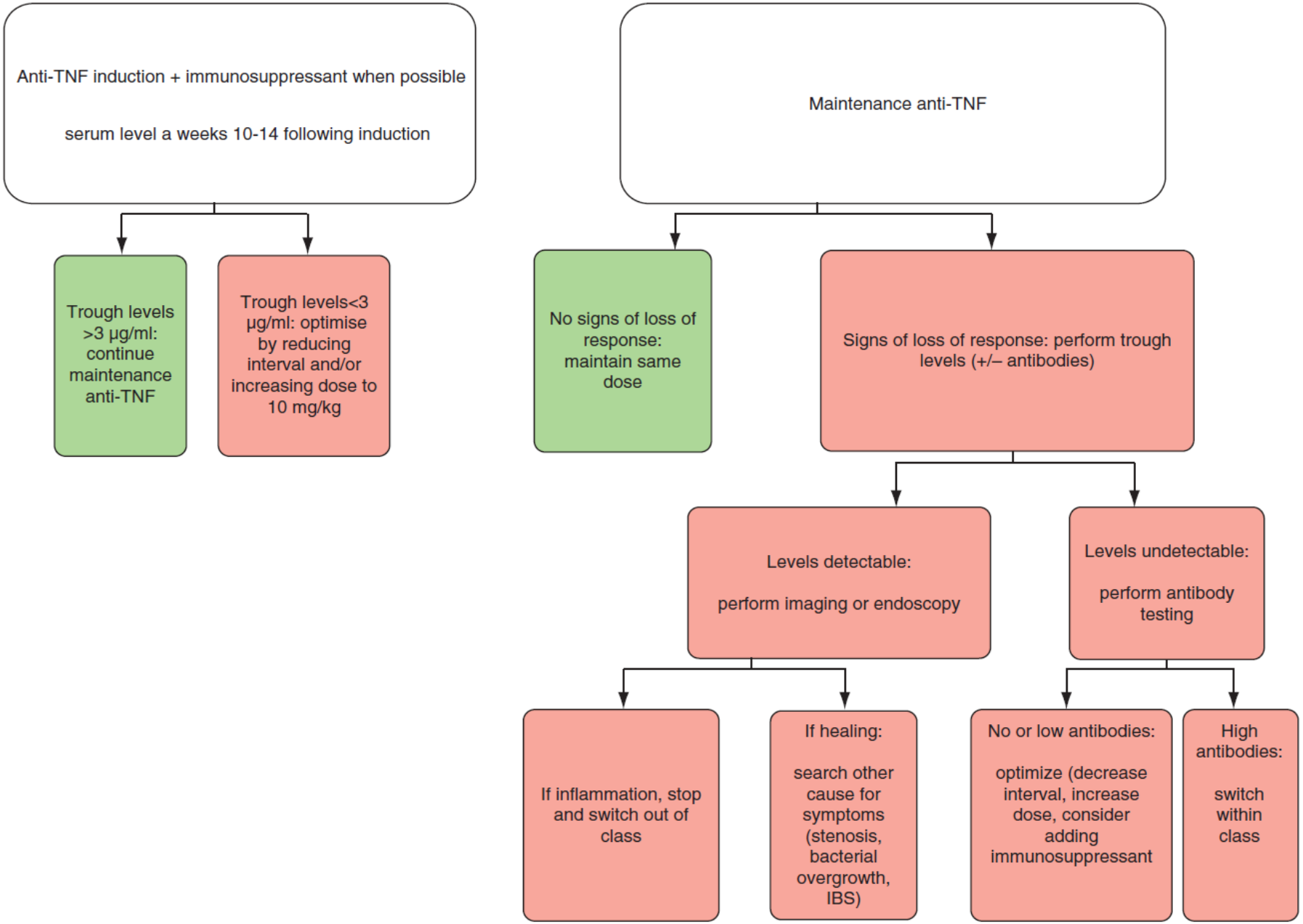
ECCO Statement 5J (new)

Loss of response to anti-TNF therapy should lead to re-evaluation of disease activity, exclusion of complications and discussion of surgical options with the patient [EL5, RG D]. For active disease, reduction in interval between doses, or dose escalation are appropriate strategies before switching to another agent [EL5 RG D]. Switching is an effective strategy [EL1b, RG A], but reduces future therapeutic options. For intolerance, especially if severe, switching to an alternative anti-TNF agent is appropriate. Response to a third anti-TNF therapy occurs in some patients and may be an appropriate option [EL3 RG C], although surgical options should also be considered and discussed. Primary lack of response may be determined within 12 weeks and an alternative anti-TNF agent tried for active disease [EL3, RG C].

S. Ben-Horin & Y. Chowers. APT 2011

Strategie terapeutiche: terapia personalizzata

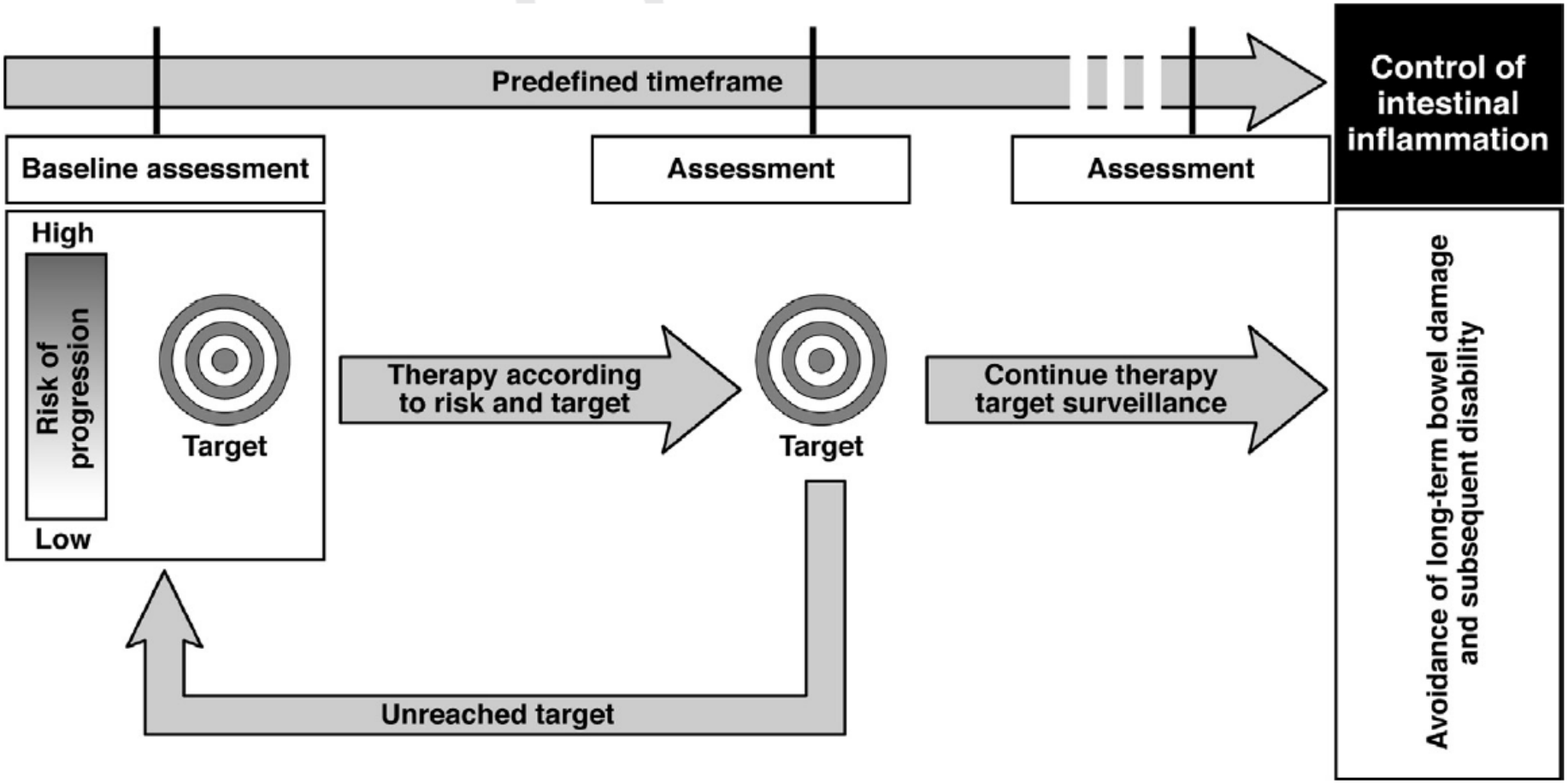
- Map the disease (ileocolonoscopy + MRI)
- Individualised choice of treatments: prognostic factors
- Molecular markers (?)
- Optimize drug treatment by measuring drug levels and metabolites



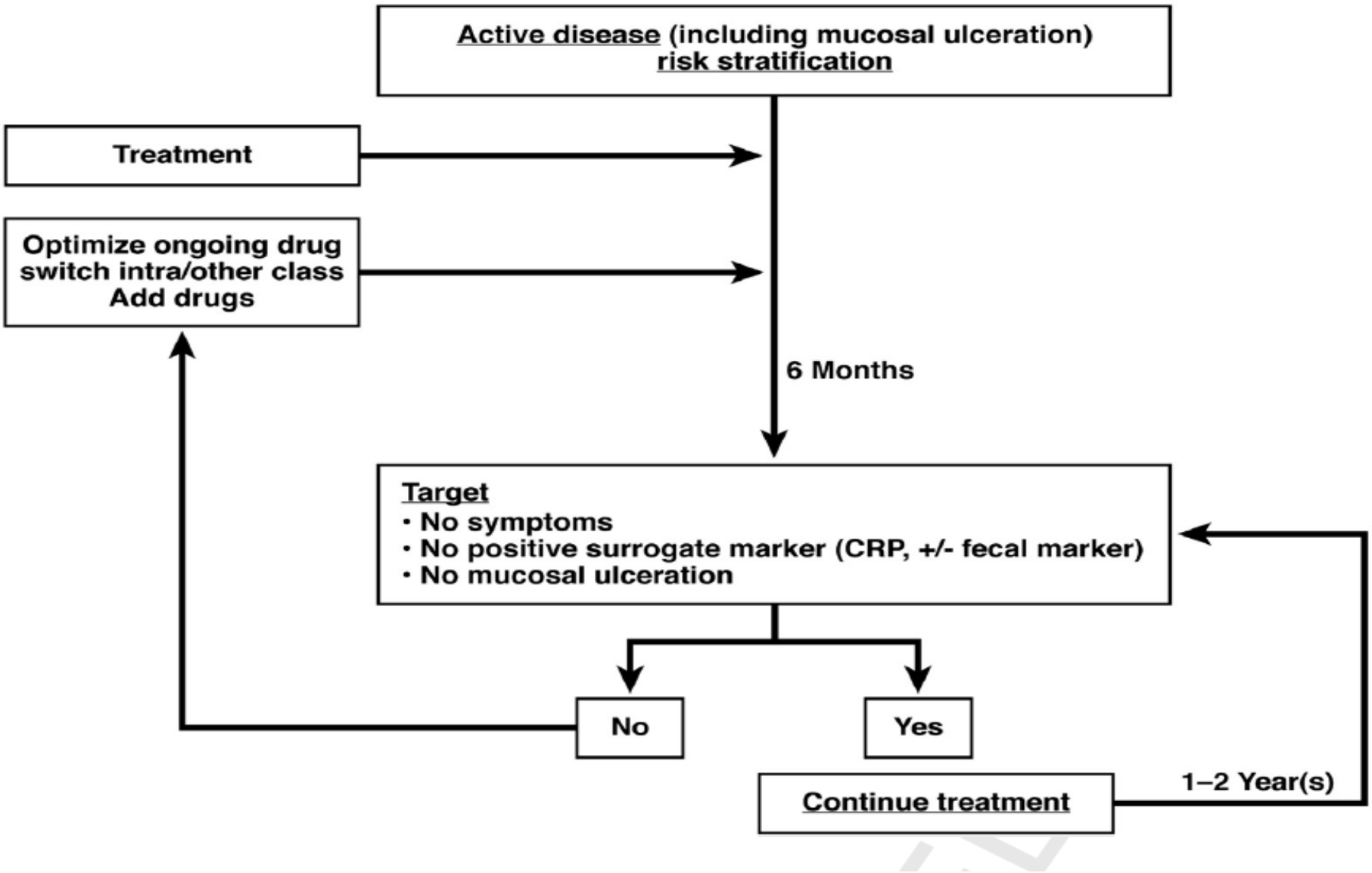
Proposed algorithm of when to perform anti-tumour necrosis factor (TNF) drug monitoring. IBS, irritable bowel syndrome.

Treat to Target: A Proposed New Paradigm for the Management of Crohn's Disease

Guillaume Bouguen,[*,‡] Barrett G. Levesque,[*] Brian G. Feagan,[§] Arthur Kavanaugh,[‖] Laurent Peyrin–Biroulet,[¶] Jean–Frederic Colombel,[#] Stephen B. Hanauer,[**] and William J. Sandborn[*]



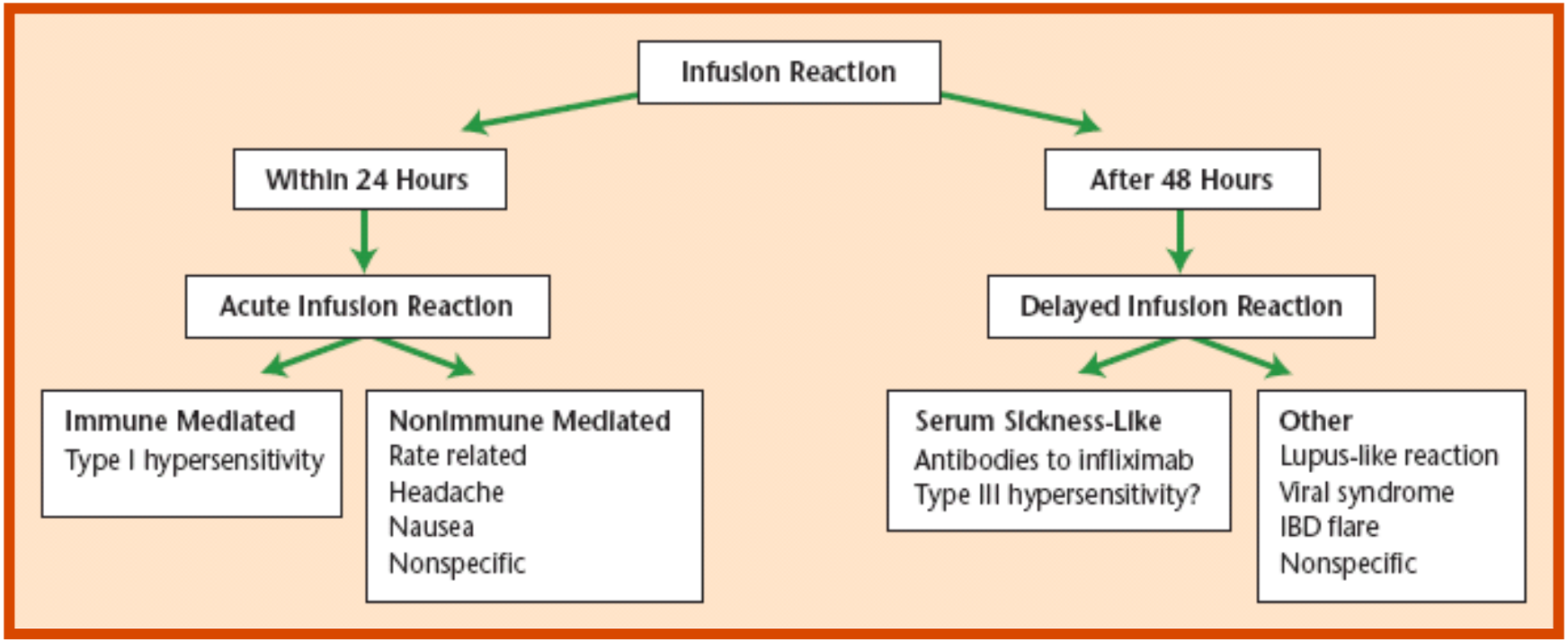
Treat to Target: A Proposed New Paradigm for the Management of Crohn's Disease



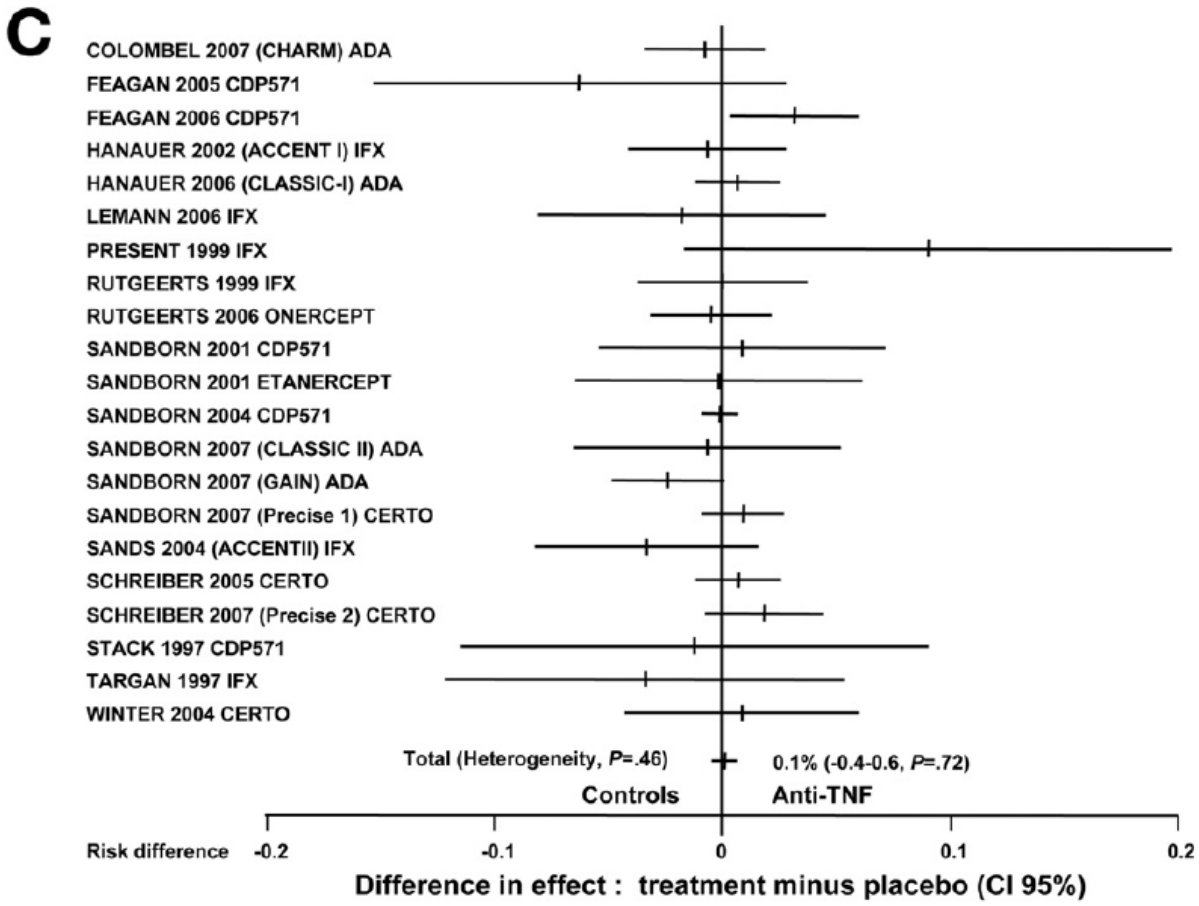
Biologici e profilo di sicurezza

- Reazioni infusionali
- Infezioni opportuniste
- Rischio di cancro
- Mortalità

Eventi avversi correlati alla immunogenicità

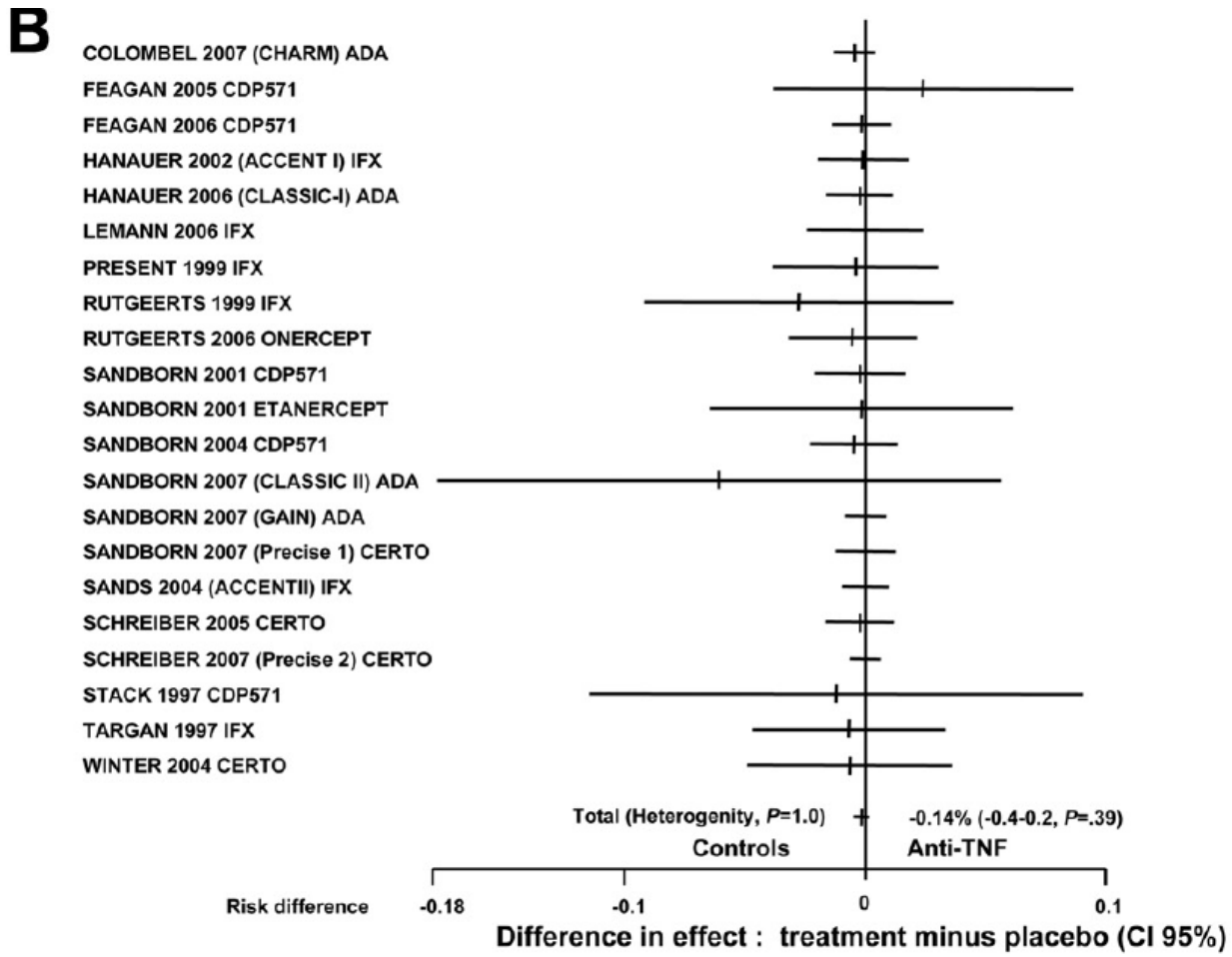


Anti-TNF e rischio di infezioni severe: la metanalisi di Peyrin-Biroulet



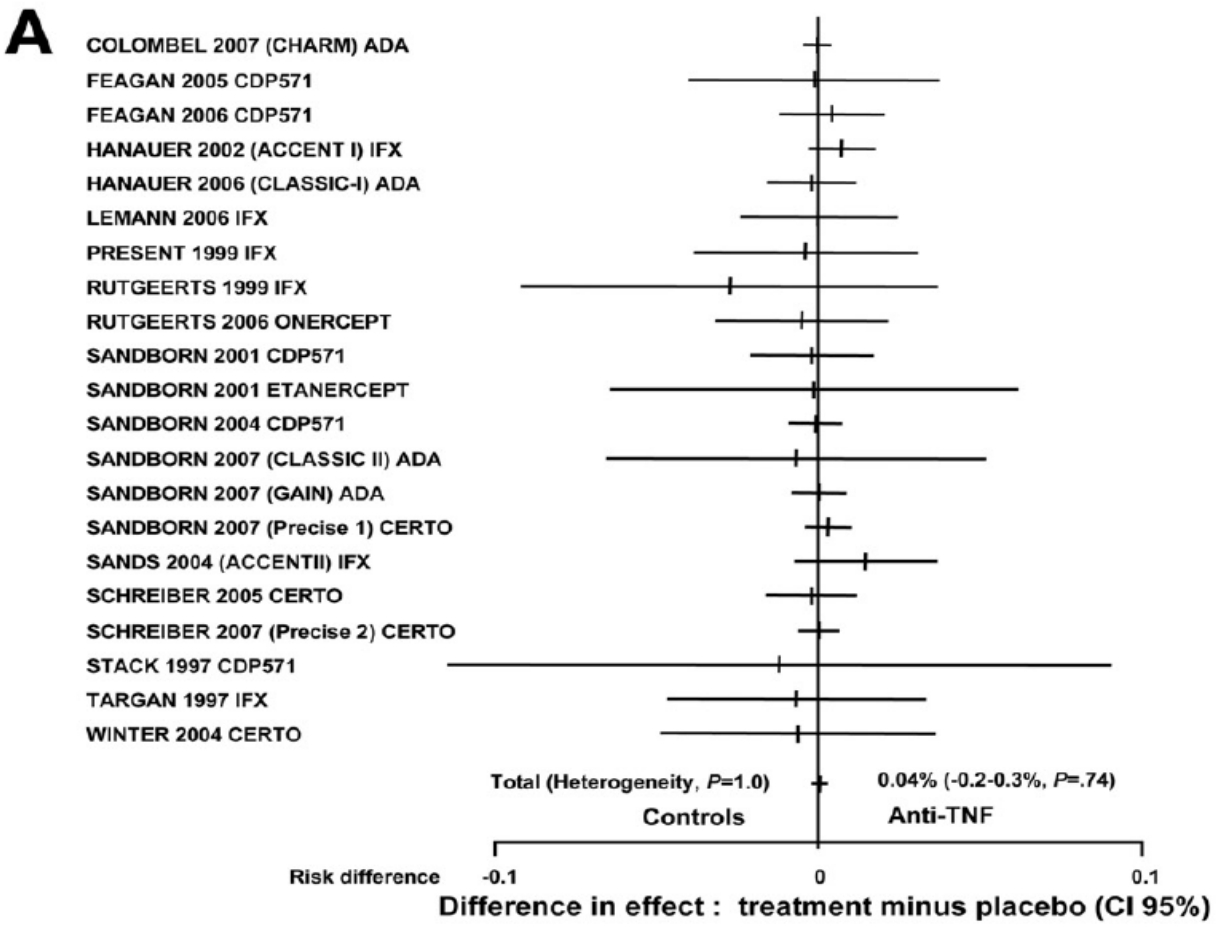
CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2008;6:644–653

Anti-TNF e neoplasie: la metanalisi di Peyrin-Biroulet



CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2008;6:644–653

Anti-TNF e mortalità: la metanalisi di Peyrin-Biroulet



CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2008;6:644–653

Risk Factors for Opportunistic Infections in Patients With Inflammatory Bowel Disease

Table 5. Association of Immunosuppressive Medication* Combinations With Opportunistic Infection

	Cases (n = 100)	Controls (n = 200)	OR (95% CI)[a]	*P* value
Number of immunosuppressive medications[b]				
None	38 (38%)	129 (64%)	1.0 (reference)	
1	38 (38%)	59 (29%)	2.9 (1.5–5.3)	<.001[c]
2 or 3	24 (24%)	12 (6%)	14.5 (4.9–43)	<.001[c]
Age at first Mayo Clinic visit for IBD			1.1 (1.0–1.2)	.02
Specific combinations[b]				
No medications	39 (39%)	129 (65%)	1.0 (reference)	
Corticosteroids alone	16 (15%)	27 (14%)	2.2 (1.0–4.9)	.04
AZA/6MP alone	20 (20%)	31 (15%)	3.4 (1.5–7.5)	.002[c]
Infliximab alone	3 (3%)	2 (1%)	11.1 (0.8–148)	.07
AZA/6MP + corticosteroids	16 (16%)	6 (3%)	17.5 (4.5–68)	<.001[c]
AZA/6MP + infliximab	1 (1%)	5 (2%)	1.6 (0.1–19)	.72
AZA/6MP + infliximab + corticosteroids	5 (5%)	0 (0%)	Infinite	<.001[c]
Age at first Mayo Clinic visit for IBD			1.1 (1.0–1.2)	.01

Toruner. Gastro 2008

Linfoma epatosplenico a cellule T e terapia di combinazione

Table 2 – Cases of HSTL reported in CD patients receiving REMICADE and azathioprine/6-mercaptopurine [22,23]

Age at Lymphoma - Diagnosis - Indication - Sex	Azathioprine and/or 6-Mercaptopurine Use	Remicade Therapy	Presentation - Type of T-cell lymphoma	Outcome
18 years CD for 8 years Male	• Azathioprine for over 5 years (100 mg qd) • Possible use of 6-mercaptopurinereporte	Total of 3 infusions (5 mg/kg)	Presented with headache, abdominal distention, and splenomegaly. Alpha-beta	Patient died after chemotherapy
19 years CD for 6 years Male	• Azathioprine for approx. 6 years (last dosing 75 mg qd) • 6-mercaptopurine, for an indeterminate period (last dosing 25 mg bid)	Total of 12 infusions (10 mg/kg, every 6-8 weeks) over 3 years	Presented with sore throat, fatigue and was hospitalized with neutropenic fevers shortly later. Alpha-beta	Patient died after chemotherapy and unrelated cord blood transplant
17 years CD for 5 years Female	• 6-mercaptopurine for 4.5 years (50-75 mg qd)	Total of 20 infusions (5 mg/kg) over 2 years	Presented with fever, malaise, right upper quadrant pain, hepatosplenomegaly and initially diagnosed as autoimmune hepatitis. Alpha-beta	Patient died in preparation for bone marrow transplant
15 years CD for 2-4 years Male	• Azathioprine and/or? • 6-mercaptopurine(duration and dosing not reported)	Total of 13 infusions (dose not reported) over 1.5 years	Gamma-delta	Patient died after chemotherapy
12 years CD for 5 years Male	• Azathioprine for approx. 4 years (dosing not reported)	Total of 21 infusions (approx. 6.8 mg/kg) over 4 approx. years	Presented with hepatosplenomegaly, thrombocytopenia, and rash. Gamma-delta	Patient responding to chemotherapy as of Mar 2006
31 years CD for 3 years Male	• 6-mercaptopurine for approx. 3 years (dosing not reported)	Received 1-2 infusions 3 years prior to diagnosis	Gamma-delta	Patient died
19 years CD for 7 years Male	• Azathioprine for >5 years (75 mg qd)	Total of 3 infusions (5 mg/kg) over 3 months	Gamma-delta	Patient died
22 years Indeterminate colitis for 7 years (presentation suggests features of UC Male	• Azathioprine for approx. 5 years (100-125 mg qd)	One infusion (5 mg/kg) 5 years prior to diagnosis	Gamma-delta	Patient is planned to begin chemotherapy and is being considered for a bone marrow transplant

Rischio di linfoma in pazienti con IBD trattati con anti-TNF (Siegel 2009)

Table 2. Rate of NHL for SEER, Immunomodulator, and Anti-TNF Treated Patients

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

Abbreviation: IM, immunomodulator; pt-yrs, patient years.
[a]IM alone is the rate of NHL in CD patients from the Kandiel meta-analysis.[11]

Anti TNF and infections

Statement 10A

The risk of infections is increased in patients treated with biologics **[EL 1]**

It is not clear if this risk is related to biologics or to steroids use, severity of disease and narcotic drugs **[EL 3b]**

The risk of severe infections is not usually increased **[EL 1]** but it seems higher in elderly patients **[EL 3]**

Biologics should not be started during infections **[EL5, RG D]**

Linee guida SIGE- IG IBD

Anti TNF and infections

Statement 10B

Tuberculosis

Before starting biologics, screening for tuberculosis is mandatory. Appropriate screening includes a full medical history, physical examination, tuberculin skin test (TST) or interferon-gamma release assay (IGRA), and a chest X-ray. The IGRA can also be used to distinguish a true positive TST from a false positive TST caused by BCG sensitization **[EL1, RG A]**

Linee guida SIGE- IG IBD

Anti TNF and infections
Statement 10C

Latent TB infection

All patients who have a TST result of ≥ 5 mm induration or a positive IGRA and planning to take a TNF-alpha inhibitor, should undergo TB chemoprophylaxis **[EL 5, RG D]**

TNF-alpha inhibitor candidates, with a negative TST <5 mm or IGRA should also be treated for LTBI if there is any evidence, on a chest X-ray, of a remote TB disease or if there is positive history of prior TB exposure **[EL 5, RG D]**

TNF-alpha inhibitor candidates with latent TB infection must receive standard therapy with isoniazid for 9 months **[EL 3b, RG B]**

If active TB is diagnosed , anti TNF-alpha therapy must be stopped and can be resumed after TB treatment and specialist consultation **[EL 4, RG D]**

Linee guida SIGE- IG IBD

Anti TNF and infections

Statement 10D

Bacterial Infections

Anti-TNF alpha therapy should be temporarily stopped until the resolution of the active bacterial infection **[EL 5, RG D]**

Clostridium difficile infection must be ruled out before starting Anti- TNF alpha therapy **[EL 2, RG B]**

Patients on immunomodulator therapy have a higher risk of pneumococcal infection **[EL 4]**

Pneumococcal vaccination is recommended in elderly patients whereas it is a valuable option in the other age groups on TNF therapy **[EL 5, RG D]**

Anti TNF and infections

Statement 10E

Fungal Infection

Consider Pneumocystis carinii pneumonia prophylaxis in patients treated with TNF-alpha inhibitors who are also receiving other immunosuppressive medications, particularly high-doses of glucocorticoids **[EL4, RG D]**

Linee guida SIGE- IG IBD

Anti TNF and infections

Statement 10F

HBV infection

During biological treatment there is an increased risk of reactivation in patients with previous and occult HBV infections **[EL 4]**

Before starting biologics screening for HBV is mandatory **[EL 5, RG D]**

Appropriate screening includes transaminases , HBsAg and Anti-HBc. If Anti-HBc is positive HBvDna is required **[EL 5, RG D]**

HBsAg positive patients should be treated with nucleoside analogues **[EL 1, RG B]**

HBsAg negative patients with positive anti-HBc (+/-anti-HBs) should be carefully monitored during Anti-TNF treatment and nucleos(t)ide analogues started at the appearance of HBsAg **[EL 4, RG C].**

Linee guida SIGE- IG IBD

Anti TNF and infections

Statement 10G

HCV infection

TNF-alpha inhibition use is safe in patients with HCV infection, although there is little data available **[EL 4, RGD]**

Active HCV infection should be treated according to a standard therapy practice without stopping biological treatment **[EL 5, RG D]**

Linee guida SIGE- IG IBD

Anti TNF and infections

Statement 10H

CMV infection

Screening for a latent or subclinical CMV infection is not necessary before starting biological therapy **[EL2, RG B]**

Systemic CMV infection is a contraindication for anti-TNF therapy; if systemic infection appears, the use of TNF-alpha inhibitor must be discontinued and antiviral therapy should be started **[EL2, RG B]**

Before starting treatment or during immunomodulator therapy, in the case of severe colitis with CMV detected in the mucosa and not in the blood, biological therapy is not a contraindication
[EL 4, RG C]

Linee guida SIGE- IG IBD

Anti TNF and infections

Statement 10I

Varicella zoster virus (VZV) infection

Previous VZV infection is not a contraindication to biological therapy, but biologics should not be started during active infection with chickenpox or herpes zoster **[EL 4, RG D]**

In the event of VZV infection during biological therapy, antiviral treatment should be started **[EL 1, RG B]** and Anti-TNF drugs discontinued **[EL 5, RG D]**

Reintroduction of Anti TNF therapy is possible after vesicles and fever have been resolved **[EL 5, RG D]**

Linee guida SIGE- IG IBD

Epstein Barr virus(EBV) infection

- Screening for EBV infection or antiviral prophylaxis before onset of biologic therapy is not justified [EL2a, RG B].
- In case of severe EBV infection during biologic therapy, treatment should be interrupted and antiviral therapy promptly initiated [EL4, RG D].

Linee guida SIGE- IG IBD

Anti TNF and infections

Statement 10L

Influenza virus

Influenza vaccination with inactivated vaccine is an effective strategy before and during anti-TNF therapy **[EL 2, RG B]**
The live attenuated vaccine is a controindication

Early antiviral treatment is recommended when influenza infection appears during biological therapy **[EL 5, RG D]**

Linee guida SIGE- IG IBD

Anti TNF and Autoimmunity

Statement 11A

In patients with lupus like syndrome biologics should be stopped **[EL 4, RG C]**

Linee guida SIGE- IG IBD

Anti TNF and Heart Failure

Statement 13A

Infliximab or Adalimumab are formally contraindicated in NYHA III-IV patients **[EL 1, RG A]**

Use with caution TNF-alpha inhibitors in patients with HF or decreased left ventricular function (NYHA I-II patients) and therapy should be discontinued if new or worsening symptoms of HF appear **[EL 2, RG B]**

Linee guida SIGE- IG IBD

Anti TNF and Liver disorders

Statement 14A

If jaundice or ALT elevations > 5 times the upper limit appear, anti-TNF therapy should be discontinued **[EL 5, RG D]**

Linee guida SIGE- IG IBD

Perioperative use of Anti-TNF

Statement 15A

Whether there is an increased risk of peri or post-operative infections during or after the use of TNF-alpha inhibitors remains controversial **[EL 4]**

Use with caution TNF-alpha inhibitors when surgery is a possible option **[EL 5, RG D]**

Linee guida SIGE- IG IBD

La terapia biologica nelle IBD: prospettive future

- Biosimilari
- Golimumab
- Vedolizumab

SPECIAL ARTICLE

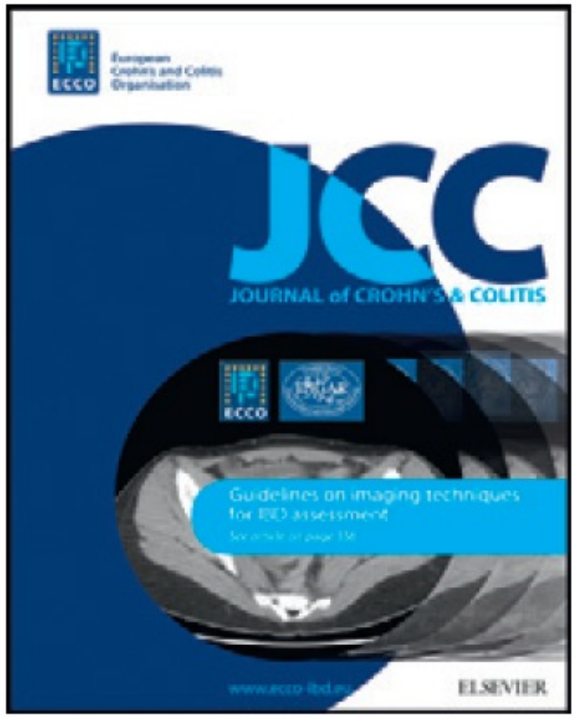
ECCO position statement: The use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD)

Silvio Danese [a,*], Fernando Gomollon [b,**] on behalf of the Governing Board and Operational Board of ECCO

Journal of Crohn's and Colitis (2013) 7, 586–589

Biological medicines are comprised of proteins or other substances derived from a biological source.[1] Biosimilar medicines ('biosimilars') are biological medicines similar to other, already authorized, biological medicines, that are able to enter the market once the patent for the original product, the reference product, has expired.[1]

Journal of Crohn's and Colitis (2013) 7, 586–589



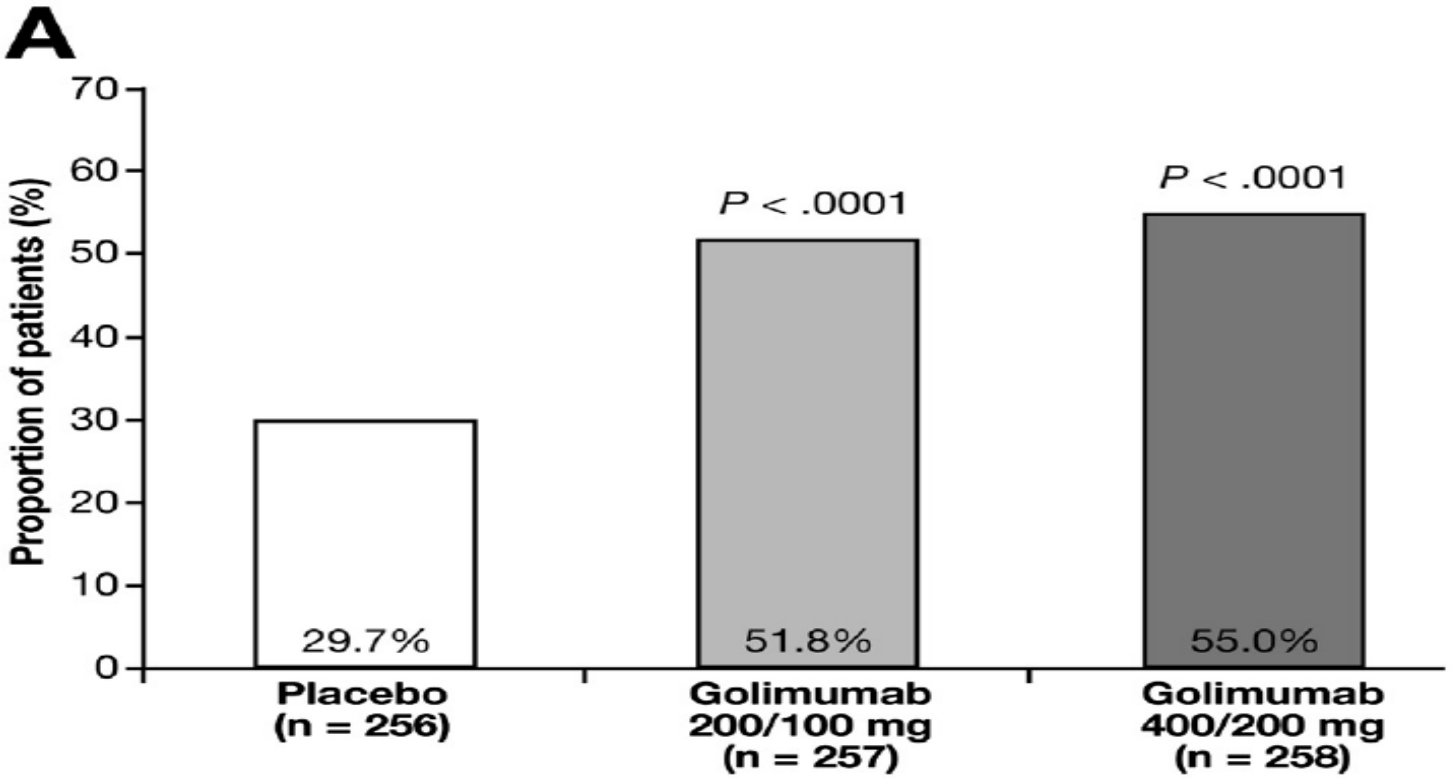
Biologics have become key agents for the management of Crohn's disease and ulcerative colitis. Biosimilars are biological medicines similar to previously authorized biologics and are already available in some countries. This ECCO Position Statement defines the collective view of European specialist in inflammatory bowel disease (IBD) concerning biosimilars. Biosimilars are not comparable to generic small molecules, since both efficacy and toxicity are difficult to predict due to subtle molecular changes that can have profound effects on clinical efficacy and immunogenicity. Direct evidence of safety and benefit from clinical trials in IBD, post-marketing pharmacoviligance, and unequivocal identification of the product as a biosimilar should be requirements before approval. Switching from an established biologic to a biosimilar to save costs is likely to be as inappropriate and inefecctive as switching between current biologics that act on the same target, except when there is loss of response.

I biosimilari: la posizione di AMICI

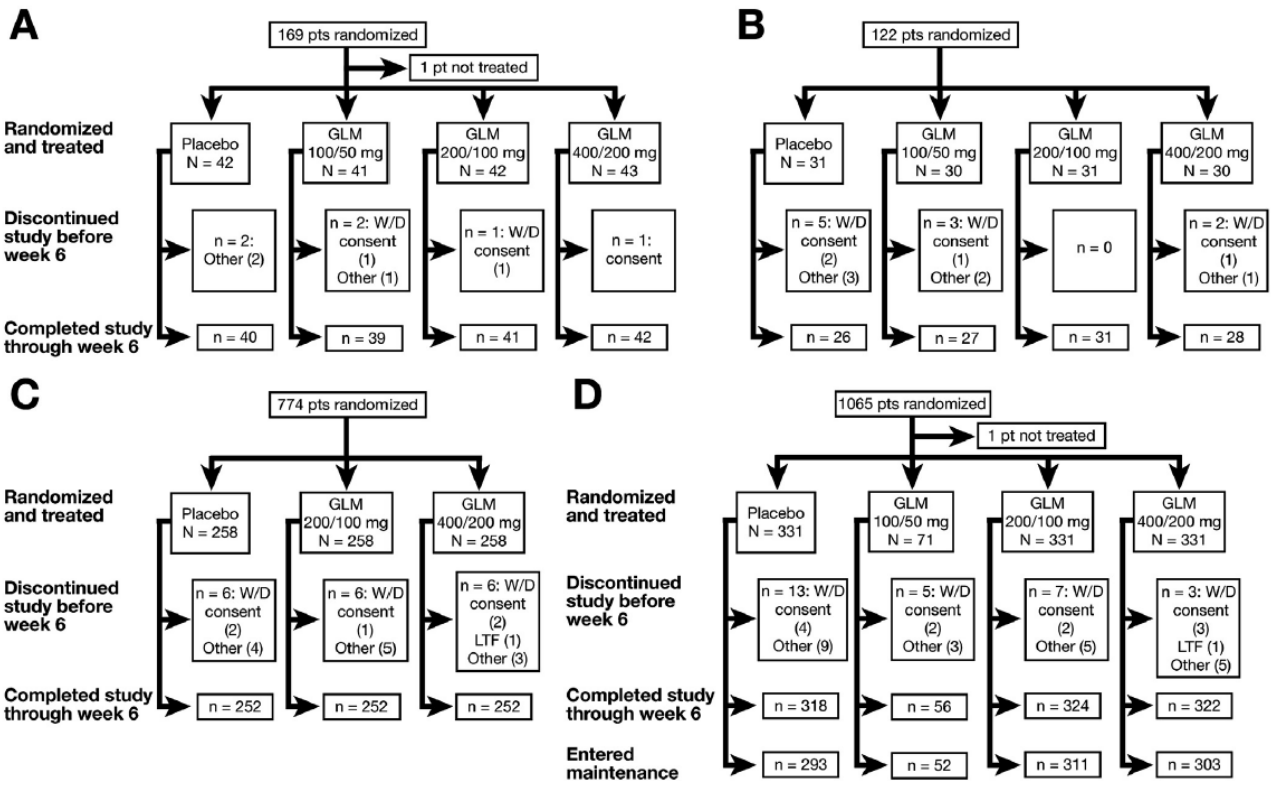
- 1) Il farmaco biosimilare non è il “generico” del farmaco biologico, poichè la complessità di formulazione e di produzione di questi farmaci non consentono la riproduzione di una molecola identica;
  2) Nonostante la disponibilità dei farmaci biosimilari possa consentire risparmi al SSN, un approccio puramente “economicistico”, che non consideri le necessarie cautele e la complessità di gestione, potrebbe vanificare i vantaggi che un corretto utilizzo dei biosimilari può produrre;
  3) L’arrivo di questi farmaci richiede attenzione e procedure di controllo medico a tutela della sicurezza dei pazienti, oltre che a specifiche misure di farmacovigilanza;
  4) L’approvazione di ciascuna indicazione terapeutica deve essere basata su evidenze scientifiche;
  5) La libertà prescrittiva del medico deve essere sempre salvaguardata a garanzia dell’appropriatezza della cura.

Subcutaneous Golimumab Induces Clinical Response and Remission in Patients With Moderate-to-Severe Ulcerative Colitis

WILLIAM J. SANDBORN,[1] BRIAN G. FEAGAN,[2] COLLEEN MARANO,[3] HONGYAN ZHANG,[3] RICHARD STRAUSS,[3] JEWEL JOHANNS,[3] OMONIYI J. ADEDOKUN,[3] CYNTHIA GUZZO,[3] JEAN-FREDERIC COLOMBEL,[4,5] WALTER REINISCH,[6] PETER R. GIBSON,[7] JUDITH COLLINS,[8] GUNNAR JÄRNEROT,[9] TOSHIFUMI HIBI,[10] and PAUL RUTGEERTS[11] for the PURSUIT-SC Study Group



Subcutaneous Golimumab Induces Clinical Response and Remission in Patients With Moderate-to-Severe Ulcerative Colitis



*The single patient randomized but never treated was assigned to the golimumab 100/50 mg group.
GLM- golimumab; LTF- lost to follow-up; pt- patient; W/D- withdrawn

Combined phase 2 and 3 study («adaptive seamless design»)

Subcutaneous Golimumab Maintains Clinical Response in Patients With Moderate-To-Severe Ulcerative Colitis

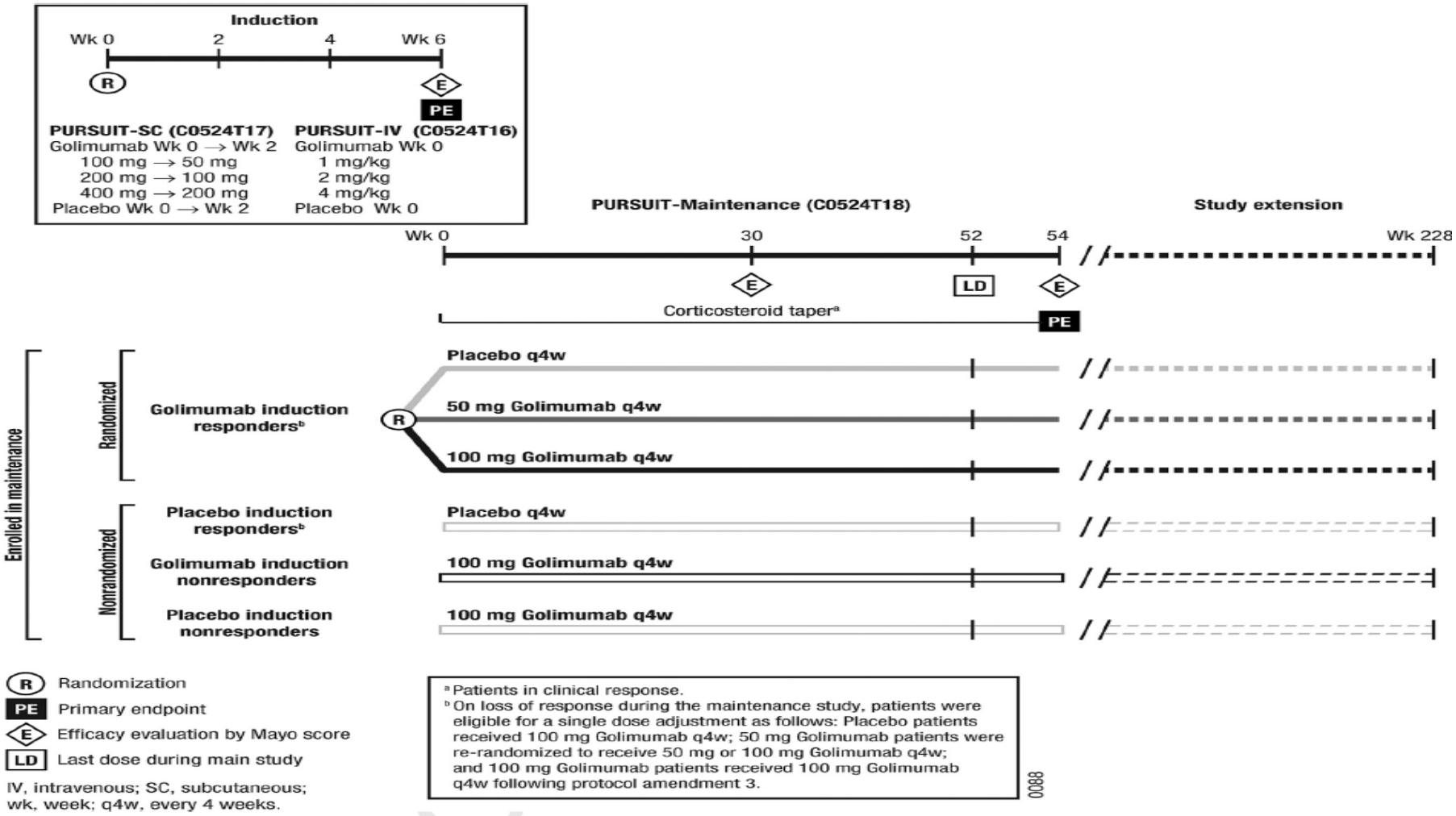
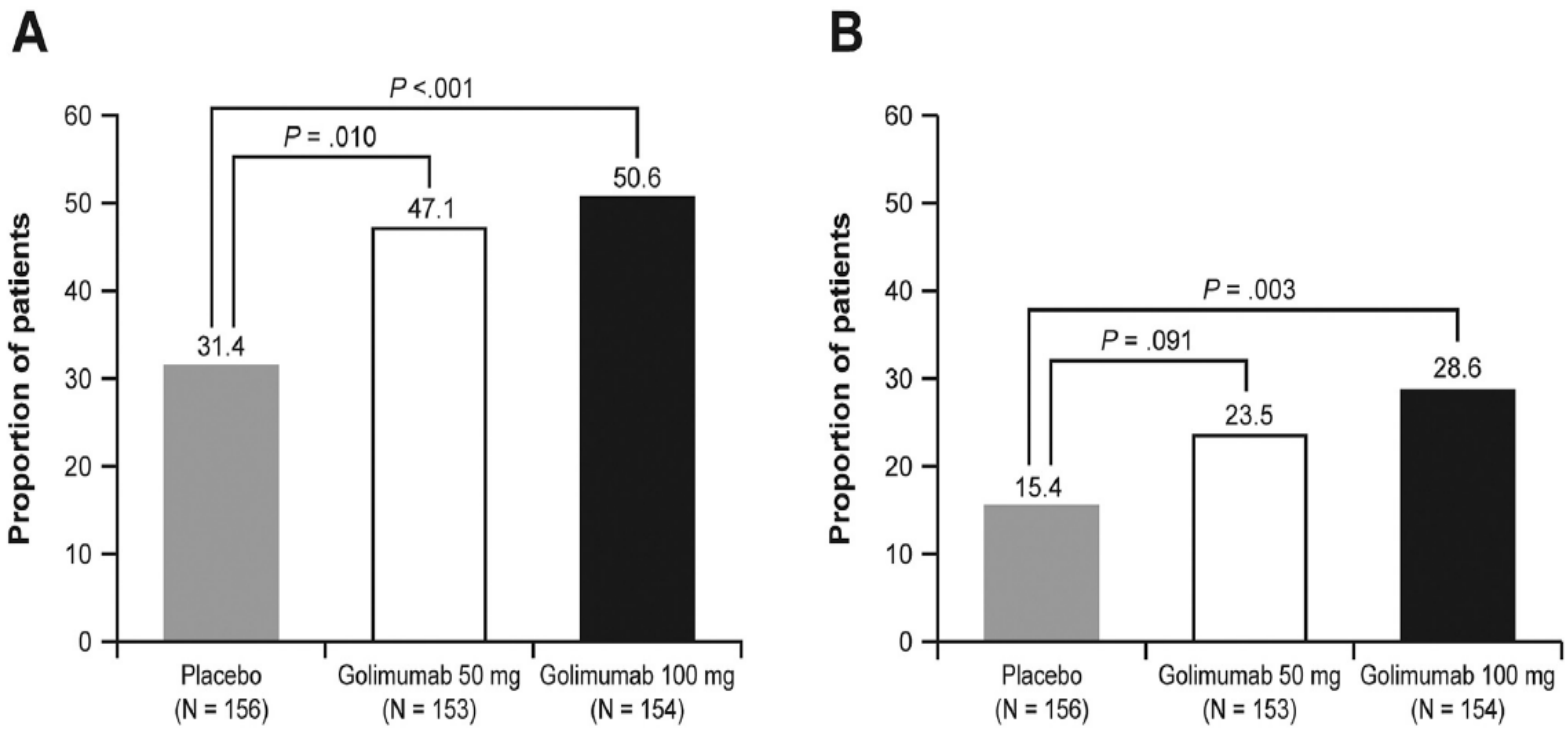


Figure 1. PURSUIT-M study design.

Subcutaneous Golimumab Maintains Clinical Response in Patients With Moderate-To-Severe Ulcerative Colitis

- RCT phase 3
- 251 sites
- Number of patients enrolled: 1228
- Number of patients randomized: 464 (week 6 responders of the induction study)
- Number of patients not randomized: 764
- Golimumab 100 mg or 50 mg monthly
- Primary end-point: maintenance of response at wk 54
- Secondary end -points:
  - clinical remission at wk 30 and 54
  - Mucosal healing at wk 30 and 54

Subcutaneous Golimumab Maintains Clinical Response in Patients With Moderate-To-Severe Ulcerative Colitis



Subcutaneous Golimumab Maintains Clinical Response in Patients With Moderate-To-Severe Ulcerative Colitis

- A study design providing **rigor not previously applied**
- Response assessed not only at fixed time points but **Throughout** the whole study using partial Mayo Score
- The patient who maintaine clinical response was in a state of **continuous response** through 54 weeks
- Safety was consistent with other anti-TNF@ studies:

	Placebo	Golimumab 50 mg	Golimumab 100 mg
SAE (%)	7.7	8.4	14.4
Serious infections (%)	1.9	3.2	3.2
Deaths (n.)			3

Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis

Brian G. Feagan, M.D., Paul Rutgeerts, M.D., Ph.D., Bruce E. Sands, M.D., Stephen Hanauer, M.D., an-Frédéric Colombel, M.D., William J. Sandborn, M.D., Gert Van Assche, M.D., Ph.D., Jeffrey Axler, M.D., ong Kim, M.D., Ph.D., Silvio Danese, M.D., Ph.D., Irving Fox, M.D., Catherine Milch, M.D., Serap Sankoh, Ph.D., Tim Wyant, Ph.D., Jing Xu, Ph.D., and Asit Parikh, M.D., Ph.D., for the GEMINI 1 Study Group*

- RCT phase 3 induction and maintenance
- 211 centres
- 895 patients enrolled
- Moderate-to-severe UC (Mayo 6-12)
- Refractory to steroids or IM or TNF-antagonists (50%)
- Induction: I.V. vedolizumab 300 mg vs placebo plus open-label cohort
- Maintenance: responders at week 6 randomized to placebo, vedolizumab 300 mg every 8 or 4 weeks

N ENGL J MED 369;8 NEJM.ORG AUGUST 22, 2013

Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis

Brian G. Feagan, M.D., Paul Rutgeerts, M.D., Ph.D., Bruce E. Sands, M.D., Stephen Hanauer, M.D., an-Frédéric Colombel, M.D., William J. Sandborn, M.D., Gert Van Assche, M.D., Ph.D., Jeffrey Axler, M.D., ong Kim, M.D., Ph.D., Silvio Danese, M.D., Ph.D., Irving Fox, M.D., Catherine Milch, M.D., Serap Sankoh, Ph.D., Tim Wyant, Ph.D., Jing Xu, Ph.D., and Asit Parikh, M.D., Ph.D., for the GEMINI 1 Study Group*

Table 2. Outcome Measures at Week 6 in the Trial of Induction Therapy.

Outcome	Placebo (N = 149)	Vedolizumab (N = 225)	Percentage-Point Difference (95% CI)*	P Value
	no. (%)			
Clinical response†	38 (25.5)	106 (47.1)	21.7 (11.6–31.7)	<0.001
Clinical remission‡	8 (5.4)	38 (16.9)	11.5 (4.7–18.3)	0.001
Mucosal healing§	37 (24.8)	92 (40.9)	16.1 (6.4–25.9)	0.001

Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis

Brian G. Feagan, M.D., Paul Rutgeerts, M.D., Ph.D., Bruce E. Sands, M.D., Stephen Hanauer, M.D., an-Frédéric Colombel, M.D., William J. Sandborn, M.D., Gert Van Assche, M.D., Ph.D., Jeffrey Axler, M.D., ong Kim, M.D., Ph.D., Silvio Danese, M.D., Ph.D., Irving Fox, M.D., Catherine Milch, M.D., Serap Sankoh, Ph.D.,

Table 3. Outcome Measures in the Trial of Maintenance Therapy.

Outcome	Placebo (N=126)	Vedolizumab Every 8 Wk (N=122)	Vedolizumab Every 4 Wk (N=125)	Between-Group Difference*			
				Every 8 Wk vs. Placebo	P Value	Every 4 Wk vs. Placebo	P Value
	number/total number (percent)			*percentage points (95% CI)*		*percentage points (95% CI)*	
Clinical remission at wk 52	20/126 (15.9)	51/122 (41.8)	56/125 (44.8)	26.1 (14.9–37.2)	<0.001	29.1 (17.9–40.4)	<0.001
Durable clinical response†	30/126 (23.8)	69/122 (56.6)	65/125 (52.0)	32.8 (20.8–44.7)	<0.001	28.5 (16.7–40.3)	<0.001
Durable clinical remission‡	11/126 (8.7)	25/122 (20.5)	30/125 (24.0)	11.8 (3.1–20.5)	0.008	15.3 (6.2–24.4)	0.001
Mucosal healing at wk 52	25/126 (19.8)	63/122 (51.6)	70/125 (56.0)	32.0 (20.3–43.8)	<0.001	36.3 (24.4–48.3)	<0.001
Glucocorticoid-free remission at wk 52§	10/72 (13.9)	22/70 (31.4)	33/73 (45.2)	17.6 (3.9–31.3)	0.01	31.4 (16.6–46.2)	<0.001

Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease

William J. Sandborn, M.D., Brian G. Feagan, M.D., Paul Rutgeerts, M.D., Ph.D., Stephen Hanauer, M.D., Jean-Frédéric Colombel, M.D., Bruce E. Sands, M.D., Milan Lukas, M.D., Ph.D., Richard N. Fedorak, M.D., Scott Lee, M.D., Brian Bressler, M.D., Irving Fox, M.D., Maria Rosario, Ph.D., Serap Sankoh, Ph.D., Jing Xu, Ph.D., Kristin Stephens, B.A., Catherine Milch, M.D., and Asit Parikh, M.D., Ph.D., for the GEMINI 2 Study Group*

Phase 3 RCT induction and maintenance

285 centres

Moderate-to-severe Crohn's disease (CDAI 220 – 450)

Age 18 – 80 years

Refractory or intolerant to glucocorticoids or IM or TNF-antagonists

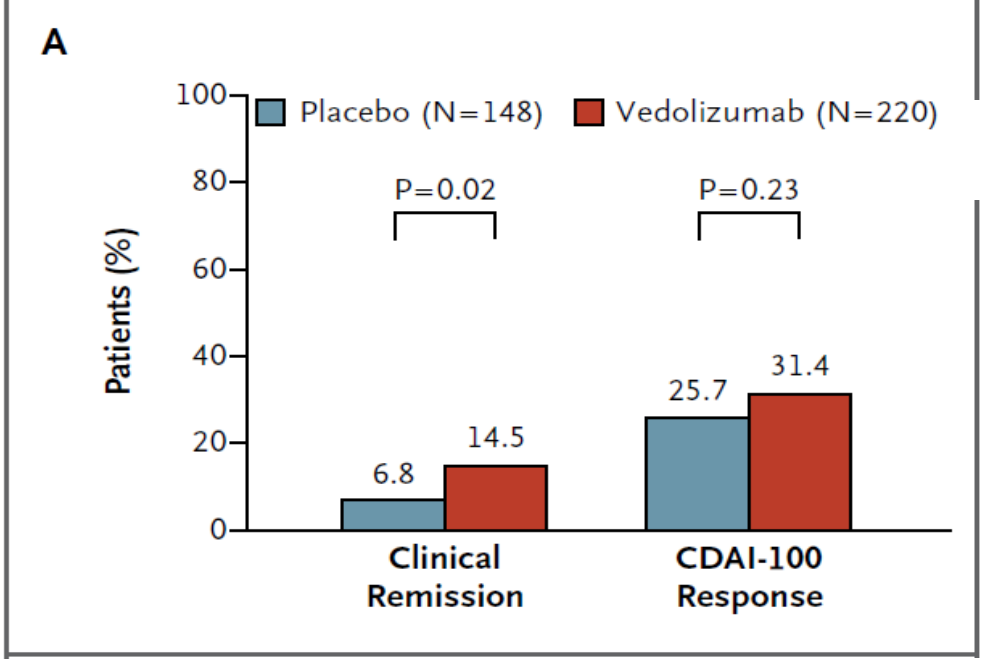
Induction: vedolizumab i.v. 300 mg or placebo 0, 2 wks (cohort 1); vedolizumb open-label (cohort 2); end-points clinical remission and CDAI-100 response at wk 6

Maintenance: 6 wk – responders vedolizumab 300 every 8, 4 wks or placebo; end-point clinical remission and CDAI 100-response at wk 52

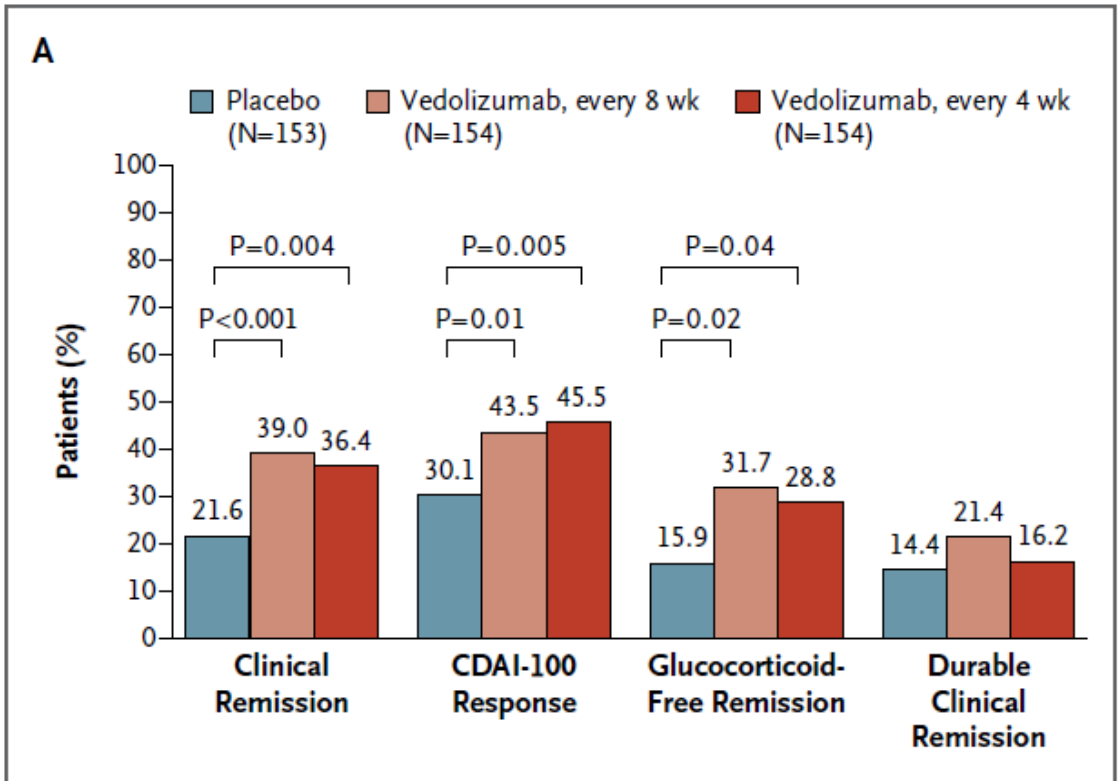
N ENGL J MED 369;8 NEJM.ORG AUGUST 22, 2013

N ENGL J MED 369;8 NEJM.ORG AUGUST 22, 2013

Vedolizumab in CD: Induction



Vedolizumab in CD: maintenance



Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease

William J. Sandborn, M.D., Brian G. Feagan, M.D., Paul Rutgeerts, M.D., Ph.D., Stephen Hanauer, M.D., Jean-Frédéric Colombel, M.D., Bruce E. Sands, M.D., Milan Lukas, M.D., Ph.D., Richard N. Fedorak, M.D., Scott Lee, M.D., Brian Bressler, M.D., Irving Fox, M.D., Maria Rosario, Ph.D., Serap Sankoh, Ph.D., Jing Xu, Ph.D., Kristin Stephens, B.A., Catherine Milch, M.D., and Asit Parikh, M.D., Ph.D., for the GEMINI 2 Study Group*

Table 2. Adverse Events Affecting at Least 5% of Patients Who Received Vedolizumab.*

Event	Placebo (N = 301)	Vedolizumab (N = 814)
	no. (%)	
Adverse event		
Crohn's disease exacerbation	65 (21.6)	164 (20.1)
Arthralgia	40 (13.3)	110 (13.5)
Pyrexia	40 (13.3)	103 (12.7)
Nasopharyngitis	24 (8.0)	100 (12.3)
Headache	47 (15.6)	97 (11.9)
Nausea	30 (10.0)	90 (11.1)
Abdominal pain	39 (13.0)	79 (9.7)
Upper respiratory tract infection	17 (5.6)	54 (6.6)
Fatigue	14 (4.7)	53 (6.5)
Vomiting	23 (7.6)	49 (6.0)
Back pain	12 (4.0)	38 (4.7)
Any serious adverse event	46 (15.3)	199 (24.4)
Any serious infection†	9 (3.0)	45 (5.5)
Any cancer‡	1 (0.3)	4 (0.5)