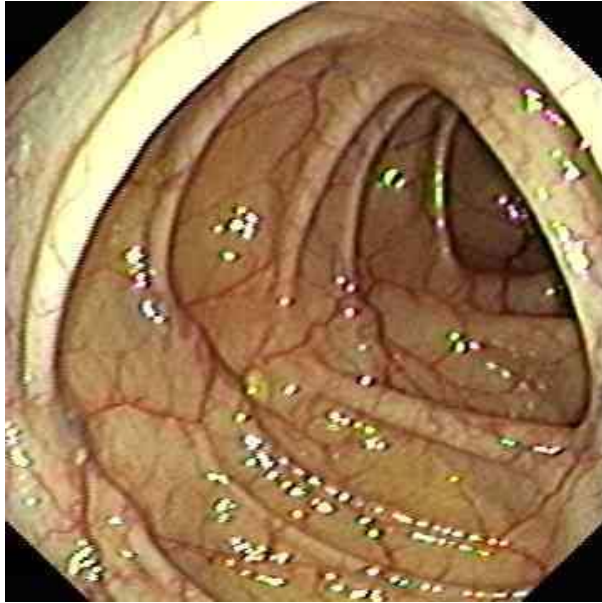


**NUOVI FARMACI PER LE  
MALATTIE  
INFIAMMATORIE  
CRONICHE INTESTINALI  
(IBD)**

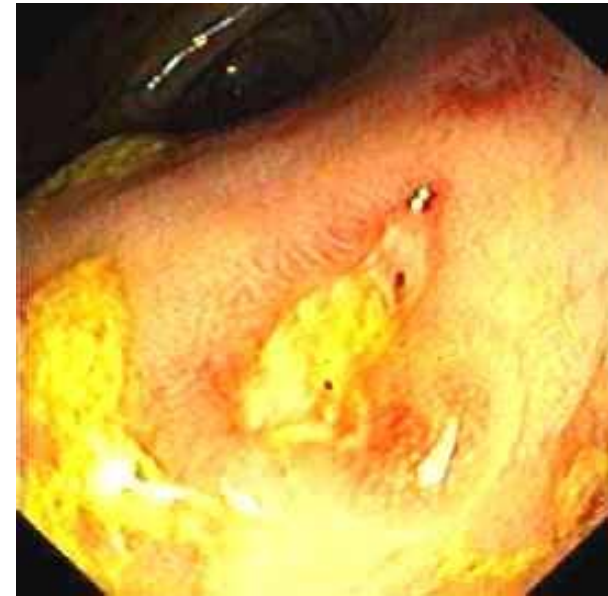
# MALATTIE INFIAMMATORIE CRONICHE INTESTINALI



Colon Normale

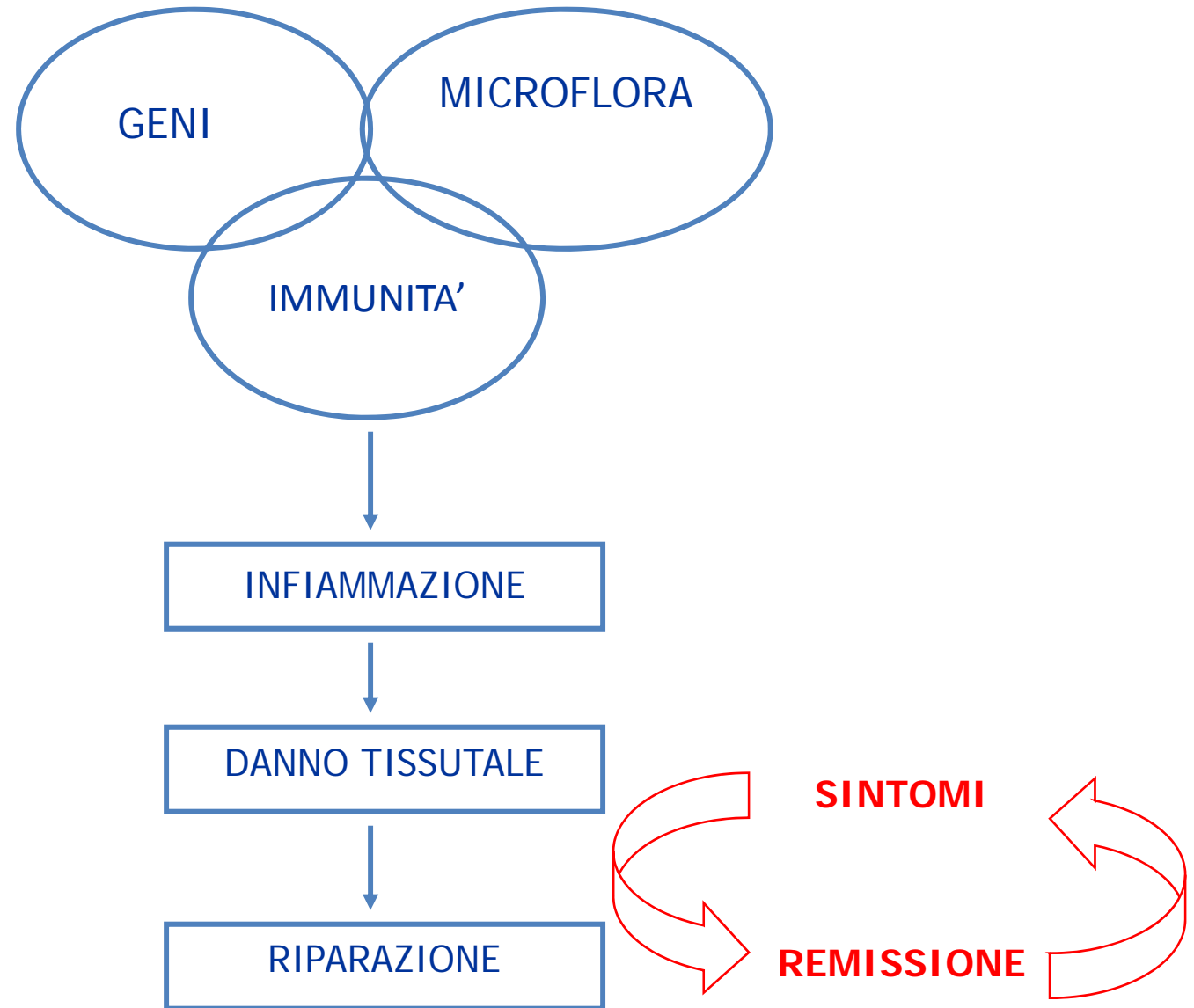


Colite ulcerosa



Morbo di Crohn

# PATOGENESI



# La pipeline delle IBD

Biologici

- Citochine/chemochine
- Molecole adesione
- Anti TNF
- Barriera mucosa
- Fattori Trascrizione
- Inibizione fosfodiesterase IV

- ABT-874/J695/ Abbott-Wyeth
- Oprelvekin/ Wyeth
- Visilizumab/ PDL
- Alicaforsen/ Isis
- Basilixmab/Novartis
- CDP-870 Celltech-UCB
- Fontolizumab/ PDL
- EGF/ Hitachi-Nippon
- Sargamostim/ Schering-Berlex
- Onercept/Serono
- Natalizumab/ Elan/Biogen
- CNI1493/ Pharma Science
- MLN-2/Millenium

- Infliximab/ Centocor/Schering-Plough
- Adalimumab/ Abbott

Pre-clinica

Fase I

Fase II

Fase III

Pre-reg.

Lanciati

● Cell homing

● Cytokine release

● OCP 6535/ Otsuka

● Lecithin/ Dr. Stremmel

● STA5236/Syntha

● RDP58/ Genzyme/SangStat



● MMX Mesalazina Giuliani)

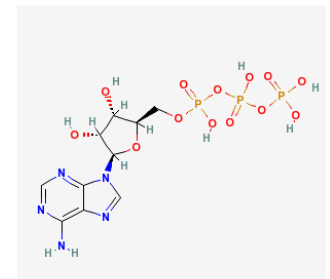
Piccole molecole

## ALTRE INDICAZIONI:

- Oprelvekin trombocitopenia post-chemol (lanciato)
- CDP-870 artrite reumatoide (Fase III)
- Adalimumab artrite reumatoide (lanciato)
- Sargamostim neutropenia post-chemio (lanciato)
- Natalizumab sclerosi multipla (pre-reg)
- Infliximab artrite reumatoide (lanciato)
- psoriasi/artrite psoriasica (pre-reg/Fase III)

# *Piccole Molecole vs Biologici*

- Le *piccole molecole* sono composti a basso PM generalmente sintetizzate con reazioni chimiche biologicamente attive, ben caratterizzate, purificate, facilmente analizzabili.
- I *biologici* sono prodotti di cellule ingegnerizzate come miscela di molecole difficili da caratterizzare .



# Size & Complexity – Small Molecule Drugs & Proteins

Size

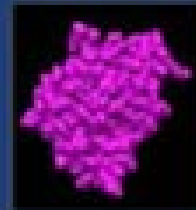
**Small Molecule Drug**

Aspirin  
21 atoms



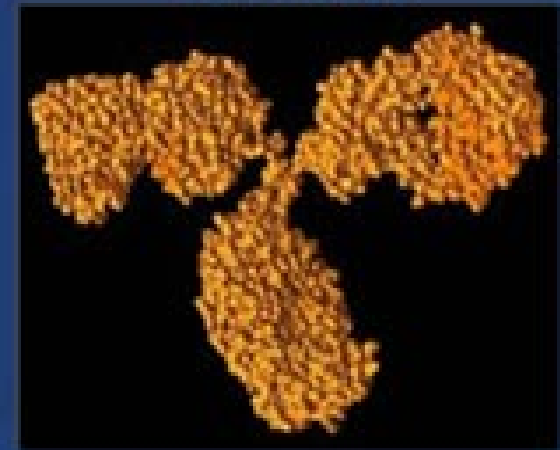
**Large Molecule Drug**

hGH  
~ 3000 atoms



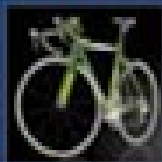
**Large Biologic**

IgG Antibody  
~ 25,000 atoms



Complexity

Bike  
~ 20 lbs

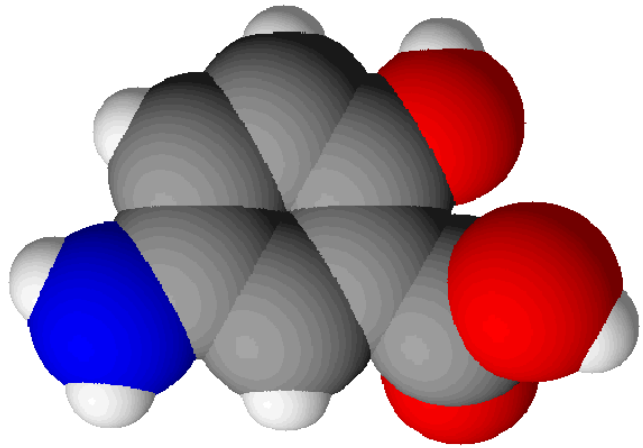


Car  
~ 3000 lbs

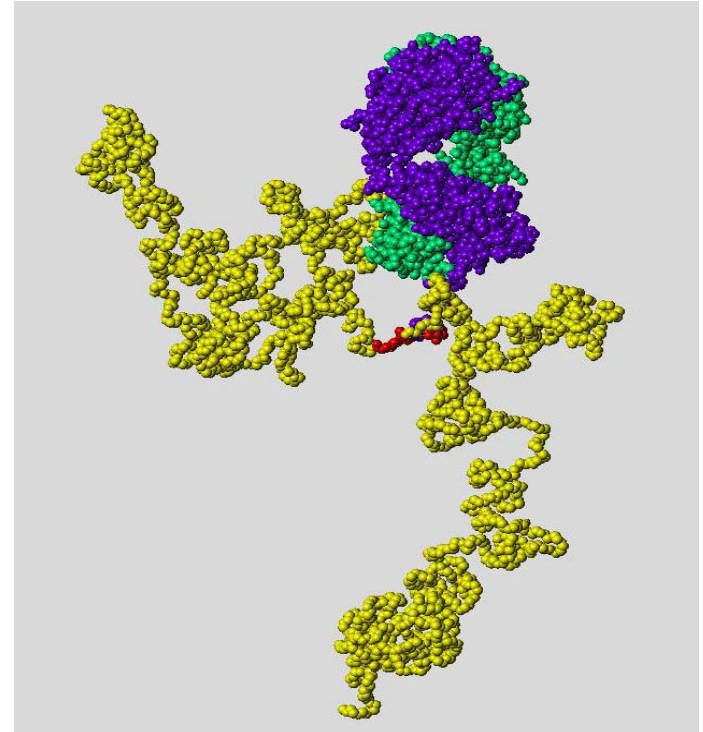


Business Jet  
~ 30,000 lbs (without fuel)





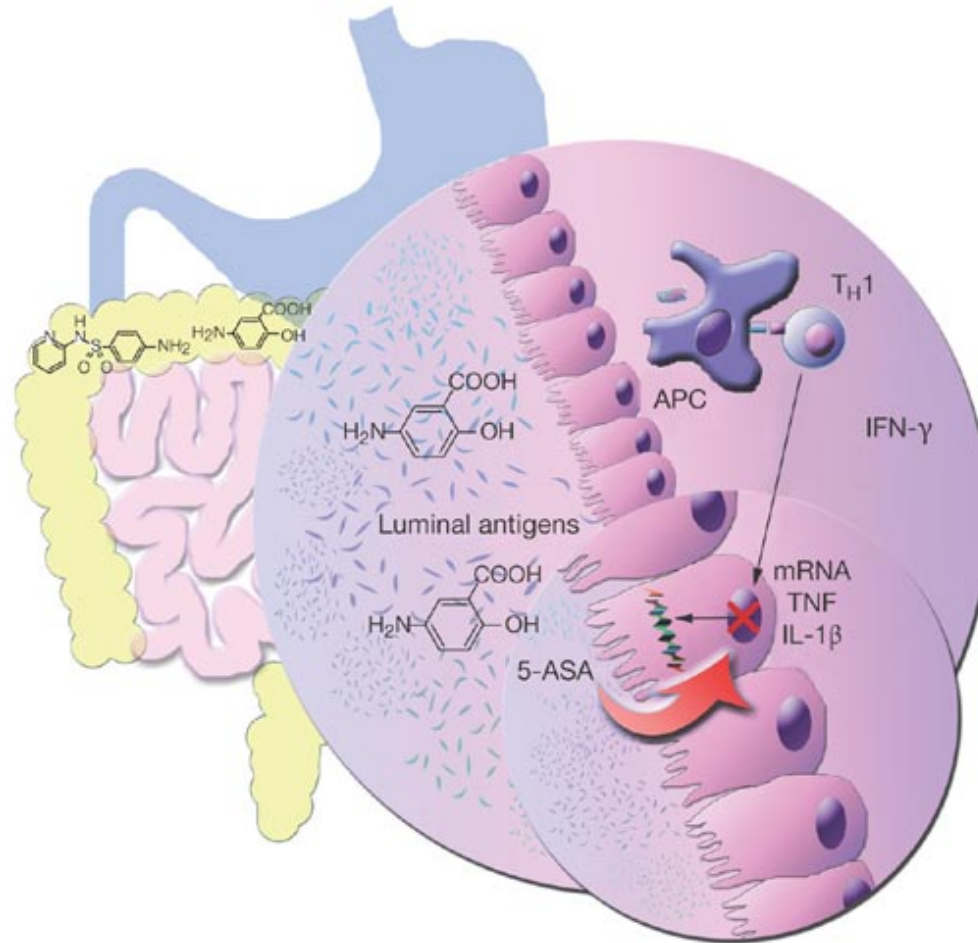
Mesalazina



Certolizumab

# Meccanismo di azione della mesalazina nel colon

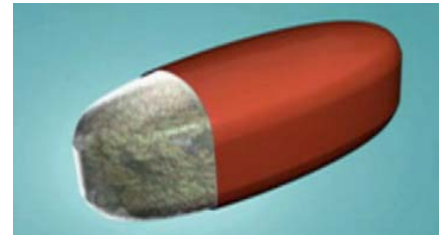
- Blocco della produzione di PGs e LK
- Inibizione della chemiotassi neutrofila
- Blocco dell'attivazione del NFκB



# MMX\*: Multi Matrix System : Meccanismo di rilascio

MMX rilascia 1200 mg di mesalazina attraverso un avanzato sistema di rilascio multimatrice formato da 3 componenti:

- **Componente A:** rivestimento gastroresistente che richiede un pH superiore a 7 per dissolversi, assicurando così che il farmaco non sia rilasciato fino a che la compressa non raggiunge l'ileo terminale



- **Componente B:** matrice idrofila che rilascia lentamente microparticelle di 5-ASA durante il transito attraverso il colon



- **Componente C:** matrice lipofila che incapsula la maggior parte delle particelle di 5-ASA per prolungare il rilascio del principio attivo nell'arco delle 24 ore

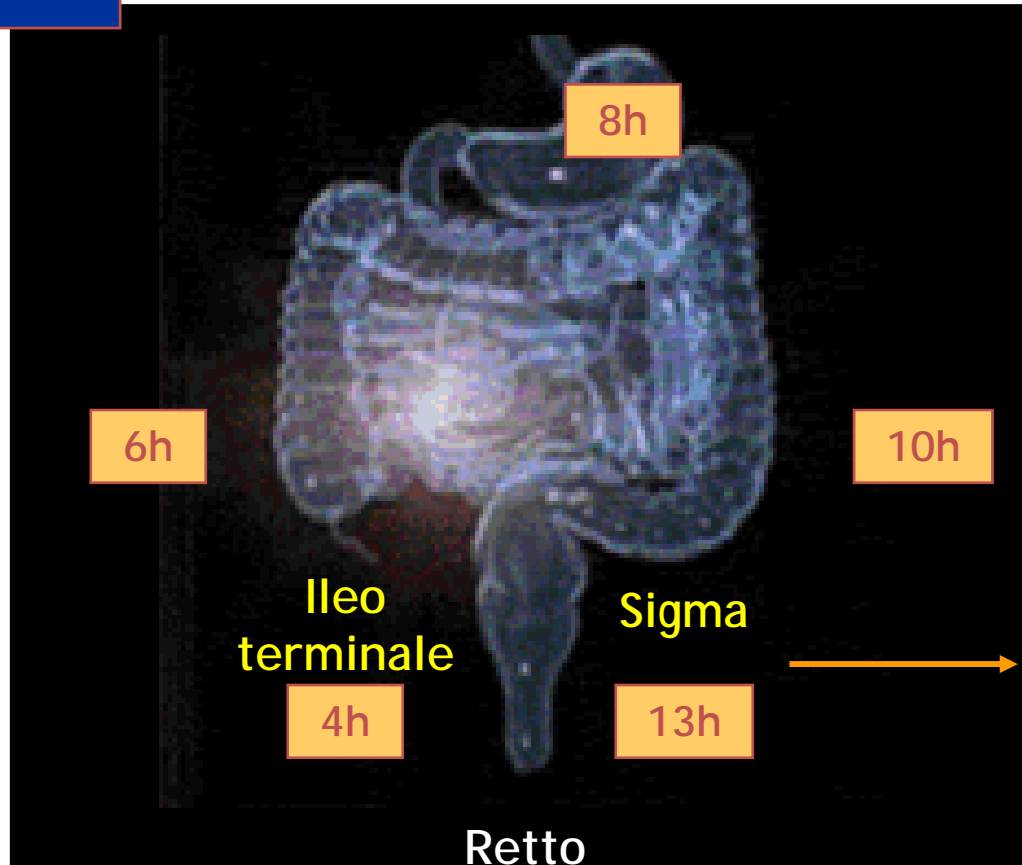


\* **Mesavancol (Giuliani)**

# MMX: Delivery di 5-ASA nel tempo

MMX: 30% di rilascio nelle prime 2 ore

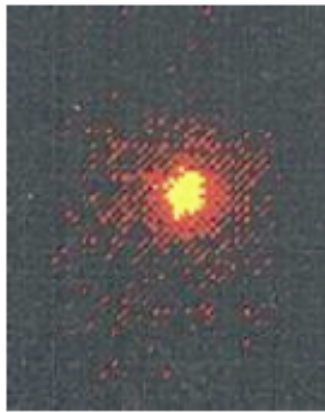
Altre mesalazine: 95% di rilascio nelle prime 2 ore



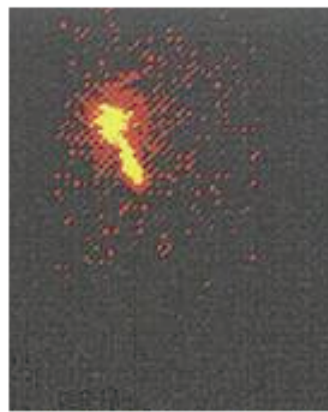
La presenza nel sigma-retto inizia dopo 13 ore e si mantiene fino a 24 ore



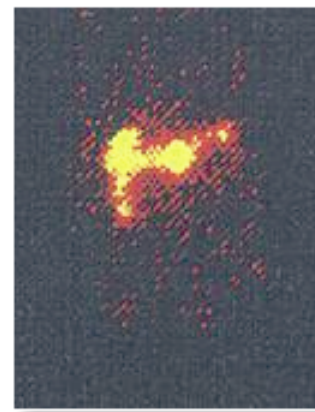
## Colonic Spread of Mesalazine MMX Assessed *in vivo* by Gamma Scintigraphy



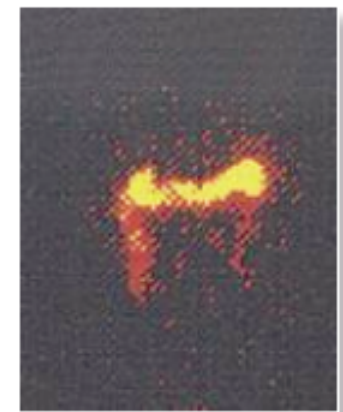
1h 30' Duodenum



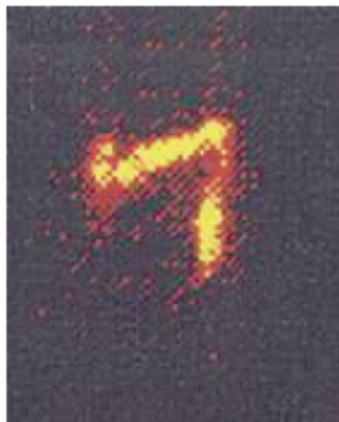
4h 30' Ascending Colon



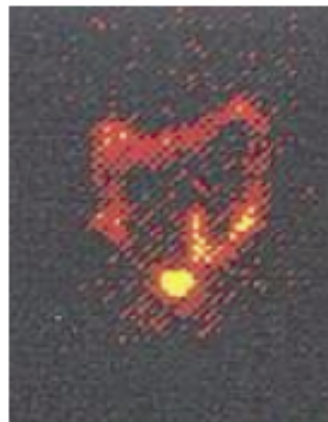
7h 30' Transverse Colon



10h Transverse Colon



16h Descending Colon

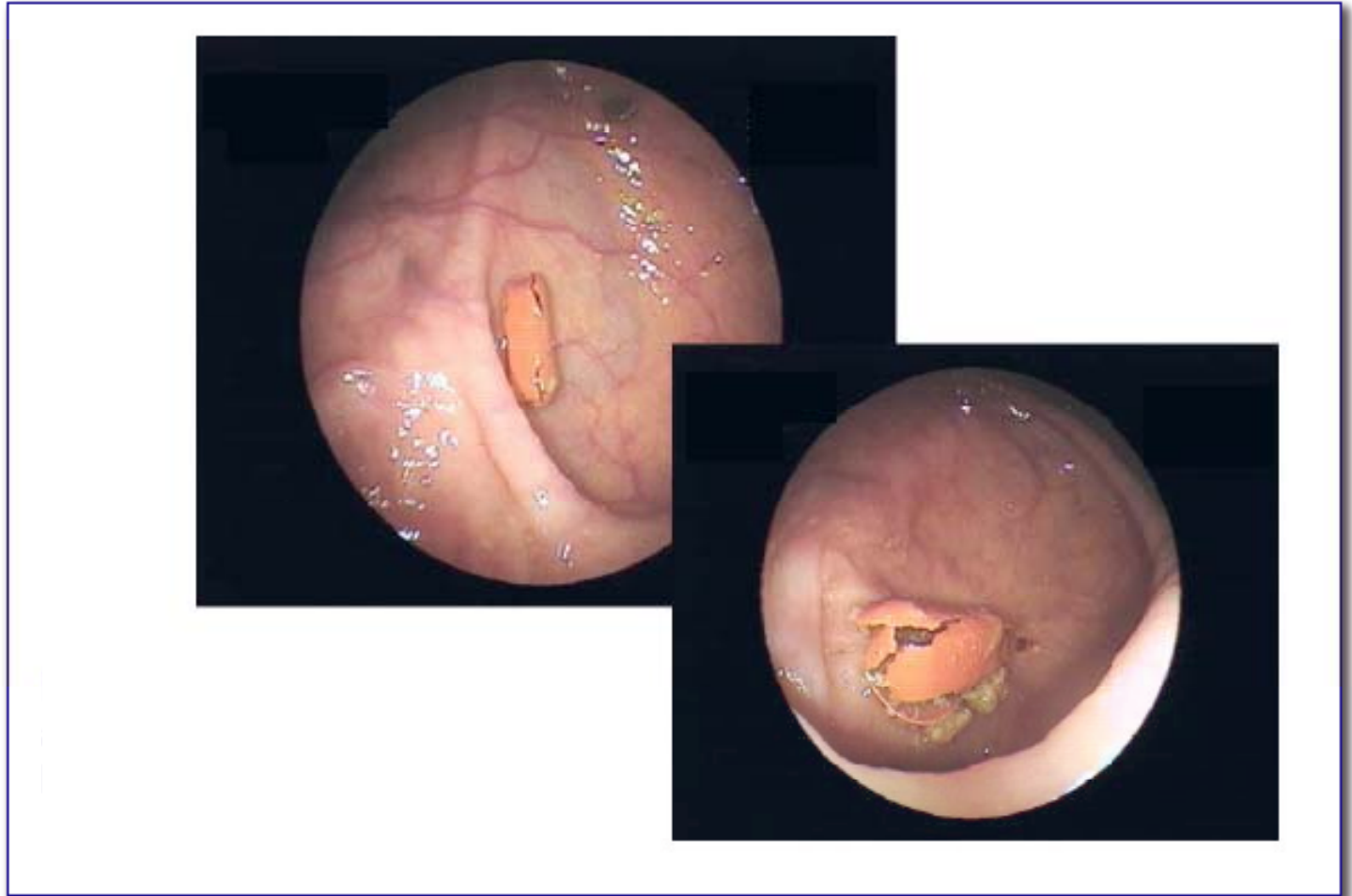


24h Rectum

The mean relative absorption  
of 5-ASA was  $19.9 \pm 18.2\%$  in  
the ileum and  $80.1 \pm 18.2\%$  in  
the colon

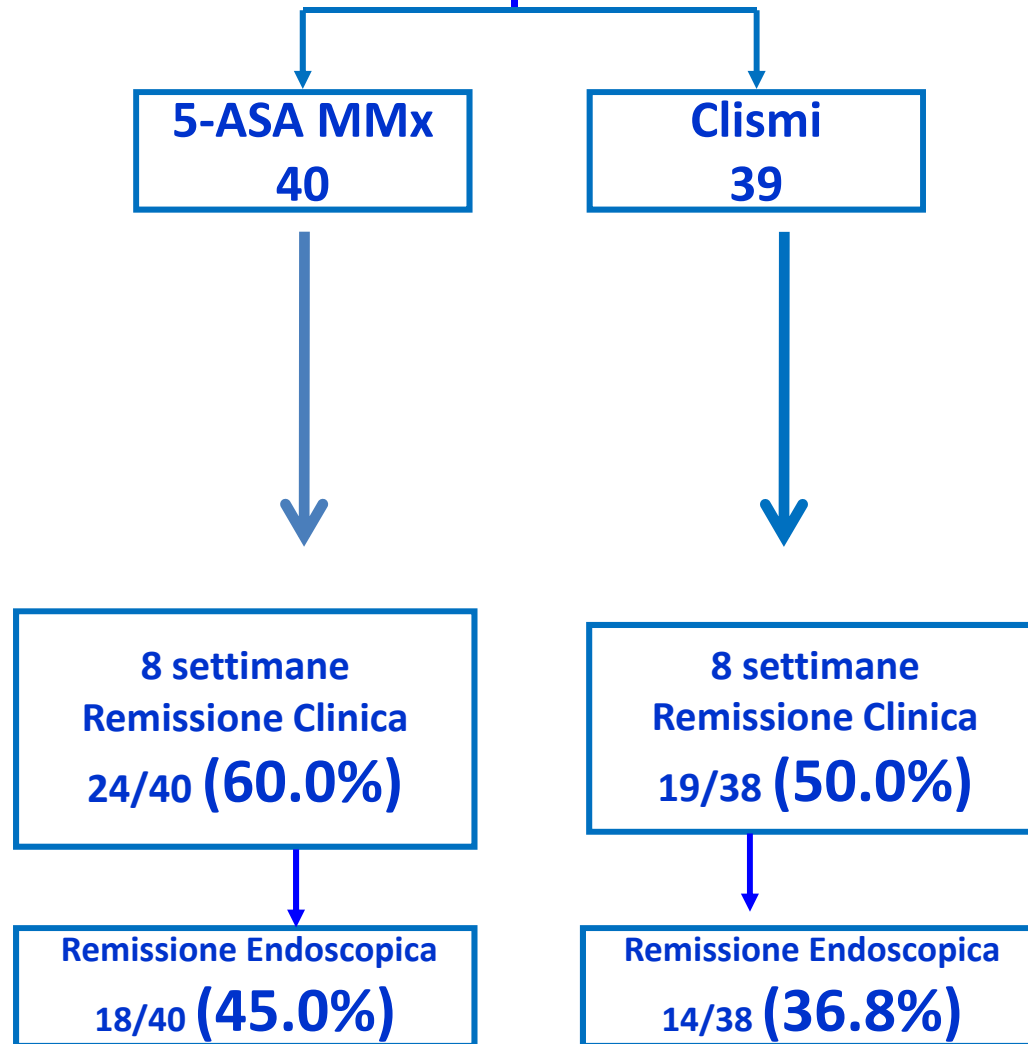
[Brunner *et al.*, *Aliment Pharmacol  
Ther* 2003; 17: 395-402]

## Dissoluzione della capsula MMX nell' ileo terminale



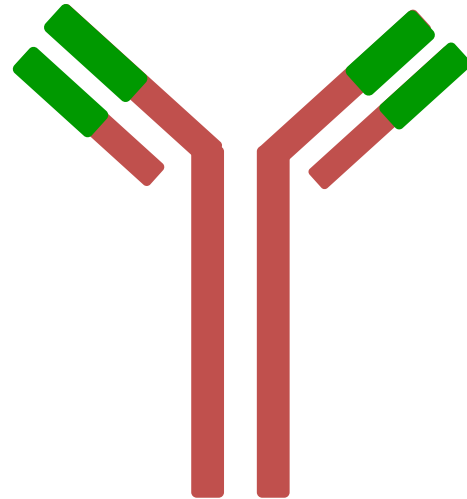
# Studio Pilota CU

Pazienti Randomizzati 79

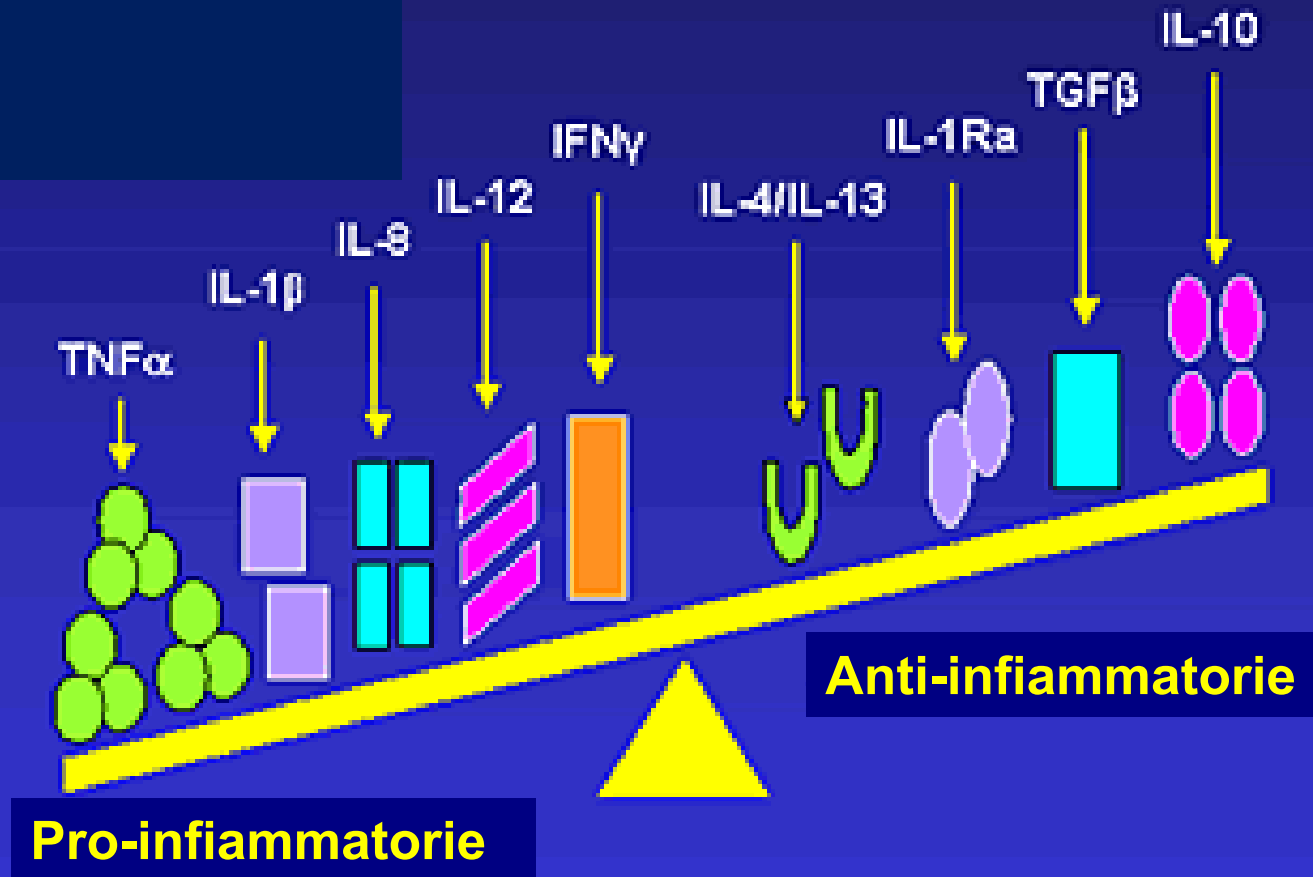


**Biologici:** farmaci prodotti partendo da materiale biologico, con procedure che possono utilizzare anche il DNA ricombinante :

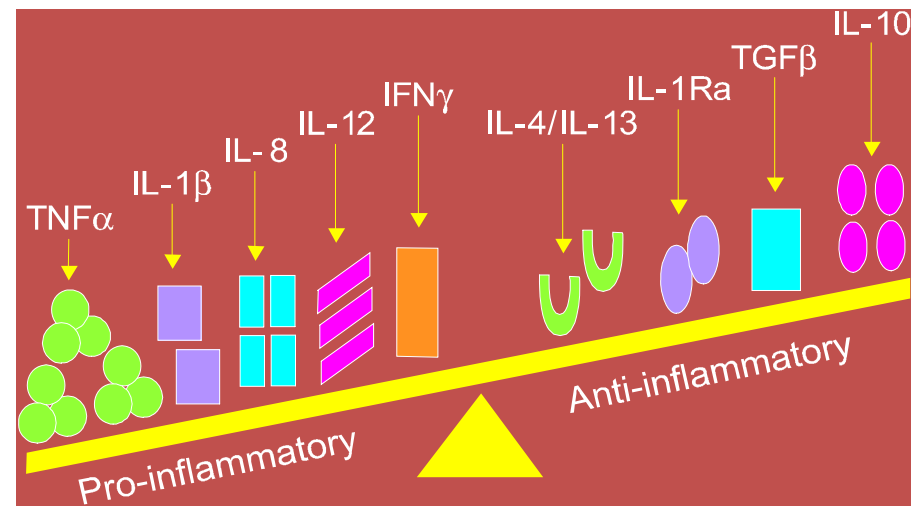
- Ormoni
- Anticorpi Monoclonali
- Emoderivati
- Interferoni
- Vaccini



# Citochine immunomodulatorie/ anti-infiammatorie



# Biologici in ricerca per le malattie infiammatorie croniche intestinali



- **Citochine**

- Il-1ra (anakinra)
- Antibodies to Il-4, Il-6, Il-8, **Il-12**, Il-15, Il-16, Il-18, Il-23
- Il-10, Il-11

- **Molecole anti-adesione cellulare**

- Antibodies to ICAM-1, VCAM-1, VLA-4,  **$\alpha$ -4 (natalizumab)**,  $\alpha$ 4 $\beta$ 7
- Composti Antisenseo per ICAM-1
- Anti NF- $\kappa$ B, anti-OX40, anti-ZAP

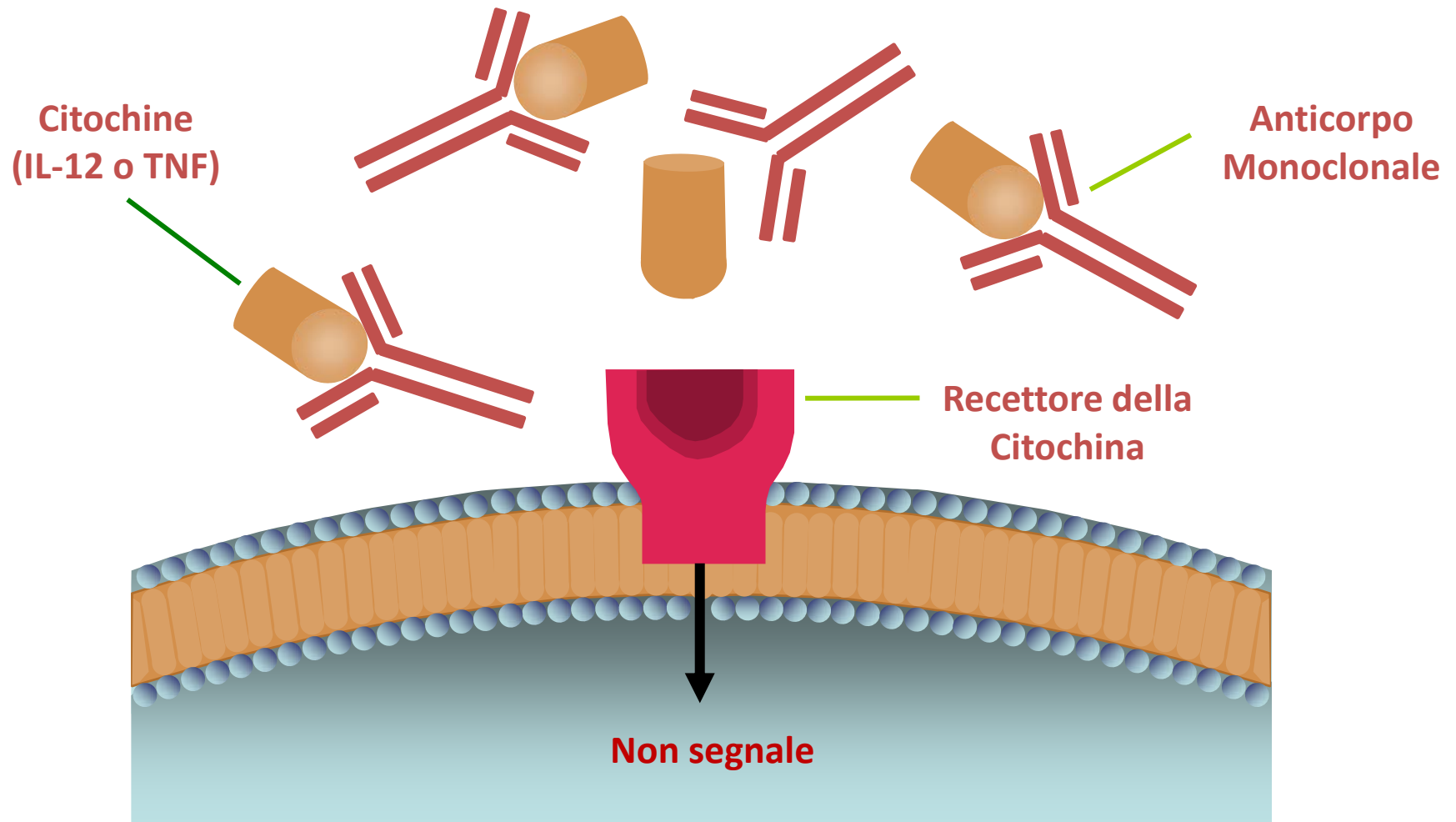
- **Altri approcci**

- ormone rhuGrowth, KGF- (fallito nei trials CU), rosiglitzone, inibitori PAF , EGF, RDP, Nu-286 (Wnt agonisti)

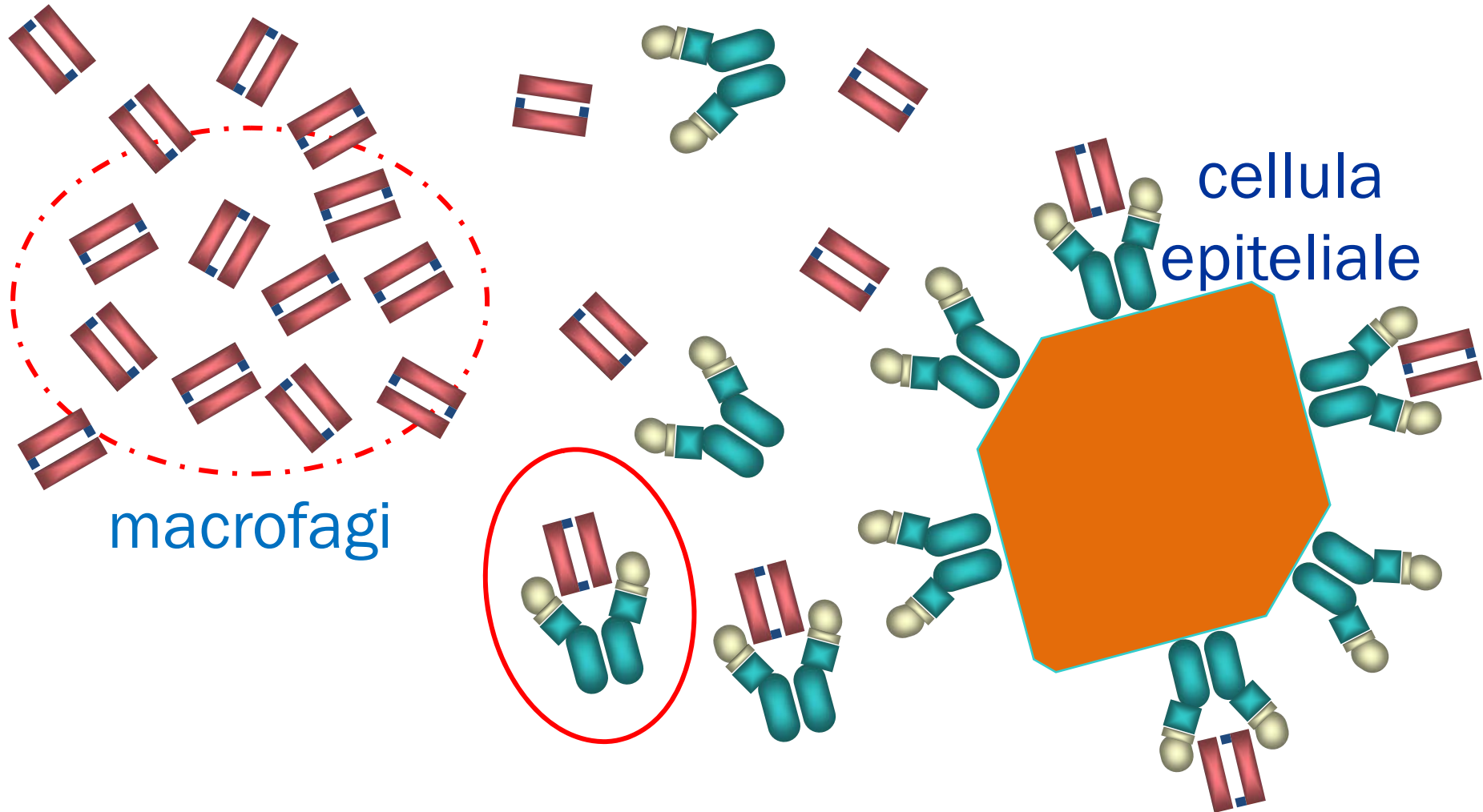
- **Strategie Anti-TNF**

- Anticorpi Chimerici
- Anticorpi “umanizzati”
- Anticorpi “umani”
- Frammenti Anticorpi
- Composti Antisenseo
- TNF-BP1
- Talidomide

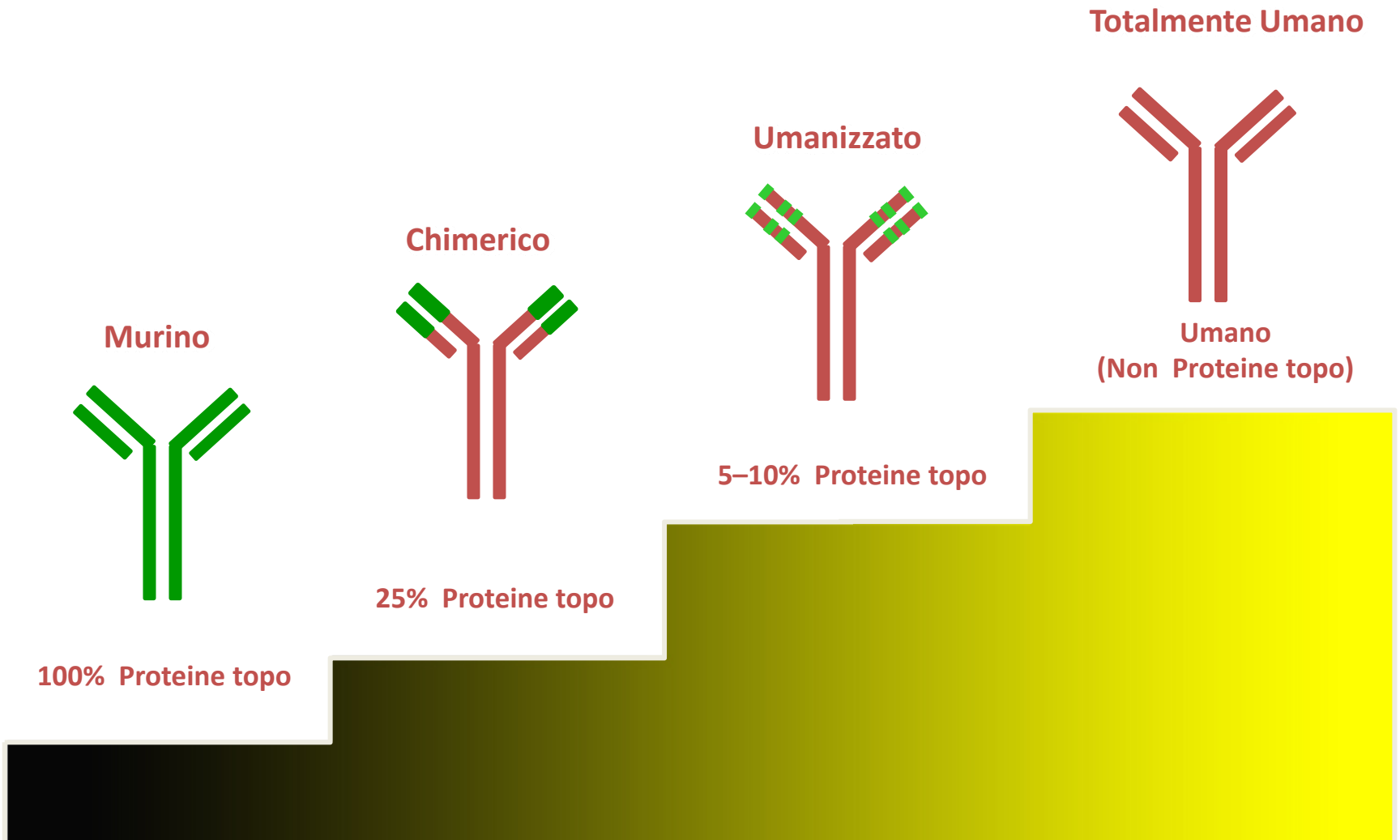
# Gli Anticorpi Monoclonali Prevedgono l'Interazione delle Citochine con i Recettori Cellulari



# Blocco dei Recettori del TNF- $\alpha$

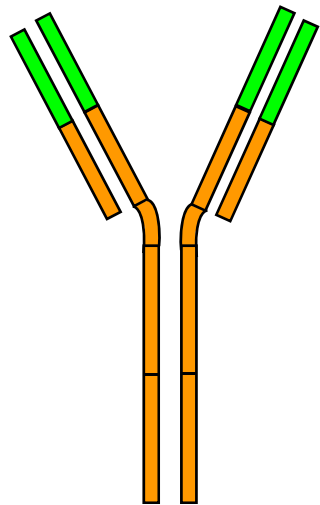


# Evoluzione degli Anticorpi Monoclonali



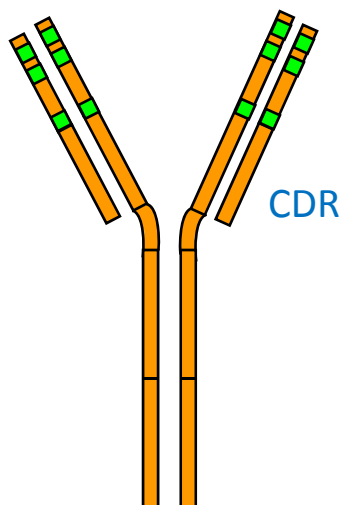
# Inibitori TNF- $\alpha$

Anticorpo  
Chimerico  
monoclonale



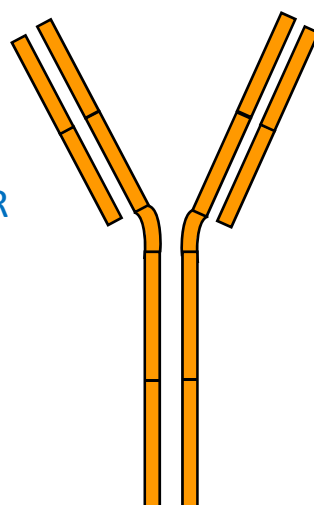
infliximab  
IgG1

Anticorpo  
monoclonale  
umanizzato



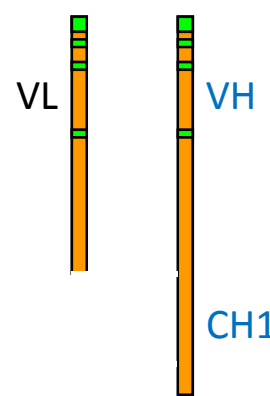
*CDP571*  
*IgG4*

Anticorpo  
umano  
ricombinante



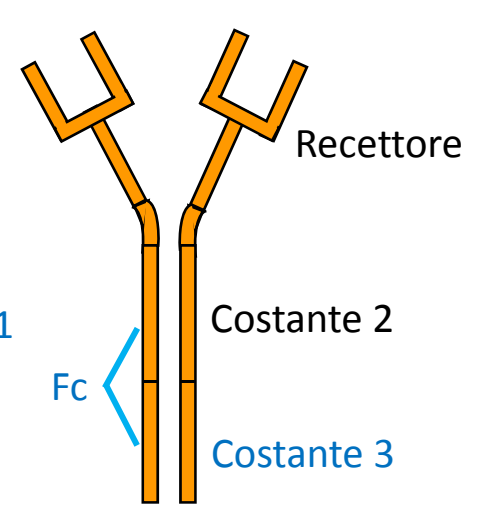
adalimumab  
IgG1

Frammento  
Fab'  
umanizzato



*certolizumab*  
*pegol*

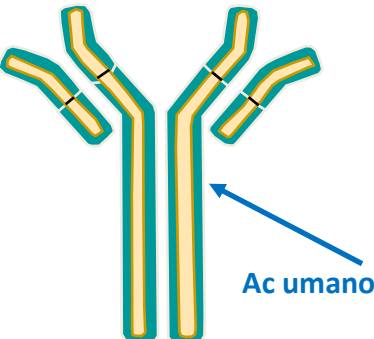
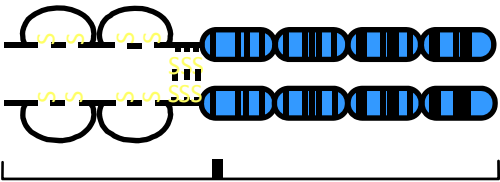
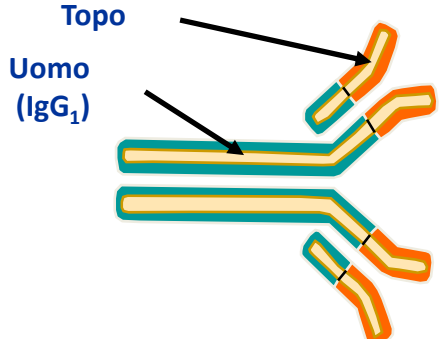
Recettore umano  
ricombinante/  
proteina fusione Fc p



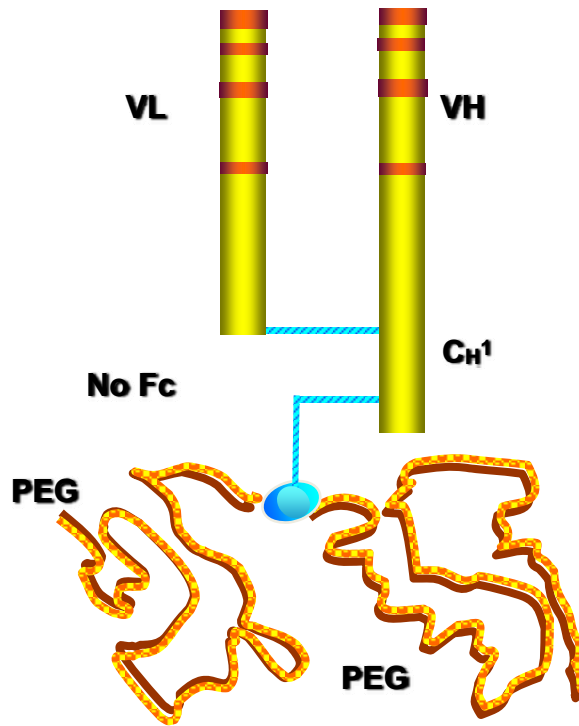
etanercept  
IgG1

■ topo  
■ umano  
CDR = Complementarity-determining region  
PEG = Polyethylene glycol

# Antagonisti TNF- $\alpha$

Adalimumab	Etanercept	Infliximab
 <p>Diagram illustrating the structure of Adalimumab, a human monoclonal antibody. It shows two heavy chain domains (green) and two light chain domains (yellow) joined by disulfide bonds. A blue arrow points to the constant region, labeled "Ac umano".</p>	 <p>Diagram illustrating the structure of Etanercept, a human TNF receptor. It shows two extracellular domains (yellow) connected by a hinge region (yellow) and a transmembrane domain (black) with intracellular domains (blue). Labels include "Regione Costante Ac umani" and "Recettore umano TNF".</p>	 <p>Diagram illustrating the structure of Infliximab, a chimeric monoclonal antibody. It shows two human heavy chain domains (green) and two mouse light chain domains (orange). Labels include "Topo" and "Uomo (IgG<sub>1</sub>)".</p>
<p>Anticorpo monoclonale umano anti-TNF-<math>\alpha</math></p>	<p>Recettore umano</p>	<p>Anticorpo monoclonale chimerico anti-TNF</p>

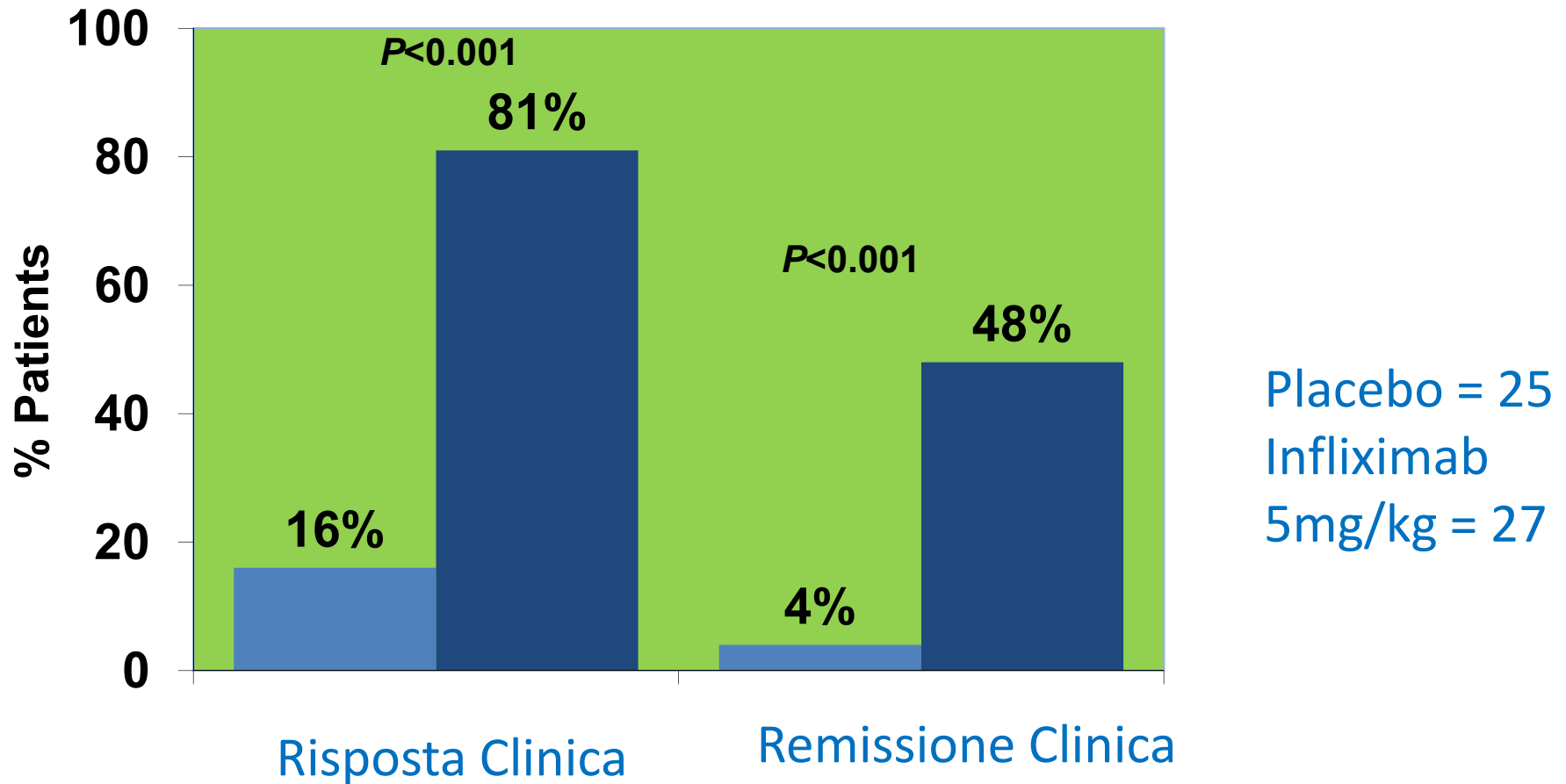
# Certolizumab Pegol



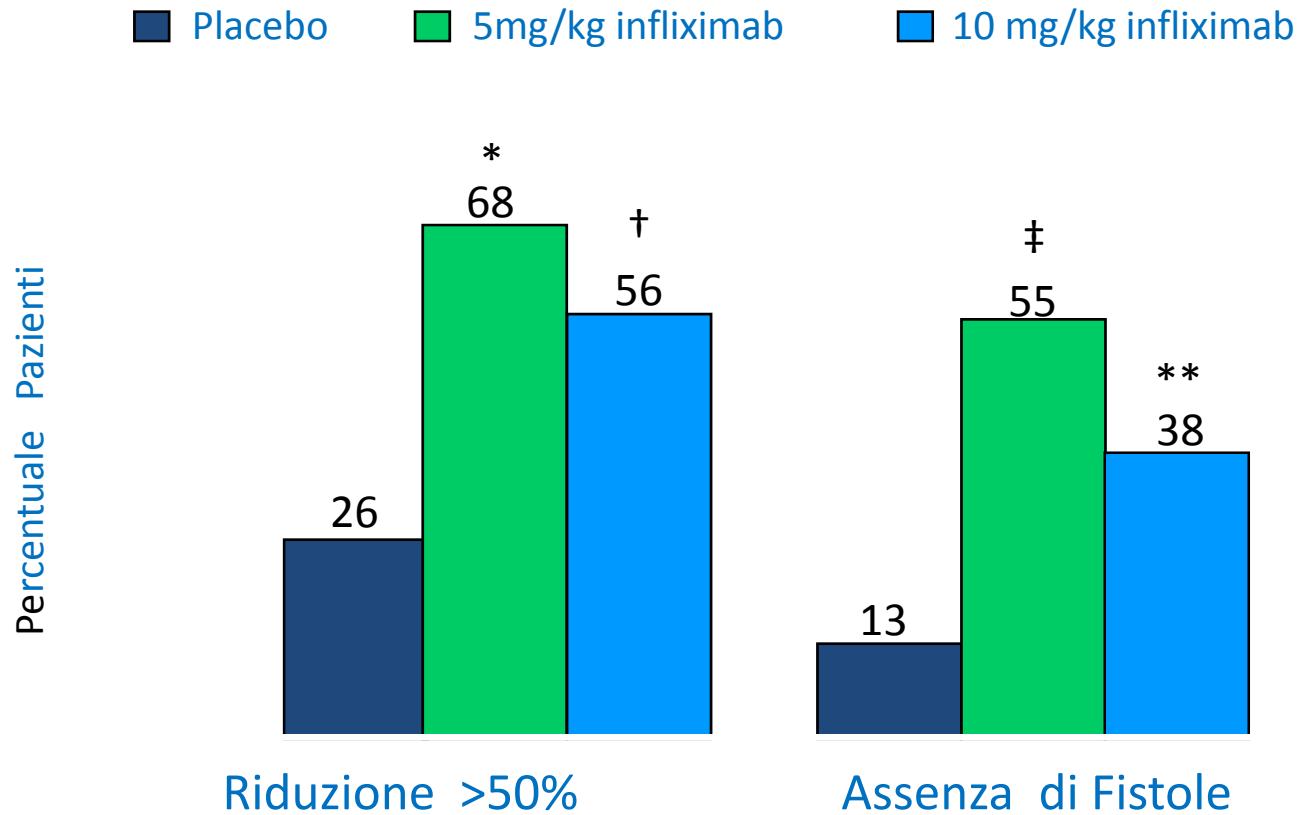
**Framment Fab'**  
**(95% umano IgG<sub>1</sub> isotipo)**

- Frammento Fab' umanizzato PEGilato
- ingegnerizzato per produzione in *E.coli*
- 2 x 20 kD PEG
  - > vita media a 14 gg
  - compatibile con somministrazione s.c.

## Risposta Clinica e Remissione con Infliximab nel m. Crohn a 4 settimane



# Infliximab: Guarigione Fistole



N=94; \*P=0.002; †P=0.02; ‡P=0.001; \*\*P=0.04.

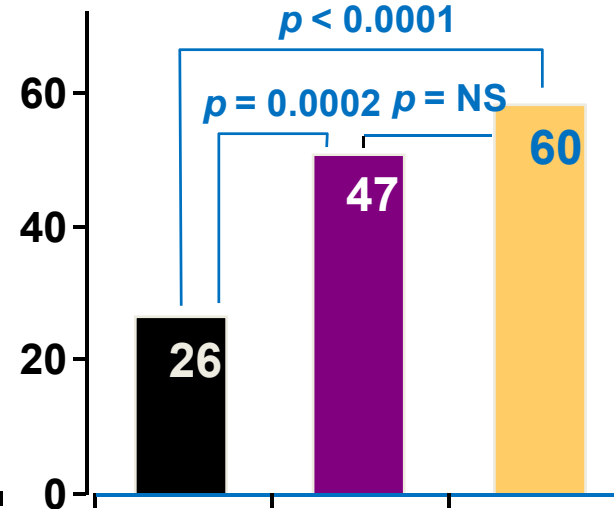
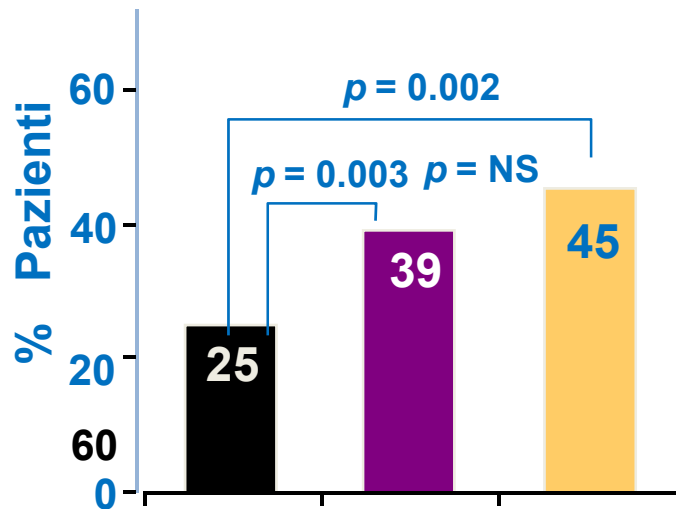
Present DH, et al. *N Engl J Med.* 1999;340:1398-1405.

# ACCENT I: Mantenimento con Infliximab per m.Crohn in *Responders* Randomizzati (N = 335)

## Remissione Clinica

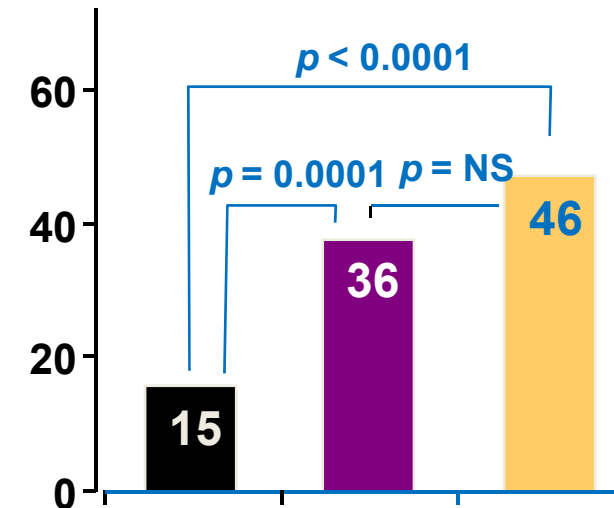
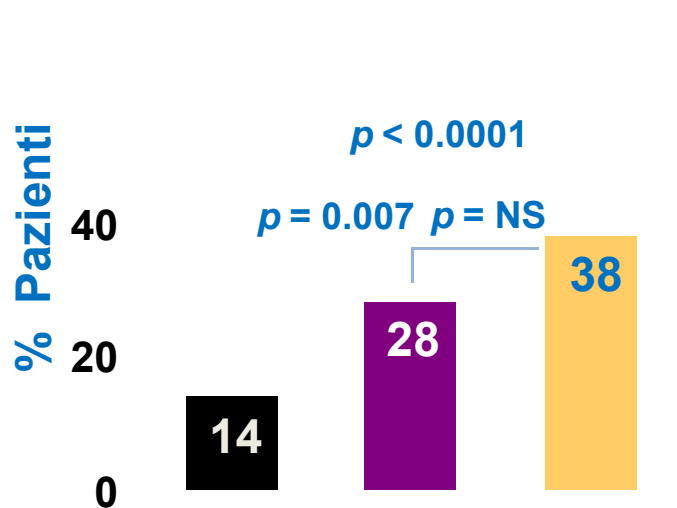
## Risposta Clinica

30 settimane



- Placebo
- Infliximab 5 mg/kg
- Infliximab 10 mg/kg

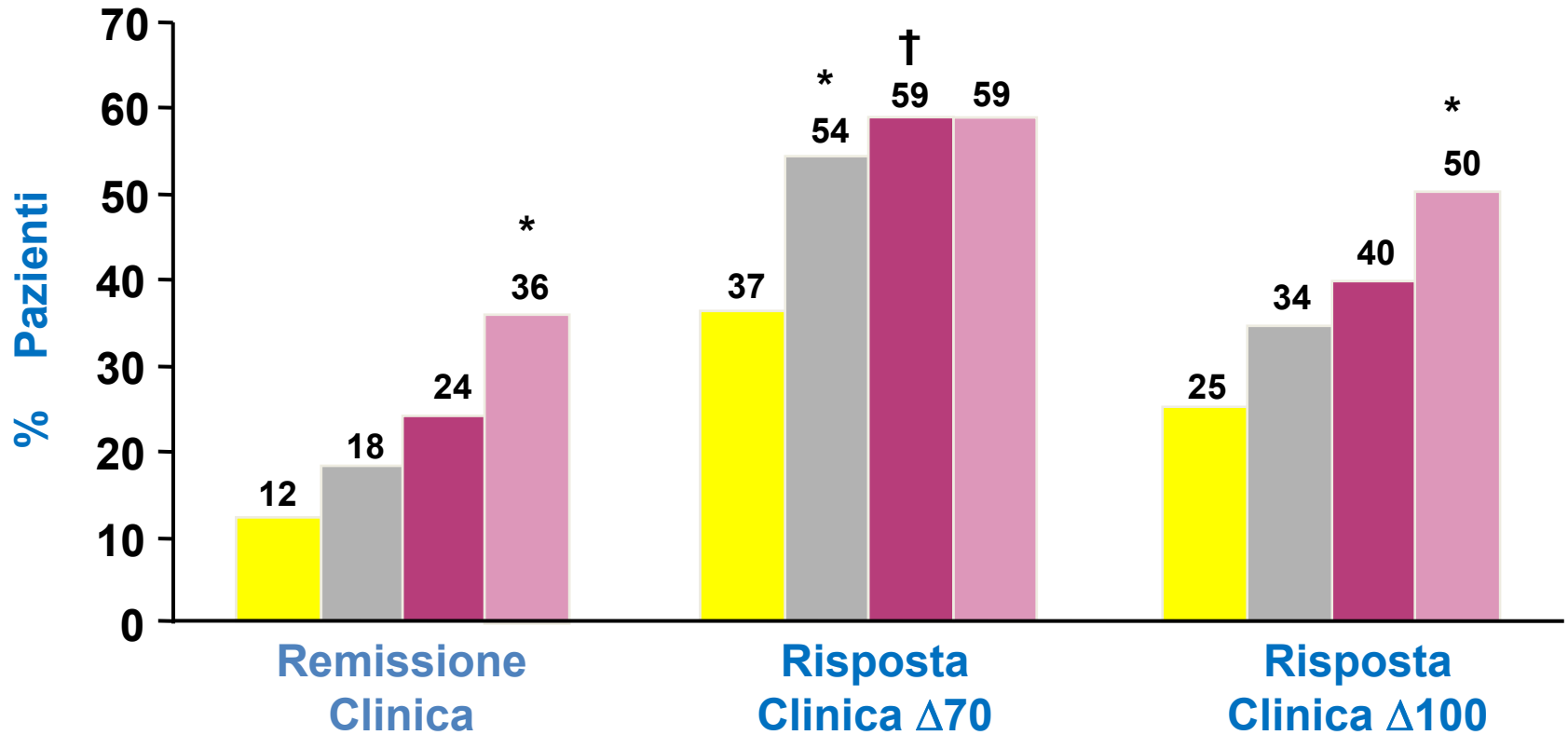
54 settimane



# CLASSIC I: ADALIMUMAB

## 4 settimane m.Crohn

■ Placebo      ■ Adalimumab 40/20  
■ Adalimumab 80/40    ■ Adalimumab 160/80



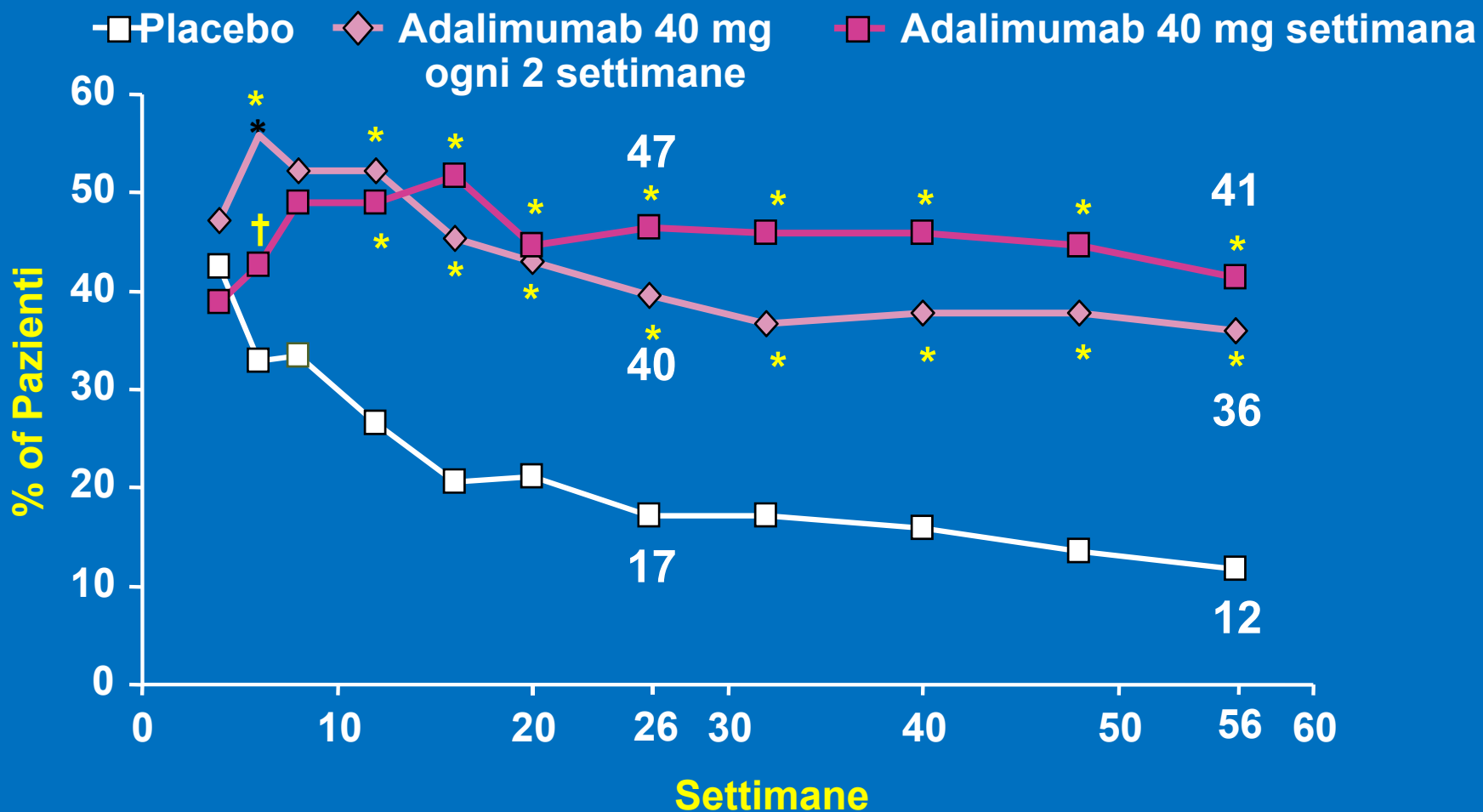
\*  $p < 0.05$  vs placebo; †  $p = 0.001$  vs placebo; ‡  $p = 0.007$  vs placebo.

Remissione Clinica = CDAI < 150; Risposta Clinica =  $\Delta 70$  or  $\Delta 100 \geq 70$  or  $\geq 100$  punti diminuzione CDAI

Hanauer S, et al. *Gastroenterology*. 2006;130:323–33.

# CHARM: Adalimumab nel m. Crohn

## Remissione Clinica a lungo termine (n = 499)

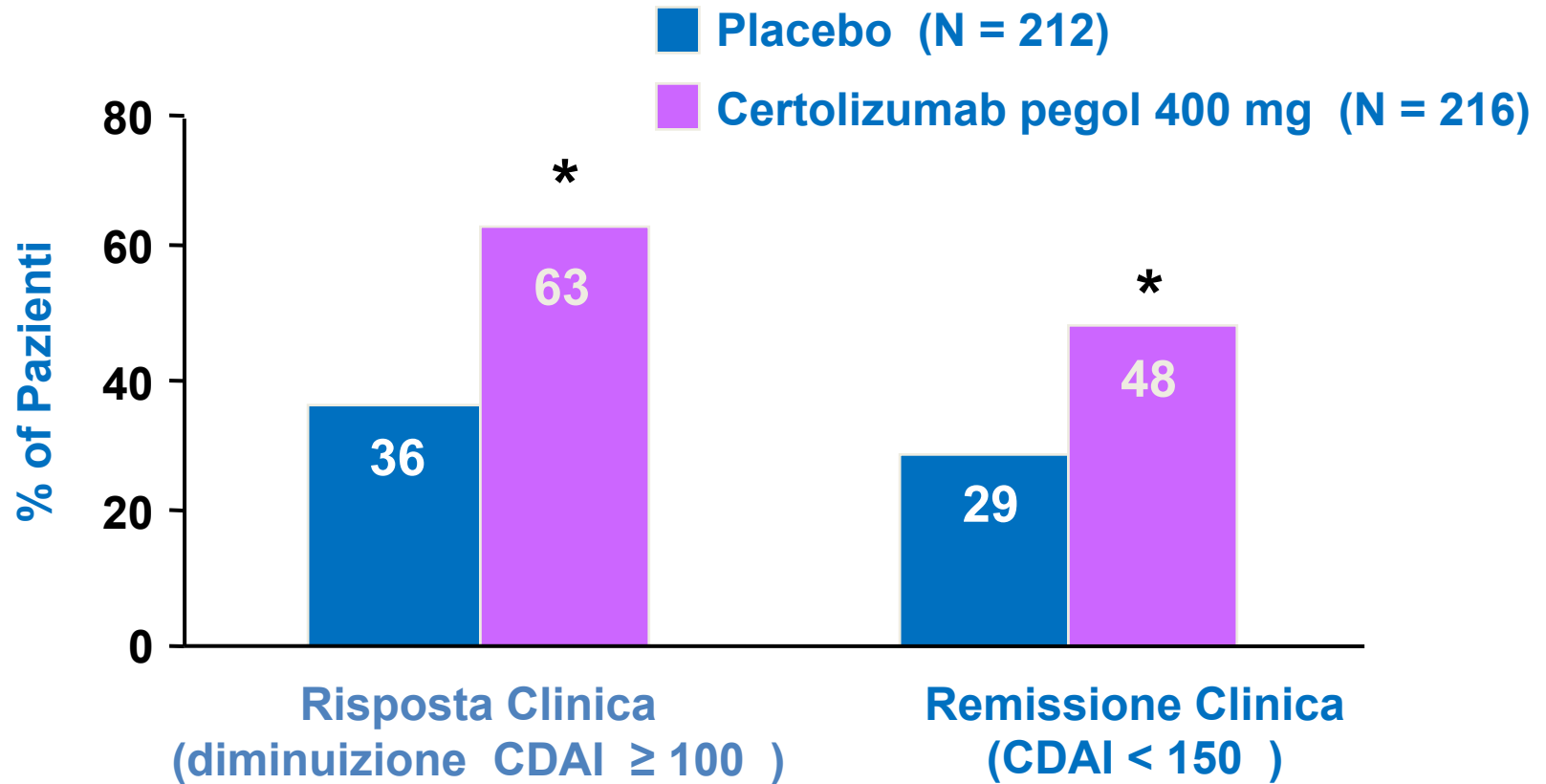


\*p < 0.001 vs placebo; †p = 0.005 vs placebo.  
 remission = CDAI < 150.

Colombel JF, et al. DDW 2006, Abstract 686d.

## PRECiSE 2: CERTOLIZUMAB

### Risposta e Remissione Clinica a 26 settimane in Pazienti con m. Crohn (N = 428)

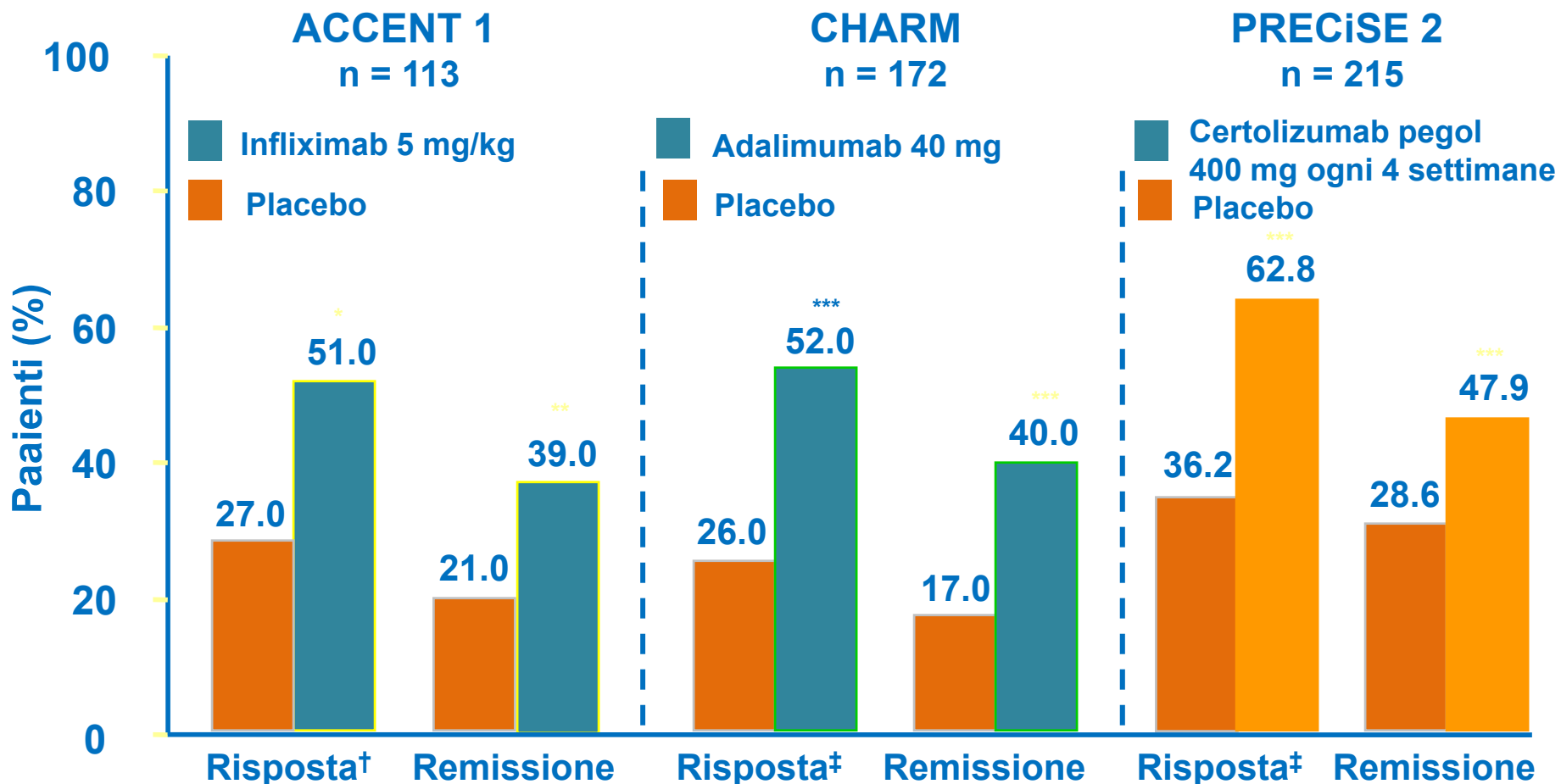


\* $p < 0.001$  vs placebo.

Schreiber S, et al. *Gut*. 2005;54(Suppl VII):A82.

# Overview dei Risultati a Lungo-Termine nei Trials con Anti-TNF- $\alpha$ nel m.Crohn

26–30 settimane



Hanauer SB et al. *Lancet*. 2002;359:1541–1549.  
 Colombel J et al. *Gastroenterology*. 2006;131:950.  
 Schreiber S et al. *Gut*. 2005;54(Suppl VII):A82.

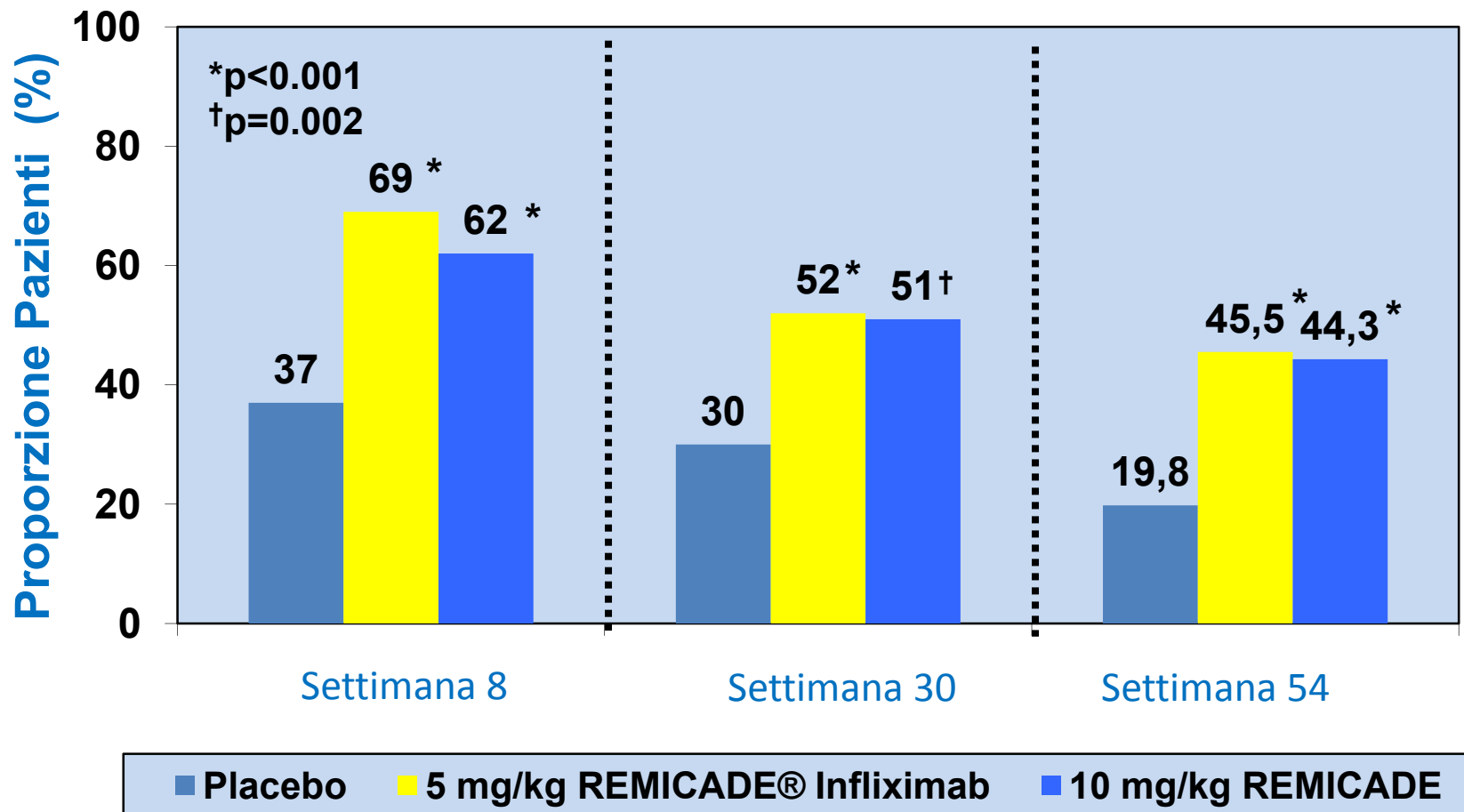
Remissione = CDAI score < 150

<sup>†</sup> < CDAI score  $\geq 70$  e  $\geq 25\%$

<sup>‡</sup> < CDAI score  $\geq 100$

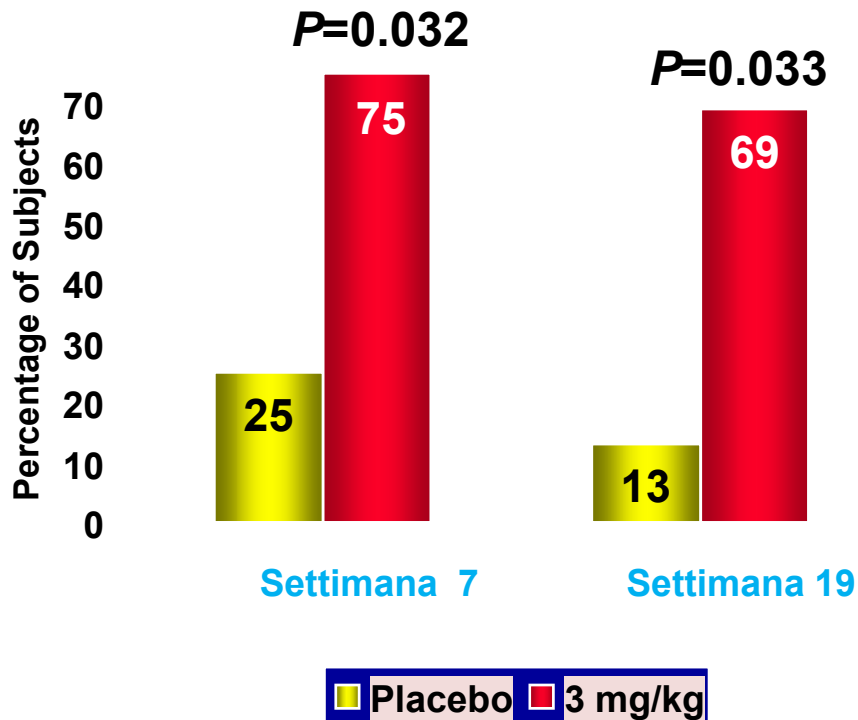
\* $P = .0002$ ; \*\* $P = .003$ ; \*\*\* $P < .001$

# Terapia con Infliximab per CU

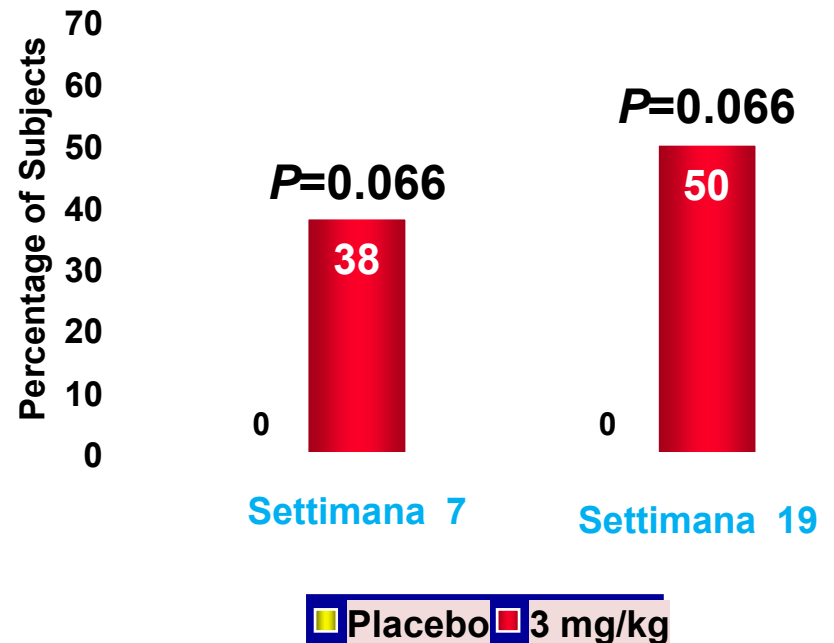


# Anti-IL-12 (ABT-874) nella Malattia di Crohn Attiva

Pazienti con Risposta Clinica  
( $< \text{CDAI} \geq 100$ )



Pazienti con Remissione Clinica  
( $\text{CDAI} \leq 150$ )



# Natalizumab

- Anticorpo Ricombinante monoclonale anti  $\alpha_4$  integrine
- Le Integrine sono recettori coinvolti nella migrazione ed attivazione dei leucociti.
- Localizzate su l' endotelio vascolare e nella matrice extracellulare
- Le Integrine sono *up regulated* nei siti di infiammazione cronica

# Costruzione del Natalizumab

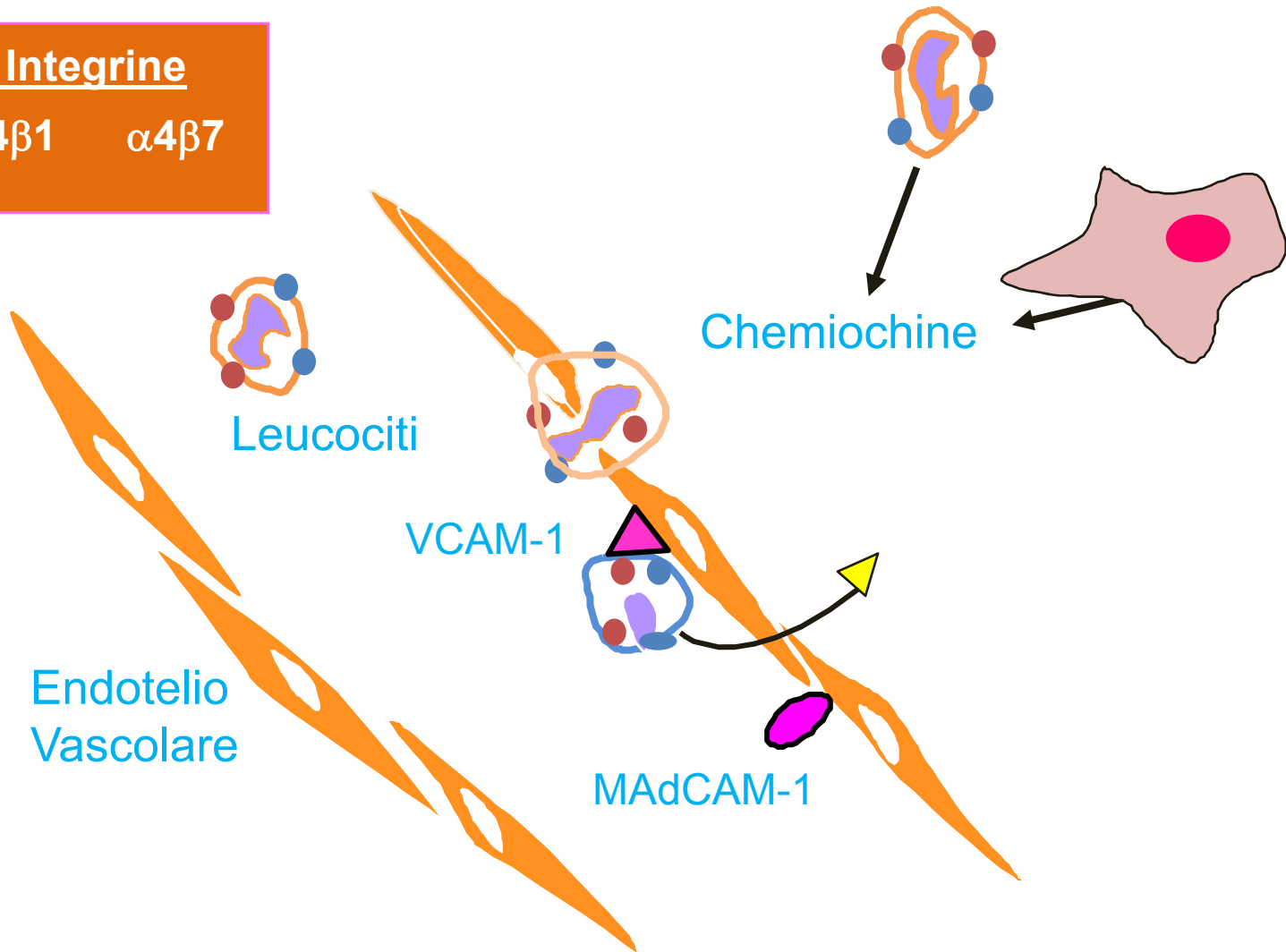


# Adesione e Arruolamento

## $\alpha 4$ Integrine

$\alpha 4\beta 1$

$\alpha 4\beta 7$



# Adesione endoteliale e leucociti: $\alpha 4$ -Integrine



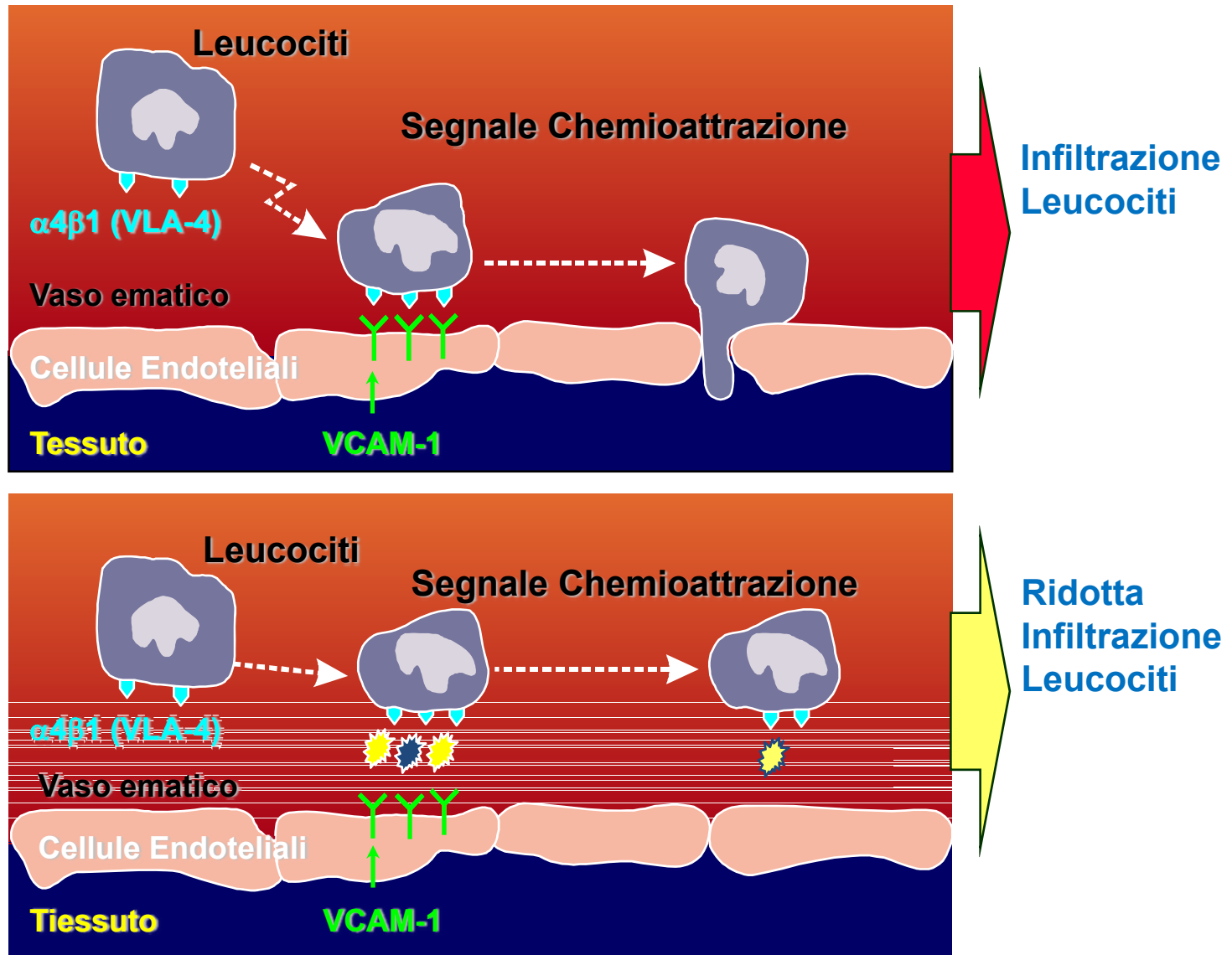
- Glicoproteine di membrana dei leucociti, sub-unità  $\beta 1$  e  $\beta 7$
- Interagiscono con i legandi endoteliali VCAM1, fibronectina, MAdCAM-1
- Mediano l'adesione ed il traffico dei leucociti

MAdCAM = mucosal addressin cellular adhesion molecule;

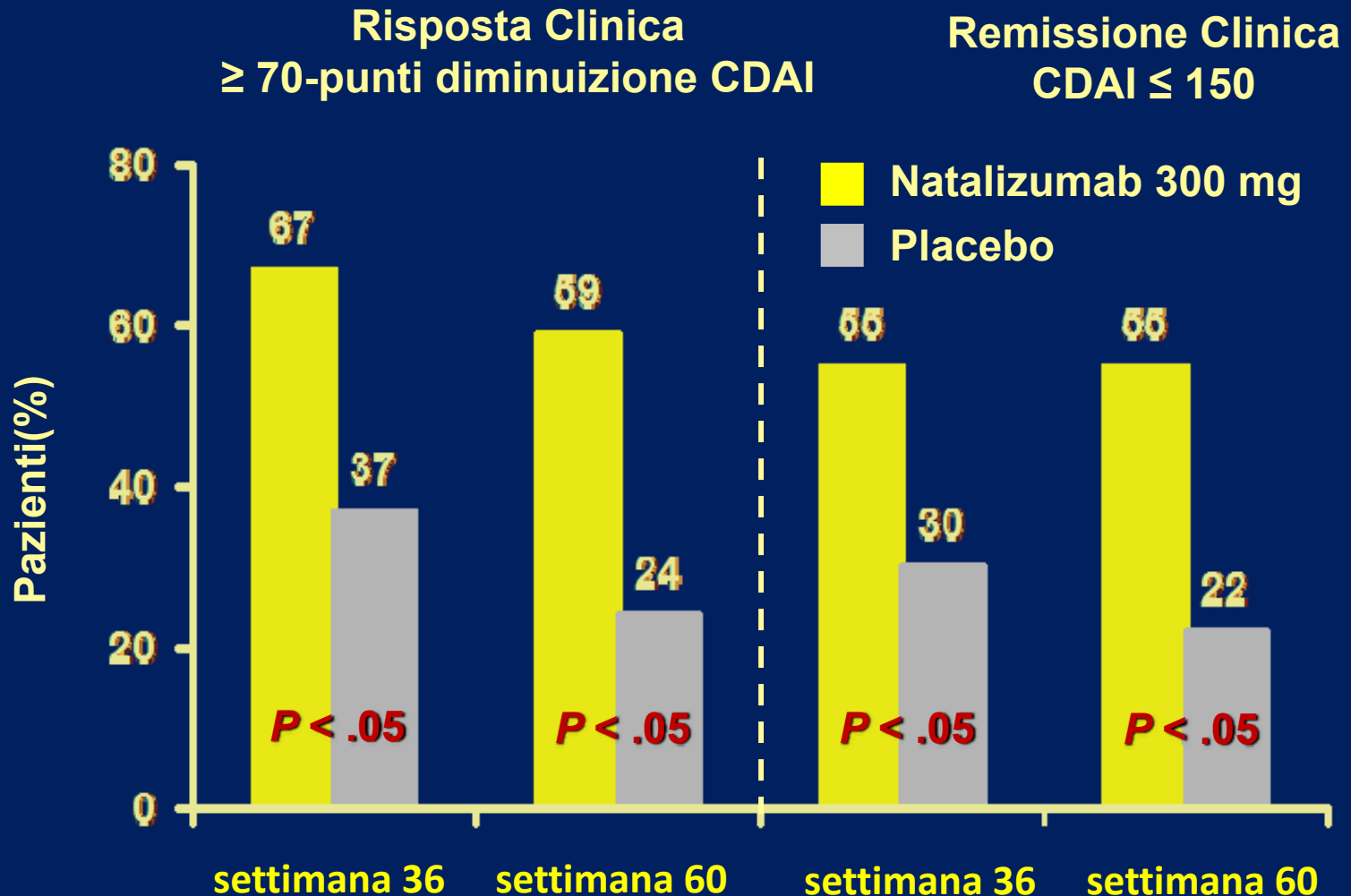
VCAM = vascular cell adhesion molecule.

Springer TA. *Cell*. 1994;76:301-314. Butcher EC, et al. *Science*. 1996;272:60-66.

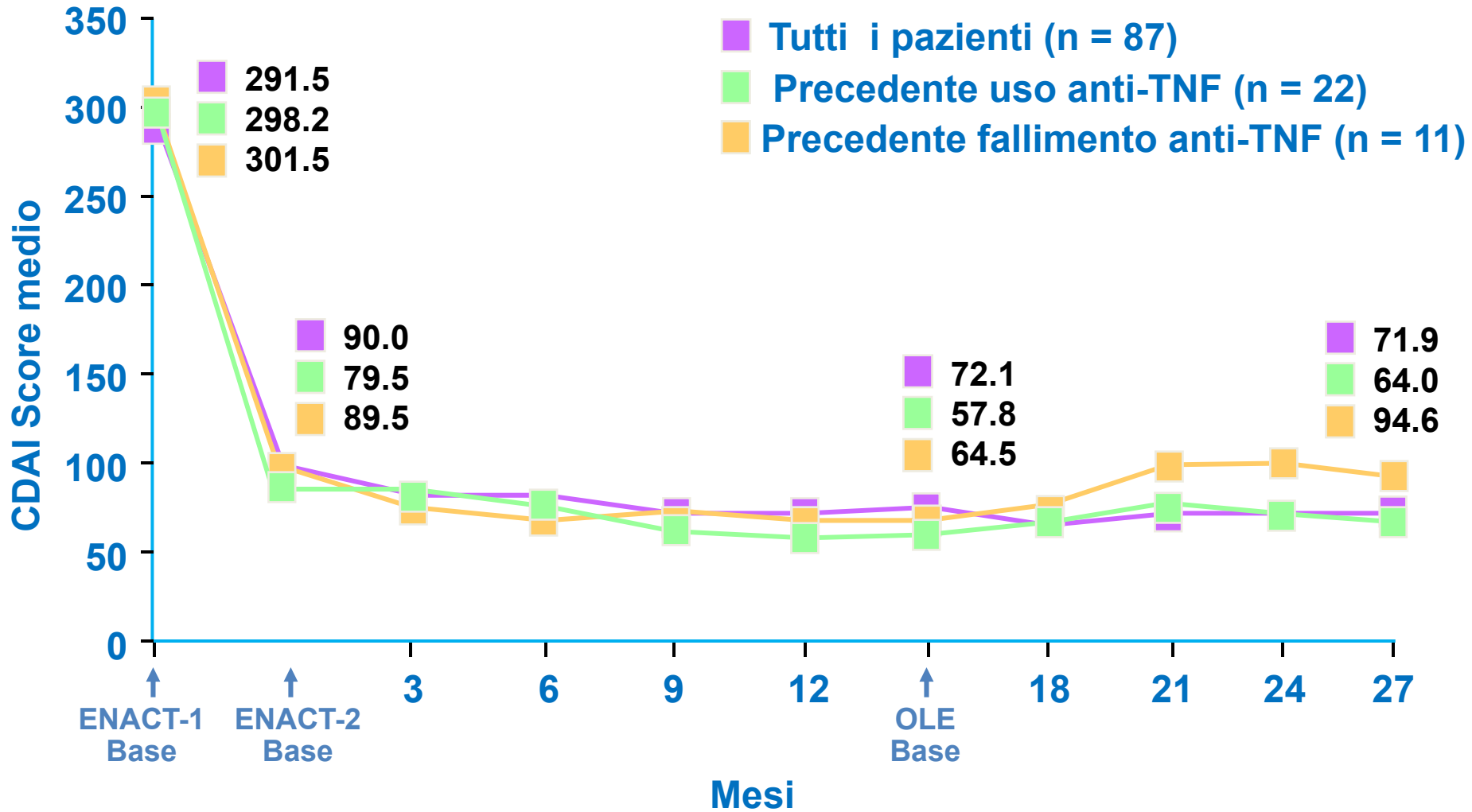
# Natalizumab: razionale terapeutico



# Natalizumab come Terapia Mantenimento per m. Crohn: *Trial ENACT-2*

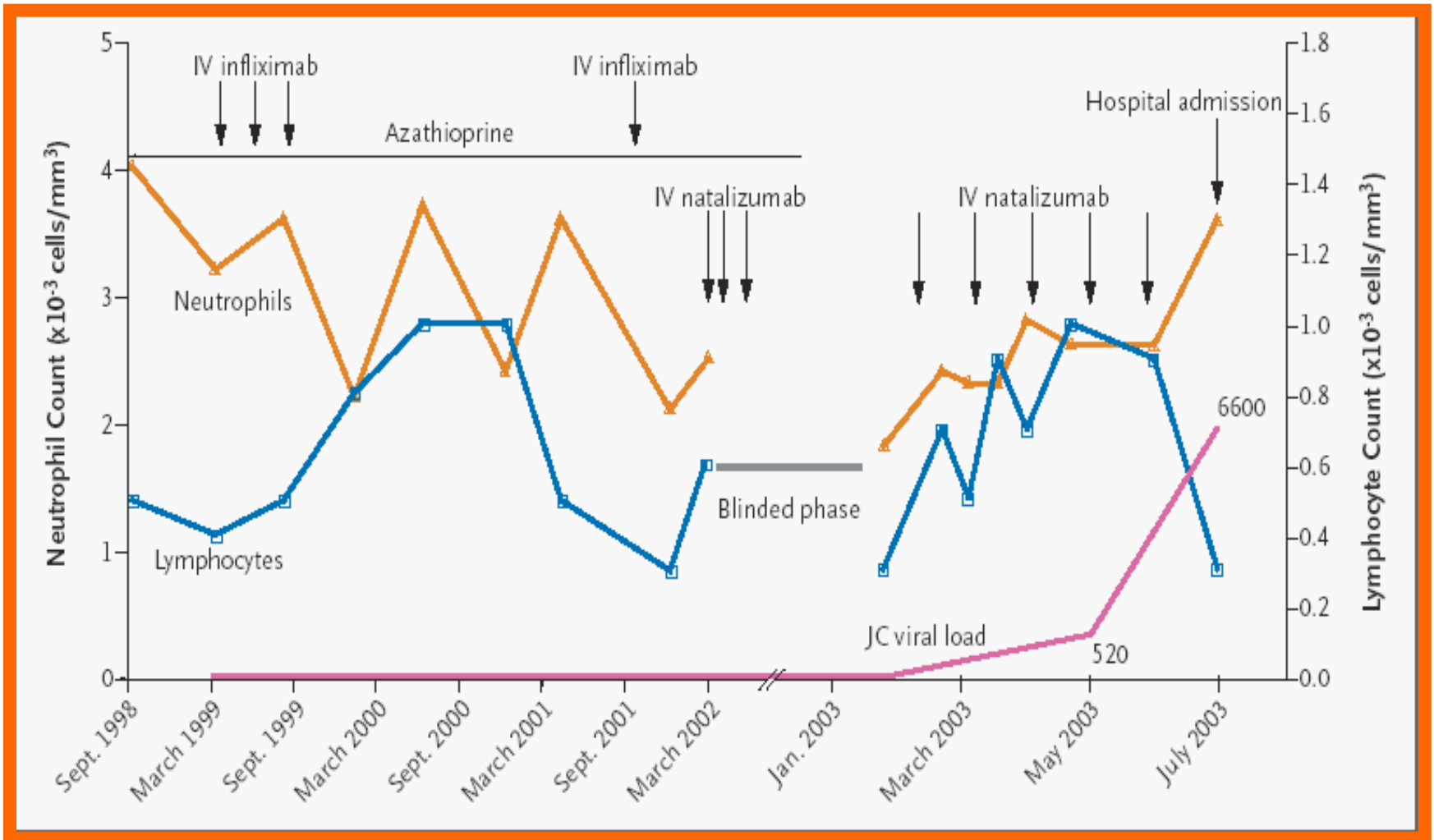


# CDAI Scores dopo 24 mesi di trattamento continuo con Natalizumab

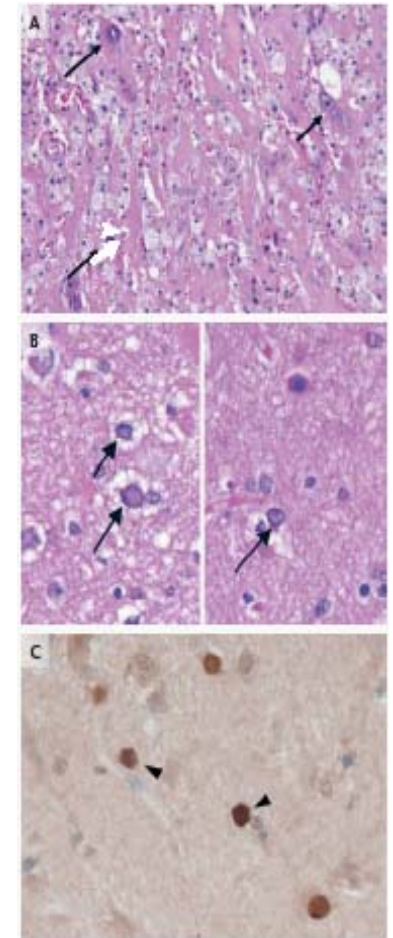
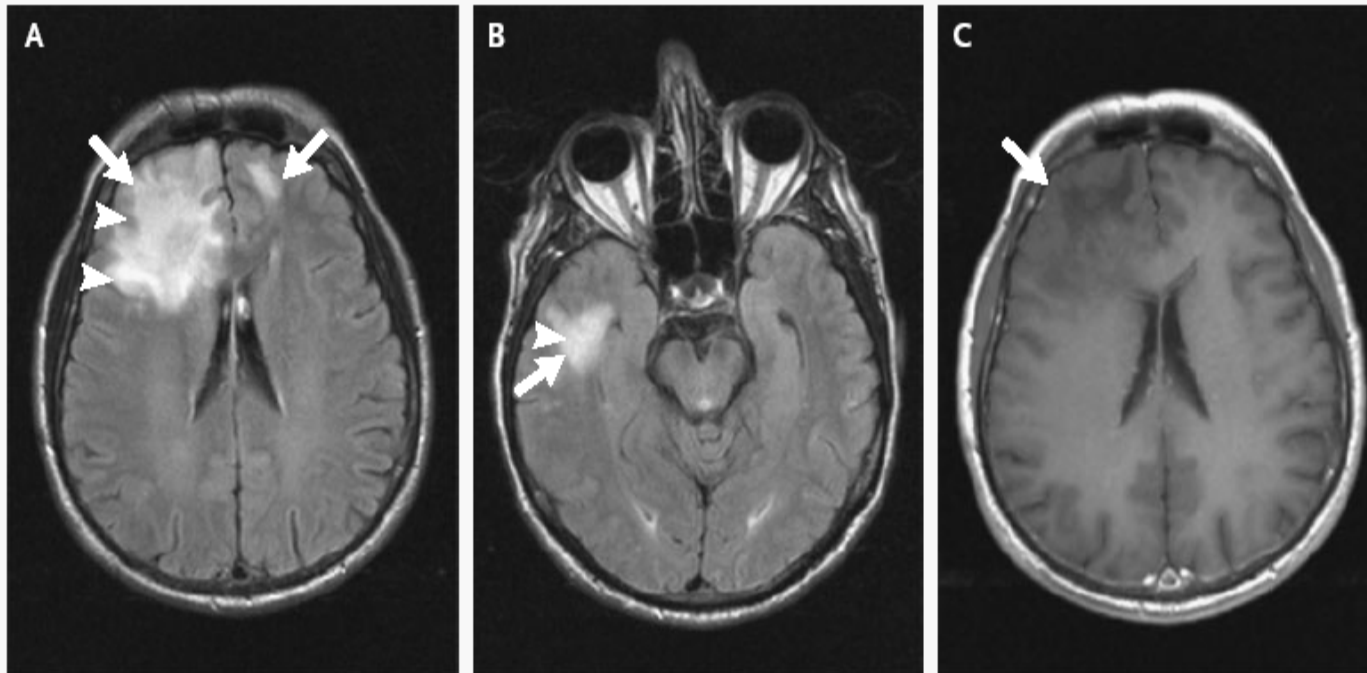


**“Progressive multifocal  
leukoencephalopathy (PML)”  
in pazienti trattati con  
Natalizumab**

# Natalizumab & Crohn's/PML

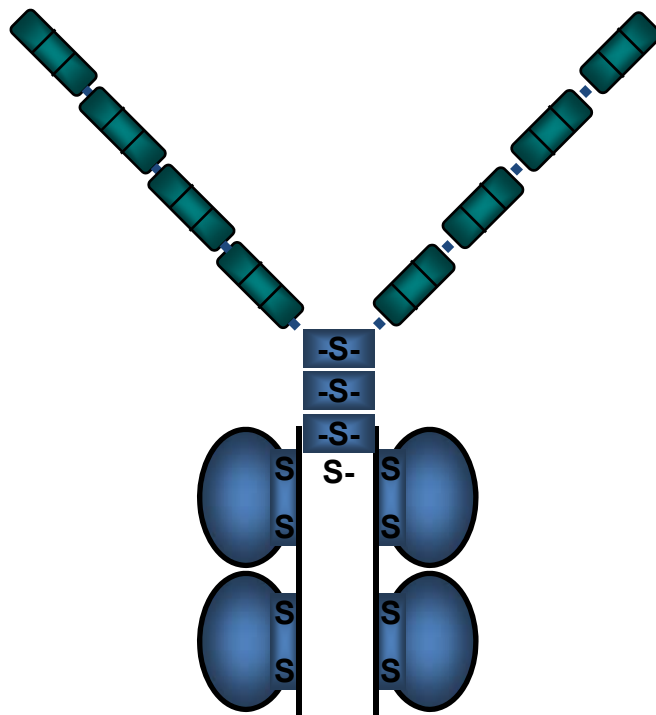


# Natalizumab Crohn's/PML



# Etanercept (Enbrel®)

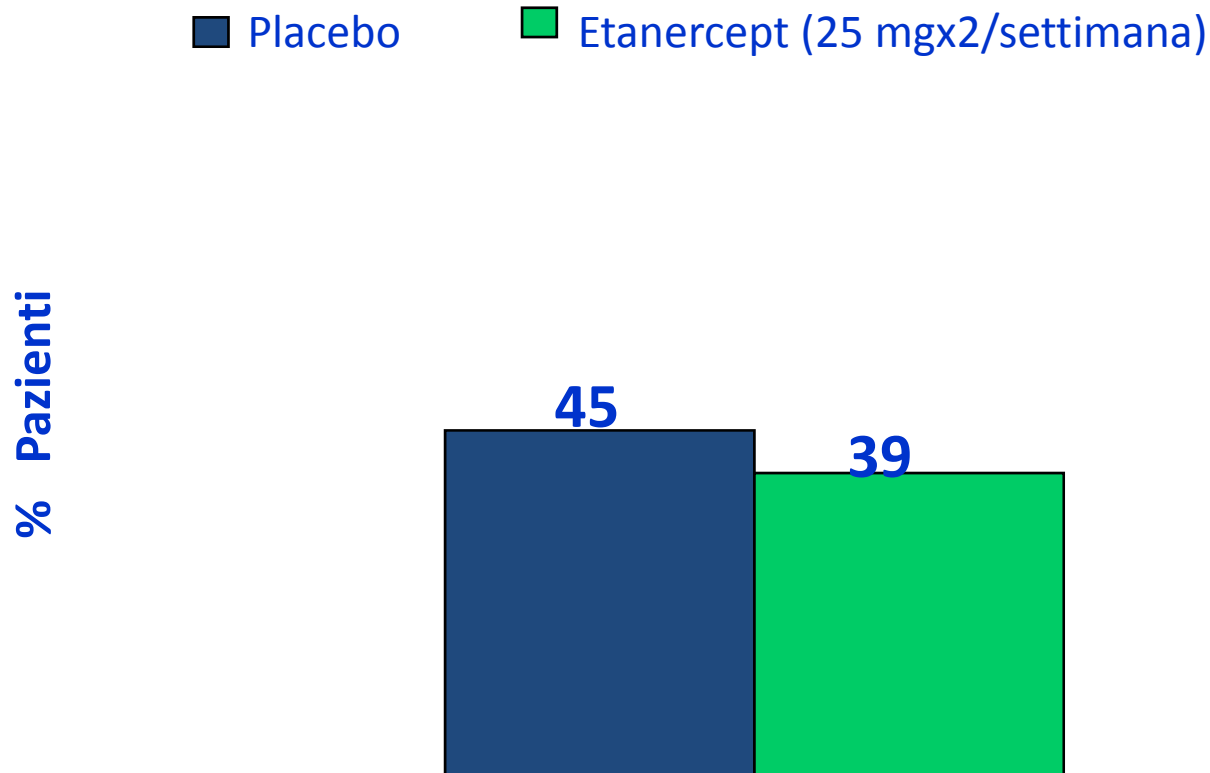
**proteina soluble per recettore TNF**



recettore extracellulare  
umano TNF- p75

dominio umano IgG1 Fc

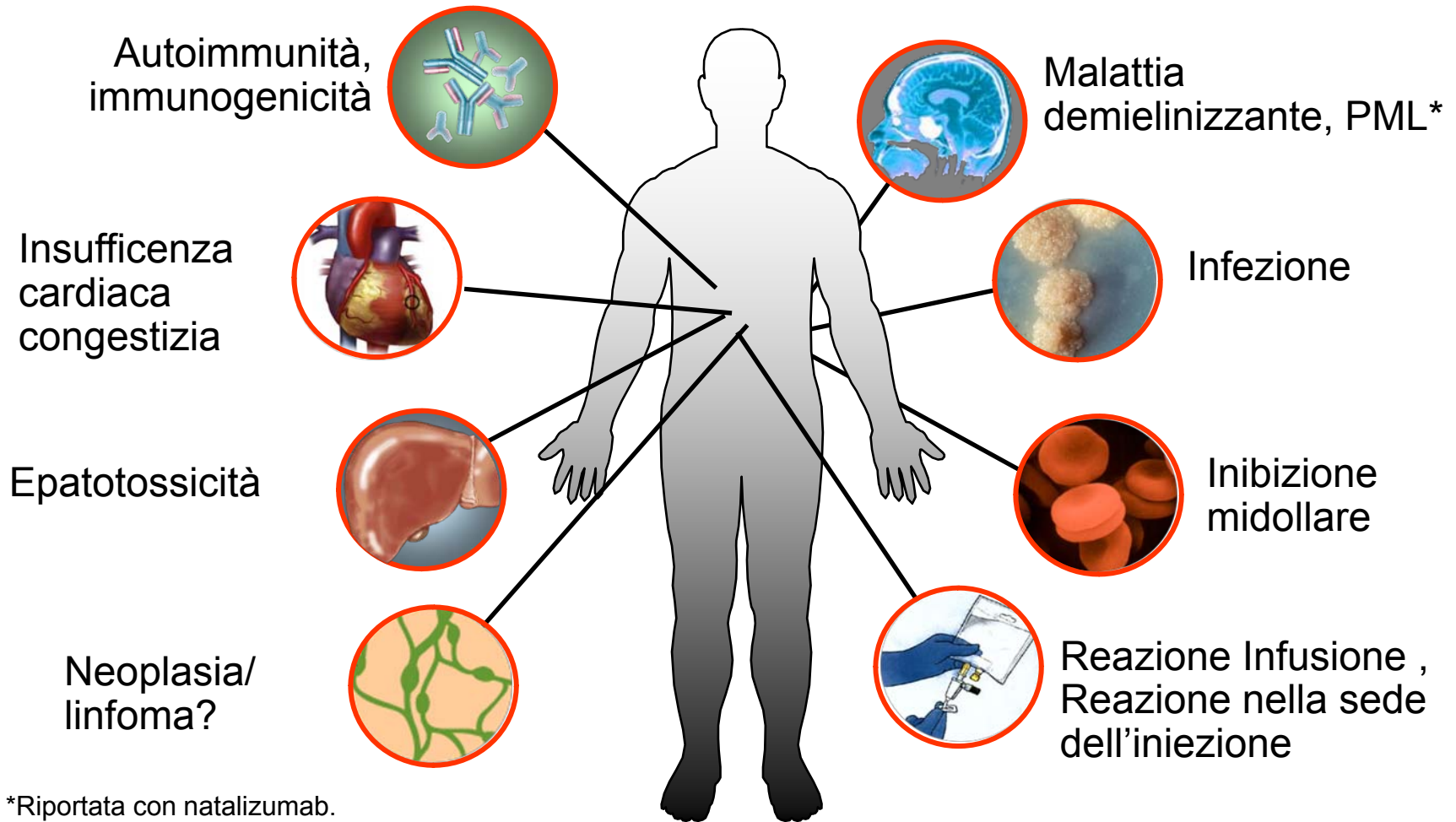
# Etanercept: Non Risposta Clinica



Risposta Clinica = CDAI < 150.

Sandborn WJ, et al. *Gastroenterology*. 2001;121:1088-1094.

# Effetti Avversi dei Biologici

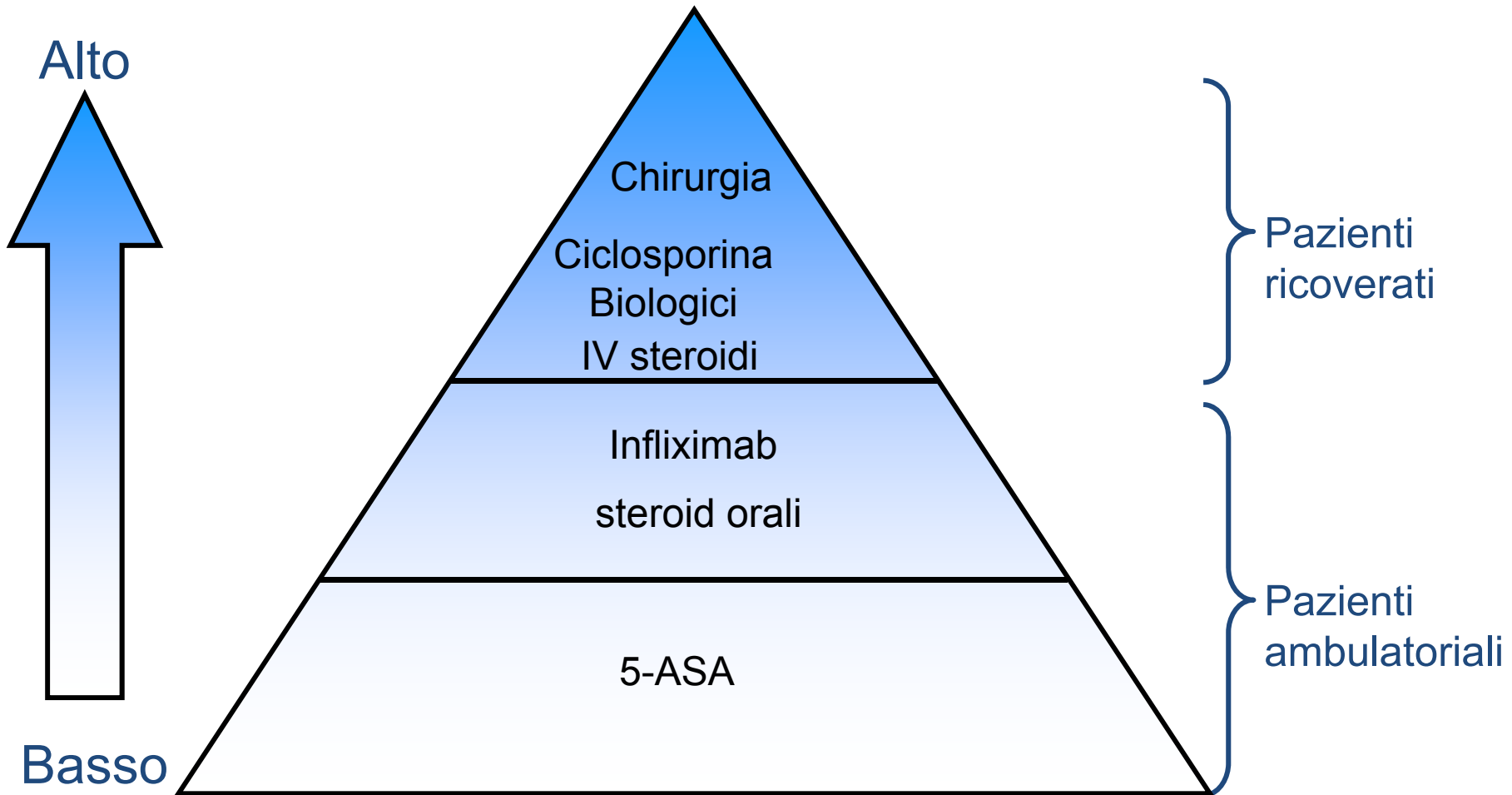


\*Riportata con natalizumab.

PML, progressive multifocal leucoencephalopathy

Clark M et al. *Gastroenterology*. 2007;133:312.  
Tysabri (natalizumab) [package insert]. South San Francisco, CA: Elan; Jan 2008.

# Terapia Tradizionale



# Invertire la Piramide?

