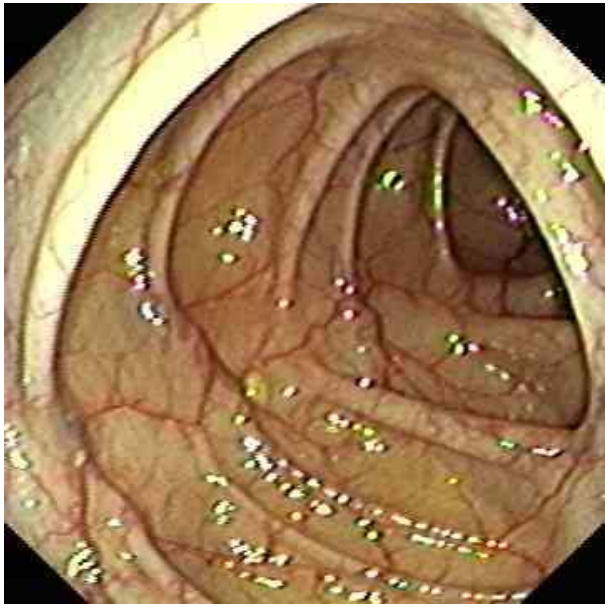
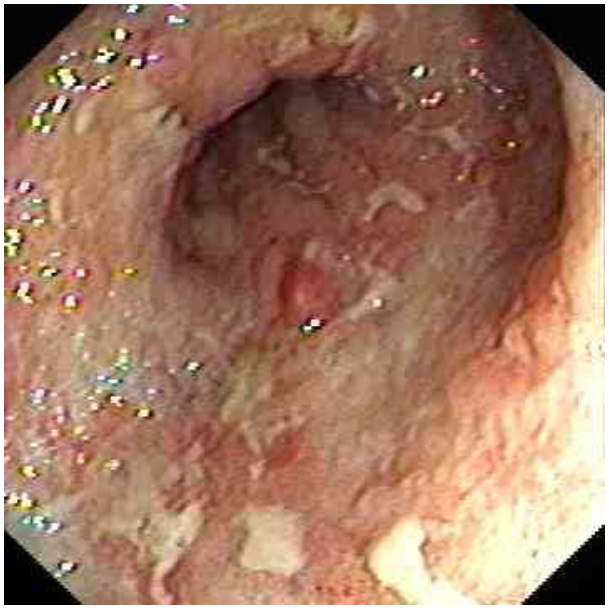
NUOVI FARMACI PER LE MALATTIE INFIAMATORIE CRONICHE INTESTINALI (IBD)

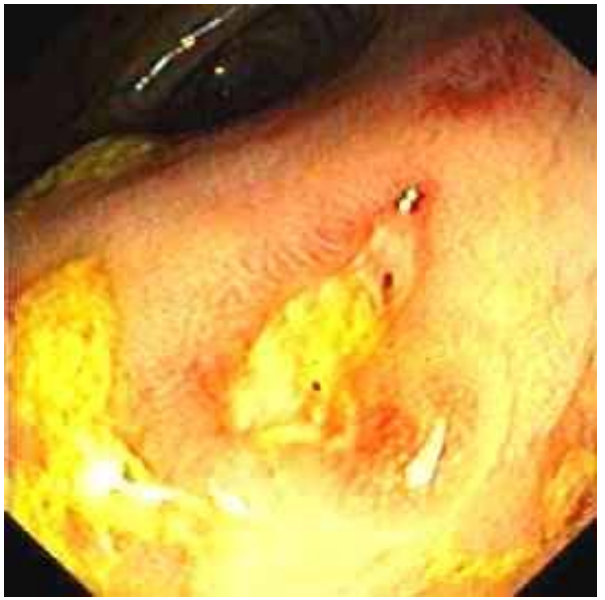
MALATTIE INFIAMMATORIE CRONICHE INTESTINALI



Colon Normale

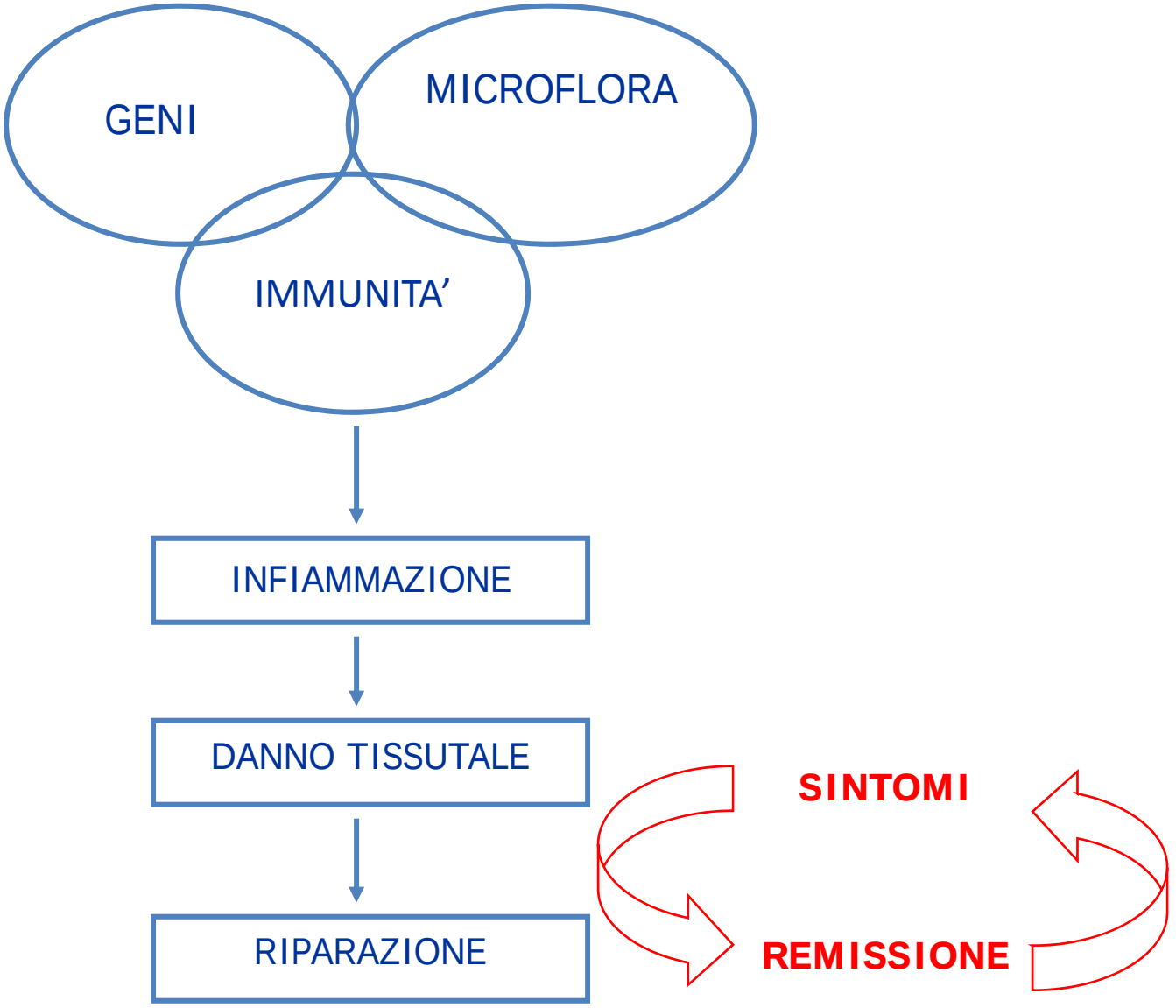


Colite ulcerosa

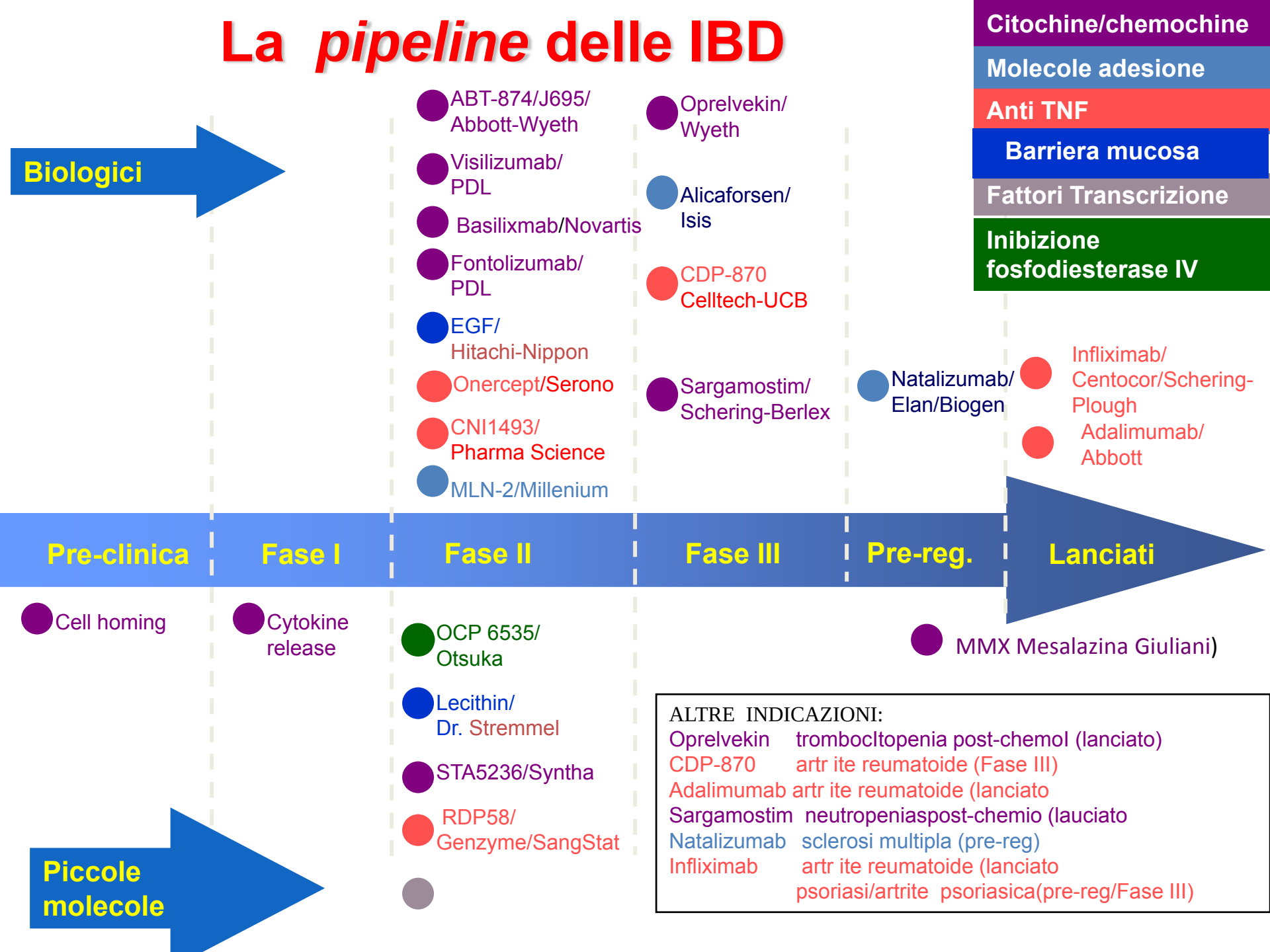


Morbo di Crohn

PATOGENESI


GENI
MICROFLORA
IMMUNITA’
INFIAMMAZIONE
DANNO TISSUTALE
RIPARAZIONE
SINTOMI
REMISSIONE

La *pipeline* delle IBD

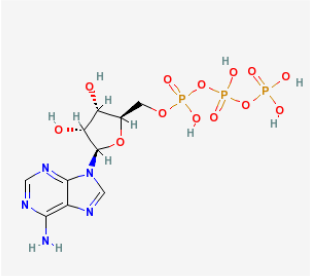


ALTRE INDICAZIONI:

Oprelvekin	trombocItopenia post-chemol (lanciato)
CDP-870	artr ite reumatoide (Fase III)
Adalimumab	artr ite reumatoide (lanciato
Sargamostim	neutropeniaspost-chemio (lauciato
Natalizumab	sclerosi multipla (pre-reg)
Infliximab	artr ite reumatoide (lanciato
	psoriasi/artrite psoriasica(pre-reg/Fase III)

Piccole Molecole vs Biologici

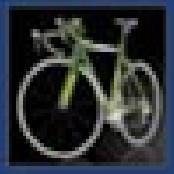
- Le *piccole molecole sono* composti a basso PM generalmente sintetizzate con reazioni chimiche biologicamente attive, be.. caratterizzate,purificate,facilmente analizzabili.

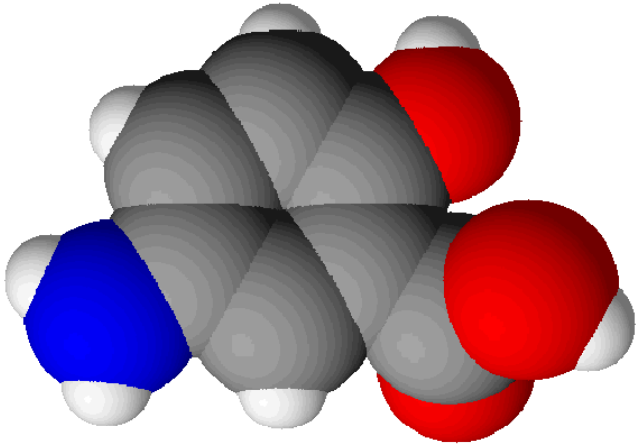


- I *biologici* sono prodotti di cellule ingegnierizzate come miscela di molecole difficili da caratterizare .

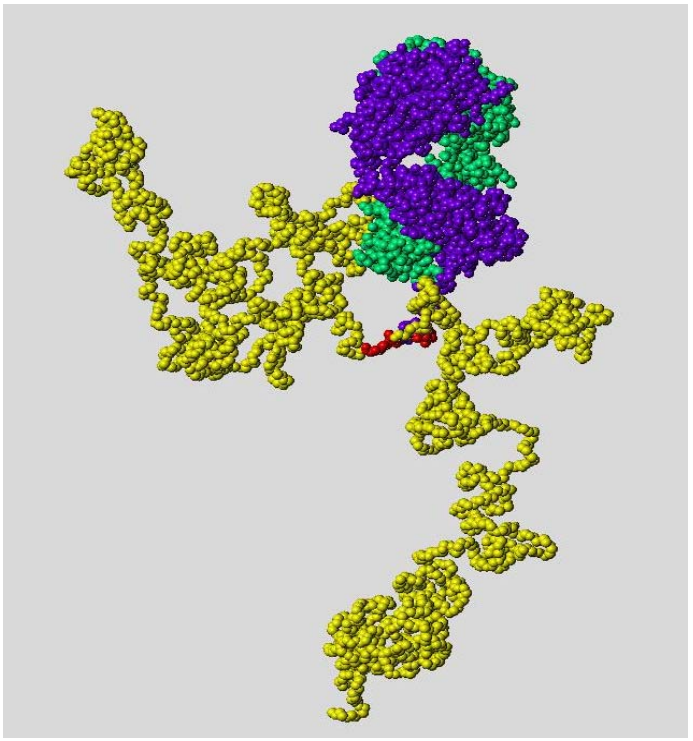
Size & Complexity – Small Molecule Drugs & Proteins

	Small Molecule Drug	Large Molecule Drug	Large Biologic
Size	Aspirin 21 atoms	hGH ~ 3000 atoms	IgG Antibody ~ 25,000 atoms
Complexity	Bike ~ 20 lbs	Car ~ 3000 lbs	Business Jet ~ 30,000 lbs (without fuel)





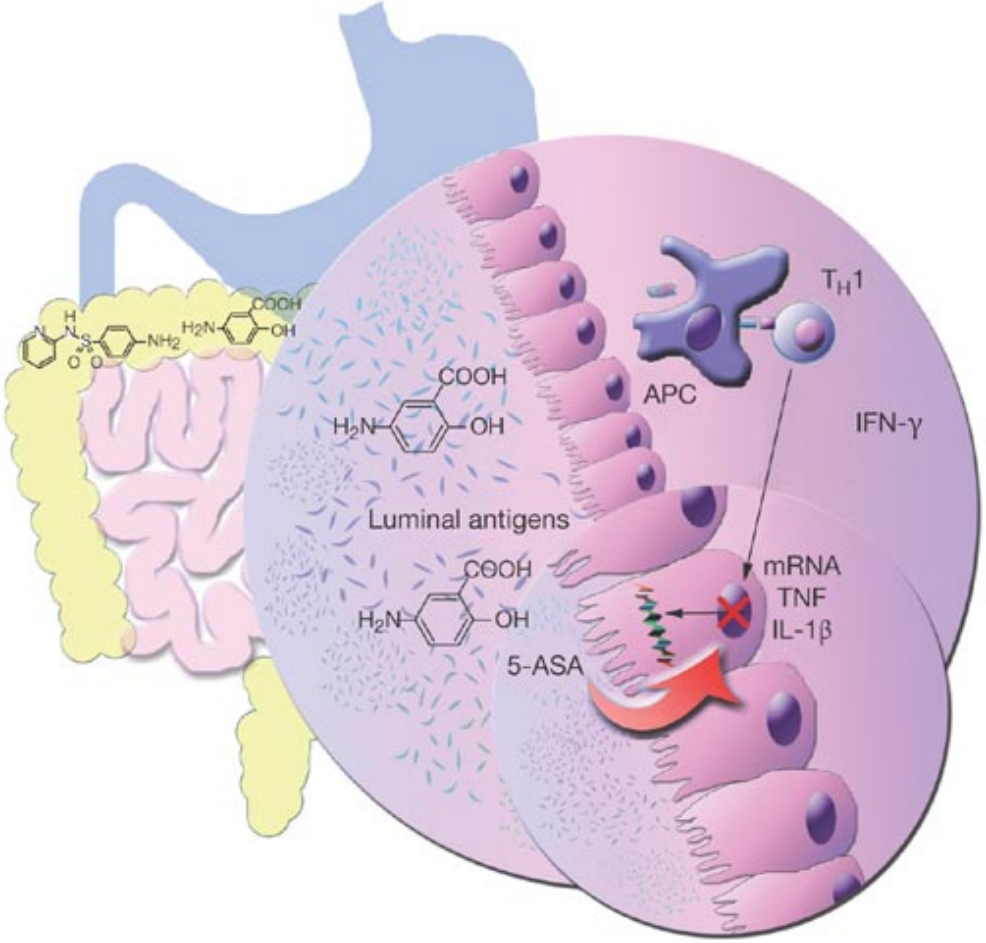
Mesalazina



Certolizumab

Meccanismo di azione della mesalazina nel colon

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

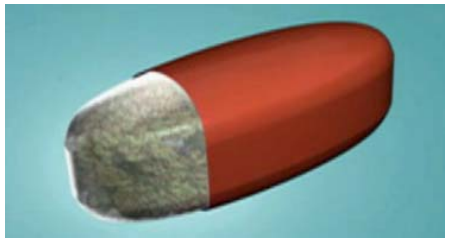


Nielsen OH and Munck LK (2007) Drug Insight: aminosalicylates for the treatment of IBD
Nat Clin Pract Gastroenterol Hepatol **4:** 160–170 doi:10.1038/ncpgasthep0696

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

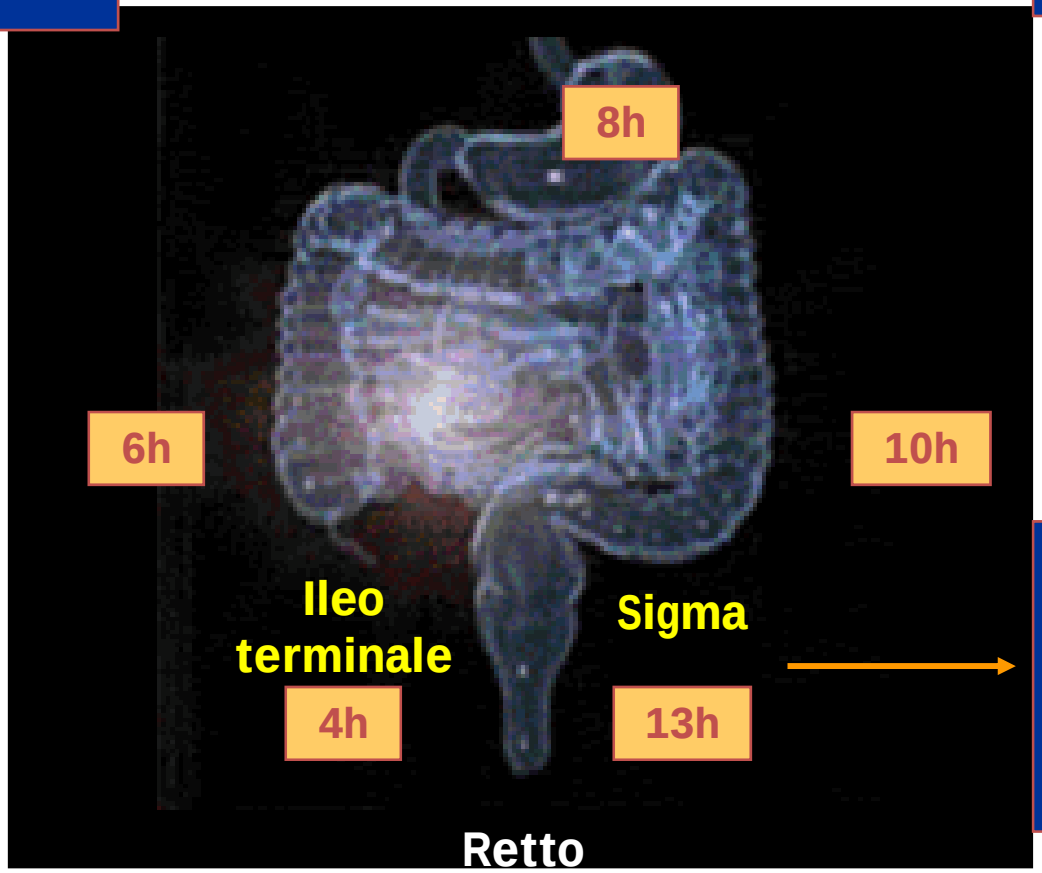
- **Componente C**: matrice lipofila che incapsula la maggior parte delle particelle di 5-ASA per prolungare il rilascio del principio attivo nell'arco delle 24 ore

* **Mesavancol (Giuliani)**

MMX: Delivery di 5-ASA nel tempo

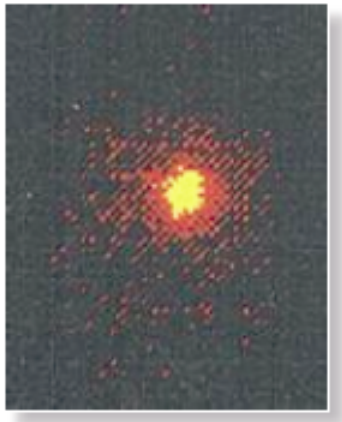
MMX: 30% di rilascio nelle prime 2 ore

Altre mesalazine: 95% di rilascio nelle prime 2 ore

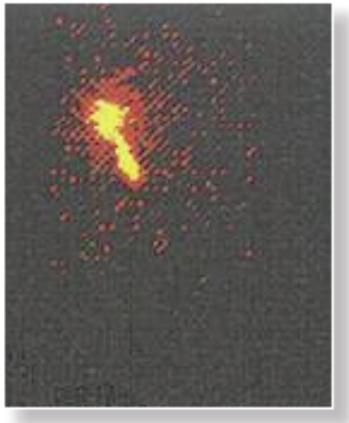


La presenza nel sigma-retto inizia dopo 13 ore e si mantiene fino a 24 ore

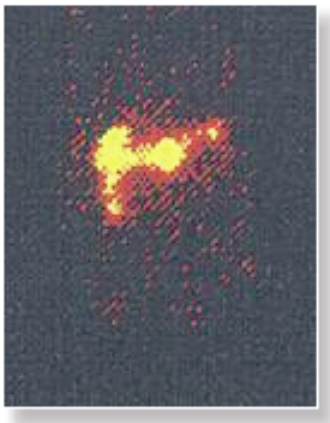
Colonic Spread of Mesalazine MMX Assessed *in vivo* by Gamma Scintigraphy



1h 30' Duodenum

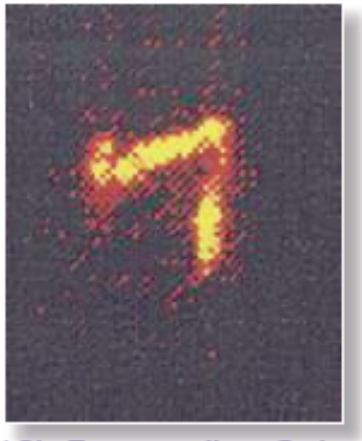


4h 30' Ascending Colon



7h 30' Transverse Colon

10h Transverse Colon



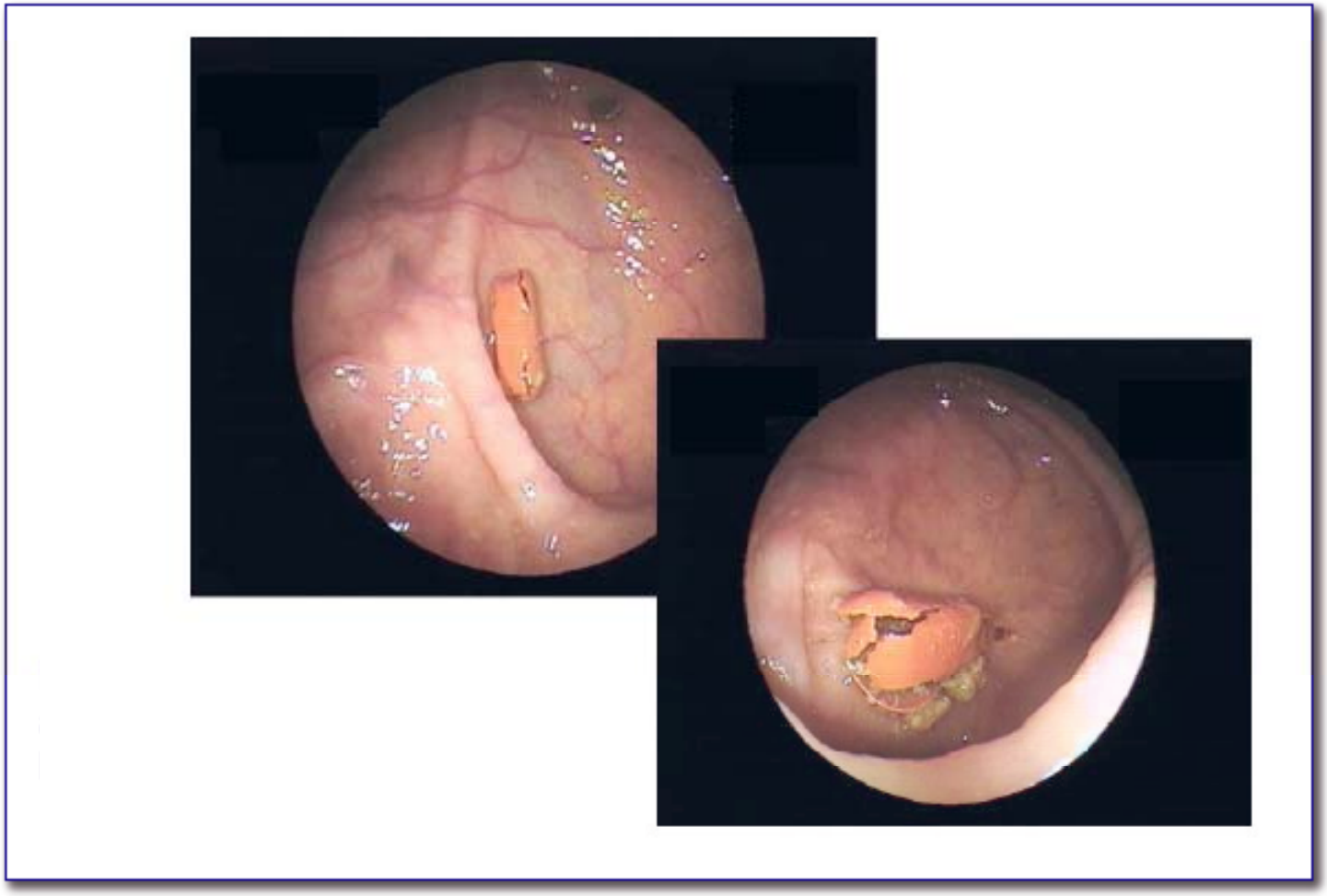
16h Descending Colon

24h Rectum

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

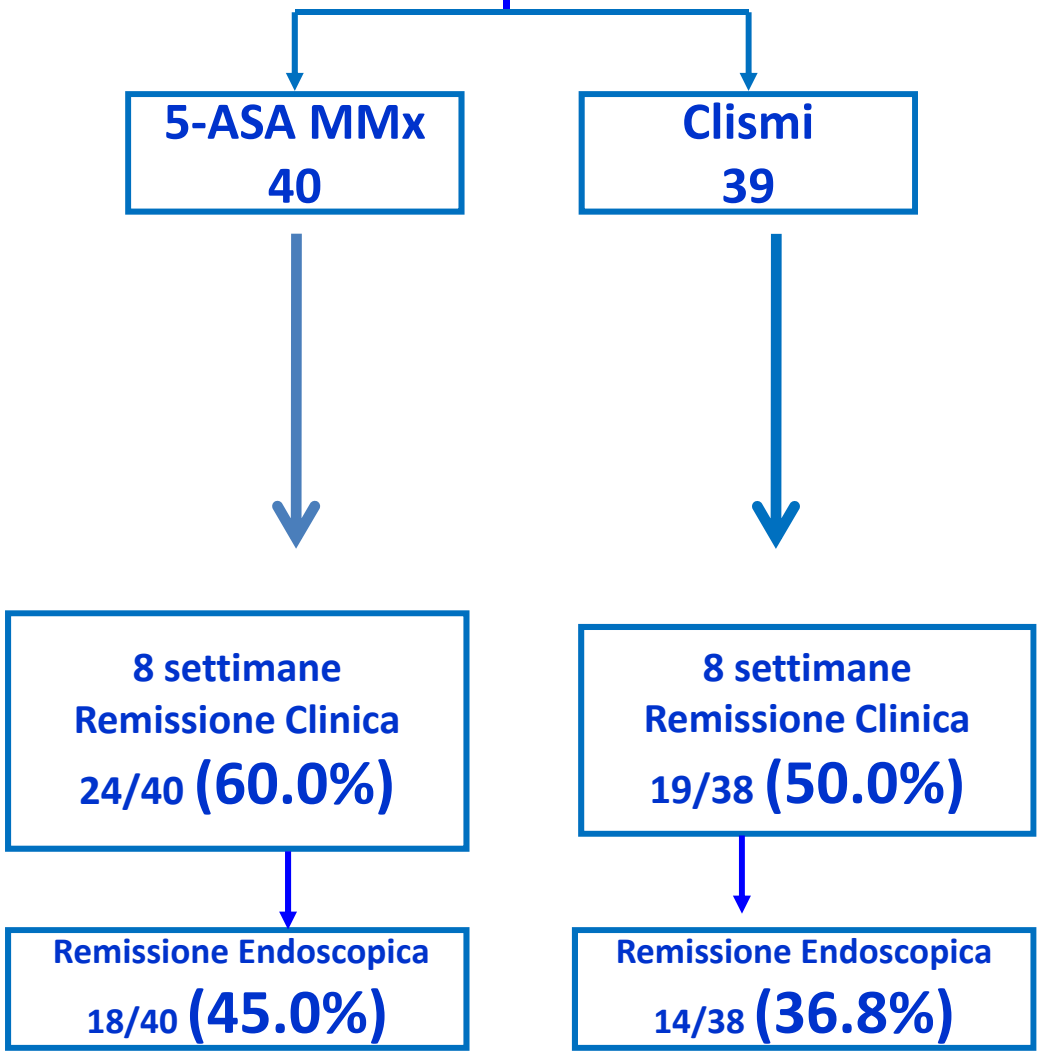
[Brunner *et al.*, Aliment Pharmacol Ther 2003; 17: 395-402]

Dissoluzione della capsula MMX nell' ileo terminale



Studio Pilota CU

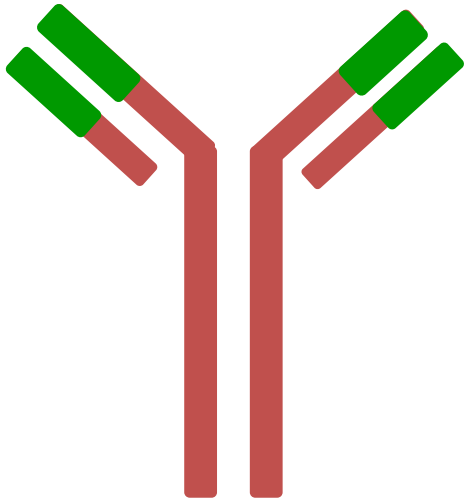
Pazienti Randomizzati 79



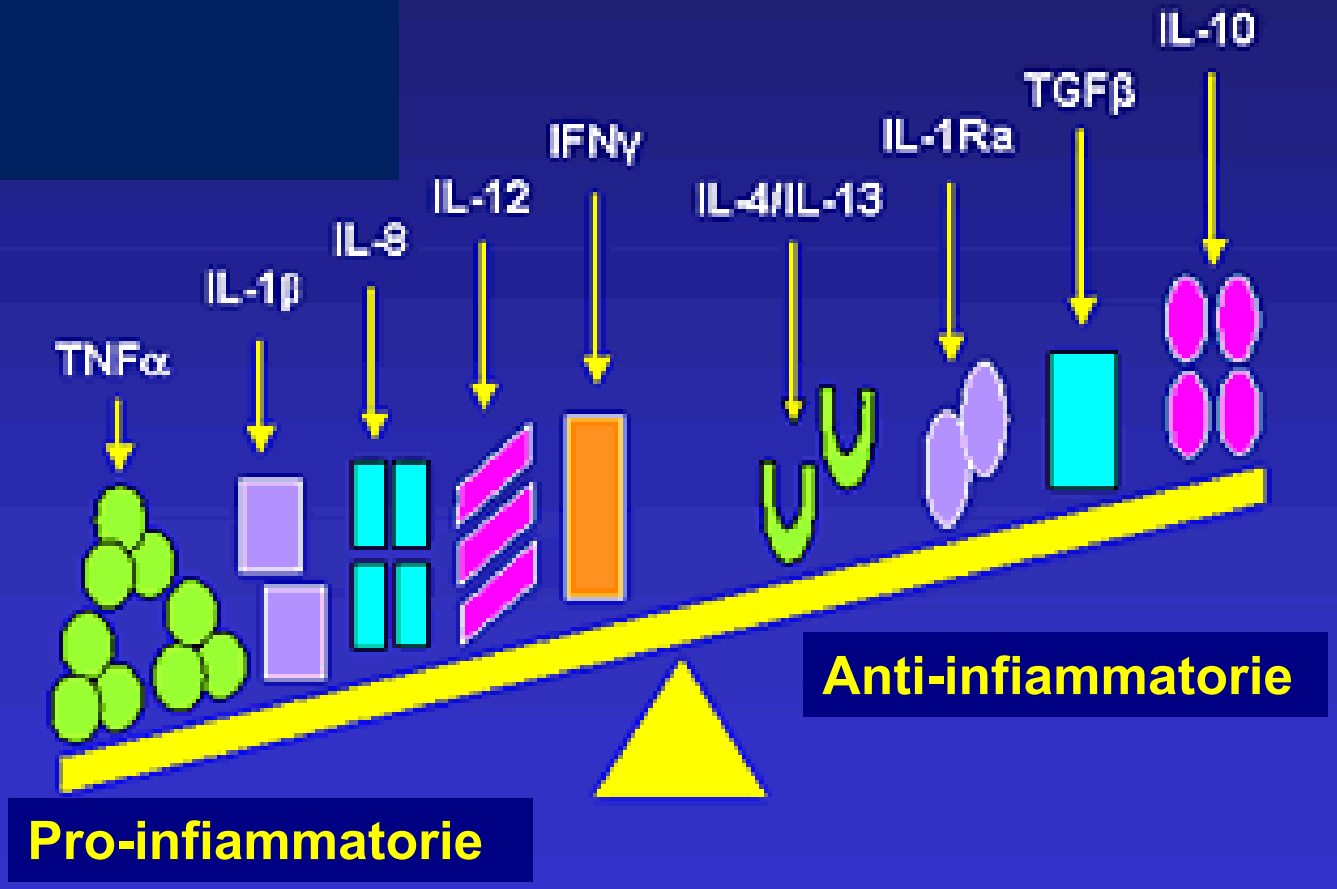
(Prantera C et al)

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

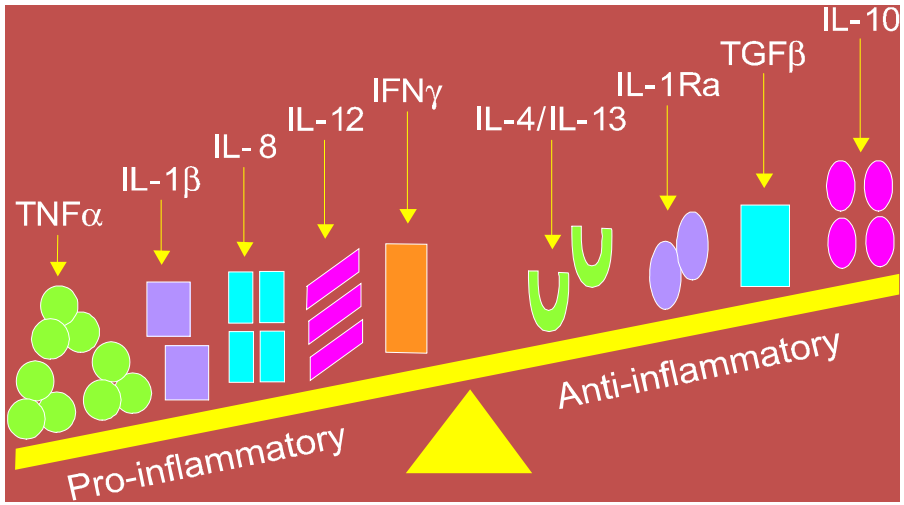
- Ormoni
- Anticorpi Monoclonali
- Emoderivati
- Interferoni
- Vaccini



Citochine immunomodulatorie/ anti-infiammatorie



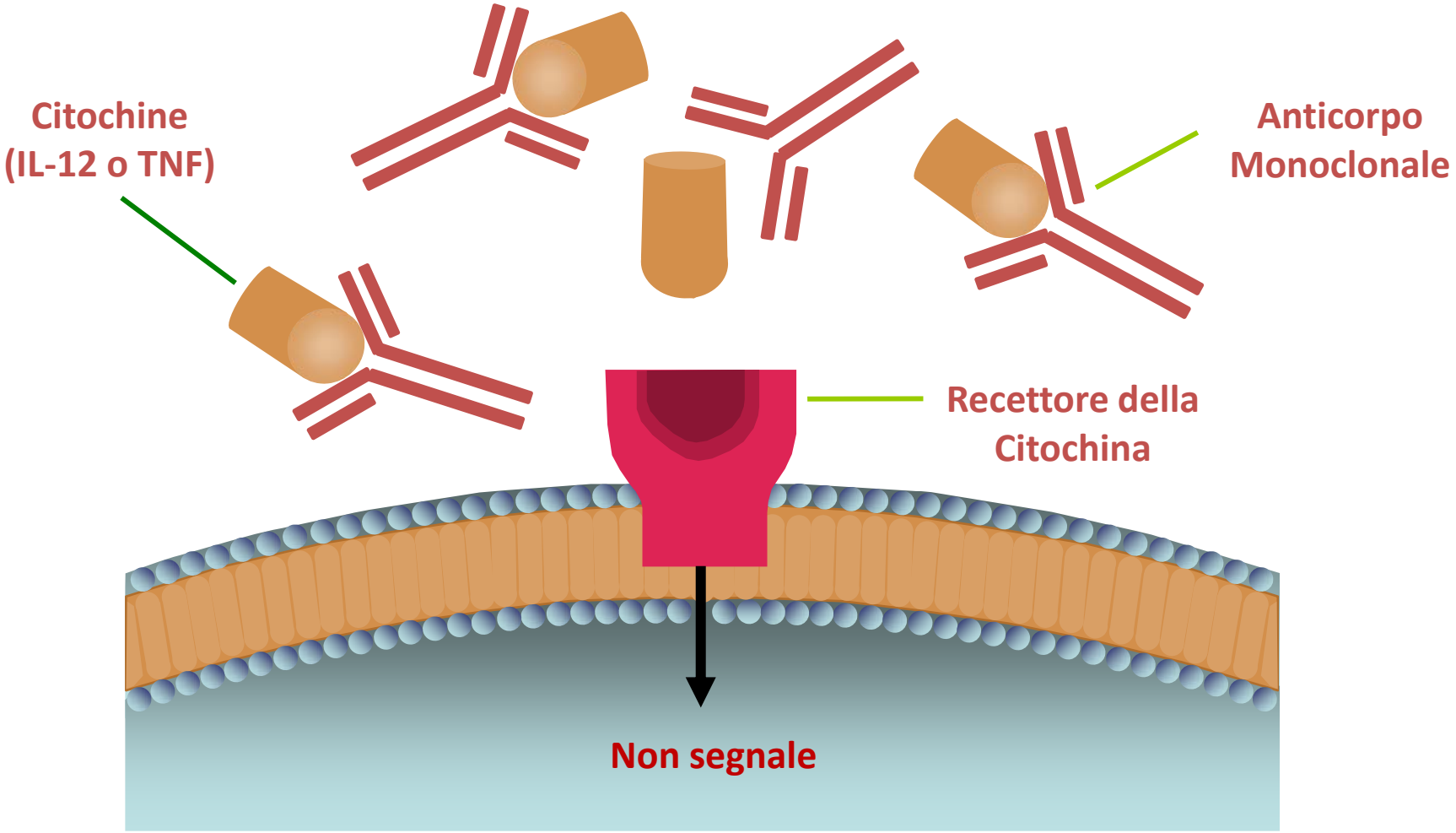
Biologici in ricerca per le malattie infiammatorie croniche intestinali



- 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, α-4 (natalizumab), α4β7
  - Composti Antisenseo per ICAM-1
  - Anti NF-κB, anti-OX40, anti-ZAP
- Altri approcci
  - ormone rhuGrowth, KGF- (faillito nei trials CU), rosiglitizone, inibitori PAF , EGF, RDP, Nu-286 (Wnt agonisti)

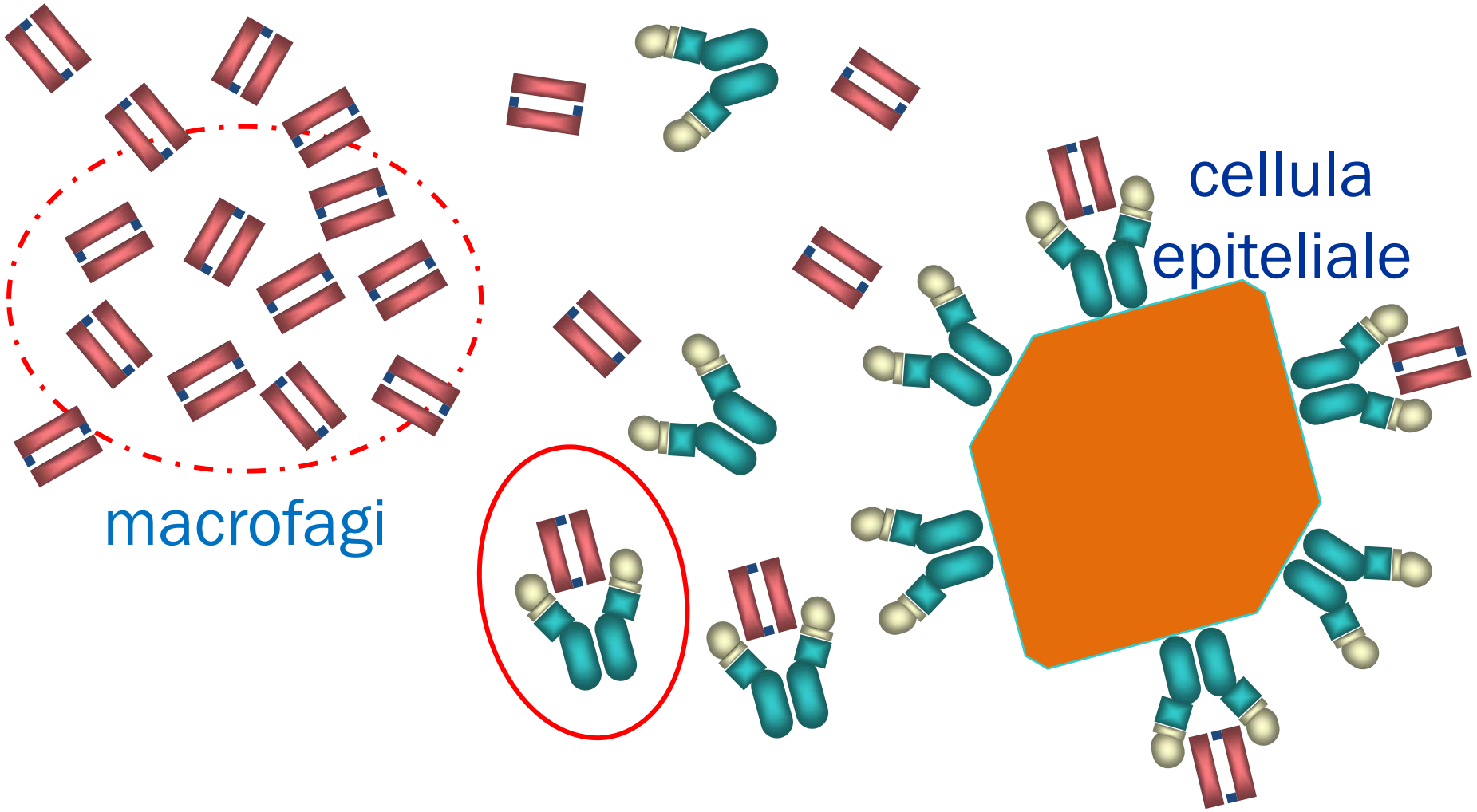
- Strategie Anti-TNF
  - Anticorpi Chimerici
  - Anticorpi “umanizzati”
  - Anticorpi “umani”
  - Frammenti Anticorpi
  - Composti Antisenso
  - TNF-BP1
  - Talidomide

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

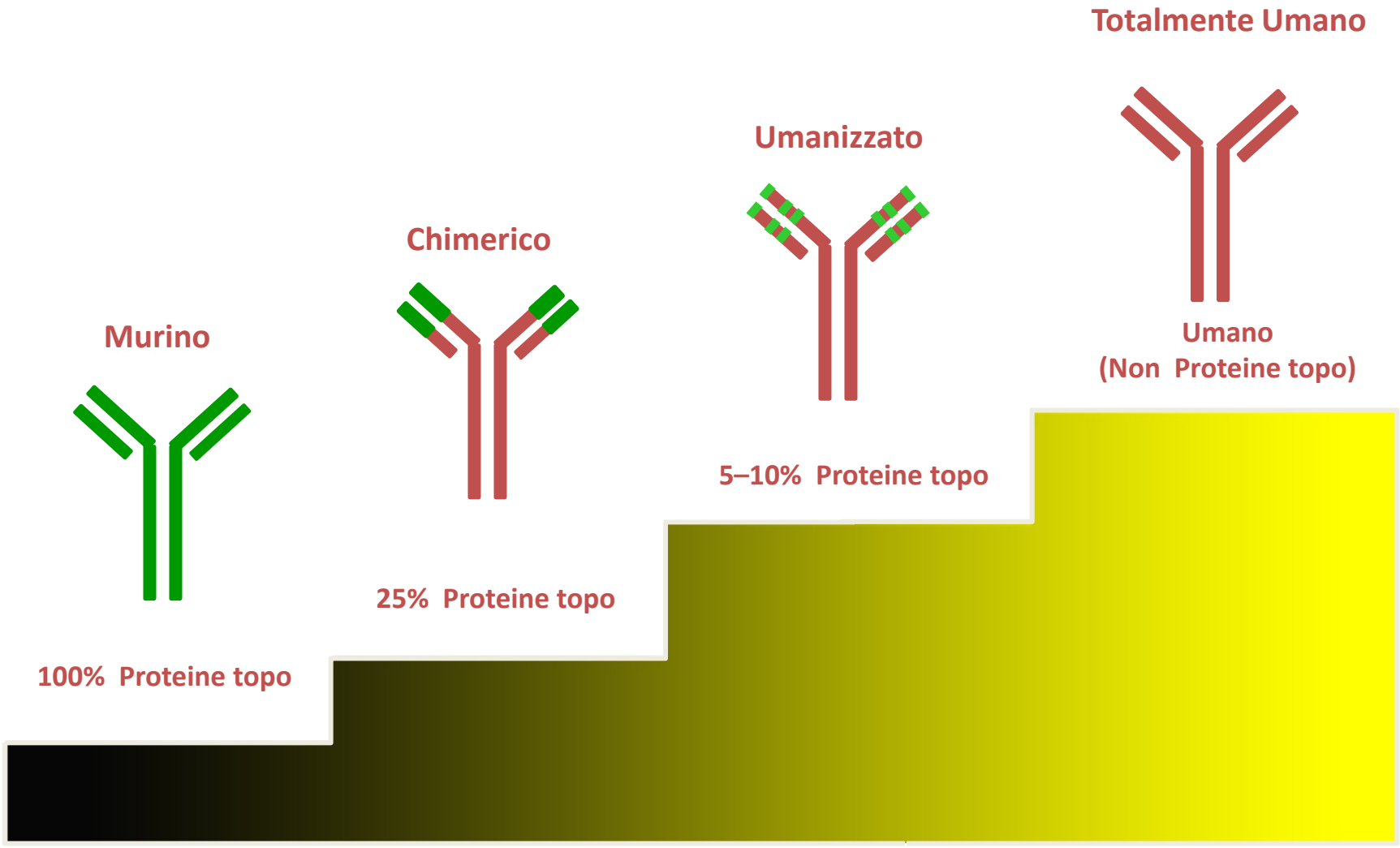


Choy EHS et al. *N Engl J Med.* 2001;344:907–16.

Blocco dei Recettori del TNF-α

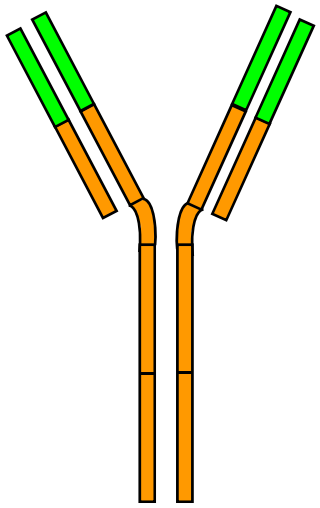


Evoluzione degli Anticorpi Monoclonali



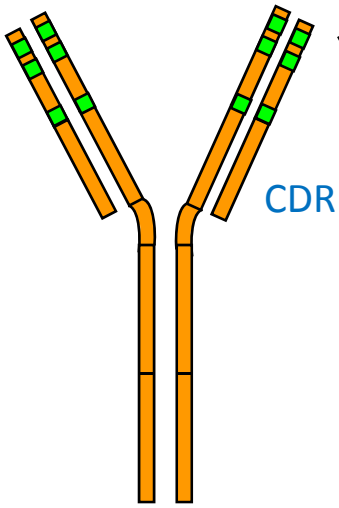
Inibitori TNF-α

Anticorpo Chimerico monoclonale



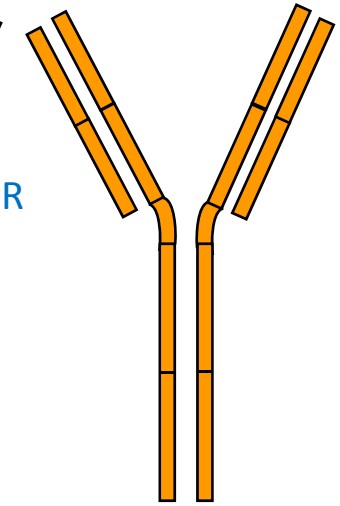
infliximab
IgG1

Anticorpo monoclonale umanizzato



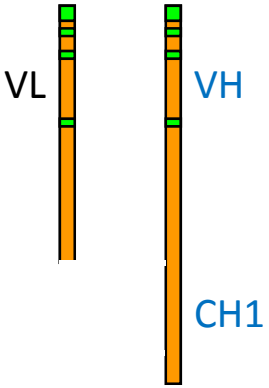
CDP571
IgG4

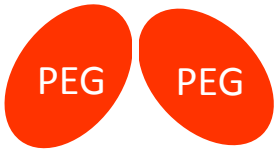
Anticorpo umano ricombinante



adalimumab
IgG1

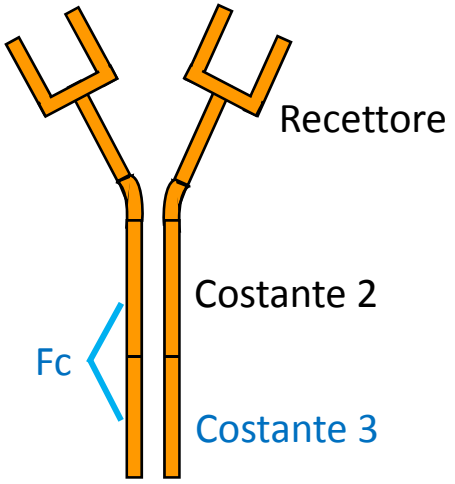
Frammento Fab' umanizzato





certolizumab pegol

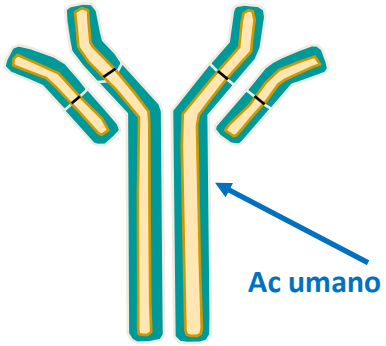
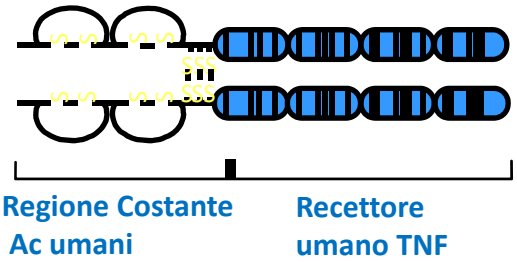
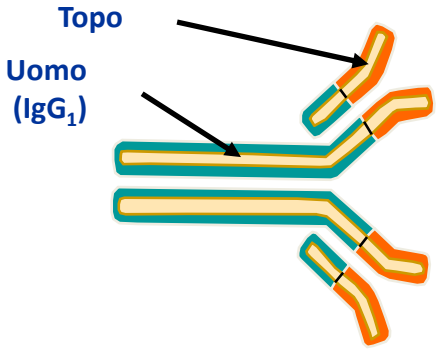
Recettore umano ricombinante/ proteina fusione Fc p



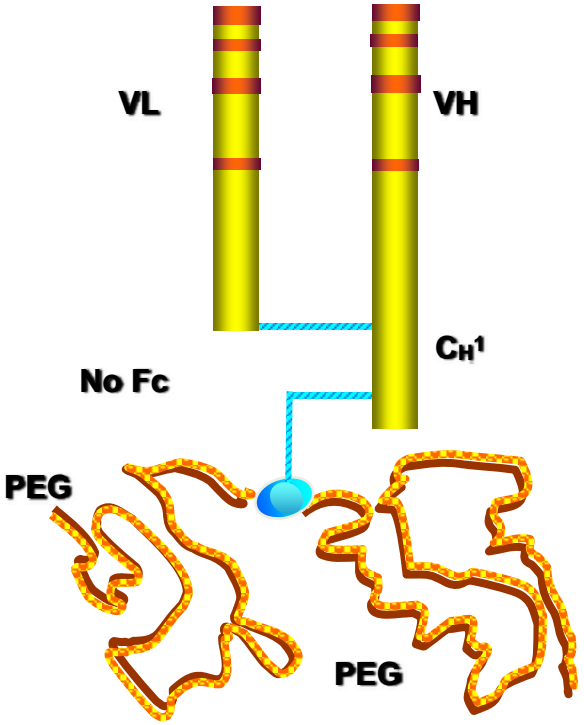
etanercept
IgG1

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

Antagonisti TNF-α

Adalimumab	Etanercept	Infliximab
		
Anticorpo monoclonale umano anti–TNF-α	Recettore umano	Anticorpo monoclonale chimerico anti-TNF

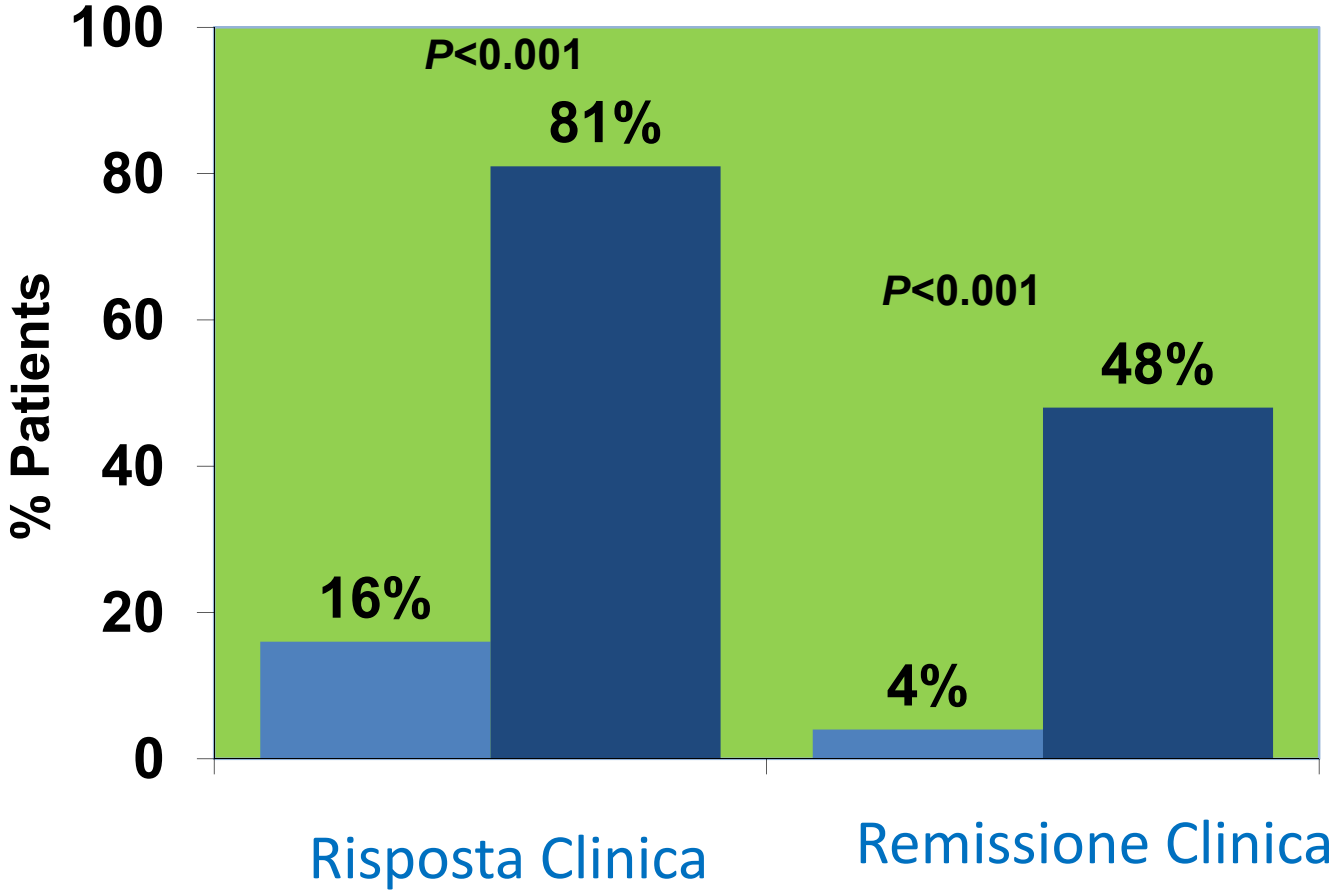
Certolizumab Pegol



Frammento Fab'
(95% umano IgG_1 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.

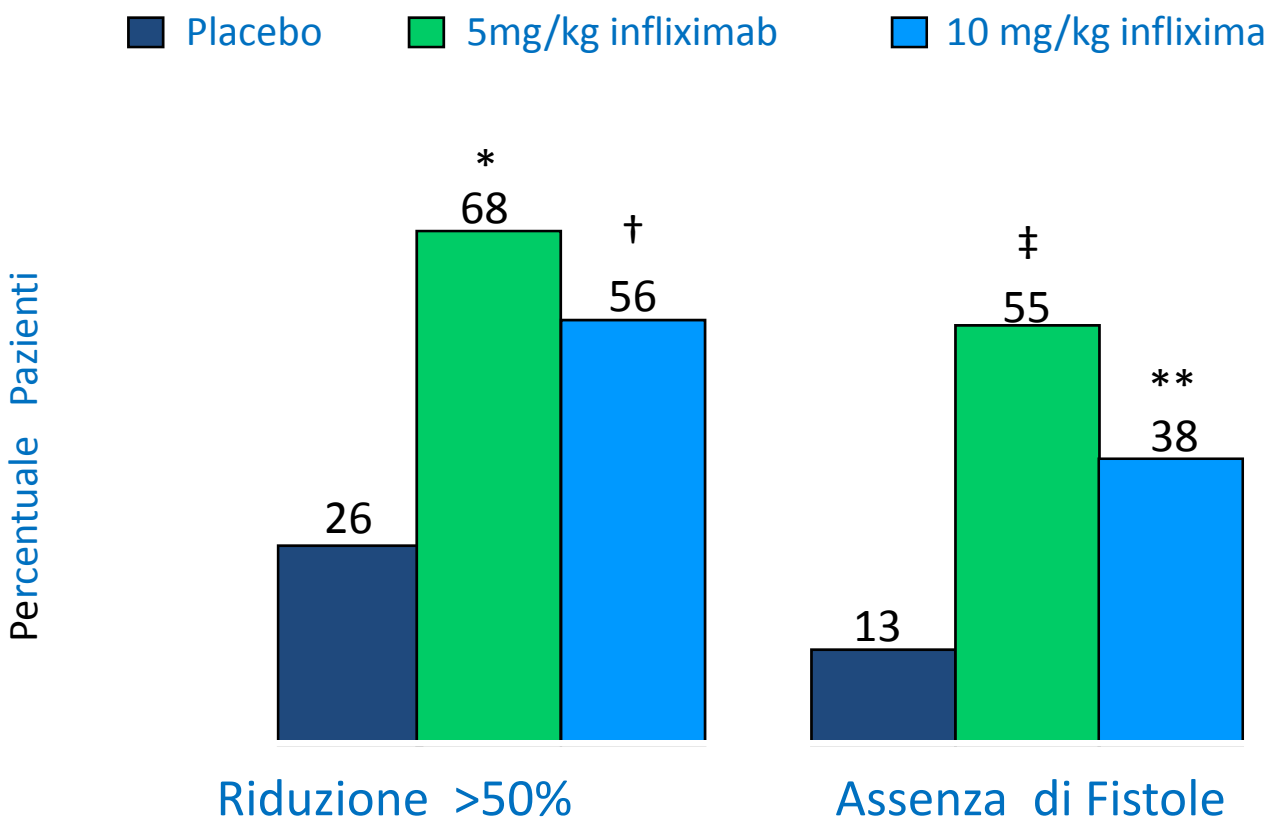
Risposta Clinica e Remissione con Infliximab nel m. Crohn a 4 settimane



Placebo = 25
Infliximab
5mg/kg = 27

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

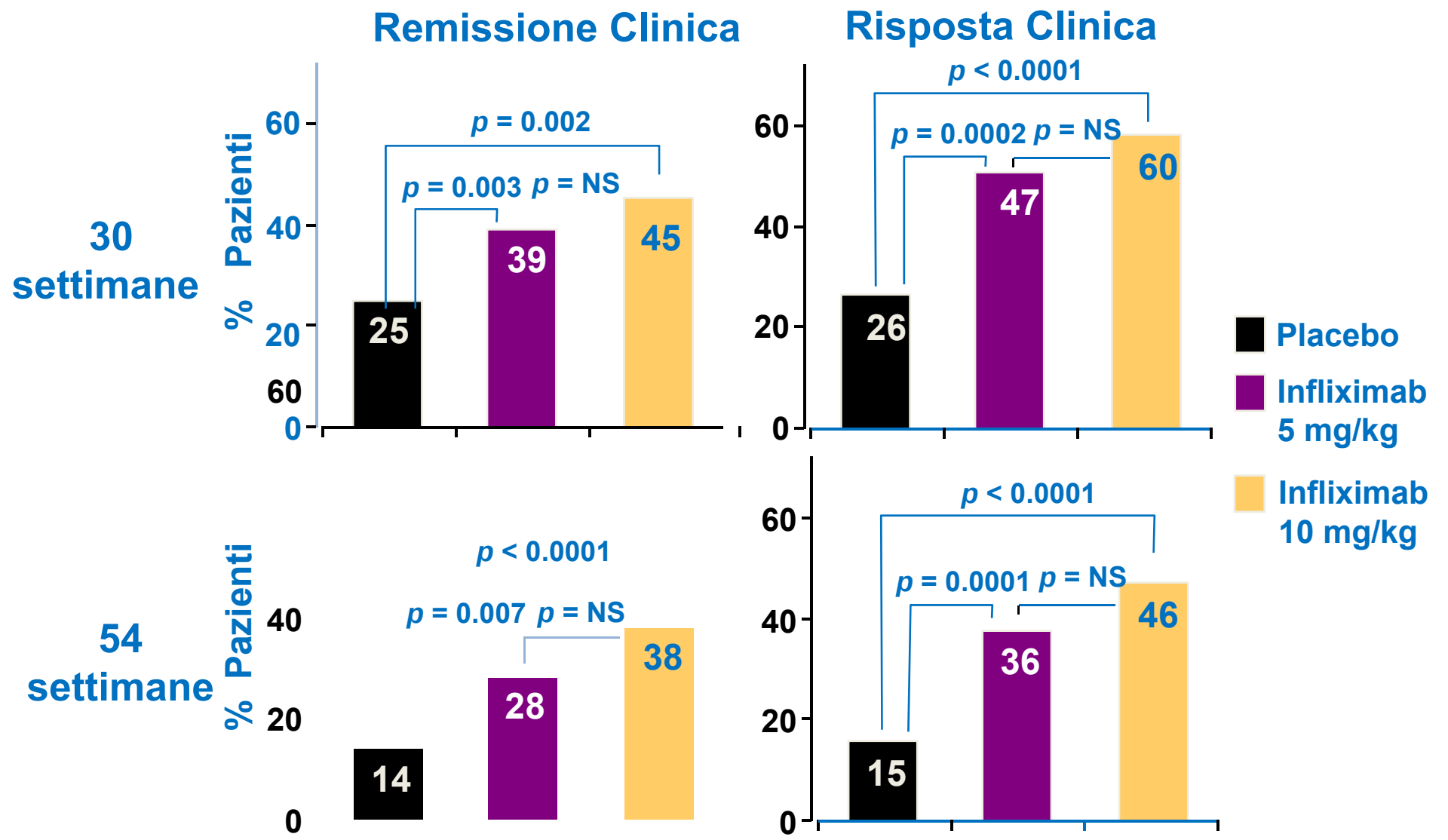
Infliximab: Guarigione Fistole



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

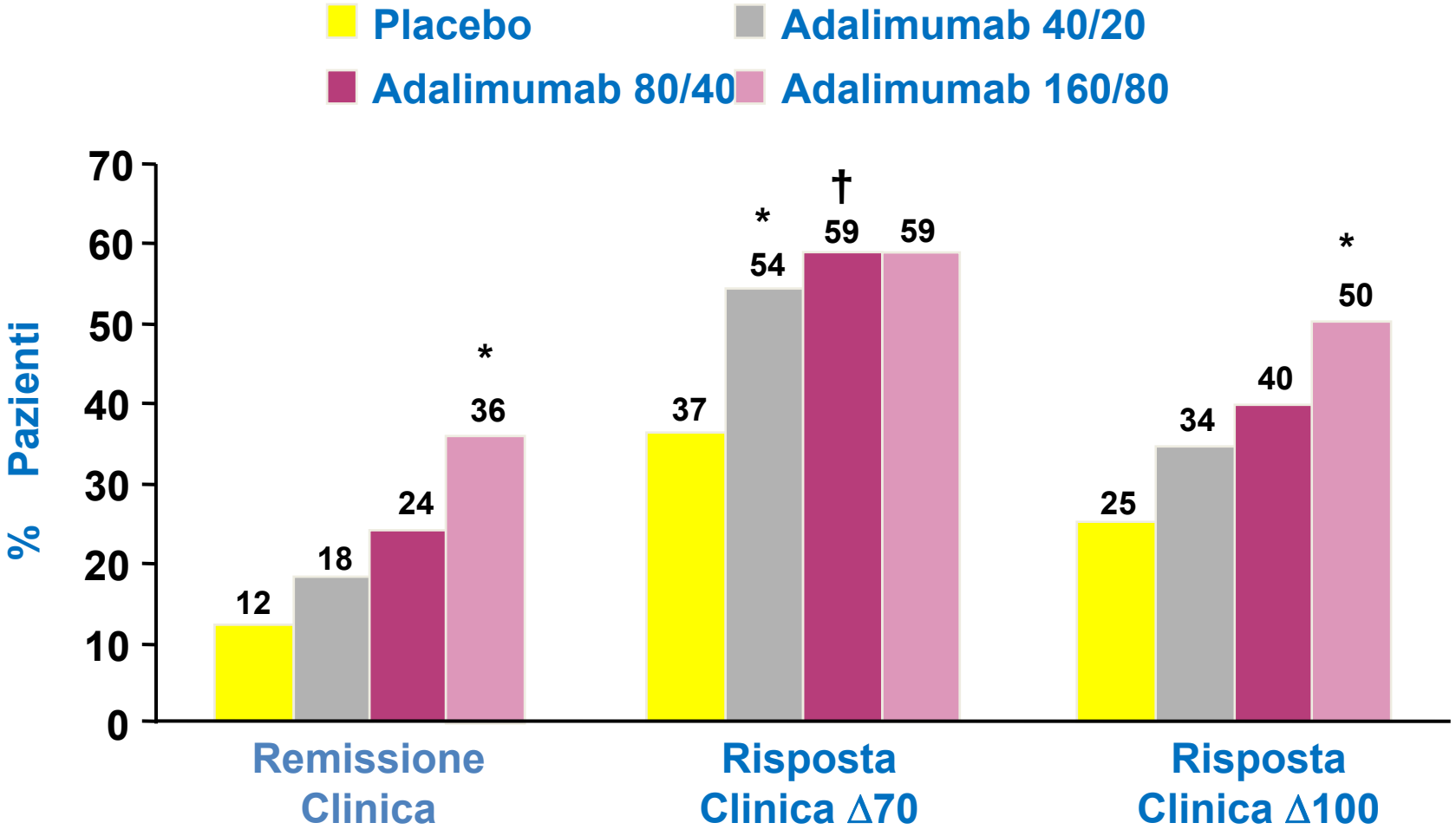
Present DH, et al. *N Engl J Med*. 1999;340:1398-1405.

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



Hanauer SB, et al. *Lancet.* 2002;359:1541–1549.

CLASSIC I: ADALIMUMAB
4 settimane m.Crohn

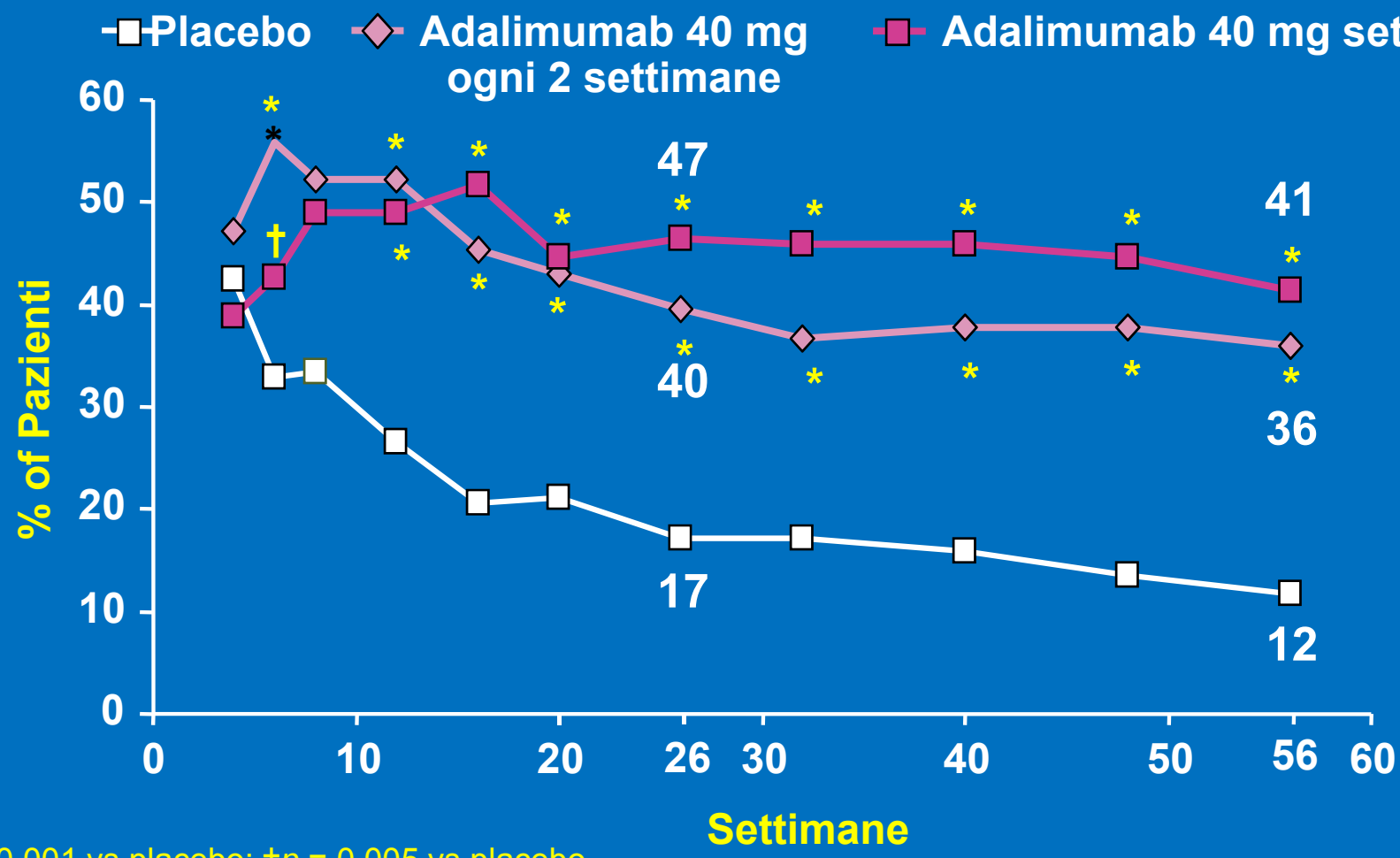


*** *p* < 0.05 vs placebo; †*p* = 0.001 vs placebo; ‡*p* = 0.007 vs placebo.**

Remissione Clinica = CDAI < 150; Risposta Clinica= Δ70 orΔ100 ≥ 70 o ≥ 100 punti diminuizione CDAI

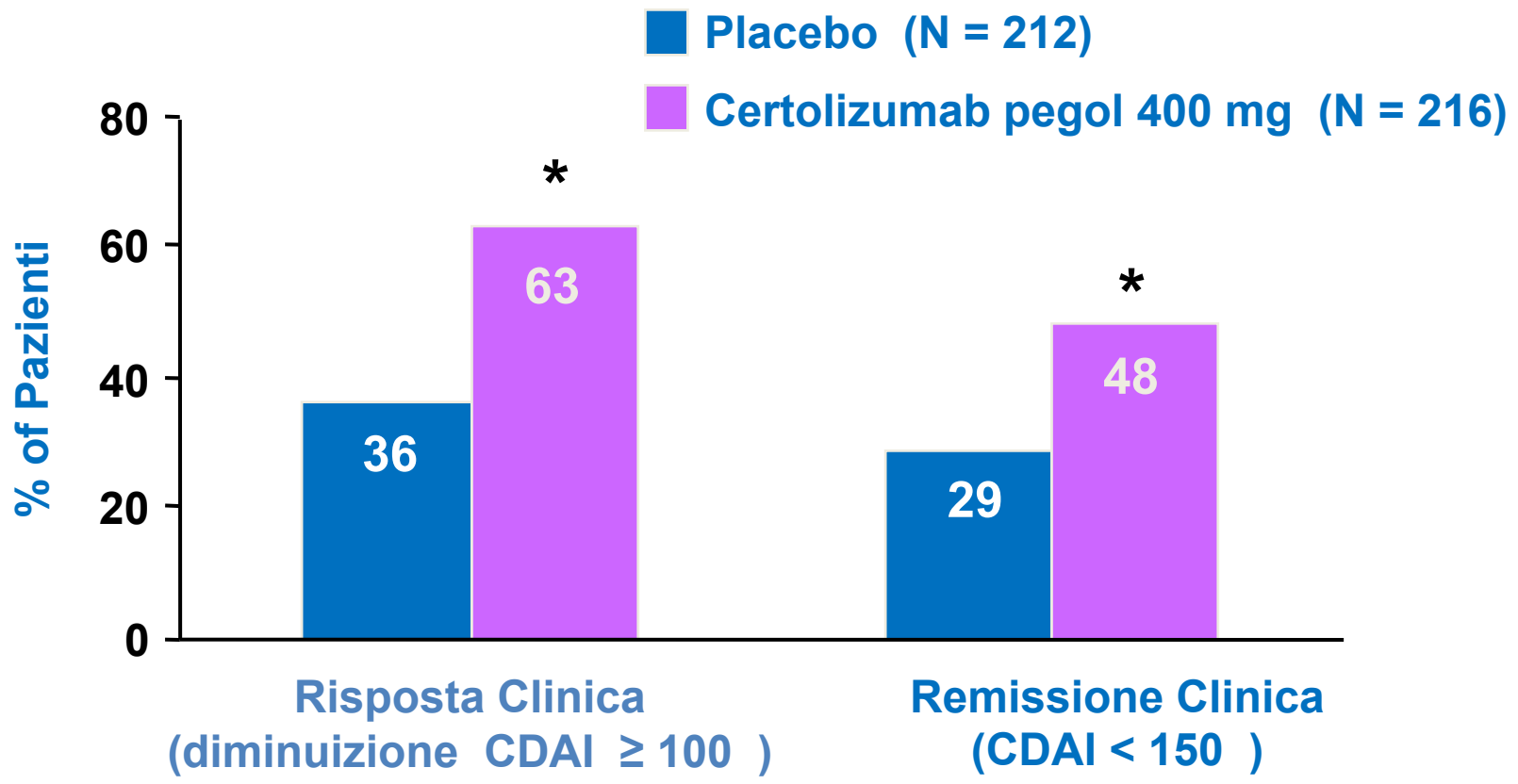
Hanauer S, et al. *Gastroenterology.* 2006;130:323–33.

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.

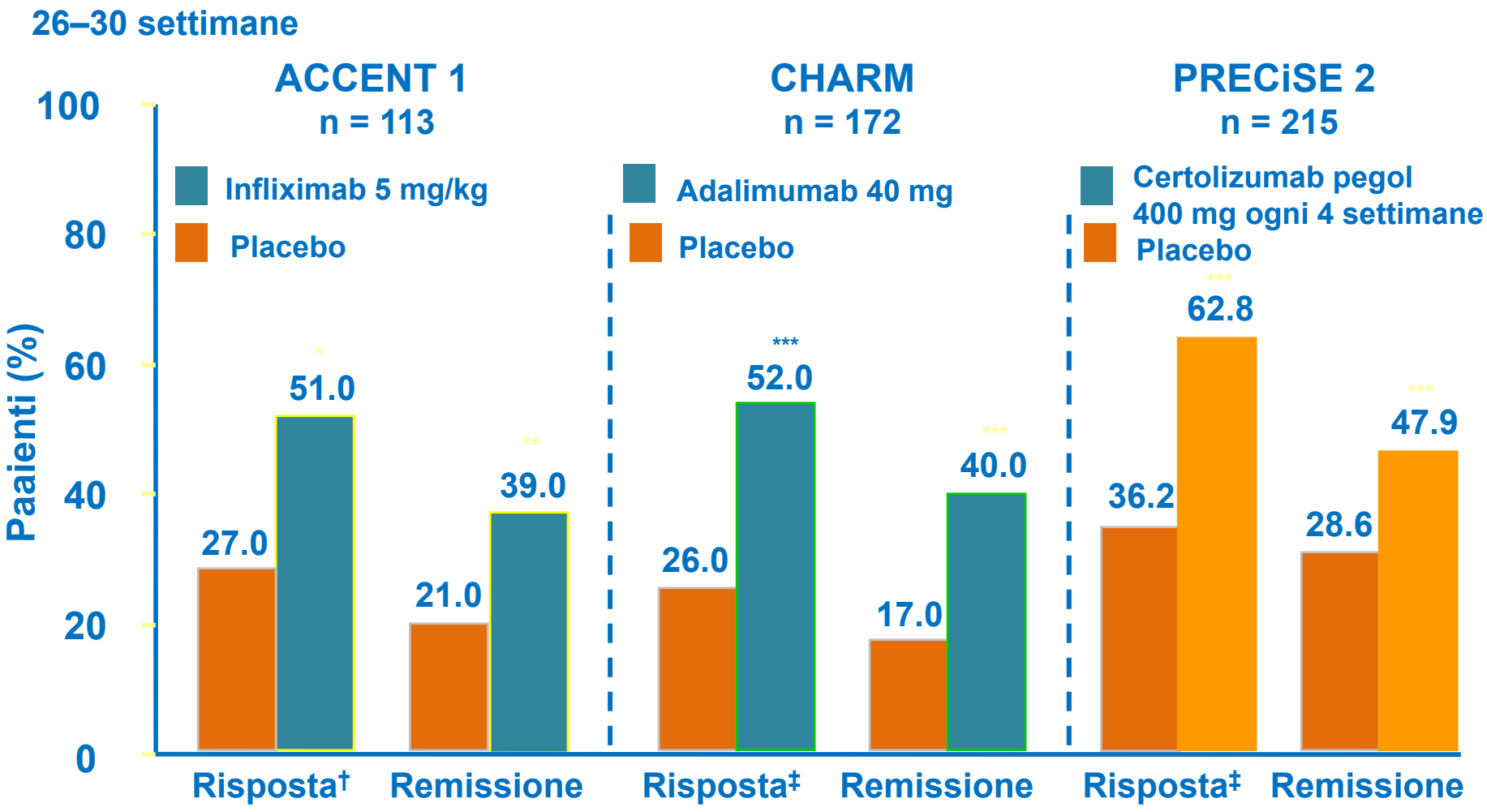
PRECiSE 2: CERTOLIZUMAB
Risposta e Remissione Clinica
a 26 settimane in Pazienti con m. Crohn(N = 428)



**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-α nel m.Crohn

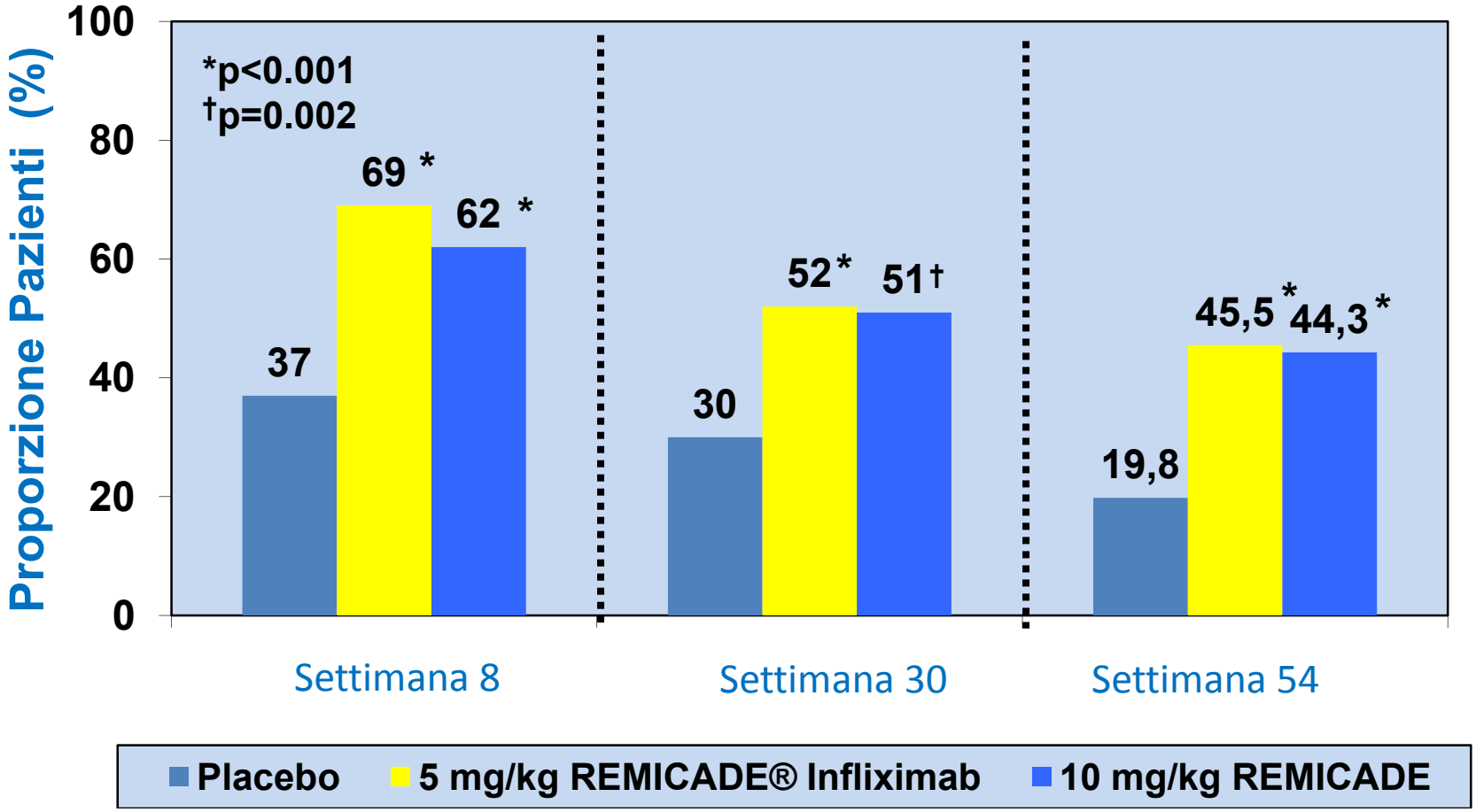


Hanauer SB et al. *Lancet*. 2002;359:1541–1549.
Colombel J et al. *Gastroenterology*. 2006;131:950.
Schreiber S et al. *Gut*. 2005;54(Suppl VII):A82.

Remissione = CDAI score < 150
† < CDAI score ≥ 70 e ≥ 25%
‡ < CDAI score ≥ 100
*P = .0002; **P = .003; ***P < .001

ACT 1

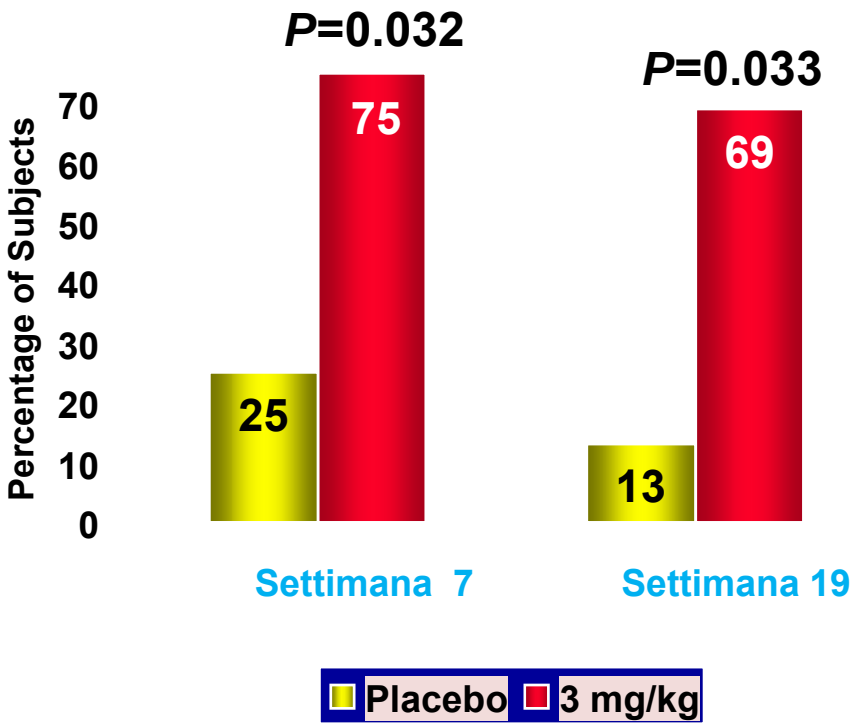
Terapia con Infliximab per CU



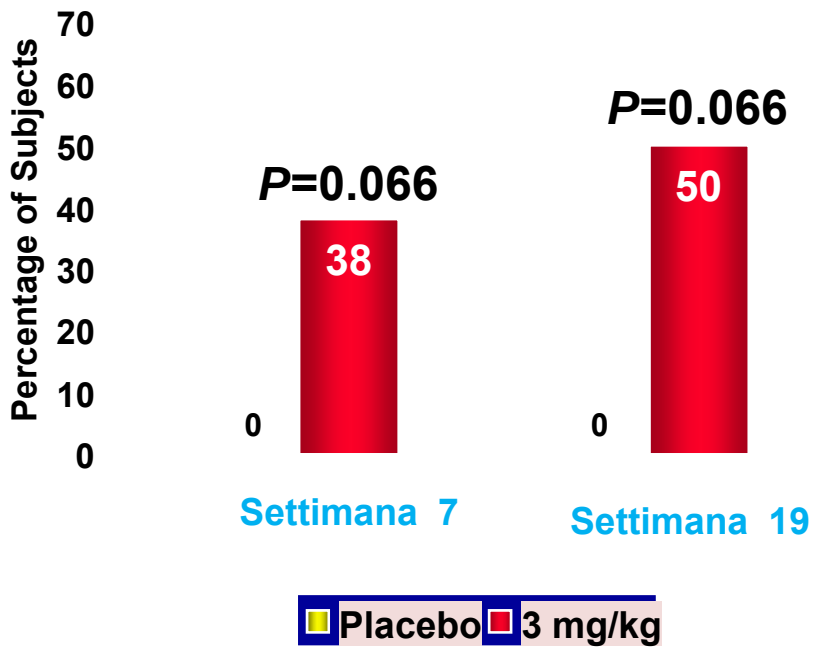
Rutgeerts P et al. *N Engl J Med*. 2005;353(23):2462-2476.

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

Pazienti con Risposta Clinica (< CDAI ≥100)



Pazienti con Remissione Clinica (CDAI ≤150)

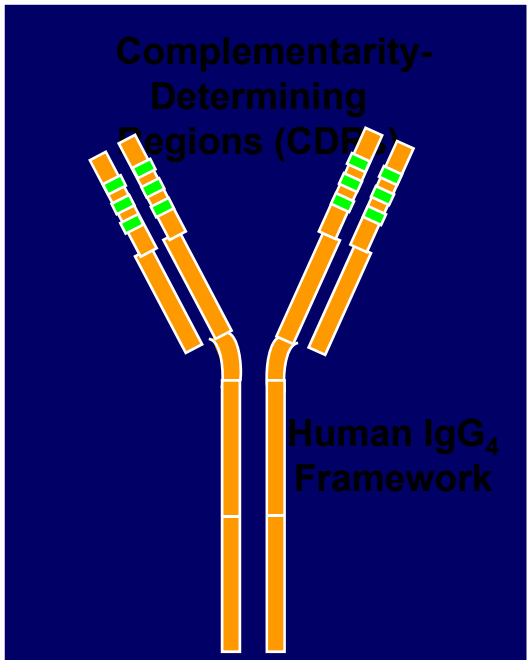


Mannon PJ et al. *N Engl J Med*. 2004;251:2069–2079.

Natalizumab

- Anticorpo Ricombinante monoclonale anti α_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 infiamazione cronica

Costruzione del Natalizumab

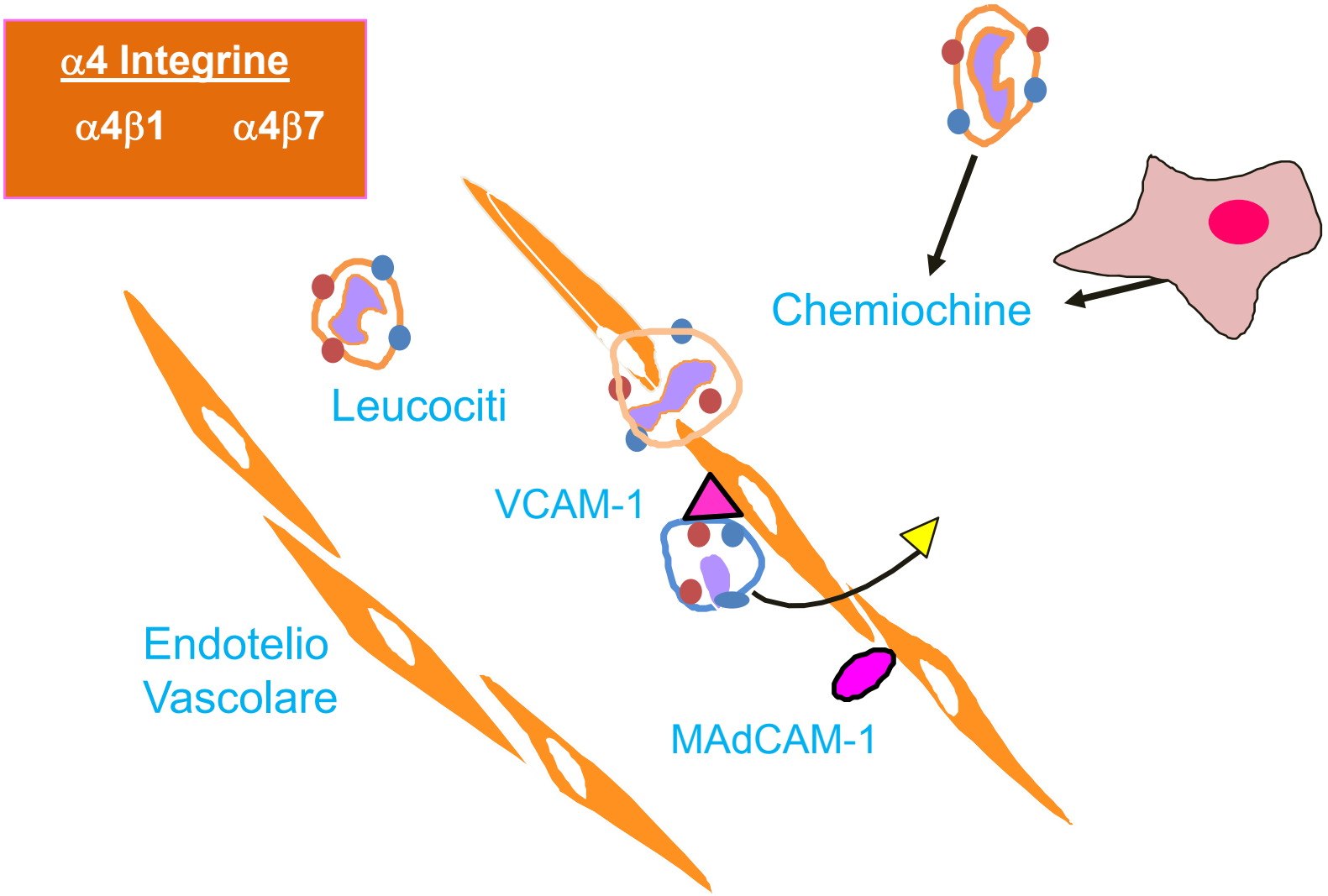


Natalizumab

Ac umanizzati contro α4-integrine

IgG_4 umane legate ad anticorpi murini

Adesione e Arruolamento

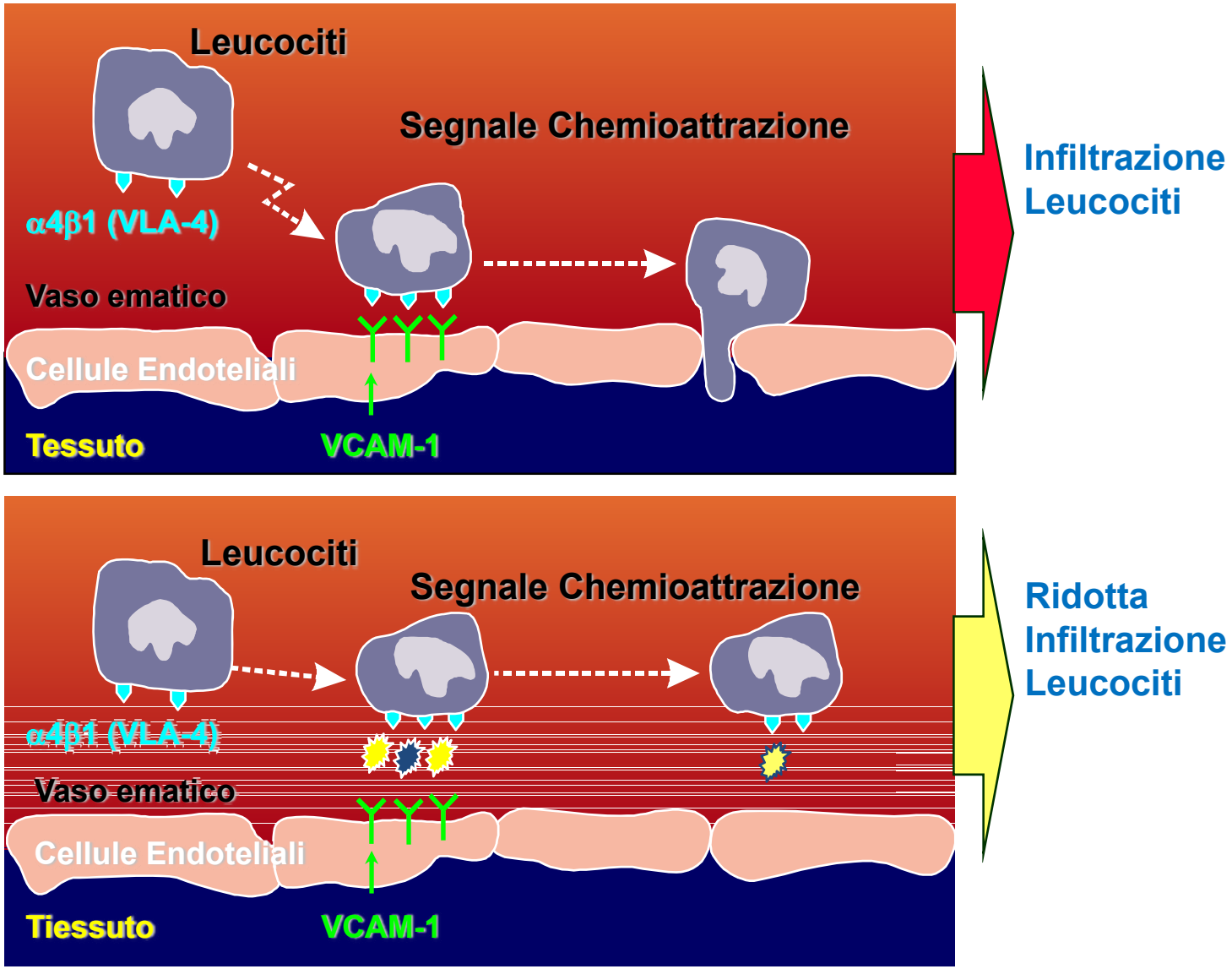


Adesione endoteliale e leucociti: α4 -Integrine

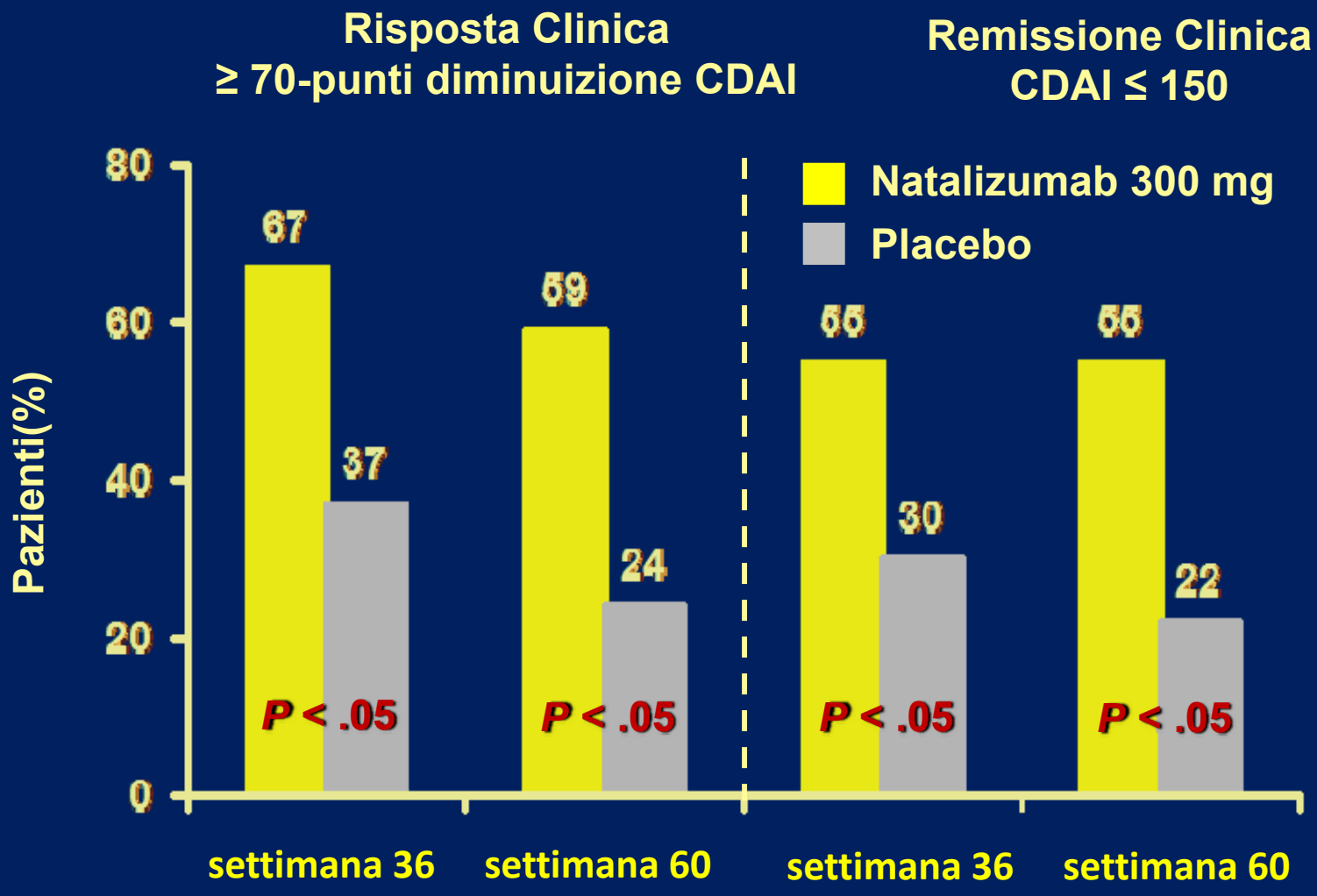
- Glicoproteine di membrana dei leucociti, sub-unità β1 e β7
- Interagiscono con i legandi endoteliali VCAM1, fibronectina, MAdCAM-1
- Mediano l'adesione ed il traffico dei leucociti

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

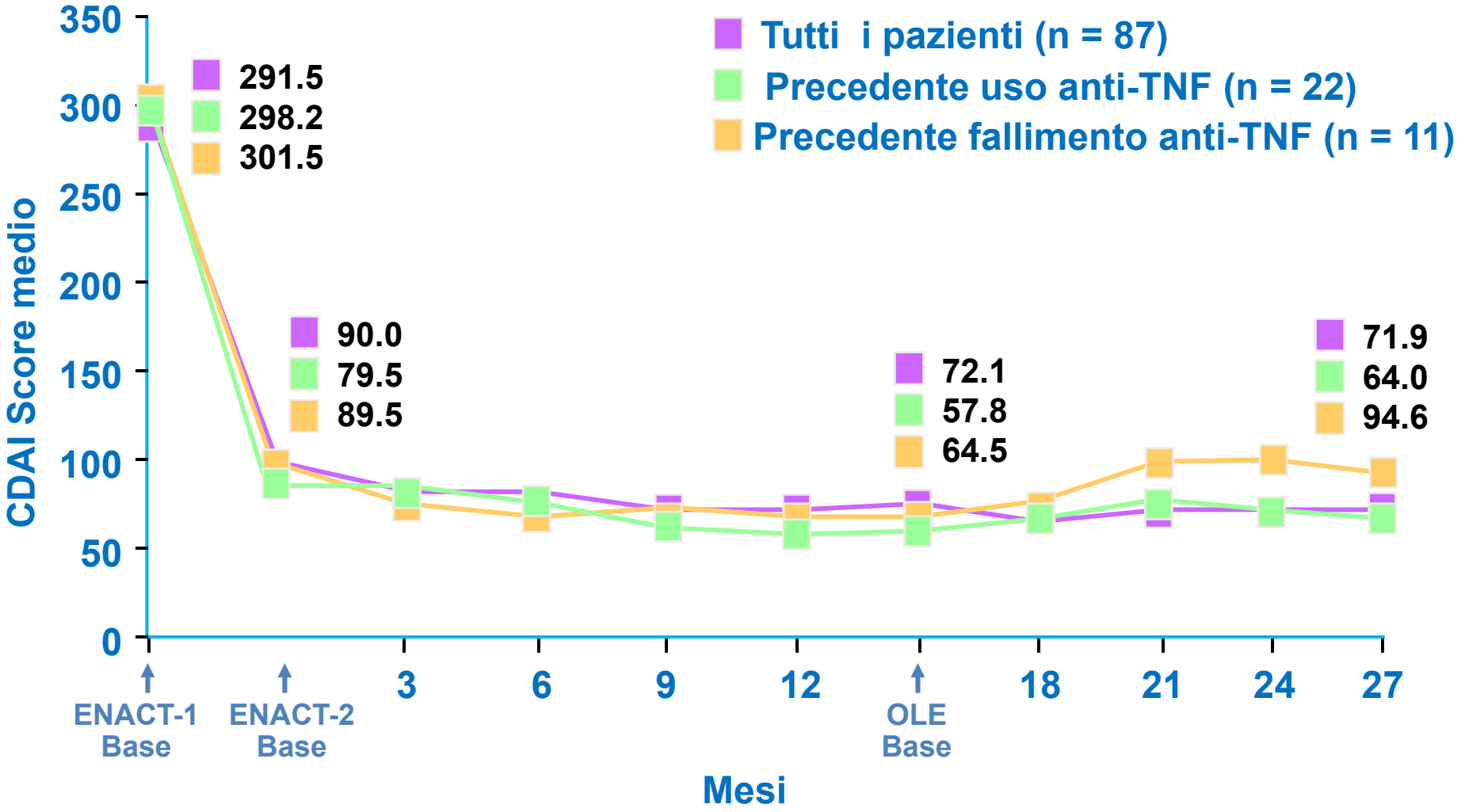


Natalizumab come Terapia Mantenimento per m. Crohn: *Trial ENACT-2*



Sandborn WJ et al. *N Engl J Med.* 2005;353:1912–1925.

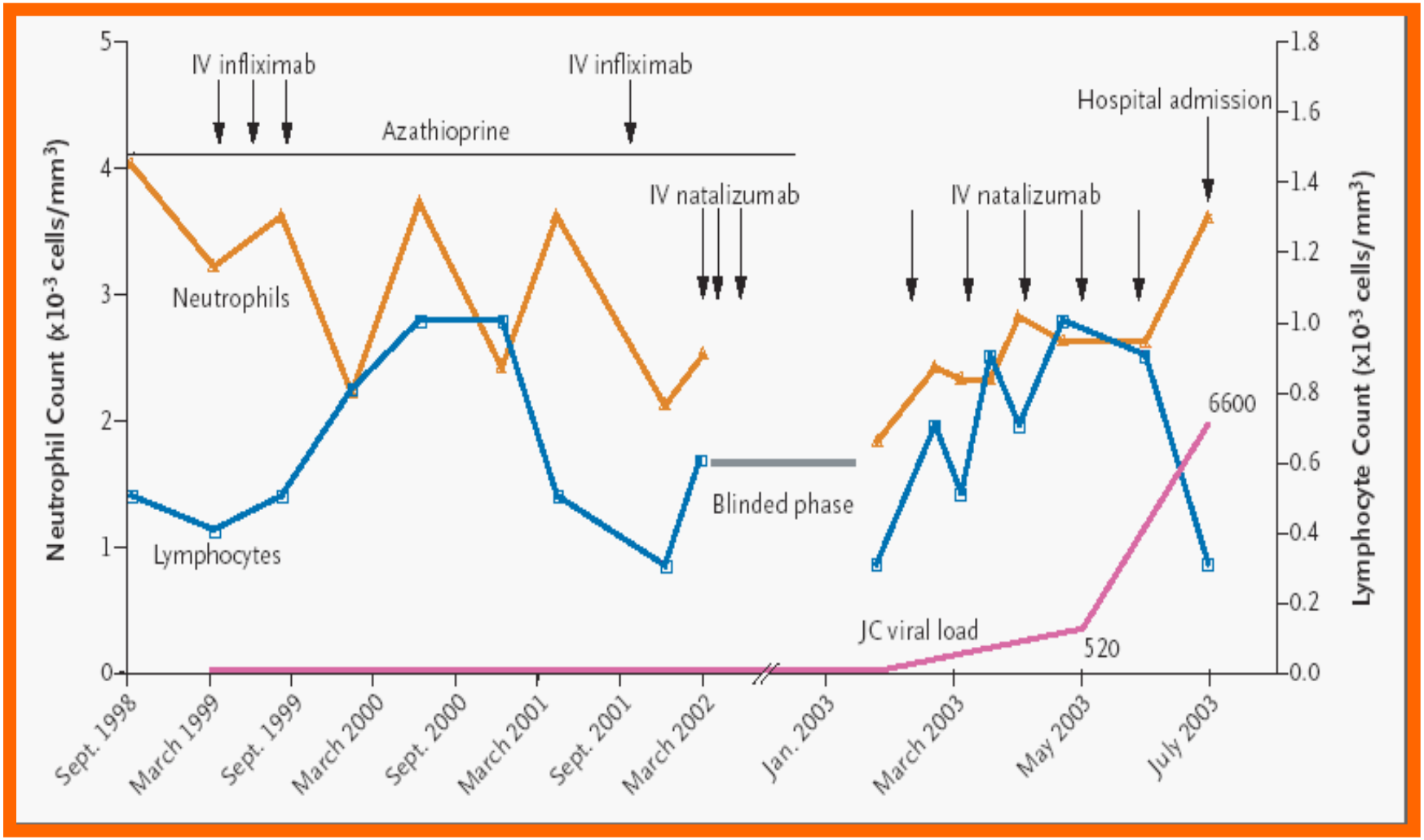
CDAI Scores dopo 24 mesi di trattamento continuo con Natalizumab



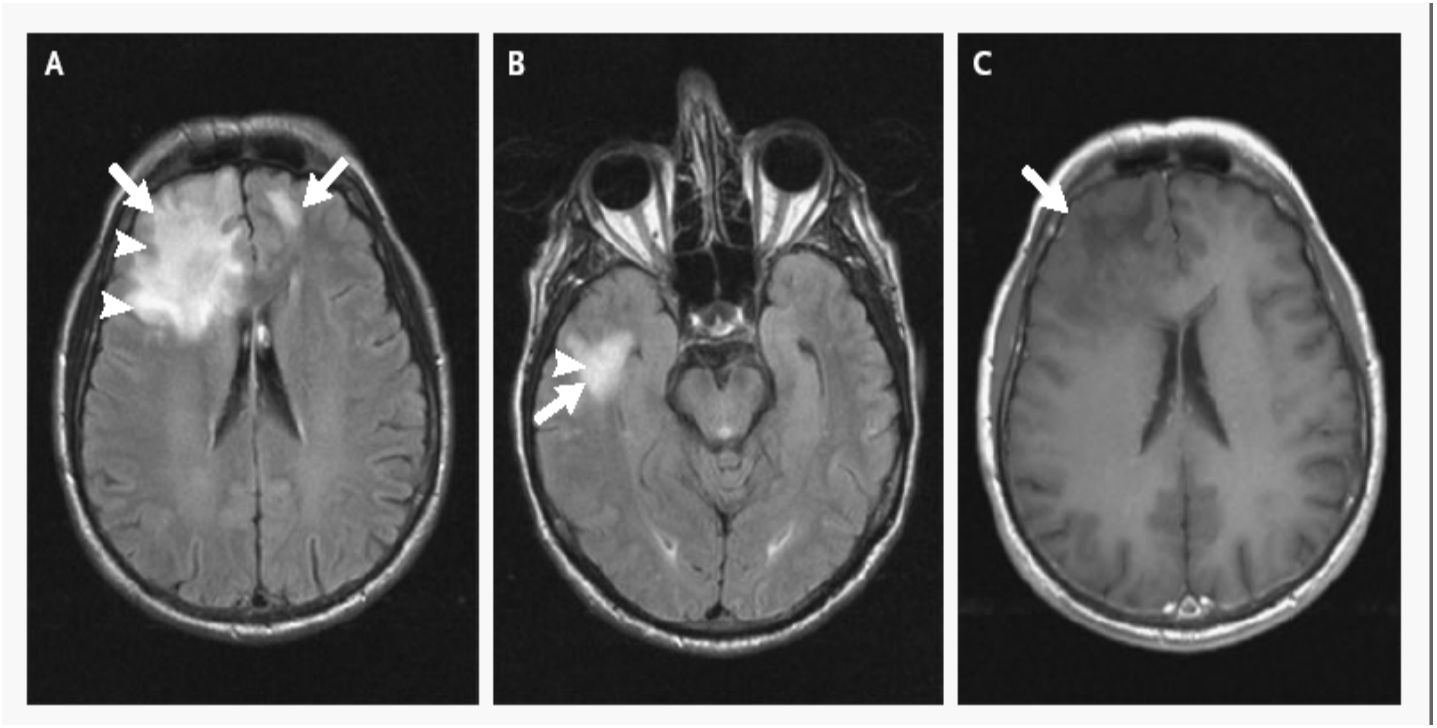
Panaccione R, et al. *Am J Gastroenterol*. 2006;101(Suppl 2):S450. Abstract 1152.

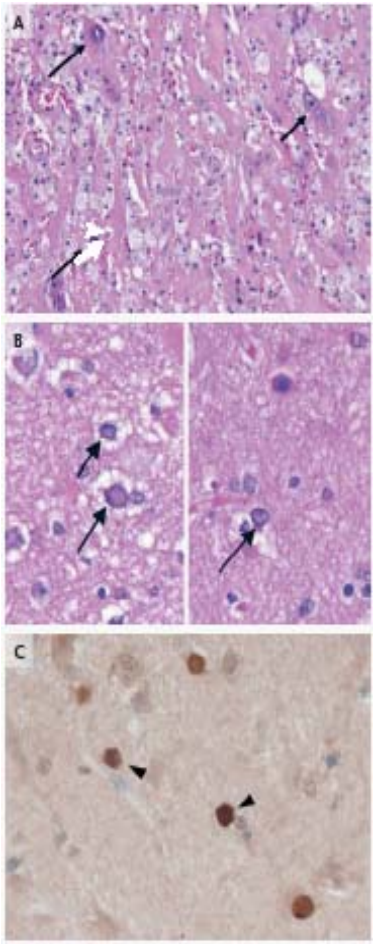
“Progressive multifocal leukoencephalopathy (PML)” in pazienti trattati con Natalizumab

Natalizumab & Crohn's/PML



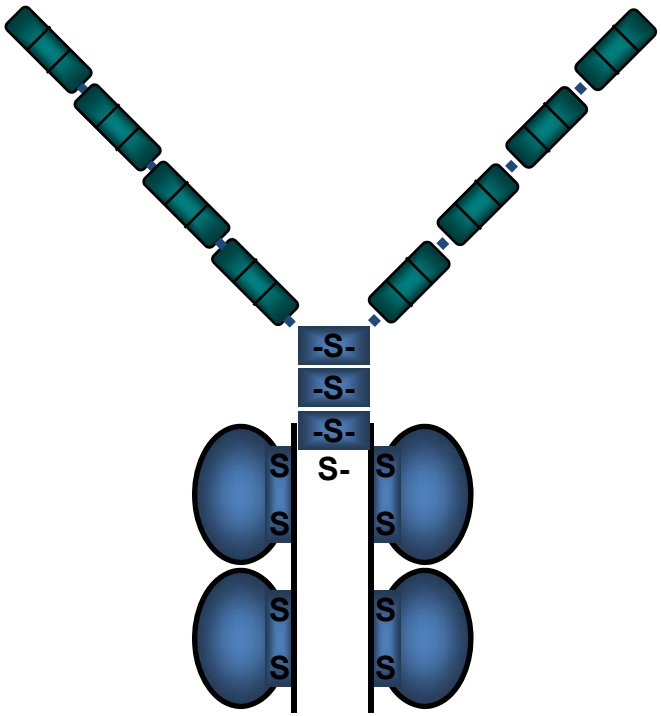
Natalizumab Crohn's/PML





Etanercept (Enbrel®)

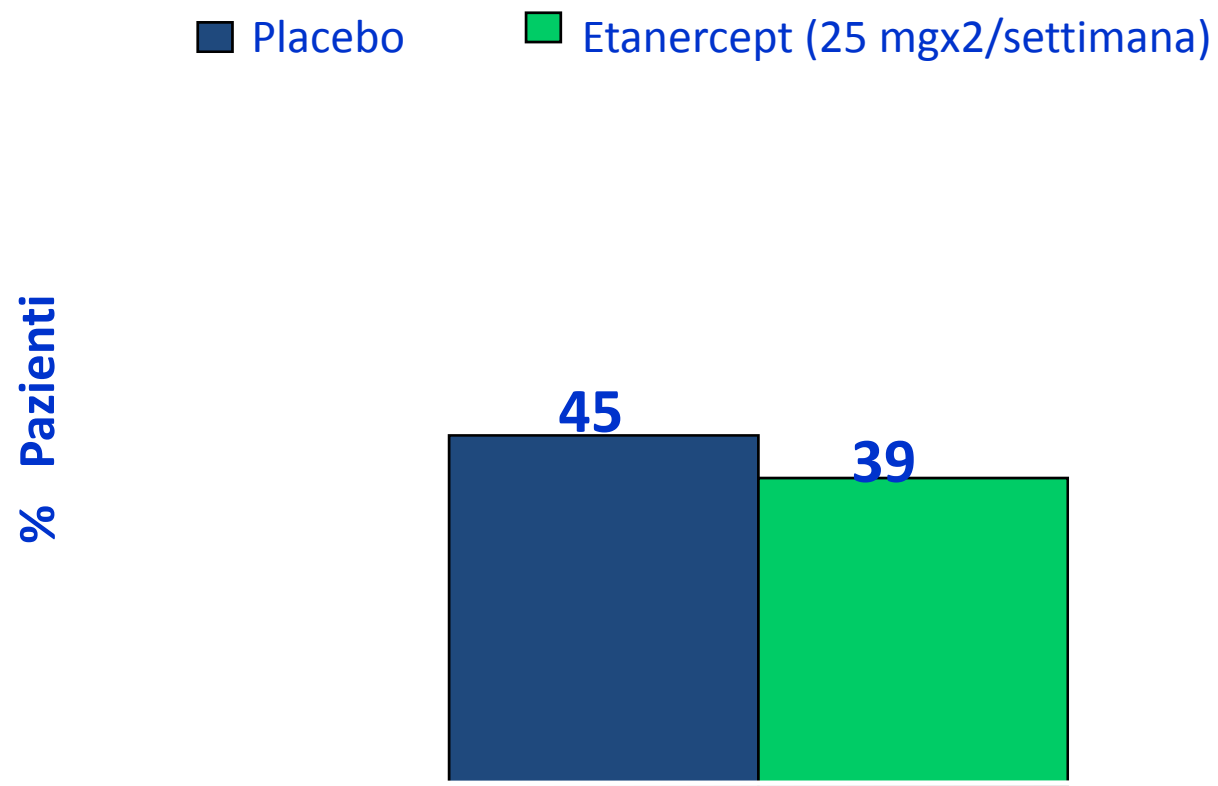
proteina soluble per recettore TNF



recettore extracellulare
umano TNF- p75

dominio umano IgG1 Fc

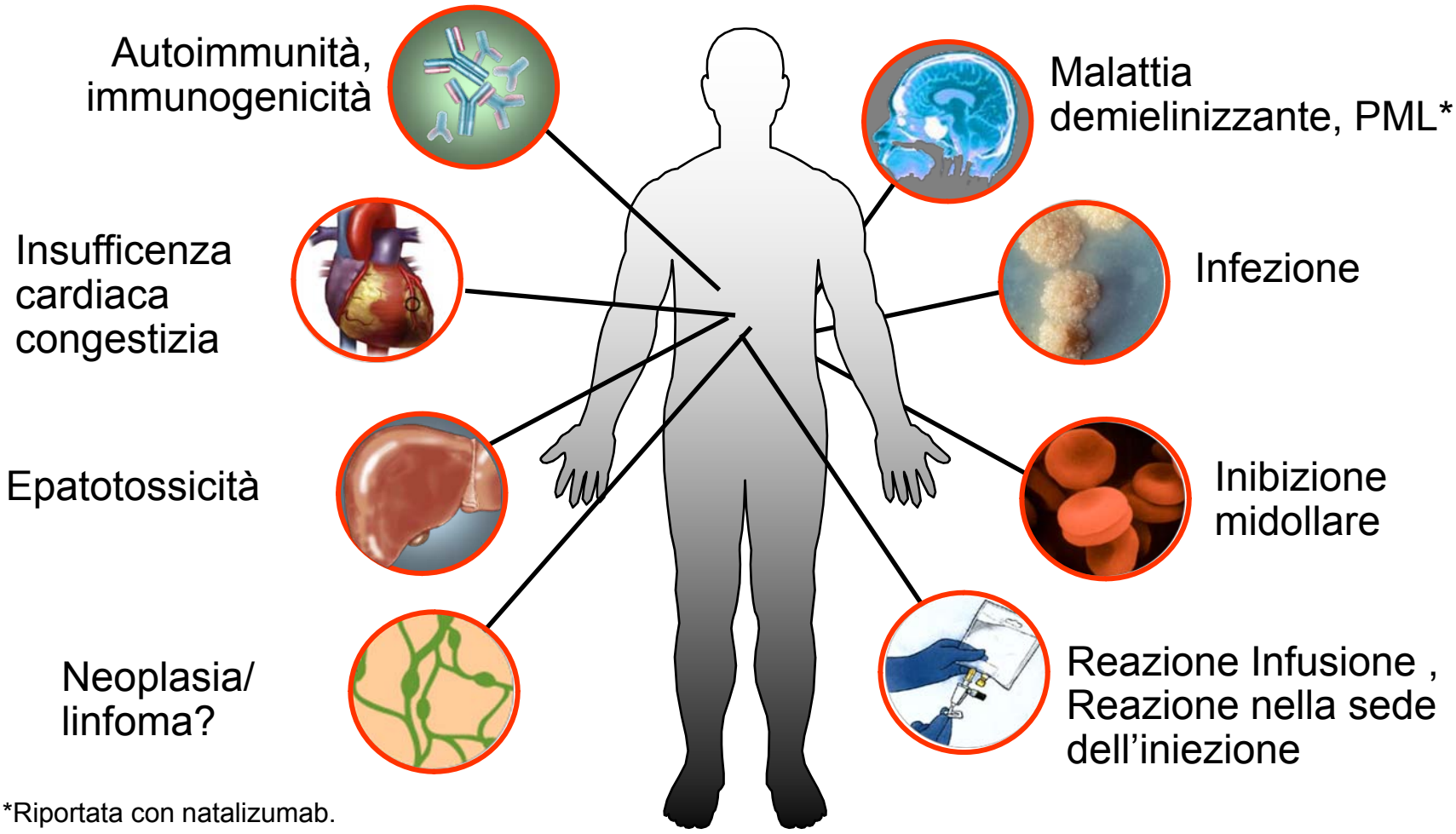
Etanercept: Non Risposta Clinica



Risposta Clinica =CDAI <150.

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

Effetti Avversi dei Biologici

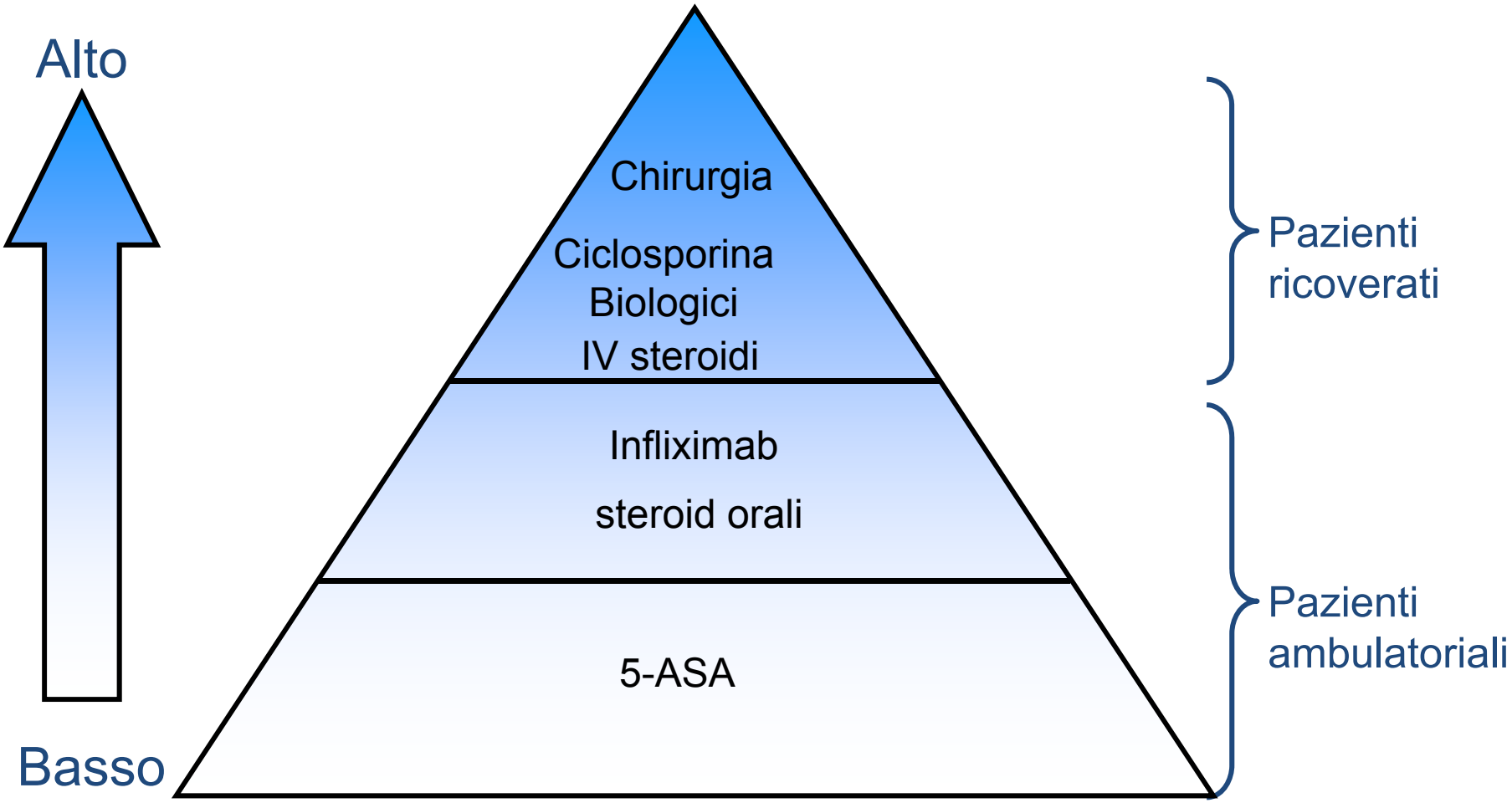


*Riportata con natalizumab.

PML, progressive multifocal leukoencephalopathy

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

Terapia Tradizionale



Kornbluth A, Sachar D. *Am J Gastroenterol.* 2004;99:1371.
Hanauer SB. *Aliment Pharmacol Ther.* 2008;27 (Suppl 1):15.

Invertire la Piramide?