Targeting cytokines in Inflammatory Bowel Diseases

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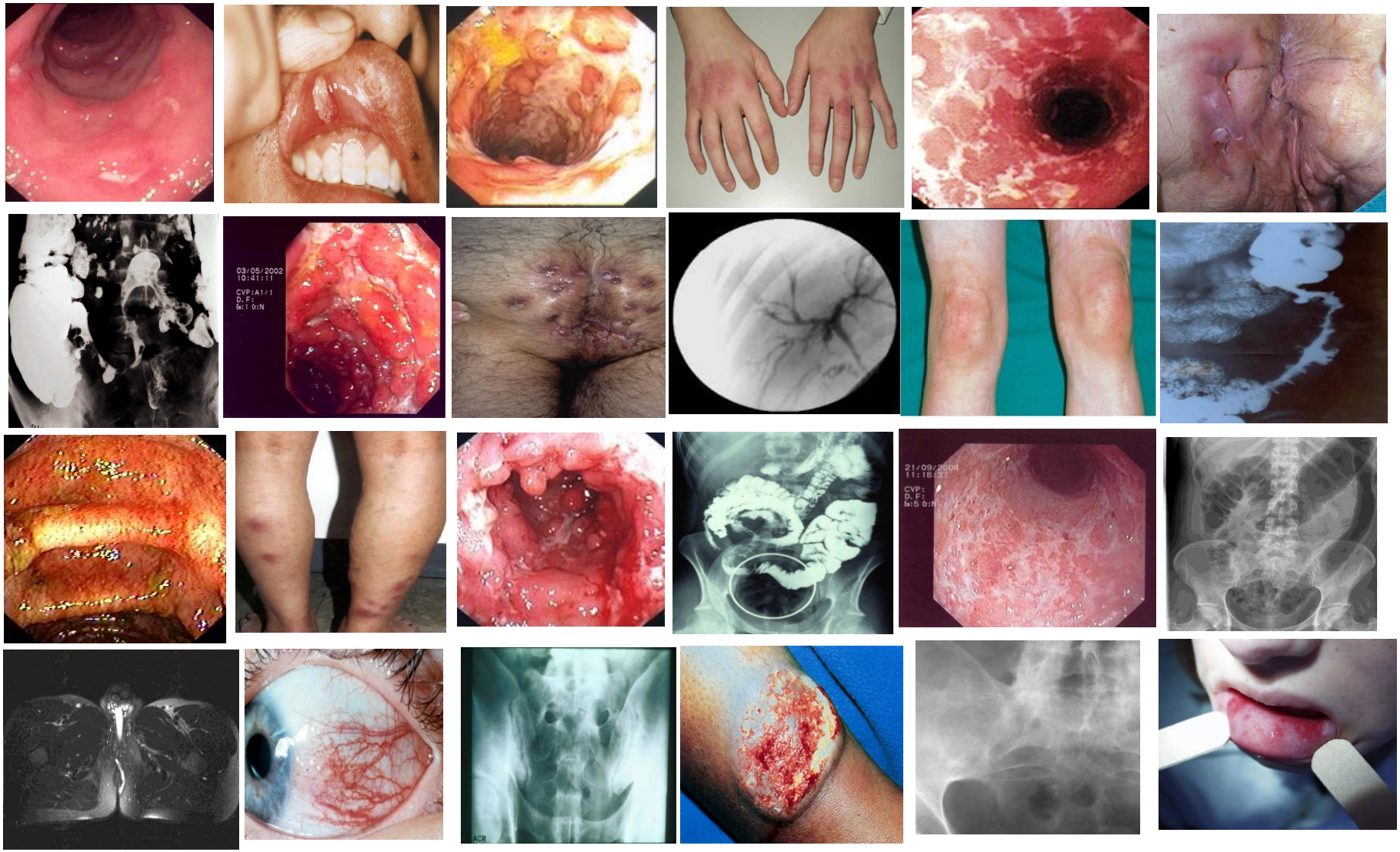
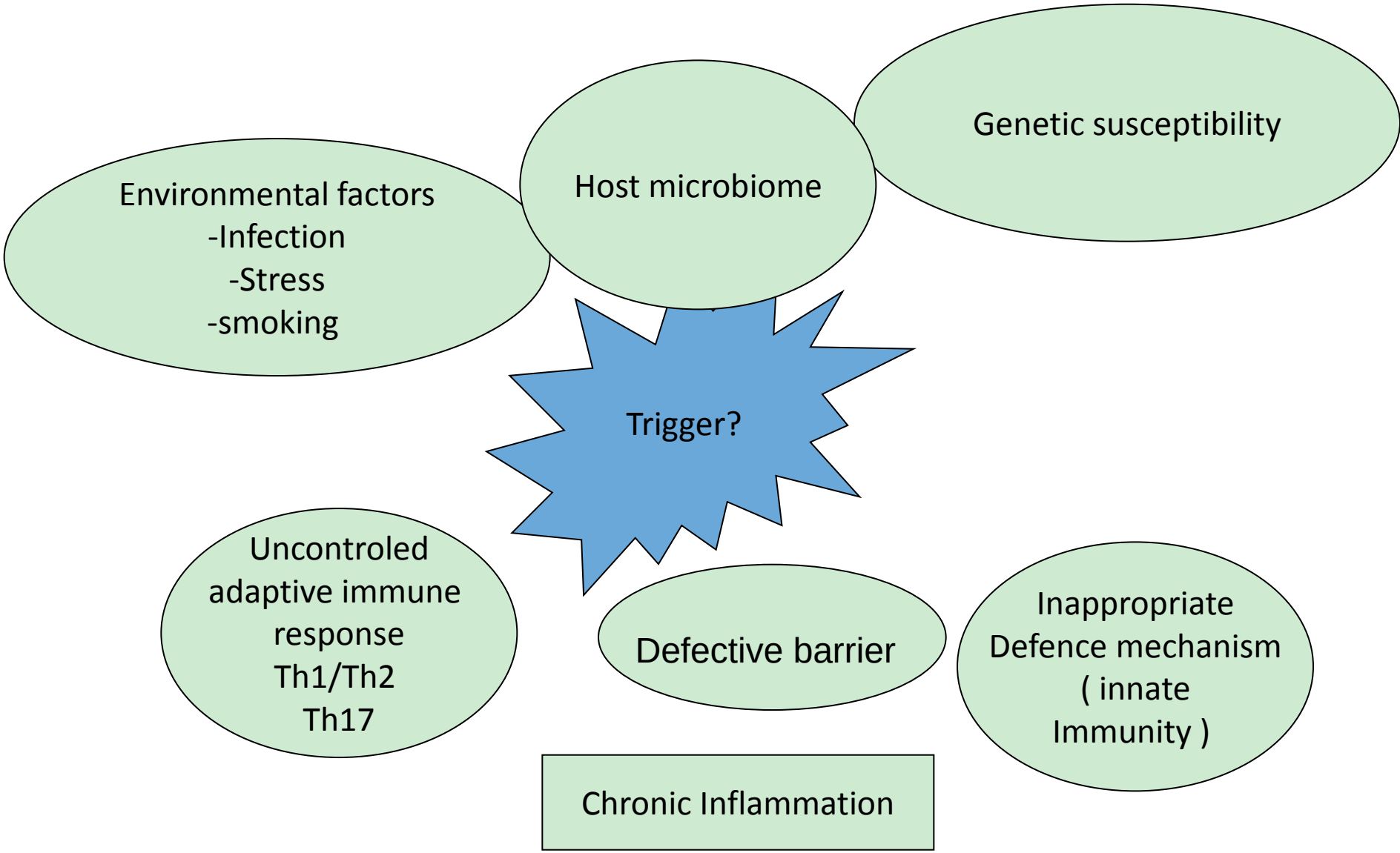
ULB Brussels Nov 10, 2015

The spectrum of IBD…

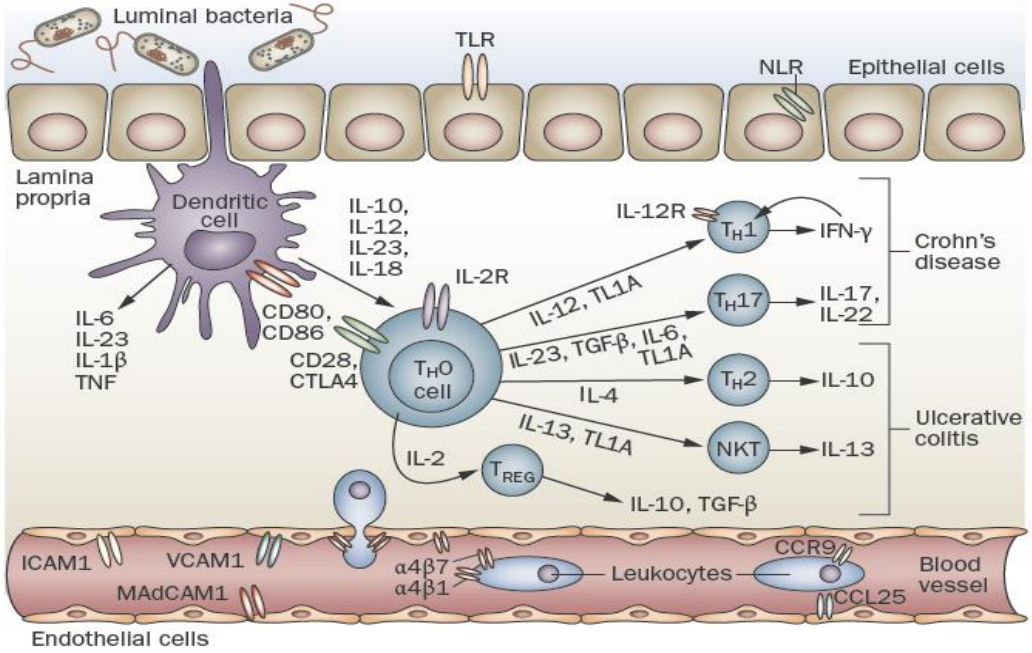


Etio-pathogenesis of Inflammatory Bowel Diseases



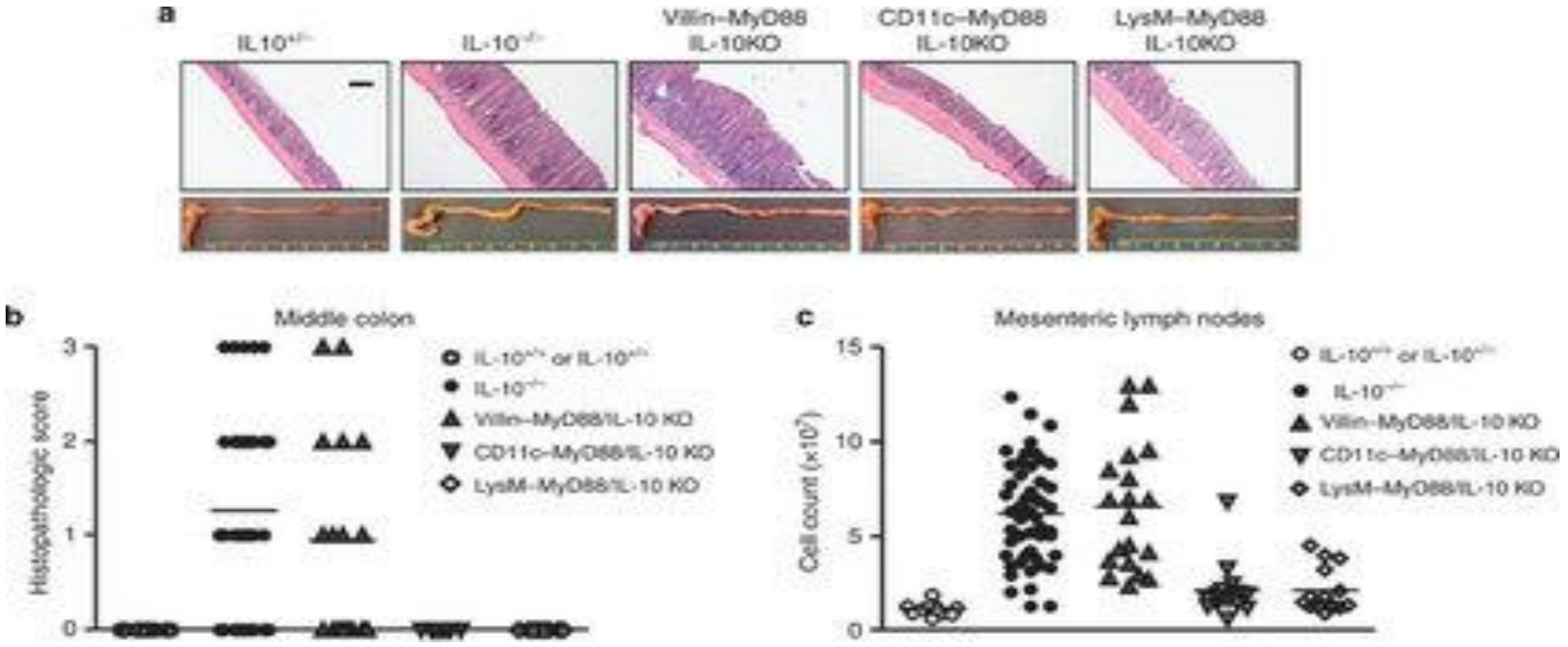
Targeting Cytokines in IBD

- Recombinant human cytokines: rhIL-10, rhIL-11
- Selective blockade of a single cytokine: monoclonal antibodies to TNF, IL-12/23, IL-23, IL-6, IL-17
- Broad blockade of intracellular pathways: JAKs, Smad7
- Anti-migration strategies inhibiting pathways; targeting α4-,α4β7-,β7- integrins or MadCam-1



Melmed GY et al. Nat Rev Gastroenterol Hepatol 2010;7:110-7

Recombinant human interleukin 10 to treat IBD

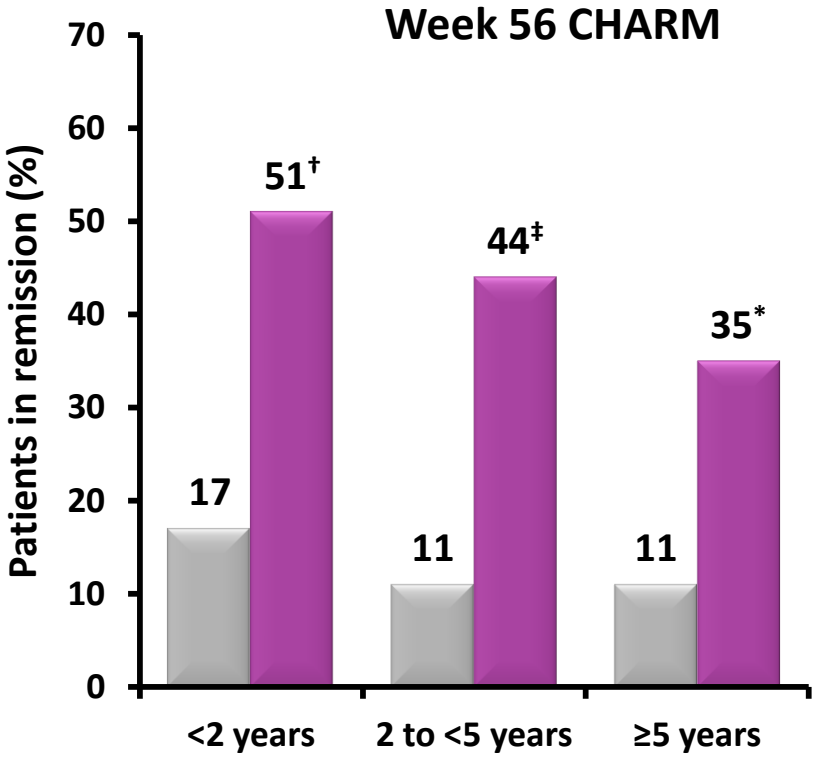


R Kühn, J Löhler, D Rennick, K Rajewsky, W Müller
Interleukin-10—deficient mice develop chronic enterocolitis
Cell, 75 (1993), pp. 263–274

Anti-TNF strategies in IBD: specifics

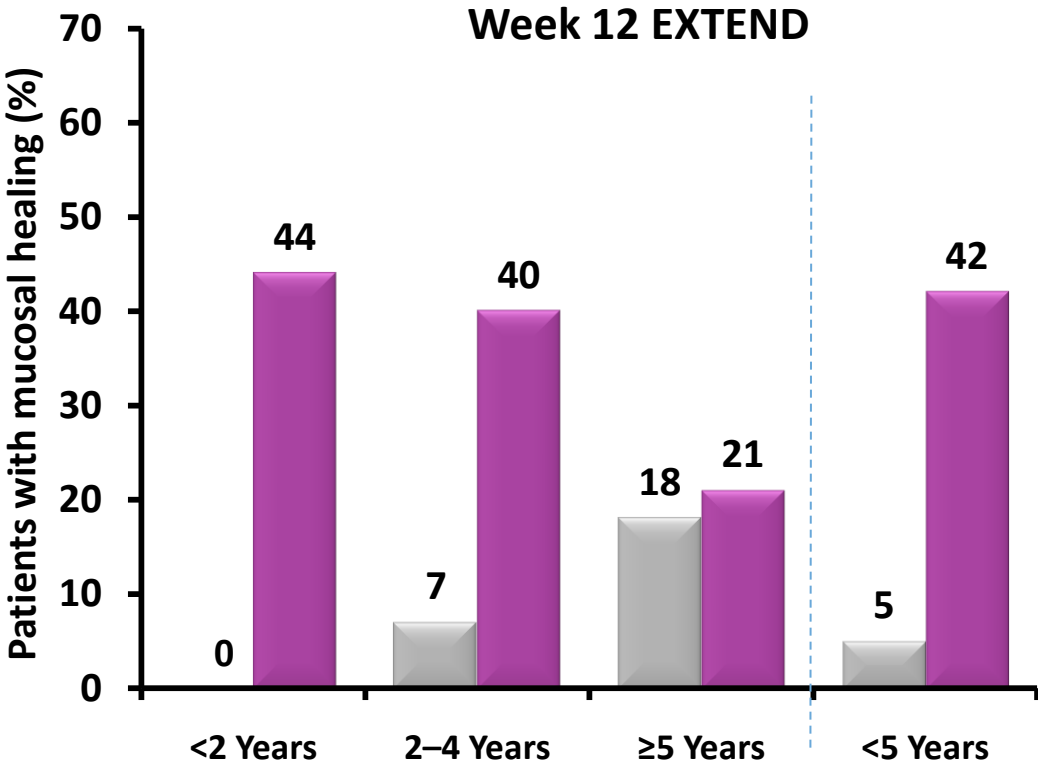
- Anti-TNF/azathioprine combination therapy is more effective than monotherapy
- Mucosal healing is the main treatment goal: treat-to-target (T2T)
- Early disease responds better to anti-TNF than late disease
- Antibodies to any anti-TNF agent are associated with treatment failure
- Drug exposure influences outcome. The importance of therapeutic drug monitoring (TDM)
- Patients who have been anti-TNF exposed respond less well to other biologicals

Early Crohn's disease shows high levels of remission and mucosal healing with adalimumab



*p<0.001; †p=0.014; ‡p=0.001; all vs placebo

<2 years: PBO n=23, HUMIRA n=39; 2 to <5 years: PBO n=36, HUMIRA n=57; ≥5 years: PBO n=111, HUMIRA n=233



NRI. N=123 patients with ulceration at baseline screening.
p=0.029 (Breslow-Day test) for the differential effect in patients with CD duration <5 years vs. ≥5 years

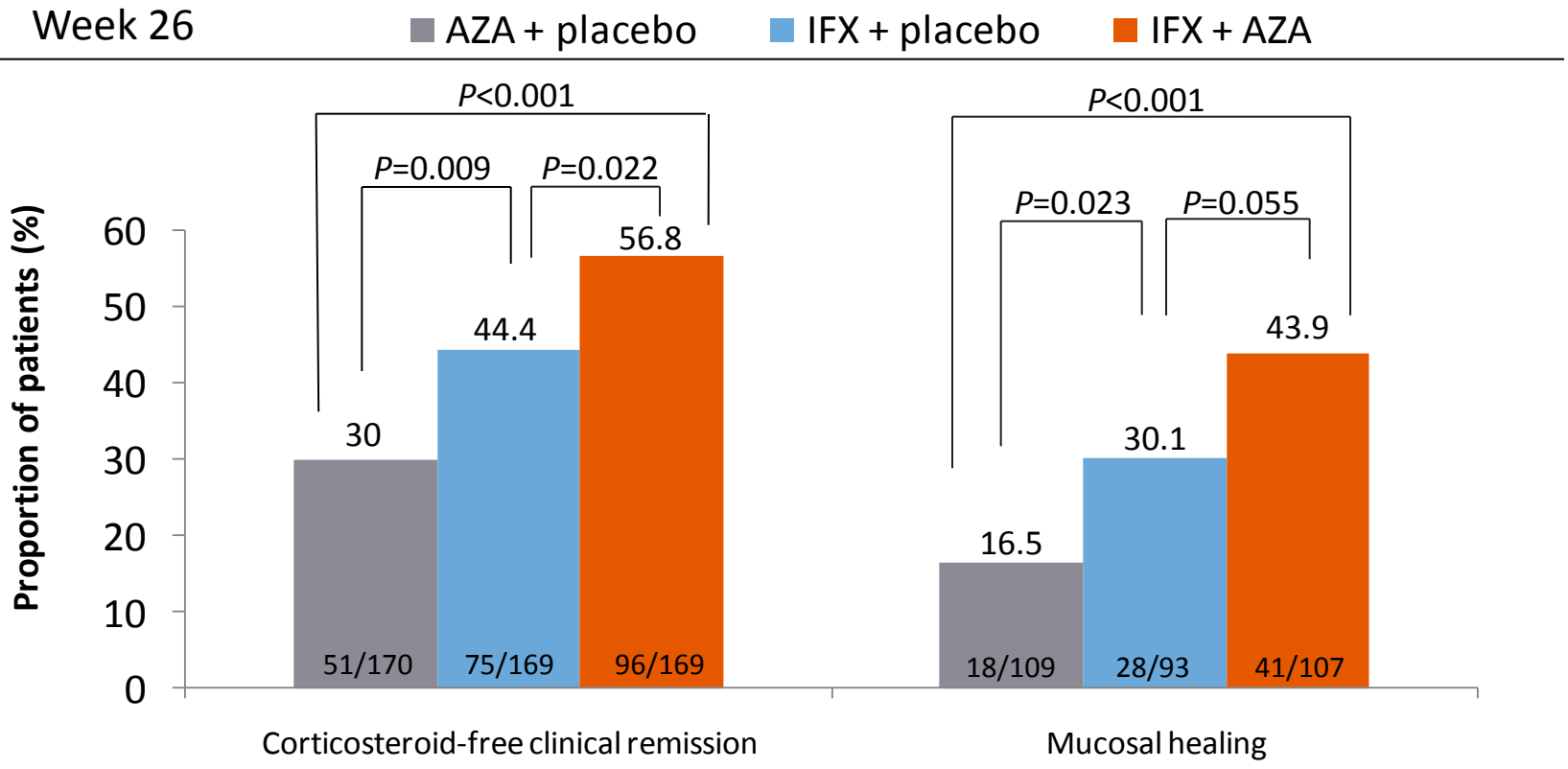
Schreiber S, *et al*. DDW 2007. #985

Sandborn WJ, et al. Gastroenterology 2010;138(Suppl 1):S-164. Poster at DDW 2010, New Orleans, USA;
Sandborn WJ, et al. J Crohns Colitis Suppl 2010;4:S36–S37. Poster P060 at ECCO 2010, Prague, Czech Republic.

Combination therapy in Crohn's disease results in improved mucosal healing and corticosteroid-free clinical remission compared to monotherapy

IBD Leuven

Sonic Study

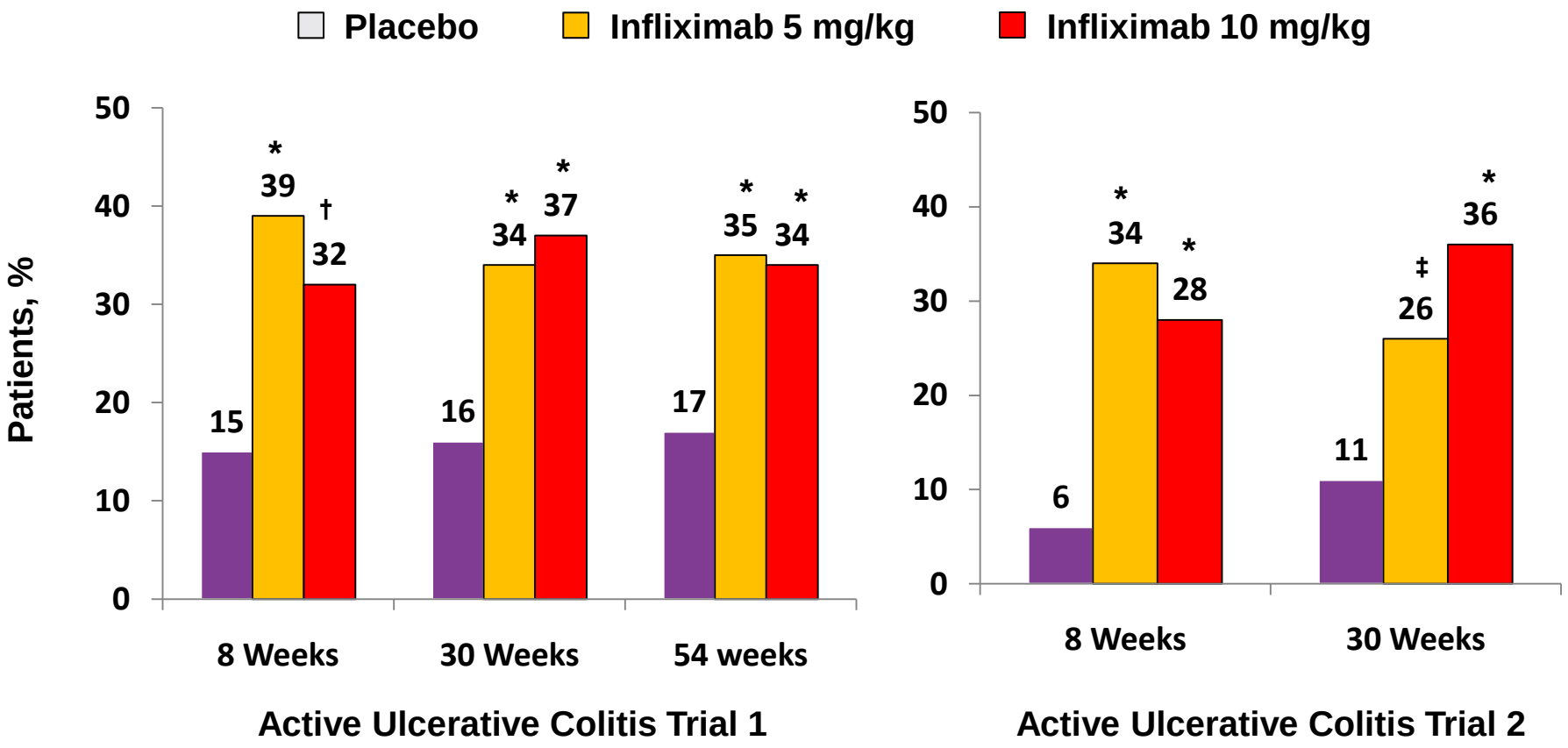


AZA: azathioprine; IFX: infliximab

Crohn's disease naïve to azathioprine and anti-TNF

Colombel JF et al. N Engl J Med 2010;362(15):1383-95

Infliximab for the Maintenance of Clinical Remission in Moderate-to-Severe Ulcerative Colitis

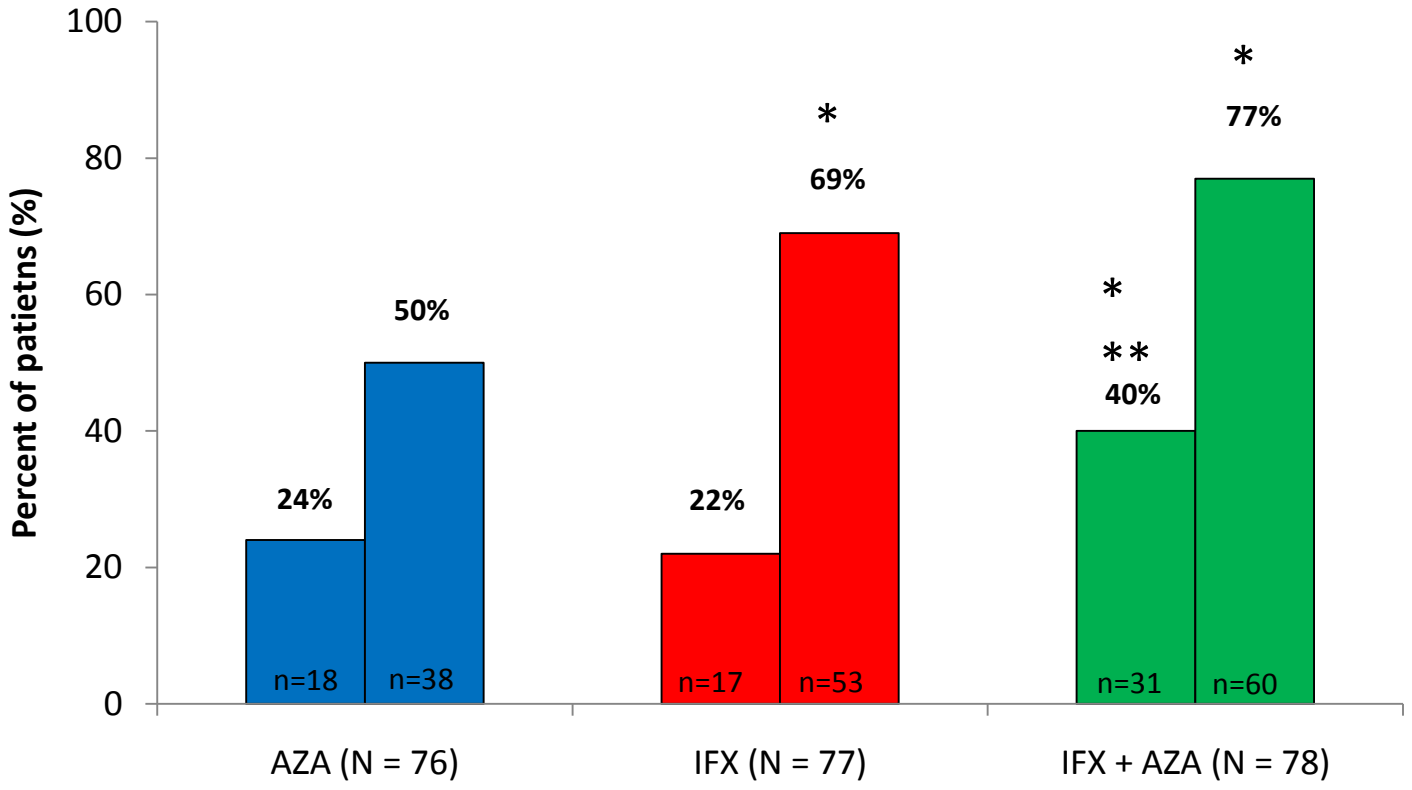


N = 364 patients in each randomized, double-blind, placebo-controlled studies.
*P <0.001; †P = 0.002; ‡P = 0.003; all comparisons vs placebo.

Rutgeerts P, et al. *N Engl J Med.* 2005;353:2462–2476.

Infliximab, Azathioprine, or Infliximab + Azathioprine for Moderate to Severe Ulcerative Colitis: UC SUCCESS Trial

Remission and response at week 16

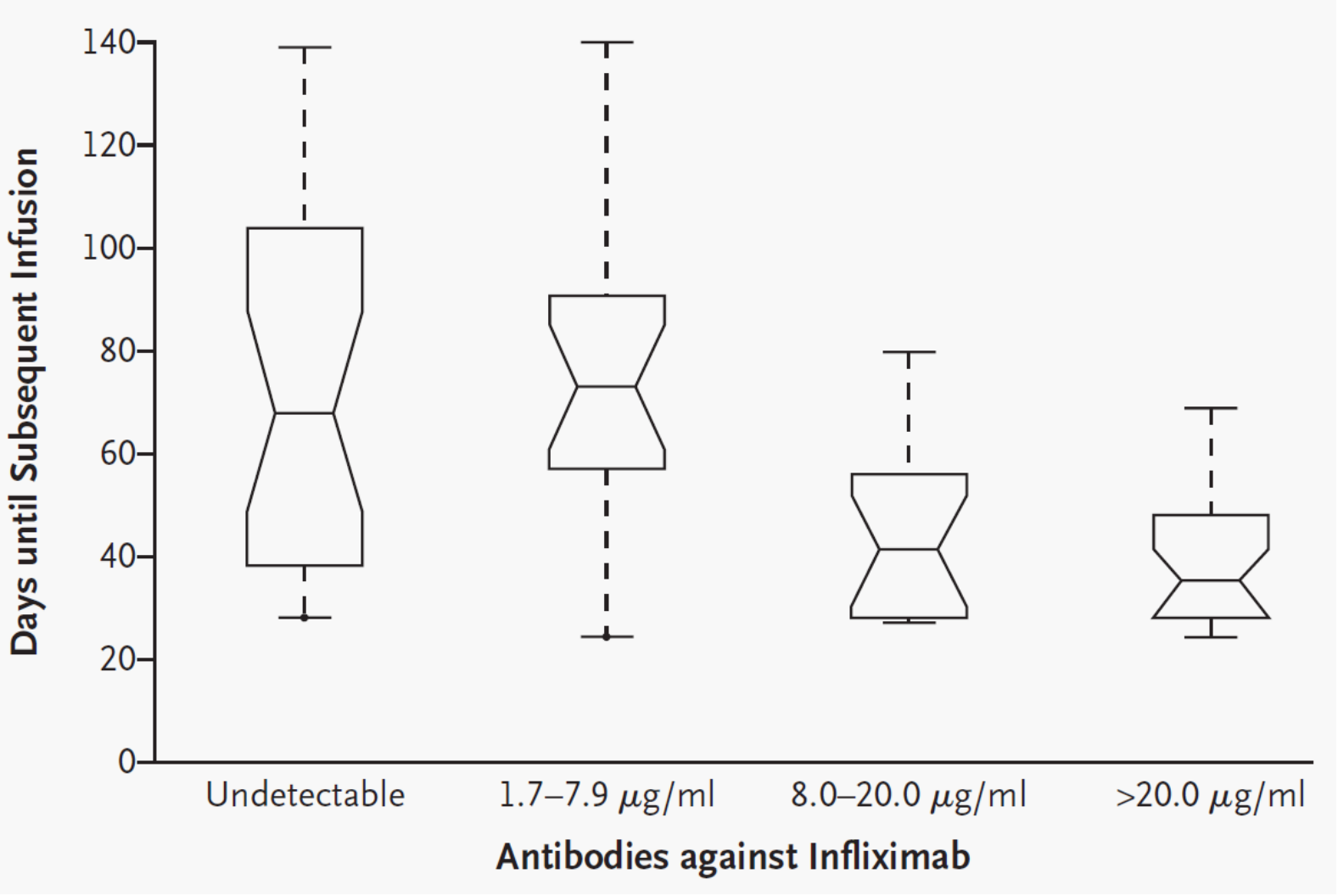


* vs AZA

** vs IFX

Panaccione R et al Gastroenterology. 2014 Feb;146(2):392-400

Duration of Response According to the Concentration of ATIs before an Infusion.

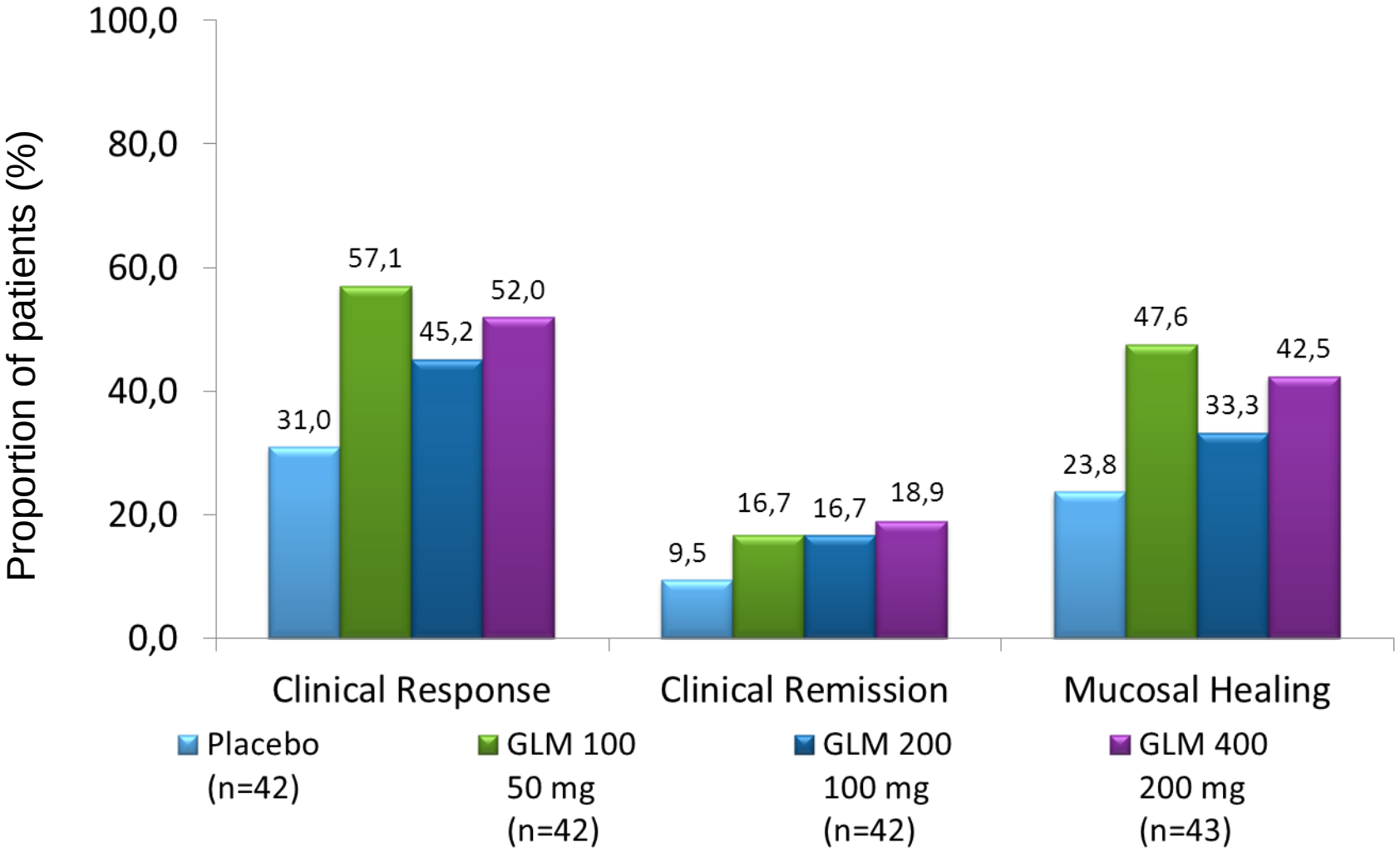


Baert F et al. N Engl J Med 2003;348:601-8

Drug Exposure : the critical factor determining efficacy of a biological agent

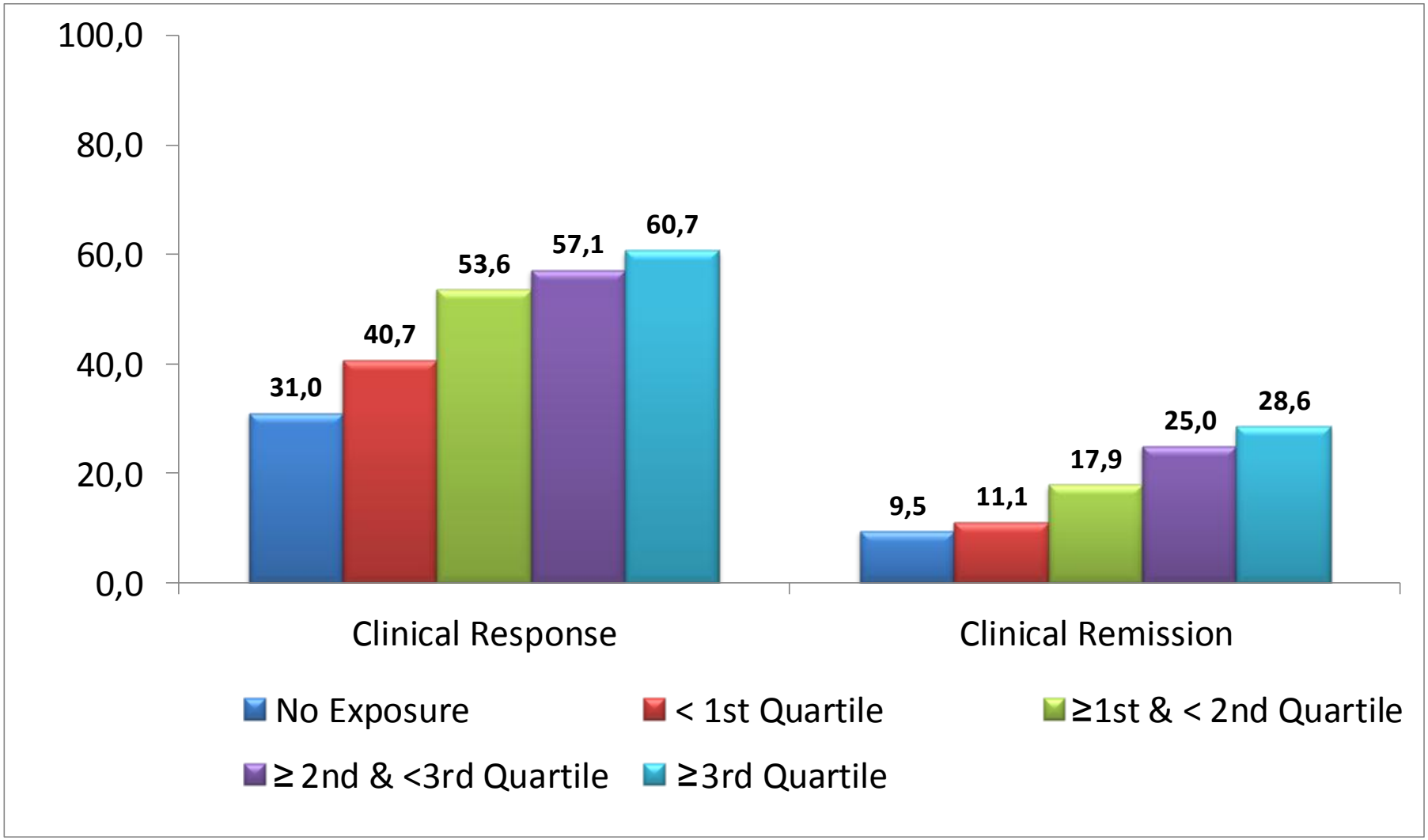
- Exposure: the amount of drug that the body has really ‘seen’. Area under the curve
- (Trough) levels determine exposure
- For small molecules there is a linear relationship between administered dose and exposure. This is not the case for biological agents
- Dose-response analyses need to be replaced by exposure-response studies

PUSUIT-SC Induction: Phase 2 Dose-Ranging of Golimumab: Clinical Endpoints at Week 6



Sandborn WJ et al Gastroenterology. 2014 Jan;146(1):96-109

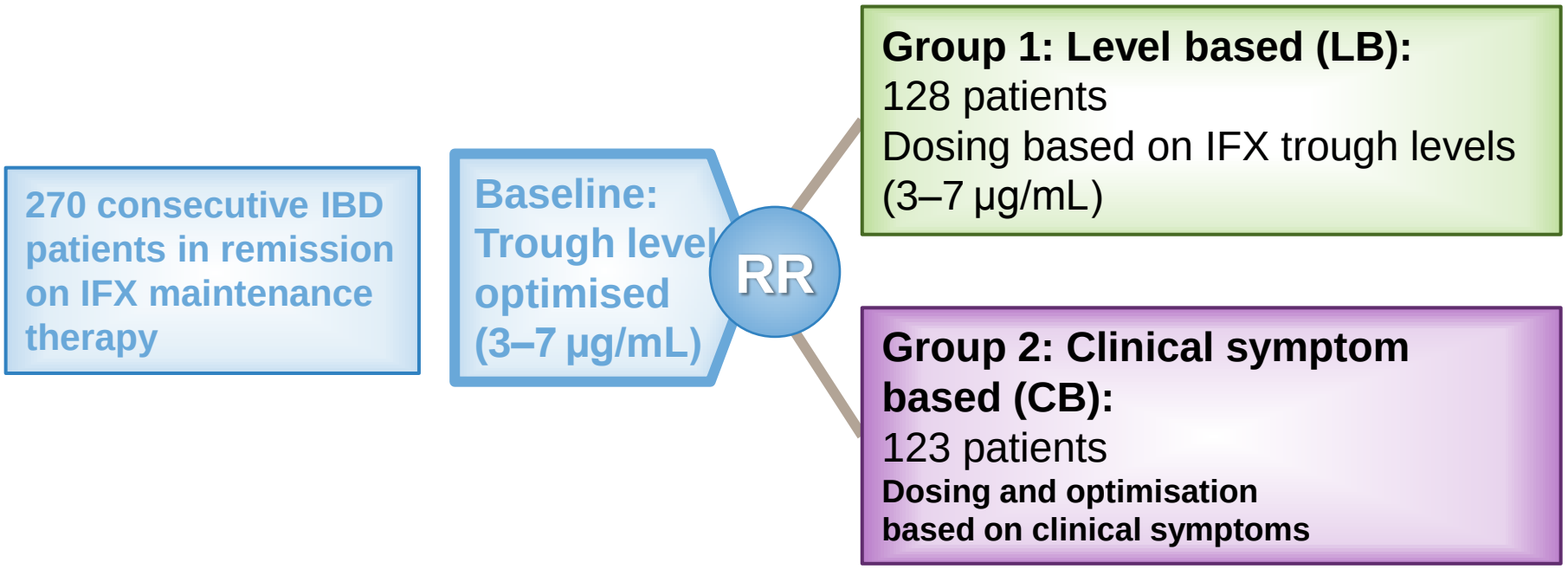
PURSUIT-SC Golimumab (Simponi)induction in anti-TNF naïve refractory UC: Phase 2 Dose- Ranging: Clinical Endpoints by Serum Golimumab Concentration Quartile at Week 6



Sandborn WJ et al Gastroenterology. 2014 Jan;146(1):96-109

TAXIT trial

Individualised infliximab treatment using therapeutic drug monitoring: A prospective controlled Trough level Adapted infliXImab Treatment trial



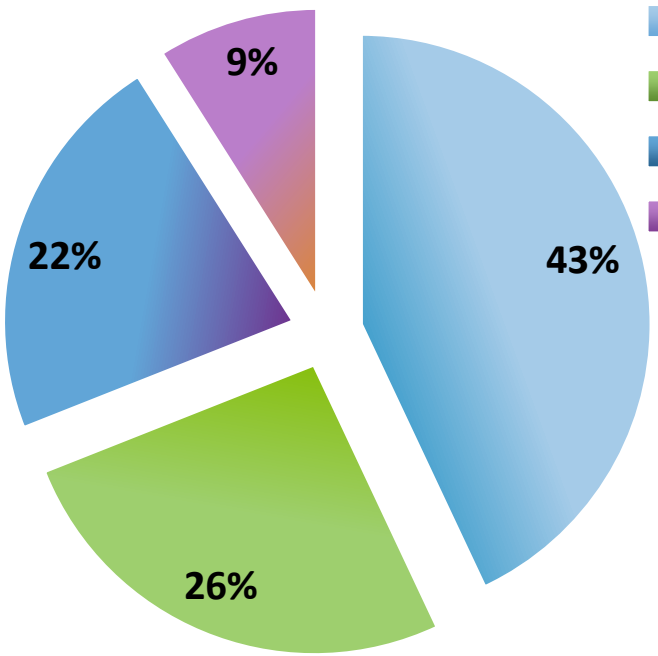
Primary endpoint:

clinical and biological (CRP <5 mg/L) **remission at one year**

Vande Casteele N, *et al*. Gastroenterology. 2015 Jun;148(7):1320-9.

TAXIT trial

Results of the optimisation phase.
Patients in clinical remission (n=260)



- IFX Trough 3–7 µg/mL
- IFX Trough >7 µg/mL
- IFX Trough <3 µg/mL
- IFX Trough undetectable

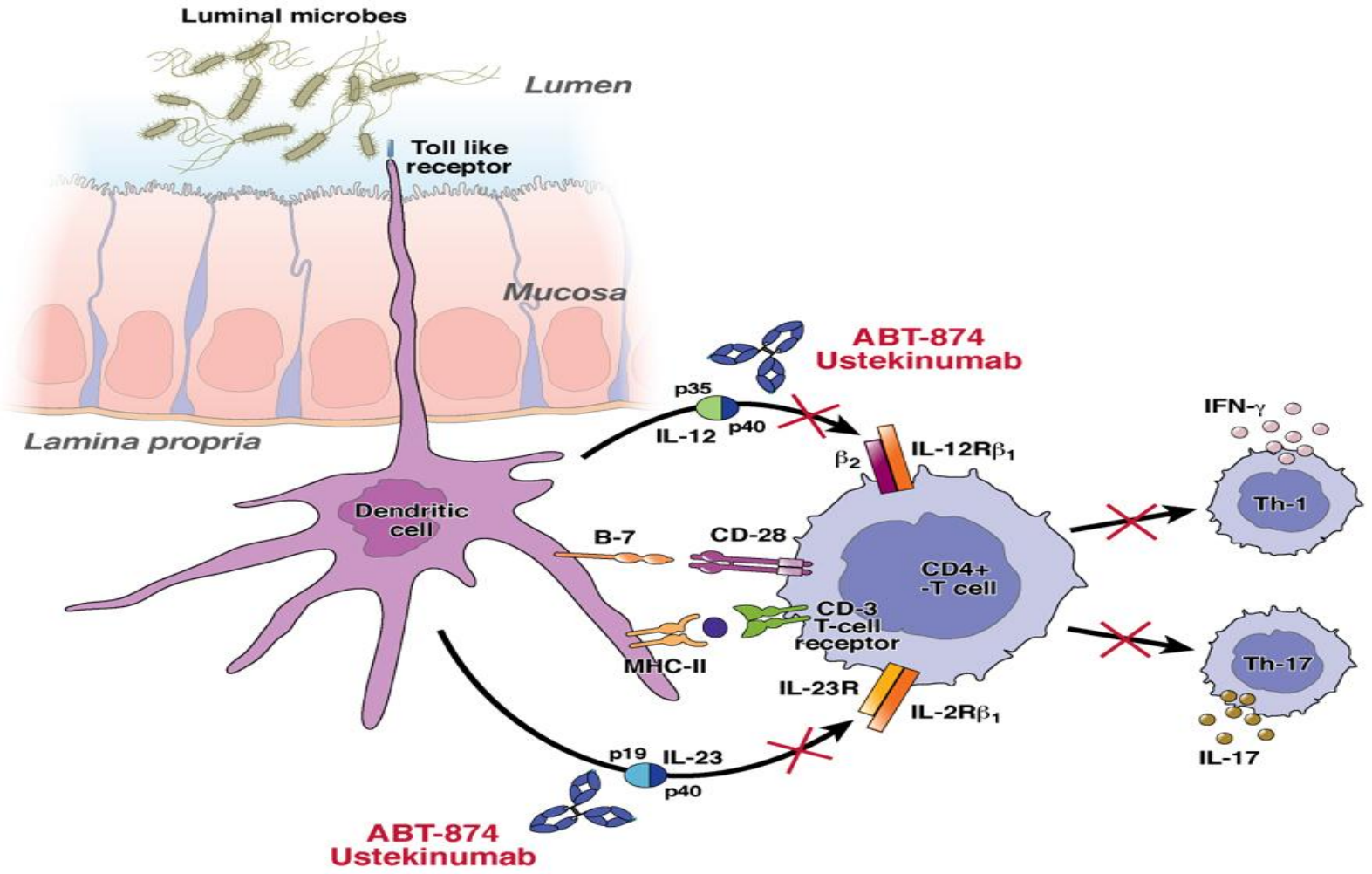
- Decrease the dose
- Increase the dose
- 77% of these had antibodies against IFX – Increase the dose

The other 23% were excluded from the study

Only 43% of patients in remission with maintenance IFX have optimal trough levels

Vande Casteele N, *et al*. Gastroenterology. 2015 Jun;148(7):1320-9.

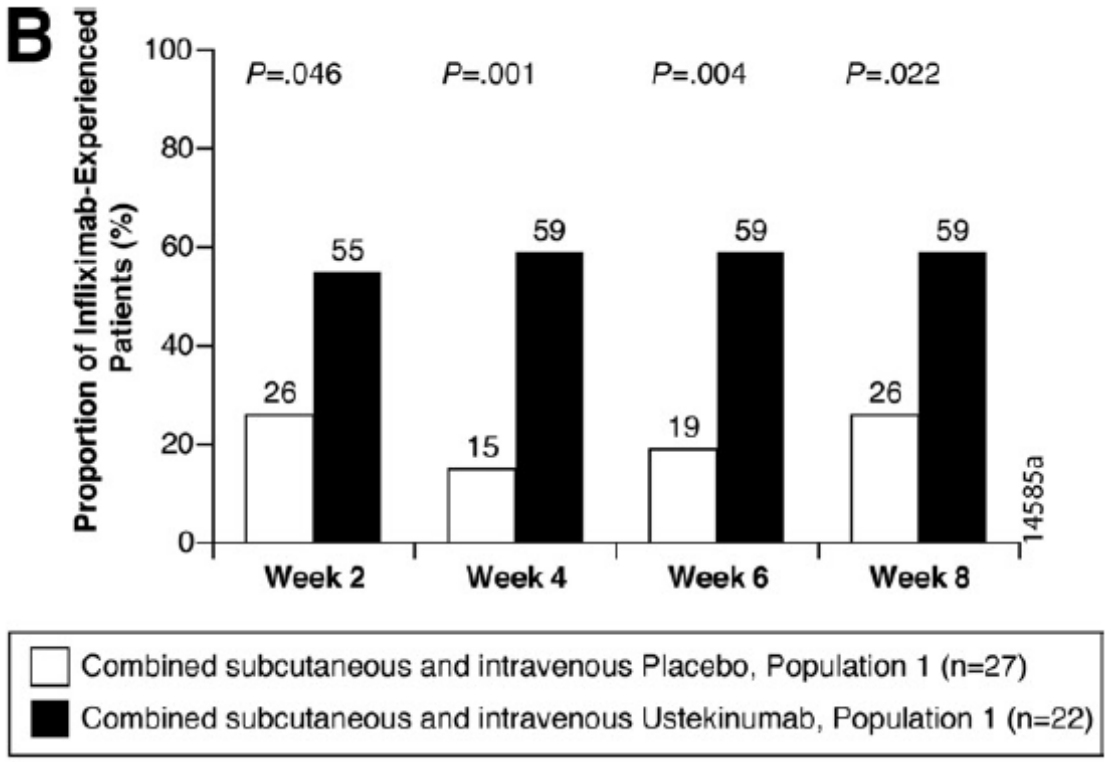
Inhibition of IL-12/23



Rutgeerts P, Vermeire S and Van Assche G; Gastroenterology 2009;136(4):1182-97

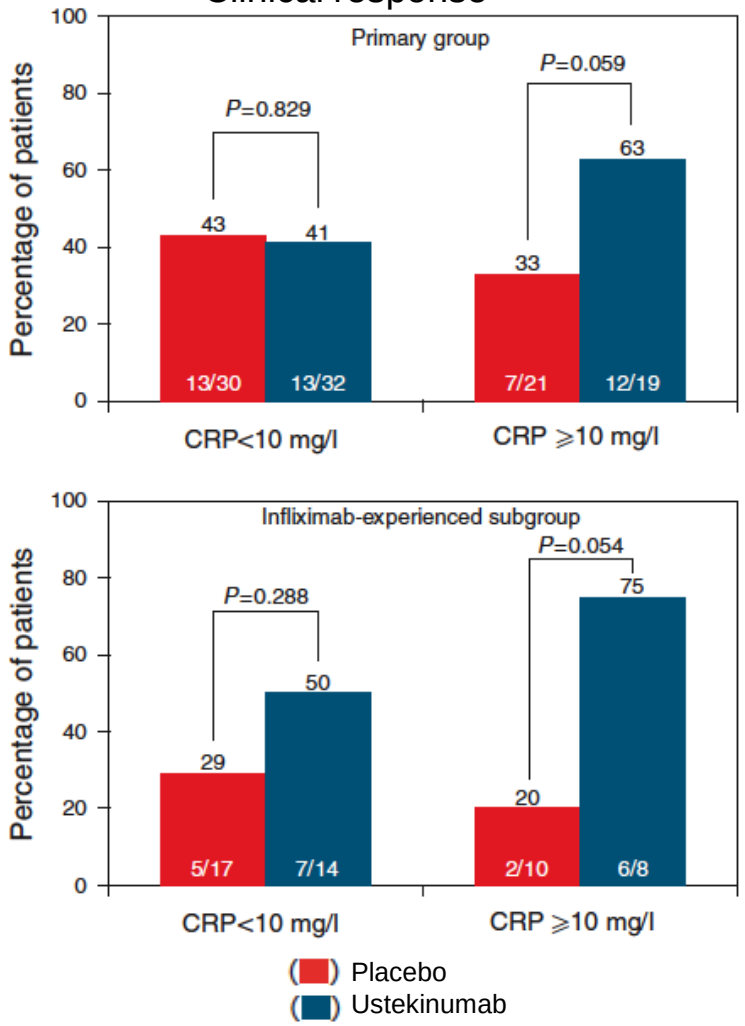
Ustekinumab Phase IIa in CD

Anti-TNF experienced and high CRP



Sandborn WJ et al Gastroenterology. 2008 Oct;135(4):1130-41

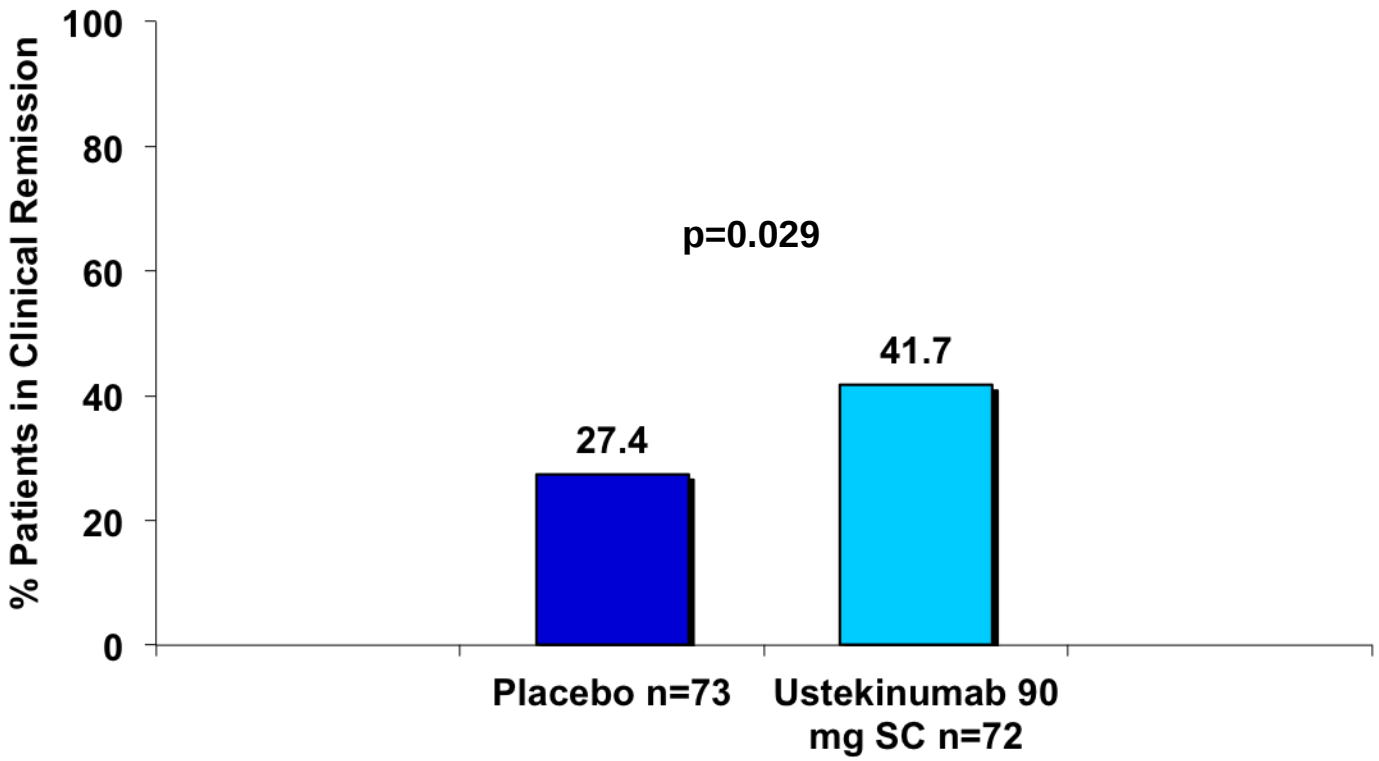
Clinical response



Toedter et al Am J Gastro 2009; 104:2768-2773b

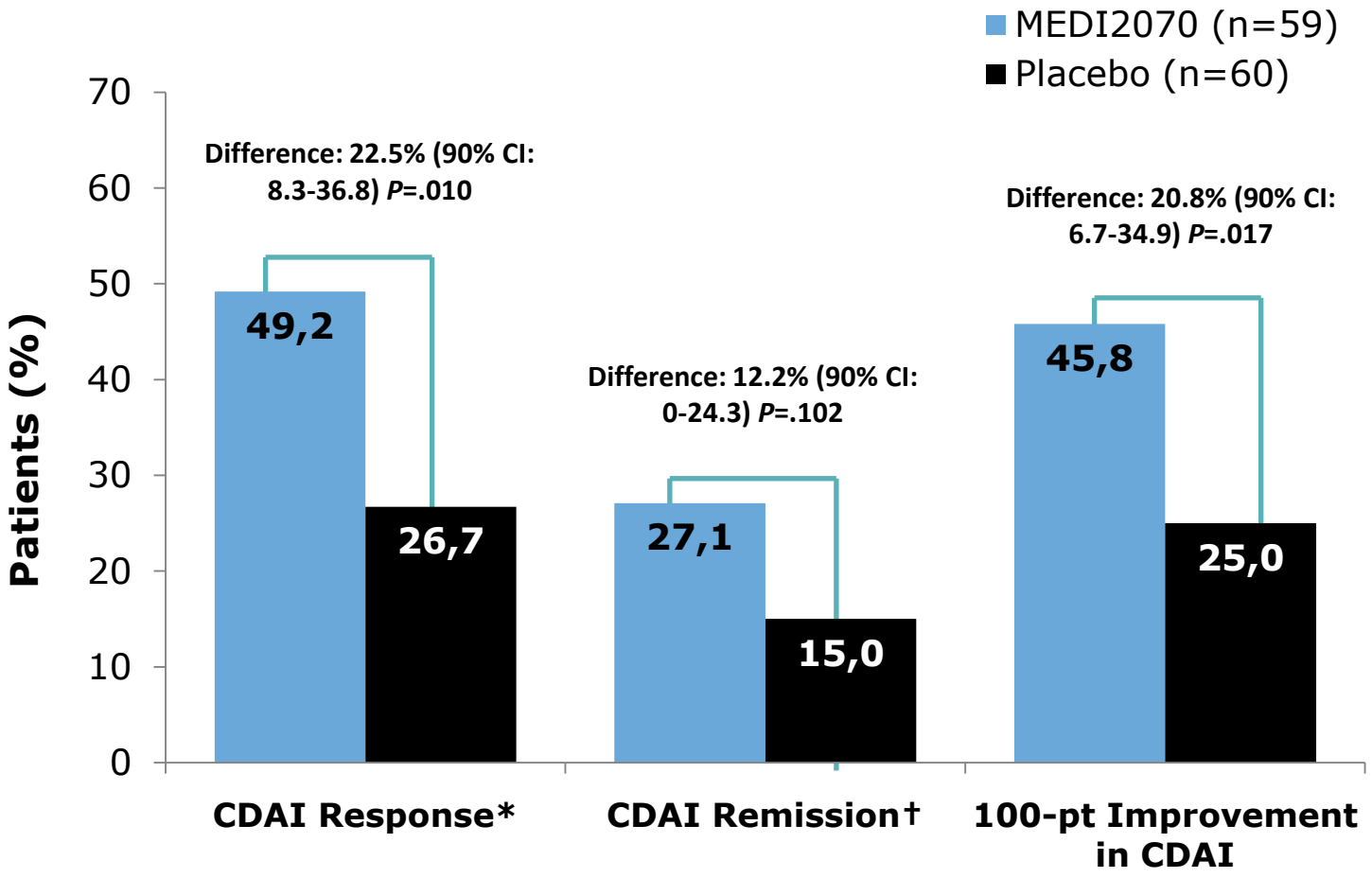
Ustekinumab Phase IIb (CERTIFI) in Infliximab experienced CD

Major Secondary endpoint: Clinical remission at Week 22
CDAI < 150



Sandborn WJ N Engl J Med. 2012 Oct 18;367(16):1519-28

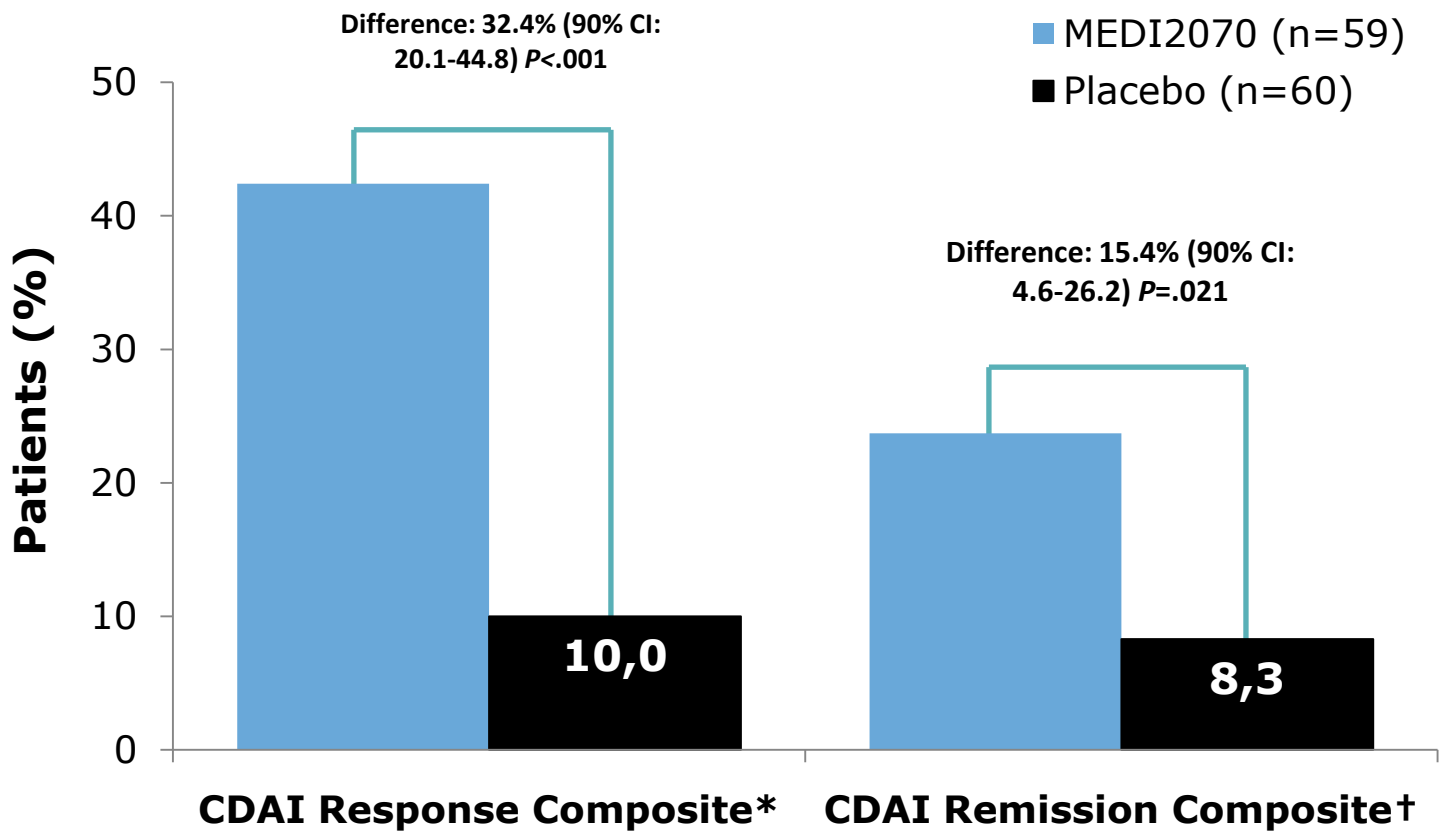
CD-IA-MEDI2070-1147 anti-IL-23 p19: Clinical Efficacy at Week 8 (mITT population)



*Defined as a CDAI score <150 or reduction from baseline in CDAI score of ≥100 points.
†Defined as a CDAI score <150.
Analyses were conducted via logistic regression (Ge, et al. 2011) at a significance level of α = 0.10.
CDAI, Crohn's Disease Activity Index; CI, confidence interval.

Sands B et al DDW 2015

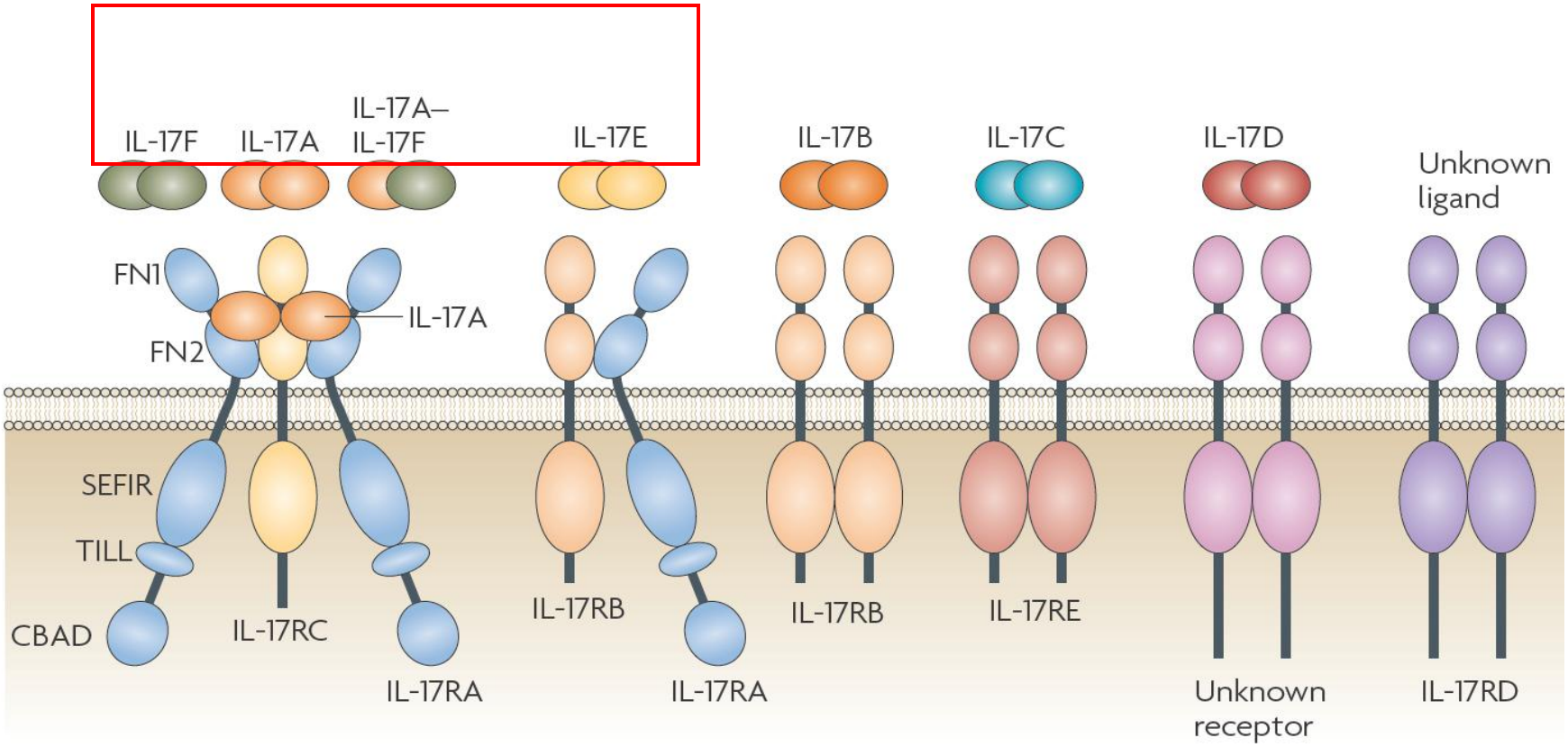
CD-IA-MEDI2070-1147 anti-IL-23 p19: Clinical Efficacy (composite Endpoints) at Week 8



*Defined as CDAI response and ≥50% reduction in FCP or CRP vs baseline.
†Defined as CDAI remission and ≥50% reduction in FCP or CRP vs baseline.
Analyses were conducted via logistic regression (Ge et al, 2011) at a significance level of α = 0.10.
CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; FCP, fecal calprotectin.

Sands B et al DDW 2015

IL-17 Ligand and Receptor Family Members



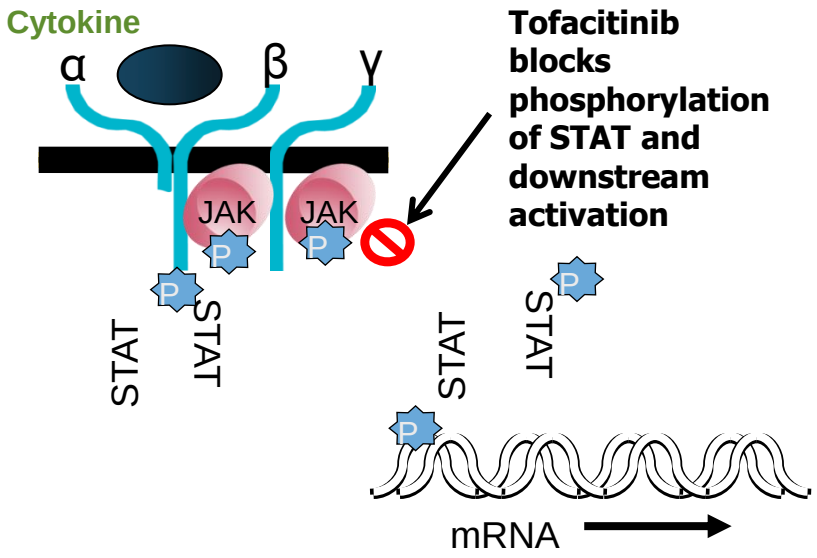
Gaffen, S., Nat Rev Immunol. 2009, 9(8):556-67.

Inhibition of IL-17A using Secukinumab in Crohn's disease: a double blind placebo controlled trial

	Secukinumab 10 mg/kg IV at week 0 and 3	Placebo
CDAI 100 response at week 6	7/39 (18%)	6/20 (30%)
Remission at week 6	4/39 (10%)	3/20 (15%)
Infections	17/39 (43%)	0/20 (0%)

Hueber W et al Gut. 2012 Dec;61(12):1693-700

Cytokine Signaling of Janus Kinase (JAK)

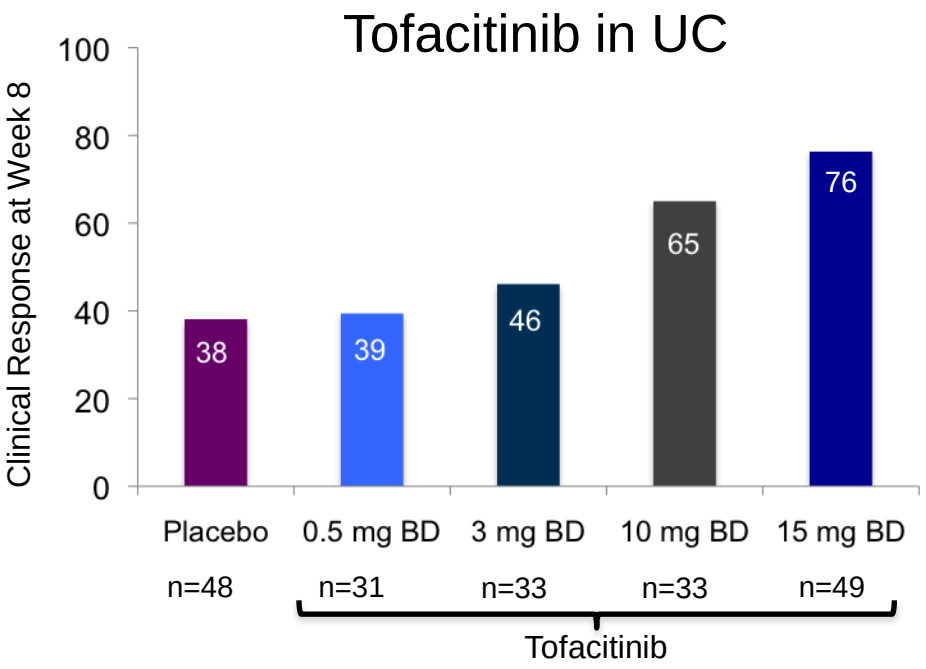


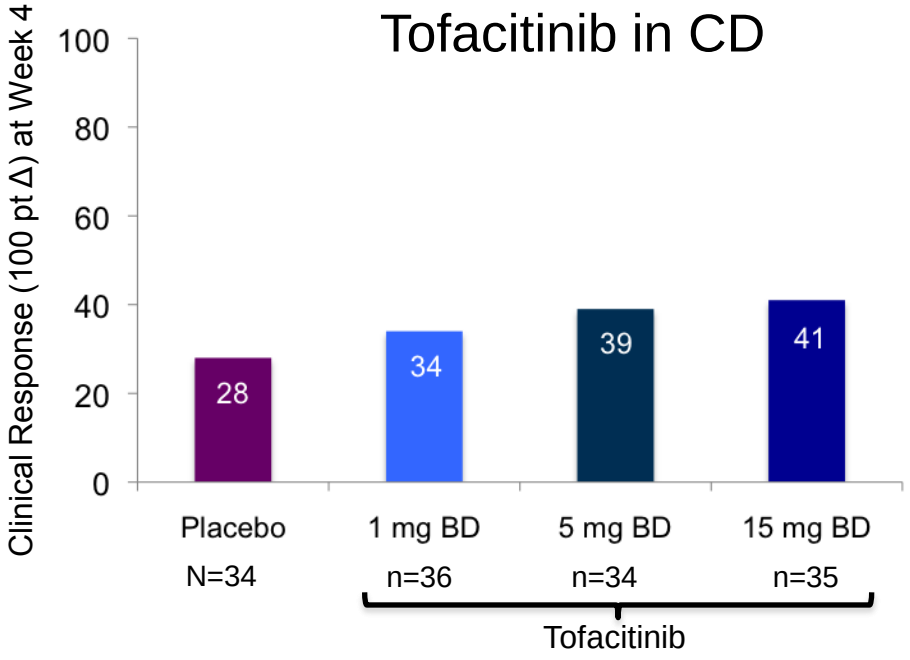
IL-2	Stimulate the proliferation and differentiation of Th, Tc, B, and NK cells
IL-4	Induce the differentiation of Th0 to Th2 Induce Ig switching
IL-7	Promote the development, proliferation and survival of T, B, and NK cells
IL-9	Stimulate intrathymic T cell development
IL-15	Promote the proliferation, cytotoxicity and cytokine production of NK cells
IL-21	Enhance T and B cell function

- Tofacitinib (CP-690,550) inhibits JAK1, JAK2, and JAK3 in vitro with functional cellular specificity for JAK1 and JAK3 over JAK2. Tofacitinib directly or indirectly modulates signaling for an important subset of pro-inflammatory cytokines including IL-2, -4, -7, -9, -15, and -21

Ig, immunoglobulin; IL, interleukin; JAK, Janus kinase; NK, natural killer; STAT, signal transducer and activator of transcription; Th, T helper; Tc , cytotoxic T cell

Biological treatments are not equally effective for CD and UC



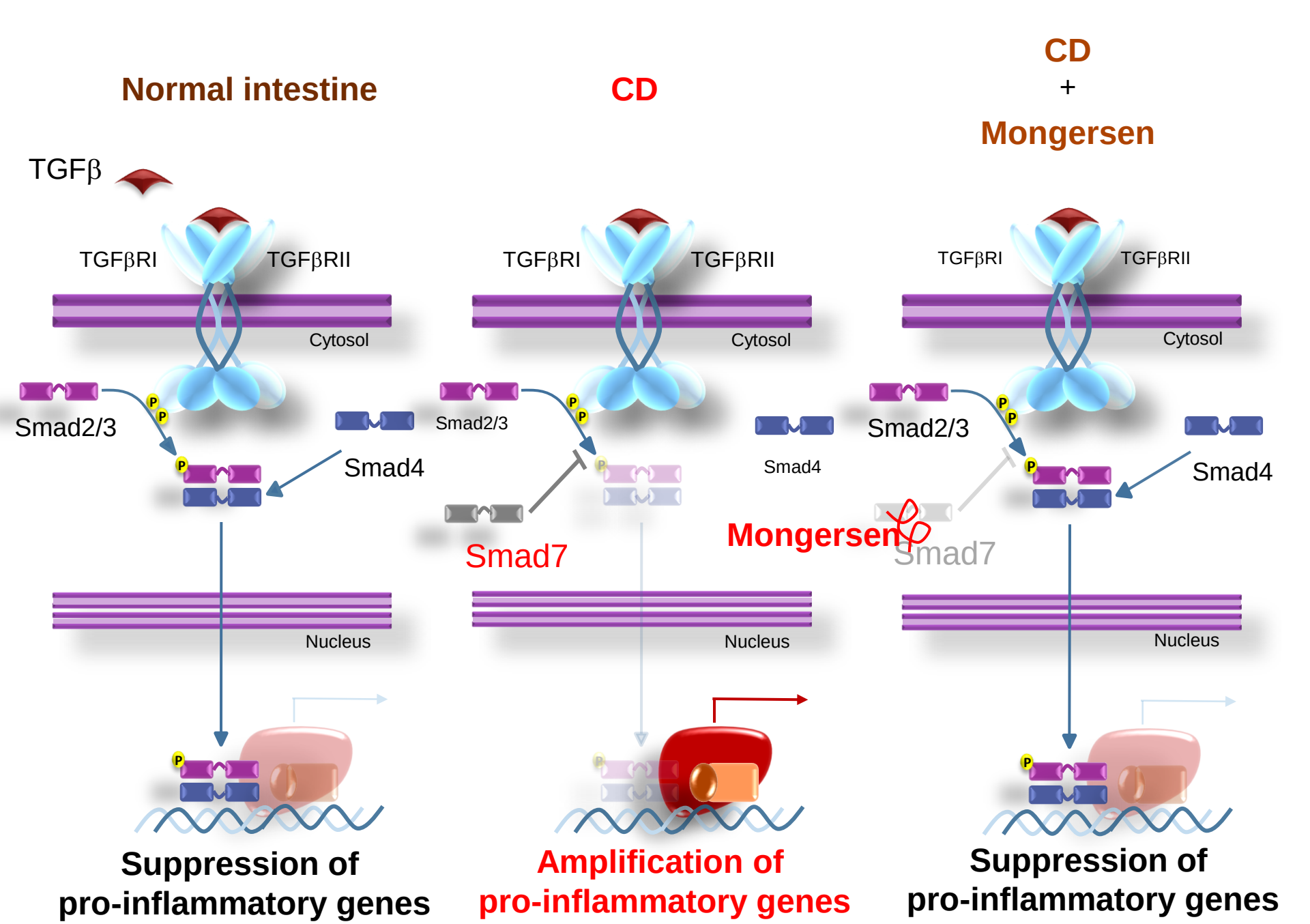


Patients, n (%) achieving	Placebo n=48	0.5 mg BD n=31	3 mg BD n=33	10 mg BD n=33	15 mg BD n=49
Clinical remission	5 (10.4)	4 (12.9)	11 (33.3)	16 (48.5)	20 (40.8)
Endoscopic remission	1 (2.1)	3 (9.7)	6 (18.2)	10 (30.3)	13 (28.5)

Patients, n (%) achieving	Placebo N=34	1 mg BD n=36	5 mg BD n=34	15 mg BD N=35
Clinical remission	7 (20.6)	11 (30.6)	8 (24.2)	5 (14.3)

Sandborn WJ et al N Engl J Med. 2012 Aug 16;367(7):616-24 ***Sandborn et al*** **Clin Gastroenterol Hepatol. 2014;;12(9):1485-93**

September 21, 2015 UC Octave studies http://www.pfizer.com/news/press-release



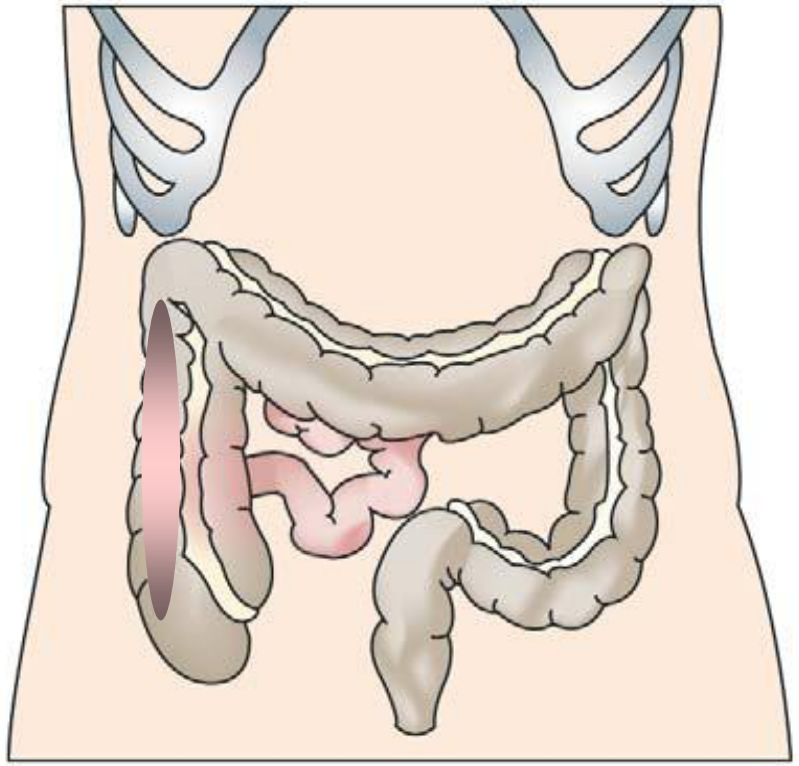
Marafini I et al Curr Drug Targets 2013 Nov;14(12):1400-4

Mongersen: oral gastro-resistant delayed release formulation

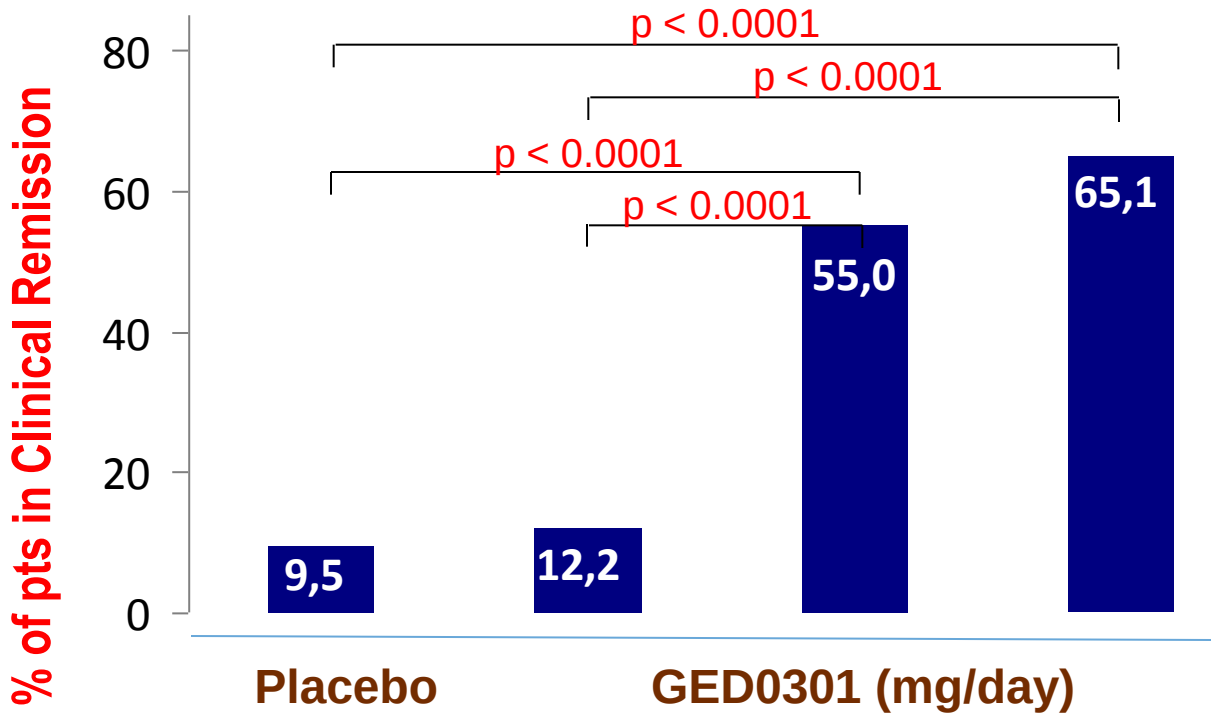
Mongersen developed as an oral gastro-resistant

Ph-dependent-release formulation to:

- **deliver Mongersen in the terminal ileum and right colon**
- **obtain a “topical” effect**
- **avoid systemic adsorption**



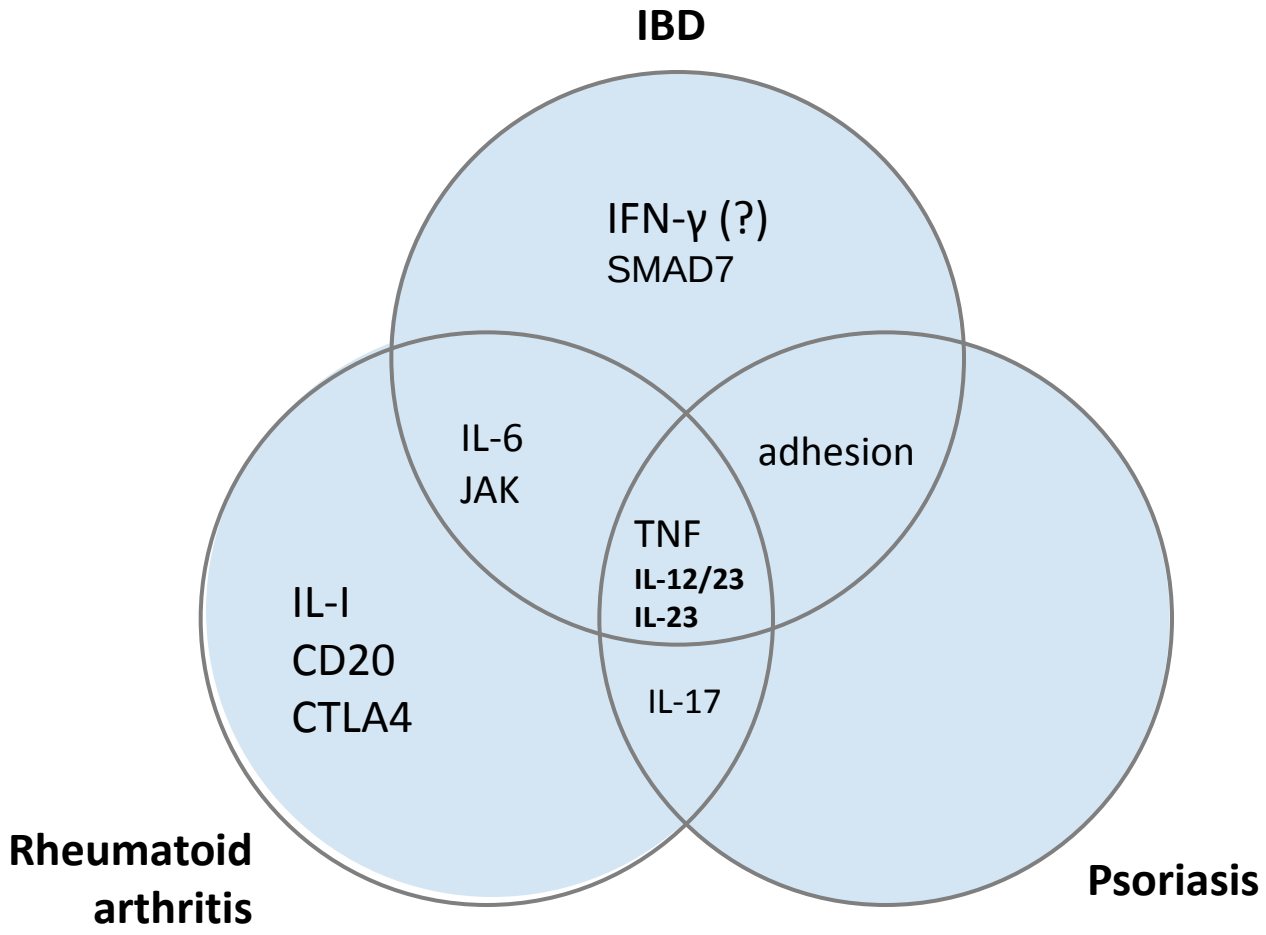
Induction of clinical remission (CDAI score <150 at day 14 and maintained at day 28)



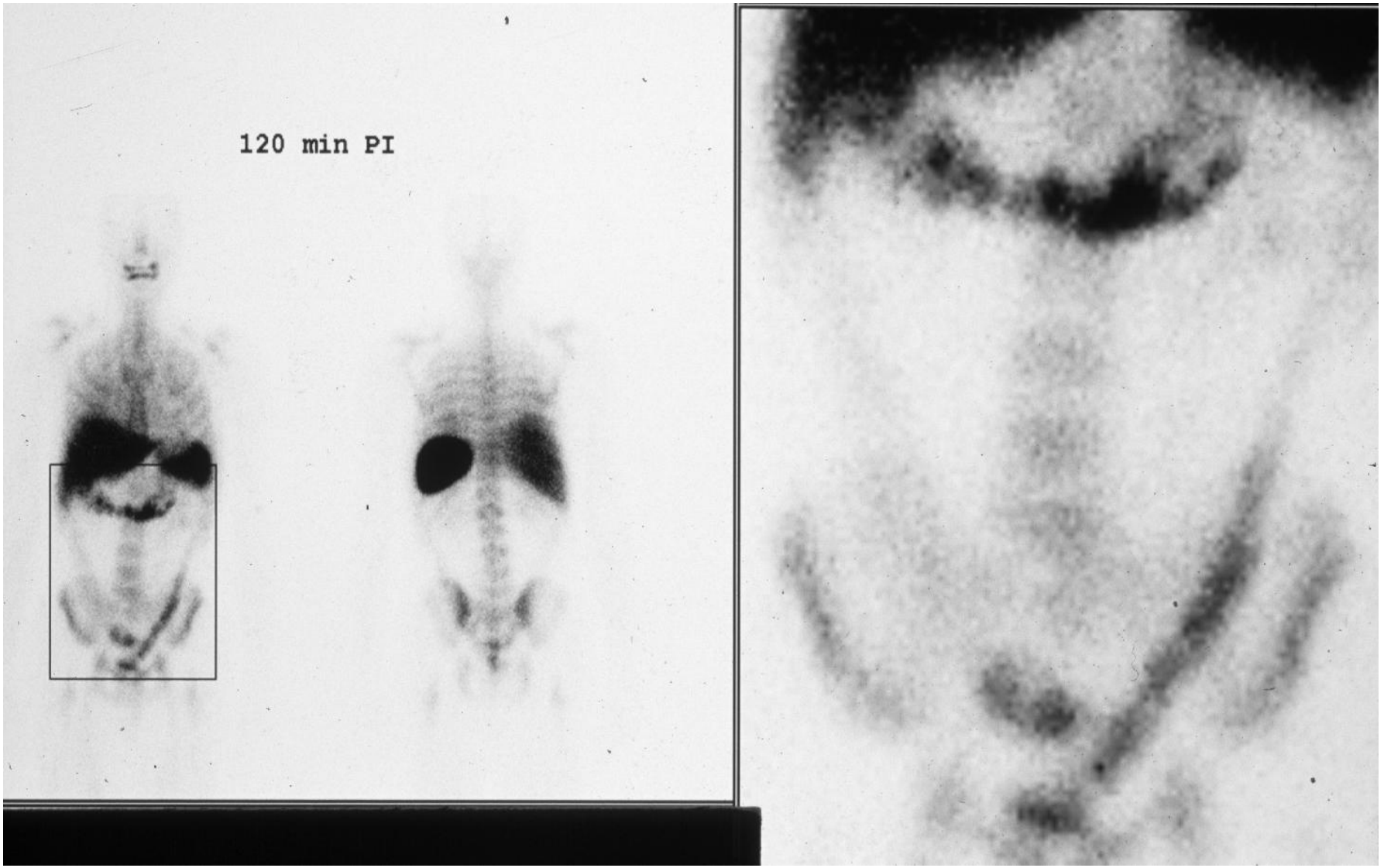
No. Pts with:		10	40	160
CDAI > 150	38	36	18	15
CDAI < 150	4	5	22	28

Monteleone G et al N Engl J Med. 2015 Jun 18;372(25):2461

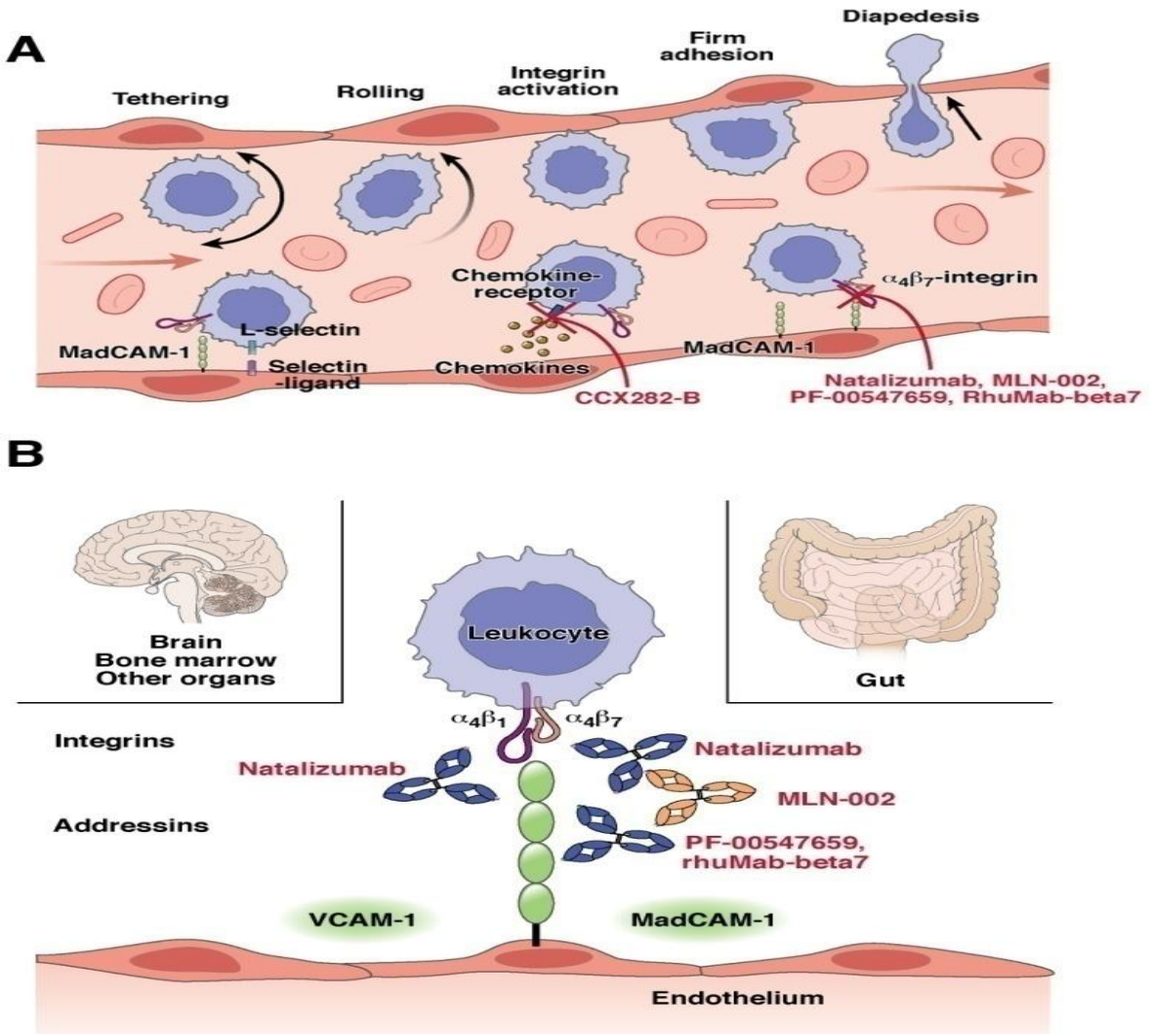
Biological therapies in immune-mediated diseases



Migration of Leucocytes plays a key role in gut inflammation in IBD



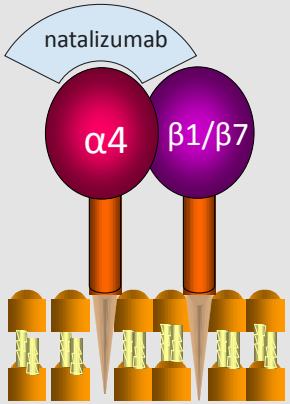
Selective Anti-Migration strategies (SAM) in IBD



Rutgeerts P et al. Gastroenterology 2009;136(4):1182-97

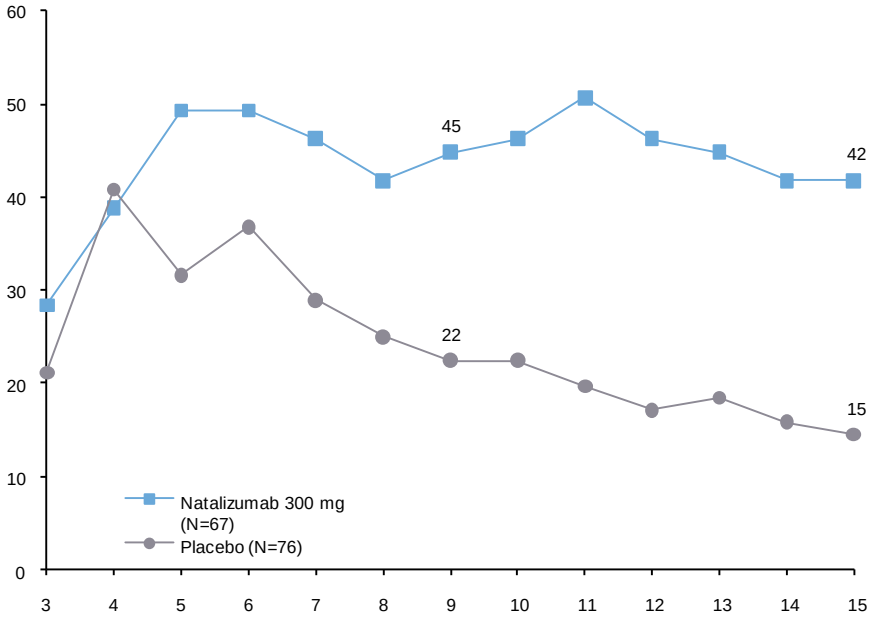
Anti-α4 (Natalizumab, Antegren, Tysabri) in the treatment of Crohn's disease

Tysabri



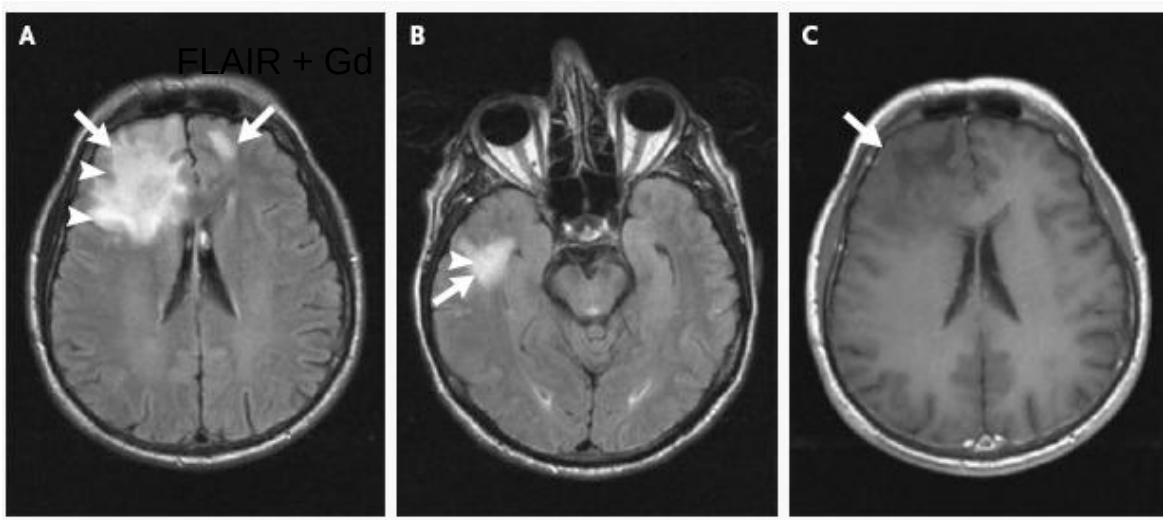
- Humanised mouse-derived monoclonal IgG4 antibody to human α4 integrin.
- Blocks adhesion of α4+ lymphocytes to VCAM1 and MAdCAM-1

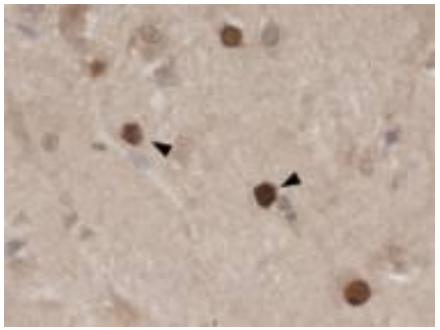
ENACT-2: Patients in sustained remission removed from concurrent steroids[1]

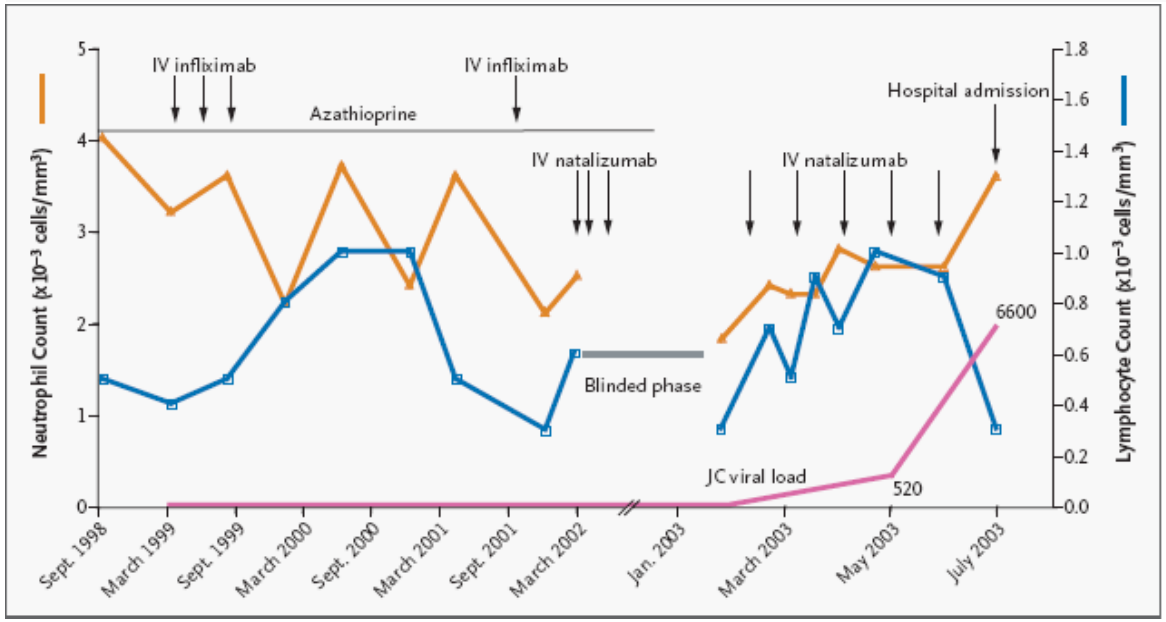


[1]Sandborn WJ et al. N Engl J Med 2005;353(18):1912-25

Progressive multifocal leukoencephalopathy in patients treated with Natalizumab







2 MS cases,
+ IFNα

1 CD case,
monotherapy

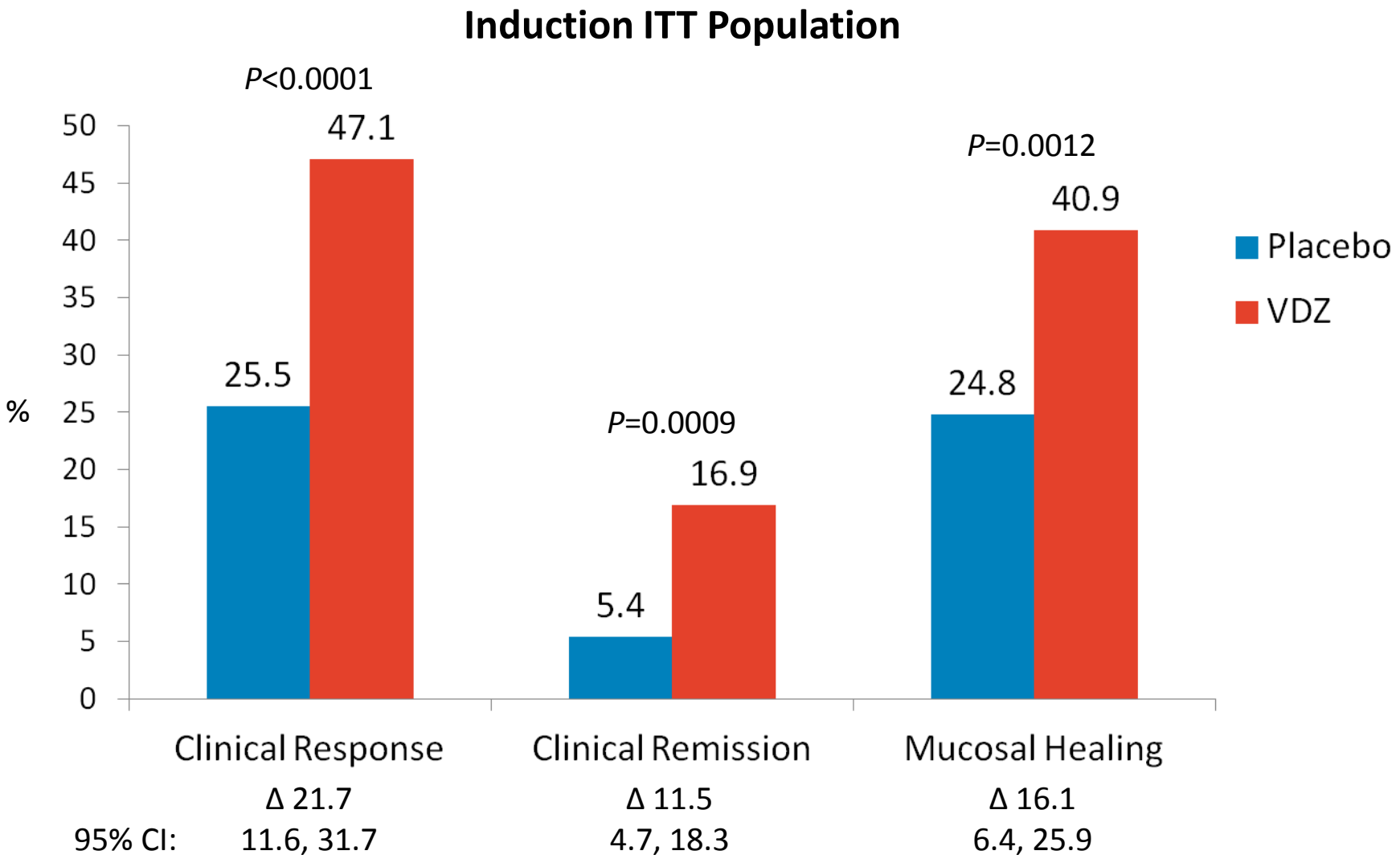
3/3,000 patients

Van Assche G et al. N Engl J Med. 2005 Jul 28;353(4):362-8

Selective Anti-Migration (SAM) therapies in IBD

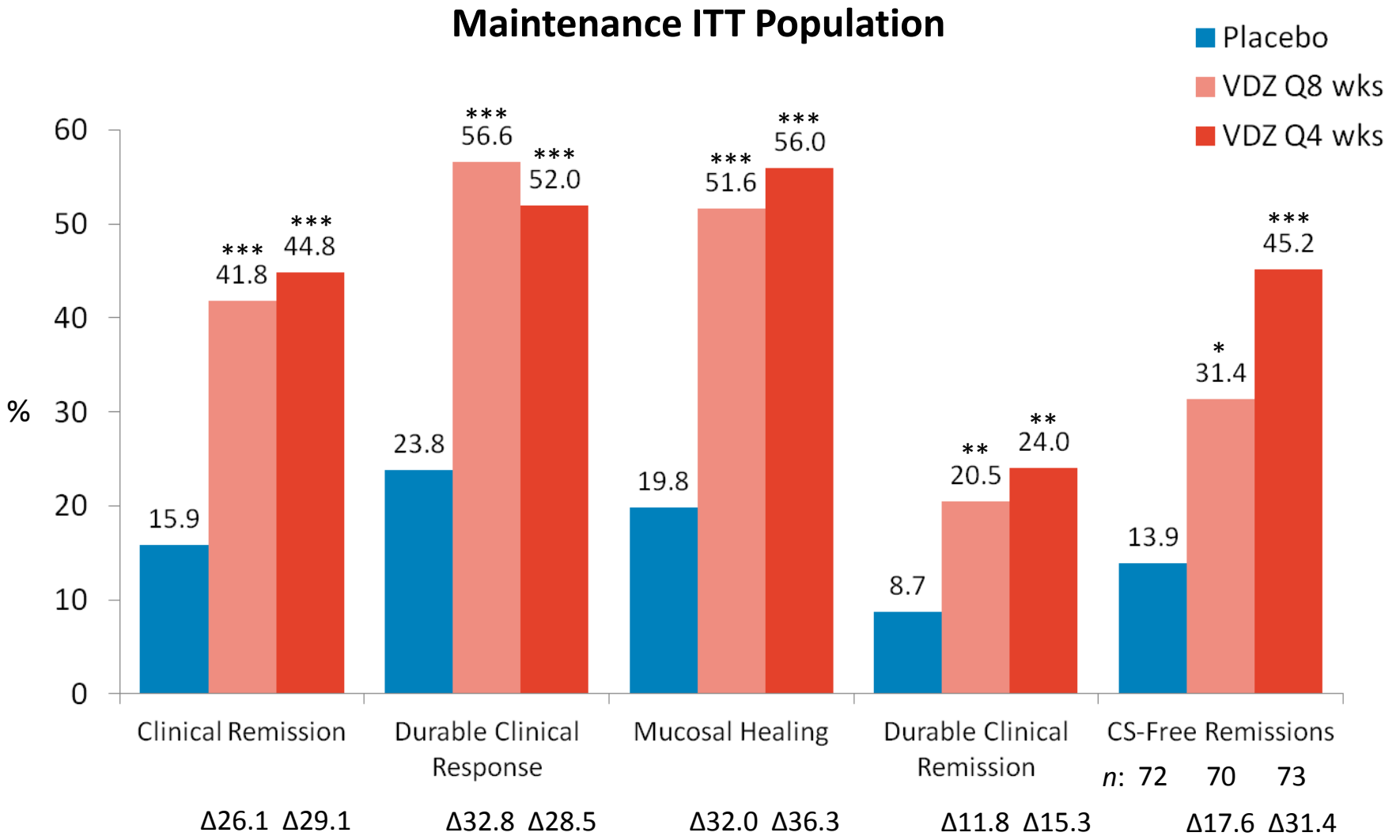
Blockade	**α_4 (β_1/β_7)**	**$\alpha_4\beta_7$**	**$(\alpha_E/\alpha_4)\beta_7$**	**MAdCAM-1**
Expression	lymphocytes monocytes eosinophils NK cells	lymphocytes monocytes eosinophils NK cells	lymphocytes monocytes eosinophils NK cells	intestinal endothelium
Ligand	MAdCAM-1 VCAM-1	MAdCAM-1	MAdCAM-1 E-cadherin	$\alpha_4\beta_7$
Target	Gut CNS	Gut	Gut Mucous membranes	Gut

Clinical Response, Remission, Mucosal Healing at 6 Weeks with Vedolizumab: GEMINI I



Feagan BG et al N Engl J Med. 2013;369(8):699-710

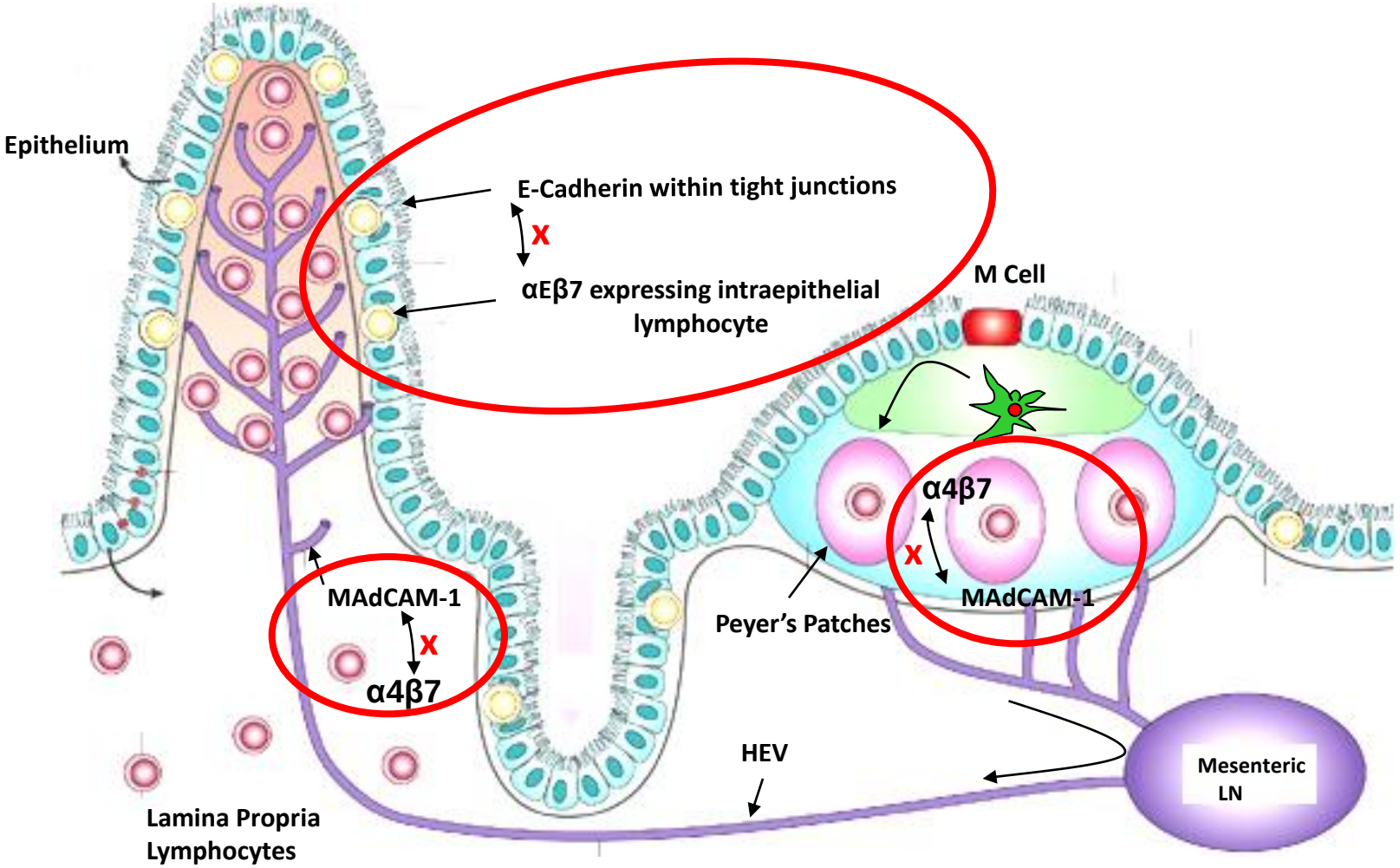
Primary and Secondary Outcomes Through 52 Weeks Vedolizumab GEMINI I



*P<0.05 **P<0.01 ***P<0.0001

Feagan BG et al N Engl J Med. 2013;369(8):699-710

RhuMAb Beta7: mechanism of action



Adapted from Cheroutre H and Madakamutil L. Nat Rev Immunol 2004;4(4):290-300

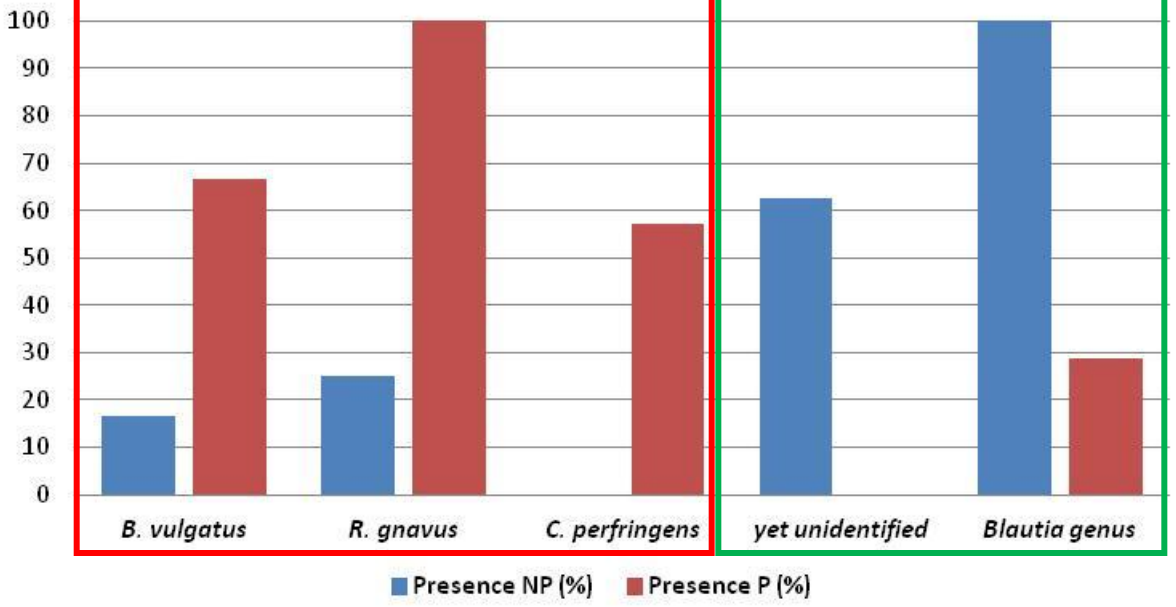
Personalized Medicine or Stratified Medicine: the solution for the cost problem?

- Maintained remission rates with biological therapies in IBD are low (<30%) and the cost of these agents is very high
- Academic institutions (in cooperation with pharma) need to identify predictors of long-term evolution of IBD and of (non-) response to the therapies
- Reliable companion diagnostics need to be developed
- Molecular assays may provide a specific therapy for an individual's condition by stratifying disease status, selecting the proper medication and tailoring dosages to that patient's specific needs
- In IBD this approach has been largely ineffective up to now

Microbial profiles before colectomy predict pouchitis at 1 year after IPAA

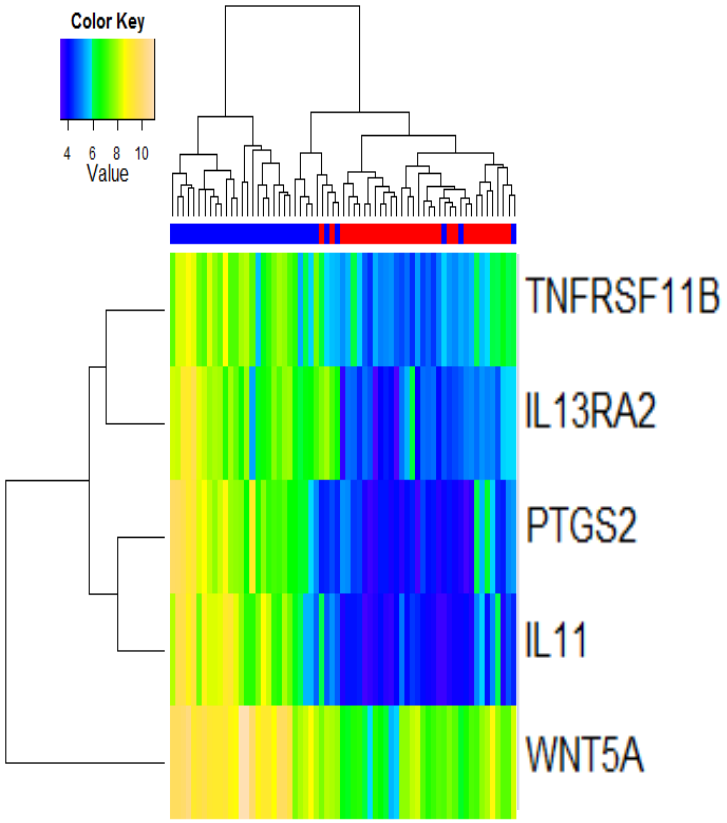
IBD Leuven

Bacterial species	*B. vulgatus*	*R. gnavus*	*C. perfringens*	yet unidentified	Blautia genus
Band-class	2.82	10.98	12.43	8.67	10.2
Presence NP (%)	16.7	25	0	62.5	100
Presence P (%)	66.7	100	57.1	0	28.6
p-value	0.034*	0.003	0.013	0.01	0.003
Median (IQR) intensity NP	0 (0-0)	0 (0-1.2)	0 (0-0)	0.7 (0-5.2)	5 (1.4-7.6)
Median (IQR) intensity P	7.76 (0-12)	5.2 (4.4-26.5)	0.6 (0-3.1)	0 (0-0)	0 (0-3.3)
p-value	0.026*	0.002	0.017	0.016	0.077

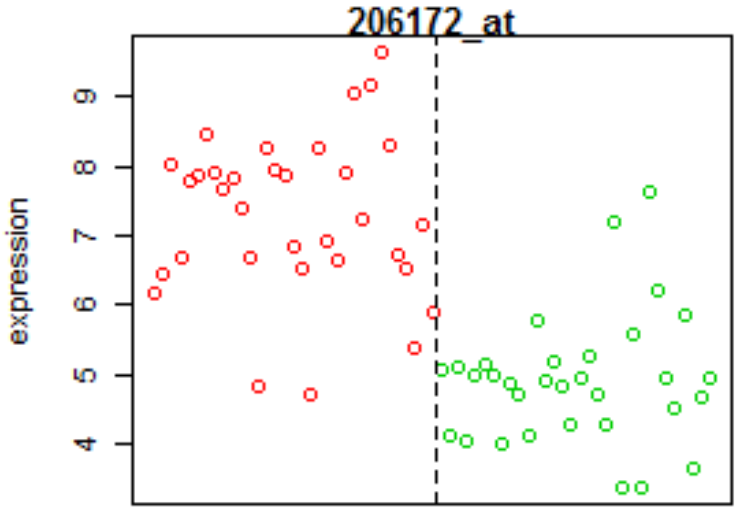


Machiels K et al Gut. 2015 Sep 30. pii: gutjnl-2015-309398. doi: 10.1136/gutjnl-2015-309398

Mucosal gene signature predicting response to infliximab in ulcerative colitis and Crohn's disease



Hierarchical clustering of the log2 expression values of the top 5 genes showed 2 distinct clusters of R versus NR

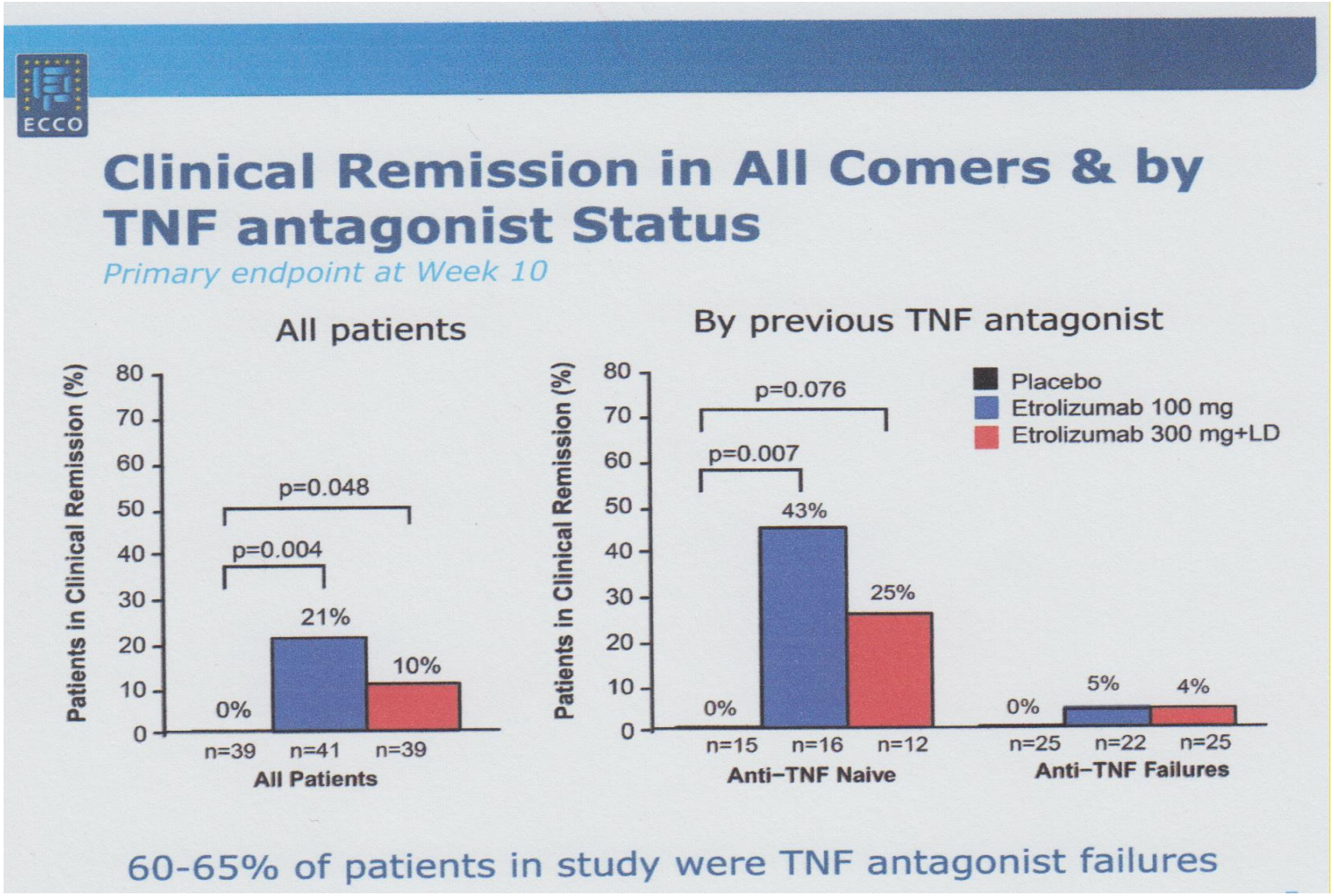


Probe set 206172_at representing IL-13Rα2 was the most significant one

Arijs et al Inflamm Bowel Dis. 2010 Apr 6

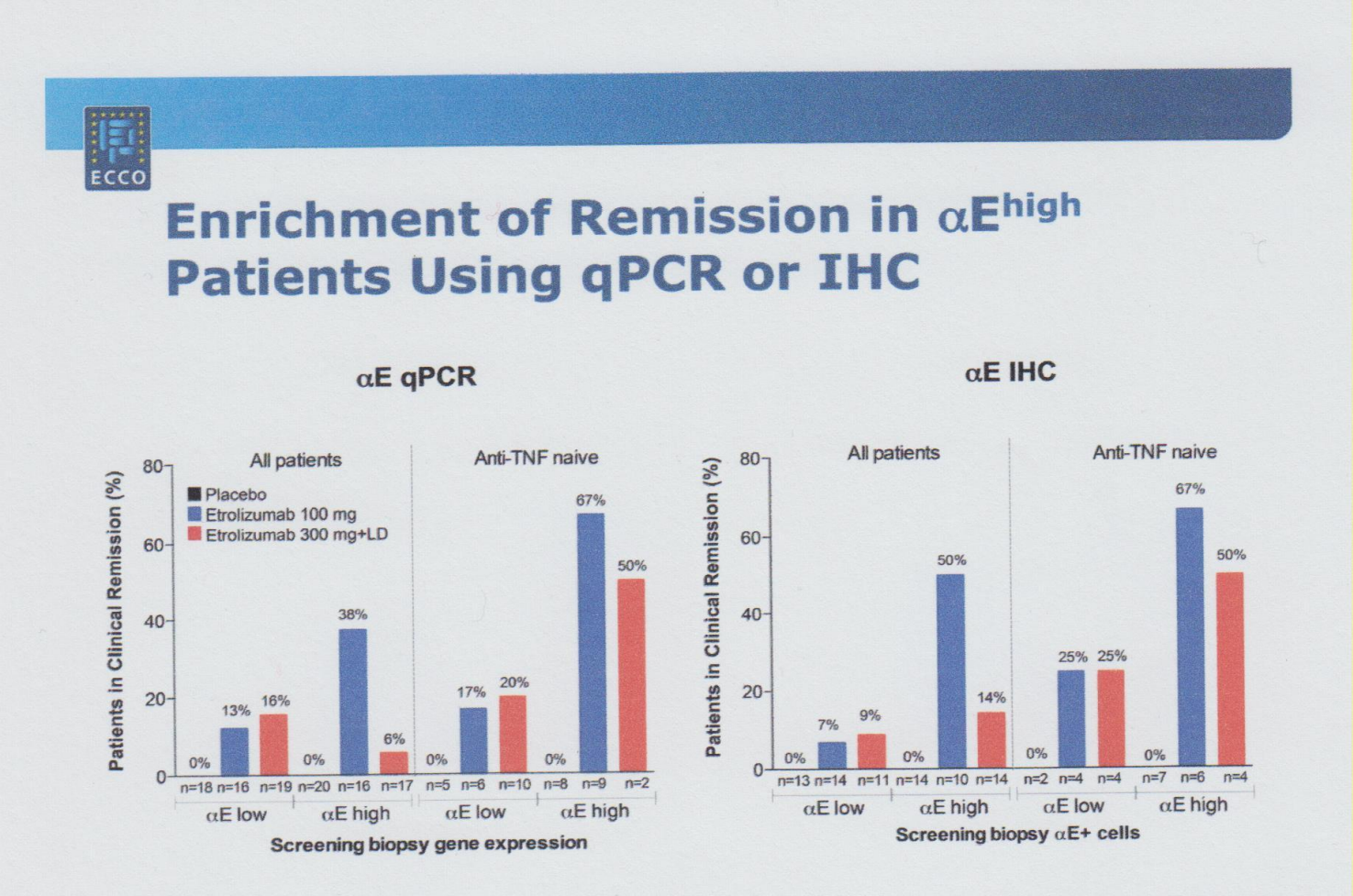
Arijs et al Gut. 2009 ;58(12):1612-9.

Prediction of response to blockade of anti-β7 with Etrolizumab in the Eucalyptus study



Vermeire S et al Lancet. 2014 Jul 26;384(9940):309-18
Tew GW et al Gastroenterology. 2015 Oct 29.

Prediction of response to blockade of anti-β7 with Etrolizumab in the Eucalyptus study



Vermeire S et al Lancet. 2014 Jul 26;384(9940):309-18
Tew GW et al Gastroenterol 2015 Oct 29

Targeting cytokines in inflammatory bowel diseases: Conclusions

- Biological therapies targeting cytokines have dramatically improved the treatment of Crohn's disease as well as Ulcerative Colitis
- The optimal use of each agent needs to be identified and sequential or combination strategies need to be investigated
- Much effort should be invested in the prediction of long-term efficacy for each strategy in order to improve efficacy/safety/cost


De stad op de berg