Many New Choices: But Who's on First?- The Evolution of IBD Therapy

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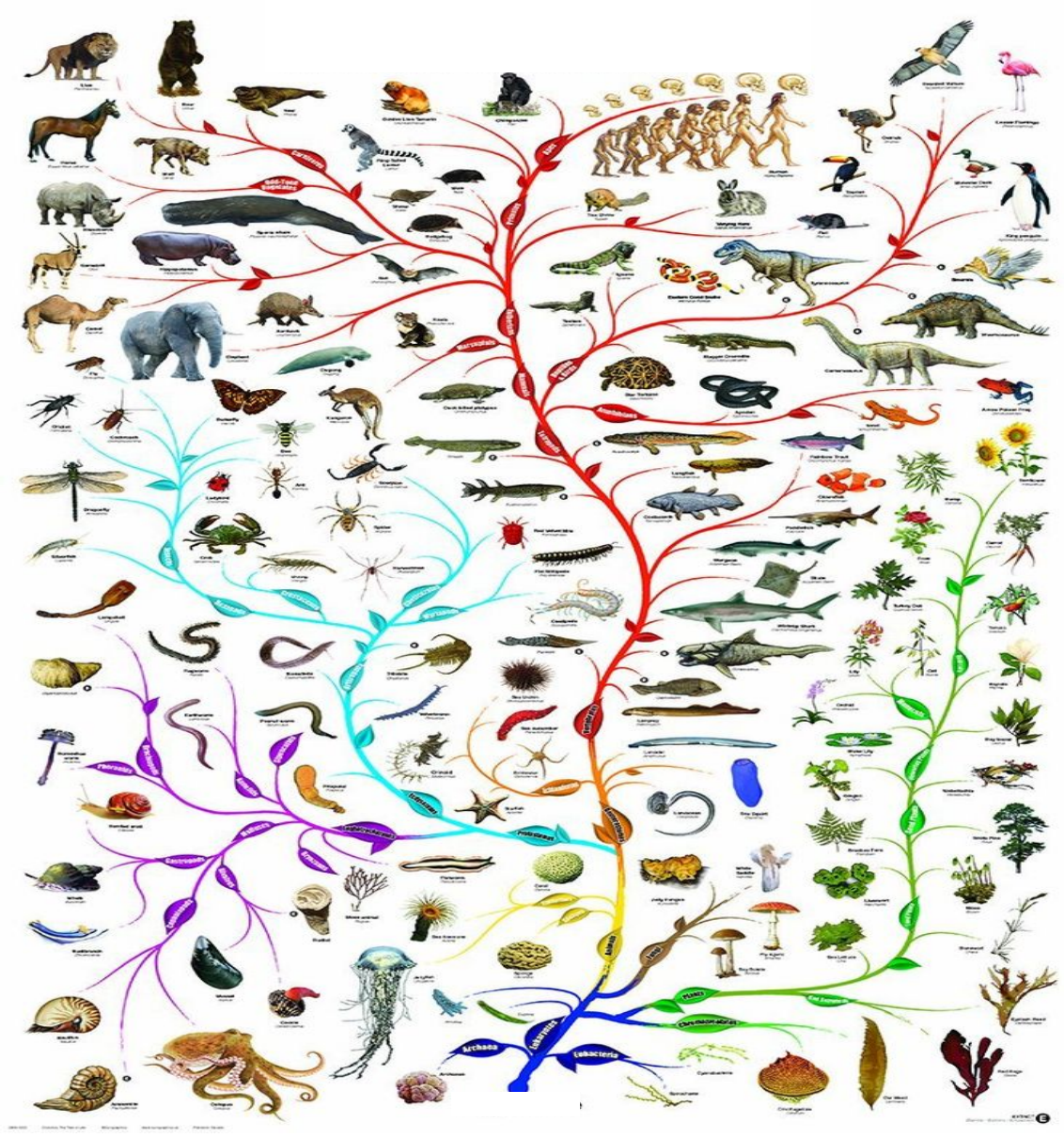

Disclosures

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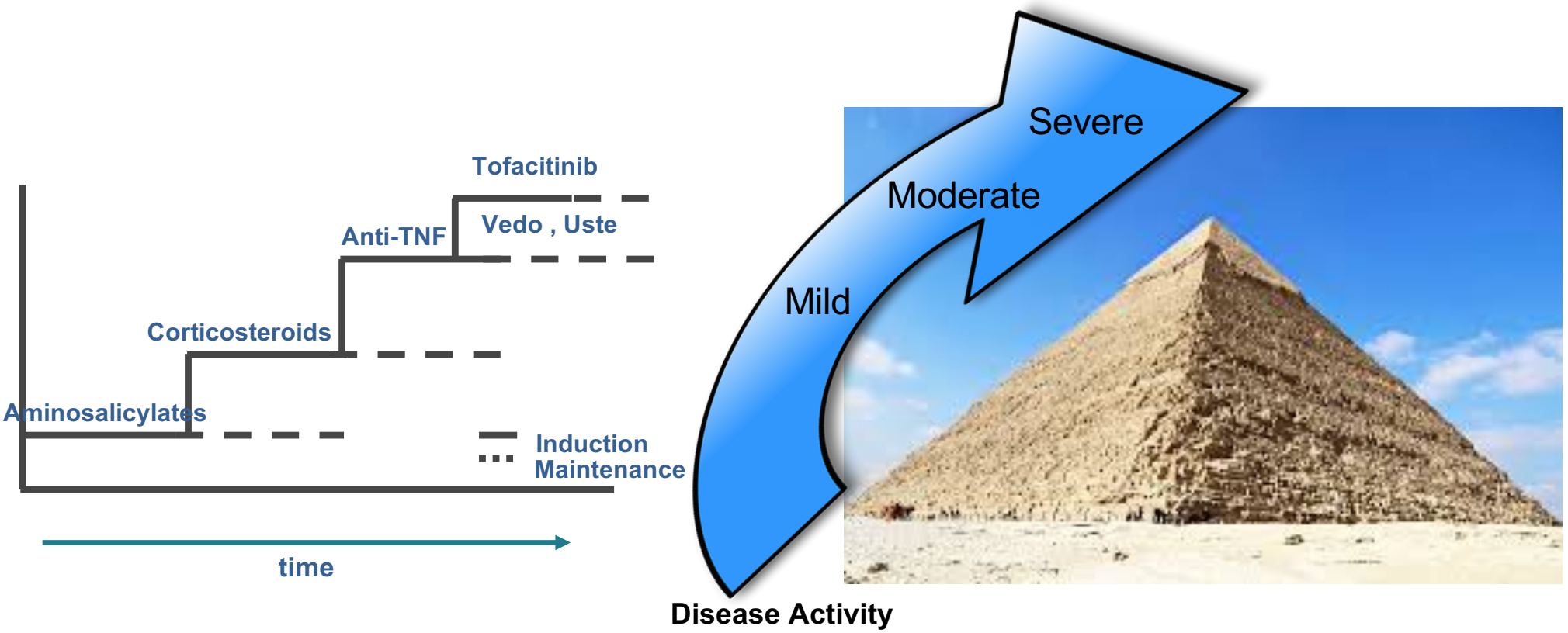
Other Financial Support	
Other Relationship/Affiliation	

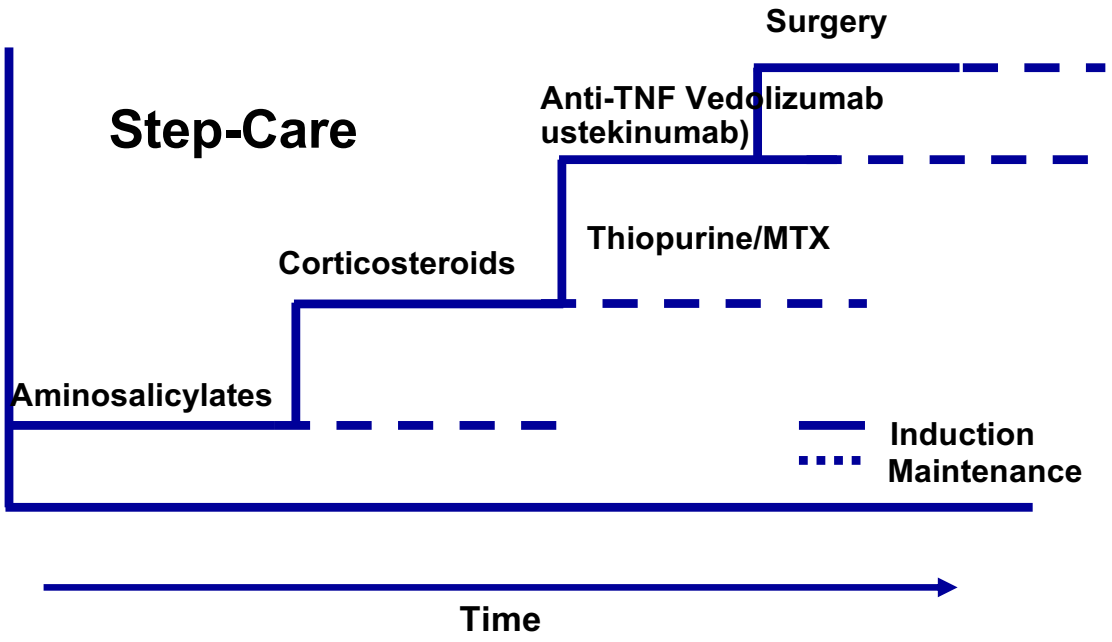
Topic to Be Covered

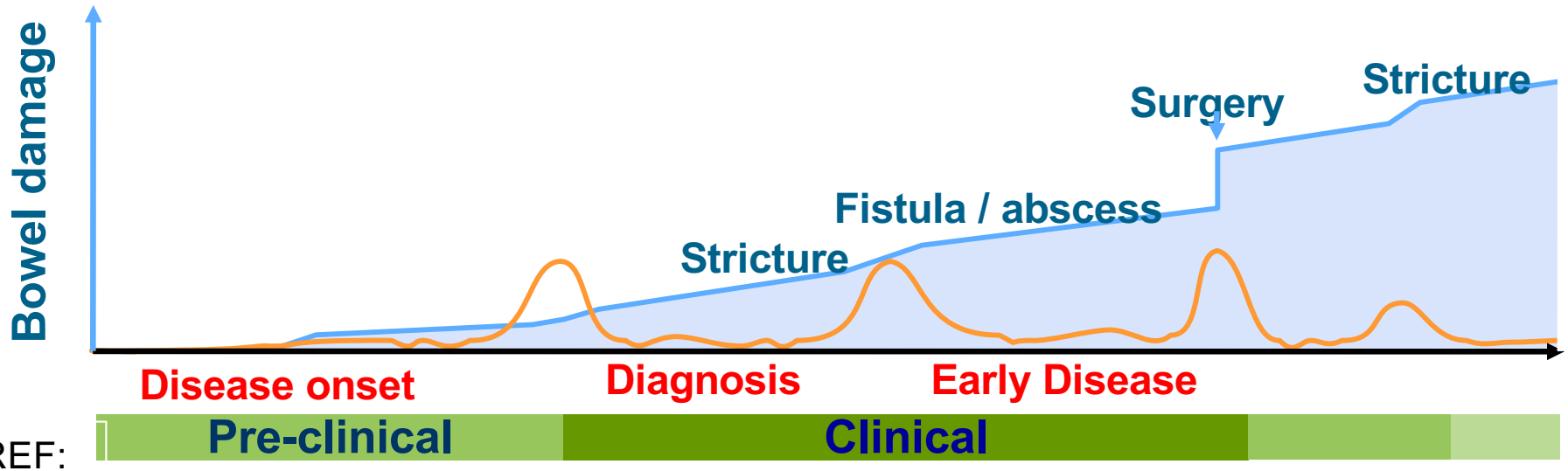
- Current Treatment Concepts in UC and CD
- Overview of First Line Drugs
  - MOAS
  - Efficacy
  - Safety
- Current Guidelines: recommendations for practice
- Future directions
- Conclusions

The Concept of Step-Care in UC is Alive and Well



…the concept of step-care in CD is flawed





REF:

“ First Line” Drug Classes

- TNF Antagonists
- Vedolizumab
- Ustekinumab

Lancet Case Report 1994

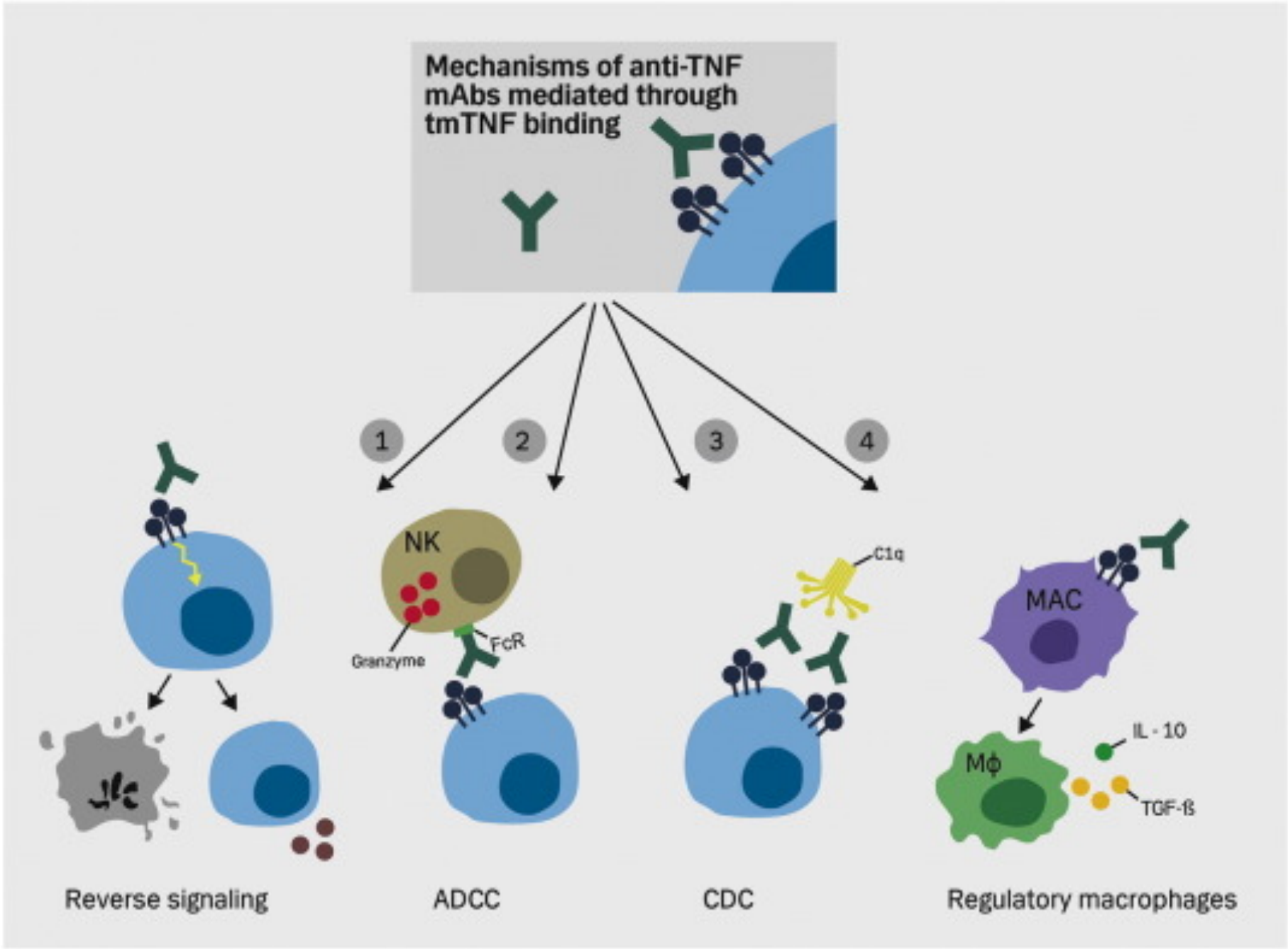
Tumour-necrosis-factor antibody treatment in Crohn's disease

SIR—We report a girl with Crohn's disease who was not responsive to medical therapy but in whom complete but temporary remission could be achieved by treatment with tumour necrosis factor (TNF) monoclonal antibodies.

At age 12 years the patient was examined because of diarrhoea of 4 months' duration, rectal blood loss, abdominal pain, fever, and loss of 4·5 kg. Colonoscopy showed multiple aphthoid lesions, skip lesions, erythema, friability, and granularity in the distal 70 cm of the colon extending into the anus. Biopsy specimens revealed severe inflammation, crypt abscesses, and granulomas. A small bowel follow-through was normal. Prednisone 30 mg per day, mesalazine 250 mg three times a day, and enemas containing 2 g aspirin and 40 mg prednisone were started. Her complaints initially abated but the disease soon relapsed despite continued anti-inflammatory treatment. Because of severe side-effects the prednisone dose had to be reduced. Colonoscopy 3 months after diagnosis showed no improvement. The treatment was intensified by raising the dose of mesalazine and adding azathioprine. Some clinical improvement was noted but her growth stunted, and it was not possible to withdraw any medication. A semi-elemental diet for 2 months and the addition of metronidazole had no effect. A year after diagnosis, she had increasing anorexia, abdominal pain, and frequent bloody diarrhoea. Colonoscopy again showed extensive colitis and perianal lesions. Over the next 14 months the patient was treated with prednisone (daily alternating up to 40 mg a day), azathioprine 75 mg a day, mesalazine 500 mg three times a day, and enemas containing beclomethasone and aspirin.

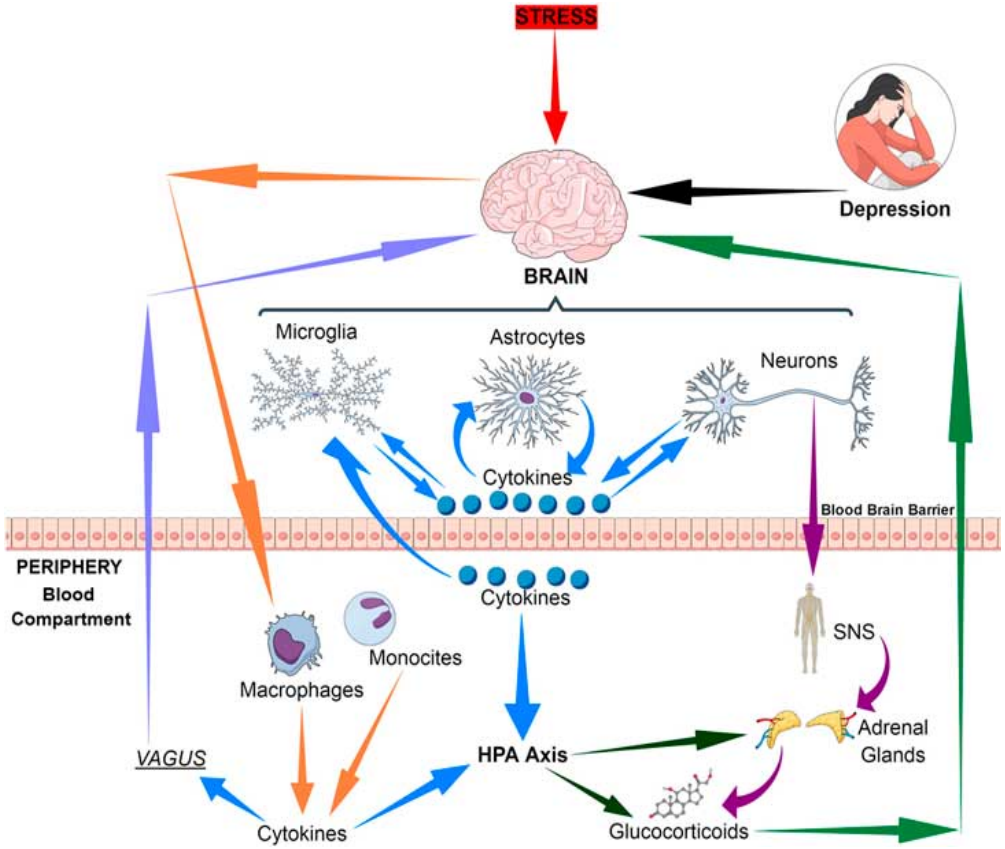
Because of unresponsive disabling disease, the possibility of anti-TNF treatment was discussed with the patient and her parents. Written consent was obtained. She was infused twice over a fortnight with anti-TNFα (chimeric monoclonal cA2,

Mechanism of Action: TNF Antagonists



Olesen C et al Pharmacology and Therapeutics 2016

Effects of TNF on Mood



Original Article

FREE

January 2013

A Randomized Controlled Trial of the Tumor Necrosis Factor Antagonist Infliximab for Treatment-Resistant Depression

The Role of Baseline Inflammatory Biomarkers

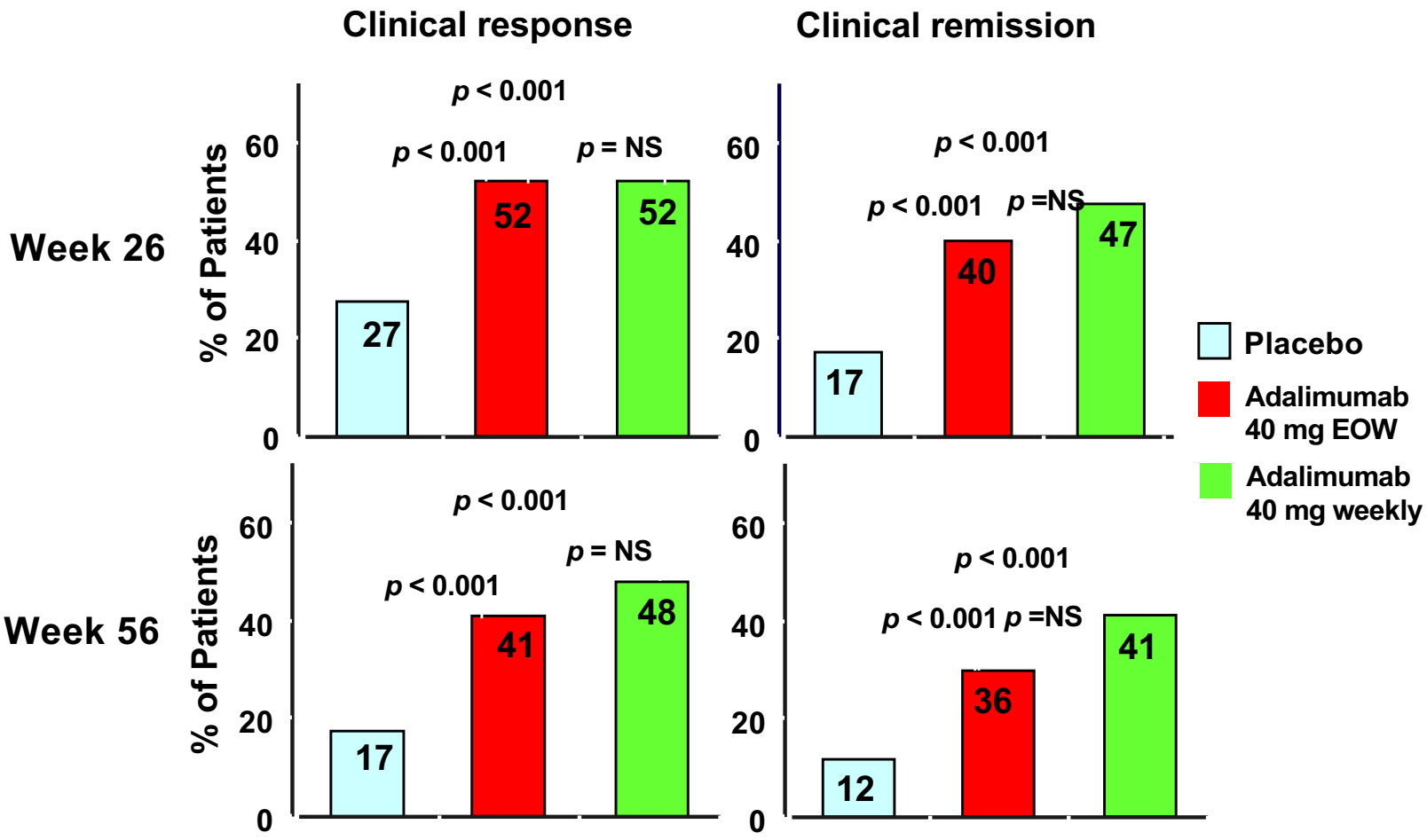
Charles L. Raison, MD; Robin E. Rutherford, MD; Bobbi J. Woolwine, MSW; et al

» Author Affiliations | Article Information

JAMA Psychiatry. 2013;70(1):31-41. doi:10.1001/2013.jamapsychiatry.4

Leonard B Acta Neuropsychiatra 2016

Efficacy -TNF antagonists for CD was a game changer- but we are a long way from perfect……



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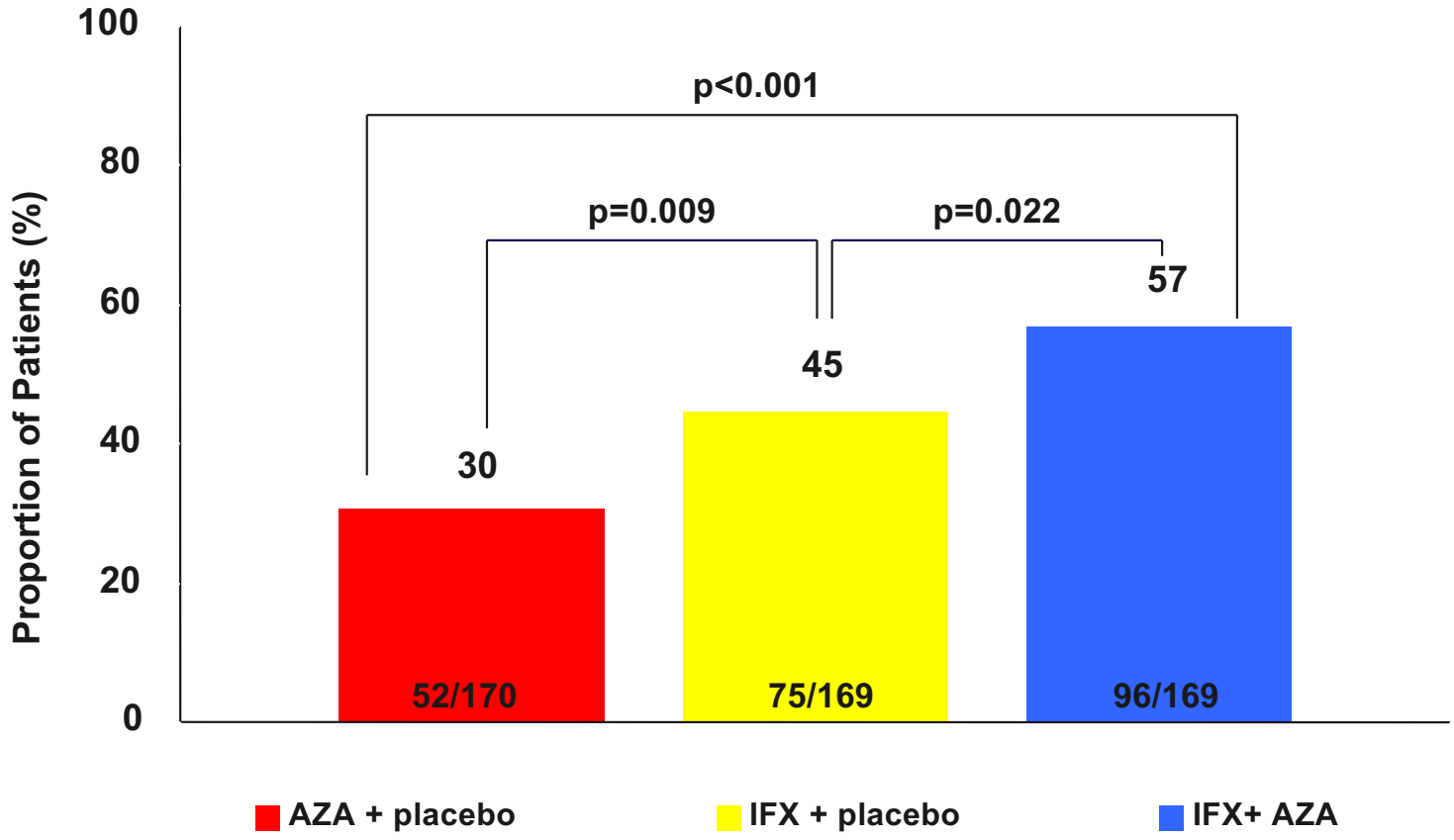
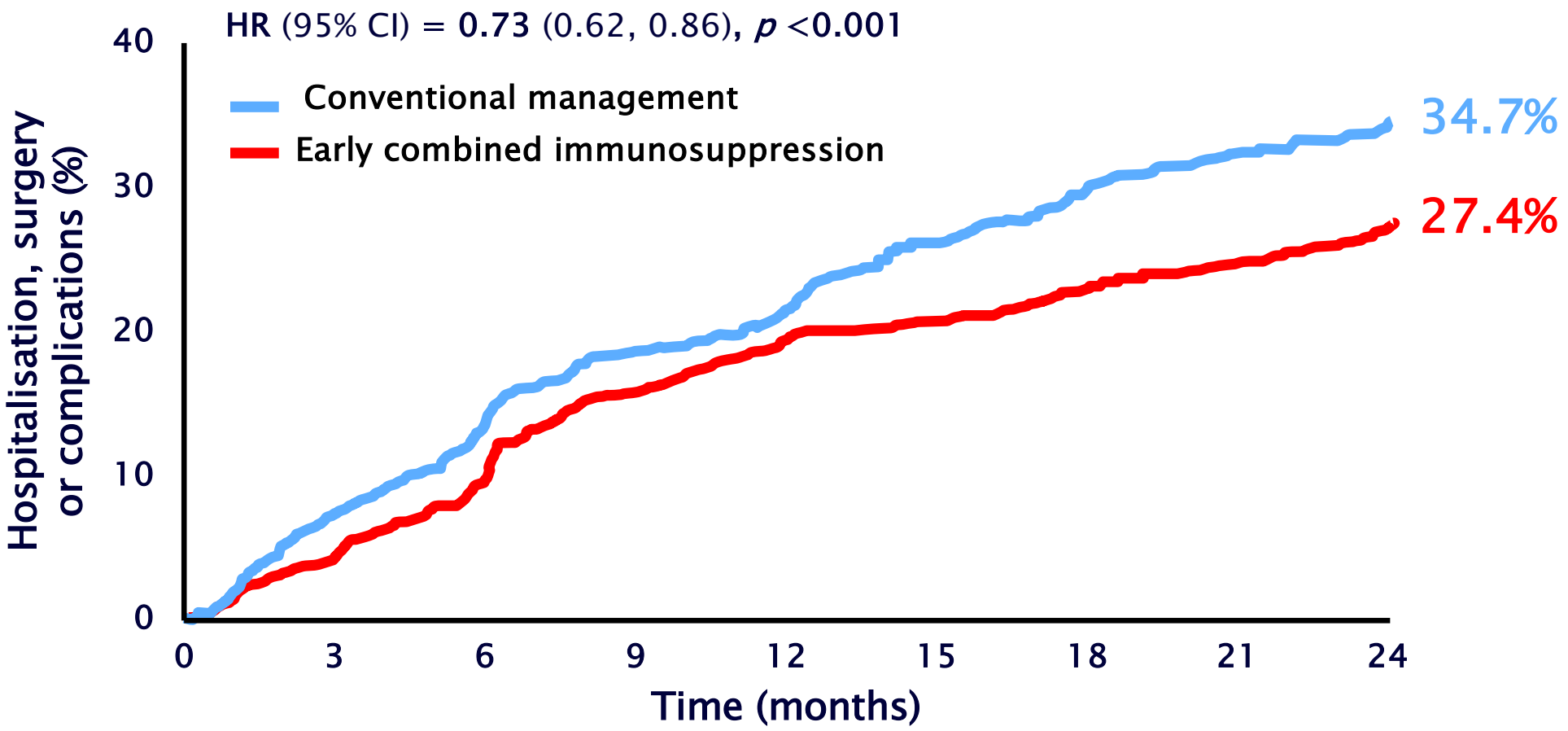
Colombel JF. et al. Gastroenterology 2007

SONIC Remission Rates: Week 26



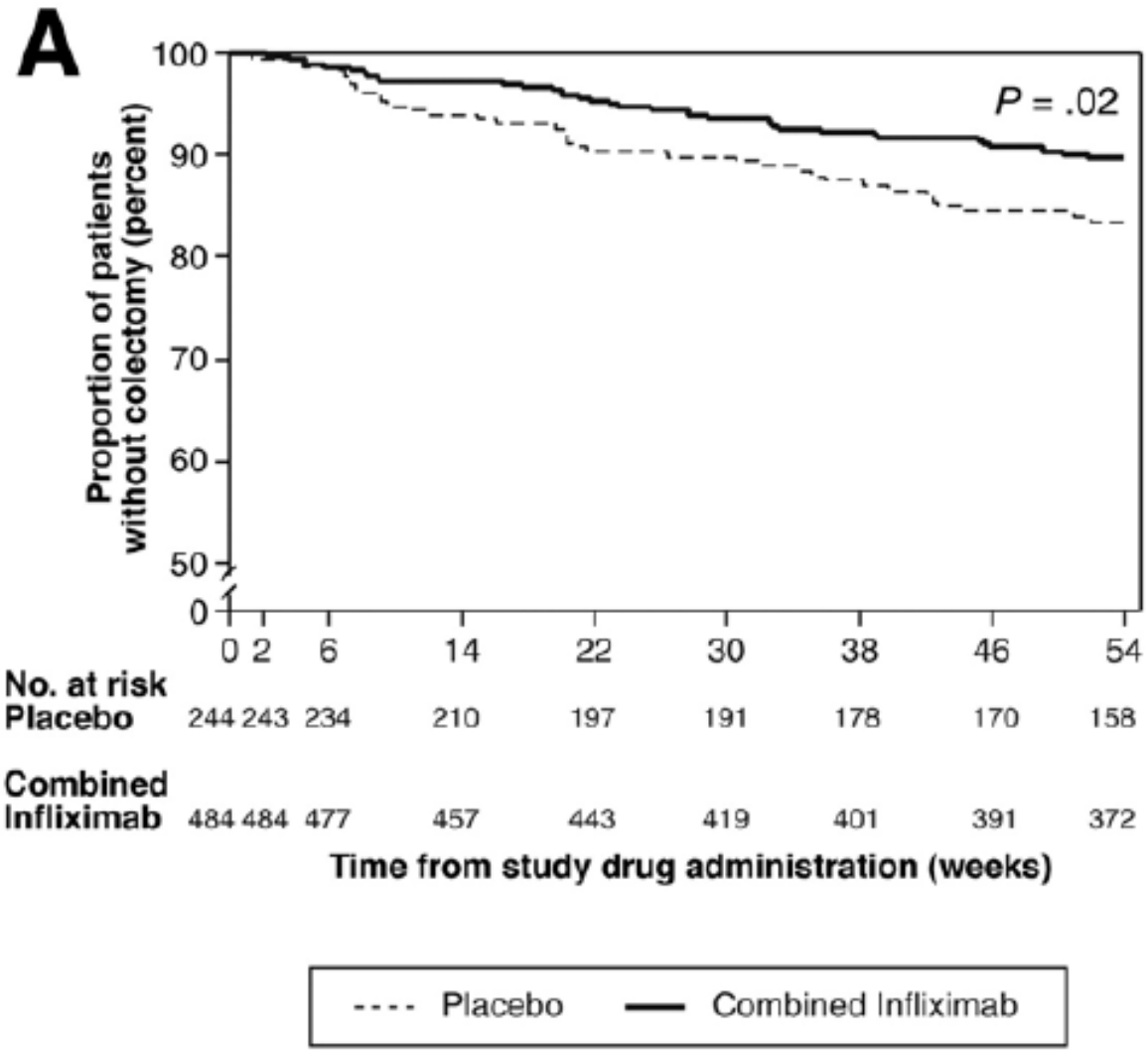
Colombel JF. et al. N Engl J Med. 2010 Apr 15;362(15):1383-95.

REACT: Time to First Hospitalization, Surgery or Complication



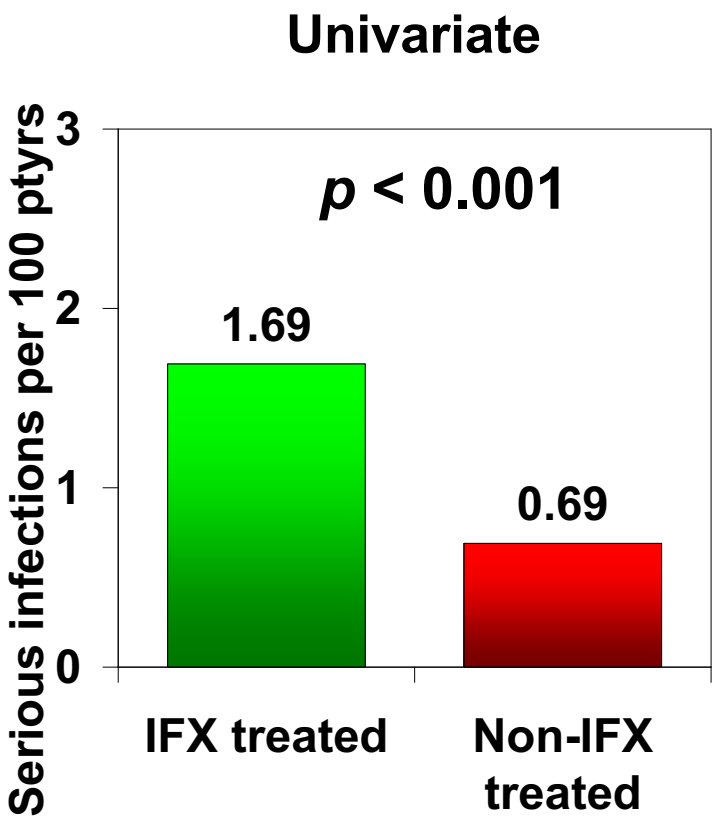
Khanna R. et al. The Lancet. 2015 Nov 7;386(10006):1825-34

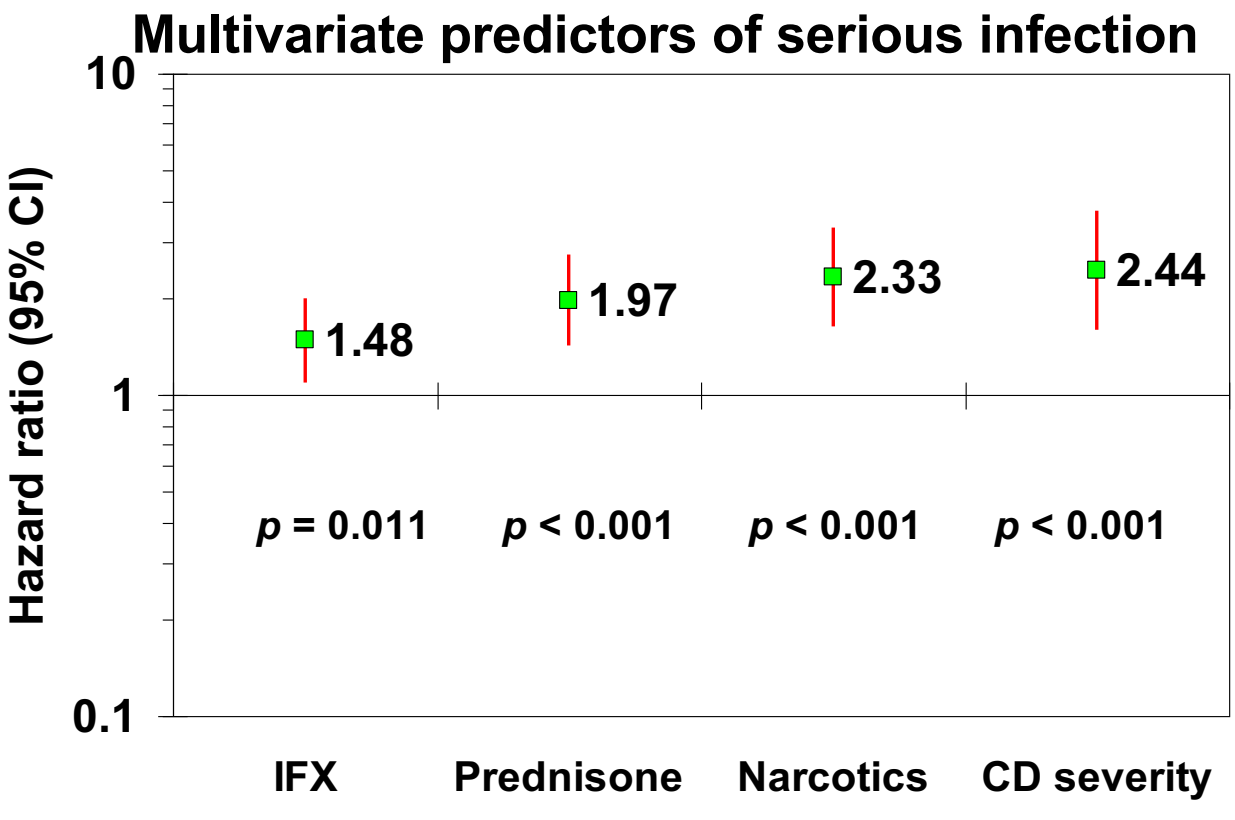
ACT 1 and 2: Time to Colectomy



Sandborn WJ, et al Gastroenterology. 2009 Oct;137(4):1250-60;

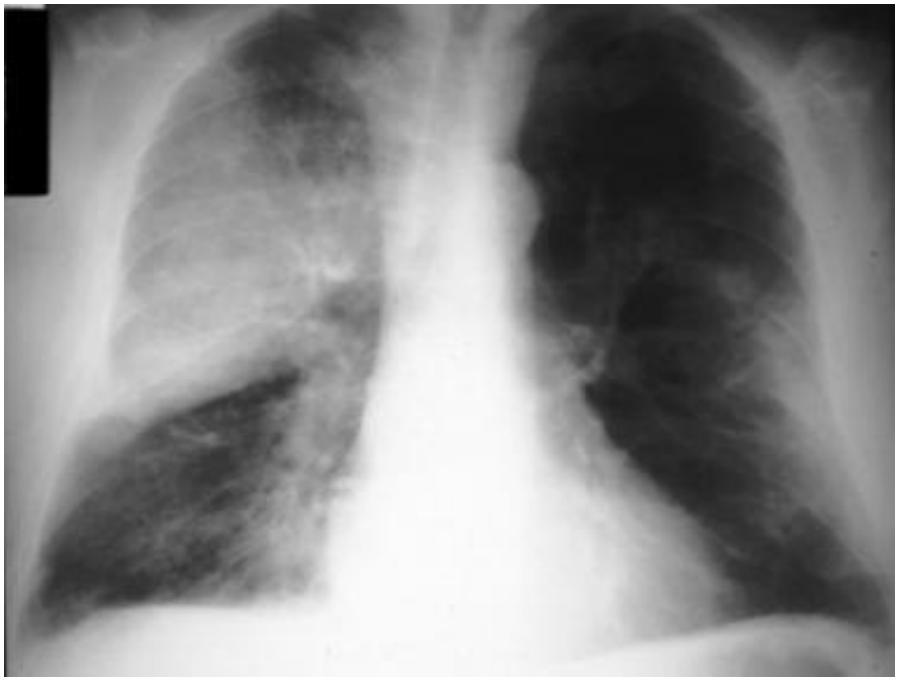
TREAT: Risk Factors for Serious Infections

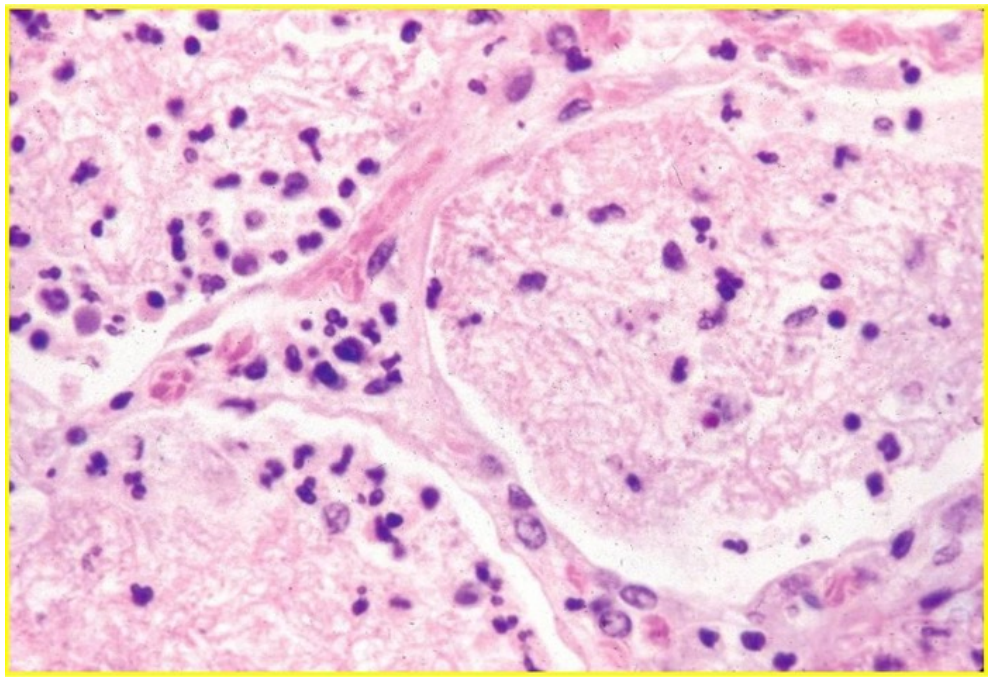




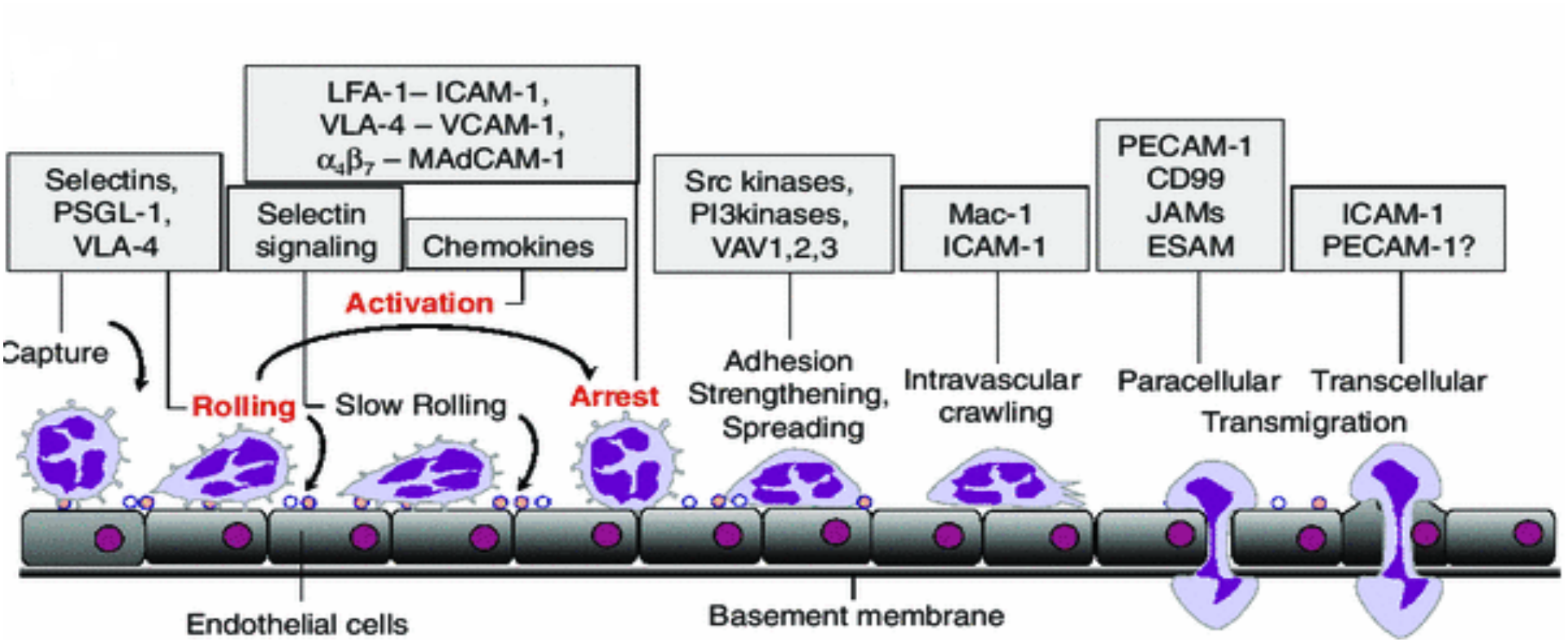
Lichtenstein, et al. DDW 2010: Abstract #T1040

Lobar Pneumonia with Pneumococcus



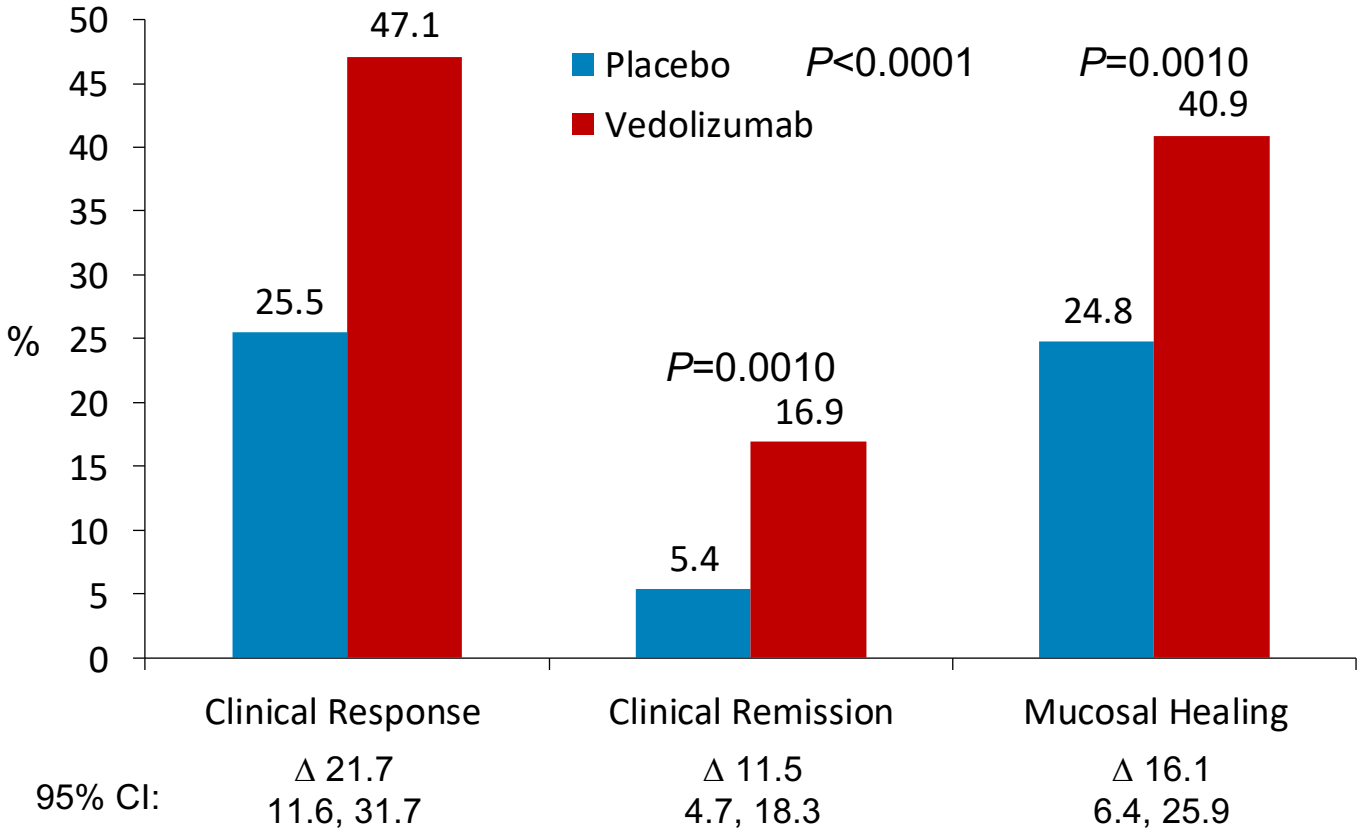


Mechanism of Action: Vedolizumab



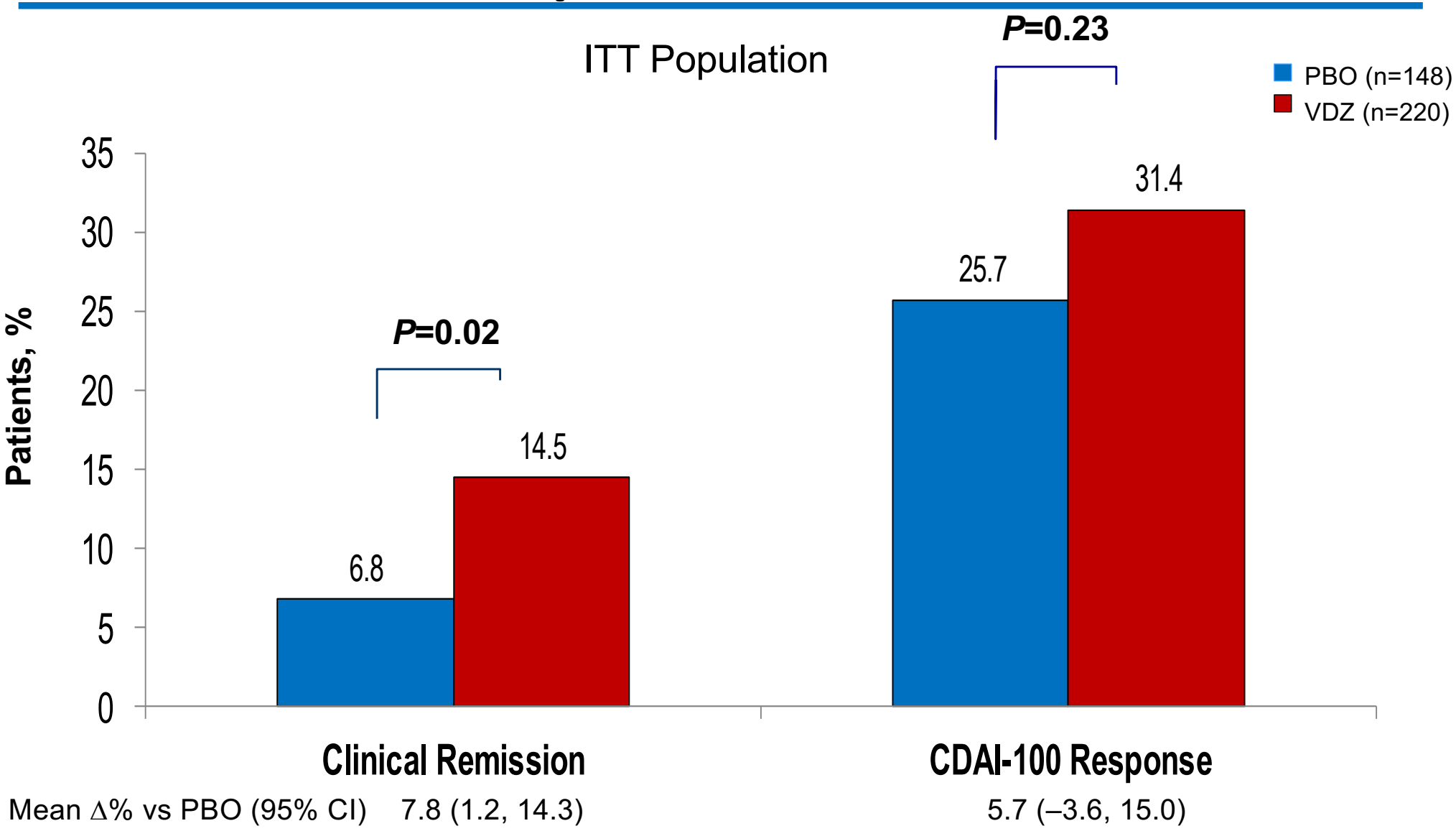
Mosli M et al, Drugs 2014; 74: 297-311

Vedolizumab Induction for UC – Week 6



Feagan et al New Eng J Med 2013;396(8):699-710

GEMINI II CD: Clinical Remission and CDAI-100 Response at Week 6



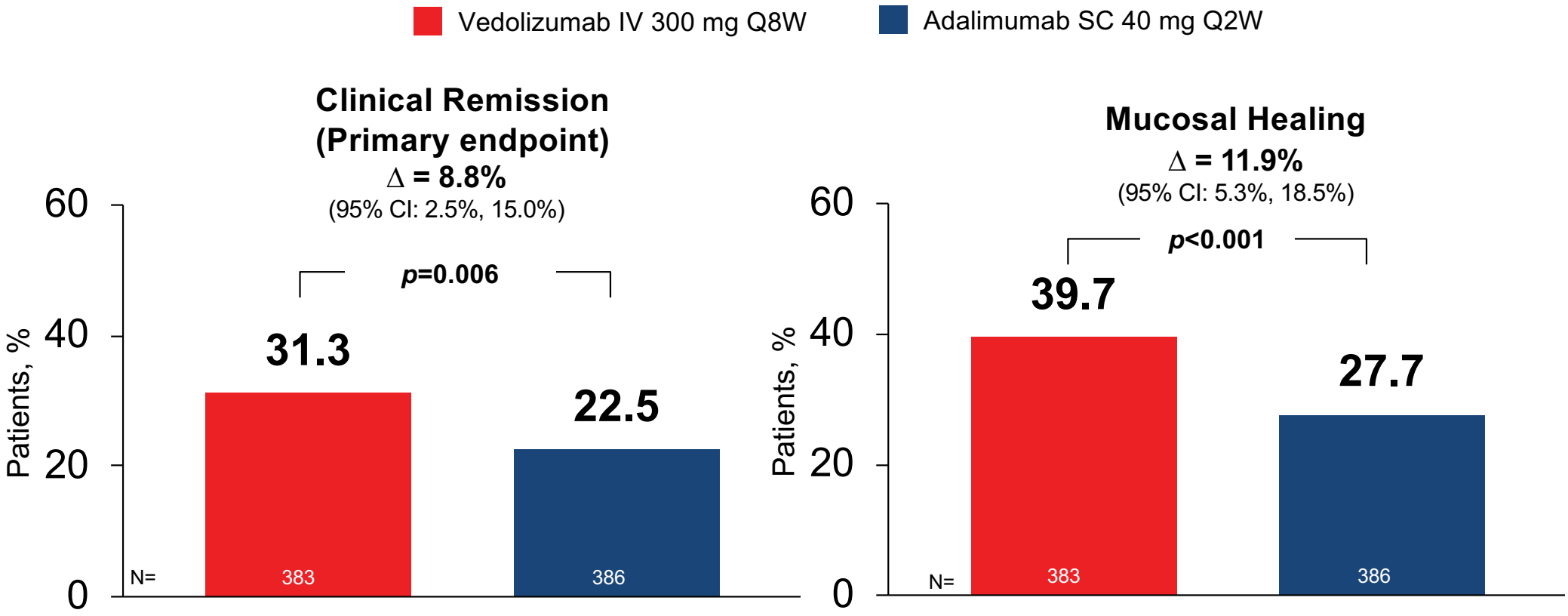
Sandborn WJ. et al. New Eng J Med 2013;369(8):711-21.

Varsity – Trial Design

- Randomized comparison of vedolizumab (IV) to adalimumab at the labelled doses in active UC
- 20% TNF antagonist exposed
- Treat right through design
- 769 patients (MCID - 7.5%)
- Primary endpoint – remission at week 52

Sands BE et al. N Engl J Med 2019;381:1215-26

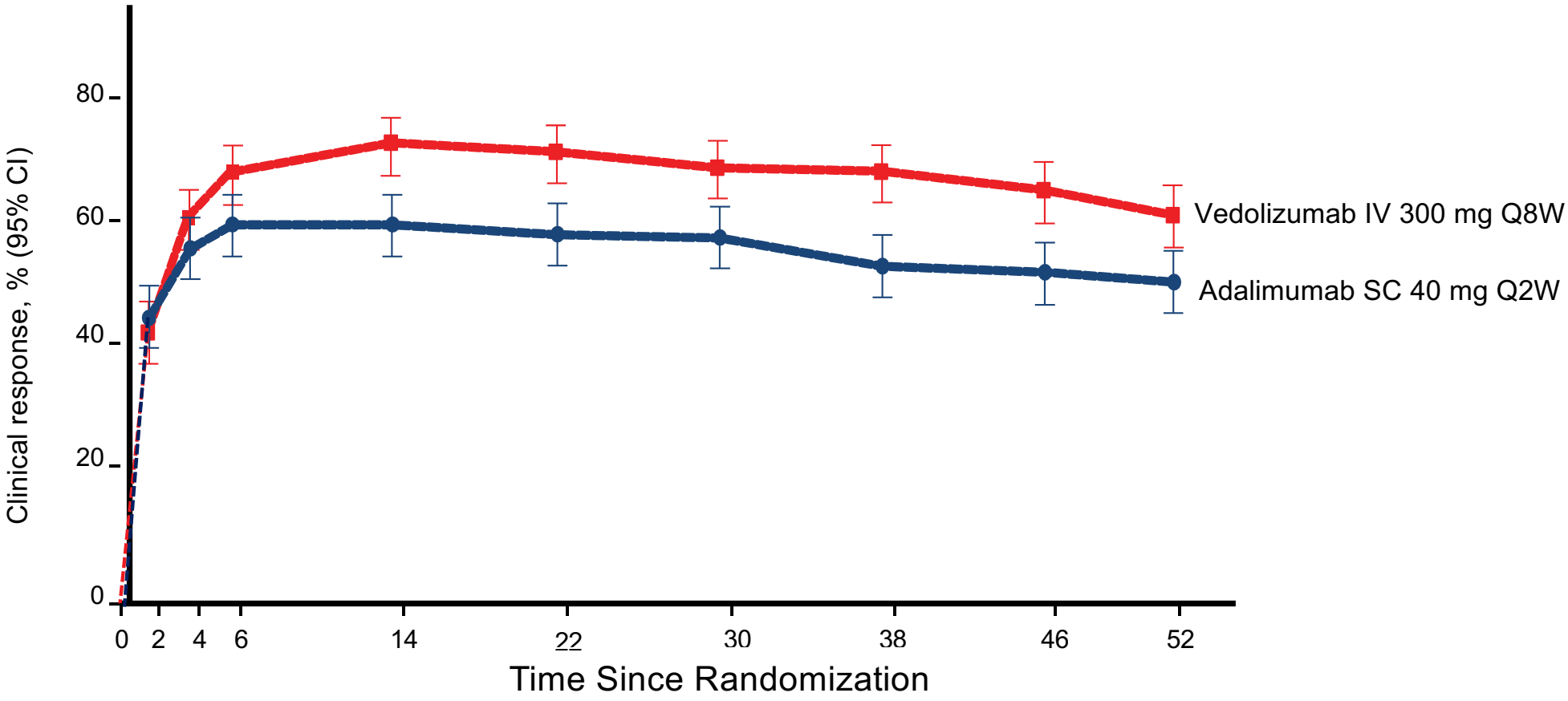
VARSITY: Vedolizumab vs Adalimumab Clinical Remission and Mucosal Healing at Week 52



Sands BE, et al. N Engl J Med 2019;381:1215-26.

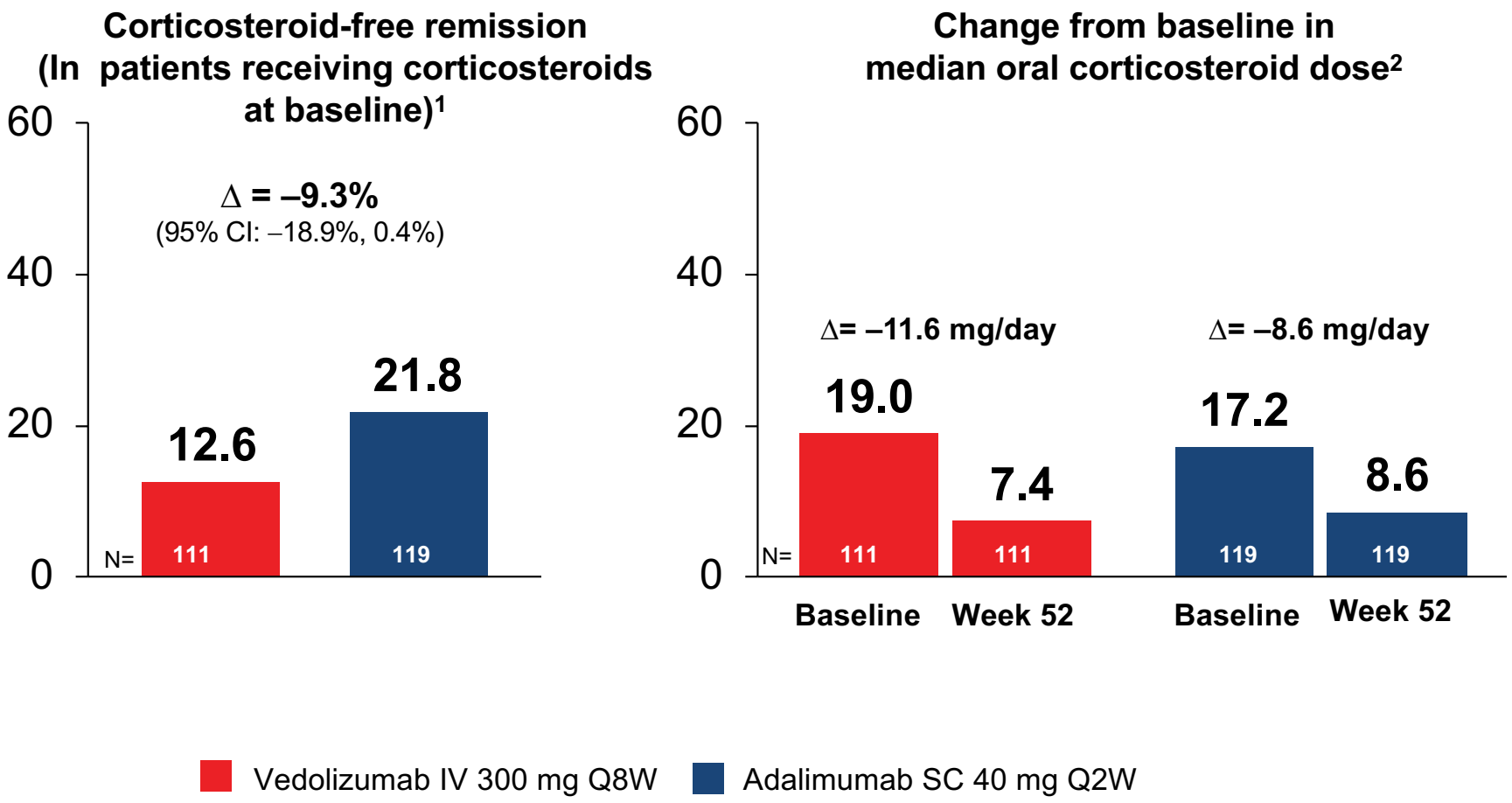
VARSITY

Response Rates by Week



Danese S, et al.. United European Gastroenterology Week 2019. Abstract OP165

VARSITY: Corticosteroid-Free Remission at Week 52



1. Sands BE, et al. N Engl J Med 2019;381:1215-26.online supplement, Fig. S7.

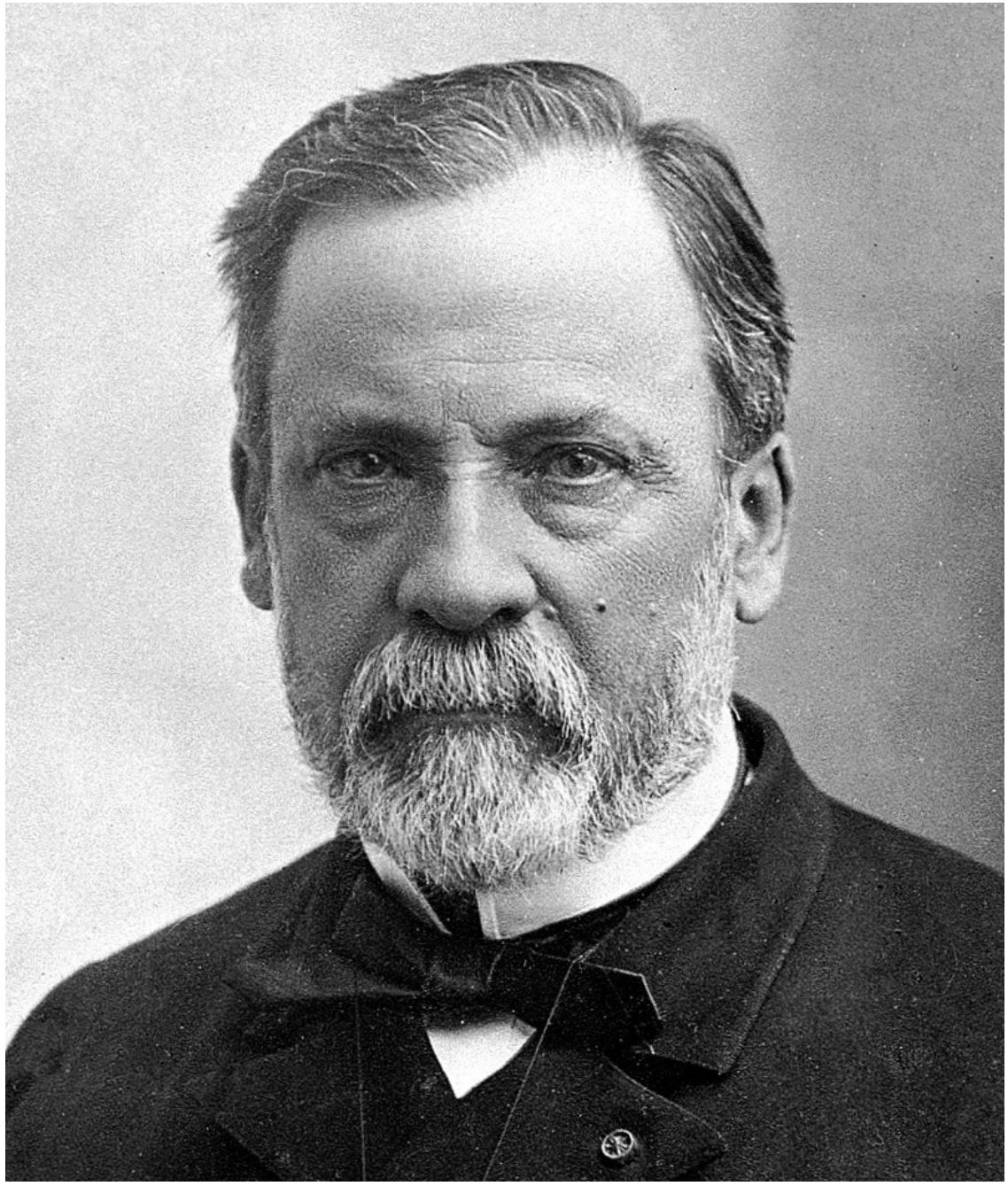
Vedolizumab: Exposure-Adjusted Incidence Rates of Infections, Serious Infections and LRTIs

	Placebo		Vedolizumab	
	UC and CD (n = 504)[a]		UC and CD (n = 2830)[d]	
Adverse event: Infection	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)
Any infection[e]	139	82.9 (68.3-97.5)	1606	63.5 (59.6-67.3)
Upper respiratory tract infections	67	34.7 (26.0-43.3)	967	28.6 (26.6-30.6)
Lower respiratory tract and lung infections	16	7.7 (3.9-11.5)	270	6.1 (5.3-6.8)

Colombel JF et al. Gut 2017;66(5):839-851

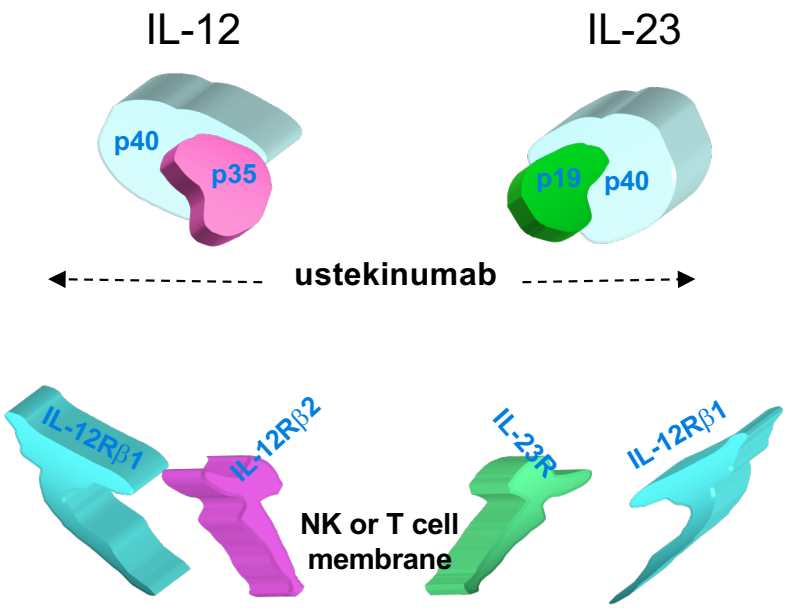
Ustekinumab

"Chance favors the prepared mind"



Louis Pasteur 1822-95

Anti-p40 Ustekinumab: MOA

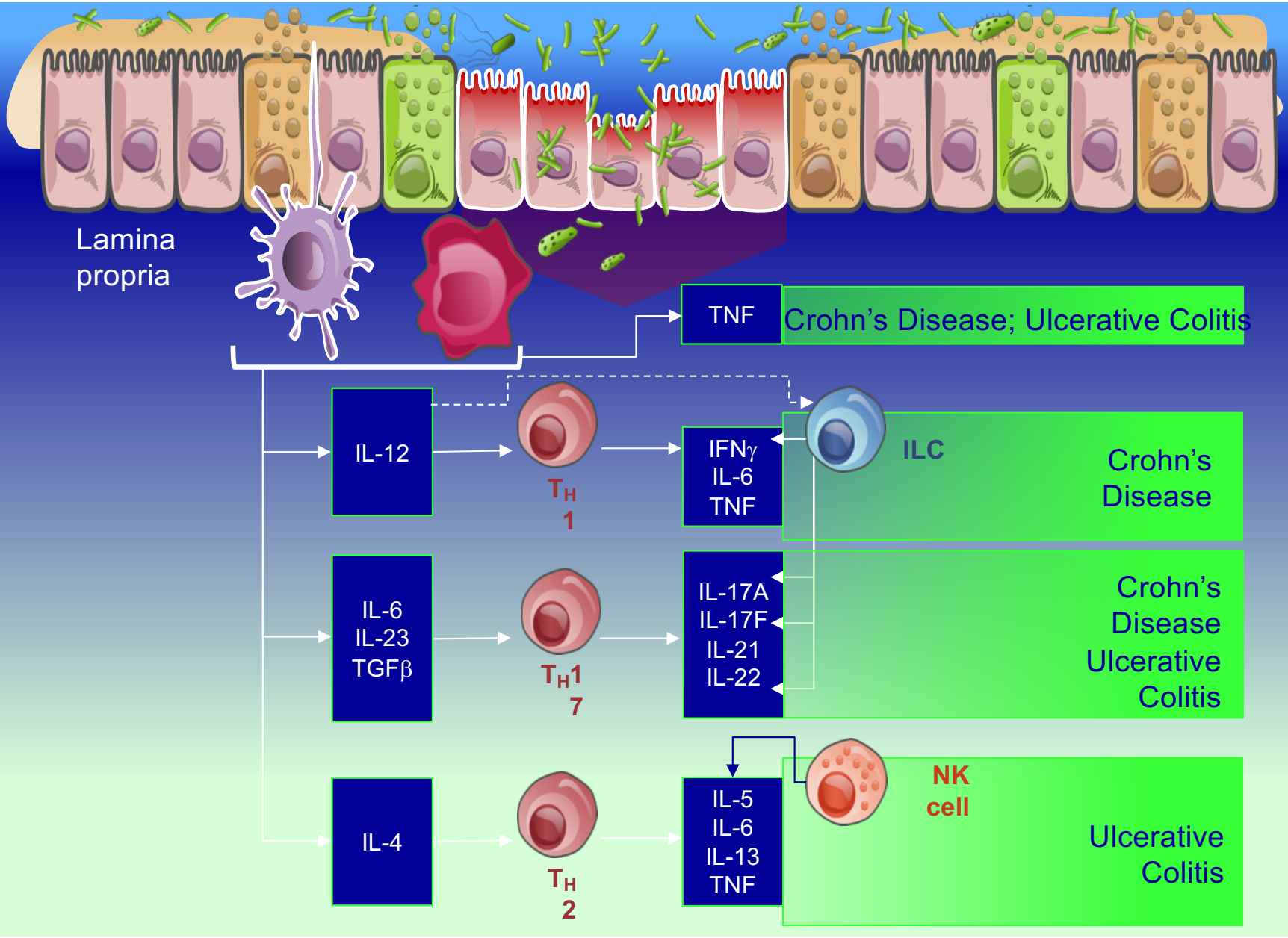


- IL-12 & IL-23 are key cytokines in the pathogenic immune cascade of Crohn's disease
- Ustekinumab is a IgG1k monoclonal antibody that binds the **p40 subunit** of interleukin-12 and -23
- Inhibits IL-12- and IL-23-mediated signaling, cellular activation, and downstream cytokine production

[1] Sandborn W, et al. Oral presentation. CCFA 2015 and Rutgeerts P, et al . Oral presentation. ECCO 2016.
[2] Feagan B, et al. Oral presentation. ACG and UEGW 2015.

Sandborn W.J., et al. DDW 2016. Presentation 768.

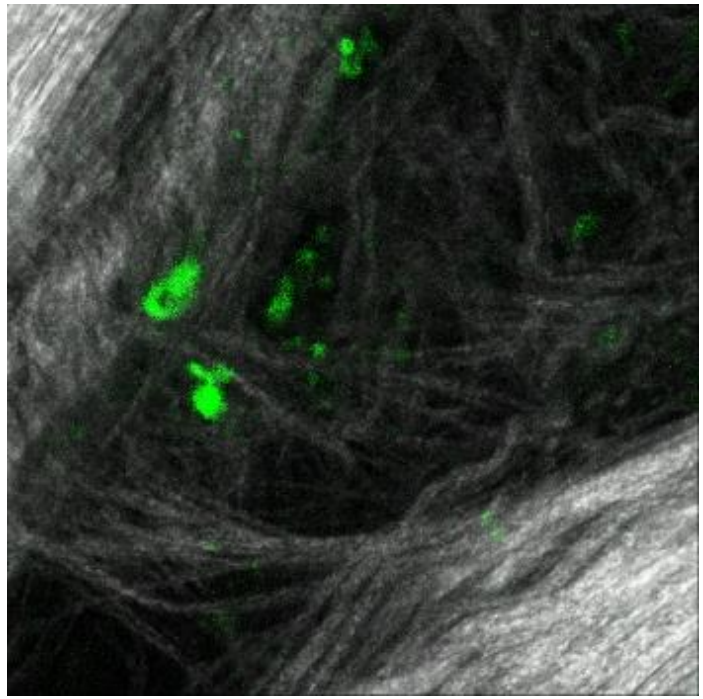
Inhibition of “Master Cytokines”?

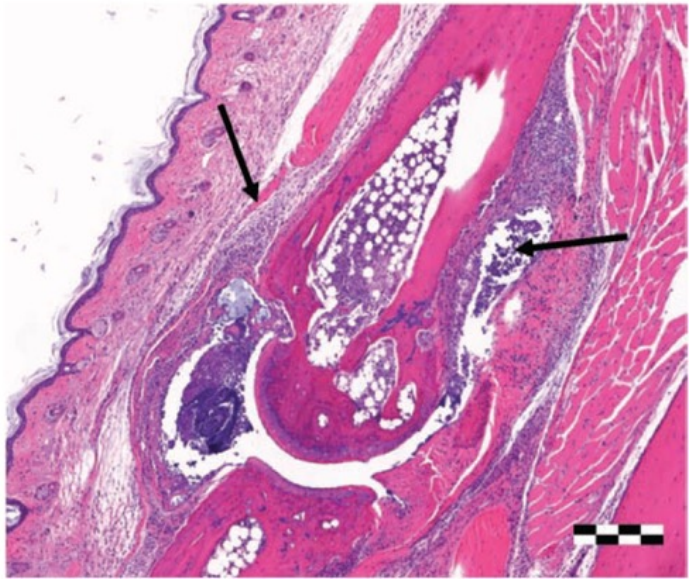


Neurath M. *Nature Reviews*. 2014;14:329-342; Dave M et al. *Gastroenterol Clin N Am.* 2014;43:405-424;.
Wallace KL et al. *World J Gastroenterol.* 2014;7:6-21.

An Alternative View of the MOA

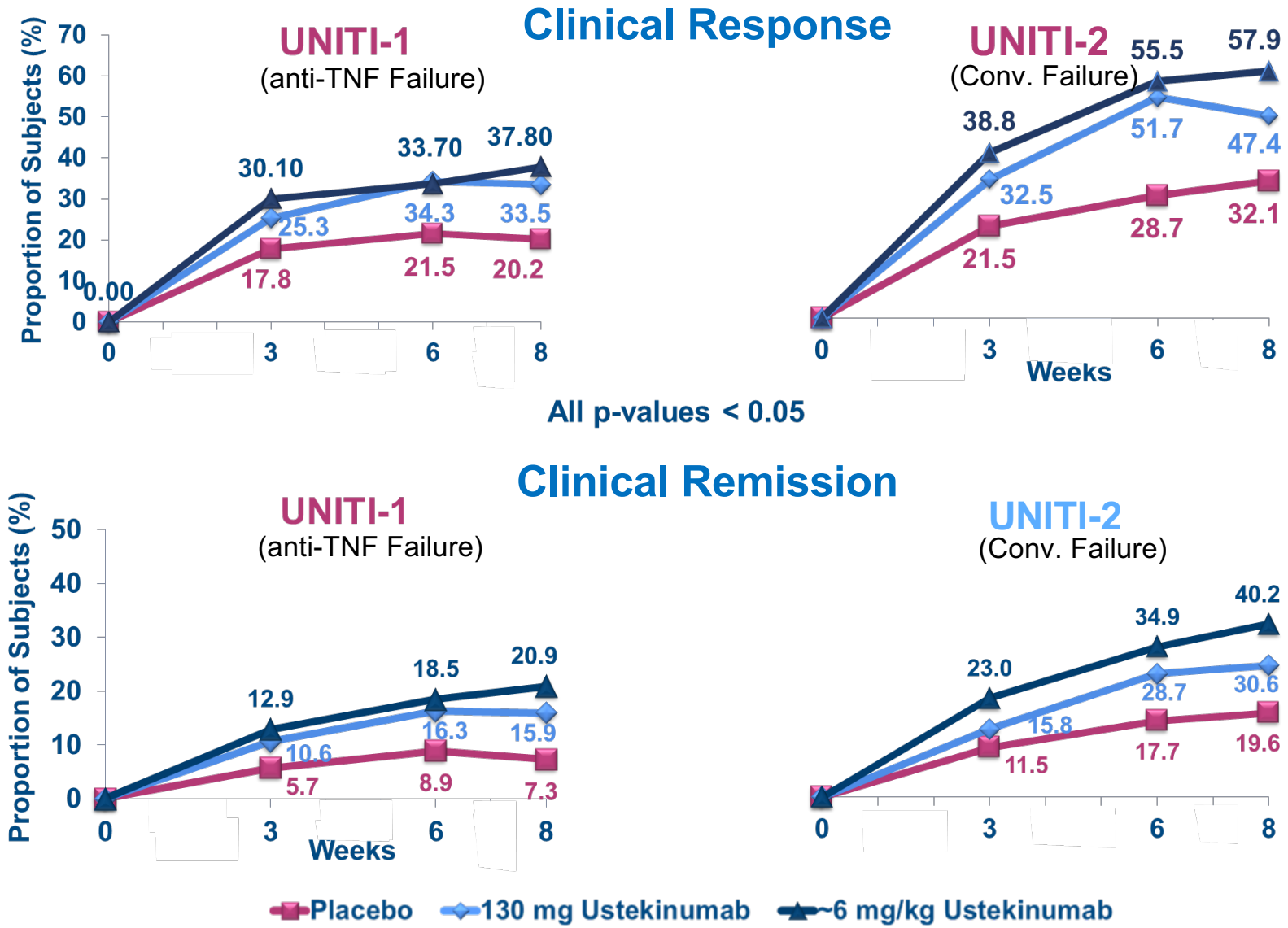
- Il-23 knockout mouse is immune competent
- Physiological role – protective against sheer stress tendons, barrier function in gut
- Hyperexpression in enthesitis (PSA, AS) and IBD
- Can reproduce psoriasis in animals with s.c. injection





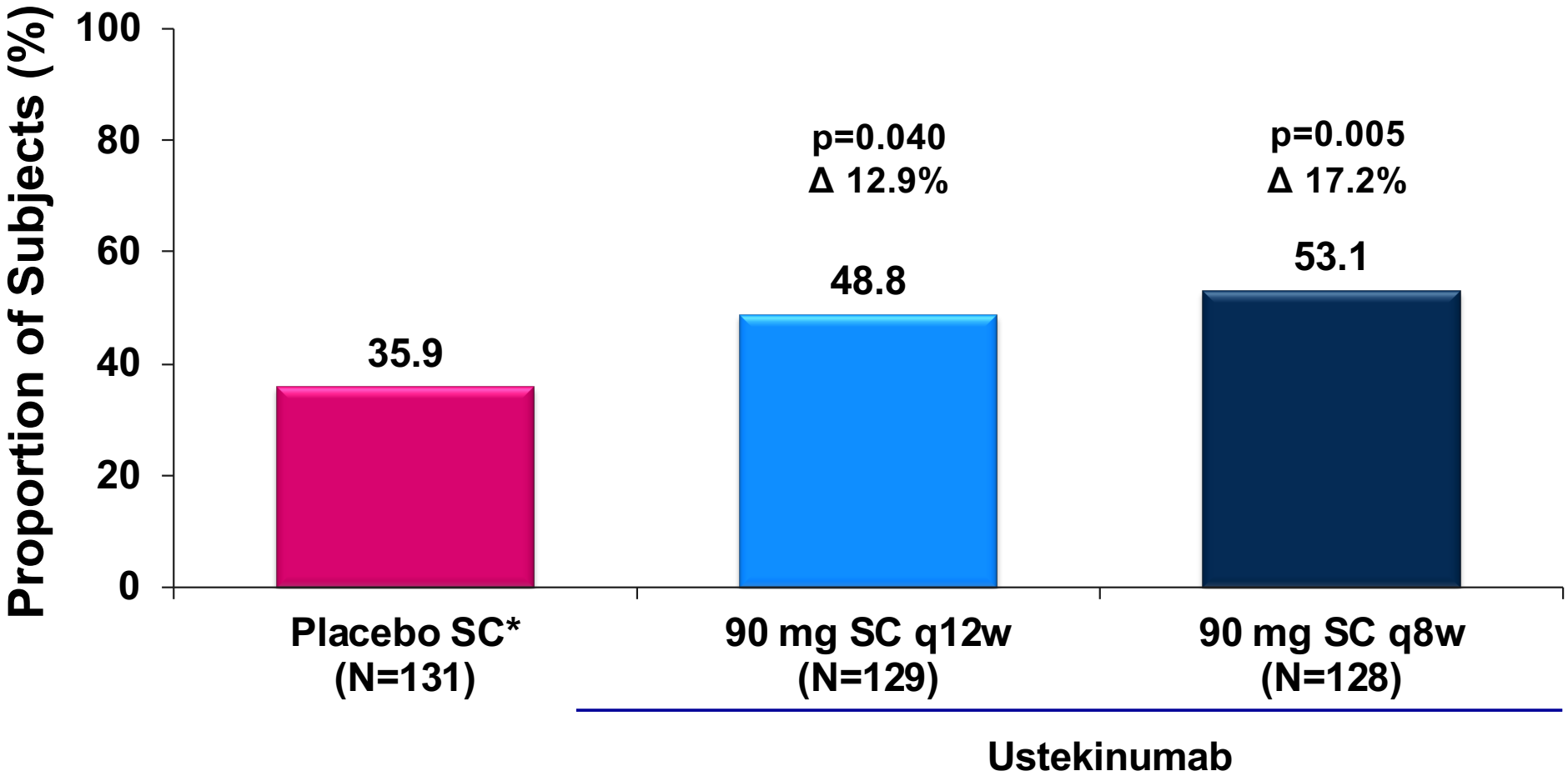
Sherlock JP. et al. Nature Medicine. 2012;18(7):1069-1077.

Clinical Response and Remission Through Week 8



Feagan BG. et al. New Eng J Med 2016;375(20):1946-1960.

UNITI: Clinical Remission at Week 44



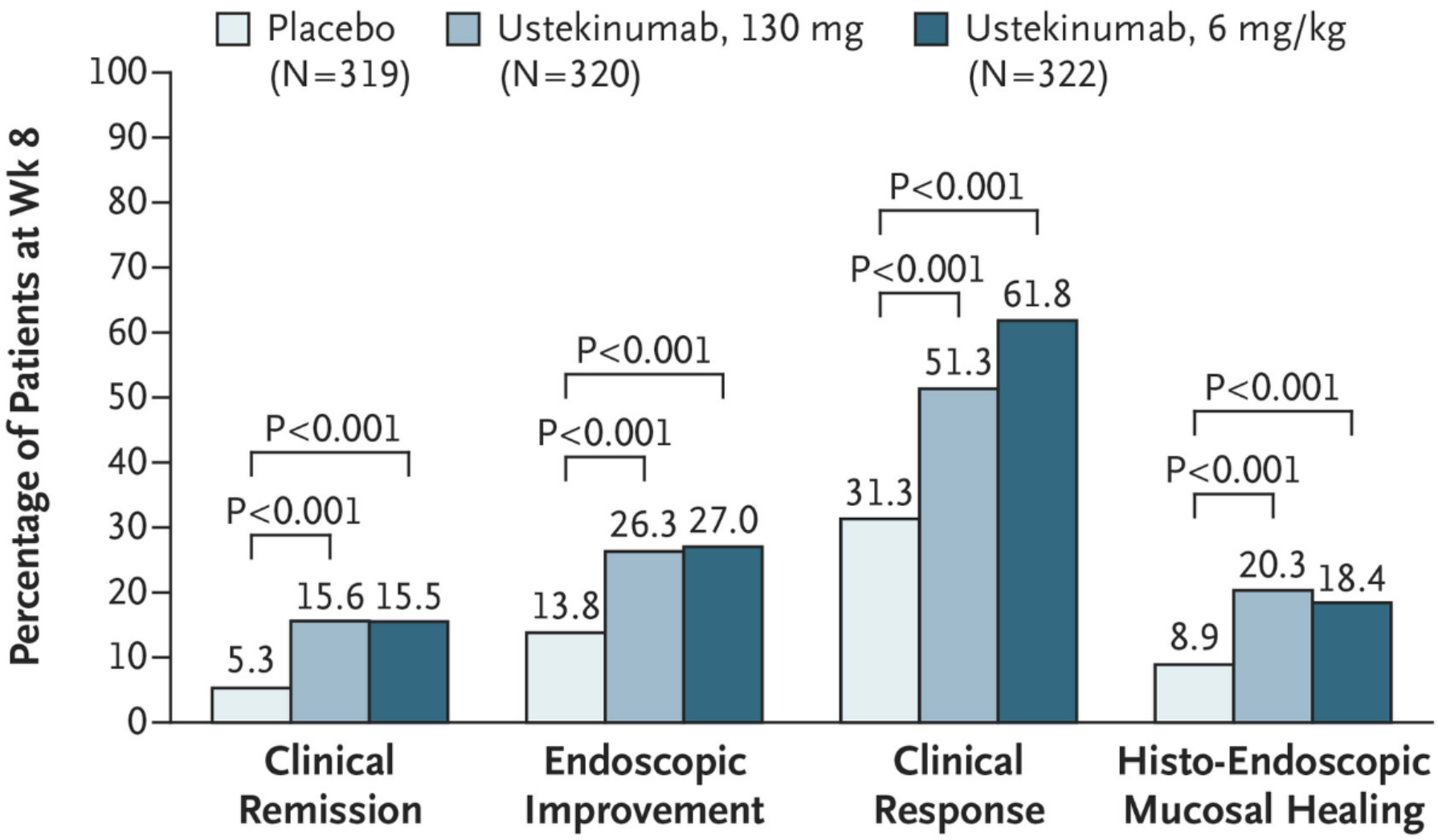
Feagan BG. et al. New Eng J Med 2016;375(20):1946-1960.

Summary of Key Safety Events Through Week 44

	Placebo SC*	Ustekinumab		
		90 mg SC q12w	90 mg SC q8w	Combined
Treated subjects who were randomized (n)	133	132	131	263
Avg. duration of follow-up (weeks)	32.0	36.6	35.2	35.9
Subjects with (%)				
Death	0%	0%	0%	0%
AEs	83.5%	80.3%	81.7%	81.0%
SAEs	15.0%	12.1%	9.9%	11.0%
Infections	49.6%	46.2%	48.1%	47.1%
Serious infections	2.3%	5.3%	2.3%	3.8%
Discontinued due to AE	6.0%	7.6%	3.1%	5.3%
Malignancies	0.8%	0%	0.8%	0%
MACE	0%	0%	0%	0%

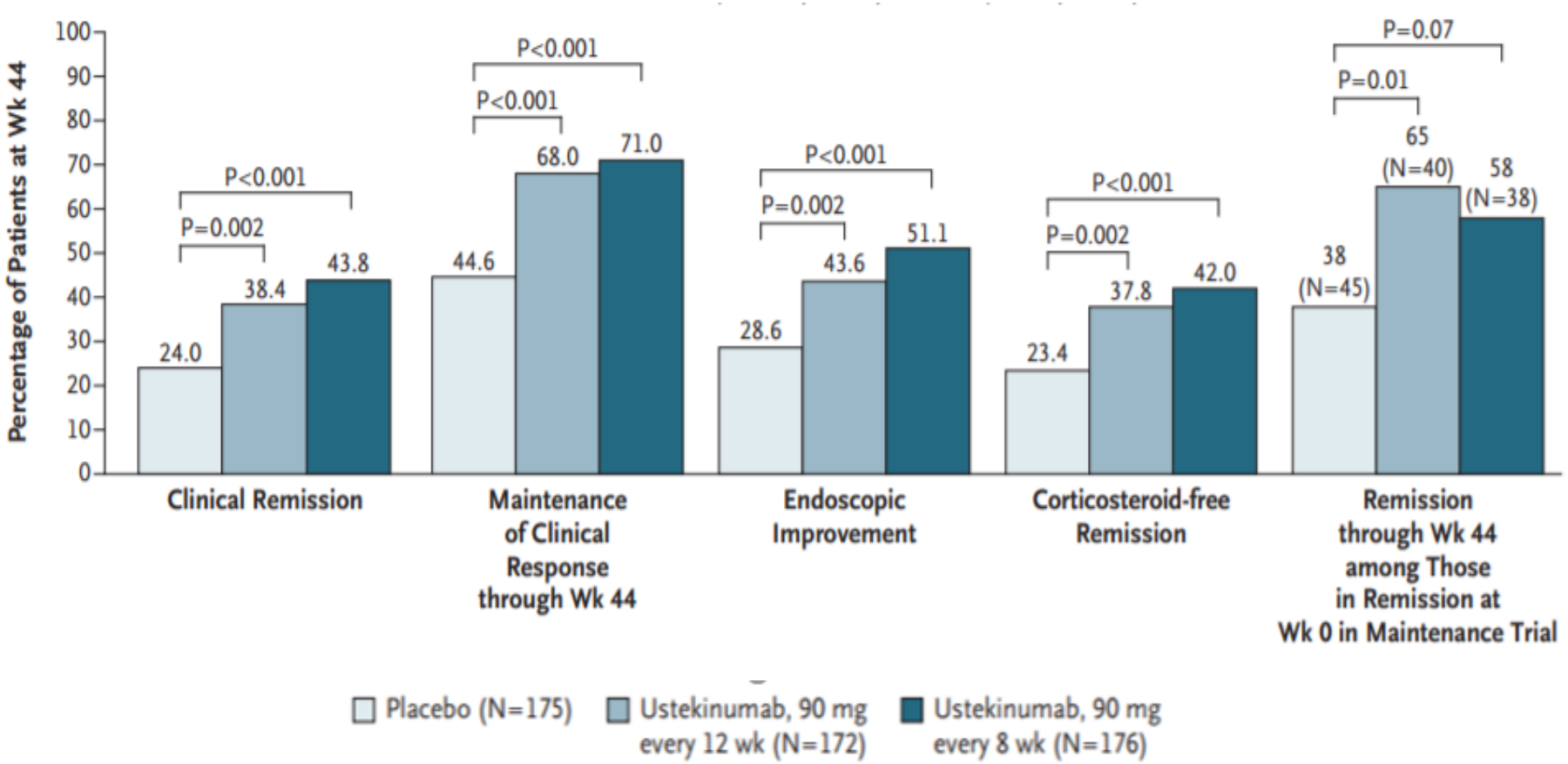
Feagan BG. et al. New Eng J Med 2016;375(20):1946-1960.

Ustekinumab for UC
UNIFI: Key Outcomes in Induction Trial



Sands B et al at New England Journal of Medicine 2019

UNIFI: Key Outcomes in Maintenance Trial



Sands B et al New England Journal of Medicine 2019

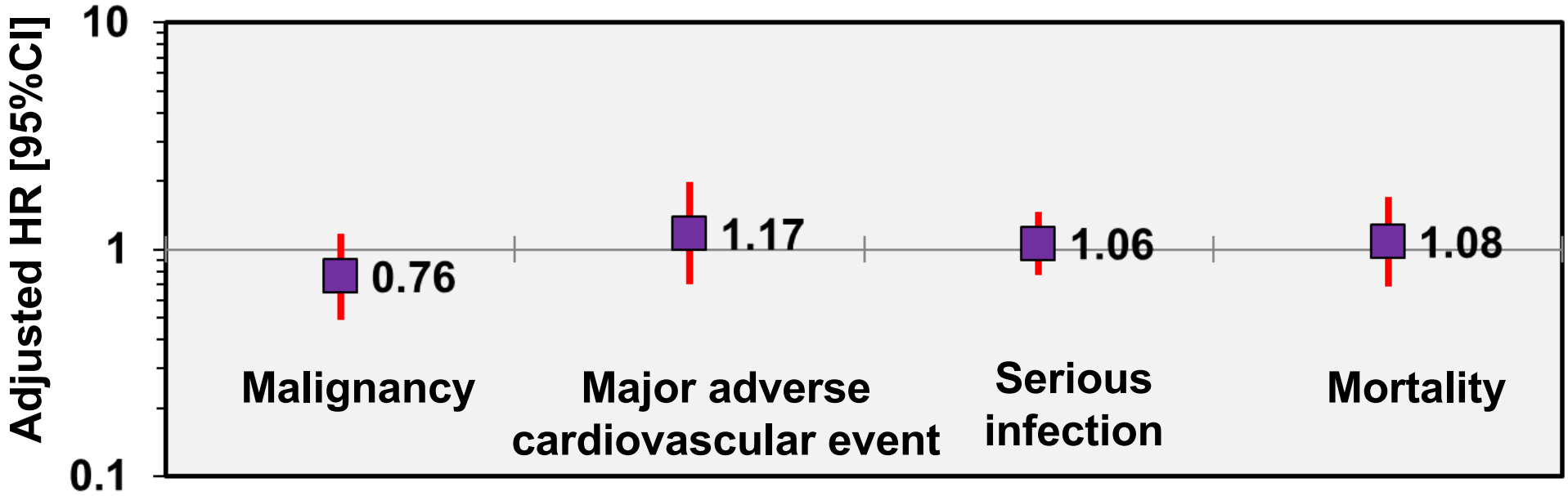
UNIFI: Safety

	Randomly Assigned Patients			Patients with No Response to IV Infusion		Randomized Population			Nonrandomized Population	
						Patients with Response to IV UST			Patients with Response to IV Placebo	Patients with Delayed Response to UST
	Placebo (N=319)	UST, 130 mg (N=321)	UST, 6 mg/kg‡ (N=320)	IV Placebo→ IV UST, 6 mg/kg‡§ (N=184)	IV UST→ SC UST, 90 mg§ (N=233)	Placebo¶ (N=175)	UST, 90 mg/12 wk (N=172)	UST, 90 mg/8 wk (N=176)	SC Placebo‖ (N=103)	SC UST, 90 mg/8 wk (N=157)
Average duration of follow-up — wk	8.7	8.6	8.6	10.2	11.5	42.3	41.8	42.2	40.8	41.8
Average no. of administrations	1.0	1.0	1.0	1.0	1.0	7.1	7.3	7.4	6.9	7.2
Death — no. (%)	0	0	1 (0.3)	0	0	0	0	0	0	1 (0.6)
Any adverse event — no. (%)	153 (48.0)	133 (41.4)	162 (50.6)	55 (29.9)	64 (27.5)	138 (78.9)	119 (69.2)	136 (77.3)	79 (76.7)	117 (74.5)
Common adverse events — no. (%)**										
Nasopharyngitis	1 (0.3)	1 (0.3)	2 (0.6)	0	0	28 (16.0)	31 (18.0)	26 (14.8)	13 (12.6)	19 (12.1)
Ulcerative colitis	18 (5.6)	9 (2.8)	8 (2.5)	12 (6.5)	20 (8.6)	50 (28.6)	19 (11.0)	18 (10.2)	28 (27.2)	26 (16.6)
Headache	14 (4.4)	22 (6.9)	13 (4.1)	2 (1.1)	2 (0.9)	7 (4.0)	11 (6.4)	18 (10.2)	4 (3.9)	9 (5.7)
Arthralgia	2 (0.6)	3 (0.9)	6 (1.9)	1 (0.5)	2 (0.9)	15 (8.6)	15 (8.7)	8 (4.5)	9 (8.7)	13 (8.3)
Upper respiratory tract infection	4 (1.3)	6 (1.9)	4 (1.2)	2 (1.1)	5 (2.1)	8 (4.6)	5 (2.9)	16 (9.1)	4 (3.9)	7 (4.5)
Anemia	11 (3.4)	7 (2.2)	8 (2.5)	4 (2.2)	1 (0.4)	12 (6.9)	9 (5.2)	7 (4.0)	9 (8.7)	9 (5.7)
Influenza	0	2 (0.6)	1 (0.3)	0	2 (0.9)	8 (4.6)	6 (3.5)	10 (5.7)	7 (6.8)	7 (4.5)
Pyrexia	6 (1.9)	4 (1.2)	6 (1.9)	1 (0.5)	0	7 (4.0)	1 (0.6)	9 (5.1)	5 (4.9)	5 (3.2)
Serious adverse events — no. (%)	22 (6.9)	12 (3.7)	11 (3.4)	7 (3.8)	12 (5.2)	17 (9.7)	13 (7.6)	15 (8.5)	8 (7.8)	11 (7.0)
Infections — no. (%)††										
Any	49 (15.4)	51 (15.9)	51 (15.9)	22 (12.0)	14 (6.0)	81 (46.3)	58 (33.7)	86 (48.9)	44 (42.7)	58 (36.9)
Serious	5 (1.6)	2 (0.6)	1 (0.3)	3 (1.6)	2 (0.9)	4 (2.3)	6 (3.5)	3 (1.7)	2 (1.9)	2 (1.3)
Adverse events leading to discontinuation of ustekinumab or placebo — no. (%)	NA‡‡	NA	NA			20 (11.4)	9 (5.2)	5 (2.8)	13 (12.6)	12 (7.6)
Cancer, excluding NMSC — no. (%)	0	0	0	0	2 (0.9)	0	1 (0.6)	1 (0.6)	1 (1.0)	0
Adverse events associated with an infusion or injection-site reactions — no. (%)§§	6 (1.9)	7 (2.2)	3 (0.9)	5 (2.7)	6 (2.6)	4 (2.3)	1 (0.6)	5 (2.8)	0	4 (2.5)

Sands B et al at N Engl J Med. 2019 Sep 26;381(13):1201-1214

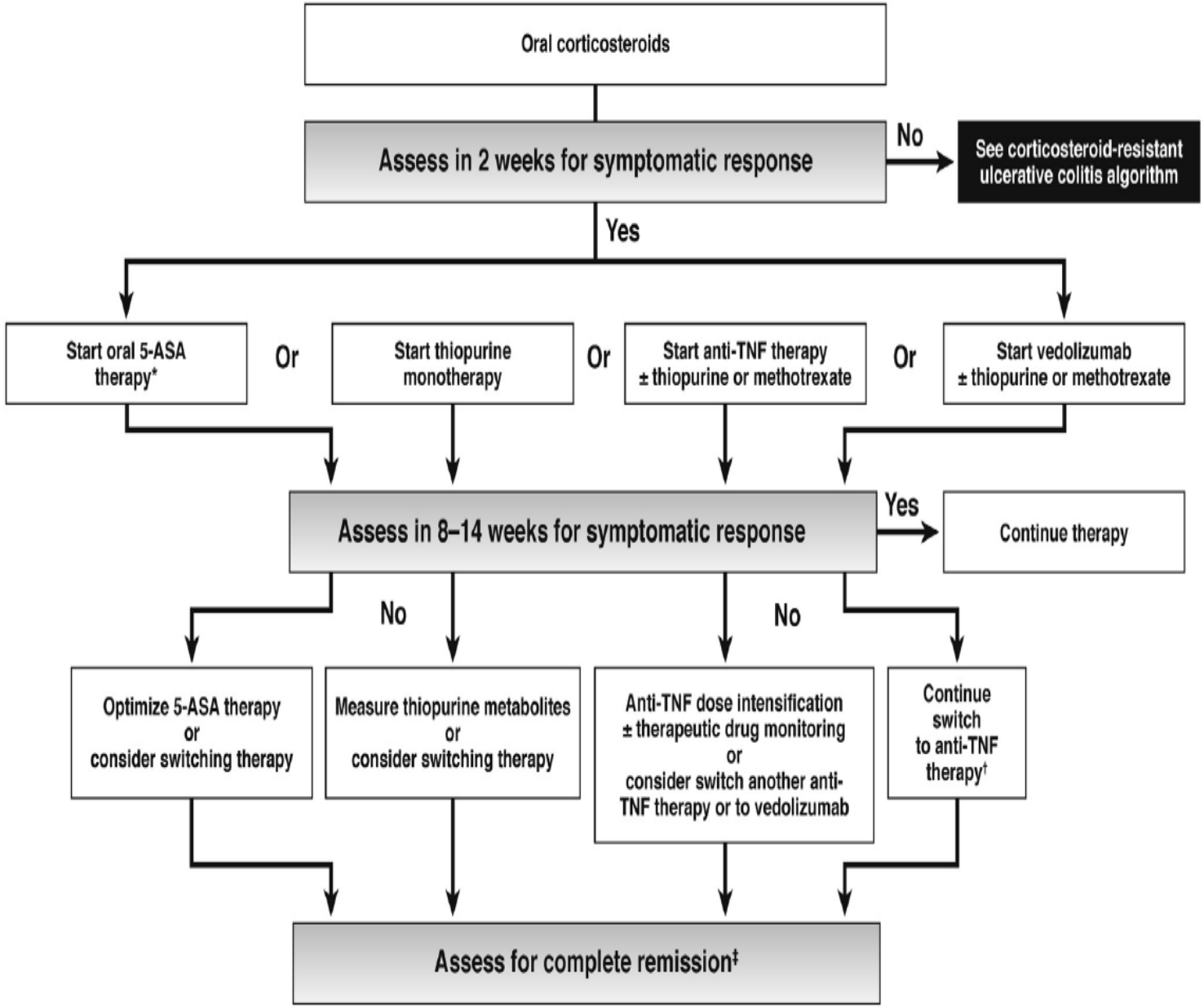
PSOLAR: Safety of Ustekinumab in Psoriasis

Independent Predictors of Time to First Event: Ustekinumab-Treated vs. Non-Biologic-Treated



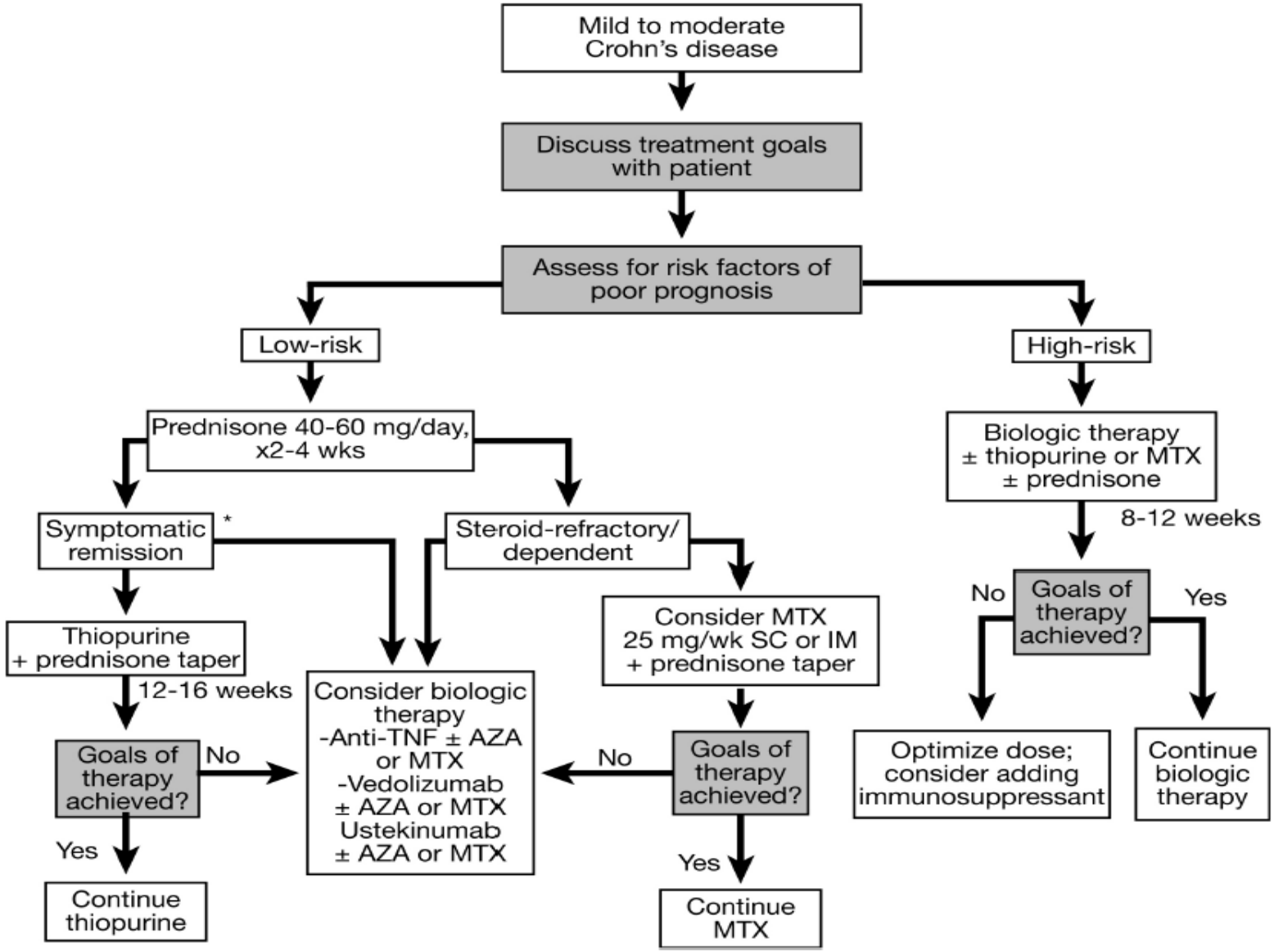
Papp K, et al. J Drugs Dermatol. 2015;14(7):706-714.

Current Guidelines: Ulcerative Colitis



Bressler B. et al. Gastroenterology 2015;148:1035-1058

Current Guidelines: Crohn's Disease



Panaccione R. et al. CAG 2019,2(3), e1-e34

Future Evolution: Two Paths Forward?

The Evolution of Psoriasis Therapy 2000-2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Ustekinumab and Etanercept for Moderate-to-Severe Psoriasis

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*The investigators participating in the Active Comparator (CNTO 1275/Enbrel) Psoriasis Trial (ACCEPT) study group are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

This article (10.1056/NEJMoa080652) was updated on January 25, 2010, at NEJM.org.

N Engl J Med 2010;362:118-28.

ABSTRACT

BACKGROUND

Biologic agents offer a range of new therapeutic options for patients with psoriasis; however, the relative benefit–risk profiles of such therapies are not well known. We compared two biologic agents, ustekinumab (an interleukin-12 and interleukin-23 blocker) and etanercept (an inhibitor of tumor necrosis factor α), for the treatment of psoriasis.

METHODS

We randomly assigned 903 patients with moderate-to-severe psoriasis to receive subcutaneous injections of either 45 or 90 mg of ustekinumab (at weeks 0 and 4) or high-dose etanercept (50 mg twice weekly for 12 weeks). The primary end point was the proportion of patients with at least 75% improvement in the psoriasis area-and-severity index (PASI) at week 12; a secondary end point was the proportion with cleared or minimal disease on the basis of the physician's global assessment. Assessors were unaware of the treatment assignments. The efficacy and safety of a crossover from etanercept to ustekinumab were evaluated after week 12.

RESULTS

There was at least 75% improvement in the PASI at week 12 in 67.5% of patients who received 45 mg of ustekinumab and 73.8% of patients who received 90 mg, as compared with 56.8% of those who received etanercept (P=0.01 and P<0.001, respectively). Similarly, 65.1% of patients who received 45 mg of ustekinumab and 70.6% of patients who received 90 mg of ustekinumab had cleared or minimal disease according to the physician's global assessment, as compared with 49.0% of those who received etanercept (P<0.001 for both comparisons). Among patients who did not have a response to etanercept, 48.9% had at least 75% improvement in the PASI within 12 weeks after crossover to ustekinumab. One or more adverse events occurred through week 12 in 66.0% of patients who received 45 mg of ustekinumab and 69.2% of patients who received 90 mg of ustekinumab and in 70.0% who received etanercept; 1.9%, 1.2%, and 1.2%, respectively, had serious adverse events. Safety patterns were similar before and after crossover from etanercept to ustekinumab.

CONCLUSIONS

The efficacy of ustekinumab at a dose of 45 or 90 mg was superior to that of high-dose etanercept over a 12-week period in patients with psoriasis. (ClinicalTrials.gov number, NCT00454584.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis

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The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Lebwohl at the Icahn Medical Institute, 2nd Fl., 1425 Madison Ave., New York, NY 10029, or at mark.lebwohl@mountsinai.org.

N Engl J Med 2015;373:1318-28.
DOI: 10.1056/NEJMoa1503824

ABSTRACT

BACKGROUND

Early clinical studies suggested that the anti–interleukin-17 receptor A monoclonal antibody brodalumab has efficacy in the treatment of psoriasis.

METHODS

In two phase 3 studies (AMAGINE-2 and AMAGINE-3), patients with moderate-to-severe psoriasis were randomly assigned to receive brodalumab (210 mg or 140 mg every 2 weeks), ustekinumab (45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg), or placebo. At week 12, patients receiving brodalumab were randomly assigned again to receive a brodalumab maintenance dose of 210 mg every 2 weeks or 140 mg every 2 weeks, every 4 weeks, or every 8 weeks; patients receiving ustekinumab continued to receive ustekinumab every 12 weeks, and patients receiving placebo received 210 mg of brodalumab every 2 weeks. The primary aims were to evaluate the superiority of brodalumab over placebo at week 12 with respect to at least a 75% reduction in the psoriasis area-and-severity index score (PASI 75) and a static physician's global assessment (sPGA) score of 0 or 1 (clear or almost clear skin), as well as the superiority of brodalumab over ustekinumab at week 12 with respect to a 100% reduction in PASI score (PASI 100).

RESULTS

At week 12, the PASI 75 response rates were higher with brodalumab at the 210-mg and 140-mg doses than with placebo (86% and 67%, respectively, vs. 8% [AMAGINE-2] and 85% and 69%, respectively, vs. 6% [AMAGINE-3]; P<0.001); the rates of sPGA scores of 0 or 1 were also higher with brodalumab (P<0.001). The week 12 PASI 100 response rates were significantly higher with 210 mg of brodalumab than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3], P<0.001). The PASI 100 response rates with 140 mg of brodalumab were 26% in AMAGINE-2 (P=0.08 for the comparison with ustekinumab) and 27% in AMAGINE-3 (P=0.007). Rates of neutropenia were higher with brodalumab and with ustekinumab than with placebo. Mild or moderate candida infections were more frequent with brodalumab than with ustekinumab or placebo. Through week 52, the rates of serious infectious episodes were 1.0 (AMAGINE-2) and 1.3 (AMAGINE-3) per 100 patient-years of exposure to brodalumab.

CONCLUSIONS

Brodalumab treatment resulted in significant clinical improvements in patients with moderate-to-severe psoriasis. (Funded by Amgen; AMAGINE-2 and AMAGINE-3 ClinicalTrials.gov numbers, NCT01708603 and NCT01708629.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis

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N Engl J Med 2017;376:1551-60.
DOI: 10.1056/NEJMoa1607017

ABSTRACT

BACKGROUND

Interleukin-23 is thought to be critical to the pathogenesis of psoriasis. We compared risankizumab (BI 655066), a humanized IgG1 monoclonal antibody that inhibits interleukin-23 by specifically targeting the p19 subunit and thus prevents interleukin-23 signaling, and ustekinumab, an interleukin-12 and interleukin-23 inhibitor, in patients with moderate-to-severe plaque psoriasis.

METHODS

We randomly assigned a total of 166 patients to receive subcutaneous injections of risankizumab (a single 18-mg dose at week 0 or 90-mg or 180-mg doses at weeks 0, 4, and 16) or ustekinumab (45 or 90 mg, according to body weight, at weeks 0, 4, and 16). The primary end point was a 90% or greater reduction from baseline in the Psoriasis Area and Severity Index (PASI) score at week 12.

RESULTS

At week 12, the percentage of patients with a 90% or greater reduction in the PASI score was 77% (64 of 83 patients) for risankizumab (90-mg and 180-mg groups, pooled), as compared with 40% (16 of 40 patients) for ustekinumab (P<0.001); the percentage of patients with a 100% reduction in the PASI score was 45% in the pooled 90-mg and 180-mg risankizumab groups, as compared with 18% in the ustekinumab group. Efficacy was generally maintained up to 20 weeks after the final dose of 90 or 180 mg of risankizumab. In the 18-mg and 90-mg risankizumab groups and the ustekinumab group, 5 patients (12%), 6 patients (15%), and 3 patients (8%), respectively, had serious adverse events, including two basal-cell carcinomas and one major cardiovascular adverse event; there were no serious adverse events in the 180-mg risankizumab group.

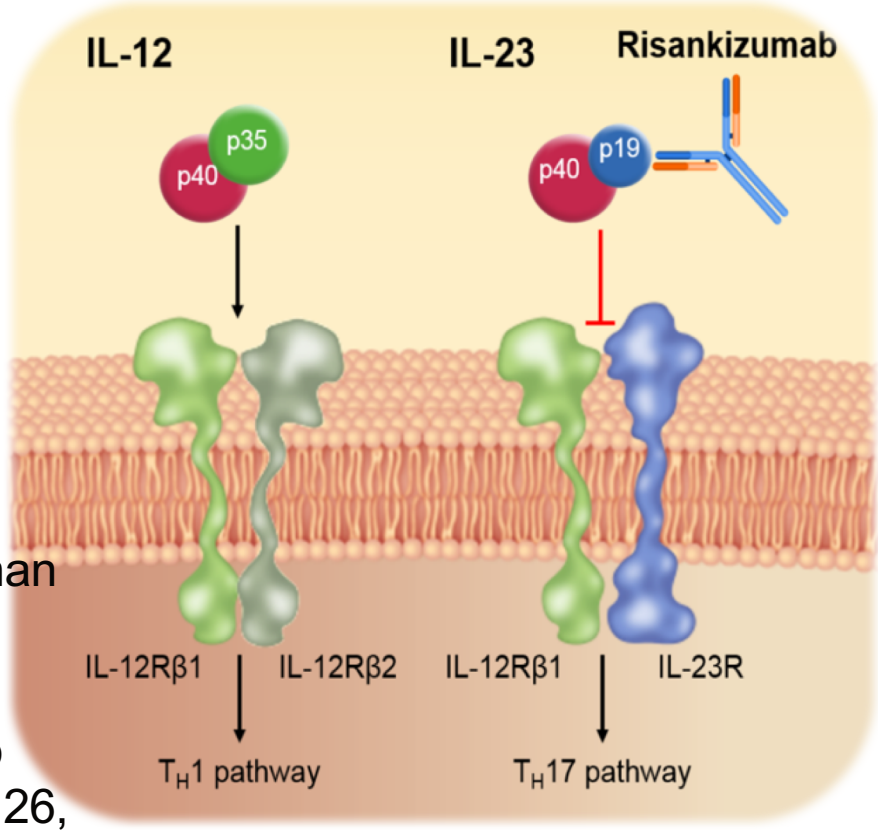
CONCLUSIONS

In this phase 2 trial, selective blockade of interleukin-23 with risankizumab was associated with clinical responses superior to those associated with ustekinumab. This trial was not large enough or of long enough duration to draw conclusions about safety. (Funded by Boehringer Ingelheim; ClinicalTrials.gov number, NCT02054481.)

Griffiths CE. et al. N Eng J Med. 2010;362(2):118-28
Lebwohl M et al. N Eng J Med. 2015;373(14):1318-28.
Papp KA, et al. N Eng J Med. 2017;376(16):1551-1560.

Risankizumab

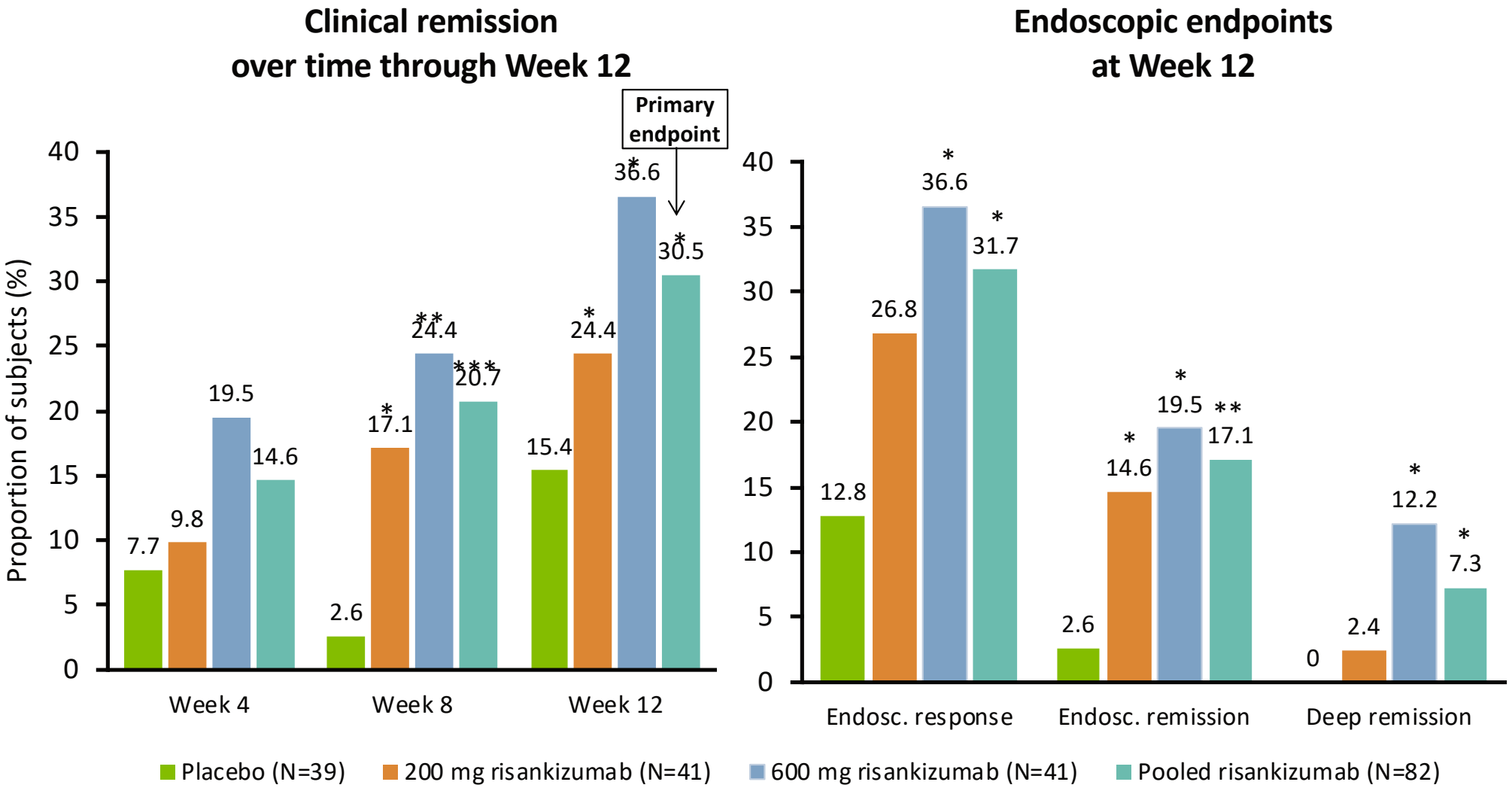
- The IL-23 pathway has been implicated in the pathogenesis of Crohn's disease[1,2]
- Risankizumab is a humanized mAb that targets the p19 subunit, specific to IL-23[3]
- In a head-to-head trial in subjects with chronic plaque psoriasis, risankizumab had superior efficacy to ustekinumab[4]
- In a Phase II proof-of-concept study in subjects with Crohn's disease, iv risankizumab was more effective than placebo for inducing clinical and endoscopic remission at 12 weeks[5]
  - Re-induction therapy with 600 mg iv risankizumab increased clinical remission rates further at Week 26, and was well tolerated over 26 weeks[6]



- **Objective**
- Assessment of the efficacy and safety of open-label 180 mg sc risankizumab maintenance therapy at Week 52

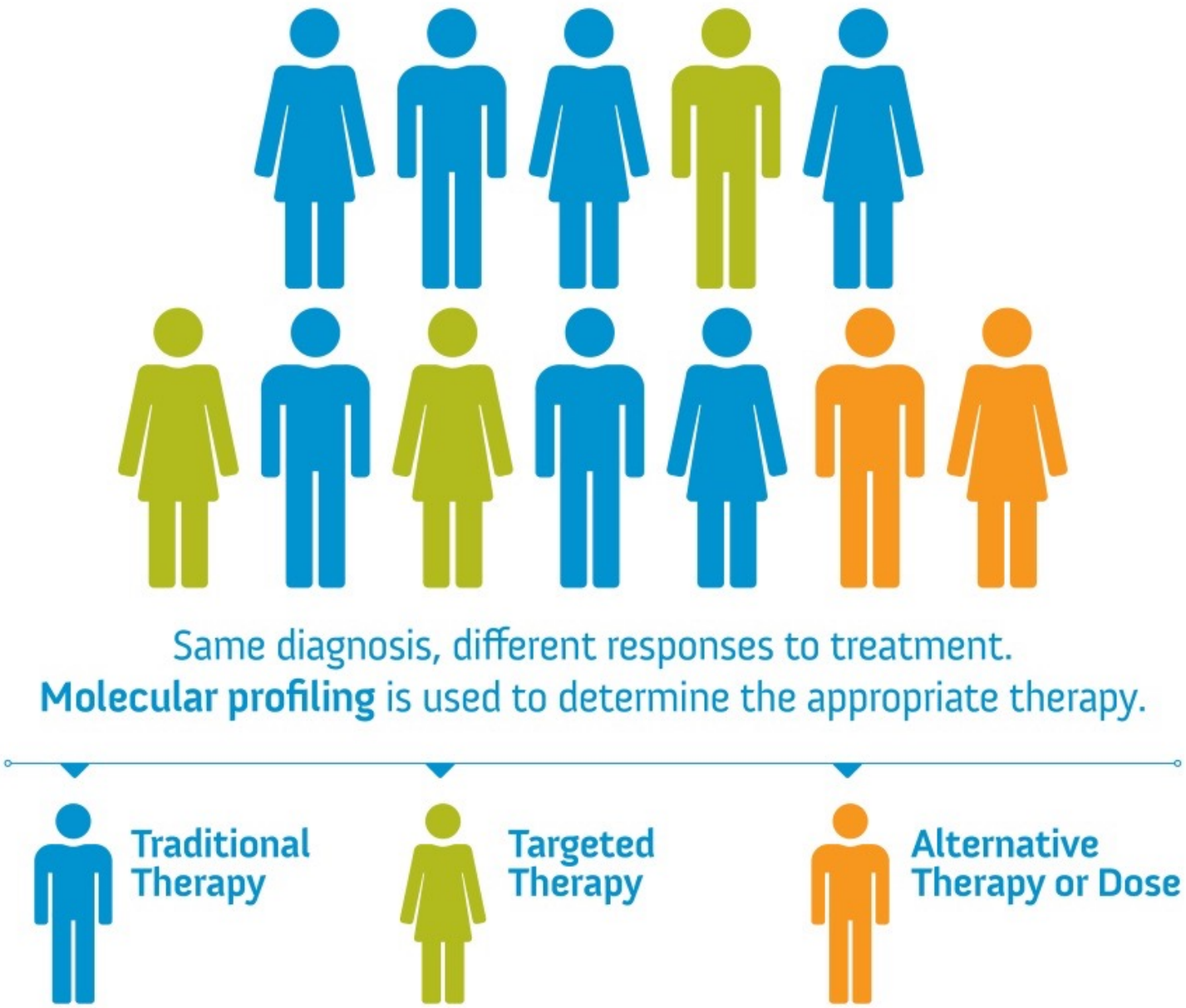
Feagan B, et al. Lancet 2017;389:1699–1709;

Induction Treatment Outcome

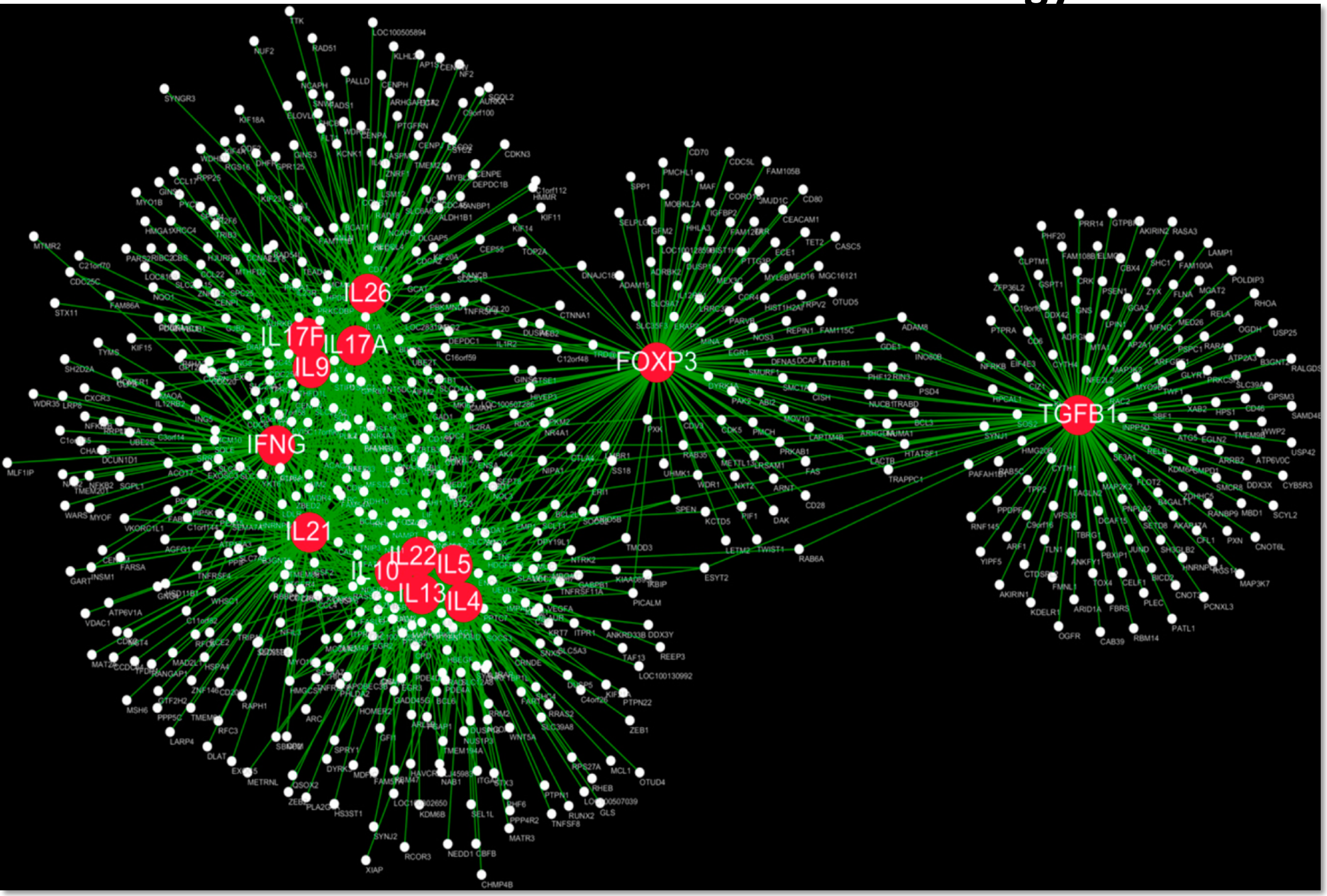


Feagan B, et al. Lancet 2017;389:1699–1709.

One Way Forward – Molecular Profiling 101

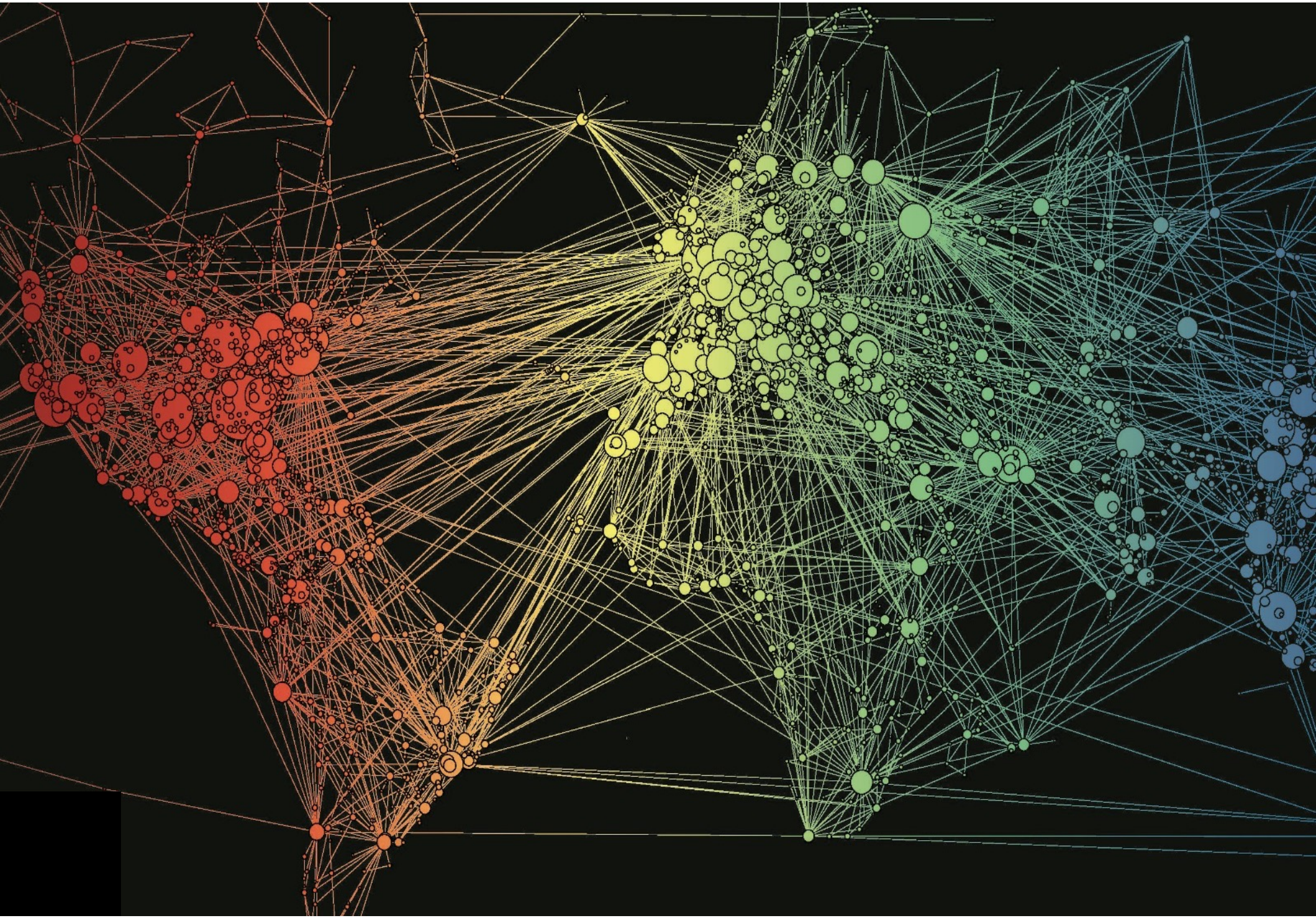


A Second Path -T Cell Network Biology



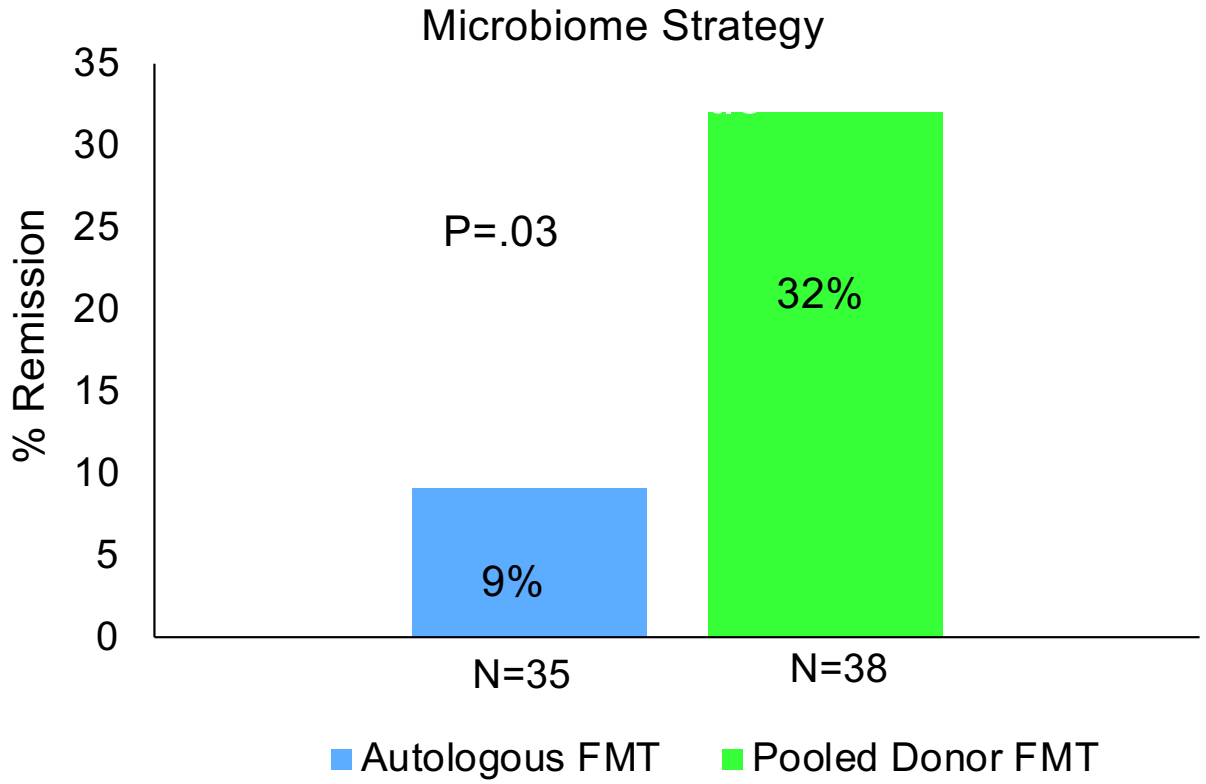
Wang P et al. *J Immunol* 2016; 197:665-673

Global Airline Networks!



Orthoganol Contrasts for Combination Therapy

- Anti-integrin plus anti-IL23
- Anti-integrin plus JAK Inhibitor
- SIP1 plus anti IL-23
- Locally acting TNF antagonist plus Anti-IL23



Costello S. et al. JAMA 2019;321(2):156-164

Final Thoughts : Whose on First?

- All three classes of biologic drugs have excellent therapeutic indices in comparison to conventional drugs (corticosteroids , small molecules)
- Vedolizumab and ustekinumab have superior safety profiles to TNF antagonists – first line agents in both UC and CD
- TNF antagonists have a role for rapid relief of symptoms – severe disease
- Greater efficacy is the new frontier -redux combination therapy is the way to get there

New Age Combination Therapy

Precision Medicine