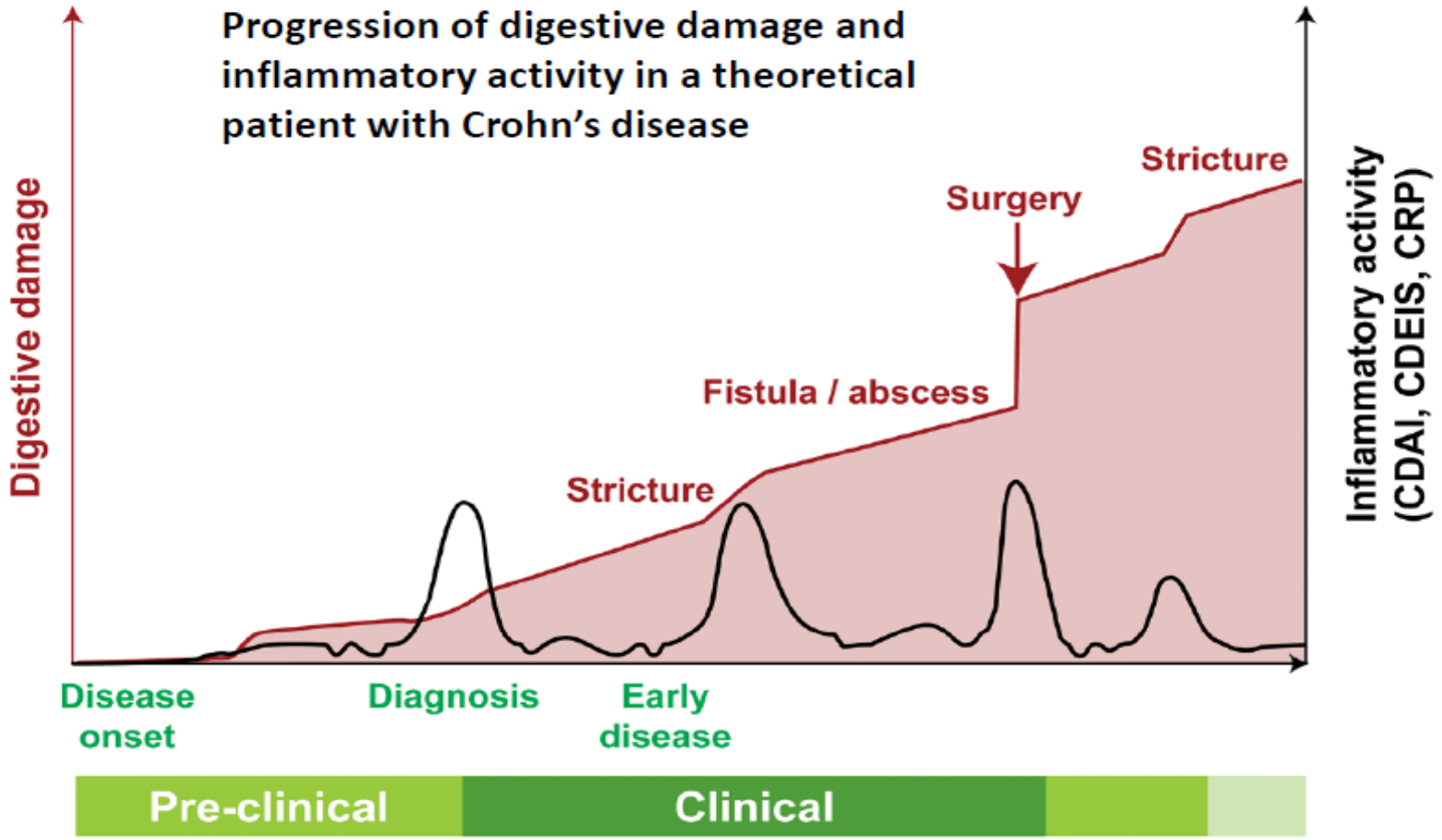
Φλεγμονώδης- στενωτική περιφερική τελική ειλείτιδα Φαρμακευτική θεραπεία

Βρακάς Σπυρίδων
Επικουρικός Επιμελητής Β
Γαστρεντερολογική Κλινική
Τζάνειο Νοσοκομείο

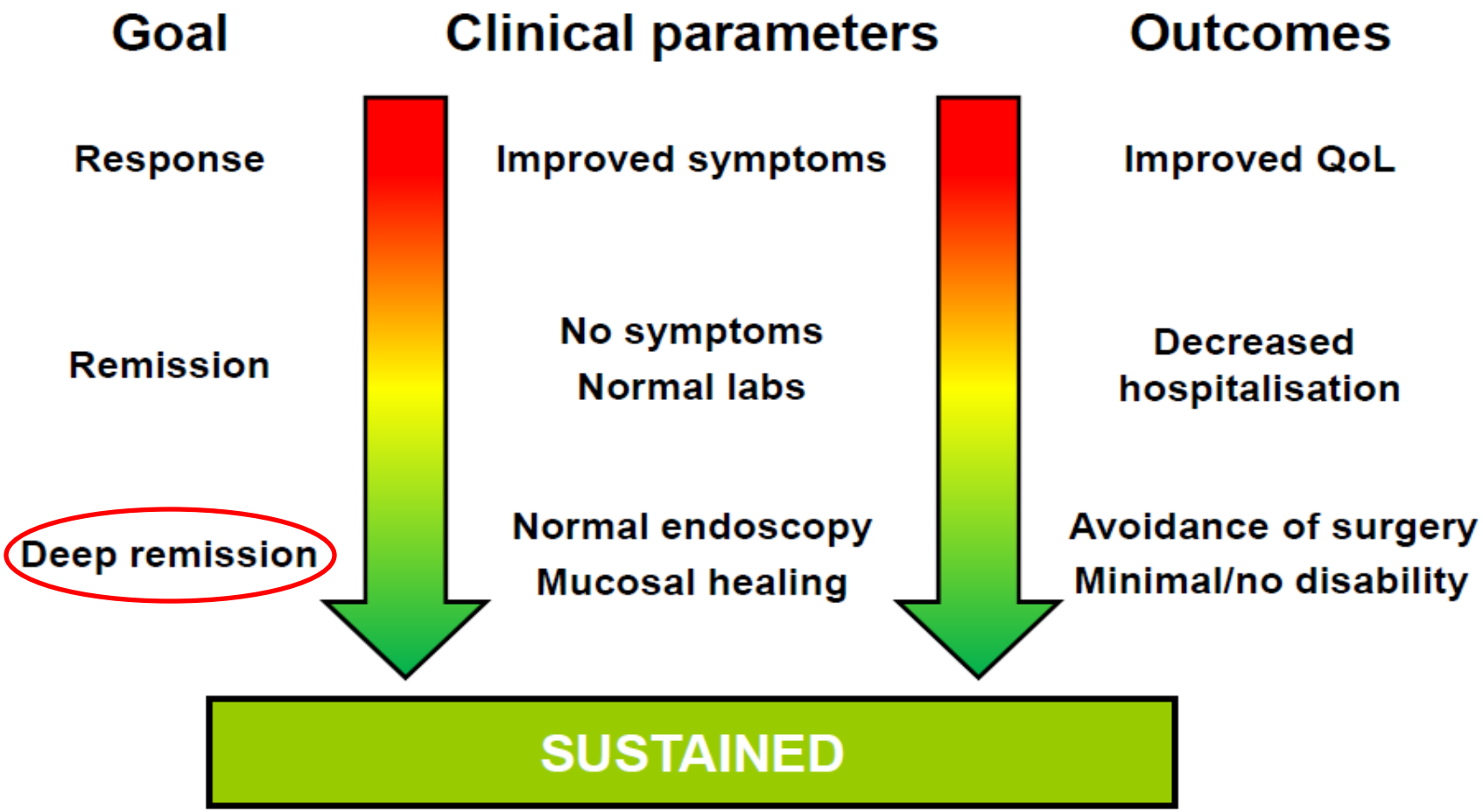
Crohn's disease is a chronic progressive disease



CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Index of Severity; CRP, C-reactive protein

Pariente B, *et al. Inflamm Bowel Dis* 2011;17:1415–22

Evolving goals of therapy for Crohn's disease



Disease activity in Crohn's disease

Mild	Moderate	Severe
Equivalent to a CDAI of 150–220 e.g. Ambulatory, eating and drinking, <10% weight loss. No features of obstruction, fever, dehydration, abdominal mass, or tenderness. CRP usually increased above the upper limit of normal.	Equivalent to a CDAI of 220–450 e.g. Intermittent vomiting, or weight loss >10%. Treatment for mild disease ineffective, or tender mass. No overt obstruction. CRP elevated above the upper limit of normal.	Equivalent to a CDAI of >450 e.g. Cachexia (BMI <18 kg m^{-2}), or evidence of obstruction or abscess. Persistent symptoms despite intensive treatment. CRP increased.

Van Assche et al. Journal of Crohn's and Colitis 2010;4:7 –27

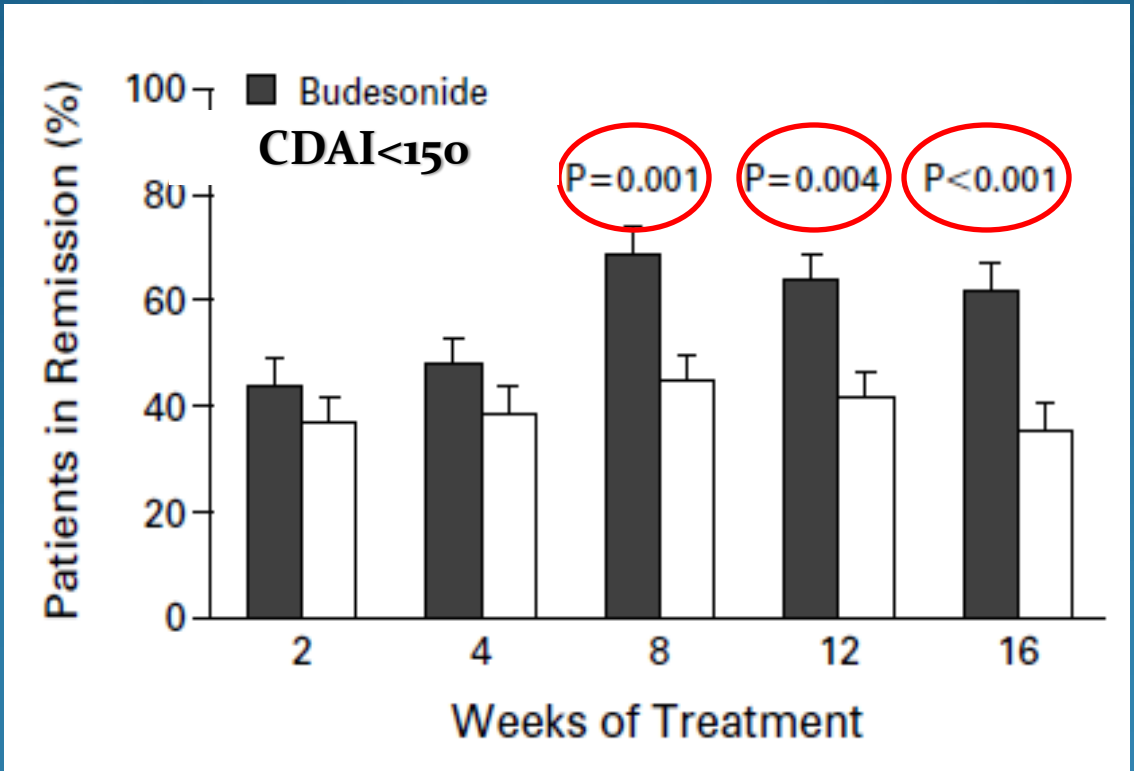
Mildly active localized CD

ECCO statement 5B

✓Oral Budesonide is the preferred treatment [EL2]

Gomollón et al. Journal of Crohn's and Colitis, 2017; 3–25

A comparison of Budesonide and Mesalamine for active Crohn's disease



Median time to remission: Budesonide 28 days vs Mesalamine 84 days (P=0.04)

Thomsen et al. N Engl J Med 1998;339:370-4.

Moderately active localized CD

ECCO statement 5C

✓Moderately active localised ileocaecal Crohn's disease should be treated with budesonide [EL1], or with systemic corticosteroids [EL1]

✓An anti-TNF based strategy should be used as an alternative for patients, who have previously been steroid-refractory or –intolerant [EL1]

✓In patients refractory to steroids and/or anti-TNF, vedolizumab is an appropriate alternative [EL1]

✓For some patients who have infrequently relapsing disease restarting steroids with an immunomodulator may be appropriate [EL2].

Gomollón et al. Journal of Crohn's and Colitis, 2017; 3–25

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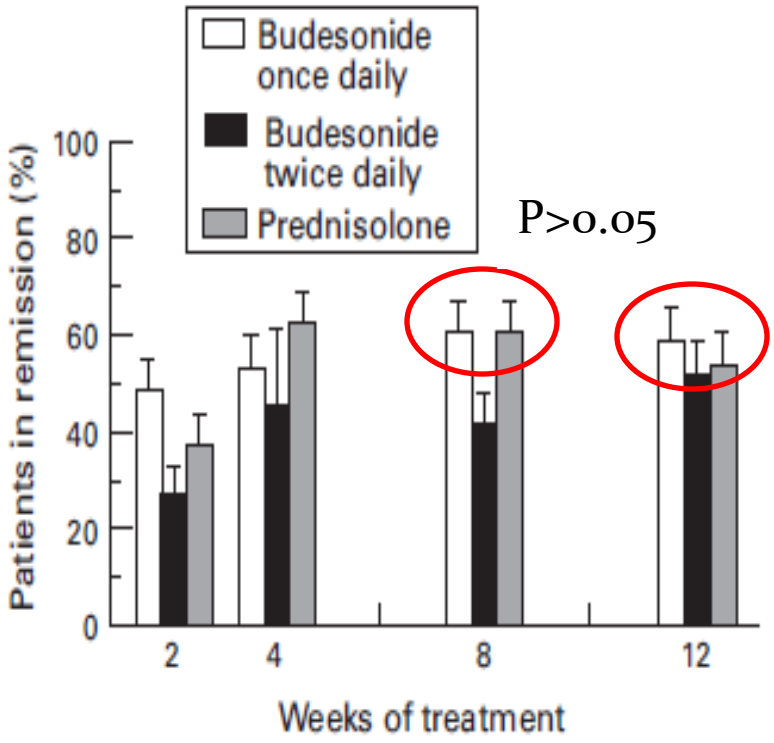
Gomollón et al. Journal of Crohn's and Colitis, 2017; 3–25

Oral budesonide is as effective as oral prednisolone in active Crohn's disease



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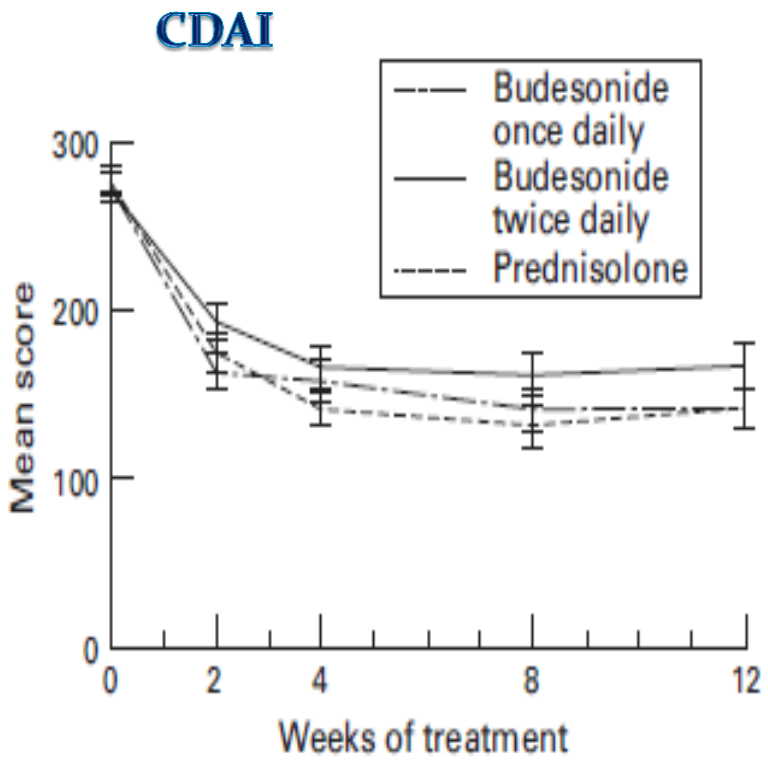

Campieri et al. *Gut 1997;* ***41: 209–214***

Severely active localized CD

ECCO statement 5D

✓Severely active localised ileocaecal Crohn's disease should initially be treated with systemic corticosteroids [EL1].

✓For those who have relapsed, an anti-TNF based strategy is appropriate [EL1]

✓In patients refractory to steroids and/or anti-TNF vedolizumab is an appropriate alternative [EL1]

✓For some patients who have infrequently relapsing disease restarting steroids with an immunomodulator may be appropriate [EL2]

✓Surgery is a reasonable alternative for patients with disease refractory to conventional medical treatment and should also be discussed [EL3]

Gomollón et al. Journal of Crohn's and Colitis, 2017; 3–25

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Gomollón et al. Journal of Crohn's and Colitis, 2017; 3–25

First presentation of localized disease

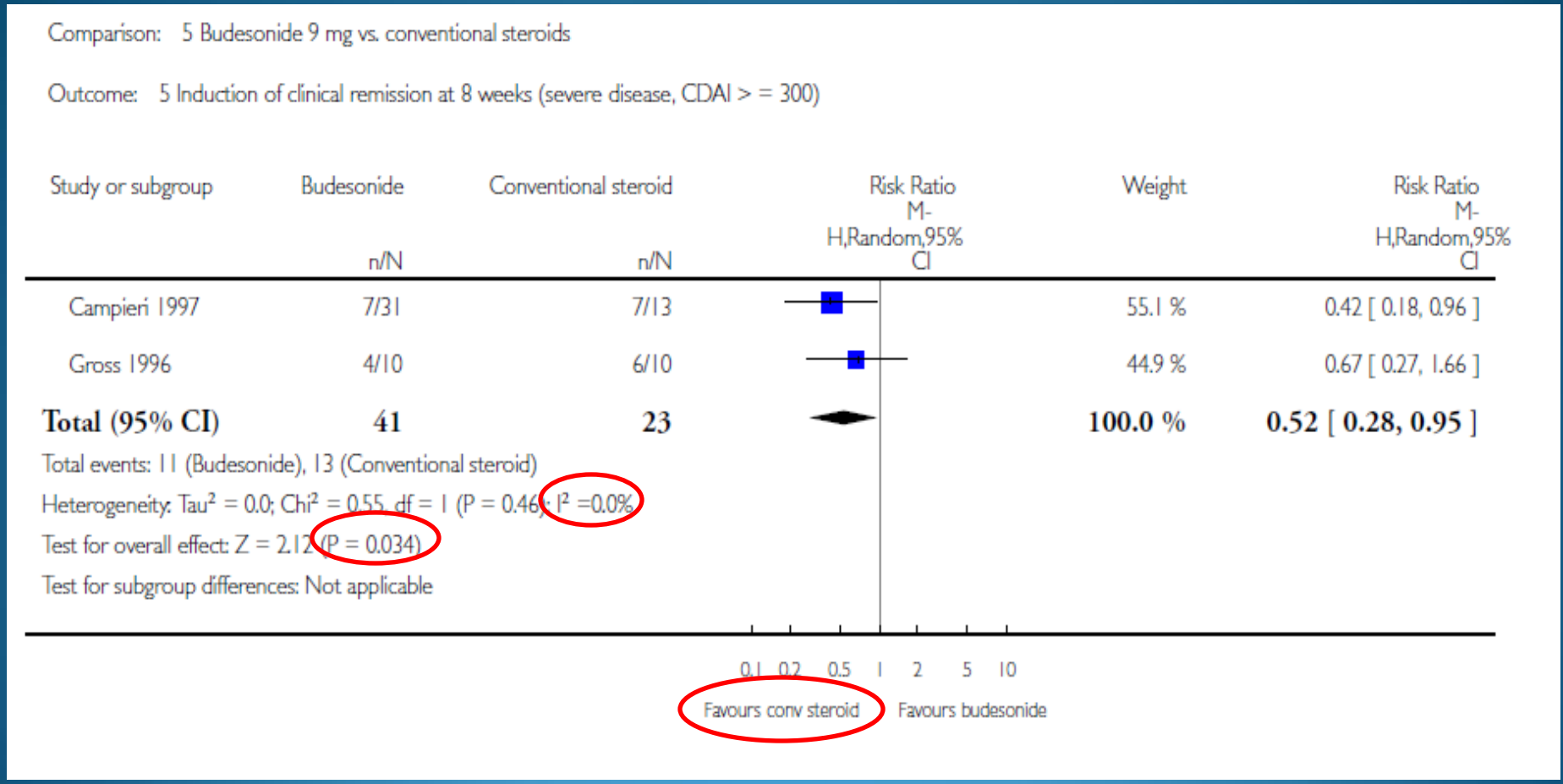
ECCO statement 6A

✓After the first presentation if remission has been achieved with systemic steroids, a thiopurine [EL1] or methotrexate [EL3] should be considered

✓No maintenance treatment is an option for some patients [EL5]

Gomollón et al. Journal of Crohn's and Colitis, 2017; 3–25

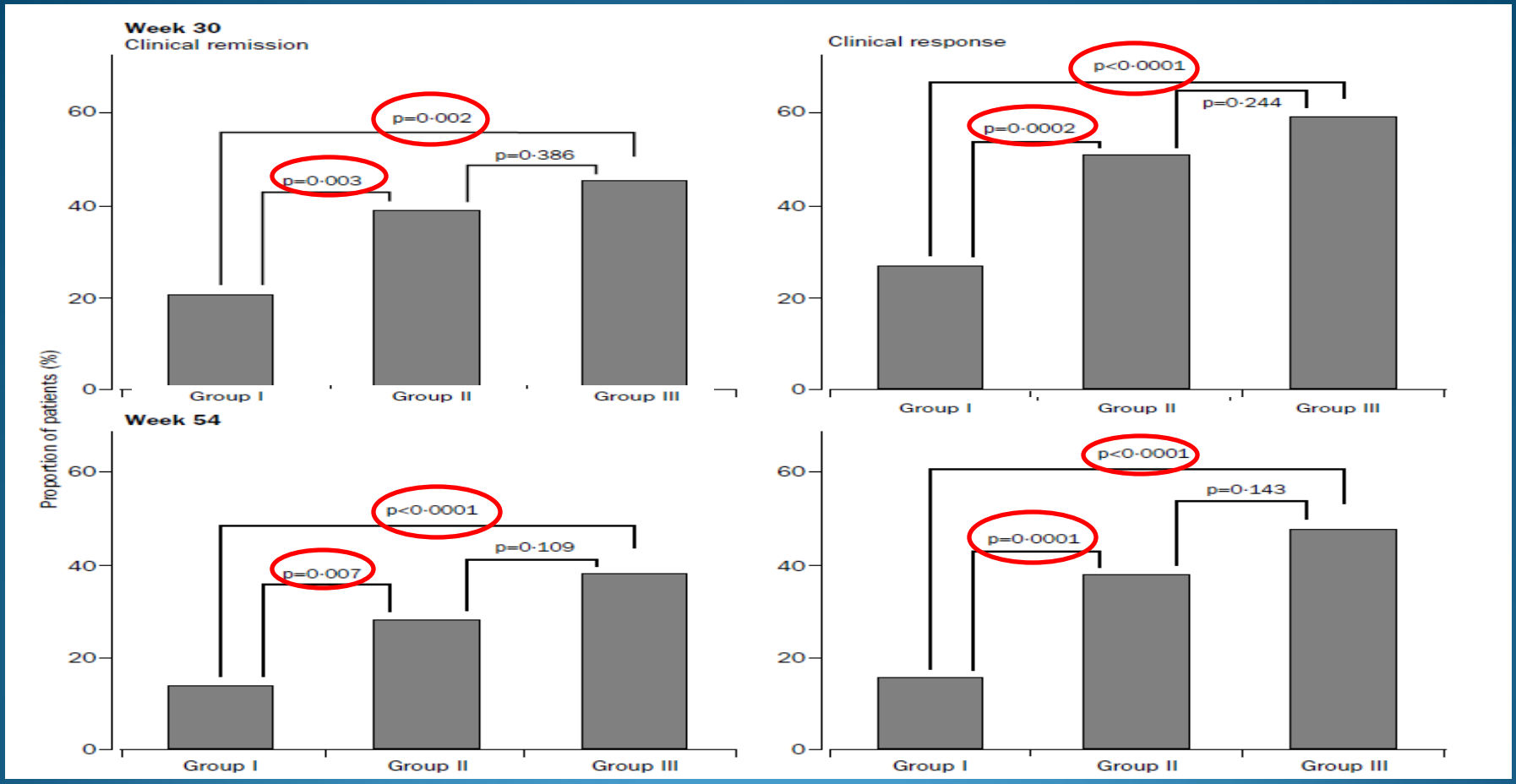
Budesonide vs conventional steroids Induction of clinical remission



Rezaie et al. Cochrane Database Syst Rev 2015;6:CD000296

Anti-TNF

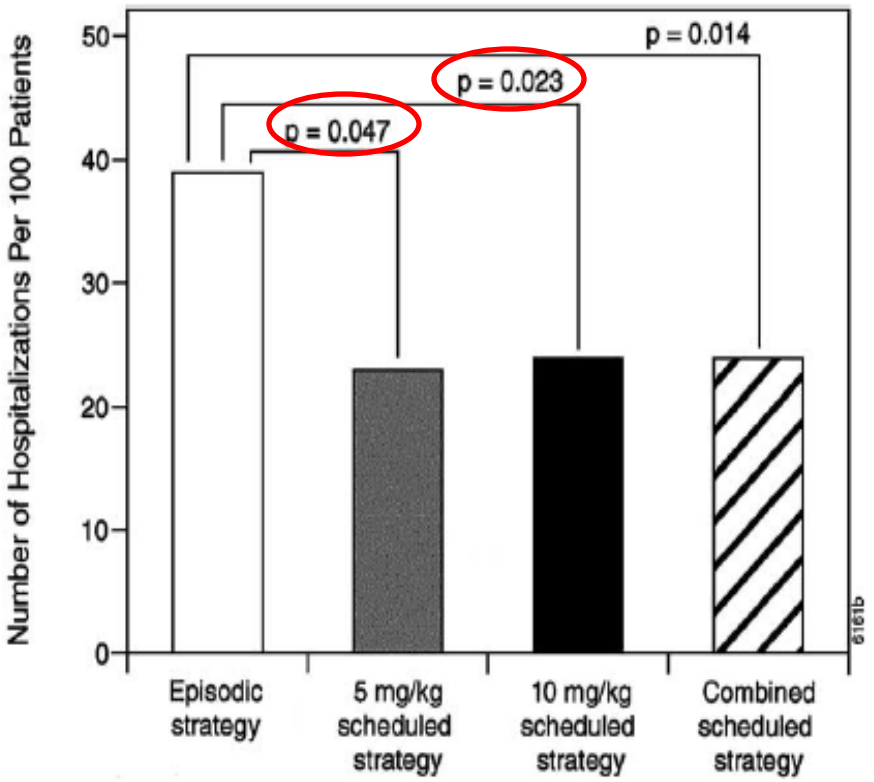
ACCENT I

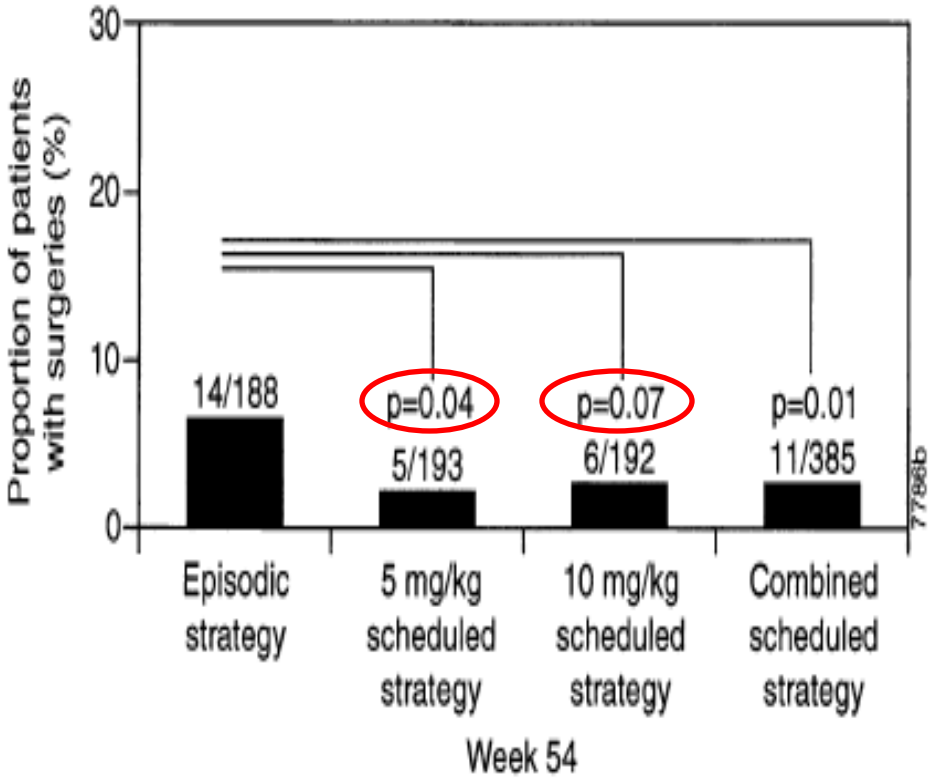


Group I=Placebo (Infliximab 5mg/Kgr at week=0, Placebo at week=2,6 and every 8 weeks)
Group II= Infliximab 5mg/Kgr (Infliximab 5mg/Kgr at weeks=0,2,6 and every 8 weeks)
Group III= Infliximab 10mg/Kgr (Infliximab 5mg/Kgr at weeks=0,2,6 and Infliximab 10mg/Kgr every 8 weeks)
Clinical remission=CDAI<150
Clinical response=μείωση του CDAI κατά 70 μονάδες και κατά 25% του αρχικού CDAI

Hanauer et al. Lancet 2002;359:1541-9

Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease





Rutgeerts et al. Gastroenterology 2004;126(2):402-13

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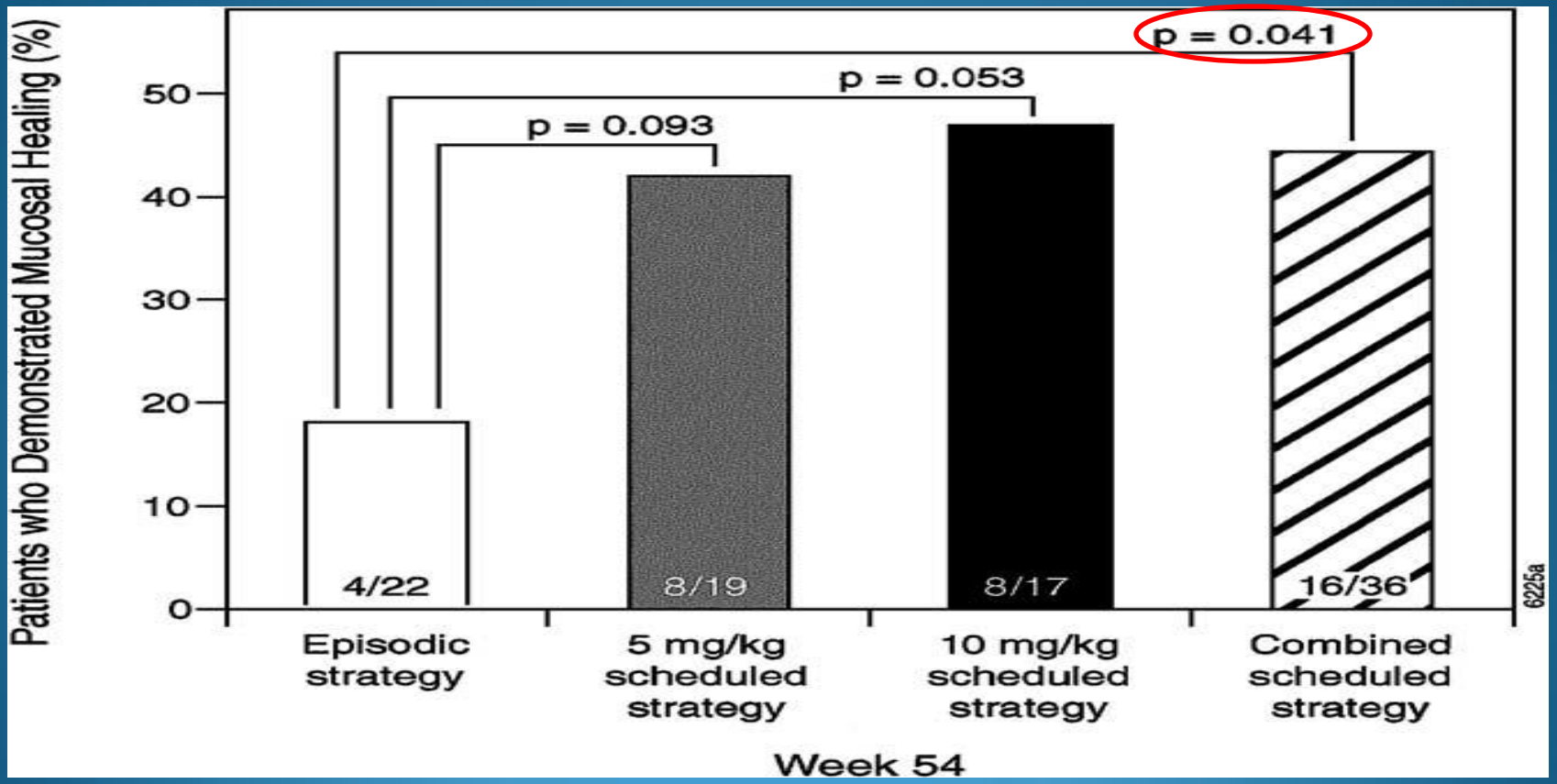
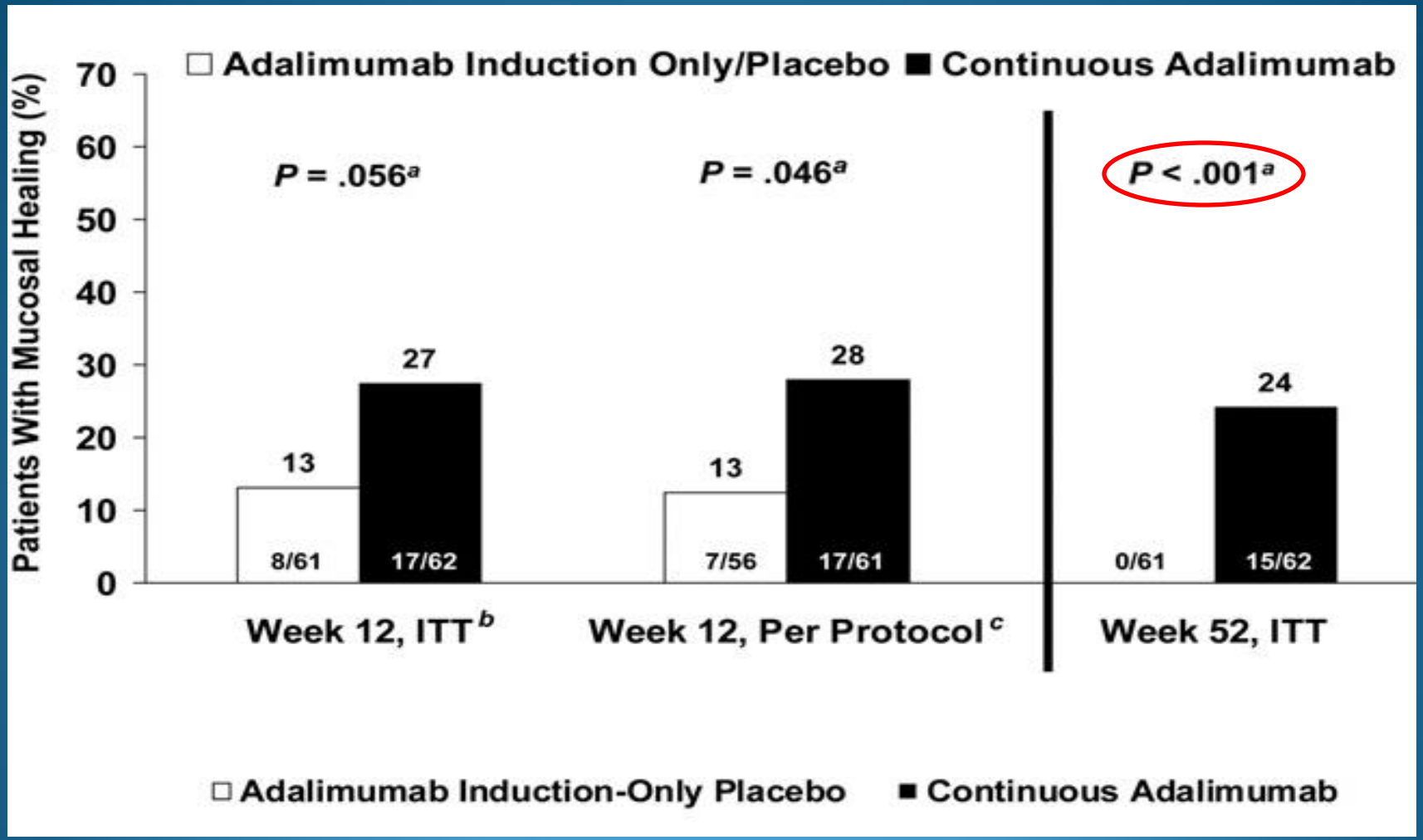


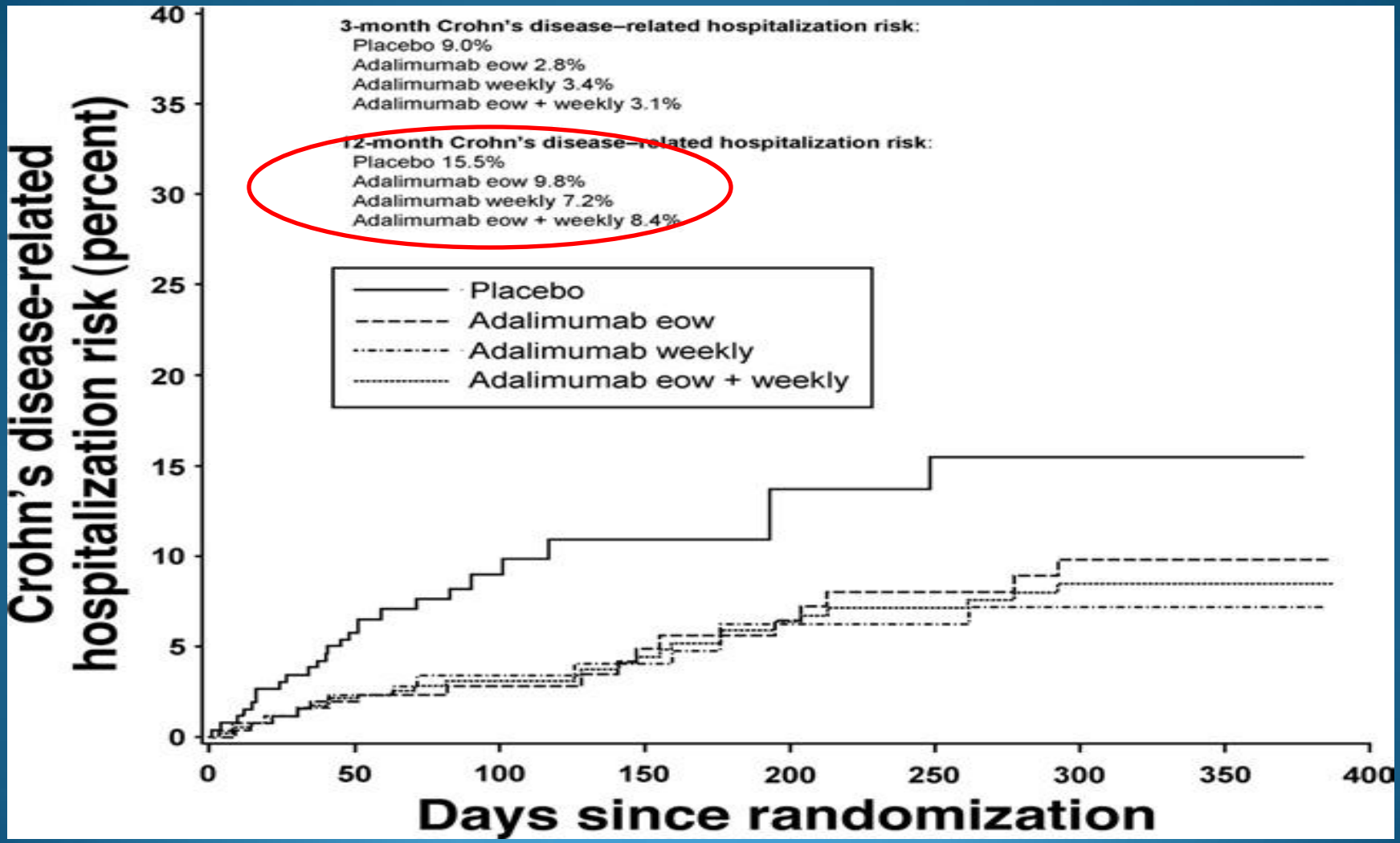
Rutgeerts et al. Gastroenterology 2004;126(2):402-13

EXTEND



Rutgeerts et al. Gastroenterology 2012;142:1102–1111

CHARM
Crohn´s disease related hospitalization risk



Faegan et al. Gastroenterology 2008;135:1493–1499

CHARM
Crohn's disease related surgeries

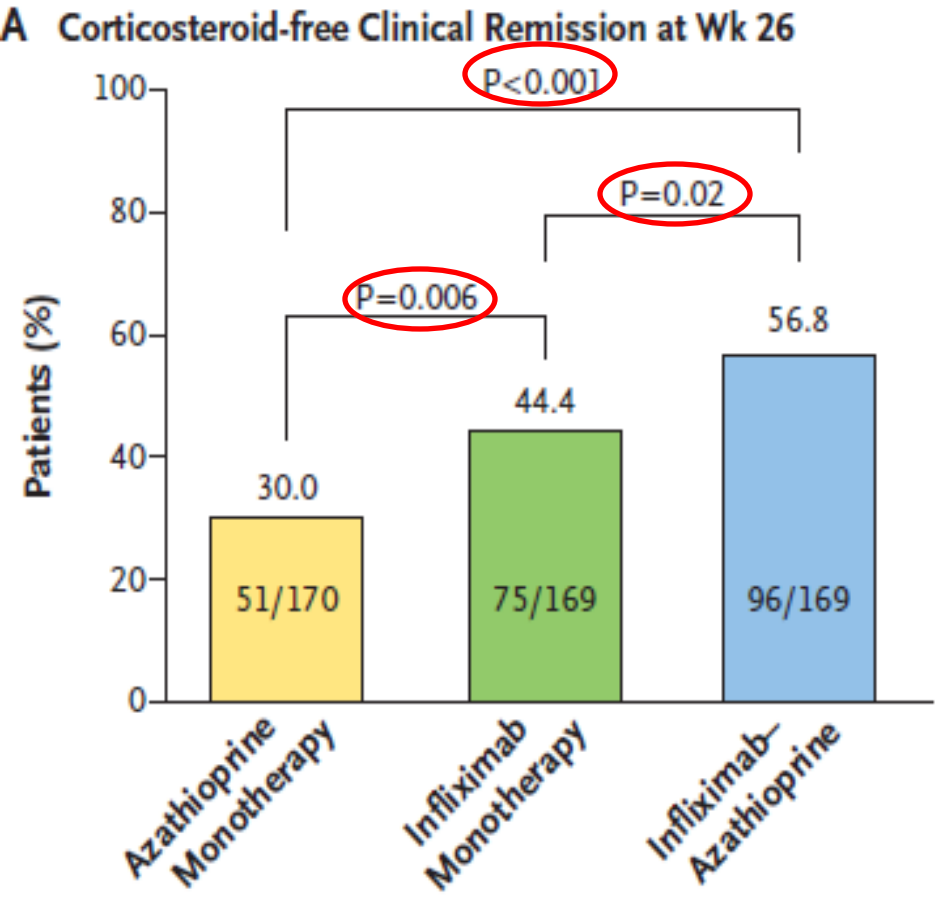
Description	Adalimumab every other week n (%)	Adalimumab weekly n (%)	Placebo n (%)
Bowel obstruction	6 (37.50)	—	3 (11.54)
Exacerbation of CD	4 (25.00)	3 (23.08)	15 (57.69)
Abscess	3 (18.75)	5 (38.46)	2 (7.69)
Abdominal pain	1 (6.25)	1 (7.69)	—
Erythema nodosum	1 (6.25)	—	—
CD-related gallstones	1 (6.25)	—	—
Pulmonary embolism thought related to CD and pneumonia	—	1 (7.69)	—
Shoulder surgery owing to chronic steroid use	—	1 (7.69)	—
Dehydration	—	1 (7.69)	—
Perianal hematoma	—	1 (7.69)	—
Abdominal mass	—	—	1 (3.85)
Fistula	—	—	1 (3.85)
CD-related appendicitis	—	—	1 (3.85)
Ileal stenosis	—	—	1 (3.85)
Purulent peritonitis	—	—	1 (3.85)
Strangulated incisional hernia	—	—	1 (3.85)

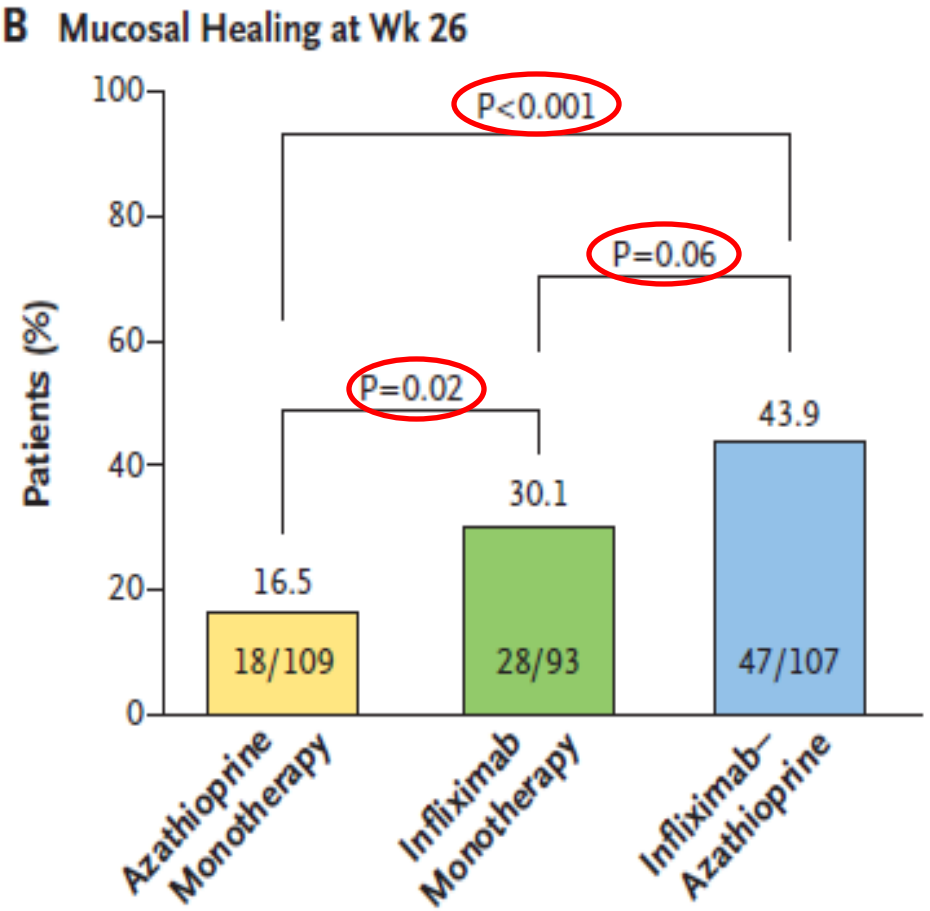
	Adalimumab every other week (n = 260)	Adalimumab weekly (n = 257)	Combined adalimumab (n = 517)	Placebo (n = 261)
Major surgery % (*n*)	0.4 (1)[a]	0.8 (2)[a]	0.6 (3)[b]	3.8 (10)
P-value (*vs placebo*)	.01	.01	.0005	

Faegan et al. Gastroenterology 2008;135:1493–1499

Οι anti-TNF παράγοντες πρέπει να χορηγούνται ως μονοθεραπεία ή σε συνδυασμό με ανοσοτροποποιητικά φάρμακα?

SONIC





Colombel JF, et al. N Engl J Med. 2010;362:22-34.

SONIC

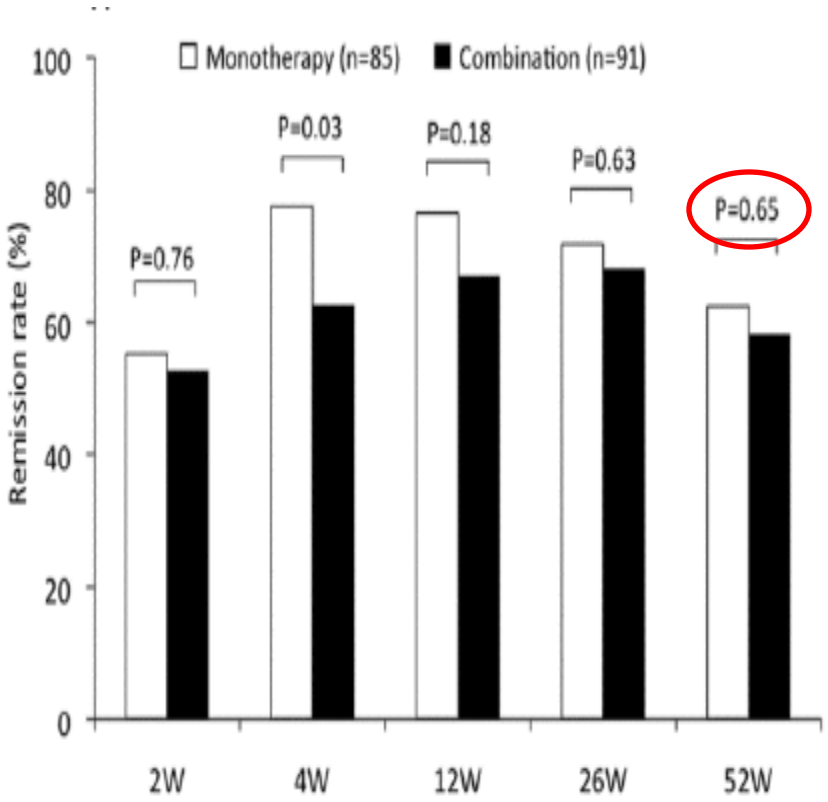
Antibodies to infliximab at week 30: 1/116 patients (0.9%) receiving combination therapy vs 15/103 patients (14.6%) receiving infliximab.

Colombel JF, et al. N Engl J Med. 2010;362:22-34.

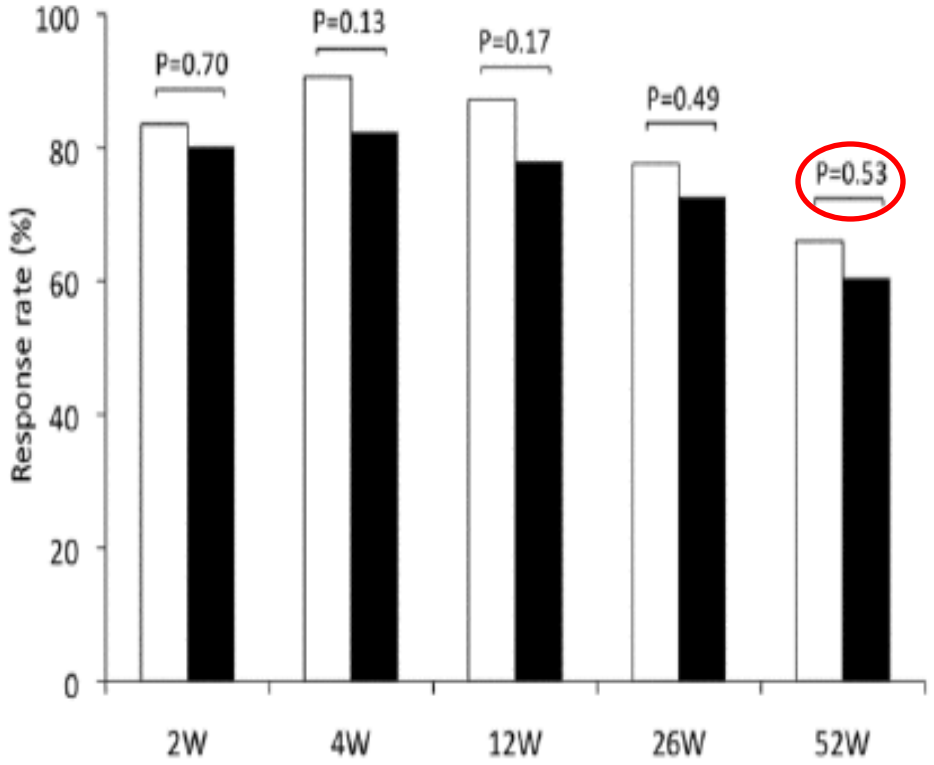
DIAMOND

Adalimumab vs AZA + Adalimumab

Clinical remission



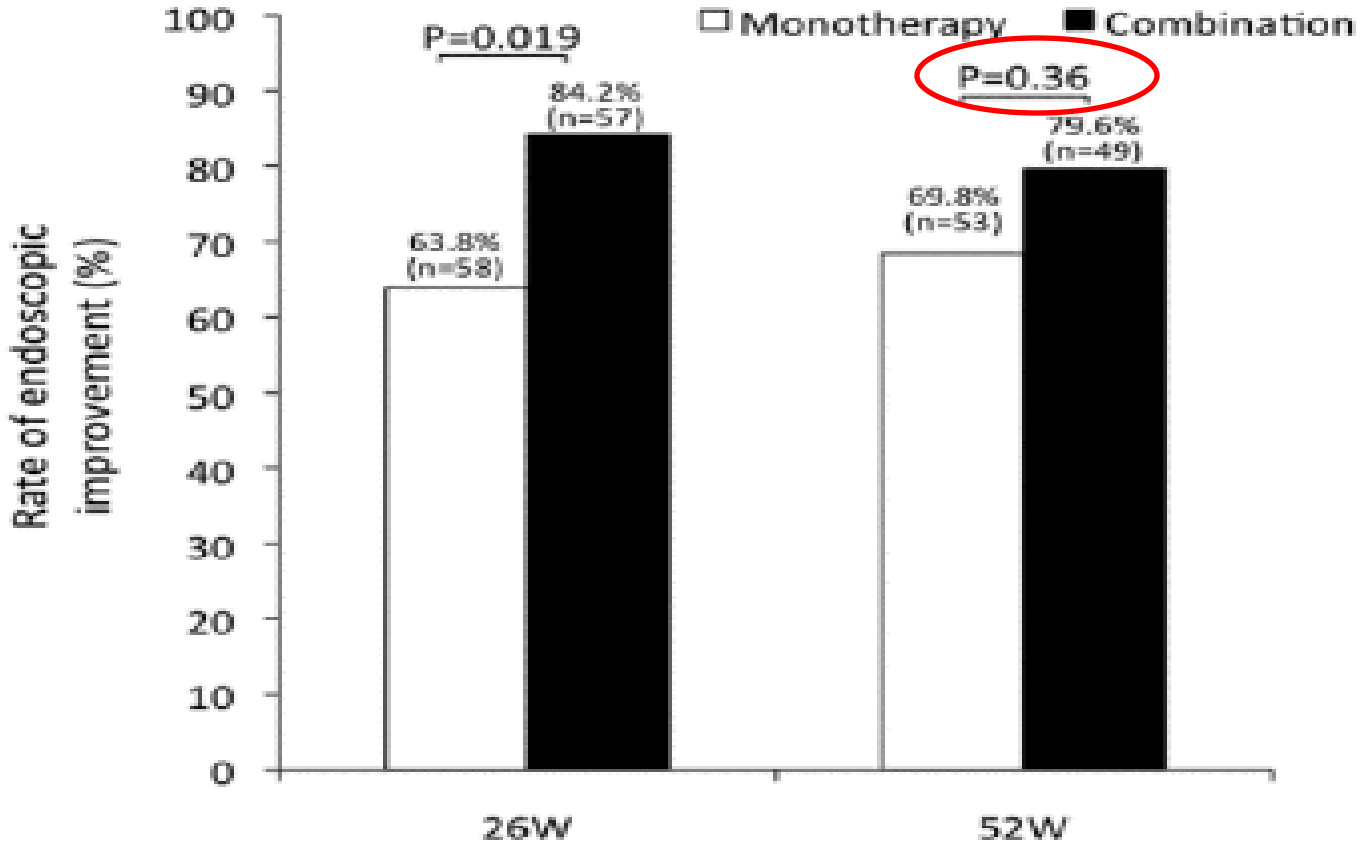
Clinical response



Matsumoto et al. Journal of Crohn's and Colitis. 2016; 10: 1259-1266

DIAMOND

Endoscopic response



Matsumoto et al. Journal of Crohn's and Colitis. 2016; 10: 1259-1266

Επιβαρυντικοί προγνωστικοί παράγοντες της πορείας της CD

Ηλικία<40

Εκτεταμένη νόσος

Περιπρωκτική νόσος

Κορτιζόνη κατά τη διάγνωση της νόσου

Gomollón et al. Journal of Crohn's and Colitis, 2017; 3–25

Προγνωστικοί παράγοντες ανταπόκρισης στους anti-TNF παράγοντες

CD < 2 έτη
Κολίτιδα
Απουσία χειρουργείου στην κοιλιακή χώρα
Ηλικία
Μη καπνιστές
CRP (>5mg/l, >8mg/l, >10mg/l)
Επαναφορά CRP σε φυσιολογικά επίπεδα μετά την έναρξη του anti-TNF
Συγχορήγηση αζαθειοπρίνης
Αυξημένα trough levels

D'Haens et al. Am J Gastroenterol 2011;106:199-212

ECCO statement 5J

All currently available anti-TNF therapies appear to have similar efficacy in luminal Crohn's disease and similar adverse-event profiles, so the choice depends on availability, route of delivery, patient preference and cost [EL5]

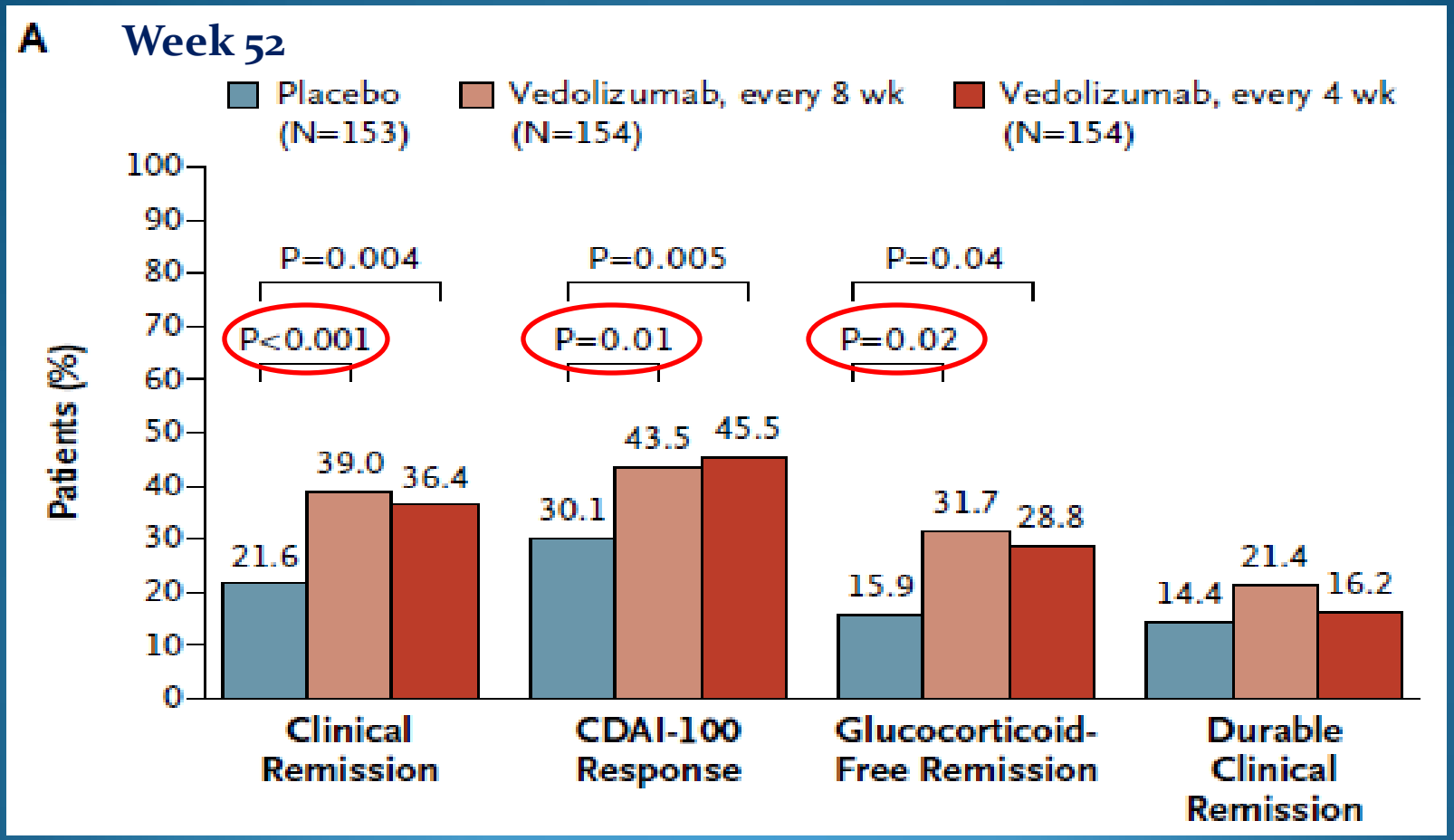
Gomollón et al. Journal of Crohn's and Colitis. 2017; 3–25

- 10-30% των ασθενών δεν ανταποκρίνεται σε anti-TNF παράγοντες (primary nonresponders)

- 50% των ασθενών που ανταποκρίνονται αρχικά στους anti-TNF παράγοντες χάνουν στην πορεία του χρόνου την ανταπόκριση (secondary nonresponders)

Olesen et al. Pharmacol. Ther. 2016; 159, 110-119

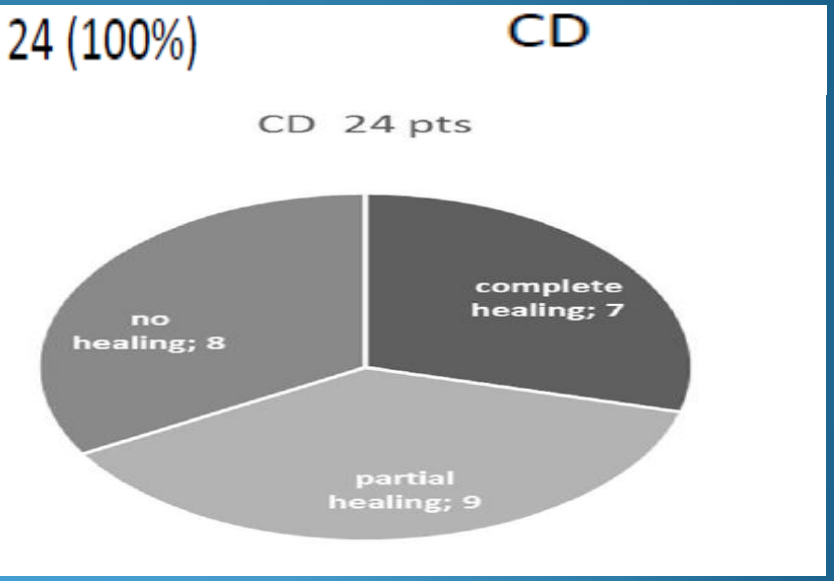
GEMINI II



Sandborn et al. N Engl J Med. 2013; 369:8

Vedolizumab induces long term mucosal healing in patients with Crohn's disease and ulcerative colitis.

Previous anti TNF exposure	24 (100%)
CD	
Endoscopic healing	Combined healing
29 % (7/24)	21 % (5/24)



Noman et al. J Crohns Colitis 2017 [Epub ahead of print]

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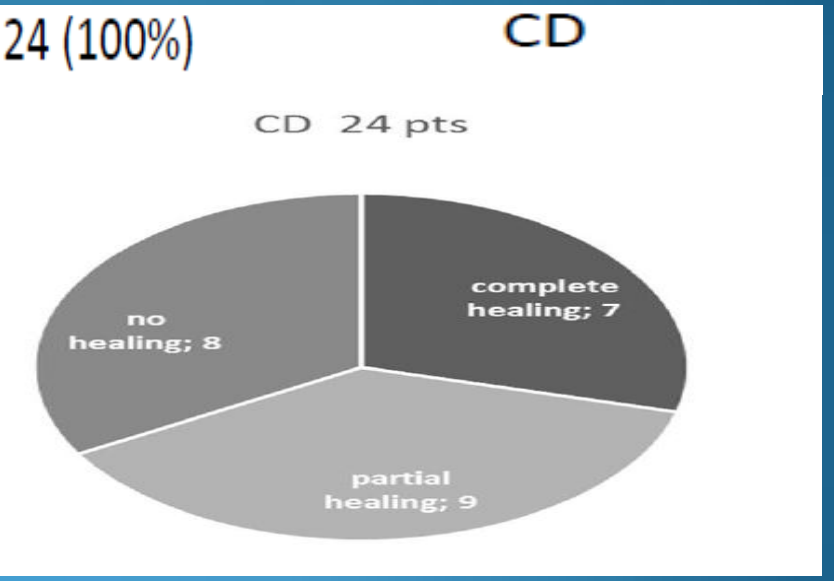

Noman et al. J Crohns Colitis 2017 [Epub ahead of print]

Novel Targeted Therapies for Inflammatory Bowel Disease

Drug	Formulation	Target	Admin.	Clinical status[b]
				CD
PF-04236921	Fully human mAb	IL-6	s.c.	–
Ustekinumab	Fully human mAb	IL-12/IL-23 (p40)	i.v./s.c.	Approved[c]
AMG-139	Fully human mAb	IL-23 (p19)	i.v./s.c.	Phase II
BI-655066	Fully human mAb	IL-23 (p19)	i.v./s.c.	Phase II
LY3074828	Humanized mAb	IL-23 (p19)	i.v./s.c.	Phase II
Tofacitinib	Small molecule	JAK1/JAK3	Oral	–[d]
Filgotinib	Small molecule	JAK1	Oral	Phase III
Peficitinib	Small molecule	JAK1/JAK3	Oral	–
Mongersen	Antisense oligonucleotide	*SMAD7*	Oral	Phase III
Laquinimod	Small molecule	?	Oral	–
Natalizumab	Humanized mAb	α_4-Integrin	i.v.	Approved[e]
AJM300	Small molecule	α_4-Integrin	Oral	–
Vedolizumab	Humanized mAb	$\alpha_4\beta_7$	i.v.	Approved[f]
AMG 181	Fully human mAb	$\alpha_4\beta_7$	s.c.	Phase II
Etrolizumab	Humanized mAb	β_7-Integrin	i.v./s.c.	Phase III
PF-00547659	Fully human mAb	MAdCAM-1	i.v./s.c.	–
Ozanimod	Small molecule	$S1P_1/S1P_5$	Oral	Phase II
Etrasimod	Small molecule	$S1P_1$	Oral	–
Amiselimod	Small molecule	$S1P_1/S1P_5$	Oral	Phase II

Coskun et al. Trends Pharmacol Sci. 2017; 127-142

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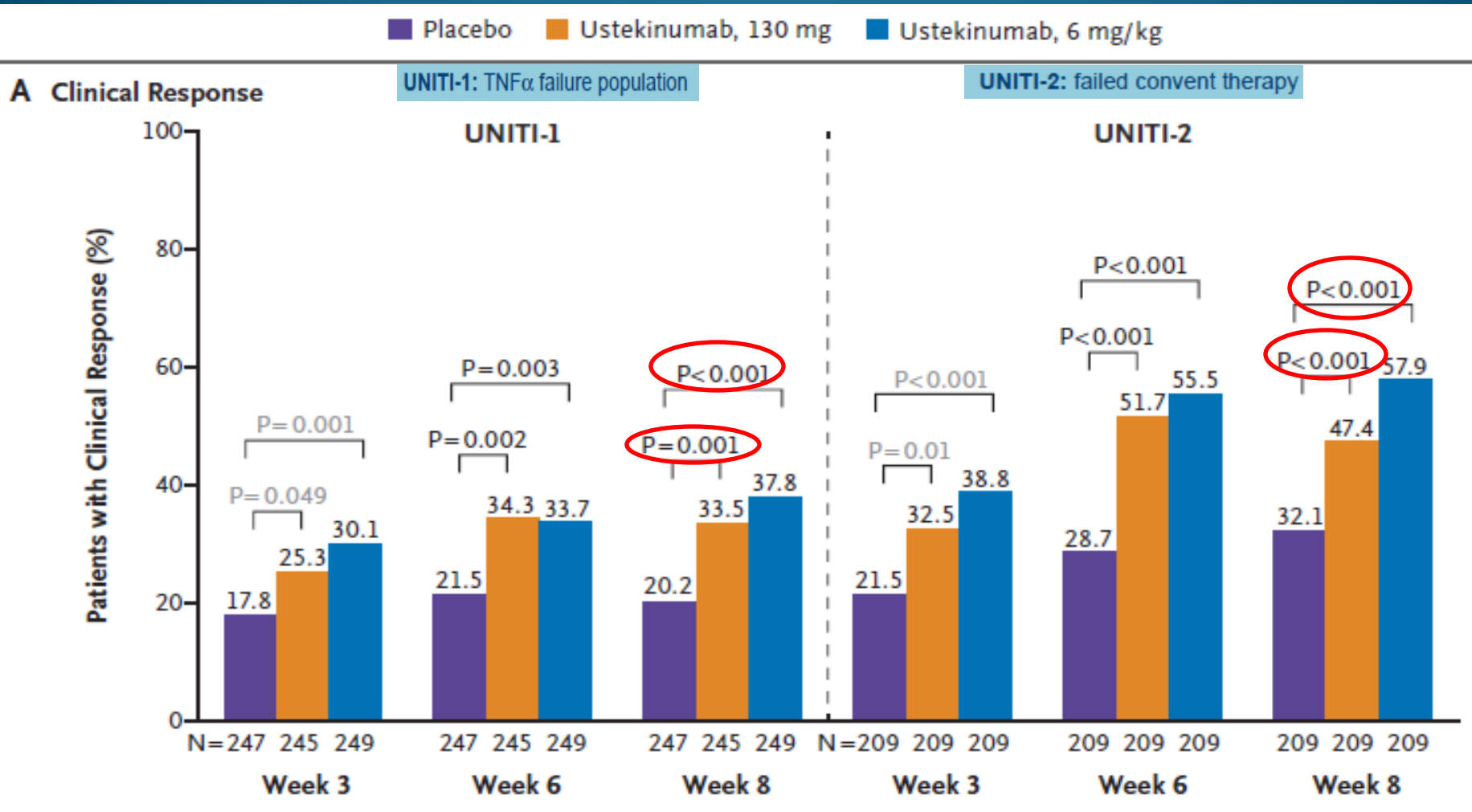
Filgotinib	Small molecule	JAK1	Oral	Phase III
Peficitinib	Small molecule	JAK1/JAK3	Oral	–
Mongersen	Antisense oligonucleotide	*SMAD7*	Oral	Phase III
Laquinimod	Small molecule	?	Oral	–
Natalizumab	Humanized mAb	α_4-Integrin	i.v.	Approved[e]
AJM300	Small molecule	α_4-Integrin	Oral	–
Vedolizumab	Humanized mAb	$\alpha_4\beta_7$	i.v.	Approved[f]
AMG 181	Fully human mAb	$\alpha_4\beta_7$	s.c.	Phase II
Etrolizumab	Humanized mAb	β_7-Integrin	i.v./s.c.	Phase III
PF-00547659	Fully human mAb	MAdCAM-1	i.v./s.c.	–
Ozanimod	Small molecule	$S1P_1/S1P_5$	Oral	Phase II
Etrasimod	Small molecule	$S1P_1$	Oral	–
Amiselimod	Small molecule	$S1P_1/S1P_5$	Oral	Phase II

Coskun et al. Trends Pharmacol Sci. 2017; 127-142

Ustekinumab as Induction and Maintenance Therapy for Crohn´s Disease



Feagan et al, N Engl J Med. 2016; 375:20

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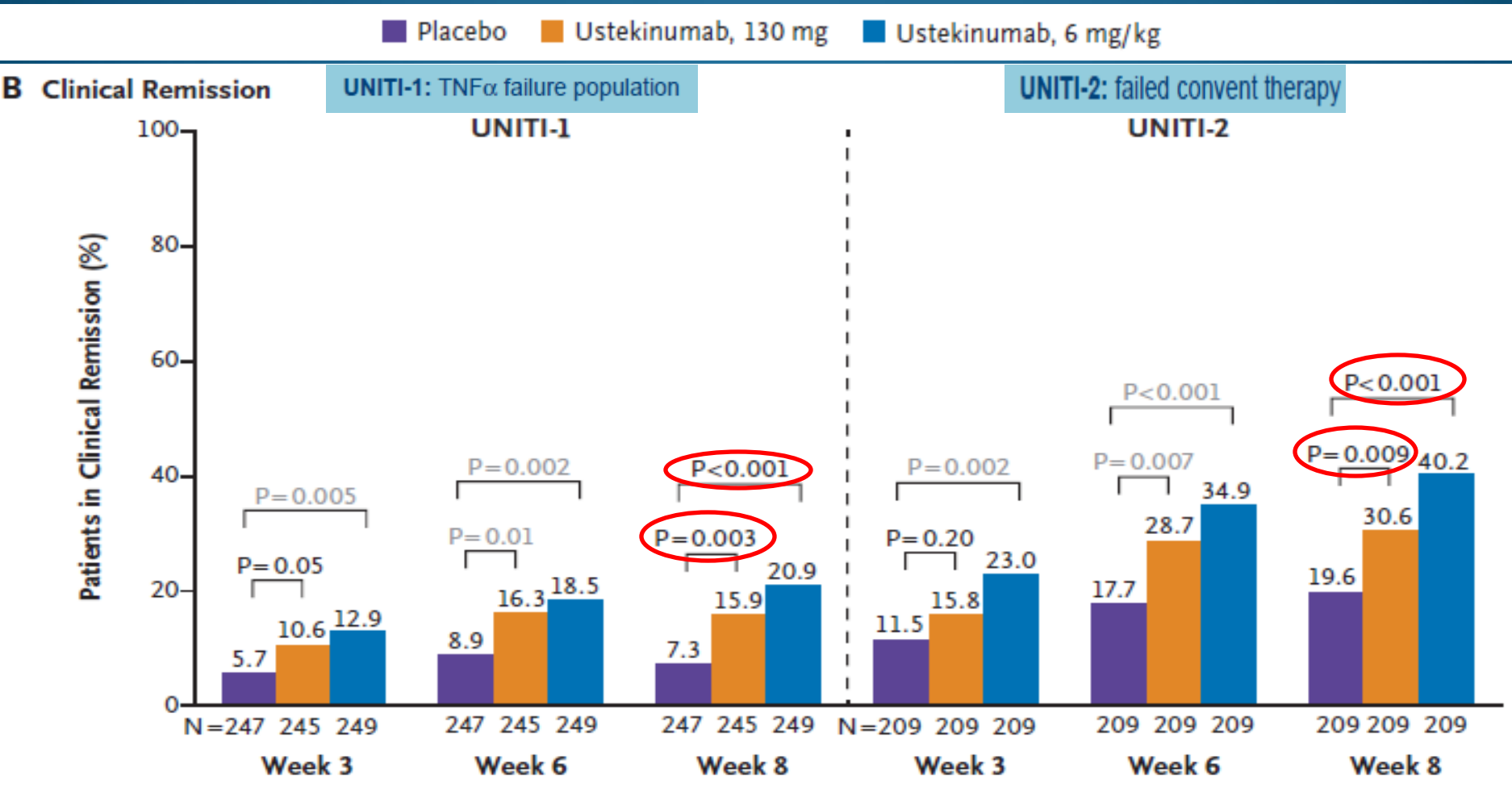
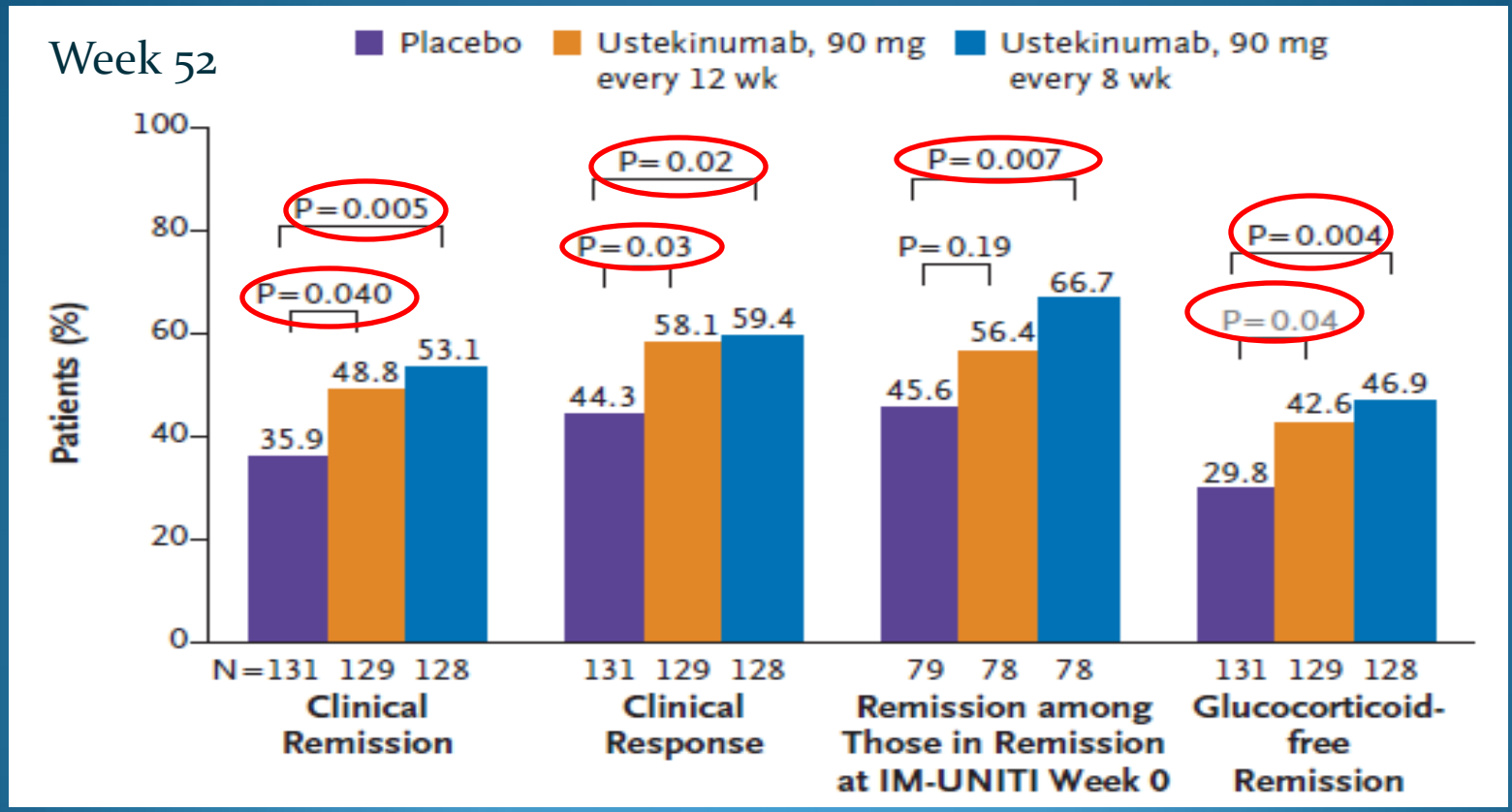
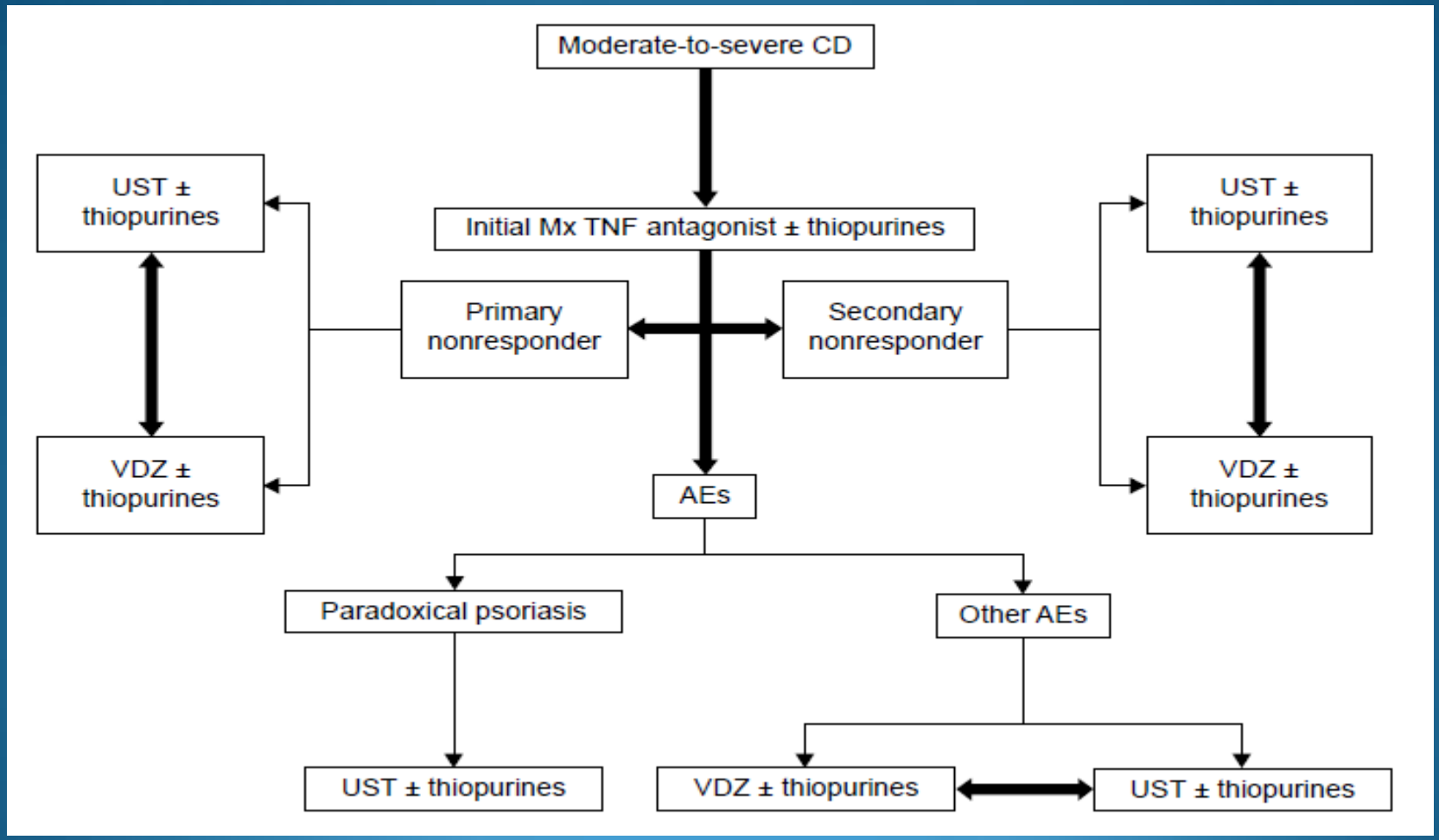


Feagan et al, N Engl J Med. 2016; 375:20

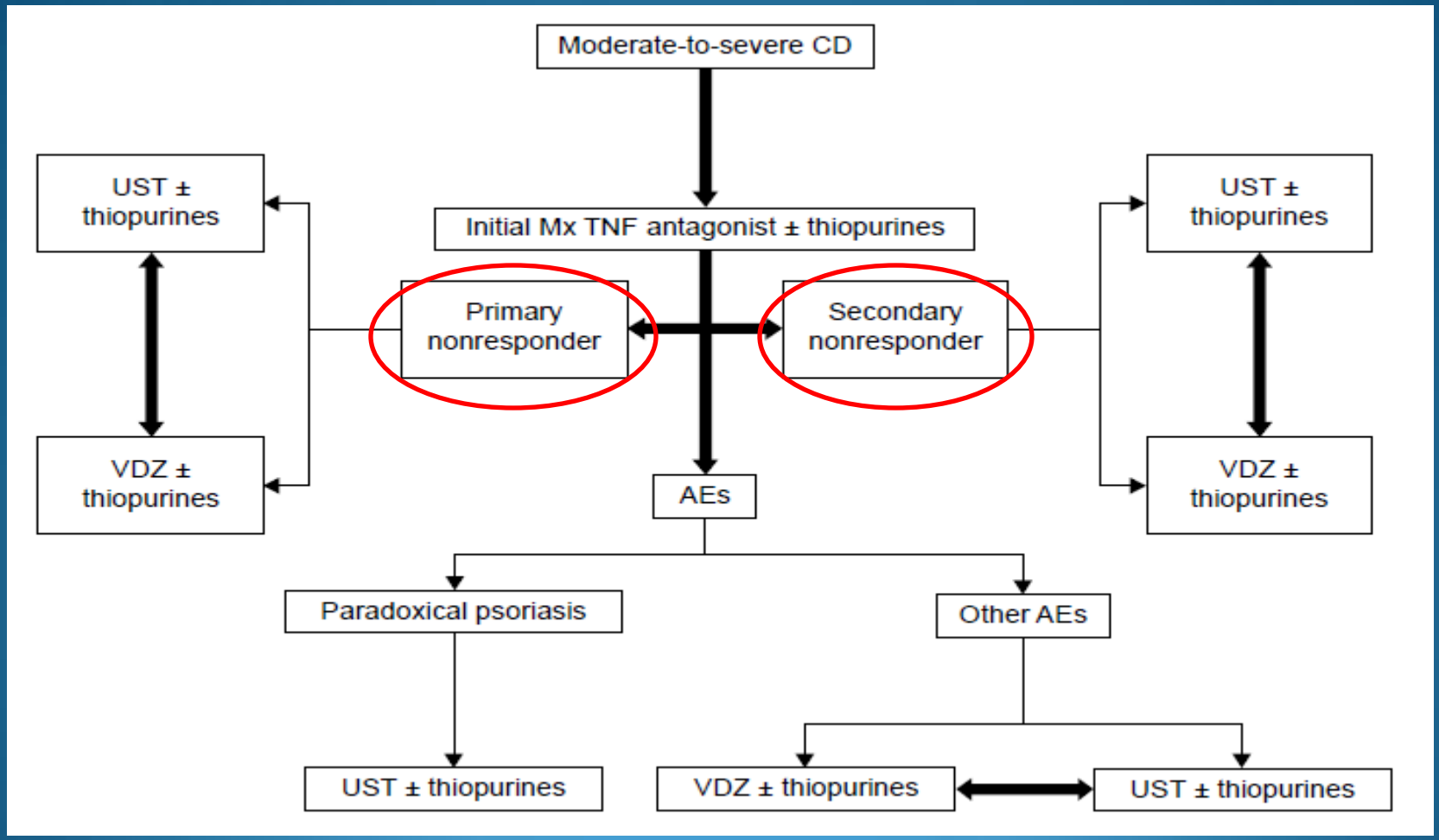
Ustekinumab as Induction and Maintenance Therapy for Crohn´s Disease



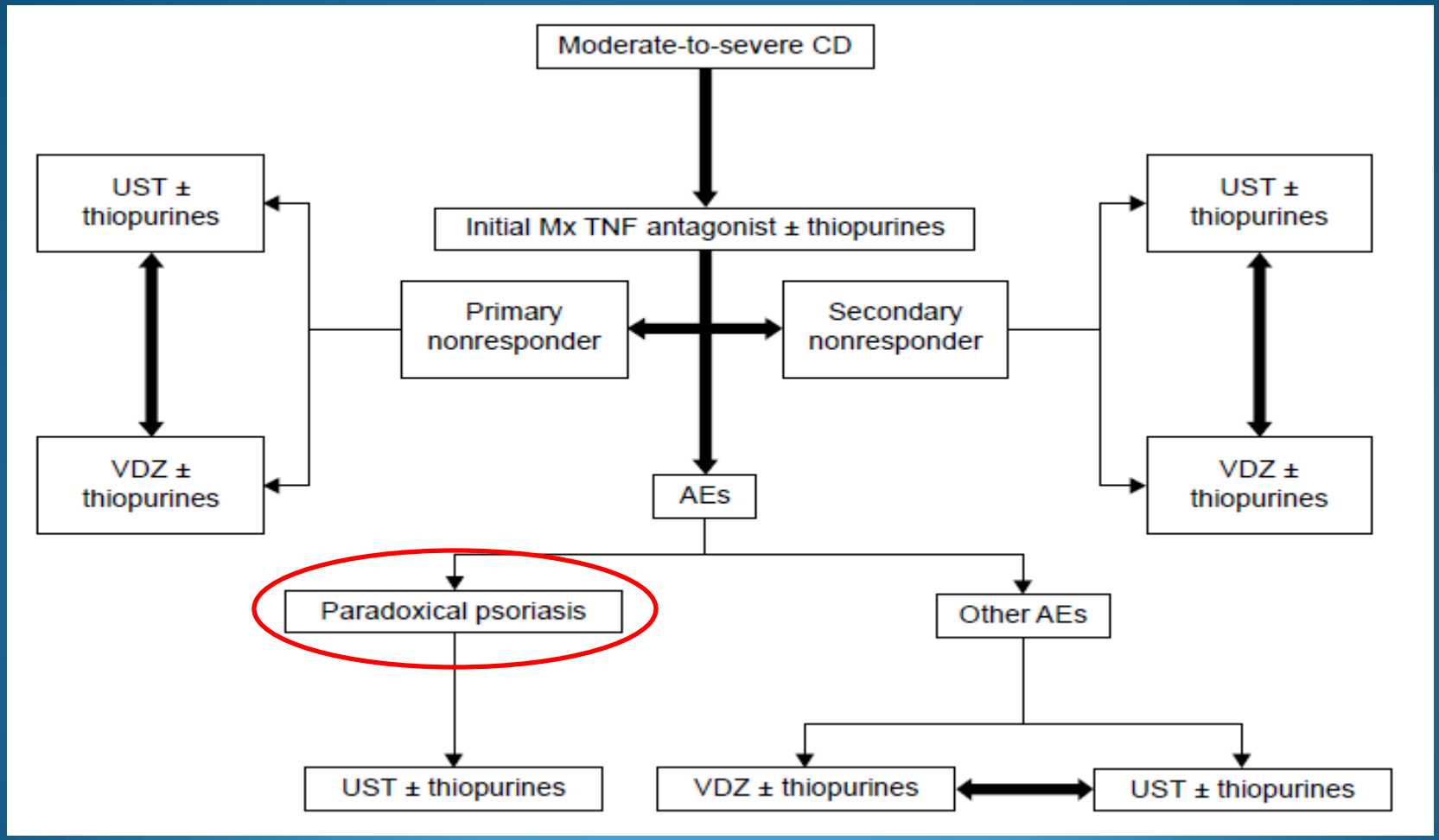
Feagan et al, N Engl J Med. 2016; 375:20



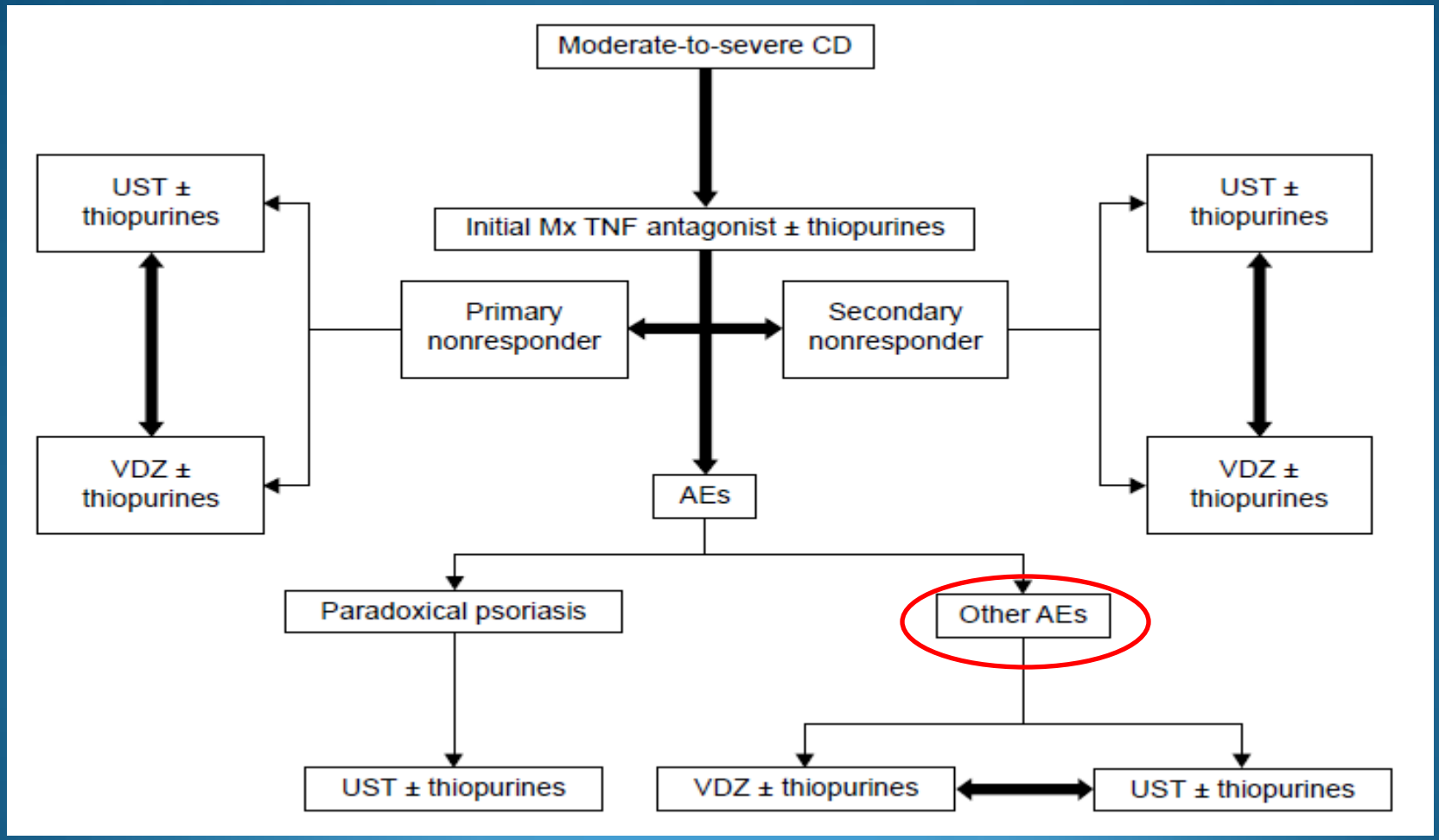
Deepak et al, Drug Design, Development and Therapy 2016:10



Deepak et al, Drug Design, Development and Therapy 2016:10



Deepak et al, Drug Design, Development and Therapy 2016:10



Deepak et al, Drug Design, Development and Therapy 2016:10

Intestinal fibrosis

✓More than 40% of CD patients with ileal disease manifestation will develop clinically apparent stricture formation and the vast majority of these patients will have to undergo surgery at least once.

✓Isolated human colonic fibroblasts from CD patients that were stimulated via bacterial components and toll-like receptors (TLR) mediated pathways revealed a significantly enhanced proinflammatory and profibrotic cytokine production

✓Activation of inflammatory cells such as monocytes and macrophages is a crucial step in fibrogenesis

✓Myofibroblasts are a major player in intestinal fibrosis. Therapeutic manipulation of these cells appears promising to stop or reverse fibrosis

✓Combined stimulation with TNF-α and INF-γ lead to a 4-fold increased apoptosis rate of intestinal fibroblasts

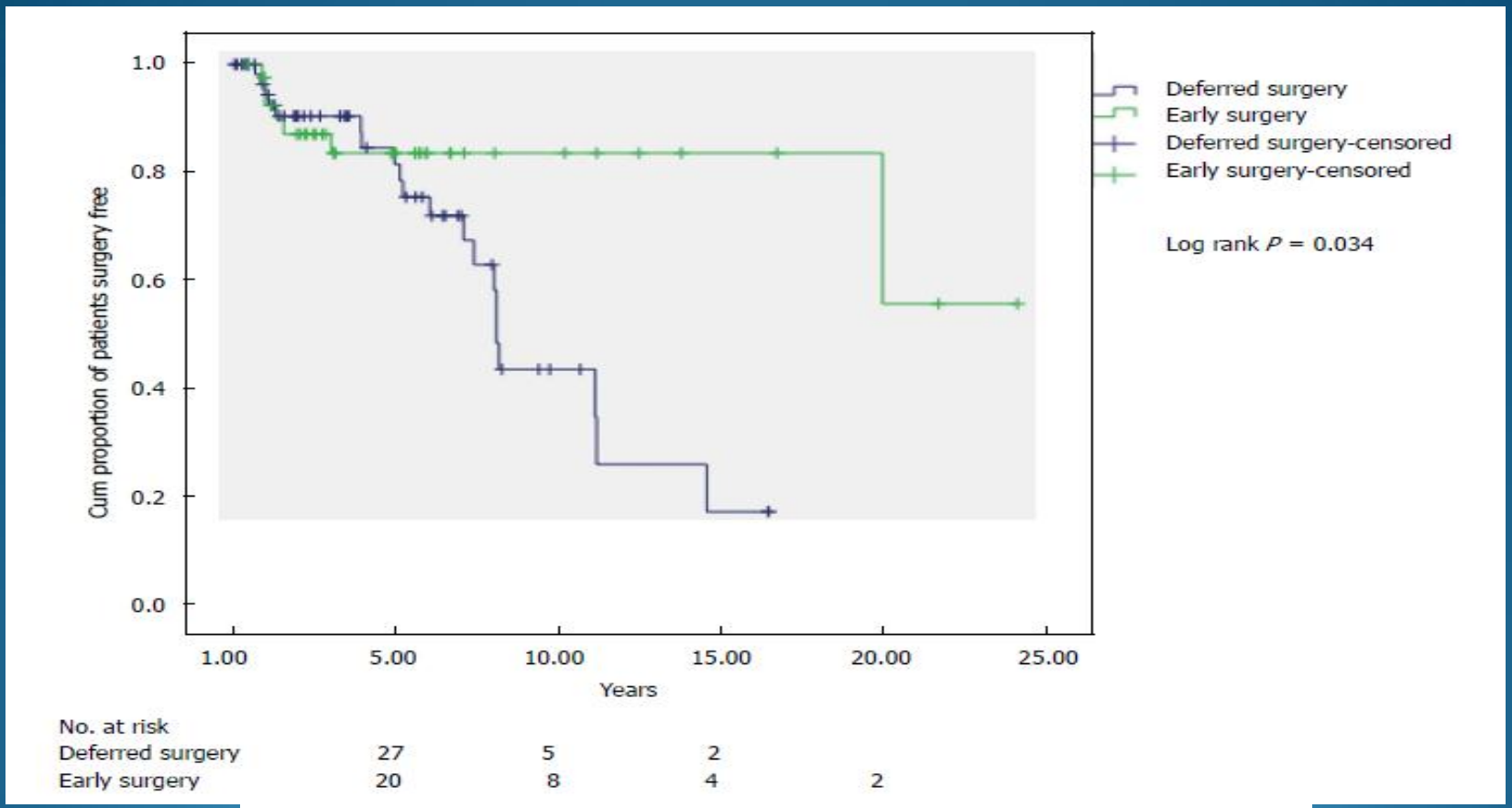
✓The ultimate goal to reverse fibrosis and to induce physiological tissue regeneration is challenging and will not readily be realized in CD patients in the near future

Latella et al. Curr Opin Gastroenterol 2017. 33

Bettenworth et al. Inflamm Bowel Dis 2016. 22:241-7

ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ

Early surgery in Crohn's disease



Cumulative event curve: Time to further surgical resection in early surgery vs deferred surgery.

ES:χειρουργική επέμβαση λόγω οξείας επιπλοκής ή επέμβαση εντός 6μήνου από τη διάγνωση της νόσου

An et al. World J Gastrointest Surg. 2016 Jul 27;8(7):492-500

Early surgery in Crohn's disease

- ✓ Operative intervention rate at 5 years in the ES group 14.2% vs 31.3% IMT group p=0.041
- ✓ Hospital admissions ES group=1 vs IMT group=3 p=0.012
- ✓ Anti-TNF therapy required ES group=33.3% vs IMT group=57% p=0.003

An et al. World J Gastrointest Surg. 2016 Jul 27;8(7):492-500

Cost-effectiveness of laparoscopic ileocecal resection versus infliximab of active terminal ileitis in Crohn's disease: a randomized controlled trial

Joline de Groof, on behalf of the LIR!C study group

- Laparoscopic ileocecal resection was as effective as infliximab in improving quality of life, but not significant on the IBDQ
- With infliximab, *32%* discontinued and *19%* needed surgery within one year
- With surgery, *4%* started with infliximab within one year
- Laparoscopic ileocecal resection was on average less costly and more effective
- Laparoscopic ileocecal resection is cost-effective