18. November 2017, Wien

Gastrohighlights 2017: Chronisch entzündliche Darmerkrankungen

Luc Biedermann

Gerhard Rogler, Klinik für Gastroenterologie und Hepatologie, UniversitätsSpital Zürich

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Übersicht - Menu

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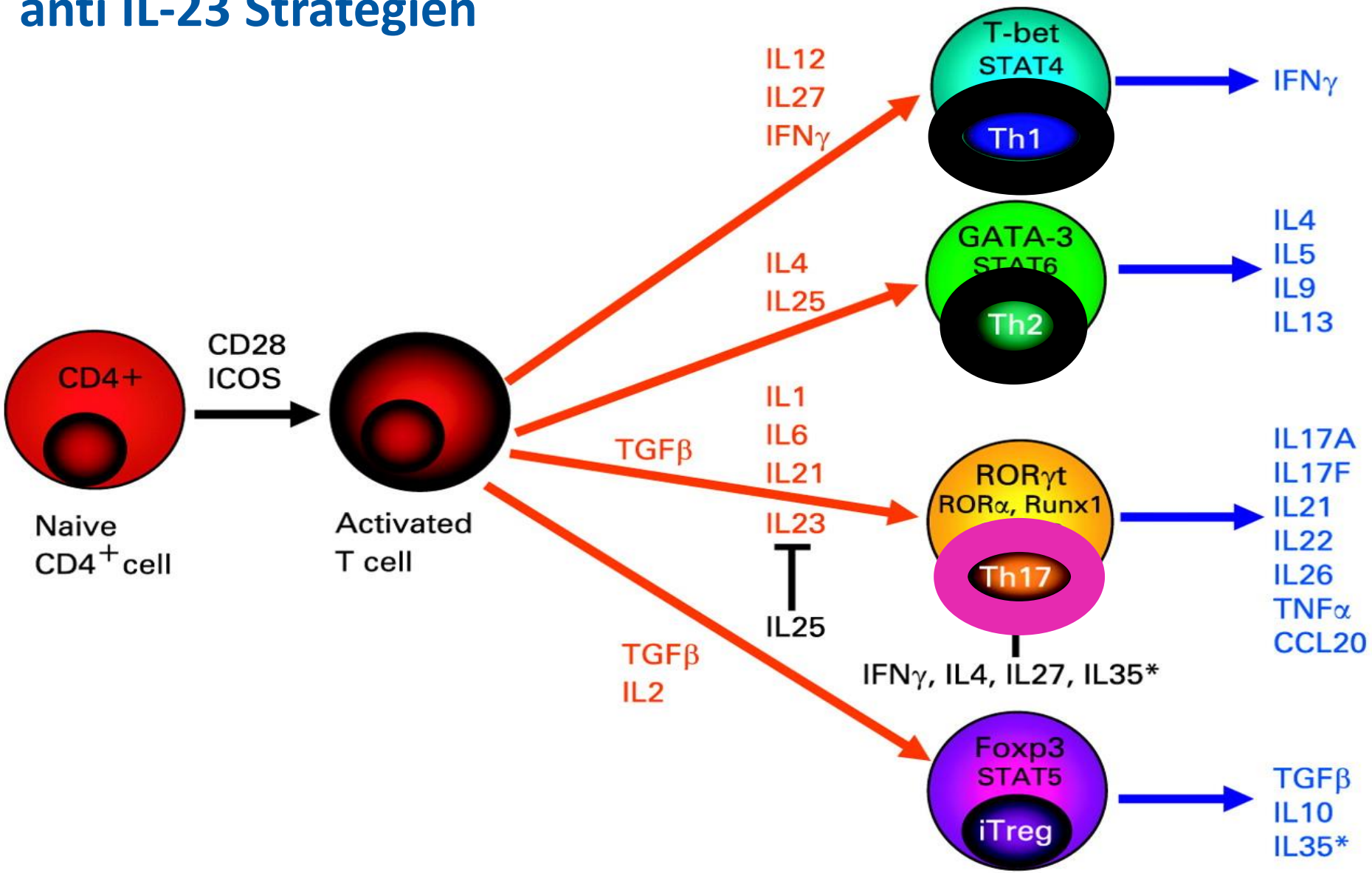
Neues zur Therapie – Morbus Crohn

“The new kid on the block”: anti-IL12/IL-23 und reine anti IL-23 Strategien



Dosierung von Ustekinumab (STELARA®) bei Morbus Crohn

Induktionstherapie

Intravenöse Einzeldosis

- von ~6 mg/kg Körpergewicht
- Erhältlich in 130 mg Durchstechflaschen als Konzentrat zur Herstellung einer Infusionslösung

Erhaltungstherapie

Subkutane Injektion

- von 90 mg
- Alle 12 Wochen (bzw. alle 8 Wochen)*

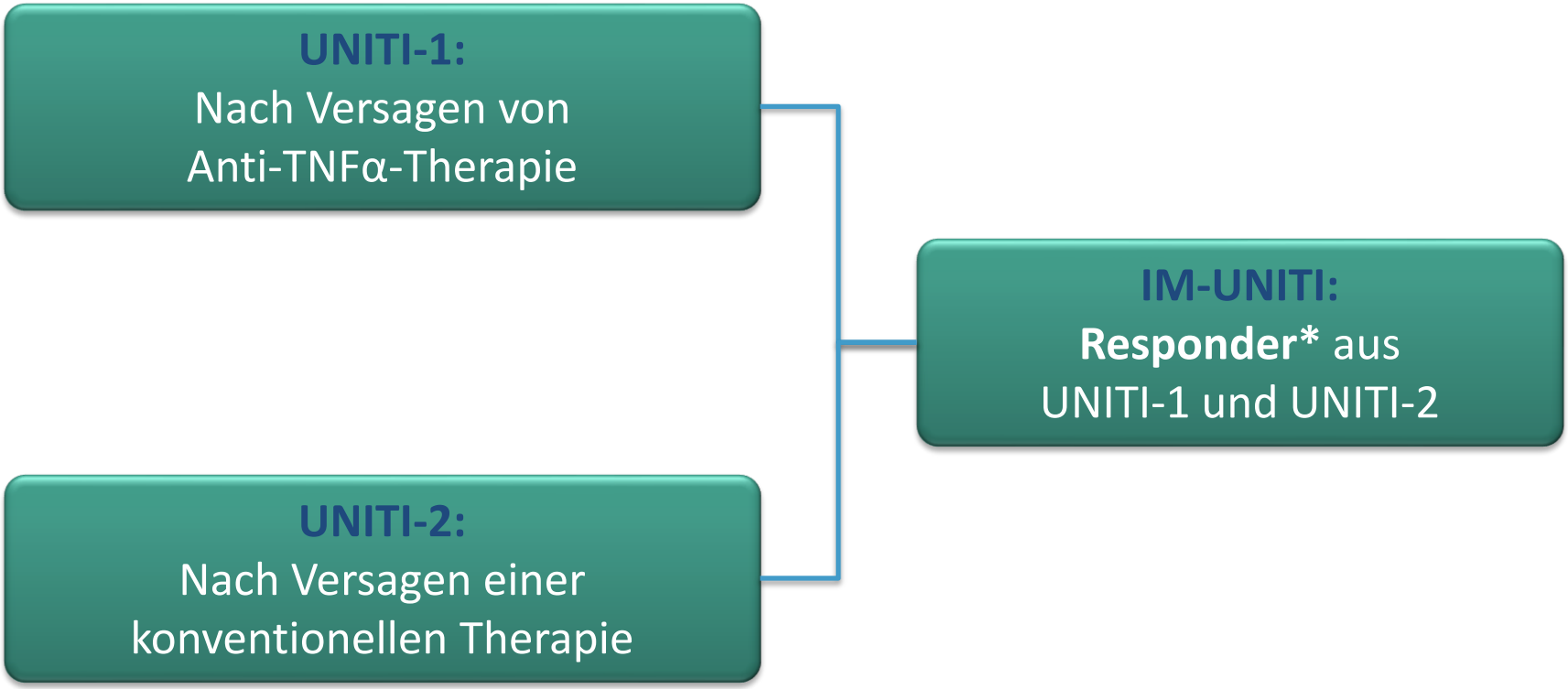
Induktionstherapie bei Morbus Crohn

Körpergewicht des Patienten	Empfohlene Dosis*	Anzahl der 130 mg STELARA®-Durchstechflaschen
≤55 kg	260 mg	2
>55 kg bis ≤85 kg	390 mg	3
>85 kg	520 mg	4

* Entspricht ca. 6 mg/kg

- STELARA® wird in der Induktionsbehandlung intravenös (i.v.) in einer Einzeldosis verabreicht.
- Es wird empfohlen, die erste subkutane (s.c.) Dosierung 8 Wochen nach der intravenösen Gabe zu verabreichen.

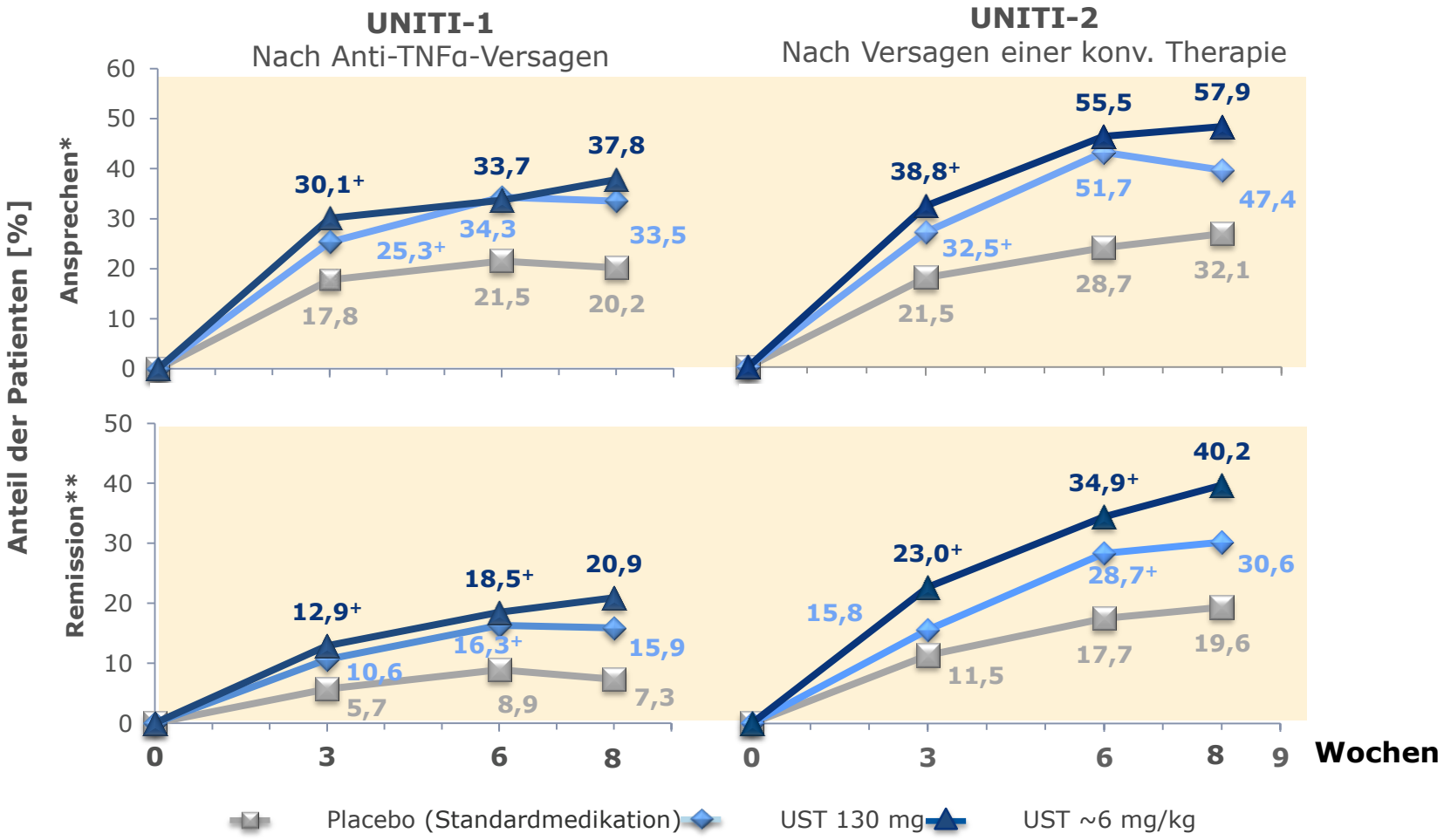
Ustekinumab bei Morbus Crohn



*Responder: CDAI-100-Ansprechen in Woche 8 (Rückgang des CDAI um 100 oder mehr Punkte)

Feagan BG et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med 2016;375:1946-60

UNITI-1 und UNITI-2: Wirksamkeit im Vergleich



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Feagan BG et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med 2016;375:1946-60

Sicherheitsdaten Uniti 1

	Placebo*	Ustekinumab	
		130 mg	~6 mg/kg
Anzahl der behandelten Patienten in der Induktionsphase	245	246	249
Durchschnittliche Dauer des Follow-ups [Wochen]	7,9	7,9	7,8
Anzahl der Ereignisse ≥1 [n (%)]			
Todesfälle	0	0	0
Unerwünschte Ereignisse (UE)	159 (64,9)	159 (64,6)	164 (65,9)
Schwere unerwünschte Ereignisse	15 (6,1)	12 (4,9)	18 (7,2)
Infektionen	58 (23,7)	57 (23,2)	64 (25,7)
Schwere Infektionen	3 (1,2)	3 (1,2)	7 (2,8)
Temporäre UE assoziiert mit Infusion	5 (2,0)	11 (4,5)	9 (3,6)
Malignitäten	0	0	0*

* Placebo bedeutet hier: Patienten unter Standardmedikation

Feagan BG et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med 2016;375:1946-60

Induktionstherapie mit dem selektiven Interleukin-23-AK Risankizumab bei Patienten mit mäßig bis schwerem MC

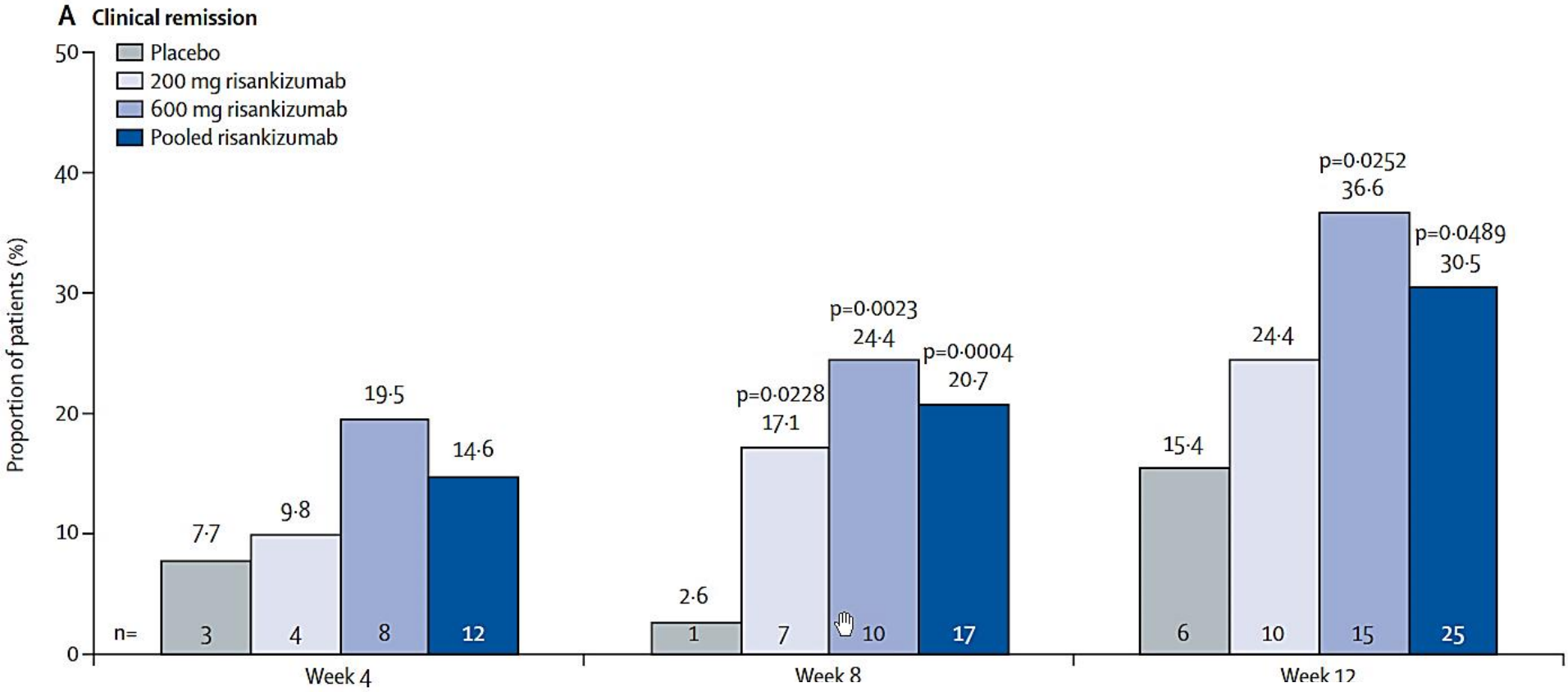
Hintergrund

- **Interleukin-23** in die Pathogenese von M. Crohn involviert.
- Wirksamkeit und Sicherheit von **Risankizumab** (BI 655066, Boehringer Ingelheim) humanisierter monoklonaler **Antikörper gegen p19-Untereinheit von Interleukin-23 bei Patienten mit mäßig- schwer aktivem MC** getestet
- Randomisierte, doppelblinde, placebo-kontrollierte Phase-2-Studie
- **121 Patienten** an 36 Zentren in Nordamerika, Europa und Südostasien (**93% anti-TNF vorbehandelt!**).
- Die Patienten wurden 1: 1: 1 randomisiert und erhielten Intravenös 200 mg Risankizumab, 600 mg Risankizumab oder Placebo, in den Wochen 0, 4 und 8.

Brian G Feagan et al., Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study; Lancet 2017; 389: 1699–709

Induktionstherapie mit dem selektiven Interleukin-23-AK Risankizumab bei Patienten mit mäßig bis schwerem MC

- 121 Patienten randomisiert
- Woche 12 25/82 (31%) klinische **Remission**; 6/39 (15%) Placebo (P = 0.049).



Brian G Feagan et al., Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study; Lancet 2017; 389: 1699–709

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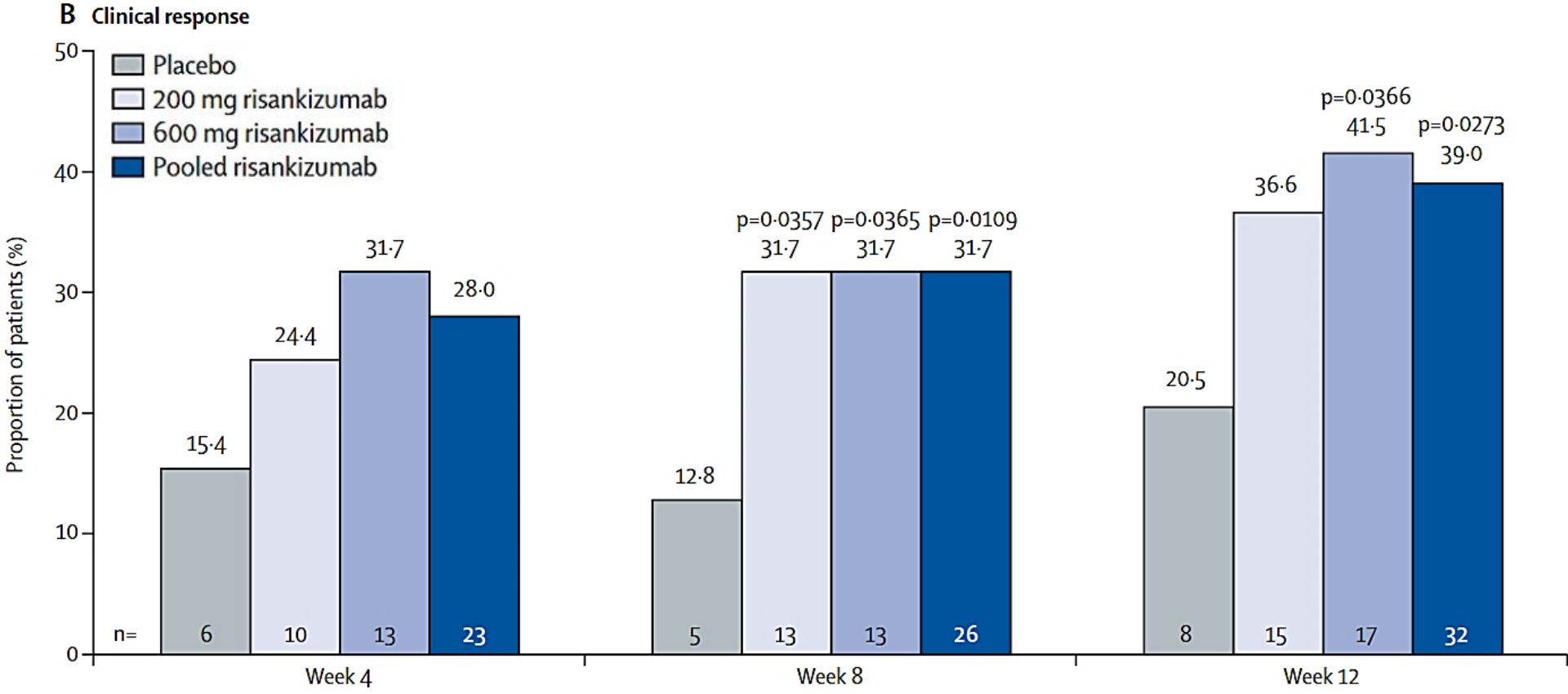
Induktionstherapie mit dem selektiven Interleukin-23-AK Risankizumab bei Patienten mit mäßig bis schwerem MC

- 121 Patienten randomisiert
- Woche 12 42% klinische **Response**; 21% Placebo (P = 0.036).



Brian G Feagan et al., Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study; Lancet 2017; 389: 1699–709

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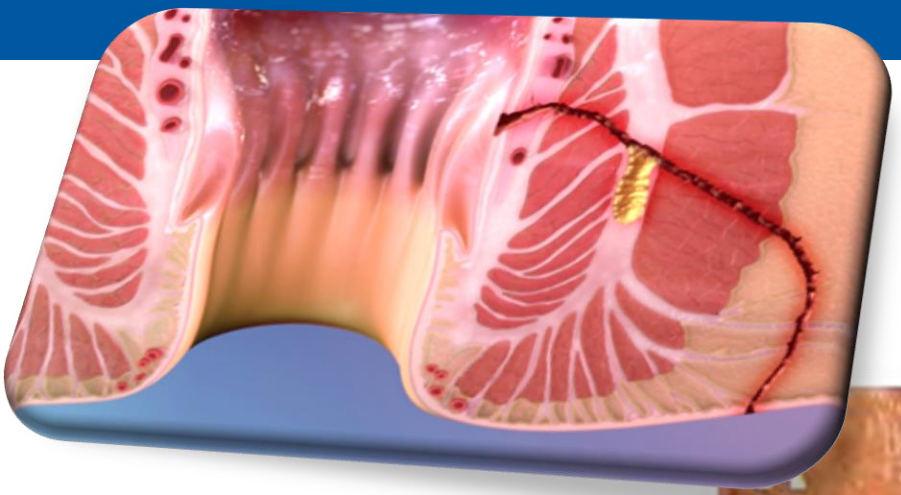
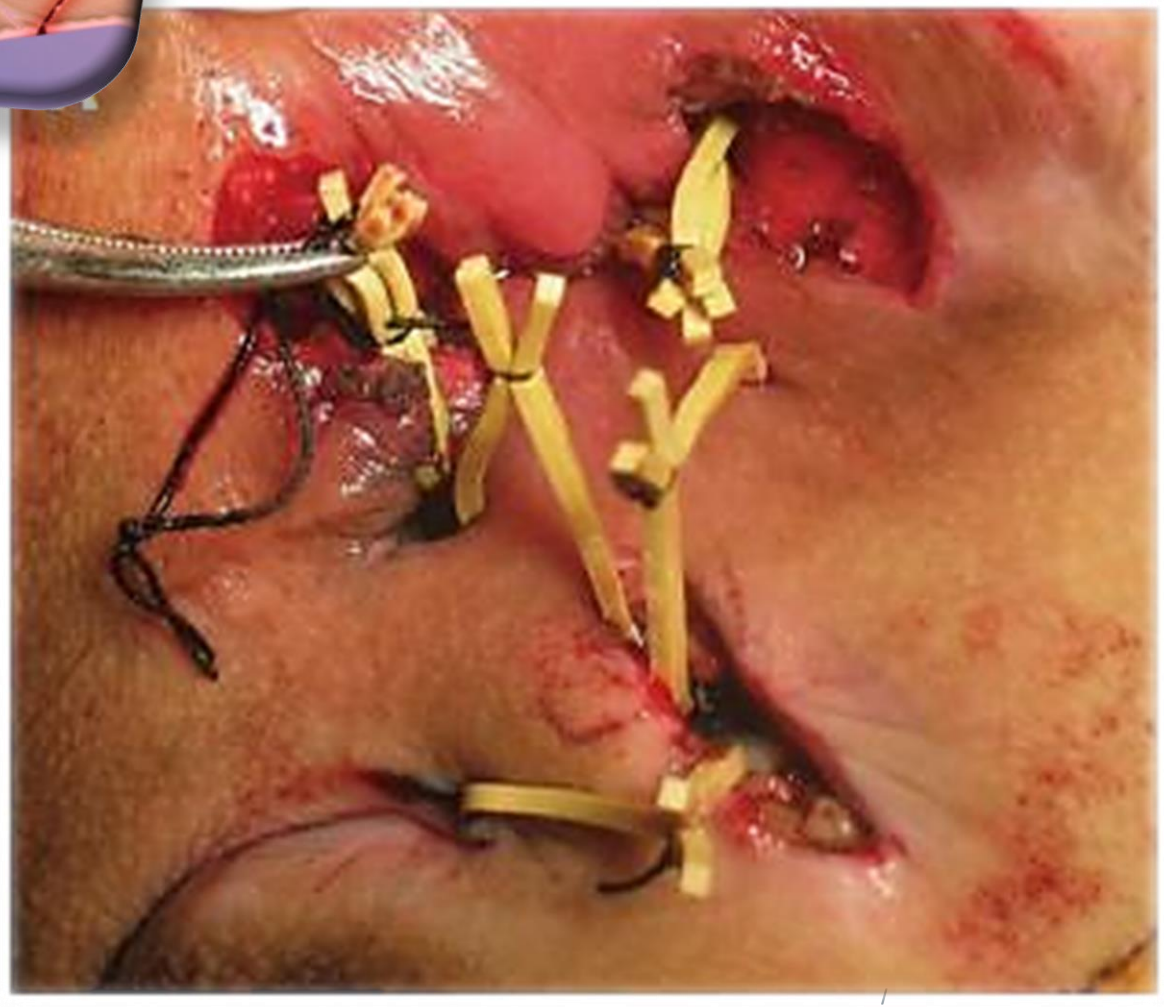
Induktionstherapie mit dem selektiven Interleukin-23-AK Risankizumab bei Patienten mit mäßig bis schwerem MC

	Placebo (n=39)	Risankizumab	
		200 mg (n=41)	600 mg (n=41)
Any adverse event	32 (82%)	32 (78%)	31 (76%)
Severe	9 (23%)	6 (15%)	3 (7%)
Drug related	8 (21%)	10 (24%)	5 (12%)
Leading to discontinuation	6 (15%)	5 (12%)	1 (2%)
Serious adverse events*	12 (31%)	9 (22%)	3 (7%)
Persistent or significant disability or incapacity	0	1 (2%)	0
Requiring or prolonging hospitalisation	10 (26%)	8 (20%)	2 (5%)
Other medically important serious event	4 (10%)	1 (2%)	1 (2%)
Common adverse events†			
Nausea	4 (10%)	8 (20%)	3 (7%)
Worsening of Crohn's disease	6 (15%)	2 (5%)	0
Abdominal pain	4 (10%)	6 (15%)	3 (7%)
Arthralgia	3 (8%)	6 (15%)	6 (15%)
Anaemia	4 (10%)	0	2 (5%)
Headache	4 (10%)	6 (15%)	4 (10%)
Vomiting	4 (10%)	3 (7%)	2 (5%)

Brian G Feagan et al., Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study; Lancet 2017; 389: 1699–709





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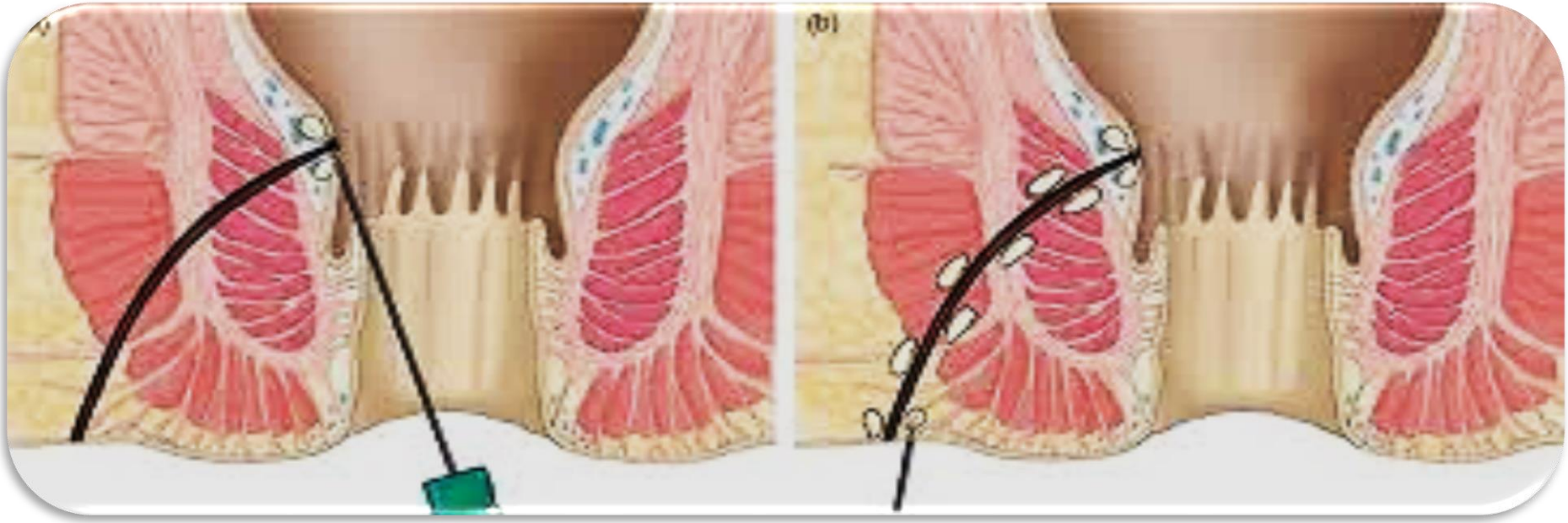
Expandierte, allogene, aus Fettgewebe isolierte mesenchymale Stammzellen (Cx601) zur Therapie komplexer perianaler Fisteln bei Morbus Crohn: Eine Phase 3 randomisierte, doppelblinde kontrollierte Studie



Einzelne intraläsionale Injektion von 120 Millionen Cx601-Zellen oder 24 ml Kochsalzlösung (Placebo)

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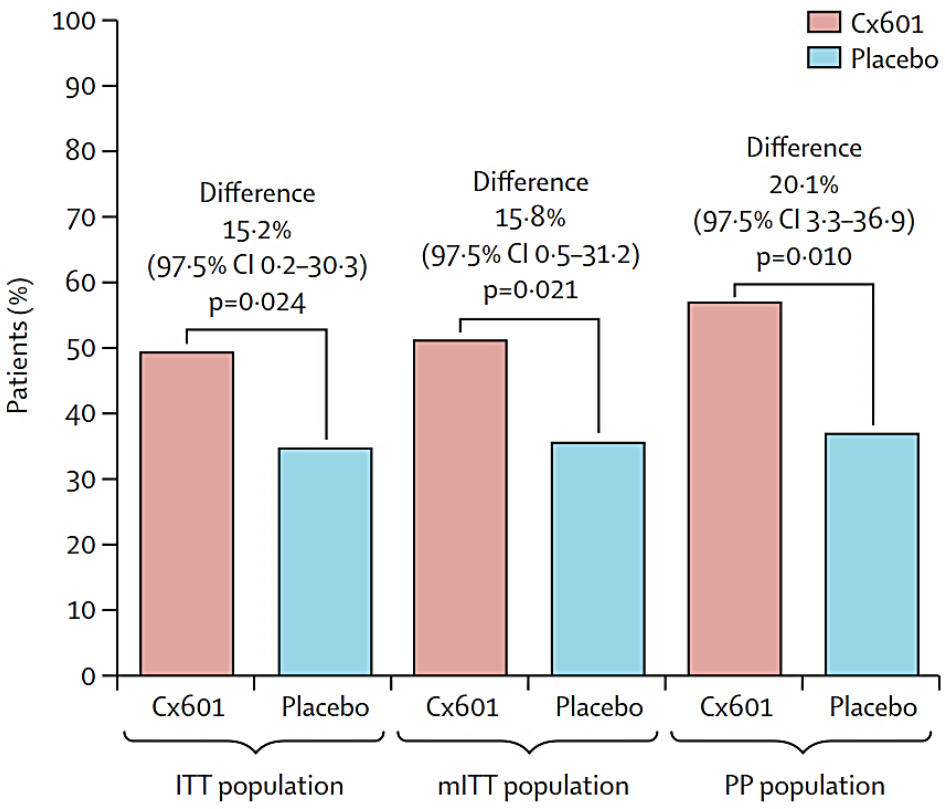
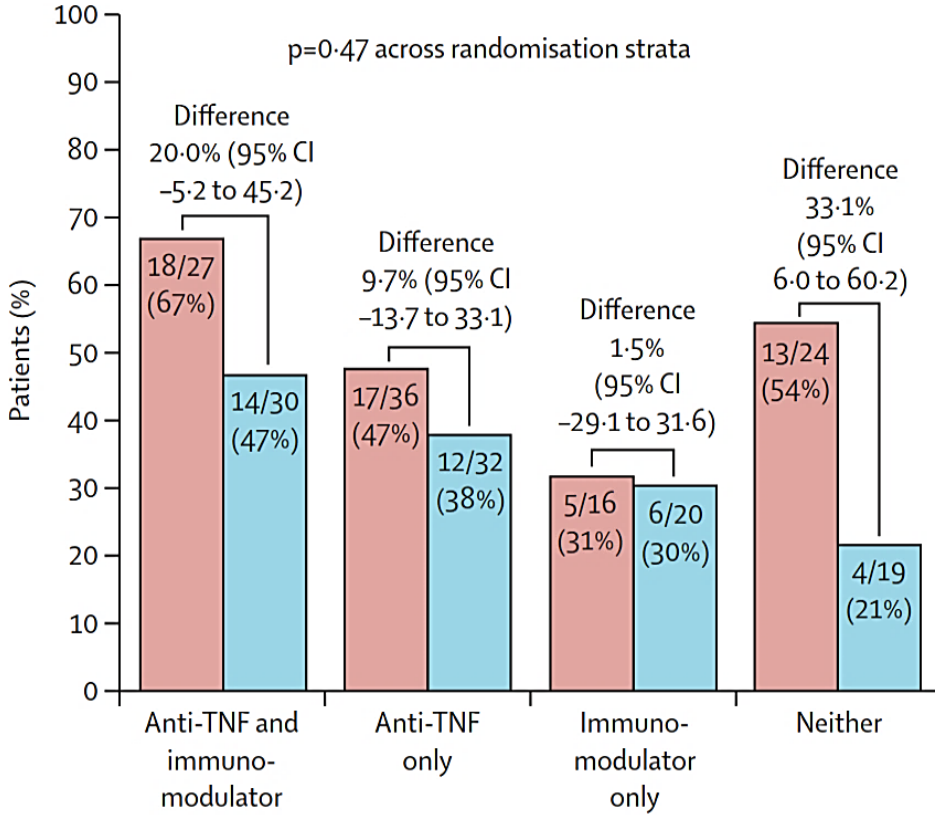
Julián Panés et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial Lancet 2016; 388: 1281–90

Expandierte, allogene, aus Fettgewebe isolierte mesenchymale Stammzellen (Cx601) zur Therapie komplexer perianaler Fisteln bei Morbus Crohn: Eine Phase 3 randomisierte, doppelblinde kontrollierte Studie





Julián Panés et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial Lancet 2016; 388: 1281–90

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Summary

Background Biomarkers of intestinal inflammation, such as faecal calprotectin and C-reactive protein, have been recommended for monitoring patients with Crohn's disease, but whether their use in treatment decisions improves outcomes is unknown. We aimed to compare endoscopic and clinical outcomes in patients with moderate to severe Crohn's disease who were managed with a tight control algorithm, using clinical symptoms and biomarkers, versus patients managed with a clinical management algorithm.

Methods CALM was an open-label, randomised, controlled phase 3 study, done in 22 countries at 74 hospitals and outpatient centres. We evaluated adult patients (aged 18–75 years) with active endoscopic Crohn's disease (Crohn's Disease Endoscopic Severity [CDEIS] >6; sum of CDEIS subscores of >6 in one or more segments with ulcers), a Crohn's Disease Activity Index (CDAI) of 150–450 depending on dose of prednisone at baseline, and no previous use of immunomodulators or biologics. Patients were randomly assigned at a 1:1 ratio to tight control or clinical management, stratified by smoking status (yes or no), weight (<70 kg or ≥70 kg), and disease duration (≤2 years or >2 years). After 8 weeks of prednisone induction therapy, or earlier if they had active disease. In both groups, treatment was escalated in a stepwise manner, from no treatment, to adalimumab induction followed by adalimumab every other week, to adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. This escalation was based on meeting treatment failure criteria, which differed between groups (tight control group before and after random assignment: faecal calprotectin ≥250 µg/g, C-reactive protein ≥5mg/L, CDAI ≥150, or prednisone use in the previous week; clinical management group before random assignment: CDAI decrease of <70 points compared with baseline or CDAI >200; clinical management group after random assignment: CDAI decrease of <100 points compared with baseline or CDAI ≥200, or prednisone use in the previous week). De-escalation was possible for patients receiving weekly adalimumab and azathioprine or weekly adalimumab alone if failure criteria were not met. The primary endpoint was mucosal healing (CDEIS <4) with absence of deep ulcers 48 weeks after randomisation. Primary efficacy and safety analyses were done in the intention-to-treat population. This trial has been completed, and is registered with ClinicalTrials.gov, number NCT01235689.

Findings Between Feb 11, 2011, and Nov 3, 2016, 244 patients (mean disease duration: clinical management group, 0·9 years [SD 1·7]; tight control group, 0·9 years [2·3]) were randomly assigned to monitoring groups (n=122 per group). 29 (24%) patients in the clinical management group and 32 (26%) patients in the tight control group discontinued the study, mostly because of adverse events. A significantly higher proportion of patients in the tight control group achieved the primary endpoint at week 48 (56 [46%] of 122 patients) than in the clinical management group (37 [30%] of 122 patients), with a Cochran–Mantel–Haenszel adjusted risk difference of 16·1% (95% CI 3·9–28·3; p=0·010). 105 (86%) of 122 patients in the tight control group and 104 (85%) of 122 patients in the clinical management group reported treatment-emergent adverse events; no treatment-related deaths occurred. The most common adverse events were nausea (21 [17%] of 122 patients), nasopharyngitis (18 [15%]), and headache (18 [15%]) in the tight control group, and worsening Crohn's disease (35 [29%] of 122 patients), arthralgia (19 [16%]), and nasopharyngitis (18 [15%]) in the clinical management group.

Interpretation CALM is the first study to show that timely escalation with an anti-tumour necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions alone. Future studies should assess the effects of such a strategy on long-term outcomes such as bowel damage, surgeries, hospital admissions, and disability.

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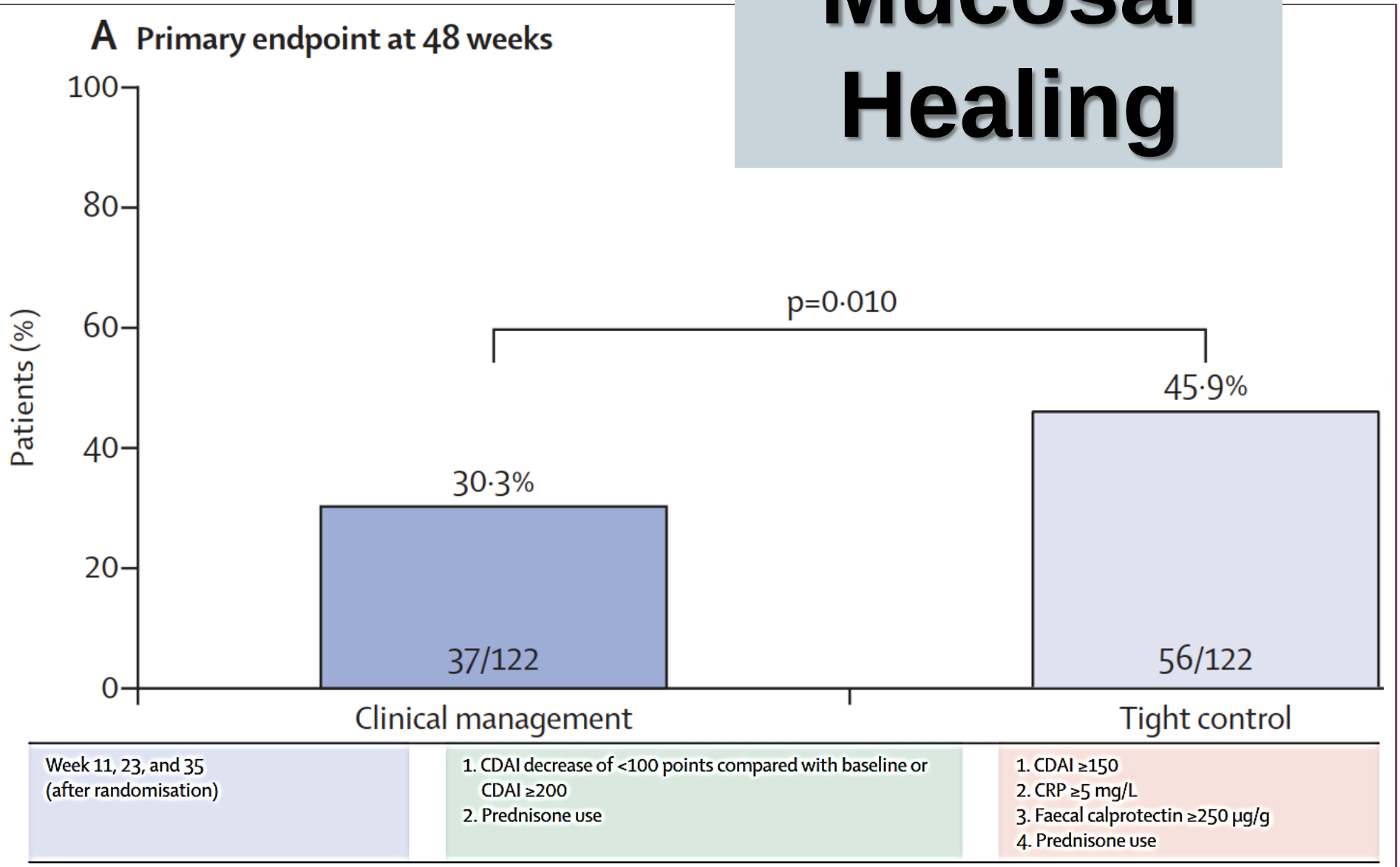
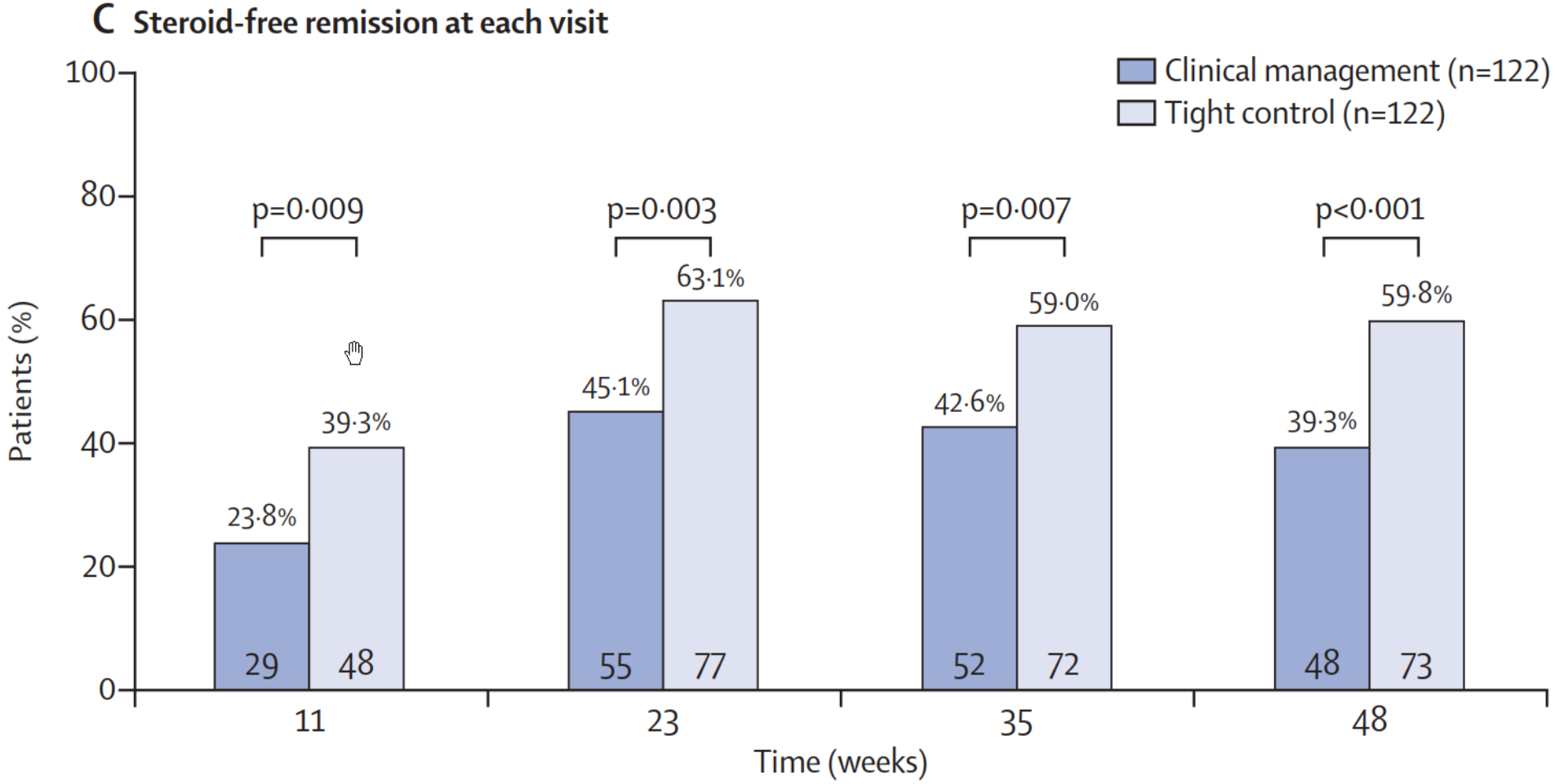
Department of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA (Prof J-F Colombel MD); **Inflammatory Bowel Disease Unit, Department of Medicine, University of Calgary, Calgary, AB, Canada** (Prof R Panaccione MD); **Imelda General Hospital, Bonheiden, Belgium** (P Bossuyt MD); **Clinical and Research Centre for Inflammatory Bowel Disease, ISCARE Clinical Centre, Prague, Czech Republic** (Prof M Lukas MD); **First Medical Faculty, Charles University, Prague, Czech Republic** (Prof M Lukas); **AZ Delta, Roeselare-Menen, Belgium** (F Baert MD); **Hepato-Gastroenterologie HK, sro, Hradec Králové, Czech Republic** (T Vanasek MD); **Department of Gastroenterology, Bezmialem Vakif University, Istanbul, Turkey** (Prof A Danalioglu MD); **Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria** (G Novacek MD, W Reinisch MD); **Presidio Columbus, Fondazione Policlinico Gemelli Università Cattolica, Rome, Italy** (A Armuzzi MD); **Service de Gastro-entérologie et Nutrition Clinique, Nice, France** (Prof X Hébuterne MD); **Université de Nice-Sophia-Antipolis, Nice, France** (Prof X Hébuterne); **Oxford**

Treat to Target: CALM

Mucosal Healing



Calprotectin als « Treat to Target » in CALM



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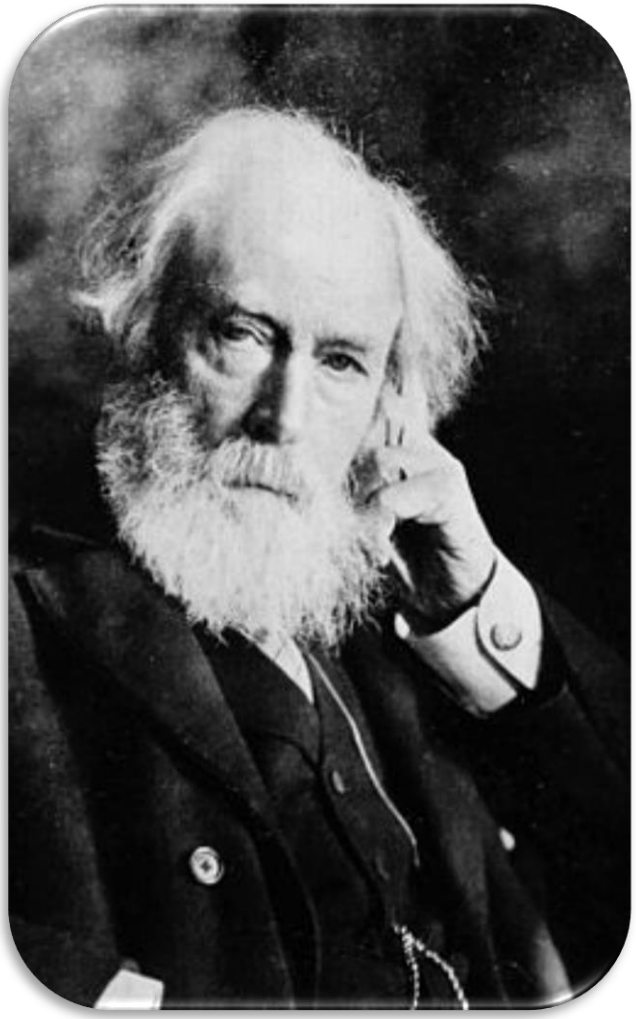
Colombel et al, Lancet 2017

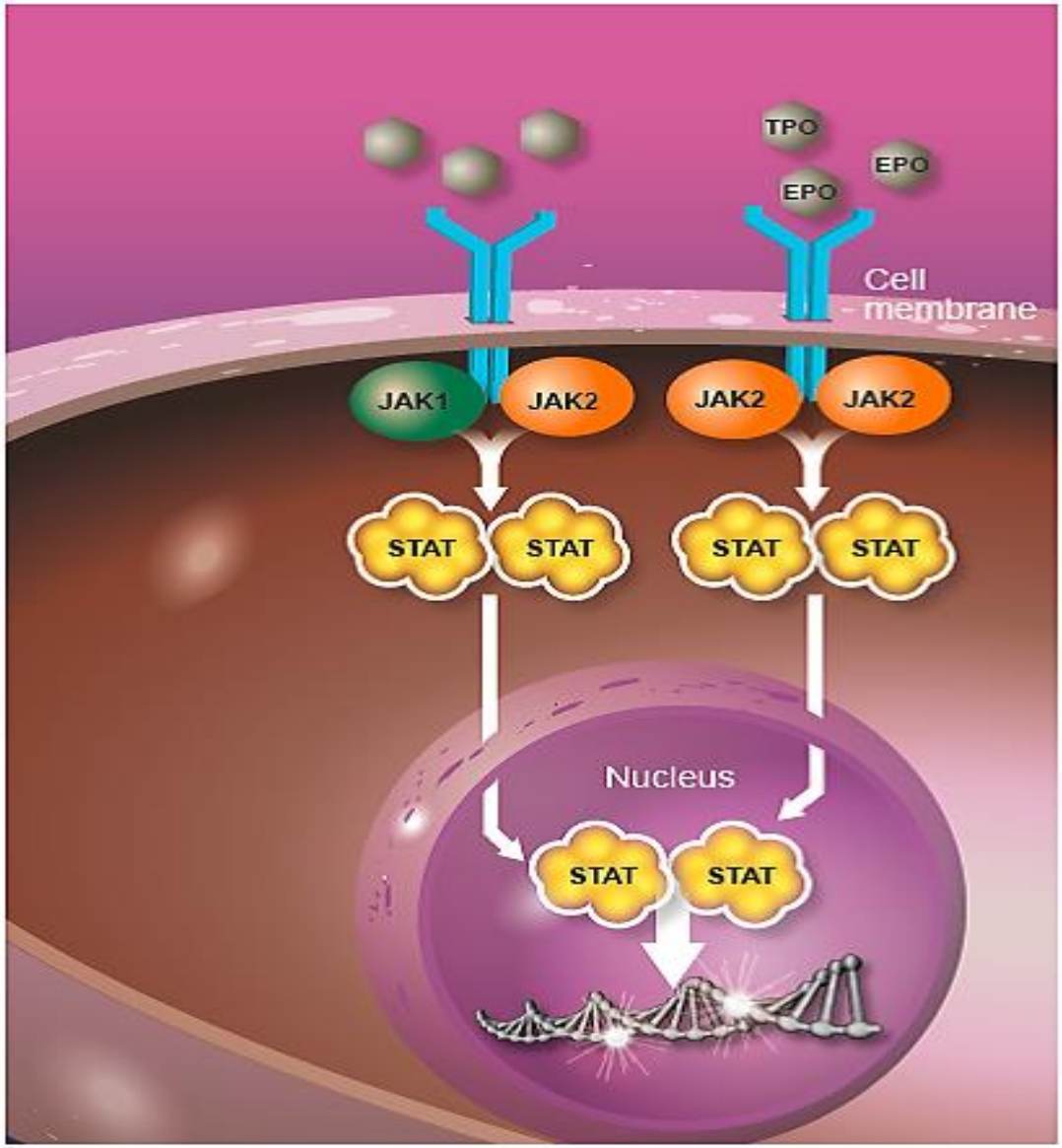
Ja – fehlt da nicht noch etwas…?

Mongersen.

Neues zur Therapie – Colitis ulcerosa



Neue JAK Inhibitoren in der Entwicklung bei CED



Cytokines, Growth Factors

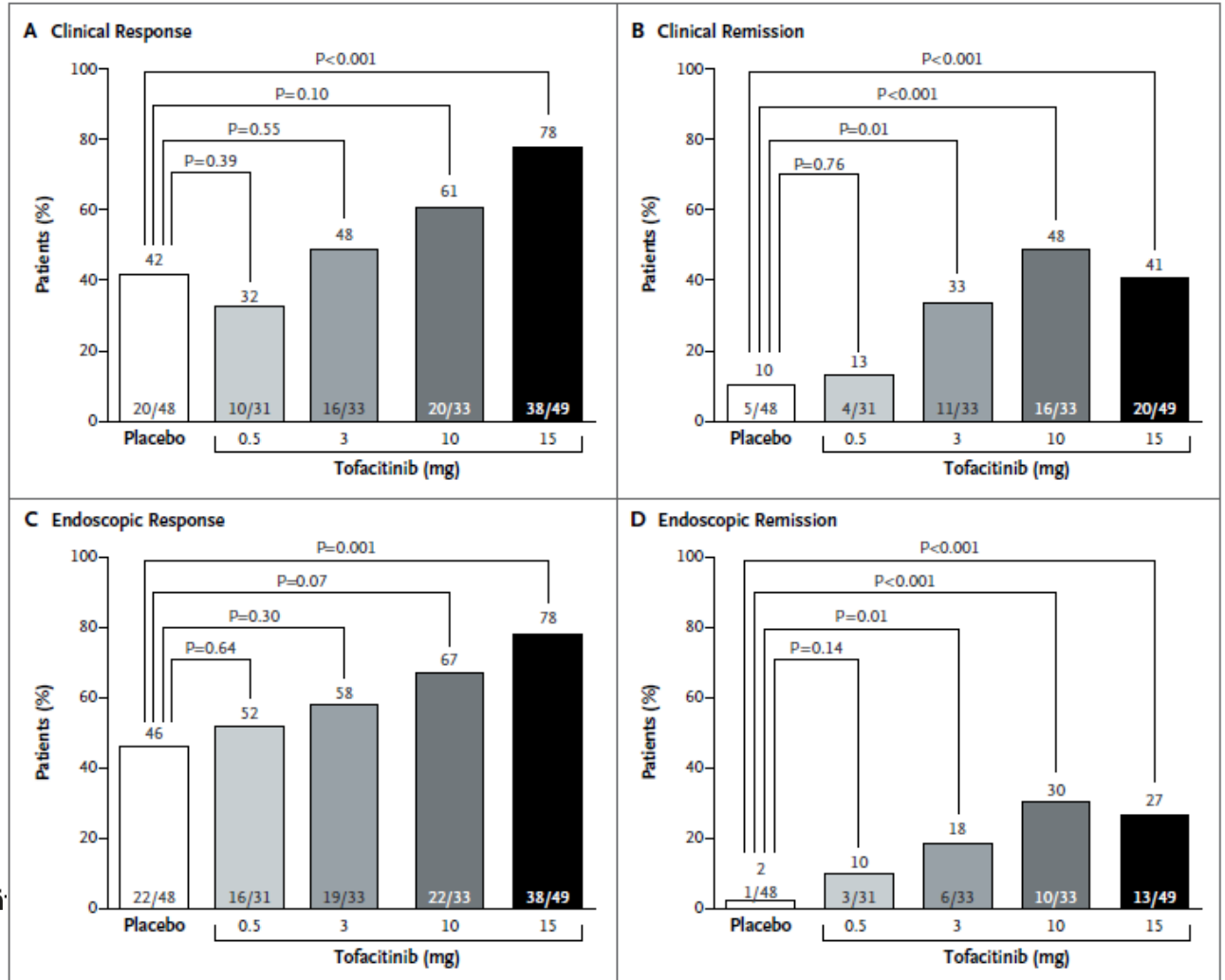
Normal JAK Signaling

Transcription

Tofacitinib Phase II Studie

194 Patienten mit aktiver CU (Mayo ≥6, ES≥2) erhielten entweder Placebo oder Tofacitinib (0.5, 3, 10 or 15 mg BID)

- Primärer Endpunkt: Klinischer Response (ΔMayo ≥3 und 30%, ES≤1) in Woche 8



Sandborn W et al.
NEJM 2012;367:616

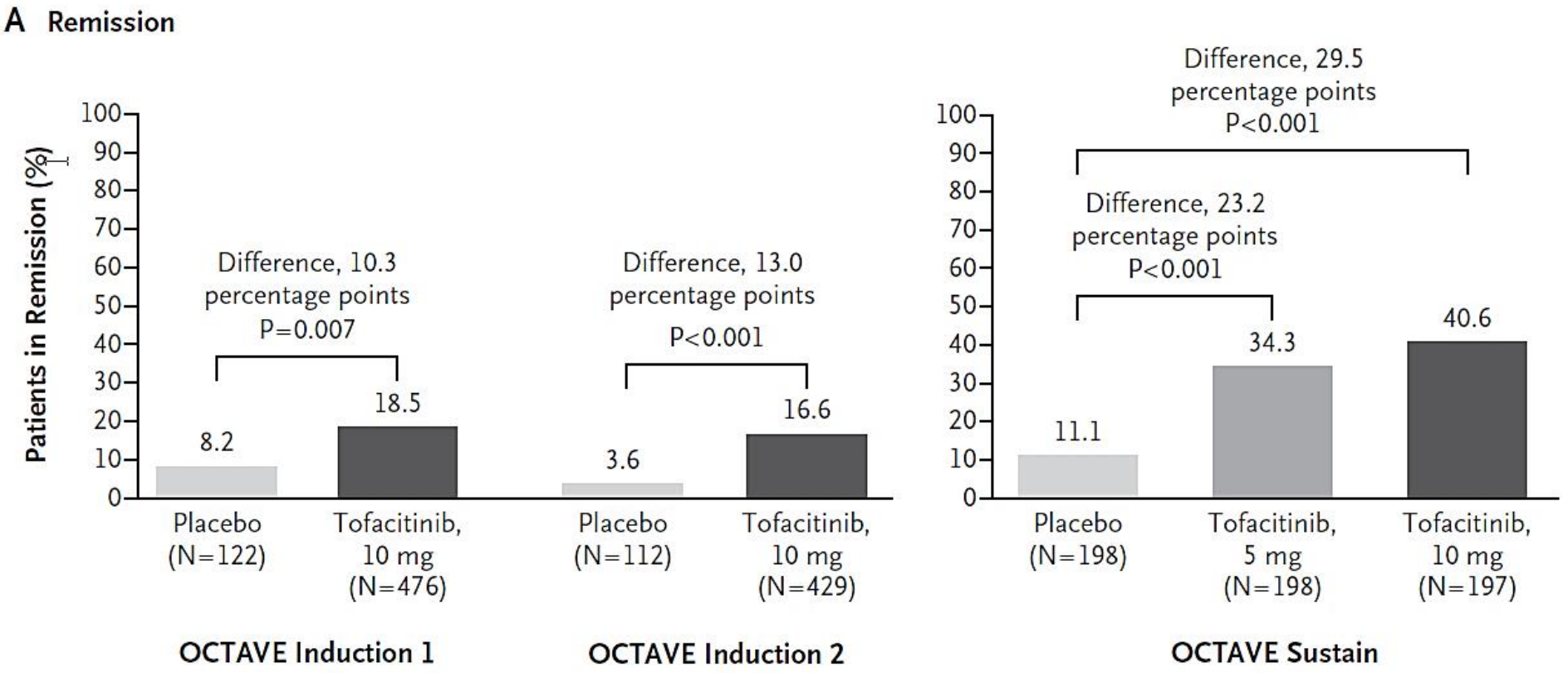
Tofacitinib zur Induktions- und Erhaltungstherapie bei aktiver Colitis ulcerosa

HINTERGRUND:

- Tofacitinib ist ein **oraler Janus-Kinase-Inhibitor**
- Drei **Phase 3**, randomisierte, doppelblinde, Placebo-kontrollierte Studien bei Erwachsenen mit Colitis ulcerosa.
- In den **OCTAVE**-Induktions-1 und 2-Studien wurden 598 bzw. 541 Patienten, die mäßig bis stark aktive Colitis ulcerosa **trotz vorheriger konventioneller Therapie oder Therapie mit einem Tumor-Nekrose-Faktor-Antagonisten** hatten, einer Induktionstherapie mit Tofacitinib (10 mg zweimal täglich) oder Placebo für 8 Wochen zugeteilt
- In der OCTAVE Sustain-Studie wurden **593 Patienten**, die eine klinische Antwort auf die Induktionstherapie zeigten, einer Erhaltungstherapie mit Tofacitinib (entweder 5 mg oder 10 mg zweimal täglich) oder Placebo für 52 Wochen zugeordnet

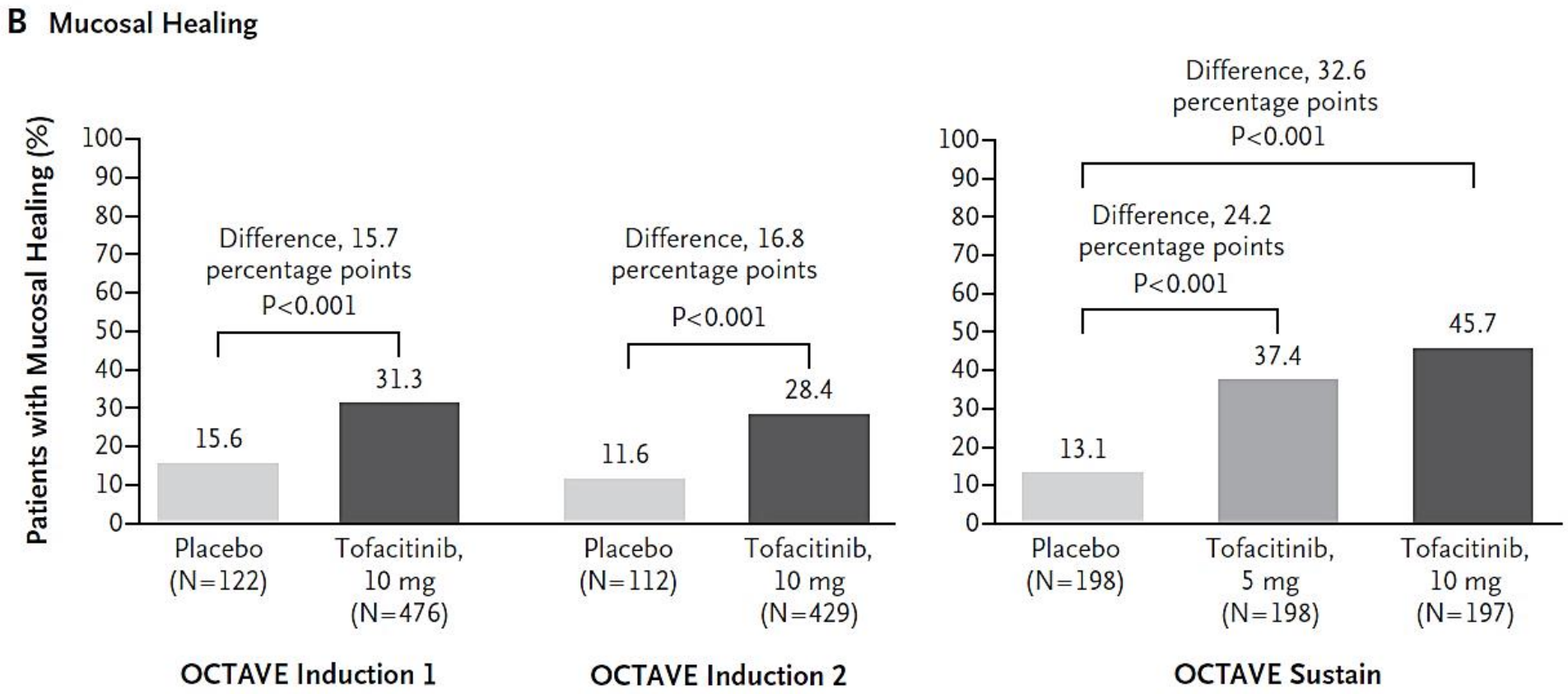
William J. Sandborn et al., Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis N Engl J Med 376;18 May 4, 2017

Tofacitinib zur Induktions- und Erhaltungstherapie bei aktiver Colitis ulcerosa



William J. Sandborn et al., Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis N Engl J Med 376;18 May 4, 2017

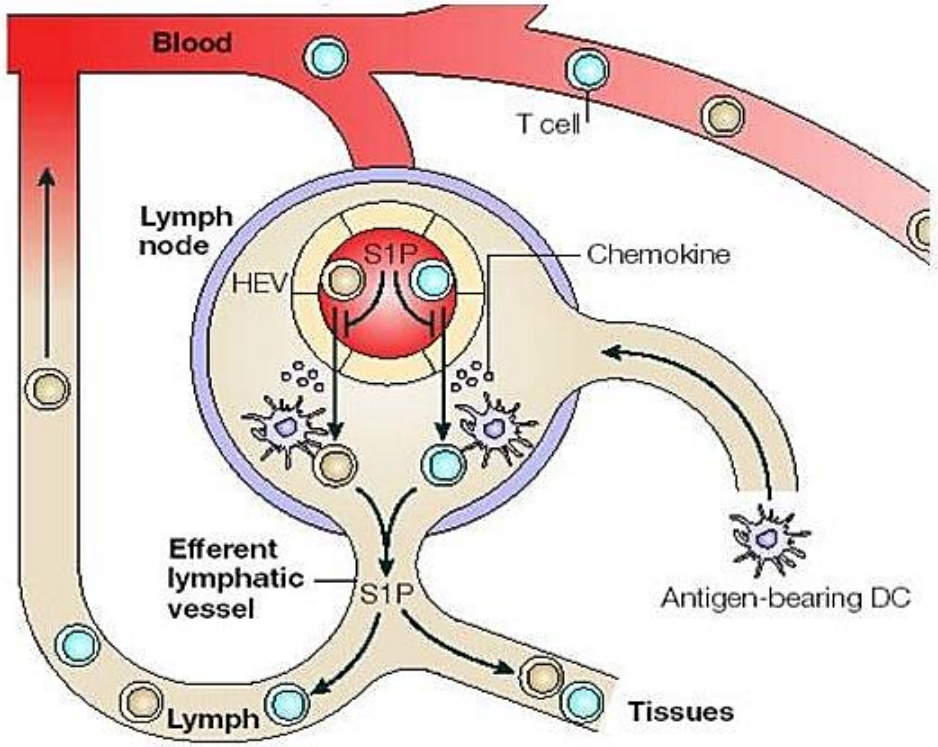
Tofacitinib zur Induktions- und Erhaltungstherapie bei aktiver Colitis ulcerosa



William J. Sandborn et al., Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis N Engl J Med 376;18 May 4, 2017

Ozanimod Induktions- und Erhaltungstherapie zur Behandlung von Colitis ulcerosa

- Ozanimod (RPC1063) ist ein **oraler Agonist der Sphingosin-1-Phosphat-Rezeptor**-Subtypen 1 und 5, der eine **periphere Lymphozyten-Sequestrierung induziert**
- doppelblinde, Placebo-kontrollierte **Phase 2-Studie**
- 197 Erwachsene mit mittelschwerer bis schwerer Colitis ulcerosa
- 1: 1: 1-Randomisierung, Placebo und Ozanimod in einer Dosis von 0,5 mg oder 1 mg über 32 Wochen



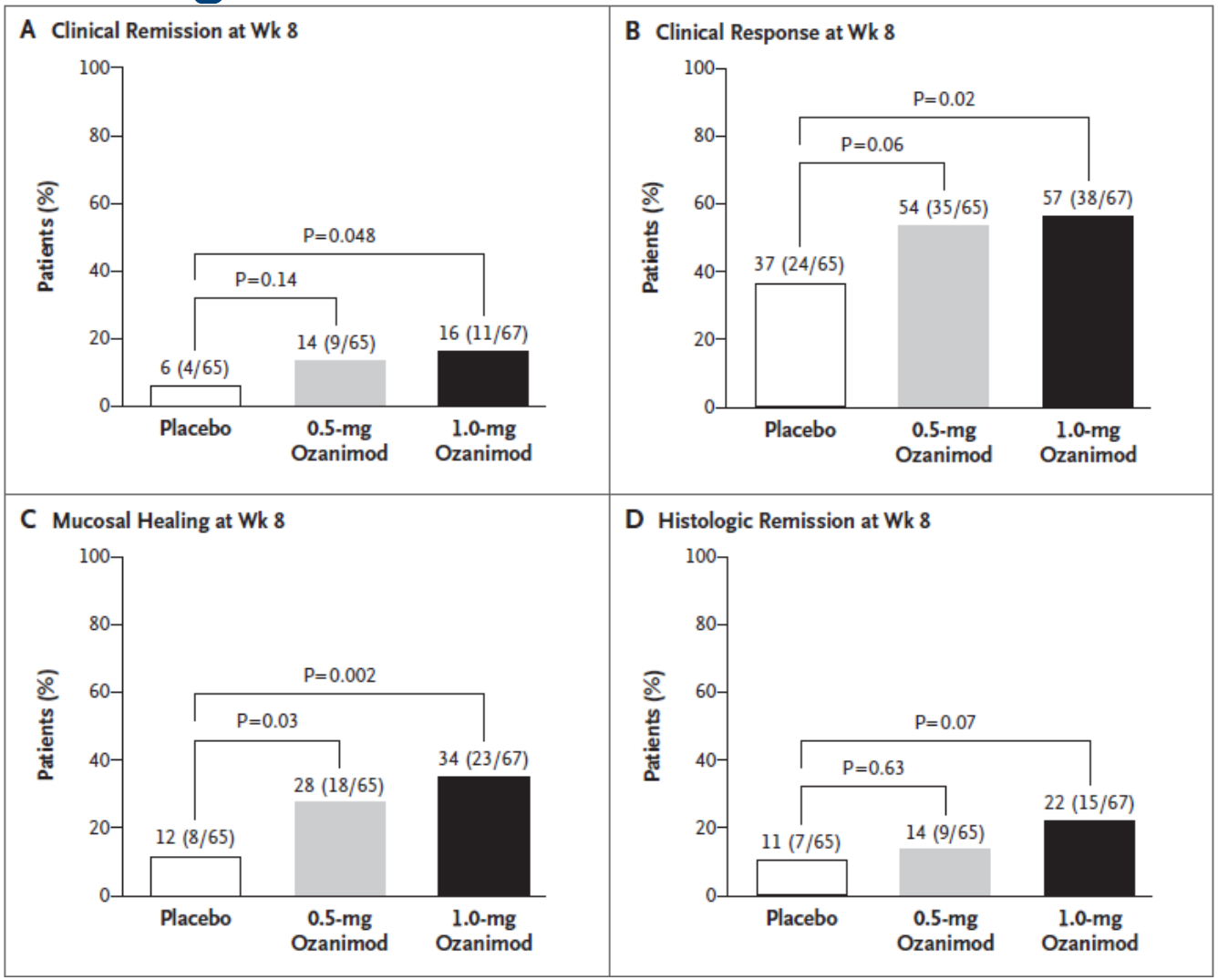
S1P Rezeptor Modulatoren: Wirkmechanismus

S1P1 Medikamente «fangen» Immunzellen in Lymphknoten
Dadruch können diese nicht in die Darmschleimhaut einwandern

William J. Sandborn et al. Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis N Engl J Med 374;18

Ozanimod Induktions- und Erhaltungstherapie zur Behandlung von Colitis ulcerosa

16% Pat. mit 1 mg Ozanimod
14% Pat. mit 0,5 mg Ozanimod erreichten Remission,
6% Placebo
(P = 0,048 und
P = 0,14, für Vergleich der Zwei Dosen Ozanimod mit Placebo).



William J. Sandborn et al. Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis N Engl J Med 374;18

Ozanimod Induktions- und Erhaltungstherapie zur Behandlung von Colitis ulcerosa

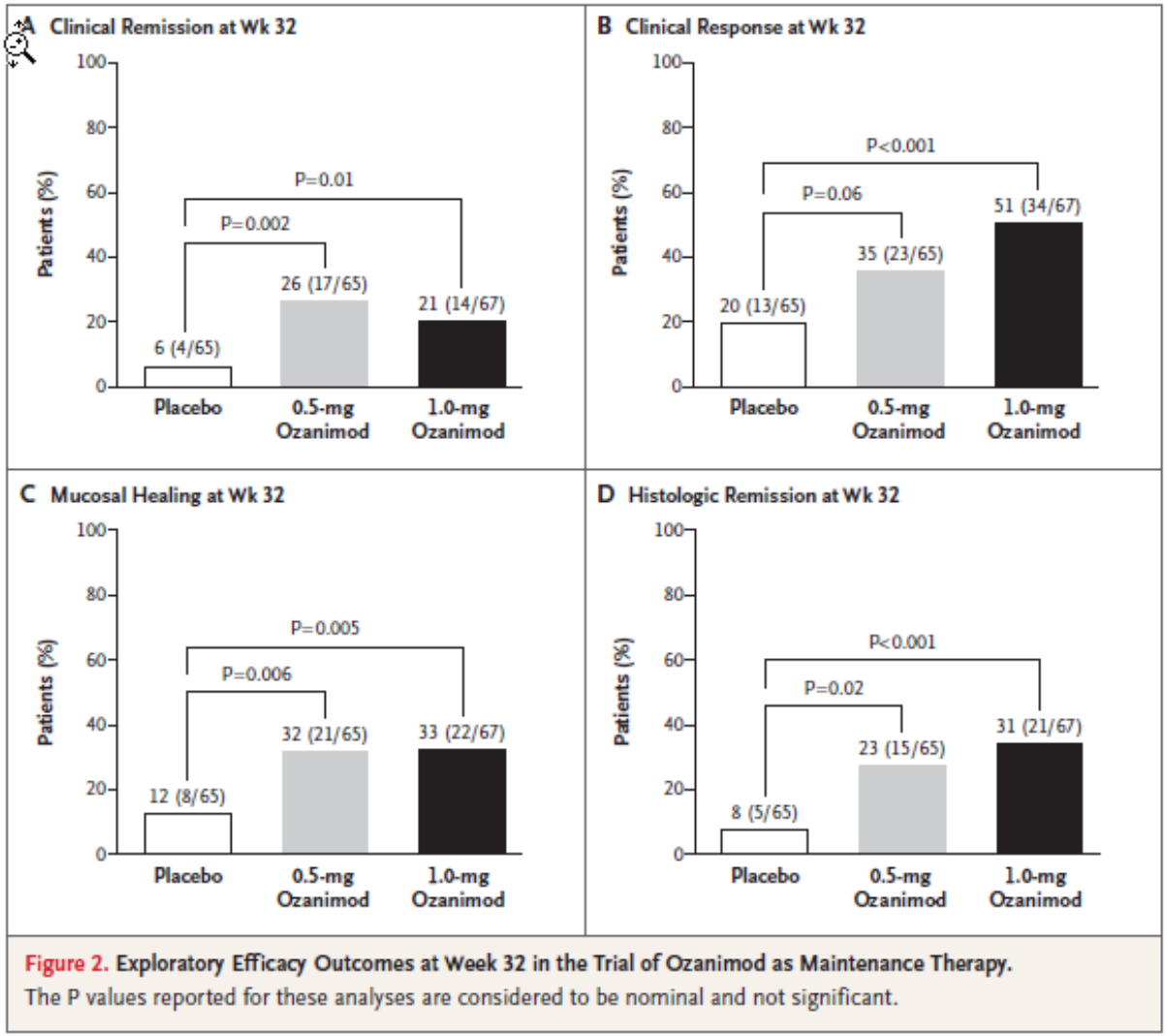
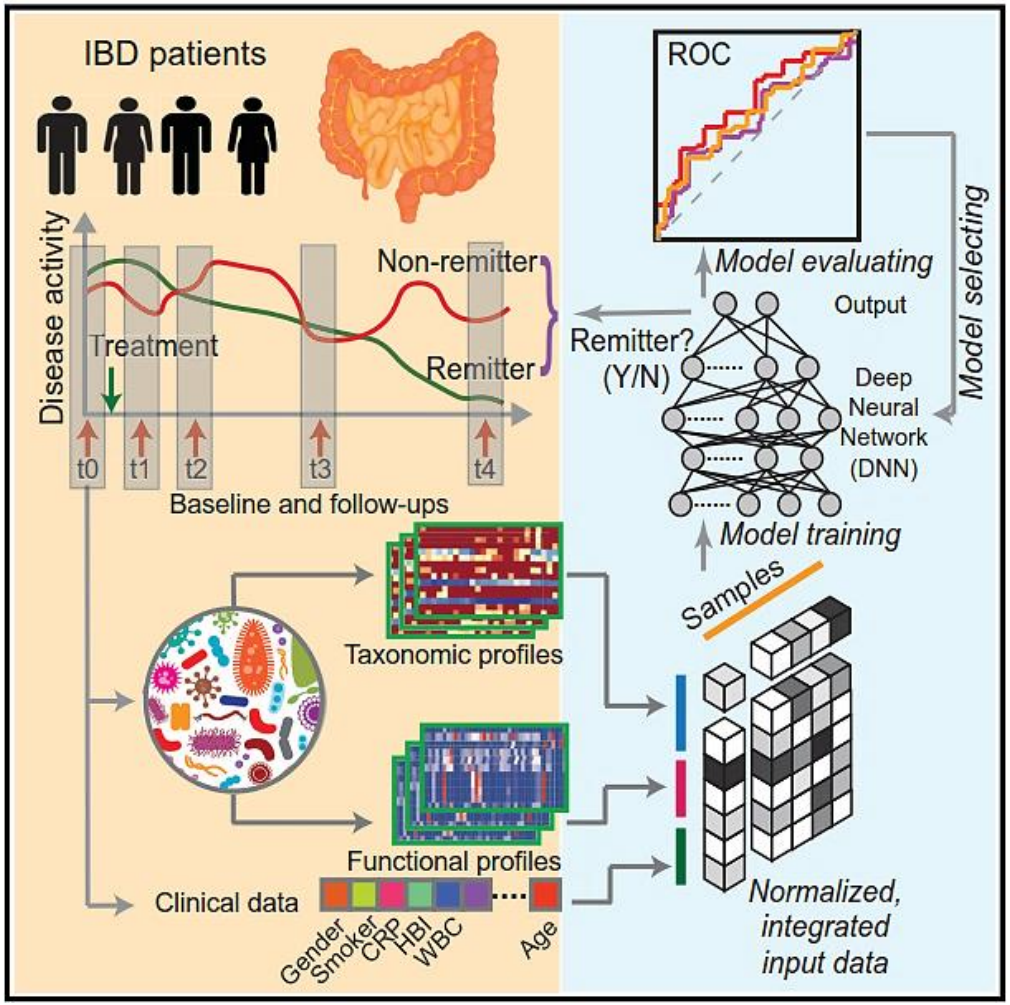


Figure 2. Exploratory Efficacy Outcomes at Week 32 in the Trial of Ozanimod as Maintenance Therapy.
The P values reported for these analyses are considered to be nominal and not significant.

William J. Sandborn et al. Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis N Engl J Med 374;18

Rendevouz zwischen basic science & klinischer Praxis

Intestinale Microbiota (Zusammensetzung und Funktion): Wertvoll für Prädiktion klinisches Ansprechen…?



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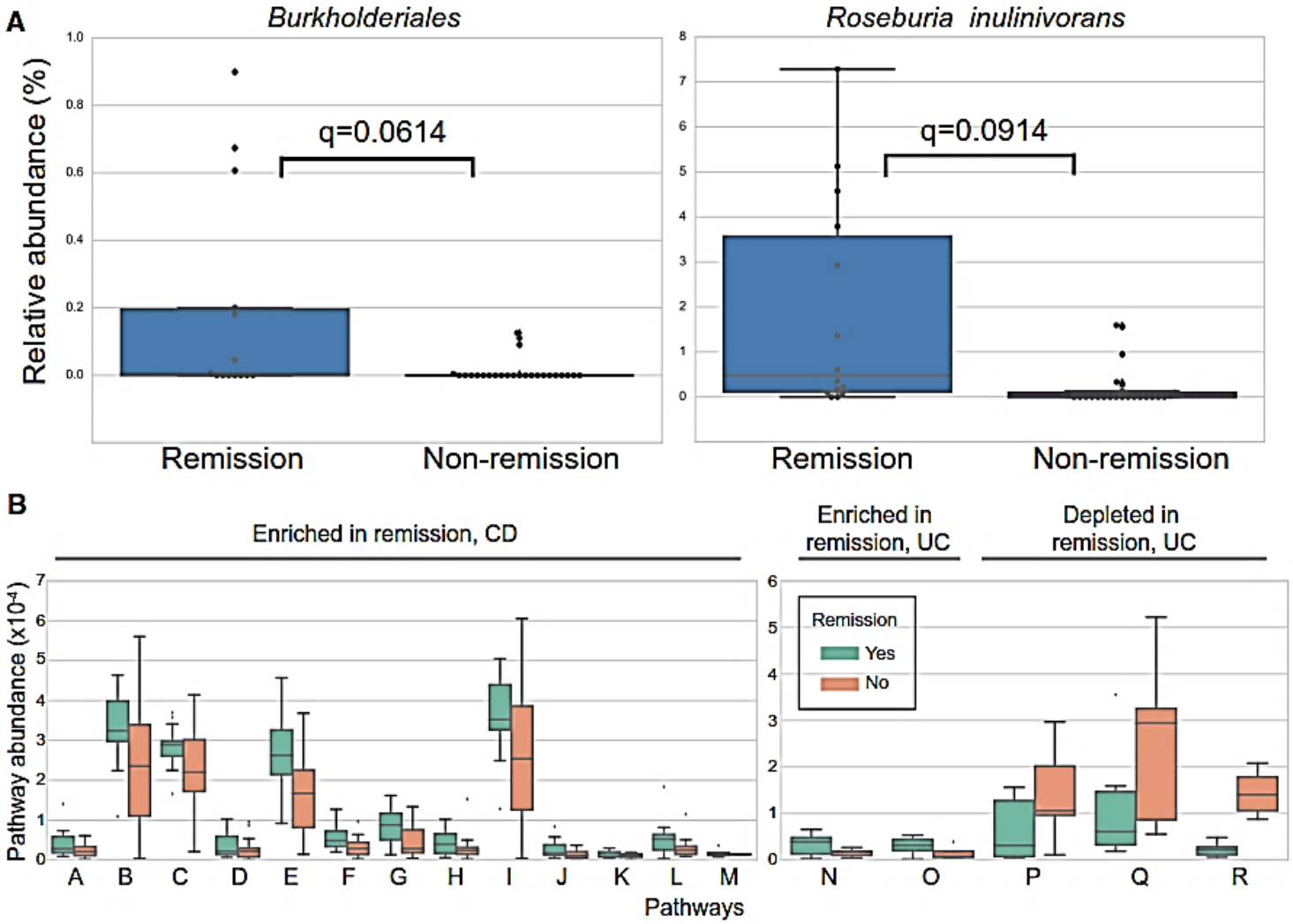
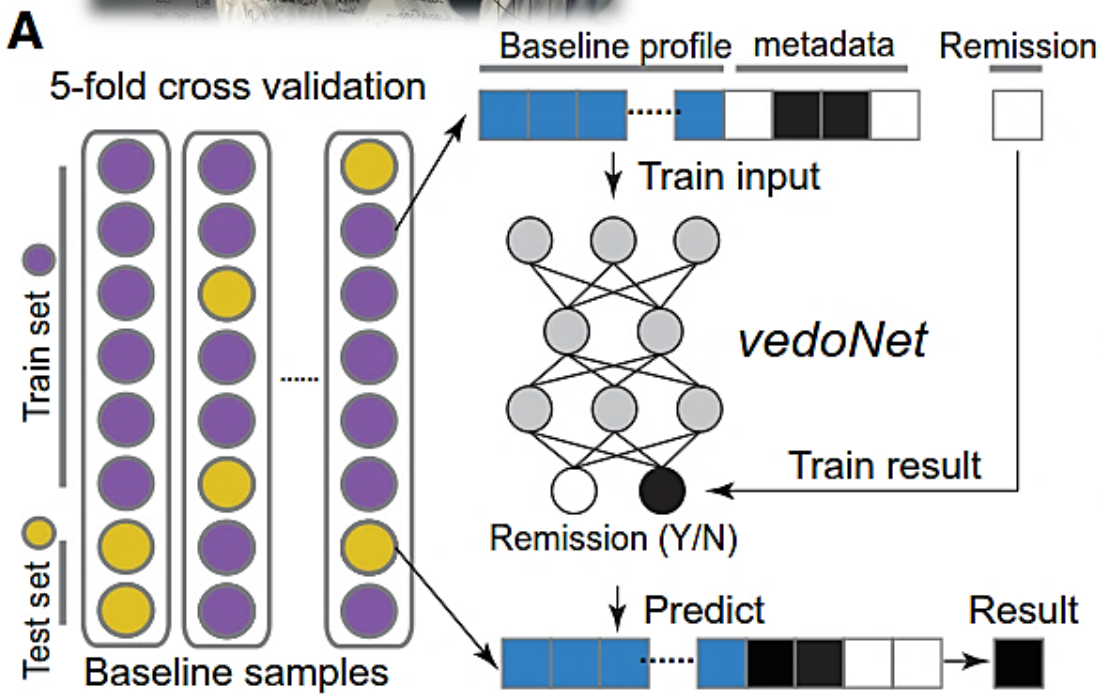
Ananthakrishnan et al., 2017, Cell Host & Microbe

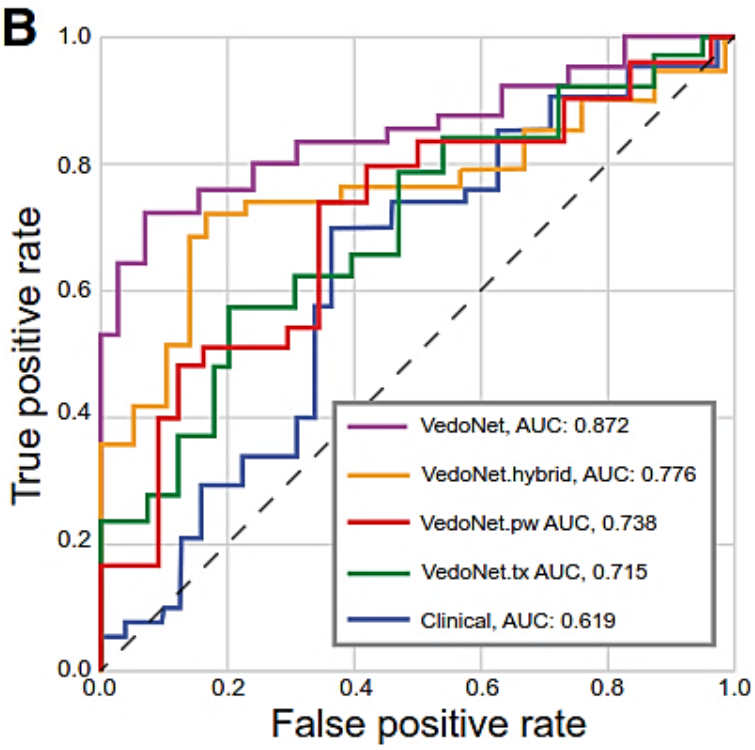
Intestinale Microbiota (Zusammensetzung und Funktion): Wertvoll für Prädiktion klinisches Ansprechen…?



Ananthakrishnan et al., 2017, Cell Host & Microbe

Intestinale Microbiota (Zusammensetzung und Funktion): Wertvoll für Prädiktion klinisches Ansprechen…?





Ananthakrishnan et al., 2017, Cell Host & Microbe

Neues zur Therapie – Crohn und Colitis

Kann man eine anti-TNF Therapie stoppen?

Anti-TNF AB sind etablierte und wirkungsvolle Therapien bei IBD

Bedenken hinischtlich einer Langzeit anti-TNF Behandlung sind:

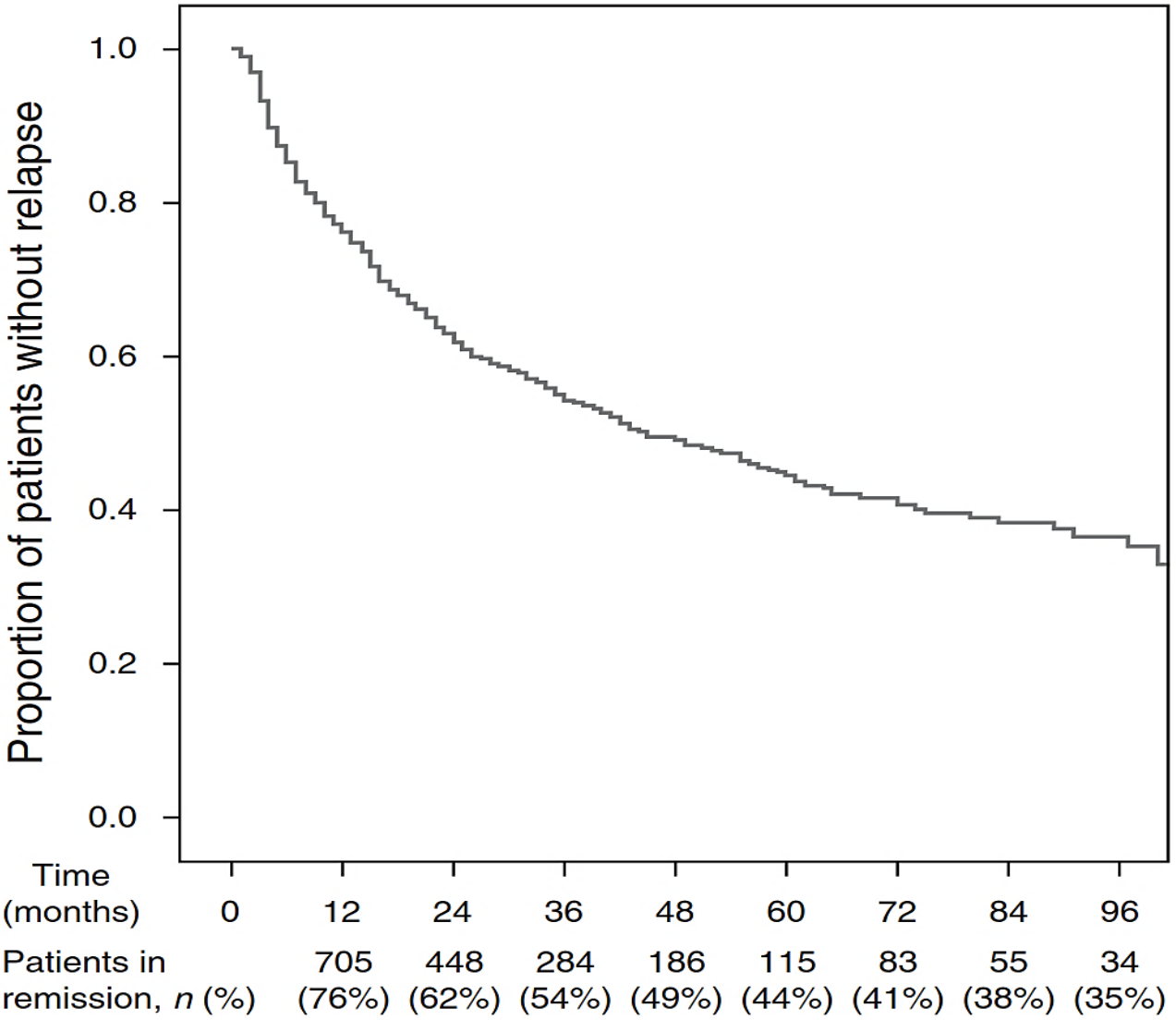
- Infektionsgefahr
- Krebserkrankungen, insbesondere Melanome (Long *et al.*, Gastroenterology, 2012)
- Gesundheitskisten

Publizierte Daten zum anti-TNF Stopp:

Autor/Publikation	Population	Anteil Relapse
Waugh APT 2010	48 CD	42% nach einem Jahr
Louis Gastro 2012	115 CD	39% nach einem Jahr
Steenholdt Scand J Gastro 2012	53 CD; 28 UC	39% nach einem Jahr (CD); 25% (UC)
Molnár APT 2012	121 CD	45% nach einem Jahr
Brooks JCC 2014	86 CD	36% nach einem Jahr
Bortlik ECCO 2015	61 CD	41% nach einem Jahr; 49% nach zwei Jahren

Neueste Daten:

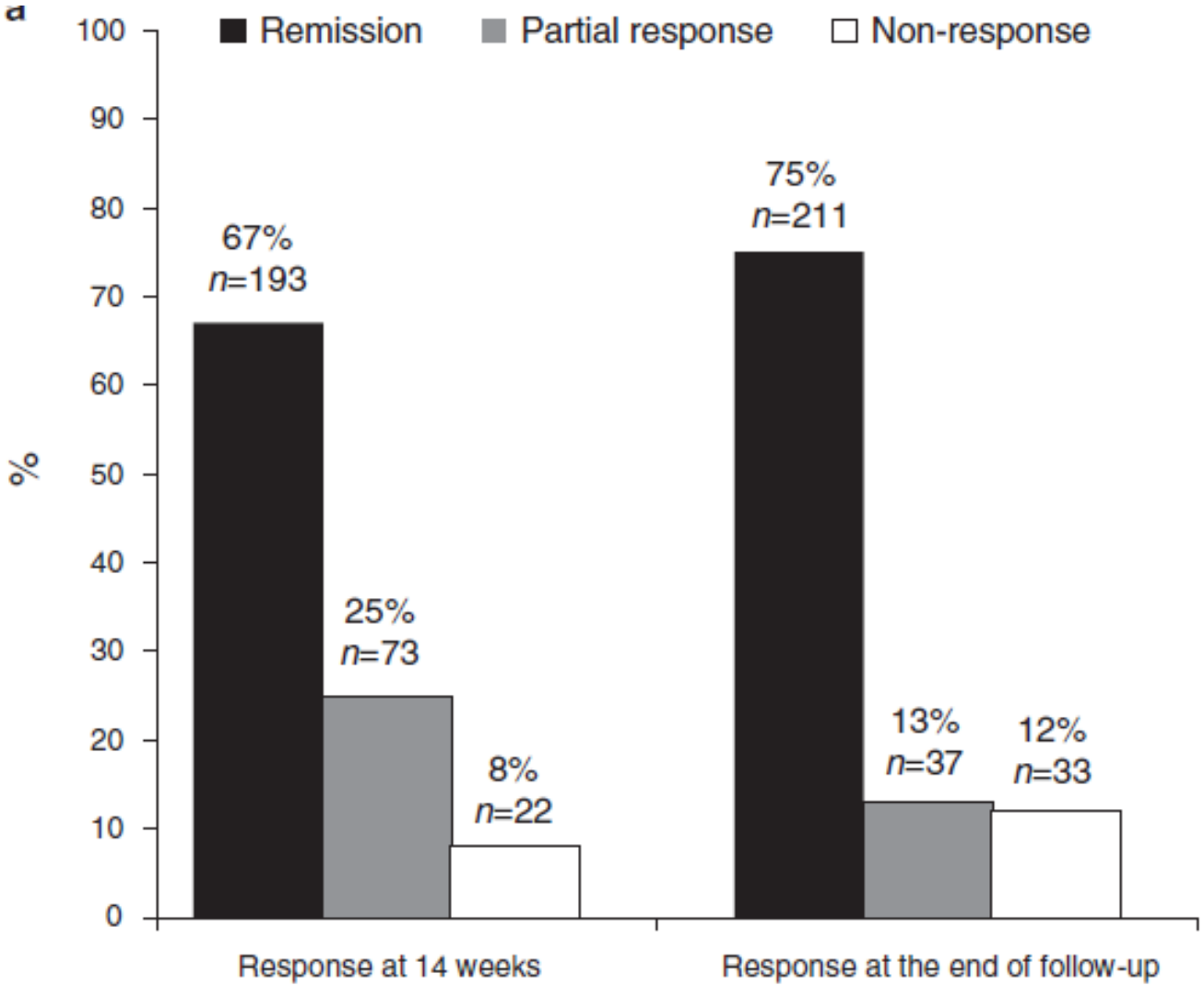
- Retrospektive, Multicenter-Beobachtungsstudie
- 1,055 IBD in klinischer Remission



- Inzidenz eines Relapse **19% pro Patienten-Jahr bei Patienten mit M. Crohn & C. ulcerosa in «**deep remission» ➔ Deep remission verhindert den Relaps **nicht**

M.J. Casanova et al. Evolution After Anti-TNF Discontinuation in Patients With Inflammatory Bowel Disease: A Multicenter Long-Term Follow-Up Study Am J Gastroenterol 2017; 112:120–131

Erfolg der erneuten Behandlung



M.J. Casanova et al. Evolution After Anti-TNF Discontinuation in Patients With Inflammatory Bowel Disease: A Multicenter Long-Term Follow-Up Study Am J Gastroenterol 2017; 112:120–131

Vitamin D zur Prophylaxe von Schüben: Die Evidenz wird immer klarer

- Viele Daten deuten darauf hin, dass Vitamin D eine signifikante Rolle zur Vermeidung von Schüben bei IBD spielt.
- IBD Patienten mit **bis zu 5-Jahres-Follow-up** aus einer longitudinalen Registry wurden untersucht.
- Insgesamt **965 IBD-Patienten** (61,9% Morbus Crohn, 38,1% Colitis ulcerosa; mittleres Alter 44 Jahre, 52,3% weiblich) wurden untersucht.
- Im Laufe des 5-jährigen Studienzeitraums benötigten Probanden mit **niedrigen Vitamin D** Spiegel deutlich **mehr Steroide, Biologika, Betäubungsmittel, CT Scans, Notfallkonsultationen, Hospitalisationen und OPs** im Vergleich zu Probanden mit normalen mittleren Vitamin D-Spiegel (P <0,05).

Toufic Kabbani et al., Association of Vitamin D Level With Clinical Status in Inflammatory Bowel Disease: A 5-Year Longitudinal Study. Am J Gastroenterol 2016; 111:712–719;

Vitamin D zur Prophylaxe von Schüben: Die Evidenz wird immer klarer

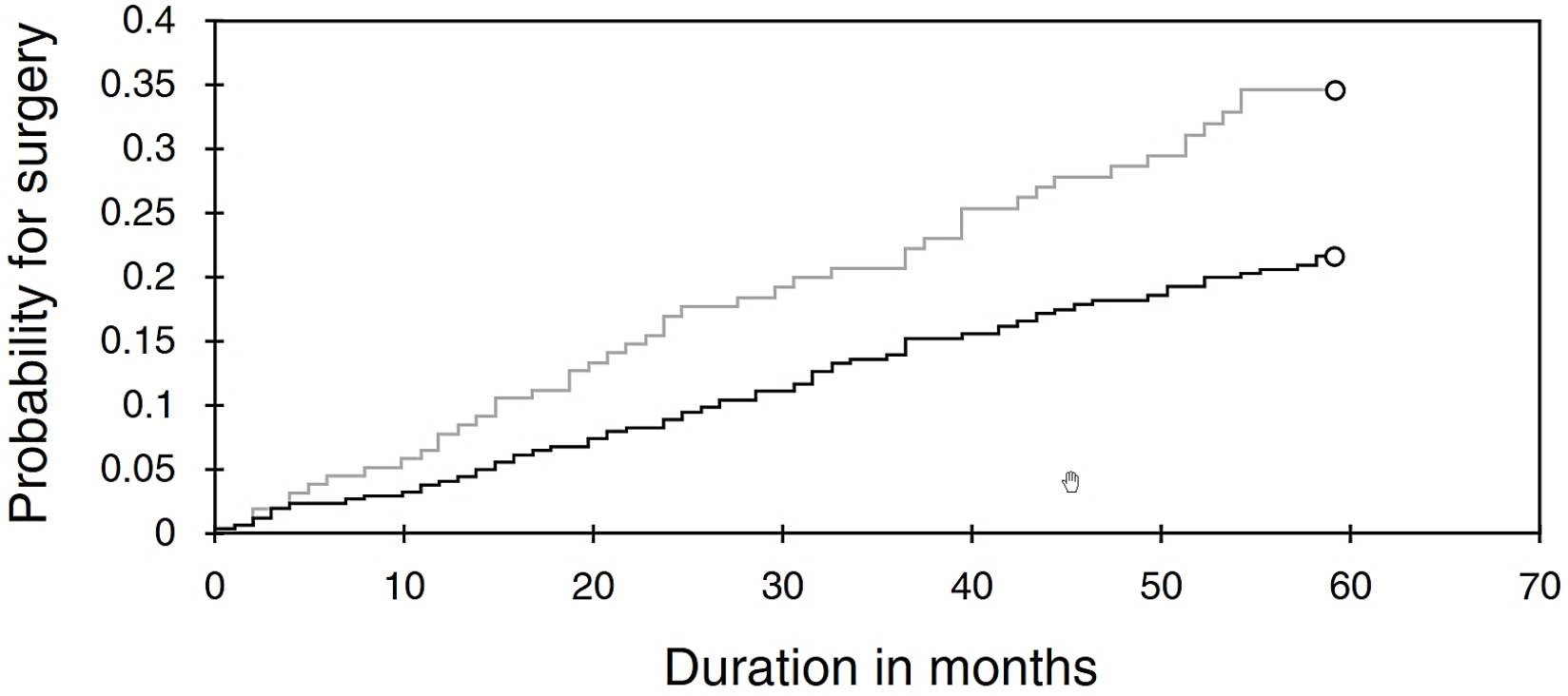


Figure 1. Kaplan–Meier surgery survival curves in inflammatory bowel disease patients evaluated in clinic, stratified by vitamin D status. Black line = normal vitamin D group; grey line = low vitamin D group.

Toufic Kabbani et al., Association of Vitamin D Level With Clinical Status in Inflammatory Bowel Disease: A 5-Year Longitudinal Study. Am J Gastroenterol 2016; 111:712–719;

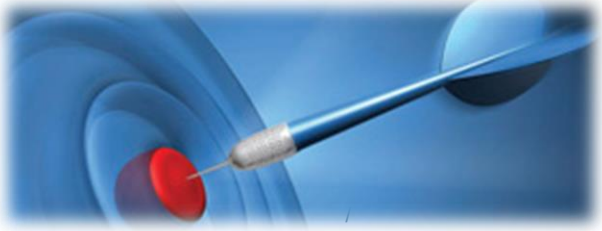
IBD highlights - Zusammenfassung I

- Ustekinumab (Stelara®) ist für die Therapie des M. Crohn zugelassen. Die Induktionstherapie erfolgt mit i.v. Gabe, die Remissionserhaltung kann s.c. erfolgen.

- Die Sicherheitsdaten für Stelara® sind ermutigend, das Infektionsrisiko ist gering.

- Die Entwicklung neuer anti-p19 (anti-IL23) Biologika ist vielversprechend.
- Expandierte, aus Fettgewebe isolierte mesenchymale Stammzellen werden vermutlich bald als neue Therapie für Fisteln bei Morbus Crohn zur Verfügung stehen

- Calprotectin eignet sich als «treat-to-target» Monitoring Marker bei Patienten mit M. Crohn

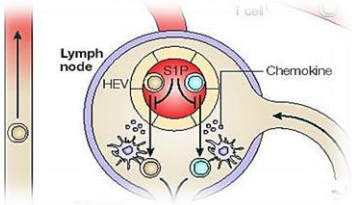


IBD highlights - Zusammenfassung II

- Mikrobielle Zusammensetzung und Funktion könnte in Zukunft die Wahl der Therapie beeinflussen

- Tofacitinib wird voraussichtlich für die Colitis ulcerosa zugelassen und ist wie andere JAK Inhibitoren vielversprechend

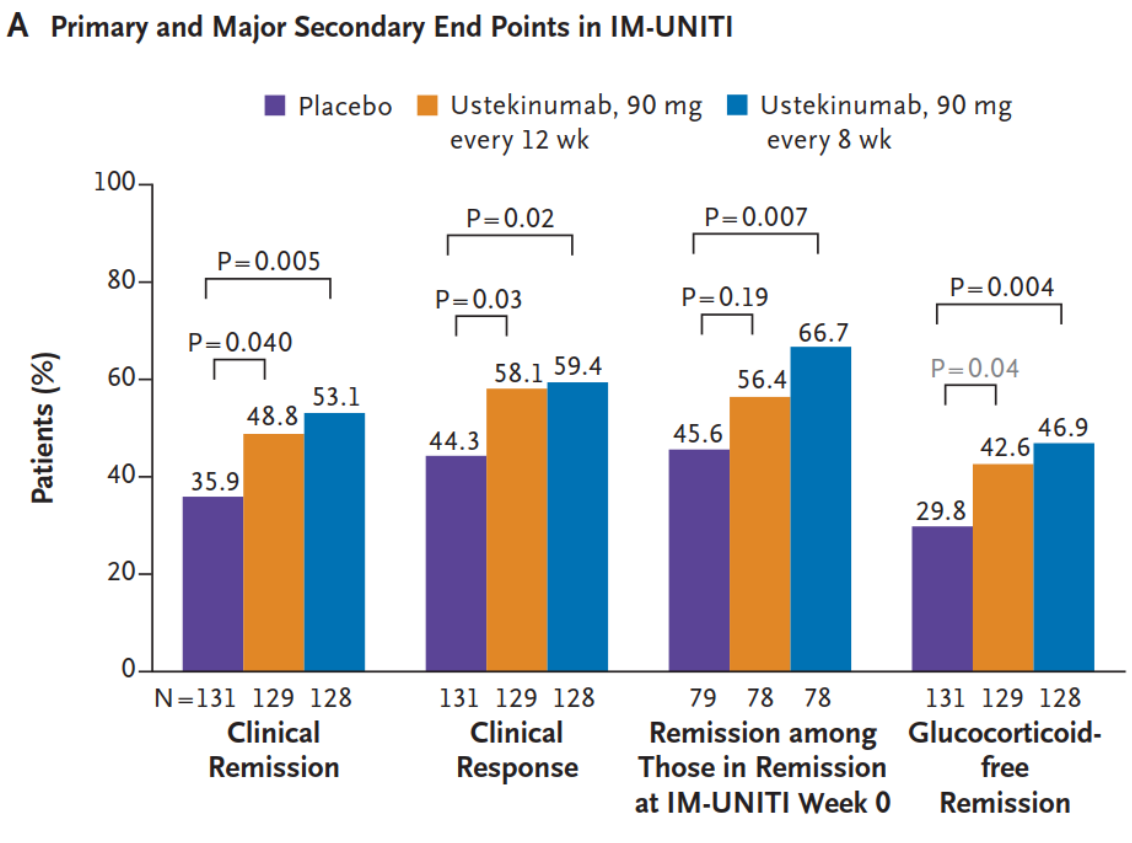
- Ozanimod ist eine weitere Neuentwicklung im Bereich der Colitis ulcerosa

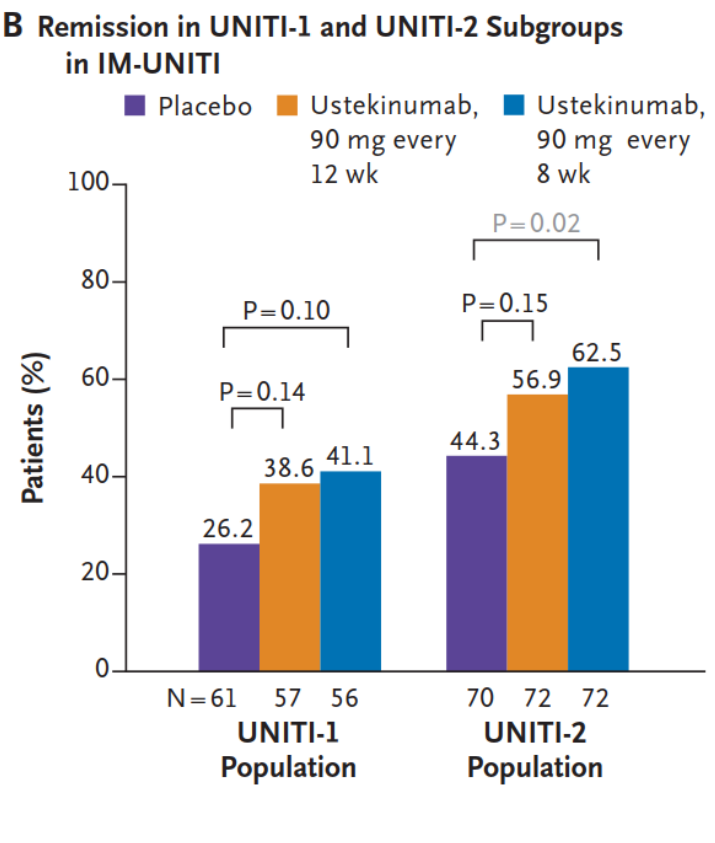


- Anti-TNF: Stopp ist möglich…
  - Relapse aber leider auch…

- (Fast) alle IBD Patienten sollten Vitamin D bekommen

Ustekinumab-IM-UNITI





Ustekinumab-IM-UNITI

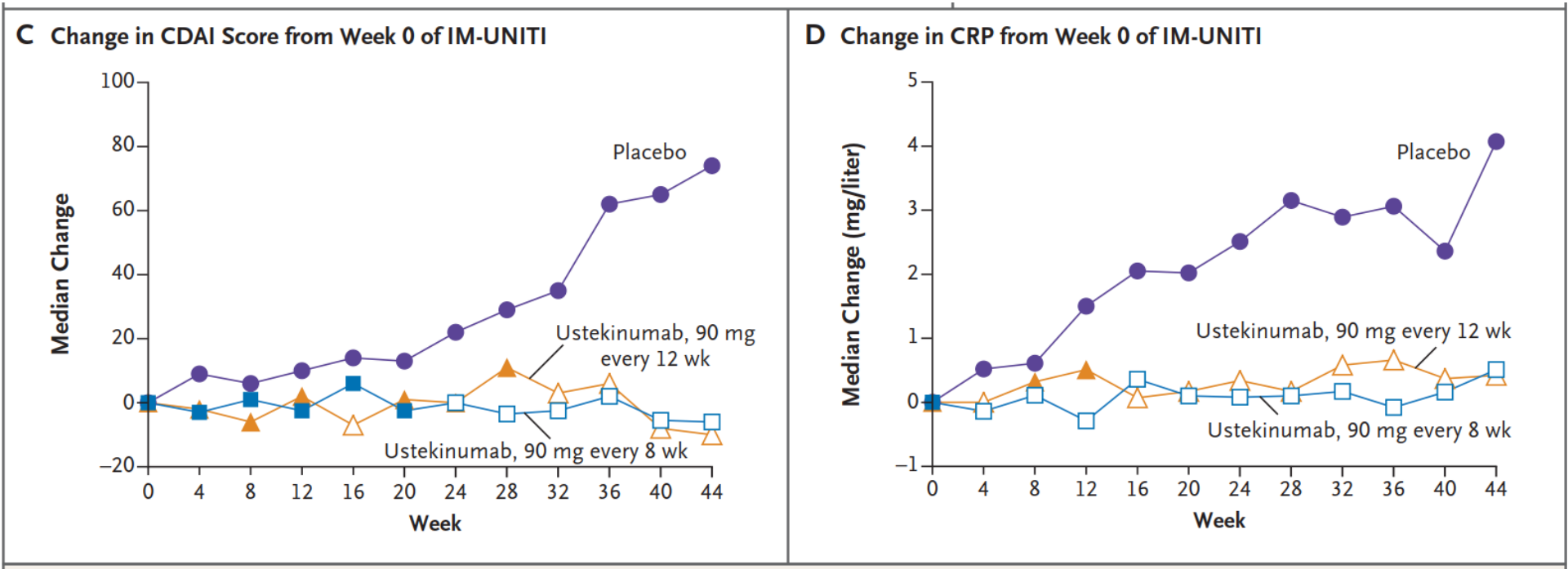


Figure 3. Patient Responses to Maintenance Therapy.

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Cx601

Methods We did this randomised, double-blind, parallel-group, placebo-controlled study at 49 hospitals in seven European countries and Israel from July 6, 2012, to July 27, 2015. Adult patients (≥18 years) with Crohn's disease and treatment-refractory, draining complex perianal fistulas were randomly assigned (1:1) using a pre-established randomisation list to a single intralesional injection of 120 million Cx601 cells or 24 mL saline solution (placebo), with stratification according to concomitant baseline treatment. Treatment was administered by an unmasked surgeon, with a masked gastroenterologist and radiologist assessing the therapeutic effect. The primary endpoint was combined remission at week 24 (ie, clinical assessment of closure of all treated external openings that were draining at baseline, and absence of collections >2 cm of the treated perianal fistulas confirmed by masked central MRI). Efficacy was assessed in the intention-to-treat (ITT) and modified ITT populations; safety was assessed in the safety population. This study is registered with ClinicalTrials.gov, number NCT01541579.

(CDAI) of 220 or less,[24] and had complex perianal fistulas, defined as one or more of the following: high inter-sphincteric, high trans-sphincteric, extra-sphincteric, or supra-sphincteric origin; at least two external openings; or associated collections. The fistulas had to have a maximum of two internal and three external openings, and had to have been draining for at least 6 weeks before inclusion.

We excluded patients if they had rectovaginal fistulas; rectal or anal stenosis; or active severe proctitis, defined as the presence of superficial or deep ulcers, since surgical closure of the internal orifice can be compromised in the

CALM

Methods CALM was an open-label, randomised, controlled phase 3 study, done in 22 countries at 74 hospitals and outpatient centres, which evaluated adult patients (aged 18–75 years) with active endoscopic Crohn's disease (Crohn's Disease Endoscopic Index of Severity [CDEIS] >6; sum of CDEIS subscores of >6 in one or more segments with ulcers), a Crohn's Disease Activity Index (CDAI) of 150–450 depending on dose of prednisone at baseline, and no previous use of immunomodulators or biologics. Patients were randomly assigned at a 1:1 ratio to tight control or clinical management groups, stratified by smoking status (yes or no), weight (<70 kg or ≥70 kg), and disease duration (≤2 years or >2 years) after 8 weeks of prednisone induction therapy, or earlier if they had active disease. In both groups, treatment was escalated in a stepwise manner, from no treatment, to adalimumab induction followed by adalimumab every other week, adalimumab every week, and lastly to both weekly adalimumab and daily azathioprine. This escalation was based on meeting treatment failure criteria, which differed between groups (tight control group before and after random assignment: faecal calprotectin ≥250 µg/g, C-reactive protein ≥5mg/L, CDAI ≥150, or prednisone use in the previous week; clinical management group before random assignment: CDAI decrease of <70 points compared with baseline or CDAI >200; clinical management group after random assignment: CDAI decrease of <100 points compared with baseline or CDAI ≥200, or prednisone use in the previous week). De-escalation was possible for patients receiving weekly adalimumab and azathioprine or weekly adalimumab alone if failure criteria were not met. The primary endpoint was mucosal healing (CDEIS <4) with absence of deep ulcers 48 weeks after randomisation. Primary and safety analyses were done in the intention-to-treat population. This trial has been completed, and is registered with ClinicalTrials.gov, number NCT01235689.

Ibied

CALM

Findings Between Feb 11, 2011, and Nov 3, 2016, 244 patients (mean disease duration: clinical management group, 0·9 years [SD 1·7]; tight control group, 1·0 year [2·3]) were randomly assigned to monitoring groups (n=122 per group). 29 (24%) patients in the clinical management group and 32 (26%) patients in the tight control group discontinued the study, mostly because of adverse events. A significantly higher proportion of patients in the tight control group achieved the primary endpoint at week 48 (56 [46%] of 122 patients) than in the clinical management group (37 [30%] of 122 patients), with a Cochran–Mantel–Haenszel test-adjusted risk difference of 16·1% (95% CI 3·9–28·3; p=0·010). 105 (86%) of 122 patients in the tight control group and 100 (82%) of 122 patients in the clinical management group reported treatment-emergent adverse events; no treatment-related deaths occurred. The most common adverse events were nausea (21 [17%] of 122 patients), nasopharyngitis (18 [15%]), and headache (18 [15%]) in the tight control group, and worsening Crohn's disease (35 [29%] of 122 patients), arthralgia (19 [16%]), and nasopharyngitis (18 [15%]) in the clinical management group.

Interpretation CALM is the first study to show that timely escalation with an anti-tumour necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early Crohn's disease results in better clinical and endoscopic outcomes than symptom-driven decisions alone. Future studies should assess the effects of such a strategy on long-term outcomes such as bowel damage, surgeries, hospital admissions, and disability.

CALM

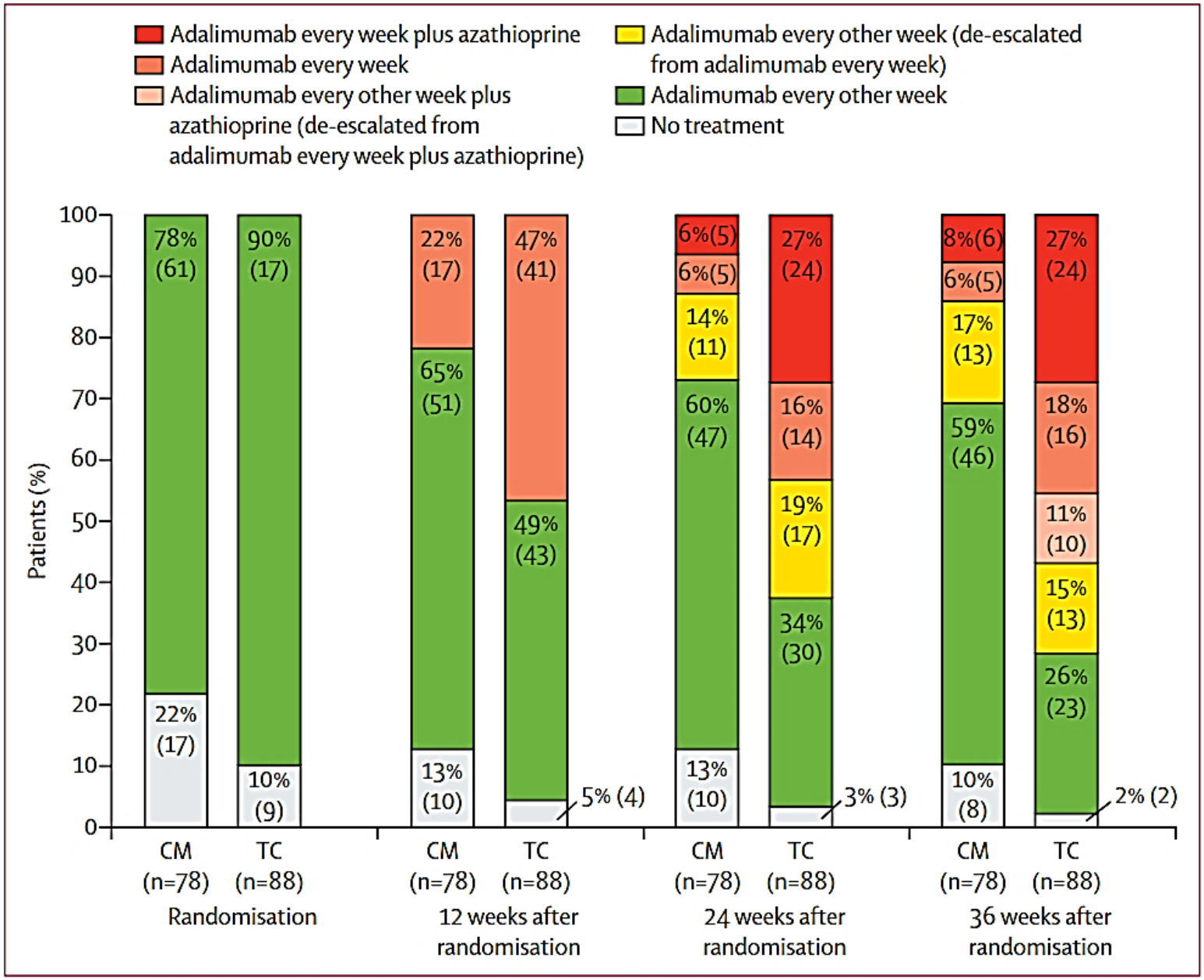

***Figure 4*: Proportion of patients receiving each treatment option at and after randomisation**
Data are expressed as % (n). Data are from patients who completed the study and did not move to the rescue group. CM=clinical management group. TC=tight control group.

Stop anti-TNF (ES)

RESULTS: A total of 1,055 patients were included. The incidence rate of relapse was 19% and 17% per patient-year in Crohn's disease and ulcerative colitis patients, respectively. In both Crohn's disease and ulcerative colitis patients in deep remission, the incidence rate of relapse was 19% per patient-year. The treatment with adalimumab vs. infliximab (hazard ratio (HR)=1.29; 95% confidence interval (CI)=1.01–1.66), elective discontinuation of anti-TNFs (HR=1.90; 95% CI=1.07–3.37) or discontinuation because of adver[Ibied]events (HR=2.33; 95% CI=1.27–2.02) vs. a top-down strategy, colonic localization (HR=1.51; 95% CI=1.13–2.02) vs. ileal, and stricturing behavior (HR=1.5; 95% CI=1.09–2.05) vs. inflammatory were associated with a higher risk of relapse in Crohn's disease patients, whereas treatment with immunomodulators after discontinuation (HR=0.67; 95% CI= 0.51–0.87) and age (HR=0.98; 95% CI=0.97–0.99) were protective factors. None of the factors were predictive in ulcerative colitis patients. Retreatment of relapse with the same anti-TNF was effective (80% responded) and safe.

Stop anti-TNF (ES)

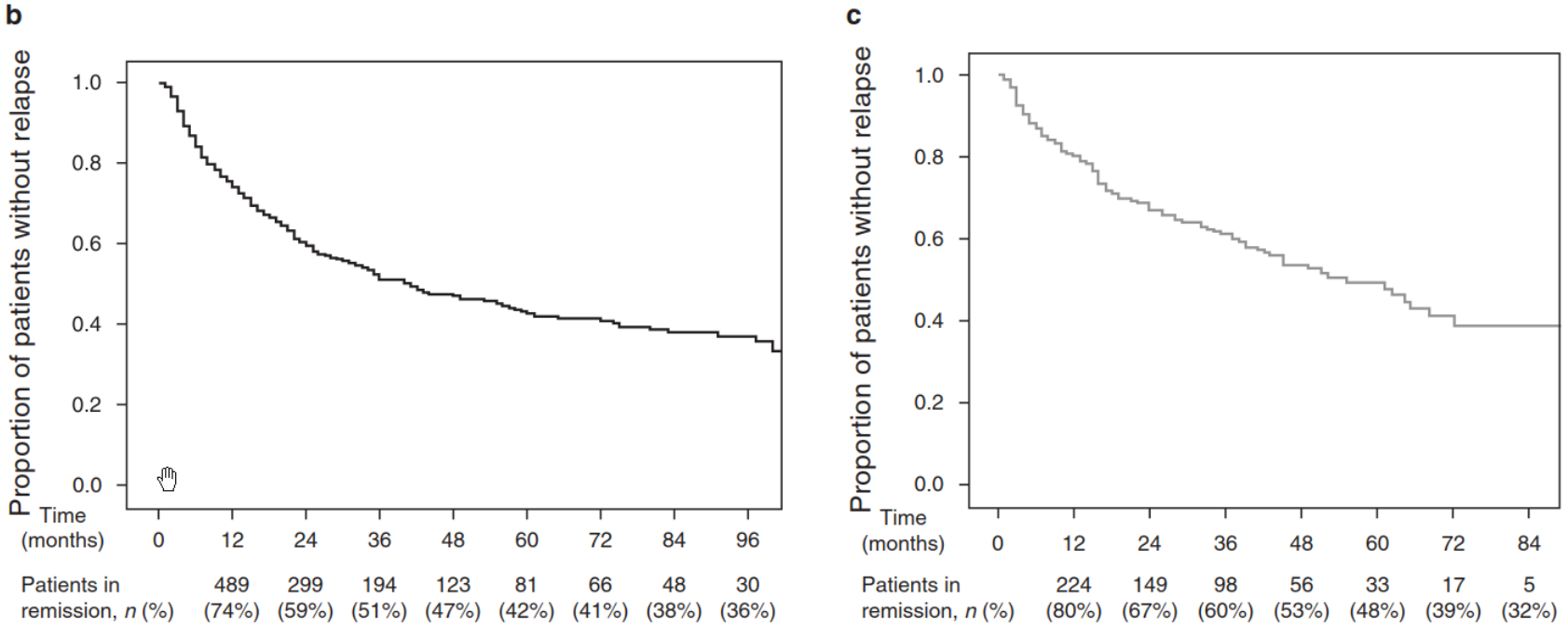

Figure 1. Evolution after anti-TNF discontinuation in IBD patients. (**a**) Kaplan–Meier curve showing the probability of survival without relapse after discontinuation of anti-tumor necrosis factor (anti-TNF) therapy for the whole study cohort. (**b**) Kaplan–Meier curve showing the probability of survival without relapse after discontinuation of anti-TNF therapy for Crohn's disease patients. (**c**) Kaplan–Meier curve showing the probability of survival without relapse after discontinuation of anti-TNF therapy for ulcerative colitis patients.

Vit D

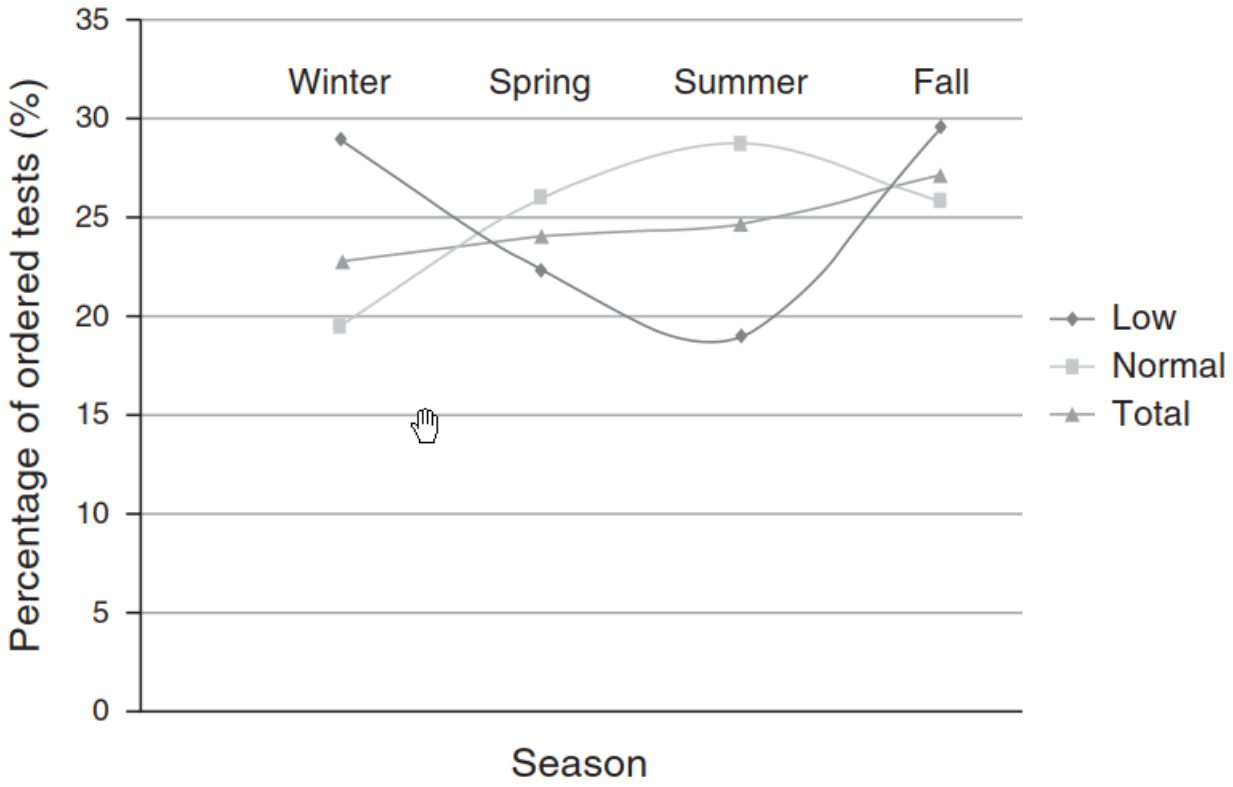

Figure 2. Frequency of vitamin D testing in inflammatory bowel disease patients by seasonality.

Vit D

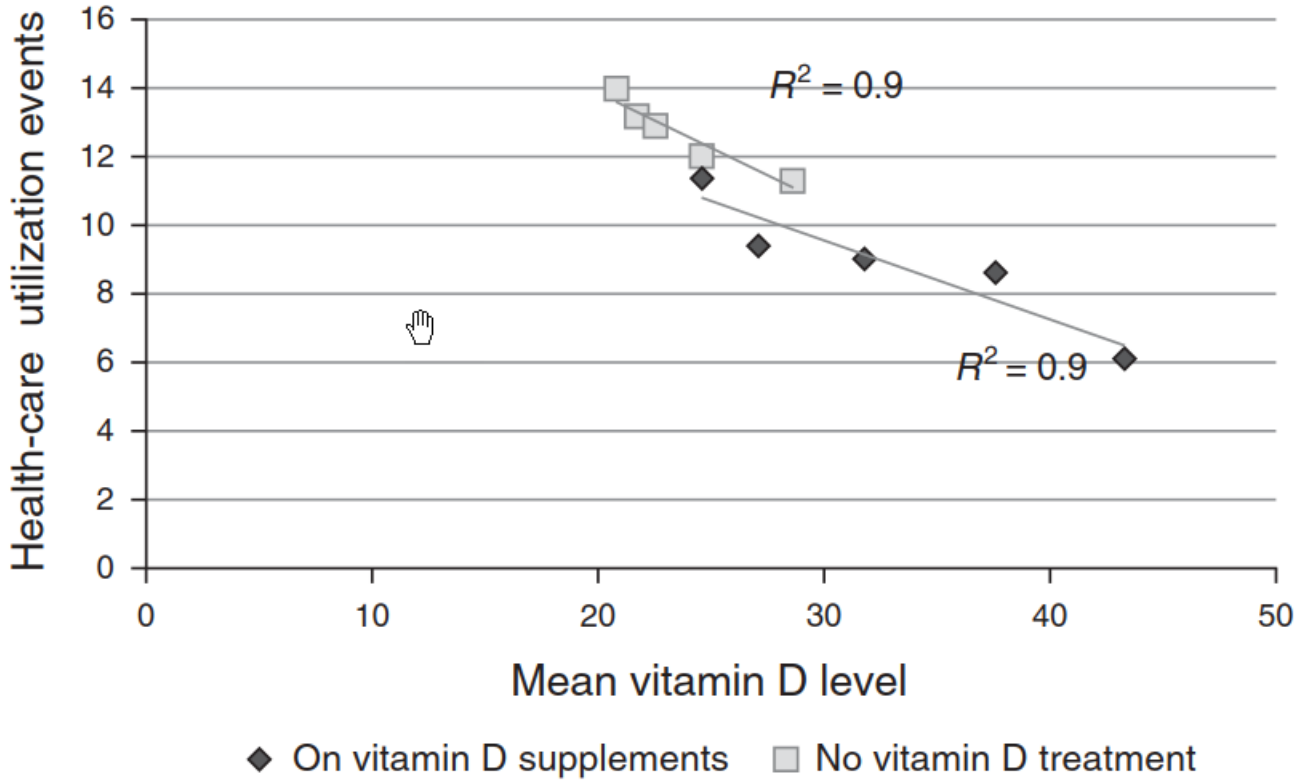

Figure 3. Effects of vitamin D supplementation on health-care utilization by inflammatory bowel disease patients.

Moreover, subjects with low vitamin D levels had worse pain, disease activity scores, and quality of life ($P<0.05$). Finally, subjects who received vitamin D supplements had a significant reduction in their health-care utilization.