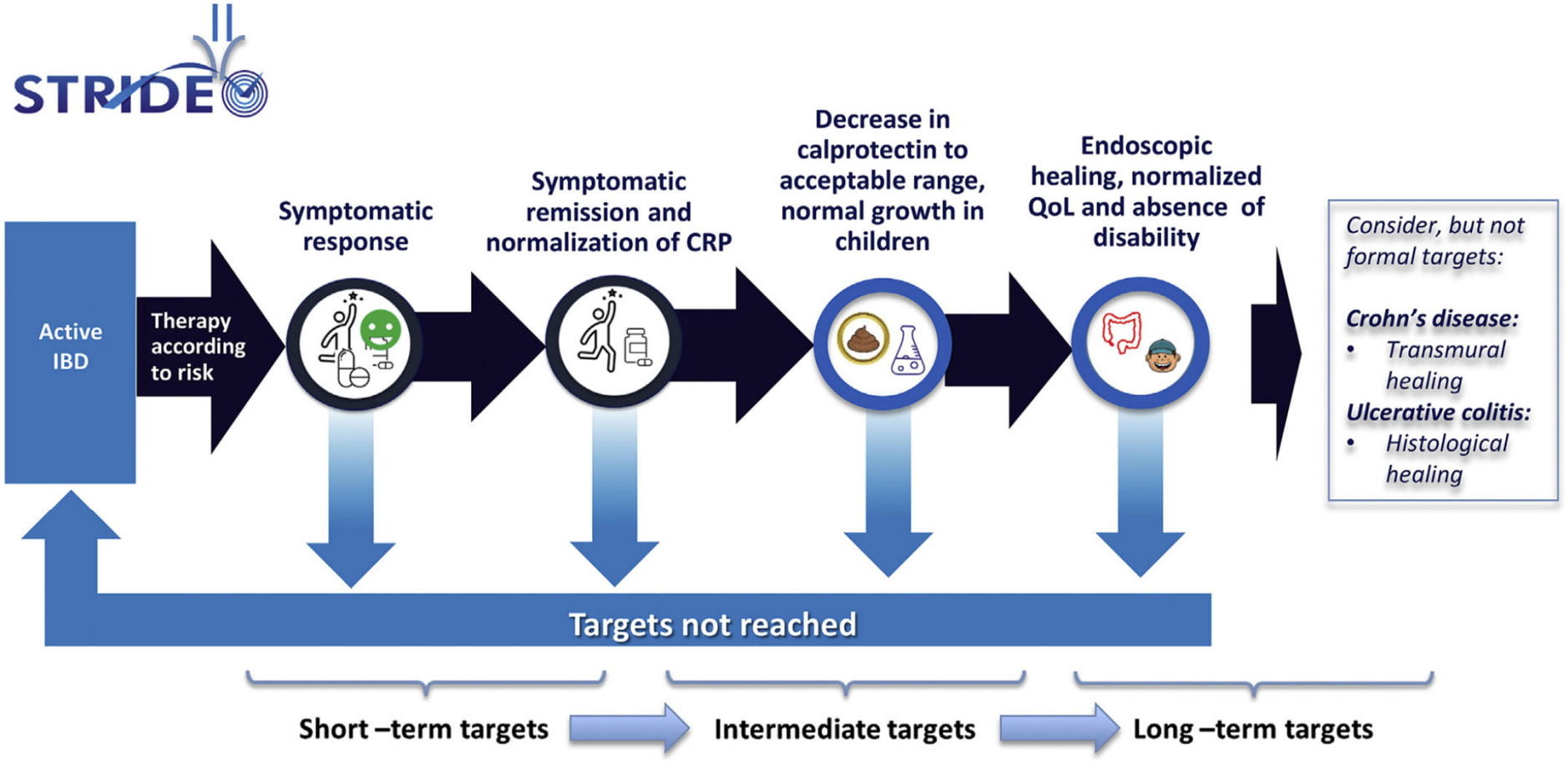
Update treatment of IBD

Bible class 5.7.2023

Benjamin Misselwitz

More ambitious treatment goals (STRIDE-II)



STRIDE: Selecting Therapeutic Targets in Inflammatory Bowel Disease

Turner D. Gastroenterology 2021;160:1570

ECCO Guideline/Consensus Paper

ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment

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ECCO Guideline/Consensus Paper

GRADE = Grading of Recommendations, Assessment, Development and Evaluations

- What is the clinical question?
- What is the population that the question applies to?
- What are the two or more alternatives?
- What is the outcomes that matter most to those faced with the decision?

Grade of evidence

1. **Risk of bias**
   Bias = results do not represent the truth because of limitations in design or conduct of a study
2. **Imprecision**
   95% confidence interval around the best estimate of the absolute effect
3. **Inconsistency**
   Do similar studies show similar effects?
4. **Indirectness**
   Does study addresses a different population/ intervention/ outcome
5. **Publication bias**
   Evidence for missing evidence

Grade of evidence

Certainty	What it means
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect

Grade of recommendation

- STRONG: almost all persons would choose that option

  → Alternative option does not need to be presented

- WEAK: variation in the decision of informed persons
  - Certainty in evidence is low
  - Close balance between desirable and undesirable consequences,
  - Substantial variation or uncertainty in patient values and preferences,
  - When interventions require considerable resources

  → shared decision making

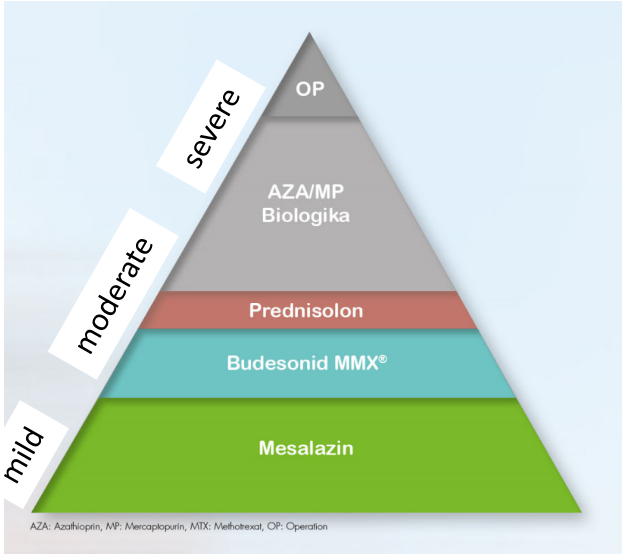
New ECCO guidelines for UC medical treatment

- GRADE methodology
- Questions were were identified and ranked
- Systematic literature review, only papers relevant to identified questions were included
- Strength of evidence
- Strength of recommendation
- 80% agreement between panel members needed for all decisions

Principles

- Recommendations for:
  - Mild + moderate
  - Moderate + severe disease
- ‘Conventional therapy’ = 5-ASA, corticosteroids, thiopurines vs. biologics/ small molecules

  but:
  - → Biologics are getting more economical (e.g. due to introduction of biosimilars)
  - → Long-term experience with biologics is now available
  - → Biologics are sometimes considered as a „conventional treatment“



5-ASA – induction of remission

Recommendation 1

We recommend 5-aminosalicylates at a dose of ≥2 g/day [d] to induce remission in patients with mildly-to-moderately active UC [strong recommendation; quality of evidence low]

Meta-analysis of 11 eligible RCTs with a total of 2156 patients evaluated for 4–12 weeks

- **Clinical remission**: RR: 1.56; 95% CI: 1.24–1.97
- **Clinical response**: RR: 1.58; 95% CI: 1.35–1.86; 59% with 5-ASA vs. 35% with placebo
- **Endoscopic response**: RR: 1.73; 95% CI: 1.0–3.0 (n=416)
- SAE 6.1% vs. 9% with placebo
  RR: 0.81; 95% CI: 0.47–1.38

Low evidence due to heterogeneity and possible publication and reporting bias
No evidence for use of higher dosages or different formulations

5-ASA induction of remission in distal UC

Recommendation 2

We recommend topical [rectal] 5-ASA at a dose of ≥1 g/d for the induction of remission in active distal colitis [strong recommendation, low-quality evidence]

8 suitable studies (≥1g, 2-8 weeks)

Clinical response:	RR: 2.46; 95% CI: 2.01–3.01
Clinical remission:	RR: 3.56; 95% CI: 2.08–6.09
Endoscopic response:	RR: 2.75; 95% CI: 2.04–3.7
No differences in SAEs	RR: 0.26; 95% CI: 0.03–2.29

Low evidence, strong recommendation due to long clinical experience.

Combination oral and topical 5-ASA

Recommendation 3

We suggest the use of oral 5-ASA [≥2 g/d] combined with topical [rectal] 5-ASA over oral 5-ASA monotherapy for induction of remission in adult patients with active UC of at least rectosigmoid extent [weak recommendation; very low-quality evidence]

Combined therapy vs. oral monotherapy

Clinical response: [RR:1.1; 95% CI: 0.95–1.27]
Clinical remission: [RR:1.45; 95% CI: 0.98–2.13] (n=331)
Endoscopic response: [RR: 1.21; 95% CI: 0.91–1.61]
SAEs [RR: 2.37; 95% CI: 0.25–22.14]

No significant results, very high risk for bias…
«trend towards better outcomes for combined therapy, clinical experience, and the low cost and risk»

Topical steroids

Recommendation 4

We recommend using topical [rectal] steroids for the induction of remission in patients with active distal colitis [strong recommendation, very low-quality evidence]

Clinical remission:	RR: 2.12; 95% CI: 1.48–3.06
Clinical response	RR: 2.18; 95% CI: 1.58–3.01
Endoscopic response	RR: 1.44; 95% CI: 1.21–1.70
SAEs	RR: 0.68; 95% CI: 0.10–4.40

Very low-quality evidence due to low patient numbers, imprecision, indirectness (for SAEs)

«The experience with topical steroids in clinical practice, the favourable balance between their potential benefits and harms … and their low cost support the recommendation of topical steroids.»

Rectal 5-ASA vs.rectal steroids

Recommendation 5

We suggest treatment with topical [rectal] 5-ASAs over topical [rectal] steroids for induction of remission in patients with active distal UC [weak recommendation, very low quality of evidence]

Clinical remission:	RR: 1.36; 95% CI: 1.19–1.56
Clinical response:	RR: 1.09; 95% CI: 0.97–1.22
Endoscopic response:	RR: 1.08; 95% CI: 0.82–1.44 (n=376)
SAEs:	RR: 1.21; 95% CI: 0.47–3.08 (n=1306)

Colonic release: Budesonid MMX

Recommendation 6

We suggest the use of colonic-release corticosteroids for induction of remission in patients with active mild-to-moderate UC [weak recommendation, low quality of evidence]

Clinical remission	RR: 2.86; 95% CI 1.62–5.04
Clinical response	RR: 1.46; 95% CI: 1.11–1.93
Endoscopic response	RR: 1.43; 95% CI: 1.10–1.84 (n=510)
SAEs/ any AEs	RR: 0.88; 95% CI: 0.33–2.41/ RR: 1.04; 95% CI: 0.79–1.37,

2 phase 3 trials combined clinical and endoscopic remission rate:

- 17.7% for budesonide MMX 9 mg/day versus 6.2% for placebo
- Odds ratio: 3.3; 95% CI: 1.7–6.4

No maintenance data

«mildly-to-moderately active disease, who are not responding to or are intolerant to optimised 5-ASA therapy»

Immunmodulators

Recommendation 7

We suggest against the use of thiopurines as monotherapy for the induction of remission in patients with active UC [weak recommendation, very low quality of evidence]

Clinical remission: RR: 1.22; 95% CI: 0.79–1.88; n=130
No data for clinical response, endoscopic response, SAE

«…due to the relatively slow onset of action of azathioprine, it may be appropriate to initiate azathioprine in patients with active disease where maintenance therapy with azathioprine is planned, but only when given alongside an effective induction agent»

Mild to moderate UC: recommendations

	Induction remission	Maintenance remission
Oral 5-ASA	**R: Strong** E: Low	**R: Strong** E: Very low
Topical 5-ASA	**R: Strong** E: Low	R: Weak R: Very low
Topical steroids	**R: Strong** E: Very low	
Budesonid	R: Weak E: Low	
Thiopurine	**R: Against** weak E: Very low	**R: Strong** E: Moderate

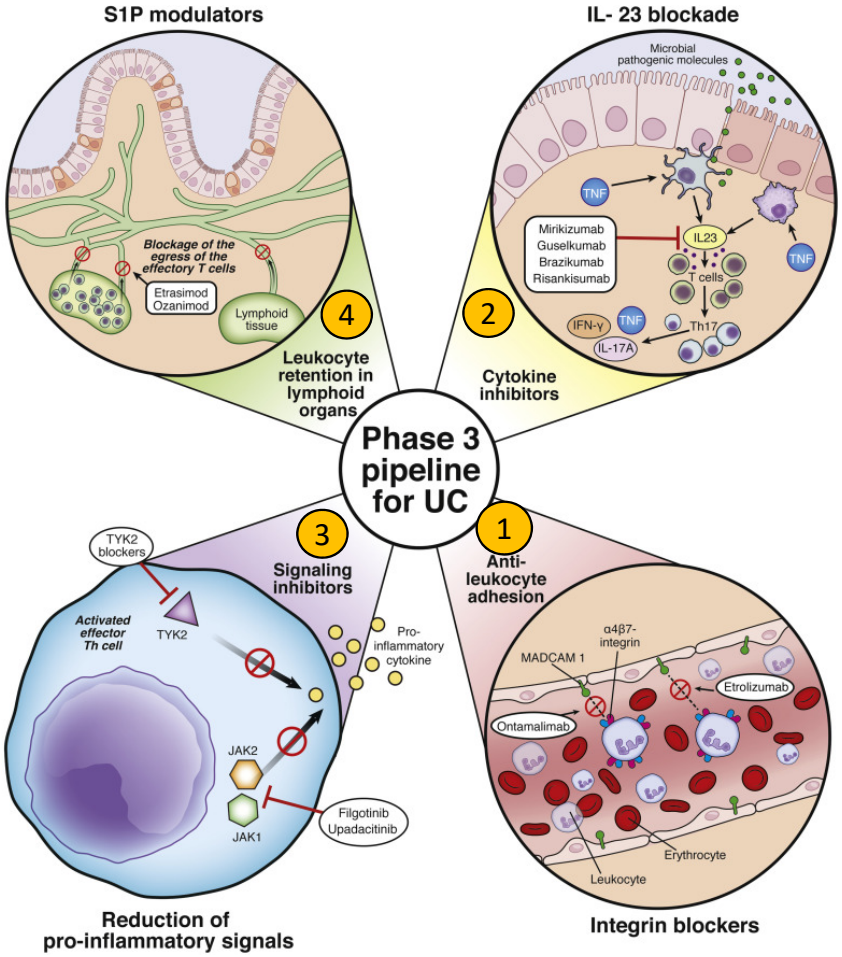
→ Oral and rectal 5-ASA remains the cornerstone for treatment of mild-moderate UC, BUT
Evidence is week and unlikely to ever get stronger

*

Moderate to severe UC

- What biologics do we have?
- When to use a biologic?

New drug targets and new drugs



(1) Integrin-blockade

anti-adhesion, prevents «homing» into the gut

- **Vedolizumab**

(2) Cytokine-blockade

- Tumor-Nekrosis factor blockade
  - **Infliximab**
  - **Adalimumab**
  - **Golimumab** (UC)
  - **Certolizumab** (CD)
- Interleukin 12/23 blockade
  - **Ustekinumab**
- Interleukin 23 blockade
  - **Guselkumab**
  - **Risankizumab**
  - **Mirikizumab**

(3) Signal blockade (JAK)

- **Tofacitinib**
- **Upadacitinib**
- **Filgotinib**

(4) S1P modulators

- **Ozanimod**
- **Etrasimod**

Switzerland: indications for use of biologics/ small molecule

Source: Compendium

- **Remicade/ Humira/ Simponi** ist indiziert zur Behandlung der mittelschweren bis schweren aktiven Colitis ulcerosa bei erwachsenen Patienten, die auf eine volle und adäquate konventionelle Therapie, einschliesslich 5-ASA, Kortikosteroide und 6-MP oder AZA, unzureichend angesprochen haben, oder diese nicht toleriert haben.
- **Entyvio (vedolizumab)** ist indiziert für die Behandlung von Erwachsenen mit mittel- bis hochgradig aktiver Colitis ulcerosa, die auf die Standardtherapie oder einen Antagonisten von Tumornekrosefaktor alpha (TNFα) nicht ausreichend oder nicht mehr ansprachen oder Unverträglichkeit zeigten.
- **Stelara (ustekinumab)** ist zur Behandlung erwachsener Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa indiziert, bei denen konventionelle Therapien oder die Behandlung mit einem Biologikum ungenügend angesprochen haben, nicht mehr ansprechen, kontraindiziert sind oder nicht vertragen wurden.
- **Zeposia (ozanimod)** ist zur Behandlung von erwachsenen Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa (CU) indiziert, die entweder auf konventionelle Therapien oder die Behandlung mit einem Biologikum ungenügend angesprochen haben, nicht mehr ansprechen oder die Therapie nicht tolerierten.
- **Xeljanz (tofacitinib)** ist indiziert zur Behandlung erwachsener Patienten mit mittelschwerer bis schwerer aktiver Colitis ulcerosa (CU), die auf eine vorherige Therapie mit Kortikosteroiden, Azathioprin (AZA), 6-Mercaptopurin (6-MP) oder einen Antagonisten des Tumornekrosefaktors (TNF) unzureichend angesprochen haben, nicht mehr darauf ansprechen oder diese Therapien nicht vertragen haben.

Moderate to severe UC + problems with „conventional“ (=other) therapies

Moderate-severe UC (summary)

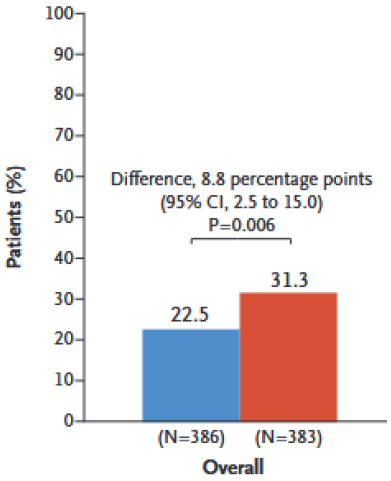
	Induction remission	Maintenance remission
Prednisone	R: Strong **E: very low**	
Anti-TNF IFX, ADA, GOL	R: Strong E: Moderate	R: Strong **E: High**
Vedolizumab	R: Strong **E: Low**	R: Strong R: Moderate
Ustekinumab	R: Strong E: Moderate	R: Strong E: Moderate
Tofacitinib	R: Strong E: Moderate	R: Strong E: Moderate

- Use of biologics/ tofacitinib for patients who have *failed conventional therapy*
- Maintenance with the same drug as used for induction
- No recommendation for/ against therapeutic drug monitoring for TNF-inhibitors
  → prospective trials are missing

Integrin-Blocker: Vedolizumab (Entyvio)

Head-to-head study: TNF blockade vs. integrin blockade in UC
→ Adalimumab vs. Vedolizumab
→ «Varsity» study

- N=769 (386 adalimumab vs. 383 vedolizumab, 21% anti-TNF-experienced
- Endpoint: remission at week 52
  Mayo-Score ≤2, no Subscore >1
- no dose escalation permitted



Primary endpoint was reached
→ analysis favored vedolizumab over adalimumab

infectious complikations:
→ vedolizumab 23.4%, vs. adalimumab 34.6%

Steroid free remission:
→ vedolizumab 12.6%, vs. adalimumab 21.8%

Entyvio: Better efficacy + better safety for Entyvio in UC

Sands et al., NEJM 2019; 3811215

Choice of one biologicum over another

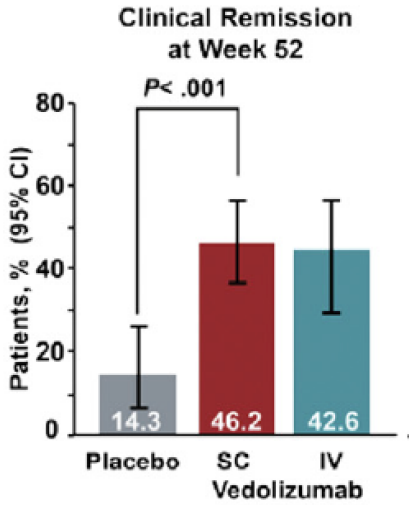
Recommendation 19

We suggest the use of vedolizumab rather than adalimumab for the induction and maintenance of remission in patients with moderately-to-severely active ulcerative colitis [weak recommendation, low level of evidence]

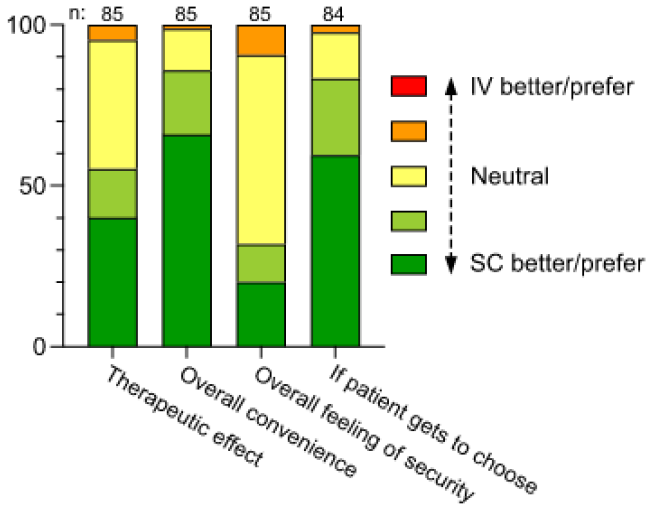
- Clinical response: RR: 1.46; 95% CI: 1.29–1.67
- Clinical remission: RR: 1.39; 95% CI: 1.10–1.76
- Endoscopic remission: RR: 1.43; 95% CI: 1.17–1.75
- Corticosteroid-free clinical remission: RR: 0.58; 95% CI: 0.32–1.05

→ ECCO does not make sweeping statements regarding anti-TNF class
→ Evidence very low, due to imprecision + inconsistencies

Vedolizumab (Entyvio) s.c.



- VISIBLE study: 216 patients
- Primary endpoint:
  Mayo ≤2, no Score >2 after 52 weeks
- 2x vedolizumab 300 mg i.v. after that:
- 1:1:1 placebo vs. i.v. (every 8 weeks) vs. s.c. (every 2 weeks)

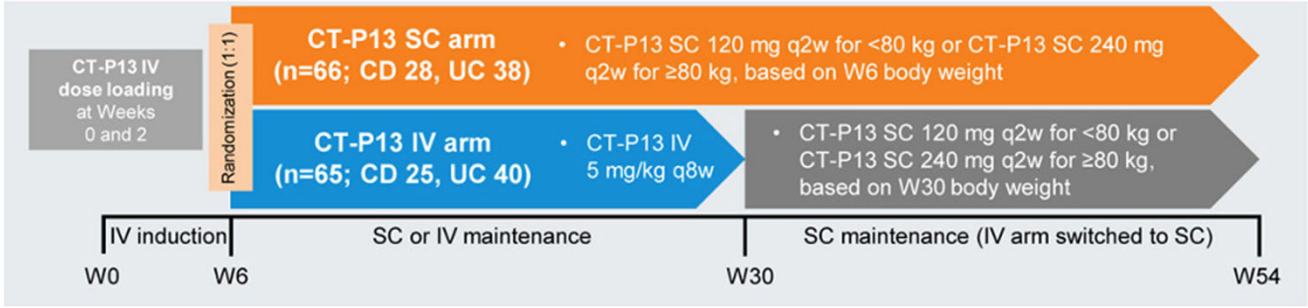


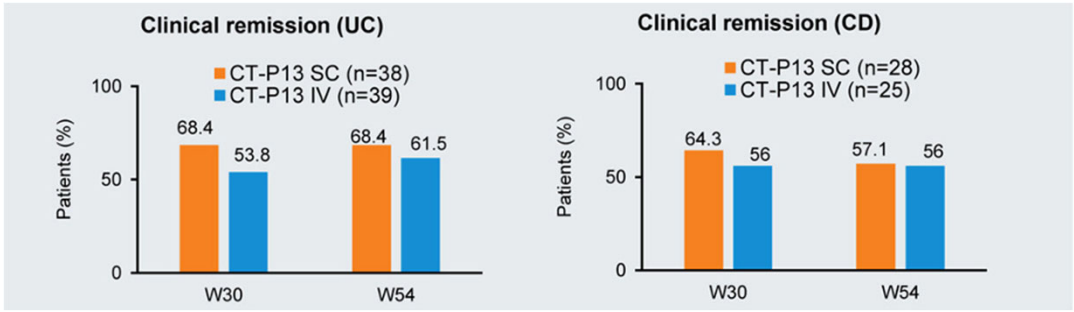
vedolizumab i.v. / s.c. are equivalent

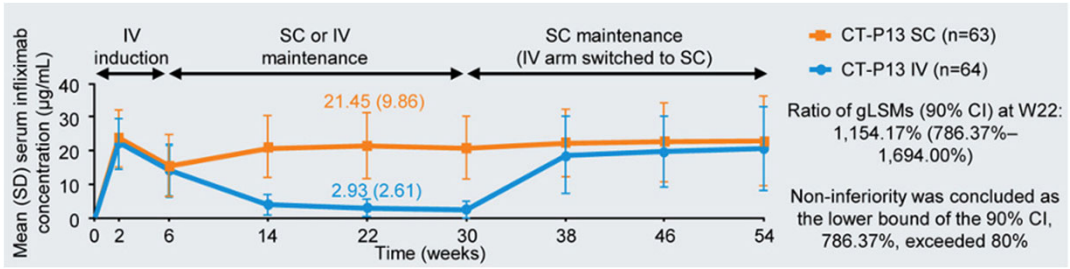
most patients prefer s.c.

Sandborn et al., Gastroenterology 2020; 158:562
Bergqvist et al., AP&T; 2022; 55:1389

s.c. infliximab: Veblocema®







RCT in UC + CD:

- IFX i.v. every 8 weeks
  - 5mg/kg
- IFX s.c. every 2 weeks
  - <80 kg: 120 mg
  - ≤80 kg: 240 mg

Similar efficacy

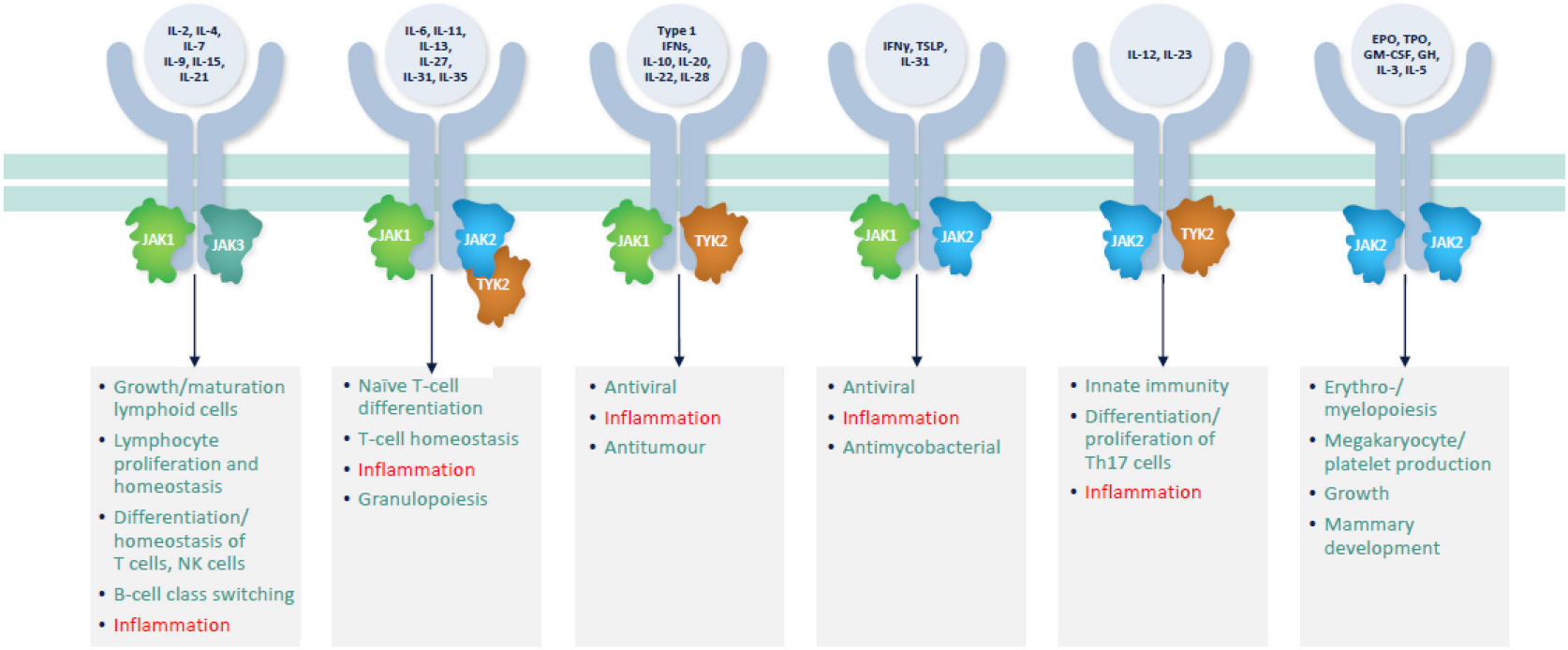
Better pharmakokincetic profile

Schreiber et al., 2021; 160:2340

Signaling inhibitors - JAK-Inhibitors

JAK = Janus kinase

Janus = Roman god of duality, begin, change, ending

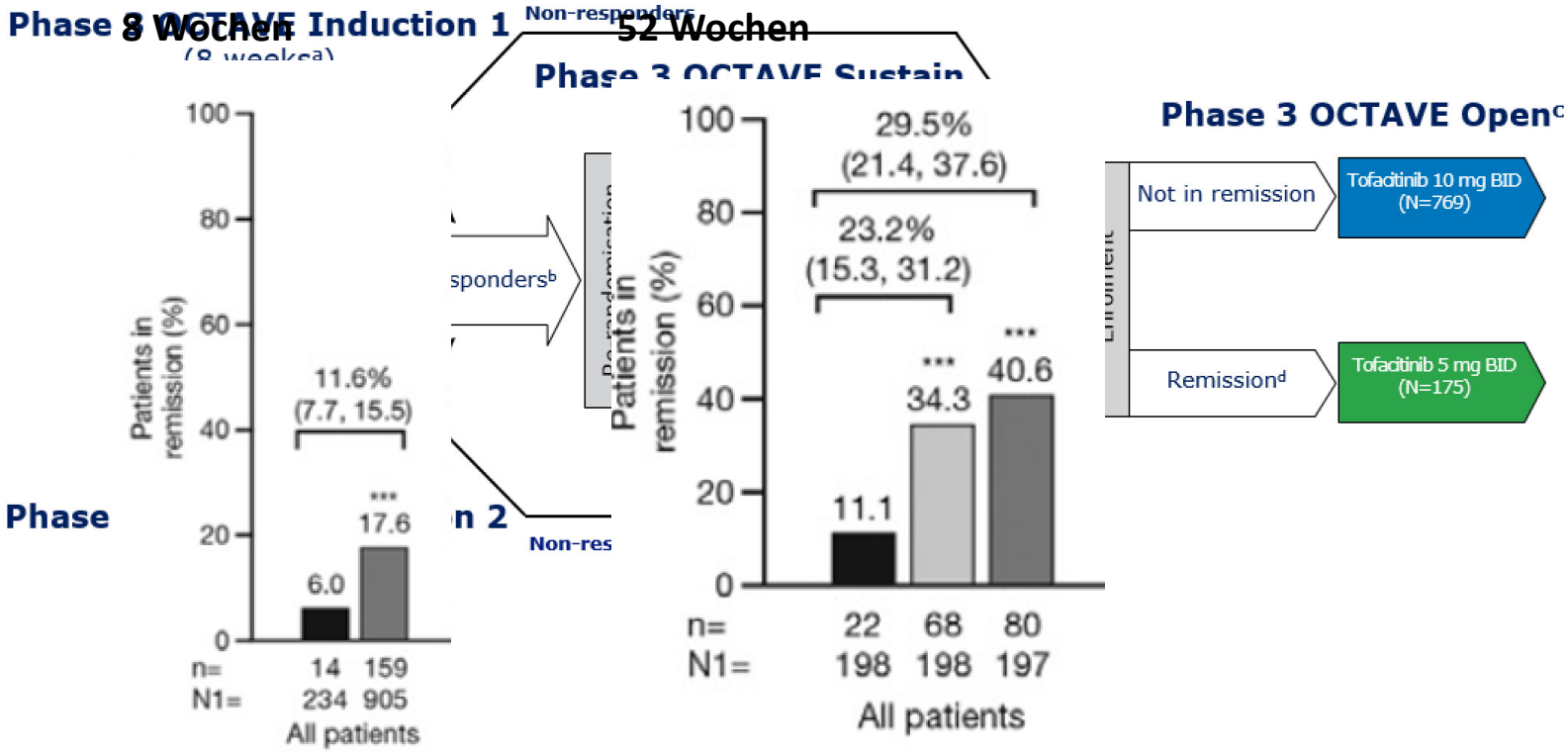


Tofacitinib: JAK1 + JAK3 inhibition. Upadacitinib: JAK1 inhibition

→ JAKs have various functions within the cell

O'Sullivan et al., Mol Immunol 2007; 44:2497; Vijayakrishnan et al., Trends Pharmacol Sci 2011; 32:25

Tofacitinib (JAK1 + JAK3) in ulcerative colitis



Tofacitinib is effective for ulcerative colitis

Sandborn et al., Clin Gastroenterol Hepatol 2019; S1542

Safety tofacitinib (Xeljanz)

- Herpes zoster:
  - Incidence ratio (IR) 3.1 if <65 Jahre, IR 7.5 if ≥65 Jahre
  - → Vaccination (Shingrix)
- No further safety signal in IBD studies

- Pass Study ORAL Surveillance in rheumatoid arthritis
  - N=4362, comparison with anti-TNF
  - Malignancy: HR 1.48 (1.04 - 2.09), especially ≥65 years
  - Thromboembolism: HR 2.82 (1.31 – 6.06), especially at 10 mg (compared to 5 mg)
  - Mortality: age ≥50 years + ≥ 1 cardiovascular risk factor
    - Tofacitinib 2x10 mg: 0.89 (0.59-1.29)
    - Tofacitinib 2x5 mg: 0.57 (0.34-0.89)
    - TNF-inhibitor 0.27 (0.12-0.51)

Cave: Herpes Zoster (vaccination!!), thromboembolism, malignancy, death

Ytterberg et al., Arthritis Rheumatol 2021; 73:S10; Sands et al., P260 ECCO 2021; www.swissmedicinfo.ch

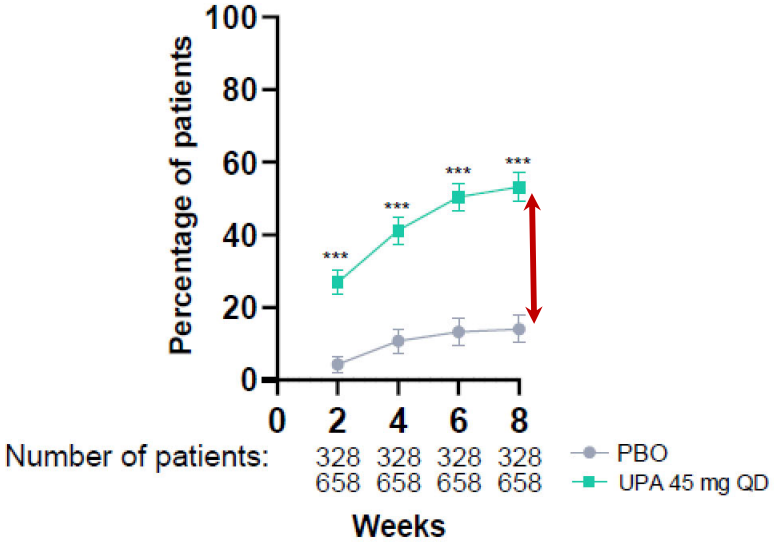
Upadacitinib (JAK1) = Rinvoq®

459 patients. 2:1 upadacitinib 45 mg vs. placebo

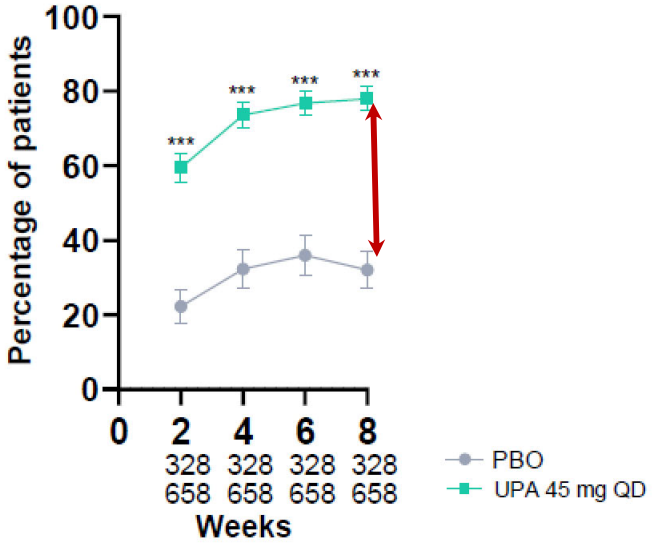
U-ACHIEVE, U-ACCOMPLISH

Primary endpoint: adapted partial Mayo score

Clinical remission (per Partial Mayo) at week 8

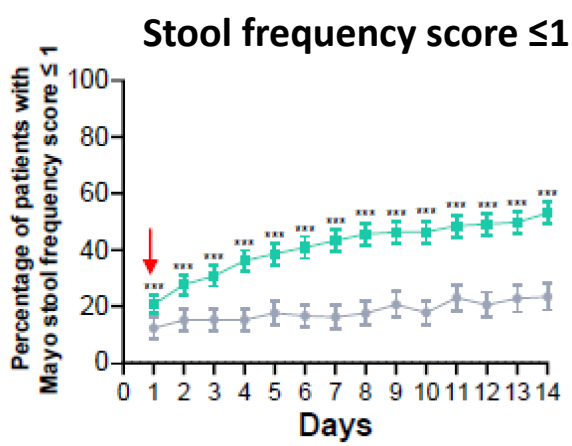


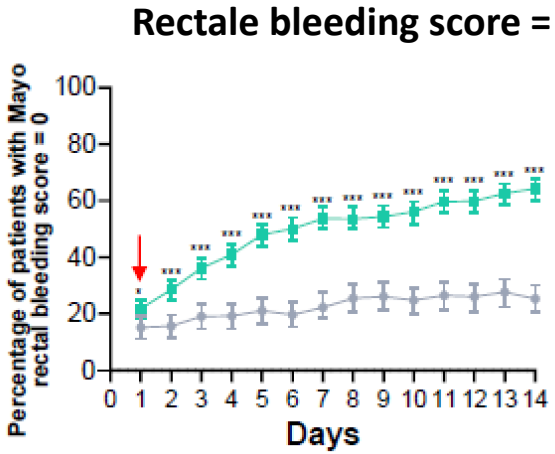
Clinical response (per Partial Mayo) at week 8

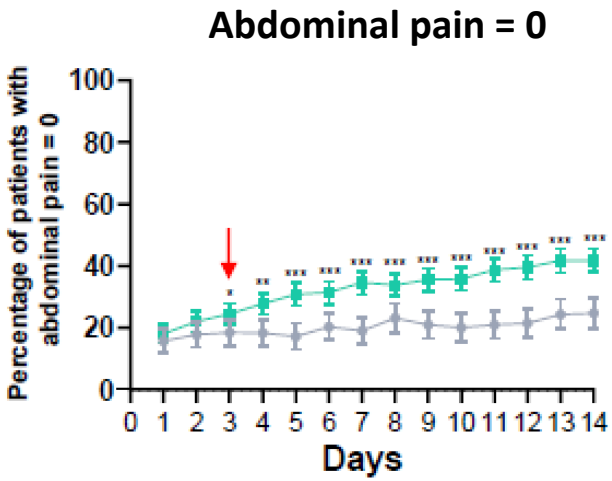


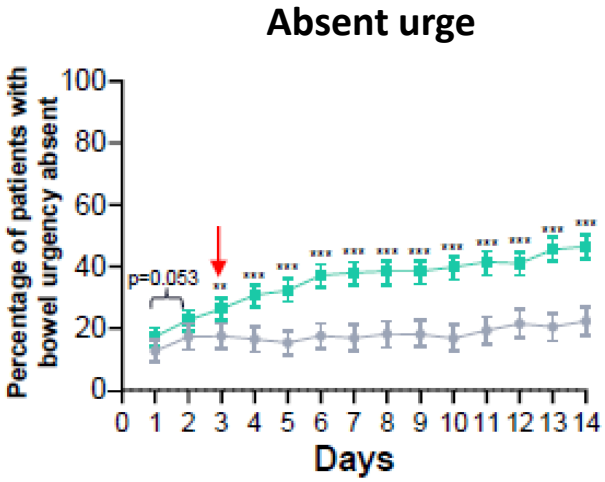
Danese et al, Lancet 2022; 399:2134

Fast mode of action of upadacitinib





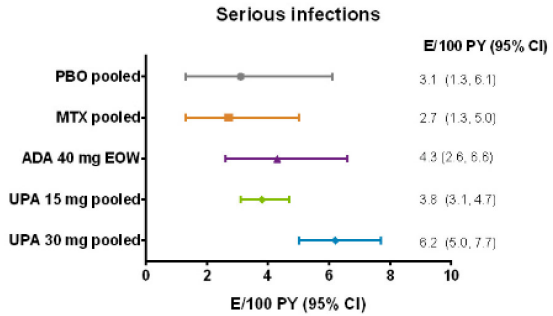


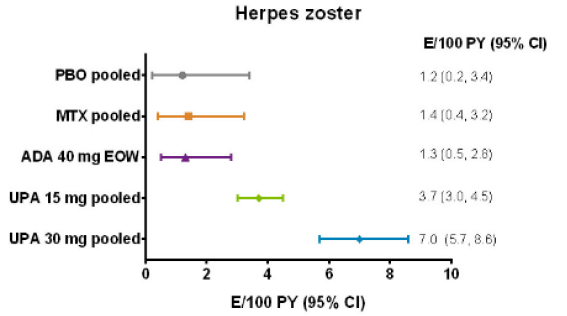


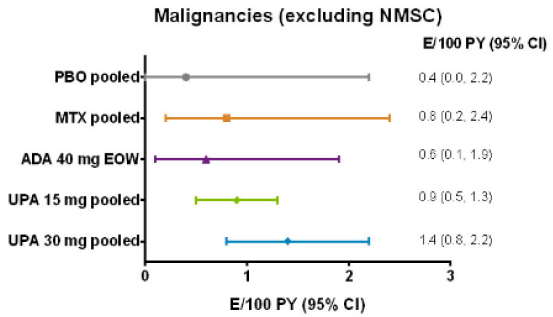
Danese et al, Lancet 2022; 399:2134

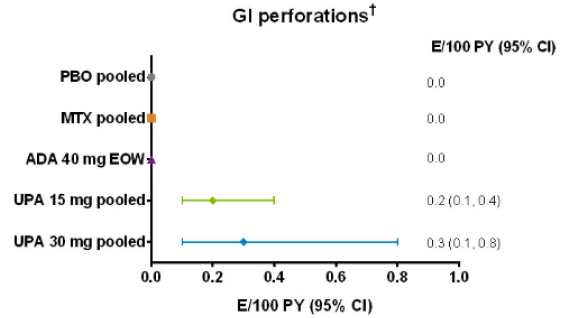
Safety profile of upadacitinib

Subanalyses of rheumatological studies
N=3834, 4020 patient years





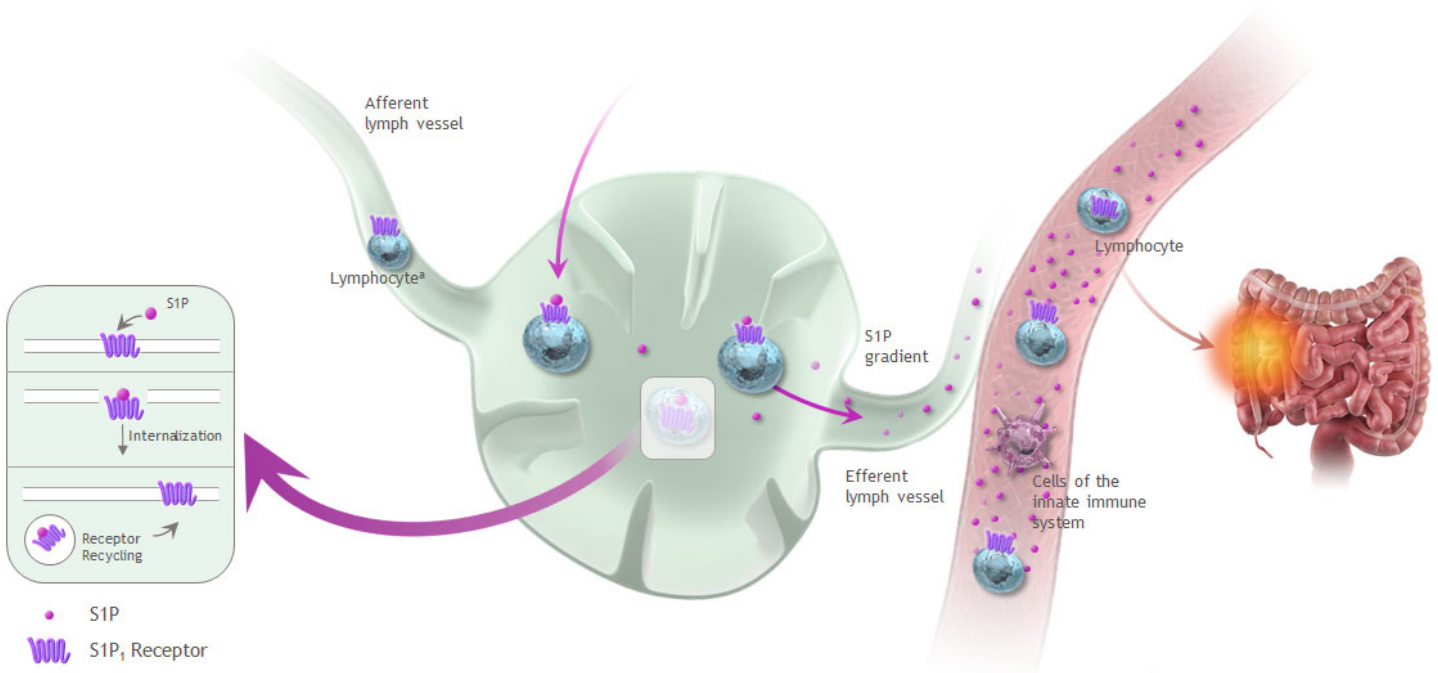




- Higher rates of infections including Herpes zoster (vaccination!!)
- Higher rates of GI-perforations
- (until now) no increased risk for thromboembolic diseases, major cardiovascular events, malignant diseases

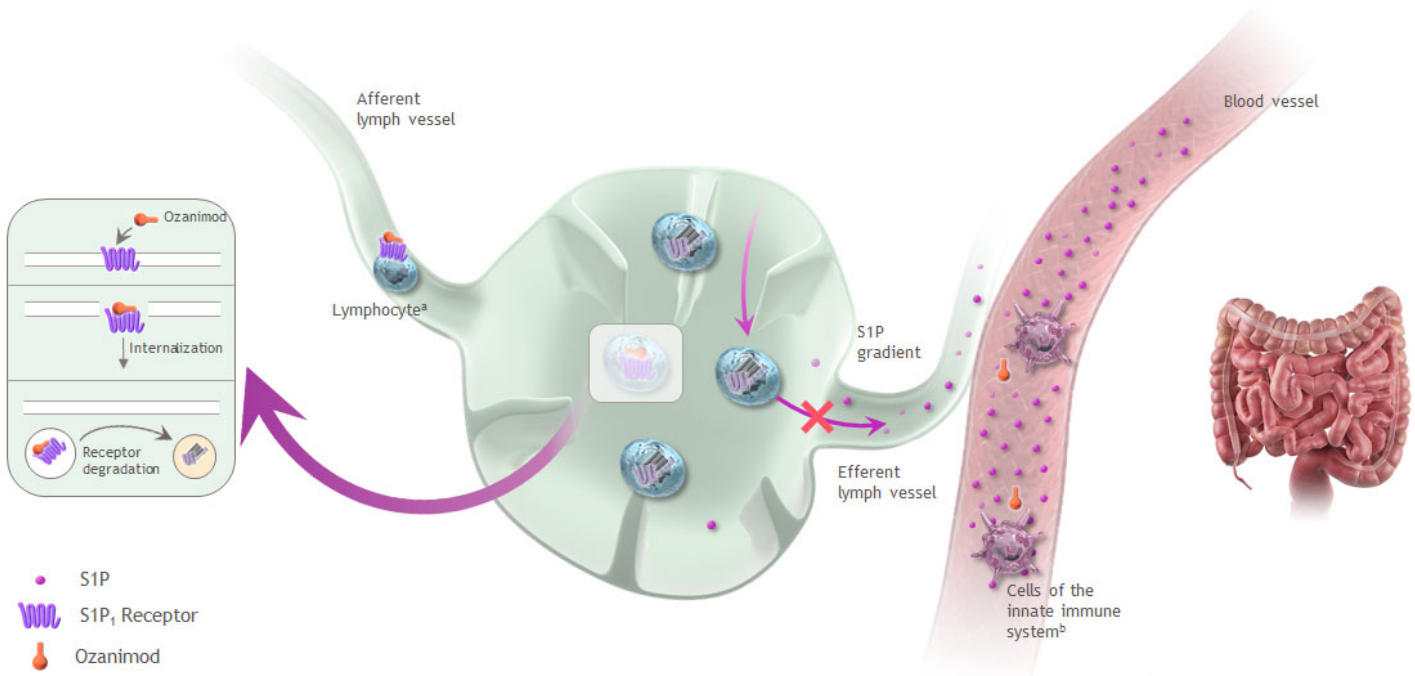
Cohen et al., Ann Rheum Dis 2021; 80:304

Sphingosin-1P mediated lymphocyte trafficking



Source: BMS

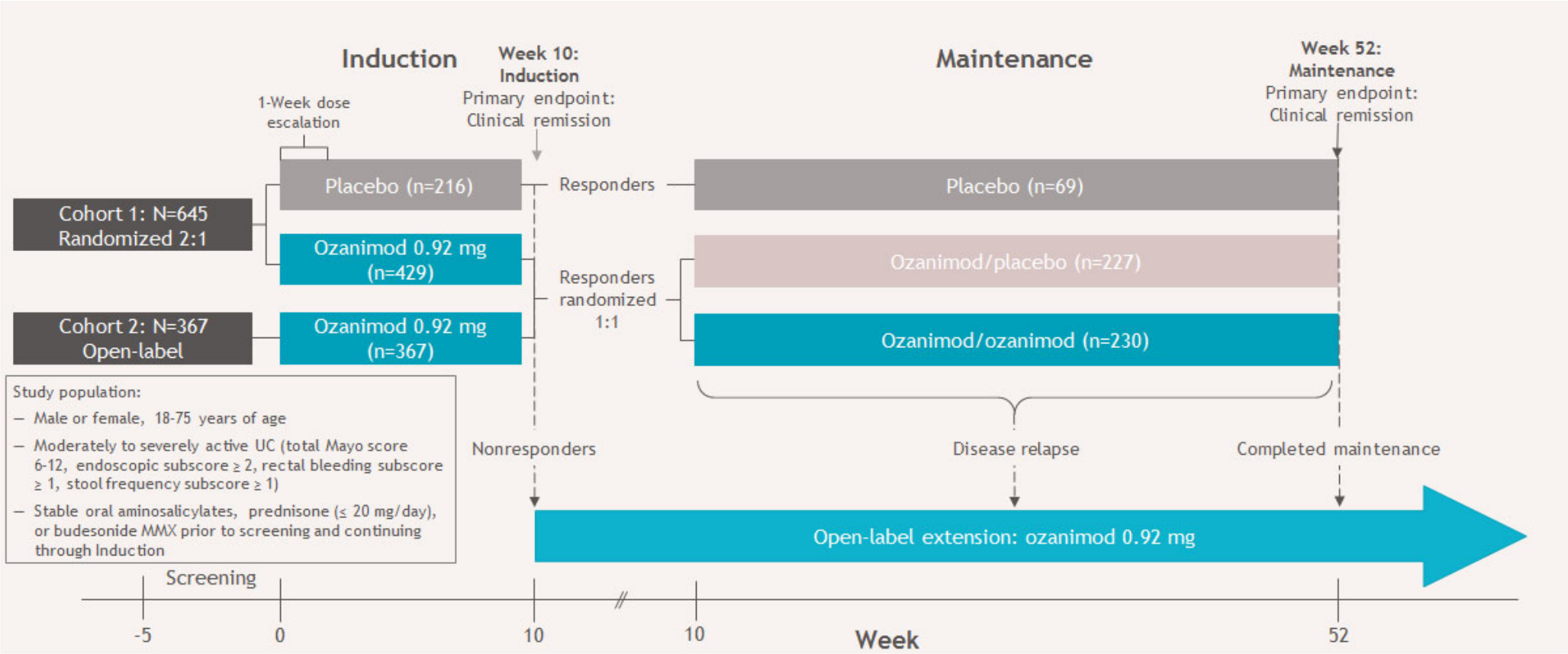
Ozanimod blocks S1P-mediated lymphocyte trafficking



Source: BMS

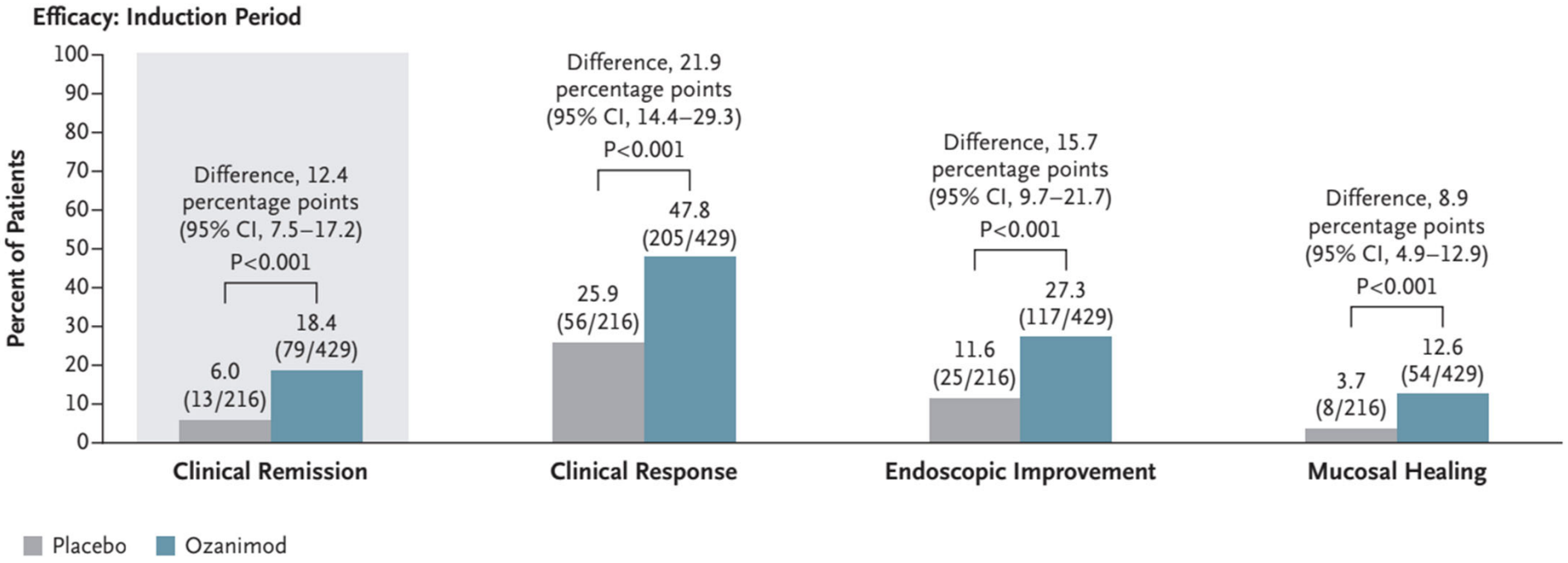
Study design

randomized, double-blind, placebo-controlled trial



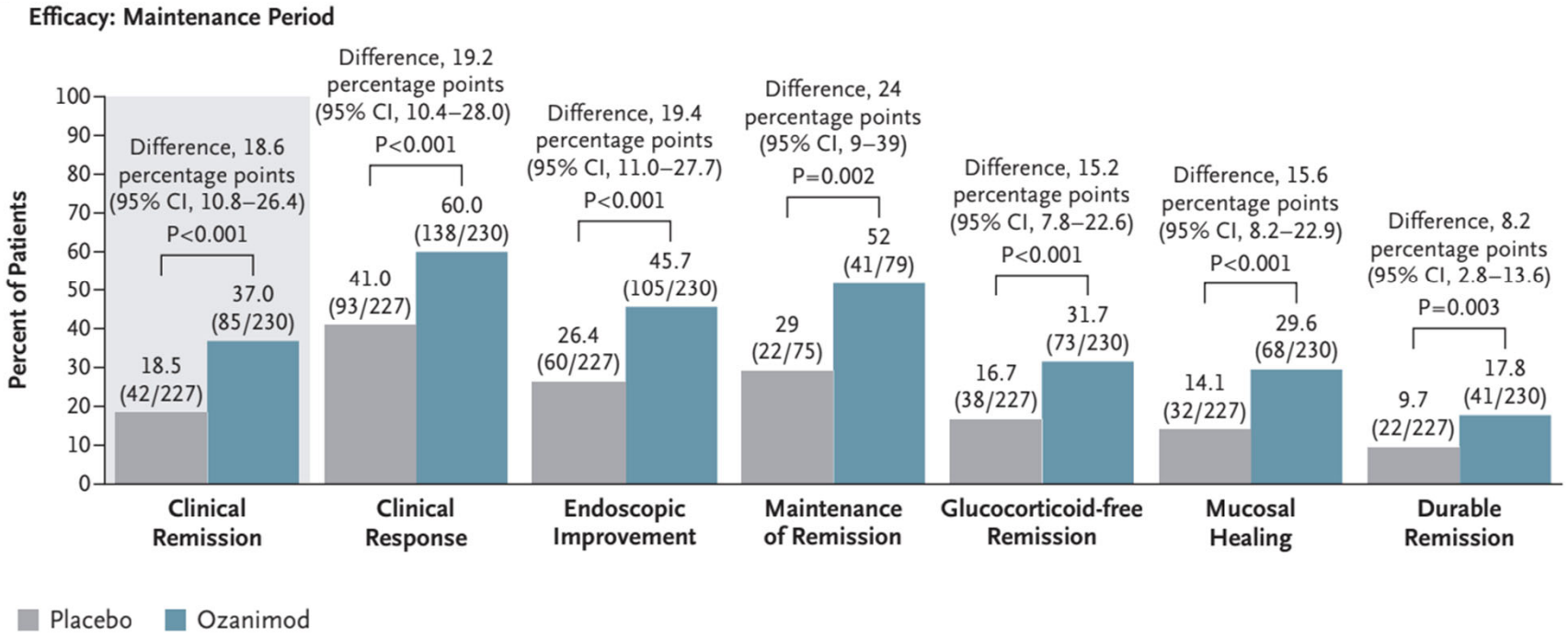
Sandborn et al., NEJM 2021; 385:14

Results – induction period



Sandborn et al., NEJM 2021; 385:14

Results maintenance period



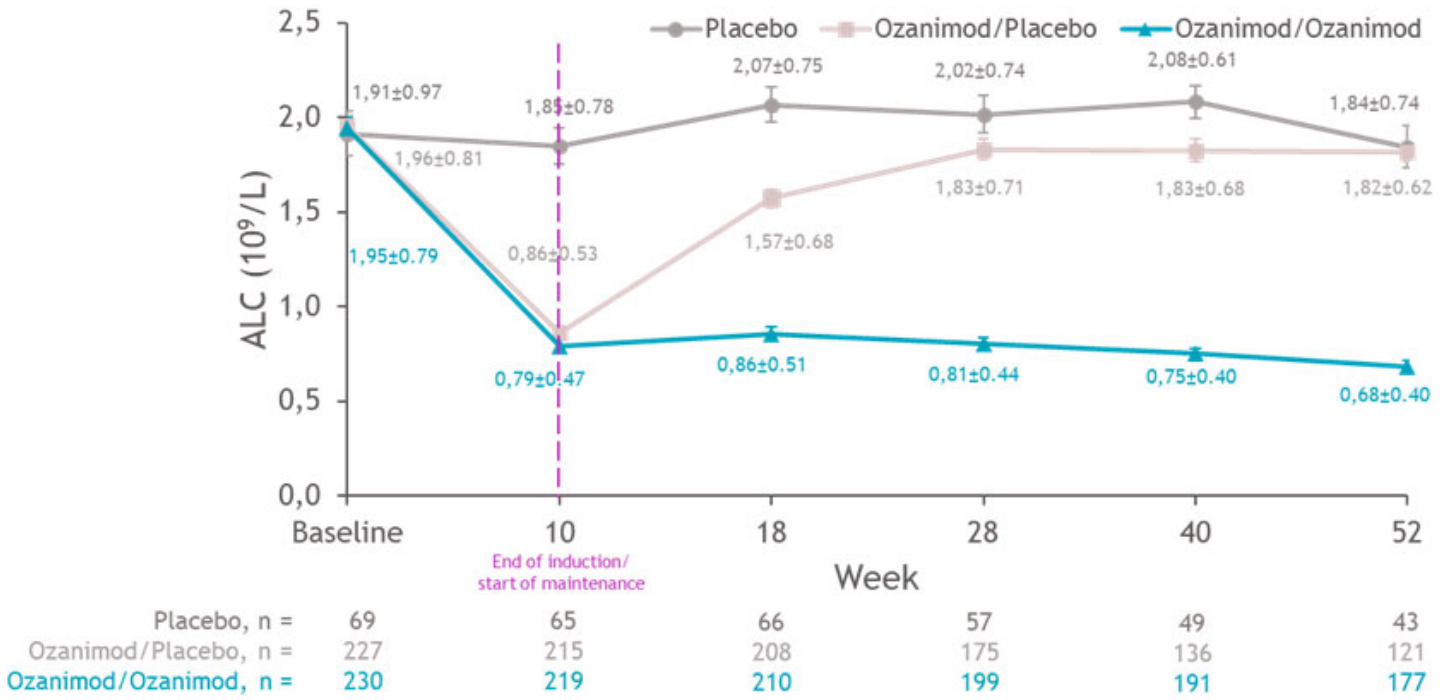
Sandborn et al., NEJM 2021; 385:14

Table 2. Safety Findings through the Final Safety Visit in the Induction and Maintenance Periods.*

Variable	Induction Period			Maintenance Period†	
	Cohort 1		Cohort 2		
	Placebo (N=216)	Ozanimod (N=429)	Ozanimod (N=367)	Placebo (N=227)	Ozanimod (N=230)
Adverse event — no. (%)	82 (38.0)	172 (40.1)	146 (39.8)	83 (36.6)	113 (49.1)
Serious adverse event — no. (%)	7 (3.2)	17 (4.0)	23 (6.3)	18 (7.9)	12 (5.2)
Serious adverse event related to ozanimod or placebo — no. (%)	2 (0.9)	1 (0.2)	3 (0.8)	1 (0.4)	0
Adverse event leading to discontinuation of the regimen — no. (%)	7 (3.2)	14 (3.3)	14 (3.8)	6 (2.6)	3 (1.3)
Most frequent adverse events — no. (%)‡					
Anemia	12 (5.6)	18 (4.2)	16 (4.4)	4 (1.8)	3 (1.3)
Nasopharyngitis	3 (1.4)	15 (3.5)	10 (2.7)	4 (1.8)	7 (3.0)
Headache	4 (1.9)	14 (3.3)	10 (2.7)	1 (0.4)	8 (3.5)
Alanine aminotransferase increased§	0	11 (2.6)	6 (1.6)	1 (0.4)	11 (4.8)
Arthralgia	3 (1.4)	10 (2.3)	5 (1.4)	6 (2.6)	7 (3.0)
γ-Glutamyltransferase increased§	0	5 (1.2)	6 (1.6)	1 (0.4)	7 (3.0)
Infection — no. (%)	25 (11.6)	46 (10.7)	46 (12.5)	27 (11.9)	53 (23.0)
Serious infection	1 (0.5)	4 (0.9)	6 (1.6)	4 (1.8)	2 (0.9)
Nasopharyngitis	3 (1.4)	15 (3.5)	10 (2.7)	4 (1.8)	7 (3.0)
Upper respiratory tract infection	1 (0.5)	5 (1.2)	8 (2.2)	4 (1.8)	2 (0.9)
Herpes zoster infection¶	0	2 (0.5)	1 (0.3)	1 (0.4)	5 (2.2)
Cancer — no. (%)					
Basal-cell carcinoma	0	0	1 (0.3)	0	1 (0.4)
Rectal adenocarcinoma	0	0	0	0	1 (0.4)
Adenocarcinoma of the colon	0	0	0	1 (0.4)	0
Breast cancer	0	0	0	1 (0.4)	0
Adverse events of special interest — no. (%)					
Bradycardia	0	2 (0.5)	3 (0.8)	0	0
Hypertension	0	6 (1.4)	7 (1.9)	3 (1.3)	4 (1.7)
Hypertensive crisis	0	1 (0.2)	0	1 (0.4)	1 (0.4)
Macular edema	0	1 (0.2)	1 (0.3)	0	1 (0.4)
Laboratory assessments — no./total no. (%)					
Alanine aminotransferase					
≥2×ULN	2/216 (0.9)	25/423 (5.9)	17/359 (4.7)	12/227 (5.3)	32/230 (13.9)
≥3×ULN	1/216 (0.5)	11/423 (2.6)	7/359 (1.9)	4/227 (1.8)	7/230 (3.0)
≥5×ULN	1/216 (0.5)	4/423 (0.9)	2/359 (0.6)	1/227 (0.4)	2/230 (0.9)
Absolute lymphocyte count					
<200 cells per mm^3	0/209	9/421 (2.1)	3/360 (0.8)	0/227	5/230 (2.2)
<500 cells per mm^3	0/209	113/421 (26.8)	114/360 (31.7)	4/227 (1.8)	100/230 (43.5)

Sandborn et al., NEJM 2021; 385:14

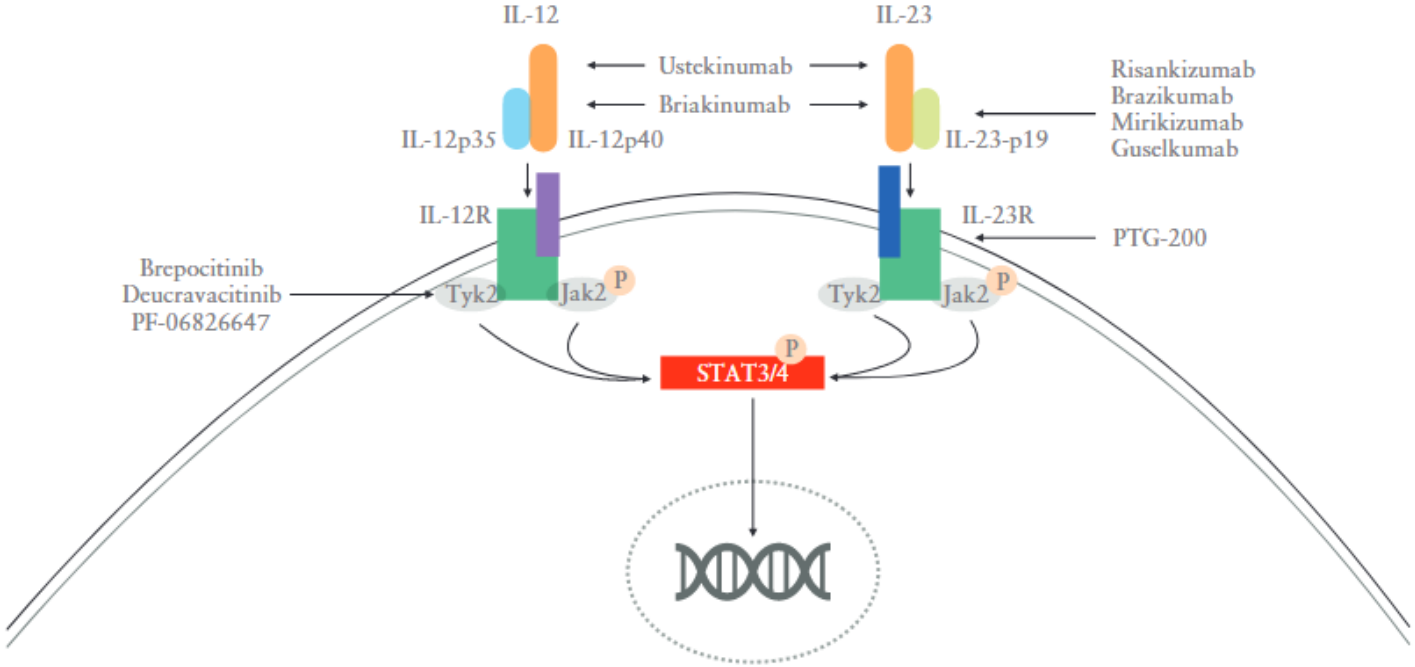
Changes in absolute lymphocyte count (ALC)



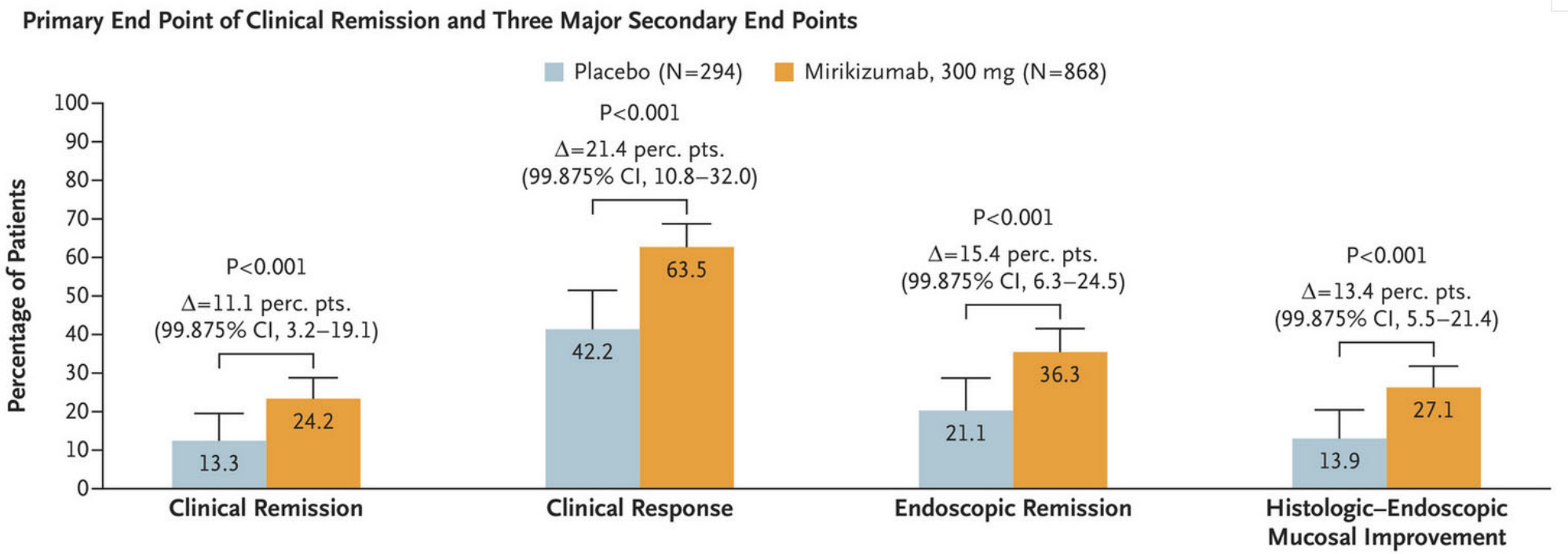
ALC changes not associated with therapeutic effects
→ biomarker for compliance but not for efficacy
ALC changes not associated with infectious complications

D'Haens G et al. UEGW (virtual) 2021. Presentation P0386.

Blocking IL-23

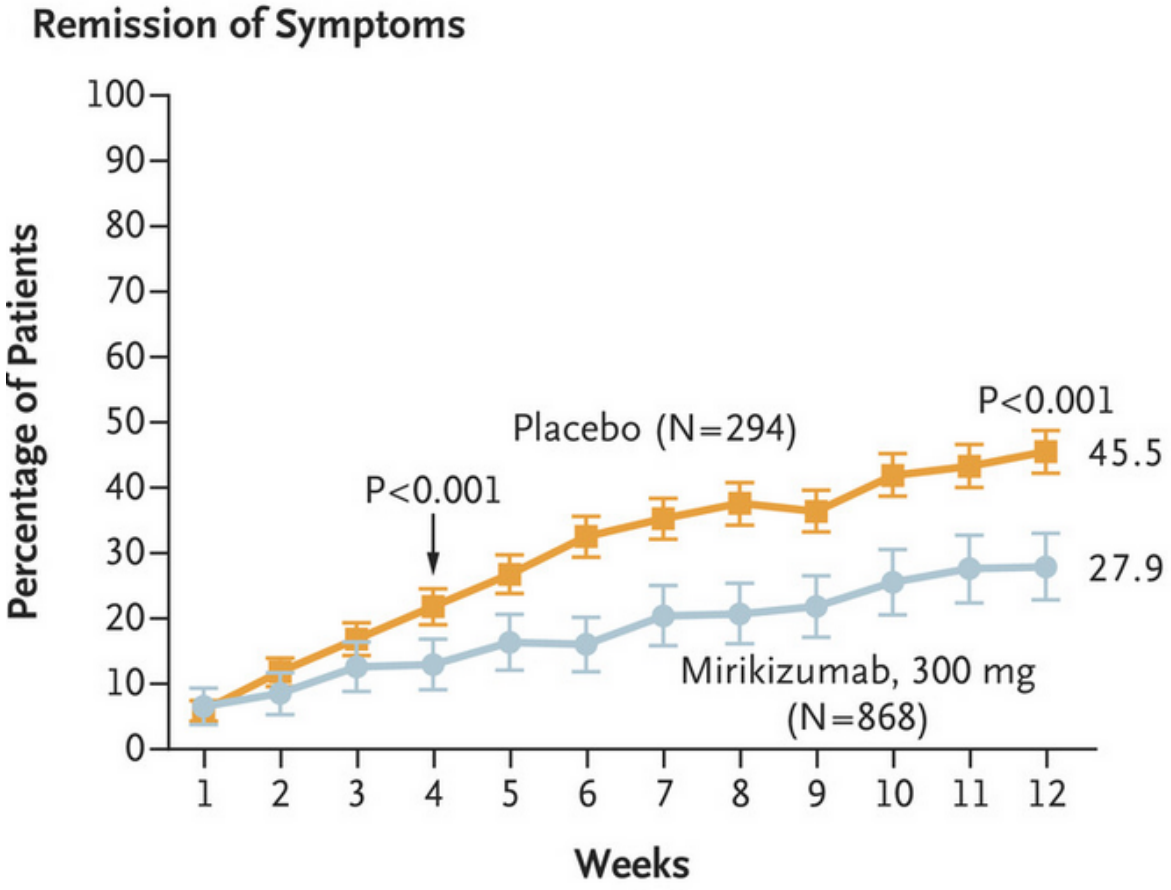


IL-23 Inhibitoren bei Colitis ulcerosa



D'Haens et al., NEJM 2023; 388:2444

IL-23 Inhibitoren bei Colitis ulcerosa



Summary

- 5-ASA cornerstone of therapy for mild-moderate UC
  but week evidence
- JAK-inhibitors: best efficacy – potential side effects
- S1-P receptor modulator: acceptable efficacy, good safety
- IL-23 inhibitors: acceptable efficacy, very good safety
- s.c. formulation increasingly used

→ No breakthrough yet

Clinical definitions: Mayo score (reminder)

Parameters	Subscore, 0–3
Stool frequency	0 = Normal number of stools for this patient
	1 = 1–2 stools more than normal
	2 = 3–4 stools more than normal
	3 = 5 or more stools more than normal
Rectal bleeding	0 = No blood seen
	1 = Streaks of blood with stool less than one-half of the time
	2 = Obvious blood with stool most of the time
	3 = Blood alone passes
Findings on endoscopy	0 = Normal or inactive disease
	1 = Mild disease (erythema, decreased vascular pattern, and mild friability)
	2 = Moderate disease (marked erythema, lack of vascular pattern, friability, and erosions)
	3 = Severe disease (spontaneous bleeding and ulcerations)
Physician's global assessment	0 = Normal
	1 = Mild disease
	2 = Moderate disease
	3 = Severe disease