Clarunis
Universitäres Bauchzentrum Basel
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New Agents on the Block for IBD Treatment

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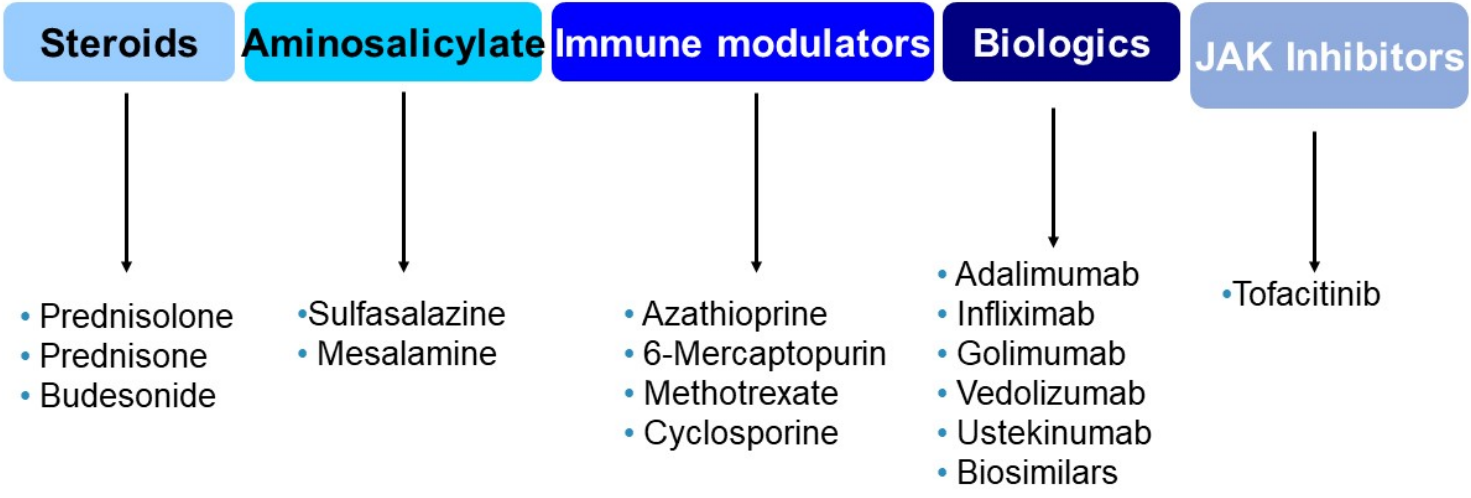
Disclosures and conflict of interests

Abbvie, Janssen, Takeda, Pfizer, Vifor, Bristol Myers Squibb, Roche, Gilead, MSD

IBD Therapy


Steroids
Aminosalicylate
Immune modulators
Biologics
JAK Inhibitors
• Prednisolone
• Prednisone
• Budesonide
•Sulfasalazine
• Mesalamine
• Azathioprine
• 6-Mercaptopurin
• Methotrexate
• Cyclosporine
• Adalimumab
• Infliximab
• Golimumab
• Vedolizumab
• Ustekinumab
• Biosimilars
•Tofacitinib

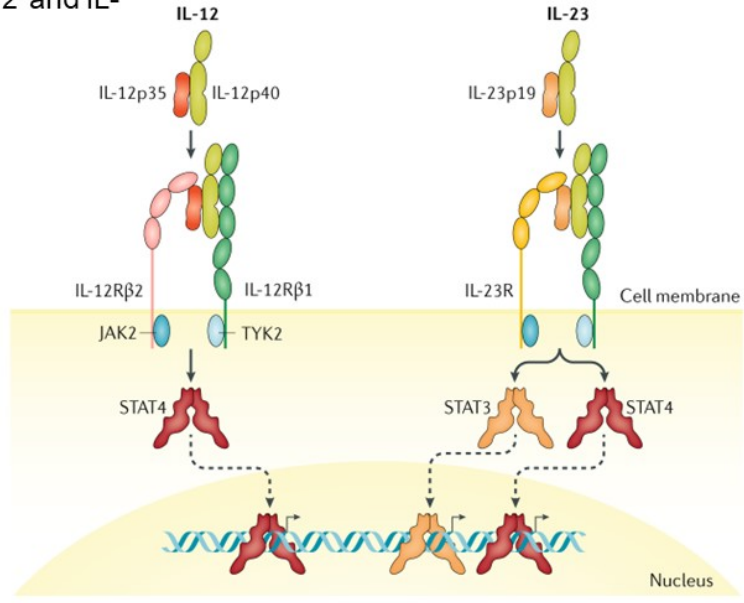
New Agents

- IL-23 p19 inhibition
- Janus kinase inhibitors
- Sphingosine 1-phosphate receptor modulators

https://www.nature.com/articles/d41586-018-05267-x

IL-23 p19 Inhibitors

Ustekinumab targets the p40 subunit inhibiting IL-12 and IL-23



Moschen, *Nat Rev Gastroenterol Hepatol*, 2019, 16:185-196

Monoclonal antibodies directed against the p19 subunit specifically inhibit IL-23

Genome-wide association studies suggests IBD protection in a coding variant of IL-23R(*Duerr et al. Science; 314:1461*)

Murine colitis models supports specific IL-23 inhibition (*Kullberg et al. J Exp Med. 203:2485)*

High efficacy in psoriasis (*Papp et al. N Engl J Med. 376:1551)*

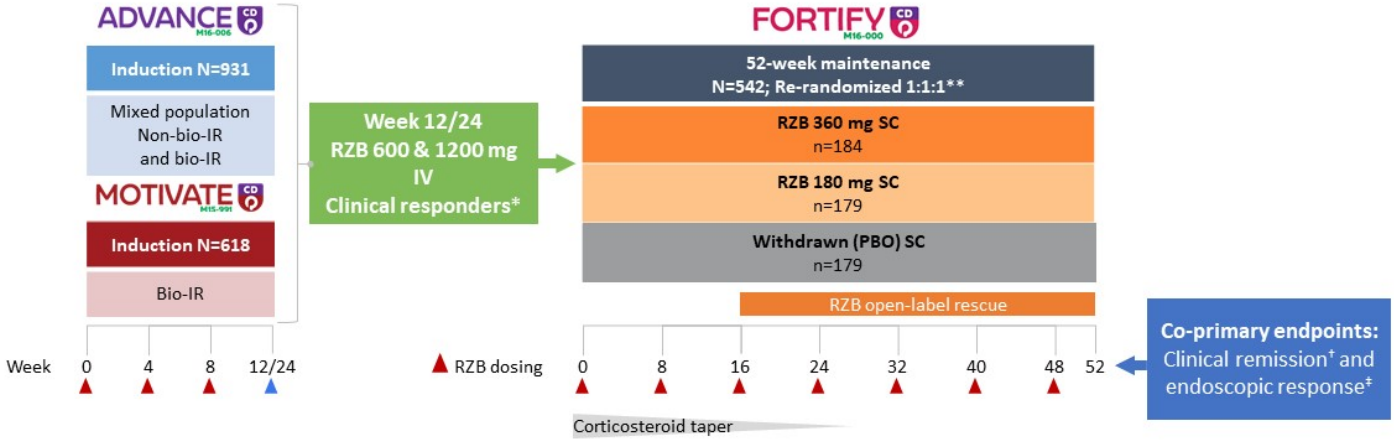
IL-23 p19 Inhibitors

	Crohn's disease		Ulcerative colitis	
	Induction	Maintenance	Induction	Maintenance
Brazikumab (AstraZeneca)	Phase 3 i.v.	Phase 3 s.c.	Phase 2 i.v.	Phase 2 s.c.
Mirkizumab (Eli Lilly)	Phase 3 i.v.	Phase 3 s.c.	Phase 3 i.v.	Phase 3 s.c.
Risankizumab* (Abbvie)	Phase 3 i.v.	Phase 3 s.c.	Phase 3 i.v.	Phase 3 s.c.
Guselkumab (Janssen)	Phase 2/3 and phase 3 i.v. or s.c.	Phase 2/3 i.v.	Phase 2/3 i.v.	Phase 2/3 s.c.

* Approved by EMA and FDA

ADVANCE / MOTIVATE and FORTIFY Study Design

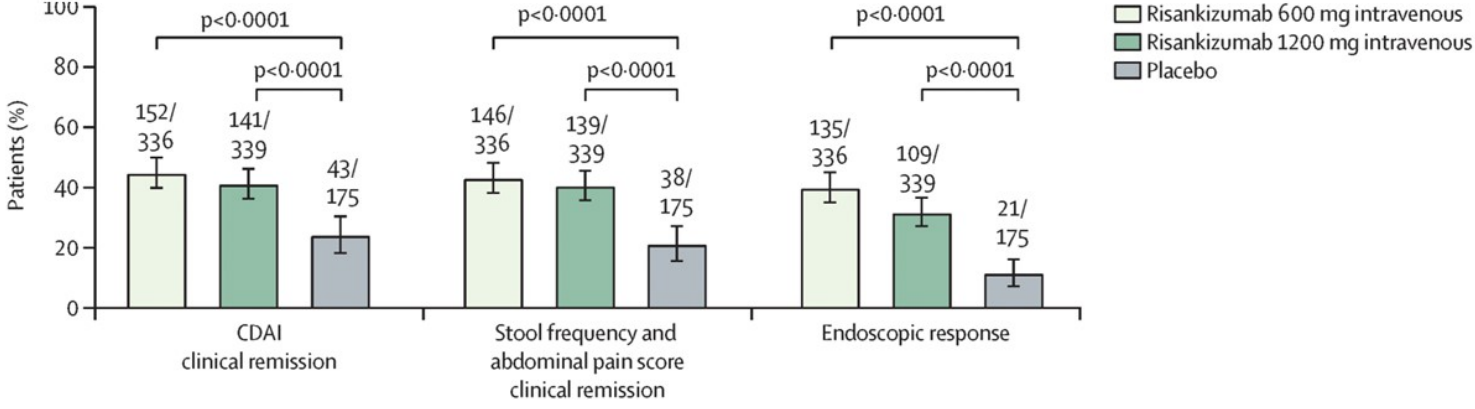
Crohn's disease



D'Haens et al. Lancet. 399:2015, Ferrante et al. Lancet. 399:2031

ADVANCE Induction Trial

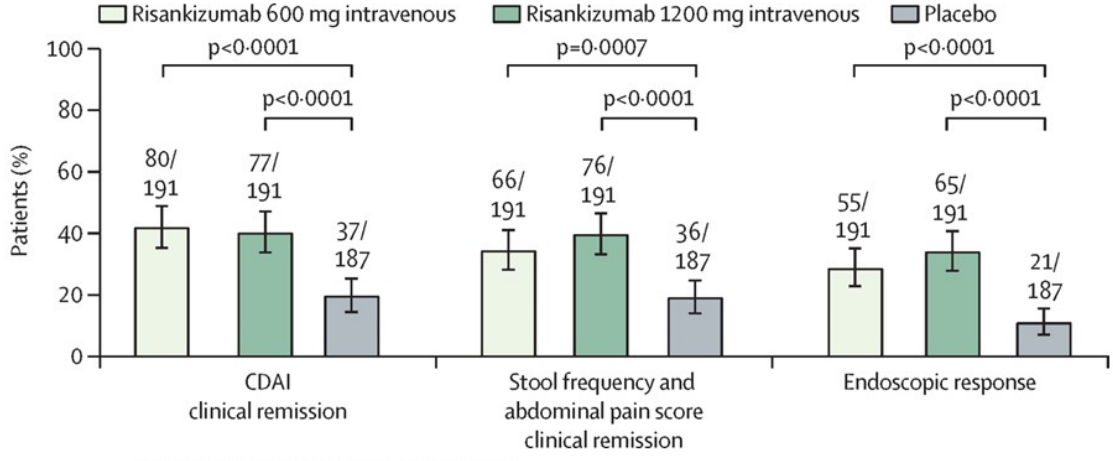
Week 12
ADVANCE study (Non BIO-failure and BIO-failure)
Clinical remission
USA: CDAI < 150
Non-USA: stool frequency <2.8; abdominal pain score < 1
Endoscopic response, decrease SES-CD > 50% from baseline



D'Haens et al. Lancet. 399:2015,

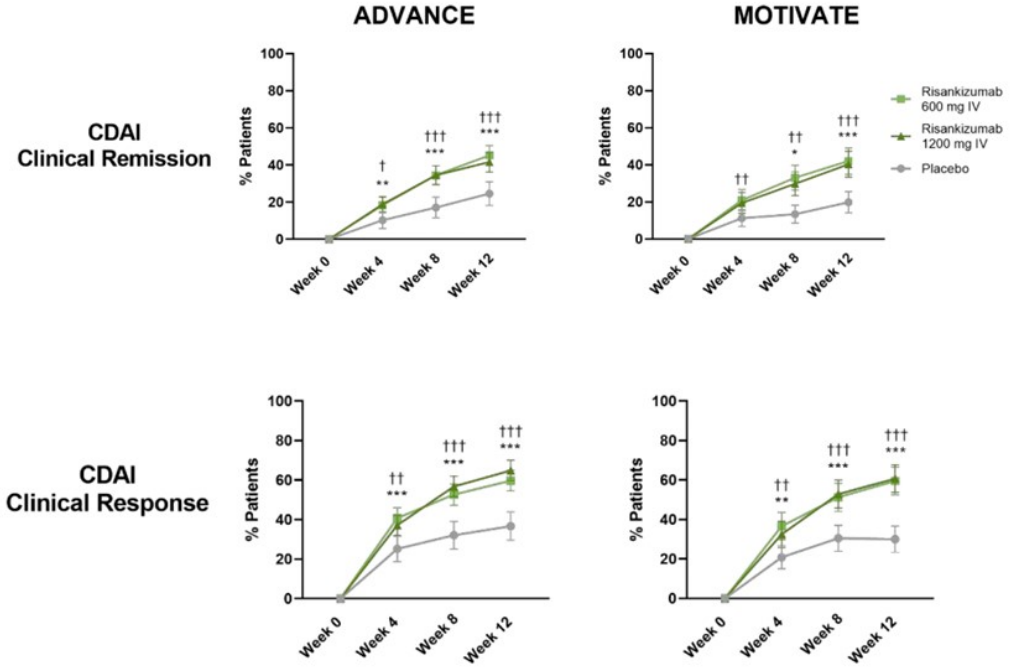
MOTIVATE Induction Trial

Week 12
MOTIVATE study (Prior BIO-failure)
Clinical remission
USA: CDAI < 150
Non-USA: stool frequency <2.8; abdominal pain score < 1
Endoscopic response, decrease SES-CD > 50% from baseline



D'Haens et al. Lancet. 399:2015

Clinical Remission and Response ADVANCE and MOTIVATE

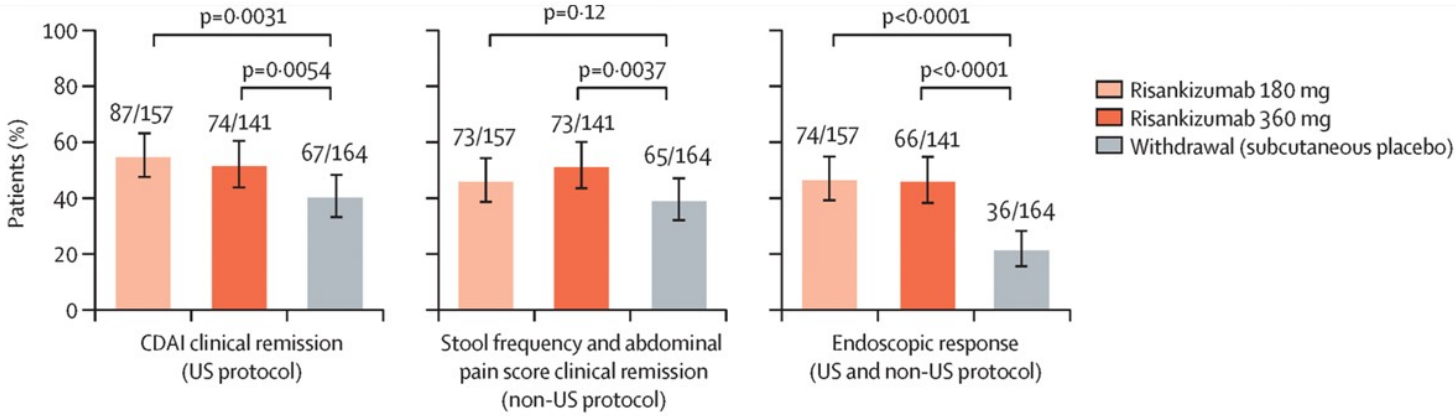


ADVANCE
Without and with prior BIO-failure

MOTIVATE
Prior BIO-failure

Risankizumab FORTIFY Maintenance Trial

Week 52



Ferrante et al. Lancet. 399:2031

Safety - FORTIFY Maintenance Trial

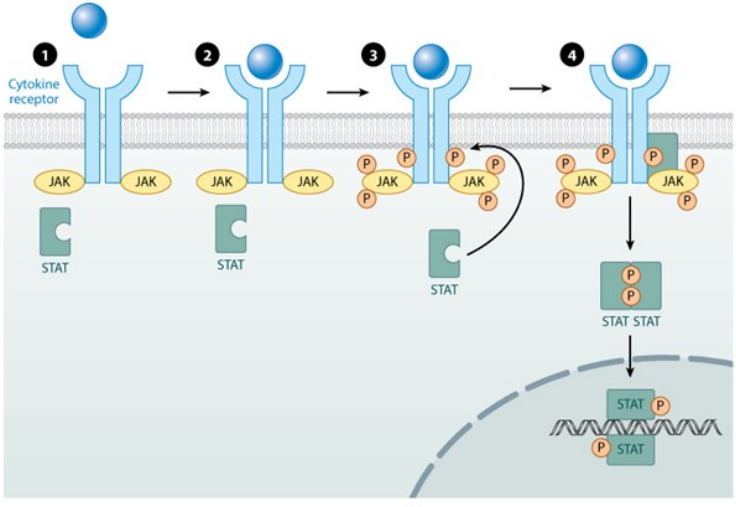
- Comparable frequencies of adverse events between treatment and placebo groups
- Nasopharyngitis, and headache are the most common adverse events, with no differences between groups
- Fewer infections in treatment groups (34% vs. 40%), with no differences in serious infections
- One malignancy (breast cancer) in the 180 mg treatment group
- One myocardial infarction in the 360 mg treatment group

IL-23 p19 Inhibition

- Induction i.v., maintenance s.c.
- Favorable safety profile
- Patients pretreated with biologicals
- Concomitant psoriasis or psoriasis arthritis

JAK Inhibitors

JAK – STAT Signaling

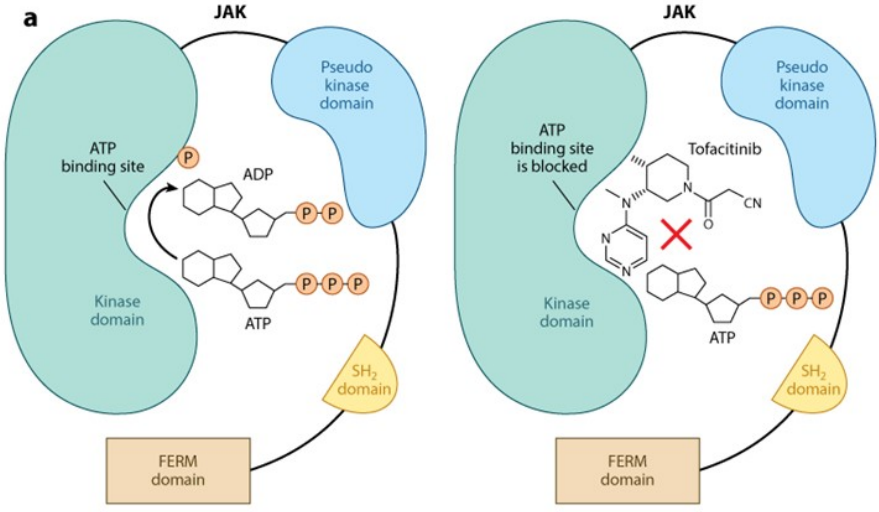


O'Shea JJ, et al. 2015.
Annu. Rev. Med. 66:311–28

JAK: *Januskinase*

STAT: *Signal Transducers and Activators of Transcription*

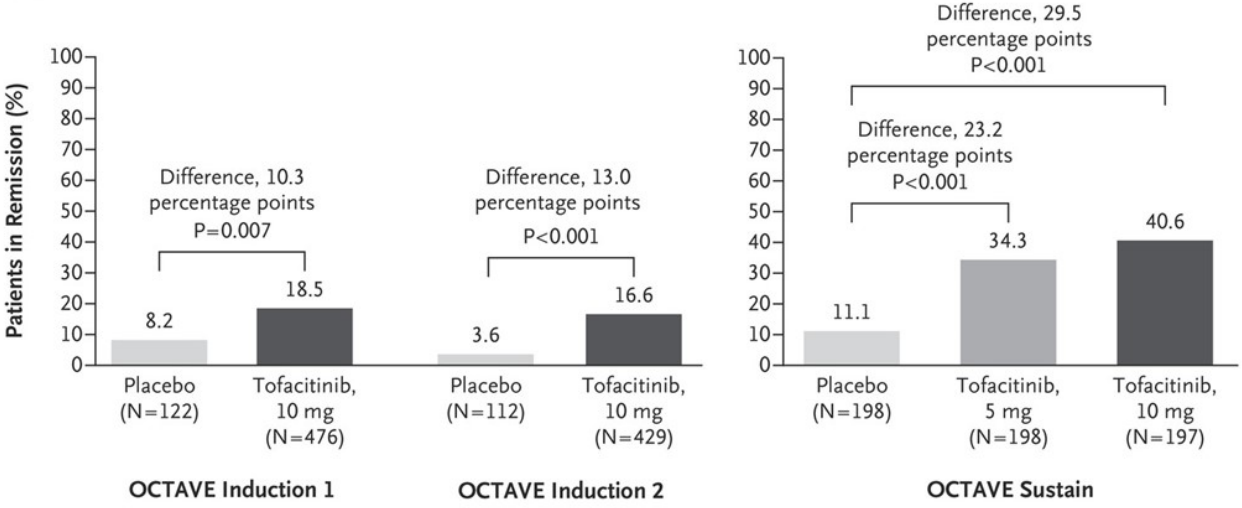
Tofacitinib - Action



O'Shea JJ, et al. 2015.
Annu. Rev. Med. 66:311–28

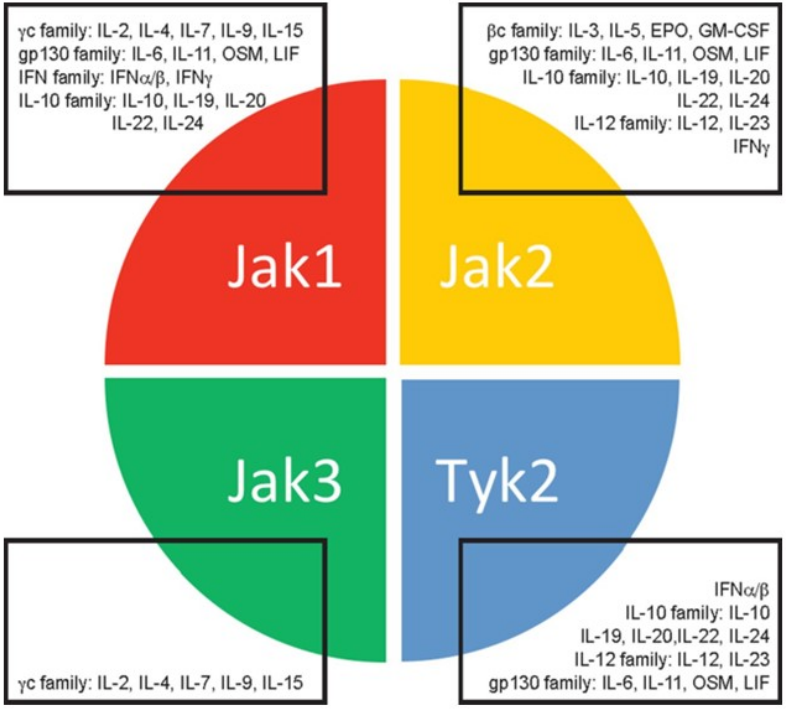
Tofacitinib – OCATAVE Trail

Ulcerative colitis
approximately 50% TNF-experienced



Sandborn WJ et al. N Engl J Med 2017;376:1723-1736.

Cytokines and JAKs



John J O'Shea et al. Ann Rheum Dis;72:ii111

JAK Inhibitors

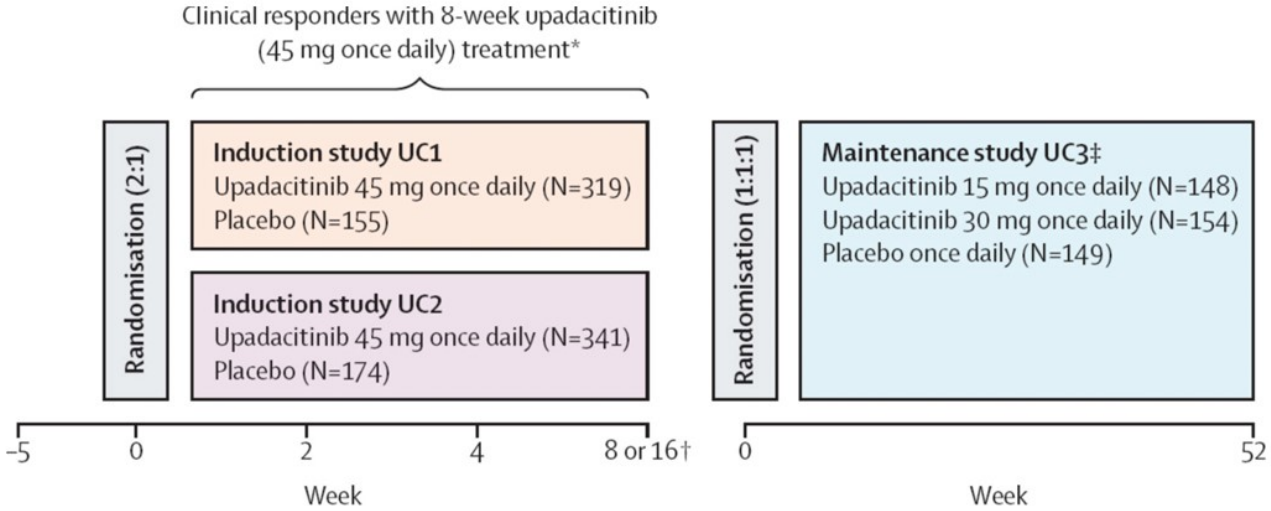
Compound	Company	Ulcerative colitis	Crohn's disease	Target	Selectivity
Tofacitinib	Pfizer	approved	terminated	JAK3 and JAK1	20-fold JAK3/1 > JAK2
Filgotinib*	Galapagos	Phase 3	Phase 3	JAK1	30-fold JAK1>JAK2
Peficitinib	Astellas, Janssen	Phase 2b	n.d.	JAK1 and JAK3	14-fold JAK1/3 > JAK2
Upadacitinib*	AbbVie	Phase 3	Phase 3	JAK1	74-fold JAK1>JAK2

* Approved by EMA and FDA for ulcerative colitis, rheumatoid arthritis

U-ACHIEVE (UC1), U-ACCOMPLISH (UC2) Induction and U-ACHIEVE Maintenance (UC3)

Ulcerative colitis
BIO-Failure approximately 50%

Clinical remission, Mayo < 2, with stool frequency < 1, rectal bleeding score, endoscopic subscore < 1
Endoscopic remission, endoscopic subscore 0



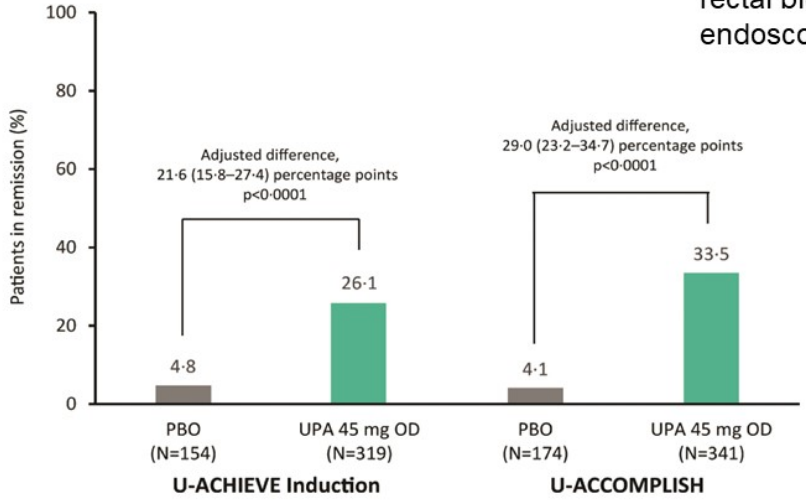
Danese et al. Lancet. 399:2113

U-ACHIEVE (UC1) and U-ACCOMPLISH (UC2) Induction

Week 8

A Clinical remission (adapted Mayo)*

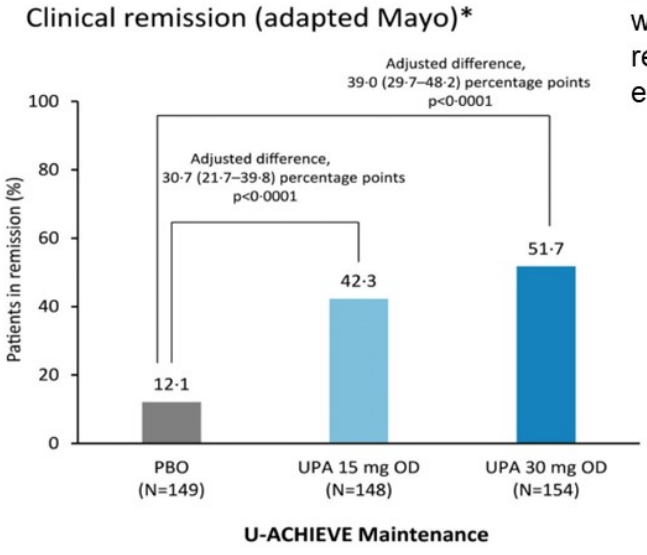
Clinical remission, Mayo < 2,
with stool frequency < 1,
rectal bleeding score,
endoscopic subscore < 1



Danese et al. Lancet. 399:2113

U-ACHIEVE Maintenance

Week 52



Clinical remission, Mayo < 2, with stool frequency < 1, rectal bleeding score, endoscopic subscore < 1

Danese et al. Lancet. 399:2113

Safety - U-ACHIEVE Maintenance

- Similar rates of adverse events between treatment and placebo groups
- Nasopharyngitis (15/18/22%), CK elevation (3/913%), arthralgia (15/9/5%), Headache (6/4/5%)
- Serious events leading to discontinuation were higher in placebo group (17/6/10%)
- No difference in serious infections (6/5/4%)
- Herpes zoster higher in treatment groups (0/4/4%)
- Two events of venous thromboembolism in the 30 mg Upadacitinib group
- One malignancy (breast cancer) in the placebo group and one (breast cancer) in the treatment groups

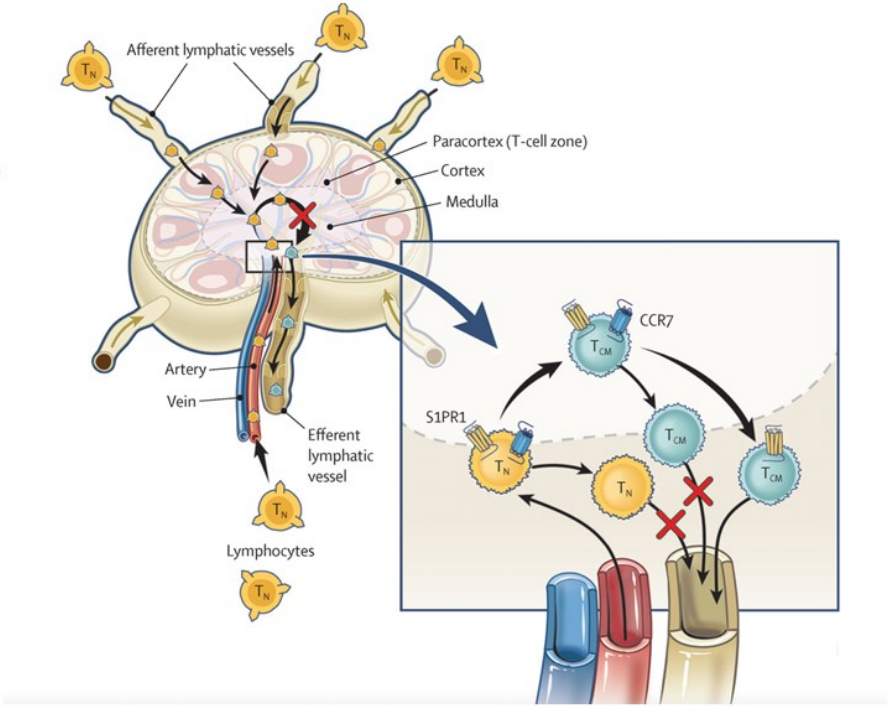
JAK1 Inhibitors

- Oral
- No immunogenicity
- Rapid response
- Patients pretreated with biologicals
- Concomitant peripheral and axial arthritis
- Venous thromboembolism, Herpes zoster

Sphingosine 1-Phosphate Receptor Modulators

Sphingosine 1-Phosphate Receptor Modulators

Sphingosine 1 phosphate receptor modulators inhibit the egress of lymphocytes from lymph nodes



McGinley and Cohen. Lancet. 398:1184

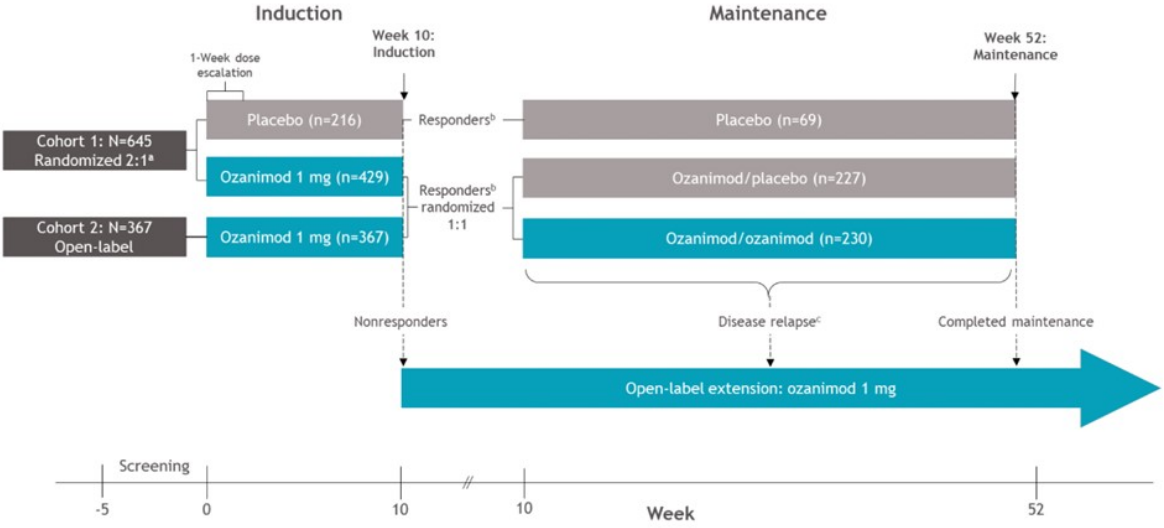
Sphingosine 1-Phosphate Receptor Modulators

	Crohn's disease		Ulcerative colitis	
	Induction	Maintenance	Induction	Maintenance
Ozanimod* (Celgene)	Phase 3 oral	Phase 3 oral	0.23 mg day 1-4 q.d. 0.46 mg day 5-7 q.d.	0.92 mg q.d.
Etrasimod (Arena Pharmaceuticals)	Phase 2/3 oral	Phase 2/3 oral	Phase 3 oral	Phase 3 oral
Amiselimod (Bausch Health America)			Phase 2 oral	Phase 2 oral

* Approved for UC

Ozanimod TrueNorth Study Design

Ulcerative colitis
Mayo Score 6 to 12, endoscopy subscore > 2, rectal bleeding score > 1
Cohort # 1 < 30% TNF pretreated
Cohort # 2 < 50% TNF pretreated



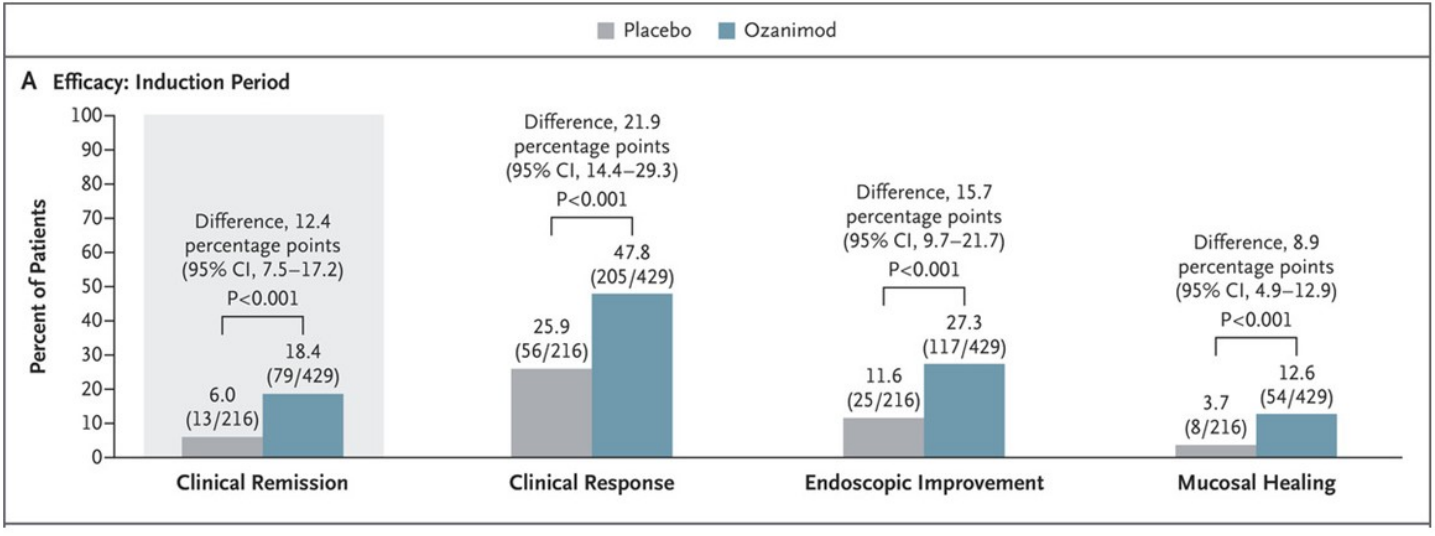
Sandborn et al., N Engl J Med. 2021;385:1280

Induction Period

Week 10

Clinical remission: Rectal bleeding 0, stool frequency < 1, endoscopy subscore < 1 (Mayo)

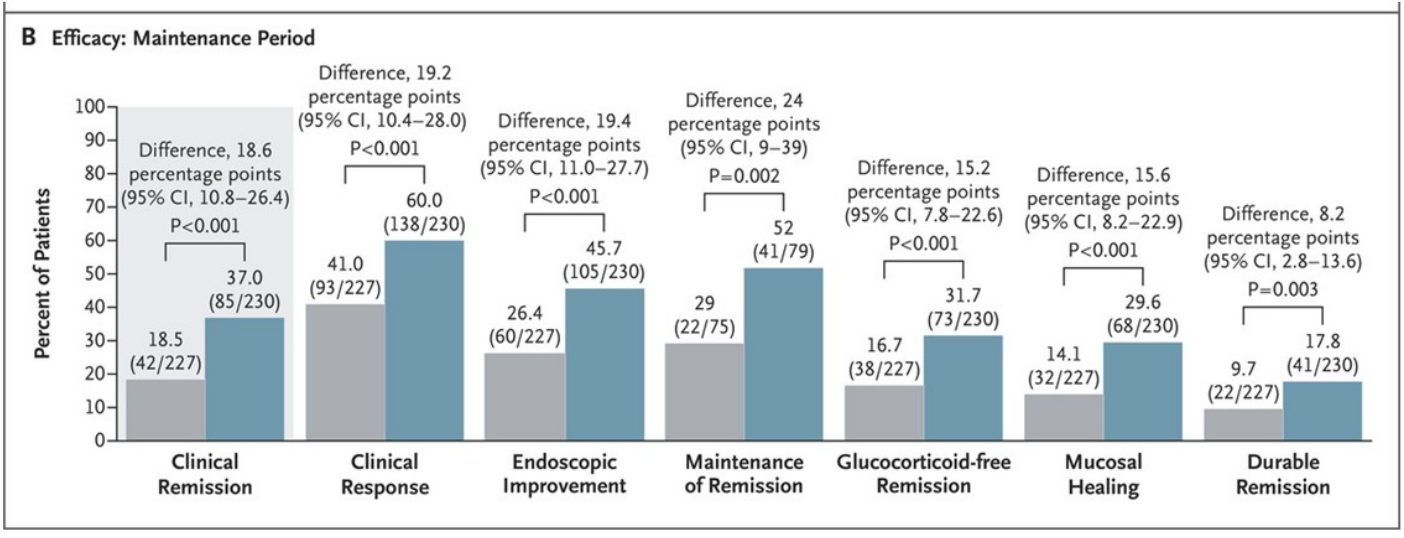
No differences between cohort # 1 and cohort # 2)



Sandborn et al., N Engl J Med. 2021;385:1280

Maintenance Period

Week 52



Sandborn et al., N Engl J Med. 2021;385:1280

Safety

- Bradycardia (0.5%) in induction, hypertension < 2%
- Lymphocyte count decreased 54%, lymphopenia < 200/mm^3 in 2% with a subsequent increase and no serious opportunistic infections
- Macular edema (0.4%)
- Hepatic events (8%), no severe liver injury, discontinuation in 4 patients (0.5%
- Infections (nasopharyngitis) in 4%, serious infection < 2%
- One patient with non-melanoma skin cancer

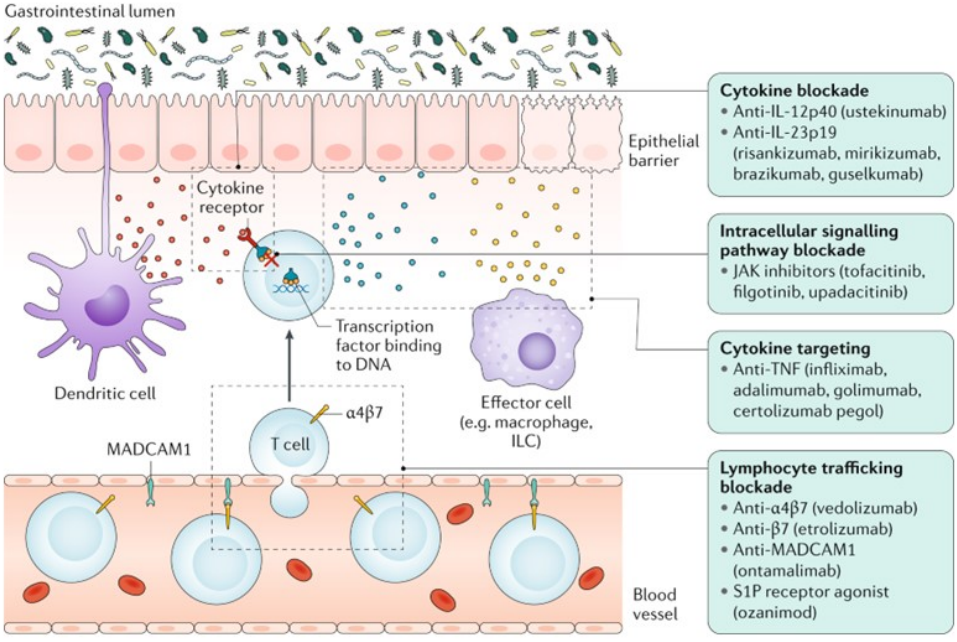
Sphingosine 1-Phosphate Receptor Modulators

- Oral therapy
- Small molecule with no immunogenicity
- Ulcerative colitis with concomitant multiple sclerosis
- Baseline screening (cardiac, ophthalmology, potential toxicities (liver))
- Extreme of age and comorbidities (hypertension, cardiac comorbidities)
- Rebound as in multiple sclerosis?

Increasing Complexity

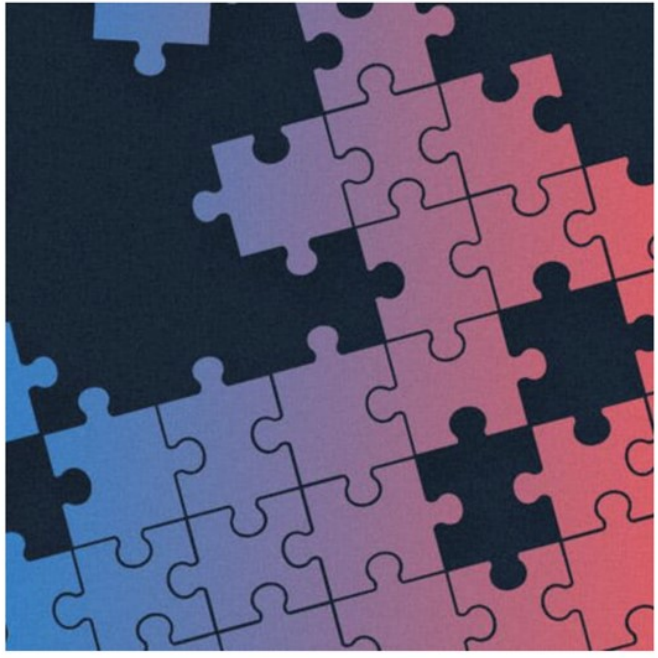
Induction

Maintenance



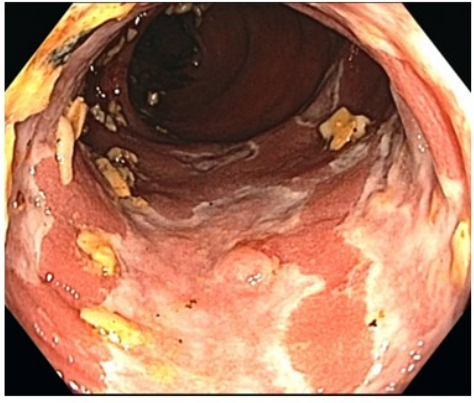
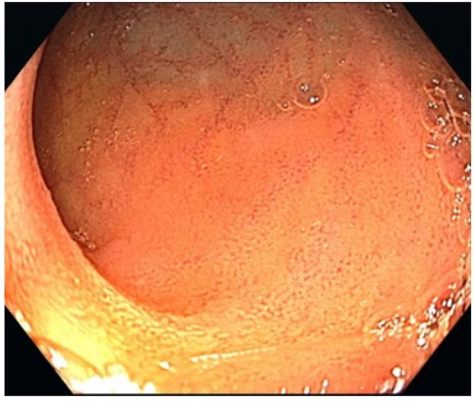
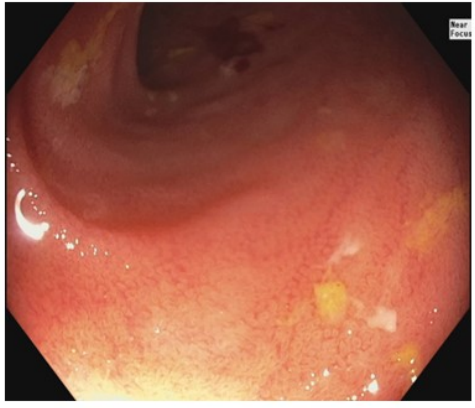
Digby-Bell, *Nat Rev Gastroenterol Hepatol*, 2019, 17:9-20

Combinations



Combinations

44-year old patient with Crohn's disease and axial spondylarthritis
Crohn's disease with no response to multiple TNF blockers and / or methotrexate
Perforation with ileocoecalresektion seven years ago

Certolizumab	Risankizumab	Risankizumab + Certolizumab
		
Axial spondylarthritis +	Axial spondylarthritis ++++	Axial spondylarthritis +

Who, What, When....

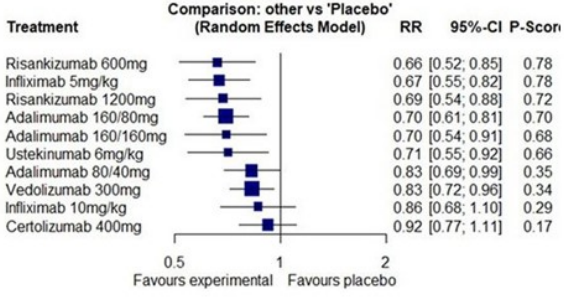
Interindividual differences

Heterogenous IBD

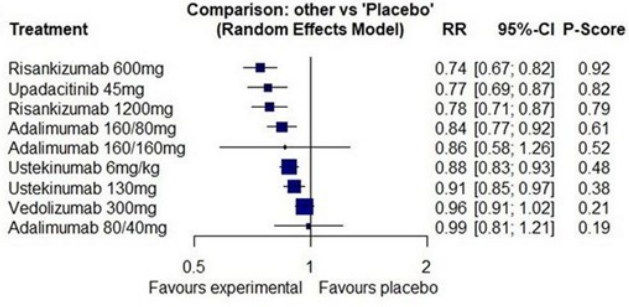
Metanalysis

Crohn's disease
Induction

naive



Biologic-experienced



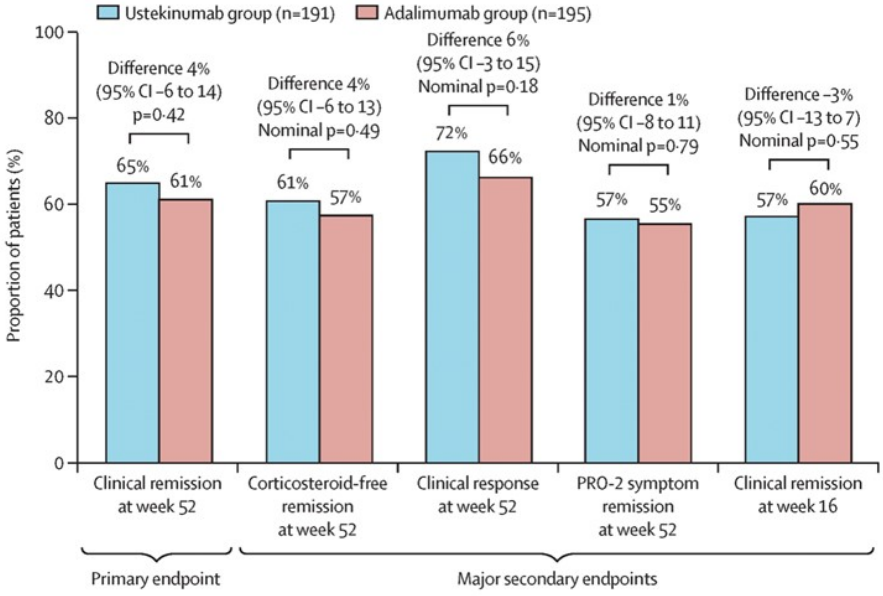
Brigida Barberio et al. Gut doi:10.1136/gutjnl-2022-328052

Head-to-Head Studies

SEAVUE study
Ustekimumab vs. adalimumab

Crohn's disease

Remission CDAI< 150, Week 52



VARSITY study
Vedolizumab vs. adalimumab

Ulcerative colitis
Sands et al. N Engl J Med; 381:1215

Sands et al., Lancet. 399:2200

Summary

- Risk stratification
- Patient preferences oral s.c. i.v.
- Time requiring for response / remission (Jak Inhibitors, TNF)
- Safety profile (Vedolizumab, IL-12/23 inhibitors)
- Extraintestinal manifestations
- Special situations (Pregnancy, fistula, pouchitis etc.)