Advanced Medical Therapies in IBD

Vipul Jairath MBChB DPhil FRCP FRCPC
Professor of Medicine
Division of Gastroenterology, Western University, Canada

Disclosures

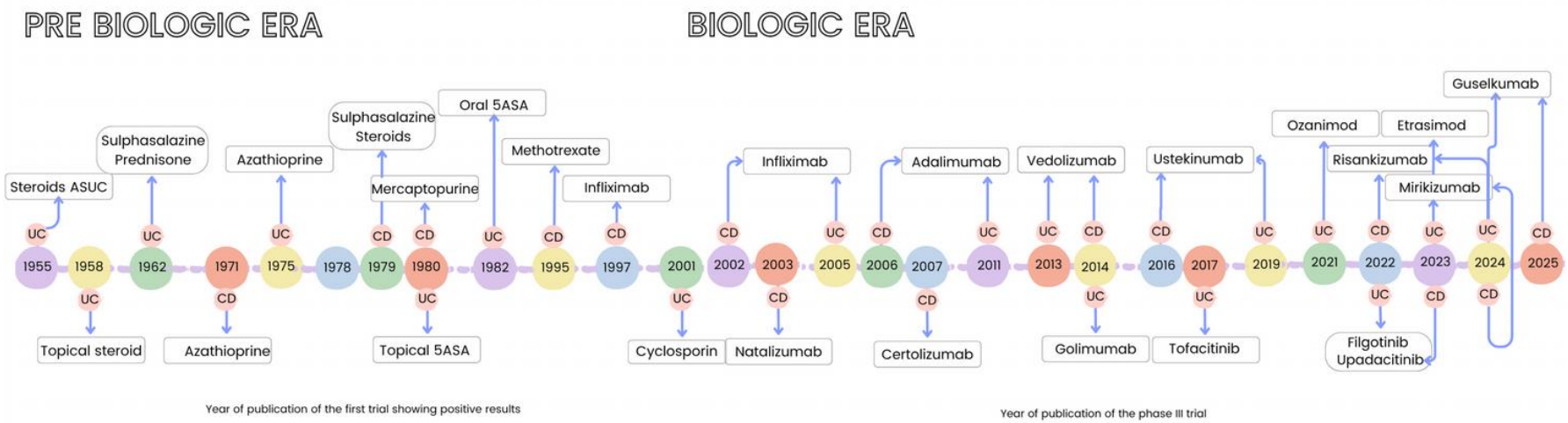
Commercial or Non-Profit Interest	Relationship
AbbVie, Alimentiv, Asieris, Astra Zeneca, Biomebank, Boehringer Ingelheim, Caldera Therapeutics, Calluna, Celltrion, Domain Therapeutics, Eli Lilly, Enthera, Ensho, Exeliom Biosciences, Ferring Ventures, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Granite Bio, Janssen, Merck, Metacrine, Mountainfield, MRM Health, Nxera, Organon, OSE Immunotherapeutics, Pandion, Pendopharm, Pfizer, Prometheus Biosciences, Roche, Salvina, Sanofi, Shattuck Labs, Sorriso, Spyre, Synedgen, Takeda, Teva, Thabor Therapeutics, Union Therapeutics, Ventus, Ventyx, Vividion, Xencor, Zealand Pharma	**Advisory Board, Consultant**
Abbvie, Ferring, Eli Lilly, Pfizer, Takeda,	**Speaker**

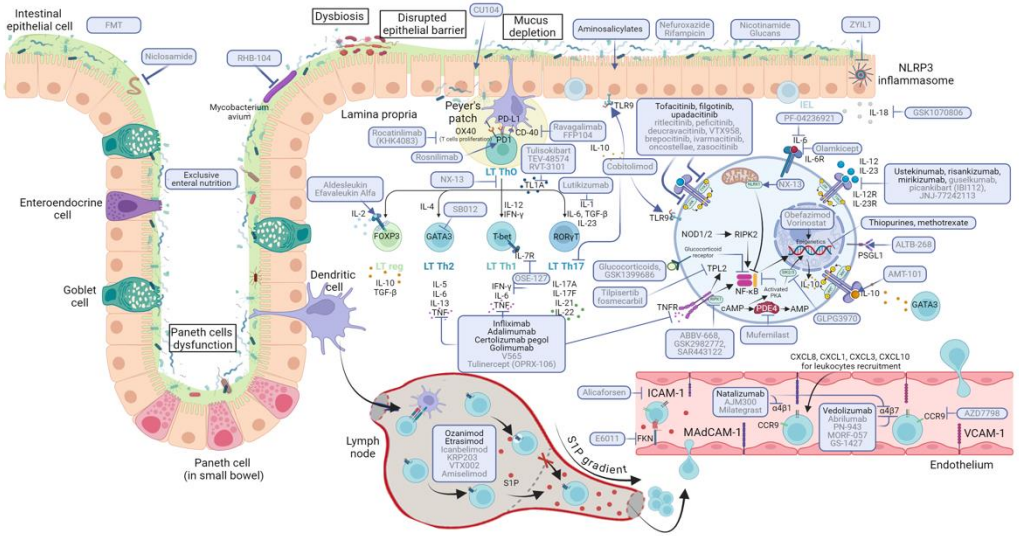
Objectives

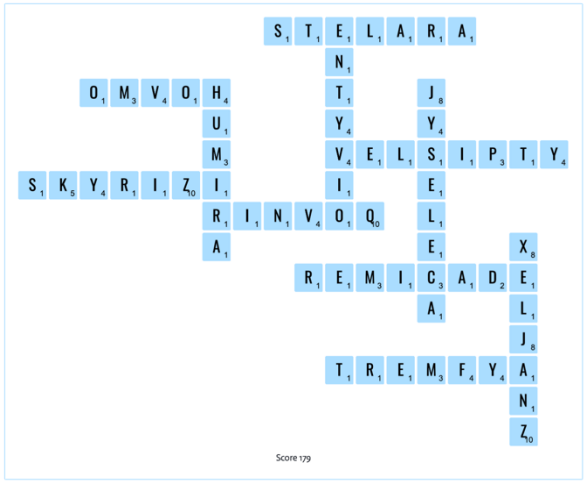
- Review the current treatment armamentarium for IBD
- Review best evidence for positioning of advanced therapies
- Review combination therapy as an emerging strategy

Evolution of the therapeutic landscape

Evolution of the Therapeutic Landscape







Gross B. https://ibd-eii.com/timeline/

Vieujean S, Jairath V, et al , Nature Review Gastro 2025

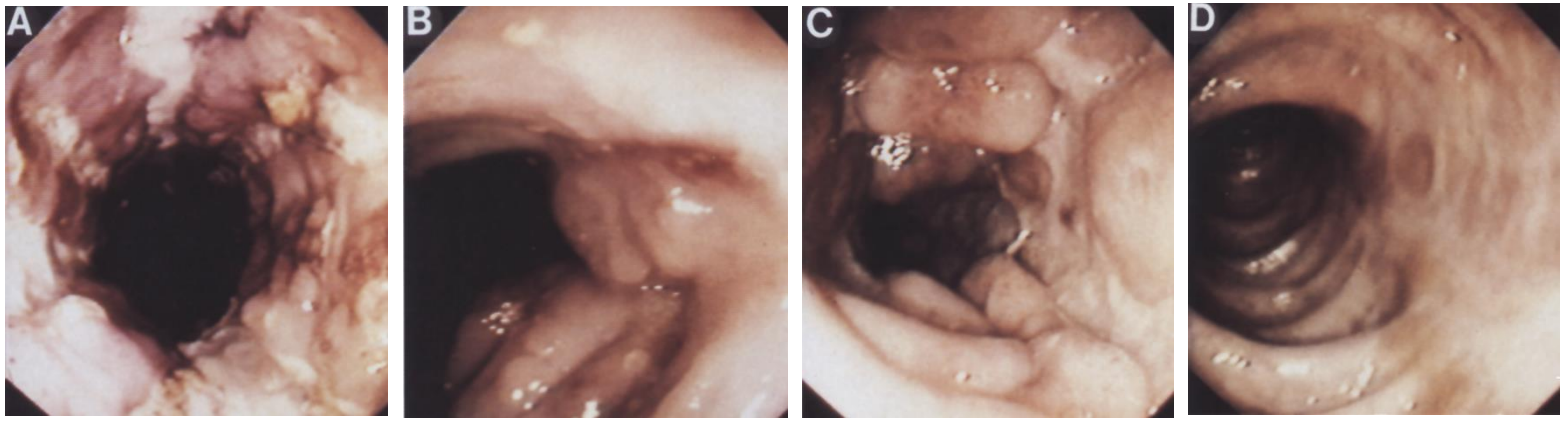
What are the key things we have learned with each major class (my summary of many studies)?

Anti-TNF

Treatment of Crohn's Disease With Anti–Tumor Necrosis Factor Chimeric Monoclonal Antibody (cA2)

Bert Derkx, Jan Taminiau, Sandra Radema, Arnold Stronkhorst, Cees Wortel, Guido Tytgat, Sander van Deventer

Departments of Paediatric Gastroenterology, Nutrition, and Gastroenterology, Academic Medical Centre, 1105 AZ Amsterdam, Netherlands



GASTROENTEROLOGY 1995;109:129–135

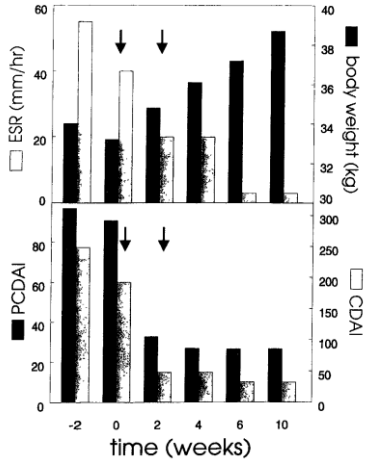
Figure 2. Healing of colonic ulcerations in 2 patients (patients 1 and 8) after treatment with cA2. (A and C) At enrollment and (B and D) 4 weeks after infusion of cA2.
Photographs were obtained from videotapes, allowing comparison of exactly the same location.
van Dullemen HM, et al. *Gastroenterology*. 1995;109(1):129-135.

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

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

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

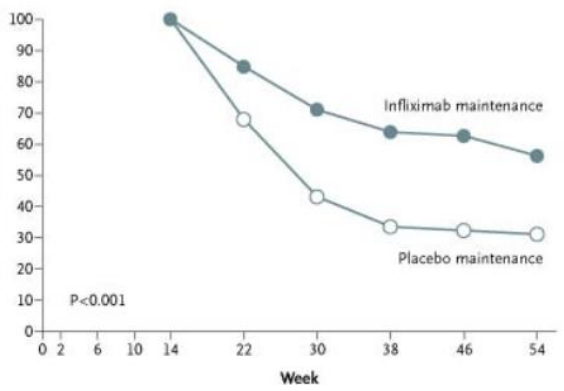
Because of unresponsive disabling disease, the possibility of anti-TNF treatment was discussed with the patient and her parents. Written consent was obtained. She was infused twice over a fortnight with anti-TNFα (chimeric monoclonal cA2,



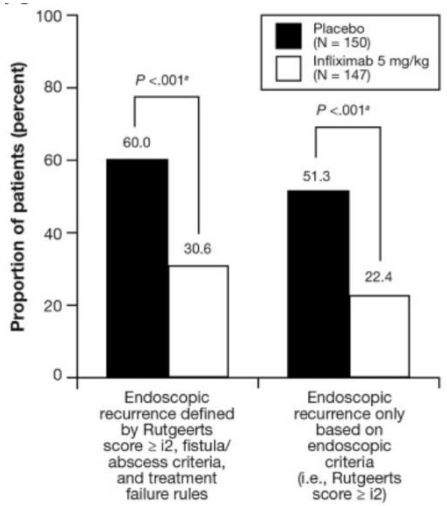
Derkx B, et al. Lancet 1993;342(8864):173-4.

Anti-TNF- Still very relevant today!

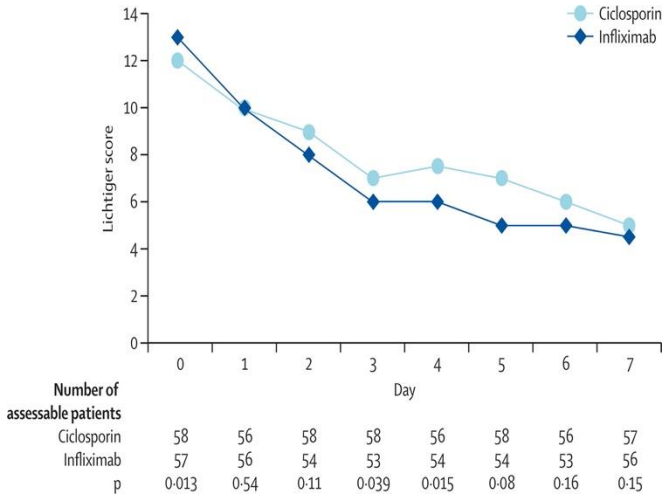
Peri-Anal CD (ACCENT 2)



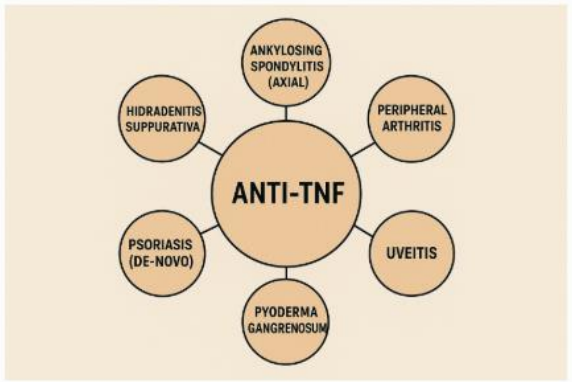
Post-Op Prophylaxis (PREVENT)



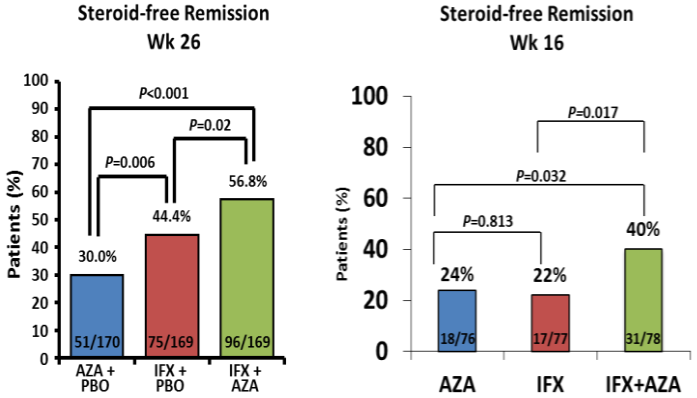
ASUC (CySIF)



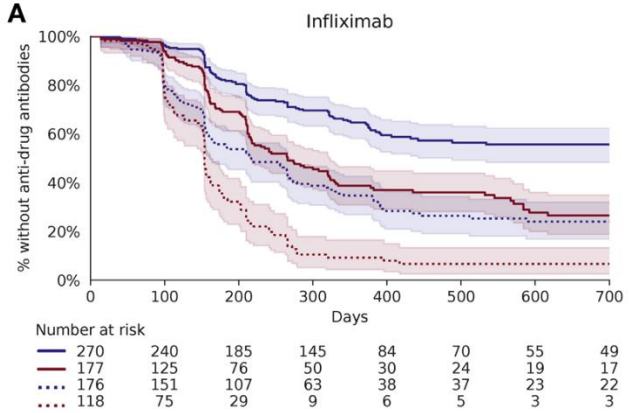
EIMs



Use combo therapy

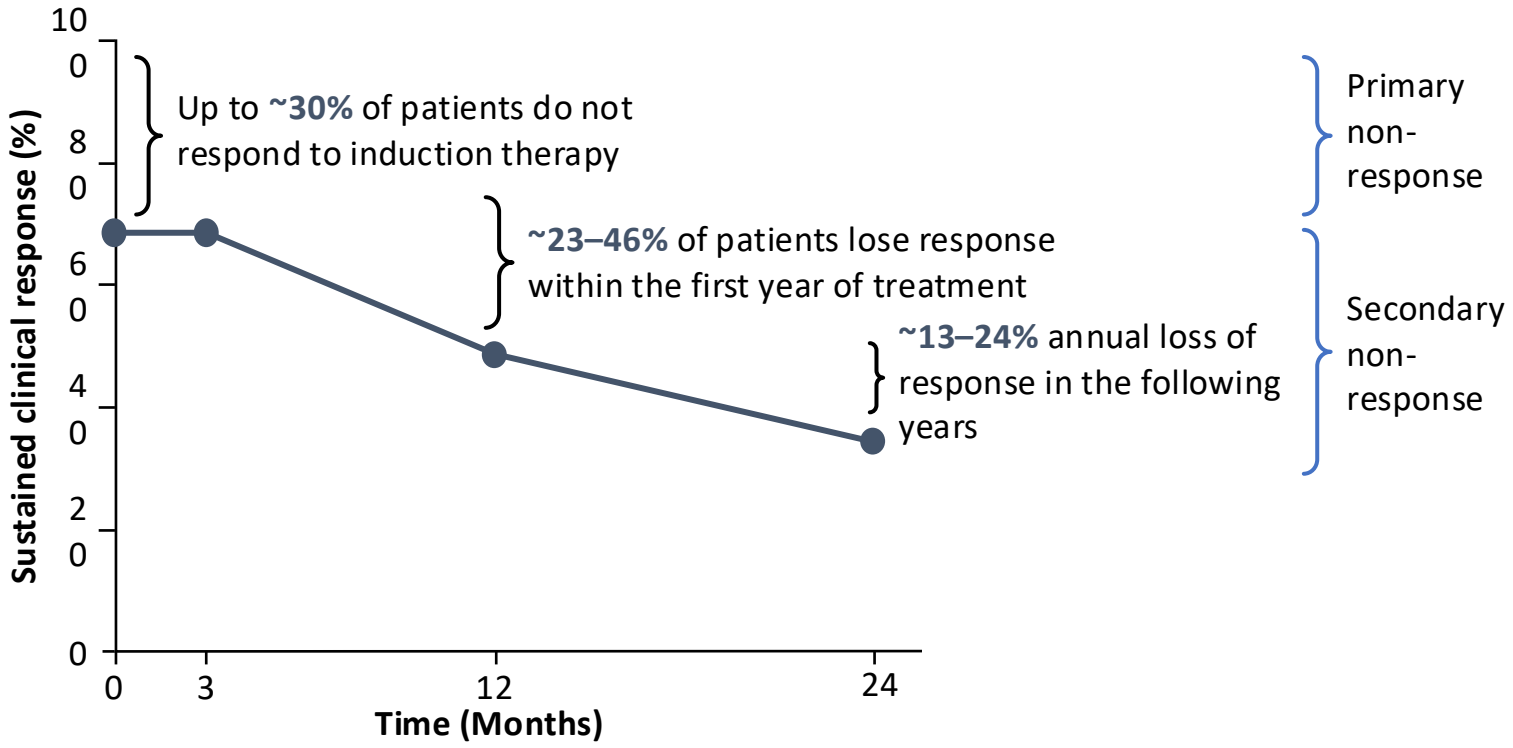


HLA testing



Anti-TNF remain a cornerstone but have limitations

Treatment response rates with infliximab and adalimumab in CD[1,2]



Anti-TNF Safety Issues

- Infection and malignancy
  - Black-box warning for serious infection and malignancy for all anti-TNF therapies[1-3]
  - Black-box warning for HSTCL (adalimumab and infliximab)[1,2]
- Reactivation of hepatitis B[3], tuberculosis
- Skin cancer[3]
- Psoriasis[4]
- Autoimmunity (lupus-like syndrome)[3]
- Immunogenicity – antibodies to anti-TNF[3]
- Demyelinating disorders, CHF, liver toxicity[3]

CHF=congestive heart failure; HSTCL= hepatosplenic T-cell lymphoma

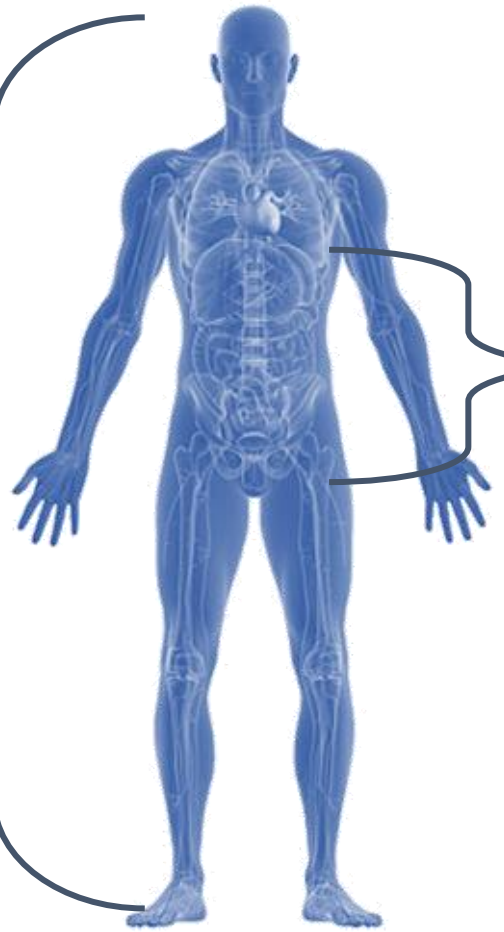
[1]Remicade [package insert]. Horsham, PA: Janssen Biotech, Inc; 2013
[2]Humira [package insert]. North Chicago, IL: AbbVie, Inc; 2013
[3]Bongartz T, et al. *JAMA.* 2006;295:2275-2285

Anti-Integrins

Vedolizumab

Systemic

Anti-TNFα	Infliximab Adalimumab	Anti-interleukin	Ustekinumab Risankizumab Mirikizumab
JAK inhibitor	Tofacitinib Filgotinib Upadacitinib	S1P inhibitor	Ozanimod Etrasimod

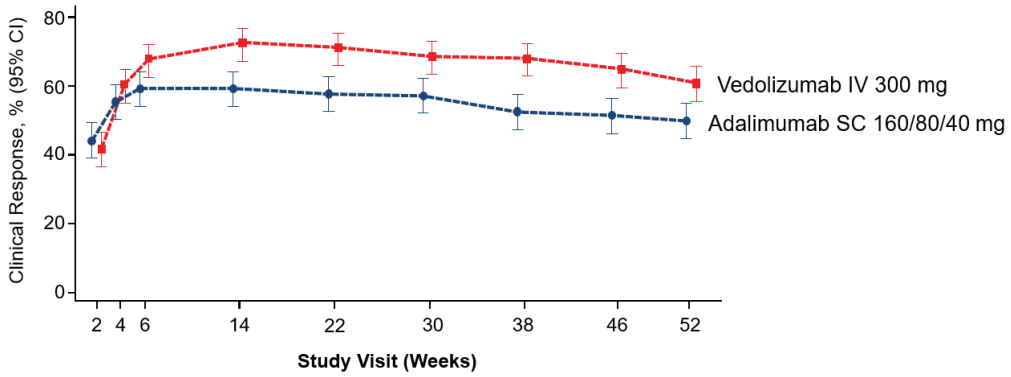


Gut-specific

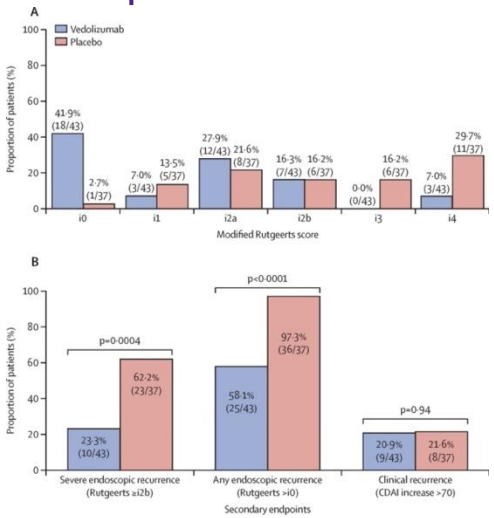
Anti-integrin	Vedolizumab

Vedolizumab

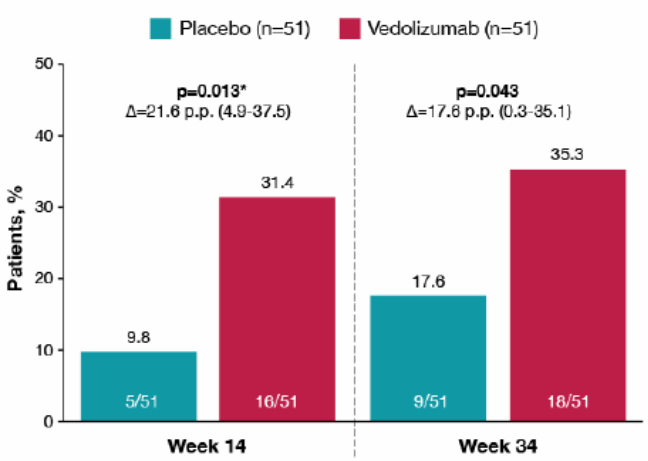
Superior to ADA in UC: VARSITY



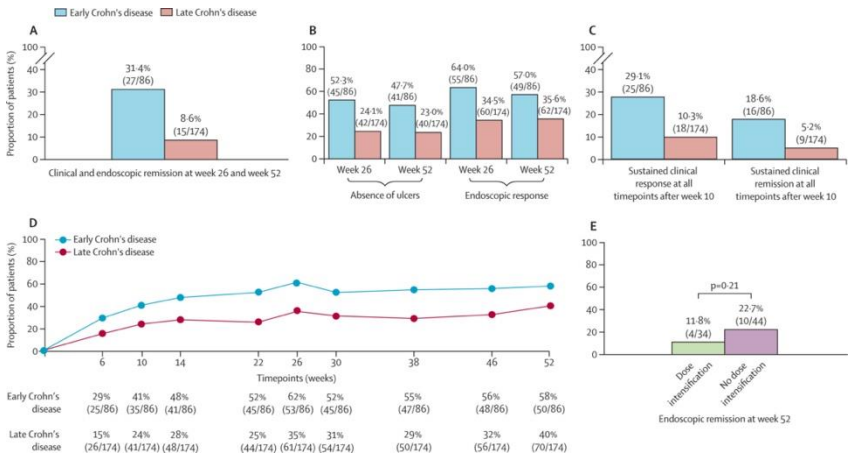
Post-Op CD Prevention: REPREVIO



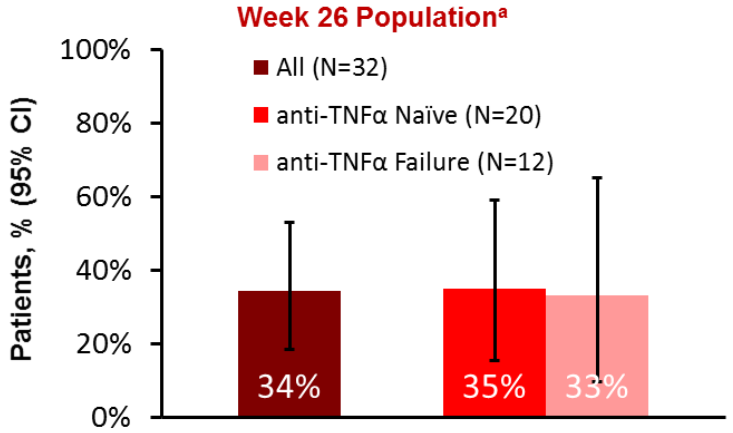
Chronic Pouchitis: EARNEST



Early CD: LOVE CD



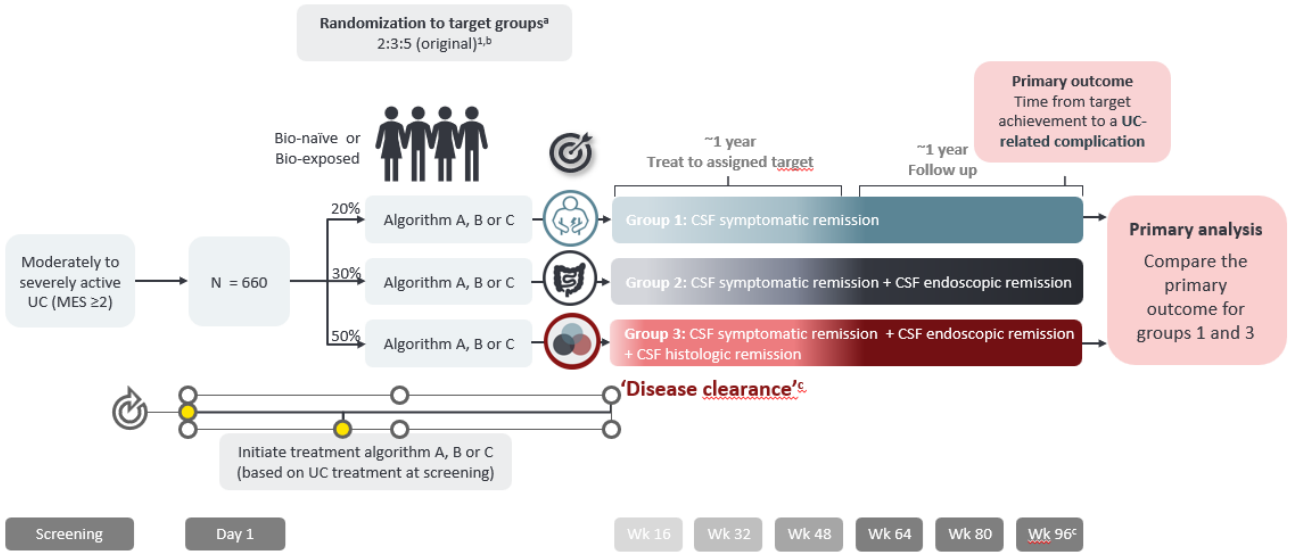
Transmural Healing: VERSIFY



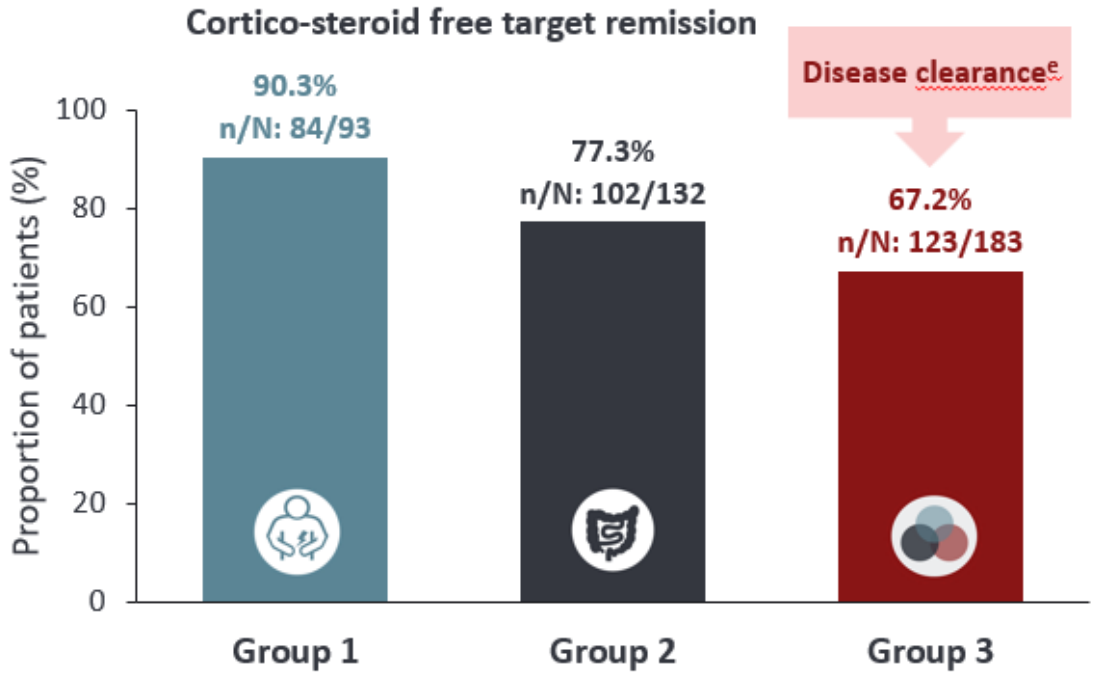
Western

Vedolizumab and Disease Clearance: VERDICT trial

Trial Design



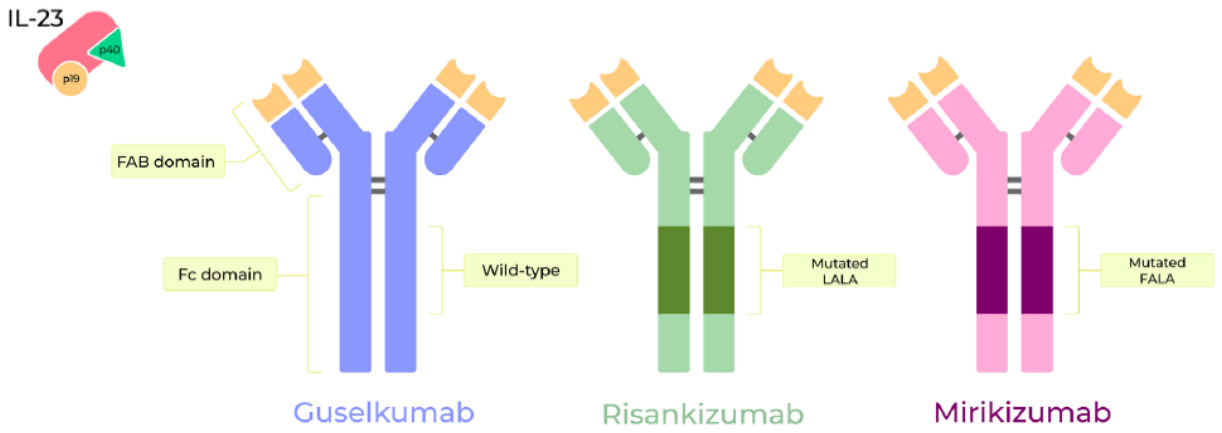
48 Week Disease Clearance



Jairath V. et al, ECCO 2025

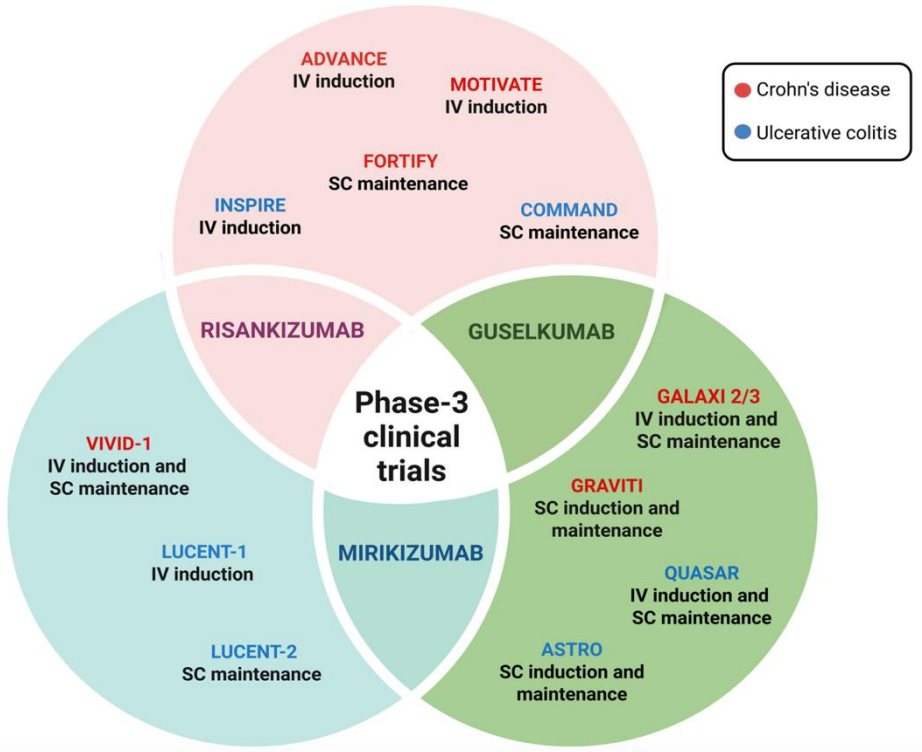
Interleukin Inhibitors

IL-23 Inhibitors: No Clinically meaningful differences to date



	Guselkumab	Risankizumab	Mirikizumab
Antibody structure	Fully human	Humanized	Humanized
Isotype	IgG1	IgG1	IgG4
Antigen	IL-23 p19	IL-23 p19	IL-23 p19
Fc domain	Wild-type	Mutated (LALA)	Mutated (FALA)

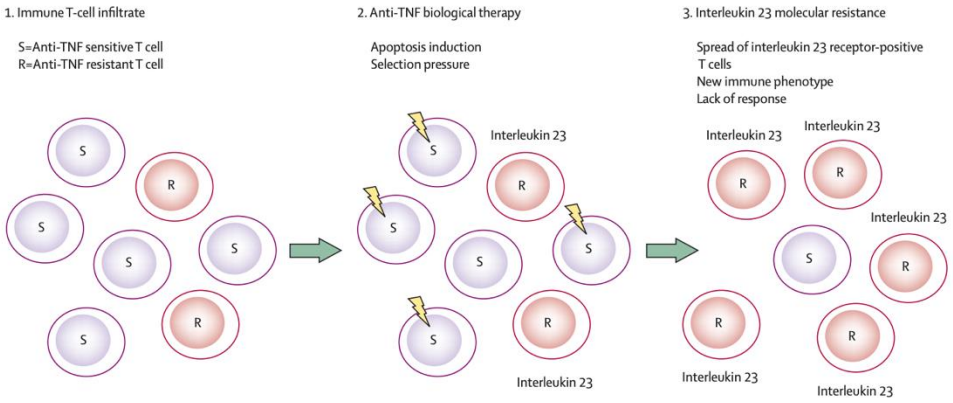
Fc, fragment crystallizable; **FAB**, fragment antigen-binding; **LALA**, leucine to alanine substitution at positions 234 and 235; **FALA**, phenylalanine to alanine substitution and leucine to alanine substitution at positions 234 and 235;



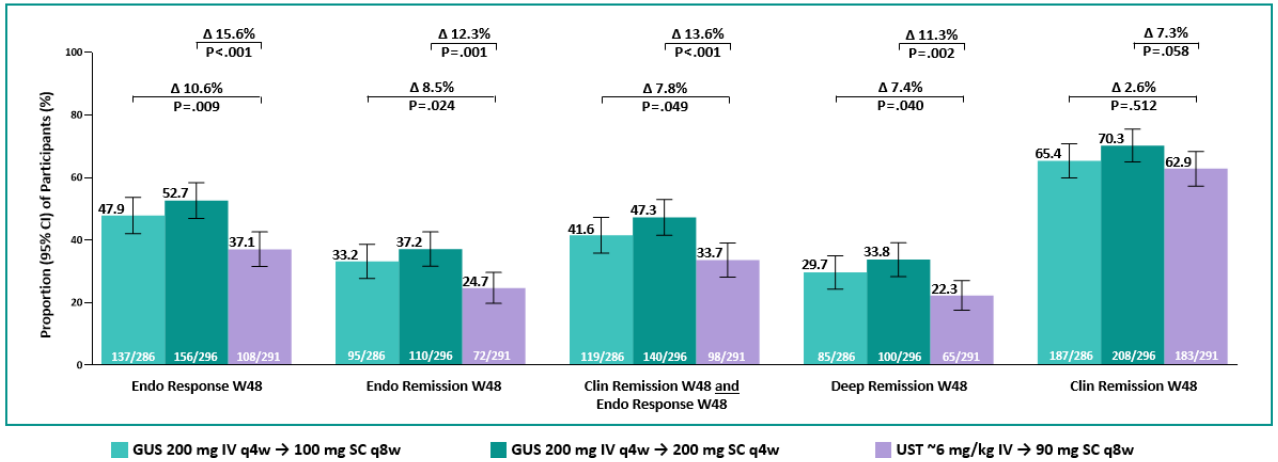
Nardone O. et al, Drugs 2025

IL-23 Inhibition has moved the needle

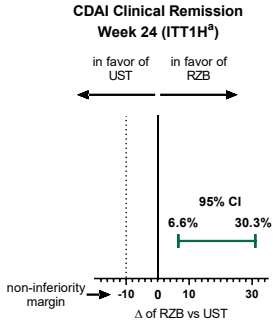
Evolutional pressure of immune therapy and drug resistance

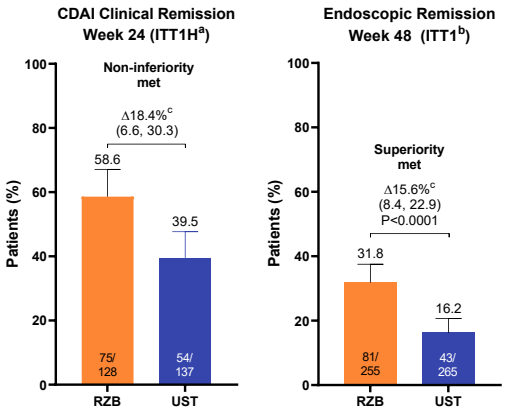


GALAXI 2&3 trials



SEQUENCE trial

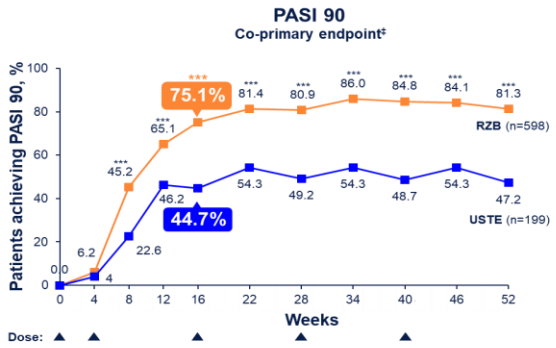


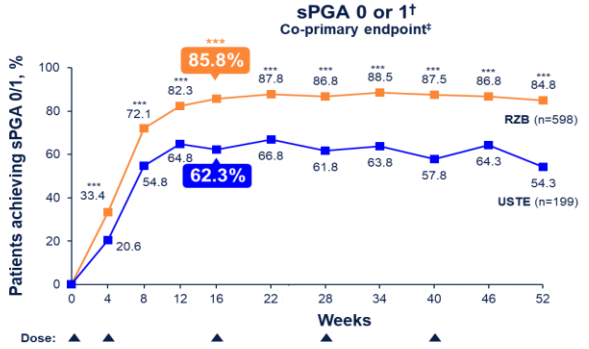


Nominal *P* <0.01 from a post hoc analysis testing for superiority

UltIMMa 1&2 trials

UltIMMa-1 and -2: Two replicate 52-week, randomized, double-blind, PBO-controlled comparative studies of RZB vs USTE (integrated analyses, NRI)





Arrows indicate RZB/USTE dosing. Efficacy analyses performed using the intention-to-treat population (all randomized patients).
***p<0.001. ‡sPGA defined as 0 (clear) or 1 (almost clear). ‡Co-primary endpoints were assessed at Week 16.
IL, interleukin; NRI, non-responder imputation; PASI, Psoriasis Area and Severity Index; PBO, placebo; RZB, risankizumab; sPGA, static Physician's Global Assessment; USTE, ustekinumab.
Lebwohl M, et al. Presented at the American Academy of Dermatology Annual Meeting, 1–5 March 2019, Washington DC, USA. Poster 8108.

Western

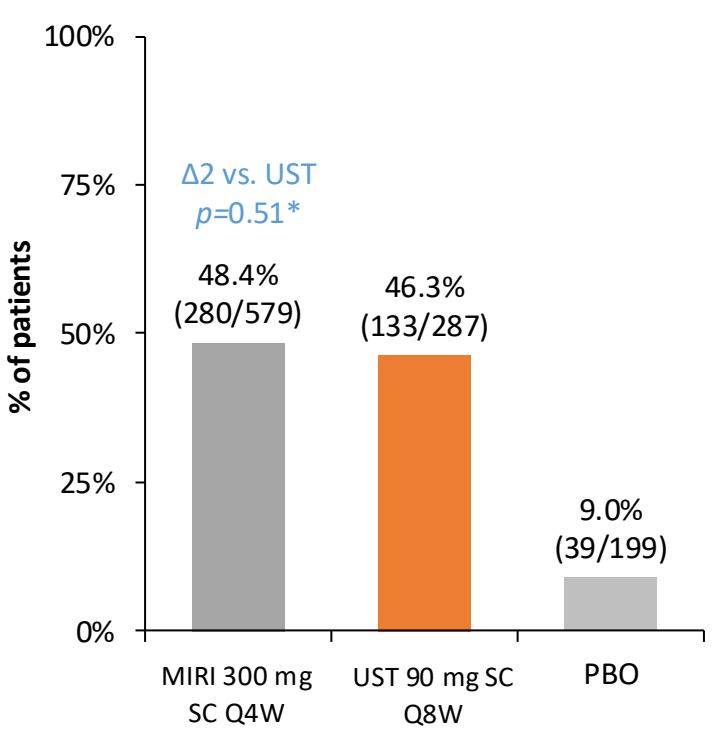
Atreya R, Neurath M. Lancet Gastroenterol Hepatol. 2018
Peyrin-Biroulet L, et al. NEJM 2024.
Panaccione R et al. DDW 2024 Late breaking abstract

Active Comparator Studies and Mucosal Healing Differentiates the IL-23 Class

These figures are intended to be a summary of individual clinical trial data only and direct comparisons between trials cannot be made.

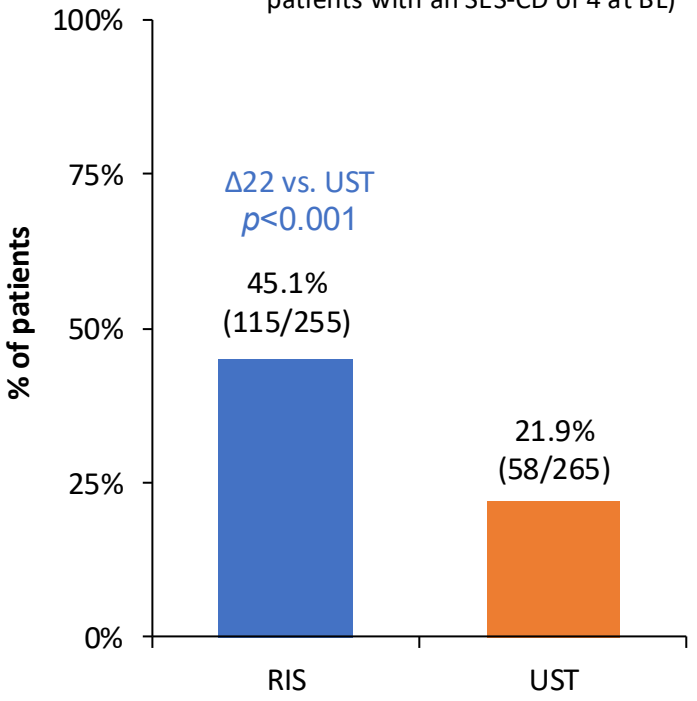
VIVID-1
Week 52, NRI[1]

Endoscopic response: ≥50% reduction from BL in SES-CD total score



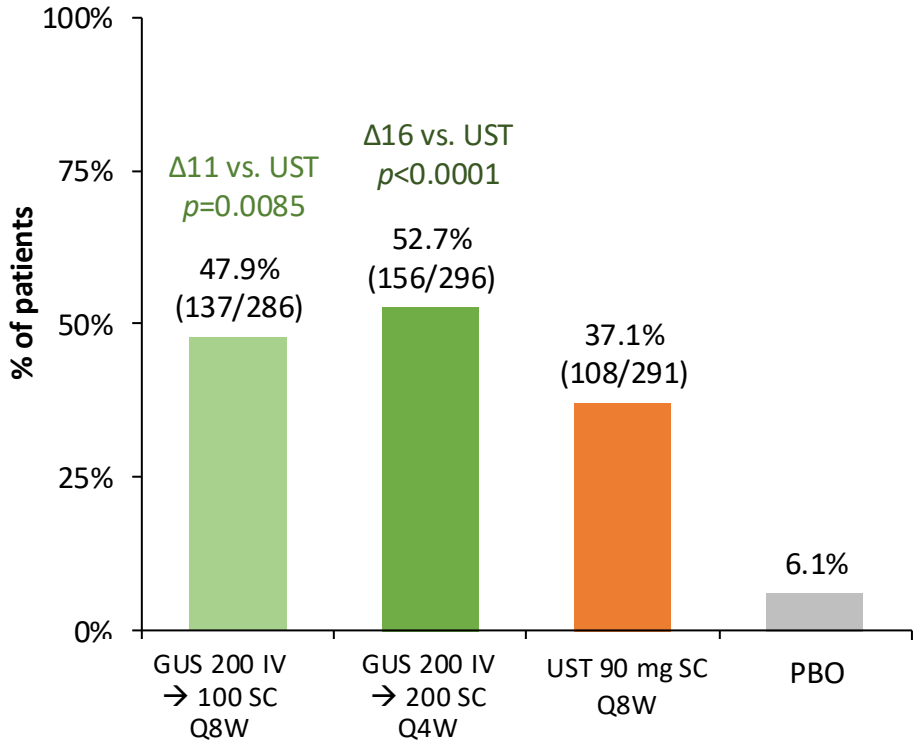
SEQUENCE
Week 48, NRI[2]

Endoscopic response: ≥50% reduction from BL in SES-CD total score (or a decrease of ≥ 2 points from BL in patients with an SES-CD of 4 at BL)



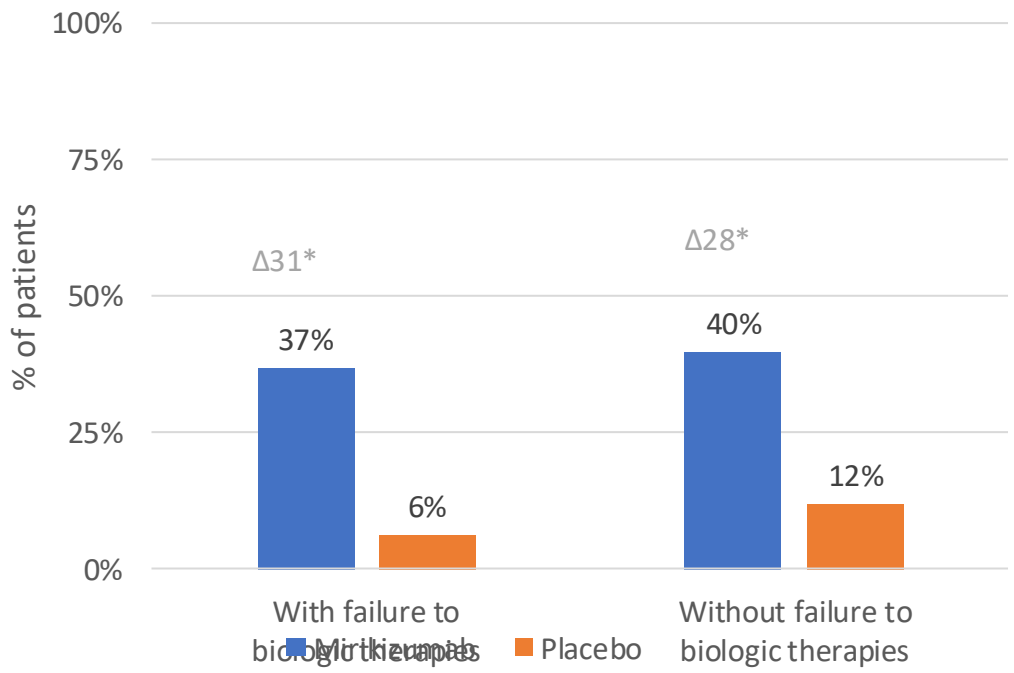
Pooled GALAXI 2 & 3
Week 48, NRI[3]

Endoscopic response: ≥50% reduction from BL in SES-CD total score or SES-CD ≤ 2

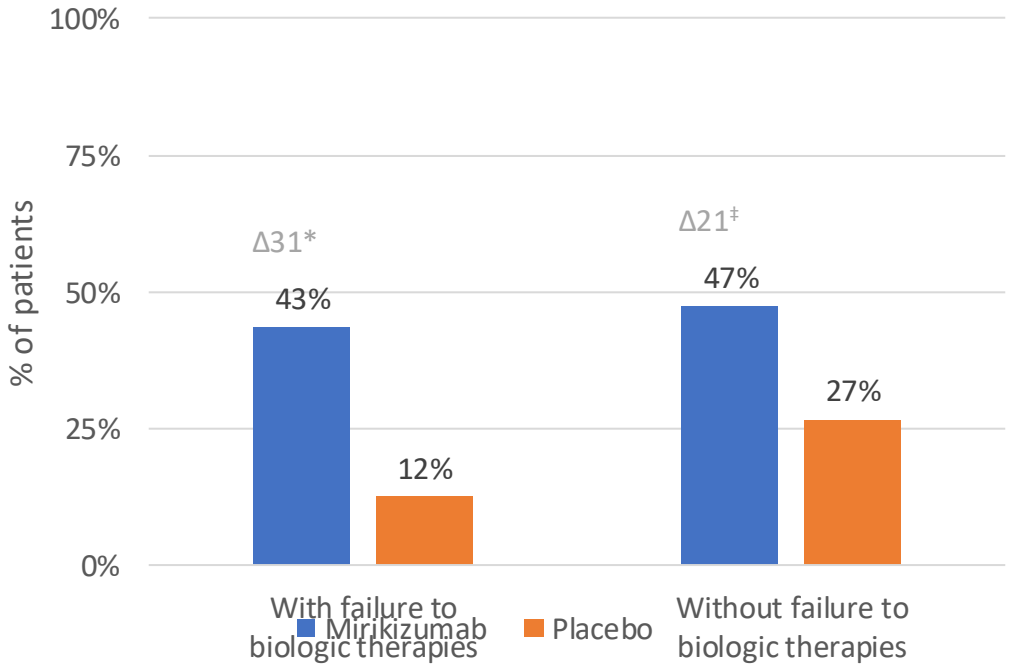


IL-23s have similar efficacy in bionaive and bioexposed patients

PRO Clinical Response[a] at Week 12 and SES-CD Endoscopic Response[b] at Week 52



PRO Clinical Response[a] at Week 12 and CDAI Clinical Remission[c] at Week 52

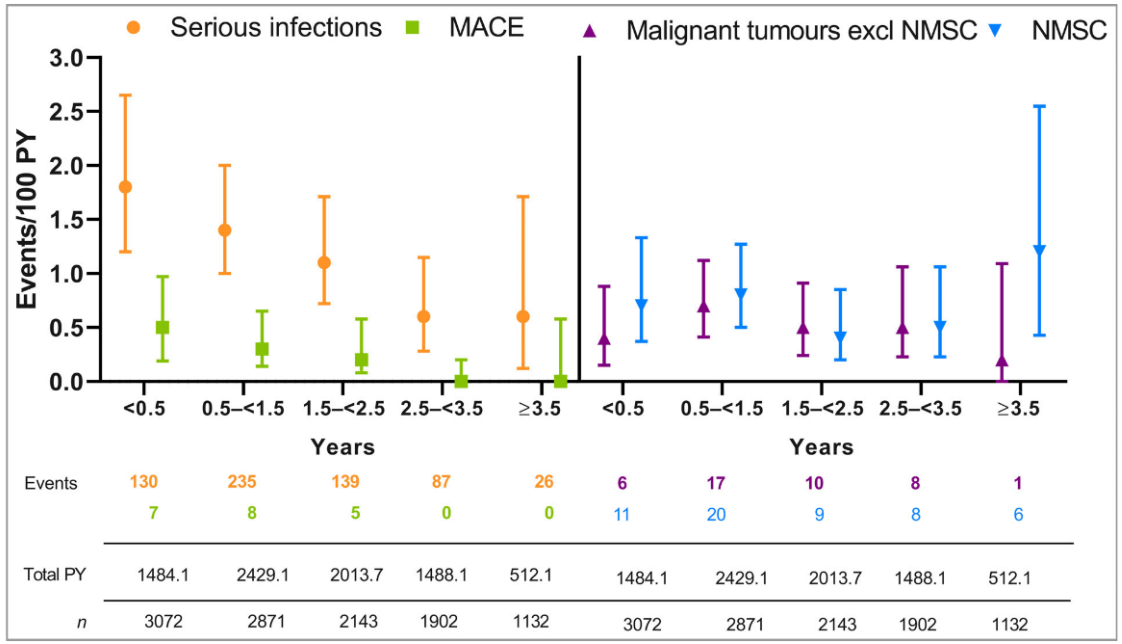


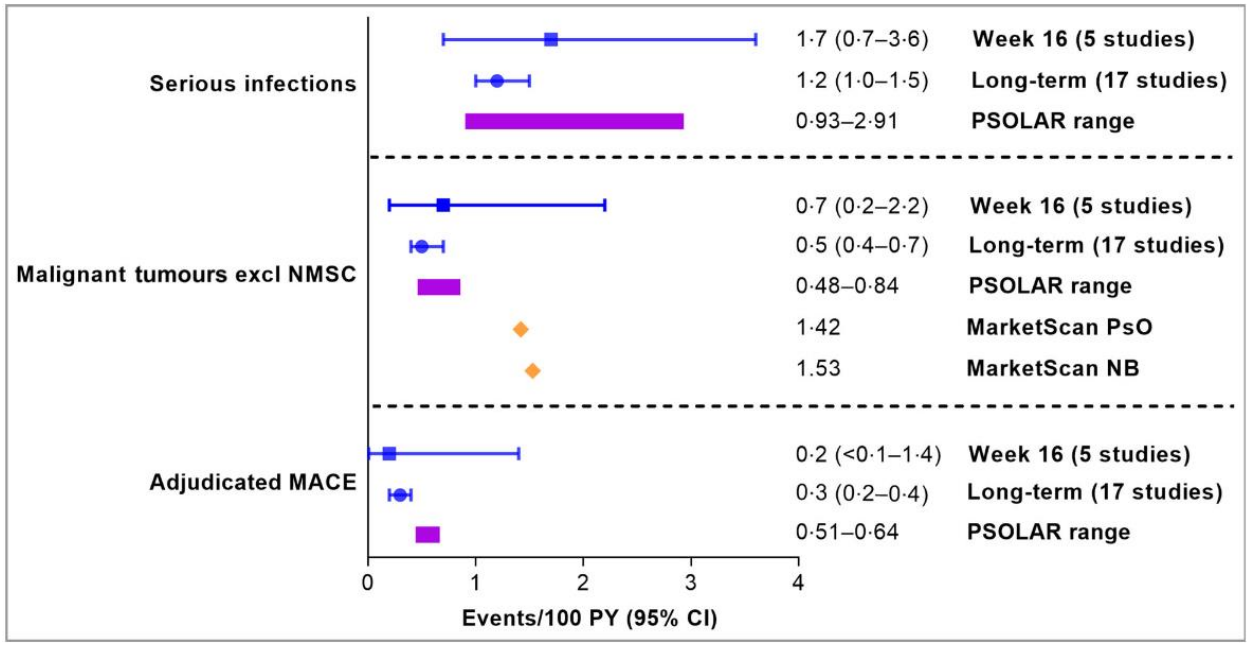
CLINICAL TRIAL

BJD
British Journal of Dermatology

Long-term safety of risankizumab from 17 clinical trials in patients with moderate-to-severe plaque psoriasis*

K.B. Gordon,[1] M. Lebwohl,[2] K.A. Papp,[3] H. Bachelez,[4] J.J. Wu,[5] R.G. Langley,[6] A. Blauvelt,[7] B. Kaplan,[8] M. Shah,[8] Y. Zhao,[8] R. Sinvhal[8] and K. Reich[9]

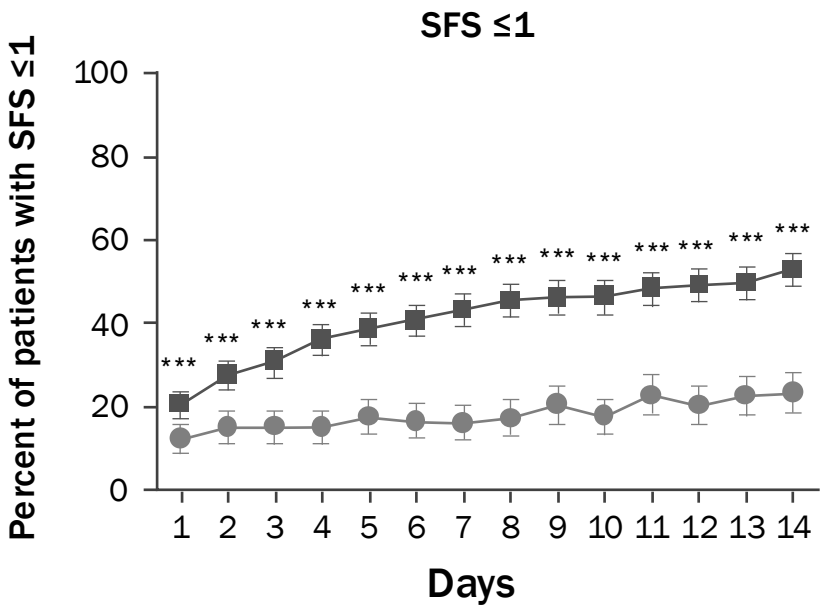




JAK Inhibition

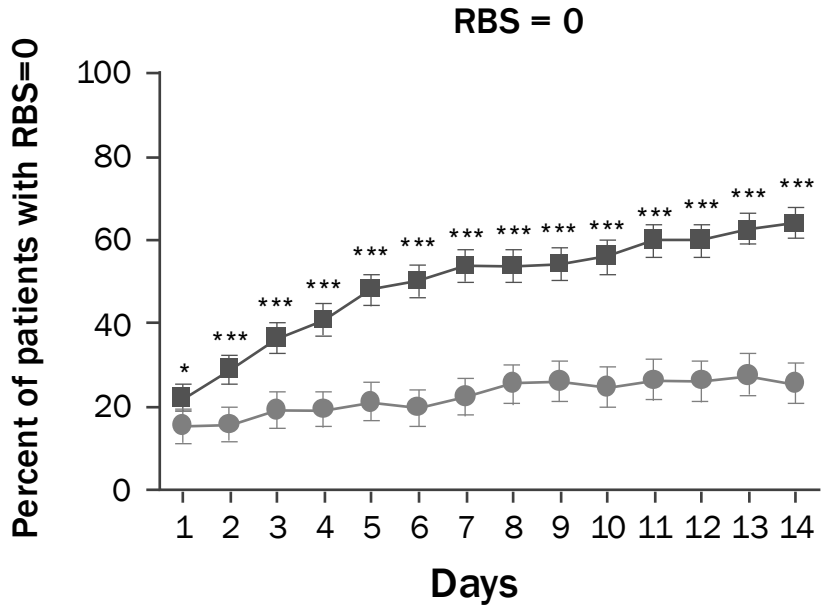
JAKs work very fast

***Post-hoc* analysis: Pooled analysis from U-ACHIEVE and U-ACCOMPLISH**
Symptom relief (SFS ≤1 and RBS = 0) Day 1 through to Day 14



Percent of patients:	12.3	16.2	23.4
	20.7	43.3	53.0

PBO (n=303–319) UPA 45 mg QD (n=613–634)



Percent of patients:	15.2	22.3	25.4
	21.9	53.7	64.3

PBO (n=303–319) UPA 45 mg QD (n=616–634)

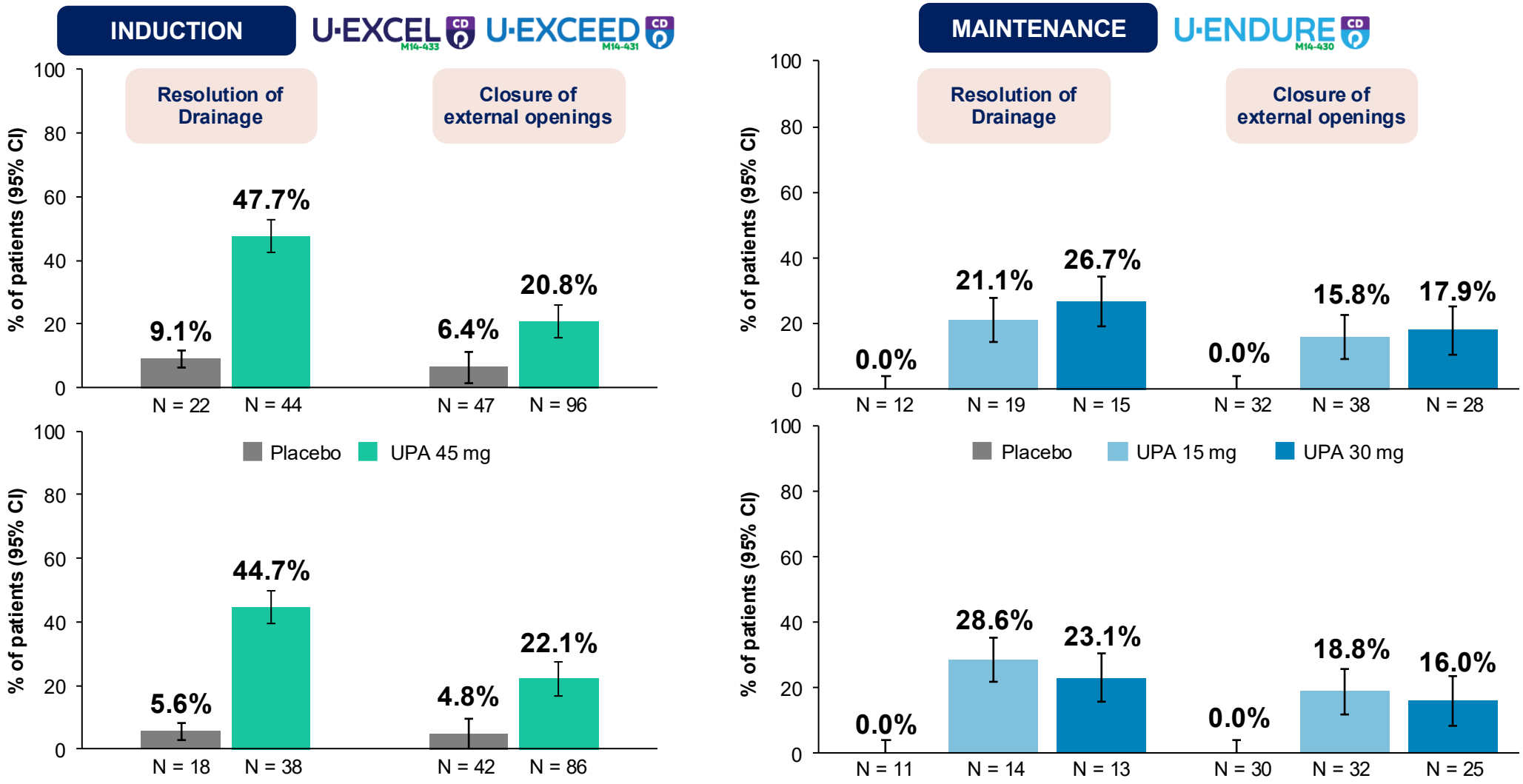
Error bars are ± 95% CI. *p≤0.05; **p≤0.01; ***p≤0.001 vs PBO. P-values are nominal and not multiplicity controlled. No clinical inferences can be drawn.
PBO, placebo; QD, once daily; RBS, rectal bleeding subscore; SE, standard error; SFS, stool frequency subscore; UPA, upadacitinib.

1. Loftus EV Jr, et al. *Clin Gastroenterol Hepatol.* 2022;S1542-3565(22)01109-0; 2. Danese S, Vermeire S, et al. *Lancet*. 2022;399(10341):2113-2128 and supplementary data.

May be beneficial for fistulas: Post hoc trial anlaysis

Any Fistulas

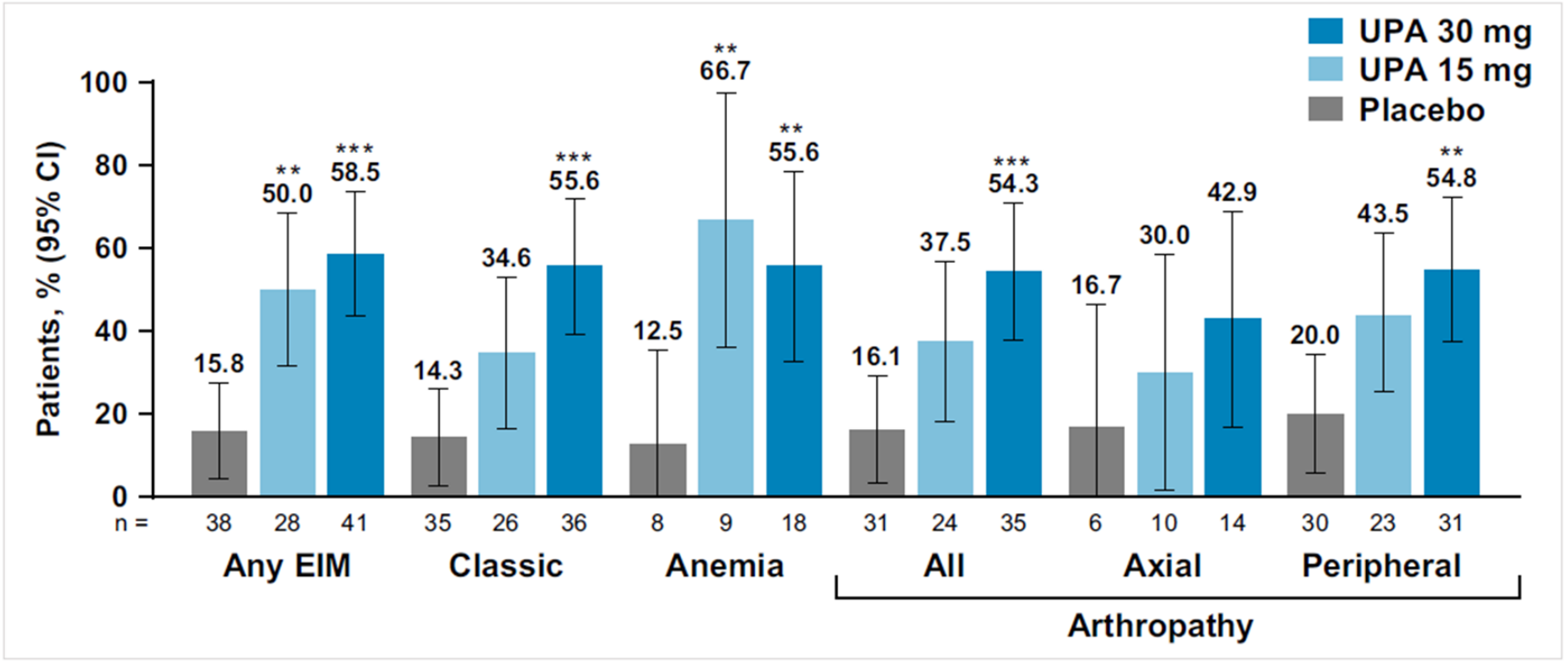
Perianal fistulas



Western

Should be our first choice for EIMs: Post hoc trial analysis

Figure 5. Continuous EIM Resolution From Week 0 Through 52 of Maintenance Therapy



EIM, extraintestinal manifestation; UPA, upadacitinib.

The proportion of patients achieving continuous EIM resolution was calculated based on the total number of patients with resolution of each EIM or EIM category at week 0 of maintenance therapy. *P* values and 95% CI were calculated based on the normal approximation to the binomial distribution. *P* values were nominal and not multiplicity adjusted.

$^{**}P \leq .01$. $^{***}P \leq .001$.

Approved Indications for Upadacitinib in Canada

- Rheumatoid Arthritis (RA)
- Psoriatic Arthritis (PsA)
- Atopic Dermatitis (Adults & Adolescents ≥12 years)
- Ankylosing Spondylitis (AS)
- Non-radiographic Axial Spondyloarthritis (nr-axSpA)
- Ulcerative Colitis (UC)
- Giant Cell Arteritis (GCA)

JAKs have potential for management of ASUC

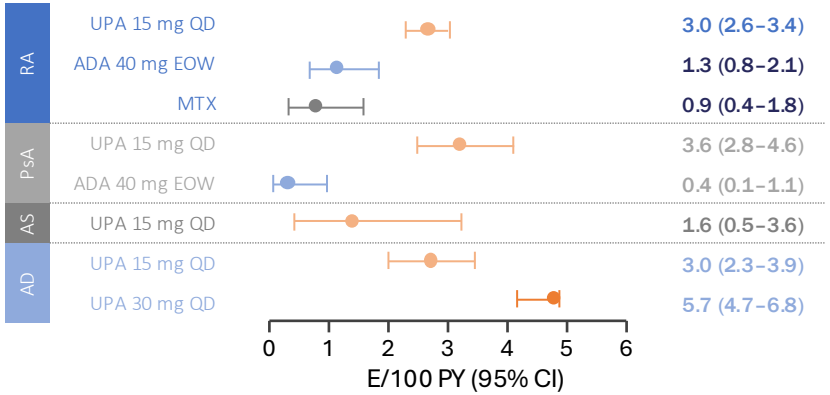
Upadacitinib for Acute Severe Ulcerative Colitis: A Systematic Review

John A. Damianos, MD,[*] Olufemi Osikoya, MD,[†] and Gregory Brennan, MD[‡]

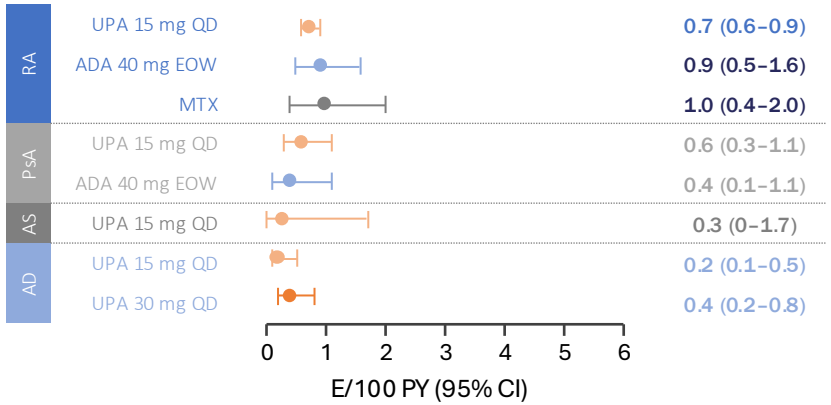
- **N=55** patients (11 studies, Largest with 25 pts)
- 76% previous IFX failure
- UPA given with steroids for induction (~50%) or after failing steroids (~50%)
- Colectomy rate at 90 days was 16.3%.
- Among those who did not get colectomy, 80% were in steroid-free remission at follow-up.
- The reported adverse events were low, including 2 venous thromboembolic events. **(~4% VTE)**

Integrated safety analysis of UPA based on more than 6000 patients and 15,000 PYs of exposure across RA, PsA, AS and AD Phase IIb/III trials

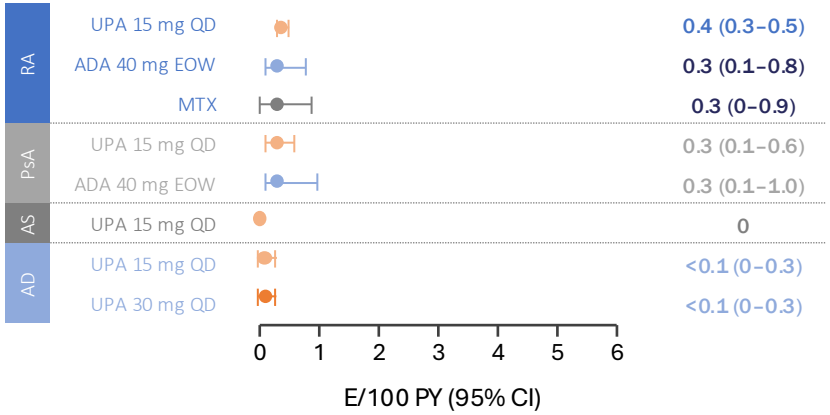
Herpes zoster



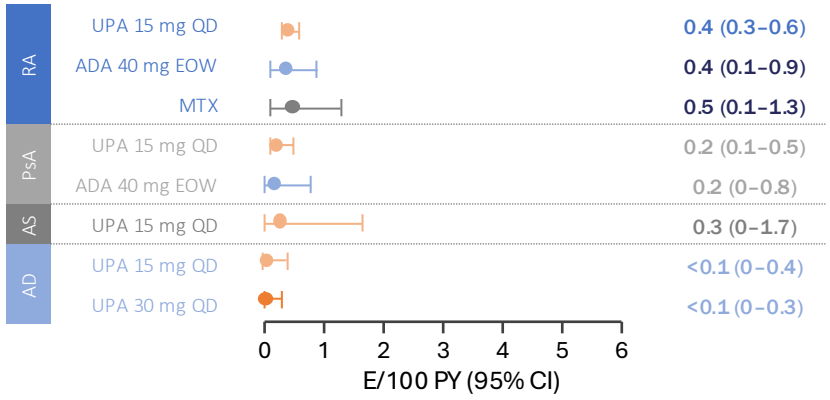
Malignancy (excl. NMSC)



MACE (adjudicated)‡



VTE (adjudicated)§



‡Defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. §Including deep vein thrombosis and pulmonary embolism.
AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CI, confidence interval; E, events; MACE, major adverse cardiac event; MTX, methotrexate; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis; PY, person-years; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib; VTE, venous thromboembolism.
Burmester GR, et al. *RMD Open*. 2023;9:e002735.

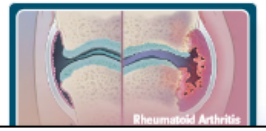
RESEARCH SUMMARY

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Ytterberg SR et al. DOI: 10.1056/NEJMoa2109927

CLINICAL PROBLEM

Tofacitinib — a targeted synthetic, disease-modifying, antirheumatic drug used to treat rheumatoid arthritis — was observed to increase serum lipid levels and the incidence of cancers during drug development. As a result, the FDA required a prospective trial of its safety as compared



- **In this trial, the number needed to harm for tofacitinib at a dose of 5 mg twice daily relative to a TNF inhibitor was 567 patient-years for MACE and 276 patient-years for cancers, which meant that during 5 years of treatment, 113 and 55 patients would need to be treated with tofacitinib at a dose of 5 mg twice daily rather than with a TNF inhibitor to result in one additional MACE and cancer, respectively**

anoma skin cancer were higher in both tofacitinib dose groups than in the TNF inhibitor group. Efficacy was similar with the use of tofacitinib or a TNF inhibitor.

LIMITATIONS

- The trial design was open-label, and discontinuation rates were high.
- The TNF inhibitor was adalimumab in North America and etanercept elsewhere.

Links: Full Article | NEJM Quick Take | Editorial

	Tofacitinib Doses		Tofacitinib Doses	
Incidence Rate* (95% CI)	0.98 (0.79 to 1.19)	0.73 (0.52 to 1.01)	1.13 (0.94 to 1.35)	0.77 (0.55 to 1.04)

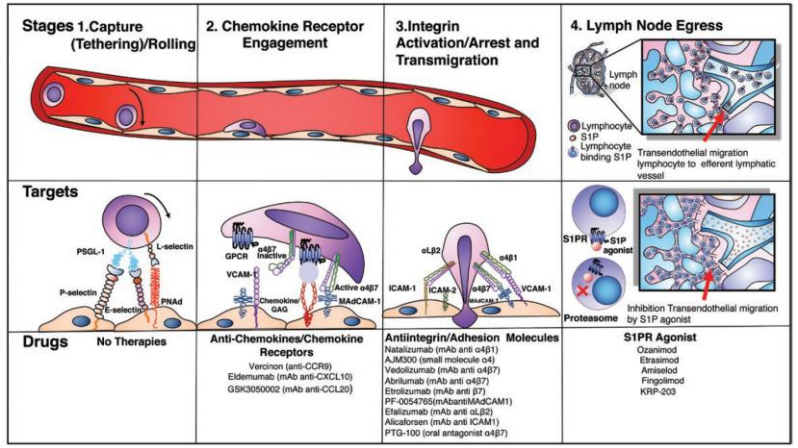
*Number of patients with first event per 100 patient-years.

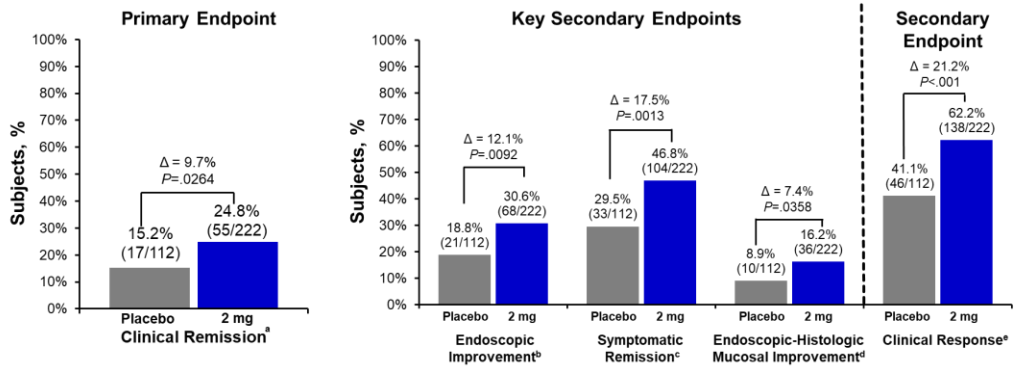
CONCLUSIONS

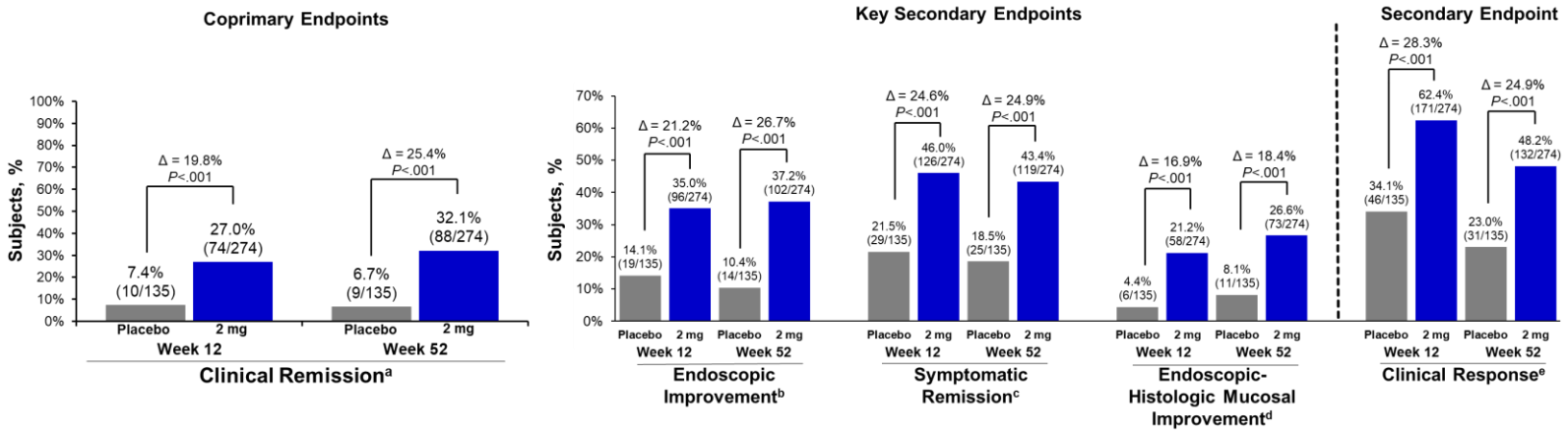
Risks of MACE and cancers were higher with tofacitinib than with TNF inhibitors among patients with rheumatoid arthritis; noninferiority of tofacitinib was not shown for these end points.

S1P1 Modulators

S1P Agonists: First line oral agents in UC







Western

Perez-Jeldres et al. *Inflamm Bow Dis* 2018 Aug 24.

Safety

It’s easy to put drugs into safety buckets…

Ustekinumab

Infectious risk

Vedolizumab

Infectious risk

Specific risks
- Headache (IV)
- Local reactions (SC)

Anti-IL23

Infectious risk

Moderate liver enzymes elevation

Anti-TNF

Infectious risk
- Tuberculosis
- Pneumonia (> 65 years)

Skin complications
- Paradoxal lesions
- Folliculitis
- Mélanoma ?

Specific risks
- Infusion-related reactions
- Serum-like disease

\+

Risk due to combination with thopurines

Anti-JAK

Infectious risk
- Herpes zoster

Skin complications
- Acnea-like leasions

Blood count
- Moderate lymphopenia

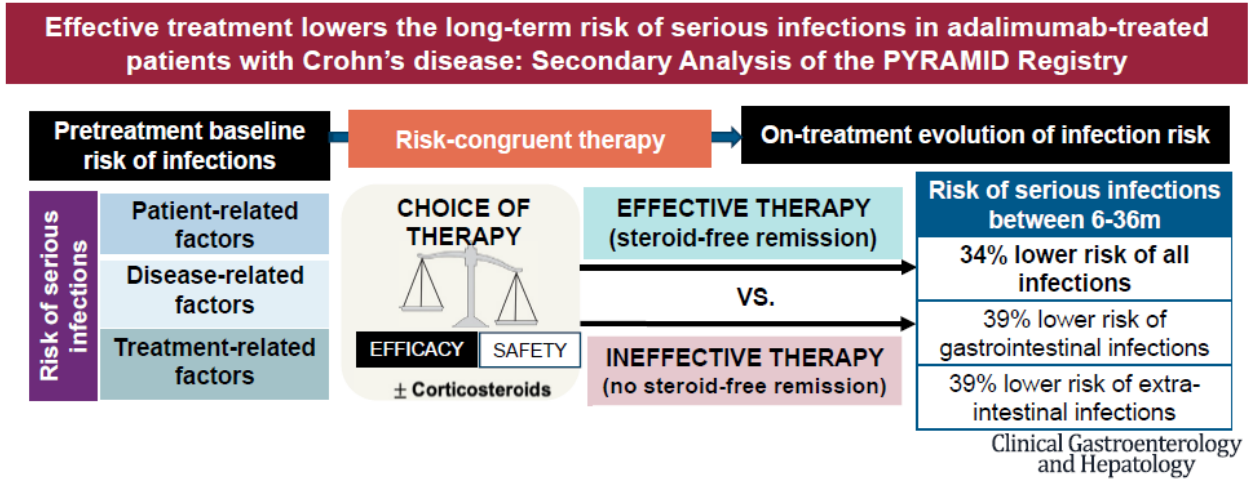
<u>Only for patients at risk*:</u>
- MACE
- Thromboembolism events
- Tumoral risk

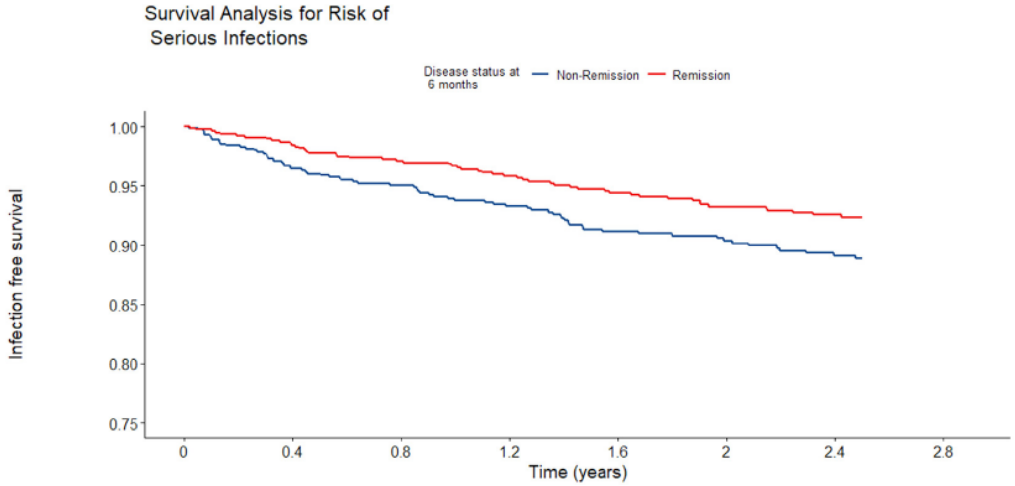
<u>*Patients at risk:</u>
- Age > 65 ans
- CV risk factors
- Cancer risk factors (long-lasting smokers)
- Risk factors of Thromboembolism events

Elderly

Safety profile

Efficacy trumps safety and lowers the risk of infections



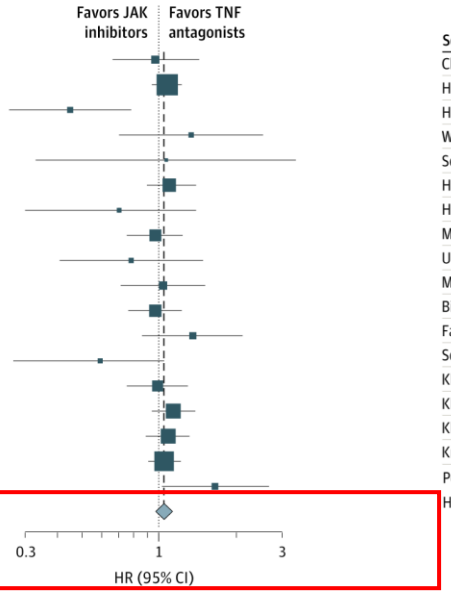


Comparative Safety of JAK Inhibitors vs TNF Antagonists in Immune-Mediated Inflammatory Diseases

Serious Infection

Source	JAK inhibitors: No. of patients with serious infection/total No. in cohort	JAK inhibitors: IR per 100 person-years (95% CI)	TNF antagonists: No. of patients with serious infection/total No. in cohort	TNF antagonists: IR per 100 person-years (95% CI)	HR (95% CI)
Ahuja et al,[52] 2025	58/856	4.85 (3.55-6.14)	891/9422	5.37 (5.00-5.74)	0.97 (0.66-1.44)
Cho et al (RA),[40] 2025	449/4992	4.80 (4.36-5.25)	868/4992	3.70 (3.50-3.99)	1.08 (0.94-1.23)
Cho et al (UC),[40] 2025	14/548	2.60 (1.23-3.95)	166/548	6.80 (5.78-7.86)	0.45 (0.26-0.78)
Tanaka et al,[51] 2024	14/253	2.46 (1.04-3.86)	27/663	2.63 (1.81-3.65)	1.34 (0.70-2.56)
Bastard et al,[29] 2024	5/152	3.48 (0.43-6.52)	150/4616	1.89 (1.59-2.19)	1.07 (0.33-3.44)
Hernández-Cruz et al (RA),[20] 2024	156/1386	4.93 (4.21-5.77)	199/2861	3.09 (2.69-3.55)	1.10 (0.90-1.40)
Hernández-Cruz et al (SpA),[20] 2024	7/256	1.86 (0.89-3.91)	194/3218	1.88 (1.64-2.17)	0.70 (0.30-1.40)
Frisell et al,[31] 2023	130/2263	3.29 (2.72-3.86)	240/8748	3.08 (2.83-3.33)	0.97 (0.75-1.24)
Uchida et al,[38] 2023	40/296	8.36 (7.79-8.93)	16/203	4.07 (3.67-4.47)	0.78 (0.41-1.49)
Choi et al,[17] 2023	48/2963	1.39 (1.05-1.85)	61/5169	1.32 (1.03-1.69)	1.04 (0.71-1.52)
Mok et al,[28] 2024	92/551	8.24 (6.56-9.93)	314/1920	5.91 (5.25-6.56)	0.97 (0.76-1.23)
Salinas et al,[12] 2023	176/7606	2.96 (2.53-3.40)	145/7606	2.19 (1.83-2.54)	1.36 (0.86-2.13)
Cheng et al,[30] 2022	17/305	8.99 (4.72-13.27)	1407/19096	7.35 (6.96-7.73)	0.59 (0.27-1.05)
Kremer et al,[36] 2021	90/1999	3.12 (2.51-3.84)	333/8358	2.83 (2.54-3.15)	0.99 (0.75-1.30)
Pawar et al (Optum),[11] 2020	49/2009	3.14 (2.26-4.02)	438/24968	2.56 (2.32-2.80)	1.14 (0.94-1.39)
Pawar et al (MarketScan),[11] 2020	58/2755	2.30 (1.71-2.89)	759/52741	1.77 (1.64-1.90)	1.09 (0.89-1.32)
Pawar et al (Medicare),[11] 2020	72/1515	6.64 (5.11-8.17)	1179/27423	6.33 (5.96-6.69)	1.05 (0.91-1.22)
de Ávila Machado et al,[15] 2018	17/164	3.67 (2.21-5.75)	490/13367	2.16 (1.98-2.36)	1.66 (1.03-2.70)
Pooled summary		5.26 (5.05-5.48)		3.96 (3.88-4.05)	1.05 (0.97-1.13)

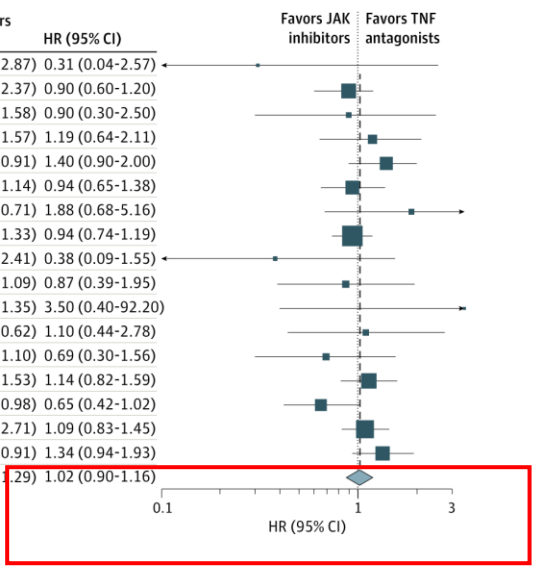
Heterogeneity: $\chi^2_{17} = 21.3$ ($P = .21$); $I^2 = 20.4\%$



Malignant Neoplasm

Source	JAK inhibitors: No. of patients with malignant neoplasms/ total No. in cohort	JAK inhibitors: IR per 100 person-years (95% CI)	TNF antagonists: No. of patients with malignant neoplasms/ total No. in cohort	TNF antagonists: IR per 100 person-years (95% CI)	HR (95% CI)
Cho et al,[40] 2024	1/200	0.52 (0.00-1.54)	7/455	1.69 (0.43-2.87)	0.31 (0.04-2.57)
Hernández-Cruz et al (RA),[20] 2024	63/1386	1.99 (1.55-2.55)	128/3513	1.99 (1.67-2.37)	0.90 (0.60-1.20)
Hernández-Cruz (SpA),[20] 2024	4/256	1.06 (0.40-2.84)	138/3313	1.34 (1.13-1.58)	0.90 (0.30-2.50)
Westermann et al,[26] 2024	19/875	1.44 (0.79-2.09)	92/3758	1.31 (1.04-1.57)	1.19 (0.64-2.11)
Sendaydiego et al,[45] 2024	22/2570	0.94 (0.59-1.43)	162/20586	0.78 (0.66-0.91)	1.40 (0.90-2.00)
Huss et al (RA),[34] 2023	38/2143	0.83 (0.65-1.25)	213/8580	1.01 (0.87-1.14)	0.94 (0.65-1.38)
Huss et al (PsA),[34] 2023	5/379	0.73 (0.11-1.61)	73/4186	0.58 (0.44-0.71)	1.88 (0.68-5.16)
Min et al,[37] 2023	81/2498	1.27 (0.99-1.54)	648/9267	1.24 (1.14-1.33)	0.94 (0.74-1.19)
Uchida et al,[38] 2023	11/296	1.61 (0.80-2.88)	4/203	0.94 (0.26-2.41)	0.38 (0.09-1.55)
Mok et al,[28] 2023	9/551	0.81 (0.28-1.34)	45/1920	0.85 (0.60-1.09)	0.87 (0.39-1.95)
Bilgin et al,[39] 2022	3/145	0.85 (0.17-2.47)	1/114	0.24 (0.00-1.35)	3.50 (0.40-92.20)
Fang et al,[41] 2022	4/822	0.26 (0.01-0.51)	22/2357	0.44 (0.26-0.62)	1.10 (0.44-2.78)
Song et al,[23] 2022	7/1064	0.54 (0.26-1.14)	58/3865	0.85 (0.66-1.10)	0.69 (0.30-1.56)
Khosrow-Khavar et al (Optum),[45] 2022	48/3304	1.68 (1.24-2.23)	284/22106	1.36 (1.21-1.53)	1.14 (0.82-1.59)
Khosrow-Khavar et al (MarketScan),[45] 2022	24/4508	0.60 (0.39-0.90)	203/25003	0.86 (0.74-0.98)	0.65 (0.42-1.02)
Khosrow-Khavar et al (Medicare),[45] 2022	62/2692	2.70 (2.07-3.46)	546/25682	2.49 (2.29-2.71)	1.09 (0.83-1.45)
Kremer et al,[36] 2021	43/1999	1.01 (0.73-1.37)	119/8538	0.76 (0.63-0.91)	1.34 (0.94-1.93)
Pooled summary		1.19 (1.09-1.30)		1.24 (1.19-1.29)	1.02 (0.90-1.16)

Heterogeneity: $\chi^2_{16} = 17.0$ ($P = .38$); $I^2 = 6.0\%$

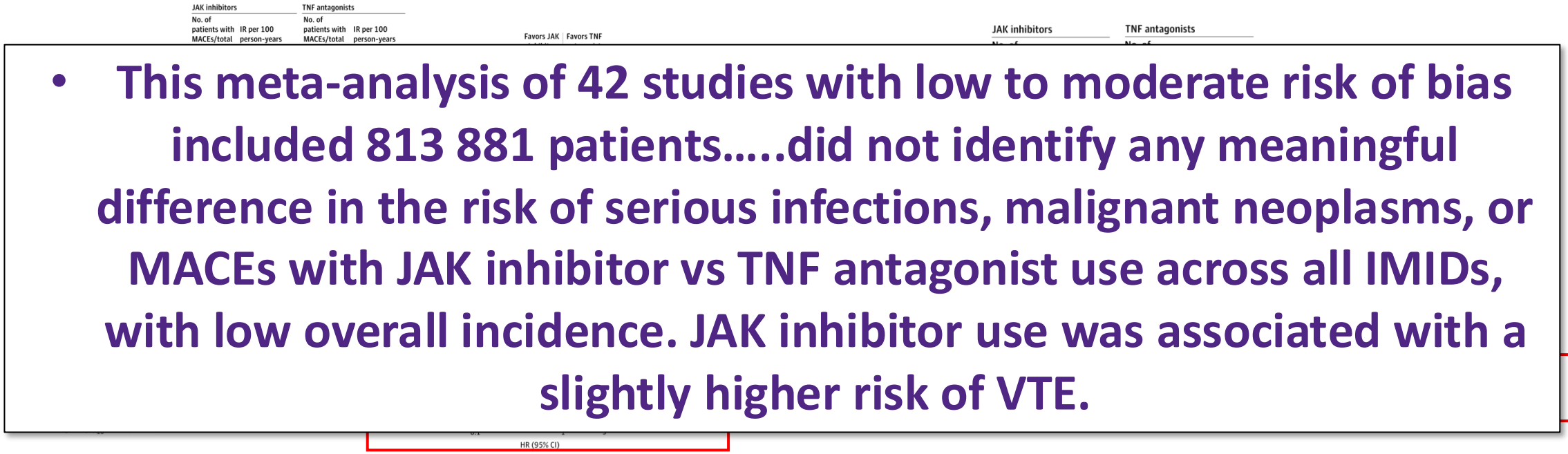


Solitano V. et al. JAMA Netw Open. 2025;8(9):e2531204.

Comparative Safety of JAK Inhibitors vs TNF Antagonists in Immune-Mediated Inflammatory Diseases

MACE

Thrombosis

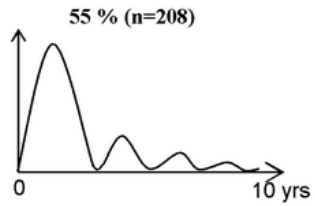


- This meta-analysis of 42 studies with low to moderate risk of bias included 813 881 patients…..did not identify any meaningful difference in the risk of serious infections, malignant neoplasms, or MACEs with JAK inhibitor vs TNF antagonist use across all IMIDs, with low overall incidence. JAK inhibitor use was associated with a slightly higher risk of VTE.

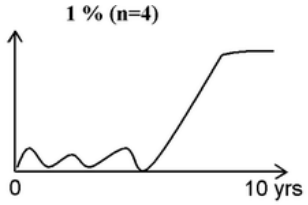
Solitano V. et al. JAMA Netw Open. 2025;8(9):e2531204.

Positioning of Drugs

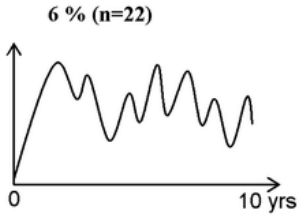
One size does not fit all



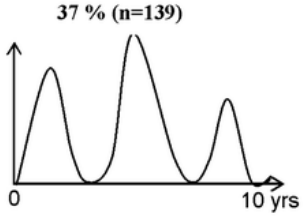
Curve1: Remission or mild severity of intestinal symptoms after initial high activity



Curve 2: Increase in the severity of intestinal symptoms after initial low activity



Curve 3: Chronic continuous symptoms



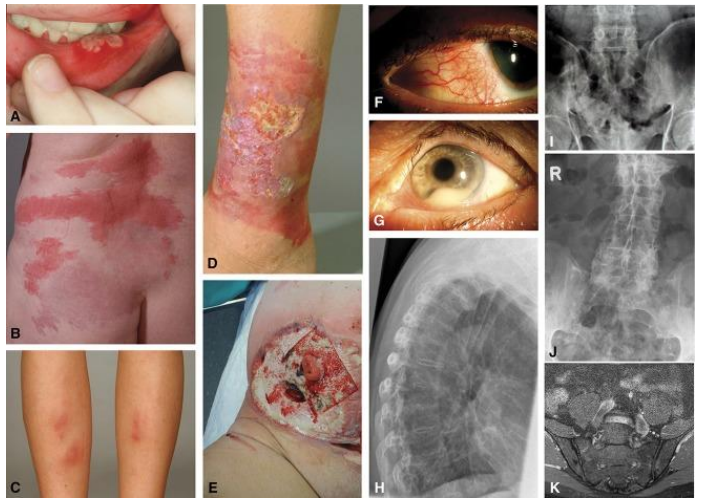
Curve 4: Chronic intermittent symptoms

Crohn's disease
At diagnosis
90% inflammatory B1

Prognostics:
who needs a more aggressive management?

Crohn's disease
After 5 to 10 years

Inflammatory B1	Stenosing B2	Penetrating B3	Fulminant disease
25%	30%	30%	5%



Comparative Effectiveness of Biologics for Endoscopic Healing of the Ileum and Colon in Crohn's Disease

Neeraj Narula, MD, MPH, FRCPC[1], Emily C.L. Wong, BHSc[1], Parambir S. Dulai, MD[2], John K. Marshall, MD, MSc, FRCPC[1], Vipul Jairath, MD, PhD[3] and Walter Reinisch, MD, PhD[4]

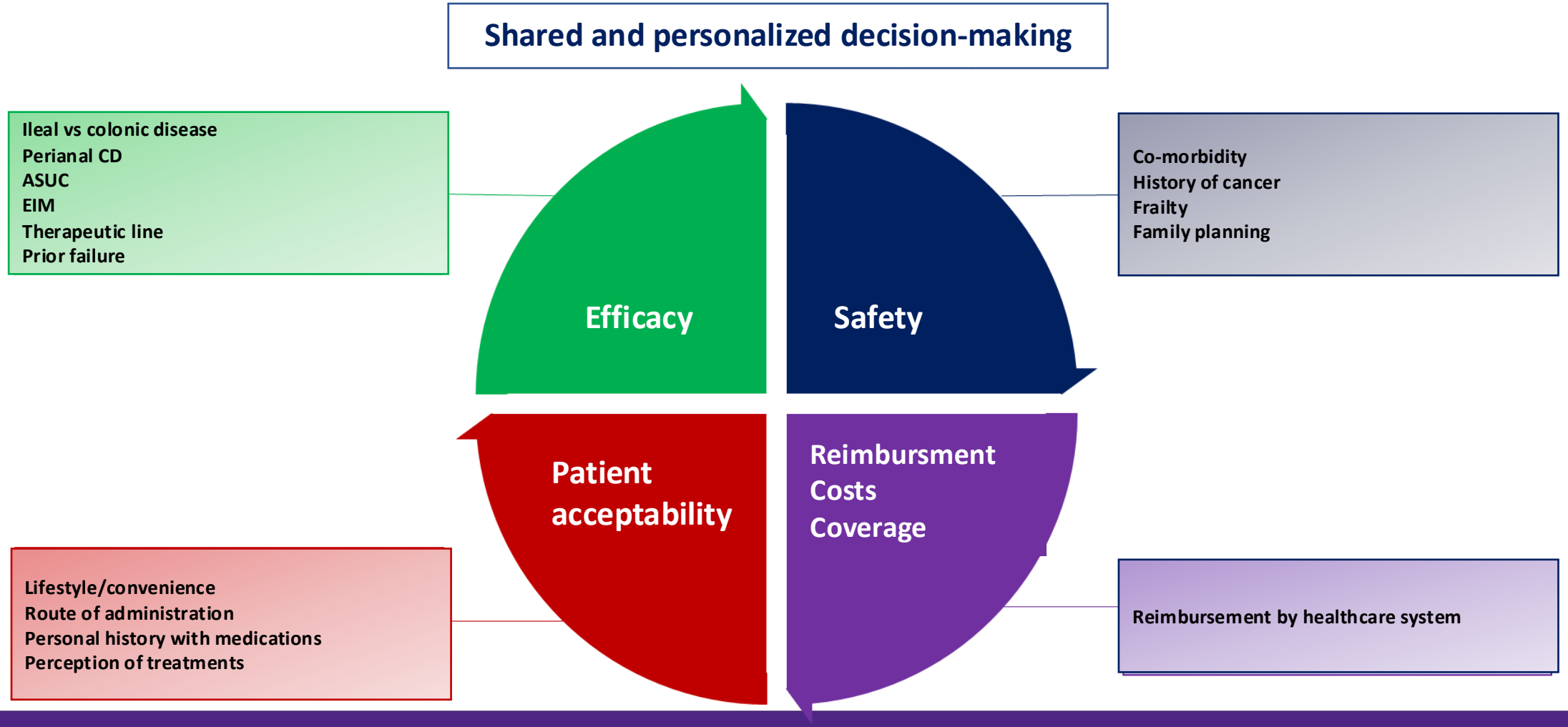
Differential efficacy of medical therapies for ulcerative colitis according to disease extent: patient-level analysis from multiple randomized controlled trials

Sudheer K. Vuyyuru,[a] Christopher Ma,[b,c] Tran M. Nguyen,[d] Guangyong Zou,[e] Laurent Peyrin-Biroulet,[f] Silvio Danese,[g] Parambir Dulai,[h] Neeraj Narula,[i] Siddharth Singh,[j] and Vipul Jairath[a,d,e,*]

[a]Department of Medicine, Division of Gastroenterology, Schulich School of Medicine, Western University, Canada
[b]Division of Gastroenterology and Hepatology, Department of Medicine, University of Calgary, Calgary, AB, Canada
[c]Departments of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
[d]Lawson Health Research Institute, London Health Sciences Center, London, ON, Canada

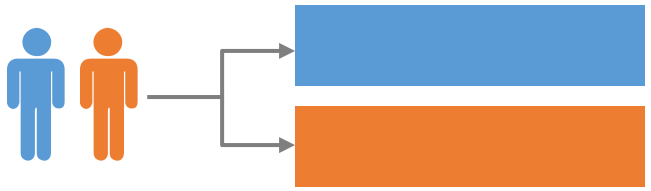
Solberg IC, et al. Scand J Gastroenterol. 2009

Selecting therapy in IBD : The Art of Medicine



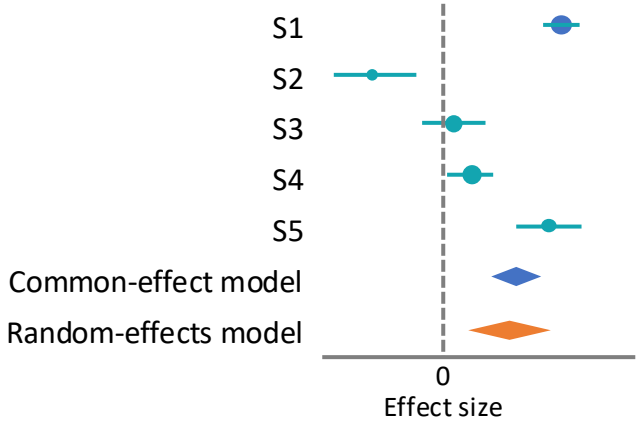
What Tools Do We Have to Inform Positioning of Drugs: Science

Head-to-head trial



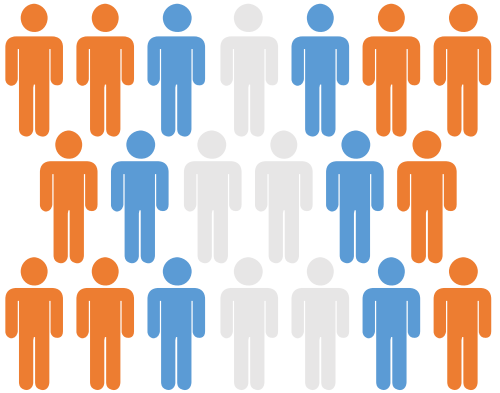
Gold standard: Designed and powered to allow formal comparison between different active therapies

Network Meta-analysis



Comparison of treatment effects from pivotal RCTs

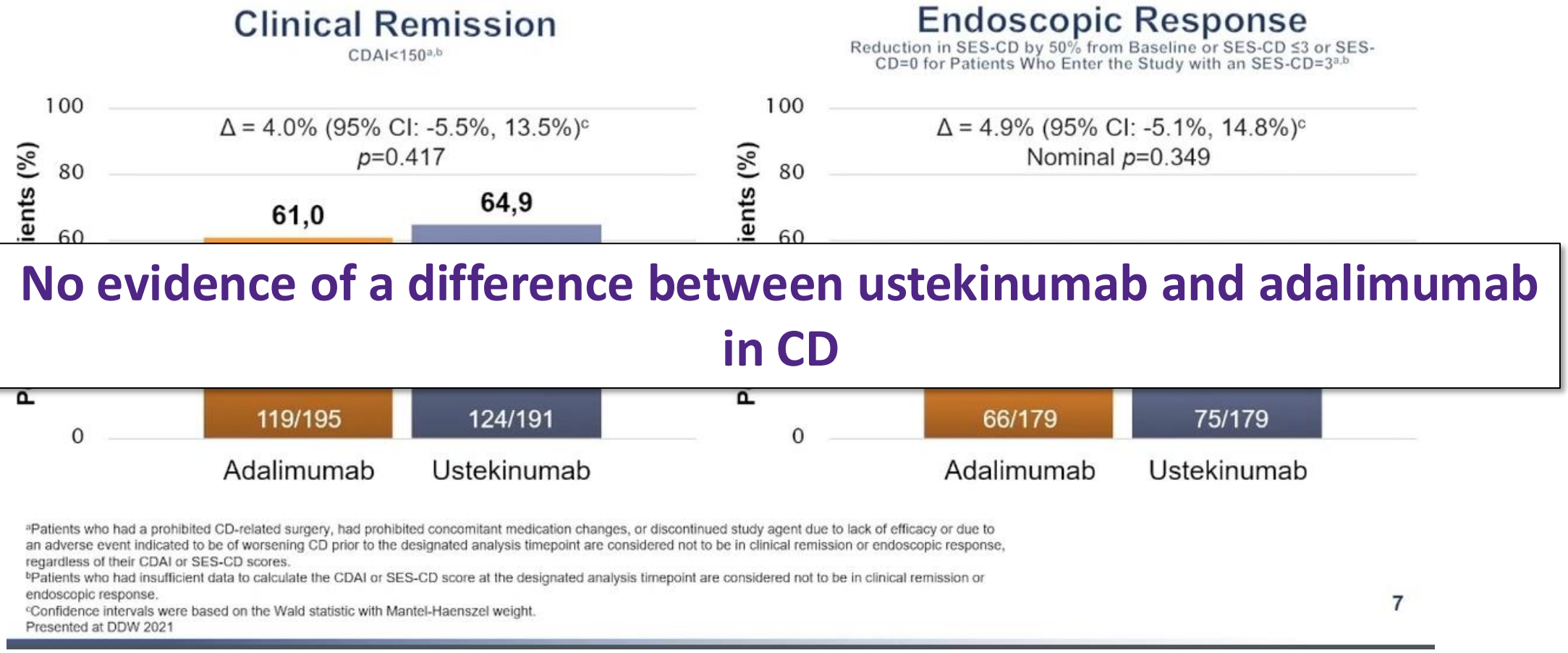
Real-world data



Routinely collects data on patient health status from many sources (eg, registries), often using propensity score-matched analysis for adequate comparisons

Positioning in CD: 1st Line

SEAVUE: Clinical remission and endoscopic response at Wk 52



- **No evidence of a difference between ustekinumab and adalimumab in CD**

[a]Patients who had a prohibited CD-related surgery, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening CD prior to the designated analysis timepoint are considered not to be in clinical remission or endoscopic response, regardless of their CDAI or SES-CD scores.
[b]Patients who had insufficient data to calculate the CDAI or SES-CD score at the designated analysis timepoint are considered not to be in clinical remission or endoscopic response.
[c]Confidence intervals were based on the Wald statistic with Mantel-Haenszel weight.
Presented at DDW 2021

Sands et al. Lancet 2022

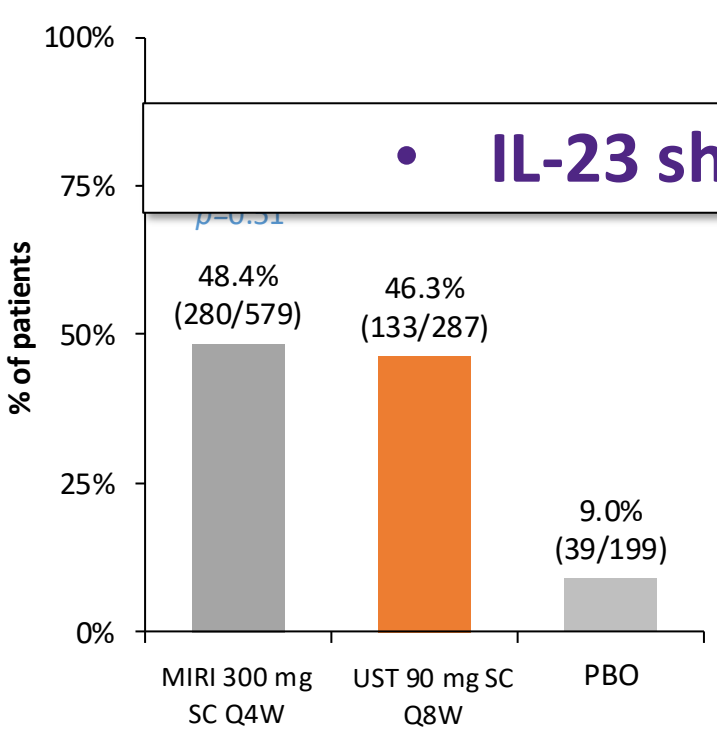
Endoscopic Response at Week 48/52: Ustekinumab as an Active Comparator in Clinical Trials in CD

These figures are intended to be a summary of individual clinical trial data only and direct comparisons between trials cannot be made.

- **IL-23 should replace ustekinumab as first line therapy**

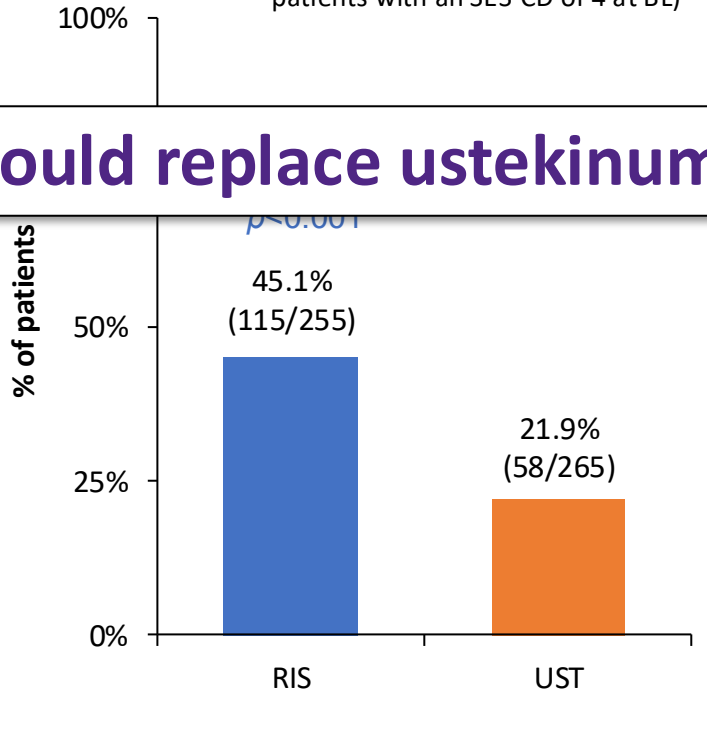
VIVID-1
Week 52, NRI[1]

Endoscopic response: ≥50% reduction from BL in SES-CD total score



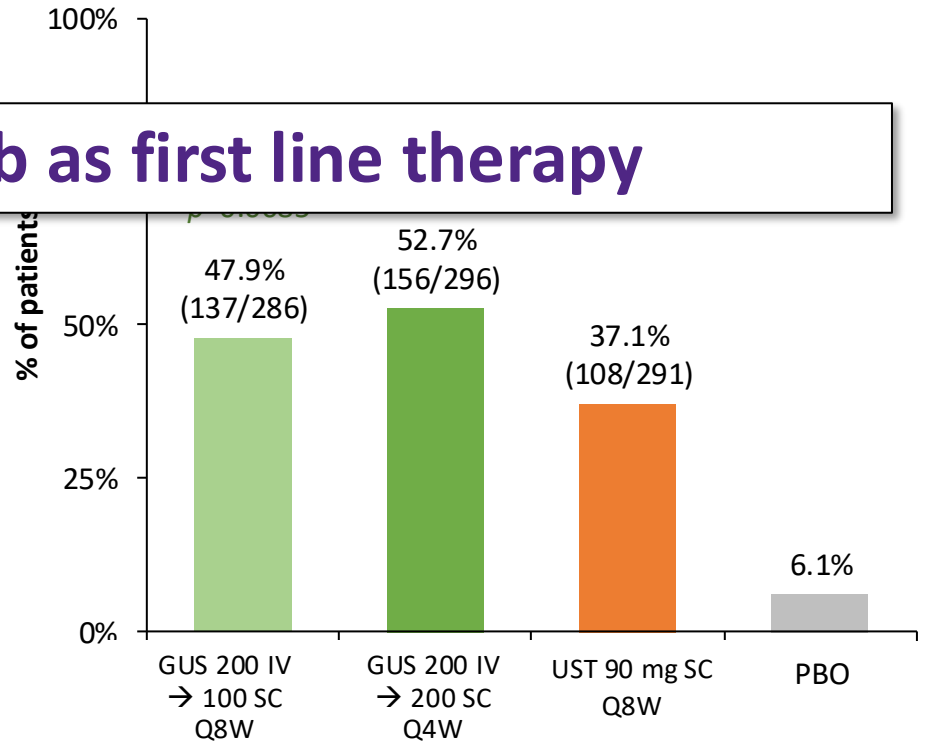
SEQUENCE
Week 48, NRI[2]

Endoscopic response: ≥50% reduction from BL in SES-CD total score (or a decrease of ≥ 2 points from BL in patients with an SES-CD of 4 at BL)



Pooled GALAXI 2 & 3
Week 48, NRI[3]

Endoscopic response: ≥50% reduction from BL in SES-CD total score or SES-CD ≤ 2



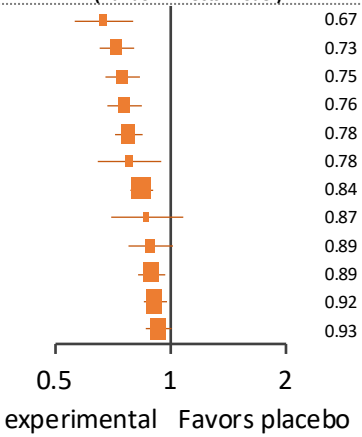
Network meta-analysis: 1st Line Advanced therapy in Luminal CD

Achievement of clinical remission in induction
CDAI < 150

All patients

A

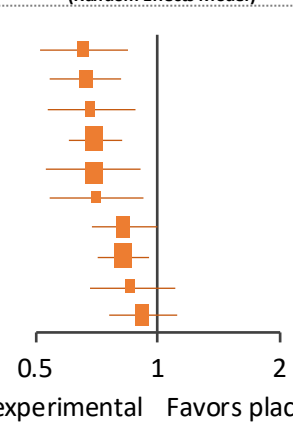
Treatment	RR	95% CI	P-Score
IFX 5mg/kg	0.67	(0.56; 0.79)	0.95
RZB 600mg	0.73	(0.66; 0.80)	0.85
UPA 45mg	0.75	(0.68; 0.83)	0.77
RZB 1200mg	0.76	(0.69; 0.84)	0.73
ADA 160/80mg	0.78	(0.72; 0.85)	0.67
ADA 160/160mg	0.78	(0.65; 0.95)	0.65
UST 6mg/kg	0.84	(0.79; 0.90)	0.47
IFX 10mg/kg	0.87	(0.70; 1.08)	0.39
ADA 80/40mg	0.89	(0.78; 1.01)	0.32
UST 130mg	0.89	(0.83; 0.96)	0.30
VDZ 300mg	0.92	(0.86; 0.98)	0.22
CTZ 400mg	0.93	(0.87; 1.00)	0.18



Bio-naïve patients

B

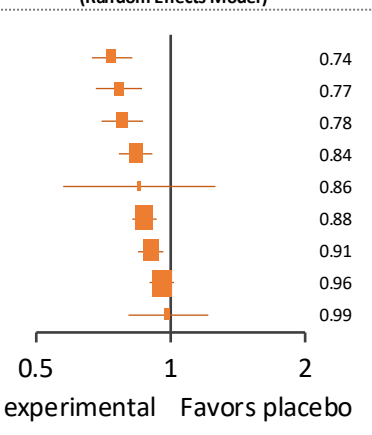
Treatment	RR	95% CI	P-Score
RZB 600mg	0.66	(0.52; 0.85)	0.78
IFX 5mg/kg	0.67	(0.55; 0.82)	0.78
RZB 1200mg	0.69	(0.54; 0.88)	0.72
ADA 160/80mg	0.70	(0.61; 0.81)	0.70
ADA 160/160mg	0.70	(0.54; 0.91)	0.68
UST 6mg/kg	0.71	(0.55; 0.92)	0.66
ADA 80/40mg	0.83	(0.69; 0.99)	0.35
VDZ 300mg	0.83	(0.72; 0.96)	0.34
IFX 10mg/kg	0.86	(0.68; 1.10)	0.29
CTZ 400mg	0.92	(0.77; 1.11)	0.17



Bio-exposed patients

C

Treatment	RR	95% CI	P-Score
RZB 600mg	0.74	(0.67; 0.82)	0.92
UPA 45mg	0.77	(0.69; 0.87)	0.82
RZB 1200mg	0.78	(0.71; 0.87)	0.79
ADA 160/80mg	0.84	(0.77; 0.92)	0.61
ADA 160/160mg	0.86	(0.58; 1.26)	0.52
UST 6mg/kg	0.88	(0.83; 0.93)	0.48
UST 130mg	0.91	(0.85; 0.97)	0.38
VDZ 300mg	0.96	(0.91; 1.02)	0.21
ADA 80/40mg	0.99	(0.81; 1.21)	0.19



IFX was only studied in bio-naïve patients.
When data are analyzed separately, RZB 600 mg ranked first for both groups, suggesting that the ranking of IFX 5 mg/kg in the pooled analysis was driven by use in biologic-naïve patients.

Western

Barberio B,. Gut. 2023 Feb;72(2):264-274.

Network Meta-Analysis of CD trials for endoscopic outcomes

Table 1. Comparative Efficacy of Biologic Agents and Oral Small Molecules for Induction of Endoscopic Response and Endoscopic Remission in Patients With Moderate-to-Severe Crohn's Disease Using Network Meta-Analysis, Expressed as RR with 95% Confidence Intervals

	Induction of endoscopic response, all patients						
Induction of endoscopic remission, all patients	JAK1 inhibitors	1·52 (0·84–2·74)	**2·34 (1·14–4·80)**	2·43 (0·90–6·59)	**3·49 (1·48–8·26)**	—	**4·21 (2·68–6·78)**
	1·33 (0·72–2·44)	IL23 antagonists	1·54 (0·87–2·71)	1·60 (0·62–4·16)	**2·30 (1·02–5·18)**	—	**2·81 (1·95–4·05)**
	1·66 (0·72–3·82)	1·25 (0·64–2·45)	IL12/23 antagonists	1·04 (0·37–2·94)	1·49 (0·60–3·71)	—	**1·82 (1·05–3·16)**
	2·35 (1·61–4·74)	1·77 (0·92–3·40)	1·41 (0·60–3·35)	TNF antagonists	1·44 (0·46–4·50)	—	1·75 (0·73–4·24)
	2·83 (1·15–6·98)	2·14 (0·90–5·07)	1·70 (0·61–4·78)	1·21 (0·48–3·06)	Etrolizumab	—	1·22 (0·59–2·52)
	—	—	—	—	—	Vedolizumab	—
	4·37 (2·73–6·99)	**3·30 (2·23–4·87)**	**2·63 (1·32–5·22)**	**1·86 (1·10–3·14)**	1·54 (0·71–3·33)	—	Placebo

Table 2. Comparative Efficacy of Biologic Agents and Oral Small Molecules for Maintenance of Endoscopic Response and Endoscopic Remission in Patients With Moderate-to-Severe Crohn's Disease Using Network Meta-Analysis, Expressed as RR With 95% Confidence Intervals

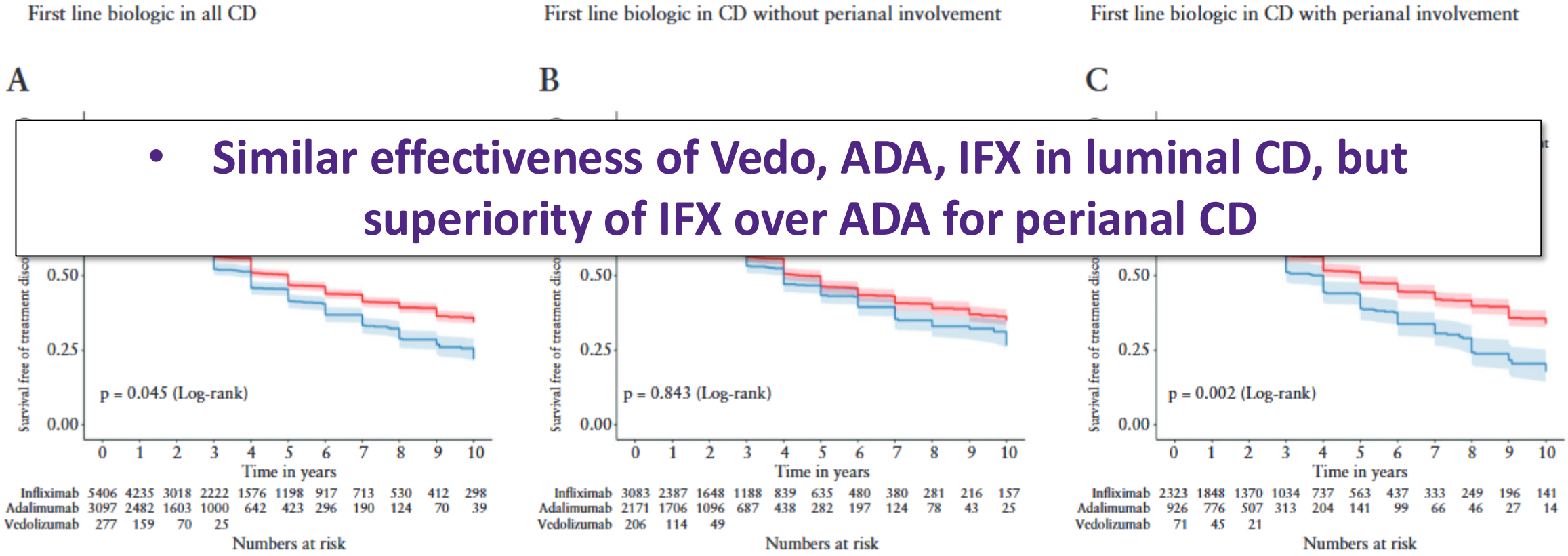
	Maintenance of endoscopic response, all patients						
Maintenance of endoscopic remission, all patients	JAK1 inhibitors	**2·17 (1·14–4·15)**	0·54 (0·12–2·52)	0·66 (0·14–3·08)	**3·18 (1·68–6·03)**	—	**4·65 (2·64–8·18)**
	1·85 (0·81–4·22)	IL23 antagonists	0·25 (0·06–1·08)	0·30 (0·07–1·32)	1·46 (0·95–2·26)	—	**2·14 (1·57–2·93)**
	0·58 (0·11–3·01)	0·31 (0·07–1·47)	IL12/23 antagonists	1·22 (0·89–1·67)	**5·87 (1·36–25·28)**	—	**8·58 (2·05–35·83)**
	0·54 (0·11–2·64)	0·29 (0·07–1·29)	0·93 (0·60–1·45)	TNF antagonists	**4·80 (1·12–20·68)**	—	**7·02 (1·68–29·31)**
	2·49 (0.95–6·40)	1·34 (0·62–2·88)	4·26 (0·84–21·52)	4·57 (0.96–21·67)	Etrolizumab	—	**1·46 (1·08–1·97)**
	2.61 (0.69–9.95)	1.41 (0.42–4.75)	4.50 (0.69–29.26)	4.82 (0.78–29.72)	1.05 (0.29–3.89)	Vedolizumab	—
	4·96 (2·46–10·00)	**2·67 (1·74–4·11)**	**8·53 (1·93–37·75)**	**9·14 (2·21–37·80)**	**1·97 (1·13–3·45)**	1.89 (0.61–5.92)	Placebo

This study suggests that JAK1 inhibitors and anti-IL23p19 agents are more effective amongst advanced therapies for induction of endoscopic outcomes.

Vuyyuru SK, et al. Clin Gastroenterol Hepatol. 2024 Jun;22(6):1190-1199.

First Line Advanced Therapy: RWD from UK Bioresource

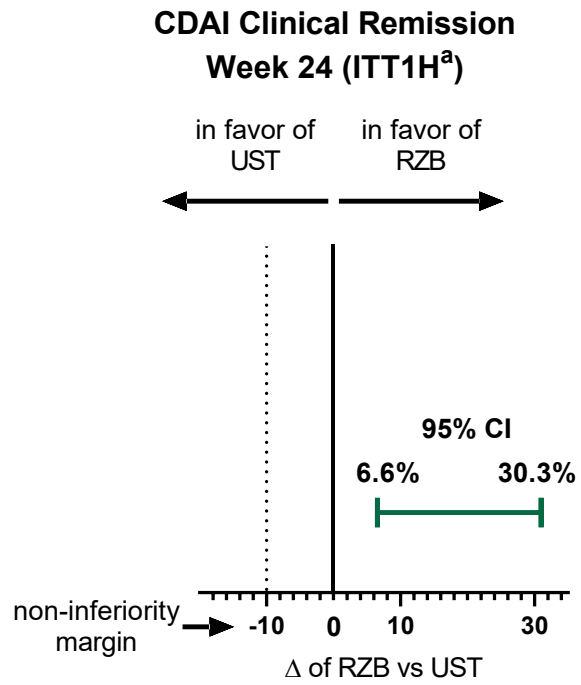
- **Similar effectiveness of Vedo, ADA, IFX in luminal CD, but superiority of IFX over ADA for perianal CD**



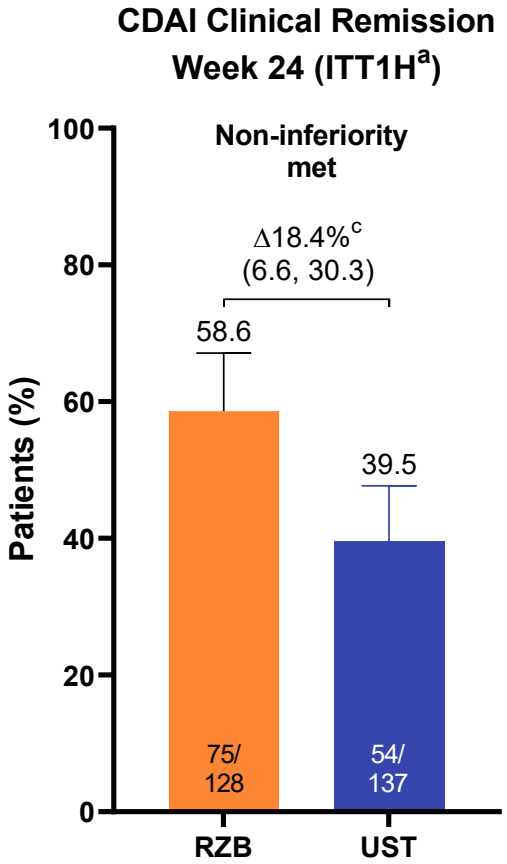
Kapizioni C. et al JCC 2024

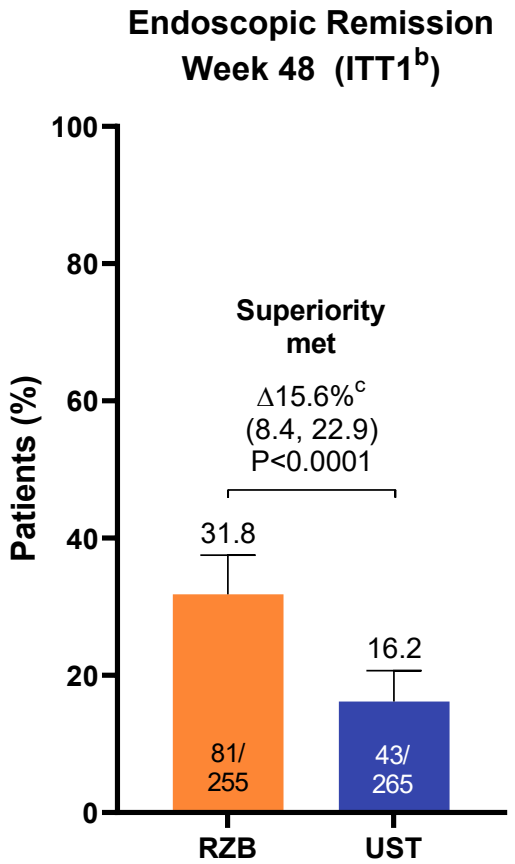
Positioning in CD: 2nd Line

SEQUENCE: Primary Endpoints



<u>CDAI clinical remission</u>: CDAI < 150
<u>Endoscopic remission</u>: SES-CD ≤ 4 and at least a 2-point reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer

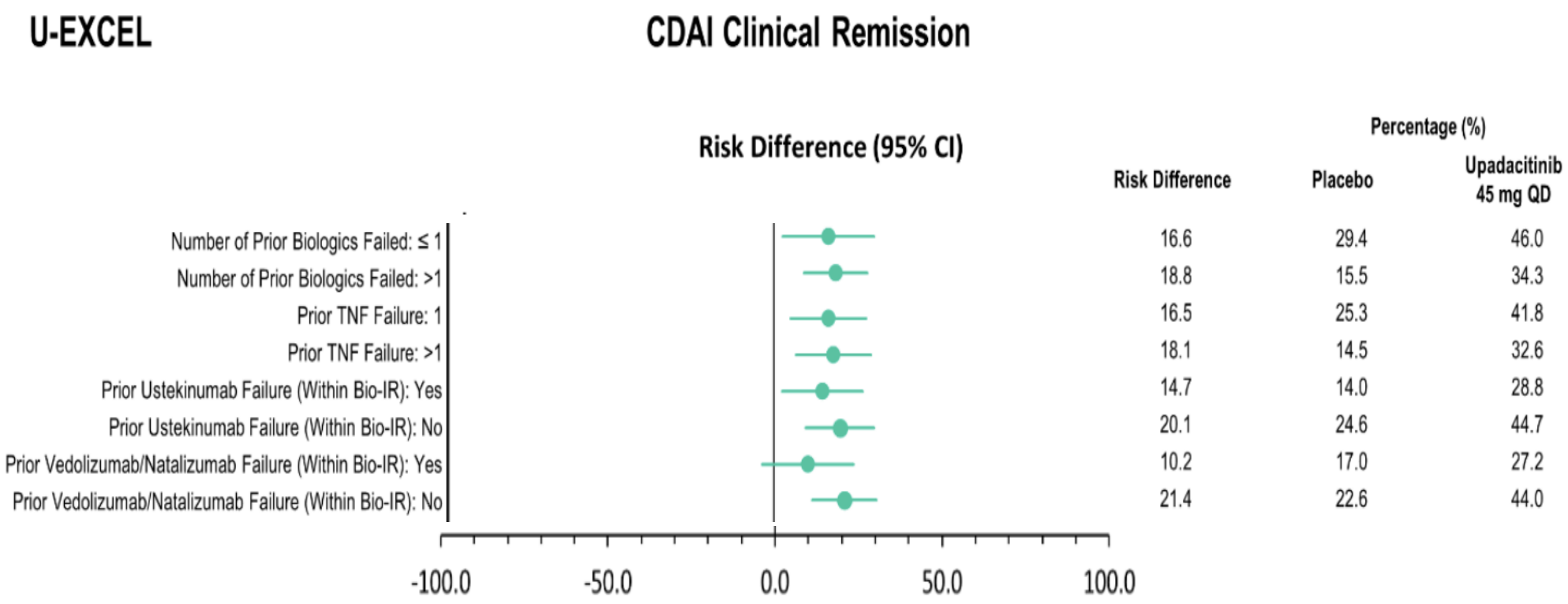




Nominal *P* <0.01 from a post hoc analysis testing for superiority

[a]ITT1H population: a subset of ITT1 population which includes the first ~50% of ITT1 patients
[b]ITT1 population includes patients who were randomized to UST or RZB (600 mg IV, 360 mg SC) and received at least one dose of study drug
[c]Differences adjusted by the stratification factors (number of times the subject failed prior anti-TNF therapy [≤ 1, > 1] and steroid use at baseline [yes, no])
% (n) represents the synthesized results from non-responder imputation incorporating multiple imputation to handle missing data
Non-inferiority for CDAI clinical remission at wk 24 was met if the lower bound of the 95% CI of adjusted risk difference was above -10%; if met, superiority for endoscopic remission at wk 48 was assessed

Upa is effective after biologic failure in CD

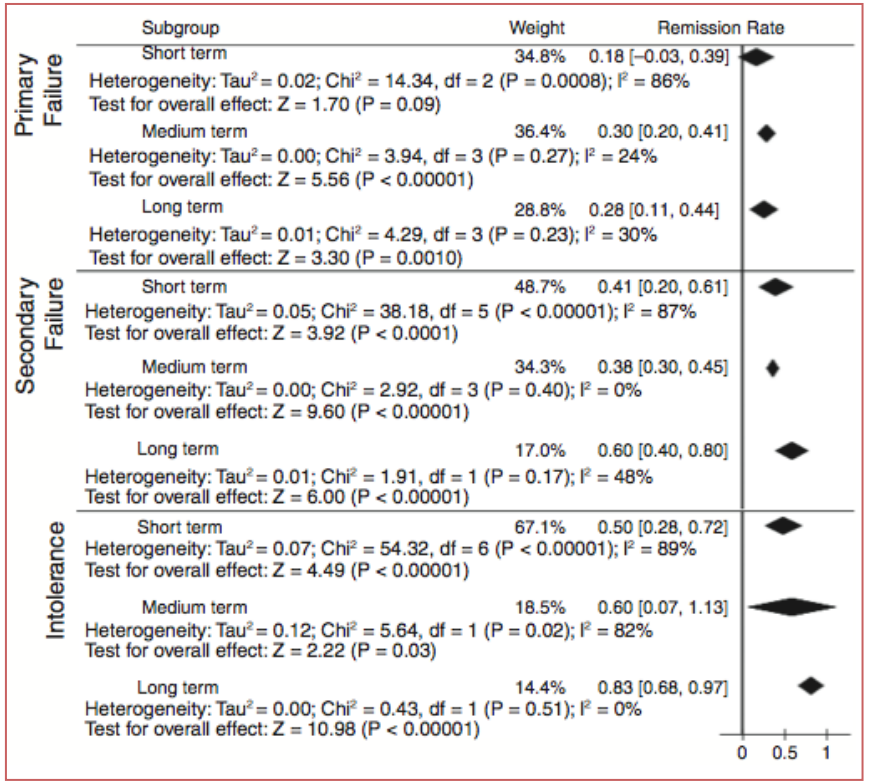


Loftus EV , et al. N Engl J Med. 2023;388:1966-1980.

Switch to a Second TNF

Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed

J. P. Gisbert*,†, A. C. Marín*,†, A. G. McNicholl*,† & M. Chaparro*,†



Meta-analysis of 46 studies

Remission rate with 2nd anti-TNF agent was :

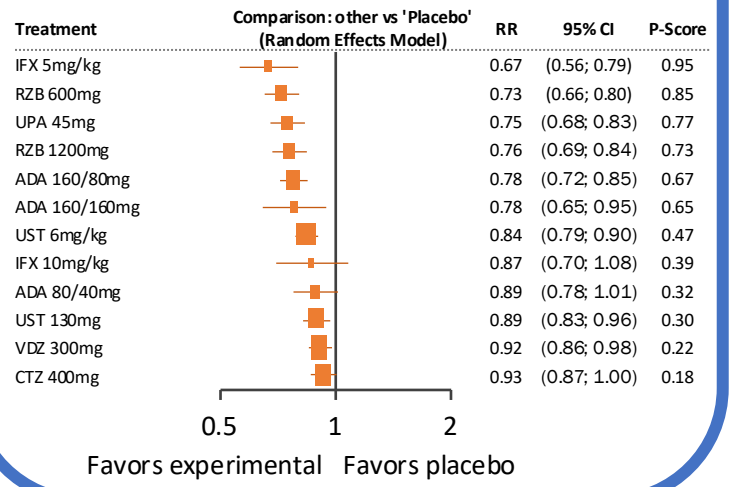
- **Better in case of intolerance to the first anti-TNF agent (61%)**
- **Lower (30%) if primary failure or secondary loss of response (45%)**

Network meta-analysis: 2nd Line Advanced therapy in Luminal CD

Achievement of clinical remission in induction
CDAI < 150

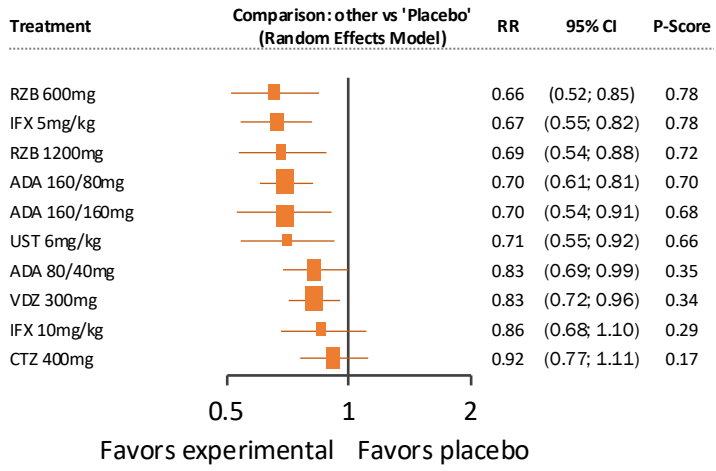
All patients

A



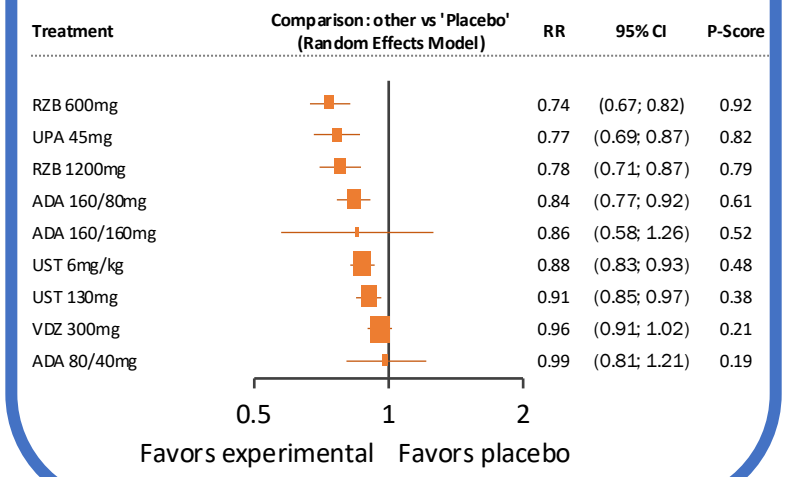
Bio-naïve patients

B



Bio-exposed patients

C

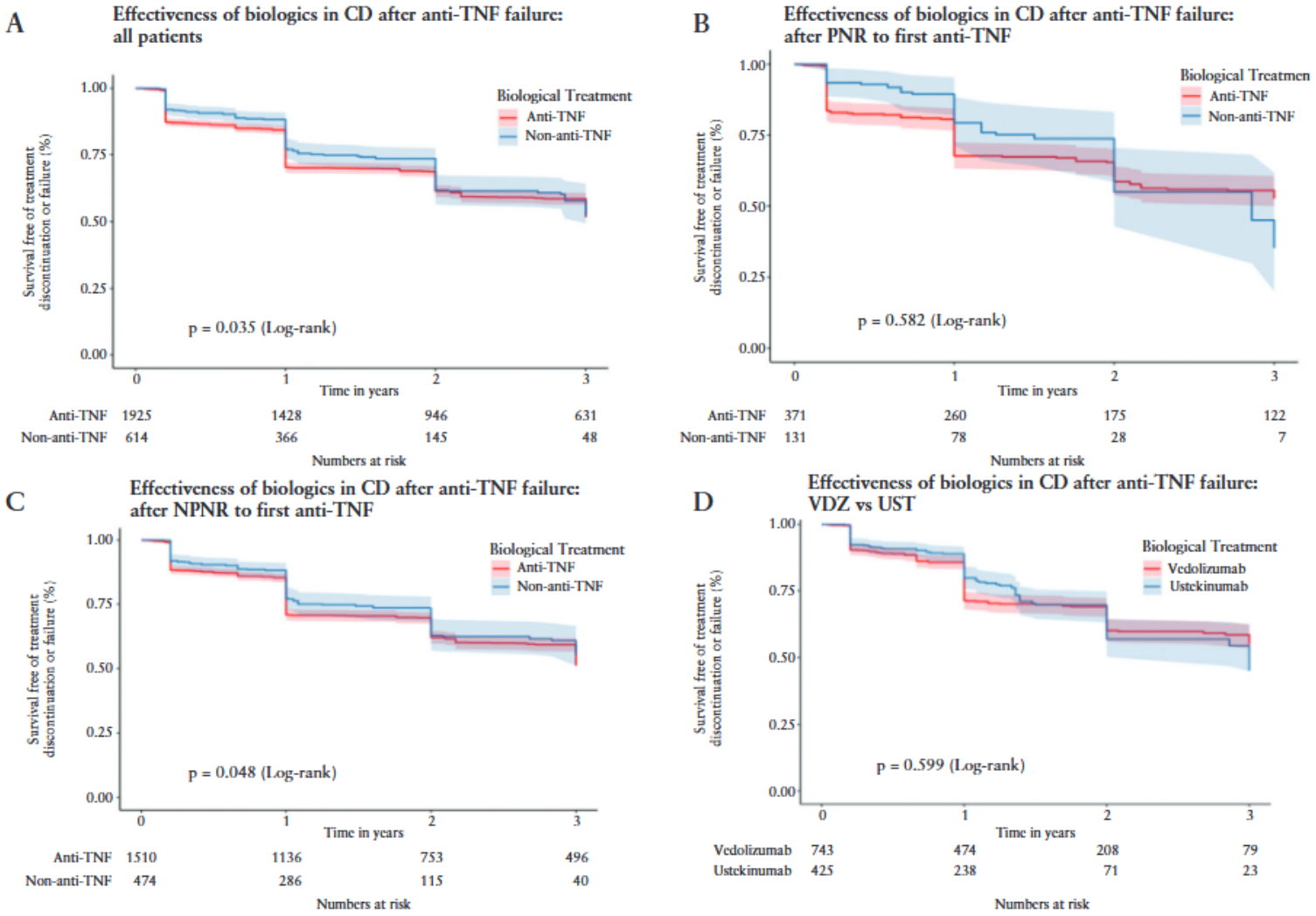


IFX was only studied in bio-naïve patients.
When data are analyzed separately, RZB 600 mg ranked first for both groups, suggesting that the ranking of IFX 5 mg/kg in the pooled analysis was driven by use in biologic-naïve patients.

Western

Barberio B,. Gut. 2023 Feb;72(2):264-274.

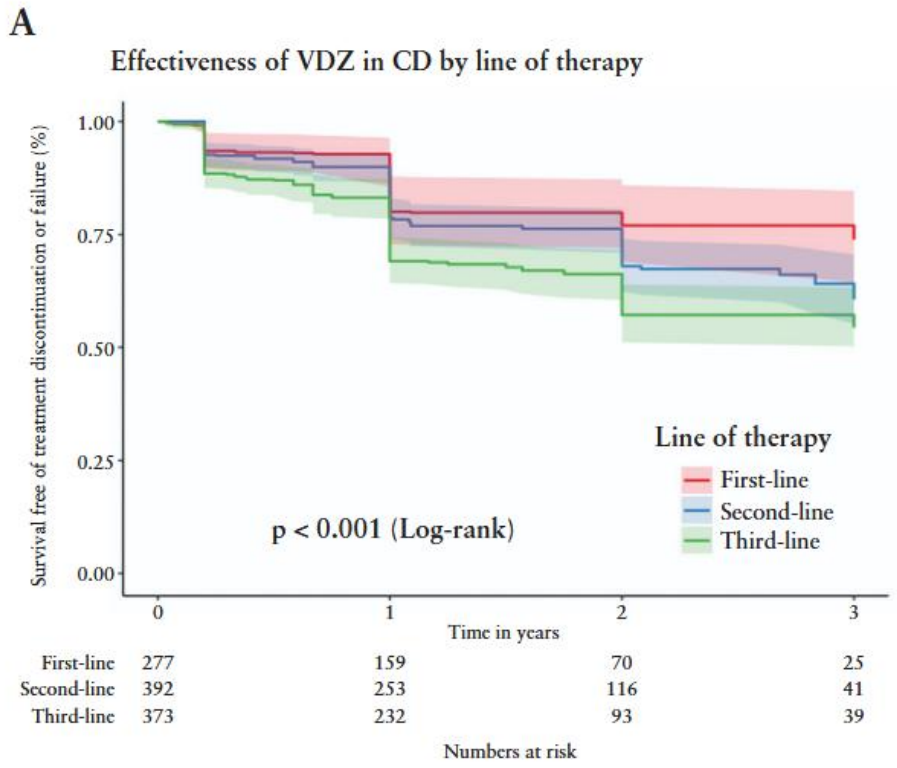
Second Line Advanced Therapy: RWD from UK Bioresource

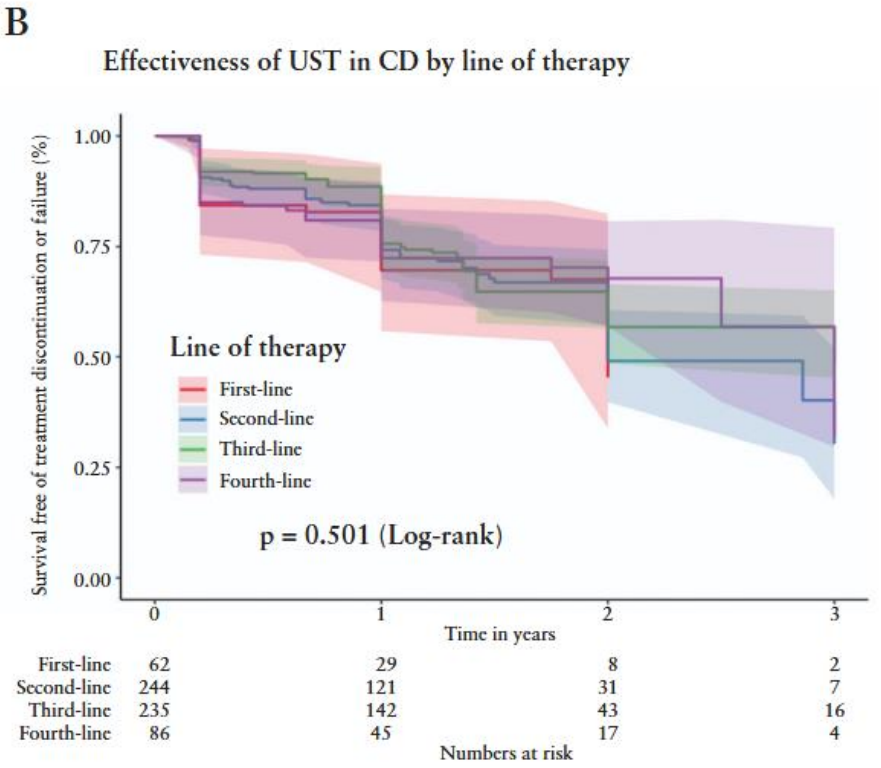


Western

Kapizioni C. et al JCC 2024

The Law of Diminishing Returns





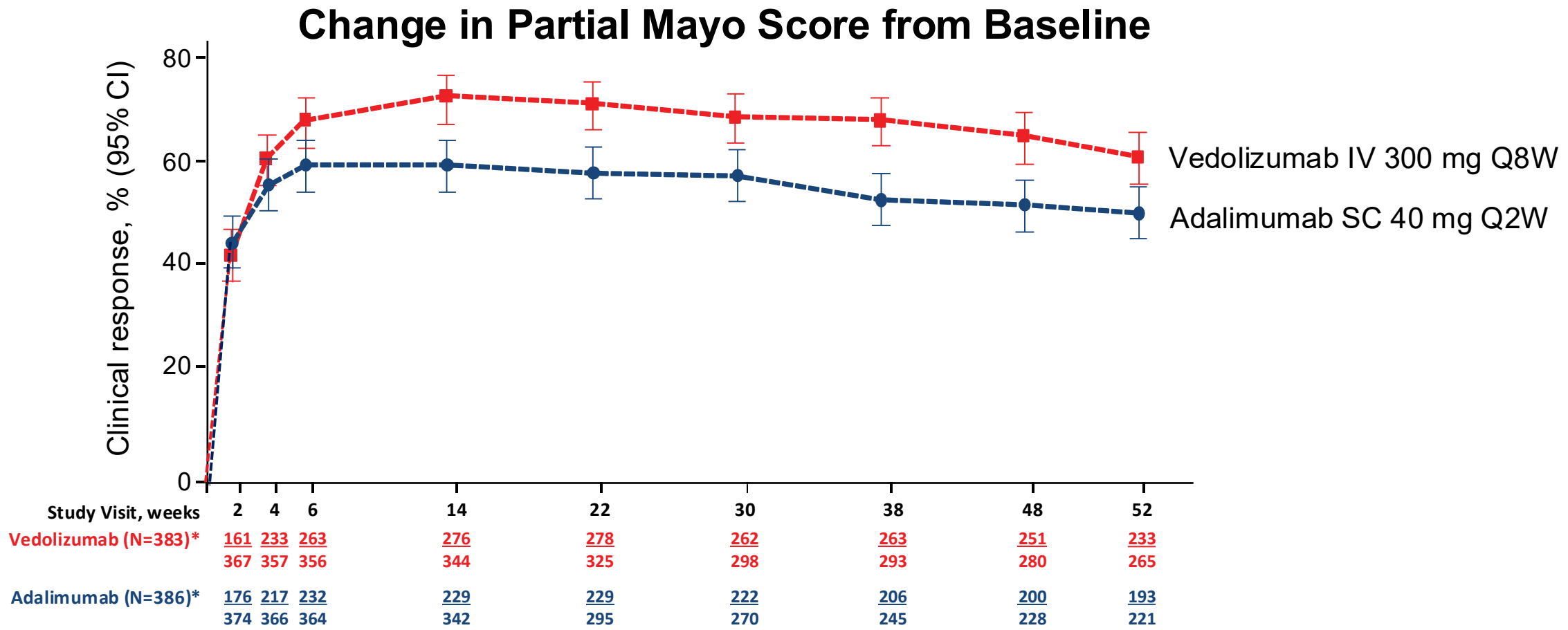
Kapizioni C. et al JCC 2024

Special situations: Peripheral spondylarthiritis & Axial arthiritis

	Peripheral SpA	Axial Arthiritis
Anti-TNF	+++	+++
Ustekinumab	+	-
Vedolizumab	-	-
Upadacitinib	+++	+++
Anti-IL23	+	-

Positioning in UC: 1st Line

VARSITY: Vedolizumab verus Adalimumab



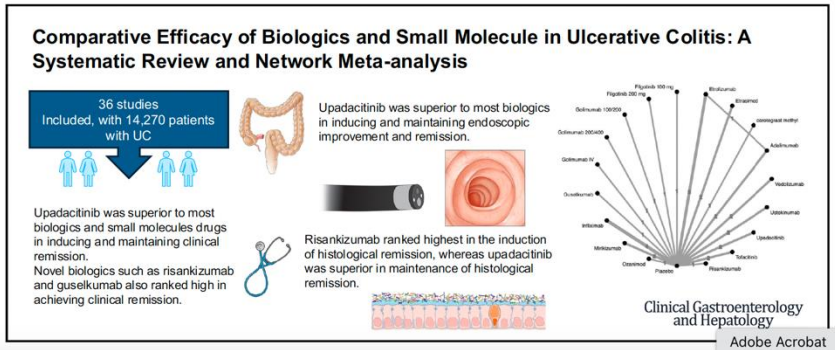
Sands BE, NEJM

Network Meta-Analysis

Comparative Efficacy of Biologics and Small Molecule in Ulcerative Colitis: A Systematic Review and Network Meta-analysis

Mohammad Shehab,[1,2] Fatema Alrashed,[2] Abdulwahab Alsayegh,[3] Usama Aldallal,[3] Christopher Ma,[4] Neeraj Narula,[5] Vipul Jairath,[6,7] Siddharth Singh,[8] and Talat Bessissow[9]

[1]Division of Gastroenterology, Department of Internal Medicine, Mubarak Alkabeer University Hospital, Kuwait; [2]Department of Pharmacy Practice, Faculty of Pharmacy, Kuwait University, Jabriya, Kuwait; [3]Department of medicine, School of Medicine, Royal College of Surgeons in Ireland, Medical University of Bahrain, Kingdom of Bahrain; [4]Division of Gastroenterology and Hepatology, Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, Alberta, Canada; [5]Department of Medicine (Division of Gastroenterology) and Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [6]Department of Medicine, Division of Gastroenterology, Western University, London, Ontario, Canada; [7]Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada; [8]Division of Gastroenterology, Department of Medicine, University of California, San Diego, La Jolla, California; and [9]Division of Gastroenterology and Hepatology, Department of Medicine, McGill University Health Center, Montreal, Quebec, Canada



Induction: Endoscopic Improvement

Intervention	SUCRA score %
Upadacitinib	99.21
Risankizumab	91.45
Tofacitinib	81.96
Ozanimod	80.68
Infliximab	76.35
Guselkumab	72.75
Mirikizumab	64.63
Etrasimod	61.91
Ustekinumab	58.98
carotegrast methyl	57.76
Filgotinib 200	48.08
Golimumab 200/400	47.28
Golimumab 100/200	35.61
Vedolizumab	32.16
Etrolizumab	27.32
Filgotinib 100	24.71
Adalimumab	20.71
Golimumab IV	6.89
Placebo	3.00

Maintenance: Endoscopic Improvement

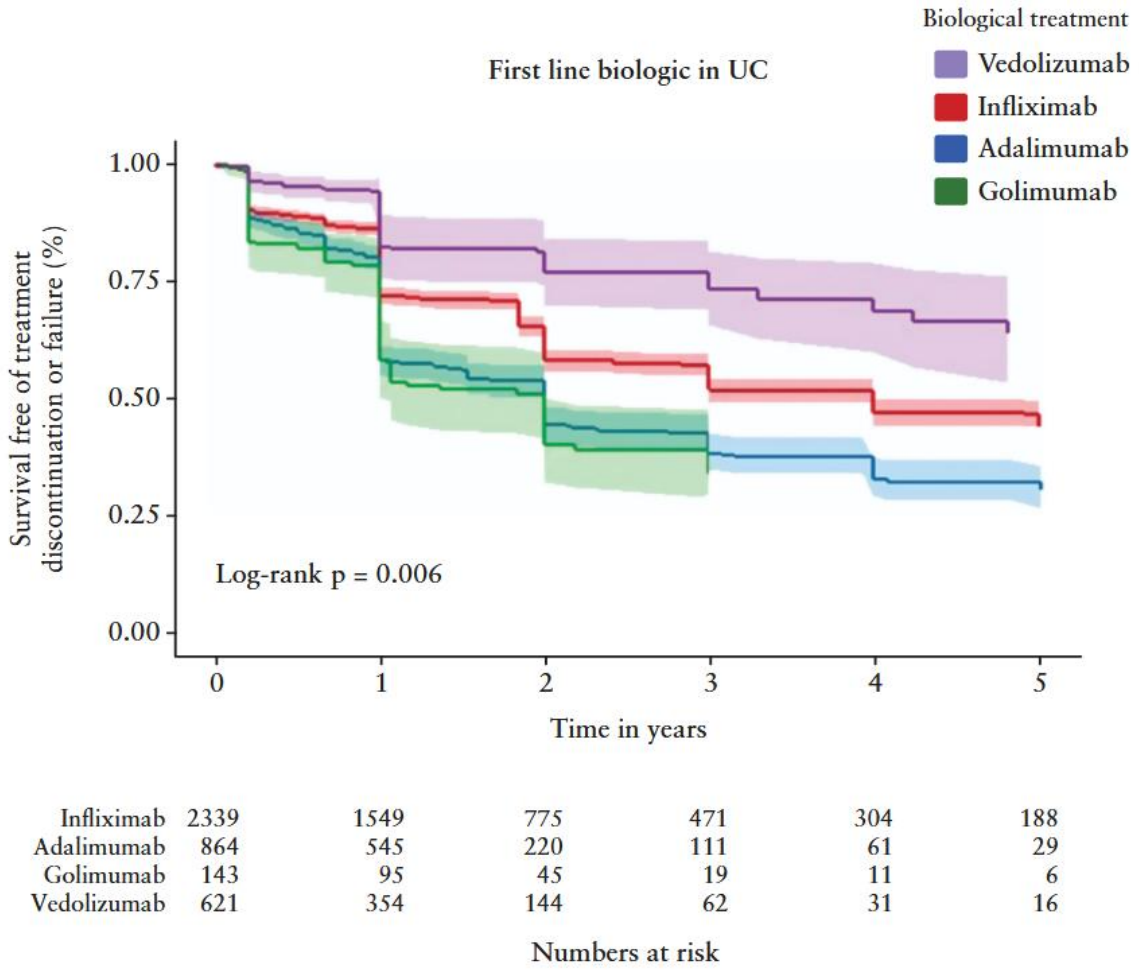
Intervention	SUCRA score %
Upadacitinib 30	98.60
Gueslkumab	86.55
Filgotinib 200	79.21
Upadacitinib 15	75.89
Tofacitinib	72.66
Golimumab	63.61
Vedolizumab	57.44
Infliximab	50.47
Infliximab sc	49.61
Ozanimod	43.55
Risankizumab 180 mg	42.97
Etrolizumab	40.21
Filgotinib 100	31.82
Risankizumab 360 mg	28.83
Ustekinumab	17.94
Adalimumab	14.18
Etrasimod	12.19
Placebo	2.6

Summary of Results

Several key findings were identified:

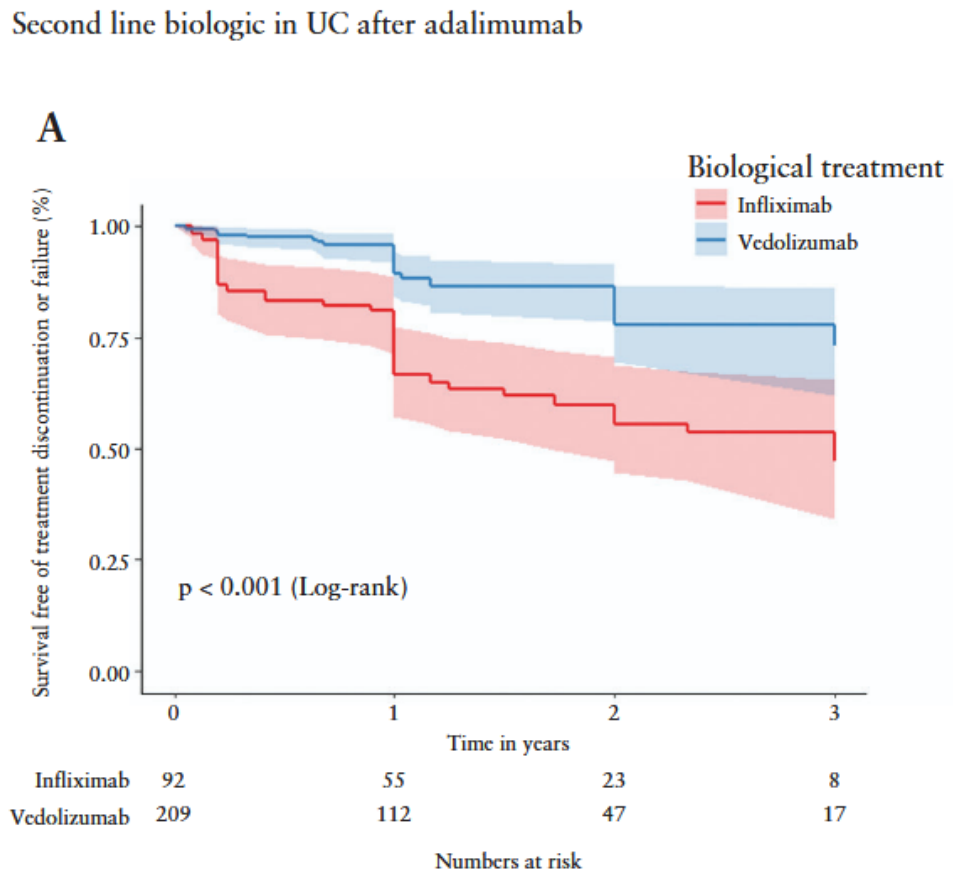
- ✓ Upadacitinib was superior in achieving all outcomes
- ✓ Novel biologic therapies such as risankuzumab, guselkumab and mirikizumab were highly ranked in achieving most outcomes such as clinical remission and endoscopic improvement.

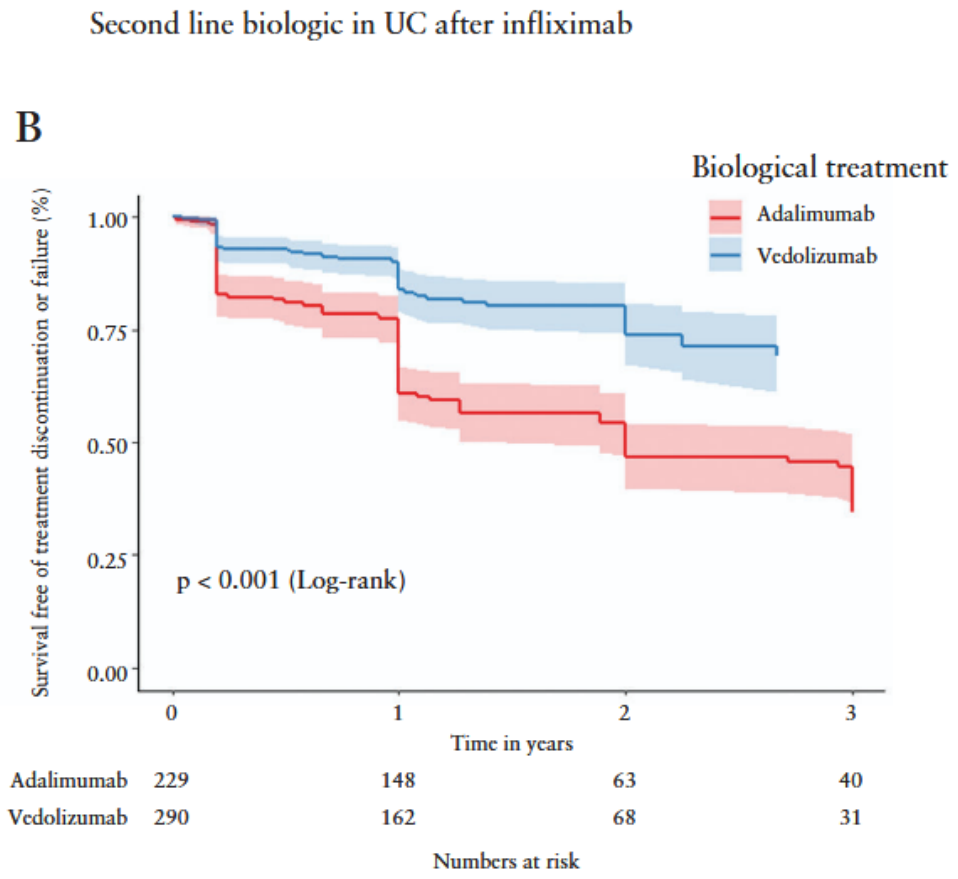
First Line Advanced Therapy: RWD from UK Bioresource



Kapizioni C. et al JCC 2024

Second Line Advanced Therapy: RWD from UK Bioresource

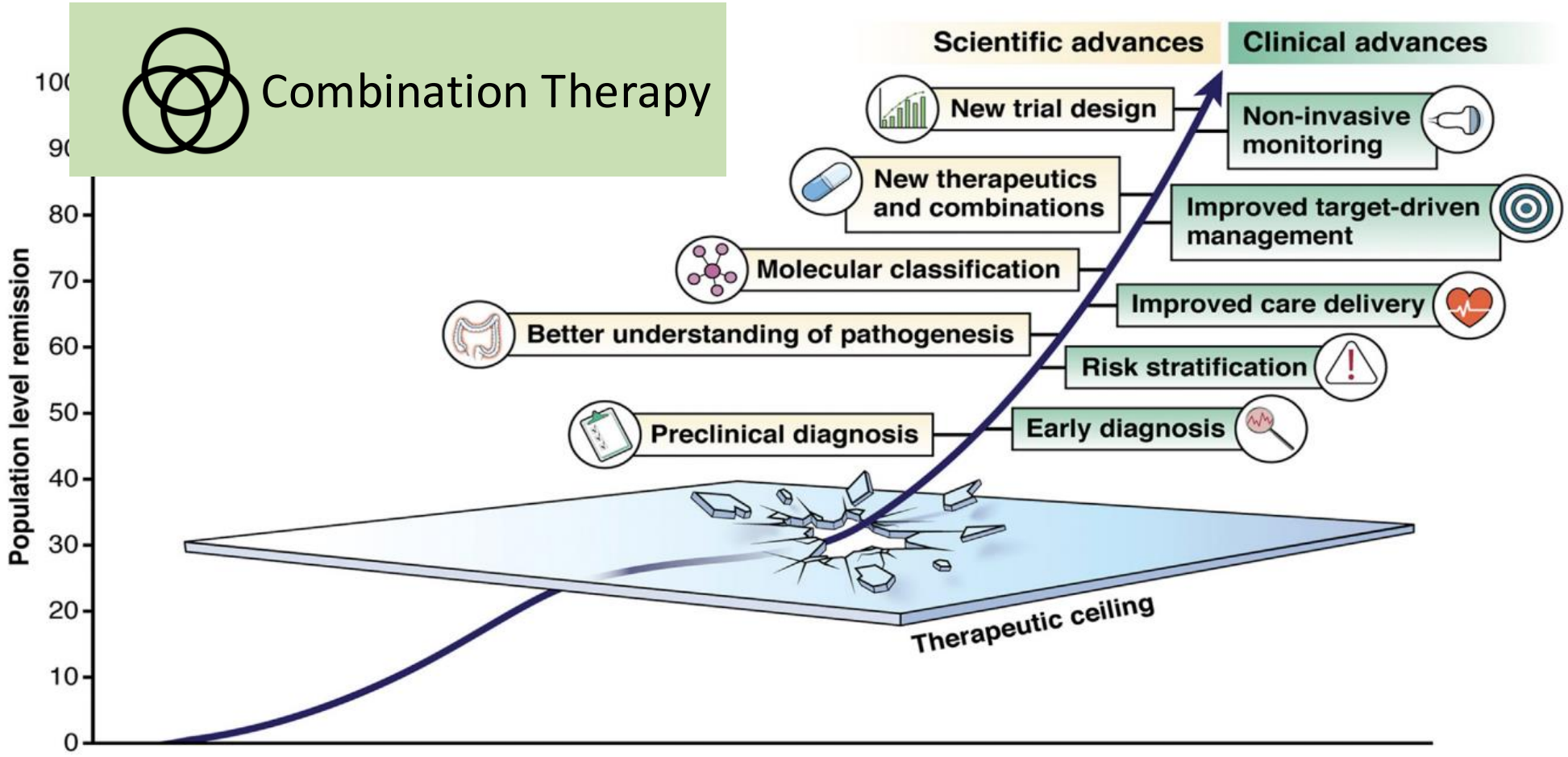




Kapizioni C. et al JCC 2024

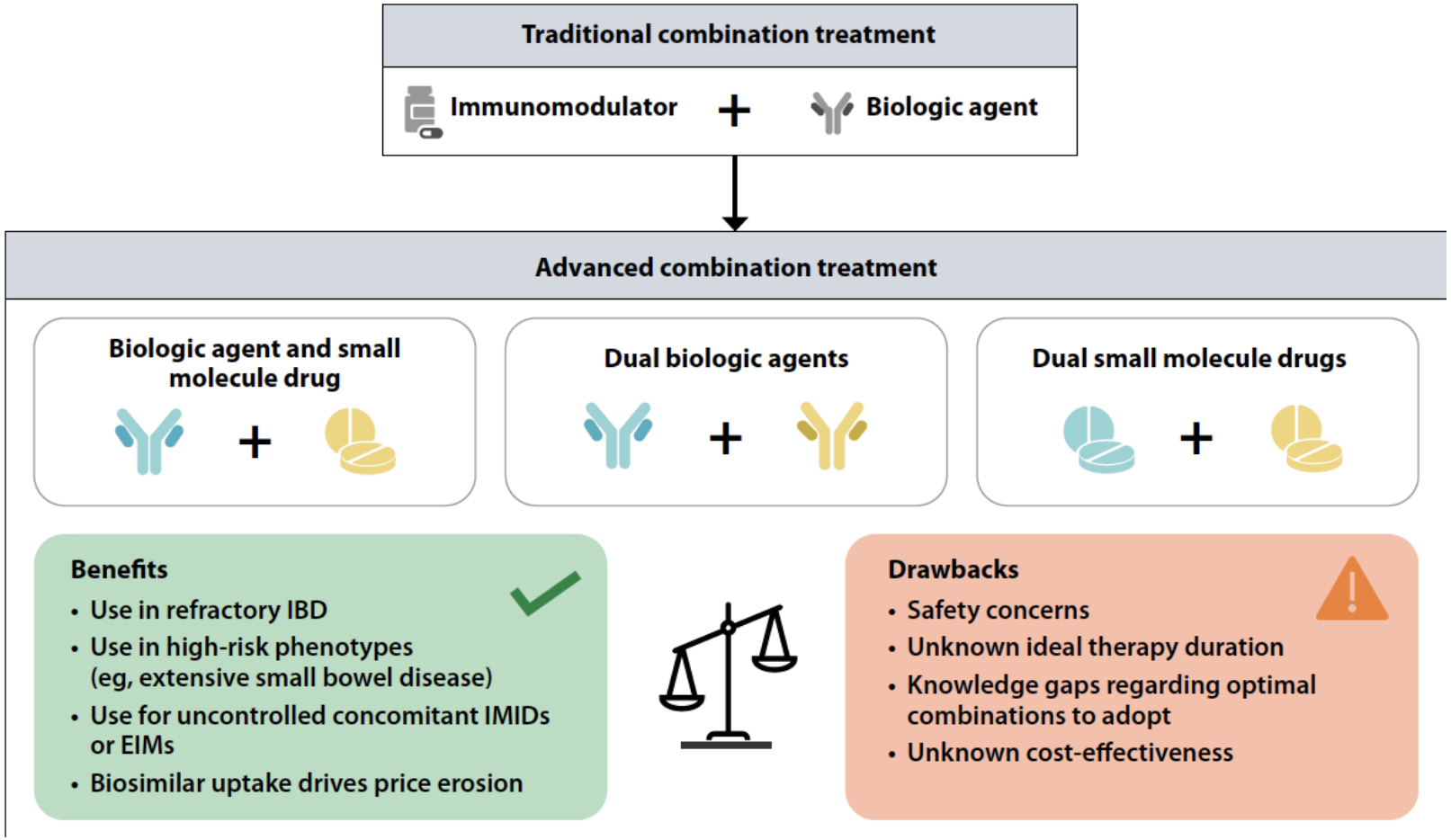
Advanced Combination Therapy

How Will We Break the Therapeutic Ceiling in IBD?



Raine T, Danese S. Gastroenterology. 2022;162:1507-1511.

From Traditional to Advanced Combination Therapy



Solitano V, Jairath V. Gastroenterology & Hepatology 2023.

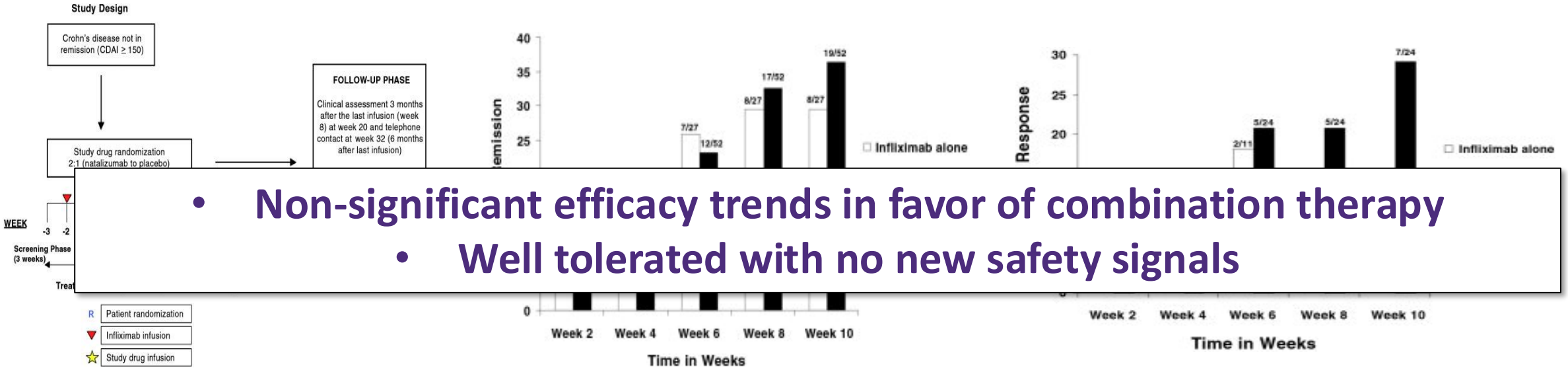
Why?

- Multiple pathways drive the immune-mediated inflammatory process
- Limited remission rates for biologics when used as single agents
- Mechanistic failure can develop over time for a single biologic agent
- Biologics used in succession tend to be less effective
- Agents effective for luminal disease may not be as effective for extraintestinal manifestations or other immune mediated disease

Who?

- Refractory IBD
- Well controlled IBD, uncontrolled concomitant immune mediated inflammatory disease (IMID)
- Uncontrolled IBD, well controlled concomitant immune mediated inflammatory disease (IMID)

RCT: Infliximab + Natalizumab in Crohn's Disease

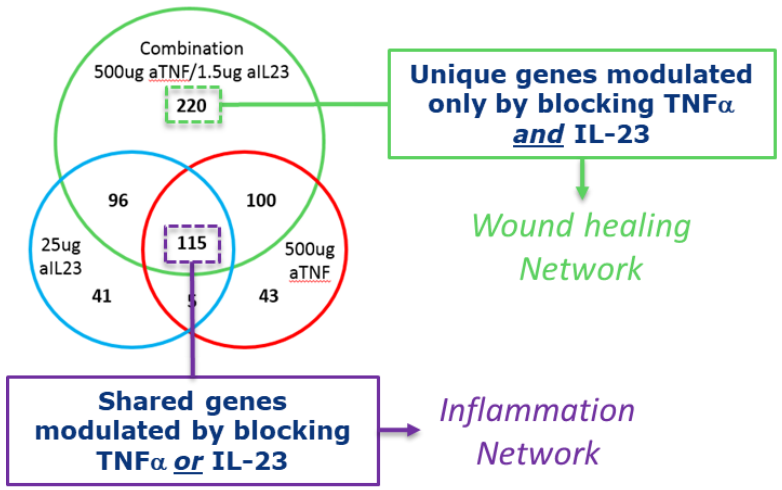


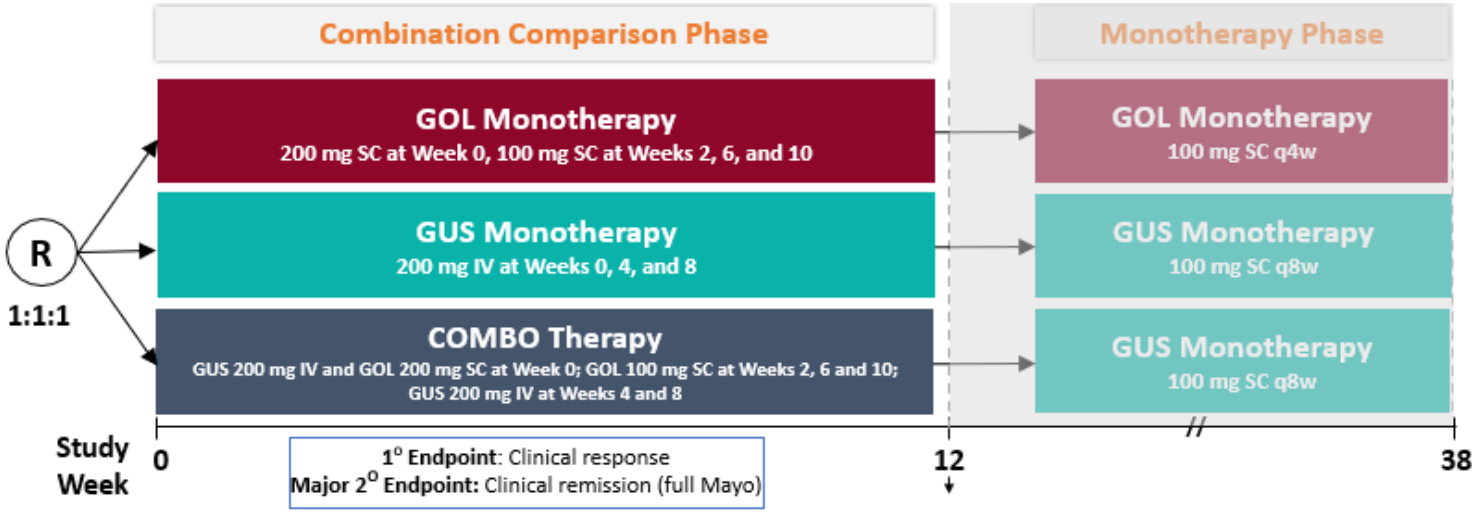
- Non-significant efficacy trends in favor of combination therapy
- Well tolerated with no new safety signals

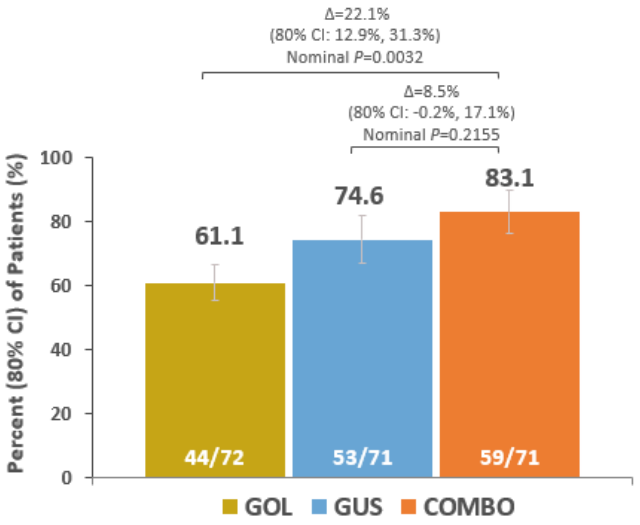
Western

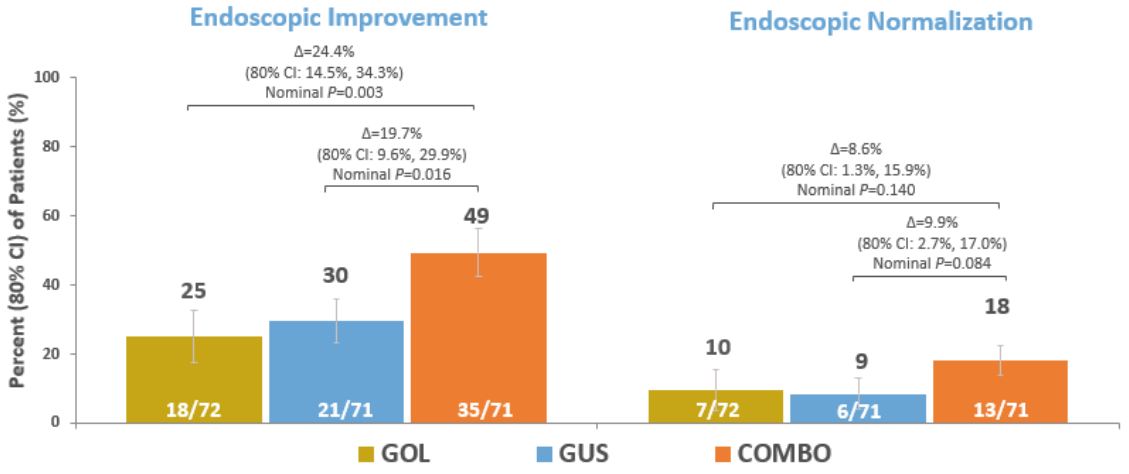
Sands B et al. Inflamm Bowel Dis 2007;13:2-11.

Combination Therapy



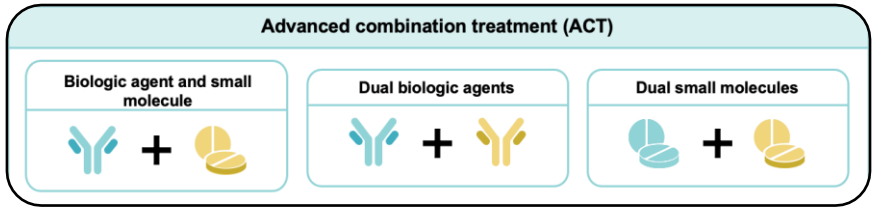






Feagan BG, et al. Lancet Gastroenterol Hepatol. 2023;8(4):307-320.

Effectiveness and Safety of ACT in patients with refractory IBD or concomitant IMIDs or EIMs: A Multi-Center Canadian Study



- **Retrospective Multicenter Study** (9 Canadian IBD centers)
- **105 Adult IBD patients** treated with **ACT** (either two biological therapies, a biological plus an oral small molecule, or two small molecules)
- **Indications**: 1) refractory IBD; 2) uncontrolled IMIDs; 3) uncontrolled EIMs

- **Primary outcomes**: cumulative rates of clinical and endoscopic response and remission at 6 and 12 months
- **Secondary outcomes**: serious adverse events and infections

- Primary reason for **ACT** was **refractory IBD** (**63.8%**).
- The **add-on approach** was used in **97.1%** cases.
- **Most frequent** combination was **anti-TNF + anti-integrin**.

Primary outcomes

Clinical, biochemical and endoscopic effectiveness

At 12 months:
- **Clinical** and **endoscopic response** rates were **60.0%** and **32.4%**.
- **Clinical** and **endoscopic remission** rates were **29.5%** and **28.6%**.

Secondary outcomes

Safety

- **Serious adverse events**: **12.4%**.
- **Infections**: **7.6%**.

Negative predictors of effectiveness outcomes

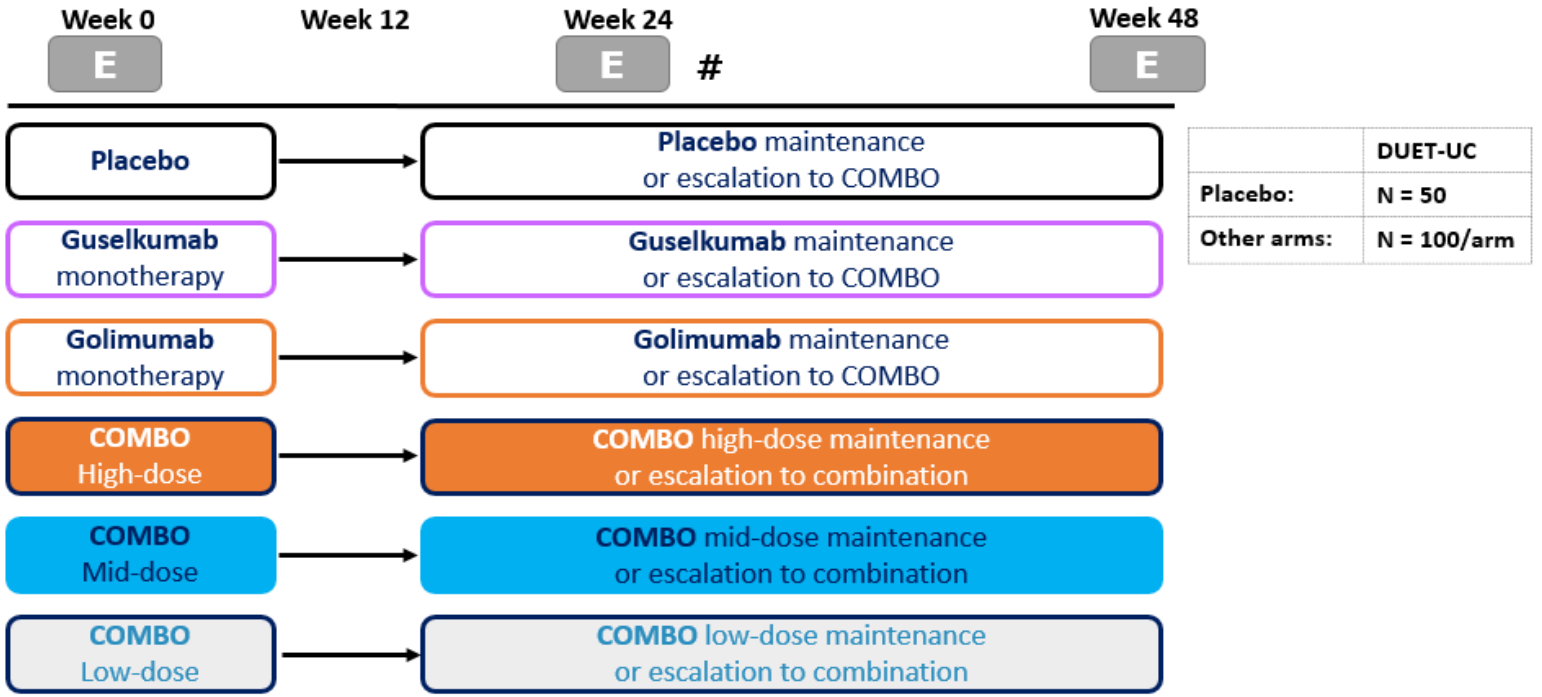
- **Longer disease duration**
- **Moderate to severe baseline activity**
- **Perianal disease**
- **Baseline corticosteroids**

AJG The American Journal of GASTROENTEROLOGY

Western

Solitano et al. The American Journal of Gastroenterology :10.14309/ajg.0000000000003573, June 05, 2025

DUET UC and CD



	DUET-UC
Placebo:	N = 50
Other arms:	N = 100/arm

https://clinicaltrials.gov/study/NCT05242471

https://clinicaltrials.gov/study/NCT05242484

Possible Combinations

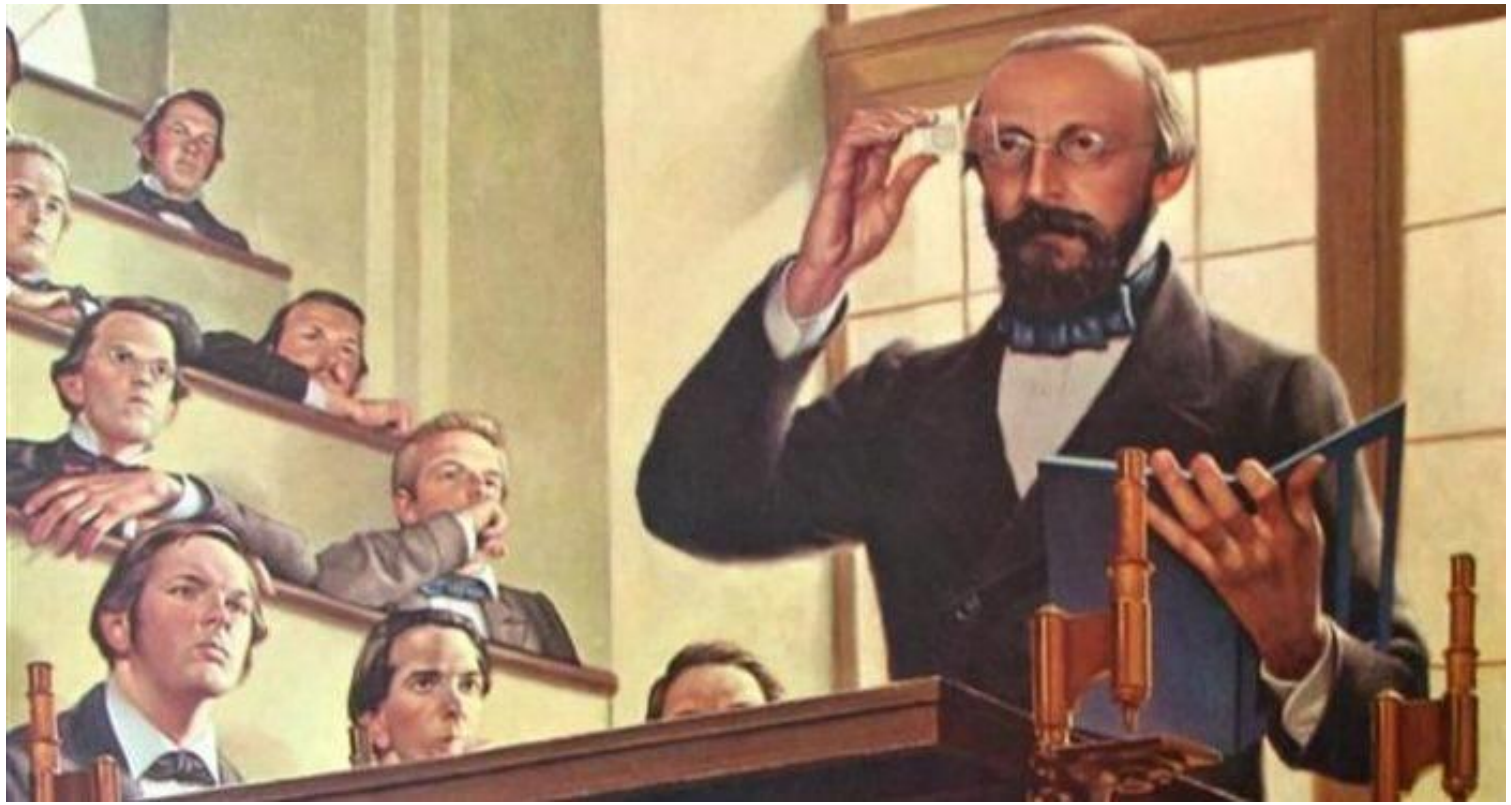
	Anti-TNF	Selective anti-integrin	Anti-IL 12/23	Anti IL 23	JAK inhibitor	S1P1 modulator
Anti-TNF	---	Yes	Yes	Yes	?	Yes
Selective anti-integrin	Yes	---	Yes	Yes	?	Yes
Anti IL 12/23	Yes	Yes	---	---	Yes	Yes
Anti IL 23	Yes	Yes	---	---	?	Yes
JAK inhibitor	?	Yes	?	?	---	Yes
S1P1 modulator	Yes	?	Yes	Yes	Yes	---

Key Recommendations for the Use of Advanced Combination Therapy in Practice

Who	Patients with IBD refractory to multiple medical therapies Patients with very high-risk phenotypes Patients with a concomitant EIM/IMID
When	The risk of doing nothing (eg, uncontrolled disease) is higher than the risk of adding a combination molecule
Where	Centers with clinical expertise and multidisciplinary teams; ensure clinical trials and surgery explored
Why	Differential and combination mechanisms of action with dual targeted treatments Lack of available options for inducing and maintaining remission and response
How	With appropriate consent and MDT Discussion
	Recycling strategy (using at least 1 agent already administered) • Simultaneous induction (starting with 2 new agents) • Add-on strategy (adding a new compound later on)
	Preference for agents with the most favorable safety profiles (eg, vedolizumab, ustekinumab
	Preference for an anti-TNF agent in CD, especially in ileal CD or with bowel damage
	Preference for vedolizumab in UC patients
	Preference for an anti-TNF agent or ustekinumab (or anti–IL-23 blocker when approved) or a JAK inhibitor in patients with concomitant EIM or IMID
	For a defined period of time with re-assessment after 6 months

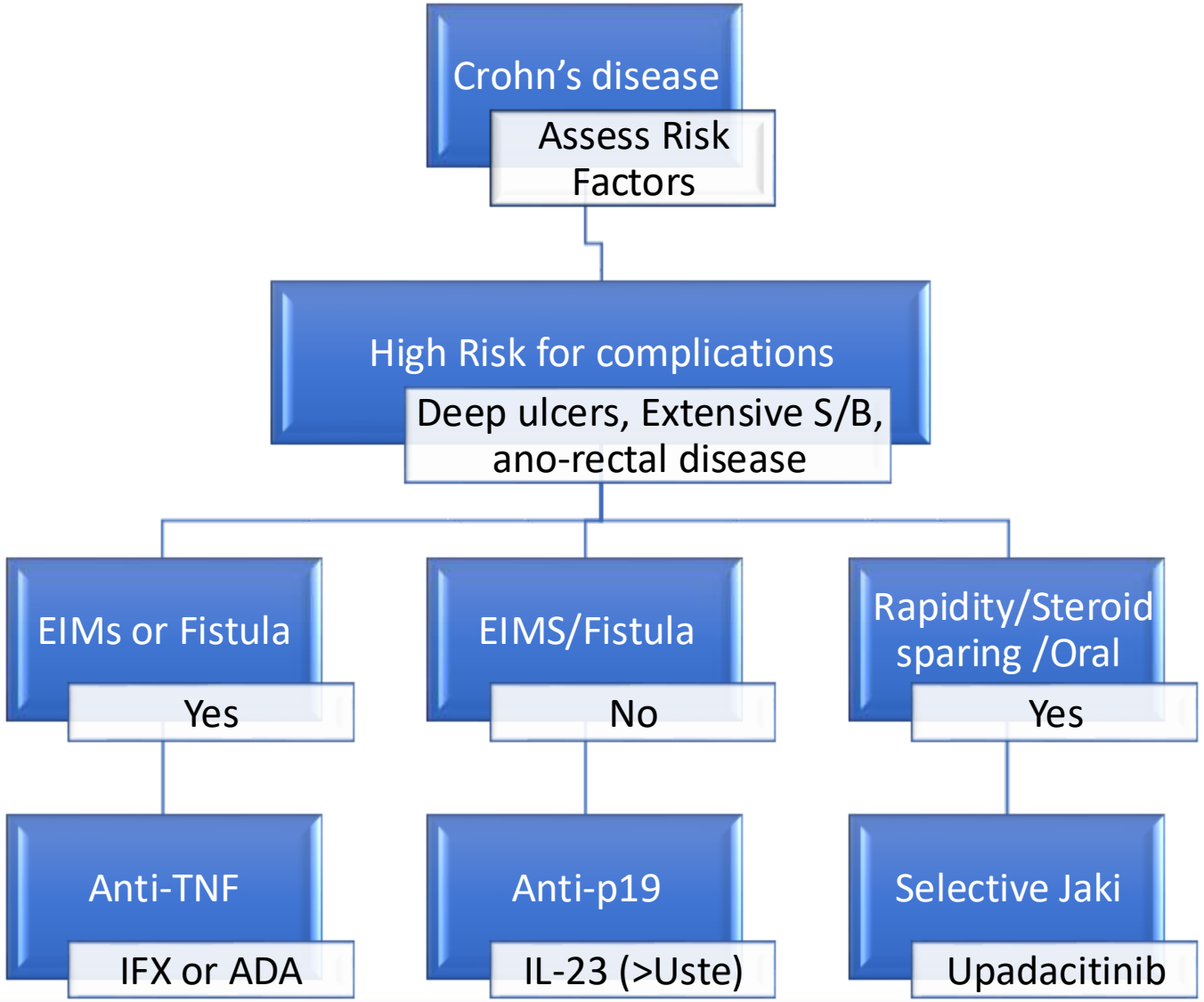
Solitano V, et al. Gastroenterology & Hepatology 2023;19:251-63.

Finally to get to the point: Opinion based medicine!



Wrapping up: How I position in practice

Positioning First-Line Therapy in CD

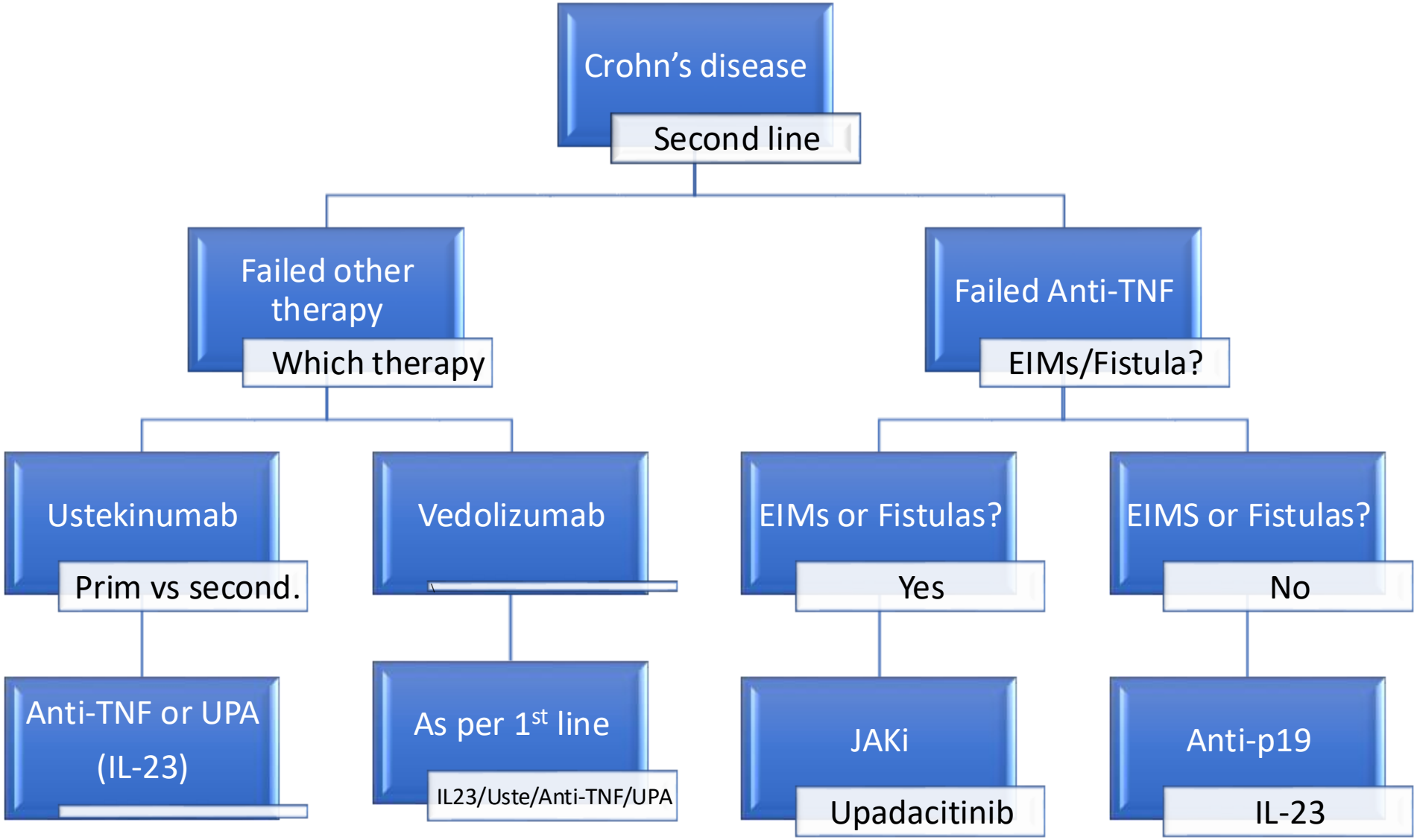


Safety Risk
Advanced age/morbidity
Malignancy

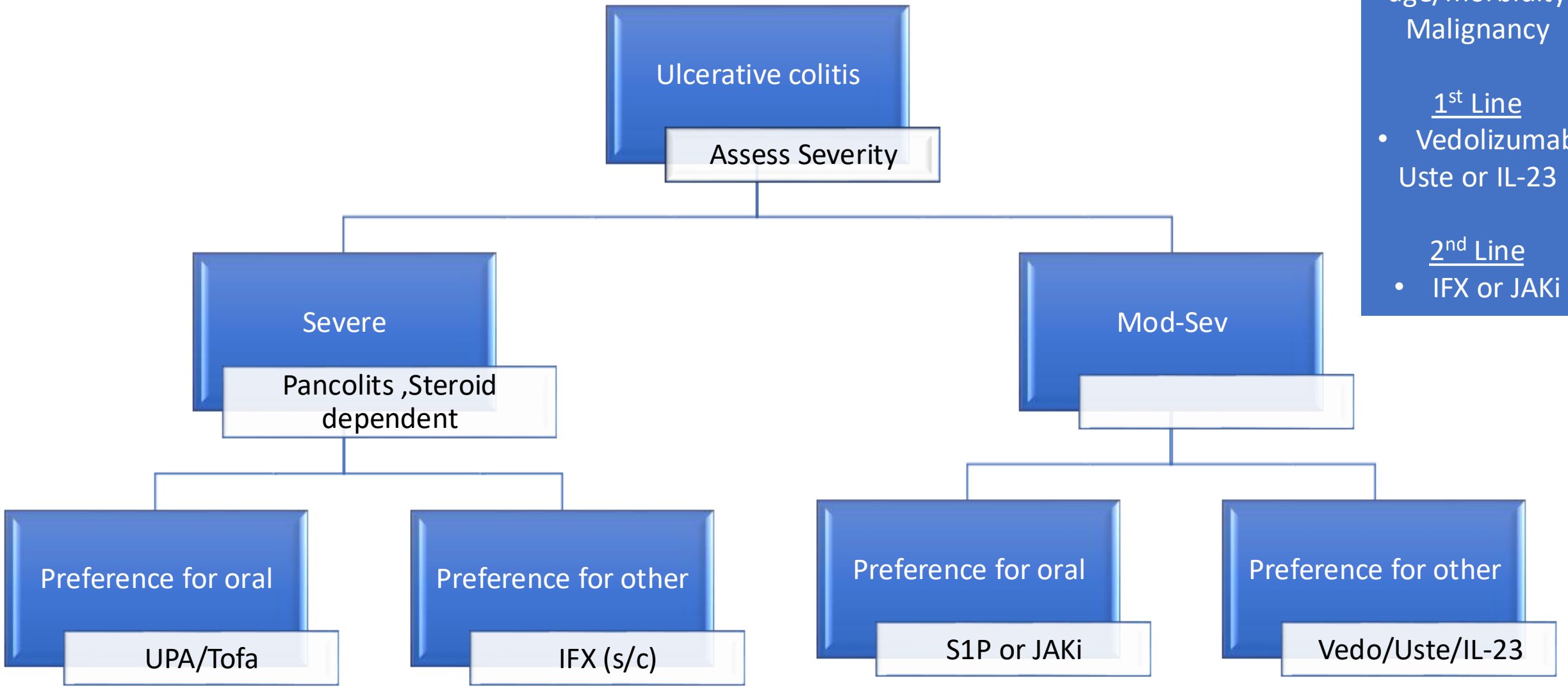
1st Line
- Vedolizumab
Uste or IL-23

2nd Line
- IFX or ADA

Positioning Second-Line Therapy in CD



Positioning First-Line Therapy in UC



Safety Risk
Advanced age/morbidity
Malignancy

1st Line
- Vedolizumab
Uste or IL-23

2nd Line
- IFX or JAKi

Positioning Second-Line Therapy in UC