

Thérapies avancées en MII : positionnement, combinaisons et innovations



Talat Bessissow, MD, MSc, FRCPC

Professeur Agrégé de Médecine et Gastroenterology

Centre Universitaire de Santé McGill

Divulgations du présentateur

Talat Bessissow, M.D., C.M., FRCPC

le(s) commanditaire(s) financier(s)

HONORAIRES DE CONSULTATION/
MEMBRE DU COMITÉ CONSULTATIF :

Abbvie, Alimentiv, BMS, CSF Vifor, Celltrion, Eli Lilly, Iterative scope, Johnson & Johnson, Mirium, Pentax, Pfizer, Sandoz, Sanofi, Takeda, Vial Pharma

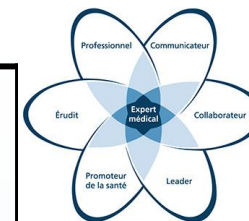
BUREAU DE CONFÉRENCIERS/HONORAIRES :

Abbvie, BMS, Celltrion, Ferring, Fresenius Kabi, Gilead, Johnson & Johnson, Merck, Pendopharm, Pentax, Pfizer, Roche, Sandoz, Takeda

SUBVENTIONS/SOUTIEN À LA RECHERCHE :

AUTRE :

Compétences CanMEDS



CANMEDS

X	Expert médical (En tant qu'experts médicaux, les médecins assument tous les rôles CanMEDS et s'appuient sur leur savoir médical, leurs compétences cliniques et leurs attitudes professionnelles pour dispenser des soins de grande qualité et sécuritaires centrés sur les besoins du patient. Pivot du référentiel CanMEDS, le rôle d'expert médical définit le champ de pratique clinique des médecins .)
	Communicateur (En tant que communicateurs, les médecins développent des relations professionnelles avec le patient et ses proches ce qui permet l'échange d'informations essentielles à la prestation de soins de qualité.)
	Collaborateur (En tant que collaborateurs, les médecins travaillent efficacement avec d'autres professionnels de la santé pour prodiguer des soins sécuritaires et de grande qualité centrés sur les besoins du patient.)
X	Leader (En tant que leaders, les médecins veillent à assurer l'excellence des soins, à titre de cliniciens, d'administrateurs, d'érudits ou d'enseignants et contribuent ainsi, avec d'autres intervenants, à l'évolution d'un système de santé de grande qualité.)
X	Promoteur de santé (En tant que promoteurs de la santé, les médecins mettent à profit leur expertise et leur influence en oeuvrant avec des collectivités ou des populations de patients en vue d'améliorer la santé. Ils collaborent avec ceux qu'ils servent afin d'établir et de comprendre leurs besoins, d'être si nécessaire leur porte-parole, et de soutenir l'allocation des ressources permettant de procéder à un changement.)
X	Érudit (En tant qu'érudits, les médecins font preuve d'un engagement constant envers l'excellence dans la pratique médicale par un processus de formation continue, en enseignant à des tiers, en évaluant les données probantes et en contribuant à l'avancement de la science.)
	Professionnel (En tant que professionnels, les médecins ont le devoir de promouvoir et de protéger la santé et le bien-être d'autrui, tant sur le plan individuel que collectif. Ils doivent exercer leur profession selon les normes médicales actuelles, en respectant les codes de conduite quant aux comportements qui sont exigés d'eux, tout en étant responsables envers la profession et la société. De plus, les médecins contribuent à l'autoréglementation de la profession et voient au maintien de leur santé.)



Objectifs

À la fin de cette présentation, le participant sera en mesure de:

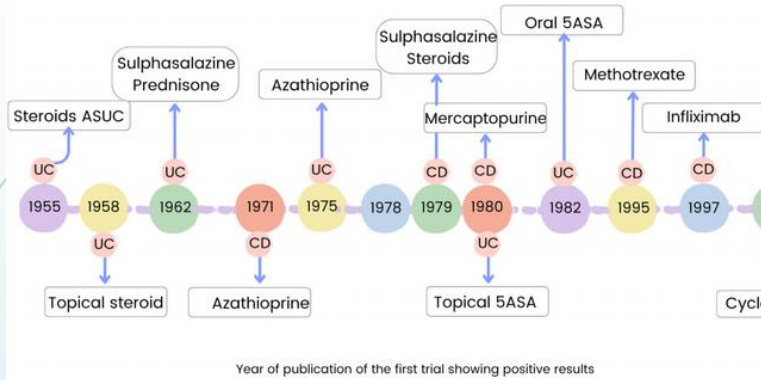
- Décrire les thérapies avancées disponibles, en mettant l'emphase sur les données probantes les plus récentes.
- Concevoir des plans de traitement utilisant les thérapies avancées en MII en adaptant la séquence d'utilisation des nouvelles thérapies à la situation clinique des patients
- Discuter de l'utilisation des thérapies combinées dans le contexte québécois



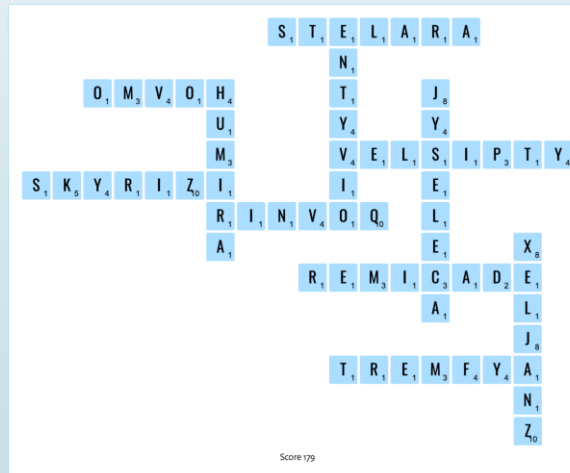
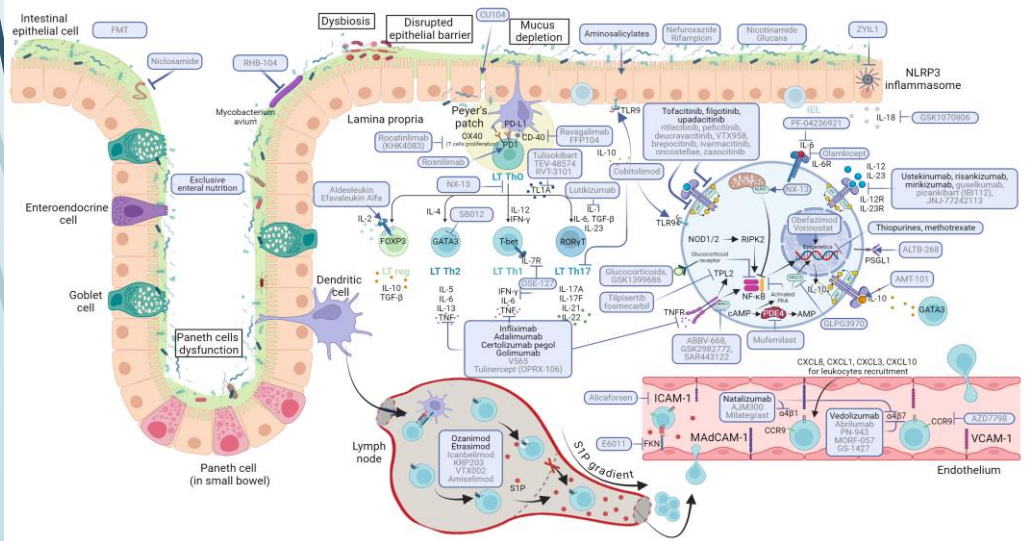
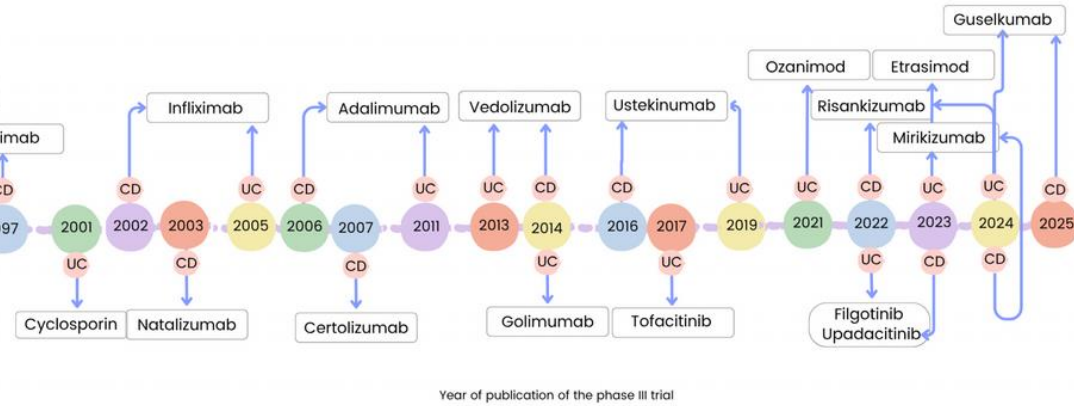
Evolution of the therapeutic landscape

Evolution of the Therapeutic Landscape

PRE BIOLOGIC ERA



BIOLOGIC ERA



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

Vieujean S, Jairath V, et al, Nature Review Gastro 20

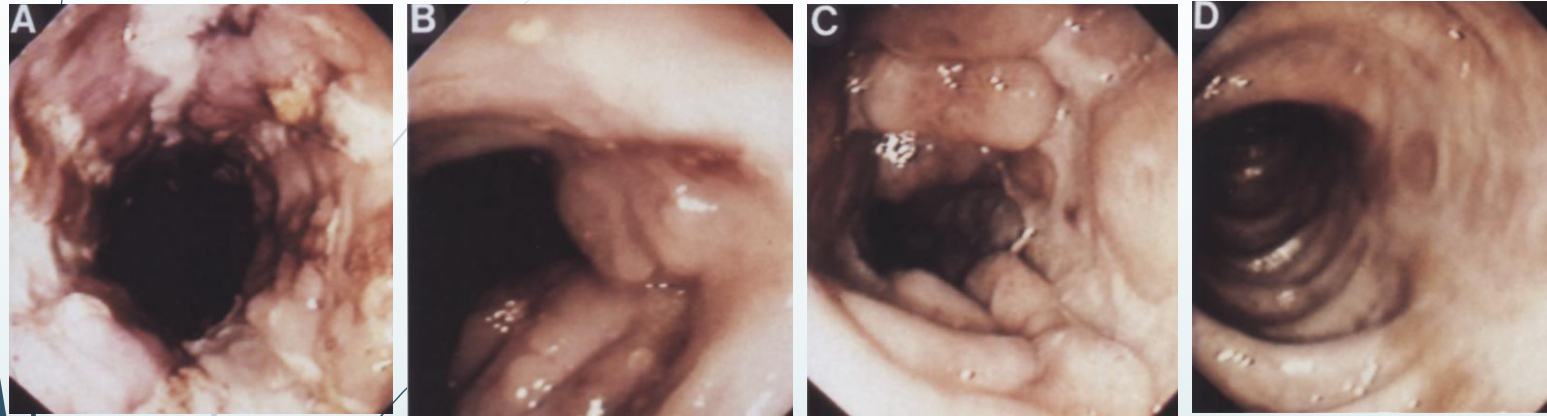


Anti-TNF

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.

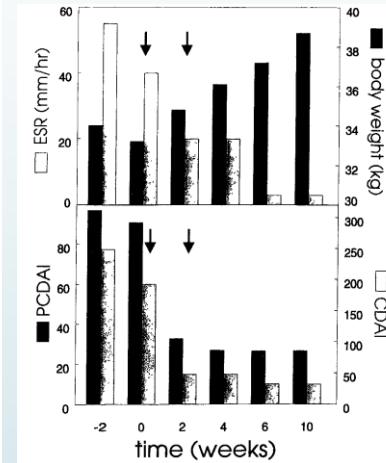
van Dullemen HM, et al. *Gastroenterology*. 1995;109(1):129-135.

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.

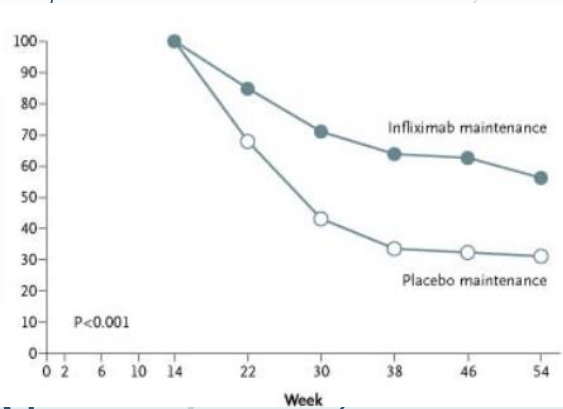
At age 12 years the patient was examined because of diarrhoea of 4 months' duration, rectal blood loss, abdominal pain, fever, and loss of 4.5 kg. Colonoscopy showed multiple aphthoid lesions, skip lesions, erythema, friability, and granularity in the distal 70 cm of the colon extending into the anus. 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-TNF α (chimeric monoclonal cA2,

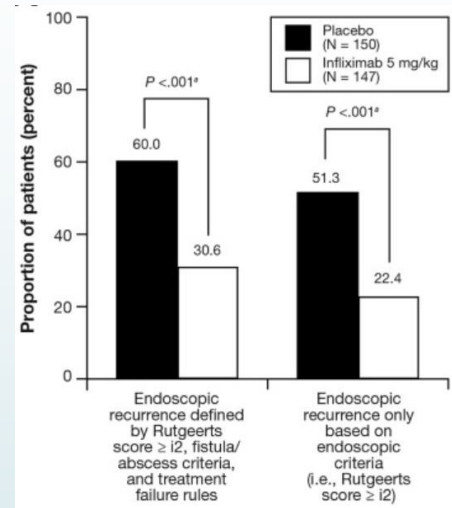


Anti-TNF- Still very relevant today!

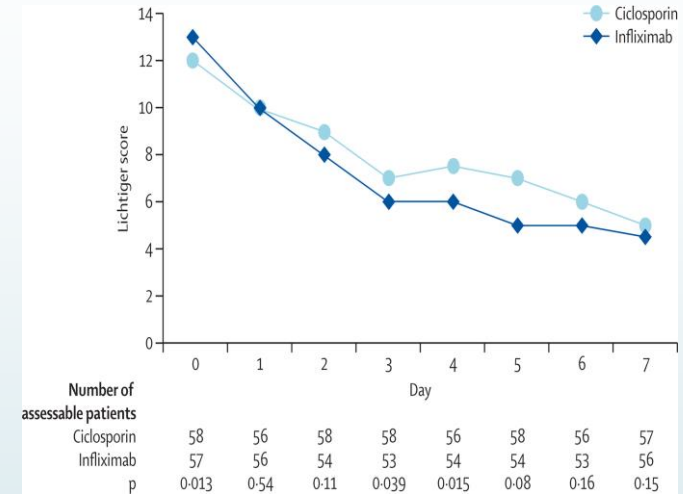
Peri-Anal CD (ACCENT 2)



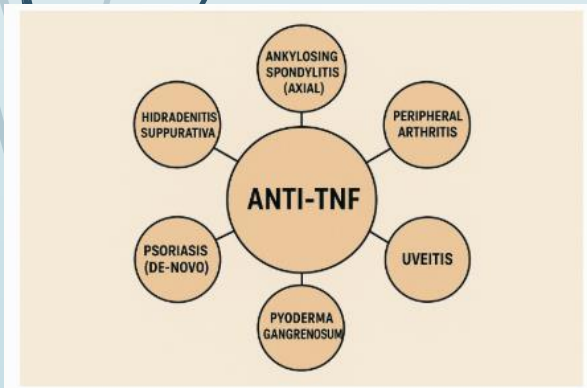
Post-Op Prophylaxis (PREVENT)



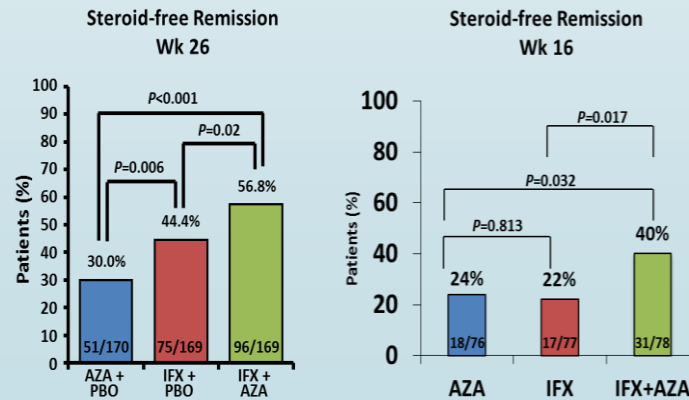
ASUC (CysIF)



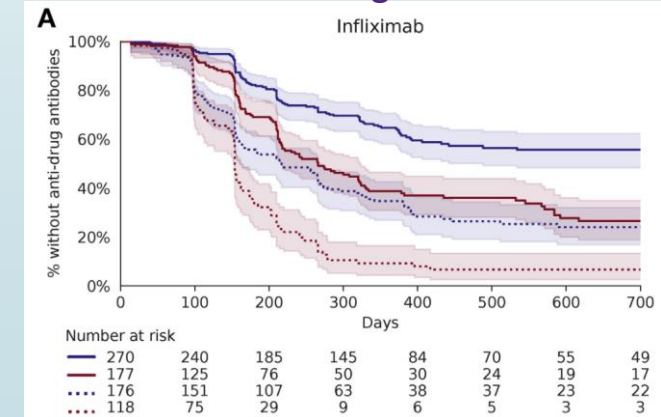
EIMs



Use combo therapy

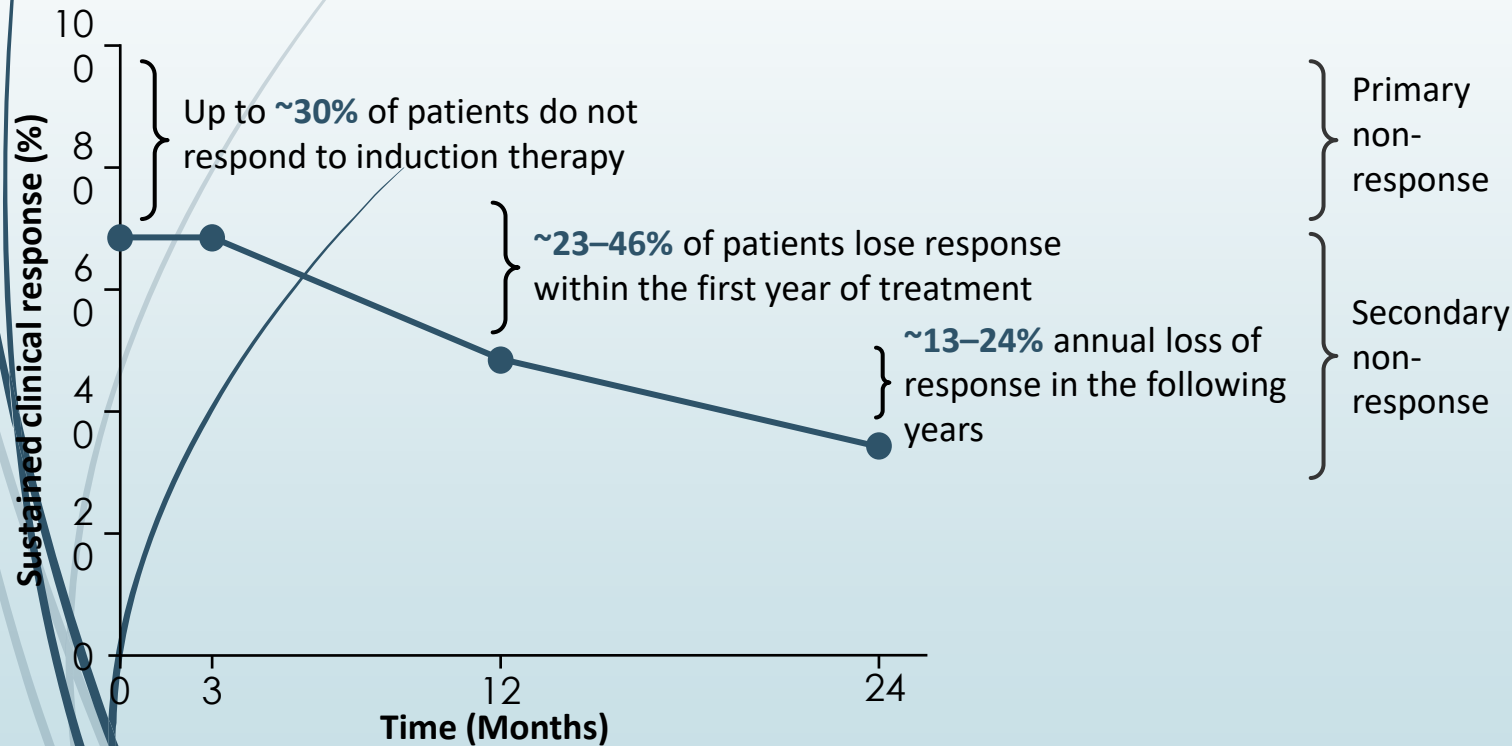


HLA testing



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 therapies¹⁻³
 - Black-box warning for HSTCL (adalimumab and infliximab)^{1,2}
- Reactivation of hepatitis B³, tuberculosis
- Skin cancer³
- Psoriasis⁴
- Autoimmunity (lupus-like syndrome)³
- Immunogenicity – antibodies to anti-TNF³
- Demyelinating disorders, CHF, liver toxicity³

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

¹Remicade [package insert]. Horsham, PA: Janssen Biotech, Inc; 2013

²Humira [package insert]. North Chicago, IL: AbbVie, Inc; 2013

³Bongartz T, et al. *JAMA*. 2006;295:2275-2285

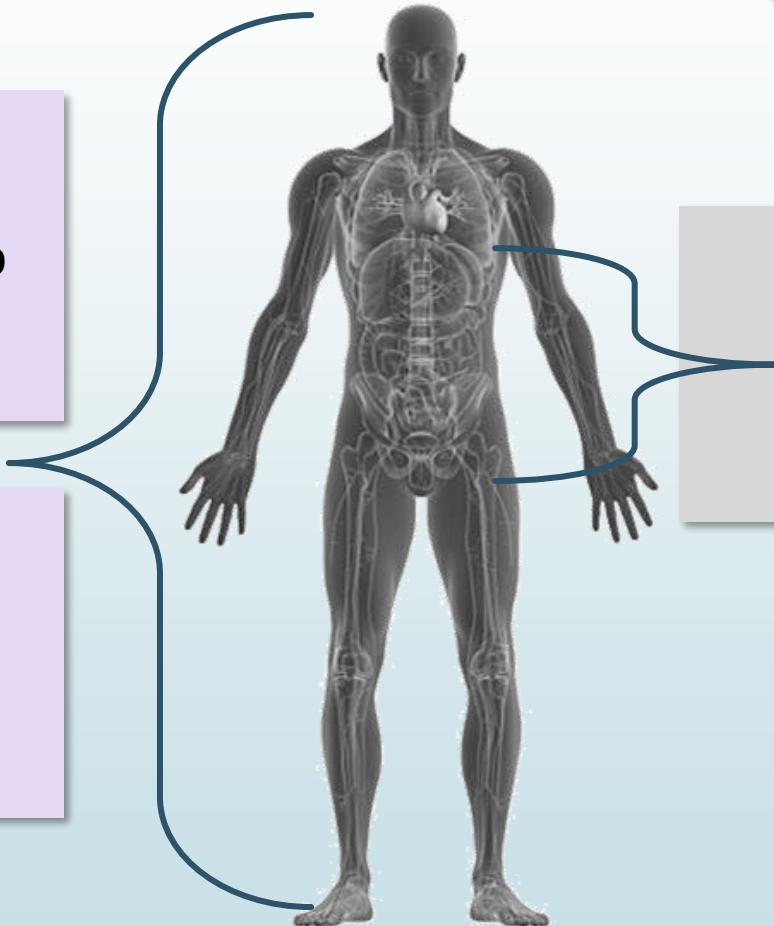


Anti-Integrins

Systemic

Gut-specific

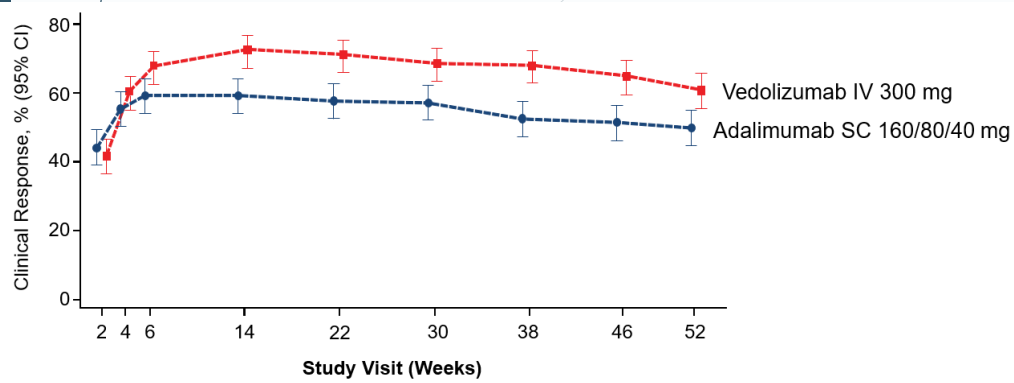
Anti-TNFα	Infliximab Adalimumab	Anti-interleukin	Ustekinumab Risankizumab Mirikizumab
JAK inhibitor	Tofacitinib Filgotinib Upadacitinib	S1P inhibitor	Ozanimod Etrasimod



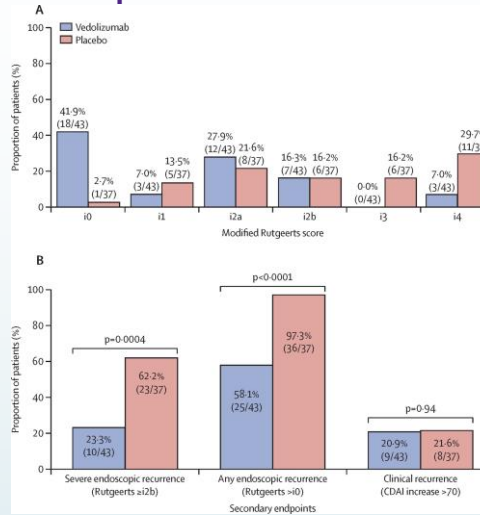
Anti-integrin
Vedolizumab

Vedolizumab

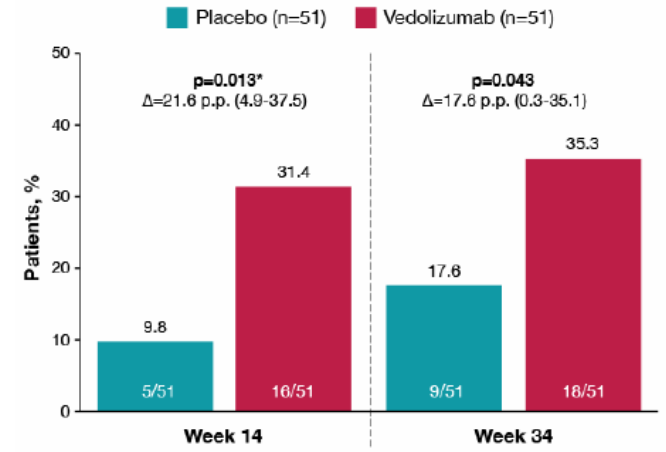
Superior to ADA in UC: VARSITY



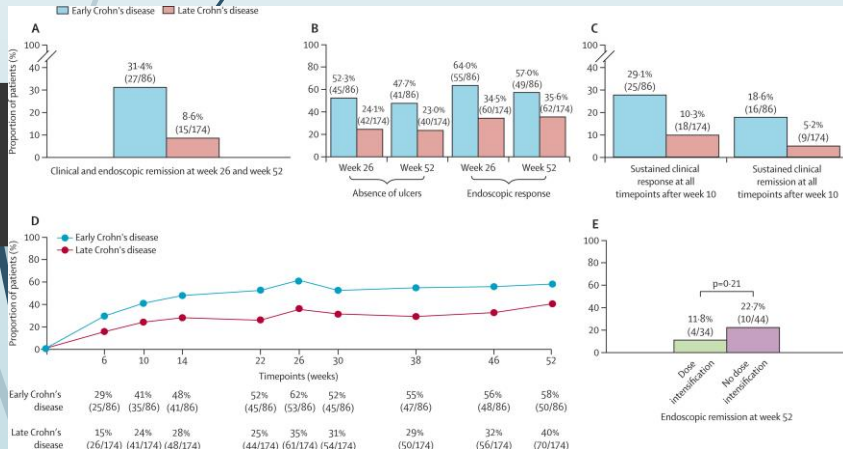
Post-Op CD Prevention: REPREVIO



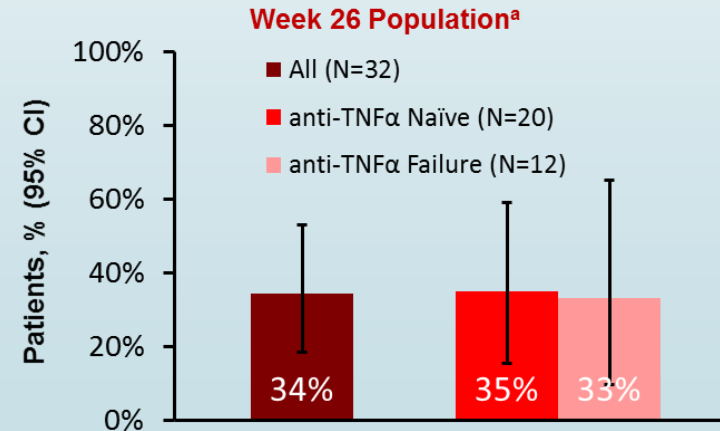
Chronic Pouchitis: EARNEST



Early CD: LOVE CD

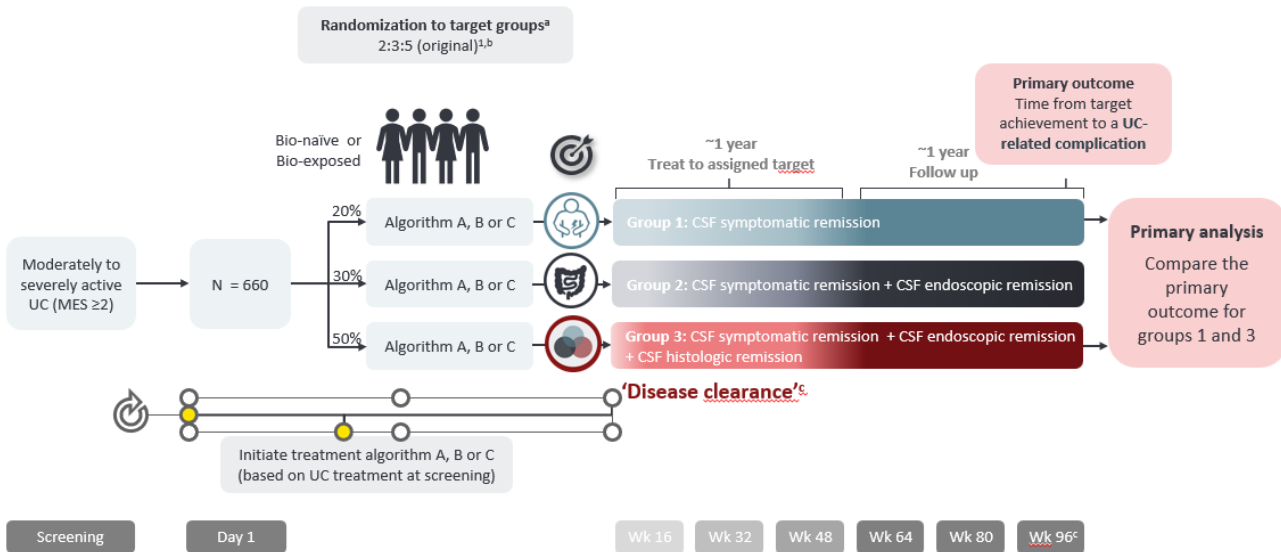


Transmural Healing: VERSIFY

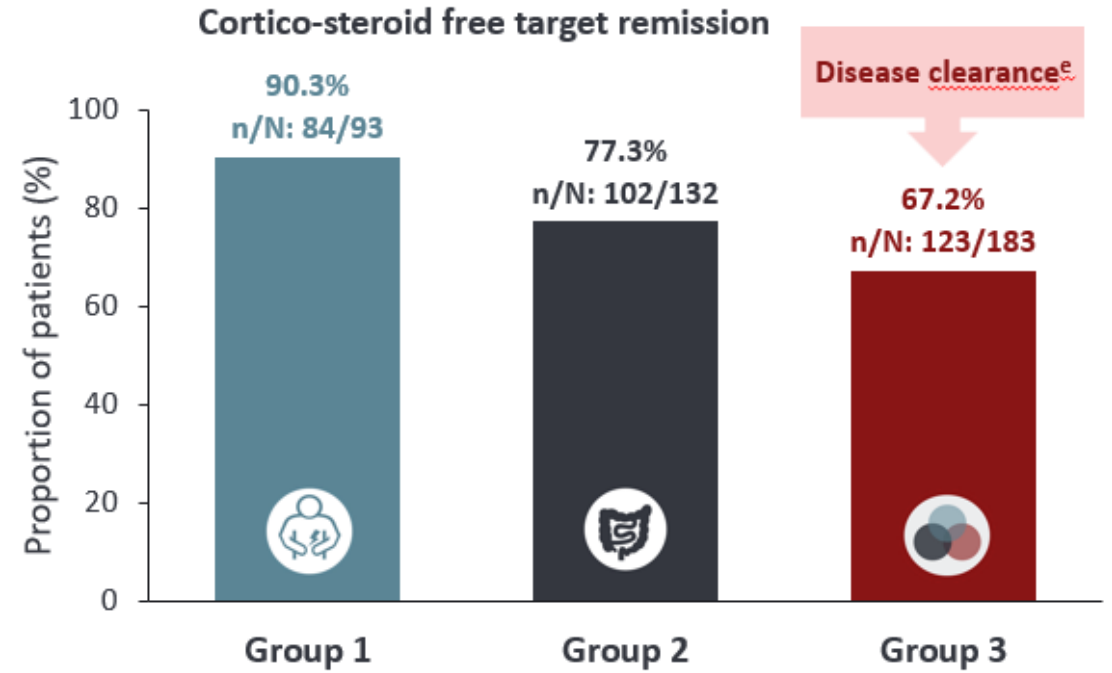


Vedolizumab and Disease Clearance: VERDICT trial

Trial Design



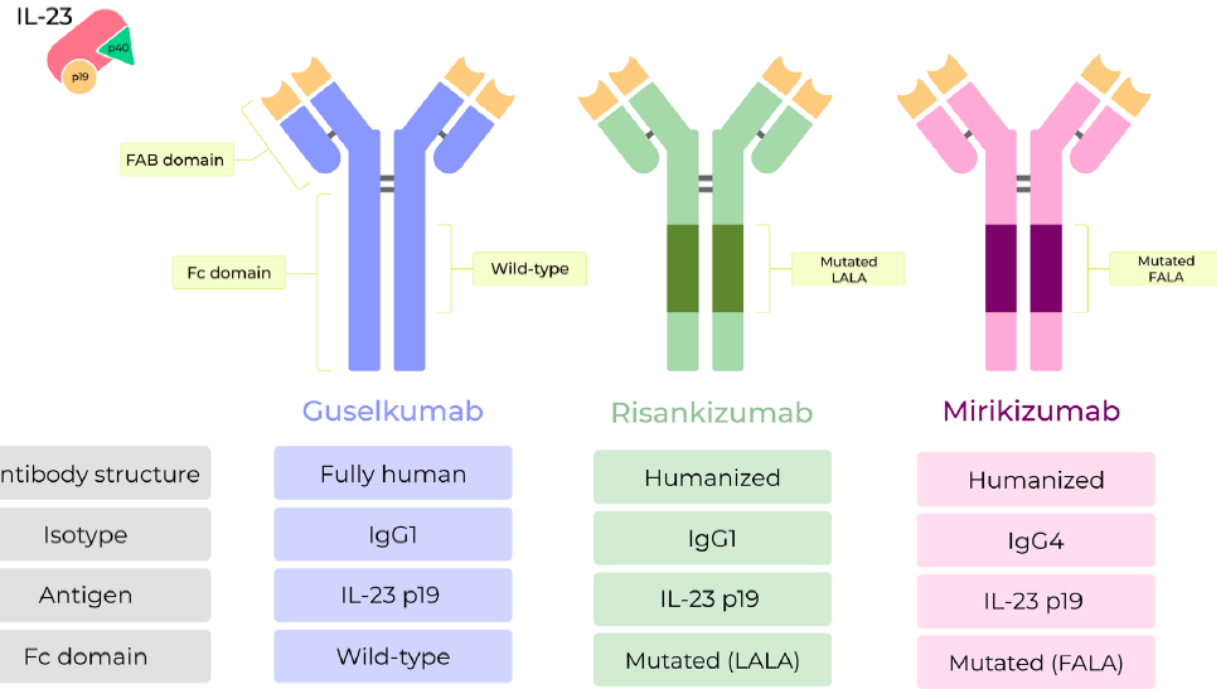
48 Week Disease Clearance



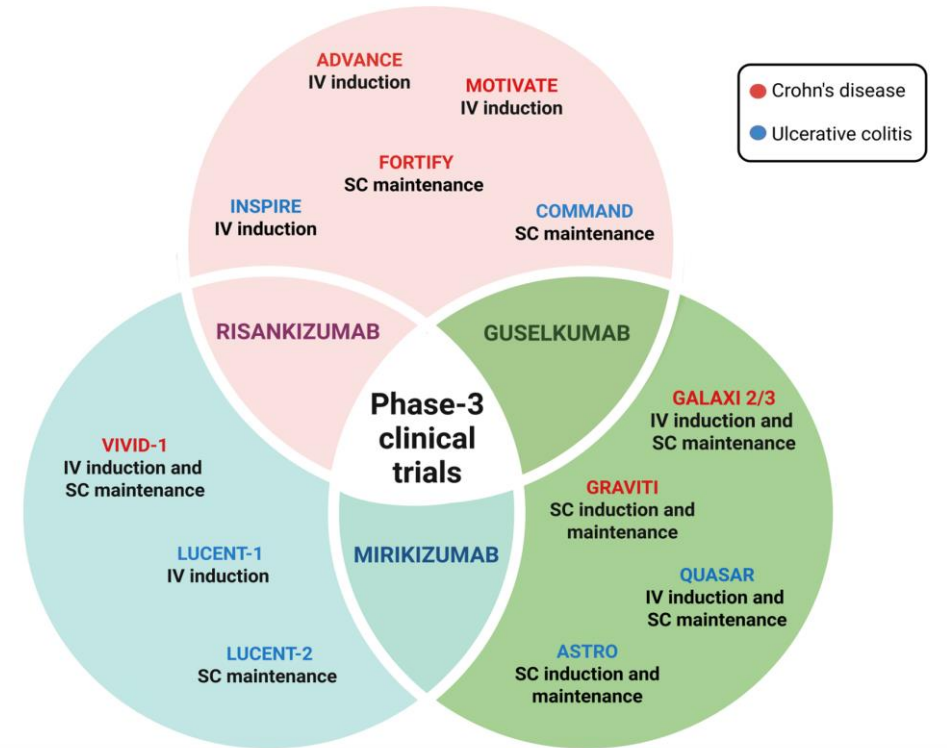


Interleukin Inhibitors

IL-23 Inhibitors: No Clinically meaningful differences to date

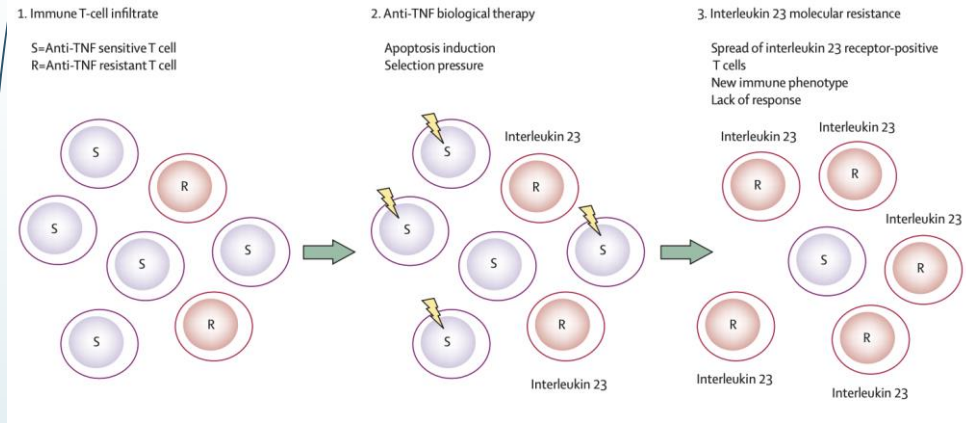


Fc, fragment crystallizable; FAB, fragment antigen-binding; LALA, leucine to alanine substitution at positions 234 and 235; FALA, phenylalanine to alanine substitution and leucine to alanine substitution at positions 234 and 235;

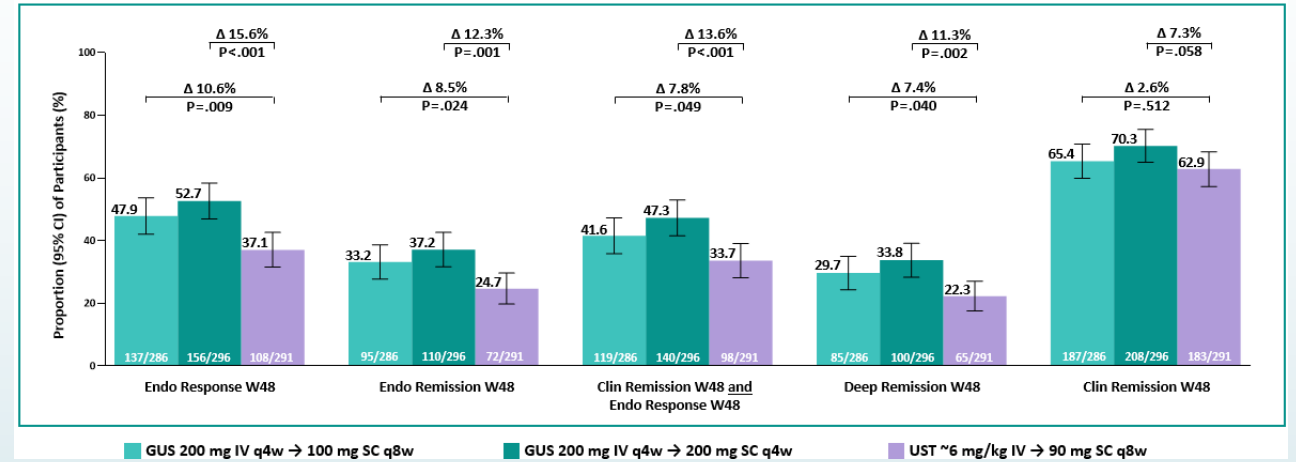


IL-23 Inhibition has moved the needle

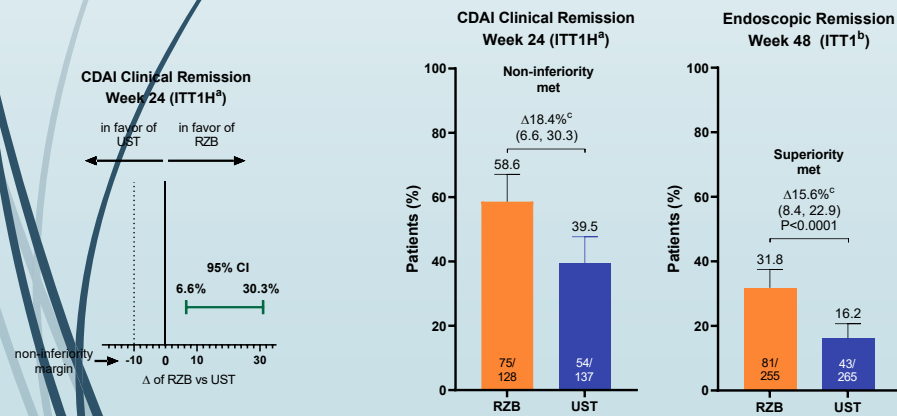
Evolutional pressure of immune therapy and drug resistance



GALAXI 2&3 trials

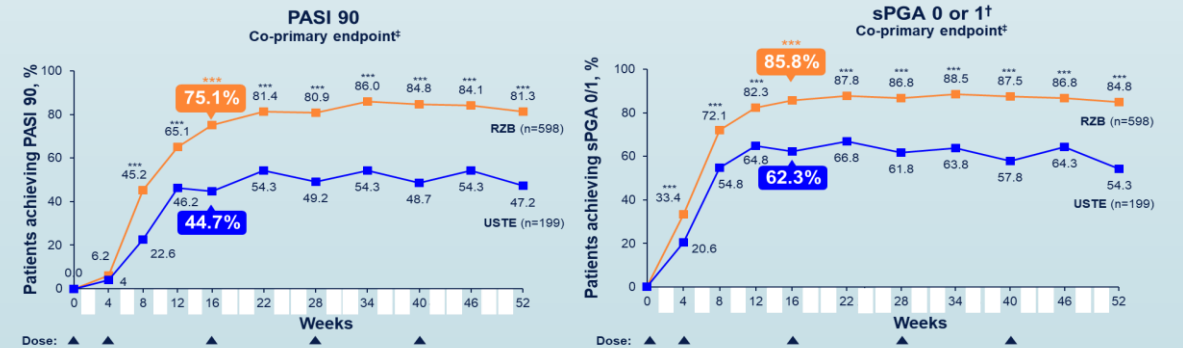


SEQUENCE trial



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).
^a $P < 0.001$. ^bsPGA 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.

Atreya R, Neurath M. Lancet Gastroenterol Hepatol. 2018

Peyrin-Biroulet L, et al. NEJM 2024.

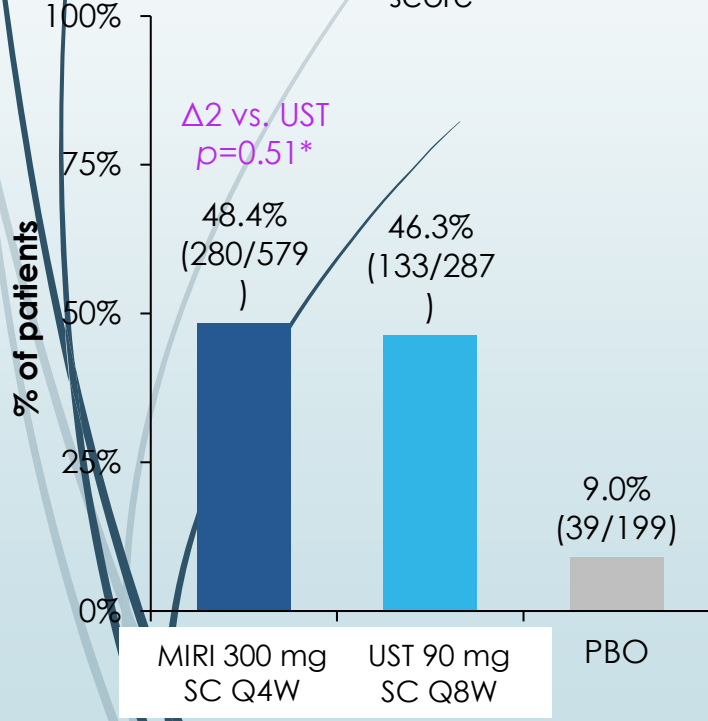
Panaccione R et al. DDW 2024

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.

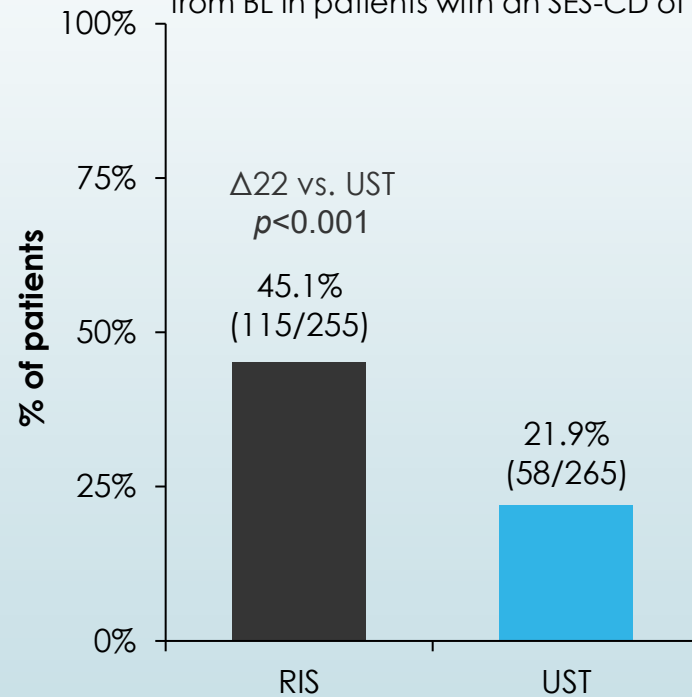
VIVID-1 Week 52, NRI¹

Endoscopic response: $\geq 50\%$ reduction from BL in SES-CD total score



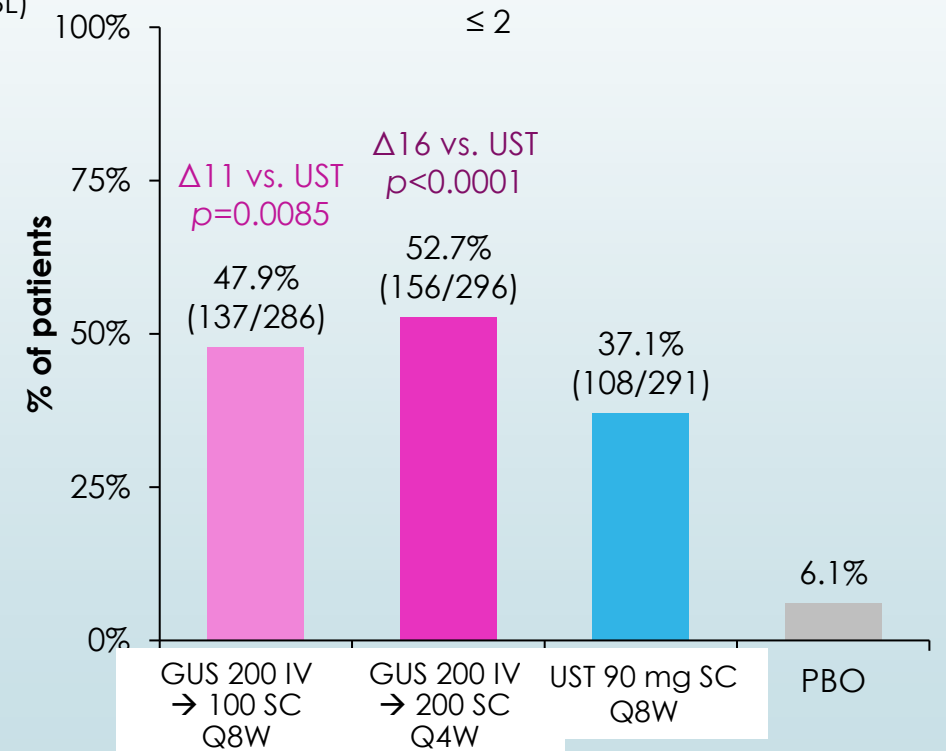
SEQUENCE Week 48, NRI²

Endoscopic response: $\geq 50\%$ 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)



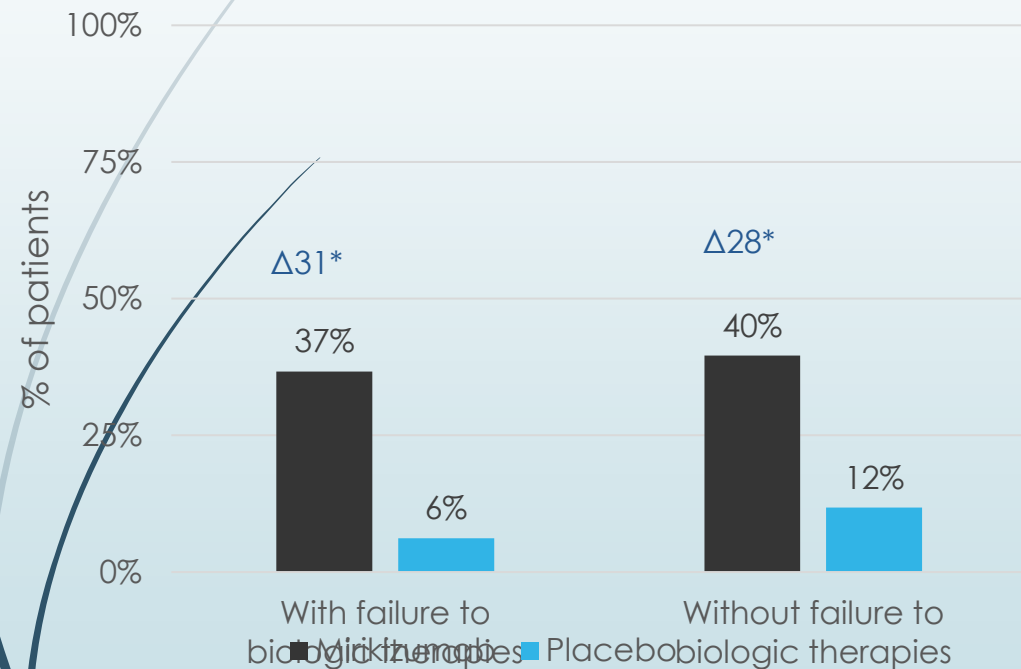
Pooled GALAXI 2 & 3 Week 48, NRI³

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

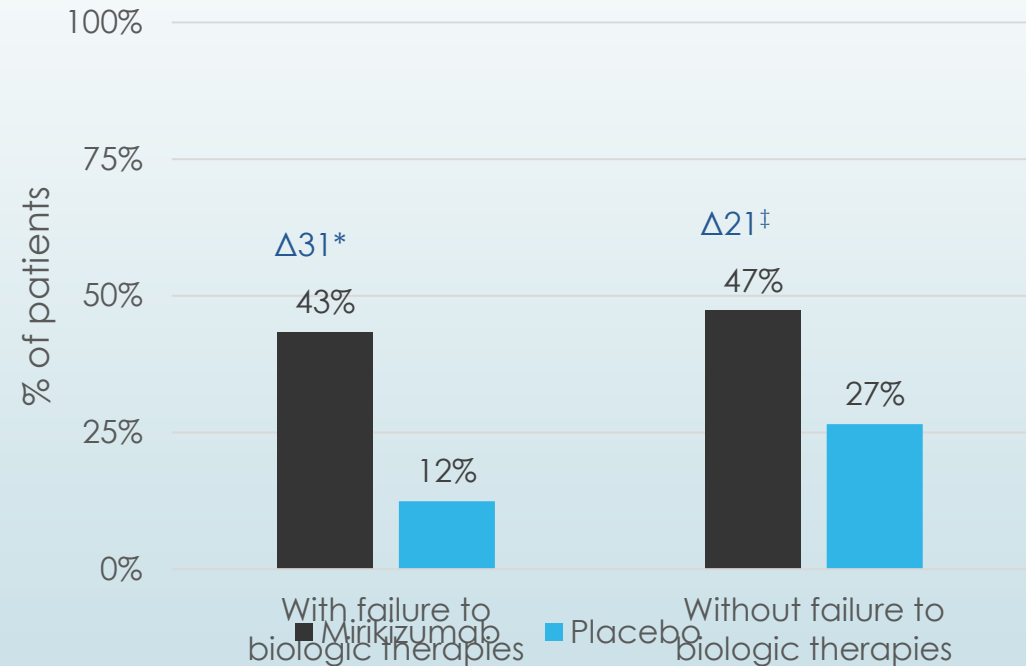


IL-23s have similar efficacy in bionaive and bioexposed patients

**PRO Clinical Response^a at Week 12 and
SES-CD Endoscopic Response^b at Week 52**

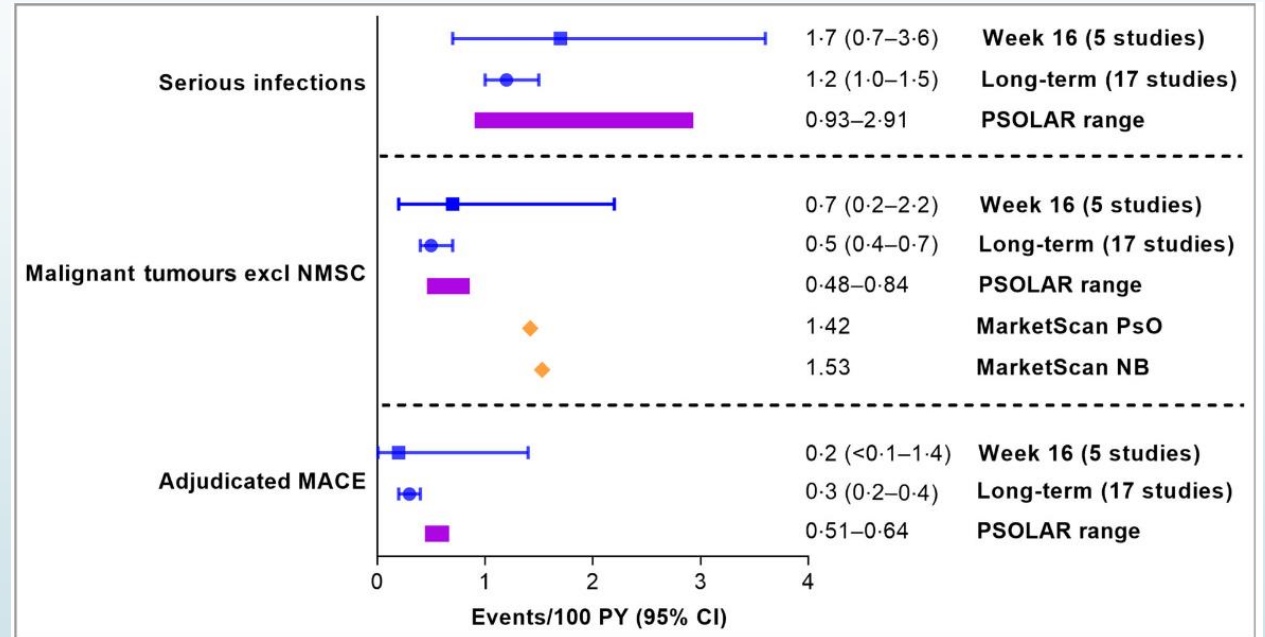
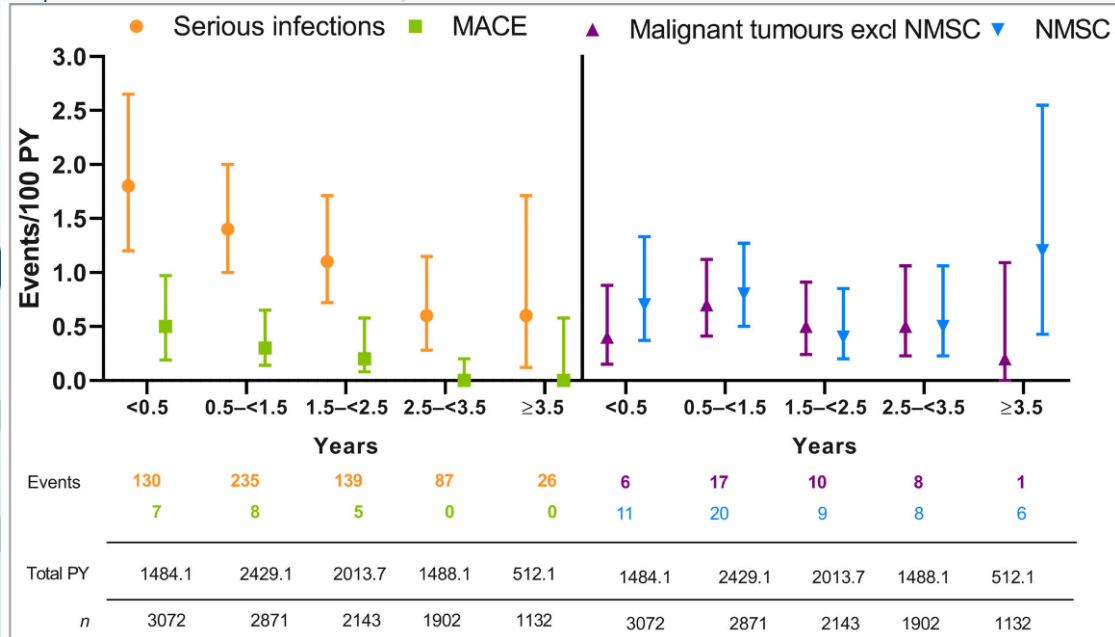


**PRO Clinical Response^a at Week 12 and
CDAI Clinical Remission^c at Week 52**



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

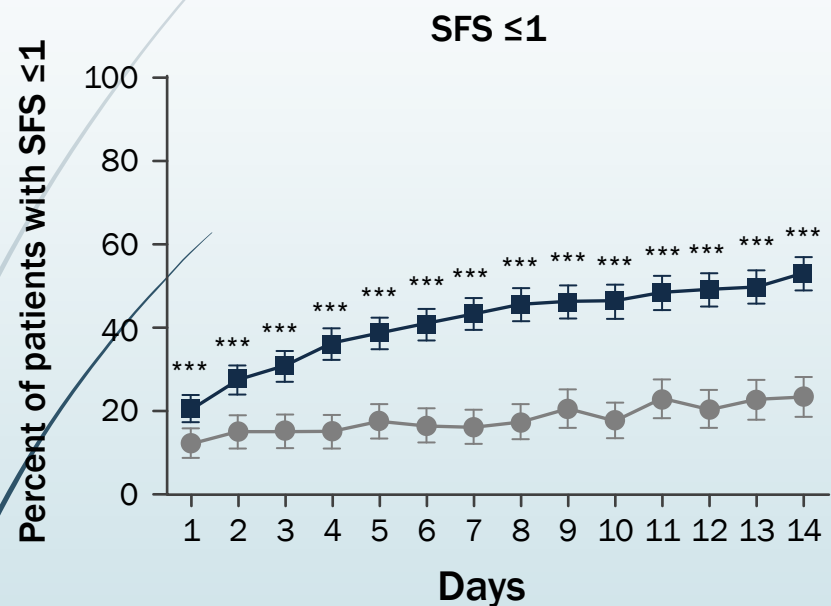




JAK Inhibition

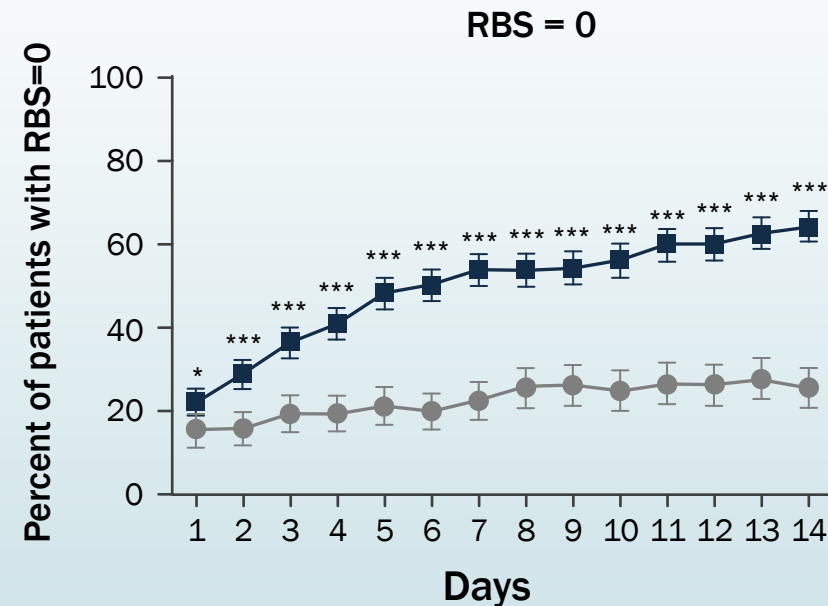
JAKs work rapidly!

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

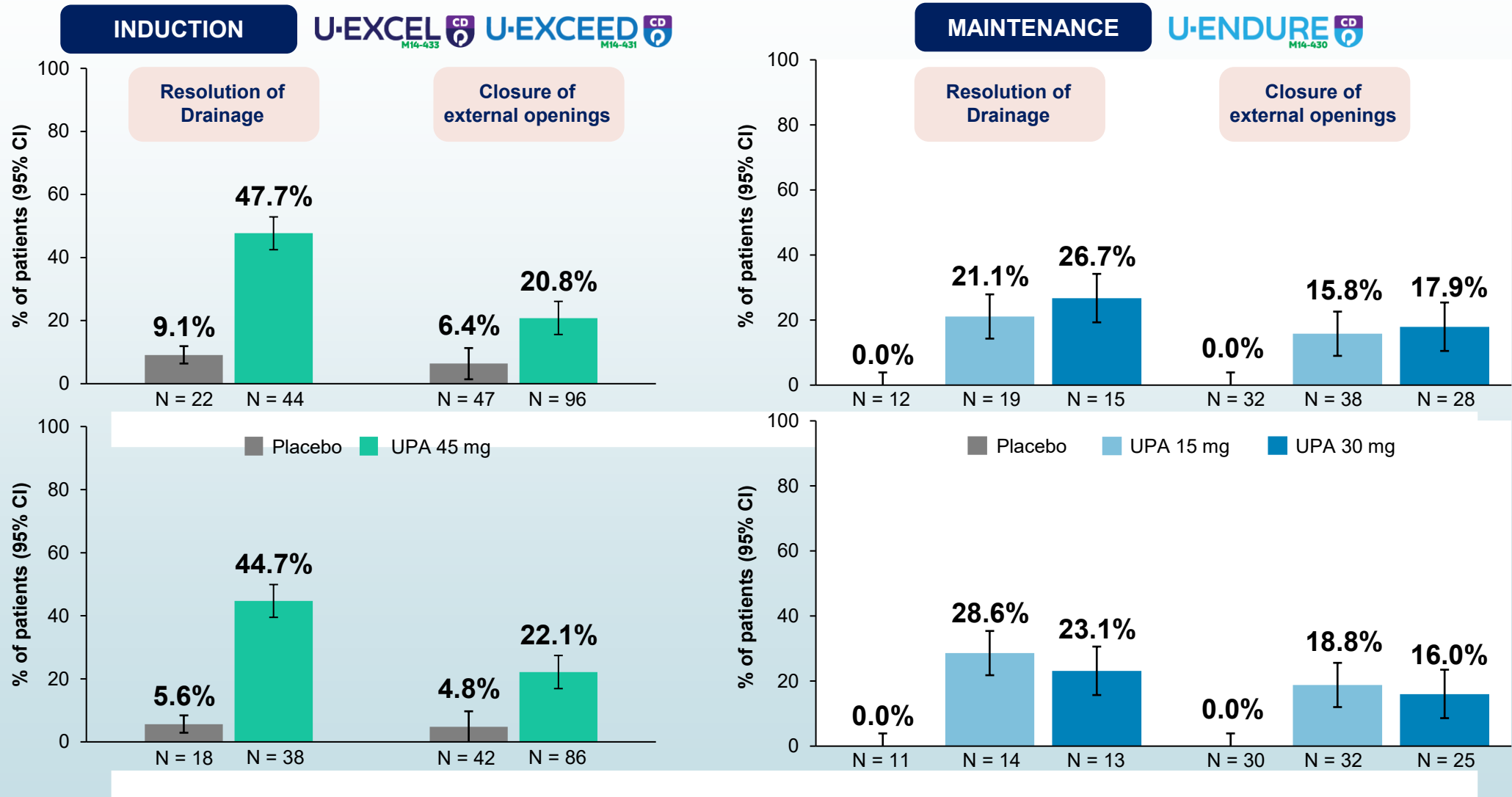
● PBO (n=303-319) ■ UPA 45 mg QD (n=616-634)

Error bars are \pm 95% CI. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ 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 analysis

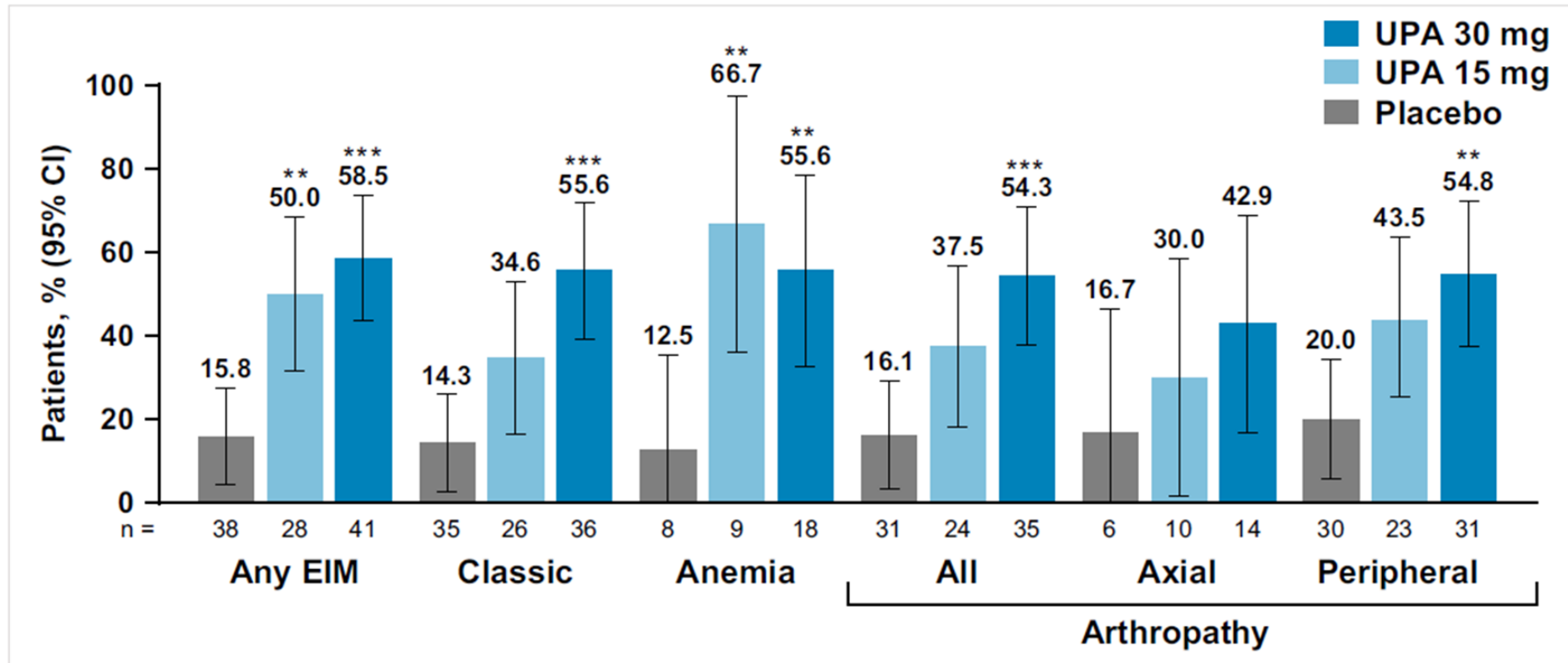
Any
Fistulas

Perianal
fistulas



Excellent 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 < 0.01. *P < 0.001.

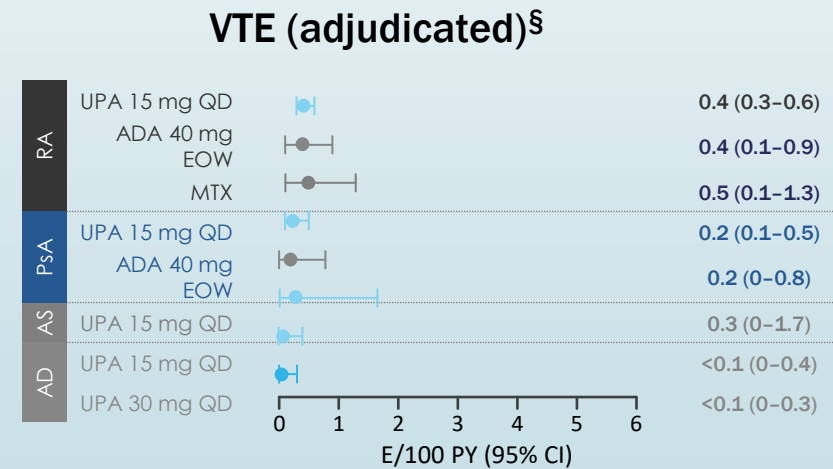
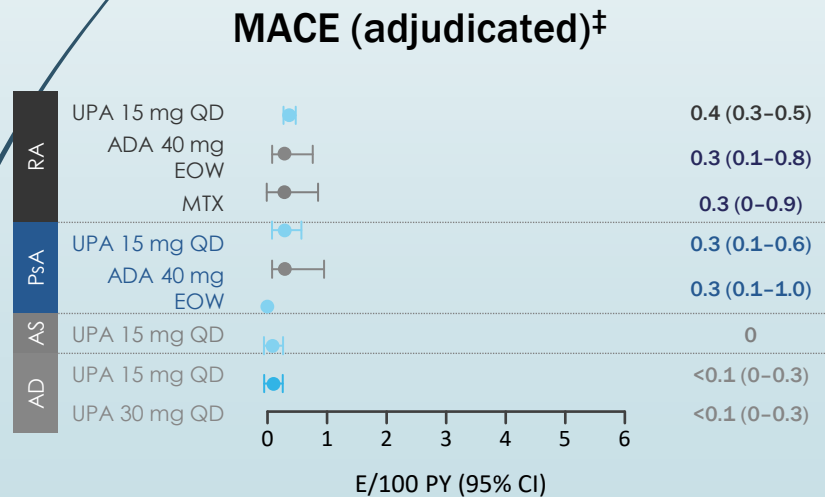
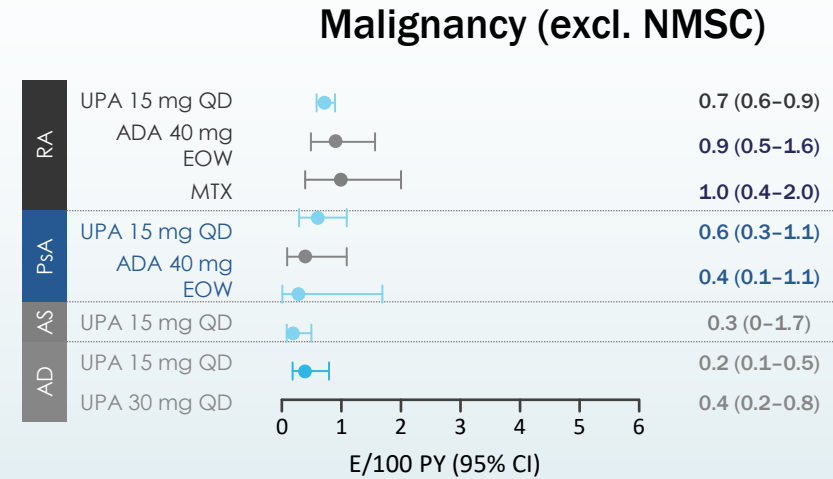
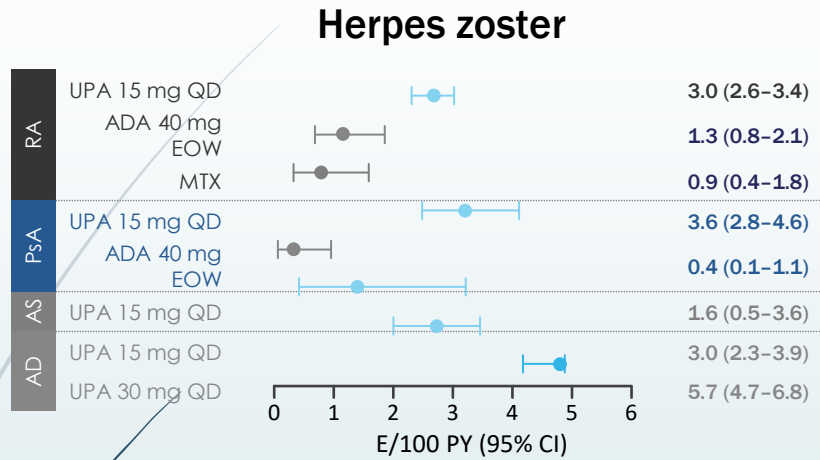
JAKs for management of ASUC?

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



[‡]Defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. [§]Including deep vein thrombosis and pulmonary embolism.

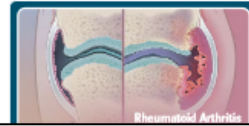
AD, atopic dermatitis; ADA, adalimumab; AS, ankylosing spondylitis; CI, confidence interval; E, events; MACE, major adverse cardiac event; MTX, methotrexate; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis; PY, person-years; QD, once daily; RA, rheumatoid arthritis; UPA, upadacitinib; VTE, venous thromboembolism.

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



Cytokines

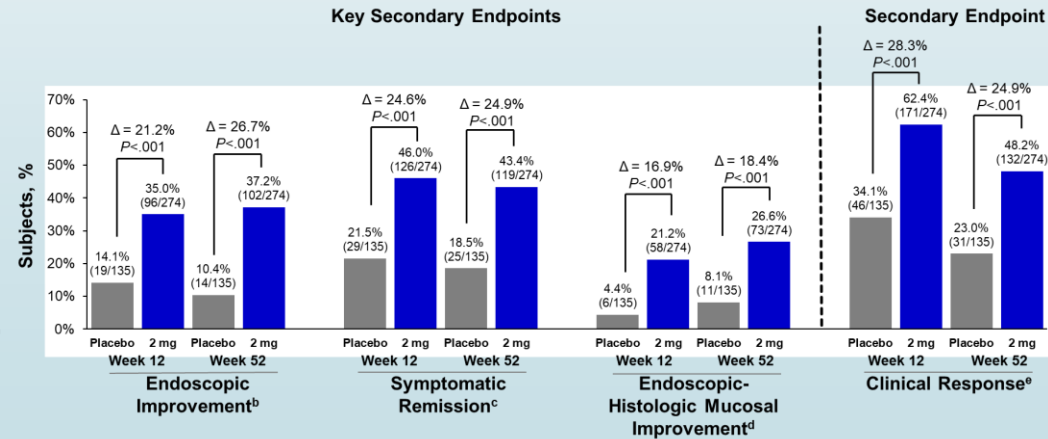
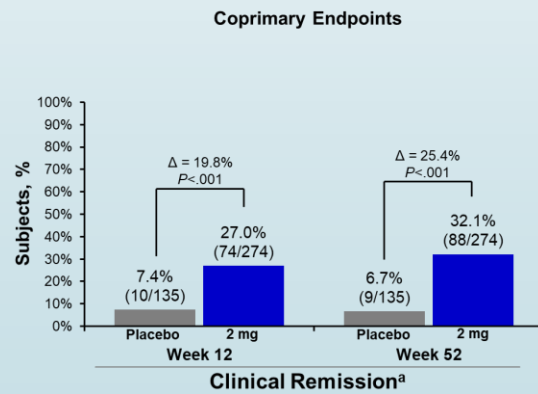
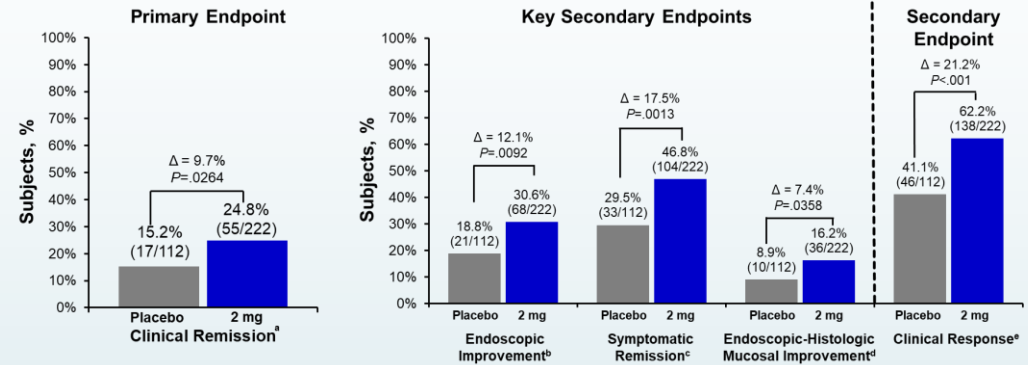
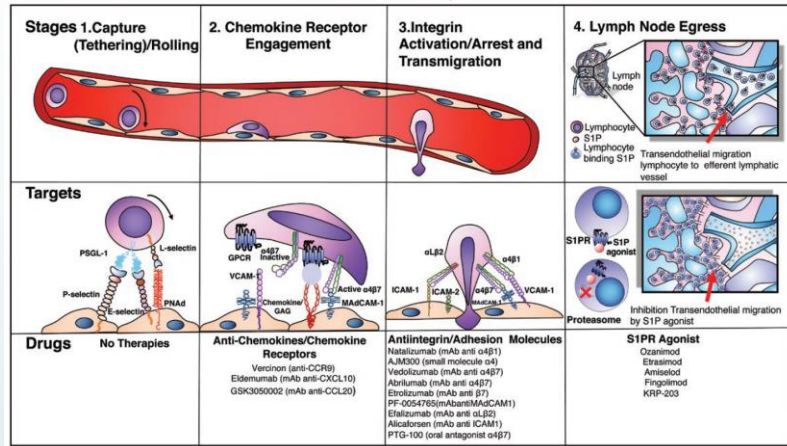
Dans cet essai, le **nombre nécessaire pour nuire** (*number needed to harm, NNH*) avec le **tofacitinib à la dose de 5 mg deux fois par jour**, comparativement à un **inhibiteur du TNF**, était de **567 années-patients pour les MACE** (*événements cardiovasculaires majeurs indésirables*) et de **276 années-patients pour les cancers**.

Cela signifie qu'au cours de **5 années de traitement**, **113 patients** et **55 patients**, respectivement, devraient être traités par **tofacitinib 5 mg deux fois par jour** plutôt que par un **inhibiteur du TNF** pour entraîner **un MACE additionnel** et **un cancer additionnel**.



S1P1 Modulators

S1P Agonists: First line oral agents in UC





Safety


It's easy to put drugs into safety buckets...

Elderly



Infectious risk

Ustekinumab



Infectious risk

Specific risks

- Headache (IV)
- Local reactions (SC)


Vedolizumab



Infectious risk

Moderate liver enzymes elevation

Anti-IL23



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-TNF



Infectious risk

- Herpes zoster

Skin complications

- Acnea-like lesions


Blood count

- Moderate lymphopenia

Only for patients at risk*:

- MACE
- Thromboembolism events
- Tumoral risk

Anti-JAK



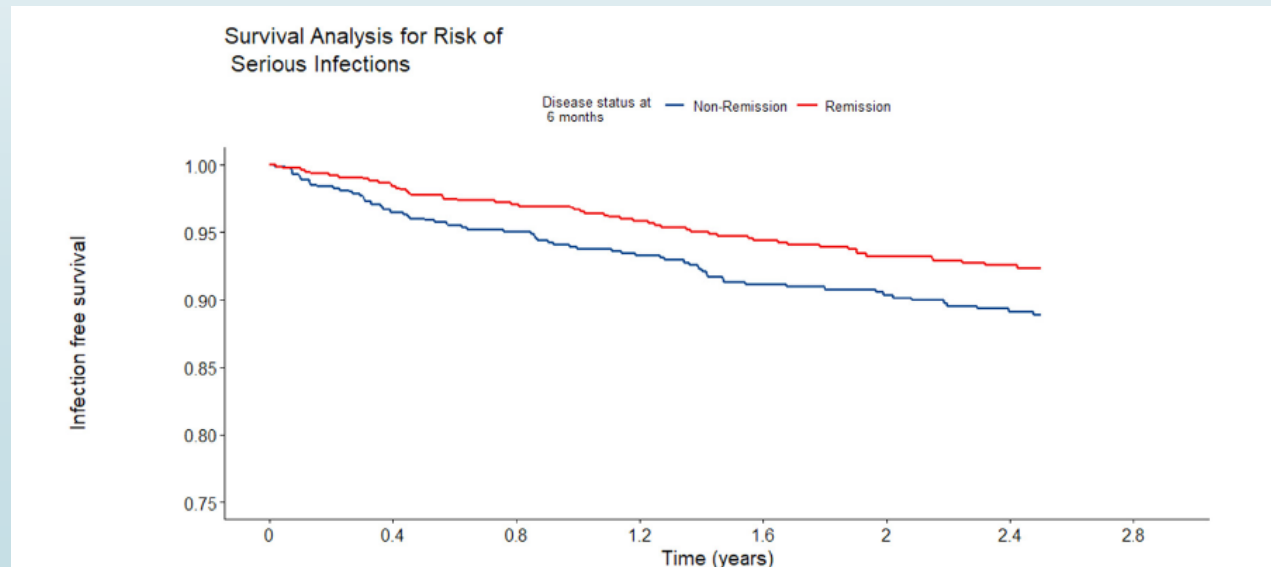
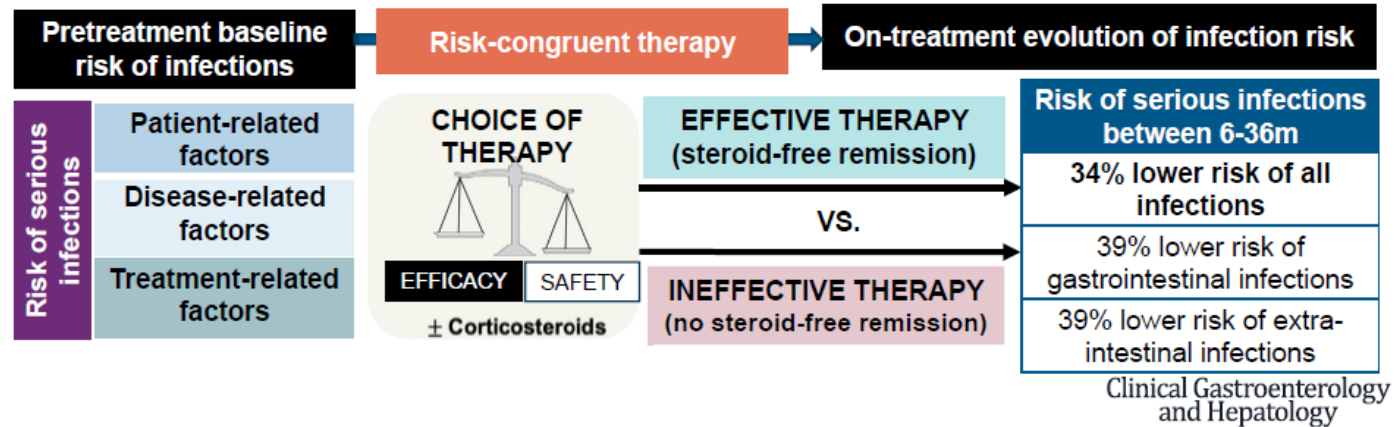
***Patients at risk:**

- Age > 65 ans
- CV risk factors
- Cancer risk factors (long-lasting smokers)
- Risk factors of Thromboembolism events

Safety profile

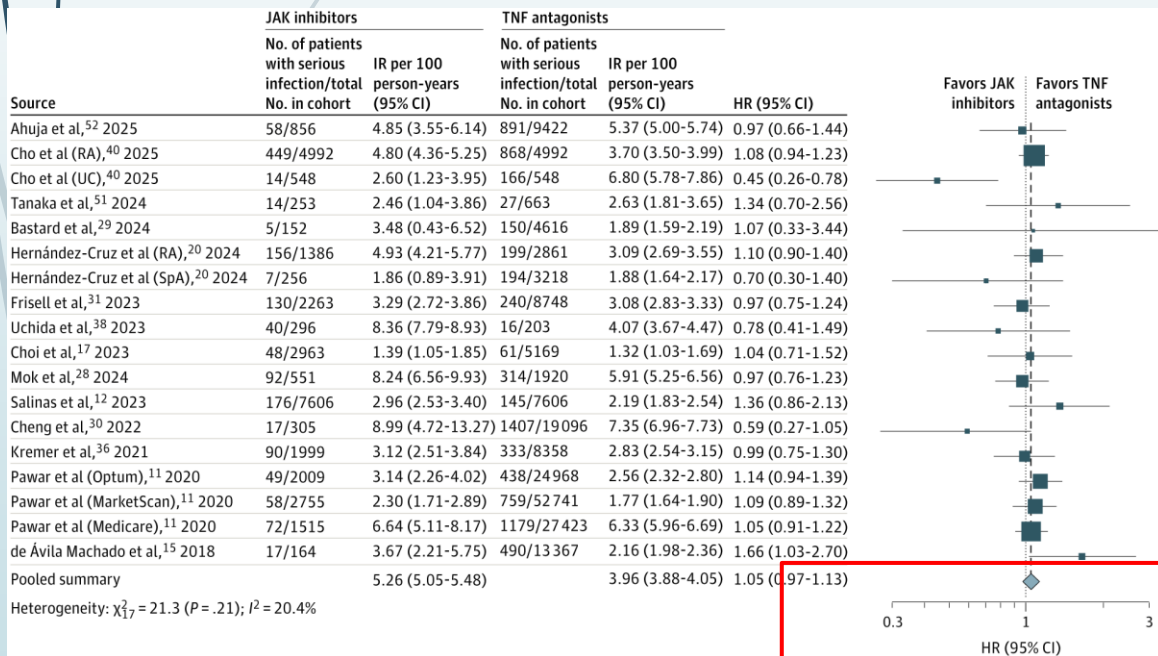
Efficacy trumps safety and lowers the risk of infections

Effective treatment lowers the long-term risk of serious infections in adalimumab-treated patients with Crohn's disease: Secondary Analysis of the PYRAMID Registry

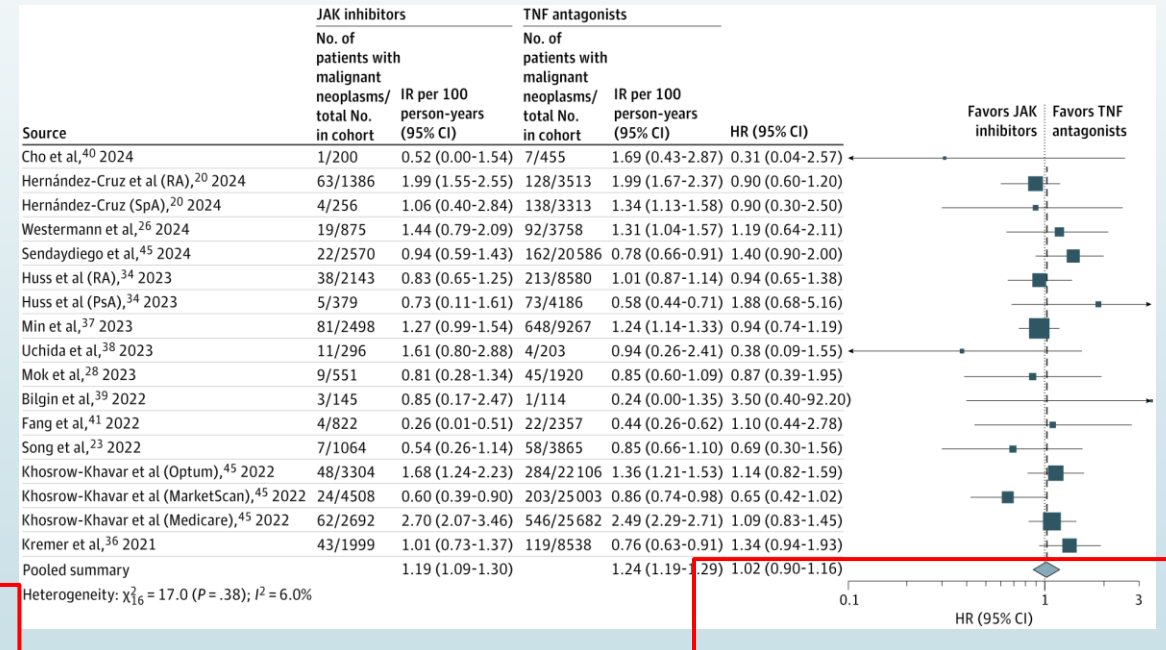


Comparative Safety of JAK Inhibitors vs TNF Antagonists in Immune-Mediated Inflammatory Diseases

Serious Infection



Malignant Neoplasm



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

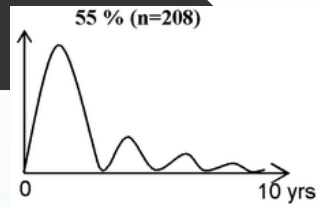
Cette **méta-analyse de 42 études**, présentant un **faible à modéré risque de biais**, incluait **813 881 patients...** et **n'a identifié aucune différence cliniquement significative** dans le risque **d'infections graves**, de **néoplasies malignes** ou de **MACE** (*événements cardiovasculaires majeurs indésirables*) entre l'utilisation des **inhibiteurs de JAK** et des **antagonistes du TNF**, toutes **MICI/IMID** confondues, avec une **faible incidence globale**.

L'utilisation des **inhibiteurs de JAK** était toutefois associée à un **risque légèrement plus élevé**

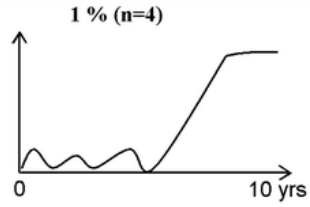


Drug Positioning

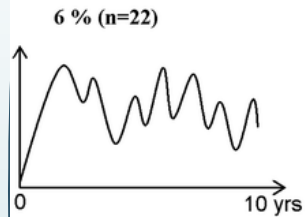
One size does not fit all



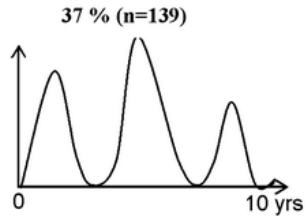
Curve 1: Remission or mild severity of intestinal symptoms after initial high activity



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



Curve 3: Chronic continuous symptoms



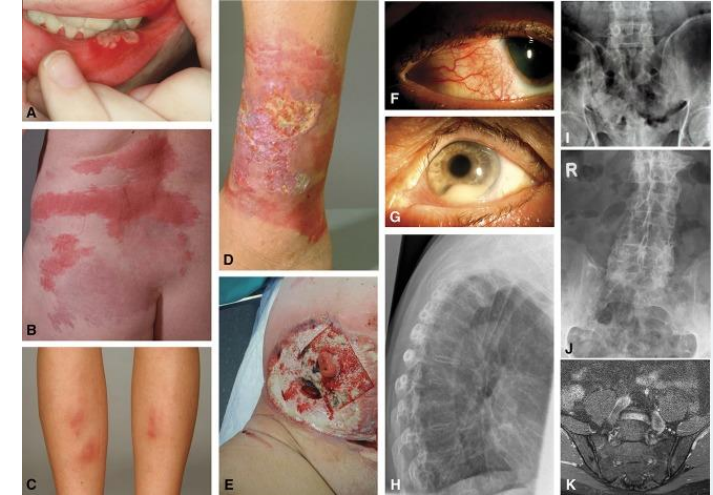
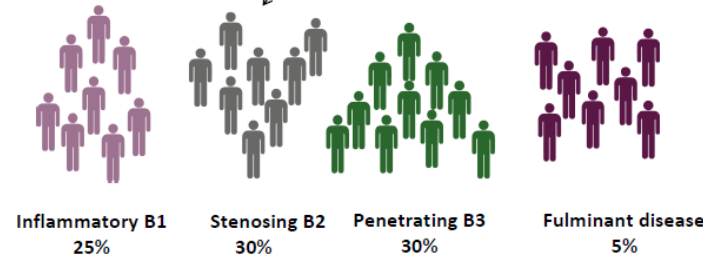
Curve 4: Chronic intermittent symptoms

Crohn's disease
At diagnosis
90% inflammatory B1



Prognostics:
who needs a more aggressive management?

Crohn's disease
After 5 to 10 years



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

Neeraj Narula, MD, MPH, FRCPC¹, Emily C.L. Wong, BSc¹, Parambir S. Dulai, MD², John K. Marshall, MD, MSc, FRCPC¹, Vipul Jairath, MD, PhD³ and Walter Reinisch, MD, PhD⁴

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,*}

^aDepartment of Medicine, Division of Gastroenterology, Schulich School of Medicine, Western University, Canada

^bDivision of Gastroenterology and Hepatology, Department of Medicine, University of Calgary, Calgary, AB, Canada

^cDepartments of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

^dLawson Health Research Institute, London Health Sciences Center, London, ON, Canada



Selecting therapy in IBD : The Art of Medicine

Shared and personalized decision-making

Ileal vs colonic disease
Perianal CD
ASUC
EIM
Therapeutic line
Prior failure

Co-morbidity
History of cancer
Frailty
Family planning

Efficacy

Safety

Patient acceptability

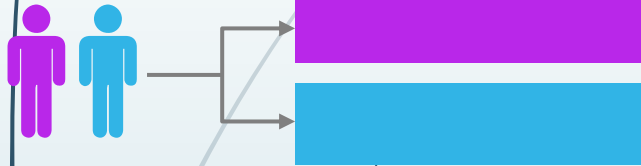
Reimbursement
Costs
Coverage

Lifestyle/convenience
Route of administration
Personal history with medications
Perception of treatments

Reimbursement by healthcare system

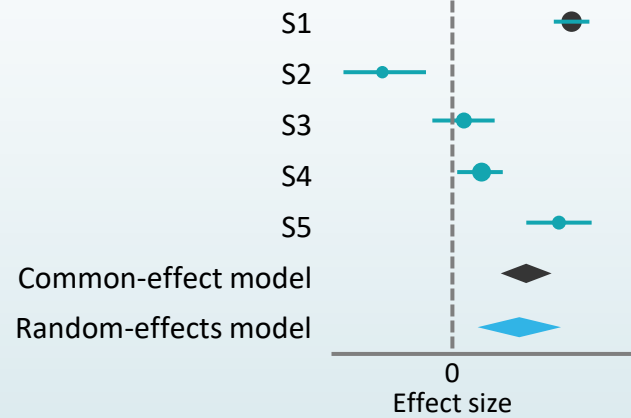
Tools to Inform Positioning of Drugs: Science

Head-to-head trial



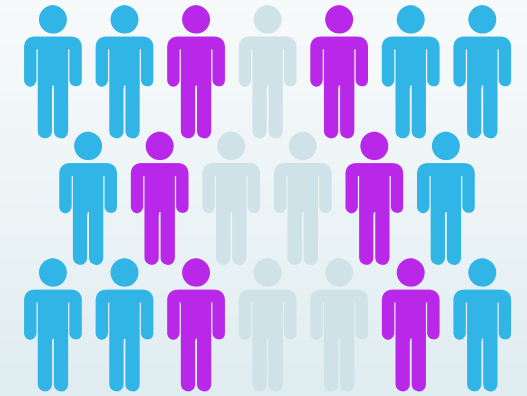
Gold standard: Designed and powered to allow formal comparison between different active therapies

Network Meta-analysis



Comparison of treatment effects from pivotal RCTs

Real-world data

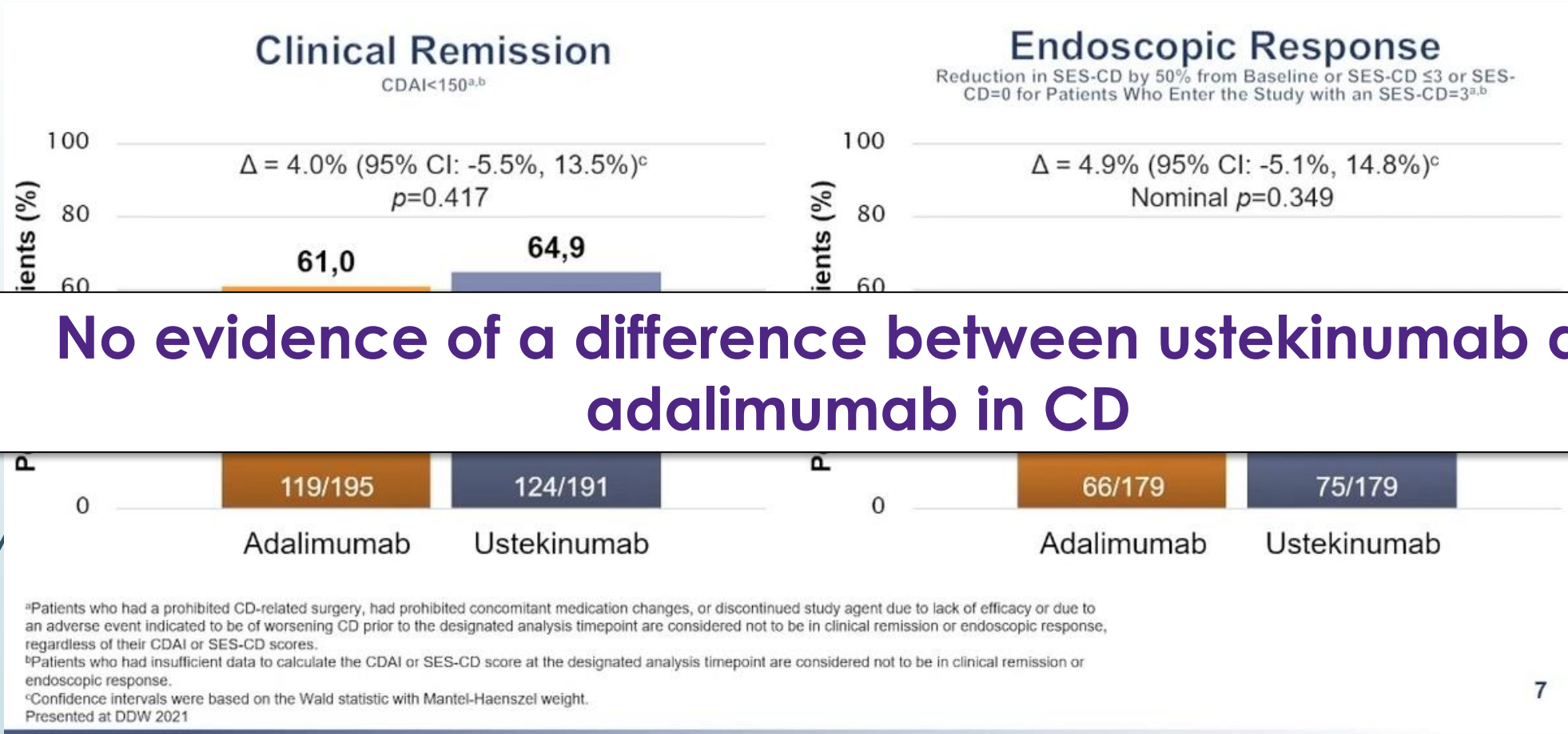


Routinely collects data on patient health status from many sources (eg, registries), often using propensity score-matched analysis for adequate comparisons



Positioning in CD: 1st Line

SEAVUE: Clinical remission and endoscopic response at Wk 52



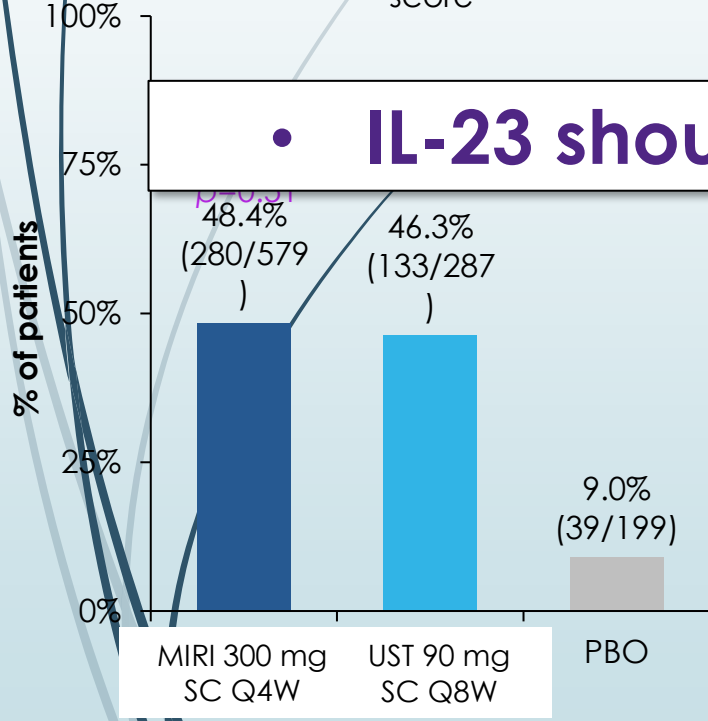
- No evidence of a difference between ustekinumab and adalimumab in CD**

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.

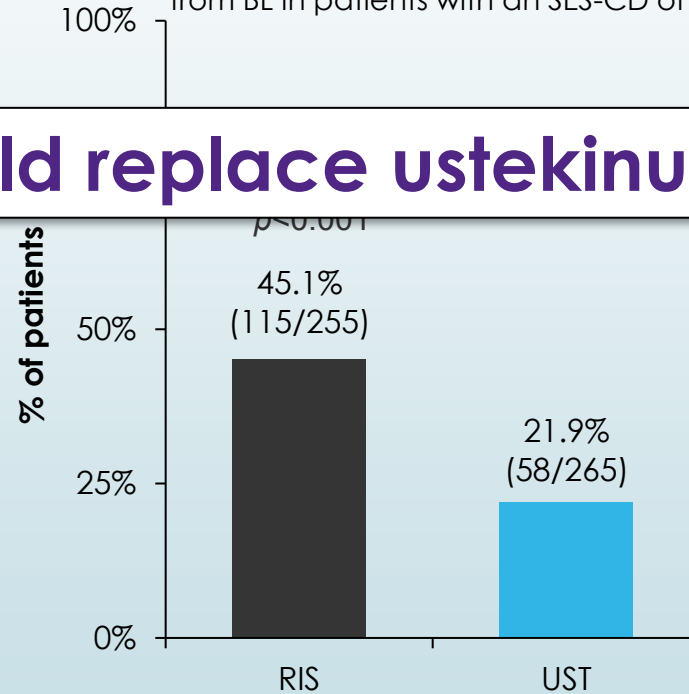
VIVID-1 Week 52, NRI¹

Endoscopic response: $\geq 50\%$ reduction from BL in SES-CD total score



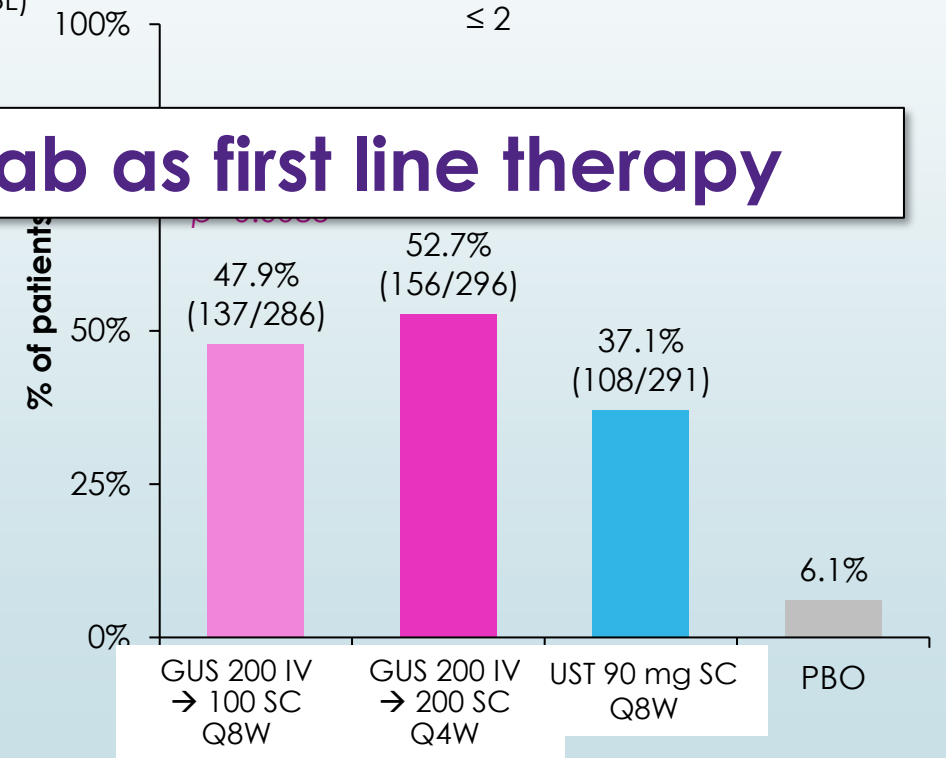
SEQUENCE Week 48, NRI²

Endoscopic response: $\geq 50\%$ 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, NRI³

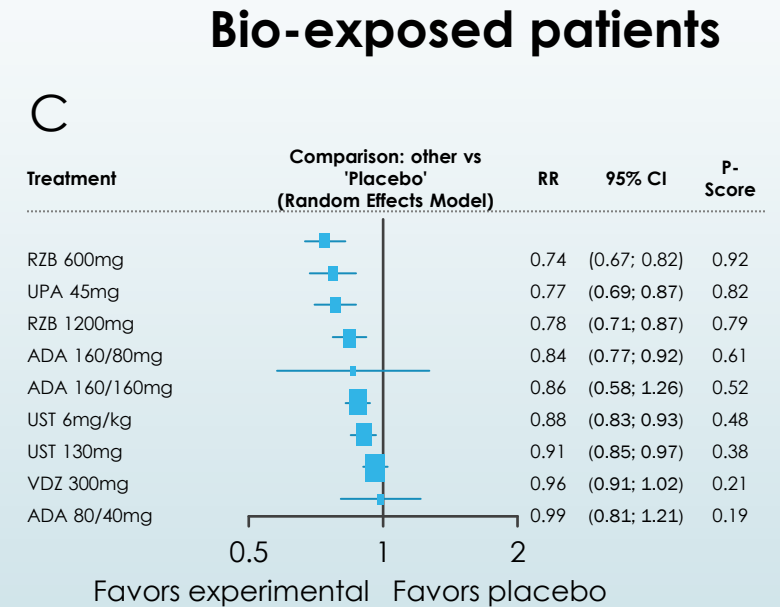
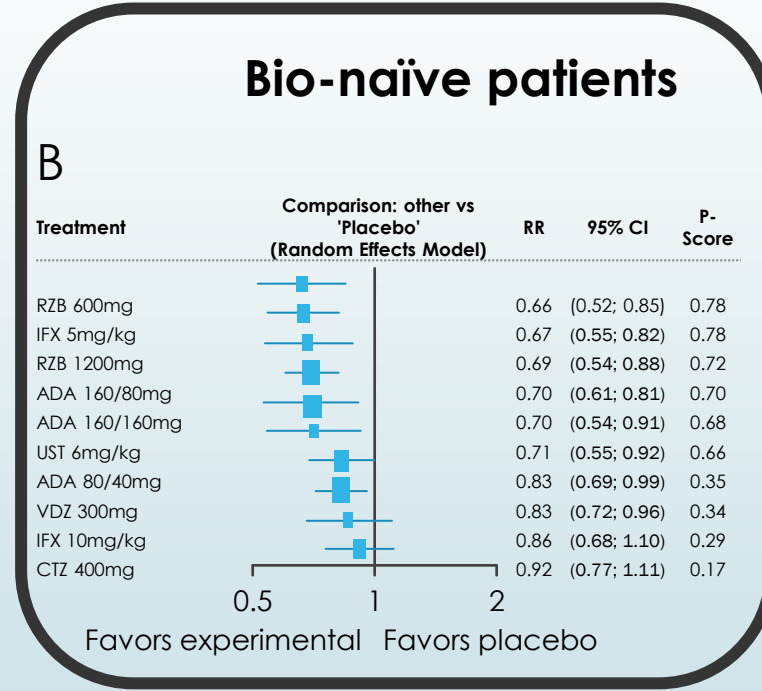
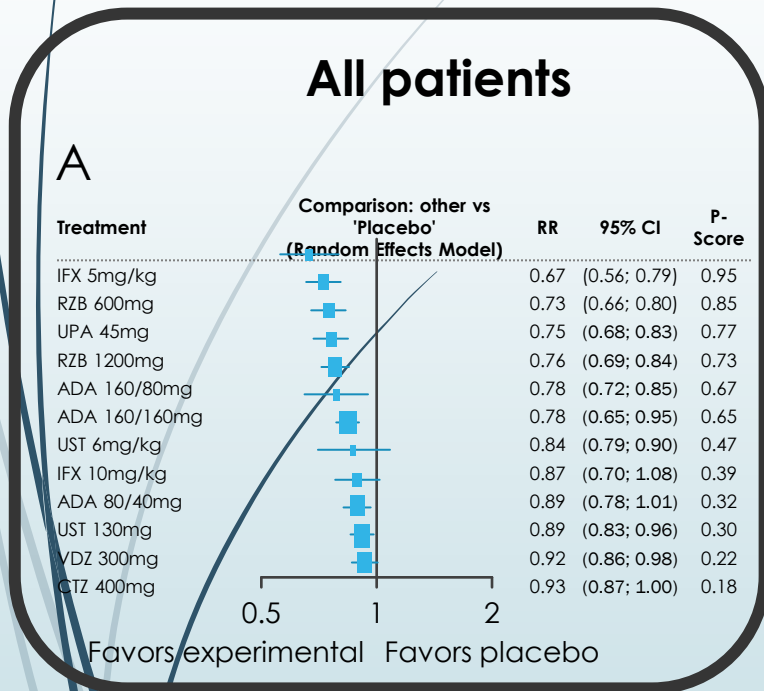
Endoscopic response: $\geq 50\%$ reduction from BL in SES-CD total score or SES-CD ≤ 2



• IL-23 should replace ustekinumab as first line therapy

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

Achievement of clinical remission in induction CDAI < 150



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.

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)
	IL23 antagonists	1.33 (0.72–2.44)	1.54 (0.87–2.71)	1.60 (0.62–4.16)	2.30 (1.02–5.18)	—	2.81 (1.95–4.05)
	IL12/23 antagonists	1.66 (0.72–3.82)	1.25 (0.64–2.45)	1.04 (0.37–2.94)	1.49 (0.60–3.71)	—	1.82 (1.05–3.16)
	TNF antagonists	2.35 (1.61–4.74)	1.77 (0.92–3.40)	1.41 (0.60–3.35)	1.44 (0.46–4.50)	—	1.75 (0.73–4.24)
	Etrolizumab	2.83 (1.15–6.98)	2.14 (0.90–5.07)	1.70 (0.61–4.78)	1.21 (0.48–3.06)	—	1.22 (0.59–2.52)
	Vedolizumab	—	—	—	—	—	—
Placebo	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)	—	—

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)
	IL23 antagonists	1.85 (0.81–4.22)	0.25 (0.06–1.08)	0.30 (0.07–1.32)	1.46 (0.95–2.26)	—	2.14 (1.57–2.93)
	IL12/23 antagonists	0.58 (0.11–3.01)	0.31 (0.07–1.47)	0.93 (0.60–1.45)	1.22 (0.89–1.67)	—	8.58 (2.05–35.83)
	TNF antagonists	0.54 (0.11–2.64)	0.29 (0.07–1.29)	0.93 (0.60–1.45)	4.82 (0.78–29.72)	—	7.02 (1.68–29.31)
	Etrolizumab	2.49 (0.95–6.40)	1.34 (0.62–2.88)	4.26 (0.84–21.52)	4.57 (0.96–21.67)	—	1.46 (1.08–1.97)
	Vedolizumab	2.61 (0.69–9.95)	1.41 (0.42–4.75)	4.50 (0.69–29.26)	1.05 (0.29–3.89)	—	—
Placebo	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)	—

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

First Line Advanced Therapy: RWD from UK Bioresource

First line biologic in all CD

First line biologic in CD without perianal involvement

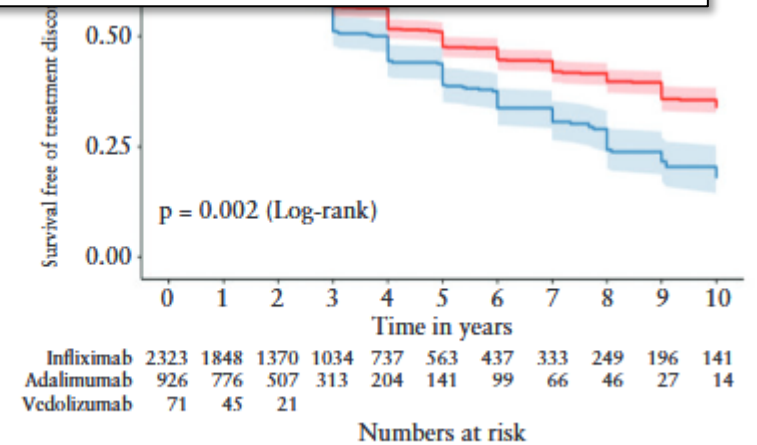
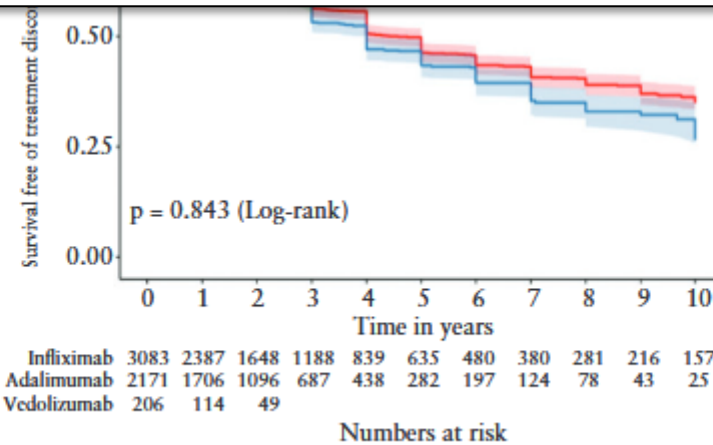
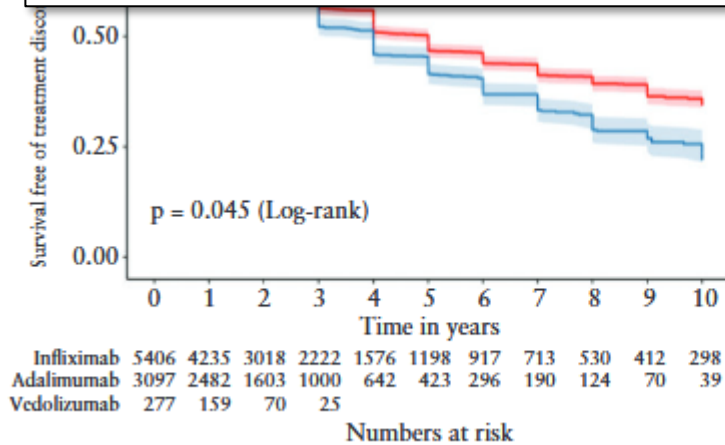
First line biologic in CD with perianal involvement

A

B

C

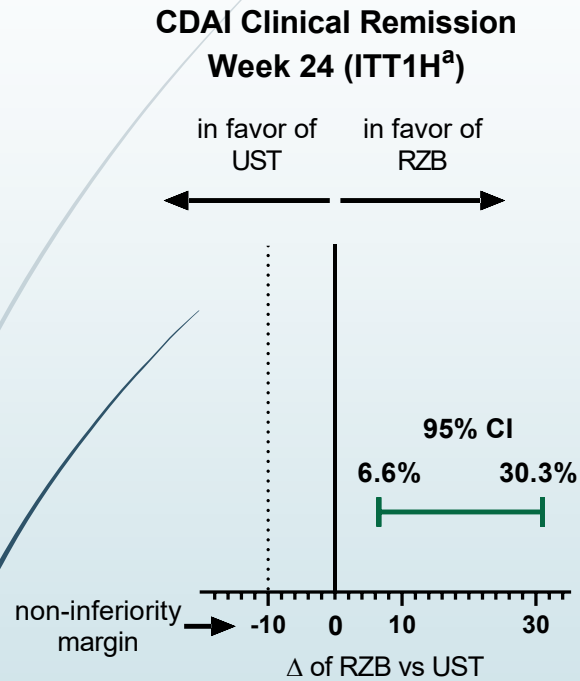
- Similar effectiveness of Vedo, ADA, IFX in luminal CD, but superiority of IFX over ADA for perianal CD



A dark grey arrow points to the right from the left edge of the slide. Below it, several thin, curved lines in shades of blue and grey sweep across the left side of the slide.

Positioning in CD: 2nd Line

SEQUENCE: Primary Endpoints



CDAI clinical remission: CDAI < 150

Endoscopic remission: 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

^aITT1H population: a subset of ITT1 population which includes the first ~50% of ITT1 patients

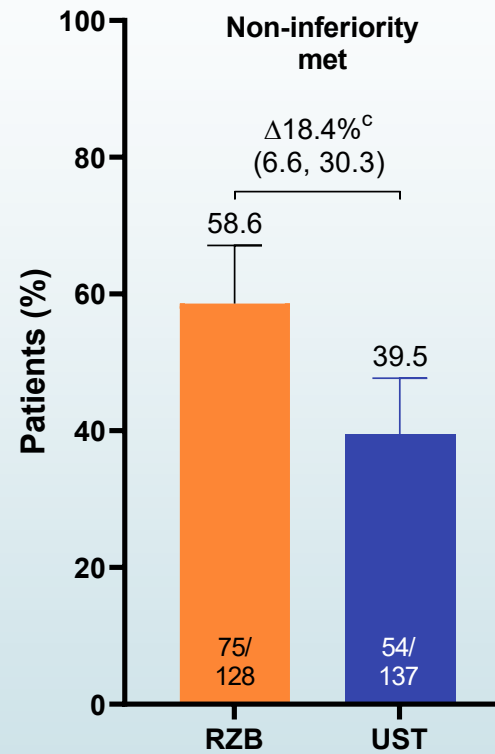
^bITT1 population includes patients who were randomized to UST or RZB (600 mg IV, 360 mg SC) and received at least one dose of study drug

^cDifferences adjusted by the stratification factors (number of times the subject failed prior anti-TNF therapy [≤ 1, > 1] and steroid use at baseline [yes, no])

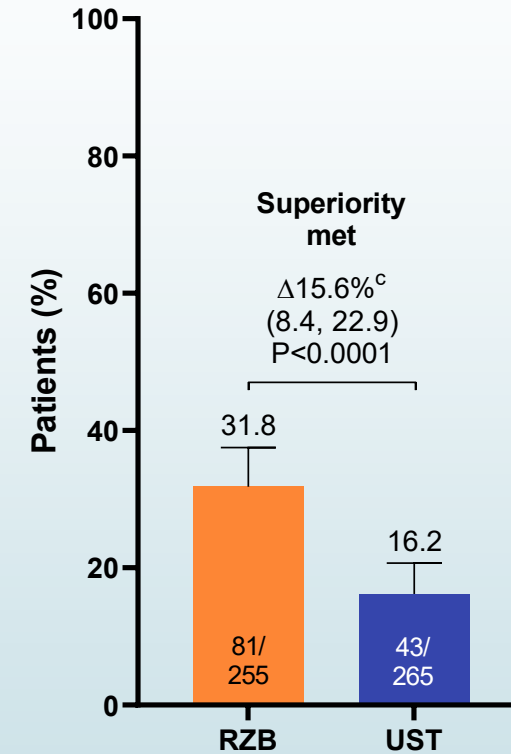
% (n) represents the synthesized results from non-responder imputation incorporating multiple imputation to handle missing data

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

CDAI Clinical Remission Week 24 (ITT1H^a)



Endoscopic Remission Week 48 (ITT1^b)



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

Upa is effective after biologic failure in CD

U-EXCEL

CDAI Clinical Remission

Risk Difference (95% CI)

Percentage (%)

Risk Difference

Placebo

Upadacitinib
45 mg QD

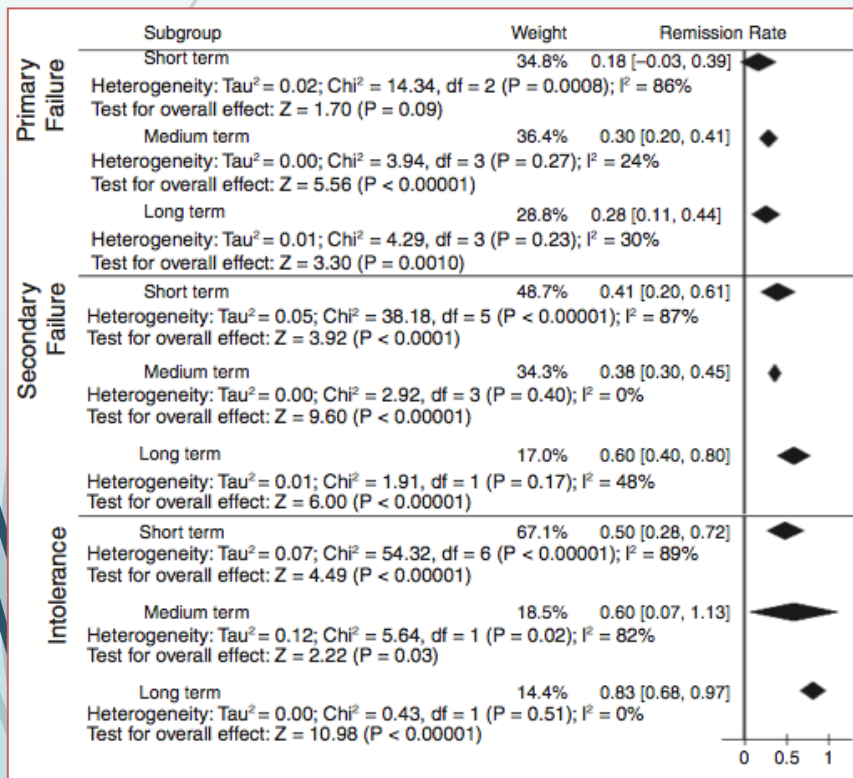
Number of Prior Biologics Failed: ≤ 1	16.6	29.4	46.0
Number of Prior Biologics Failed: >1	18.8	15.5	34.3
Prior TNF Failure: 1	16.5	25.3	41.8
Prior TNF Failure: >1	18.1	14.5	32.6
Prior Ustekinumab Failure (Within Bio-IR): Yes	14.7	14.0	28.8
Prior Ustekinumab Failure (Within Bio-IR): No	20.1	24.6	44.7
Prior Vedolizumab/Natalizumab Failure (Within Bio-IR): Yes	10.2	17.0	27.2
Prior Vedolizumab/Natalizumab Failure (Within Bio-IR): No	21.4	22.6	44.0

-100.0 -50.0 0.0 50.0 100.0

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 :

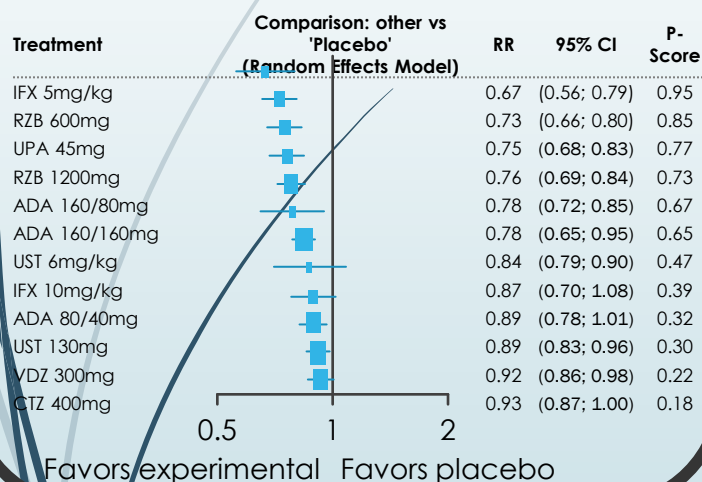
- Better in case of intolerance to the first anti-TNF agent (61%)
- Lower (30%) if primary failure or secondary loss of response (45%)

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

Achievement of clinical remission in induction CDAI < 150

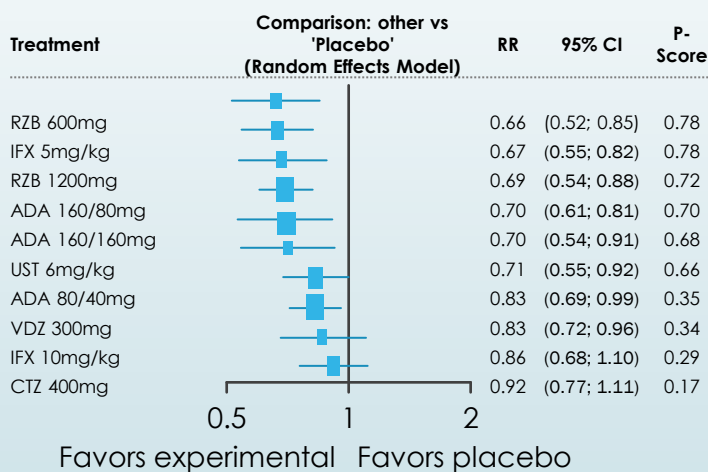
All patients

A



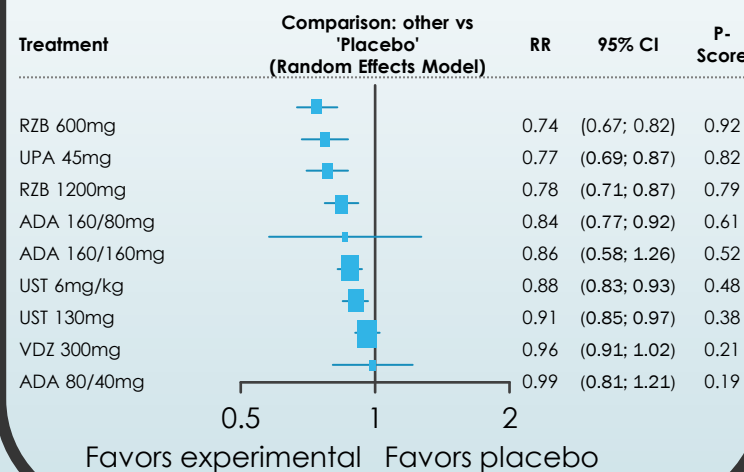
Bio-naïve patients

B



Bio-exposed patients

C

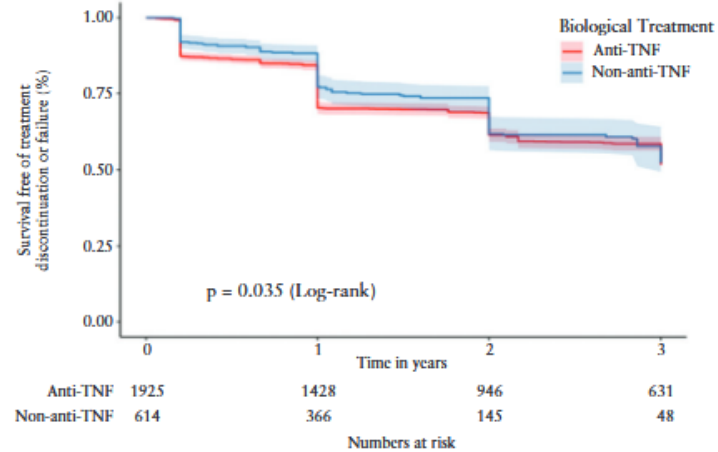


IFX was only studied in bio-naïve patients.

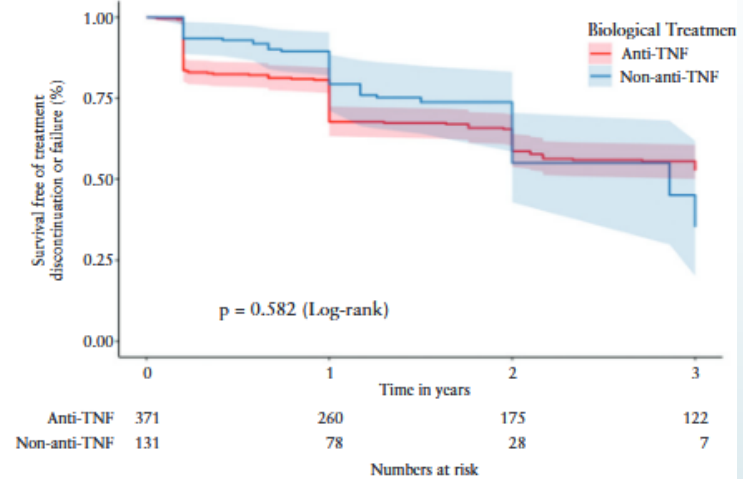
When data are analyzed separately, RZB 600 mg ranked first for both groups, suggesting that the ranking of IFX 5 mg/kg in the pooled analysis was driven by use in biologic-naïve patients.

Second Line Advanced Therapy: RWD from UK Biobank

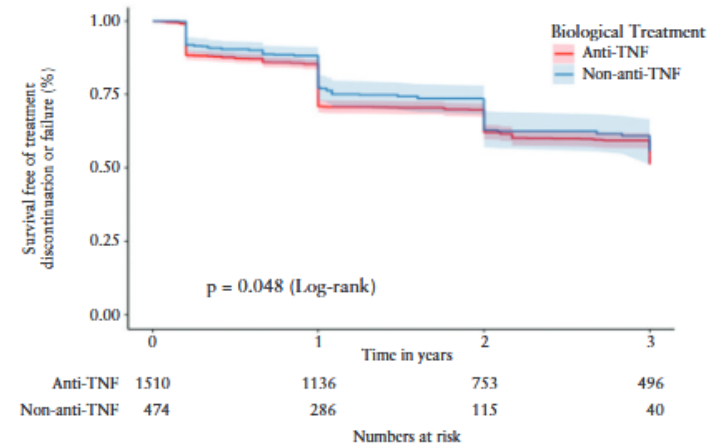
A Effectiveness of biologics in CD after anti-TNF failure: all patients



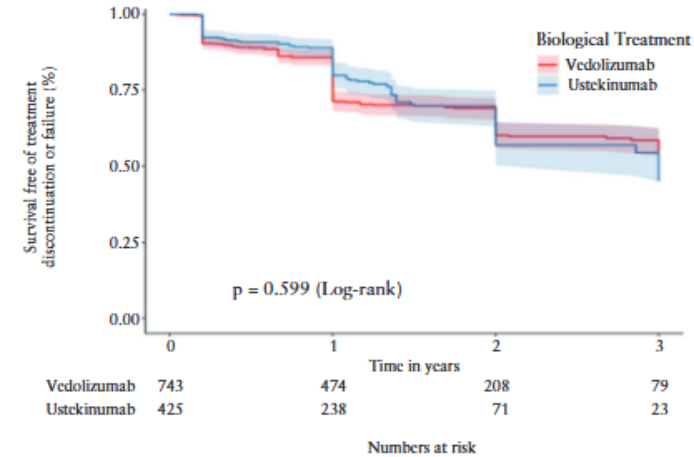
B Effectiveness of biologics in CD after anti-TNF failure: after PNR to first anti-TNF



C Effectiveness of biologics in CD after anti-TNF failure: after NPNR to first anti-TNF



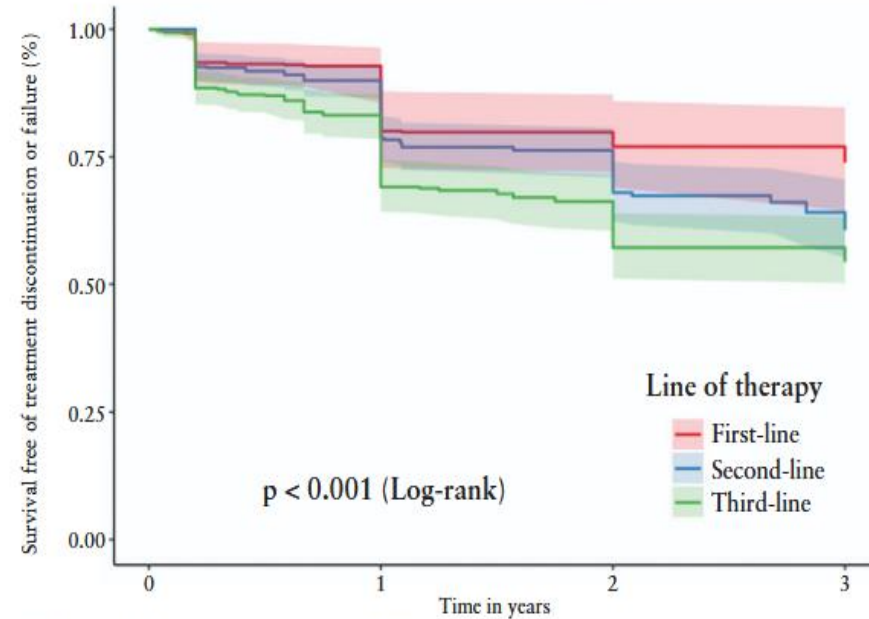
D Effectiveness of biologics in CD after anti-TNF failure: VDZ vs UST



The Law of Diminishing Returns

A

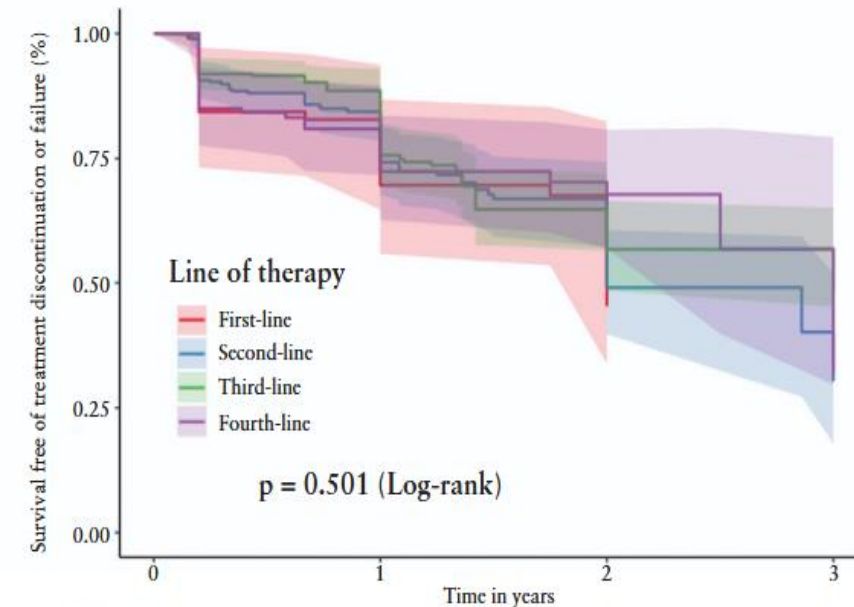
Effectiveness of VDZ in CD by line of therapy



	0	1	2	3
First-line	277	159	70	25
Second-line	392	253	116	41
Third-line	373	232	93	39
	Numbers at risk			

B

Effectiveness of UST in CD by line of therapy



	0	1	2	3
First-line	62	29	8	2
Second-line	244	121	31	7
Third-line	235	142	43	16
Fourth-line	86	45	17	4
	Numbers at risk			

Special situations: Peripheral spondylarthritis & Axial arthritis

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

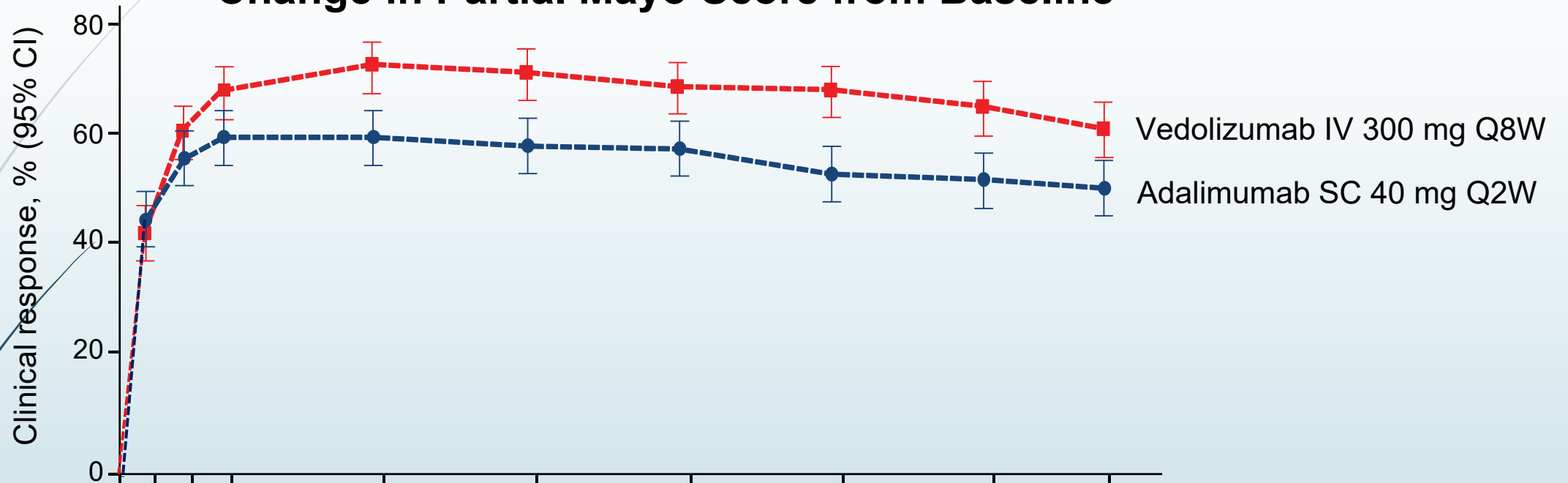


Positioning in UC: 1st Line

VARSIITY: Vedolizumab versus Adalimumab

BE.

Change in Partial Mayo Score from Baseline



Study Visit, weeks	2	4	6	14	22	30	38	48	52
Vedolizumab (N=383)*	<u>161</u> 367	<u>233</u> 357	<u>263</u> 356	<u>276</u> 344	<u>278</u> 325	<u>262</u> 298	<u>263</u> 293	<u>251</u> 280	<u>233</u> 265
Adalimumab (N=386)*	<u>176</u> 374	<u>217</u> 366	<u>232</u> 364	<u>229</u> 342	<u>229</u> 295	<u>222</u> 270	<u>206</u> 245	<u>200</u> 228	<u>193</u> 221

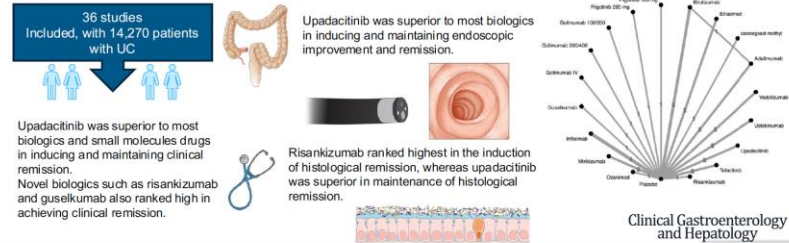
Network Meta-Analysis

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 Bessissow⁹

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

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



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

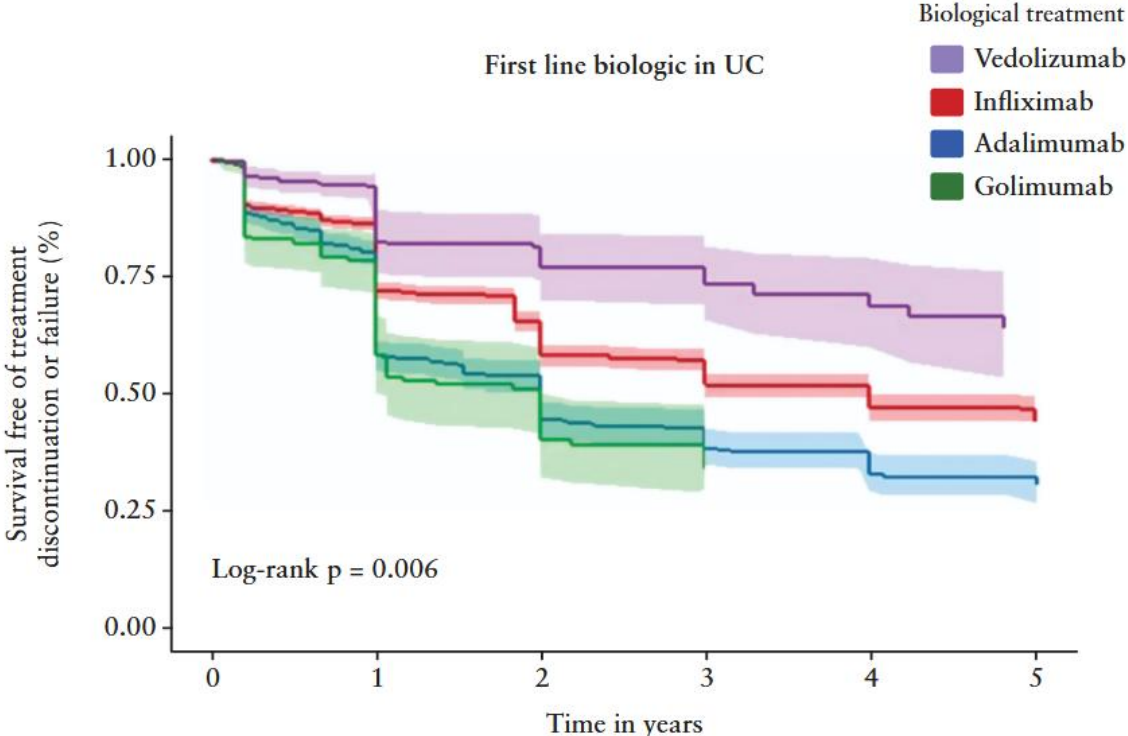
Intervention	SUCRA score %
Upadacitinib 30	98.60
Guselkumab	86.55
Filgotinib 200	79.21
Upadacitinib 15	75.89
Tofacitinib	72.66
Golimumab	63.61
Vedolizumab	57.44
Infliximab	50.47
Infliximab sc	49.61
Ozanimod	43.55
Risankizumab 180 mg	42.97
Etrolizumab	40.21
Filgotinib 100	31.82
Risankizumab 360 mg	28.83
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 Biobank

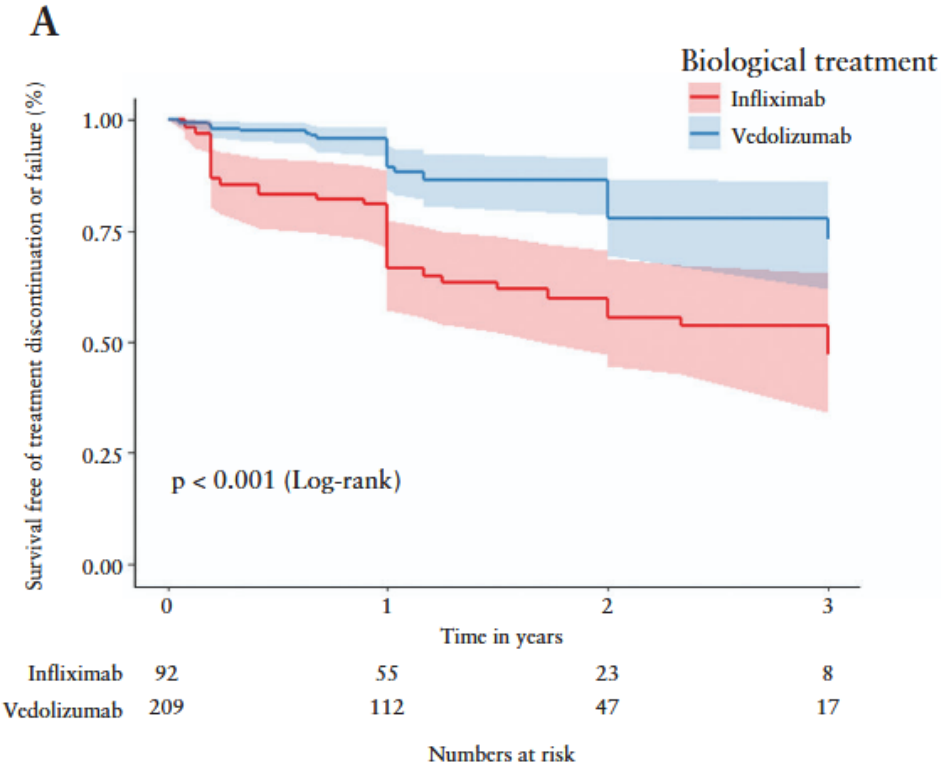


Infliximab	2339	1549	775	471	304	188
Adalimumab	864	545	220	111	61	29
Golimumab	143	95	45	19	11	6
Vedolizumab	621	354	144	62	31	16

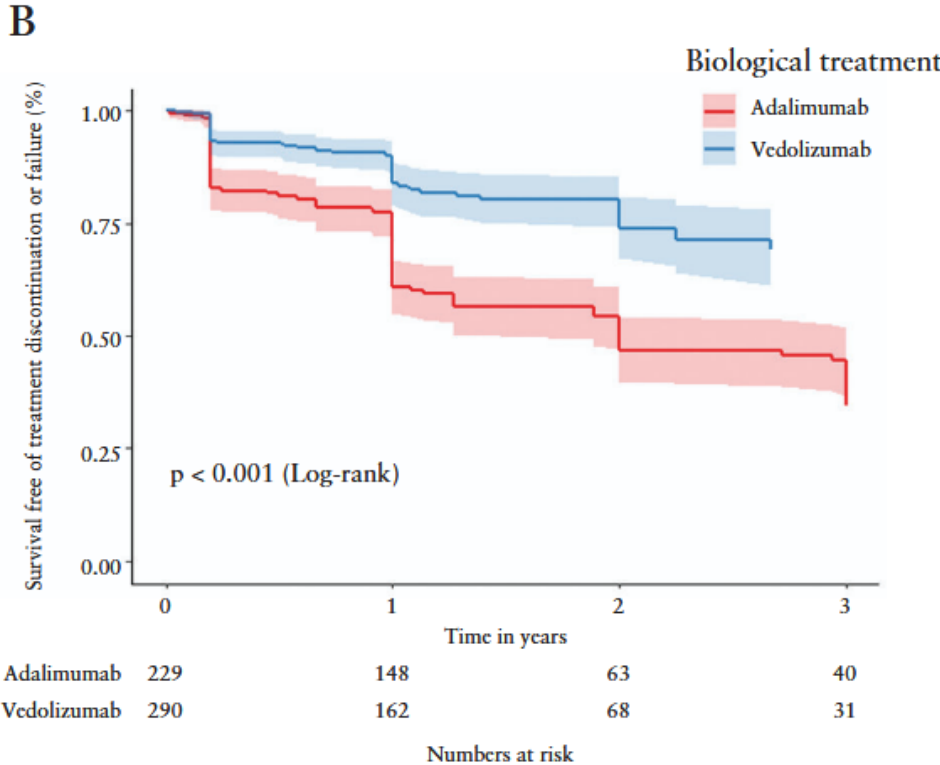
Numbers at risk

Second Line Advanced Therapy: RWD from UK Bioresource

Second line biologic in UC after adalimumab



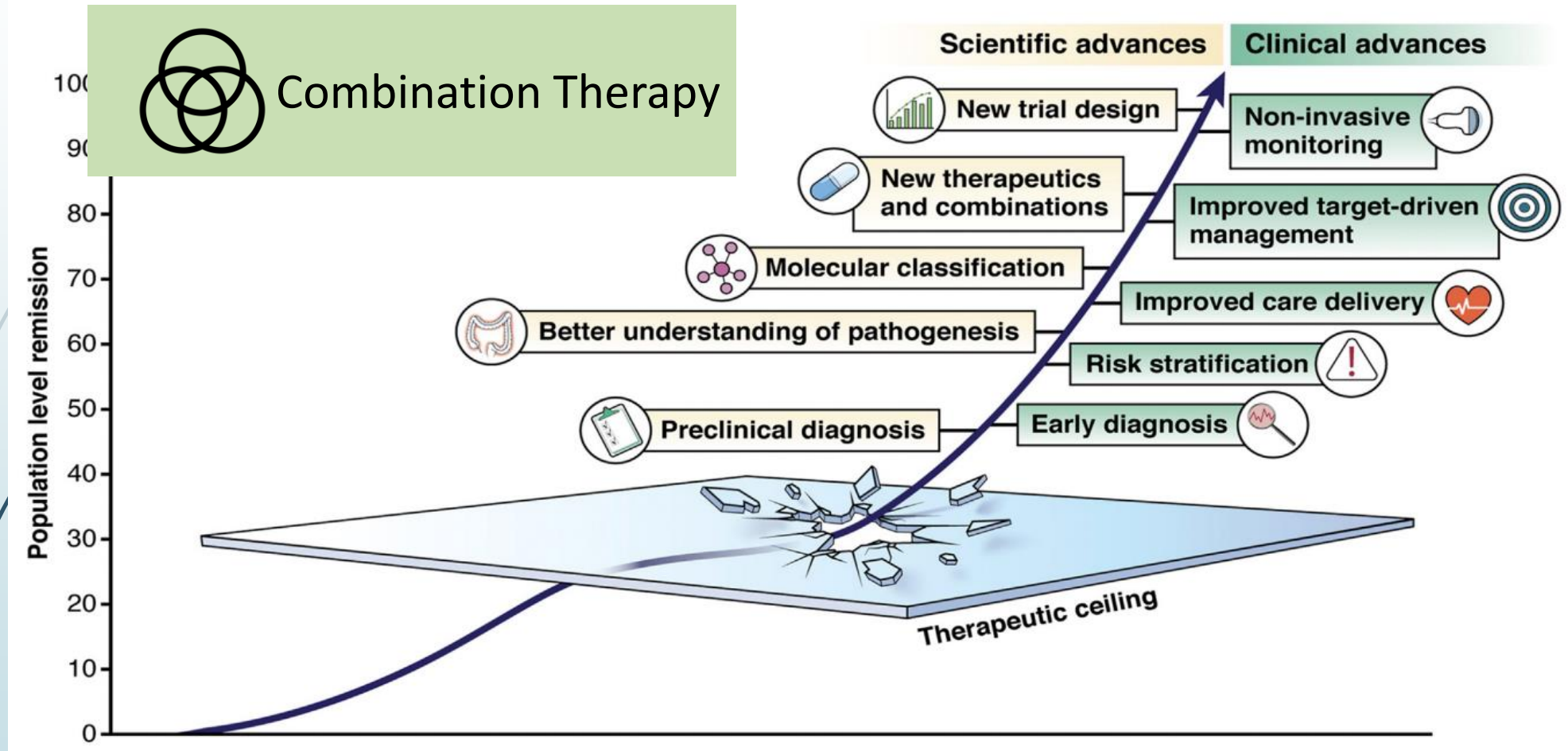
Second line biologic in UC after infliximab



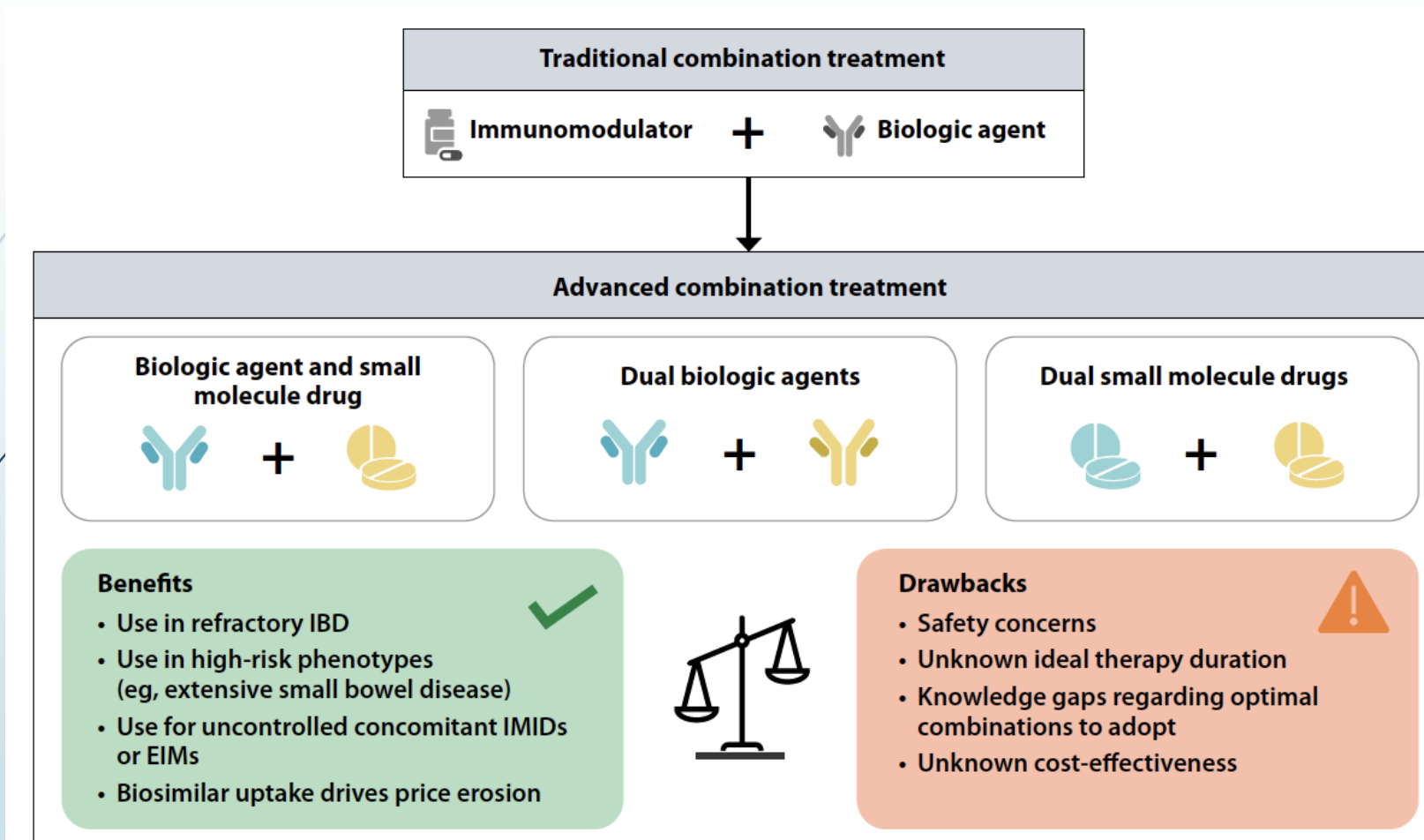


Advanced Combination Therapy

How Will We Break the Therapeutic Ceiling in IBD?



From Traditional to Advanced Combination Therapy



POURQUOI?

- ▶ De multiples voies biologiques participent au processus inflammatoire à médiation immunitaire
- ▶ Un échappement mécanistique peut survenir avec le temps sous un même agent biologique
- ▶ Les biologiques utilisés successivement ont tendance à être moins efficaces
- ▶ Les agents efficaces pour la maladie luminale peuvent être moins efficaces pour les manifestations extra-intestinales ou d'autres maladies à médiation immunitaire

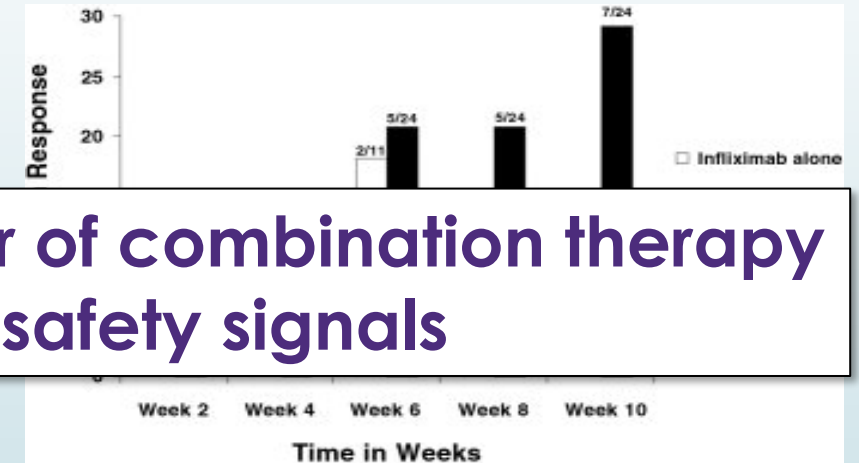
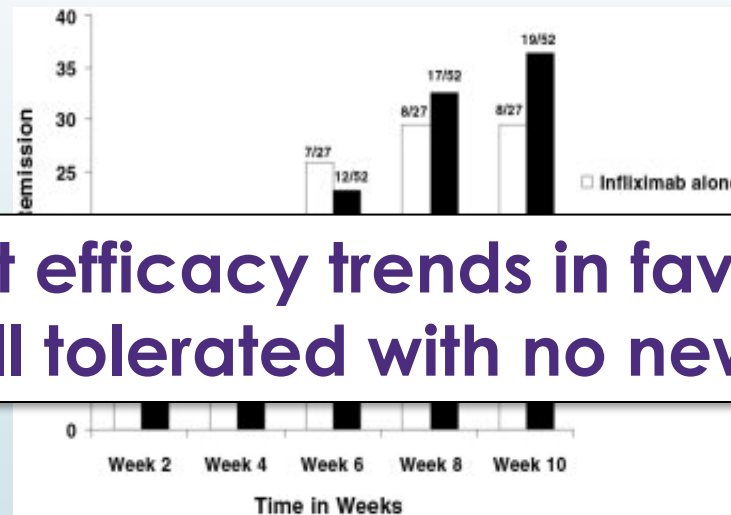
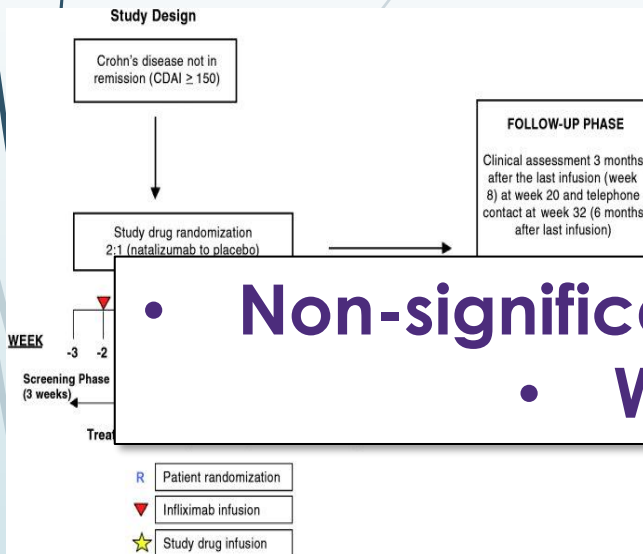
QUI?

- ▶ MII réfractaire
- ▶ MICI bien contrôlée avec maladie inflammatoire à médiation immunitaire (IMID) concomitante non contrôlée
- ▶ MICI non contrôlée avec maladie inflammatoire à médiation immunitaire (IMID) concomitante bien contrôlée

RCT: Infliximab + Natalizumab in Crohn's Disease

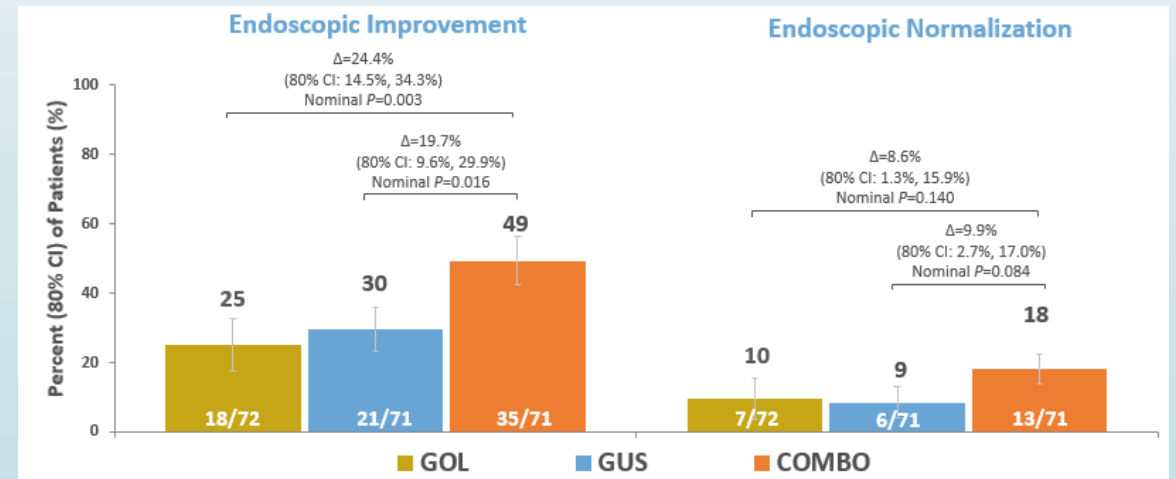
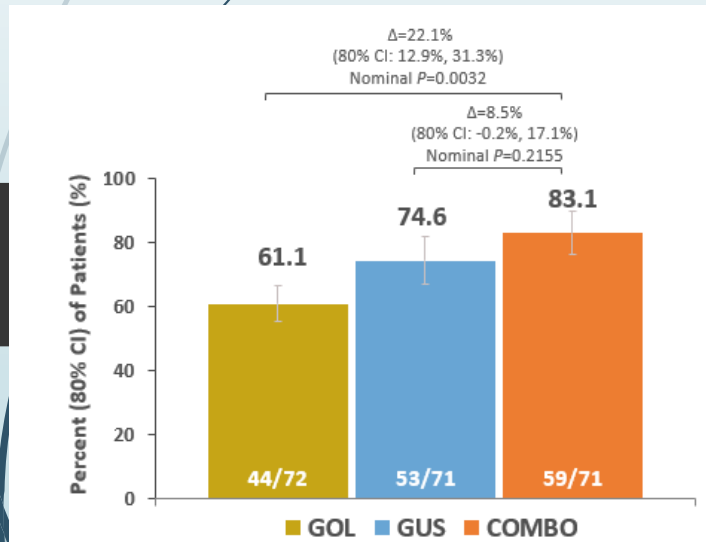
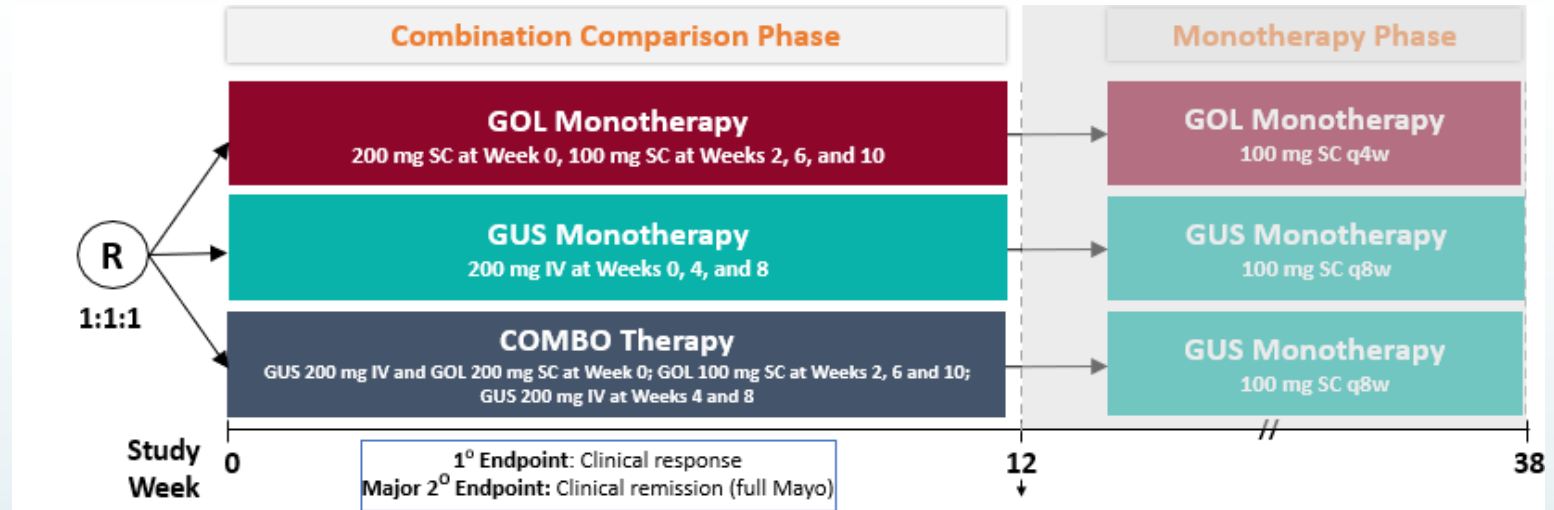
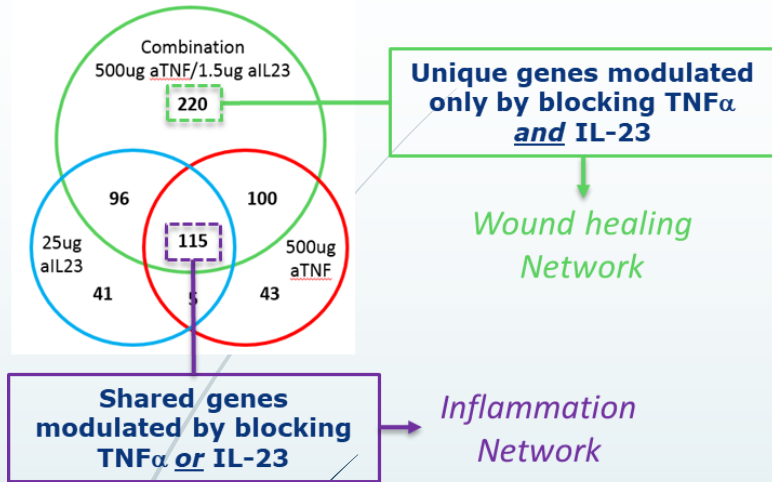
Clinical remission (CDAI < 150) over time

Clinical remission (CDAI < 150) in patients with baseline elevated CRP



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

Combination Therapy



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

Advanced combination treatment (ACT)

Biologic agent and small molecule



Dual biologic agents



Dual small molecules

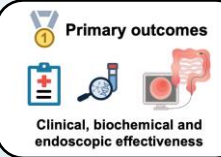


- **Retrospective Multicenter Study** (9 Canadian IBD centers)
 - **105 Adult IBD patients** treated with ACT (either two biological therapies, a biological plus an oral small molecule, or two small molecules)
 - **Indications:** 1) refractory IBD; 2) uncontrolled IMIDs; 3) uncontrolled EIMs

- **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**.



- 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%**.



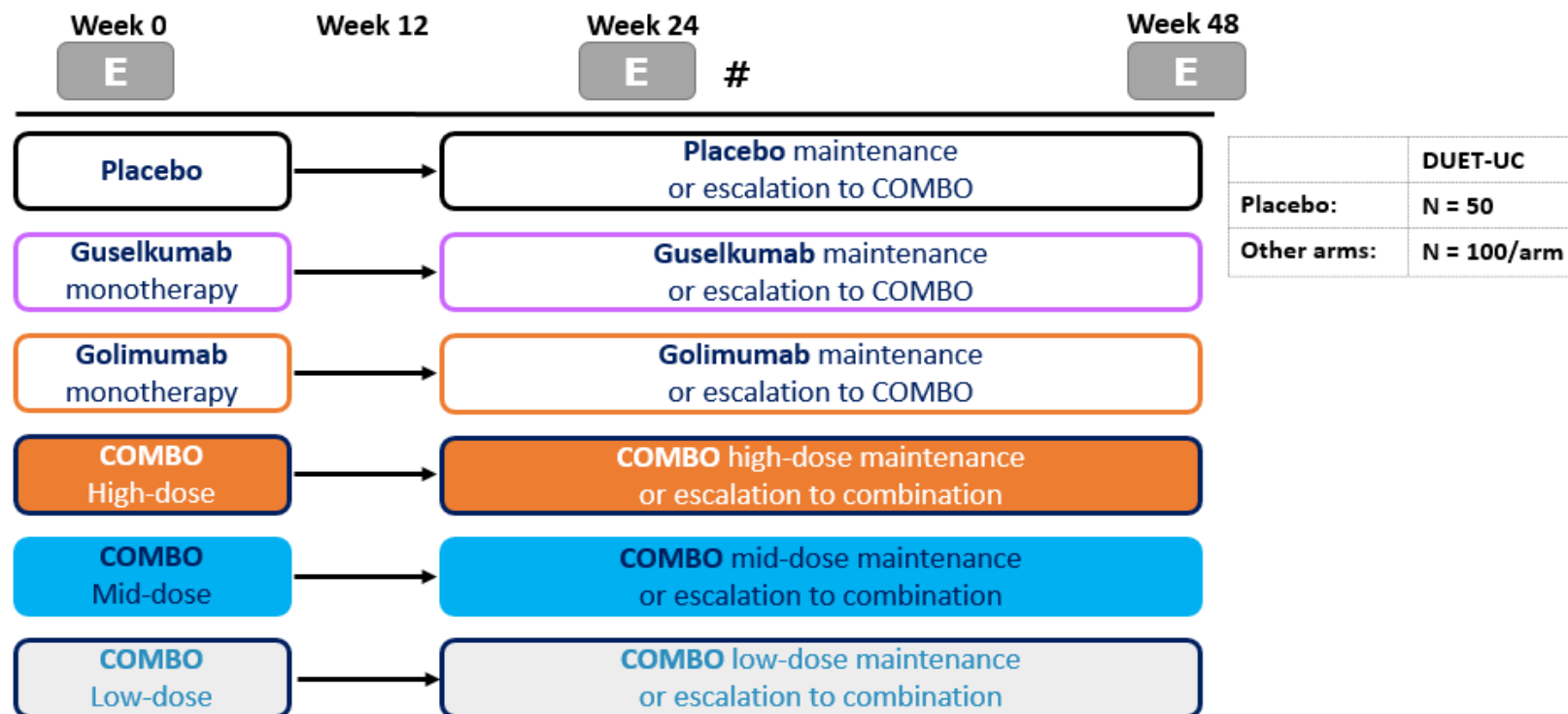
- **Serious adverse events: 12.4%**
 - **Infections: 7.6%**



Negative predictors of effectiveness outcomes

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

DUET UC and CD



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	---

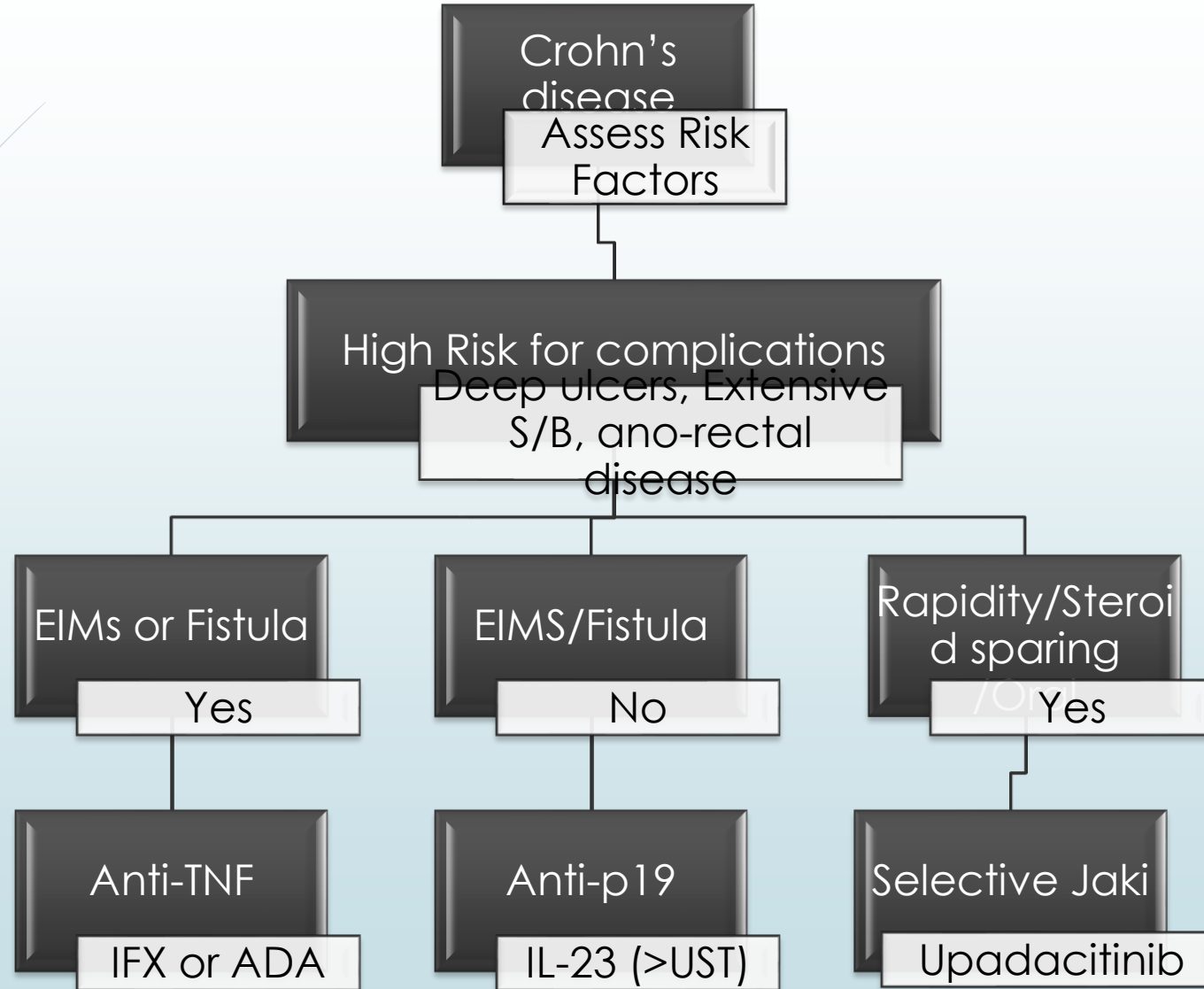
Key Recommendations for the Use of Advanced Combination Therapy in Practice

Who	<p>Patients with IBD refractory to multiple medical therapies</p> <p>Patients with very high-risk phenotypes</p> <p>Patients with a concomitant EIM/IMID</p>
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	<p>Differential and combination mechanisms of action with dual targeted treatments</p> <p>Lack of available options for inducing and maintaining remission and response</p>
How	<p>With appropriate consent and MDT Discussion</p> <p>Recycling strategy (using at least 1 agent already administered)</p> <ul style="list-style-type: none"> • Simultaneous induction (starting with 2 new agents) • Add-on strategy (adding a new compound later on) <p>Preference for agents with the most favorable safety profiles (eg, vedolizumab, ustekinumab)</p> <p>Preference for an anti-TNF agent in CD, especially in ileal CD or with bowel damage</p> <p>Preference for vedolizumab in UC patients</p> <p>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</p> <p>For a defined period of time with re-assessment after 6 months</p>

A dark grey arrow points to the right from the left edge of the slide. Several thin, light blue lines curve upwards from the bottom left corner towards the center of the slide.

Summary: How to best position advanced therapies

Positioning First-Line Therapy in CD



Safety Risk
Advanced age/morbidity
Malignancy

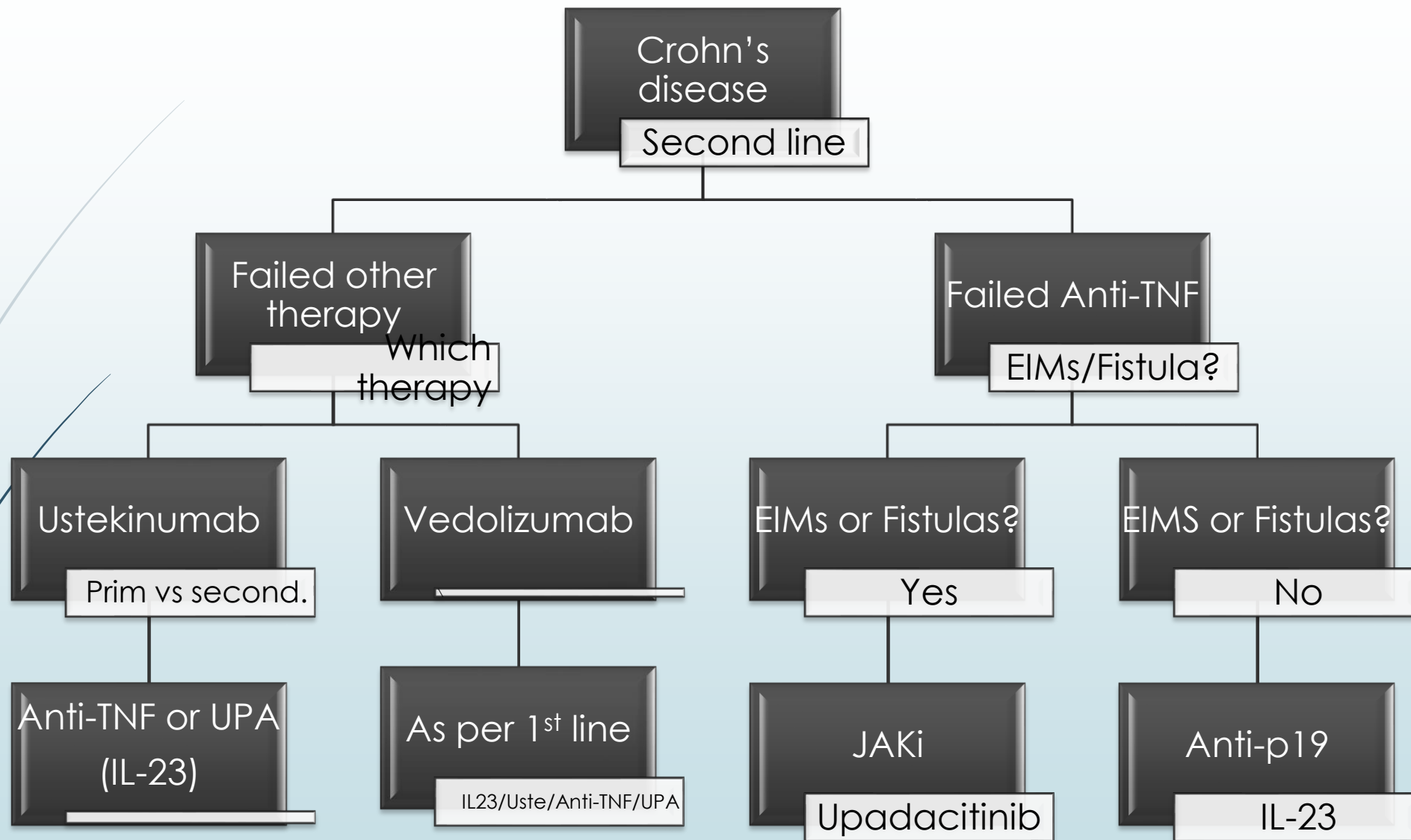
1st Line

- Vedolizumab
Uste or IL-23

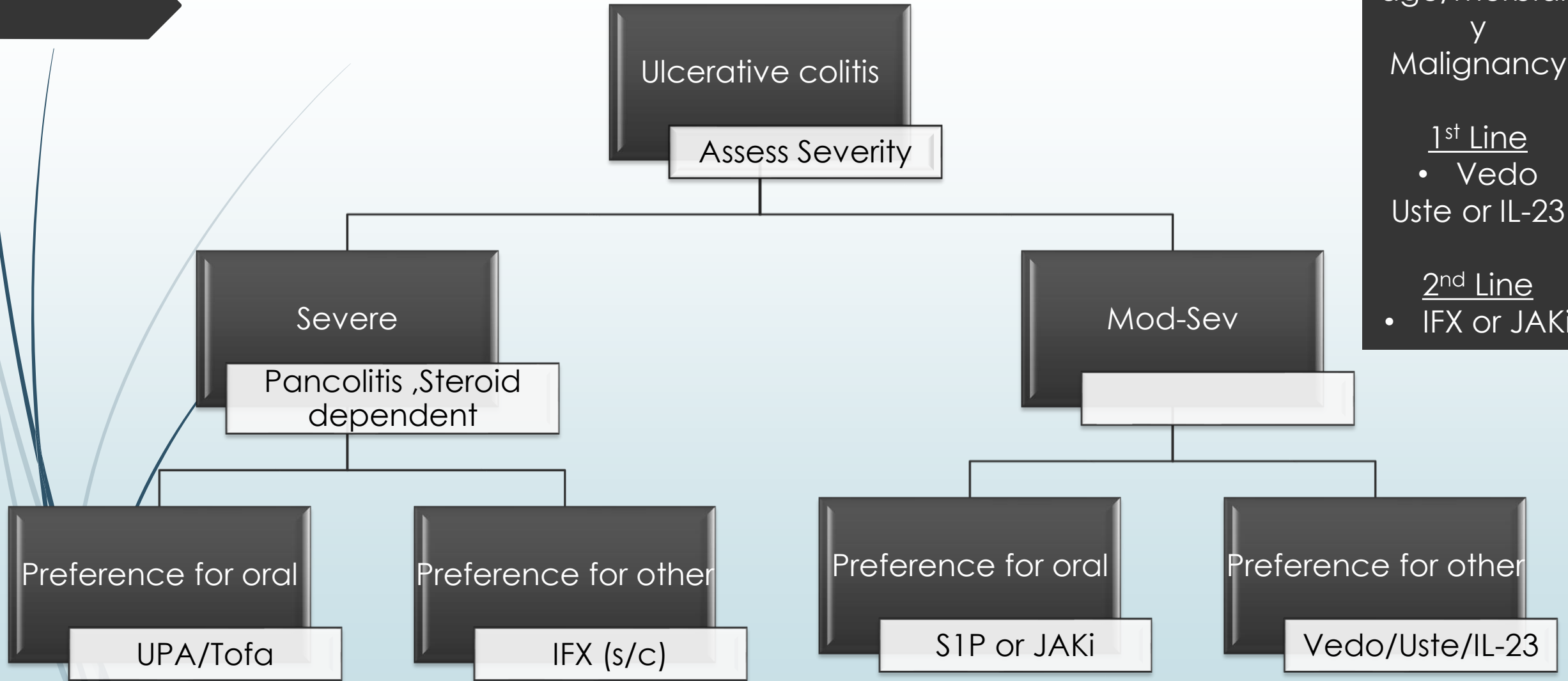
2nd Line

- IFX or ADA/JAK

Positioning Second-Line Therapy in CD



Positioning First-Line Therapy in UC



Safety Risk
Advanced age/morbidity
&
Malignancy

1st Line
• Vedo
Uste or IL-23

2nd Line
• IFX or JAKi

Positioning Second-Line Therapy in UC

