
2023 SCSG
GI SYMPOSIUM

Positioning therapies in IBD: The Art (and Science) of IBD!

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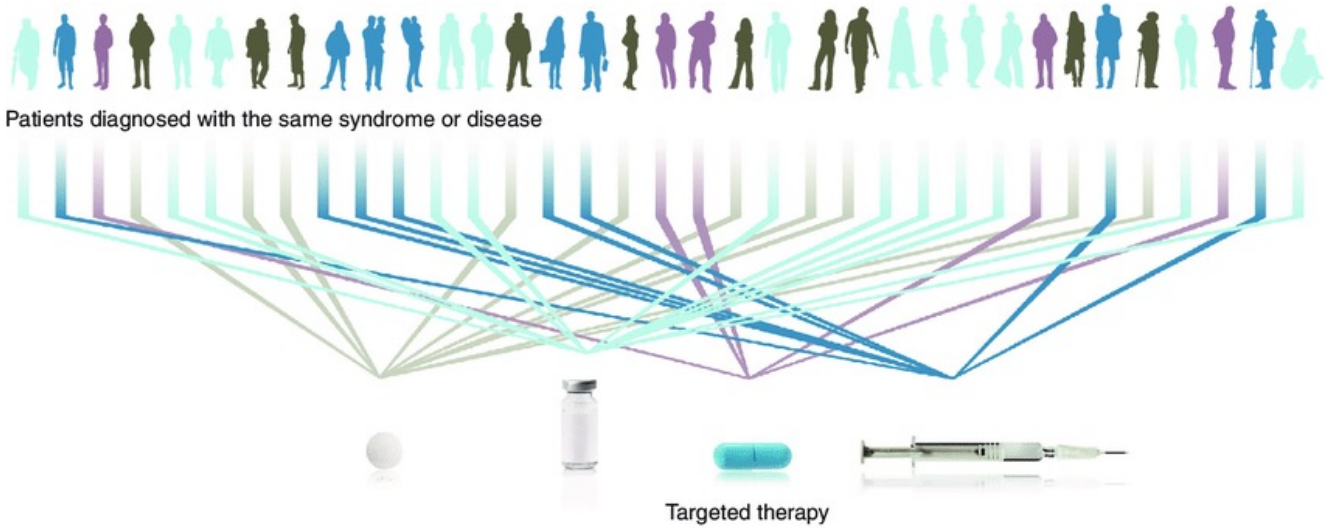
Conflict of Interest Disclosure
(over the past 24 months)

Commercial	Relationship
Pfizer	Research support, ad-hoc grant review panel

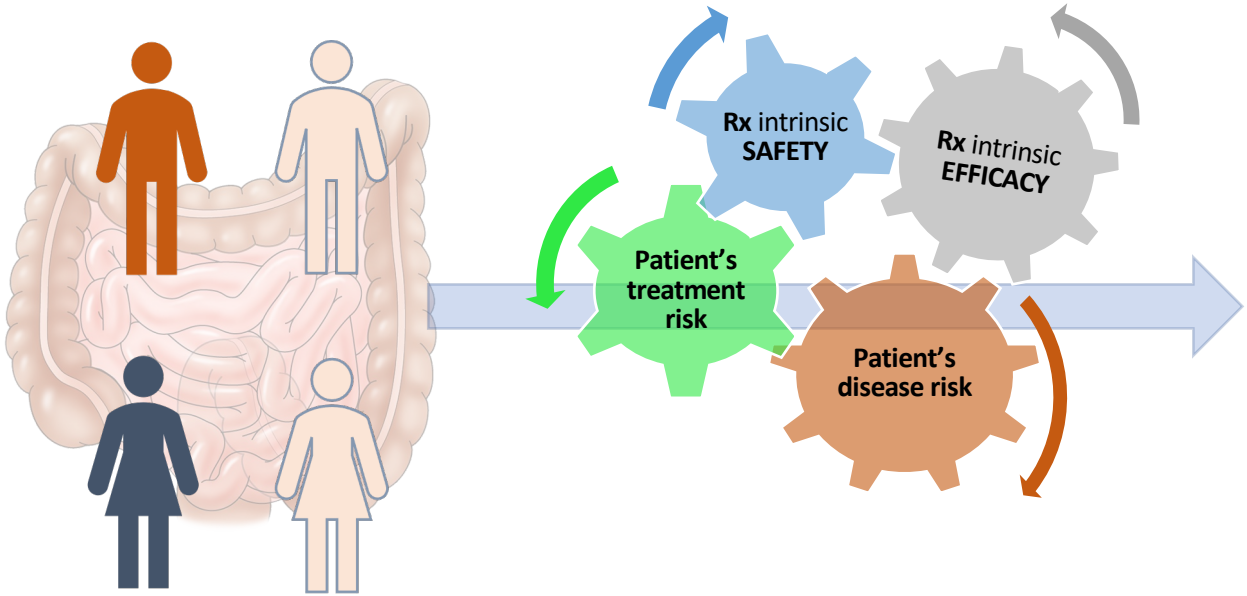
Three Take-Home Points

1. We are moving from a TNF era, to a non-TNF era …. But should we?
2. The future is JAK'ed up …. if the JAKs can tone it down
3. Right drug, right patient, right time …. is there a road to Utopia?



Drug Discovery Today: Therapeutic Strategies

Conceptual Model

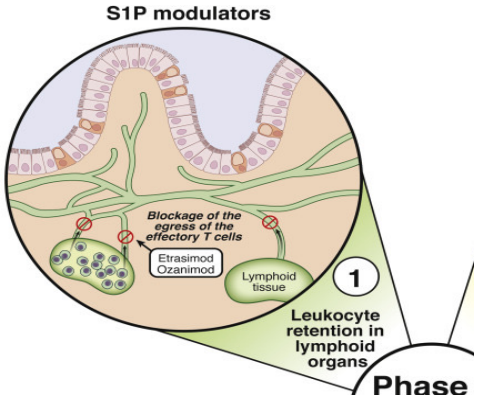


Favorable Outcomes
Sustained remission
No disease complications or surgery
No treatment complications or infections
No disability

Evolving Therapeutic Pipeline in IBD

OZANIMOD (UC)

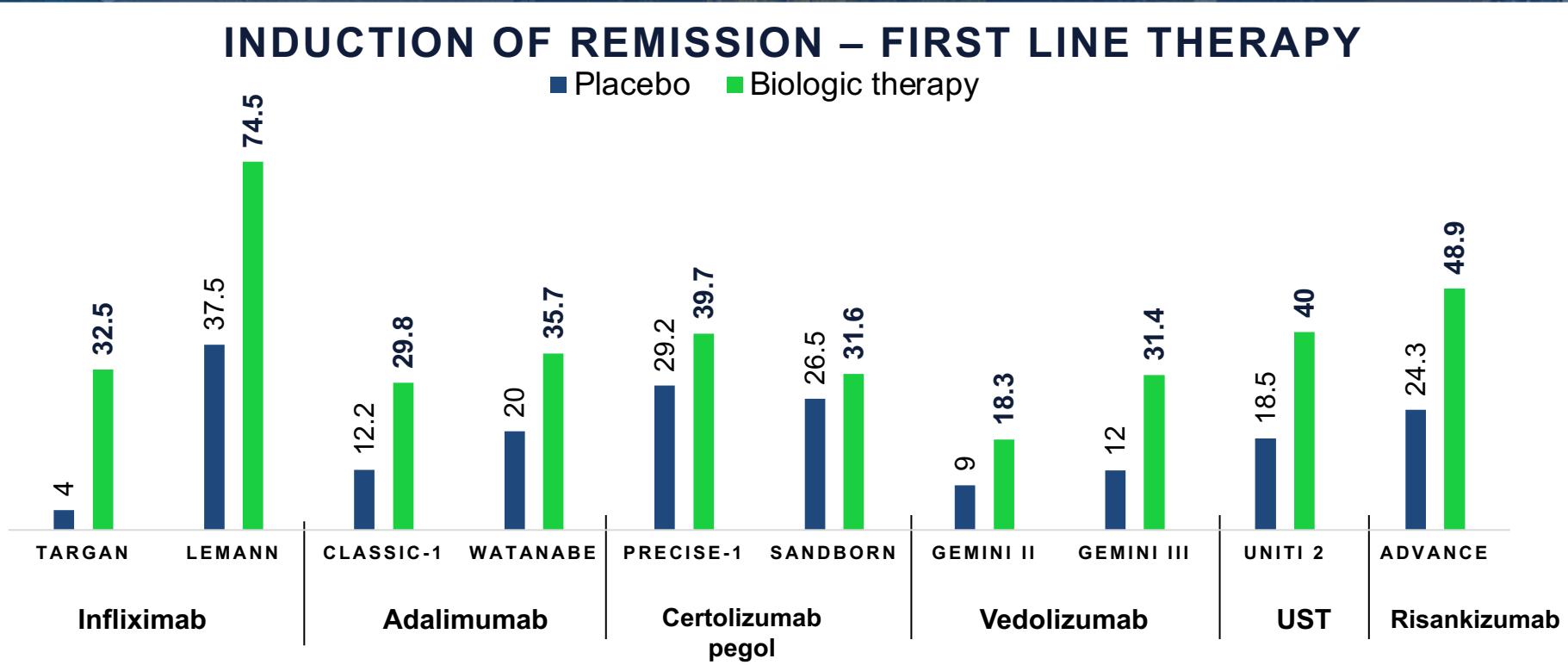
ETRASIMOD



Danese et al. *Gastro*. 2022.

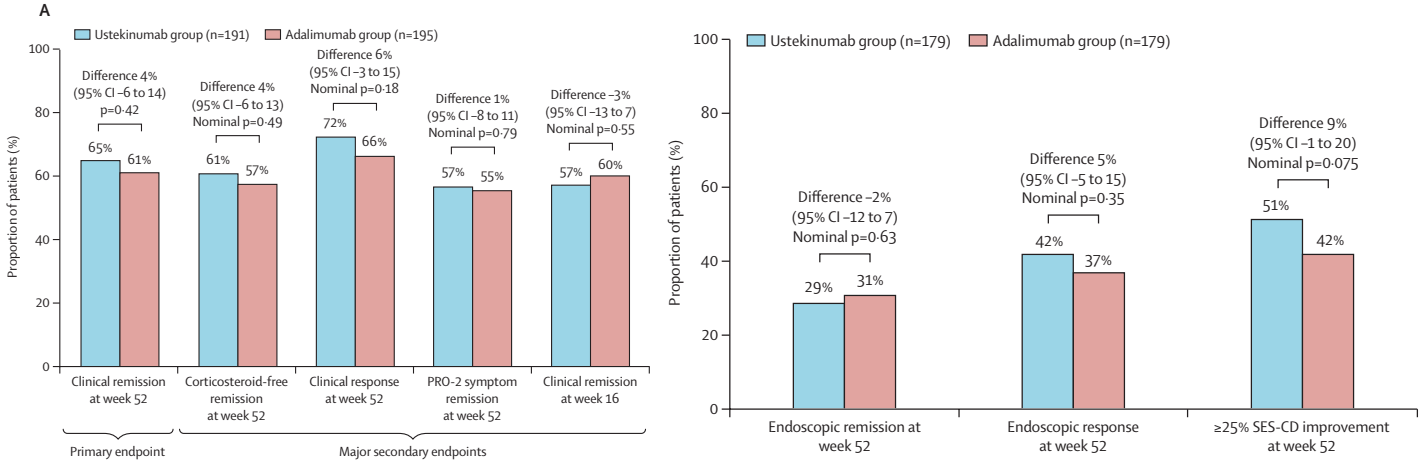
Comparative Efficacy and Positioning of Current Therapies for Management Of IBD

Efficacy of Biologics in **CROHN'S DISEASE**
Biologic-Naïve Patients



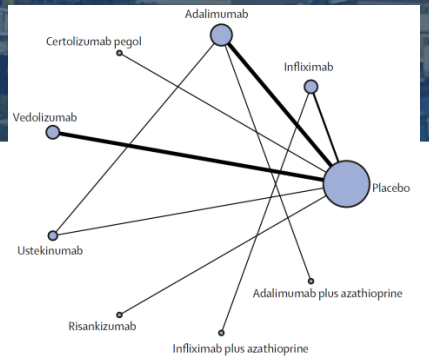
Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial

*Bruce E Sands, Peter M Irving, Timothy Hoops, James L Izanec, Long-Long Gao, Christopher Gasink, Andrew Greenspan, Matthieu Allez, Silvio Danese, Stephen B Hanauer, Vipul Jairath, Tanja Kuehbacher, James D Lewis, Edward V Loftus Jr, Emese Mihaly, Remo Panaccione, Ellen Scherl, Oksana B Shchukina, William J Sandborn, on behalf of the SEAVUE Study Group**



Only **monotherapy** with ADA and UST

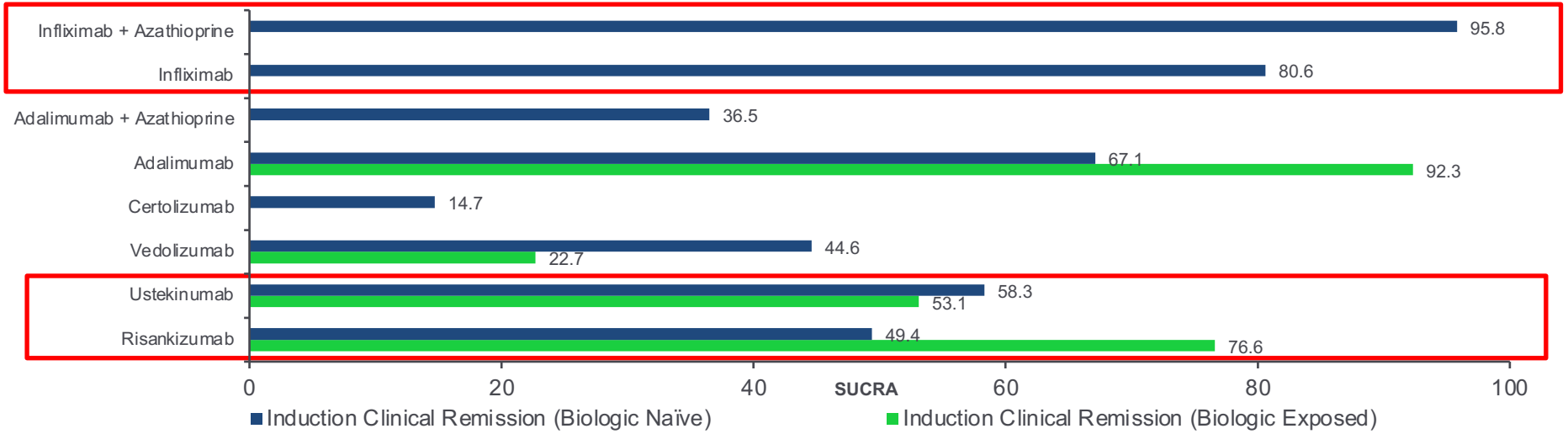
Sands et al. *Lancet.* 2022.



Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease: a systematic review and network meta-analysis

Siddharth Singh, M Hassan Murad, Mathurin Fumery, Rocio Sedano, Vipul Jairath, Remo Panaccione, William J Sandborn, Christopher Ma

Lancet Gastroenterol Hepatol
2021



Singh, …, Ma. *Lancet Gastroenterol Hepatol.* 2021.

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]

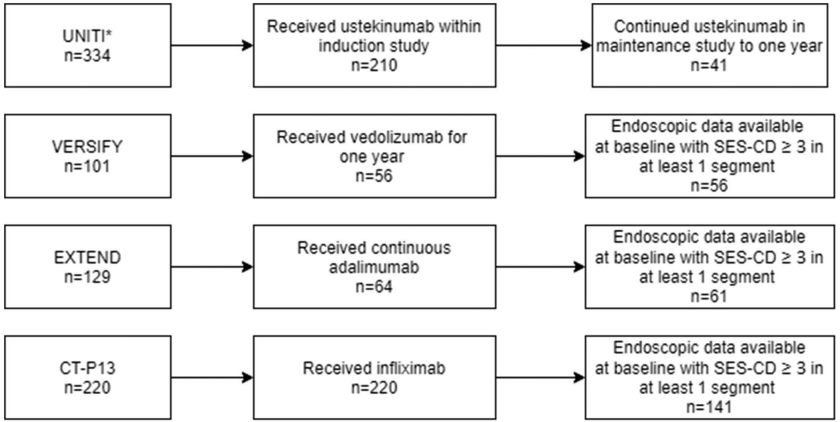
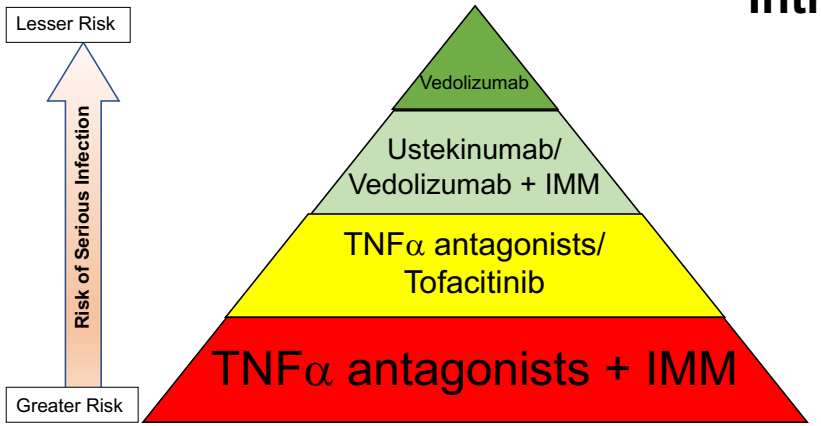


Table 2. Endoscopic outcomes at 1 year among all participants

Endoscopic healing at 1 yr among participants (n = 299)				
Treatment	**N**	**Endoscopic healing at 1 yr, n (%)**	***P* (pairwise)[a]**	***P***
Adalimumab	61	17/61 (27.9)	0.004	0.009
Infliximab	141	39/141 (27.7)	0.002	
Ustekinumab	41	7/41 (17.1)	0.128	
Vedolizumab	56	4/56 (7.1)	N/A	

Narula et al. *Am J Gastroenterol*. 2022.

Two Key Factors Influence Safety:



Intrinsic systemic immune suppression potential of therapy

(long-term risk of infections) …

And **treatment effectiveness in controlling disease**

(short-term risk of infections)

Safety of a treatment strategy >> safety of specific agent

Clinical Gastroenterology and Hepatology 2021;

Comparative Risk of Serious Infections With Tumor Necrosis Factor α Antagonists vs Vedolizumab in Patients With Inflammatory Bowel Diseases

Siddharth Singh,[*,‡] Herbert C. Heien,[§] Jeph Herrin,[||] Parambir S. Dulai,[*] Lindsey Sangaralingham,[§] Nilay D. Shah,[§,¶] and William J. Sandborn[*]

Vedolizumab vs. TNFα antagonists (reference), adjusted HR (95% CI)	All serious infections	Extra-intestinal serious infections	Gastrointestinal serious infections
All patients with IBD	0.79 (0.56-1.13)	0.81 (0.45-1.43)	**1.82** **(1.08-3.07)**
IBD phenotype • **Crohn's disease** • **Ulcerative colitis**	1.30 (0.80-2.11) **0.54** **(0.35-0.83)**	1.43 (0.73-2.79) 0.41 (0.15-1.12)	**2.90** **(1.21-6.94)** 1.20 (0.57-2.53)

Vedolizumab is safer than TNFa antagonists in patients with UC …

But no difference in risk of serious infections in patients with CD (and vedolizumab may be associated with higher-risk of disease-related infections in patients with CD)

Risk of Serious Infections With Advanced Therapies for IBD
Meta-Analysis of 20 Head-To-Head Studies

Ustekinumab vs. TNFα antagonists
(5 cohorts; 23,232 patients)

- **CD**: **51% lower risk** of serious infections with ustekinumab
- **UC**: Knowledge gap

Vedolizumab vs. TNFα antagonists
(17 cohorts; 51,596 patients)

- **CD**: **No difference** in risk of serious infections (OR, 1.03)
- **UC**: **32% lower risk** of serious infections with vedolizumab

Ustekinumab vs. vedolizumab
(5 cohorts; 1,420 patients)

- **CD**: **60% lower risk** of serious infections with ustekinumab
- **UC**: Knowledge gap

Safety profile of advanced therapies for IBD varies, and is influenced by treatment effectiveness and intrinsic immune suppression

Solitano, …, Singh. *Clin Gastroenterol Hepatol.* 2022.

So, Should We Choose …

EFFECTIVENESS? VS. SAFETY?

We should (almost) always choose an ‘effective’ drug over a ‘safer’ drug

CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease

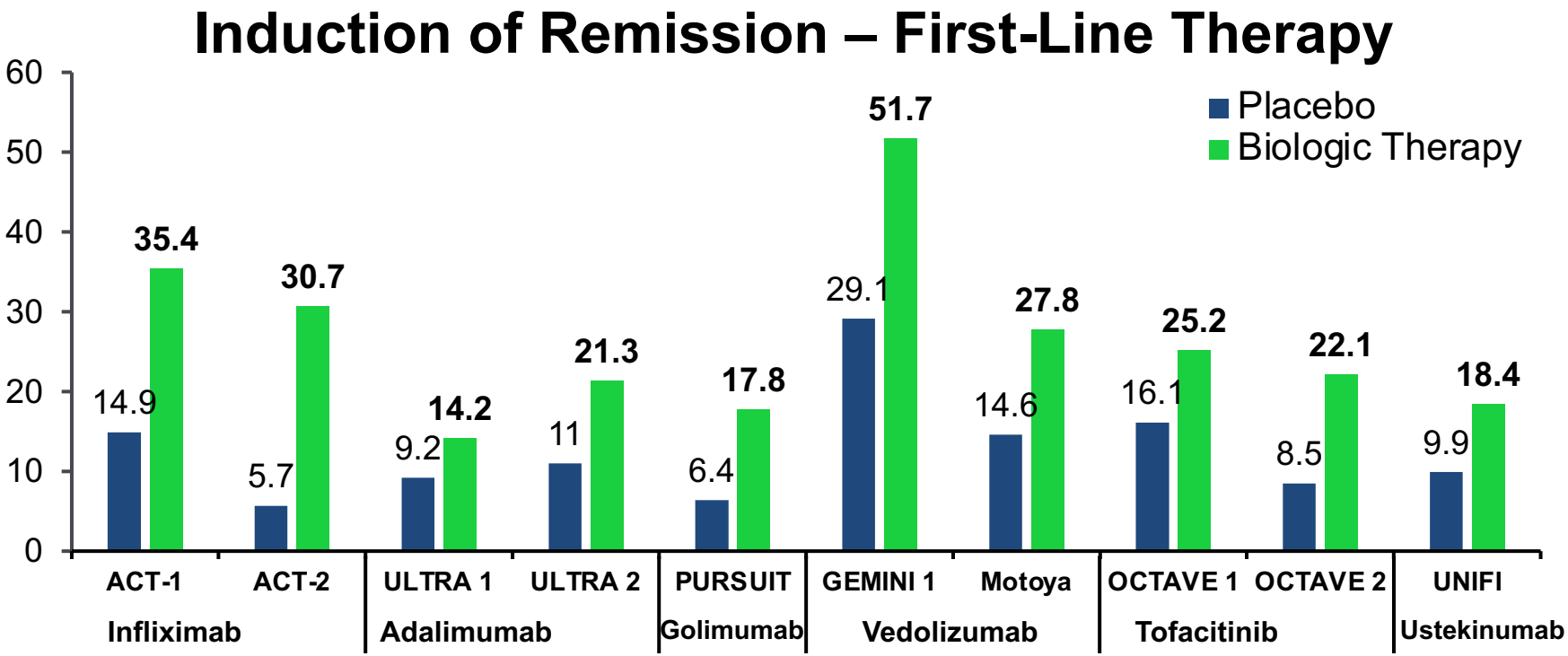
Gastroenterology 2021;160:2496–2508

A. In adult outpatients with moderate to severe CD, who are *naïve to biologics* the AGA
Recommends the use of infliximab, adalimumab or ustekinumab* over certolizumab pegol (Strong recommendation, moderate certainty of evidence)
Suggests the use of vedolizumab over certolizumab pegol (Conditional recommendation, low certainty of evidence)
B. In adult outpatients with moderate to severe CD, who have never responded to TNFα antagonists (primary non-response), the AGA
Recommends the use of ustekinumab* (Strong recommendation, moderate certainty of evidence)
Suggests the use of vedolizumab (Conditional recommendation, low certainty of evidence)
C. In adult outpatients with moderate to severe CD, who have previously responded to infliximab (secondary non-response), the AGA
Recommends the use of adalimumab or ustekinumab* (Strong recommendation, moderate certainty of evidence)

Feuerstein et al. *Gastroenterology.* 2021; Singh, et al. *Gastroenterology.* 2021.

*Findings also likely extend to Risankizumab

Efficacy Of Biologics in **ULCERATIVE COLITIS**
Biologic-Naïve Patients



CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis Gastroenterology 2020;158:1450–1461

A. In adult outpatients with moderate to severe UC, who are *naïve to biologics* the AGA

Suggest use of infliximab or vedolizumab, rather than adalimumab

Conditional recommendation, moderate certainty of evidence

Comment: Patients, particularly those with less severe disease, who place higher value on the convenience of self-administered subcutaneous injection, and a lower value on the relative efficacy of medications, may reasonably chose adalimumab as an alternative

B. In adult outpatients with moderate to severe UC, who have never responded to infliximab (primary non-response), the AGA

Suggest using ustekinumab or tofacitinib*, rather than vedolizumab or adalimumab

Conditional recommendation, moderate certainty of evidence

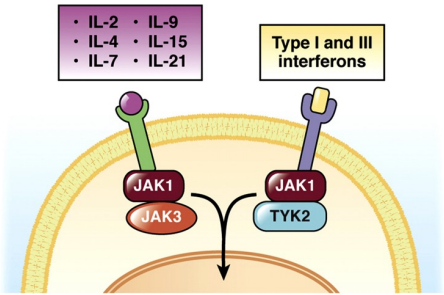
Comment: Patients, particularly those with less severe disease, who place higher value on the potential safety of medications, and a lower value on the relative efficacy, may reasonably chose vedolizumab as an alternative

*Based on FDA guidance, tofacitinib is not recommended as first-line immunosuppressive therapy in patients with ulcerative colitis

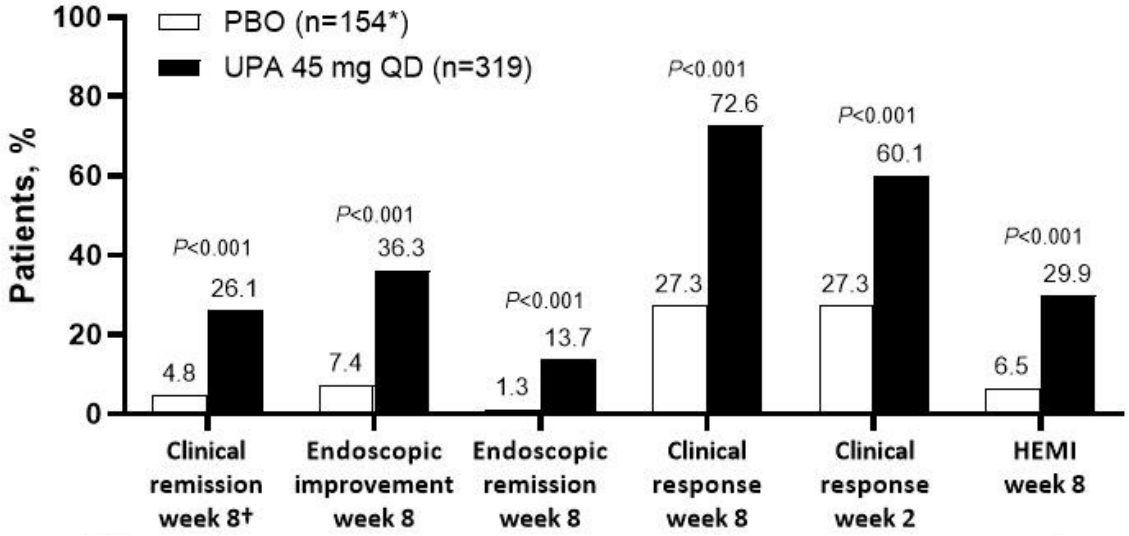
Feuerstein,…, Singh. *Gastroenterology.* 2020; Singh, Allegretti et al. *Gastroenterology.* 2020.

March 16, 2022

RINVOQ® (upadacitinib) Receives FDA Approval for the Treatment of Adults with Moderately to Severely Active Ulcerative Colitis



Drug	JAK1	JAK3	TYK2	Gut selectivity	IBD type
Upadacitinib	Yes			No	CD UC
Filgotinib	Yes			No	CD UC
TD-1473	Yes	Yes	Yes	Yes	CD UC
PF-06651600 PF-06700641	Yes	Yes	Yes	No	CD UC
BMS-986165			Yes	No	CD UC
Tofacitinib	Yes	Yes	Yes	No	UC

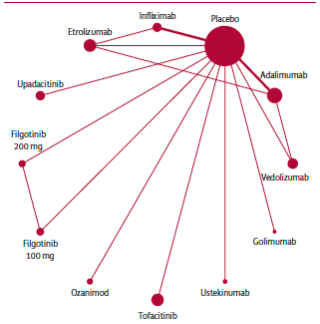


Vermeire et al. *ECCO.* 2021.

Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis

Juan S Lasa*, Pablo A Olivera*, Silvio Danese, Laurent Peyrin-Biroulet

Lancet Gastroenterol Hepatol
2022; 7: 161–70



Upadacitinib	2·70 (1·18–6·20)	4·49 (2·18–9·24)	6·15 (2·98–12·72)	2·84 (1·28–6·31)	4·91 (2·59–9·31)	2·92 (1·31–6·51)	3·56 (1·84–6·91)	3·00 (1·32–6·82)	4·64 (2·47–8·71)	2·70 (1·18–6·20)	9·54 (5·45–16·69)
3·01 (1·59–5·67)	Ozanimod	1·65 (0·77–3·55)	2·27 (1·05–4·89)	1·05 (0·45–2·41)	1·81 (0·91–3·60)	1·07 (0·46–2·49)	1·31 (0·65–2·67)	1·10 (0·47–2·61)	1·71 (0·87–3·37)	0·93 (0·47–1·85)	3·52 (1·91–6·49)
2·91 (1·19–7·10)	0·97 (0·39–2·39)	Filgotinib 200 mg	1·37 (0·71–2·62)	0·63 (0·30–1·31)	1·09 (0·63–1·89)	0·65 (0·31–1·35)	0·79 (0·44–1·41)	0·66 (0·31–1·42)	1·03 (0·60–1·77)	0·56 (0·32–0·97)	2·12 (1·34–3·35)
5·96 (2·35–15·14)	1·98 (0·77–5·09)	2·04 (0·66–6·33)	Filgotinib 100 mg	0·46 (0·22–0·95)	0·79 (0·45–1·39)	0·47 (0·22–0·99)	0·57 (0·32–1·03)	0·48 (0·22–1·03)	0·75 (0·43–1·30)	0·41 (0·23–0·71)	1·54 (0·97–2·45)
3·05 (1·68–5·51)	1·01 (0·55–1·86)	1·04 (0·43–2·50)	0·51 (0·20–1·27)	Tofacitinib	1·72 (0·90–3·29)	1·02 (0·45–2·30)	1·25 (0·64–2·45)	1·05 (0·46–2·41)	1·63 (0·86–3·08)	0·89 (0·46–1·69)	3·35 (1·90–5·91)
4·71 (2·83–7·83)	1·56 (0·92–2·66)	1·61 (0·71–3·65)	0·78 (0·33–1·86)	1·54 (0·96–2·48)	Etrolizumab	0·59 (0·31–1·14)	0·72 (0·48–1·08)	0·61 (0·31–1·21)	0·94 (0·69–1·29)	0·51 (0·36–0·72)	1·94 (1·42–2·64)
3·45 (1·90–6·24)	1·14 (0·62–2·11)	1·18 (0·49–2·83)	0·57 (0·23–1·44)	1·13 (0·64–1·99)	0·73 (0·45–1·18)	Ustekinumab	1·22 (0·62–2·39)	1·02 (0·44–2·35)	1·59 (0·83–3·02)	0·86 (0·45–1·66)	3·26 (1·83–5·79)
4·71 (2·68–8·28)	1·56 (0·87–2·81)	1·61 (0·68–3·79)	0·79 (0·32–1·93)	1·54 (0·90–2·63)	1·00 (0·64–1·55)	1·36 (0·79–2·33)	Vedolizumab	0·84 (0·41–1·68)	1·30 (0·96–1·74)	0·71 (0·45–1·10)	2·67 (1·87–3·80)
4·52 (2·55–8·01)	1·50 (0·83–2·72)	1·54 (0·65–3·65)	0·75 (0·30–1·86)	1·48 (0·86–2·55)	0·95 (0·61–1·51)	1·31 (0·76–2·26)	0·95 (0·57–1·60)	Golimumab	1·54 (0·79–3·01)	0·84 (0·43–1·65)	3·17 (1·74–5·79)
5·41 (3·30–8·86)	1·79 (1·07–3·01)	1·85 (0·82–4·15)	0·90 (0·38–2·12)	1·77 (1·11–2·81)	1·14 (0·88–1·49)	1·56 (0·98–2·48)	1·15 (0·75–1·75)	1·19 (0·77–1·84)	Adalimumab	0·54 (0·37–0·79)	2·05 (1·54–2·73)
2·75 (1·66–4·55)	0·91 (0·54–1·54)	0·94 (0·41–2·14)	0·46 (0·19–1·09)	0·90 (0·56–1·44)	0·58 (0·43–0·78)	0·79 (0·49–1·27)	0·58 (0·37–0·91)	0·60 (0·39–0·95)	0·51 (0·37–0·69)	Infliximab	3·76 (2·77–5·12)
8·23 (5·32–12·75)	2·74 (1·72–4·34)	2·82 (1·30–6·12)	1·38 (0·60–3·14)	2·71 (1·81–4·02)	1·74 (1·34–2·26)	1·74 (1·34–2·26)	1·74 (1·22–2·49)	1·82 (1·25–2·63)	1·52 (1·21–1·92)	3·00 (2·33–3·82)	Placebo

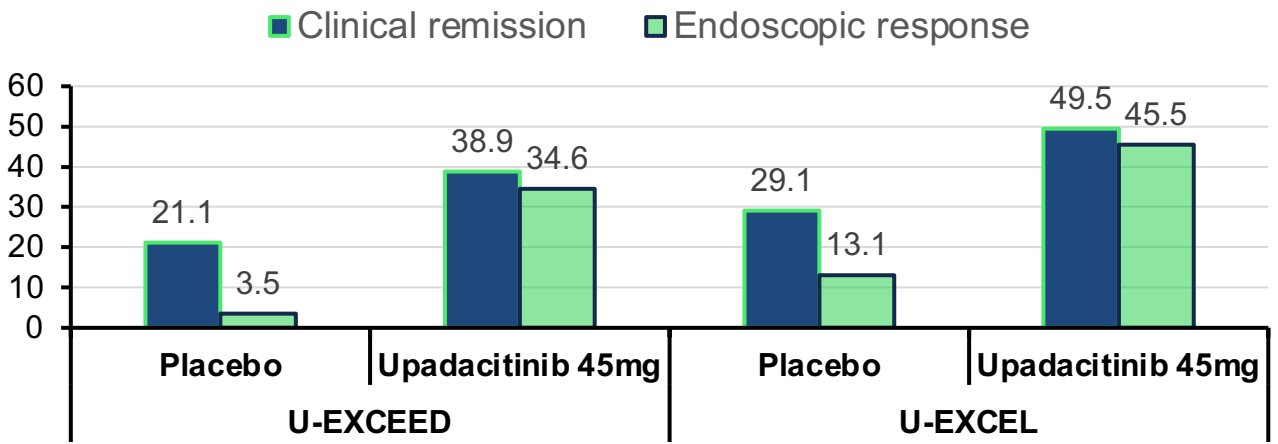
Endoscopic improvement

Clinical remission

Lasa, Olivera et al. *Lancet Gastroenterol Hepatol.* 2022.

Upadacitinib Induction and Maintenance Therapy for Crohn's Disease

E.V. Loftus, Jr., J. Panés, A.P. Lacerda, L. Peyrin-Biroulet, G. D'Haens, R. Panaccione, W. Reinisch, E. Louis, M. Chen, H. Nakase, J. Begun, B.S. Boland, C. Phillips, M.-E.F. Mohamed, J. Liu, Z. Geng, T. Feng, E. Dubcenco, and J.-F. Colombel



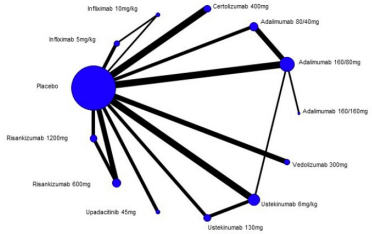
May 18, 2023

U.S. FDA Approves RINVOQ® (upadacitinib) as a Once-Daily Pill for Moderately to Severely Active Crohn's Disease in Adults

Loftus et al. *New Engl J Med.* 2023.

Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis

Brigida Barberio,[1] David J Gracie,[2] Christopher J Black ,[2] Alexander C Ford [2,3]



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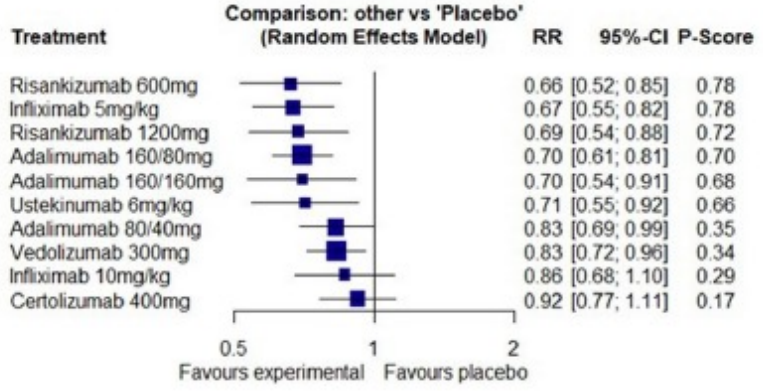
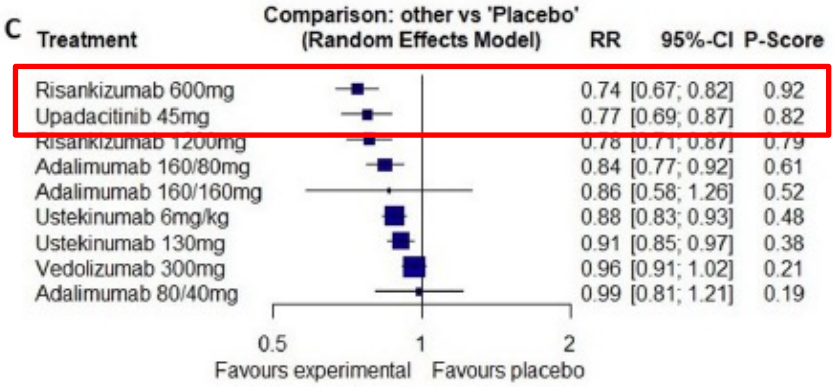


Biologic-naïve patients

C



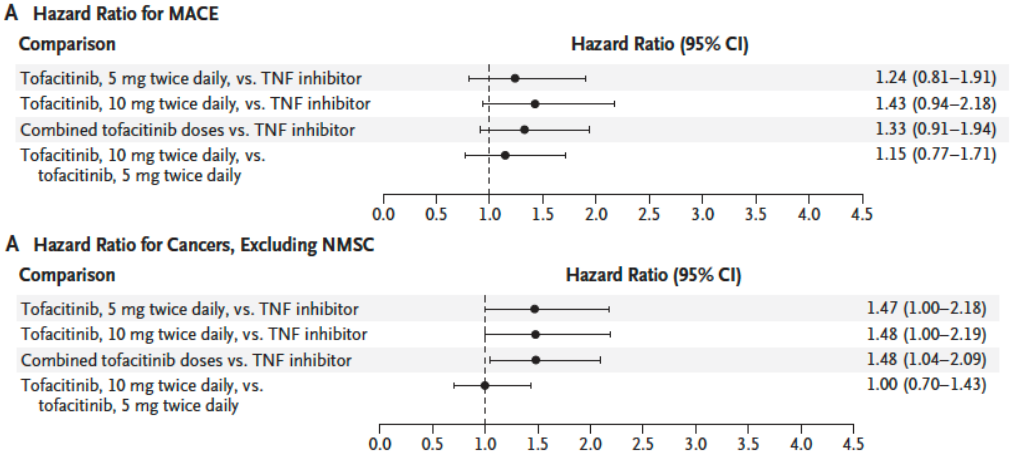
Biologic-exposed patients

Lasa, Olivera et al. *Lancet Gastroenterol Hepatol.* 2022.

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

ORAL Surveillance Investigators*

The NEW ENGLAND JOURNAL of MEDICINE



Event (vs. TNF antagonist)	Tofacitinib 5mg BID	Tofacitinib 10mg BID
Serious infections	1.17 (0.92–1.50)	1.48 (1.17–1.87)
Opportunistic infections	1.82 (1.07–3.09)	2.17 (1.29–3.66)
Hepatic event	1.29 (0.83–2.00)	2.14 (1.43–3.21)
Non-melanoma skin cancer	1.90 (1.04–3.47)	2.16 (1.19–3.92)
Pulmonary embolism	2.93 (0.79–10.83)	8.26 (2.49–27.43)
Venous thromboembolism	1.66 (0.76–3.63)	3.52 (1.74–7.12)
Death	1.49 (0.81–2.74)	2.37 (1.34–4.18)

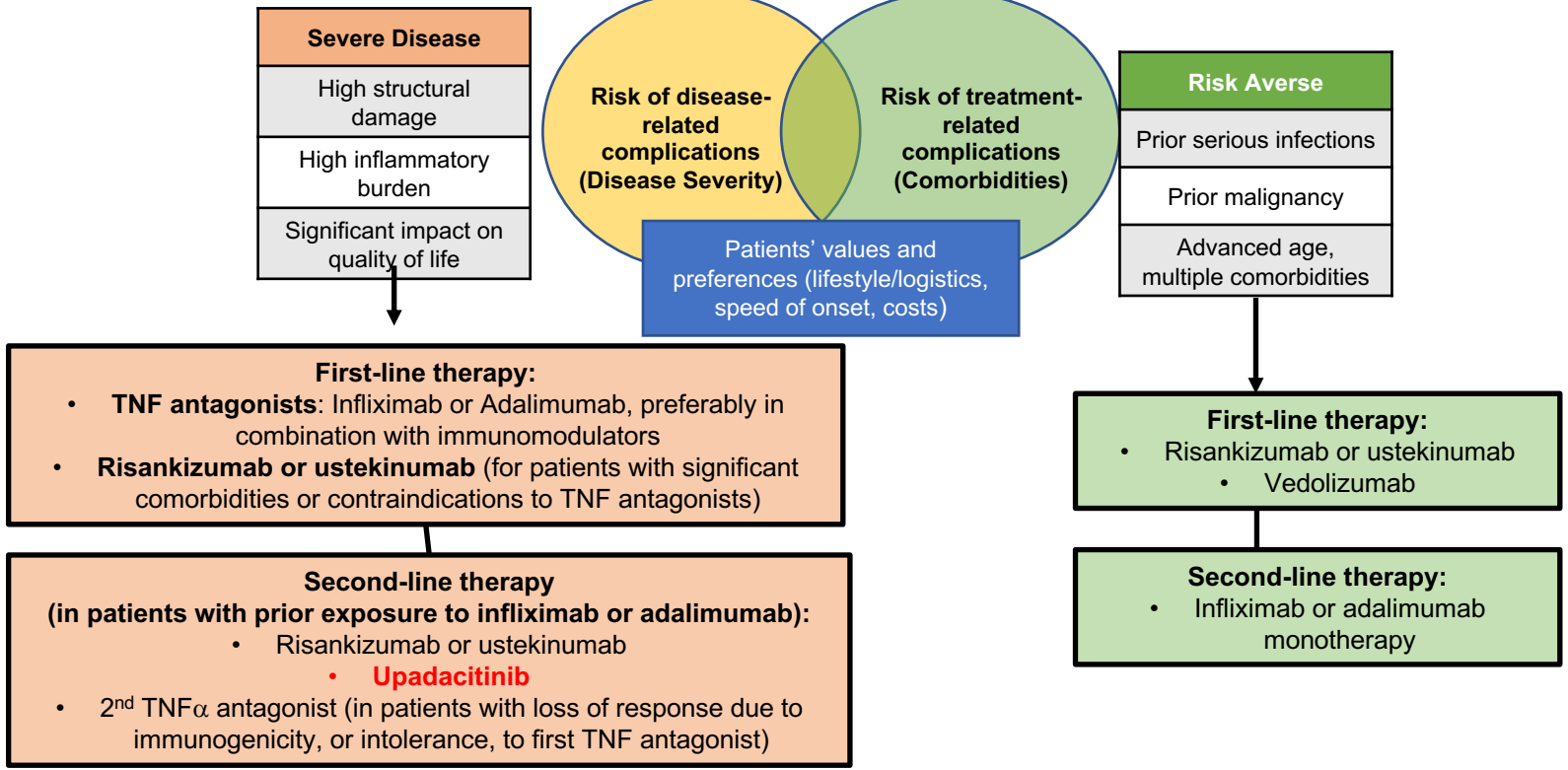
Ytterberg et al. *N Engl J Med.* 2022.

FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions

Approved uses also being limited to certain patients

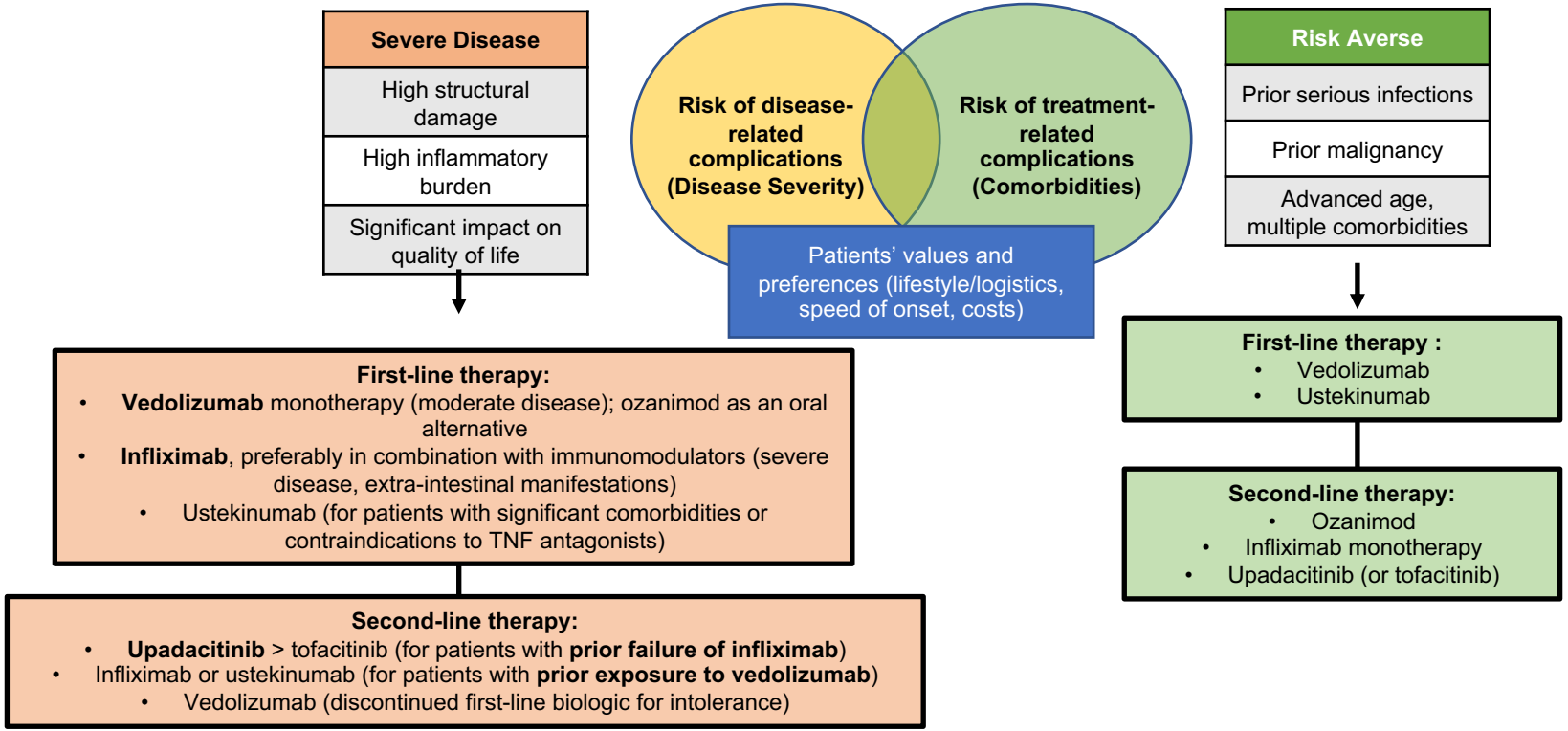
"… we are limiting all approved uses of JAK inhibitors (tofacitinib, upadacitinib, baricitinib) to certain patients **who have not responded or cannot tolerate one or more TNF blockers**"

Moderate to Severely Active **CROHN'S DISEASE**



Singh. *Nat Rev Gastroenterol Hepatol.* 2023.

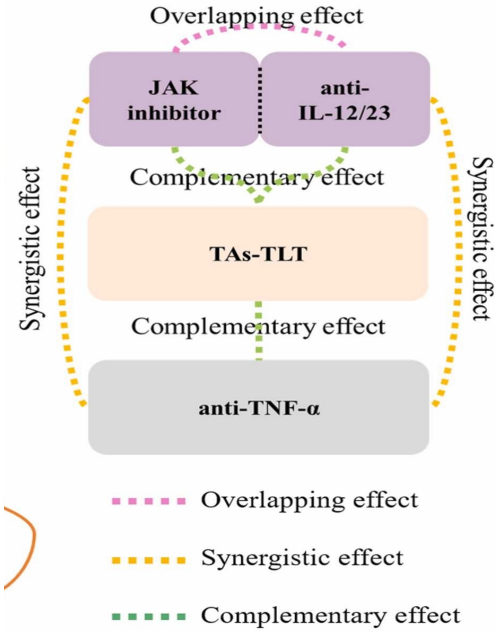
Moderate to Severely Active **ULCERATIVE COLITIS**

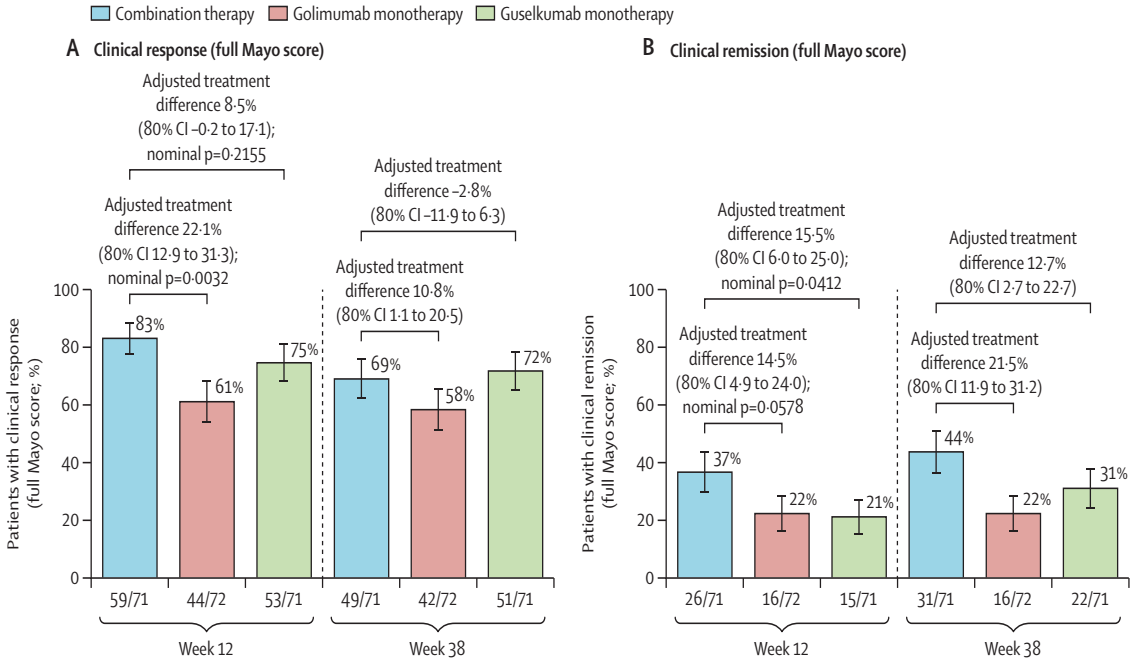


Singh. *Nat Rev Gastroenterol Hepatol.* 2023.


Right Drug, Right Patient, Right Time ….
The Road to Utopia

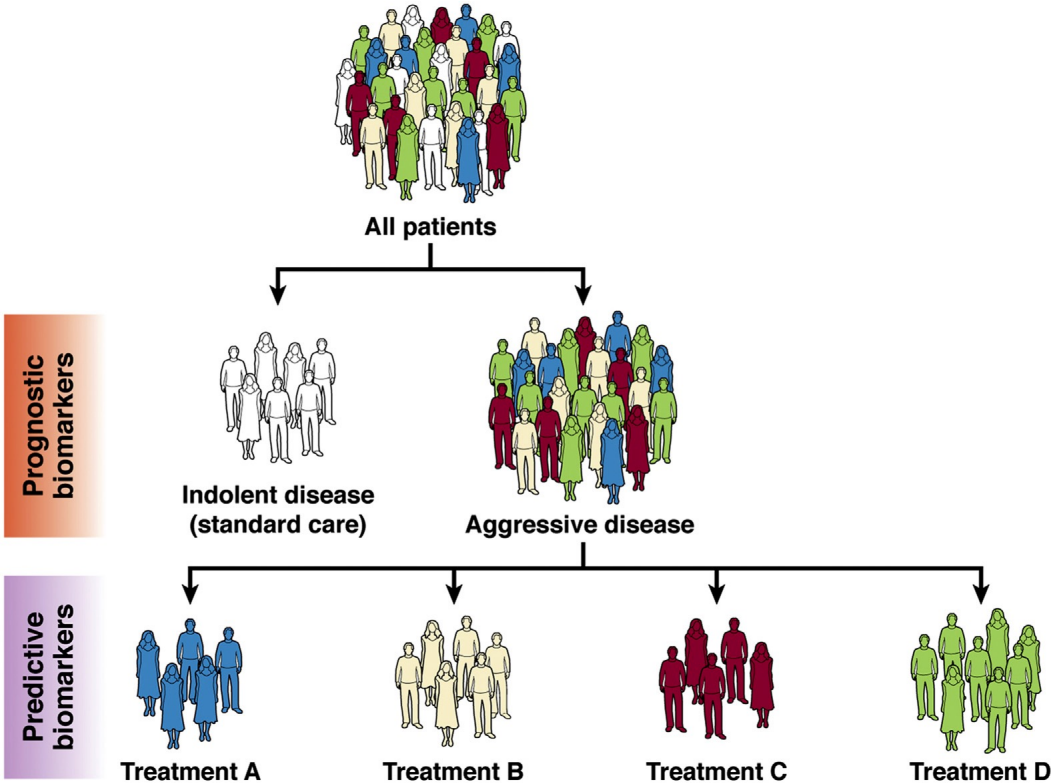
IBD Matchmaking (Rational Combination Therapy) Works





Feng et al. *Biomed Pharmacother*. 2023; Feagan et al. *Lancet Gastroenterol Hepatol*. 2023.

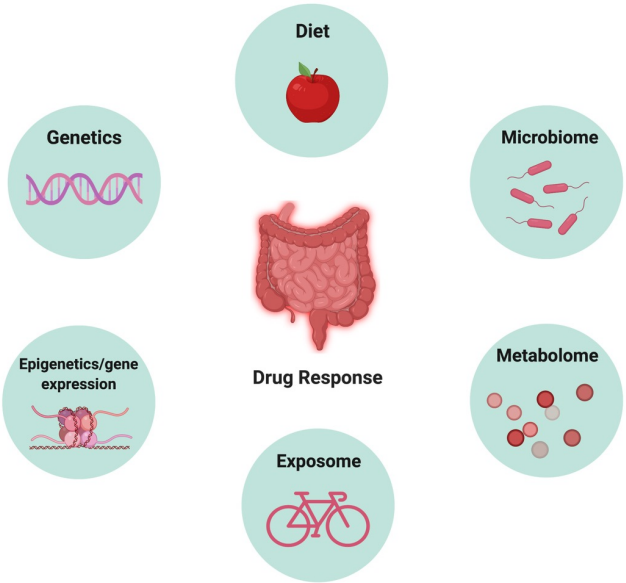
Predictive and Prognostic Biomarkers in IBD



Verstockt et al. *Gastroenterology.* 2021.

What Determines Response to a Therapy?

What LIKELY determines response?



What we know now that associates with response?

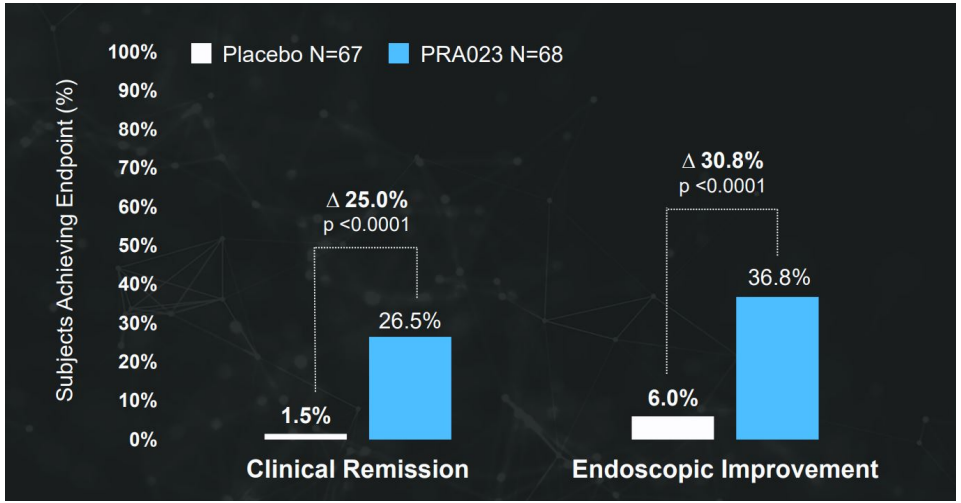
- **Clinical phenotype**
- **Pharmacological factors**

FAVORABLE factors	UNFAVORABLE factors
Younger age at initiation	Complicated disease phenotype (perianal disease, fistulizing disease)
Early clinical and/or endoscopic response to therapy	Severe disease activity at time of induction
No prior exposure to anti-TNF therapy	High inflammatory burden (high CRP, low albumin)
Concomitant immunomodulator use	Deep and/or extensive ulcers
Colonic disease location (vs. ileum-dominant disease)	Low trough concentrations, and presence of anti-drug antibodies
	High BMI

Barre et al. *Aliment Pharmacol Ther*. 2018.

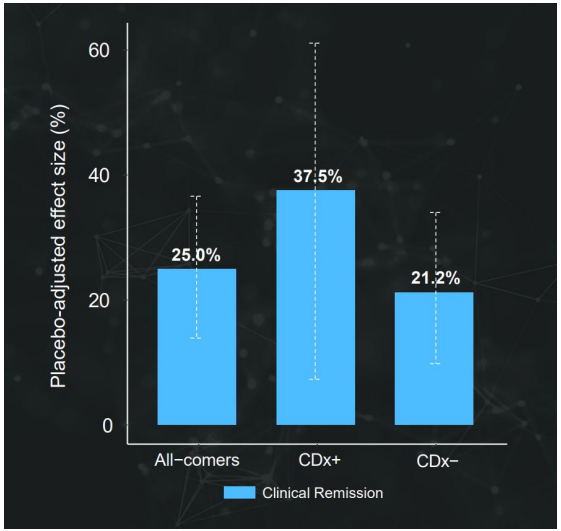
News Release

Prometheus Biosciences Announces Positive Results for PRA023 in Both ARTEMIS-UC Phase 2 and APOLLO-CD Phase 2a Studies Enabling Pathway to Both First-in-Class and Best-in-Class Anti-TL1A mAb

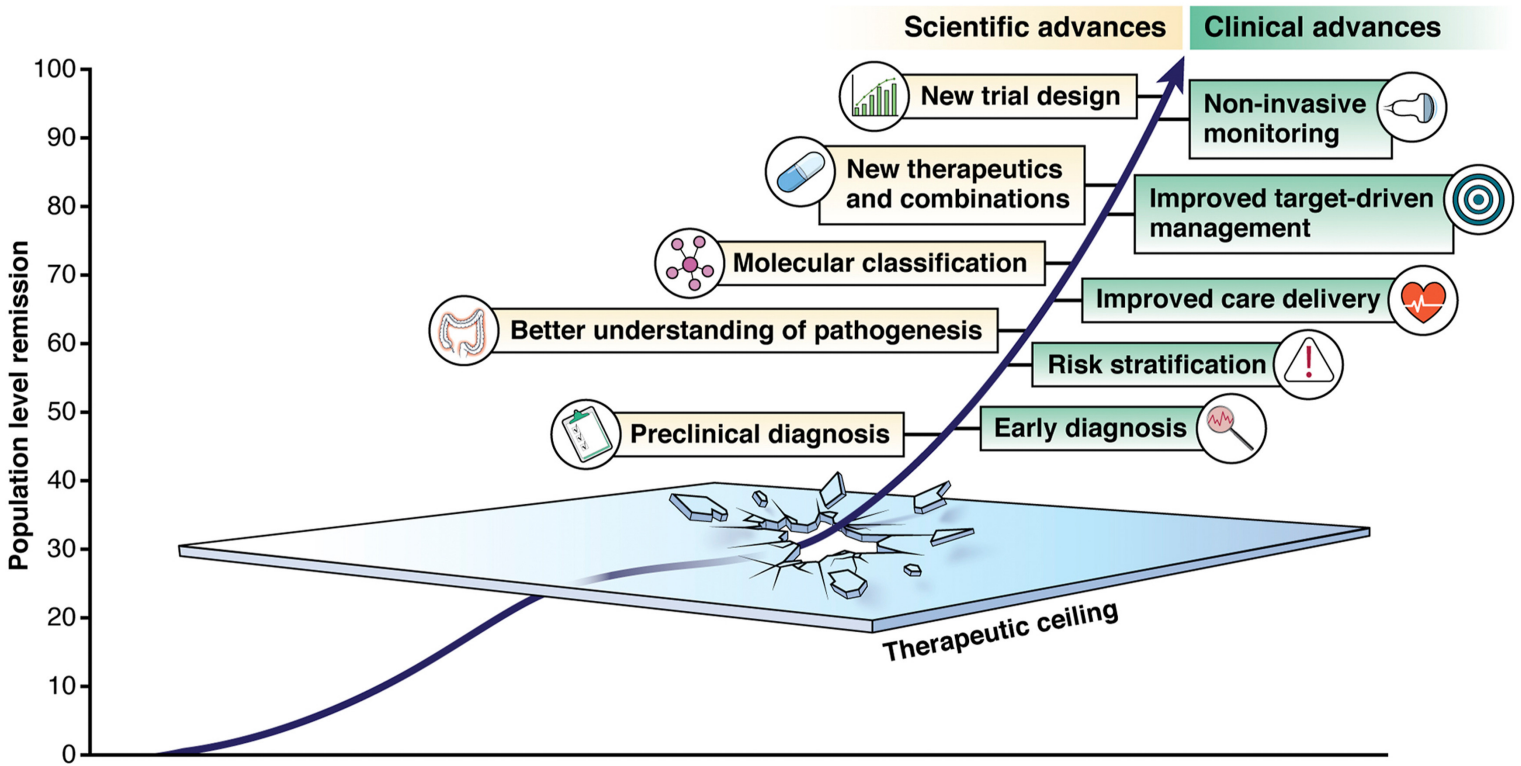


Evaluate Vantage December 07, 2022

Precision pays off for Prometheus



Press release by Prometheus Biosciences.



Raine and Danese. *Gastroenterology*. 2022.

Three Take-Home Points

1. TNFa antagonists still the best option for CD and severe UC
2. JAK1 inhibitors are potentially game-changing oral therapies for UC
3. The road to Utopia is long – till then, mass personalization based on comparative efficacy and safety is better than playing the lottery