So many choices: Positioning advanced therapies in Crohn's disease

Anne M Griffiths, MD, FRCPC
Co-Lead, Inflammatory Bowel Disease Centre
SickKids Hospital,
Professor of Pediatrics,
University of Toronto

UNIVERSITY of TORONTO

SickKids | Inflammatory Bowel Disease Centre

Disclosures of potential conflicts of interest

- Personal Consulting or Advisory board membership fees: Abbvie, Amgen, Janssen, Lilly, Merck, Pfizer
- Speaker fees: Abbvie, Alimentiv, Janssen, Takeda

- I will talk about therapies that are not yet Health Canada-approved for children and adolescents who have not reached their 18th birthday

Positioning “advanced therapies” in Crohn’s disease: choices not so long ago

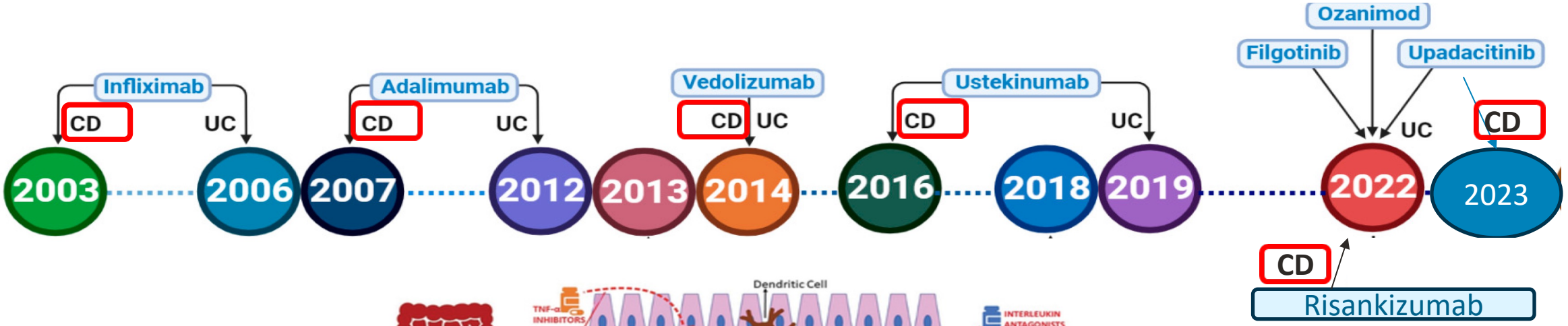
TIMEPOINT	UNTIL RECENTLY
Choosing FIRST advanced therapy	**When** to start? **Which anti-TNF**?
Choosing SUBSEQUENT advanced therapy	When first anti-TNF has “failed”? When is a change needed?

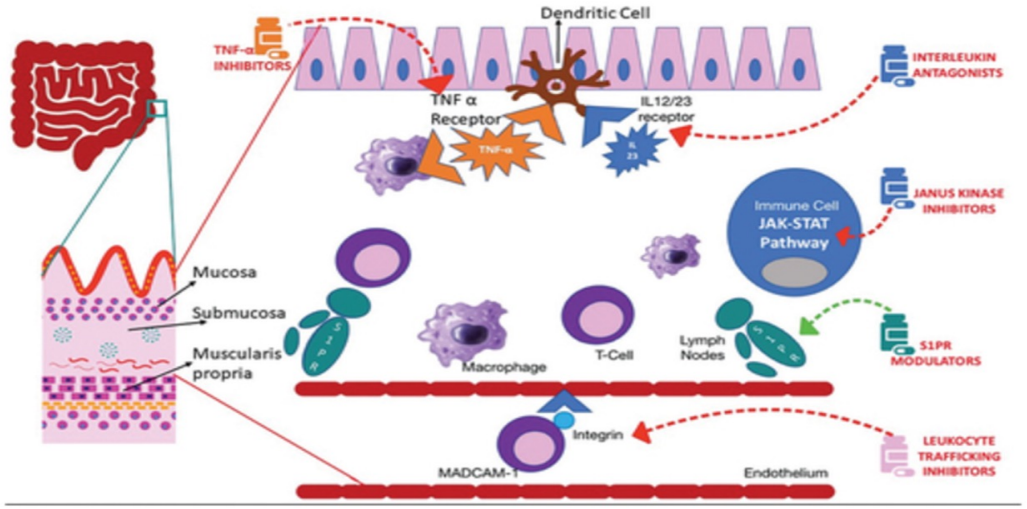
Types of “FAILURE”

Primary non-response/incomplete, unsatisfactory response?
(lack of clinical remission or failure to achieve other target?)
(Pharmacokinetic/pharmacodynamic?)
Intolerance?

Secondary loss of response related to anti-drug antibodies?
Secondary loss of response NOT related to anti-drug antibodies?

Increasing choices of “advanced therapies” (biologics and targeted oral small molecules) in Crohn’s disease





Positioning “advanced therapies” in Crohn’s disease: choices to make now

TIMEPOINT	NOW
Choosing FIRST advanced therapy	**When** to start? **Which biologic (or targeted oral small molecule)** ?
Choosing SUBSEQUENT advanced therapy	Which biologic or targeted oral small molecule **when first has failed?**

Types of “FAILURE”

Primary non-response/incomplete, unsatisfactory response?
(lack of clinical remission or failure to achieve other targets?)
(Pharmacokinetic/pharmacodynamic)
Intolerance

With biologics: secondary loss of response related to anti-drug antibodies?
Secondary loss of response NOT related to anti-drug antibodies?

Considerations in choosing therapies: as patients and families ask…

Will it work?
Is it safe?
How fast will I/my child or family member feel better?
Will it keep working?
What is involved with taking it?

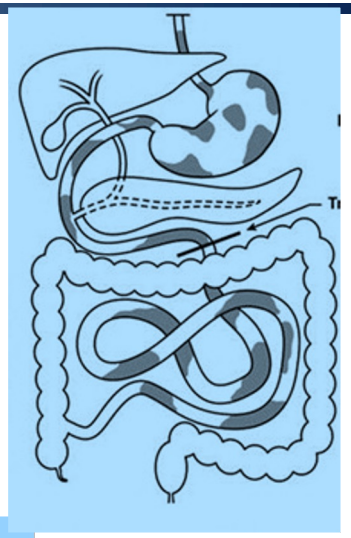
Clinician's considerations are similar

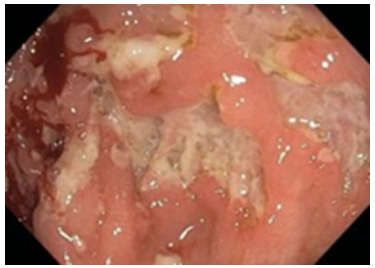
Reliable induction of **steroid-free clinical remission + efficacy in achieving healing**
Favorable safety profile……learning curve
Knowledge of how optimize efficacy (dosing, therapeutic drug monitoring)
Durability of remission (including Immunogenicity; need for/advisability of concomitant IM)
Rapidity of onset
Patient preference for mode of administration
Access
Cost
Efficacy in special situations (e.g. perianal fistulizing disease; associated arthritis)

Consider phenotypic heterogeneity of Crohn's disease

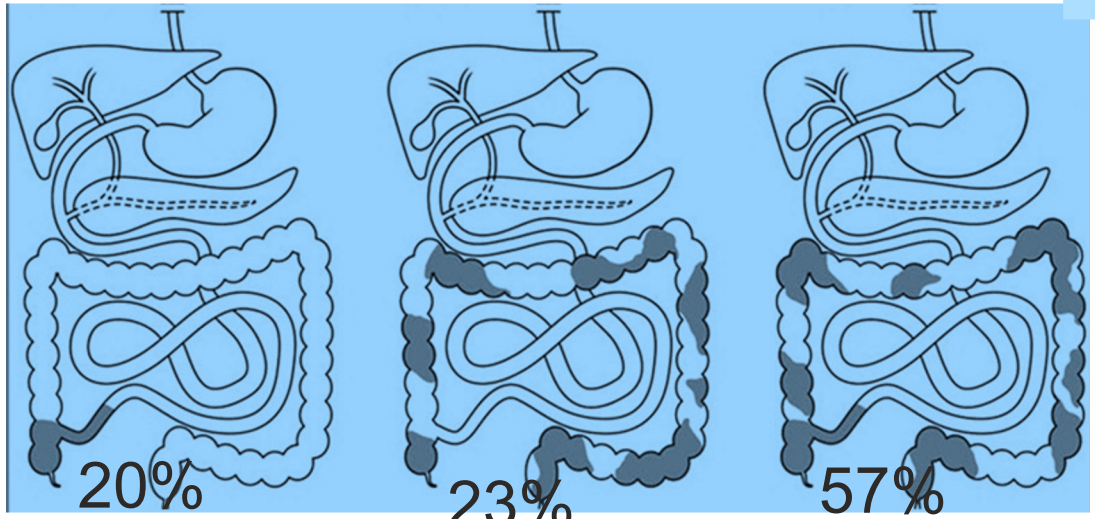
N= 698 (age 2 - <17yrs)	
Median age (IQR)	12.9 years (10.9, 14.8)
Gender	59% male
Perianal fistulizing	16%

Additional "proximal" small bowel involvement 27% L4b





Lower intestinal Tract (L1/L2/L3)



Dhaliwal J Crohn Colitis 2020 May 21;14:445-454

CIDsCaNN
Canadian Children Inflammatory Bowel Disease Network
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Advanced therapies in Crohn's disease: Questions faced in clinical practice

POSITIONING

- Early vs later initiation?: ……before versus after a trial of conventional immunomodulators?
- "Advanced therapy" for all? Who should not get?

SEQUENCING

- Is there a "better" "advanced therapy" to utilize first rather than anti-TNF?
- Advanced therapy if anti-TNF "fails"?.....what to switch to

Advanced therapy positioning in CD: Early vs later?

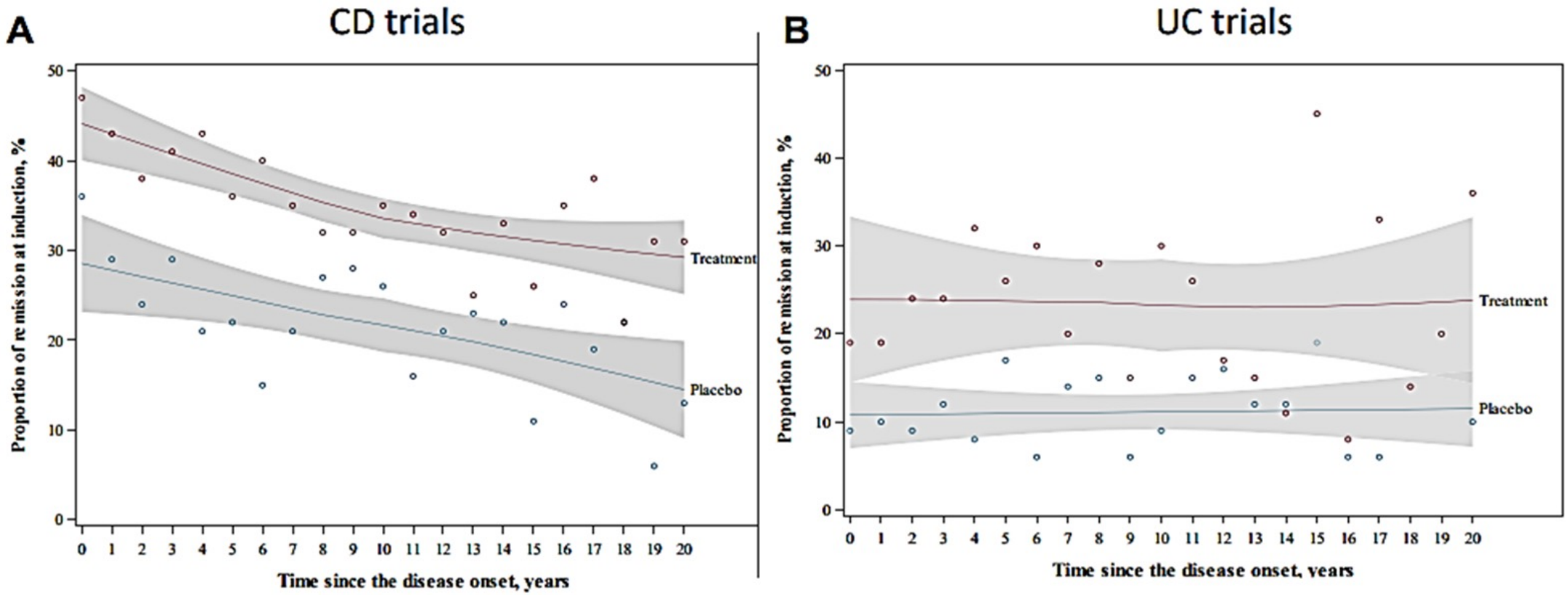


Figure 3. Rate of remission induction by duration of disease at initiation of treatment for *(A)* CD and *(B)* UC trials. The *dots* denote proportion of an outcome averaged per the respective year.

Ben-Horin S, Gastroenterology 2022;162:482-494

Advanced therapies in Crohn's disease: Questions faced in clinical practice

POSITIONING

- Early vs later initiation?: ……before versus after a trial of conventional immunomodulators?
- "Advanced therapy" for all? Who should not get?

SEQUENCING

- Is there a "better" "advanced therapy" to utilize first rather than anti-TNF?
- Advanced therapy if anti-TNF "fails"?.....what to switch to

What can help us compare efficacy?

- Head-to-head randomized clinical trials
  - *ustekinumab vs adalimumab (SEAVUE)* bionaive
  - *ustekinumab vs risankizumab (SEQUENCE)* prior anti-TNF failure

- Indirect evidence of comparative efficacy and safety
  - network meta-analyses of randomized controlled trial data

  - propensity-score matched analyses of individual patient data
    - from randomized placebo-controlled trials of different agents

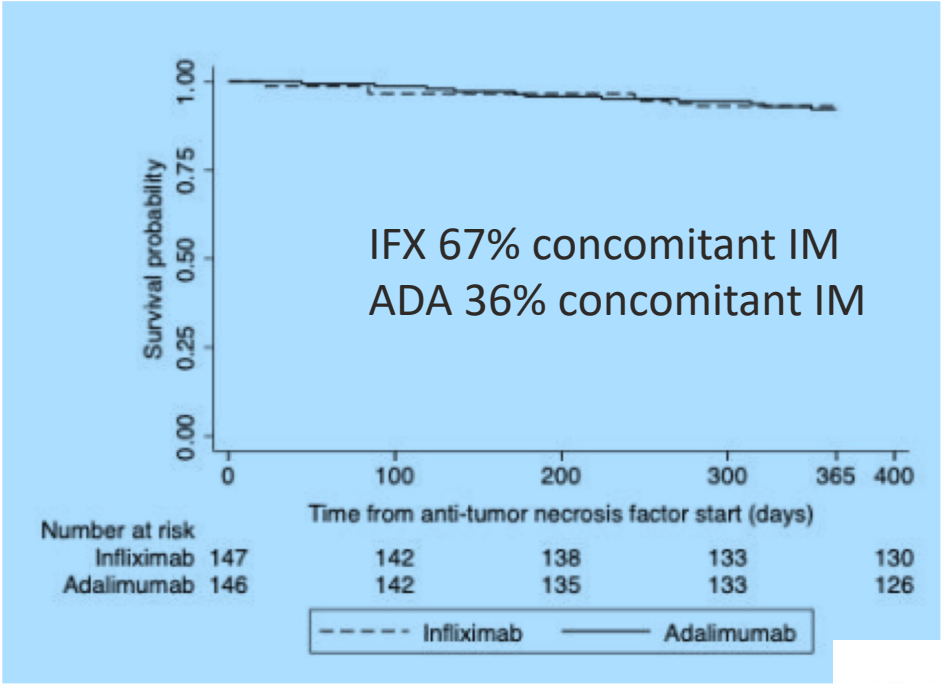
    - from observational data (real-world effectiveness)

Choice of first anti-TNF in luminal Crohn's disease?

	IFX n=435 (60% males)	IFX matched N=147	ADA n=176 (63% males)
AGE (yrs)	13.0 (11.0-14.8)	14.0 (12.9-15.8)	14.0 (12.1-15.6)
Duration (mos)	2 (1-6)	4 (1-12)	5 (2-11)
Location	13% L1 28% L2 56% L3	29% L1 14% L2 55% L3	27% L1 15% L2 56% L3
Perianal disease	21%	7%	8%
wPCDAI	45.0 (22.5-70.0)	30.0 (15.0-50.0)	30.0 (10.0-52.5)
SES-CD	16 (9-22)	12 (6-18)	12 (7-17)

Within PS-matched cohort

	IFX	ADA
One year steroid-free clinical + CRP remission	59%	54%



Debruyn J et al Am J Gastroenterol on-line

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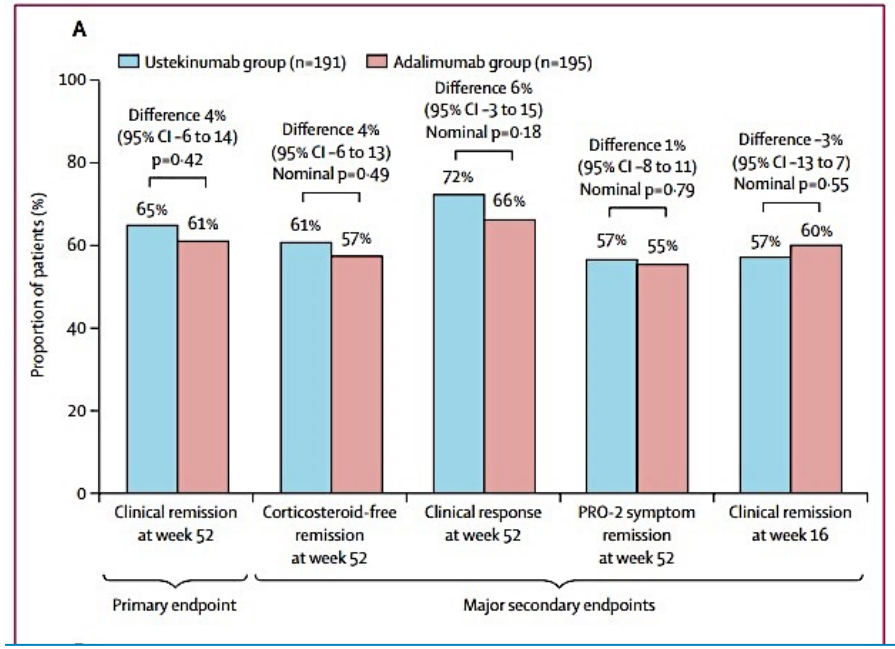
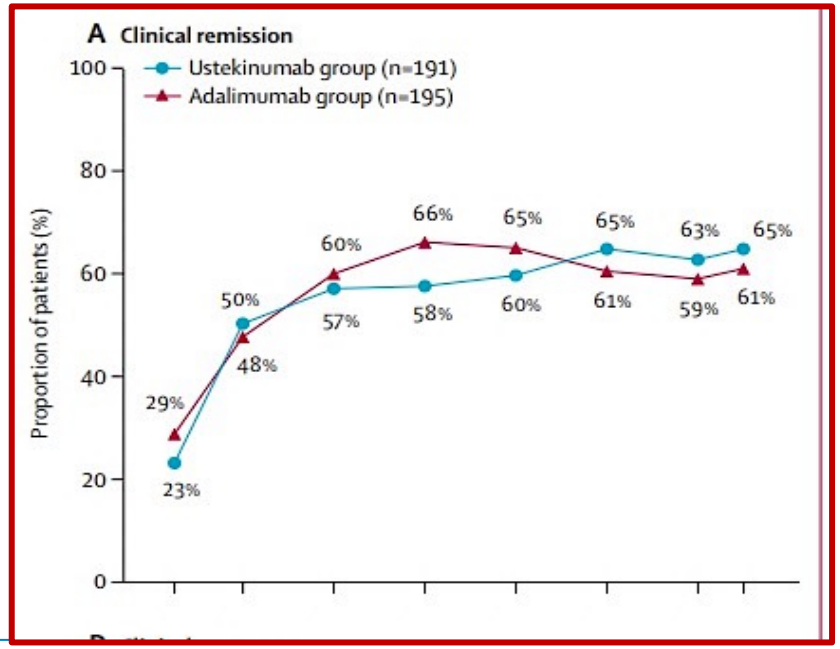
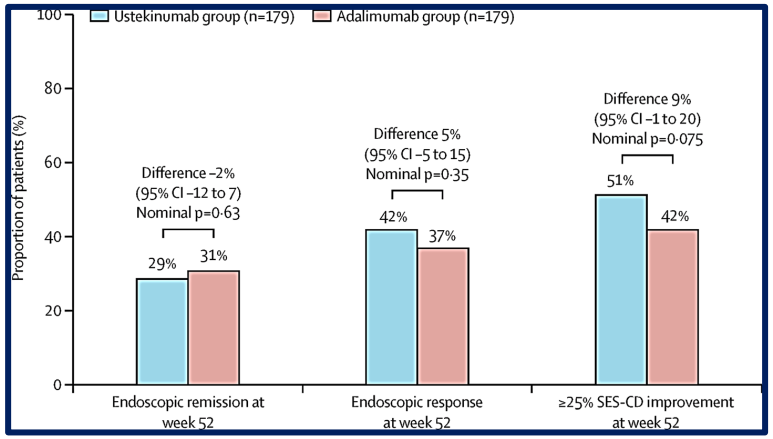
Sequencing advanced therapy in Crohn's disease: is there a "better" first therapy than anti-TNF?

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**







Lancet 2022; 399: 2200–11

Sequencing “advanced therapy” in Crohn’s disease: is there a “better” first therapy than anti-TNF?

Comparative Efficacy and Rapidity of Action for Infliximab vs Ustekinumab in Biologic Naïve Crohn’s Disease

Neeraj Narula,* Emily C. L. Wong,* Parambir S. Dulai,‡ Neil K. Sengupta,* John K. Marshall,* Jean-Frederic Colombel,§ and Walter Reinisch‖

Clin Gastro Hepatol 2022: 20: 1579-1587

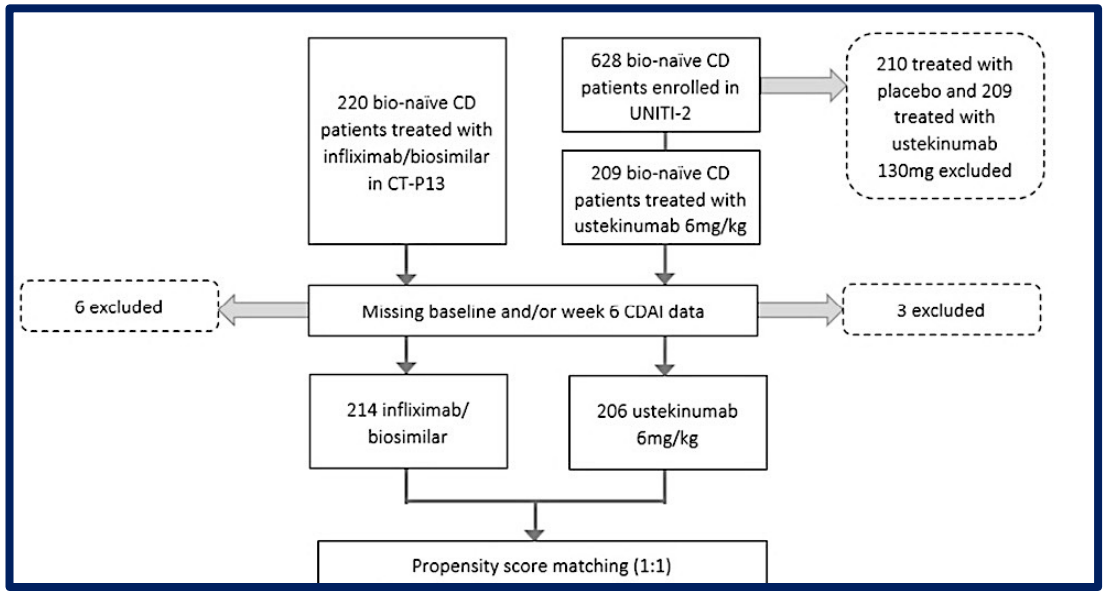
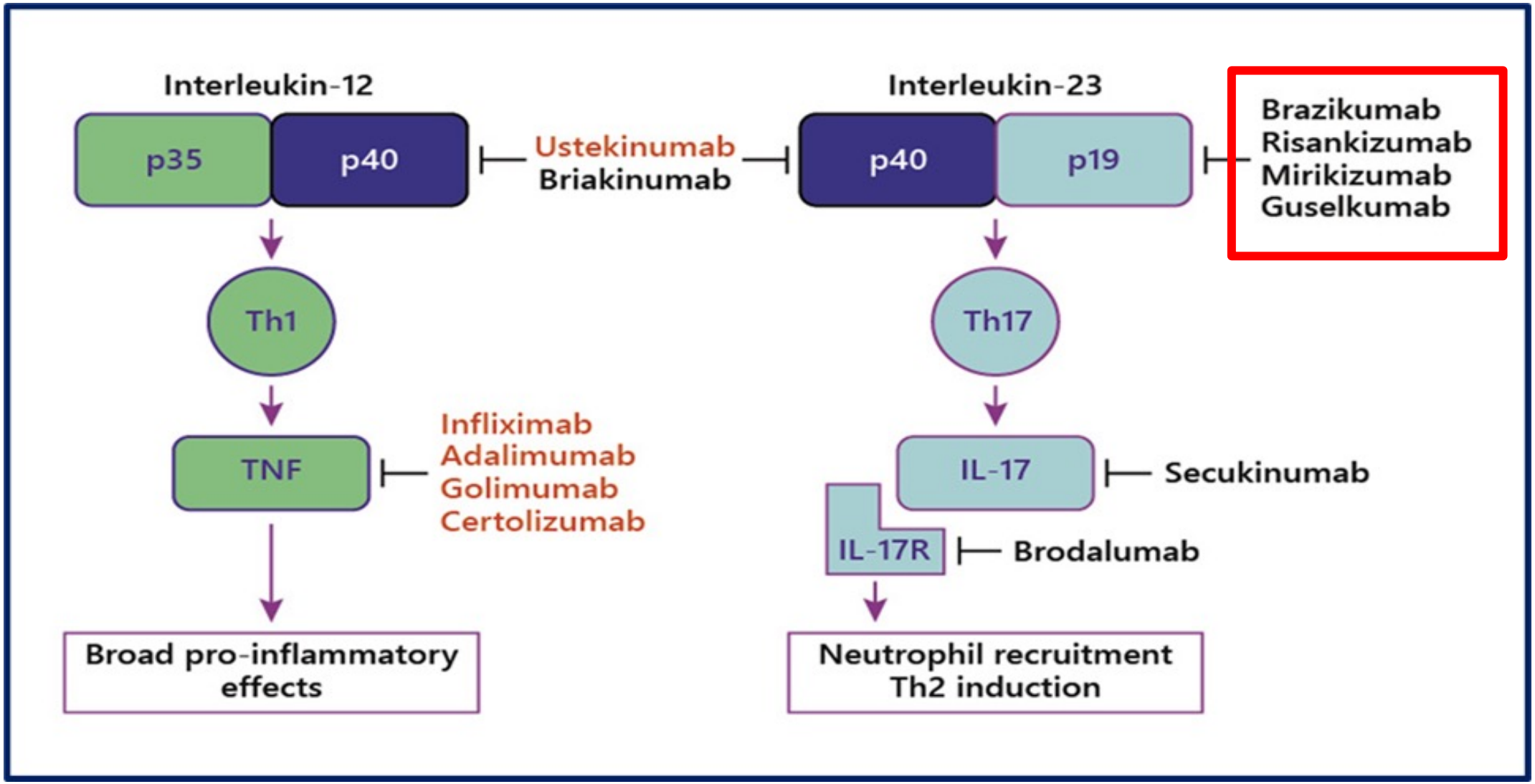


Table 3. Clinical Outcomes Achieved by Patients Treated With Ustekinumab and Infliximab

	Infliximab (n = 214)	Ustekinumab (n = 206)	P
Overall cohort			
Week 6 clinical response, n (%)	125 (58.4)	113 (54.9)	
Week 6 clinical remission, n (%)	96 (44.9)	78 (37.9)	
Baseline fecal calprotectin level >250 mcg/L and week 6 fecal calprotectin level <250 mcg/L, n (%)	55/130 (42.3)	43/124 (34.7)	
Baseline fecal calprotectin level >250 mcg/L and week 6 fecal calprotectin level <50 mcg/L, n (%)	19/130 (14.6)	9/124 (7.3)	
	Infliximab (n = 168)	**Ustekinumab (n = 168)**	
Propensity score matched cohort			
Week 6 clinical response, n (%)	101 (60.1)	94 (56.0)	
Week 6 clinical remission, n (%)	73 (43.5)	65 (38.7)	
Baseline fecal calprotectin level >250 mcg/L and week 6 fecal calprotectin level <250 mcg/L, n (%)	47/106 (44.3)	38/113 (33.6)	
Baseline fecal calprotectin level >250 mcg/L and week 6 fecal calprotectin level <50 mcg/L, n (%)	14/106 (13.2)	7/113 (6.2)	

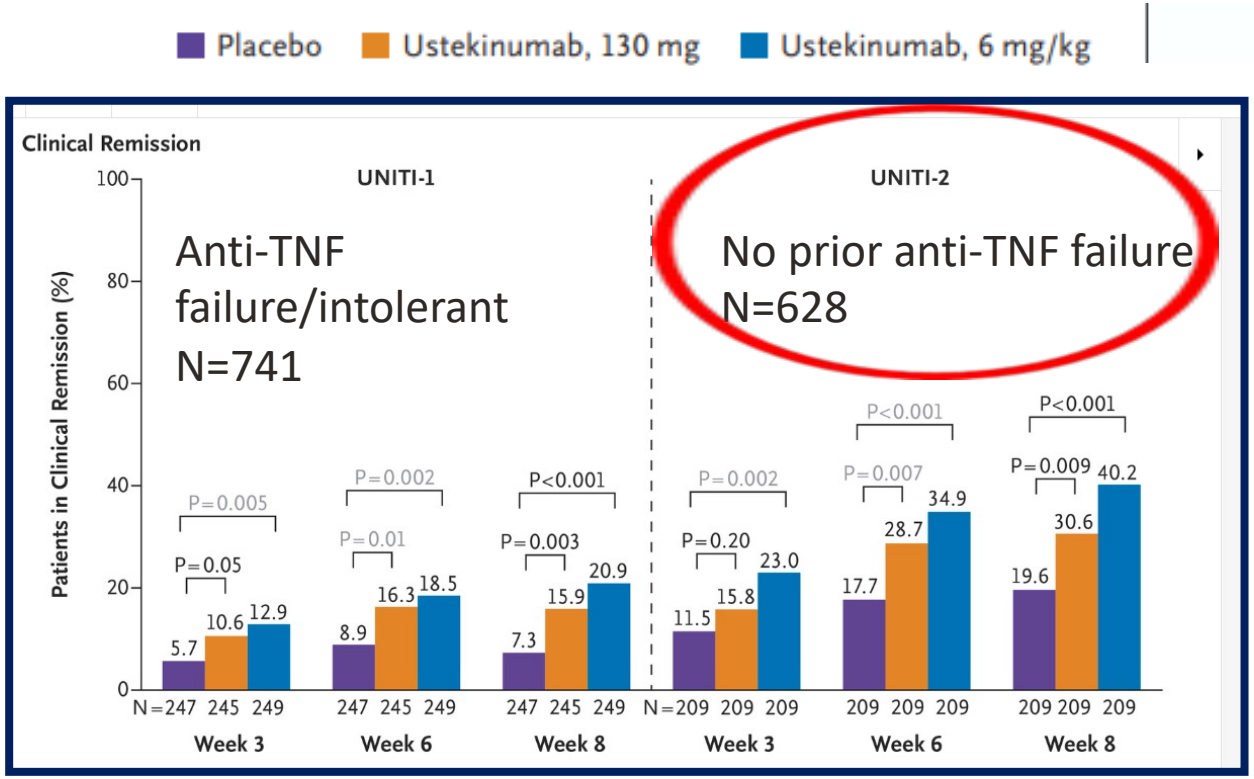
Also: Wong E,…….Narula N. Inflamm Bowel Dis 2023, 29, 1015–1023
One year outcomes among responders to induction

Interleukin-12/23 pathway biologics



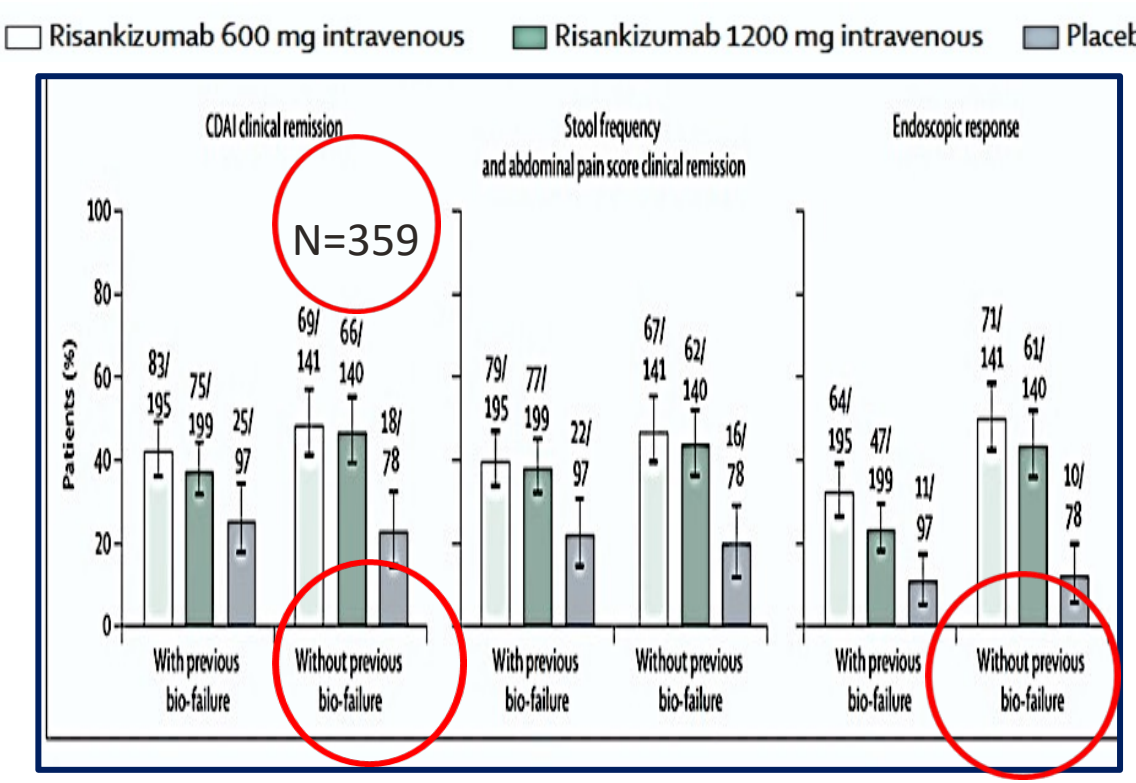
Anti-IL-12/23 and anti-IL23 in Crohn's disease

Ustekinumab week 8 outcomes



Feagan BG et al. NEJM 2016;375:1946-60.

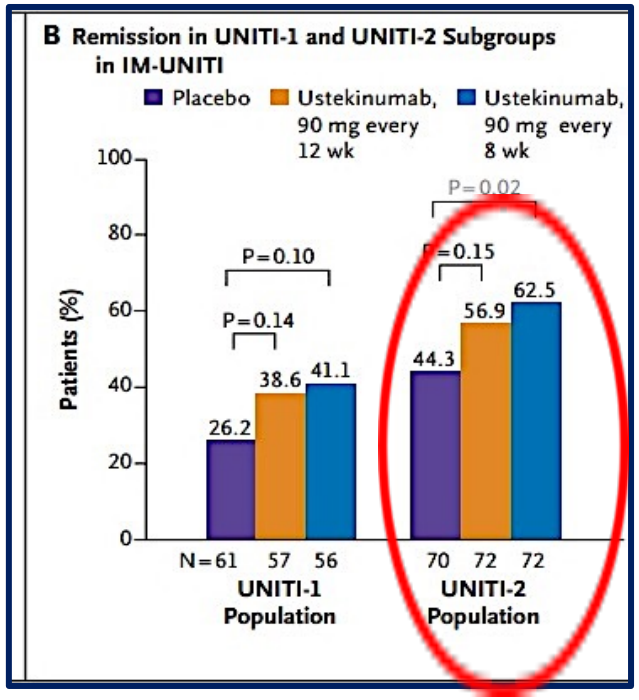
Risankizumab (ADVANCE) week 12 outcomes



D'Haens G et al Lancet 2022; 399: 2015-2030

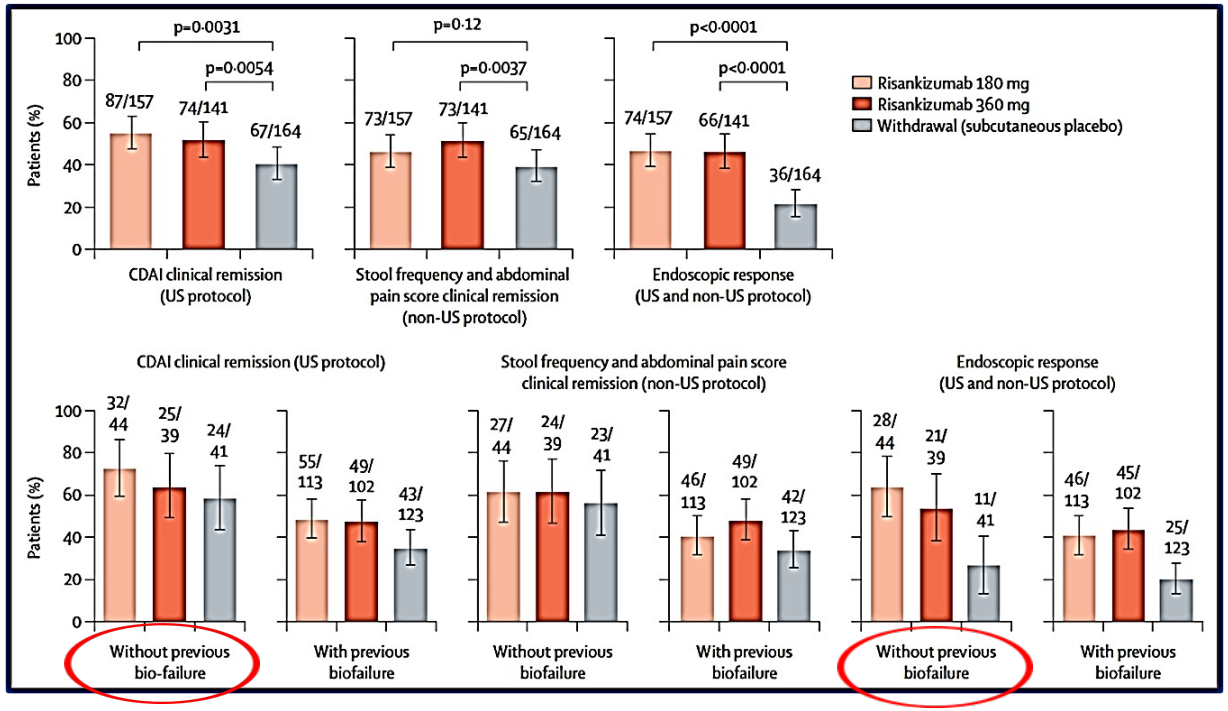
Anti-IL-12/23 and anti-IL23 in Crohn's disease

Ustekinumab week 52 outcomes (IM-UNITI)
(responders to induction re-randomized)



Feagan BG et al NEJM 2016;375:1946-60.

Risankizumab week 52 outcomes (FORTIFY)
(responders to induction re-randomized)



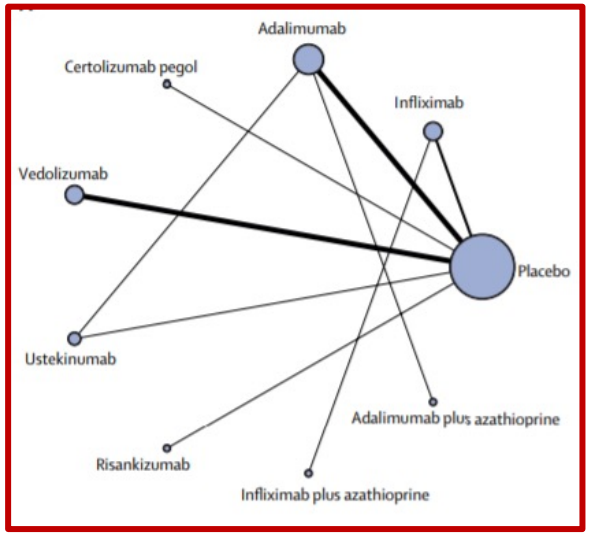
Ferrante M et al, Lancet 2022; 399: 2031-46

Positioning of anti-TNFs in Crohn's disease: is there a "better" first advanced therapy?

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

31 trials (total 8020 participants)



INDUCTION: Bio-Naive

Induction of clinical remission

Induction of clinical response								
Infliximab	0·61 (0·31–1·19)	1·50 (0·54–4·22)	2·65 (0·70–10·02)	1·72 (0·61–4·87)	2·07 (0·63–6·87)	2·28 (0·73–7·06)	4·53 (1·49–13·79)	6·17 (2·54–15·01)
0·56 (0·36–0·87)	Infliximab plus thiopurines	2·49 (0·73–8·52)	4·38 (0·99–19·45)	2·85 (0·83–9·82)	3·43 (0·87–13·54)	3·76 (1·01–14·03)	7·49 (2·04–27·49)	10·20 (3·34–31·10)
8·84 (1·95–40·03)	15·88 (3·29–76·64)	Adalimumab	1·76 (0·76–4·08)	1·15 (0·66–1·99)	1·38 (0·51–3·69)	1·51 (0·61–3·74)	3·01 (1·25–7·27)	4·10 (2·31–7·27)
"	"	"	Adalimumab plus thiopurines	0·65 (0·24–1·77)	0·78 (0·21–2·85)	0·86 (0·25–2·95)	1·71 (0·51–5·77)	2·33 (0·84–6·43)
7·90 (1·78–35·10)	14·18 (2·99–67·26)	0·89 (0·61–1·31)	"	Ustekinumab	0·83 (0·31–2·21)	1·32 (0·54–3·23)	2·63 (1·10–6·28)	3·58 (2·05–6·25)
"	"	"	"	"	Risankizumab	1·10 (0·38–3·19)	2·19 (0·77–6·21)	2·98 (1·33–6·64)
12·76 (2·76–59·08)	22·91 (4·64–113·02)	1·44 (0·75–2·80)	"	1·62 (0·87–3·00)	"	Vedolizumab	1·99 (0·75–5·26)	2·71 (1·34–5·48)
15·08 (3·46–65·83)	27·08 (5·81–126·25)	1·71 (1·02–2·84)	"	1·91 (1·21–3·00)	"	1·18 (0·67–2·10)	Certolizumab pegol	1·36 (0·70–2·66)
22·00 (5·17–93·56)	39·49 (8·68–179·61)	2·49 (1·62–3·82)	"	2·79 (1·94–3·99)	"	1·72 (1·04–2·85)	1·46 (1·11–1·92)	Placebo

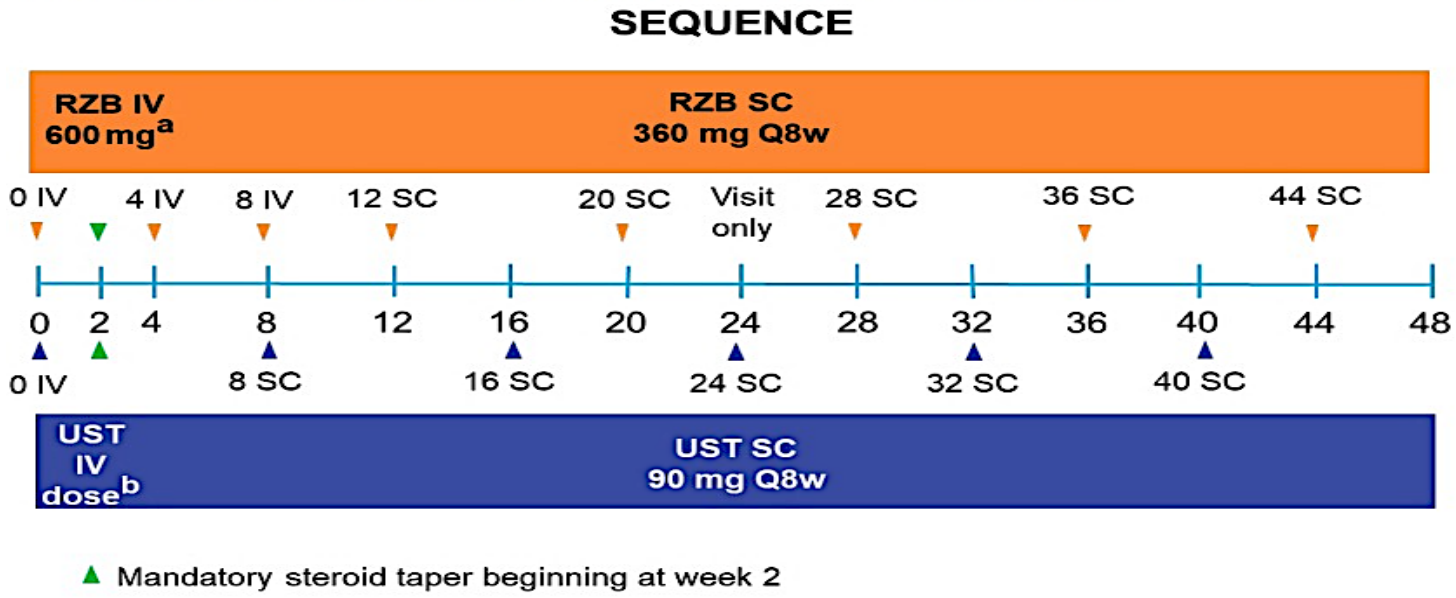
Lancet Gastroenterol Hepatol 2021; 6: 1002–14

Oral presentation UEGW, October 15, 2023

Risankizumab Versus Ustekinumab for Patients With Moderate to Severe Crohn's Disease: Results From the Phase 3b SEQUENCE Study

Laurent Peyrin-Biroulet,[1] J. Casey Chapman,[2,3,4] Jean-Frederic Colombel,[5] Flavio Caprioli,[6,7] Geert D'Haens,[8] Marc Ferrante,[9] Stefan Schreiber,[10] Raja Atreya,[11] Silvio Danese,[12] James O. Lindsay,[13] Peter Bossuyt,[14] Britta Siegmund,[15] Peter Irving,[16] Remo Panaccione,[17] Ezequiel Neimark,[18] Kori Wallace,[18] Toni Anschutz,[18] Kristina Kligys,[18] W Rachel Duan,[18] Valerie Pivorunas,[18] Xiu Huang,[18] Sofie Berg,[18] Lei Shu,[18] Marla Dubinsky[19]

- Moderate-severe CD
- Prior failure of >/= 1 anti-TNF
- SES-CD >/= 6 (central read) (>/= 4 for isolated ileal)



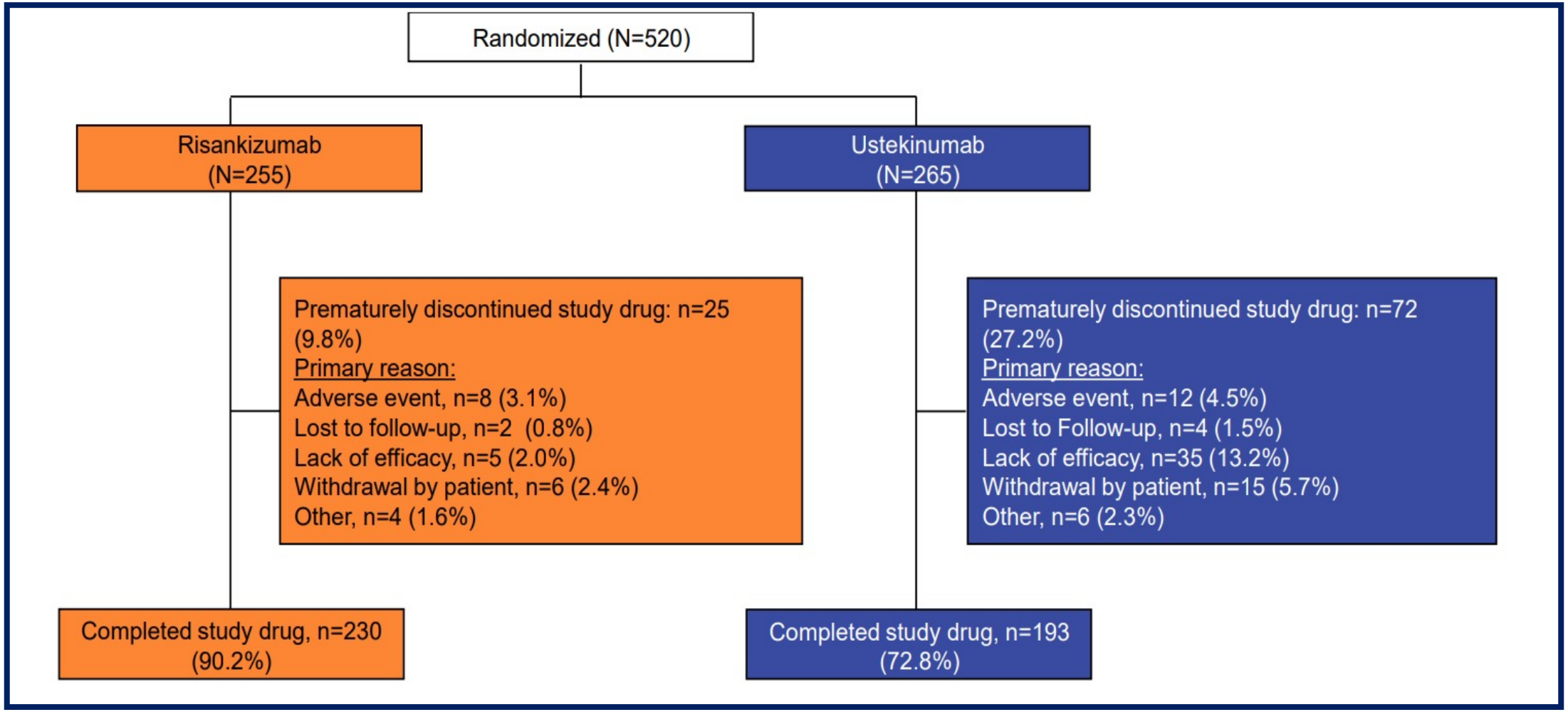
PRIMARY ENDPOINTS: 1) CDAI remission at week 24
2) endoscopic remission at week 48 (SES-CD <4 and >/= 2 point drop and no subscore >1)

SEQUENCE: Patient Characteristics

BMI, mean (SD)	23.8 (5.5)	24.8 (6.0)
Disease duration, years, mean (SD)	9.4 (7.8)	9.4 (8.7)
SES-CD, mean (SD)	13.5 (7.1)	14.1 (7.4)
Daily abdominal pain, n, mean (SD)	251,1.9 (0.5)	263,1.9 (0.6)
Daily stool frequency, n, mean (SD)	251, 5.5 (2.7)	263, 5.6 (2.5)
Immunomodulator use, n (%)	34 (13.3)	47 (17.7)
Corticosteroid use[b], n (%)	58 (22.7)	71 (26.8)
Baseline fecal calprotectin (mg/kg), median (min, max)	1030 (30, 26823)	1515 (30, 26361)
Baseline hs-CRP (mg/L), median (min, max)	8.20 (0.2, 287.1)	9.40 (0.2, 196.6)
CDAI, mean (SD)	309.4 (61.7)	310.1 (62.6)
Failed > 1 anti-TNFs[b], n (%)	59 (23.1)	61 (23.0)
Disease location, n (%)		
Ileal only	42 (16.5)	45 (17.0)
Colonic only	102 (40.0)	106 (40.0)
Ileal-colonic	111 (43.5)	114 (43.0)

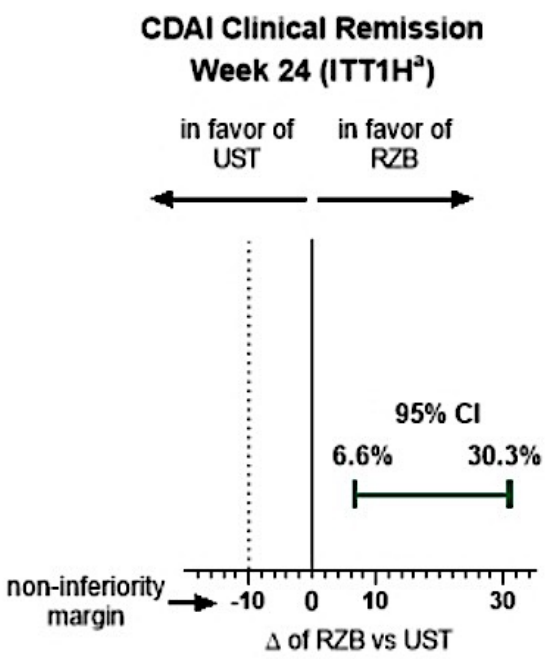
ly mass index; CD, Crohn's disease; CDAI, CD activity index; hs-CRP, high-sensitivity C-reactive protein; SES-CD, simple endoscopic score for CD; SF, stool frequency; TNF, tumour necrosis factor; UST, ustekinumab
pulation: includes patients who were randomized to UST or RZB (600 mg IV, 360 mg SC) and received at least one dose of study drug

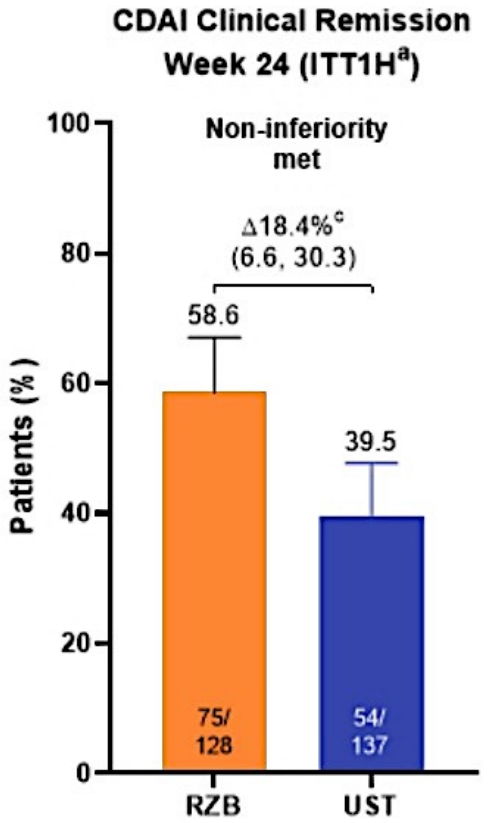
SEQUENCE: Patient disposition

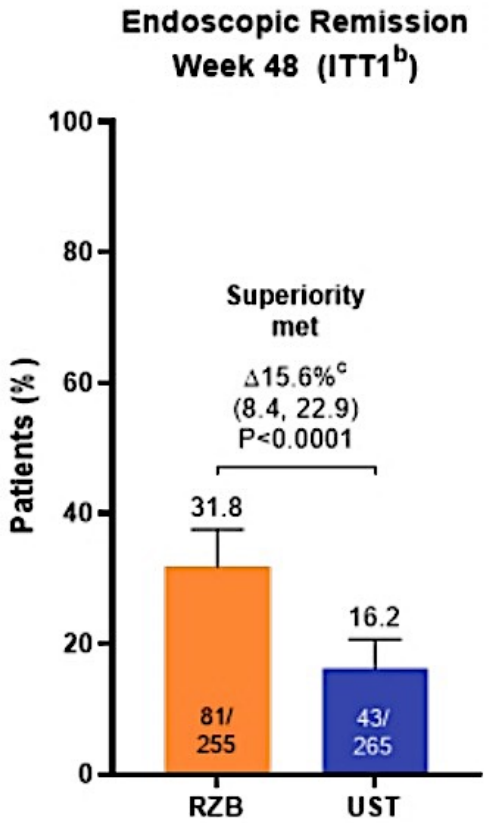


Mean time (days) study drug discontinuation: for risankizumab 182.6 ; for ustekinumab 156.3

SEQUENCE: Primary Outcomes (intent-to-treat analyses)







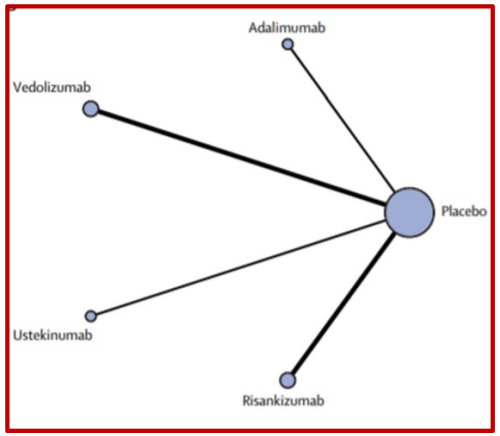
CDAI clinical remission: CDAI < 150
Endoscopic remission: SES-CD ≤ 4 and at least a 2-point reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer

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

CD: Advanced therapy following anti-TNF “failure”?

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

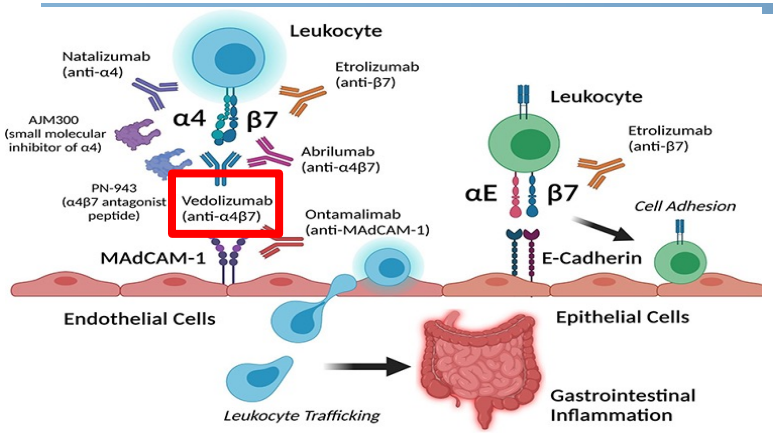


Induction of clinical response	Induction of clinical remission				
	Risankizumab	1·34 (0·79–2·27)	0·74 (0·35–1·57)	**2·10 (1·12–3·92)**	**2·64 (1·89–3·68)**
	1·34 (0·62–2·90)	**Ustekinumab**	0·56 (0·25–1·22)	1·57 (0·80–3·06)	**1·97 (1·31–2·97)**
	1·51 (0·64–3·56)	1·13 (0·51–2·51)	**Adalimumab**	**2·82 (1·20–6·62)**	**3·55 (1·82–6·93)**
	1·87 (0·87–4·02)	1·40 (0·68–2·87)	1·24 (0·55–2·77)	**Vedolizumab**	1·26 (0·74–2·14)
	3·31 (1·86–5·90)	**2·47 (1·49–4·09)**	**2·19 (1·17–4·09)**	**1·77 (1·07–2·92)**	**Placebo**

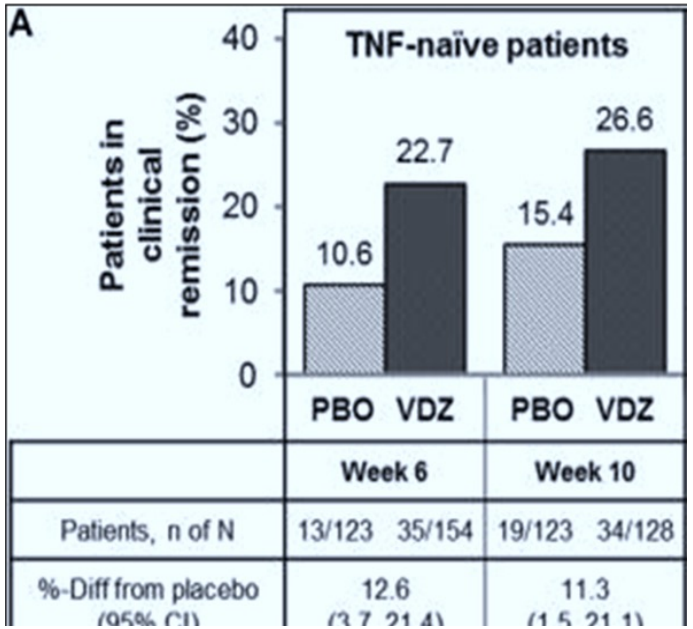
INDUCTION: prior biologic exposure

Lancet Gastroenterol Hepatol 2021; 6: 1002–14

Sequencing advanced therapy in Crohn's disease: what about vedolizumab?

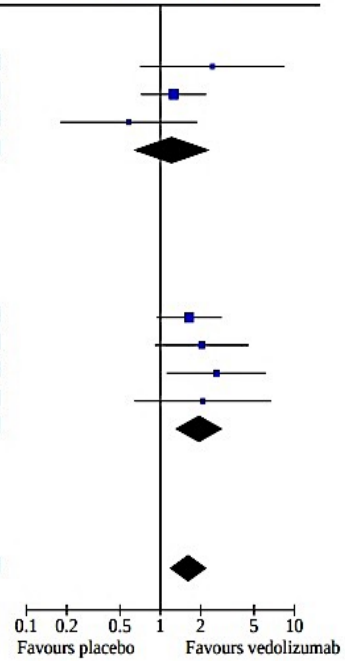


GEMINI



Analysis 1.1. Comparison 1: Induction studies – vedolizumab versus placebo, Outcome 1: Induction of clinical remission

Study or Subgroup	Vedolizumab Events	Vedolizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Prior TNF inhibitor failure						
Sandborn 2013 – Induction Phase	11	105	3	70	5.7%	2.44 [0.71 , 8.45]
Sands 2014	24	158	19	157	28.0%	1.26 [0.72 , 2.20]
Watanabe 2020 – Induction Phase	4	61	7	62	6.3%	0.58 [0.18 , 1.88]
Subtotal (95% CI)		**324**		**289**	**40.0%**	**1.21 [0.65 , 2.25]**
Total events:	39		29			
Heterogeneity: Tau² = 0.09; Chi² = 2.75, df = 2 (P = 0.25); I² = 27%						
Test for overall effect: Z = 0.61 (P = 0.54)						
1.1.2 No prior TNF inhibitor						
Feagan 2008	43	127	12	58	28.0%	1.64 [0.94 , 2.86]
Sandborn 2013 – Induction Phase	21	115	7	78	13.5%	2.03 [0.91 , 4.55]
Sands 2014	16	51	6	50	12.0%	2.61 [1.11 , 6.14]
Watanabe 2020 – Induction Phase	7	18	3	16	6.4%	2.07 [0.64 , 6.70]
Subtotal (95% CI)		**311**		**202**	**60.0%**	**1.94 [1.32 , 2.84]**
Total events:	87		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 3 (P = 0.84); I² = 0%						
Test for overall effect: Z = 3.39 (P = 0.0007)						
Total (95% CI)		**635**		**491**	**100.0%**	**1.61 [1.20 , 2.17]**
Total events:	126		57			
Heterogeneity: Tau² = 0.00; Chi² = 5.83, df = 6 (P = 0.44); I² = 0%						
Test for overall effect: Z = 3.15 (P = 0.002)						
Test for subgroup differences: Chi² = 1.59, df = 1 (P = 0.21), I² = 37.2%						



Hui S, Cochrane Database Sys Reviews 2023

Sandborn WJ, N Engl J Med 2013; 369:711-721

Comparative effectiveness in achieving endoscopic healing in bio-naive patients with CD

Data from:
UNITI (USTE)

Extend (ADA)

Versify (VEDO)

CT-P13 (IFX)

Endoscopic healing at 1 yr among participants (n = 240)				
Treatment	**N**	**Endoscopic healing at 1 yr, n (%)**	***P* (pairwise)[a]**	***P***
Adalimumab	36	12/36 (33.3)	0.011	0.072
Infliximab	141	39/141 (27.7)	0.018	
Ustekinumab	22	5/22 (22.7)	0.161	
Vedolizumab	41	4/41 (9.8)	N/A	
Absence of ulcers at 1 yr among participants with very large ulcers at baseline (n = 60)				
Treatment	**Very large ulcer at baseline, n**	**Absence of ulcers at 1 yr, n (%)**	***P* (pairwise)[a]**	***P***
Adalimumab	10	2/10 (20.0)	0.476	0.848
Infliximab	29	5/29 (17.2)	0.519	
Ustekinumab	10	1/10 (10.0)	0.943	
Vedolizumab	11	1/11 (9.1)	N/A	
Absence of ulcers at 1 yr among participants with large ulcers at baseline (n = 187)				
Treatment	**Large ulcer at baseline, n**	**Absence of ulcers at 1 yr, n (%)**	***P* (pairwise)[a]**	***P***
Adalimumab	28	7/28 (25.0)	0.042	0.142
Infliximab	110	27/110 (24.6)	0.024	
Ustekinumab	17	3/17 (17.7)	0.210	
Vedolizumab	32	2/32 (6.3)	N/A	

N/A, not available.
[a]Vedolizumab as the comparator.

Narula N, et al Am J Gastroenterol 2022;117:1106–1117

Real-world effectiveness

Inflammatory Bowel Diseases, 2023, **XX**, 1–11
https://doi.org/10.1093/ibd/izad138
Advance access publication 31 July 2023
Original Research Articles - Clinical

CROHN'S & COLITIS FOUNDATION

Real-World Effectiveness of Vedolizumab vs Anti-TNF in Biologic-naïve Crohn's Disease Patients: A 2-year Propensity-score-adjusted Analysis from the VEDO$_{IBD}$-Study

Bernd Bokemeyer, MD,[*,†,‡,#] Sandra Plachta-Danielzik, PhD,[*,#] Romina di Giuseppe, PhD,[*] Philipp Efken, MD,[§] Wolfgang Mohl, MD,[¶] Martin Hoffstadt, MD,[‖] Thomas Krause, MD,[**] Axel Schweitzer, MD,[††] Elisabeth Schnoy, MD,[‡‡] Raja Atreya, MD,[§§] Niels Teich, MD,[¶¶] Leo Trentmann, MD,[‖‖] Robert Ehehalt, MD,[***] Petra Hartmann,[§] and Stefan Schreiber, MD,[‡,##]

Journal of Crohn's and Colitis, 2023, **XX**, 1–10
https://doi.org/10.1093/ecco-jcc/jjad124
Advance access publication 31 July 2023
Original Article

JCC — OXFORD

Comparative Study of the Effectiveness of Vedolizumab Versus Ustekinumab After Anti-TNF Failure in Crohn's Disease (Versus-CD): Data from the ENEIDA Registry

María José García[a], Montserrat Rivero[a], Agnès Fernández-Clotet[b], Ruth de Francisco[c], Beatriz Sicilia[d], Francisco Mesonero[e], María Luisa de Castro[f], María José Casanova[g],

The Real-World Effectiveness and Safety of Vedolizumab for Moderate–Severe Crohn's Disease: Results From the US VICTORY Consortium

Parambir S. Dulai, MD[1], Siddharth Singh, MD, MS[1,2], Xiaoqian Jiang, PhD[2], Farhad Peerani, MD[3], Neeraj Narula, MD[3], Khadija Chaudrey, MD[4], Diana Whitehead, MD[5], David Hudesman, MD[6], Dana Lukin, MD[7], Arun Swaminath, MD[8], Eugenia Shmidt, MD[3], Shuang Wang, PhD[2], Brigid S. Boland, MD[1], John T. Chang, MD[1], Sunanda Kane, MD[4], Corey A. Siegel, MD, MS[5], Edward V. Loftus, MD[4], William J. Sandborn, MD[1], Bruce E. Sands, MD[3] and Jean-Frederic Colombel, MD[3]

BOWEL DISEASE

Am J Gastroenterol 2016; 111:1147–1155

Real-World Evidence Comparing Vedolizumab and Ustekinumab in Antitumor Necrosis Factor-Experienced Patients With Crohn's Disease

Michael D. Kappelman, MD, MPH[1], Sruthi Adimadhyam, PhD[2], Laura Hou, MS[2], Audrey E. Wolfe, MPH[2], Samantha Smith, BA[2], Andrew L. Simon, ScM[2], Érick Moyneur, MA[3], Juliane S. Reynolds, MPH[2], Sengwee Toh, ScD[2], Angela Dobes, MPH[4], Lauren E. Parlett, PhD[5], Kevin Haynes, PharmD, MSCE[5], Mano Selvan, PhD[6], Qianli Ma, MS[6], Vinit Nair, MS, RPh[6], Jessica Burris, MD[7], Jennifer E. Dorand, PhD[4], Ghadeer K. Dawwas, PhD[8], James D. Lewis, MD, MSCR[9] and Millie D. Long, MD, MPH[1]

Am J Gastroenterol 2023;118:674–684

Targeted oral small molecules: Janus kinase (JAK) inhibitors

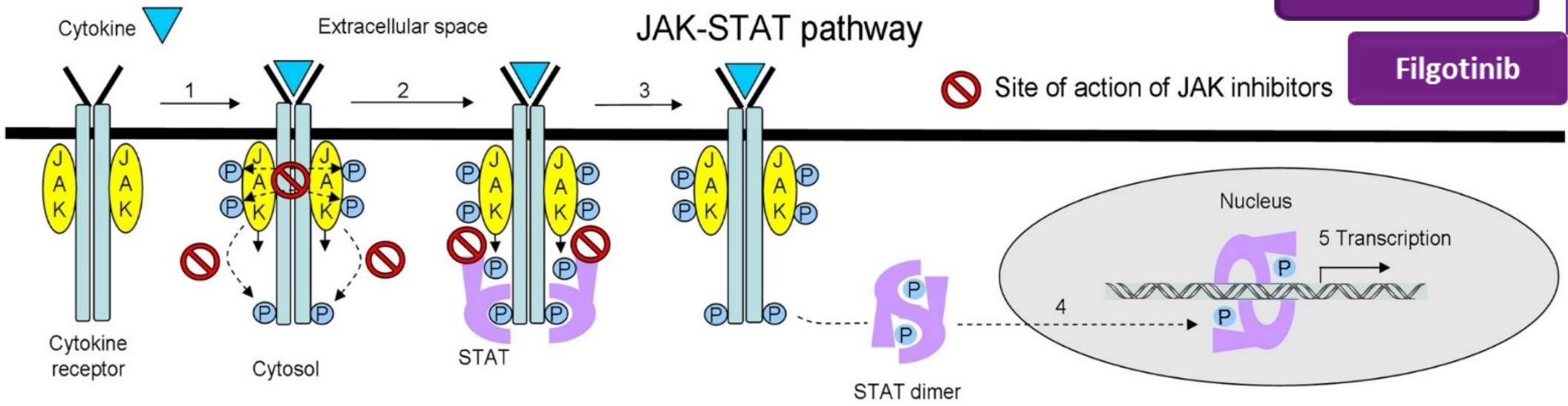
-JAKS comprise a family of 4 intracellular tyrosine kinases (JAK1, JAK2, JAK3, TYK2)

-Associated with intracellular domains of cytokine receptors

Tofacitinib — Non-selective

Upadacitinib — JAK1 > 2,3

Filgotinib



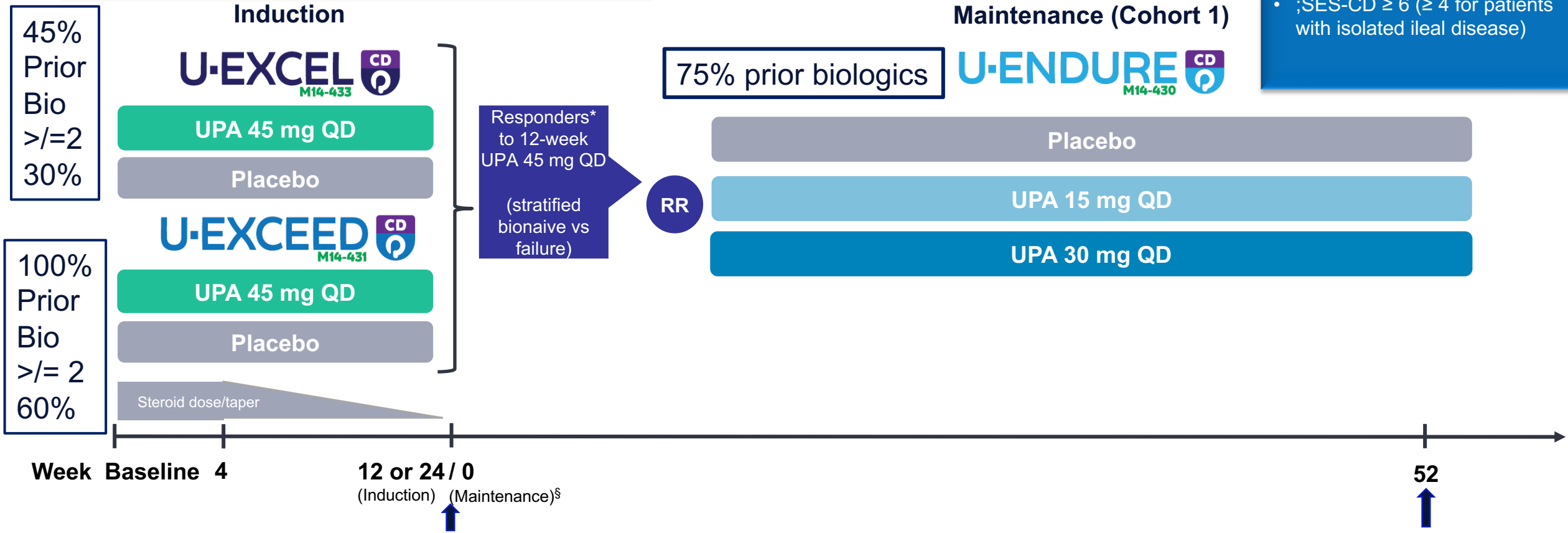
- Interact with STATs: “signaling transducers and activators of transcription”: genes involved in innate and adaptive immunity

ORIGINAL ARTICLE

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

KEY INCLUSION CRITERIA
- 18-75 years of age
- Average daily SF ≥ 4 and/or average daily APS ≥ 2
- ;SES-CD ≥ 6 (≥ 4 for patients with isolated ileal disease)



Induction Co-Primary Endpoints:
Clinical Remission
Endoscopic Response

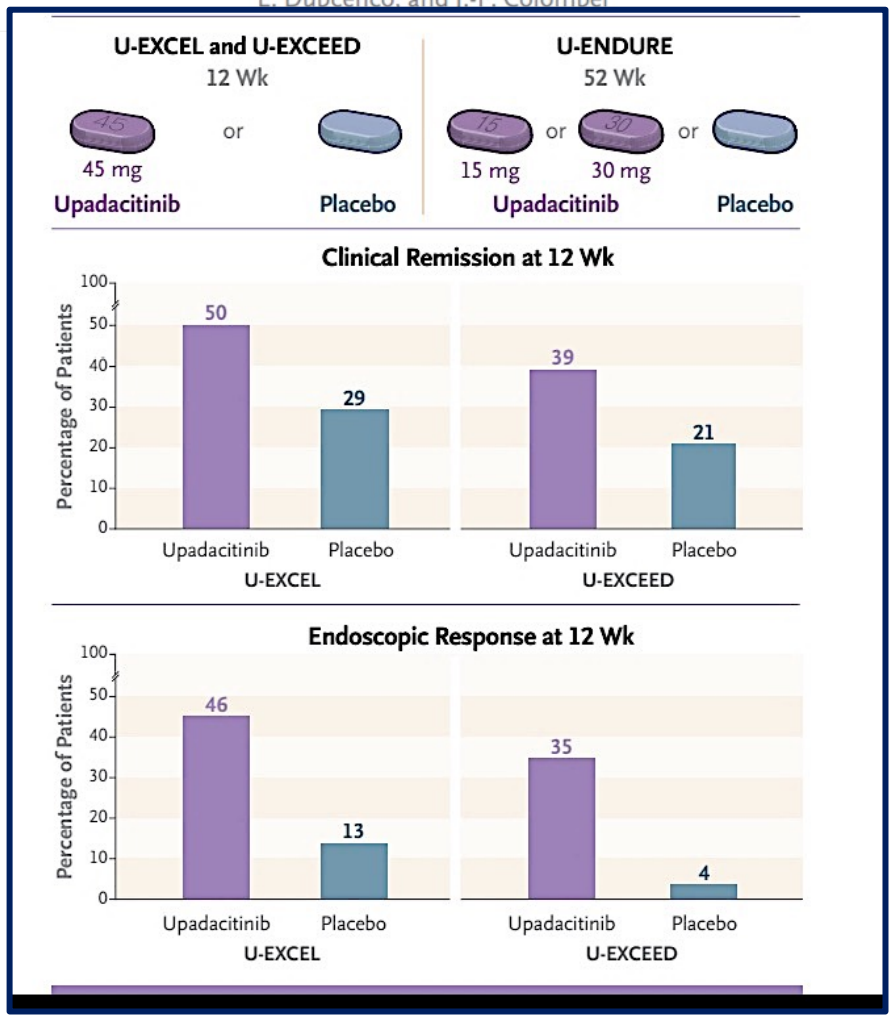
Maintenance Co-Primary Endpoints:
Clinical Remission
Endoscopic Response

NEJM 2023; 388(21):1966-1980

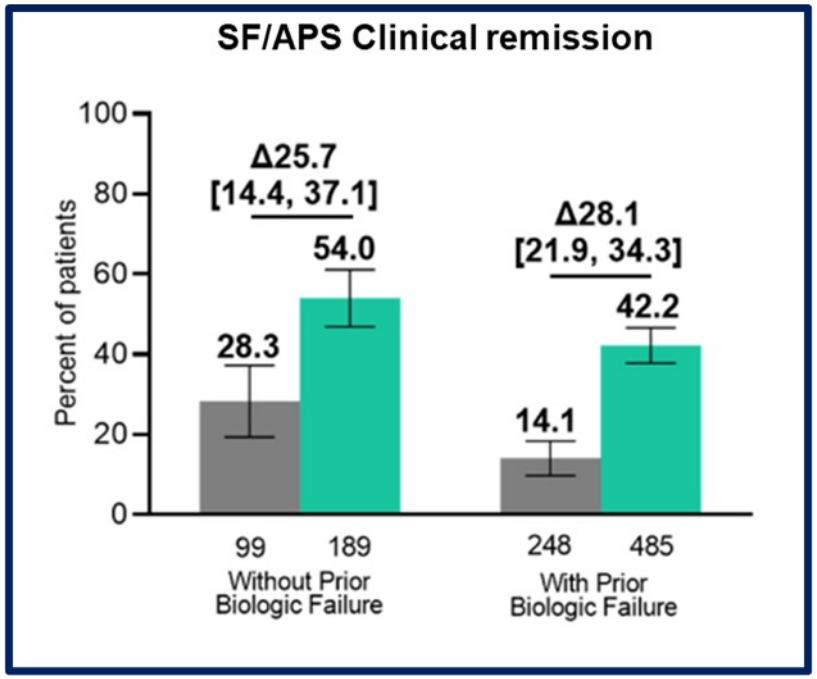
ORIGINAL ARTICLE

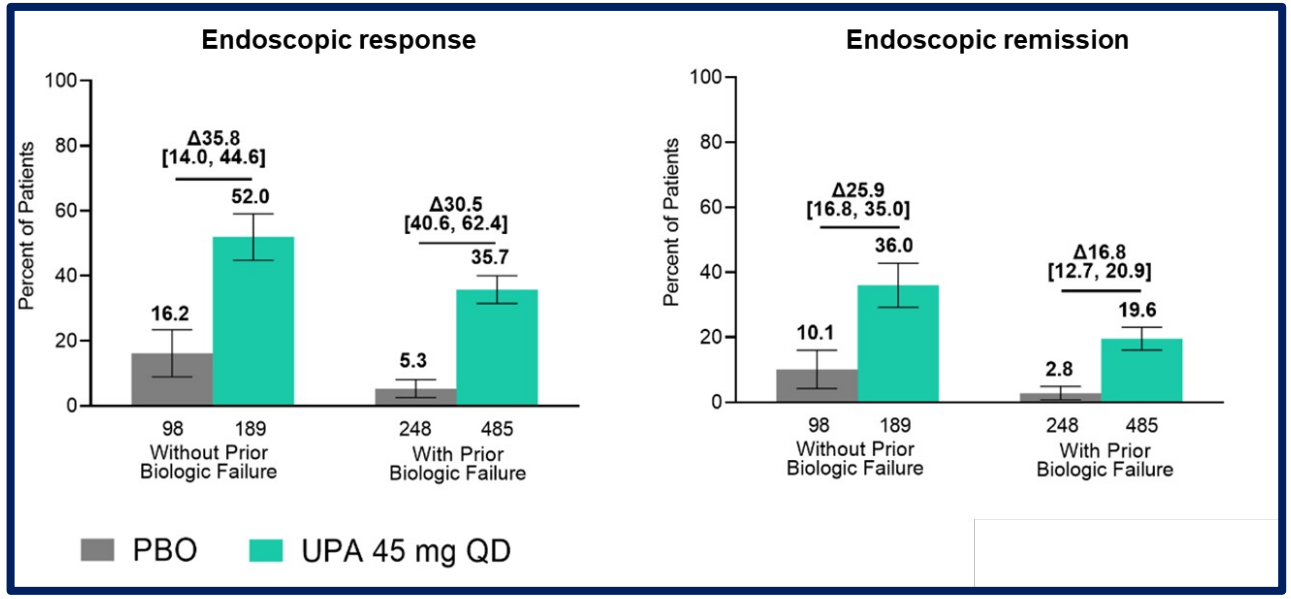
Upadacitinib Induction and Maintenance Therapy for Crohn's Disease

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



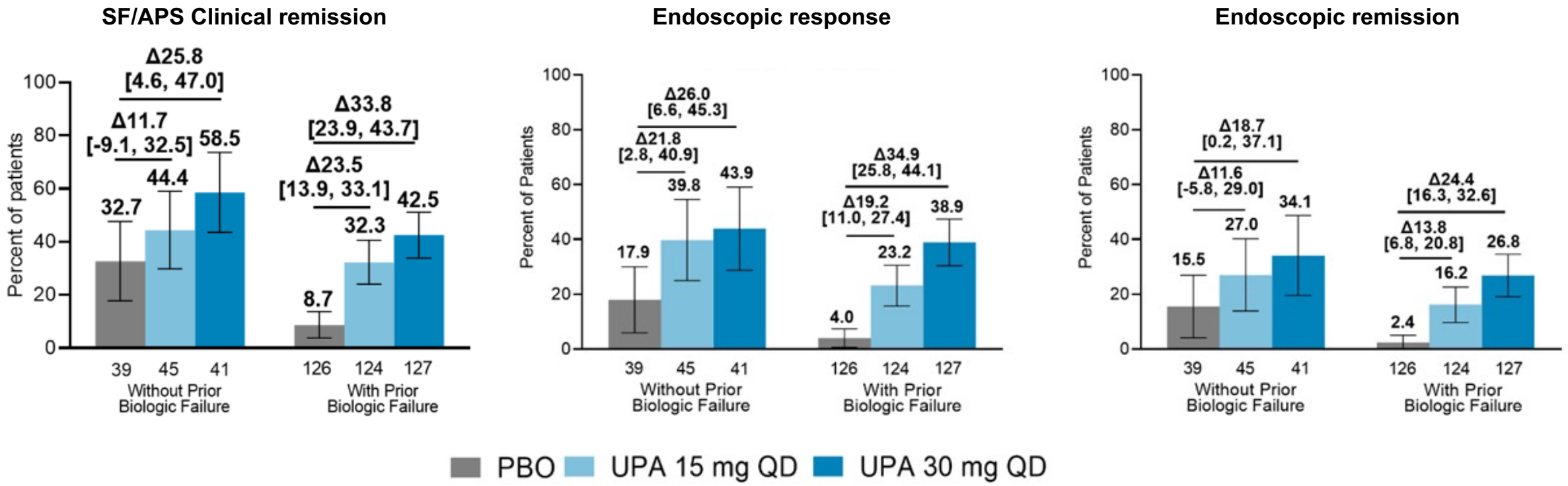
Week 12 - Pooled Induction Data from U-EXCEL and U-EXCEED





Upadacitinib Clinical & Endoscopic Outcomes in CD Patients by Prior Biologic Failure Status

Week 52 – Maintenance Data from U-ENDURE

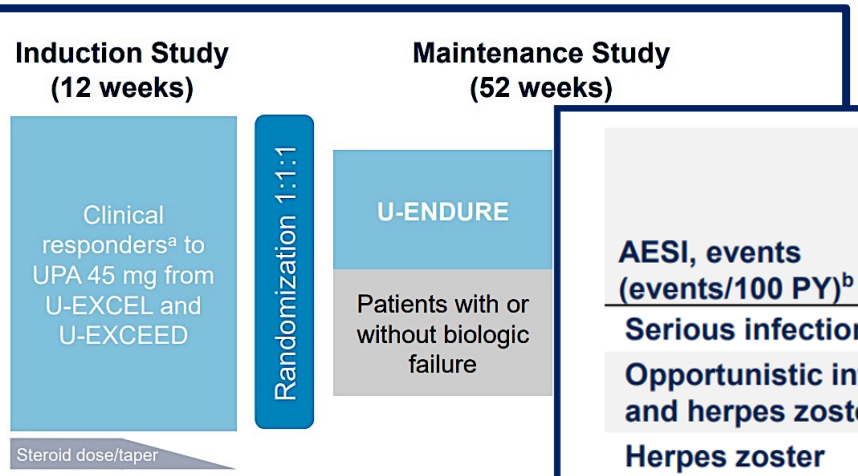


Feagan B., et al. ECCO 2023, March 1-4, Copenhagen, Denmark. OP17. Schreiber S., et al . ECCO 2023, March 1-4, Copenhagen, Denmark, P630.

Efficacy and Safety of Upadacitinib Maintenance Therapy in Patients With Moderately to Severely Active Crohn's Disease: Final Results From the Phase 3 U-ENDURE Study

Regueiro M.…Panes J

UEGW October 2023



AESI, events (events/100 PY)[b]	Full Safety Analysis Set[a] PBO n = 223 (PYs = 111.5)	UPA 15 mg n = 221 (PYs = 153.7)	UPA 30 mg n = 229 (PYs = 177.2)
Serious infection	10 (9.0)	9 (5.9)	13 (7.3)
Opportunistic infections, excluding tuberculosis and herpes zoster[c]	0	1 (0.7)	1 (0.6)
Herpes zoster	5 (4.5)	6 (3.9)	13 (7.3)
Adjudicated gastrointestinal perforation	1 (0.9)	1 (0.7)	1 (0.6)
Anemia	13 (11.7)	15 (9.8)	11 (6.2)
Neutropenia	1 (0.9)	3 (2.0)	6 (3.4)
Lymphopenia	10 (9.0)	6 (3.9)	11 (6.2)
Creatine phosphokinase elevations	3 (2.7)	5 (3.3)	10 (5.6)
Hepatic disorders	3 (2.7)	12 (7.8)	17 (9.6)
Renal dysfunction	2 (1.8)	0	0
Malignancies excluding NMSC[d]	0	1 (0.7)	2 (1.1)
Adjudicated venous thromboembolic event[e]	0	0	1 (0.6)

Sequencing “advanced therapies” in Crohn’s disease

TIMEPOINT		NOW
FIRST		Infliximab or adalimumab risankizimab or ustekinumab vedolizumab
SUBSEQUENT (after anti-TNF)		risankizumab (ustekinumab) upadacitinib

Primary non-response: Risankizumab or upadacitinib

Intolerance: risankizumab/ustekinumab

Primary incomplete (unsatisfactory?) response: case by case

Secondary LOR related to anti-drug antibodies: 2nd anti-TNF or switch

Secondary LOR unrelated to anti-drug antibodies: risankizumab/ upadacitinib

Positioning and sequencing advanced therapies in Crohn's disease: Questions will keep increasing

POSITIONING

- Early vs later initiation?: ……before versus after a trial of conventional immunomodulators?
- "Advanced therapy" for all? Who should not get?.....

SEQUENCING

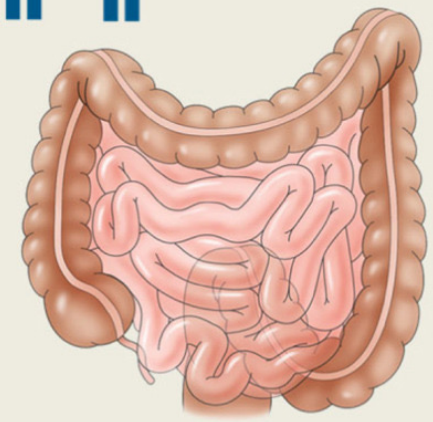
- Is there a "better" "advanced therapy" to utilize first rather than anti-TNF?....or should we combine?
- Advanced therapy if anti-TNF "fails"?.....what to switch to…..or should we combine?

Combination biologics (EXPLORER)

Phase 4, open-label study of vedolizumab, adalimumab, and methotrexate combination therapy in Crohn's disease

Patients

N = 55



Biologic naïve patients with newly diagnosed, moderate to high risk CD

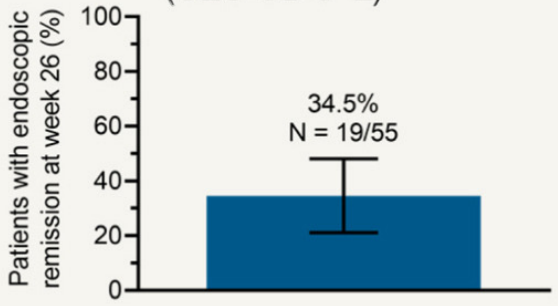
Treatment

Triple combination therapy

- IV vedolizumab 300 mg at weeks 0, 2, and 6 and every 8 weeks until week 102
- SC adalimumab 160 mg at week 0, 80 mg at week 2, and 40 mg every 2 weeks until week 26
- Oral methotrexate 15 mg weekly until week 34

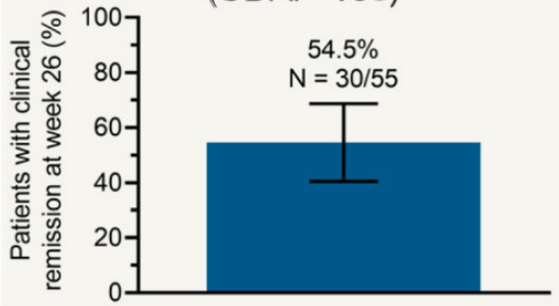
Primary end point

Endoscopic remission at week 26 (SES-CD 0–2)



Secondary end point

Clinical remission at week 26 (CDAI <150)



Post hoc Bayesian analysis[a]

Probability that triple combination therapy produces higher endoscopic remission than benchmark rates for…

- …placebo ≥99.9%
- …vedolizumab monotherapy = 86.3%
- …adalimumab monotherapy = 71.4%

[a]*Beta*(1.667, 5) prior. Posterior mean endoscopic remission rate = 33.5% (95% credible interval: 22.4, 45.7).
CD, Crohn's disease; CDAI, Crohn's Diseas e Activity Index; IV, intravenous; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease

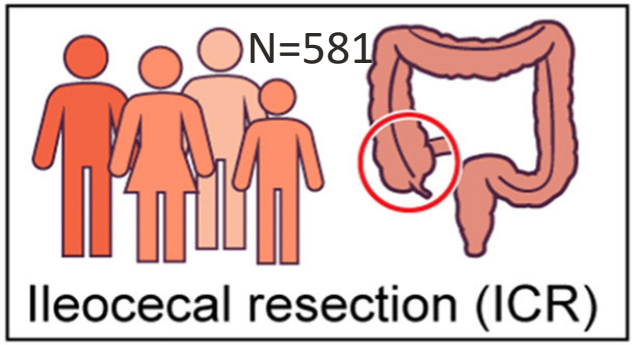
Clinical Gastroenterology and Hepatology

Colombel J-F et al on-line September 2023

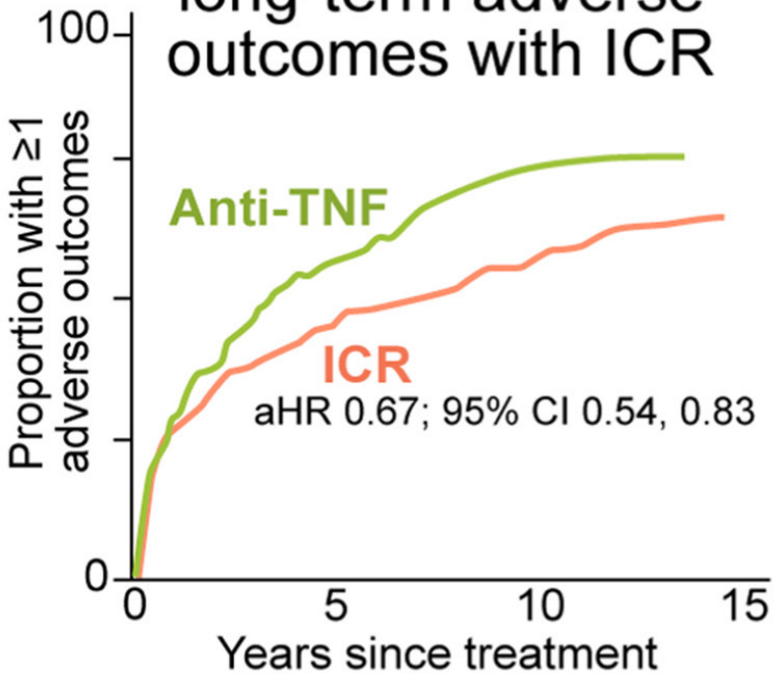
Early Ileocecal Resection for Crohn's Disease Is Associated With Improved Long-term Outcomes Compared With Anti-Tumor Necrosis Factor Therapy: A Population-Based Cohort Study

Manasi Agrawal,[1,2] Anthony C. Ebert,[1] Gry Poulsen,[1] Ryan C. Ungaro,[2] Adam S. Faye,[3] Tine Jess,[1,4] Jean-Frederic Colombel,[2] and Kristine H. Allin[1,4]

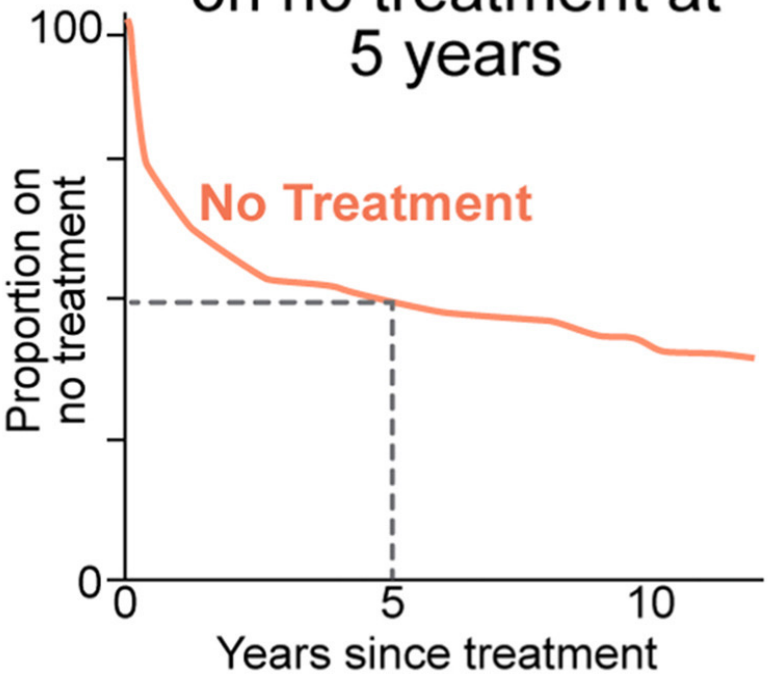
Analysis of Danish nation-wide cohort of recently diagnosed ileal/ileocecal Crohn's disease, 2003-2018



33% lower risk of long-term adverse outcomes with ICR

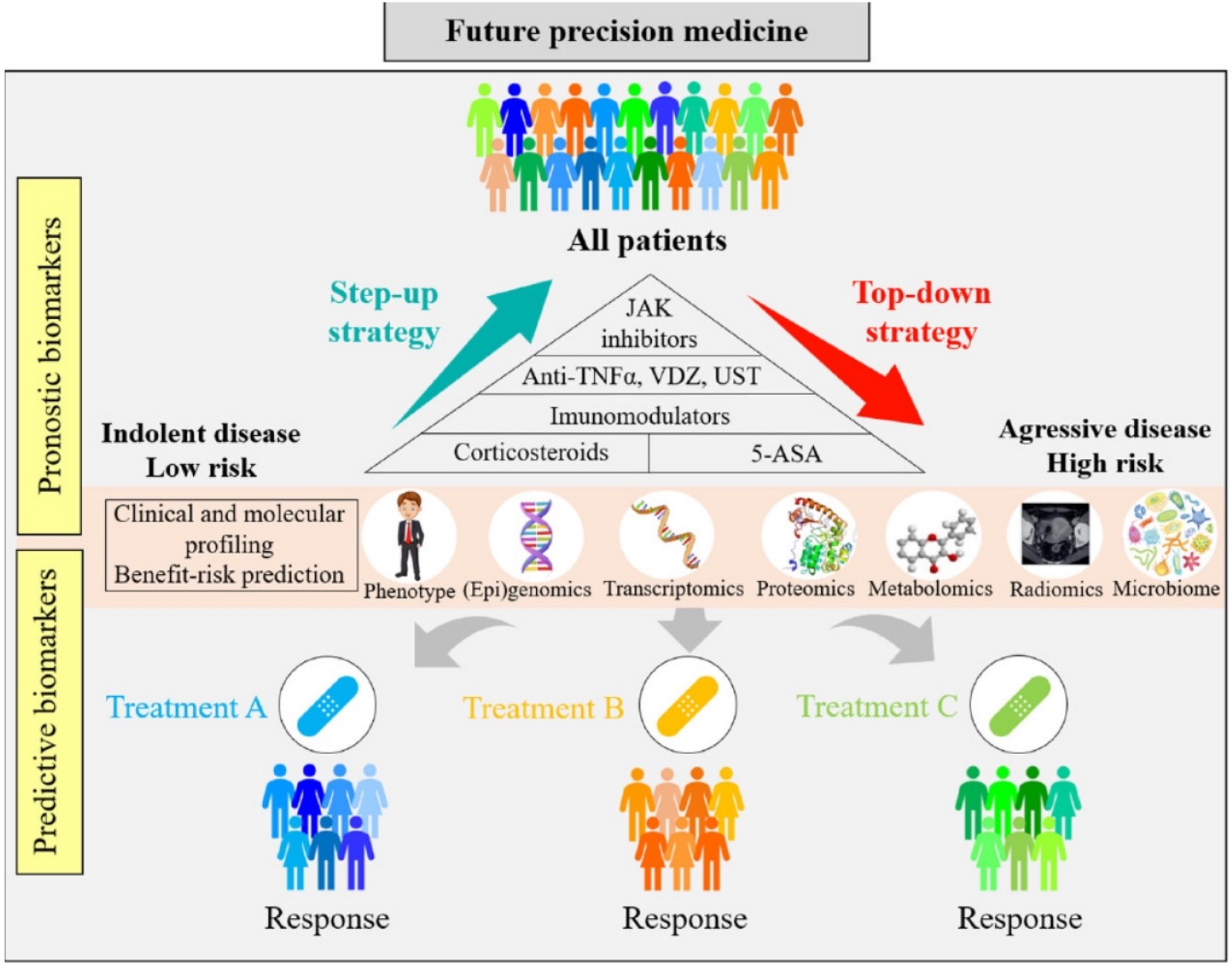


50% of ICR group on no treatment at 5 years



PREDICT

Gastroenterology
2023; 165: 976-985



From Vieujean S and Louis E, Ther Adv Gastroenterol 2023; 16: 1–52

Time to ask some expert adult IBD-ologists!

Thank you!