Advanced therapies in IBD: positioning and sequencing

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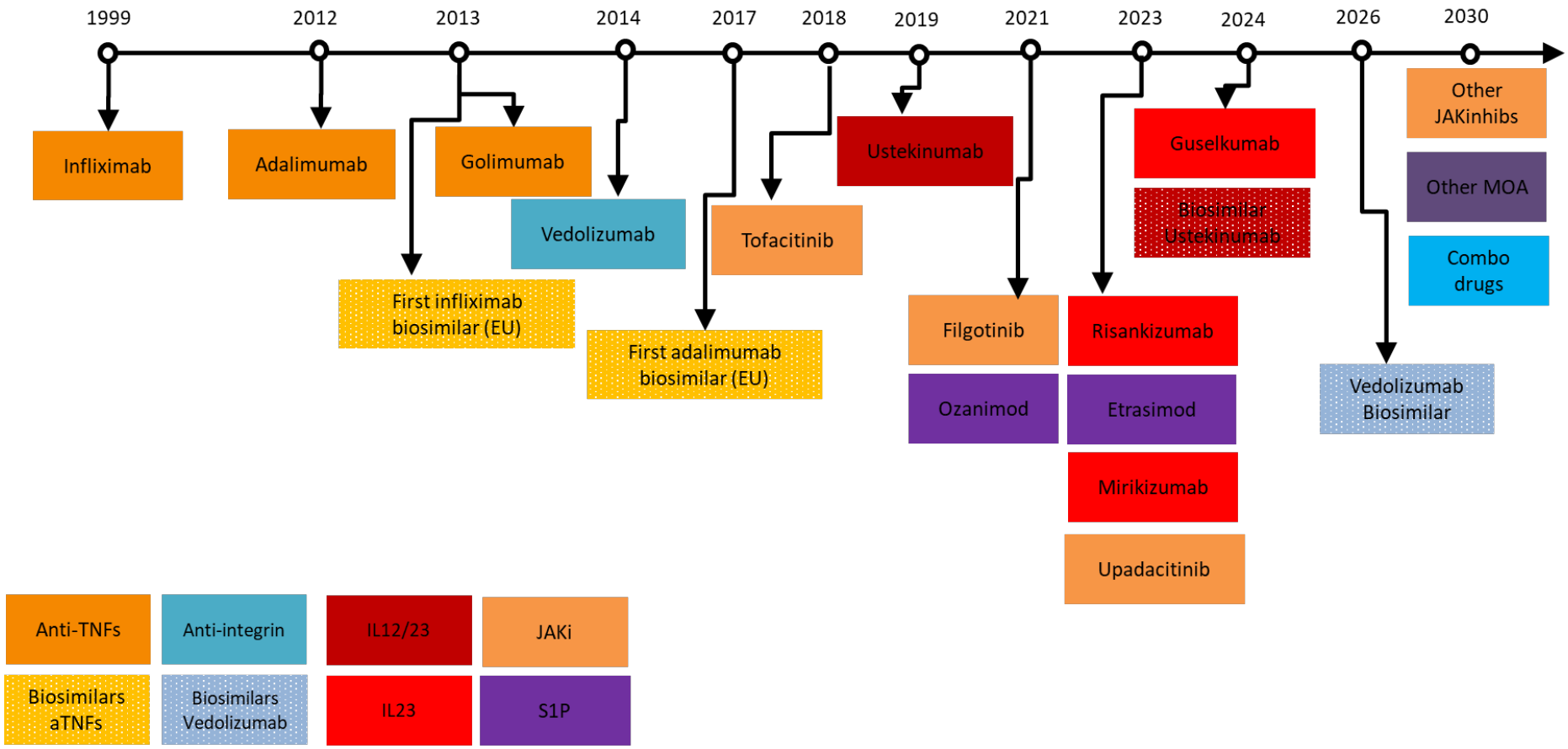
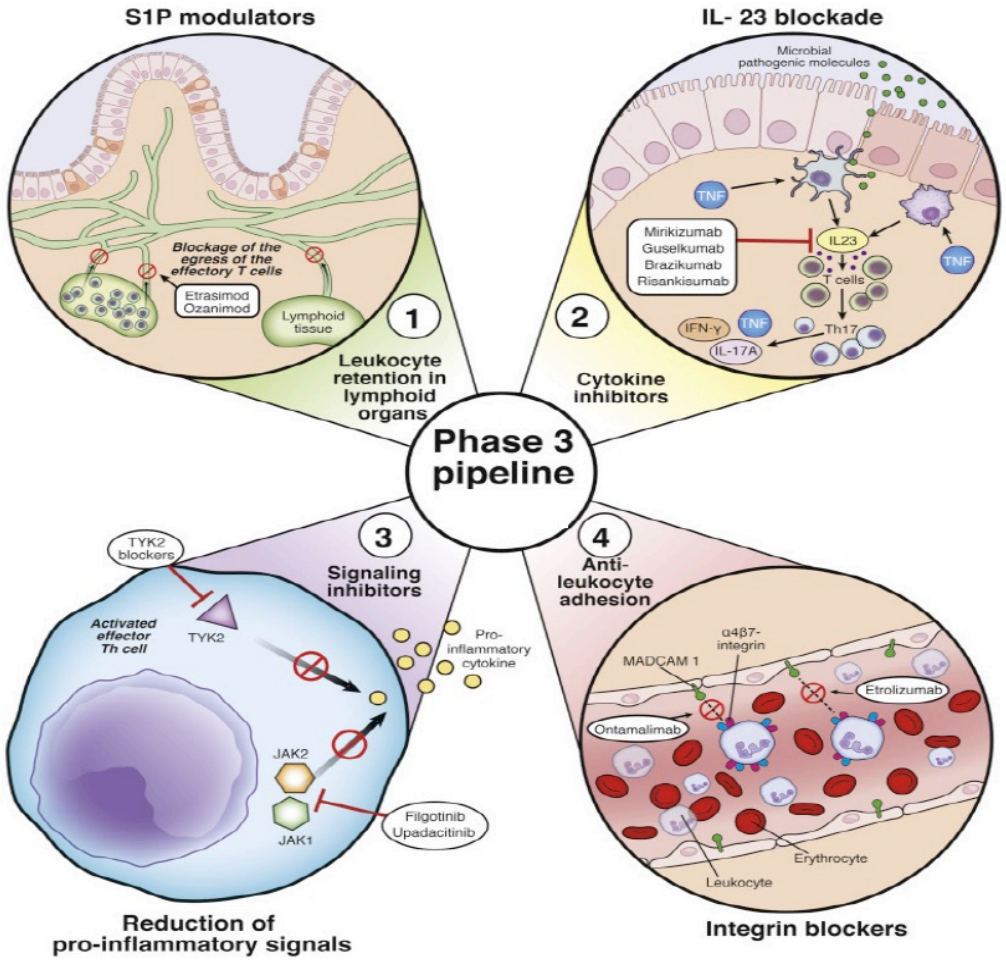
Jean-Frederic Colombel has received research grants from AbbVie, Janssen Pharmaceuticals and Takeda; has received payment for lectures from AbbVie, Amgen, Allergan, Bristol-Myers Squibb Company, Ferring Pharmaceuticals, Shire, and Takeda; has received consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb Company, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Gilead, Iterative Scopes, Ipsen, Immunic, lmtbio, Inotrem, Janssen Pharmaceuticals, Landos, LimmaTech Biologics AG, Medimmune, Merck, Novartis, O Mass, Otsuka, Pfizer, Shire, Takeda, Tigenix, Viela bio; and hold stock options in Intestinal Biotech Development.

Taking advantage of the new therapeutic landscape



Taking advantage of the new therapeutic landscape



Danese S et al. Gastroenterology 2022

Positioning/sequencing: current evidence

- Comparative effectiveness research
- Benefit/risk assessment research

Comparative Effectiveness Research

Head to head clinical trials

- Lack of a placebo arm in head-to-head trials reduces loss of chance for study participants and facilitates recruitment
- Allows for rigorous evaluation of a single variable in a precisely defined patient group

Network Meta-Analyses Propensity Score Matching

- Relative effectiveness of treatments can be estimated even if no studies directly compare them
- Through network meta-regression, uncovering "true" relative effectiveness of each drug is theoretically possible

Comparisons Between RCTs of Different Therapies

- Study patients across trials may be different (in disease and risk factor status)
- Methodologic quality may vary across trials

Real-world Observational Evidence

- Variances in data quality
- Relies on the implicit assumption that the physicians' reports are complete and accurate

Expert Recommendation

- Based on real life experiences and pragmatism; supported where possible by published literature
- Generated by a group of physicians and represent medical priorities that may be different from those of allied healthcare professionals or IBD patients

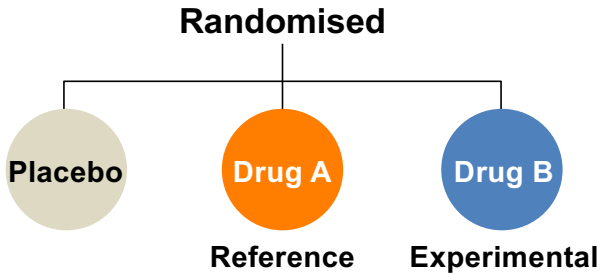
Personal Opinion

- Heterogeneity of treatment effects: variation in direction and/or magnitude of response to same treatment
- A function of an individual's characteristics or those of the disease, treatment, care setting, providers, or external factors

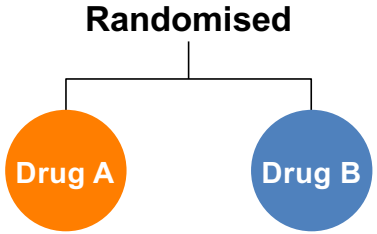
Reviewed in Ahuja D and Singh S. Curr Opin Gastroenterol 2022

Head to head trials in IBD

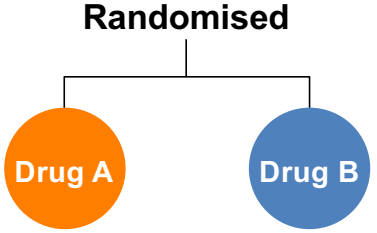
Placebo controlled with nonpowered reference arm



Noninferiority



Superiority



Fewer participants needed than conventional RCTs

Appropriate for evaluating new therapeutics

Appropriate for approving new therapeutics

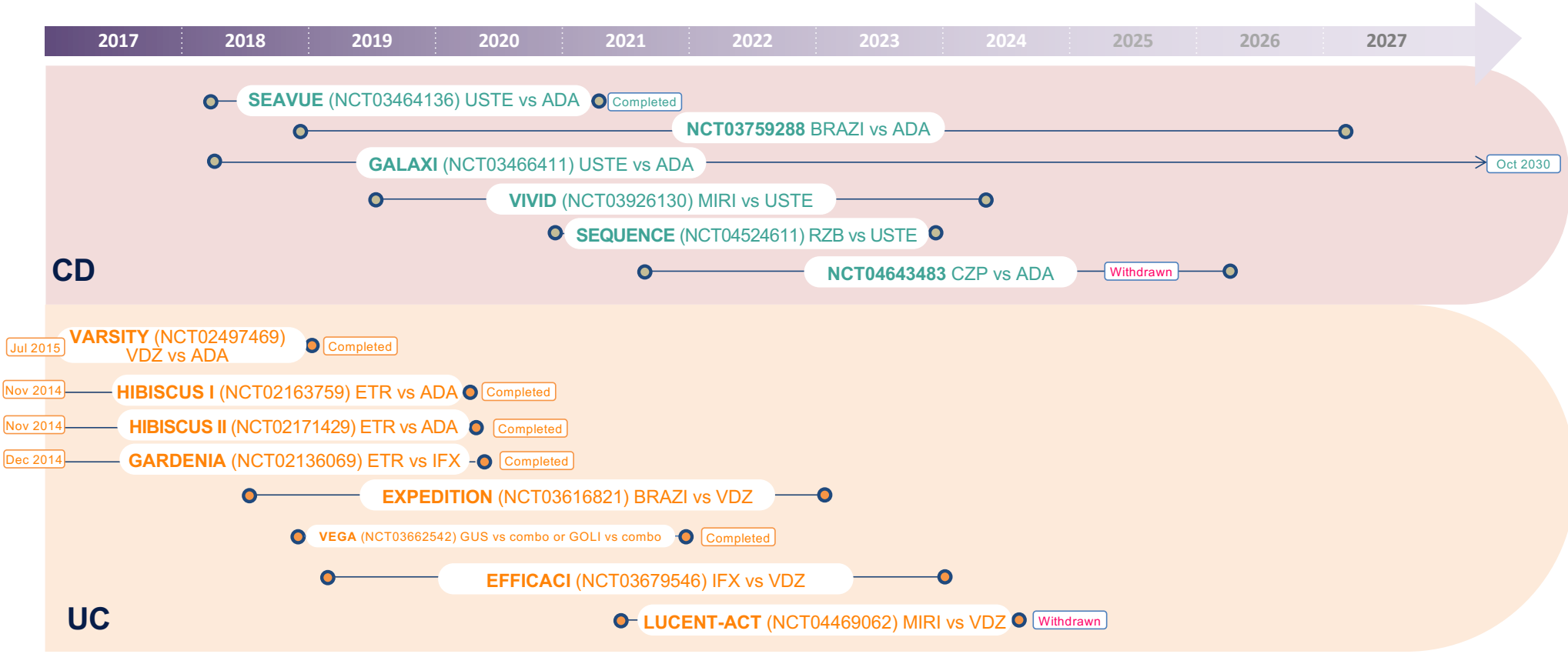
May change routine clinical practice, impact reimbursement of approved drugs

No conclusions can be drawn from underpowered reference arm

Key methodologic issue: defining noninferiority margin

Difficult to demonstrate superiority of a new agent over established agents

Head-to-head superiority trials in IBD



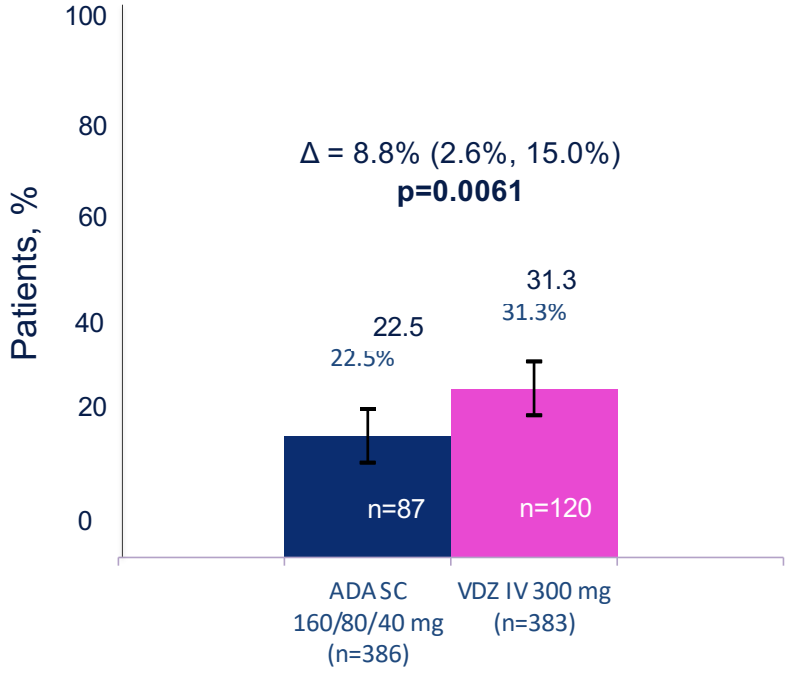
ADA, adalimumab; BRAZI, brazikumab; CZP, certolizumab pegol; ETR, etrolizumab; GOLI, golimumab; GUS, guselkumab; IFX, infliximab; MIRI, mirikizumab; RZB, risankizumab; USTE, ustekinumab; VDZ, vedolizumab.

ClinicalTrials.gov. Available at: www.clinicaltrials.gov. Accessed: February 2022.

Head-to-head superiority trials in IBD

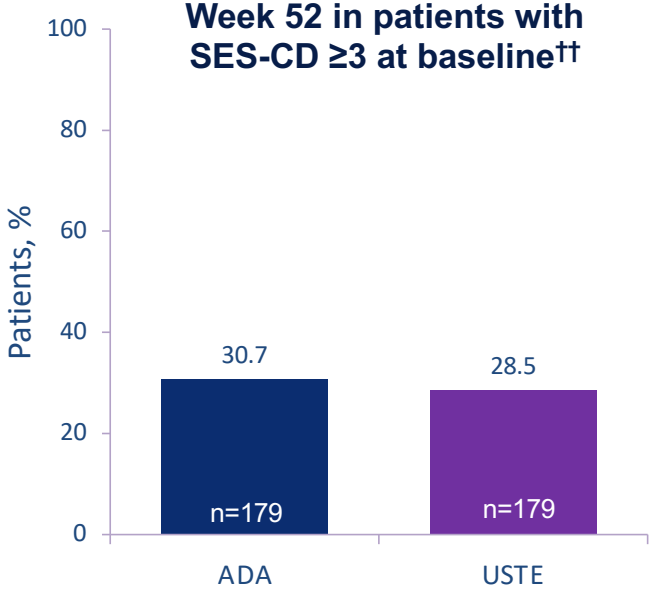
VARSITY

Overall clinical remission† at Week 52‡



SEAVUE

Endoscopic remission at Week 52 in patients with SES-CD ≥3 at baseline††

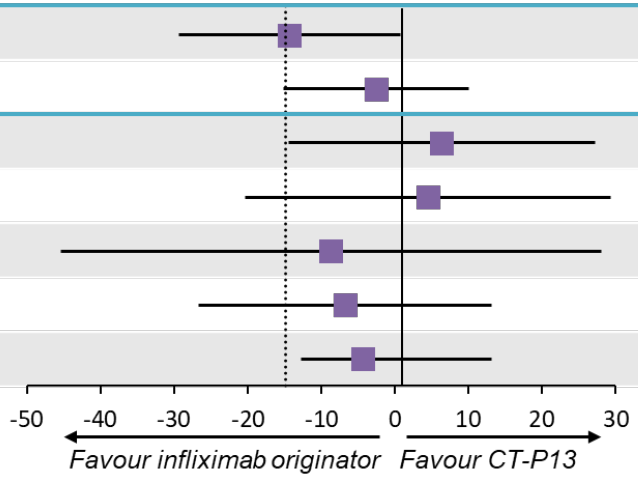


The primary endpoint was clinical remission at Week 52. No significant difference (p=0.417) was found between USTE§ (65%) and ADA¶ (61%)

Sands B et al. N Engl J Med 2019; Sands B et al. Lancet 2017

Non-inferiority trials in IBD: NOR-SWITCH

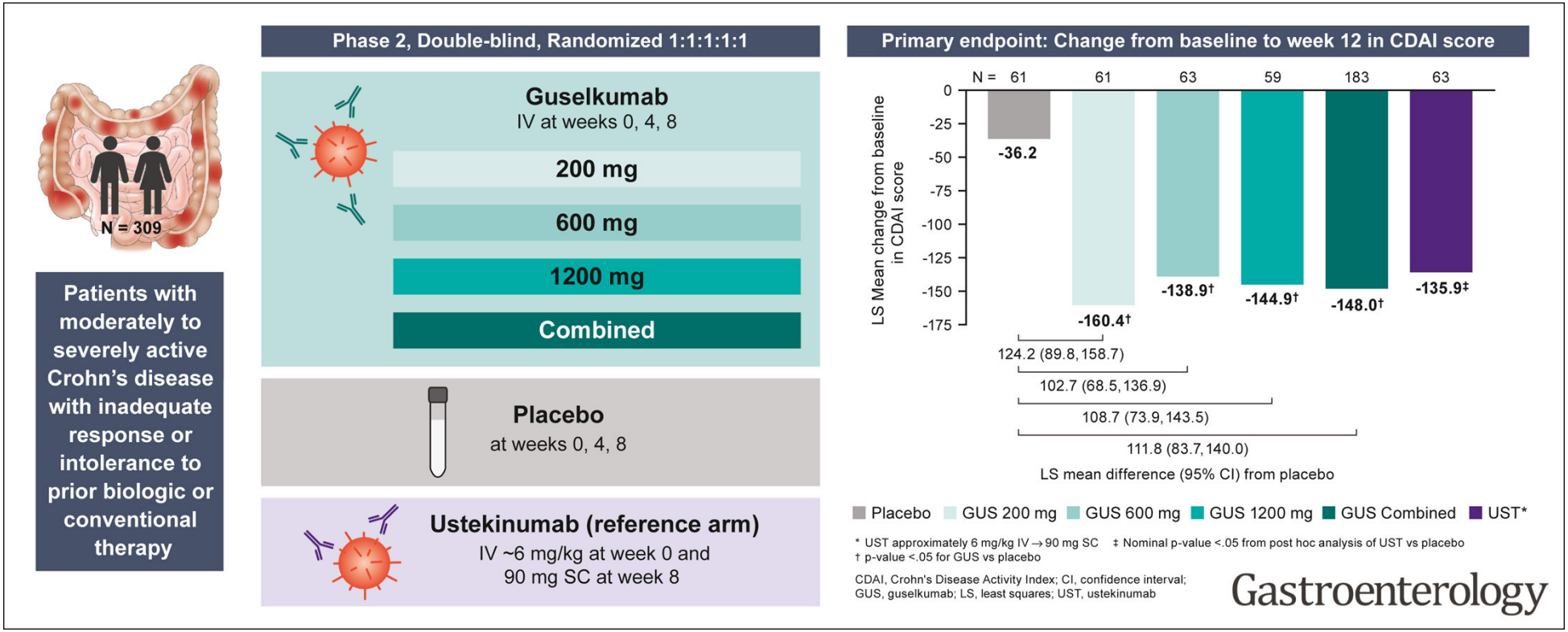
Diagnosis, n (%)	Infliximab originator n=202	CT-P13 n=206	Risk difference (95% CI)
Crohn's disease	14 (21.2)	23 (36.5)	-14.3 (-29.3, 0.7)
Ulcerative colitis	3 (9.1)	5 (11.9)	-2.6 (-15.2, 10.0)
Spondyloarthritis	17 (39.5)	14 (33.3)	6.3 (-14.5, 27.2)
Rheumatoid arthritis	11 (36.7)	9 (30)	4.5 (-20.3, 29.3)
Psoriatic arthritis	7 (53.8)	8 (61.5)	-8.7 (-45.4, 28.1)
Psoriasis	1 (5.9)	2 (12.5)	-6.7 (-26.7, 13.2)
Overall	53 (26.2)	61 (29.6)	-4.4 (-12.7, 13.2)



- Randomised, noninferiority, double-blind, phase 4 trial comparing originator infliximab vs biosimilar CT-P13
- Switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator based on prespecified noninferiority margin of 15%
- The choice of a sensible noninferiority margin is challenging; in NOR-SWITCH, the 15% margin may have been too wide to exclude all clinically important differences

CI, confidence interval.
Jørgensen KK et al. Lancet. 2017;389:2304-16.

Placebo-controlled trials with a non-powered reference arm: GALAXI 1



Sandborn WJ. Gastroenterology 2022;162:1650-64

Network meta-analysis: efficacy of current therapies in CD

Induction of clinical response	Induction of clinical remission								
	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**

Figure 3: Comparative efficacy of biologics for induction of clinical remission and clinical response in biologic-naive patients with moderate-to-severe Crohn's disease

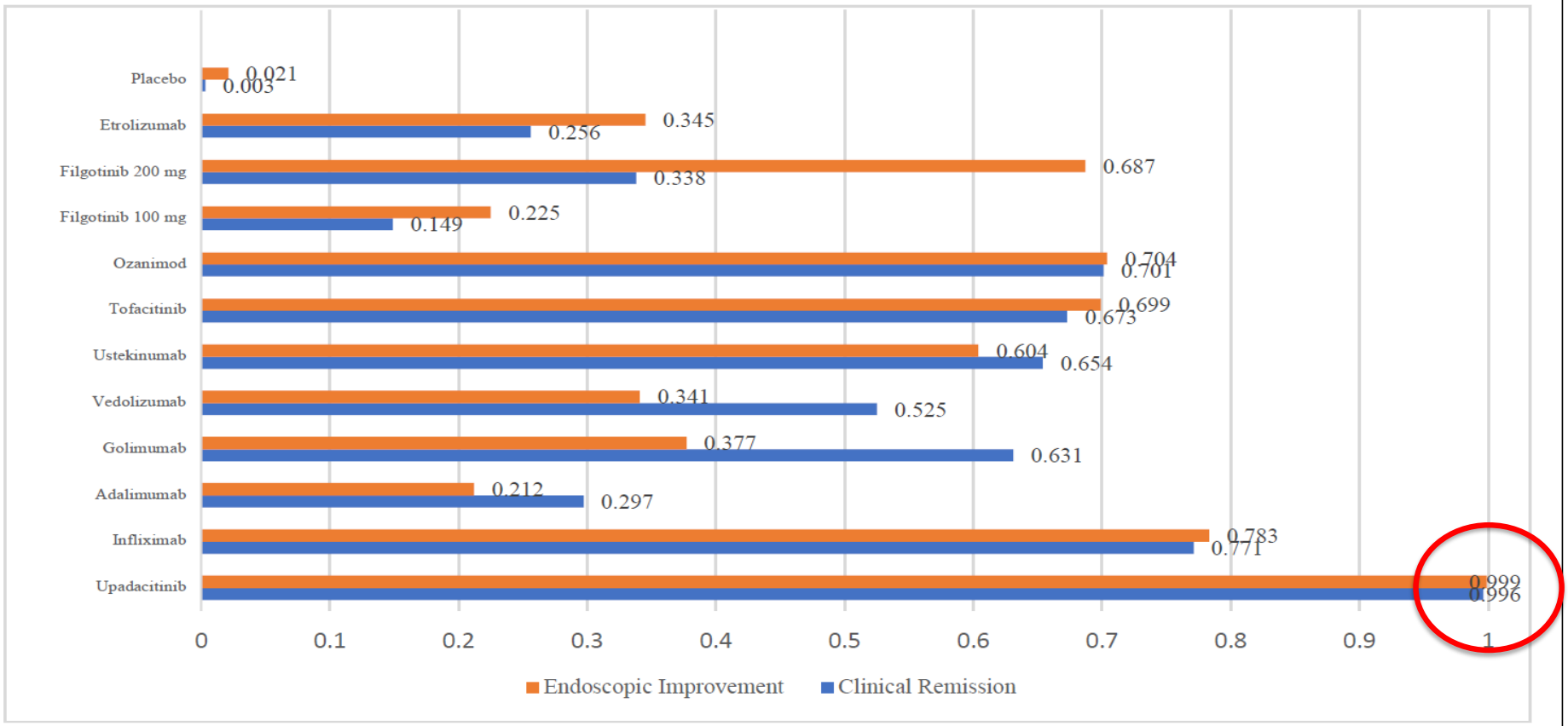
Conclusion In a network meta-analysis, infliximab 5 mg/kg ranked first for induction of clinical remission in all patients with luminal CD, but risankizumab 600 mg was first in biologic-naïve and biologic-exposed patients. Upadacitinib 30 mg once daily ranked first for maintenance of remission.

Barberio B et al. Gut 2022

Interpretation Although biologic treatment choices in patients with moderate-to-severe Crohn's disease must be individualised for each patient, this analysis suggests that either infliximab with azathioprine or adalimumab might be preferred as a first-line therapy, and adalimumab (after infliximab loss of response) or risankizumab might be preferred as a second-line therapy, for induction of clinical remission.

Singh S et al. Lancet Gastroenterol Hepatol 2021

Network meta-analysis: efficacy of current therapies in UC (induction)



SUCRA: surface under the cumulative ranking.

Lasa JS et al. Lancet Gastroenterol Hepatol 2021

Meta-analysis: safety of current therapies in IBD

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)	**Vedolizumab vs. TNFα antagonists** (17 cohorts; 51,596 patients)	**Ustekinumab vs. vedolizumab** (5 cohorts; 1,420 patients)
• **CD**: **51% lower risk** of serious infections with ustekinumab • **UC**: Knowledge gap	• **CD**: **No difference** in risk of serious infections (OR, 1.03) • **UC**: **32% lower risk** of serious infections with vedolizumab	• **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

Clinical Gastroenterology and Hepatology

Solitano V et al. Clin Gastroenterol Hepatol 2022

Indirect treatment comparisons using individual patient-level data from placebo-controlled trials

Comparative effectiveness of biologics for endoscopic healing

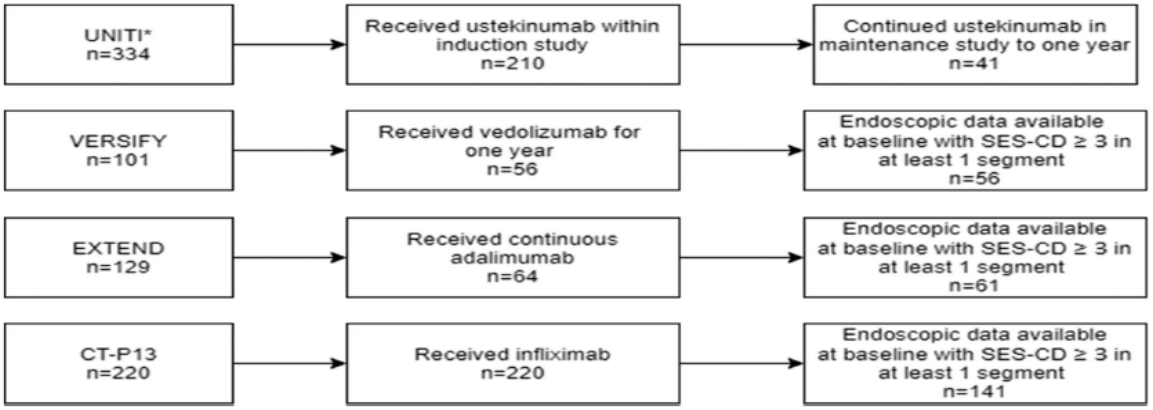


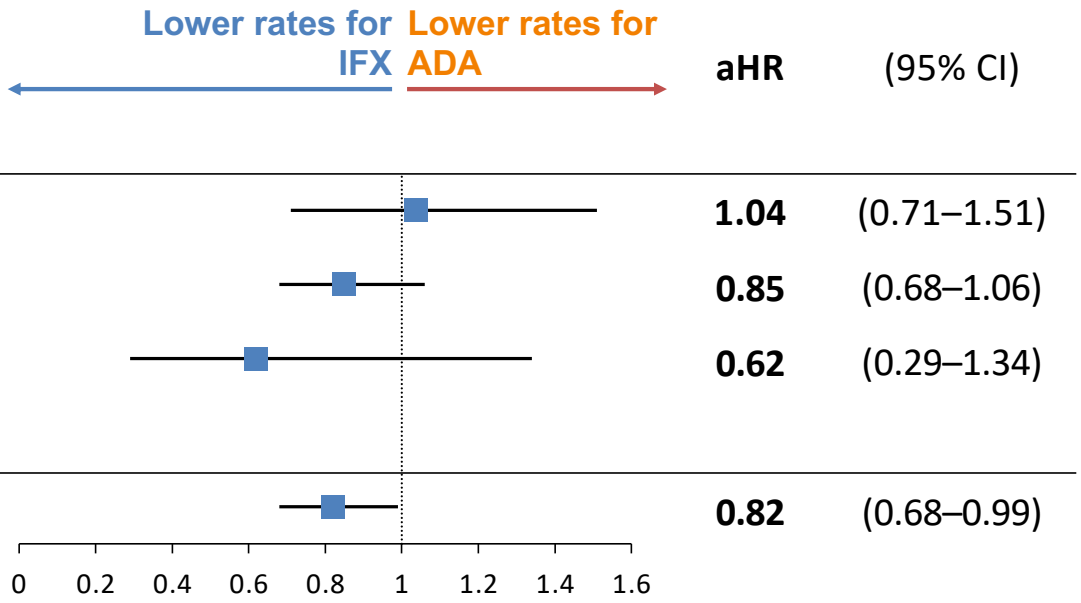
Table 2. Endoscopic outcomes at 1 year among all participants

		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 N et al. Clin Gastroenterol Hepatol 2022

RWE: Infliximab and adalimumab had comparable benefits in UC patients based on propensity score-matched analysis

1400 biologic-naïve UC patients (Optum Labs)



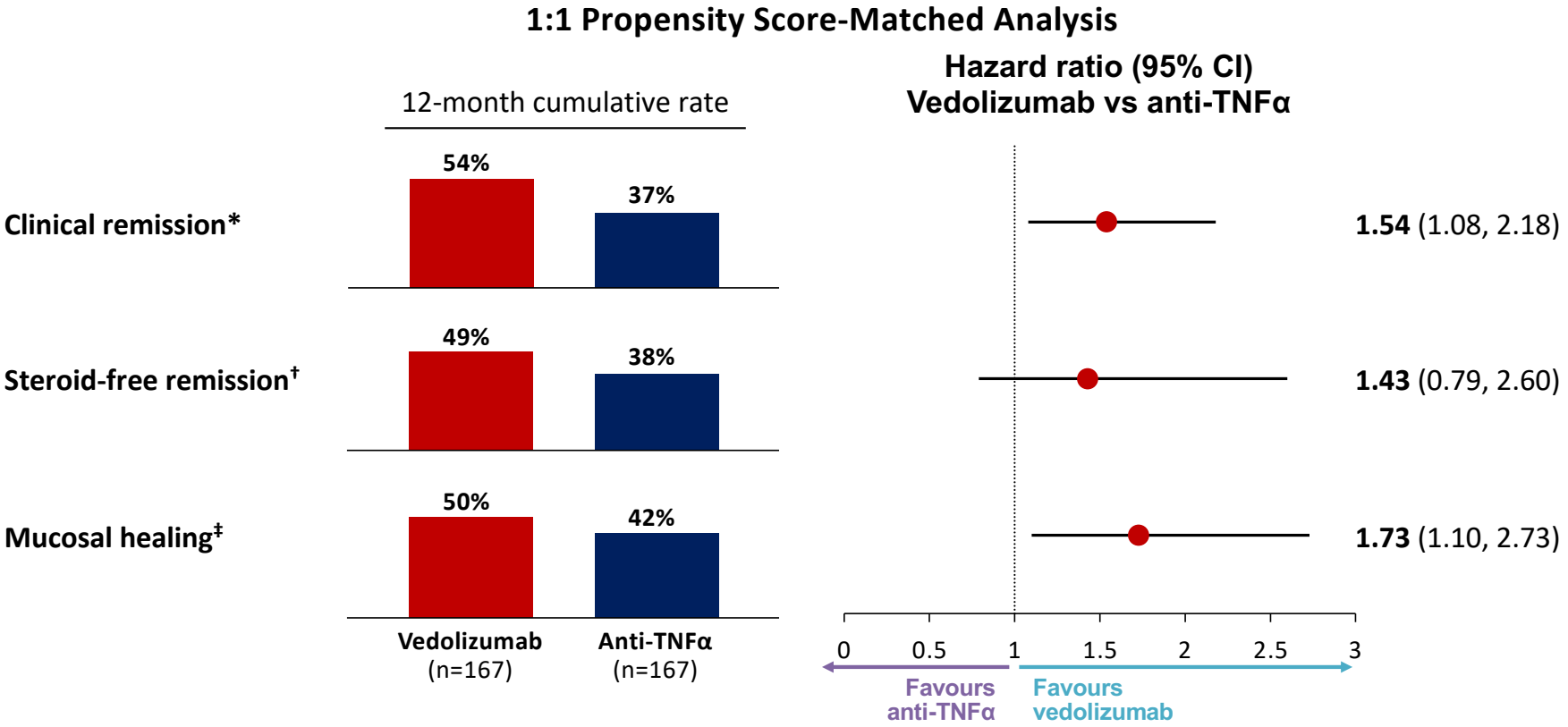
Considerations

Limited data availability—claims data

- **Required adjustment for variables not balanced by propensity score matching**
- **Limits interpretation: no longer average treatment effect for population, but rather conditional**

Singh S et al. Aliment Pharmacol Ther. 2016 May;43:994-1003.

RWE: Higher rates of clinical remission and mucosal healing with vedolizumab vs anti-TNF in UC patients



Lukin D et al. Clin Gastroenterol Hepatol 2022

AGA clinical practice guideliness

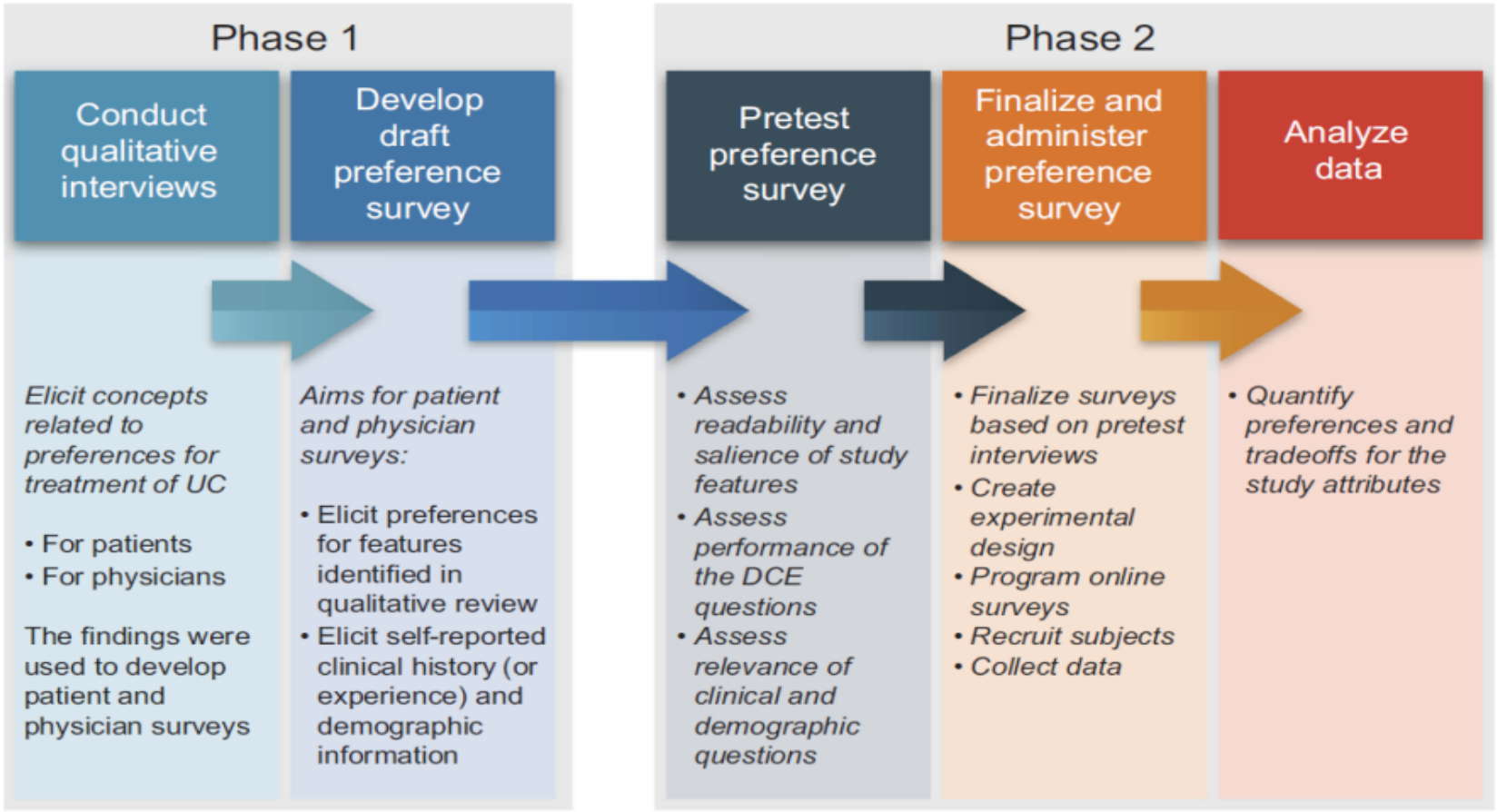
A. In adult outpatients with moderate to severe CD, who are *naïve to biologics* the AGA
Recommends the use of infliximab, adalimumab or ustekinumab over certolizumab pegol (Strong recommendation, moderate certainty of evidence)
Suggests the use of vedolizumab over certolizumab pegol (Conditional recommendation, 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 JD et al. Gastroenterology 2021

Positioning/sequencing: current evidence

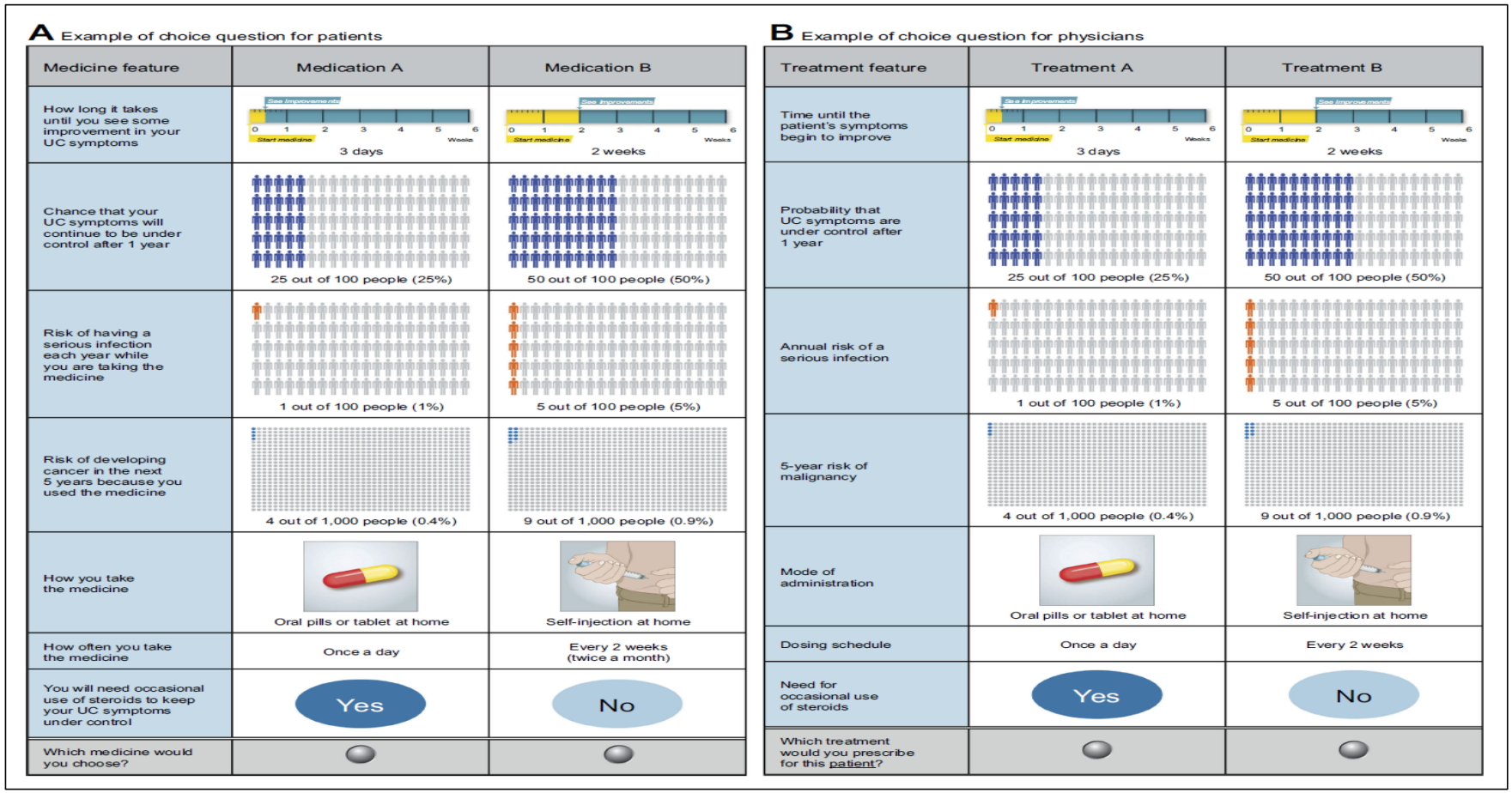
- Comparative effectiveness research
- Benefit/risk assessment research

Discrete choice experiment: study design



Boeri M et al. Clin Exp Gastroenterol 2019

Patient and physician preferences: discrete choice experiment



A Example of choice question for patients

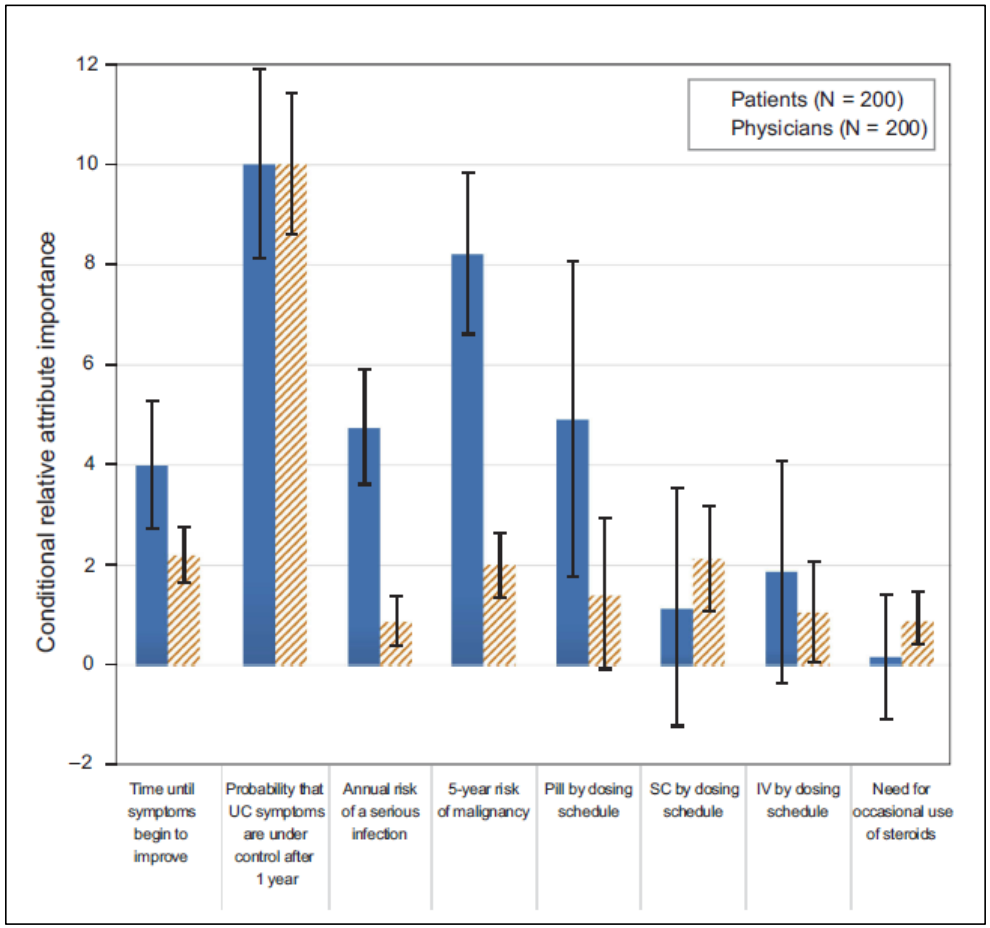
Medicine feature	Medication A	Medication B
How long it takes until you see some improvement in your UC symptoms	3 days	2 weeks
Chance that your UC symptoms will continue to be under control after 1 year	25 out of 100 people (25%)	50 out of 100 people (50%)
Risk of having a serious infection each year while you are taking the medicine	1 out of 100 people (1%)	5 out of 100 people (5%)
Risk of developing cancer in the next 5 years because you used the medicine	4 out of 1,000 people (0.4%)	9 out of 1,000 people (0.9%)
How you take the medicine	Oral pills or tablet at home	Self-injection at home
How often you take the medicine	Once a day	Every 2 weeks (twice a month)
You will need occasional use of steroids to keep your UC symptoms under control	Yes	No
Which medicine would you choose?		

B Example of choice question for physicians

Treatment feature	Treatment A	Treatment B
Time until the patient's symptoms begin to improve	3 days	2 weeks
Probability that UC symptoms are under control after 1 year	25 out of 100 people (25%)	50 out of 100 people (50%)
Annual risk of a serious infection	1 out of 100 people (1%)	5 out of 100 people (5%)
5-year risk of malignancy	4 out of 1,000 people (0.4%)	9 out of 1,000 people (0.9%)
Mode of administration	Oral pills or tablet at home	Self-injection at home
Dosing schedule	Once a day	Every 2 weeks
Need for occasional use of steroids	Yes	No
Which treatment would you prescribe for this patient?		

Boeri M et al. Clin Exp Gastroenterol 2019

Conditional relative importance for patients and physicians (UC)



Patients considered symptom control at one year 2.5 times as important as time to symptom improvement and 5-year risk of malignancy almost as important as long-term symptom control

For physicians, symptom control at one year was the most important attribute and was five times as important as the risk of malignancy.

Boeri M et al. Clin Exp Gastroenterol 2019

Positioning/sequencing: current evidence

Different methods
Different results
Different conclusions
Different recommendations

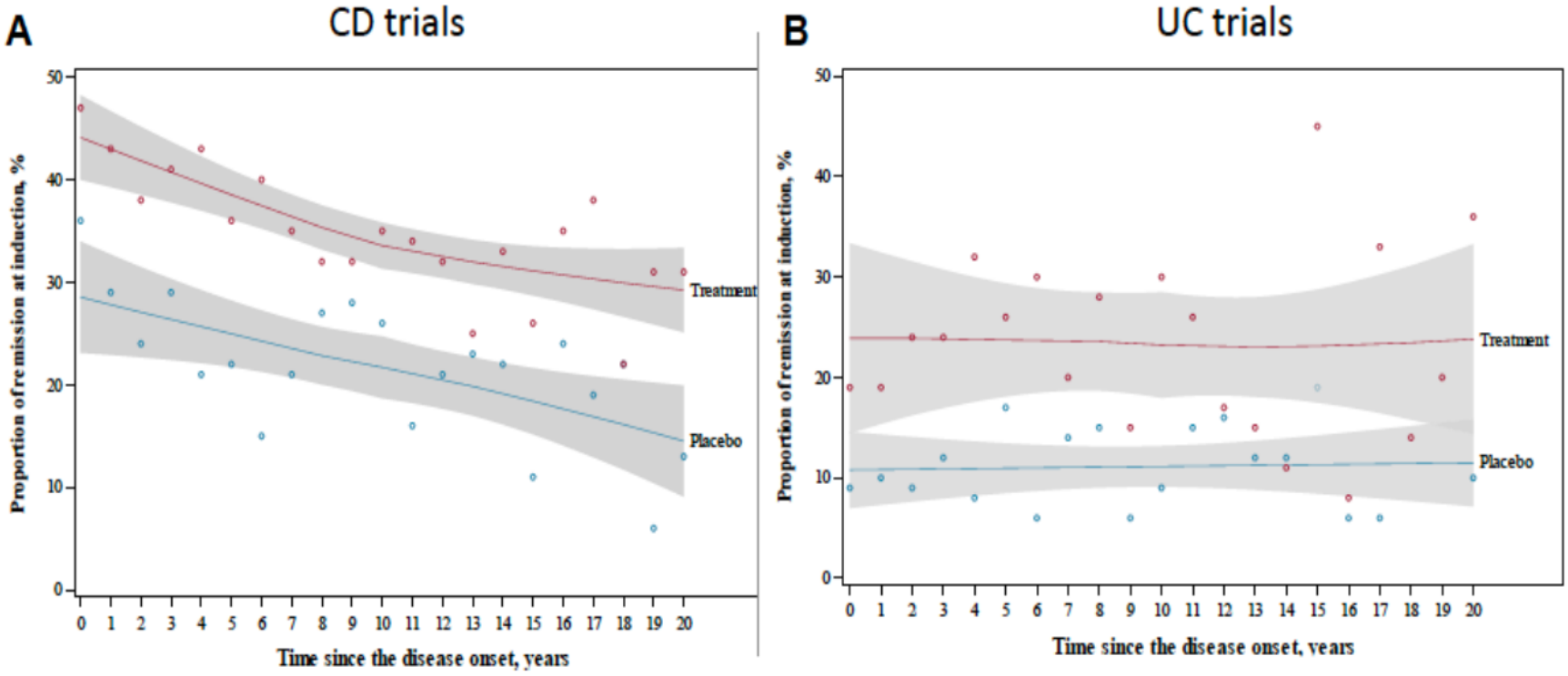
….we can draw endless clinical vignettes….final choice is still be evidence + experience+ patient/Dr agreement until further innovation…

Choosing Therapy for IBD
Special Situations

- Elderly
- Co-morbidities
- Pregnancy
- EIMs
- Acute severe UC
- Primary fistulizing Crohn's disease
- Post-operative prophylaxis
- …

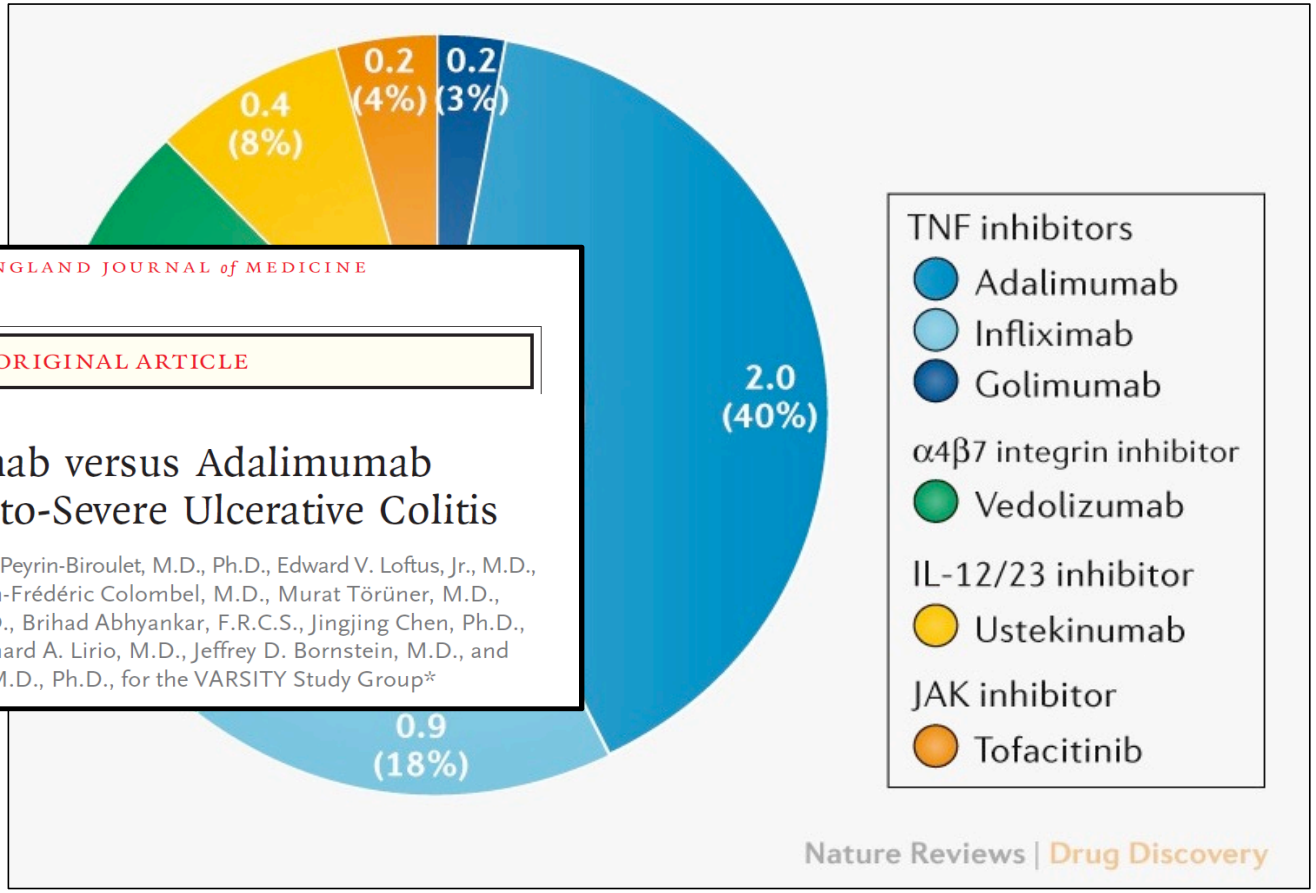
Your First Shot is Your Best Shot (especially in CD) !

Impact of disease duration on anti-TNF efficacy



Ben Horin S. Gastroenterology 2022

Insurance vs evidence based medicine



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis

Bruce E. Sands, M.D., Laurent Peyrin-Biroulet, M.D., Ph.D., Edward V. Loftus, Jr., M.D., Silvio Danese, M.D., Jean-Frédéric Colombel, M.D., Murat Törüner, M.D., Laimas Jonaitis, M.D., Ph.D., Brihad Abhyankar, F.R.C.S., Jingjing Chen, Ph.D., Raquel Rogers, M.D., Richard A. Lirio, M.D., Jeffrey D. Bornstein, M.D., and Stefan Schreiber, M.D., Ph.D., for the VARSITY Study Group*

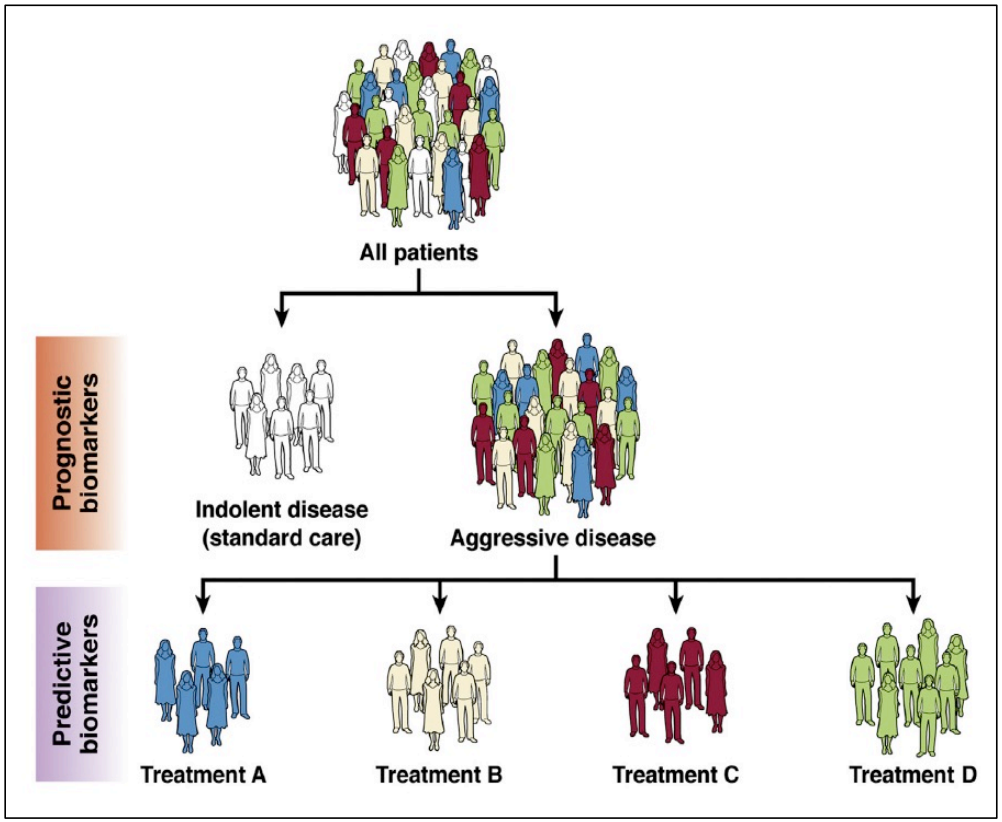
Al Horani R. Nat Rev Drug Discovery 2021

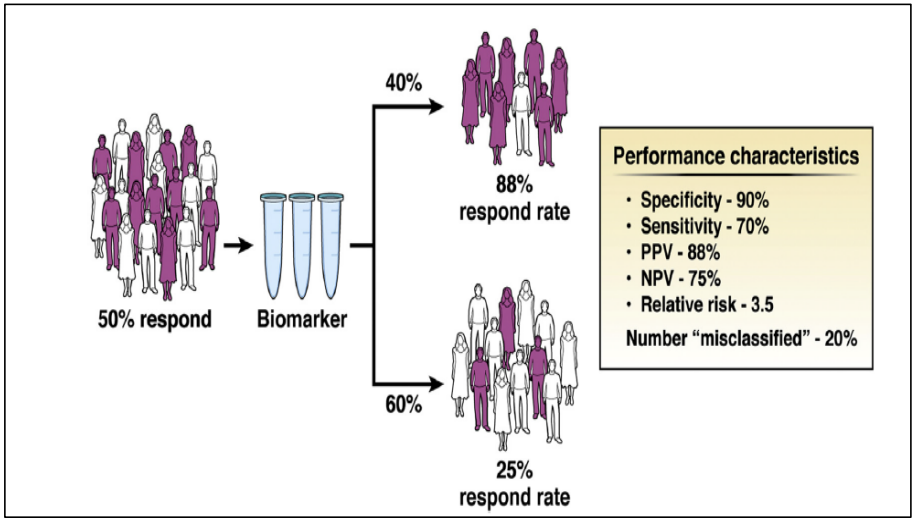
Advanced therapies in IBD

- Positioning/sequencing : current evidence

- Positioning/sequencing in the future

Personalization





Verstockt B et al. Gastroenterology 2022

Biomarkers investigated for potential to predict response to anti-TNFs in IBD

Genes and RNA biomarkers

Polymorphisms in:

- FCGR3A
- TLR2
- TLR4
- TLR9
- TNFRSF1A
- IFNγ
- IL6

IL1B
IL6
IL11
IL17A
IL13RA2
IFNγ
Apoptotic index
Oncostatin M
Osteoprotegerin
PTGS2
Stanniocalcin-1
TNFα

Microbiome biomarker

F.Prausnitzii in UC

Prediction of Anti-TNF response

Serological biomarkers

Hemoglobin
pANCA
sANCA
Serum albumin
CRP

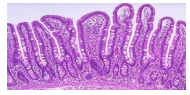
profile

Stool biomarker

Lactoferrin
Infliximab

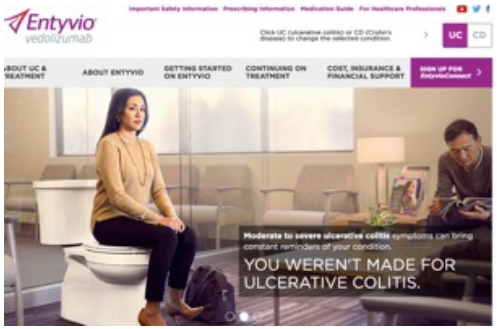
Mucosal biomarker

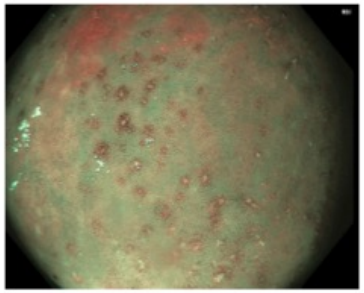
Confocal microscopy imaging of TNF+cells
Inflammatory phenotype of CD
GIMATS module



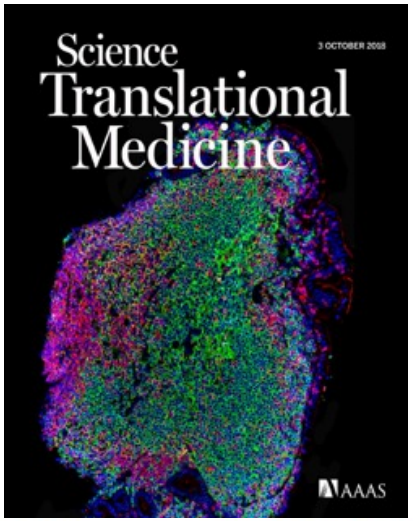
Problems with biomarkers: reproducibility and practicality

Main problem: In a majority of cases, drug mechanisms of action are not well defined!





Endoscopic recognition of lymphoid aggregates



- First line agent in the management of Ulcerative Colitis
- **Sales of $1.3 billion in 2018**
- **MOA not well understood**

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HIV

Anti-α4β7 therapy targets lymphoid aggregates in the gastrointestinal tract of HIV-1–infected individuals

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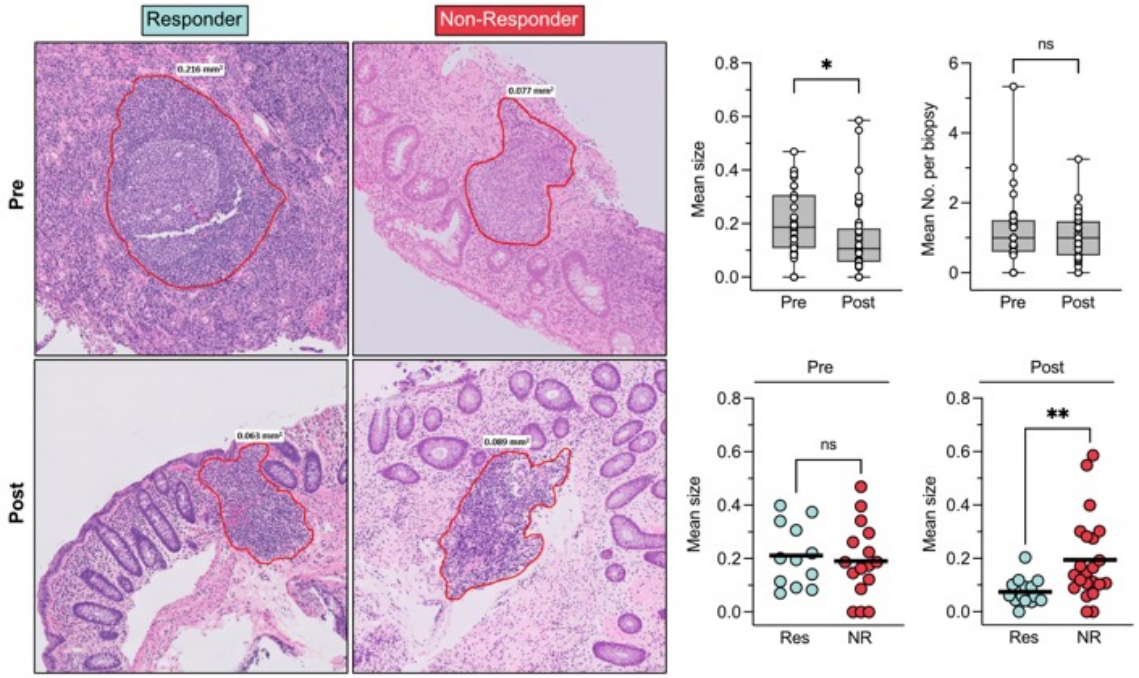
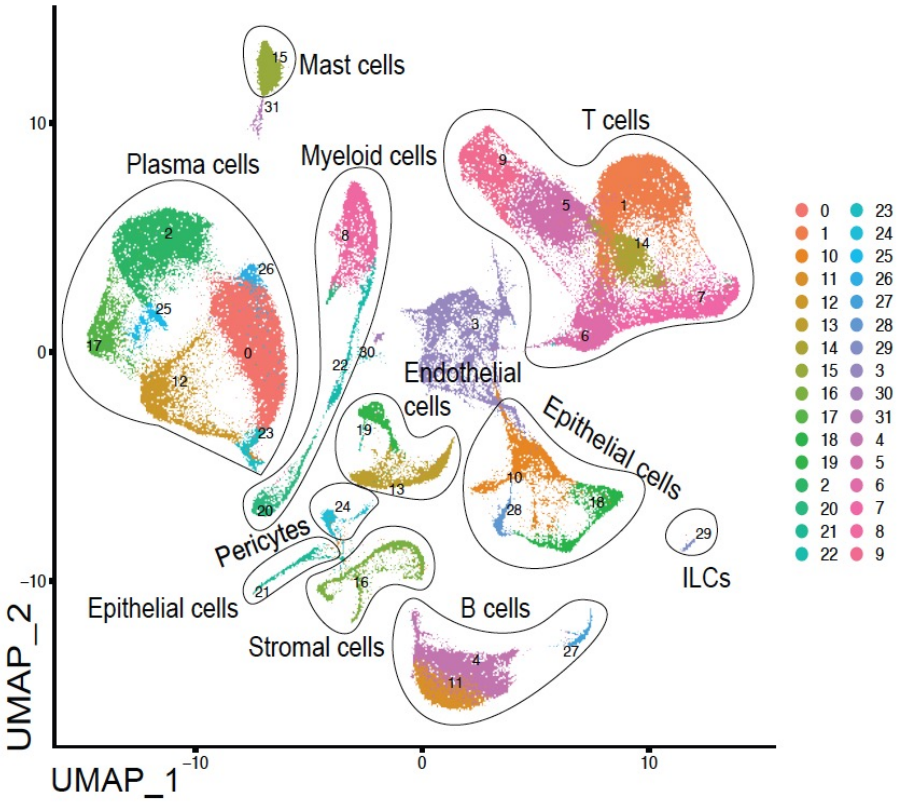
Personalization based on the mechanisms of action of drugs

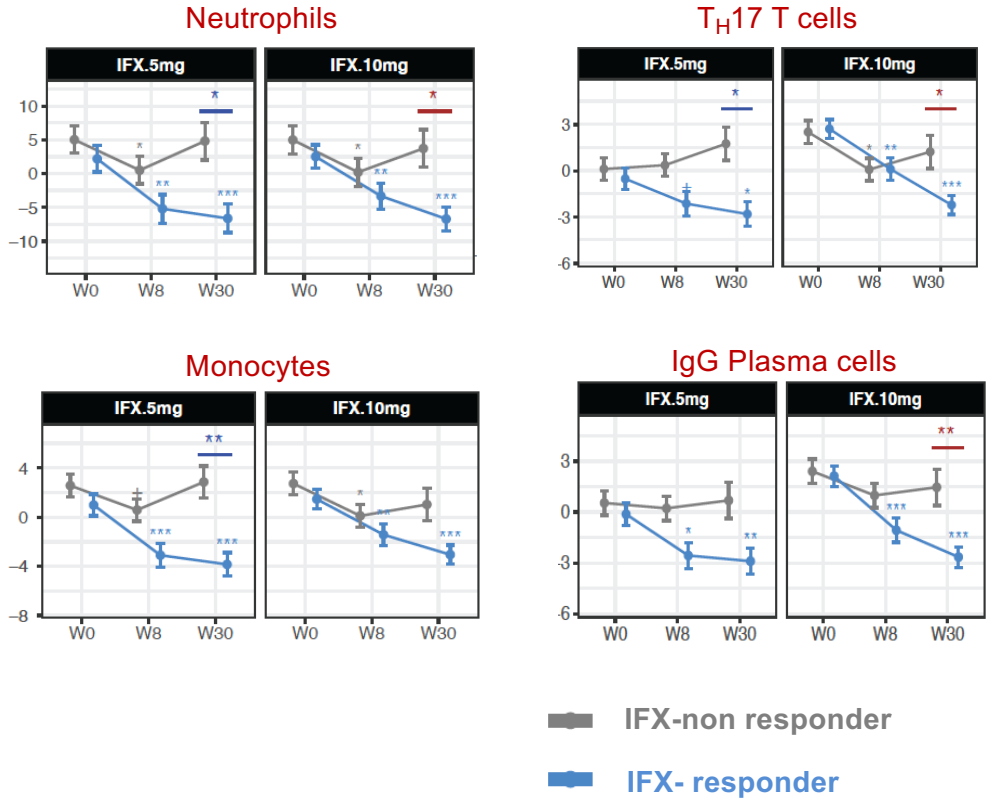
Longitudinal sampling of tissues before and after therapy; ex: vedolizumab



Canales-Herrerias…Mehandru S et al. Unpublished

Longitudinal high dimensional immune cell profiling for rational drug combinations and sequencing: anti-TNF in UC





Jha….Mehandru. Unpublished

Conclusion

- With more drugs available positioning and sequencing is complex
- Comparative effectiveness and risk/benefit research offers some clues but results may be inconsistent
- Personalization is attractive but replication is hard
- A plea for rationalizing positioning, sequencing

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NIH National Institute of Mental Health
Crohn's & Colitis Foundation
Litwin IBD Pioneers Crohn's & Colitis Foundation
Kenneth Rainin Foundation
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