North Carolina Society of Gastroenterology
2024 Annual Meeting

Sequencing of IBD Therapies

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Agenda

- What is Sequencing of IBD therapies?
- SMART Trials
- The problem of previous biologic failure
- What we do know from retrospective data
- Where we go from here

In a Perfect World…

- We would have randomized studies to inform our choices of 1st, 2nd, and 3rd line therapy in IBD
  - Including information on the patient's prior therapies and why they failed
  - We often don't know these very well (especially the why – stricture? Ab?)
- Instead, we mostly have phase 3 trials to show that drugs are slightly better than placebo
  - Not necessarily better than 5-ASA or Azathioprine (S1PRs?)
- And once in a great while, we get a randomized head-to-head study in which everyone tries to beat up on the ***weakest*** drug in a class, or on the one drug that is ***about to go biosimilar***.

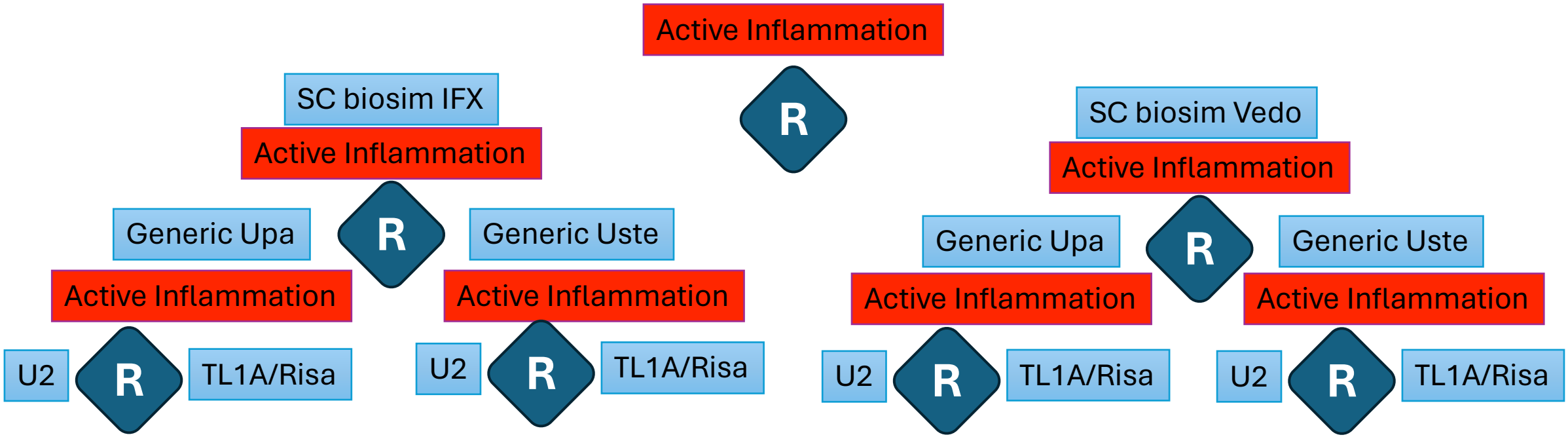
SMART design

- Sequential Multiple-Assignment Randomized Trial
- Enroll everyone
- Randomize to 1st line therapies
  - Define and measure failure – inflammation without stricture
- Then randomize to 2nd line therapies
  - If & when these fail,
- Then randomize to 3rd line therapies
- You learn the best ***sequence*** of therapies

SMART baseline measurement

- Measure on each patient at entry
  - Severity of inflammation
  - Genetic markers
  - Gene expression markers in inflamed bowel
  - Intestinal leak (Albumin, lactulose/mannitol ratio)
  - Strictures
  - Penetrating complications
  - Other predictors of success or failure
- These will help pathway / sequencing predictions

Pooled outcomes



U2 = Upadacitinib + Ustekinumab

Answers multiple Comparative Effectiveness Questions:

1. 1st line: IFX vs Vedo
2. 2nd line: Upa vs Uste
3. 3rd line: U2 vs TL1A/Risa Combo

Test for interactions: Does prior failed therapy affect the success of 2nd line, 3rd line Rx if you are changing class?

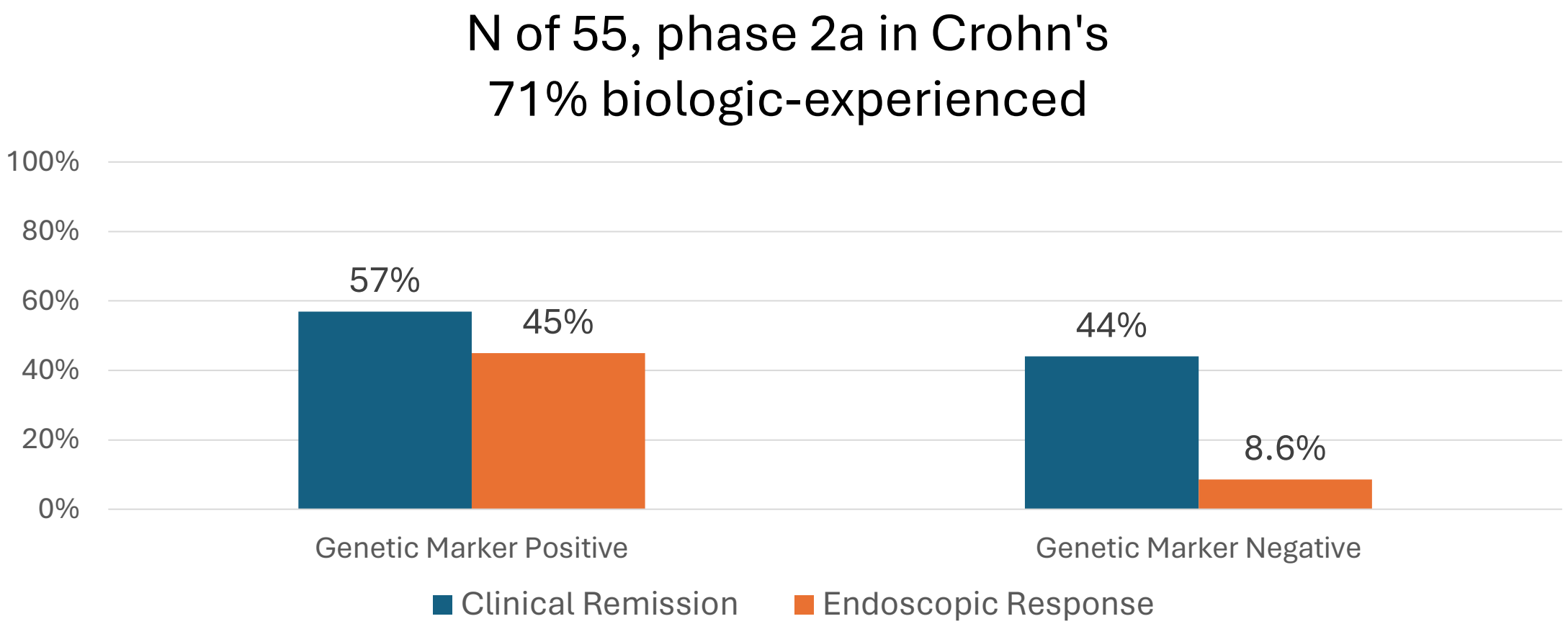
Learn: best pathway (Sequencing)

- If a patient has a (baseline)
  - CRP > 60 mg/L
  - Perianal fistulae
  - Albumin <30 g/dL
  - Genetic marker (SNP) *rs2066844* in NOD2
- What is the best treatment ***pathway*** for them?
  - Upa → Vedo → Uste ?
- These pathways can be learned from an IBD SMART

In Our Not-so Perfect World

- Companies don't want to share their drugs, or to share funding for studies
  - These studies are really hard to do / to get funded
  - Good for patients, less so for companies
  - PCORI might help us out here (but at big cost with our current model)
- Predictive therapeutic Biomarkers (precision medicine) rarely work outside of CF, or very specific cancers
  - Anti-TL1A might have a predictive genetic marker

Precision Medicine in IBD?
Possible Genetic Marker for PRA023/MK7240



Journal of Crohn's and Colitis, Volume 17, Issue Supplement_1, February 2023, Pages i162–i164, https://doi.org/10.1093/ecco-jcc/jjac190.0127

What We Know

- Little or no Prospective, Randomized data on IBD therapy sequencing
- Not entirely clear whether current therapy "polarizes" the immune system, leads to resistance
- Does this mean that specific therapeutic sequences (Which therapy comes next?) actually matter?
- Most of the time we don't consider therapeutic Hx very much
  - Often lost in records elsewhere – frequently change doctors
  - Often constrained by insurance coverage/denials – insurers often don't know therapeutic Hx prior to their coverage – IBD patients change insurer about q 3 years

When does Therapeutic History Matter?

- Anti-TNFα therapy
  - First anti-TNF works the best
  - Increasingly less response to 2nd, 3rd anti-TNF
  - Generally true across biologics
  - Clinical trials will often exclude a patient who has failed 4+ biologics

Biologic Experience Matters for Biologics

- Data here

Even More data here

Clinical Trials Experience

- A phase 3 clinical trial in IBD costs about $20M
- No one wants to bet on repeated biologic failures for their next biologic
- It is common to exclude patients with 3+ failures

Biologic "Experience" is Complicated

- Primary Non-Response (PNR)
  - Was it low trough/rapid clearance/antibodies? More likely if very sick / leaky
  - Was it an inflammation problem?
    Or trying to treat a stricture with anti-TNF?
    (usually lose that fight eventually)
  - Was it mechanism failure? Anti-TNF at good level, did not work?
- Delayed Loss of Response (LOR)
  - Measurable improvement in biomarkers, scan, scope, biopsies
  - Later return of inflammation
    - Some low trough / anti-biologic antibodies/ rapid clearance
    - Some good levels, true mechanism failure
- Often what really happened is not deeply investigated/documented

Biologic Experience Matters Much Less for JAK inhibitors

- Data
- Why?

Is Immune "polarization" a thing?

- Anecdotal reports
  - The patient who develops palmopustular psoriasis on an anti-TNF is rare and different (pictures)
  - Similar response if try a 2nd anti-TNF (more pictures)
  - But does AMAZINGLY well on an anti-IL12/23 or anti-IL23
- By blocking TNF, are we selecting for anti-TNF resistance?
  - Microbes stimluating gut immune system, one pathway blocked
  - Nature finds another way – IL-23 pathway?
  - Does anti-TNF therapy prime (some) patients to respond to anti-IL23?

Data on autoimmune skin disease

Data on serum IL22 in anti-IL23?

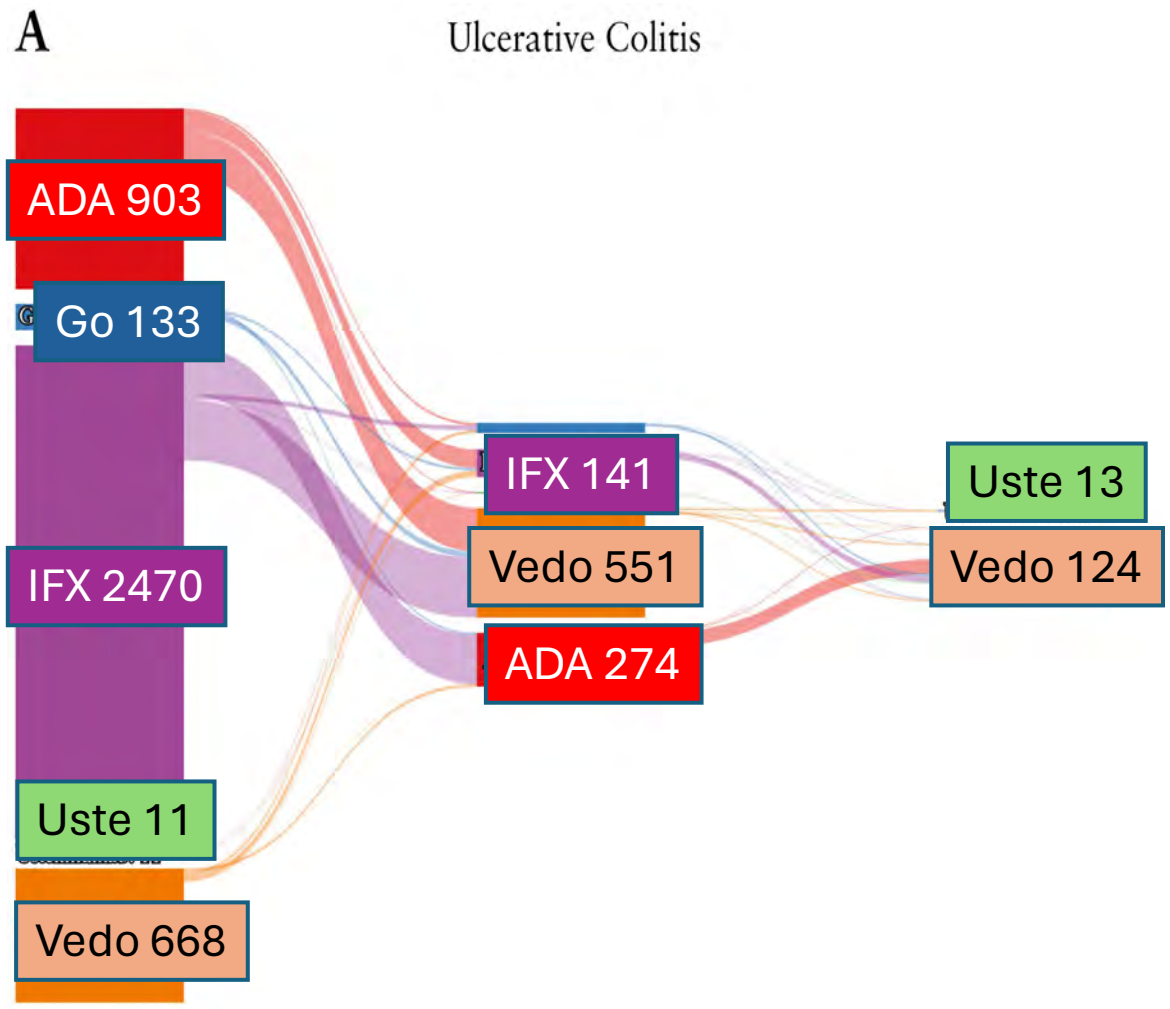
Does Immune "Polarization" Work Both Ways?

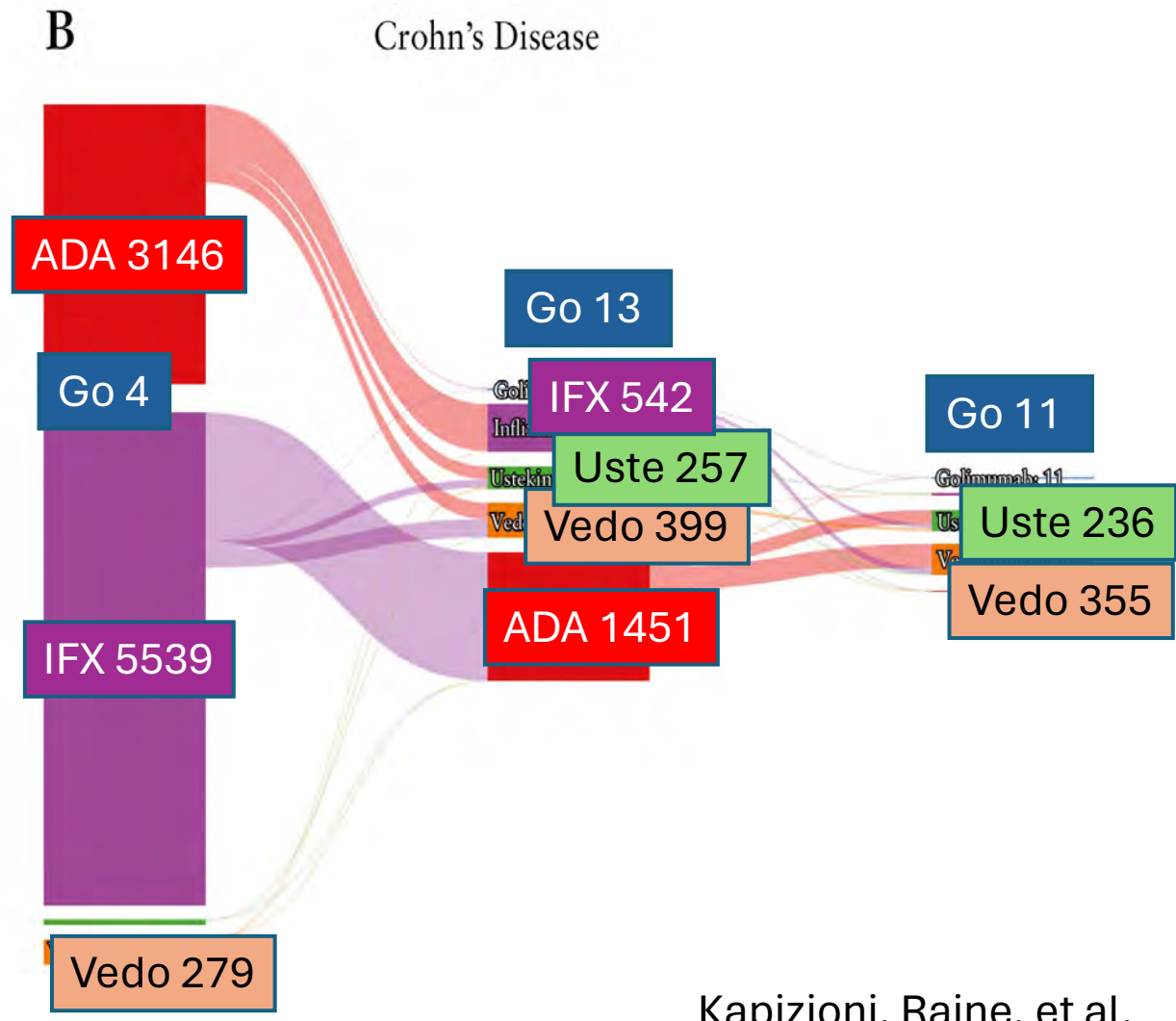
- Does anti-IL-23 mechanistic failure prime patients to respond to anti-TNF?
- Hints, rumors, anecdotes
- Maybe… needs further study

What About Retrospective Data?

- If we had a unified health-care system, we could track who took which IBD drugs in which order, and look at outcomes
- We could determine whether sequence effects matter
- December 2023, *Journal of Crohn's and Colitis*, Kapizioni, Tim Raine, *et al.*, https://doi.org/10.1093/ecco-jcc/jjad203
  Biologic Therapy for Inflammatory Bowel Disease: Real-World Comparative Effectiveness and Impact of Drug Sequencing in 13,222 Patients within the UK IBD BioResource
- Looked at Durability of Biologics without rising inflammation on scope, scan, biomarker, and no surgery or ED visits.
- Type of drug failure coded by local clinician in 106 hospitals.

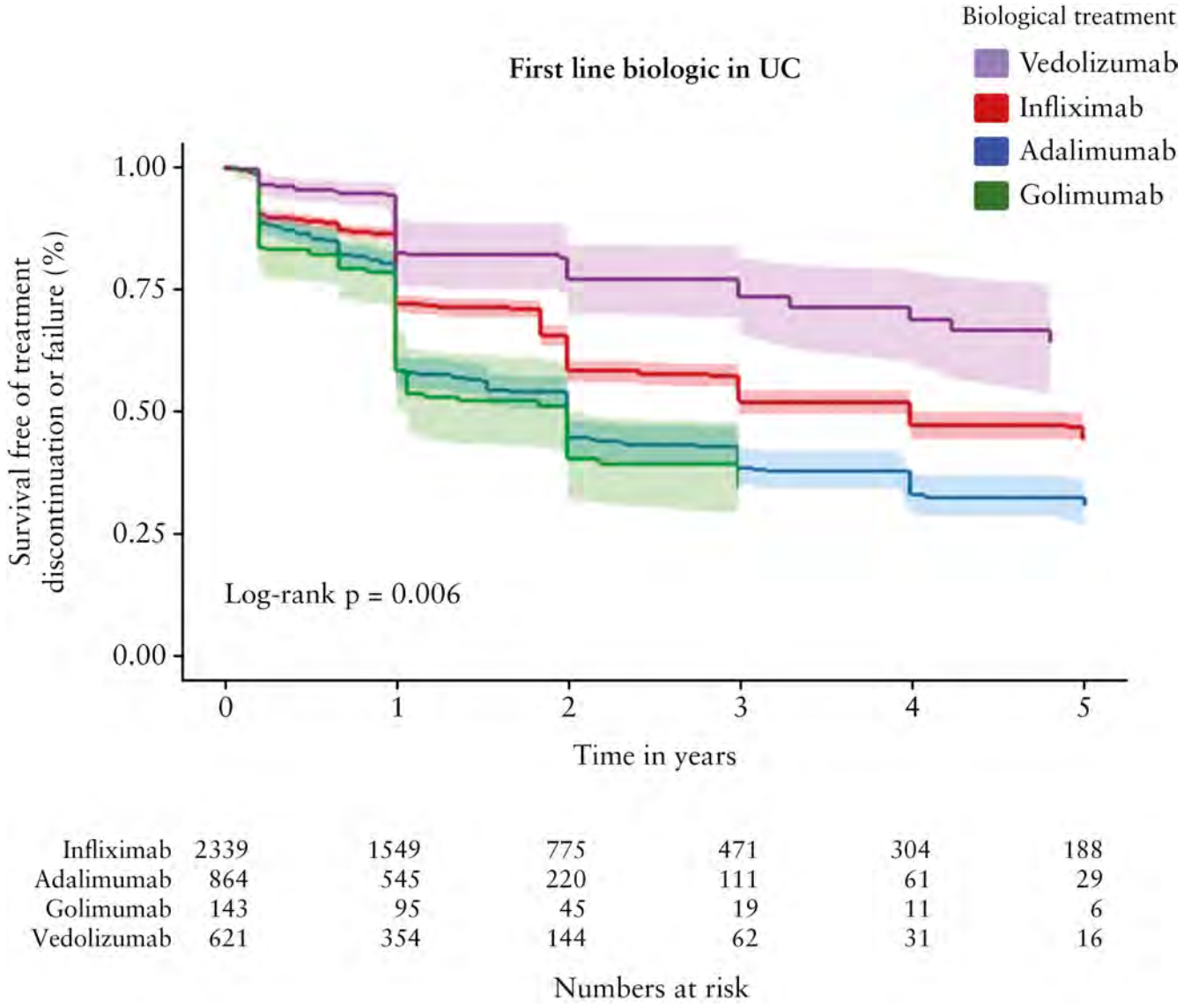
Therapeutic Sequencing for IBD in the UK





Kapizioni, Raine, et al.

How Long Do 1st Line UC Therapies Last?

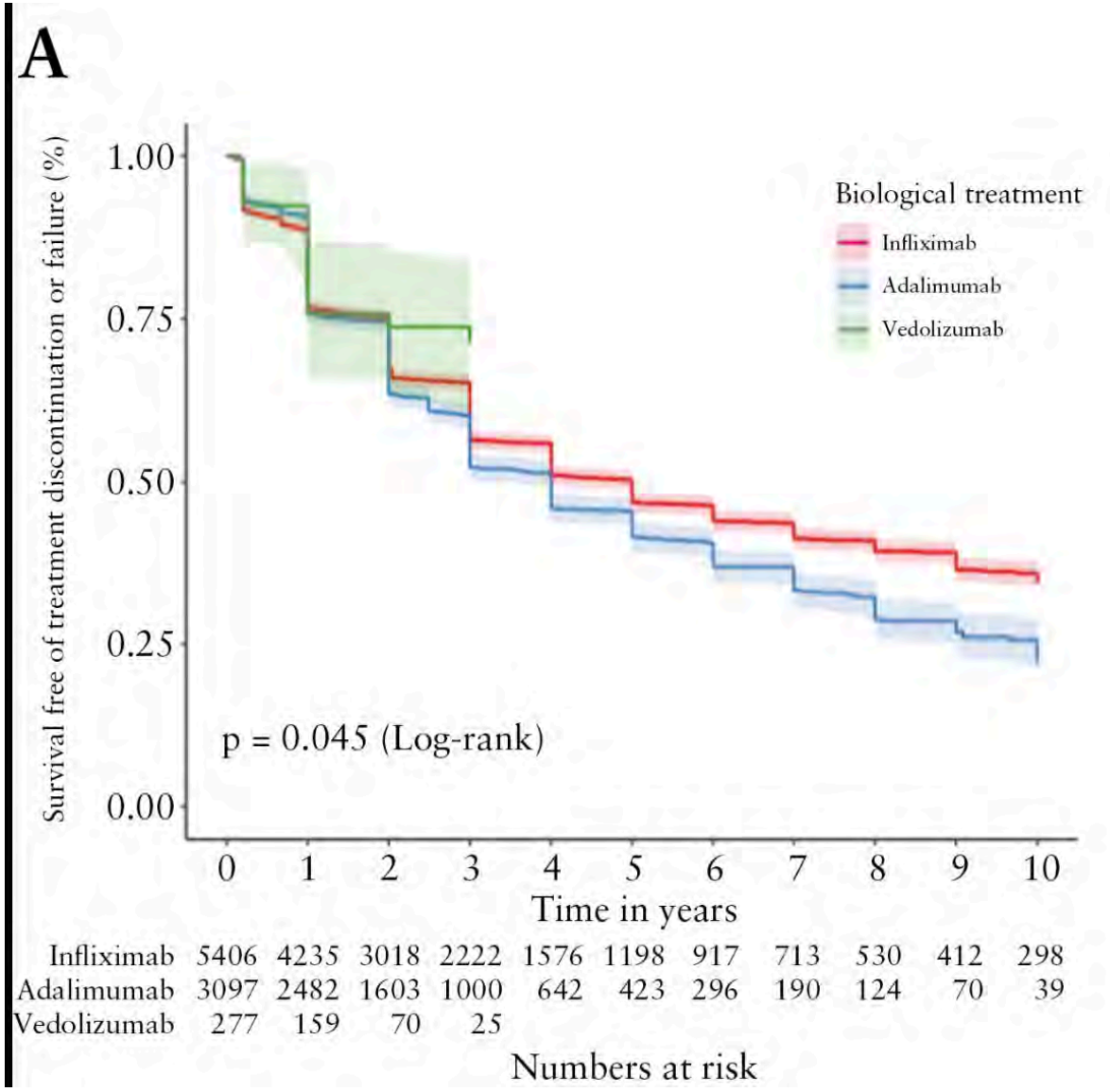


- More than 50% have to switch by year 3
- Vedo starts to pull away after 1 year
- IFX appears a notch better than ADA/GO

NOTE: not randomized.
Vedo patients might be less sick / do better (confounding by indication/ docs smart).

Kapizioni, Raine, et al.

How Long Do 1st Line Crohn's Therapies Last?

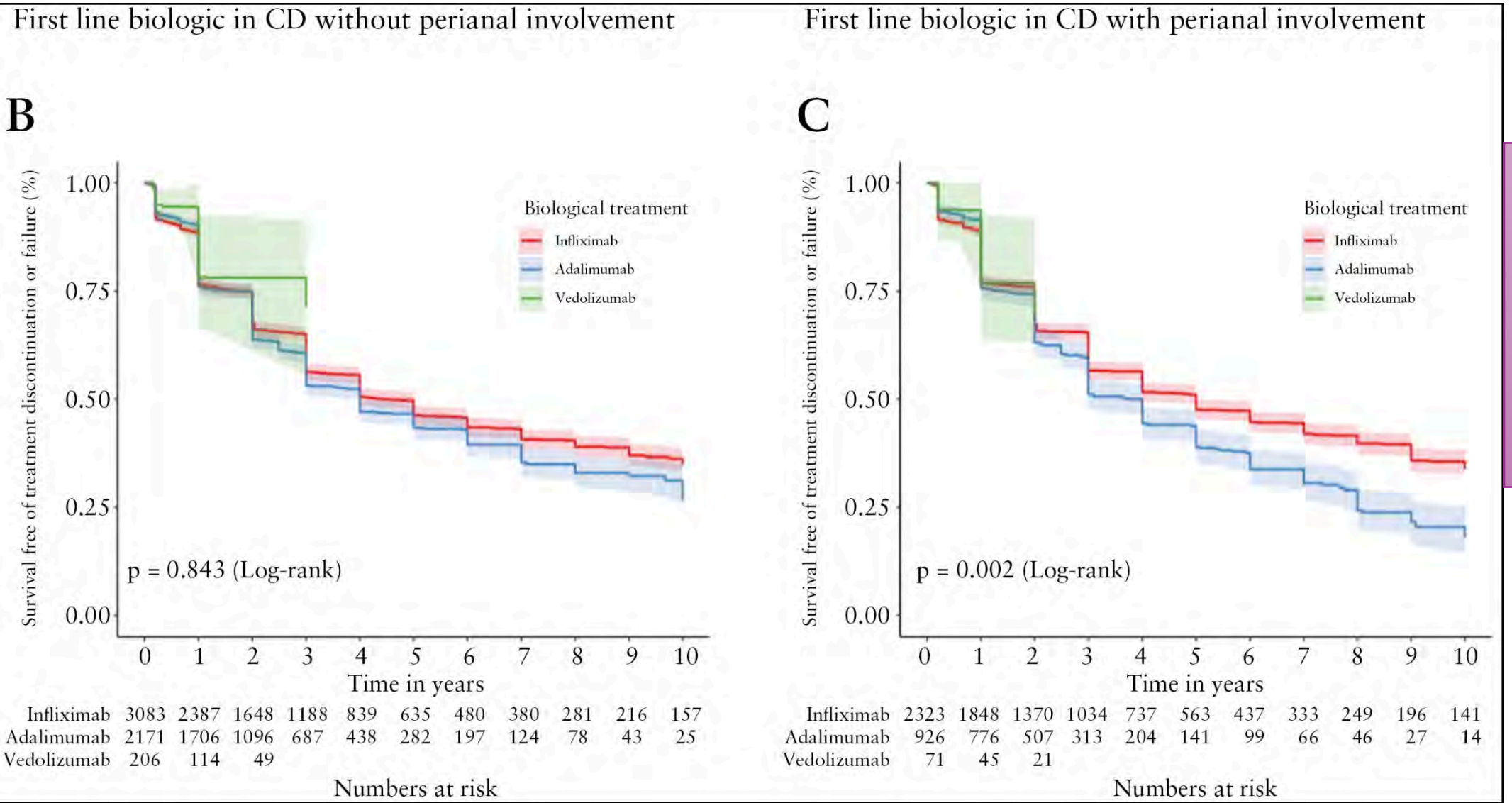


- Big dropoff early – steeper than UC
- More than 50% have to switch by **year 2**
- Vedo possible small advantage after 2 years
- IFX appears a notch better than ADA in the patients who make it to year 5

NOTE: not randomized.
May be treating for inflammation/foiled by strictures not getting better.
Vedo patients might be less sick / do better (confounding by indication/ docs smart).

Kapizioni, Raine, et al.

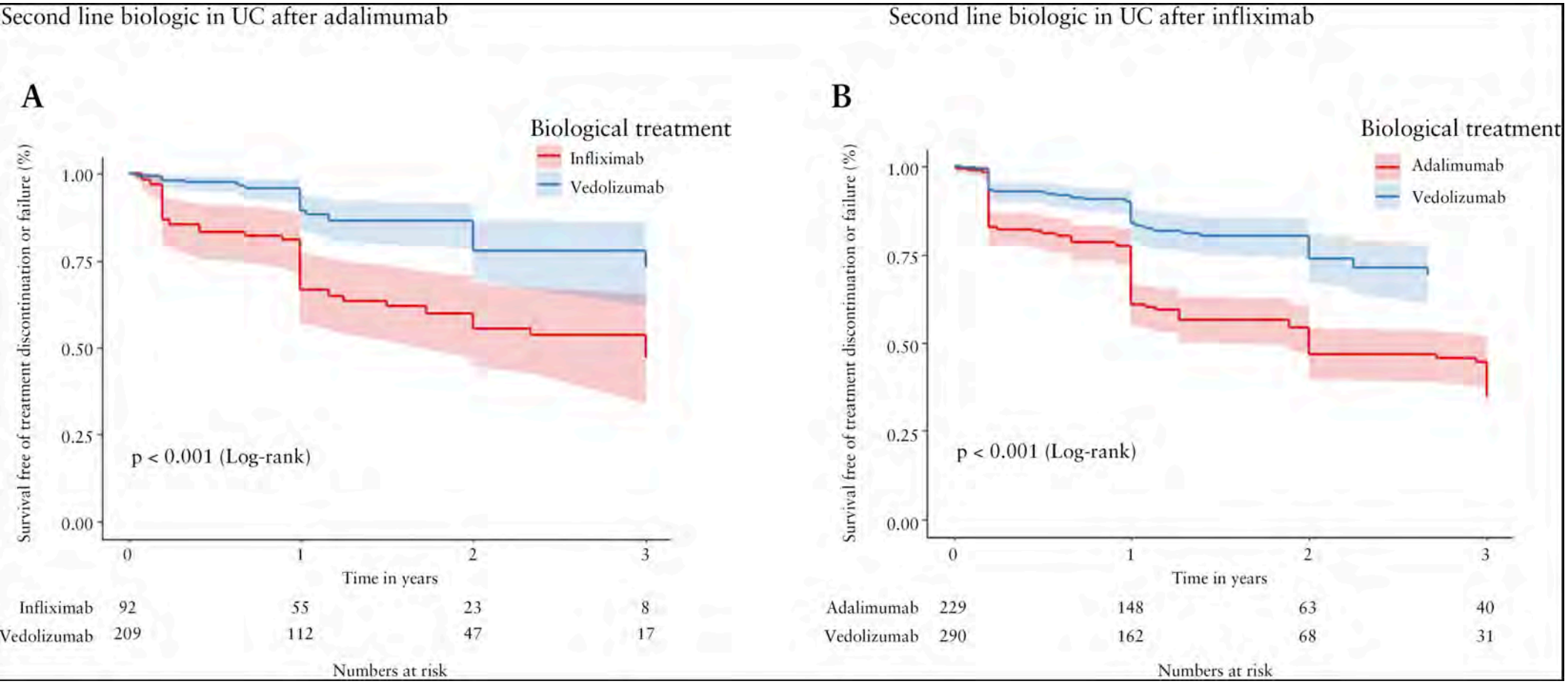
Durability in CD, Depending on Perianal Fistulae



- Vedo **might** do a little better without perianal (NS) involvment in CD.
- IFX has a bigger advantage over ADA in perianal CD

Kapizioni, Raine, et al.

Durability in 2nd line biologic in UC after TNF

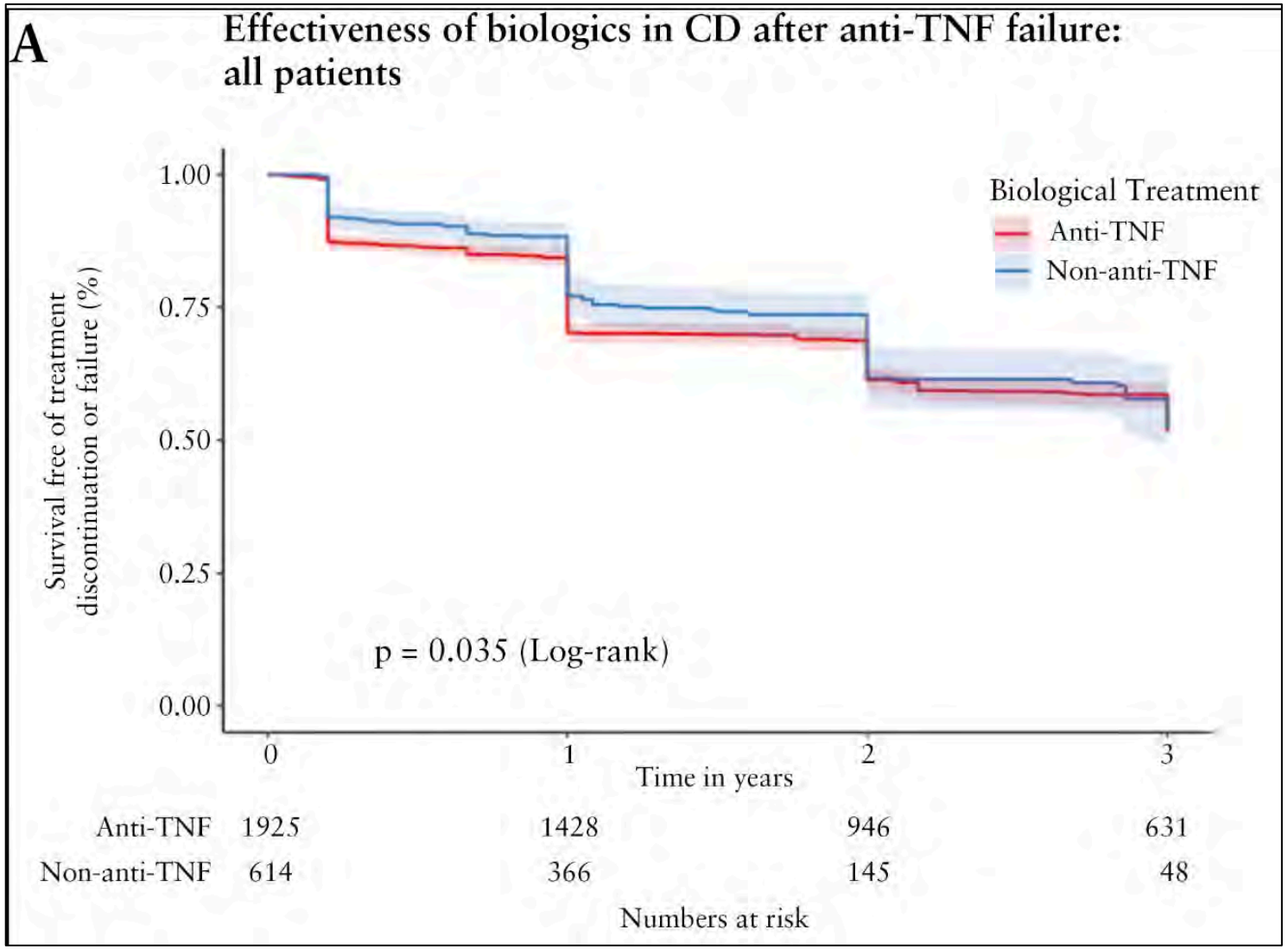


- Switching class (Vedo > anti-TNF) Is a winning 2nd line strategy in UC

NOTE: not randomized

Kapizioni, Raine, et al.

Durability in 2nd line biologic in CD after TNF

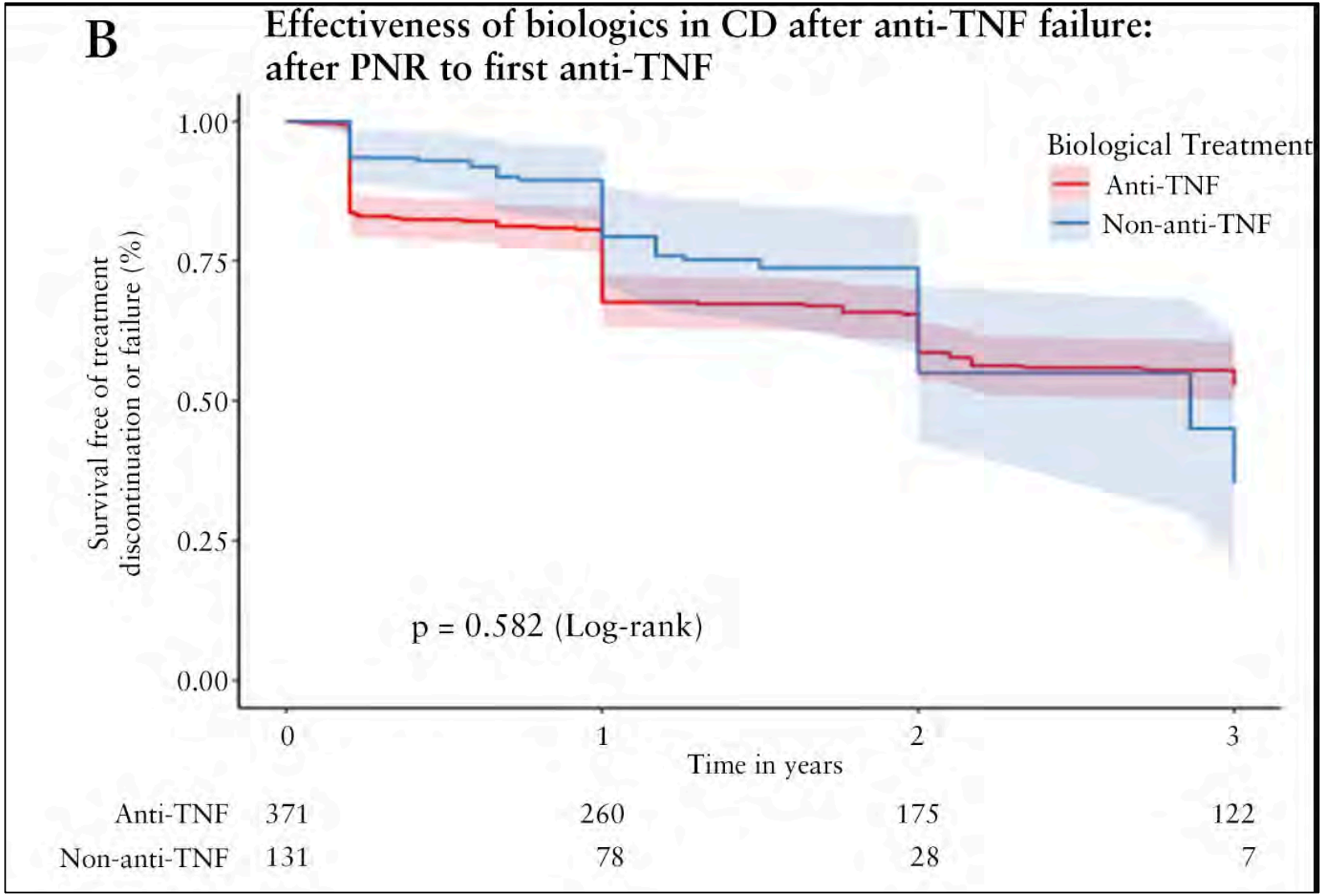


- Switching class (All mechanisms > anti-TNF) appears slightly better (sig) in CD
- contaminated by strictures, type of LOR

NOTE: not randomized

Kapizioni, Raine, et al.

Durability in 2nd line biologic in CD in PNR

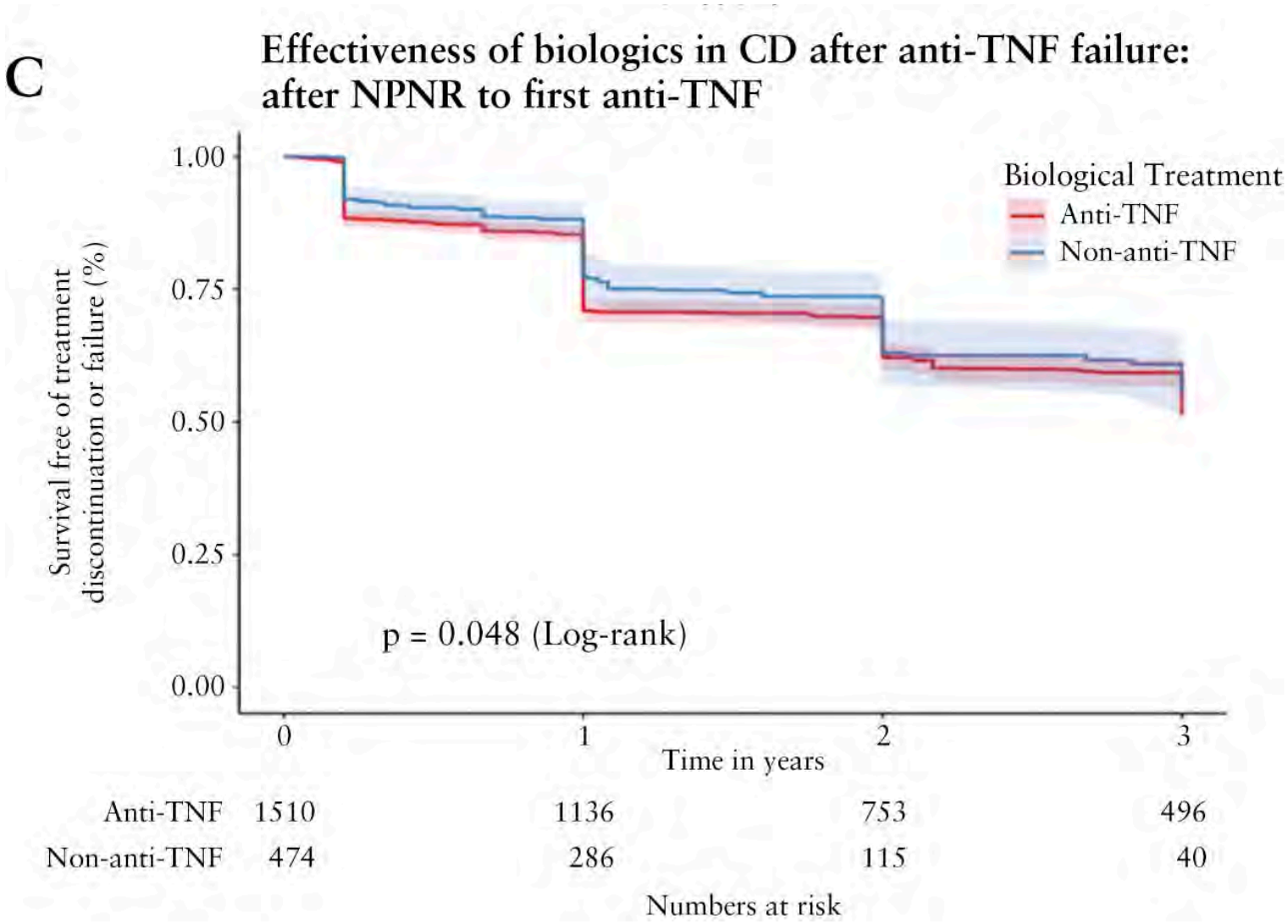


- Maybe an early benefit to switching class, but NS overall

NOTE: not randomized

Kapizioni, Raine, et al.

Durability in 2nd line biologic in CD in Delayed LOR

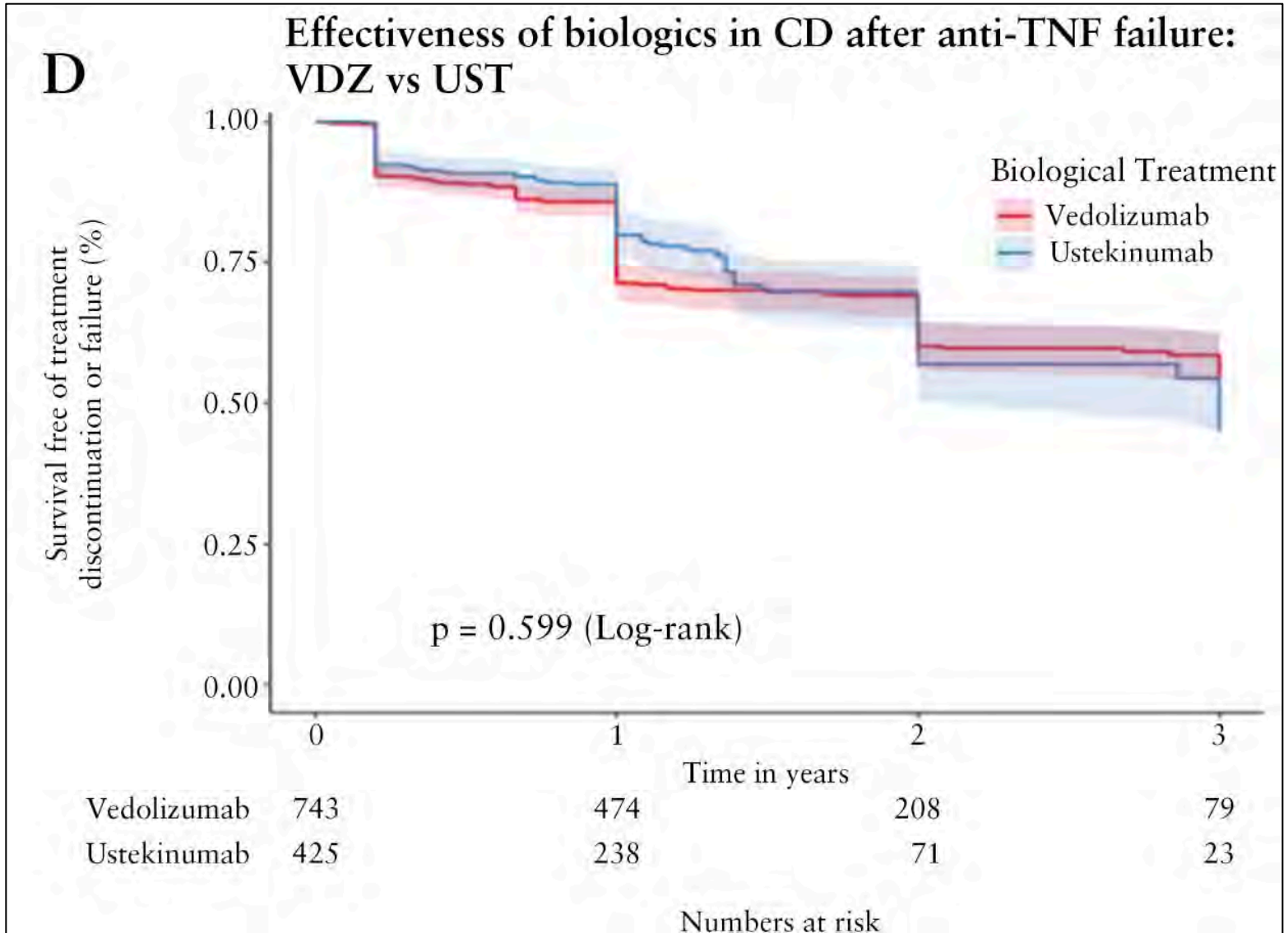


- Significant but small benefit to switching class for 2nd line Rx if delayed LOR/NPNR

NOTE: not randomized

Kapizioni, Raine, et al.

Durability in 2nd line biologic in CD Compared

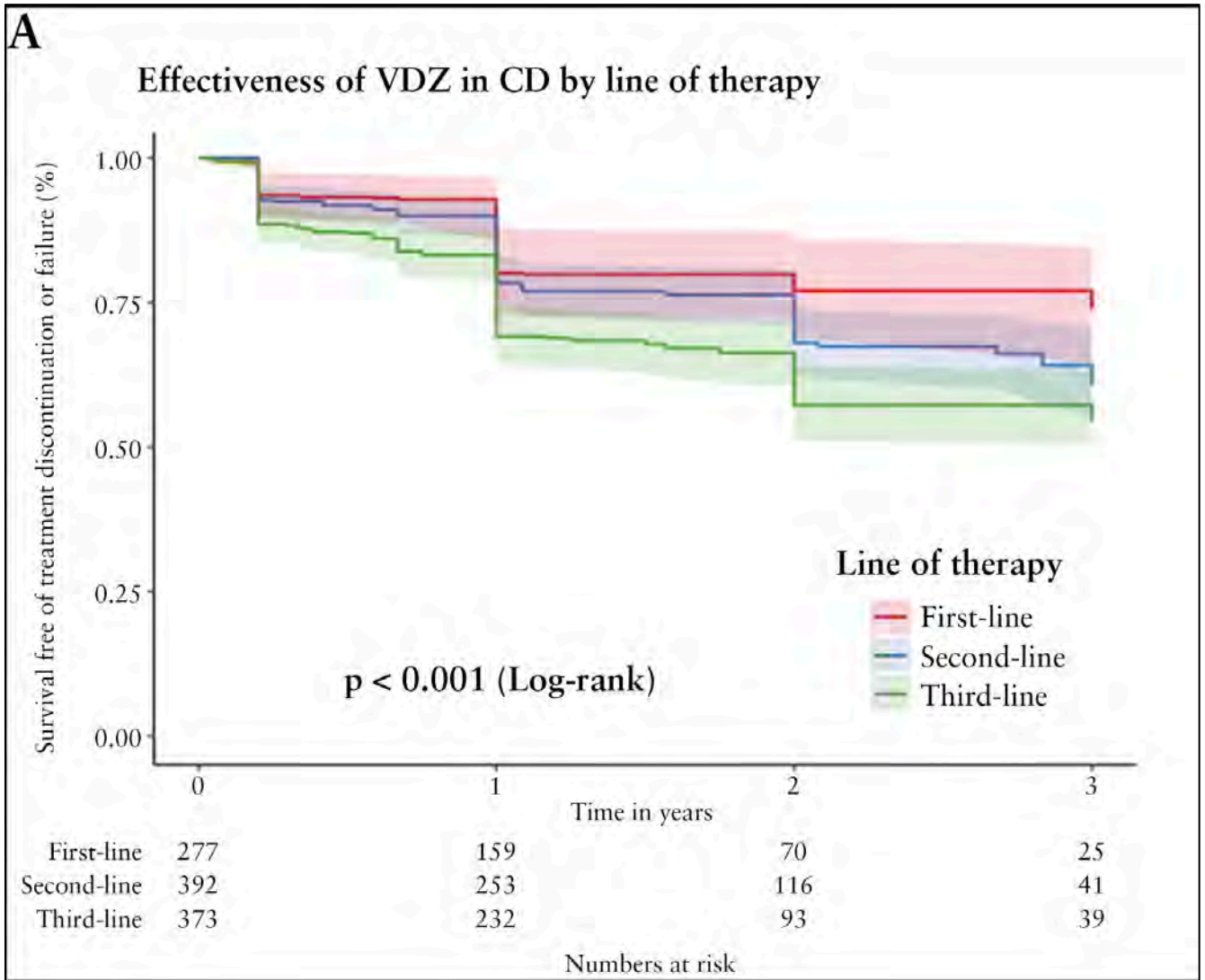


- No significant difference between VDZ vs UST
- Decent numbers for at least 1 year

NOTE: not randomized

Kapizioni, Raine, et al.

Effectiveness of Vedo in CD by Line of Therapy

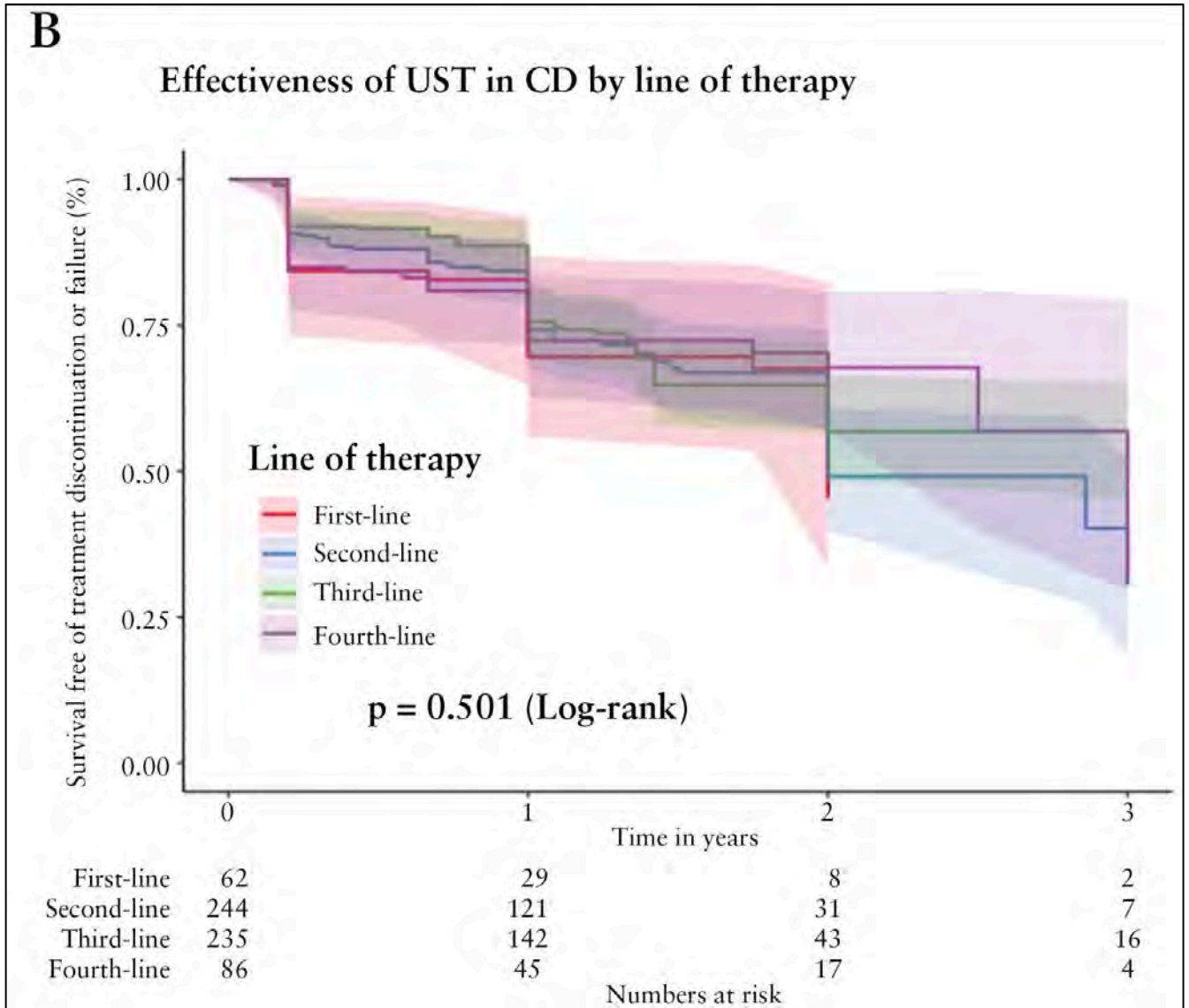


- Use of Vedo earlier in CD
(1^{st} vs 2^{nd} line,
2^{nd} vs 3^{rd} line) is significantly more beneficial
- Decent numbers for at least 1 year

NOTE: not randomized

Kapizioni, Raine, et al.

Effectiveness of Uste in CD by Line of Therapy



- Use of Uste earlier in CD
(1st vs 2nd line,
2nd vs 3rd line) does not seem to make a difference
- Decent numbers for at least 1 year

NOTE: not randomized

Kapizioni, Raine, et al.

Take Home Points from Raine, *et al*.

- Not randomized, but good data from > 13K patients
- Sicker patients (perianal fistulae) may have been treated differently
- BUT, given these caveats
  - Vedo is a good first line in UC > IFX > ADA/GO
  - First line in CD – NS for 2y, then Vedo (not perianal) > IFX > ADA beyond year 2. In perianal CD, IFX = Vedo > ADA beyond year 3
  - For 2nd line in UC – switch class to Vedo > 2nd anti-TNF
  - For 2nd line in CD – small benefit to switch class, more in delayed LOR. NS difference between Vedo vs Uste
  - More benefit to Using Vedo early-line in CD, Uste NS (more like JAKi)

What Do We Know About Sequencing?

- We have no randomized SMART data
- All retrospective data are confounded by
  - Bias from confounding - treat sicker patients with perceived stronger Rx?
  - Near-futility of treating strictures with anti-inflammatory Rx in CD
  - Confusion from role of clearance, antibodies in older anti-TNFs
- But, given the caveats
  - Less benefit to anti-TNFs in 2nd, 3rd line.
  - We should probably switch class early
  - We should use Vedo early, less often in penetrating disease
  - We should about JAKi early in 2nd, 3rd line

Is Immune "Polarization" Real?

- We need more data
  - Is switch from anti-TNF to anti-IL23 especially effective?
  - Or only for folks who develop psoriasis?
  - Is a switch from anti-IL23 to anti-TNF especially effective?
  - How to measure immune "polarization"? – Raja Atreya paper?
- An oncologist enters the chat
  - "Duh, this means you need to combine anti-TNF with anti-IL23, like we do with combination chemotherapy. Hit both mechanisms up front."
  - Not likely until biosimilar Uste in 2025.
  - But an interesting future trial of bio-better SC IFX plus biosim SC Uste?

Is combination therapy for IBD the future?

- Maybe?

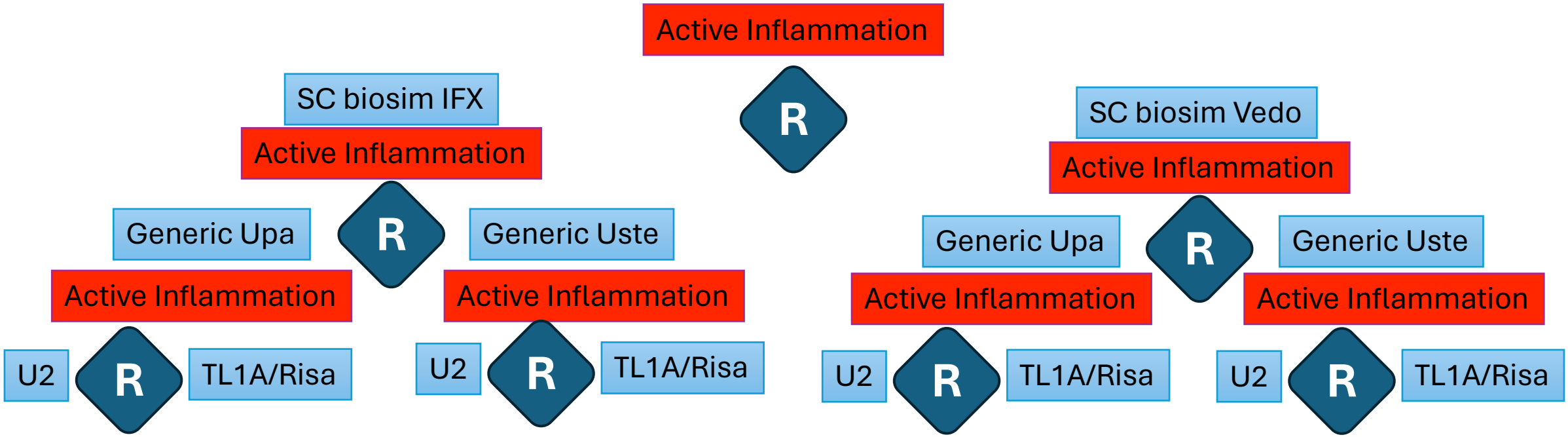
Is Precision Medicine for IBD the Future?

- Maybe not – this is not panning out well for oncology
  - And we think of cancer as a 100% genetic disease (CD ~ 10%)
- NCI-MATCH trial – only 23% had matching mutations to direct Rx
- SHIVA trial
  - 99 patients treated based on mutations – 2.3 m survival
  - 96 patients treated by physician choice (no DNA sequence) - 2m survival
- Estimate: only 1.5% of patients with relapsed and refractory solid tumors will benefit from the precision medicine approach.

What can help us move forward?

- PCORI - comparative effectiveness trials - https://www.pcori.org/
- SMART trial designs - https://evidence.nejm.org/doi/full/10.1056/EVIDe2300031
- Big pragmatic trials - https://rethinkingclinicaltrials.org/
- Enroll everyone with IBD (more like oncology)
  - No placebo, always on an approved effective drug
  - Rigorous definitions of failure (no stricture, yes active inflammation)
  - Rapidly switch from one therapy to the next with no (insurance) delay

Future SMART?



IFX = Infliximab, Vedo = Vedolizumab
Upa = Upadacitinib, Uste = Ustekinumab
U2 = Upadacitinib + Ustekinumab
TL1A = cousin of antiTNFs, now in trials
Risa = Risankizumab
No prednisone....

Subgroup Stories to Watch

- Do Black patients do less well on anti-TNF?
  - 2.5x more hospitalization
  - Higher rates of endoscopic inflammation (62 vs 34%)
  - https://academic.oup.com/ibdjournal/article/29/12/1847/7049417
- Does central obesity in UC mean worse outcomes for anti-TNF?
  - 40% more treatment failure
  - https://journals.sagepub.com/doi/full/10.1177/1060028019900660?casa_token=Ztvc6zAuCDkAAAAA%3Au-jkytnIx5-yPCSgRZb1EaSgcg34vsuynRze8F9GIlBdR5rlvND0PVYSJgmTdiDoWvnc3-uEtxfT-A

Take Home Points

- We know remarkably little about the best sequencing of IBD Rx
- There is retrospective evidence that later biologics work less well
- Vedo and anti-TNFs (especially) benefit from being used early
- Switching class upon IBD therapy failure often works better
  - Except for strictures – scan and scope – inflammation without stricture
- Immune polarization (by anti-TNFs and anti-IL12/23) might be real
  - Possible case for combination Rx in some patients
- We need the comparative effectiveness studies that pharma is not incentivized to do – PCORI and SMART designs

CME/MOC Question:

Based on the UK IBD BioResource retrospective data on over 13,000 IBD patients on biologics, if a patient fails first-line infliximab after 2 years of remission, what should your 2nd line therapy be?

A. Depends on antibody level
B. Vedolizumab
C. Risankixumab
D. Adalimumab

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CME/MOC Answer

Based on the UK IBD BioResource retrospective data on over 13,000 IBD patients on biologics, if a patient fails first-line infliximab after 2 years of remission, what should your 2nd line therapy be?

A. Depends on antibody level – did not matter
B. **Vedolizumab – significantly better durability than ADA**
C. Risankizumab – not FDA approved for UC
D. Adalimumab – significantly worse 2nd line after IFX – switch class

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