Objectives for the Use of New Therapies

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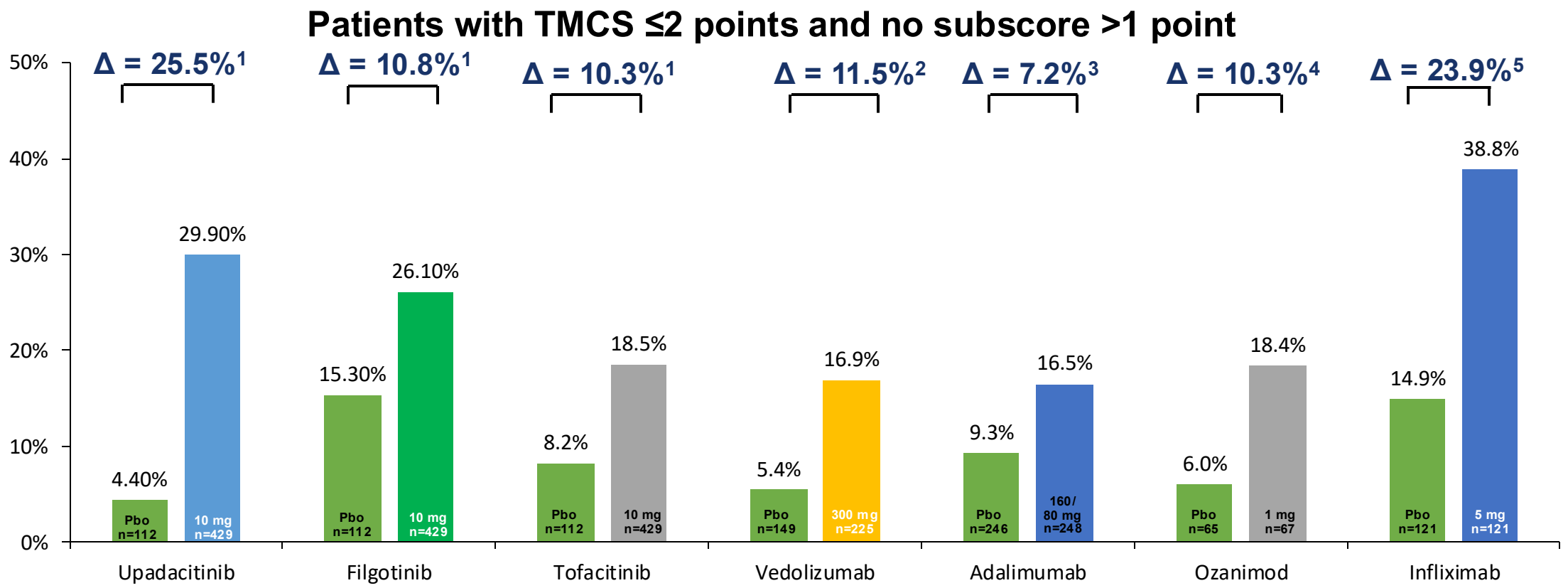
Disclosures

- Personal fees were received from Abbvie, Amgen, Arena, Biogen, Bristol Meyers Squibb, Celgene, Celltrion, Falk, Ferring, Fresenius Kabi, Galapagos, Gilead, IMAB, Janssen, Lilly, Morphic, MSD, Mylan, Novartis, Pfizer, Protagonist, Provention Bio, Roche, Sandoz/Hexal, Shire, Takeda, Theravance, Ventyx

The Proportion of Patients with UC Reaching Remission



Note: No direct head-to-head data available – caution advised when comparing data across clinical studies

Caution should be used when comparing across clinical trials due to differences in trial design, Upadacinitib and Ozanimod

Pbo, placebo; TMCS, Total Mayo Clinic Score. Source: Etrasimod: Post-hoc analysis. Δ=% difference from placebo estimated using Mantel-Haenszel method adjusted with current oral corticosteroid use and prior exposure to TNFα antagonists. 1. Sandborn, et al. *N Engl J Med*. 2017; 2. Feagan, et al. *N Engl J Med*. 2013; 3. Sandborn, et al. *Gastroenterology*. 2012; 4. Sandborn, et al. *N Engl J Med*. 2021; 5. Rutgeerts, et al. *N Engl J Med*. 2005, 6. Feagan et al., *Lancet* 2021, Danese et al. *N Engl J Med*2022

Regulatory advice from the FDA and the EMA on clinical trials in IBD

- **General principles:**
  - Efficacy assessment should be based on[1–3]:

PROs to evaluate symptoms and signs

AND

Endoscopy[†] to evaluate mucosal inflammation (based on evidence that resolution of mucosal inflammation is associated with improved long-term outcomes)

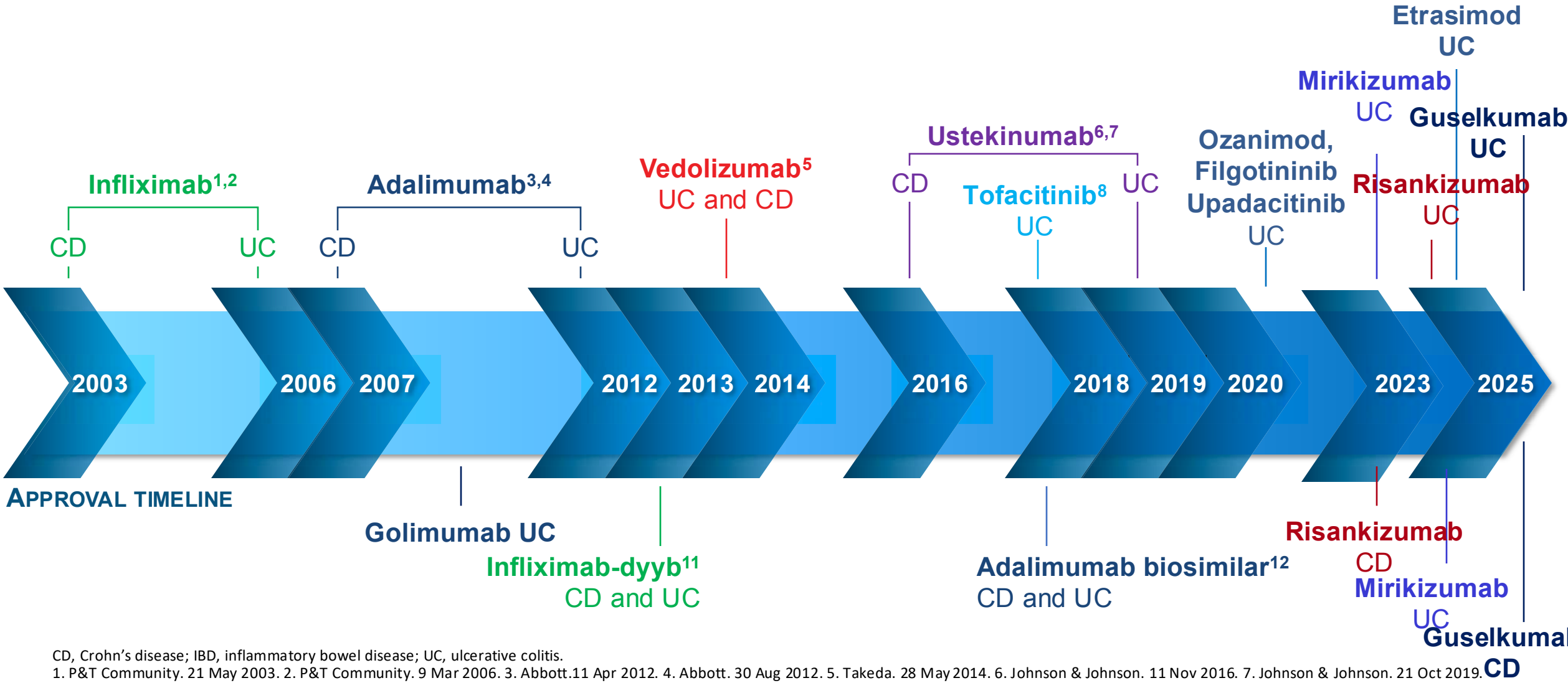
  - CDEIS or SES-CD/Mayo ES are accepted for evaluation of mucosal inflammation[1]
  - Fully validated PRO measures are needed[1–3] but are not yet available[4]

[†]Endoscopic assessment should be documented by the endoscopist performing the procedure, and, ideally, by blinded central readers reviewing video recordings of the procedure[3]; mucosal healing claims must be based on histological as well as endoscopic assessment (which requires validation).[3]

CDEIS, Crohn's Disease Endoscopic Index of Severity; EMA, European Medicines Agency; FDA, Food and Drug Administration; PRO,patient-reported outcome; SES-CD, Simple Endoscopic Score for Crohn's Disease.

1. EMA guideline on the development of new medicinal products for the treatment of Crohn's disease. Available at: https://wwwema.europa.eu/en/documents/scientific-guideline/guideline-development-new-medicinal-products-treatment-crohns-disease-revision-2_en.pdf Accessed; March 2022; 2. EMA guideline on the development of new medicinal products for the treatment of ulcerative colitis. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-development-new-medicinal-products-treatment-ulcerative-colitis-revision-1_en.pdf Accessed: March 2022; 3. FDA ulcerative colitis: Clinical trial endpoints guidance for industry. Available at: https://www.fda.gov/files/drugs/published/UlcerativeColitis--Clinical-Trial-Endpoints-Guidance-for-Industry.pdf Accessed: March 2022; 4. Williet N, et al. *Clin Gastroenterol Hepatol.* 2014;12:1246–56.e6.

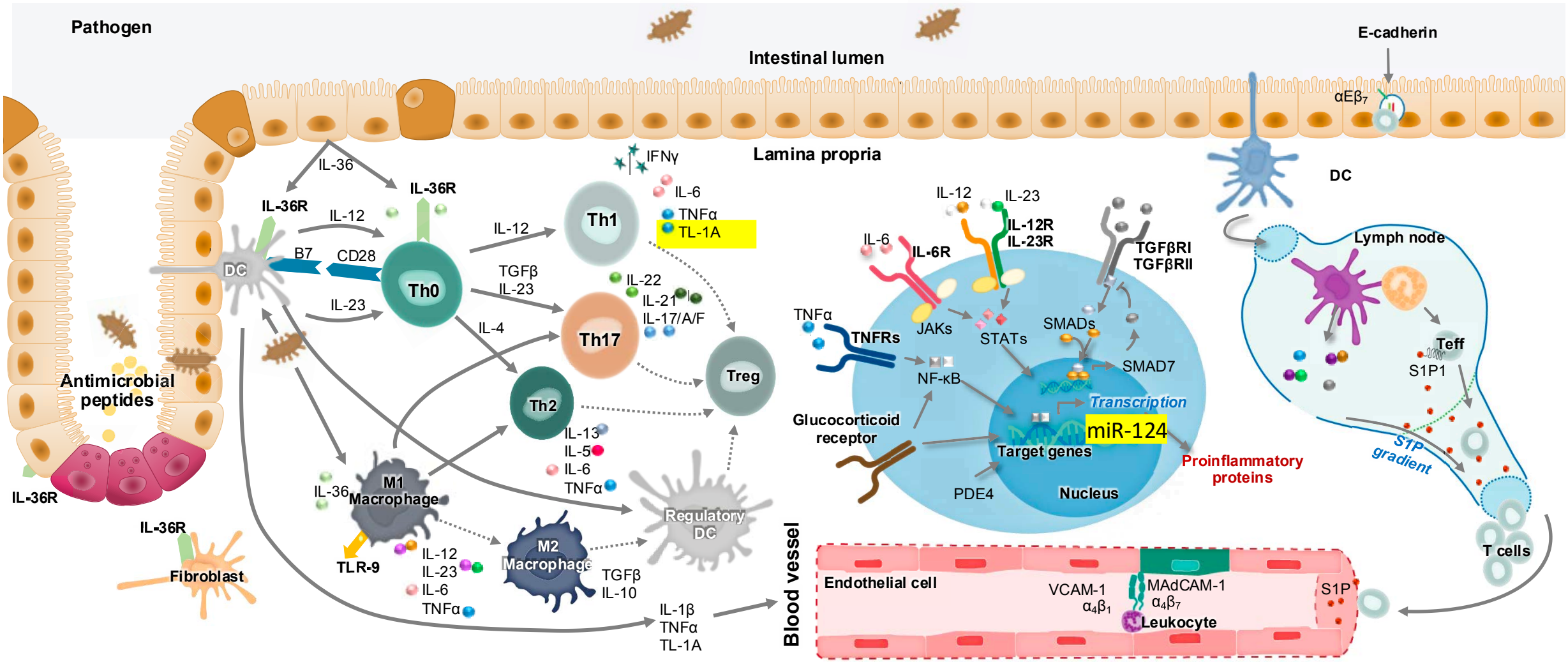
With expanding therapeutic options in IBD, we now have more choices for first-line treatment



CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

1. P&T Community. 21 May 2003. 2. P&T Community. 9 Mar 2006. 3. Abbott.11 Apr 2012. 4. Abbott. 30 Aug 2012. 5. Takeda. 28 May 2014. 6. Johnson & Johnson. 11 Nov 2016. 7. Johnson & Johnson. 21 Oct 2019. 8. Pfizer. 1 Aug 2018. 9. Pérez-Jeldres T, et al. Front Pharmacol. 2019;10:212. 10. Rawla P, et al. J Inflamm Res. 2018;11:215-26. 11. Cision PR Newswire. 10 Sep 2013. 12. Sandoz. 27 Jul 2018.

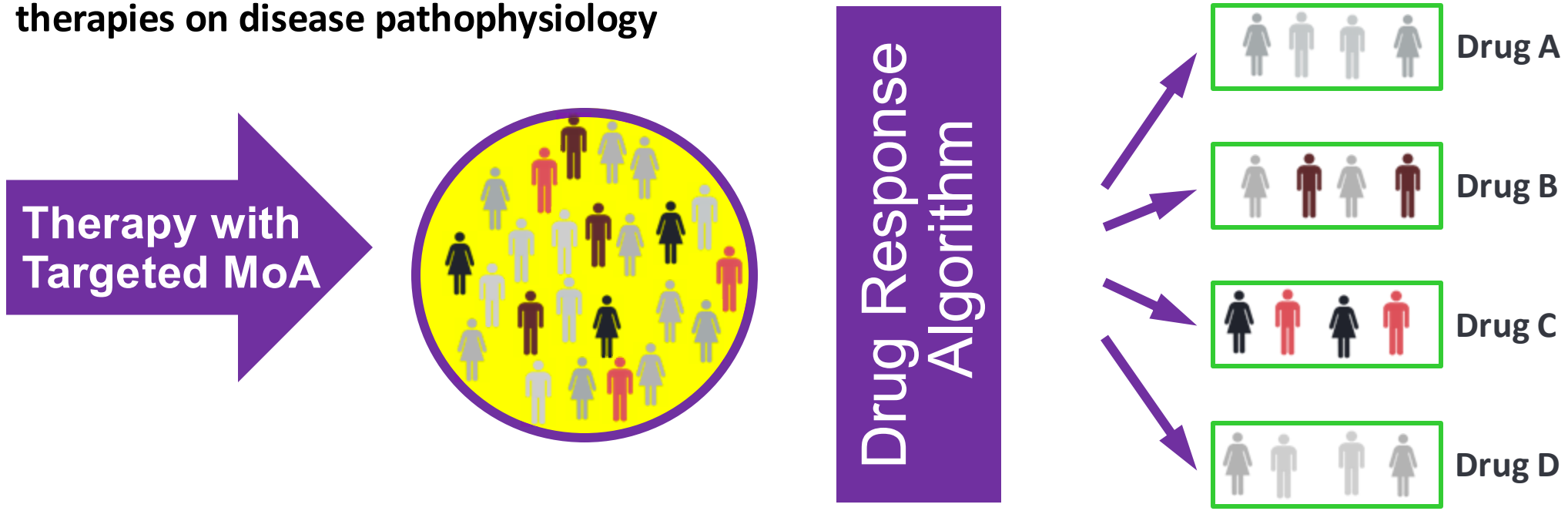
Therapeutic Targets in the Diverse Pathophysiology of IBD



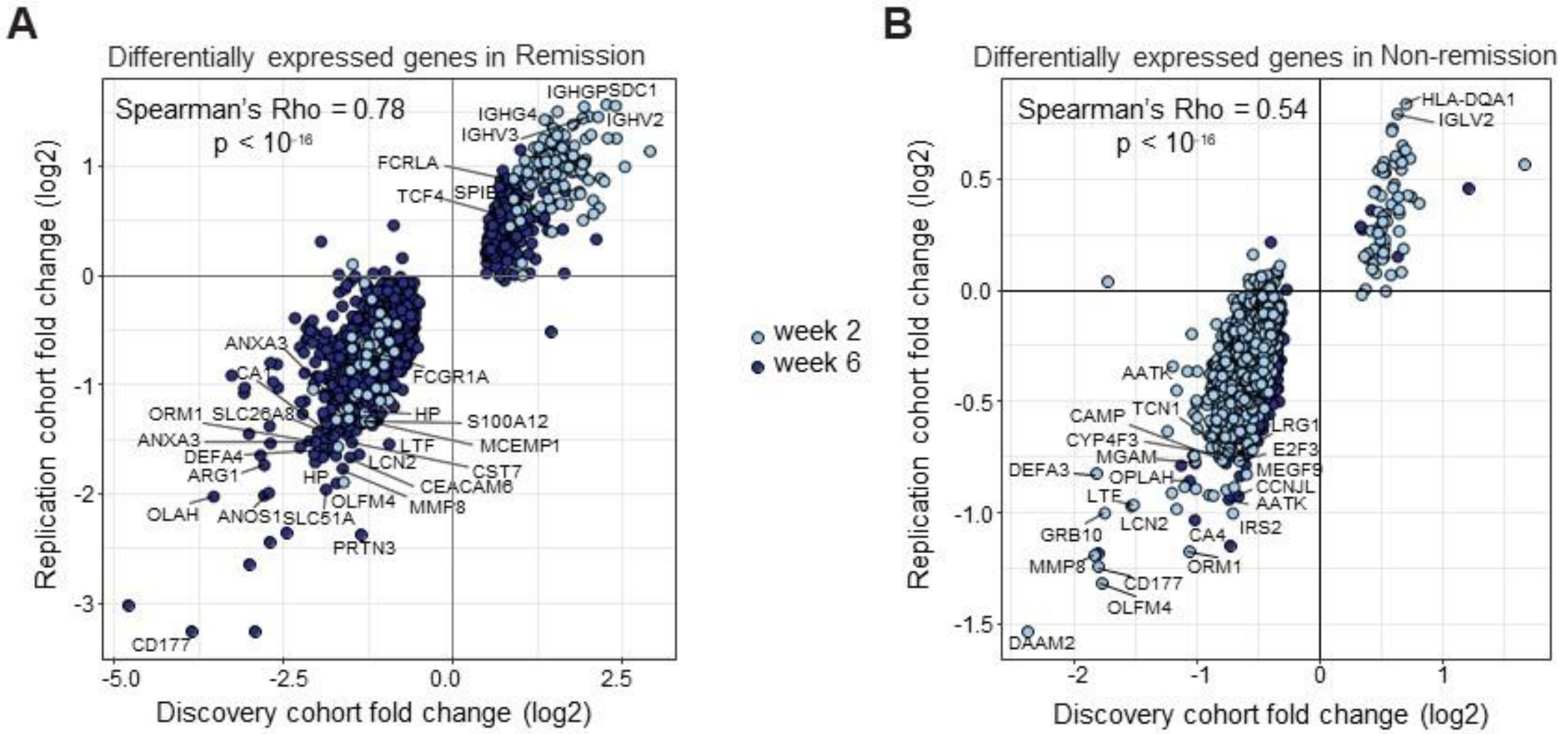
Different Response Rates – Different Pathophysiologies

Assignment of Drug Specific Transcriptome Changes – A Step toward precision medicine

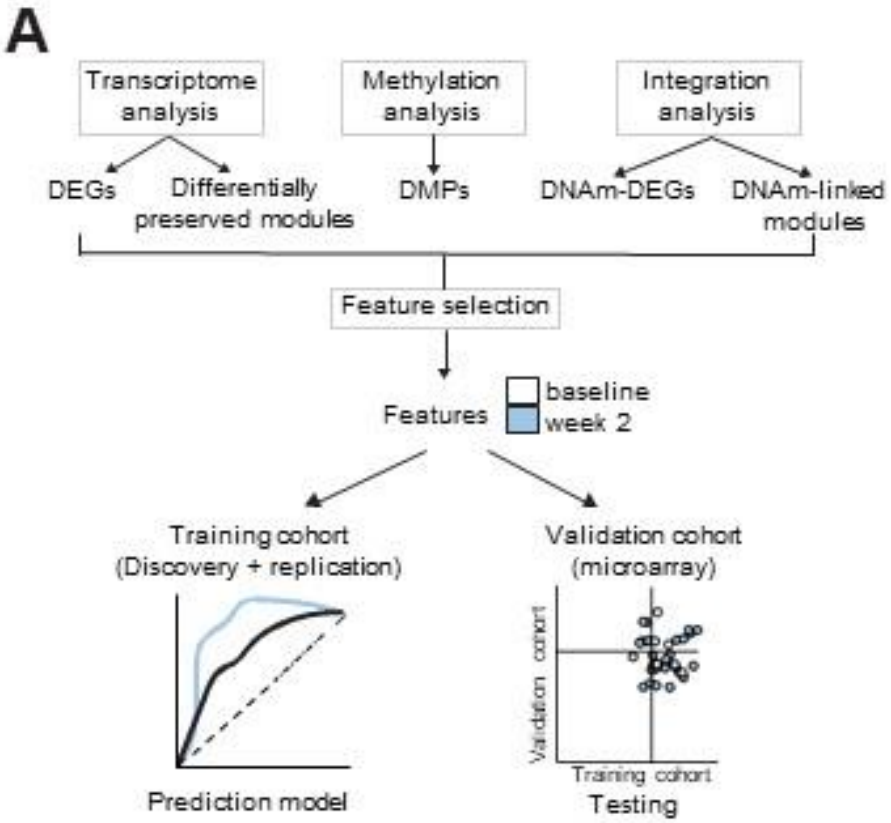
***ex post* prediction – adapted choice algorithm through impact of targeted therapies on disease pathophysiology**

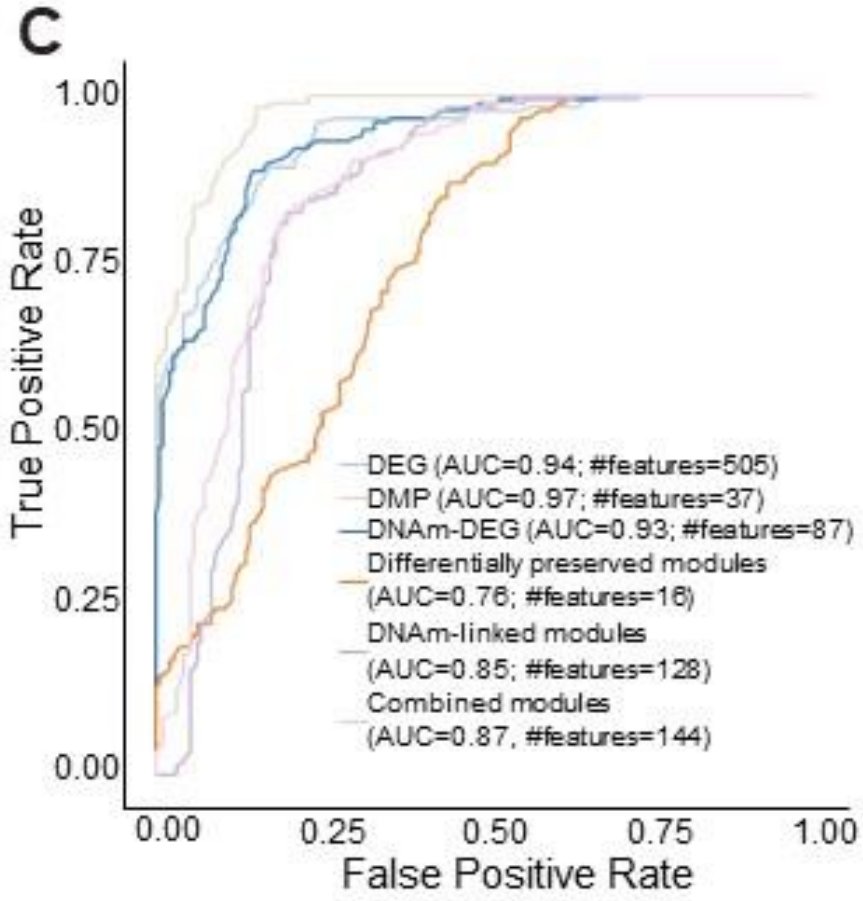


Replication



Prediction


A
Transcriptome analysis
Methylation analysis
Integration analysis
DEGs
Differentially preserved modules
DMPs
DNAm-DEGs
DNAm-linked modules
Feature selection
Features
baseline
week 2
Training cohort
(Discovery + replication)
Validation cohort
(microarray)
Validation cohort
Training cohort
Prediction model
Testing


C
True Positive Rate
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
False Positive Rate
DEG (AUC=0.94; #features=505)
DMP (AUC=0.97; #features=37)
DNAm-DEG (AUC=0.93; #features=87)
Differentially preserved modules
(AUC=0.76; #features=16)
DNAm-linked modules
(AUC=0.85; #features=128)
Combined modules
(AUC=0.87, #features=144)

Conflicting Confounders

CD Studies Have Observed Higher Rates of Induction of Remission With Biologics in Early CD

Specifically in CD, earlier disease intervention may be associated with improved efficacy

Aim
Investigate the efficacy of biologics in patients with short-duration disease vs those with long-duration disease

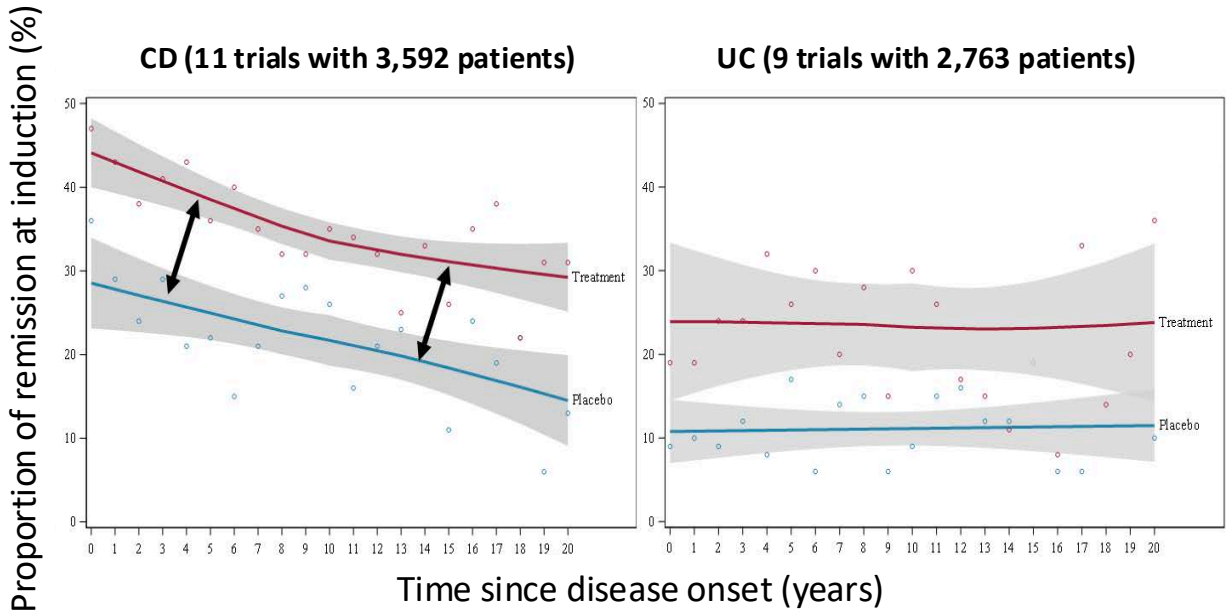
Methods
Systematic review and individual patient data meta-analysis included eligible studies of patients with IBD; 16 CD and 9 UC studies were identified

Primary outcome
Proportion of induction of remission by biologics in short-duration* vs long-duration† patients with IBD

CD trials
N=3,592

Induction of remission
Active arm: 37.8%
Placebo arm: 26.5%

Pooled rate of induction of remission
Short duration: 41.4%
Long duration: 29.8%
OR: 0.75 (95% CI 0.61–0.92)



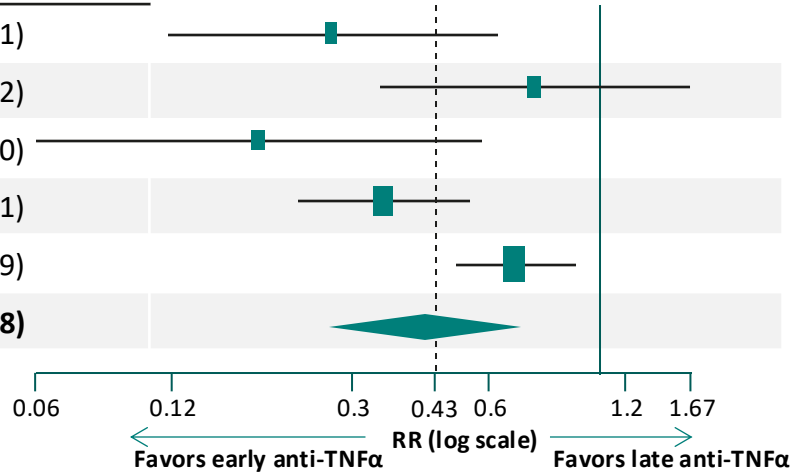
Patients with early CD achieved higher rates of remission with a shorter disease duration compared with a longer disease duration, indicating duration of disease modulates response to therapy

*≤18 months; †>18 months.
CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; UC, ulcerative colitis.
Ben-Horin S, et al. Gastroenterology. 2022;162:482–94.

Effective Biologic Therapy Within 3 Years Since Diagnosis Reduced the Need for Surgery and the Rate of Disease Progression by ~50%

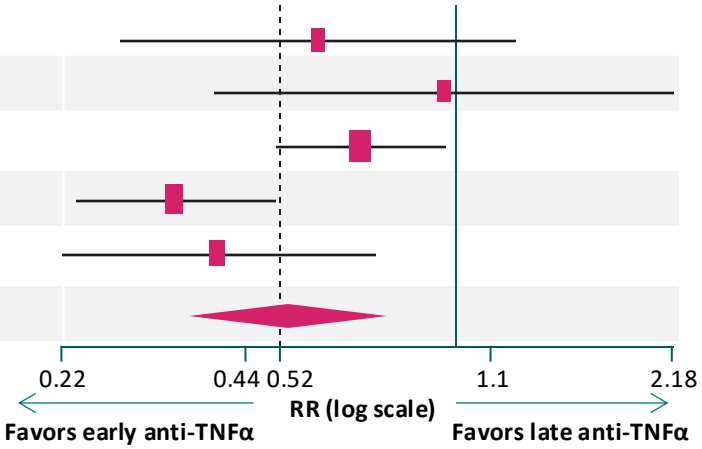
Risk of surgery

Studies	Estimate (95% CI)
De Chambrum et al. 2015	0.268 (0.116–0.621)
Nuji et al. 2015	0.762 (0.347–1.672)
Ma et al. 2016	0.185 (0.060–0.570)
Oh et al. 2017	0.349 (0.225–0.541)
Frei et al. 2019	0.682 (0.501–0.929)
Overall (p=0.013)	**0.431 (0.266–0.698)**



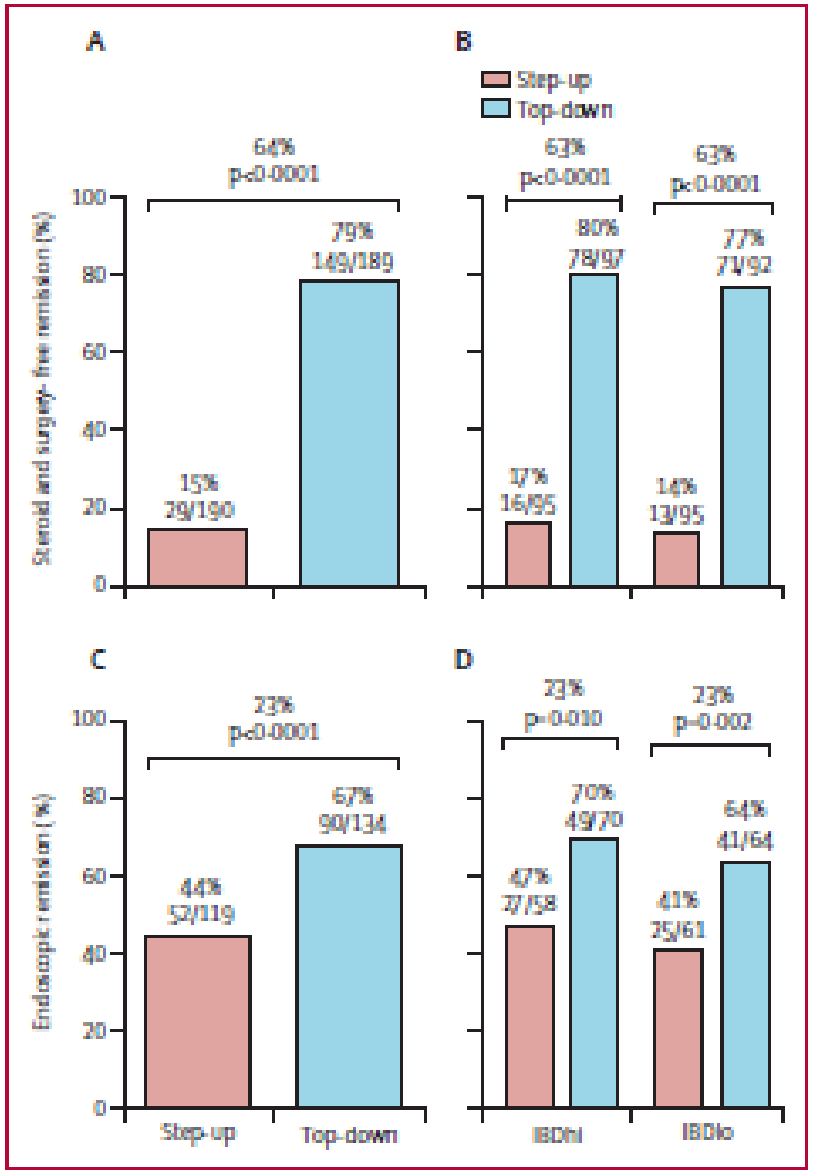
Risk of disease progression

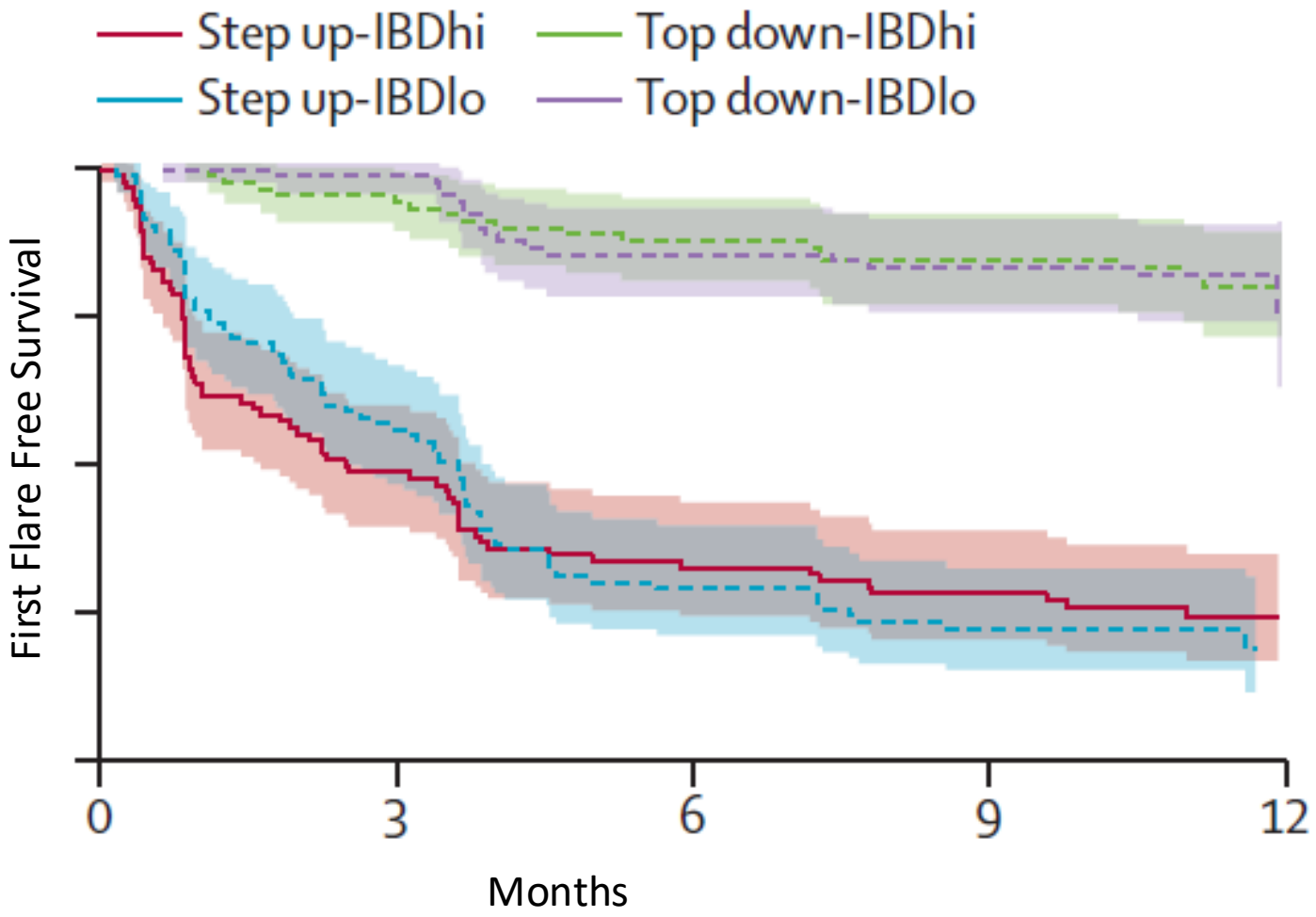
Studies	Estimate (95% CI)
Colombel et al. 2014	0.575 (0.273–1.210)
De Chambrum et al. 2015	0.922 (0.389–2.184)
Ma et al. 2016	0.674 (0.491–0.927)
Oh et al. 2017	0.336 (0.231–0.488)
Frei et al. 2019	0.395 (0.220–0.709)
Overall (p=0.034)	**0.516 (0.355–0.750)**



Systematic review and meta-analysis of 11 studies (N=2,501).
CI, confidence interval; RR, relative risk; TNFα, tumor necrosis factor-α.
Hamdeh S, et al. Inflamm Bowel Dis. 2020;26:1808–18.

Early IFX beats the Step Up Paradigm



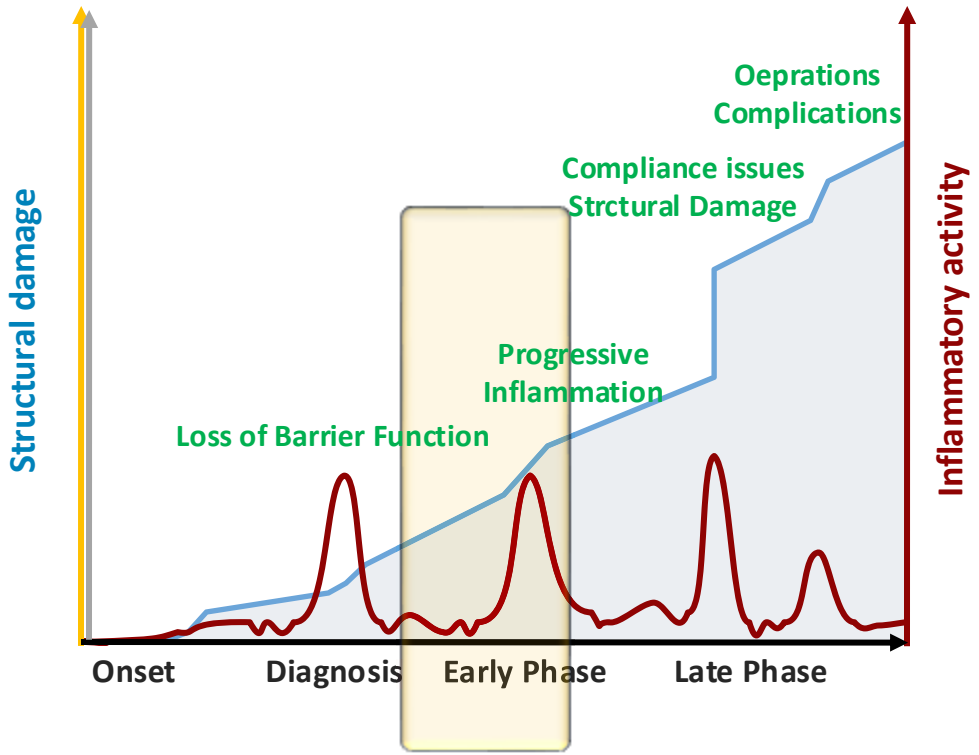


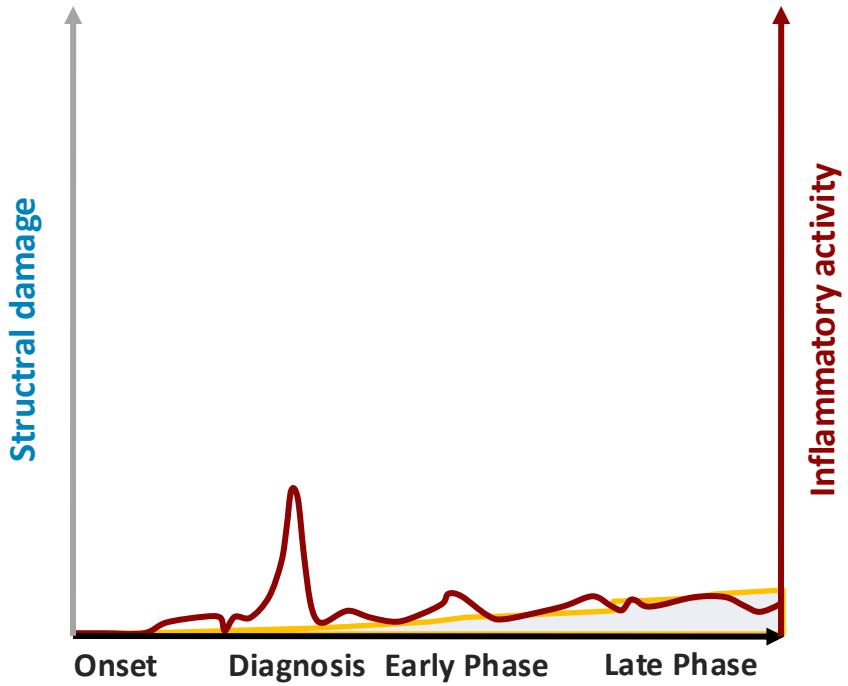
Noor NM, Lancet Gastroenterol Hepatol 2024; 9: 415–27

Use the „Window of Opportunity“

Chronic inflammatory activity leading to structural damage

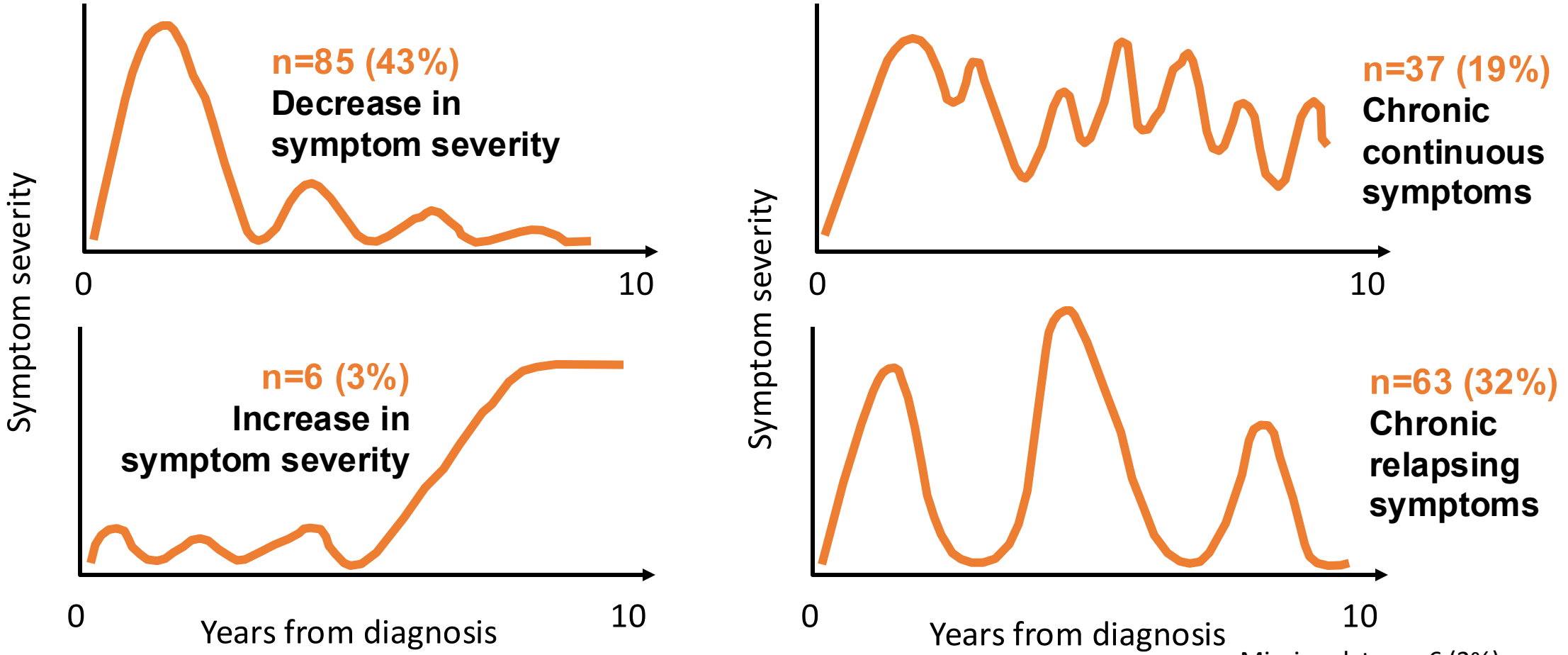
Early „T2T“ reduces/controls inflammation and prevents structural damage





Pariente B, et al. *Inflamm Bowel Dis* 2011;17:1415–22; Colombel JF, et al. *Gastroenterology* 2017;152:351–61.

CD disease course



Missing data: n=6 (3%)

>50% of all CD patients have ongoing disease activity[2]

Solberg IC, et al. *Clin Gastroenterol Hepatol* 2007;5:1430-1438.

UC is a progressive disease

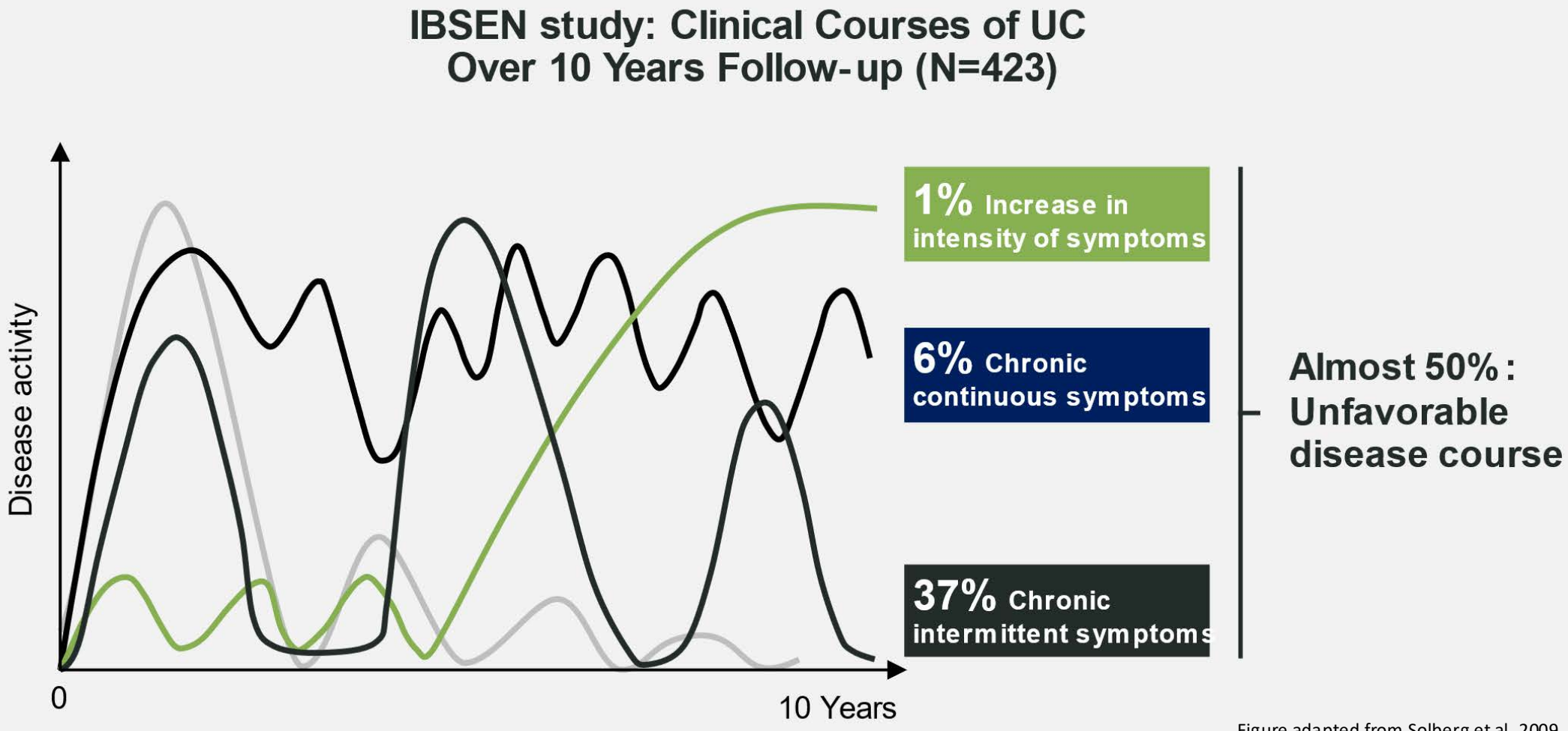
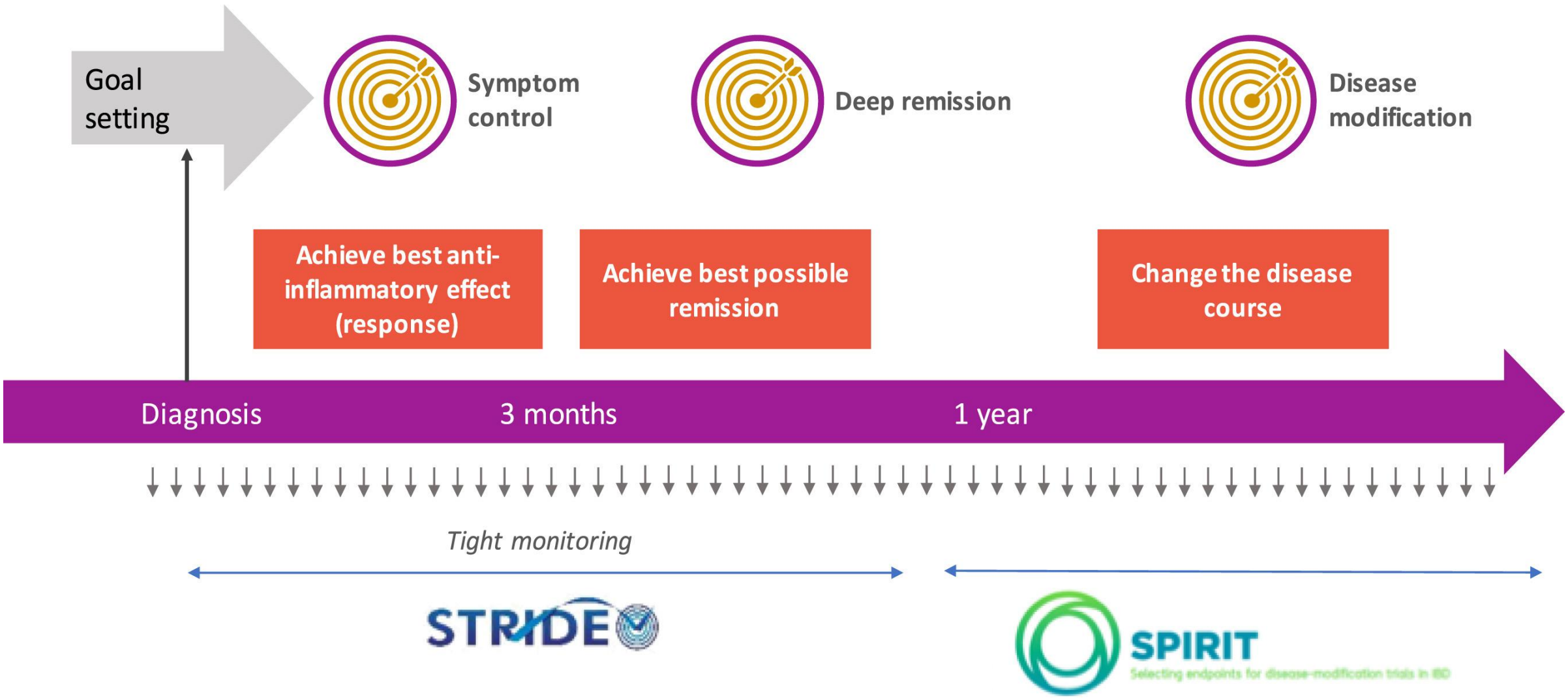


Figure adapted from Solberg et al, 2009

UC, ulcerative colitis
Grey line: 55% decrease in intensity of symptoms over time.
Solberg IC, et al. *Scand J Gastroenterology* 2009;44:431–440.

Striving to Go Further

Building a Consensus to Define Treatment Goals



STRIDE-2 – Updated Treat-to-Target-Recommendations for Ulcerative Colitis

Composite endpoints

Clinical/PRO response

An immediate treatment target

- In adults, decrease of at least 50% in **PRO2** (rectal bleeding and stool frequency)
- In children, decrease in PUCAI of at least 20 points

Endoscopic healing

A long-term target

- Assessment achieved by sigmoidoscopy or **colonoscopy**
- Measured by **Mayo** endo subscore = 0, or **UCEIS ≤ 1 points**

Biomarkers

An intermediate treatment target

- **Normalization of CRP** (to values under the upper limit of normal)
- **Normalization of fCal** (to 100–250 µg/g)

Quality of life and disability

Long-term treatment targets

- Absence of **disability** and normalized **HR-QoL**

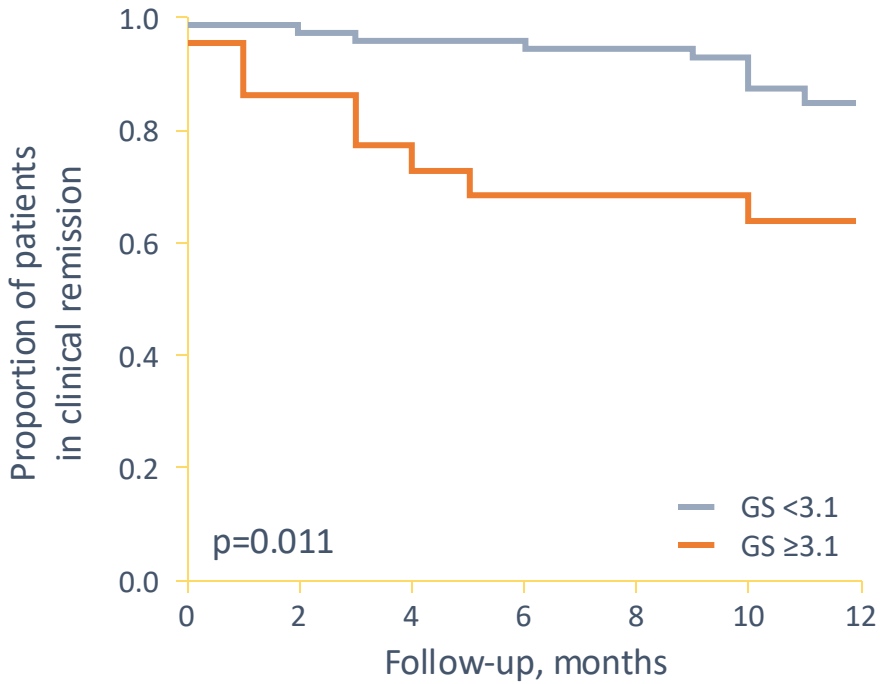
PUCAI, pediatric UC activity index;
UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

Turner D et al., Gastroenterology. 2021

Histological remission is associated with reduced risk of relapse in UC

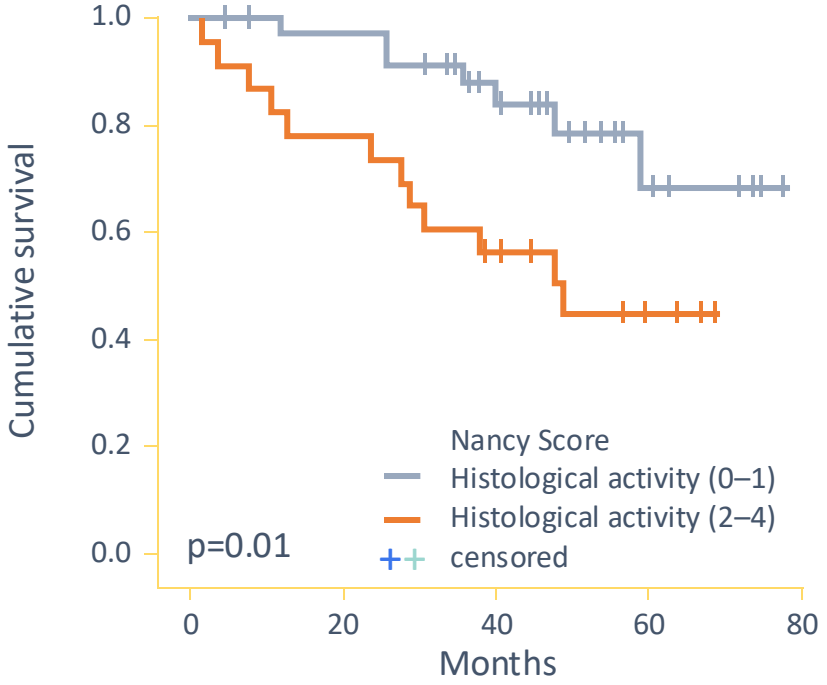
Prospective study of asymptomatic patients with ESS ≤1 (n=96)[1]

Risk of relapse according to grade of histological activity



Prospective study of patients with UC in clinical remission and endoscopic remission (ESS ≤1) post-surgery (n=60)[2]

Recurrence-free time according to histological activity



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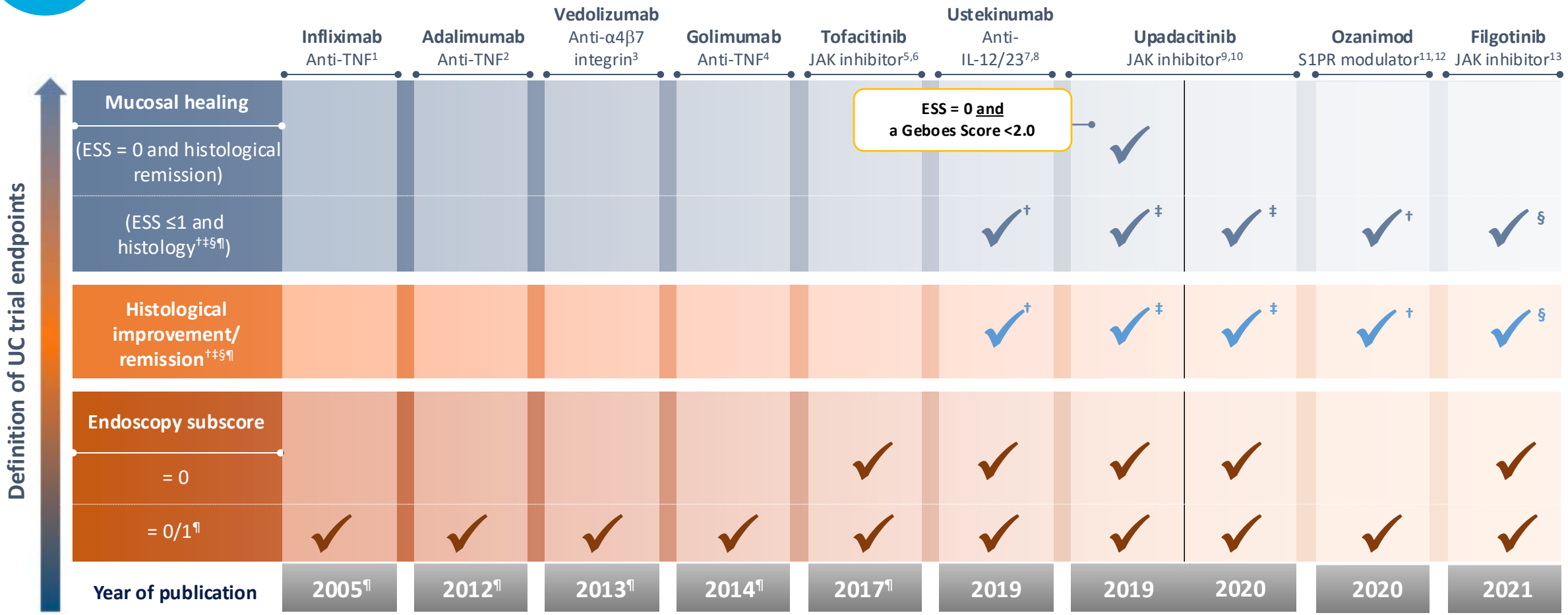
Mucosal endpoints in UC clinical trials have evolved over time to reflect the importance of mucosal healing



†Histological improvement/remission with ustekinumab/ozanimod defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue. ‡Histological improvement with upadacitinib defined as decrease from baseline in Geboes Score. §Histological remission with filgotinib based on Geboes Scores (absence of neutrophils in the lamina propria or the epithelium). ¶ESS ≤1 was referred to as 'mucosal healing'.

Upadacitinib is an investigational agent for patients with UC and is not currently approved for clinical use.

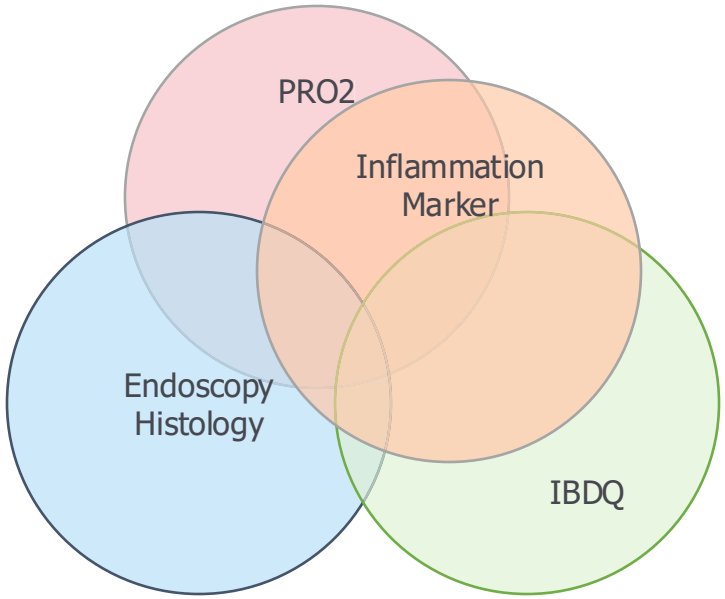
ESS, endoscopic subscore; IL, interleukin; JAK, Janus kinase; S1PR, sphingosine-1-phosphate receptor; TNF, tumour necrosis factor.

1. Rutgeerts P, et al. *N Engl J Med*. 2005;353:2462–76; 2. Sandborn WJ, et al. *Gastroenterology*. 2012;142:257–65.e1–3; 3. Feagan BG, et al. *N Engl J Med*. 2013;369:699–710; 4. Sandborn WJ, et al. *Gastroenterology*. 2014;146:85–95; 5. Sandborn WJ, et al. *N Engl J Med*. 2017;376:1723–36 and supplementary appendix; 6. Tofacitinib SmPC 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf. Accessed: February 2022; 7. Sands BE, et al. *N Engl J Med*. 2019;381:1201–14; 8. Ustekinumab SmPC 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf. Accessed: February 2022; 9. Sandborn WJ, et al. Presented at the 14th Congress of the European Crohn's and Colitis Organisation, 6–9 March 2019, Copenhagen, Denmark: OP14; 10. Sandborn WJ, et al. *Gastroenterology*. 2020;158:2139–49.e14; 11. Sandborn W, et al. Presented at the 14th Annual Scientific Meeting of the American College of Gastroenterology, 23–28 October 2020, Virtual: P025; 12. Sandborn WJ, et al. Presented at the 28th United European Gastroenterology Week, 11–13 October 2020, Virtual: poster LB02; 13. Feagan BG, et al. *Lancet*. 2021;397:2372–84.

23

Sequential Assessment of Endpoints

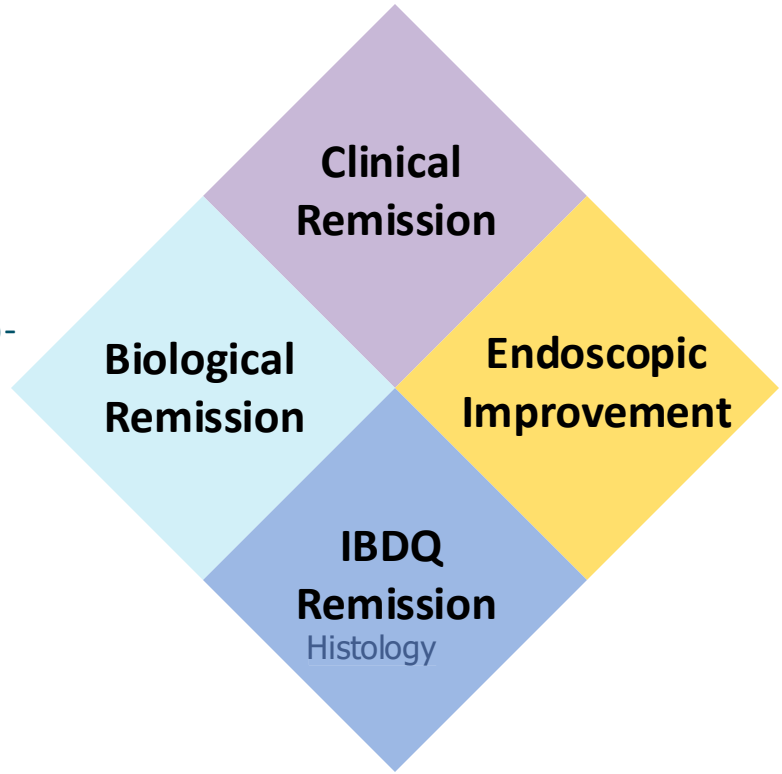
- Regularory endpoints (PRO2) and endoscopy are assessed as co-primary
- Other endpoints are addressed independently
- Responder Populations do not overlap



The Anatomy of a Combined Endpoint

Comprehensive Disease Control (CDC) in a retrospective analysis of Selection (Filgotinib in UC)

- **Clinical remission:**
  - Partial Mayo score ≤ 2 and no sub-score > 1 (excluding endoscopy sub-score)
- **Endoscopic improvement:**
  - Mayo endoscopic score of 0 or 1
- **Biological Remission:**
  - Fecal calprotectin < 150 µg/g
- **Inflammatory bowel disease questionnaire (IBDQ) Remission:**
  - IBDQ > 170



*Clinical remission and endoscopic improvement were assumed absent if missing data. Fecal calprotectin and IBDQ were imputed using last observation carried forward.

A Subset of Patients Reaches CDC

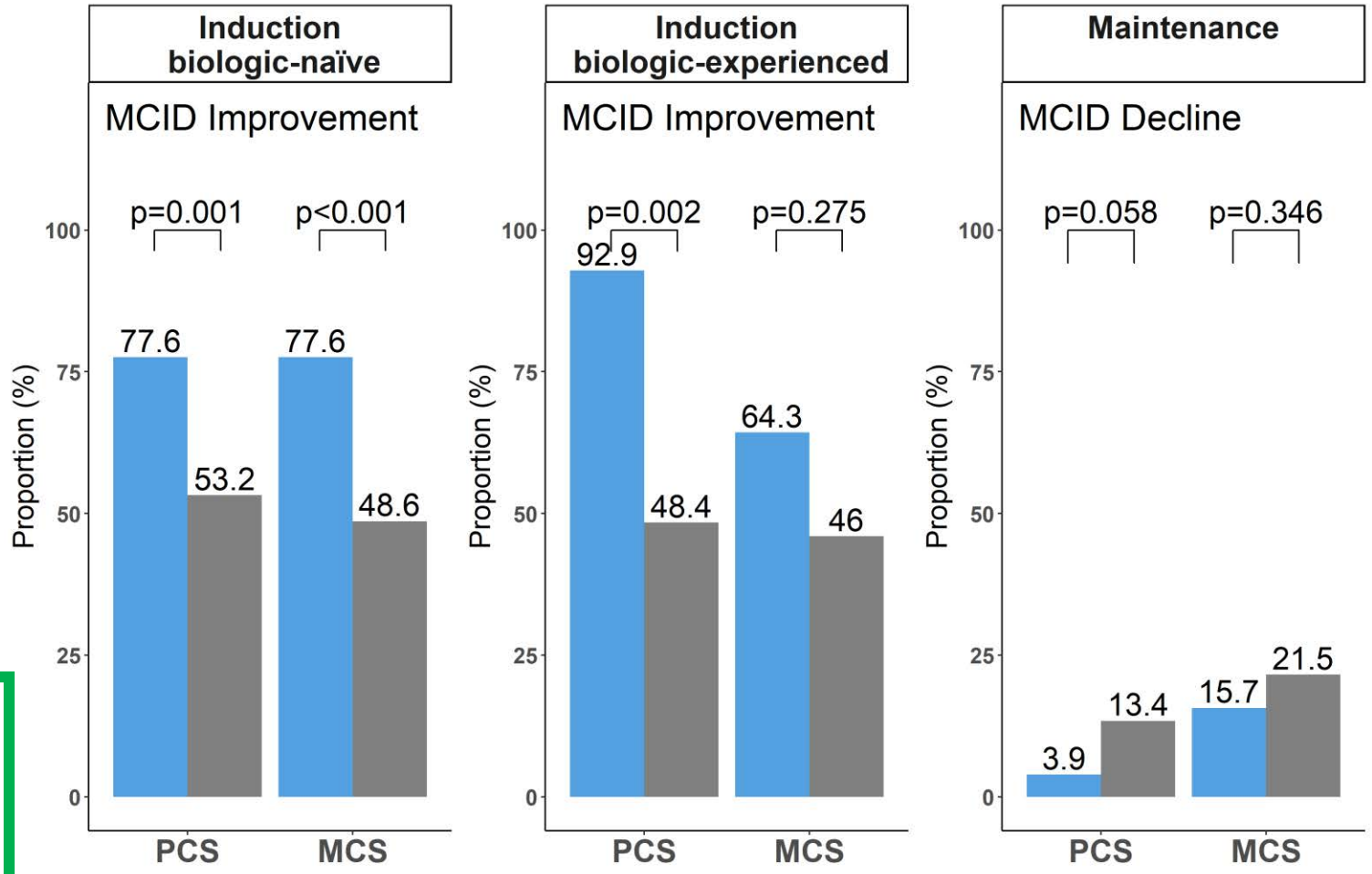
Outcome	FIL200 n (%)	PBO n (%)	P-value
Induction, biologic-naïve	**N = 245**	**N = 136***	
Combined endpoint	43 (17.6%)	6 (4.4%)	**<0.001**
Clinical remission	132 (53.9%)	43 (31.6%)	**<0.001**
Endoscopic improvement	83 (33.9%)	30 (22.1%)	**0.0213**
Biological remission	102 (41.6%)	28 (20.7%)	**<0.001**
IBDQ remission	137 (55.9%)	49 (36.0%)	**<0.001**
Induction, biologic-experienced	**N = 260***	**N = 141***	
Combined endpoint	12 (4.6%)	2 (1.4%)	0.167
Clinical remission	86 (33.1%)	12 (8.5%)	**<0.001**
Endoscopic improvement	45 (17.3%)	12 (8.5%)	**0.024**
Biological remission	50 (19.3%)	9 (6.4%)	**<0.001**
IBDQ remission	116 (44.6%)	26 (18.4%)	**<0.001**
Maintenance	**N = 199**	**N = 98**	
Combined endpoint	44 (22.1%)	7 (7.1%)	**0.002**
Clinical remission	123 (61.8%)	26 (26.5%)	**<0.001**
Endoscopic improvement	81 (40.7%)	15 (15.3%)	**<0.001**
Biological remission	88 (44.2%)	44 (44.9%)	0.990
IBDQ remission	143 (71.9%)	55 (56.1%)	**0.010**

*Excludes 4 patients from the full analyses set without disease-specific HRQoL Data

Benchmarking to health: SF36

Improved quality of life was defined by the minimal clinically important difference (MCID) for each subscale.[2] The proportion of patients with improved quality of life across PCS, MCS, and all SF-36 subscales was higher in patients achieving the combined endpoint from baseline to week 10 of induction.

A numerically lower proportion of patients achieving the combined endpoint experienced MCID decline during maintenance, indicating the improvements achieved during induction were sustained in maintenance.



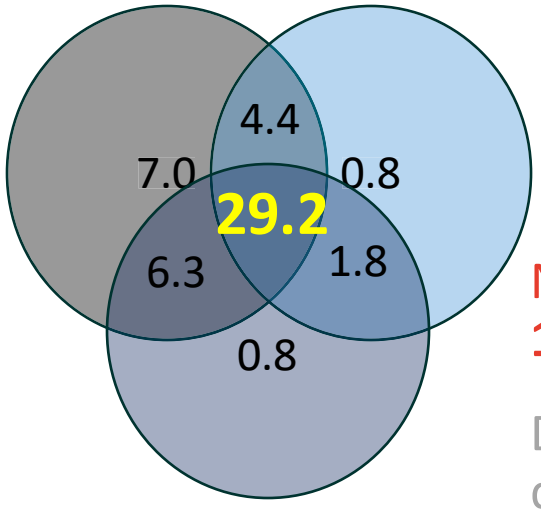
Induction: MCID improvement from baseline to week 10.
Patients without a valid baseline assessment (out-of-window) were excluded. Maintenance: MCID decline from maintenance baseline to week 58.
MCIDs defined based on published thresholds[2-4].
SF-36; 36-item short-form questionnaire; MCID; minimally clinically important difference

PCS: Physical Component Summary
MCS: Mental Component Summary

Percentage of patients with "disease control" at Week 52 with vedolizumab and adalimumab

Data from a VARSITY *post-hoc* analysis (N = 769)[1]*

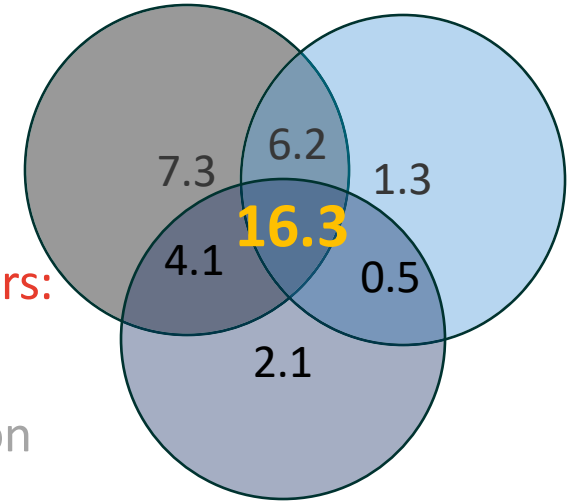
Vedolizumab (n = 383)



Non-responders: **13.3%**

Discontinuation due to lack of efficacy: **10.7%**

Adalimumab (n = 386)



Non-responders: **13.5%**

Discontinuation due to lack of efficacy: **21.2%**

Partial Mayo Score of ≤ 2 and no individual subscore > 1 (excluding sigmoidoscopy subscore)

"Disease clearance" at Week 52		
✓	**Clinical remission**	
✓	**Mucosal healing**	Mucosal healing (endoscopic improvement): Mayo Endoscopic Subscore of ≤ 1
✓	**Histological improvement**	Minimal histologic disease activity per RHI (defined as RHI score of < 5)

× × × **Non-response (completed treatment)**

This is the Dawn of MRD in IBD

Endophenotypes?

Understanding the profile of patients who achieve disease control and how quickly treatment decisions can be made with confidence has enormous impact for patient care and drug development alike

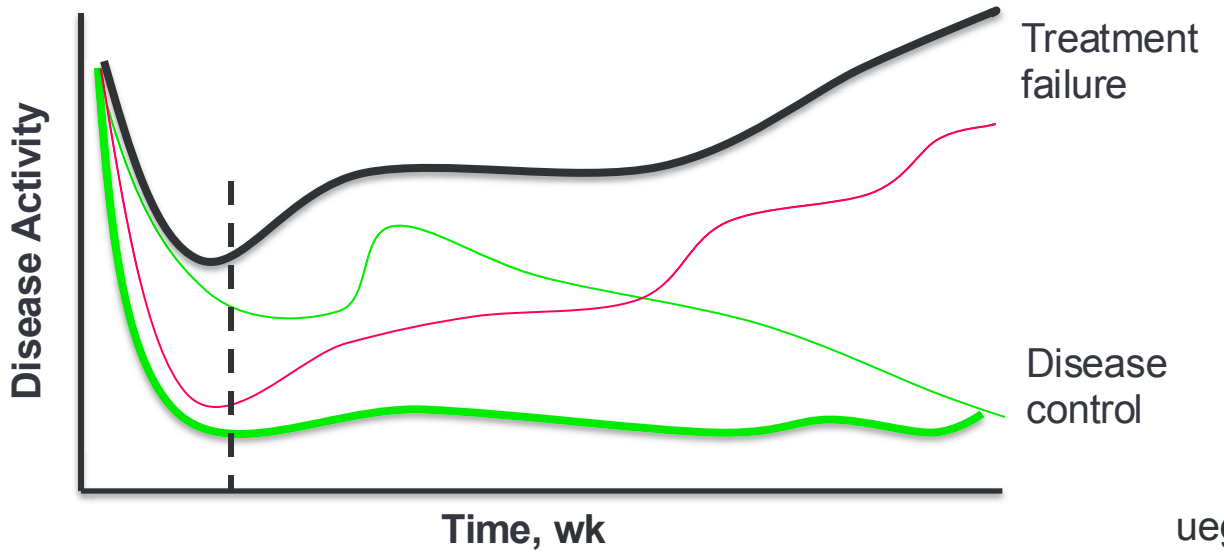
Drug development

- Proactively balance arms to ensure equal distribution of potential R and NR patient profiles

Disease trajectory

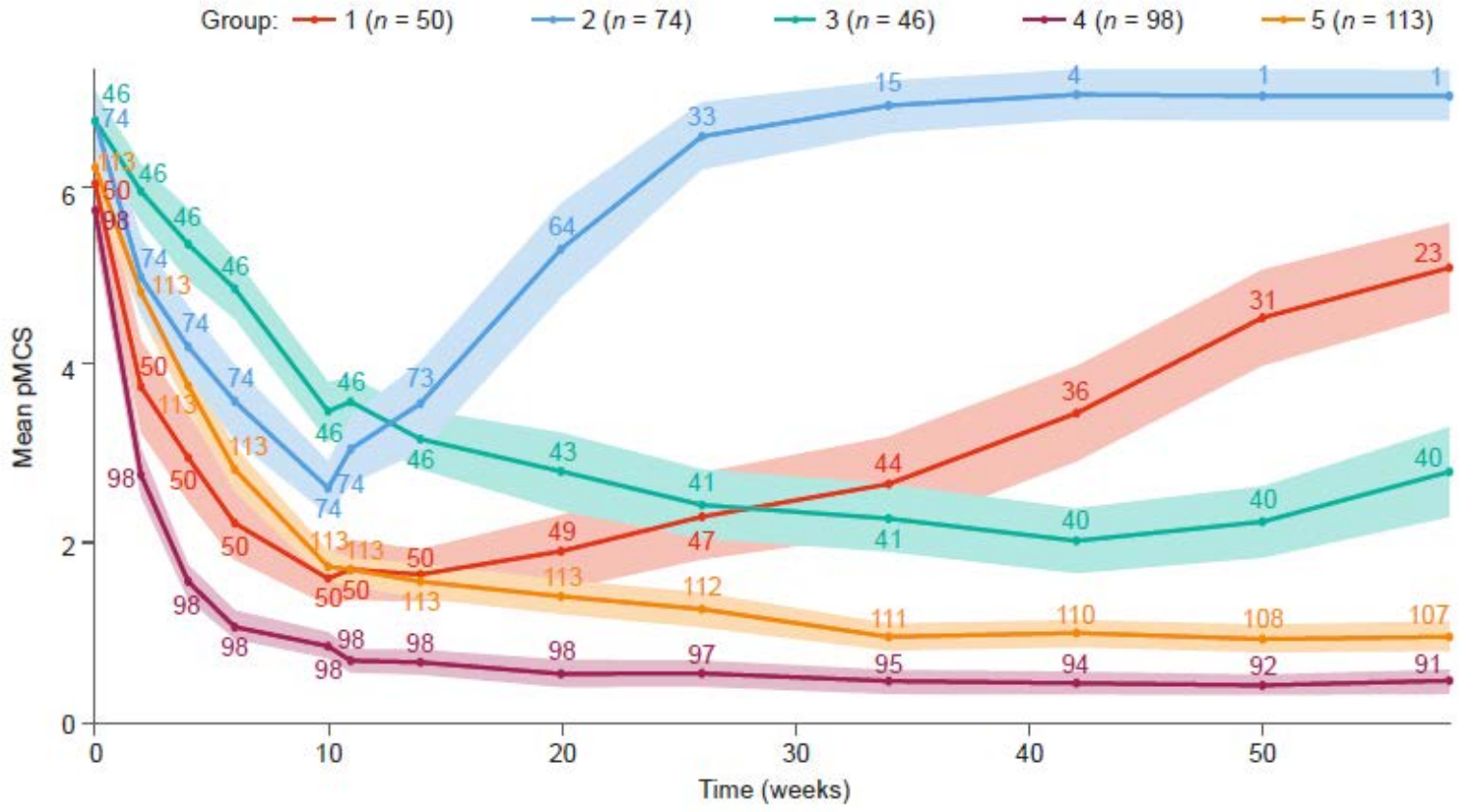
- Objective measures to help identify patients who are most likely to progress or require more intense or different intervention
- Correlate disease control with impact on QoL to measure restoration of health

Disease Control Analysis	Disease Trajectory Analysis
Allows to define **baseline characteristics** and **early change markers** to identify patients who are "most likely to respond" to ANY therapy	Will define subgroups with different **response kinetics** to treatment (slope) and may inform **how likely they are to stay** in remission



; R, responder; NR, nonresponder; QoL, quality of life

Group Based Trajectory Modeling – a Machine Learning Tool Applied to the Phase 3 Trial of Filgotininb in UC („Selection“)



CDC
n (%)

0(0)

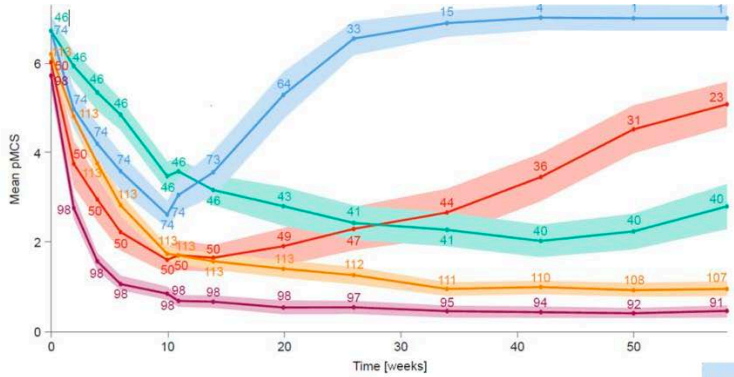
0(0)

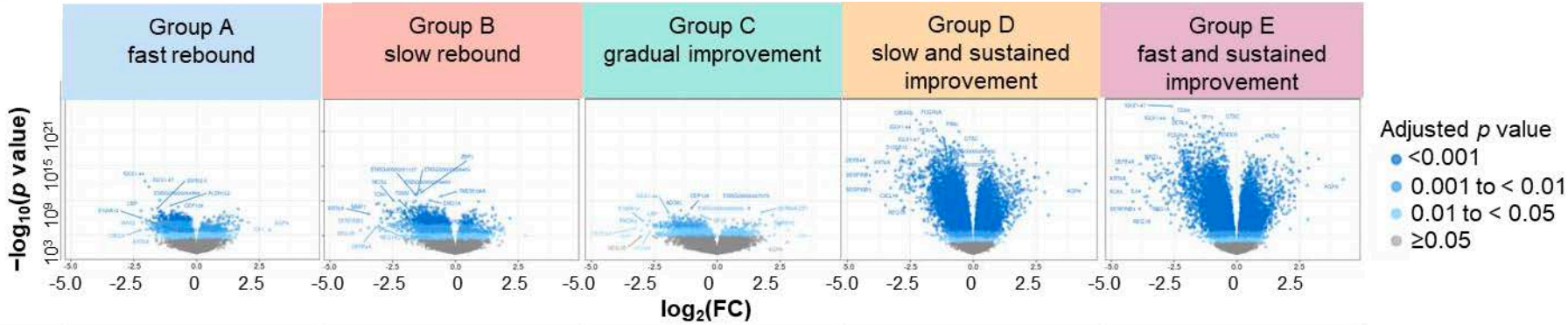
3(7)

36(32)

30(31)

EXPRESSION PROFILES UNDERLAY SYMPTOM TRAJECTORIES



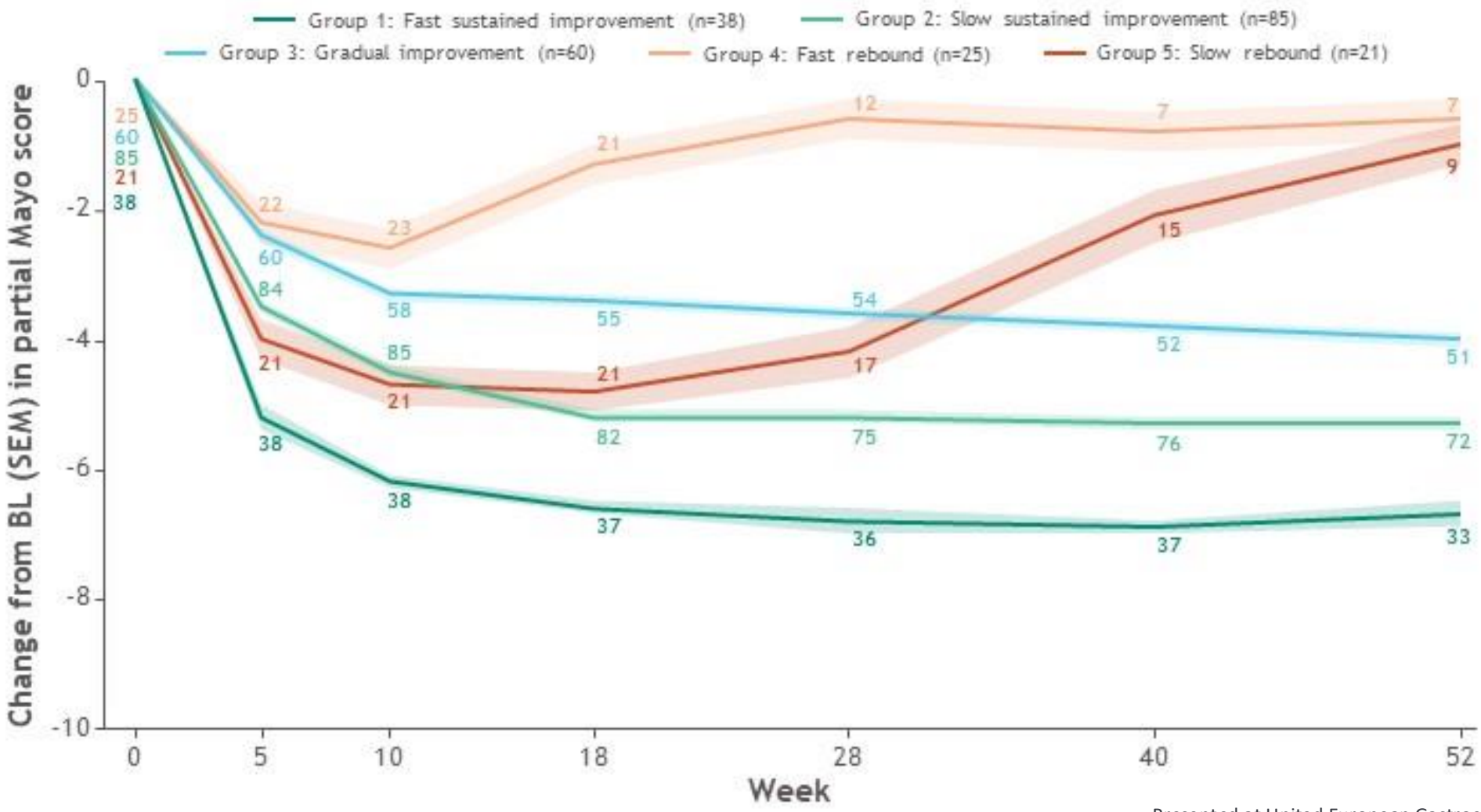


Total DEG, n	4683	4356	1306	14690	14677
Upregulated, n	1450	1595	299	6850	7410
Downregulated, n	3233	2761	1007	7540	7267
Proportion of total expressed genes, %	8.9	8.2	2.5	27.8	27.7

Volcano plots of the DEGs from baseline to week 10 in each trajectory group. Significant DEGs (p <0.05) are coloured in blue and non-significant genes are coloured in grey. The top 10 genes with the highest significance and/or highest $\log_2$(FC) are named.

DEG, differentially expressed gene; FC, fold change.

Ozanimod Disease trajectories in IBD: Understanding the individual path of a patient



Endoscopic Healing (MES=0)

0%

4%

28%

38%

47%

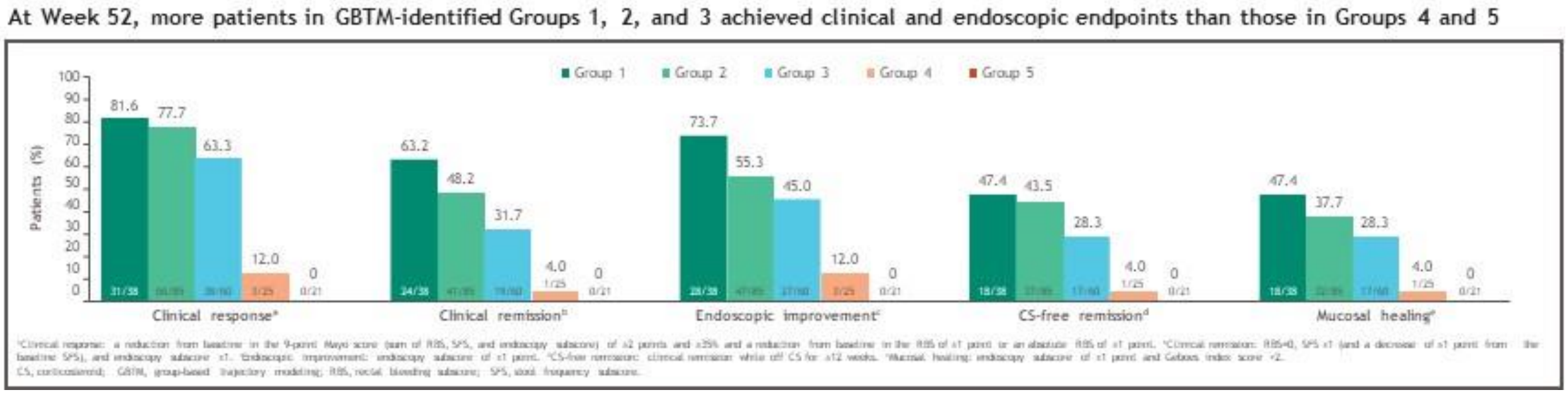
Presented at United European Gastroenterology Week (UEGW), 2023 © Schreiber et al.

ueg.eu

CDC, comprehensive disease control; GBTM, group-based trajectory modelling; IBD, inflammatory bowel disease; pMCS, partial Mayo Clinical Score; UC, ulcerative colitis.

[a]SELECTION (NCT02914522) phase 2b/3, double-blind, placebo-controlled, randomised trial to evaluate preferential Janus kinase 1 inhibitor filgotinib in patients with UC

Ozanimod Disease trajectories in IBD: Understanding the individual path of a patient



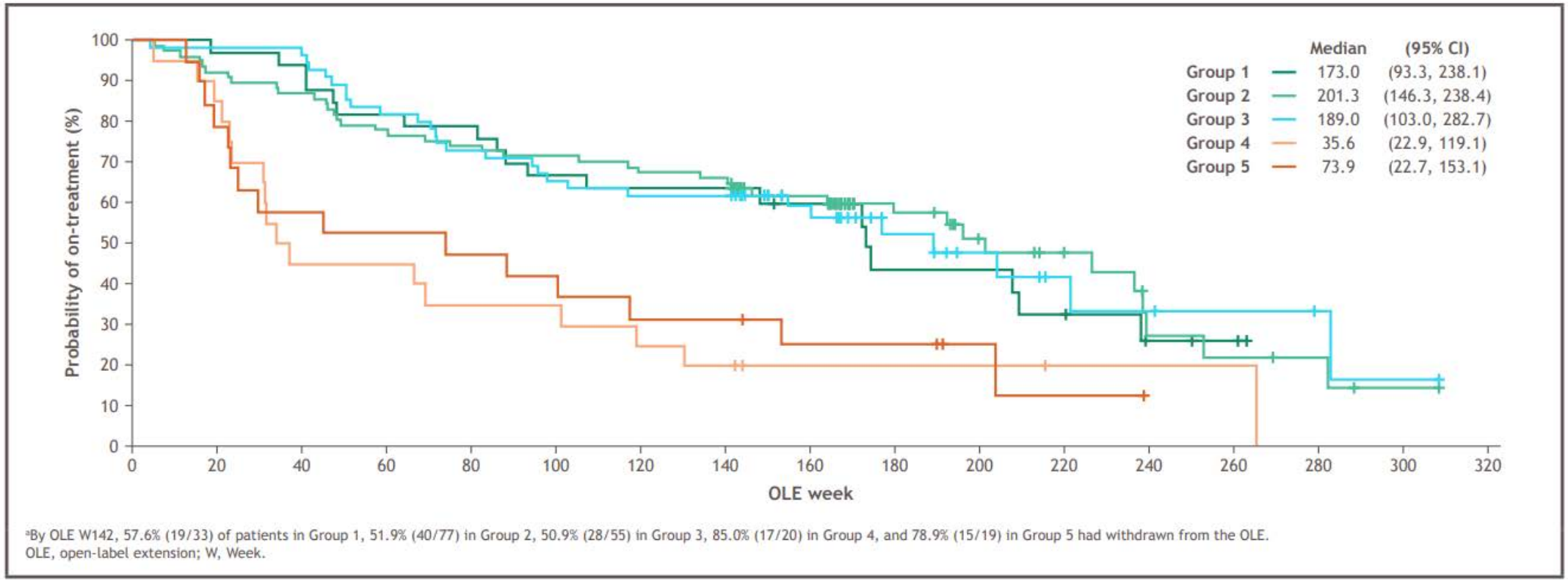
Presented at United European Gastroenterology Week (UEGW), 2023 © Schreiber et al.

CDC, comprehensive disease control; GBTM, group-based trajectory modelling; IBD, inflammatory bowel disease; pMCS, partial Mayo Clinical Score; UC, ulcerative colitis.
[a]SELECTION (NCT02914522) phase 2b/3, double-blind, placebo-controlled, randomised trial to evaluate preferential Janus kinase 1 inhibitor filgotinib in patients with UC

Long Term Outcome

At the time of data cutoff (June 30, 2023), all 204 patients who had entered the OLE either completed OLE W46, W94, and W142 or withdrew from the study.[a]

- Notably, more patients in Groups 1-3 completed OLE W142 than those in Groups 4 and 5

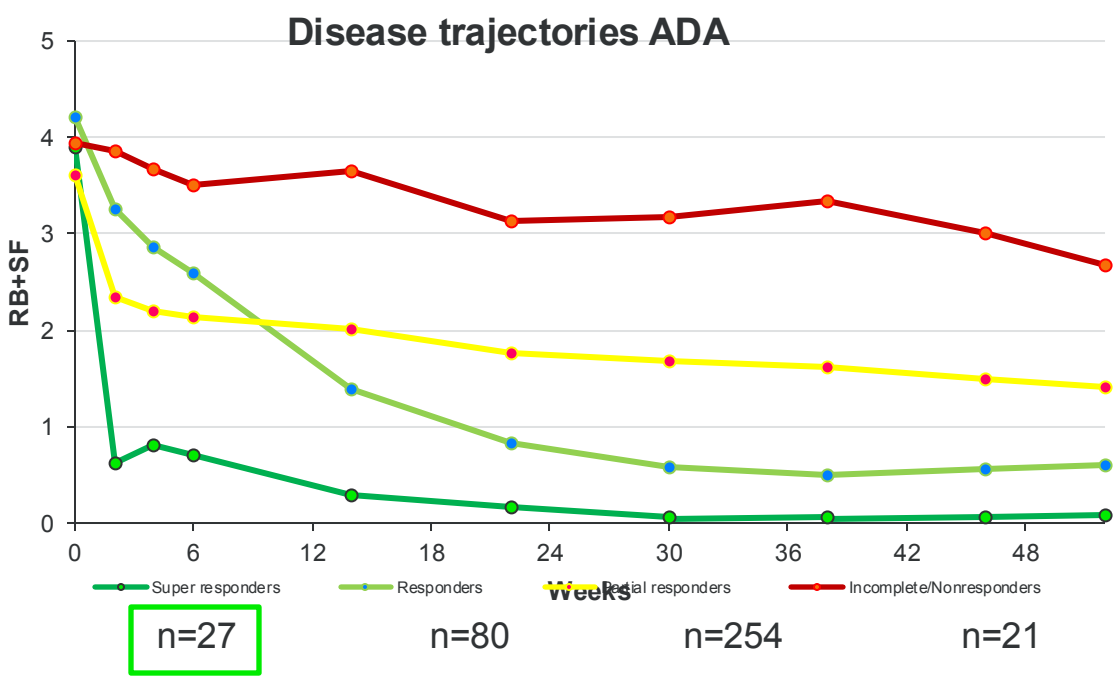


[a]By OLE W142, 57.6% (19/33) of patients in Group 1, 51.9% (40/77) in Group 2, 50.9% (28/55) in Group 3, 85.0% (17/20) in Group 4, and 78.9% (15/19) in Group 5 had withdrawn from the OLE.
OLE, open-label extension; W, Week.

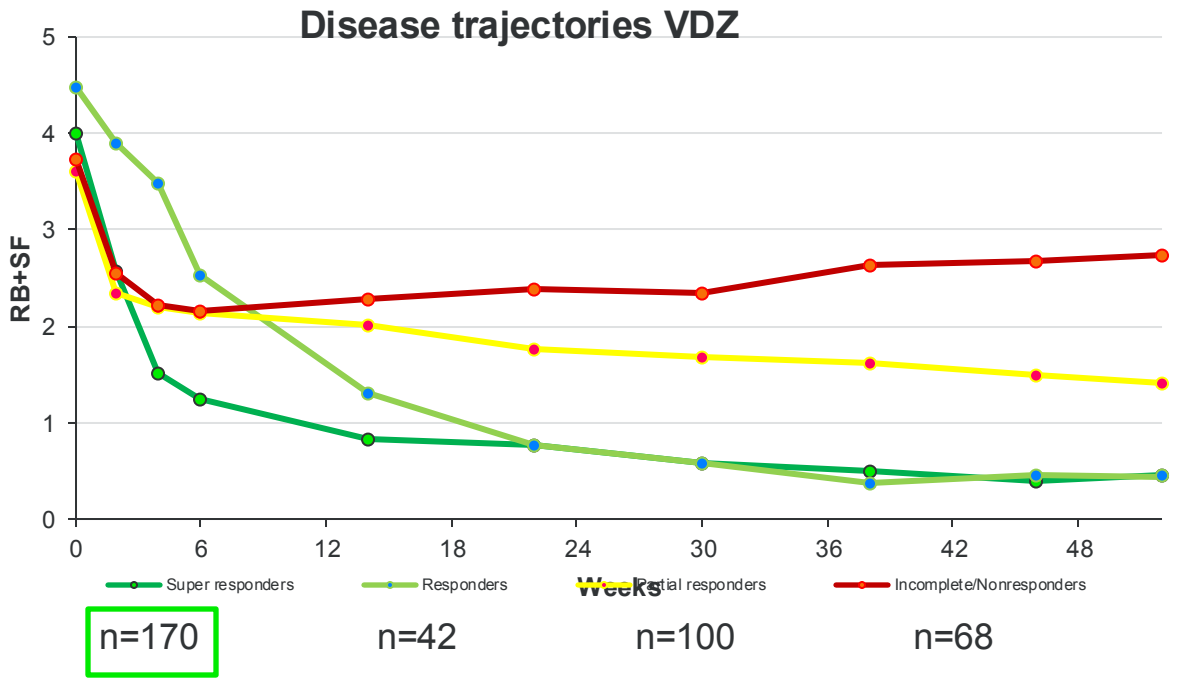
[a]On OLE W142 (data cutoff: June 30, 2023), 57.6% (19/33) of patients in Group 1, 51.9% (40/77) in Group 2, 50.9% (28/55) in Group 3, 85.0% (17/20) in Group 4, and 78.9% (15/19) in Group 5 had withdrawn from the OLE.
OLE, open-label extension; W, Week.

• Schreiber S. et al. ECCO 2024

Varsity: Super responder and fast responder groups are enriched for patients who achieve disease control



n=27 n=80 n=254 n=21



n=170 n=42 n=100 n=68

ADA, n (%)	Clinical Remission	Mucosal Healing	Disease Control
Super responder	14 (52%)	14 (52%)	4 (15%)
Fast Responder	39 (49%)	46 (58%)	13 (16%)
Partial responder	33 (13%)	45 (18%)	8 (3%)
Incomplete/NR	1 (5%)	2 (9%)	0 (0%)

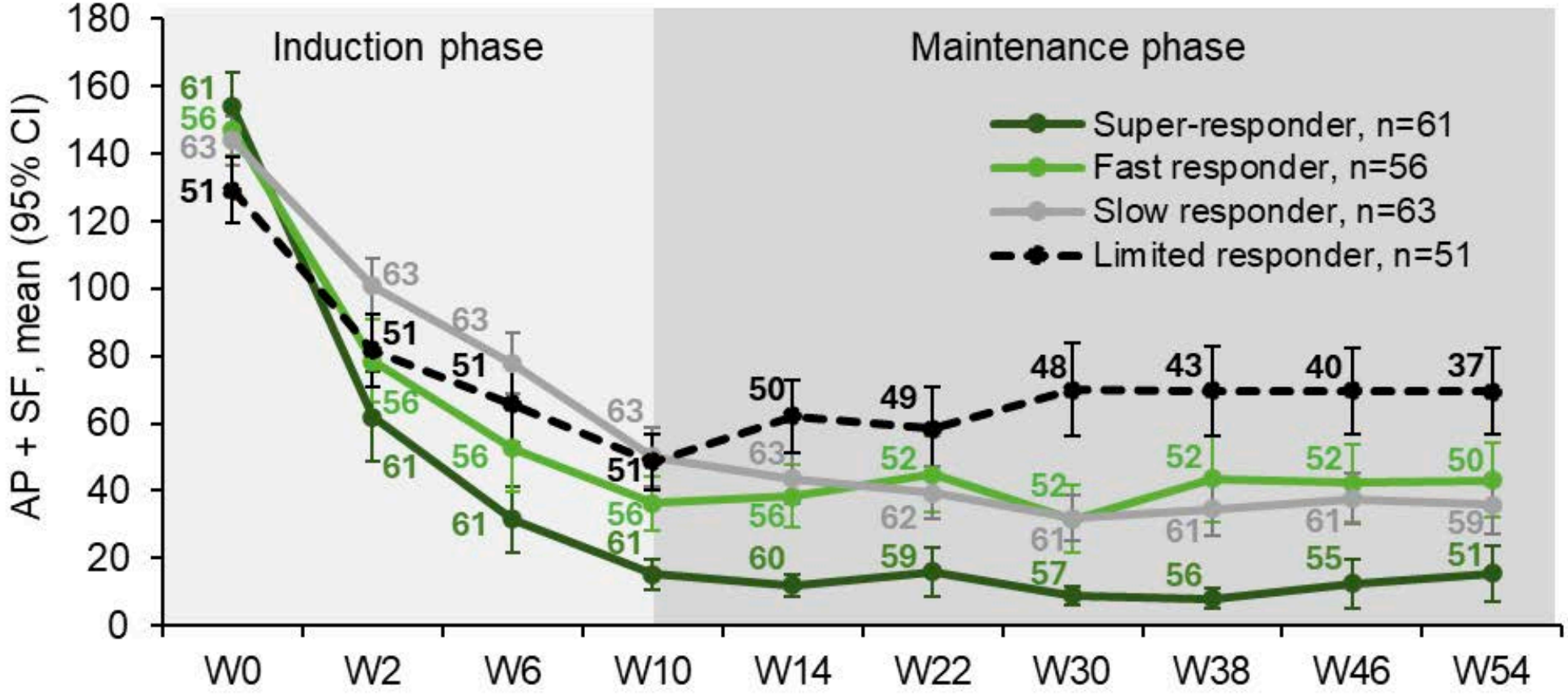
VDZ, n (%)	Clinical Remission	Mucosal Healing	Disease Control
Super responder	72 (42%)	84 (49%)	31 (18%)
Fast Responder	17 (40%)	22 (52%)	8 (19%)
Partial responder	30 (30%)	43 (43%)	10 (10%)
Incomplete/NR	1 (1%)	3 (4%)	1 (1%)

ADA, adalimumab; VDZ, vedolizumab; R, Responder; NR, nonresponder; RB rectal bleeding; SF, stool frequency;

SC Infliximab in the Liberty CD Study

A Placebo controlled study of IV/SC Infliximab sequence therapy against placebo

- Notably, only patients on active therapy are analyzed



- Schreiber S. et al. DDW 2024

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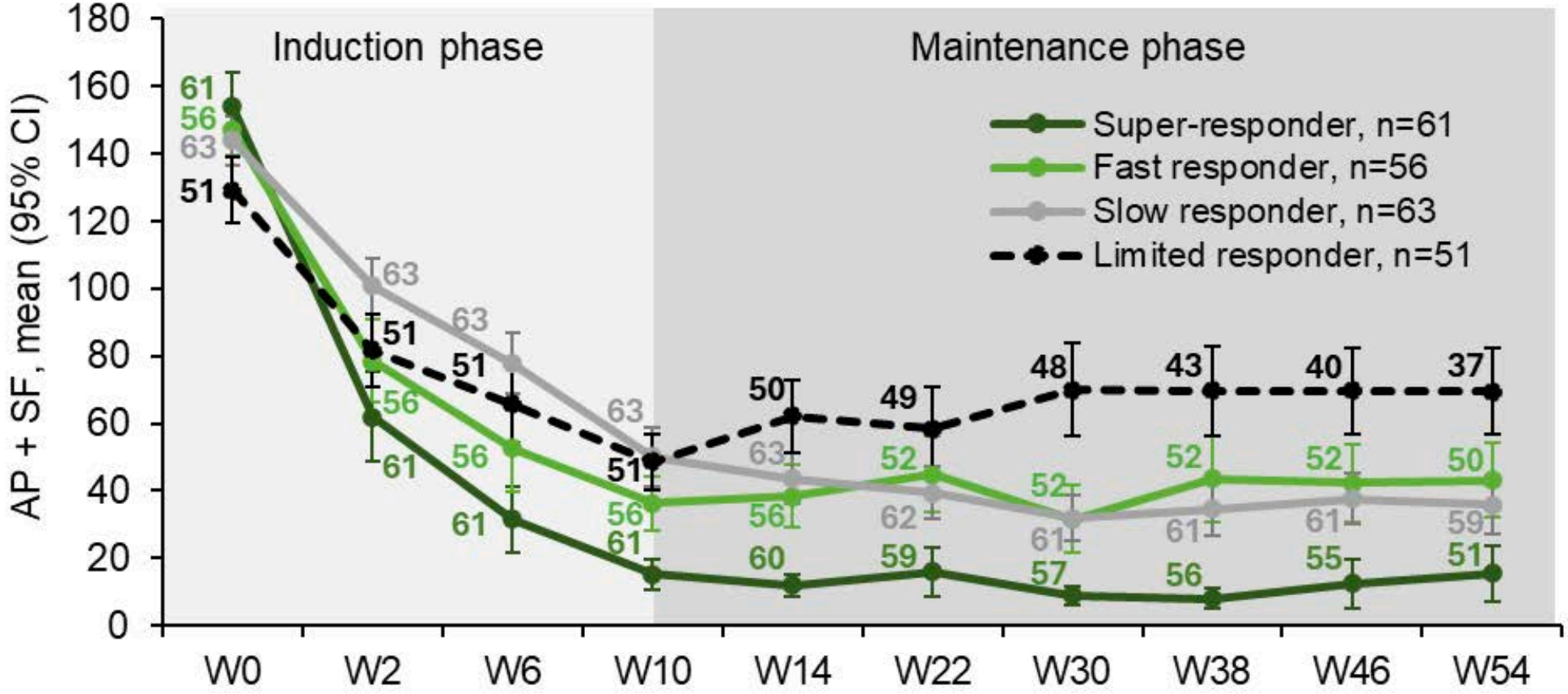
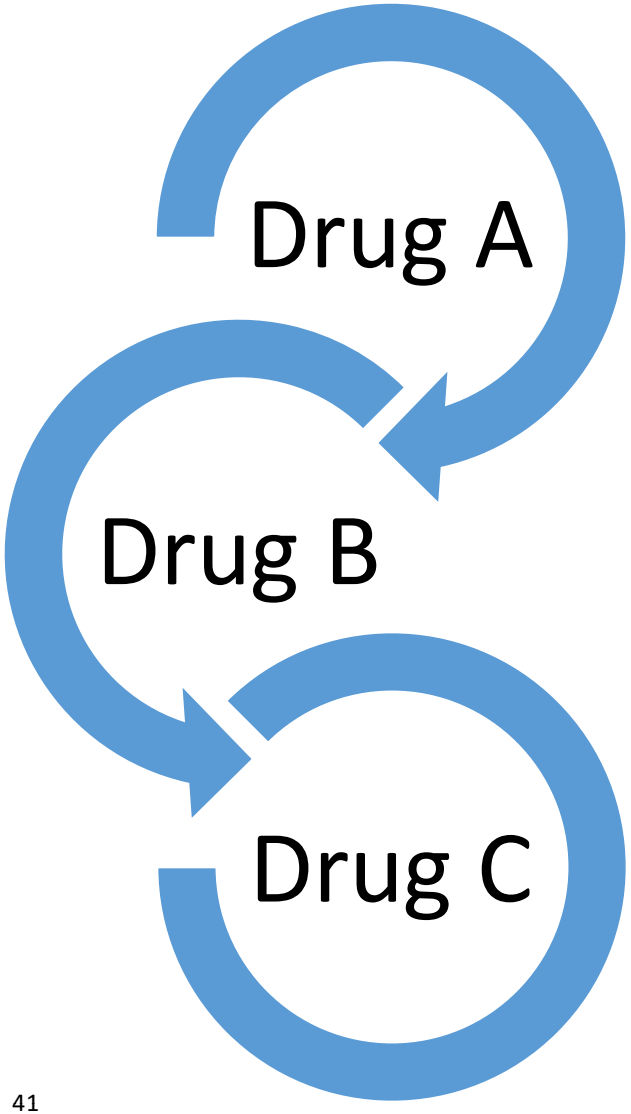


- Schreiber S. et al. DDW 2024

Clinical Interpretation

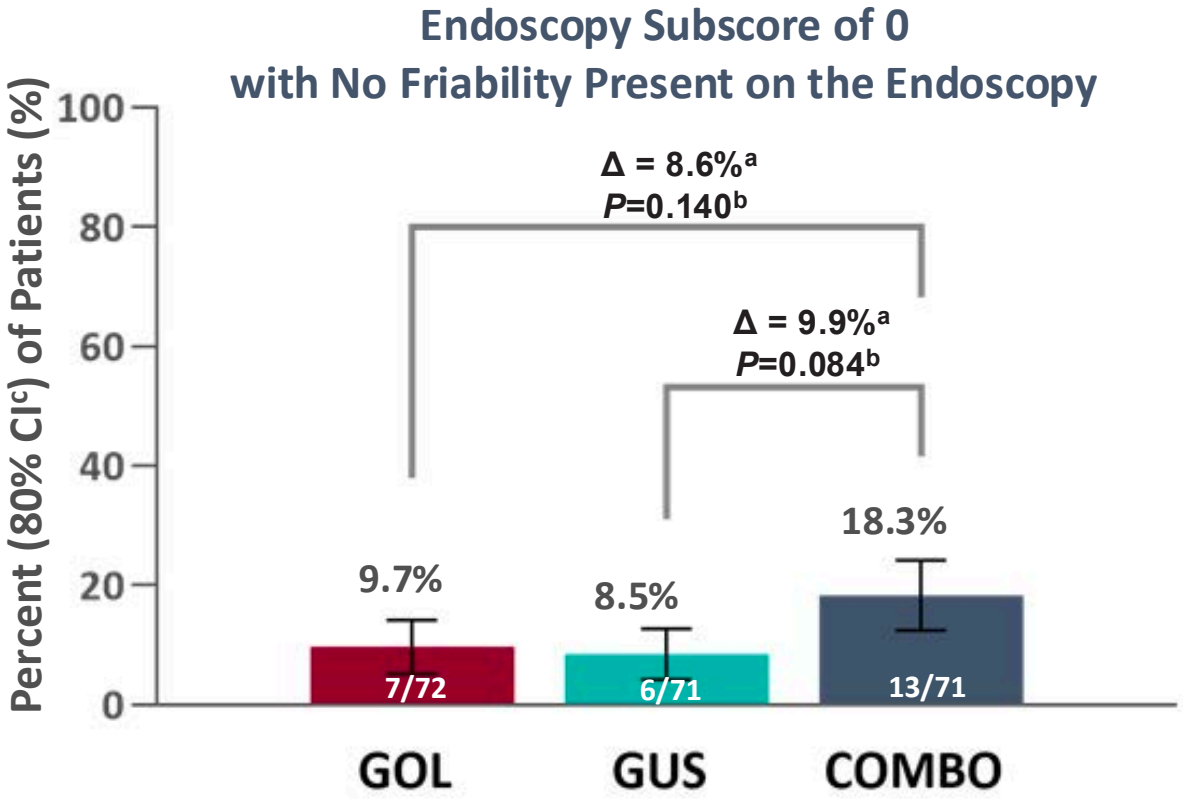
How to Use this Information to Match Patients with their best Therapies ?



Early change of therapies for "mismatched" patients

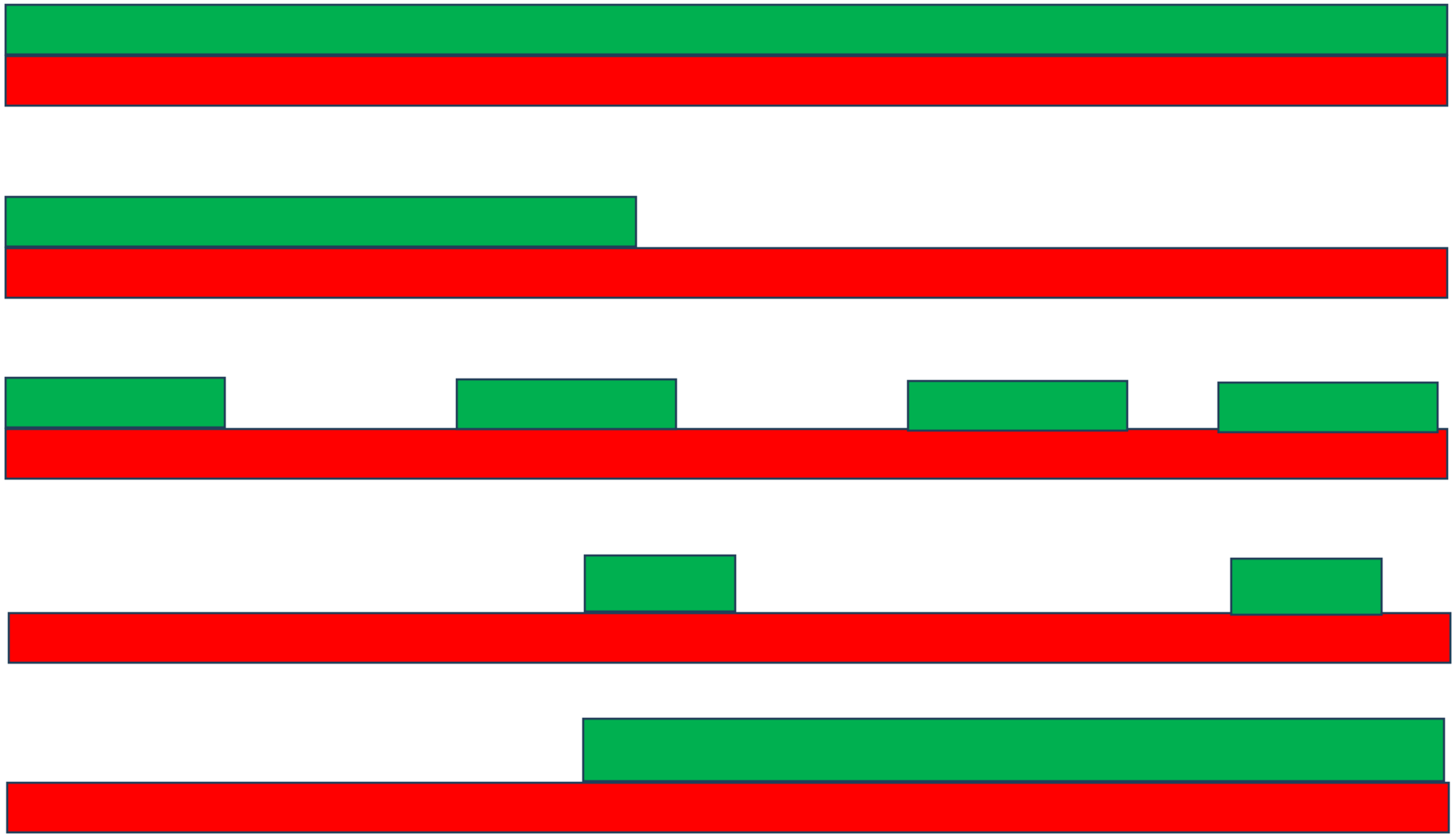
Choices guided by biomarkers

Combinations to reach more patients



Sands BE, et al. Oral presentation at ECCO 2022;OP36.

Strategies to Combine Drugs



fixed combination

co-induction

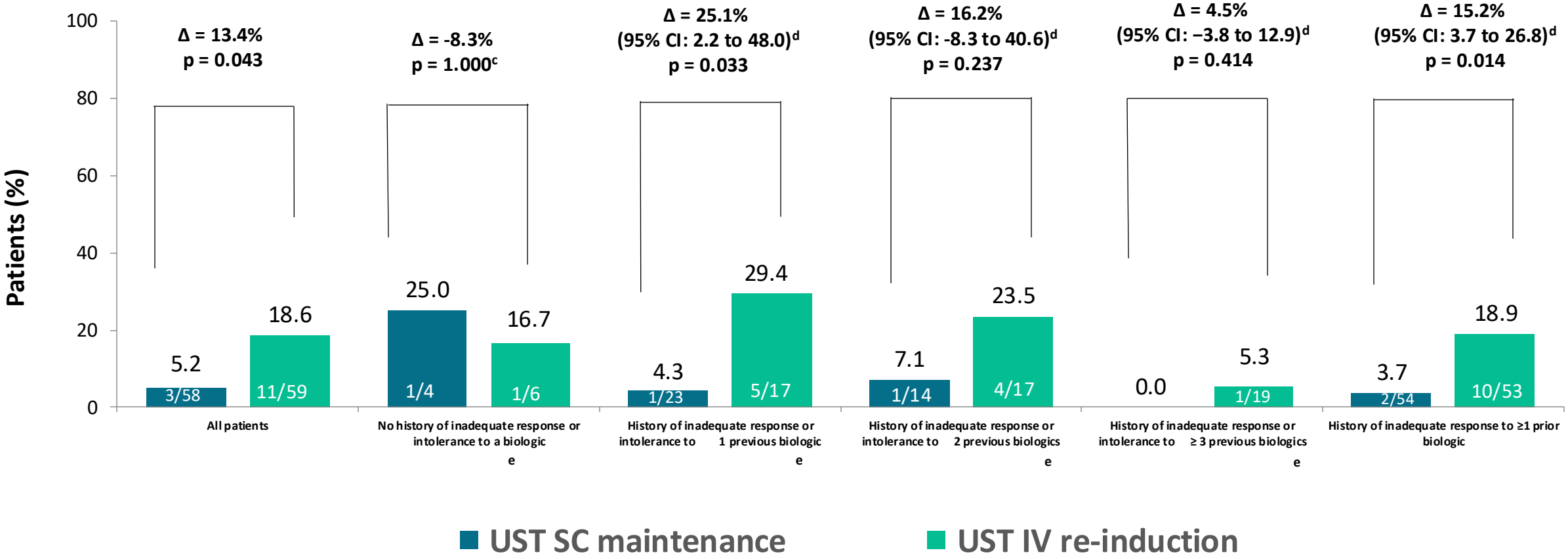
on/off induction

use as needed

step-up into combo

UST RE-INDUCTION: Endoscopic Remission at Week 16

Based on number of prior failed biologics among patients who elected to undergo endoscopies and had SES CD score ≥ 3 at baseline[a,b]



[a] Endoscopic remission is defined as SES-CD score ≤3 or SES-CD=0 for subjects who enter the study with an SES-CD=3

[b] Patients who had insufficient data at the designated analysis timepoint, a prohibited CD-related surgery, or a prohibited concomitant medication change and those discontinued due to a lack of efficacy or due to an adverse event indicating a worsening of CD prior to the designated analysis timepoint were not considered to have achieved the endpoint (regardless of CDAI score).

[c] The p-value is based on Fisher's exact test for this table due to smaller sample size.

[d] The confidence intervals were based on the Wald statistic with Mantel–Haenszel weights.

[e] Tumor necrosis factor inhibitors or vedolizumab.

$p < 0.05$ was the threshold for significance; p-values should be considered nominal as primary endpoint was not met.

Data are presented as n (%) Δ (95% CI) p-value.

Clinical Conclusions

- Therapeutic efficacy may be uplifted by combination of MOA (Short time, on demand or long-term)
- Combination of formulations to overcome pharmacokinetic problems
- Early understanding of responses may guide optimization of long-term outcomes
- More prospective studies and less registers are needed