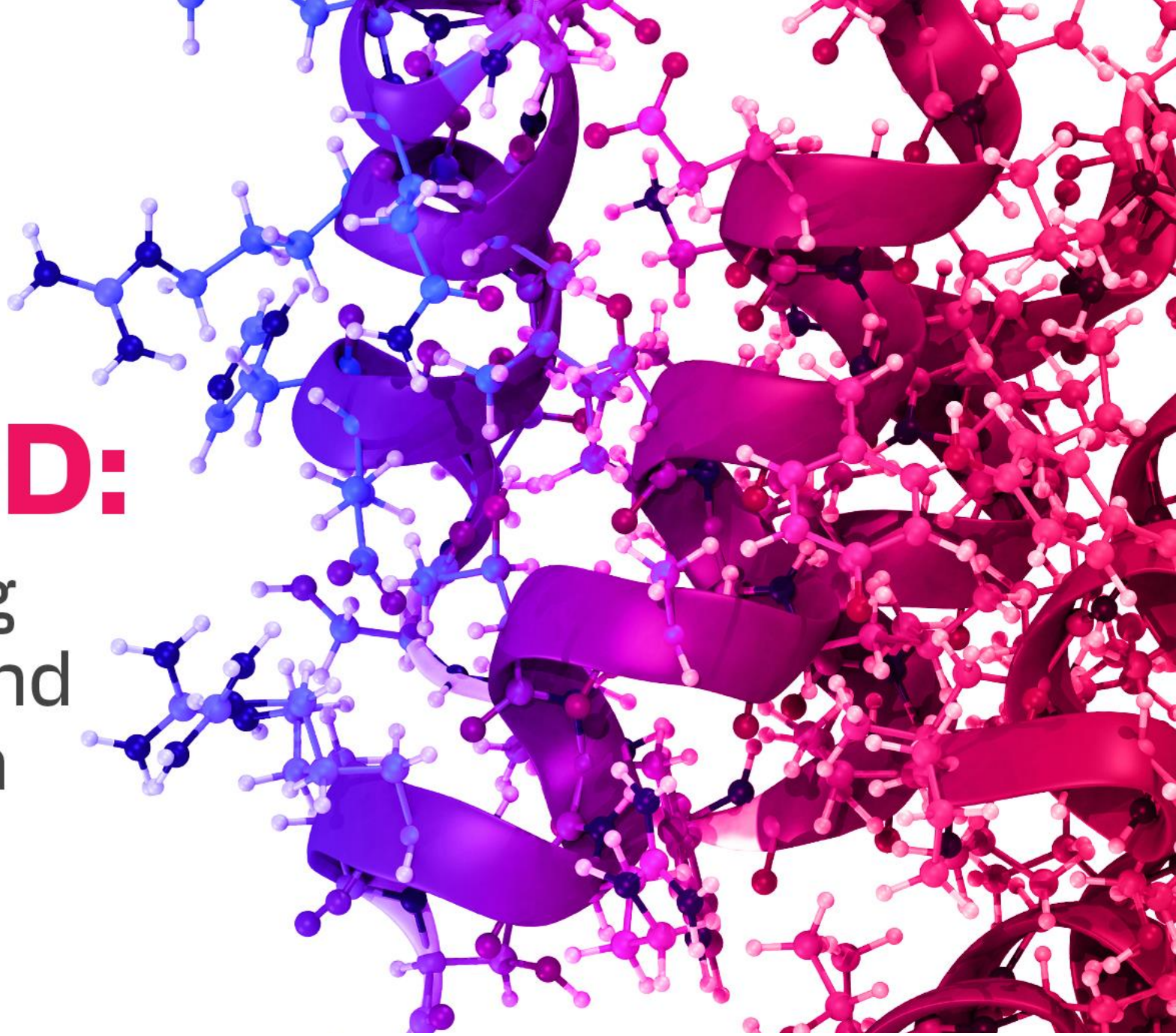
Targeting TNFα in IBD:

Innovations in Drug Design, Delivery, and Clinical Application



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This session is supported by an independent educational grant from Celltrion, Inc.

Learning Objectives

- Evaluate the clinical utility of TNFα inhibitors in IBD, including their effects on endoscopic and histologic outcomes
- Examine the latest clinical and real-world data on the safety and efficacy of TNFα inhibitors in the treatment of IBD, with a focus on newer formulations and innovative delivery approaches
- Apply evidence-based strategies to support the optimal use of TNFα inhibitors in the treatment of IBD, with emphasis on the potential benefits of early intervention and the importance of maintaining stable serum drug levels during treatment

TNFα = tumor necrosis factor alpha; IBD = inflammatory bowel disease.

Clinical Utility of Anti-TNF in IBD

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Disclosures

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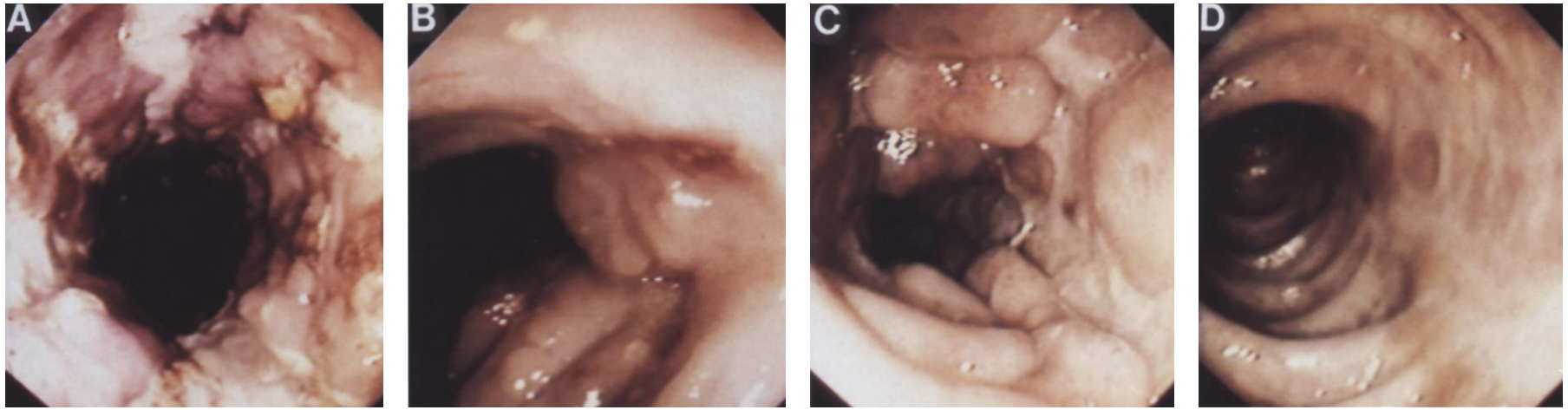
Revolution of Anti-TNF Therapy in IBD

Gastroenterology

Treatment of Crohn's Disease With Anti–Tumor Necrosis Factor Chimeric Monoclonal Antibody (cA2)



Healing of colonic ulcerations in 2 patients (patients 1 and 8) after treatment with cA2. (A and C) At enrollment and (B and D) 4 weeks after infusion of cA2. Photographs were obtained from videotapes, allowing comparison of exactly the same location.

van Dullemen HM, et al. *Gastroenterology*. 1995;109(1):129-135.

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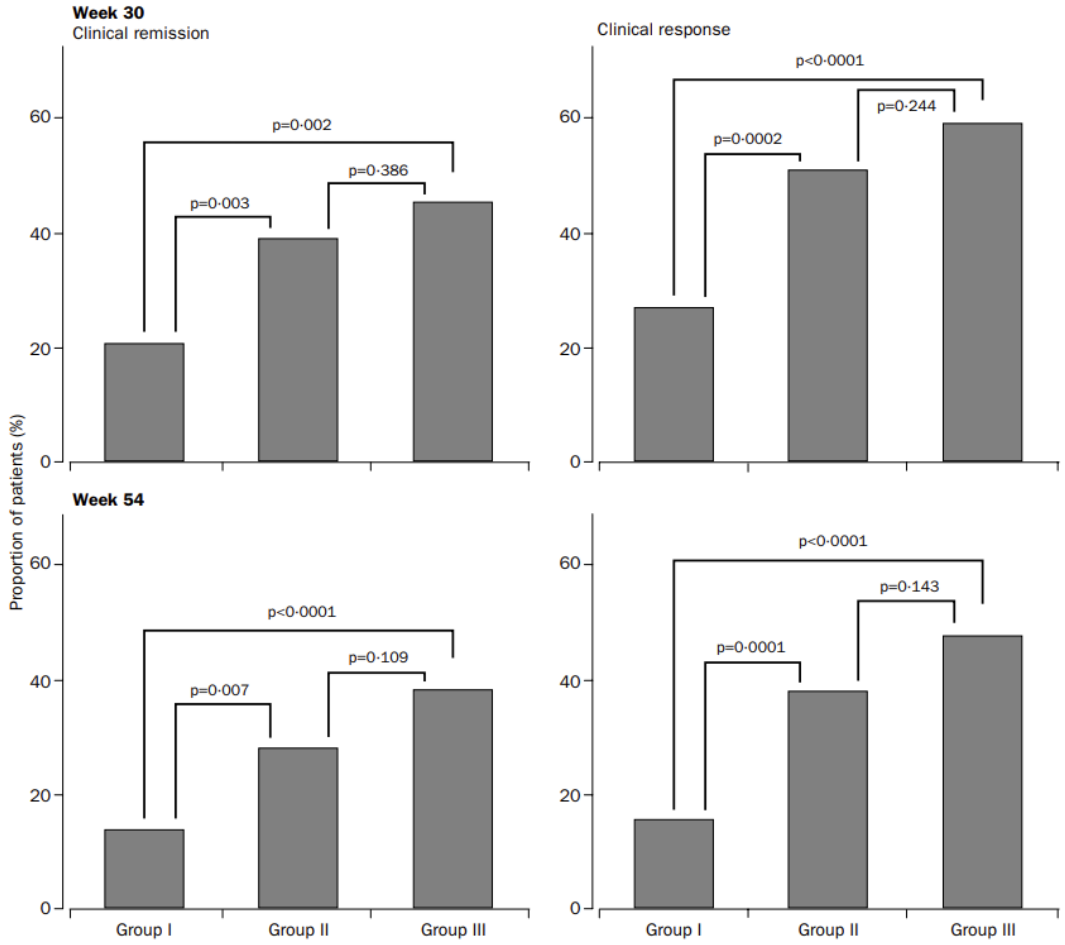
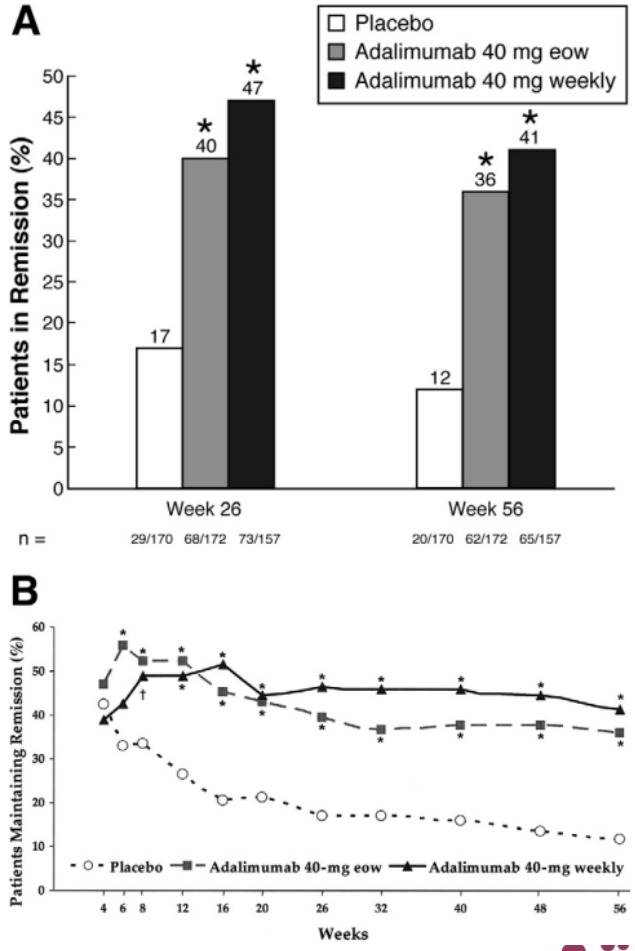
Anti-TNFs: Immense Hope in Clinical Response and Remission

ACCENT 1 – Infliximab



CHARM – Adalimumab



Hanauer SB, et al. *Lancet*. 2002;359(9317):1541-1549. Colombel JF, et al. *Gastroenterology*. 2007;132(1):52-65.

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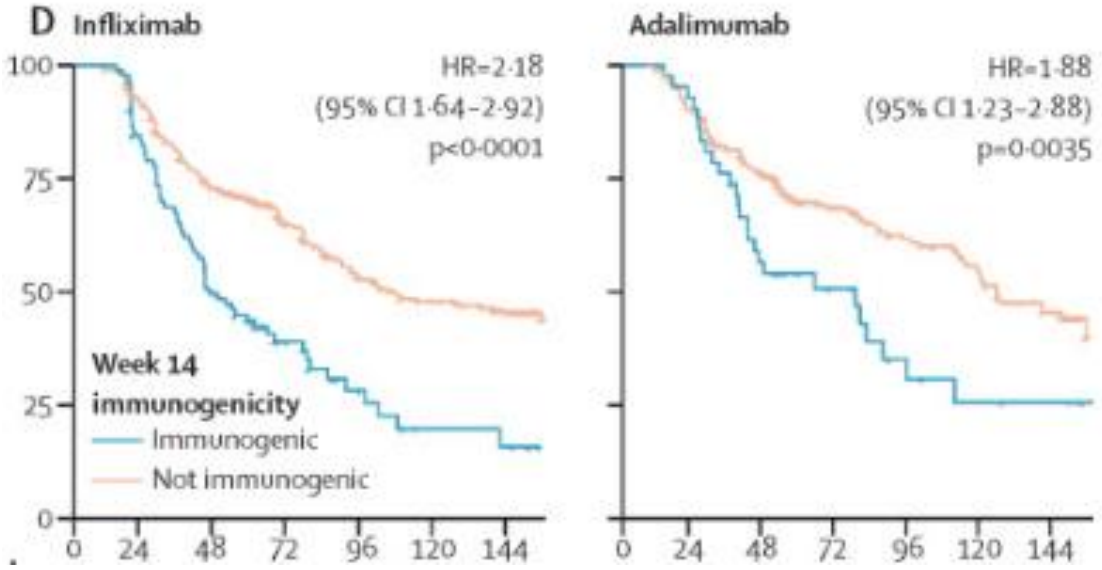
Lack of Durability with Anti-TNF over Time

- Approximately 30% of patients with IBD primary non-responders to anti-TNF
- Annual risk of loss of response to IFX is approximately 13% per person-year
- In the PANTS cohort study
  - 1 year % LOR for IFX 34.4% (95% CI 30.4–38.2); ADA 32·1% (26.7–37.1)
  - 2 year % LOR for IFX 54.5% (49.4–59.0); ADA 47.2% (40.2–53.4)
  - 3 year % LOR for IFX 60.0% (54.1–65.2); ADA 68.4% (50.9–79.7)

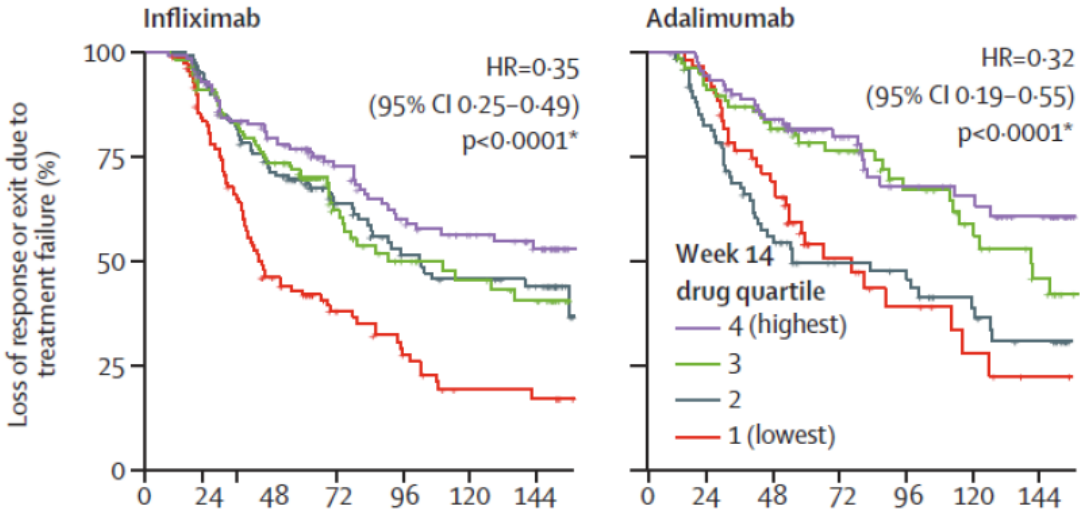


IFX = infliximab; ADA = adalimumab; LOR = loss of response.

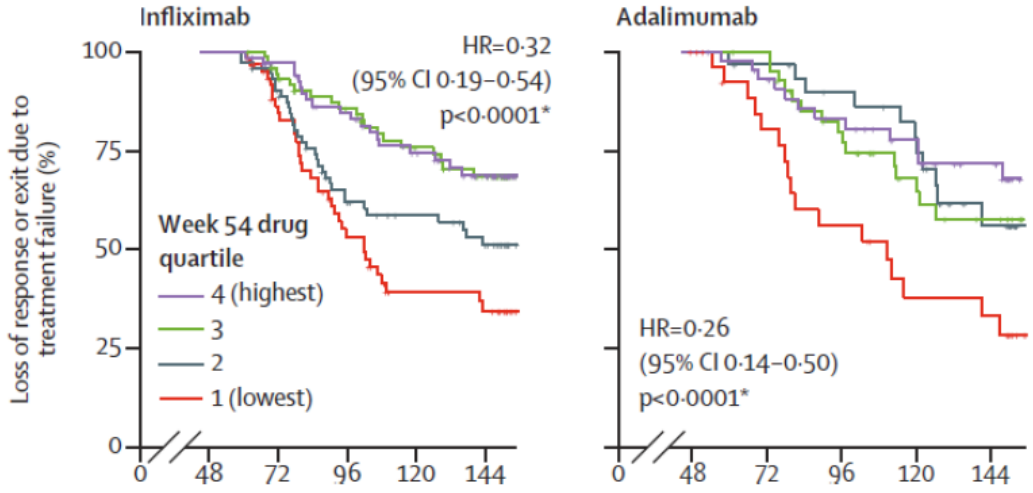
Ben-Horin S, Chowers Y. *Aliment Pharmacol Ther.* 2011 May;33(9):987-995. Gisbert JP, Panés J. *Am J Gastroenterol.* 2009;104(3):760-767. Chanchlani N, et al. *Lancet Gastroenterol Hepatol*. 2024;9(6):521-538.

Low Drug Concentration Predicts Anti-TNF Failure in PANTS Study

Loss of Response or Exit Due to Treatment Failure by Week 14 Anti-TNF Drug Concentration*



Loss of Response or Exit Due to Treatment Failure by Week 54 Anti-TNF Drug Concentration†



*Week 14 anti-TNF drug concentration (quartile 1: infliximab < 1·9 to 3·1 mg/L, adalimumab < 0·8 to 7·5 mg/L; quartile 2: infliximab 3·2 to 5·9 mg/L, adalimumab 7·6 to 10·8 mg/L; quartile 3: infliximab 6·0 to 10·5 mg/L, adalimumab 10·9 to 14·4 mg/L; and quartile 4: infliximab > 10·5 mg/L, adalimumab > 14·4 mg/L.
†Week 54 anti-TNF drug concentration (quartile 1: infliximab < 1·9 to 2·3 mg/L, adalimumab < 0·8 to 5·7 mg/L; quartile 2: infliximab 2·4 to 4·3 mg/L, adalimumab 5·8 to 10·0 mg/L; quartile 3: infliximab 4·4 to 7·7 mg/L, adalimumab 10·1 to 14·1 mg/L; and quartile 4: infliximab > 7·7 mg/L, adalimumab > 14·1 mg/L.

CD = Crohn's disease.

Chanchlani N, et al. *Lancet Gastroenterol Hepatol*. 2024;9(6):521-538.

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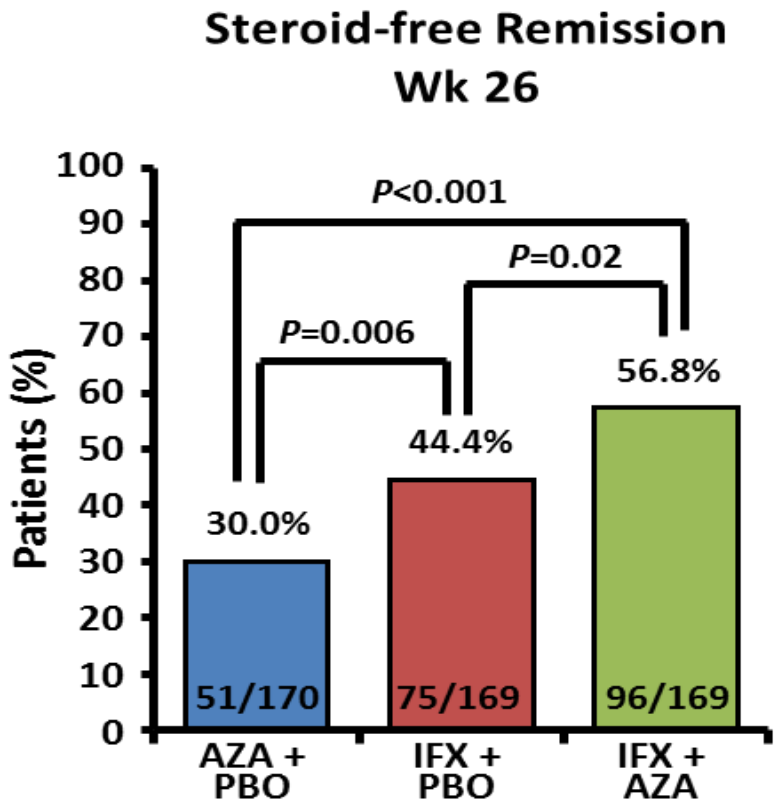
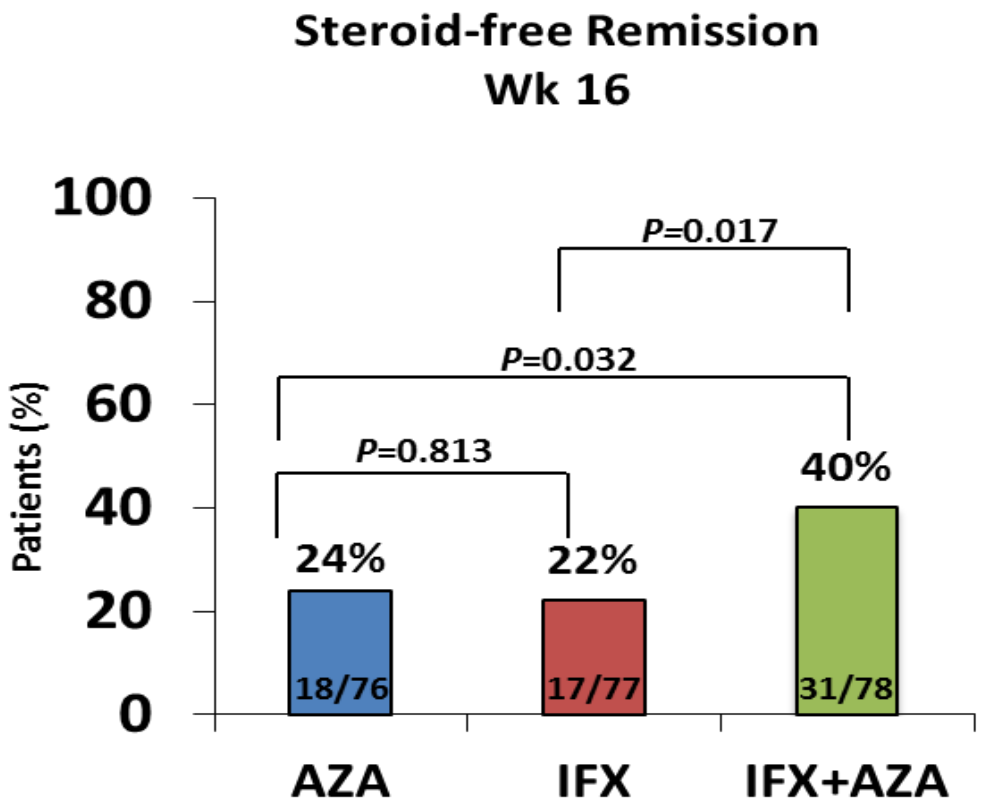
Strategies to Improve Anti-TNF Efficacy: Combination Therapy

SONIC Trial (CD)



UC SUCCESS Trial



UC = ulcerative colitis; AZA = azathioprine; PBO = placebo.

Colombel JF, et al. *N Engl J Med*. 2010;362(15):1383-1395. Panaccione R, et al. *Gastroenterology*. 2014;146(2):392-400.e3.

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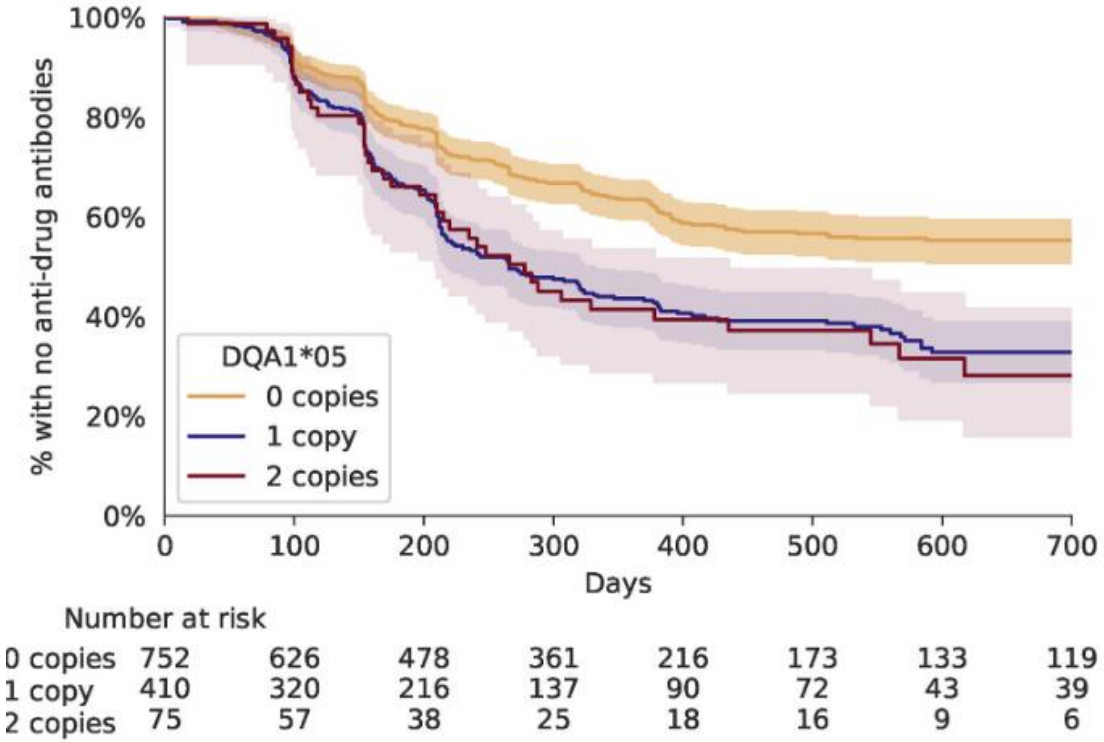
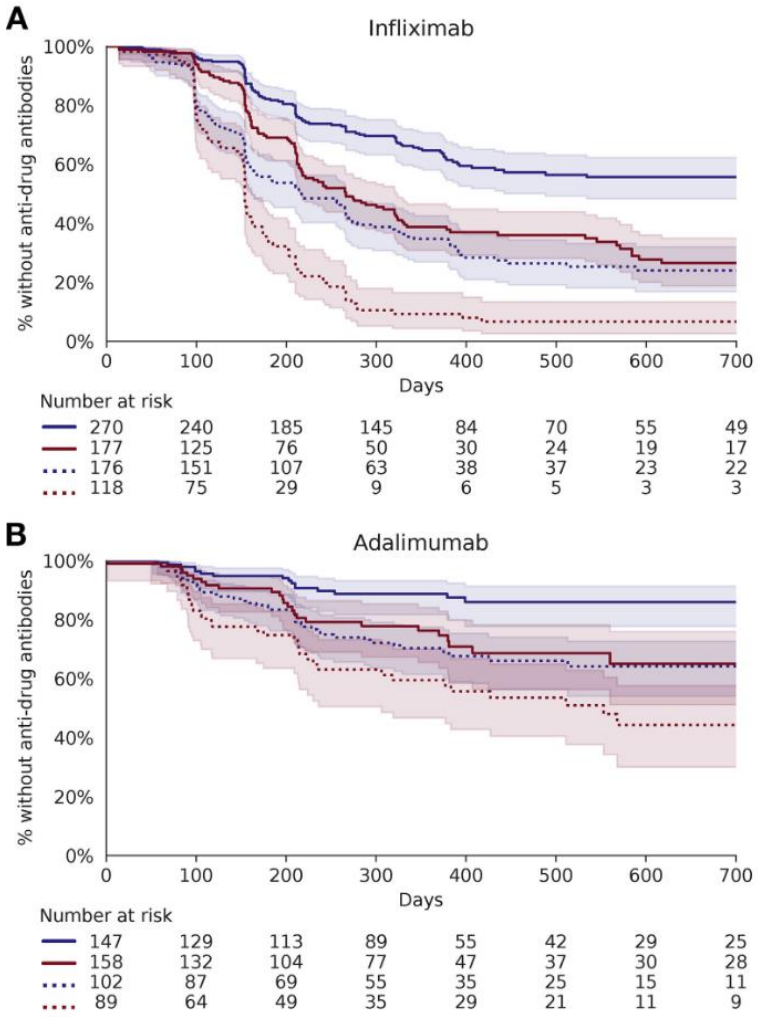
Strategies to Improve Anti-TNF Efficacy: HLA-DQA1*05 and Immunogenicity





Blue= non-carriers
Red= carriers
Dotted = monotherapy
Solid= combotherapy

Sazonovs A, et al. *Gastroenterology*. 2020;158(1):189-199.

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TDM as a Means to Manage Immunogenicity w/ Anti-TNF

- Reactive drug monitoring
  - Await symptom or biomarker changes then alter therapy
  - **TDM in the setting of primary or secondary loss of response to a biologic agent**
- Proactive drug monitoring
  - Preemptively change drug dosing from the onset
  - **Measurement of trough concentration and antibody levels with the goal of optimizing drug concentrations to achieve a threshold drug concentration at specific time-points (eg. during induction, at end of induction, or during maintenance)**

TDM = therapeutic drug monitoring.

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Potential Factors Affecting Biologic Drug Levels/Clearance

Anti-drug antibody/drug complex formation
Concomitant treatment with immunomodulators
Leakage/loss to gut lumen
Inflammatory burden and drug consumption
CRP levels
TNF-α levels
FcRn (Brambell receptor) rescue system
Albumin levels
Body weight
Male gender

CRP = C-reactive protein; FcRn = neonatal Fc receptor.
Marsal J, et al. *Front Med (Lausanne).* 2022;9:897936.

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Strategies to Improve Immunogenicity: TDM in PAILOT Trial

- Pediatric Crohn's disease ADA level-based optimization treatment trial
- Multicenter RCT (non-blinded)
- Biologic naïve children with CD who responded to ADA induction at week 4 randomly assigned to proactive and reactive groups; with adjustment of dose or intervals to maintain levels higher than 5 ug/ml in proactive group, physicians only informed of trough levels when clinically indicated in reactive arm (based on symptoms and/or elevated biomarkers)
- Endpoint: Sustained steroid free remission from wk 8 to 72 (PCDAI<10)

PCDAI = Pediatric Crohn's Disease Activity Index.

Assa A, et al. *Gastroenterology*. 2019;157(4):985-996.e2.

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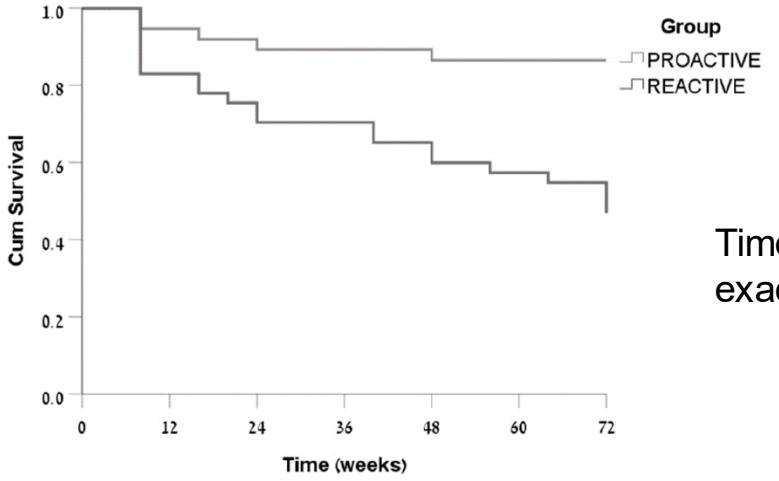
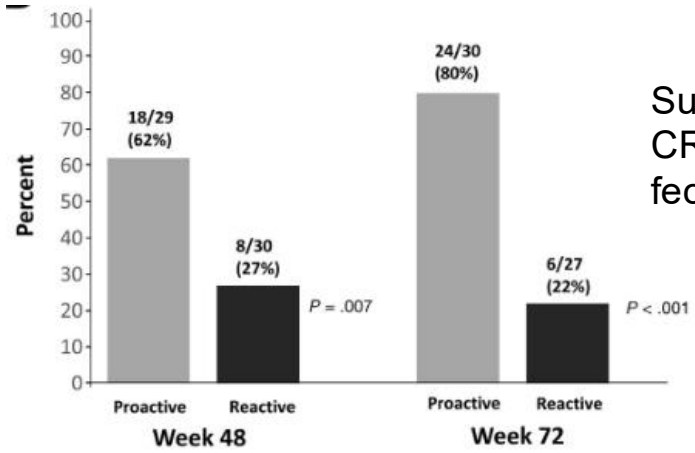
Strategies to Improve Immunogenicity: TDM in PAILOT Trial

- Total of 80 patients (43% on combination therapy with IMM)
- 87% of children met the primary endpoint in proactive vs 49% reactive (<0.001)
- Clinical indicies, CRP, fecal cal correlated with trough concentrations



Kaplan–Meyer curve representing time to disease exacerbation.

Time to disease exacerbation



Sustained CSFR, CRP <0.5 and fecal cal <150

IMM = immunomodulator; CSFR = colony stimulating factor receptor.

Assa A, et al. *Gastroenterology*. 2019;157(4):985-996.e2.

Assays for Measurement of Anti-TNF Levels in Practice

- Assays
  - Enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), homogenous mobility shift assay (HMSA)
    - Drug sensitive: Inability to detect ADA in the presence of drug
    - Drug tolerant: Allows measurement of drug antibodies in the presence of drug
- Anti-drug antibodies (ADA)
  - Neutralizing ADA: Tend to be "high," decrease drug concentration, increase risk of loss of response; increase hypersensitivity to biologic
  - Non-neutralizing ADA: Low level, temporary and without impact.
- Drug levels
  - Good correlation across different assays (linear correlation 0.73 to 0.99)
- Anti-drug antibodies
  - Because of different measures of quantification and lack of international standards, low or no agreement between ADA values across assays.
- **From clinical practice – goal levels essentially: > 10.0 µg/ml for anti-TNF[a]**

[a]From clinical practice.

Vande Casteele N. *Frontline Gastroenterol*. 2017;8(4):236-242.

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Proposed Target Levels of Anti-TNF for Clinical Decision Making

Clinical time point	Infliximab	Adalimumab	Golimumab
After induction (week 14)	4-15 µg/mL	N/D	N/D
During remission (therapeutic)	4-8 µg/mL	5-10 µg/mL	1.4-4 µg/mL[a]
To treat flare or before discontinuing due to loss of response (supratherapeutic)	> 10 µg/mL	> 12 µg/mL	N/D
For fistula healing	> 12 µg/mL	> 14 µg/mL	N/A

[a]Assay dependent.
N/A = not applicable; N/D = no consistent data.
Marsal J, et al. *Front Med (Lausanne).* 2022;9:897936.

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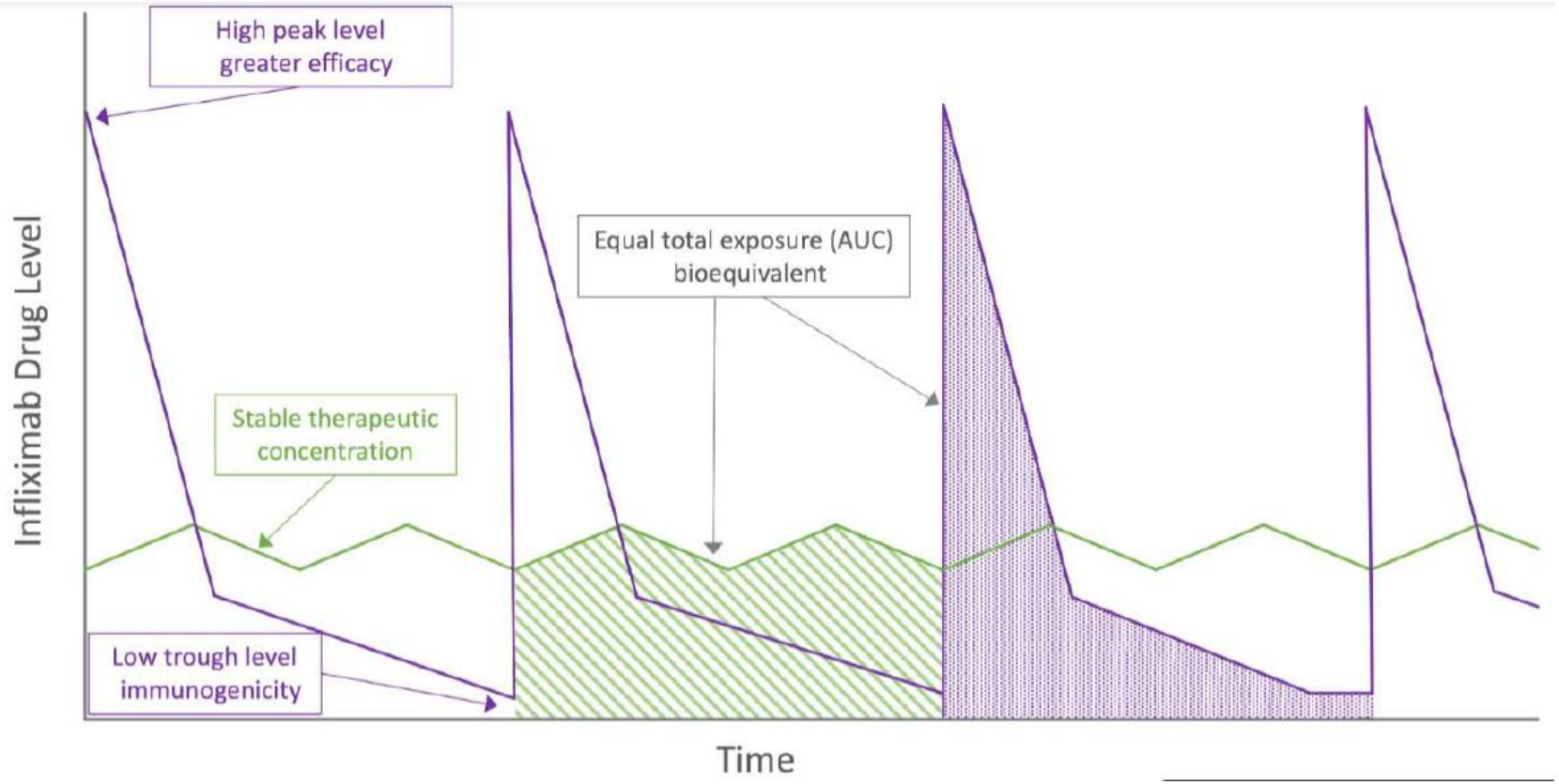
Strategies to Improve Immunogenicity: Reduce Level Peaks and Valleys

Figure 2. Visual representation of proposed theoretical pharmacokinetic advantages and disadvantages between intravenous (purple) and subcutaneous (green) infliximab. AUC = area under the curve.



Little RD, et al. *J Clin Med*. 2022;11(20):6173

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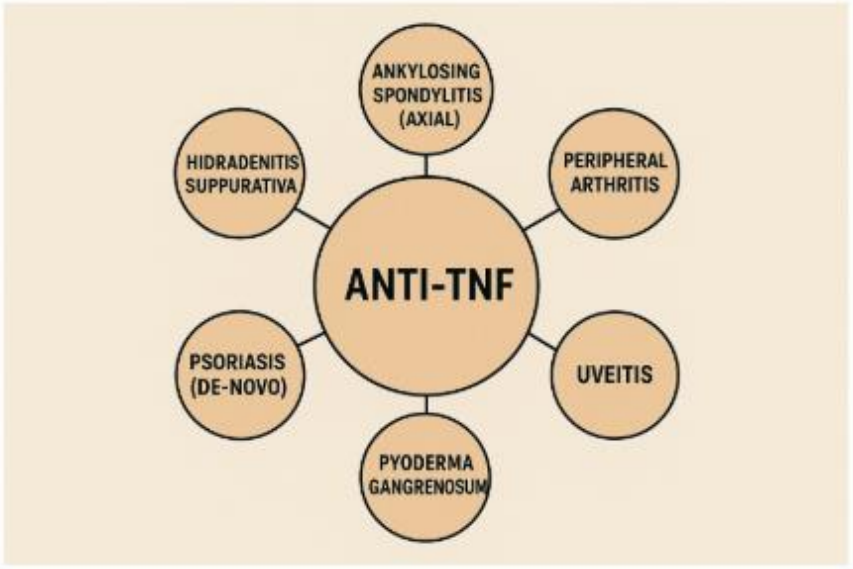
Anti-TNF Is Indicated with Extraintestinal Manifestations

- Ankylosing spondylitis (axial)
- Peripheral arthritis
- Uveitis
- Pyoderma gangrenosum
- Psoriasis (*de novo*)
- Hidradenitis suppurativa



- Swiss cohort: Of the 366 patients with at least 1 EIM, 213 (58.2%) were ever treated with an anti-TNF
- Anti-TNF is mainstay of therapy for EIMs

EIM = extraintestinal manifestations.

Vavricka SR, et al. *Inflamm Bowel Dis*. 2015;21(8):1982-92.

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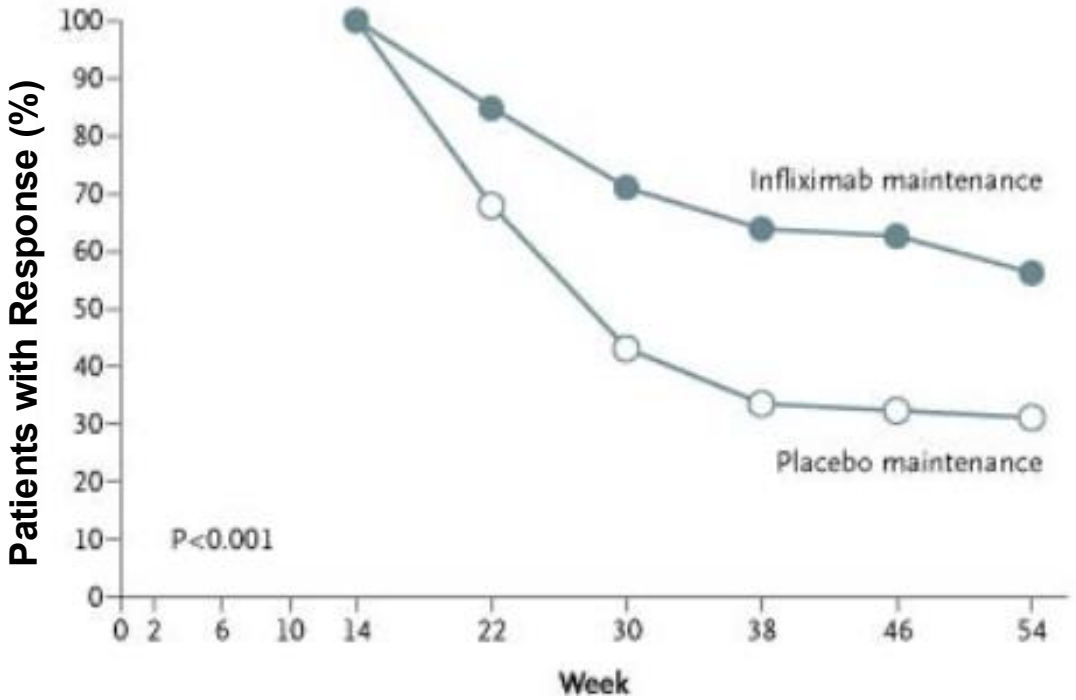
Specific Phenotype with Indication for Anti-TNF: ACCENT II Perianal Dz

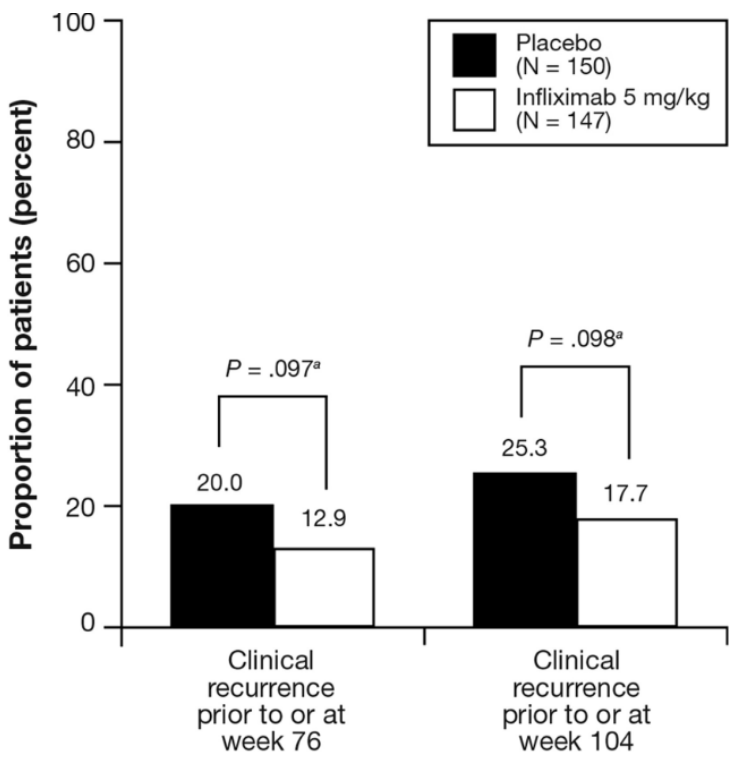
- RCT of patients with CD with single or multiple draining fistulas for 3 months
- After induction, evaluated the efficacy and safety of repeated maintenance infusions of IFX in maintaining closure of draining fistulas
- Fistula response: Defined as reduction of at least 50% from base line in the number of draining fistulas at consecutive visits four or more weeks apart

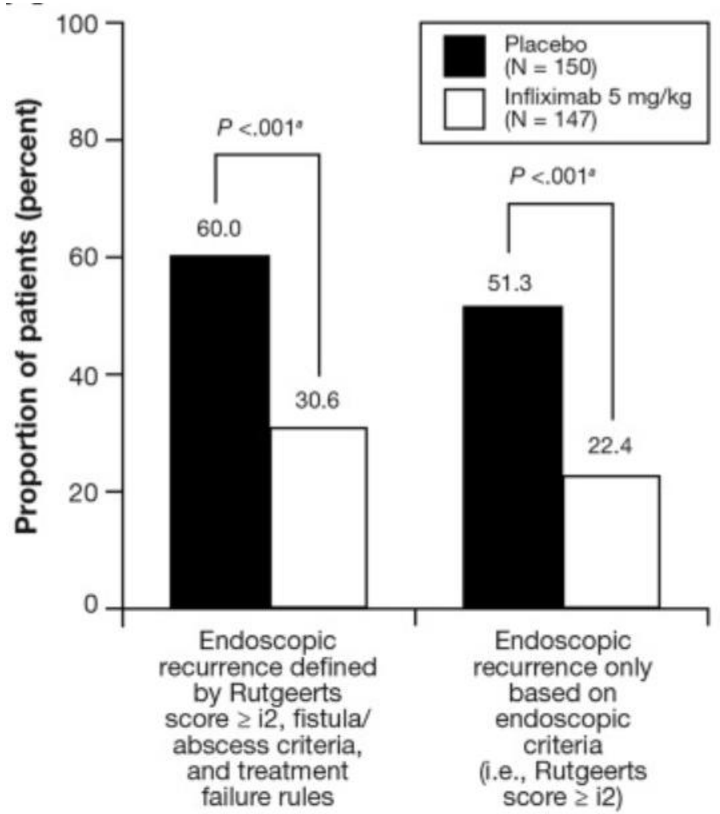


Sands BE, et al. *N Engl J Med.* 2004;350(9):876-885.

Specific Phenotype with Indication for Anti-TNF: PREVENT Post-Op CD

- RCT of IFX vs placebo
- Primary end point was clinical recurrence wk 76, defined by a ≥70-point increase and CDAI score ≥200 and Rutgeerts score of ≥i2
- Secondary outcome: Endoscopic recurrence of CD; Rutgeerts score of ≥i2



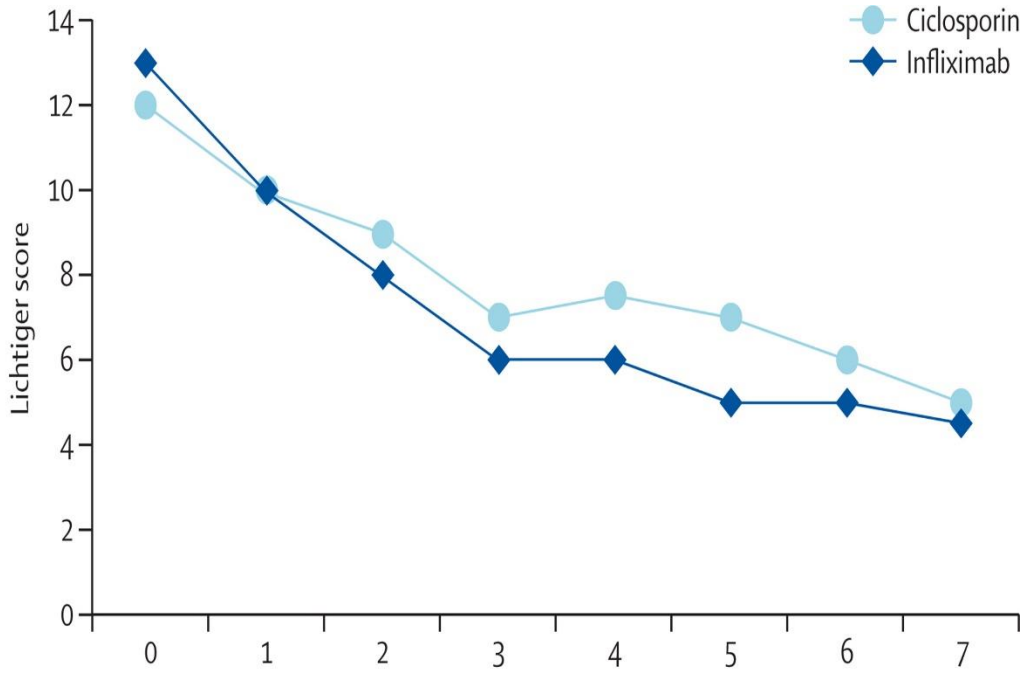


Reguerio M, et al. *Gastroenterol*. 2016;150(7):1568-1578.

Specific Phenotype with Indication for Anti-TNF: ASUC

- 115 patients randomized to receive IV CSA 2 mg/kg/day vs IFX 5 mg/kg at 0, 2, and 6 weeks
  - AZA started in both groups

- **Treatment failure** (no response by day 7, relapse between day 7 and 98, requirement for steroids at day 98, AE requiring drug withdrawal, colectomy, or death)
  - CSA: 60%
  - IFX: 54%



Number of assessable patients								
Ciclosporin	58	56	58	58	56	58	56	57
Infliximab	57	56	54	53	54	54	53	56
p	0·013	0·54	0·11	0·039	0·015	0·08	0·16	0·15

CSA = ciclosporin A; AE = adverse event; ASUC = acute severe ulcerative colitis.

Laharie D, et al. *Lancet*. 2012;380(9857):1909-1915.

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Safety Considerations with Anti-TNF: Infectious Complications

Infectious complication	Disease or pathogen	Differential factor	Frequency (% or events/p-y)
Viruses	Hepatitis B virus reactivation	HBsAg	12-39
		Anti-HBcAb+, sAg-	5
	Herpes zoster reactivation		1.01/100
Bacteria	TB		116.7/100,000
	Nocardiosis		8.66/100,000
	Listeriosis		6.93/100,000
Fungi	Invasive candidiasis		
	Pneumocystosis		0.5
Serious infections			4.5-14.0/100

TB = tuberculosis.

Davis JS, et al. *Clin Microbiol Rev*. 2020;33(3):e00035-19.

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Safety Considerations with Anti-TNF: Lymphoma

- Nationwide cohort study based on French National Health Insurance databases
- Included 189 289 patients followed up for a median of 6.7 years
- IR 0.26; 95% CI, 0.23-0.29 unexposed),IR, 0.41; 95% CI, 0.27-0.55 TNF monotherapy)

Table 3. HRs Comparing the Risk of Lymphoma in Patients Exposed to Thiopurine Monotherapy, Anti-TNF Monotherapy, and Combination Therapy vs Unexposed Patients

	Exposed to Thiopurine Monotherapy vs Unexposed to Thiopurines or Anti-TNF Agents		Exposed to Anti-TNF Monotherapy vs Unexposed to Thiopurines or Anti-TNF Agents		Exposed to Combination Therapy vs Unexposed to Thiopurines or Anti-TNF Agents	
Lymphoma Type	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[a]	Crude HR (95% CI)	Adjusted HR (95% CI)[a]
All Patients						
All lymphoma	2.06 (1.58-2.70)	2.60 (1.96-3.44)	1.57 (1.08-2.28)	2.41 (1.60-3.64)	3.60 (2.10-6.19)	6.11 (3.46-10.8)
Hodgkin lymphoma	2.78 (1.45-5.33)	2.83 (1.37-5.84)	2.21 (0.92-5.35)	2.23 (0.81-6.13)	11.4 (4.76-27.2)	12.1 (4.46-33.1)
Non-Hodgkin lymphoma	1.95 (1.45-2.62)	2.57 (1.90-3.49)	1.47 (0.97-2.22)	2.48 (1.58-3.89)	2.38 (1.17-4.84)	4.48 (2.15-9.34)
Patients With Incident IBD						
All lymphoma	1.58 (0.84-3.00)	2.35 (1.16-4.75)	0.98 (0.39-2.48)	1.49 (0.54-4.12)	3.14 (1.13-8.71)	5.90 (1.79-19.4)

Abbreviations: HR, hazard ratio; IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

[a] Multivariable Cox model adjusted for baseline characteristics including sex, age, affiliation to Complementary Universal Health Insurance, IBD diagnosis and duration, exposure to methotrexate and aminosalicylates, comorbidities and time-dependent covariates including exposure to corticosteroids, and IBD-related hospitalizations and surgical procedures.

Lemaitre M, et al. *JAMA*. 2017;318(17):1679-1686.

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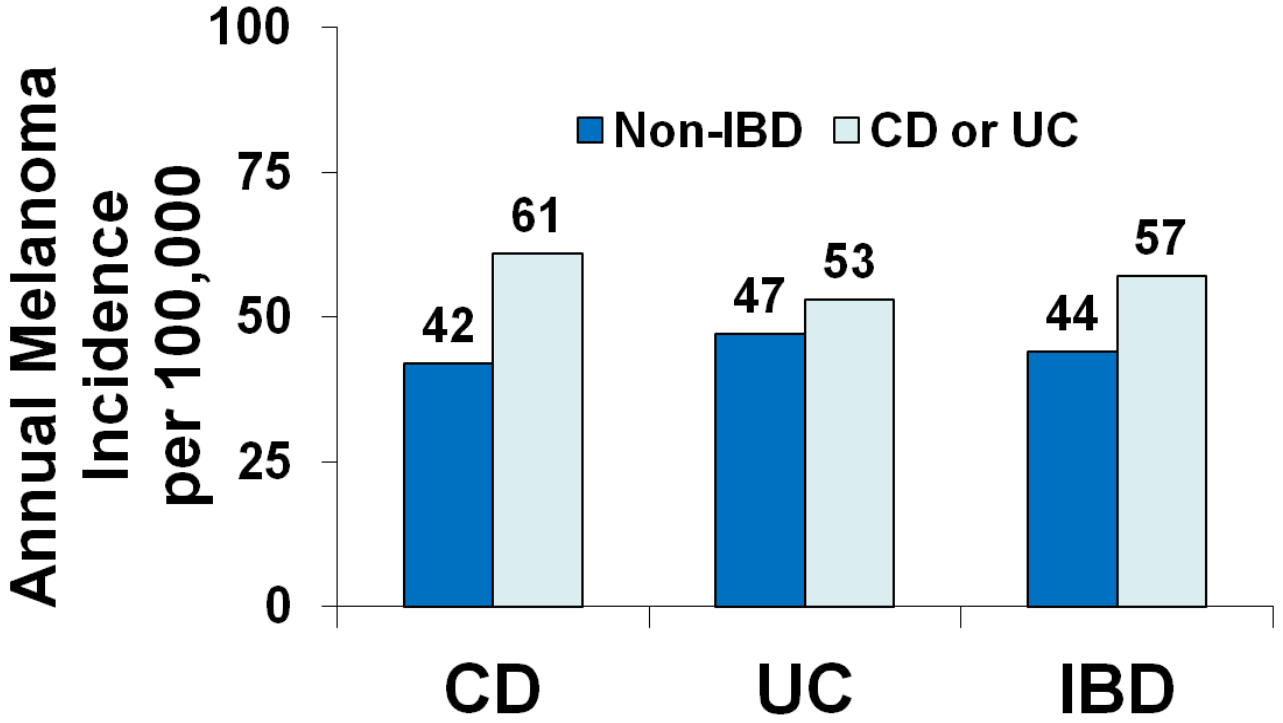
Safety Considerations: Melanoma

- Large US retrospective cohort
  - IRR 1.29; 95% CI 1.09-1.53
- Meta-analysis (12 studies)
  - IBD with increased risk (RR 1.37; 95% CI, 1.10-1.70
  - Highest risk with CD (RR 1.80; 95% CI, 1.17-2.75)



	CD	UC	IBD
IRR	1.45	1.13	1.29
95% CI	1.13-1.85	0.89-1.42	1.09-1.53

IRR = incidence rate ratio; RR = relative risk.

Long MD, et al. *Gastroenterology*. 2012;143(2):390-399.e1. Singh S, et al. *Clin Gastroenterol Hepatol.* 2014;12(2):210-218.

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Safety Considerations: Melanoma

Crohn's disease

Medication Class[a]	IBD overall	Crohn's disease	Ulcerative colitis
5-ASA	1.06 (0.77-1.45)	0.98 (0.63-1.53)	1.22 (0.76-1.96)
Anti-TNF	1.88 (1.08-3.29)	1.94 (1.03-3.68)	1.73 (0.53-5.63)
Thiopurine	1.10 (0.72-1.67)	0.92 (0.53-1.59)	1.31 (0.66-2.60)

[a]Any use, adjusted OR controlled for other medication use, comorbidities, health care utilization.
ASA = aminosalicylic acid.
Long MD, et al. *Gastroenterology*. 2012;143(2):390-399.e1

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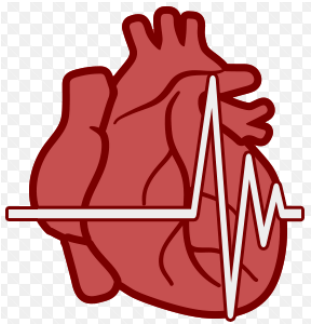
Safety Considerations: Understanding Comorbidities in IBD

- Most common comorbidity w/ IBD is cardiovascular disease; also prevalent in general population
  - IBD may predispose to CV disease
  - Active inflammation and young age (<55) have been shown to a risk factor for acute arterial events in IBD (ASCVD, CVA, peripheral artery disease)
  - Markedly increased risk of ischemic heart disease in the first year after initial IBD diagnosis
  - IBD patients hospitalized with CHF may have higher mortality



ASCVD = atherosclerotic cardiovascular disease; CVA = cardiovascular disease; CHF = congestive heart failure.

Kirchgesner J, et al. *Gut*. 2018;67(7):1261-1268. Ehrenpreis ED, et al. *PLoS One*. 2016;11(7):e0158926. Rungoe C, et al. *Gut*. 2013;62(5):689-694.

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Comorbid Medical Conditions and Therapy: Contraindications

- Congestive heart failure
  - Anti-TNF use may be associated with heart failure
  - Concern stems from RCTs of TNF-alpha inhibitors as a potential therapy for heart failure (ATTACH)
    - Use in class III or IV heart failure (IFX vs PBO), IFX with 16% death rate, placebo 8%
  - Early postmarketing surveillance data gathered by the FDA
    - 47 cases of HF associated with anti-TNF, 38 w/ new-onset HF, and 9 w/ HF exacerbation
  - A more recent cohort showed that risk of HF with anti-TNF dropped off after 2002, w/ no increased risk of CHF hospitalization for patients with RA treated with anti-TNF vs disease-modifying anti-rheumatic drugs (DMARD)
- Recommendation
  - Avoid anti-TNF in class III,IV CHF
  - Can use in well controlled CHF w/ cardiologist, prior echo, and lowest dose

Chung ES, et al. *Circulation*. 2003;107(25):3133-3140. Kwon HJ, et al. *Ann Intern Med*. 2003;138(10):807-811. Solomon DH, et al. *Ann Rheum Dis*. 2013;72(11):1813-1818.

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Summary of Available Anti-TNF Therapies for UC and CD

Therapy	Route	Indication	Trial Name	EU Approval	US Approval
Infliximab[1]	IV	CD	ACCENT I	1999	1998
Infliximab[2]	IV	UC	ACT 1/ACT 2	2006	2005
Adalimumab[3]	SC	CD	CLASSIC I, CHARM, GAIN	2007	2007
Certolizumab pegol[4,5]	SC	CD	PRECiSE 1, PRECiSE 2	2008	2008
Adalimumab[6,7]	SC	UC	ULTRA 1, ULTRA 2	2012	2012
Golimumab[8,9]	SC	UC	PURSUIT-SC, PURSUIT-M	2013	2013
Infliximab-dyyb[10]	SC	UC/CD (maintenance)	LIBERTY	2020	2023

EU = European Union.

Hanauer SB, et al. *Lancet*. 2002;359(9317):1541-1549. Rutgeerts P, et al. *N Engl J Med*. 2005;353(23):2462-2476. Lichtenstein GR, et al. *Therap Adv Gastroenterol*. 2008;1(1):43-50. Sandborn WJ, et al. *N Engl J Med*. 2007;357(3):228-238. Schreiber S, et al. *N Engl J Med*. 2007;357(3):239-250. Reinisch W, et al. *Gut*. 2011;60(6):780-787. Sandborn WJ, et al. *Gastroenterology*. 2012;142(2):257-265.e1-3. Sandborn WJ, et al. *Gastroenterology*. 2014;146(1):85-95. Sandborn WJ, et al. *Gastroenterology*. 2014;146(1):96-109.e1. Hanauer SB, et al. *Gastroenterology*. 2024;167(5):919-933.

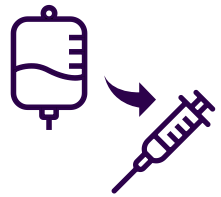
AIBD

Summary: Anti-TNFs

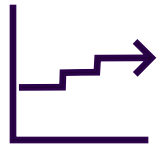
PROS

Mucosal healing

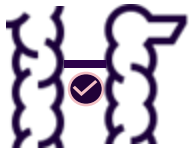
Fast onset of action



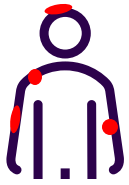
Evolution of IV to SC



Durable response w/ monitoring



Efficacy for perianal fistulas



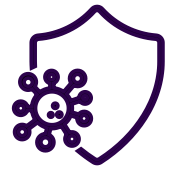
Efficacy for EIMs

Post-op use

CONS

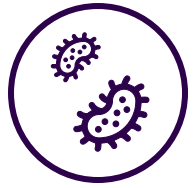
Initially IV for IFX

Need for combo use



Immunogenicity

Risk of malignancy



Risk of infections

Fudman DI, et al. *Clin Gastroenterol Hepatol*. 2025;23(3):454-468. Lichtenstein GR, et al. *Am J Gastroenterol*. 2025;120(6):1225-1264. Rubin DT, et al. *Am J Gastroenterol*. 2025;120(6):1187-1224.

AIBD

Key Learning Points

- TNFα inhibitors are highly effective in IBD, with advantages including fast onset of action, mucosal healing, efficacy in EIMS, perianal disease, post operative CD, ASUC
- When utilizing TNFα inhibitors, MUST have a strategy for immunogenicity
  - Combination therapy with IMM and/or proactive TDM
- Safety considerations include
  - Infectious complications, risks of lymphoma, melanoma
- TNFα inhibitors should be avoided w/ certain comorbidities
  - Advanced CHF, multiple sclerosis
- Various TNFα inhibitors are available for CD and UC, including subq options of delivery

AIBD

Targeting TNFα in IBD:
Innovations in Drug Design, Delivery,
and Clinical Application

Ulcerative Colitis: Focus on Subcutaneous IFX

Ben Cohen, MD, MAS

Vice Chair, Dept. of Gastroenterology, Hepatology, & Nutrition
Co-Section Head Inflammatory Bowel Diseases
Digestive Disease Institute
Cleveland Clinic

Disclosures

- **Ben Cohen, MD, MAS:** Advisory board – Abbvie, ALPCO, Johnson & Johnson Innovative Medicine, Lilly, Pfizer, Takeda; consultant – Abbvie, ALPCO, Johnson & Johnson Innovative Medicine, Lilly, Pfizer, Takeda; speaker's bureau – AbbVie, Takeda; DSMB – Emmes Biopharma; CME – i3 Health

Case 1: 30-Year-Old Woman with Moderate to Severe UC

- New onset of moderate to severe left-sided UC
- Also has AS with significant morning stiffness that is impacting QoL
- Currently treated with 5-ASA and oral prednisone
- Reports 2 flares over the past 6 months, treated with prednisone; unable to taper off completely since most recent flare
- Presenting GI symptoms include bloody diarrhea, abdominal cramping, 4-5 bowel movements daily with urgency
- Has a 3-year-old son and hopes to have more children
- Indicates she would prefer to limit her time at an infusion center due to work schedule and family
- Wants quick resolution of her symptoms

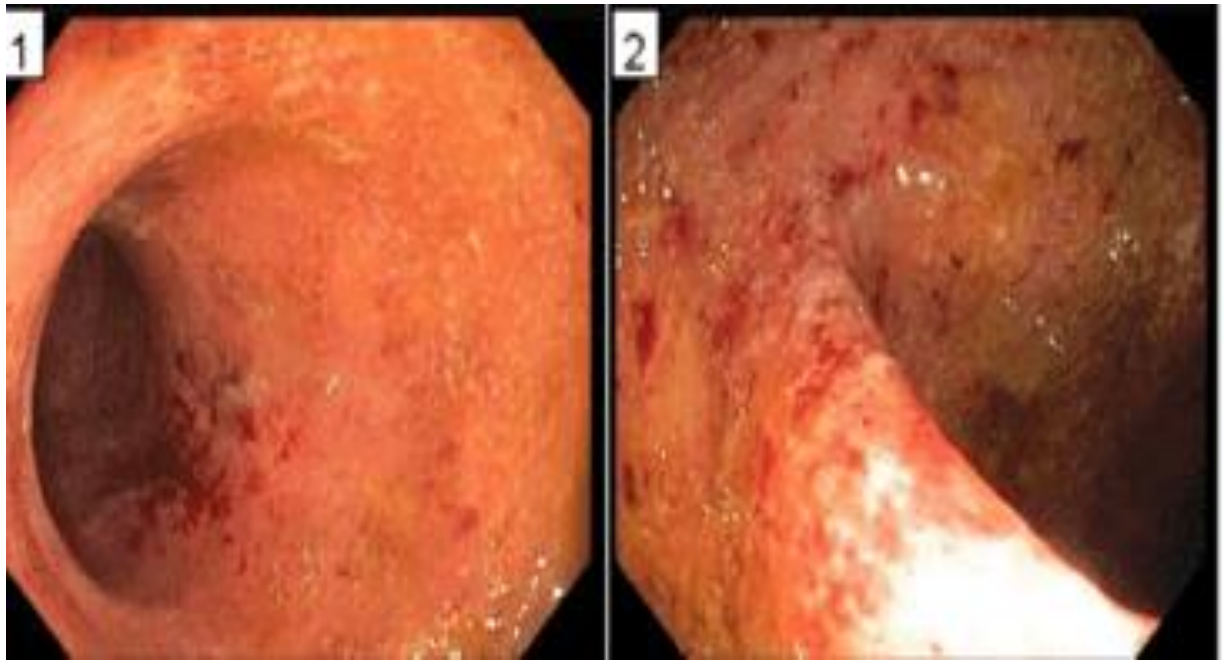
QoL = quality of life; GI = gastrointestinal; AS = ankylosing spondylitis.

AIBD

Case 1: 30-Year-Old Woman with Moderate to Severe UC

Hgb	11.5 g/dL	Range: 13.3-16.2
Albumin	3.2 g/dL	Range: 4.0-5.0
CRP	8 mg/dL	Range: 0-0.3
ESR	30 mm/hr	Normal for female < 50: ≤ 20 mm/h
Fcal	1200 µg/g	Normal < 50 µg/g
Stool culture	Negative for *Clostridioides difficile*	

Negative for HBsAg, anti-HBc, and anti-HBs; TB negative



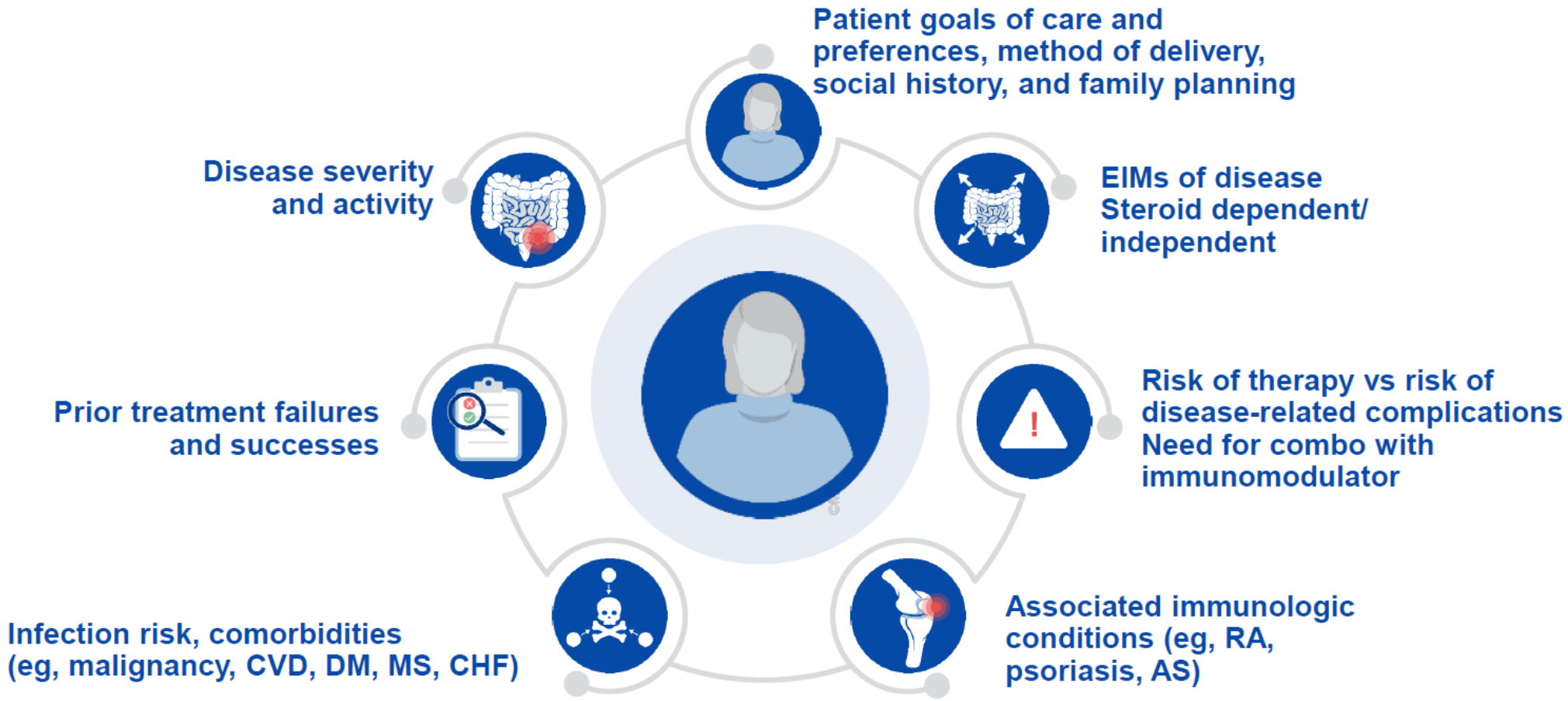
- **Impression: Mayo 2 left-sided UC**
- **Pathology**
  - Ileum – normal
  - Right colon, transverse colon – normal
  - Rectum, sigmoid, descending – moderate chronic active colitis
  - No dysplasia. CMV negative

CMV = cytomegalovirus.

AIBD ADVANCES IN INFLAMMATORY BOWEL DISEASES

What are the options?

Factors Influencing Medication Choice



DM = diabetes mellitus; MS = multiple sclerosis; RA = rheumatoid arthritis.

Fudman DI, et al. *Clin Gastroenterol Hepatol*. 2025;23(3):454-468.

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Highlights of UC ACG Guidelines 2025

1. Patients with mildly to moderately active UC who are not responsive (or are intolerant) to 5-ASA therapies **should be treated as patients with moderate-to-severe disease**
2. Patients with UC should have all medical options available as recommended by their doctor and healthcare team. **Third-party payers and requirements for step therapy should not come between the patient and their healthcare** team in making decisions about treatment for UC
3. Given the expanding number of therapies per mechanistic class, a **distinction between primary non-response and secondary non-response is important** in order to select the next therapeutic option
4. **Infliximab is the preferred anti-TNF therapy** for patients with moderately to severely active UC

ACG = American College of Gastroenterology.

Rubin DT, et al. *Am J Gastroenterol*. 2025;120(6):1187-1224.

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Highlights of UC ACG Guidelines 2025

5. When IFX is used as induction therapy for patients with moderately to severely active UC, **we recommend combination therapy with a thiopurine** (Strong recommendation, moderate quality of evidence for AZA)
   - Data on combination anti-TNF and IM in moderate to severe UC only exists for IFX and thiopurines
6. Subcutaneous IFX and vedolizumab are considered equivalent to the standard intravenous maintenance dosing of these agents. The equivalence of the subcutaneous formulations for induction or as substitution for escalated doses of these therapies has not been robustly established
7. Initial and subsequent therapies for moderately to severely active UC may be **chosen based on EIMs**, including the involvement of joints or skin, in which therapies that have efficacy in both UC and in the extra-intestinal organ is known
   - Examples: Inflammatory arthropathy – anti-TNF or JAKi; psoriasis – anti-IL23

JAKi = Janus kinase inhibitor; IL = interleukin.

Rubin DT, et al. *Am J Gastroenterol*. 2025;120(6):1187-1224.

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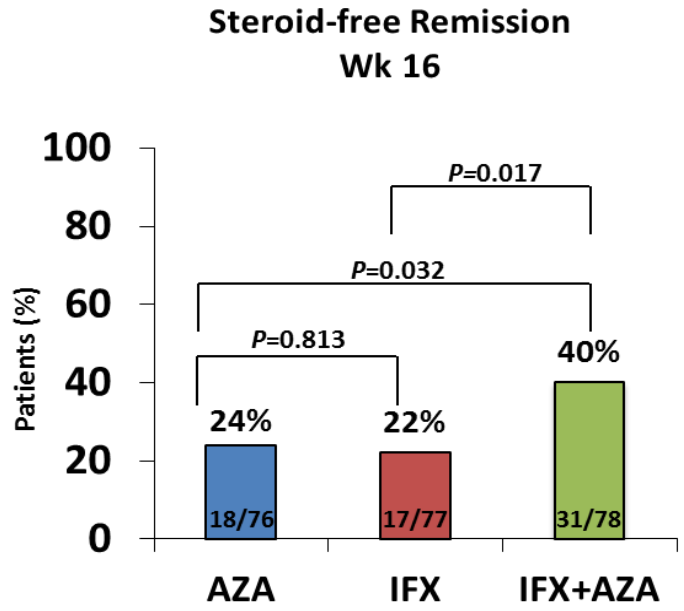
Special Considerations: Use of Anti-TNF with IMM

- ACG Guidelines 2025
  - **Anti-TNF with immunomodulator use data** exist for IFX in moderately to severely active UC
  - Patients with **non-response or loss of response on anti-TNF therapy should be assessed with trough serum concentrations** to identify reason and if existing therapy can be optimized
  - Patients who are non-responders to anti-TNF should be evaluated and **considered for a different class of therapy**
  - There is **insufficient evidence for proactive TDM** in all unselected patients with UC in remission

UC SUCCESS trial



Rubin DT, et al. *Am J Gastroenterol*. 2025;120(6):1187-1224. Panaccione R, et al. *Gastroenterology*. 2014;146(2):392-400.

AGA Positioning of Advanced Therapies in Adults with UC

ADVANCED THERAPY-NAÏVE PATIENTS (FIRST-LINE THERAPY)

SUGGEST using a HIGHER efficacy, or INTERMEDIATE efficacy medication, rather than a lower efficacy medication.

(Conditional recommendation, low certainty of evidence)

HIGHER EFFICACY MEDICATIONS: Infliximab, Vedolizumab, Ozanimod, Etrasimod, Upadacitinib*, Risankizumab, Guselkumab

INTERMEDIATE EFFICACY MEDICATIONS: Golimumab, Ustekinumab, Tofacitinib*, Filgotinib*, Mirikizumab

LOWER EFFICACY MEDICATIONS: Adalimumab

PRIOR EXPOSURE TO ONE OR MORE ADVANCED THERAPIES, PARTICULARLY TNF ANTAGONISTS

SUGGEST using a HIGHER efficacy, or INTERMEDIATE efficacy medication, rather than a lower efficacy medication.

(Conditional recommendation, low certainty of evidence)

HIGHER EFFICACY MEDICATIONS: Tofacitinib, Upadacitinib, Ustekinumab

INTERMEDIATE EFFICACY MEDICATIONS: Filgotinib, Mirikizumab, Risankizumab, Guselkumab

LOWER EFFICACY MEDICATIONS: Adalimumab, Vedolizumab, Ozanimod, Etrasimod

***In adult outpatients with moderate-to-severe UC, **AGA suggests the use of IFX in combination with an IMM** over IFX or an immunomodulator alone. **AGA suggests the use of ADA or golimumab in combination with an IMM** over ADA, golimumab, or immunomodulator monotherapy.

***At the time of these guidelines the FDA label recommended the use of JAKis only in patients with prior failure or intolerance to TNF antagonists. Filgotinib is not available for use in the United States.**

AGA = American Gastroenterological Association; FDA = Food and Drug Administration.

Singh S, et al. *Gastroenterology*. 2024;167(7):1307-1343.

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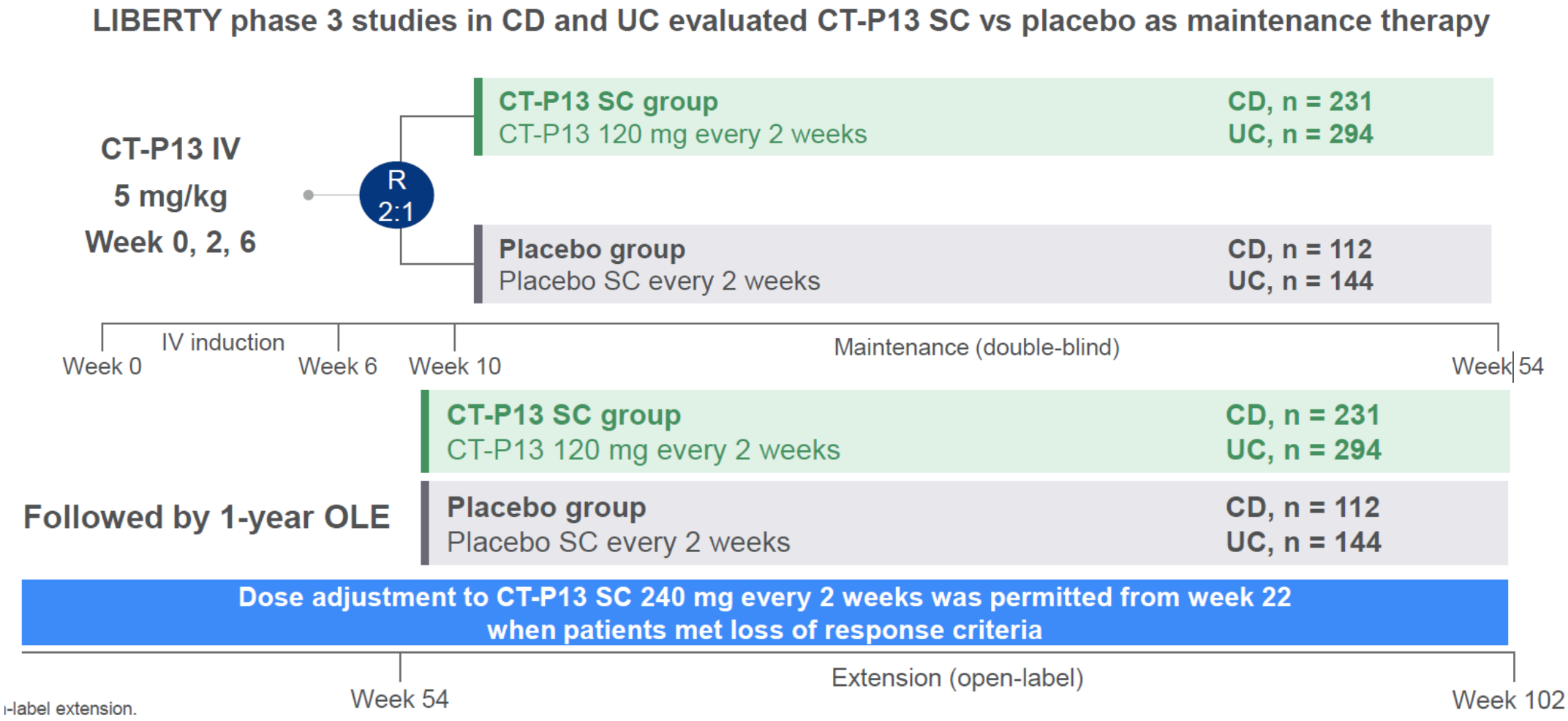
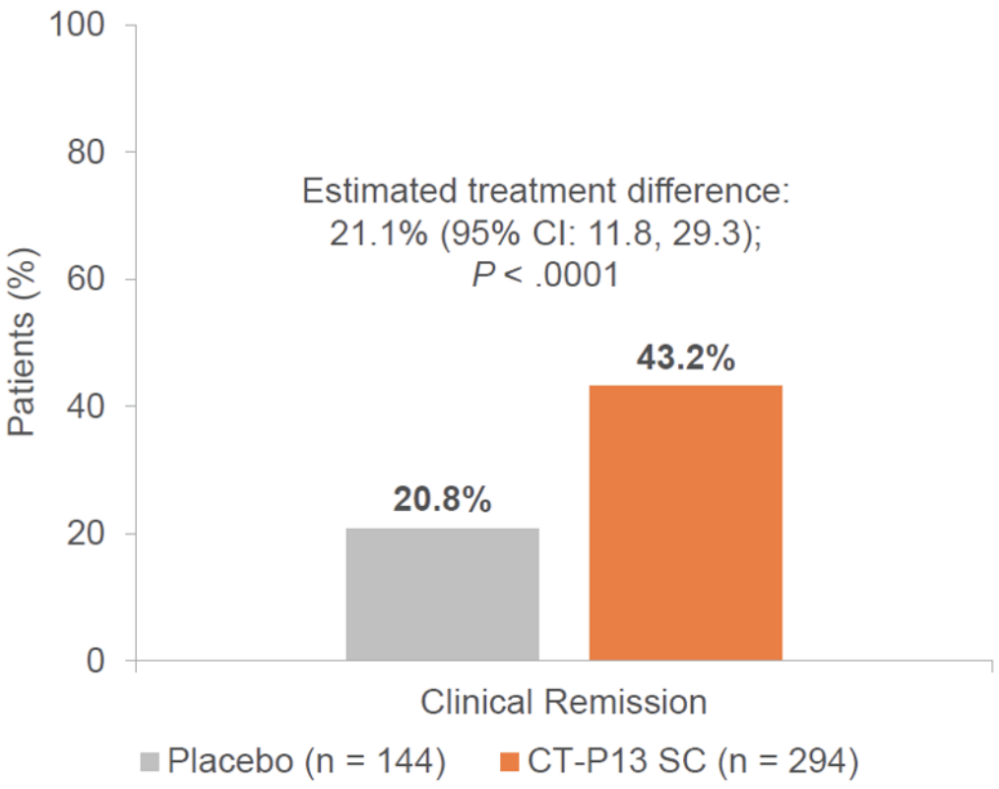
SC Infliximab as Maintenance Therapy in UC or CD: LIBERTY TRIAL



OLE = open-label extension.

Hanauer SB, et al. *Gastroenterology*. 2024;167(5):919-933.

LIBERTY UC: Primary Endpoint Clinical Remission at Wk 54



- During the maintenance phase, 172 patients (72.3%) and 65 patients (61.9%) in the CD study and 200 patients (67.6%) and 83 patients (59.3%) in the UC study experienced ≥1 TEAEs in the CT-P13 (infliximab-dyyb) SC and placebo groups, respectively
- Most treatment-emergent serious AEs not considered related to study drug
- The most frequent TEAE with CT-P13 SC during the maintenance phase of both studies was COVID-19
- Rates of systemic injection reaction were low and comparable between groups; no delayed hypersensitivity events

TEAE = treatment-emergent AE.

Hanauer SB, et al. *Gastroenterology*. 2024;167(5):919-933.

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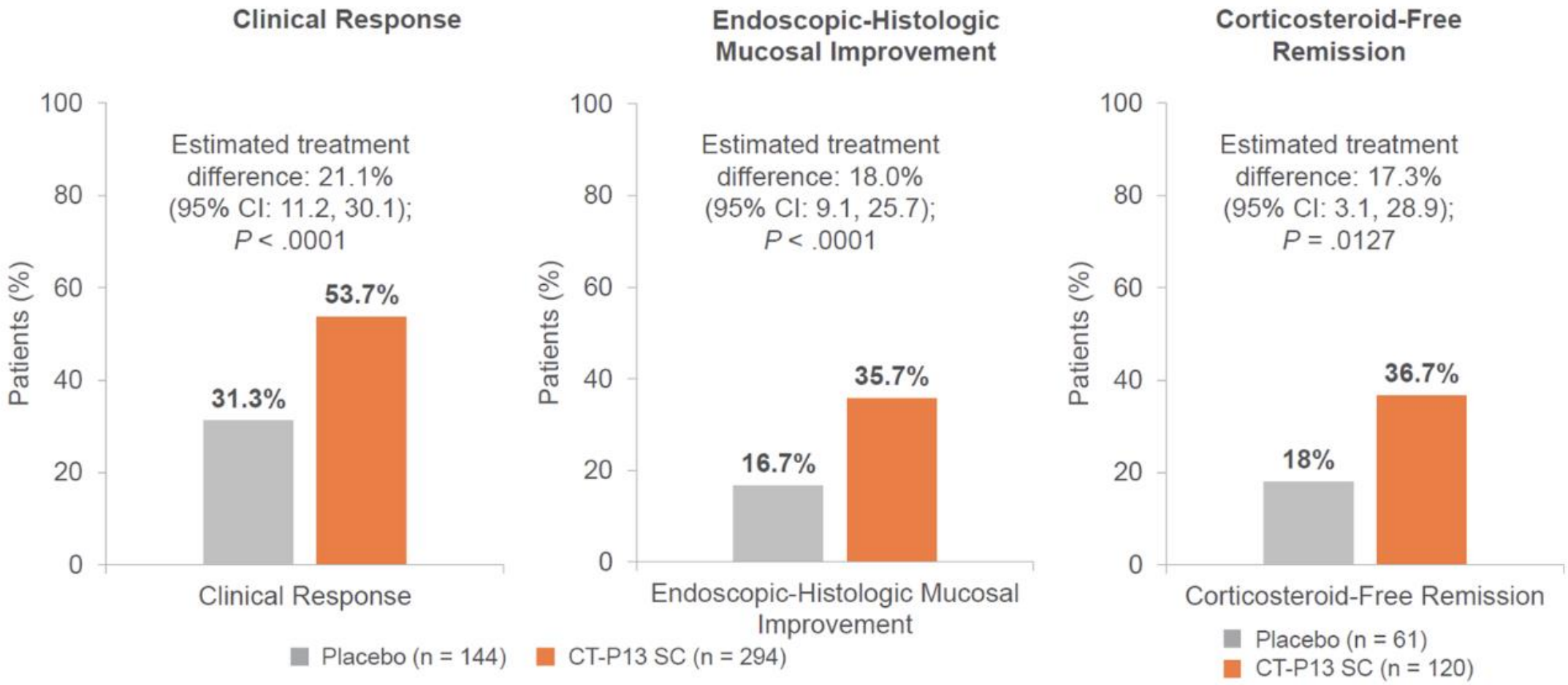
LIBERTY UC: Key Secondary Endpoints at Wk 54



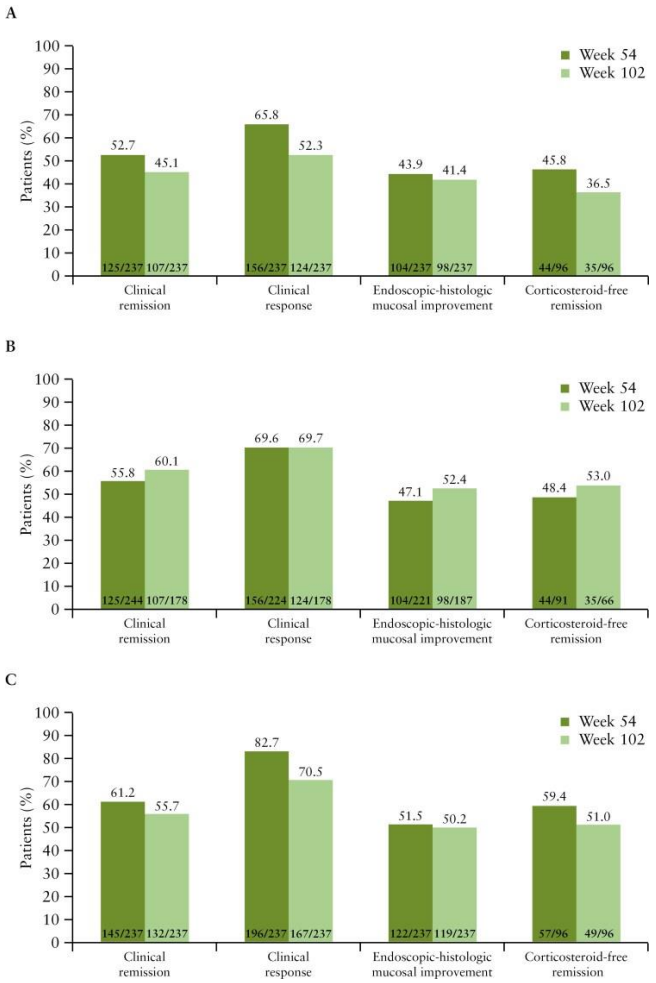
Hanauer SB, et al. *Gastroenterology*. 2024;167(5):919-933.

Subcutaneous IFX 2-Year Maintenance Data from LIBERTY-UC

Non-Responder Imputation

As-Observed

Response Regardless of Dose Adjustment

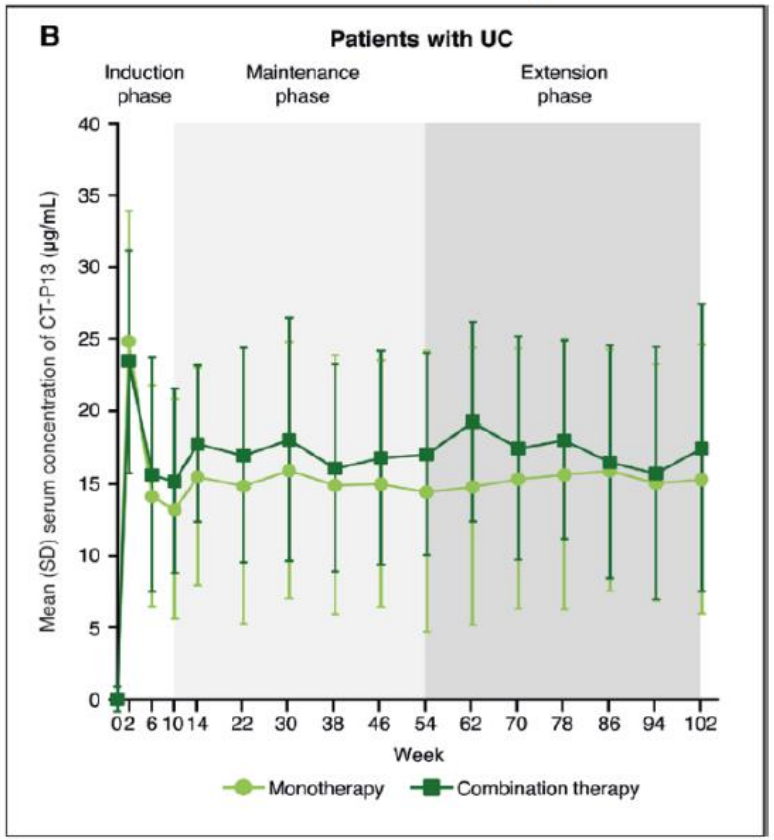


SC infliximab maintained clinical remission rates up to 2 years

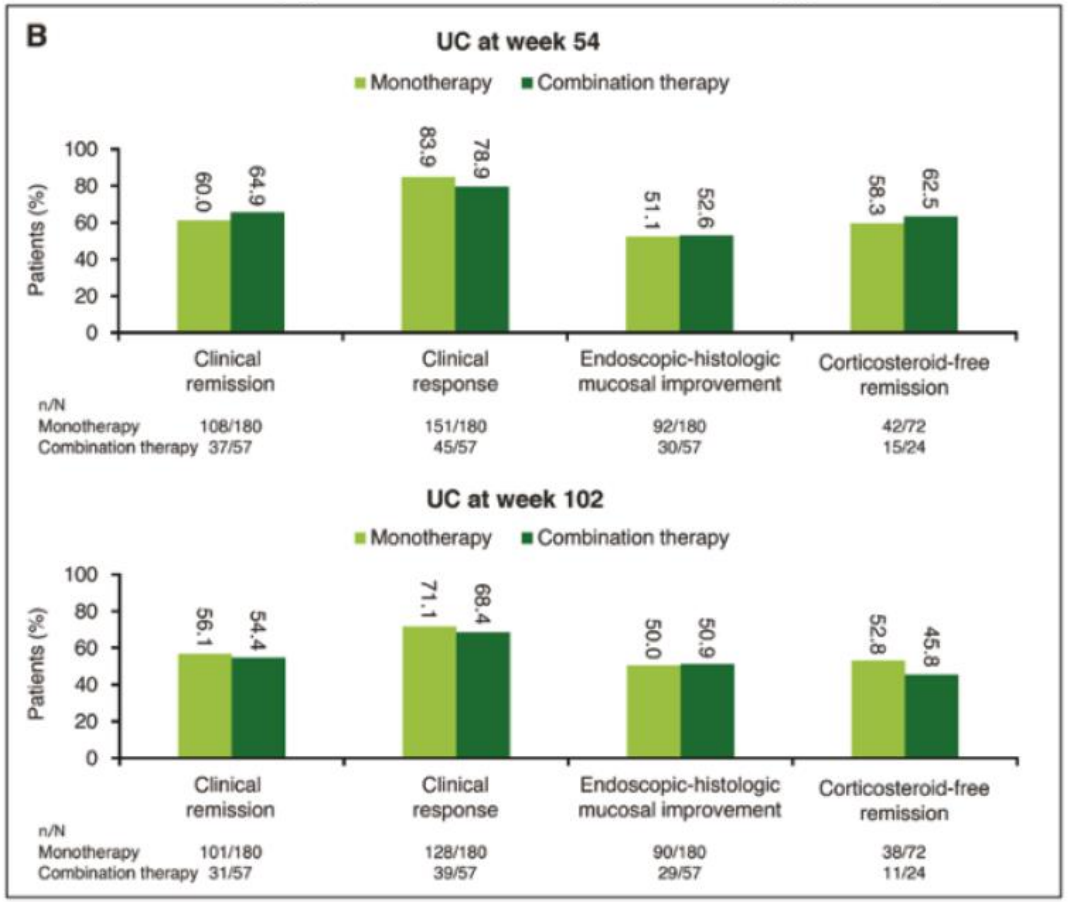
Colombel JF, et al. *J Crohns Colitis*. 2025;19(6):jjaf060.

Post-Hoc Analysis of LIBERTY-UC: By Baseline Immunosuppressant Use

Mean (SD) Serum Dose Concentration of CT-P13 up to Week 102 for Monotherapy and Combination Groups



Efficacy Endpoints in NRI Analysis by Monotherapy and Combination Therapy Groups

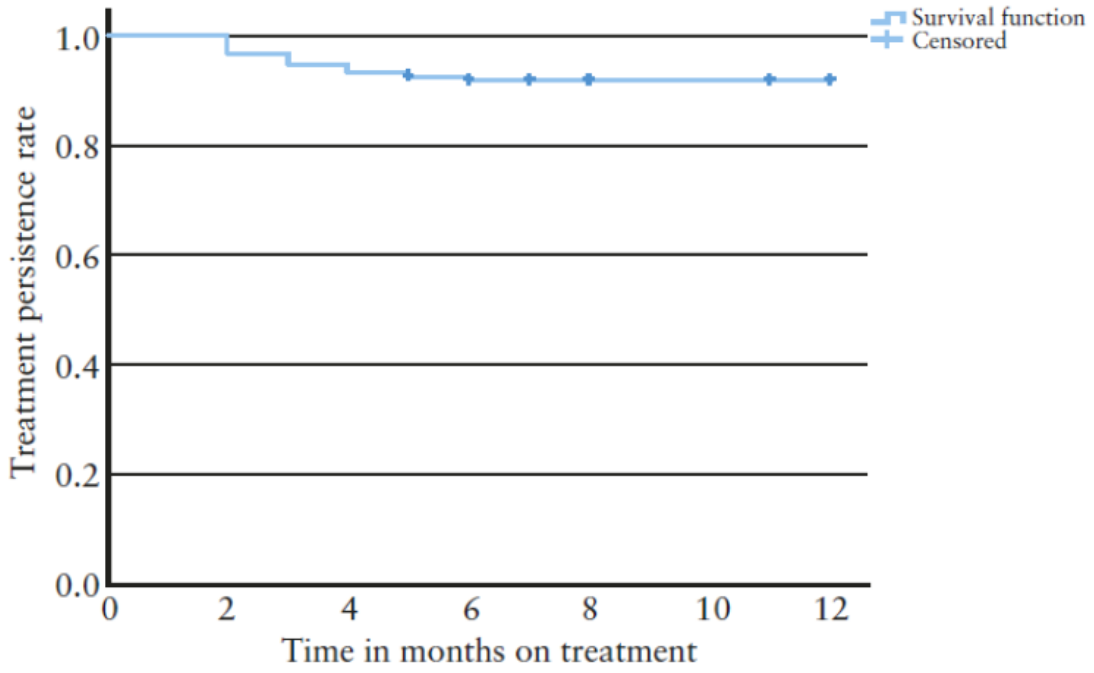


NRI = non-responder imputation.

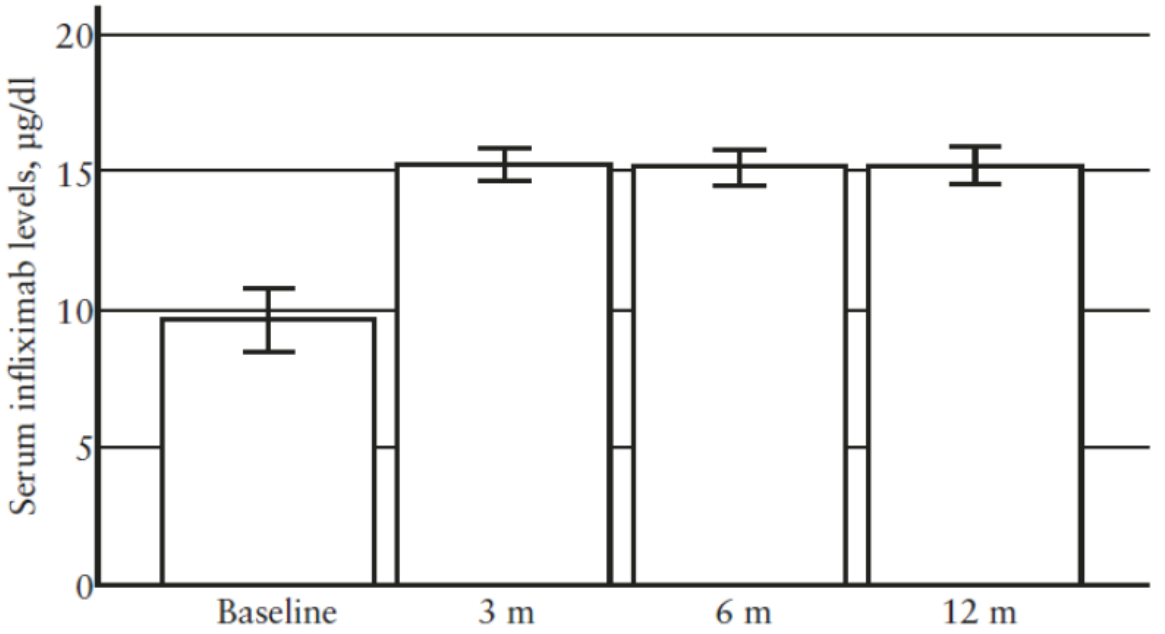
Schreiber S, et al. *Inflamm Bowel Dis.* 2025;31(10):2714-2724.

Real-World Data on Efficacy of Switching from IV to SC IFX in IBD

Treatment Persistence With SC Infliximab after Switching From IV Infliximab



Trends in Serum Infliximab Concentrations in Patients Switching to SC Infliximab



P values vs. baseline: vs. 3 m: <0.001, vs. 6 m: <0.001, vs. 12 m: <0.001

Smith PJ, et al. *J Crohns Colitis*. 2022;16(9):1436-1446.

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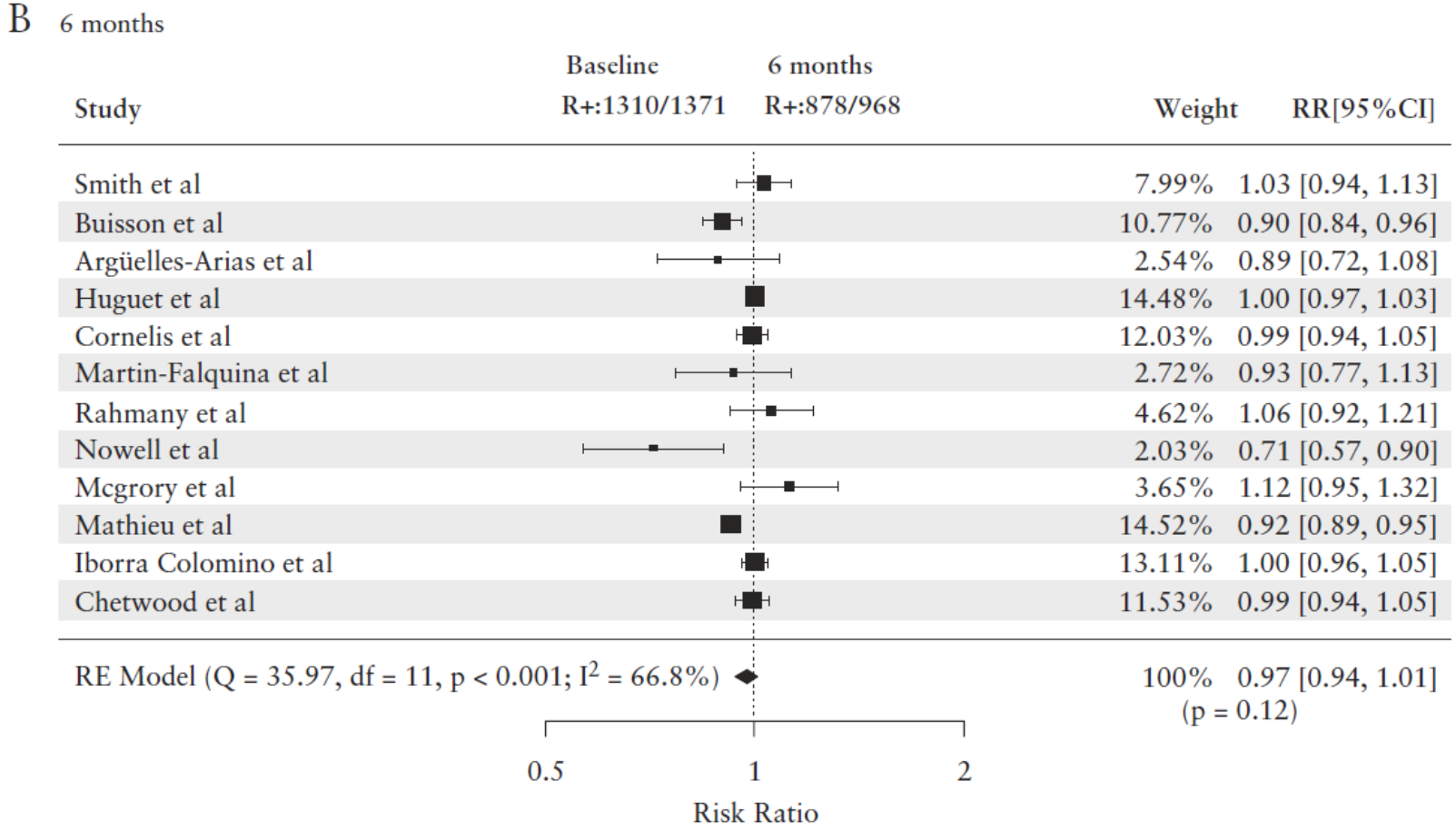
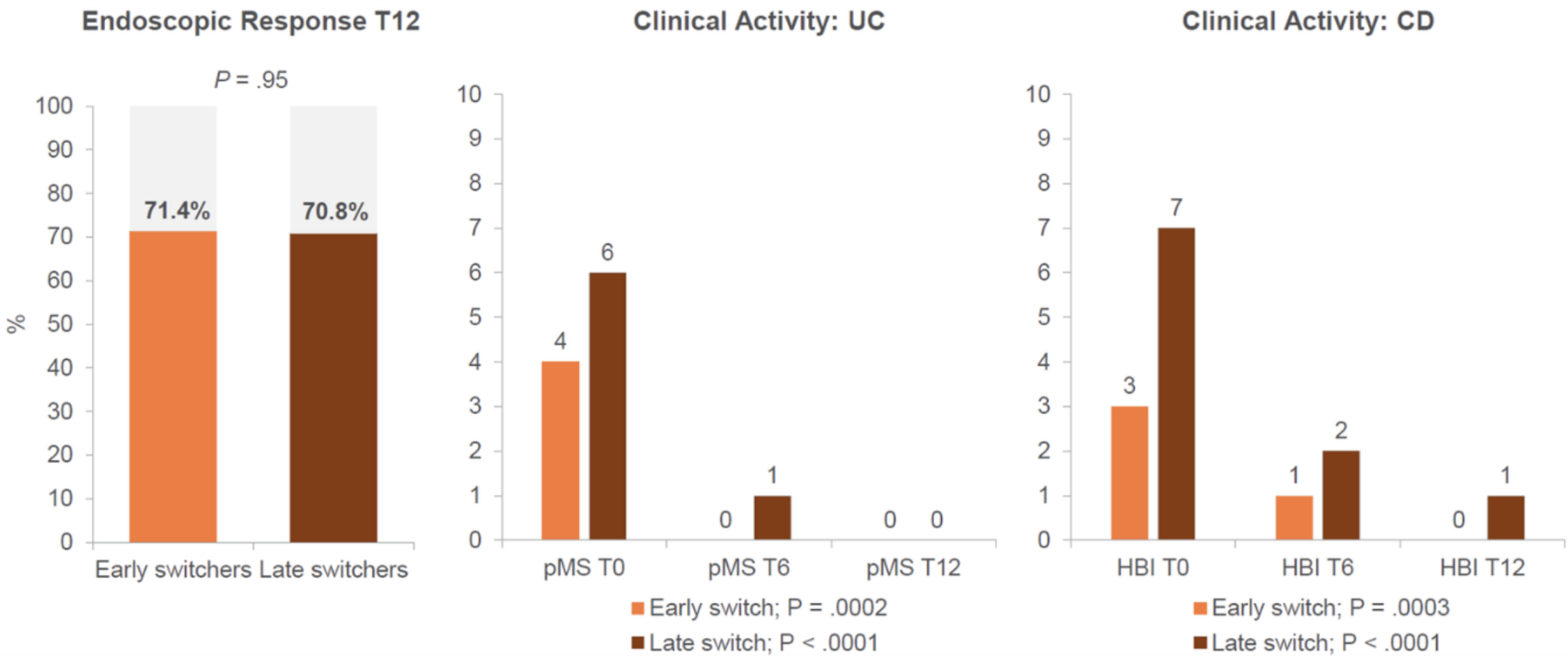
Efficacy of IV vs SC IFX in IBD: Systematic Review and Meta-Analysis

Clinical Efficacy of SC Infliximab in IBD (overall) at 6 Months



Chetwood JD, et al. *J Crohn's Colitis*. 2024;18:1440-1449.

Early vs Late Switching from IV to SC IFX in IBD: RE-WATCH Study



Bertani L, et al. *Inflamm Bowel Dis*. 2025:izaf172. [Epub ahead of print.]

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Case Wrap Up: UC

- 30-year-old woman with biologic naïve moderate to severe left sided UC and AS requiring multiple prednisone courses over the last year
- Patient received infliximab 5 mg/kg induction weeks 0, 2, 6 in combination with azathioprine 125 mg daily (normal TPMT)
- Bleeding resolved by week 2 and tapered off steroids by week 4
- Following induction transitioned to infliximab subcutaneous 120 mg q2 weeks beginning at week 10. At that time GI symptoms were at baseline and morning stiffness was resolved
- Colonoscopy 6 months after therapy initiation was Mayo 0
- Patient and her husband are now planning to have a 2nd child

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Key Learning Points

- UC treatment selection should account for disease characteristics including activity/severity and EIMs, safety, efficacy, and patient choice
- Infliximab is the preferred anti-TNF for treatment of moderate to severely active UC
- Subcutaneous infliximab is considered equivalent to the standard IV infliximab maintenance dosing in UC
- Combination therapy with a thiopurine is recommended for infliximab induction therapy in UC
- Post-hoc data from the LIBERTY-UC trial suggests similar long-term clinical efficacy and safety between maintenance subcutaneous infliximab monotherapy and combination therapy

Rubin DT, et al. *Am J Gastroenterol*. 2025;120(6):1187-1224. Schreiber S, et al. *Inflamm Bowel Dis*. 2025;31(10):2714-2724.

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Targeting TNFα in IBD:
Innovations in Drug Design, Delivery,
and Clinical Application

Crohn's Disease: Focus on Subcutaneous IFX

Aline Charabaty, MD

Associate Professor of Clinical Medicine
Johns Hopkins School of Medicine

Disclosures

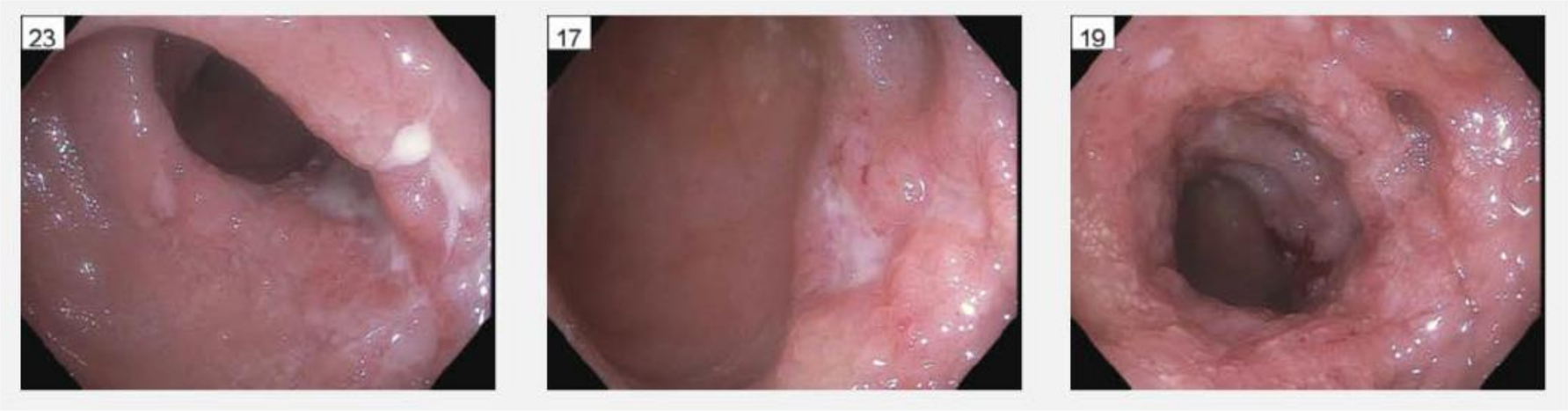
- **Aline Charabaty, MD:** Advisory board – AbbVie Inc, Eli Lilly, Janssen, Pfizer, Sanofi, Takeda; consultant – AbbVie Inc, Eli Lilly, Janssen, Pfizer, Sanofi, Takeda

Case 2: 25-Year-Old Man with Perianal CD

- Crohn ileitis – did well on ustekinumab for 1 year
- However, now presents with new GI symptoms and perianal fistula
- Current symptoms include AP, moderate urgency, 3-4 loose bowel movements/day with occasional blood when wiping; mild fatigue; intermittent pain; and drainage of blood and pus from fistula
- Wants to discuss next steps and other treatment options

Case 2: 25-Year-Old Man with Perianal CD

- Repeat colonoscopy shows erosions and deep ulcerations in terminal ileum (throughout extent of exam–10 cm), normal colon
- Biopsies indicate moderate to severely active chronic ileitis consistent with idiopathic IBD



- Recent MRE shows 15 cm of active ileitis
- MR of pelvis shows trans-sphincteric branching fistula, no abscess

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AIBD ADVANCES IN INFLAMMATORY BOWEL DISEASES

What are the options?

ACG Recommendations for Perianal/Fistulizing CD

	Recommendation	Level of Evidence
Use for induction of remission		
Infliximab	Strong	Moderate
Adalimumab	Conditional	Low
Vedolizumab	Conditional	Very low
Ustekinumab	Conditional	Very low
Upadacitinib	Conditional	Very low
Use to improve clinical response		
Antibiotics + infliximab or adalimumab	Conditional	Very low

Lichtenstein GR, et al. *Am J Gastroenterol*. 2025;120(6):1225-1264.

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ACG Recommendations for Use of Anti-TNF Agents in CD

Anti-TNF agents (IV infliximab, SC adalimumab, SC certolizumab pegol) for induction and maintenance of remission (strong recommendation, moderate level of evidence)

IV infliximab with immunomodulators (thiopurines) as compared with treatment with either immunomodulators alone or IV infliximab alone in patients naive to those agents (strong recommendation, moderate level of evidence)

SC infliximab as an option for maintenance of remission in patients who respond to IV induction with infliximab (strong recommendation, moderate level of evidence)

Lichtenstein GR, et al. *Am J Gastroenterol*. 2025;120(6):1225-1264.

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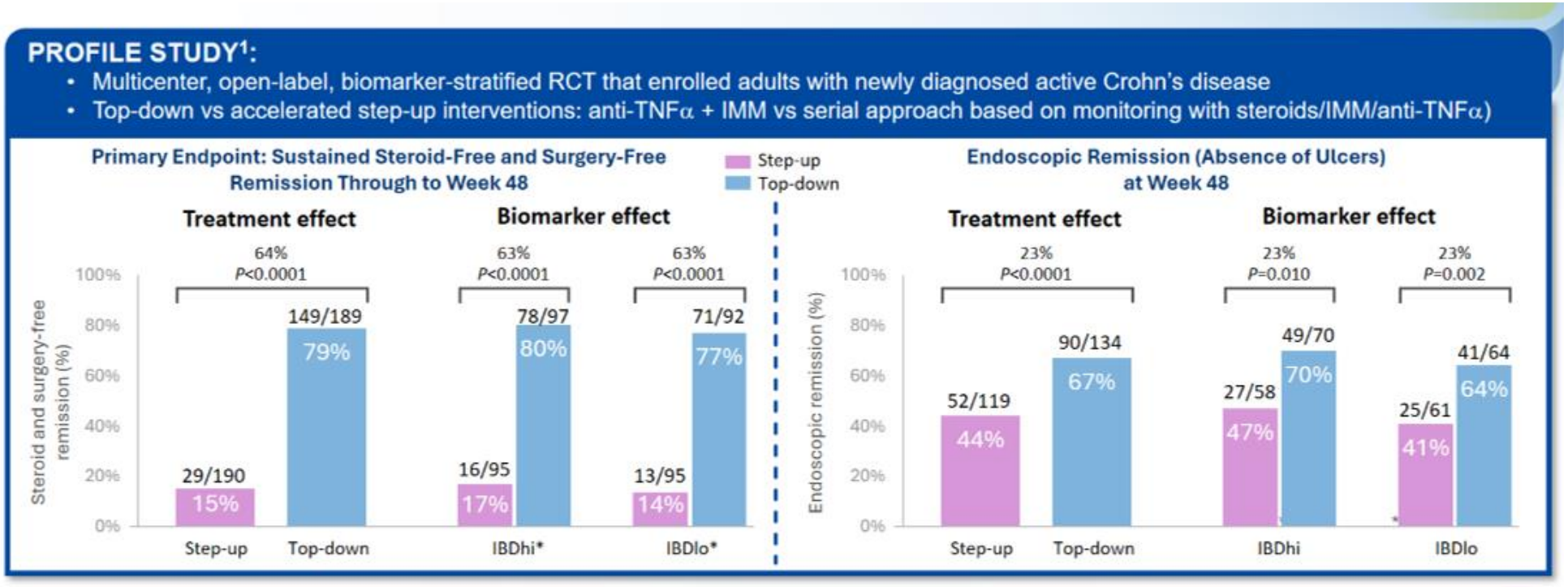
ACG CD Guideline: Statement on Conventional vs Advanced Therapy

- We suggest **against** requiring failure of conventional therapy before initiation of advanced therapy for the management of Crohn's disease (CD) (conditional recommendation, low level of evidence)



Noor NM, et al. *Lancet Gastroenterol Hepatol*. 2024;9(5):415-427. Lichtenstein GR, et al. *Am J Gastroenterol*. 2025;120(6):1225-1264.

AGA Positioning of Advanced Therapies in Adults with CD

Adult outpatients with moderate-to-severely active Crohn's disease

Moderate-to-severely active Crohn's disease defined as:

- Moderate-to-severe abdominal pain and/or diarrhea due to inflammation
- Mild symptoms, with high burden of inflammation
- Patients with corticosteroid-dependence, or refractory to oral corticosteroids
- Significant extent of disease or upper GI involvement

SUGGEST upfront use of advanced therapies, rather than step-up therapy after corticosteroids and/or immunomodulator monotherapy

(Conditional recommendation, very low certainty of evidence)

RECOMMEND using any of the following, over no treatment:
Infliximab, adalimumab, ustekinumab, risankizumab, guselkumab, mirikizumab, or upadacitinib*

(Strong recommendation, moderate to high certainty of evidence)

SUGGEST using any of the following, over no treatment:
Certolizumab pegol, vedolizumab

(Conditional recommendation, moderate certainty of evidence)

Implementation considerations:

- Biosimilars of infliximab, adalimumab, and ustekinumab can be considered equivalent to their originator drug in their efficacy in terms of therapy selection
- Subcutaneous formulations of infliximab and vedolizumab have shown comparable efficacy to the respective intravenous maintenance doses
- In some patients with suboptimal response to standard dosing, particularly those with more severe disease, extended induction regimens or dose escalation may be beneficial for most advanced therapies
- There are two dosing options available for maintenance therapy for risankizumab, guselkumab, and upadacitinib. Higher maintenance doses may be preferred in patients with high burden of inflammation and/or more severe disease, and those who have previously failed TNF antagonists

Advanced therapy-naïve patients (first-line therapy)

SUGGEST using a HIGHER efficacy rather than a lower efficacy medication

(Conditional recommendation, low to high certainty of evidence)

HIGHER EFFICACY MEDICATIONS: Infliximab, adalimumab, vedolizumab, ustekinumab, risankizumab, mirikizumab, guselkumab

LOWER EFFICACY MEDICATIONS: Certolizumab pegol, upadacitinib*

Prior exposure to one or more advanced therapies, particularly TNF antagonists

SUGGEST using a HIGHER efficacy, or INTERMEDIATE efficacy medication, rather than a lower efficacy medication

(Conditional recommendation, low to moderate certainty of evidence)

HIGHER EFFICACY MEDICATIONS: Adalimumab, risankizumab, guselkumab, upadacitinib

INTERMEDIATE EFFICACY MEDICATIONS: Ustekinumab, mirikizumab

LOWER EFFICACY MEDICATIONS: Certolizumab pegol, vedolizumab

*The FDA label recommends the use of JAK inhibitors only in patients with prior failure or intolerance to TNF antagonists

AIBD

Scott FI, et al. *Gastroenterology*. 2025;169(7):1397-1448.

ECCO Guidelines on Pharmacologic Therapeutics in CD

	Induction	Maintenance	Perianal Disease	Peripheral Spondylo-arthropathy	Axial Spondylo-arthropathy	Pregnancy	> 65 Years
Systemic corticosteroids	Can be considered	Not recommended	Not recommended	Can be considered	Can be considered	Can be considered	Can be considered
Enteral release corticosteroids	Recommended	Not recommended	Not recommended	Not recommended	Not recommended	Recommended	Recommended
Enteral nutrition	Can be considered	Can be considered	Not recommended	Not recommended	Not recommended	Can be considered	Can be considered
Thiopurines monotherapy	Not recommended	Can be considered	Not recommended	Not recommended	Not recommended	Can be considered	Not recommended
Methotrexate	Can be considered	Can be considered	Not recommended	Can be considered	Not recommended	Not recommended	Can be considered
Infliximab	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended
Adalimumab	Recommended	Recommended	Can be considered	Recommended	Recommended	Recommended	Recommended
Certolizumab	Can be considered	Can be considered	Not recommended	Recommended	Recommended	Can be considered	Can be considered
Vedolizumab	Recommended	Recommended	Insufficient evidence	Not recommended	Not recommended	Recommended	Recommended
Ustekinumab	Recommended	Recommended	Insufficient evidence	Can be considered	Not recommended	Recommended	Recommended
Risankizumab	Recommended	Recommended	Insufficient evidence	Can be considered	Not recommended	Insufficient evidence	Can be considered
Upadacitinib	Recommended	Recommended	Can be considered	Can be considered	Recommended	Not recommended	Can be considered

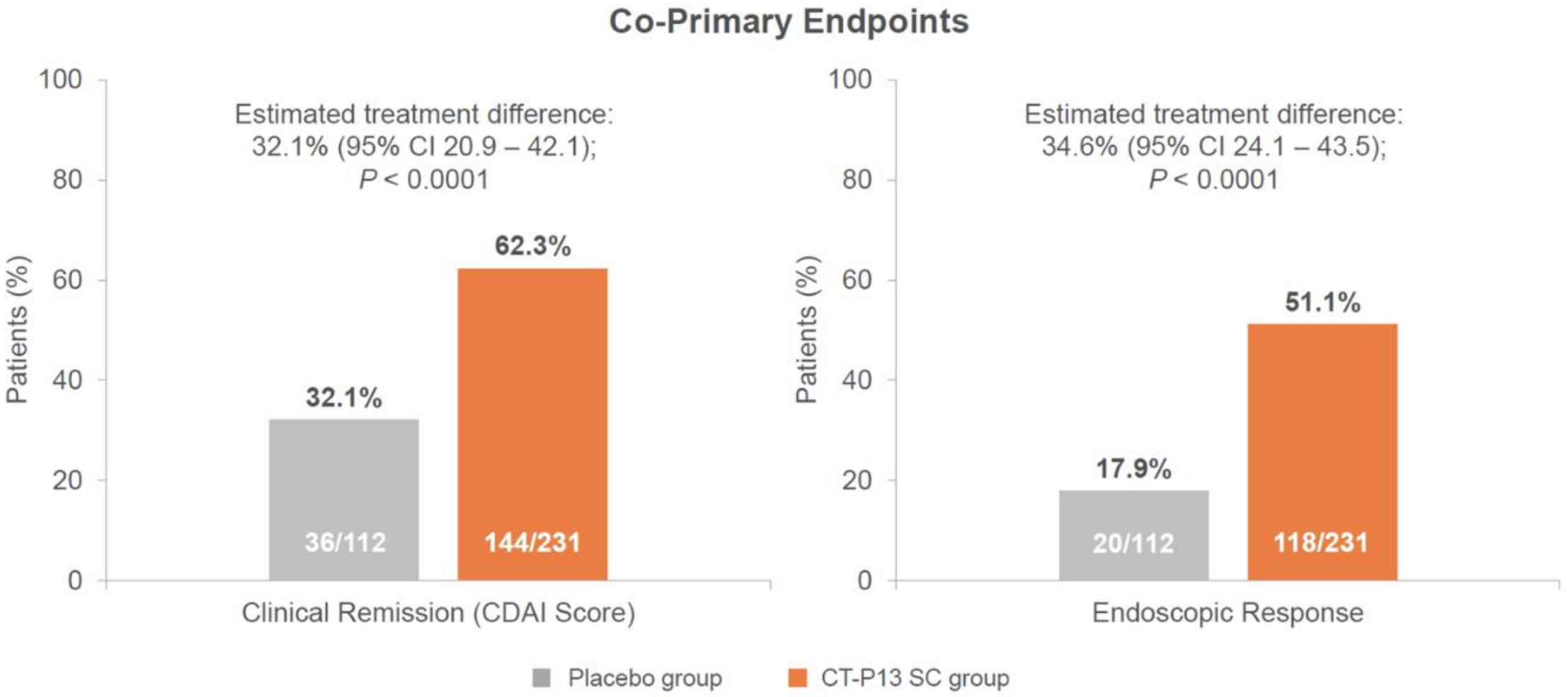
Recommended | Can be considered | Not recommended | Insufficient evidence

ECCO = European Crohn's and Colitis Organisation.

Gordon H, et al. *J Crohns Colitis*. 2024;18(10):1531-1555.

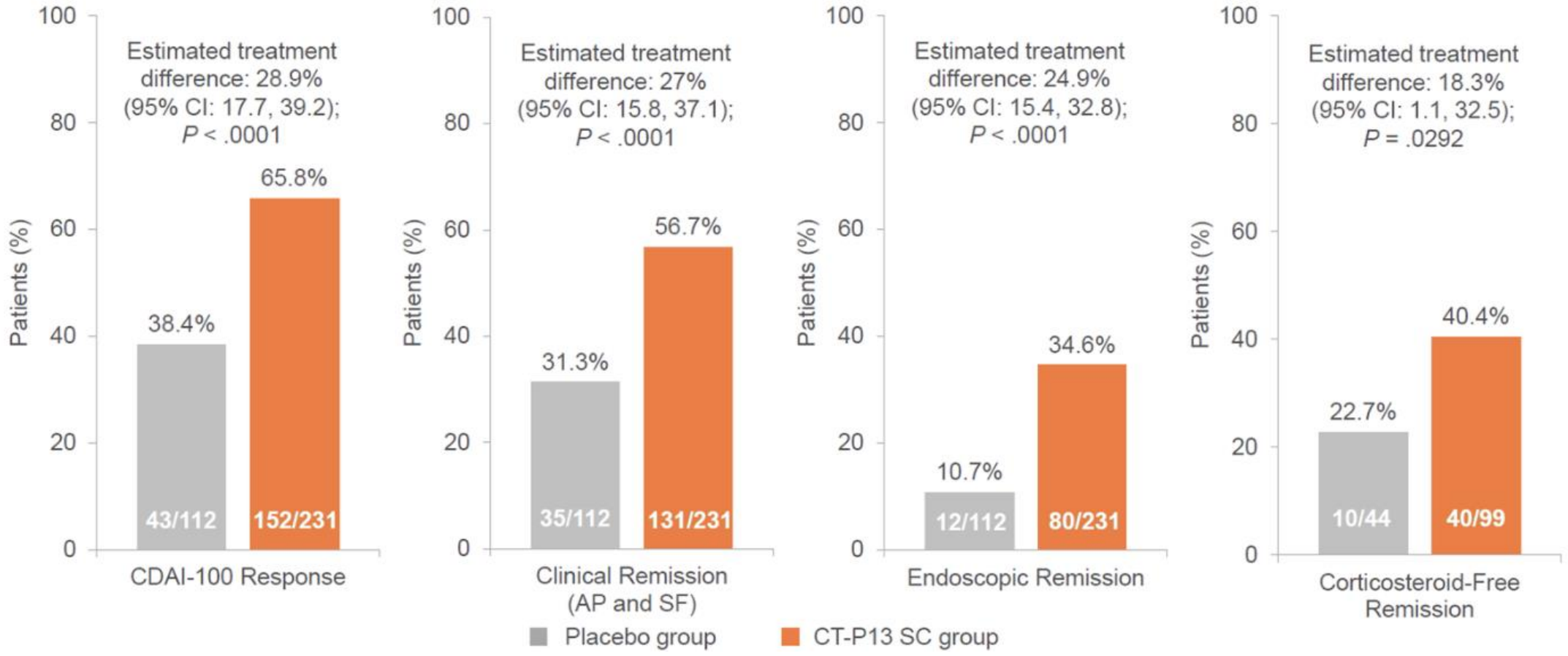
AIBD

LIBERTY-CD Trial: Primary Endpoints at Wk 54



Hanauer SB, et al. *Gastroenterology*. 2024;167(5):919-933.

LIBERTY-CD: Key Secondary Endpoints at Wk 54

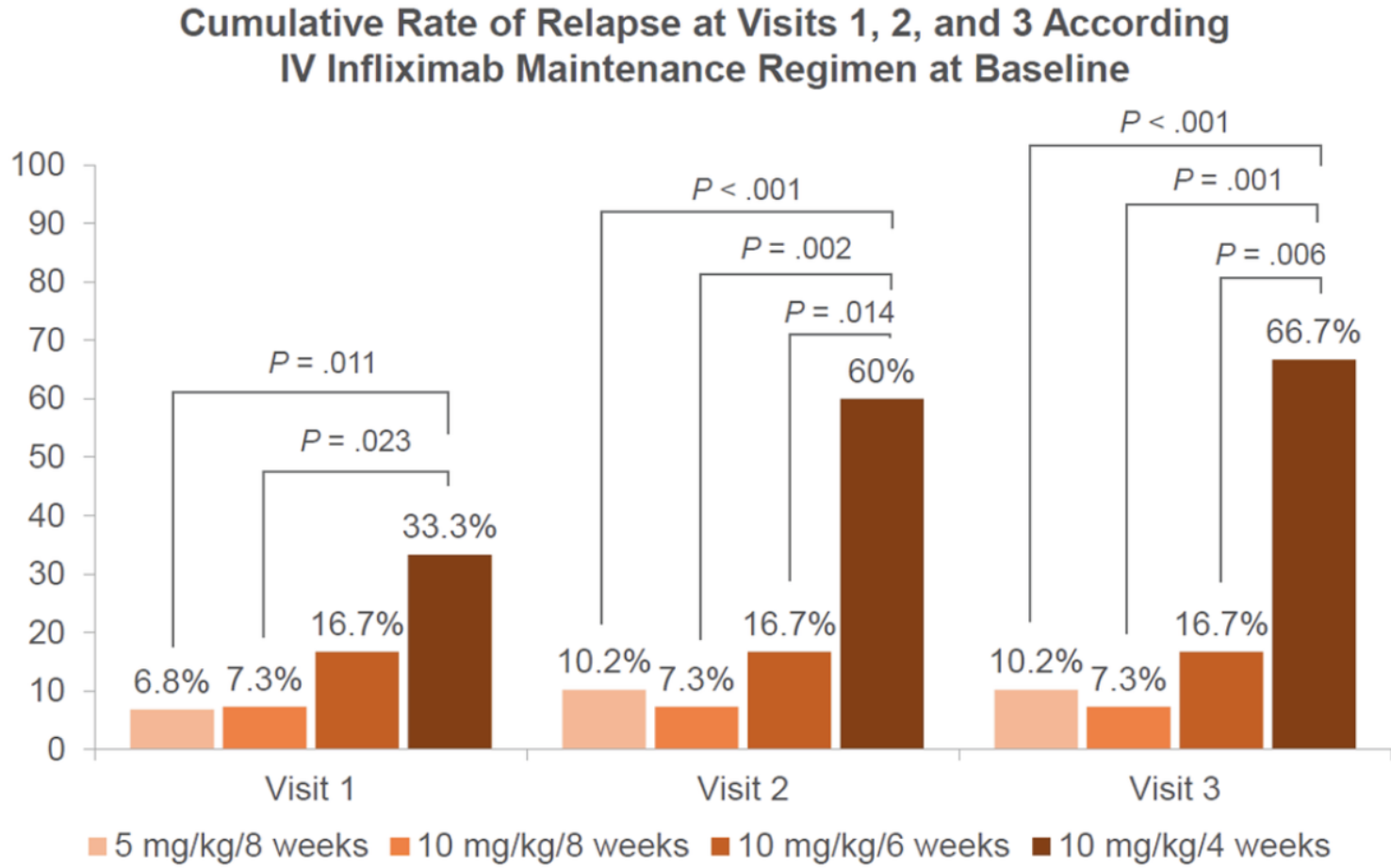


AP = abdominal pain; SF = stool frequency.

Hanauer SB, et al. *Gastroenterology*. 2024;167(5):919-933.

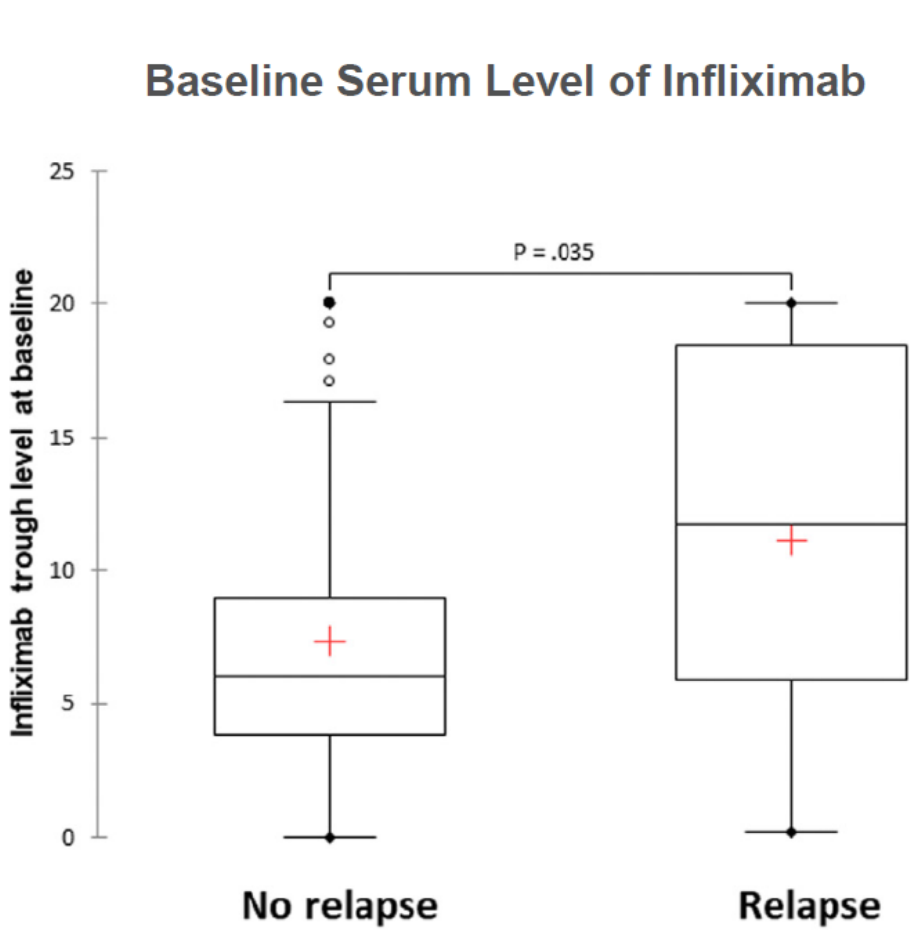
REMSWITCH: Effectiveness of Switching from IV to SC IFX

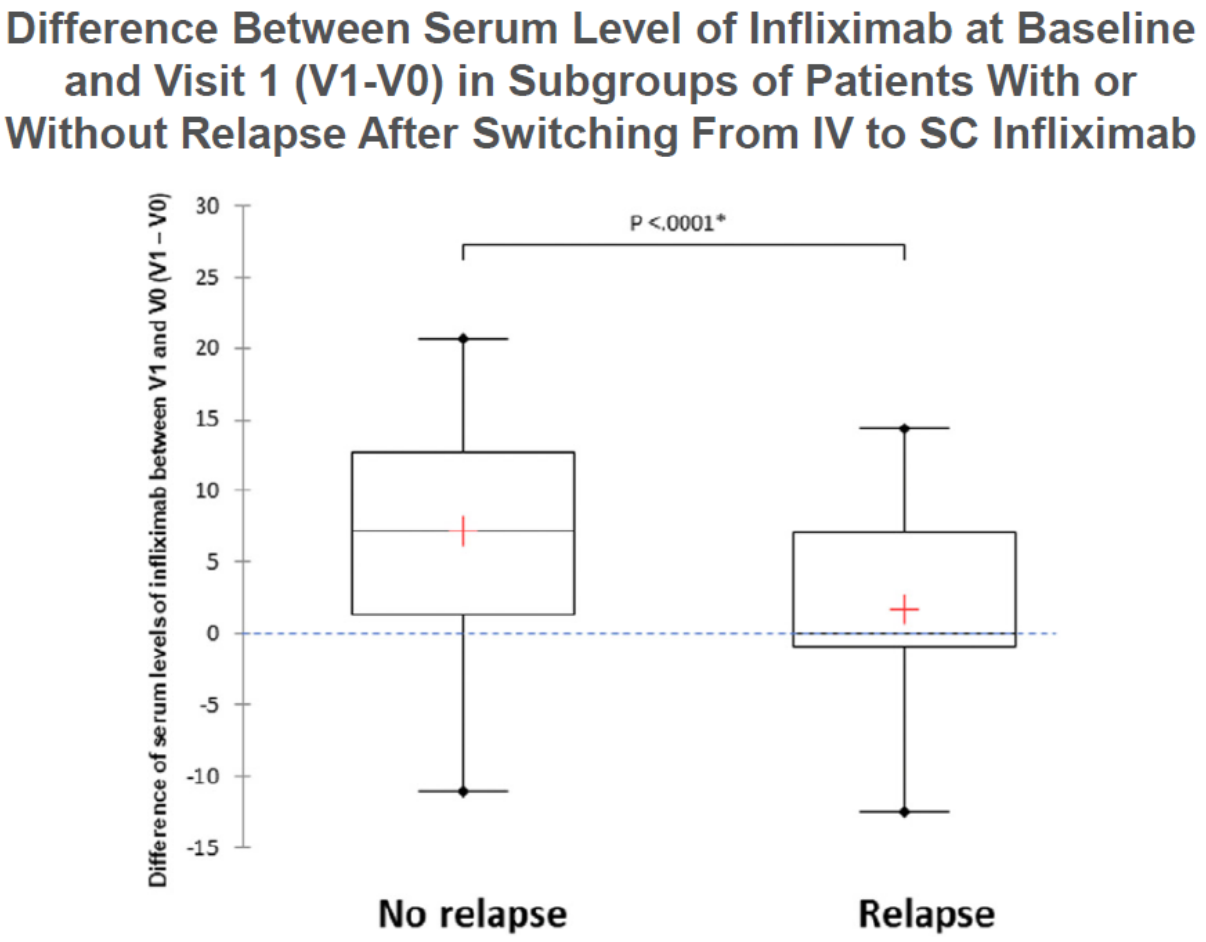
- Visit 1: 4-8 weeks after the switch
- Visit 2: 8-16 weeks after the switch
- Visit 3: 16-24 weeks after the switch



Buisson A, et al. *Clin Gastroenterol Hepatol.* 2023;21(9):2338-2346.e3.

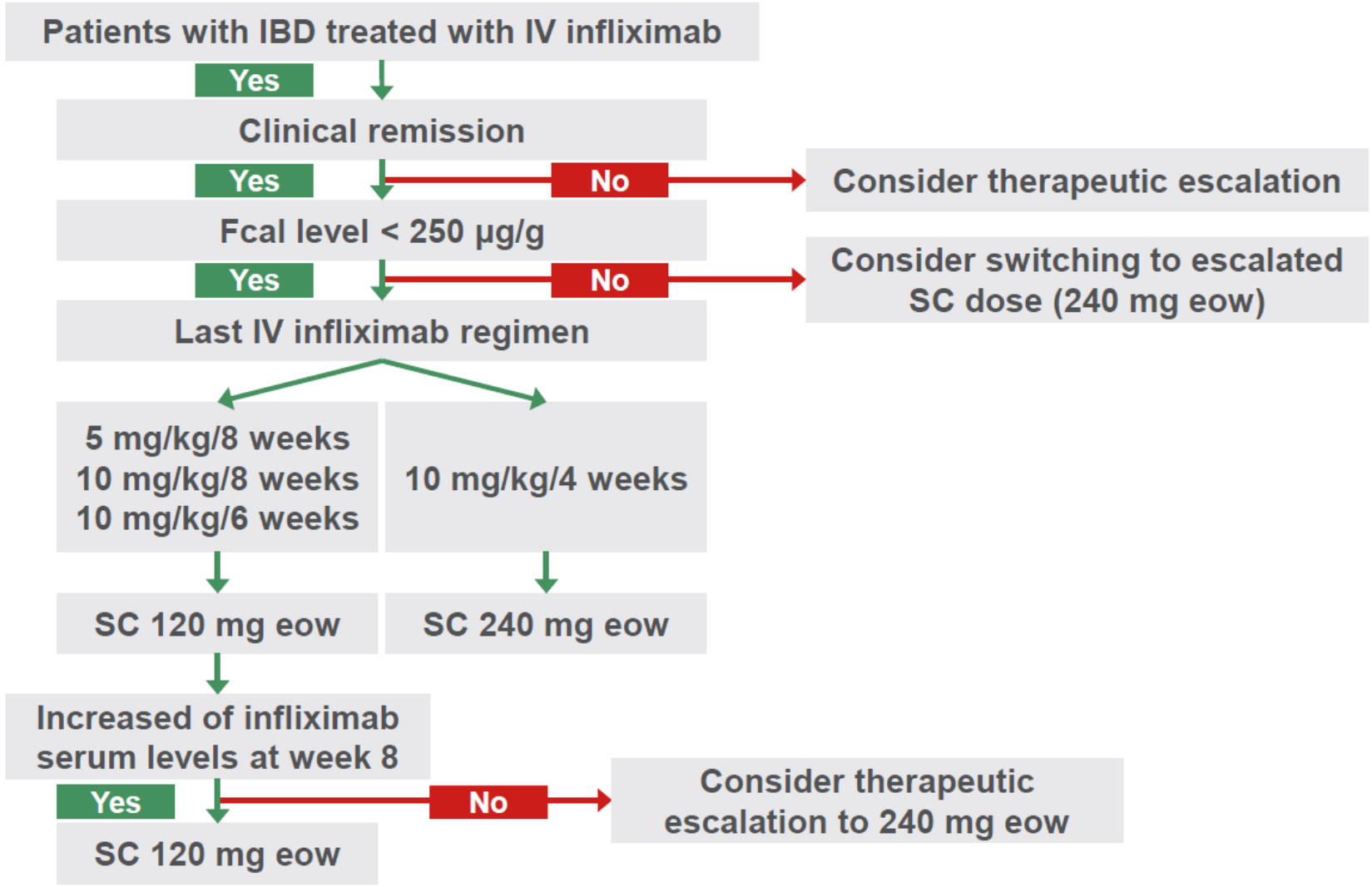
REMSWITCH: IFX Levels and Relapse





Buisson A, et al. *Clin Gastroenterol Hepatol.* 2023;21(9):2338-2346.e3.

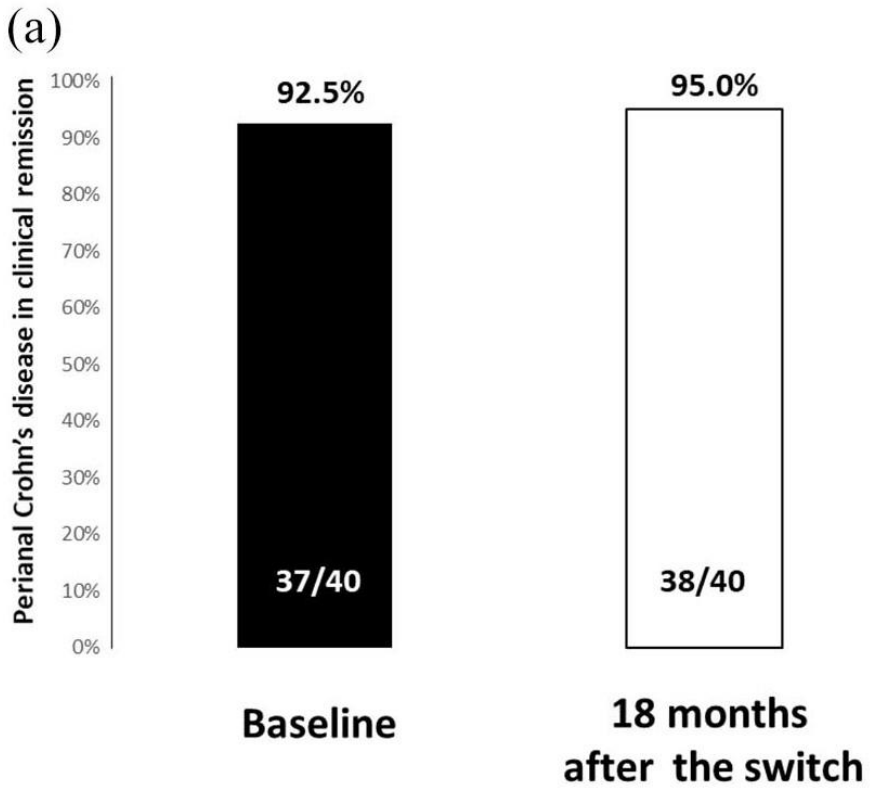
REMSWITCH: Suggested Algorithm for Switching IV to SC IFX

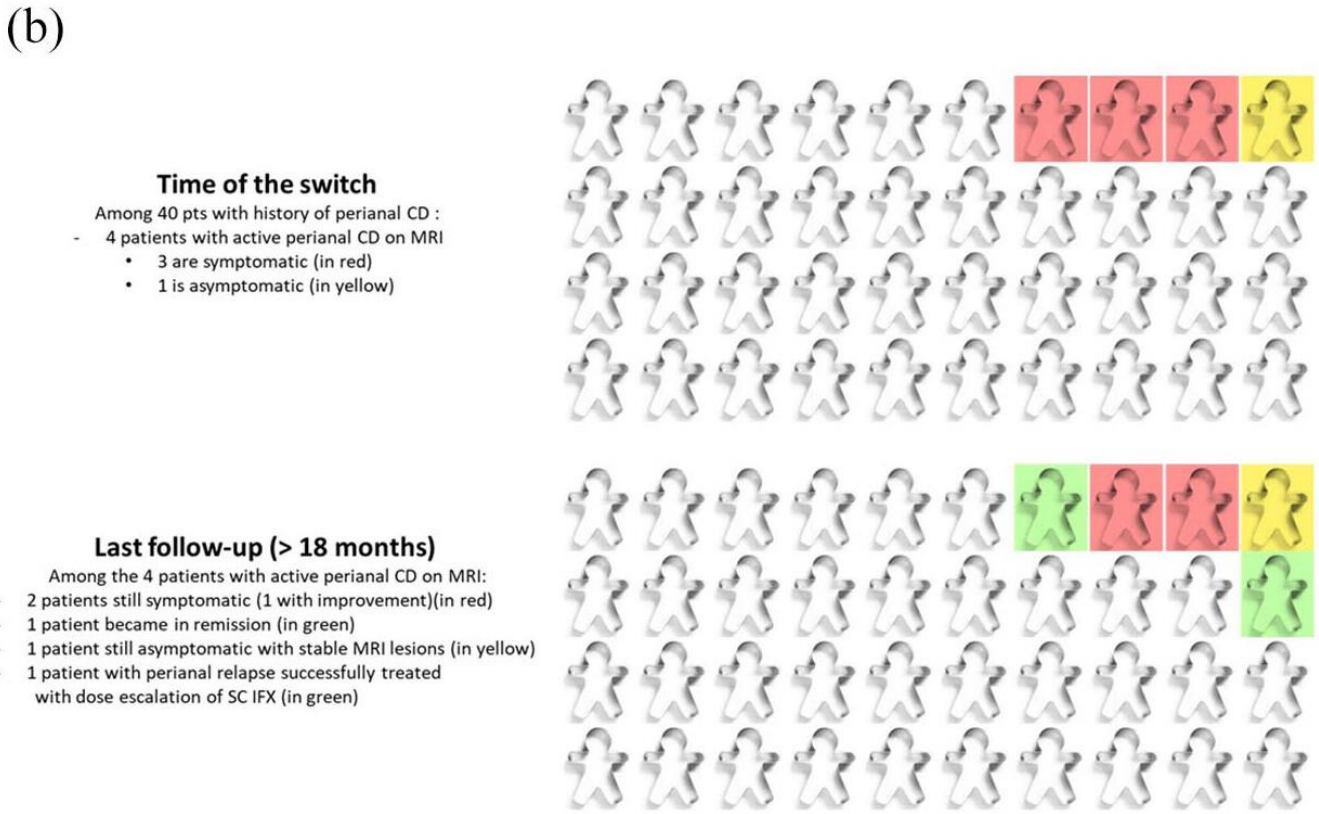


Buisson A, et al. *Clin Gastroenterol Hepatol.* 2023;21(9):2338-2346.e3.

REMSWITCH: Perianal CD Subgroup

Rate of patients in perianal clinical remission (a) and evolution of perianal Crohn's disease (b) after switching from IV to SC infliximab

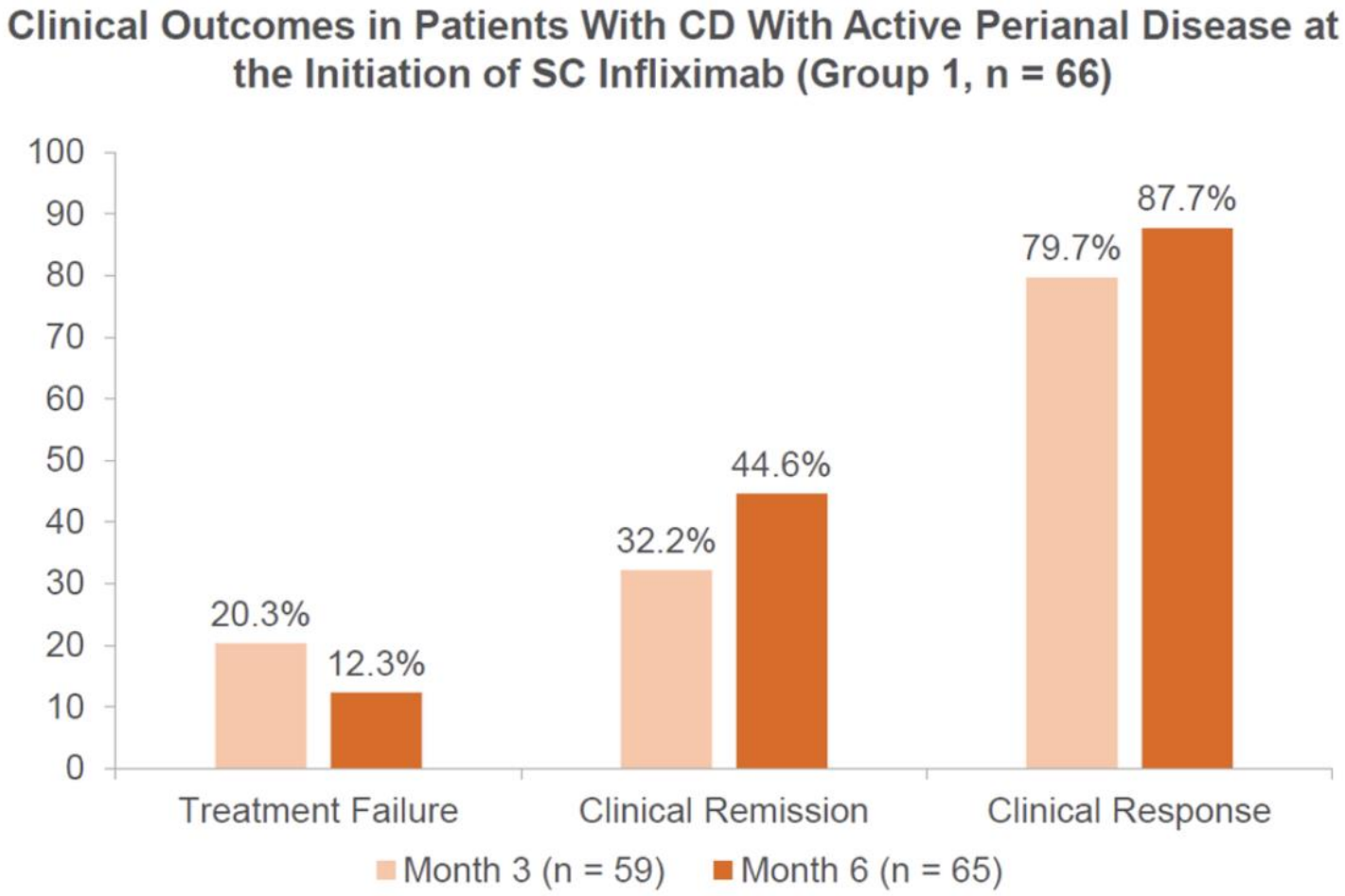




Wils P, et al. *Therap Adv Gastroenterol*. 2025;18:17562848251326471.

SC IFX for Perianal CD: BioLap-Rem Study from GETAID

- Multicenter retrospective cohort study from GETAID, including patients with active (Group 1) or inactive (Group 2) perianal CD when they started SC infliximab
- Conclusion: SC infliximab is effective and safe for treatment of perianal CD and maintaining remission after switch from IV to SC



Marie A, et al. *Am J Gastroenterol*. 2025 [Epub ahead of print.]

Case Wrap Up: CD

- 25 y/o male with Crohn's ileitis and new perianal fistula while on ustekinumab
- Started on IV IFX 10mg/kg + AZA 150mg/day
- Resolution of GI symptoms after the 2 IFX induction doses
- Resolution of perianal drainage after 4-5 months of therapy
- IFX TL 16
- Patient was switched to SQ IFX 120mg every other week
- He continues to do well and the SQ method of administration better fits his work and life schedule

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Key Learning Points

- Anti-TNF still relevant in 2025, although use can be limited by durability
- Must have a strategy for immunogenicity
  - Need to consider the risk profile of a combined immunomodulator
  - Need to use reactive or proactive TDM for monitoring
- Anti-TNF should be used in specific phenotypes: Severe disease, perianal phenotype, EIMs, and post-operatively
- Certain contraindications to anti-TNF exist w/ comorbidities
- Subcutaneous IFX now available; may help with immunogenicity due to consistent trough levels
  - RCT and real-world data show efficacy and safety in both UC and CD

AIBD

Targeting TNFα in IBD:

Innovations in Drug Design, Delivery, and Clinical Application

Q&A Session