CME OUTFITTERS

THE FORCE AWAKENS

Unlocking the Potential of IL-23–Targeted Therapies in the Treatment of IBD

Supported by an educational grant from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC, both are Johnson and Johnson companies.

In support of improving patient care, CME Outfitters LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Activity Credit Types

Physicians (ACCME)

CME Outfitters LLC designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses (ANCC)

This activity is designated for 1.5 contact hours.

California residents: provider approved by the California Board of Registered Nursing, Provider # CEP 15510, for 1.5 Contact Hours.

CME Outfitters LLC has been authorized by the American Academy of PAs (AAPA) to award AAPA Category 1 CME credit for activities planned in accordance with AAPA CME Criteria. This activity is designated for 1.5 AAPA Category 1 CME credits. Approval is valid until expiration date. PAs should only claim credit commensurate with the extent of their participation.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

Completion of this accredited CME activity meets the expectations of an Accredited Safety or Quality Improvement Program (IA_PSPA_28) for the Merit-based Incentive Payment Program (MIPS). Clinicians should submit their improvement activities by attestation via the CMS Quality Payment Program website.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.5 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This activity may include discussions of products or devices that are not currently labeled for use by the U.S. Food and Drug Administration (FDA).

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any uses not approved by the FDA) of products or devices.

To Ask a Question

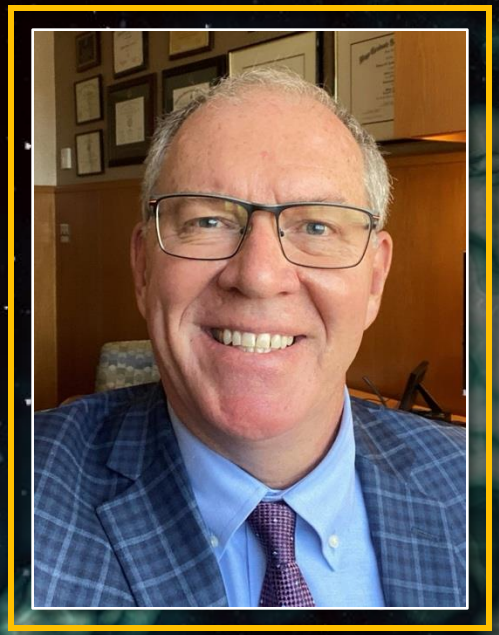
To submit a question, please go to the *Ask Question* tab at the bottom of the screen.

Miguel Regueiro, MD (moderator)

Chief, Digestive Disease Institute
Professor in the Department of Medicine
Cleveland Clinic Lerner College of Medicine
of Case Western Reserve University
Cleveland, Ohio

Marita Kametas
MSN, APN, FNP-BC, CMSRN, COCN

Inflammatory Bowel Disease Advanced Practice Nurse
Manager of Gastroenterology Advanced Practice Provider Services
The University of Chicago Medicine
Chicago, Illinois



Edward V. Loftus, Jr., MD

Maxine and Jack Zarrow Family Professor of Gastroenterology Specifically in IBD
Division of Gastroenterology and Hepatology
Mayo Clinic College of Medicine and Science
Co-Director, Advanced Inflammatory Bowel Disease Fellowship
Mayo Graduate School of Medicine
Rochester, Minnesota

Millie D. Long, MD, MPH

Professor of Medicine
Chief, Division of Gastroenterology and Hepatology
Department of Medicine
University of North Carolina
Chapel Hill, North Carolina

Disclosures

Miguel Regueiro, MD, reports the following financial relationships:

Consultant—AbbVie Inc., Amgen Inc., Boehringer Ingelheim, Bristol Myers Squibb Company, Celgene Corporation, Genentech Inc., Gilead Sciences Inc., Janssen Pharmaceuticals Inc., Lilly, Pfizer Inc., Prometheus Biosciences Inc., Salix Pharmaceuticals, Takeda Pharmaceuticals U.S.A. Inc., and UCB Inc.

Marita Kametas, MSN, APN, FNP-BC, CMSRN, COCN, reports the following financial relationships:

Advisory board—Lilly and Pfizer Inc.

Consultant—TKG Therapeutics Inc.

Grants—GI Research Foundation

Speakers bureau—AbbVie Inc., Janssen Pharmaceuticals Inc., and Pfizer Inc.

Edward V. Loftus, Jr., MD, reports the following financial relationships:

Advisory board—Lilly and Morphic Therapeutic Inc.

Consultant—AbbVie Inc., Alvotech, Amgen Inc., Arena Pharmaceuticals Inc., Astellas Pharma Inc., Avalo Therapeutics Inc., Boehringer Ingelheim, Bristol Myers Squibb Company, Celltrion Inc., Fresenius Kabi; Genentech Inc., Gilead Sciences Inc., GlaxoSmithKline, Gossamer Bio, Iterative Health, Janssen Pharmaceuticals Inc., Ono Pharma USA Inc., Protagonist Therapeutics Inc., Sun. Pharma, Surrozen, Takeda Pharmaceuticals U.S.A., TR1X Bio, and UCB Inc.

Grants—AbbVie Inc., AstraZeneca, Bristol Myers Squibb Company, Celgene Corporation/Receptos Inc., Genentech Inc., Gilead Sciences Inc., Janssen Pharmaceuticals Inc., Takeda Pharmaceuticals U.S.A., Theravance Biopharma, and UCB Inc.

Stock shareholder (directly purchased)—Exact Sciences Corporation

Millie D. Long, MD, MPH, reports the following financial relationships:

Consultant—AbbVie Inc., Bristol Myers Squibb Company, Intercept Pharmaceuticals Inc., Janssen Pharmaceuticals Inc., Lilly, Pfizer Inc., Prometheus Biosciences Inc., Takeda Pharmaceuticals U.S.A. Inc., and Target RWE

Research support—Lilly, Pfizer Inc., and Takeda Pharmaceuticals U.S.A. Inc.

Disclosures

The following individuals have no financial relationships to disclose:

- Rebecca Vargas Jackson, MD (peer reviewer)
- Albert Eubanks, Jr., RN (peer reviewer)
- Chelsey Goins, PhD (planning committee)
- Nichole Lainhart (planning committee)
- Scott J. Hershman, MD, FACEHP, CHCP (planning committee)
- Sandra Caballero, PharmD (planning committee)
- Sharon Tordoff (planning committee)

All identified conflicts of interest have been mitigated.

LEARNING OBJECTIVE

Assess the role of pro-inflammatory cytokines such as IL-23 in the pathogenesis of inflammatory bowel disease (IBD)

LEARNING OBJECTIVE

Differentiate IL-23 binding among the IL-23p19–targeted therapies

LEARNING OBJECTIVE

Evaluate the safety and efficacy of IL-23p19–targeted therapies available for the treatment of IBD

LEARNING OBJECTIVE

Incorporate IL-23p19–targeted therapies into the multidisciplinary management of appropriate patients with IBD

What factors most heavily influence your selection of therapy for IBD? *(Please pick your top 3.)*

A. Treatment mechanism of action
B. Clinical trial safety/efficacy data
C. Severity of disease
D. Patient preference
E. Route/ease of administration
F. Experience with a particular treatment

Navigating the IL-23/Th17 Pathway and the Role of IL-23 Inhibitors in IBD

Why Target IL-23 in IBD?

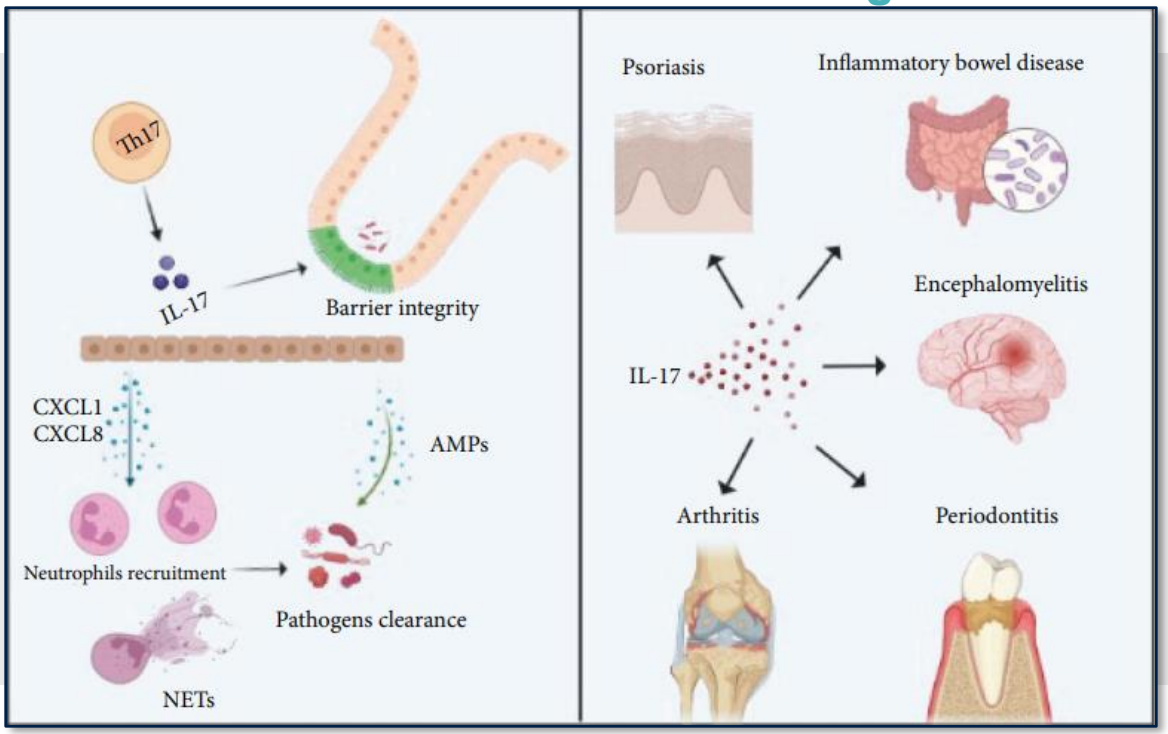
- Inhibition of IL-23
  - Decreases mucosal inflammation
  - Improves epithelial barrier integrity
  - Suppresses gut inflammation in T-cell mediated colitis
- Anti–IL-23 therapy preserves protective IL-17 gut functions
  - Animal models of IL-17 blockade—mixed results
  - Trials of anti–IL-17A/IL-17A receptor antagonists in IBD resulted in worse outcomes vs placebo

IBD, inflammatory bowel disease.

Hohenberger M, et al. *J Dermatolog Treat.* 2018;29(1):13–18. Vuyuru SK, et al. *Drugs*. 2023;83(10):873–891.
Wallace KL, et al. *World J. Gastroenterol.* 2014;20(1):6–21.

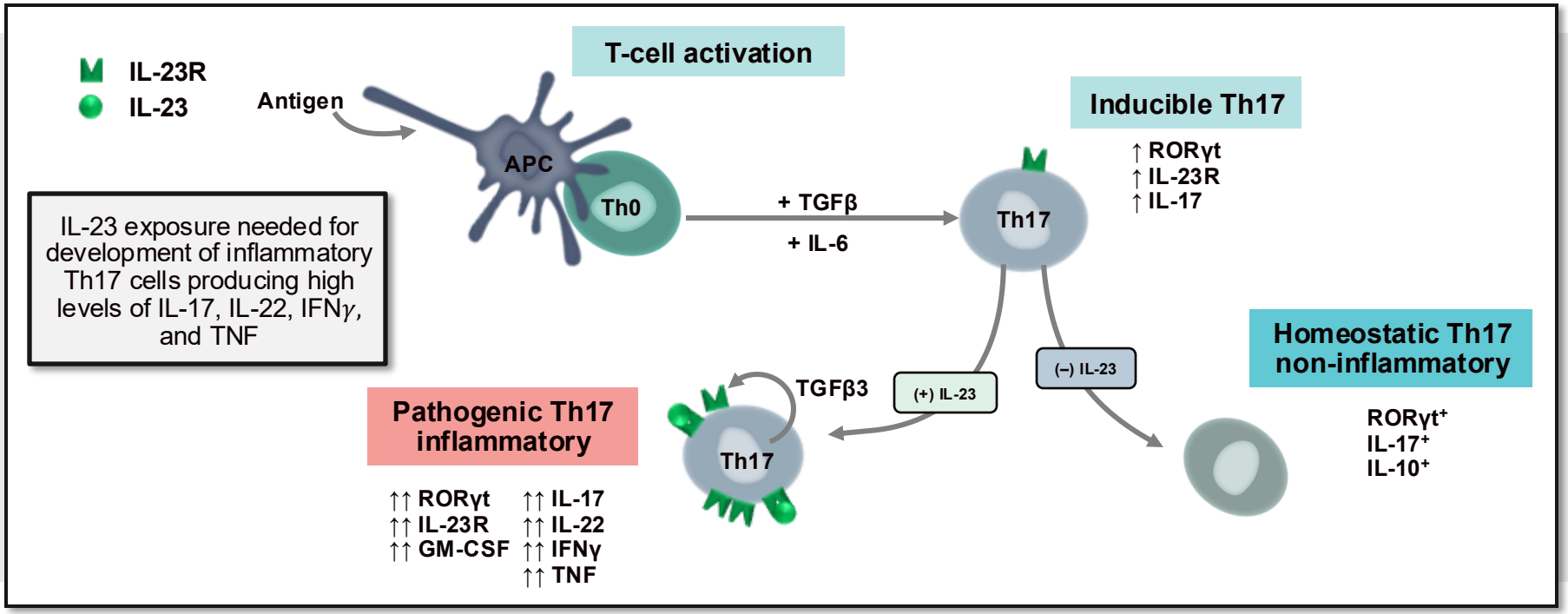
Role of Th17 and IL-17

Pathogenic and Protective Immunity



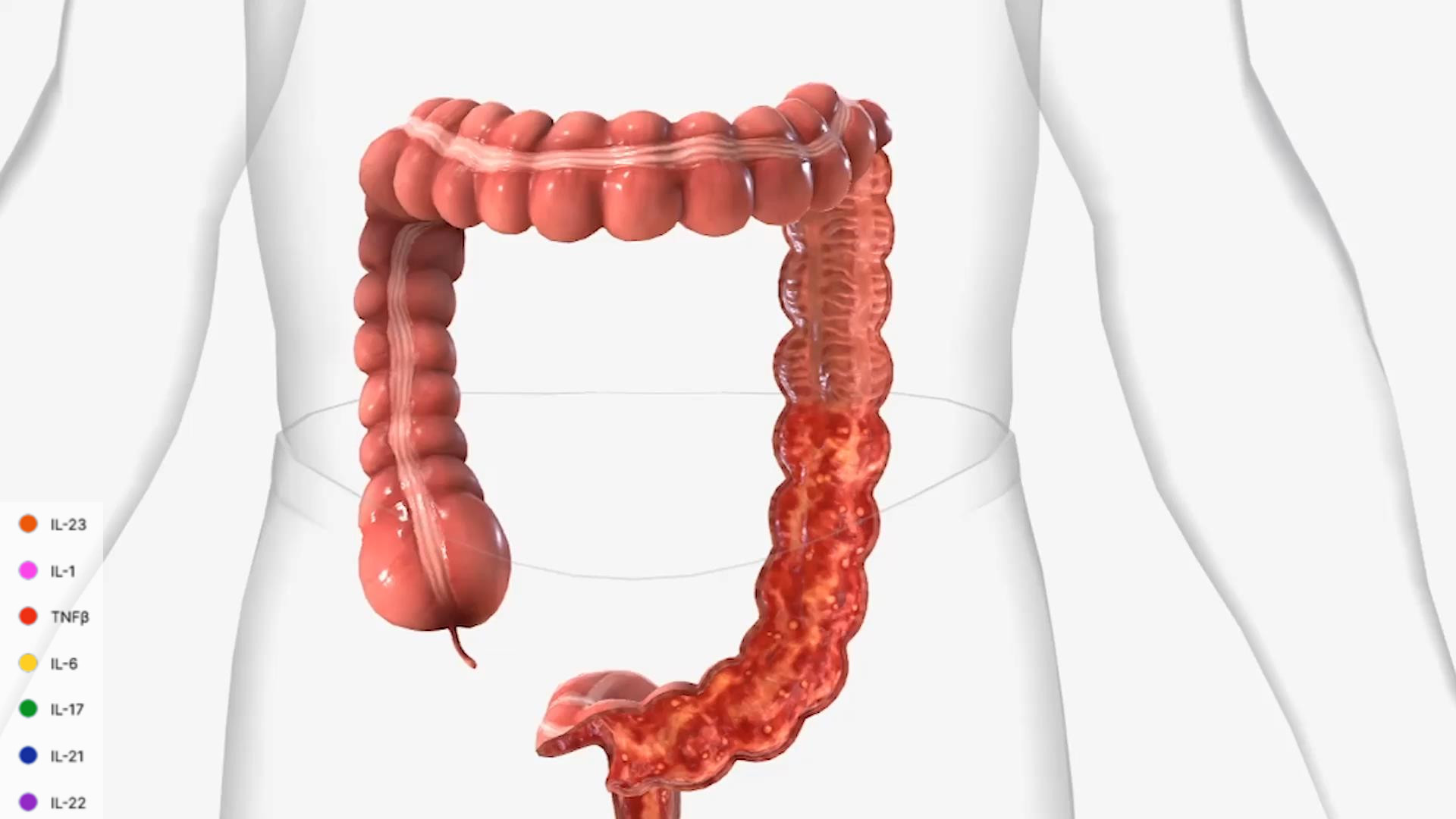
AMPs, antimicrobial peptides; IL, interleukin; NETs, neutrophil extracellular traps; Th, T helper cell.
Sun L, et al. *J Immunol Res*. 2023;1:3360310.

IL-23 Drives Development of Inflammatory Pathogenic Th17 Cells

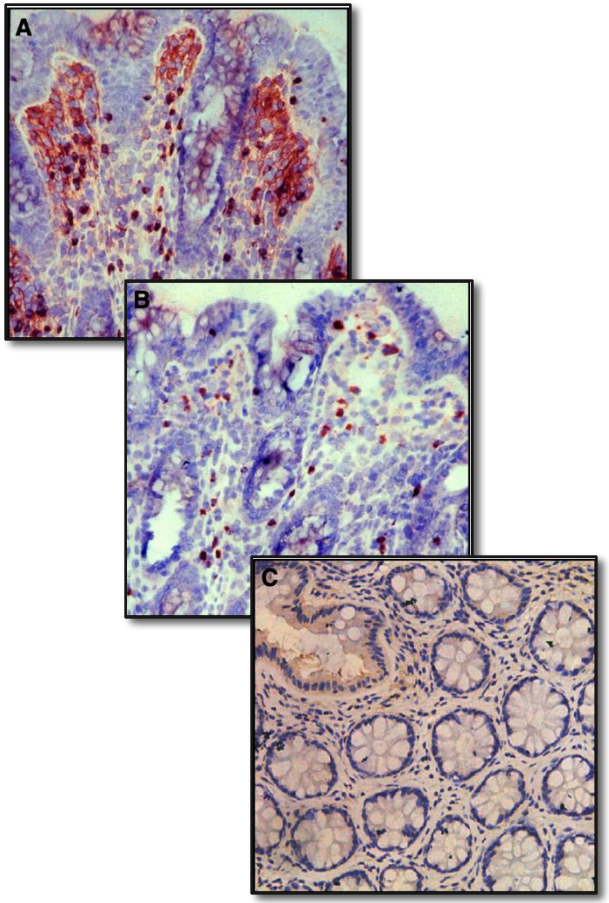


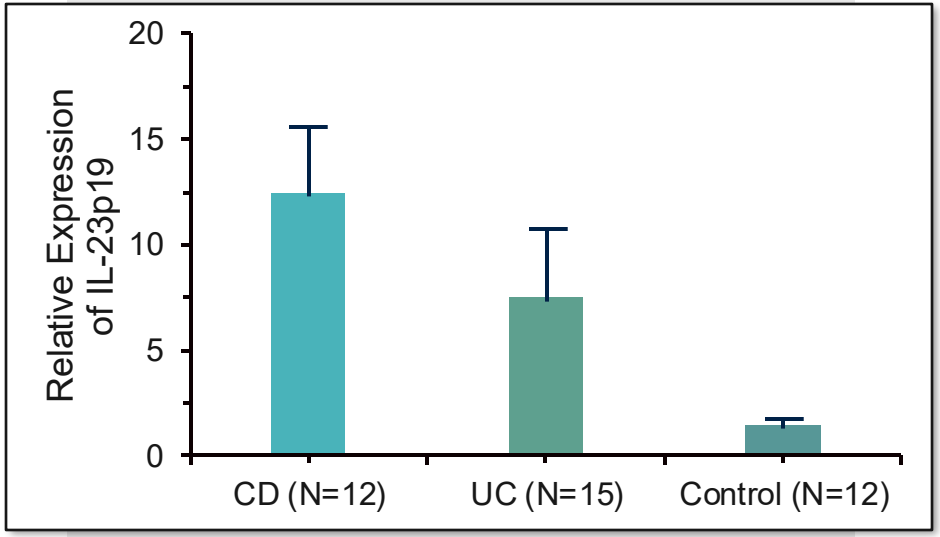
APC, antigen-presenting cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL-23R, interleukin-23 receptor; RORγt, retinoic acid receptor-related orphan receptor gamma t; TGF, transforming growth factor, TNF, tumor necrosis factor.

Adapted from Zúñiga LA, et al. *Immunol Rev*. 2013;252(1):78–88.
Gaffen SL, et al. *Nat Rev Immunol*. 2014;14(9):585–600. Schmitt H, et al. *Front Immunol*. 2021;12:622934.


IL-23
IL-1
TNFβ
IL-6
IL-17
IL-21
IL-22

IL-23 Expression in Patients with IBD



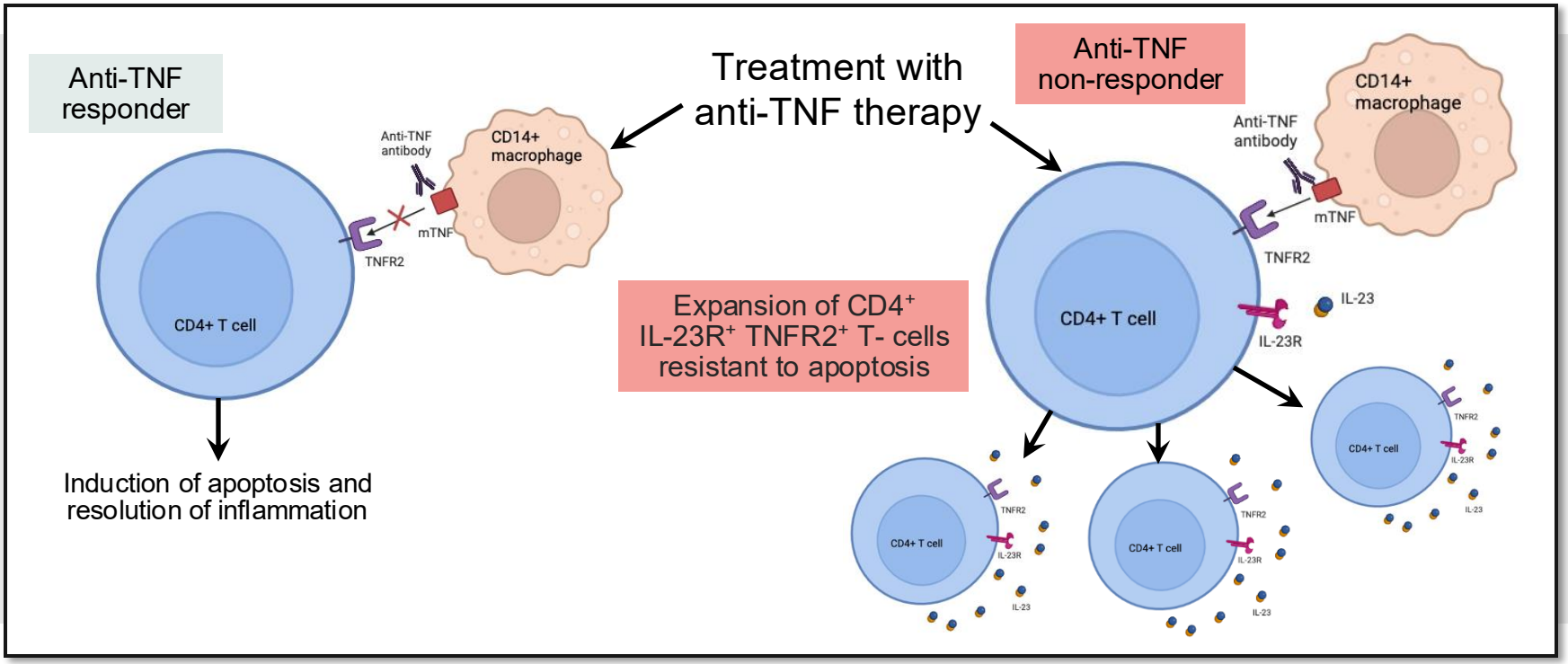


*P=0.05 vs control

CD, Crohn's disease; UC, ulcerative colitis.

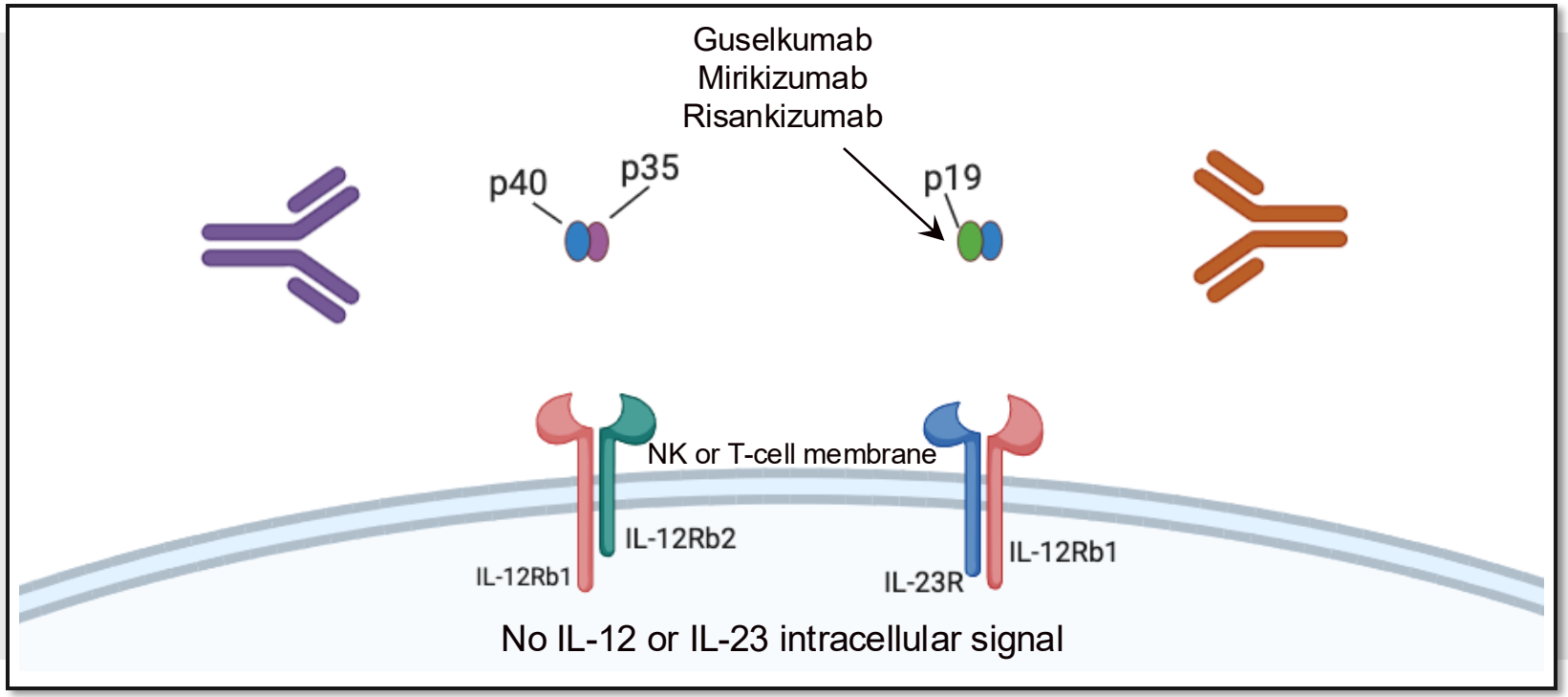
Liu Z, et al. *J Leukoc Biol*. 2011;89(4):597–606.

IL-23–mediated Resistance to Anti-TNF



CD#, cluster of differentiation #; mTNF, membrane-associated tumor necrosis factor; TNFR2, tumor necrosis factor receptor 2.
Adapted from Schmitt H, et al. *Semin Immunopathol*. 2019;41(6):737–746. Schmitt H, et al. *Gut*. 2019;68(5):814–828.

IL-23p19 Inhibitor Binding of IL-23

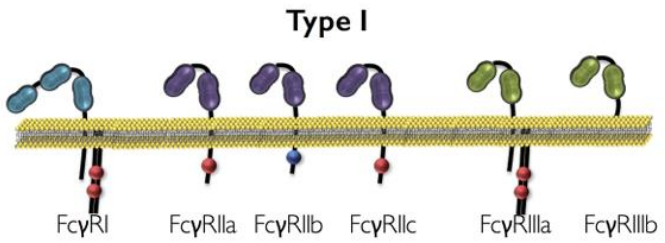


NK, natural killer cell.

Adapted from Gately MK, et al. *Ann Rev Immunol.* 1998;16(1):495–521. Wilson NJ, et al. *Nat Immunol*. 2007;8(9):950–957. Nickoloff BJ, et al. *J Clin Invest.* 2004;113(12):1664–1675. Nestle FO, et al. *J Invest Dermatol*. 2004;123(6):xiv–xv. Created with Biorender.

Importance of Fcγ Receptors and CD64 Receptors

- Fcγ receptors—surface receptors on immune cells that recognize the Fc portion of IgG
- CD64 (FcγRI) is the only Fcγ receptor with high affinity for IgG1
- CD64+ cells are the primary cellular source of IL-23 in IBD



	Type I						Type II	
	FcγRI	FcγRIIa	FcγRIIb	FcγRIIIc	FcγRIIIa	FcγRIIIb	DC-SIGN	CD23
Neutrophils	#	+	+	–	–	+	–	#
Eosinophils	#	+	+	–	–	#	–	#
Basophils	#	+	+	–	–	±	–	#
Monocytes	+	+	+	–	±	–	–	#
Macrophages	±	+	+	–	±	–	±	#
Dendritic cells	–/#	+	+	–	–/#	–	+	–
Platelets	–	+	–	–	–	–	–	–

+ Constitutive expression – No expression # Inducible expression

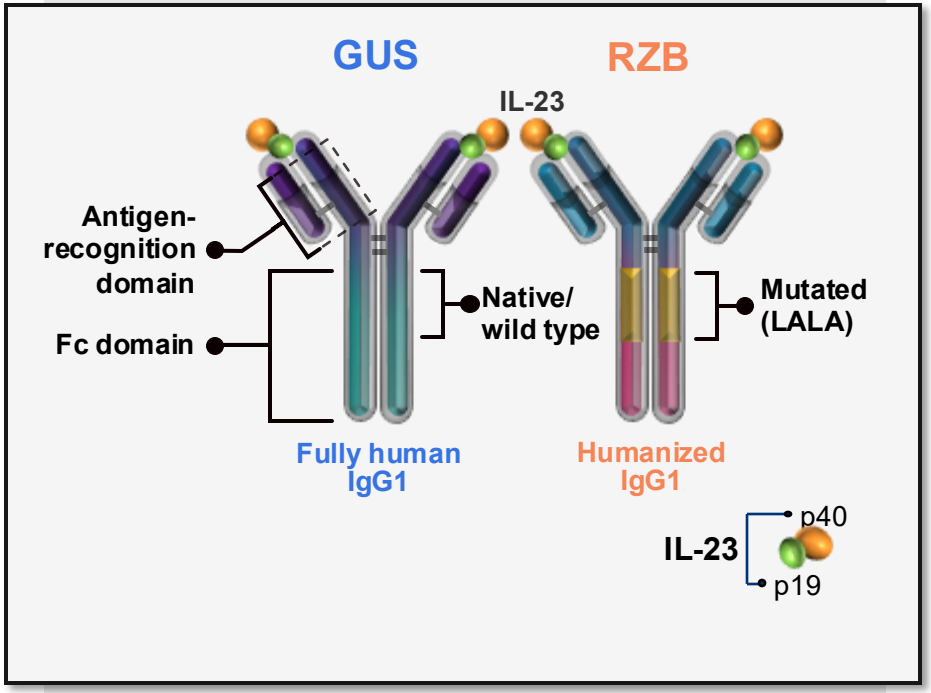
DC-SIGN, dendritic cell–specific intracellular adhesion molecule-3-grabbing nonintegrin; Fc, fragment, crystallizable; IgG, immunoglobulin G.

Bournazos S, et al. *Microbiol Spectr*. 2016;4(6):10.

Differences between IL-23p19 Antibodies

Guselkumab (GUS) and Risankizumab (RZB)

- GUS and RZB are monoclonal antibodies (mAbs) that selectively target the p19 subunit of IL-23
- Both have shown efficacy in the treatment of inflammatory bowel diseases
- GUS and RZB have differences in the Fc region that affect binding to Fc-gamma receptors
  - GUS is a fully human IgG1 with a native Fc region, which allows binding to CD64
  - RZB is a humanized IgG1 processing a mutated LALA Fc region intended to diminish binding to FCγRs

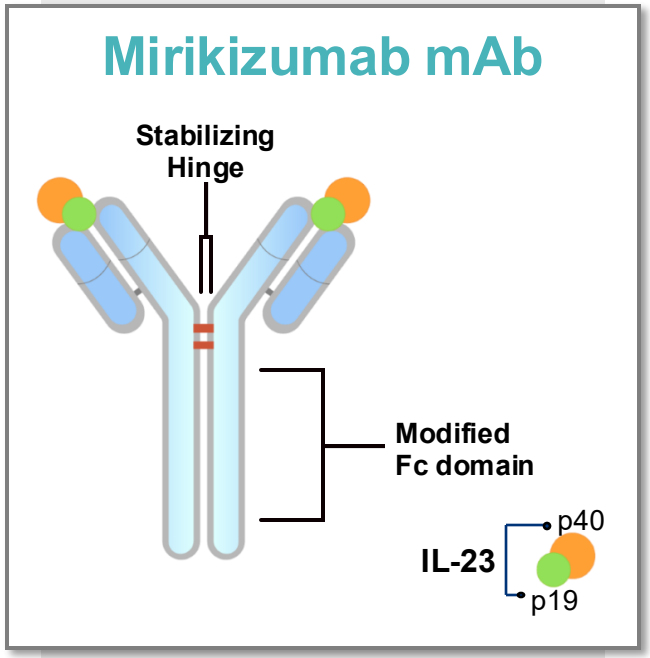


LALA, leucine to alanine substitutions at positions 234 and 235.

D'Haens G, et al. *Lancet*. 2022;399(10340):2015–2030. Ferrante M, et al. *Lancet*. 2022;399(10340):2031–2046. Sachen KL, et al. *Front Immunol.* 2025;16:1532852. Sandborn WJ, et al. *Gastroenterology*. 2022;162(6):1650–1664. Dignass A, et al. *J Crohns Colitis*. 2022;16(Suppl 1):i025–i026. Wojtal KA, et al. *PLoS One*. 2012;7(8):e43361. Pang Y, et al. *Clin Transl Sci.* 2024;17(1):e13706.

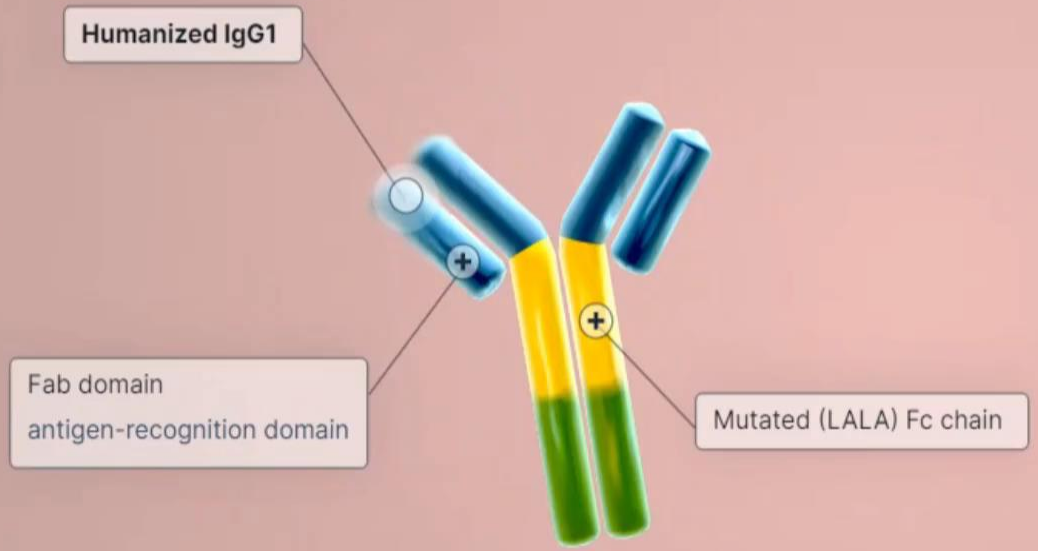
Differences between IL-23p19 Antibodies

Mirikizumab (MIRI)

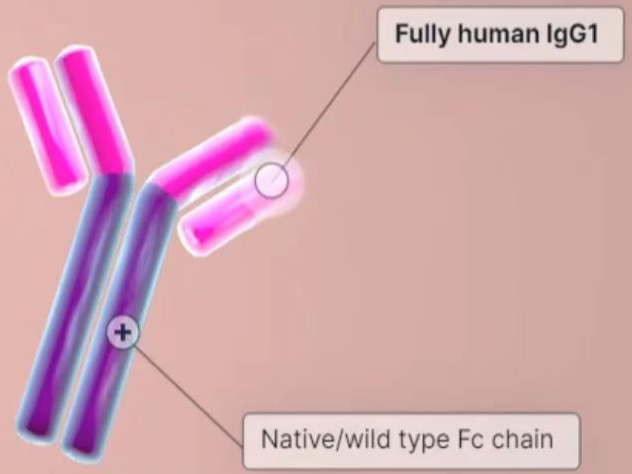


- Humanized IgG4 mAb that selectively binds to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor
- The Fc domain of MIRI was modified to significantly reduce FcγR binding and interaction

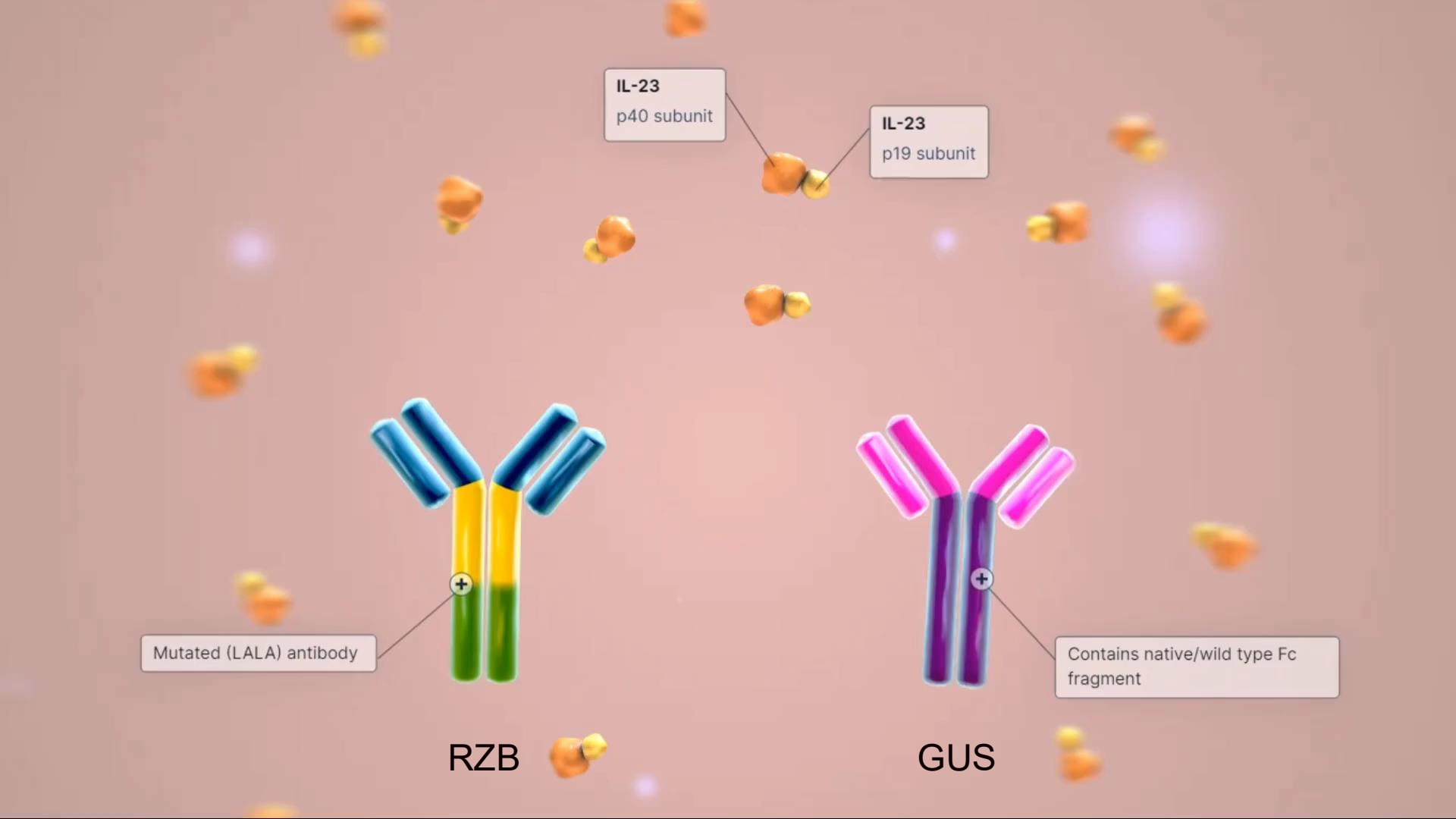
Strohl WR. *Antib Ther*. 2024;7(2):132–156.


Humanized IgG1
Fab domain
antigen-recognition domain
Mutated (LALA) Fc chain

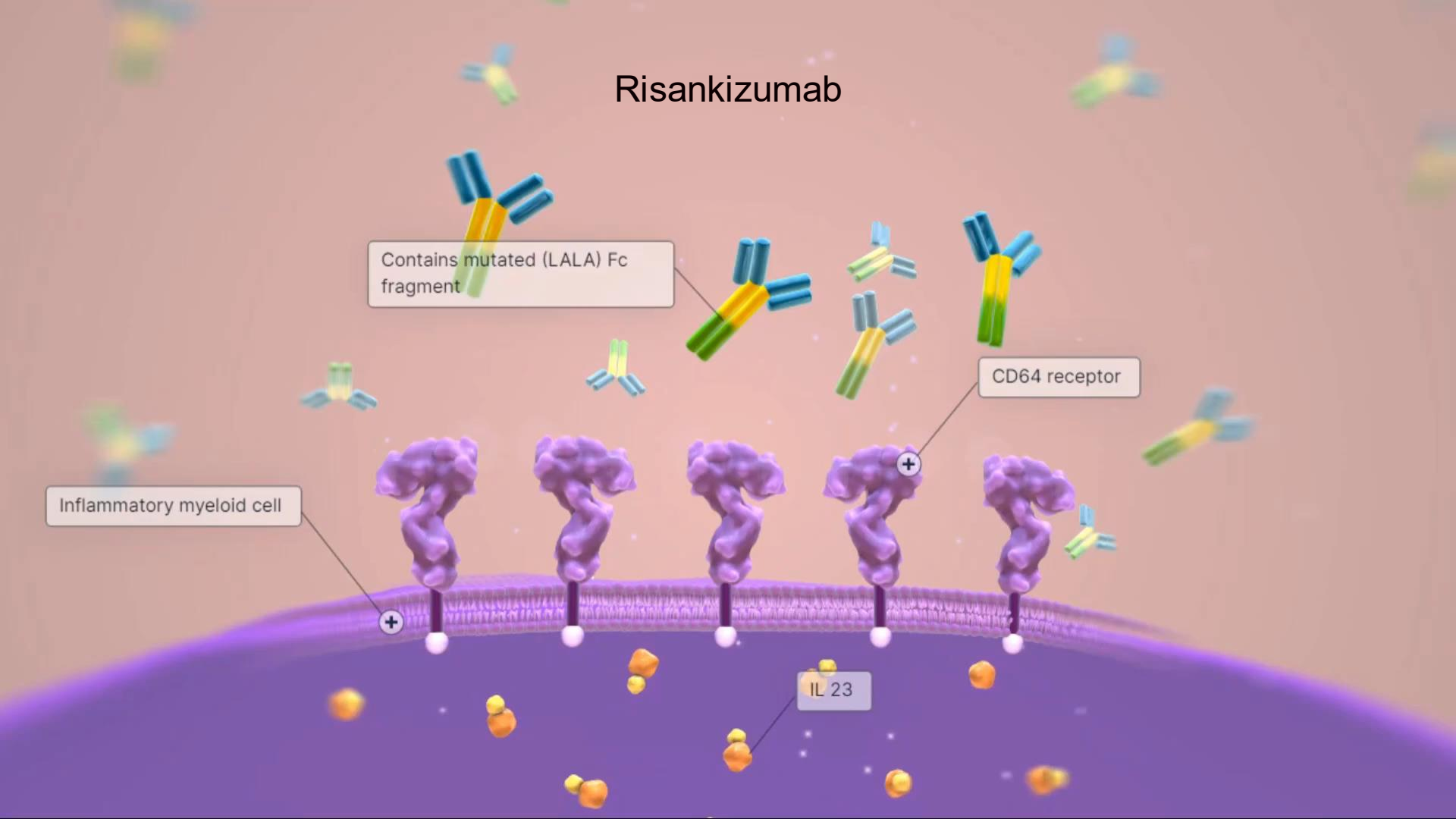
RZB


Fully human IgG1
Native/wild type Fc chain

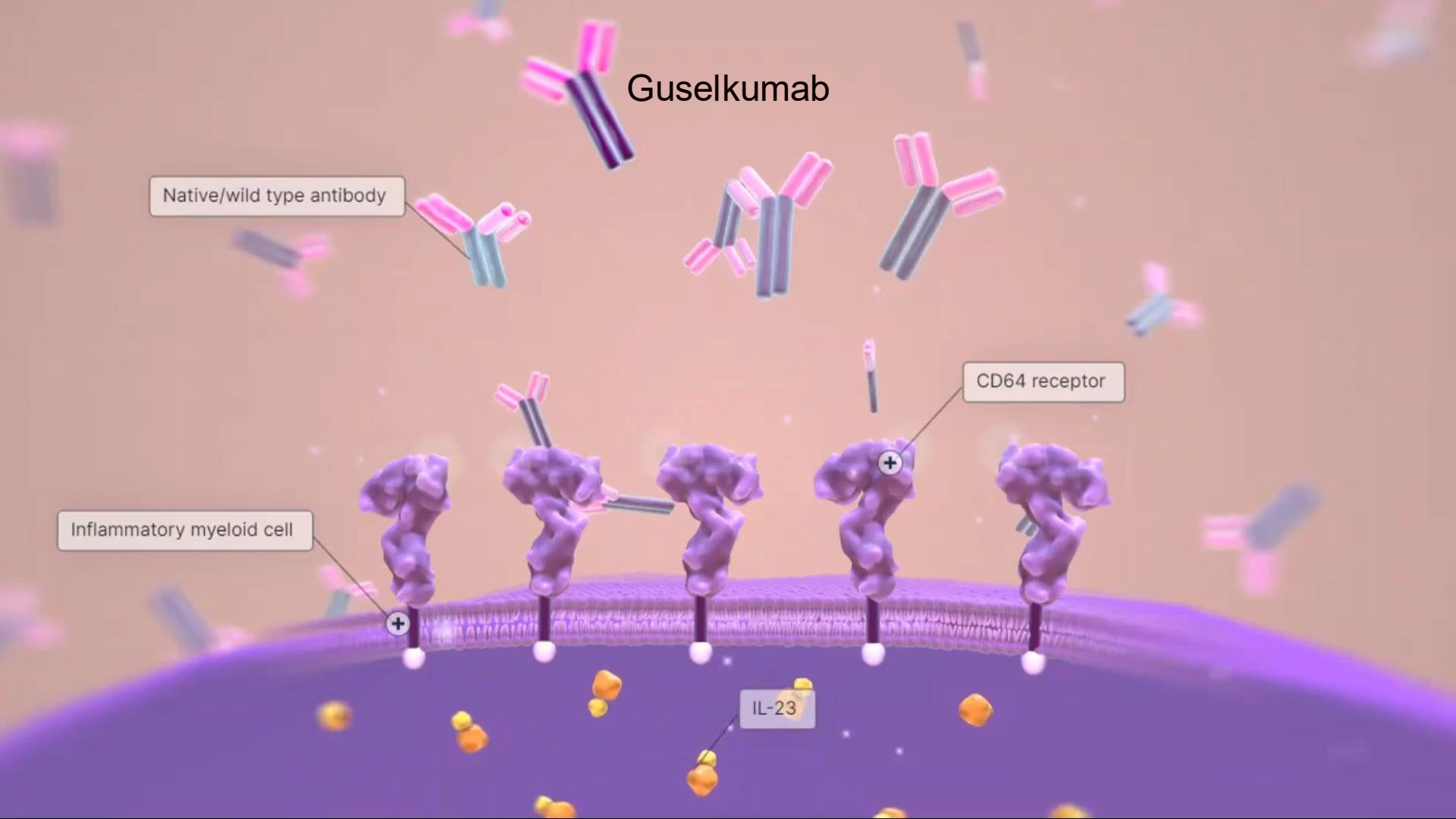
GUS


IL-23
p40 subunit
IL-23
p19 subunit
Mutated (LALA) antibody
Contains native/wild type Fc fragment
RZB
GUS

Risankizumab

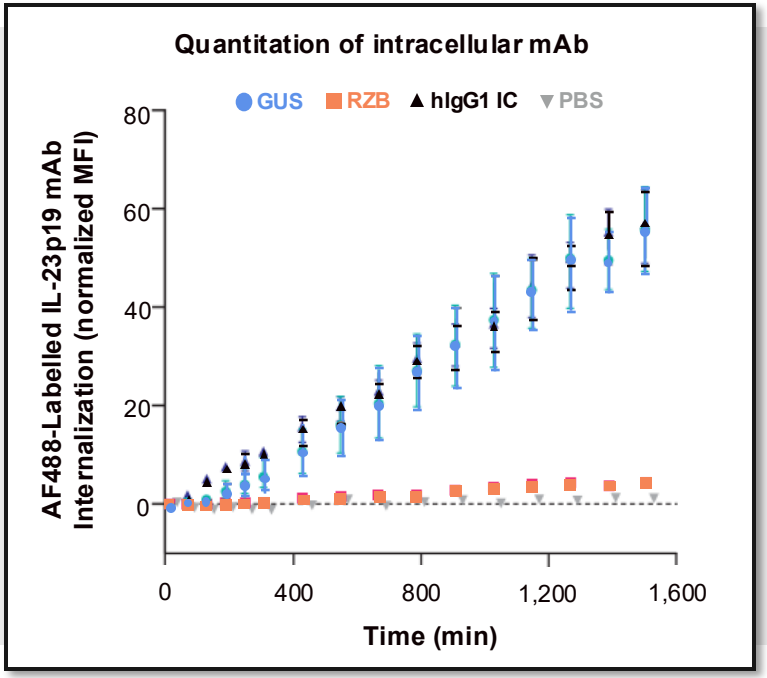


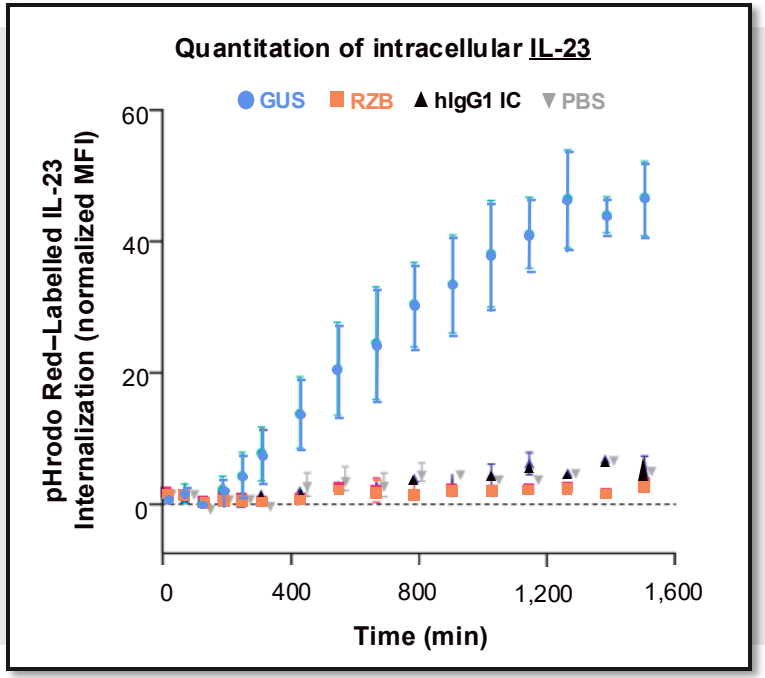
Guselkumab


Native/wild type antibody
CD64 receptor
Inflammatory myeloid cell
IL-23

In Vitro Evaluations of CD64 and IL-23 Binding
GUS and RZB

Quantitation of mAb MFI and IL-23 MFI in intracellular compartments of CD64+ inflammatory macrophages following treatment with IL-23p19 mAbs and IL-23





MFI, mean fluorescence intensity; PBS, phosphate buffered saline.

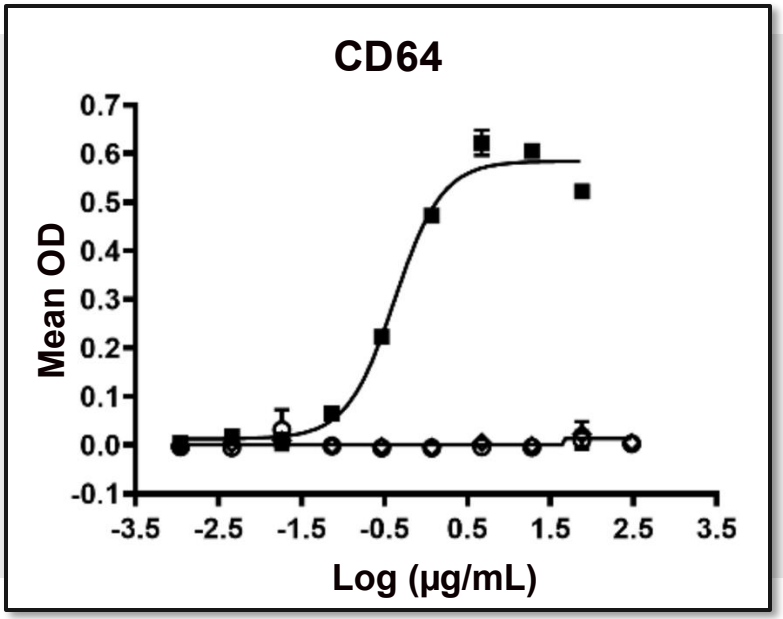
Atreya R, et al. *J Crohns Colitis*. 2024;18(Suppl 1):i470. Sachen KL, et al. *Front Immunol*. 2025;16:1532852.

In Vitro Evaluations of CD64 and IL-23 Binding

MIRI

Assessment of Fc Receptor Activation and Complement Binding

MIRI is a humanized IgG4 anti-human IL-23p19 mAb



Data are mean + standard deviation (SD) of duplicate wells.

Steere B, et al. *J Pharmacol Exp Ther*. 2023;387(2):180–187.

Warp Speed Ahead

Integrating Novel IL-23p19 Inhibitors into Clinical Practice

Case 1: Maya H

Maya H. is a 31-year-old woman who presents with changes in bowel habits, including more than 6 stools per day with rectal bleeding and abdominal pain.

Exam findings

- Colonoscopy: Mayo 2 with active disease up to 60 cm
- Calprotectin: 679 µg/mg
- CRP: 11.6 mg/L

Diagnosis: moderately active ulcerative colitis

She is initially treated with mesalamine but experiences no improvement in symptoms.

CME OUTFITTERS

CRP, C-reactive protein.

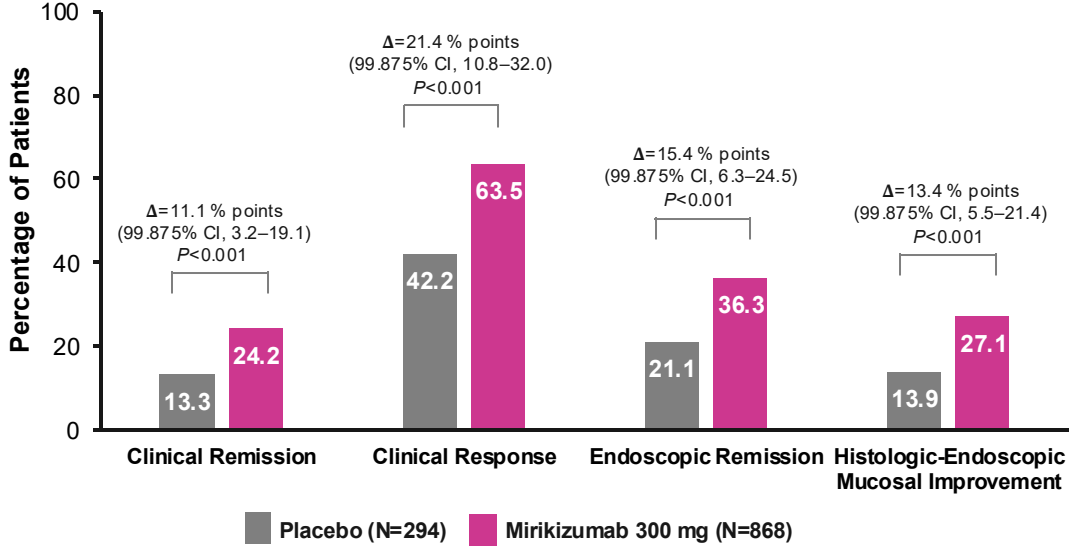
What treatment would you suggest for this patient?

A. Mesalamine + budesonide
B. TNF inhibitor
C. Vedolizumab
D. Ustekinumab
E. IL-23p19 inhibitor
F. S1P modulator
G. JAK inhibitor
H. I'm not sure

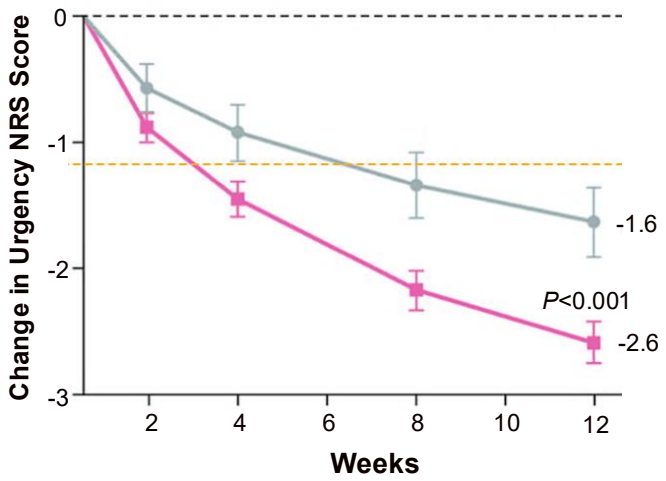
Mirikizumab Induction in UC

LUCENT-1

Primary Endpoint of Clinical Remission and Three Major Secondary Endpoints



Change in Bowel Urgency from Baseline

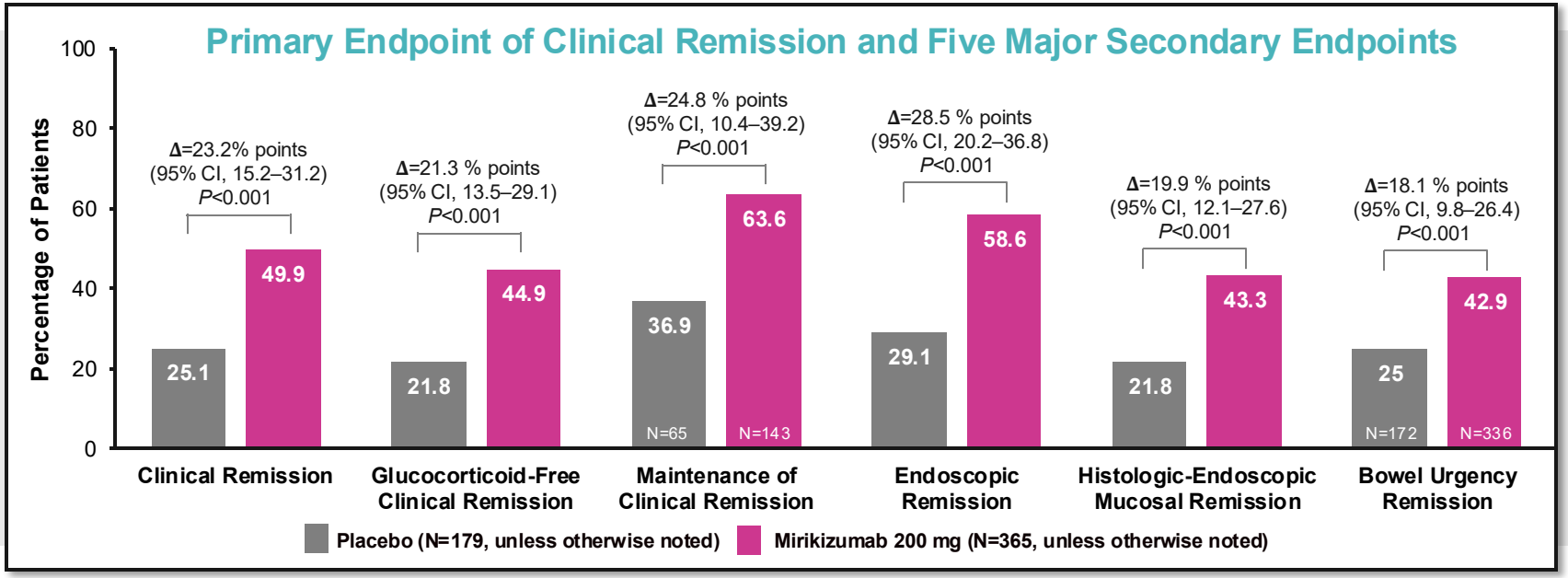


NRS, numeric rating scale.

D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444–2455.

Mirikizumab Maintenance in UC

LUCENT-2 Week 40 Endpoints



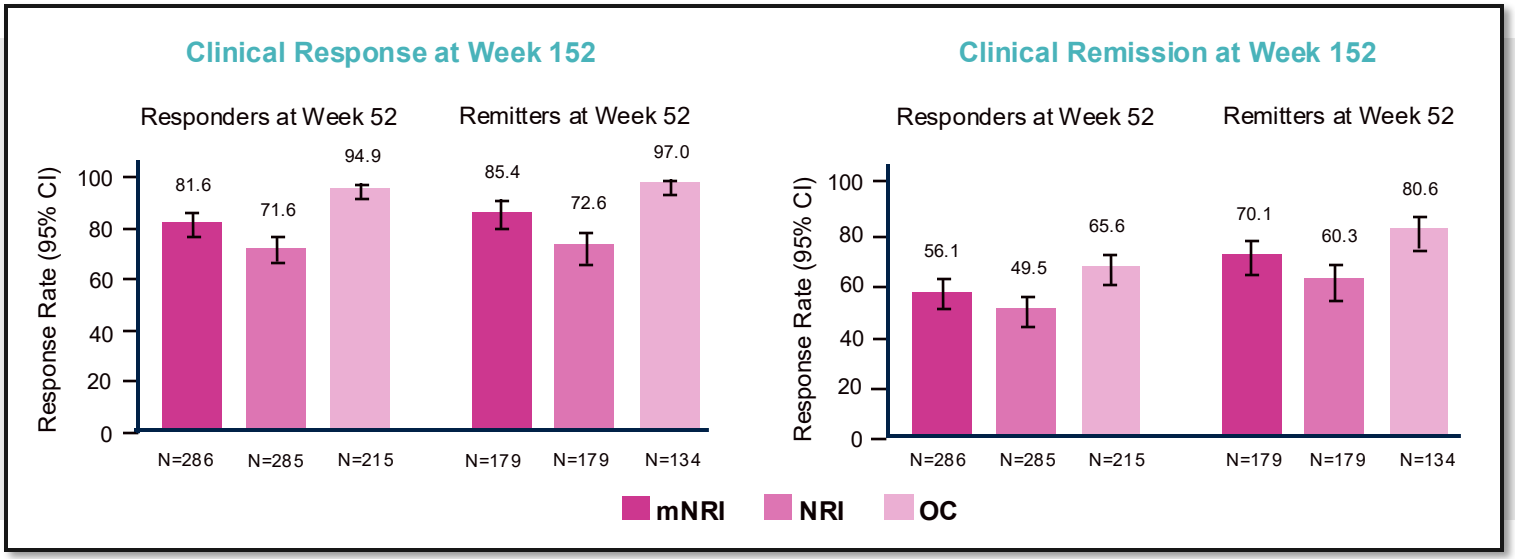
Clinical remission: stool frequency (SF)=0, or SF=1 with a ≥1-point decrease from baseline; rectal bleeding (RB)=0; endoscopic subscore (ES)=0 or 1 (excluding friability); endoscopic remission: ES=0 or 1 (excluding friability), clinical remission at week 40, remission of symptoms at week 28, and no glucocorticoid use for ≥12 weeks before week 40.

D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444–2455.

Mirikizumab Maintenance in UC

Long-term Follow-up from LUCENT-3

LUCENT-3 open-label extension study of patients completing 52 weeks of maintenance treatment in LUCENT-2



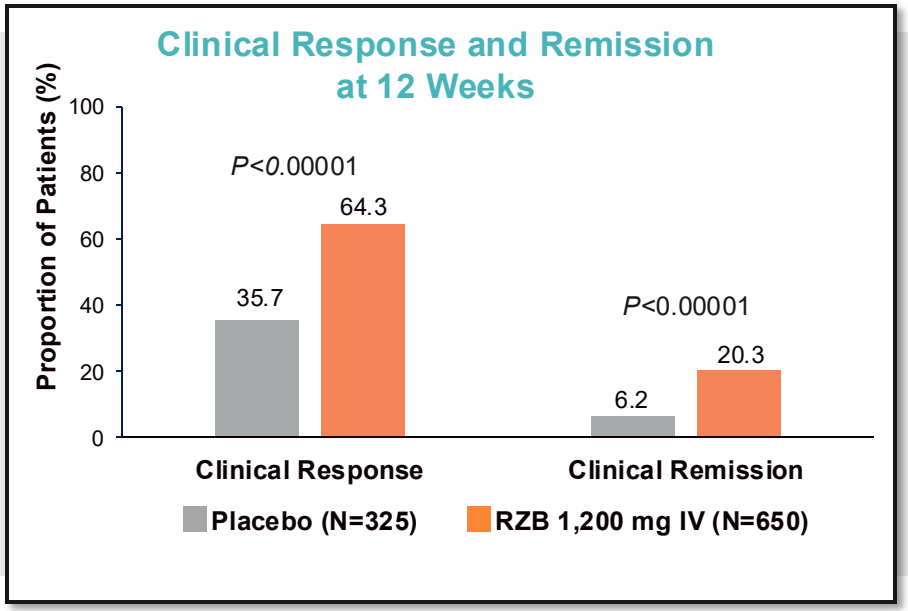
Clinical remission: SF=0 or 1 with ≥ 1-point decrease in modified Mayo score (MMS) from baseline, RB=0, and ES=0 or 1 (excluding friability).
Clinical response: ≥2-point and ≥30% decrease in the MMS from baseline, RB=0 or 1, or RB ≥1-point decrease from baseline.

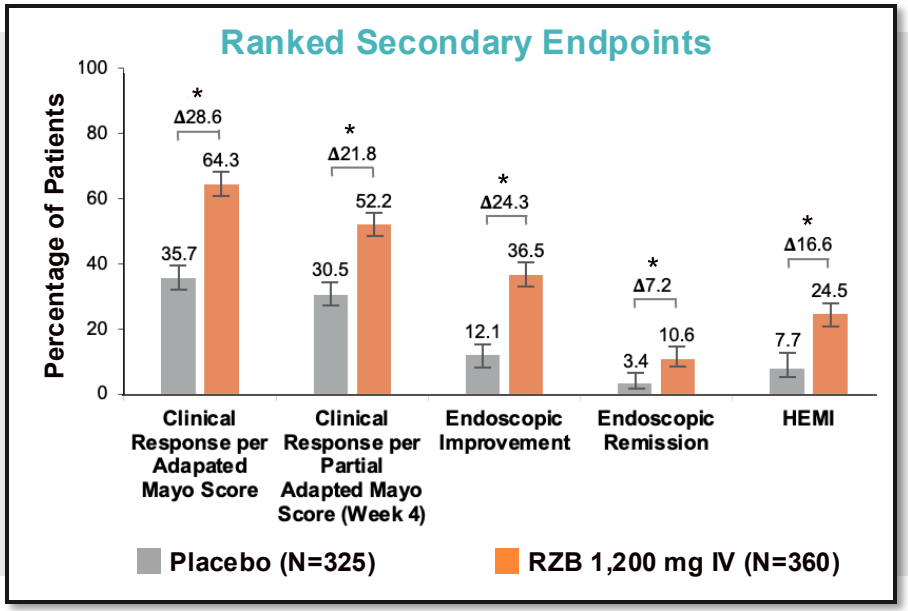
NRI, non-responder imputation; mNRI, modified NRI; OC, observed case.

Sands BE, et al. *Inflamm Bowel Dis*. 2024:izae253.

Risankizumab Induction in UC

INSPIRE





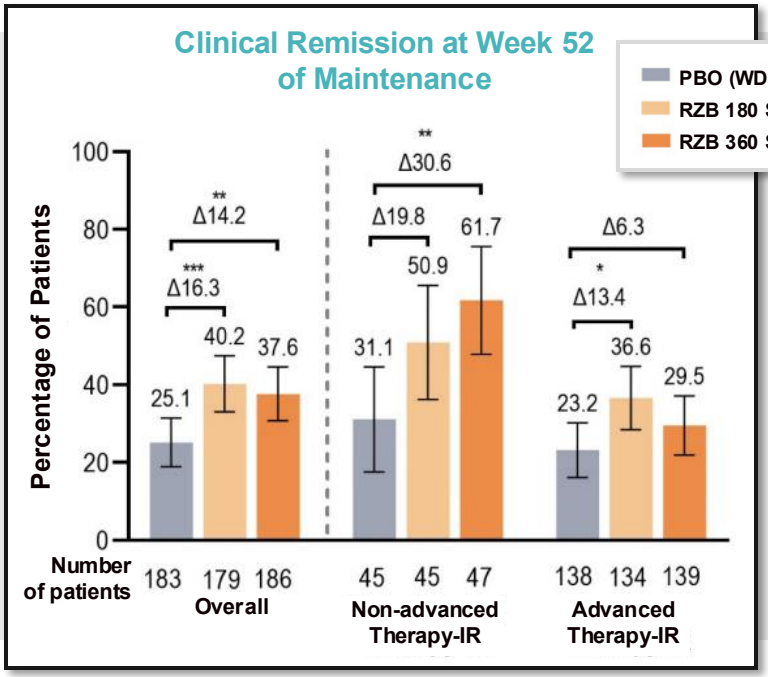
*P<0.00001 vs PBO.

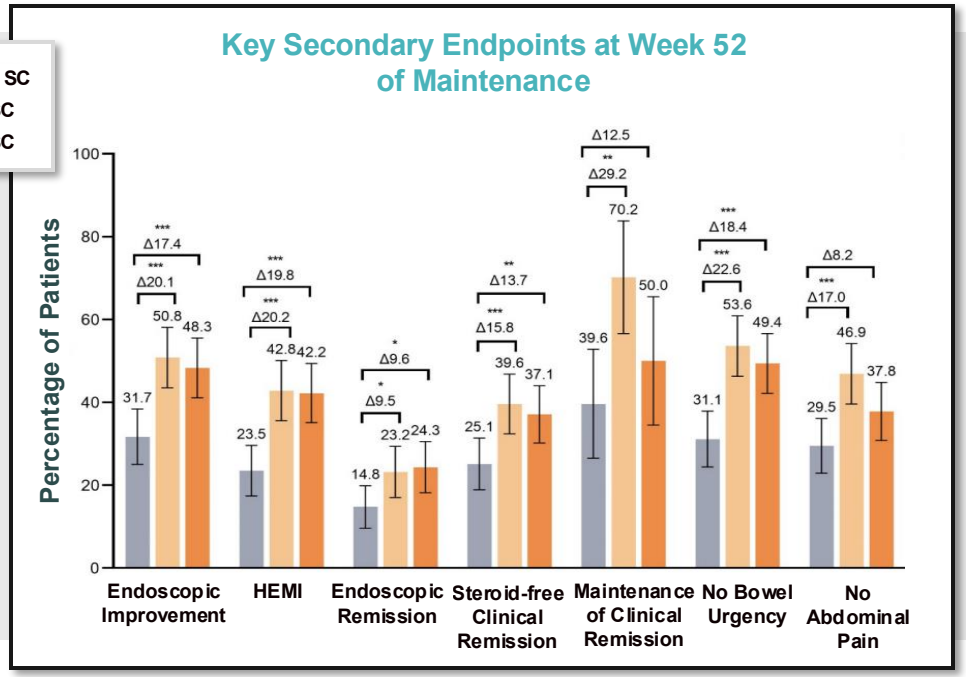
Clinical remission per Adapted Mayo Score is defined as stool frequency subscore (SFS) ≤1 and not greater than baseline, rectal bleeding subscore (RBS) of 0 and ES ≤1 without friability. Clinical response is defined as a decrease from baseline in the Adapted Mayo score ≥2 points and ≥30% from baseline, plus a decrease in RBS ≥1 or an absolute RBS ≤1.

Louis E, et al. *Am J Gastroenterol*. 2023;118(10S):S624–S625.

Risankizumab Maintenance in UC

COMMAND





*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$ vs PBO (WD) SC.

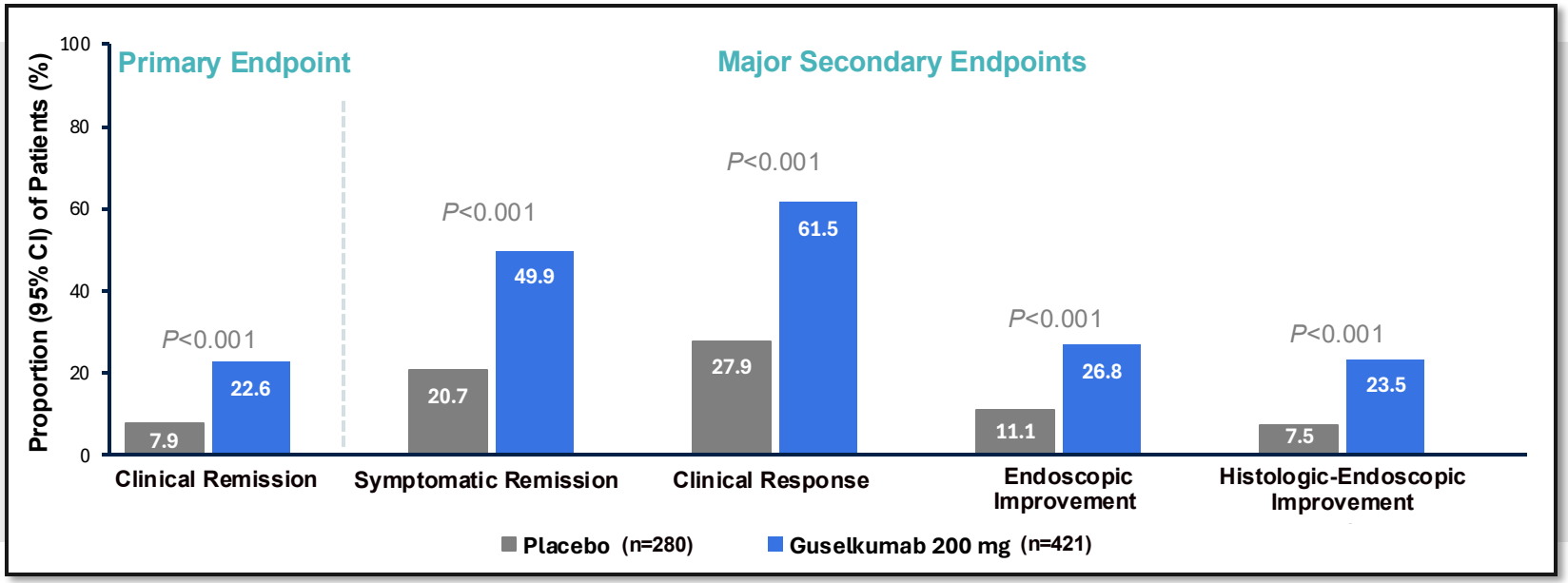
HEMI, histo-endoscopic mucosal improvement; IR, inadequate response; PBO, placebo; SC, subcutaneous; WD, withdrawal.

Louis E, et al. *J Crohns Colitis.* 2024;18(Suppl 1):i10–i12.

CME OUTFITTERS

Guselkumab Induction in UC

QUASAR Phase III Week 12 Endpoints

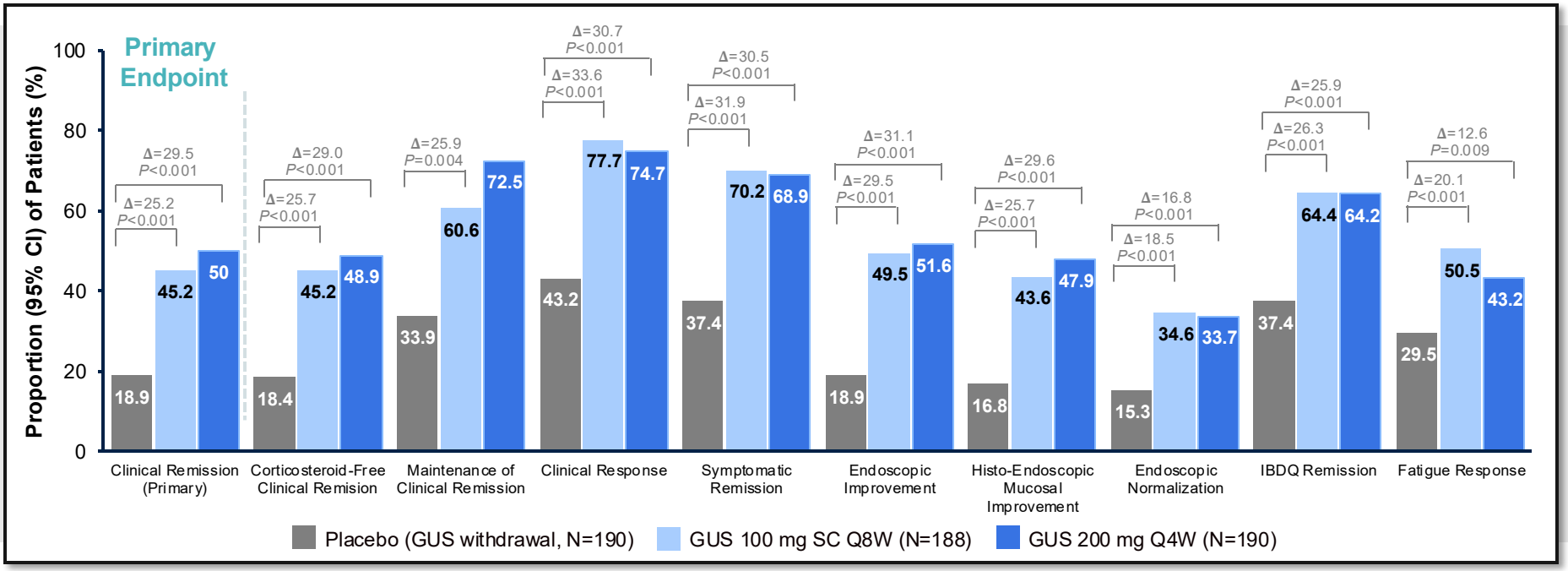


Clinical remission defined as a Mayo SFS of 0 or 1 with no increase from baseline, an RBS of 0, and a Mayo ES of 0 or 1 with no friability.

Rubin DT, et al. *Lancet.* 2025;405(10472):33–49.

Guselkumab Maintenance in UC

QUASAR Phase III Week 44 Endpoints



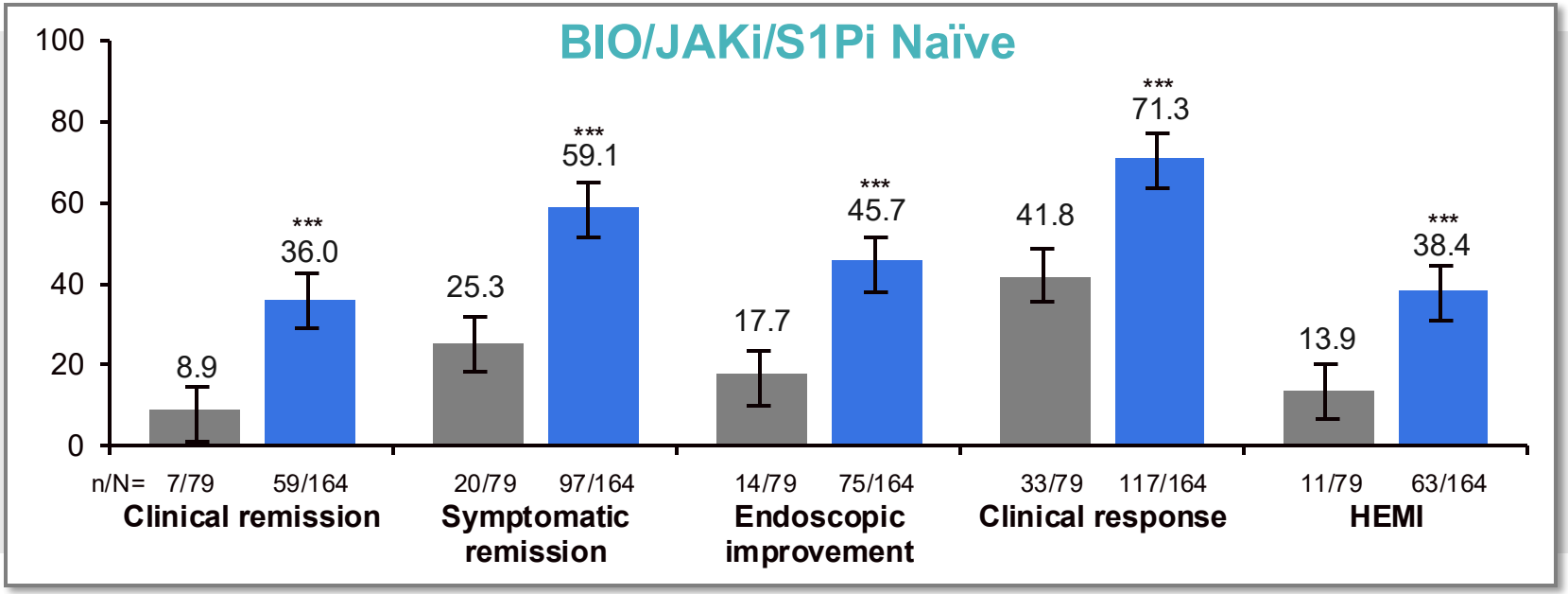
Primary analysis population: randomized patients with an MMS of 5–9 at induction who received at least one maintenance study treatment dose.

IBDQ, IBD questionnaire.

Rubin DT, et al. *Lancet.* 2025;405(10472):33-49.

Subcutaneous Guselkumab in UC

ASTRO Phase III Week 12 Endpoints



***Nominal *P*<0.001

Clinical remission defined as Mayo SFS 0/1 and not increased from BL, a Mayo RBS=0, and MES 0/1 with no friability; symptomatic remission defined as SFS 0/1 and not increased from BL, and RBS=0; endoscopic improvement MES 0/1 with no friability; clinical response ≥30% and ≥2-point decrease from BL in modified Mayo score with ≥1-point decrease from BL in RBS or RBS 0/1.

BL, baseline.

Peyrin-Biroulet L, et al. *J Crohns Colitis.* 2025;19(Suppl 1):i19–i20.

Mirikizumab Safety in UC

Outcome, n (%)	200 mg Mirikizumab Q4W SC (n=289)
TEAEs	184 (63.7)
AEs of special interest	
Infections (all)	87 (30.1)
Infections (serious)	3 (1.0)
Cerebrocardiovascular events	2 (0.7)
Malignancies	0 (0)
Immediate hypersensitivity reaction	4 (1.4)
Injection site reactions	16 (5.5)
Death	0 (0)
Discontinuation due to AE	8 (2.8)

AE, adverse event; Q#W, every # weeks; TEAE, treatment-emergent AE.
Sands BE, et al. *Inflamm Bowel Dis*. 2024;30(12):2245–2258.

Risankizumab Safety in UC

TEAEs among Safety Population through Week 52[a]			
Events/100 Patient Years	**PBO (WD) SC** n=196; PY=174.9	**RZB 180 mg SC** n=193; PY=185.4	**RZB 360 mg SC** n=195; PY=173.5
Any AE	399 (228.1)	399 (215.2)	406 (234.0)
AE related to COVID-19	28 (16.0)	21 (11.3)	29 (16.7)
AE with reasonable possibility of being drug related[b]	75 (42.9)	85 (45.9)	61 (35.2)
Severe AE	14 (8.0)	3 (1.6)	7 (4.0)
Serious AE	20 (11.4)	11 (5.9)	11 (6.3)
AE leading to discontinuation of study drug	4 (2.3)	5 (2.7)	5 (2.9)
All deaths	0	0	1 (0.6)[c]
Serious infections[d]	4 (2.3)	2 (1.1)	1 (0.6)
Infusion/injection site reactions[e]	3 (1.7)	14 (7.6)	10 (5.8)

[a]The safety population included all patients who clinically responded to IV RZB at 12 or 24 weeks, were randomized to COMMAND at maintenance week 0 and received at least one dose of study drug during 52-week maintenance period. [b]As assessed by the investigator. [c]One death was reported in the RZB 360 mg arm in a patient diagnosed with colon adenocarcinoma, which was retrospectively found in the screening biopsy tissue. [d]Serious infections in RZB-treated patients included COVID-19, COVID-19 pneumonia, abscess limb, and pneumonia. [e]All infusion/injection site reaction events were nonserious and did not lead to study discontinuation.

PY, patient years.

Louis E, et al. *J Crohns Colitis.* 2024;18(Suppl 1):i10–i12.

Guselkumab Safety in UC

Outcome	Placebo (n=105)	Guselkumab 200 mg IV (n=101)	Guselkumab 400 mg IV (n=107)	Combined (n=208)
Any AE	59 (56.2)	45 (44.6)	53 (49.5)	98 (47.1)
AE within 1 hour of infusion	2 (1.9)	2 (2.0)	0	2 (1.0)
Serious AE	6 (5.7)	1 (1.0)	3 (2.8)	4 (1.9)
Death	0	0	0	0
Discontinuation for AE	3 (2.9)	1 (1.0)	0	1 (0.5)
Malignancy	0	0	0	0
Infection	13 (12.4)	14 (13.9)	10 (9.3)	24 (11.5)
Serious infection	2 (1.9)	0	0	0

Peyrin-Biroulet L, et al. *Gastroenterology*. 2023;165(6):1443–1457.

IL-23 Inhibitors

History of Safety in PSO Phase III Studies

Adverse Event, n (0/0)	Ustekinumab (n=556)	Guselkumab (n=494)	Risankizumab (n=598)
Any AE	378 (68.0)	235 (47.6)	285 (47.7)
Serious AE	8 (1.4)	8 (1.6)	13 (2.2)
Severe AE	NA	NA	13 (2.2)
AE leading to discontinuation	8 (1.4)	7 (1.4)	3 (0.5)
Death	2 (0.4)	NA	1 (0.2)
Nasopharyngitis	55 (9.9)	35 (7.1)	NA
Upper respiratory infection	35 (6.3)	16 (3.2)	28 (4.7)
Psoriasis	NA	NA	0 (0)
Injection-site reaction	22 (4.0)	NA	NA
Severe infection	12 (2.2)	1 (0.2)	4 (0.7)

PSO, psoriasis

Yang K, et al. *Am J Clin Dermatol.* 2021;22:173–192.

AGA Living Guidelines on Treatment of Moderate to Severe 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

*The FDA label recommends 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.

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

Faculty Discussion

Managing biologic-naïve ulcerative colitis

Case 2: Cassie L

Cassie L. is a 26-year-old woman who was initially diagnosed with UC at 17 years.

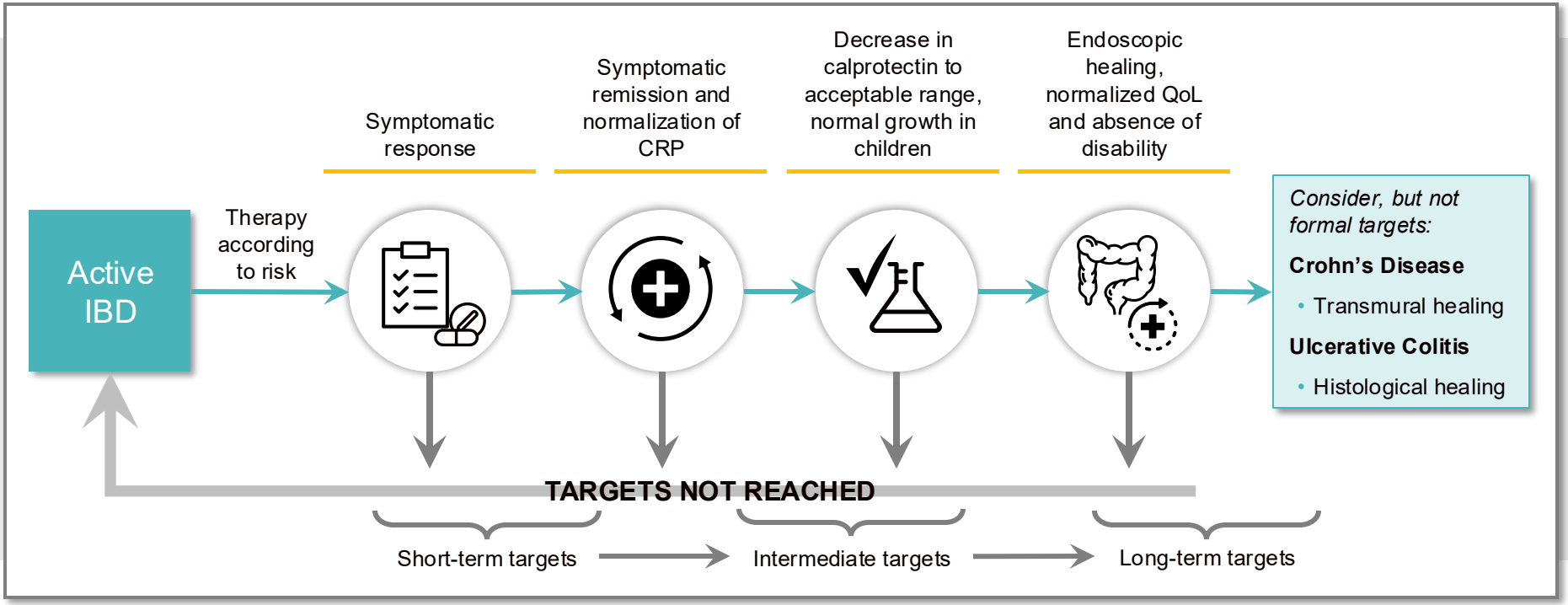
She is currently being treated with adalimumab weekly, but has experienced several flare-ups in the past year, including 2 hospitalizations.

Her symptoms include multiple loose, bloody stools each day with fecal urgency that has impacted her social and work life.

What would you do next?

A. Add prednisone to current treatment
B. Switch to infliximab
C. Switch to vedolizumab
D. Switch to ustekinumab
E. Switch to IL-23p19 inhibitor
F. Switch to S1P modulator
G. Switch to JAK inhibitor
H. I’m not sure

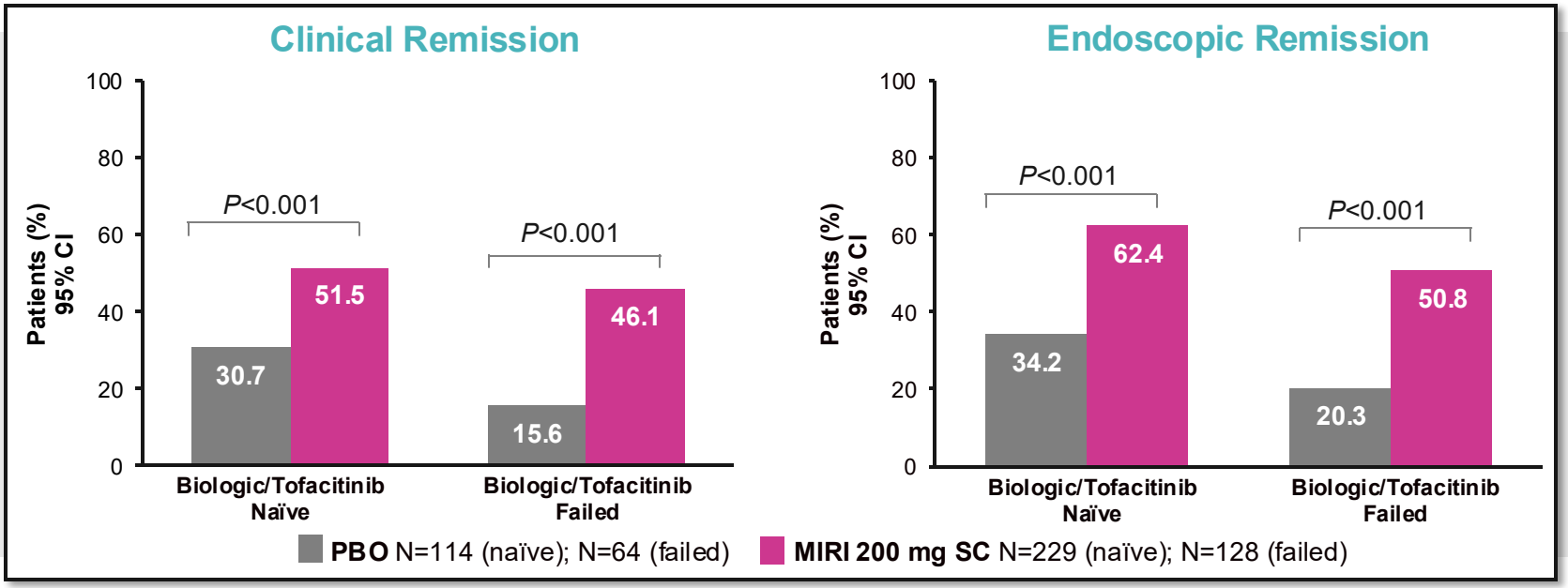
When to Switch Therapies



QoL, quality of life.

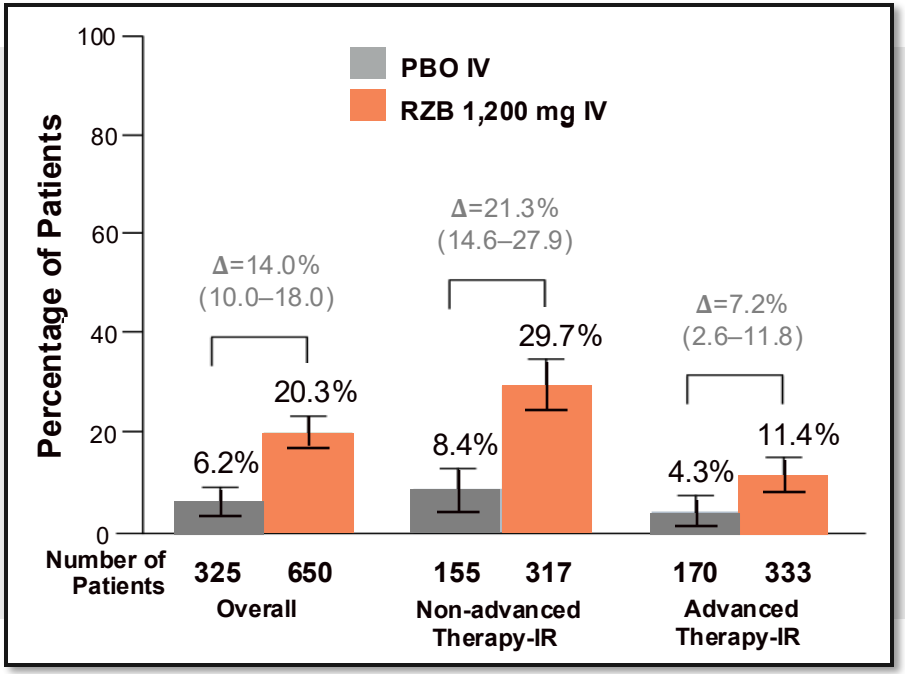
Turner D, et al. *Gastroenterol.* 2021;160(5):1570–1583.

MIRI in Treatment-naïve and Treatment-experienced Patients with UC: *LUCENT-2*



D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444–2455.

RZB in Treatment-naïve and Treatment-experienced Patients with UC: *INSPIRE*

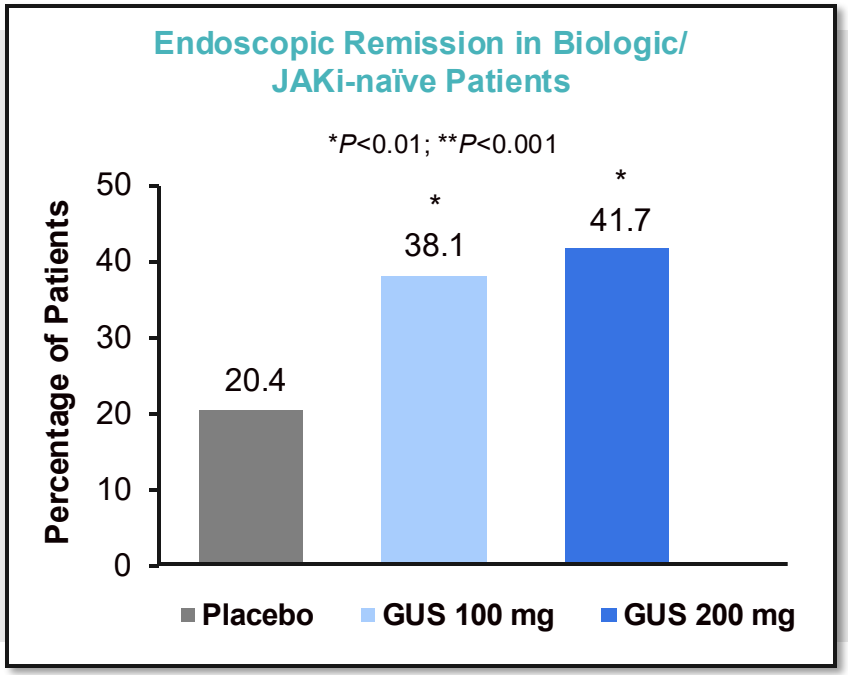


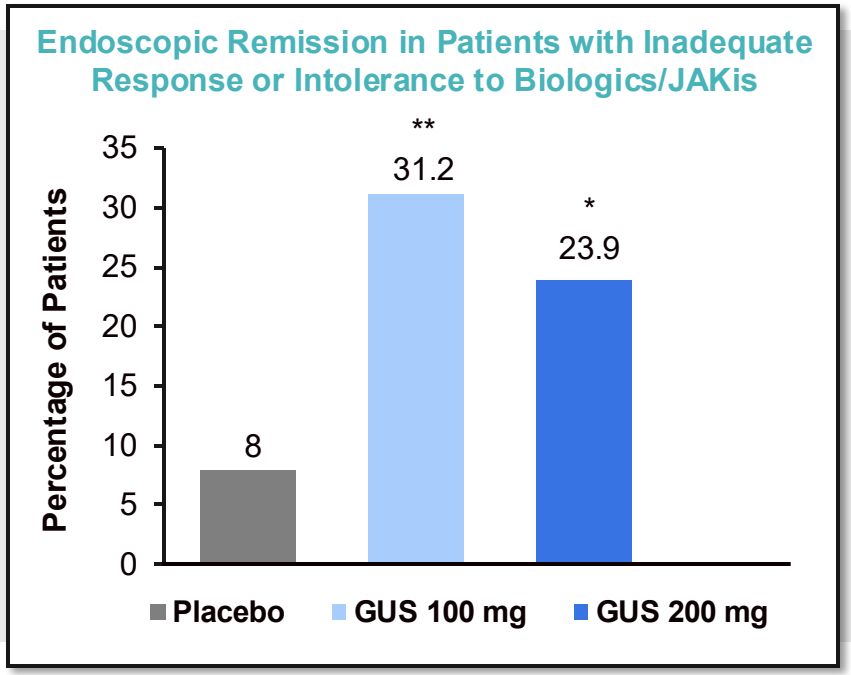
Primary Endpoint
Clinical remission* at week 12

*Clinical remission per Adapted Mayo Score: SFS ≤1 and not greater than baseline, RBS of 0, and ES ≤1 without friability.

Louis E, et al. *JAMA*. 2024;332(11):881–897.

GUS in Treatment-naïve and Treatment-experienced Patients with UC at Week 44: *QUASAR*





Rubin DT, et al. *Lancet*. 2025;405(10472):33–49

AGA Living Guidelines on Treatment of Moderate to Severe UC

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: mirikizumab, risankizumab, guselkumab

LOWER EFFICACY MEDICATIONS: adalimumab, vedolizumab, ozanimod, etrasimod

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

Faculty Discussion

Managing biologic-experienced ulcerative colitis

Case 3: Ronald P

Ronald P. is a 53-year-old man with a history of type 2 diabetes who was encouraged by his wife to come in for an exam after experiencing several worrying symptoms over the past 3 months, including abdominal pain and cramping, >5 loose stools per day with occasional blood, and weight loss of 12 pounds.

Labs: elevated CRP and ESR, stools negative for infectious or enteric pathogens

Imaging: thickening of the terminal ileum with evidence of mesenteric fat stranding

Colonoscopy: patchy areas of inflammation with ulceration and cobble stoning in the terminal ileum, consistent with Crohn's disease

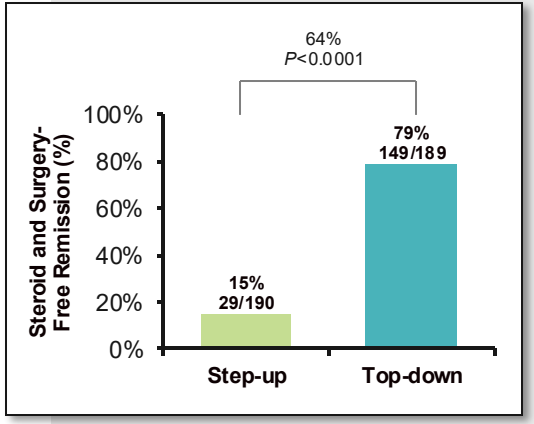
ESR, erythrocyte sedimentation rate.

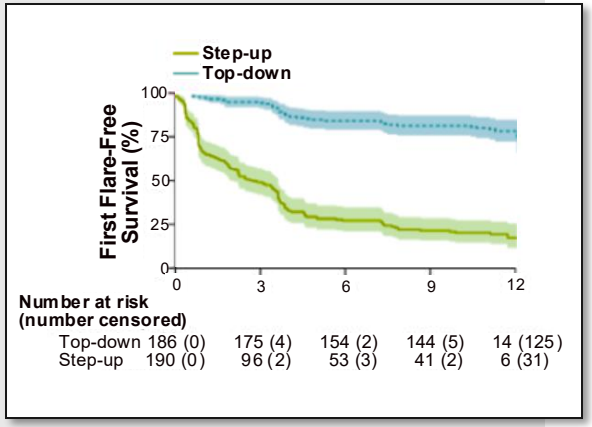
How would you treat this patient?

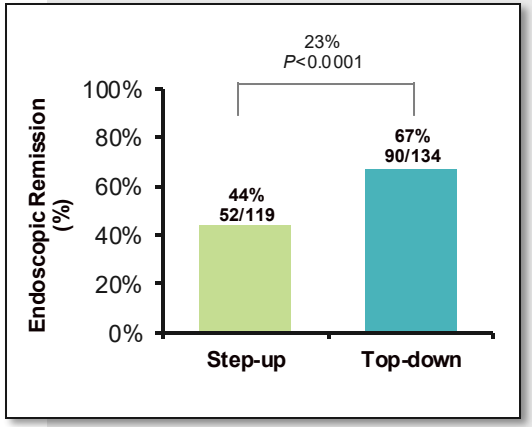
A. Budesonide
B. Mesalamine
C. Vedolizumab
D. Anti-TNF
E. IL-23p19 inhibitor
F. I’m not sure

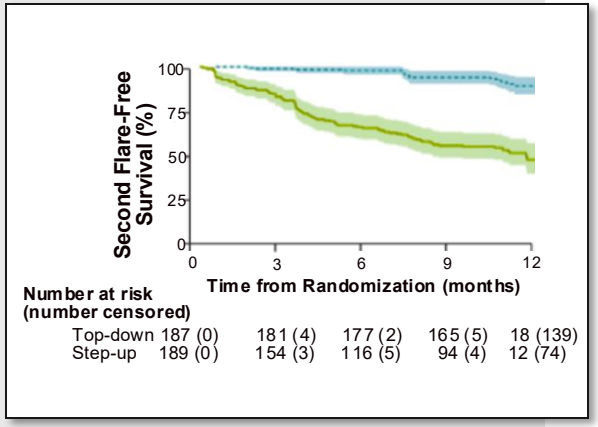
Early Effective Advanced Therapy Predicts CD Outcomes

- Median of 12 days (IQR 0–191) from time of diagnosis to enrollment and start GCC (-2 weeks to randomized)
- Median of 15 days (IQR 13–20) days from time of randomization and first dose of infliximab





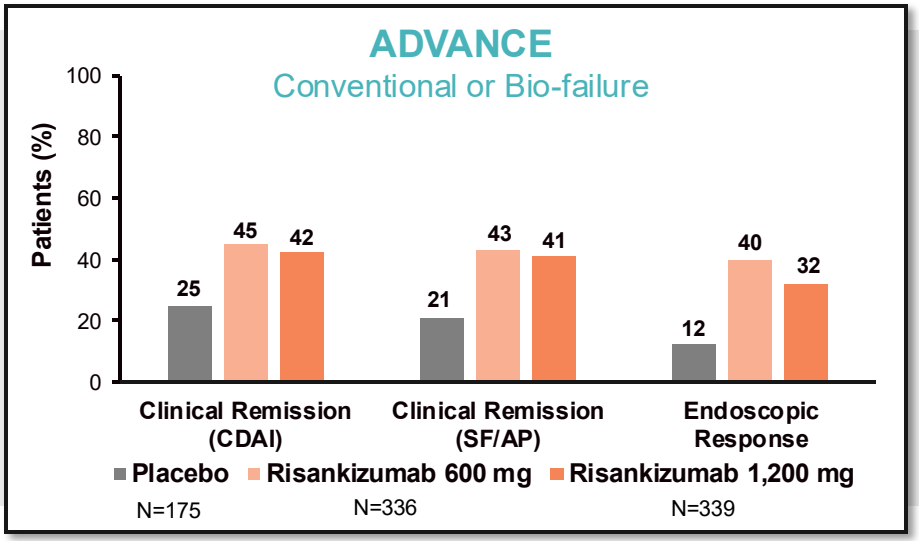


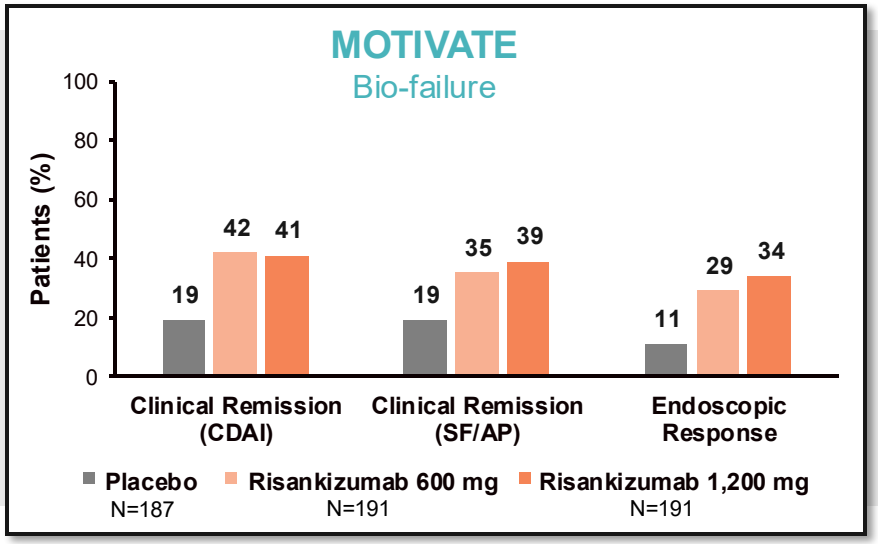


IQR, interquartile range, GCC, glucocorticoids.

ADVANCE and MOTIVATE

RZB Induction in CD



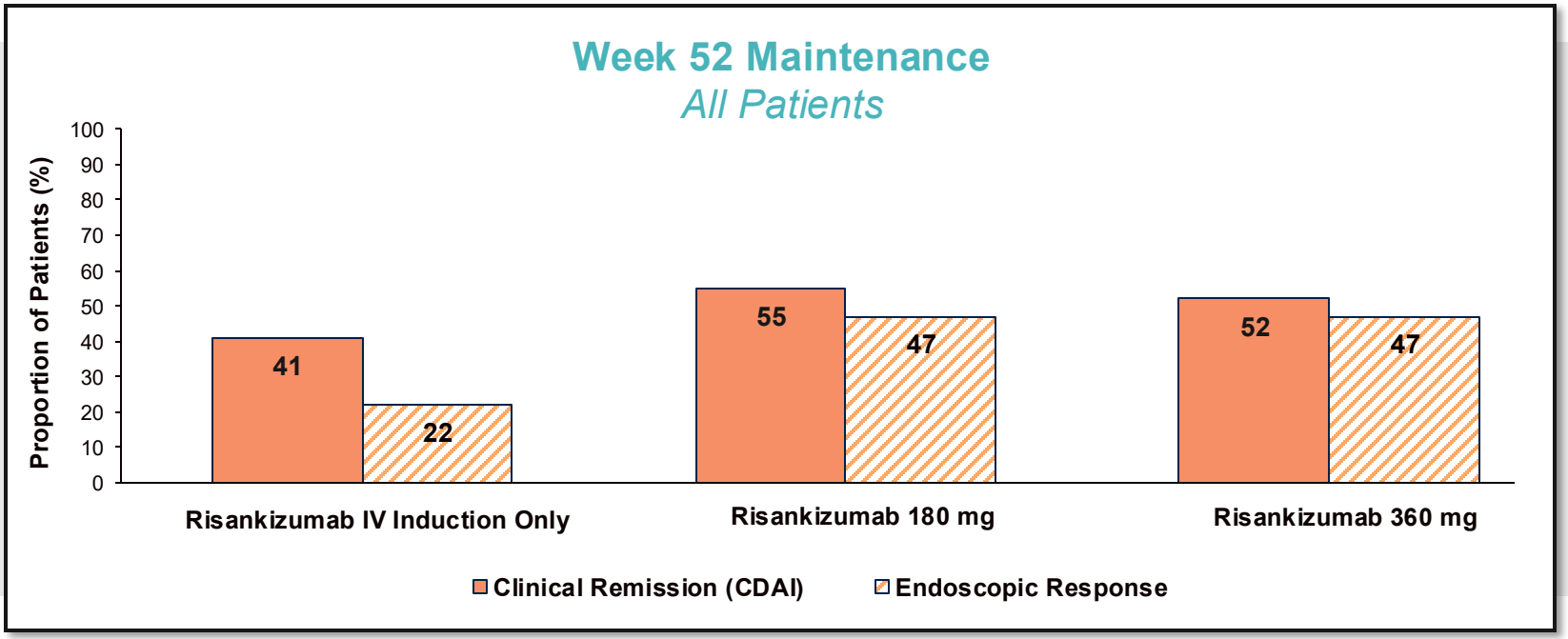


Clinical responders defined as ≥30% decrease in average daily stool frequency or abdominal pain score (APS) and not worse than baseline; endoscopic response defined as >50% decline in simple endoscopic score (SES-CD) vs baseline by central reviewer (or in patients with SES-CD of 4 at baseline, ≥2-point decrease vs baseline); CDAI clinical remission, a CDAI of <150.

CDAI, Crohn's disease activity index; SF/AP, stool frequency/abdominal pain.

D'Haens G, et al. *Lancet.* 2022;399(10340):2015–2030. Ferrante M, et al. *Lancet.* 2022;399(10340):2031–2046.

FORTIFY
RZB Maintenance in CD

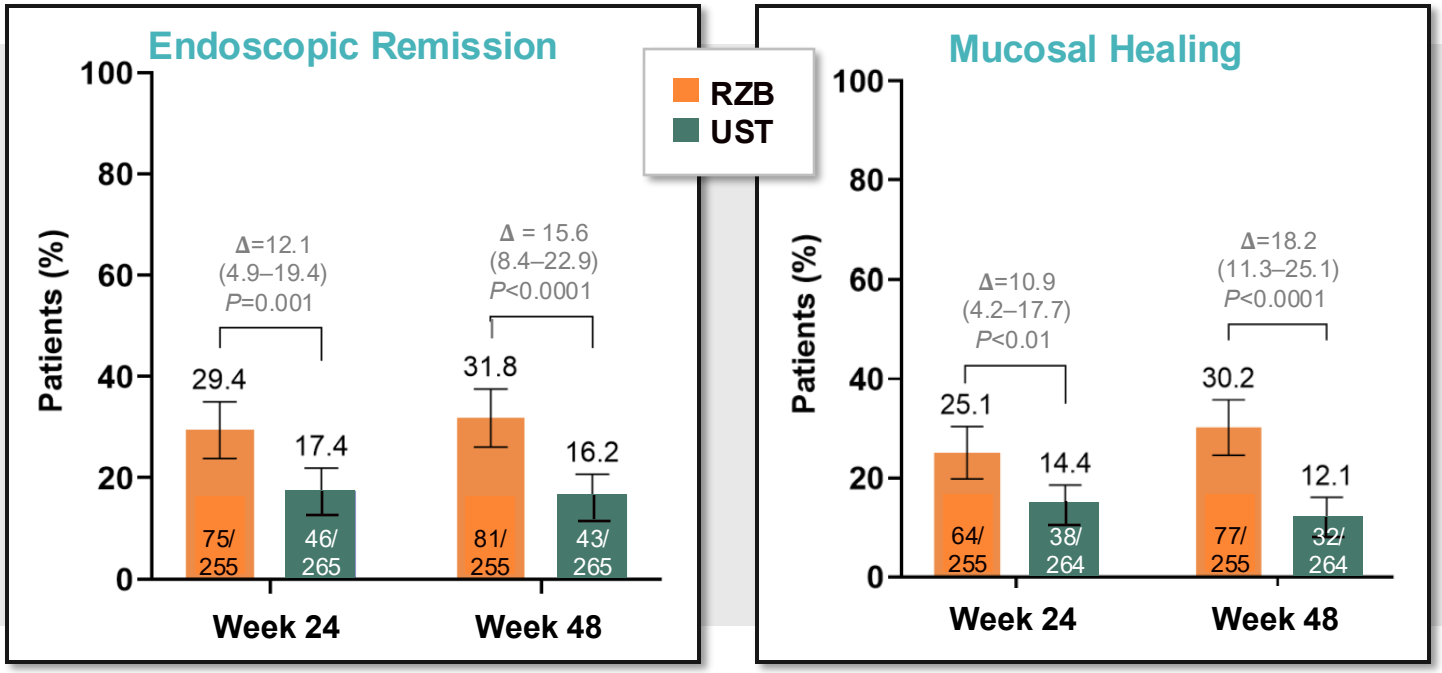


Endoscopic response defined as >50% decline in SES-CD vs baseline by central reviewer (or in patients with SES-CD of 4 at baseline, ≥2-point decrease vs baseline); CDAI clinical remission, a CDAI of <150.

Ferrante M, et al. *Lancet.* 2022;399(10340):2031–2046.

RZB vs UST in Patients with CD

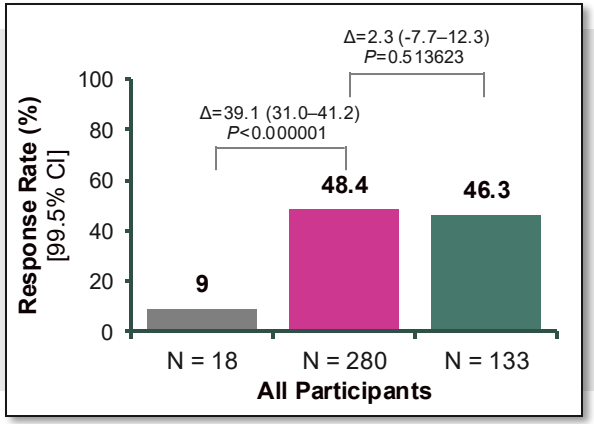
Phase IIIb SEQUENCE Trial



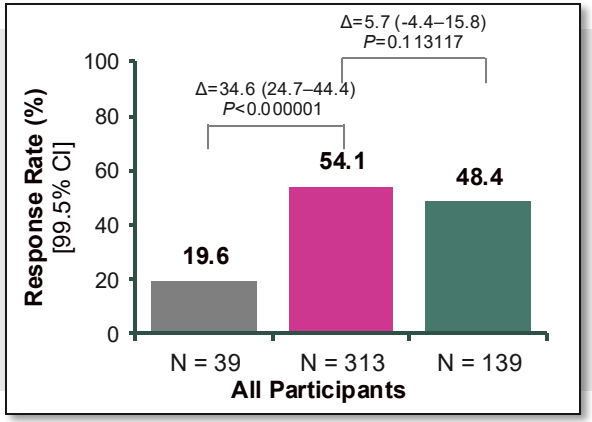
Peyrin-Biroulet L, et al. *N Engl J Med*. 2024;391:213–223.

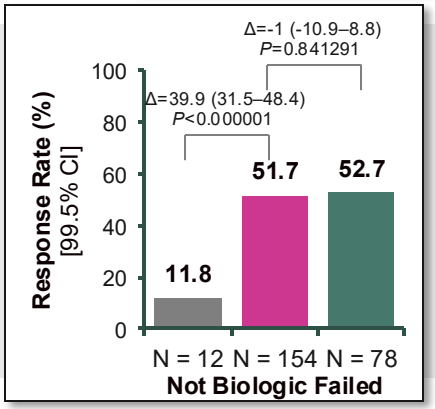
VIVID-1: *MIRI vs UST in Moderate-to-Severe CD*

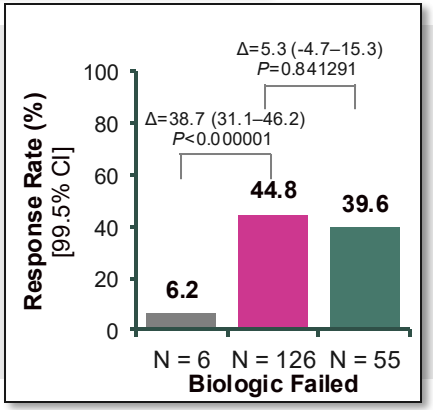
Endoscopic Response (NRI) at Week 52

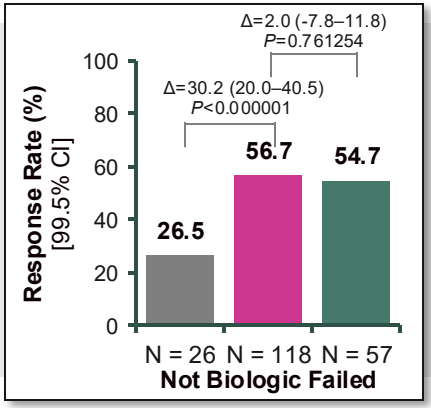


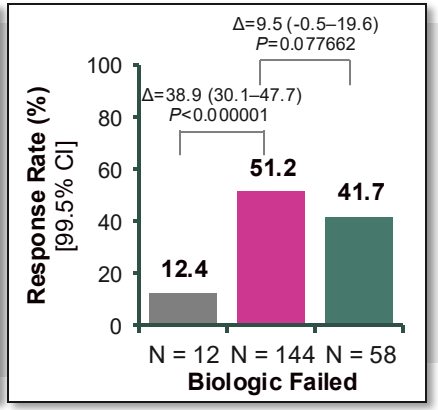
Clinical Remission by CDAI (NRI) at Week 52









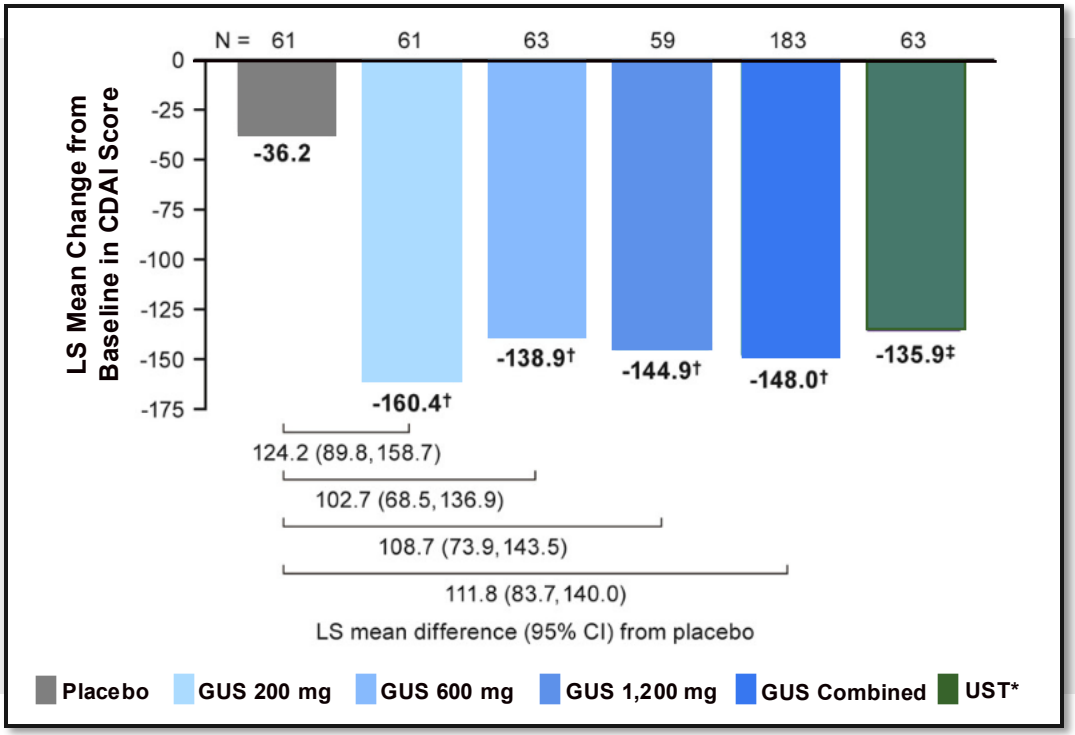


NRI, non-responder imputation.

Ferrante M, et al. *Lancet*. 2024;404(10470):2423–2436.

GUS vs UST in CD at 12 Weeks

GALAXI-1



Primary Endpoint

- Change from baseline in CDAI score at week 12

- GALAXI-1 is a DBPC trial
- Randomized patients 1:1:1:1:1 to
  - 3 different doses of IV GUS given at weeks 0, 4, and 8
  - IV UST at week 8
  - Placebo
- UST was a reference arm
- N=309

*UST 6 mg/kg IV → 90 mg SC; †*P* value <0.05 for GUS vs placebo; ‡Nominal *P* value <0.05 from post hoc analysis of UST vs placebo.

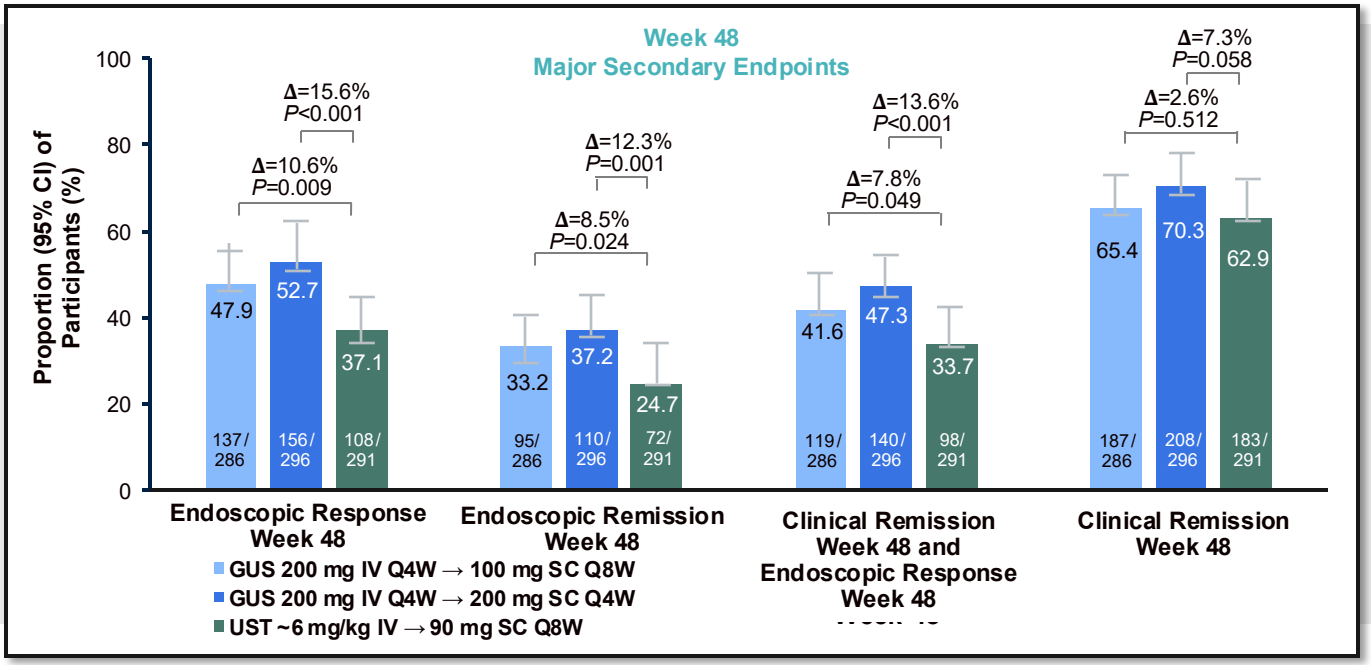
DBPC, double-blind placebo controlled; LS, least squares.

Sandborn W, et al. *Gastroenterology*. 2022;162(6):1650–1664.

GUS vs UST in CD at 48 Weeks

GALAXI 2 and 3

GALAXI 2 and 3 are identical 48-week, randomized, double-blind, double-dummy, placebo, and active-comparator (UST) treat-through trials assessing the efficacy and safety of GUS in patients with moderately to severely active CD



Clinical Response: ≥100-point reduction from baseline in CDAI or CDAI <150

Endoscopic Response: ≥50% improvement from baseline in SES-CD or SES-CD ≤2

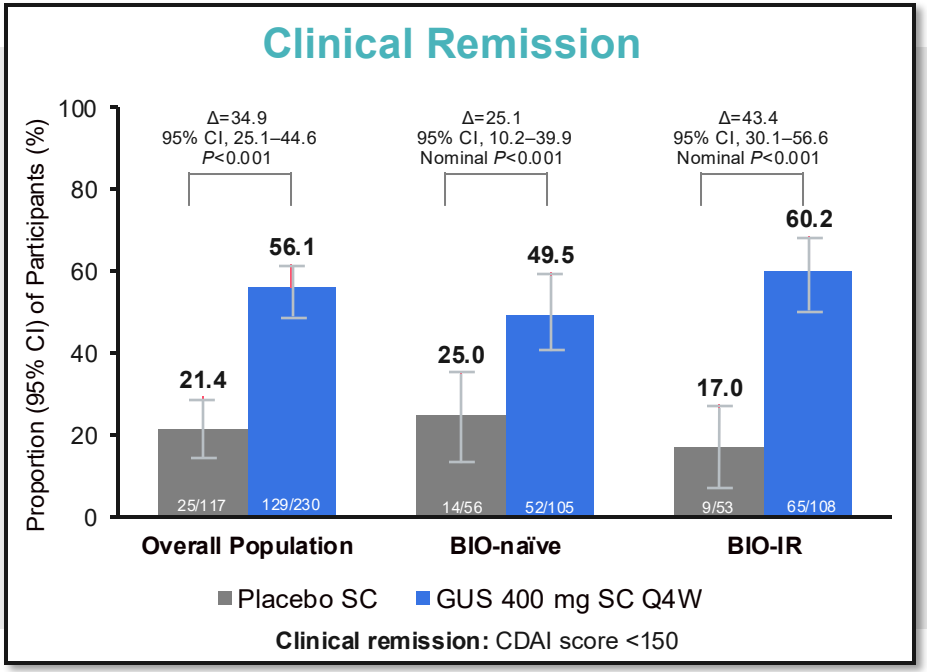
Clinical Remission: CDAI <150

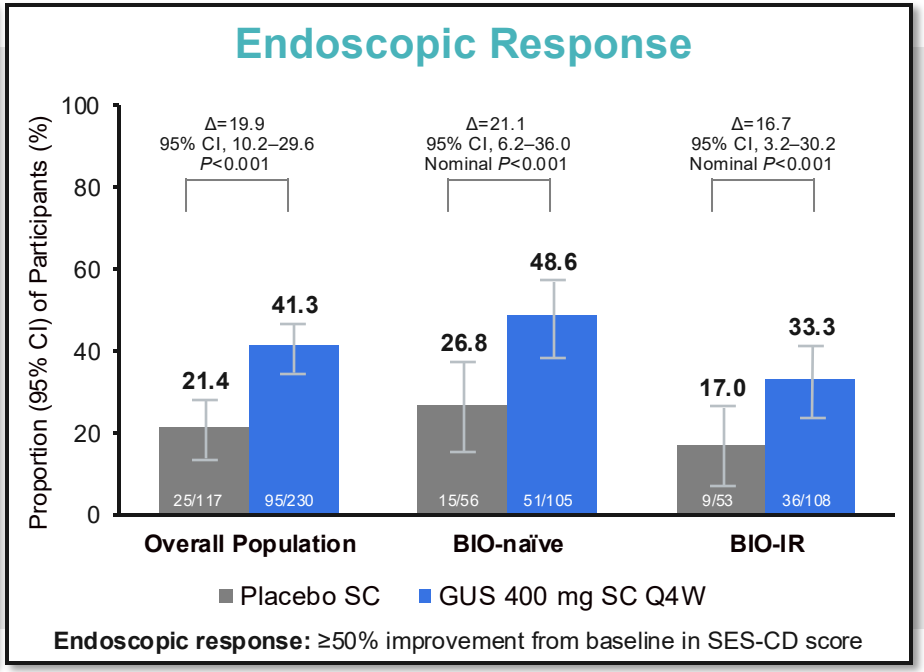
Endoscopic Remission: SES-CD ≤4 and a ≥2-point reduction from baseline and no subscore greater than 1 in any individual component

Panaccione R, et al. American College of Rheumatology (ACR) Convergence 2024. Abstract 1136. https://acrabstracts.org/abstract/efficacy-and-safety-of-guselkumab-therapy-in-patients-with-moderately-to-severely-active-crohns-disease-results-of-the-galaxi-2-3-phase-3-studies/.

Subcutaneous GUS in CD

Phase III GRAVITI Study Responses at Week 12

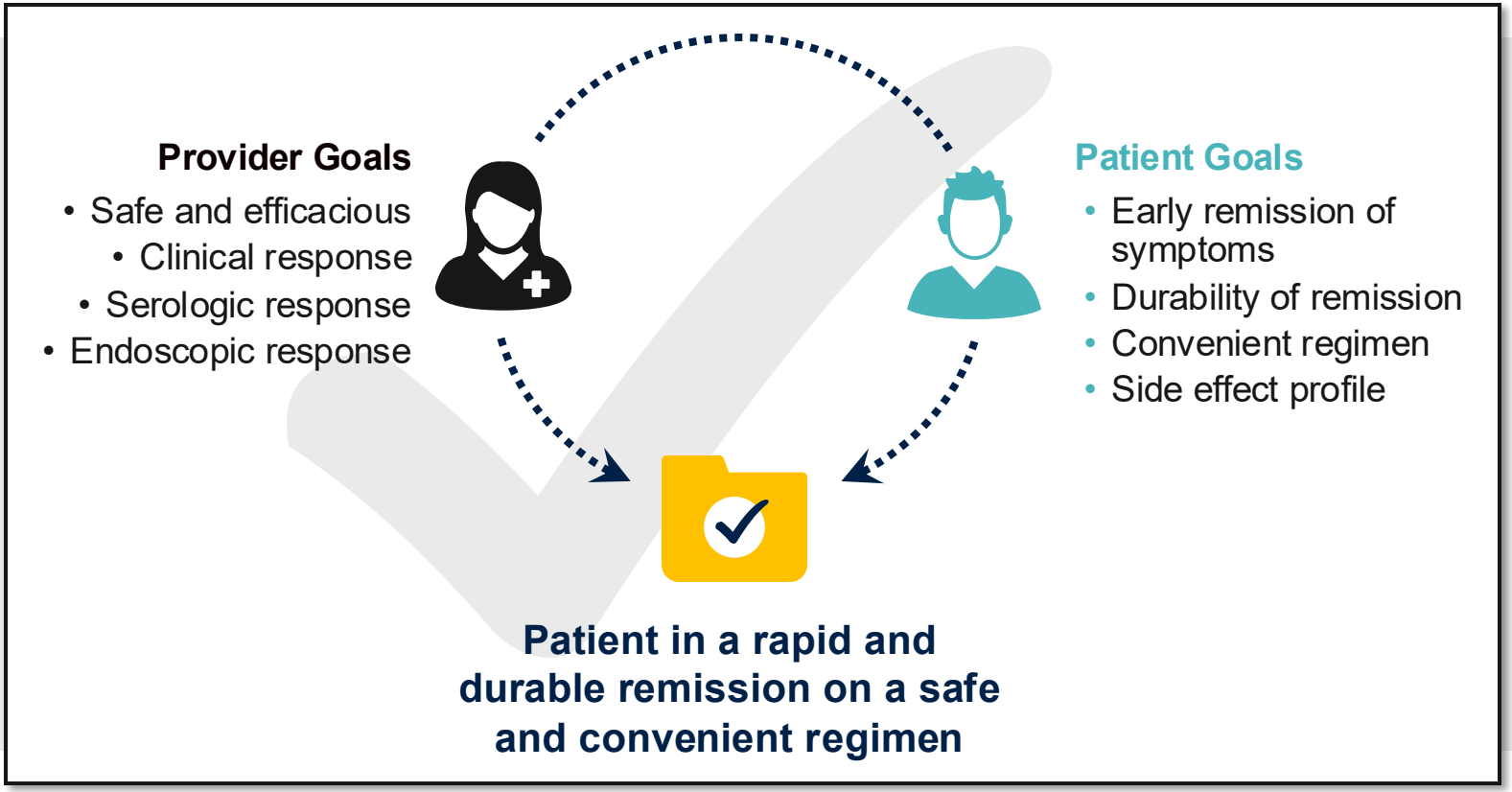




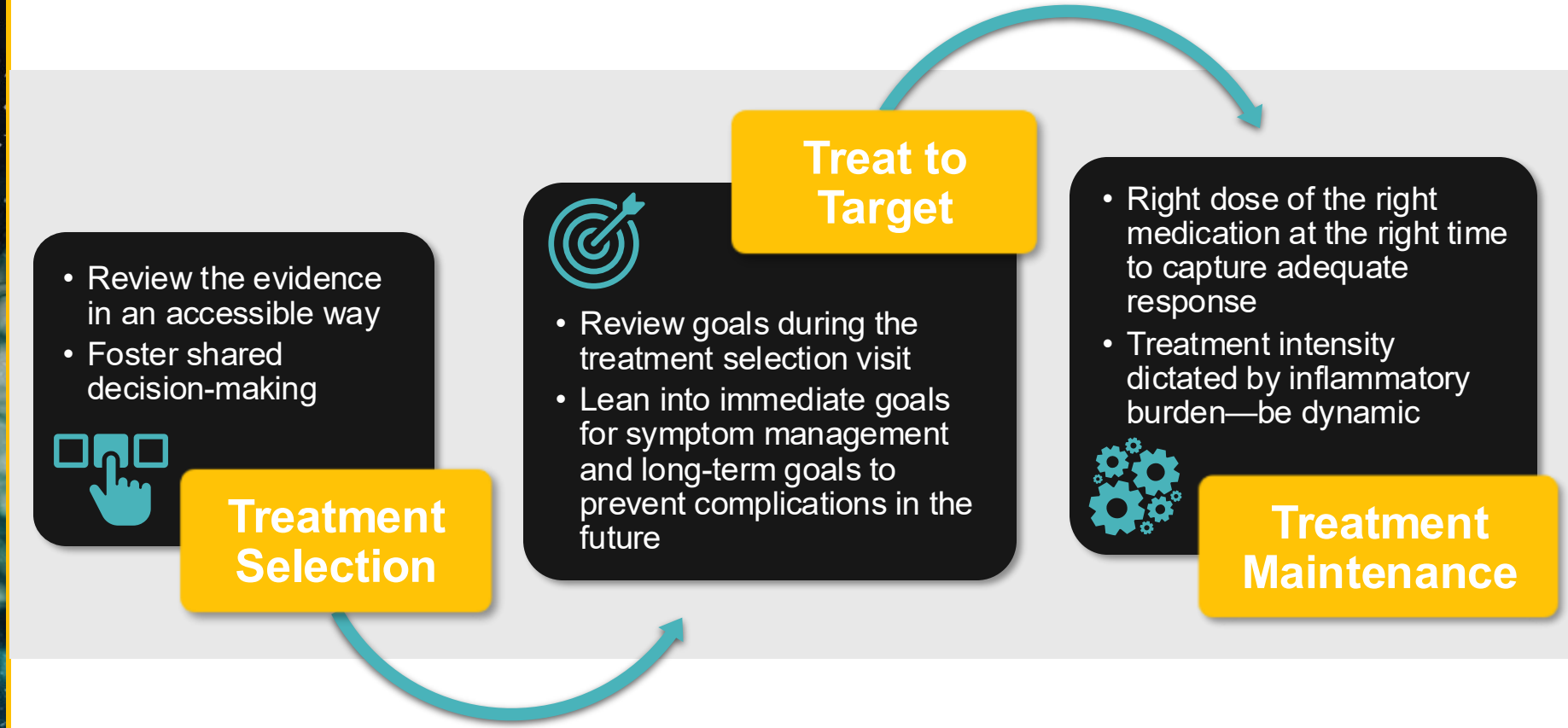
Hart A, et al. *Gastroenterol.* March 18, 2025. Online ahead of print.

CME OUTFITTERS

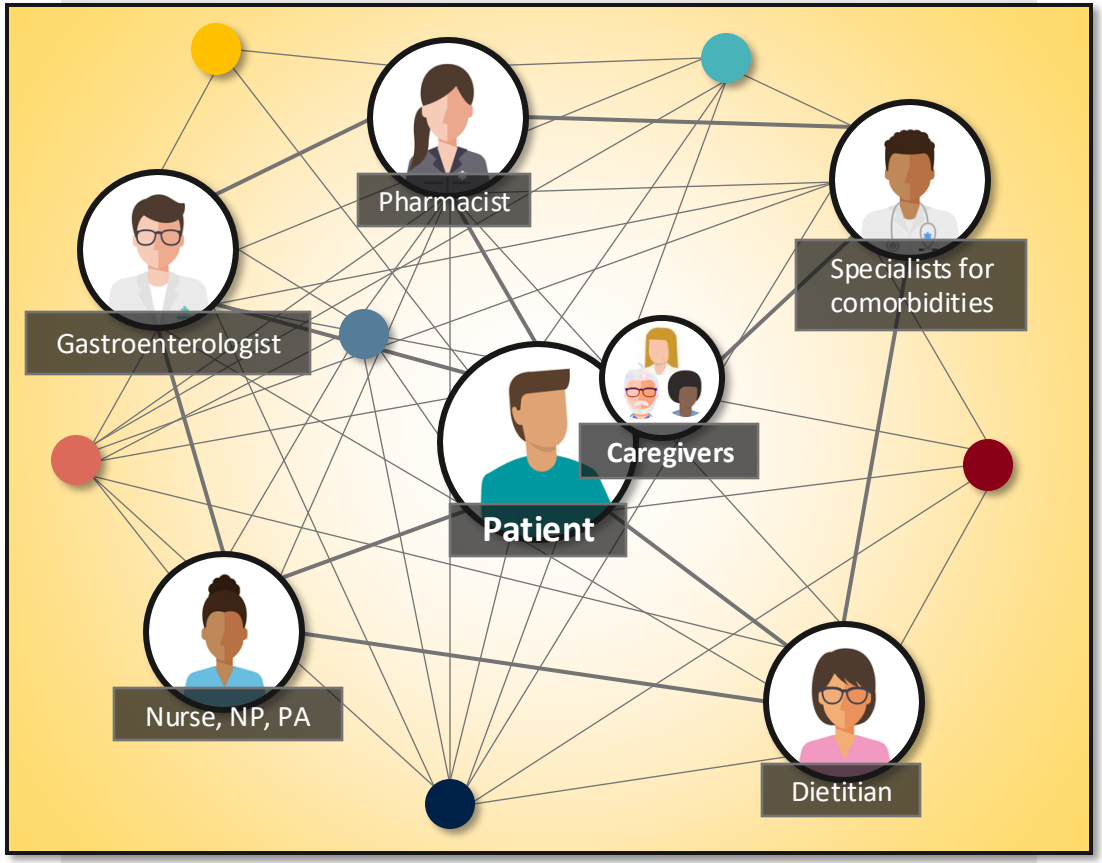
Aligning on Treatment Goals with Patients



Education to Ensure Alignment



Team-based Approach for the Management of IBD



Faculty Discussion

Managing biologic-naïve Crohn's disease

Case 4: Clara J.

Clara J. is a 43-year-old woman with a history of Crohn's disease that has been successfully managed with infliximab for the past 3 years.

In recent months, symptoms of her CD have returned, including weight loss, bloody stools, and cramping, and imaging reveals active disease. Testing reveals a therapeutic infliximab level of 12 ug/mL.

She has a family history of cardiovascular disease and last summer experienced a deep vein thrombosis (DVT) and would like to take this into consideration when selecting her next treatment option.

What treatment would you recommend?

A. Increase dose of infliximab
B. Switch to another TNFi
C. Switch to vedolizumab
D. Start IL-23p19 inhibitor
E. Start a JAK inhibitor
F. I’m not sure

How Do We Put Together the Puzzle of Therapy Selection?

DRUG

Efficacy

Indication
Rapidity of onset
Durability
Pharmacokinetics/TDM
Combination vs monotherapy
Positioning and sequence

Safety

Infection
Cancer
Specific concerns by agent or mechanism

PATIENT

Individual Characteristics

Age
Stages of disease
Comorbidities and other inflammatory conditions
Preferences
Access to treatment

Disease Characteristics

CD vs UC
Disease behavior/complication
Disease severity
Early vs late
EIMs
Treatment history

TDM, therapeutic drug monitoring; EIM, extraintestinal manifestation.

Safety of IL-23p19 Inhibitors in CD

Adverse Event	Risankizumab N=373	Mirikizumab N=630	Guselkumab N=595
AEs	210 (56%)	495 (78.6%)	458 (77.0%)
Serious AEs	27 (7%)	65 (11.5%)	53 (8.9%)
Discontinuation due to AE	9 (2%)	32 (5.1)	40 (6.7%)
Serious infections	0	14 (2.2%)	4 (0.6%)

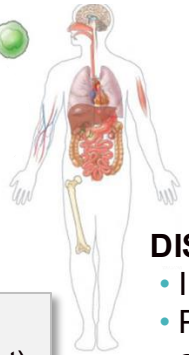
D'Haens G, et al. *Lancet.* 2022;399(10340):2015–2030. Ferrante M, et al. *Lancet.* 2024;404(10470):2423–2436.
Panaccione R, et al. Digestive Disease Week (DDW). May 18–21, 2024. Abstract 1057b. https://acrabstracts.org/abstract/efficacy-and-safety-of-guselkumab-therapy-in-patients-with-moderately-to-severely-active-crohns-disease-results-of-the-galaxi-2-3-phase-3-studies/.

Cardiovascular Safety of IL-23 Inhibitors

Risk of Major Adverse Cardiovascular Events (MACE) in Immune-mediated Inflammatory Disorders on Biologics and Small Molecules: Network Meta-analysis

Study Population

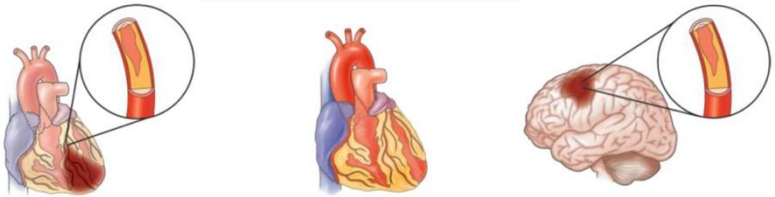
DRUGS
- Anti–IL-23
- Anti–IL12/23
- Anti–TNF-α
- JAKi



- 40 studies (36 RCT, 4 cohort)
- 126,961 patients

DISEASE STATES
- IBD
- Psoriasis/psoriatic arthritis
- Rheumatoid arthritis
- Ankylosing spondylitis

Key Findings



INCREASED RISK OF MACE
- Anti–IL-12/23: or 3.15 (crl:1.01–13.35)
- Anti–TNF-α: or 2.49 (crl: 1.14–5.62)
- JAKi: OR 2.64 (crl: 1.26–5.99)

NO INCREASED RISK OF MACE
- Anti–IL-23: or 2.65 (crl:0.85–10.03)

No difference in magnitude of MACE risk between drug classes or disease state

Mattay SS, et al. *Clin Gastroenterol Hepatol.* 2024;22(5):962–970.

ORAL Surveillance

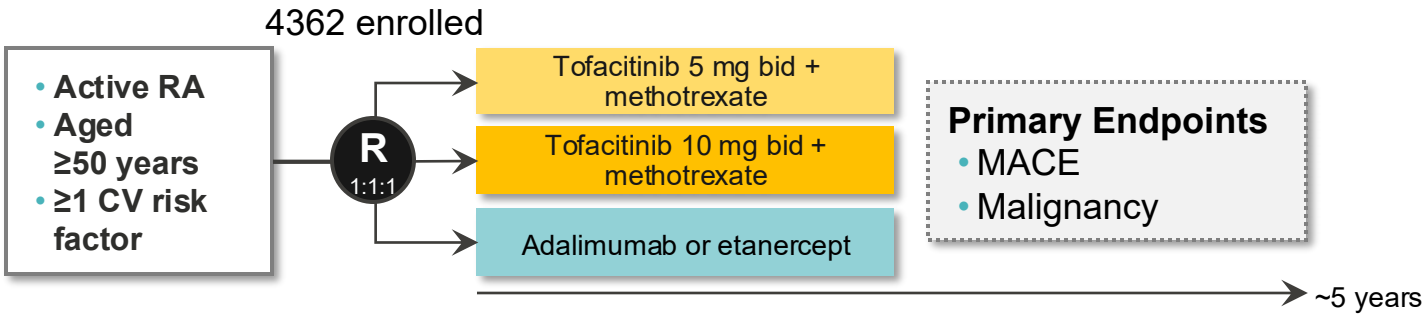
Tofacitinib Safety (MACE and Malignancy) in Patients with RA Aged ≥50 Years and ≥1 Additional CV Risk Factor

Following FDA approval of tofacitinib in 2012, the manufacturer was mandated to conduct a post-marketing trial due to concerns of a potential increased risk of cancer, CV events, and serious infections.

Dose-dependent safety signals for a number of AESIs led to the approval of tofacitinib 5 mg bid **only** for use in RA

ORAL SURVEILLANCE

Prospective, phase 3b-4, randomized, head-to-head, event-driven noninferiority trial



~4,000 patients or at least 1,500 patients completing 3 years of follow-up were required to achieve prespecified number of events: 103 MACEs (including cardiovascular death, nonfatal MI, and nonfatal stroke) and 138 malignancies (excluding NMSCs)

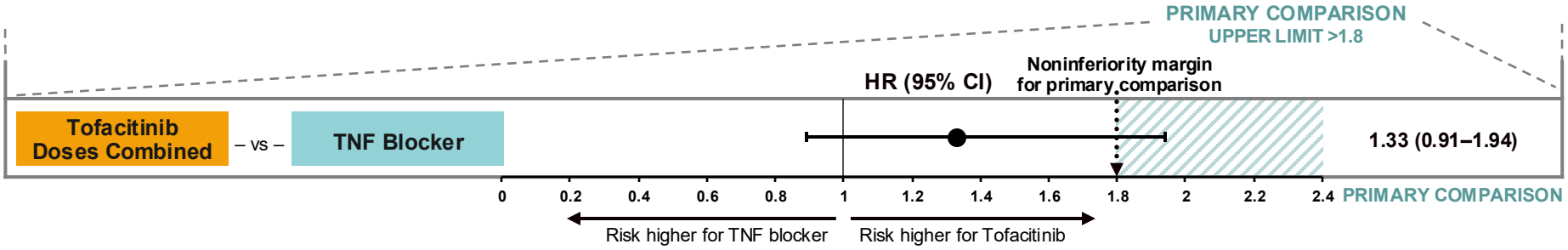
AESI, adverse event of special interest; CV, cardiovascular; MACE, major adverse cardiac event; NMSC, non-melanoma skin cancer; RA, rheumatoid arthritis.

Ytterberg SR, et al. *N Engl J Med*. 2022;386(4):316–326.

ORAL Surveillance
Adjudicated MACE

- On methotrexate (MTX) without adequate symptom control and ≥50 years old and ≥1 CV risk factor:
  - Current cigarette smoker, hypertension, diabetes mellitus, high-density lipoprotein <40 mg/dL
  - H/O coronary artery disease, H/O premature CVD or sudden death in first-degree relative
  - Extra-articular disease associated with RA

	Tofacitinib 5 mg BID (N=1,455)	Tofacitinib 10 mg BID (N=1,456)	Tofacitinib Doses Combined (N=2,911)	TNF Blocker (N=1,451)
Patient with 1st event within risk period, n (%)	47 (3.23)	51 (3.50)	98 (3.37)	37 (2.55)
Total exposure (PY)	5,166.32	4,871.96	10,038.28	5,045.27
IR (95% CI)	0.91 (0.67–1.21)	1.05 (0.78–1.38)	0.98 (0.79–1.19)	0.73 (0.52–1.01)
HR (95% CI) for Tofa vs TNF blocker	1.24 (0.81–1.91)	1.43 (0.94–2.18)	**1.33 (0.91–1.94)**	—

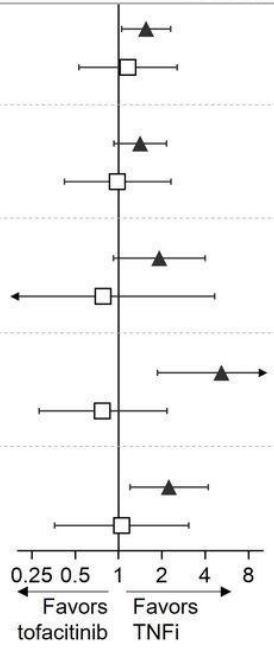


ORAL Surveillance Stratified by High Risk vs Low Risk

Impact of Age and Smoking

▲ **Age ≥65 years or Ever smoked (High-risk)**
Tofacitinib (N=1895) vs TNFi (N=926)

□ **Age <65 years and Never smoked (Low-risk)**
Tofacitinib (N=1016) vs TNFi (N=525)



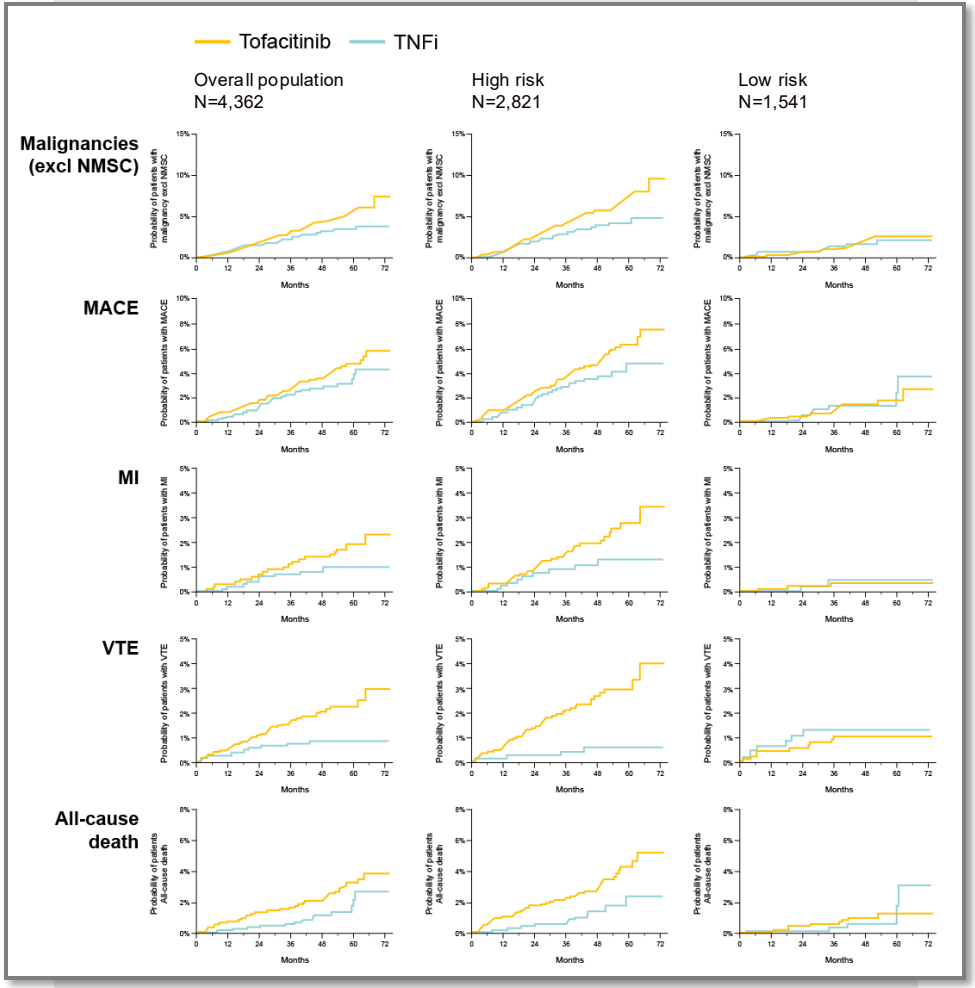
	HR vs TNFi (95% CI)	n (%)	IR (95% CI)	PY	IR difference vs TNFi (95% CI)	Interaction p-value	NNH (PY) vs TNFi
Malignancies (excl NMSC)	1.55 (1.05, 2.30)	102 (5.4%)	1.48 (1.21, 1.80)	6886.2	0.53 (0.09, 0.96)	0.114	190
	1.16 (0.53, 2.55)	20 (2.0%)	0.51 (0.31, 0.79)	3917.0	0.07 (-0.30, 0.43)		1485
MACE	1.41 (0.93, 2.15)	83 (4.4%)	1.31 (1.04, 1.62)	6340.8	0.38 (-0.06, 0.82)	0.173	262
	0.98 (0.42, 2.31)	15 (1.5%)	0.41 (0.23, 0.67)	3697.5	-0.01 (-0.37, 0.34)		-8892
Myocardial infarction	1.92 (0.92, 4.00)	35 (1.8%)	0.55 (0.38, 0.76)	6369.8	0.26 (0.00, 0.52)	0.071	379
	0.78 (0.13, 4.65)	3 (0.3%)	0.08 (0.02, 0.24)	3712.0	-0.02 (-0.19, 0.15)		-4369
VTE	5.19 (1.86, 14.46)	42 (2.2%)	0.67 (0.48, 0.90)	6307.4	0.54 (0.30, 0.78)	0.002	186
	0.77 (0.28, 2.17)	9 (0.9%)	0.25 (0.11, 0.47)	3666.7	-0.07 (-0.37, 0.23)		-1421
All-cause death	2.24 (1.20, 4.19)	55 (2.9%)	0.86 (0.65, 1.12)	6364.3	0.48 (0.17, 0.80)	0.030	208
	1.05 (0.36, 3.07)	10 (1.0%)	0.27 (0.13, 0.50)	3682.4	0.01 (-0.27, 0.29)		9898

Kristensen LE, et al. *Ann Rheum Dis.* 2023;82(7):901–910.

ORAL Surveillance Stratified by High Risk vs Low Risk

Impact of Age and Smoking on Mortality

Age ≥65 years and smoking play a major role in risk of cardiovascular side effects of tofacitinib vs TNF inhibitors



Kristensen LE, et al. *Ann Rheum Dis*. 2023;82(7):901–910.

Faculty Discussion

Managing biologic-experienced Crohn's disease

Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- Appreciate the role of the IL-23/Th17 axis in driving the inflammatory pathogenesis of IBD
- Differentiate between IL-23 targeted therapies based on their unique characteristics to individualize and optimize patient treatment
- Consider early use of IL-23 therapies in appropriate patients based on the latest evidence and recommendations
- Collaborate with your patients to identify the best treatment option for their goals

QUESTIONS & ANSWERS

Thank you for joining us.
Don’t forget to collect your credit.

CME OUTFITTERS

Visit the Gastroenterology Hub

Free resources and education to educate health care professionals and patients

https://www.cmeoutfitters.com/gastrohub/

Claim Credit

Scan the appropriate QR code for your mode of participation in this activity and create or log in to a CME Outfitters learner account. Complete the necessary requirements (e.g., pre-test, post-test, evaluation) and then claim your credit.*

Thank you for your participation!

*To receive credit, participants must register an account and apply for credit within 10 days of the live activity. For questions or technical difficulties, please contact info@cmeoutfitters.com.

In-Person

Livestream

Claim ABIM MOC Credit

3 Steps to Complete

1. Actively participate in the discussion today by **responding to questions** and/or **asking the faculty questions**
   (MOC credit can be claimed even if a question goes unanswered or an incorrect response is entered)
2. Complete the post-test and evaluation at the conclusion of the webcast
3. Enter your **ABIM ID number** and **DOB** (MM/DD) on the evaluation, so credit can be submitted to ABIM

ABIM CME MOC ACCREDITED

CME for MIPS Improvement Activity

How to Claim This Activity as a CME for MIPS Improvement Activity

- Actively participate today by responding to ARS questions and/or asking the faculty questions
- Complete the post-test and activity evaluation at the link provided
- Over the next 3 months, actively work to incorporate improvements from this presentation into your clinical practice
- In approximately 3 months, complete the follow-up survey from CME Outfitters

CME for MIPS IMPROVEMENT ACTIVITY

CMEO will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity.

CME OUTFITTERS

THE FORCE AWAKENS

Unlocking the Potential of IL-23–Targeted Therapies in the Treatment of IBD

Supported by an educational grant from Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC, both are Johnson and Johnson companies..