

Visualizing the Future

Advances in IL-23-Targeted Therapies in the Treatment of IBD

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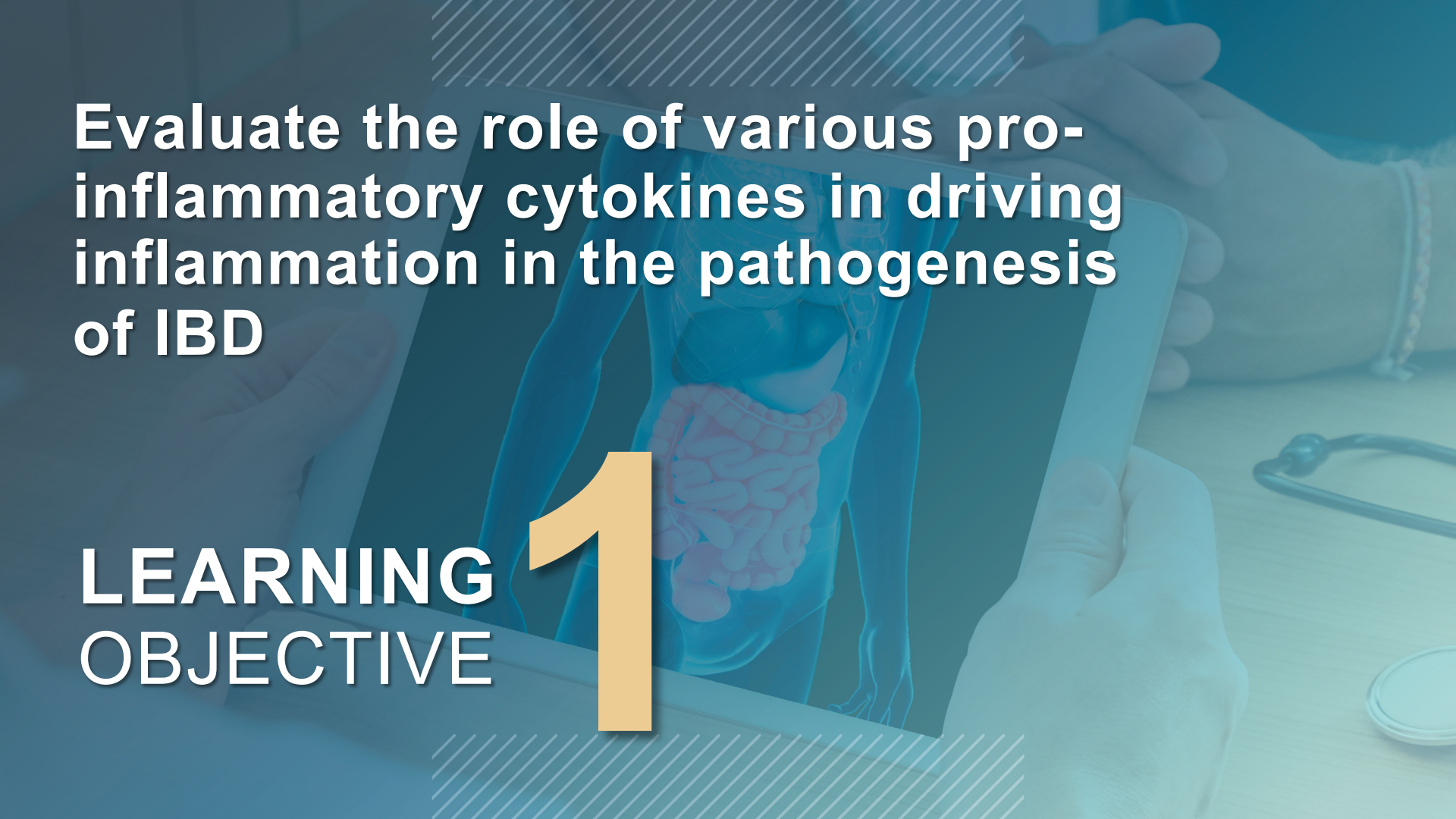
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Evaluate the role of various pro-inflammatory cytokines in driving inflammation in the pathogenesis of IBD

**LEARNING
OBJECTIVE**

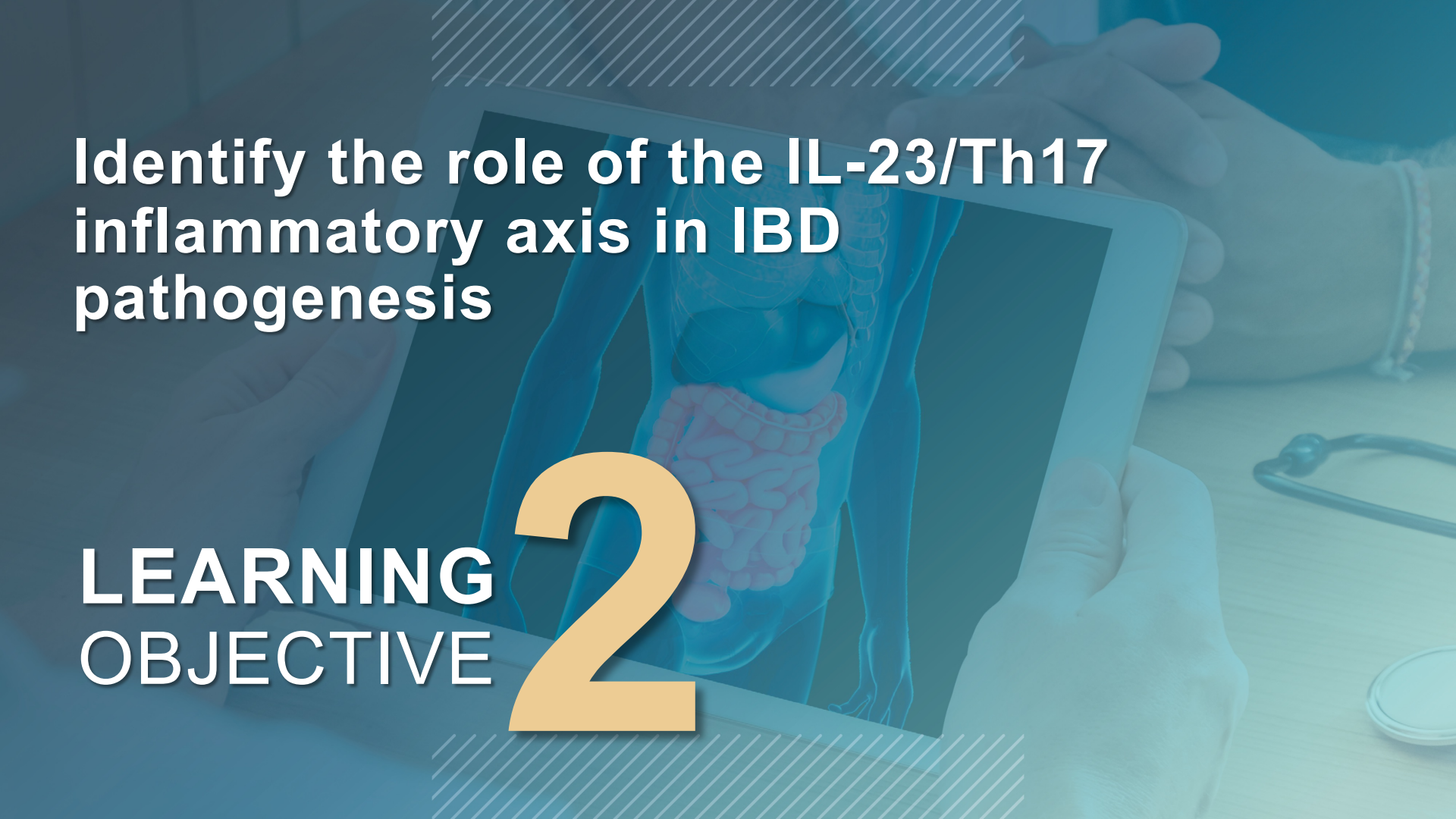
1



Identify the role of the IL-23/Th17
inflammatory axis in IBD
pathogenesis

LEARNING
OBJECTIVE

2



Assess the potential clinical implications of the ability of anti-IL-23 agents used in the treatment of IBD to bind to CD64 receptors on IL-23-producing cells

**LEARNING
OBJECTIVE**

3

Audience Response - Icebreaker

What is the most difficult aspect of patient care for IBD? (pick your top 3)

- A. Knowledge of drugs
- B. Prior authorizations
- C. Drug positioning
- D. Loss of response
- E. Lack of time with patients
- F. Staffing challenges

What is the most difficult aspect of patient care for IBD?

Faculty Icebreaker



Section 1

Overview of the IL-23/Th17 Pathway in the Pathogenesis of IBD

Jessica R. Allegretti, MD, MPH, FACG, AGAF

IBD Pathogenesis

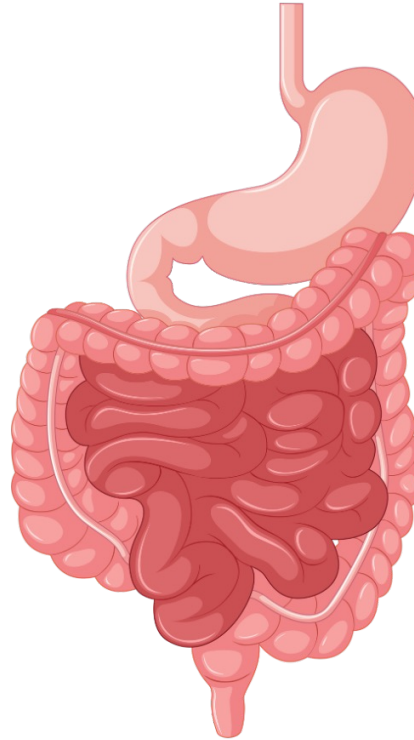


Genetics

- IGRM
- NOD₂
- IL23R
- ATG16L1
- LRRK2
- IBD5
- others

Environment

- Diet
- Lifestyle
- Smoking
- Stress
- Drugs
- Antibiotics
- Infection
- Latitude
- Others



Immunology

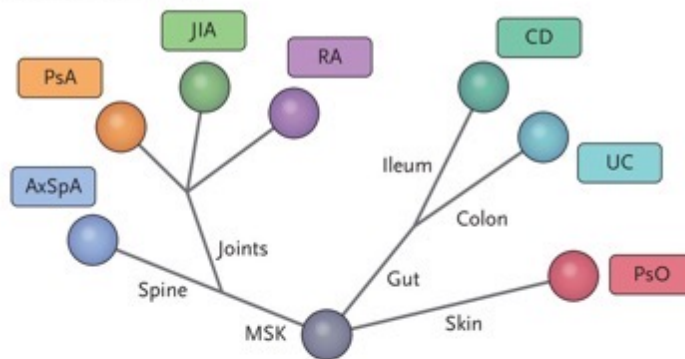
- Immune dysregulation
- Impaired epithelial barrier function
- Defective autophagy
- Skewed lymphocyte populations
- Altered cytokine production

Gut Microbiome

- ↑ Enterobacteriaceae
- ↑ Pasteurellaceae
- ↑ Veillonellaceae
- ↑ Fusobacteriaceae
- ↓ Erysipelotrichales
- ↓ Bacteroidetes
- ↓ Clostridioides

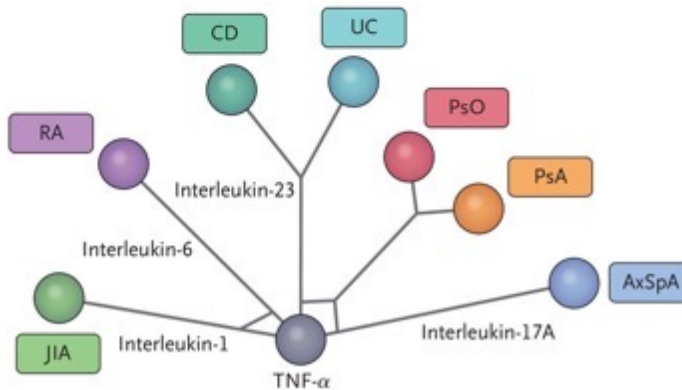
Cytokine Connections in Immune-Mediated Inflammatory Diseases

Organ-Based Concept



	Joints	Spine	Ileum	Colon	Skin
RA	Dark Brown	Light Brown	White	White	White
PsA	Dark Brown	Light Brown	Light Brown	Light Brown	Light Brown
JIA	Dark Brown	Light Brown	White	White	White
AxSpA	Light Brown	Dark Brown	Light Brown	Light Brown	Light Brown
CD	Light Brown	Light Brown	Dark Brown	Light Brown	Light Brown
UC	Light Brown	Light Brown	White	Dark Brown	Light Brown
PsO	Light Brown	Light Brown	Light Brown	Light Brown	Dark Brown

Signature Cytokine-Based Concept



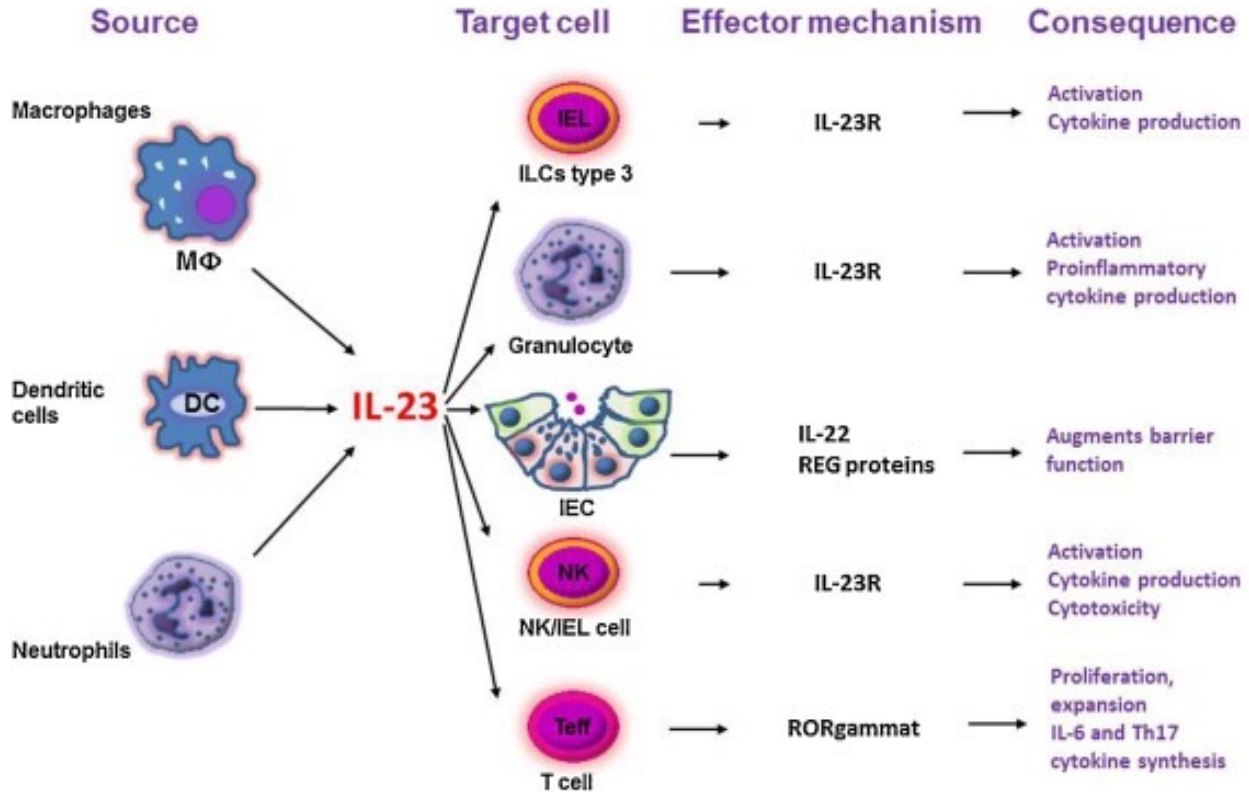
	TNF- α	Interleukin-6	Interleukin-23	Interleukin-17A	Interleukin-1
RA	Dark Brown	Dark Brown	White	White	White
PsA	Dark Brown	White	Light Brown	Light Brown	White
JIA	Dark Brown	Dark Brown	White	White	Dark Brown
AxSpA	Dark Brown	White	White	Light Brown	White
CD	Dark Brown	White	Dark Brown	White	White
UC	Dark Brown	White	Dark Brown	White	White
PsO	Dark Brown	White	Dark Brown	Dark Brown	White

Why Target IL-23 in IBD?

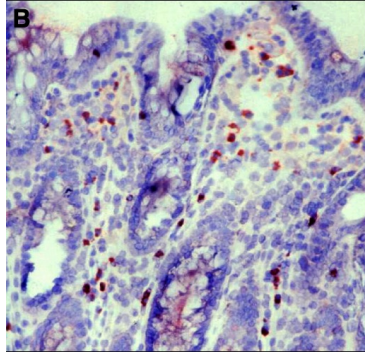
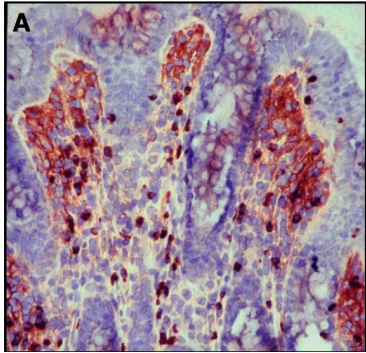
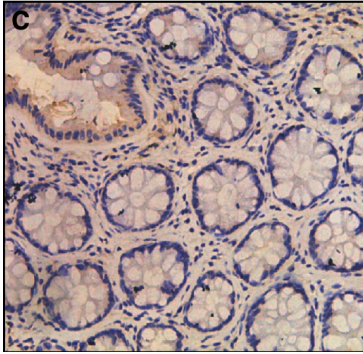


- ▶ Inhibition of IL-23 decreases mucosal inflammation and improves epithelial barrier integrity
- ▶ Inhibiting IL-23 suppresses gut inflammation in T-cell-mediated colitis
- ▶ Anti-IL-23 therapy preserves protective IL-17 gut functions
 - ▶ Animal models of IL-17 blockade in colitis had mixed results
 - ▶ Trials of anti-IL-17A/IL-17A receptor antagonists in IBD resulted in worse outcomes vs placebo

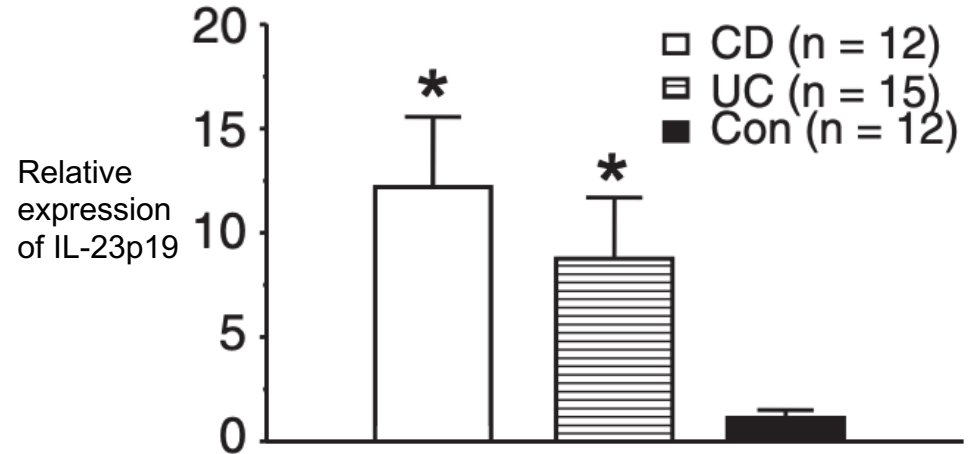
Sources of IL-23 in IBD



IL-23p19 is Highly Expressed in Inflamed Mucosa of IBD



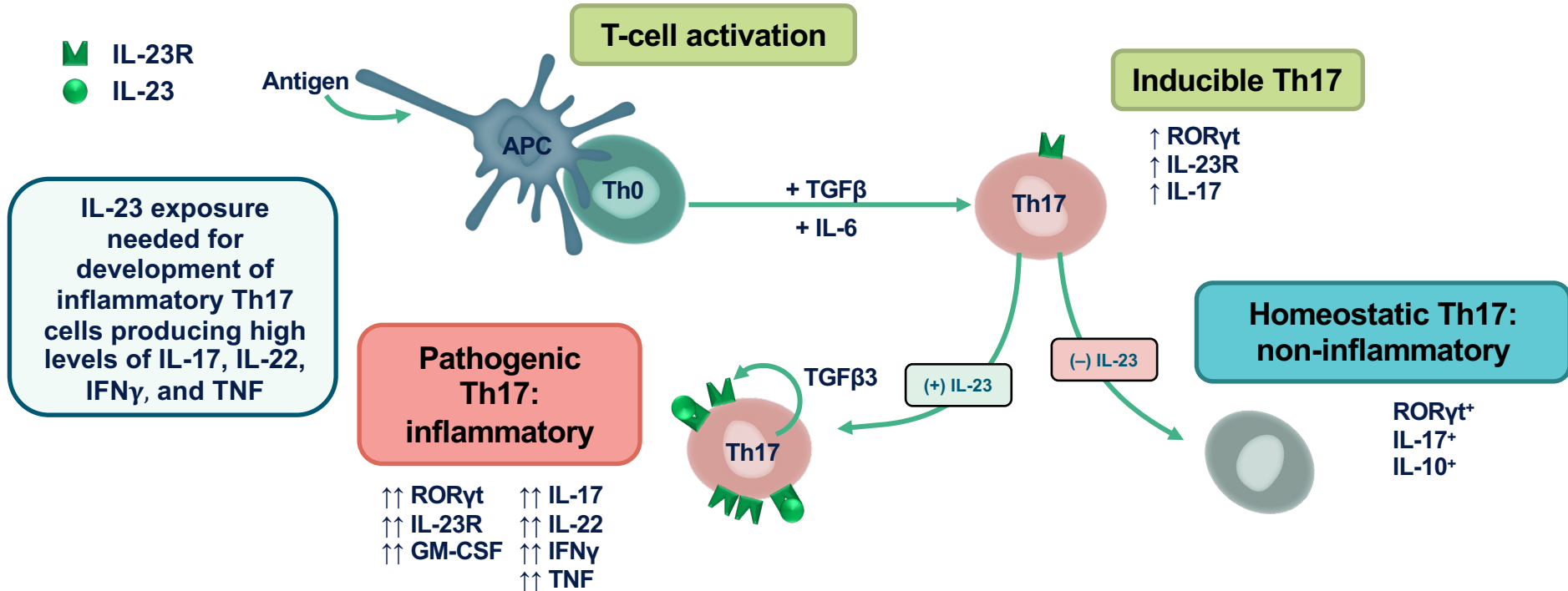
mRNA levels of IL-23p19 in intestinal mucosa



*P < 0.05 versus control; Con = control

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

IL-23 Drives Development of Inflammatory Pathogenic Th17 Cells



APC = antigen-presenting cell; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; RORγt = retinoic acid receptor-related orphan receptor γt; TGF = transforming growth 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.

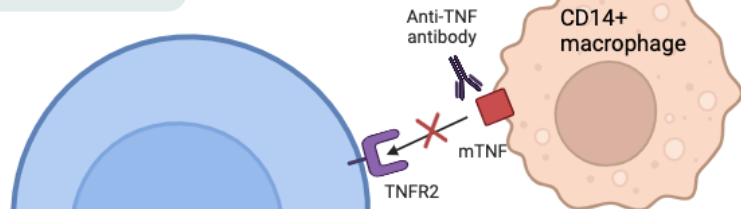
Audience Response

Which of the following is a potential cause of anti-TNF non-response in patients with IBD?

- A. Drug interactions between anti-TNF agents and immunomodulators
- B. Heightened production of IL-23 and development of apoptosis resistant T-cells
- C. Down regulation of TNF- α receptors on monocytes
- D. I don't know

IL-23 Mediated Resistance to Anti-TNF

Anti-TNF responder

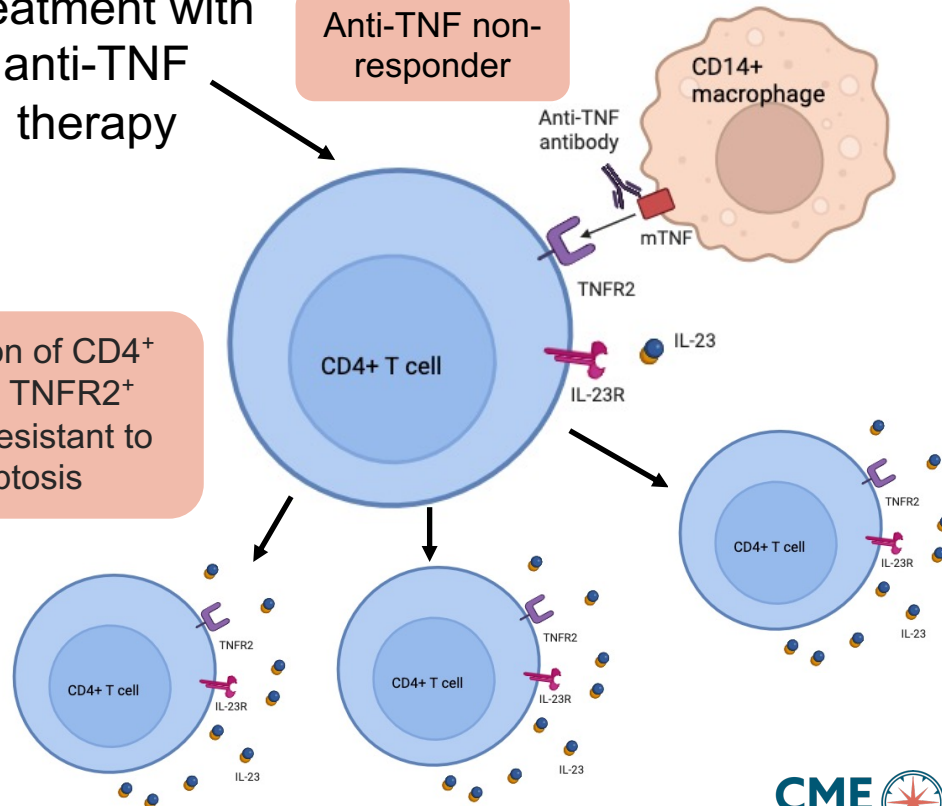


Induction of Apoptosis and Resolution of Inflammation

Treatment with anti-TNF therapy

Anti-TNF non-responder

Expansion of CD4⁺ IL-23R⁺ TNFR2⁺ T-cells resistant to apoptosis



Audience Response



Which of the following is a potential cause of anti-TNF non-response in patients with IBD?

- A.** Drug interactions between anti-TNF agents and immunomodulators
- B.** Heightened production of IL-23 and development of apoptosis resistant T-cells
- C.** Down regulation of TNF- α receptors on monocytes

Final Thoughts: Cytokines and Pathogenesis



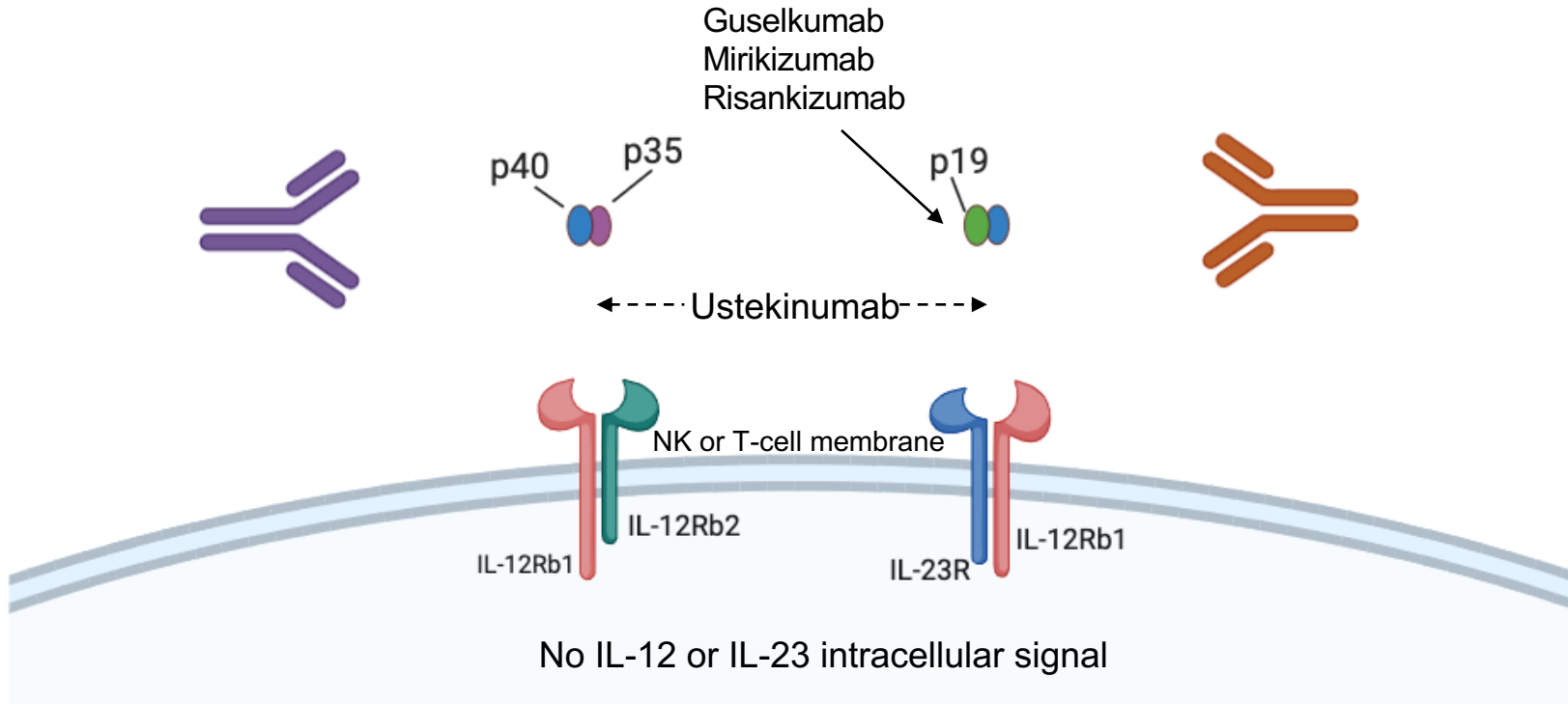
Faculty Discussion

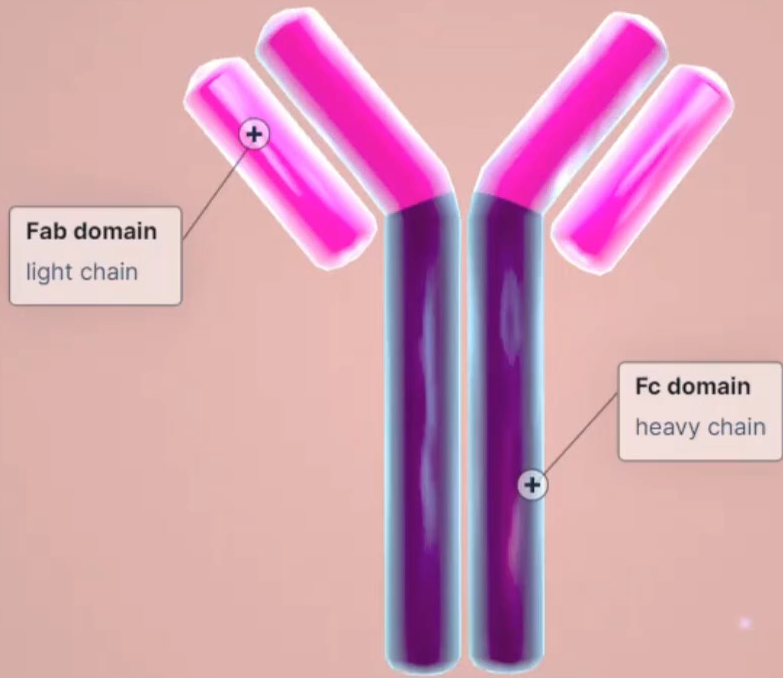
Section 2

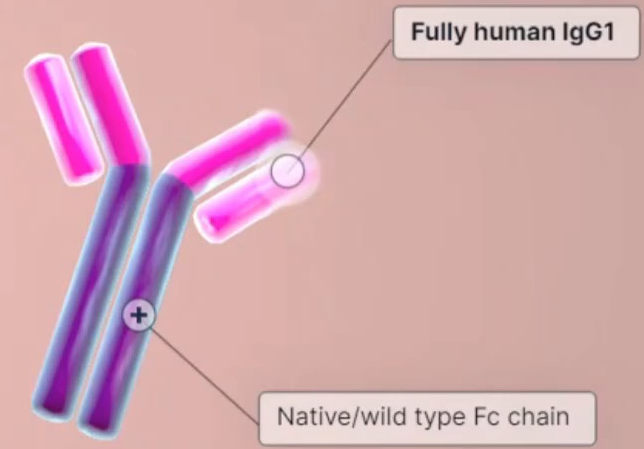
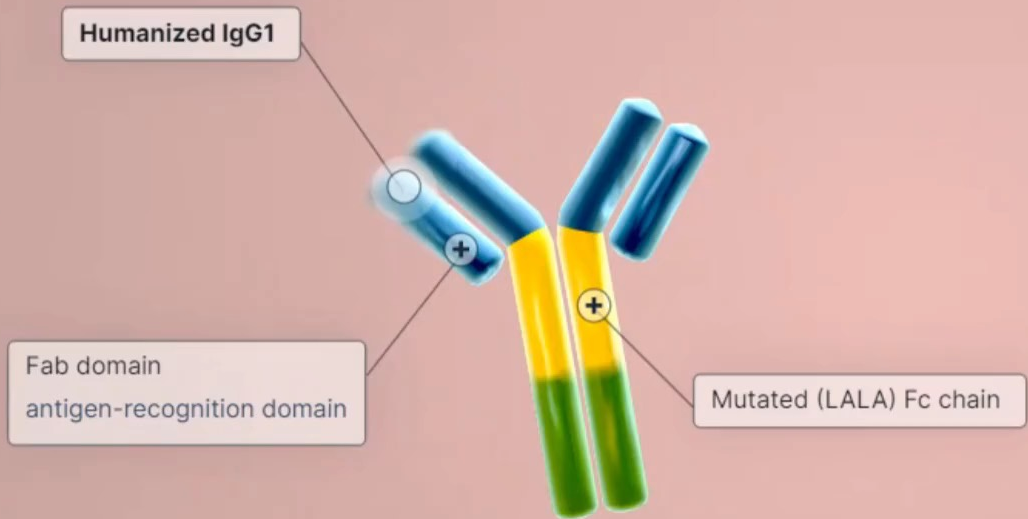
Enhancing IL-23 Inhibition ***Why is Targeting CD64+ Cells Important?***

Jessica R. Allegretti, MD, MPH, FACG, AGAF

Anti-p40 (IL-12/23) and Anti-p19 (IL-23)

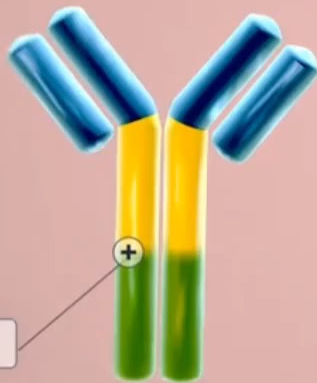




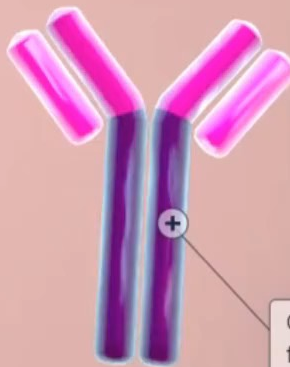


IL-23
p40 subunit

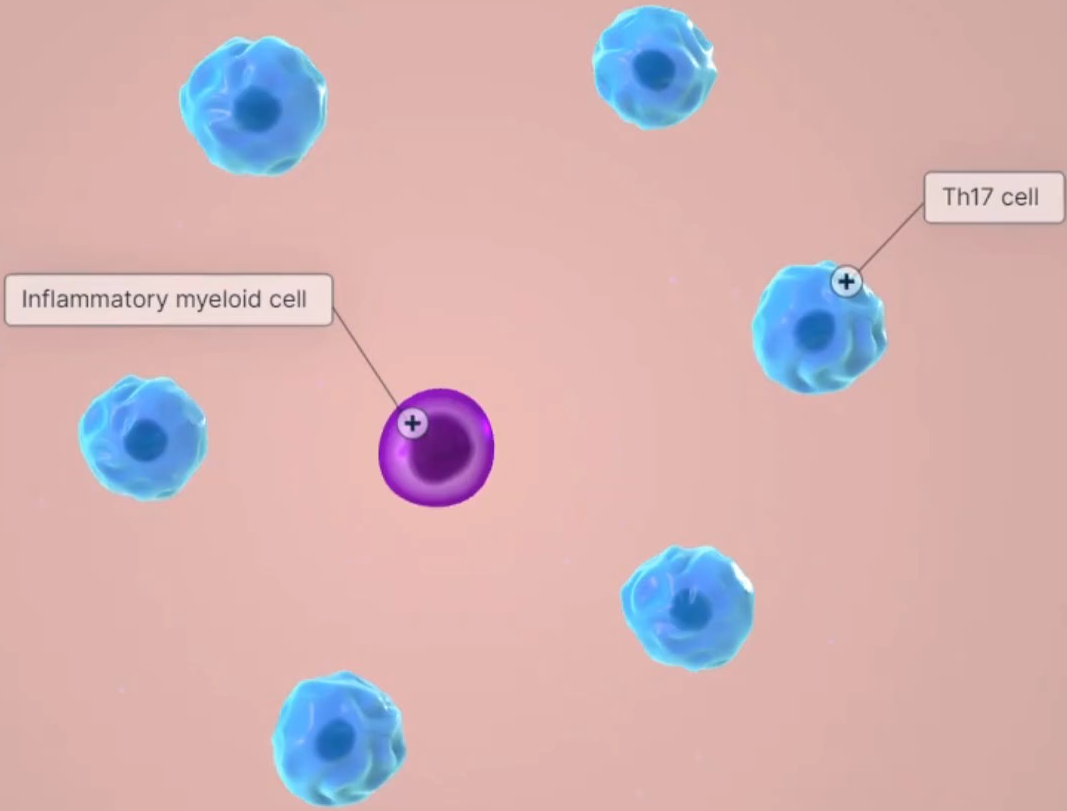
IL-23
p19 subunit



Mutated (LALA) antibody



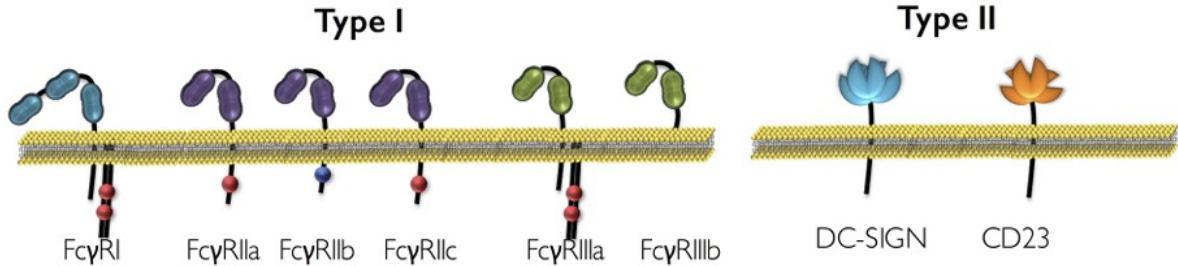
Contains native/wild type Fc fragment



● IL-23

What are 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



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

+ Constitutive expression
 - No expression
 # Inducible expression

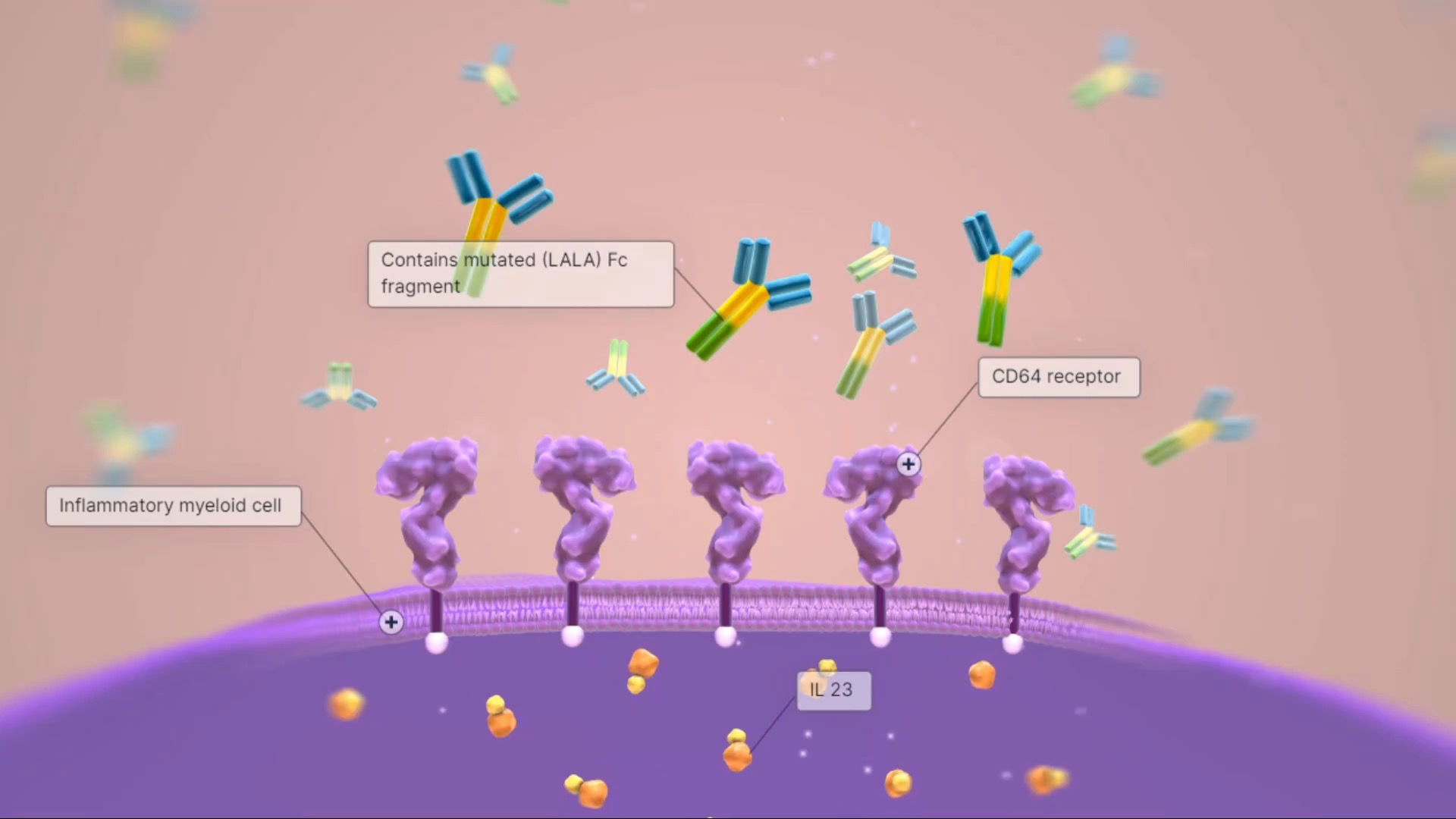
CD = cluster of differentiation; Ig = immunoglobulin.
 Bournazos S, et al. *Microbiol Spectr.* 2016;4(6):10.

Contains mutated (LALA) Fc fragment

CD64 receptor

Inflammatory myeloid cell

IL 23

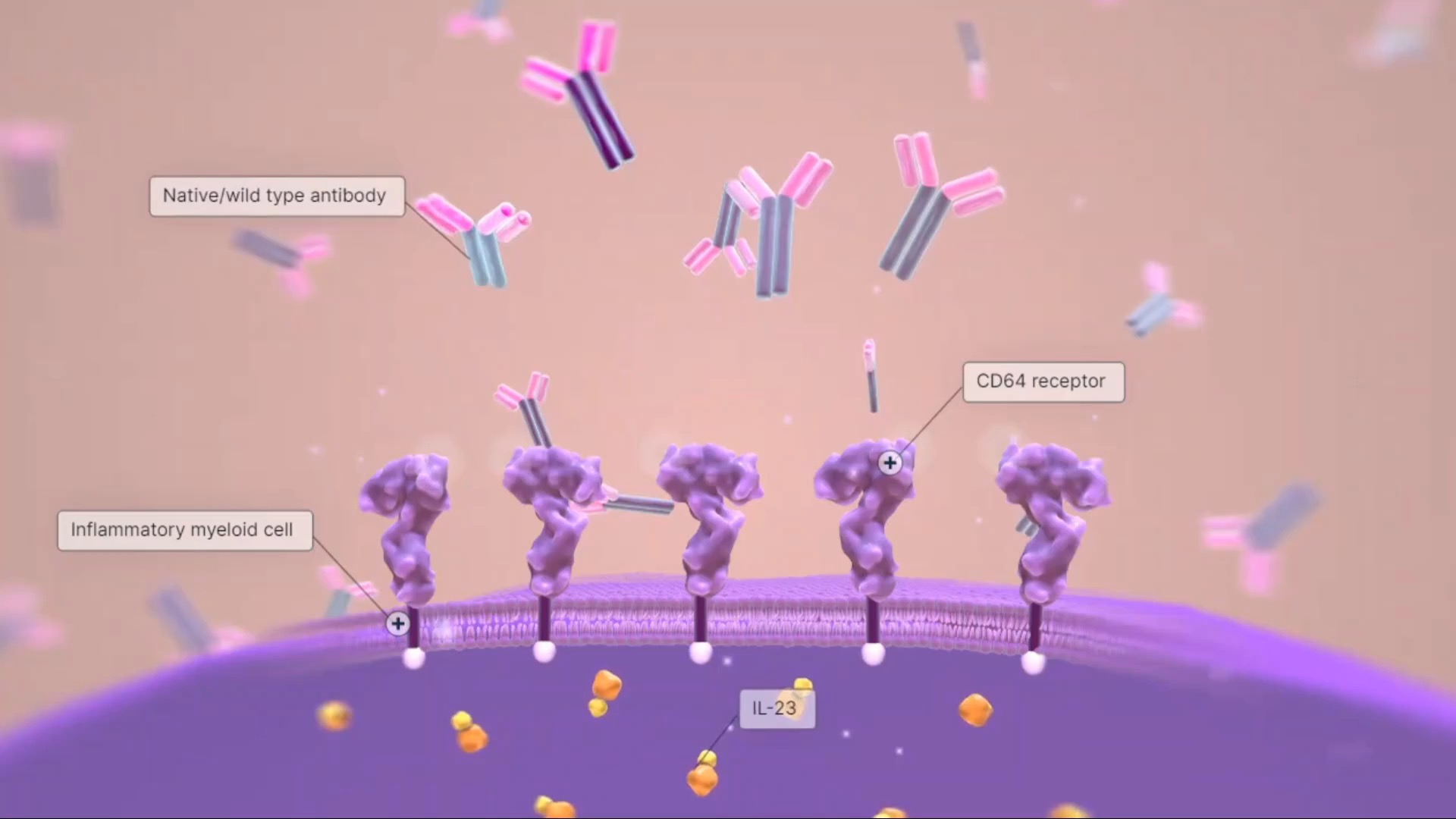


Native/wild type antibody

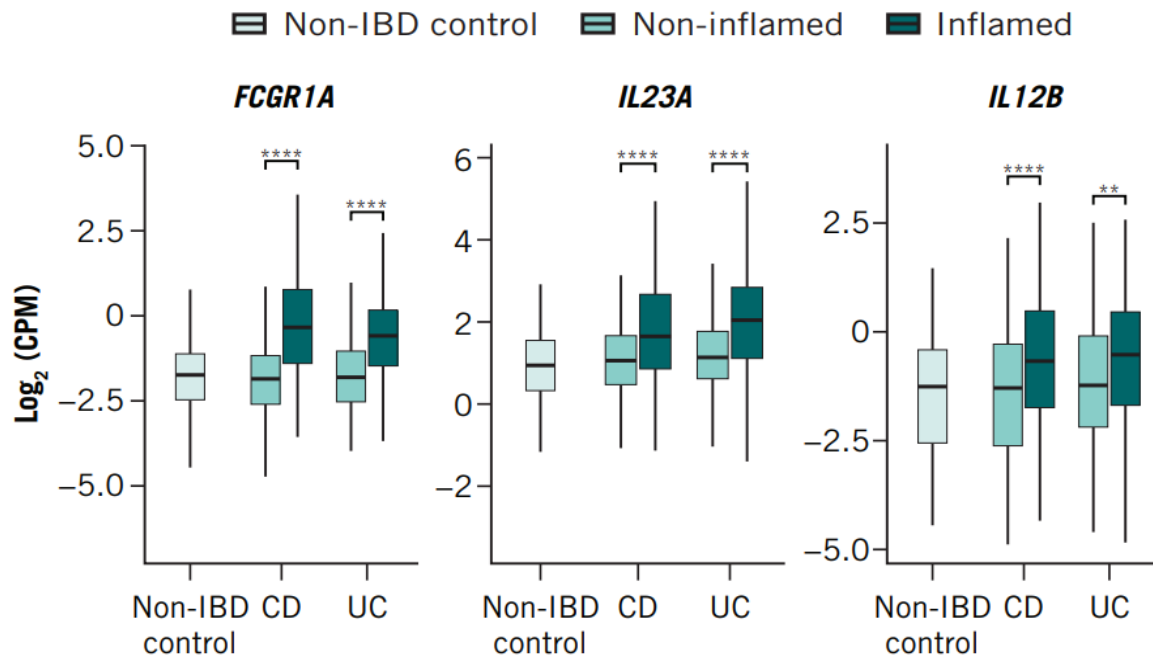
CD64 receptor

Inflammatory myeloid cell

IL-23



CD64 Expression in Diseased IBD Tissue



▶ *FCGR1A* (CD64), *IL23A* (IL-23p19), and *IL12B* (IL-23p40) expression were significantly increased in inflamed vs non-inflamed IBD gut biopsies

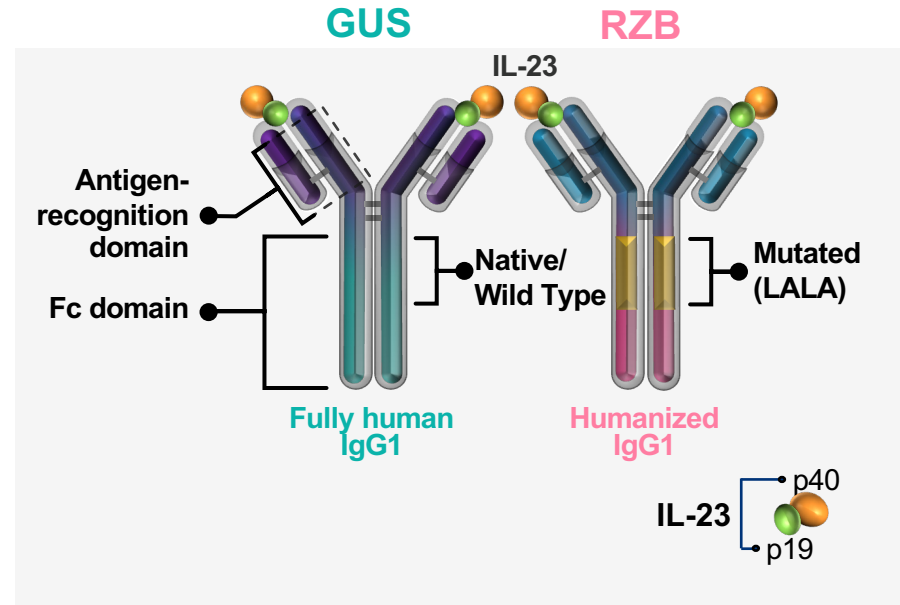
Audience Response

Which of the following is true regarding binding affinity of IL-23i's to CD64 receptors?

- A. Binding of CD64 occurs with only risankizumab
- B. Binding of CD64 occurs with only guselkumab
- C. Binding of CD64 occurs with only mirikizumab
- D. Binding of CD64 occurs with risankizumab, guselkumab, and mirikizumab
- E. I don't know

Clinically Relevant Differences Between Anti-IL-23 Therapeutic Antibodies May Be Related to Their Unique Molecular Attributes

- ▶ Guselkumab (GUS) and risankizumab (RZB) are mAbs that selectively target the p19 subunit of IL-23
- ▶ GUS and RZB have shown efficacy in the treatment of inflammatory bowel diseases*
- ▶ Potential differences in the therapeutic profiles may be related to their unique molecular attributes
- ▶ GUS and RZB have differences in the Fc region that affect binding to Fc-gamma receptors



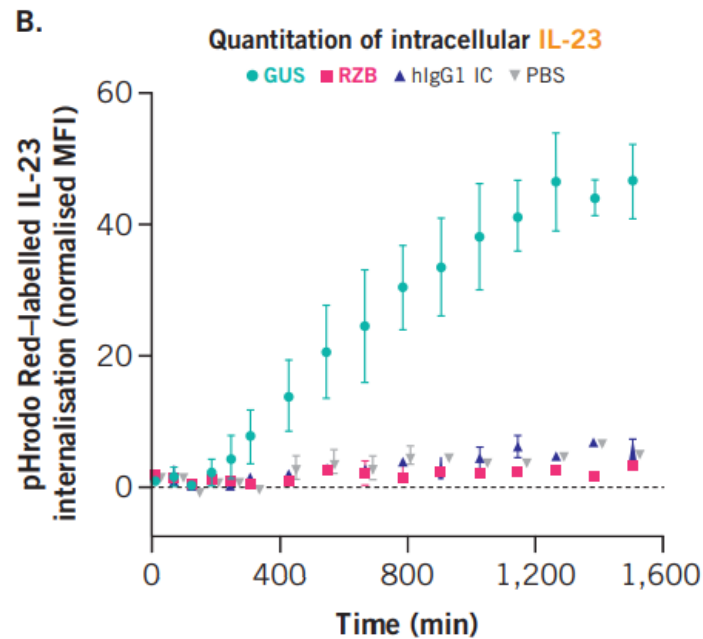
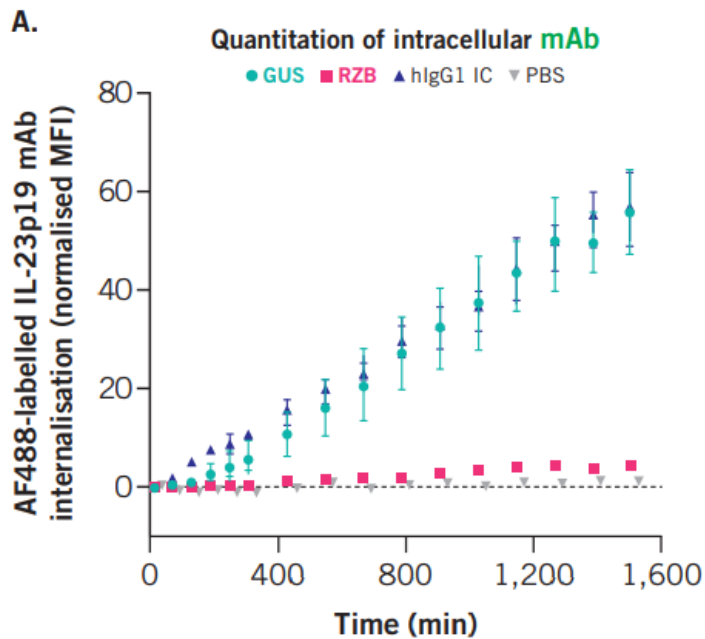
mAb = monoclonal antibody; Fc = fragment crystallizable; LALA = leucine to alanine substitutions at positions 234 and 235; IgG = immunoglobulin G.

*GUS is approved for adult patients with moderate-to-severe plaque psoriasis and active psoriatic arthritis. RZB is approved for adult patients with moderate-to-severe plaque psoriasis, active psoriatic arthritis, and moderately to severely active Crohn's disease.

1. D'Haens G, et al. *Lancet*. 2022;399(10340):2015-2030. 2. Ferrante M, et al. *Lancet*. 2022;399(10340):2031-2046. 3. Sandborn WJ, et al. *Gastroenterology*. 2022;162(6):1650-1664. 4. Dignass A, et al. *J Crohns Colitis*. 2022;16(Supplement 1):i025-i026. 5. Louis E, et al. *Aliment Pharmacol Ther*. 2004;19(5):511-519. 6. Vos AC, et al. *Gastroenterology*. 2011;140(1):221-230. 7. Wojtal KA, et al. *PLoS One*. 2012;7(8):e43361.

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

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

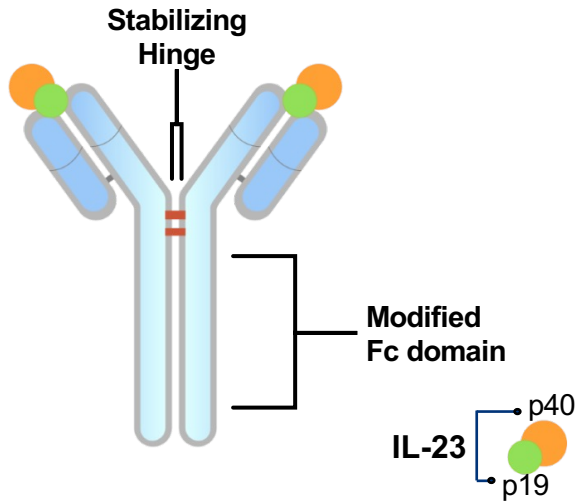


MFI = Mean fluorescence intensity

Atreya R, et al. *J Crohns Colitis*. 2024;18(Supplement 1):i470-i470.

In-Vitro Evaluations of CD64 and IL-23 Binding: Mirikizumab

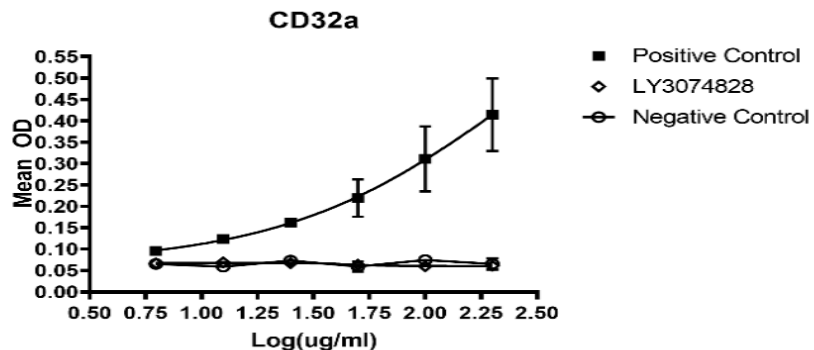
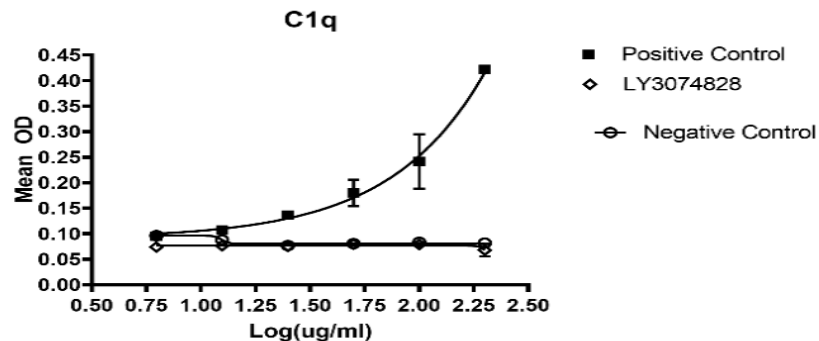
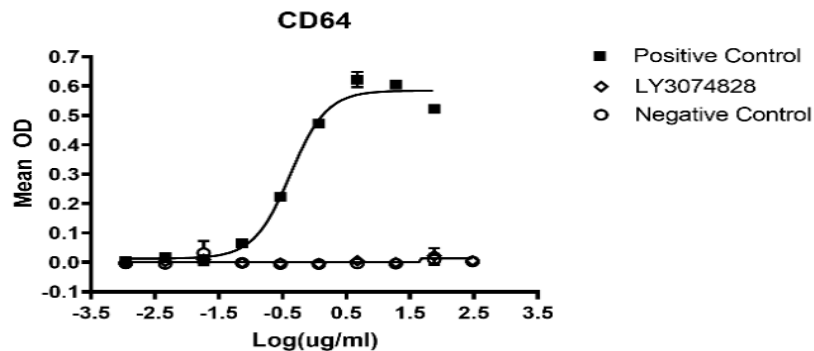
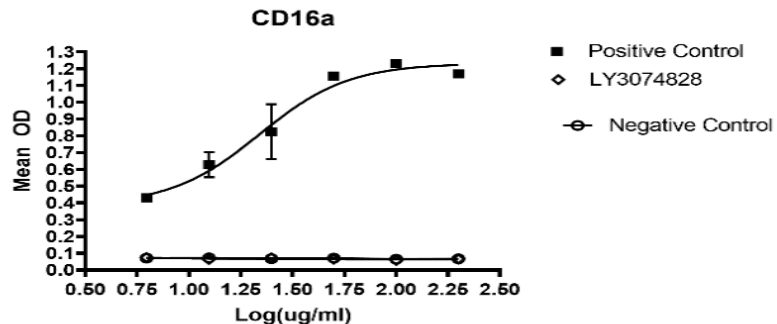
Mirikizumab Antibody



- ▶ Humanized IgG4 monoclonal antibody that selectively binds to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor
- ▶ IgG4k isotype containing the hinge-stabilizing S/P mutation
- ▶ Mirikizumab was additionally modified to significantly reduce FcγR binding and interaction
- ▶ Reduces the potential for unwanted interactions with the immune system and other possible toxicities

In-Vitro Evaluations of CD64 and IL-23 Binding: Mirikizumab

Assessment of Fc Receptor Activation and Complement Binding



Audience Response

Which of the following is true regarding binding affinity of IL-23i's to CD64 receptors?

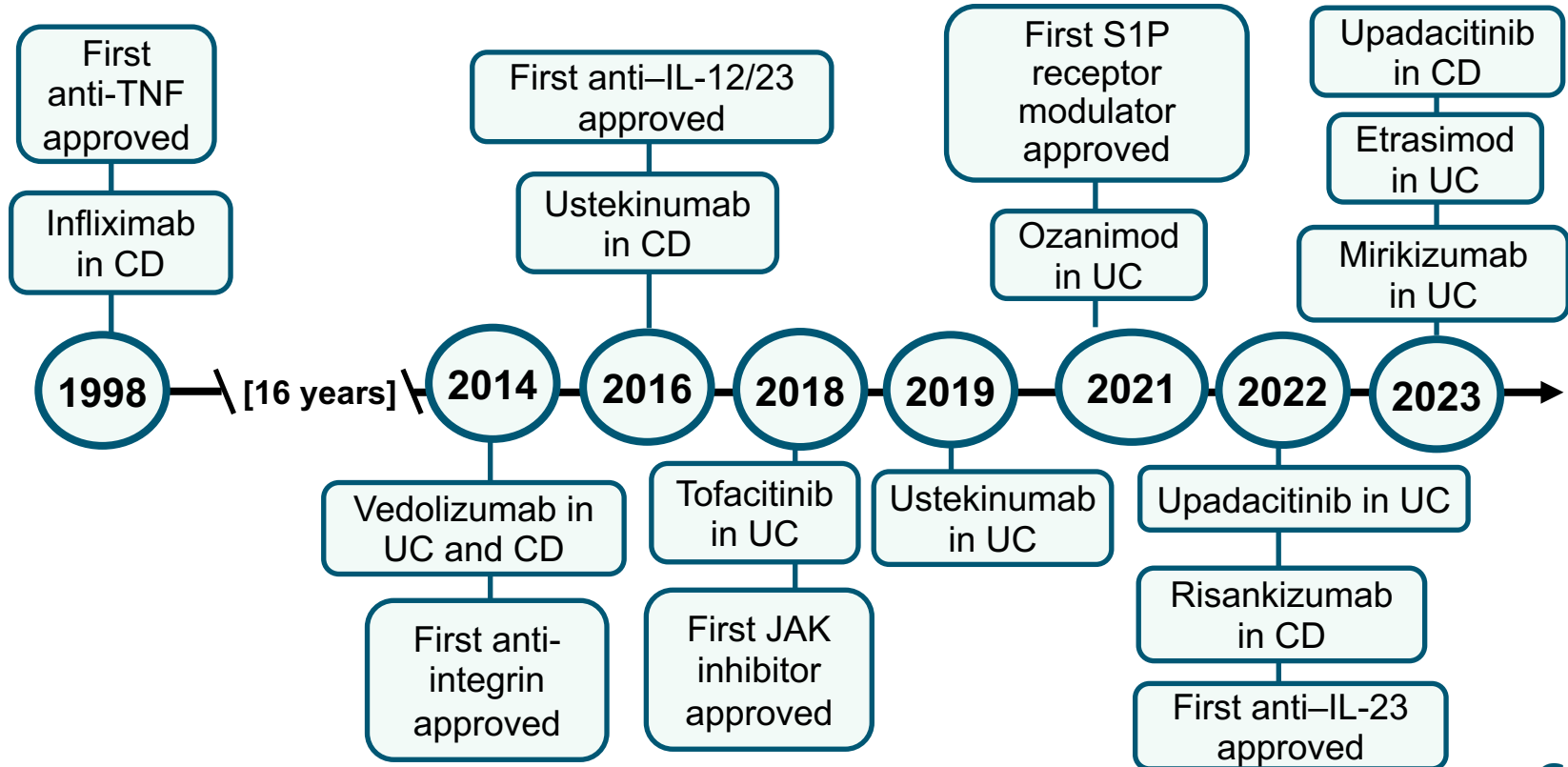
- A. Binding of CD64 occurs with only risankizumab
- B. Binding of CD64 occurs with only guselkumab
- C. Binding of CD64 occurs with only mirikizumab
- D. Binding of CD64 occurs with risankizumab, guselkumab, and mirikizumab

Section **3**

Review of IL-23 Inhibitor Current Studies

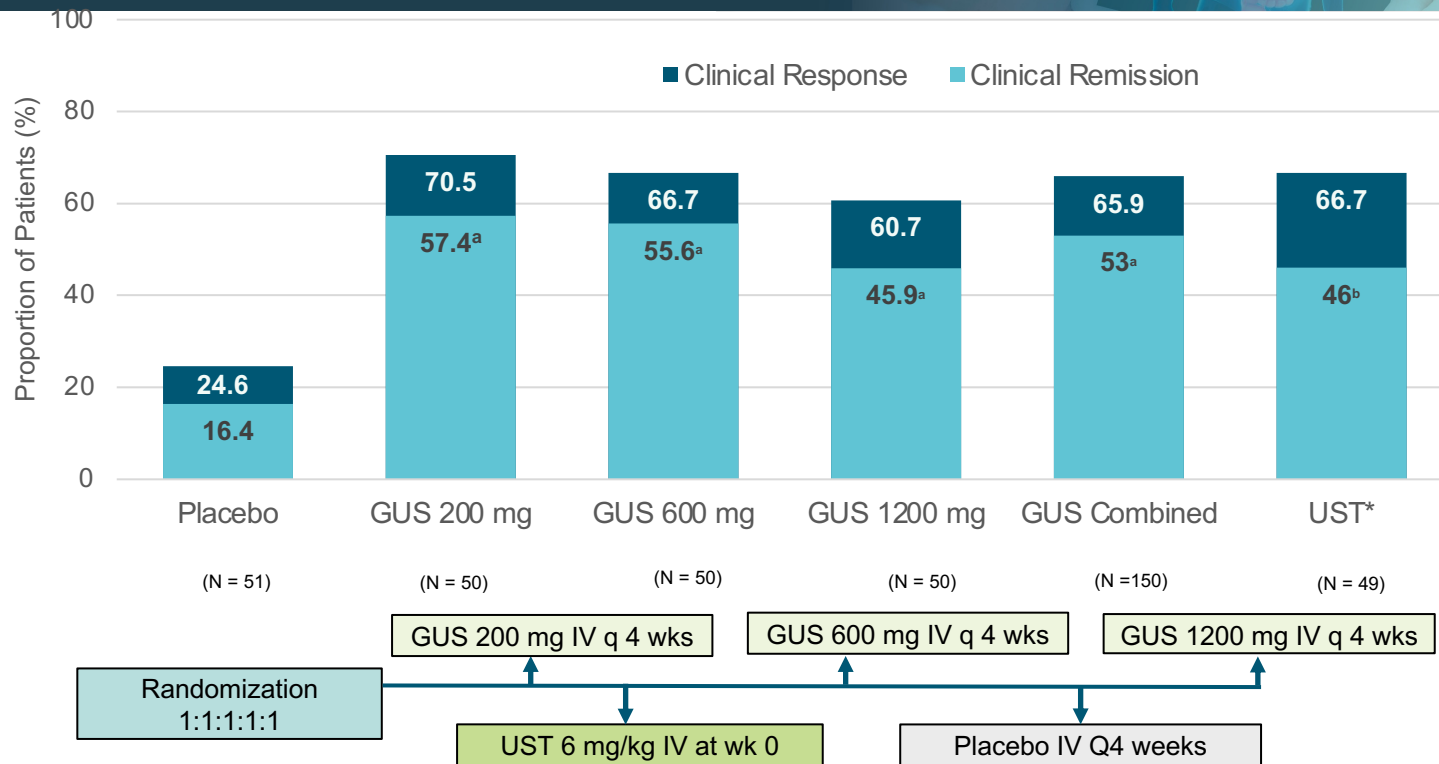
Edward V. Loftus, Jr., MD

Evolution of IBD Treatment Landscape



CD = Crohn's disease; IBD = inflammatory bowel disease; IL = interleukin; JAK = Janus kinase; TNF = tumor necrosis factor; UC = ulcerative colitis.
 Modified from Pouillon L, et al. *Nat Rev Gastroenterol Hepatol.* 2021;18(2):143. OMVOH® (mirikizumab-mrkz) [package insert]. Indianapolis, IN: Eli Lilly and Company.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761279s000lbl.pdf

GALAXI-1: Guselkumab Induction in CD**



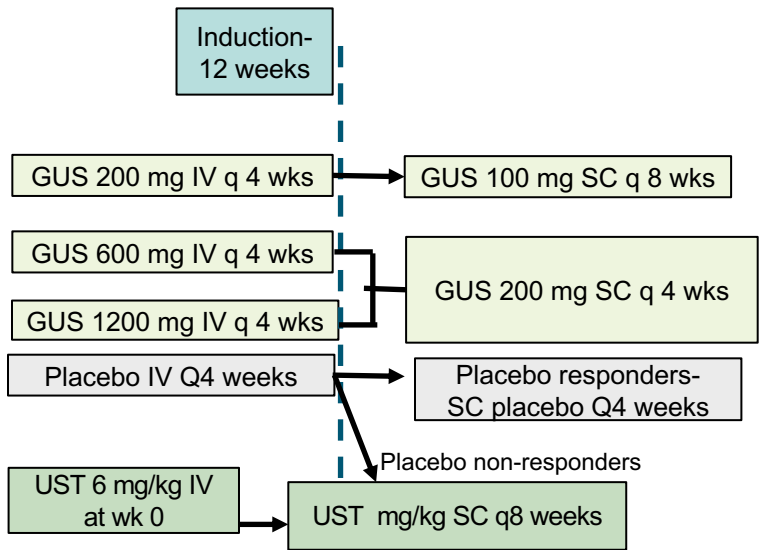
UST = ustekinumab.

^a $p < 0.001$ ^b $p = 0.001$; *UST approx. 6 mg/kg IV \Rightarrow 90 mg SC. Clinical Response = 100-point reduction from baseline CDAI score or CDAI < 150; Clinical Remission = CDAI < 150

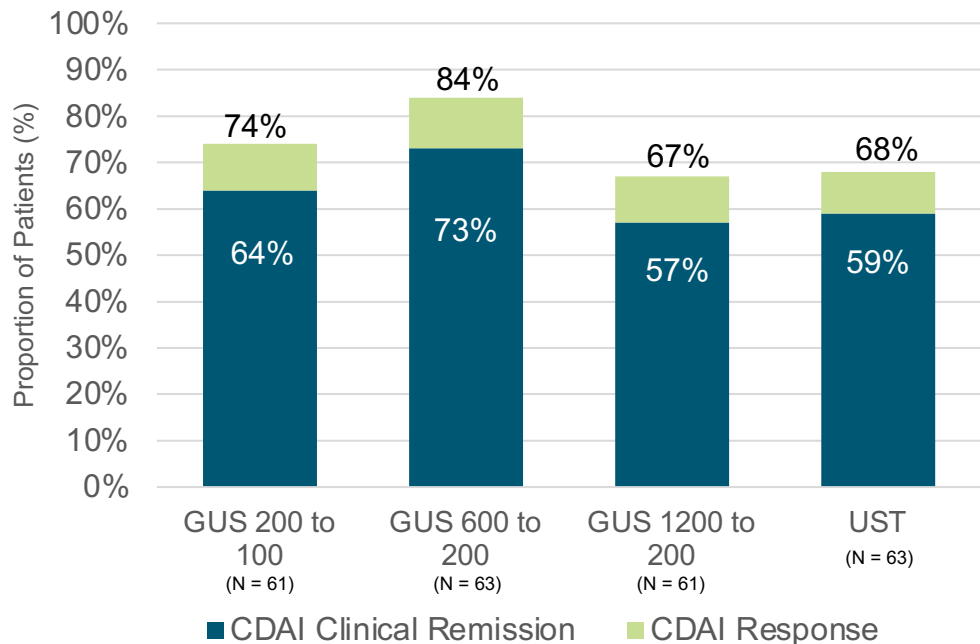
**Guselkumab is not FDA-approved for the treatment of CD.

Sandborn W, et al. *Gastroenterology*. 2022;162(6):1650-1664.e8.

GALAXI-1: Guselkumab Maintenance in CD*



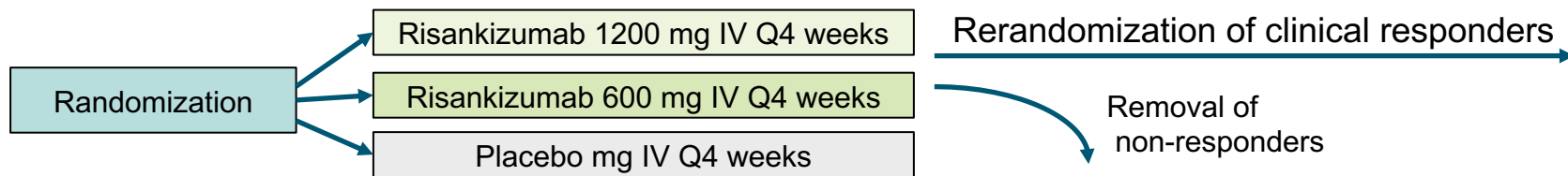
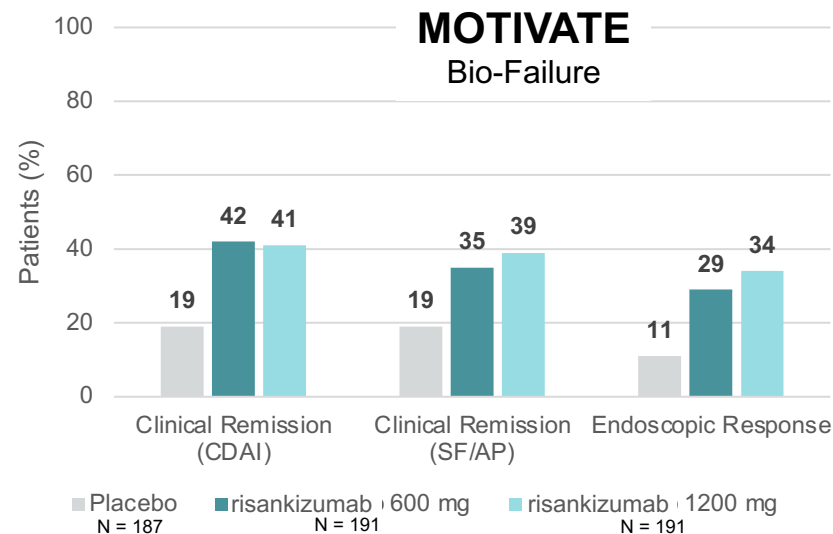
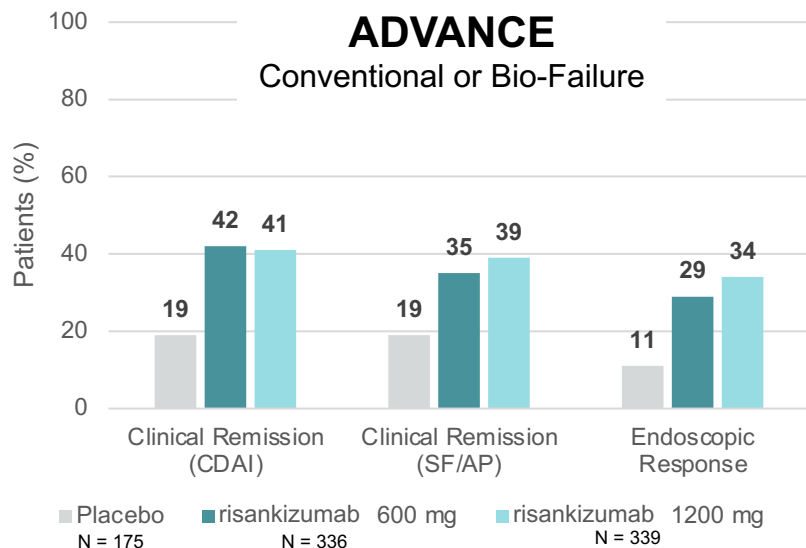
CAAI Response and Remission at week 48



*guselkumab is not FDA-approved for the treatment of CD.
 Clinical Response = 100-point reduction from baseline CDAI score or CDAI < 150; Clinical Remission = CDAI < 150
 Danese S, et al. *Lancet Gastroenterol Hepatol.* 2024;9(2):133-146.



ADVANCE and MOTIVATE: Risankizumab Induction in CD

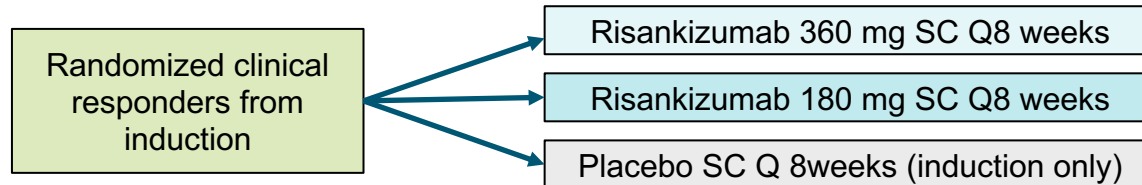
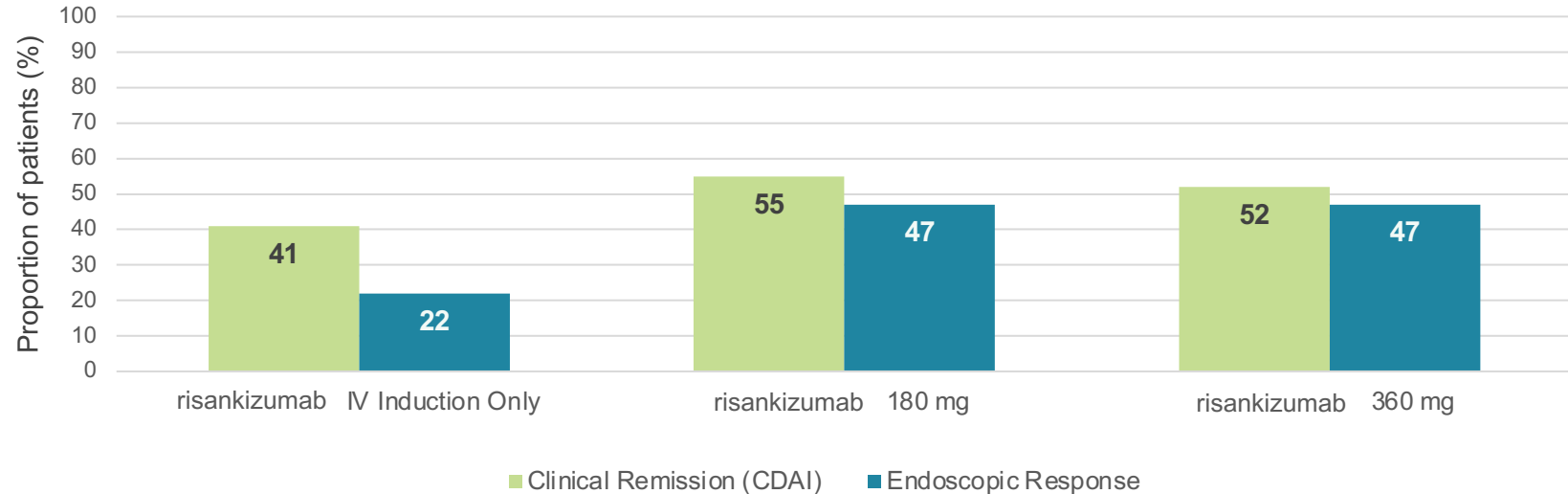


CDAI = Crohn's disease activity index; SF/AP = stool frequency/abdominal pain.; *Clinical responders defined as $\geq 30\%$ decrease in average daily stool frequency or APS and not worse than baseline; *Endoscopic response defined as $> 50\%$ decline in SES-CD vs BL by central reviewer (or in pts with SES-CD of 4 at BL, ≥ 2 -point decrease vs BL); CDAI clinical remission a CDAI < 150 .

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

FORTIFY: Risankizumab Maintenance in CD

Week 52 Maintenance – All Patients

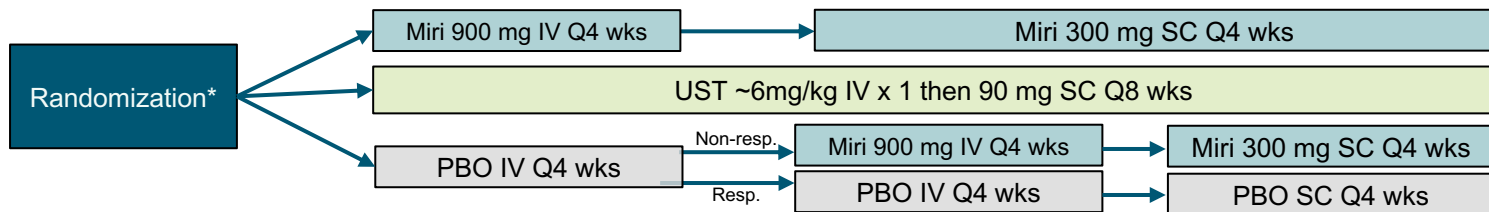
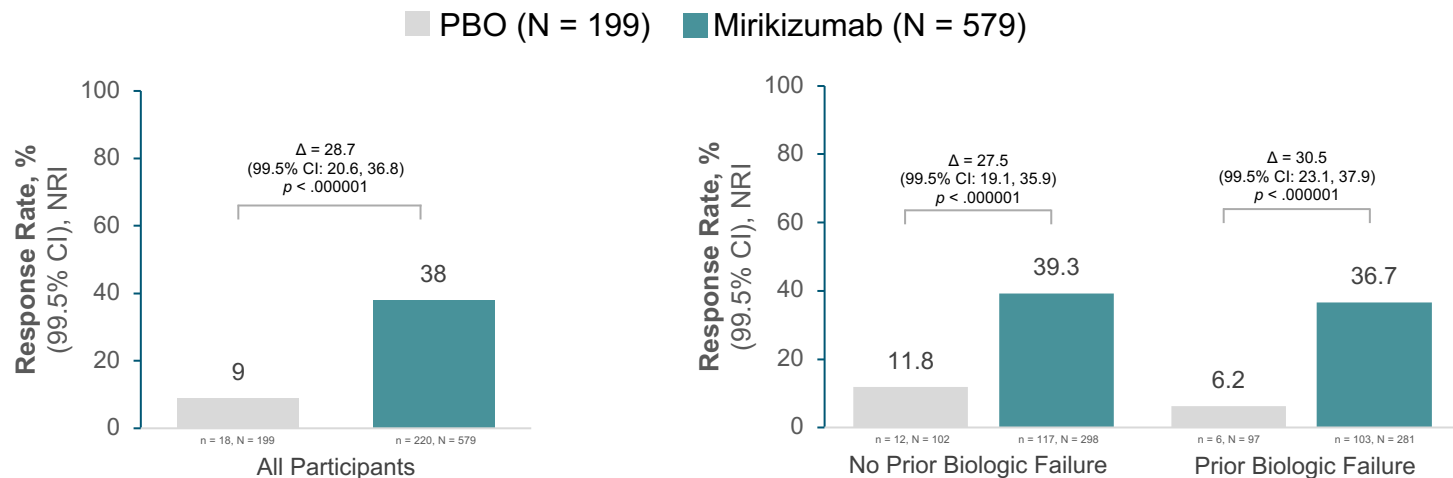


Endoscopic response defined as >50% decline in SES-CD vs BL by central reviewer (or in pts with SES-CD of 4 at BL, ≥ 2 -point decrease vs BL); CDAI clinical remission a CDAI < 150.

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

VIVID-1: Mirikizumab Comparison in Moderate-to-Severe CD

Clinical Response by PRO at Week 12 and Endoscopic Response by SES-CD at Week 52

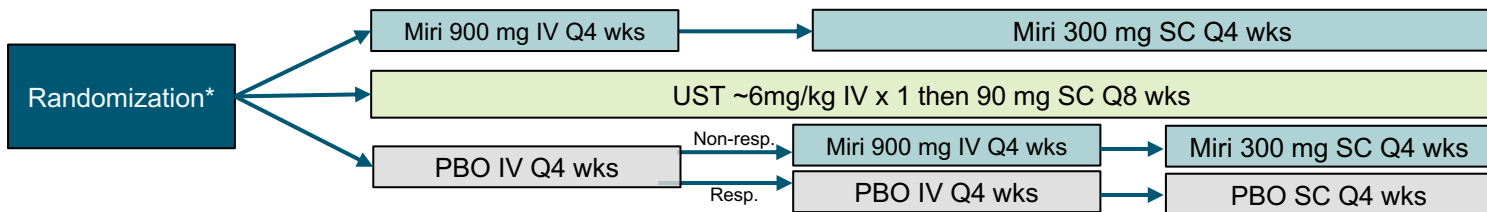
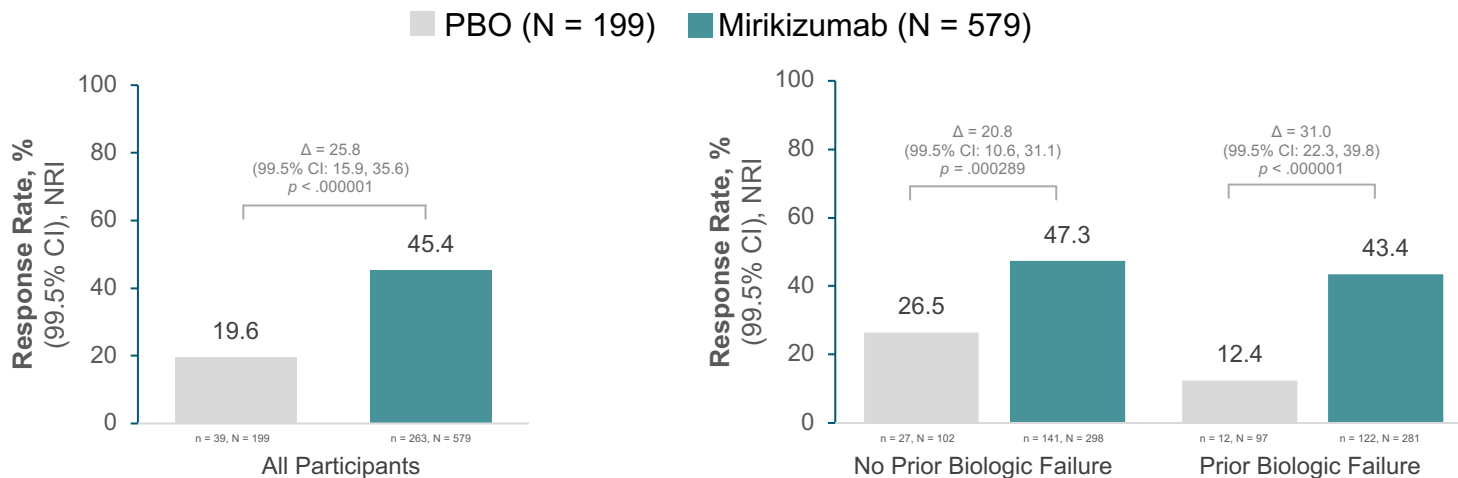


Miri = mirikizumab.

*Randomized 6:3:2 to mirikizumab, ustekinumab, and placebo. Ferrante M, et al. *J Crohns Colitis*. 2024;18(Supplement 1):i7-i9.

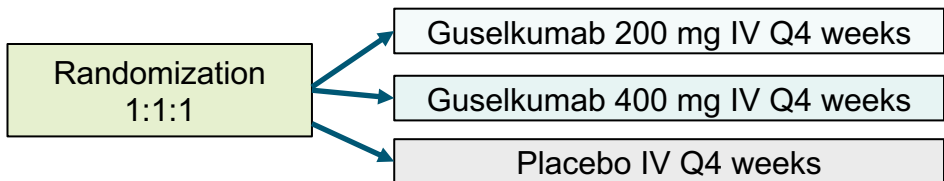
VIVID-1: Mirikizumab Comparison in Moderate-to-Severe CD

Clinical Response by PRO at Week 12 and Clinical Remission by CDAI at Week 52

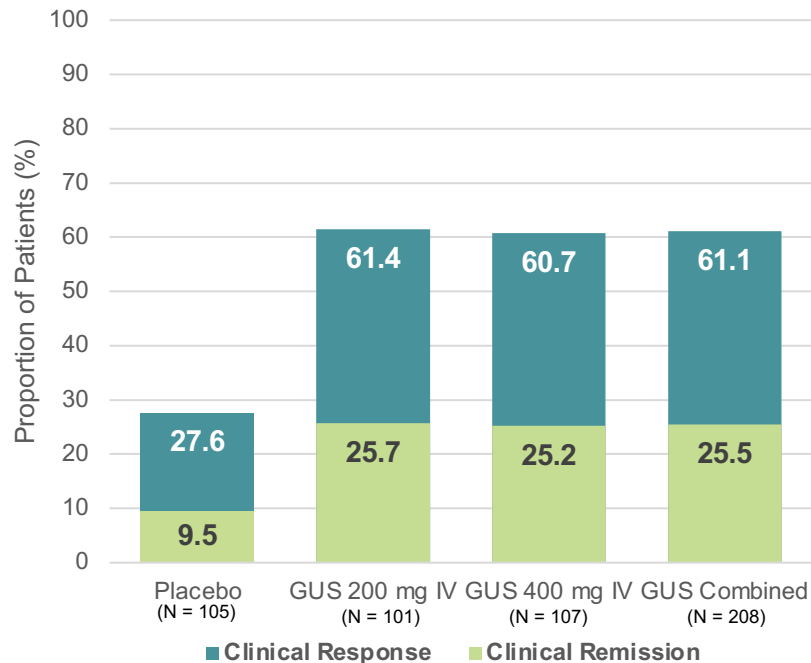


*Randomized 6:3:2 to mirikizumab, ustekinumab, and placebo. Ferrante M, et al. *J Crohns Colitis*. 2024;18(Supplement 1):i7-i9.

QUASAR: Guselkumab Induction in UC*



Clinical Response and Clinical Remission at Week 12



*guselkumab is not FDA-approved for the treatment of UC. GUS = guselkumab.

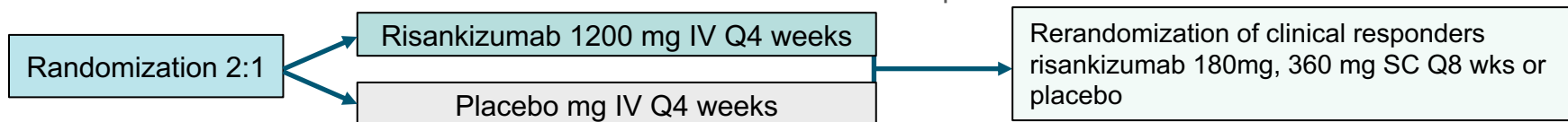
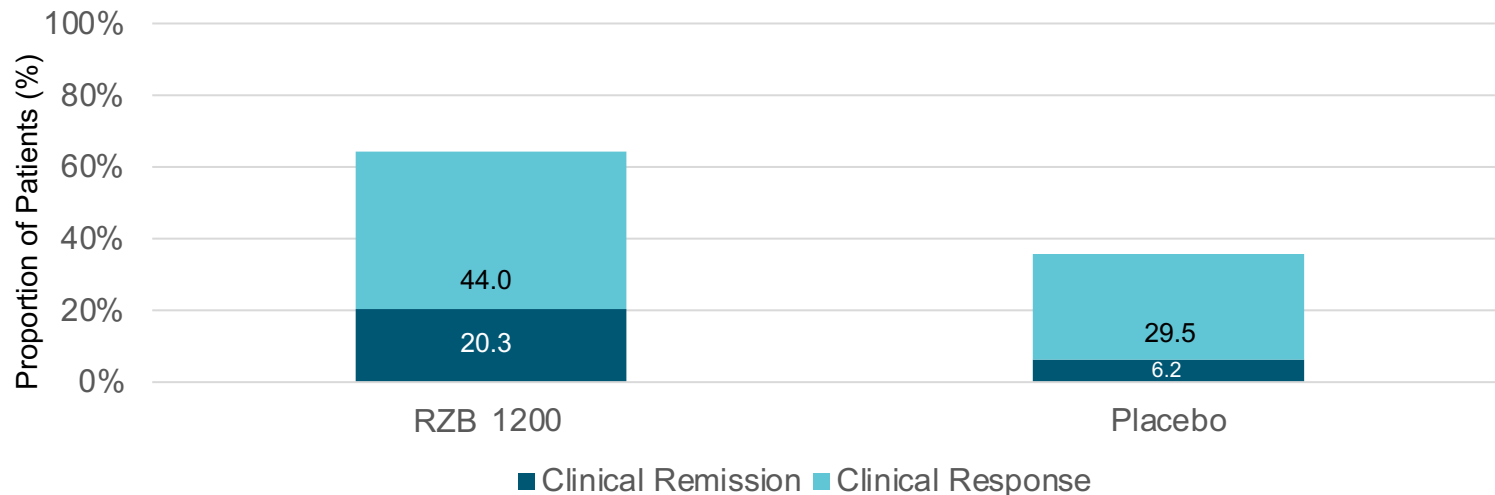
Clinical response = modified Mayo score decrease $\geq 30\%$ and ≥ 2 points, rectal bleeding subscore ≥ 1 -point decrease or subscore of 0/1;

Clinical remission = Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy

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

INSPIRE: Risankizumab Induction in UC*

Clinical Response and Remission at 12 Weeks

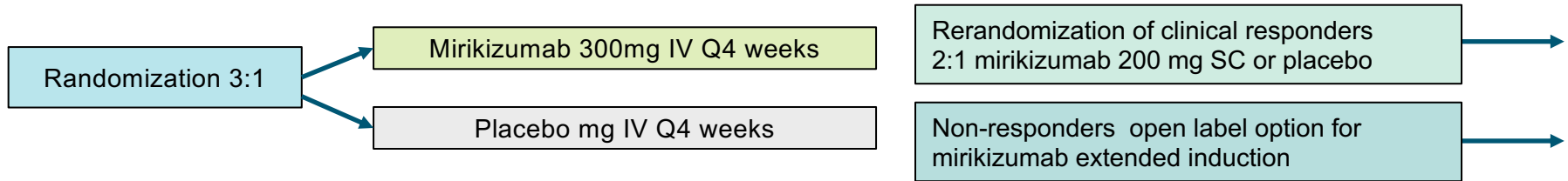
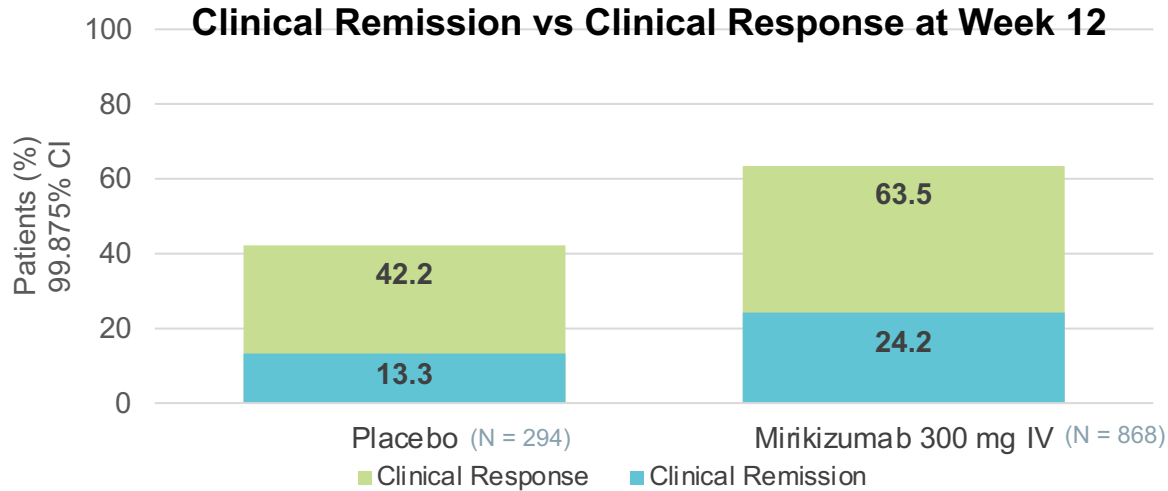


*Risankizumab is not FDA-approved for the treatment of UC.

*Clinical responders defined as $\geq 30\%$ decrease in average daily stool frequency or APS and not worse than baseline; *Endoscopic response defined as $>50\%$ decline in SES-CD vs BL by central reviewer (or in pts with SES-CD of 4 at BL, ≥ 2 -point decrease vs BL); CDAI clinical remission a CDAI < 150 .

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

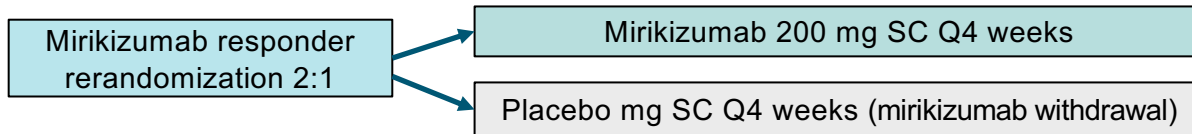
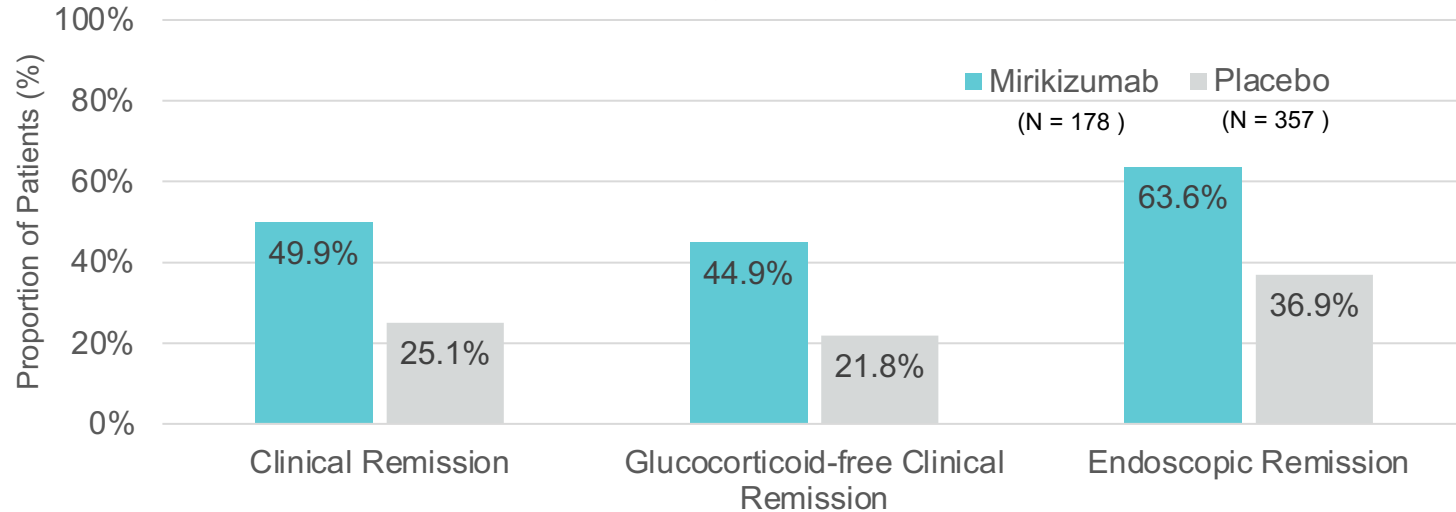
LUCENT-1: Mirikizumab Induction in UC



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); clinical response: MMS of ≥ 2 points and $\geq 30\%$ decrease from baseline, and a decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1

LUCENT-2: Mirikizumab Maintenance in UC

Primary and Secondary Outcomes at 40 Weeks



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

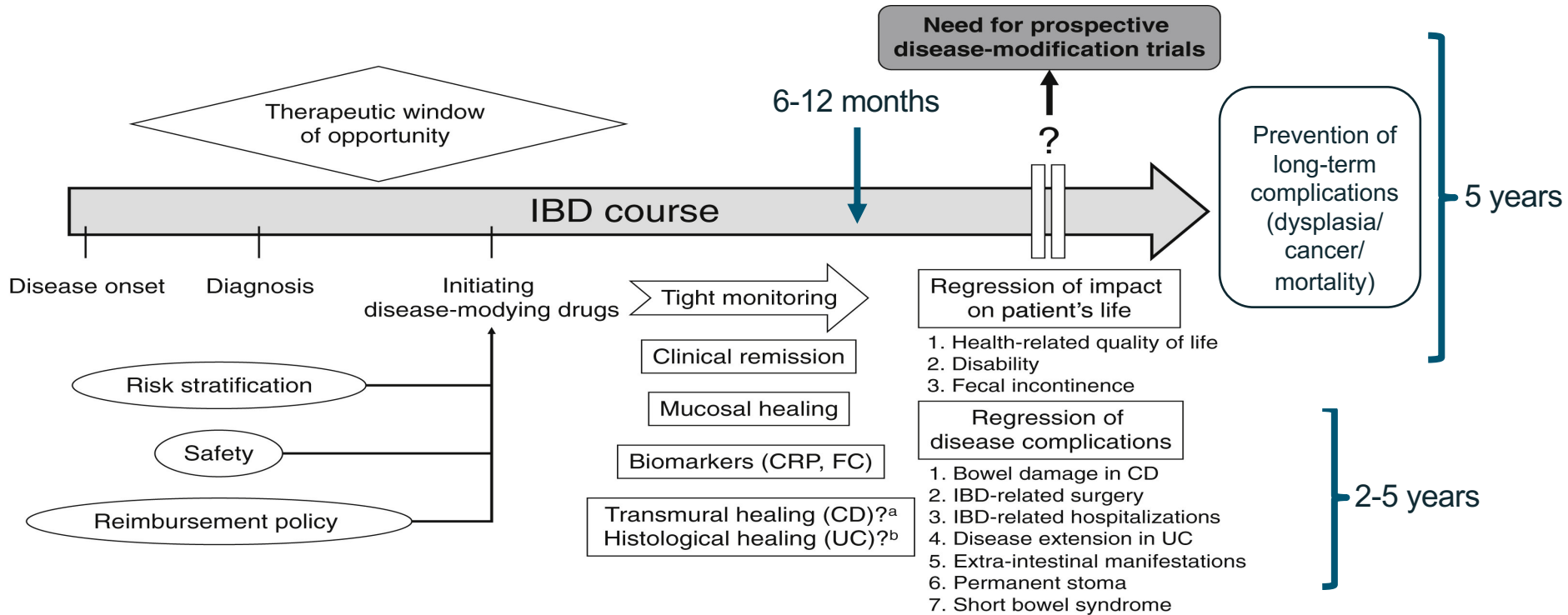
D'Haens G, et al. *N Engl J Med.* 2023;388:2444-2455.

Section 4

Clinical Implications to Practice

Angelina E. Collins, MSN, ANP-BC

Defining Goals for Treatment



FC = fecal calprotectin

^aTransmural healing may be the ultimate therapeutic goal in CD; ^bHistologic healing may be the ultimate therapeutic goal in UC

Le Berre C, et al. *Gastroenterology*. 2022;162(5):1424-1438.

Dosing of IL-23 Inhibitors

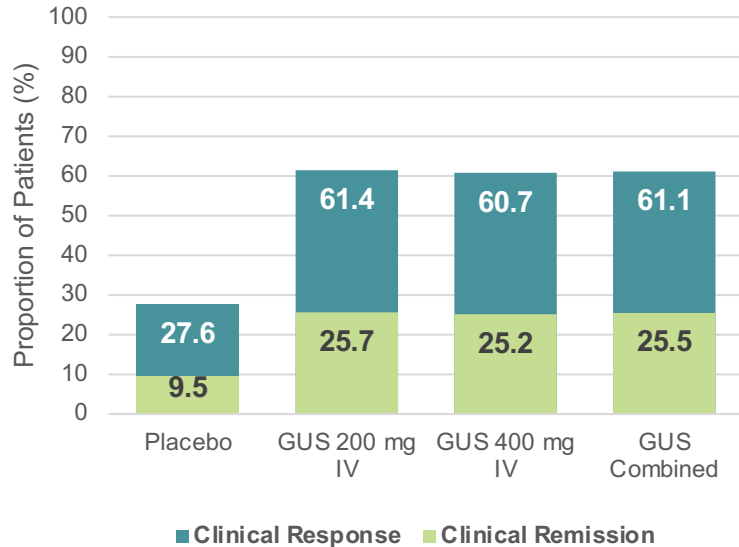
Drug	Dose	Induction Schedule	Indication	Trial
Guselkumab*	200-400mg IV	Q4W X 3	UC	QUASAR
Risankizumab*	1200mg IV	Q4W X 3	UC	INSPIRE
Mirikizumab	300mg IV	Q4W X 3	UC	LUCENT-1
Guselkumab*	200-1200mg IV	Q4W X 3	CD	GALAXI-1
Risankizumab	600-1200mg IV	Q4W X 3	CD	ADVANCE, MOTIVATE
Mirikizumab*	200-1000mg IV	Q4W X 3	CD	SERENITY

*Not FDA-approved for treatment in disease indicated
McDonald BD, et al. *J Crohn's Colitis*. 2022;16(Supplement 2):ii42-ii53.

IL-23 Inhibitors in Treatment-Naïve and Treatment- Experienced Patients

QUASAR: Guselkumab* in Ulcerative Colitis, Phase 2b

Clinical Response and Clinical Remission at Week 12



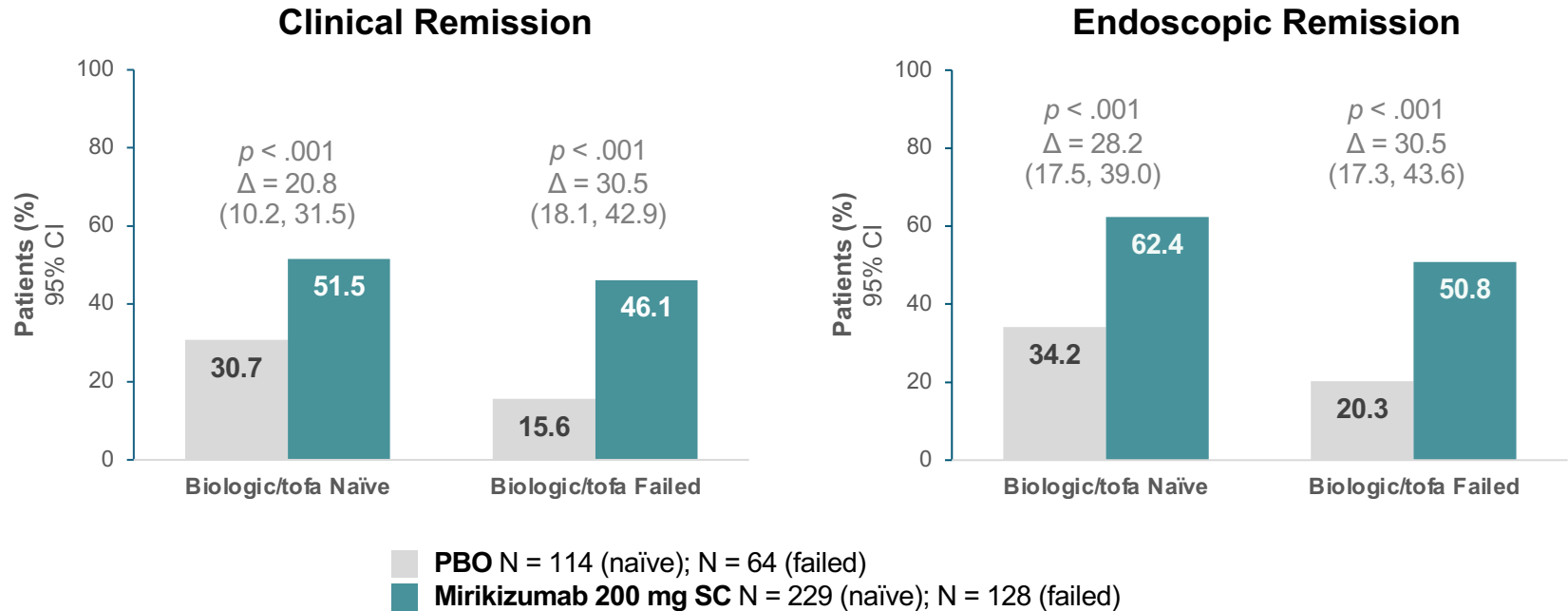
History of inadequate response or intolerance to 1 or more advanced therapies in 47% of patients

	Placebo (N = 105)	Guselkumab		Total (N = 313)
		200 mg IV (N = 101)	400 mg IV (N = 107)	
History of inadequate response/intolerance to ≥ 1 UC advanced therapy, ^c n (%)	51 (48.6)	46 (45.5)	51 (47.7)	148 (47.3)
≥ 1 TNF- α antagonist, n/n (%)	46/51 (90.2)	41/46 (89.1)	46/51 (90.2)	133/148 (89.9)
Vedolizumab, n/n (%)	29/51 (56.9)	22/46 (47.8)	27/51 (52.9)	78/148 (52.7)
Tofacitinib, n/n (%)	15/51 (29.4)	10/46 (21.7)	6/51 (11.8)	31/148 (20.9)
1 advanced therapy class, n/n (%)	23/51 (45.1)	27/46 (58.7)	25/51 (49.0)	75/148 (50.7)
≥ 2 advanced therapy classes, n/n (%)	28/51 (54.9)	19/46 (41.3)	26/51 (51.0)	73/148 (49.3)

*Guselkumab is not FDA-Approved for the treatment of UC.
Peyrin-Biroulet L, et al. *Gastroenterology* 2023;165(6):1443-1457.

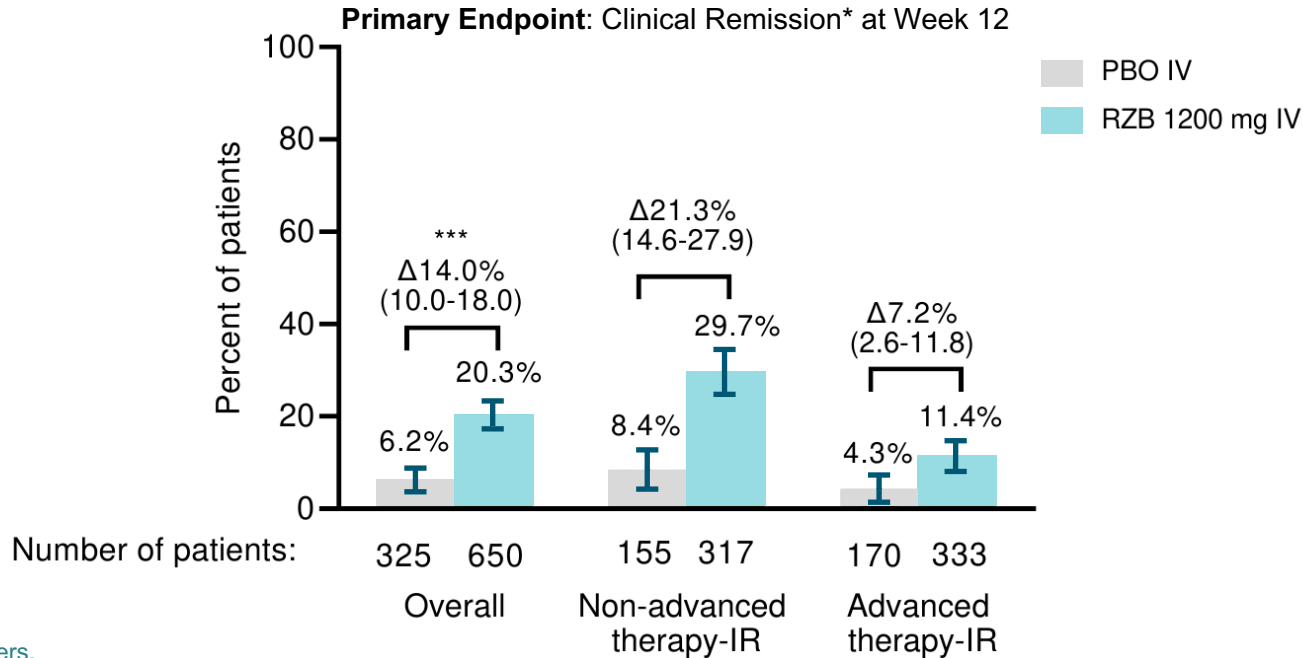
IL-23 Inhibitors in Treatment-Naïve and Treatment- Experienced Patients

LUCENT-2: Mirikizumab Endpoints by Biologic/Tofacitinib Failure Status Ulcerative Colitis



IL-23 Inhibitors in Treatment-Naïve and Treatment- Experienced Patients

INSPIRE: Risankizumab Endpoints by non-Advanced and Advanced Therapy-IR – Ulcerative Colitis

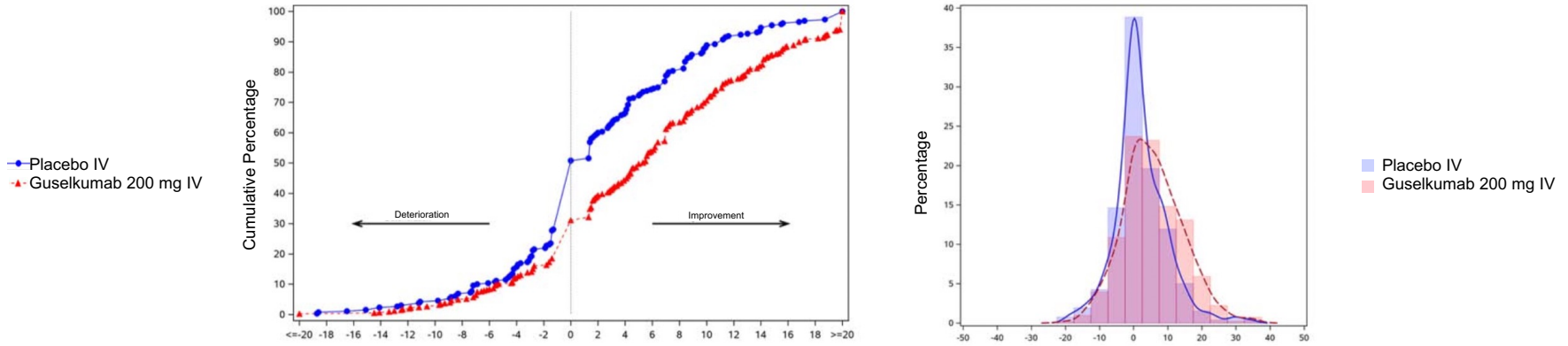


IR = inadequate responders.

*Clinical Remission per Adapted Mayo score: Stool frequency subscore ≤ 1 and not greater than baseline, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1 without friability. Louis E, et al. *Am J Gastroenterol.* 2023;118(Supplement 12):S2-S2.

IL-23 Inhibitors and Fatigue in Patients with Moderate-to-Severe UC – QUASAR Trial (GUS)

Improvement from Baseline in PROMIS-Fatigue Short Form 7a T-score at Week 12



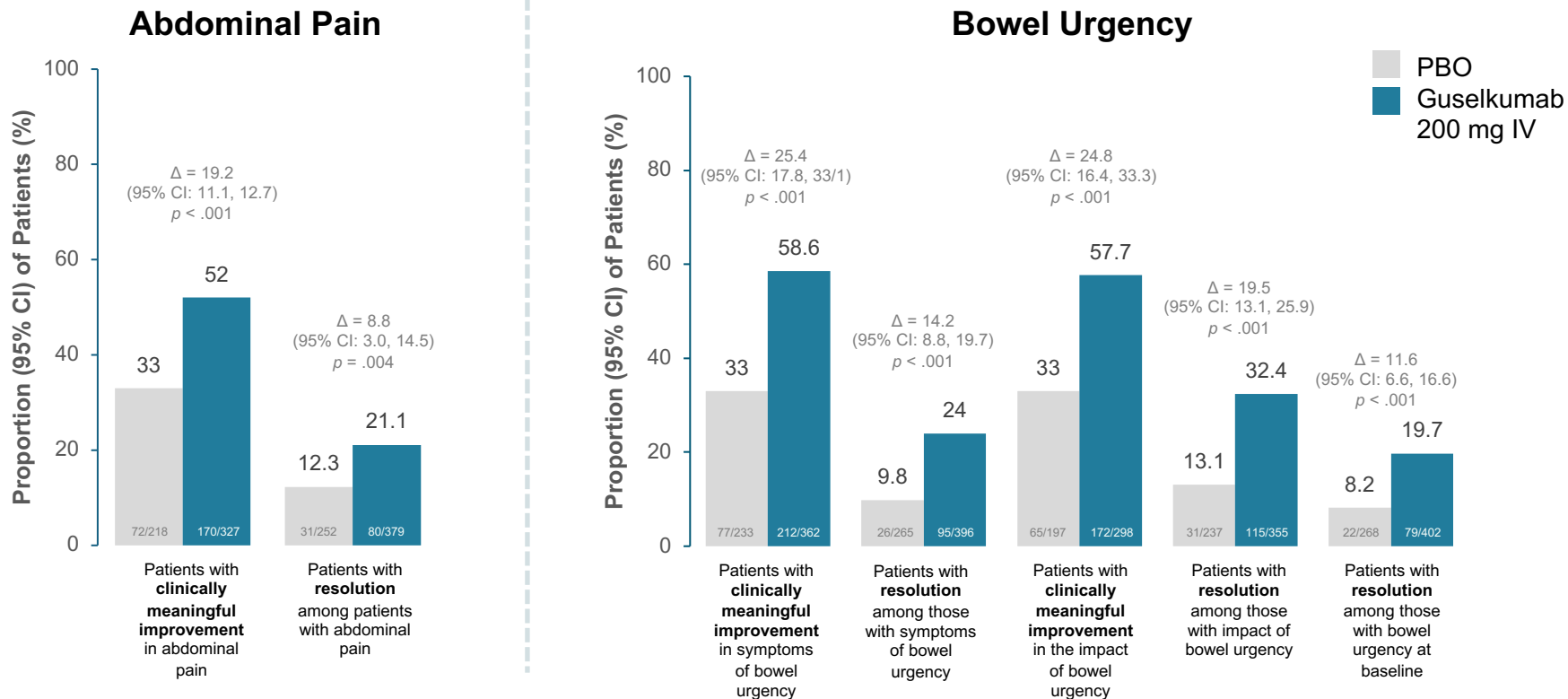
Fatigue response at Week 12: Overall and by history of inadequate response/intolerance to advanced therapy (ADT-IR)

	Overall		Non-ADT-IR		ADT-IR	
	Placebo IV	GUS 200 mg IV	Placebo IV	GUS 200 mg IV	Placebo IV	GUS 200 mg IV
Primary analysis population, N	280	421	144	213	136	208
Fatigue response at Week 12, N (%)	60 (21.4%)	173 (41.1%)	42 (29.2%)	93 (43.7%)	18 (13.2%)	80 (38.5%)
Adjusted treatment difference, (95% CI)		19.8 (13.1%, 26.4%)**		14.5% (4.5%, 24.5%)*		25.2% (16.6%, 33.9%)**

*Nominal p-value < 0.01; **Nominal p-value < 0.001

Dignass A, et al. *J Crohns Colitis*. 2024;18(Supplement 1):i166-i167.

IL-23 Inhibitors and Abdominal Pain and Urgency in Patients with Moderate-to-Severe UC - QUASAR Trial (GUS)

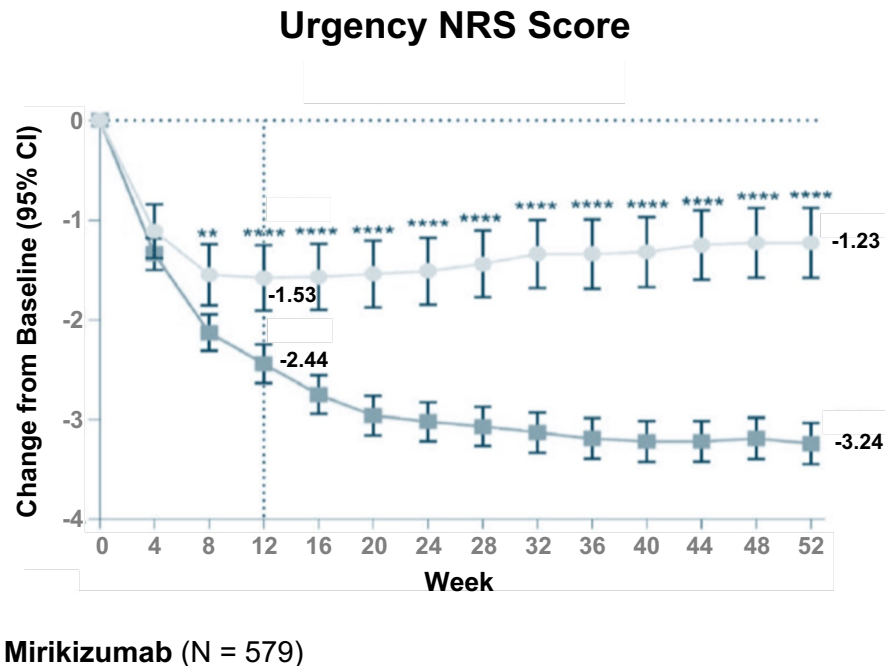
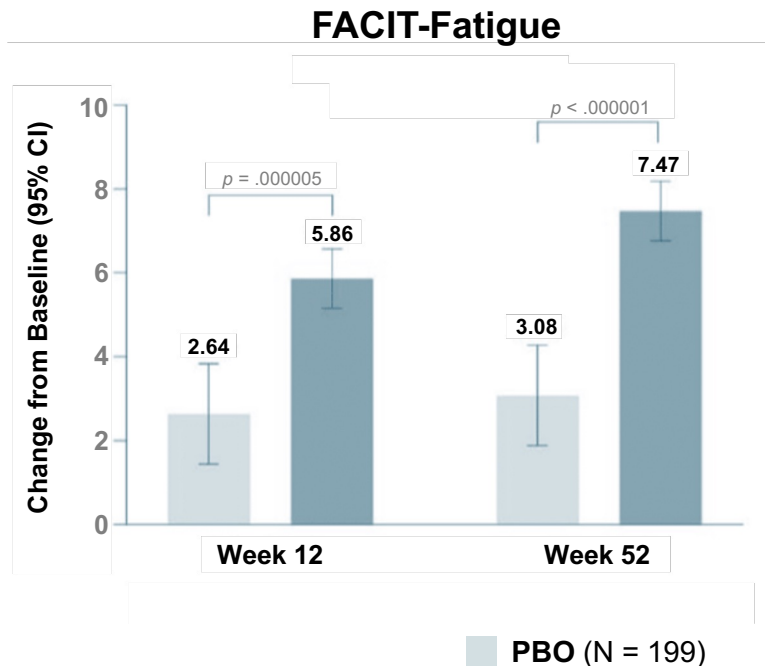


IL-23 Inhibitors and Symptom Resolution in Moderate-to-Severe UC – INSPIRE and COMMAND Trials (RZB)

Endpoints at weeks 12 and 52 point estimate [95% CI]	Induction (week 12)		Between group diff. (RZB 1200 mg vs PBO)	Maintenance (week 52)			Between group diff. (RZB 180 mg vs PBO)	Between group diff. (RZB 360 mg vs PBO)
	PBO IV	RZB 1200 mg IV		PBO (withdrawal) SC	RZB 180 mg SC	RZB 360 mg SC		
No abdominal pain	26.5 [21.7, 31.3]	35.8 [32.1, 39.4]	9.3** [3.4, 15.3]	29.5 [22.9, 36.1]	46.9 [39.6, 54.2]	37.8 [30.8, 44.8]	17.0*** [7.4, 26.7]	8.2 [-1.3, 17.7]
No bowel urgency	27.7 [22.8, 32.6]	44.1 [40.3, 47.9]	16.3*** [10.3, 22.4]	31.1 [24.4, 37.9]	53.6 [46.3, 60.9]	49.4 [42.2, 56.6]	22.6*** [13.1, 32.2]	18.4*** [8.8, 28.0]
No tenesmus	30.2 [25.2, 35.1]	48.7 [44.9, 52.6]	18.6*** [12.4, 24.8]	23.5 [17.4, 29.6]	36.9 [29.8, 43.9]	36.8 [29.8, 43.8]	13.1** [4.6, 21.7]	14.4** [5.7, 23.0]
No fecal incontinence	58.2 [52.8, 63.5]	70.5 [67.0, 74.1]	12.5*** [6.2, 18.8]	30.6 [23.9, 37.3]	41.3 [34.1, 48.6]	39.6 [32.5, 46.6]	10.4* [1.8, 19.0]	9.8* [1.2, 18.5]
No nocturnal bowel movement	43.1 [37.7, 48.5]	67.3 [63.7, 70.9]	24.2*** [17.9, 30.5]	30.1 [23.4, 36.7]	41.9 [34.7, 49.1]	43.5 [36.3, 50.6]	12.0** [3.3, 20.6]	14.8*** [6.1, 23.5]
No sleep interruption	40.3 [35.0, 45.6]	62.3 [58.6, 66.0]	22.0*** [15.6, 28.4]	30.1 [23.4, 36.7]	39.7 [32.5, 46.8]	44.0 [36.9, 51.2]	9.5* [0.9, 18.1]	15.3*** [6.6, 24.0]
Comprehensive symptom resolution	9.5 [6.3, 12.7]	21.8 [18.7, 25.0]	12.2*** 7.8, 16.7	14.2 [9.1, 19.3]	23.5 [17.3, 29.7]	19.4 [13.7, 25.1]	8.9* [1.5, 16.3]	5.7 [-1.8, 13.1]

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

IL-23 Inhibitors and Fatigue and Bowel Urgency in Moderate-to-Severe CD – VIVID-1 Trial (MIRI)



** $p < 0.01$, **** $p < 0.0001$

FACIT-Fatigue = functional assessment of chronic illness therapy – fatigue; NRS = numeric rating scale.

Travis S, et al. *J Crohns Colitis*. 2024;18(Supplement 1):i21-i23.

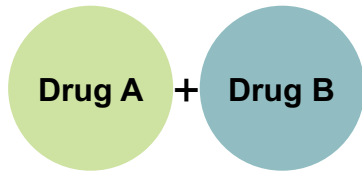
How do we position IL-23 therapies in practice?



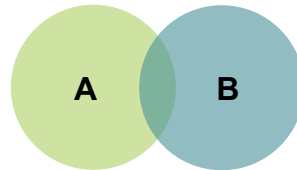
Faculty Discussion

Considerations for Combination Therapy

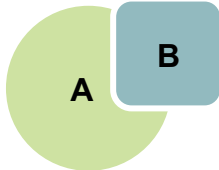
Independent MOAs



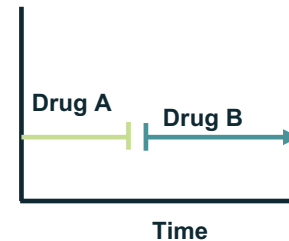
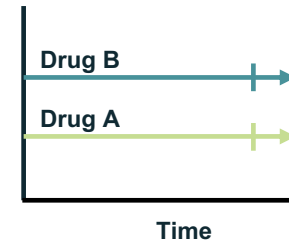
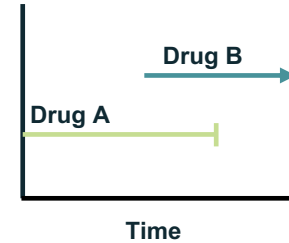
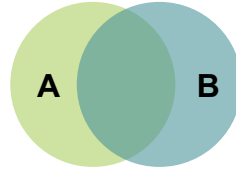
Medium activity overlap/crosstalk



Complementary MOAs



High activity overlap/crosstalk



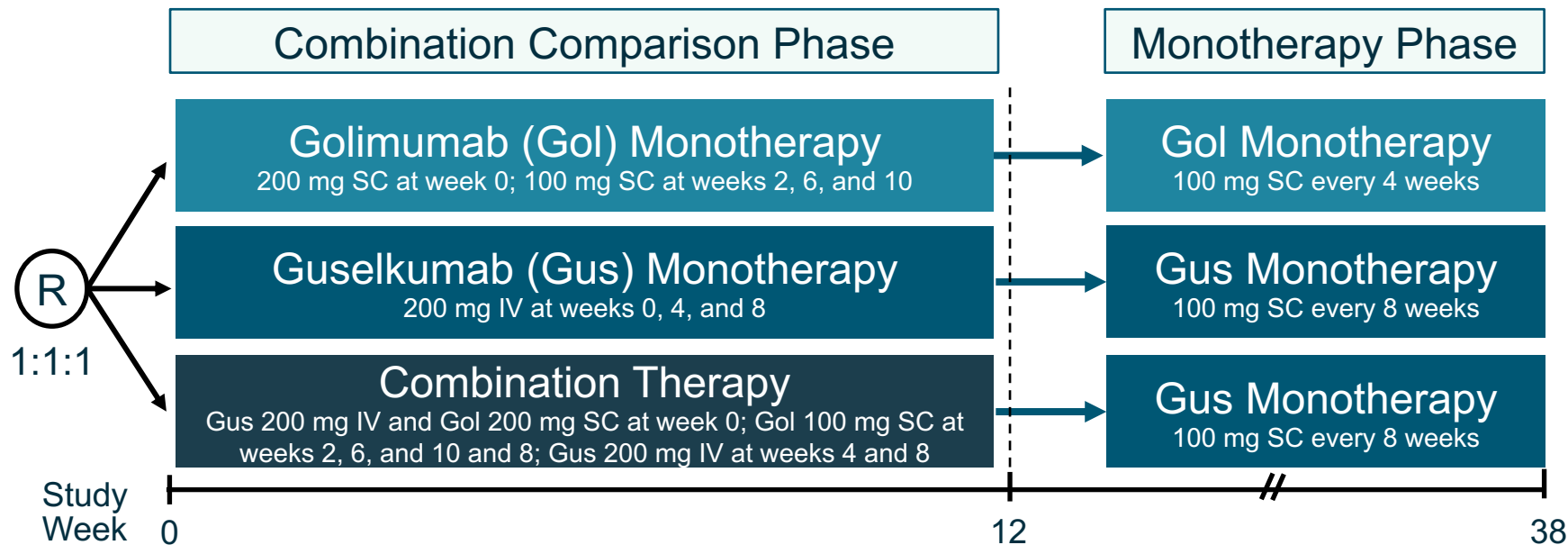
Advanced Combination Therapy



- ▶ Anti-IL-23 + anti-TNF
 - ▶ VEGA
 - ▶ DUET-CD
 - ▶ DUET-UC
- ▶ Anti-integrin + anti-TNF + methotrexate
 - ▶ EXPLORER

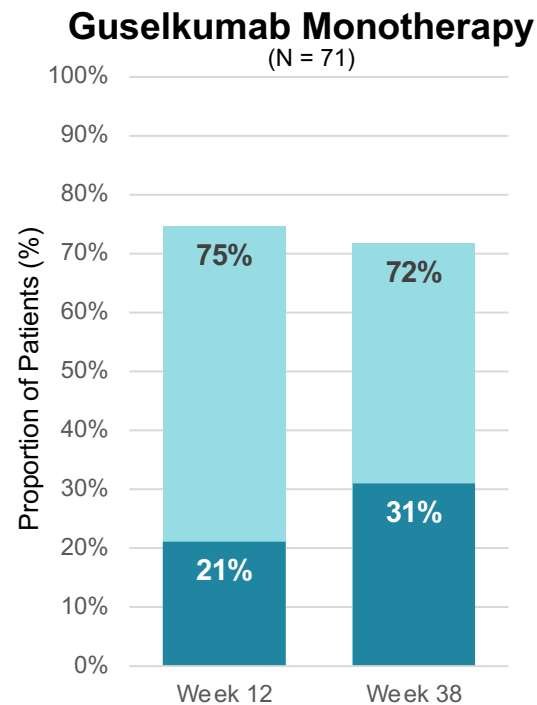
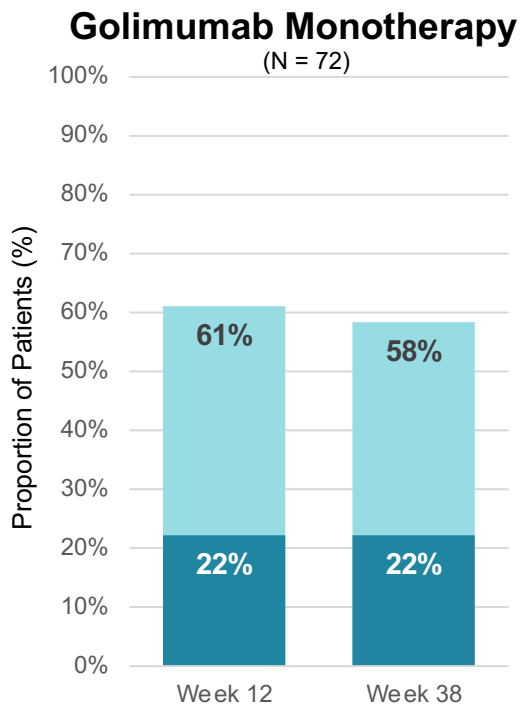
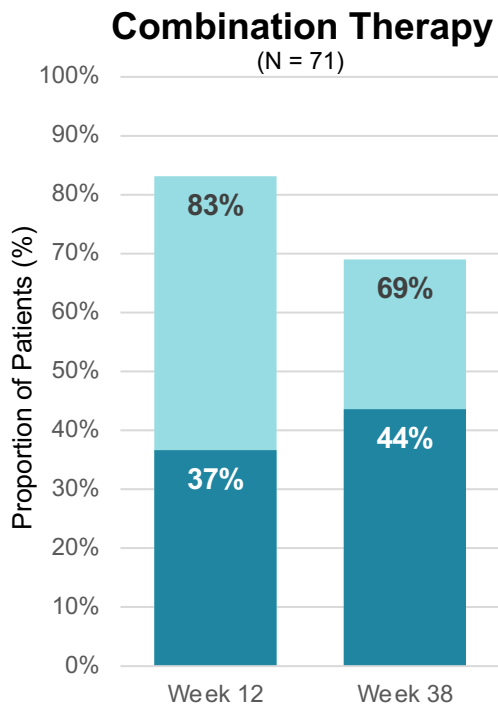
VEGA: Golimumab, Guselkumab*, or Combination Therapy in UC

- ▶ Included TNF-naïve patients refractory to conventional therapy (e.g., immunomodulators, corticosteroids)



*Guselkumab is not FDA-approved for the treatment of UC.
Feagan BG, et al. *Lancet Gastroenterol Hepatol.* 2023;8(4):307-320.

VEGA: Golimumab, Guselkumab*, or Combination Therapy in UC



■ Clinical response (full Mayo score) ■ Clinical remission (full Mayo score)

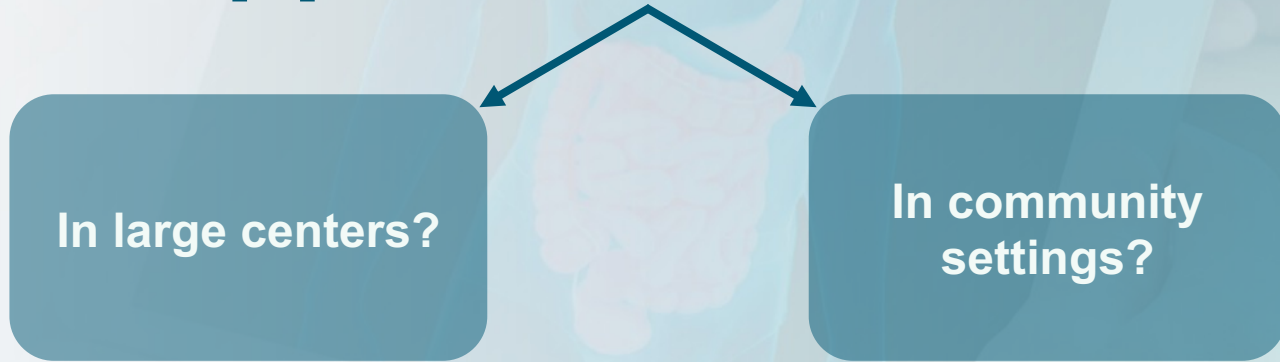
*Guselkumab is not FDA-approved for the treatment of UC.
Feagan BG, et al. *Lancet Gastroenterol Hepatol.* 2023;8(4):307-320.

**How do we translate this data
into clinical practice?**



Faculty Discussion

How do we optimize an interdisciplinary team approach to care?



Faculty Discussion

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- ▶ Consider the underlying mechanisms behind the inflammatory pathways implicated in IBD, such as those impacting IL-23 and Th17 pathways, when considering treatment options
- ▶ Differentiate between IL-23-targeted therapies and their unique characteristics to individualize and optimize patient treatment
- ▶ Increase utilization of clinical data from treatments targeting IL-23 when developing treatment plans for patients with IBD



QUESTIONS & ANSWERS

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

Additional Resources

The background of the slide features a teal-tinted image of a person's hands holding a tablet. The tablet screen displays a 3D anatomical model of a human torso, showing the ribcage and internal organs. The overall scene is set against a teal background with a faint stethoscope and a pill visible on the right side.

To learn more, and to access additional resources, including an interactive 3D digital animation, visit www.cmeoutfitters.com

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