LIVESTREAM

The Force Awakens—Unlocking the Potential of IL-23–Targeted Therapies in the Treatment of IBD

SYLLABUS & COURSE GUIDE

A Free, 90-minute Live Activity
Premiere Date: Sunday, May 4, 2025
6:30 PM–8:00 PM PT | 9:30 PM–11:00 PM ET



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FACULTY
Miguel Regueiro, MD (Moderator)
Marita Kametas, MSN, APN, FNP-BC, CMSRN, COCN
Edward V. Loftus, Jr., MD
Millie D. Long, MD, MPH

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Information for Participants

STATEMENT OF NEED

The therapeutic armamentarium for inflammatory bowel disease (IBD) is expanding with the advent of anti–IL-23 therapies. The unique clinical profiles of new and emerging agents make it necessary that treatment decisions are guided by evolving knowledge of the science surrounding cytokine-targeting therapies. With an established efficacy in treating both bio-naïve and bio-experienced patients, and the increased flexibility in administration routes (intravenous vs subcutaneous), the growing class of distinctive IL-23–targeting agents amplifies the importance of clinicians utilizing the most current research and guidelines when determining with patients where to best position IL-23 agents in the treatment of their IBD.

In this CME Outfitters livestream symposium, faculty will examine the role of pro-inflammatory cytokines in the pathogenesis of IBD, discern differences in IL-23 binding among IL-23p19–targeted therapies, assess the safety and efficacy of IL-23p19–targeted therapies for the treatment of IBD, and explore when to incorporate IL-23p19–targeted therapies into the management of patients with IBD.

LEARNING OBJECTIVES

At the conclusion of this activity, learners will be able to better:

- Assess the role of pro-inflammatory cytokines such as IL-23 in the pathogenesis of IBD
- Differentiate IL-23 binding among the IL-23p19–targeted therapies
- Evaluate the safety and efficacy of IL-23p19–targeted therapies available for the treatment of IBD
- Incorporate IL-23p19–targeted therapies into the multidisciplinary management of appropriate patients with IBD

FINANCIAL SUPPORT

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

TARGET AUDIENCE

Gastroenterologists, gastroenterology fellows/trainees, physician associates (PAs), nurse practitioners (NPs), and nurses

Faculty

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

Miguel Regueiro, MD, is the chair of the Digestive Disease and Surgery Institute at Cleveland Clinic in Ohio, as well as a professor in the Department of Medicine of Cleveland Clinic Lerner College of Medicine at Case Western Reserve University. His main clinical and research interest is inflammatory bowel diseases (IBD) with a focus on the natural course of Crohn's disease and ulcerative colitis. He leads research on postoperative prevention of Crohn's disease as well as on developing new models of health care, including the first-of-its kind specialty medical home for IBD.

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

Marita Kametas, MSN, APN, FNP-BC, CMSRN, COCN, is a family nurse practitioner and ostomy specialist who treats adult patients with inflammatory bowel disease (IBD). She serves as the manager for the Advanced Practice Gastroenterology Service at the University of Chicago in Illinois. She volunteers her time as a mentor for the Crohn's and Colitis Advanced Practice Provider (APP) mentorship program and delivers empowering lectures to APPs to optimize their care of patients with IBD. She was awarded the honor of Distinguished APP of 2023 at the University of Chicago. She currently is pursuing a doctorate in nursing practice and a master's degree in public health at Johns Hopkins University in Baltimore, Maryland, with an emphasis on diversity, equity, and inclusion.

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

Edward V. Loftus, Jr., MD, is a gastroenterologist with extensive experience as a lecturer and clinician researcher in the field of inflammatory bowel diseases. He is the Maxine and Jack Zarrow Family Professor of Gastroenterology Specifically for IBD at Mayo Clinic College of Medicine and Science in Rochester, Minnesota. Dr. Loftus has published more than 475 original articles, book chapters, and editorials, and over 700 abstracts. He was awarded the American Gastroenterologist Association's Distinguished Clinician Award and the Research Mentor Award in Immunology, Microbiology, and Inflammatory Bowel Diseases (IMIBD) in 2019. Dr. Loftus has been the principal investigator on several funded studies focusing on the epidemiology and natural history of inflammatory bowel disease and has served as the local PI on multiple clinical trials of investigational agents for IBD. He currently serves on the steering committees of several clinical development programs in IBD.

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

Millie D. Long, MD, MPH, is board certified in internal medicine, preventive medicine, and gastroenterology. She received her medical degree from University of Virginia in 2002. She then completed residency in internal medicine and a chief residency at University of Alabama–Birmingham. She completed fellowships in gastroenterology and hepatology, preventive medicine, and inflammatory bowel disease, all at University of North Carolina. She is currently a professor of medicine in the Department of Medicine and director of the Gastroenterology and Hepatology Fellowship Program at University of North Carolina–Chapel Hill.

Dr. Long's clinical practice is at the UNC Multidisciplinary Inflammatory Bowel Diseases (IBD) Center. Her research interests include prevention of complications of IBD, women's health, and clinical epidemiology. Dr. Long has contributed to more than 200 peer-reviewed publications, book chapters, and review articles, and to the medical literature. She is the current co-editor in chief of the *American Journal of Gastroenterology*. She also serves as an invited reviewer for journals such as *Inflammatory Bowel Diseases* and *Gastroenterology*.

Dr. Long is a fellow of the American College of Gastroenterology, where she serves on the board of trustees. She is also a fellow of the American Gastroenterological Association and the Crohn's and Colitis Foundation, where she co-chairs the Clinical Research Alliance.

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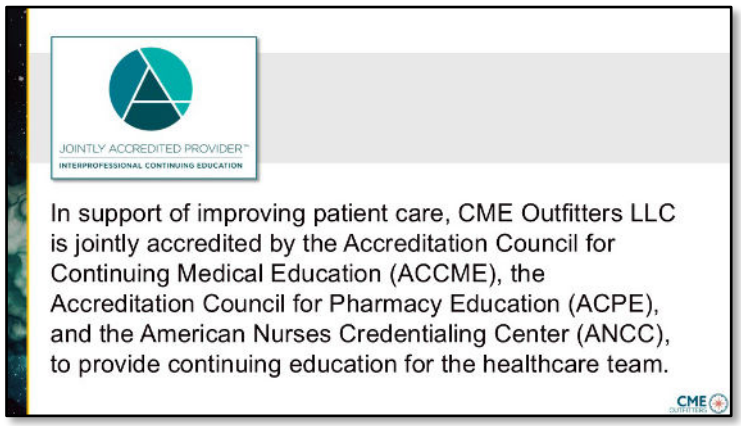
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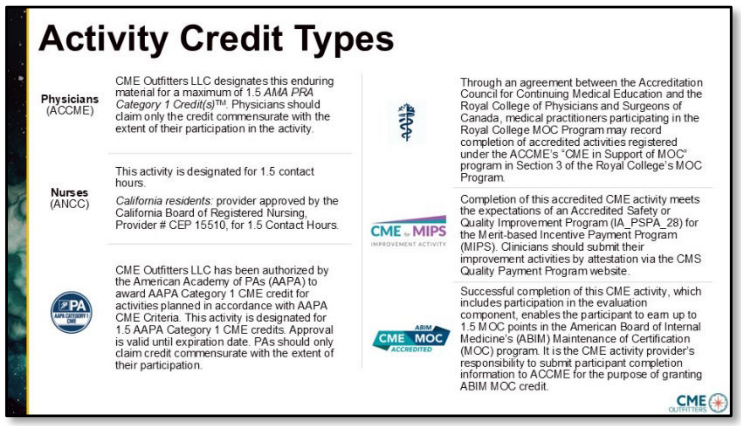
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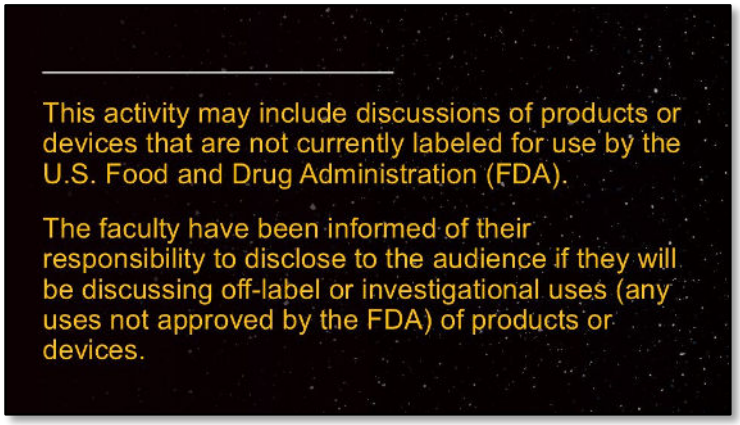
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To Ask a Question

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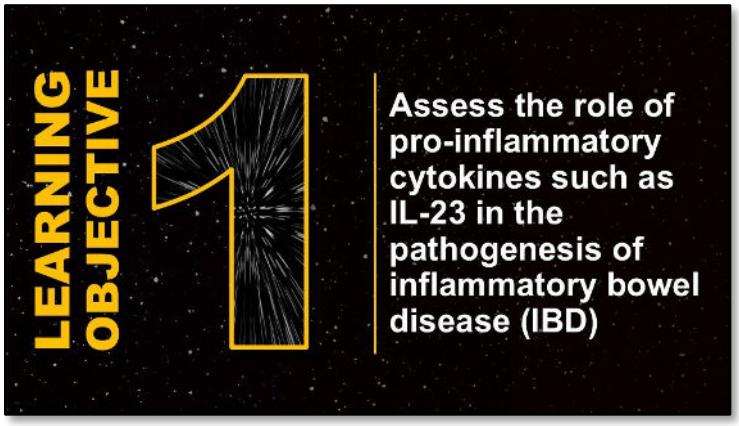
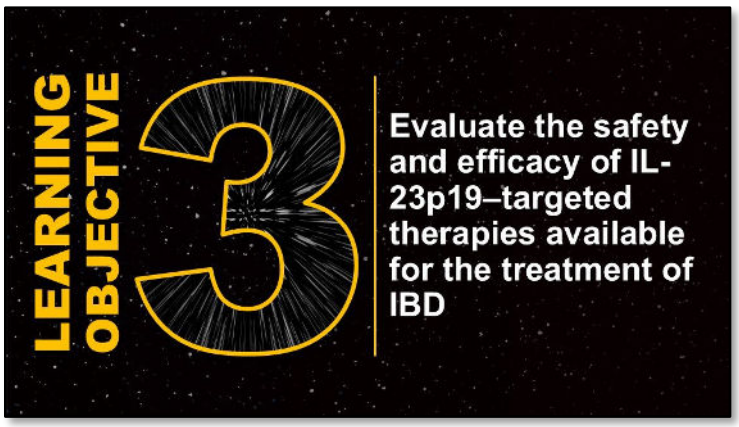



LEARNING OBJECTIVE
2
Differentiate IL-23 binding among the IL-23p19–targeted therapies


LEARNING OBJECTIVE
3
Evaluate the safety and efficacy of IL-23p19–targeted therapies available for the treatment of IBD


LEARNING OBJECTIVE
4
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
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Navigating the IL-23/Th17 Pathway and the Role of IL-23 Inhibitors in IBD

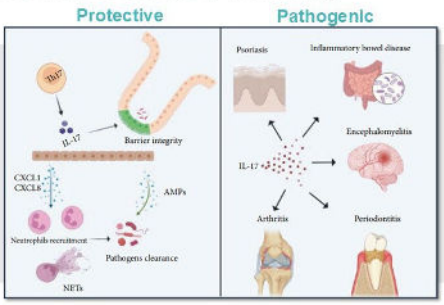
Why Target IL-23 in IBD?

- 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.

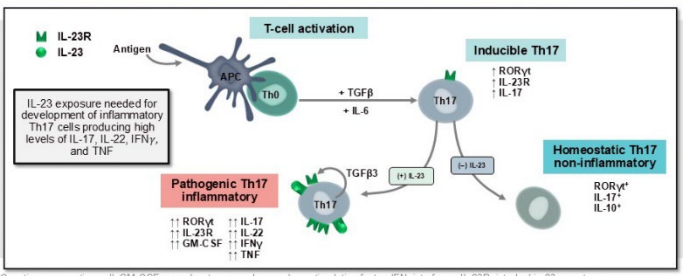
Role of Th17 and IL-17

Pathogenic and Protective Immunity

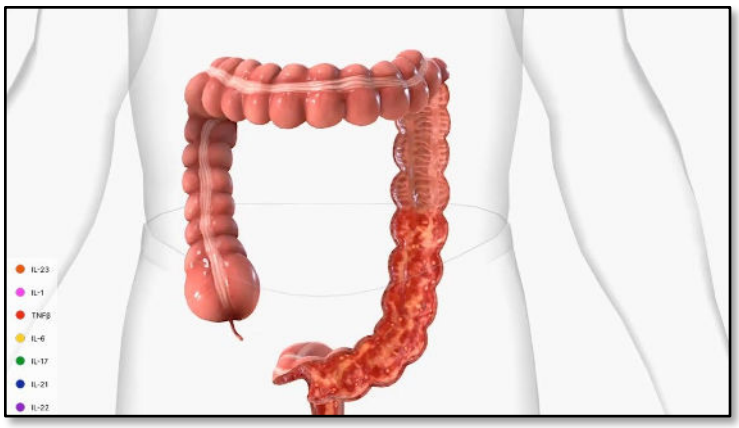


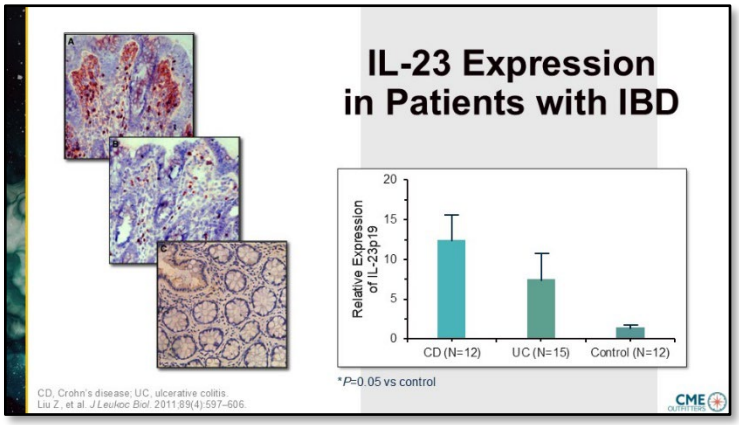
AMPs, antimicrobial peptides; IL, interleukin; NETs, neutrophil extracellular traps; Th, T helper cell.
Sun L, et al. *J Immunol Res*. 2023;1:3360310.

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
A
B
C
Relative Expression of IL-23p19
20
15
10
5
0
CD (N=12)
UC (N=15)
Control (N=12)
*P=0.05 vs control
CD, Crohn's disease; UC, ulcerative colitis.
Liu Z, et al. J Leukoc Biol. 2011;89(4):597–606.
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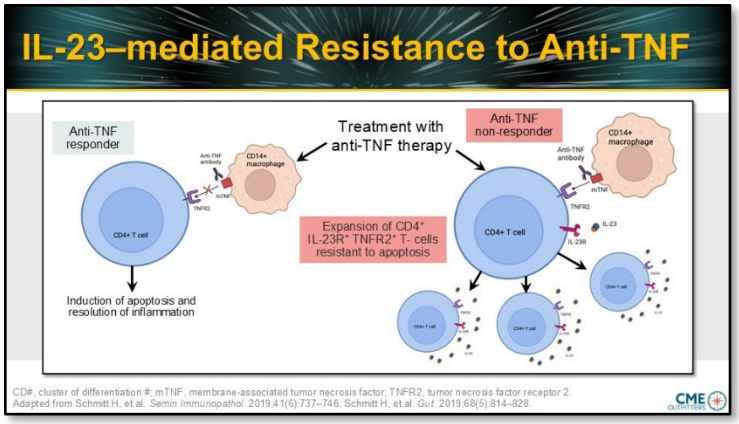
IL-23–mediated Resistance to Anti-TNF
Anti-TNF responder
Treatment with anti-TNF therapy
Anti-TNF non-responder
CD14+ macrophage
Anti-TNF antibody
mTNF
TNFR2
CD4+ T cell
IL-23
IL-23R
Expansion of CD4+ IL-23R+ TNFR2+ T- cells resistant to apoptosis
Induction of apoptosis and resolution of inflammation
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.
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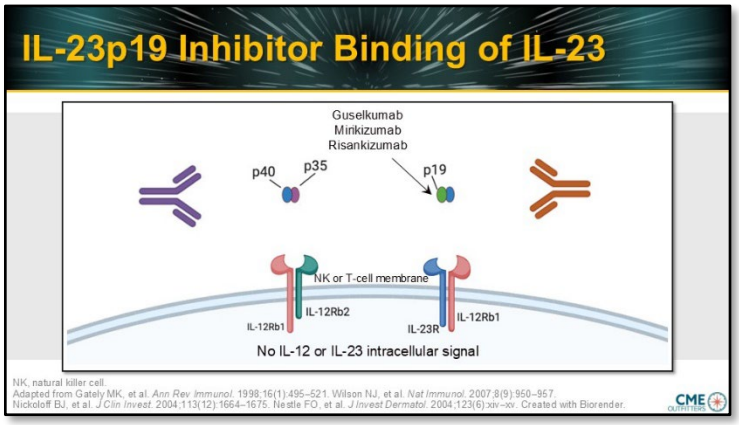
IL-23p19 Inhibitor Binding of IL-23
Guselkumab
Mirikizumab
Risankizumab
p40
p35
p19
NK or T-cell membrane
IL-12Rb1
IL-12Rb2
IL-23R
IL-12Rb1
No IL-12 or IL-23 intracellular signal
NK, natural killer cell.
Adapted from Gately MK, et al. Ann Rev Immunol. 1998;16(1):495–521. Wilson NJ, et al. Nat Immunol. 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.
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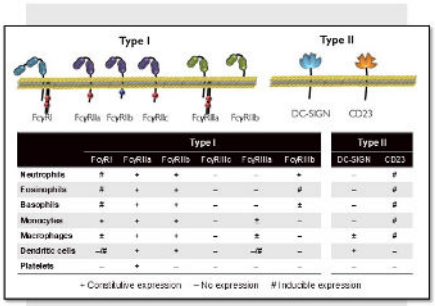
Importance of Fcγ Receptors and CD64 Receptors

- 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	FcγRIIc	FcγRIIIa	FcγRIIb	DC-SIGN	CD23
Neutrophils	#	+	+	–	–	+	–	#
Eosinophils	#	+	+	–	–	#	–	#
Basophils	#	+	+	–	–	±	–	#
Monocytes	+	+	+	–	+	–	–	#
Macrophages	±	+	+	–	±	–	±	#
Dendritic cells	–/#	+	+	–	–/#	–	+	–
Platelets	–	+	–	–	–	–	–	–

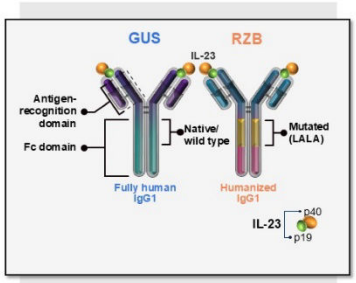
+ Constitutive expression – No expression # Inducible expression

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)

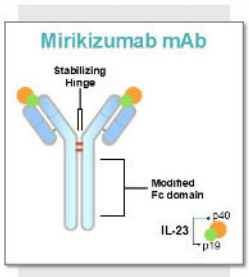
- GUS and RZB are monoclonal antibodies (mAbs) that selectively target the p19 subunit of IL-23
- Both have shown efficacy in the treatment of inflammatory bowel diseases
- GUS and RZB have differences in the Fc region that affect binding to Fc-gamma receptors
  - GUS is a fully human IgG1 with a native 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):i25–i26.
Wojtal KA, et al. *PLoS One*. 2012;7(8):e43361. Pang Y, et al. *Clin Transl Sci*. 2024;17(1):e13706.

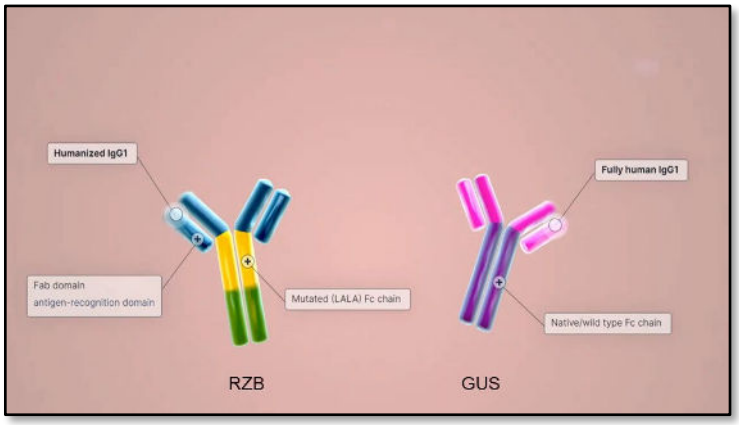
Differences between IL-23p19 Antibodies

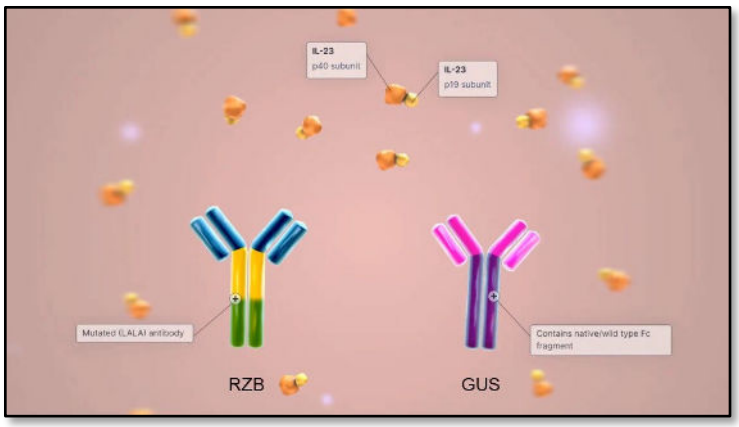
Mirikizumab (MIRI)

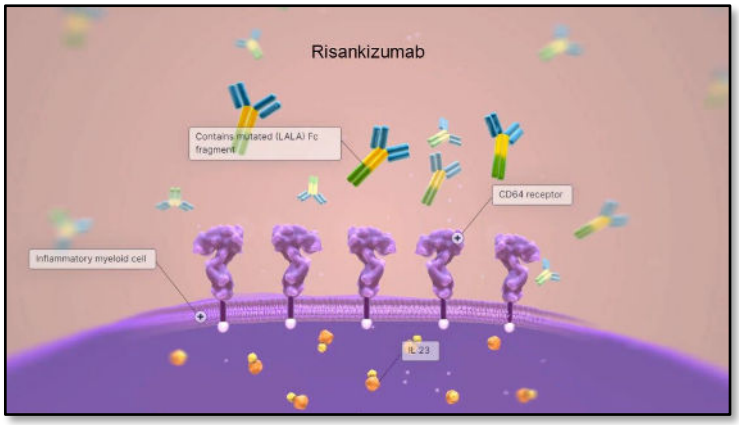


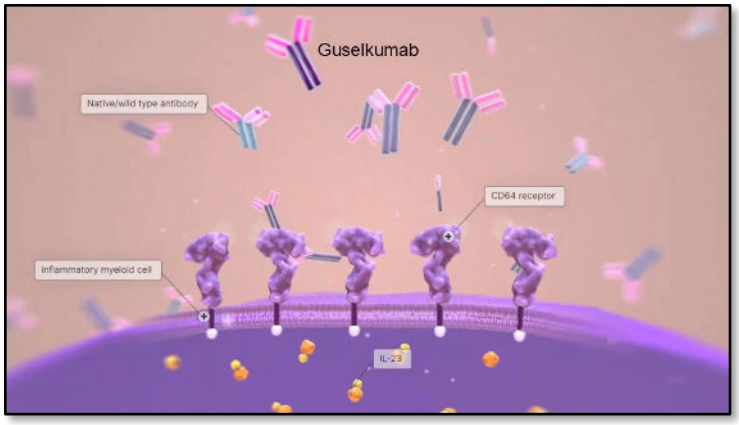
- Humanized IgG4 mAb that selectively binds to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor
- The Fc domain of MIRI was modified to significantly reduce FcγR binding and interaction

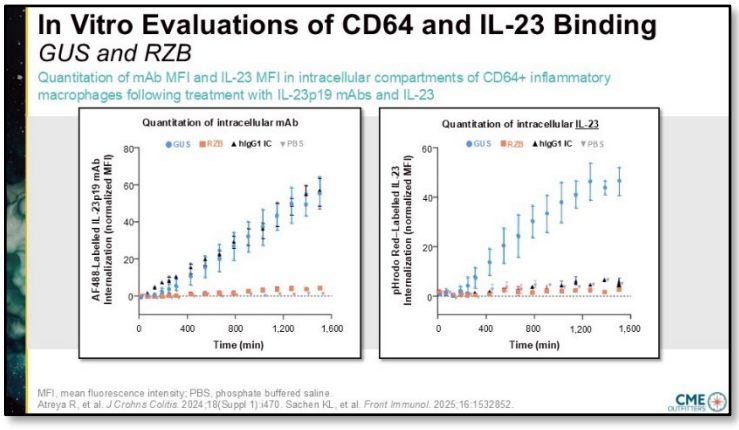
Stohl WR. *Antib Ther*. 2024;7(2):132–156.




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


Risankizumab
Contains mutated (LALA) Fc fragment
CD64 receptor
Inflammatory myeloid cell
IL-23

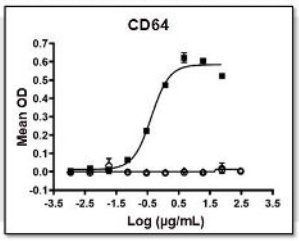

Guselkumab
Native/wild type antibody
CD64 receptor
Inflammatory myeloid cell
IL-23


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
Quantitation of intracellular mAb
GUS RZB hIgG1 IC PBS
AF488-Labelled IL-23p19 mAb Internalization (normalized MFI)
Time (min)
Quantitation of intracellular IL-23
GUS RZB hIgG1 IC PBS
pHrodo Red–Labelled IL-23 Internalization (normalized MFI)
Time (min)
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
CME OUTFITTERS

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



- Positive control
- Mirikizumab
- Negative control

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

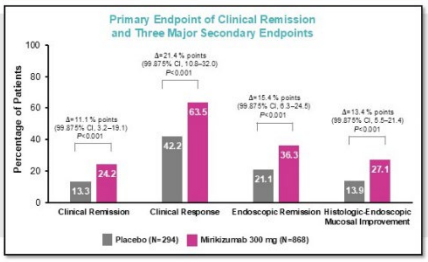
She is initially treated with mesalamine but experiences no improvement in symptoms.

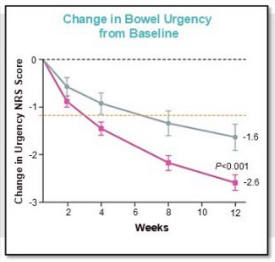
CRP, C-reactive protein.

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

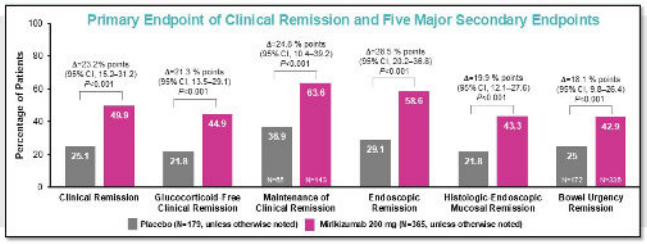




NRS, numeric rating scale.
D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444–2455.

CME OUTFITTERS

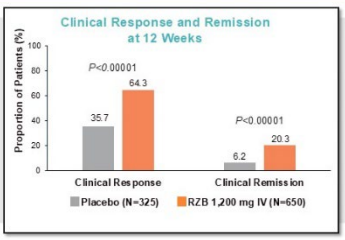
Mirikizumab Maintenance in UC
LUCENT-2 Week 40 Endpoints

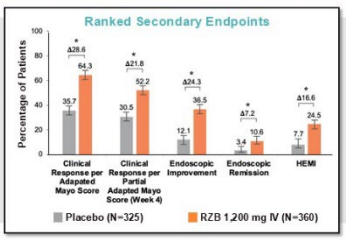


Clinical remission, stool frequency (SF)=0, or SF=1 with a >1-point decrease from baseline; rectal bleeding (RB)=0; endoscopic subscore (ES)=0 or 1 (excluding friability); endoscopic remission: ES=0 or 1 (excluding friability); clinical remission at week 40; remission of symptoms at week 28; and no glucocorticoid use for ≥12 weeks before week 40.
D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444–2455.

CME OUTFITTERS

Risankizumab Induction in UC
INSPIRE

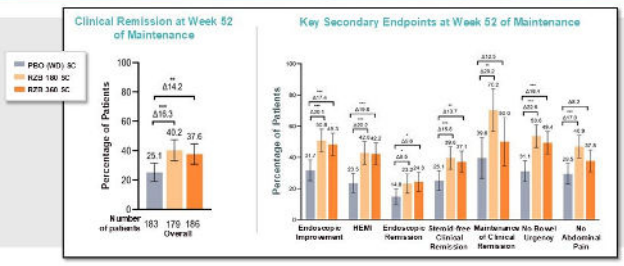




*P<0.00001 vs PBO.
Clinical remission per Adapted Mayo Score is defined as stool frequency subscore (SFS) ≤1 and not greater than baseline, rectal bleeding subscore (RBS) of 0 and ES ≤1 without friability. Clinical response is defined as a decrease from baseline in the Adapted Mayo score ≥2 points and ≥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.

CME OUTFITTERS

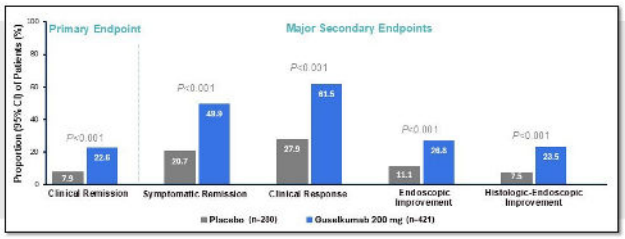
Risankizumab Maintenance in UC
COMMAND – Week 52 Endpoints



*P≤0.05; **P≤0.01; ***P≤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.

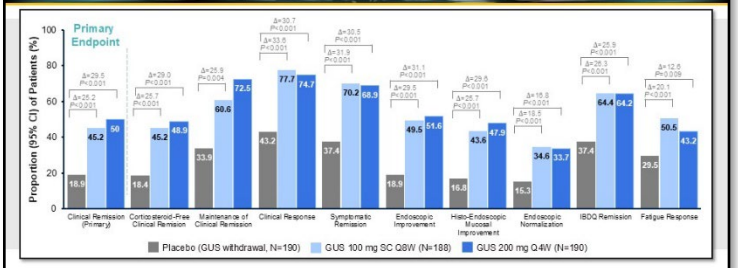
CME OUTFITTERS

Guselkumab Induction in UC
QUASAR Phase III Week 12 Endpoints



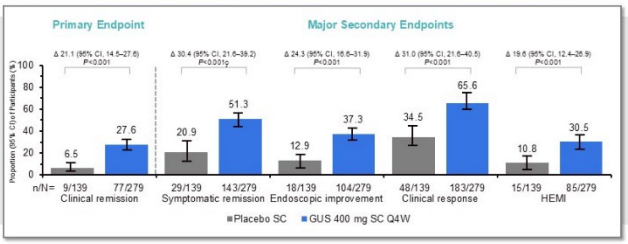
Clinical remission defined as a Mayo SFS of 0 or 1 with no increase from baseline, an RBS of 0, and a Mayo ES of 0 or 1 with no friability.
Rubin DT, et al. *Lancet*. 2025;405(10472):33–49.

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 Induction in UC*
ASTRO Phase III Week 12 Endpoints



*Guselkumab is not approved for subcutaneous induction therapy in UC.
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.

Now, what treatment would you suggest for our patient, Maya?

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

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.

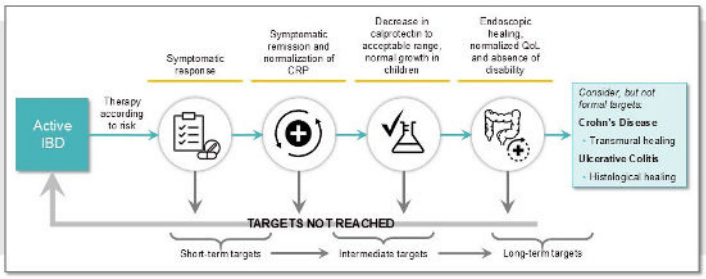
She is currently being treated with adalimumab weekly, but has experienced several flare-ups in the past year, including 2 hospitalizations.

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?

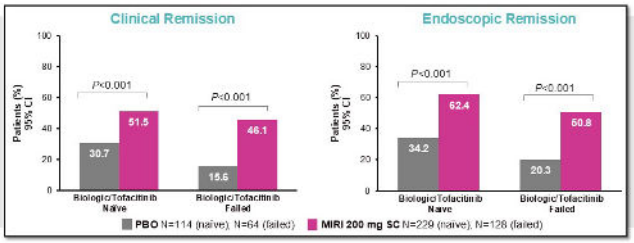
A. Add prednisone to current treatment
B. Switch to infliximab
C. Switch to vedolizumab
D. Switch to ustekinumab
E. Switch to IL-23p19 inhibitor
F. Switch to S1P modulator
G. Switch to JAK inhibitor
H. I'm not sure

When to Switch Therapies



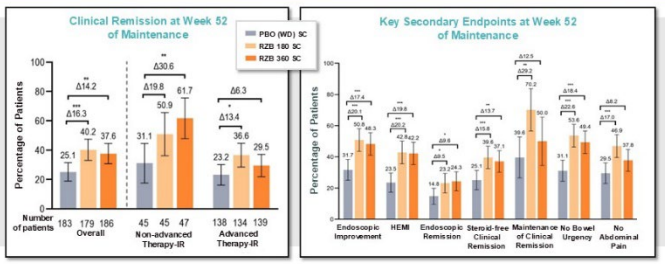
QoL, quality of life.
Turner D, et al. *Gastroenterol*. 2021;160(5):1570–1583.

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



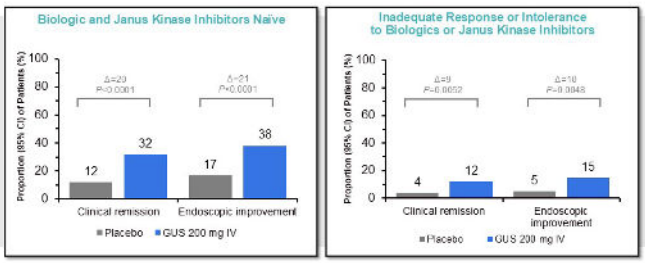
D'Haens G, et al. *N Engl J Med*. 2023;388(26):2444–2455.

Risankizumab Maintenance in UC *COMMAND*



*P≤0.05; **P ≤0.01; ***P≤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.

GUS in Previously Treated 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.

CME OUTFITTERS

Now, what treatment would you suggest for our patient, Maya?

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

CME OUTFITTERS

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

CME OUTFITTERS

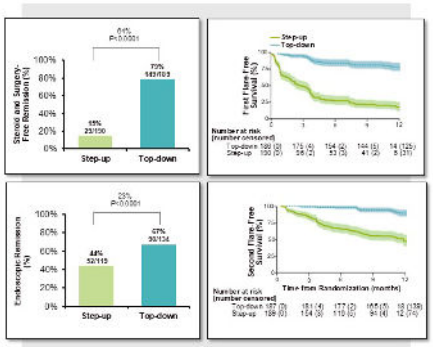
ESR, erythrocyte sedimentation rate.

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

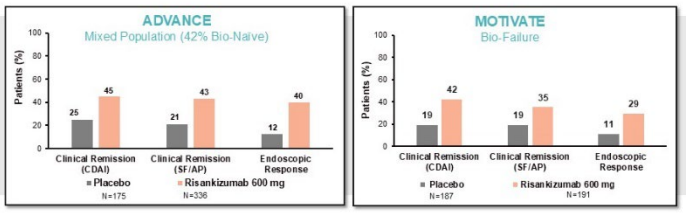
- Median of 12 days (IQR 0–191) from time of diagnosis to enrollment and start GCC (-2 weeks to randomized)
- Median of 15 days (IQR 13–20) days from time of randomization and first dose of infliximab



IQR, interquartile range; GCC, glucocorticoids.

Noor V, et al. *Lancet Gastroenterol Hepatol*. 2024;9(5):415–427.

ADVANCE and MOTIVATE
RZB Induction in CD

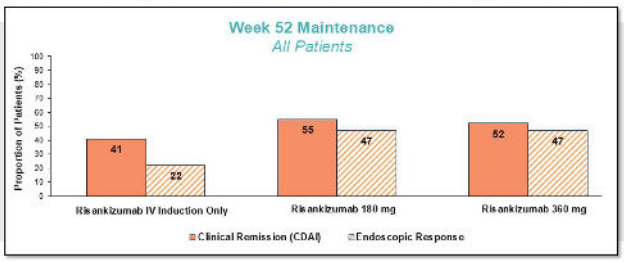


Clinical responders defined as ≥30% decrease in average daily stool frequency or abdominal pain score (APS) and not worse than baseline; endoscopic response defined as >50% decline in simple endoscopic score (SES-CD) vs baseline by central reviewer (or in patients with SES-CD of 4 at baseline, ≥2-point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

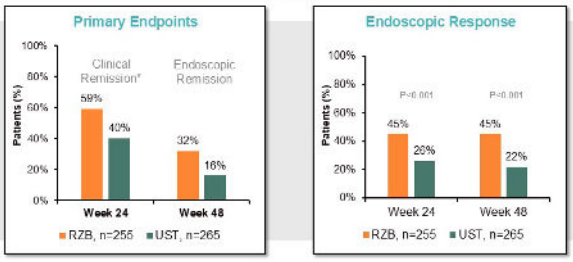
FORTIFY
RZB Maintenance in CD



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.

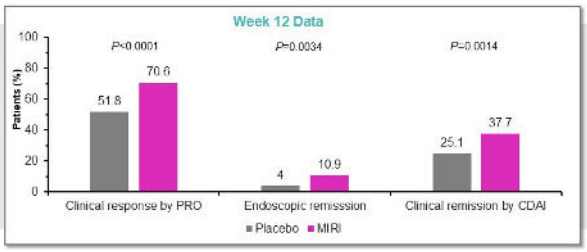
Ferrante M, et al. *Lancet*. 2022;399(10340):2031–2046.

RZB vs UST in Patients with CD
Phase IIIb SEQUENCE Trial



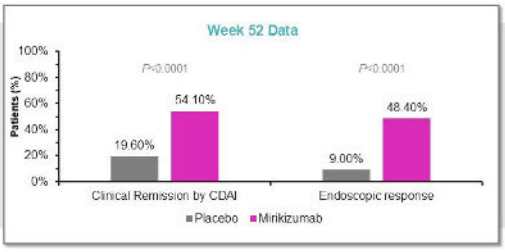
* = noninferiority met.
Peyrin-Biroulet L, et al. *N Engl J Med*. 2024;391:213–223.

VIVID-1
MIRI Induction in CD



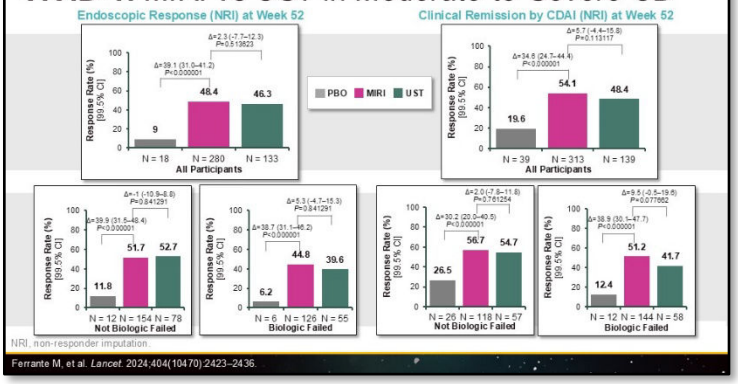
Ferrante M, et al. *Lancet*. 2024;404(10470):2423–2436.

VIVID-1
MIRI Maintenance in CD



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

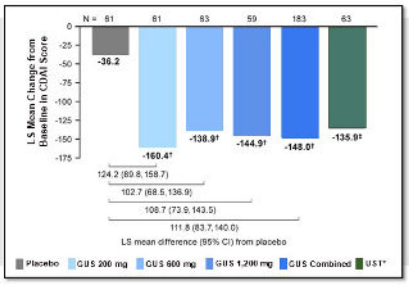
VIVID-1: *MIRI vs UST in Moderate-to-Severe CD*



NRI, non-responder imputation.

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

GUS vs UST in CD at 12 Weeks
GALAXI-1



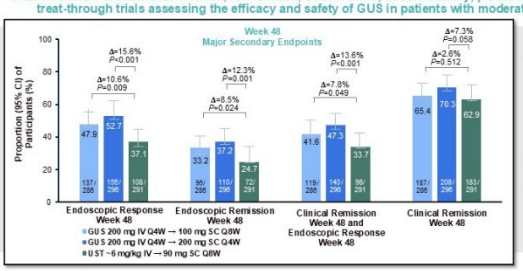
Primary Endpoint
- Change from baseline in CDAI score at week 12

- 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

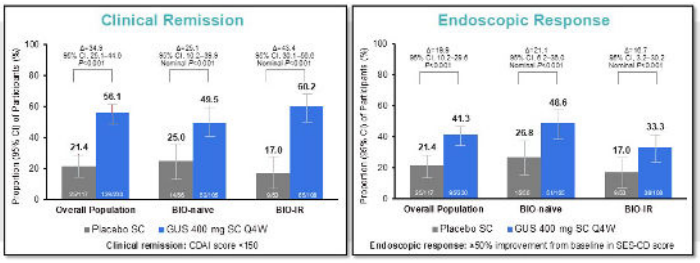
Endoscopic response: ≥50% improvement from baseline in SES-CD or SES-CD ≤2

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

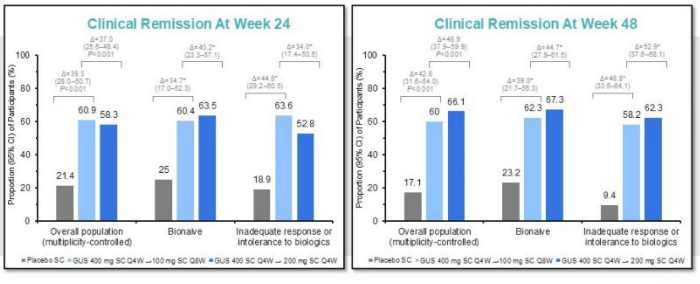
Panaccione R, et al. American College of Rheumatology (ACR) Convergence 2024. Abstract 1136. https://acrabstracts.org/abstract/efficacy-and-safety-of-guselkumab-therapy-in-patients-with-moderately-to-severely-active-crohns-disease-results-of-the-galaxi-2-3-phase-3-studies/

Subcutaneous GUS in CD
Phase III GRAVITI Study Responses at Week 12



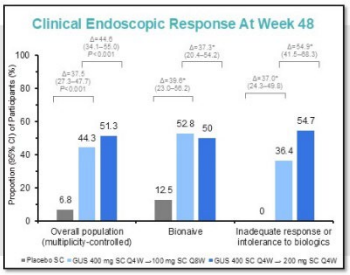
Hart A, et al. *Gastroenterol*. March 18, 2025. Online ahead of print.

GRAVITI Study
Subcutaneous GUS in CD Week 24 and 48



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

GRAVITI Study
Subcutaneous GUS in CD Week 24 and 48



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

CME OUTFITTERS

Aligning on Treatment Goals with Patients

Provider Goals
- Safe and efficacious
  - Clinical response
  - Serologic response
  - Endoscopic response

Patient Goals
- Early remission of symptoms
- Durability of remission
- Convenient regimen
- Side effect profile

Patient in a rapid and durable remission on a safe and convenient regimen

CME OUTFITTERS

Education to Ensure Alignment

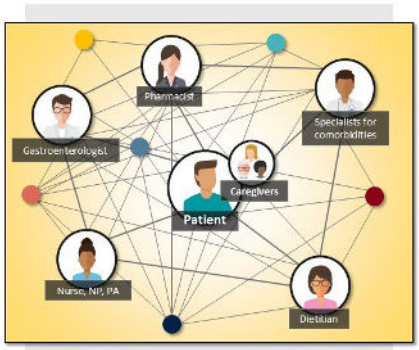
Treatment Selection
- Review the evidence in an accessible way
- Foster shared decision-making

Treat to Target
- Review goals during the treatment selection visit
- Lean into immediate goals for symptom management and long-term goals to prevent complications in the future

Treatment Maintenance
- Right dose of the right medication at the right time to capture adequate response
- Treatment intensity dictated by inflammatory burden—be dynamic

CME OUTFITTERS

Team-based Approach for the Management of IBD



CME OUTFITTERS

Now, how would you manage Ronald?

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

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.

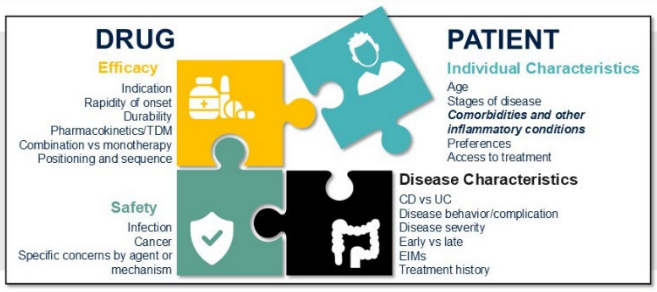
In recent months, symptoms of her CD have returned, including weight loss, bloody stools, and cramping, and imaging reveals active disease. Testing reveals a therapeutic infliximab level of 12 ug/mL.

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?



TDM, therapeutic drug monitoring; EIM, extraintestinal manifestation.

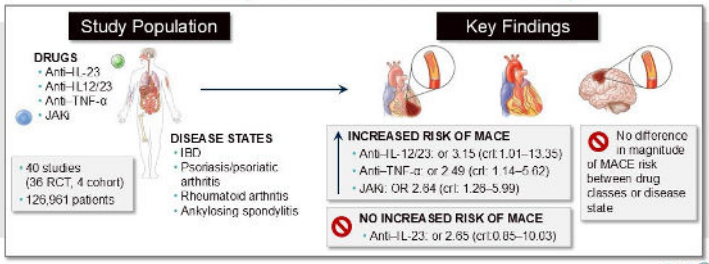
Safety of IL-23p19 Inhibitors in CD

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



Mallay 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

4362 enrolled

- Active RA
- Aged ≥50 years
- ≥1 CV risk factor

R 1:1:1

- Tofacitinib 5 mg bid + methotrexate
- Tofacitinib 10 mg bid + methotrexate
- Adalimumab or etanercept

Primary Endpoints
- MACE
- Malignancy

~5 years

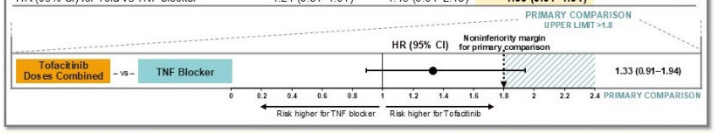
~4,000 patients or at least 1,500 patients completing 3 years of follow-up were required to achieve prespecified number of events: 103 MACEs (including cardiovascular death, nonfatal MI, and nonfatal stroke) and 138 malignancies (excluding NMSCs)

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

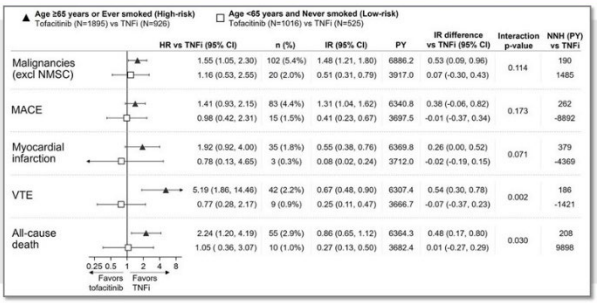
- On methotrexate (MTX) without adequate symptom control and ≥50 years old and ≥1 CV risk factor:
  - Current cigarette smoker, hypertension, diabetes mellitus, high-density lipoprotein <40 mg/dL
  - H/O coronary artery disease, H/O premature CVD or sudden death in first-degree relative
  - Extra-articular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



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

ORAL Surveillance Stratified by High Risk vs Low Risk
Impact of Age and Smoking

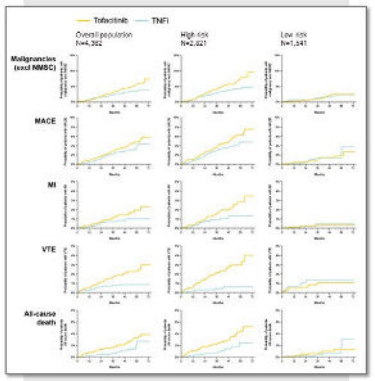


Kristensen LE, et al. *Ann Rheum Dis*. 2023;82(7):901–910.

CME OUTFITTERS

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



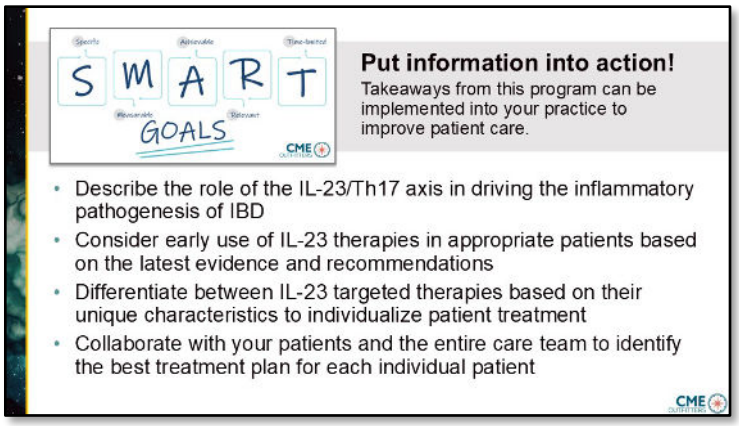
Kristensen LE, et al. *Ann Rheum Dis*. 2023;82(7):901–910.

Now, what treatment would you recommend for Clara?

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

CME OUTFITTERS


Faculty Discussion
Managing biologic-experienced Crohn's disease


S M A R T
GOALS
Put information into action!
Takeaways from this program can be implemented into your practice to improve patient care.
• Describe the role of the IL-23/Th17 axis in driving the inflammatory pathogenesis of IBD
• Consider early use of IL-23 therapies in appropriate patients based on the latest evidence and recommendations
• Differentiate between IL-23 targeted therapies based on their unique characteristics to individualize patient treatment
• Collaborate with your patients and the entire care team to identify the best treatment plan for each individual patient


QUESTIONS & ANSWERS
Thank you for joining us.
Don't forget to collect your credit.


CME OUTFITTERS
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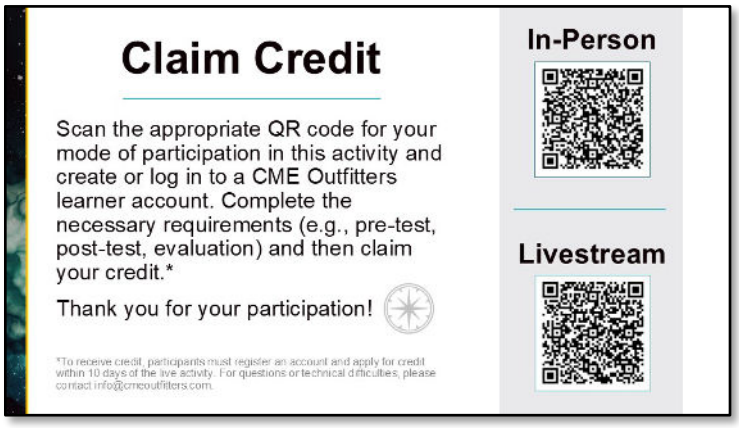
Free resources and education to educate health care professionals and patients
https://www.cmeoutfitters.com/gastrohub/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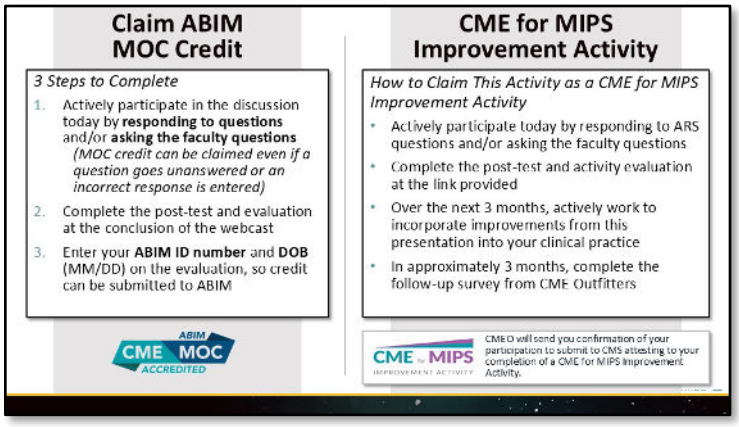
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THE FORCE AWAKENS
Unlocking the Potential of IL-23–Targeted Therapies in the Treatment of IBD
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