Optimizing Treatment in Moderate-to-Severe UC in the New Landscape

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The LAST ROSE WITH GASTROS

Ontario Association of Gastroenterology
Liver and IBD Review 2024

Disclosures

Christopher Ma

Consulting fees: AbbVie, Alimentiv, Amgen, AVIR Pharma Inc, Bristol Myers Squibb, Celltrion, Ferring, Fresenius Kabi, Janssen, McKesson, Mylan, Pendopharm, Pfizer, Prometheus Biosciences Inc., Roche, Sanofi, Takeda, Tillotts Pharma

Speaker's fees: AbbVie, Amgen, AVIR Pharma Inc, Alimentiv, Bristol Myers Squibb, Ferring, Fresenius Kabi, Janssen, Organon, Pendopharm, Pfizer, Sanofi, Takeda

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Objectives

Choosing the right therapeutic strategy

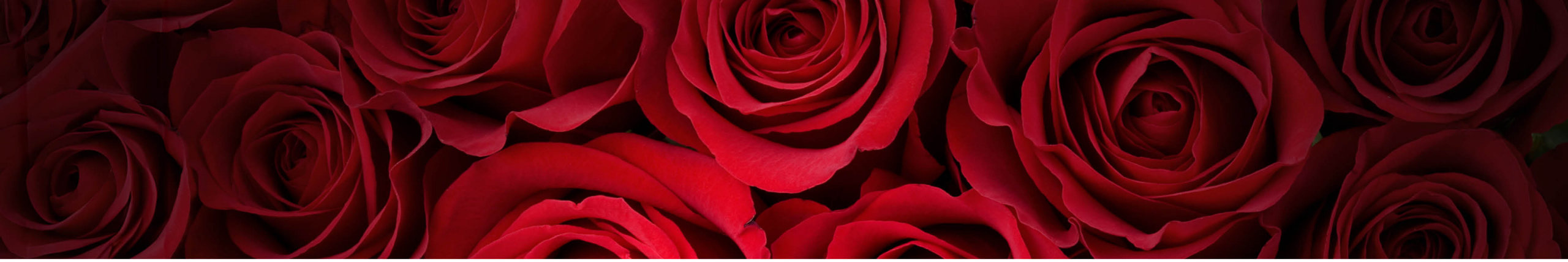
What are the pros and cons of **early escalation** to advanced therapy for UC versus **optimization of conventional therapy**?

Choosing an advanced oral therapy

Identify the appropriate place in therapy for **new oral targeted therapies** for managing moderate-to-severe UC

Choosing the right patient

Select patients who are appropriate candidates for targeted oral therapies, including **S1P receptor modulators**



Choosing the Right Therapeutic Strategy

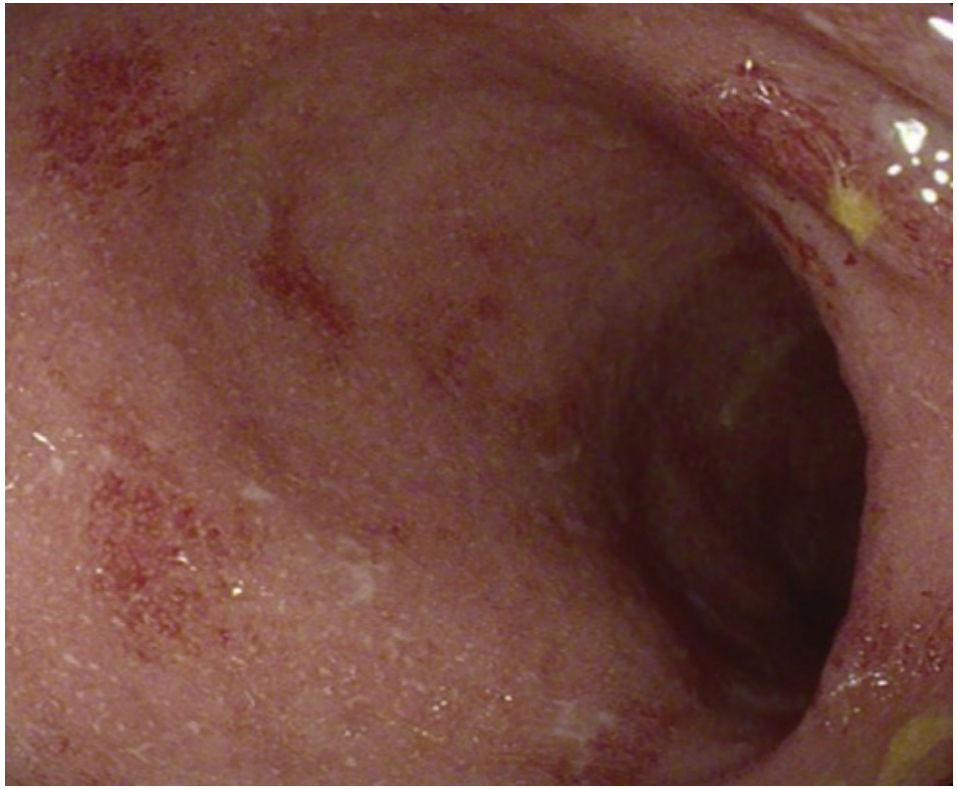
Case: Flaring UC

45M

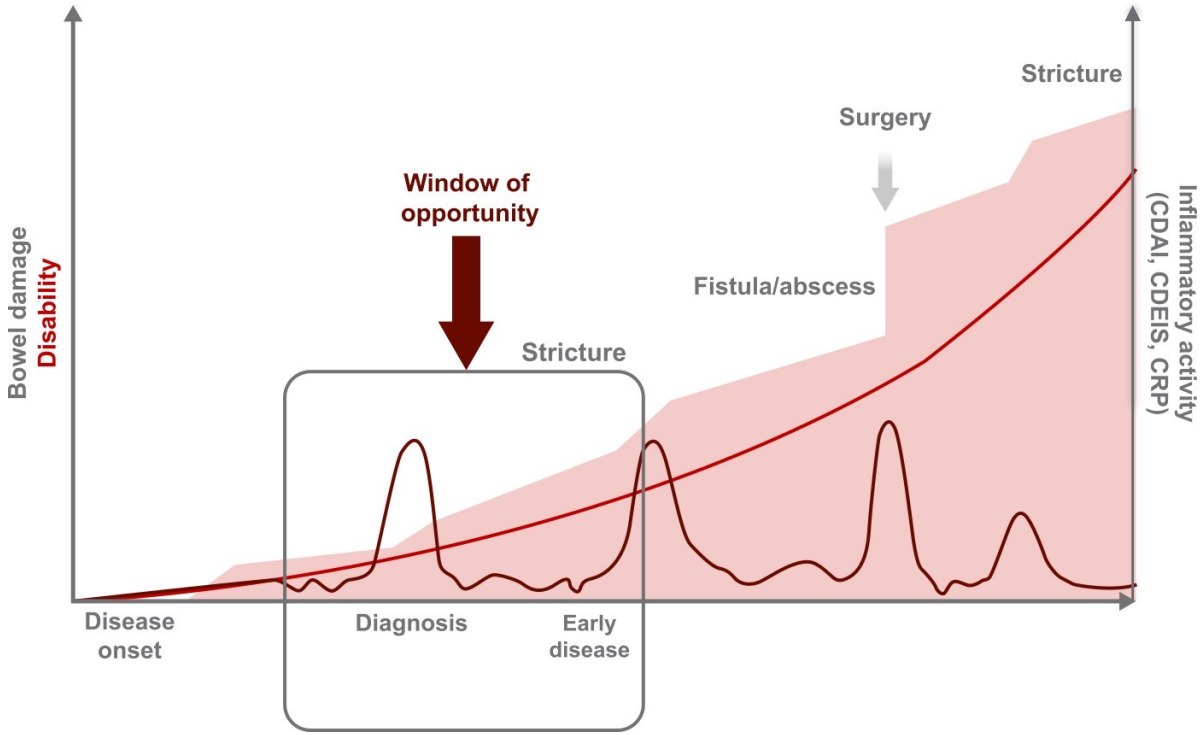
- Engineering professor, moved from Toronto to Calgary
- Diagnosed with left-sided UC 6 months ago
- Initially mild endoscopic appearance
- Complete clinical remission with 8 weeks of budesonide MMX® and started on 4.8g Mezavant daily

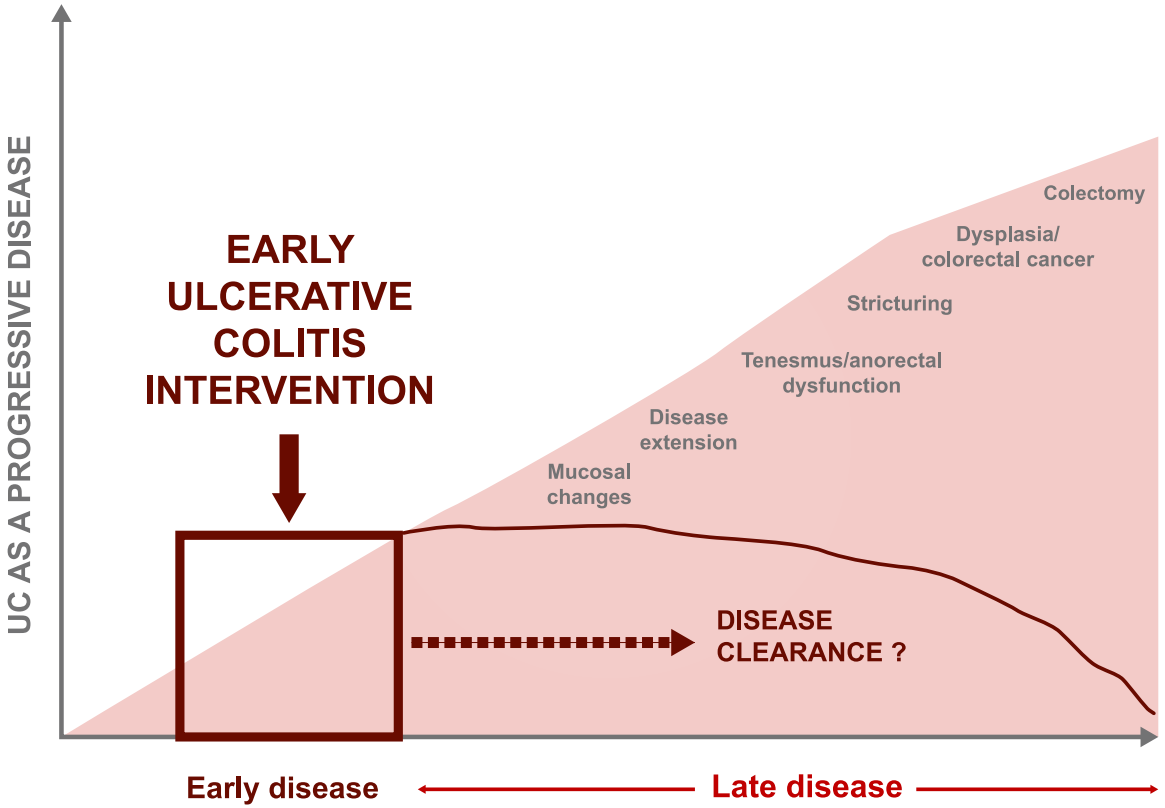
- Moved to Calgary, ran low on his prescription, dropped his dose to 2.4g Mezavant daily
- Now presents with 4-6 weeks of increasing stool frequency (3-5x/day), intermittent rectal bleeding
- Hb 140, albumin 36, CRP 5.0, fecal calprotectin 550 ug/g

What would you do next?



Is There a Window of Opportunity for Medical Therapy in Ulcerative Colitis?[1-3]





1. Solitano, V. et al. *J Clin Med.* 2020; 9(8) 2646. 2. Burisch, J. et al. *J Crohns Colitis*. 2023. 3. Ben-Horin, S. et al. *Gastroenterology*. 2022;162:482-94.

Is There a Window of Opportunity for Medical Therapy in Ulcerative Colitis?[1-3]

A CD trials

B UC trials

Study	No benefit for the outcomes	Definition of early disease	Follow-up duration	Patient numbers
Mandel *et al*. 2014	Hospitalization rates	≤3 years		*n* = 42
Nuij *et al*. 2013	Abscess formation, fistula formation, extraintestinal manifestations, mucosal healing, or surgery over a median	≤16 months	Median of 39 months	*n* = 27
Ma *et al*. 2016	Colectomy, UC-related hospitalization, clinical secondary loss of response	≤3 years	Median of 175.6 weeks	*n* = 115
Faleck *et al*. 2019	Clinical remission, corticosteroid-free remission, endoscopic remission	≤2 years	6 months	*n* = 437
Han *et al*. 2020	Need for colectomy, UC-related emergency room visits, UC-related hospitalization or new corticosteroid use	≤2 years	1.7 years	*n* = 698
Targownik *et al*. 2022	Hospitalization rates, adjusted cumulative rate of IBD hospitalizations, or all-cause hospitalizations, or surgery	≤2 years	Up to 5 years	*n* = 318

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Time since the disease onset, years

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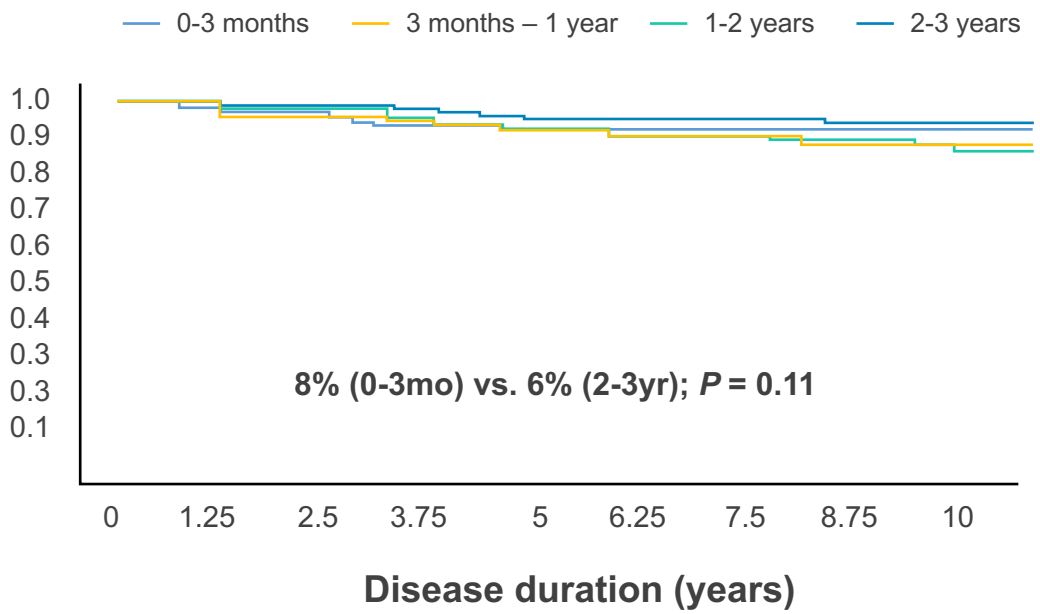
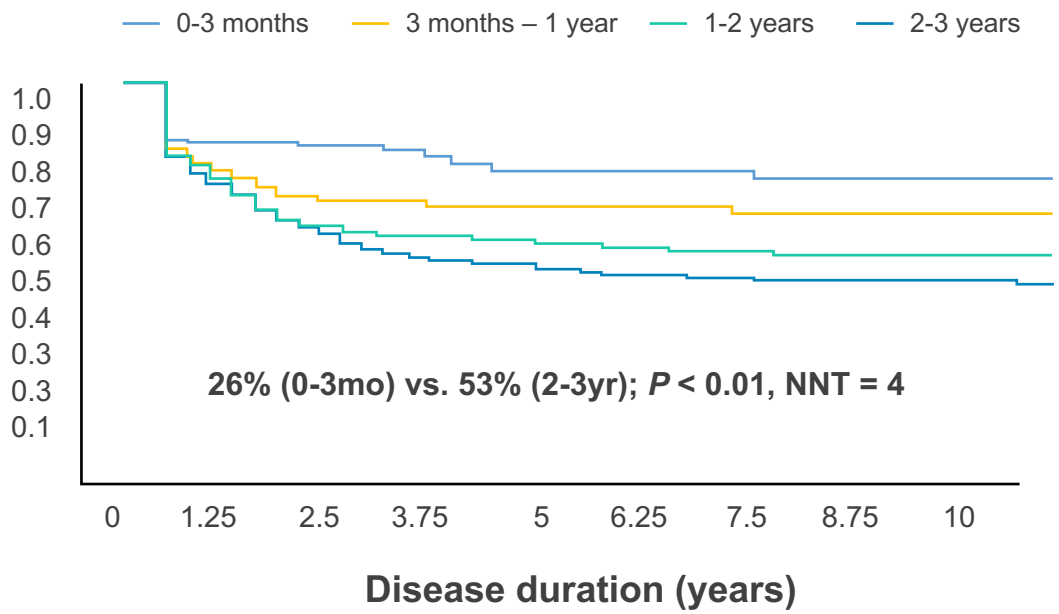
Is There a Window of Opportunity for Medical Therapy in Ulcerative Colitis?

UC Time to Colectomy



UC Time to Steroid Dependency



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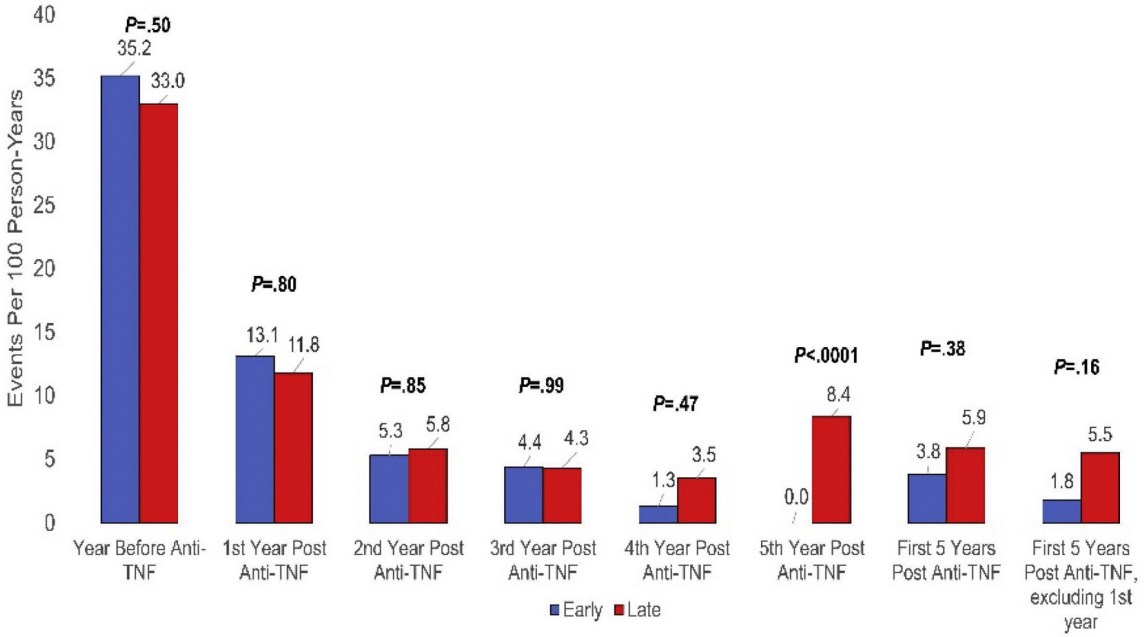
Focht et al. *J Crohns Colitis.* 2023;17(S1):OP12

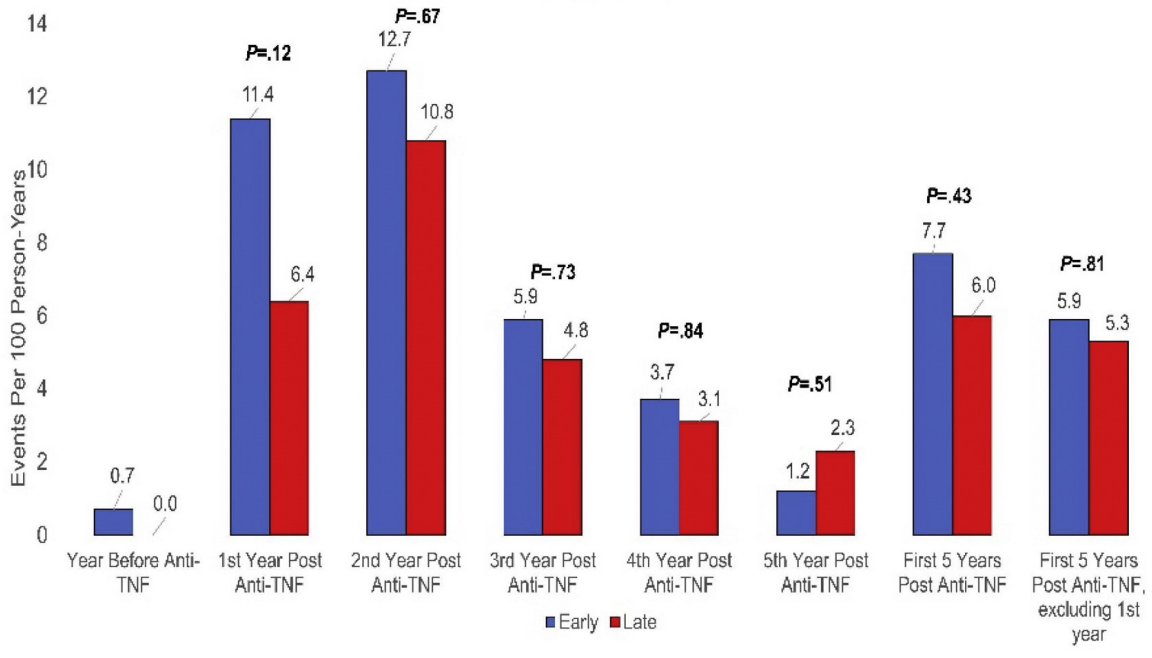
Is There a Window of Opportunity for Medical Therapy in Ulcerative Colitis?

Total IBD-Related Hospitalizations Ulcerative Colitis



Early (n)	123	104	85	60	47	47	47
Late (n)	195	161	138	115	94	94	94

Total IBD-Related Resective Surgeries Ulcerative Colitis



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Late (n)	195	161	138	115	94	94	94

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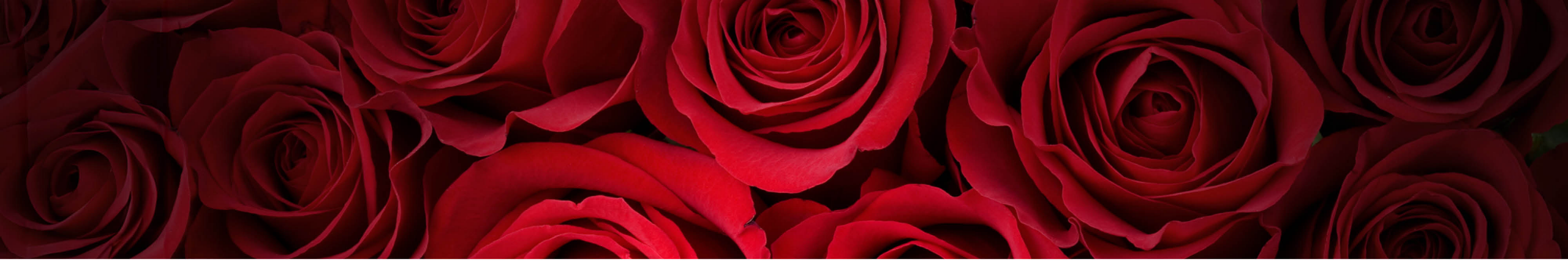
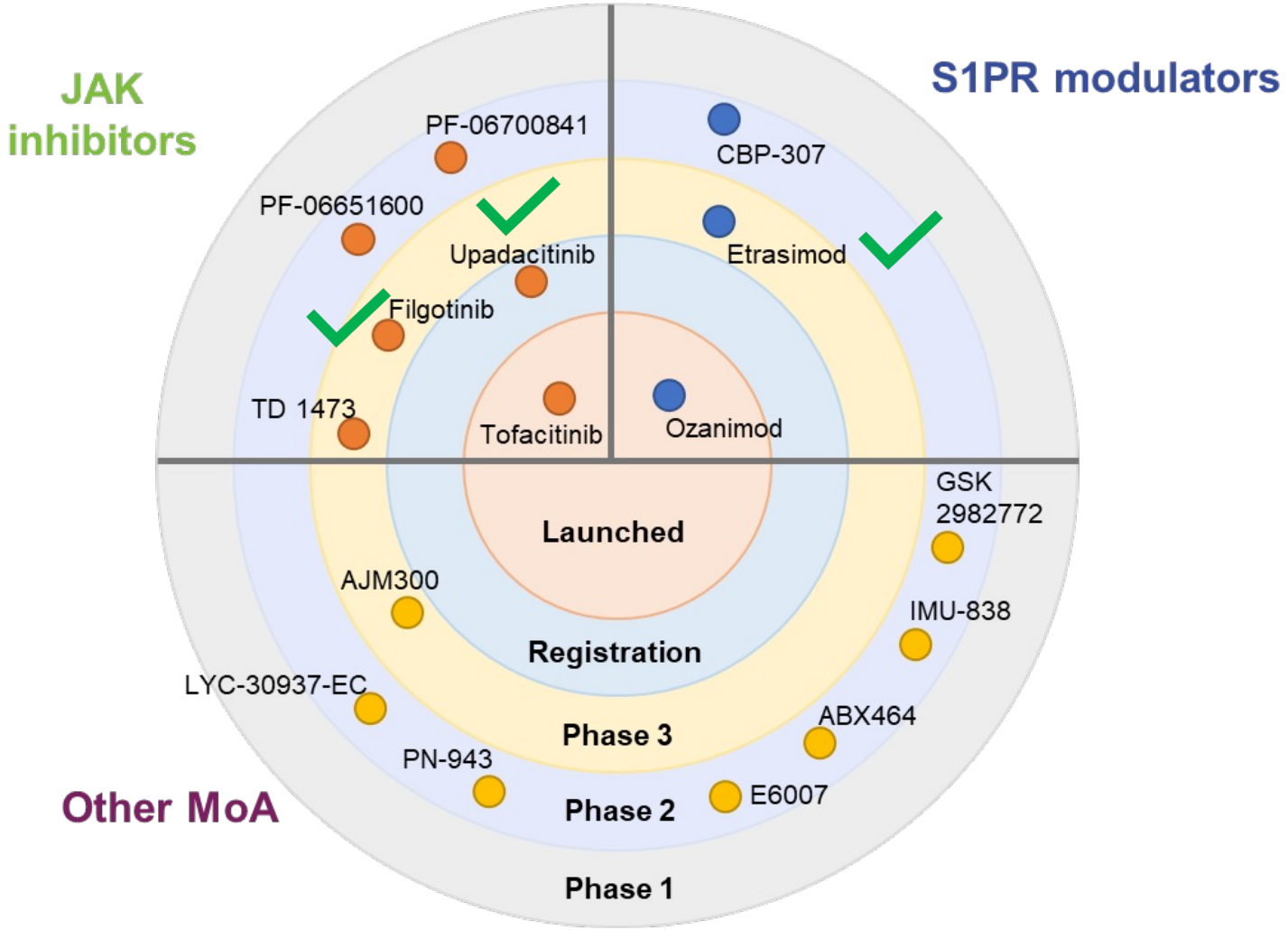
Targownik LE, et al. *Clin Gastroenterol Hepatol.* 2022;20(11):2607-2618



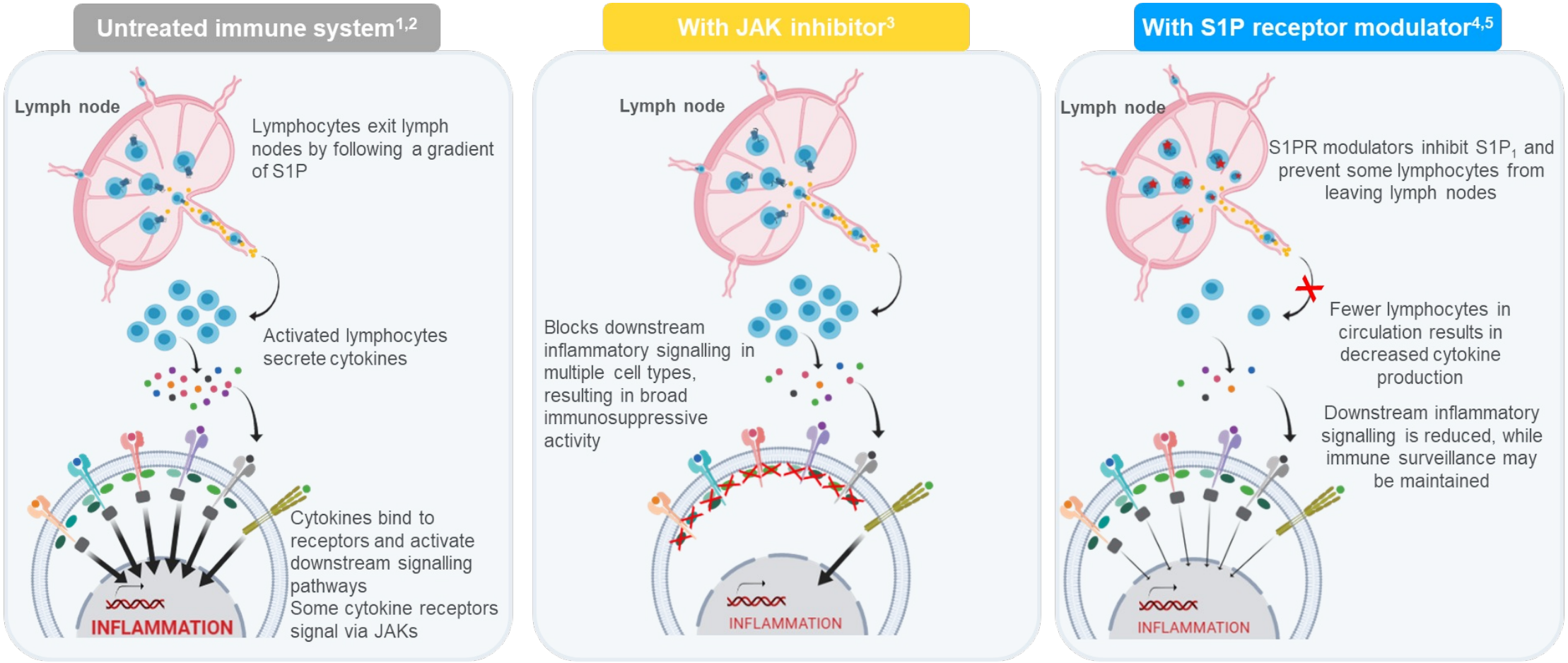
Choosing an Advanced Oral Therapy

Oral Small Molecules in Development



Olivera P, et al. *Gut*. 2017; (2):199-209.

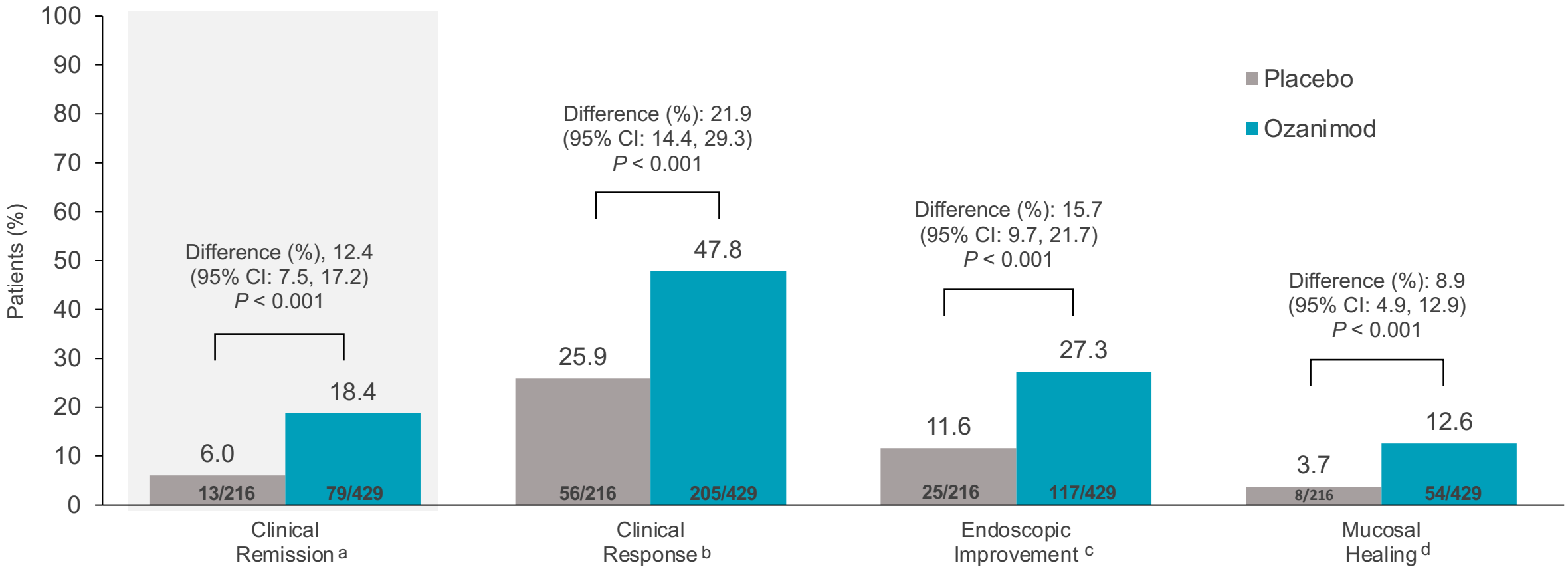
Mechanisms of Action of Existing Small Molecule Therapies



JAK, Janus kinase; S1P, sphingosine 1-phosphate; S1PR, sphingosine-1-phosphate receptor; STAT, signal transducer and activator of transcription.

1. Spiegel S, et al. *Nat Rev Immunol*. 2011;11:403–415. 2. Blaho VA, et al. *J Lipid Res*. 2014;55:1596–1608. 3. Hodge JA, et al. *Clin Exp Rheumatol.* 2016;34:318–328.
4. Peyrin-Biroulet L, et al. *Autoimmun Rev*. 2017;16:495–503. 5. Danese S, et al. *J Crohns Colitis*. 2018;12:S678–S686.

Efficacy of Ozanimod for Moderate-to-Severe UC

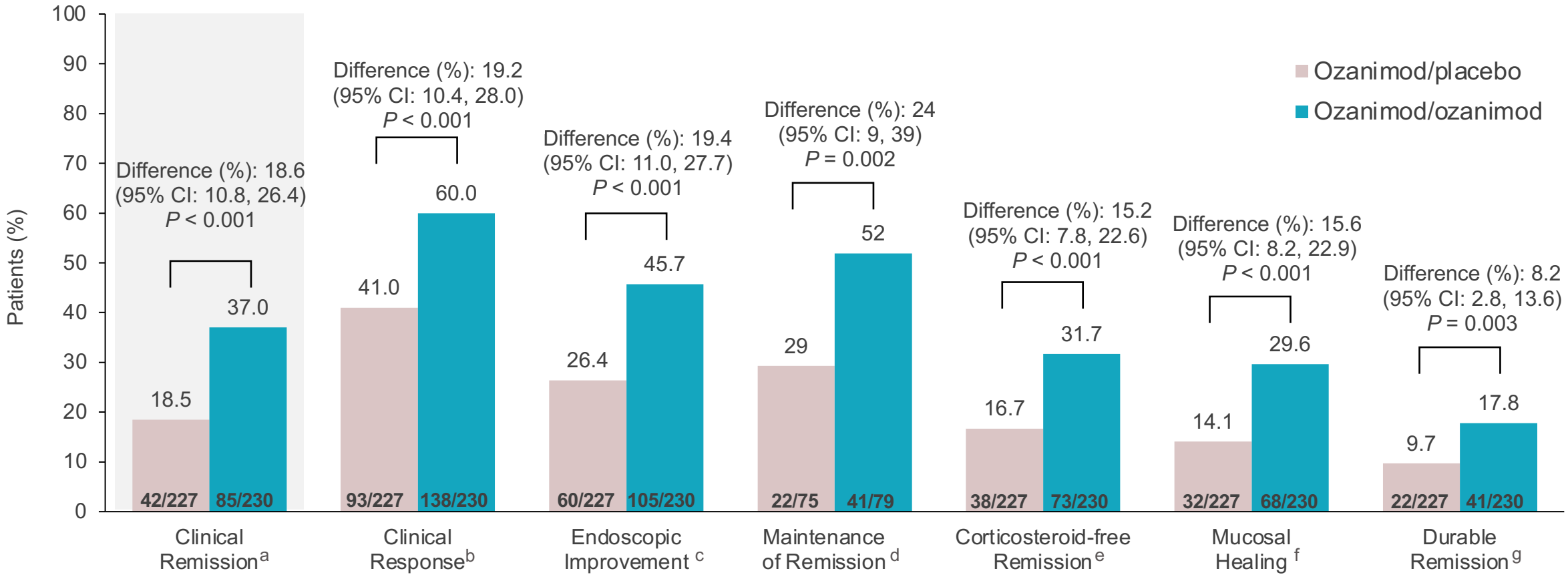


[a]Defined as RBS = 0, SFS ≤ 1 (plus ≥ 1-point reduction from baseline), and MES ≤ 1 without friability. [b]Defined as reduction in 3-component Mayo score of ≥ 2 points and ≥ 35%, and reduction in RBS of ≥ 1 point or absolute RBS of ≤ 1 point. [c]Defined as MES ≤ 1 without friability. [d]Defined as endoscopic improvement plus histologic remission (Geboes index score < 2.0 and absence of neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue in the same patient).

MES, mucosal endoscopy subscore; RBS, rectal bleeding subscore; SFS, stool frequency subscore; TNF, tumor necrosis factor.

Sandborn WJ, et al. *N Engl J Med*. 2021;385(14):1280-1291.

Efficacy of Ozanimod for Moderate-to-Severe UC



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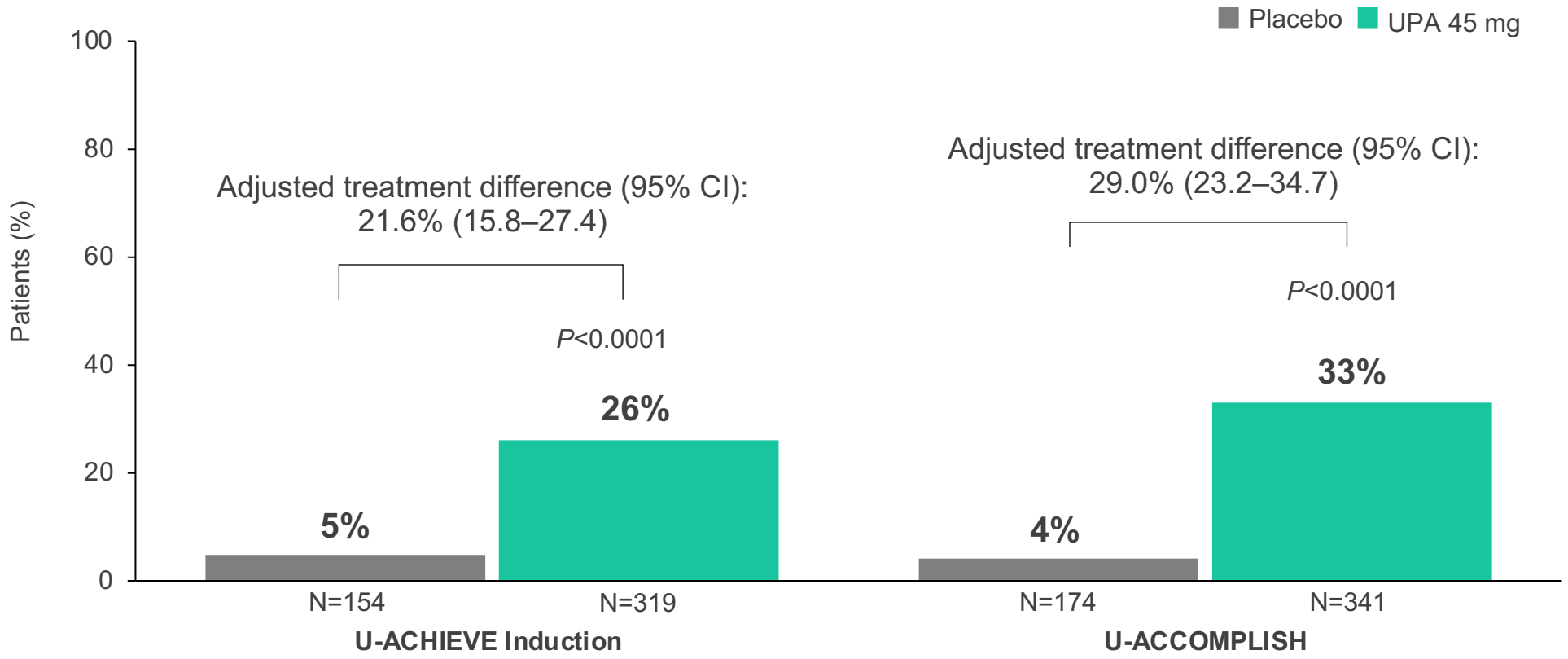
MES, mucosal endoscopy subscore; RBS, rectal bleeding subscore; SFS, stool frequency subscore; TNF, tumor necrosis factor.

Sandborn WJ, et al. *N Engl J Med*. 2021;385(14):1280-1291.

Efficacy of Upadacitinib for Moderate-to-Severe UC

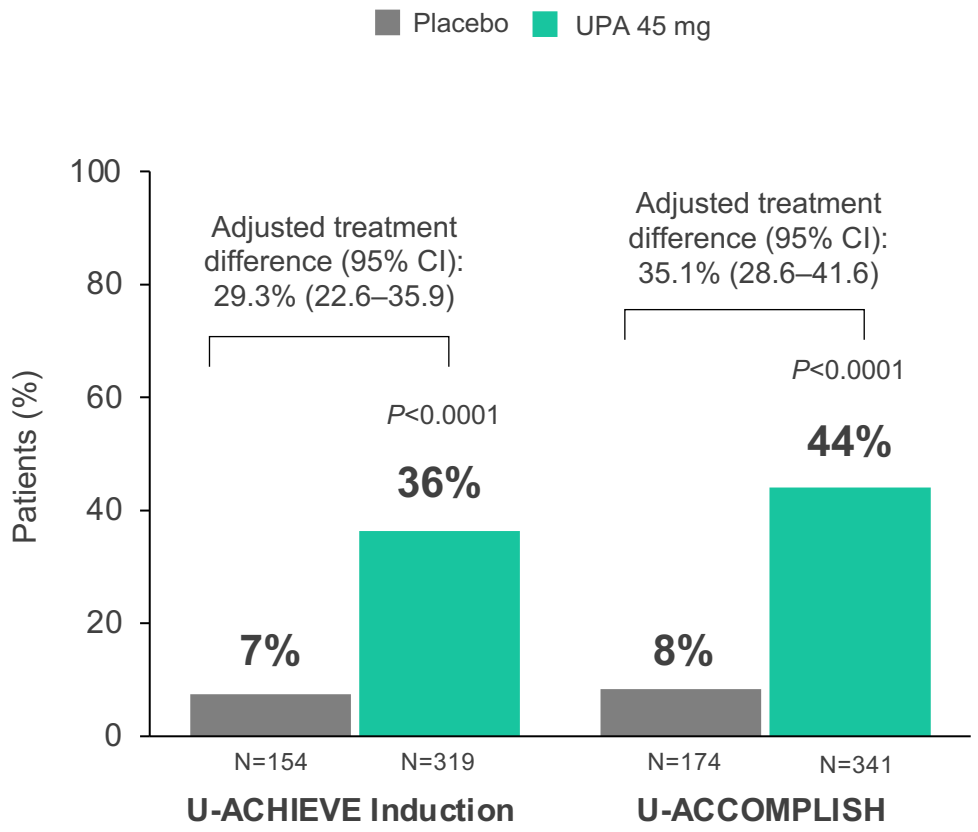


Clinical remission per adapted Mayo score: adapted Mayo score ≤2, with SFS ≤1 and not greater than baseline, RBS of 0, and endoscopic subscore ≤1 without friability

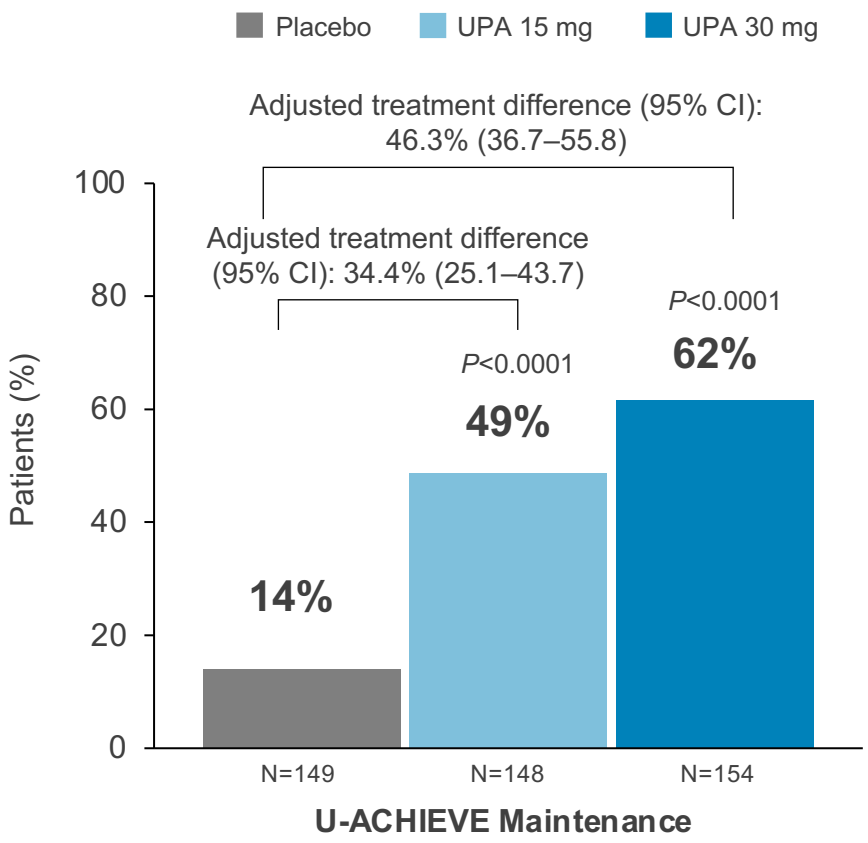
Danese S, et al. *Lancet*. 2022; 399(10341):2113-2128.

Efficacy of Upadacitinib for Moderate-to-Severe UC

Endoscopic Improvement at Week 8



Endoscopic Improvement at Week 52



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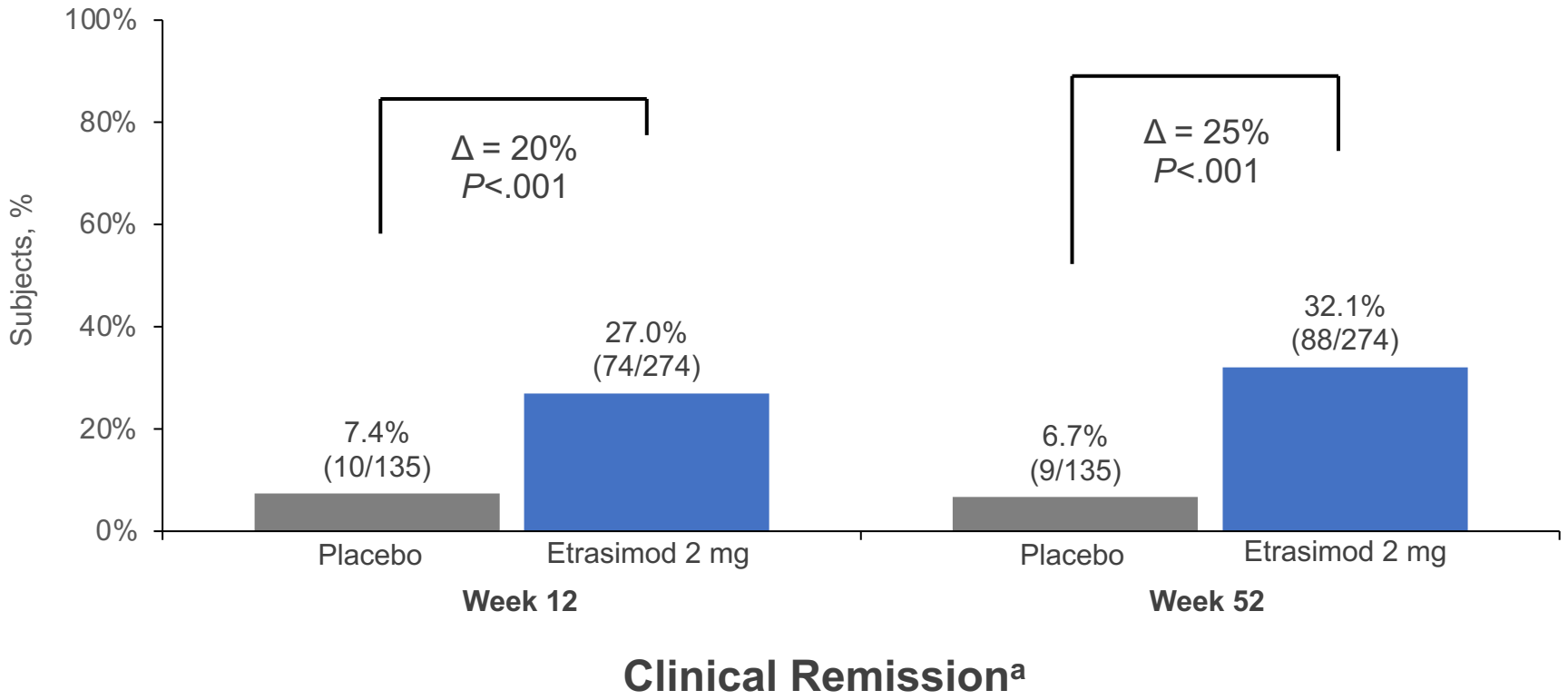
Efficacy of Etrasimod for Moderate-to-Severe UC

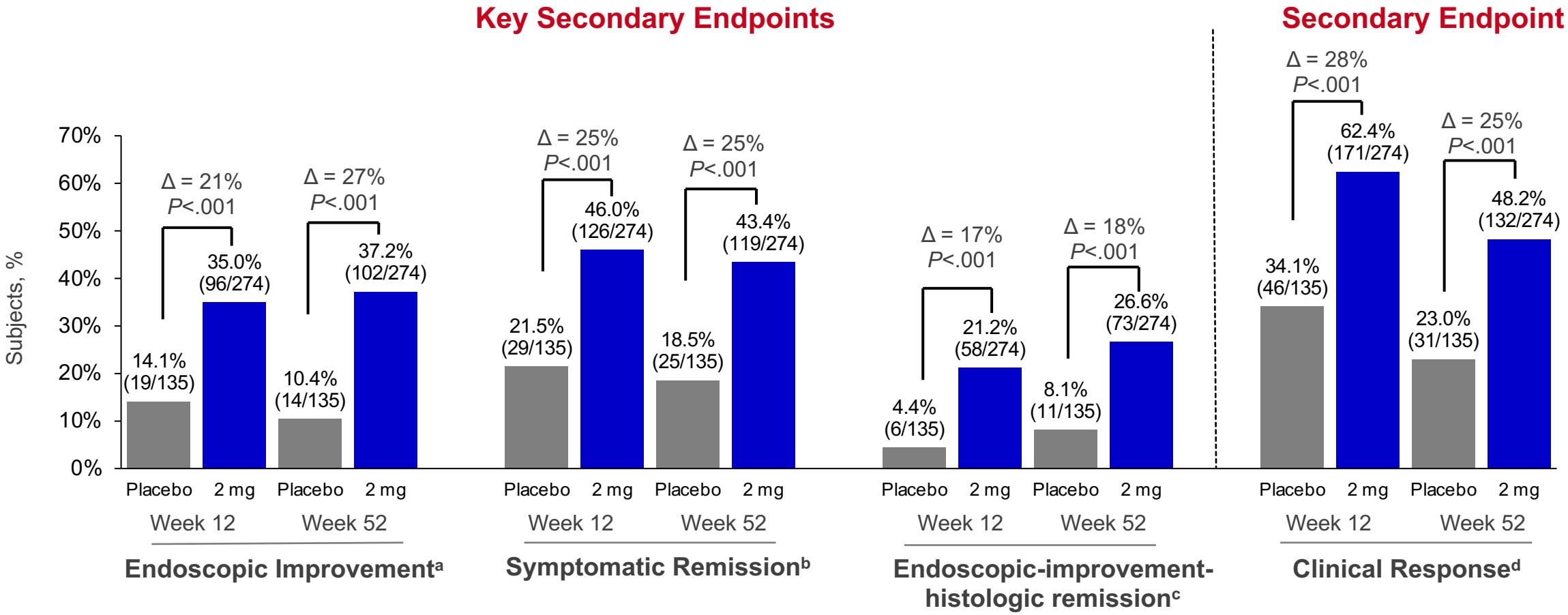


Data were from reported randomized strata. Percentage of patients with clinical remission was derived from Cochran-Mantel-Haenszel analysis. [a]Clinical remission was defined as SF subscore 0 (or 1 with a ≥1-point decrease from baseline), RB subscore 0, and ES ≤1 (excluding friability).

ES, endoscopic subscore; MMS, modified Mayo Score; RB, rectal bleeding; SF, stool frequency.

Sandborn WJ, et al. *Lancet*. 2023;401(10383):1159-1171.

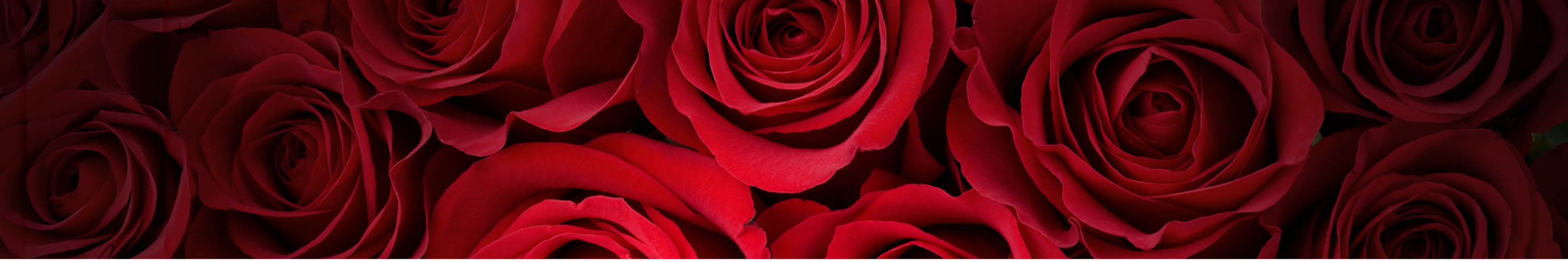
Efficacy of Etrasimod for Moderate-to-Severe UC



[a] Endoscopic improvement defined as ES ≤1 (excluding friability).
[b] Symptomatic remission was defined as SF subscore 0 (or 1, with a ≥1-point decrease from baseline) and RB subscore 0.
[c] Endoscopic-improvement-histologic remission (previously referred to as "Mucosal Healing") was defined as ES of ≤1 (excluding friability) with histologic remission by a Geobes score <2.
[d] Clinical response was defined as ≥2 point and ≥30% decrease from baseline in MMS, ≥1-point decrease from baseline in RB subscore, or an absolute RB subscore ≤1.

ES, endoscopic subscore; MMS, modified Mayo Score; RB, rectal bleeding; SF, stool frequency.

Sandborn WJ, et al. *Lancet*. 2023;401(10383):1159-1171.



Choosing the Right Patient

Factors to Consider When Choosing an Oral Therapy

Efficacy

- Disease extent
- Disease activity
- Prior treatment exposure
- Rapidity of onset

Safety

- Comorbidities (cardiac, ocular)
- Risk of infections
- Risk of drug-drug interactions
- Adverse events of special interest

Other Factors

- Adherence to treatment
- Cost and coverage
- Monitoring regimen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