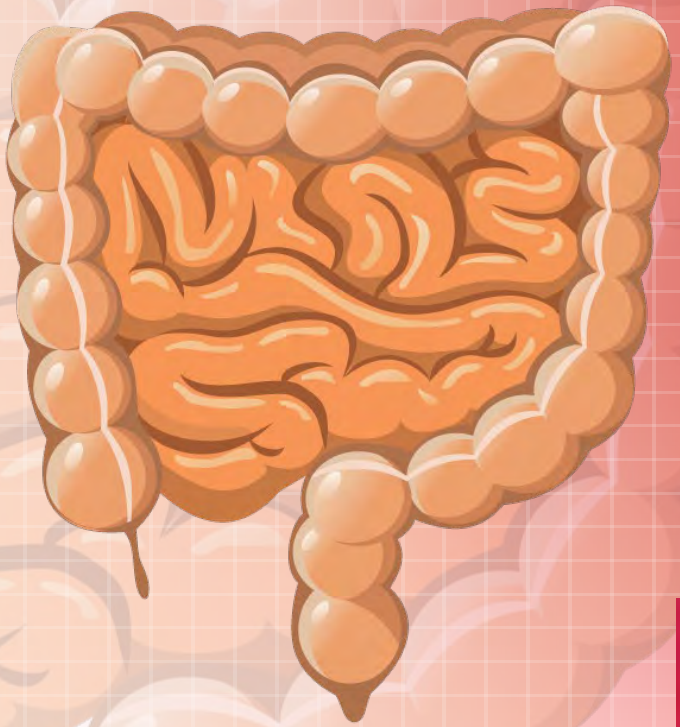


Advanced Therapies in IBD

Pascal Kuka
MMed, MRCP(UK)
Gastroenterology Fellow
University of the Witwatersrand

Project ECHO®
Gastroenterology Foundation

G-ECHO
GI HEPATOLOGY ECHO
OF SUB-SAHARAN AFRICA
ESTABLISHED 2020

Introduction

- Advanced therapies are considered in
  - Failure or intolerance to conventional treatment
  - High disease burden
  - High risk of complications

- Goal : avoid disease related disability and maintain good quality of life

- *Raine. Journal of Crohn's and Colitis*, 2022,

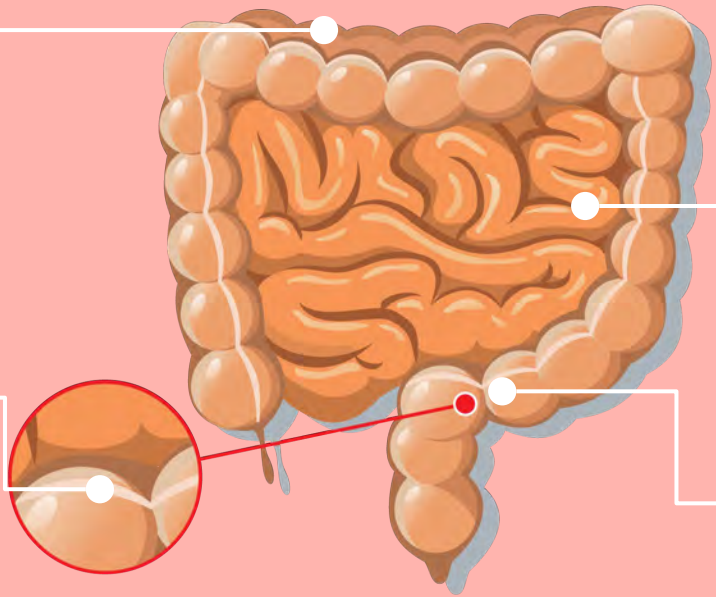
Pathophysiology of IBD

Genetics

Environmental

Infections Diet

Smoking Drugs Surgery



Immune Dysfunction

Gut Microbiome

Dysbiosis

Sleisenger and Fordtran's gastrointestinal and liver disease. Elsevier health sciences, 2020
Kobayashi. Nature Reviews. 2020

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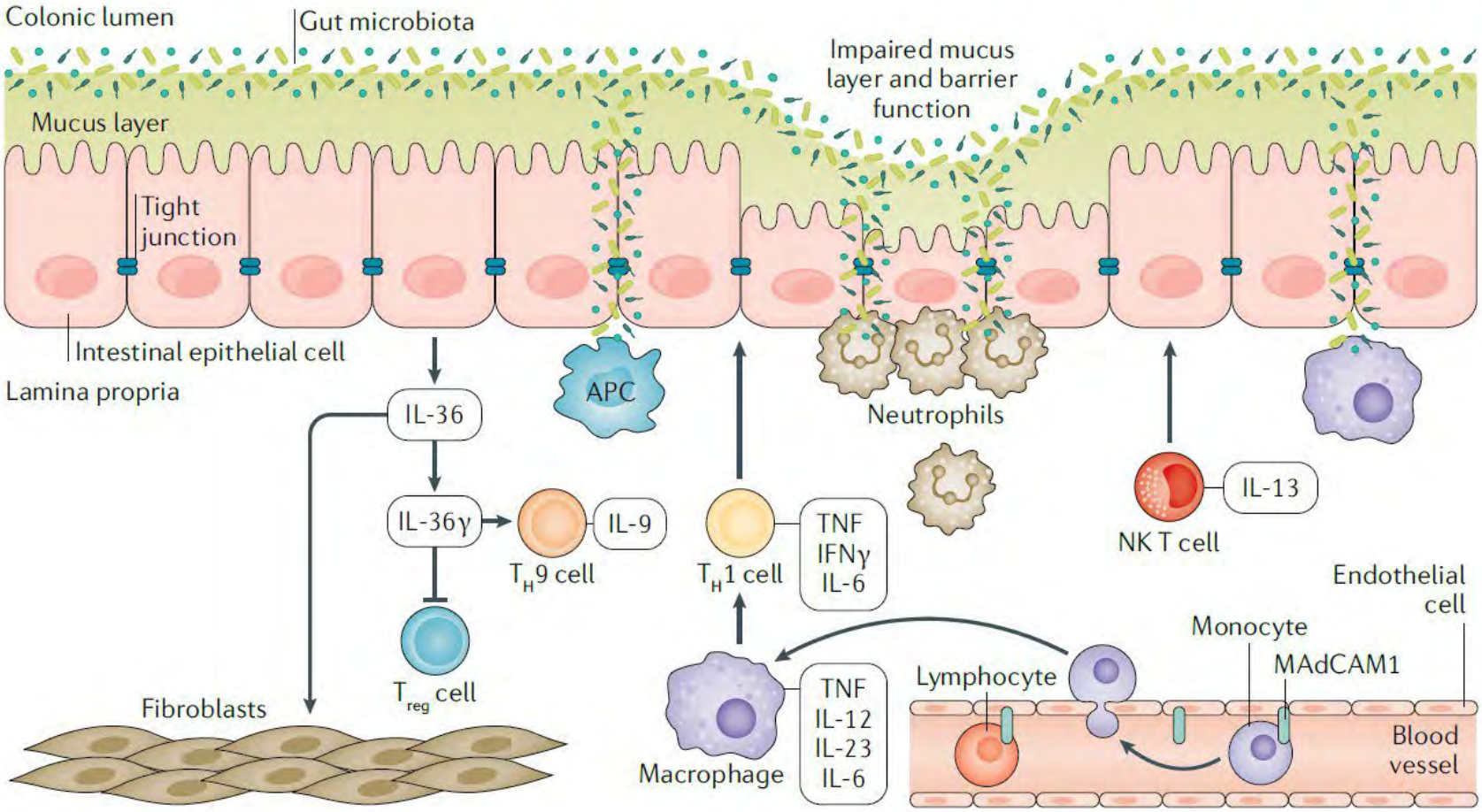


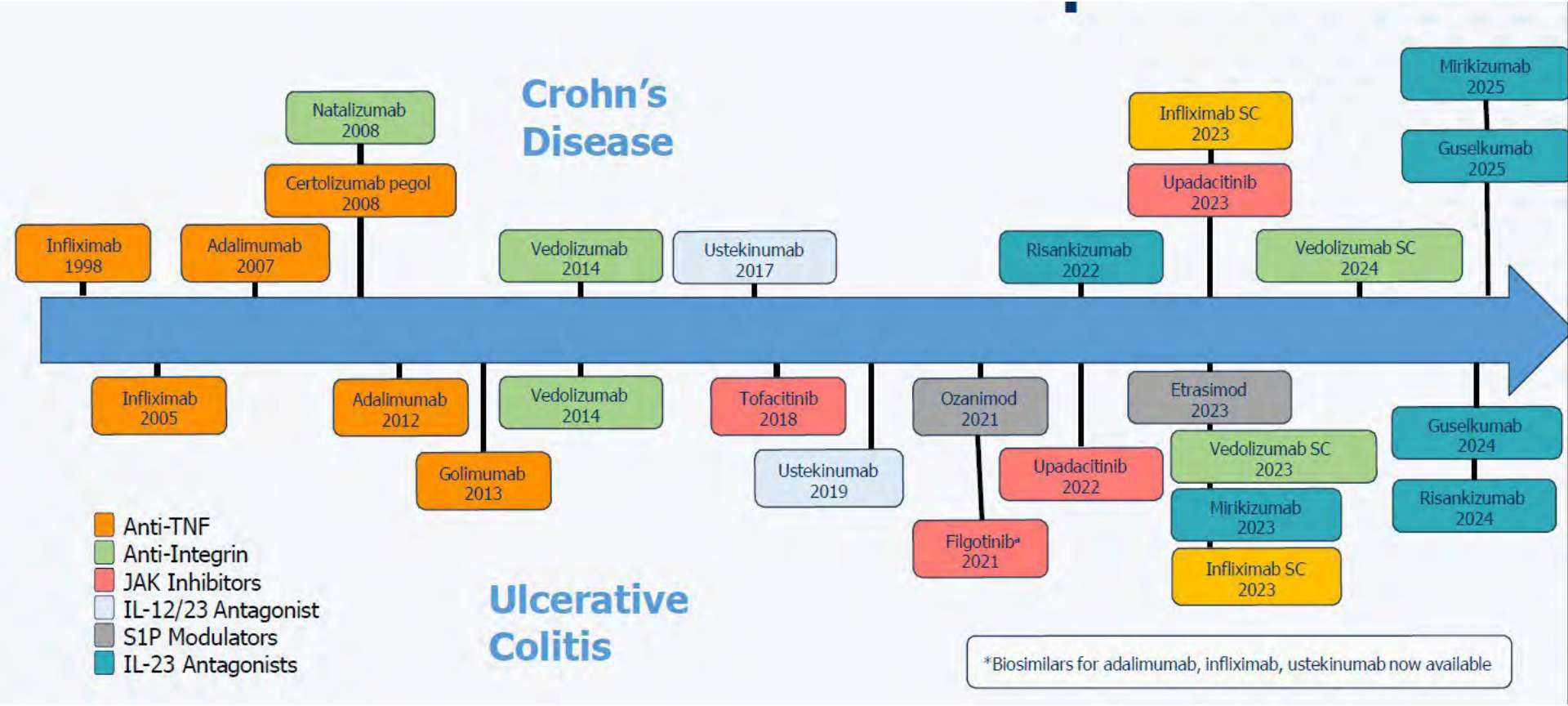
Pathophysiology of IBD

Kobayashi. Nature Reviews. 2020

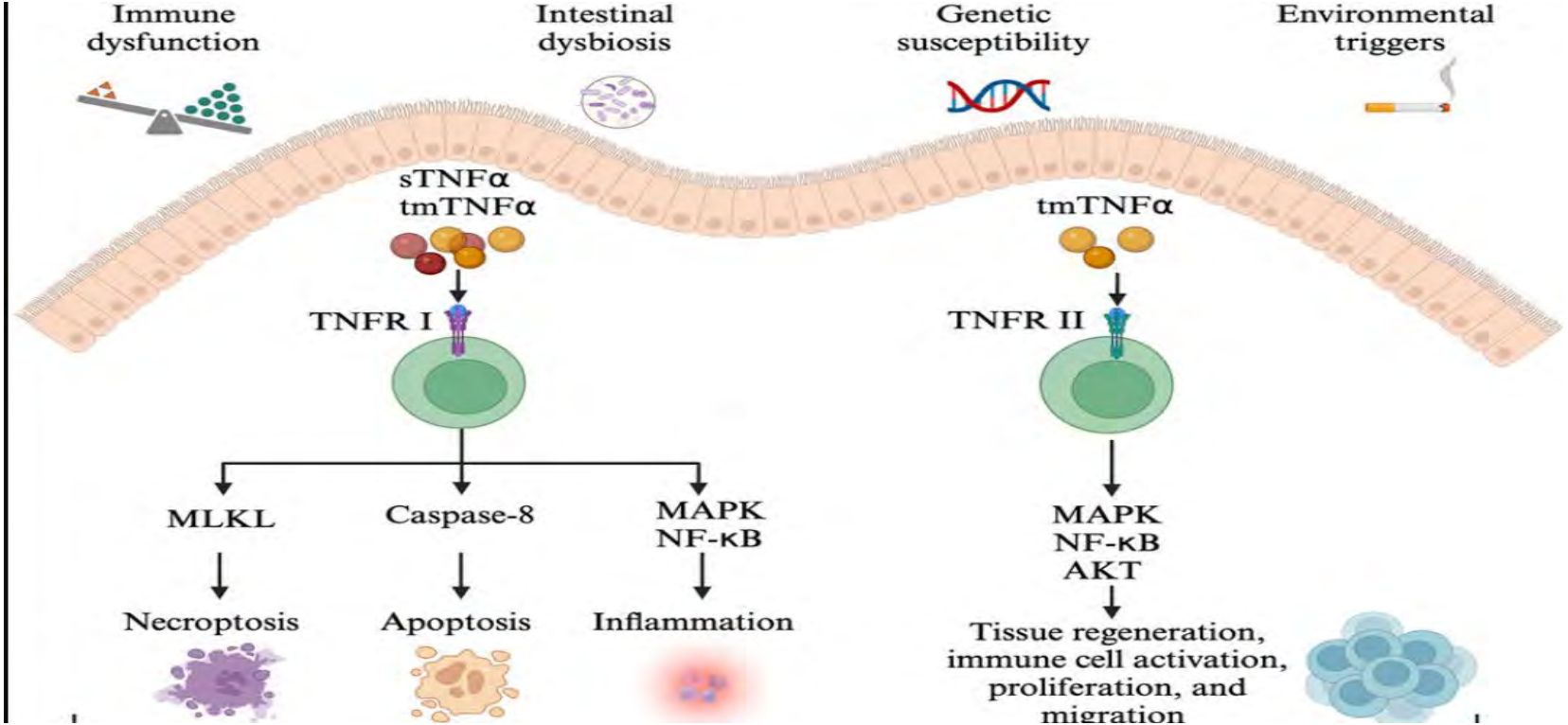
Advanced Therapies

Biologics	Targeted small molecules
Large	Small, simple
Immunogenic	Non immunogenic
Parenteral	Oral
Long half life	Short half life
Target: cytokines, receptors	Target : intracellular signalling

Dodson. Curr Allergy Asthma Rep. 2022


Crohn's Disease
Infliximab 1998
Adalimumab 2007
Natalizumab 2008
Certolizumab pegol 2008
Vedolizumab 2014
Ustekinumab 2017
Risankizumab 2022
Infliximab SC 2023
Upadacitinib 2023
Vedolizumab SC 2024
Mirikizumab 2025
Guselkumab 2025
Infliximab 2005
Adalimumab 2012
Golimumab 2013
Vedolizumab 2014
Tofacitinib 2018
Ustekinumab 2019
Ozanimod 2021
Filgotinib* 2021
Upadacitinib 2022
Etrasimod 2023
Vedolizumab SC 2023
Mirikizumab 2023
Infliximab SC 2023
Guselkumab 2024
Risankizumab 2024
Anti-TNF
Anti-Integrin
JAK Inhibitors
IL-12/23 Antagonist
S1P Modulators
IL-23 Antagonists
Ulcerative Colitis
*Biosimilars for adalimumab, infliximab, ustekinumab now available

AntiTNFs in IBD



Zeng. Front. Pharmacol., 2024

AntiTNFs in IBD

			Induction	Maintenance	Landmark Trials
Infliximab	IV , SC	CD, UC	5mg/kg 0, 2, 6 weeks	Q 8 weekly	ACCENT 1,2 (2002, 2004) ACT 1,2 (2005)
Adalimumab	SC	CD, UC	160 mg Day 0 80 mg Day 15	40 mg Q 2 weeks	CHARM (2007) ULTRA (2012)
Golimumab	SC	UC	200 mg Day 1 100mg q4 weeks	100mg Q 4 weeks	PURSUIT (2014)
Certolizumab	SC	CD	400 mg Day 1, 15, 26	400 Q 4 weeks	PRECISE (2007)

Rubin. AmJ Gastroenterol 2025, Lichtenstein. . Am J Gastroenterol 2025

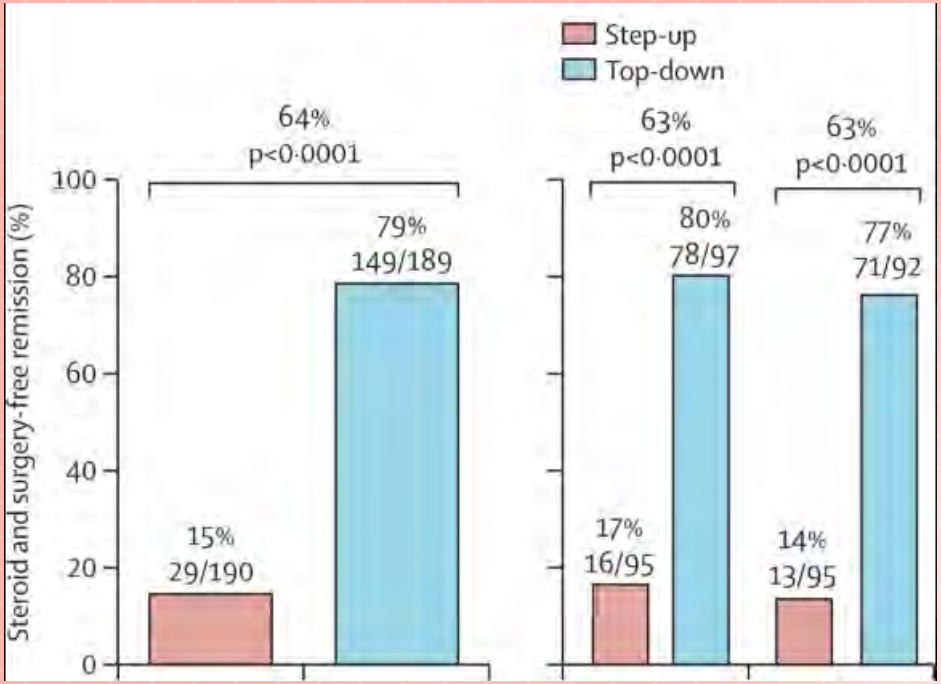
AntiTNFs in IBD

- ASUC : Infliximab
- Perianal /Penetrating CD : Infliximab, Adalimumab
- Extra intestinal manifestations :
    - (Non) / Axial spondyloarthropathy
    - Pyoderma gangrenosum
    - Refractory uveitis, scleritis
- Avoid : lymphoma, melanoma, Multiple sclerosis, heart failure

Moran GW, et al. Gut2025, Gordon. Journalof Crohn's and Colitis, 2024

Early Treatment with antiTNF in Crohn's Disease

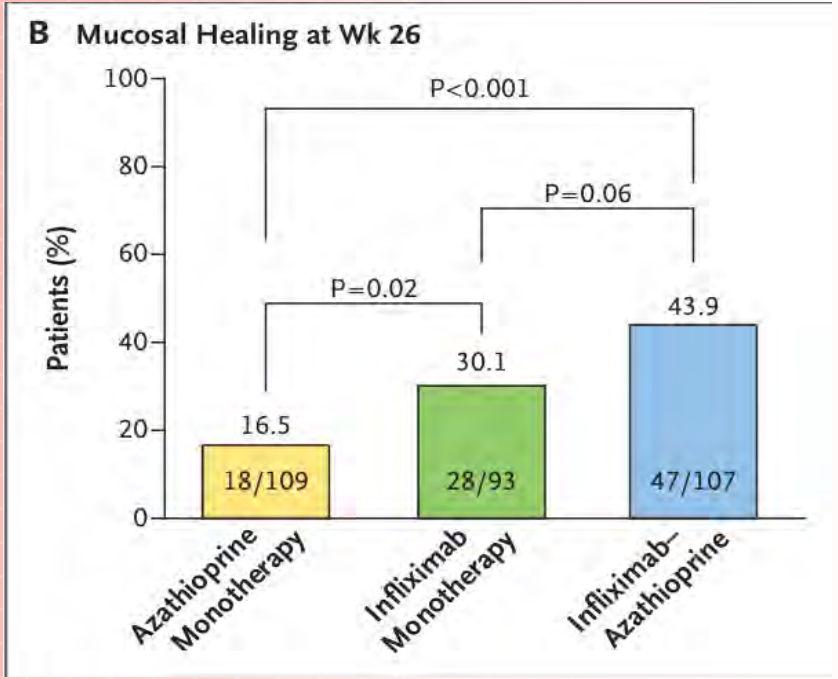
- Failed conventional therapy
- High risk : young, ileal location, extensive disease, fistulizing
- Refractory EIM :



Noor. Lancet Gastroenterology.2025

Immunogenicity of antiTNFs

- SONIC (CD), SUCCESS (UC) Combination with azathioprine
- Risk of lymphoma : elderly, long duration, young males
- PANTS : low drug levels week 14 , antibodies, HLA-DQA1*05 – risk of failure at 2,3 years
- Proactive vs Reactive monitoring

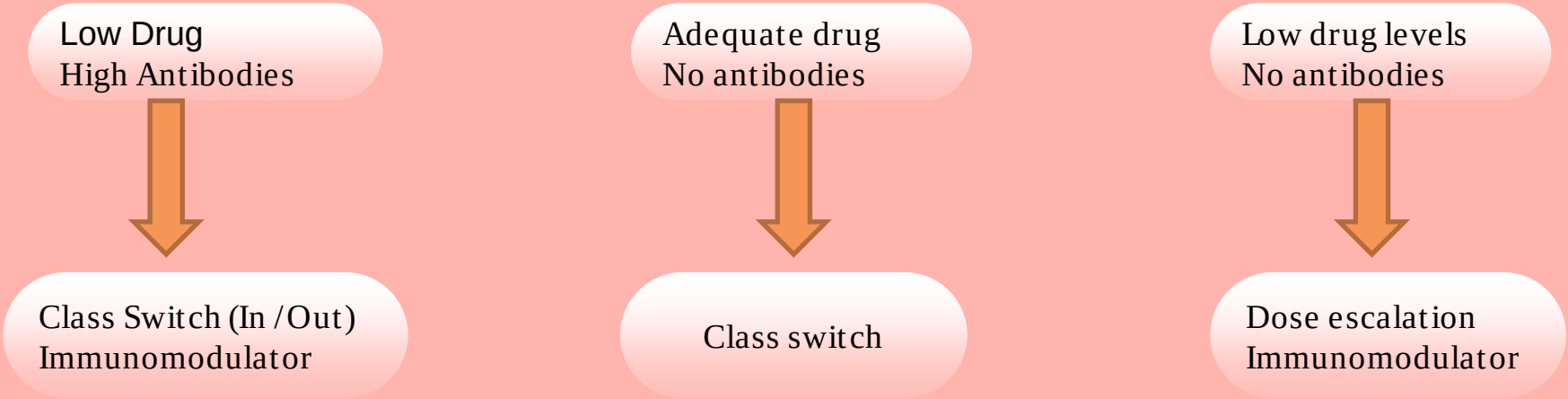


Colombel. N Engl J Med 2010
Chanchlani. Lancet Gastroenterol Hepatol 2024
Nguyen. Gastroenterology 2022

Loss of response to AntiTNFs

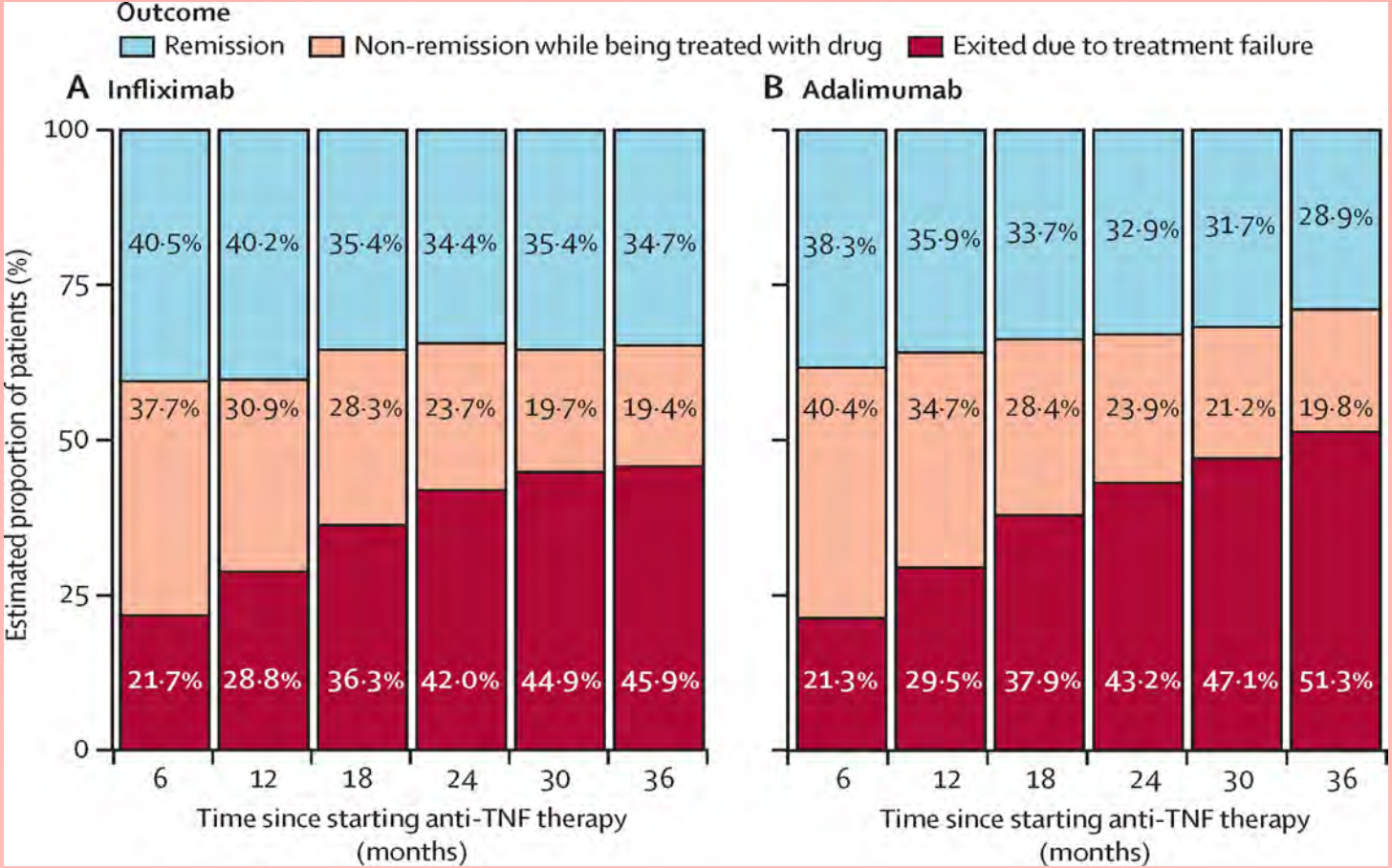
Primary Non Response : Pharmaco: kinetics vs dynamics

Secondary Non Response : Mechanistic or Immunologic



Roda. Clinical and Translational Gastroenterology (2016
Sparrow.*Journal of Crohn's and Colitis*, 2020

PANTS COHORT STUDY



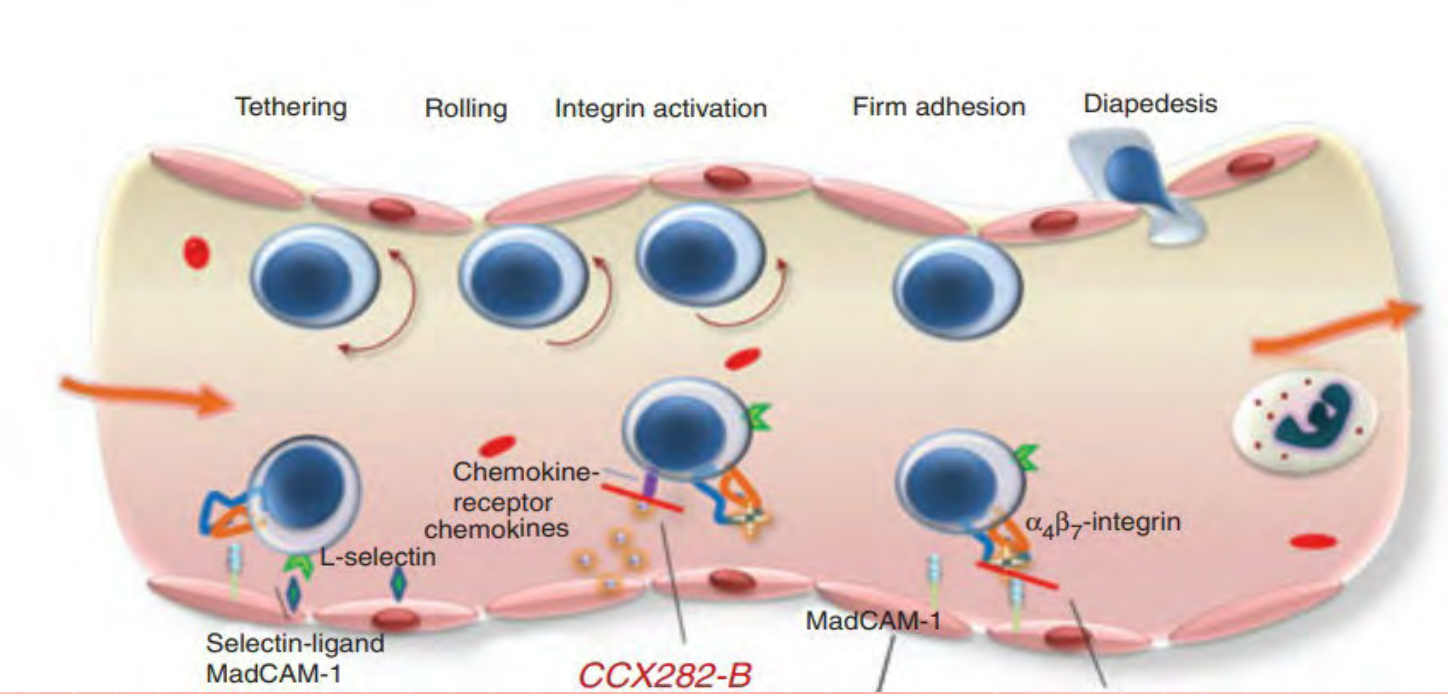
The Lancet Gastroenterology & Hepatology 2024 9521-538DOI: (10.1016/S2468-1253(24)00044-X)

Safety of antiTNFS

Opportunistic reactions and reactivation
Malignancies :lymphoma, NMSC
Congestive heart failure
Drug-induced lupus
Demyelinating disorders
Skin rashes (psoriasis-like)
Allergic reactions
Liver toxicity
Headache
Dizziness

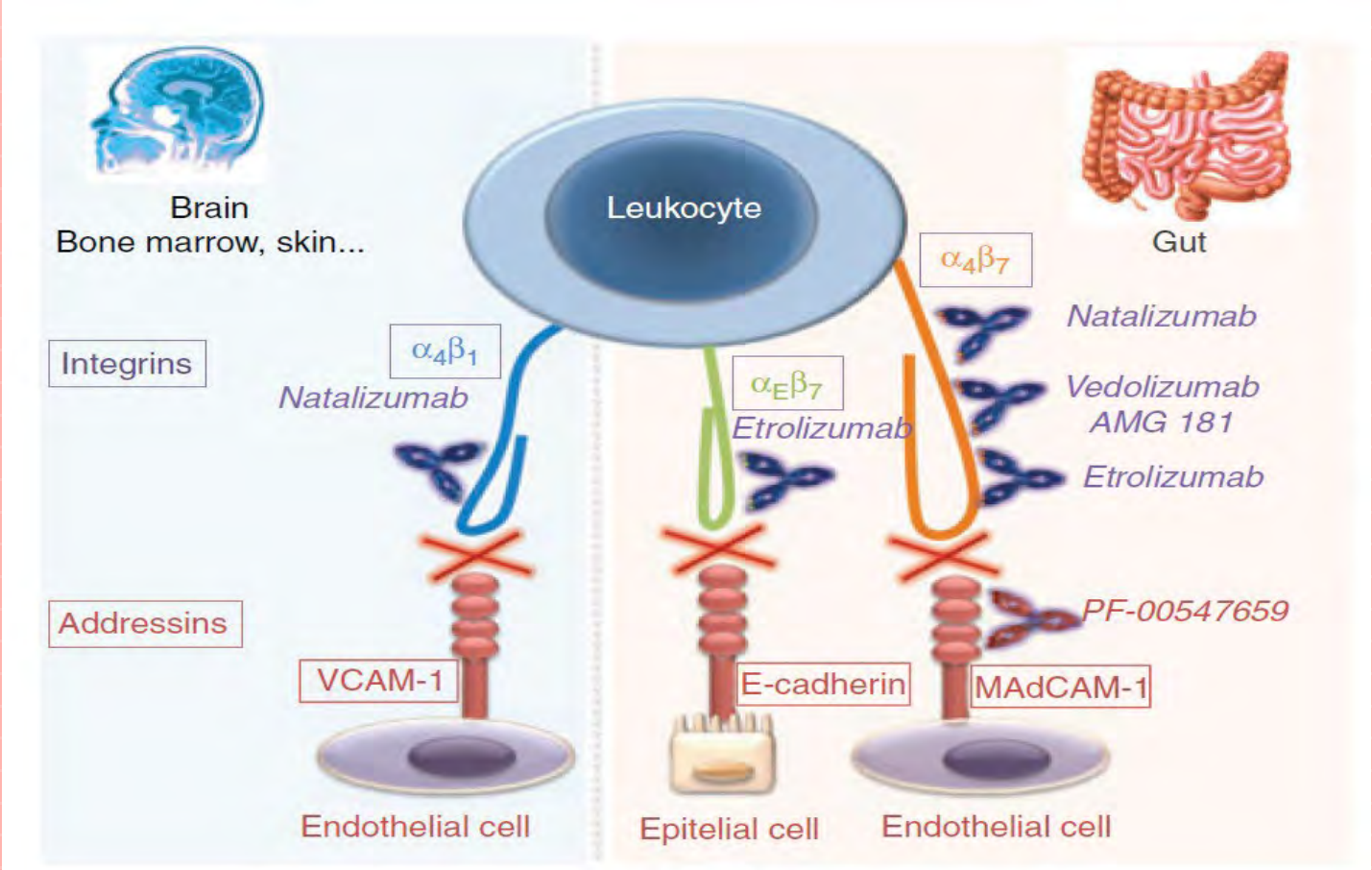
Moran GW, et al. Gut 2025

Anti Integrin inhibitors



Lobaton. Aliment Pharmacol Ther 2014

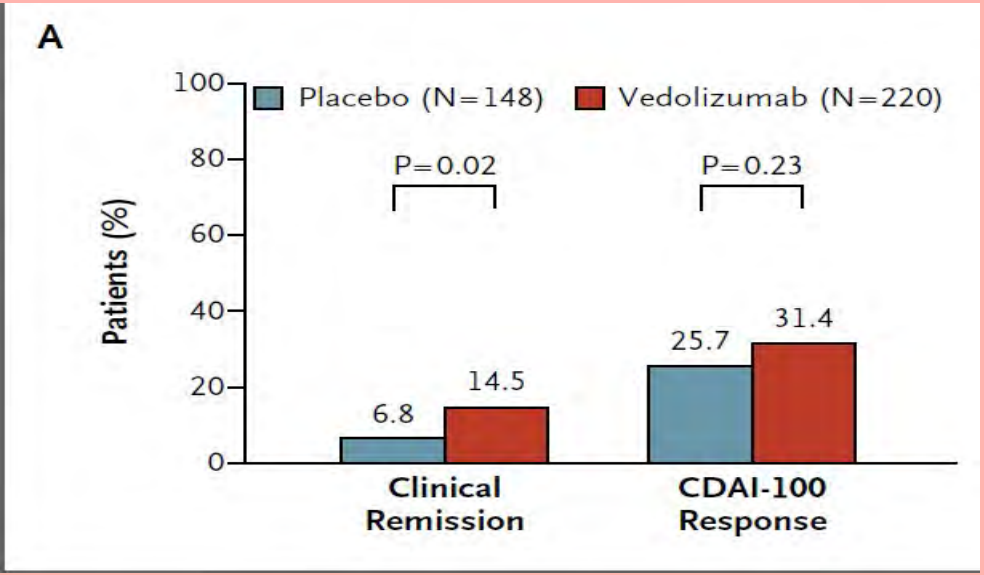
Anti Integrins MOA

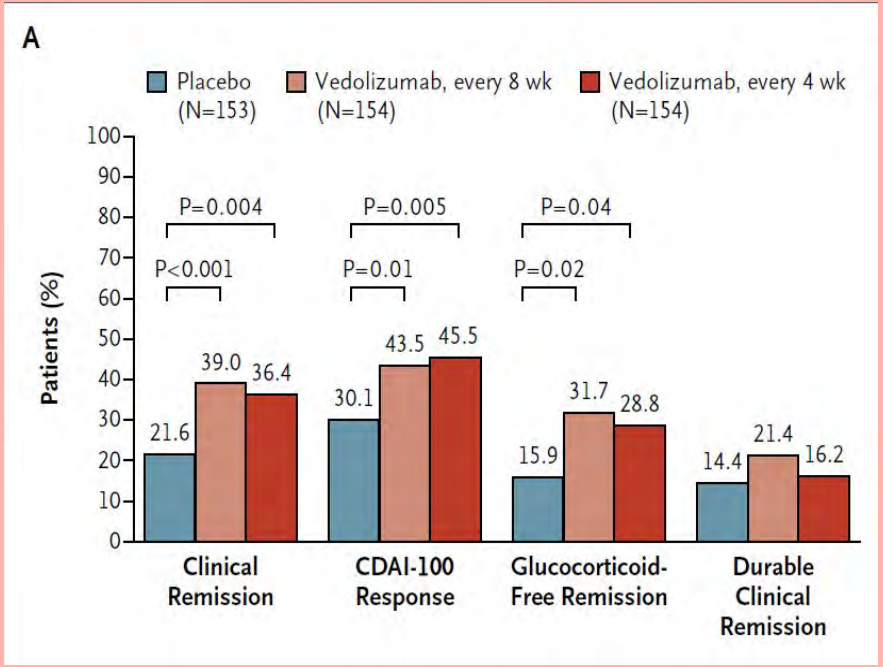


Lobaton. Aliment Pharmacol Ther 2014

Vedolizumab in Crohns Disease

GEMINI 2 (2013) : phase 3, randomized, double-blind, placebo controlled study





- Failure on or intolerance to steroids, methotrexate and antiTNF (63%)

Sandborn. N Engl J Med 2013

Vedolizumab in Ulcerative colitis

GEMINI (2013) : phase 3, randomized, double-blind, placebo controlled study

Table 2. Outcome Measures at Week 6 in the Trial of Induction Therapy.

Outcome	Placebo (N = 149)	Vedolizumab (N = 225)	Percentage-Point Difference (95% CI)*	P Value
	no. (%)			
Clinical response†	38 (25.5)	106 (47.1)	21.7 (11.6–31.7)	<0.001
Clinical remission‡	8 (5.4)	38 (16.9)	11.5 (4.7–18.3)	0.001
Mucosal healing§	37 (24.8)	92 (40.9)	16.1 (6.4–25.9)	0.001

40% : antiTNF exposure

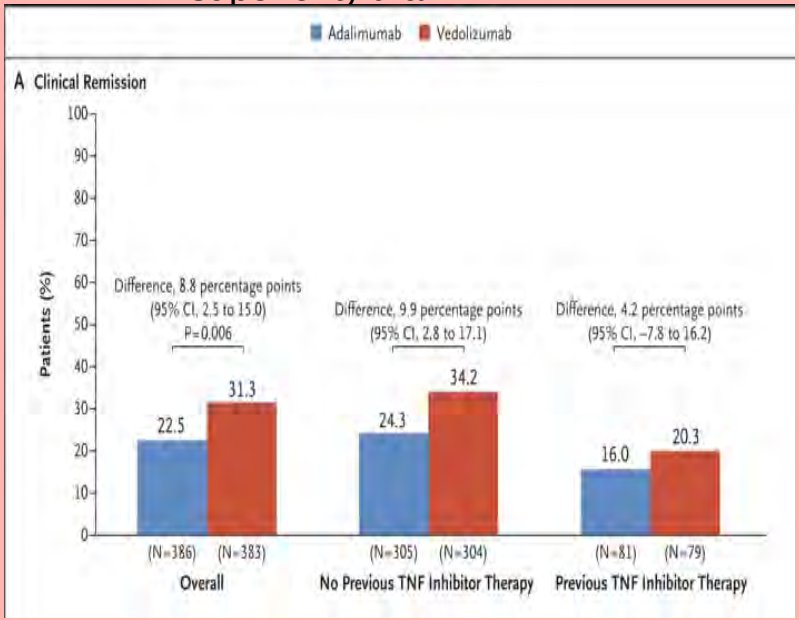
Table 3. Outcome Measures in the Trial of Maintenance Therapy.

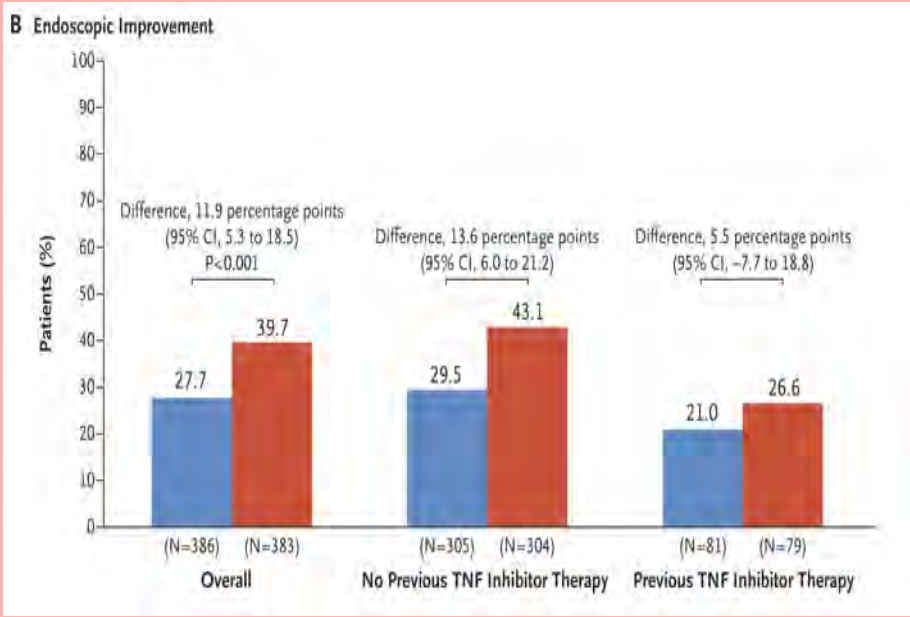
Outcome	Placebo (N = 126)	Vedolizumab Every 8 Wk (N = 122)	Vedolizumab Every 4 Wk (N = 125)
	number/total number (percent)		
Clinical remission at wk 52	20/126 (15.9)	51/122 (41.8)	56/125 (44.8)
Durable clinical response†	30/126 (23.8)	69/122 (56.6)	65/125 (52.0)
Durable clinical remission‡	11/126 (8.7)	25/122 (20.5)	30/125 (24.0)
Mucosal healing at wk 52	25/126 (19.8)	63/122 (51.6)	70/125 (56.0)
Glucocorticoid-free remission at wk 52§	10/72 (13.9)	22/70 (31.4)	33/73 (45.2)

Feagan. N Engl J Med 2013

Vedolizumab vs Adalimumab in Ulcerative colitis

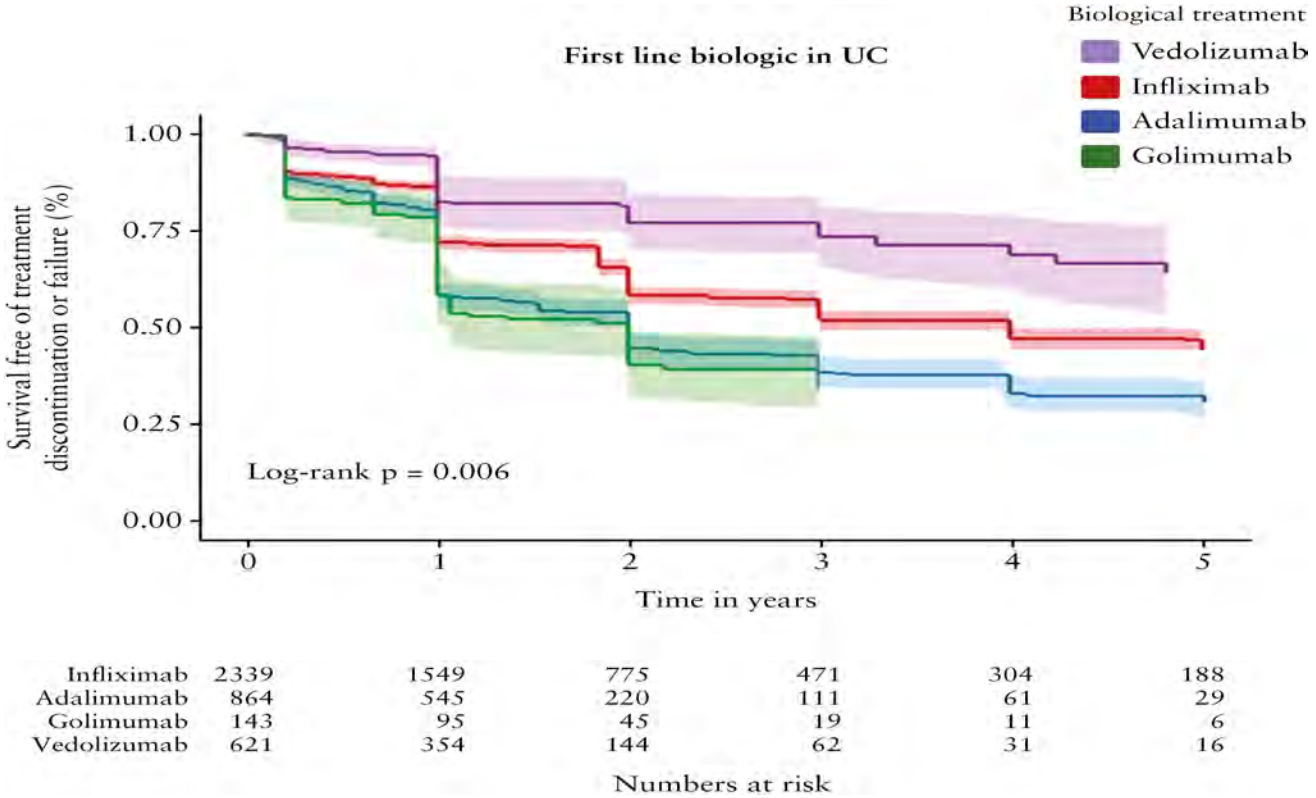
VARSITY (2019) : phase 3b, randomized, double-blind, double-dummy, active-controlled superiority trial





Sands. N Engl J Med 2019

Effectiveness of first-line biologics in patients with ulcerative colitis

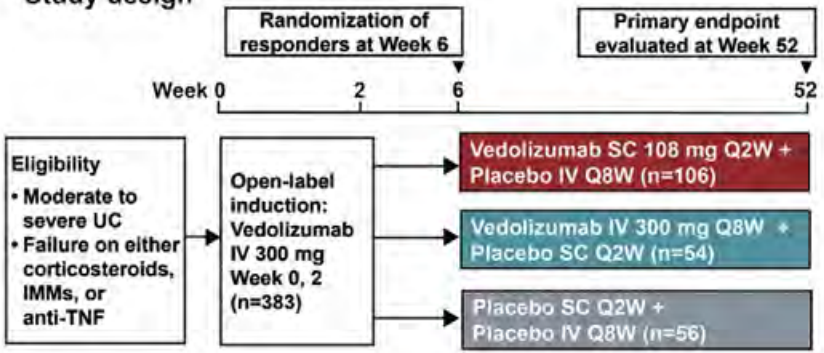


J Crohns Colitis, Volume 18, Issue 6, June 2024, Pages 790–800,

Subcutaneous Vedolizumab

VISIBLE 1 Trial of Vedolizumab Subcutaneous (SC) in Ulcerative Colitis

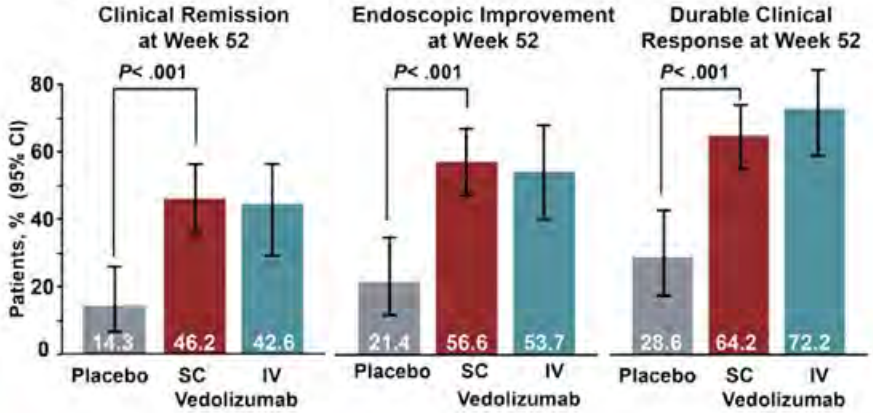
Study design



Safety / tolerability

n (%)	Placebo (N=56)	Vedolizumab SC (N=106)	Vedolizumab IV (N=54)
Adverse events	43 (76.8)	69 (65.1)	41 (75.9)
Serious adverse events	3 (5.4)	6 (5.7)	1 (1.9)
Abdominal and GI infections	5 (4.7)	2 (3.7)	1 (1.8)
Injection site adverse events	0	11 (10.4)	1 (1.9)

Efficacy



Vedolizumab SC effective as maintenance therapy in patients with moderate to severe UC after clinical response to IV induction

Vedolizumab SC safety / tolerability profile consistent with the well-established profile of vedolizumab IV

Sandborn. Gastroenterology 2020

Safety of Vedolizumab

GEMINI LTS : Phase 3, single-arm, open-label, multinational study
Period : 2009 – 2017
22423 Patients

6 – 10% Serious infections

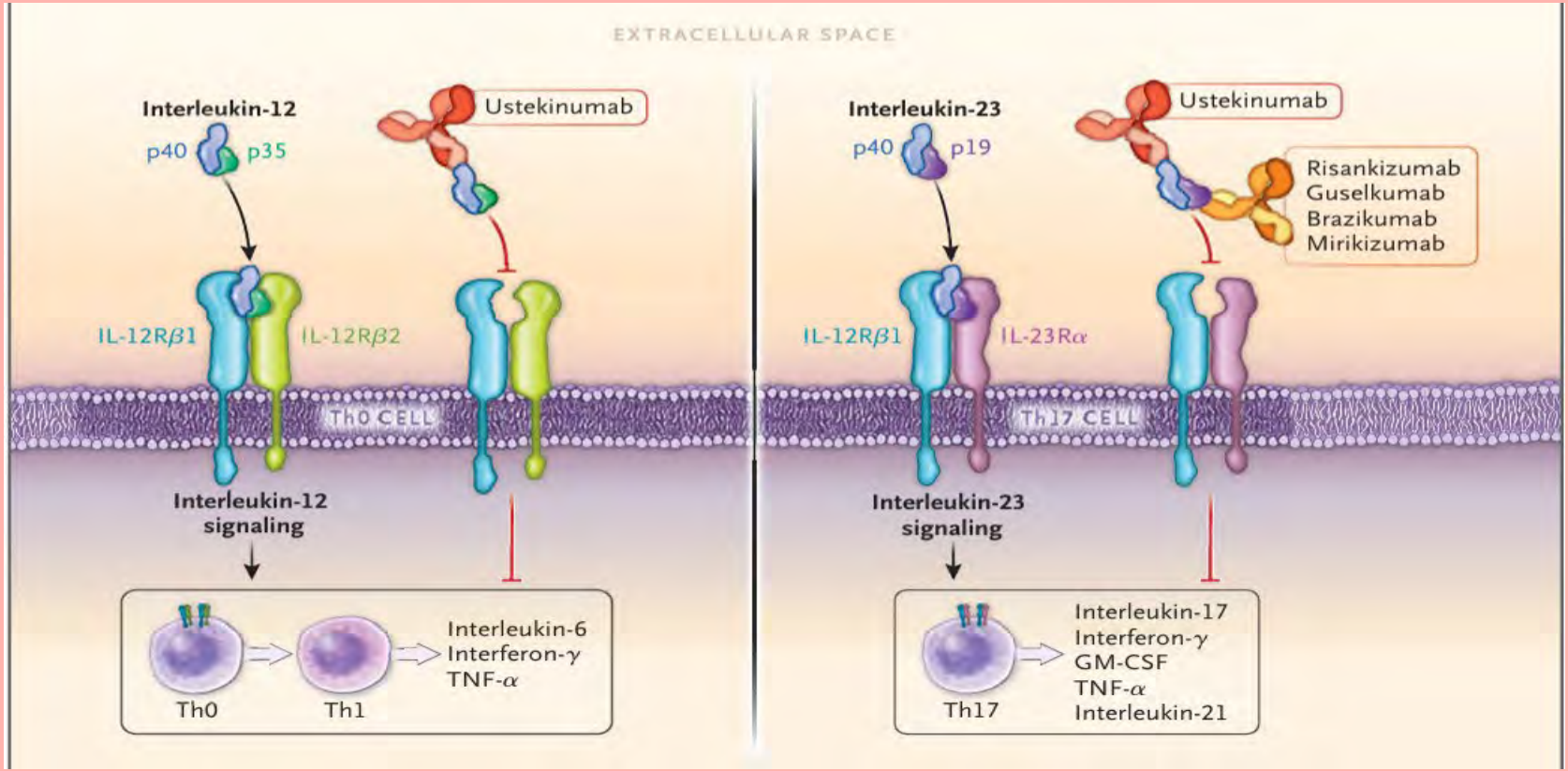
0 case of PML

6 % Malignancies

New EIM: Arthralgia 13 – 19%

Loftus Jr. Aliment Pharmacol Therapy. 2020

Anti IL12 / 23 Inhibitors



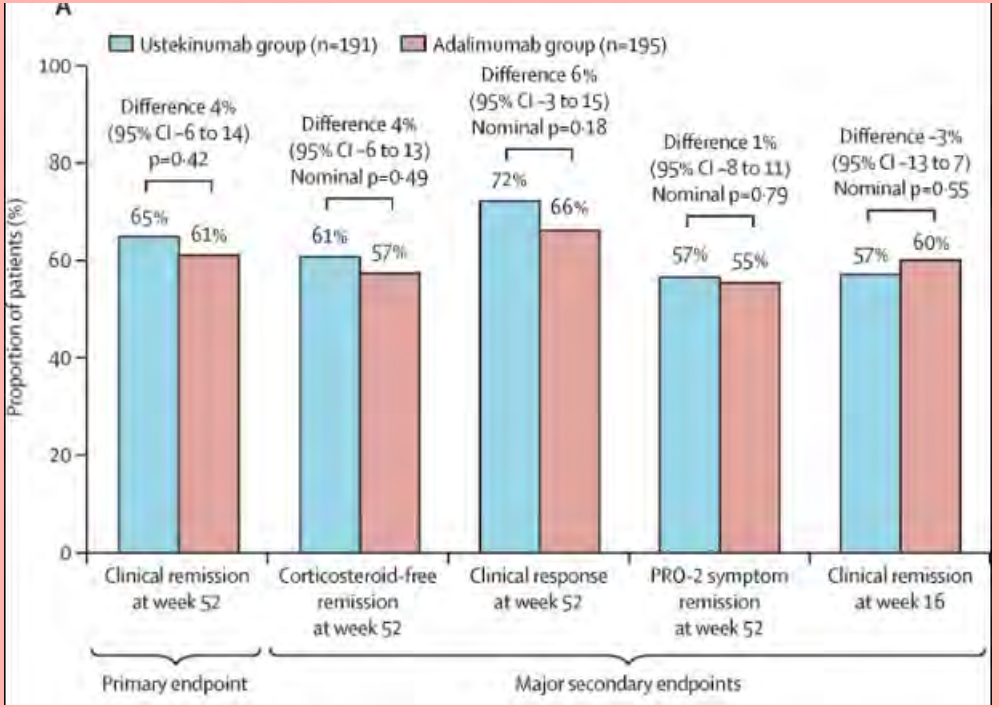
Baumgart. NEJM.2021

Anti IL12 / 23 Inhibitors

	Key Trials	Mode	Other Approved Indications
Ustekinumab **P49 IL12 ,p19 IL23**	CD (UNITI1 , UNITI 2, IM UNITI) UC (UNIFI)	IV : induction SC: maintenance	Psoriasis Psoriatic arthritis
Risankizumab **(p19 IL23)**	CD (ADVANCE, MOTIVATE, FORTIFY) UC (INSPIRE, COMMAND	IV Induction SC Maintenance	Psoriasis Psoriatic arthritis
Mirikizumab **(p19 IL23)**	UC (LUCENT 1, 2)	IV Induction SC	
Guselkumab **(p19 IL23)**	CD (GALAXI 1, 2,3) GRAVITY UC (QUASAR)	IV : SC:	Psoriasis Psoriatic arthritis

SEAVUE :Ustekinumab vs Adalimumab

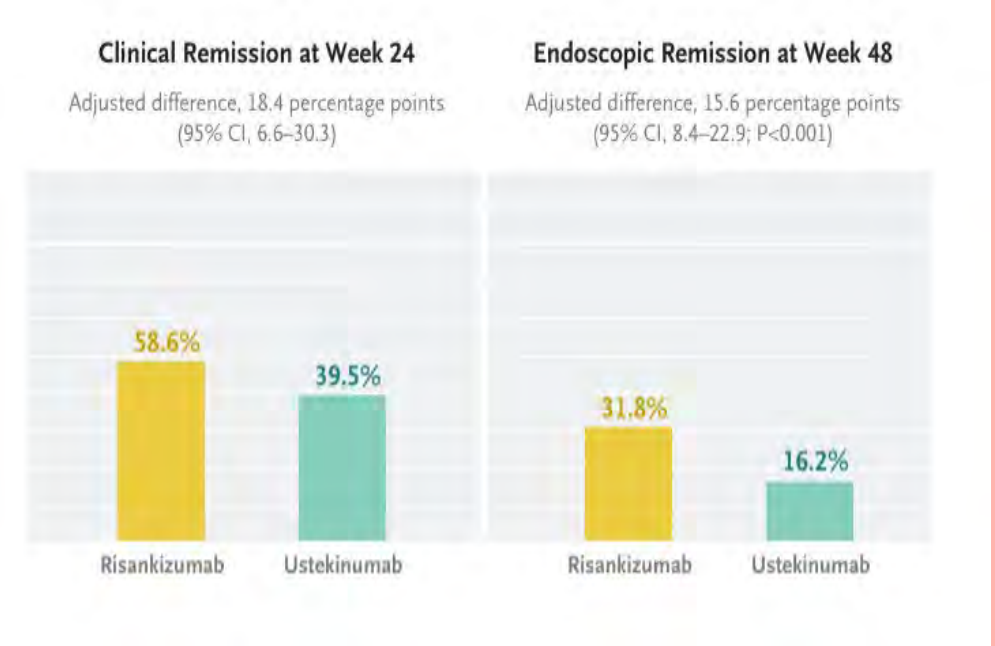
- Phase 3b trial randomized, double-blind, parallel-group, active-comparator
- Ustekinumab vs Adalimumab: efficacy and safety
- CD patients : biologic naïve



Sands. The Lancet. 2022

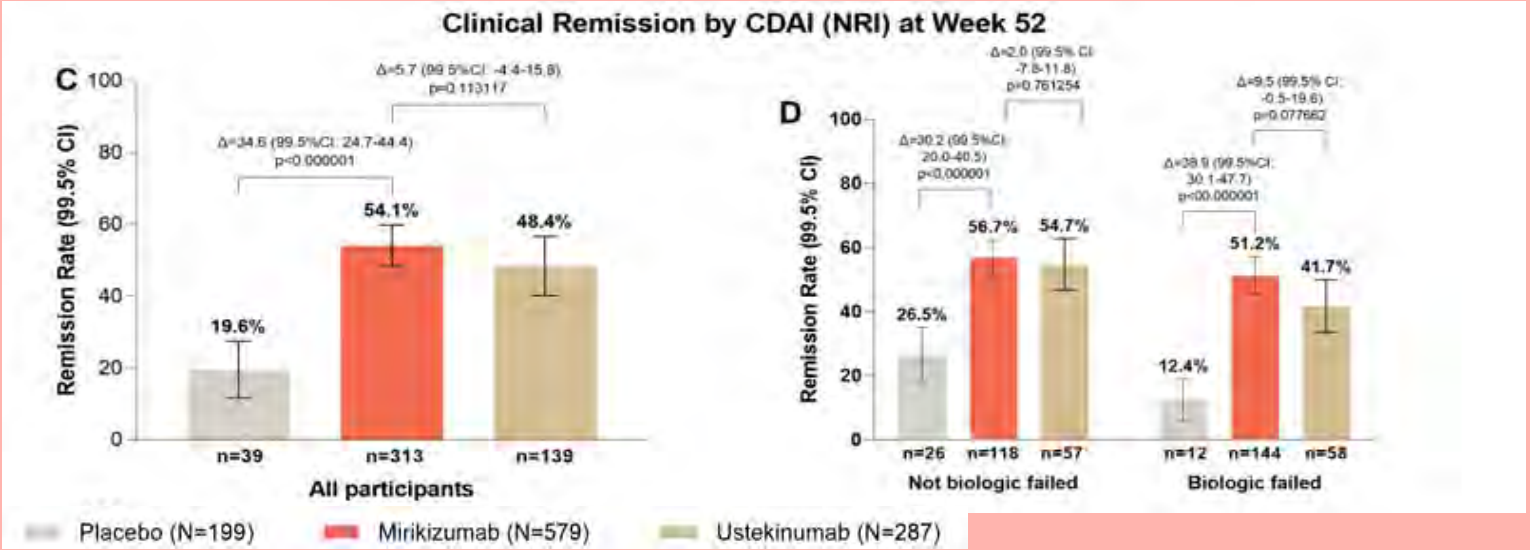
SEQUENCE Risankizumab vs Ustekinumab

- Phase3b, multicenter, open-label, randomized, controlled
- CD patients
- Failed / intolerant to antiTNF



Peyrin-Biroulet. N Engl J Med2024

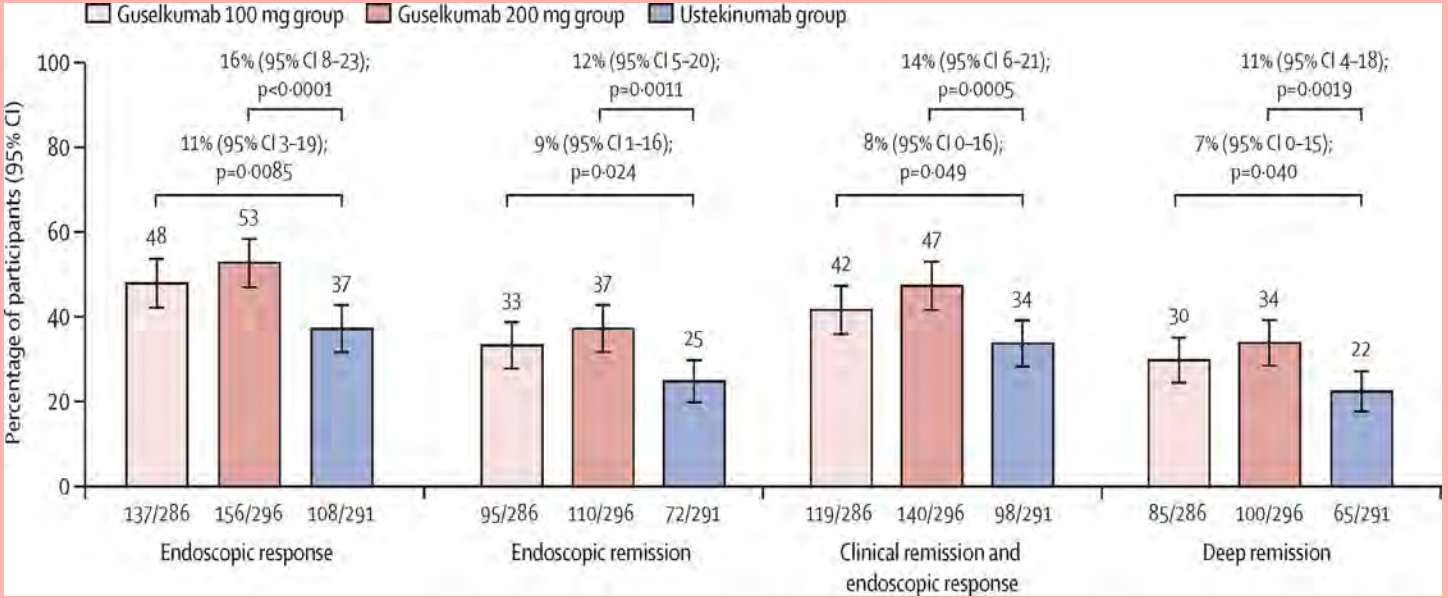
VIVID – 1 :Mirikizumab vs Ustekinumab



- Phase3, randomized, double-blind, double-dummy
- CD patients

Jairath.Journal of Crohn's and Colitis. 2024

GALAXY 2, 3: Guselkumab vs Ustekinumab



The Lancet 2025 406358-375DOI: (10.1016/S0140-6736(25)00681-6)

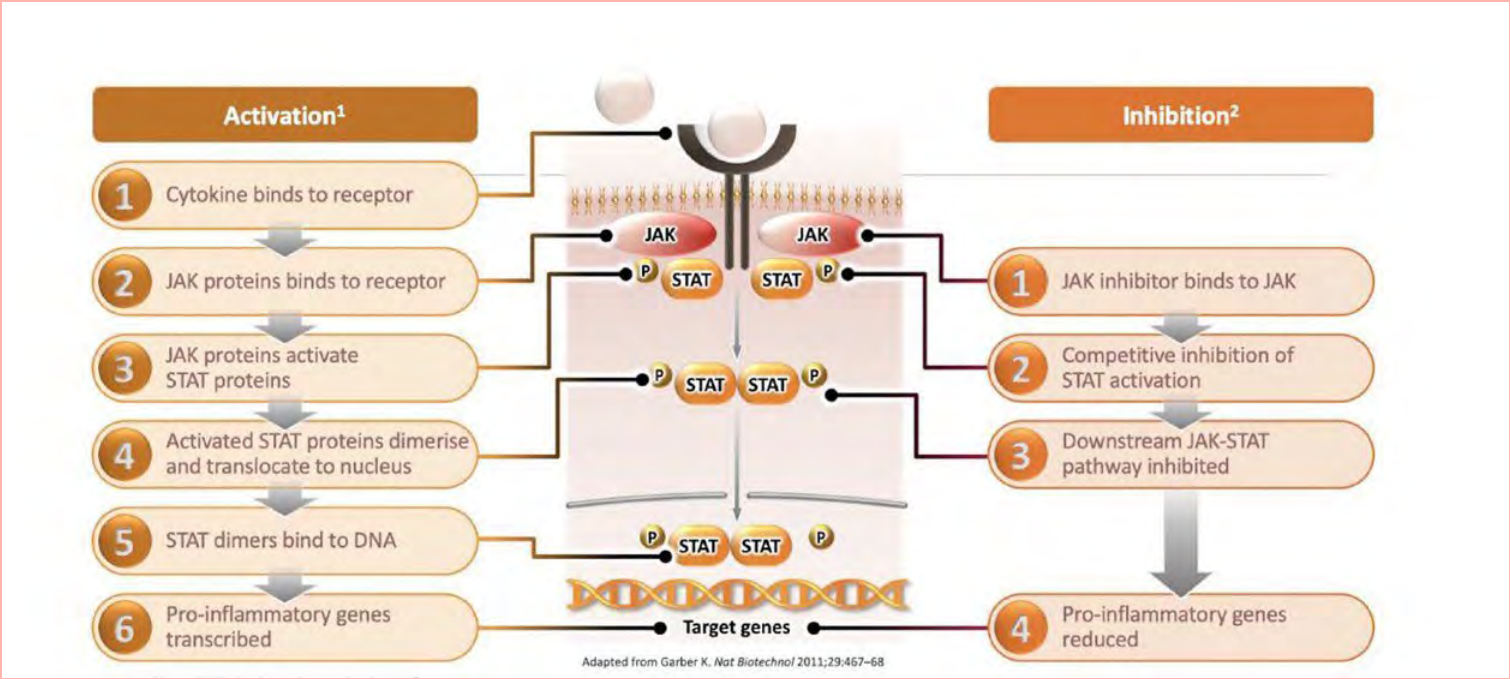
Safety of IL12/23 Inhibitors

- Infections,
- Injection site reactions,
- Abdominal pain,
- Nausea,
- Arthralgia
- Headache

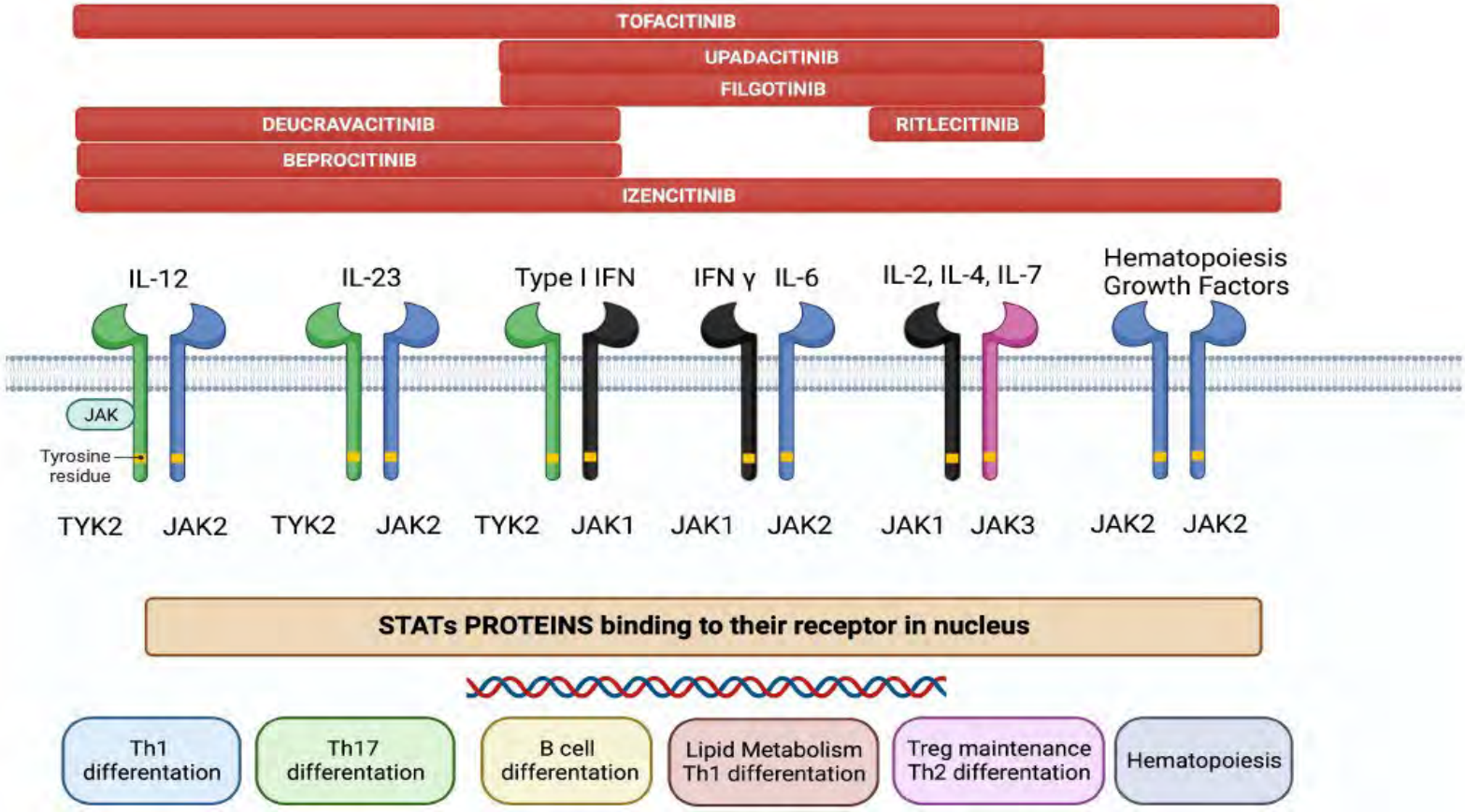
"no increased risk of adverse and serious adverse events with ustekinumab when compared with placebo"

Davis. Cochrane Database of Systematic Reviews 2019

JAK- STAT SIGNALLING PATHWAY



Ernest-Suarez. Ther Adv Gastroenterol 2023



Herrera-deGuise. Front. Med 2023

Upadacitinib in Crohn's Disease

U- EXCEL

Induction : 45 mg or placebo OD for 12 weeks

45% : >1 biologic/conventional failed / intolerant

CR : 49.5 % (45mg) , 29.1 % (placebo) (p<0.001)

U- EXCEED

Induction : 45 mg or placebo OD for 12 weeks

>1 biologic/ conventional failed / intolerant

CR : 38.9% (45mg) , 21.1% (placebo)) (p<0.001)

U-ENDURE

Maintenance : 15 mg, 30 mg or placebo

CR : 37.2% (15mg) , 47.6% (30mg), 7.3% (placebo)) (p<0.001

Loftus EV,. N Engl J Med. 2023; Panaccione R Clin Gastroenterol Hepatol. 2025

Upadacitinib in Ulcerative Colitis

U- ACHIEVE

Induction : 45 mg or placebo OD for 12 weeks

CR : 26 % (45mg) , 5% (placebo)) (p<0.001)

U- ACCOMPLISH

Induction : 45 mg or placebo OD for 8 weeks

CR : 34 % (45mg) 4 % (placebo) (p<0.001)

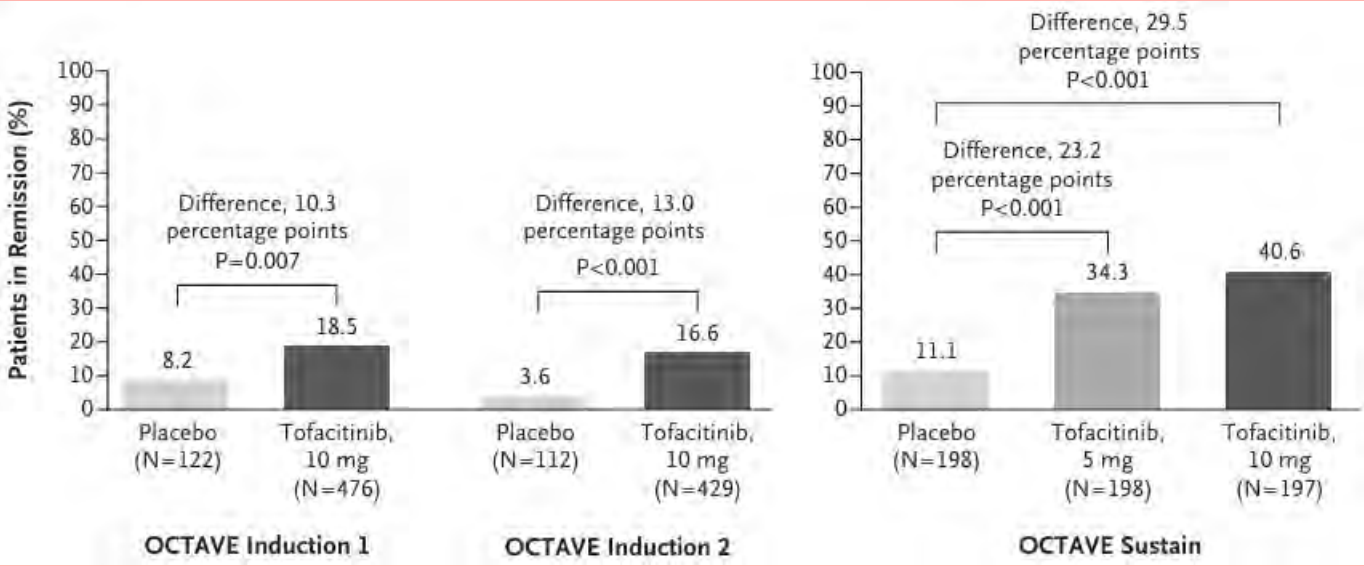
U- ACHIEVE

Maintenance : 15 mg, 30 mg or placebo

CR : 40.4% (15mg) , 53.6% (30mg), 10.8% (placebo)) (p<0.001

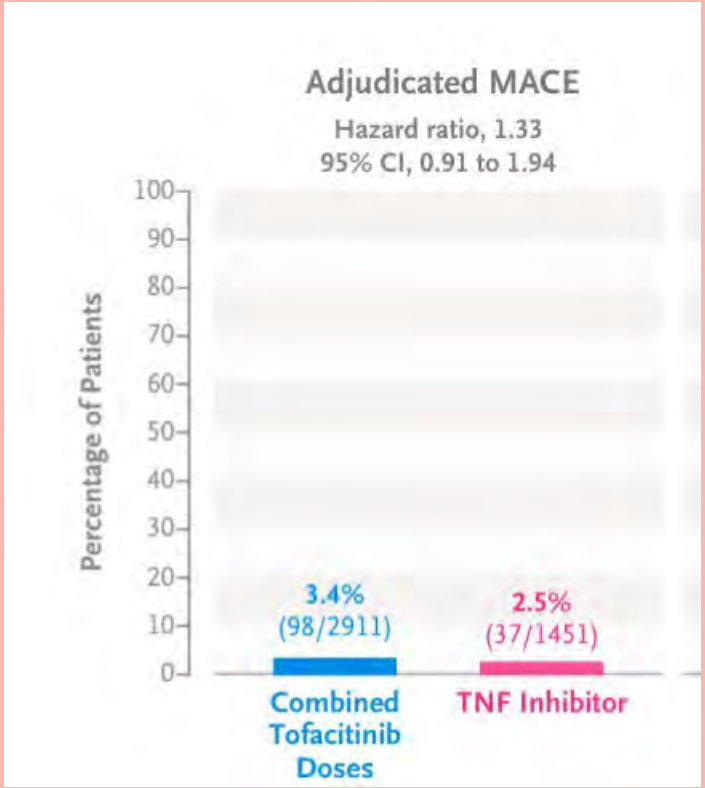
Danese Lancet 2022, Vermeire Lancet Gastroenterol Hepatol. 2023

Tofacitinib in Ulcerative colitis



Sandborn. N Engl J Med 2017

Safety of JAK inhibitors



High Risk :

- > 65 years
- Smokers

Review + Meta-analysis in CD[3]

No increase MACE

Ytterberg N Engl J Med2022, Kristensen, Annals of the Rheumatic Diseases2023, [3]Niu, Clin Drug Investig **44**, 371–385 (2024)

Safety of JAK Inhitors

Venous thromboembolism

Herpes Zoster infection

Elevated cholesterol

Infections : URTI

Teratogenicity

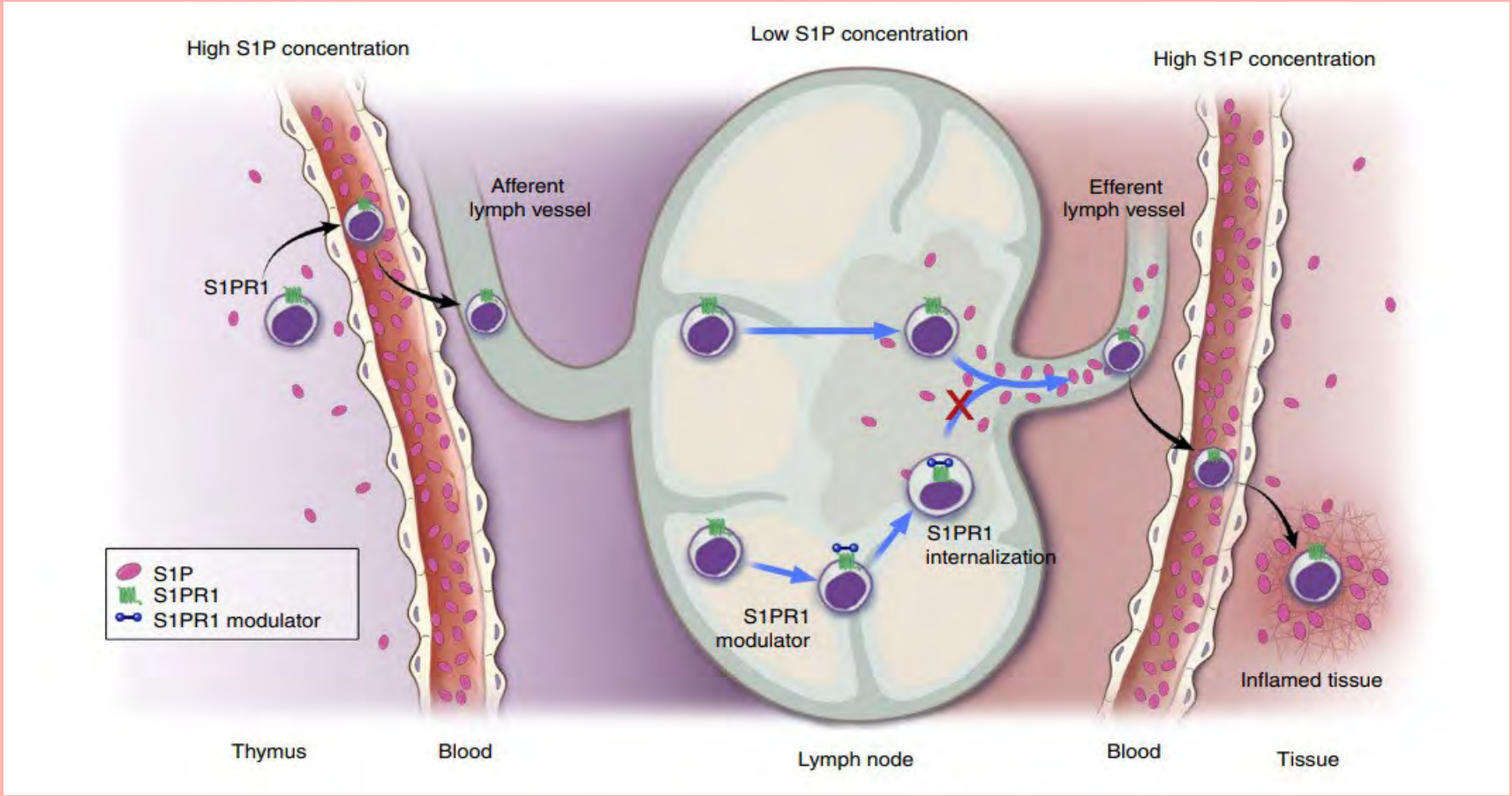
Cytopenia

CPK elevation

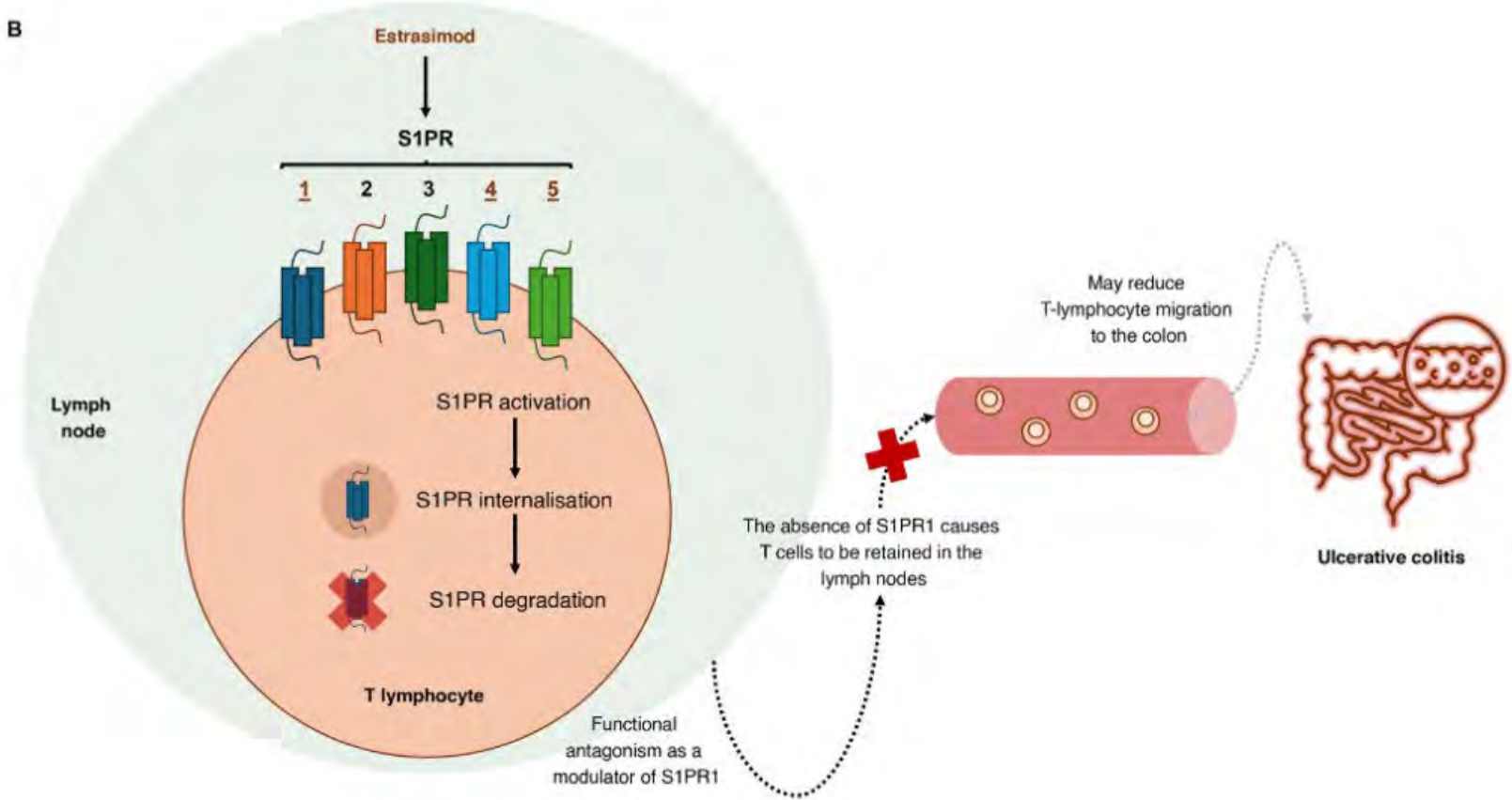
NM skin cancer

Danese Lancet2022; Niu, Clin Drug Investig**44**, 371–385

Sphingosine 1 Receptor Inhibitors

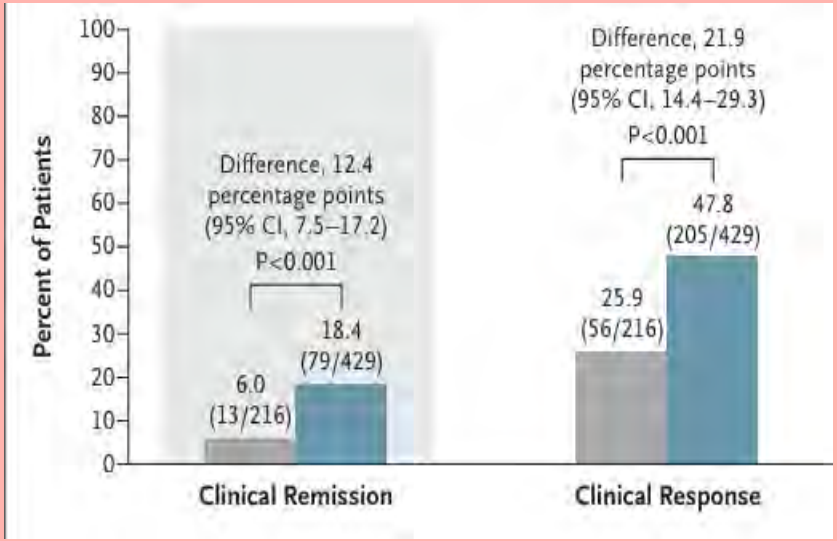


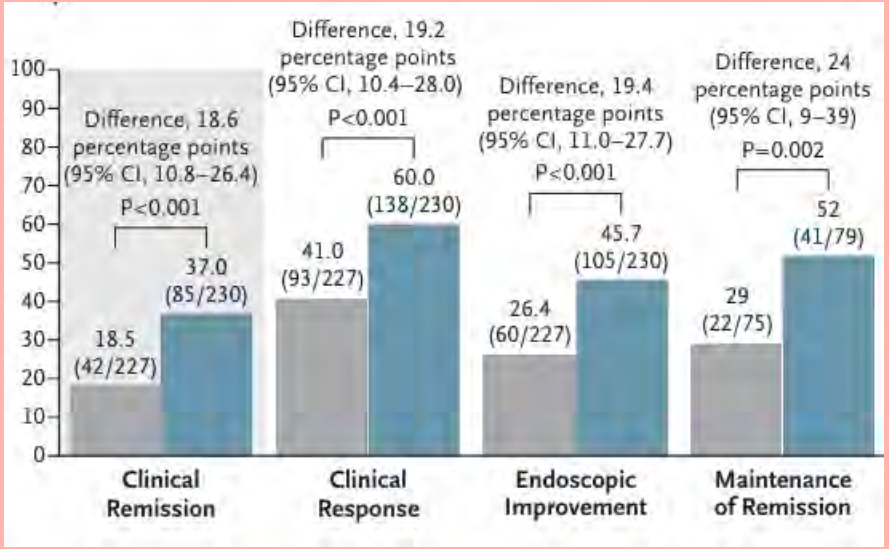
Wang. Aliment Pharmacol Ther. 2022



Gispert. Gastroenterología y Hepatología 48 (2025)

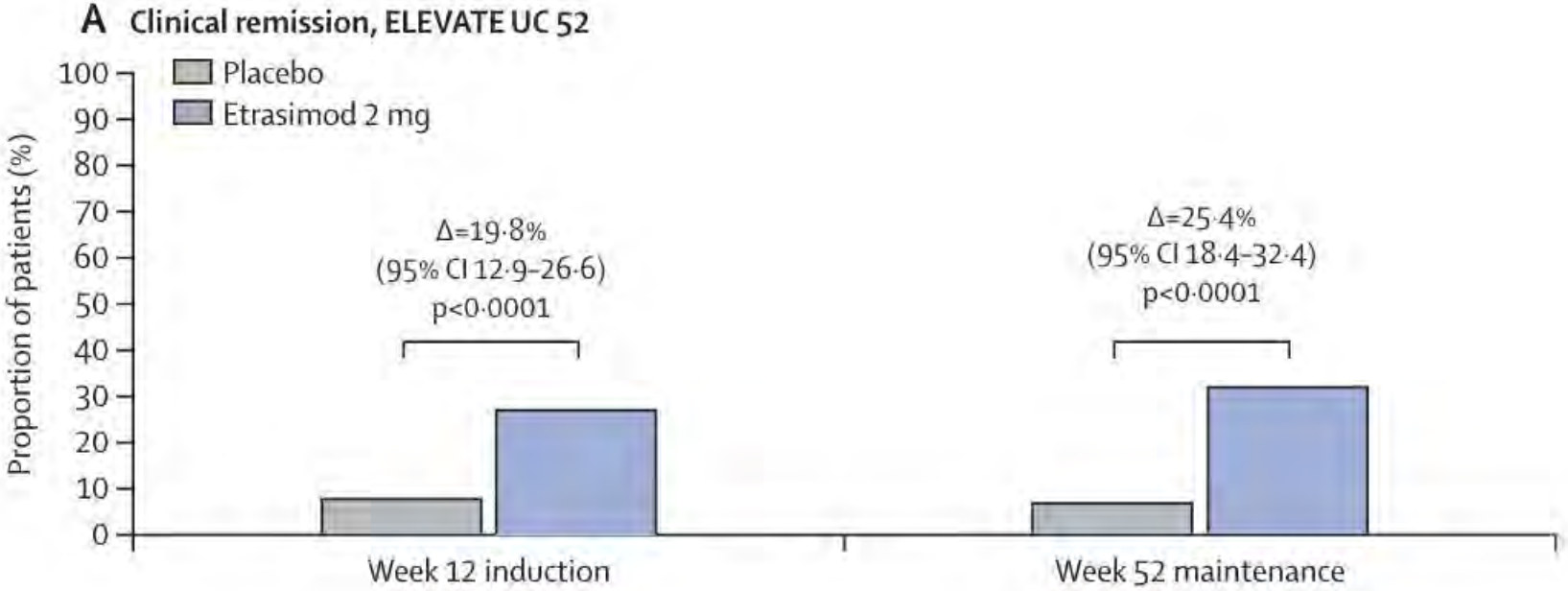
TRUE NORTH : Ozanimod in Ulcerative colitis





Sandborn N Engl J Med 2021

ELEVATE UC : Etrasimod in Ulcerative colitis



Sandborn Lancet 2023; 401: 1159–71

Safety of S1 P receptors

Lymphopenia

Infections : nasopharyngitis

Herpes zoster

Elevated liver enzymes

Malignancies : no increased risk

Bradycardia : not significantly elevated. Exclude pre treatment

Macular edema : pretreatment ophthalmic in high risk

Sandborn N Engl J Med 2021, Sandborn Lancet 2023; 401: 1159–71

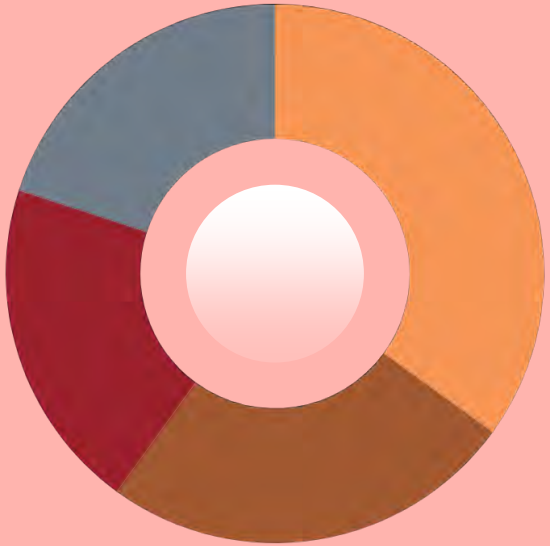
POSITIONING THERAPY

PATIENT

Age, Pregnancy,
Comorbidities, Preferences

Drug

Indication
Rapidity, Durability
Combination
Sequencing



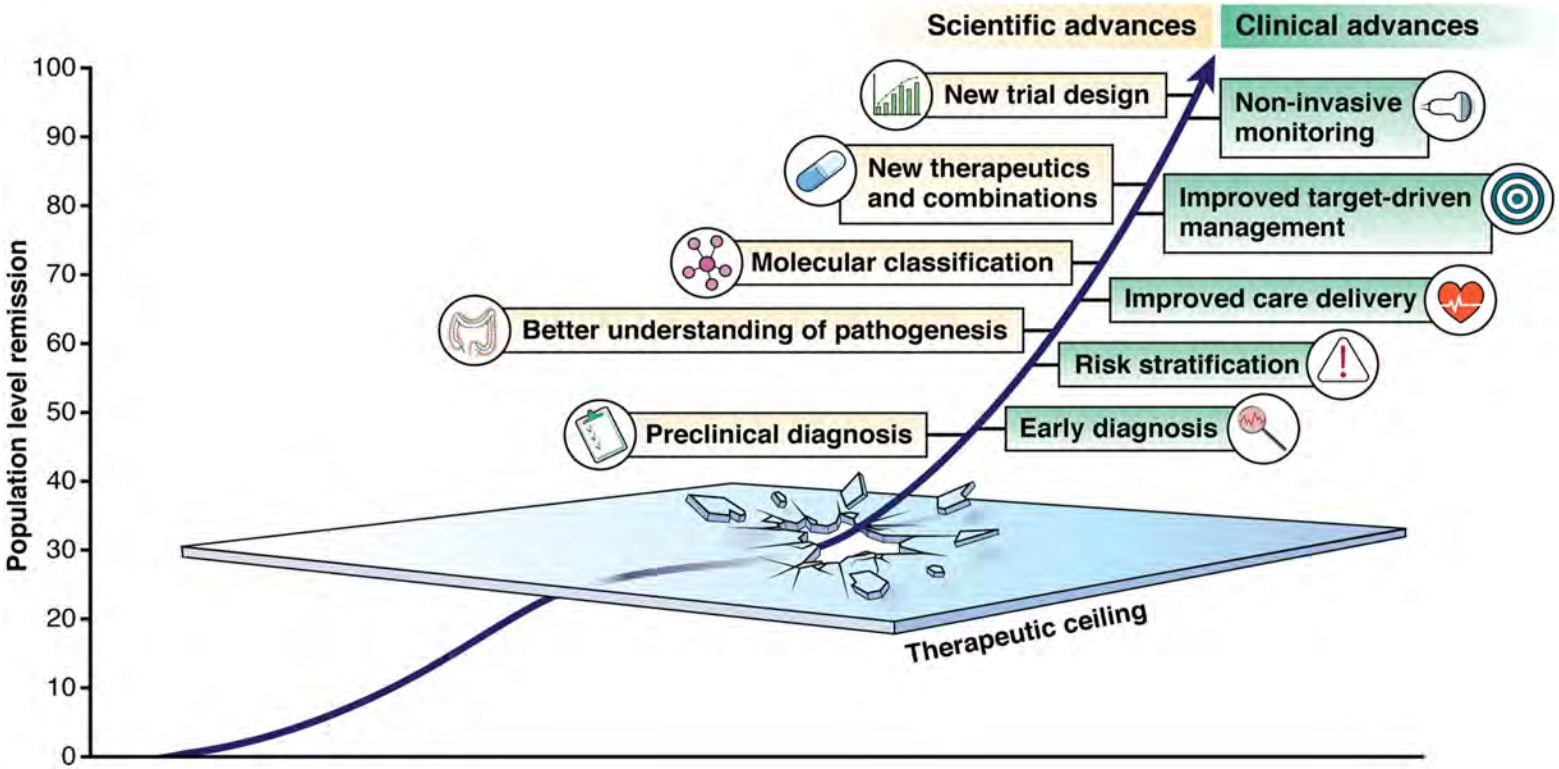
Disease

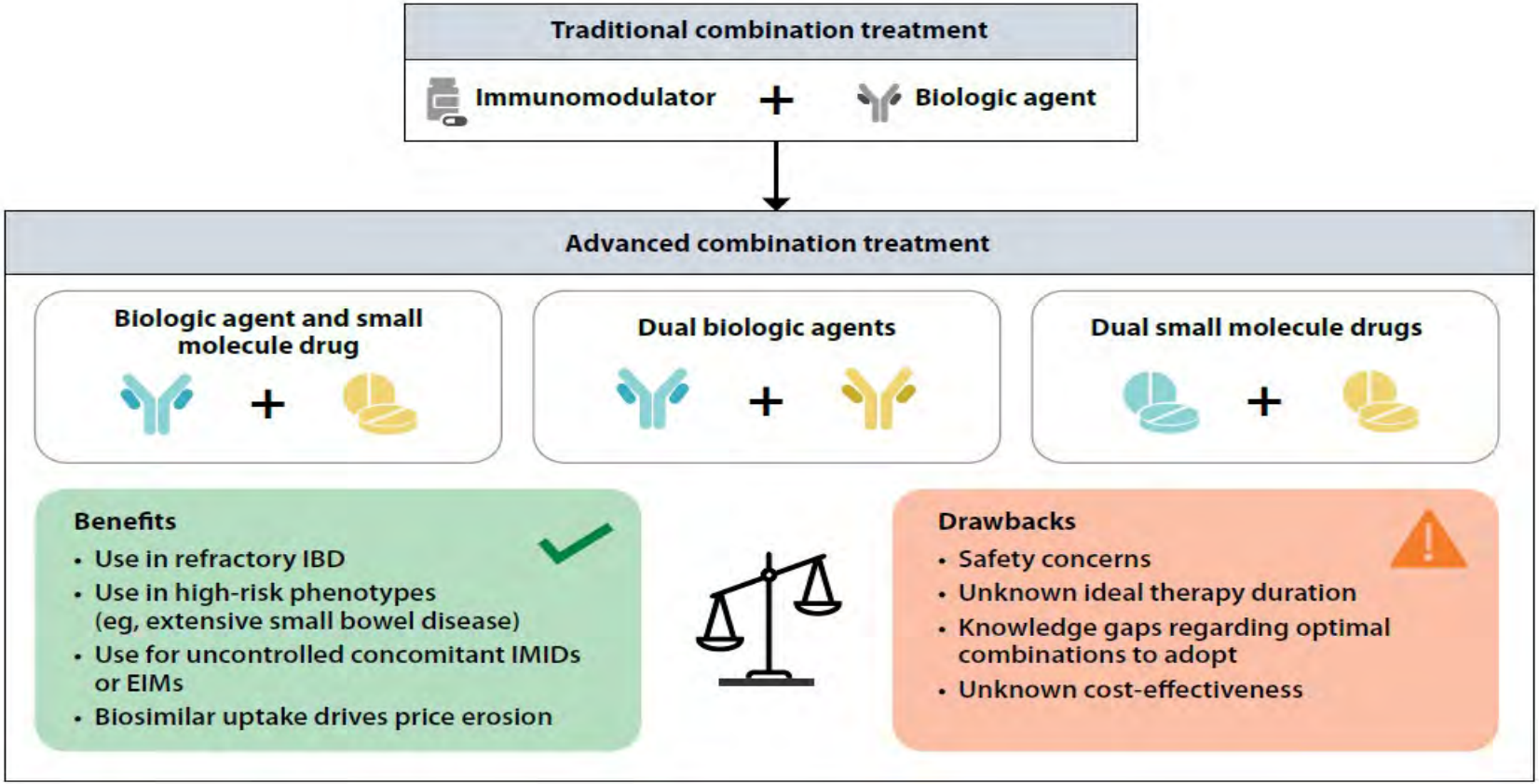
CD vs UC
Disease length, severity
EIM
Prior treatment

Safety

Infection
Cancer
Class specific
Drug interactions

Therapeutic Ceiling





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QUESTIONS and COMMENTS

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