



IV CONGRESSO
NAZIONALE
IG - IBD

*Where tradition
meets
innovation*

IBD
The Italian Group for the study of
Inflammatory Bowel Disease

FIRENZE
Convitto della Calza
29 novembre - 1 dicembre 2018

Small molecules and new therapeutic targets

Flavio Caprioli

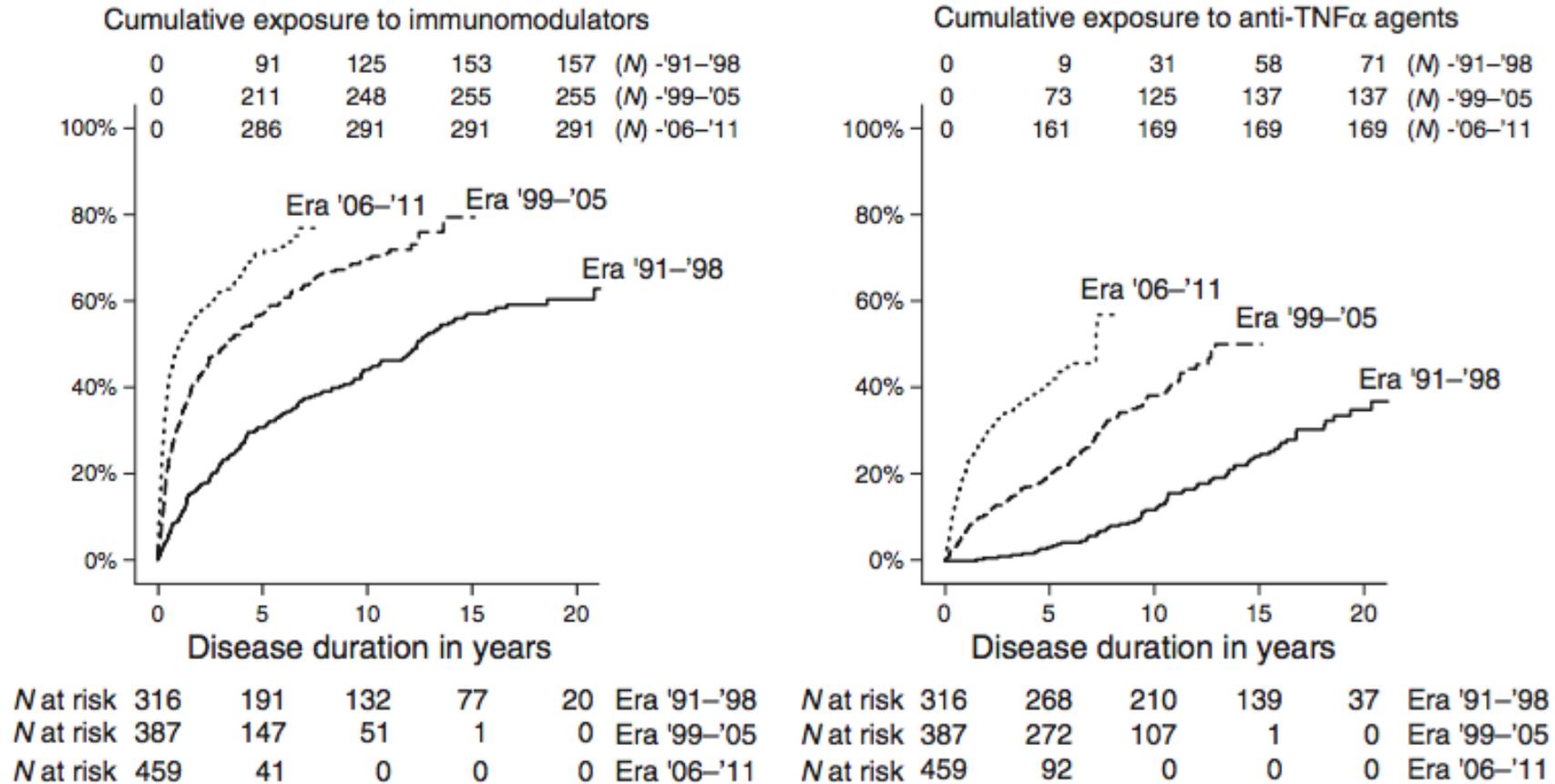
Università degli Studi di Milano
Fondazione IRCCS Cà Granda, Ospedale Policlinico di Milano



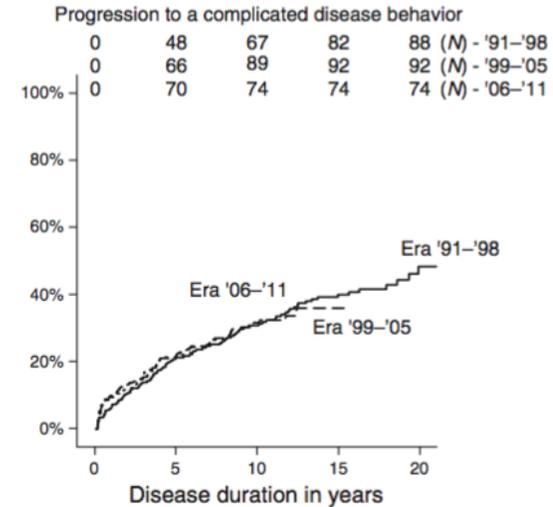
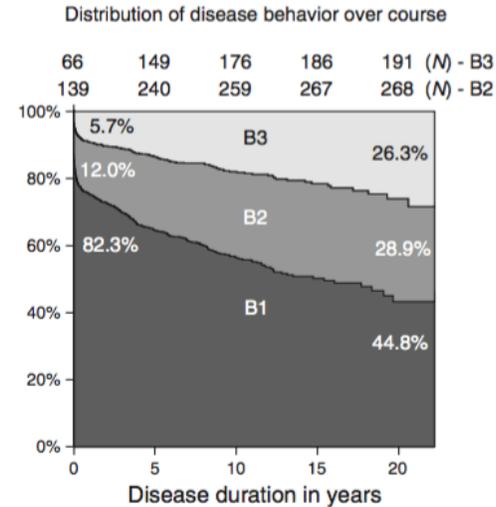
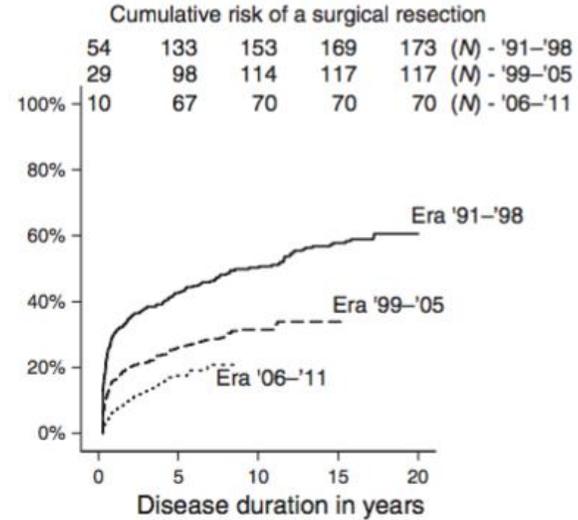
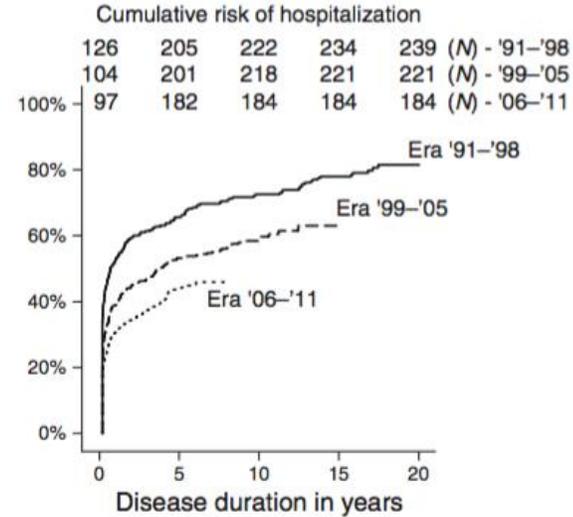
Do we really need new drugs for IBD patients?



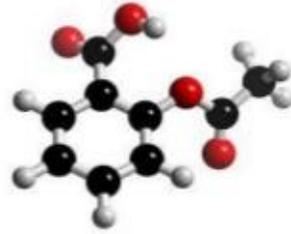
Cumulative probability of thiopurines and antiTNF use – Dutch cohort 1991-2011



Cumulative hosp & surg rates for Crohn's disease

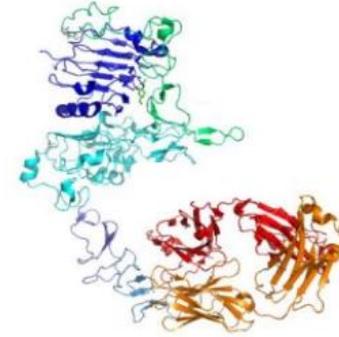


Future panorama of IBD drugs



Small molecules

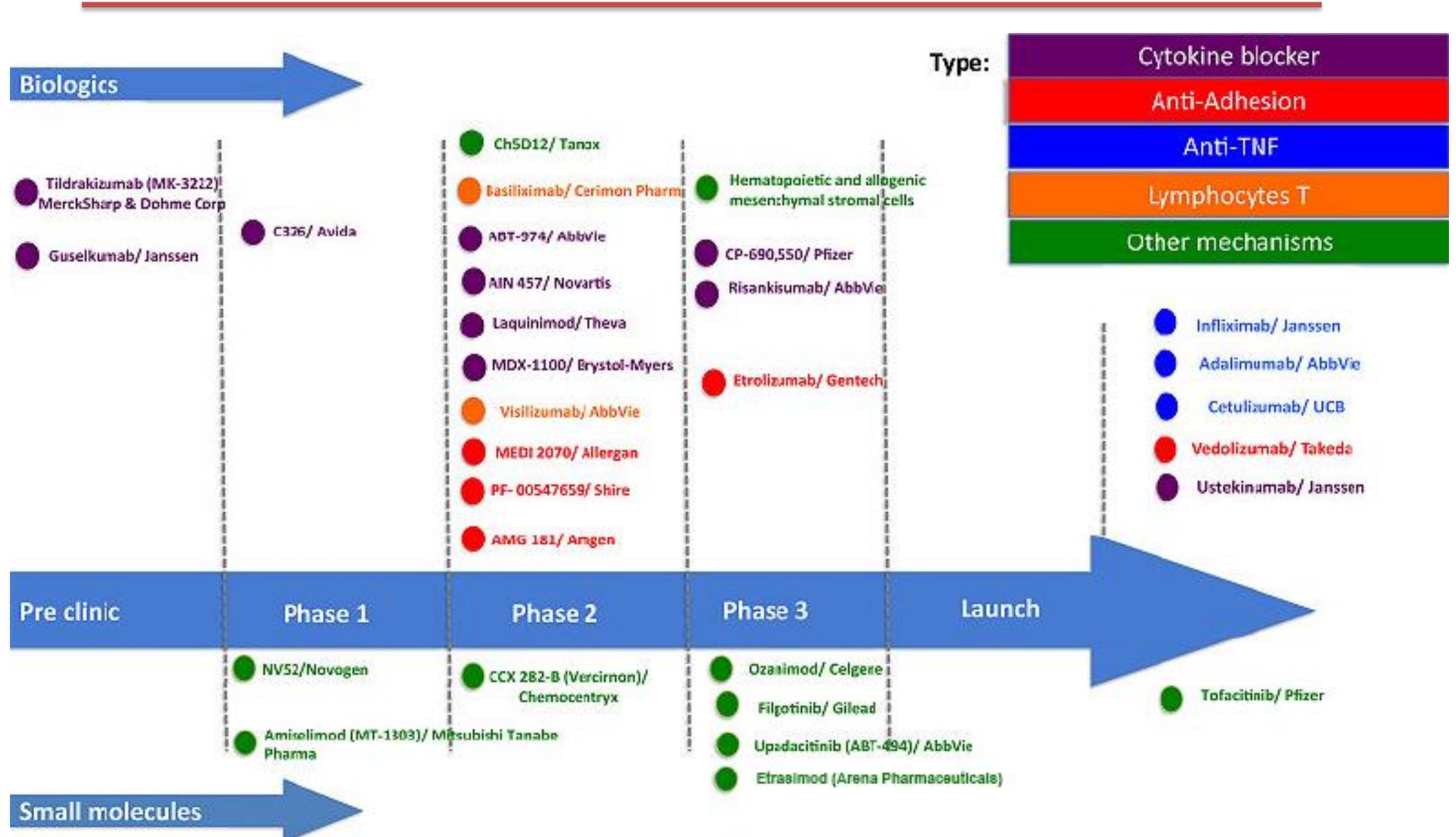
Molecular weight	Small (<1000 daltons)
MoA	Receptor or enzyme inhibition
Location of target	Intracellular
Target specificity	Less (compared to biologics) <ul style="list-style-type: none">• Toxicities generally non-specific/not related to target (“off-target toxicity”)
Half-life	Short (compared to antibodies) <ul style="list-style-type: none">• Minutes – hours - days
Distribution	Potential for extensive distribution within the body
Immunogenicity	Generally not a concern

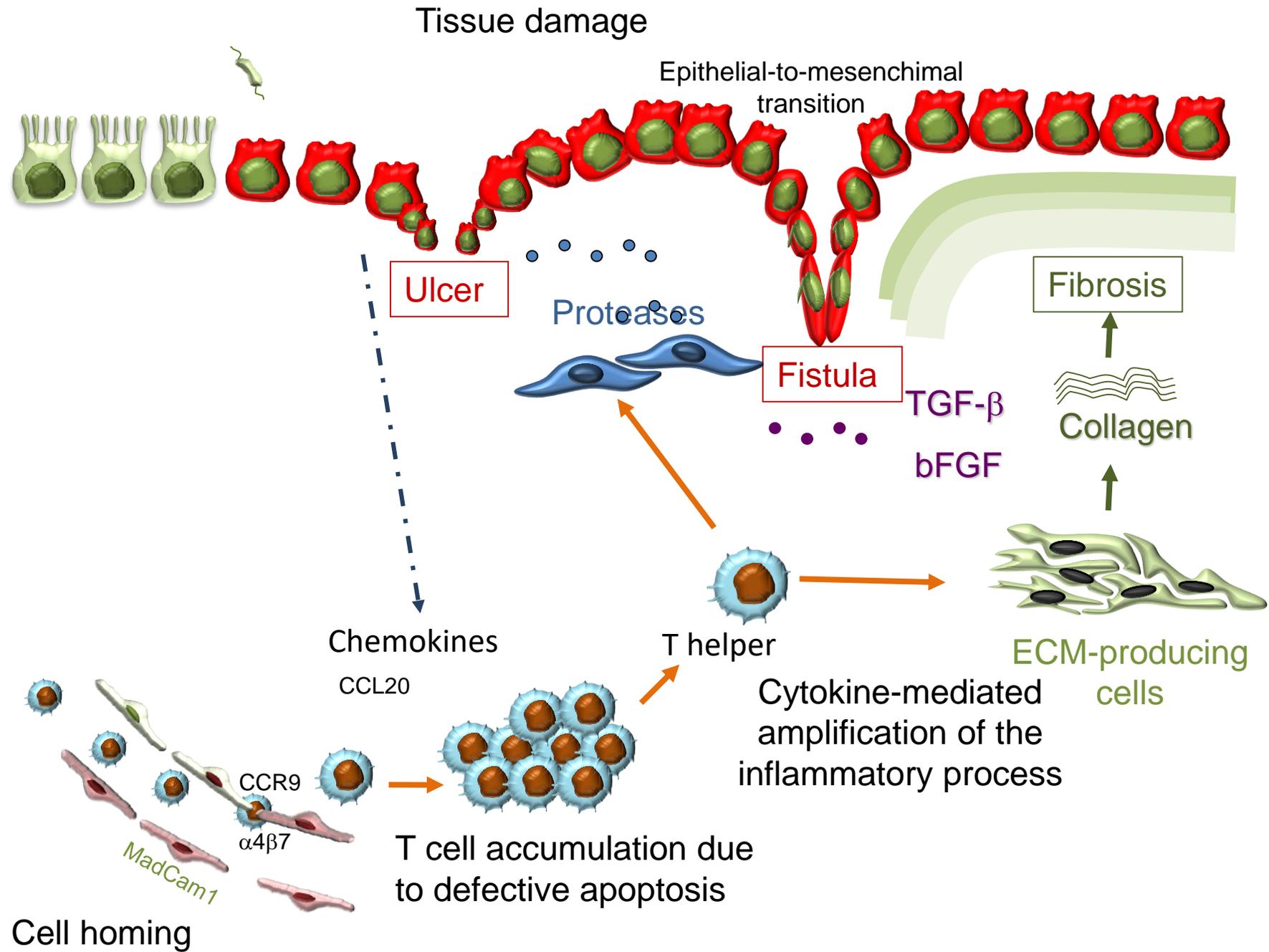


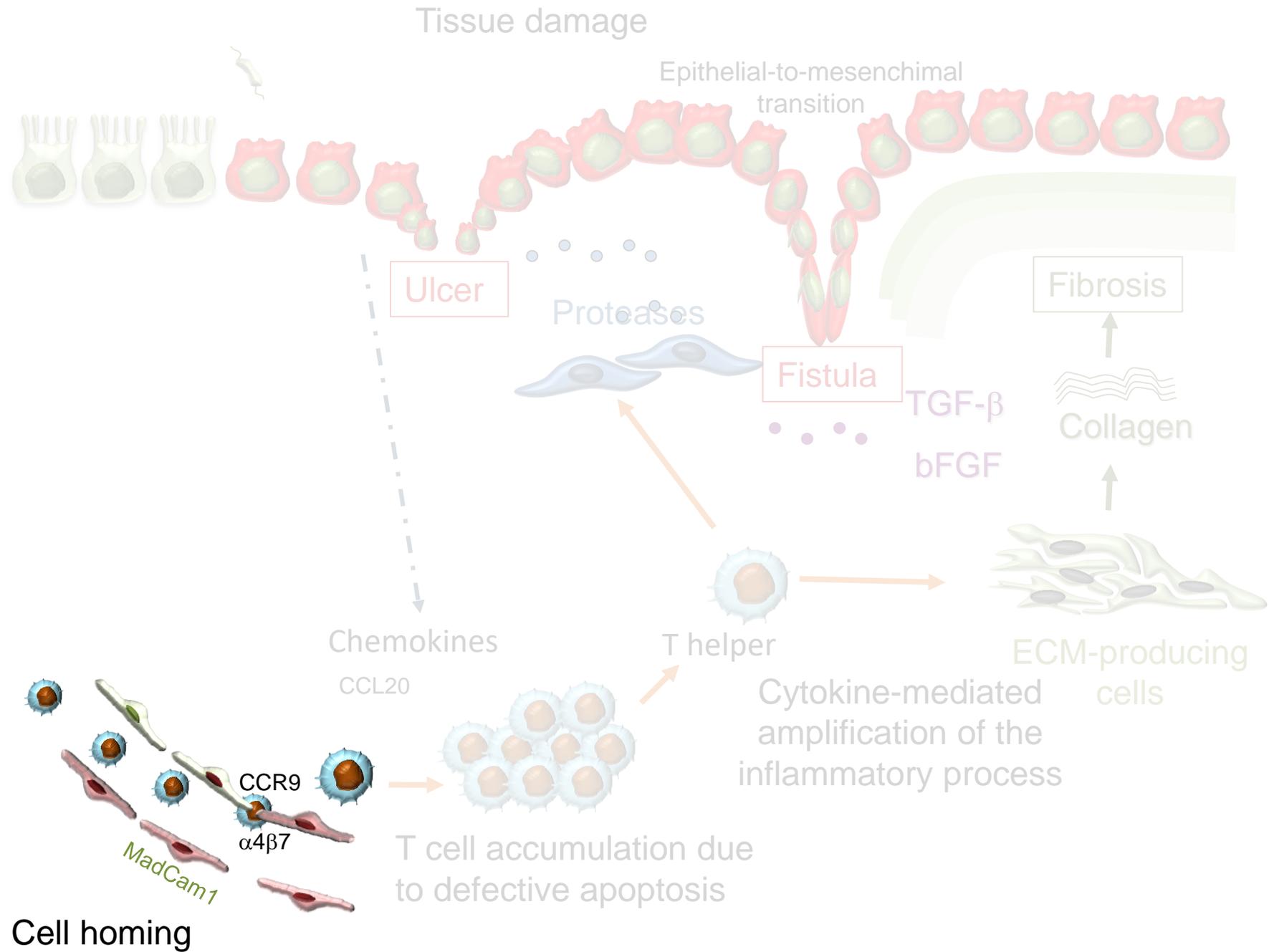
Monoclonal antibodies

Molecular weight	Large (e.g. mAb = 150 kDa)
MoA	Depletion
Location of target	Extracellular
Target specificity	High target specificity <ul style="list-style-type: none">• Toxicity generally related to target/pharmacology or “on-target toxicity”
Half-life	Long – especially molecules with Fc or IgG FcRn receptor, protects IgG from catabolism
Distribution	More limited distribution within body <ul style="list-style-type: none">• Initially, largely confined to vascular space
Immunogenicity	Common challenge in animals and humans

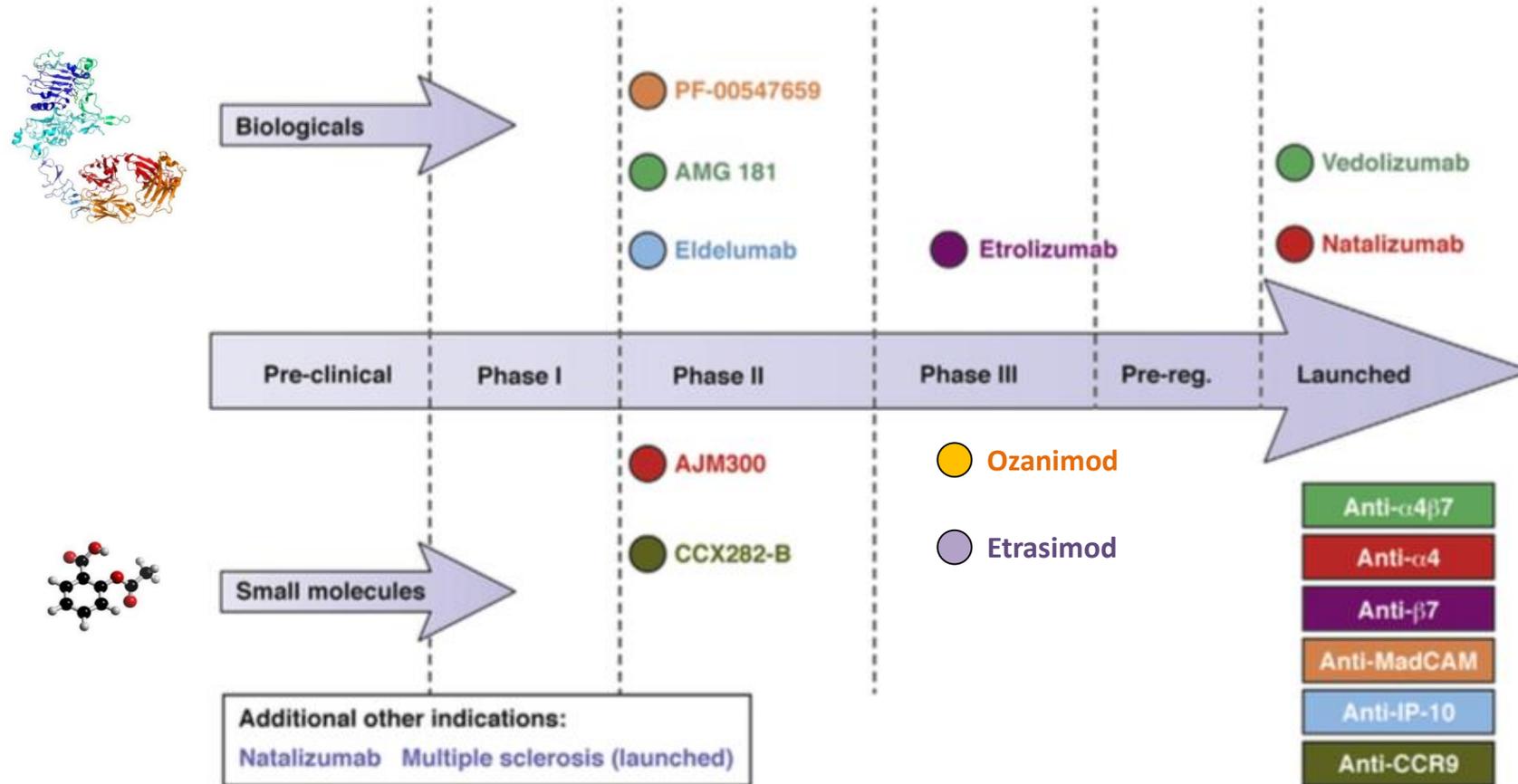
Future panorama of IBD drugs



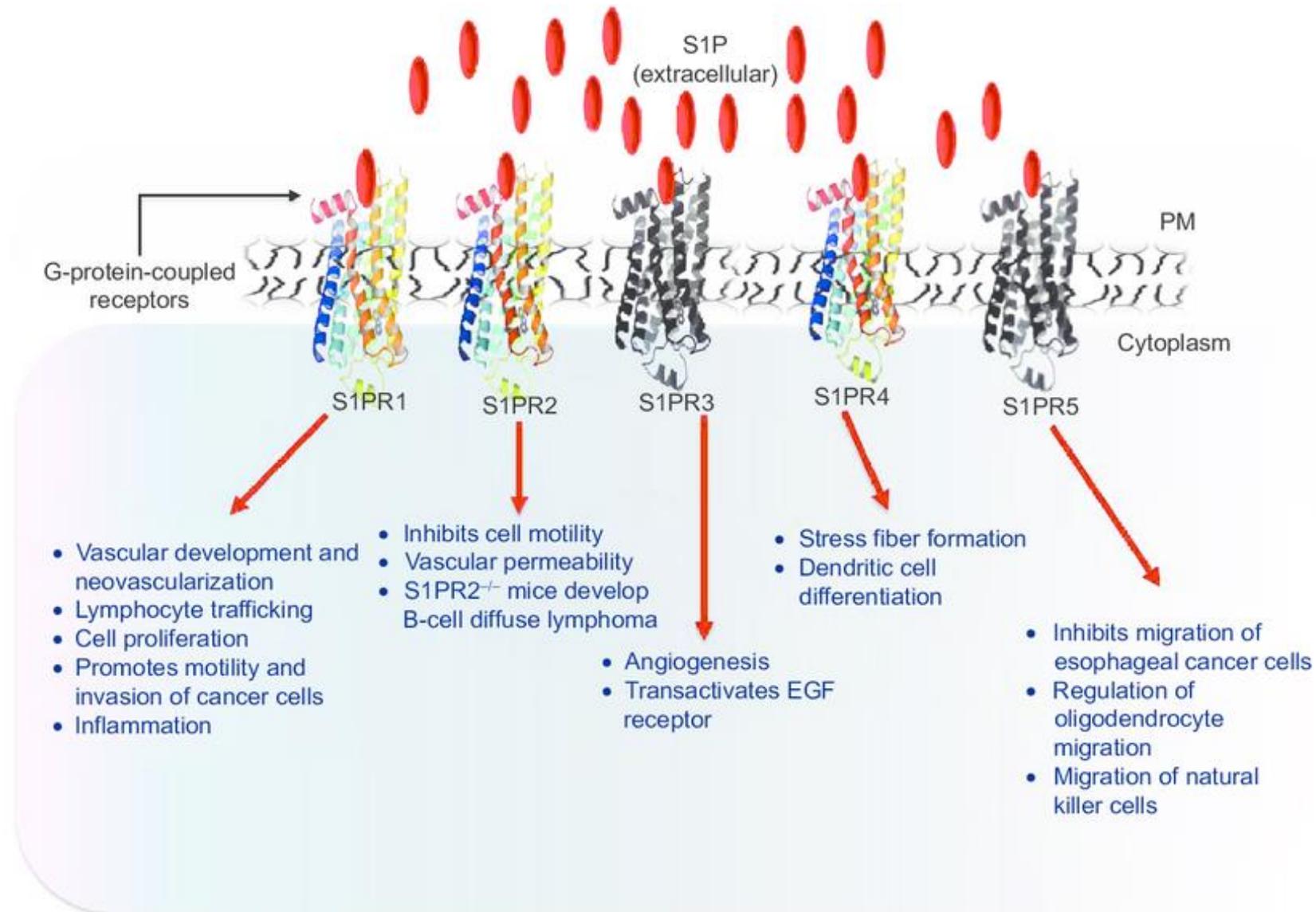




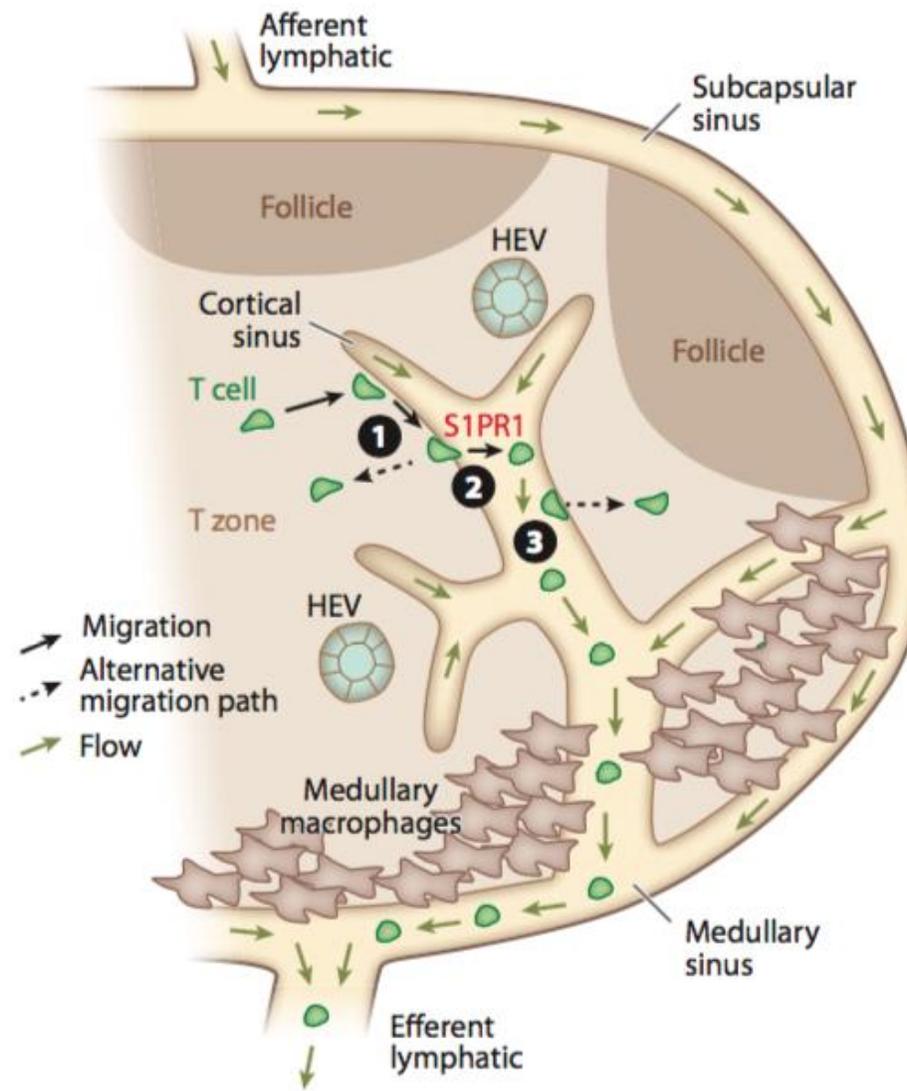
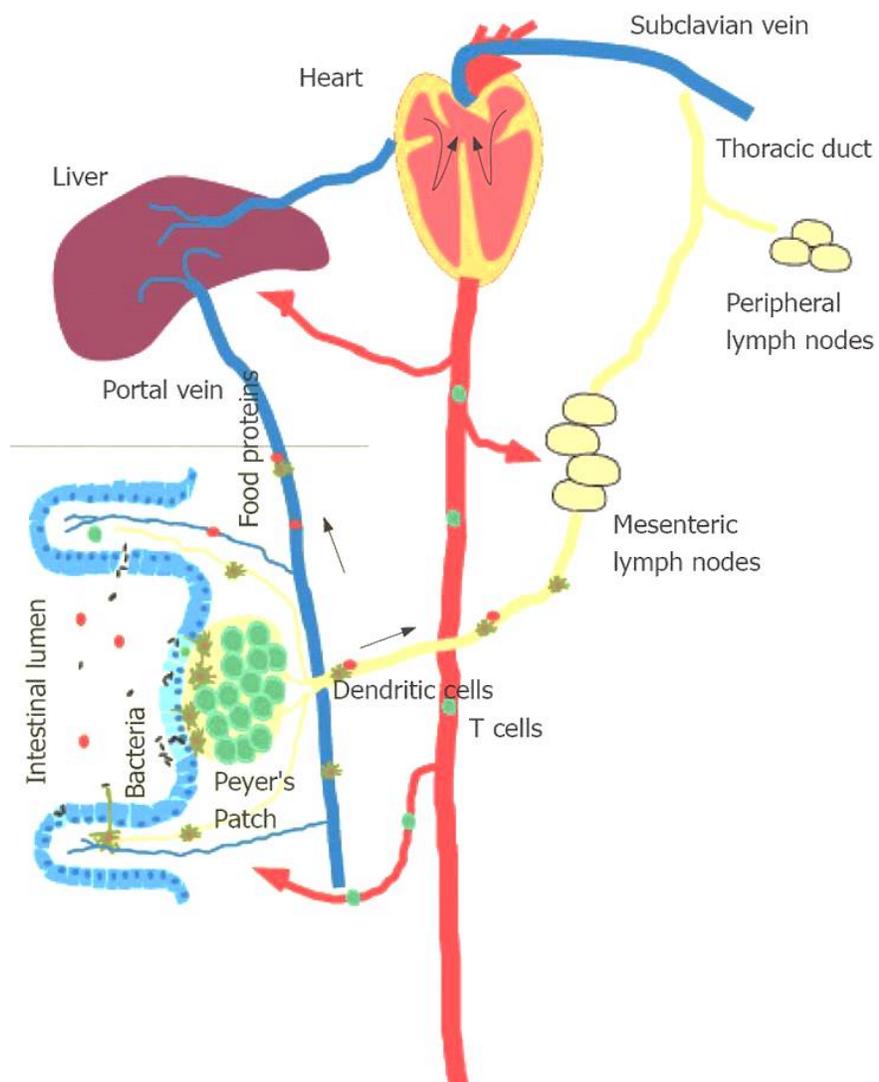
Drugs targeting lymphocyte homing in the gut



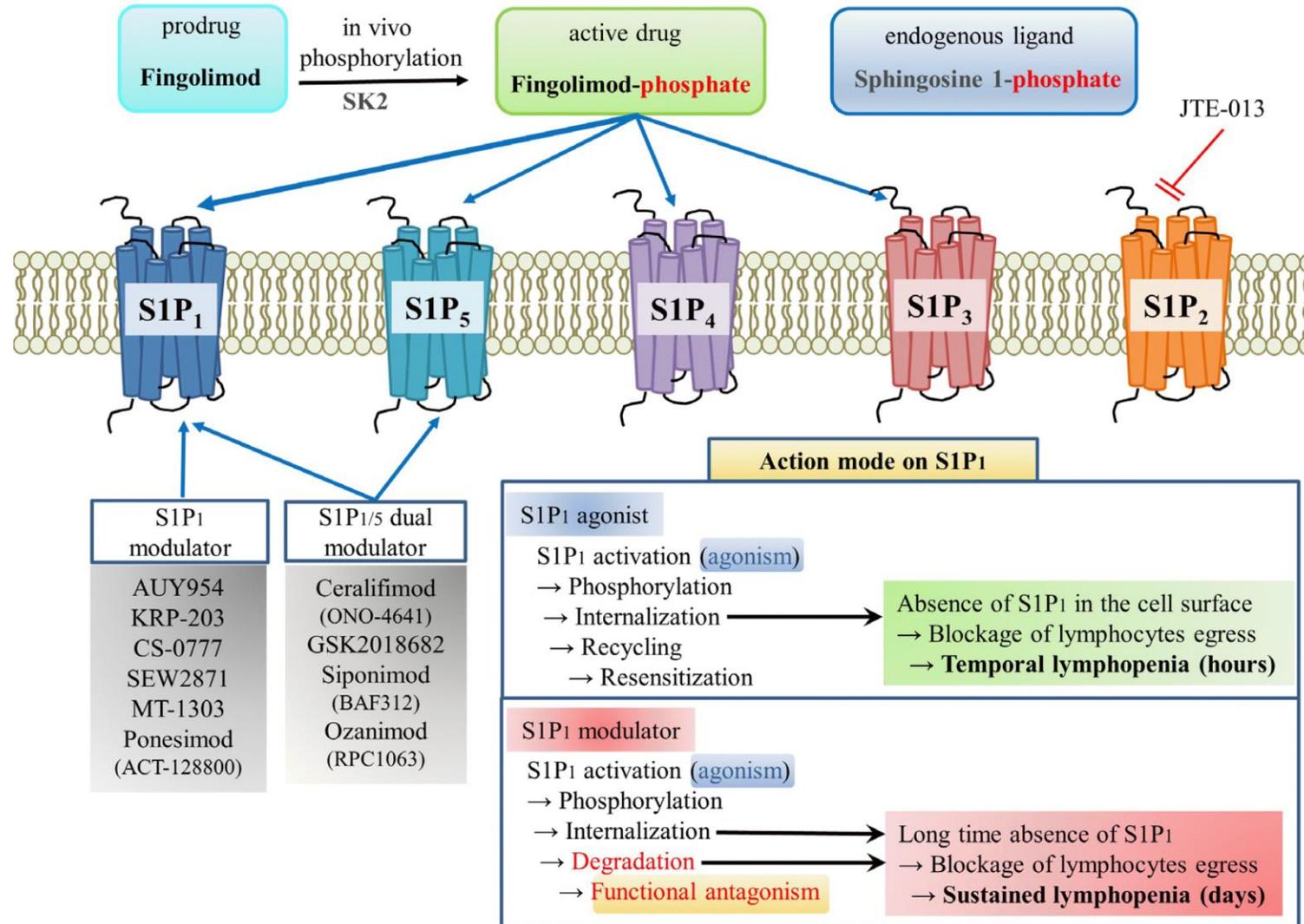
Sphingosine-1 Phosphate receptors (S1PR)



S1PR1 regulate lymphocyte egress from lymph nodes

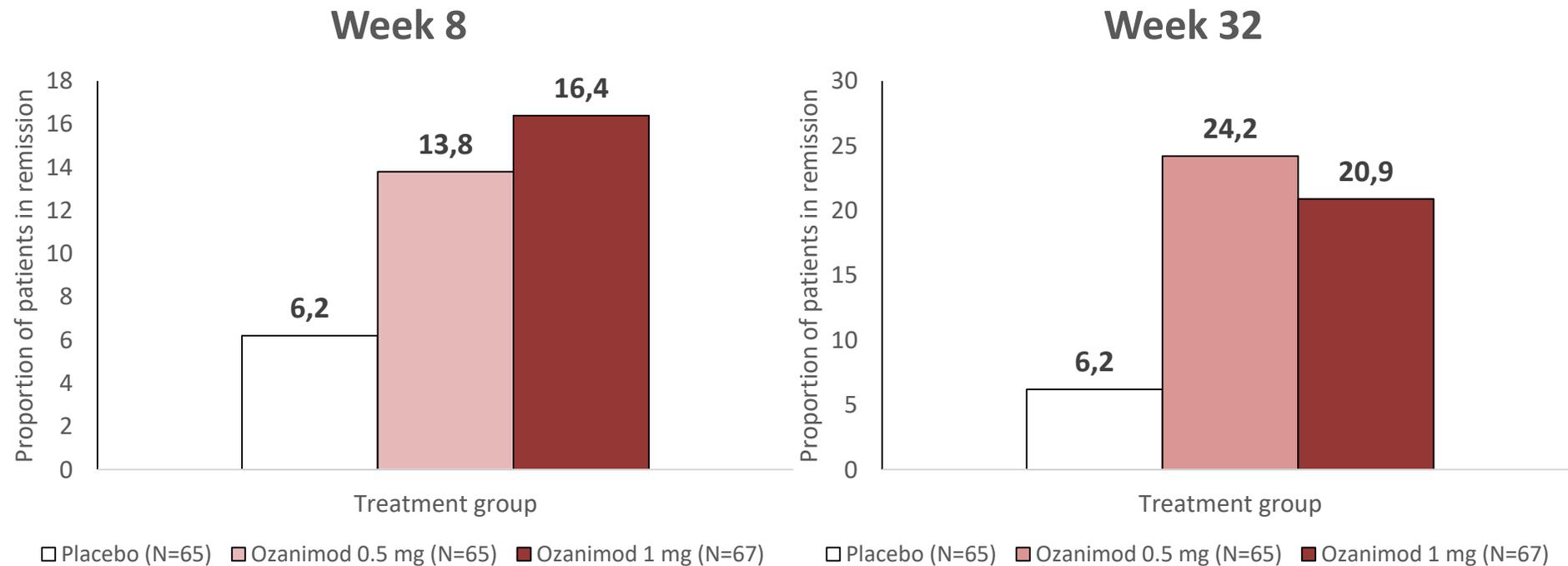


Ozanimod, a next generation S1PR modulator with selectivity for S1P1R and S1P5R



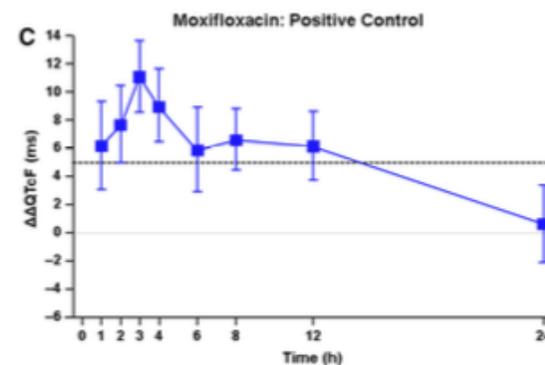
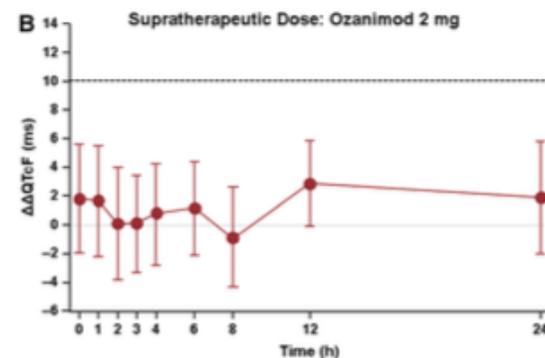
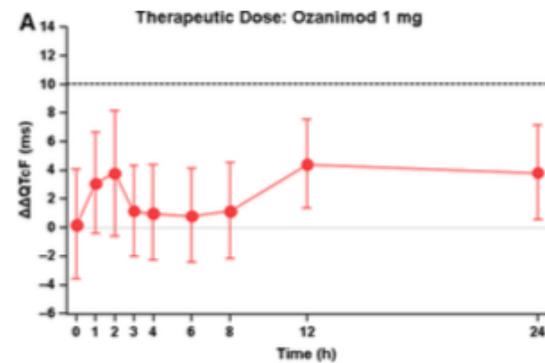
Ozanimod efficacy in ulcerative colitis

Phase II
N= 197



Cardiovascular safety of ozanimod

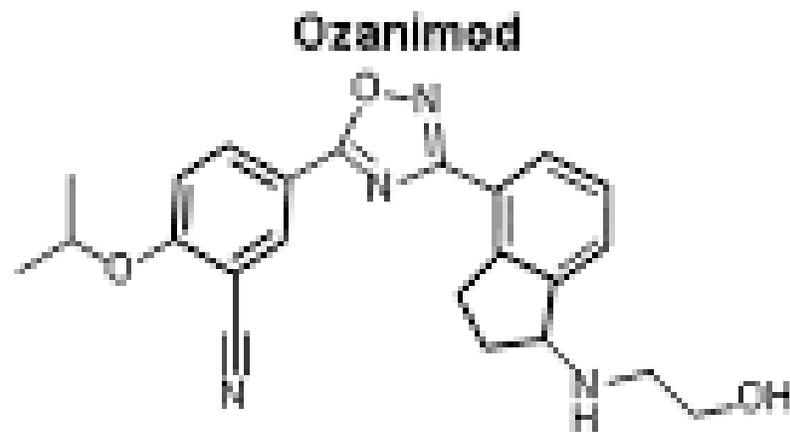
Event	Placebo (N=65)	Ozanimod, 0.5 mg (N=65)	Ozanimod, 1 mg (N=67)
No. of adverse events	59	45	51
Adverse event — no. of patients (%)	26 (40)	26 (40)	26 (39)
Serious adverse event — no. of patients (%)*	6 (9)	1 (2)	3 (4)
Adverse event leading to discontinuation of regimen — no. of patients (%)	4 (6)	3 (5)	1 (1)
Adverse cardiac event — no. of patients (%)	2 (3)	1 (2)	0
Adverse event occurring in ≥ 2 patients receiving ozanimod — no. of patients (%)			
Ulcerative colitis flare	5 (8)	2 (3)	3 (4)
Anemia	4 (6)	3 (5)	0
Headache	3 (5)	0	2 (3)
Nausea	2 (3)	1 (2)	2 (3)
Pyrexia	0	1 (2)	3 (4)
Arthralgia	1 (2)	1 (2)	2 (3)
Alanine aminotransferase increased	0	1 (2)	3 (4)
Back pain	1 (2)	1 (2)	1 (1)
Rash	0	1 (2)	2 (3)
Abdominal pain	1 (2)	1 (2)	1 (1)
Vomiting	0	0	2 (3)
Orthostatic hypotension	0	2 (3)	0
Aspartate aminotransferase increased	0	1 (2)	1 (1)
Hyperbilirubinemia	0	1 (2)	1 (1)
Insomnia	0	1 (2)	1 (1)
Nasopharyngitis	0	2 (3)	0
Proctalgia	0	1 (2)	1 (1)



S1P receptor modulators under study in IBD

S1P receptor modulator	Target	Clinical development		Clinicaltrials.gov ID
		UC	CD	
Ozanimod	S1P ₁₋₅	Phase III	Phase II	NCT02435992 NCT02531113
Etrasimod (APD-334)	S1P ₁	Phase II		NCT02447302 NCT02536404
Amiselimod (MT-1303)	S1P receptor (unknown subtype)		Phase II	NCT02378688 NCT02389790

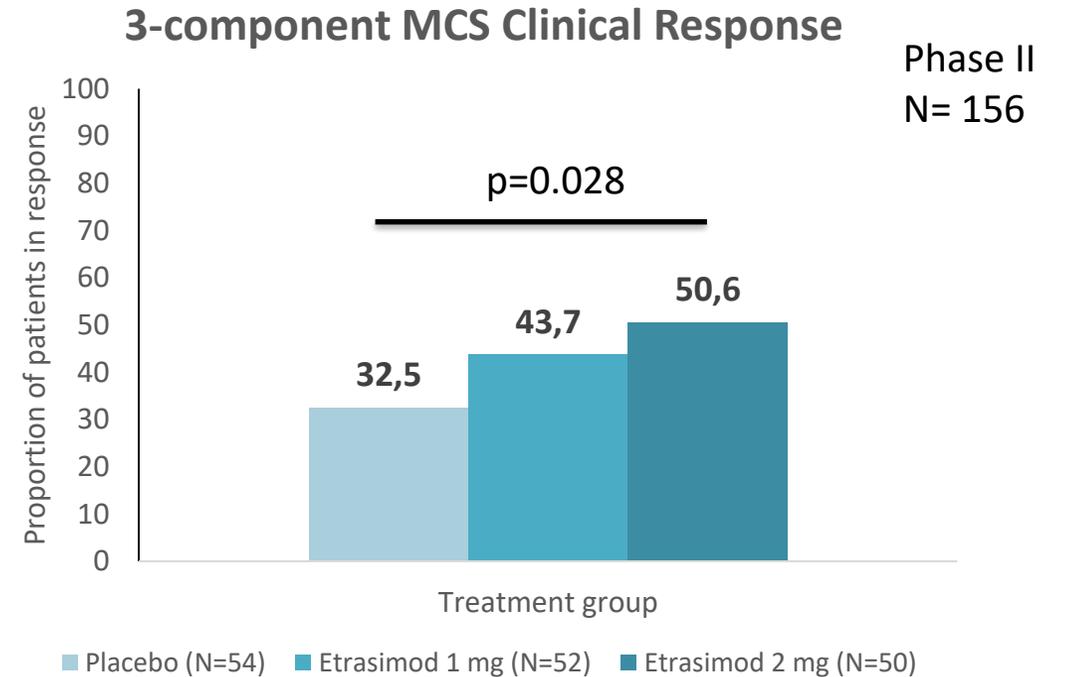
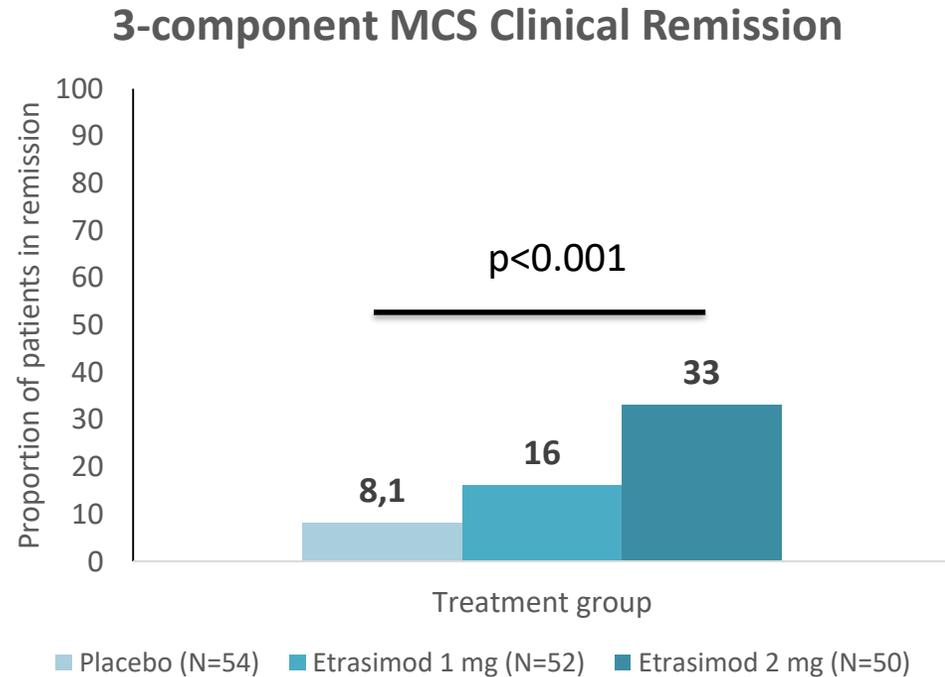
Sphingosine-1 Phosphate receptor selectivity



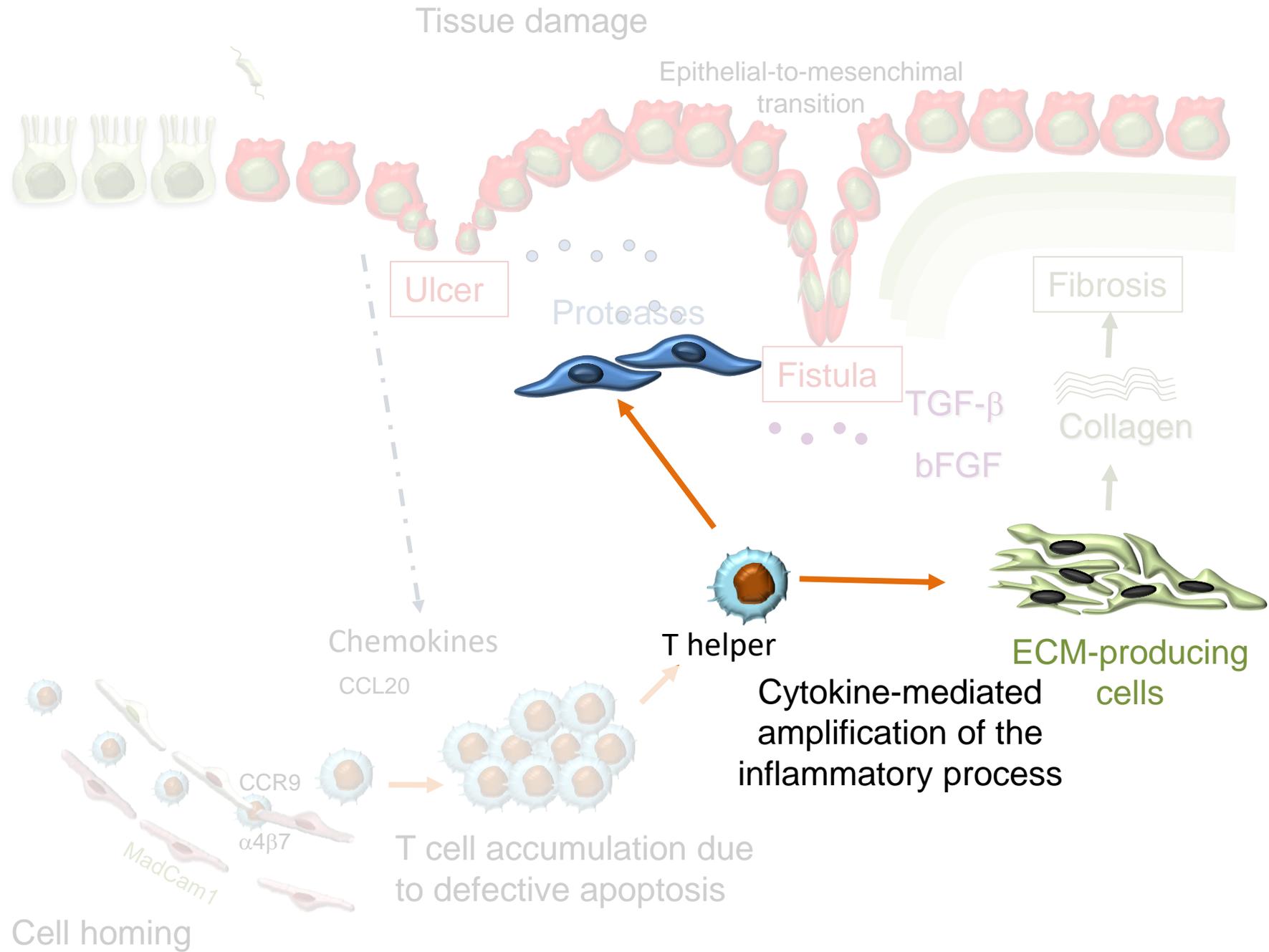
pEC ₅₀	S1P1	S1P2	S1P3	S1P4	S1P5
S1P	7.1–9.4	8.1–8.5	8.4–9.8	7.2–8.1	7.4–8.9
Fingolimod-phosphate	8.1–9.5	7.5	7.8–9.4	6.6–9.2	8.2–9.5
Ozanimod (RPC1063)	9.8	No response ^a	No response ^a	No response ^a	7.3
Etrasimod (APD334) ^b	6.10	No response	No response	147	24.4

Etrasimod explorative efficacy in UC

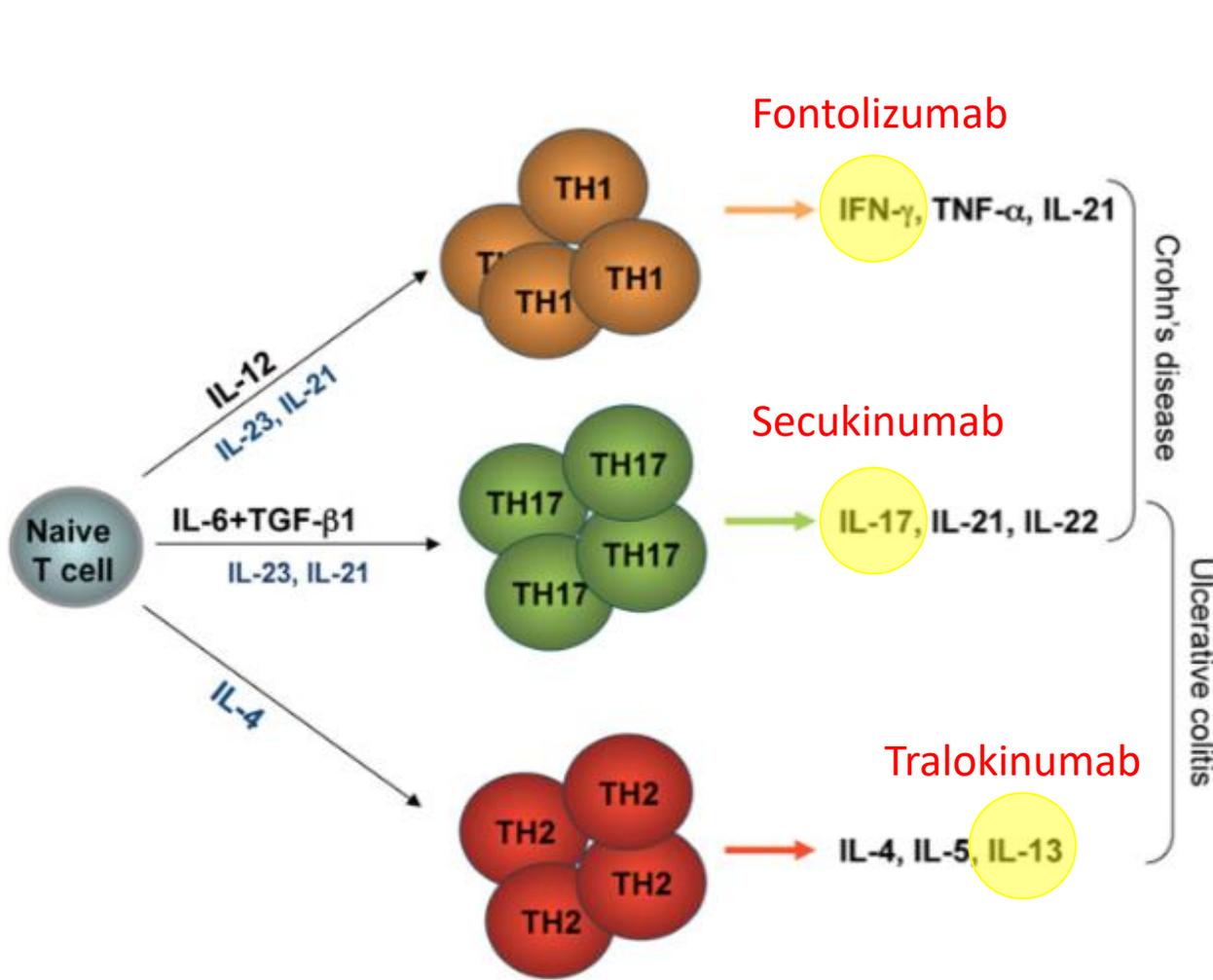
Week 12



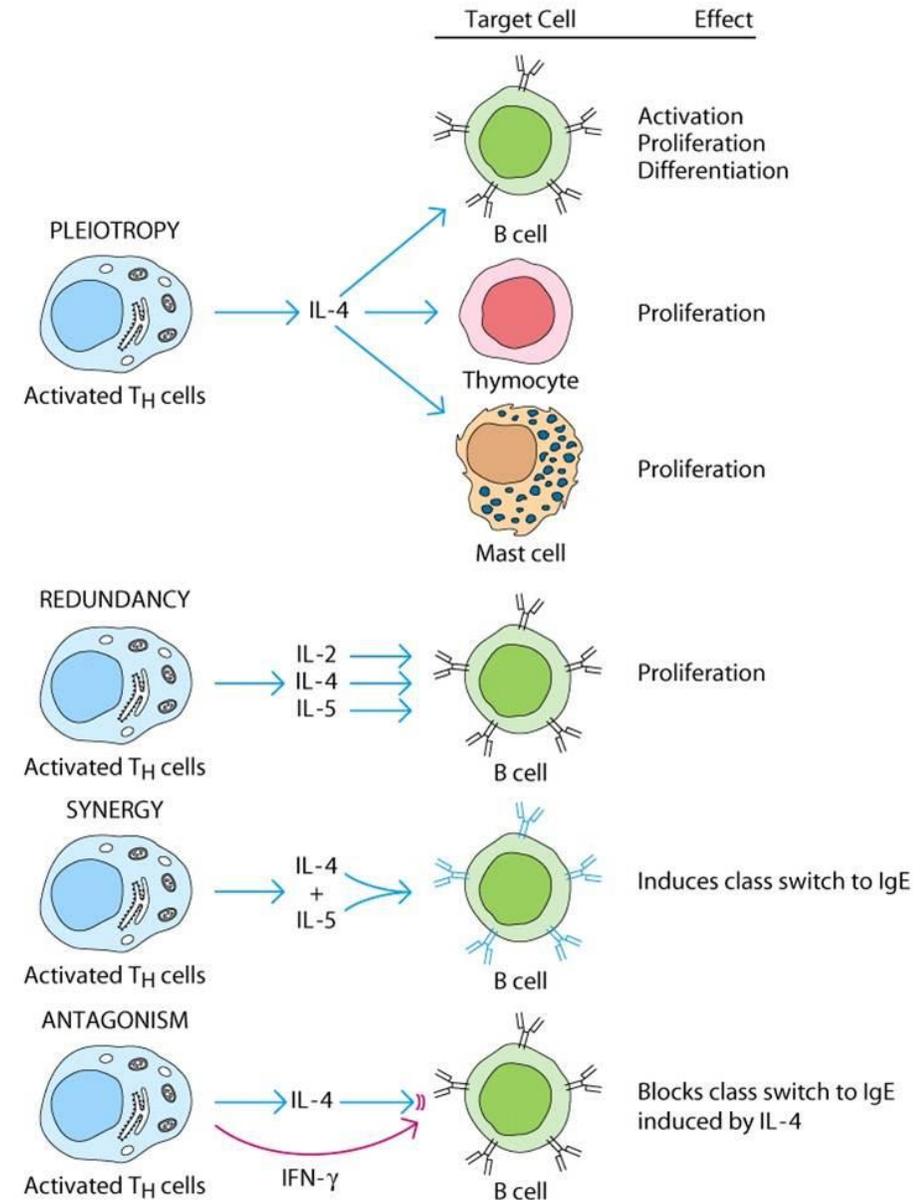
Phase II
N= 156



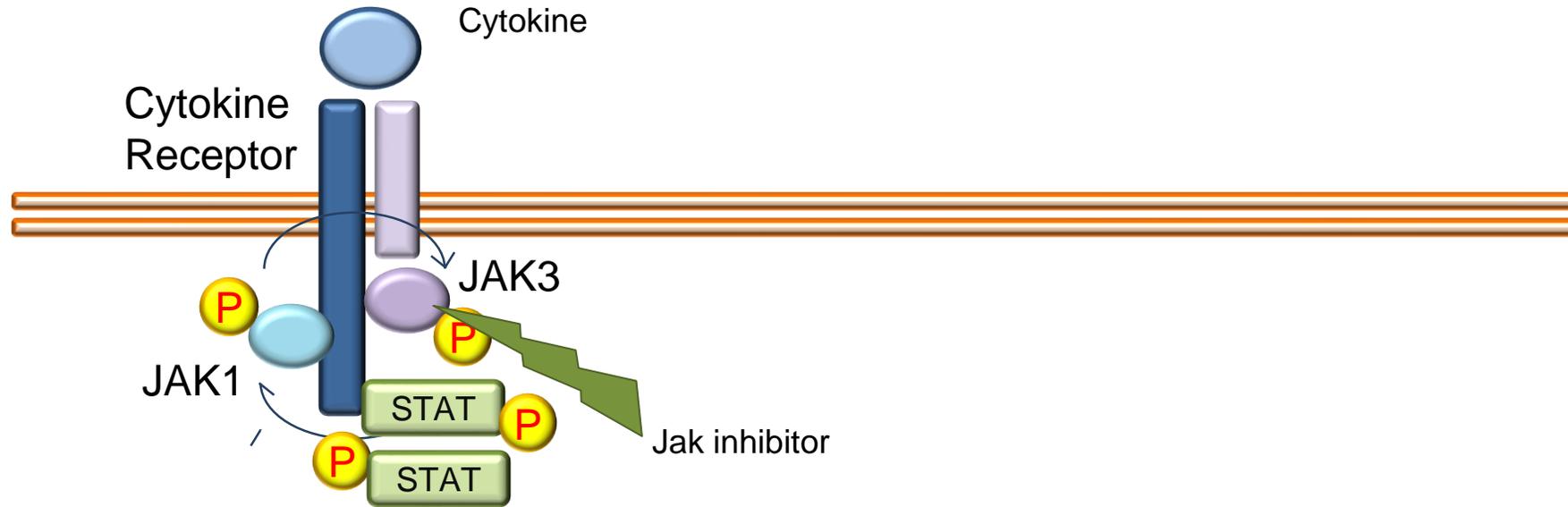
Jak inhibitors as a potential therapy for IBD



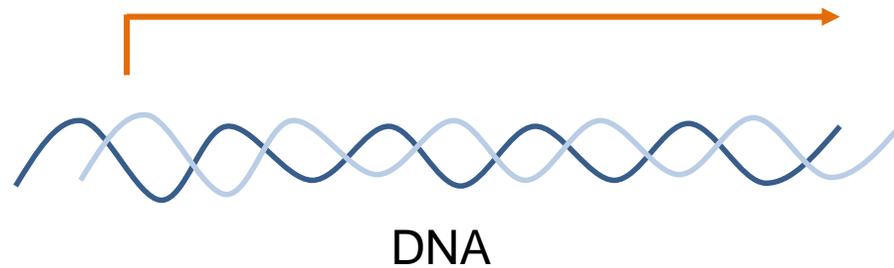
Monteleone G and Caprioli F. Clin Sci 2010



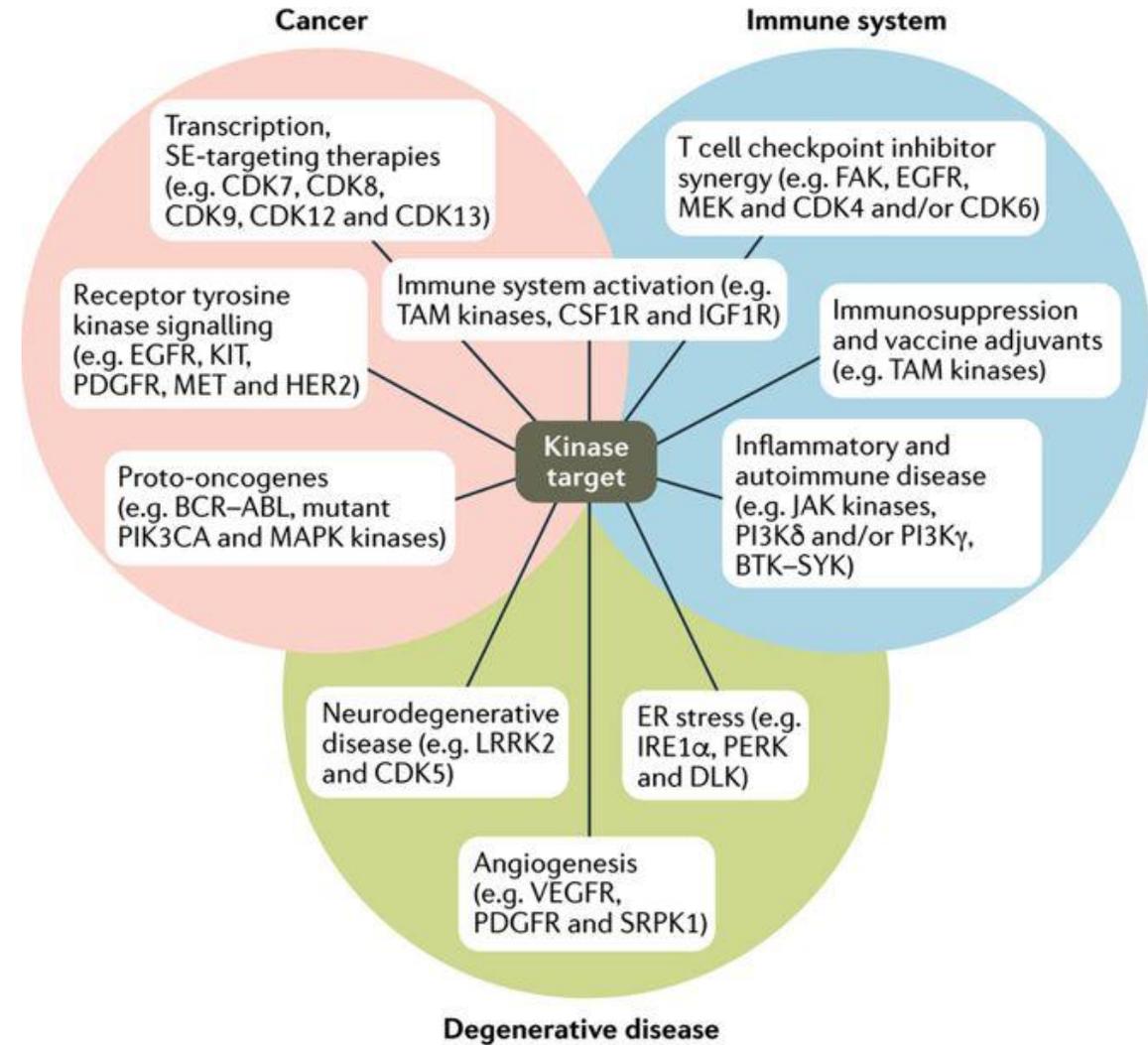
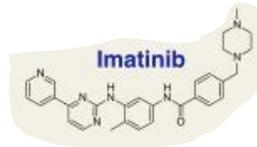
Jak inhibitors as a potential therapy for IBD



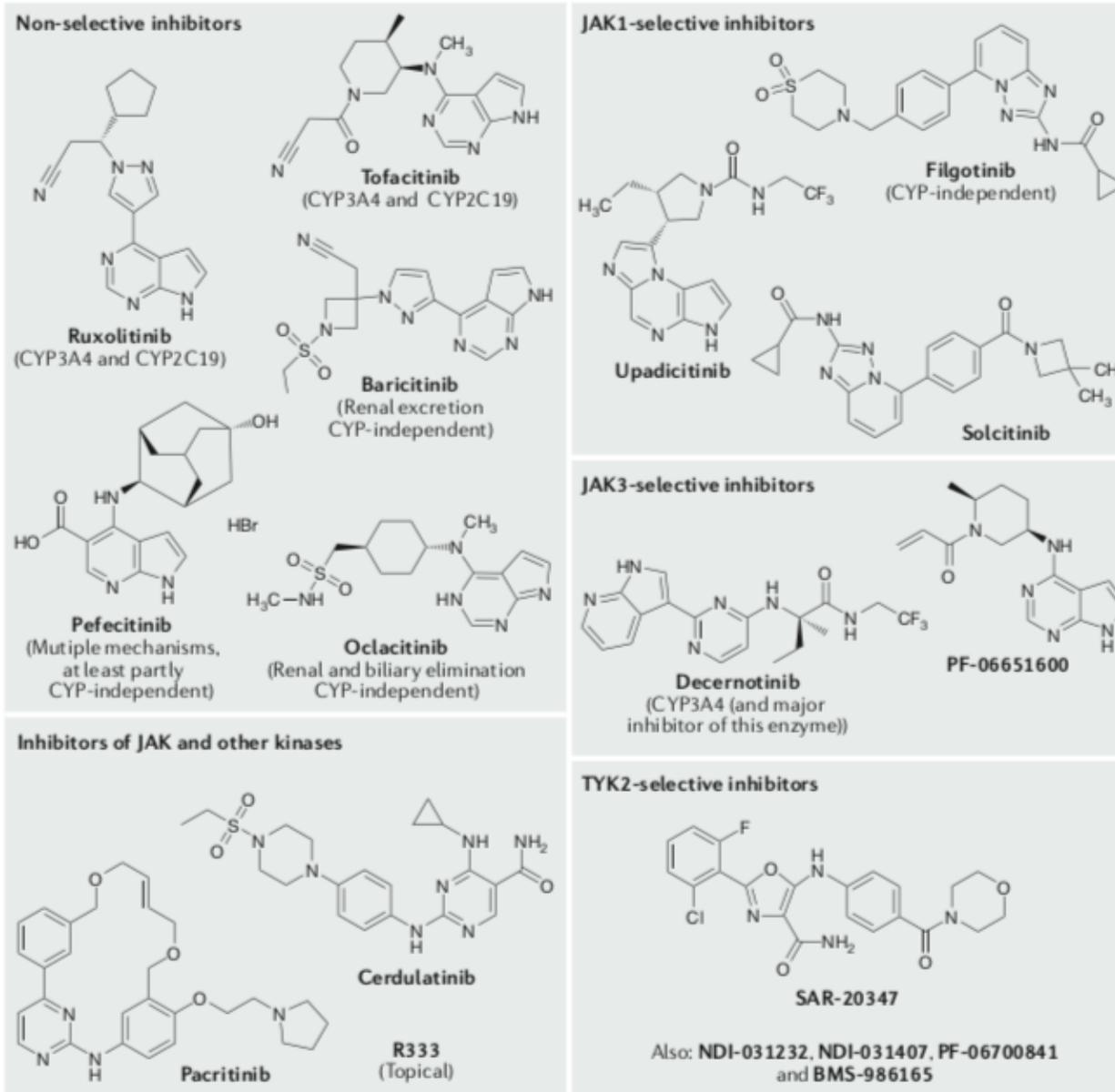
Gene expression



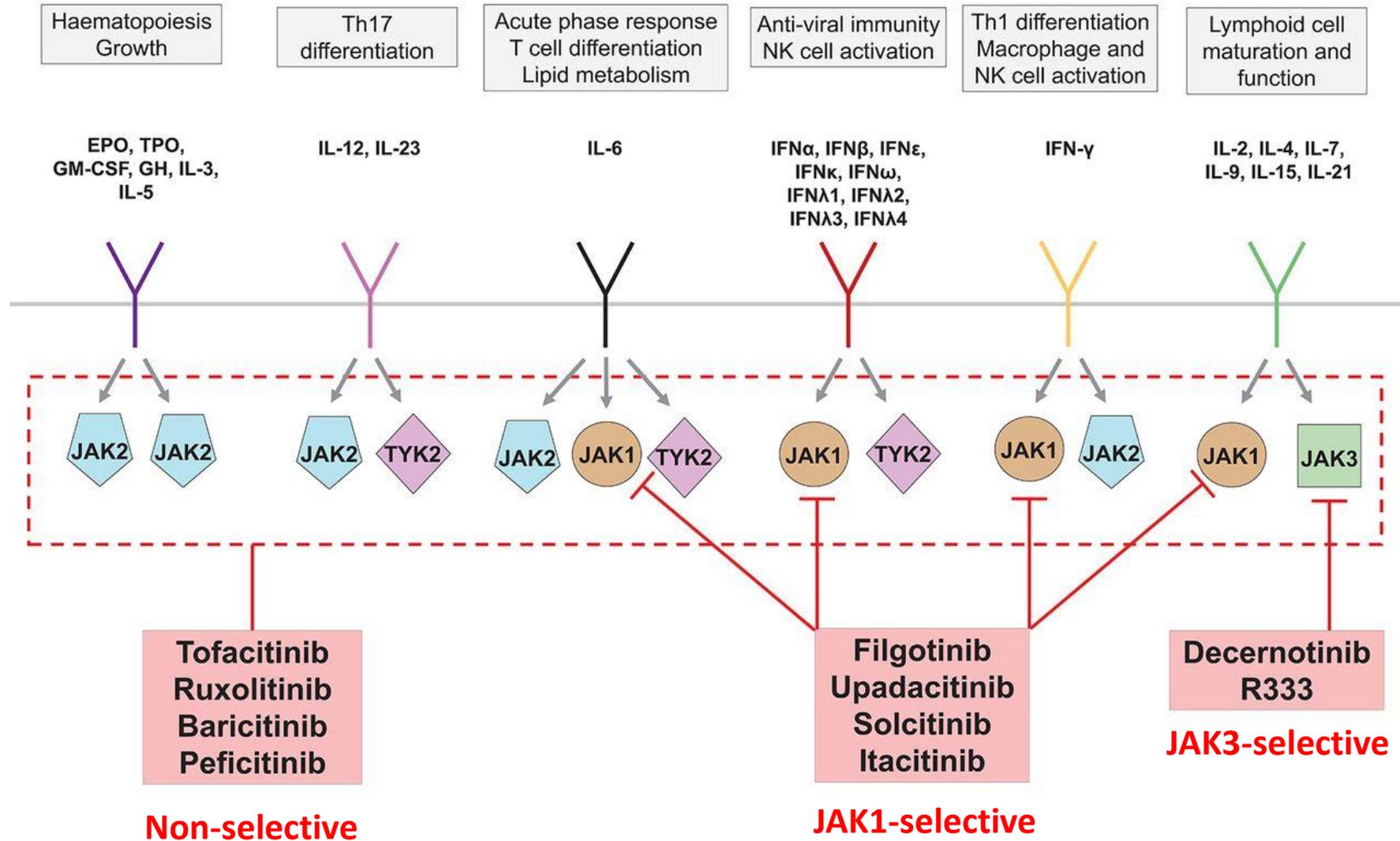
Kinase inhibitors as novel therapies



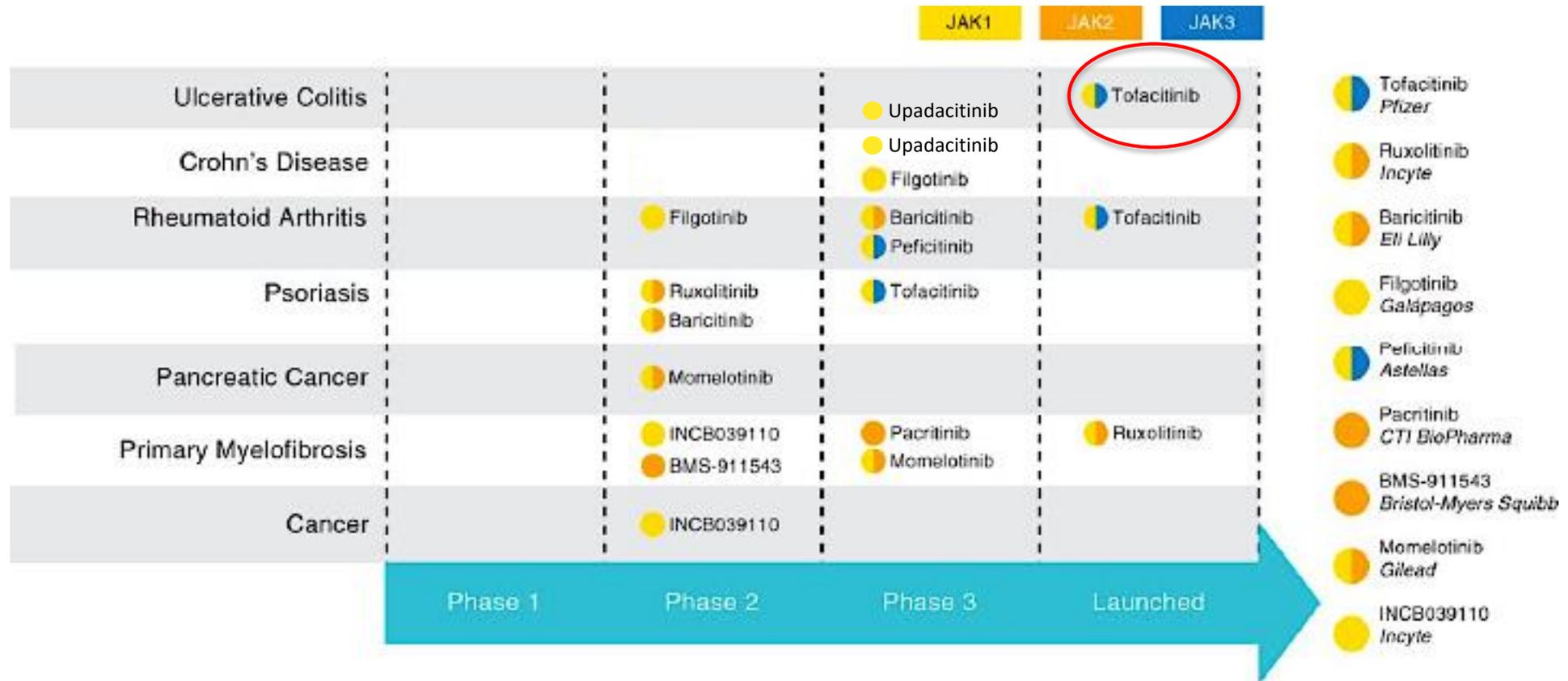
Currently available JAK inhibitors



Jak inhibitors as a potential therapy for IBD



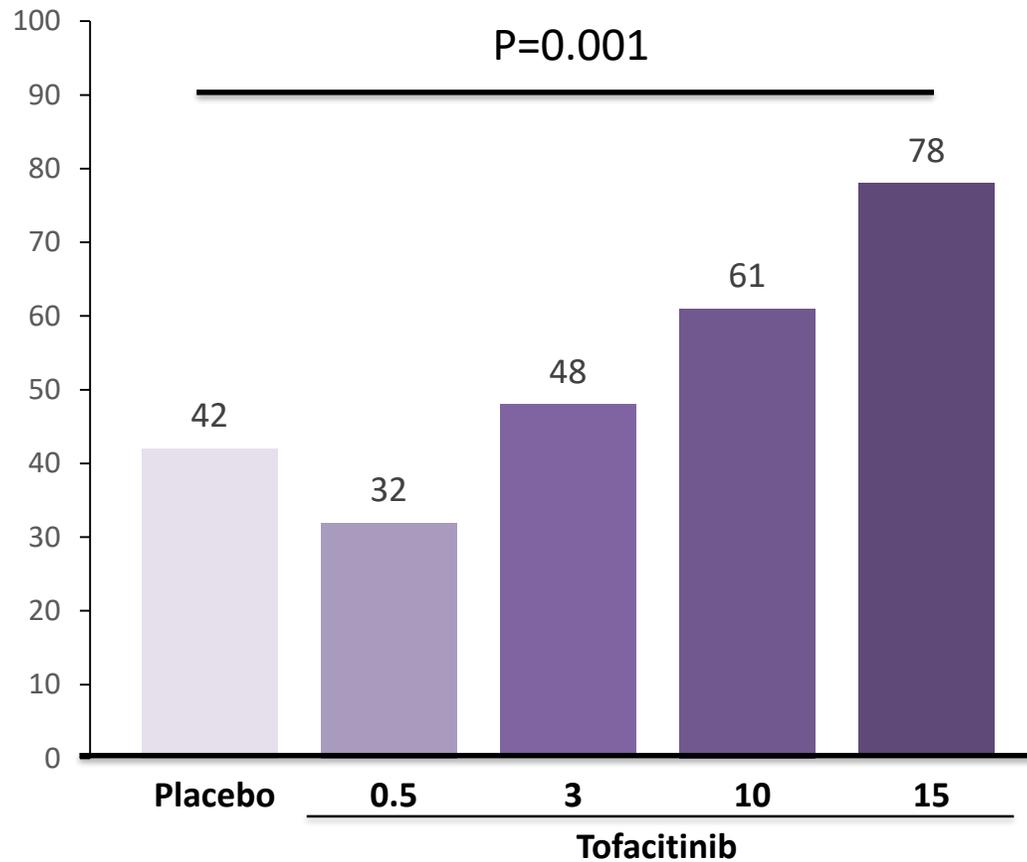
Jak inhibitors as a potential therapy for IBD



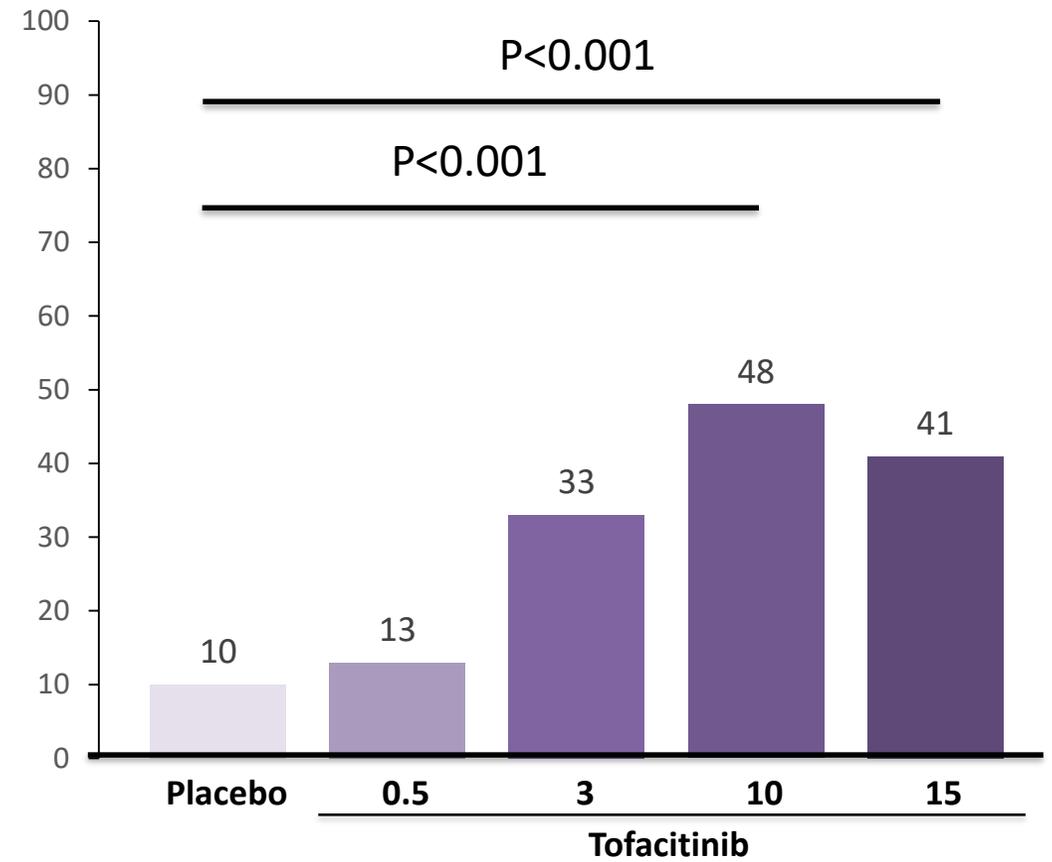
Tofacitinib efficacy in ulcerative colitis

Phase II

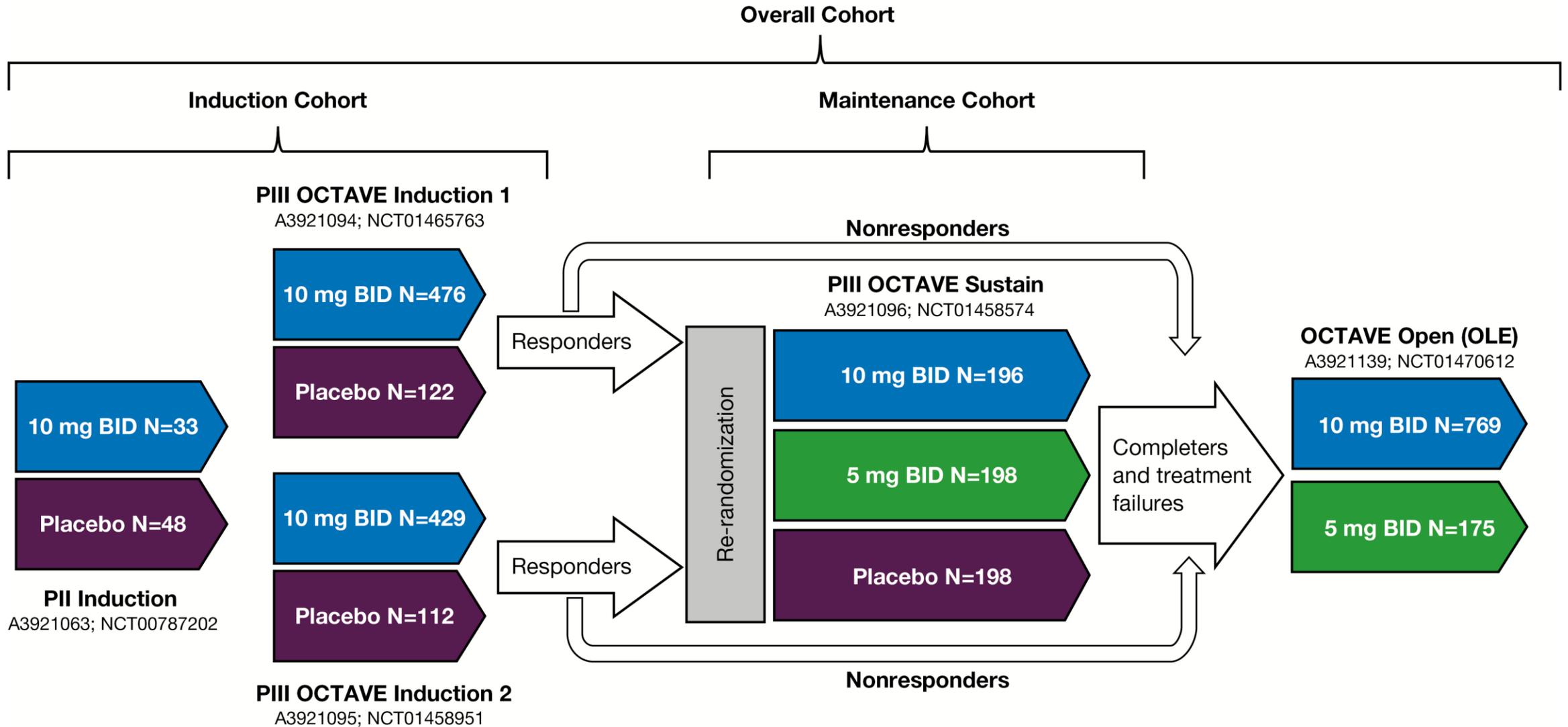
CLINICAL RESPONSE



CLINICAL REMISSION



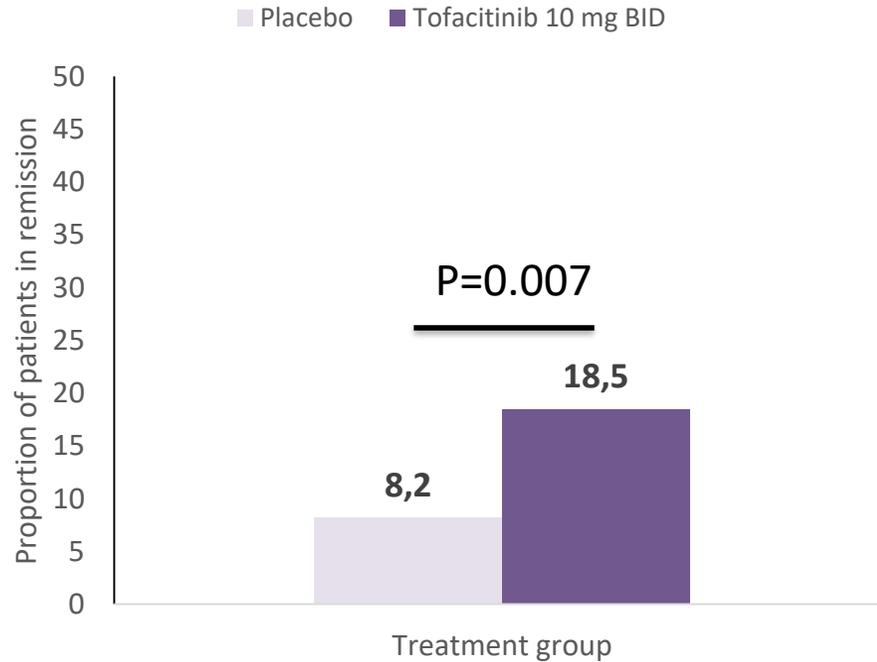
Tofacitinib efficacy in ulcerative colitis



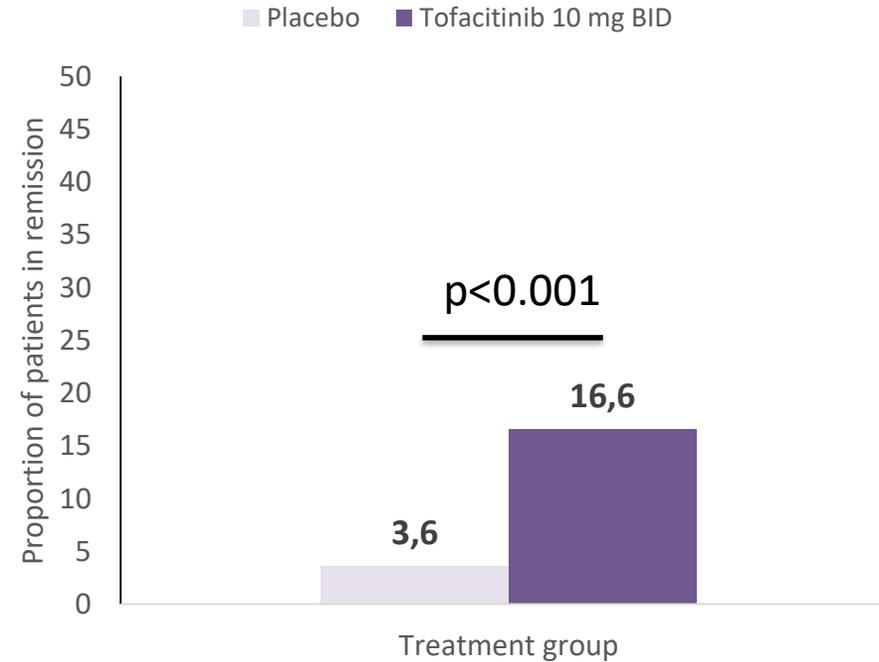
Tofacitinib efficacy in ulcerative colitis

WEEK 8 RESULTS

OCTAVE INDUCTION 1



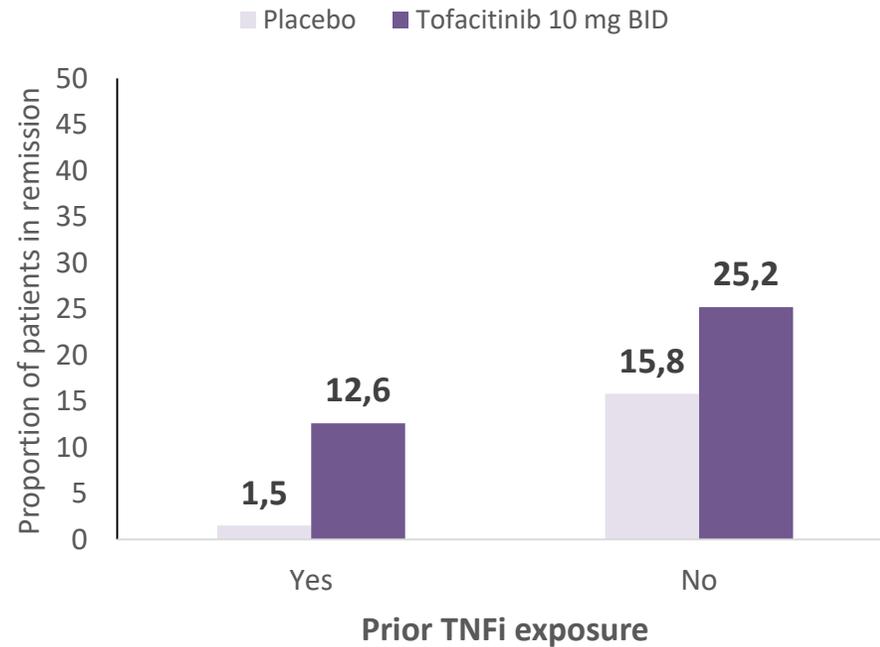
OCTAVE INDUCTION 2



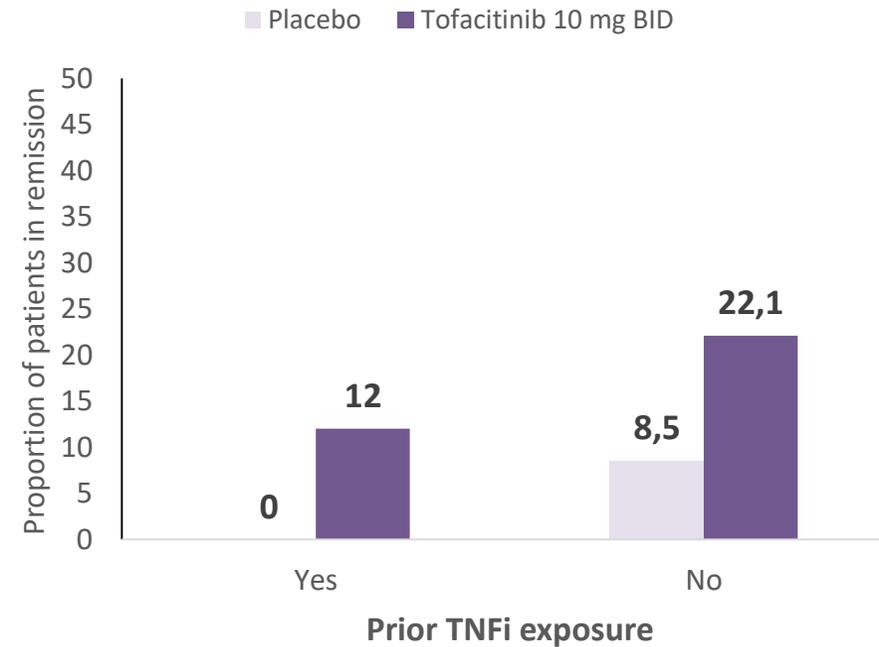
Tofacitinib efficacy in ulcerative colitis

WEEK 8 RESULTS BY PREVIOUS ANTI-TNF EXPOSURE

OCTAVE INDUCTION 1



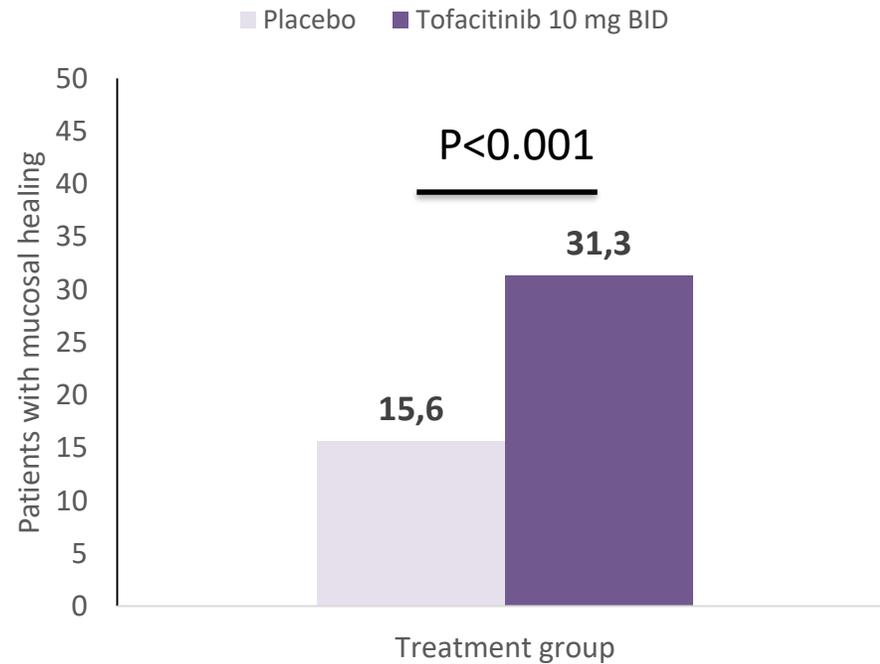
OCTAVE INDUCTION 2



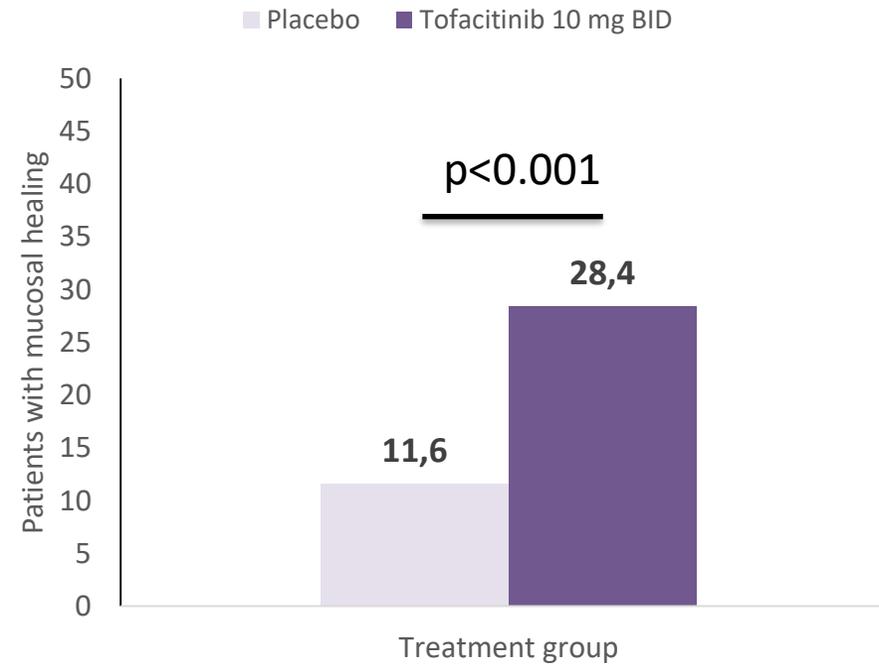
Tofacitinib efficacy in ulcerative colitis

MUCOSAL HEALING

OCTAVE INDUCTION 1



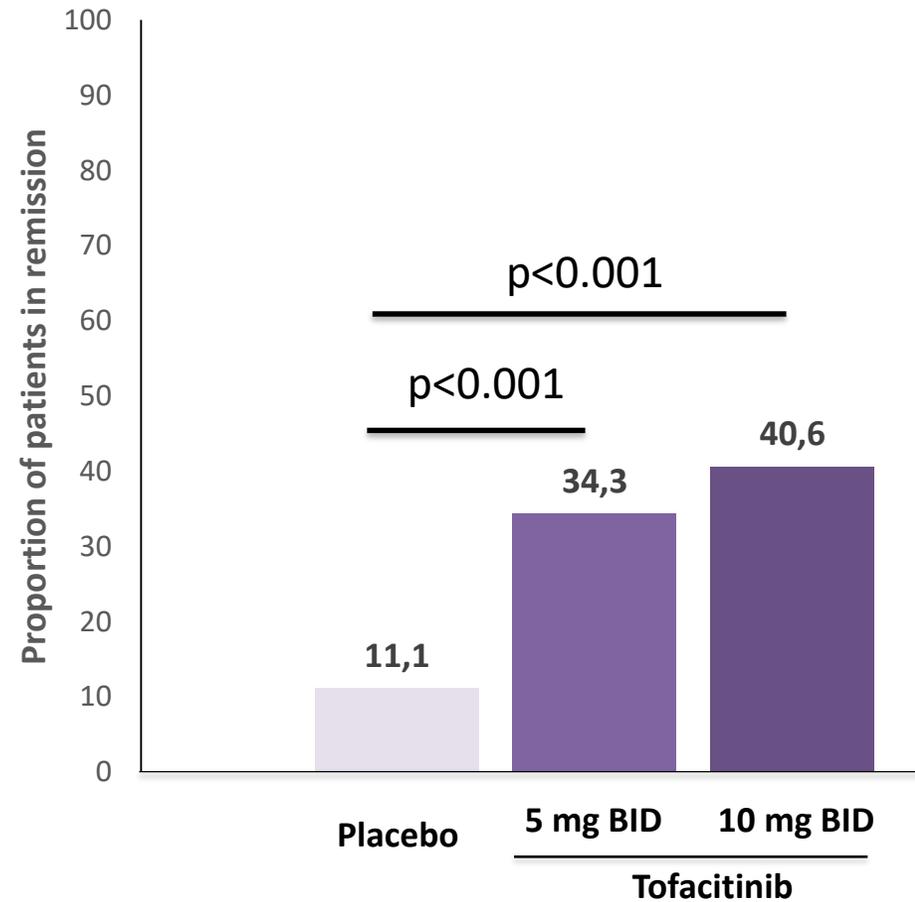
OCTAVE INDUCTION 2



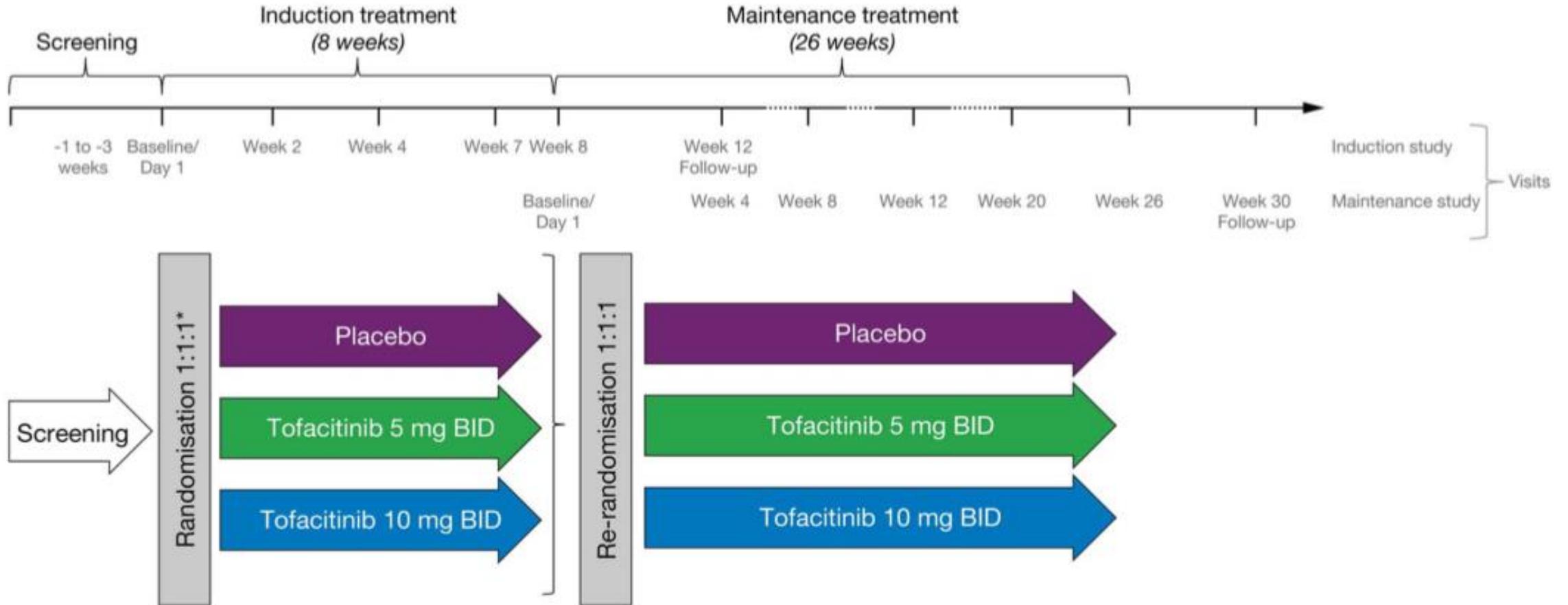
Tofacitinib efficacy in ulcerative colitis

WEEK 52 RESULTS

OCTAVE SUSTAIN

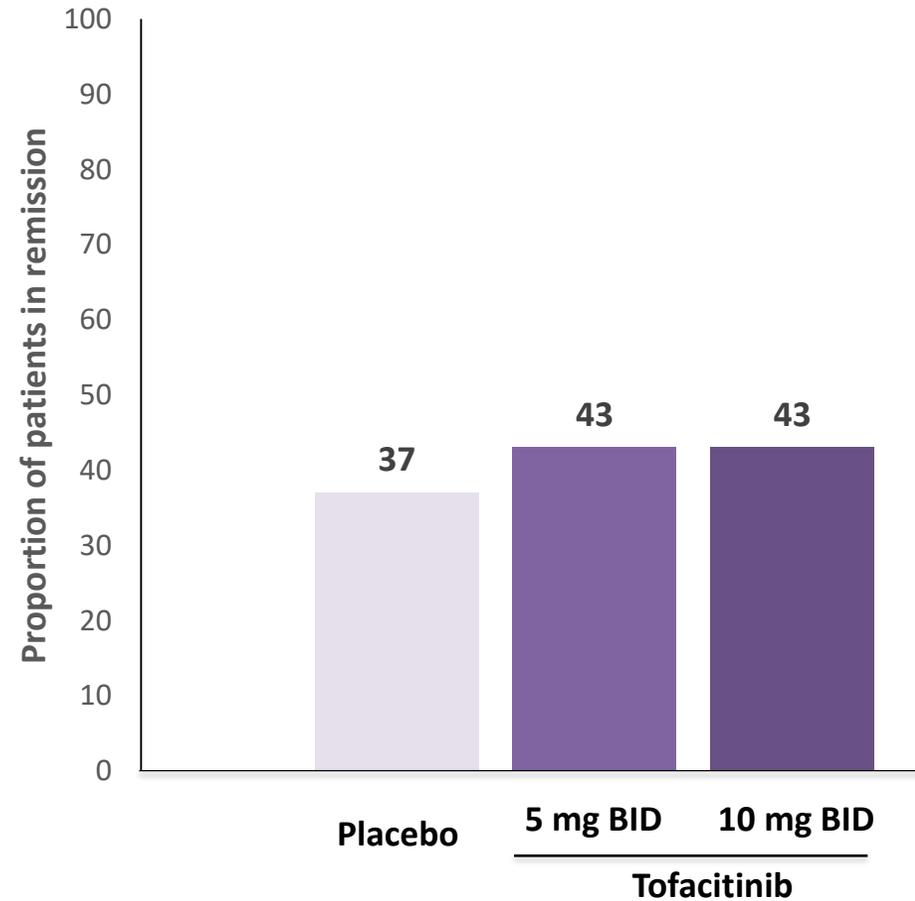


Tofacitinib efficacy in Crohn's disease



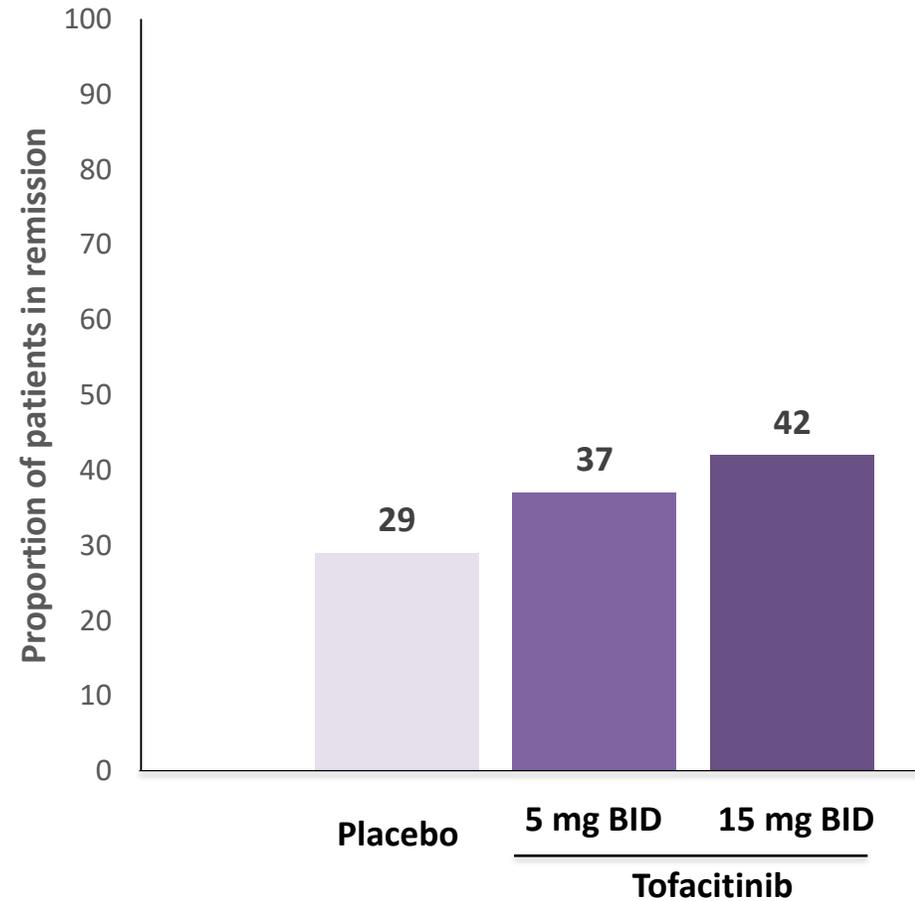
Tofacitinib efficacy in Crohn's disease

WEEK 8 RESULTS CLINICAL REMISSION



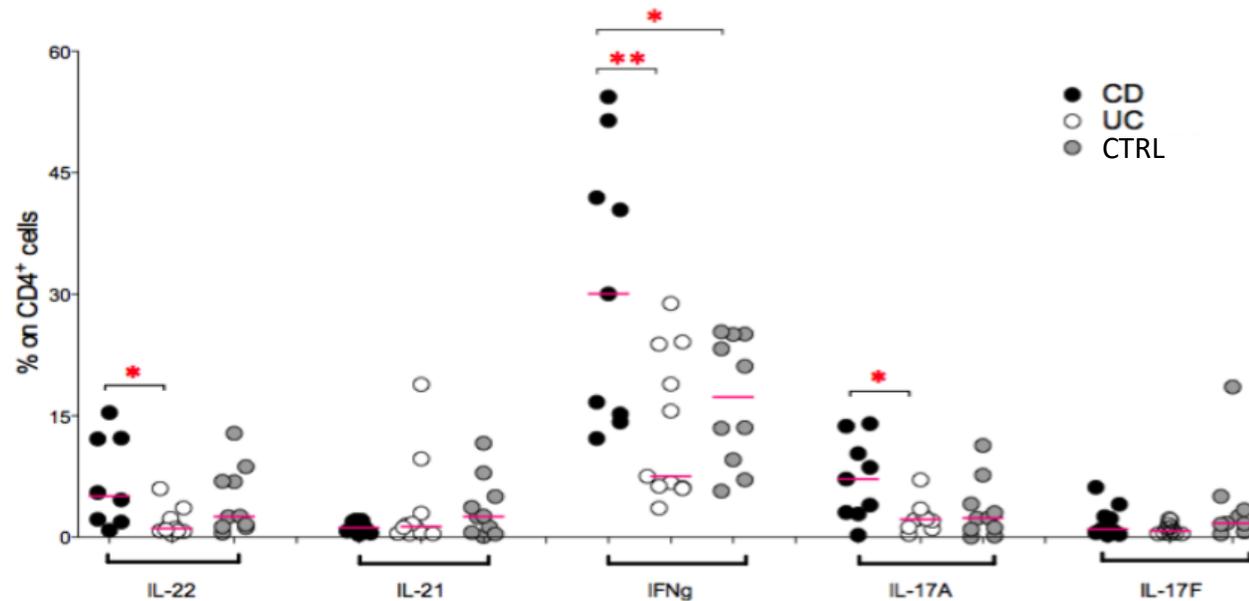
Tofacitinib efficacy in Crohn's disease

WEEK 26 RESULTS CLINICAL REMISSION



Different Tofacitinib efficacy between CD and UC

- Different cytokine milieu between Crohn's disease and ulcerative colitis



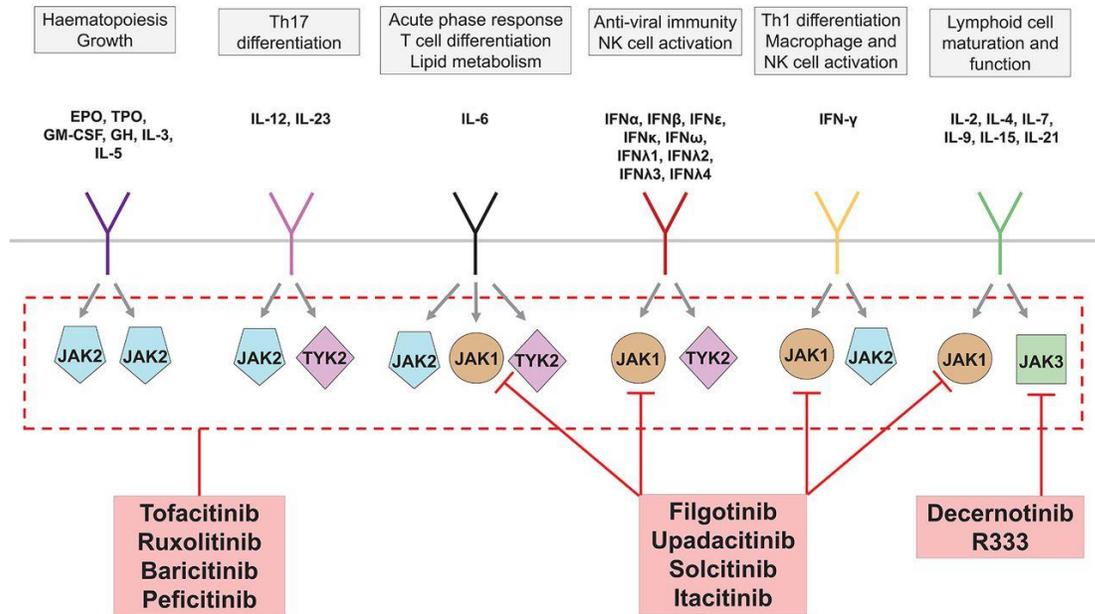
Paroni M, unpublished

- Role of IL9 and IL22, whose signaling is inhibited by Tofacitinib, in mucosal barrier integrity
- Unknown alterations in microbial ecology of the intestinal mucosa (bacterial, fungal, viral)

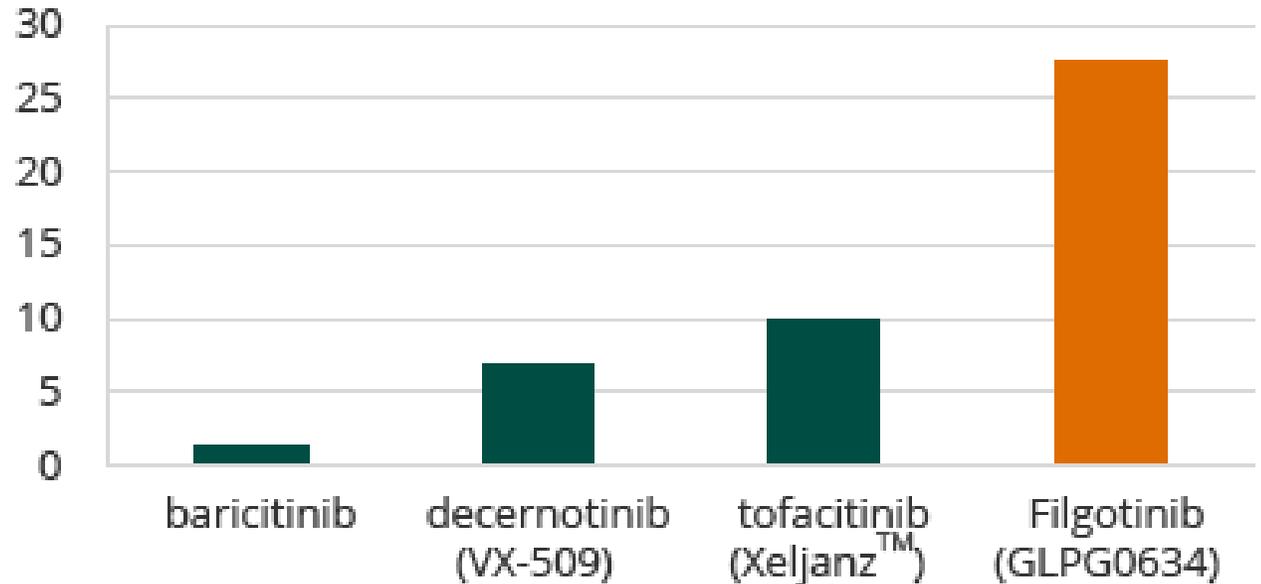
Other JAK-inhibitors under study for IBD

JAK inhibitor name	Target	Clinical development		Clinicaltrials.gov ID
		UC	CD	
Upadacitinib (ABT-494)	JAK1	Phase III	Phase III	NCT03006068, NCT02782663, NCT02819635, NCT02365649
Filgotinib (GLPG0634)	JAK1	Phase II	Phase III	NCT02048618, NCT02914600, NCT02914535, NCT03077412, NCT03046056, NCT02914561, NCT02914522
PF-06651600	JAK3	Phase II		NCT02958865
PF-06700841	JAK1, TYK2	Phase II		NCT02958865

JAK1 inhibitors in Crohn's disease

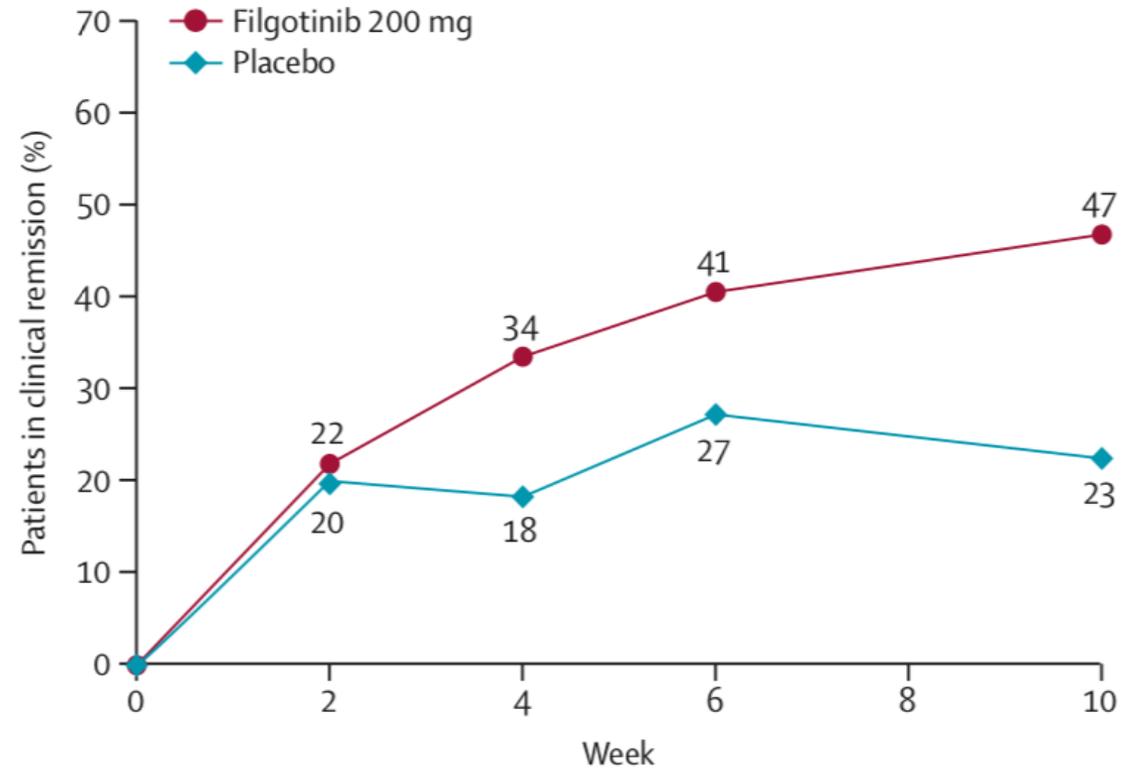
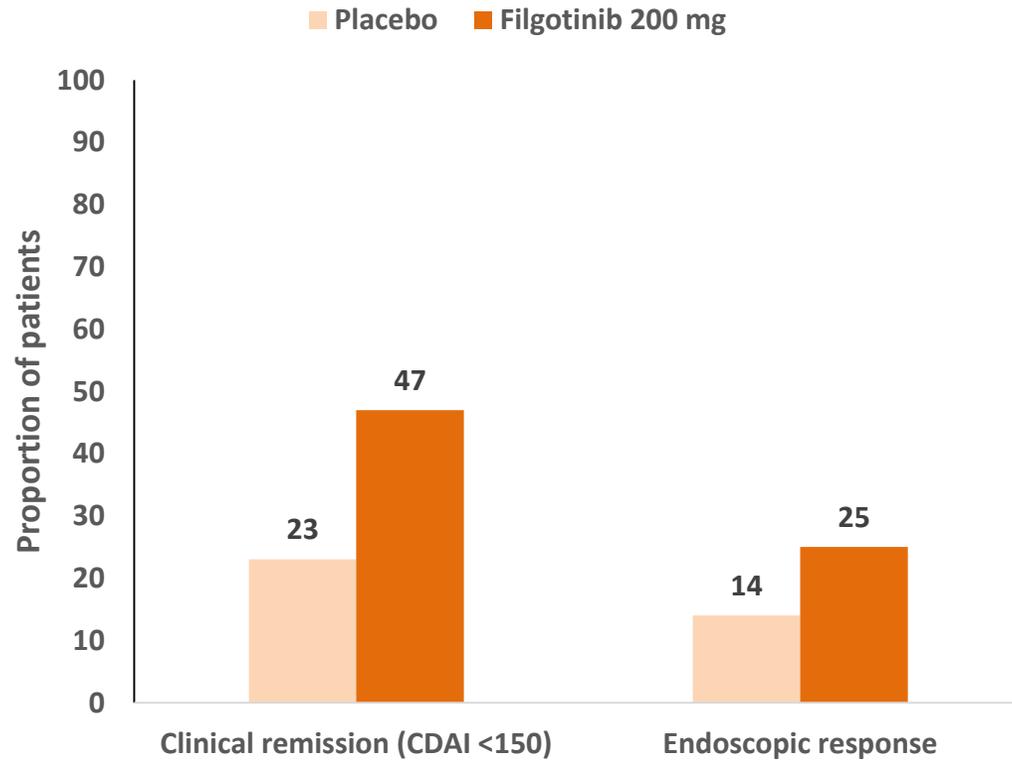


Ratio JAK1/JAK2 in Human Whole Blood Assay



Filgotinib efficacy in Crohn's disease

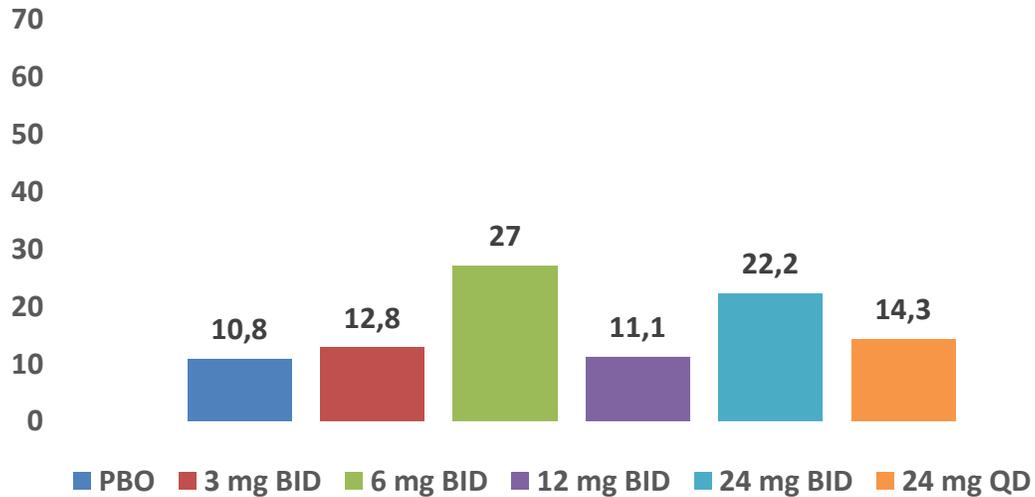
WEEK 10 RESULTS



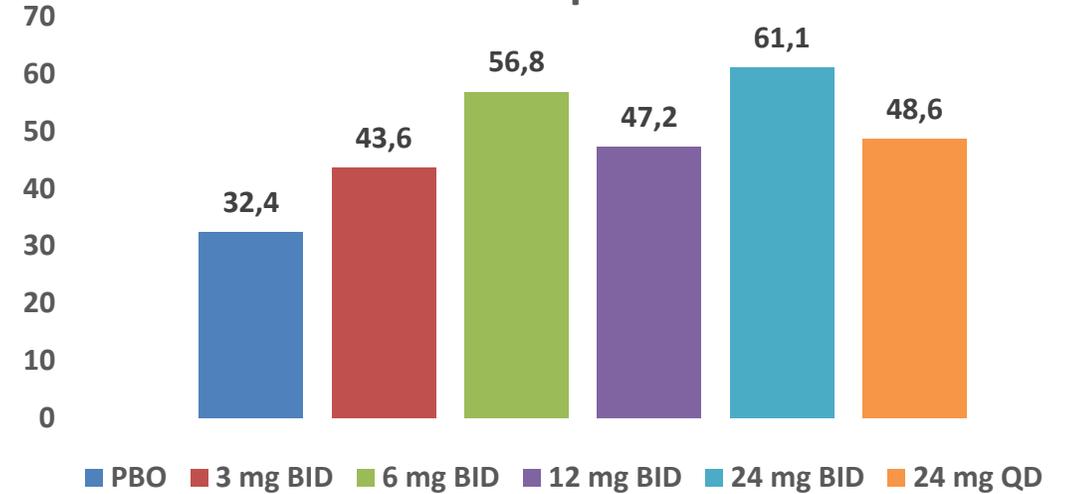
Upadacitinib efficacy in Crohn's disease

Phase II - CELEST

Clinical remission at week 16



Clinical response at week 16

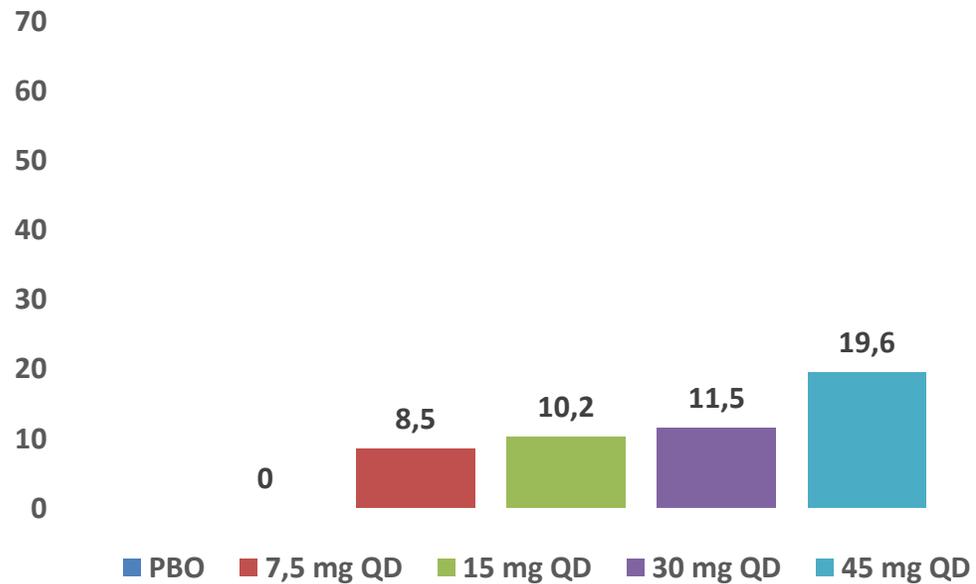


Prior TNFi	%
0	5
1	41
2	41
≥ 3	14
Other prior biologics	38
Vedolizumab	27

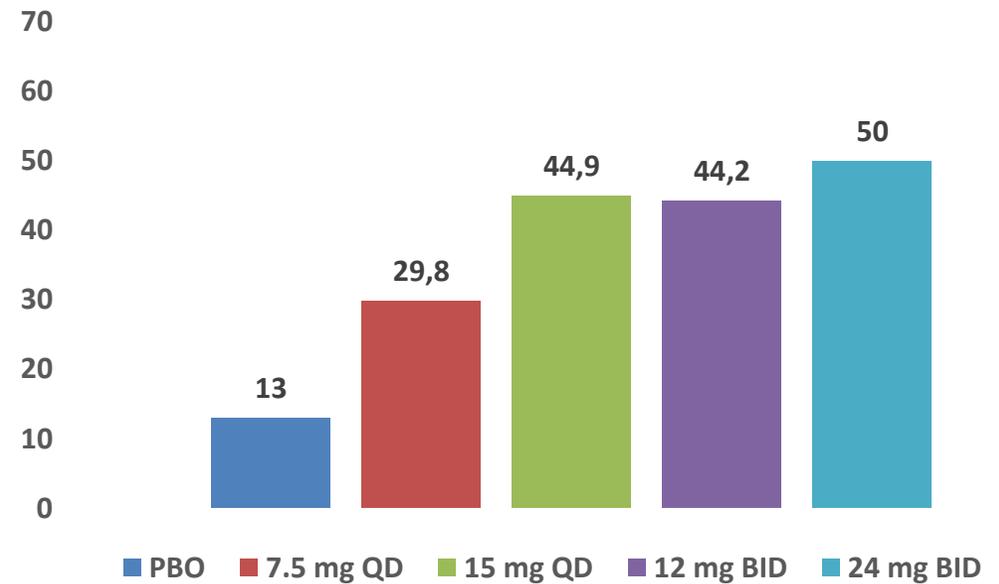
Upadacitinib efficacy in ulcerative colitis

Phase II-III – U-ACHIEVE

Clinical remission at week 8



Clinical response at week 8



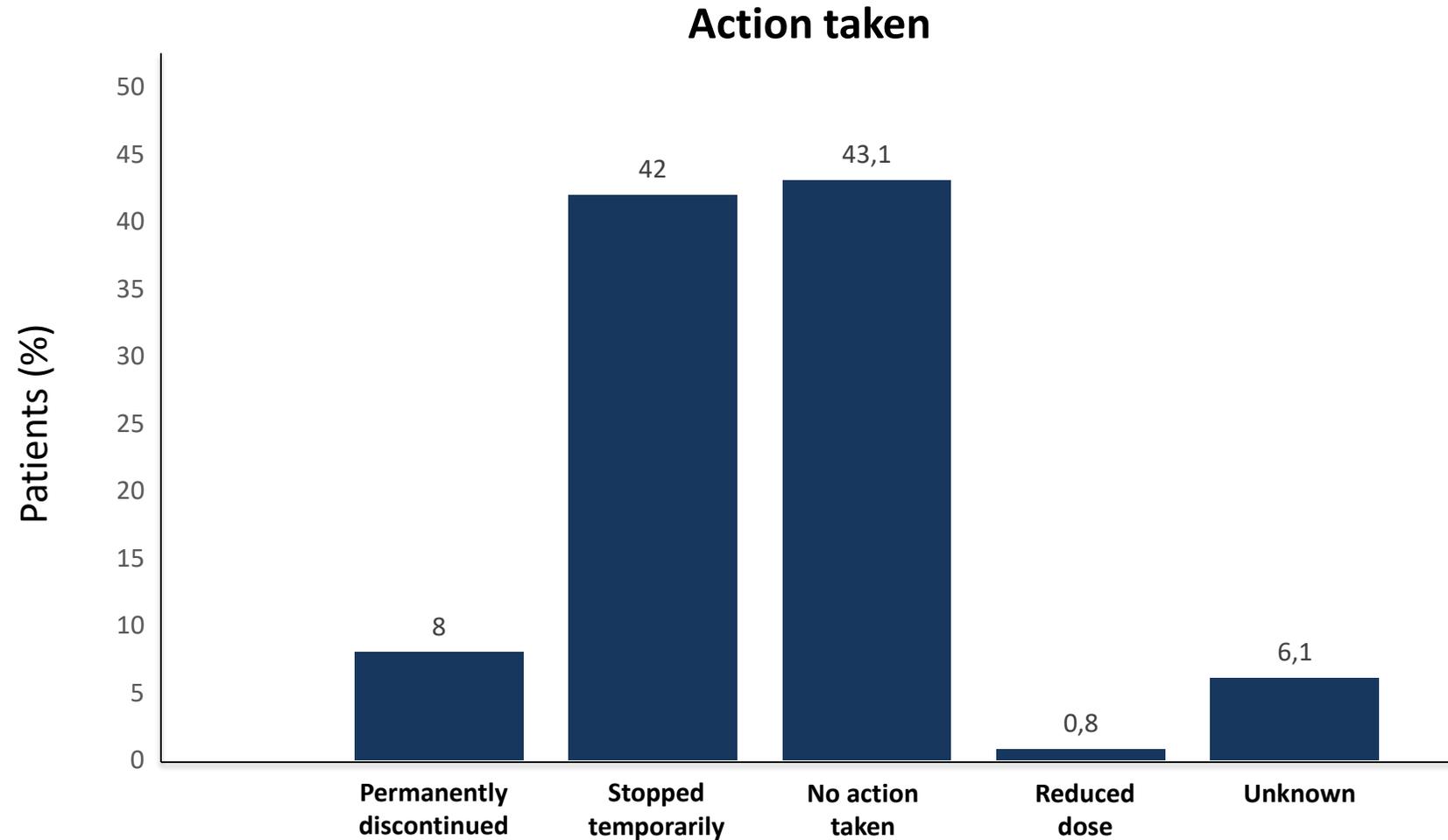
Safety of JAK inhibitors in clinical trials

	Tofacitinib vs. placebo (OCTAVE Sustain W52)	Filgotinib vs. placebo (FITZROY W20)	Upadacitinib vs. placebo (CELEST W16)
Any adverse event	72%-80% vs. 75%	75% vs. 67%	76-84% vs. 73%
Serious AEs	5%-6% vs. 7%	9% vs. 4%	8%-20% vs. 5%
Aes leading to discontinuation	9%-10% vs. 19%	18% vs. 9%	3%-14% vs. 14%
Serious infections	0.5%-1% vs. 1%	3% vs. 0%	0%-8% vs. 0%
Herpes Zoster	13 patients	1 patient	1 patient
CV events	2 patients	NA	2 patients
Malignancy	3 patients	NA	1 patient
GI perforations	1 patient (OCTAVE induction 1)	NA	2 patients

Tofacitinib: Summary of Adverse Events

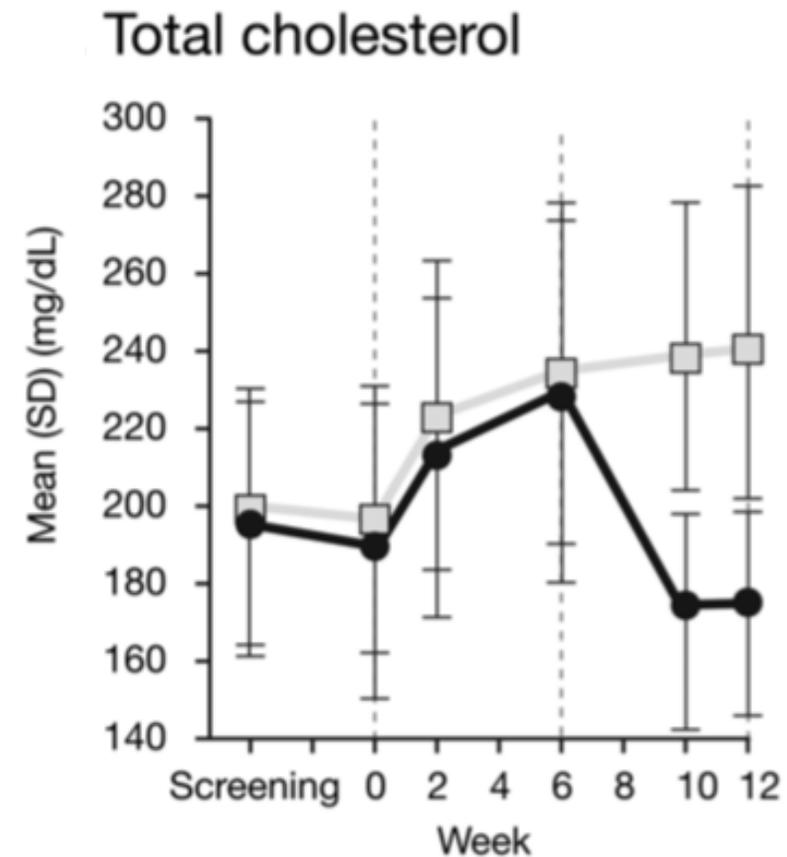
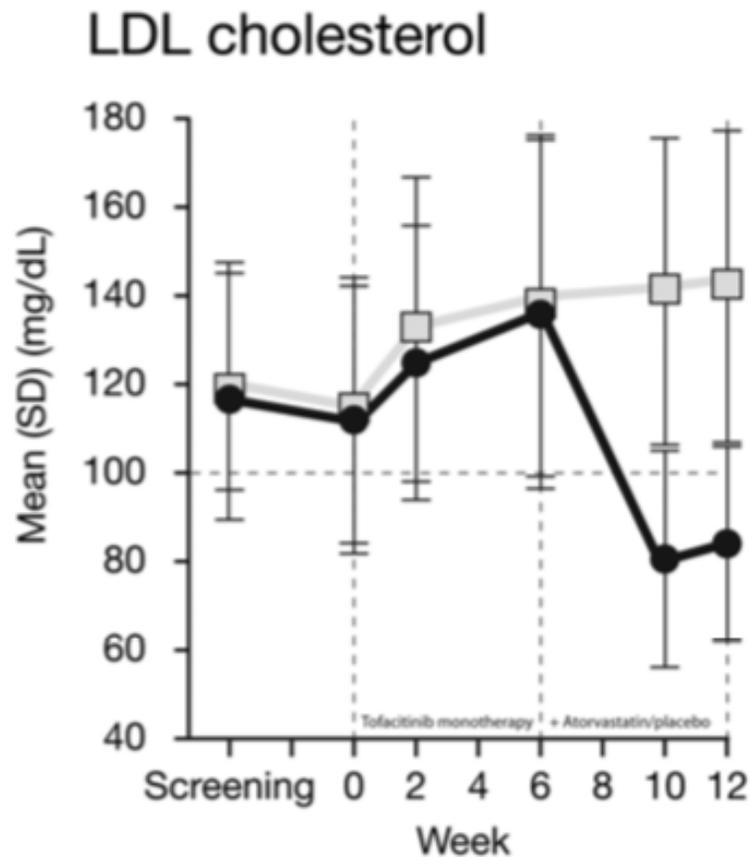
- Herpes zoster (up to 5% in higher dose maintenance arm) – twice the rate of anti-TNFs and similar to thiopurines
- Non-melanoma skin cancer increased (SCC and BCC)
- Gastrointestinal perforation: risk not increased over placebo
- LDL and HDL cholesterol increase (no cardiovascular impact)
 - Cholesterol levels should be checked 4-8 weeks after starting treatment. Should we treat high LDL with cholesterol lowering meds?
- No immunogenicity with small molecules

Zoster in tofacitinib-treated RA patients: a manageable issue

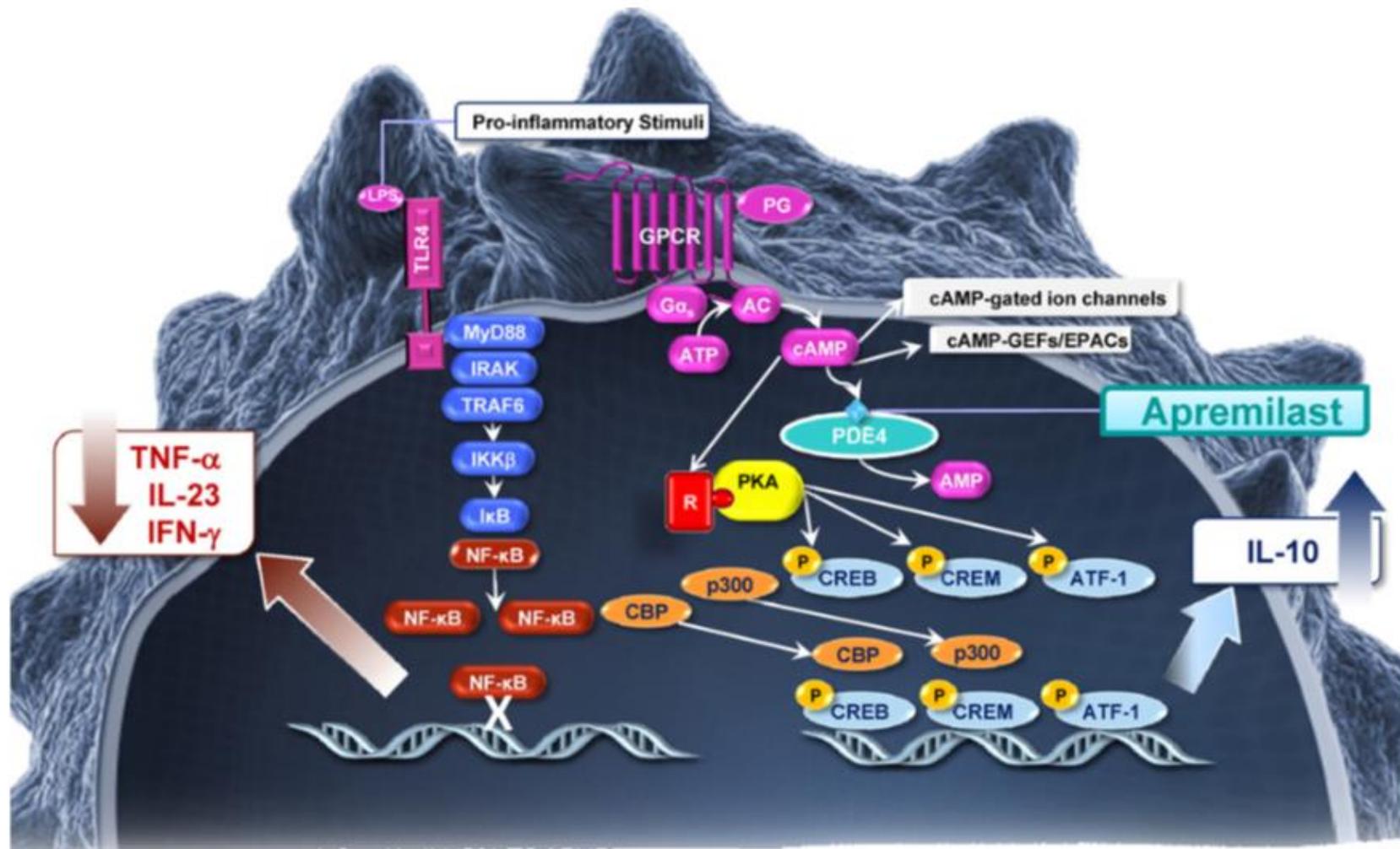


Changes in LDL are reversible with statin therapy

- Atorvastatin + tofacitinib 10 mg bid
- Placebo + tofacitinib 10 mg bid



Apremilast mechanism of action



Apremilast efficacy in ulcerative colitis

