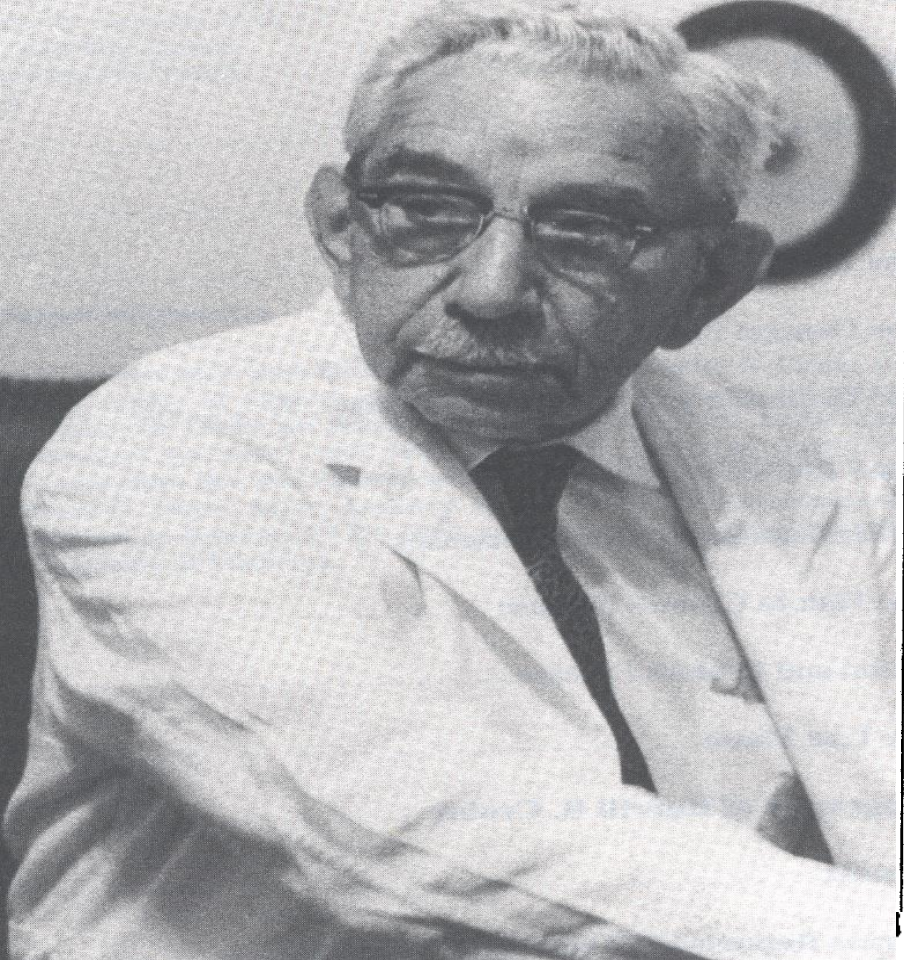
«ΙΦΝΕ: Μεγαλομοριακοί βιολογικοί παράγοντες ή ενδοκυττάρια στόχευση με μικρομόρια;»

Κωνσταντίνος Χ. Κατσάνος
Αναπληρωτής Καθηγητής Γαστρεντερολογίας
Πανεπιστημίου Ιωαννίνων



Landmark Article
Oct 15, 1932
(*JAMA* 1932;99:1323-1329)

Regional Ileitis

A Pathologic and Clinical Entity

Burrill B. Crohn, M.D.

Leon Ginzburg, M.D.

and

Gordon D. Oppenheimer, M.D.

New York

We propose to describe, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.

The disease is clinically featured by symptoms that resemble those of ulcerative colitis, namely, fever, diarrhea and emaciation, leading eventually to an obstruction of the small intestine; the constant occurrence of a mass in the right iliac fossa usually requires surgical

tracts.

Such, in essence, is the definition of a disease, the description of which is based on the study, to date, of fourteen cases. These cases have been carefully observed and studied in their clinical course; the pathologic details have resulted from a close inspection of resected specimens from thirteen of fourteen patients operated on by Dr. A. A. Berg.

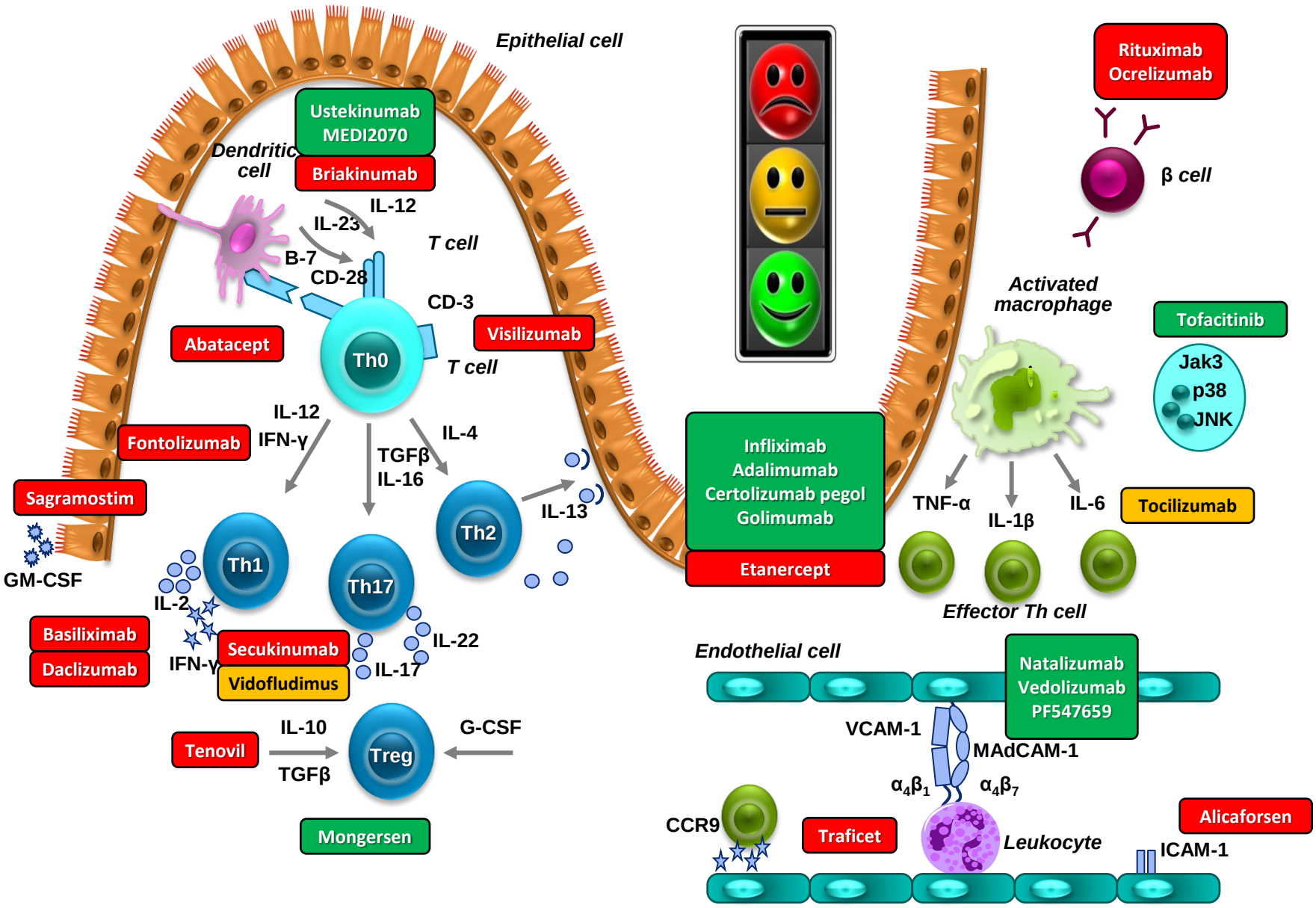
RELATIONSHIP OF REGIONAL ILEITIS TO OTHER BENIGN INTESTINAL PROCESSES

There exists in the medical literature a heterogenous group of benign intestinal lesions which have now and then been described under the caption of "benign

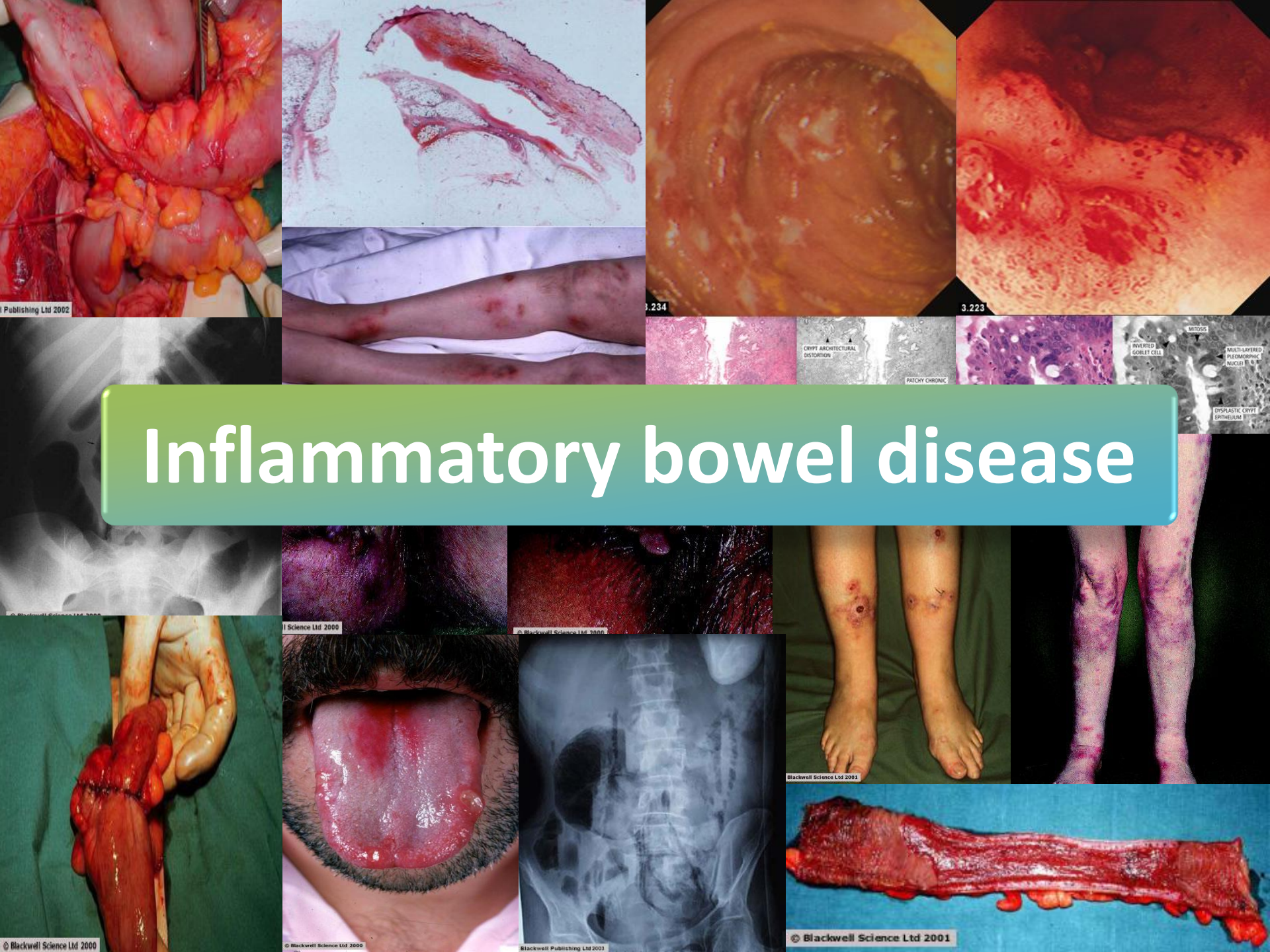
covers a multiplicity
and small intestines
chronic inflammatory
gy is either unknown
al agent. It represents
which are thrown all
al tumors which are
ecific bacterial agent.
tions of foreign body
with gross inflamma-
entery with intestinal
late productive reac-
s of the intestinal wall
ditions. The so-called
nor-like inflammatory
arcinoma but which
obably an infectious
e multiplicity of the

The etiology of the process is unknown; it belongs in none of the categories of recognized granulomatous or accepted inflammatory groups. The course is relatively benign, all of the cases that survive operation being alive and well.

Success and failure in IBD drug development



Adapted from Danese S, *et al. Gut* 2012;61:918–932.


Inflammatory bowel disease

The “new age” of IBD therapy

New dogma

Anti-adhesion | **Novel Tx** | **Anti-TNF**

Targeted therapies in patient subpopulations

clinical immunologic genetic

Patient classification

2000

Generalized immunosuppresion for all patients

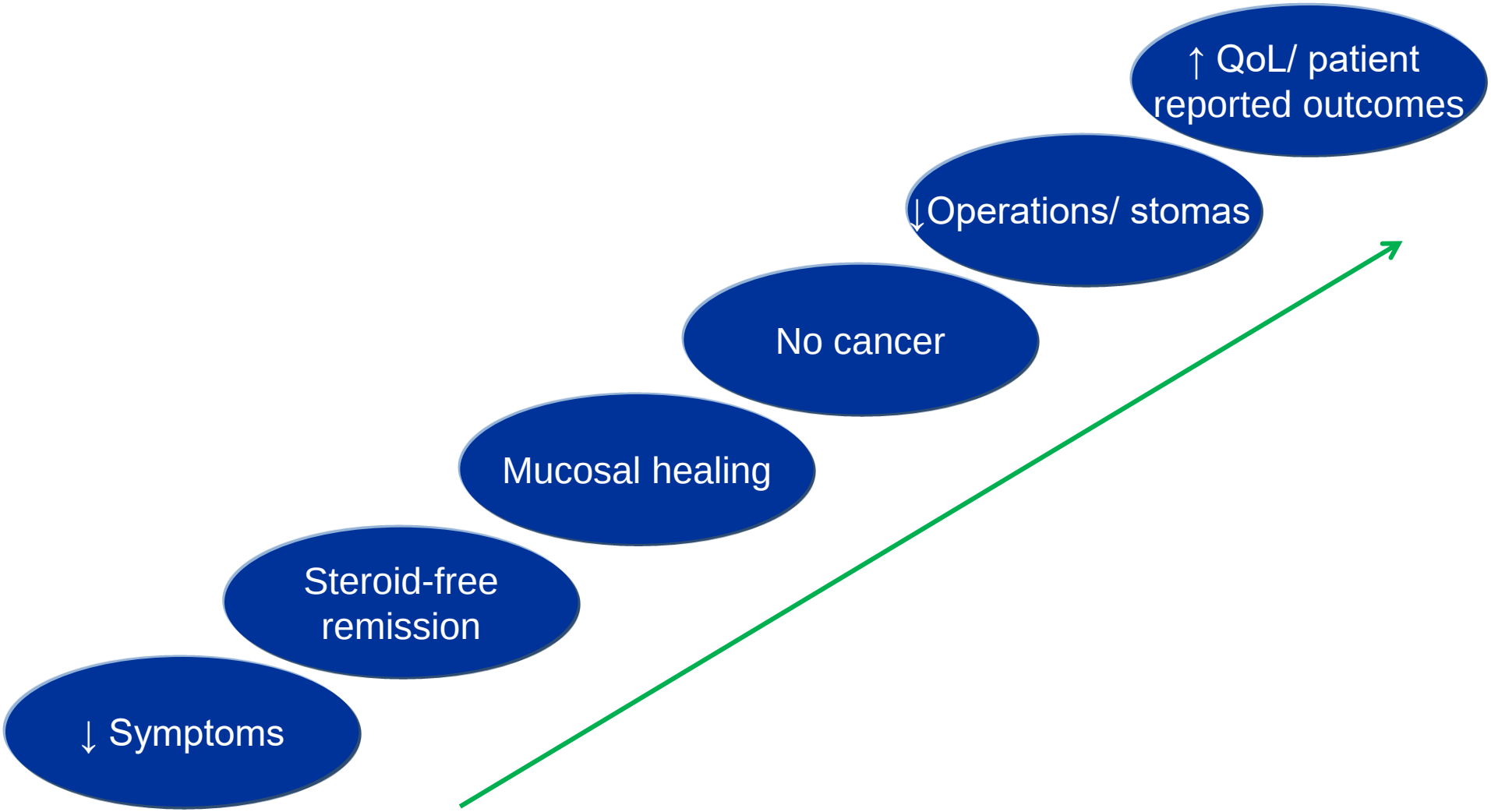
Thiopurines | **MTX**

Corticosteroids

5-ASA

Old dogma

Aims of management



Two Major Types of New Drugs

- **Conventional = "small molecules"**
  - Synthesized by organic chemistry
    - Potentially cheaper
  - Usually can be oral (pills)
  - Usually short half life (take daily)
  - Can someday be generic
- **Biologics = Biologicals = Biopharmaceuticals**
  - Synthesized in a cultured cell line, in a "Bioreactor"
    - Very expensive to make
  - Cannot be oral: must be IV or shots
  - Long half life (wks to mos)
  - Can someday be "biosimilar", not generic

Characteristics of Biologic and Small Molecule Therapies

- Characteristics of Biologic and Small Molecule Therapies

	Biologics	Small Molecules
Chemical composition[1]	Protein	Organic
Administration[1]	Parenteral	Oral/topical
Molecular weight[1]	>1 kDa	<700 Da
In vivo half-life[1]	(Usually) Long	(Usually) Short
Target[1]	Extracellular	(Usually) Intracellular
Generics[1]	Biosimilar	Identical
Immunogenicity[2]	Possible	Not expected

1. Mócsai A et al. *BMC Medicine*. 2014;12:43. 2. Zhao L et al. *Acta Pharmacologica Sinica.* 2012;33:1339-1347.

The 2 decades of biologicals…

- Infliximab / Inflectra /Remsima…
- Adalimumab /Hulio /Amgevita…
- Certolizumab pegol

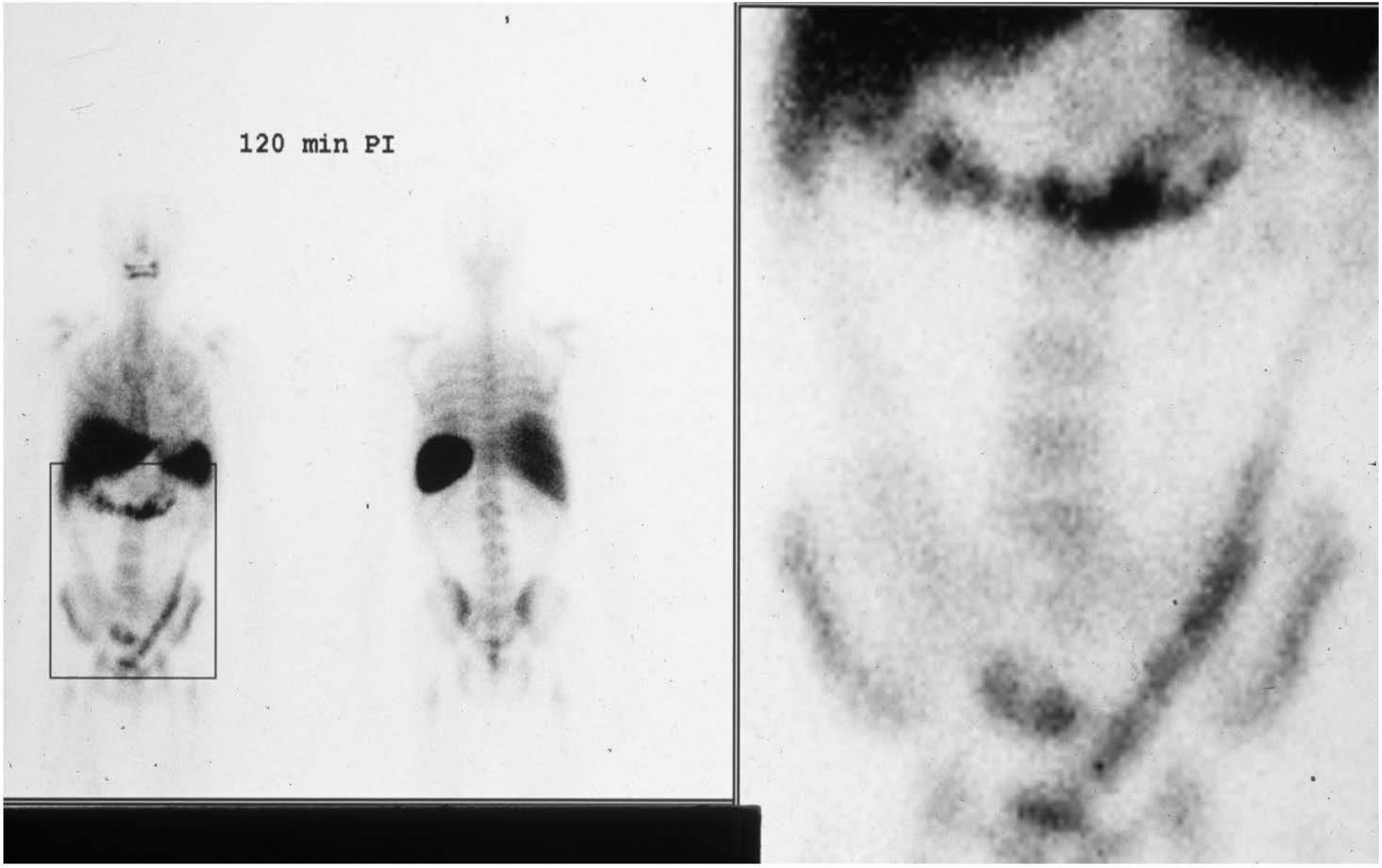
- Natalizumab
- Vedolizumab

- Ustekinumab

TNF Antagonist Failure History

		Ustekinumab				
	Placebo	1 mg/kg	3 mg/kg	6 mg/kg	Combined	Total
Subjects randomized	132	131	132	131	394	526
Subjects with inadequate initial response, %	33.3	29.8	31.1	27.5	29.4	**30.4**
Subjects with response followed by LOR, %	68.9	73.3	74.2	72.5	73.4	**72.2**
Subjects with intolerance, %	31.1	36.6	30.3	35.9	34.3	**33.5**
Subjects with inadequate initial response/ LOR/ intolerance, %	99.2	100.0	100.0	99.2	99.7	99.6
1 TNF antagonist	53.8	48.9	50.0	50.4	49.7	**50.8**
2 TNF antagonists	34.8	40.5	36.4	39.7	38.8	**37.8**
3 TNF antagonists	10.6	10.7	13.6	9.2	11.2	**11.0**

Migration of Leucocytes plays a key role in gut inflammation in IBD

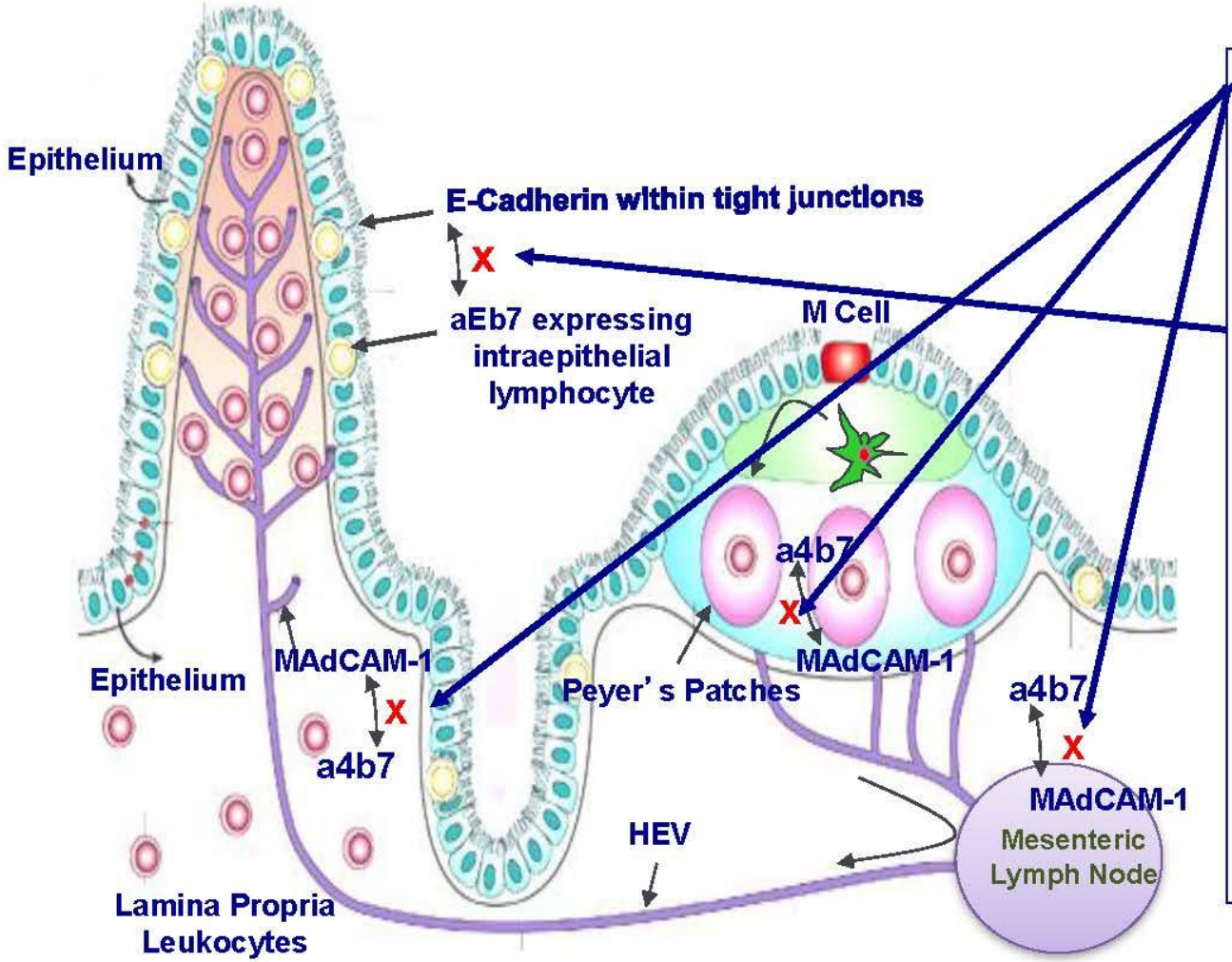


Bennink R et al Clin Nucl Med. 2001;26:99-104.

Anti-leukocyte trafficking

Etrolizumab Mechanism of Action

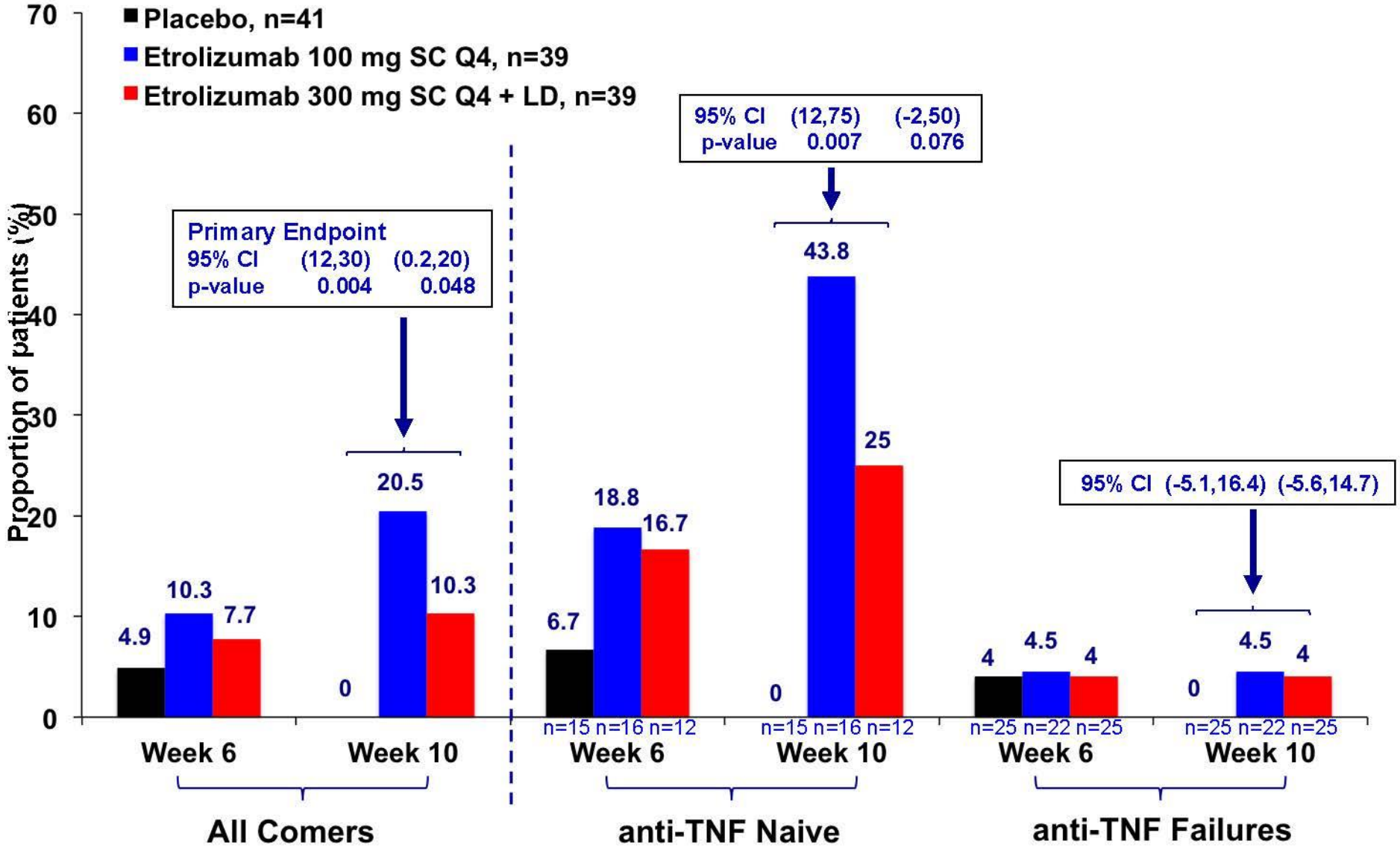
Humanized IgG$_1$ Monoclonal Antibody to the β7 Integrin



- Blocks trafficking into the GI mucosa
  - Clinically validated target
- Blocks retention of lymphocytes in the mucosal epithelium
  - Role in human IBD unknown
  - Exploration in Phase II
- Does not interfere with leukocyte trafficking to the CNS or other non-mucosal tissues
  - No PML expected

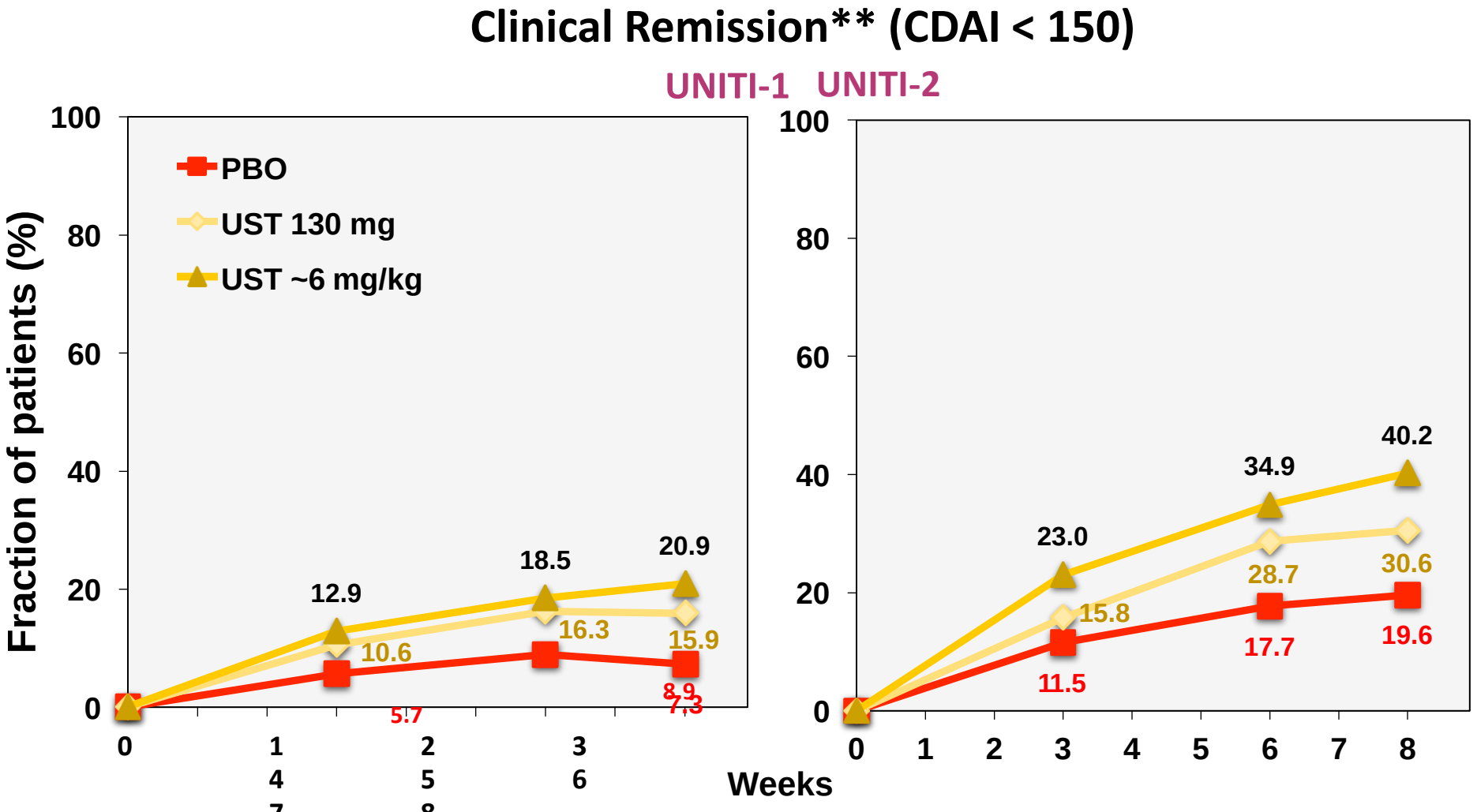
Etrolizumab: Clinical Remission in All Comers & by Anti-TNF status

Primary endpoint at Week 10



Vermeire S et al Lancet 2014, 384:309-18

Ustekinumab Induces Clinical Remission Through Week 8



**All p-values < 0.05 except 130 mg dose at Week 3, any UST vs. PBO

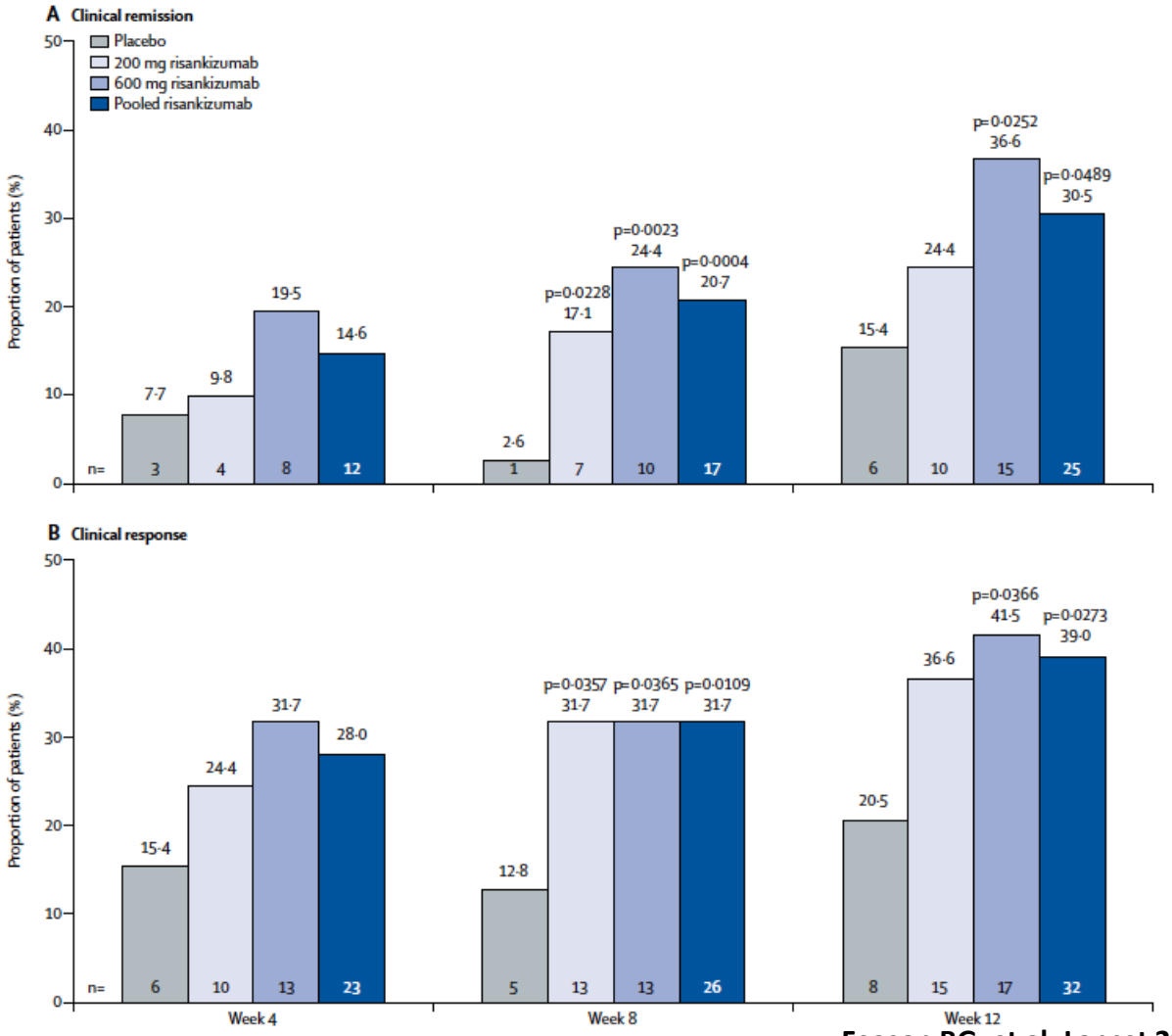
Feagan BG, Sandborn et al. NEJM 2016

Ustekinumab: Overall Population Summary Safety Findings Through Week 44

- No deaths
- No serious opportunistic infections
  - A single case of non-serious esophageal candidiasis in IV Ustekinumab Induction non-responder group ✎ Ustekinumab q8w maintenance
- A single case of active TB in a patient in an endemic area, which occurred 10 months ager receiving IV Ustekinumab Induction ✎ Placebo Maintenance
- Other than NMSCs, a single patient in the IV Placebo Induction non-responder ✎ Ustekinumab q12w Maintenance group had metastatic small bowel adenocarcinoma and an incidental carcinoid tumor found at resection
- 2.3% (27/1154) of subjects developed antibodies, which did not preclude efficacy

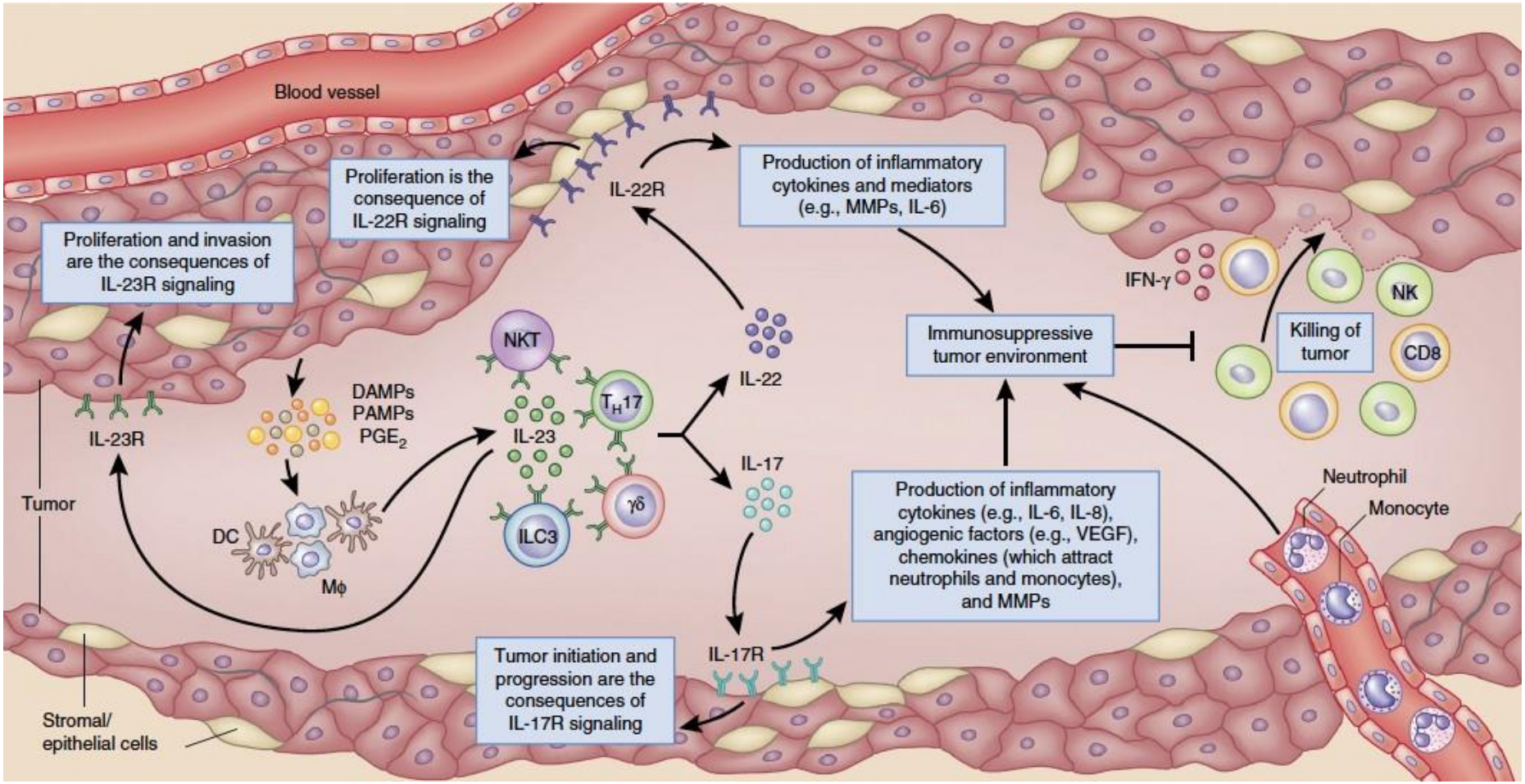
Feagan BG, Sandborn W.J., et al. NEJM 2016.

Risankizumab (anti-p19/IL-23 antibody) for Crohn's disease



Feagan BG, et al. Lancet 2017; 389: 1699–709

Role of IL-23 in tumorigenesis, growth and metastasis



Teng MWL, et al. Nature Med. 2015;21:719-29.

SMAD7 inhibition

The NEW ENGLAND JOURNAL of MEDICINE

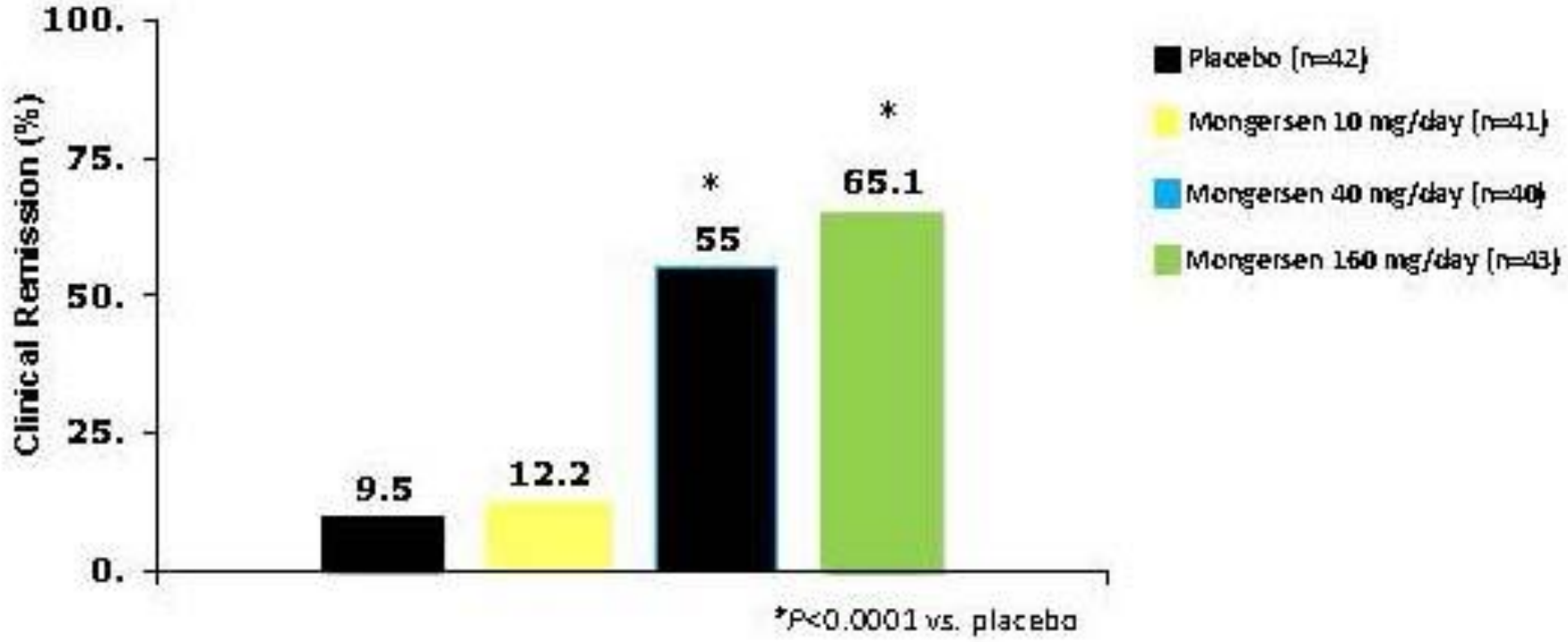
ORIGINAL ARTICLE

Mongersen, an Oral *SMAD7* Antisense Oligonucleotide, and Crohn's Disease

- Phase II, placebo controlled, double-blinded trial
- N=166 patients with moderate Crohn's disease
- Daily doses of placebo or 10, 40, or 160 mg Mongersen for two weeks, then stopped
- Patients followed out to 12 weeks to evaluate response

Mongersen (GED-0301) safe and effective in steroid dependent or resistant Crohn's disease

- Mongersen is an oral locally active antisense oligonucleotide that targets Smad7
- Phase 2 RCT, week 12 remission: not affected by hsCRP, disease duration; lower remission with higher baseline CDAI

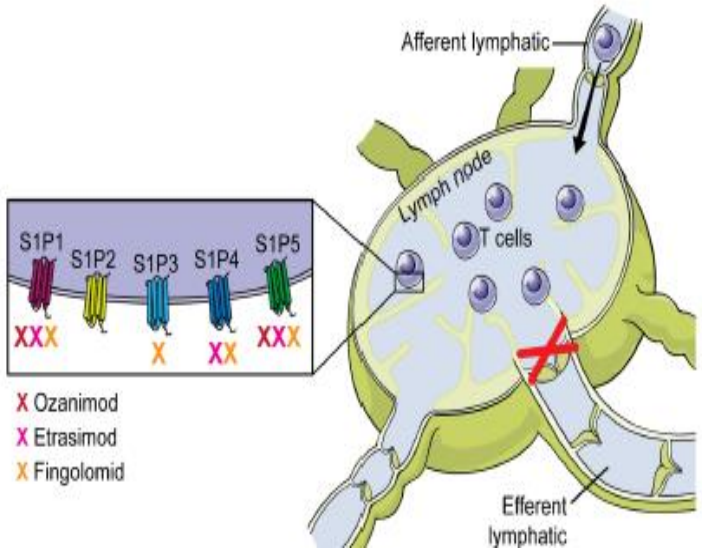


Monteleone G. Abstract 827 at DDW 2015.

Drawbacks to study

- Outcomes were subjective (symptoms)
- Enrolled patients had moderate (not severe) IBD
- No "hard" (objective) endpoints
  - Colonoscopy/biopsies?
  - Stool tests for inflammation (calprotectin)?
- Unclear what happens beyond 12 weeks

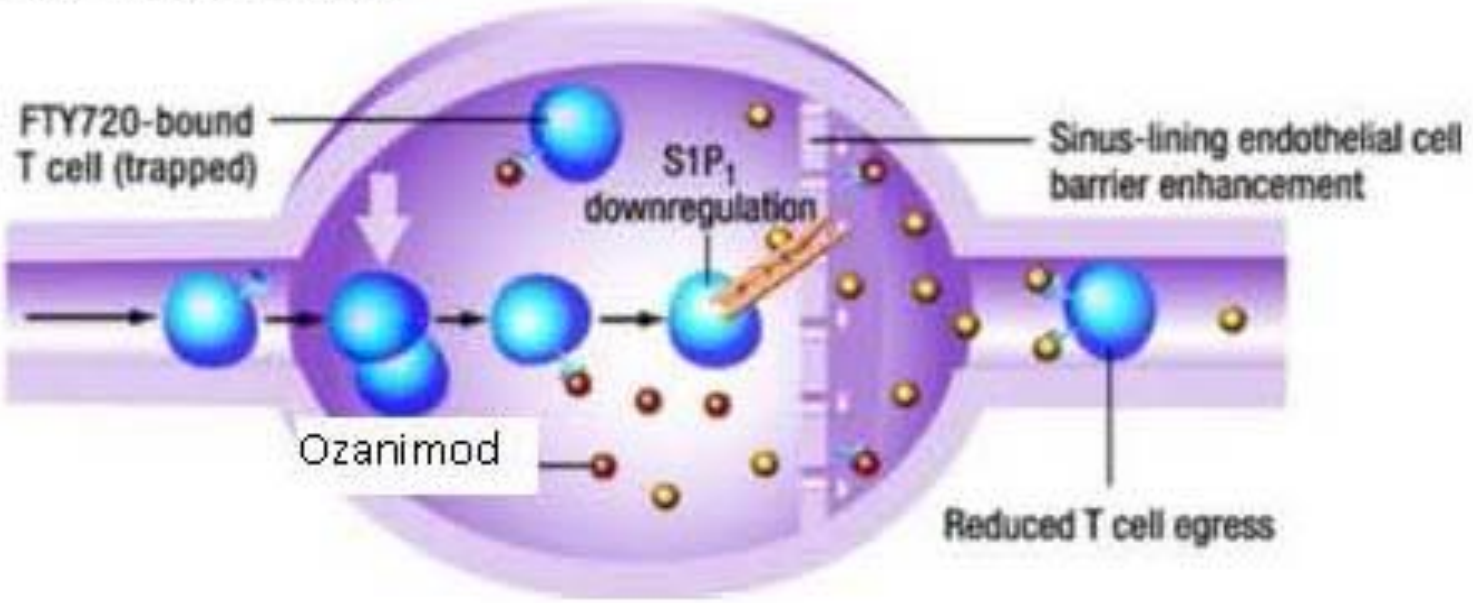
Sphingosine-1 phosphate receptor modulation



Ozanimod

Ozanimod

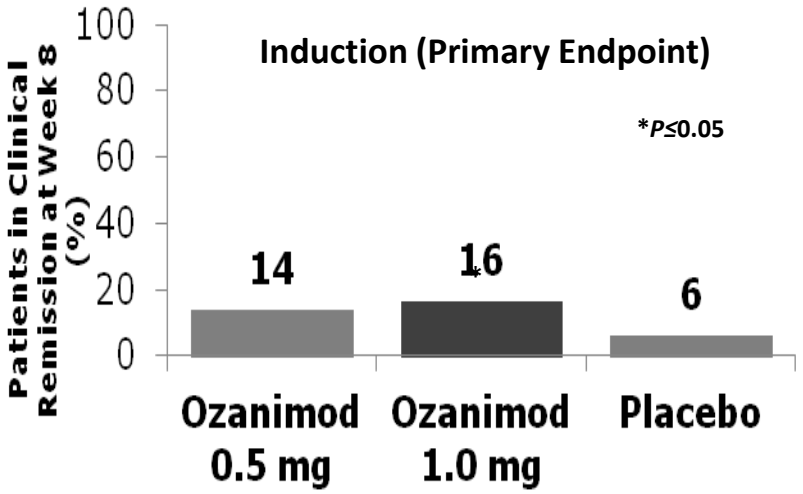
- Oral pills
- Activates the S1P1 Receptor, used by lymphocytes to "smell" their way out of a lymph node
- S1P1 receptor gets down-regulated, and lymphocytes get trapped in lymph nodes, so they cannot go to inflamed tissues

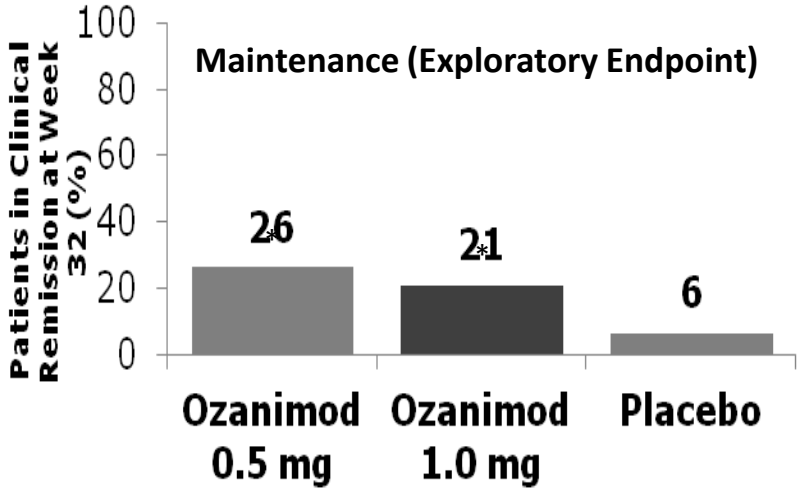


Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis (TOUCHSTONE Phase 2 Study)

- **Study Design**
  - Randomized, double-blind, placebo-controlled trial
    - Ozanimod 0.5 mg (n=65)
    - Ozanimod 1.0 mg (n=67)
    - Placebo (n=65)
- **Primary Endpoint**
  - Clinical remission[a] at Week 8 (induction)
- **Exploratory Endpoints**

  - clinical response, clinical remission, mucosal healing and change in the Mayo Clinic score at week 32 and histologic at weeks 8 and 32.
- **Safety**
  - No important differences in the most commonly reported AEs were observed between treatment groups
    - The most common AEs were worsening UC and anemia
  - Transient ALT ≥3x ULN occurred in 4 ozanimod-treated patients
  - Ozanimod treatment resulted in large reductions from baseline in ALC





Sandborn WJ et al, N Engl J Med 2016; 374:1754-1762

[a]Defined as Mayo score of ≤2, with no individual subscore >1.

P661 Early histological improvement demonstrated with oral **ozanimod** in patients with moderately to severely **active Crohn's disease** in the **STEPSTONE trial.** B. G. Feagan, G. D'Haens, K. Usiskin, J. Liu, D. Paul, R. K. Pai

- STEPSTONE was an open-label uncontrolled phase 2 multi-centre trial of ozanimod for 12 weeks, followed by an extension period.
- Patients with active CD received ozanimod 1 mg daily. Sixty-nine patients were enrolled.

Table 1 presents the mean change in RHI for paired segments from baseline to Week 12

Robarts Histopathology Index (RHI): incorporates 4 histological descriptors

Study Group	N (ITT N=69)	Mean (Standard Deviation)
Overall Population	52	-4.5 (9.48)
Biologic Exposure		
Prior Biologic Exposure	30	-4.0 (8.59)
Biologic Naive	22	-5.1 (10.75)
Segment		
Rectum	48	-1.7 (3.27)
Left Colon	45	-1.6 (3.41)
Transverse Colon	47	-0.1 (2.56)
Right Colon	42	-0.3 (3.69)
Ileum	41	-1.5 (3.26)

Note: Preliminary data

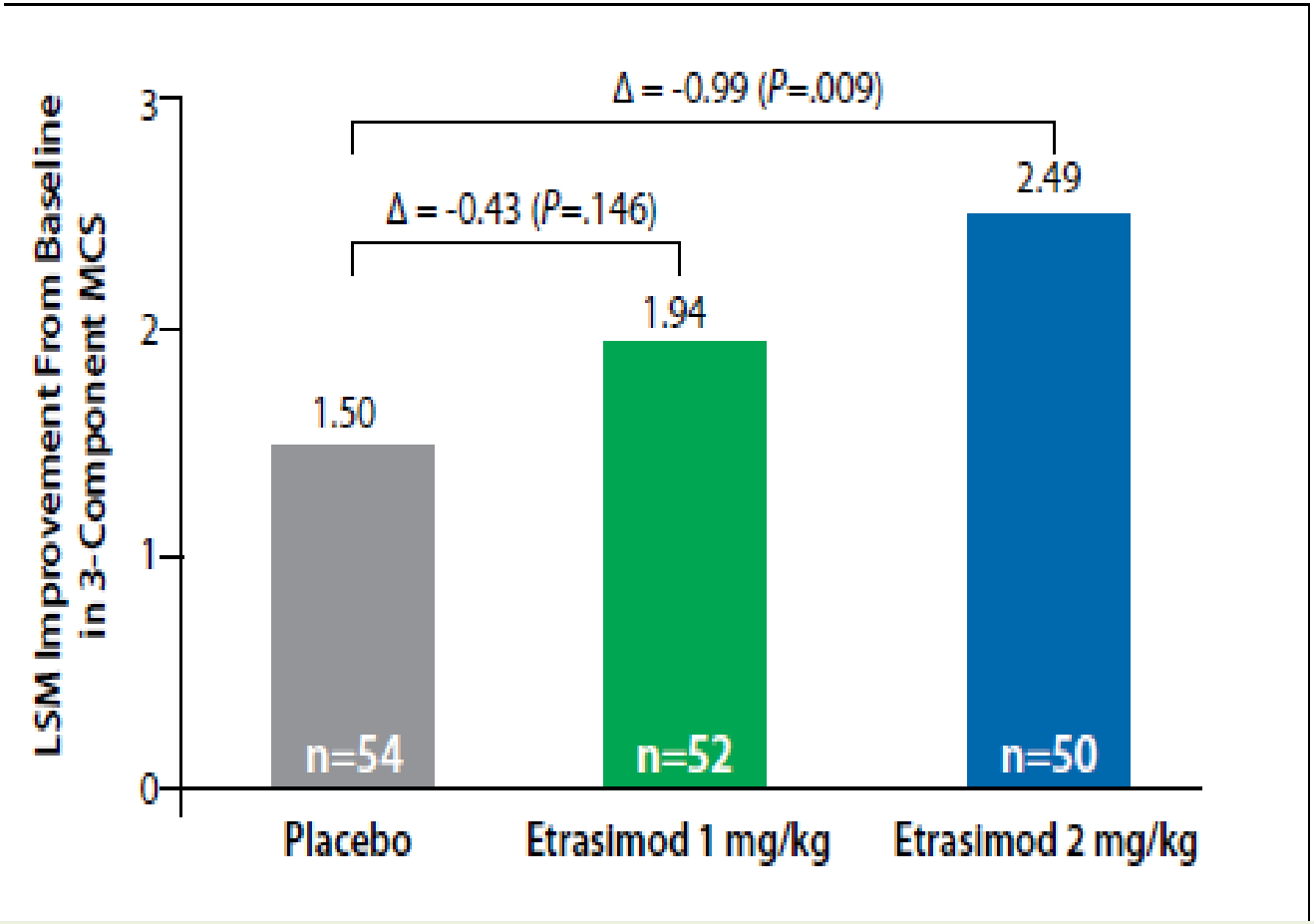
Safety: through 12 weeks, most non-serious and serious adverse events appeared to be related to underlying moderate to severe CD. No new safety signals were identified

Conclusion

- ✓ Results of the STEPSTONE trial demonstrated **early histological improvements** among patients with moderately to severely active **CD** who were treated for 12 weeks with ozanimod.
- ✓ These improvements were seen in the patients with and without prior biologic exposure and across all segments.

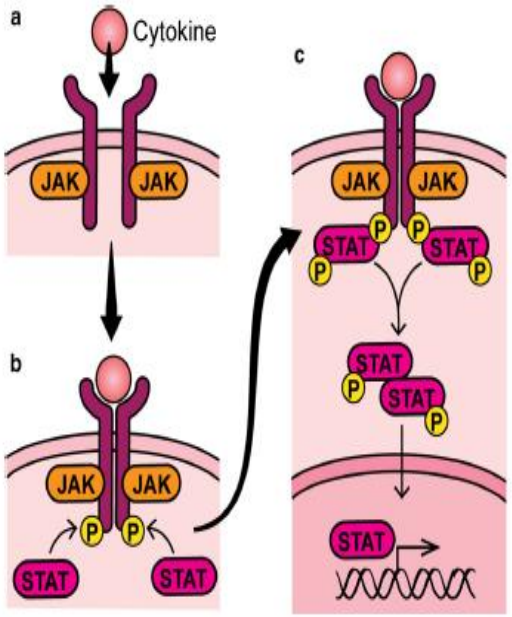
Etrasimod

OP242 | A randomized, double-blind, placebo-controlled trial of a selective, oral sphingosine 1-phosphate receptor modulator, etrasimod (APD334), in moderate to severe ulcerative colitis: Results from the OASIS study (Lead author: W Sandborn, US)

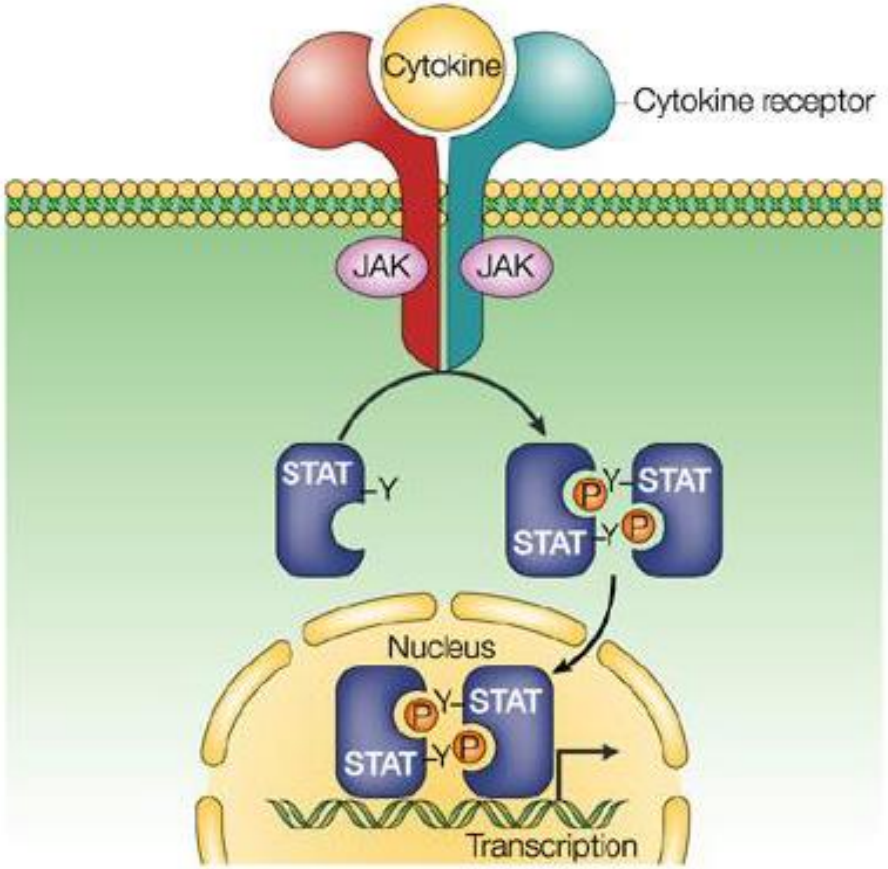


Key takeaway: Etrasimod achieved statistically significant difference in efficacy and safety endpoints

JAK-inhibition



JAK inhibition in inflammatory diseases

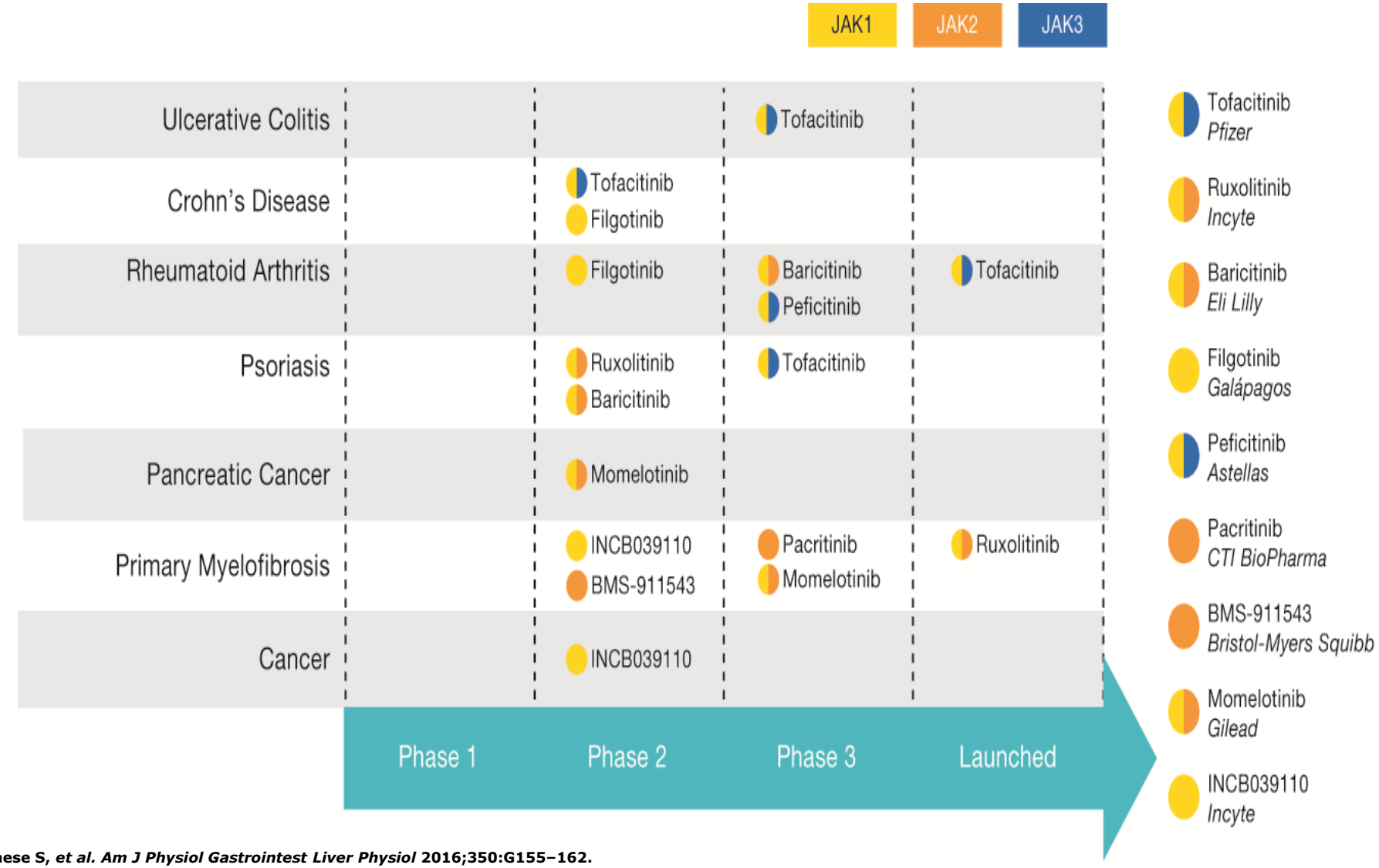


Nature Reviews Immunology 2003 **3:** 900-911

Diseases with dysregulated JAK pathway

- Crohn's Disease
- Alopecia Areata
- Ulcerative Colitis
- Atopic Dermatitis
- RA
- cGVHD
- Lupus
- Uveitis

Pipeline of JAK inhibitors



Danese S, *et al. Am J Physiol Gastrointest Liver Physiol* 2016;350:G155–162.

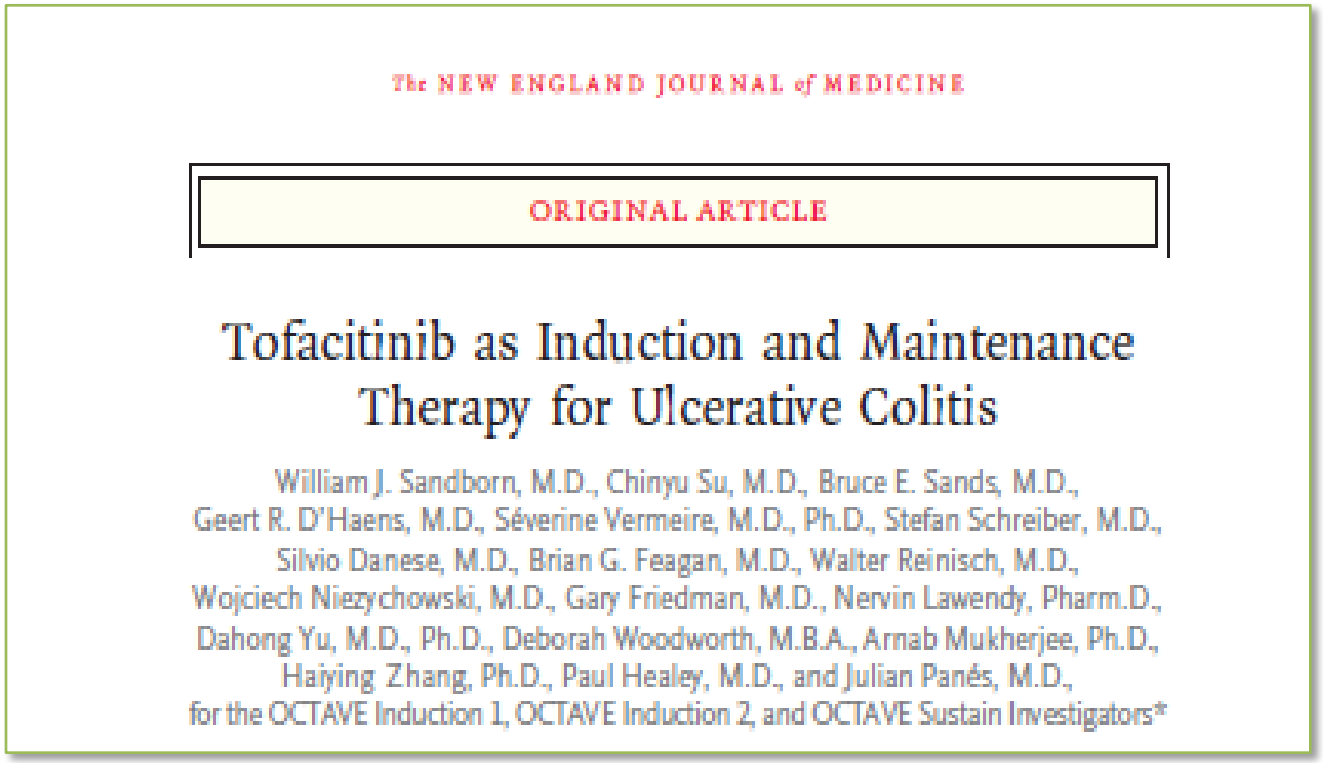
JAK Inhibitors in Clinical Development for UC

JAK Inhibitor	Company	UC Status*	Target	Selectivity
Tofacitinib	Pfizer[1]	Approved	JAK1 and JAK3[2] 	• 20-fold selectivity for JAK3 over JAK2[3] • IC_{50} (nM)[4]: • JAK1=3.8; JAK2=10.7; JAK3=1.4; TYK2=24
Filgotinib	Gilead, Galapagos[1]	Phase 3[1]	JAK1[1,3] 	• 30-fold selectivity for JAK1 over JAK2[3] • IC_{50} (nM)[3]: • JAK1=10; JAK2=28; JAK3=810; TYK2=110
Upadacitinib	AbbVie[1]	Phase 2/3[3,5]	JAK1[1] 	• 74-fold selectivity for JAK1 over JAK2[3]

Tofacitinib

(JAK 1-3 inhibitor)

OCTAVE Induction 1, Induction 2 in *NEJM*, May 2017



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

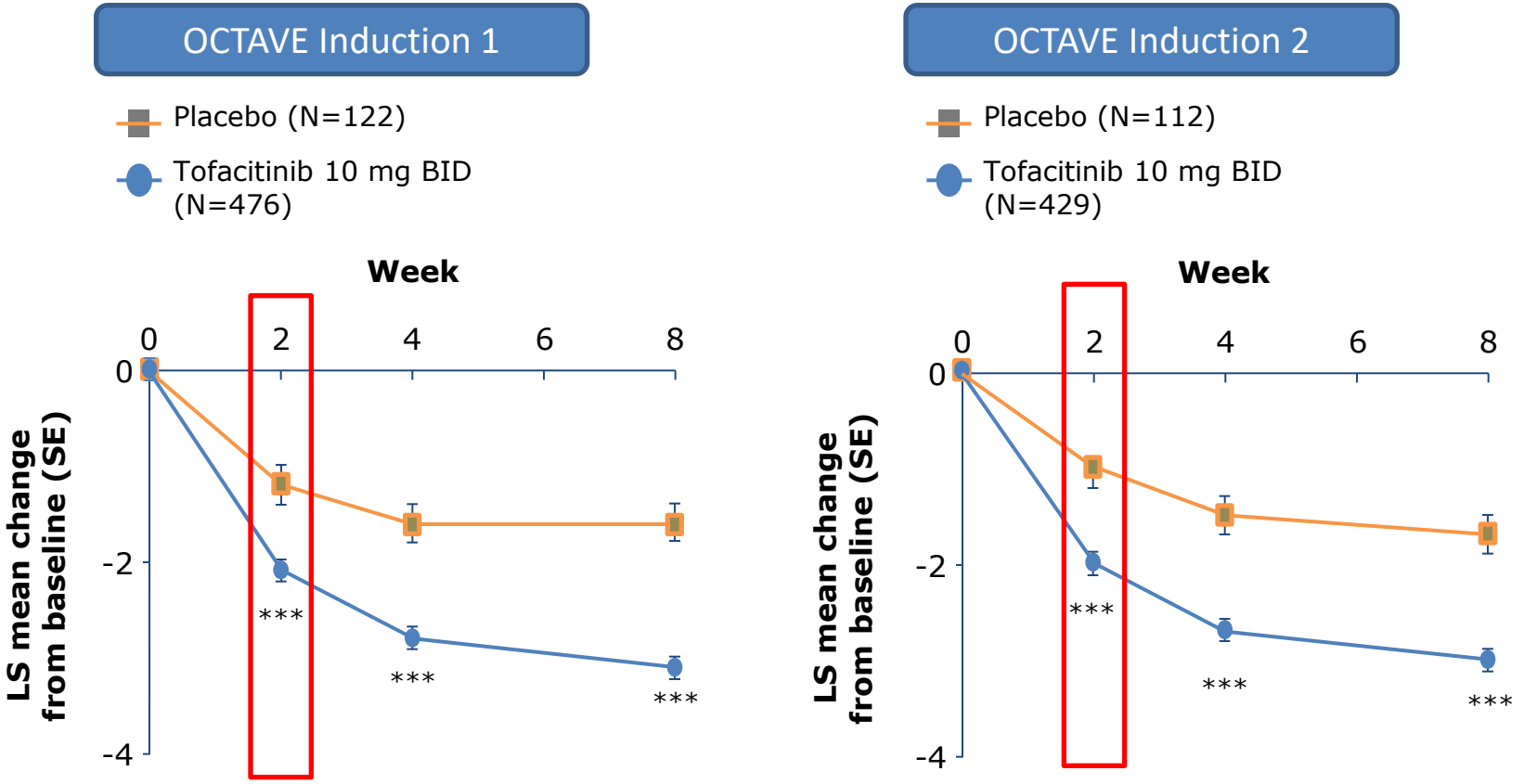
Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis

William J. Sandborn, M.D., Chinyu Su, M.D., Bruce E. Sands, M.D., Geert R. D'Haens, M.D., Séverine Vermeire, M.D., Ph.D., Stefan Schreiber, M.D., Silvio Danese, M.D., Brian G. Feagan, M.D., Walter Reinisch, M.D., Wojciech Niezychowski, M.D., Gary Friedman, M.D., Nervin Lawendy, Pharm.D., Dahong Yu, M.D., Ph.D., Deborah Woodworth, M.B.A., Arnab Mukherjee, Ph.D., Haiying Zhang, Ph.D., Paul Healey, M.D., and Julian Panés, M.D., for the OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators*

- Global clinical trial programme[1]
  - **OCTAVE Induction 1:** 178 locations in 28 countries
  - **OCTAVE Induction 2:** 182 locations in 29 countries
  - **OCTAVE Sustain:** 275 locations in 32 countries

1. ClinicalTrials.gov. NCT01465763 (OCTAVE Induction 1); NCT01458951 (OCTAVE Induction 2); NCT01458574 (OCTAVE Sustain).
2. Sandborn WJ, et al. *N Engl J Med*. 2017;376:1723-1736.

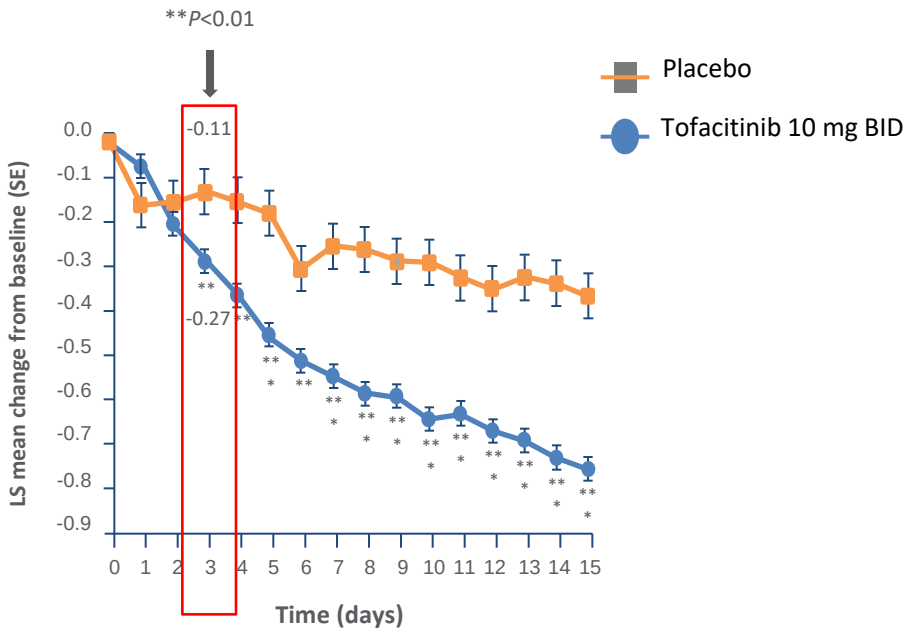
Partial Mayo till week 8



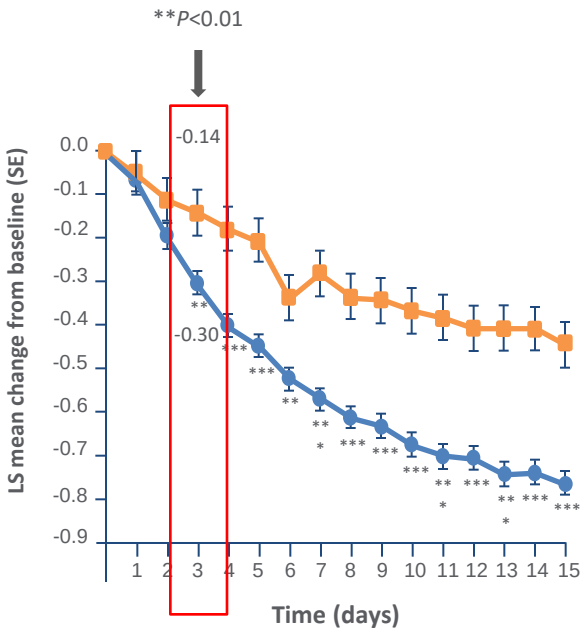
***$P<0.0001$ vs placebo.
BID=twice daily; LS=least squares; SE=standard error.
Sandborn WJ, et al. *N Engl J Med*. 2017;376(suppl):1723-1736.

PROs : Symptom improvement from day 3

Stool frequency[1]



Rectal bleeding[1]



There was a significant improvement in stool frequency and rectal bleeding subscores by day 3 with tofacitinib treatment compared with placebo[1]

**P<0.01; ***P<0.0001 vs placebo.
BID=twice daily, LS=least-squares, SE=standard error.

1. Hanauer S, et al. *Clin Gastroenterol Hepatol.* 2018 doi:10.1016/j.cgh.2018.07.009. [Epub ahead of print].

17 May 2019
EMA/267216/2019 Rev.1[1]

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Restrictions in use of Xeljanz while EMA reviews risk of blood clots in lungs

- An increased risk of pulmonary embolism and overall mortality has been observed in a study with tofacitinib 10 mg twice daily in rheumatoid arthritis.
- These results come from study A3921133, an ongoing open-label clinical trial evaluating the safety of tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily compared with a tumour necrosis factor (TNF) inhibitor in patients with rheumatoid arthritis. Patients in the study are 50 years of age or older with at least one additional cardiovascular risk factor.
- The preliminary results of the study showed that there were 19 cases of pulmonary embolism out of 3,884 patient-years in the tofacitinib 10 mg twice daily arm of the study compared with 3 cases out of 3,982 in the TNF inhibitor arm. Additionally, there were 45 deaths from all causes out of 3,884 patient-years in the 10 mg twice daily arm compared with 25 cases out of 3,982 patient-years in the TNF inhibitor group.

EMA PRAC Recommendation (May 2019)

- ♦ Tofacitinib Dose of 10 is contraindicated to the patients with 1 or more of the following conditions
- Hormanal or contraceptives use
- Heart failure
- History of DVT
- Inherited pro-coagulative disorders
- Malignancy
- Patients undergoing major surgical intervention
- ♦ Other factors to consider are
- age,
- obesity,
- smoking
- immobilization.

Filgotinib

(JAK 1 inhibitor)

Filgotinib was efficacious in CD (Phase 2 data)

THE LANCET

Articles

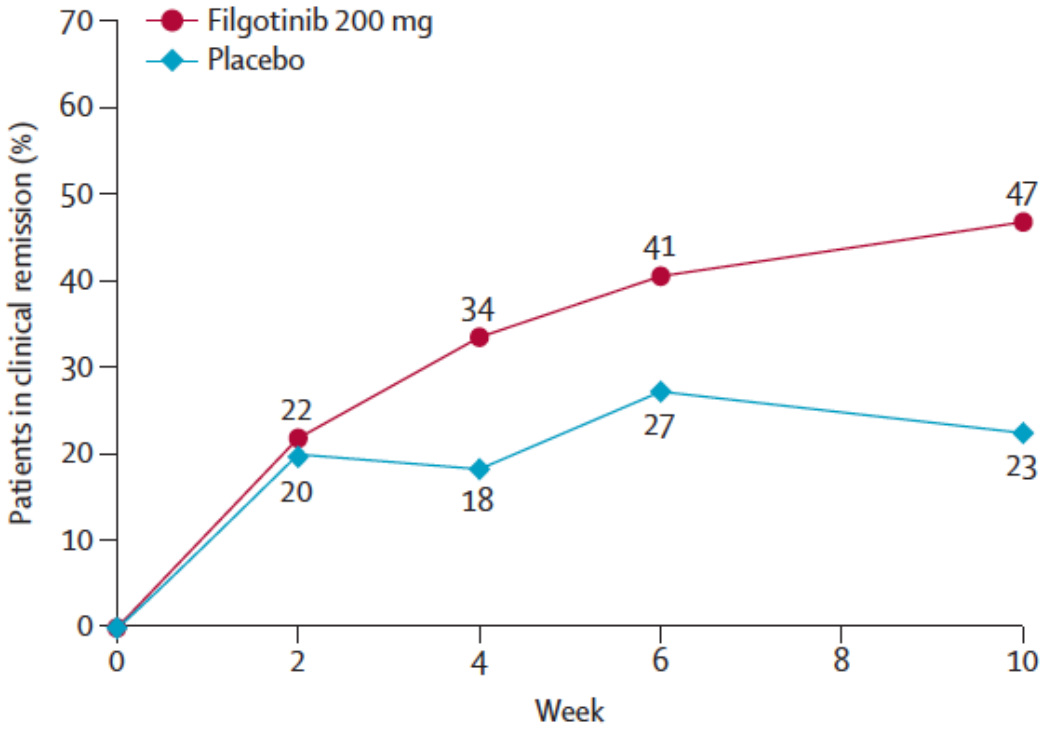
Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial

Prof Séverine Vermeire, MD, Prof Stefan Schreiber, MD, Robert Petryka, MD, Prof Tanja Kuehbacher, Dr med habil, Prof Xavier Hebuterne, MD, Xavier Roblin, MD, Maria Klopocka, PhD, Adrian Goldis, MD, Maria Wisniewska-Jarosinska, MD, Prof Andrey Baranovsky, MD, Robert Sike, MD, Kremena Stoyanova, MD, Chantal Tasset, PhD, Annegret Van der Aa, PhD, Pille Harrison, DPhil

Published: 14 December 2016

Filgotinib (JAK 1 inhibitor) for Moderate-to-Severe CD

- Filgotinib is a selective once-daily oral JAK1 inhibitor
- 174 patients randomized filgotinib 200 mg QD or placebo for 10 weeks
- All immunosuppressants discontinued
- Primary endpoint: CDAI <150 at 10 weeks



Vermeire S, et al. Lancet 2017; 389: 266–75

Key safety findings

Infections

- Serious infections, sometimes fatal, have been reported
- Overall infection rates are higher in active arms over placebo
- The rate of serious infections ~ < 3% across trials
- Pneumonia is an *adverse drug reaction*

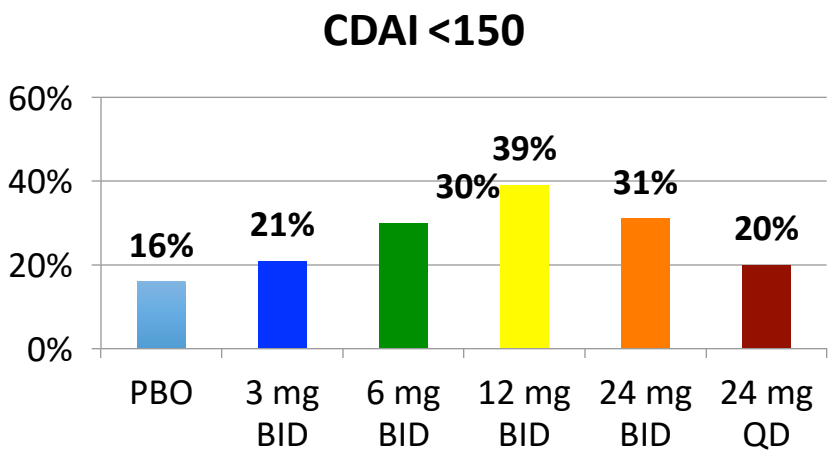
Malignancies

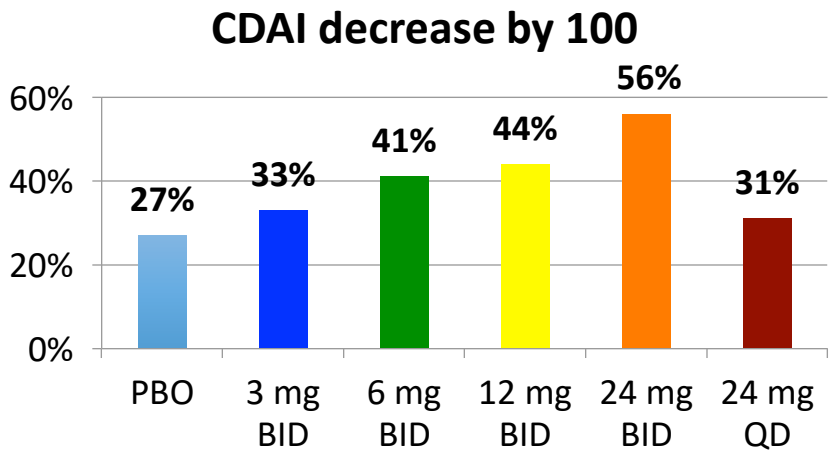
- 3 cases of non-Hodgkin's lymphoma reported as of January 2017
- All in subjects with RA
- A causal association between filgotinib and lymphoma/malignancies has not been determined

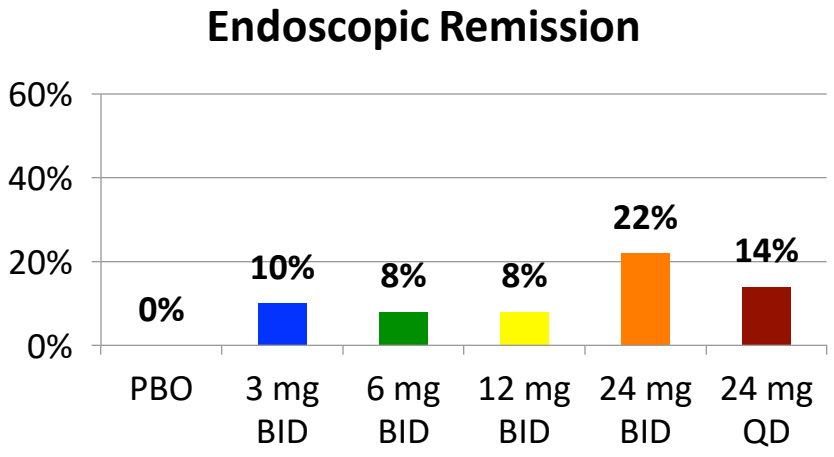
Upatacitinib

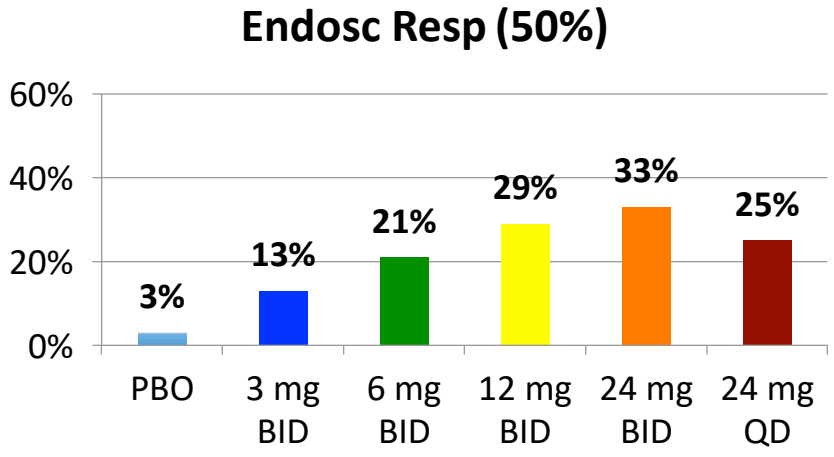
(JAK 1 inhibitor)

Upadacitinib (ABT-494, JAK1 inhibitor) for moderate-to-severe CD at week 16









Sandborn WJ, et al. Gastroenterology 2017;152:S1308-9.

OP14 Improved endoscopic outcomes and mucosal healing of upadacitinib as an induction therapy in adults with moderately to severely active ulcerative colitis: data from the U-ACHIEVE study

W. J. Sandborn, S. Schreiber, S. D. Lee, J. O. Lindsay, X. Hebuterne, W. Zhou, F. Cataldi, A. P. Lacerda, B. Huang, W. Xie, E. V. Loftus Jr

Proportion of patients achieving endoscopic improvement, endoscopic remission, histological improvement, histological remission, and mucosal healing at Week 8.

Endpoints, n (%)	Placebo n=46	UPA 7.5 mg QD n=47	UPA 15 mg QD n=49	UPA 30 mg QD n=52	UPA 45 mg QD n=56
Endoscopic improvement	1 (2.2)	7 (14.9)*	15 (30.6)***	14 (26.9)***	20 (35.7)***
Endoscopic remission	0	3 (6.4)	2 (4.1)	5 (9.6)*	10 (17.9)**
Histologic improvement	3 (8.1)	15 (35.7)**	25 (55.6)***	23 (52.3) ***	27 (56.3) ***
Histologic remission	1 (2.6)	6 (13.6)$^{+}$	11 (24.4)**	16 (35.6)***	23 (45.1)***
Mucosal healing	0	1 (2.1)	1 (2.0)	3 (5.8)*	8 (14.3)*

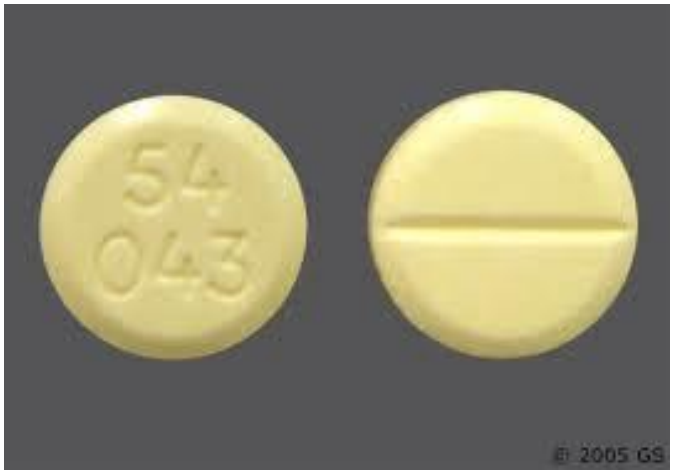
***, **, *, $^{+}$ statistically significant at 0.001, 0.01, 0.05, and 0.1 levels, respectively.
UPA: upadacitinib; QD: once daily.

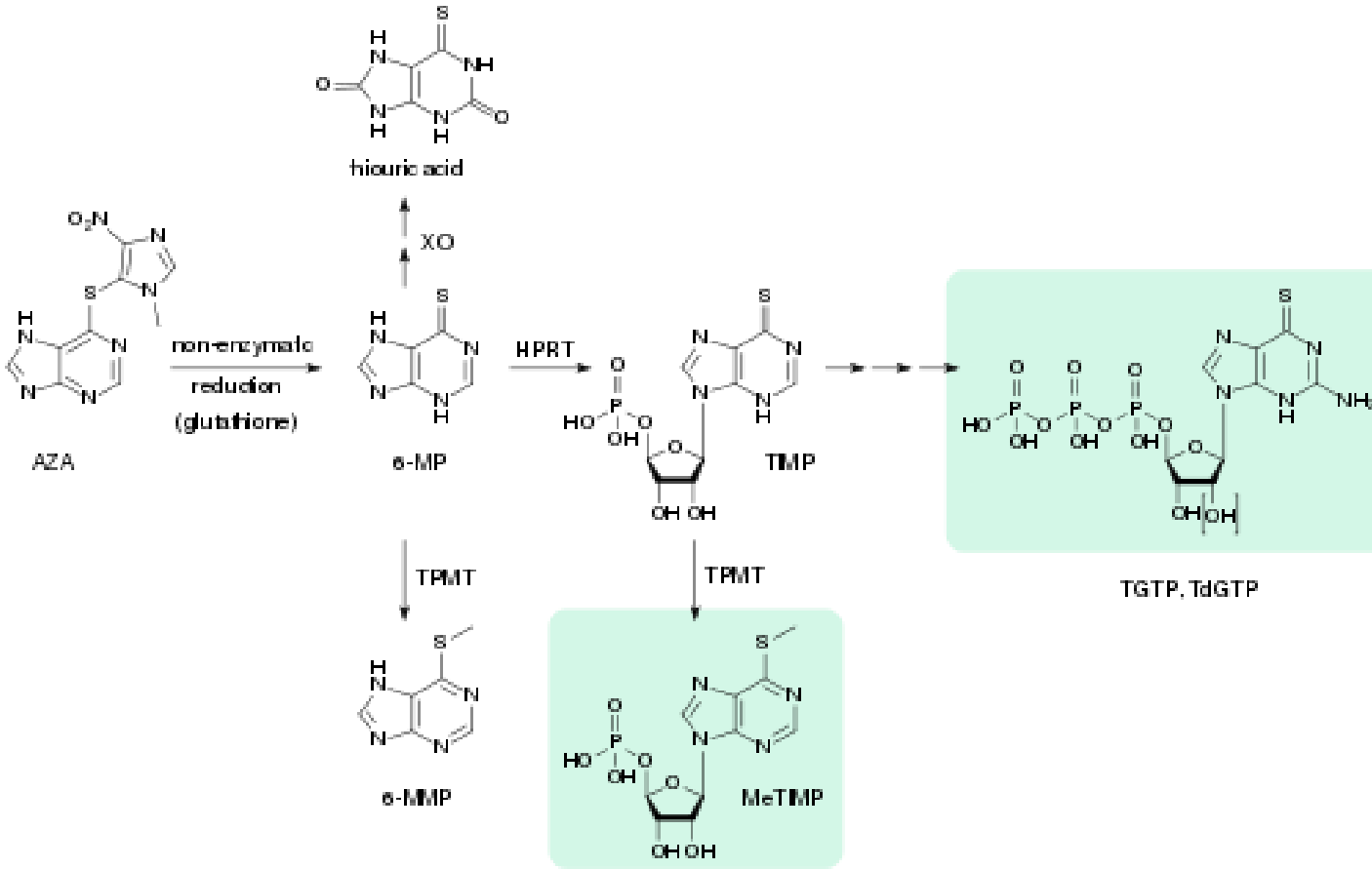
- ✓ In this dose-ranging 8-week induction study (phase 2b), **upadacitinib 30 and 45 mg QD** consistently demonstrated significant improvement in endoscopic outcomes, histological outcomes, and mucosal healing compared with placebo in patients with moderately-to-severely active ulcerative colitis.

Sandborn WJ et al, J Crohns Colitis 2019; 13(Suppl.1): S009 (#OP14)

Structure Of Azathioprine:

- Iupac Name: 6-(3-methyl-5-nitroimidazol-4-yl)sulfanyl-7H-purine
- Molecular Formula: $C_9H_7N_7O_2S$
- Molecular Weight: 277.262 g/mol





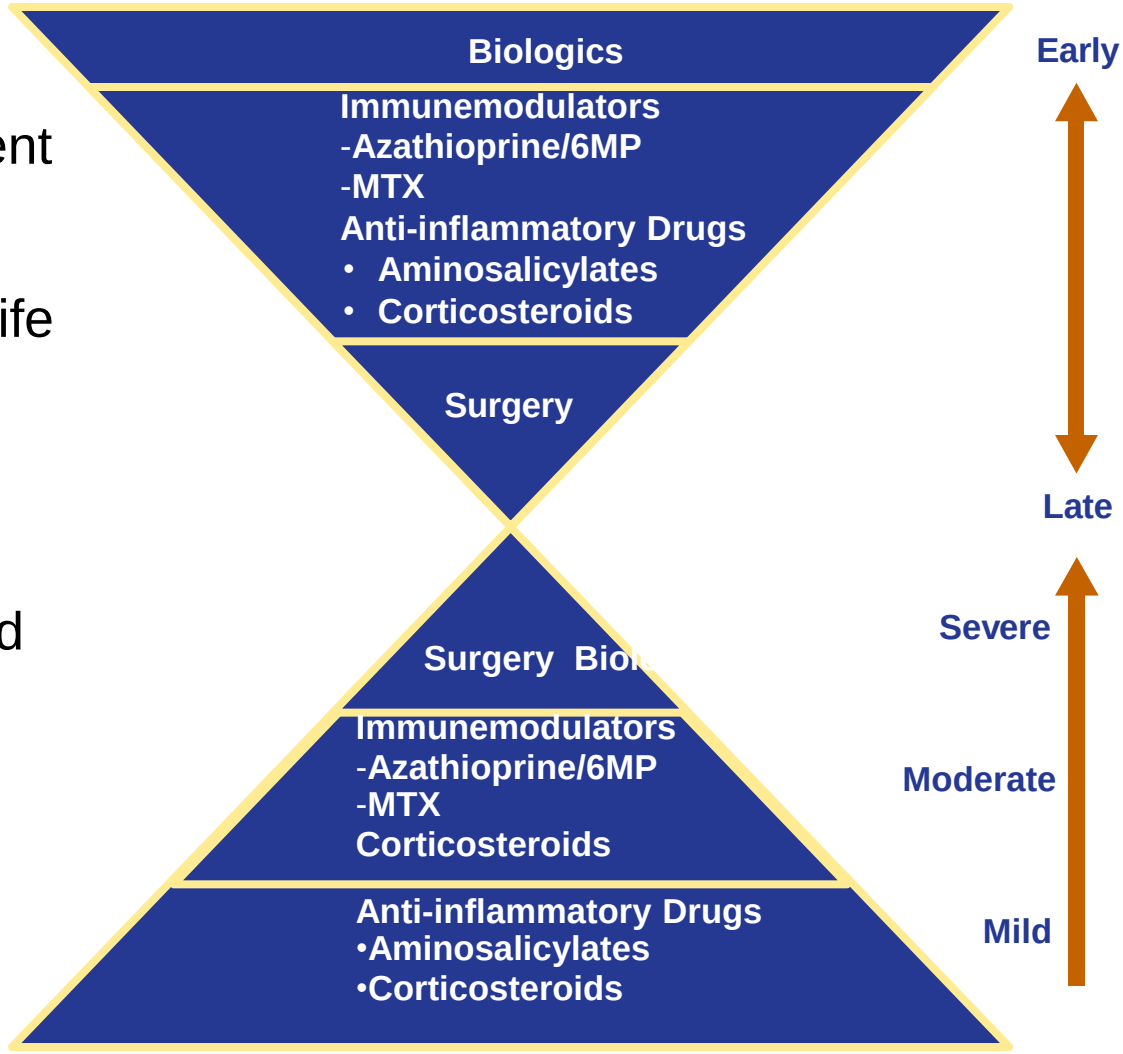
IBD Treatment Strategy

"Top-down" Strategy

- Early, appropriate use of biologic as initial treatment
- Induces rapid clinical response
- May enhance quality of life

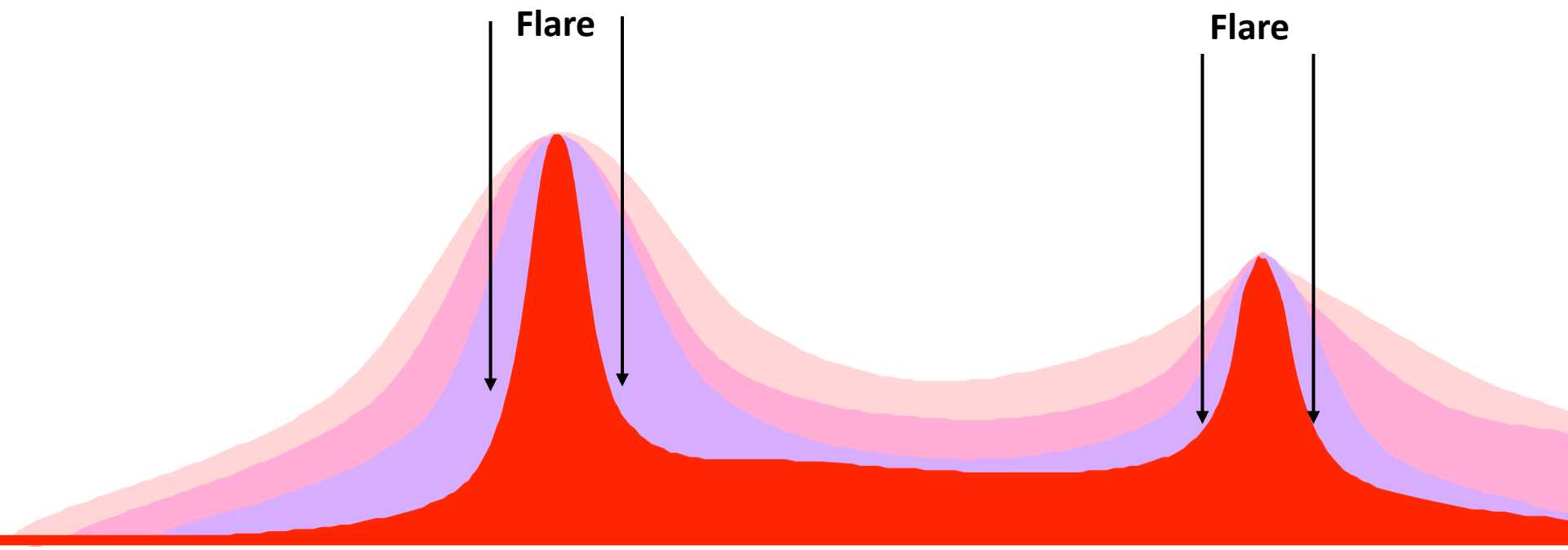
"Step-up" Strategy

- Standard, sequential treatment for remission and maintenance
- Cost-effective
- Minimal side effects

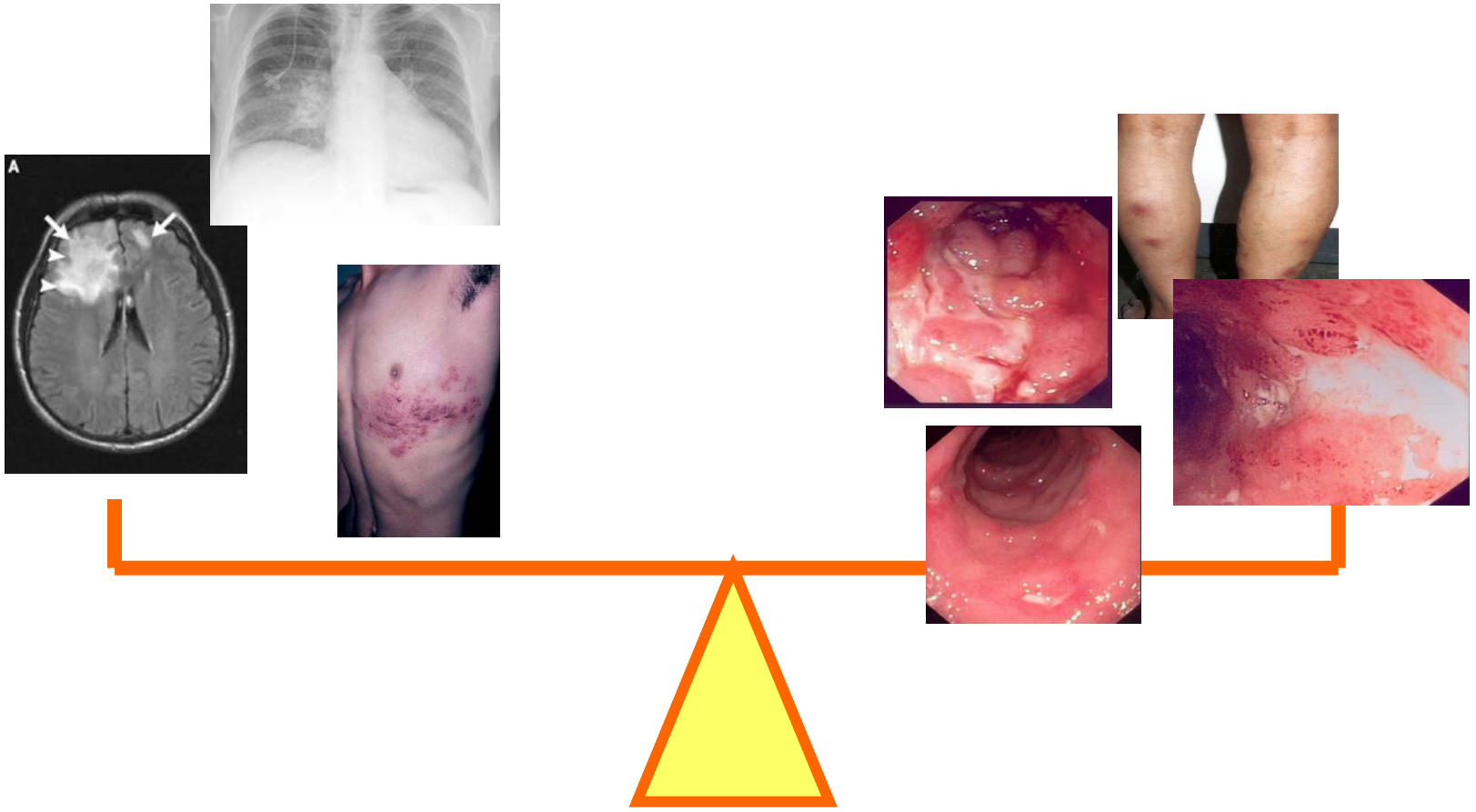


What should be the target ?

- **Symptoms**
- **CRP/calprotectin**
- **Endoscopy**
- **Histology/MRI**
- **...**



Αναλυτική συζήτηση με τον ασθενή



	Indication	Severe, Extensive Fistula, Inpatient	Safety (Thiopurine would increase risk)	Concom IMM for immunog	Pregnancy	Ability to measure Drug level and abs	Adherence	Extra Intestinal Manifest.
IFX	UC/CD	++ ↓albumin ↑CRP	t +	Yes	+	+	IV monitored	++ Rheum Derm Postop Peds
ADA	UC/CD	+/-	+	Yes	+	+	SQ self	++ Rheum Derm Postop Peds
CTZ	CD	+/-	+	Yes	++	+	SQ self	+
GOL	UC	+/-	+	Yes	+	-	SQ self	+
NATA	CD	+/-	+ - if JCV	Yes	?+	-	IV monitored	+ MS
VEDO	UC/CD CD	+/-	++ >50y?	Yes Yes	?+	+	IV monitored	- ?PSC
UST		+ after TNF	+		?+	- (soon?)	IV induction SQ maint	++ Rheum Derm

Summary: Small molecules for IBD

Advantages include:

- Reliable PK
- No immunogenicity
- Oral dosing

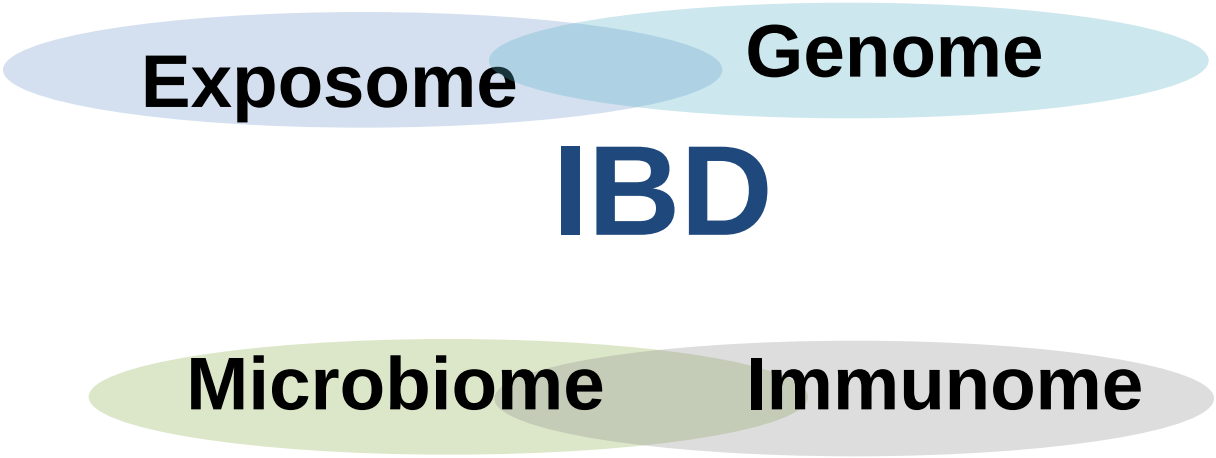
Diverse mechanisms directed at:

- Leukocyte trafficking
- S1P1r modulation
- JAK inhibition
- SMAD7 inhibition
- PDE4 inhibition

Βασικές αρχές

1. Προσεκτικό screening
2. Δεν αλλάζουμε εύκολα φάρμακο-εξάντληση δυνατοτήτων δοσολογίας
3. Εκτίμηση ανάγκης ΆΖΑ-ΜΤΧ
4. Ακούμε τον ασθενή για αποτελεσματικότητα και παρενέργειες

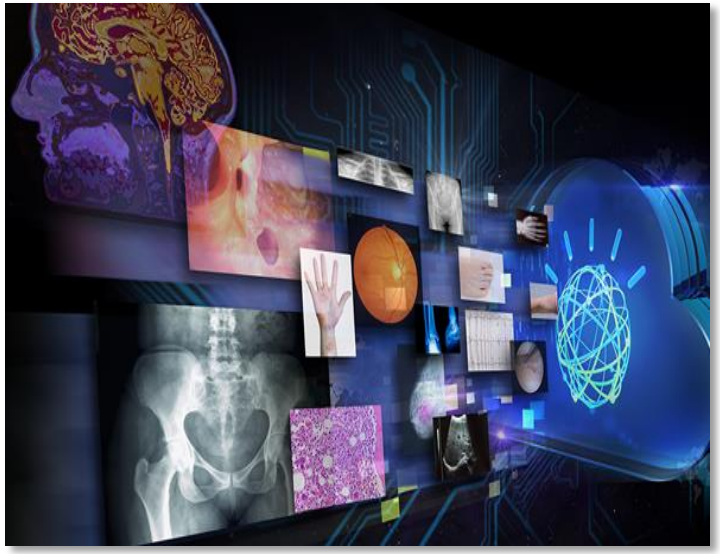
The “new” IBD perspective: targeting the IBD interactome



Danese S, et al. Gut 2016;65:1233–1239

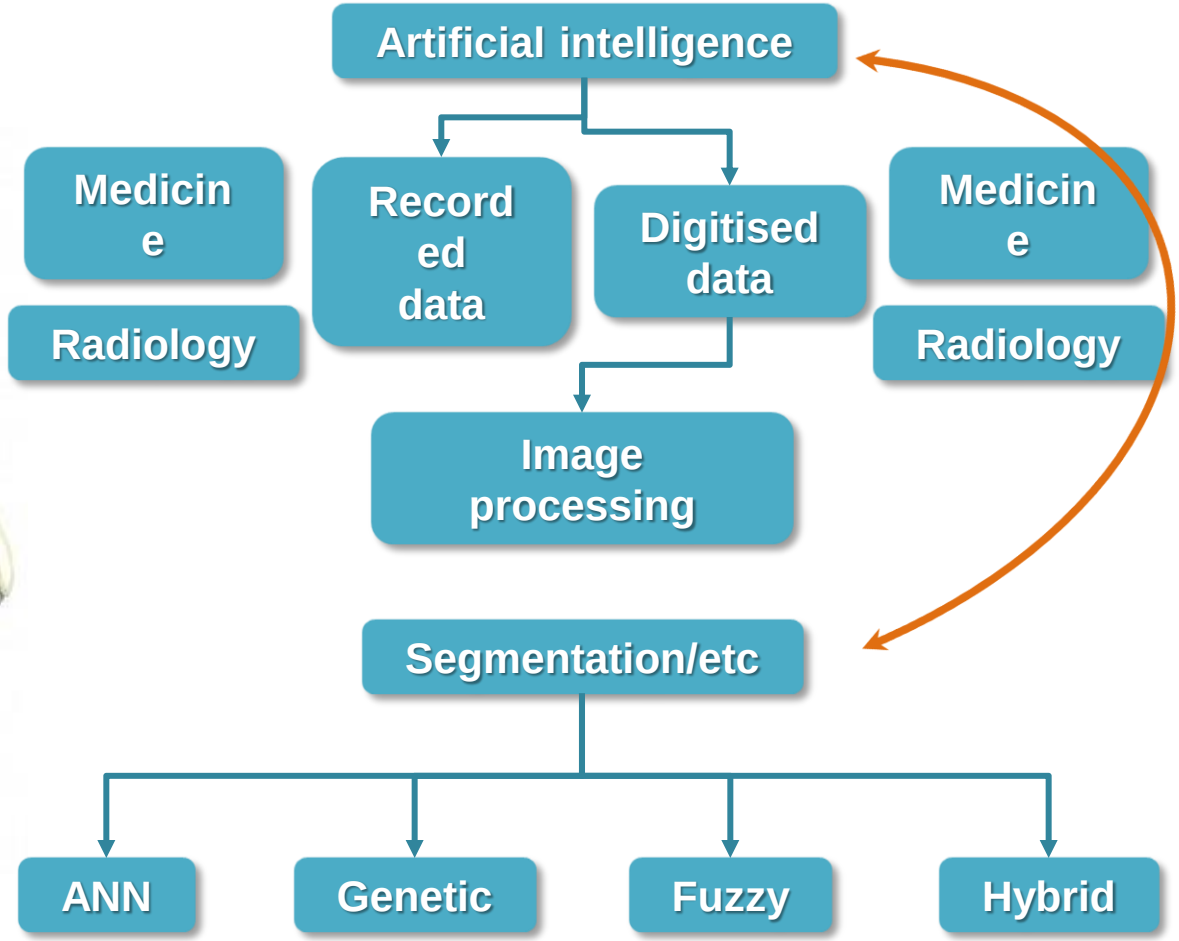
Artificial intelligence in medical decision support

- Use of cognitive computers in assisting medical decisions
- IBM's supercomputer, named Watson, can process over 200 million pages of medical data in seconds
  - Genomics: Watson can help to create personalized treatment strategies for patients, based on results from genetic testing
  - Drug discovery: Watson can help researchers uncover new pathways to identify novel drug targets and new indications for existing drugs



Available from: www.ibm.com/watson/health/#solutions. Accessed February 2018.

Do we need doctors or algorithms?



Slideshare: Artificial intelligence in medical image processing. Available at: https://www.slideshare.net/jahedif/artificial-intelligence-in-medical-image-processing (accessed May 2017)

Συμπεράσματα

- Νέα φάρμακα
- Πολυπλοκότητα θεραπειών
- Επιλογή κατάλληλης θεραπείας/εξατομίκευση
- Ανάλυση των αιτίων αποτυχίας των φαρμάκων
- Πολλά νέα προγράμματα σε πολλές φαρμακευτικές εταιρίες με στόχο διαφορετικά μόρια και μηχανισμούς

Συμπεράσματα

- Ανάγκη για καλύτερες θεραπείες
- Ταυτοποίηση του προφίλ των ασθενών
- Καλύτερα σχεδιασμένες μελέτες με ενεργό συμμετοχή των ασθενών (PRO)
- Συμμετοχή του ασθενούς στην ευθύνη της σωστής λήψης της θεραπείας
- Καλύτερη συνεργασία ομάδας (ασθενείς-ιατροί-νοσηλευτές-διαιτολόγοι).

Panes J, et al. Journal of Crohn's and Colitis (2014) 8, 919–926
Thomas Ochsenkuhn, Geert D'Haens. Gut 2011;60:1294e1299

"Crohn's disease"
Courtesy of the painter E. Vogiatzi