Biologics – Matching Drugs to Patients

William J. Sandborn MD
Professor and Chief, Division of Gastroenterology
Director, UCSD IBD Center

UC San Diego
HEALTH SYSTEM

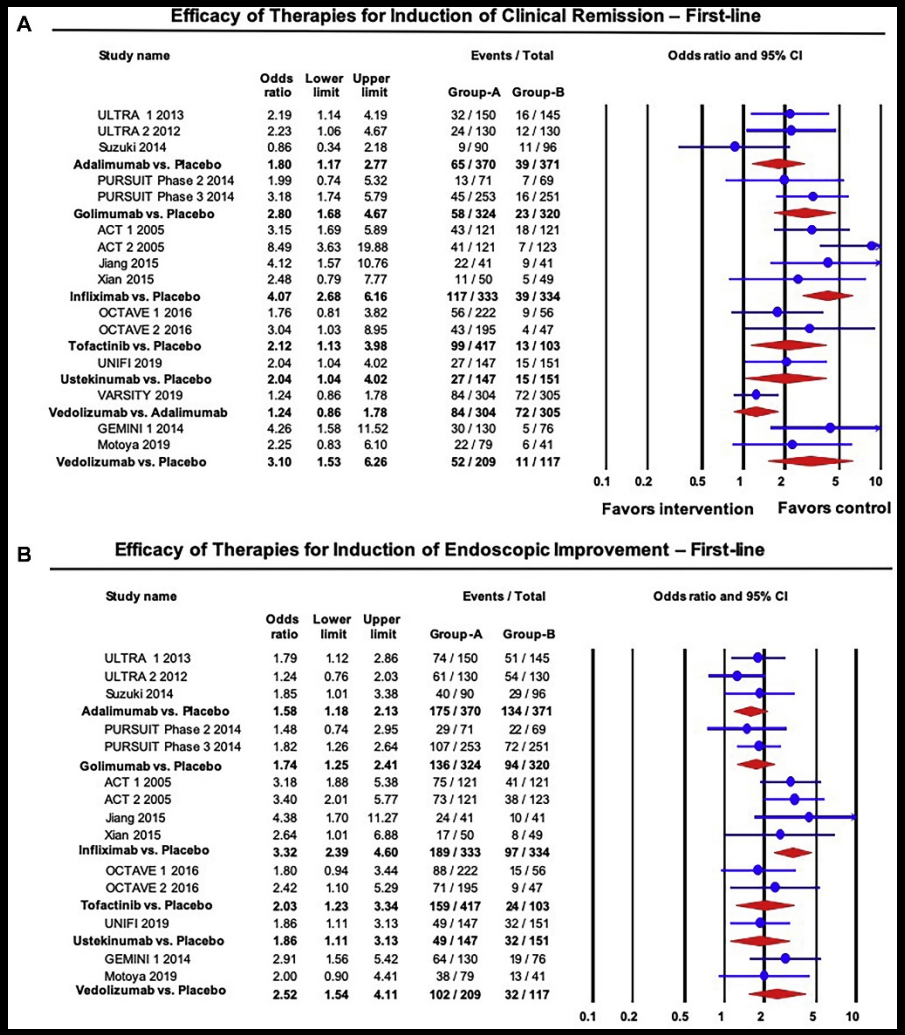
Where discoveries are delivered.SM

Outline

- Treatment sequencing
- New agents
  - IBD pipeline
  - Local delivery of drugs to the GI tract
  - Combination therapy
- Individual therapies (precision medicine)

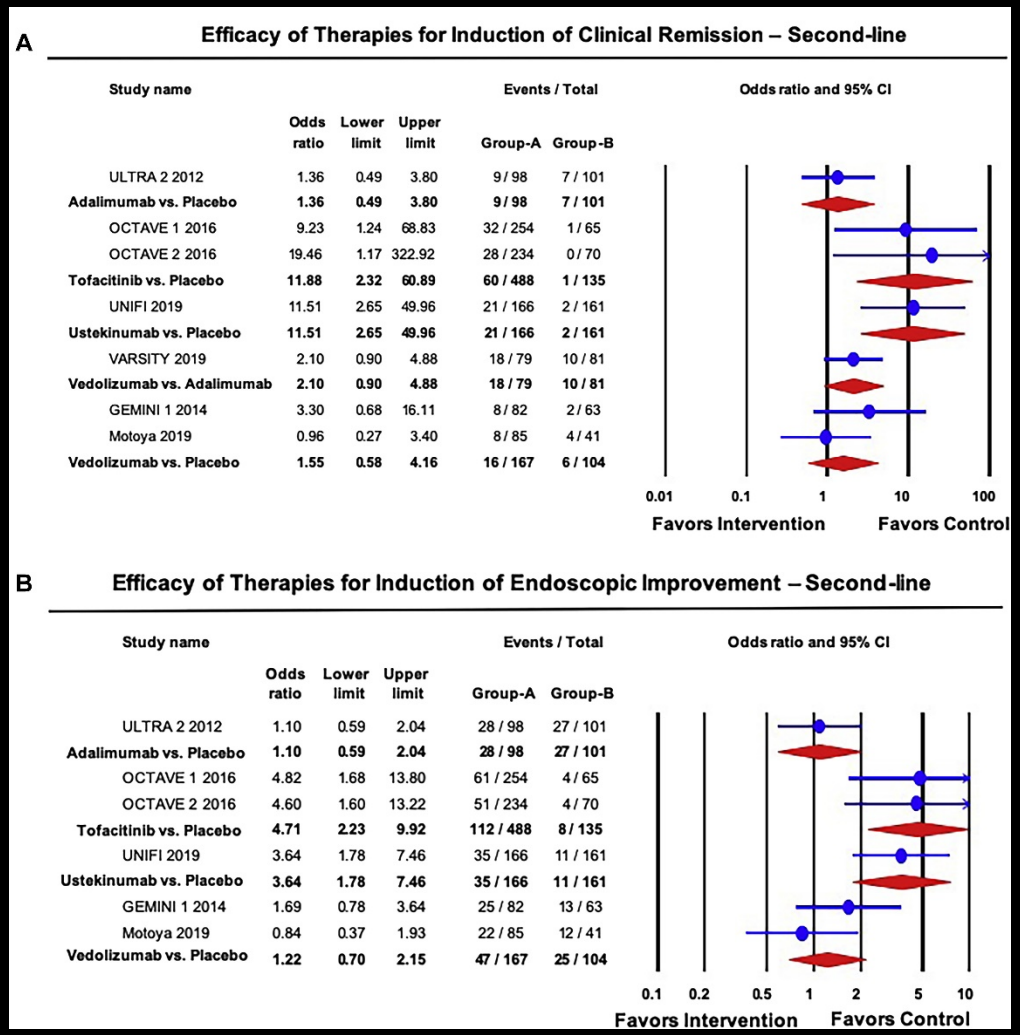
Treatment Sequencing

First- and Second-Line Pharmacotherapies for Patients With Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis



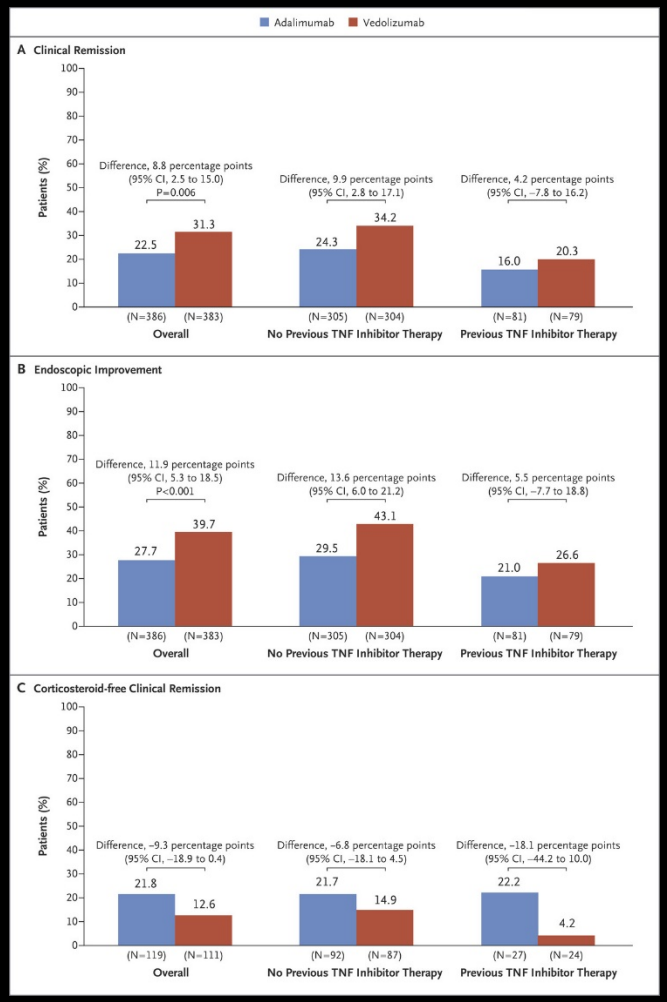
Singh S, Sandborn WJ. Clinical Gastroenterology and Hepatology 2020 182179-2191.

First- and Second-Line Pharmacotherapies for Patients With Moderate to Severely Active Ulcerative Colitis: An Updated Network Meta-Analysis



Singh S, Sandborn WJ. Clinical Gastroenterology and Hepatology 2020 182179-2191.

Vedolizumab Versus Adalimumab for Active Ulcerative Colitis



BE Sands et al. N Engl J Med 2019;381:1215-1226.

The NEW ENGLAND JOURNAL of MEDICINE

Systematic review with network meta-analysis: first-line induction pharmacotherapy for moderate-severe Crohn's disease

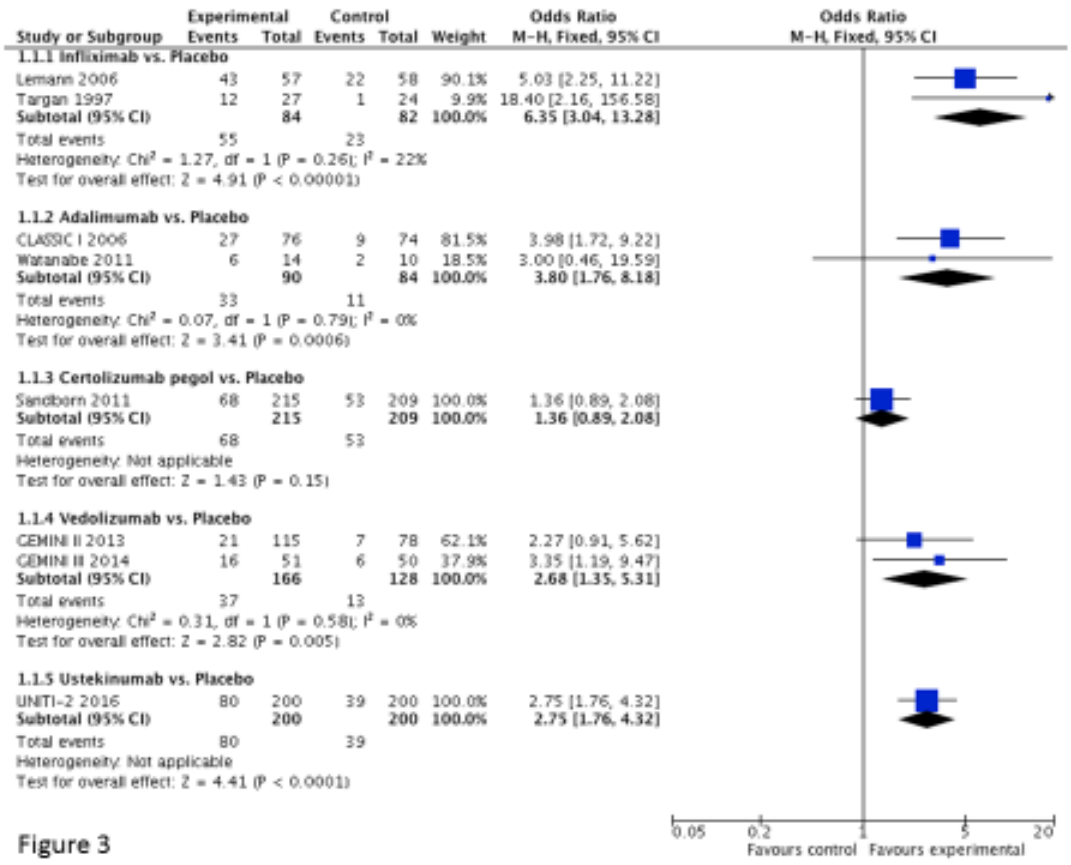


Figure 3

Singh S, Sandborn WJ. Alimentary Pharmacology & Therapeutics 2018.

Systematic review with network meta-analysis: second-line induction pharmacotherapy for moderate-severe Crohn's disease

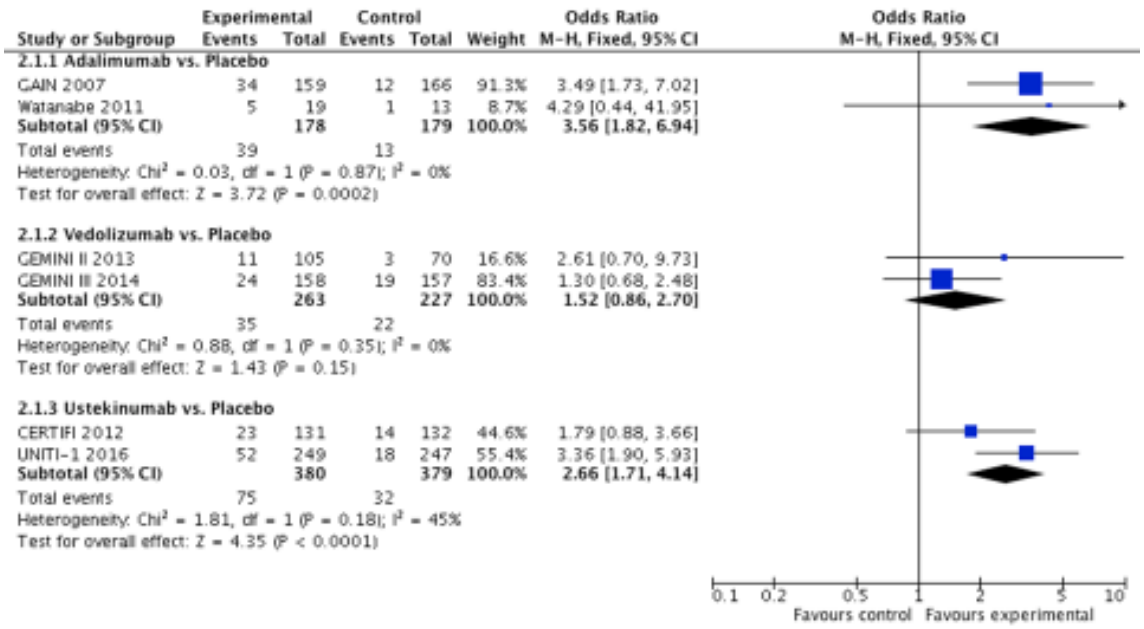


Figure 4

Singh S, Sandborn WJ. Alimentary Pharmacology & Therapeutics 2018.

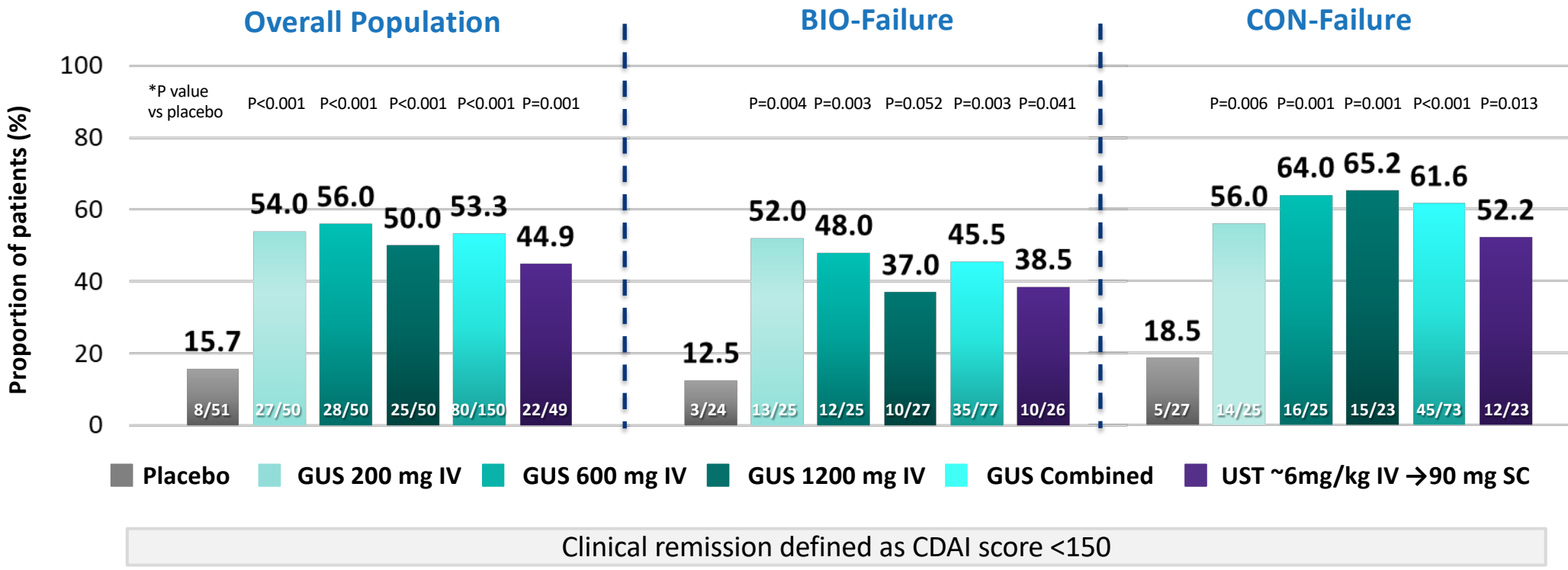
Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year (SEAVUE)

ClinicalTrials.gov Identifier: NCT03464136

Recruitment Status : Active, not recruiting
First Posted : March 13, 2018
Last Update Posted : September 30, 2020

Guselkumab induction therapy in patients with moderate-to-severe Crohn's disease

Clinical Remission



Clinical remission defined as CDAI score <150

Sandborn W. UEGW 2020 Abstract.

New Agents

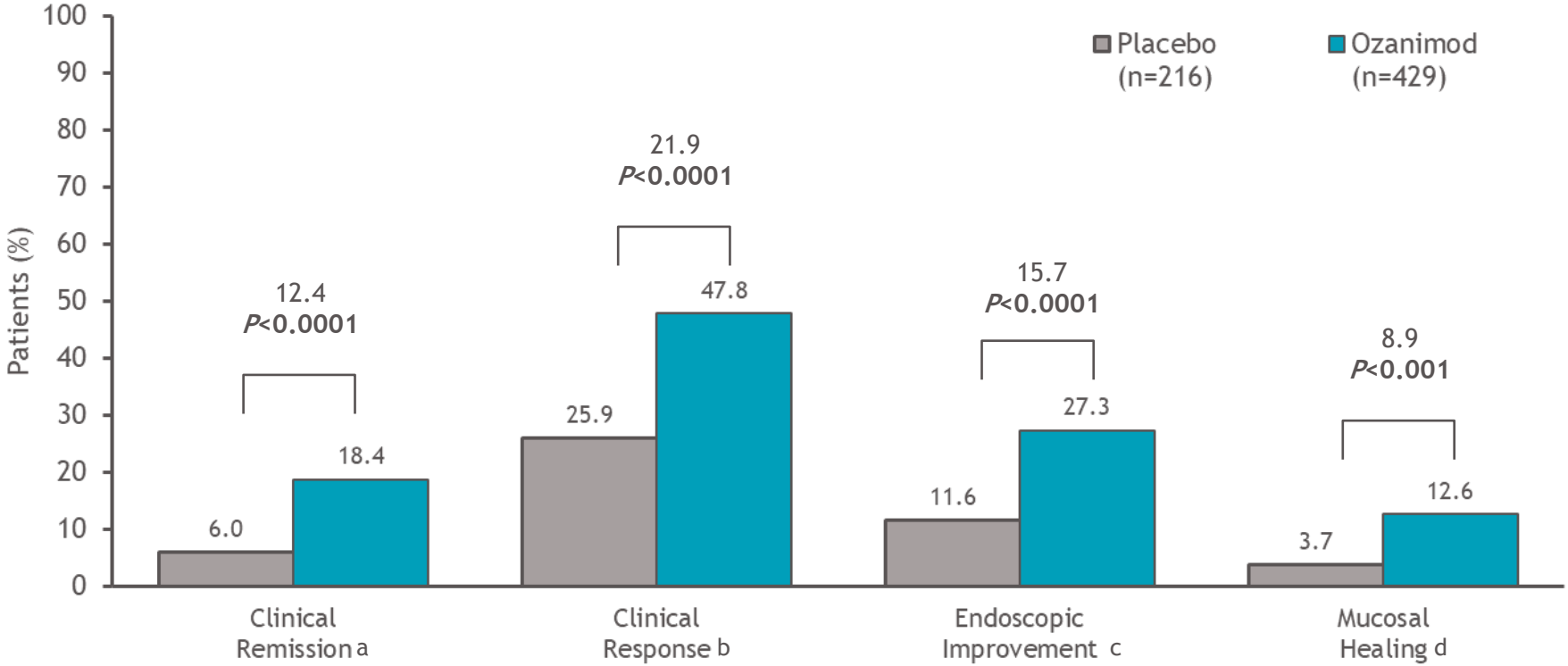
The IBD Pipeline

- Anti-integrin therapy
  - Etrolizumab
  - PTG-200
  - ZP10000
  - MORF-057
- Janus kinase (JAK) inhibitor therapy
  - Filgotinib – JAK1
  - Upadacitinib – JAK1
  - Izencitinib (TD-1473) – JAK 1,2,3
  - Abrocitinib (PF-06700841) – JAK1
  - Ritlecitinib (PF 06651600) – JAK3
  - Brepocitinib (PF-06700841) – Tyk2
  - Deucravacitinib (BMS-986165) – Tyk2
- S1P1 modulator therapy
  - Ozanimod
  - Etrasimod
  - Amiselmod
- Lymphocyte Activation Gene-3
  - GSK'781
- Anti-interleukin 12 (p19) therapy
  - Geselkumab
  - Risankizumab
  - Mirikizumab
  - Brazikumab
- Microbiome
  - SER-287
- HIF-a Stabilizer
  - GB004
- Anti-TL1A therapy
  - PF-06480605
  - PRA023
- Cyclosporine
  - ST-0529
- Cap binding complex/micro RNA 124
  - ABX464
- TLR-9 antisense
  - Cobitolimod
- LANCL2
  - BT11

New Agents in Phase 3

- JAK inhibitors
  - Filgotinib
  - Upadacitinib
- Anti-p19 (interleukin 23) antibodies
  - Risankizumab
  - Mirikizumab
  - Guselkumab
  - Brazikumab
- S1P modulators
  - Ozanimod
  - Etrasimod

Ozanimod induction therapy in patients with moderate-to-severe ulcerative colitis: results at Week 10

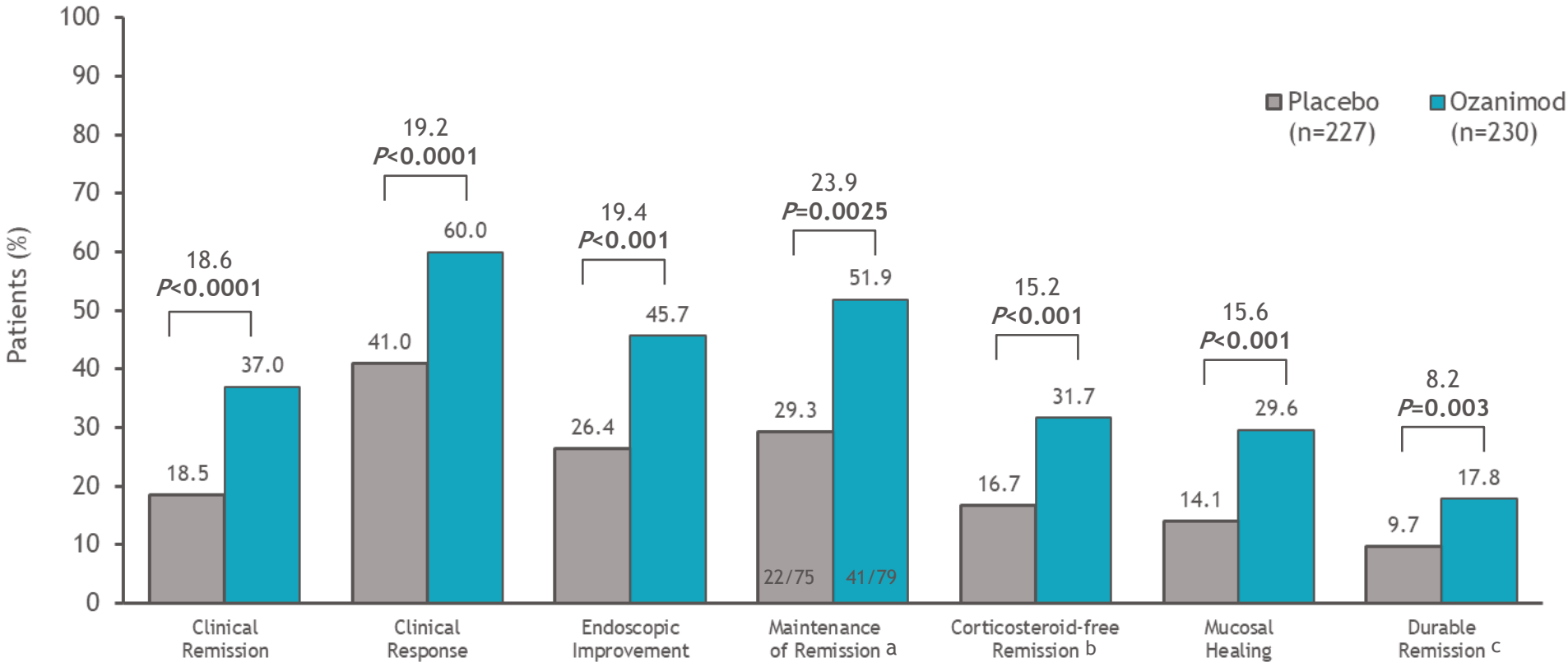


[a]3-component Mayo score results: rectal bleeding score (RBS) = 0, stool frequency score ≤1 and ≥1-point reduction from baseline, and mucosal endoscopy score (MES) ≤1 without friability; [b]Reduction in 3-component Mayo score of ≥2 points and ≥35%, and reduction in RBS of ≥1 point or absolute RBS of ≤1 point; [c]MES ≤1 without friability; [d]Endoscopic improvement plus histological remission (Geboes<2.0; no 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.

Data based on all randomized patients who received ≥1 dose of study treatment (intent-to-treat population). Missing data handled using non-responder imputation. *P*-values refer to odds ratios (not shown) based on 2-sided Cochran-Mantel-Haenszel test.

Sandborn W. UEGW 2020 Abstract.

Ozanimod maintenance therapy in patients with moderate-to-severe ulcerative colitis who responded to ozanimod induction therapy: results at Week 52



[a]Clinical remission at 52 weeks in the subset of patients who were in remission at Week 10; [b]Clinical remission at 52 weeks without corticosteroids for ≥12 weeks; [c]Remission at Weeks 10 and 52 in all patients who entered the maintenance phase.

Data based on all randomized patients who received ≥1 dose of study treatment (intent-to-treat population). Missing data handled using non-responder imputation. *P*-values based on odds ratios (not shown) using a 2-sided Cochran-Mantel-Haenszel test.

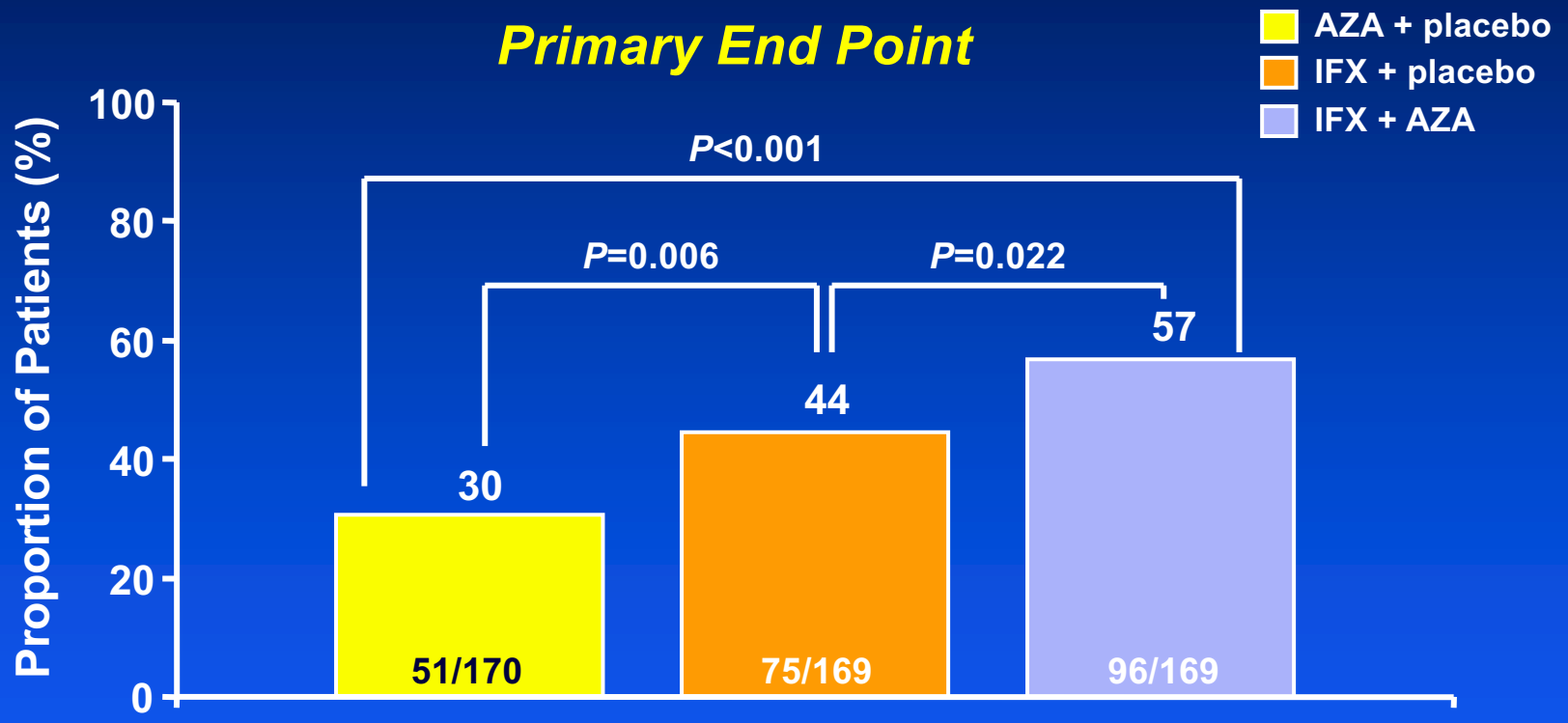
Sandborn W. UEGW 2020 Abstract.

Local Delivery of Drugs to the GI Tract

- Small molecules
  - Mesalamine
  - Budesonide
  - Izencitinib (TD-1473)
  - MORF-057
  - GB004
  - ST-0529
- Antisense
  - Cobitolimod
- Antibodies
  - V565
  - TP10
- Peptides
  - PTG-200
  - PN943
  - ZP10000

Combination Therapy

SONIC: Clinical Remission Without Corticosteroids at Week 26 in Crohn's Disease



IFX, infliximab
AZA, azathioprine

Colombel JF, Sandborn WJ, et al. *N Engl J Med*. 2010 Apr 15;362(15):1383-1395.

AP&T Alimentary Pharmacology & Therapeutics WILEY

Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease

Edward Yang[1] | Nicola Panaccione[2] | Natalie Whitmire[1] | Parambir S. Dulai[1] | Niels Vande Casteele[1] | Siddharth Singh[1] | Brigid S. Boland[1] | Angelina Collins[1] | William J. Sandborn[1] | Remo Panaccione[3] | Robert Battat[1,4]

	Baseline	Post treatment
PRO-2 score (median)	24.1	13.4
Clinical remission	0/22 (0%)	9/22 (41%)
Mild	2/22 (9%)	2/22 (9%)
Moderate	20/22 (91%)	9/22 (41%)
Severe	0/22 (0%)	2/22 (9%)
Clinical response	n/a	11/22 (50%)
Endoscopic		
Remission	0/23 (0%)	6/23 (26%)
Improvement	n/a	10/23 (43%)

Combination Biologics: Prospective Trials

- Vedolizumab, adalimumab, methotrexate
- Geselkumab, golimumab

Possible Combinations

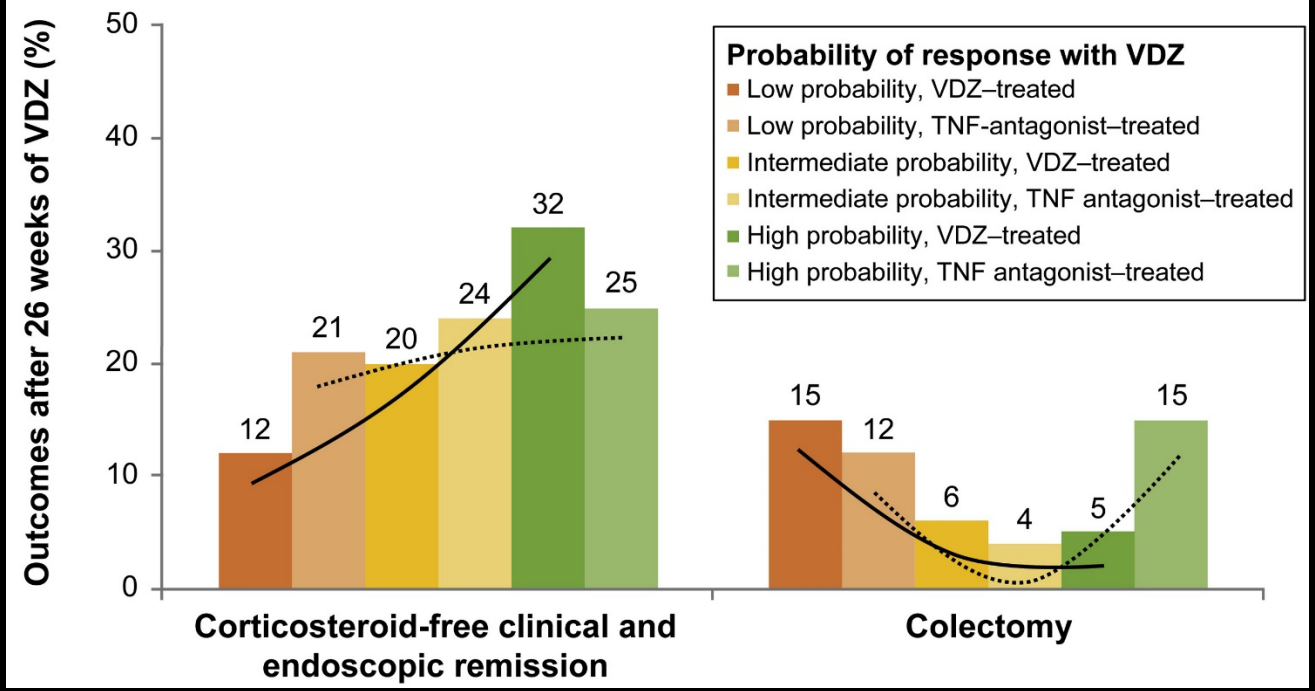
	Anti-TNF	Selective anti-integrin	Anti-IL 12/23	Anti IL 23	Systemic JAK inhibitor	Local JAK inhibitor	S1P1 modulator
Anti-TNF	NA	Yes	? No	?	No	Yes	? No
Selective anti-integrin	Yes	NA	Yes	Yes	Yes	Yes	Yes
Anti IL 12/23	? No	Yes	NA	NA	? No	Yes	?
Anti IL 23	?	Yes	NA	NA	No	Yes	?
Systemic JAK inhibitor	No	Yes	No	No	NA	Yes	? Yes
Local JAK inhibitor	Yes	Yes	Yes	Yes	Yes	NA	Yes
S1P1 modulator	? No	Yes	Yes	Yes	No	Yes	NA

Individual Therapies (Precision Medicine)

- Clinical decision support tools
- Therapeutic drug monitoring
- Companion diagnostic tests

Prognostic Clinical Decision Support Tool (CDST) with stratified treatment outcomes in the VICTORY consortium in patients with ulcerative colitis

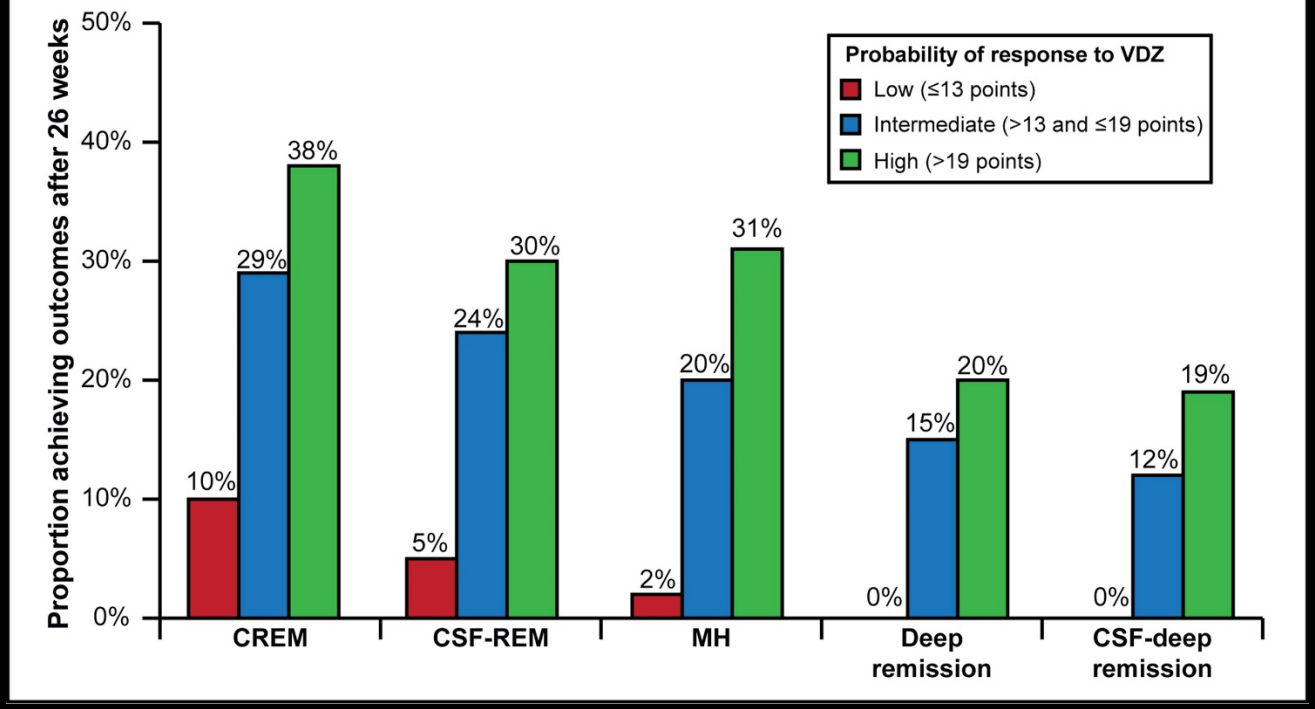
Disease duration ≥2 years	No prior TNF antagonist	Baseline endoscopy moderate activity	Baseline albumin concentration
+3 points	+3 points	+2 points	+0.65 points per unit (g/L)



Dulai PS, Sandborn WJ. Clinical Gastroenterology and Hepatology 2020.

Prognostic Clinical Decision Support Tool (CDST) with stratified treatment outcomes in the VICTORY consortium in patients with Crohn's disease

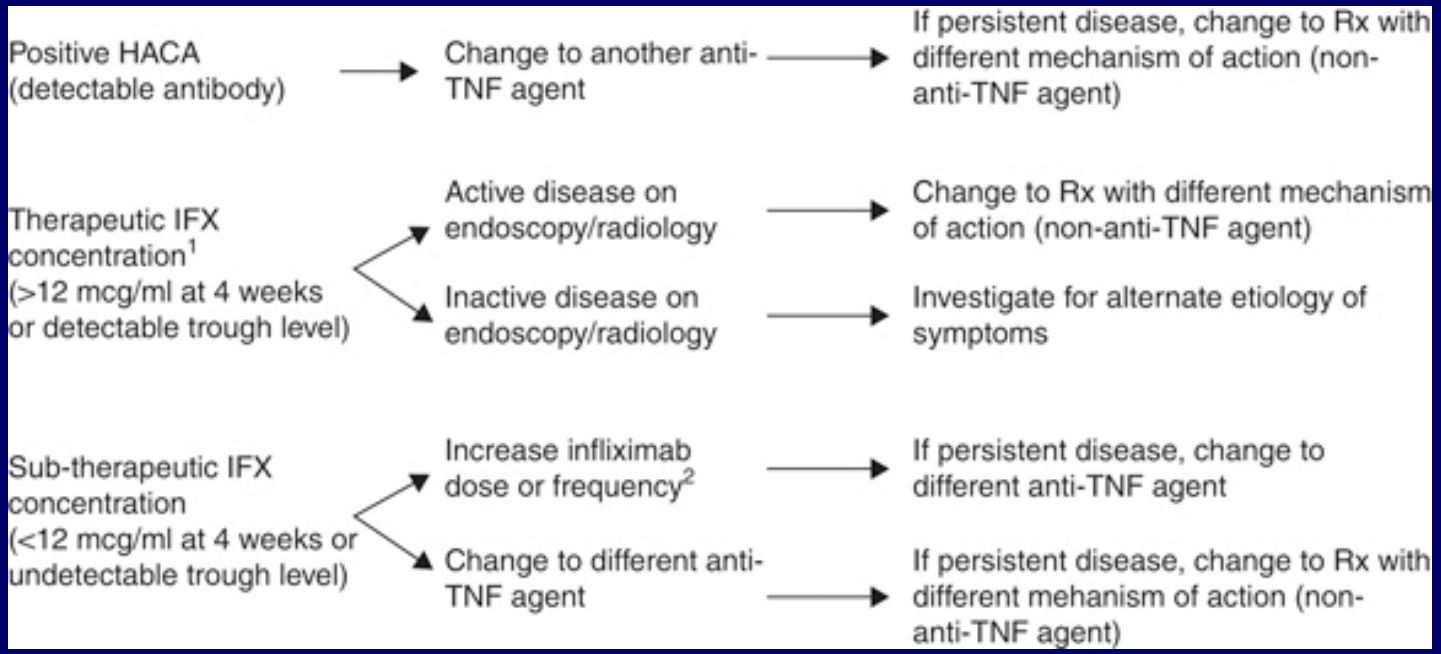
No prior bowel surgery	No prior TNFα-antagonist	No prior fistulizing disease	Baseline albumin	Baseline CRP
+ 2 points	+ 3 points	+ 2 points	+ 0.4 points per unit (g/L)	– 0.5 points if 3.0 –10.0 mg/L – 3.0 points if >10 mg/L



Gastroenterology 2018 155, 687-695.e10DOI: (10.1053/j.gastro.2018.05.039)

Dulai P, Sandborn WJ. Gastroenterology 2018

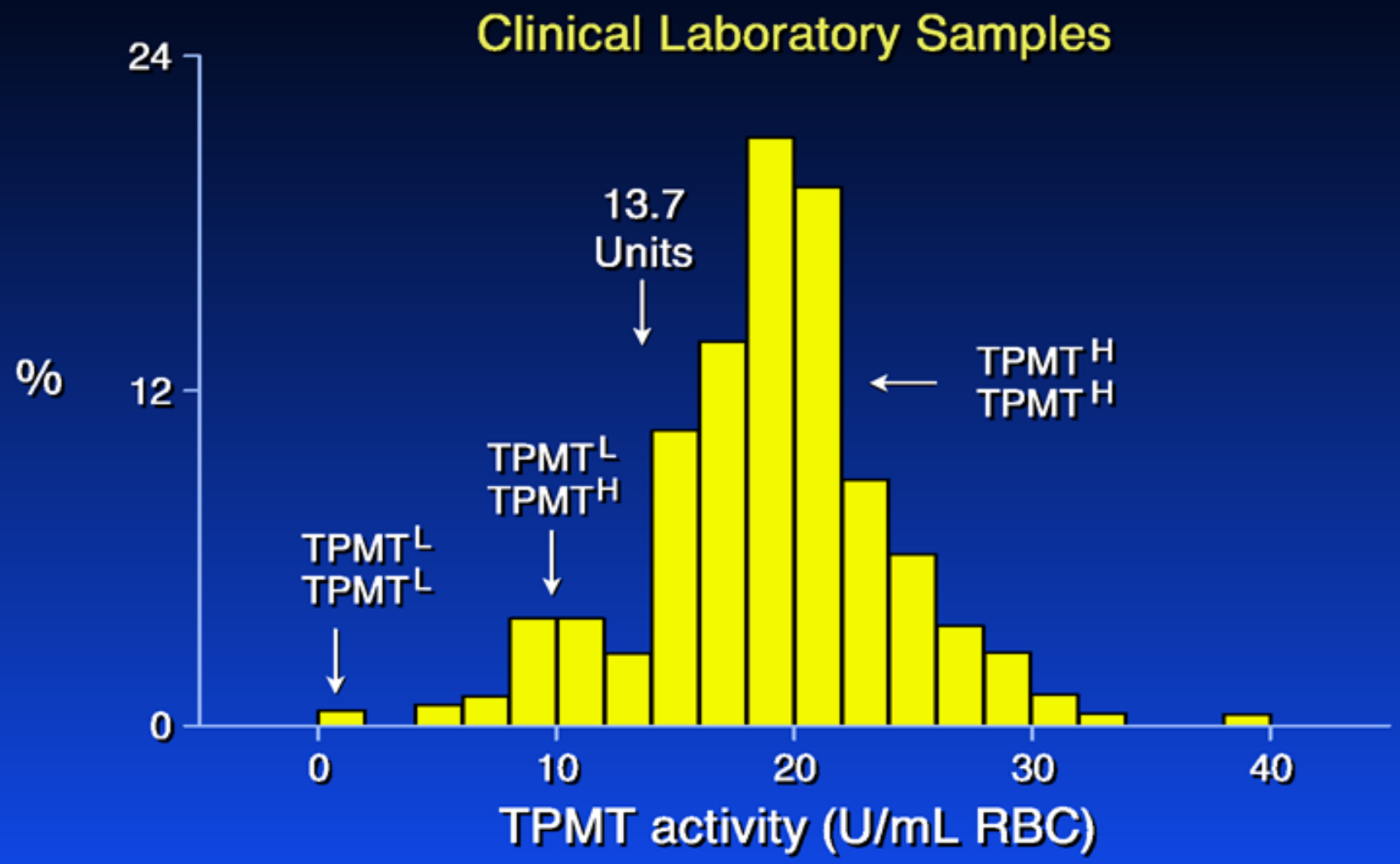
Treatment algorithm in patients with clinical symptoms (infliximab and HACA concentrations)



[1]Patients should have endoscopic or radiologic imaging
[2]This strategy may be preferable
HACA, human anti-chimeric antibody; TNF, tumor necrosis factor

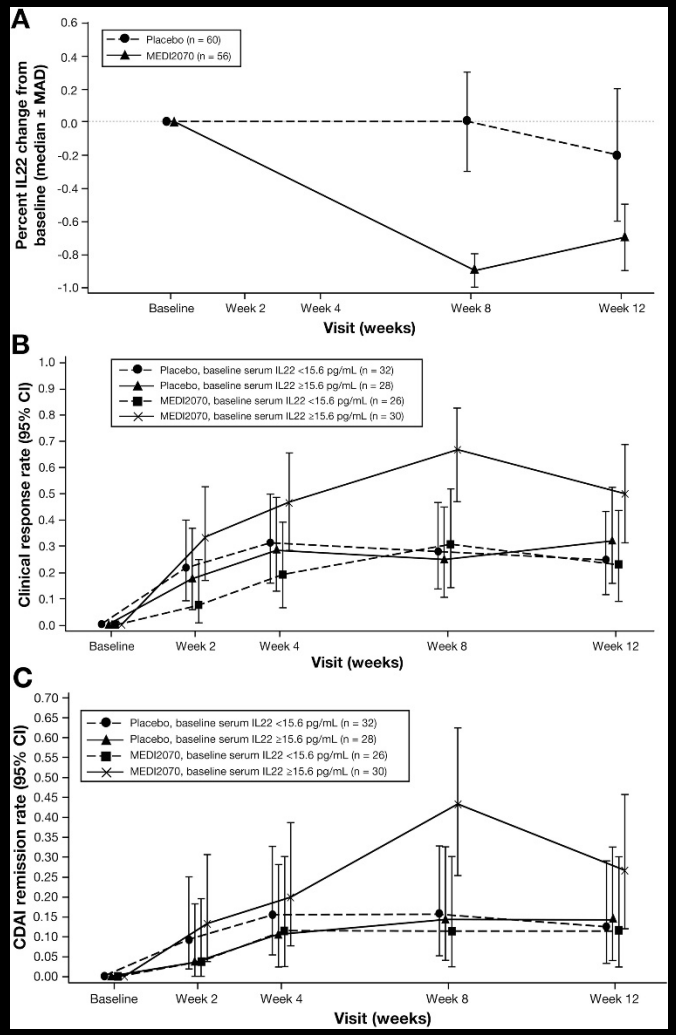
Afif W, Sandborn WJ. Am J Gastroenterol 2010

RBC Thiopurine Methyl Transferase (TPMT) Enzyme Activity in 283 Clinical Laboratory Samples



Otterness: Clin Pharmacol Ther, 1997

Percent change from baseline in serum IL22 levels in MEDI2070 and placebo groups (A) and percentage of patients with clinical response (B) and with clinical remission (C) over time, by baseline serum IL22 levels.



Sands BE. *Gastroenterology* 2017 153, 77-86.e6DOI: (10.1053/j.gastro.2017.03.049)

What Does the Future Hold

- Combination therapy AND
- Local delivery of drugs to the GI tract AND
- Precision medicine

Conclusions

- Positioning of biologics can be informed by network meta-analyses and head to head trials
- There is a large pipeline of new agents for IBD. Late stage products are focused on JAK inhibitors, anti-p19 (interleukin 23) antibodies, and S1P modulators
- Multiple agents targeting gut delivery are in early stage development
- Precision medicine will play an increasing role in the care of IBD patients