Future combinations in inflammatory bowel diseases

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Combination therapy in IBD: summary

- Rationale for combining therapies in IBD
- Efficacy of biologic combinations in RCT
- Real life effectiveness of biologic combinations
- Safety of biologic combinations: real life evidences
- Future perspectives

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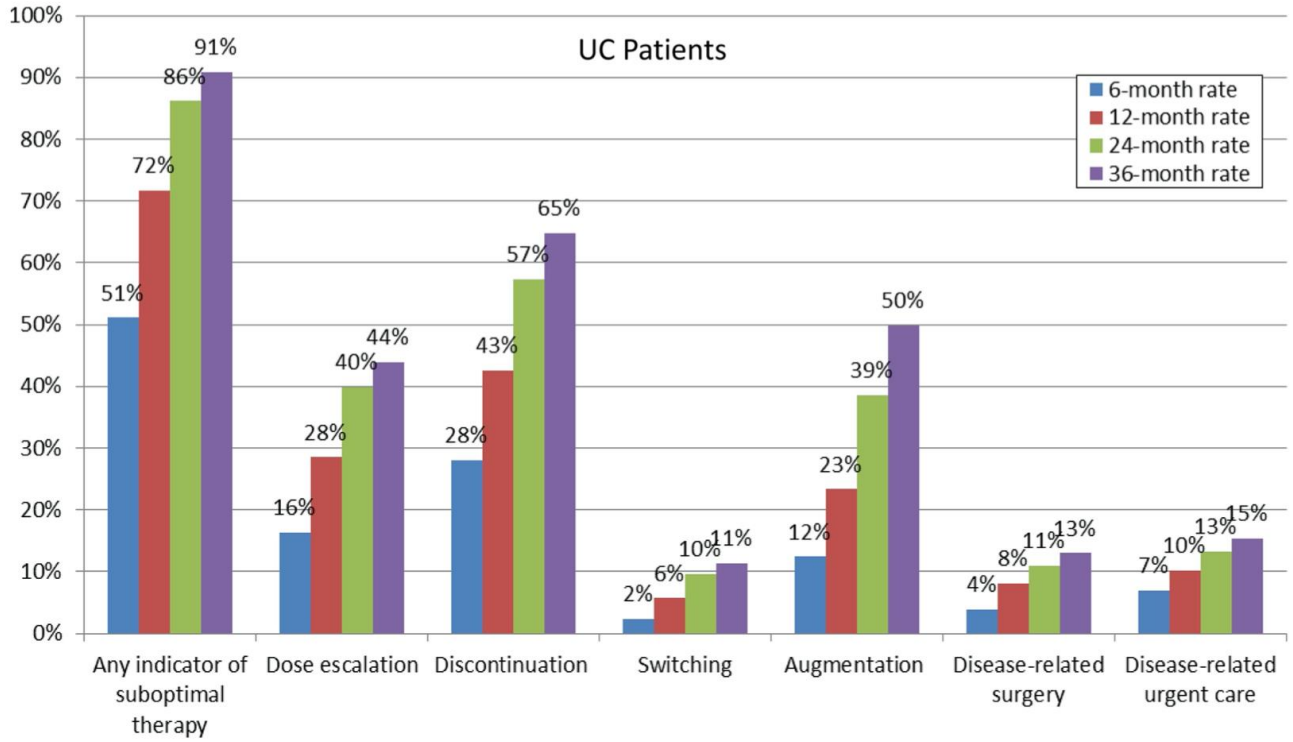
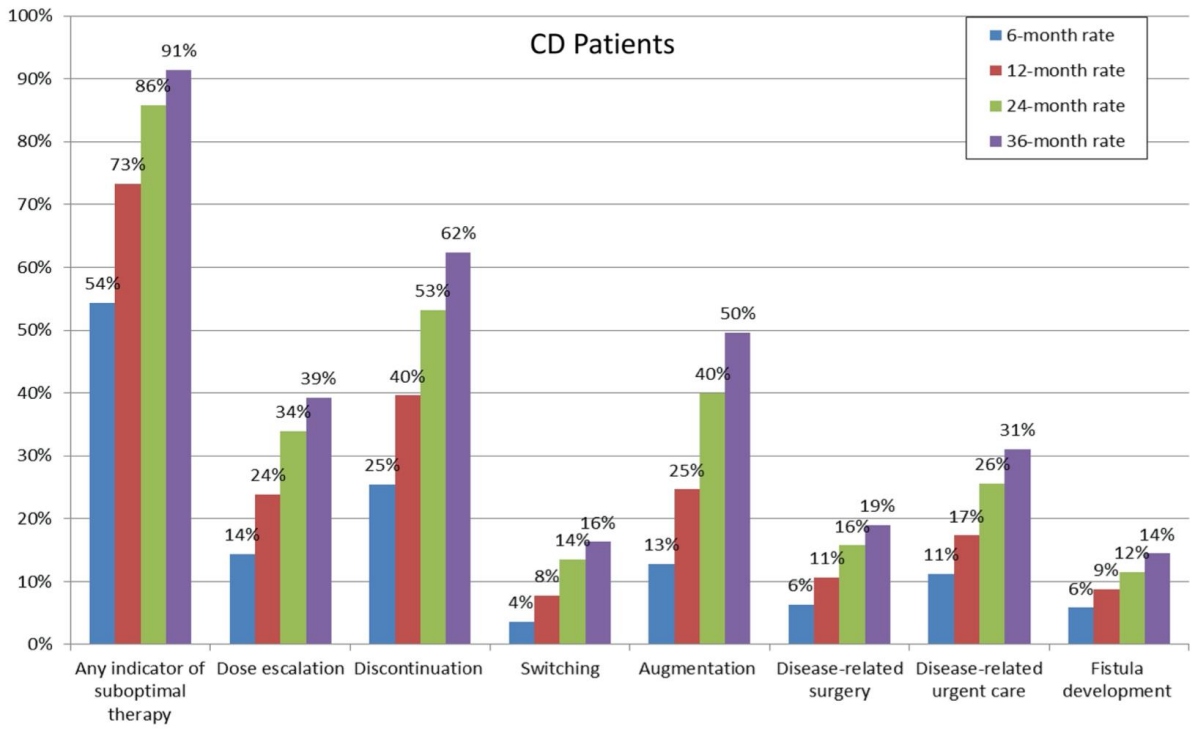
Combo therapy rationale: 1) therapeutic gap

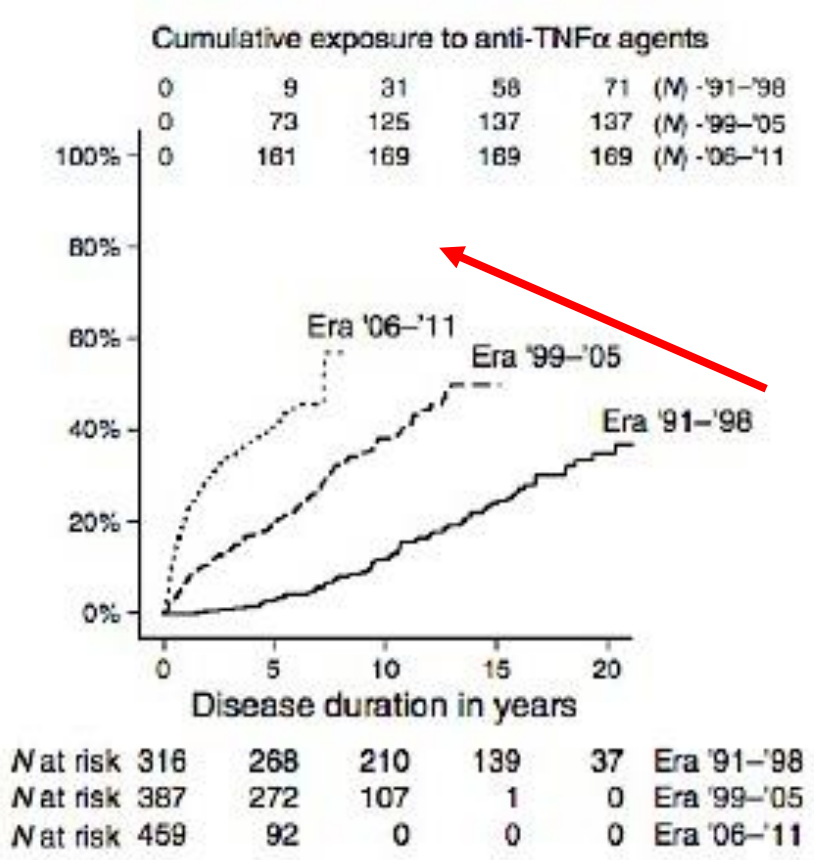
US database (2005–2013): 1,699 UC and 4,569 CD

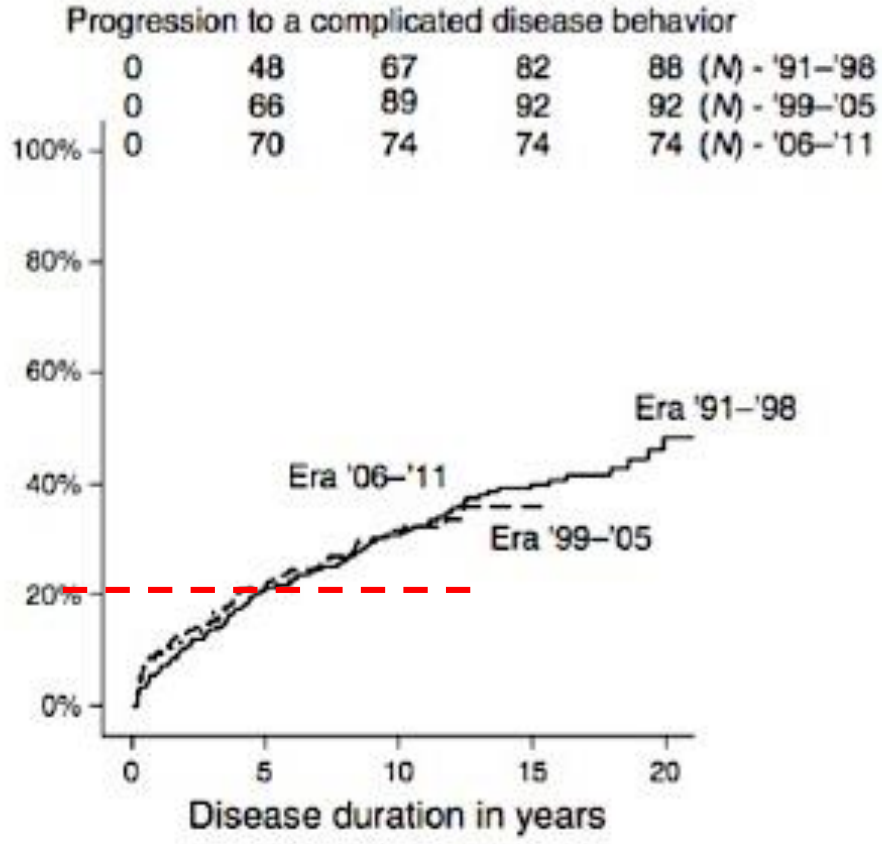




Patel et al. Plos One 2017

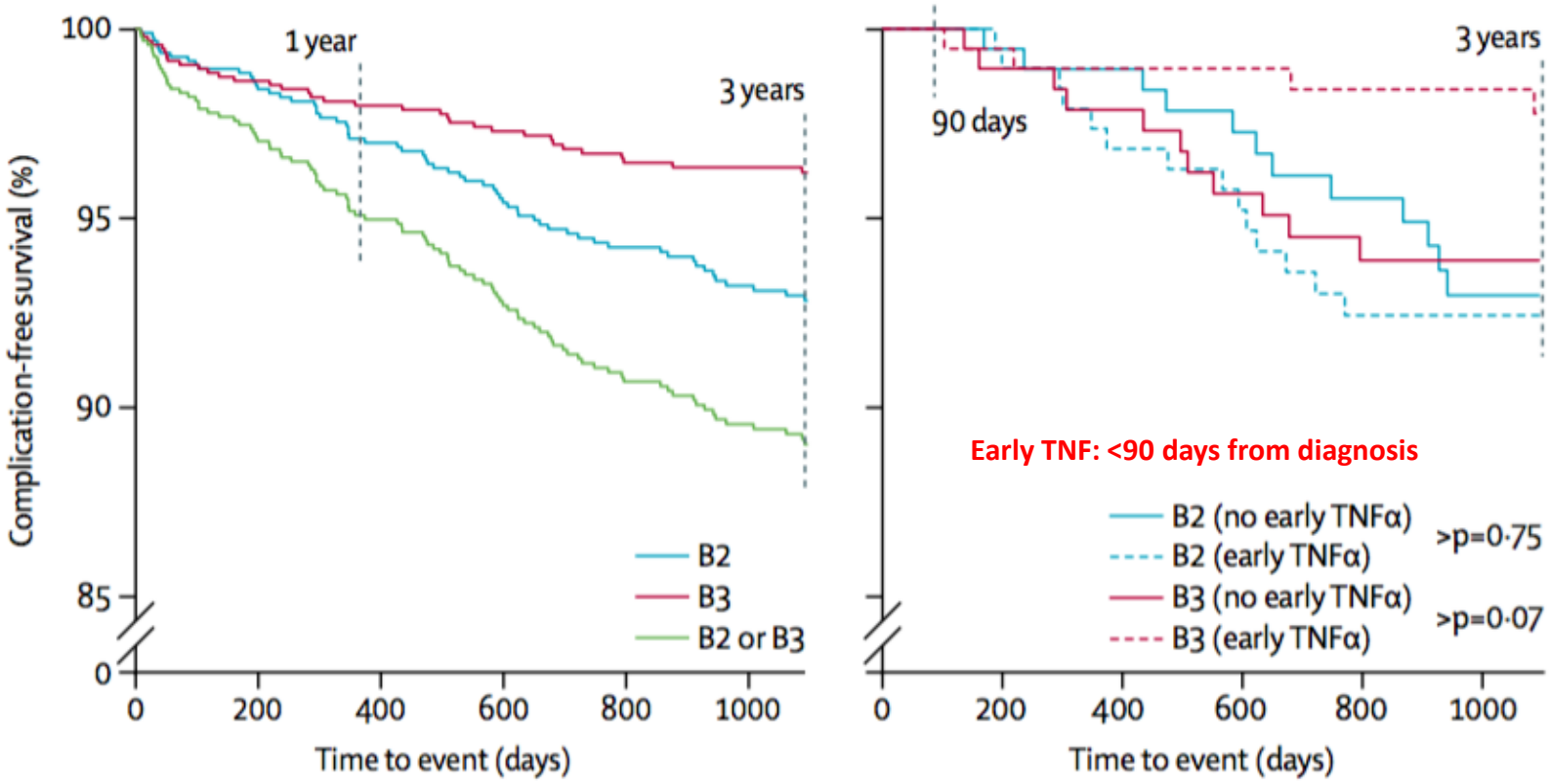
Therapeutic gap in inflammatory bowel diseases





Jeuring et al. Am J Gastroenterol 2017

Therapeutic gap in inflammatory bowel diseases



Kugathasan et al. Lancet 2017

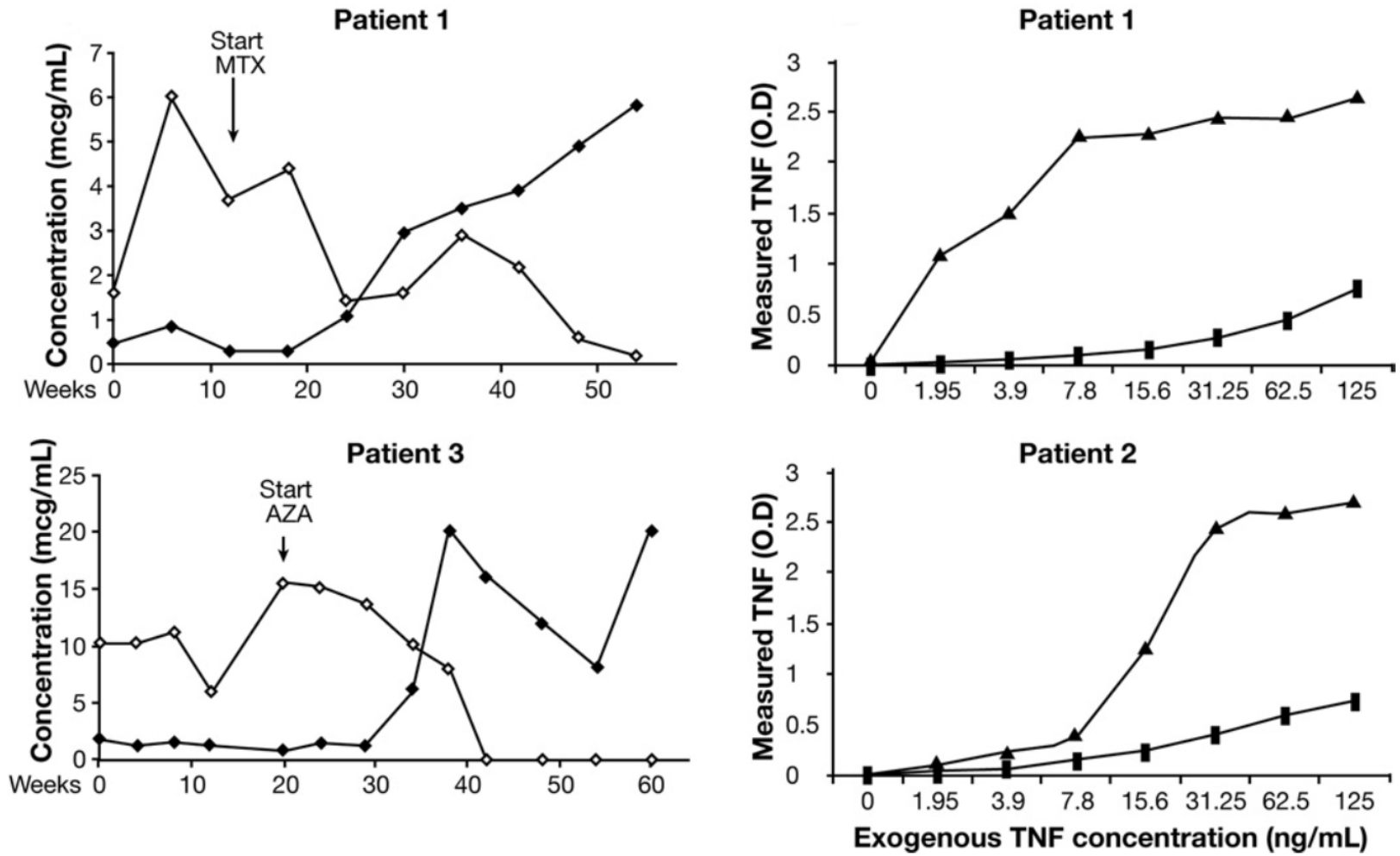
Why do antiTNF treatment failures occur?

Non-inflammatory mechanisms
• IBS
• Fibrostenotic strictures
• Cancer
• Dietary (e.g. lactose ingestion)
• Miscellaneous e.g. bile salt diarrhea, bacterial overgrowth, and amyloidosis

Inflammatory mechanisms	
Non-IBD-related inflammation	• Infection • Ischemic colitis • Vasculitis
Uncontrolled IBD-related inflammation (caused by inadequate anti-TNFα blockade)	• ADAs • Relentless TNF-mediated flare consuming all anti-TNFα antibodies • Non-immune drug clearance • Non-adherance
Uncontrolled IBD-related inflammation (adequate anti-TNFα in serum)	• Paradoxical exacerbation of inflammation by anti-TNFα agents • Shift of disease pathway away from TNF to other mediators

Courtesy of Shomron Ben-Horin

Immunosuppressants in patients with secondary LOR



Ben-Horin et al. Clin Gastroenterol Hepatol 2013

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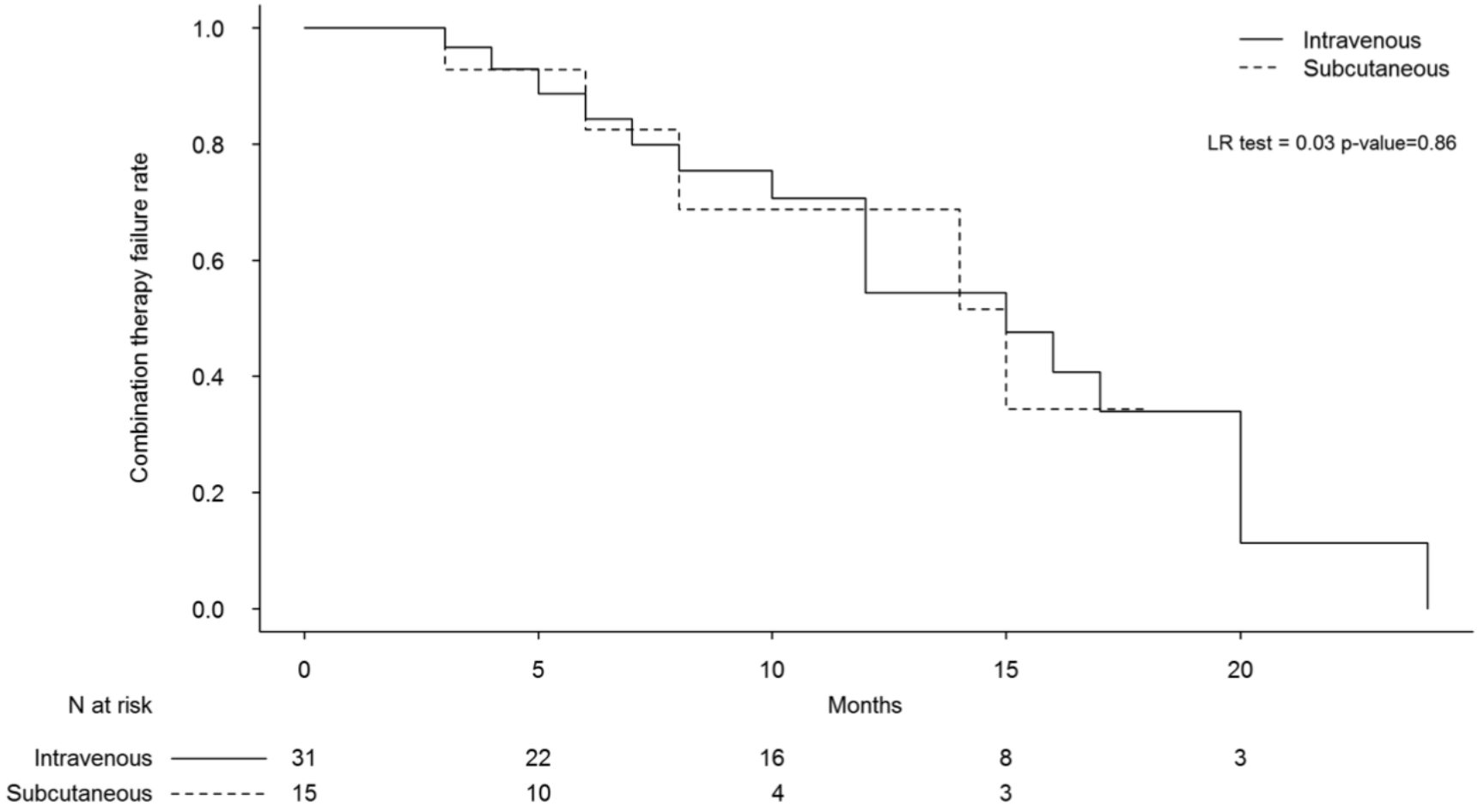
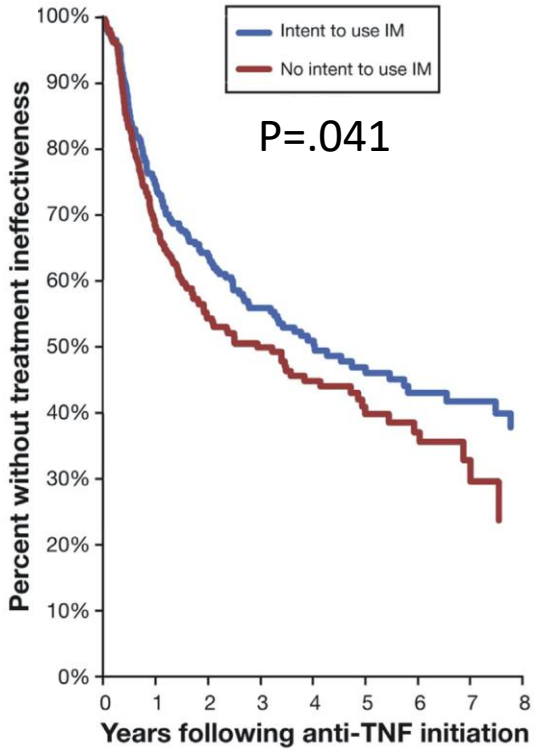


Macaluso et al. Inflamm Bowel Dis 2018

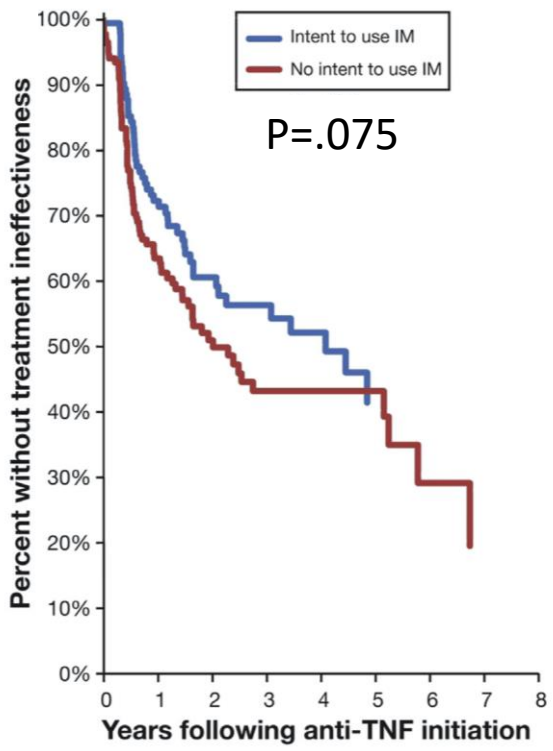
AntiTNF/IM combo therapy in IBD: latest evidences

Manitoba Inflammatory Bowel Disease (IBD) Epidemiology database (n=1155)

Crohn's disease



Ulcerative colitis

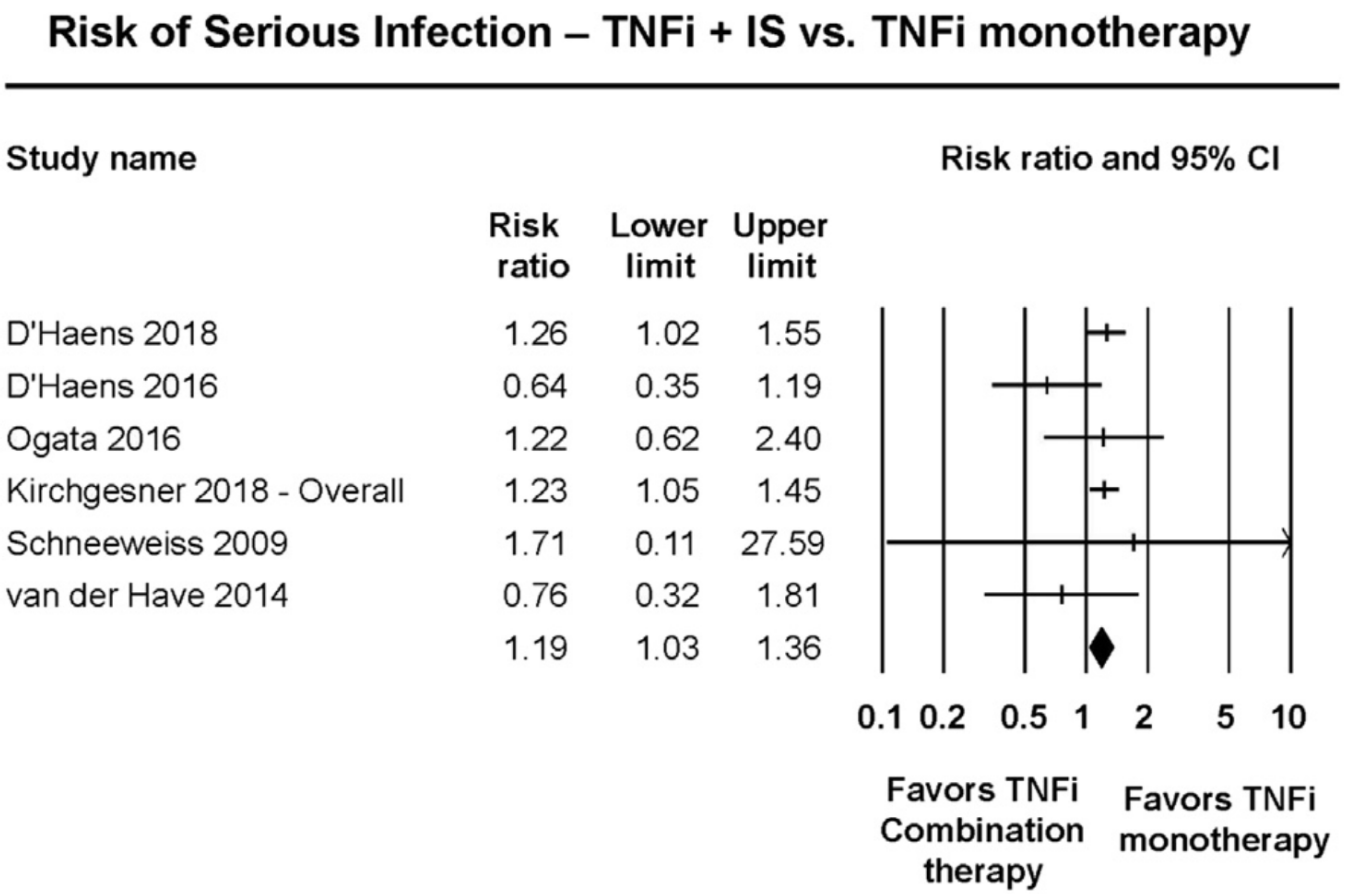


In CD, combination therapy associated with increased time to

- CD-related hospitalization (aHR 0.62)
- Switching to alternate anti-TNF (aHR 0.63)

Targownik et al. Clin Gastroenterol Hepatol 2019

AntiTNF/IM combo therapy in IBD: latest evidences



- Metaanalysis of observational studies
- 188,000 IBD patients

Singh et al. Clin Gastroenterol Hepatol 2019 (epub)

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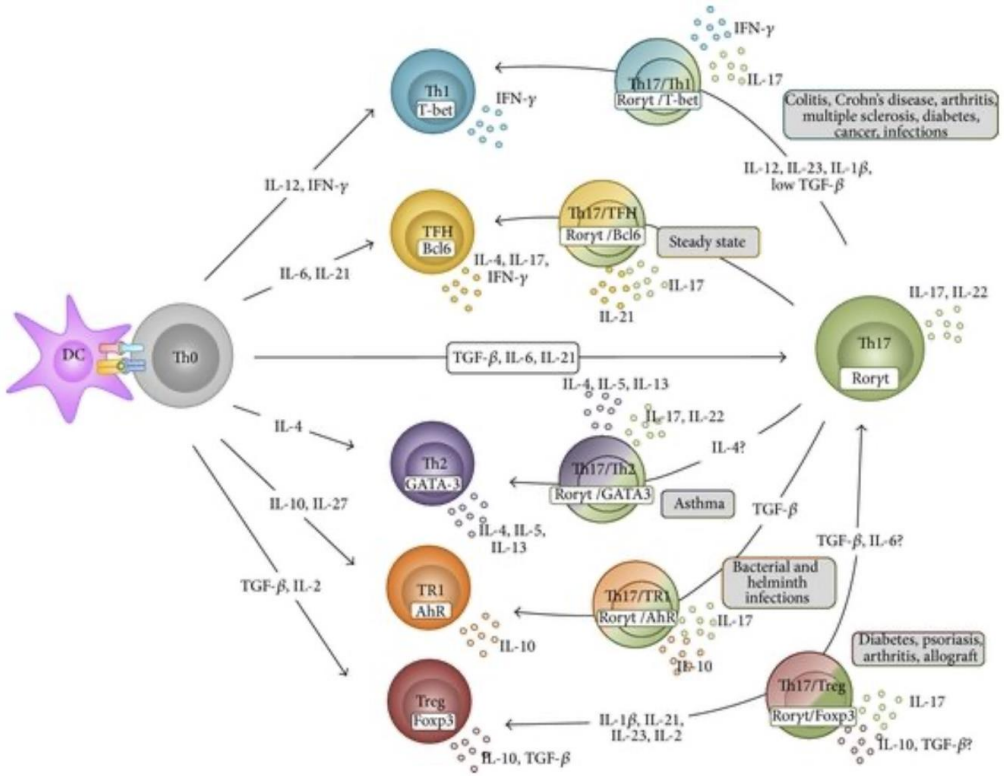
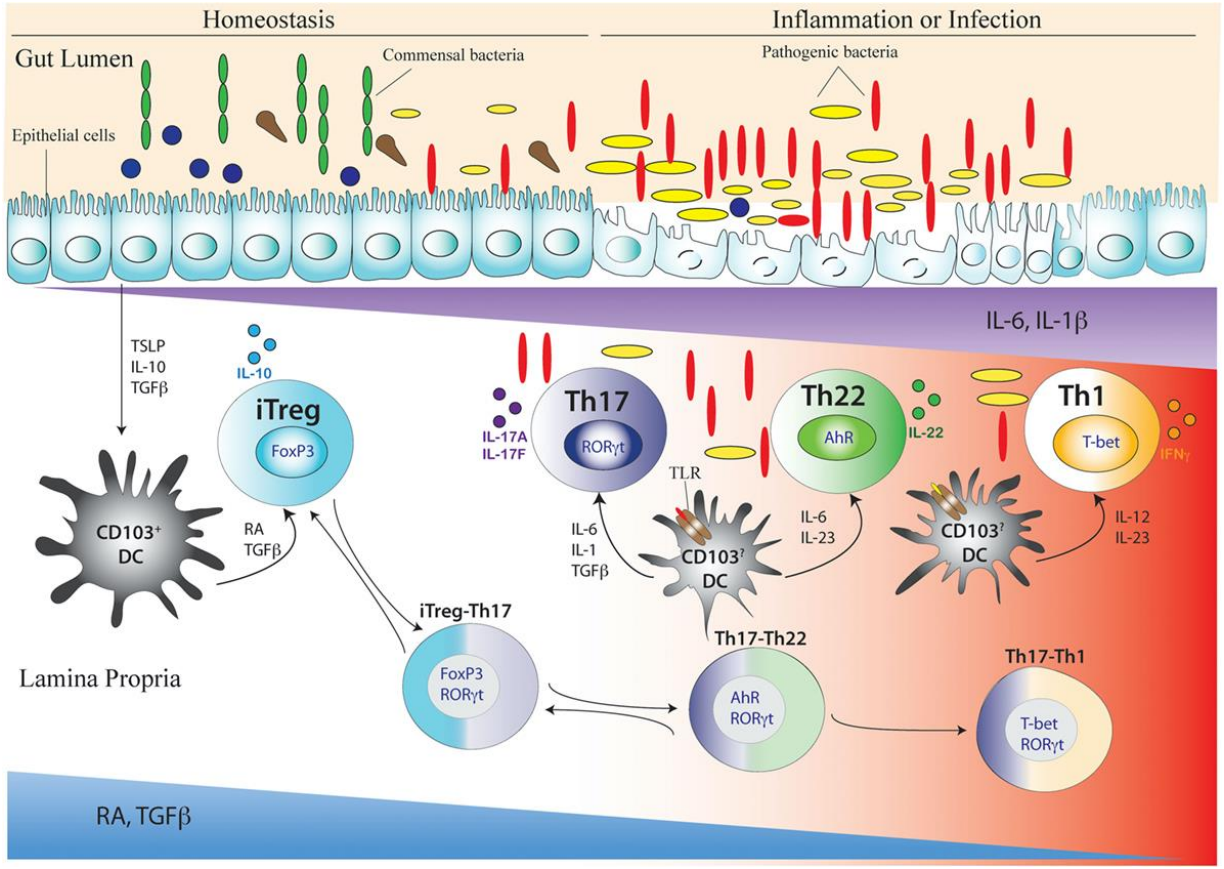
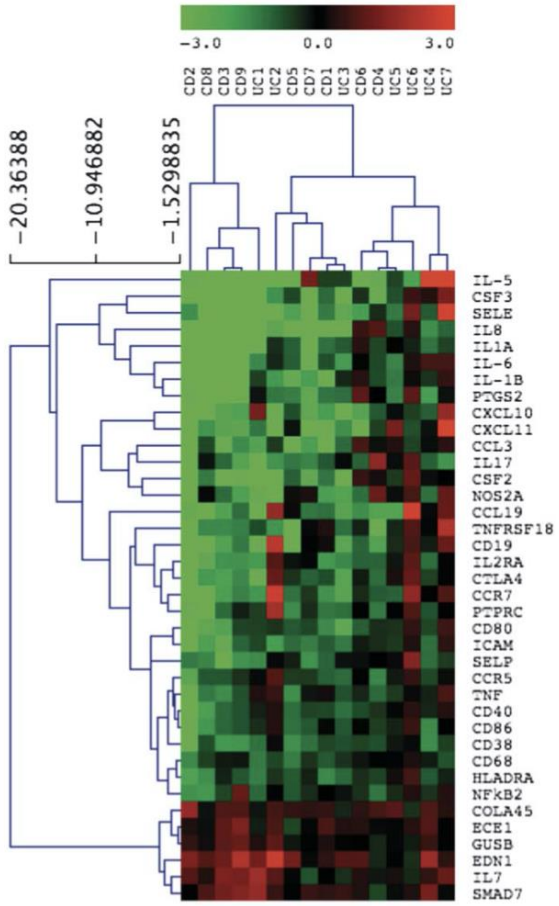
Plasticity of T cell responses in the gut

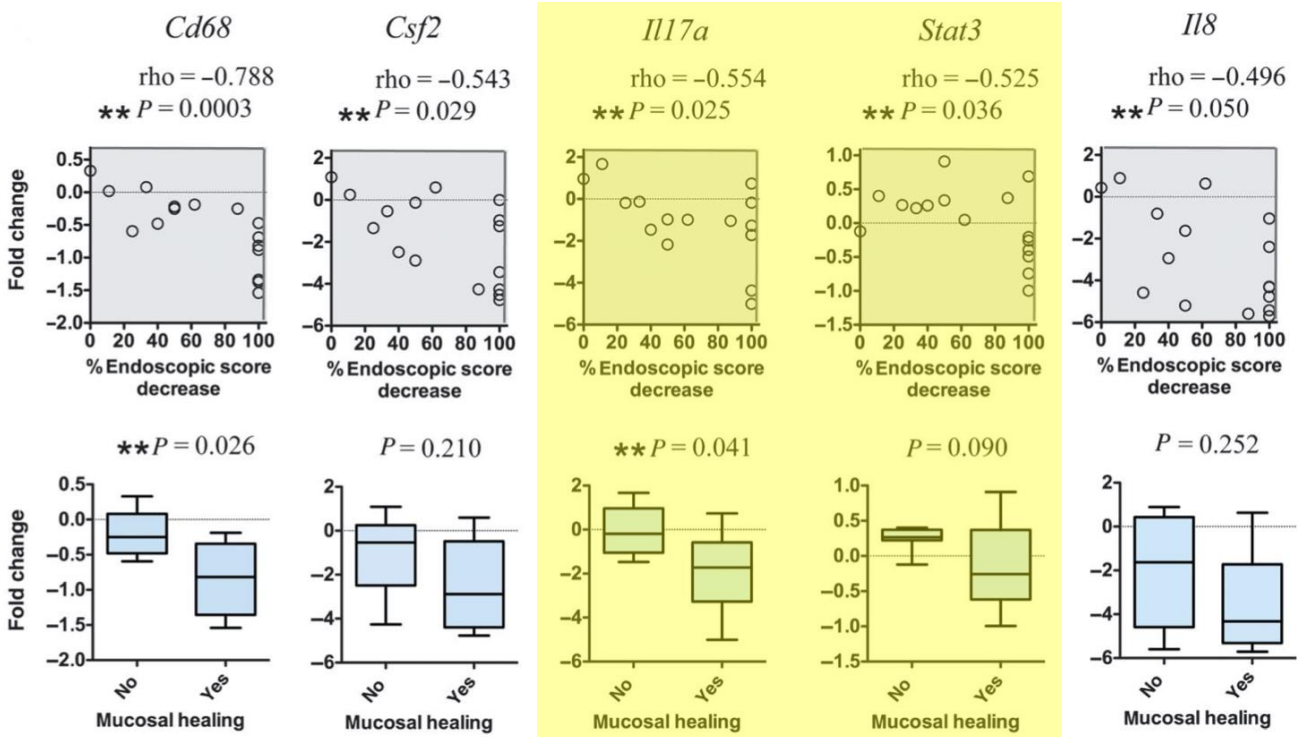




Gueryand et al. 2015
Bhaumik et al. Front Immunol 2017
Nizzoli et al. Journal Crohn's Colitis 2018

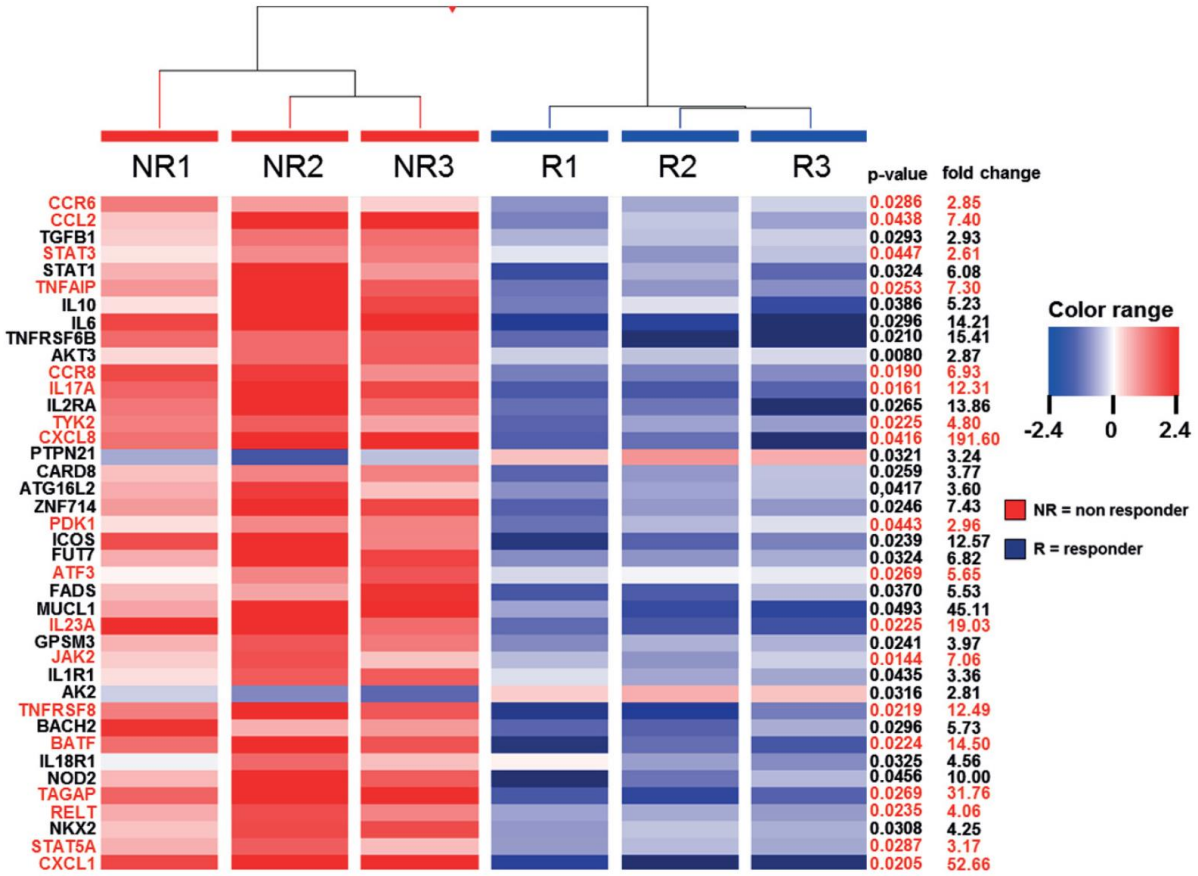
Immune shift in antiTNF NR towards IL23-Th17 axis

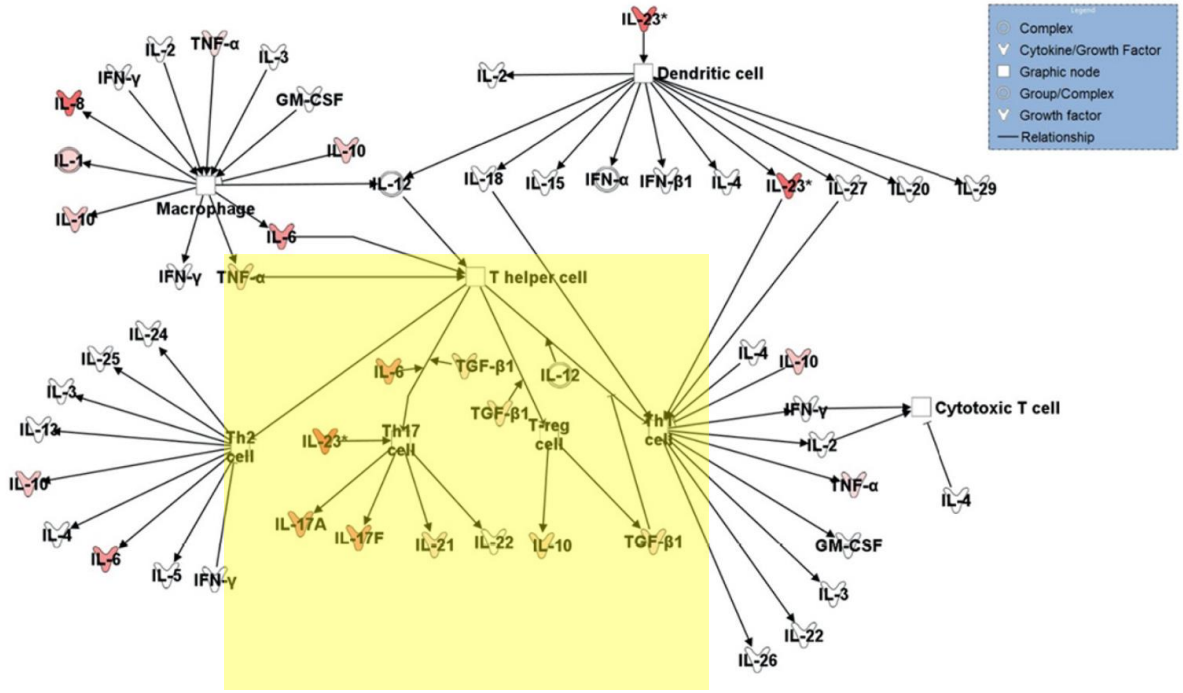




Caprioli et al. Inflamm Bowel Dis 2013

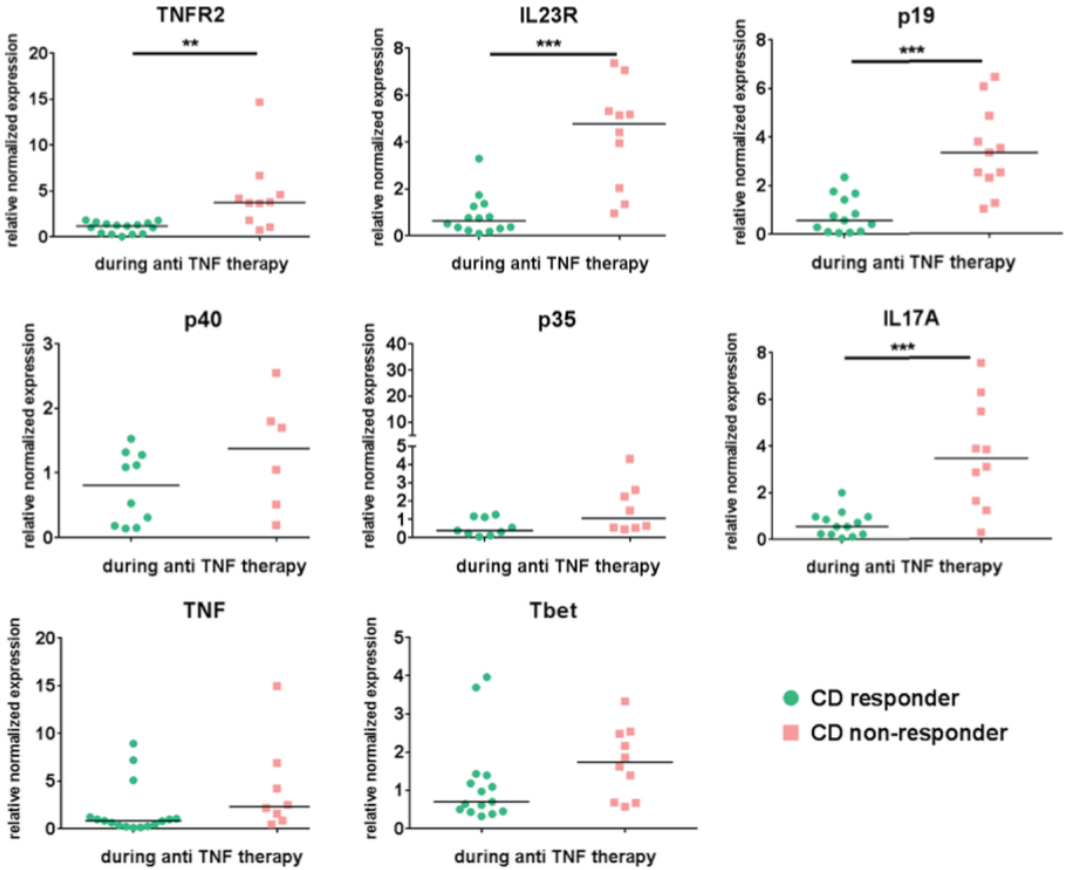
Immune shift in antiTNF NR towards IL23-Th17 axis

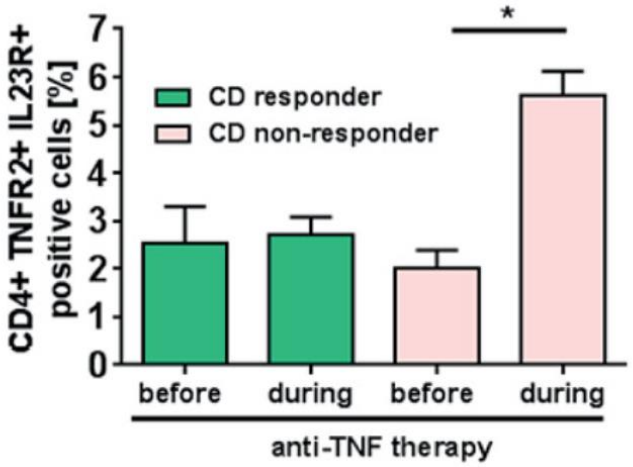


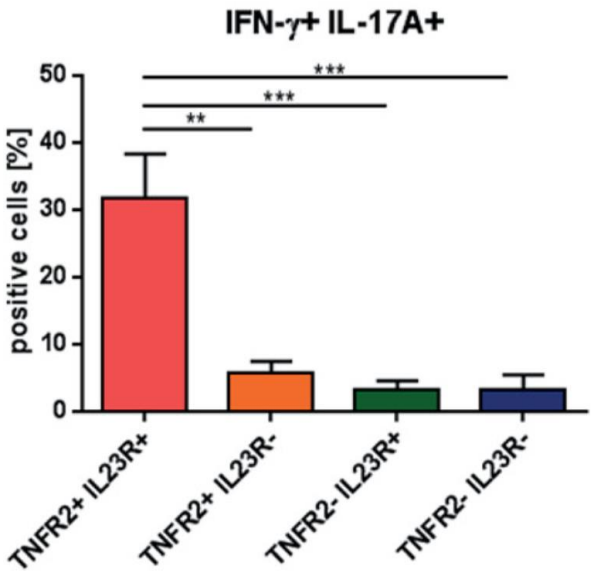


Schmitt et al. Gut 2019

Immune shift in antiTNF NR towards IL23-Th17 axis







Schmitt et al. Gut 2019

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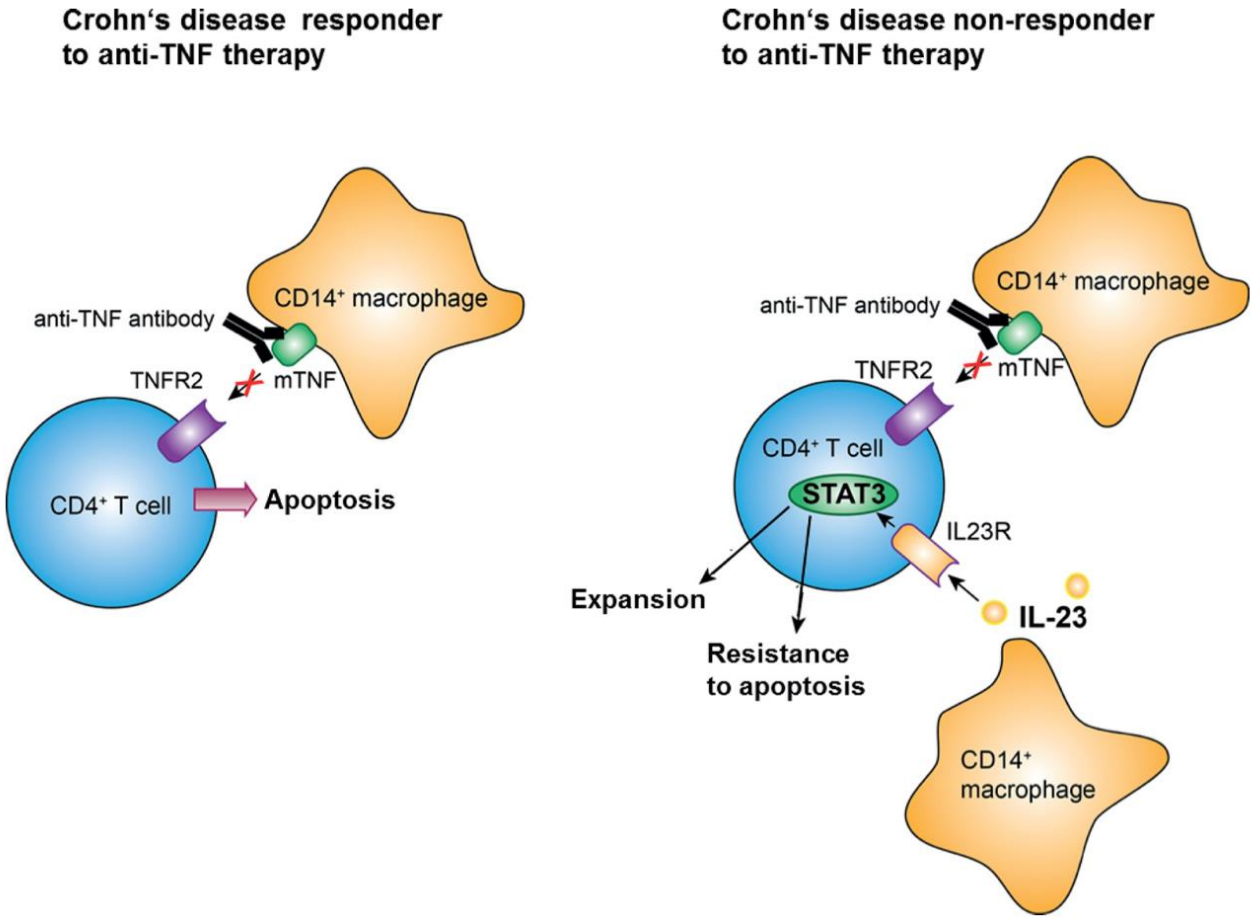
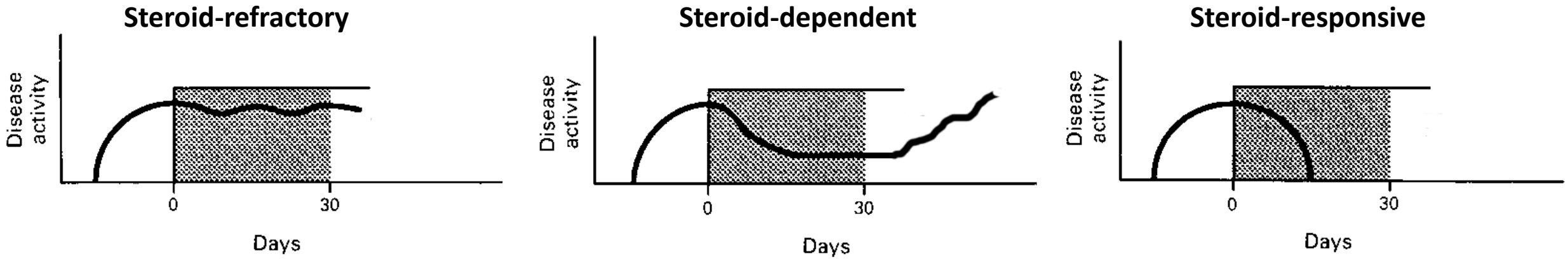
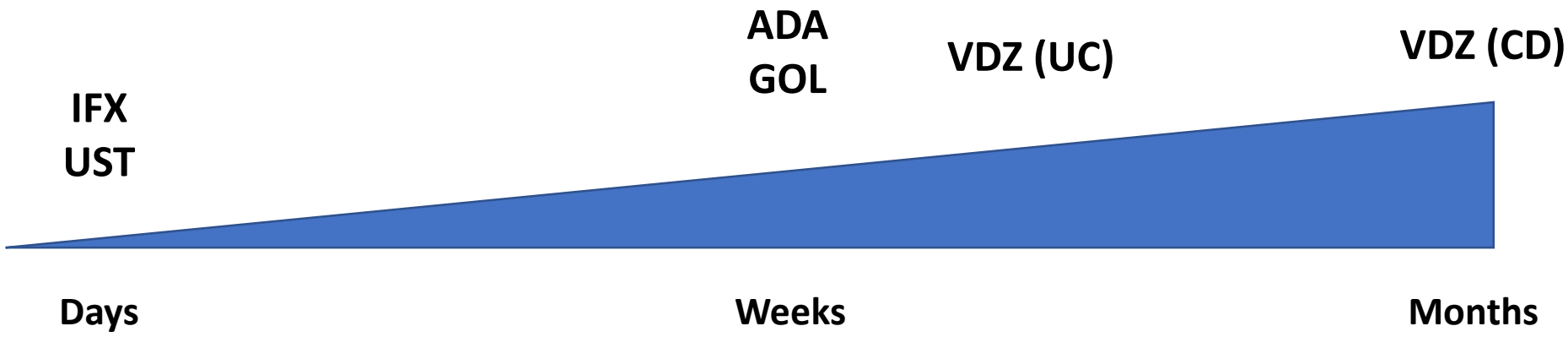


Rationale for combined anti-TNF and anti-IL23 treatment

Schmitt et al. Gut 2019

Combo therapy rationale: 2) response latency

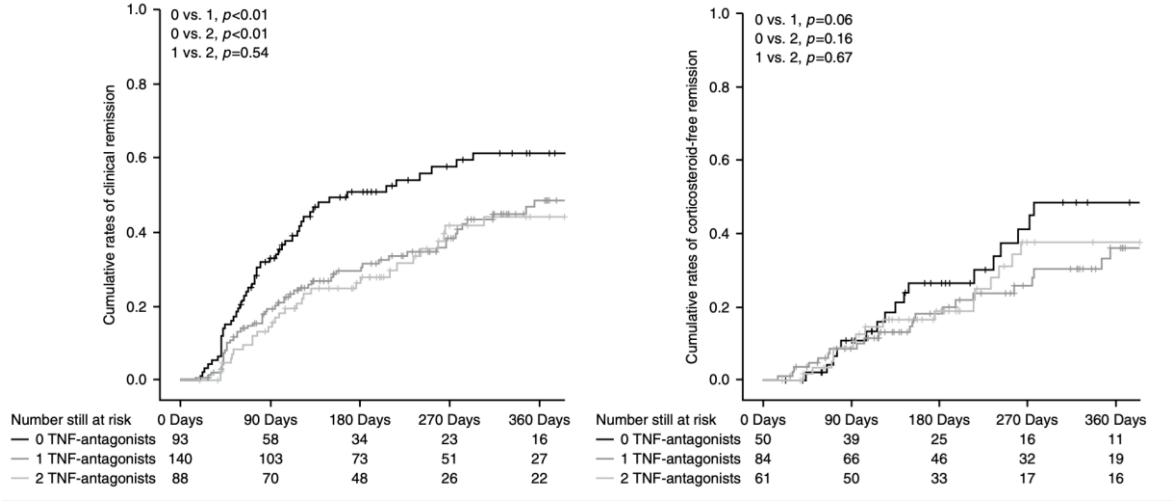




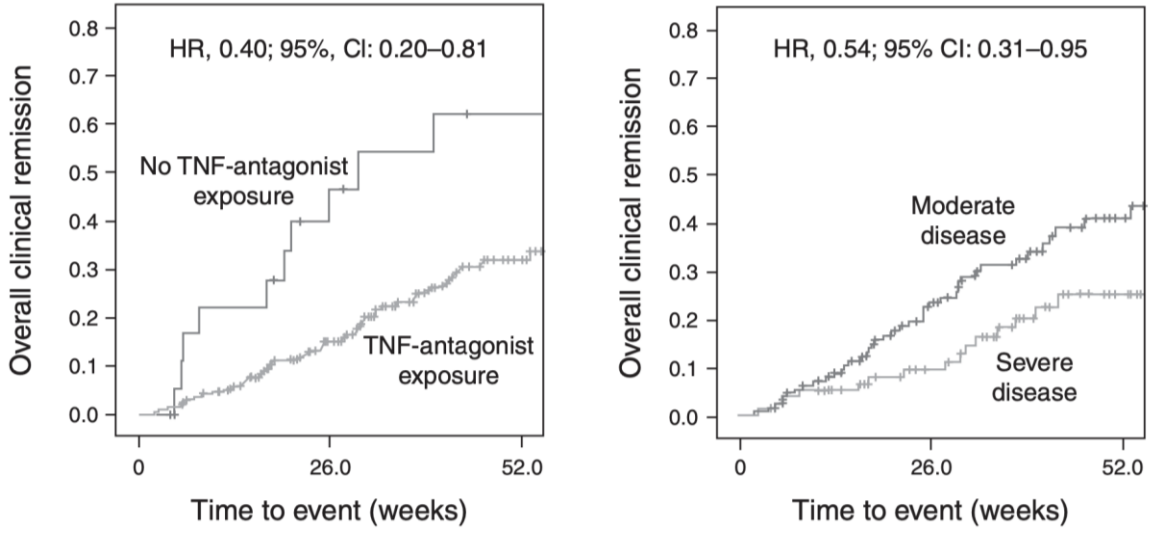
Time to clinical remission

Response latency to vedolizumab in IBD

Victory UC

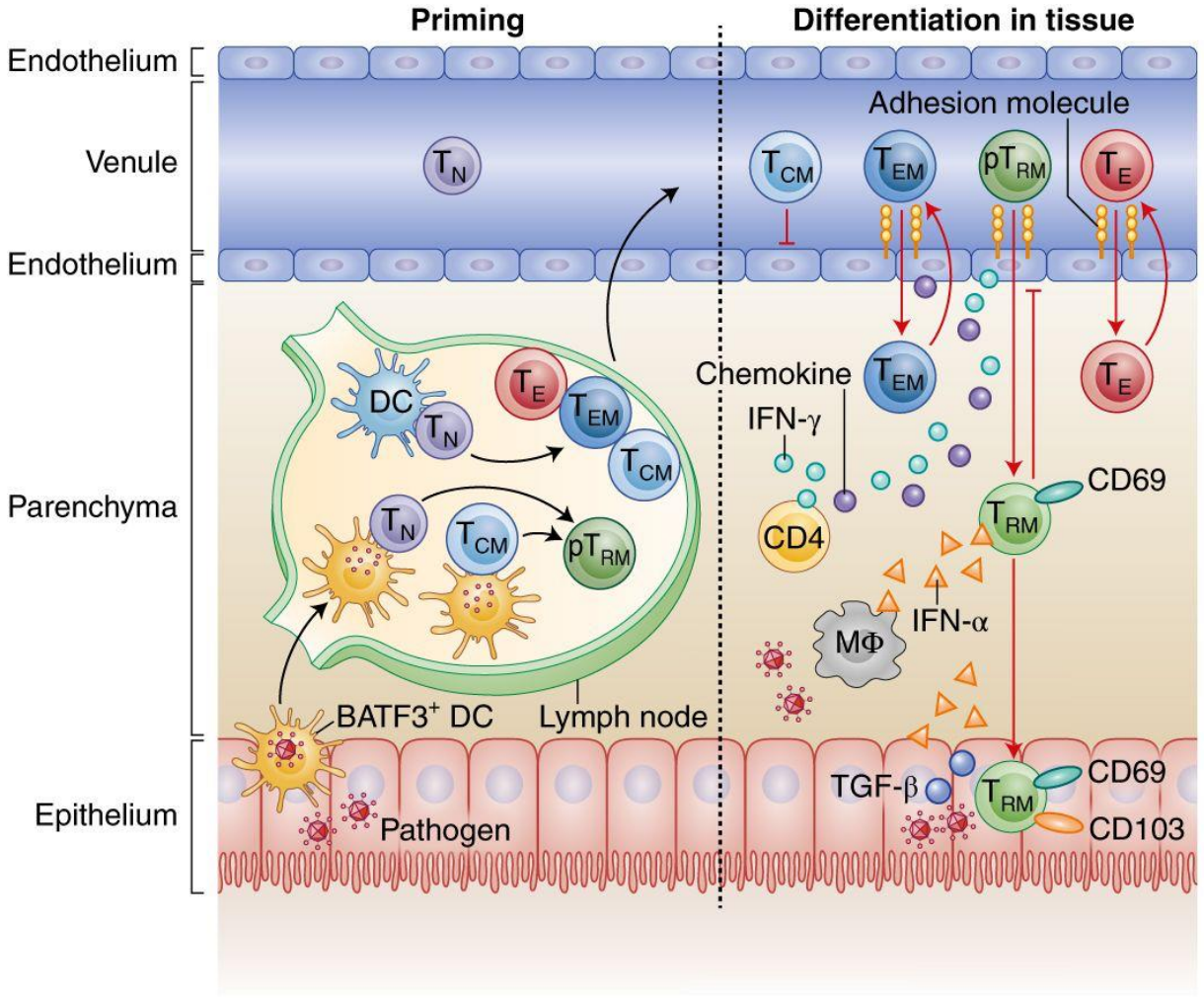


Victory CD



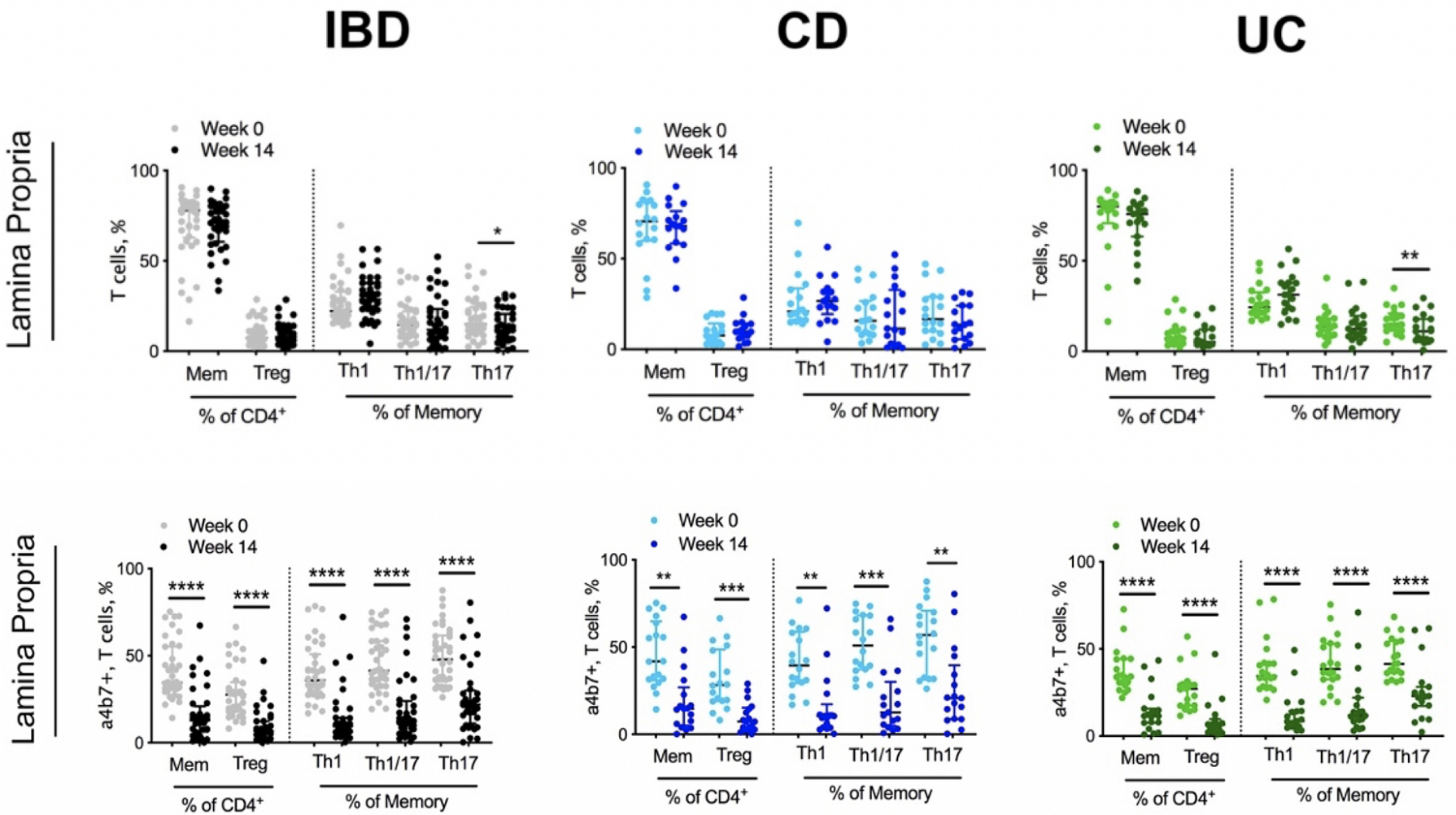
Dulai et al. Am J Gastro 2016
Narula et al. Am J Gastro 2018

Migratory versus tissue memory resident T cells



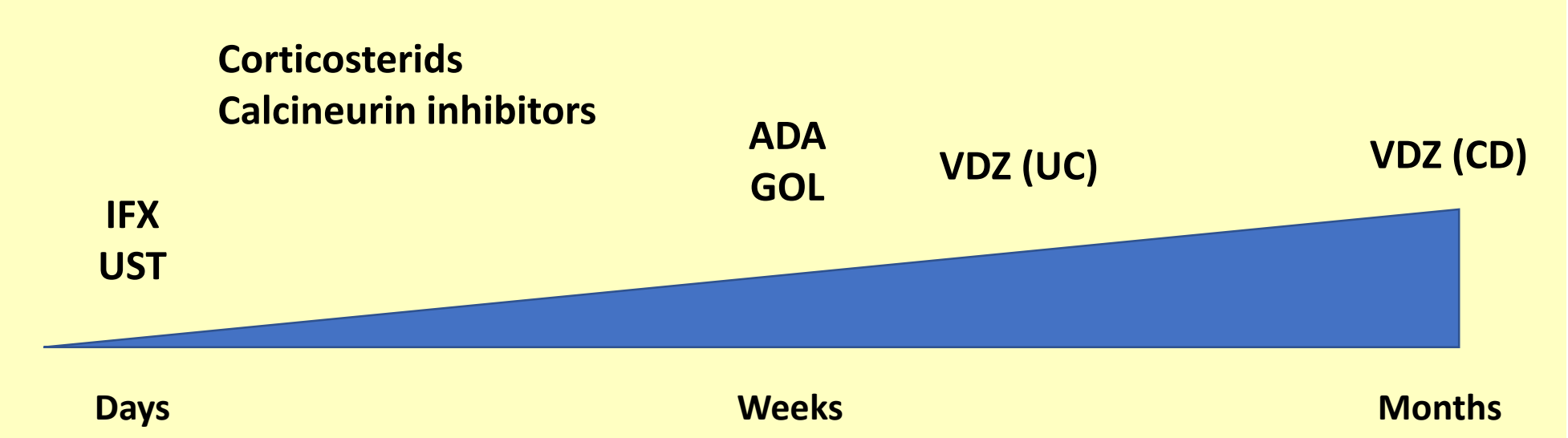
Amsen et al. Nature Immunol 2018

Vedolizumab reduces a4b7 T cell infiltration in the gut



Coletta et al. under revision

Combo therapy rationale: 2) response latency

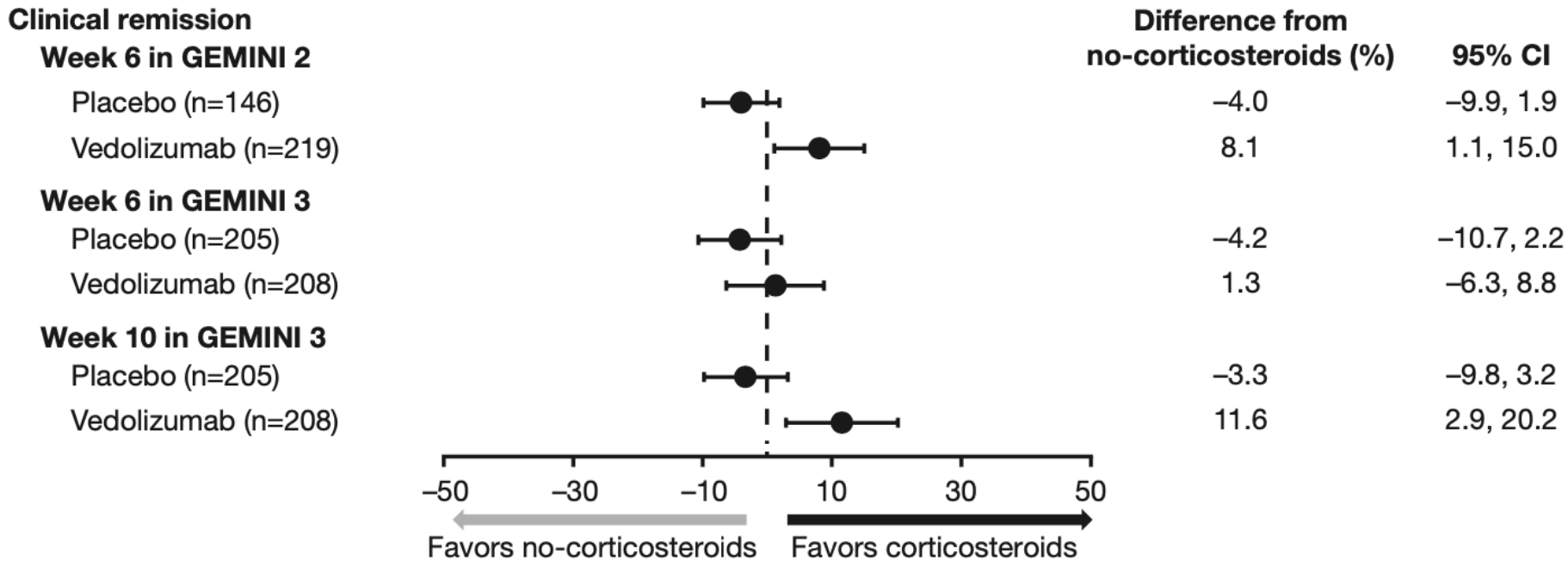


Time to clinical remission

Rationale for combined vedolizumab and induction treatment

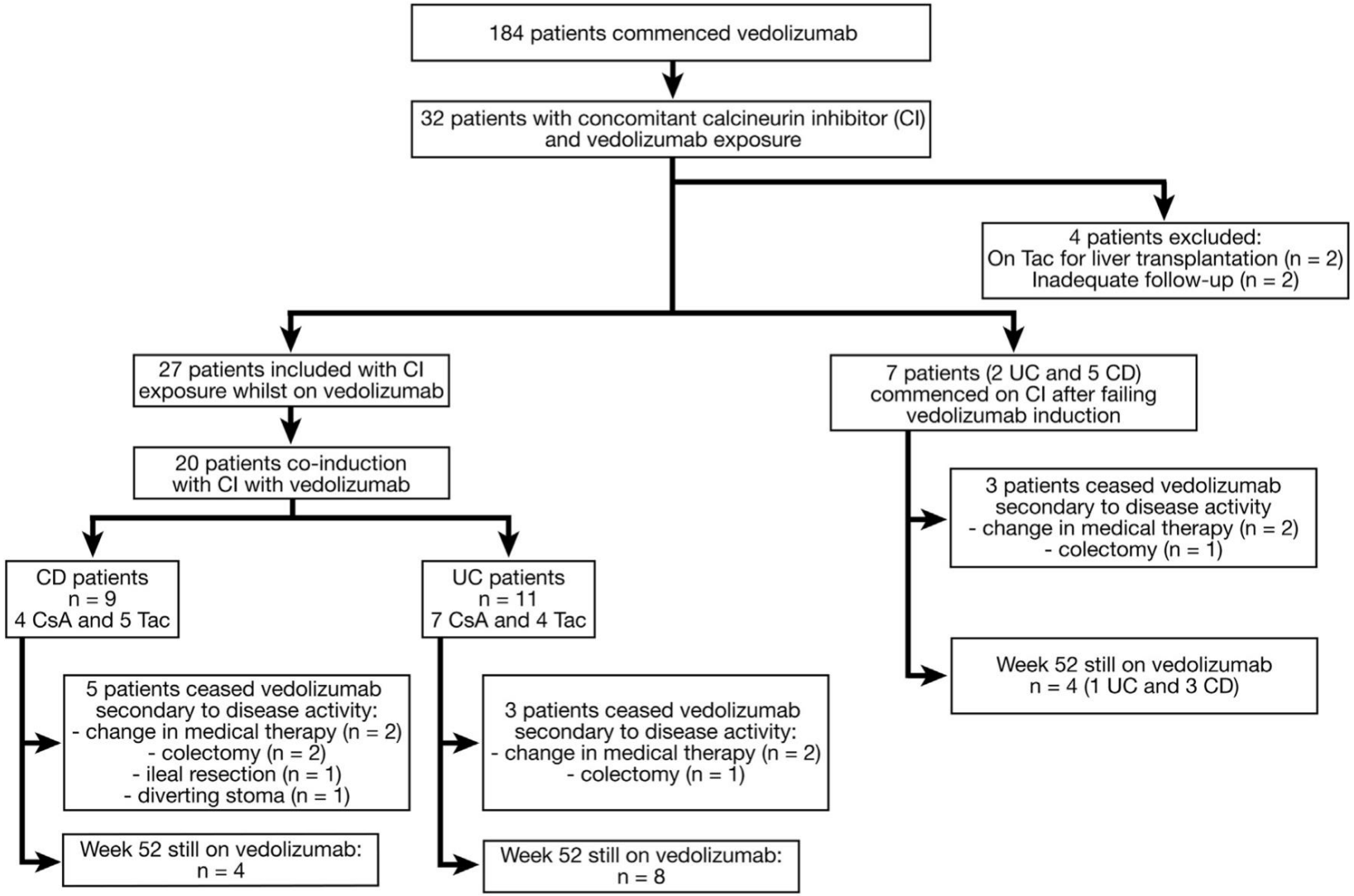
Corticosterids
Calcineurin inhibitors

Combination of vedolizumab and steroids in CD



Sands et al. Inflamm Bowel Dis 2019

Combination of vedolizumab and calcineurin inhibitors in IBD

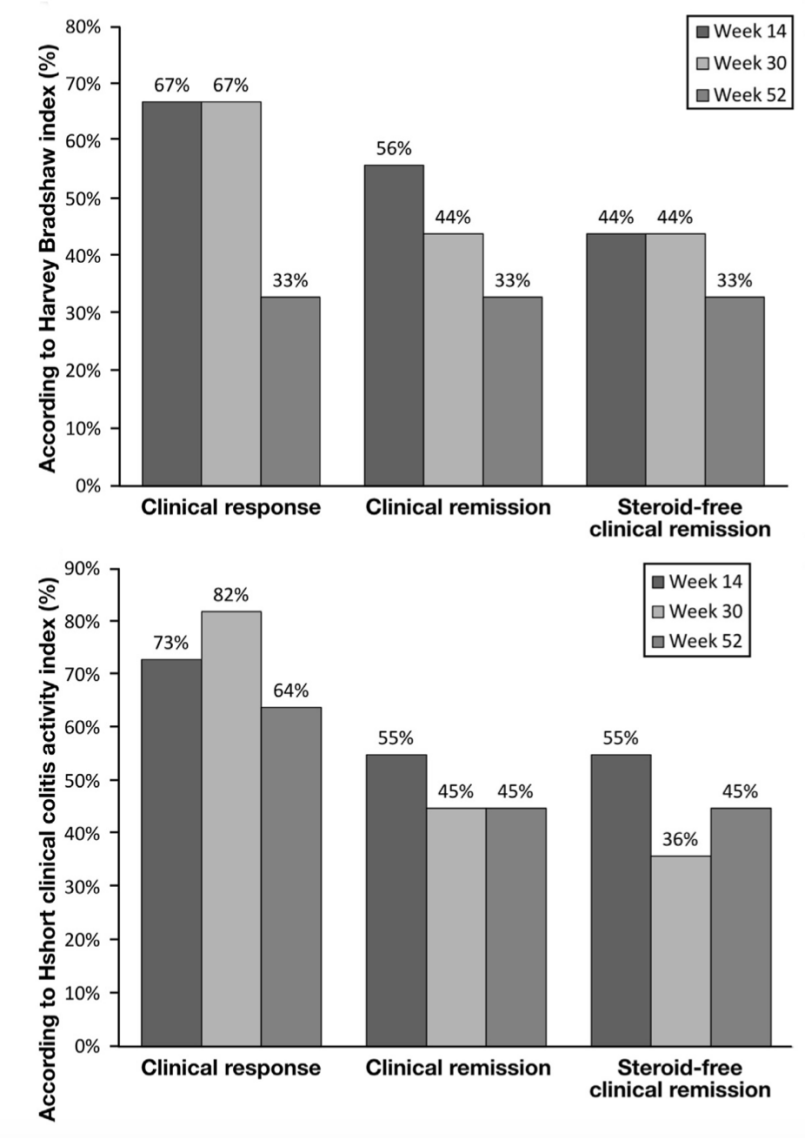


Christensen et al. Clin Gastroenterol Hepatol 2019

Combination of vedolizumab and calcineurin inhibitors in IBD

CD

UC

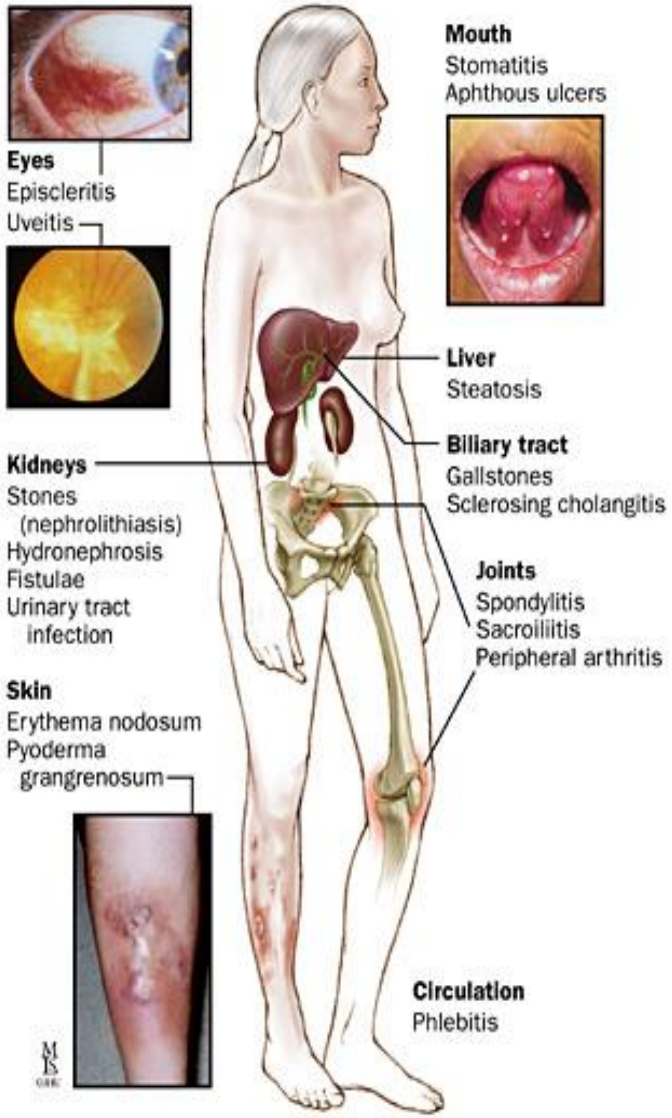


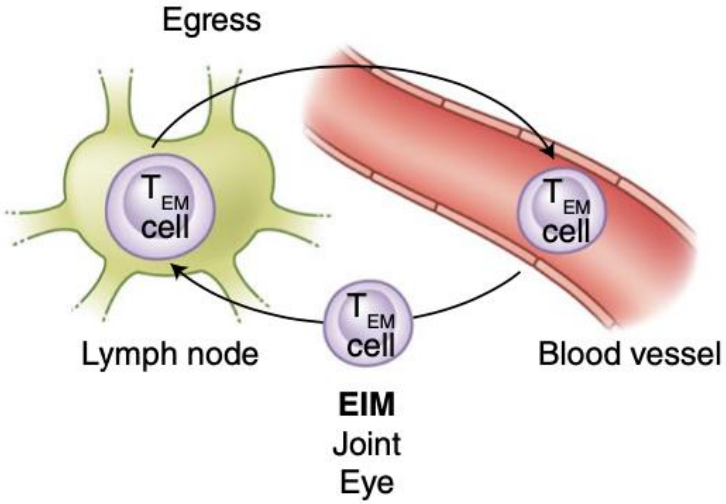
Event	Patients with IBD (n = 27)
Adverse event: noninfectious	
Neurologic complaints (n = 4)	4 total: 1 paresthesia, 1 migraine, 2 mild tremor
Pruritis	1 total
Rheumatologic	2 total: 1 new-onset arthralgia, 1 leg cramps
Infusion-related reaction	1 infusion reaction[a]
Cancer	No cancer documented
Constipation	2 total
Perianal disease	1 total: worsening perianal fistula
Fatigue	1 total
Orofacial complications	1 total: gum sensitivity
Any serious noninfectious event	1 total
Adverse event: infection	
Enteric infection	2 total: 1 viral enteritis,[a] 1 cytomegalovirus and *C difficile* colitis colectomy[a]
Sinopulmonary infections	1 sinusitis
Postoperative complications	2 total: 1 delayed perineal healing, 1 mucocutaneous separation of stoma
Miscellaneous	1 urinary tract infection
Any serious infection	4 total

IBD, inflammatory bowel disease.
[a]A serious adverse event or infection was defined as any adverse event when leading to treatment interruption, antibiotic therapy, hospitalization, disability or persistent damage, colectomy, or death.

Christensen et al. Clin Gastroenterol Hepatol 2019

Combo therapy rationale: 3) extraintestinal manifestations





Combo therapy rationale: 3) extraintestinal manifestations

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals
MEETING ABSTRACTS

ABSTRACT NUMBER: 2826

Emergence of Severe Spondyloarthropathy Related Entheseal Pathology Following Successful Vedolizumab Therapy for Inflammatory Bowel Disease

Sayam Dubash[1,2], Marianayagam Thiraupathy[3], Ilaria Tinazzi[4], Tariq Al Araimi[5], Christian Pagnoux[6], Adam Weizman[7], Pascal Richette[8,9], My-Linh Tran Minh[10], Mattieu Allez[10], Animesh Singh[11], Francesco Ciccia[12], John Hamlin[13], Ai Lyn Tan[1,2], Helena Marzo-Ortega[1,2] and Dennis McGonagle[1,2], [1]Rheumatology, Chapel Allerton Hospital, NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of

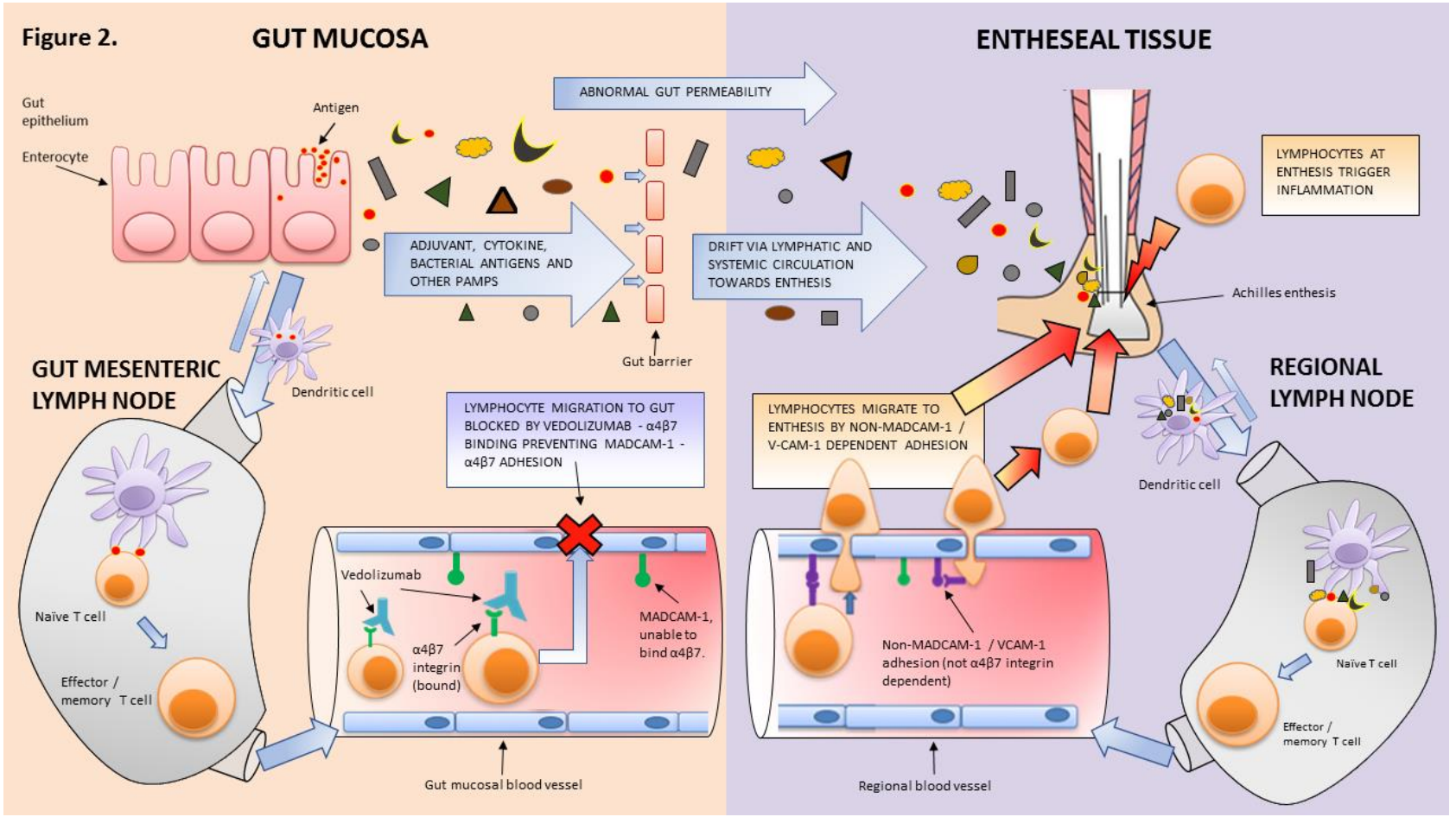
Dubash et al. Arthritis Rheumatol. 2018; 70 (suppl 10).

Combo therapy rationale: 3) extraintestinal manifestations

Patient number	1	2	3	4	5	6	7	8	9	10	11
Age, M/F	28, M	48, M	33, F	50, M	35, F	40, F	21, F	52, M	45, F	44, F	72, M
Hospitalised	Y	N	N	N	Y	Y	N	N	Y	N	N
Vedolizumab exposure (weeks)	14	20	20	6	8	10	5	12	4	52	20
Pre-existing SpA	Y	N	N	N	N	N	N	N	Y	N	N
axSpA	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N
perSpA	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y
Osteitis or Enthesitis	+++	++	++	+++	NA	++	++	+++	+++	+++	+++
MRI/USS (imaging feature)	MRI: Extreme Perifacetal spinal vertebral oedema	MRI: Bilateral sacroiliitis	MRI: Bilateral sacroiliitis	MRI: Extensive severe thoraco-lumbar vertebral oedema/ osteitis and IRLs	MRI –ve, nr-axSpA	MRI: Enthesitis/periostitis distal tibio-fibular	MRI: Right sided sacroiliitis (also XR +ve, fulfilling mNY criteria)	USS: Marked Achilles enthesitis PD +ve	MRI: Bilateral sacroiliitis	MRI: Bilateral sacroiliitis USS: Knee synovitis, hand flexor tenosynovitis, PD +ve	USS: elbow, knee and wrist synovitis, common extensor enthesitis.
HLA-B27	N	NA	NA	N	Y	NA	N	N	N	N	NA
Smoker (cpd)	15	NA	NA	25	N	N	N	N	N	N	N
EAMs (Uveitis, PsO)	N	N	PsO	N	PsO	N	N	N	PsO	N	PsO
IBD type/ activity	CD/ Low/ controlled	IC/ Low/ controlled	CD/NA	CD/ Active (high)	UC/ Low/ controlled	UC/ Low/ controlled	IC/ Low/ controlled	CD/ Active (moderate)	UC/ Low/ controlled	CD/Active (high)	UC/ Low/ controlled
CRP at flare (mg/l)	216	<5	<5	24	24	28	55	68	33	80	88
Concomitant DMARD	MTX 15mg o.w	AZA 150mg o.d	Pred 0.5mg o.d	None	None	Pred 4mg o.d	None	None	MTX 7.5mg o.w	No	Pred 15mg o.d
TNFi failure	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N
Previous TNFi /DMARDs	IFX ADA CZP	ADA IFX	AZA IFX ADA	IFX ADA	MSZ CYSP IFX ADA	6-MP AZA ADA	IFX	6-MP, AZA	IFX Secukinumab ADA	IFX CZP GLM	None
Vedolizumab discontinued	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y
Treatment change	GLM	Patient declined treatment for SpA.	Bilateral sacroiliac joint injection and switched to UST	CZP	CZP: intolerance. SZP: intolerance. Switched to GLM.	TOFA+ ZOL	ADA	ADA+Pred	VDZ +Pred 10mg o.d + Apremilast; developed significant depression. Apremilast switched back to MTX 7.5mg o.w.	ETN+ VDZ	ADA
Outcome	Moderate IBD and SpA activity at 6 months, CRP 58 BASDAI 6.9 (previous 8.8)	IBD in remission at 6 months (colonoscopy normal) SpA outcomes: NA	NA	IBD: controlled SpA: mild to moderate activity at 6 months, CRP 19	IBD in remission. SpA activity is moderate at 6 months.	Periostitis and enthesitis resolved at 6 months.	Mild axSpA. Skin and perSpA in remission at 1 month.	Achilles enthesitis much improved. Moderate CD activity at 1 month	IBD/ SpA /Skin PsO all well controlled at 6 months.	IBD and SpA in drug controlled remission at 6 months.	NA

Dubash et al. Arthritis Rheumatol. 2018; 70 (suppl 10).

Combo therapy rationale: 3) extraintestinal manifestations



Rationale for combined anti-TNF and anti-integrin treatment

Dubash et al. Arthritis Rheumatol. 2018; 70 (suppl 10).

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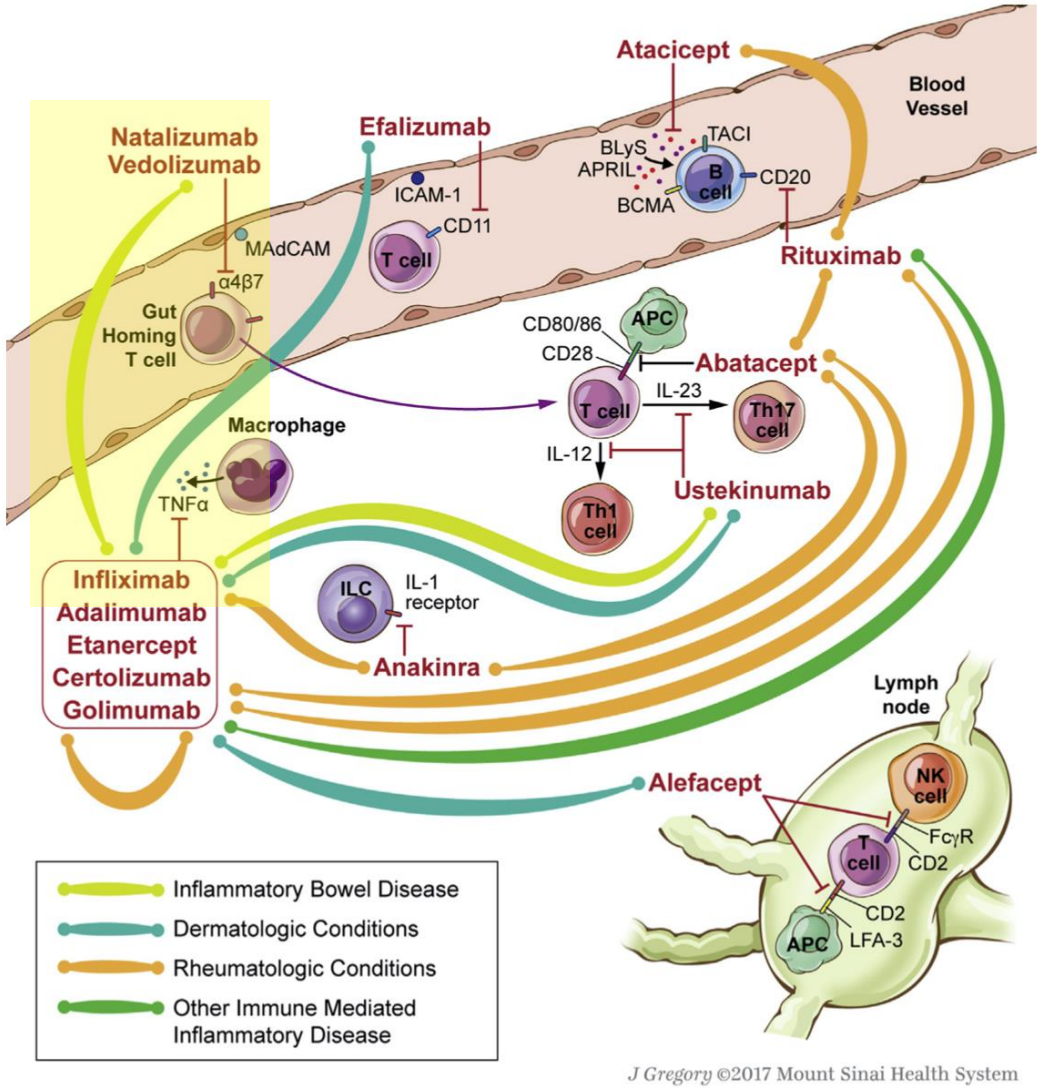
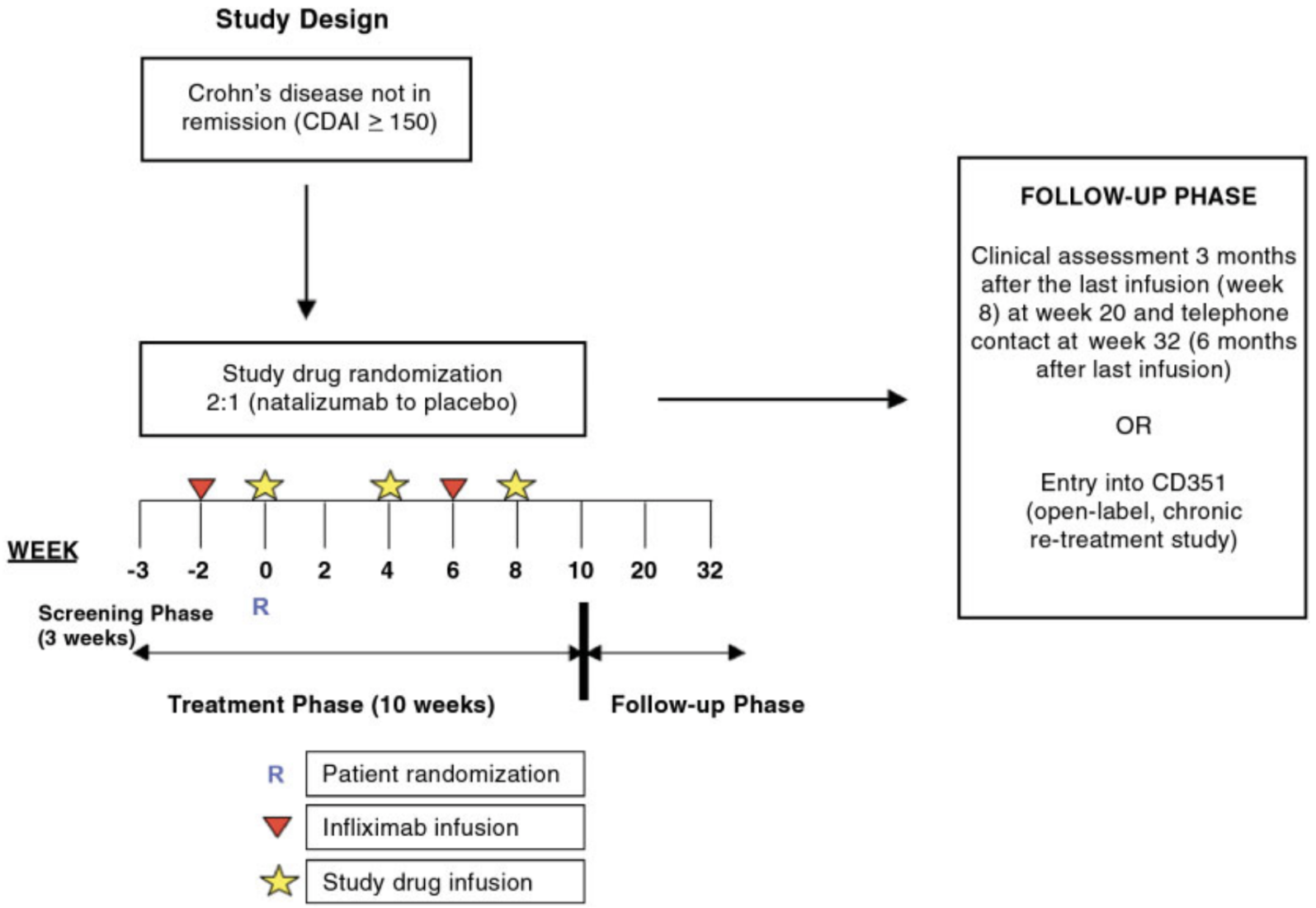
Combinations of biologics in autoimmune diseases



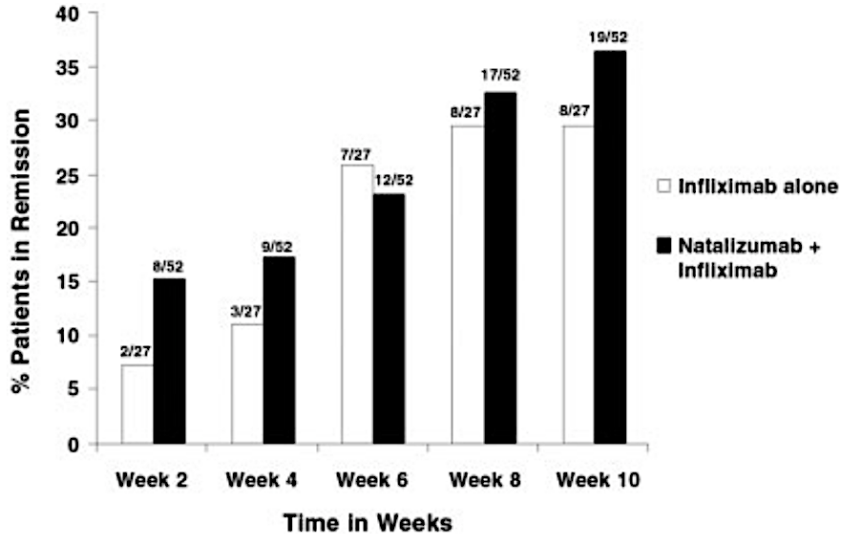
Hirten et al. Clin Gastroenterol Hepatol 2018

Combined natalizumab and infliximab treatment in CD



Sands et al. Inflamm Bowel Dis 2007

Combined natalizumab and infliximab treatment in CD



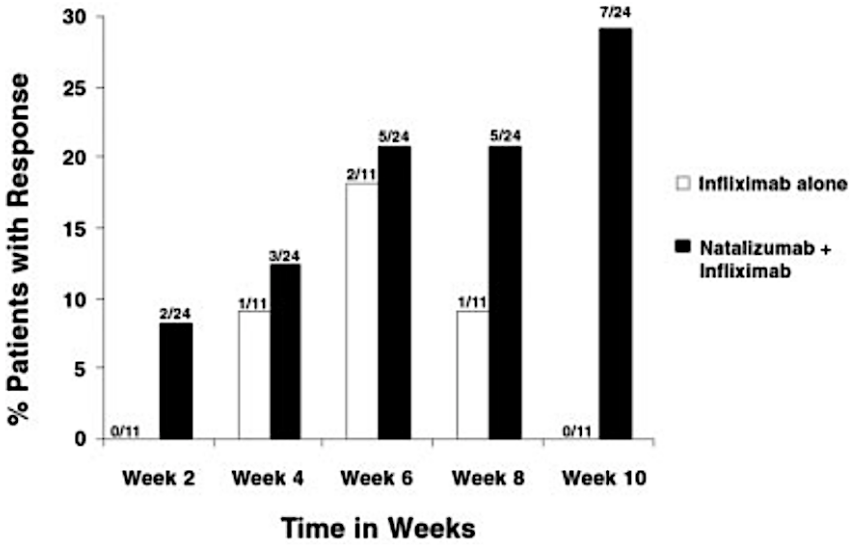


TABLE II. Incidence of Adverse Events Occurring in More Than 5% of Patients in Natalizumab + Infliximab Group

Adverse event	Placebo + infliximab (N = 27), n (%)	Natalizumab + infliximab (N = 52), n (%)
Headache	6 (22)	12 (23)
Fatigue	2 (7)	7 (13)
Exacerbation of Crohn's disease	4 (15)	5 (10)
Dizziness	1 (4)	5 (10)
Nasopharyngitis	3 (11)	5 (10)
Nausea	3 (11)	5 (10)
DNA antibody positive	3 (11)	4 (8)
Dyspepsia	1 (4)	4 (8)
Abdominal pain	0	3 (6)
Antinuclear antibody positive	1 (4)	3 (6)
Arthralgia	2 (7)	3 (6)
Back pain	2 (7)	3 (6)
Insomnia	1 (4)	3 (6)
Pyrexia	0	3 (6)
Upper respiratory tract infection	1 (4)	3 (6)

Note: A patient was counted only once for each type of adverse event.

Sands et al. Inflamm Bowel Dis 2007

Combination therapy in IBD: summary

- Rationale for combining therapies in IBD
- Efficacy of biologic combinations in RCT
- Real life effectiveness of biologic combinations
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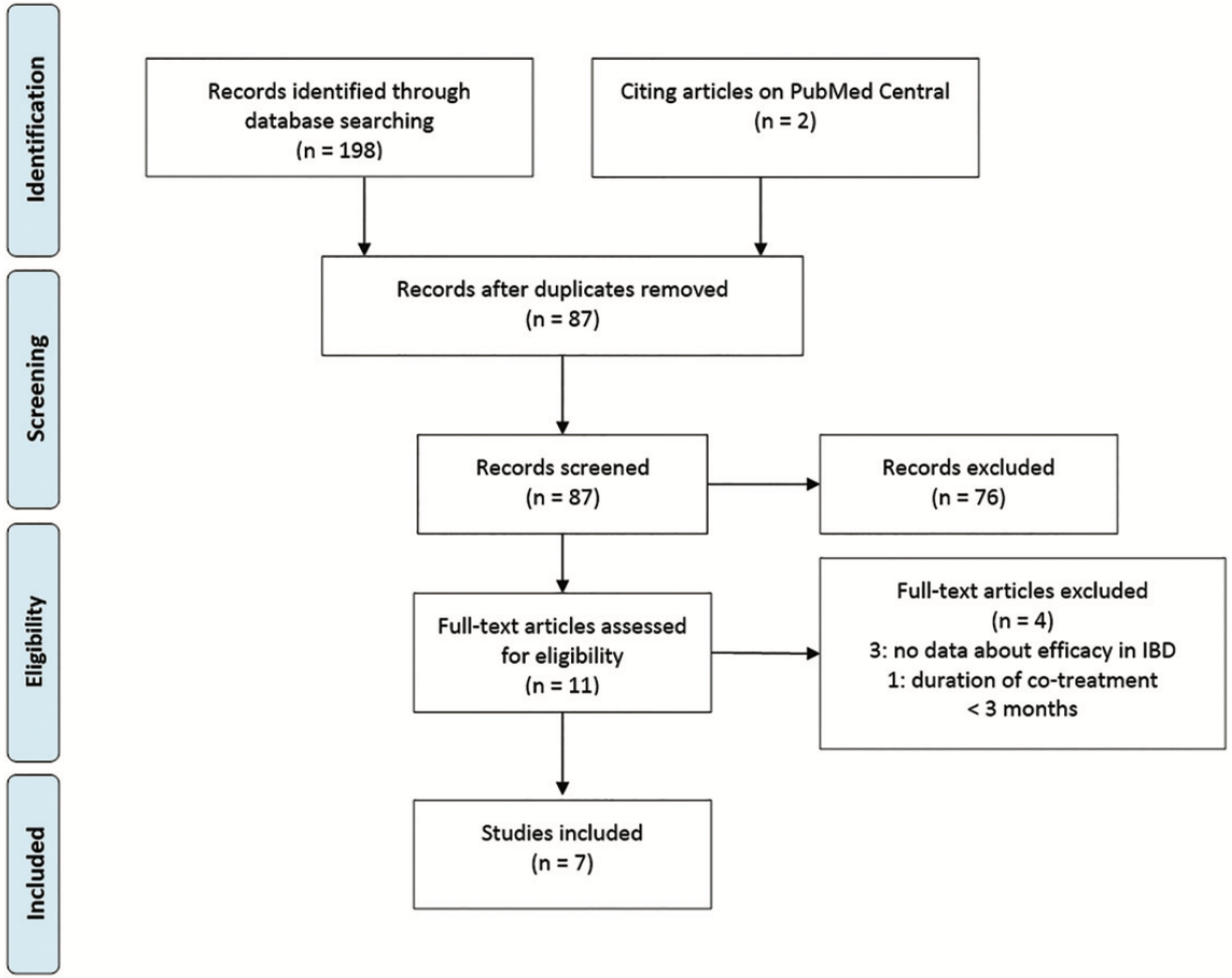
- Future perspectives

Real life effectiveness of biologic combinations

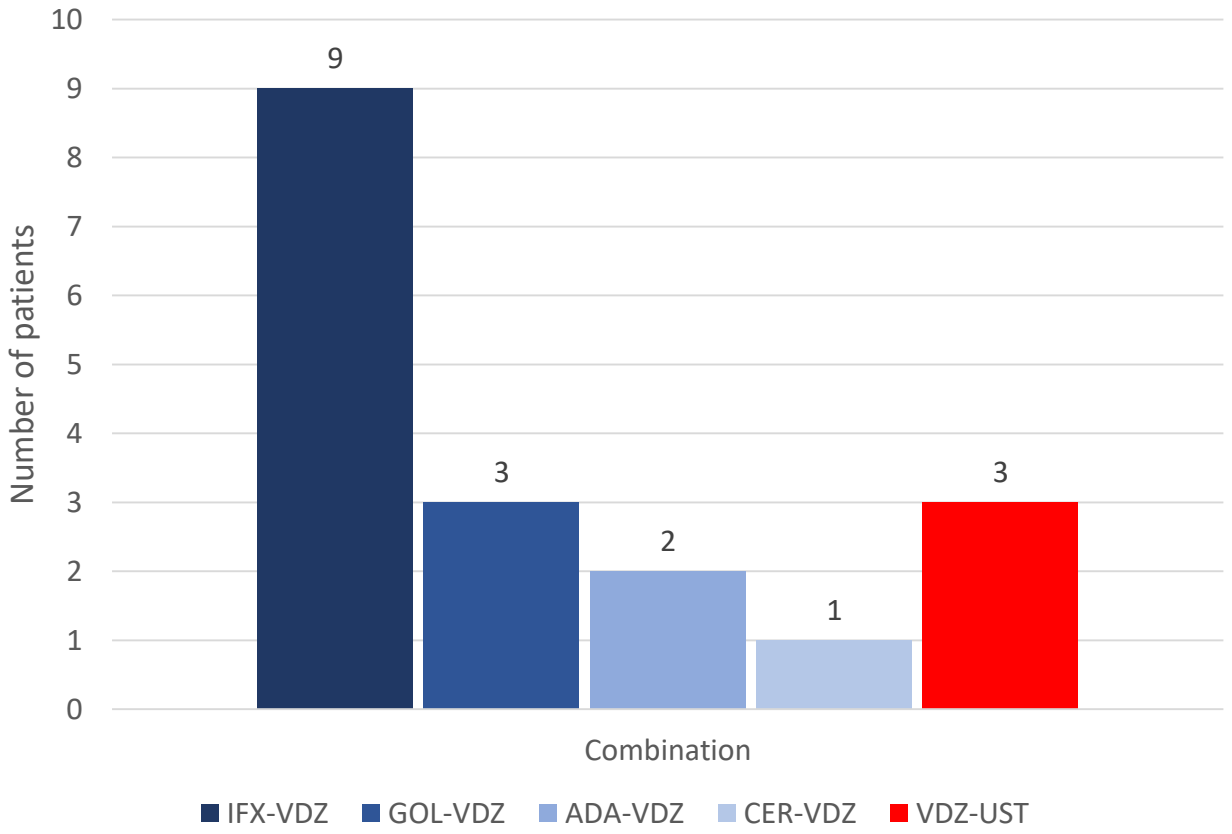


Ribaldone et al. Scand J Gastroenterol 2019

Real life effectiveness of biologic combinations

Sex (*n*; %)	Disease (*n*; %)	Drugs (*n*; %)
M: 8; 44	CD: 10; 56	Ada-Ved: 2; 11.1
F: 10; 56	UC: 8; 44	Cer-Ved: 1; 5.6
		Gol-Ved: 3; 16.7
		Ifx-Ved: 9; 50
		Ved-Ust: 3; 16.7

M: male; F: female; CD: Crohn's disease; UC: ulcerative colitis; Ada: adalimumab; Ved: vedolizumab; Cer: certolizumab; Gol: golimumab; Ifx: infliximab; Ust.: Ustekinumab



Ribaldone et al. Scand J Gastroenterol 2019

Real life effectiveness of biologic combinations

Table 1. Studies about dual biological therapy in inflammatory bowel disease (IBD).

Author	Year	Type of study	Disease	Indication	Drugs	Immunomodulator or prednisone	Months of dual therapy
Afzali et al. [4]	2016	Case report	CD	Active IBD	Ada-Ved	Yes	6
Fischer et al. [5]	2017	Case report	UC	Active IBD and spondyloarthritis	Cer-Ved	No	21
Roblin et al. [6]	2018	Case report	UC	IBD and active ankylosing spondylitis	Gol-Ved	No	12
Buer et al. [7]		Case series	6 UC 4 CD	Active IBD	9 Ifx-Ved 1 Ada-Ved	5 Yes 5 No	>6
Huff-Hardy et al. [9]		Case report	CD	Active luminal and vulvar IBD	Ved-Ust	Yes	12
Liu et al. [10]		Case report	CD	Active luminal and perianal	Ved-Ust	Yes	6
Mao et al. [8]		Case series	CD	Active IBD	1 Ved-Ust 2 Gol-Ved	1 No 2 Yes	5-37

CD: Crohn's disease; Ada: adalimumab; Ved: vedolizumab; Cer: certolizumab; Gol: golimumab; Ifx: infliximab; U.A.I.: upper airway infection; Dysp.: dyspnea; *cile* infection; N/A: not available; SLVI: self-limited viral illnesses.

Ribaldone et al. Scand J Gastroenterol 2019

Real life effectiveness of biologic combinations

Table 1. Studies about dual biological therapy in inflammatory bowel disease (IBD).

Author	Year	Type of study	Disease	Indication	Drugs	Immunomodulator or prednisone	Months of dual therapy	Clinical improvement	Endoscopic improvement
Afzali et al. [4]	2016	Case report	CD	Active IBD	Ada-Ved	Yes	6	Yes	Yes
Fischer et al. [5]	2017	Case report	UC	Active IBD and spondyloarthritis	Cer-Ved	No	21	Yes	Yes
Roblin et al. [6]	2018	Case report	UC	IBD and active ankylosing spondylitis	Gol-Ved	No	12	Yes	Yes
Buer et al. [7]		Case series	6 UC 4 CD	Active IBD	9 Ifx-Ved 1 Ada-Ved	5 Yes 5 No	>6	Yes	9 Yes 1 No
Huff-Hardy et al. [9]		Case report	CD	Active luminal and vulvar IBD	Ved-Ust	Yes	12	Yes	Yes
Liu et al. [10]		Case report	CD	Active luminal and perianal	Ved-Ust	Yes	6	Yes	Yes
Mao et al. [8]		Case series	CD	Active IBD	1 Ved-Ust 2 Gol-Ved	1 No 2 Yes	5-37	Yes	N/A

CD: Crohn's disease; Ada: adalimumab; Ved: vedolizumab; Cer: certolizumab; Gol: golimumab; Ifx: infliximab; U.A.I.: upper airway infection; Dysp.: dyspnea; Ust.: Ustekinumab; Rot.: rotavirus infection; CDI: *cile* infection; N/A: not available; SLVI: self-limited viral illnesses.

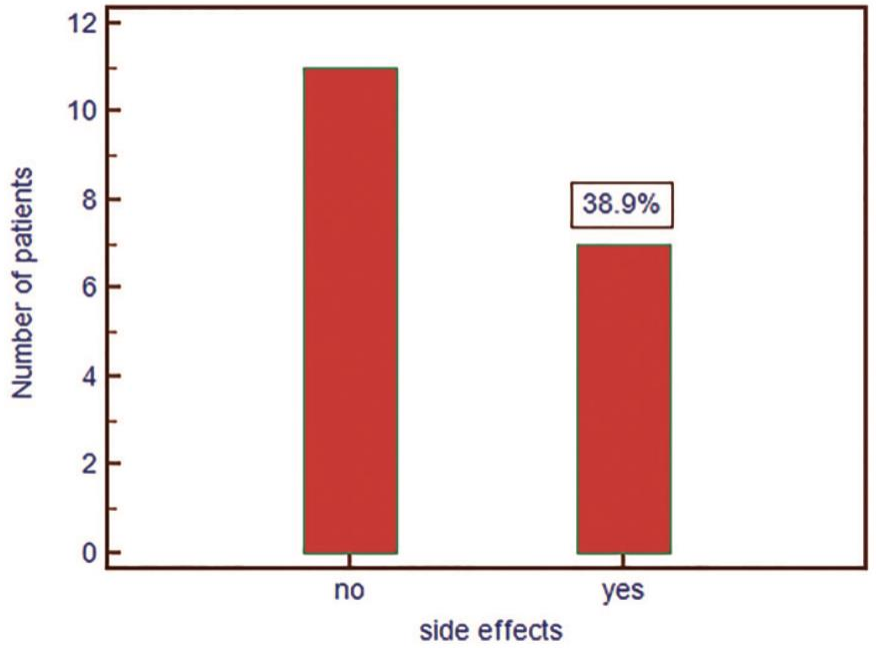
Ribaldone et al. Scand J Gastroenterol 2019

Real life safety of biologic combinations

Table 1. Studies about dual biological therapy in inflammatory bowel disease (IBD).

Author	Year	Type of study	Disease	Indication	Drugs	Immunomodulator or prednisone	Months of dual therapy	Side effects
Afzali et al. [4]	2016	Case report	CD	Active IBD	Ada-Ved	Yes	6	No
Fischer et al. [5]	2017	Case report	UC	Active IBD and spondyloarthritis	Cer-Ved	No	21	No
Roblin et al. [6]	2018	Case report	UC	IBD and active ankylosing spondylitis	Gol-Ved	No	12	No
Buer et al. [7]		Case series	6 UC 4 CD	Active IBD	9 Ifx-Ved 1 Ada-Ved	5 Yes 5 No	>6	3 U.A.I. 1 Dysp.
Huff-Hardy et al. [9]		Case report	CD	Active luminal and vulvar IBD	Ved-Ust	Yes	12	Rot
Liu et al. [10]		Case report	CD	Active luminal and perianal	Ved-Ust	Yes	6	No
Mao et al. [8]		Case series	CD	Active IBD	1 Ved-Ust 2 Gol-Ved	1 No 2 Yes	5-37	1 CDI 1 SLVI

CD: Crohn's disease; Ada: adalimumab; Ved: vedolizumab; Cer: certolizumab; Gol: golimumab; Ifx: infliximab; U.A.I.: upper airway infection; Dysp.: dyspnea; Ust.: Ustekinumab; Rot.: rotavirus infection; CDI: *Clostridium difficile* infection; N/A: not available; SLVI: self-limited viral illnesses.



Reported side effects:

- Upper airways infections
- Dyspnea
- Rotavirus infection
- C. difficile infection
- Viral illness

Ribaldone et al. Scand J Gastroenterol 2019

Real life safety of biologic combinations

Reference	Year	Study type	Disease	Number of subjects	Medications (n)	Efficacy	Adverse events	Follow-up period
Cuchacovich et al[10]	2012	Case report	Psoriasis + PSA	1	Etanercept + UST	Composite psoriatic disease activity index, significant improvement	None	11 mo
Babalola et al[11]	2015	Case report	Psoriasis + PSA	1	Etanercept + UST	Resolved joint and skin manifestations	Unstable angina/cardiac stent	6 mo
Heinecke et al[12]	2013	Case report	Psoriasis + PSA	1	UST + etanercept → adalimumab	Skin improved but joint symptoms continued	Furuncles + autoimmune hemolytic anemia	—
Gniadecki et al[13]	2016	Case series	Psoriasis + PSA	4	UST + etanercept (2) or adalimumab → golimumab (1) or adalimumab → certolizumab (1)	Improved skin and joint symptoms	Herpes zoster, retrotonsillar abscess, erysipelas, bacterial pneumonia, cellulitis	7–62 mo 16.2 patient-years of exposure

BCC, basal cell carcinoma; LRI, lower respiratory tract infection; PSA, psoriatic arthritis; SCC, squamous cell carcinoma; URI, upper respiratory tract infection; UST, ustekinumab.

Hirten et al. Clin Gastroenterol Hepatol 2018

Combination therapy in IBD: summary

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Ongoing clinical trials (CD)

U.S. National Library of Medicine
ClinicalTrials.gov

Triple Combination Therapy in High Risk Crohn's Disease (CD)

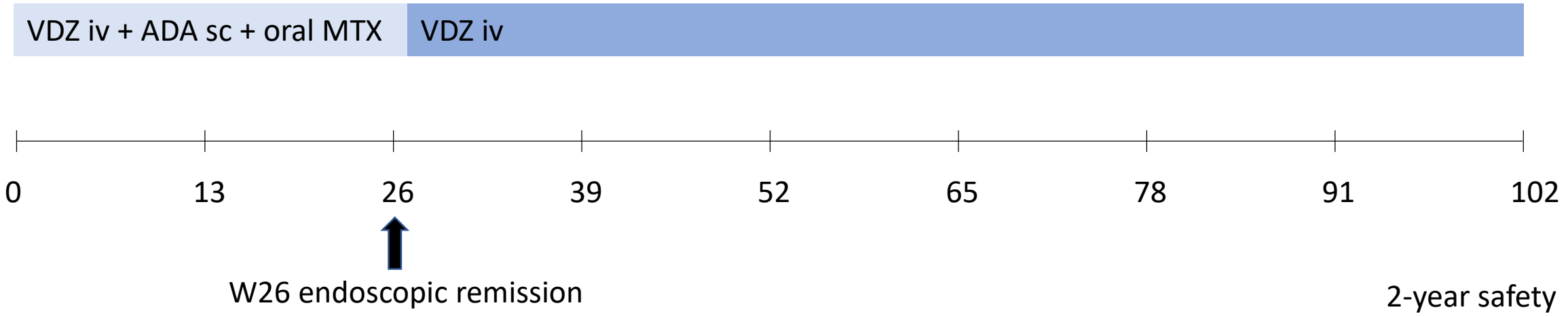
The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02764762

Recruitment Status : Recruiting
First Posted : May 6, 2016
Last Update Posted : September 23, 2019

See **Contacts and Locations**

Sponsor:
Takeda



Ongoing clinical trials (CD)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Synergistic Effect of Vedolizumab and Pentoxifylline

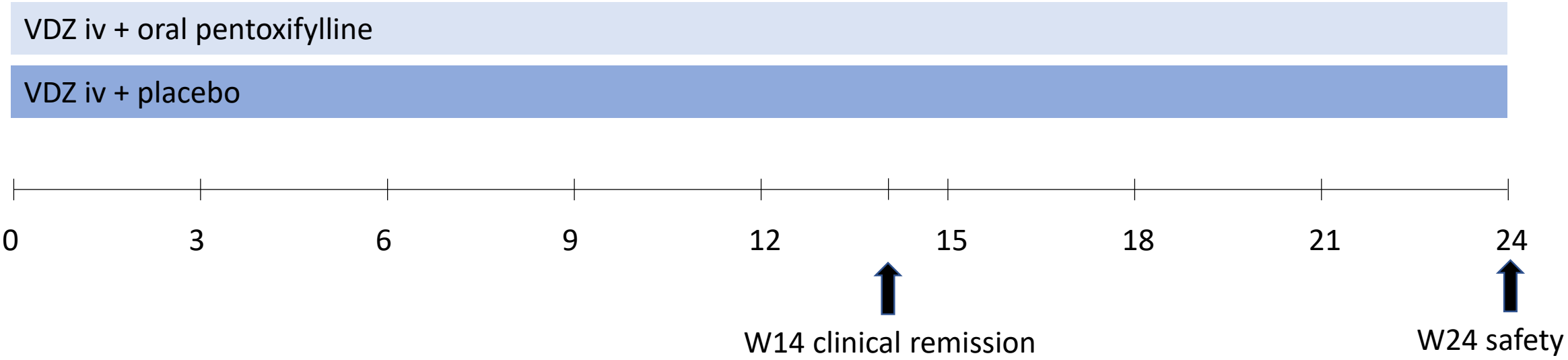
The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02953275

Recruitment Status : Completed
First Posted : November 2, 2016
Last Update Posted : July 11, 2019

Sponsor:
University of Miami

Collaborator:
Takeda



Ongoing clinical trials (UC)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

A Study of Efficacy and Safety of Combination Therapy With Guselkumab and Golimumab in Participants With Moderately to Severely Active Ulcerative Colitis (VEGA)

ClinicalTrials.gov Identifier: NCT03662542

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Recruitment Status : Recruiting
First Posted : September 7, 2018
Last Update Posted : November 1, 2019

See **Contacts and Locations**

Sponsor:
Janssen Research & Development, LLC

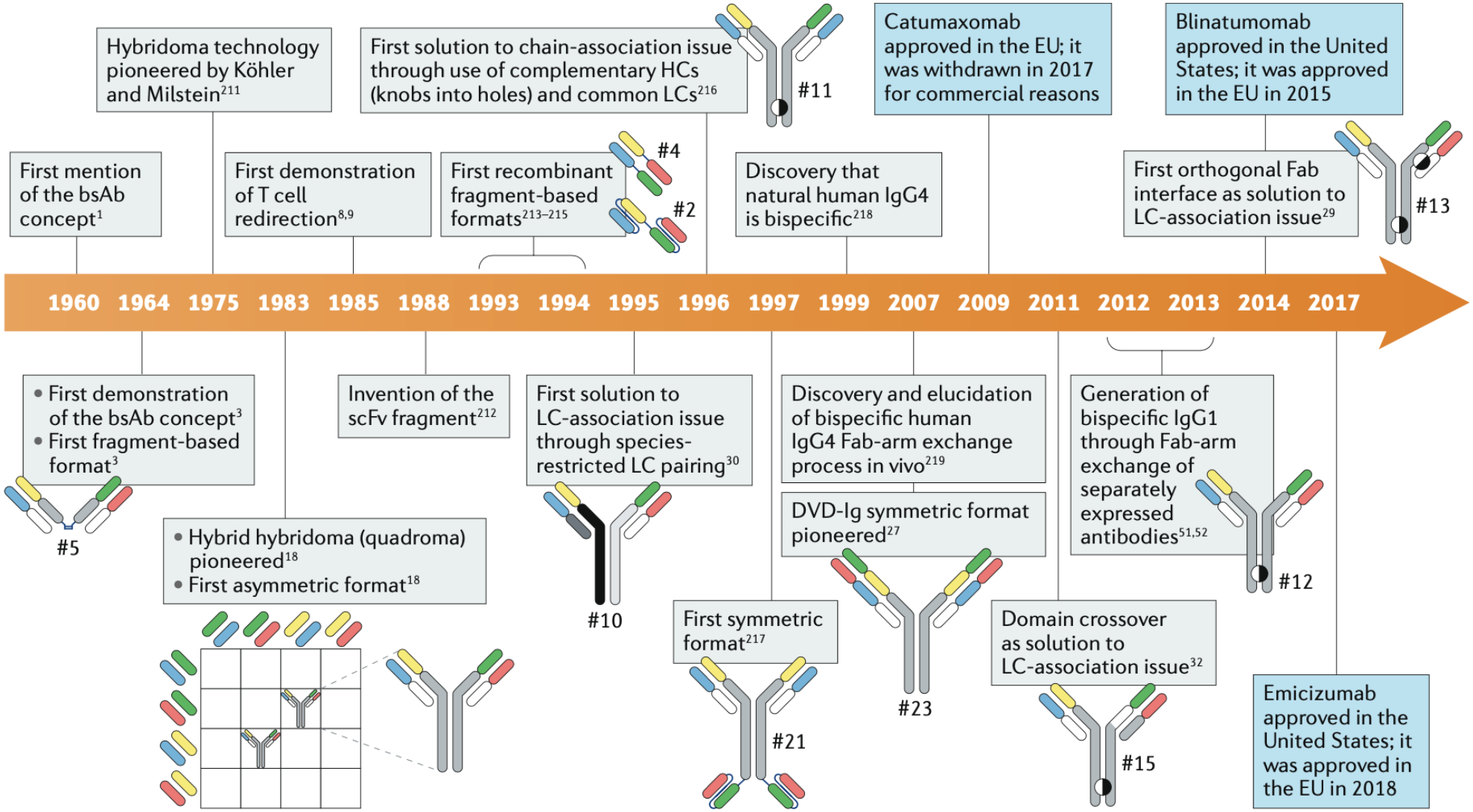
Guselkumab iv/sc

Golimumab sc

Guselkumab iv/sc + Golimumab sc

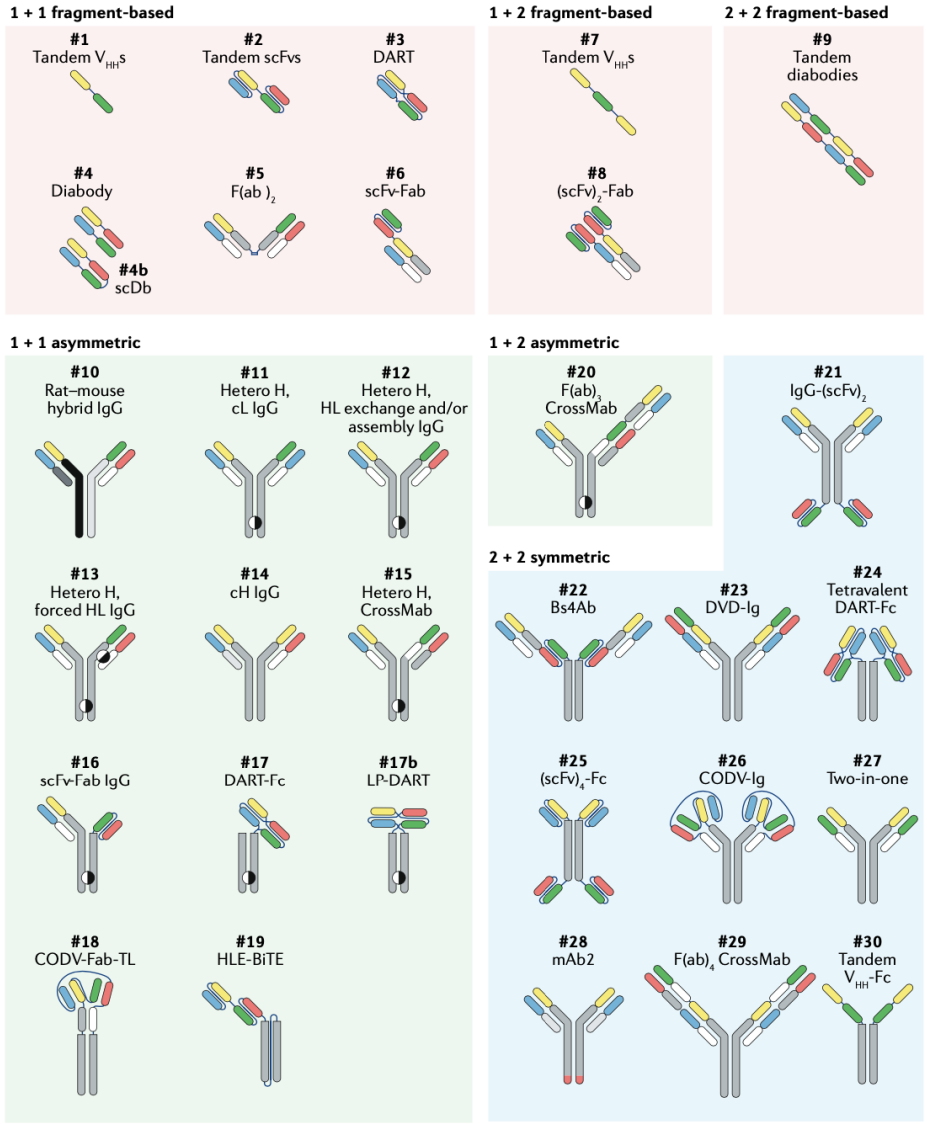

“AND ONE MORE THING”
-STEVE JOBS

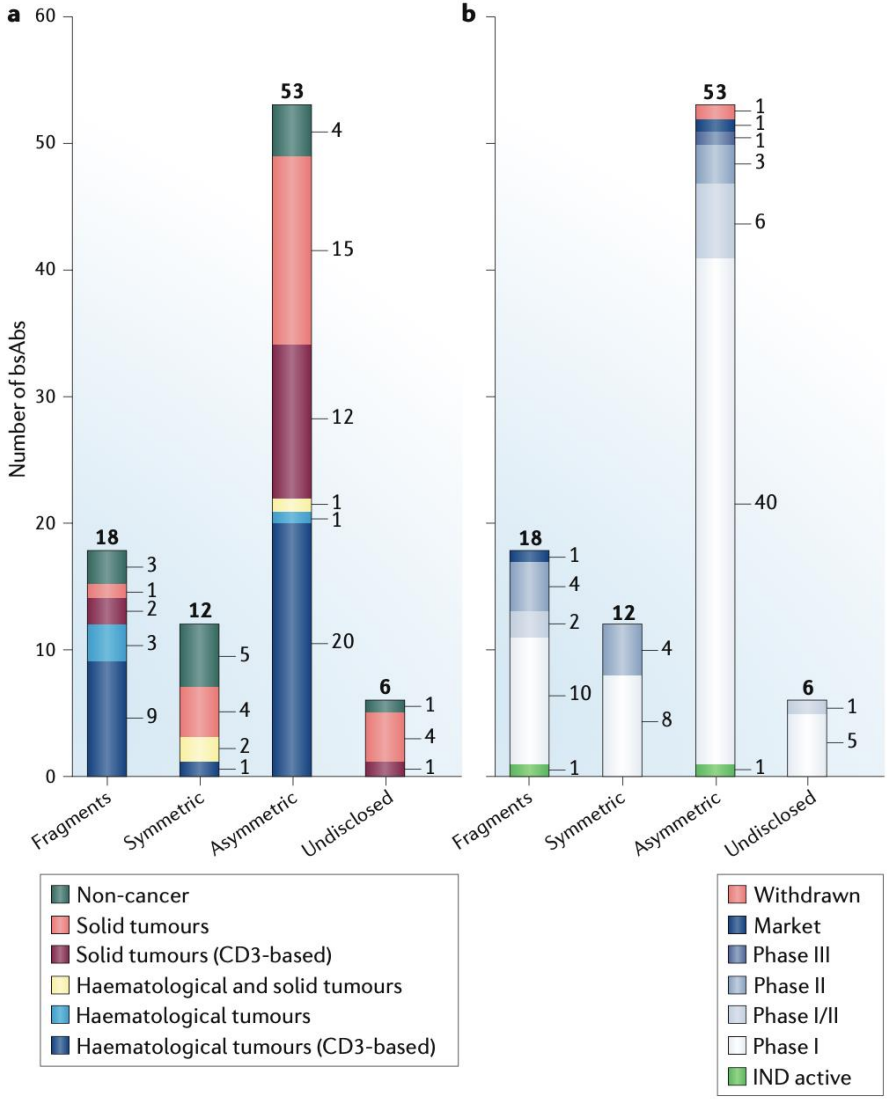
Bispecific antibodies



Labrijn et al. Nat Rev Drug Discovery 2019

Bispecific antibodies





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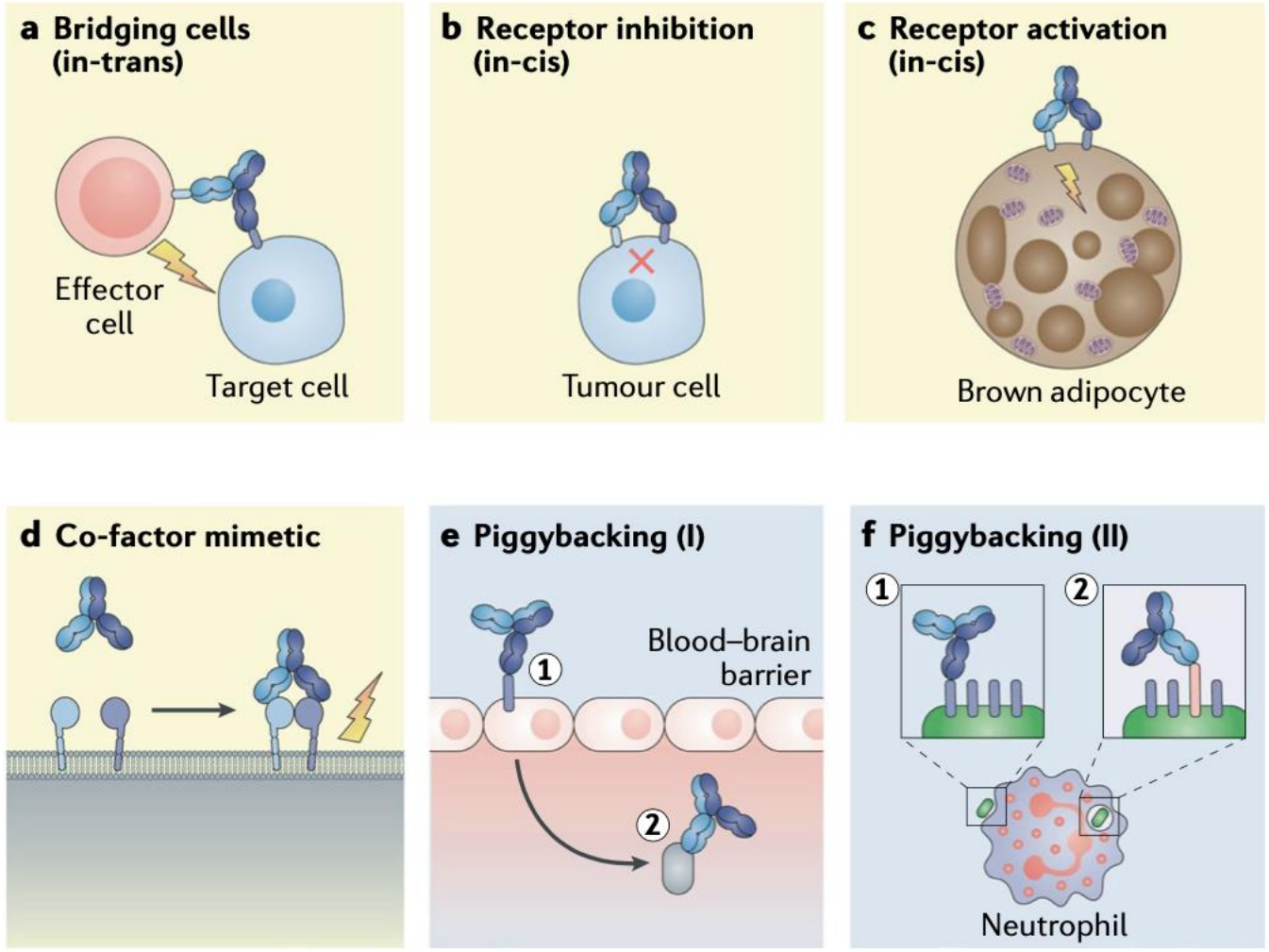
Bispecific antibodies: MoA



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Bispecific antibodies for noncancer indication

BsAb names (sponsors)	Targets	Format[a] and engineering	Disease area (selected indications)	Status (selected trials)
Bridging cells (in-trans): T cell redirection and/or activation				
MGD014 (Macrogenics)	CD3 x HIV-1 Env	• Tandem domain-exchanged Fv-Fc(G1) (#17, DART-Fc, ASYM, 1 + 1) • Hetero HH: T366W x T366S-L368A-Y407V (KiH), L234A-L235A (Fc-silencing), H435R (purification)	HIV-1 infection	Phase I (NCT03570918)
Bridging receptors (in-cis)				
MGD010, PRV-3279 (Macrogenics)	CD32b x CD79b	• Tandem domain-exchanged Fv (#3, DART, FRAG, 1 + 1)	Immune-mediated disorders (phase I in healthy volunteers)	Phase I (NCT02376036)
BFKB8488A, RG7992 (Genentech)	FGFR1 x KLB	• Hetero H, HL assembly IgG1 (#12, ASYM, 1 + 1) • Hetero HH: T366W x T366S-L368A-Y407V (KiH), N297G (Fc-silencing)	Diabetes (phase I in overweight volunteers with likely insulin resistance, patients with type 2 diabetes mellitus and patients with NAFLD)	Phase I (NCT02593331 and NCT03060538)
Cofactor mimetic				
Emicizumab, Hemlibra, ACE910, RO5534262 (Chugai, Roche)	FIXa x FX and/or FXa	• Hetero H, cL IgG4 (#11, ART-Ig, ASYM, 1 + 1) • Hetero HH: E356K x K439E, HL-pairing: cL, S228P (hinge-stabilization), G446del-K447del (reduction charge-heterogeneity), K196Q-F296Y (pI-engineering), H435R (purification)	Routine prophylaxis of patients with haemophilia A with and without FVIII inhibitors	Marketed
Piggyback				
MEDI3902 (AstraZeneca)	Psl x PcrV	• Fab-scFv-Fc(G1) (#22, SYM, 2 + 2)	Prevention of *Pseudomonas aeruginosa* pneumonia in mechanically ventilated subjects	Phase II (NCT02255760 and NCT02696902)
Piggyback (bispecific molecules for half-life extension)				
Vobarilizumab, ALX-0061 (Ablynx)	IL-6 R x HSA	• Tandem V_{HH} (#1, nanobody, FRAG, 1 + 1, anti-HSA for half-life extension)	SLE and rheumatoid arthritis	Phase II (NCT02518620 and NCT02437890)
Ozoralizumab, ATN103 (Ablynx)	TNF x HSA	• Tandem V_{HH} (#7, nanobody, FRAG, 1 + 2, anti-HSA for half-life extension)	Rheumatoid arthritis	Phase II (NCT01063803)

Data available as of 1 March 2019. ART-Ig, asymmetric reengineering technology-immunoglobulin; ASYM, asymmetric; bsAb, bispecific antibody; cL, common light; DART, dual-affinity re-targeting; Env, gp120 envelope glycoprotein; Fab, antigen-binding fragment; FGFR1, fibroblast growth factor receptor 1; FIXa, activated coagulation factor IX; FRAG, fragment-based; HSA, human serum albumin; Ig, immunoglobulin; IL-6R, IL-6 receptor; KiH, knobs into holes; KLB, β-klotho; NAFLD, non-alcoholic fatty liver disease; PcrV, *Pseudomonas aeruginosa* needle tip protein of the serotype-independent type III secretion system; pI, isoelectric point; Psl, *P. aeruginosa* persistence factor; scFv, single-chain variable fragment; SLE, systemic lupus erythematosus; SYM, symmetric; TNF, tumour necrosis factor; V_{HH}, heavy chain variable domain. [a]Format data provided in the first bullet point in cells in the third column include the bsAb format number (#) in FIG. 2, technology trade name, class and valency; see FIG. 2 for additional information on format class (FRAG, SYM or ASYM) and valency. Engineering data provided in the second bullet point in cells in the third column include additional constant region mutations, which were obtained from public documents (scientific literature, abstracts, posters and patent publications).

Labrijn et al. Nat Rev Drug Discovery 2019

Bispecific antibodies for noncancer indication

BsAb names (sponsors)	Targets	Format[a] and engineering	Disease area (selected indications)	Status (selected trials)
Targeting ligand redundancy				
AMG570, MEDI0700 (Amgen, AstraZeneca)	BAFF x B7RP1	• IgG–peptide fusion; IgG with carboxy-terminal BAFF-binding peptide (SYM, 2 + 2)	SLE and rheumatoid arthritis	Phase I (NCT02618967 and NCT03156023)
Tibulizumab, LY3090106 (Eli Lilly)	BAFF x IL-17A	• IgG4-$(scFv)_2$ (#21, SYM, 2 + 2) • S228P (hinge-stabilization)	Sjögren syndrome	Phase I (NCT03736772 and NCT02614716)
RO7040547, BITS7201A, RG7990 (Genentech)	IL-17 x IL-13	• Undisclosed	Asthma	Discontinued after phase I[b]
IL-23 × CGRP bsAb (Eli Lilly)	IL-23 x CGRP	• Undisclosed	Autoimmune diseases	Phase I
Romilkimab, SAR156597 (Sanofi)	IL-4 x IL-13	• Tandem Fv-IgG4 (#23,DVD-Ig, SYM, 2 + 2) • S228P (hinge-stabilization), L235E (Fc-silencing)	Diffuse cutaneous systemic sclerosis	Phase II (NCT02921971)
MEDI7352 (AstraZeneca)	NGF x TNF	• TNFR2-Fc fusion with carboxy-terminal anti-NGF scFv (SYM, 2 + 2)	Painful osteoarthritis of the knee and painful diabetic neuropathy	Phase II (NCT02508155 and NCT03755934)
Faricimab, RO6867461, RG7716 (Roche)	VEGFA x ANG2	• IgG1 (#15, CrossMab, ASYM, 1 + 1) • Hetero HH: T366W x T366S-L368A-Y407V (KiH), HL-pairing: CrossMab, L234A-L235A-P329G (Fc-silencing), I253A-H310A-H435A (FcRn knockout to increase plasma clearance)	Neovascular wet age-related macular degeneration and diabetic macular oedema	Phase III (NCT03622593, NCT03622580, NCT03823300 and NCT03823287)

Data available as of 1 March 2019. ANG2, angiopoietin 2; ASYM, asymmetric; B7RP1, B7-related protein 1; BAFF, B cell-activating factor; bsAb, bispecific antibody; CGRP, calcitonin gene-related peptide; DVD, dual variable domain; FcRn, neonatal Fc receptor; Ig, immunoglobulin; KiH, knobs into holes; NGF, nerve growth factor; scFv, single-chain variable fragment; SLE, systemic lupus erythematosus; SYM, symmetric; TNF, tumour necrosis, factor; VEGFA, vascular endothelial growth factor A. [a]Format data provided in the first bullet point in cells in the third column include the bsAb format number (#) in FIG. 2, technology trade name, class and valency; see FIG. 2 for additional information on format class (SYM or ASYM) and valency. Engineering data provided in the second bullet point in cells in the third column include additional constant region mutations, which were obtained from public documents (scientific literature, abstracts, posters and patent publications). [b]Molecules active in 2018 that were discontinued by March 2019.

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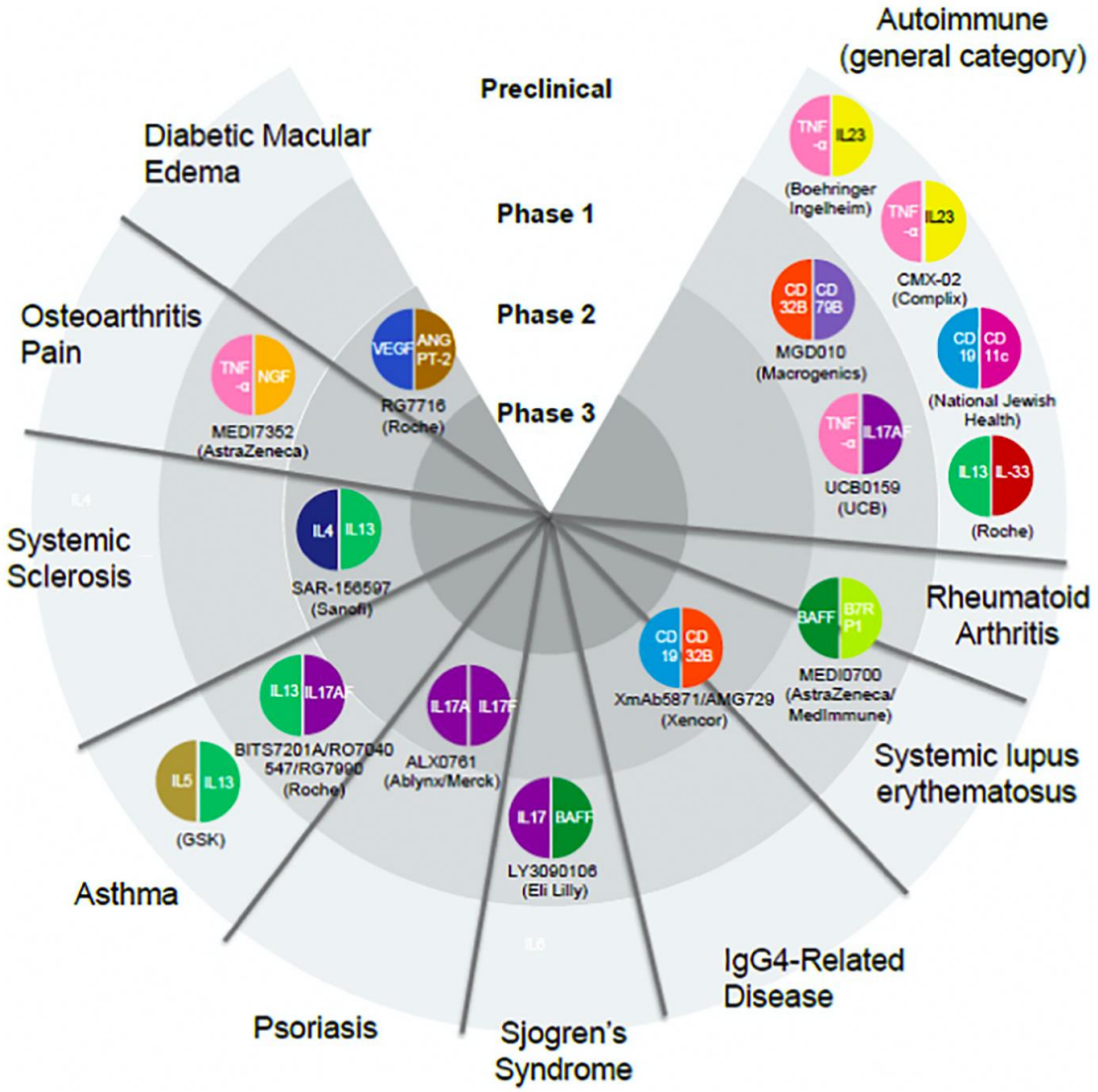
Bispecific antibodies for noncancer indication



Peyrin-Biroulet et al. Autoimm Rev 2019