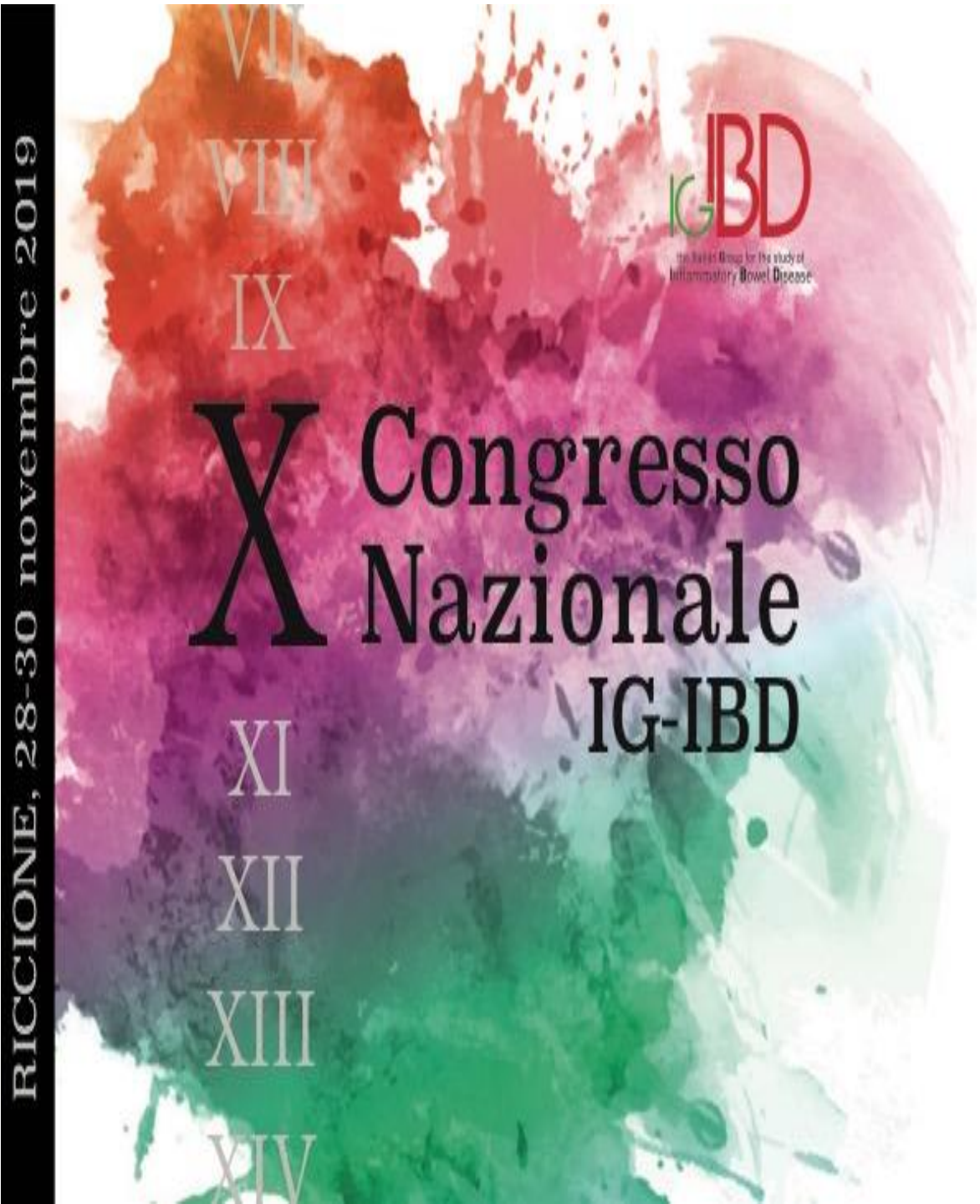


PERCORSO TERAPEUTICO B

28-29 NOVEMBRE 2019 SALA POLISSENA B

USTEKINUMAB IN IBD:
FROM THE EXPERIENCE IN CD TOWARDS THE LABEL IN UC

UNMET MEDICAL NEEDS IN THE ERA OF NEW BIOLOGICS

Mariabeatrice Principi

Curr Treat Options Gastro
DOI 10.1007/s11938-018-0173-3

Inflammatory Bowel Disease (G Lichtenstein, Section Editor)

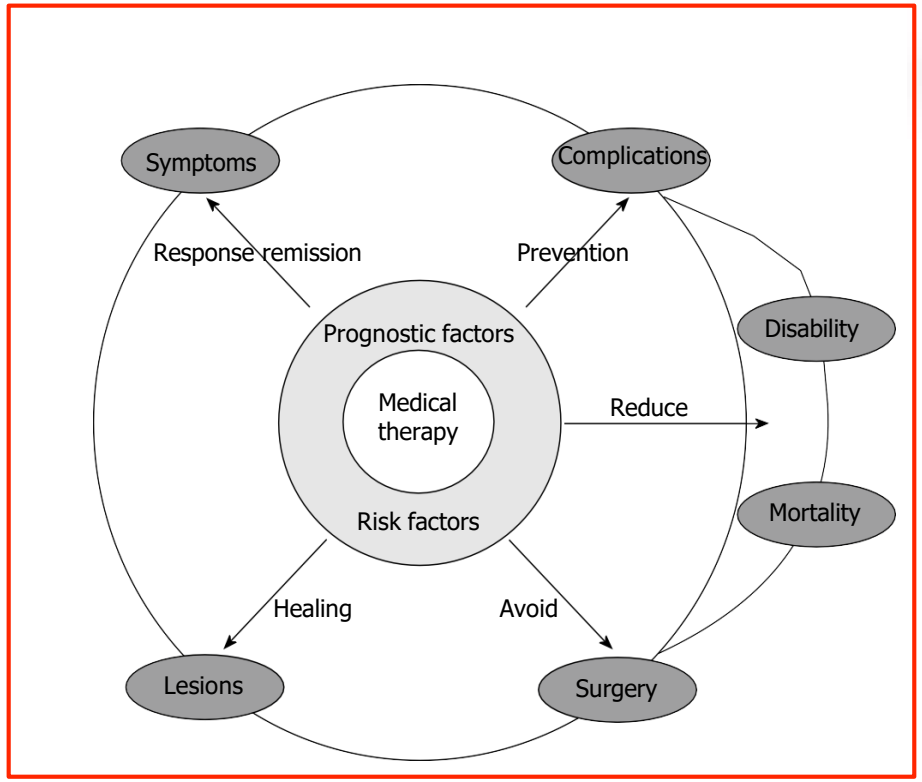
The Natural History of IBD: Lessons Learned

Petra Weimers, MD, PhD*
Pia Munkholm, MD, DMSci

Treatment

Disease course

Mortality risk



Latella; WJG 2012

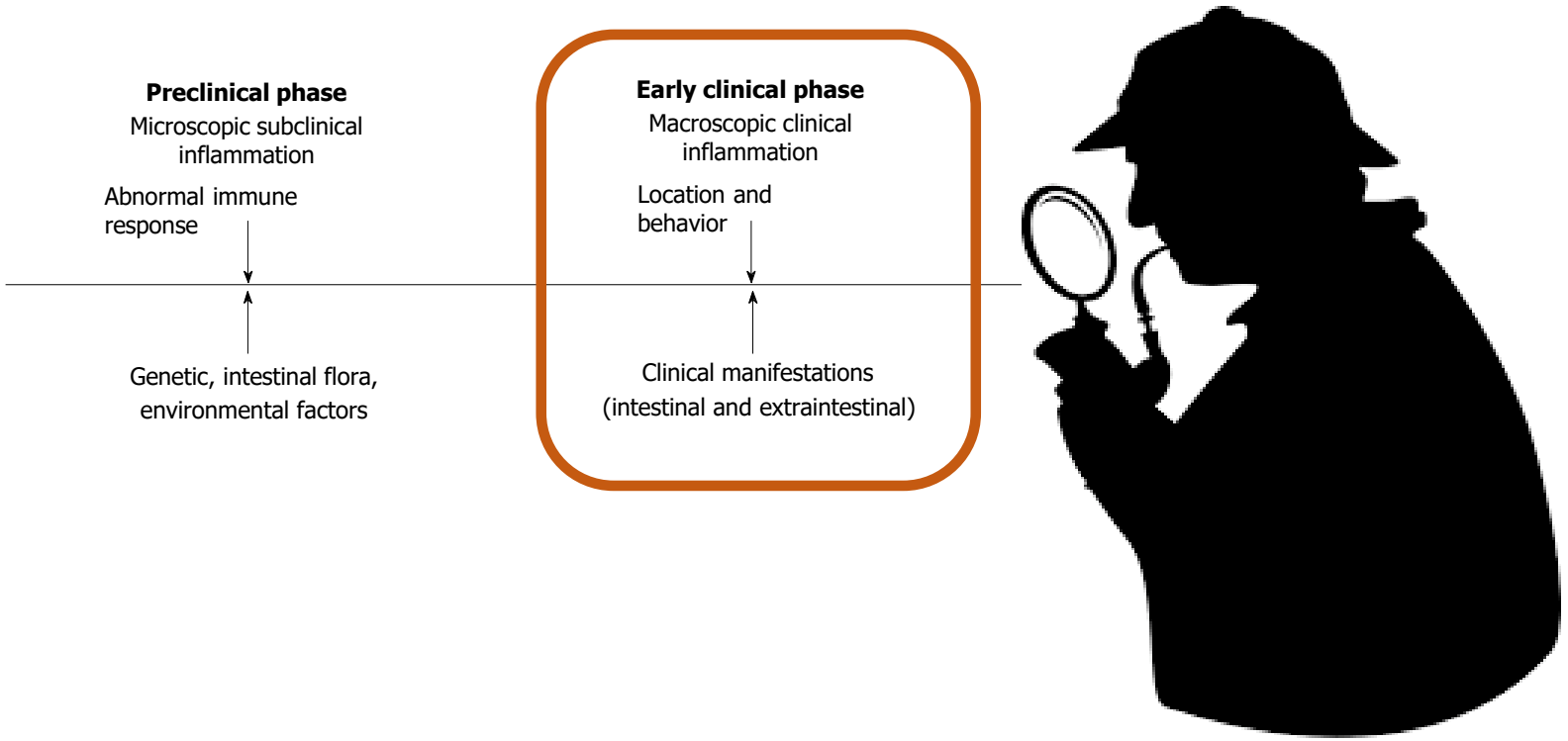
Goals of therapy in IBD

20 years ago …

Treat symptoms, induce remission and treat on flare

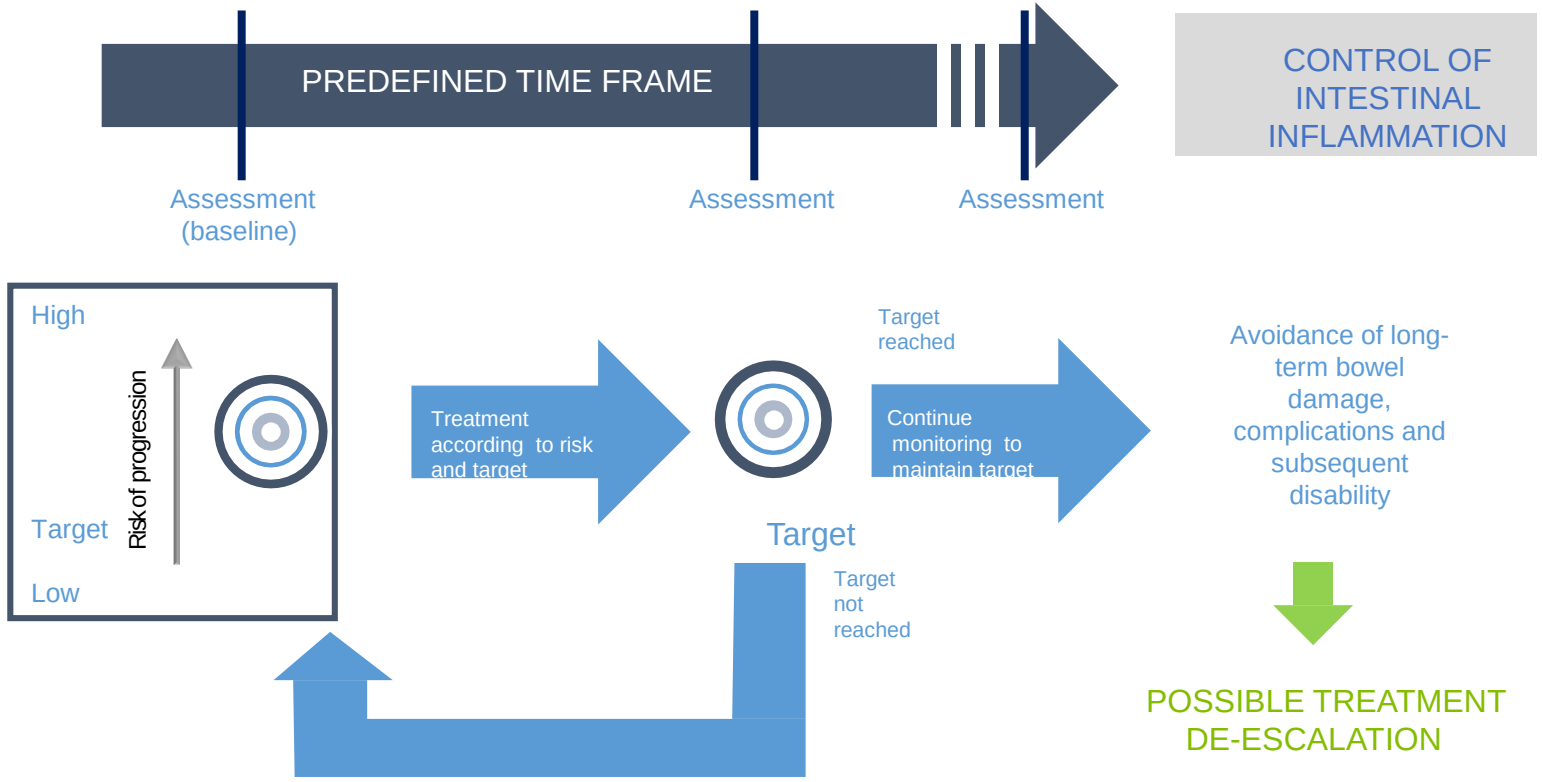
… Today in BIOLOGICAL ERA

Disease cure (early) with long-term strategy



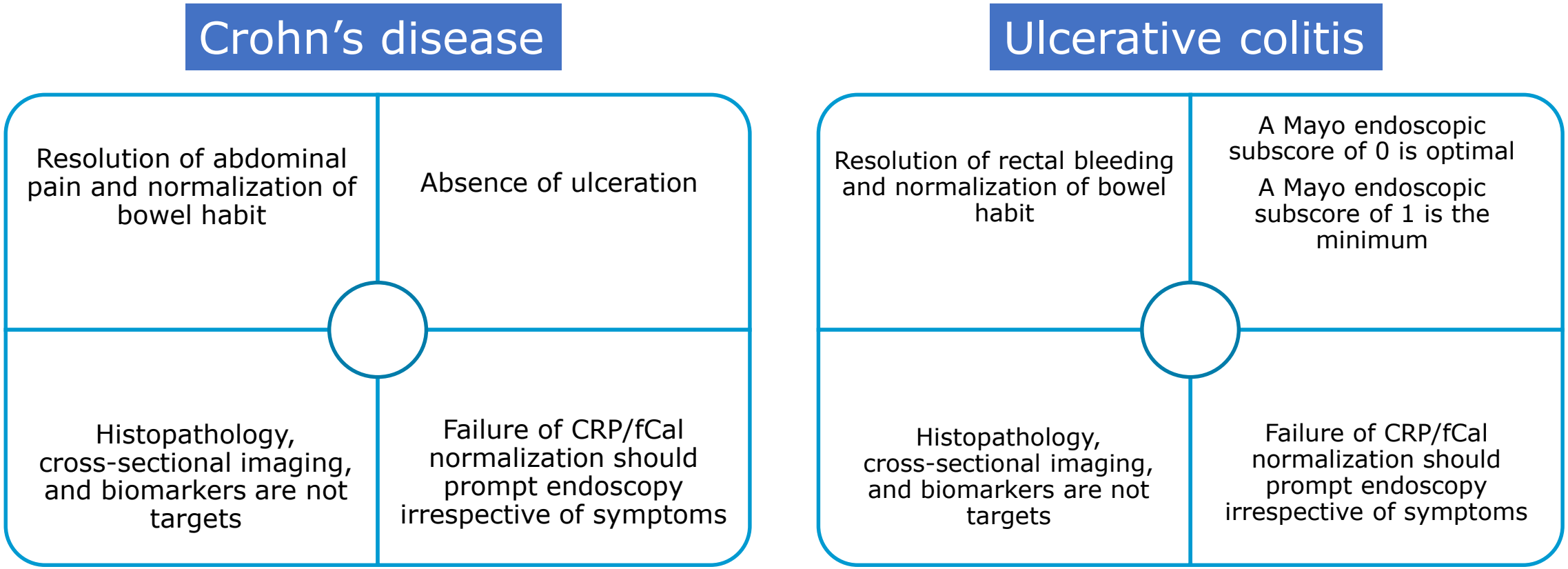
Latella G et al WJG 2012

Treat-to-target concept in IBD



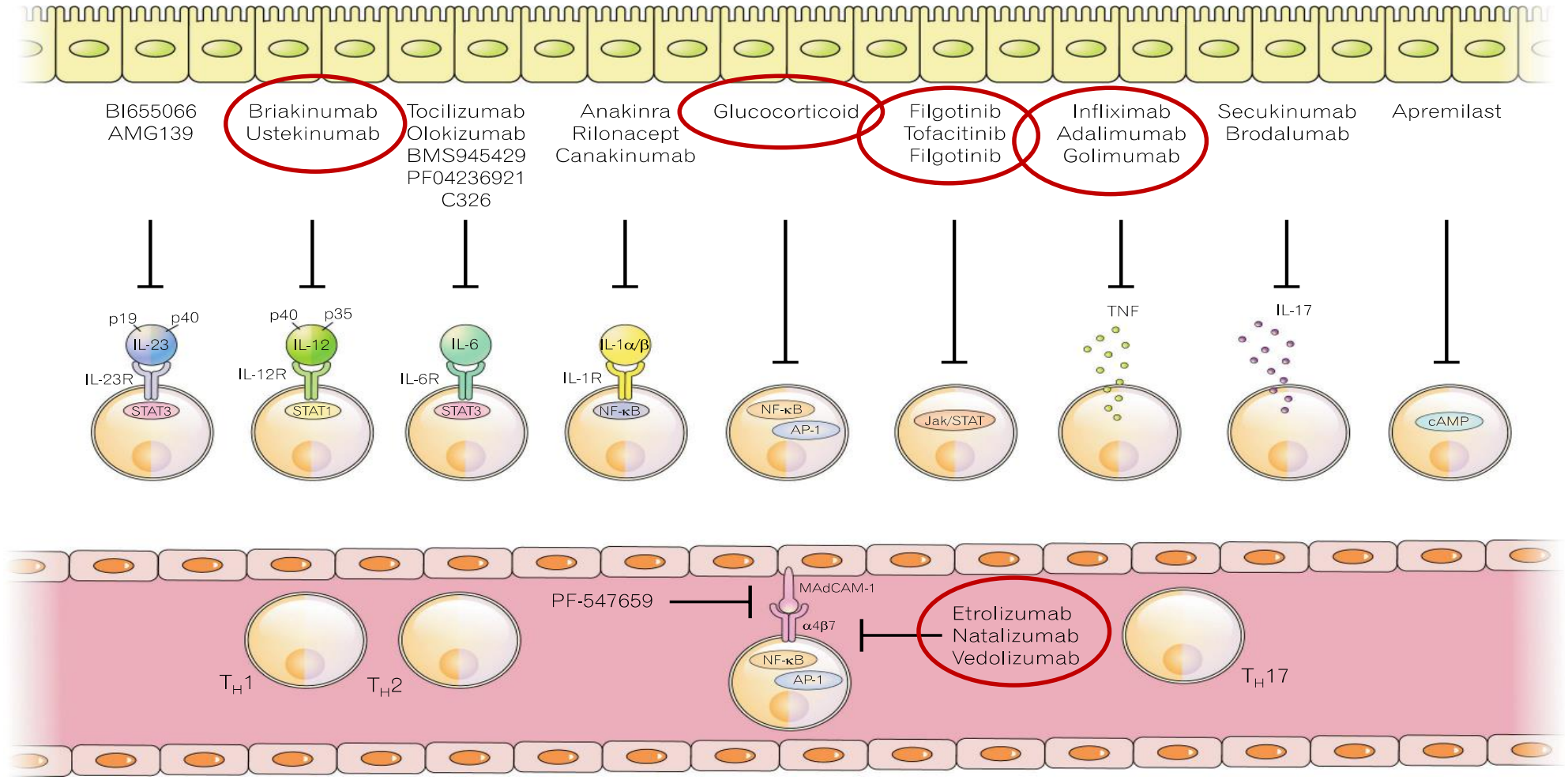
Bouguen G, et al. *Clin Gastroenterol Hepatol* 2015;13:1042-50; Colombel JF, et al. *Gastroenterology* 2017;152:351–61

STRIDE recommendations: What are the treatment goals in IBD?



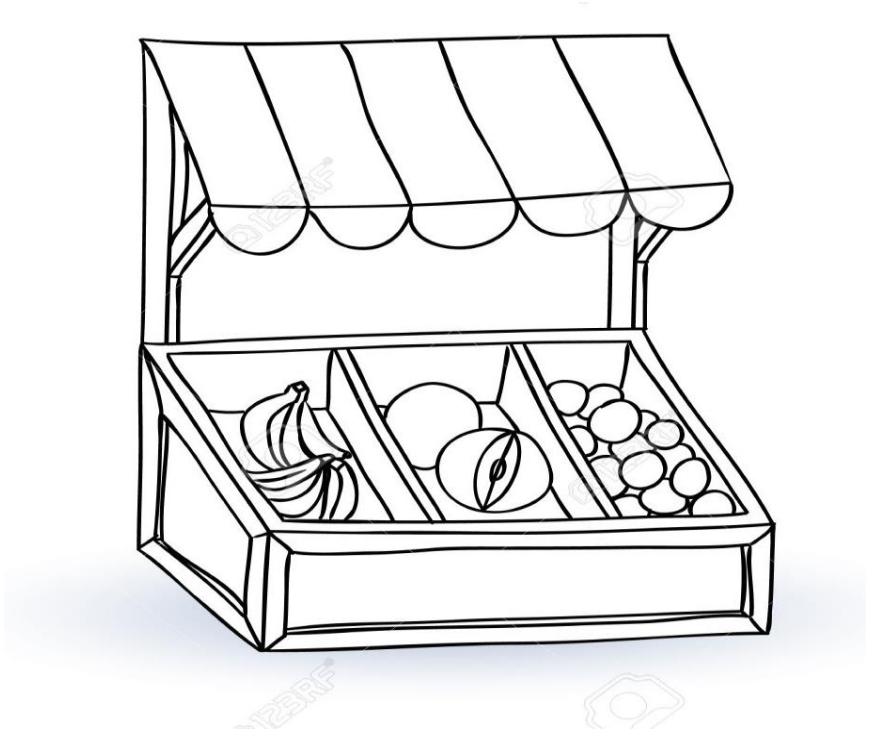
Peyrin-Biroulet L, et al. Am J Gastroenterol. 2015;110:1324-38.

Targets and drugs in IBD



S H Lee et al Intest Res 2018

"More" Biologics



New BIOLOGICS

New targets

More safety

GASTROENTEROLOGY 2008;135:1130–1141

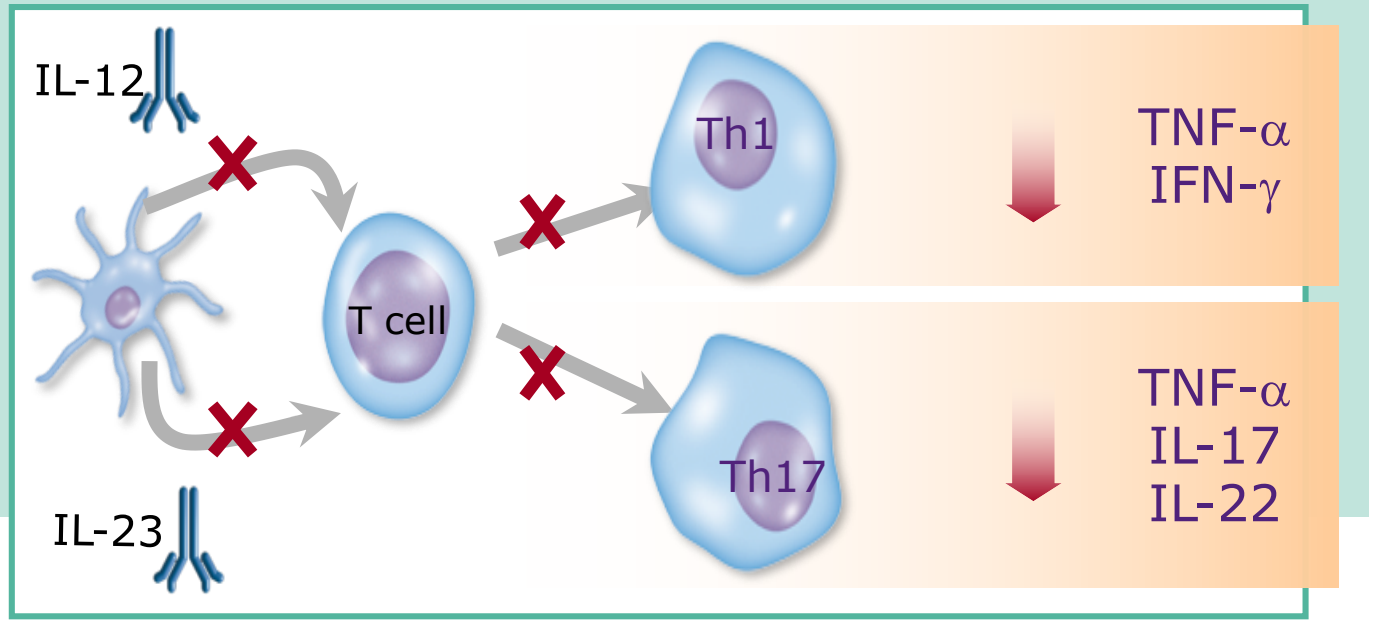
A Randomized Trial of Ustekinumab, a Human Interleukin-12/23 Monoclonal Antibody, in Patients With Moderate-to-Severe Crohn's Disease

WILLIAM J. SANDBORN,* BRIAN G. FEAGAN,‡ RICHARD N. FEDORAK,§ ELLEN SCHERL,‖ MARK R. FLEISHER,¶ SEYMOUR KATZ,# JEWEL JOHANNS,** MARION BLANK,** and PAUL RUTGEERTS,‡‡ for the Ustekinumab Crohn's Disease Study Group

Antibody binds to the p40 subunit of IL-12 and IL-23, preventing binding to their cell surface receptors

Differentiation and clonal expansion of Th1 and Th17 subsets is prevented

Down-regulation of inflammatory cytokines



1. Gately MK, et al. Annu Rev Immunol. 1998;16:495-521. 2. Wilson NJ, et al. Nat Immunol. 2007;8(9):950-7. 3. Nickoloff BJ, Nestle FO. J Clin Invest. 2004;113(12):1664-75. 4. Nestle FO et al. J Invest Dermatol. 2004; 123:xiv-xxv.

Blockade of Cell-Activating Signals: ustekinumab

Ustekinumab

- Ustekinumab – antibody blocking IL-12/23 Interleukins
- Blocks IL-12/23 mediated Activation of T-cells, Agents normalize IL-12/23 mediated signaling, cellular activation, and and cytokine production, thereby reducing inflammation
- Currently approved for treatment of Psoriasis and Psoriatic Arthritis (tradename: Stelera®)
- IV induction then Subcutaneous every 4 weeks.

UNMET MEDICAL NEEDS IN THE ERA OF «OLD» BIOLOGICS?

To which extent do conventional and biologic therapies meet treatment goals?

	5-ASA	Steroids	AZA	MTX	Anti-TNFα	Anti-integrins
Short-term endpoints						
Clinical remission	UC[1]	CD[2]+UC[3]	CD[2]+(UC[1])	CD[4]	CD[5]+UC[3]	CD[11]+UC[10]
Steroid-free remission	?	No	(CD[2]+UC[1])	CD[4]	CD[5,6]+UC[3]	CD[11]+UC[10]
Clinical and mucosal remission (deep remission)	UC[1]	UC[3]	CD[7]+UC[1]	?	CD[5,6]+UC[3]	CD[11]+UC[10]
Long-term disease modification						
Reduction of surgical risk	?	?	Conflicting[8]	?	CD+UC[9]	?
Reduction of disability	?	?	?	?	?	?
Reduction of 'damage'	?	?	?	?	?	?

5-ASA, 5-aminosalicylic acid; AZA, azathioprine; MTX, methotrexate. 1. Ardizzone S, et al. Gut. 2006;55:47-53; 2. Candy S, et al. Gut. 1995;37:674-48; 3. Sandborn WJ, et al. Gastroenterology. 2012;142:257-65; 4. Feagan B, et al. N Engl J Med. 1995;332:292-7; 5. Rutgeerts P, et al. Gastroenterology. 2012;142:1102-11; 6. Colombel JF, et al. N Engl J Med. 2010;362:1383-95; 7. D'Haens G, et al; Gastroenterology. 1997;112:1475-81; 8. Lakatos PL, et al. Am J Gastroenterol. 2012;107:579-88; 9. Peyrin-Biroulet L, et al. J Crohns Colitis. 2011;5:477-83. 10 Feagan BJ, et al. NEJM 2013; 369:699-710 11. Sandborn WJ NEJM 2013; 369: 711-20

Modified from S Danese

Hindawi
Gastroenterology Research and Practice
Volume 2019, Article ID 3108025, 9 pages
https://doi.org/10.1155/2019/3108025

Research Article

Unmet Medical Needs in the Management of Ulcerative Colitis: Results of an Italian Delphi Consensus

Marco Daperno,[1] Alessandro Armuzzi,[2,3] Silvio Danese,[4] Walter Fries,[5] Giuseppina Liguori,[6] Ambrogio Orlando,[7] Claudio Papi,[8] Mariabeatrice Principi,[9] Fernando Rizzello,[10] Angelo Viscido,[11] and Paolo Gionchetti[10]

		% consensus
Treatment		
1	There is a need for a treatment strategy that can induce sustained corticosteroid-free remission and mucosal healing in the majority of patients	95.1
2	There is a need for a therapy with rapid onset of action	75.6
3	There is a need for drugs that are associated with only minimal or no loss of response	95.1
4	There is a need for therapies that can effectively treat moderate-to-severe disease	80.5
5	There is an unmet need for individualised treatment based on reliable predictors of response	95.1
6	There is an unmet need for a therapeutic strategy that can reduce hospitalisation and need for surgery	85.4
Monitoring and risk management		
7	There is an unmet need for validated, noninvasive methods to monitor disease activity	75.6
8	There is an unmet need for management strategies with better benefit/risk ratio	75.6
9	There is a need for effective and appropriate strategies that can limit the risk of developing colorectal cancer	61.0
Patient-related issues		
10	There is an unmet need for therapies that are more compatible with patients' expectations and comorbidities	80.5
11	There is a need for consensus regarding assessment of quality of life, fatigue, psychological symptoms, social problems, and disability	85.4

✔ Loss of response to anti-TNFs

Molnar T at al J Gastroentestin Liver Dis 2012
Dignass A et al Crohn´s Colitis 2010

Optimizing biologic therapy

Escalation
De-escalation
Immunosuppressors
Withdrawal
Switch, *Swap*

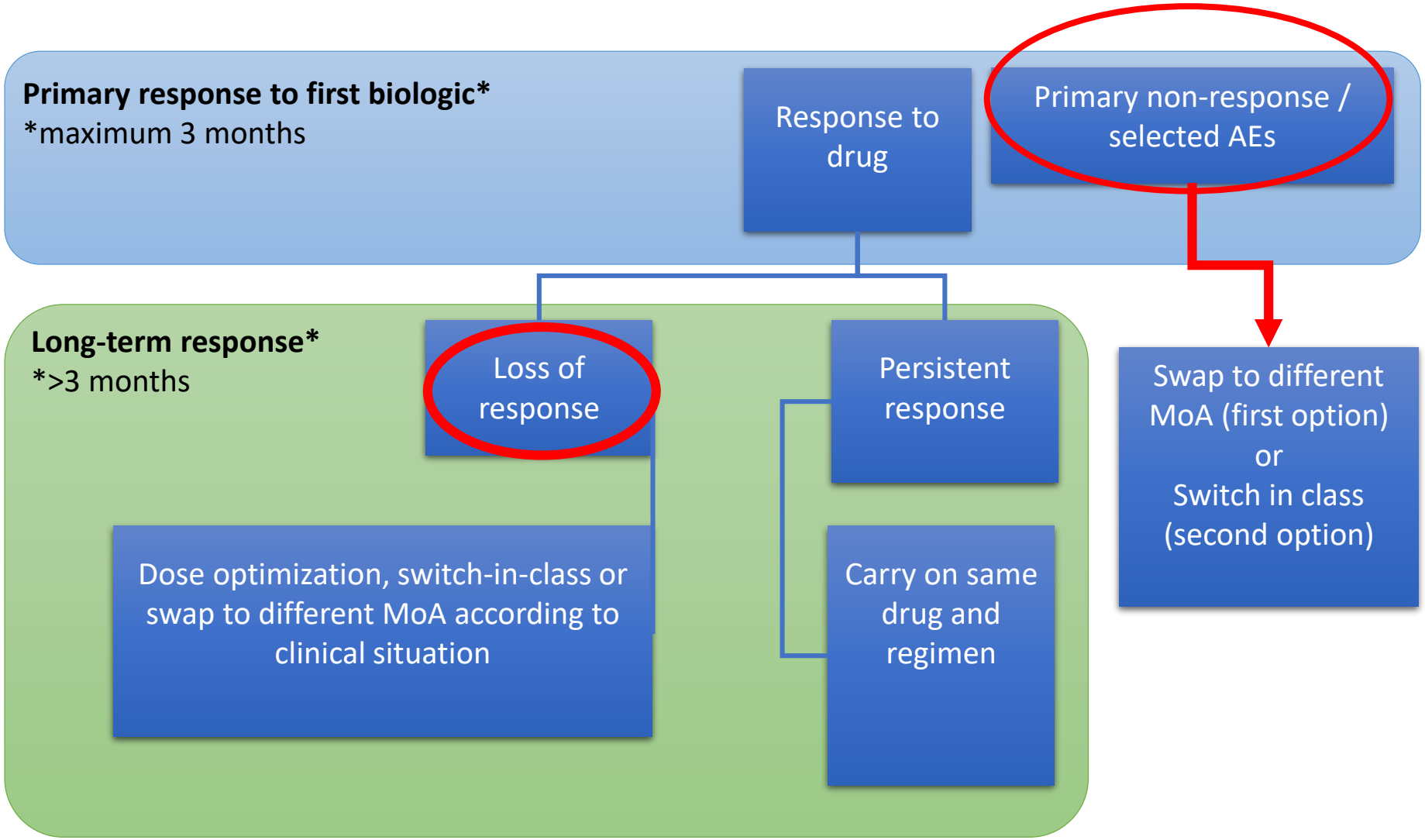
TDM

PROACTIVE

CLINICAL

REACTIVE

De Cruz P et al Inflamm Bowel Dis 2013



Armuzzi A, et al. Dig Liver Dis 2018;50(7):653-660

Journal of Crohn's and Colitis, 2019, 1–10
doi:10.1093/ecco-jcc/jjz110
Advance Access publication June 3, 2019
Original Article

Original Article

IM-UNITI: Three-year Efficacy, Safety, and Immunogenicity of Ustekinumab Treatment of Crohn's Disease

Stephen B. Hanauer,[a] William J. Sandborn,[b] Brian G. Feagan,[c] Christopher Gasink,[d] Douglas Jacobstein,[e] Bin Zou,[e] Jewel Johanns,[e] Omoniyi J. Adedokun,[e] Bruce E. Sands,[f] Paul Rutgeerts,[g] Willem J. S. de Villiers,[h] Jean-Frédéric Colombel,[f] Subrata Ghosh[i]

Number of patients who discontinued study agent through week 156

	Placebo	Ustekinumab 90 mg q12w	Ustekinumab 90 mg q8w	Dose adjusters[b]
N	61	84	82	71
Patients who discontinued *N* [%]	57 [93.4%]	23 [27.4%]	18 [22.0%]	24 [33.8%]
Reason for discontinuation				
Adverse events	11.5%	6.0%	8.5%	12.7%
Lack of efficacy	8.2%	6.0%	2.4%	8.5%
Protocol violation	0	0	0	0
Study terminated by sponsor	0	0	0	0
Physician decision	0	1.2%	2.4%	1.4%
Lost to follow-up	1.6%	1.2%	1.2%	0
Withdraw of consent	6.6%	11.9%	7.3%	8.5%
Death	0	1.2%	0	2.8%
Placebo patients discontinued due to unblinding	65.6%	0	0	0

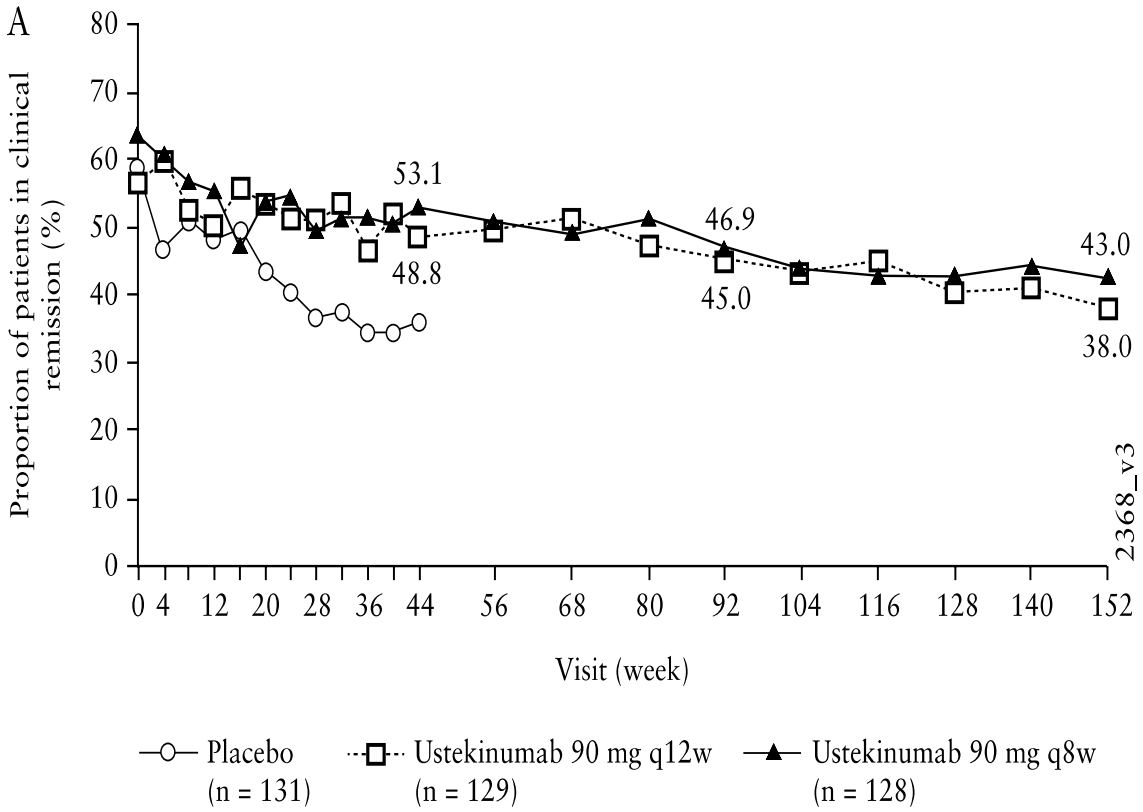
Through Week 156, 29.6% of ustekinumab-treated patients discontinued.

Journal of Crohn's and Colitis, 2019, 1–10
doi:10.1093/ecco-jcc/jjz110
Advance Access publication June 3, 2019
Original Article

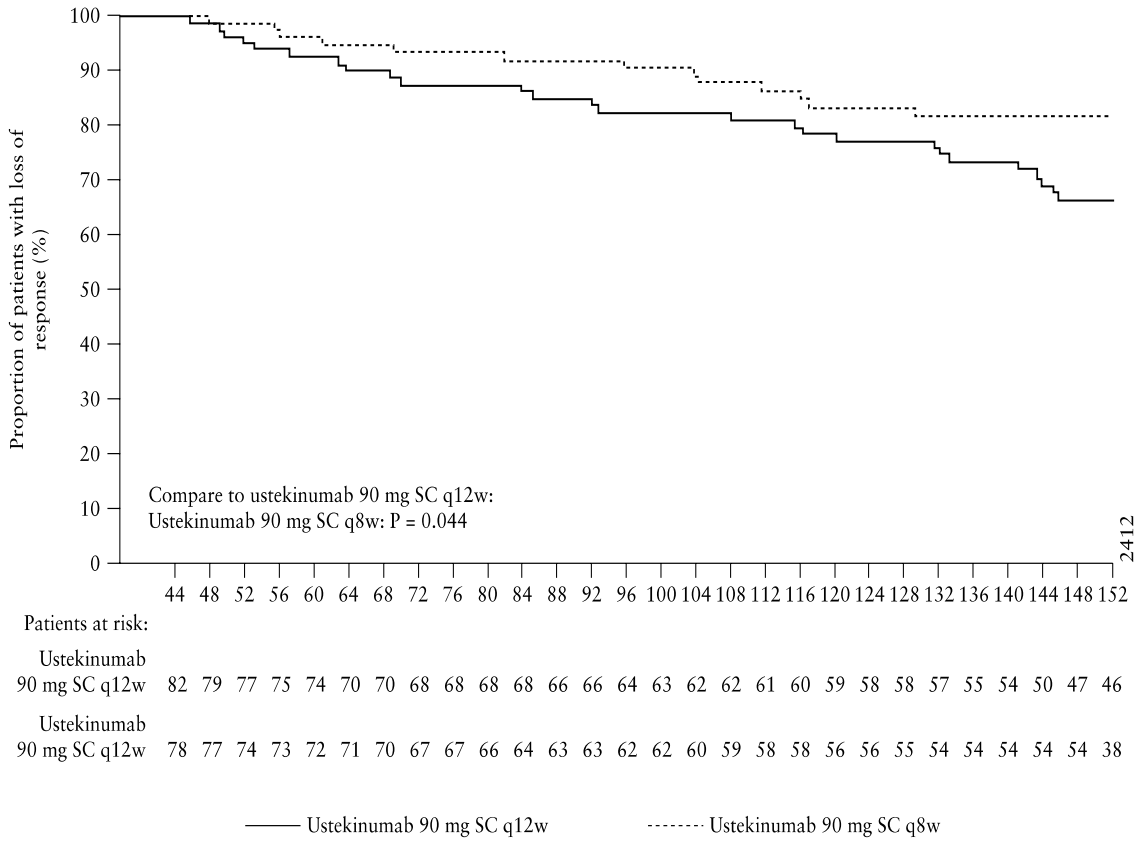
Original Article

IM-UNITI: Three-year Efficacy, Safety, and Immunogenicity of Ustekinumab Treatment of Crohn's Disease

Stephen B. Hanauer,[a] William J. Sandborn,[b] Brian G. Feagan,[c] Christopher Gasink,[d] Douglas Jacobstein,[e] Bin Zou,[e] Jewel Johanns,[e] Omoniyi J. Adedokun,[e] Bruce E. Sands,[f] Paul Rutgeerts,[g] Willem J. S. de Villiers,[h] Jean-Frédéric Colombel,[f] Subrata Ghosh[i]



Remission rates at Week 152 were:
56.3% for q12w and
55.1% for q8w

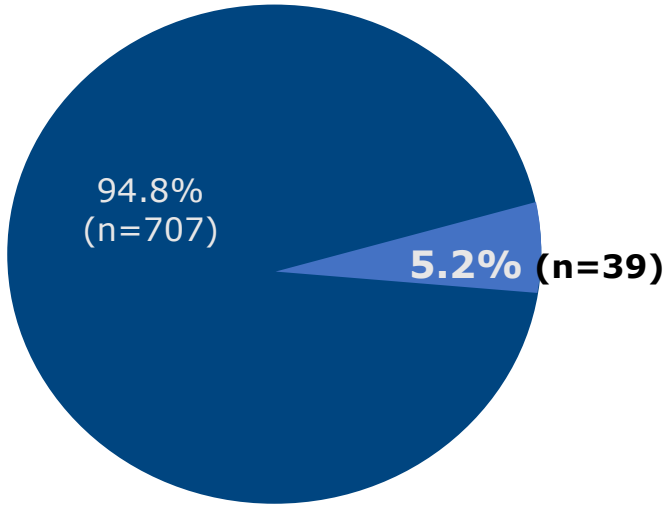


The time to loss of response was longer for the q8w group compared with the q12w group.
log rank test $p = 0.044$

Immunogenicity rates

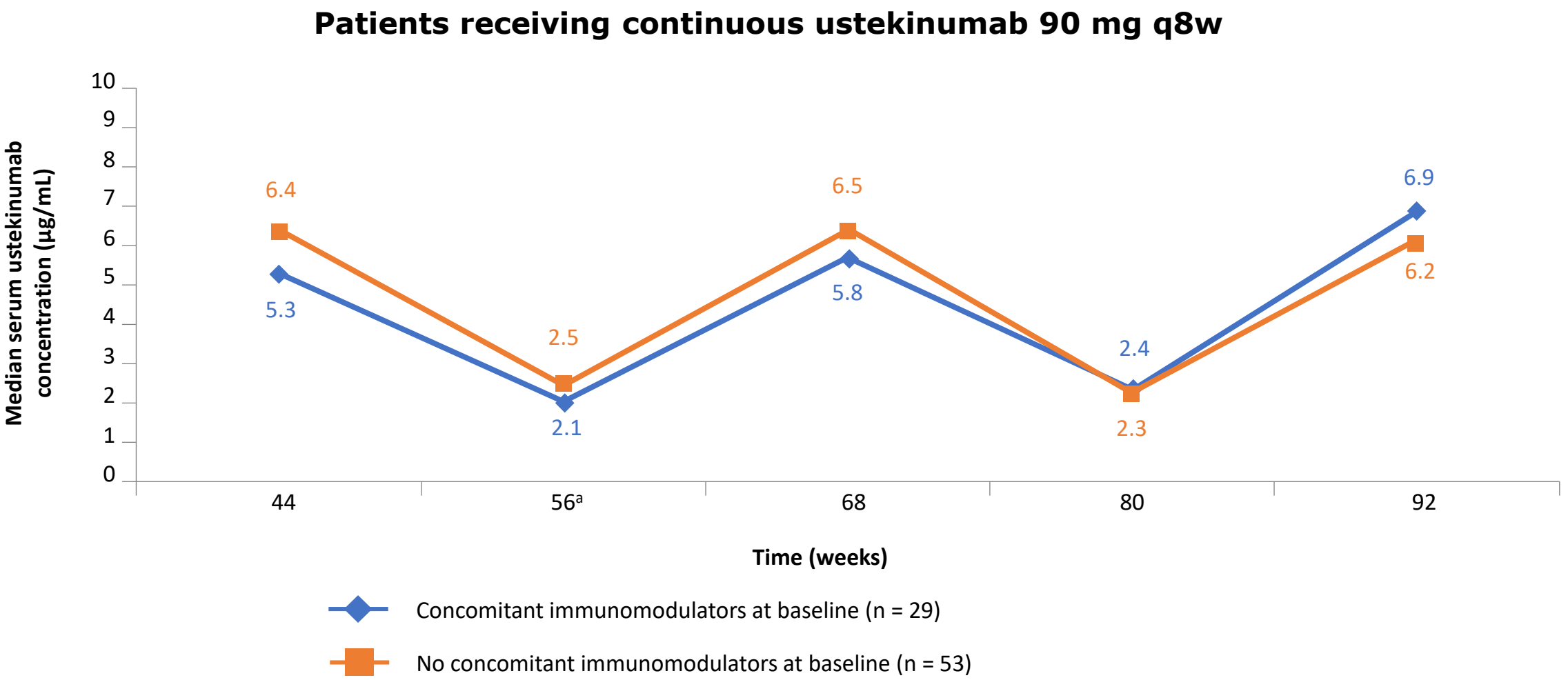
	Placebo SC[a]	90 mg SC q12w[a]	90 mg SC q8w	Previous dose adjustment[b]	Combined	All ustekinumab
N[c]	61	84	82	71	153	237
Antibody status *N* [%]						
Positive for antibodies to ustekinumab at any time through Week 156[d,e]	5 [8.2%]	4 [4.8%]	2 [2.4%]	5 [7.0%]	7 [4.6%]	11 [4.6%]
Negative for antibodies to ustekinumab through Week 156[d,f]	56 [91.8%]	80 [95.2%]	80 [97.6%]	66 [93.0%]	146 [95.4%]	226 [95.4%]

Long-term treatment with ustekinumab in psoriasis



Kimball AB, et al. J Eur Acad Dermatol Venereol.

Immunomodulator use did not affect serum ustekinumab concentrations in CD patients



[a] Serum levels measured prior to ustekinumab dosing.

Ghosh S, et al. Poster presented at ECCO 2019; P680.

Digestive and Liver Disease 51 (2019) 1232–1240

Contents lists available at ScienceDirect

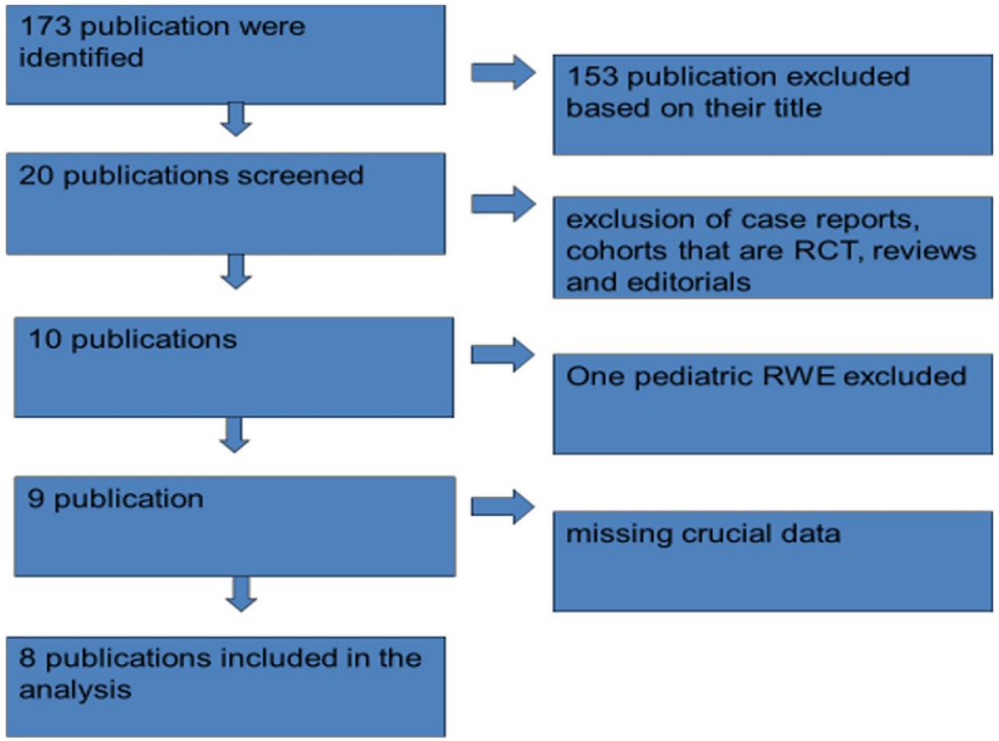
Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Effectiveness and safety of Ustekinumab for Crohn's disease; systematic review and pooled analysis of real-world evidence

Tal Engel[a,*], Diana E. Yung[b], Christopher Ma[c], Benjamin Pariente[d], Pauline WIls[d], Rami Eliakim[a], Bella Ungar[a], Shomron Ben-Horin[a], Uri Kopylov[a]



Digestive and Liver Disease 51 (2019) 1232–1240

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Effectiveness and safety of Ustekinumab for Crohn's disease; systematic review and pooled analysis of real-world evidence

Tal Engel[a,*], Diana E. Yung[b], Christopher Ma[c], Benjamin Pariente[d], Pauline WIls[d], Rami Eliakim[a], Bella Ungar[a], Shomron Ben-Horin[a], Uri Kopylov[a]

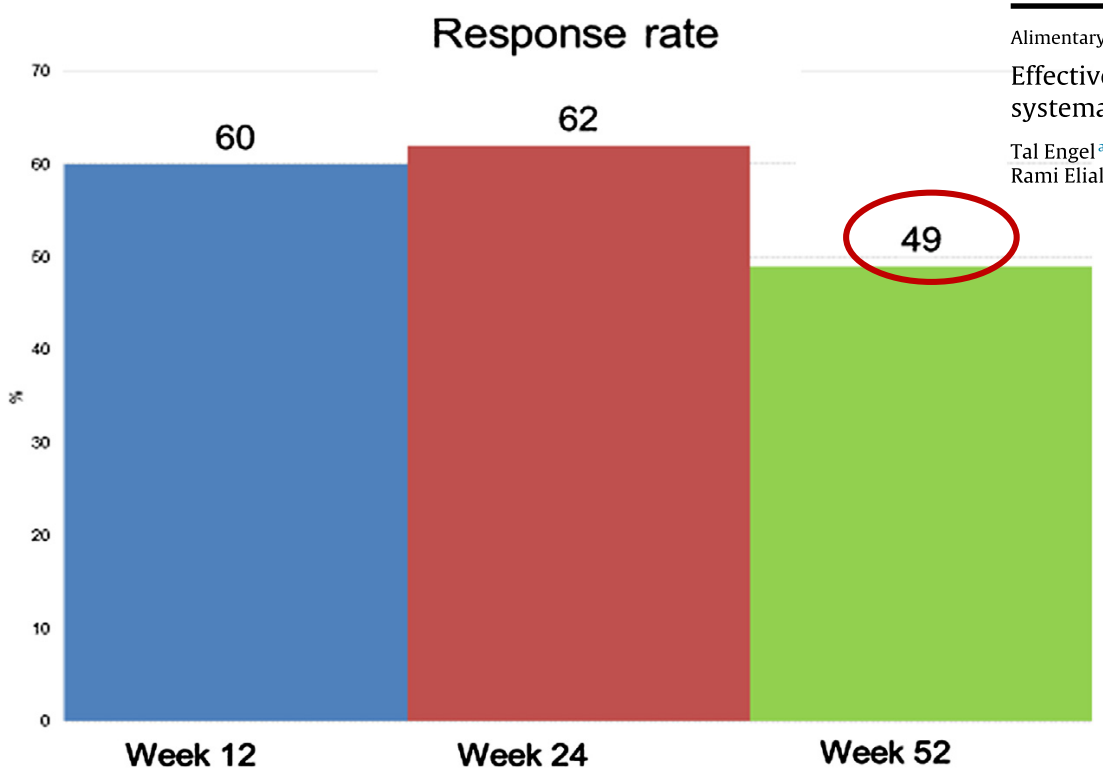


Fig. 2. Pooled efficacy of UST, response rate week 12, 24 and 52.

Pooled remission rate was 39% (95% CI (0.18-0.65)) at 24 weeks,
Pooled endoscopic response rate was 63% (95% CI (0.53-0.72) after approximately one year of UST;

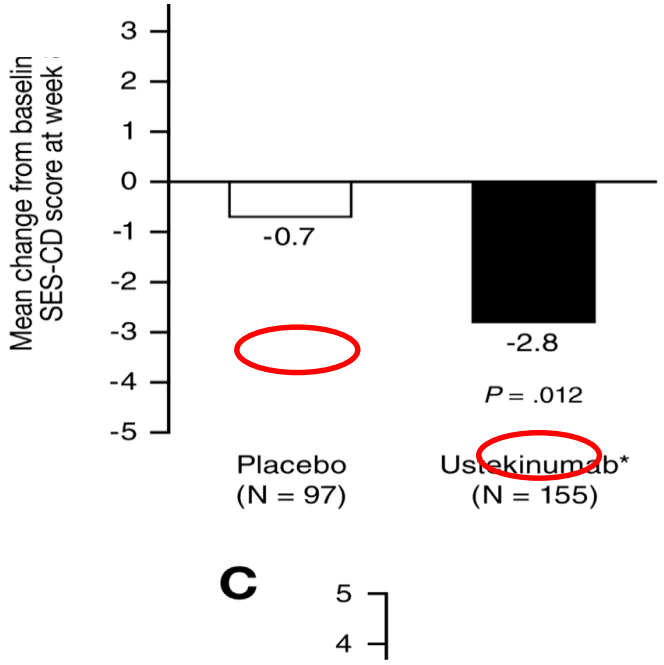
Engel T et al Dig Liv Dis 2019

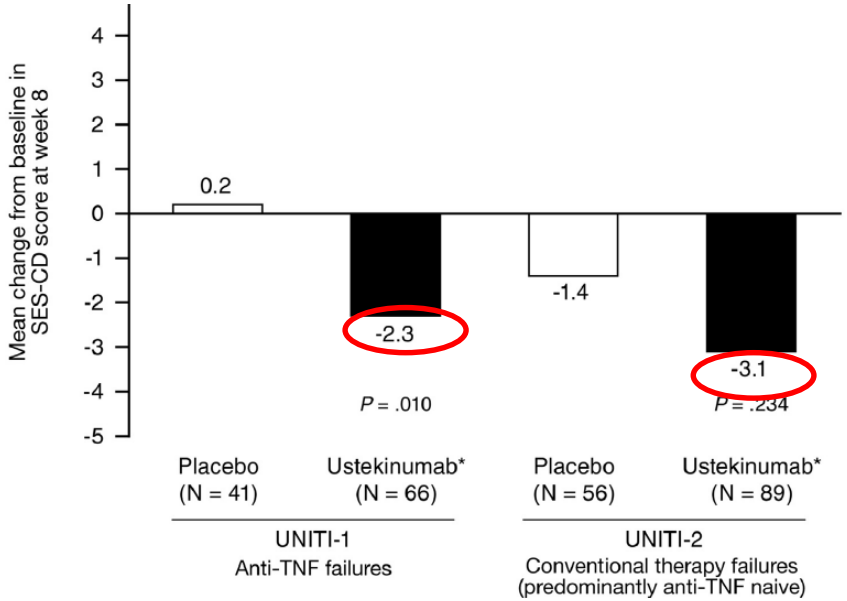
✔ Rapid Mucosal Healing Target

Gastroenterology 2018;155:1045–1058

Efficacy of Ustekinumab for Inducing Endoscopic Healing in Patients With Crohn's Disease

Paul Rutgeerts,[1] Christopher Gasink,[2] Daphne Chan,[2] Yinghua Lang,[2] Paul Pollack,[2] Jean-Frederic Colombel,[3] Douglas C. Wolf,[4] Douglas Jacobstein,[2] Jewel Johanns,[2] Philippe Szapary,[2] Omoniyi J. Adedokun,[2] Brian G. Feagan,[5] and William J. Sandborn[6]



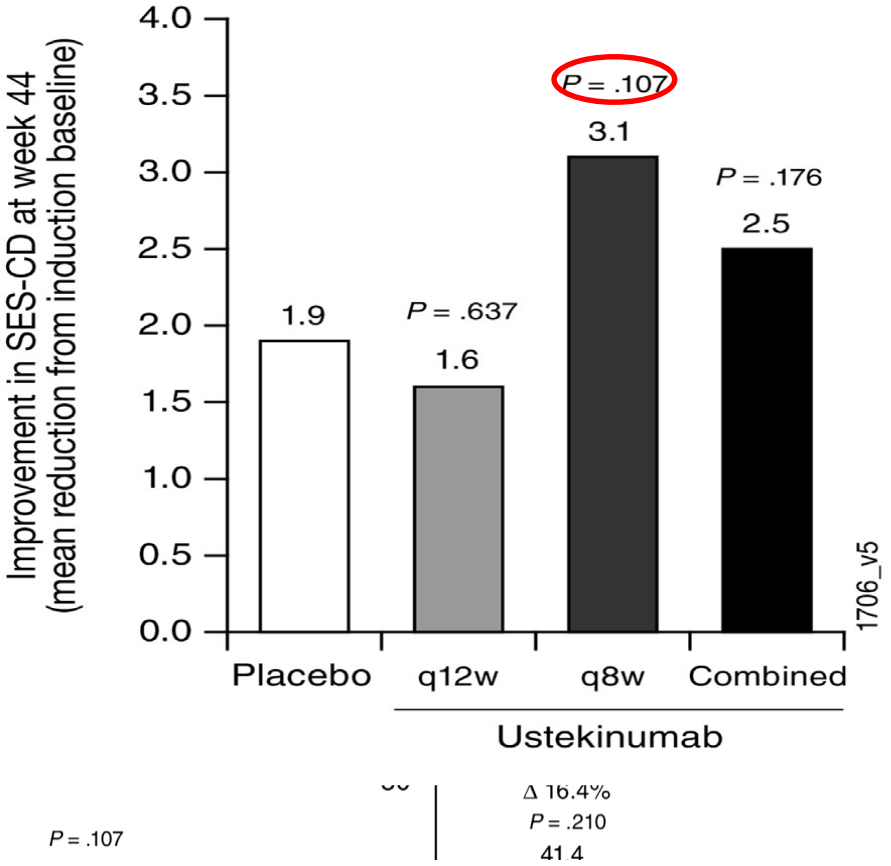


SES-CD reduction (SES-CD score > 3 points) from the induction baseline time point until week 8

Gastroenterology 2018;155:1045–1058

Efficacy of Ustekinumab for Inducing Endoscopic Healing in Patients With Crohn's Disease

Paul Rutgeerts,[1] Christopher Gasink,[2] Daphne Chan,[2] Yinghua Lang,[2] Paul Pollack,[2] Jean-Frederic Colombel,[3] Douglas C. Wolf,[4] Douglas Jacobstein,[2] Jewel Johanns,[2] Philippe Szapary,[2] Omoniyi J. Adedokun,[2] Brian G. Feagan,[5] and William J. Sandborn[6]



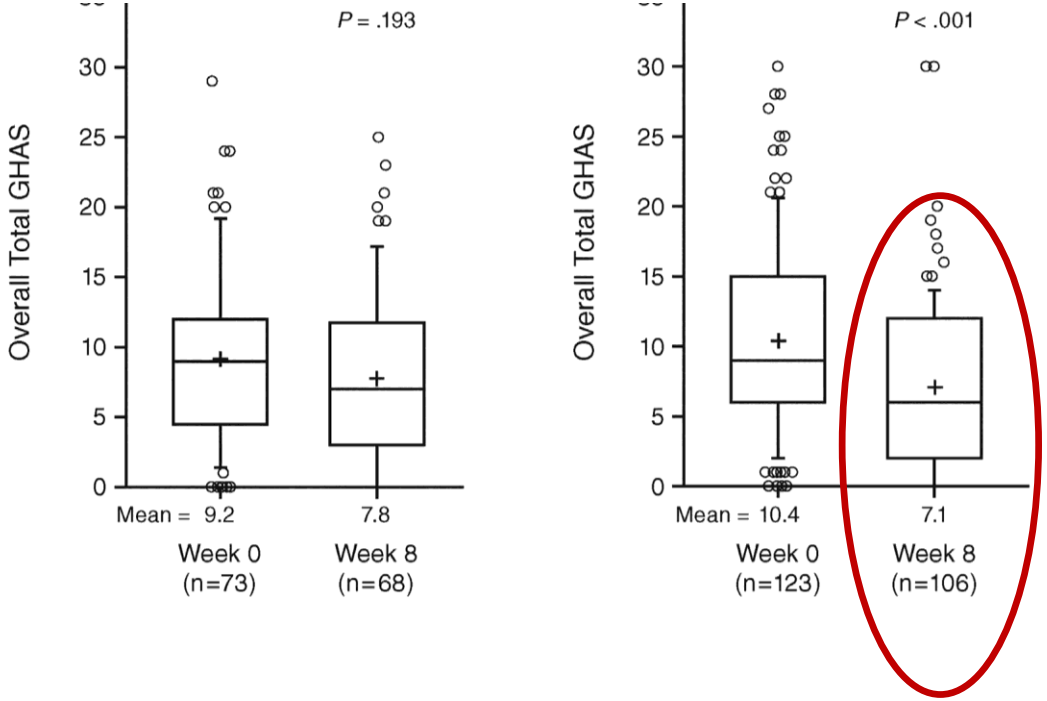
SES-CD reduction (SES-CD score > 3 points)
from the induction baseline time point until week 44

Gastroenterology 2019;157:1019–1031

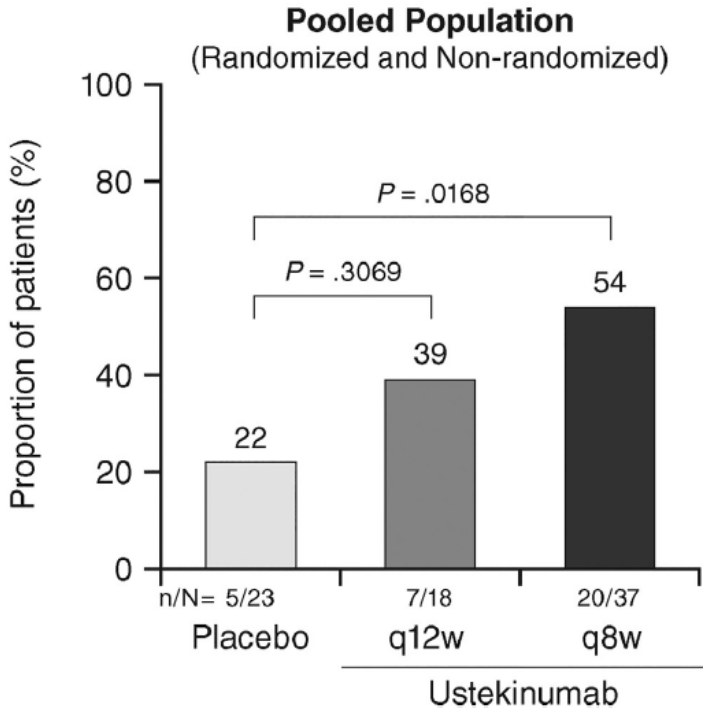
Effects of Ustekinumab on Histologic Disease Activity in Patients With Crohn's Disease

Katherine Li,[1] Joshua R. Friedman,[1] Daphne Chan,[1] Paul Pollack,[1] Feifei Yang,[1] Douglas Jacobstein,[1] Carrie Brodmerkel,[1] Christopher Gasink,[2] Brian G. Feagan,[3] William J. Sandborn,[4] Paul Rutgeerts,[5] and Gert De Hertogh[5]

Analysis post-hoc of UNITI-1 and UNITI-2 and IM-UNITI studies

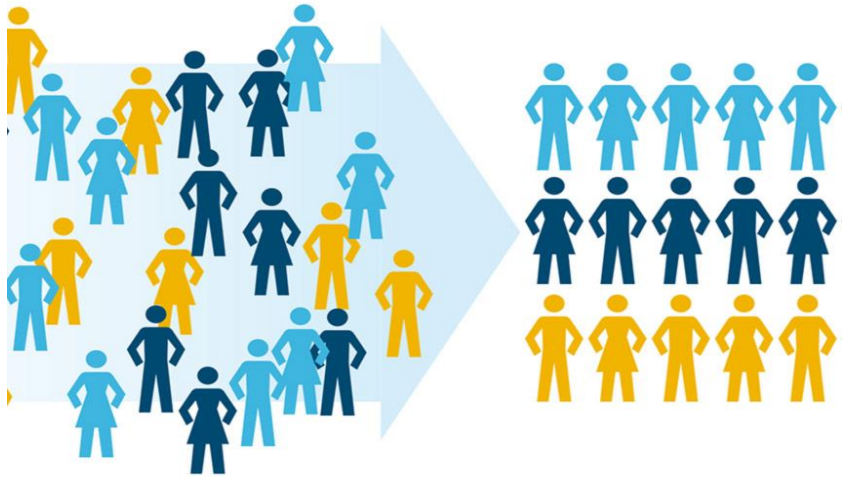


Mean overall global histology activity score (GHAS) between patients receiving ustekinumab and placebo at week 0 and 8 in the randomized induction population



Proportion of randomized maintenance and pooled population who achieved histologic response (ie, ≧50% drop of overall GHAS from baseline) at week 44.

✔ PROFILING



Indolent

Aggressive

Predictors of biologics *indication*

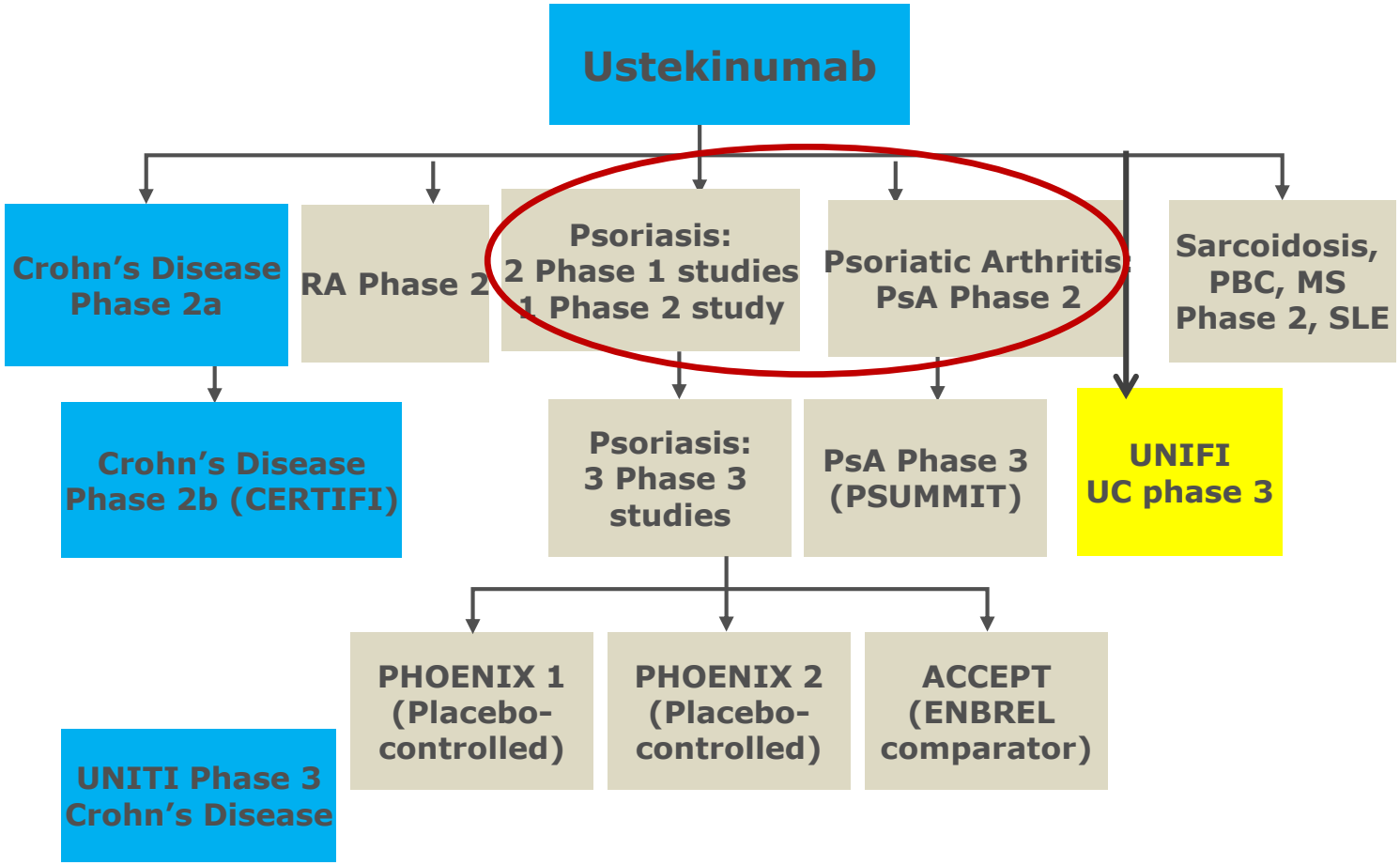
Predictors of biologics *efficacy*

Beaugerie L *et al. WJG 2012*

✔ Patient phenotype

EIMS
PERIANAL DISEASE

Ustekinumab development program Psoriasis, PsA and CD clinical studies



Clinical development of emerging drugs in spondyloarthritis.

Drug	Mechanism	Indication	Primary end point	Phase/Status	ClinicalTrials.gov ID/ Name	Sponsor
Secukinumab	IL-17A	nr-axSpA	ASAS40 at week 16	III, ongoing	NCT02696031	Novartis
Ixekizumab	IL-17A	nr-axSpA	ASAS40 at week 16	III, ongoing	NCT02757352, COAST-X	Eli Lilly
Bimekizumab	IL-17A,F	AS	ASAS40 at week 12	II, completed	NCT02963506	UCB
		AS	ASDAS change at week 12	II, recruiting	NCT03215277	
		AS	Safety and efficacy	II, ongoing	NCT03355573	
		PsA	ACR50 at week 12	II, completed	NCT02969525	
Brodalumab	IL-17 A receptor	axSpA	ASAS20 at week 16	II, withdrawn	NCT02429882	Amgen
		axSpA	ASAS40 at week 16	III, ongoing	NCT02985983	Kyowa Hakko Kirin Co.
		PsA	ACR20 at week 16	III, terminated	NCT02029495, AMVISION-1	Valeant
		PsA	ACR20 at week 16	III, completed	NCT02024646, AMVISION-2	Amgen
BCD-85	IL-17A	AS	ASAS20 at week 16	II, completed	NCT02763111	Biocad
		AS	ASAS40 at week 16	III, recruiting	NCT03447704	
		PsA	ACR20 at week 24	III, recruiting	NCT03598751, PATERA	
Ustekinumab	IL-12/IL-23, p40 subunit	AS	ASAS40 at week 24	III, terminated	NCT02437162	Janssen
		AS, TNFi-IR	ASAS40 at week 24	III, terminated	NCT02438787	
		nr-axSpA	ASAS20 at week 24	III, terminated	NCT02407223	
Risankizumab	IL-23, p19 subunit	PsA	ACR20 at week 16	II, completed	NCT02719171	Abbvie
		PsA	ACR20 at week 24	III, not yet recruiting	NCT03675308	
		PsA	ACR20 at week 24	III, not yet recruiting	NCT03671148, IMMpact2	
Tildrakizumab	IL-23, p19 subunit	axSpA	ASAS40 at week 24	II, ongoing	NCT02980705	Sun Pharma
		PsA	Response at week 24	II, ongoing	NCT02980692	
Guselkumab	IL-23, p19 subunit	PsA	ACR20 at week 24	III, ongoing	NCT03158285	Janssen
		PsA	ACR20 at week 24	III, ongoing	NCT03162796, Discover-1	
Apremilast	PDE4 inhibitor	AS	ASAS20 at week 16	III, ongoing	NCT01583374, POSTURE	Celgene
Tofacitinib	Pan-JAK inhibitor	AS	ASAS20 at week 12	II, completed	NCT01786668	Pfizer
		AS	ASAS20 at week 16	III, recruiting	NCT03502616	
Upadacitinib	JAK1 inhibitor	AS	ASAS40 at week 14	IIb/III, ongoing	NCT03178487, SELECT Axis 1	Abbvie
		PsA	ACR20 at week 12	III, recruiting	NCT03104400, SELECT-PsA1	
		PsA	ACR20 at week 12	III, recruiting	NCT03104374, SELECT-PsA2	
Filgotinib	JAK1 inhibitor	AS	ASDAS change at week 12	II, completed	NCT03117270, TORTUGA	Galapagos
		PsA	Adverse events	II, ongoing	NCT03320876	

ACR: American College of Rheumatology, AS: ankylosing spondylitis, ASAS: Assessment in Spondyloarthritis international Society, ASDAS: Ankylosing Spondylitis Disease Activity Score, axSpA: axial spondyloarthritis, IL: interleukin, JAK: Janus kinase, nr-axSpA: non-radiographic axSpA, PDE: phosphodiesterase, PsA: Psoriatic arthritis, TNFi-IR: tumor necrosis factor inhibitor inadequate responders.

Best Practice & Research Clinical Rheumatology 32 (2018) 472–484

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

11

Emerging treatment options for spondyloarthritis

Murat Torgutalp [a, b] Denis Poddubnyy [b, c, *]

[a] Division of Rheumatology, Department of Internal Medicine, Ankara University Faculty of Medicine, Hacettepe Mahallesi, Adnan Saygun Caddesi 35, 06080, Altındag, Ankara, Turkey
[b] Department of Gastroenterology, Infectiology and Rheumatology, Campus Benjamin Franklin Charité – Universitätsmedizin, Berlin, Germany
[c] Department of Epidemiology, German Rheumatism Research Centre, Berlin, Germany

✔ SAFETY

Safety profile of current biological therapies

Therapeutic Classes	Safety Profile
TNFα inhibitors	Increased risk of: ▪ Infection, including opportunistic infections, tubercolosis[1] ▪ Risk of local site or acute infusion reactions and delayed hypersensitivity[1] ▪ Melanoma and uneven malignancies ▪ Risk of paradoxical inflammation (dermatological or rheumatological manifestations)
Anti-integrins	Increased risk of: • Infections, particularly of the upper respiratory tract[3]

Kaser A, et al. Expert Opin Ther Targets. 2008;12:553-63; Mariette X, et al. Ann Rheum Dis. 2011;70:1895-904.
Sandborn WJ, et al. New Engl J Med. 2013;369:711-21, Armuzzi A. et al. Dig Liv Dis 2018;50(7):653-660

Long-term safety of ustekinumab for Crohn's disease through the second year of therapy

	Placebo	SC UST 90 mg q12w	SC UST 90 mg q8w	All UST
N	151	213	354	567
Average duration of follow-up (weeks)	84.1	93.8	93.4	93.5
Total patient-years of follow-up	244.2	384.3	635.6	1020.0
Deaths	0	1[b]	2	3
Number of specified events per hundred patient-years of follow-up (95% confidence interval)				
Adverse events	484.39 (457.18, 512.80)	413.70 (393.62, 434.55)	468.36 (451.68, 485.49)	447.76 (434.87, 460.94)
Serious adverse events	19.24 (14.14, 25.59)	19.51 (15.35, 24.46)	18.41 (15.22, 22.06)	18.82 (16.26, 21.68)
Infections	105.64 (93.14, 119.35)	112.66 (102.30, 123.79)	120.51 (112.13, 129.36)	117.55 (110.99, 124.40)
Serious infections	4.09 (1.96, 7.53)	5.72 (3.59, 8.67)	2.99 (1.80, 4.67)	4.02 (2.88, 5.45)

Sandborn W.J. et al Aliment Pharmacol Ther 2018

Digestive and Liver Disease 51 (2019) 1232–1240
Contents lists available at ScienceDirect
Digestive and Liver Disease
journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Effectiveness and safety of Ustekinumab for Crohn's disease; systematic review and pooled analysis of real-world evidence

Tal Engel[a,*], Diana E. Yung[b], Christopher Ma[c], Benjamin Pariente[d], Pauline Wils[d], Rami Eliakim[a], Bella Ungar[a], Shomron Ben-Horin[a], Uri Kopylov[a]

Study author	Journal	Adverse events total (n)	Severe adverse events (n)	Infection (n)	MSK-myalgia arthralgia arthritis (n)	Headaches (n)	Clostridium difficile infection (n)	Skin eruption (n)	Fatigue (n)	Neurologic	Cancer	Death	Other
Wils P	CGH + APT 2018	20/122	4/20	9/122	5/122			3/122			1/122(anal adenocarci-noma)		2/122 (depression, allergic)
Greenup AJ	Scand J Gastroen-terol. Dec 2017	18/73	1/18	3/73 (2 abscess and 1 pneumo-nia)	6/73	1/73		3/73		1/73 (Amy-otrophic lateral sclerosis)			
Battat r	Clin Gas-troenterol Hepatol	31/62	3/62	3/62	8/62	14/62		6/62	8/62		2/62(HGD CRC)		3/62 (nephrolithiasis)
Ma C	APT2017 +Inflamm Bowel Dis	53/167	11/53	20/167	21/167	6/167	2/167	5/167				1/167	
Khorrami S	IBD J	11/116		3/116	1/116	2/116		1/116					4/116
Kopylov U	JCC	1/38					1/38						
SUM		134/578	19/134	38/578	41/578	23/578	3/578	18/578	8/578	1/578	3/578	1/578	9/578

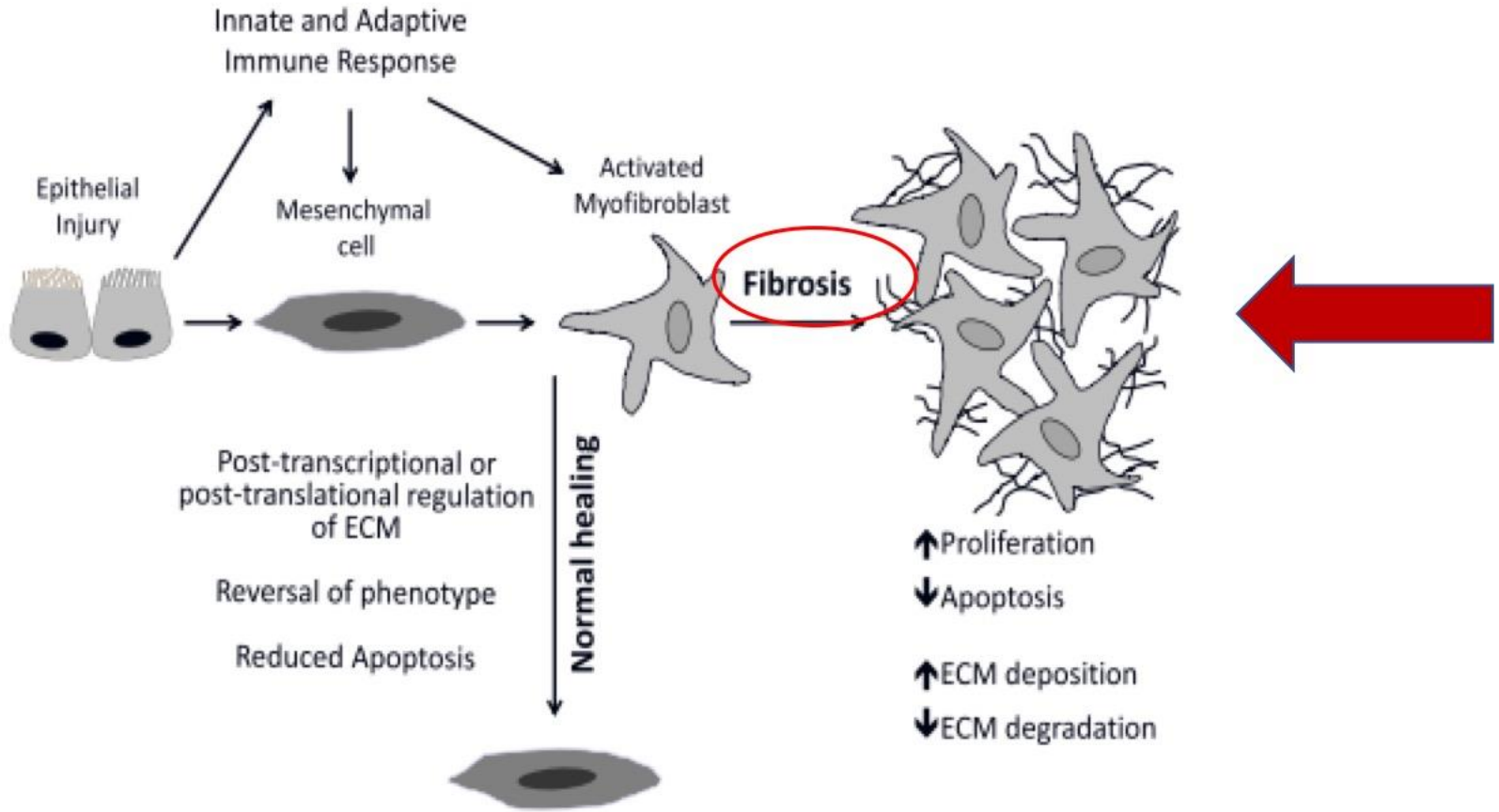
134 adverse events (AE) were reported in total, pooled proportion 21% (95% CI (0.12-0.35).
Serious AE were reported in 19 patients, pooled proportion 5% (95% CI (0.03-0.08).
Infections were reported in 38, pooled proportion 6% (95% CI (0.04-0.11)).

Engel T et al Dig Liv Dis 2019

UNMET MEDICAL NEEDS IN «IBD THERAPY»

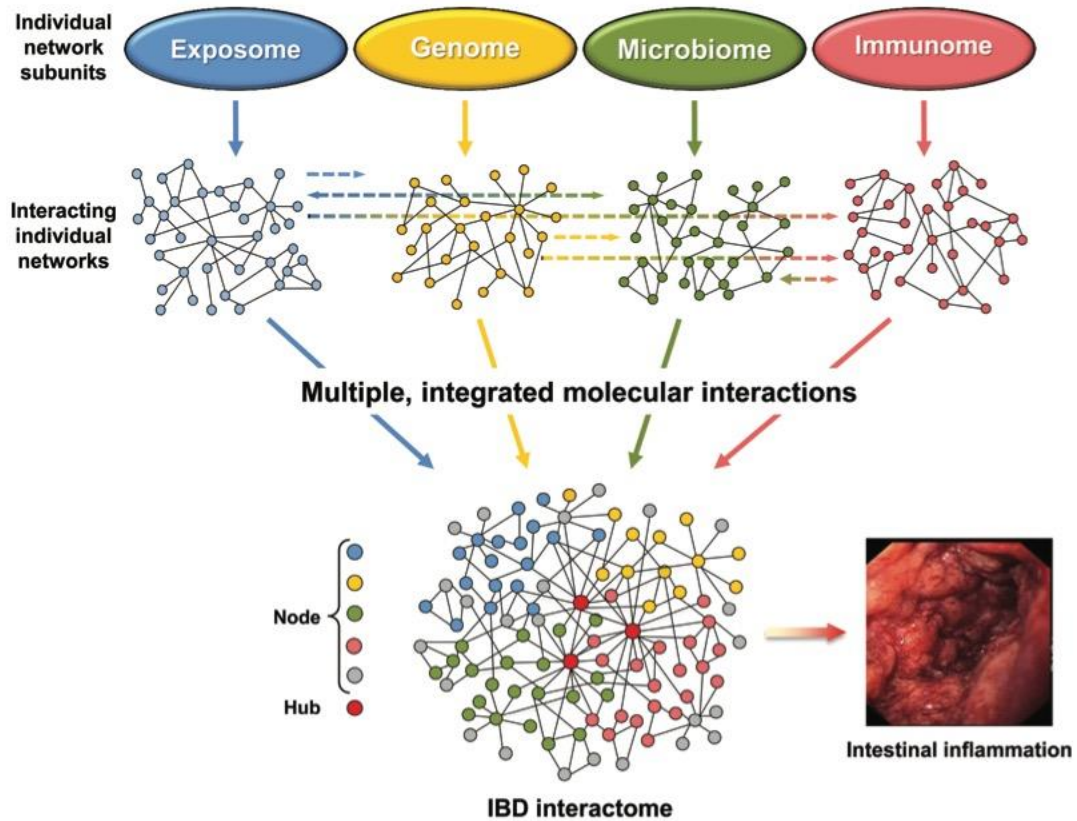
nowadays

✔ INTESTINAL DAMAGE



Lawrance IC et al JCC 2014

✔ PROFILING



Heitor S.P. de Souza, and Claudio Fiocchi, IBD 2018

THANKS FOR YOUR ATTENTION!