CAG Symposium: IBD- Managing Biologics "Optimizing Response"

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CanMEDS Roles Covered

X	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
	Communicator (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	**Leader** (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
	Health Advocate (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
X	**Professional** (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Dr. Waqqas Afif

Financial Interest Disclosure

(over the past 24 months)

Commercial Interest	**Relationship**
Janssen/Abbvie	Advisory board/consultant/investigator
Takeda/Pfizer/Merck/Shire/Ferring	Advisory board
Prometheus/Theradiag/ Buhlmann	Investigator

Learning Objectives

At the end of this session, participants will be able to:

- Compare the risks and benefits of combination therapy versus monotherapy in the treatment of patients with IBD
- Assess the utility of premedication in the treatment of patients with IBD on biologic therapy
- Manage the treatment of patients with IBD on biologic therapy using therapeutic drug monitoring

Combination Therapy in IBD

A very long history …

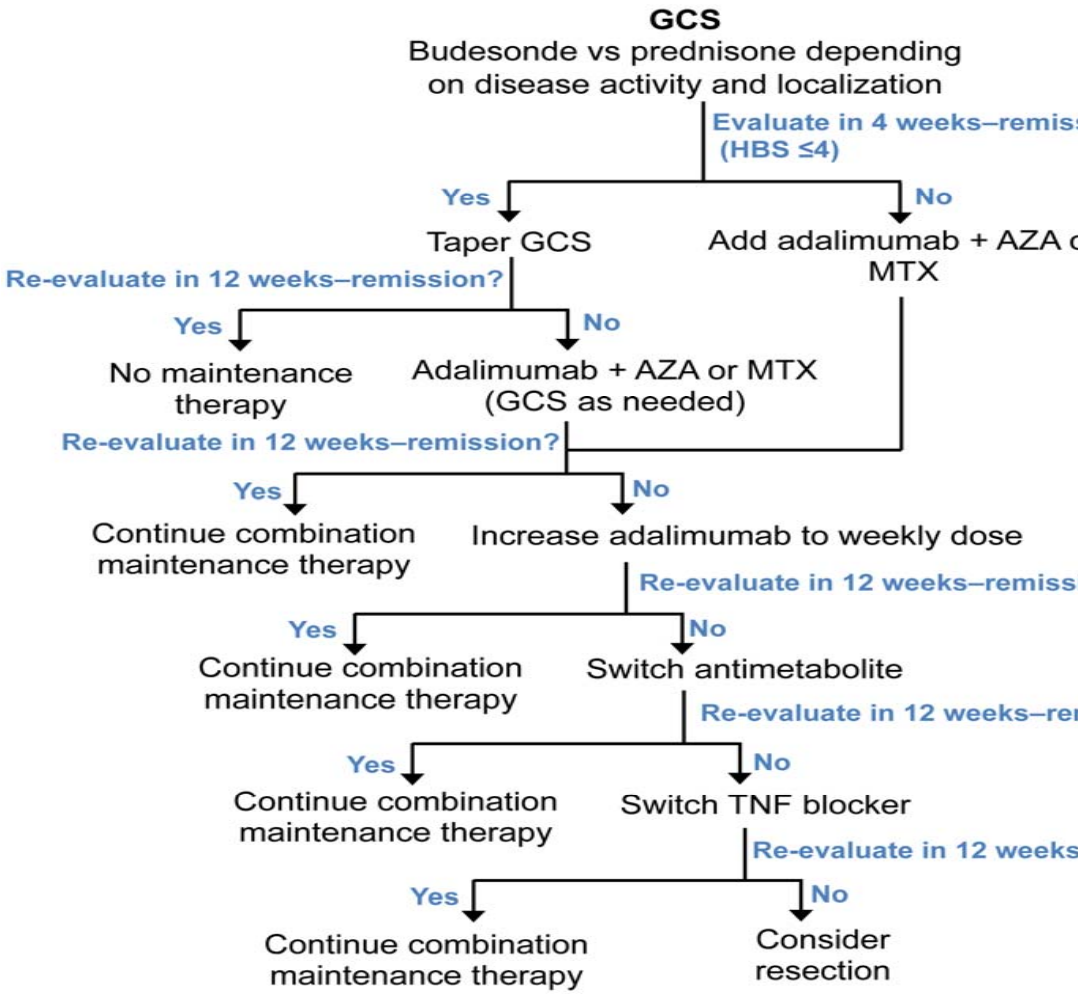
REACT Trial: Algorithm-based Treatment with Early Combined Immunosuppression Reduced Complications in CD

nter-level cluster randomisation to
rly combined immunosuppression
gorithm or current best practice

patients recruited from 40 centers
=1982)
Regular clinical review at 4 weeks and
then Q12 weeks
Used algorithm to treat to target
Followed for 24 months

imary endpoint: clinical remission
BI <5 & no steroids) at 12 months

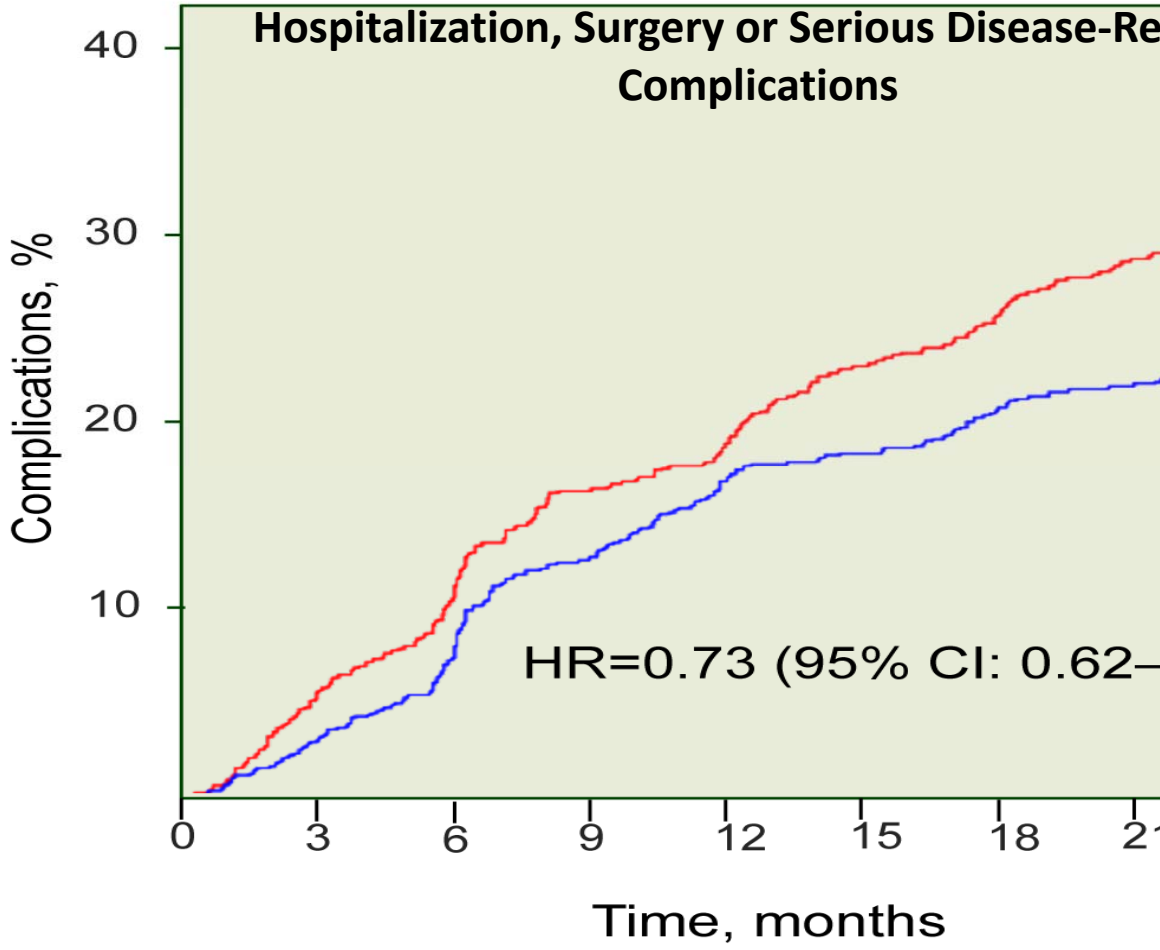
Therapeutic Algorithm for CD



Khanna R, et al., La

ACT Trial: Algorithm-based Treatment with Early Combin
Immunosuppression (ECI) Reduced Complications in CD

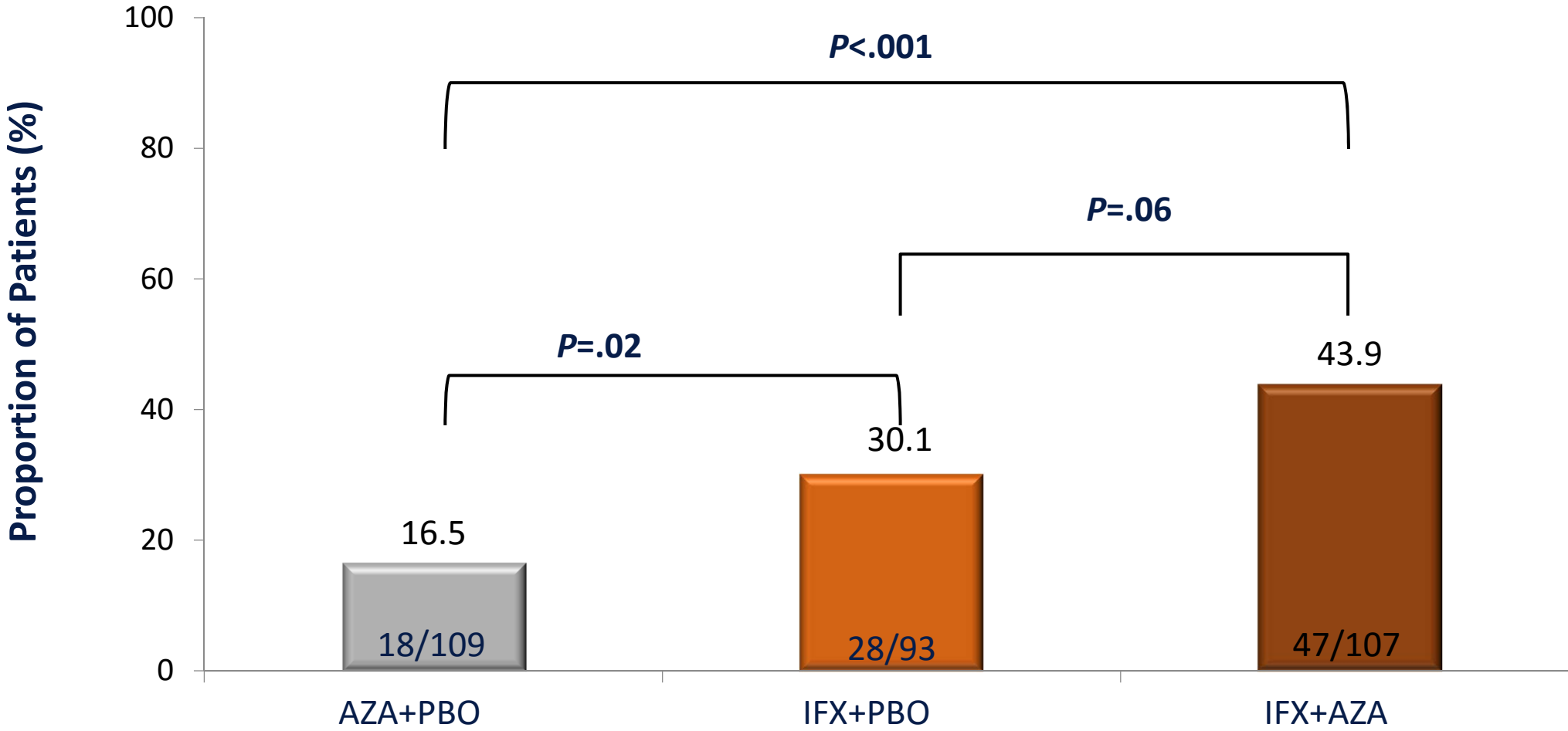
rimary endpoint
ymptomatic remission)
as not met BUT →



Khanna R, et al., La

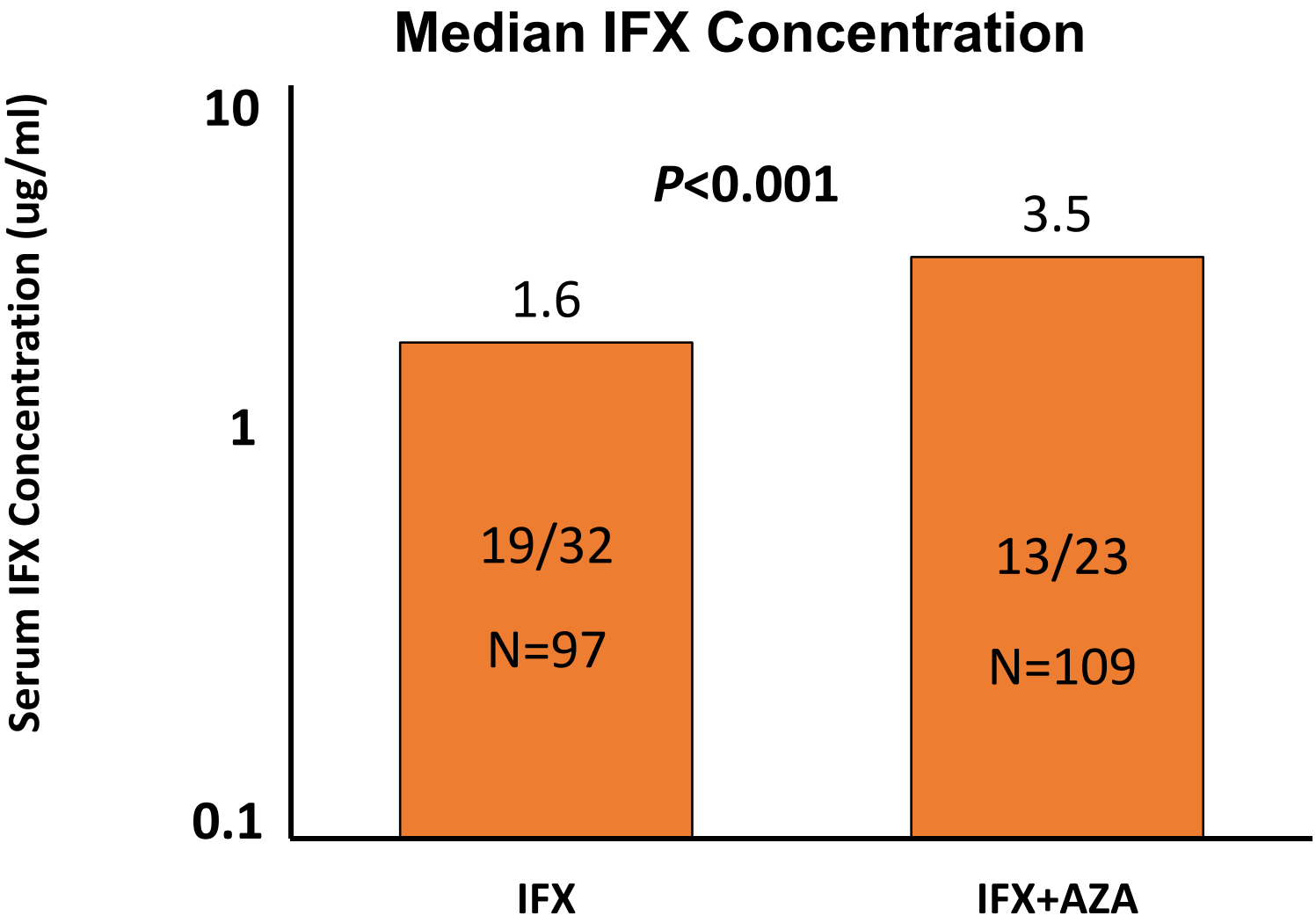
SONIC: Mucosal Healing at Week 26

Median disease duration 2.4 years



Sandborn WJ et al. N

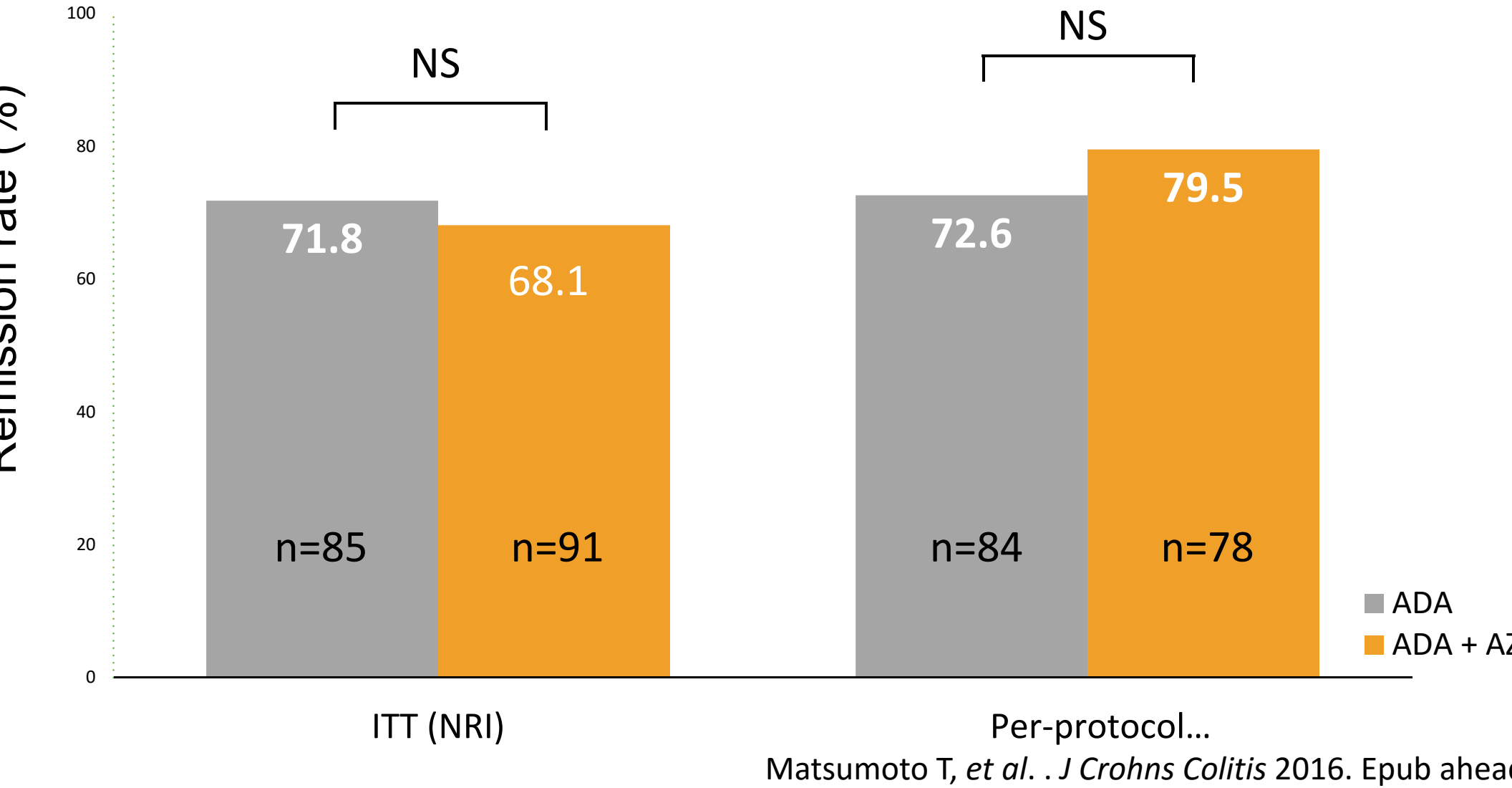
SONIC Study:
Serum Infliximab Trough Levels at Week 30



Colombel JF et al, N Engl J Med 2010;362

DIAMOND

mbination therapy vs monotherapy with ADAL: Primary Endpoint at week

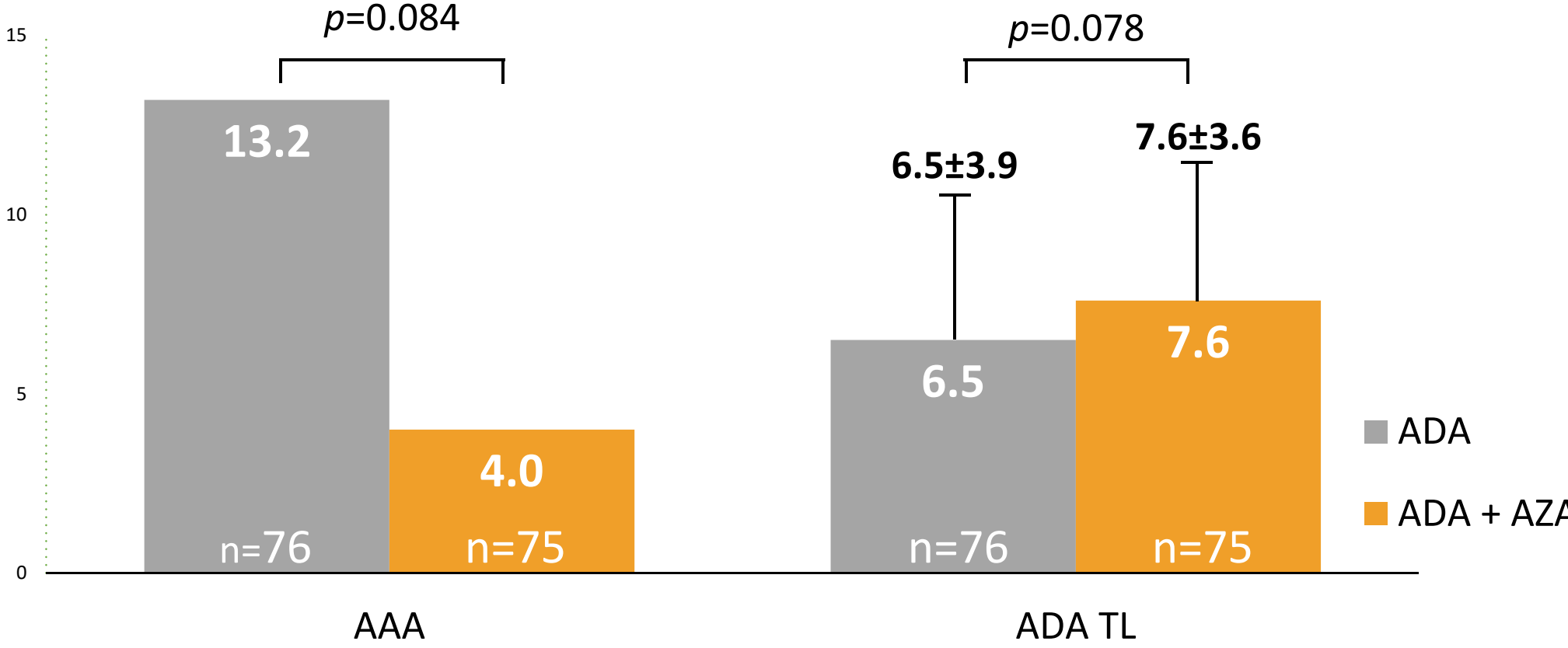


Matsumoto T, *et al*. . *J Crohns Colitis* 2016. Epub ahead

DIAMOND

mbination therapy vs monotherapy with ADAL: Primary Endpoint at wee

- ADA Trough Level (μg/ml)

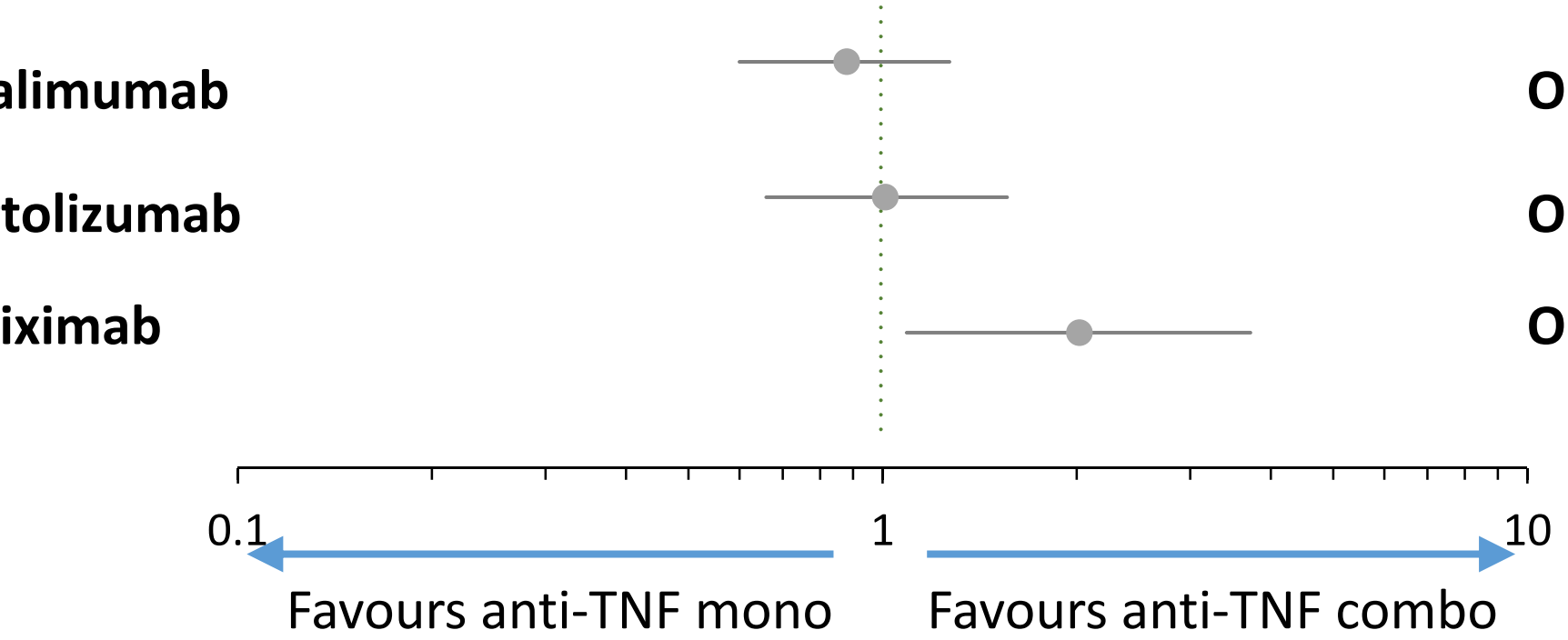


Positive Rate of AAA (%)

Matsumoto T, *et al*. . *J Crohns Colitis* 2016. Epub ahea

Meta-analysis:
Anti-TNF mono- or combination therapy:

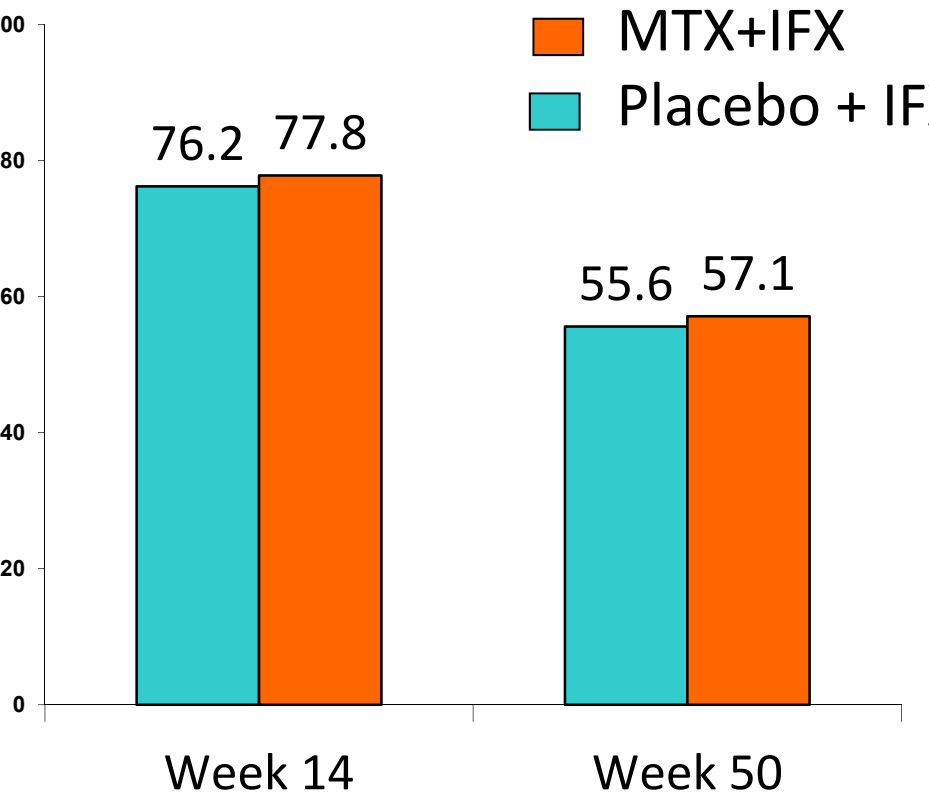
- Induction of clinical response (between week 4 to 14) and concomitant IMM use



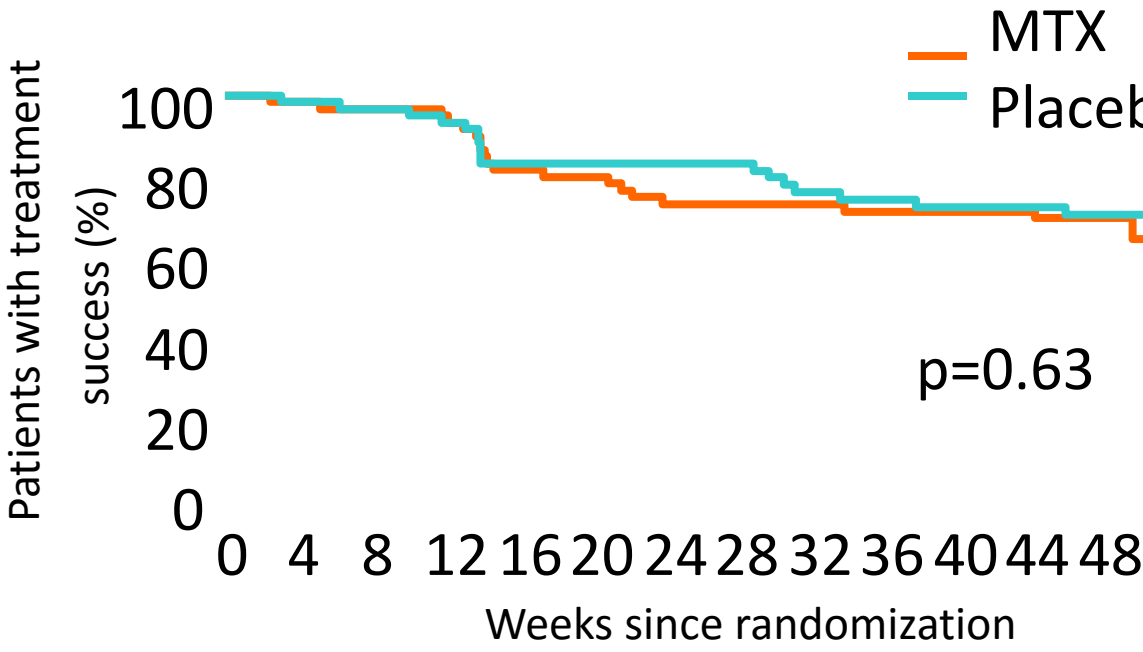
ystematic review of 11 RCTs in patients with luminal and/or fistulising CD who received anti-TNF herapy with/without concomitant IM therapy; combination therapy was not associated with erious adverse events compared to monotherapy across all anti-TNF therapies

Jones J, *et al. Clin Gastroenterol Hepatol* 2015;13

COMMIT: MTX plus IFX in CD



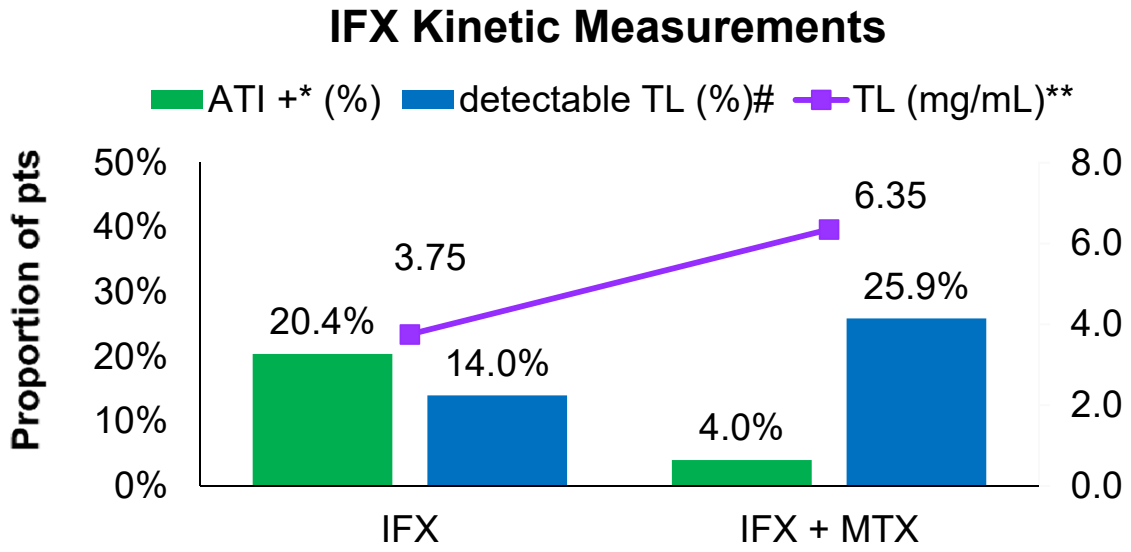
Proportion of patients with treatment

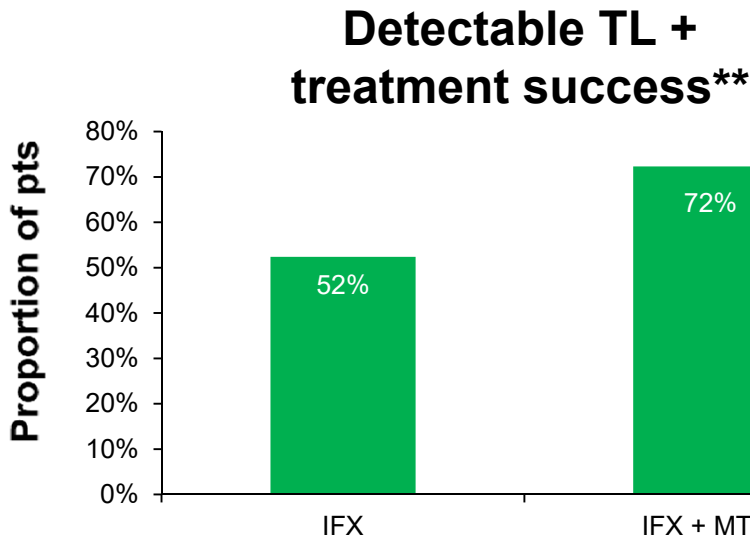


Feagan et al. Gastroenterology. 2014;146(3

COMMIT: MTX for the Prevention of ADA

ods: 126 MTX-naïve CD pts (63 w/ IFX) – ATI and Trough levels (TL) were measured

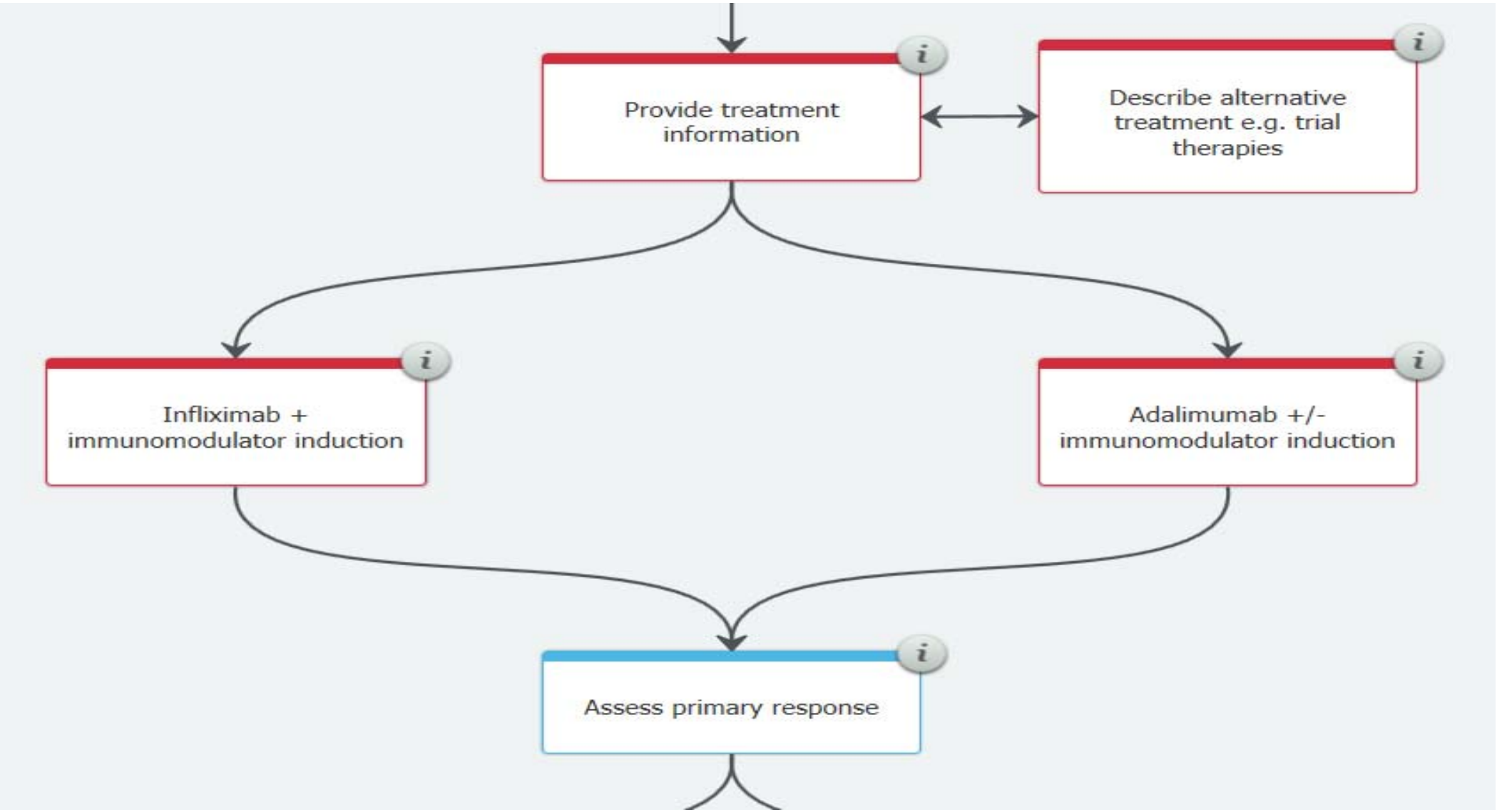




0.01 **P=0.08 #P=0.13

Feagan et al. Gastroenterology. 2014;146(3

2016 ECCO Guidelines: CD and UC



uropean Crohn's and Colitis Organisation. Anti-TNF therapy. http://www.e-guide.ecco-ibd.eu/algorithm/anti-t

Safety: Combination Therapy

EACT: Safety of Early Combined Immunosuppressio
No increased risk of infections

tes of Complications / SAEs

	Conventional Management (n=898)	Early Combined Immunosuppression (n=1084)
orsening Disease	92 (32%)	97 (36%)
sease Related Complications	134 (47%)	113 (42%)
tra-Intestinal Manifestations	50 (17%)	47 (17%)
ocedural Complication	2 (0.7%)	2 (0.7%)
edication Related	10 (3.5%)	10 (3.7%)

Khanna R, et al., La

CESAME: Risk of Lymphoma with Thiopurines

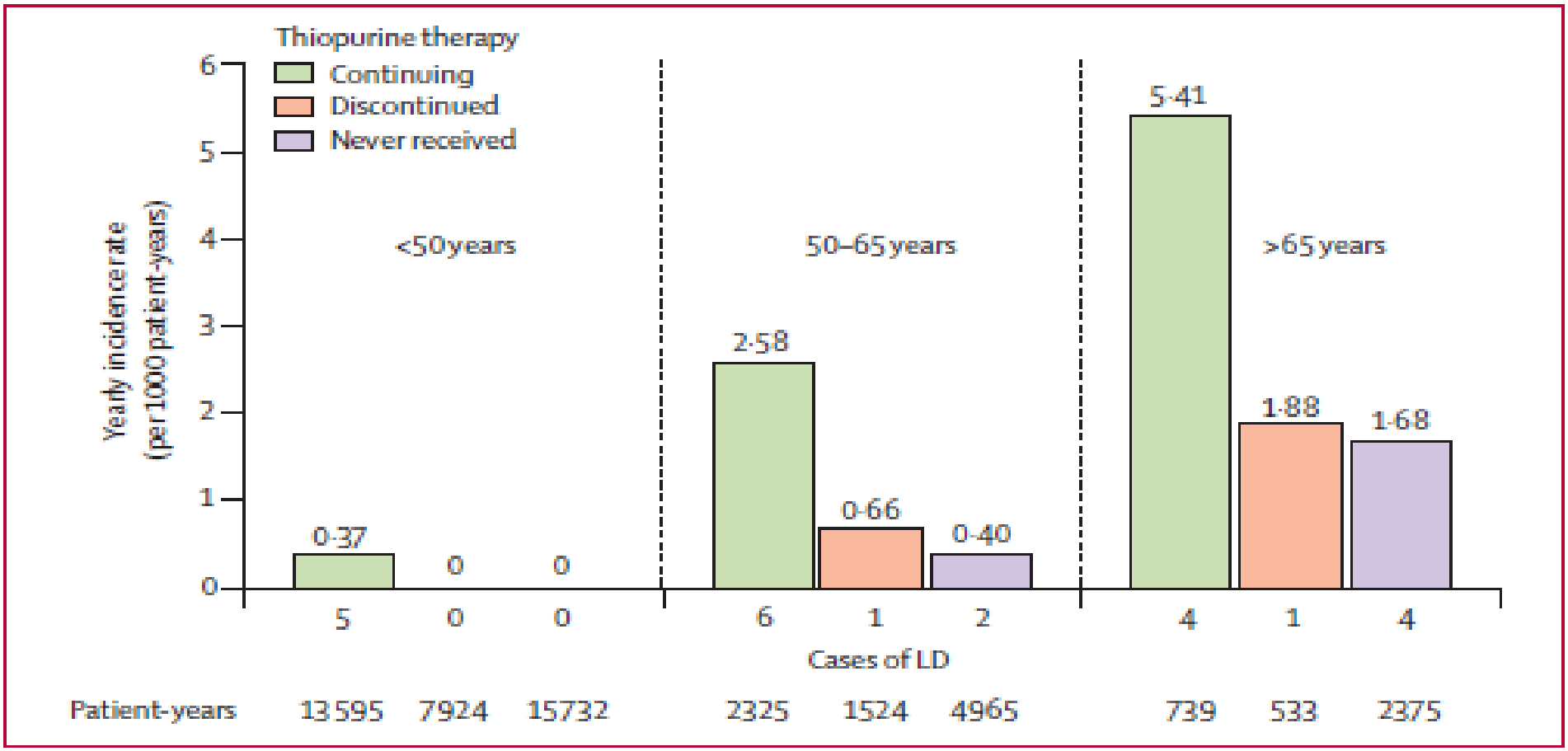
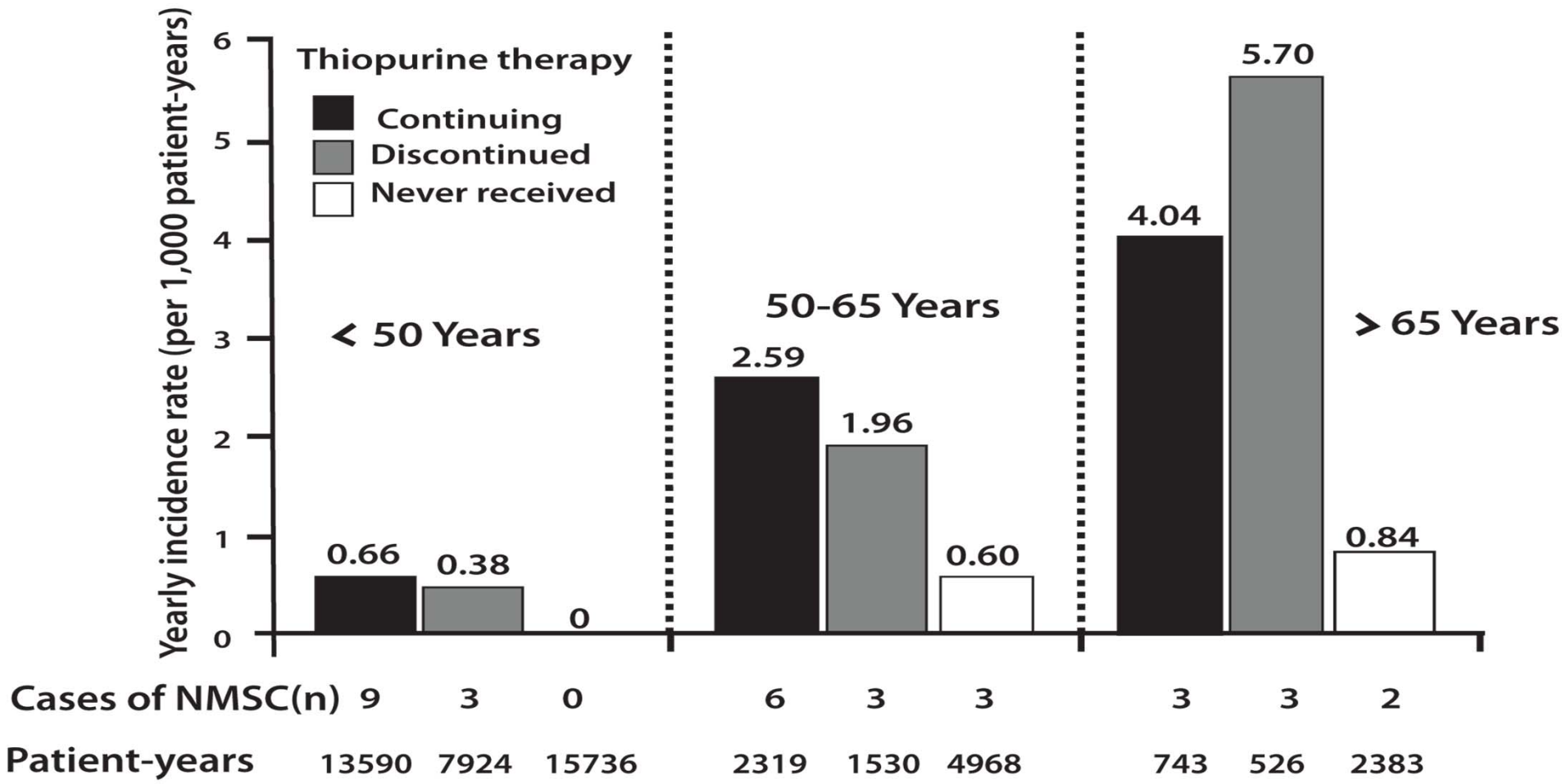


Figure: **Incidence rates of lymphoproliferative disorders according to thiopurine exposure grouped by age at entry in the cohort**

LD=lymphoproliferative disorder.

Beaugerie et al. Lancet

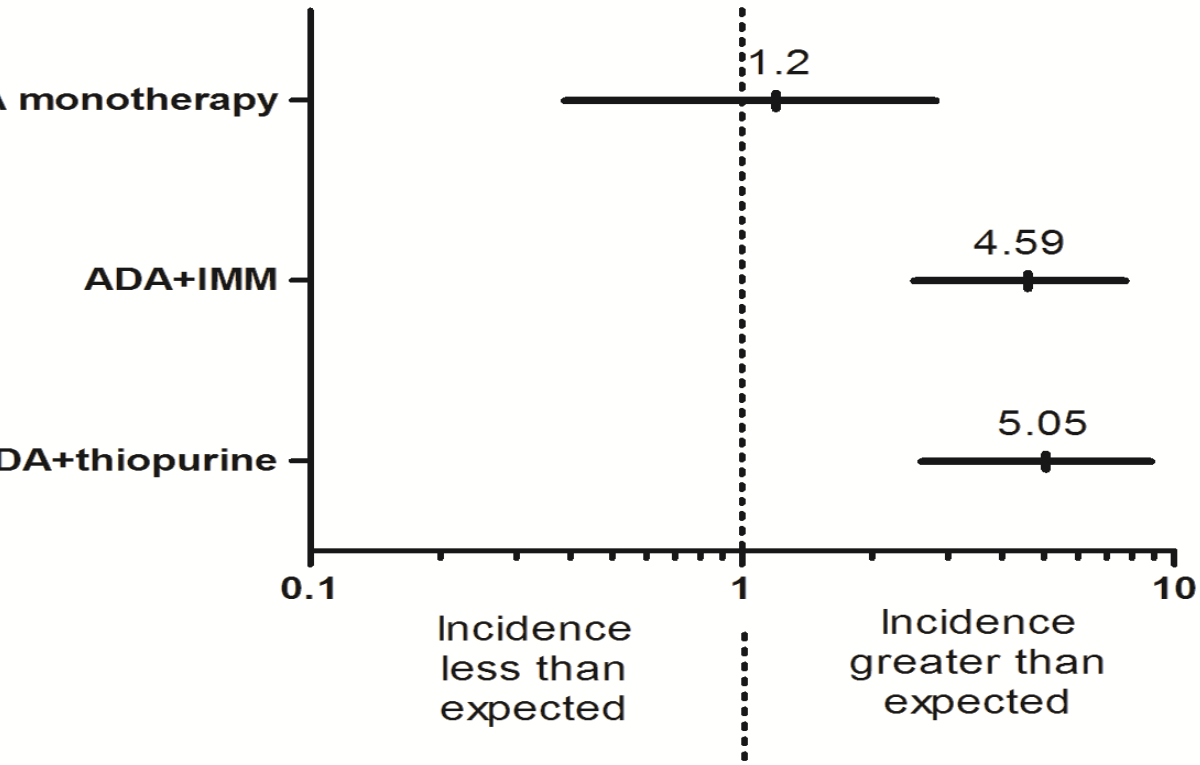
CESAME: Risk of NMSC with Thiopurines



Peyrin-Biroulet et al. *Gastroenterology* 2011;141:1

NMSC: Risk with combination therapy likely attributable to immunomodulators

f NMSC with ADA monotherapy or combination therapy compared to the general popu



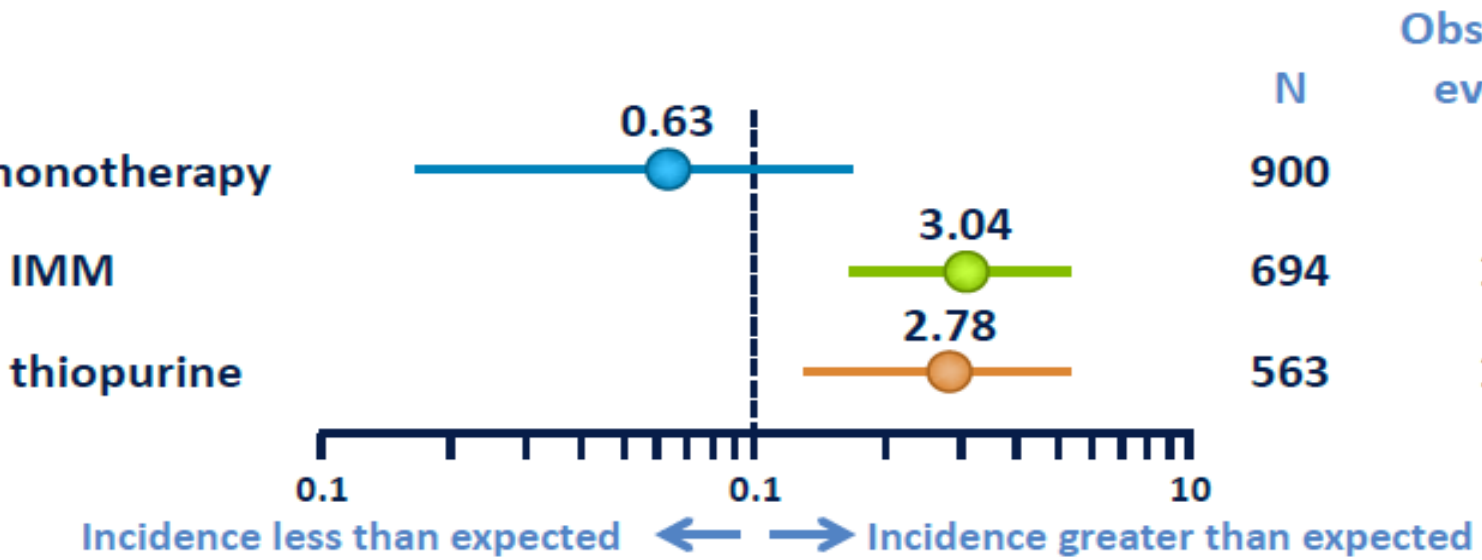
	N	Observed events	Expected events	SIR (95% CI)
monotherapy	900	5	4.16	1.2 (0.39-2.80
ADA+IMM	694	14	3.05	4.59 (2.51-7.7(
DA+thiopurine	563	12	2.38	5.05 (2.61-8.82

tients treated with adalimumab combination therapy (either with any IMM or with thiopurine) gnificant 5-fold increased risk of NMSC when compared to the general population.

Osterman et al., *Gastroenterology* 2014;146(4

Malignancies excluding NMSC: Risk with combination therapy likely attributable to immunomodulators

of malignancies excluding NMSC with ADA monotherapy or combination therapy compa
eneral population



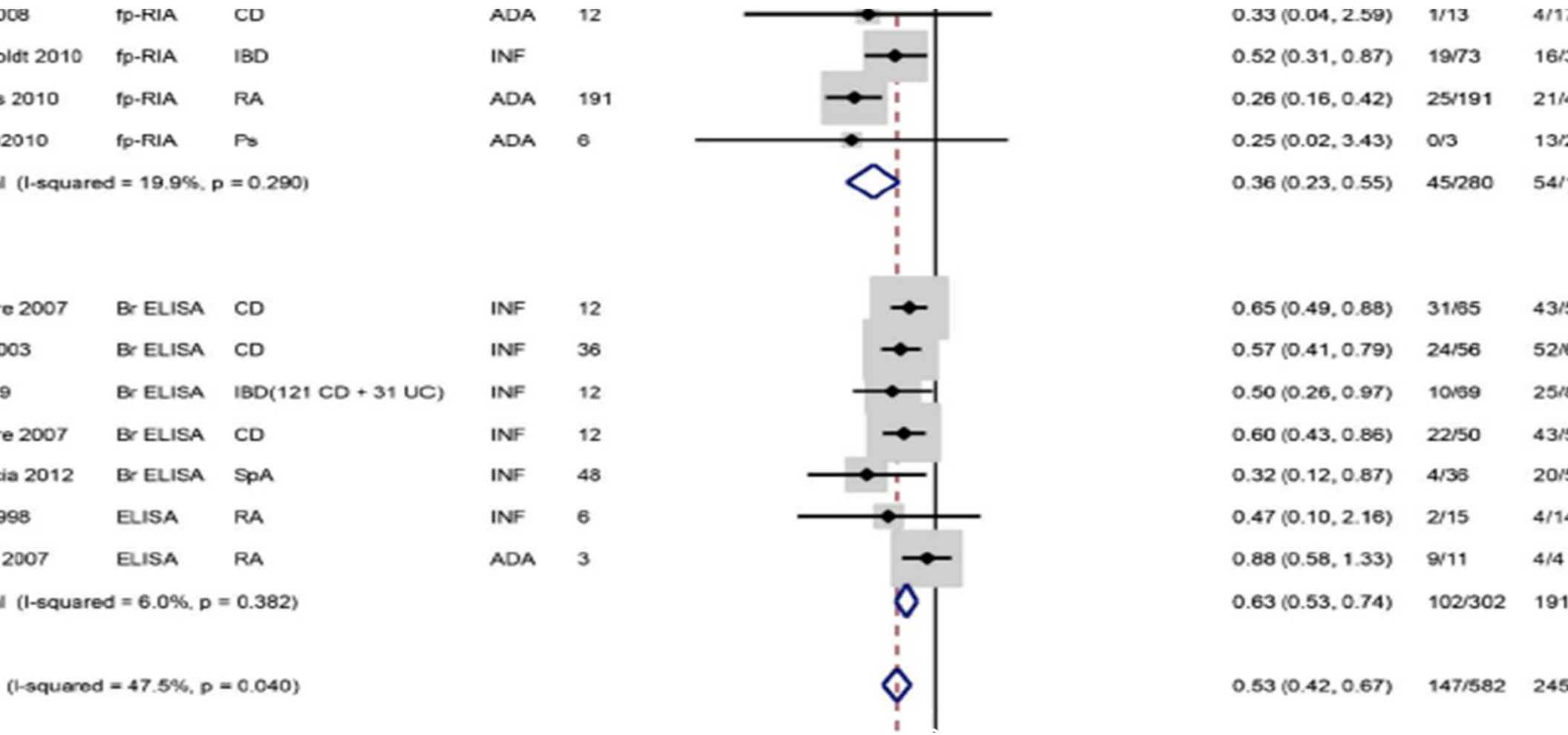
	N	Observed events	Expected events	SIR (9
nonotherapy	900	4	6.31	0.63 (0.1
IMM	694	14	4.61	3.04 (1.6
thiopurine	563	10	3.6	2.78 (1.3

tients treated with adalimumab combination therapy (either with any IMM or with thiopurine)
nificant 3-fold increased risk of malignancies other than NMSC when compared to the ge
pulation.

Osterman et al., *Gastroenterology* 2014;146(4

Do we need to continue immunosuppression long term ?

Meta-analysis: Decreased antibody formation with IS Rx



Garces et al. Ann Rheum

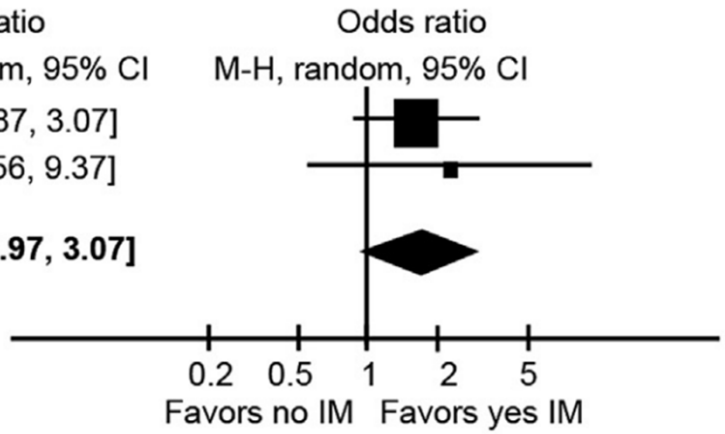
Meta-analysis:
Maintenance anti-TNF mono- or combination therapy

6 month remission for infliximab

Study or subgroup	Yes IM Events	Yes IM Total	No IM Events	No IM Total	Weight	Odds ratio M-H, random, 95% CI
ACCENT 1	28	53	61	150	83.4%	1.63 [0.87, 3.07]
RUTGEERTS	12	18	7	15	16.6%	2.29 [0.56, 9.37]
Total (95% CI)		**71**		**165**	100.0%	**1.73 [0.97, 3.07]**
Total events	40		68			

Heterogeneity: Tau² = .00, Chi² = 0.18, df = 1 (*P* = .67); I² = 0%

Test for overall effect Z = 1.86 (*P* = .06)

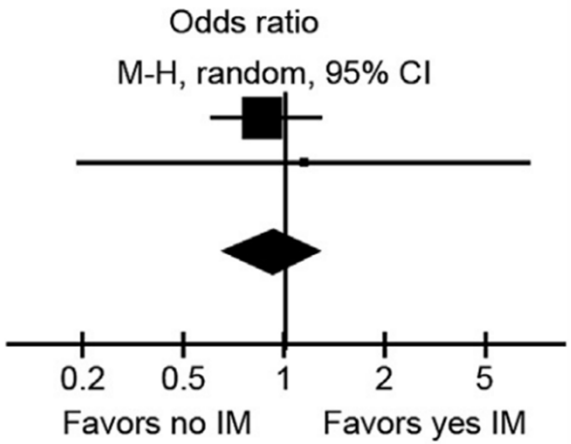


6 month remission for adalimumab

Study or subgroup	Yes IM Events	Yes IM Total	No IM Events	No IM Total	Weight	Odds ratio M-H, random, 95% CI
CHARM	64	156	77	173	17.3%	0.87 [0.56, 1.34]
CLASSIC 2	7	9	21	28	5.6%	1.17 [0.19, 6.98]
Total (95% CI)		**165**		**201**	100.0%	**0.88 [0.58, 1.35]**
Total events	71		98			

Heterogeneity: Tau² = .00, Chi² = 0.10, df = 1 (*P* = .75); I² = 0%

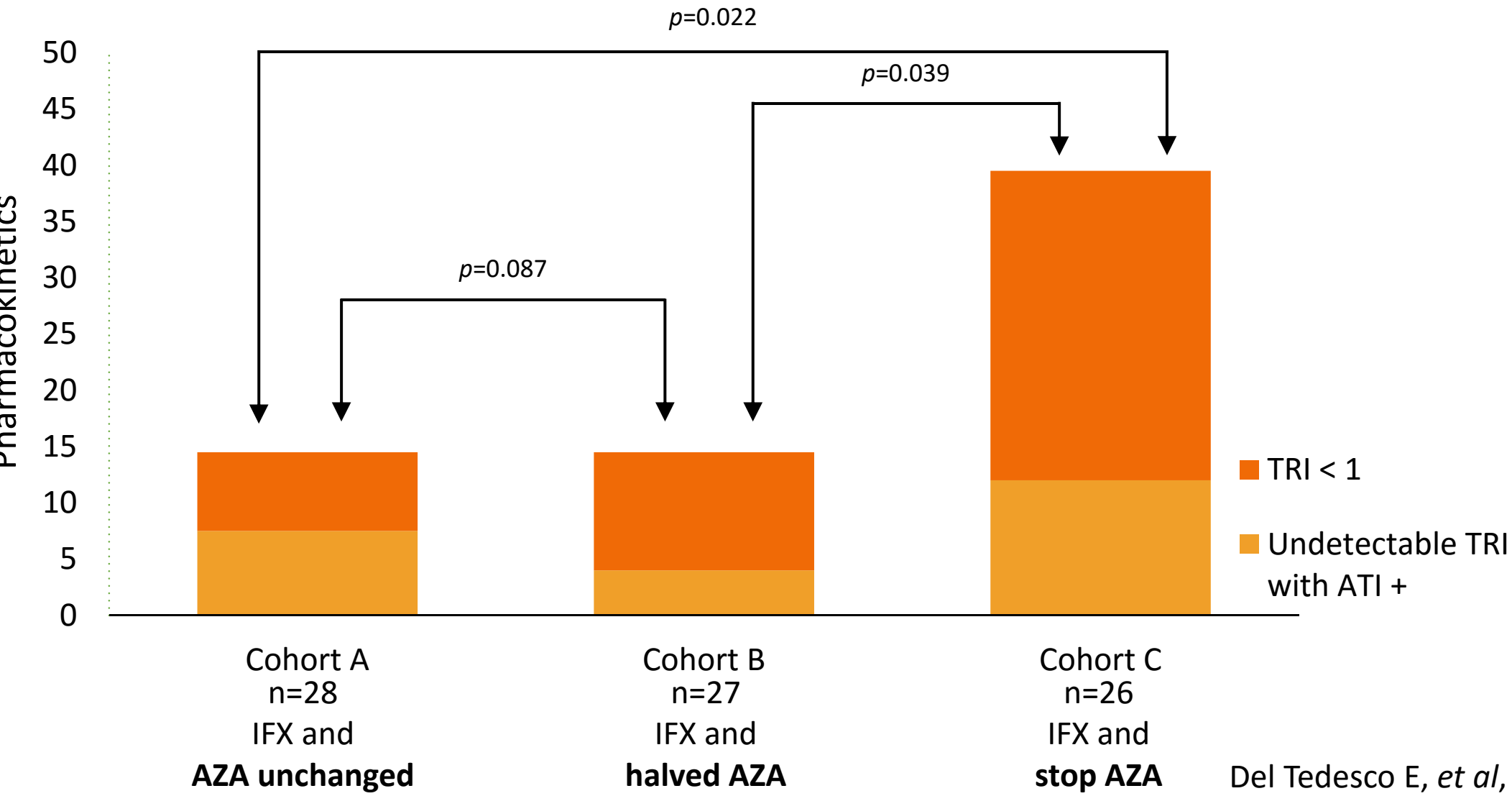
Test for overall effect Z = 0.58 (*P* = .56)



Jones J, *et al. Clin Gastroenterol Hepatol* 2015;13

AZA Dose Reduction in Patients on Combination Therapy

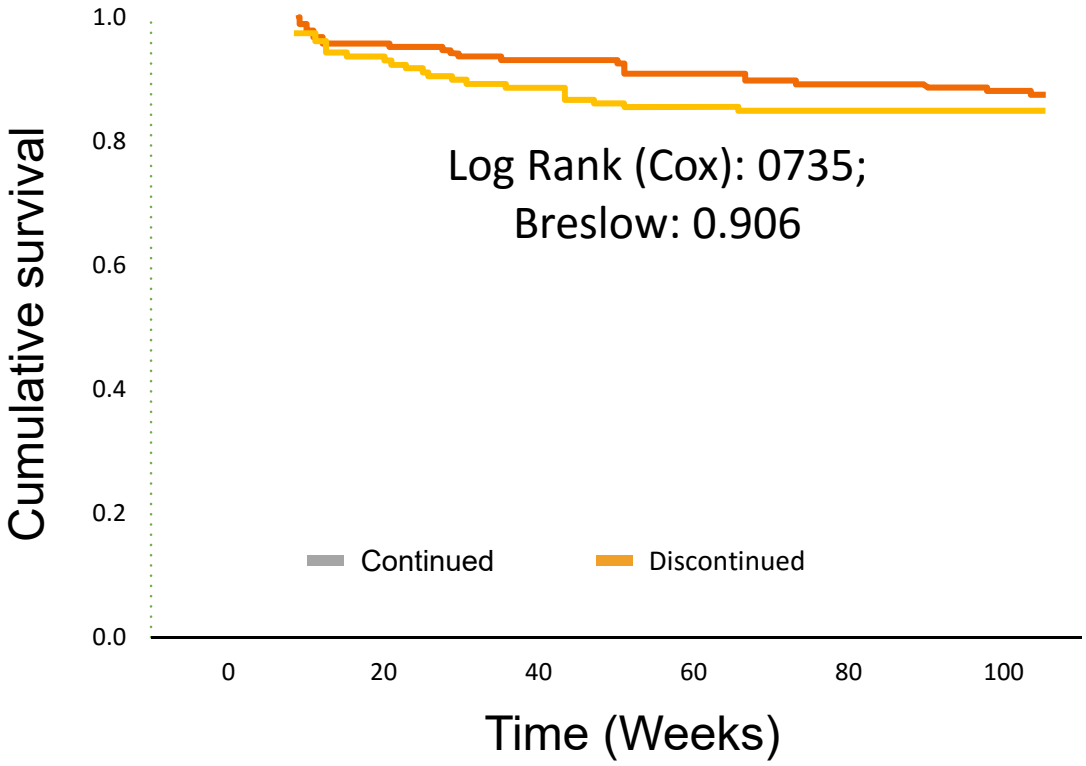
- Unfavourable evolution of IFX pharmacokinetics at Week 52

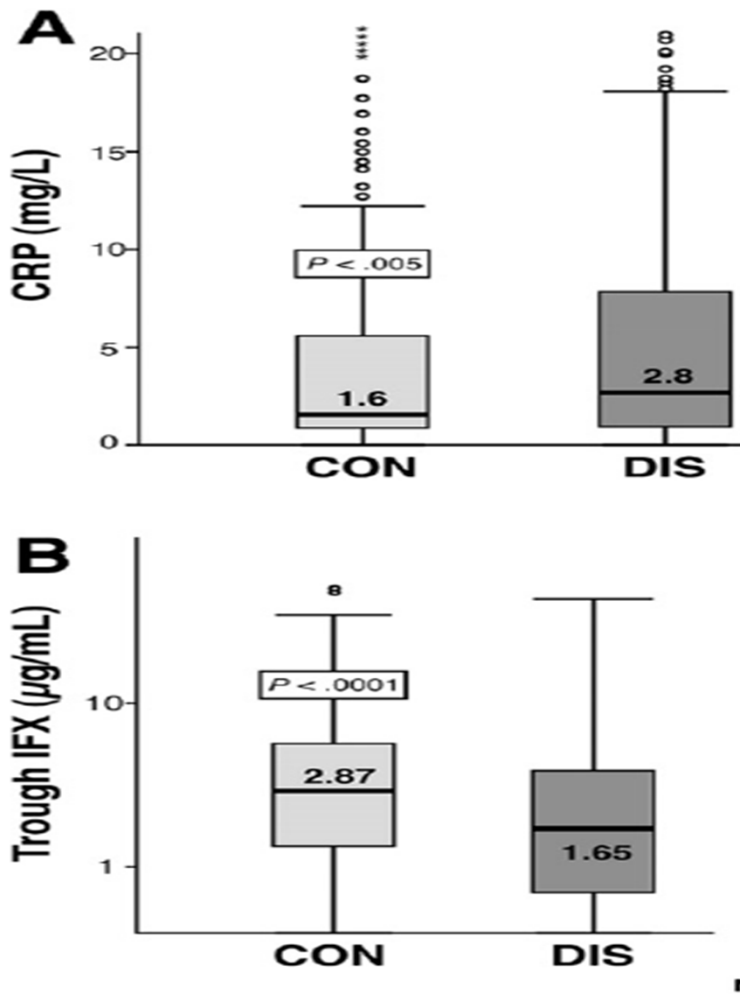


Del Tedesco E, *et al*,

Withdrawal of immunosuppression

Primary Endpoint:
No need for early 'rescue' IFX

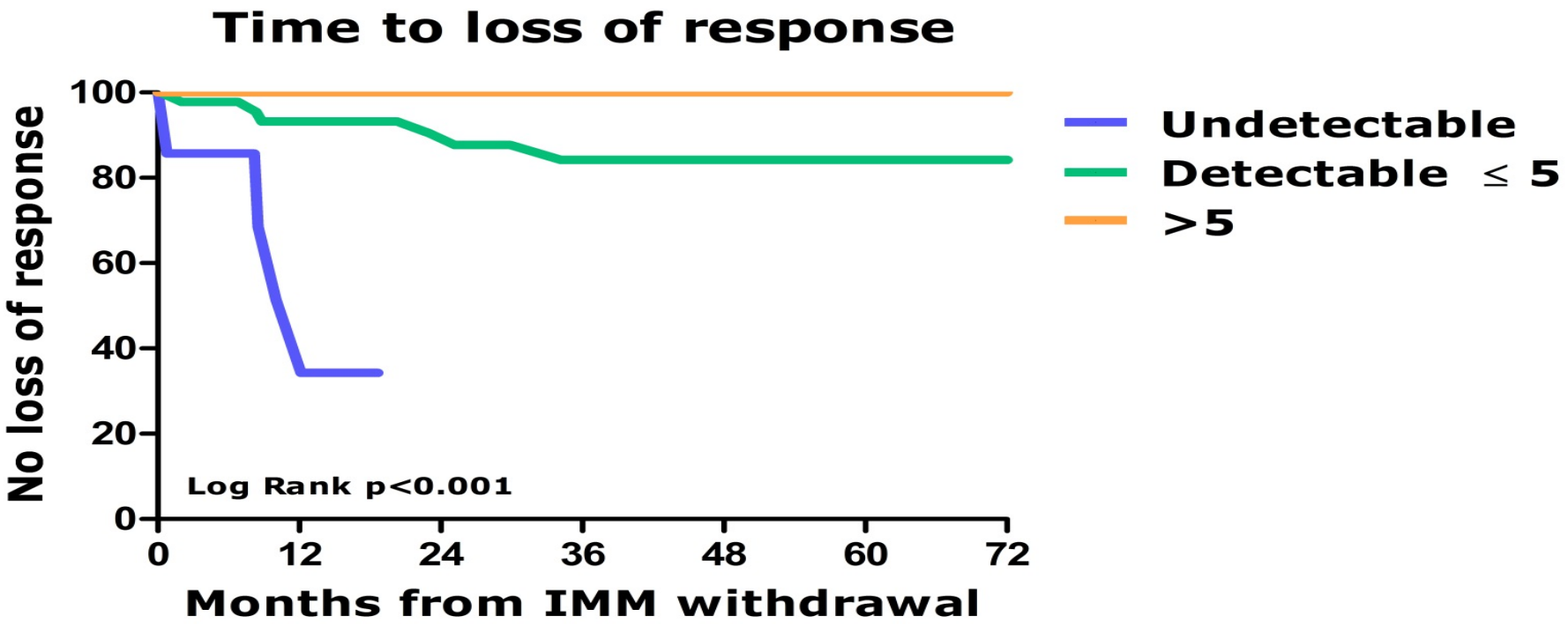




- Van Assche G, *et al. Gastroenterology*. 2008 Jun;13

FX trough levels at the time of withdrawal predicts loss of response

=223 CD on IFX maintenance
rial serum samples for TLs



Drobne D et al., Gastroenterology 2011; 140(5) (Suppl) S-62. (oral pres

Optimizing Therapy: Combination Therapy

Consider combination therapy during induction

Increased risk of malignancy with thiopurines

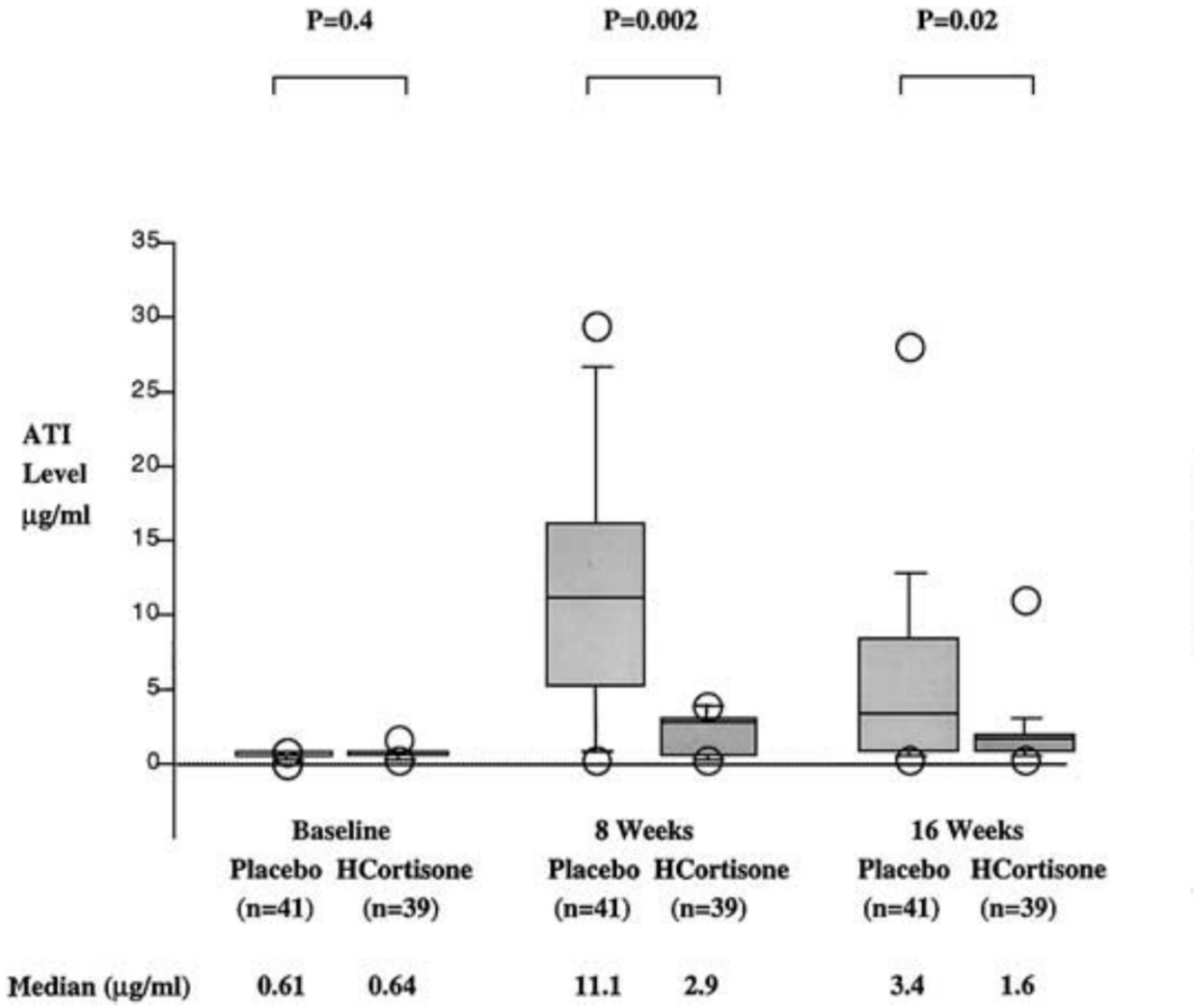
After 6-12 months, consider ½ dose thiopurine versus low dose MTX

Consider withdrawal in patients with a durable response and adequate drug concentrations

Optimizing Therapy

Premedication

Premedication with IV corticosteroids in episodic therapy
Decreased antibody formation with regular dosing



Farrell RJ, Alsahli M, Jeen YT et al. Gastroenterology 2003; 124

medication: No decrease in infusion reaction

	Level	Cohort	Study type	Premedication	% IR, group A	% IR, group B
27]	1B	*n*=355, RA	DB PL RCT	A. Oral betamethasone 0·15mgkg^{-1} 30min pre-infusion B. No premedication	16·8	10·2
[24]	1B	*n*=80, CD	DB PL RCT	A. Hydrocortisone 200mg i.v. immediately prior to infusion B. No premedication	15	24
et al.	2B	*n*=113, RA	Prosp cohort	A. Diphenhydramine 25mg (95%) or 50mg (25%) i.v. 30min pre-infusion B. No premedication	14·7	14·3

ase; DB, double blind; IR, infusion reaction; i.v., intravenous; NS, not significant; PL, placebo controlled; Prosp, prospective; RA, rheumatoid arthritis; RCT, randomized controlled trial.

Pediatric IBD study of 243 pts (Jacobson et al.):

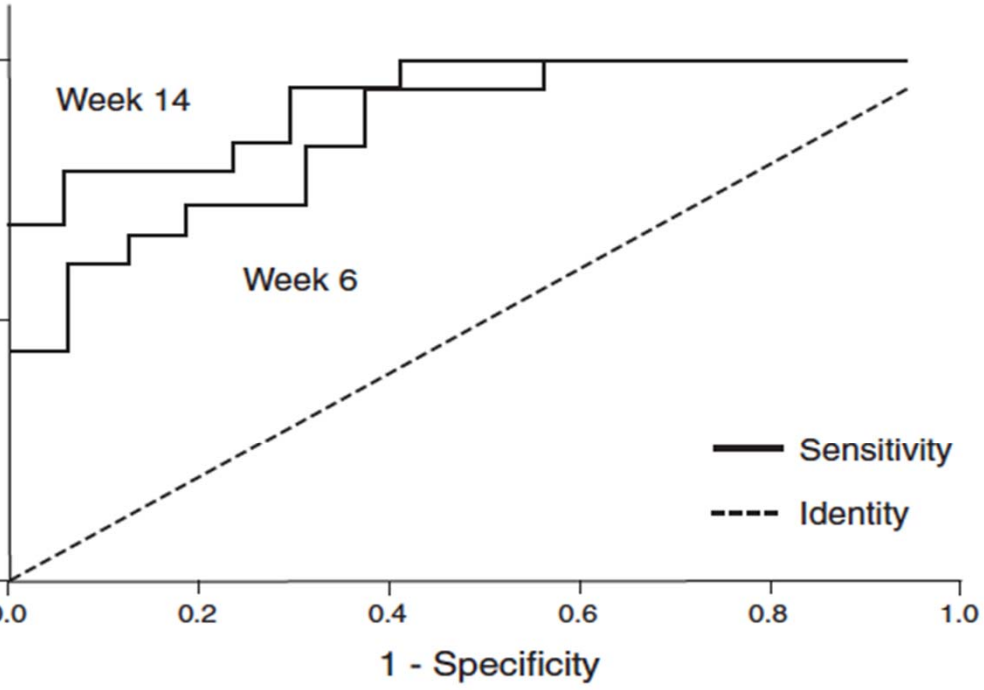
- No decreased risk of infusion reactions with pre-medications
- Non significant trend towards less **repeat** infusion reactions with pre-medica

Lecluse et al., The British Journal of Dermatology. 2008;159(3):527-536.
Jacobstein DA, Markowitz JE, Kirschner BS et al.. Inflamm Bowel Dis 2005;

Optimizing Therapy

Post-induction

Post Induction TDM



Receiver operator curve (ROC) of infliximab (IFX) trough level at
nd week 14 for the prediction of antibody to IFX (ATI) formation.
6: area under the curve=0.865 (s.e.=0.06; $P<0.001$) and for
area under the curve=0.929 (s.e.=0.04; $P<0.0001$).

ROC analysis of TLI at week 14 showed that a TLI<2.2
gave 94% specificity and 79% sensitivity for ATI forma

An IFX trough level at week 14 <2.2 µg/ml predicted I
discontinuation due to persistent loss of response (LC
hypersensitivity reactions with 74% specificity and 82
sensitivity (likelihood ratio 3.1; P=0.0026).

Vande Casteele et al.

Post Induction TDM

ediatric IBD prospective cohort

ypothesis: Trough levels at week 14 predict IFX durability

esults

Trough level at week 14	>3mcg/mL	>4mcg/mL	>7mcg/mL
PPV for week 54 clinical remission without IFX intensification	64%	76%	100%

nfliximab trough level <3µg/ml: 4 fold increased risk of developing ADA

Singh, N., et al.. Inflamm Bowel Dis, 2014. **20**(10): p

Post Induction TDM

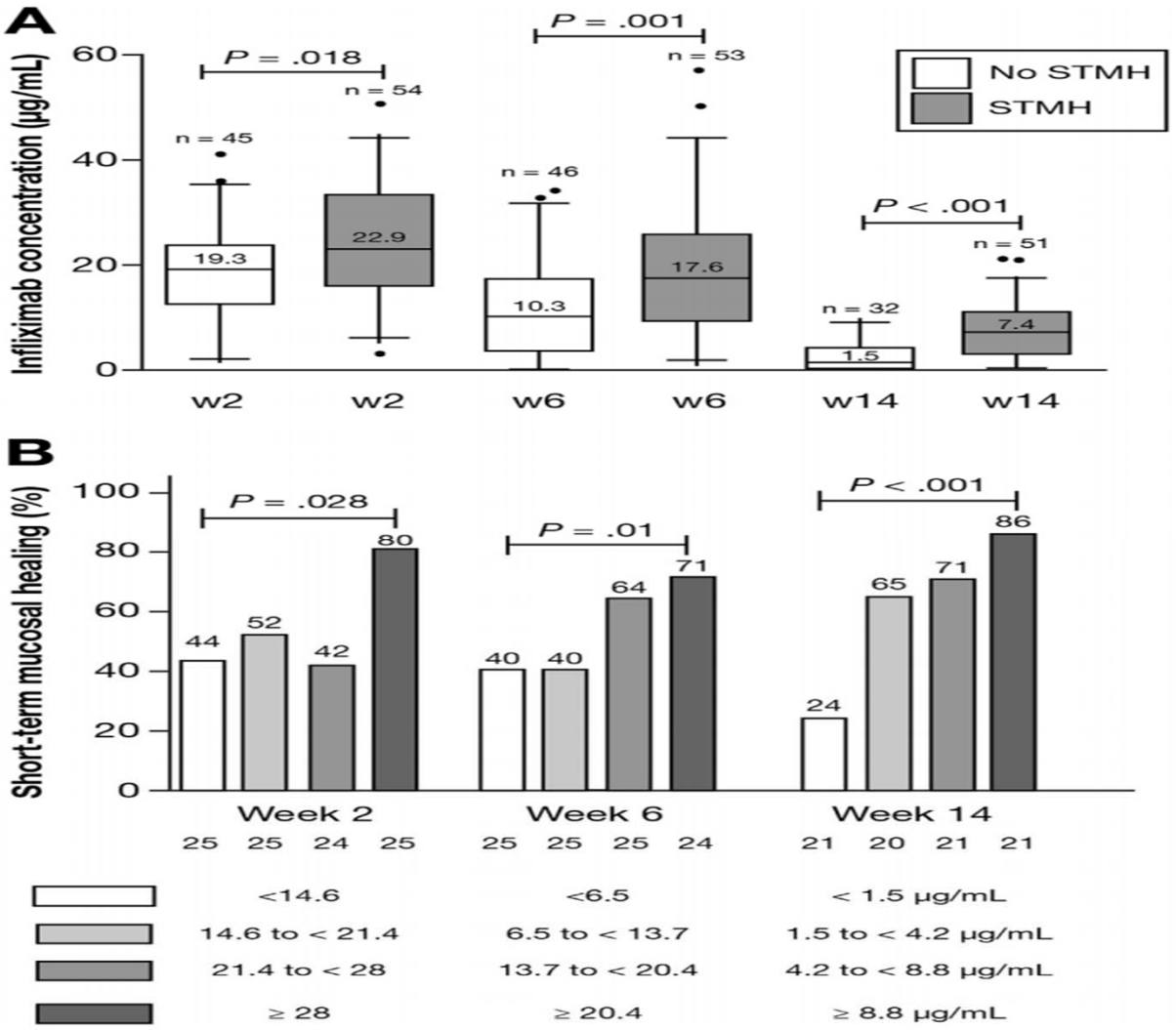
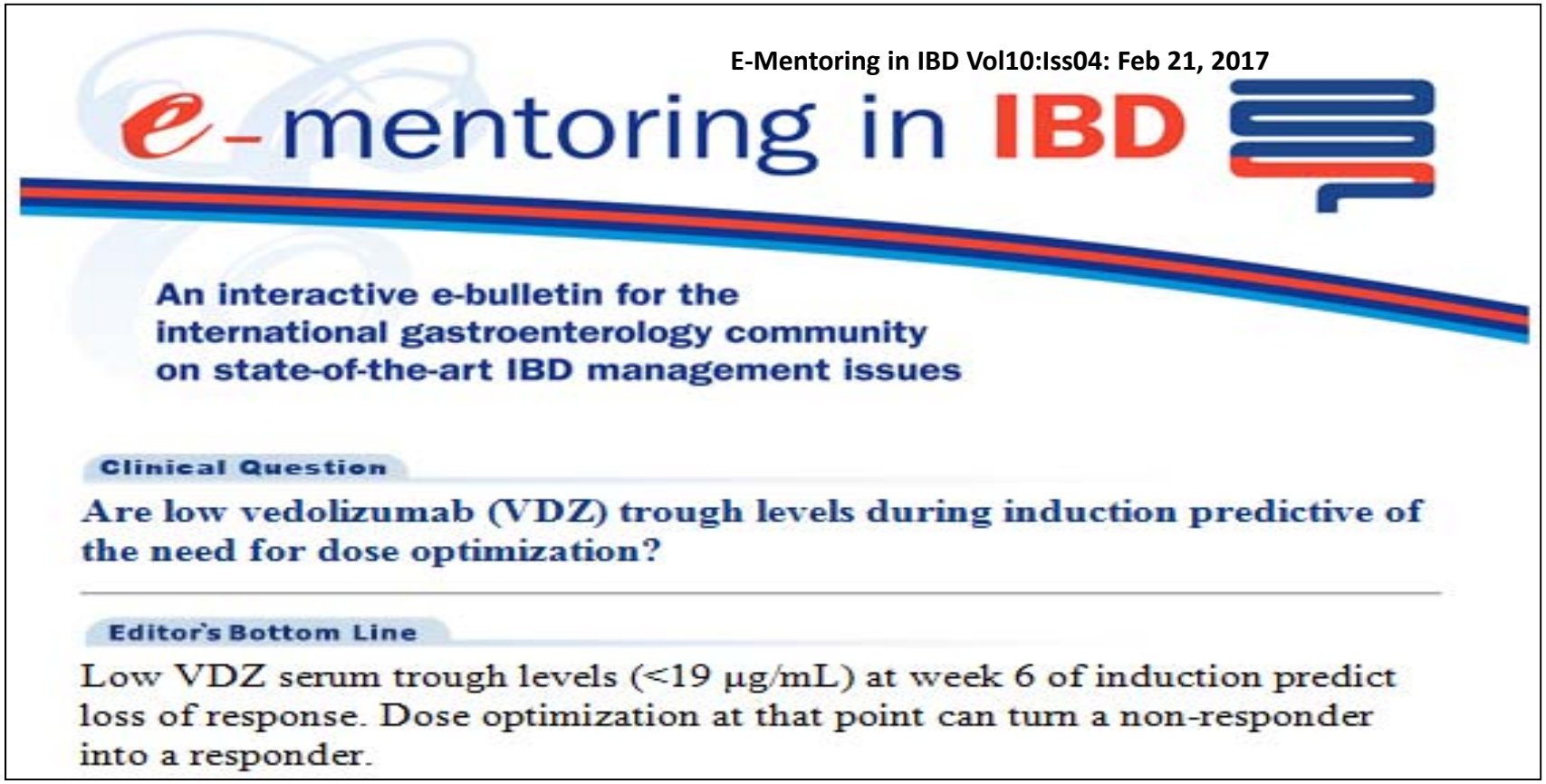


Figure 3. Distribution of serum infliximab concentrations during induction therapy on the basis of STMH. *Gray boxes* represent

Papamichael et al.,

Association Between Low VDZ TLs During Induction Predicts Need for Optimization Within 6 months



E-Mentoring in IBD Vol10:Iss04: Feb 21, 2017

e-mentoring in IBD

An interactive e-bulletin for the international gastroenterology community on state-of-the-art IBD management issues

Clinical Question

Are low vedolizumab (VDZ) trough levels during induction predictive of the need for dose optimization?

Editor's Bottom Line

Low VDZ serum trough levels (<19 µg/mL) at week 6 of induction predict loss of response. Dose optimization at that point can turn a non-responder into a responder.

ective study of 27 CD and 7 UC pts starting VDZ, low TL's at week 6 (<19 µg/mL) are associated wit
ditional doses (given at week 10 and then every 4 weeks)

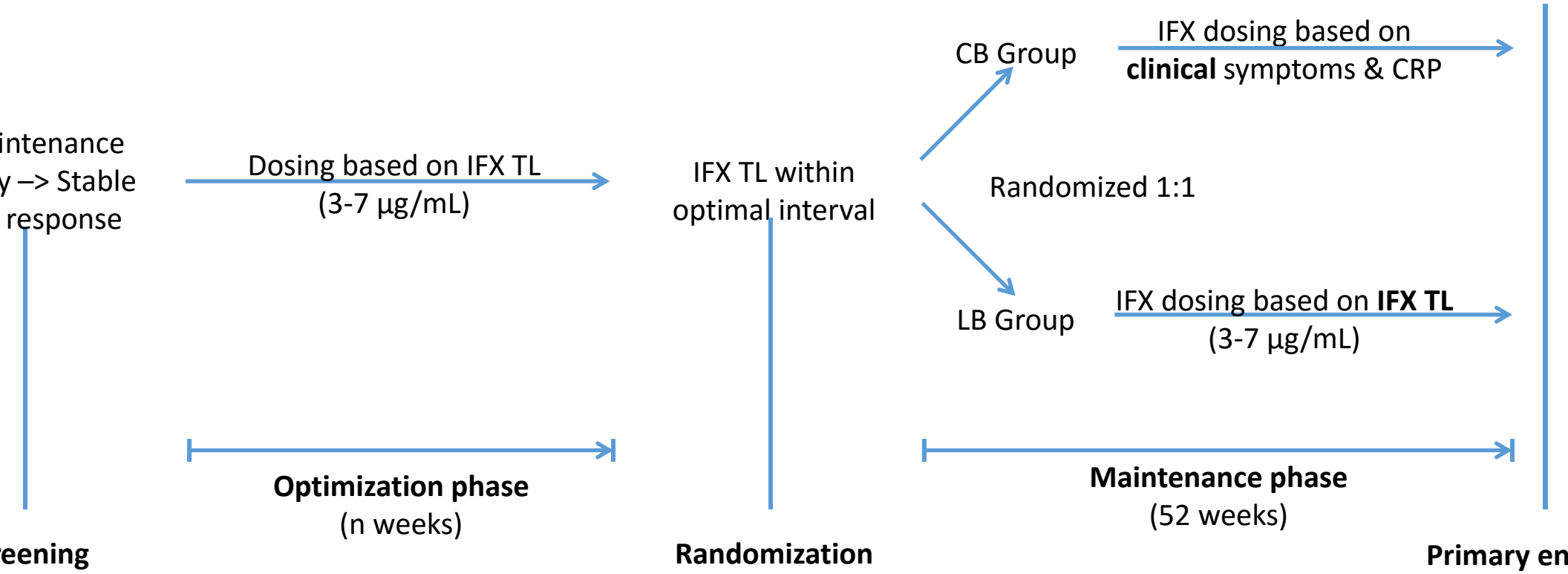
tients receiving these additional doses achieved a clinical response 4 weeks later

Williet et al. Clin Gastroenterol Hepatol 2016 Nov 24. (16

Optimizing Therapy

Maintenance Treatment

pective Controlled Trial of Trough Level Adapted Infliximab Treatment (TA



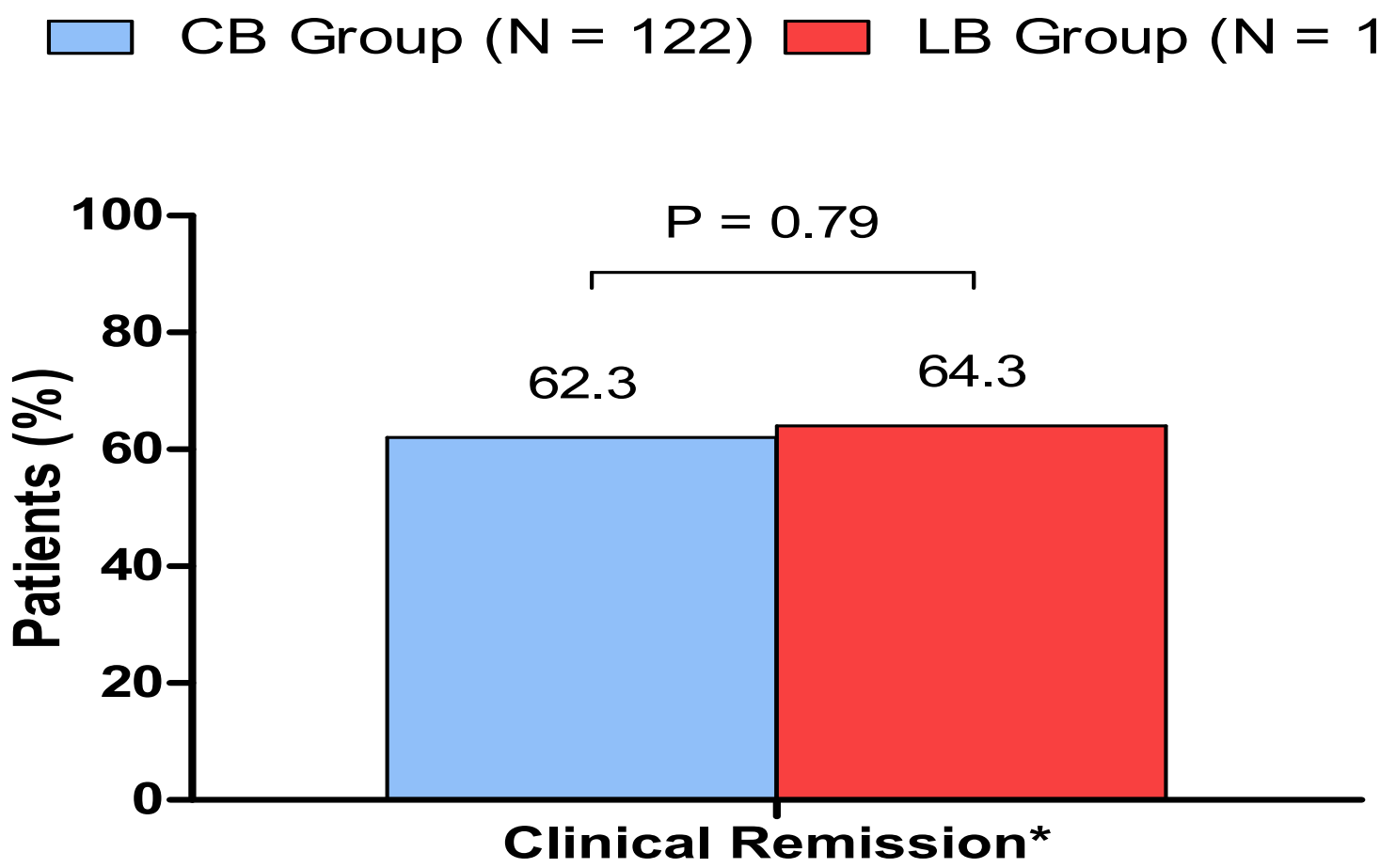
ry end point = rate of clinical (Harvey-Bradshaw or Partial Mayo score) and biological (C-reactive protein ≤5 mg/l) remissio
year after randomization in each group

nically Based Group; LB Group= Level Based Group

Vande Casteele N, et al. Gastroenterology 2015;14

TAXIT Results: Maintenance Phase

Primary end point

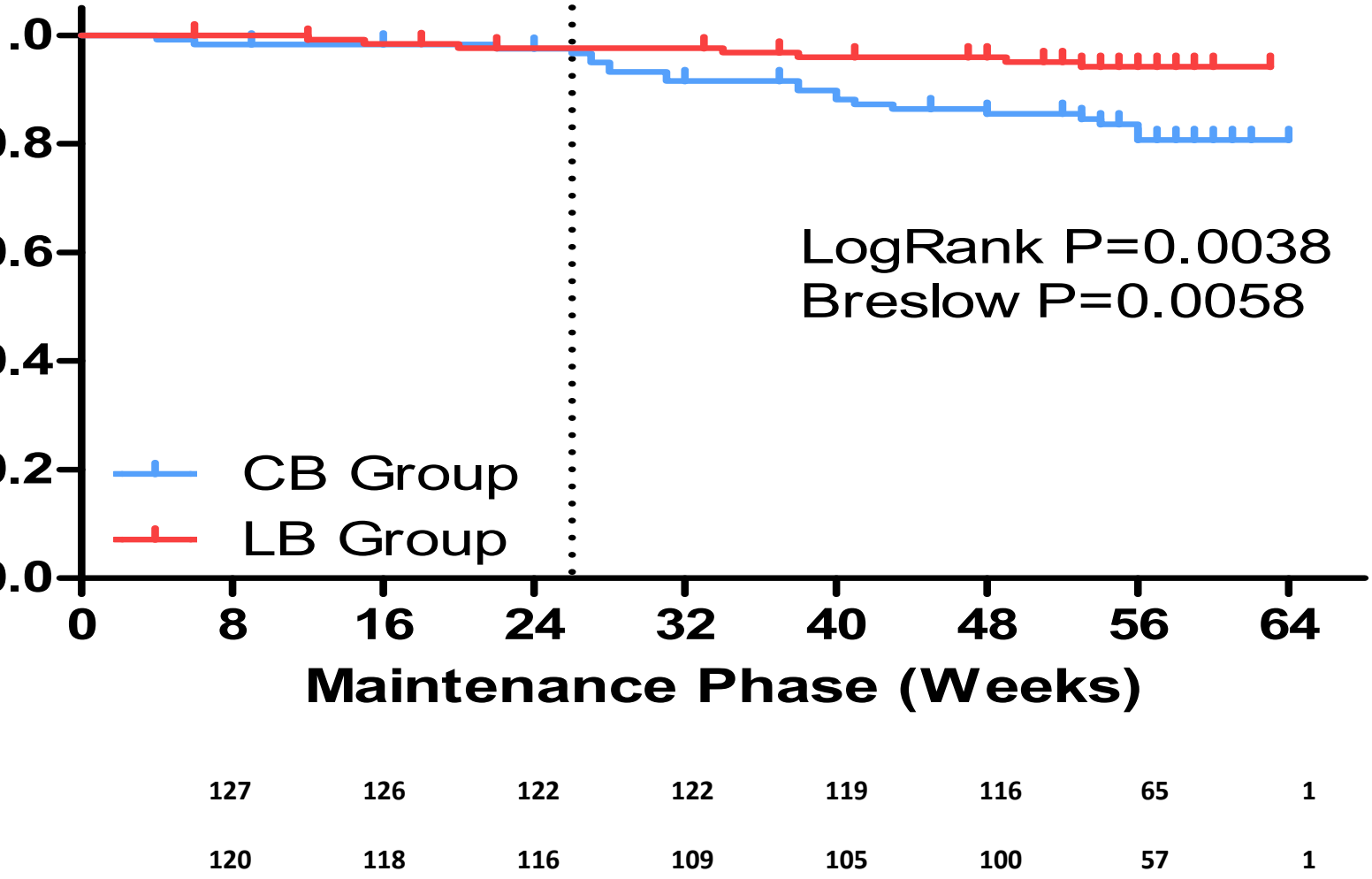


*Harvey-Bradshaw index score ≤4 (CD) or Partial MAYO score ≤2 (UC) and C-reactive protein level ≤5 mg/l. Primary end point could not be calculated for 3 Patients (1 CD from CB and 1 UC and 1 CD from LB group).

Vande Casteele N, et al. Gastroenterology 2015;14

TAXIT Results: Maintenance Phase

Secondary end point (loss of response and need for an intervention)



17.3% of CB Group
of LB Group needed
therapy by the end
maintenance ph

Vande Casteele N, et al. Gastroenterology 2015;14

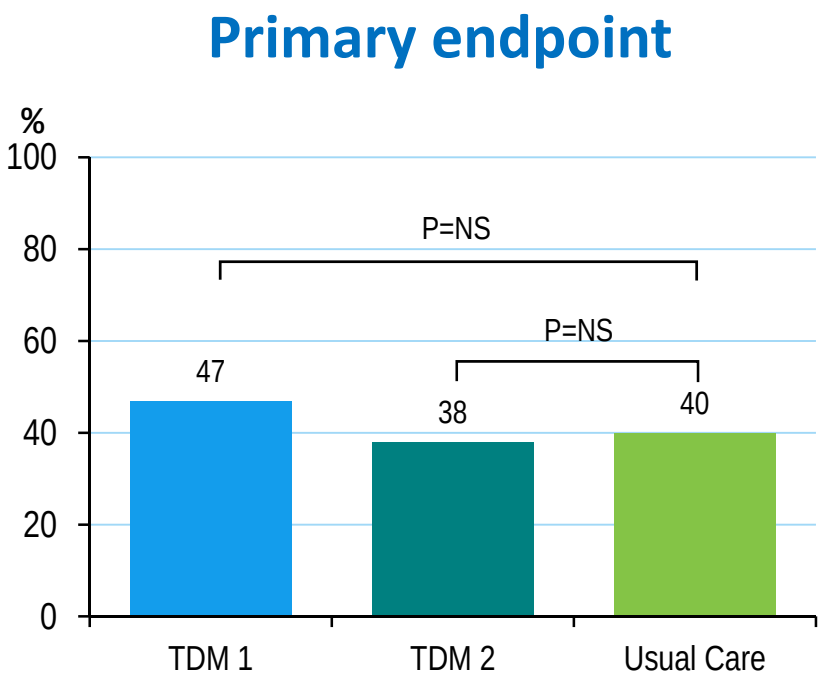
TAILORIX: Proactive TDM in Maintenance

esults:

oactive trough-level–based dose
tensification was <u>not</u> superior to dose
tensification based on symptoms alone.

ose increase of 2.5mg/kg as effective as
ng/kg

etailed pharmacokinetic,
mmunogenicity, and biomarker analysis
ending



*Steroid-free clinical remission from weeks 22-54 & absence of ulceratio

ECCO 2016. OP029 G. D'Haens et a

uboptimal IFX concentrations of the TDM grou

Additional outcomes

Percent of patients	TDM1	TDM2	Usual care
IFX dose escalation	51	65	40
Sustained IFX > 3 µg/ml weeks 14-52	**47**	**46**	**60**
CD Endoscopic Index of Severity < 3	49	51	45
Absence of ulcers			
Week 12	36	16	40
Week 54	36	43	48

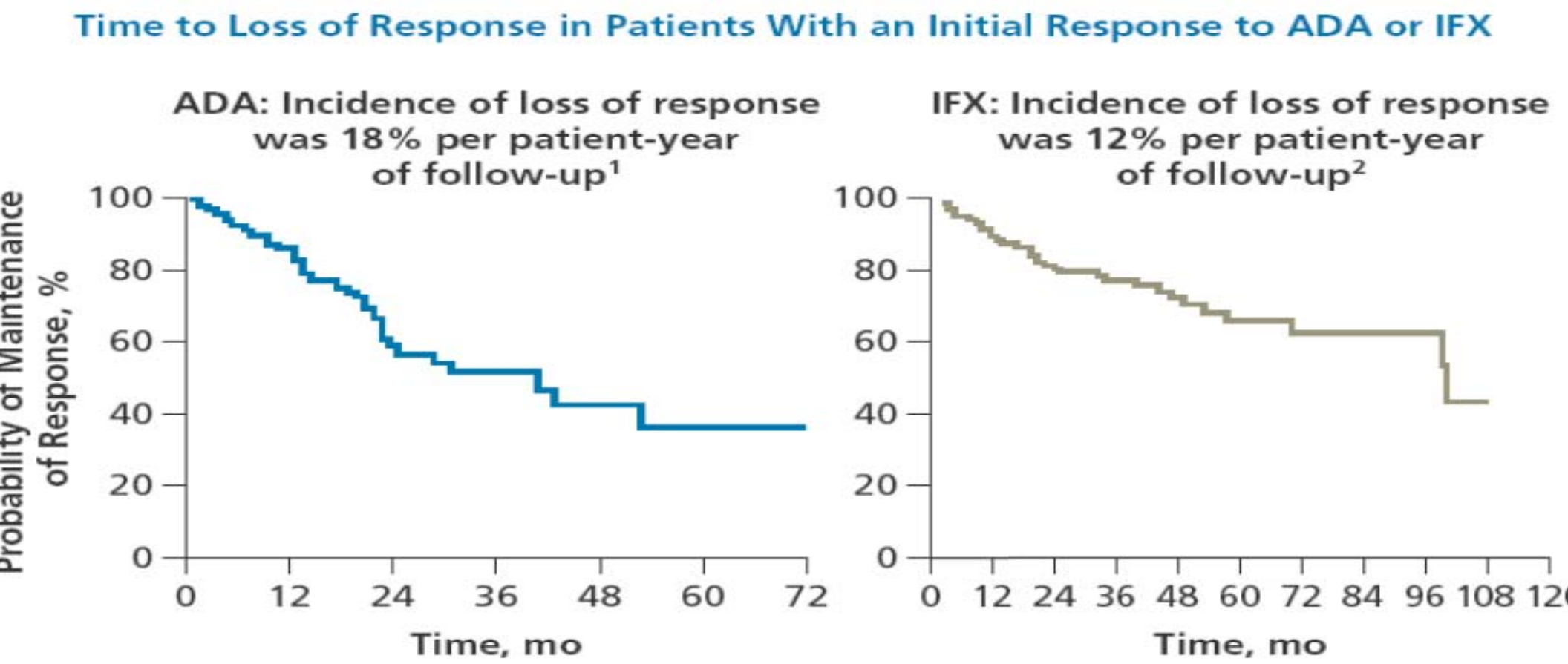
ECCO 2016. OP029 G. D'Haens et a

Optimizing Therapy

Loss of Response

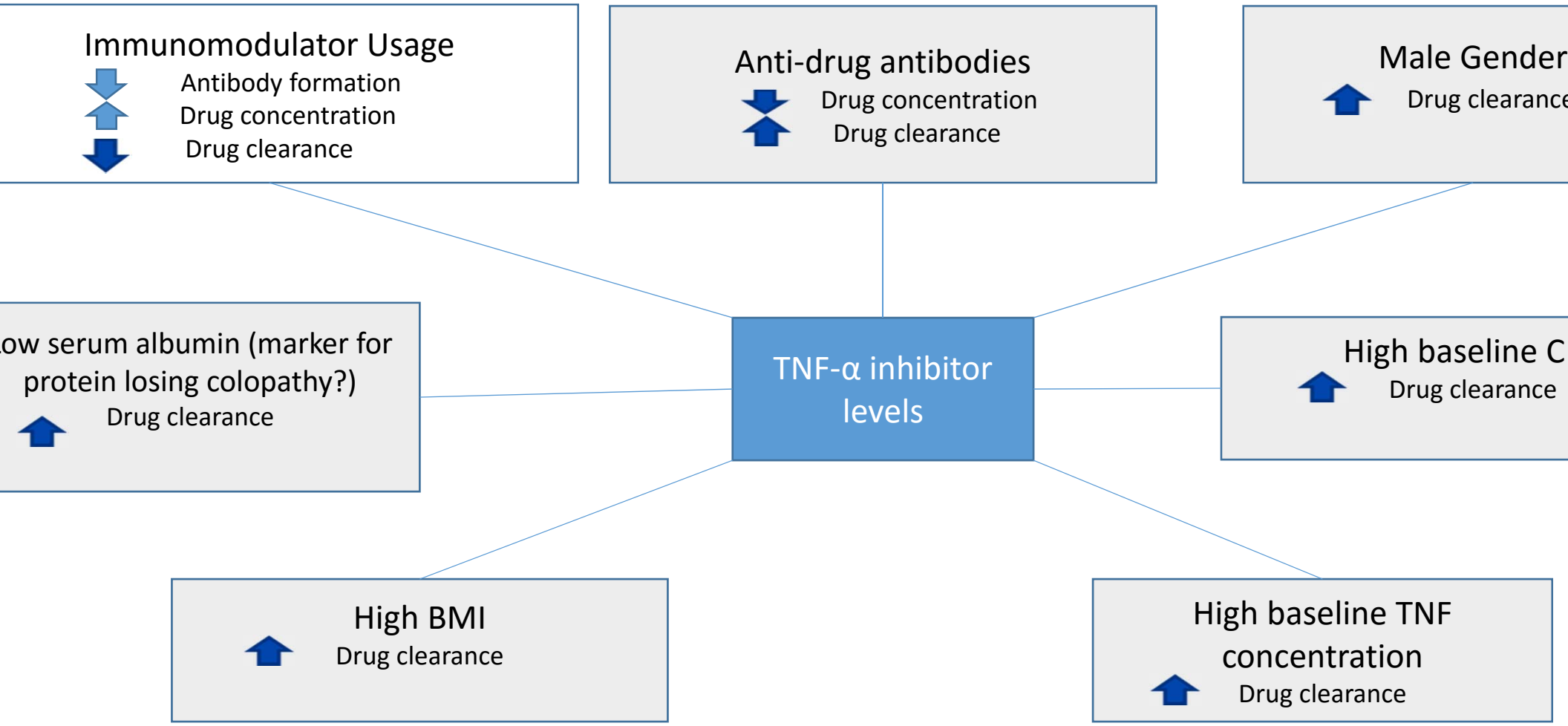
Progressive LOR to Anti-TNF Therapy in CD

ary non responder rate ; 20%



1. Chaparro M et al. IBD doi:10.2001/
2. Chaparro M et al. Clin Gastro 2011;

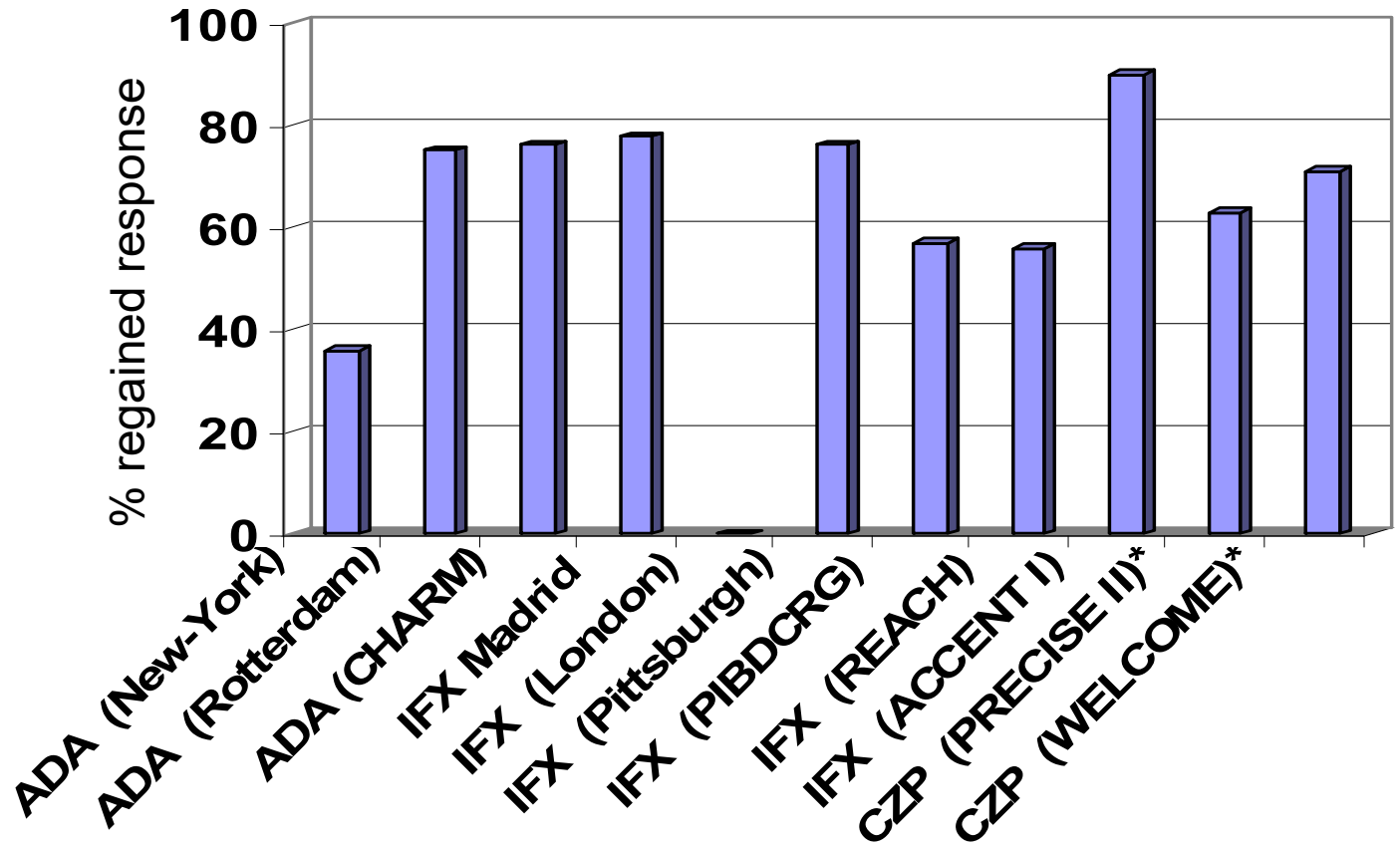
Variables Affecting TNF-α Inhibitor Levels



Ordás I, et al. Clin Gastroenterol Hepatol. 2012 Oct;10(

Managing loss of response: dose intensification

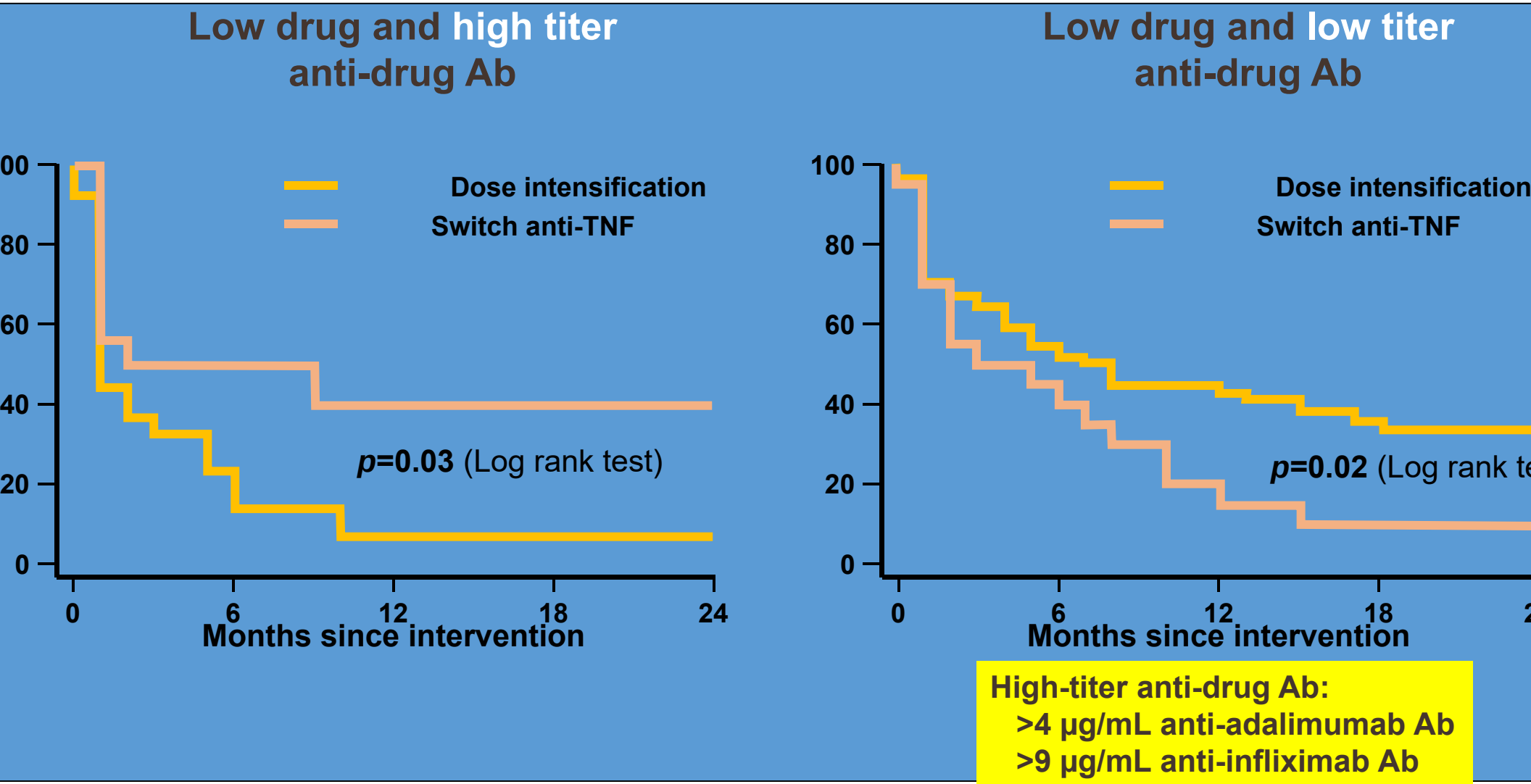
Dose escalation results in ~60-70% short-term response



Ben-Horin S, *Aliment Pharmacol*

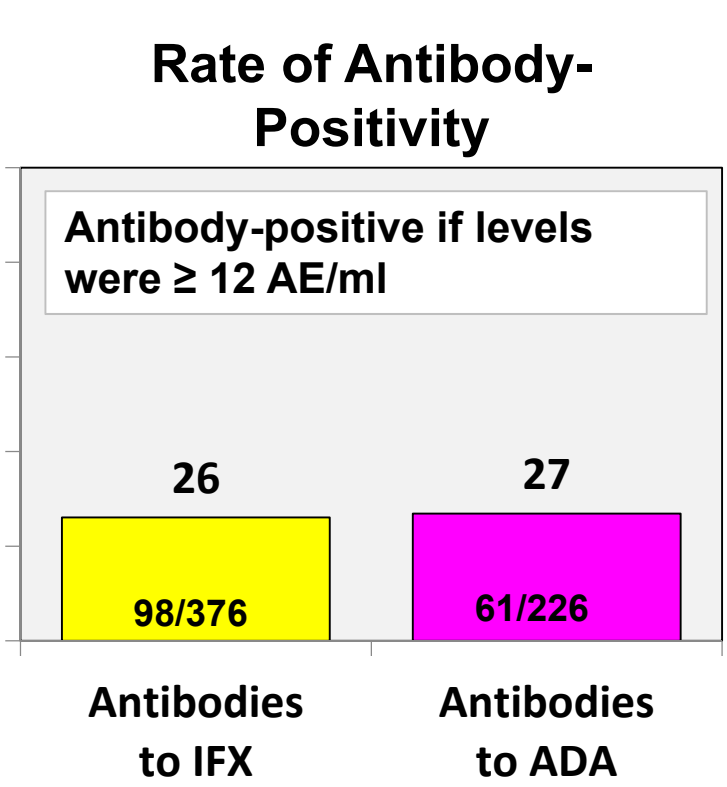
n drug (and anti-drug antibodies) concentrations gu
which intervention is best for loss of response ?

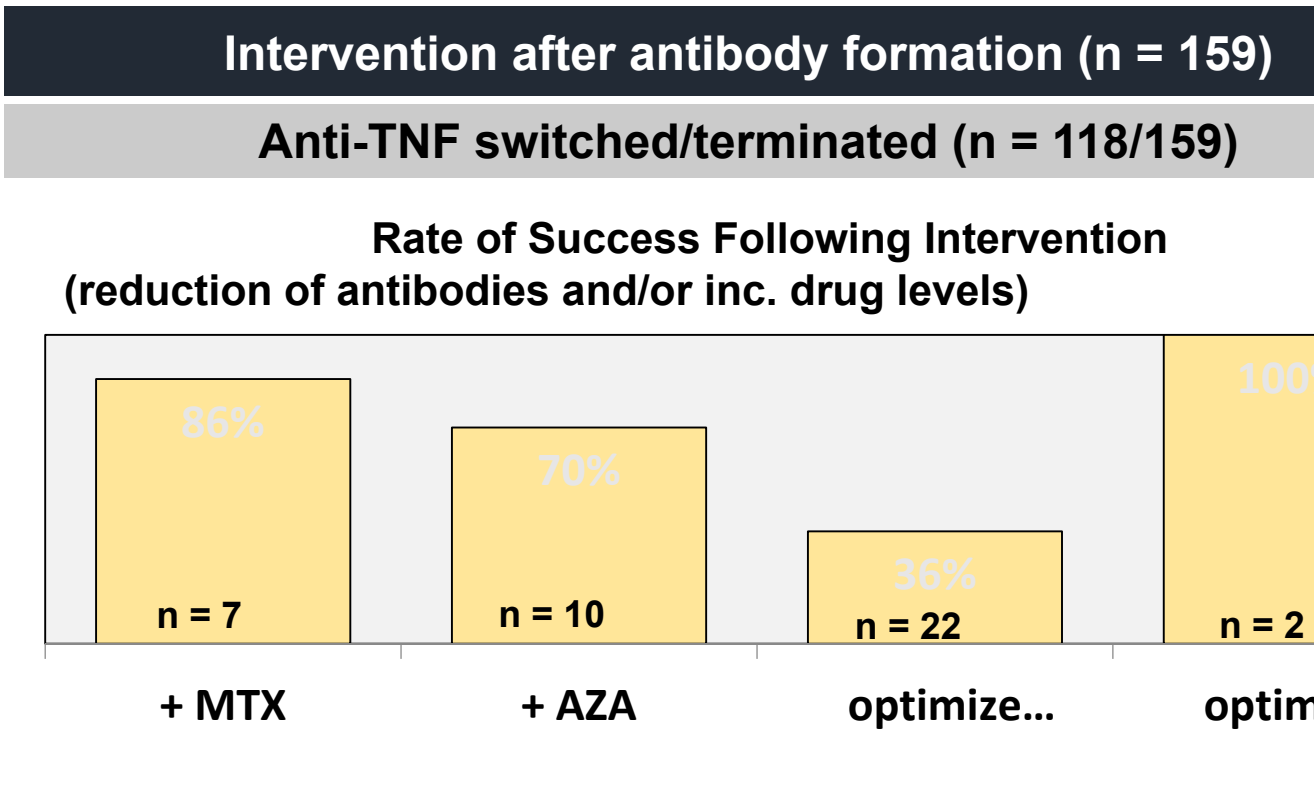
vels of drug/anti-drug antibodies and outcome of interventions after loss response to infliximab or adalimumab



Yanai H, *Clin Gastroenterol Hep*

Disappearance of Anti-Drug Antibodies to IFX and ADA Following Immunosuppressant in IBD





ectional study of 602 IBD pts receiving aTNF therapy

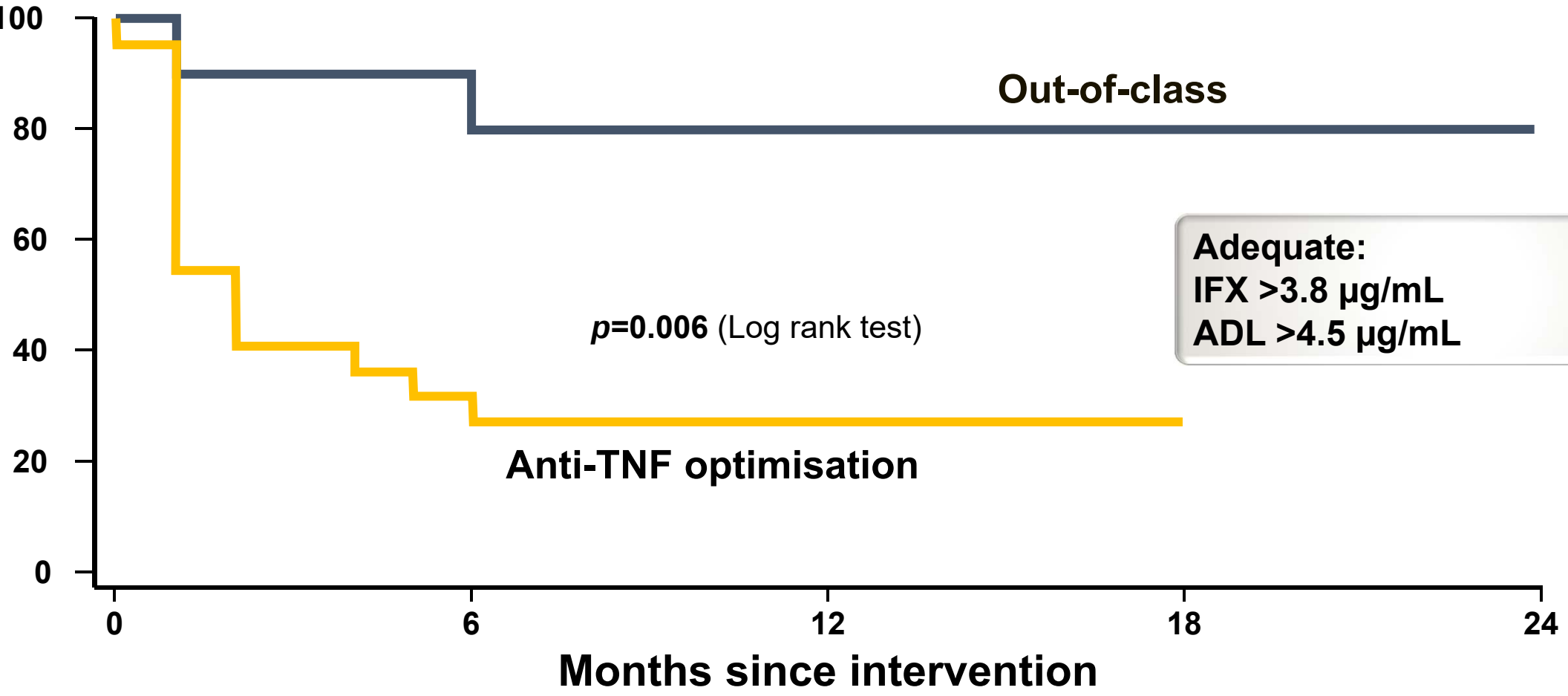
body levels measured with ELISA and RIA, respectively (Sanquin)

Strik et al. ECCO 2016

ne titer of measurable antibodies predicts response to dose-escalation versus switch

Anti-TNF concentrations

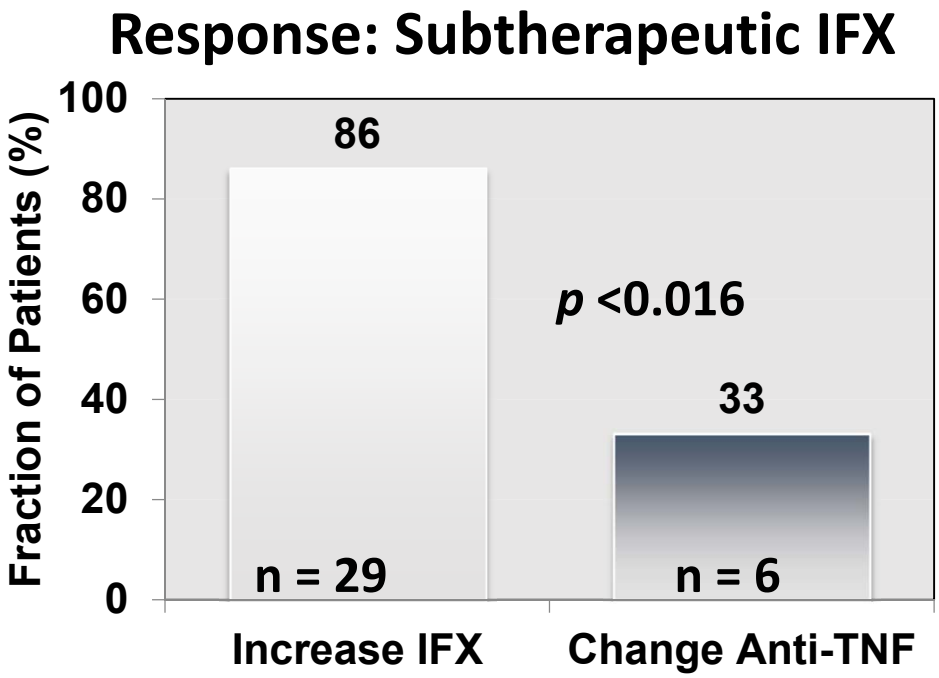
Drug concentration is adequate and IBD inflammation: switch out-of-class is better than anti-TNF optimization

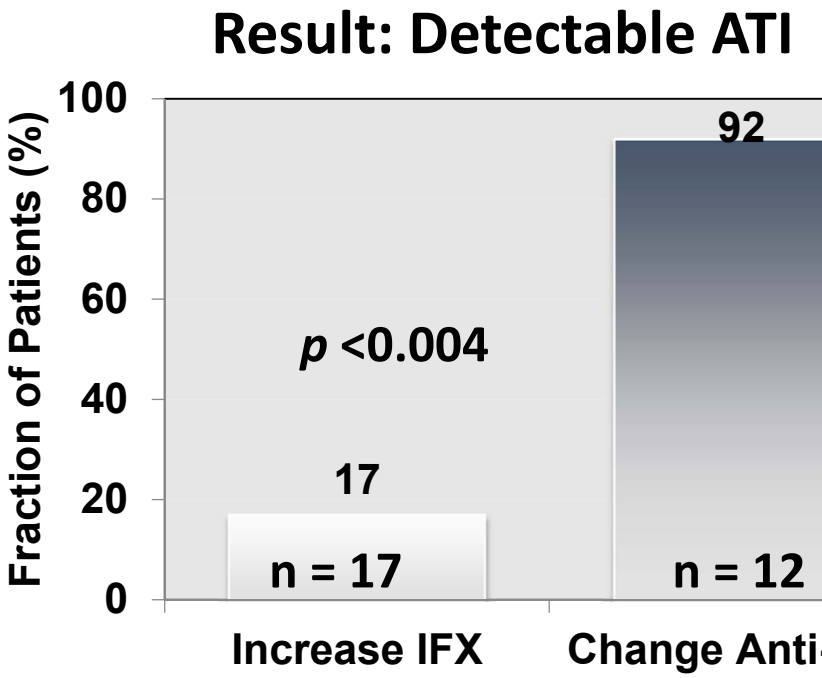


Yanai H, *Clin Gastroenterol Hep*

Centre universitaire de santé McGill

proved outcomes using TDM





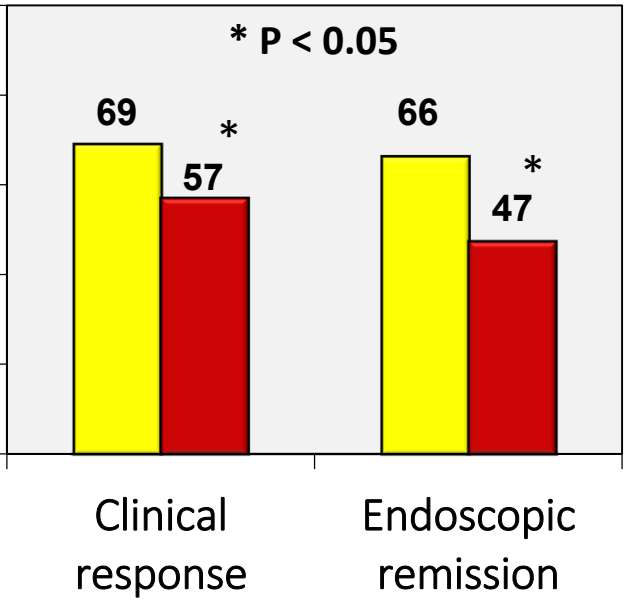
gle centre, retrospective study, n = 155 pts with TDM test

us ELISA assay

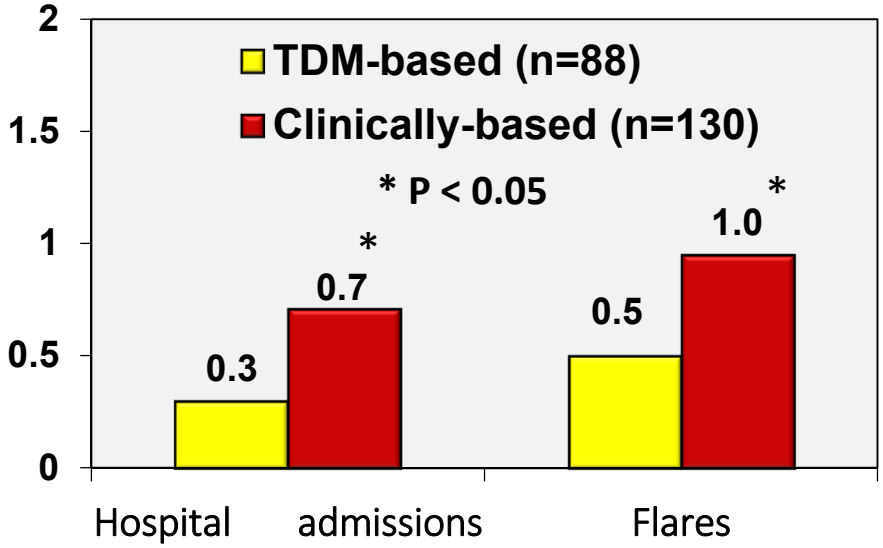
Afif et al. Am J Gastroenterol 2010;105:

Dose Optimization Using TDM is More Effective Than Dose timization Based on Clinical Assessment Alone

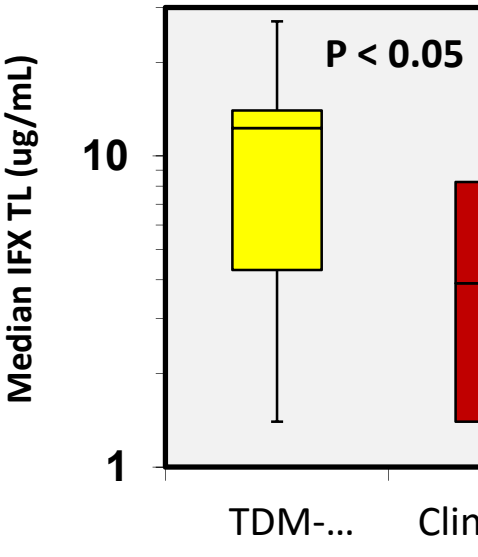
Clinical Outcomes



Post Dose Adjustment



Trough Lev



IBD pts → IFX dose optimization following secondary LOR (2008-2014)

-based optimization led to higher rates of clinical response, endoscopic remission, pitalization and flares (all p < 0.05)

improvement in symptoms + biomarkers markers and/or endoscopic response;

c Remission: Mayo subscore ≤ 1 or SES-CD < 3 or Rutgeert's score ≤ i1, Assay: Prometheus HMSA

Kelly et al. DDW 2015, Abstra

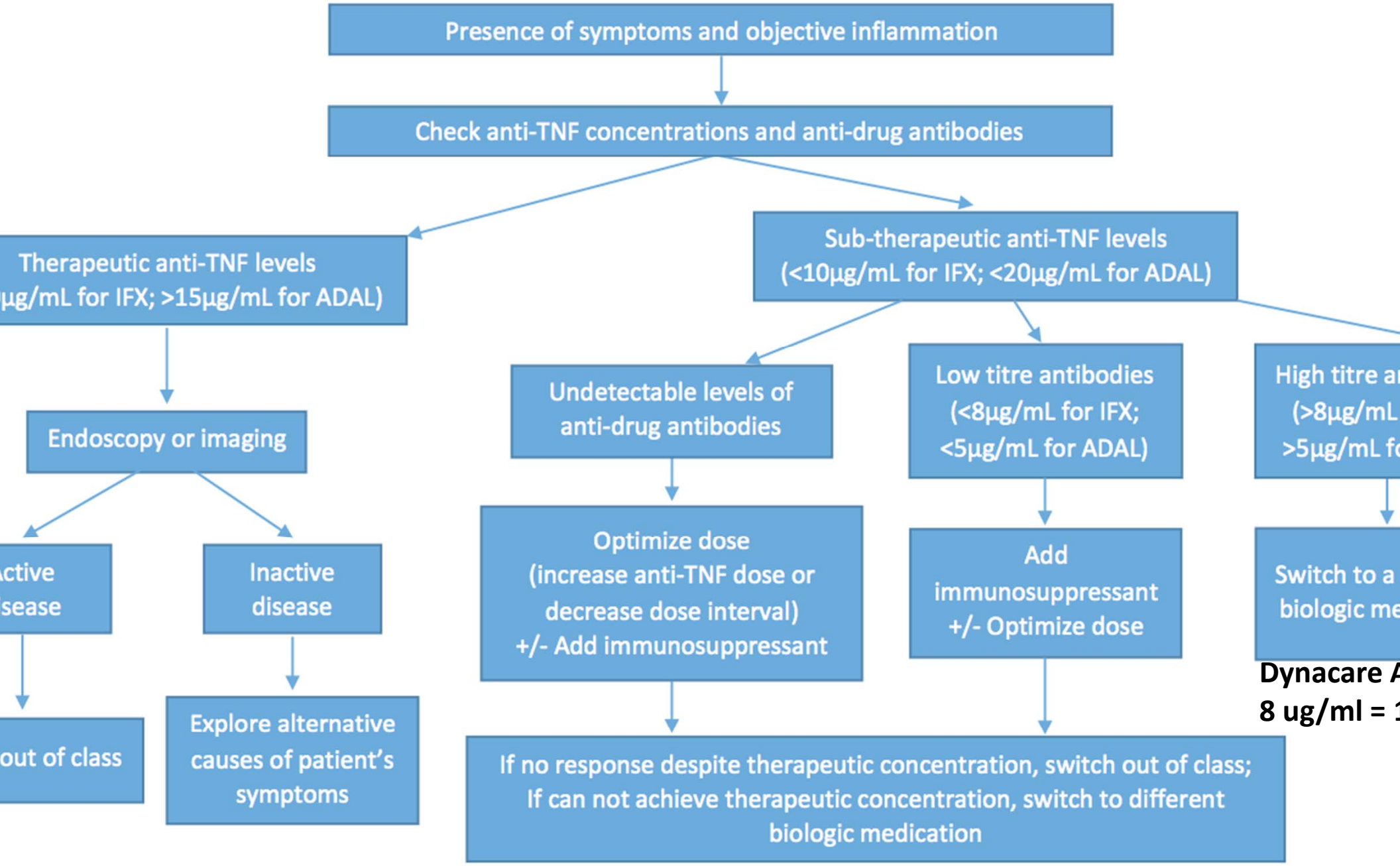
TDM Results and Algorithm

erify that the patient is taking the drug!

Up to 15%–29% of adalimumab/infliximab-treated patients are no
adherent to their injections

(Missed at least one injection/infusion during the last 3 months)

Billioud V, *et al. Inflamm Bowel Dis* 2011;1
Lopez A, *et al. Inflamm Bowel Dis* 2013;19



Dynacare A
8 ug/ml = 1

Heron and Afif, GCNA, 2017 (ahea

Optimizing therapy for differing phenotypes Perianal fistulising disease

117 Crohn's patients with perianal fistulising disease

Higher concentration for fistula healing vs active fistulas. Median infliximab trough level

- 18.5µg/mL versus 6.5µg/mL, P<0.0001

Incremental improvement in perianal fistula healing			
Trough level (ug/ml)	≥2.9	≥10.1	≥20.2
Fistula healing rate %	65	79	86

Yarur, A., et al., 514. Gastroenterology, 2016. 150(4, S1): p. S

Optimizing treatment using TDM in IBD

Secondary loss of response/partial response:	yes
Post induction prior to maintenance therapy	likely
Maintenance therapy in patients in remission	no
Withdrawal of immunosuppression in combination therapy	yes
Dose de-escalation	*yes*
After drug holiday	*yes*
Use for UST and VDZ	*likely*

Heron and Afif, GCNA, 2017 (ahead of

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